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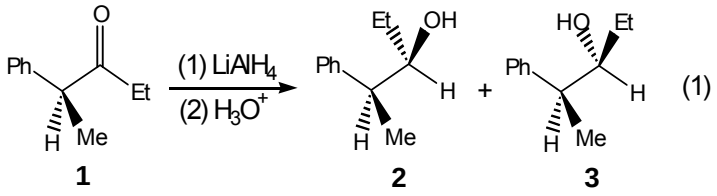
Chapter 1. Introduction

Historical Overview

Stereoselective additions of nucleophiles to aldehydes. With the discovery of the stereoselective reduction of acyclic chiral ketones, Cram and coworkers[1] and, shortly thereafter, Felkin and Anh[2] proposed similar models for predicting the stereochemical outcome of such reactions. In a typical example (eq 1), the chiral ketone **1** gives a 2:1 mixture of diastereomers (**2**:**3**) when treated with lithium aluminum hydride.[1] In the Felkin-Anh model, the three substituents bound to the stereogenic carbon are assigned R_L,



for a sterically demanding large substituent, R_S, for a small substituent, and R_M, for substituents of intermediate steric bulk (Fig. 1). In this model, R_L is oriented to minimize the tortional strain between R_L and both the carbonyl oxygen and R' such that the tortional angle between R_L and R' is approximately 90°. This assumption allows two possible conformers: (1) R_M is in closer proximity to R' or (2) R_S is in closer proximity to R'. If conformer (2) is more stable *and* the

[1] Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
[2] Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

nucleophile approaches the carbonyl from the less hindered face (opposite R_L), then a correct prediction regarding the stereoselectivity of this reaction can be made. In fact, in support of this idea, it was observed that when increasing the size of R', the reaction was more selective.[1] The model also successfully predicted the selectivity of the treatment of chiral aldehydes (R' = H) Grignard reagents ($Nu:^-$ = RMgX).[1]

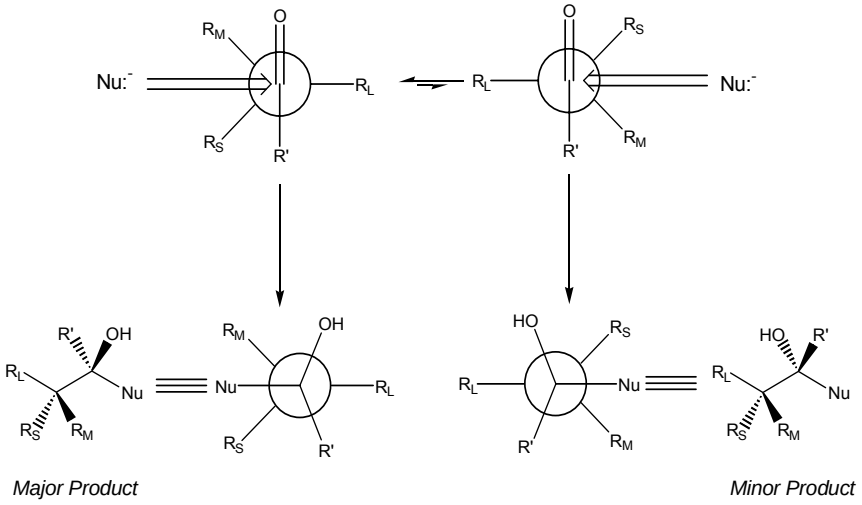
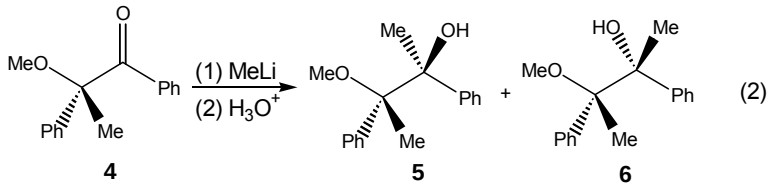


Figure 1. Felkin-Anh transition states and predicted product distribution.

When an aldehyde or ketone contains a heteroatom in either an α or β position, a different model is used to predict the outcome of the reaction.[1,3] For example, with the methylation of **4**, one might assign the methoxy group as R_M, the phenyl group as R_L and the methyl as R_S (eq.2) The simple Felkin-Anh model predicts **6** to be the major product. However, in this reaction, **5** is found to

[3] Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.,* **1959**, *81*, 2748.

be the major product. This new model, called the "Cram-chelate" model, takes



into account that metals, depending on the number of available coordination sites, may bond with more than one heteroatom to form 5- or 6-membered cyclic intermediates. The nucleophile then attacks from the less hindered side (Fig. 2).

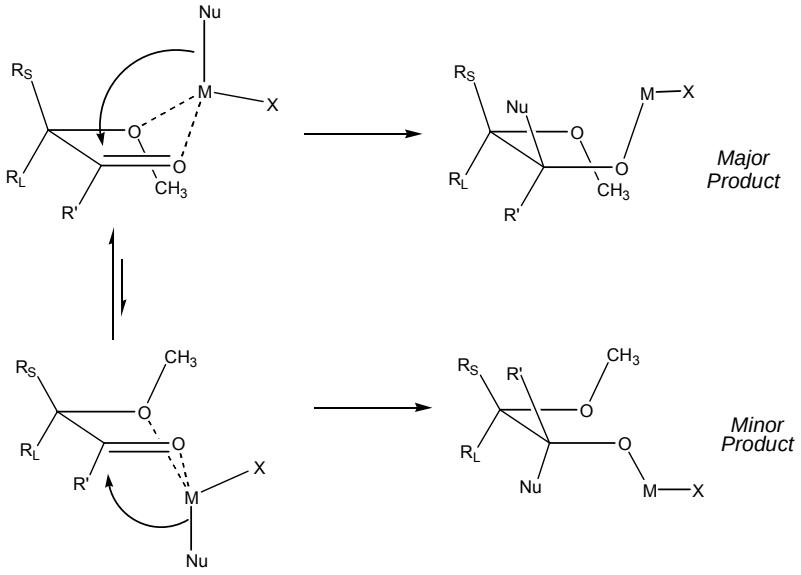
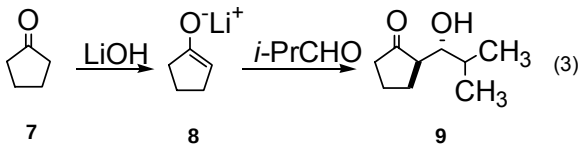


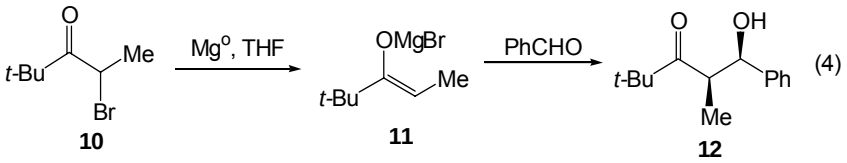
Figure 2. The Cram chelate model.

Stereoselective Aldol Reactions. Cyclic enolates react with aldehydes to give *anti* aldol adducts (eq 3).[4,5] Shortly thereafter, it was discovered that

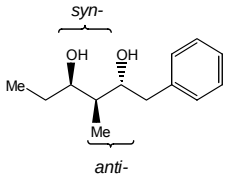
[4] Throughout this paper the stereochemical descriptors syn- and anti- will be used rather than erythro- and threo-. When the backbone of a structure is written in an extended (zig-zag) manner and two substituents are shown to be on the same side of the chain, they are given the term "syn". When the two substituent are on opposite sides of the chain, they are designated "anti".

bromomagnesium enolates gives predominantly *syn* aldol adducts (eq 4).[6] As the cyclic enolate **8** is unambiguously of the *E* configuration and it has been shown that **11** is of the *Z* configuration, the following generalization was made: *E* enolates are *anti*- selective while Z enolates are *syn*- selective. Unfortunately, a





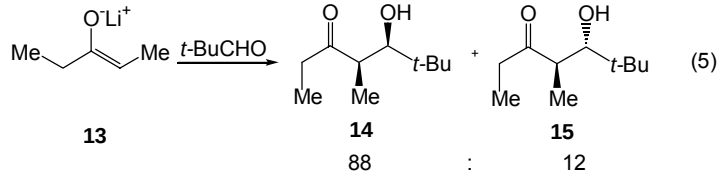
later study challenged the reliability of this generalization when it was discovered that the *Z*-lithium enolate (eq 5) of 3-pentanone **13** was highly *syn*- selective toward pivaldehyde (88:12 *syn*:*anti*), while the *E*-enolate (eq 6) was, unselective (48:52 *syn*:*anti*).[7,8]



[5] (a) DuBois, J. E.; Dubois, M. *Tetrahedron Lett.,* **1967**, 4215. (b) DuBois, J. E.; Dubois, M. *Tetrahedron Lett*., **1968**, 1567. (c) DuBois, J. E.; Dubois, M. *Bull. Soc. Chem. Fr*., **1969**, 3120. (d) DuBois, J. E.; Dubois, M. *Bull. Soc. Chem. Fr*., **1969**, 3553.

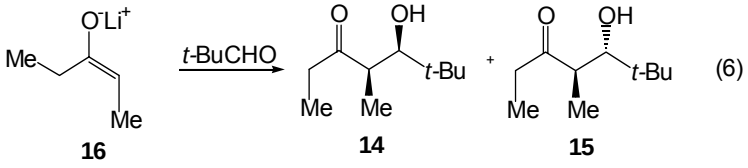
[6] DuBois, J. E.; Fellman, P. *Tetrahedron,* **1978**, *34*, 1307.

[7] Throughout this paper, enolates are derived from ketones that contain one α-alkyl substituent and two acidic α-hydrogens. The terms "*E*-enolate" and "*Z*-enolate" refer to the relative positions of the enolate oxygen and the alkyl substituent about the enolate double bond. A Z-enolate is one in which the oxygen and the substituent are on the same side of the double bond, while in an E-enolate, they are on opposite sides.



13 **14** : **15**

88 : 12



16 **14** : **15**

48 : 52

Chair-like transition state models (Figs. 3 and 4), commonly called Zimmerman-Traxler transition states,[9] have successfully predicted the *syn*- and *anti*- selectivities of such simple enolates. This type of transition state is also termed a "closed" transition state because the metal involved in enolate formation is also coordinated to the approaching aldehyde. In this model there are two possible transition states which explain the stereochemical outcome of these reactions. One possibility involves the approach of the aldehyde such that, in the transition state, the bulk of the aldehyde (R) is in a pseudoequatorial position. The other possibility places the bulk of the aldehyde in a pseudoaxial position. The situation in which the bulk of the aldehyde is pseudoequatorial predicts the selectivities of both *E* and *Z* enolates.

---

[8] DuBois, J. E.; Fellman, P. *Tetrahedron Lett.,* **1975**, 1225.
[9] Zimmerman, H.; Traxler, M. *J. Am. Chem. Soc.,* **1957***, 79*, 1920.

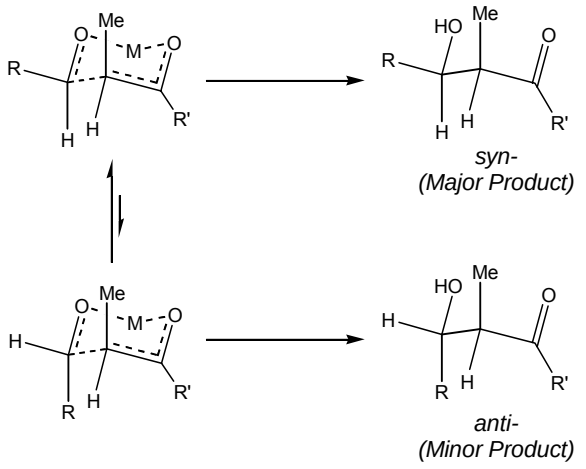


Figure 3. Zimmerman-Traxler transition state models for *Z*-enolates[9]

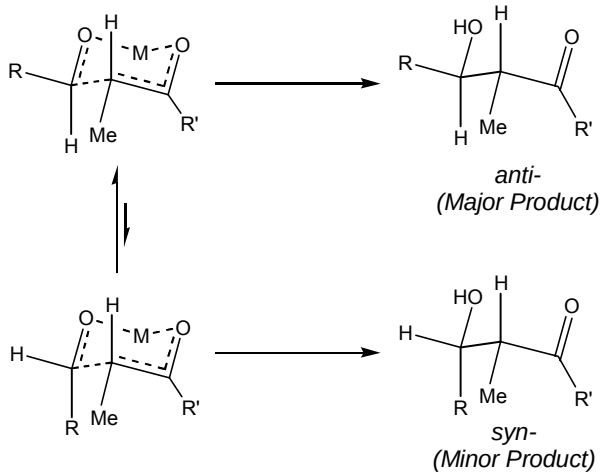


Figure 4. Zimmerman-Traxler transition state models for *E*-enolates[9]

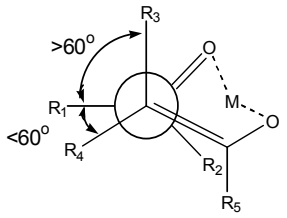


Figure 5. Asymmetric chair like transition state[10]

Additionally, it has been suggested that the transition state does not take on the shape of a true "chair", but rather it is somewhat twisted (Fig. 5).[10] This idea supports the indiscriminate selectivity of the *E*-enolate of 3-pentanone toward pivaldehyde (eq 6). For example, with the *Z*-enolate, the *tert*-butyl group of the aldehyde is obviously pseudoequatorial (Fig. 6). But, when an *E*-enolate is involved, the steric demand in both the pseudoaxial and the pseudoequitorial situations is similar (Fig. 7). Thus, one would expect diminished selectivities when *E*-enolates are involved compared to *Z*-enolates. Indeed, it is generally accepted that *E*-enolates are less *anti*-selective than *Z*-enolates are *syn*-selective.

[10] Zimmerman, H.; Traxler, M. *J. Org. Chem.,* **1980***, 45*, 1966.

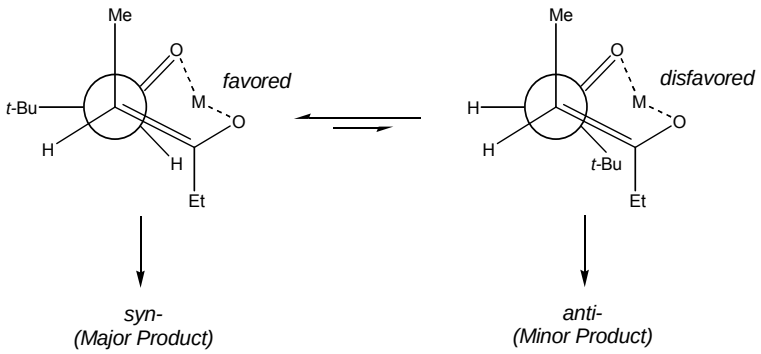


Figure 6. Transition state rationale for high *syn*- selectivity in *Z* enolates

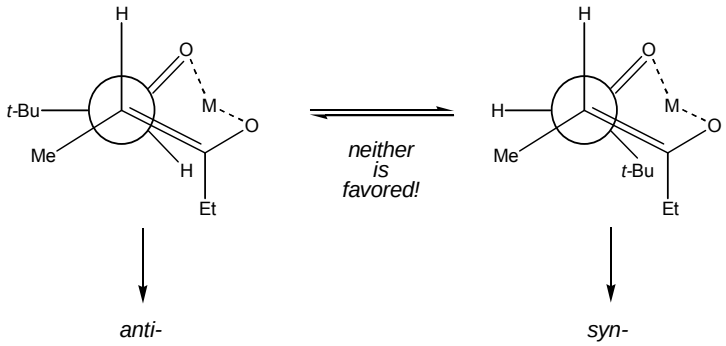


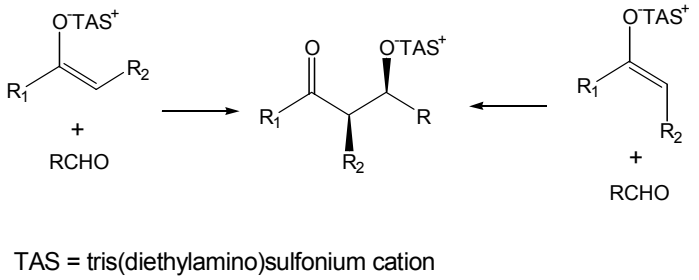
Figure 7. Transition state rationale for poor *anti*- selectivity in *E* enolates

In 1981, Noyori and co-workers[11] reported that, tris(diethylamino)-sulfonium enolates derived from silyl enol ethers (Mukaiyama reactions), are *syn*-selective regardless of whether they are of the *E* or the *Z* configuration (Scheme 1). In the absence of a metal, chair-like "closed" transition states are not possible. Noyori therefore argued that the *syn*- selectivity is the result of an "open" transition state (Fig. 8). According to this hypothesis, the enolate and the aldehyde approach each other such that the oxygens are as far apart as

[11] Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.

possible. This mechanism would be favored, according to Noyori, "since the electostatic repulstion of the negatively charged oxygens is minimized through such an atomic arrangement."[11] The bulky substituents on both the aldehyde and the enolate would be arranged such that R and R_2 would not be in a sterically demanding gauche arrangement. Thus, regardless of the geometry of the enloate, the *syn*- product is always favored in an "open" transition state.

Scheme 1



TAS = tris(diethylamino)sulfonium cation

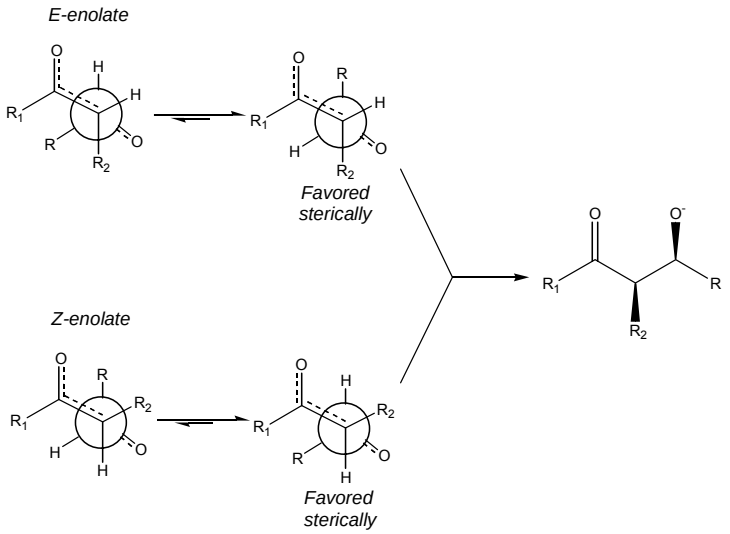
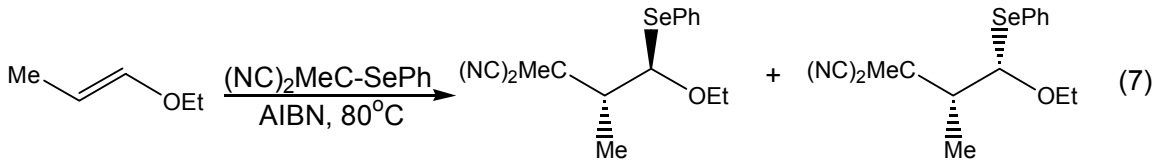


Figure 8. Open transition state models illustrating syn- selectivity regardless of enolate geometry

Stereoselective reactions of free-radicals. With the advent of the Felkin-Anh and Cram chelate models, free radical additions to olefins were studied in search of similar models. It was discovered that upon the formation of a prochiral, carbon-centered, oxygen-bearing free-radical adjacent to a stereogenic center, significant trends in the product distribution appeared (eqs 7 and 8).[12] The Felkin-Anh rule for free-radicals (Fig. 9) was developed to explained this phenomenon.[13] Similar to the traditional Felkin-Anh model (Fig. 1), the addition of free radicals occurs opposite R_L. Presumably R_L is perpendicular to the groups attached to the pro-chiral radical center, and that R_S is situated nearest the larger of these substituents (R_L'). A chelate model similar to that of the Cram chelate model was also proposed to explain the selectivities regarding additions to prochiral radicals adjacent to heteroatom bearing stereogenic centers (Fig. 10).[14]



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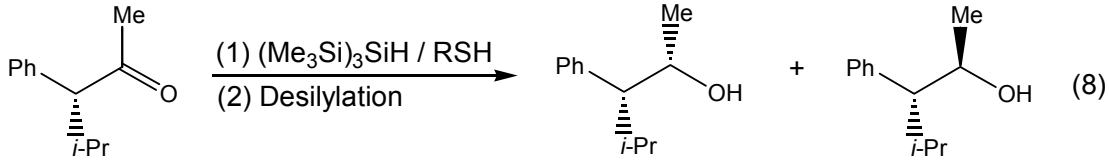
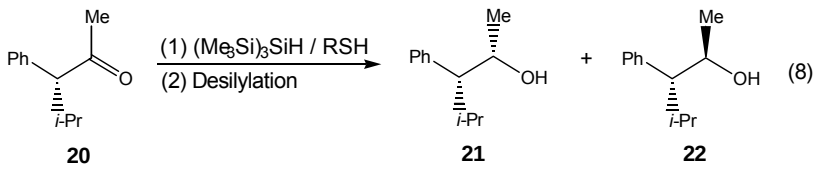


20 **21** **22** (8)

[12] Giese, B.; Damm, W.; Dickhaut, J.; Wetterlich, S. S.; Curran, D. P. *Tetrahedron Lett*. **1991**, *32*, 6097.
[13] Curran, D. P.; Eichenberger, E.; Collis, M.; Roepel, G. T. *J. Am. Chem. Soc*. **1994**,*116*, 4279.
[14] Guindon, Y.; Lavallee, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt J. *J. Am. Chem. Soc*. **1991**,*113*, 9701.



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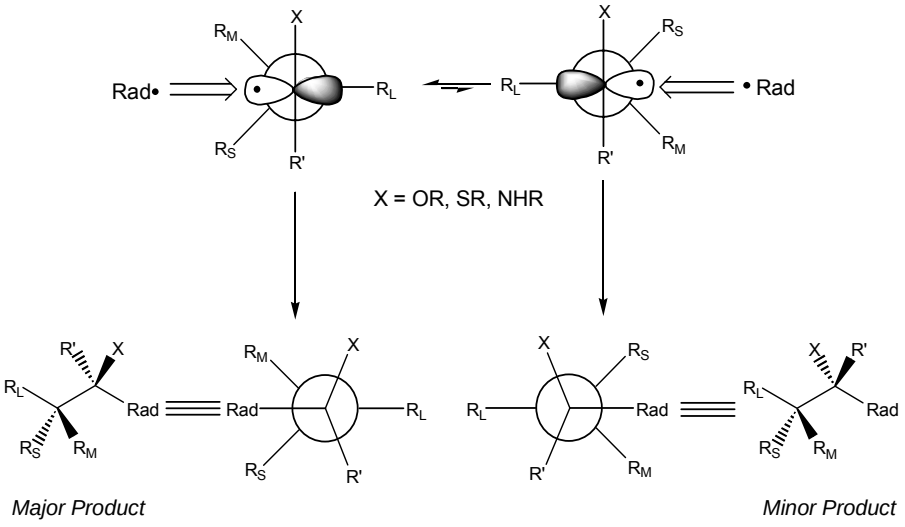


Figure 9. Felkin-Anh rule for free radicals and predicted product distribution.

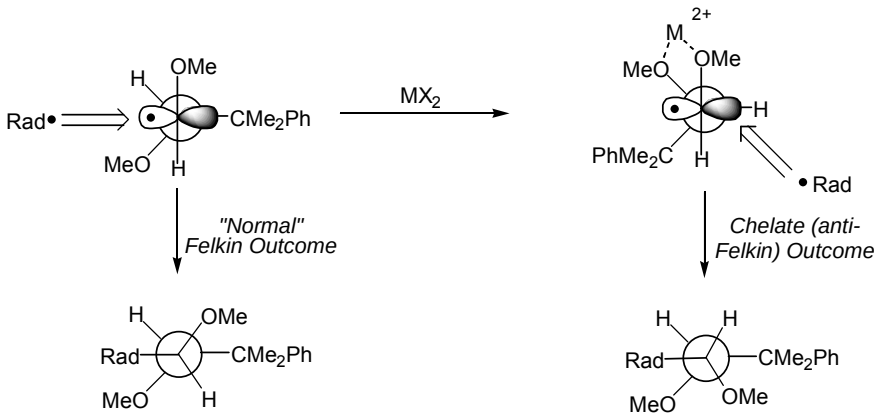


Figure 10. Felkin and chelate (anti-Felkin) predictions for free radicals.

Prochiral free radicals combine in a fashion similar to Noyori's open transition state to minimize steric interactions. For example, when two phenethyl free radicals combine (Scheme 2, R = Me), the selectivity is such that the anti-arrangement is slightly favored. As the bulk of R increases so does the selectivity.[15] Thus, it is reasonable that in the transition state, the large phenyl groups are as far away from one another as are the R groups (Fig. 11). Strangely, no one has yet studied the stereochemistry of the addition of prochiral free radicals to prochiral alkenes.

Scheme 2

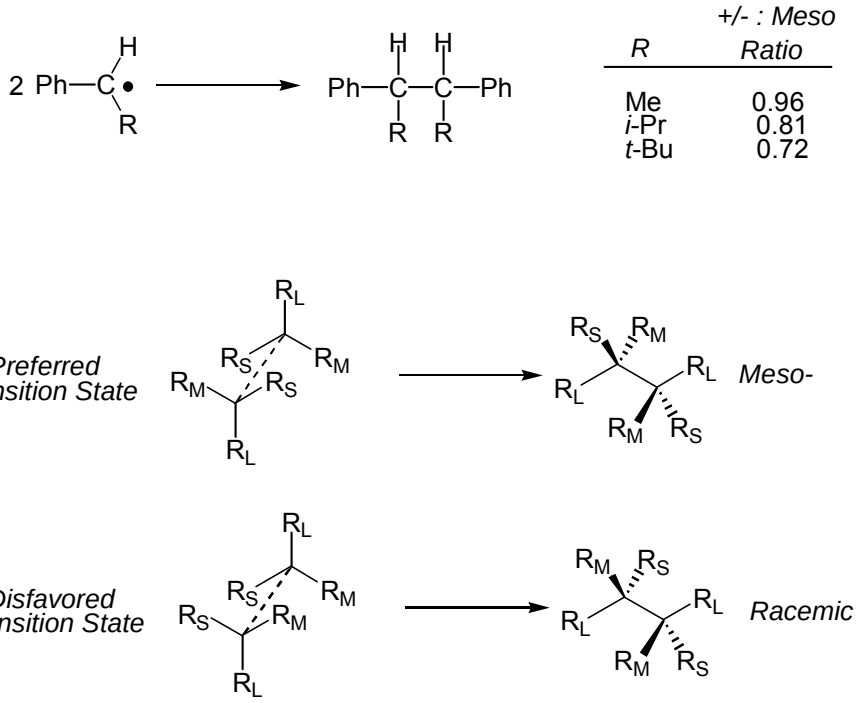


Figure 11. Predicted outcome of combining prochiral free-radicals.

[15] Porter, N. A.; Krebs, P. J. *Topics in Stereochemistry*, Eliel, L.; Wilen, S. H. Eds, J. Wiley and Sons, New York, **1988**, *18*, p. 97.

Strategies for absolute stereocontrol (Enolates)

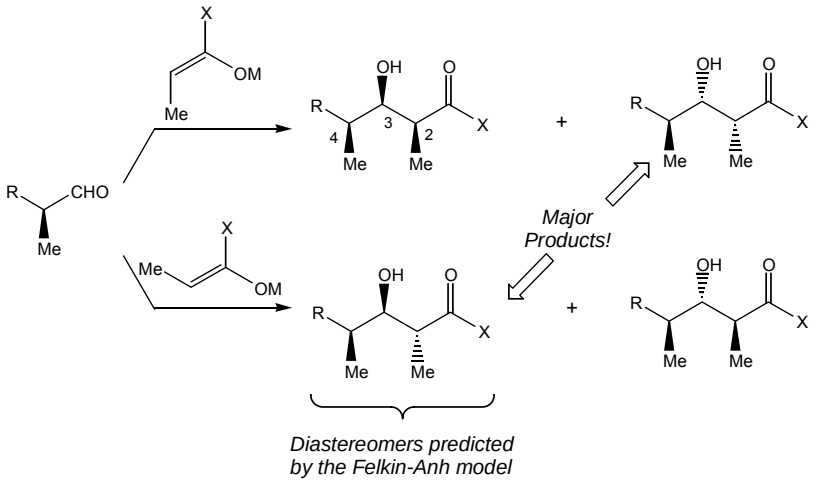
Substrate control. In the absence of a chiral environment, absolute stereocontrol is not possible. For example, although equation 5 is highly *syn*-selective, a racemic mixture of *syn*- isomers is produced. A common strategy for generating only one stereoisomer over all other possible stereoisomers is called substate control. In a substrate controlled reaction, a stereocenter on an optically active compound directs the stereochemical outcome of the reaction and remains bound throughout the process such that this chiral center also appears in the product (eq 1): the chiral center α to the carbonyl remains fixed throughout the reduction, directs the approach of the hydride, and is of the same configuration in the product.

In aldol reactions, chiral aldehydes can direct the approach of the nucleophilic enolate. To predict the outcome, a combination of the Felkin-Anh and Zimmerman-Traxler models must be applied. A thorough survey of the literature appeared in 1991 addressing this very issue.[16] According to the two models, if boron or lithium *Z* enolates reacted with chiral aldehydes in a Felkin-Anh fashion "all *syn-" (*2,3-*syn*-3,4-*syn)* products would predominate, while the *E* enolates should give primarily a 2,3-*anti*-3,4-*syn* product (Scheme 3). Aldol reactions involving chiral aldehydes generally hold to the Zimmerman-Traxler

[16] Roush, W. R. *J. Org. Chem*. **1991**, *56*, 4151.

model but do not always adhere to the Felkin-Anh model. The cases that seemed to violate the Felkin-Anh model were those in which the R group (Scheme 3) was extremely large ($R>>CH_3$). Additionally, this so-called "anti-Felkin" selectivity was *only* observed with *Z*-enolates. Roush eloquently explained these findings by suggesting "that the dominant stereocontrol element that determines aldehyde diastereofacial selectivity is the minimization of gauche pentane interactions in the competing cyclic, chair-like transition states". Figures 12 and 13 illustrate this point. If a Z-enolate were to approach a chiral aldehyde in a "normal" Felkin fashion, the steric interactions between the substituents on the aldehyde and methyl of the enolate

Scheme 3



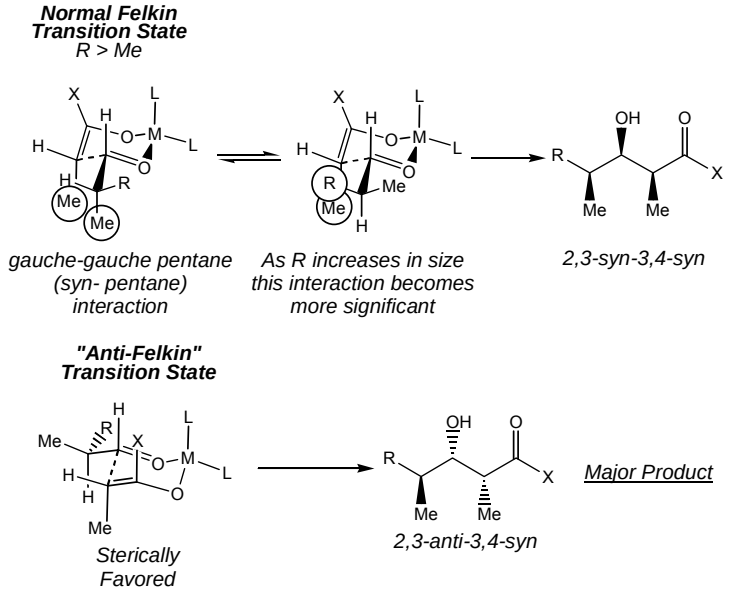


Figure 12. Transition state models illustrating anti-Felkin selectivity of *Z*-enolates

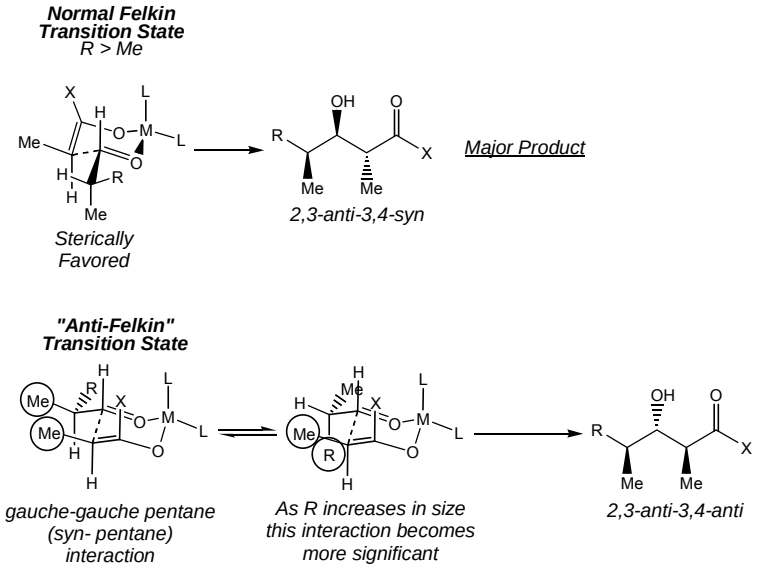
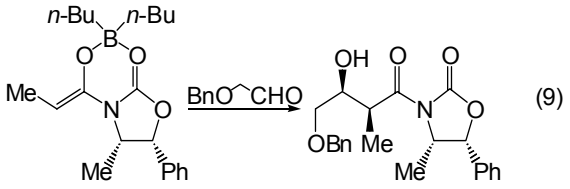


Figure 13. Transition state models illustrating Felkin selectivity of *E*-enolates

would be quite significant (Fig. 12). Rotation about the carbonyl carbon- α-carbon bond does little to alleviate this strain. In an “anti-Felkin” transition state,

this interaction is lessened. A similar argument can be made regarding the observed selectivities when *E*-enolates are involved (Fig. 13).

By reacting *chiral* enolates with achiral aldehydes, the absolute stereochemistry of the adduct may also be manipulated. A common strategy for achieving this type of stereoselectivity is called the chiral auxiliary approach. Chiral auxiliaries are asymmetric functional groups that have been bound to an otherwise achiral starting material. An example of chiral auxilliary control, for example, appeared in the early stages of Yamada's total synthesis of the marine macrolide Aplyronin A (eqs 9 and 10).[17] In these cases the diastereomers **24** and **26** were formed in 79% and 85% yields respectively over all other stereoisomeric products. Representative chiral amide and oxazoline auxiliaries are shown in Figure 14.[18]



23 **24** (9)

[17] Kigoshi, H.; Ojika, M.; Suenaga, K.; Mutou, T.; Hirano, J.; Sakakura, A.; Ogawa, T.; Nisiwaki, M.; Yamada, K. *Tetrahedron Lett.* **1994**, *35*, 1247.

[18] (a) Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 959. (b) Soai, *J. Chem Soc. Perkin I,* **1987**, 1909. (c) Oppolzer, W.; Poli, G. *Tetrahedron Lett.* **1986**, *27*, 4717. (d) Koga, K, blah blah. *Tetrahedron Lett.* **1986**, *27*, 369. (e) Evans, D. A. in "Asymmetric Synthesis", Morrison, J. D., Ed.; Academic Press: Orlando 1984, vol. 3, pt. B, pp 1-110. (f) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi. T *Tetrahedron Lett.* **1994**, *35*, 8225.

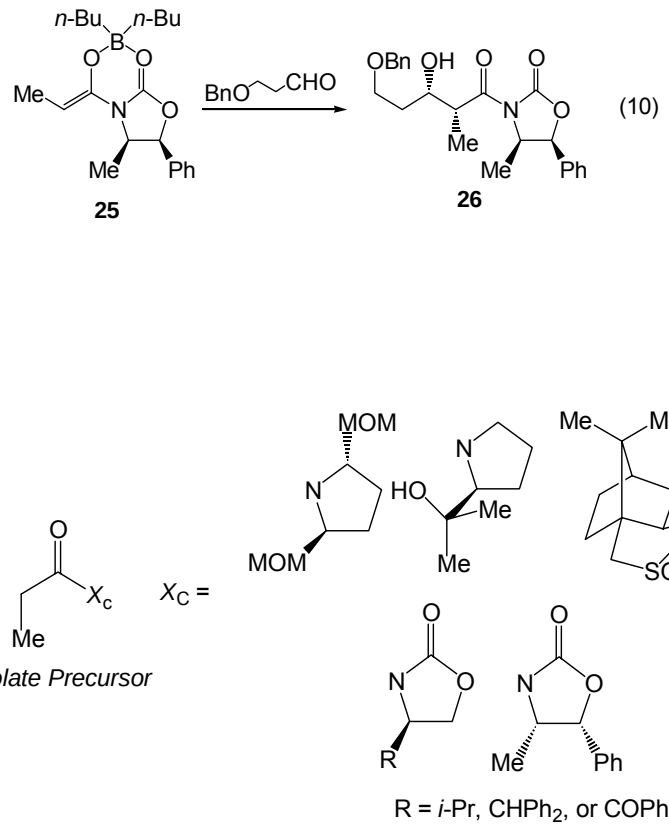
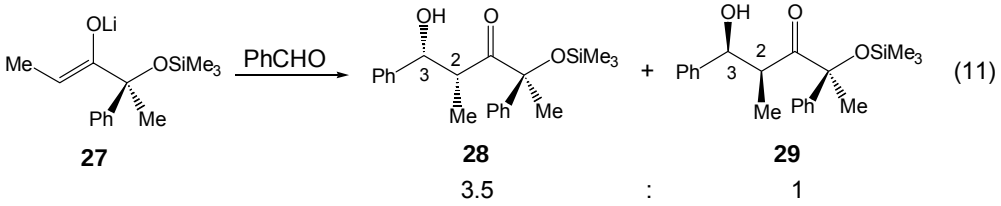


Figure 14. Amide and oxazoline chiral auxiliaries

Care must be taken when forming new stereogenic centers by combining two chiral species. While one chiral starting material might be direct the formation of the new stereogenic center toward a specific configuration, the chiral species to which it is adding might have the opposite influence. Thus, a loss in selectivity would be expected. For example, it has been shown that the addition of chiral lithium enolate **27** to benzaldehyde forms **28** over **29** in a 3.5:1 ratio (eq 11).[19] Also, achiral enolate **30** is anti-Felkin-Anh selective (Fig. 13) with respect

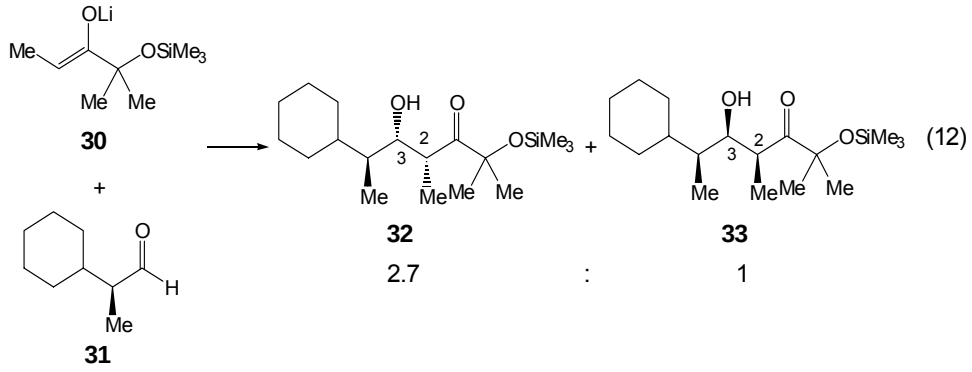
[19] Masamune, S.; Ali, A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed Engl.* **1980**, *19*, 557.

to the chiral aldehyde **31**, to give a product 2.7:1 ratio of **32** and **33** (eq 12).[20]



27 **28** : **29**

3.5 : 1

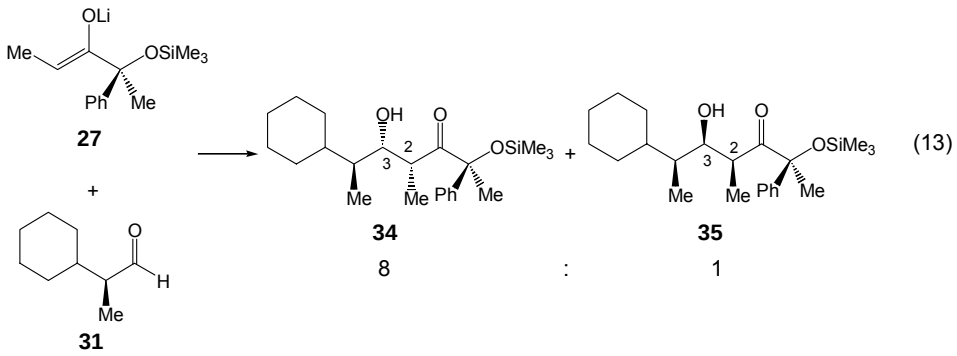


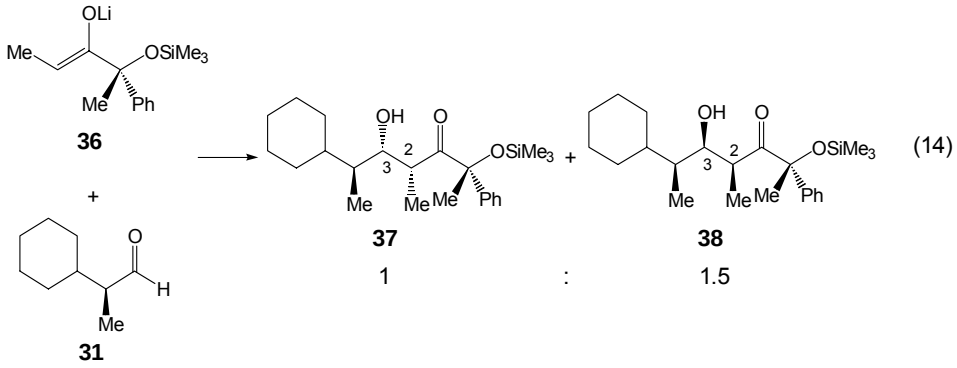
32 **33**

2.7 : 1

31 and **27** are both selective for the same configuration of the newly formed hydroxyl at C_3 and methyl at C_2 in their respective reactions. An increase in selectivity occurs if **27** is added to **31**. When both chiral species have the same influence over the configuration of a forming stereogenic center, an increase in selectivity is observed (eq 13). In this case, the ratio of **34** and **35** was found to be 8:1. To study the effect of competing selectivities, the enantiomer of **27** (**36**) was added to **31** (eq 14).[21] Not only was a decrease in selectivity observed, but a *reversal* in selectivity occured such that the all *syn*- diastereomer **38** was produced over **37** in a 1.5:1 ratio. This phenomenon is refered to as double

[20] Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc*. **1977**, *99*, 8109.

