"What is a C-H···O hydrogen bond?" In the same vein one might well ask, "What is an O-H···O or an N-H···O hydrogen bond?" At a practical level, structural chemists have not been used to thinking in terms of C-H···O bonds, and it is in order to reexamine older ideas about crystal packing in this new light. For example, there is every indication that phenomena such as three-center bonding (bifurcation) and cooperative and resonance-assisted hydrogen bonding exist for C-H···O networks, and hence chemists will find it worthwhile to consider *all* interactions, weak (C-H···O, O-H···C) and strong (O-H···O, N-H···O), while attempting to understand hydrogen-bond arrangements and indeed crystal packing, in general. References to C-H···O bonds in the physical organic literature are even more sparse, but here again, these forces have been invoked to explain some surprising observations.[47,48] In conclusion, it seems appropriate to state (with due apologies to Donohue) that a better answer to the question in the title of this Account and this section is: "*It certainly is.*"

Warm thanks are due to the following students, past and present, who have worked with me on the topic of C-H···O hydrogen bonding in organic crystals: J. A. R. P. Sarma, K. V. Radha Kishan, V. R. Pedireddi, C. V. K. M. Sharma, and B. N. Murty. I thank J. P. Glusker and A. Gavezzotti for their valuable comments on this manuscript. It is impossible to list all the colleagues with whom I have had spirited discussions on this controversial subject, but I must mention C. Ramakrishnan and R. Parthasarathy, who filled me in on the early days of C-H···O bonds, especially in the G. N. Ramachandran group in Madras.

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Acyclic Stereochemical Control in Free-Radical Reactions

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Since Gomberg's discovery of the persistent triphenylmethyl radical over 90 years ago,[1] there has been a steady increase in interest in free radicals. Recent years have seen the emergence of new free-radical synthetic methods that are efficient and convenient,[2,3] and new chain-propagation schemes have been reported that are based on tin hydride-alkyl halide or borohydride-mercurial reductions, halogen atom transfer reactions,[3] thiohydroxamate[4] or allylstannane addition-fragmentation processes,[5,6] and manganese(III) oxidations.[7]

Ring construction by free-radical cyclization has proved to be particularly useful, and five-membered rings are readily produced by this approach. The fundamental work of Walling, Beckwith, and Ingold[8] provided information about the regiochemistry, absolute rate, and stereochemistry of cyclizations. Synthetic efforts have benefited tremendously from this body of mechanistic work, and the cyclization reaction has been put to good synthetic use.[9,10] Intermolecular free-radical addition reactions have also received renewed interest. Systematic studies have shown that polar and steric effects are most important in controlling the rate of addition of radicals to carbon-carbon double bonds, and there are many examples of the useful incorporation of intermolecular radical additions into synthetic sequences.[2,3]

Despite major advances in the past 10 years, a significant barrier for the application of free-radical methodology in organic synthesis remains: there is no general approach to the control of acyclic stereochem-

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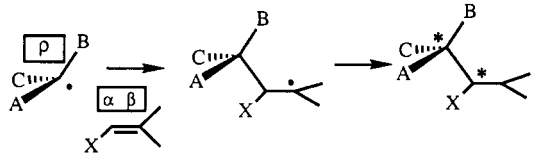
istry in free-radical reactions. For free radicals to become mature synthetic intermediates, a general understanding of this problem is required. Over the last three years, the first significant steps toward understanding acyclic stereocontrol in radical reactions have been taken, and this combined Account summarizes the progress in our three laboratories.

Most of the recent advances in free-radical stereocontrol have come in the study of free-radical addition to carbon–carbon double bonds. In the addition of a radical to an alkene, two new stereogenic centers may be constructed in the addition step (simple diastereoselection) if the radical and the alkene are suitably substituted. One of these two centers derives from a prochiral radical (which we define as the ρ center) while the second center results from the prochiral alkene center to which addition occurs.



The control of stereochemistry at the α or ρ centers may be exerted by resident groups that make the radical or alkene faces diastereotopic (diastereoface selection). Radical diastereoface selection may result from reactions of chiral radicals that have diastereotopic ρ faces with achiral alkenes. Alkene diastereoface selection may result from reactions of achiral radicals with chiral alkenes that have diastereotopic alkene faces. For alkene diastereoface selection, we further distinguish the location of the resident chiral control element as being attached either α or β with respect to the site of radical attack.

Significant levels of diastereofacial control have been achieved in free-radical addition reactions involving cyclic radicals or alkenes.[11] Steric effects are important in these reactions, and addition occurs on the face of cyclopentyl radicals opposite from substituents in the 2-position (anti addition) with ρ selectivities as high as 98:2. The stereoselectivity of radical addition to cyclic alkenes is also influenced by steric effects in a similar manner.

There were only a few reports of control of stereochemistry in addition reactions of acyclic alkenes or radicals before 1988.[12-15] In these isolated examples, no principles emerge that allow a general understanding of the acyclic stereoselection problem. With no clear precedents in free-radical chemistry, the lessons of auxiliary-controlled acyclic stereoselection in enolate and enamine alkylations served as precedents to guide the free-radical chemistry.

Consideration of the problem of ρ or α acyclic free-radical stereocontrol with enolate and enamine chemistry as a reference leads to the following general conclusions: (1) the resident chiral group intended to control the configuration of the new stereogenic center formed in radical addition must be fixed relative to that center, and (2) the resident chiral group must differentially shield the diastereotopic radical or alkene faces.