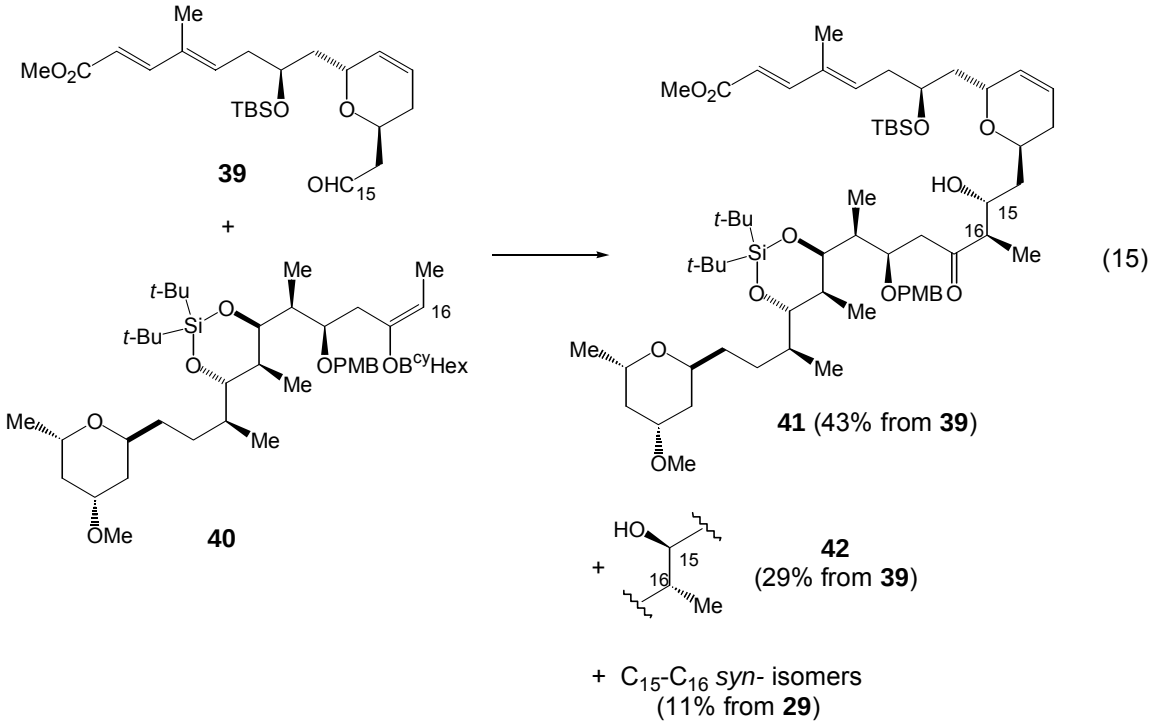




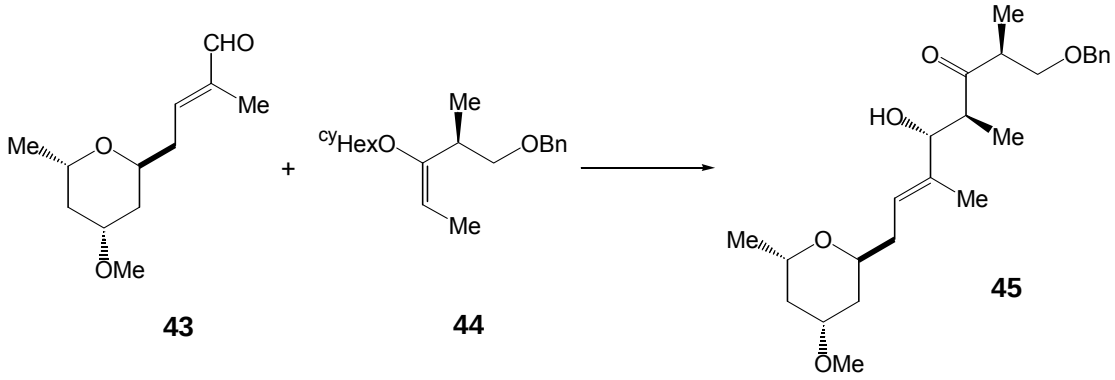
stereodifferentiation or double asymmetric synthesis. Cases that involve the combination of two chiral species which are of competing selectivities are called "mismatched" (eq 14) and those in which both species influence the newly formed stereocenter toward the same configuration are called "matched" (eq 13). Examples of matched and mismatched aldol additions appeared in Paterson's total synthesis of Preswinholide A (eqs 15 and 16).[21] Even though it has been established that *E*-enolates are *anti*-selective, equation 15 shows a significant amount of *syn*-isomer formation which, as discussed previously, is typically resultant from the corresponding *Z*-enolate. Additionally, the absolute

[21] (a) Paterson, I.; Cumming, J. G. *Tetrahedron Lett*. **1992**, *33*, 2847. (b) Paterson I.; Smith, J. D. *J. Org. Chem*. **1992**, *57*, 3261. (c) Paterson, I.; Smith, J. D. *Tetrahedron Lett*. **1993**, *34*, 5351. (d) Paterson I.; Smith, J. D.; Ward, R. A.; Cumming, J. G. *J. Am. Chem. Soc*. **1994**, *116*, 2615.

stereocontrol over the two *anti*- isomers was poor. Conversely, equation 16, demonstrates a matched case in which a chiral *E*-enolate was added to a chiral aldehyde such that only one observable diastereomer was produced in 84% yield.[22]

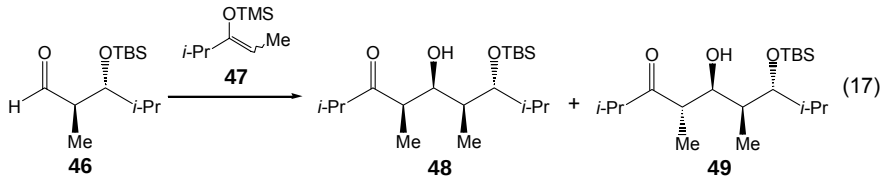


(15)



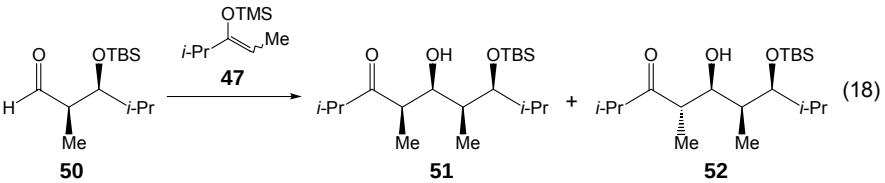
(16)

For aldol type reactions involving “open” transition states, Evans and coworkers, en route to the synthesis of 6-deoxyerythronolide B and oleandolide,[22] explored the effects of double stereodifferentiating reactions involving silyl enol ethers and aldehydes.[23] This study demonstrated that the absence of the syn-pentane interaction experienced in “closed” transition states[16] gives Felkin-Anh selectivity with respect to the aldehyde regardless of the geometry about the enolate double bond (eqs 17 and 18). The selectivity of chiral enolsilanes and achiral aldehydes was then explored. To reinforce the



(17)

Enolate Geometry	**48**:**49**
E-**47**	95:5
Z-**47**	87:13



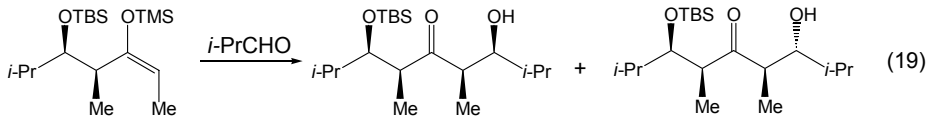
(18)

Enolate Geometry	**51**:**52**
E-**47**	70:30
Z-**47**	91:9

arguement put forth by Noyori, it was shown that “open” transition states in aldol type reactions are syn- selective. Additionally, a remarkable degree of absolute stereocontrol was observed when adding chiral enolsilanes to achiral aldehydes

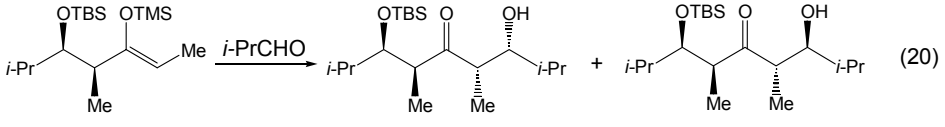
[22] Evans. D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L.; Kim, A. S *J. Am. Chem. Soc.* **1995**, *117*, 9598.
[23] Evans, D. A.; Kim, A. S; Metternich, R.; Novack, V. J *J. Am. Chem. Soc.* **1998**, *120*, 5921.

such that the syn-aldol adducts **53** and **56** were formed over the anti-diastereomers in ratios of 95:5 and 59:41 respectively (eqs 19 and 20). Further study showed that the dominant stereocontrolling element was the absolute configuration of the aldehyde (Felkin selective) when performing a double asymmetric synthesis with a chiral silyl enol ethers and a chiral aldehyde.[24] In other words, "there is no direct correlation product stereochemistry and the enolsilane geometry" (eqs 21-24).[23]



52 **53** **54**

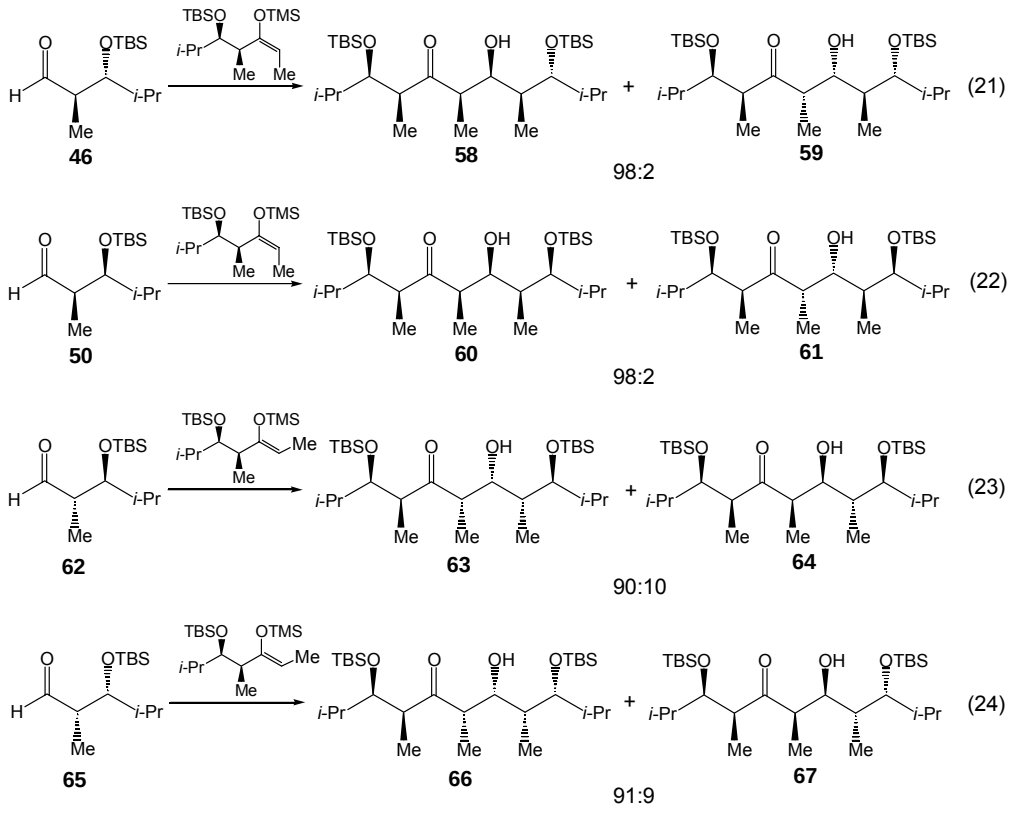
95 : 5 (19)



55 **56** **57**

59 : 41 (20)

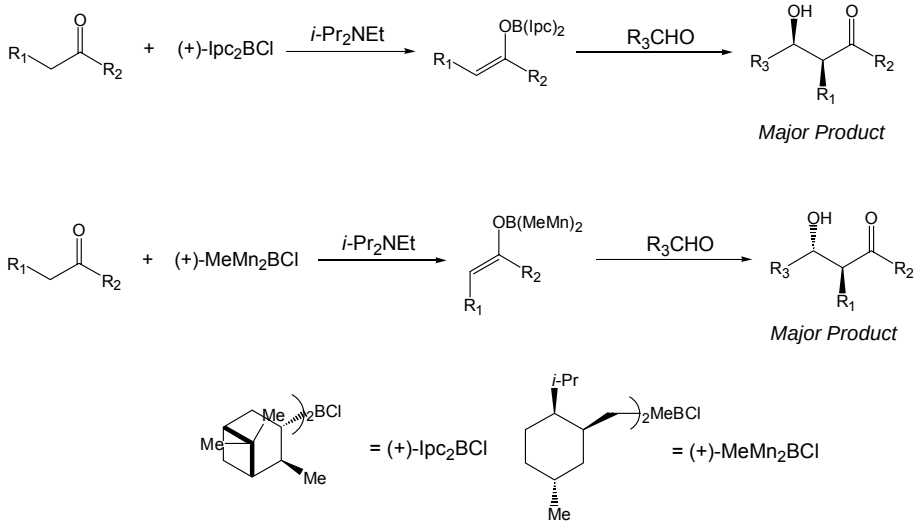
[24] Cases giving the best selectivity are shown (ref. 12).



Reagent Control. Another method for providing a chiral environment to achieve absolute stereocontrol is called “reagent control”. This method is similar to auxiliary controlled reactions in that a chiral additive is bound to an otherwise achiral substrate and removed later. The difference between reagent control and substrate control is, in a typical reagent controlled reaction, the chiral additive is *weakly* bound during the formation of a new stereogenic center (e.g. weakly coordinated metals). The additive is later removed and recovered, usually during the work-up or purification. For example, it is possible to use chiral ligands in boron mediated aldol reactions. Although many metals have been used for this

purpose, none have enjoyed more success than chiral boron compounds.[25] Two such chiral boron additives are the diisopinocampheyl borane system (Ipc_2B)[26] and the dimethylmenthyl system ($MeMn_2B$).[27] When using simple enolate precursors (R_1 and R_2 are alkyl) and simple aldehydes. (R_1 = alkyl or furyl), the *syn*- to *anti*- ratio has been shown to be 20:1 or greater while using the Ipc_2B system bound to *Z*-enolates. The ratio inverts when employing the $MeMn_2B$ system bound to *E*-enolates where they have been shown to be 85:15 or greater (Scheme 4). Additionally, both chiral additives give excellent absolute stereocontrol.

Scheme 4

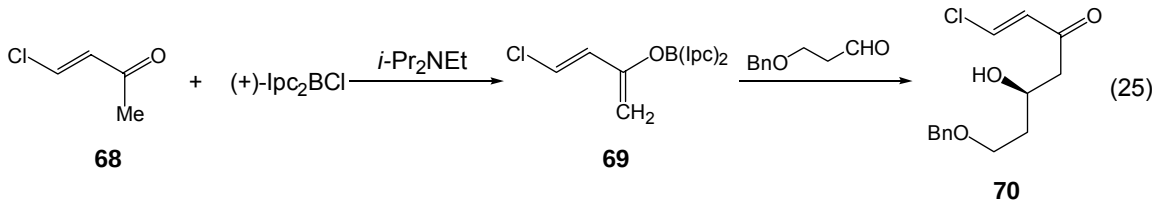


[25] Uses for metals other than boron as chiral reagents will be discussed in the section exploring reagent controlled free-radical additions. Some of these compounds have also appeared in the aldol literature.

[26] Paterson, I.; Goodman, J. M.; Lister, M. A.; Shumann, R. C.; McClure, C. K. *Tetrahedron*, **1990**, *46*, 4663.

[27] Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.*, **1992**, *57*, 5173.

Paterson demonstrated the synthetic utility of the Ipc_2B system in the intitial stages of his total synthesis of Preswinholide A (eq 25).[28] Other metals have been used for this purpose, however (+)-Ipc_2BCl and related systems are by far the most common in the aldol literature.[26]

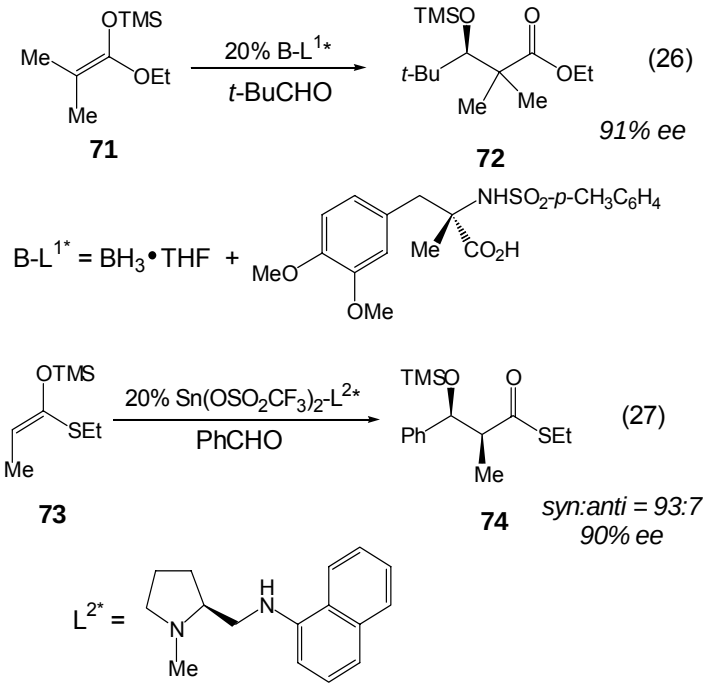


68 **69** **70** (25)

Asymmetric Catalysis (Chiral Metal Complexes). Because of the expense of chiral auxiliaries and chiral reagents, the most desirable type of absolute stereo-control is, by far, asymmetric catalysis. Unlike substrate and reagent controlled processes, asymmetric catalysis provides a chiral environment by using a substochiometric amount of a chiral additive. Of course, in order to be highly selective, the catalyst must be in "intimate" contact with the substrate during the mechanistic step in which the new chiral center is formed. Although there are many examples of asymmetric catalytic Mukaiyama reactions, aldol reactions are rare. A few examples regarding asymmetric catalytic Mukaiyama reactions using boron[29] and tin[30] are shown (eqs 26 and 27). The general mechanism for the process is shown in Scheme 5. It is generally accepted that the Lewis acid

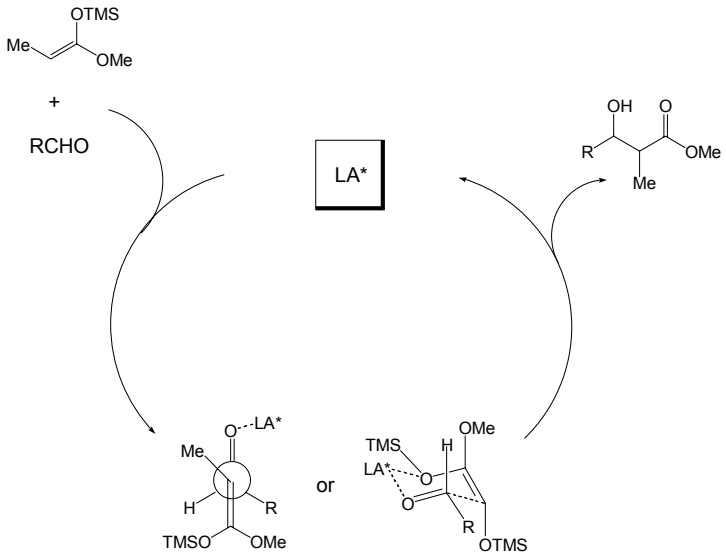
[28] (a) Paterson, I.; Smith , J. D. *J. Org. Chem.*, **1992**, *57*, 3261. (b) Paterson, I.; Smith, J. D. *Tetrahedron Lett.*, **1993**, *34*, 5351.
[29] (a) K. Furuta, K.; Maruyama, T.; Yamamoto, *Synlett.* **1991**, 439. (b) K. Furuta, K.; Maruyama, T.; Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 1041.
[30] Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett*. **1990**, 129.

coordinates to the aldehyde for electronic reasons. Depending on the number of available coordination sites on the Lewis acid, when the activated aldehyde may then engage the silyl enol ether in an “open” or a “closed” type transition state. As Scheme 5 shows, during the generation of the new carbon-carbon bond, the Lewis acid regenerates itself as the trimethyl silyl moves from the forming carbonyl to the forming alkoxy oxygen.[31]



[31] Mahrwald, R. *Chem. Rev*. **1999**, *99*, 1095.

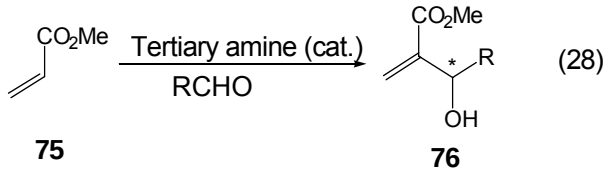
Scheme 5



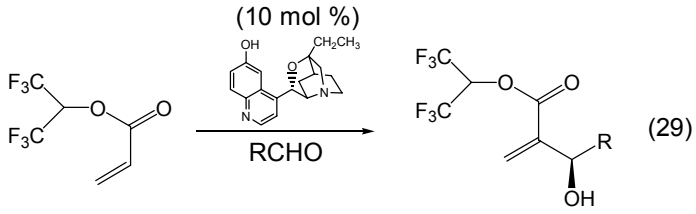
Asymmetric Catalysis (Covalently Bound Intermediates). One of the most effective ways to bring about absolute stereocontrol in a catalytic process is through the formation of reactive intermediates in which the chiral catalyst and the reactant(s) are covalently bound. For example, asymmetric catalysis involving the formation of chiral enolate-like intermediates from acrylic esters is found in a reaction that has become known as the Baylis-Hillman reaction.[32] In the Baylis-Hillman reaction (eq 28), an acrylic ester, activated by a tertiary amine, reacts with an aldehyde to give the corresponding allylic alcohols. The most widely accepted mechanism for this reaction is shown in Scheme 6. Because the catalyst is bound to the substrate during the step in which the new stereogenic center is formed, it was reasonable to assume that if the catalyst were chiral, the stereochemical outcome of the reaction might be controlled.

[32] Drewes, S. E.; Poos, G. H. P. *Tetrahedron*, **1988**, *44*, 4653.

Indeed, it was found that the use of chiral amines as catalysts (Fig. 15) gives a small amount of selectivity (8-12% ee).[35] However, to date, only one example of substantial absolute stereocontrol (>92% ee) has been shown (eq 29).[33]

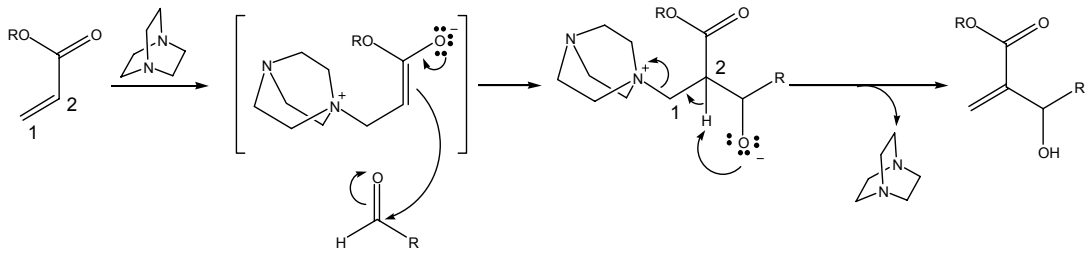


75 **76**



77 **78**

Scheme 6



[33] Iwabuchi, Y.; Nakatani, M.; Yokohama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

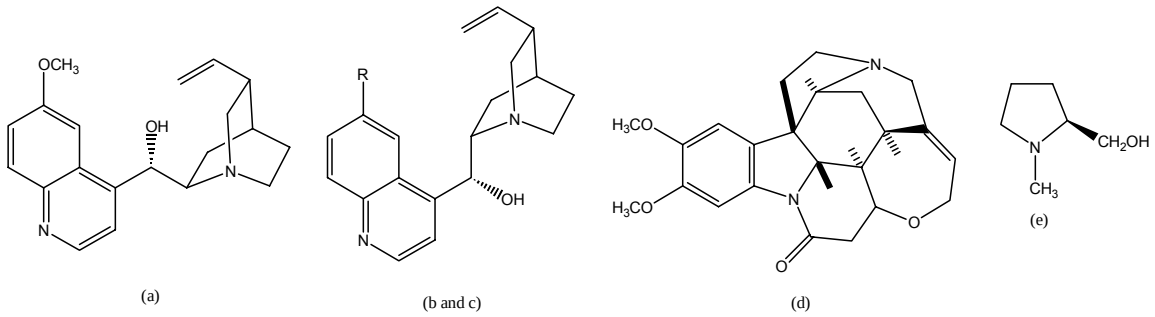
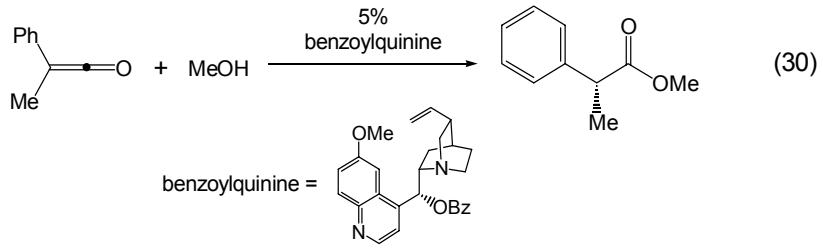


Figure 15. Chiral amine catalysts used in the Baylis-Hillman reaction:[35] (a) quinidine, (b) quinine (R = OCH_3), (c) cinchonidine (R = H), (d) brucine, (e) (S)-(-)-*N*-methyl prolinol.

As early as 1964, it was recognized that modified cinchonidine alkaloids could be used in the tertiary amine aided addition of achiral alcohols to ketenes (eq 30).[34] It was initially thought that the mechanism involved a hydrogen bond

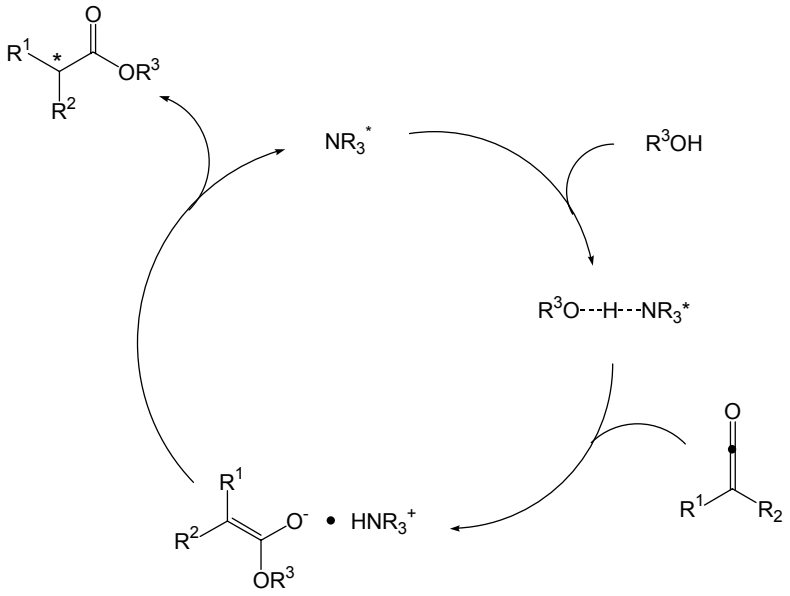


between the alcohol and the catalyst (Scheme 7). This intimate interaction not only made the alcohol more nucleophilic, but also provided the necessary chiral environment for asymmetric induction. Because of more recent evidence regarding the dimerization of ketenes (*vide infra*) in the presence tertiary amine

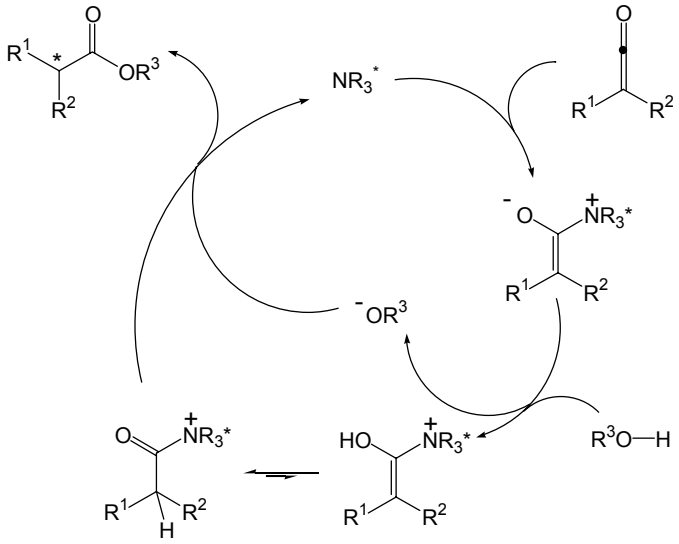
[34] Buschmann, H.; Scharf, H.-D.; Hoffmann, H.; Esser, P. *Angew. Chem., Int. Ed. Engl.,* **1991**, *30*, 477.

catalysts, a new mechanism regarding the addition of alcohols to ketenes is proposed here (Scheme 8). After the nucleophilic addition of the amine to the

Scheme 7

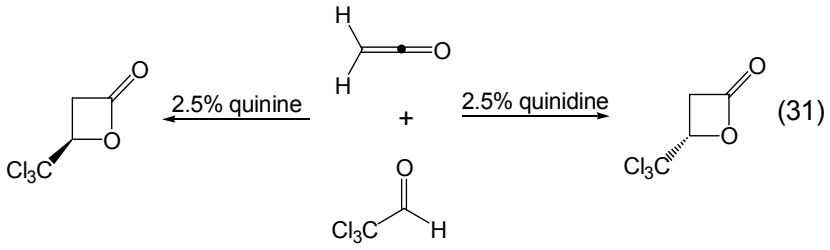


Scheme 8



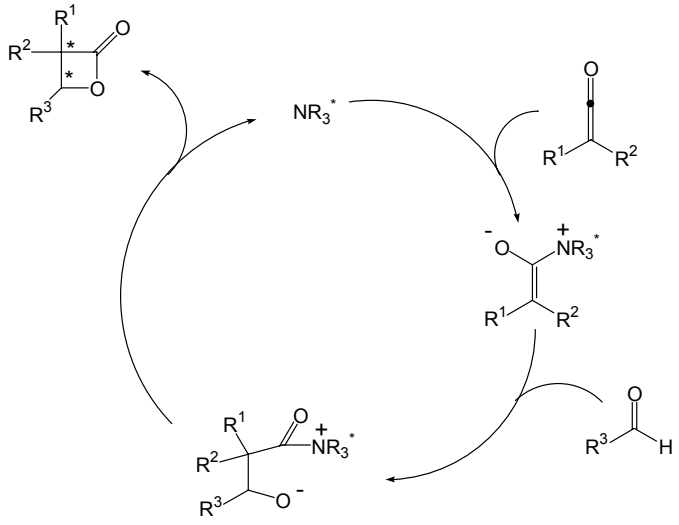
carbonyl carbon, the anionic oxygen might then deprotonate the alcohol. Tautomerization favoring the keto- form might then occur reforming the carbonyl, after which, nucleophilic attack by the alkoxide and regeneration of the catalyst would then lead to the observed product.

In addition to the asymmetric addition of alcohols to substituted ketenes, it was observed that unsubstituted ketene in the presence of catalytic amounts of the cinchonidine alkaloids quinine and quinidine will add to aldehydes to form chiral β-lactones (eq 31).[35] A possible mechanism is shown in Scheme 9. It was from this mechanism that the newly proposed mechanism for the asymmetric addition of alcohols to substituted ketenes was derived (Scheme 8). Only two differences are present: (1) the nature of the electrophile which is attacked by the enolate (Scheme 8 features a proton rather than a carbonyl carbon as the electrophile), and (2) intramolecular ester formation rather than an inter-molecular process. Catalytic processes similar to these were employed by our group for the asymmetric dimerization of methyl ketene, the details of which have been reserved for a later section.



[35] (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.*, **1982**, *104*, 116. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.*, **1985**, *50*, 1997.

Scheme 9



Strategies for absolute stereocontrol (Radical Additions to Alkenes)

Substrate Control. Unlike reactions involving enolates, there are comparatively few examples of substrate controlled reactions regarding free-radicals. In addition to the aforementioned Felkin-Anh rules regarding free-radical additions to double bonds and the examples given, it has been demonstrated that absolute stereocontrol when adding carbon centered free radicals to chiral auxiliary bearing alkenes is possible. This methodology, therefore, is a type of substrate control. Two such examples are shown in equations 32 and 33. In equation 32 a chiral dimethyl pyrrolidine amide serves as the auxiliary, and depending on the nature of the free-radical, a moderate to high degree of selectivity can be

achieved.[36] In this example, the diastereomeric ratios of **83:84** was found to be 24:1 while that of **85:86** was only 1.2:1. The investigators made no attempt to control the regioselectivity of this reaction and it was discovered that with the addition of a variety of free radicals, the ratio of α attack to β attack with respect to the amide carbonyl was approximately 1:1. Similar to that which was demonstrated in the aldol literature, chiral oxazoline auxiliaries have been used for free-radical additions to alkenes. The example shown in equation 33 is an elegant demonstration of the use of bulky chiral oxazolines as auxiliaries and how Lewis acidic additives increase the selctivities of such reactions.[37] In the absence of a Lewis acid additive, the ratio of **88**:**89** was only 1.3:1. However, when two molar equivalents of $MgBr_2{\cdot}Et_2O$ or $Yb(OTf)_3$ were added, the selectivities increased to 6:1 and 25:1 respectively with yields of greater than 90%. In the absence of an additive, the selectivity decreases because of rotation about carbon-nitrogen bond. A metal capable of coordinating to both carbonyl oxygens effectively "locks" the auxiliary in place such that it shields one face of the alkene (Fig. 16). Unfortunately, there are no examples or models depicting the addition of prochiral free radicals to prochiral alkenes. The development of an asymmetric free-radical reaction of this type would certainly generate more interest in the subject because of the usefulness of being able to form two chiral centers with a single carbon-carbon bond forming reaction. Developments of such a reaction will be described in more detail in a later section.

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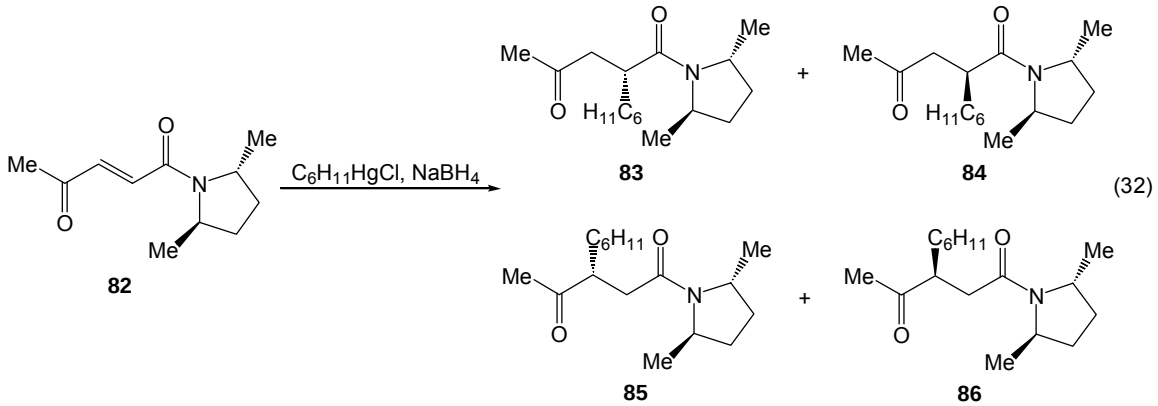
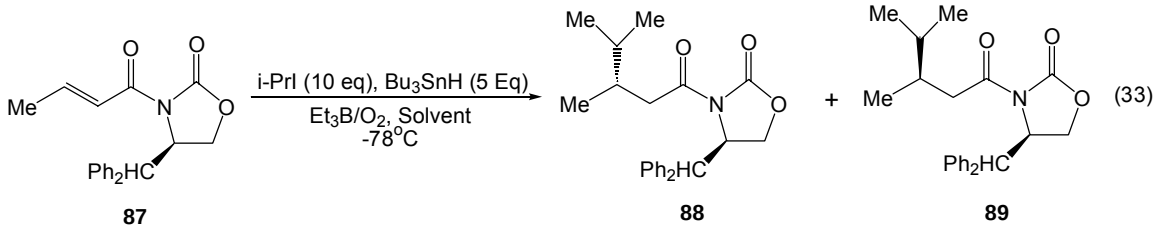
[36] Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791.
[37] Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc*., **1999**, *121*, 7517.