Scheme I
C–C(O) Conformational Control in Alkenes and Radicals

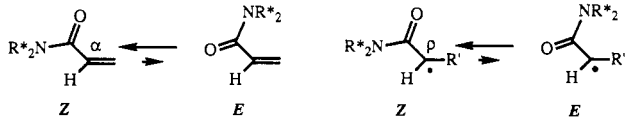
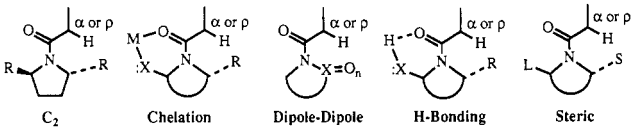


Chart I
N–C(O) Conformational Control in Amide- or Imide-Substituted Alkenes and Radicals



With these general guidelines, it seems clear that chiral amides or imides are appropriate targets for use as auxiliaries in α and ρ stereoselection. For amide or imide groups substituted on alkenes or radicals, the orientation of the C–C(O) bond is fixed since the NR_2 group is large relative to the carbonyl oxygen and this fixes the C–C(O) conformation in the *Z* arrangement (Scheme I). Experimental support for the notion of amide or imide C–C(O) conformational control exists in NMR and EPR studies for alkenes and radicals.[16,17] Radicals substituted by carbonyl groups are stabilized by resonance delocalization of the radical into the carbonyl, and the C–C(O) bond therefore has appreciable double-bond character.[18,19]

To fix the residual chiral group relative to the ρ or α center, control of the orientation about the amide or imide N–C(O) bond is also essential. Several strategies can be envisioned, with the lessons of enolate and enamine chemistry again providing guidance. The C_2 symmetry strategy[20] has been used successfully in enamine alkylations while chelation control has been used extensively in enolate and cycloaddition chemistry[21-24] (Chart I). Dipole–dipole control of imide rotamer population has been successfully applied to carbanion alkylation and cycloaddition problems,[25,26] and control of N–C(O) rotamer population might also be possible with hydrogen bonding or steric effects. The amide carbonyl oxygen is smaller than the α- or ρ-center carbon that bears a hydrogen atom, and this steric difference should bias the N–C(O) rotamer population such that the large group on the amide would be cis to the carbonyl and the small group of the amide would be cis to the α or ρ carbon. Of the possible methods for N–C(O) rotamer control, the C_2 and dipole–dipole precedents suggest the use of these strategies in free-radical reactions, and these approaches were the first to be investigated.

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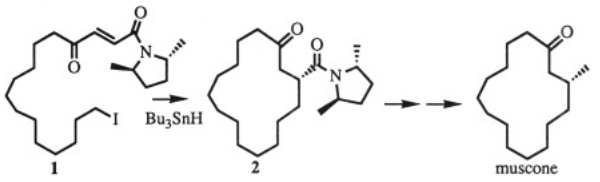
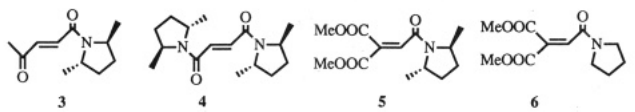
Radical Additions to Chiral Alkenes

α-Attached Auxiliary. High diastereoselectivities in radical additions to α,β-unsaturated amides were first observed at Duke[27] in studies of free-radical macrocyclization of the iodide **1** leading to enantiomerically enriched muscone. In this intramolecular addition,



four stereoisomeric products are formed, two diastereomers resulting from exo radical cyclization and two from endo cyclization. The endo:exo product ratio is approximately 8:1, and the two exo products are formed with no diastereoselectivity while the two endo products are formed with a selectivity of 14:1 at 80 °C, the major product having the structure **2**. This example illustrates that the C_2 amide auxiliary is effective if substituted on the α carbon while it has no effect on diastereoselectivity if it is attached to the β carbon of the alkene undergoing addition.

Intermolecular radical additions to dimethylpyrrolidine amide-substituted alkenes are also selective if the amide is substituted on the α alkene carbon.[28,29] One alkene studied was the unsymmetrical monoamide derived from 4-oxo-2-pentenoic acid, **3**, while the other substrate examined was the diamide of fumaric acid, **4**. Hexyl, cyclohexyl, and *tert*-butyl radical addition



to **3** gave approximately equal amounts of addition at the ketone and amide ends of the alkene. The two stereoisomeric products derived from addition at the ketone end were formed in a nearly 1:1 product ratio while the products derived from addition at the amide end were formed in ratios as high as 40:1 (*tert*-butyl addition at 0 °C). Addition of cyclohexyl or *tert*-butyl radical to **4** gives essentially one stereoisomer (diastereomeric ratio = 50:1 and 80:1 at room temperature).

The trisubstituted olefin **5**[30,31] is a very reactive alkene in reactions with nucleophilic alkyl radicals, and additions can be carried out over a wide temperature range. Cyclohexyl radical addition gives only one regioisomer with very high diastereoselectivity (diastereomeric ratio >125:1 at −80 °C) in yields exceeding 90%. Substitution of the geminal carbomethoxy groups in **5** makes the alkene more electrophilic than **3** or **4** and directs addition of the alkyl radical to occur at the opposite end of the alkene from the carbomethoxy groups where the auxiliary is α substituted.

The alkene **5** is crystalline, and single-crystal X-ray analysis[31] provides support for the C–C(O) and N–C(O)

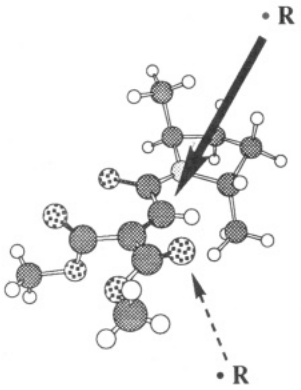


Figure 1. Solid-state conformation of **5** and vectors of addition for alkyl radicals.

conformational control arguments presented above for this auxiliary group. The amide carbonyl oxygen in crystalline **5** is in a "*Z*" orientation with respect to the olefin, and the pyrrolidine is in a half-chain conformation with the methyl substituents occupying pseudo-axial positions. There is severe steric crowding of the vinylic C-α hydrogen with groups on the pyrrolidine substituted α to the nitrogen, and this steric interaction is minimized by adoption of an axial orientation for the larger methyl (compared to hydrogen) pyrrolidine substituent.