(32)



(33)

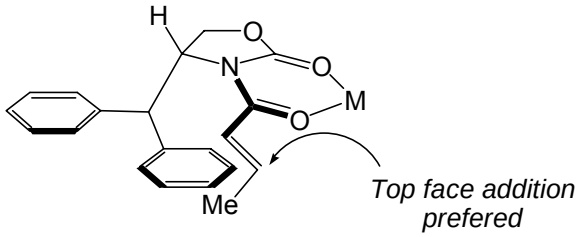
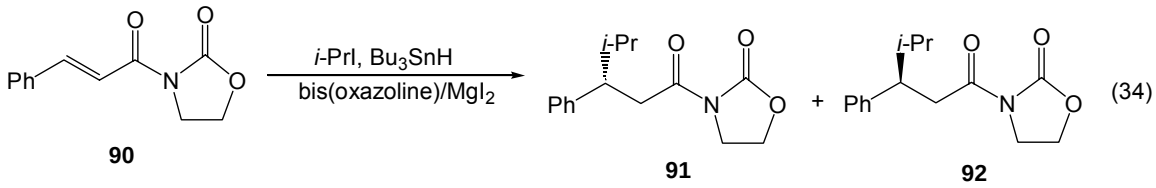


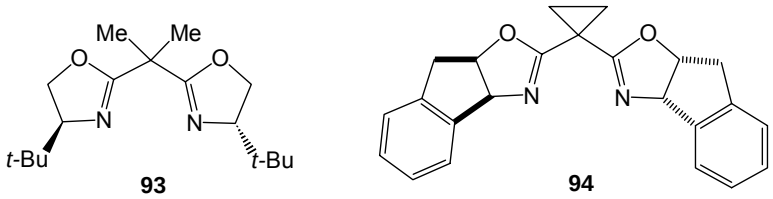
Figure 16. Rationale for increased selectivity of radical additions toward olefins bearing chiral oxazoline auxiliaries in the presence of Lewis acid additives.

Reagent Control. Analogous to reagent controlled aldol reactions, the addition of equimolar amounts of Lewis acidic reagents bearing chiral ligands provide for

excellent absolute stereocontrol in free radical additions to carbon-carbon double bonds. The most common such reagents are those in which the metal is bound to optically pure C_2-symmetric bis-oxazoline ligands (eq 34).[38] In the example shown, it was found that when **93** was used as a chiral ligand, the % ee of the reaction was 82% favoring **92**. When chiral ligand **94** was used the % ee increased to 98%. Because these discoveries are relatively recent, the use of both substrate controlled and reagent controlled intermolecular free radical additions to alkenes has not yet been seen in a total synthesis of a natural product.



bis(oxazolines)



[38] (a) Sibi, M. P.; Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.,* **1996**, *118*, 9200. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem Res.,* **1999**, *32*, 163.

Chapter 2

Catalytic Asymmetric Dimerization of Methylketene and its Synthetic Utility.

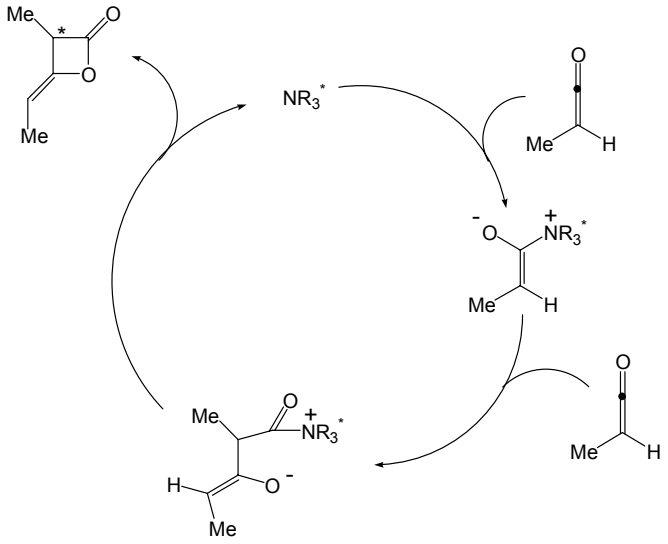
Catalytic Asymmetric Dimerization of Methylketene. The specific aim of this study was to develop chiral synthons that would be used for the synthesis of biologically active polyketides. The efficiency of such syntheses was taken to be of utmost importance in that it was hoped to eliminate the use of chiral auxiliaries, a common strategy used by earlier investigators, by using asymmetric catalysis and auxiliary-free substrate control for the formation of new chiral centers. Such strategies take fewer synthetic steps than those using chiral auxiliaries for the simple fact that after auxiliaries are attached, an additional step is needed for removal, adding at least two steps to the synthesis.

The dimerization of ketene and substituted ketenes in the presence of a tertiary amine catalyst has been described (Scheme 10).[39] Similar to the asymmetric catalytic addition of aldehydes to ketenes (eq 31, Scheme 9), it has been proposed that the dimerization of methyl ketene occurs by nucleophilic attack on the ketene carbonyl carbon followed by addition to a second equivalent of methyl ketene by the resulting enolate (Scheme 10). Cyclization and regeneration of the catalyst completes the cycle. Our group has shown that the dimerization in the presence of a chiral tertiary amine catalyst occurs

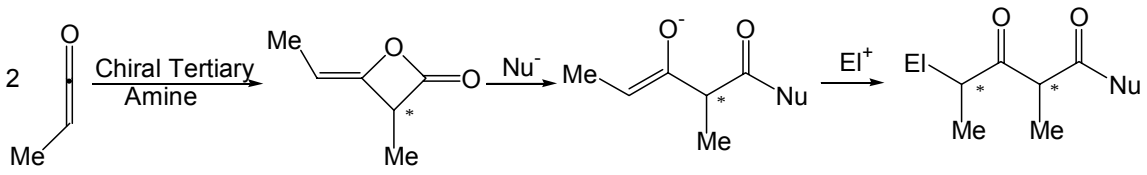
[39] (a) Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444. (b) Samtleben, R.; Pracejus, H. *J. Prakt. Chem*. **1972**, *314*, 157.

stereoselectively to produce enantiomerically enhanced mixtures of β-lactones[40] which might then be transformed to other more stable and useful synthons by the sequential addition of various nucleophiles and electrophiles (Scheme 11).

Scheme 10



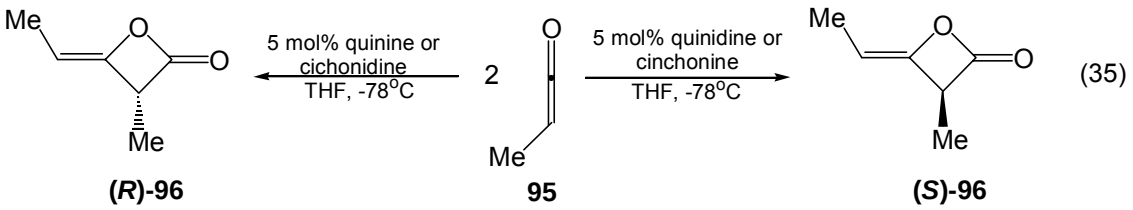
Scheme 11



The configuration of the newly formed stereocenter in the β-lactone may be easily manipulated by the use of the appropriate cinchona amine (eq 35). This newly discovered route was attractive for a variety of reasons. First, methyl

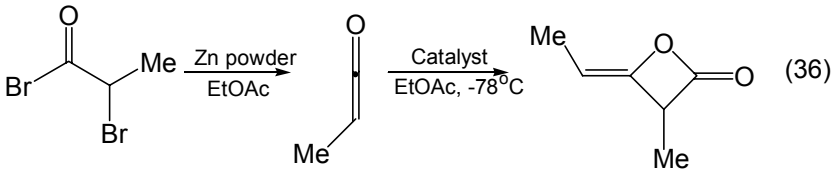
[40] Calter, M. A. *J. Org. Chem*. **1996**, *61*, 8006.

ketene is easily produced by either the pyrolysis of propionic anhydride or by the reaction of powdered zinc and 2-bromopropionyl bromide. Secondly, only a 5 mole percent of amine catalyst is necessary to give high enantiomeric excesses. Finally, the catalysts are naturally occuring, relatively inexpensive, nontoxic, commercially available materials.



(*R*)-96 **95** **(*S*)-96** (35)

In initial studies, methylketene was generated by the reaction of zinc and 2-bromopropionyl bromide **97** in ethyl acetate followed by the addition of a solution of catalyst, also in ethyl acetate (eq. 36). The results are shown in table 1. Apparently, the presence of an aryl methoxy moiety on the catalyst enhances the enantiomeric excess of the resulting dimer. Therefore, the remainder of the study focused on the catalysts quinine and quinidine.

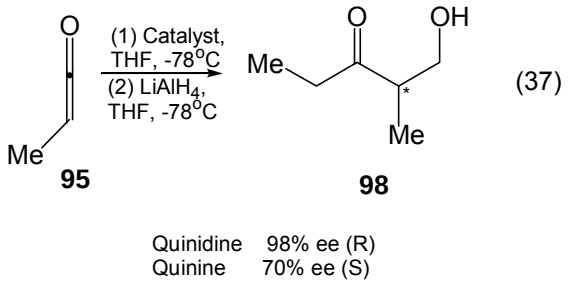


97 **95** **96** (36)

Table 1. Asymmetric dimerization of methylketene.

Catalyst	% ee of 98 (configuration)
Quinine	60 (R)
Cinchonidine	57 (R)
Quinidine	71 (S)
Cinchonine	64 (S)

Inconsistencies in the enantiomeric excesses and yields arose from reaction to reaction as the study progressed. Presumably, this was due to trace amounts of acetic acid in the solvent leading to a deactivation of the catalyst and/or epimerization of the newly formed chiral center. This problem was resolved by changing to THF as the solvent. It was found that the % ee of the β-lactone increased dramatically when THF was used and also allowed for an *in situ* reduction of the dimer to the corresponding β-hydroxy ketone **98** by reducing the lactone with lithium aluminum hydride (eq 37).[41]



(37)

[41] It was found that using TMS-quinine increases the %ee of the *S*- enantiomer from 70% to 97% (ref 40).

Several things must be considered regarding the catalyst and methyl ketene to fully understand and rationalize the dimerization process and the cause of the stereoselectivity. Like allene, the two π bonds of methyl ketene are perpendicular to each other. The consequence of this particular feature is such that nucleophiles approach the π* of the carbonyl passing over the hydrogen or the bulky methyl group (fig 17). Of course, the preferred approach is over the

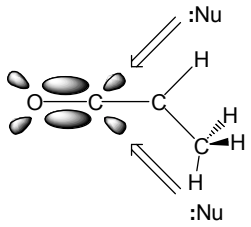


Figure 17. Approach of nucleophiles toward π* of the carbonyl in methylketene (Note: The three carbons and the oxygen are all in the same plane in this illustration).

hydrogen resulting in a *Z*- enolate. This newly formed nucleophilic enolate would then attack a second equivalent of methyl ketene in a similar fashion. This explains the *E/Z* geometry about the double bond in the resulting β-lactone upon cyclization (Scheme 12, **:**NR_3 = Nu**:**). The rationale regarding the facial selectivity toward the initially formed enolate by the second equivalent of methylketene is shown in Figure 18. It has been proposed that rotomer B in the figure is of the lowest energy because of the orientation of the bulky methyl group away from the catalyst.[40] If this is an accurate depiction, the only possible approach is toward the face of the enolate that is not shielded by the bulky aryl moiety of the catalyst.

This description correctly predicts the configuration of the stereogenic α-carbon in the resulting lactone.

Scheme 12

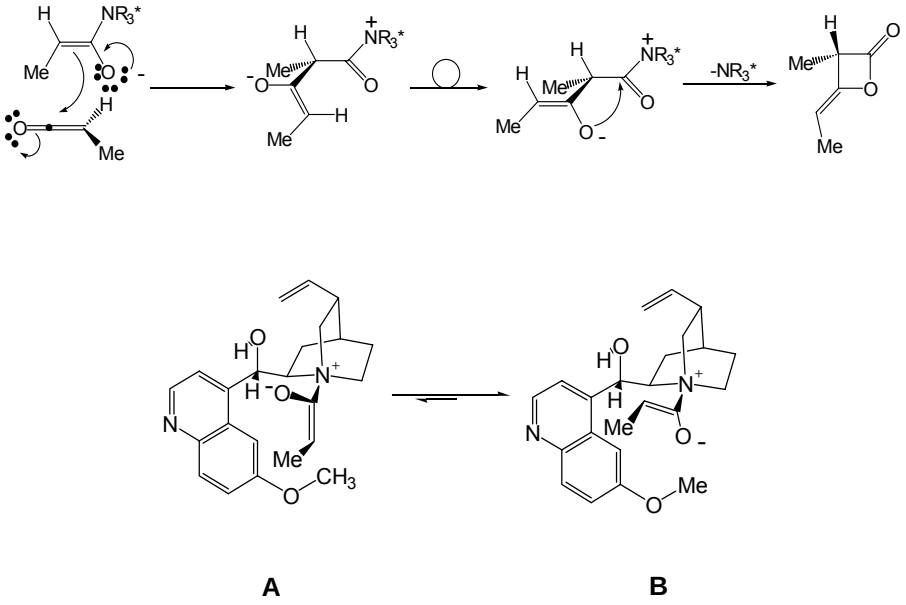


Figure 18. Rationale for the facial bias of a second equivalent of methylketene during asymmetric dimerization.

With a reliable method to produce both enantiomers of the methylketene dimer, manipulation of these β-lactones into more stable, less volatile compounds was the next phase of this study. With the aim of optimizing the yield of the chiral β-hydroxy ketones, a study of a variety of reductants was conducted (eq 37). This study was of particular importance because of our intention of using this intermediate as a starting material for the synthesis of a natural product (*vide infra*). The reduction of the β-lactone varied greatly in terms of yield and % ee

(Table 2). In fact, it was found that from run to run, using the same reductant, under the same conditions, the outcome of the reaction was unpredictable.

Table 2. Reduction of chiral methylketene dimer

Reductant	% Yield	% ee
$LiAlH_4$	17-38	83-98
DIBAL-H	16-19	<74%
Red-Al	11-26	13-98
$NaBH_4$	0*	Diol Products* (2:1 Syn:Anti)

* ^{1}H-NMR evidence suggests the formation of 2-methyl-1,3-pentanediol. It is assumed that chelate controlled reduction of the hydroxy ketone produces the syn-diastereomer preferentially.

A more successful study regarding a reliable production of enantio-pure synthons from the chiral β-lactone was developed through the treatment of the lactone with various secondary amines (Scheme 13). The results of this study are shown in Table 3.[42] It was discovered that, not only was it possible to form chiral β-keto amide, but *in situ* reduction of these ketones to the corresponding β-hydroxy amides generating two chiral centers in a "one pot" reaction was also possible. Additionally, it was found that the synthesis of "Weinreb" amides was also possible, although their synthesis necessitated the use of an acyl transfer

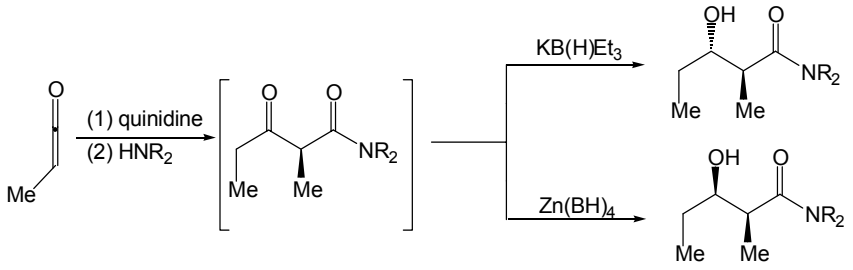
[42] Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308.

catalyst. These N,O-dimethylhydroxyamides are of particular interest in contemporary organic synthesis because of the ease with which they can be refunctionalized to the corresponding aldehyde without first being converted to the alcohol.[43]

Table 3. Yields and enantioselectivities for the production of chiral β-hydroxy amides.

Amine	Reductant	% ee	% yield
Pyrrolidine	$Zn(BH_4)_2$	99	42
Pyrrolidine	$KB(H)Et_3$	98	48
HN(OMe)Me	$Zn(BH_4)_2$	99	40
HN(OMe)Me	$KB(H)Et_3$	99	46

Scheme 13



It was also discovered that, by using lithiated amines, it was possible to form amide functionalized lithium enolates which would then be available for *in situ* aldol additions (scheme 14). By this method, three stereocenters in an all

[43] Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, 4171.

syn- arrangement can be generated in “one pot” with good stereoselectivity (Table 4).[44]

Scheme 14

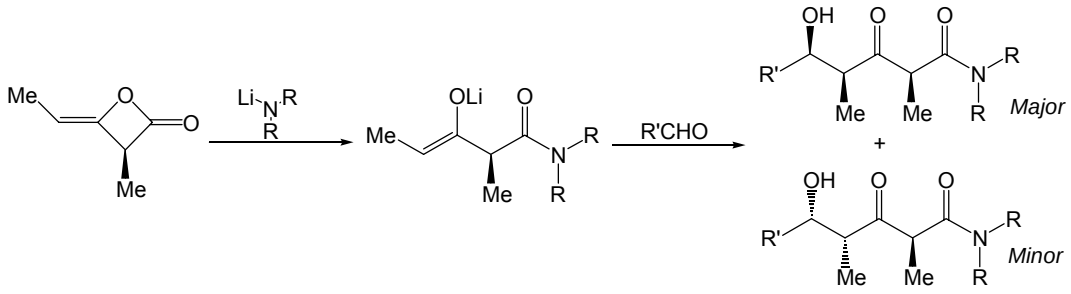


Table 4. Selectivities and yields for aldol reactions

R	syn-,syn-:*anti-,syn-* ratio	% yield of all *syn-* diastereomer
i-Pr	95:5	52
n-pentyl	89:11	48
Phenyl	84:16	50
	84:16	48

[44] Calter, M. A.; Guo, X.; Liao, W. *Org. Lett.*, **2001**, *3*, 1499.

Synthesis of the (2*S*, 4*S*, 6*S*) Trimethylnonyl Subunit of the Siphonarienes.

The siphonariene class of natural products contain polypropionate carbon skeletons. Specifically, many members of this class of natural products share the common attribute of a (2*S*, 4*S*, 6*S*) trimethyl nonyl unit bound to different olefinic and oxygen containing moieties. Several members of this class exhibit powerful antiviral and antibacterial activity making them popular targets for total synthesis. The structures of several siphonarienes are shown in Figure 19.

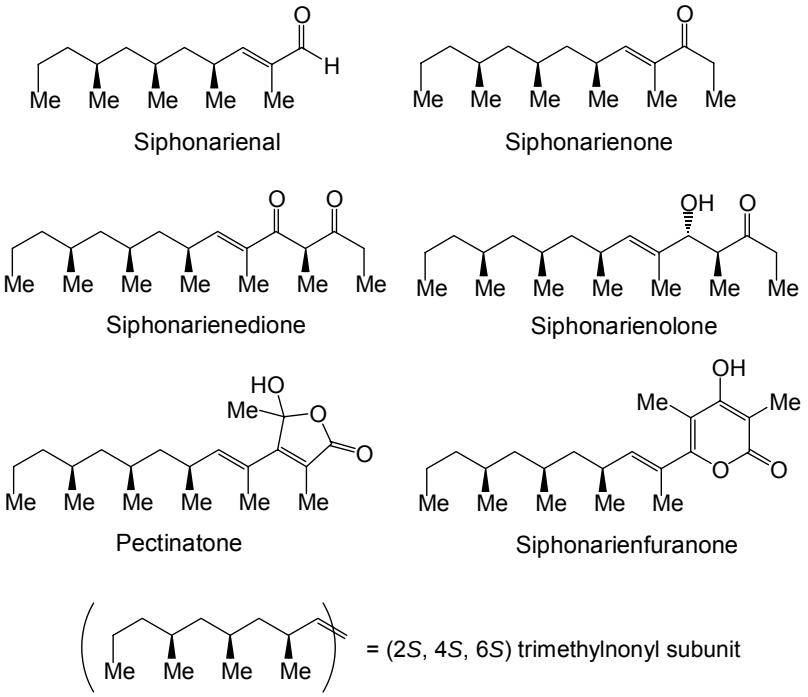
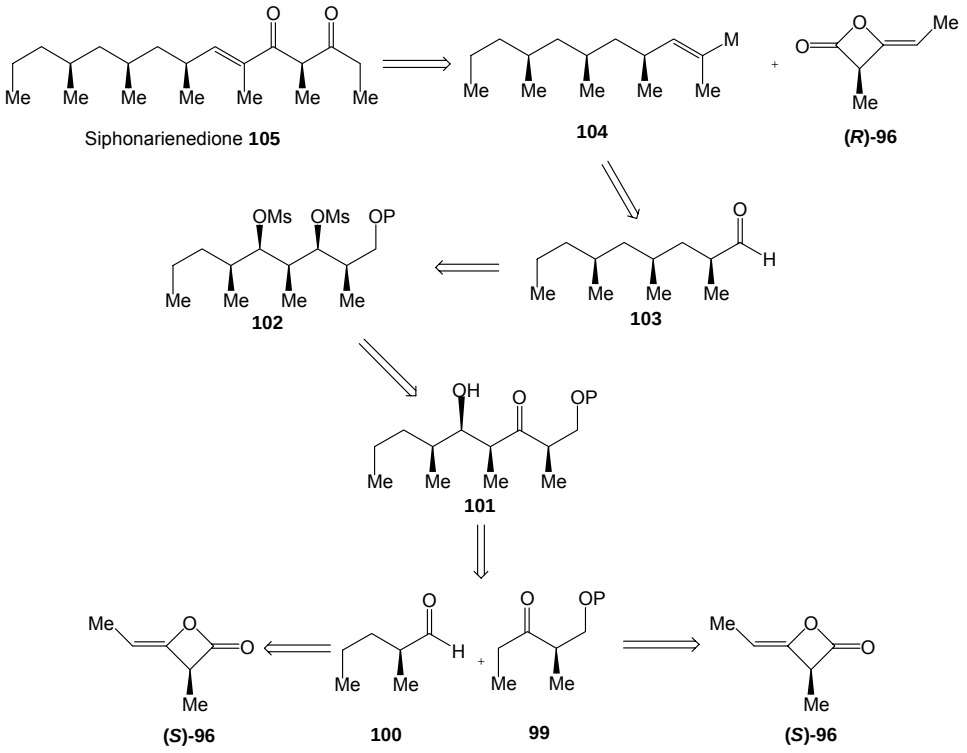


Figure 19. Representative members of the siphonariene class of natural products.

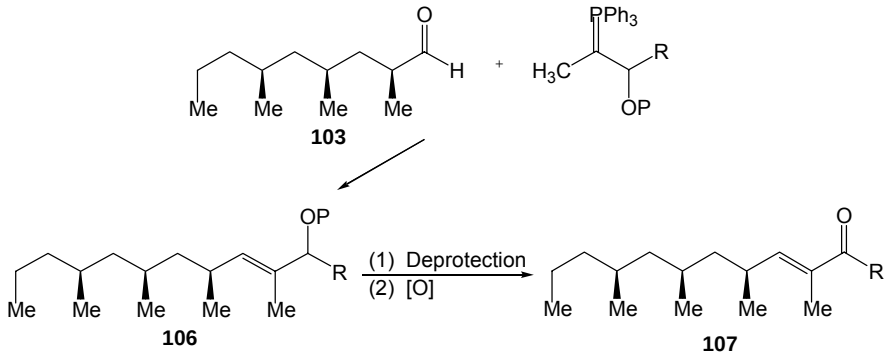
Our intention was to use the chiral methyl ketene dimer and the subsequent β-hydroxy ketones and β-keto amides as a source for the methyl bearing chiral centers found in the polypropionate backbones of the siphonarienes. With this in mind, the initial target for total synthesis was

Siphonarienedione (**105**), the retrosynthesis of which is shown in Scheme 15. It should be noted that a key intermediate in the synthesis of virtually all the siphonarienes is the aldehyde **103** which contains the (2S, 4S, 6S) trimethyl nonyl unit and can be functionalized further using a Horner-Emmons-Wadsworth/Wittig strategy en route to many of the siphonarienes. For example, **103** can be converted to siphonarienal by the reaction between the aldehyde and the protected Wittig reagent obtained from 2-bromo-1-propanol (R=H) (Scheme 16). The protected allylic alcohol **106** could then be converted to the target compound in two additional steps. Siphonarienone could be obtained similarly with the appropriate Wittig reagent. E/Z selectivity regarding this reaction is of key importance.

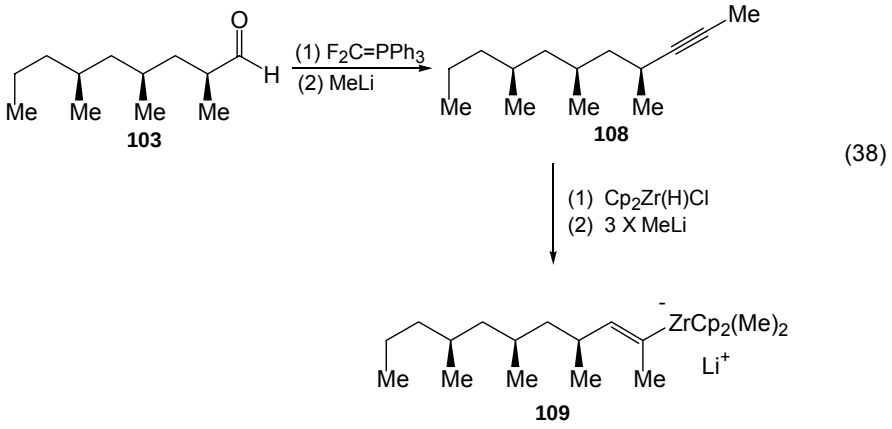
Scheme 15



Scheme 16

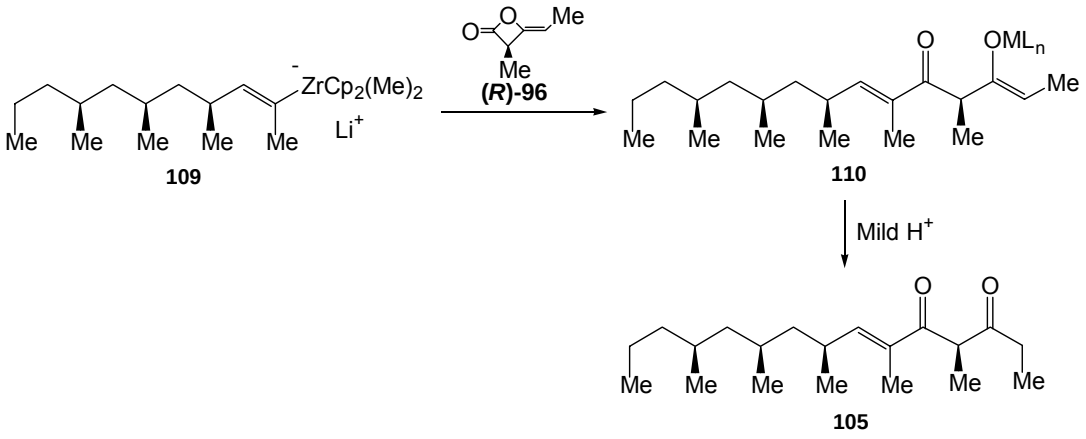


In the case of siphonarienedione, it was hoped that the transformation of aldehyde **103** to the corresponding difluoroalkene, followed by Nakai's elimination/addition procedure would then afford the internal alkyne shown (**108**). This compound might then be transformed into the zirconate complex **109** (eq 38).



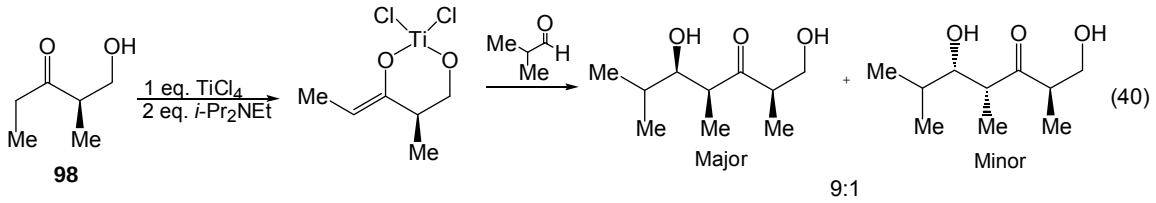
(38)

With formation of this unprecedented zirconate, it was our intention to, by first treating this nucleophilic complex with an equivalent of the appropriate diastereomer of chiral β-lactone dimer, form the enolate **110**. By means of protonation under mildly acidic conditions, **110** might then be transformed to siphonarienedione **105** (eq 39).



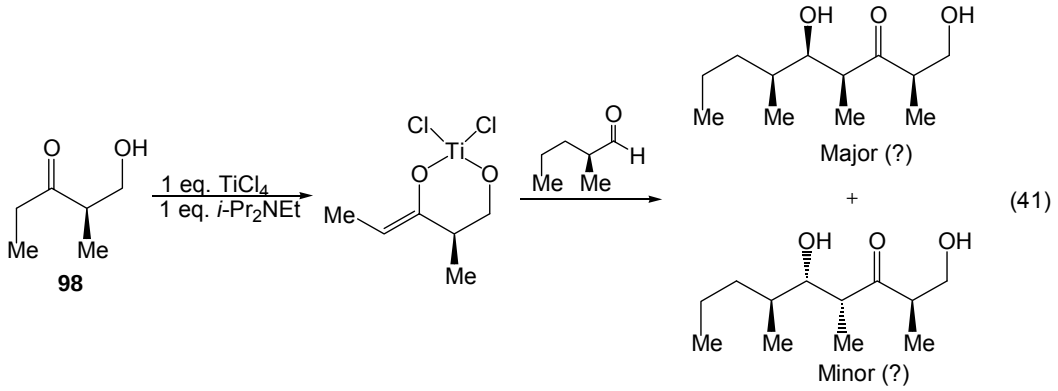
(39)

The retrosynthesis of the key intermediate **103** is shown in scheme 15. In Two of the three chiral centers are formed via our newly developed catalytic asymmetric synthesis of the β-lactone **96**. To generate the remaining chiral center, a diastereoselective aldol coupling of hydroxyketone **98** and aldehyde **100** was to be used. Regarding this aldol coupling, a similar reaction involving isobutyraldehyde and enantio-pure β-hydroxyketone **98** has appeared in the literature where the all *syn*- aldol adduct was the major diastereomer by a ratio of 9:1 with respect to the *anti*- aldol adduct (eq 40).[45] It was hoped that the all *syn*-aldol product would also be the major product when coupling the same hydroxyl-ketone and chiral 2-methylpentanal **100** (eq 41), both of which can be generated by the new route.



(40)

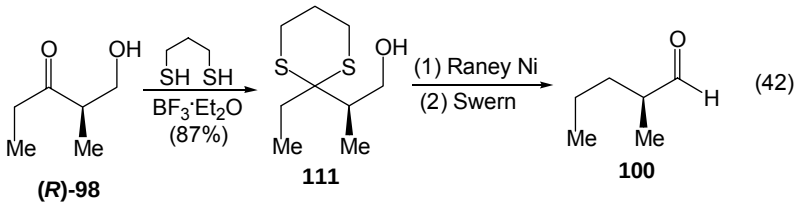
[45] Luke, G. P.; Morris, J. *J. Org. Chem*. **1995**, *60*, 3013.



(41)

To test our strategy, we set out to repeat the work of Luke and Morris[45] by first reducing the β-lactone to the β-hydroxyketone **98** then performing the aldol addition as described in the literature. We hoped that this would not only reinforce the precedent, but also allow us to familiarize ourselves with the technique and possibly optimize the reaction. As was described earlier, a variety of reductants were used to generate the desired β-hydroxyketone **98**. Unfortunately, the reaction was unreliable in that, although the yields were consistently moderate to high, it was difficult to control the optical purity. A few attempts to synthesize this compound did, however, result in product mixtures of high enantiopurity. It was initially believed that the aqueous acidic work up was causing epimerization to occur either by the involvement of trace localized amounts of hydroxide and subsequent deprotonation/reprotonation alpha to the carbonyl, or by acid catalyzed enolate formation. To remedy this problem, the reducing agent was quenched with ethyl acetate prior to a brine wash. This method was also unpredictable with respect to the % ee even with newly opened bottles of HPLC grade ethyl acetate. Acetone was also used for this same purpose, but to no avail.

With purified β-hydroxyketone **98** of 96% ee or better, we repeated the aldol reaction first performed by Luke and Morris (eq 40). To our delight, we were able to perform the this aldol with *syn-, syn-* selectivities equal to or greater than that of the original investigators (> 9:1) in somewhat higher yields (>78 %). The reassurance that this aldol addition provided, allowed us to continue with the synthesis of the aldehyde **103** by now focusing on the synthesis of chiral 2-methylpentanal **100**. The initial stategy for this synthesis is shown (eq 42). By transforming optically enhanced β-hydroxyketone **98** into the thioketal **111**, it was hoped that subsequent Raney nickel desulfurization[46] and Swern oxidation[47] would provide us with a convenient method for the synthesis of **100**. Although we discovered that formation of thioketal was efficient, the Raney nickel reduction was problematic in that not only was the resulting alcohol difficult to isolate because of its solubility in both water and a variety of organic solvents as well as its low boiling point, but epimerization also occured, presumably via hydrogen radical abstraction/ addition at the chiral center giving alcohols in 72% ee or less. A new route, therefore, was sought.

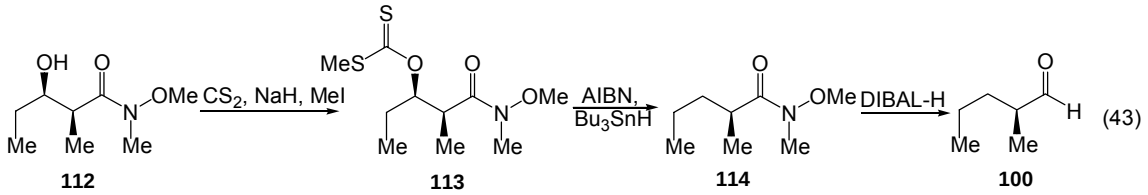


(***R***)-**98** **111** **100** (42)

As was previously described, our group had developed an efficient synthesis of the β-hydroxy and β-keto Weinreb amides (Scheme 13). It was

[46] Mehta, G.; Murthy, A. M. *J. Org. Chem*. **1987**, *52*, 2875.
[47] (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480.

decided to exploit Barton's method of deoxygenating alcohols to the corresponding methylene by converting β-hydroxy amide **112** to the corresponding methyl xanthate[48] **113** which would then undergo free-radical reduction with Bu_3SnH (eq 43).[49] The resulting chiral Weinreb amide **114** might then be reduced to the desired aldehyde. Fortunately, this route afforded **114** in high yields and without epimerization. It is unclear as to the reasons for



(43)

epimerization when using the Raney nickel desulfurization route compared to that of the Bu_3SnH route when both processes rely on radical processes.[50] Unfortunately, the reduction of the newly formed amide to the aldehyde was troublesome in that the low-boiling aldehyde was difficult to remove from the reaction solvent (Et_2O) giving overall yields of less than 17% from bromo-propionylbromide.

With the exception of the reduction of the amide moiety itself, the ease with which the refunctionalization of these and similar compounds encouraged us to abandon the original aldol route, as illustrated in equation 41, in favor of a new route shown in Scheme 17. This new route allowed us to explore the possibilities regarding the formation of the lithium enolate **115** from the methylketene dimer *in situ*, thus allowing for a subsequent aldol addition with chiral aldehyde **100**.

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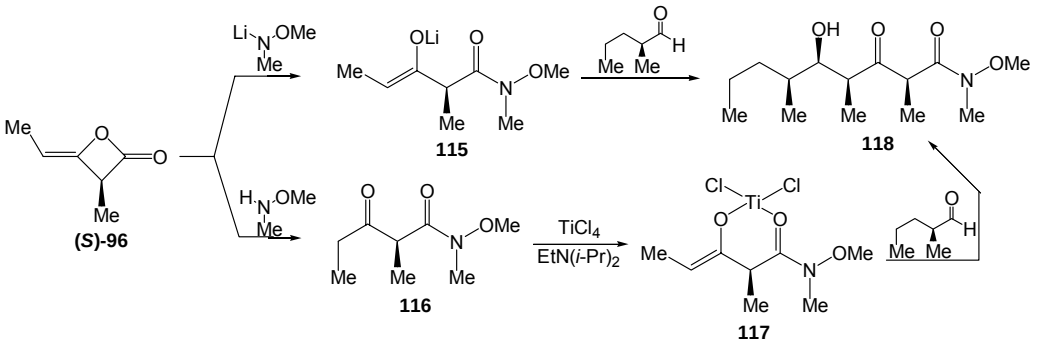
[48] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perk. Trans. I* **1975**, 1574.
[49] Boyd, S. A.; Mantei, R. A.; Hsiao, C.-N.; Baker, W. R. *J. Org. Chem*. **1991**, *56*, 438.
[50] For mechanisms, see Ref. 29 for Xanthate reductions and Owens and Ahmberg in *Can. J. Chem*. **1962**, *40*, 941.