Carbon radicals are nucleophilic, and transition states for addition of nucleophilic radicals to electron-deficient olefins such as **5** are reactant-like.[11,32] Because of the early transition state, factors that influence the ground-state alkene conformation should influence the transition state. Approach of the radical to the amide end of the alkene on a nucleophilic trajectory suggests a facial bias in the addition, as can be seen in Figure 1. For addition of carbon radicals to unactivated olefins, calculations suggest that the C(ρ)–C(α) distance is in excess of 2.2 Å in the transition state and the angle of approach of the radical is close to the tetrahedral value.[32] The proximate methyl substituent on the pyrrolidine protects the bottom face from addition while the other methyl substituent is remote from the trajectory of approach of the radical to the top face of the alkene. The model presented in Figure 1 is consistent with the stereochemistry of the major diastereomer formed in every example investigated.

Competition experiments of the alkene **5** with model alkene **6** for cyclohexyl radical show that the rate of addition to the disfavored face of **5** is 20-fold less than the rate of addition to **6**, consistent with steric hindrance being the origin of the selectivity. Furthermore, in all of the examples of α selectivity examined thus far, stereoselectivity is temperature dependent. Arrhenius plots show that the selectivity is enthalpy controlled, $\Delta\Delta H^{\ddagger}$ for addition to the diastereomeric alkene faces being on the order of 1.5–3.0 kcal/mol.

The dimethylpyrrolidine auxiliary is difficult to remove after addition, but a C_2-symmetric pyrrolidine that is substituted at positions 2 and 5 with protected hydroxymethyl groups, and is removable,[33,34] has been

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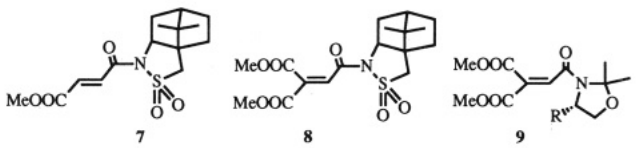
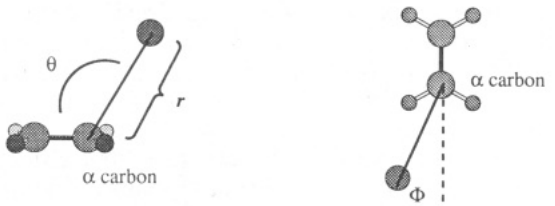
shown to give substantially higher selectivities than the dimethylpyrrolidine.[35] Additional auxiliaries that show promise in α selectivity include the Oppolzer camphorsultam (shown in the alkenes **7** and **8**) and oxazolidines (e.g., **9**) prepared in two steps from amino acid precursors. The addition of cyclohexyl radical to **7**



7 **8** **9**

occurs at the alkene center adjacent to the carbomethoxy (β auxiliary group) with little selectivity (2:1).[36] The trisubstituted alkene with the sultam auxiliary[37] undergoes addition α to the sultam with significant diastereoselectivity (~12:1) observed at 0 °C. The sulfonimide can be removed by hydrolysis or reduction. These results underscore the importance of α attachment for the simple amide auxiliaries. Little or no selectivity is observed if the auxiliary is attached at the β position while the same auxiliary gives significant stereoselectivity if the attachment is α to the alkene center undergoing addition.

The dimethylpyrrolidine amide and the Oppolzer sulfonimide appear to have little in common that would identify them as successful auxiliaries. However, consideration of the polar coordinates of resident centers relative to the α carbon provides a reasonable framework for evaluation of potential auxiliaries. The distance of groups from the α carbon, r, and the two angles Φ and θ as shown herein are important parameters for evaluation of selectivity. Groups which occupy a



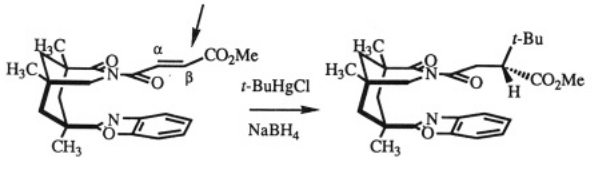
volume of space with coordinates $\Phi \sim 0°$ and $\theta \sim 110°$ and with a small r value (2.5–4.0 Å) protect electrophilic alkenes from addition of nucleophilic radicals.[31] For the alkene **5**, the pyrrolidine methyl that protects the bottom face from addition (Figure 1) has coordinates of $r = 3.34$, $\Phi = 10.8°$, and $\theta = 141°$. Analysis of the single-crystal X-ray structure of the acrylamide of the Oppolzer sultam[26] gives $r = 3.28$, $\Phi = 9.7°$, and $\theta = 146°$ for one of the sultam oxygens, very close to the position of the protecting methyl of the pyrrolidine. Thus, the pyrrolidine which has a C_2 axis and the imide which has a dipole–dipole controlled conformation both place shielding groups in similar volumes of space relative to the α center.

Recent studies with acyloxazolidines such as **9**[38] provide a potentially useful alternative auxiliary to the C_2-symmetry pyrrolidines and the Oppolzer sultam. Amides such as **9** are prepared in situ by reaction of the amino alcohol with acetone[39] followed by acylation of the intermediate oxazolidine. Addition of cyclohexyl radical to **9** with R = alkyl at 0 °C gives selectivities that range from 9:1 with R = Me to >80:1 for R = *t*-Bu.[38] The oxazolidine with R = *t*-Bu gives the highest selectivity observed for cyclohexyl addition to any of the trisubstituted alkenes studied thus far, and the oxazolidine can be removed by acid-catalyzed hydrolysis without loss of configuration at the α stereogenic center.

β-Attached Auxiliary. The development of general strategies for the additions of nucleophilic radicals to chiral alkenes with β-attached chiral auxiliaries is an especially important goal because typical amide, imide, and ester-based auxiliaries naturally direct radical attack to the β position. However, the early work indicated that this would be a challenging problem. The above model indicates that auxiliaries like the 2,5-dimethylpyrrolidine and Oppolzer's camphorsultam fail in β induction not because of problems with control of conformation but because the face-shielding groups are located in a poor position in space. Indeed it seems likely that most popular classes of chiral auxiliaries in use today will not meet the demanding requirements for β stereocontrol in radical additions.

The approach to this problem in Pittsburgh was to build a molecule with a shape such that a face-shielding group was located directly above (or below) both the α *and* β positions. The inspiration for the shape of these molecules came from Rebek's conceptions and applications of molecules based on Kemp's triacid to problems in molecular recognition.[40] Some first-generation auxiliaries based on this idea were used successfully in nitrile oxide cycloadditions,[41] but it was soon found that these compounds were not the answer to the radical problem.[42] A second-generation auxiliary, **10**, was prepared and was found to give remarkable selectivities in free-radical additions.[43]

Addition of *tert*-butyl radical (by the mercury method) to mixed fumarimide **10** at −40 °C provided only two of the four possible products in a ratio of 97:3. Both products resulted from attack of the radical β to the imide, and the major stereoisomer has the structure **11**. The minor product is the stereoisomer (not a regioisomer) of **11**. The benzoxazole auxiliary can be removed by hydrolysis with LiOOH[44] (conditions which leave the ester unaffected) and recovered. Additions of primary and secondary radicals to **10** gave similar products, but the stereoselectivities were somewhat lower.



10 **11**

A working model for this high selectivity observed with benzoxazole **10** has three features: (1) the imide carbonyls are opposed to minimize dipole repulsion, (2) the fumarimide is *Z* (s-cis), and (3) the radical attacks the face opposite the benzoxazole ring. The key in-

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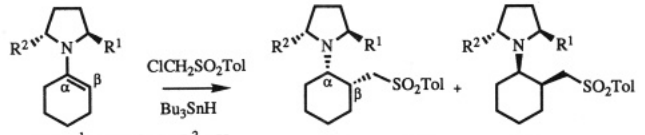
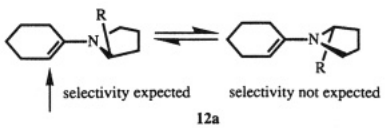
gredient to this third feature is the "U-turn", which places the benzoxazole ring directly below both the α and β positions of **10**. Almost as interesting as the β stereoselectivity of **10** is the unprecedented regioselectivity (<5% products formed from radical attack α to the auxiliary). This unexpected bonus means that additional directing features are not needed to insure attack of radical β to the chiral auxiliary. The benzoxazole **10** meets all the requirements for practical utility save one: it is not commercially available (the synthesis takes seven steps from Kemp's triacid). More important than this, it points the way to future developments by showing how to achieve β stereocontrol by relying entirely on the structure of the auxiliary. Clearly auxiliaries like **10** might also have uses outside radical chemistry for any reaction that must rely completely on an unaided chiral auxiliary for stereocontrol.

Renaud and Schubert have recently reported the first examples of additions of electrophilic radicals to nucleophilic alkenes bearing chiral auxiliaries.[45] Strictly speaking, these are not examples of acyclic stereocontrol (a bond is formed to an existing ring); however, the auxiliary is attached by a freely rotating single bond, and the principles that emerge should be fully applicable to acyclic systems. Radical additions to enamines **12a** and **12b** were conducted by the tin hydride method. With prolinol-derived enamine **12a**, no stereoselectivity was observed at the β position, although high cis selectivity was observed due to the large β substituent. In contrast, the C_2-symmetric dimethylpyrrolidine enamine **12b** provided essentially a single product, **13b**.

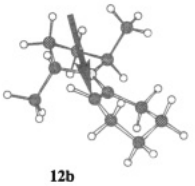


12a $R^1 = CH_2OMe$, $R^2 = H$ **13a** 1/1 **14a**
12b $R^1 = R^2 = Me$ **13b** >95/5 **14b**

Even though this is an example of β stereocontrol, the understanding of this selectivity follows directly from the principles outlined in the section on α stereocontrol in additions to unsaturated amides. This is because one fewer atom separates the auxiliary stereocenters from the site of attack in the enamine compared to the unsaturated amide.



12a

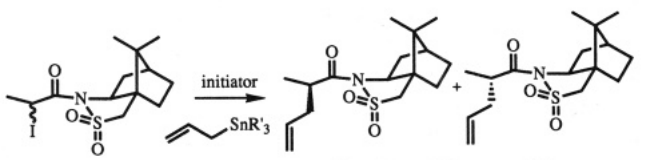


12b

Additions to Chiral Radicals: ρ Selectivity

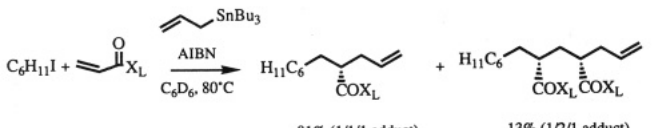
The first examples of high acyclic ρ selectivity in radical additions[46,47] and cyclizations[46] as well as in C–D and C–S[48] bond-forming reactions appeared in 1990, and these reports have formed the basis for subsequent work. The introduction alluded to the similarities between α,β-unsaturated amides and radicals adjacent to amides. It was precisely these similarities that stimulated the study of Oppolzer's camphorsultam[49,50] and the dimethylpyrrolidine in ρ selectivity.

That acrylate derivatives of Oppolzer's sultam possess all the features required for unaided asymmetric cycloaddition reactions[26,51] strongly implied that they would also provide ρ selectivity when directly attached to a radical. This simple analogy turned out to be correct.[51–53] Asymmetric allylation reactions of the 2-iodopropionamide derivative of Oppolzer's camphorsultam (**15**) proceeded with good selectivity at 80 °C, and the selectivity increased as the temperature decreased. Excellent yields of **16**/**17** were obtained down to −20 °C, where the level of selectivity was 25:1. Below −20 °C, the selectivity increased even further, but difficulties with chain propagation greatly reduced the conversion rate. At 25 °C, radical allylations of Oppolzer's sultam are more selective than most ionic addition reactions to related acrylate derivatives,[49] and at −20 °C, the radical allylation is marginally more selective than allylation of the lithium enolate of the propionamide derived from Oppolzer's sultam.[54] These results help to dispel any fears that radical reactions might be fundamentally less selective than their ionic counterparts. Oppolzer's camphorsultam also served as the template for the first asymmetric radical cyclization and annulation reactions.[46]