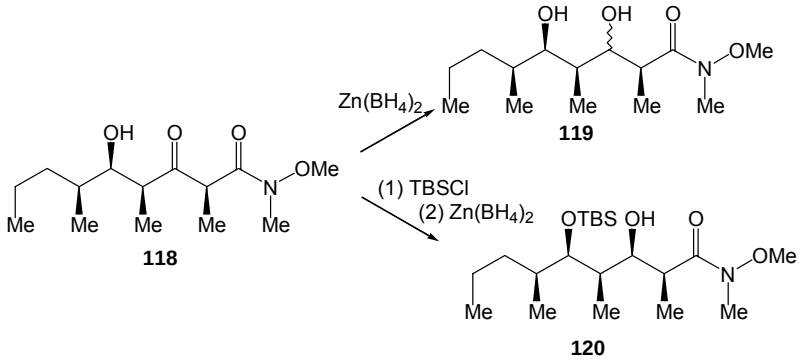
Scheme 17



The aldol reactions between the chiral aldehyde and the titanium enolate **117** generated from the corresponding β-keto amide **116** and the lithium enolate generated directly from the chiral β-lactone were investigated. We discovered that both processes produced a mixture of adducts favoring the desired all *syn*-diastereomer which was isolated by silica gel chromatography. The yields from these reactions were 47% from **116** when using the titanium enolate route and 55% when the lithium enolate route was employed. Additionally, it was found that using racemic 2-methylpentanal, produced the desired diastereomer in 25% overall yield from the corresponding β-lactone (12% from bromopropionyl bromide). This is notable in that this reaction produces all three methyl bearing chiral centers necessary for the construction of the (2*S*, 4*S*, 6*S*) trimethylnonyl subunit in one synthetic step. Through a chelate controlled reduction of the aldol adduct with $Zn(BH_4)_2$ (Scheme 18), it was hoped that the resultant diol (**119**) would be easily deoxygenated to the amide precursor of the desired trimethylnonyl aldehyde. We discovered that the reduction produced a 1:1 mixture of diastereomers unless the hydroxyl of the aldol adduct was protected

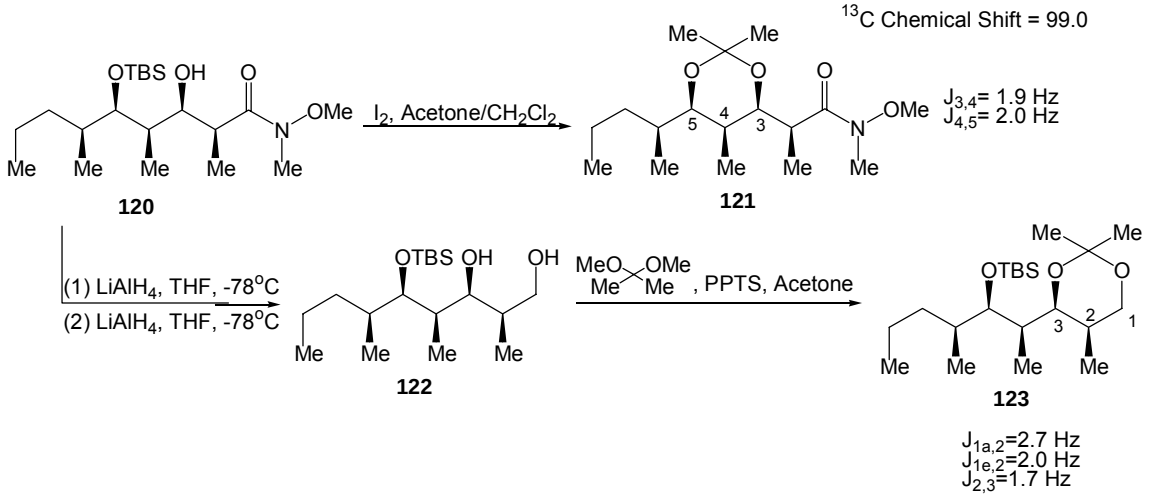
(TBS) first. This route produced only one detectable diastereomer **120** in 77% yield from **118**.

Scheme 18

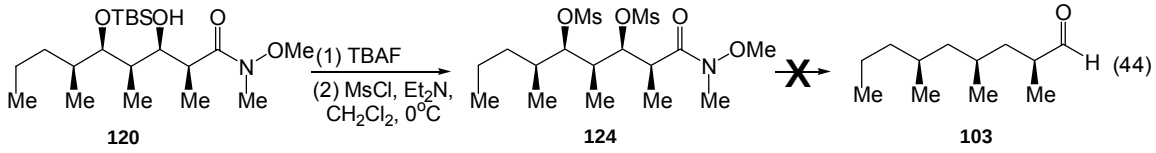


With the protected diol in hand, the internal acetonide was synthesized for the purpose of determining the relative stereochemistry about carbons C_3, C_4, and C_5 (Scheme 19). The ^{13}C chemical shift of the acetonide carbon and the small coupling constants between the protons between C_3 and C_4 as well as between C_4 and C_5 show that diol is of an all syn- arrangement. Additionally, exhaustive reduction of the amide moiety allowed for the acetonide formation about C_1, C_2 and C_3. By this method, it was possible to show that the methyl at C_2 was in an axial position, leading to the stereochemical assignments shown.

Scheme 19



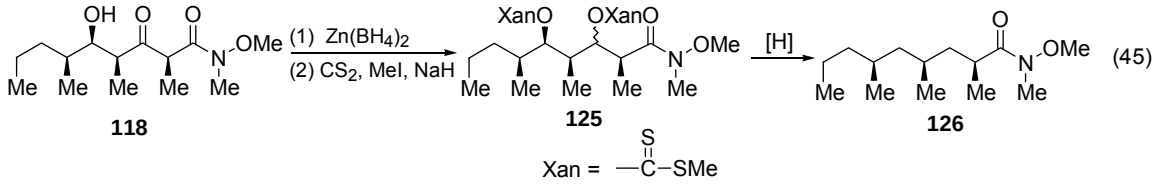
By refunctionalizing the diol to the bis-tosylate or bis-mesylate, it was hoped that a subsequent single synthetic step might be performed which would not only excise the undesired oxygens, but reduce the amide to the aldehyde as well. A similar deoxygenation route was used by Norte.[51] Unfortunately, we discovered that, not only did this route reduce the Weinreb amide moiety, but led to a variety of elimination products as was evident by the large number of vinyl proton signals in the ^{1}H-NMR of the crude product mixture.



Future Prospects. Although the prediscribed synthesis failed to produce the trimethylnonyl subunit of the siphonarienes, the diol precursor **118** might yet prove valuable. Drawing on the successes regarding the deoxygenation of the

[51] Norte, M.; Fernandez, J. J.; Padilla, A. *Tetrahedron Lett.* **1994**, *35*, 3413.

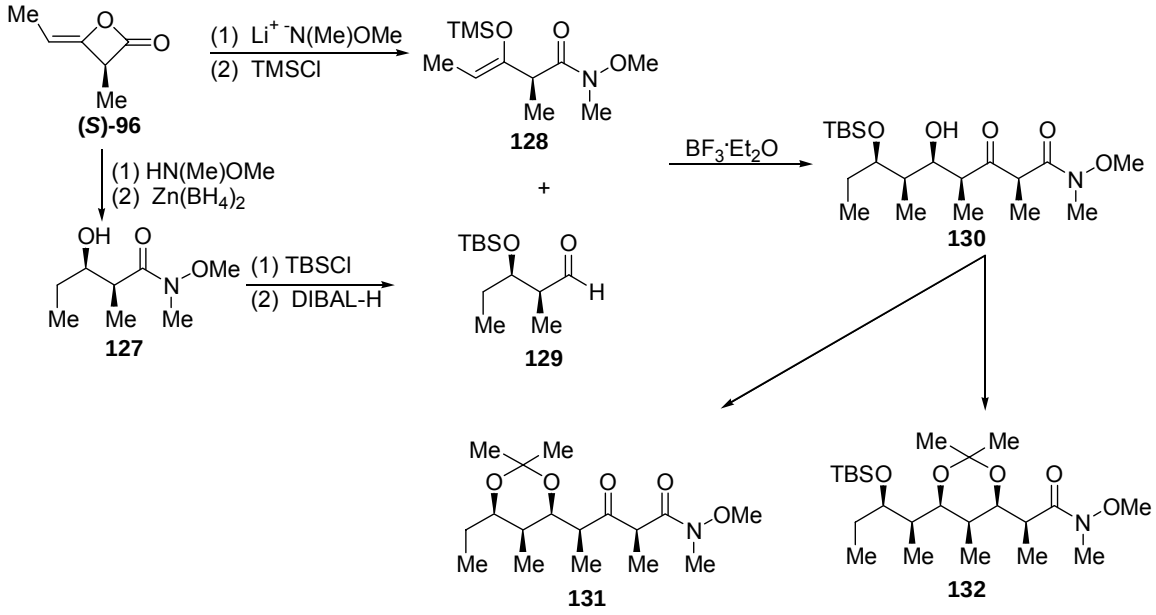
hydroxyamide **112** (eq 43) it might be possible to synthesize a bis-xanthate **125** which could be reduced to amide **126**. This amide might then be reduced to the desired aldehyde **103** (eq. 45).



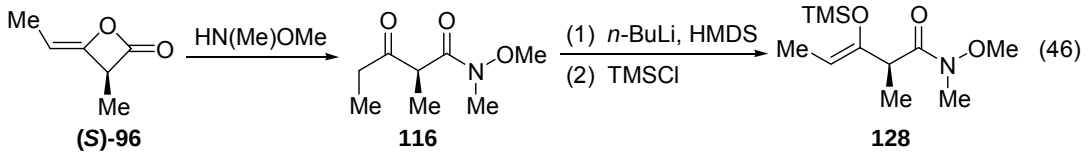
118 **125** **126** (45)

Regarding the efficiency the aldol addition which generates the chiral center at C_4, the possibility of using silyl enol ethers rather than other metallated enolates was considered (Scheme 20). Aldol reactions using silyl enol ethers which proceed through open transition states have demonstrated excellent *syn*-selectivity and are only weakly effected by the configuration of the aldehyde. By avoiding a closed transition state, the somewhat poor selectivity which was observed would be avoided by eliminated the undesirable *syn*- pentane interaction described by Roush. Additionally, the use of an open transition state aldol reaction provides for the opportunity to use aldehydes such as **129**. Not only would the additional bulk have a minimal effect the outcome of the aldol addition, but would also provide for a less volatile aldehyde which could be easily produced. Also, this route would provide a synthetic handle with which the stereochemical configuration at C_6 could be proven.

Scheme 20



In exploring the feasibility of this new strategy, aldehyde **129** was made by first synthesizing the β-hydroxy amide **127**. This compound was easily protected and reduced to the required aldehyde. Unfortunately, the TMS-enol ether **128** was not so easily synthesized. Attempts to make this compound directly from the β-lactone proved unsuccessful as did all attempts to synthesize it using the chiral β-keto amide (eq 46). **128** has been reported in the literature, but it was used *in situ* and its yield was approximated at 55%.[52] For the aldol reaction, it is



(46)

[52] Calter, M. A.; Bi, F. C. *Organic Letters* **2000**, 2, 1529.

conceivable that an *in situ* generation of **128** followed by subsequent additions of **129** and $BF_3{\cdot}Et_2O$ might generate the desired configuration at C_4. However, the presence of $BF_3{\cdot}Et_2O$ would certainly remove the TBS protecting group giving a deprotected version of **130** (Scheme 20).

Chapter Three

Addition of Free-Radicals to Allyl Bromides.

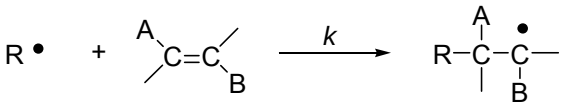
Review (alkyl radical additions to multiple bonds). The development of new methods for functional group transformation and the formation of carbon-carbon bonds lie at the heart of organic synthesis. Although the majority of organic reactions involve two-electron, heterolytic pathways, the development and use of single electron, free radical synthetic routes are equally important in offering alternatives when heterolytic strategies fail.

Additions of alkyl radicals to alkenes, particularly in the polymer industry, are among the most common methods for creating new carbon-carbon bonds in a homolytic fashion. Although initiation pathways in radical chain processes and the generation of alkyl radicals is important, this discussion will focus primarily on the reactivity of various alkyl radical species toward compounds with carbon-carbon multiple bonds and the synthetic usefulness of such reactions.

In general terms, neutral free radicals should be characterized as neither electro- nor nucleophilic. From Lewis theory, neutral oxygen, halogen and carbon centered radicals should be considered neither electron rich nor electron poor because they are electroneutral, yet they are reactive because of unsatisfied valences in that they have incomplete octets. Their behavior in terms of “electro-” and “nucleophilicity” should, therefore, be determined empirically.

Substituent effects on rates of addition. Giese reported that the rates of addition of alkyl radicals to alkenes is affected by electron donating and withdrawing substituents on both the adding free radical and the alkene.[53] A general reaction showing the addition of an alkyl radical to a substituted alkene is shown in Scheme 21. For the sake of discussion, the substituent bound to the carbon of the alkene to which the alkyl radical attaches will be called the α-substituent and given the generic group –A. Likewise, the β-substituent, the substituent on the neighboring carbon, will be given the label –B. This review will first explore what is now called the β-substituent effect by discussing additions of alkyl radicals to monosubstituted and 1,1-disubstituted alkenes. The α-substituent effect will then be explored by examining additions to 1,2-disubstituted alkenes.

Scheme 21

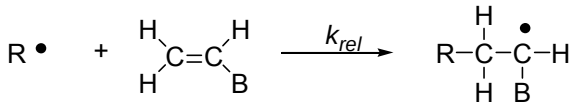


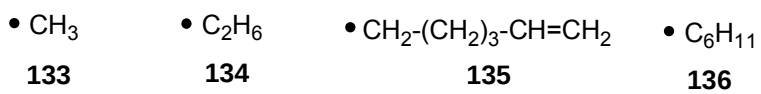
The relative addition rates of alkyl radicals to various monosubstituted alkenes is given in order of decreasing electron withdrawing ability of a β-substituent in Table 5 (Scheme 22).[53] The rates of addition decrease as the electron withdrawing ability of the β-substituent decreases. In other words, as the electrophilicity of the alkene increases, so does the rate. It should also be

[53] Giese, B. *Angew. Chem. Int. Ed.* **1983**, *22*, 753.

noted that the substituent effect diminishes when adding primary radicals at elevated temperatures (compare entries A, B, and C when $R^{\cdot}$ = **133**, **135**, or **136**). That is to say, the addition of secondary radicals is affected to a greater extent than primary radicals as the electron withdrawing ability of the β-substituent changes. A comparison of additions of cyclohexyl radicals to various 1,1-disubstituted alkenes reinforced the notion that as the withdrawing ability of the β-substituent decreases, the rate decreases (Scheme 23, Table 6). This evidence, in itself, seems to indicate that alkyl radicals are nucleophilic. The nucleophilic behavior of alkyl radicals toward substituted alkenes has been supported by Hammett studies[54] and is reinforced by frontier orbital theory.[53,55] Additionally, there is only a small steric effect regarding the β-substitiuent. The absence of a steric effect is evident when comparing substituents of similar electron withdrawing ability, but differ in terms of bulk (compare entries E, F and G; Table 6).

Scheme 22



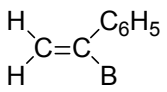


[54] (a) Geise, B.; Kretzschmar, G. *Chem. Ber.* **1983**, *116*, 3267. (b) Geise, B.; Meisner, J. *Chem. Ber.* **1981**, *114*, 2138.
[55] Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* **1972**, *94*, 9205.

Table 5. Effects on k_{rel} of additions of primary and secondary radicals to alkenes with respect to β-substituents.[53]

Entry	-B =	k_{rel} R· = **133** (65 °C)	k_{rel} R· = **134** (100 °C)	k_{rel} R· = **135** (69 °C)	k_{rel} R· = **136** (20 °C)
A	-CN	2.2	5.1	7.5	24
B	$-COCH_3$	2.3	-	5.8	13
C	$-CO_2CH_3$	1.3	1.9	3.5	6.7
D	-Ph	(1.0)	(1.0)	(1.0)	(1.0)
E	$-OCOCH_3$	-	0.05	-	0.016

Scheme 23



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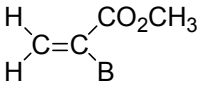

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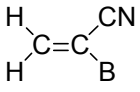

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Table 6. Relative rates of the addition of cyclohexyl radical ($\cdot C_6H_{11}$) to various styrenes, methyl acrylates, and acrylonitriles at 20 °C.[54b,56]

Entry	-B =	**137**	**138**	**139**
A	-CN	66	310	-
B	$-CO_2CH_3$	6.4	150	310
C	-Cl	-	12	31
D	-Ph	0.51	6.4	66
E	-H	0.15	(1.0)	3.6
F	$-CH_3$	0.14	0.75	2.0
G	$-C(CH_3)_3$	-	0.26	0.9
H	$-OC_2H_5$	-	-	-0.5
I	$-OCH_3$	-	0.16	-

To compare α and β effects, an examination of the addition rates of alkyl radicals to 1,1-disubstituted alkenes with the analogous 1,2-disubstituted alkenes was conducted (Table 7, Scheme 24). The most obvious trend is that 1,1-disubstituted alkenes react faster. Also, in addition to polar effects, which seem

[56] (a) Geise, B.; Meisner, J. *Angew. Chem.* **1977**, *89*, 178. (b) Geise, B.; Meisner, J. *Angew. Chem. Int. Ed. Engl.* **1977**, *10*, 178.

to be the dominating factor in k_{rel} regarding β-substituents, this study revealed a significant retardation in addition rates as the steric demand of the α-substituent increased (five orders of magnitude comparing A = H and A = *tert*-butyl, table 7). Only a slight drop in rate regarding the analogous β-substituted alkenes was observed (less than one order of magnitude comparing B = H and B = *tert*-butyl, table 7).

Scheme 24

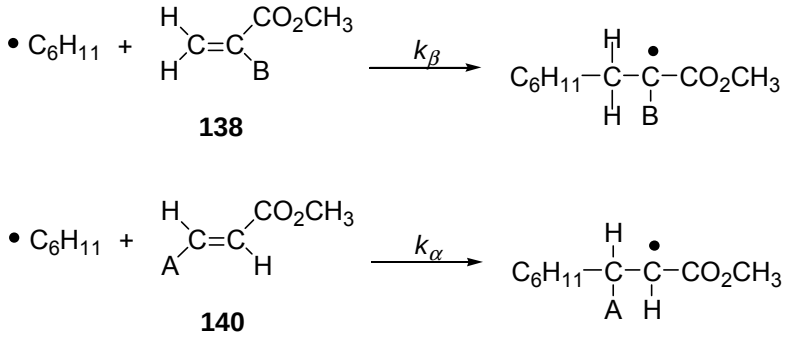


Table 7. Relative rate comparison of α- and β-substituent effects when adding cyclohexyl radical ($^{\cdot}C_6H_{11}$).[53,57]

Entry	-A or -B	k_β	k_α	k_β/k_α
A	-CN	310	6.0	51
B	$-CO_2CH_3$	150	5.0	30
C	-Cl	10	0.067	149
D	-Ph	6.4	0.009	710
E	-H	(1.0)	(1.0)	(1.0)
F	$-CH_3$	710×10^{-3}	11×10^{-3}	65
G	$-C_2H_5$	550×10^{-3}	6.6×10^{-3}	83
H	$-CH(CH_3)_2$	430×10^{-3}	1.5×10^{-3}	290
I	$-C(CH_3)_3$	240×10^{-3}	0.05×10^{-3}	4800

[57] (a) Geise, B.; Lachhein, S. *Angew. Chem*. **1981**, *93*, 1016. (b) Geise, B.; Lachhein, S. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 967.

In summary, the following conclusions can be made regarding α- and β-substituents: the rates of alkyl radical additions to substituted alkenes are substantially affected by the electron withdrawing ability but not the steric bulk of β-substituents, yet both steric and polar factors are important regarding the α–substituent.

Radical reactivity. The effect of substituents bound to the attacking radical were studied with respect to the rates of addition to substituted alkenes. This study demonstrates further the nucleophilic character of carbon-centered radicals by showing that electron donating substituents on the free-radical increase their rates of addition (Scheme 25, Tables 8 and 9).[53,58,59] For example, entries B, C, and D in Table 8 shows how radicals of similar steric bulk demonstrate a gradual increase in rate as the substituents increase in their electron donating ability. In comparison, radicals which contain electron withdrawing substituents are slower in adding to alkenes (compare entries H, I, and J). Tertiary radicals are the most reactive and primary radicals are least reactive. However, when substituents having a large stabilizing effect are present (i. e. phenyl), this trend diminishes (Table 9). In terms of steric effects, the bulk of the adding radical becomes important when adding free-radicals to 1,2-disubstituted alkenes and interactions between the radical and the α-substituent become prominant (Scheme 26; Tables 10 and 11). This effect is largely absent regarding steric interactions between the adding radical and the β-substituent.

To summarize, unless there is a substantially stabilizing substituent on the adding radical, both steric and polar factors exerted by the substituents of the the adding radical become important in the rates of addition to substituted alkenes.

Scheme 25

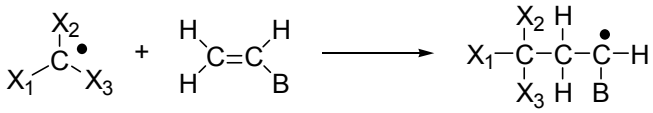


Table 8. Electronic effects on rates of addition of substituted carbon centered free radicals to electrophilic monosubstituted alkenes.[53,58]

Entry	X_1	X_2	X_3	B	k [L·mol^{-1}·sec^{-1}]	Temp (^{o}C)
A	H	H	H	$PO(OC_2H_5)$	2.5 x 10^3	-40
B	CH_3	H	H	$PO(OC_2H_5)$	2.6 x 10^3	-40
C	n-C_3H_7	H	H	$PO(OC_2H_5)$	5.0 x 10^3	-40
D	CH_3O	H	H	$PO(OC_2H_5)$	6.8 x 10^3	-40
E	CH_3	CH_3	H	$PO(OC_2H_5)$	1.2 x 10^4	-40
F	CH_3	CH_3	CH_3	$PO(OC_2H_5)$	5.9 x 10^4	-40
G	n-C_6H_{13}	H	H	CN	5.9 x 10^5	0
H	CH_3	CH_3	H	CN	4.3 x 10^6	0
I	OAc	CH_3	H	CN	1.1 x 10^5	25
J	CN	alkyl	H	CN	10^2 - 10^3	25

Table 9. Addition of benzyl and cumyl radicals to electrophilic monosubstituted alkenes.[59]

Entry	X_1	X_2	X_3	B	k [mol^{-1}·sec^{-1}]
A	Ph	H	H	CO_2Me	430
B	Ph	CH_3	CH_3	CO_2Me	800
C	Ph	H	H	Ph	1100
D	Ph	CH_3	CH_3	Ph	1200
E	Ph	H	H	CN	2200
F	Ph	CH_3	CH_3	CN	2200

[58] (a) Caronna. T.; Citterio, A..; Ghirardini, M.; Minisci, F. *Tetrahedron*, **1977**, *33*, 793. (b) Baban, J. A.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. 2* **1981**, 161.
[59] Gonzalez, C.; Sosa, C.; Schlegel, H. B. *J. Phys. Chem.* **1989**, *93*, 2435.

Scheme 26

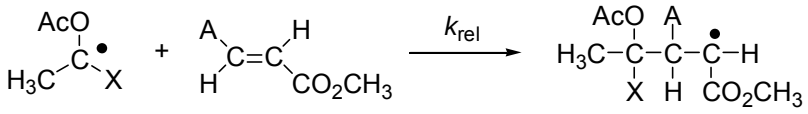


Table 10. Relative rates of addition of sterically different carbon centered free radicals to a monosubstitued electrophilic alkene.[60]

Entry	X	A	k_{rel}
A	CH_3	H	20.0
B	*i*-C_3H_7	H	5.0
C	*t*-C_4H_9	H	1

Table 11. Relative rates of addition of sterically different carbon centered free radicals to a disubstitued electrophilic alkene.[60]

Entry	X	A	k_{rel}
A	CH_3	CO_2CH_3	260
B	*i*-C_3H_7	CO_2CH_3	28.9
C	*t*-C_4H_9	CO_2CH_3	1

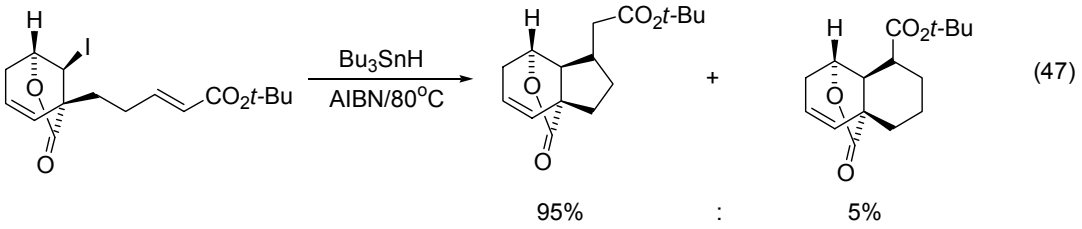
Examples in synthesis. In terms of the synthetic usefulness of adding alkyl free radicals to substituted alkenes, examples of intra- and intermolecular additions have appeared in the chemical literature and are given in equations 47 – 52.[61] Intramolecular processes tend to favor five membered rings over six membered rings (eqs 47 – 49). This is most likely a kinetic phenomenon as outlined by Baldwin's rules.[62] Equation 49 is an apparent violation to α and β effects in that the convention seems to give the least substituted, and most reactive, sp^2 carbon of the alkene the α- designation. In this example, the radical species attaches to

[60] Values for k_{rel} were calculated from data reported in Giese, B. *Angew. Chem. Int. Ed.* **1983**, *22*, 753 (Ref. 53).

[61] (a) Chuang, C. P.; Hart , D. J. *J. Org. Chem*. **1983**, *48*, 1782. (b) Danishefsky, S.; Chackalamannil, B.-J. Uang *J. Org. Chem*. **1982**, *47*, 2231. (c) Ladlow, M.; Pattenden, G. *Tetrahedron Lett*. **1984**, *25*, 4317. (d) Burke, S. D.; Fovare, W. B.; Arminsteadt, D. M. *J. Org. Chem*. **1982**, *47*, 3348. (e) Geise, B.; Kretzschmar, G. *Angew. Chem. Int. Ed*. **1981**, *20*, 965. (f) Huval, C. C.; Singleton, D. A. *Tetrahedron Lett*. **1993,** *34*, 3041.

[62] For a discussion of Baldwin's rules see: Smith, M. In Organic Synthesis McGraw-Hill, Inc.: New York, 1994, pp. 601-611.

the more highly substituted carbon. This may be a consequence of the relative stabilites between two possible products: a fused five- and six-membered bicyclic product and a bridged bicyclic system (in parentheses, eq 49). Intermolecular processes, however, give the expected products where the free radical adds to the α-carbon (eqs 50 – 52). In cases which involve potentially stable free-radical species at the allylic position (Cl in eq 52), the alkene reforms after the addition at the α-carbon.



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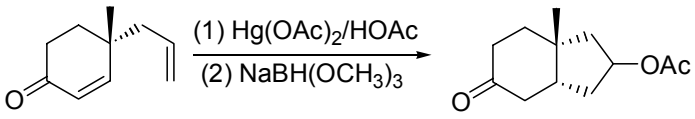

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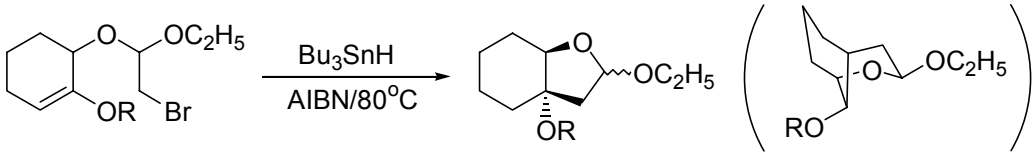

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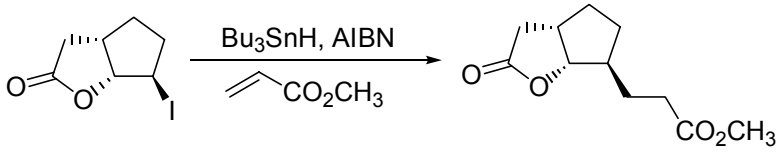
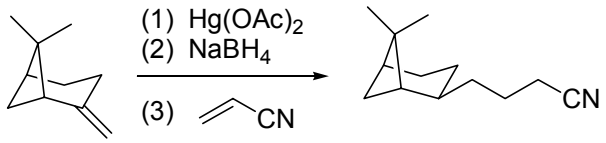
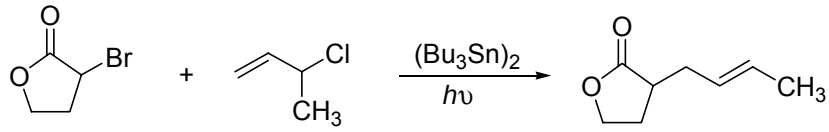


(50)



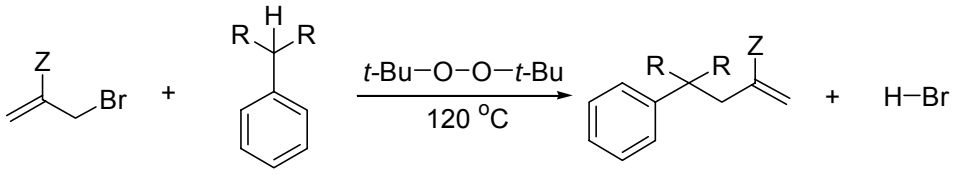
(51)



(52)

Additions of alkyl radicals to allyl bromides. The discovery of a new free radical based condensation reaction involving allyl bromides by Tanko and Sadeghipour provided a means for a new, potentially stereoselective, radical addition to carbon-carbon double bonds which does not rely on the use of toxic metals for free radical generation.[63] A summary of the yields using a variety of substituted allyl bromides in the presence of benzyl and cumyl radicals is shown in Table 12. The general reaction is shown in Scheme 27.

Scheme 27



[63] Tanko, J. M.; Sadeghipour, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 159 - 161.

Table 12. Summary of free-radical additions to various allyl bromides.[63,64]

Z	% Yield (Benzyl Radical)	% Yield (Cumyl Radical)
-H	45	not determined
-Ph	92	100
$-CO_2Et$	58	48*
-CN	66*	80

*$(BzO)_2$ used as an initiator at 80 ^oC.

Our aim was to expand upon earlier research by: 1) developing generalized, efficient syntheses[65] of various allyl bromides with Z groups suitable for exploring stereoselective free radical additions and 2) to study this addition/elimination reaction in terms of its mechanism and synthetic usefulness. As will be explained in much more detail later in this account, these goals were realized in that we were able to develop and optimize the synthesis of various allyl bromides which contain substituents that are commonly used as chiral auxiliaries (Z = amide and oxazolidinone). Also, the synthetic usefulness of the addition of carbon-centered radicals to these compounds was explored in terms of yield. The stereochemical potential of this reaction remains unknown because only achiral model compounds were studied. Additionally, we reinforced previously observed trends regarding this addition/elimination reaction by means of chain length and competition experiments. And finally, new insight into the mechanism of this reaction was gained by studying additions to trisubstituted alkenes/allyl bromides.

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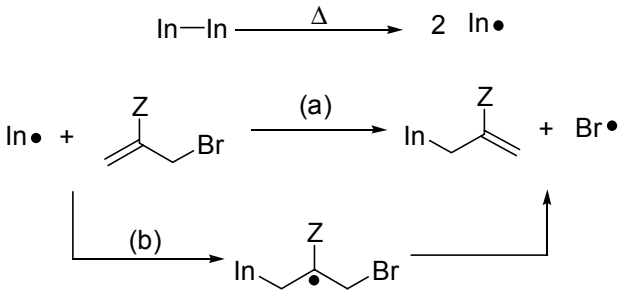
[64] Ph.D Thesis of Mitra Sadeghipour, Virginia Polytechnic Institute and State University, 1998.

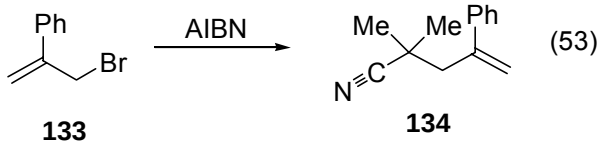
[65] By "generalized route", it is meant that a variety of compounds might be produced from common starting materials using common reagents and reactions. "Efficient syntheses" are often thought of as those which require only a few, simple synthetic steps using inexpensive starting materials and reagents.

Mechanistic details. The treatment of allyl bromides in toluene or cumene with common free radical initiators, such as AIBN, benzoyl peroxide, and di-*tert*-butyl peroxide, gave way to a chain process where bromine radical acts as the chain carrier. Certain details, however, regarding the mechanism are unclear. For example, there is little evidence regarding the mode of initiation. Control experiments have shown that homolysis of the allylic carbon-bromine bond does not occur at elevated temperatures in the absence of an initiator. In other words, this reaction is not self-initiating. Free-radicals generated from AIBN, benzoyl peroxide, and di-*tert*-butyl peroxide must therefore be ultimately responsible for the generation of the bromine radical. A few possibilities regarding the initiation and bromine radical generation are shown in Schemes 28 and 30. One such possibility involves the direct addition of the initiating species to the carbon-carbon double bond. The result of this addition may be such that a two-step process is responsible for the generation of bromine radical (Scheme 28, route b). This route may involve a resonance stabilized free-radical (Z = -CN, -CO_2R, or –Ph) followed by the reformation of a carbon-carbon double bond and a bromine free radical.

Scheme 28

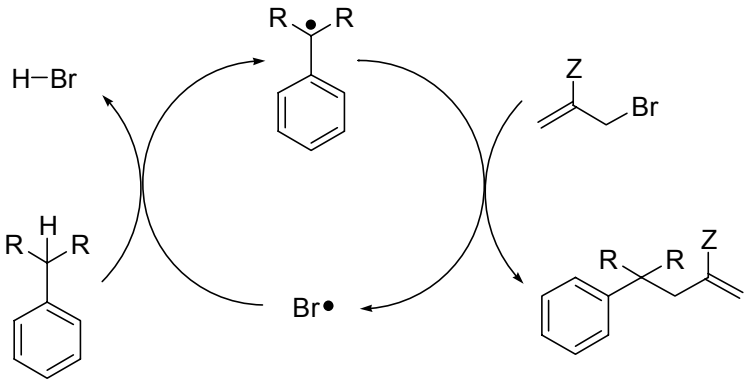


An alternative mechanism may simply involve a one-step concerted addition/elimination process (Scheme 28, route a). It has been shown that when AIBN is used as the initiator in the presence of α-bromomethyl styrene (Z = phenyl) addition of the 2-cyano-2-propyl radical to the carbon-carbon double bond occurs such that **133** is formed in approximately 13% yield (eq 53). However, analogous products were not observed when benzoyl peroxide or di-*tert*-butyl peroxide were used. Once the bromine radical has been formed, it is available to abstract a hydrogen radical from toluene or cumene which may then add to the allyl bromide and ultimately generate an additional bromine radical (Scheme 29).

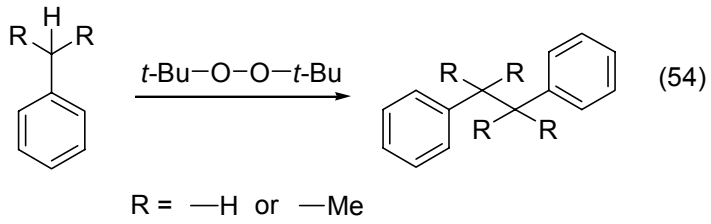


133 **134** (53)

Scheme 29

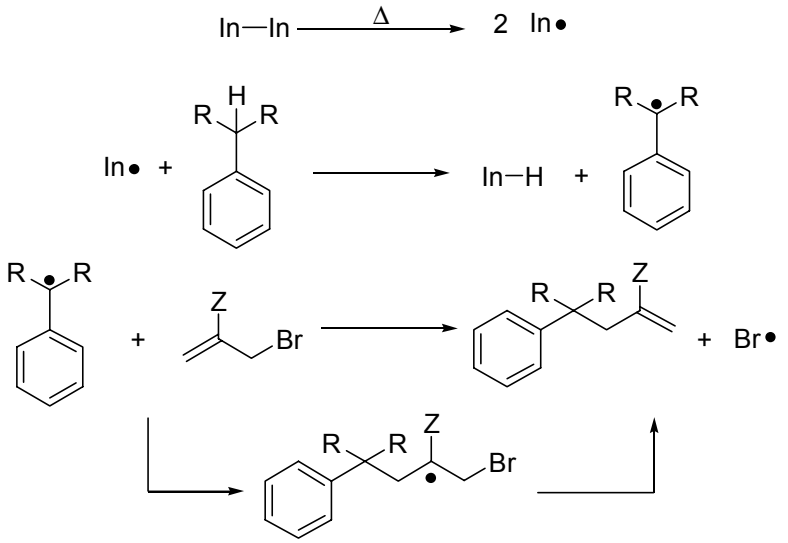


Another possibility regarding the initiation involves the direct generation of benzyl or cumyl radical from hydrogen radical abstraction by the initiating species (Scheme 30). It has been observed that 1,2-diphenylethane (bibenzyl) and 2,2-dimethyl-2,2-diphenylbutane (bicumyl) can be made by simply heating either toluene or cumene in the presence of an initiator (eq 54). These products were observed while conducting various additions to substituted allyl bromides, but it is not clear if the alkyl radicals are initially formed through hydrogen abstraction by initiator radicals or bromine radicals or by a combination of these two processes.



(54)

Scheme 30



Regardless of how bromine radicals are formed, there is good evidence suggesting that they act as a chain carrier in this process. In terms of the ability of bromine to abstract hydrogen radicals to form benzyl radicals, the rates of rates of abstraction are such that 3^o benzyl > 2^o benzyl > 1^o benzyl (for the reaction between bromine radical and toluene, the rate of hydrogen radical abstraction has been measured to be 10^5 $M^{-1}\cdot sec^{-1}$ at 40 ^oC).[66] Thermodynamically, because the bond dissociation energy of HBr is about 87 kcal/mol and that of benzylic hydrogens (PhC**H**R_2) are between 84 and 88, the process in essentially thermoneutral.[67]

By means of a competition experiment involving the selective addition of benzyl and cumyl radicals toward α-bromomethyl styrene, Sadeghipour showed that the selectivity increased favoring the addition of cumyl radical as the amount of HBr scavenger (1,2-epoxybutane) decreased (Scheme 31, Table 13). If halohydrin formation is a fast process, the data suggest that hydrogen radical abstraction is a reversible process such that at low HBr scavenger concentrations the relative amounts of products do not reflect the *initial rates* of hydrogen abstraction, but rather an equilibrium. The initial rate of hydrogen radical abstraction is more accurately expressed by eliminating, or dramatically retarding, the reverse process. Sadeghipour observed that selectivity decreases as the molar equivalents of acid scavenger increases eventually becoming constant at one molar equivalent. With sufficient amounts of acid scavenger

[66] Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry," 3rd ed. Harper & Row Publishers, New York, 1987.
[67] Anderson, H. R., Jr.; Scherage, H. A.; VanArtsdalen, E. R. *J. Chem. Phys*. **1953**, *21*, 1258.

present, thus eliminating the reverse process, the carbon-centered free radicals formed from hydrogen radical abstraction are now available to add to any allyl bromide species present resulting in more bromine radical and therefore continuing the chain. Although the rates of hydrogen abstraction by bromine radical is expressed in terms of adduct formation, it should be noted that this selectivity (3^o benzylic : 2^o benzylic : 1^o benzylic) was reported to be 59:25:1 in a previous study.[68]

Scheme 31

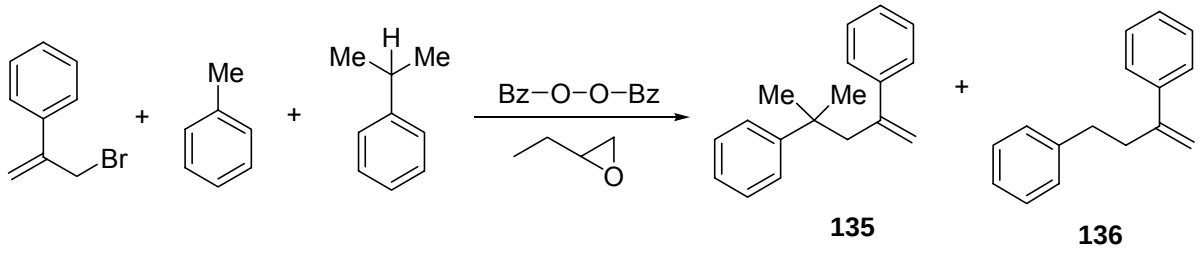


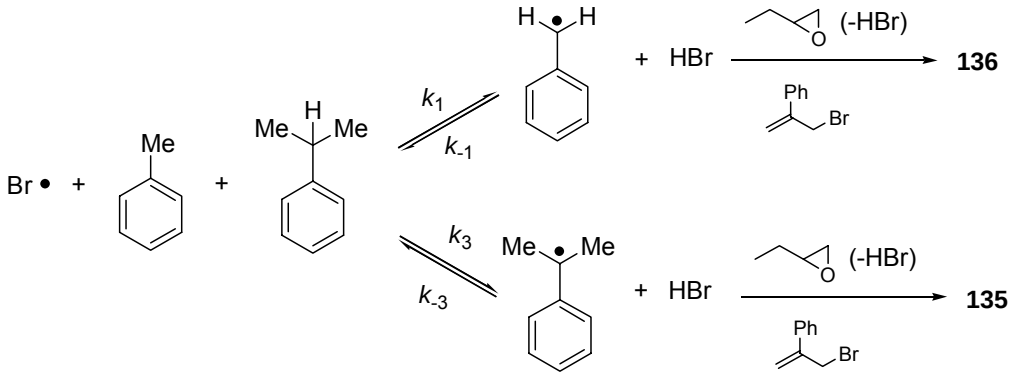
Table 13. Competition experiments involving cumyl and benzyl free-radicals to α-bromomethyl styrene in the presence of varying amounts of HBr scavenger.[64]

Equiv. 1,2-epoxybutane (with respect to α-bromomethyl styrene)	R($3^o/1^o$) at 80°C
0.05	50
0.10	48
0.50	34
1.10	25
2.00	25

*0.2 equivalents $(BzO)_2$ used as an initiator at 80 °C.