15 **16** 12/1 at 80°C, 25/1 at −25°C **17**

Chiral radicals can also be generated by radical additions to acrylate derivatives of Oppolzer's camphorsultam, as the following reaction illustrates. Here selectivity at high temperatures is especially important because this more complex radical chain will not propagate well at temperatures below 80 °C. The major product is a 1:1:1 adduct in this radical sequence, but a small amount of a minor 1:2:1 adduct that was isolated served to illustrate an interesting point: the chiral auxiliary should control relative stereochemistry along a growing carbon chain. In other words, polymerization of the acrylate derivative of Oppolzer's camphorsultam



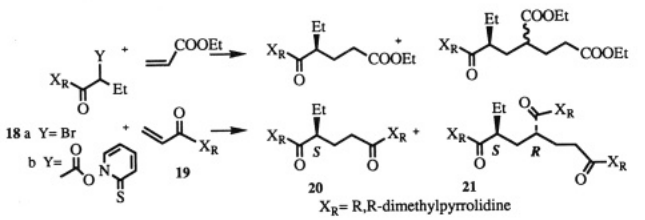
X_L = L-(+)-2,10-camphor sultam

81% (1/1/1 adduct) 13% (1/2/1 adduct)

(45) (a) Renaud, P.; Schubert, S. *Synlett* **1990**, 625. (b) structures 13/14 were not rigorously proven, but were assigned by analogy to a related system.
(46) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738.
(47) (a) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. (b) Porter, N. A.; Breyer, R.; Swann, E.; Allen, T.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.*, in press.
(48) Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741.
(49) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39.
(50) Heffner, T. M.S. Thesis, University of Pittsburgh, 1989.
(51) (a) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555. (b) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.
(52) Shen, W. Ph.D. Thesis, University of Pittsburgh, 1991.
(53) Zhang, J. Ph.D. Thesis, University of Pittsburgh, 1990.
(54) Oppolzer, W.; Moretti. R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603.
(55) In a very similar reaction, the Duke group observed lower selectivity (4:1) at a lower temperature (−78 °C).

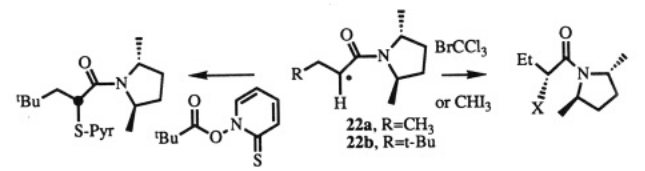
should provide primarily an isotactic polymer. In contrast, radical polymerizations of unsaturated esters and amides usually produce atactic polymers (stereocenters are randomly oriented along the polymer chain). This control of tacticity was featured more prominently in the early work utilizing the dimethylpyrrolidine auxiliary.[47]

A series of addition reactions were conducted with the bromide **18a** or the Barton thiohydroxamate precursor **18b** where conditions were deliberately chosen such that a mixture of products was formed. In the reaction of **18** with ethyl acrylate, 1:1 adducts formed with good stereocontrol, but the 1:2 adducts formed with stereocontrol only at the carbon bearing the chiral auxiliary and not at the carbon bearing the ester. The inability of either the chiral auxiliary or the first-formed stereocenter to control the second-formed stereocenter of this 1:2 adduct is not surprising. Substitution of the chiral acrylamide derivative **19** for ethyl acrylate provided the 1:1 adduct **20** with good stereocontrol, and now the 1:2 adduct **21** was also formed with a comparable level of selectivity. In more recent work,[47b] tel-



omerization reactions of the acrylamide derivative have been conducted in the presence of bromotrichloromethane. A single major stereoisomer is produced for each of the telomers from $n = 1$ to $n = 5$. The telomerization is capped off by a bromine transfer from bromotrichloromethane, and even this step proceeds with good selectivity.

Another example of ρ stereocontrol in halogen atom transfer reactions was observed in Barton–Hunsdiecker decarboxylation[56] of **18b**.[47b] In the presence of bromide or iodide donors, radical **22a** abstracts halogens with a selectivity as high as 17:1 (bromide at 0 °C). The addition of *tert*-butyl radical to the acrylamide **19** by the Barton method generated radical **22b**, which was found to abstract a thiopyridyl group from the thiohydroxamate with a good level of asymmetric induction.[48,55]



Models for the ρ selectivities observed with Oppolzer's camphorsultam and the dimethylpyrrolidine amide are shown in Figure 2. For Oppolzer's sultam, the model has three important features: (1) the amide and sultam oxygens are opposed to minimize dipole repulsion, (2) the radical has a Z geometry, and (3) O^2 shields one face much more effectively than O^1 shields the other. For the dimethylpyrrolidine: (1) C_2 symmetry eliminates C–N rotamer concerns, (2) the radical also

(56) Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. *Z. Tetrahedron* **1987**, *43*, 2733.

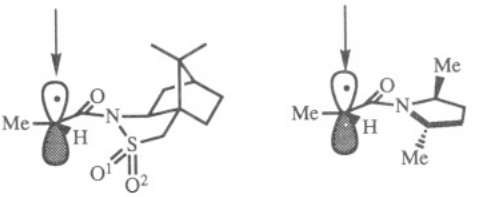
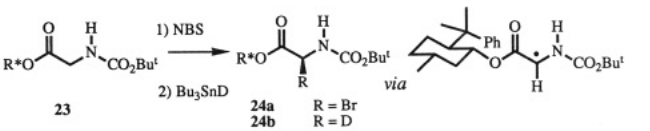


Figure 2. Comparison of models for Oppolzer's camphorsultam (left) and dimethylpyrrolidine (right) auxiliaries.

has a Z geometry, and (3) the "cis" methyl group shields one face much more effectively than the "trans" methyl group shields the other (rate studies associated with α selectivity imply that the *trans*-methyl group has no shielding effect at all). Thus, despite major structural differences, we believe that the two chiral auxiliaries work for similar reasons. Taken together, these results with acrylate derivatives of Oppolzer's sultam and the dimethylpyrrolidine suggest that a general strategy of chiral auxiliary control can now be introduced to the field of radical additions and cyclizations.

Typical ester-based auxiliaries give poor levels of asymmetric induction.[14,57] The problem is that esters sacrifice a key element that controls the Z/E rotamer preference of either the alkene or the radical. If some feature of the radical could reinstate the Z/E preference, then highly selective additions to secondary esters might be possible. Recent observations could very well be the first illustrations of this point.[58] Bromination of 8-phenylmenthol glycine derivative **23** with NBS under standard radical conditions (CCl_4, 80 °C) gave a single bromoglycine assigned structure **24a**. Re-



duction of **24a** with tributyltin deuteride at −78 °C provided deuterioglycine derivative **24b** and its stereoisomer in a ratio of 95:5. Resubjection of **24b** to bromination and then reductive debromination with tributyltin hydride regenerated the starting material **23** (lacking deuterium).

These observations indicate that atoms are abstracted from and delivered to the same face of the phenylmenthol glycine derivative (shown herein).[59] The authors proposed that the Z radical might be more stable than the E isomer due to intramolecular hydrogen bonding. Another explanation is suggested by ESR studies[60] and measurements of bond dissociation energies,[61] which show that captodative radicals do indeed have a strong preference for the Z rotamer due to favorable dipolar effects.[60]

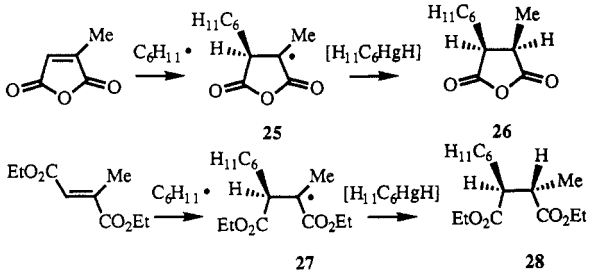
ρ-1,2-Asymmetric Induction

During the past 18 months, there has been a dramatic upsurge of interest in the stereochemical outcome of reactions of radicals bearing adjacent stereocenters (1,2-asymmetric induction). In this short time, a solid foundation for understanding and predicting selectiv-

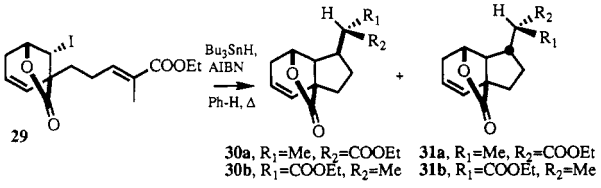
(57) Stack, J.; Curran, D. P., manuscript in preparation.
(58) Hamon, D. P. G.; Razzino, P.; Massey-Westropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 332.
(59) Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280.
(60) Beckwith, A. L. J.; Brumby, S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1801.
(61) Bordwell, F. G.; Gallagher, T.; Zhang, T. *J. Am. Chem. Soc.* **1991**, *113*, 3495.

ities has begun to emerge. Looking back we can now see important early indications that 1,2-asymmetric induction was possible in radical reactions.[62] That these early observations were largely overlooked is not surprising given the many examples of poor selectivity and the apparent lack of unifying principles in moderately selective examples.

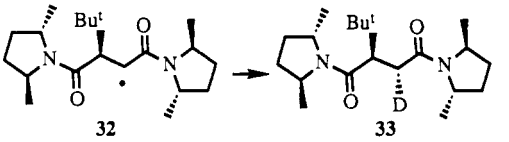
In early experiments, the stereochemistry of hydrogen abstraction during radical addition reactions with methylmaleic anhydride was studied.[63] The addition of cyclohexyl radical generated a stereogenic center in intermediate **25**. Subsequent hydrogen abstraction at the adjacent radical center occurred predominantly trans to the alkyl group and yielded erythro product **26**. Experiments were also carried out with methylfumaric bis(ethyl ester), and the preferred formation of threo product **28** was observed.[64] Thus, cyclic radical **25** and acyclic radical **27** reacted with opposite 1,2-asymmetric induction. Recently, another example of reversed selectivity in cyclic and acyclic systems was reported.[65]



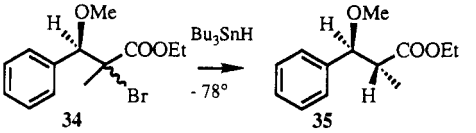
In 1985, a highly selective example of 1,2-asymmetric induction was reported[13] that later proved to be useful in the synthesis of pleurotin.[66] Reductive cyclization of iodide **29** provided four products that were isolated in yields of 80%, 4%, 4%, and 4%. As expected, the exo products **31a,b** were minor and were formed without selectivity. The surprise was that the endo product **30a** was greatly favored over its stereoisomer **30b**. A subsequent sequence of experiments led to the conclusion that A strain is important in these reactions, and the selectivities observed were explained on the basis of the size of allylic substituents[66]



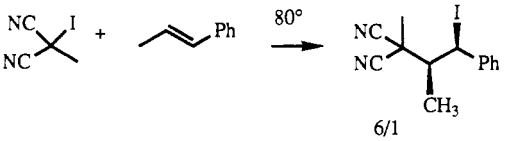
Acyclic stereochemical control observed over 15 years ago in Darmstadt[63,64] was brought to light again in Basel when 1,4-induction (auxiliary control) was compared with 1,2-induction (substrate control).[48] Radical **32**, generated via *tert*-butyl radical addition to chiral diamide **4**, is attacked by the hydrogen donor preferentially at the face that is shielded by a methyl group of the chiral auxiliary (**32** → **33**). Thus the adjacent chiral center (1,2-asymmetric induction) is more important than the influence of the chiral auxiliary (1,4-asymmetric induction).