[68] (a) Russell, G. A.; Desmond, K. M. *J. Am. Chem. Soc*. **1963**, *85*, 3139. (b) Friedrich, S. S.; Friedrich, E. C.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem*. **1969**, *34*, 900.

Scheme 32

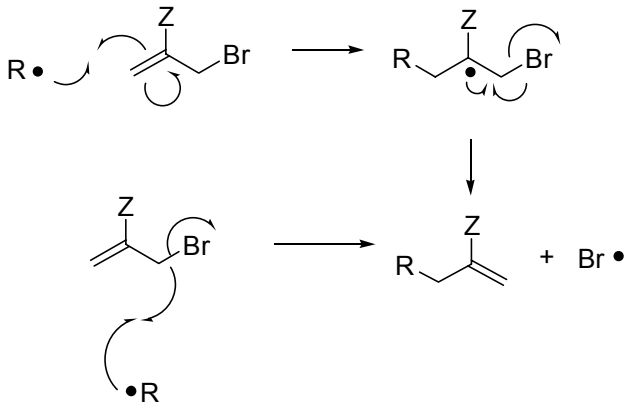


$$R(3^o/1^o) = \frac{3k_3}{k_1} = \frac{[\mathbf{135}]_{final} \times [PhCH_3]_{init.}}{[\mathbf{136}]_{final} \times [PhCH(CH_3)_2]_{init.}} \times 3$$

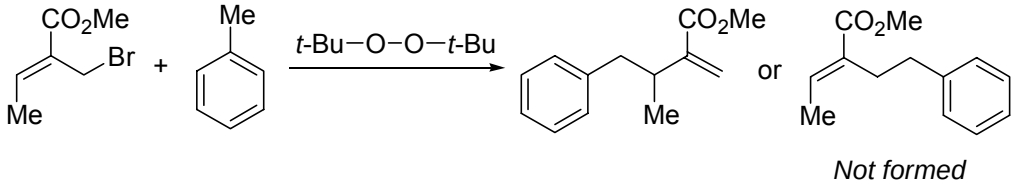
One particularly important mechanistic aspect that had not been addressed involves evidence demonstrating that alkyl free radicals add to the double bond of allyl bromides rather than directly displacing the bromine atom (Scheme 33). Although the two mechanisms are different, they give identical products. In lieu of evidence suggesting some sort of product rearrangement, it has recently been shown that the addition occurs at the double bond rather than at the allylic carbon. This was evident from the ^{1}H-NMR of the major product resulting from the reactions between benzyl radical and methyl substituted allyl bromides such as that shown in Scheme 34 using di-*tert*-butyl peroxide as an initiator. This reaction produced the 2,2-disubstituted alkene exclusively. There was no evidence for the formation of the other possible product indicating that direct displacement of bromine radical at the allylic carbon does not occur. This result is consistent with that observed by Huval and Singleton (eq 52).[61f] The

results of free radical additions to this and similar methyl substituted allyl bromides will be described in more detail later.

Scheme 33



Scheme 34



Stereoselective aspects. One of the goals of this research was to explore the viability of this reaction in terms of stereoselectivity. To set the groundwork, it was decided to study the addition of prochiral carbon centered radicals to simple allyl bromides as well as the addition of prochiral radicals to prochiral methyl bearing allyl bromides (Scheme 35). Additionally, it was hoped that by combining a prochiral carbon-centered radicals with prochiral allyl bromides, two

stereocenters could be formed in one reaction which might ultimately provide an alternative to asymmetric aldol additions. In order to provide the necessary chiral environment to bring about absolute stereoselectivity, the allyl bromides shown in Figure 20 were considered to be appropriate models in that substituted oxazolidinones and pyrrolidine amides have proven useful as chiral auxiliaries.[69]

Scheme 35

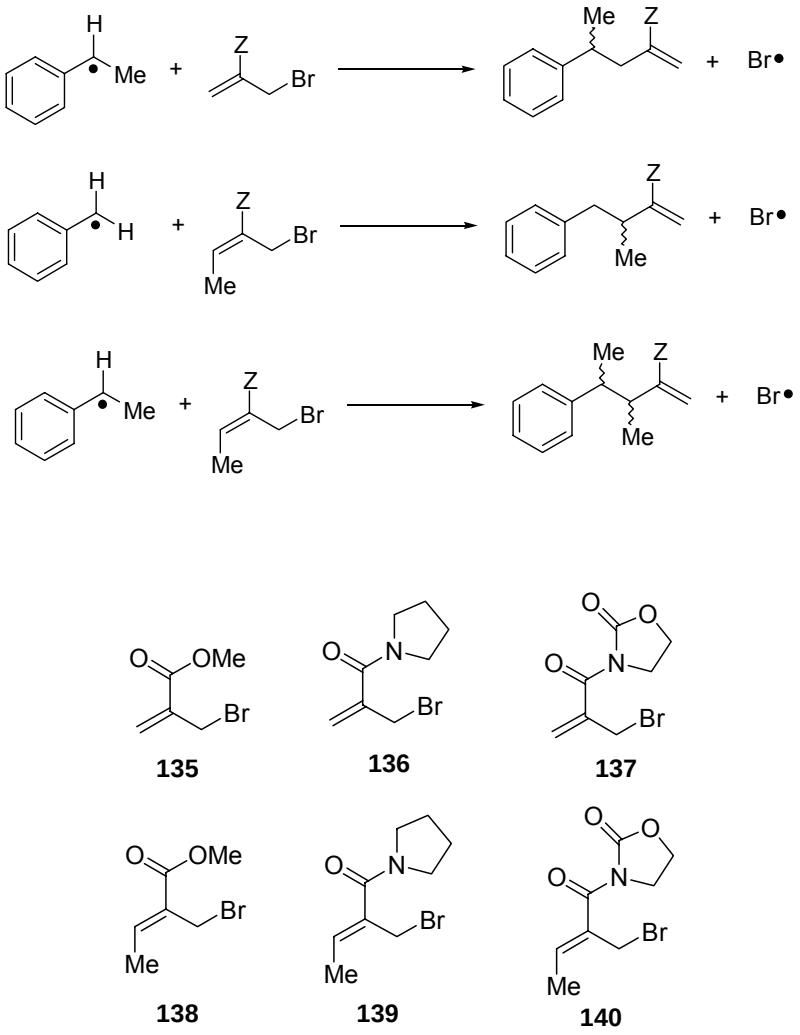
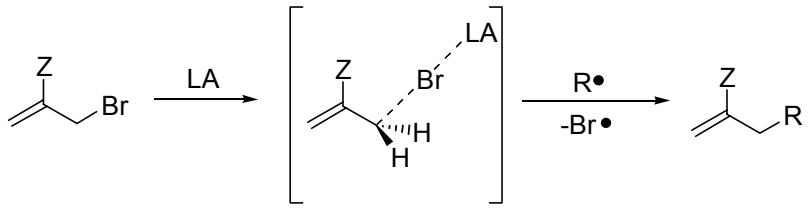


Figure 20. Model compounds for asymmetric free radical addition studies.

[69] Compare to Fig. 14 and eqs 32 & 33.

All of the compounds in Figure 20 could be studied using an oxophilic metal with chiral ligands in a reagent controlled approach similar to that illustrated earlier (eq 23). Two issues that must be addressed regarding this approach are the coordination of metallic species to the bromine as well as the number of molar equivalents of chiral reagent with respect to the allyl bromide. The former concern may very well cause difficulties when using Lewis acids for a reagent controlled approach because of the possibility of removing the bromine to form stable allylic cations in a Friedel-Crafts fashion. Also, certain metals might coordinate to the bromine and weaken the bromine carbon bond, thereby activating the species for direct displacement of the bromine by free radicals (Scheme 36). In the event that a Lewis acidic metal is found that preferentially coordinates to the oxygen of the model compounds over the bromine, it would be important to determine the number of molar equivalents

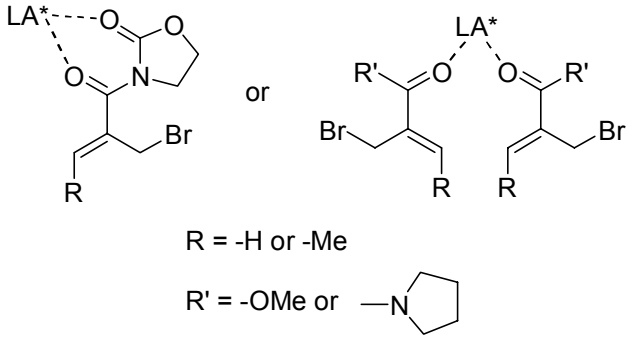
Scheme 36



necessary for good stereoselectivity. For example, when bidentate allyl bromides such as compounds **137** and **140** in Figure 20 are used, equimolar amounts of Lewis acidic reagent and allyl bromide would be necessary if only two coordination sites are available on the metal (Scheme 37). However, it might be

possible to use substoichiometric amounts of chiral reagent in the presence of the monodentate allyl bromides. If two coordination sites were available on the metal, then only 0.5 molar equivalents would be required (Scheme 37).

Scheme 37

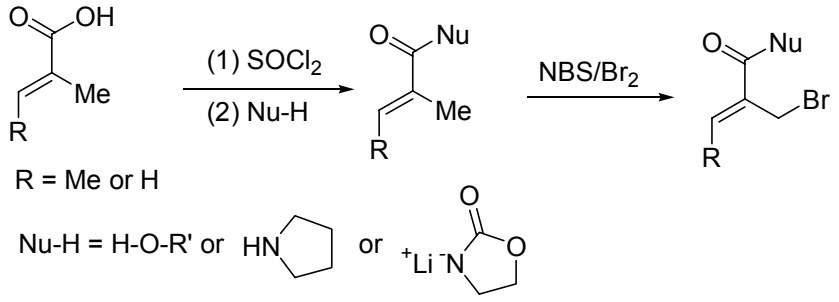


Compounds **136** – **137** and **139** - **140** in Figure 20 are good models for exploring possible chiral auxiliary mediated stereocontrol. A variety of chiral oxazolidinones have appeared in the literature regarding stereoselecive aldol and free radical additions (Figure 14). Also, Whitsell's pyrrolidine (C_2 symmetric 2,5 – dimethylpyrrolidine) has been shown to provide for moderate absolute stereocontrol when adding free radicals to olefins.[70] Additionally, an approach similar to that used by Sibi (eq 33)[37] might also be employed here in the event an appropriate Lewis acid is found.

[70] Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Geise, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791.

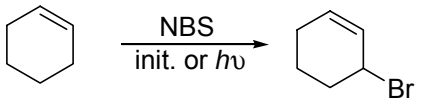
Results: Development of efficient generalized syntheses of allyl bromides.[65] In an effort to develop an inexpensive and general method for synthesizing a variety of substituted allyl bromides, several routes were considered. What might be considered to be a very inexpensive, direct, and general route to synthesizing a wide variety of allyl bromides was attempted by first refunctionalizing methacrylic acid (R = Me, Scheme 38) followed by the free radical addition of bromine to the allylic carbon via *N*-bromosuccinimide (NBS). Although the formation of the acrylic amides was high yielding (92% from

Scheme 38

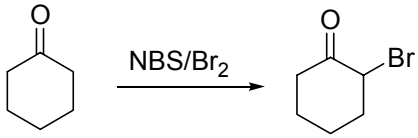


methacrylic acid), the free radical bromination with NBS was entirely unsuccessful, even with the addition of a catalytic amount of Br_2. The NBS bromination of methylmethacrylate also failed. To our knowledge, free radical brominations of compounds of the type shown in Scheme 38 have not appeared in the literature although examples of additions to alkyl substituted alkenes and heterolytic additions of bromine α to the carbonyl of non-conjugated carbonyl

containing compounds are prevalent (eqs 55 and 56).[71] Because of these



(55)



(56)

unsuccessful attempts to synthesize the simple allyl bromides, the methyl substituted analogs using tiglic acid (R = Me, Scheme 38) as a starting material, were not attempted. Had free radical bromination been possible, reactions involving the more highly substituted alkene would have certainly resulted in a mixture of brominated products reducing the overall yield of the desired product. This strategy, therefore, was quickly abandoned.

Because there are reports of being able to produce methyl ester subsitituted allylic alcohols by means of a vinyl carbanion equivalent (Scheme 39), we thought to use this strategy to produce a variety of allyl bromides. The syntheses of methyl ester substituted allyl bromides (Nu = -OMe) using the Baylis-Hillman reaction (eq 28,Scheme 6) to generate the vinyl anion equivalent have been reported in the literature giving modest overall yields from methylacrylate (62% with R = H[72] 68% and Me[73]). Regardless of the stereochemistry of the allylic alcohol, the *Z*- diastereomer is produced exclusively

[71] (a) Djerassi, C. *Chem. Rev*. **1948**, *43*, 271. (b) Catch, J. R.; Hey, D. H.; Jones, E. R. H.; Wilson, W. J. *J. Am. Chem. Soc*. **1948**, *70*, 276.
[72] (a) Drewes. S. E.; Loizou, G.; Roos, G. H. P. *Synth. Comm*. **1987**, *17*, 291. (b) Drewes, S. E.; Emslie, N. D. *J. Chem. Soc. Perkin Trans. I*, **1982**, 2079.
[73] Roush, W. R.; Brown, B. B. *J. Org. Chem*. **1993**, *58*, 2151.

from the allylic alcohol via an S_N2' displacement of involving the alcohol oxygen and the sulfur of the Me_2S (Figure 21).[74]

Scheme 39

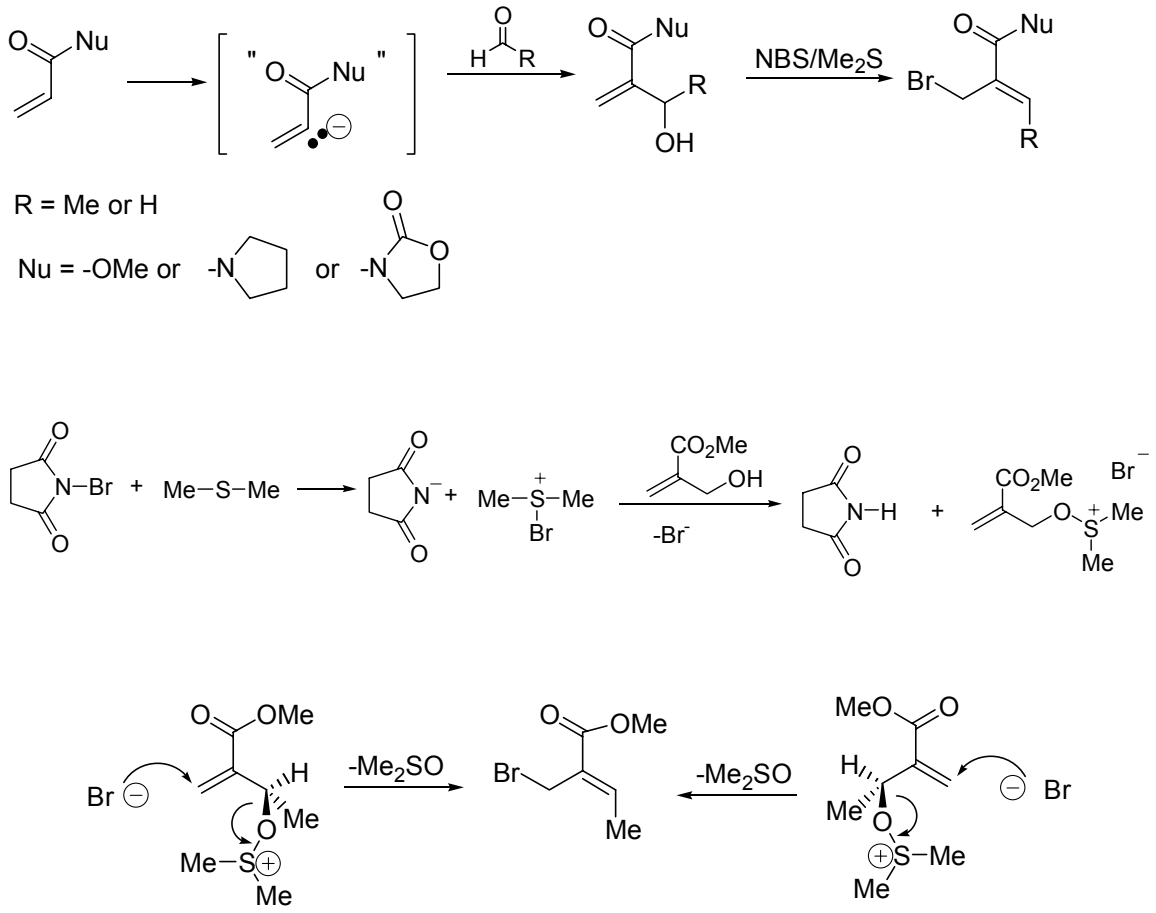


Figure 21. S_N2' displacement of Me_2SO demonstrating the formation of the *Z*- diastereomer of the product regardless of the stereochemical configuration of the starting material.

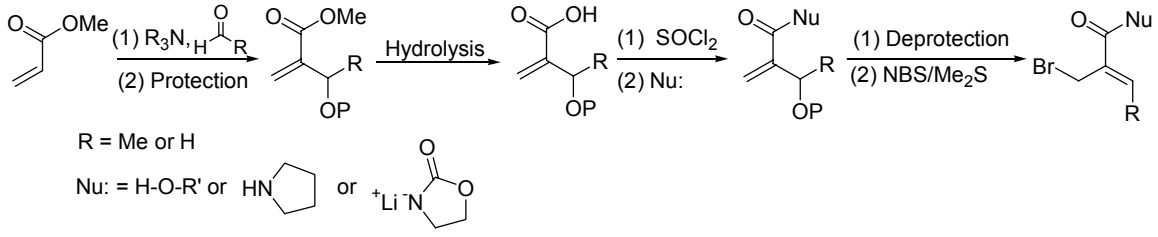
The idea of using a vinyl carbanion equivalent was attractive in that, by starting with the appropriate acrylic ester, amide, or oxazolidinone, the possibility existed to convert these compounds to the desired allylic alcohols, followed by conversion to the allyl bromide. This Baylis-Hillman route was successful with

[74] Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

acrylic esters (80% yield from the methylacrylate when R = Me and 61% when R = H), but failed when attempting the synthesis of the analogous amides and oxazolidinones. It is believed that, because the mechanism for the Baylis-Hillman reaction involves the addition of a tertiary amine to the acrylic system in a Michael fashion, acrylic esters are susceptible to such an addition yet acrylamides are not because they are not good Michael acceptors.[75]

Because of the success experienced with the Baylis-Hillman reaction involving methylacrylate, it was thought that the necessary amide and oxazolidinone substituted allyl bromides might be synthesized by first hydrolyzing the ester moiety after protection of the hydroxyl (Scheme 40). With the hydroxyl protected acrylic acid in hand, conversion to the desired compounds would be trivial. Unfortunately, all attempts using both acid and base catalyzed hydrolysis under mild conditions failed and under harsh conditions, the protecting groups, trimethylsilyl, tert-butyldimethylsilyl, and tert-butyldiphenylsilyl were removed prior to hydrolysis.

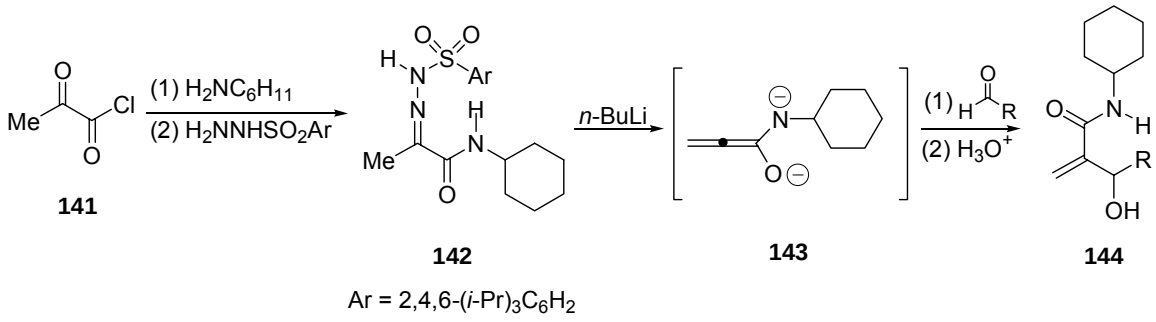
Scheme 40



[75] Correspondence with Dr. Michael Calter, The University of Rochester.

An alternate approach using a vinyl carbanion equivalent strategy involved a strategy developed by Adlington and Barrett (Scheme 41).[76] In this particular investigation, it was found that treatment of the hydrazone **142** with 3.2 – 3.4 molar equivalents of *n*-butyllithium gave the dianionic allenyl intermediate **143** which reacted with a variety of aldehydes to give **144**. It was hoped that, rather than using the somewhat exotic 2,4,6-triisopropylbenzenesulphonylhydrazone that the aforementioned investigators used, we might simply use the much less expensive tosylhydrazone analog and 2.0 – 2.5 molar equivalents of *n*-butyl lithium (Scheme 42). This route also failed, giving only complex product mixtures. It is not clear whether this failure was due to the absence of an amide hydrogen which is necessary for the production of a dianionic species similar to **143**, or the use of the simpler hydrazone. Interestingly, the use of ester analogs for this reaction, which are electronically similar to the secondary amides, also failed according to their account.[76]

Scheme 41

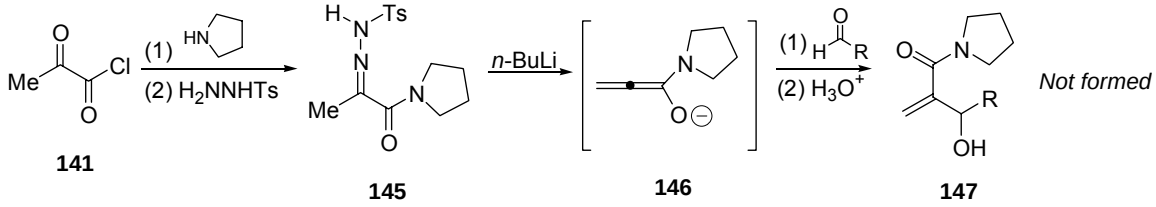


141 **142** **143** **144**

Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

[76] Adlington, R. M.; Barrett, A. G. M. *Tetrahedron*, **1981**, *37*, 3935.

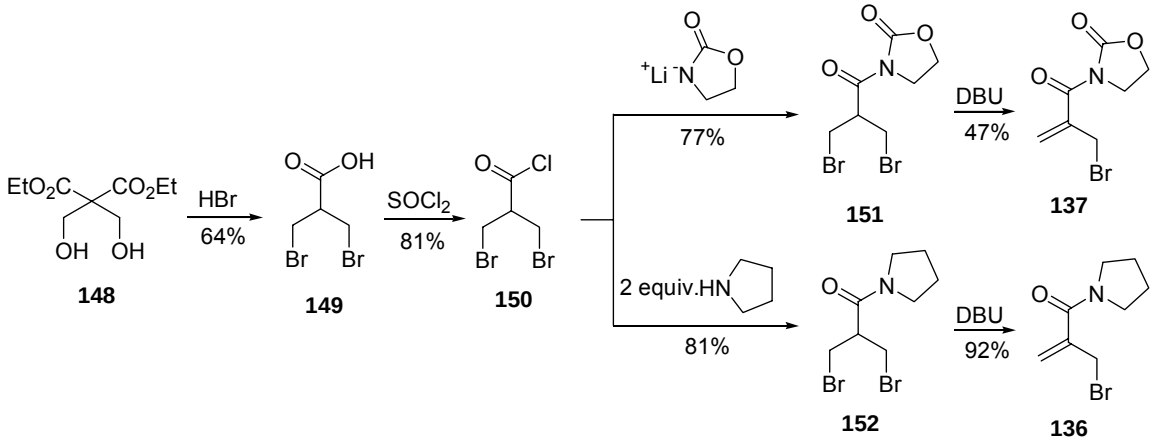
Scheme 42



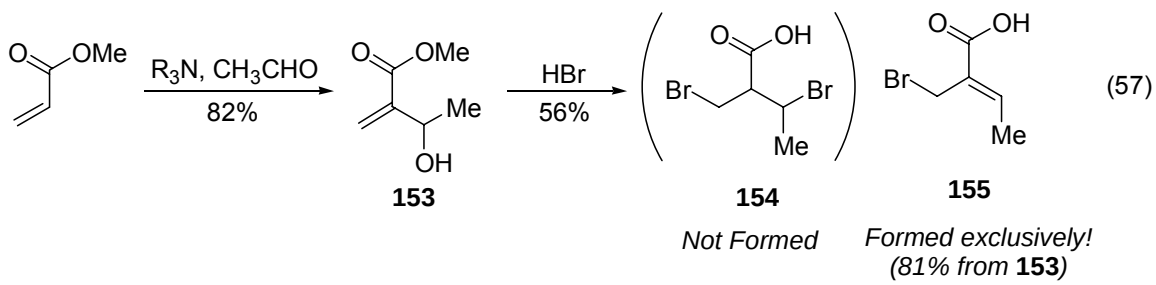
We abandoned the vinyl carbanion methodology in favor of the more straight forward elimination pathway shown in Scheme 43. Prior to our attempts at using a vinyl carbanion strategy,[77] the literature had revealed an existing synthesis of amide substituted allyl bromides. Because of the expense of the starting material **149** (Aldrich $14.00/gram) and thus did not fit our stated goal as an *efficient* route, this synthesis was not attempted. However, we soon discovered that this material is easily synthesized in 64% yield by treating diethyl bis(hydroxymethyl)malonate **148** (Aldrich $1.08/gram) with 15 equiv. of HBr.[78] This route was completely successful giving overall yields of 63% (**136**) and 22% (**137**) from **149**. Finally, a general route which produced all of the desired simple allylbromides had been developed. Although it was trivial to produce the methyl ester substituted allyl bromide by the established method (Scheme 39, Nu = -OMe), more complicated esters could be synthesized by using the appropriate alcohol in a synthetic route similar to that of Scheme 43.

[77] Knochel, P.; Normant, J. F. *J. Organomet. Chem*. **1986**, *30*, 1.
[78] Singh, R.; Whitesides, G. M. *J. Am. Chem. Soc.***1990**, *112*, 1190.

Scheme 43



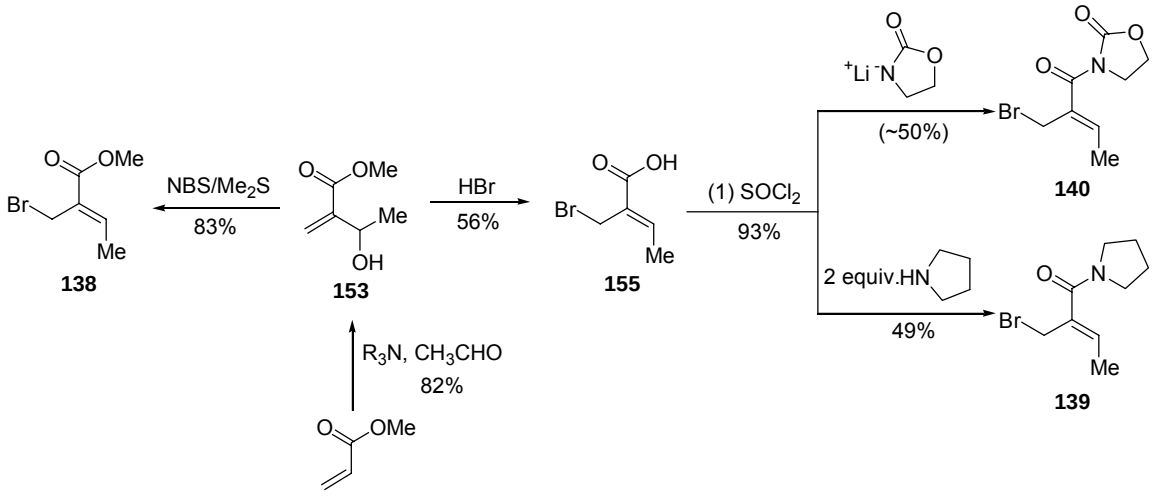
In order to synthesize the methyl substituted allyl bromides **138** – **140**, we decided to treat **153** with 15 molar equivalents of HBr in the hope that a variety of dibrominated products would result. It was thought that by studying the product distribution of this reaction, we might control the thermodynamic and kinetic factors such that **154** would be formed preferentially and, by using an appropriate base, the more highly substituted olefin might be produced via an elimination reaction. To our delight, it was discovered that treatment of **153** with a 15 molar excess of HBr produced **155** exclusively in high yields (eq 57)! This compound was easily refuntionalized into the desired amide (Scheme 44). Thus, from



(57)

methylacrylate, **138**, **139**, and **140** were produced in 68%, 17%, and 20%[79] percent yields respectively (Scheme 44). Regarding **140**, purification by column or preparative thin-layer chromatography was impossible. The compound proved unstable to silica gel and racemization about the carbon-carbon double bond was observed when alumina was used as a chromatographic medium. Additionally, the compound could not be purified by distillation, even at reduced pressure. Thus, with the exception of **140**, generalized, efficient routes have been developed to generate all of the desired allyl bromides.

Scheme 44

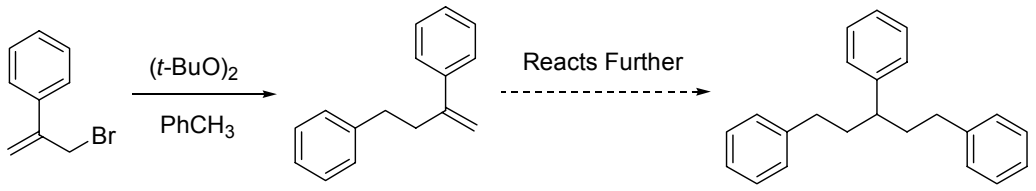


Results: Reactions of Allyl Bromides with Carbon Centered Free-Radicals. With a variety of substituted allyl bromides in hand, their reactivity toward benzyl

[79] Due to its instability to silica gel, this product was not isolated. Thus, the yield is estimated.

and phenethyl radicals was studied. Previously,[64] it was found that the optimal conditions required that the reactions be run in degassed pressure tubes at 120 ^{o}C. Such reactions involved the substrate, the benzyl radical precursor as the solvent (toluene or cumene), 0.2 molar equivalents of *tert*-butylperoxide, and an appropriate HBr scavenger. We extended the previous study in terms of the chain length and competition experiments that were performed, as well as, the utility of these reactions in terms of their synthetic usefulness.

In a typical reaction of the type just described, the product yield increases steadily and rapidly as a function of time. It became apparent that from overexposure to these reaction conditions caused the product to react further with benzyl radical. The reaction of bromomethylstyrene with benzyl radical is shown in equation 58. The result of this study and a plot of mmols of product vs. time are shown in Table 14 and Figure 22.



(58)

Table 14. Summary of product formation as a function of time with regards to the addition of benzyl radical to α-bromomethylstyrene.[65]

Reaction Time (min.)	Unreacted Bromo-methylstyrene (mmol)	Product (mmol)	*t*-BuO· produced (x 10^3) mmol
15	0.47	0.11	0.36
30	0.42	0.17	0.70
60	0.33	0.24	1.4
150	0.22	0.29	3.6
300	0.22	0.36	6.9
600	0.14	0.38	14
1158	0.16	0.48	26
2160	0.04	0.49	45
4320	0	0.41	82
8642	0	0.35	134

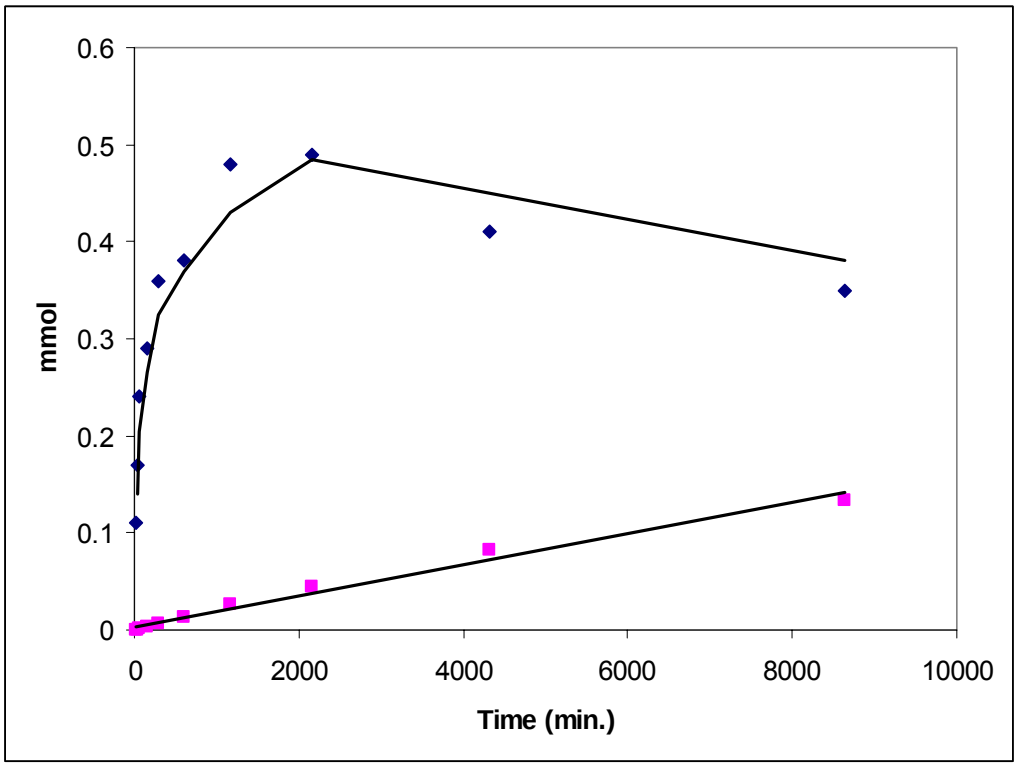


Figure 22. Product formation (♦) and initiating radical (■) formation as a function of time.

For the purpose of measuring a chain length for such reactions, the initial chain length was measured taking into account only the formation of product prior to reacting further with additional benzyl radical. A good estimate of the initial chain length is obtained by dividing the amount of product formed at a particular time by the amount of initiating radical formed at that time ($P/I^{\cdot}$). By plotting log ($P/I^{\cdot}$) vs. time and extrapolating to time = 0, the initial chain length can be estimated. The amount of initiating radical, in this case di-*tert*-butylperoxide, at any time can be calculated by using the well established rate constant for its first order degradation at 120 ^{o}C ($k = 1.72 \times 10^{-6}\ s^{-1}$) (Scheme 45).[58] Thus, for bromomethylstyrene, the chain length was calculated to be $10^{2.561}$ or 364 (Figure 23). Conceptually, chain length may be thought of as the number of product-yielding cycles prior to a termination step (Figure 24). Chain length may also be thought of as the number of propagation steps per initiation step.

Scheme 45

$$I\text{—}I \xrightarrow{k} I\bullet$$

$$[I_2]_t = [I_2]_o e^{-kt}$$

$$[I^{\cdot}] = 2 \times ([I_2]_o - [I_2]_t)$$

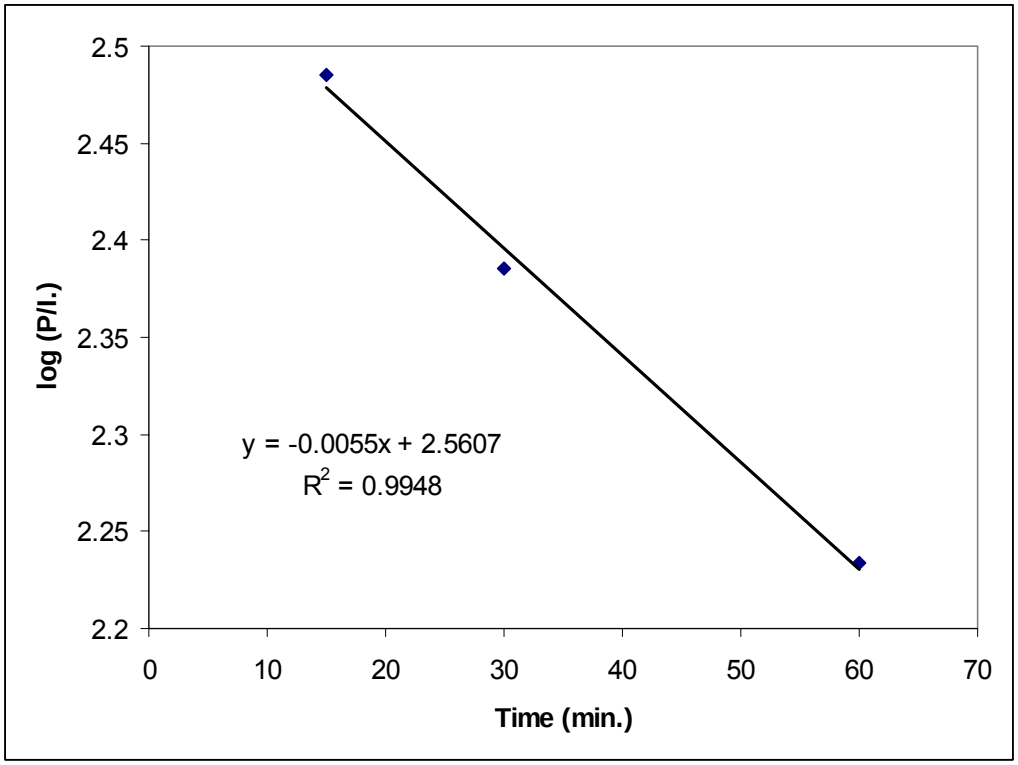
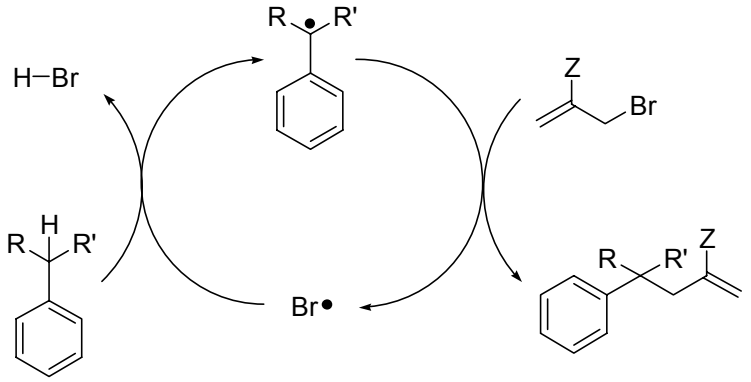


Figure 23. Chain length experiment for the addition of benzyl radical to α-bromomethylstyrene.