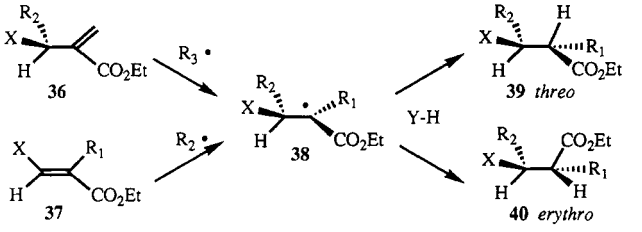
There has also been a recent report of high stereoselectivities in hydrogen atom and allyl transfer to radicals α to esters.[67] A series of substrates were examined, and selectivities as high as 75:1 were reported in reactions carried out at −78 °C. In one example, the tertiary bromide **34** was converted to the product **35** with a selectivity of 32:1.



Interest in 1,2-asymmetric induction was sparked by the surprising observation of a highly selective iodine transfer reaction.[68a,b] In a related but simpler system, it was convincingly demonstrated that the observed stereoselectivity is due to 1,2-asymmetric induction in the abstraction of an iodine atom by a benzyl radical.[68c] Since iodomalonates are excellent iodine donors, even this modest level of selectivity is significant.



These early experiments stimulated a detailed study of ρ-1,2-asymmetric induction. The radical **38** was generated from alkenes **36** and **37**, respectively.[69] Subsequent hydrogen abstraction led to threo product **39** and erythro product **40**. In all cases threo isomers



39 were formed predominantly when R_2 was larger than X, whereas erythro isomers **40** were the main products when X was larger than R_2. For example, with R_2 = Bu^t and X = CO_2Me a 98:2 threo/erythro mixture results, but substituents R_2 = Me and X = $OSiPh_2Bu^t$ reverse the stereoselectivity to threo:erythro = 3:97 at 0 °C.[69]

Thus it is likely that radical **38** adopts a preferred conformation in which substituents R_2 and X at the chiral carbon atom shield opposite faces of the adjacent

(62) (a) Podesta, J. C.; Chopa, A. B.; Ayala, A. D. *J. Organomet. Chem.* **1981**, *212*, 163. (b) Podesta, J. C.; Chopa, A. B. *J. Organomet. Chem.* **1982**, *229*, 223. (c) Chopa, A. B.; Koll, L. C.; Savini, M. C.; Podesta, J. C.; Neumann, W. P. *Organometallics* **1985**, *4*, 1036. (d) Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024.

(63) Giese, B.; Meixner, J. *Tetrahedron Lett.* **1977**, *18*, 2783.

(64) Meixner, J. Ph.D. Thesis, TH Darmstadt, 1980.

(65) Bulliard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423.

(66) Hart, D. J.; Huang, H. C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

(67) (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallee, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845. (b) Guindon, Y. U.; Lavallee, J.-F.; Boisvert, L.; Chabot, L.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27.

(68) (a) Seong, C. M. Ph.D. Thesis, University of Pittsburgh, 1990. (b) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9401. (c) Curran, D. P.; Thoma, G. *Tetrahedron Lett.*, in press.

(69) Giese, B.; Bulliard, M.; Zeitz, H.-G. *Synlett* **1991**, 425.

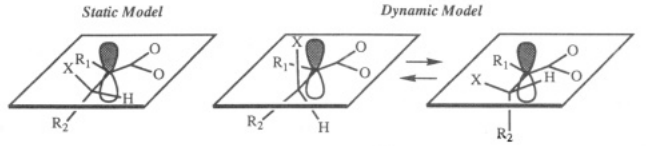


Figure 3. Effect of allylic strain on the conformation of radical **38**.

radical center. A theory that explains this preferred conformation is based on allylic strain effects.[66,69,70] An ester-substituted radical like **38** is a heteroallyl system because of the conjugation between the radical center and the ester group.[18,19] The three carbons (the chiral center, the radical center, and the carbonyl group) and the two oxygens of the ester lie almost in one plane. Allylic strain is smallest if the radical adopts a conformation in which the C–H bond of the chiral center points in the direction of the carbonyl oxygen atom (Figure 3, static model). In this preferred conformation, substituent X shields one face and substituent R_2 shields the other face of the adjacent radical. The bulk of these substituents controls the direction of attack.[69,71]

In further studies,[72–74] it was observed that ρ-1,2-asymmetric induction occurred also in phenyl-, ketone-, and amide-substituted radicals. On the other hand, no 1,2-stereoinduction with nitrile- or sulfone-substituted radicals could be detected.[69,73] These experiments are in full accord with the allylic strain effects since nitriles and sulfones are not subject to A-strain effects. Special intramolecular forces like H bonding or Lewis acid complexation can of course also change the conformation of the radical.

If the C–H bond at the chiral center is exactly in the plane of the allyl or heteroallyl system (as shown in Figure 3 in the static model), then a small substituent R_1 should not influence the 1,2-asymmetric induction. But first experiments show that a secondary radical (R_1 = H) seems to be always less selective than a tertiary radical (R_1 = CH_3). Presumably, the chiral group is slightly twisted because of the different repulsion between R_1 at the radical and X and R_2 at the chiral center (as shown in Figure 3, dynamic model). This model takes into account suggestions that forming bonds in transition states should be approximately staggered,[74] and it still recognizes the importance of A strain. One must now consider the relative energies of four possible transition states: top and bottom of either rotamer. Of these, the two with forming bonds staggered should be favored.

There are already exceptions to the model.[75] It was observed that allylations or tin deuteride reductions of acetate **41a** gave the expected syn product based on the A-strain model, but that alcohol **41b** and *tert*-butyldimethylsilyl ether **41c** gave good selectivity in the opposite direction. It is tempting to suggest that reversal in selectivity for the alcohol is due to a transition state with an intramolecular hydrogen bond, but preliminary experiments do not support this idea (similar selectivities are observed in benzene and DMSO). The

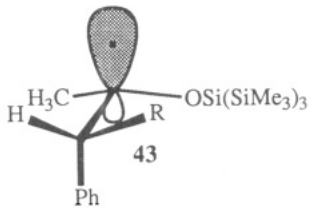
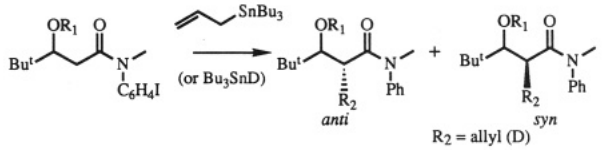


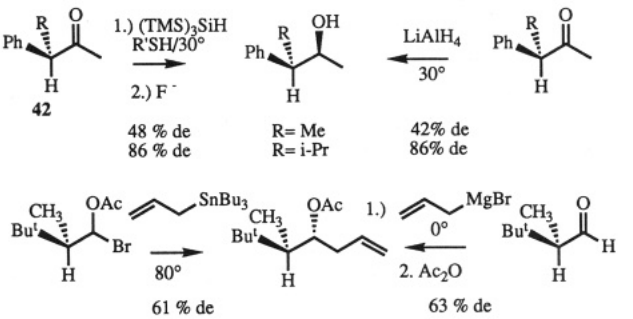
Figure 4. Conformation of radical **43**.

reason for reversal of selectivity in the TBS ether **41c** is also not clear. However, this substrate is very unreactive, as indicated by the complete failure of the allylation. Perhaps when two large groups are present, both faces are effectively shielded in the lower energy rotamers, and reactions occur from higher energy rotamers.



41a	R_1= $COCH_3$	10/90	(23/77)
41b	R_1= H	93/7	(88/12)
41c	R_1= TBS	no rxn	(90/10)

All this work has relied on A-strain as an essential ingredient for 1,2-asymmetric induction, but some recent experiments suggest that A-strain is not required for ρ-1,2-induction. In the classic experiments leading to Cram's rule, ketone **42** was reduced with $LiAlH_4$.[76] In order to compare ionic with radical 1,2-asymmetric induction, the radical **43** was generated (Figure 4) via addition of tris(trimethylsilyl)silyl radical to ketone **42**.[77] With R = Me and *i*-Pr, we observed the preferred formation of the threo isomer with nearly the same stereoinduction of the radical and the ionic reactions. Allylation reactions with a secondary acetoxyalkyl radical and the respective aldehyde were carried out, and again 1,2-asymmetric induction of the radical and the ionic processes turned out to be similar.



Radicals like **43** with an oxygen function at the radical center are not controlled by allylic strain effects. Because of comparable stereoselectivity of radical and ionic reactions, it is reasonable to use the Felkin–Anh model also for radical reactions.[78] According to this model, radical **43** reacts from the conformation that is shown in Figure 4 and hydrogen abstraction occurs anti to the phenyl group. First ESR experiments indicate

(70) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(71) Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412.
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that this indeed is the favored conformer in the ground state.

Conclusions

Free-radical reactive intermediates have long had the reputation of reacting with little chemoselectivity and virtually no stereoselectivity. Most organic chemists first encounter free radicals in introductory courses by studying reactions that emphasize these characteristics. Chlorination of alkanes has minimal chemoselectivity, and polymerization of vinyl monomers occurs with virtually no control of stereochemistry. Research developments of the past 15 years indicate that this reputation is undeserved. Chain processes have been developed that are exquisitely chemoselective,[2-7] and high levels of stereoselection in cyclic systems have also been well-documented.[11] We now assert that there are straightforward solutions to the problem of free-radical acyclic stereoselectivity. The lessons of stereocontrol in carbanion and concerted reactions serve as a good guide for experiments in free-radical reactions, and the results of these first experiments indicate that free-radical acyclic stereoselectivity is comparable to that observed for other reactive intermediates in parallel reactions. Synthetic chemists can now approach complex problems with a "free-radical solution" and have every expectation that stereochemistry will not necessarily present an insurmountable barrier.

Alkynyl Carboxylate, Phosphate, and Sulfonate Esters

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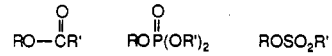
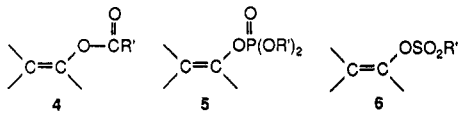
Among the most important compounds in organic chemistry are the three major classes of esters: carboxylate **1**, phosphate **2**, and sulfonate **3**.[1] All three types are widely used in synthetic organic chemistry as well as in mechanistic investigations.[2] Carboxylate



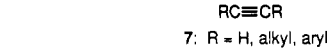
1 **2** **3**

esters in particular are ubiquitous in nature and are the essence of the fragrances of many flowers and the major components in the characteristic flavors of most fruits, such as amyl butyrate (apricot), isopentyl acetate (banana), benzyl acetate (peach), octyl acetate (orange), etc. Phosphate esters in turn play a critical role in biochemistry.[3] Likewise, their unsaturated counterparts, vinyl (enol) esters **4-6** are well-known and have an important role in numerous organic processes.

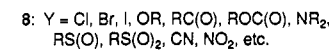


4 **5** **6**

Another valuable functionality in organic chemistry is the carbon-carbon triple bond.[4] A wide variety of acetylenes, from ones bearing simple hydrocarbon substituents, **7**, to diversely substituted, functionalized alkynes, **8**, are well-known, are generally stable, and play a key role in diverse organic transformations. In fact, both the esters and acetylenes are so common and readily available that they are often taken for granted by most chemists.

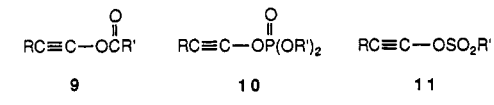


7: R = H, alkyl, aryl



8: Y = Cl, Br, I, OR, RC(O), ROC(O), NR_2, SR, PR_2, SiR_3, SnR_3, $RS(O)$, $RS(O)_2$, CN, NO_2, etc.

Despite the importance and widespread occurrence of both numerous esters **1-6** and alkynes **7** and **8**, acetylenic esters of any kind, carboxylate **9**, phosphate **10**, or sulfonate **11**, were unknown until the mid-1980s when we first prepared and reported them. This is all the more surprising as these acetylenic esters, **9-11**, simply combine into a single, novel derivative two of the most common and readily available organic functionalities. In this Account, I wish to discuss our recent synthesis, properties, and reactions of these novel alkynyl esters **9-11**.



9 **10** **11**

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