R = R' = H: benzyl
R = H, R' = Me: phenethyl
R = R' = Me: cumyl

Figure 24. Chain process demonstrating the feasibility of bromine radical acting as a chain carrier.

Preparative Scale Free-Radical Additions to Allyl Bromides. Prior to each of the chain-length experiments outlined in the previous section, the reactions (eqs. 60-67) were carried out on a preparative scale to determine the synthetic usefulness of such reactions, for product characterization and to generate GC response factors. In each case, 15-20 mL of a 0.15 M solution of one of the allyl bromides **135-140** in either toluene or ethylbenzene as the solvent/free radical precursor with 1.1 equiv of K_2CO_3 were placed in a pressure tube along with 0.5 equiv of di-*tert*-butyl peroxide. The tubes were degassed by means of three to five freeze-pump-thaw cycles. The tubes were heated in a constant temperature oil bath at 120 ^{o}C for one hour after which, the tube was cooled under cold tap water to stop the reaction and the resulting solution was analyzed by GC. If the GC analysis revealed the presence of allyl bromide, the reaction mixture was treated with an additional 0.5 equiv of initiator, degassed and heated to 120 ^{o}C for an additional hour. This process was repeated until no more allyl bromide was apparent by GC. The solvent was removed by vacuum distillation and the remaining oil was purified by preparative thin layer chromatography. The results of these preparative experiments in comparison to the yields calculated from the chain length experiments are given in Table 20 (Scheme 45). It is important to note that by adding 0.5 equivalents of initiator every hour in a preparative experiment, by the end of the experiment, the amount of initiator is in excess with respect to the allyl bromide. It is therefore difficult to compare the yield of any chain length experiment to its respective preparative experiment. However, the

moderate yields observed from the preparative experiments (53% - 72%) are promising in terms of the synthetic usefulness of this experiment.

Scheme 45

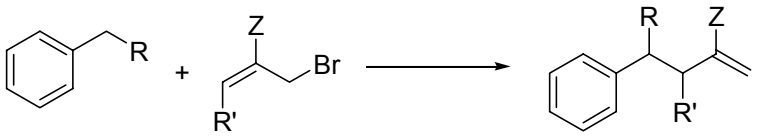
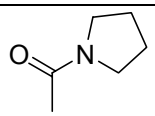
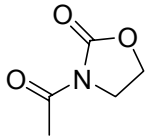
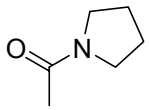
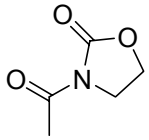
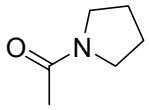


Table 20. Yields from additions of benzyl and phenethyl radical additions to various allyl bromides.

Eqn #	-R	-R'	-Z	Yield (Time) Chain Length	Yield (Time) Preparative
60	-H	-H	$-CO_2Me$	23.8% (90 min.)	63% (3 hr.)
61	-H	-H		15.2% (90 min.)	72% (4 hr.)
62	-H	-H		9.2% (90 min.)	53% (8 hr.)
63	$-CH_3$	-H	$-CO_2Me$	29.2% (90 min.)	57% (3 hr.)
64	$-CH_3$	-H		11.3% (90 min.)	66% (5 hr.)
65	$-CH_3$	-H		2.7% (90 min.)	59% (10 hr.)
66	-H	$-CH_3$	$-CO_2Me$	5.7% (90 min.)	57% (13 hr.)
67	-H	$-CH_3$		7.8% (90 min.)	69% (12 hr.)

Discussion. In comparing the initial chain length measurements regarding the addition of benzyl radical to various allyl bromides, it is evident that there is a correlation between the length of the chain process and the electron withdrawing capacity of –Z (Scheme 46, Table 21).[80] When no electron-withdrawing substituent is present (-Z = H), the chain length is at a minimum. This is probably because radical additions to unactivated substates are expected to be slow. This may also indicate that termination processes are quite competitive with propagation in the absence of an electron withdrawing group. By introducing functional groups that are in conjugation with the alkene moiety of the allyl bromide, the chain becomes more efficient. This is consistent with the β-effect observed when adding free radicals to various mono- and disubstituted alkenes (Schemes 22 and 23, Tables 5 and 6).

In terms of the effect on rate with respect to the steric bulk of –Z, it is difficult to argue whether steric effects play a greater role in the additions of radicals to allyl bromides compared to additions to simpler mono- and disubstituted alkenes. As was discussed earlier, β-effects seem to be dominated by the electron withdrawing or donating ability of the substituent rather than its bulk. In the case of additions to allyl bromides however, especially when –Z is an ester or an amide, steric effects may play a greater role. For example, one might argue that as the bulk of the amide or ester increases, the alkene/carbonyl relationship is more likely to take on an *s-trans*-like configuration (Figure 47). This would most likely retard the addition rates in that the bulk of –Z would inhibit

[80] For data and plots pertaining to chain-length experiments using oxazoline, amide, and methyl ester containing allyl bromides, see Appendix A.

the approach of any free-radicals. Additionally, the bulk of the ester or amide might also affect overlap of the p-orbitals contained within the carbon-carbon double bond and the carbonyl as a result of the steric interaction between -R and the vinyl hydrogens. As a result of this loss of conjugation the overall electron withdrawing abililty of the substituent may diminish and, as a consequence, slow the reaction.

Scheme 46

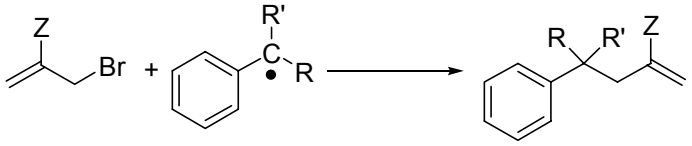
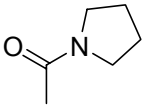
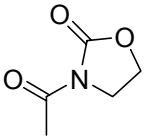
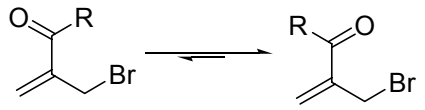


Table 21. Comparison of chain lengths of various carbon centered free-radicals and various allyl bromides.

-Z	R = R' = H Initial Chain Length (Relative Chain Length)	R = Me; R' = H Initial Chain Length	R = R' = Me Initial Chain Length
-H	11 (1)	-	-
-Ph	376 (34)	-	59
-CO_2Et	825 (75)	-	64
-CO_2Me	374 (34)	118	-
-CN	737 (67)	-	427
	52 (4.7)	57	-
	20 (1.8)	21	-

Scheme 47



preferred rotomer
as R increases in size?

Steric effects may also be particularly important if the mechanism involves a *concerted* addition/elimination pathway. For example, there appears to be a substantial difference in the relative chain lengths regarding the addition of benzyl radical to ethyl and methyl ester substituted allyl bromides. This may simply illustrate the "crudeness" of the reaction mixture analysis (GC). However, this might also be explained in terms of rotation about the carbonyl carbon – vinyl carbon double bond (Figure 41). The methyl, or ethyl, group would exist mainly in an orientation such that the distance between it and the $-CH_2Br$ group would be at a maximum and the carbonyl would still be in conjugation with the carbon – carbon double bond (rotomer **A**; Figure 41). With the less sterically demanding methyl ester, rotation about this bond is expected to occur much easier than with a bulkier ester. Additionally, it is expected that this second most prevalent rotomer (rotomer **B**; Figure 41) would also have both double bonds in conjugation. A consequence of this conformation may be such that their would be poor overlap between the forming carbon - carbon π-bond and the breaking carbon-bromine σ-bond (dihedral angle greater than or less than 90^o). Thus, in Figure 41, when R is methyl, rotomer **B** is more likely to occur than when R is

ethyl. The high population of this unreactive species might, therefore, explain the difference in relative chain lengths between the two esters.

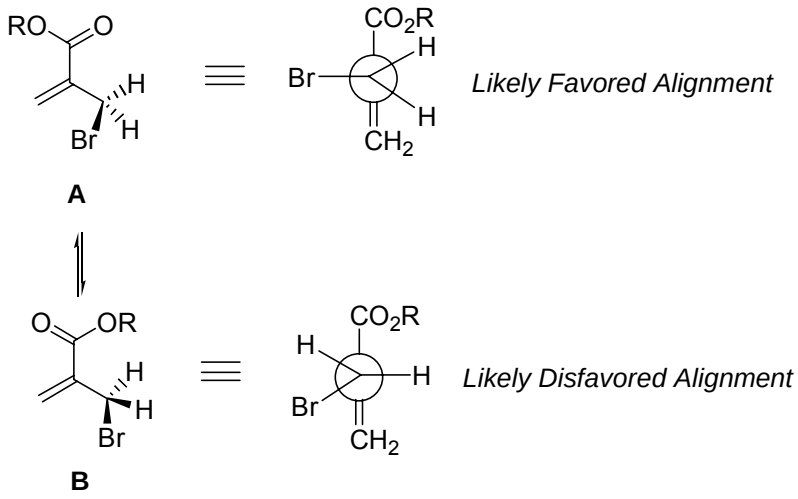


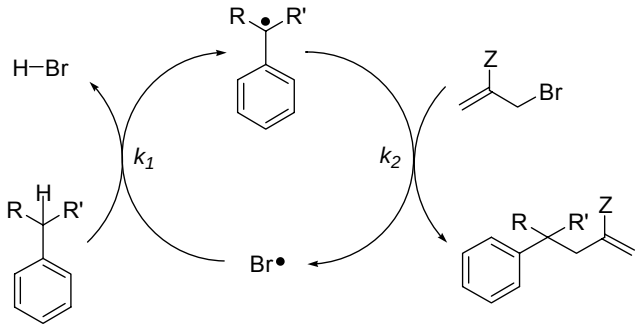
Figure 41. A comparison of conjugated rotomers of ester substituted allyl bromides.

To summarize, the effect on the rates of addition regarding the substituent –Z may be affected by electron withdrawing ability and possibly sterics in terms of hindering the approach of the carbon centered radicals, loss of conjugation, and misalignment of the carbon-carbon pi-bond of the allyl bromide and the carbon-bromine bond.

Regarding the carbon-centered free-radical, it has been noted that steric and polar effects are observed when adding radicals to mono- and disubstituted alkenes. These effects might be even more pronounced when dealing with radicals that contain strongly stabilizing phenyl substituents. Although a direct comparison cannot be made between relative reactivities of phenethyl radical and cumyl radical from the data (Table 21), it is reasonable to rank the rates of

addition of carbon-centered free-radicals to allyl bromides such that benzyl > phenethyl > cumyl (k_2 in Scheme 48). The relative rates of hydrogen abstraction by bromine radical (k_1 in Scheme 48) have been shown to be on the order of $58_{(cumene)} > 25_{(ethylbenzene)} > 1_{(toluene)}$.[62] Although, cumyl radicals are formed more readily than phenethyl and benzyl radicals by means of hydrogen radical abstraction by bromine radical, the stability and steric bulk of cumene radical diminishes their rate of addition to allyl bromides such that chain lengths involving cumene are shorter than those involving less bulky radicals. Therefore, regarding the adding carbon-centered free radical, the chain lengths are more greatly affected by the sterics and stability of the free radical rather than their rates of formation. In summary, $k_{1(cumene)} > k_{1(ethylbenzene)} > k_{1(toluene)}$ and $k_{2(benzyl)} > k_{2(phenethyl)} > k_{2(cumyl)}$.

Scheme 48



R = R' = H: benzyl
R = H, R' = Me: phenethyl
R = R' = Me: cumyl

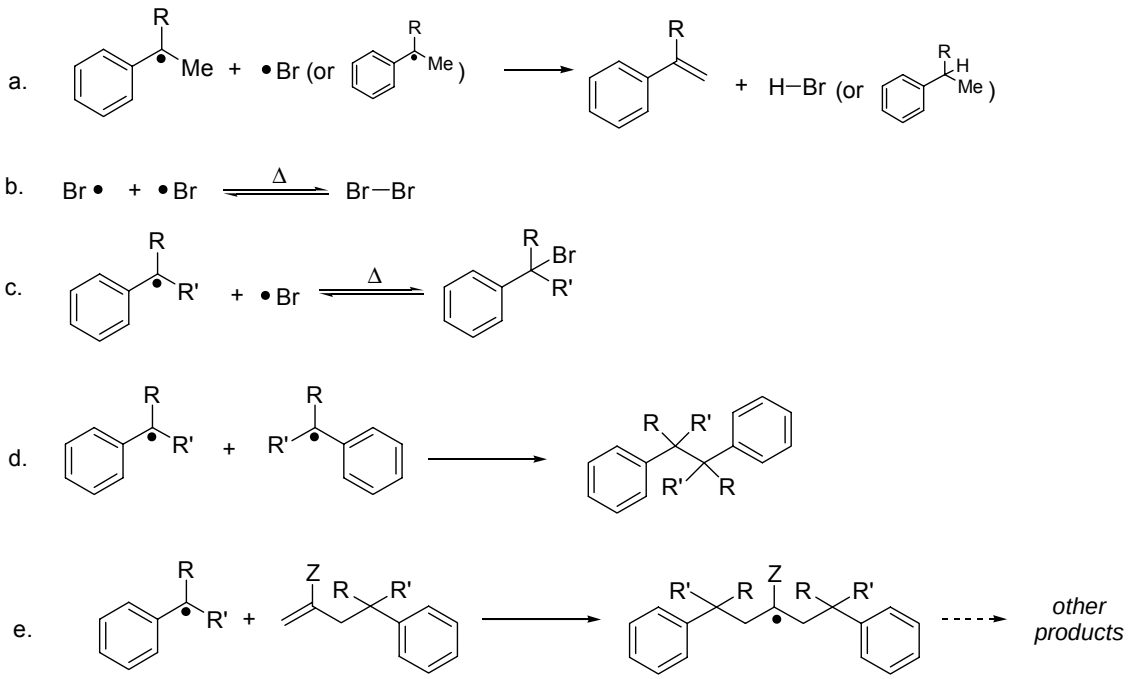
The termination processes which are most likely to compete with k_2 are probably termination by disproportionation (a; scheme 49) and combination of

free-radicals (b – d; Scheme 49). When benzyl radical is formed, dipropor-tionation becomes a non-issue. The rates of disproportionation compared to the rates of combination have been measured for both phenethyl radical and cumyl radical and have been shown to favor combination by factors of 43 and 200 respectively.[81] Thus, the consumption of carbon centered radicals prior to their addition to alkenes and allyl bromides, is most likely to occur by means of a combination process.

Of the possible combination processes, three seem to be the most likely: the combination of 1) two bromine radicals, 2) a bromine and an alkyl radical, and 3) the combination of two alkyl radicals (routes b-d; Scheme 49). The combination of two bromine radicals (b; Scheme 49) is thought have a minor effect on the initial chain length. Because there is an overwhelming amount of solvent which also acts as the benzyl radical precursor (toluene, ethyl benzene, and cumene), it is unlikely that a two bromine radicals would combine prior to abstracting a hydrogen radical from a solvent molecule. Similarly, it is unlikely that termination route c in Scheme 49 is significant since this also involves the combination of bromine radicals with other radicals. In other words, if we assume that bromine radicals are consumed rapidly by their abstraction of hydrogen radicals from solvent, they are most likely short-lived and at low concentrations. It is unclear how much benzyl bromide and analogous compounds are produced by these reactions. This is because the reaction mixtures are analyzed by GC and the solvent, being either toluene,

[81] (a) Green, F. D.; Berwick, M. A.; Sowell, J. C. *J. Am. Chem. Soc*. **1968**, *90*, 283. (b) Nelsen, S. F.; Bartlett, P. D. *J. Am. Chem. Soc*. **1966**, *88*, 137.

Scheme 49



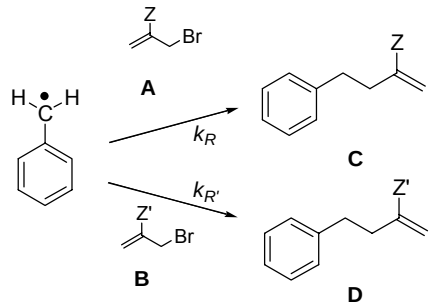
ethylbenzene, or cumene, eclipses all other low boiling materials in the chromatogram. The combination of carbon centered radicals is undeniably an important termination process since bibenzyl, 2,3-diphenylbutane, and bicumyl appear in the reaction mixtures as the reactions progress.[82] Lastly, a mode of termination that becomes increasingly significant as the substrate is consumed is illustrated as pathway e in Scheme 49. The free radical product from this reaction can react further form dimers and high molecular weight alkanes by a combination route, high molecular weight alkenes by losing a hydrogen radical through a disproportionation pathway, or abstract a hydrogen radical from the

[82] GC retention time studies comparing the reaction mixtures with authentic samples of bibenzyl, 2,3-diphenylbutane, and bicumyl, as well as, GC/MS analyses have provided this evidence.

solvent. Indeed, compounds resulting from the latter pathway appear as the reaction progresses.[83]

The relative rate constants were determined by comparing the relative amounts of two different substrates and their corresponding products by means of competition experiments by adding benzyl radical to various allyl bromides (Scheme 50). The results of these studies are shown in Tables 22[65] and 23. For the most part, these data match those in Tables 5 and 6 (β-effect) and demonstrate that the overall rate increases as a function of the electron withdrawing ability of the –Z substituent. It is difficult, however, to determine from this data whether or not the relative rates are significantly affected by the bulk of the substituent –Z.

Scheme 50



$$k_R/k_{R'} = \frac{\ln\{[\mathbf{A}]_o/([\mathbf{A}]_o - [\mathbf{C}])\}}{\ln\{[\mathbf{B}]_o/([\mathbf{B}]_o - [\mathbf{D}])\}}$$

[83] See eq. 58, pg. 87.

Table 22. Relative reactivities of various allyl bromides towards benzyl radicals at 80 °C.[65]

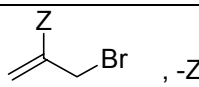
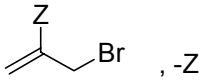
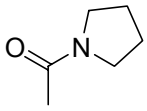
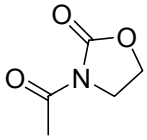
 , -Z =	k_{rel} at 80 °C
-H	1
-Ph	65
-CO_2Et	110
-CN	180

Table 23. Relative reactivities of various allyl bromides towards benzyl radicals at 120 °C.

 , -Z =	k_{rel} at 120 °C
-CO_2Me	71
-CO_2Et	75
	1.23
	1

Regarding carbon centered radical additions to prochiral allyl bromides **138** and **139**, it is not surprising that the chain length diminishes when R = Me compared to when R = H (Scheme 51). This retardation in rate is most likely an α-steric effect which had also been observed in the additions of carbon centered radicals to alkenes (Scheme 24; Table 7).

Scheme 51

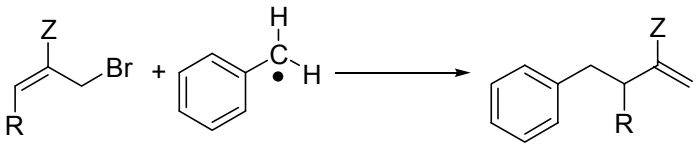
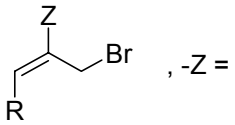
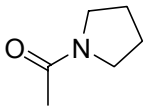
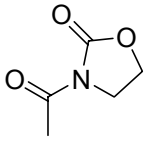


Table 24. Initial chain lengths from the addition of benzyl radical to various allyl bromides using t-butyl peroxide as an initiator at 120 °C.

 , -Z =	Initial Chain Length R = H	Initial Chain Length R = Me
$-CO_2Me$	374	47
	52	3.2
	20	-

Conclusion and Outlook. This research has embellished upon several features regarding the synthesis of allyl bromides and their reactivities. First, we have shown that various allyl bromides capable of accommodating an amine or oxazolidinone chiral auxiliary may be synthesized using inexpensive starting materials in only a few synthetic steps (Fig. 42). Second, we have shown that if starting with a prochiral free radical precursor (ethyl benzene) or a prochiral allyl bromide (compounds **135** – **139**) new methyl bearing stereogenic centers may be formed via our free radical addition/elimination reaction (Scheme 52). In doing so, we have reinforced our originally proposed mechanism in that the free radical adds to the double bond prior to the “ejection” of a bromine radical in a single

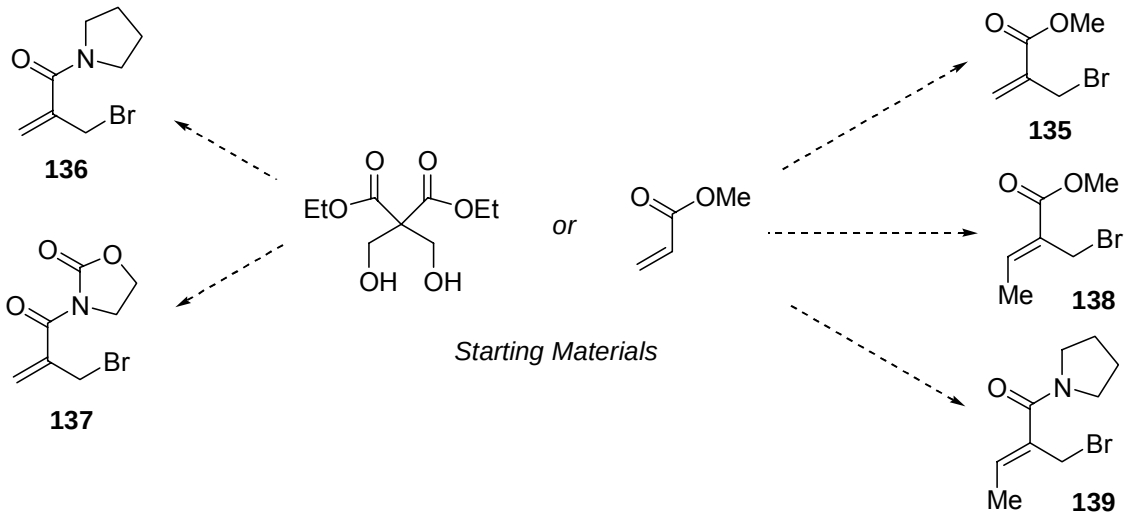
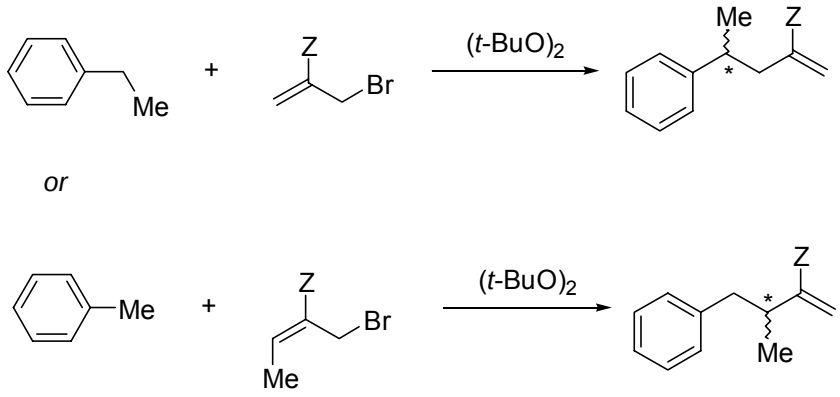


Figure 42. Inexpensive starting materials and products of allyl bromide syntheses.

step concerted pathway or a two step addition/elimination pathway rather than displacing the bromine directly in a single step substitution type mechanism (Scheme 33). Additionally, by showing that all of the allyl bromides have chain lengths of greater than one, we have given credence to the notion that bromine radical does indeed act as a chain carrier in these reactions. The competition experiment data also supports this idea. We have also shown that α- and β-reactivity trends concerning free radical additions to allyl bromides are similar to those observed with simpler alkenes although it is suspected that sterics may play a greater role with allyl bromides. Finally, by showing that moderate yields of addition/elimination products can be obtained on a preparative scale (53 – 72%), the potential synthetic usefulness of this reaction has been established.

Scheme 52



The most logical progression for this work would include a study which uses chiral auxiliaries to determine the degree of stereocontrol that might be achieved. For example, chiral auxiliaries like Oppolzer's sultam, asymmetric 2,5-disubstituted pyrrolidines and chiral mono- and disubstituted oxazolines (Fig. 43) have found applications in free radical additions to alkenes and aldol additions.[18,36,37] Additionally, carbon centered free radicals from sources other than toluene, ethylbenzene, and cumene might be used to expand upon the synthetic usefulness of this reaction. For example, it was previously shown

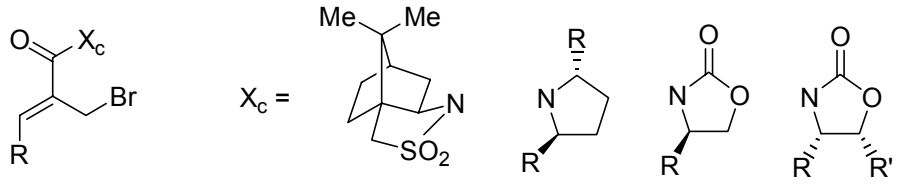
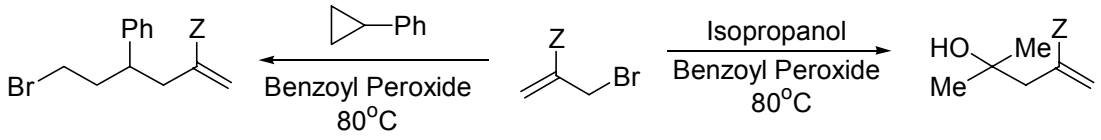


Figure 43. Common sultam, pyrrolidine, and oxazoline chiral auxiliaries.

that phenylcyclopropane and isopropanol react with various substituted allyl bromides (Scheme 53).[65] Similar free radical precursors might be used in

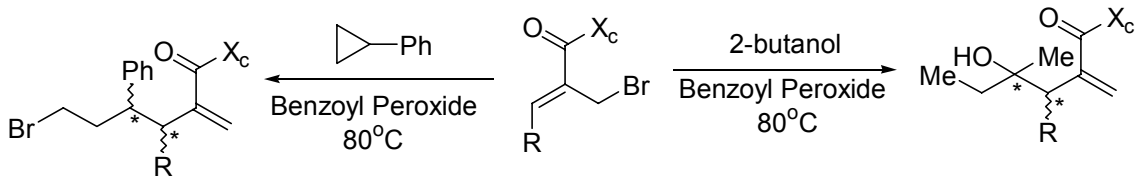
conjunction with chiral auxiliary bearing allyl bromide to generate products with additional functional groups (Scheme 54). Thus, by providing additional synthetic "handles", this addition/ elimination reaction becomes more versatile.

Scheme 53



Z = Ph or CN

Scheme 54



R = H or Me

Chapter 4

Experimental Section (Asymmetric Catalysis)

General. Unless otherwise noted, all reactions were conducted in flame-dried glassware with magnetic stirring under a dry nitrogen atmosphere. When necessary, solvents were dried prior to use. Tetrahydrofuran (THF) was dried over lithium aluminum hydride. Dichloromethane and diisopropylethylamine were distilled over calcium hydride. Isobutyraldehyde and 2-methylpentanal were distilled over anhydrous sodium sulfate. Deuterochloroform was flushed through basic alumina and stored over molecular sieves. All other reagents were used as they were received from the vendor.

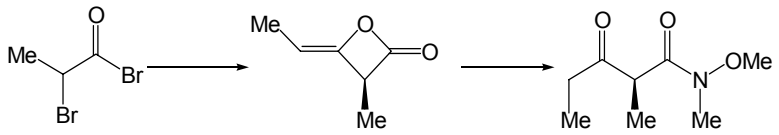
Solvents for extraction and chromatography were HPLC grade. Bench top forced flow chromatography (flash chromatography)[84] using the indicated solvent mixtures were performed using Baker silica gel (60 – 200 mesh) unless otherwise specified. Analytical gas chromatography (GC) was performed on a Varian 3400 gas chromatograph equipped for flame ionization detection with a split-mode capillary injection system. Fused silica capillary columns wall-coated with SE-30 (Alltech), or CP – Chirasil-Dex CB (Chrompack), were used with helium as a carrier gas.

Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium (λ = 589, D line) lamp and are reported in terms of [α],

[84] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978,** *43*, 2923.

(*c* = g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1800 FT-IR spectrometer. ^{1}H – NMR spectra were recorded on a Jeol 500 MHz spectrometer. All NMR spectra were performed using deuterochloroform as the solvent unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane as an internal standard (deuterochloroform: δ 7.26 ppm) and coupling constants (J) are reported in hertz (Hz). Multiplicities are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, and coupling constants.

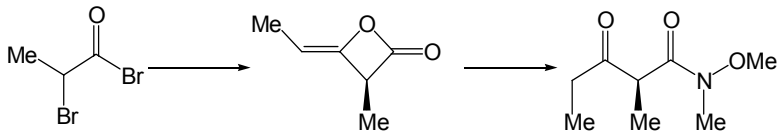
Analytical thin layer chromatography (TLC) was performed on EM reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished using a UV light source, iodine chamber, or conventional potassium permanganate and anisaldehyde stains. Mass spectra were performed in house by Virginia Tech Analytical Services using fast atom bombardment (FAB). Combustion data were compiled and reported by Atlantic Microlab (Norcross, Georgia).



(*S*)-96 **112**

3*R*-Hydroxy-2*S*-methyl-*N*-methyl-*N*-methoxypentanamide. Zn powder (8.62 g, 129 mmol) was suspended in 30 mL of THF in a 100 mL round bottom flask fitted with a short path distillation head and the pressure of the system was adjusted to approximately 110 torr as to bring about a mild reflux. A solution of 4.8 mL 2-bromopropionyl bromide (9.9 g, 46 mmol) in 30 mL THF was added to the stirring zinc/THF solution via teflon canulla over 5 to 10 minutes such that the evolving methylketene gas did not cause bumping. The methylketene was collected as a THF solution in a receiver flask that had been cooled in liquid nitrogen. Upon completion of the addition the receiver flask was removed and allowed to warm to -78 ^{o}C while under a N_2 atmosphere to give a yellow-green solution. This solution was added quickly (less than a minute) to a cooled (-78 ^{o}C) stirring solution of quinidine (45.2 mg, 0.139 mmol) in 25 mL of THF after which the solution was allowed to stir for one hour. The newly formed ketene dimer **(*S*)-96** was treated with 0.80 mL (0.66 g, 10.9 mmol) of *N,O*-dimethyl-hydroxylamine and 61 mg of 2-hydroxypyridine (0.64 mmol). The reaction was warmed to 0 ^{o}C and stirred for four hours. The resulting solution was cooled to -78 ^{o}C, treated with 35 mL of $Zn(BH_4)_2$ in THF (0.48 M, 18.8 mmol), and allowed to stir for two hours after which it was warmed to 0^{o}C and stirred an additional two hours. This solution was treated with 40 mL saturated aqueous NH_4Cl in a dropwise fashion. The organic layer was removed and the aqueous layer was

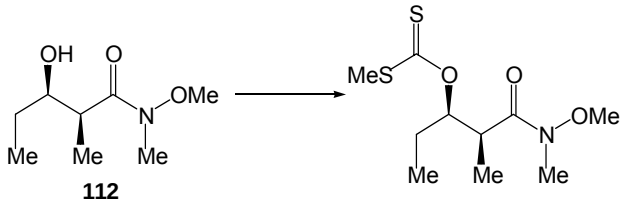
extracted with two 40 mL portions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil which was purified by silica gel chromatography (step gradient from 10% EtOAc in hexanes, 5% steps) yielding 1.79 g **112** (43.6%, 10.2 mmol). $[\alpha]^{23}_D = 17.8^o$ (c 2.6, $CHCl_3$); IR (neat) 3421 (br), 2964, 2879, 1641, 1462, 1386, 1156, 1085, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.75 (m, 1H), 3.75 (m, 1H) 3.69 (s, 3H), 3.19 (s, 3H), 2.90 (br m, 1H), 1.60-1.35 (m, 2H), 1.15 (d, 3H, J = 7.1), 0.95 (t, 3H, J = 7.6); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 178.5, 73.1, 61.6, 38.2, 32.0, 26.8, 10.5, 10.1. HRMS: calcd for $C_8H_{17}NO_3$, 175.2248, found, 175.2244.



(S)-96 **116**

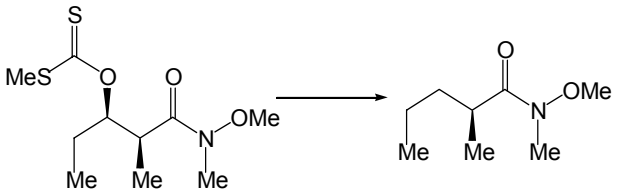
3-Keto-2*S*-methyl-*N*-methyl-*N*-methoxypentanamide Methylketene dimer was prepared in an identical fashion as described in the synthesis if **112**. The newly formed ketene dimer was treated with 0.80 mL (0.66 g, 10.9 mmol) of *N,O*-dimethyl-hydroxylamine and 61 mg of 2-hydroxypyridine (0.64 mmol). The reaction was warmed to 0 ^oC and stirred for four hours. The THF solution was treated with 55 mL water. The resulting solution was extracted with four 85 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica gel chromatography (30% EtOAc/Hexanes) giving 1.90 g of **116** (48%, 11.0 mmol).

^{1}H NMR (360 MHz, $CDCl_3$) δ 3.69 (q, 1H, J = 7.3 Hz), 3.64 (s, 3H), 3.20 (s, 3H), 2.48 (dq, 2H, J = 9.2, 3.7), 1.30 (d, 3H, J = 7.1), 1.03 (t, 3H, J = 7.2); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ. HRMS: calcd for $C_8H_{15}NO_3$, 173.2090, found, 173.2074.



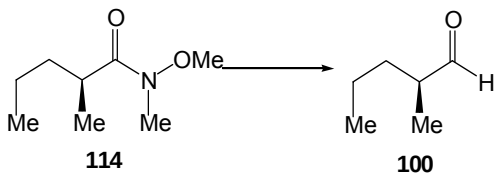
112 **113**

Methyl Xanthate of 112 (113). To a cooled (0 ^{o}C), stirring solution of **112** (271.5 g, 1.55 mmol) in 30 mL THF was added CS_2 (6.75 mL, 112 mmol), iodomethane (6.70 mL, 108 mmol), and NaH (136.3 g as a 60% mineral oil suspension, 3.4 mmol). No starting material was apparent after stirring the solution for 30 min. The solution was poured over approximately 60 g of ice, warmed to room temperature and extracted with four 15 mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give crude **113** as a light yellow oil. This material was purified by silica gel chromatography (5% EtOAc/Hexanes to remove the mineral oil followed by 50% EtOAc/Hexanes) to give 353.5 mg (85.9%, 1.33 mmol) pure **113**. IR (neat) 2975, 2953, 2883, 1668, 1462, 1383, 1220, 1047, 994 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.95 (m, 1H), 3.67 (s, 3H), 3.29 (m, 1H), 3.15 (s, 3H), 2.53 (s, 3H), 1.76 (m, 2H), 1.16 (d, 3H, J = 7.0), 0.90 (t, 3H, J = 7.4); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 216.1, 174.3, 85.7, 61.5, 38.7, 32.3, 25.0, 18.8, 13.5, 9.7. Anal. calcd for $C_{10}H_{19}NO_3S_2$: C, 45.27; H, 7.22; N, 5.28; S, 24.12. Found: C, 45.34; H, 7.35; N, 5.26; S, 24.22.



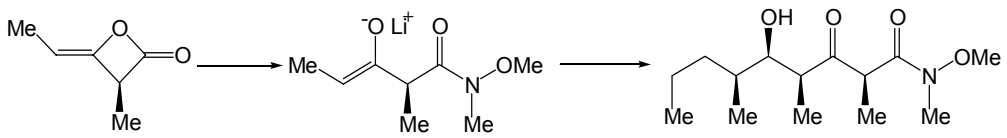
113 **114**

2*S*-methyl-*N*-methyl-*N*-methoxypentanamide (114). To stirring 273.2 mg **113** (1.029 mmol) dissolved in 15 mL freshly distilled toluene (CaH_2) was added 1.5 mL of tributyltin hydride (1.6 g, 5.6 mmol) and 65.8 mg AIBN (0.401 mmol). The reaction flask was fitted with a condenser and heated to reflux. After 1.5 h, the reaction mixture was cooled, the toluene removed *in vacuo*, and the resulting viscous oil was flash chromatographed on silica gel (initially 100% hexane followed by 30% EtOAc/Hexanes to give 156.8 mg **114** (95.7%, 0.985 mmol) as a clear oil. IR (neat) 2963, 2873, 1663, 1462, 1384, 1313, 1178, 1113, 996 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.16 (s, 3H), 2.97 (br m, 1H), 1.68-1.23 (m, 4H), 1.08 (d, 3H, J = 6.8), 0.87 (t, 3H, J = 7.0). ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 61.6, 36.2, 35.0, 32.4, 20.9, 17.6, 14.3. Anal. calcd for $C_8H_{17}NO_2$: C, 60.33; H, 10.77; N, 8.80. Found: C, 59.87; H, 10.41; N, 8.67.



2S-methyl-pentanal (100).[85] A stirring solution of **114** (726.2 mg, 4.56 mmol) in 30 mL dry Et_2O was cooled to -78 ^oC upon which 1.20 mL (957.6 mg, 6.73 mmol) DIBAL-H was added neat over 5 minutes. After the reaction was allowed to proceed for 1.5 hours it was quenched with 2 mL (27.2 mmol) acetone and stirred an additional 20 minutes. The reaction mixture was poured into a stirring biphasic mixture of 0.5 M aqueous tartaric acid (90 mL) and pentane (40 mL). After the solids had dissolved, the organic layer was removed and the aqueous layer was washed with three 20 mL portions of pentane. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo in a room temperature water bath until approximately 7 to 8 mL of residue remained. The product was then purified by Kugelrohr distillation to give 354.3 mg (77.3%, 3.53 mmol) of **100**.[86] $[\alpha]^{23}_D$ (c 2.6, $CHCl_3$) +22.1^o; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, 1H, J = 1.8), 2.34 (m, 1H), 1.71-1.32 (m, 4H), 1.07 (d, 3H, J = 7.1), 0.92 (t, 3H, J = 5.3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.5, 46.2, 32.7, 20.2, 14.1, 13.3.

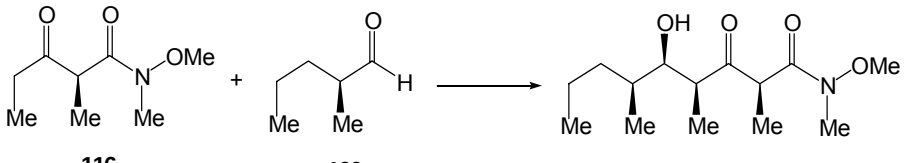
[85] The combined purified products of several xanthate reductions were used for this transformation.
[86] ^{1}H-NMR indicated the presence of trace amounts of pentane.



[2*S*, 4*S*, 5*R*, 6*S*]-5-Hydroxy-N-methoxy-3-oxo-N-2,4,6-tetramethylnonamide (118).[87] To a stirring, -78 ^{o}C solution of N,O-dimethylhydroxylamine 0.8 mL (0.66g, 10.9 mmol) in 50 mL THF was added 4 mL (10 mmol) of a solution of n-BuLi in hexanes (2.5 M). After 45 minutes, the resulting lithiated amine solution was added to a stirring solution of the methylketene dimer which was prepared in the usual fashion. After 5 minutes, 1.25 mL (12.1 mmol) neat racemic 2-methyl pentanal was added. After 45 minutes at the reaction was quenched by adding 275 mL water and 50 mL 1 M HCl. The mixture was warmed to room temperature and the organic layer was removed. The aqueous layer was then extracted with two 100 mL portions of CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was flash chromatographed on silica gel (230-400 mesh, 5% EtOAc/Hexanes step gradient in 2.5% steps) giving 588.1 mg **118** (19.8%, 2.15 mmol). $[\alpha]^{23}_{D}$ = +0.19^{o} (*c* 0.22, CH_2Cl_2); IR (neat) 3470, 2933, 2877, 1708, 1664, 1374 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (q, 1H, J = 7.06 Hz), 3.68 (s, 3H), 3.60 (dd, 1H, J = 7.6, 3.4 Hz), 3.18 (s, 3H), 2.88 (qd, 1H, J = 7.2, 2.4 Hz), 1.57-1.43 (m, 1H), 1.31 (d, 3H, J = 7.2 Hz), 1.28-1.17 (m, 2H), 1.09 (d, 3H, J = 7.1Hz), 1.06-0.97 (m, 2H), 0.92 (d, 3H, J = 6.6 Hz), 0.86 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 211.2,

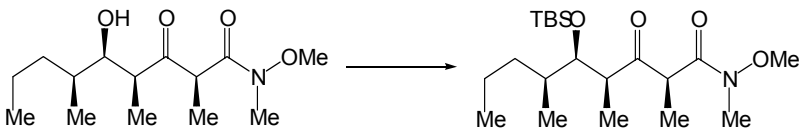
[87] Calter, M. A.; Guo, X.; Liao, W. *Org. Lett.*, **2001**, *3*, 1499.

171.4, 74.6, 61.3, 48.9, 46.1, 35.1, 34.8, 32.5, 19.5, 15.1, 14.2, 13.0, 10.4. HRMS calcd for $C_{14}H_{27}NO_4$, 273.3674, found, 273.3668.[88]



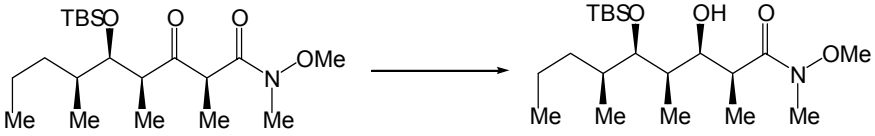
[2*S*, 4*S*, 5*R*, 6*S*]-5-Hydroxy-N-methoxy-3-oxo-N-2,4,6-tetramethylnonamide (118). To a stirring -78 ^{o}C solution of 437 mg **116** (2.52 mmol) in 25 mL CH_2Cl_2 was added 0.3 mL (0.52 g, 2.74 mmol) freshly distilled $TiCl_4$ giving a yellow/orange slurry. After approximately two minutes, 0.53 mL (393 mg, 3.04 mmol) $EtN(i\text{-}Pr)_2$ was added at which time the solution turned a dark red color. This solution was stirred for an hour prior to the addition of 226.8 mg (2.23 mmol) aldehyde **100** in 1.5 mL CH_2Cl_2. The reaction was allowed to stir an additional two hours. 15 mL saturated aqueous NH_4Cl was added and the mixture was allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with three 30 mL portions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was flash chromatographed on silica gel (230-400 mesh, 5% EtOAc/Hexanes step gradient in 2.5% steps) giving 291 mg **118** (1.07mmol). The spectral data matched that of the previous lithium mediated aldol procedure.

[88] The procedure using chiral 2-methyl pentanal differed only in that 0.9 equivalents of aldehyde was used with respect to the lithium enolate.



118

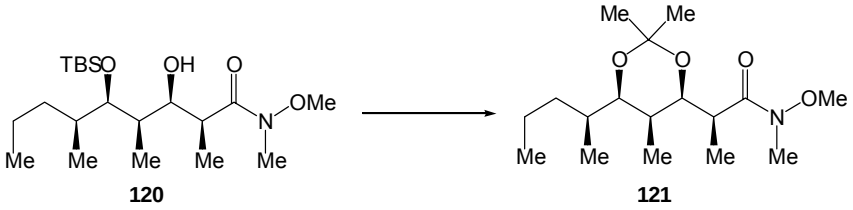
TBS- protection of 118. To a solution of 0.482 g **118** (1.76 mmol) in 5 mL of anhydrous DMF was added 720 mg of TBSCl (10.6 mmol) and 0.60 g of imidizole (8.8 mmol). The reaction was stirred at room temperature for 20 hours after which it was poured into 40 mL of diethyl ether and washed sequentially with three 10 mL portions of water and 30 mL brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography to give 0.405 g of TBS protected adduct (96%, 1.69 mmol).



120

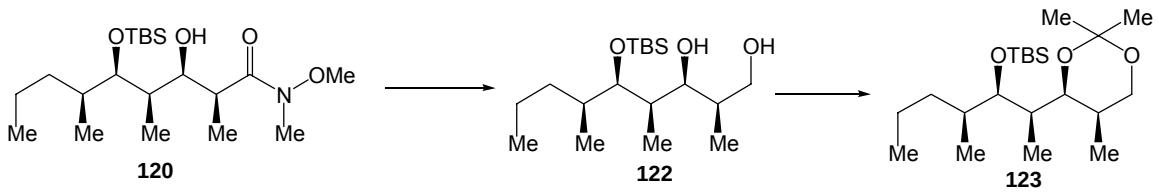
Preparation of 120. To a stirring solution of 0.405 g of TBS protected aldol adduct (1.69 mmol) in 24 mL of THF at -78 ^oC was added 3.4 mmol of $Zn(BH_4)_2$ (7.0 mL as a 0.48 M solution in THF). The reaction was stirred for one hour, slowly warmed to 0 ^oC and allowed an additional 2 h to ensure completion. The reaction was quenched by the careful addition of saturated aqueous NH_4Cl (20 mL). The mixture was rapidly stirred and allowed to warm to room temperature. 40 mL of CH_2Cl_2 was added and the organic layer was removed. The aqueous

layer was extracted with three 30 mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (10% EtOAc/ Hexanes) to give 0.530 g of **120** (80 %, 1.36 mmol).

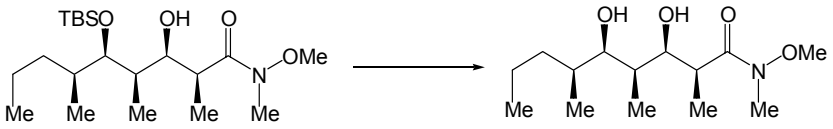


120 **121**

Acetonide of 120. In 2.4 mL 1:1 CH_2Cl_2:acetone at 0 ^oC was added 14.2 mg **120** (0.036 mmol) and a few crystals of I_2. After stirring for three hours the reaction mixture was treated with 5 mL water and an additional 5 mL portion of CH_2Cl_2. The organic layer was removed and the aqueous layer was washed with three 5 mL portions of CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated *in vacuo* to give 12.2 mg crude **121**. This material was passed through a short plug of silica gel with 50% EtOAc/Hexanes to give 10.3 mg **121** which was of sufficient purity for NMR analysis.



Reduction of 120 and acetonide formation of 123. To a solution of 28.2 mg of **120** in 10 mL THF was added 0.25 mL of 1.0M $LiAlH_4$ in THF at -78 ^oC. After 3 h, the mixture was treated with 5 mL of 1M aqueous HCl which had been saturated with NaCl. The mixture was allowed to warm to room temperature at which time 10 mL CH_2Cl_2 was added. The organic layer was removed and the aqueous layer was extracted with three 10 mL of portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give 12.9 mg of crude aldehyde which was reduced further in a similar fashion to give 10.2 mg of the crude diol **120** which was purified by passing the residue through a short (approximately 2 in.) plug of silica gel using 10% EtOAc/Hexanes as an eluent. The purified diol was then converted to the acetonide **123** by dissolving it in 10 mL acetone and then treating the solution with 3 mL of 2,2-dimethoxypropane and a few crystals of PPTS with stirring. After 18 hours the solution was treated with 10 mL water. The resulting solution was extracted with five 10 mL portions of Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give 11.7 mg of the crude acetonide **123** of sufficient purity for NMR analysis for the purpose of stereochemical proof.



120

Deprotection of 120. To a solution of **120** (288.3 mg, 0.740 mmol) in 14 mL THF at room temperature was added TBAF (1.1 mL, 1.1 mmol, 1.0 M in Hexanes) dropwise and the reaction was stirred for 32 hours. The reaction mixture was poured into a mixture of 10 mL CH_2Cl_2 and 10 mL water and the organic layer was removed. The organic layer was extracted with two 20 mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude diol was then purified by silica gel chromatography (100% Et_2O initially followed by 15% EtOAc/Et_2O) to give 196 mg of purified product (96 %, 0.710mmol).

Chapter 5

Experimental Section (Syntheses of Allyl Bromides)

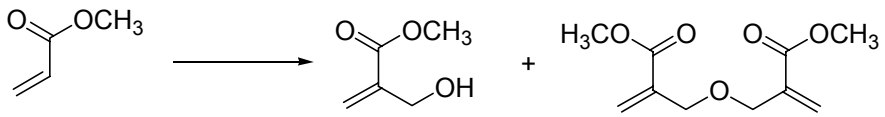
General. Unless otherwise noted, all reactions were conducted in flame-dried glassware with magnetic stirring under a dry nitrogen atmosphere. When necessary, solvents were dried prior to use. Tetrahydrofuran (THF) was dried over lithium aluminum hydride. Dichloromethane was distilled over calcium hydride. Deuterochloroform was flushed through basic alumina and stored over molecular sieves. All other reagents were used as they were received from the vendor.

Solvents for extraction and chromatography were HPLC grade. Bench top forced flow chromatography (flash chromatography)[69] using the indicated solvent mixtures were performed using Baker silica gel (60 – 200 mesh) unless otherwise specified. Analytical gas chromatography (GC) was performed on a Hewlett-Packard 5890A gas chromatograph equipped for flame ionization detection with a split-mode capillary injection system. A fused silica capillary columns wall-coated with SE-30 (Alltech) using helium as a carrier gas was used.

Infrared spectra were recorded on a Perkin-Elmer 1800 or a Nicolet Avatar-360 FT-IR spectrometer. ^{1}H – NMR spectra were recorded on a Jeol 500 MHz spectrometer. All NMR spectra were performed using deuterochloroform as the solvent unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane as an internal standard (deuterochloroform:

δ 7.26 ppm) and coupling constants (J) are reported in hertz (Hz). Multiplicities are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, and coupling constants.

Analytical thin layer chromatography (TLC) was performed on EM reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished using a UV light source, iodine chamber, or potassium permanganate stain. Mass spectra were performed in house by Virginia Tech Analytical Services using fast atom bombardment (FAB).

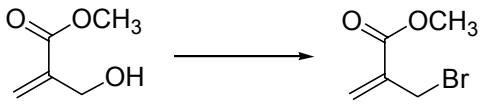


167

Baylis-Hillman reaction of methylacrylate and formaldehyde. A heated (95^{o}C) mixture of 35.79 g of methyl acrylate (416 mmol), 18.80 g of paraformaldehylde (624 mmol), and 2.24 g of diazabicyclooctane (DABCO, 20 mmol) was stirred in a sealed round bottom flask (***caution:*** due to the high vapor pressure anticipated from the evolution of formaldehyde gas, a vessel suitable for minimization of headspace was chosen. In this case a 100 mL round bottom flask. Additionally, the ground glass stopper used to seal the flask was tightly wired to the vessel and the reaction was carried out behind a blast shield).[89]

[89] The authors of the article from which this procedure was taken (ref. 59a) used an autoclave with Teflon sealed vessels to carry out this reaction.

After 5 hours, the mixture was cooled to room temperature and the two products were separated by silica gel chromatography (30% EtOAc/Hexane) to give 22.34 g of the ether as a white solid (50.1%, 104.3 mmol) and 12.2 g of the alcohol as a colorless oil (25.3%, 103.6 mmol). Spectral data for the ether: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.33 (m, 2H), 5.92 (m, 2H), 4.23 (m, 4H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.1, 137.0, 125.8, 68.8, 51.7. Spectral data for the alcohol: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.27 (m, 1H), 5.87 (m, 1H), 4.33 (m, 2H), 3.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.6, 139.5, 125.0, 61.1, 51.6.



167 **135**

1-Bromomethylmethylacrylate. To 10.2 g of **167** (87.8 mmol) was added 40 mL of conc. HBr (48% v/v, 237 mmol) and 2 mL of H_2SO_4. After stirring for 16 hours, the mixture was extracted with CH_2Cl_2 (5 x 50 mL).[90] The organic layers were combined and washed with two 150 mL portions of water. The organic layer was dried, filtered, and concentrated in vacuo. The resulting oil was distilled under reduced pressure to give 12.9 g of **135** (72.3 mmol, 82.3%). All spectral data closely matched that reported in the literature.[59b]

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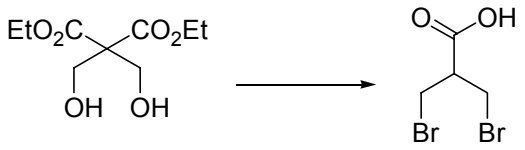
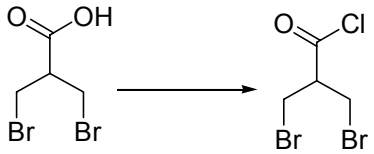
[90] A typographical error appeared in the literature (ref. 59b) in that the authors claimed to have carried out this extraction with diethyl ether.



148 **149**

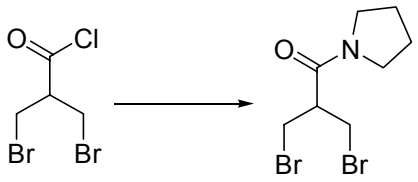
1,3-Dibromoisobutyric acid. Under Dean-Stark conditions, a stirring solution of 20.3 g (49.3 mmol) **148** in 125 mL conc. HBr (48% v/v, 740 mmol) was vigorously refluxed for eight hours during which time all of the resulting ethyl bromide and approximately 200 mL water was removed. After the solution was allowed to cool to room temperature and stand overnight a crystalline material appeared. The solution was filtered through a coarse sintered glass frit, the solid from which was recrystallized in hexanes yielding 7.80 g of **149** as needles (64.3%, 31.7 mmol). m.p. = 100-101^{o}C; IR (KBr pellet) 3038 (br), 2360, 2342, 1697, 1440, 1426, 1409, 1302, 1244, 1201, 1188, 918, 864, 813 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81-3.72 (m, 4H), 3.26 (quintet, 1H, J = 6.4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 175.5, 48.5, 29.9; (HRMS: 245.8642).



149 **150**

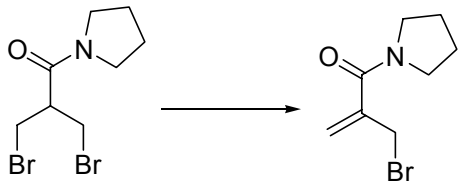
1,3-Dibromoisobutyroyl chloride. Under a dry N_2 atmosphere, a stirring solution of 7.10 g (28.9 mmol) of **149** in 12mL of CH_2Cl_2 and 2.55 mL of $SOCl_2$ (35.0 mmol) mildly refluxed for 2 h. The excess $SOCl_2$ and CH_2Cl_2 was removed

by distillation (approx 80-85^{o}C). The remaining oil was vacuum distilled to give 6.20 g (23.5 mmol, 81.3 %) of **150** (94^{o}C at 8 mm Hg). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.80 (m, 4H), 3.59 (quintet, 1H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 171.2, 59.1, 28.9.



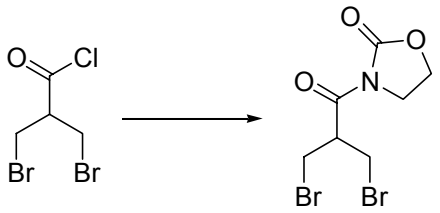
150 **152**

N-(3-bromo-2-bromomethylpropanoyl)pyrrolidine. 2.20 mL of pyrrolidine (1.87g, 26.4 mmol) in 55 ml of CH_2Cl_2 was added dropwise to a cooled solution (-78 ^{o}C) of **150** (3.1 g, 11.8 mmol) in 80 ml of dry CH_2Cl_2 over 45 minutes. After three and a half hours, the resulting yellow solution was washed with two 50 mL portions of water followed by brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* giving a thick yellow oil as crude **152**. This material was purified by silica gel chromatography using 3:7 ethyl acetate:hexanes as the eluent giving 2.86 g pure **152** (9.56 mmol, 81.0 %). IR (neat) 2971, 2876, 2359, 1639, 1450, 1340, 1227, 1188, 1170, 1038, 983, 915 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.60 (m, 4H), 3.53 (apparent t, 2H, J = 6.9 Hz), 3.47 (dd, 2H, J = 5.75, 10.1), 3.37 (m, 1H), 1.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 168.8, 49.2, 47.1, 46.2, 31.4, 26.1, 24.5; (HRMS: 299.0843).



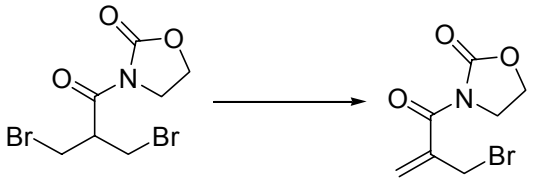
152 **136**

N-(2-bromomethylpropenoyl)pyrrolidine 136. To a cooled (0 ^{o}C) stirring solution of **152** (2.71 g, 9.06 mmol) in 90 mL of CH_2Cl_2 was added 1.50 mL (1.53 g, 10.1 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The solution was allowed to stir for two hours at which time TLC analysis indicated that the reaction had not gone to completion. An additional 0.50 mL portion of DBU was added and the solution went from colorless to a light yellow. After subsequent water and brine washes, the solution was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude yellow oil which was purified by silica gel chromatography using 1:1 ethyl acetate:hexanes as the eluent giving 1.81 g pure **136** as a colorless oil (8.32 mmol, 91.8 %). IR (neat) 2085, 1639, 1456, 1188, 1098 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.54 (s, 1H), 5.27 (s, 1H), 4.19 (s, 2H), 3.52 (m, 4H), 1.87 (br m, 4H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.5, 141.9, 118.5, 49.0, 45.7, 33.0, 26.2, 24.5; (HRMS: 218.3544).



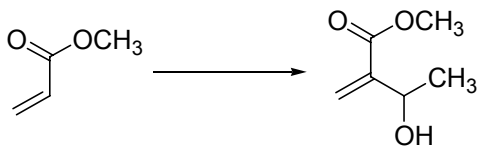
150 **151**

Oxazolidinone 151. To a cooled (0 ^{o}C) stirring solution of 2-oxazoline (1.10 g, 12.6 mmol) in 250 mL of THF was added 5.0 mL *n*-BuLi (12.5 mmol, 2.5 M in hexanes). A white precipitate formed and persisted after stirring for 1.5 h. The heterogeneous solution was transferred to a stirring solution of 3.0g (11.4 mmol) of **150** in 115 mL of THF (0 ^{o}C) via teflon canulla. The solution was stirred for 4 h (0 ^{o}C) at which time the solids (presumably LiCl) were filtered and washed with additional THF. After concentrating the THF solution in vacuo, the resulting black/brown solid was purified by silica gel chromatography using 2:8 ethyl acetate:CH_2Cl_2 giving **151** as a crystalline solid (2.77 g, 8.80 mmol, 77.2 % yield). m.p. 71-73^{o}C; IR (neat) 2989, 2942, 1771, 1696, 1796, 1434, 1390, 1269, 1224, 1110, 1039, 924, 898, 758 cm^{-1} ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.48 (m, 1H), 4.46 (t, 2H, J = 8.3 Hz), 4.06 (t, 2H, J = 7.8 Hz), 3.75-3.63 (m, 4H), ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.1, 153.2, 62.5, 47.0, 42.7, 30.6; (HRMS: 315.1077)



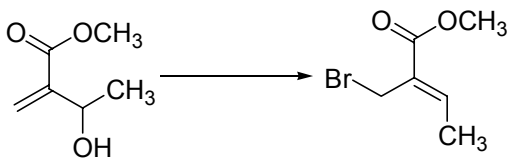
151 **137**

1-bromomethyl-2-oxazoline acrylamide. To a cooled (0°C) stirring solution of **151** (2.63 g, 8.35 mmol) in 17 mL of CH_2Cl_2 was added 1.85 mL (1.89 g, 12.4 mmol) of diazabicycloundecane (DBU) The solution was allowed to stir for 2 h at which time TLC analysis indicated that the reaction had gone to completion. After subsequent water and brine washes, the solution was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil which was purified by silica gel chromatography using 1:1 ethyl acetate:hexanes as the eluent (oil, 1.37 g, 5.85 mmol, 47.2 % yield). IR (neat) 2968, 1747, 1697, 1633, 1475, 1433, 1392, 1330, 1227, 1190, 1115, 1065, 765 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.75 (s, 1H), 5.65 (s, 1H), 4.46 (t, 2H, J = 8.0 Hz), 4.26 (s, 2H), 4.07 (t, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.7, 152.9, 139.9, 124.7, 62.6, 43.1, 31.0; (HRMS: 234.2519)



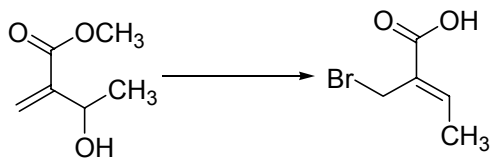
153

Methyl 3-hydroxy-2-methylenebutanoate. A mixture of 48.0 mL of methyl-acrylate (46.4 g, 0.54 mol), 20.0 mL of acetaldehyde (15.8 g, 0.36 mol), and 4.6 g of DABCO (40 mmol) was stirred at room temperature in a sealed round bottom flask. Daily monitoring by ^{1}H NMR indicated that the reaction proceeded cleanly and to completion after 7 days. The mixture was diluted with 250 mL Et_2O and the resulting solution was washed with 400 mL of H_2O. The aqueous layer was removed and acidified with 1 M HCl to pH = 5-6. The aqueous layer was then extracted with an additional 400 mL Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo giving crude **153**. The product was purified by vacuum distillation (93-95 ^{o}C, 15 mmHg) giving 38.3 g of pure **153** (0.295 mol, 81.8 %). IR (neat) 3427 (br), 2978, 2955, 1716, 1630, 1440, 1369, 1291, 1197, 1164, 1095, 1042, 958, 925, 869, 821, 711 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz) δ 6.16, (d, 1H, J = 1.4Hz), 5.80 (d, 1H, J = 1.2Hz), 4.57 (m, 1H), 3.73 (s, 3H), 2.67 (br, 1H), 1.32 (d,3H, J = 6.8); ^{13}C NMR ($CDCl_3$, 125.8MHz) δ 167.1, 143.6, 124.2, 67.1, 52.0, 22.2.



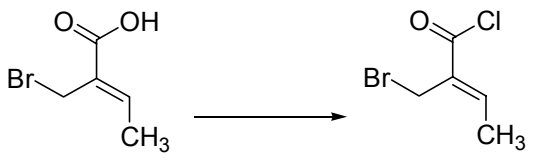
153 **138**

Methyl (*Z*)-2-(Bromomethyl)-2-butenoate. To a 0 ^{o}C soloution of *N*-bromosuccinimide (53.4 g, 0.297 mol) in 300 mL of CH_2Cl_2 was added a solution of freshly distilled dimethyl sulfide (23.9 mL, 20.2 g, 0.324 mol) in 175 mL of CH_2Cl_2 over 30 min. Then a solution of 35.1 g (0.270 mol) of **153** in 160 mL of dry CH_2Cl_2 was then added over 20 min. to the stirring solution producing a light yellow solution which was allowed to stir overnight (approximately 16 h) at ambient temperature. The solution was diluted with additional CH_2Cl_2 (300 mL), poured into 1 L of a 0 ^{o}C solution of 1:1 H_2O:brine. The aqueous layer was separated and extracted with three 300 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was purified by silica gel chromatography (15% EtOAc/Hexanes) to give 43.3 g of pure **137** (0.224 mol, 83.0%). IR (neat) 2993, 2953, 1719, 1644, 1437, 1282, 1218, 1195, 1165, 1053, 765 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.07 (q, 1H, J = 6.9 Hz), 4.23 (s, 2H), 3.79 (s, 3H), 1.91 (d, 3H, J = 6.9Hz); ^{13}C NMR ($CDCl_3$, 125.8MHz) δ 169.5, 143.3, 130.1, 52.1, 23.9, 14.5; (HRMS: 193.4910).



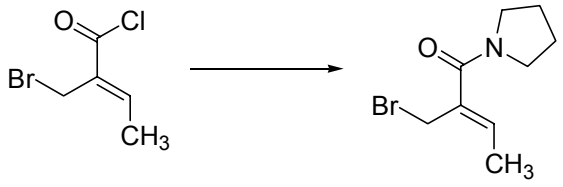
153 **155**

(*Z*)-2-(Bromomethyl)-2-butenoic acid. To 31.8 g of **153** (0.245 mmol) was added 620 mL of conc. HBr (48% v/v, 3.68 mol). The mixture was heated to reflux for two hours over which time 35 mL of fluid was removed using a Dean-Stark trap. The pot was allowed to cool slowly to room temperature. While cooling, the solution turned cloudy and a crystalline material appeared. This solid was filtered and washed with an excess of water. The solid was dissolved in 250 mL CH_2Cl_2 and the organic solution was washed with equal volume portions of water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give 24.70 g **155** as a slightly yellowed solid (0.138 mol, 56.3%). This material was pure by ^{1}H NMR and gave a sharp melting point (108-110^{o}C), and was used without additional purification. IR (KBr pellet) 2998 (br), 2683, 2564, 1670, 1438, 1305, 1212, 1188, 1130, 927, 878, 804, 765, 649, 560 cm^{-1}. ^{1}H NMR (CD_2Cl_2, 500MHz) δ 7.22 (m, 1H), 4.24 (s, 2H), 1.45 (d, 3H, J = 7.3 Hz); ^{13}C NMR (CD_2Cl_2, 125.8 MHz) δ 170.9, 146.5, 129.7, 23.6, 14.8.



155 **168**

(Z)-2-(Bromomethyl)-2-butenoyl chloride. Under a dry N_2 atmosphere at ambient temperature, a solution of 17.3 g (96.6 mmol) of **155** 100 mL of CH_2Cl_2 and 8.50 mL (117 mmol) of $SOCl_2$ was stirred for 12 h. The solution was then heated to 85 ^oC under slightly reduced pressure to remove any remaining $SOCl_2$ and CH_2Cl_2. The remaining 17.7 g (90.0 mmol, 93.2%) of **168** which appeared as an orange oil seemed to be pure by both ^1H NMR and ^{13}C NMR and was used with out further purification.[91] ^1H NMR ($CDCl_3$, 500MHz) δ 7.48 (q, 1H, J = 7.3), 4.18 (s, 2H), 2.05 (d, 3H, 7.1); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.2, 152.6, 135.2, 22.8, 15.7.



168 **139**

N-[(*Z*)-2-bromomethyl-2-butenyl)pyrrolidine. A solution of pyrrolidine (7.55 mL, 6.42 g, 90.6 mmol) in 95 ml CH_2Cl_2 was added dropwise via canulla to a cooled solution (-78^oC) of **168** (16.2 mg, 82.2 mmol) in 170 mL of CH_2Cl_2 over 45 minutes. Midway through the addition a pale yellow precipitate appeared. After 3 h, enough water was added to the suspension to dissolve the solids, and the organic layer was removed. The aqueous layer was washed with three 150 mL portions of CH_2Cl_2 to give crude **139.** This material was purified by silica gel

[91] It was discovered that excessive heating caused isomerization about the double bond to occur in the product.

chromatography using 3:7 ethyl acetate:hexanes as the eluent to afford 9.33 g of pure **139** (40.2 mmol, 48.9%). IR (neat) 2980, 2885, 1646, 1585, 1455, 1383, 1342, 1188, 1089, 1029 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.91 (m, 1H), 4.38 (s, 2H), 3.52 (br m, 4H), 1.89 (br m, 4H), 1.84 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 169.2, 134.7, 130.9, 39.5, 27.2, 13.5. (HRMS: 233.9421)

Chapter 6

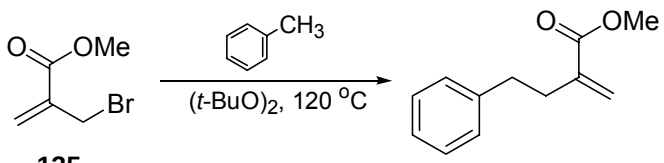
Experimental Section (Additions of Free-Radicals to Allyl Bromides)

General. Analytical gas chromatography (GC) was performed on a Hewlett-Packard 5890A gas chromatograph equipped for flame ionization detection with a split-mode capillary injection system. A fused silica capillary column wall-coated with SE-30 (Alltech) using helium as a carrier gas was used.

Infrared spectra were recorded on a Perkin-Elmer 1800 FT-IR spectrometer. IR bands are reported in cm^{-1}. ^1H NMR spectra were recorded on a Jeol 500 MHz spectrometer. All NMR spectra were performed using deuterochloroform as the solvent unless otherwise indicated. Deuterochloroform was flushed through basic alumina and stored over molecular sieves. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane as an internal standard (deuterochloroform: δ 7.26 ppm) and coupling constants (J) are reported in hertz (Hz). Multiplicities are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, and coupling constants.

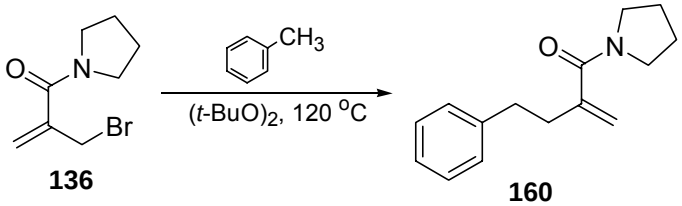
GC/MS data was obtained using a Hewlett-Packard HP5890 gas chromatograph equipped with a methylsilicone capillary colum and a HP5097B EI mass spectrometer.

Preparative Scale Syntheses (General). In each case, 15-20 mL of a 0.15 M solution of one of the allyl bromides **135-140** in either toluene or ethyl benzene as the solvent/free radical precursor with 1.1 equivalents of K_2CO_3 were placed in a pressure tube along with 0.5 equivalents of di-*tert*-butyl peroxide. The tubes were degassed by means of three to five freeze-pump-thaw cycles. The tubes were heated in a constant temperature oil bath at 120 ^oC for one hour after which, the tube was cooled under cold tap water to stop the reaction and the resulting solution was analyzed by GC. If the GC analysis revealed the presence of allyl bromide, the reaction mixture was treated with an additional 0.5 equivalents of initiator, degassed and heated to 120 ^oC for an additional hour. This process was repeated until no more allyl bromide was apparent by GC. The solvent was removed by vacuum distillation and the remaining oil was purified by preparative thin layer chromatography (PTLC) using Whatman silica gel plates (UV_{254}; prep: Analtech, silicagel G & GF preparative UNIPLATES, 20 x 20 cm, thickness: 500, 1000 and 1500 μm) using ethyl acetate/hexane, ethyl acetate/diethyl ether or reagent grade diethyl ether as the eluent. All other reagents, including toluene (Fisher), ethyl benzene (Aldrich), and di-*tert*-butyl peroxide (Aldrich), were used as they were received from the vendor.



135 **159**

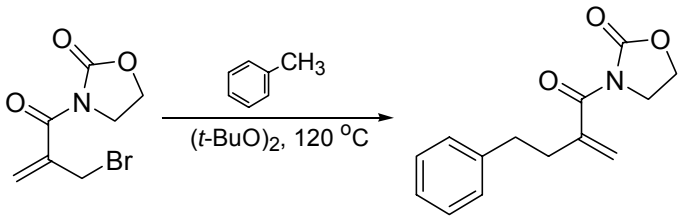
Reaction of 135 with toluene. A mixture of 536 mg (2.99 mmol) of **135**, in 20 mL of toluene with 460 mg (3.33 mmol) of K_2CO_3 and 280 μL (1.5 mmol) of di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 3 h and the oil remaining after vacuum distillation was purified by PTLC using 1:9 ethyl acetate:hexanes giving 361 mg of **159** (1.90 mmol, 63.3%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 – 7.30 (m, 5H), 6.12 (d, 1H, J = 1.4 Hz), 5.51 (q, 1H, J = 1.4 Hz), 3.74 (s, 3H), 2.79 (m, 2H), 2.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.4, 141.6, 140.1, 128.5, 128.3, 125.9, 125.0, 51.7, 34.8, 33.9; GC/MS (EI) m/e 190 (M), 158, 130, 115, 91 (M – 99, 100%), 77, 65.



136 **160**

Reaction of 136 with toluene. A mixture of 652 mg (2.99 mmol) of **136** in 20 mL of toluene with 457 mg (3.30 mmol) K_2CO_3 and 280 μL (1.5 mmol) di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 4 hrs and the oil remaining after vacuum

distillation was purified by PTLC using 1:4 ethyl acetate:hexanes giving 494 mg of **160** (2.16 mmol, 72.1%) ^{1}H NMR[92] ($CDCl_3$, 500 MHz) δ 7.10 – 7.28 (m, 5H), 5.55 (s, 1H), 5.23 (s, 1H), 3.2 – 3.6 (br m, 4H), 2.79 (t, 2H, J = 8.5 Hz), 2.65 (t, 2H, J = 8.3 Hz), 1.72 – 1.96 (br m, 4H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.1, 167.5, 145.5, 142.0, 141.3, 128.5, 126.0, 118.5, 115.7, 49.0, 48.8, 45.7, 45.5, 35.3, 34.0, 33.0, 26.2, 24.5; GC/MS (EI) m/e 229 (M), 158, 138, 115, 91 (M – 138, 100%).

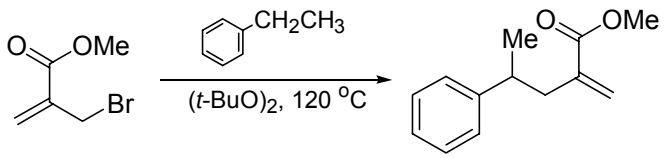


137 **161**

Reaction of 137 with toluene. A mixture of 520 mg (2.22 mmol) of **137** in 15 mL of toluene with 347 mg (2.51 mmol) K_2CO_3 and 210 μL (1.13 mmol) di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 8 hrs and the oil remaining after vacuum distillation was purified by PTLC using 1:5 ethyl acetate:diethyl ether giving 288 mg of **161** (1.17 mmol, 52.8%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 – 7.30 (m, 5H), 5.45 (apparent d or 2 x s, 2H), 4.38 (t, 2H, J = 7.8 Hz), 3.90 (t, 2H, J = 7.8 Hz), 2.82 (t, 2H, J = 8.2 Hz), 2.71 (t, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 143.6, 141.2, 128.5, 128.3, 126.0, 119.5, 62.4, 60.3, 42.9, 34.8, 34.2,

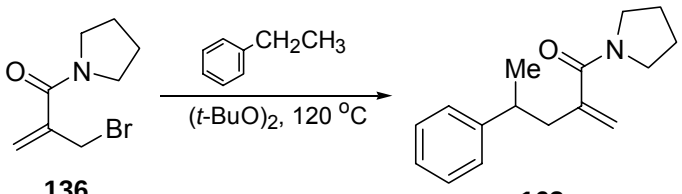
[92] ^{1}H and ^{13}C NMR spectra for these types of pyrrolidine amides are complicated presumably due to rotation about the carbonyl carbon – vinyl carbon σ-bond. All observed peaks are reported.

14.0. GC/MS (EI) m/e 245 (M), 158 (M – 87, 100%), 154, 130, 115, 104, 91 (M – 154, 93%), 65.



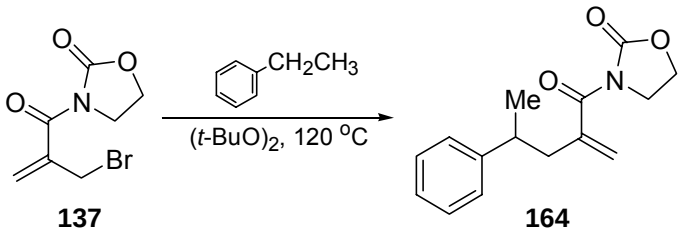
135 **162**

Reaction of 135 with ethylbenzene. A mixture of 532 mg (2.98 mmol) of **135** in 20 mL of ethyl benzene with 465 mg (3.37 mmol) K_2CO_3 and 280 μL (1.5 mmol) di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 3 hrs and the oil remaining after vacuum distillation was purified by PTLC using 1:9 ethyl acetate:hexanes giving 344 mg of **162** (1.68 mmol, 56.6%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 – 7.28 (m, 5H), 6.04 (d, 1H, J = 1.4), 5.36 (q, 1H, J = 1.2), 3.69 (s, 3H), 2.95 (sextet, 1H, J = 7.3 Hz), 2.55 (ddd, 2H, J = 7.3, 7.2, 1.1 Hz), 1.23 (d, 3H, J = 6.9); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.5, 146.7, 139.1, 128.3, 127.1, 126.1, 126.0, 51.6, 40.8, 38.7, 21.3. GC/MS (EI) m/e 204 (M), 173, 128, 105 (M – 99, 100%), 91, 79, 77.



136 **163**

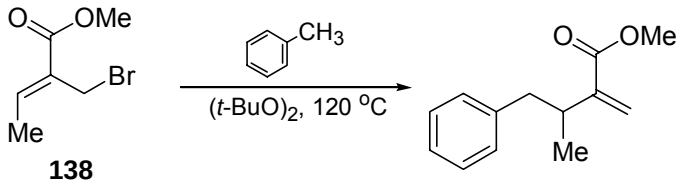
Reaction of 136 with ethylbenzene. A mixture of 657 mg (3.01 mmol) of **136** in 20 mL of ethyl benzene with 452 mg (3.27 mmol) K_2CO_3 and 280 μL (1.5 mmol) di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 5 hrs and the oil remaining after vacuum distillation was purified by PTLC using 1:4 ethyl acetate:hexanes giving 486 mg of **163** (2.00 mmol, 66.2%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 – 7.29 (m, 5H), 5.17 (d, 1H, J = 1.2), 5.07 (s, 1H), 3.25 – 3.39 (m, 2H), 3.10 (m, 1H), 2.88 – 2.97 (m, 2H), 2.58 – 2.67 (m, 2H), 1.61 – 1.99 (br m, 2H), 1.25 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 169.8, 146.5, 144.6, 128.4, 127.2, 126.2, 117.3, 48.7, 45.6, 42.3, 38.9, 26.1, 24.3, 23.3; GC/MS (EI) m/e 243 (M), 139, 138, 105 (M – 228, 100%), 91, 77, 55.



137 **164**

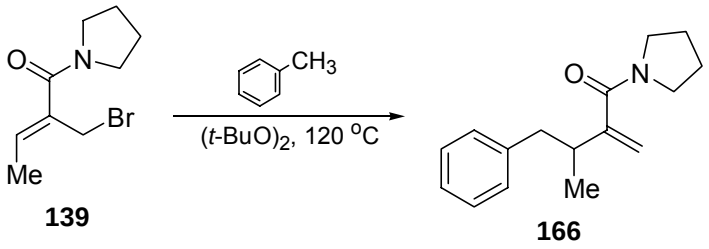
Reaction of 137 with ethyl benzene. A mixture of 524 mg (2.24 mmol) of **137** in 15 mL of ethyl benzene with 344 mg (3.49 mmol) K_2CO_3 and 210 μL (1.13

mmol) di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 10 hrs and the oil remaining after vacuum distillation was purified by PTLC using 1:5 ethyl acetate:diethyl ether giving 259 mg of **164** (1.31 mmol, 58.6%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 – 7.26 (m, 5H), 5.42 (s, 1H), 5.39 (s, 1H), 4.26 (m, 2H), 3.63 – 3.77 (m, 2H), 2.88 (m, 2H), 2.62 (m, 1H), 1.28 (d, 3H, J = 6.9); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.4, 152.7, 146.1, 142.2, 128.3, 127.5, 126.3, 122.2, 62.1, 42.9, 42.3, 39.4, 22.1; GC/MS (EI) m/e 259 (M), 172, 154, 128, 105 (M – 154, 100%), 77.



138 **165**

Reaction of 138 with toluene. A mixture of 581.4 mg (3.01 mmol) of **138** in 20 mL of toluene with 457 mg (3.31 mmol) K_2CO_3 and 280 μL (1.5 mmol) di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 13 hrs and the oil remaining after vacuum distillation was purified by PTLC using 1:9 ethyl acetate:hexanes giving 348 mg of **165** (1.70 mmol, 56.5%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 – 7.41 (m, 5H), 6.18 (s, 1H), 5.52 (s, 1H), 3.75 (s, 3H), 3.00 (sextet, 1H, J = 7.1 Hz), 2.52 (m, 2H), 1.05, (d, 3H, J = 6.9 Hz; ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ. GC/MS (EI) m/e 204 (M), 172, 144, 91 (M – 113, 100%), 65.



139 **166**

Reaction of 139 with toluene. A mixture of 701 mg (3.02 mmol) of **139** in 20 mL of toluene with 472 mg (3.42 mmol) K_2CO_3 and 280 μL (1.5 mmol) di-*tert*-butyl peroxide were heated in a degassed pressure tube according to the general procedure. The total reaction time was 12 hrs and the oil remaining after vacuum distillation was purified by PTLC using 1:5 ethyl acetate:hexanes giving 509 mg of **166** (2.09 mmol, 69.2%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 – 7.26 (m, 5H), 5.21 (s, 1H), 5.13 (s, 1H), 3.47 (m, 2H), 3.30 (m, 2H), 2.92 (m, 2H), 2.54 (m, 1H), 1.7 – 1.9 (m, 4H), 1.06 (d, 3H, J = 6.9 Hz), ; ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.6, 150.5, 140.6, 129.3, 128.2, 126.0, 113.9, 48.9, 45.5, 41.8, 38.8, 26.2, 24.4, 18.8; GC/MS (EI) m/e 243 (M), 228, 152, 125, 124, 91 (M – 152, 100%), 55.

Chain Length Measurements (General). In a typical reaction, a 0.14 M stock solution of the substrate was prepared in a 25 mL volumetric flask using either toluene or ethylbenzene as the solvent. 0.2 equivalents of di-*tert*-butyl peroxide was used as an initiator and 1.1 equiv of 1,2 epoxy butane was used as the HBr

scavenger. A 4 mL portion of the solution was measured in to each pressure tube and, after degassing each solution by the freeze-pump-thaw method, the tubes were heated in a constant temperature oil bath which has an accuracy of +/- 0.1 ^{o}C. At the appropriate times, the reactions were cooled under tap water and a solution of phenanthrene, in either toluene or ethylbenzene was added as an internal standard. The mixtures were then analyzed by GC and the initial chain length was calculated using linear regression of the product yields and produced radicals. The results of these experiments are tabulated on page 115.

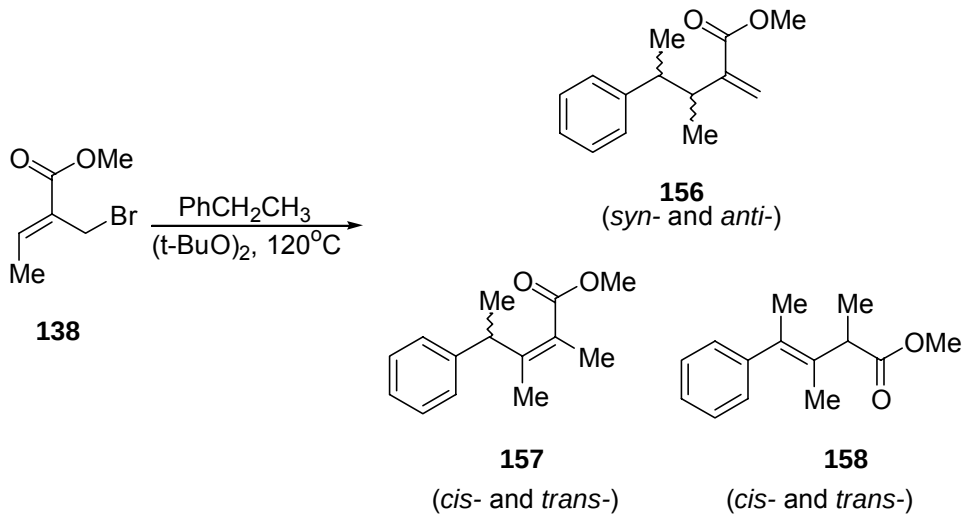
Competition Reactions (General). In a typical run, the two competing substrates were dissolved in 5 mL of either toluene. The slower reacting substrate was five times more concentrated than the faster reacting substrate; 0.7 M and 0.14 M respectively. With respect to the slower reacting substrate, 0.2 equivalents of initiator (di-tert-butyl peroxide) and 1.1 equivalents of 1,2-peroxy butane were added to the reaction mixture. The solutions were degassed in a pressure tube in the usual way and heated to 120 ^{o}C for one hour. After heating, the tubes were cooled under tap water and analyzed by GC using a phenanthrene solution as an internal standard. The results of these experiments are shown in table 23 on page 114.

Appendix

Chain Length Experiments. What follows is a compilation of the data gathered from the additions of benzyl and phenethyl radicals to allyl bromides **135** – **139** with regards to the initial chain length. All reactions were performed in a degassed pressure tube using the free-radical precursor as a solvent (toluene or ethylbenzene). The substituted allyl bromides were in a 0.14 M concentration and 0.2 molar equivalents of di-*tert*-butylperoxide was used as the initiator. The tubes were heated to 120 ^{o}C in a constant temperature oil bath (+/- 1 ^{o}C) and cooled under tap water to stop the reaction at the specified times. Yields were determined by gas chromatography (GC) using phenanthrene as an internal standard.

Regarding the reaction between phenethyl radical and **138** (eq 59), four diastereomers were expected: the two syn- diastereomers and the two anti- diastereomers. Thus, four peaks were predicted upon analysis by GC. However, six peaks were observed by GC after only 30 minutes of reaction time. By analyzing the reaction mixture by GC/mass spectrometry, it was found that all six peaks had the same molecular ion, as well as, very similar fragmentation patterns. It is likely, therefore that the two extraneous peaks are due to migration of the double bond to give compounds **158** and **159**. These stereoisomers were not isolable by conventional bench top flash chromatography or preparative thin layer chromatograpgy. Response factors were therefore unobtainable. Because of this complication coupled with an apparent slow reaction rate, the addition of

phenethyl radical to the pro-chiral allyl bromides **138** – **140** was not explored further.



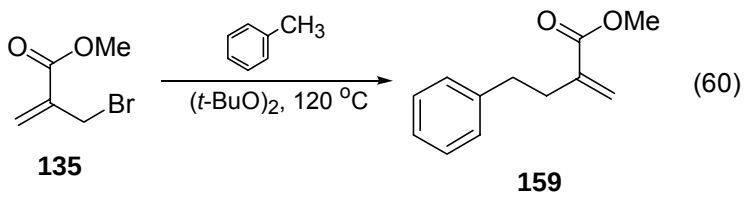
138

156
(*syn*- and *anti*-)

157
(*cis*- and *trans*-)

158
(*cis*- and *trans*-)

(59)



135 **159** (60)

Chain Length: 374

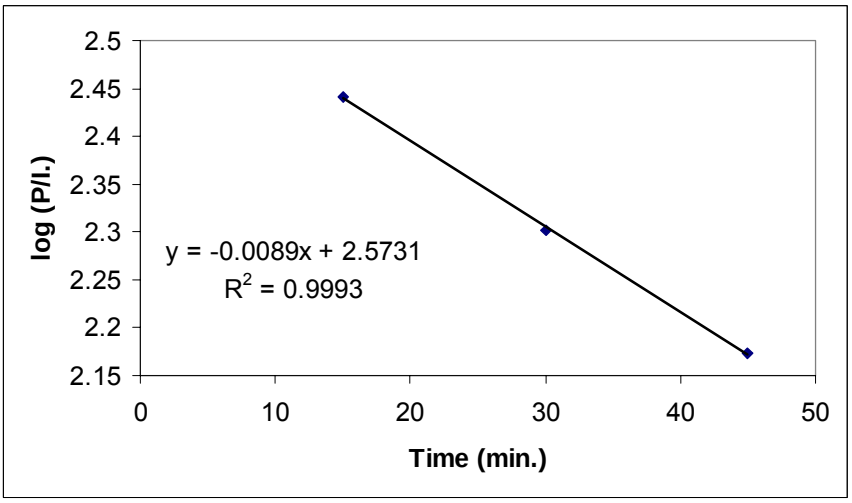


Figure 25. Chain length data for the reaction of **135** and benzyl radical.

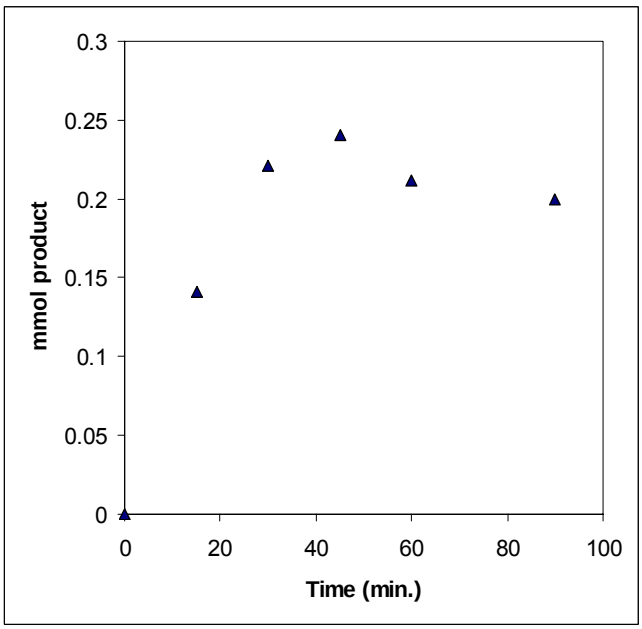
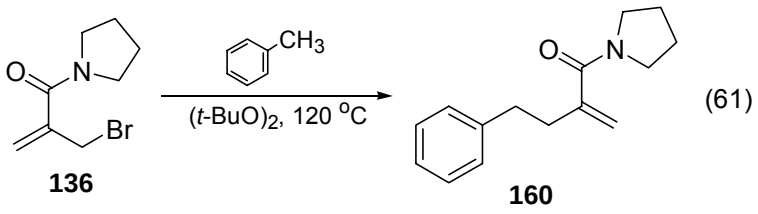


Figure 26. Absolute yield (mmol of product) of **159** as a function of time.



136 **160** (61)

Chain Length: 52

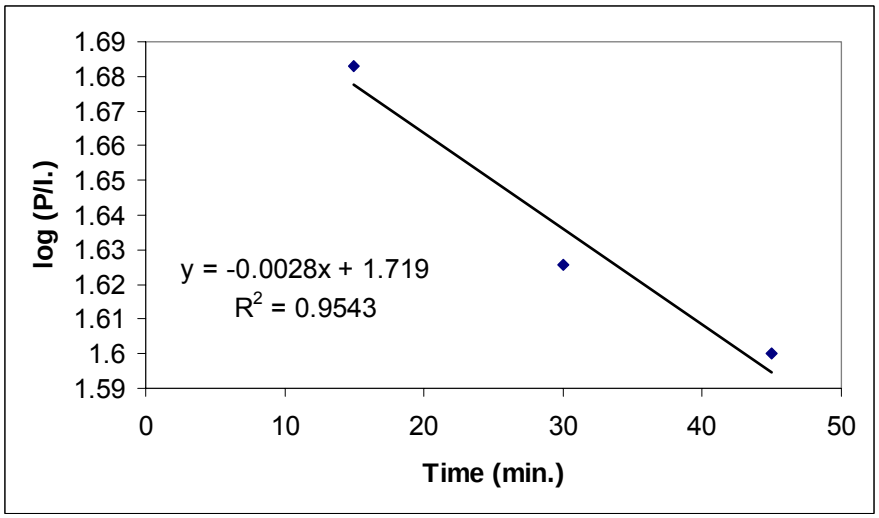


Figure 27. Chain length data for the reaction of **136** and benzyl radical.

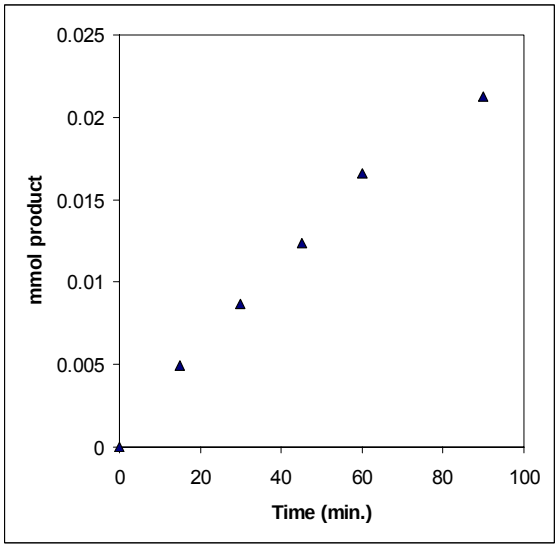
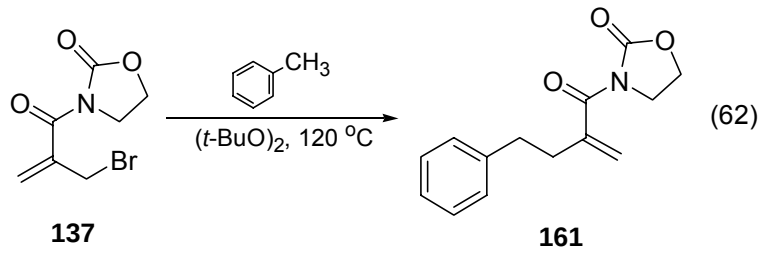


Figure 28. Absolute yield (mmol of product) of **160** as a function of time.



137 **161** (62)

Chain Length: 20

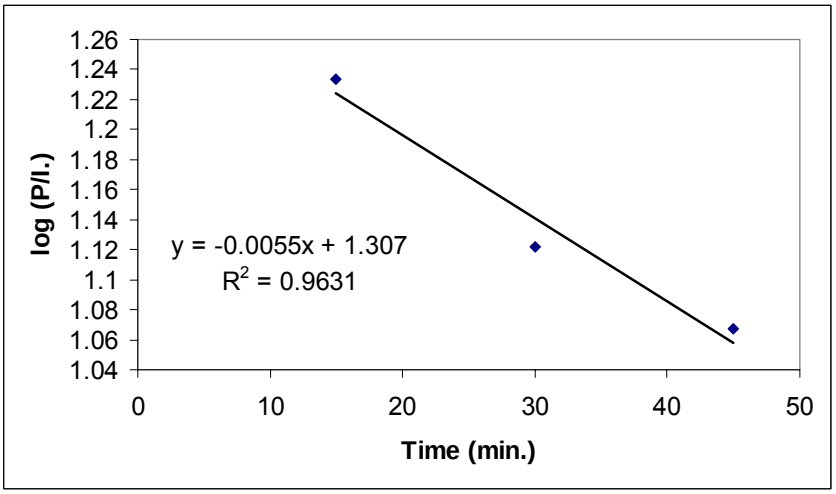


Figure 29. Chain length data for the reaction of **137** and benzyl radical.

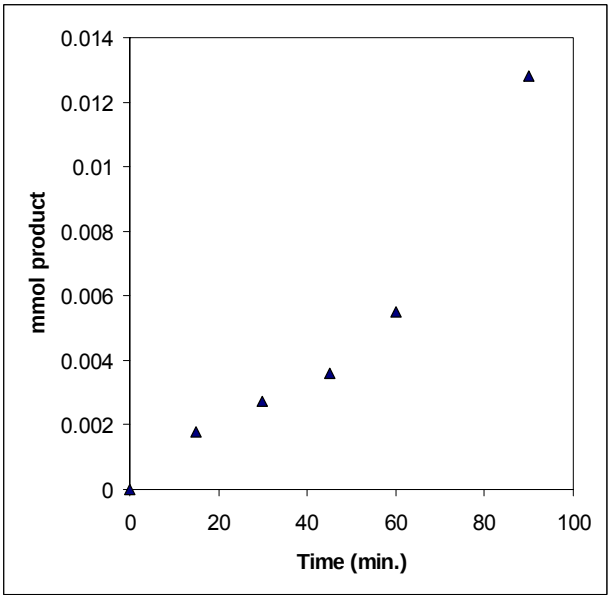
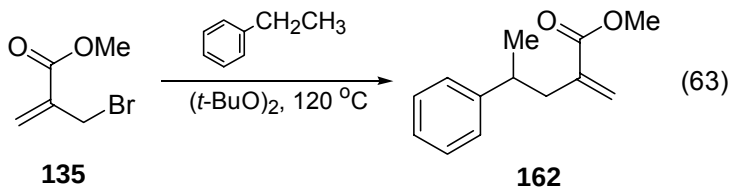


Figure 30. Absolute yield (mmol of product) of **161** as a function of time.



135 **162** (63)

Chain Length: 188

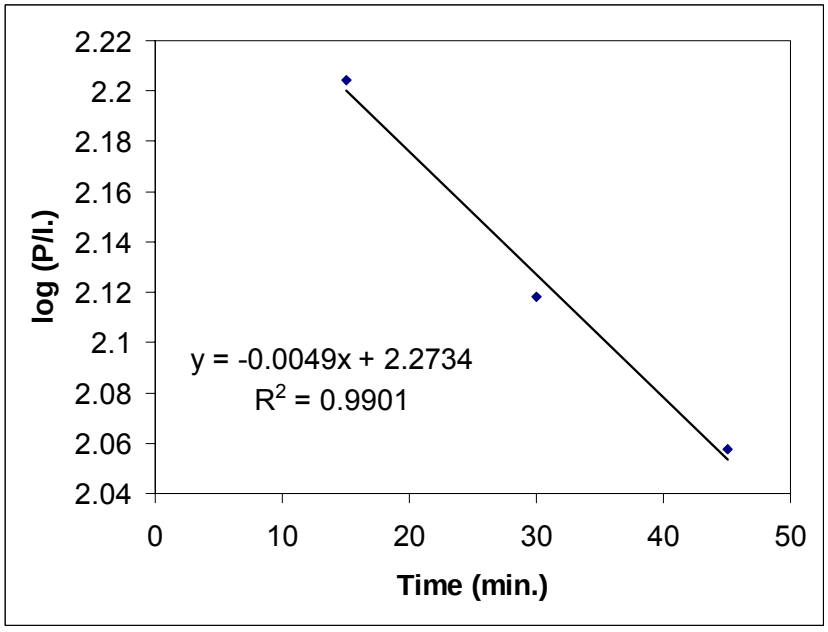


Figure 31. Chain length data for the reaction of **135** and phenethyl radical.

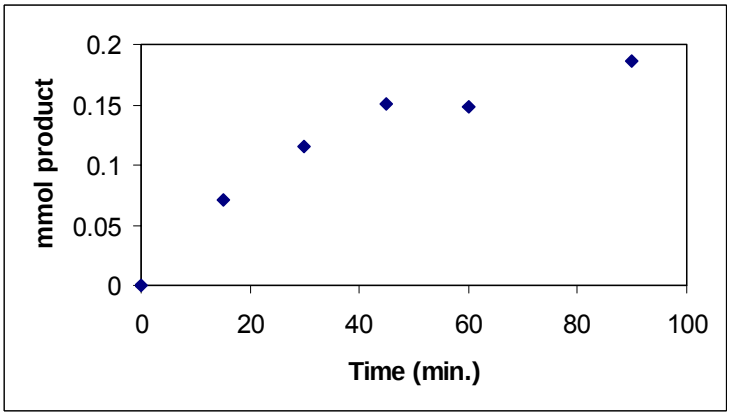
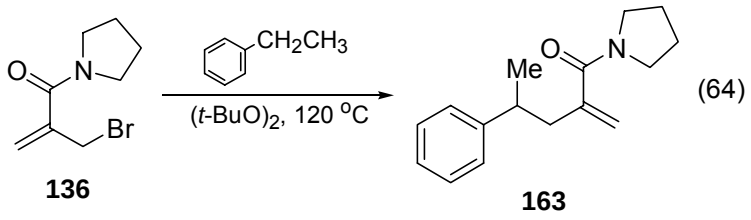


Figure 32. Absolute yield (mmol of product) of **162** as a function of time.



136 **163** (64)

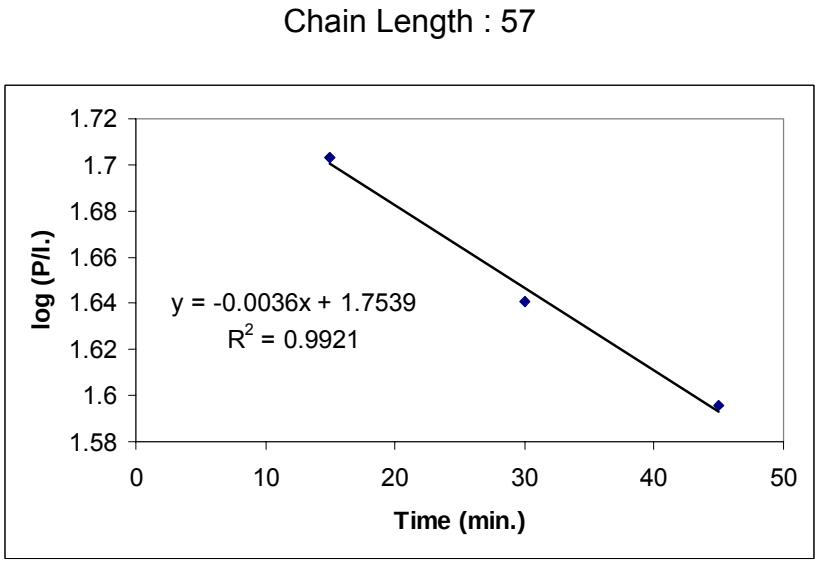


Figure 33. Chain length data for the reaction of **136** and phenethyl radical.

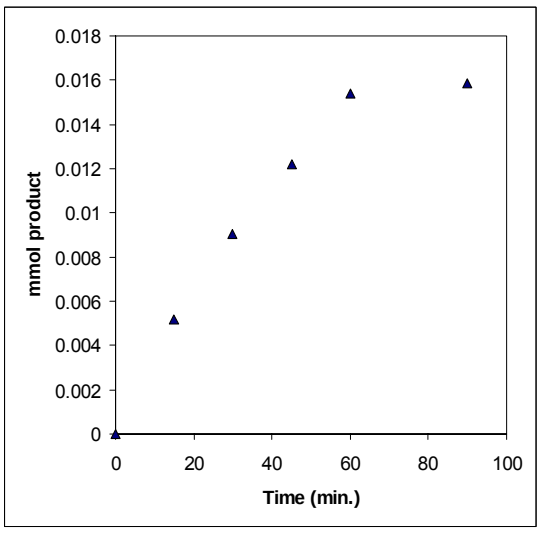
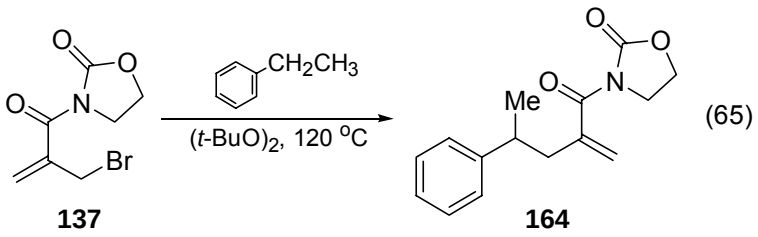


Figure 34. Absolute yield (mmol of product) of **163** as a function of time.



137 **164** (65)

Chain Length: 21

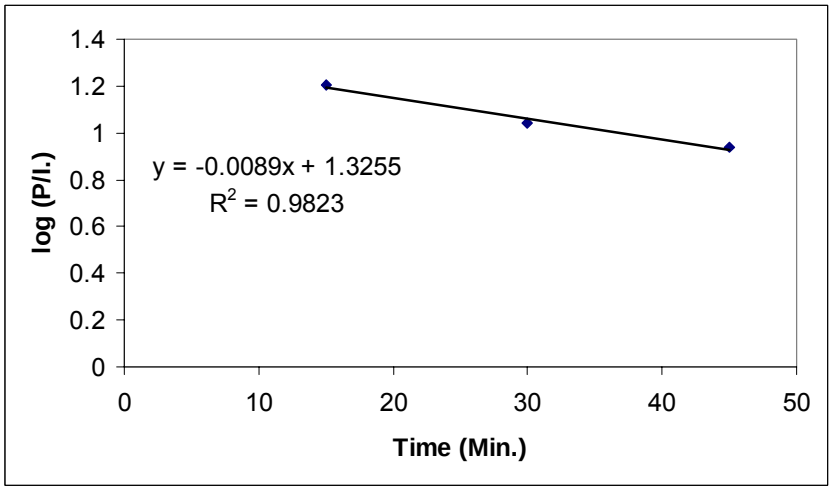


Figure 35. Chain length data for the reaction of **137** and phenethyl radical.

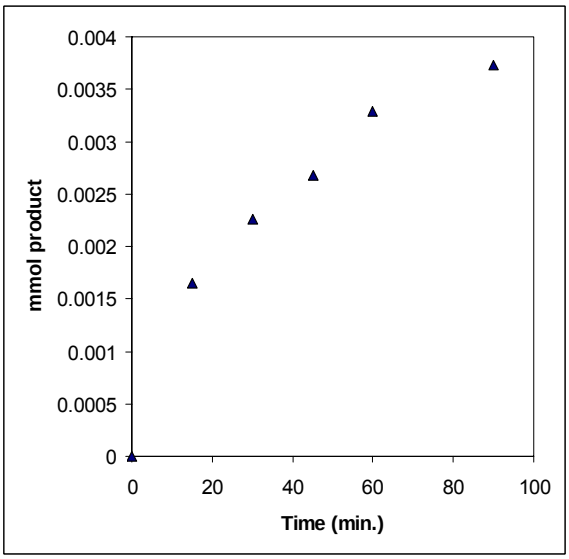
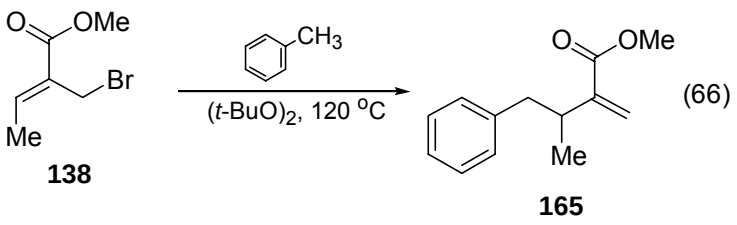


Figure 36. Absolute yield (mmol of product) of **164** as a function of time.



138 **165** (66)

Chain Length: 47

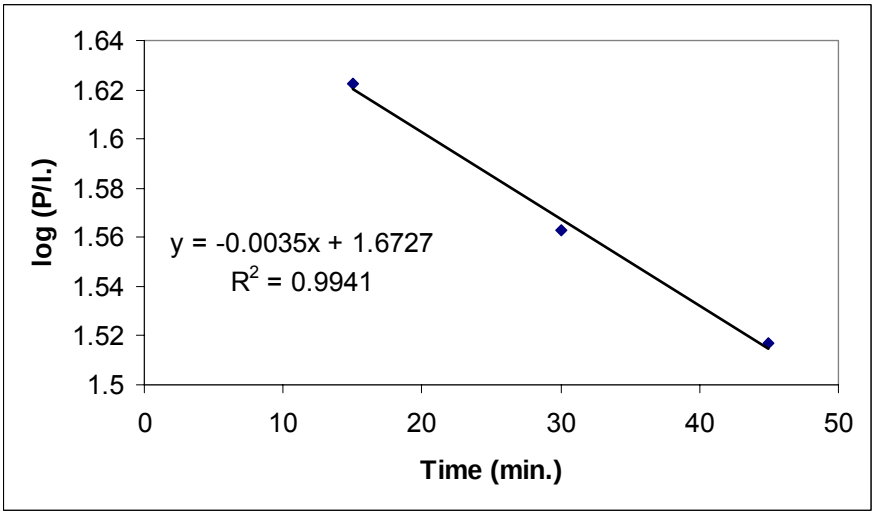


Figure 37. Chain length data for the reaction of **138** and benzyl radical.

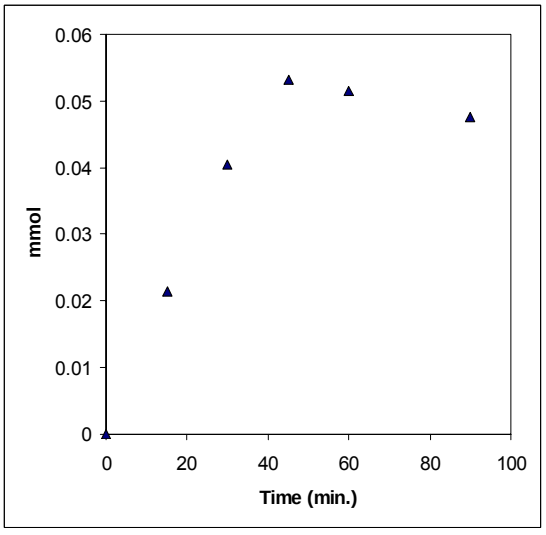
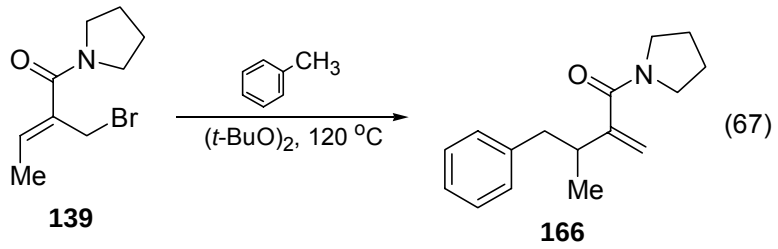


Figure 38. Absolute yield (mmol of product) of **165** as a function of time.



139 **166** (67)

Chain Length: 3.2

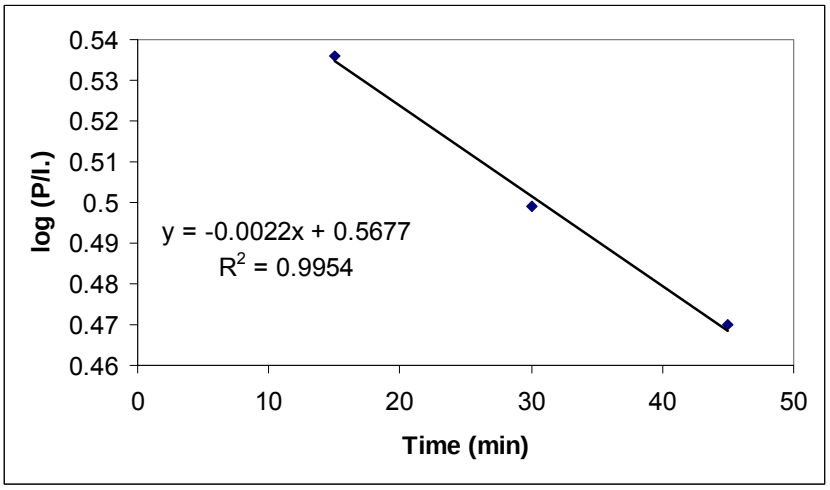


Figure 39. Chain length data for the reaction of **139** and benzyl radical.

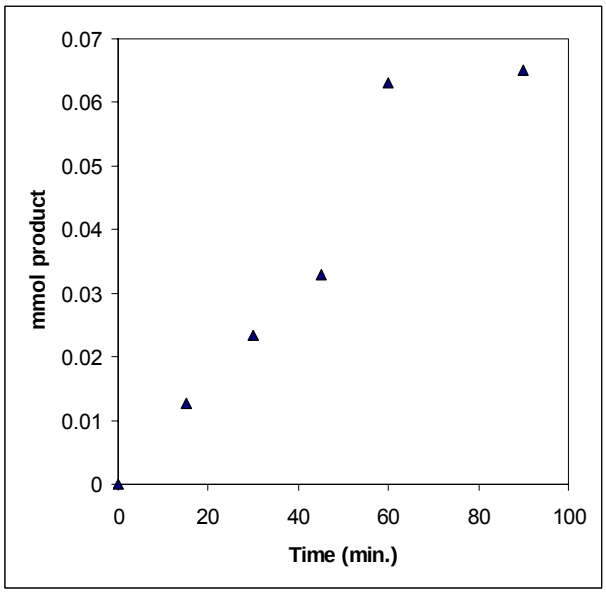
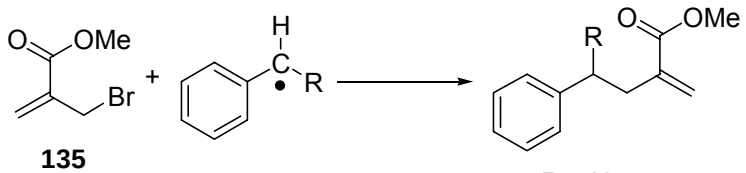


Figure 40. Absolute yield (mmol of product) of **166** as a function of time.

Scheme 40



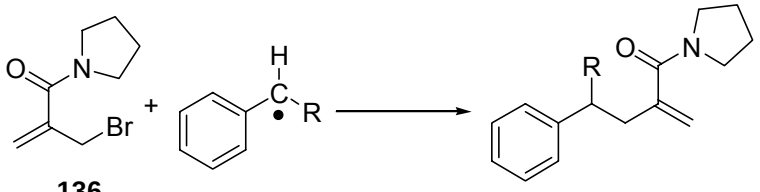
135

R = H, **159**
R = Me, **162**

Table 15. Reaction of **135** with carbon centered radicals: % yield with respect to reaction time.

Time (min.)	% Yield **159**	% Yield **162**
15	16.8	11.0
30	26.3	18.1
45	28.7	23.5
60	25.2	23.0
90	23.8	29.2

Scheme 41



136

R = H, **160**
R = Me, **163**

Table 16. Reaction of **136** with carbon centered radicals: % yield with respect to reaction time.

Time (min.)	% Yield **160**	% Yield **163**
15	3.55	3.72
30	6.23	6.45
45	8.80	8.71
60	11.8	11.0
90	15.2	11.3

Scheme 42

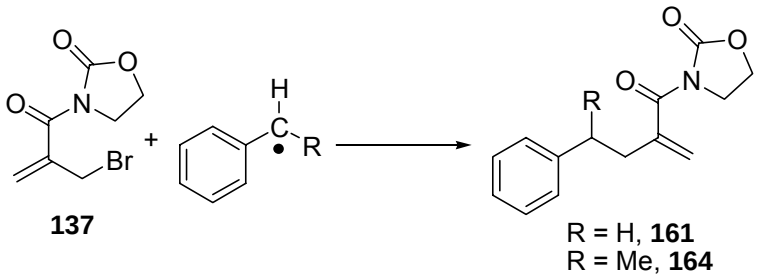


Table 17. Reaction of **137** with carbon centered radicals: % yield with respect to reaction time.

Time (min.)	% Yield **161**	% Yield **164**
15	1.26	1.18
30	1.95	1.61
45	2.58	1.91
60	3.92	2.34
90	9.15	2.66

Scheme 43

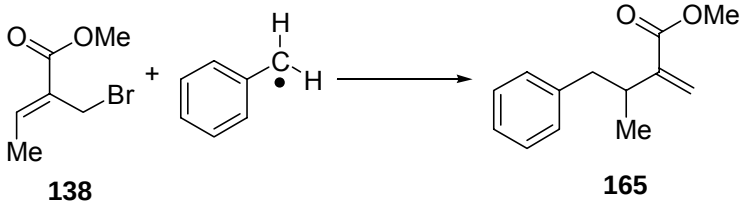
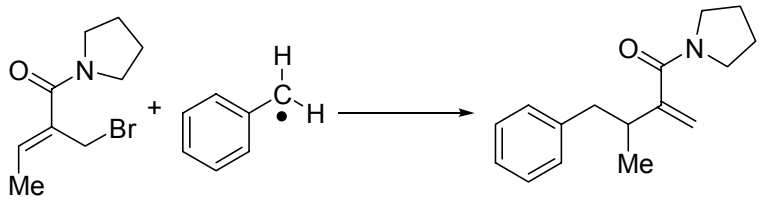


Table 18. Reaction of **138** with carbon centered radicals: % yield with respect to reaction time.

Time (min.)	% Yield **165**
15	2.5
30	5.8
45	6.3
60	6.1
90	5.7

Scheme 44



139 **166**

Table 19. Reaction of **139** with carbon centered radicals: % yield with respect to reaction time.

Time (min.)	% Yield **166**
15	1.52
30	2.79
45	3.91
60	7.52
90	7.75

Vita

John Struss was born August 12, 1970 in Peoria, Illinois to Karl and Ina Struss. He graduated from Berea Community High School in Berea, Kentucky in 1988. In the fall of that year he enrolled at Berea College and received a Bachelor of Arts in chemistry in 1996. Shortly after graduating college, John was employed at an environmental testing firm for about 18 months until he joined the Fossil Fuels group of the Energy Sciences division at Oak Ridge National Laboratory where, under the guise of Dr. A. C. Buchanan, he worked toward a better understanding of the mechanisms involved with the maturation of lignan and low grade coals. It was here that he was encouraged to enroll in the graduate school. In the fall of 1996, he entered Virginia Polytechnic Institute and State University in Blacksburg, Virginia where he worked under Doctors Michael Calter and James Tanko in the areas of asymmetric organic synthesis and physical organic chemistry. He received a Doctor of Philosophy in chemistry in August, 2002.

In August, 2001, John started a tenure track position as an Assistant Professor at the University of Tampa, Tampa, Florida, USA.