Hydrocarbon Functionalization via a New Free Radical-Based Condensation Reaction

Mitra Sadeghipour

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James M. Tanko, Chair

Harold M. Bell

Karen J. Brewer

Neal Castagnoli

David G. I. Kingston

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Blacksburg, Virginia

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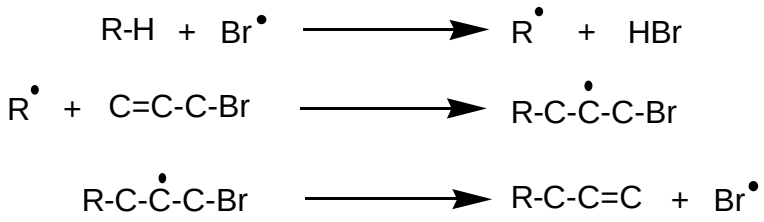
Hydrocarbon Functionalization via a New Free Radical-Based Condensation Reaction

Mitra Sadeghipour

(Abstract)

A new free radical chain process for the allylation of hydrocarbons and some other substrates utilizing substituted allyl bromides (R-H + C=C-C-Br $\rightarrow$ R-C-C=C + HBr) has been developed. Good to excellent yields were observed in all cases. Kinetic chain measurements and competition experiments were performed in order to elucidate the mechanism of the reaction. Overall, the results are consistent with the free radical chain process depicted below:



Substitution effect on the reactivity of the allyl bromides (CH_2=C(Z)CH_2Br) and its influence on the overall reaction rate were studied by conducting several competition experiments. The relative rate constants for addition of $PhCH_2^{\bullet}$ to CH_2=C(Z)CH_2Br are: Z=CN(180), COOEt(110), Ph(65), H(1.0). The trend of electronegativity/reactivity of these reactions was very similar to that reported for addition of $PhCH_2^{\bullet}$ to substituted alkenes. Other than alkyl aromatics ($PhCH_3$, $PhCH(CH_3)_2$), other substrates (i.e., 2- propanol, phenyl cyclopropane) were also tested for this allylation reaction. The magnitude and scope of these reactions, and their synthetic utility is discussed.

Acknowledgement

I would like to express my sincere gratitude to Professor James M. Tanko for his guidance, patience and friendship during my graduate career. His advisement in chemistry and life will be always with me. Dr. Tanko, you have challenged me to be independent and self-sufficient. Words can not express my appreciation for your invaluable mentorship; thank you. I am very grateful to all of my committee members for their generosity in donating time and expertise in their field of chemistry to make this project possible. I have truly benefited from the wisdom of this committee; thank you.

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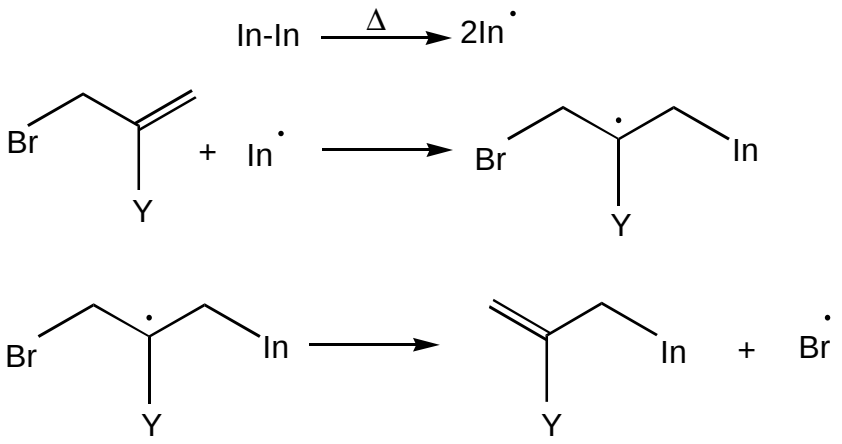
CHAPTER 1. LITERATURE REVIEW

1.1 Description of dissertation

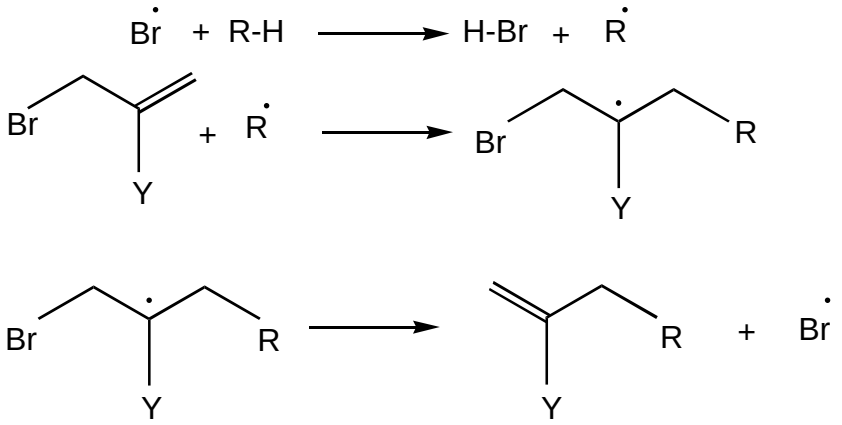
Organic chemists are interested in making complex molecules for specific purposes. For example, certain compounds have medicinal properties but are not available from natural sources. Biochemists are interested in making molecules which mimic metabolic pathways in order to study the nature of biological systems. Physical organic chemists design molecules in order to measure their physical constants, chemical behavior, and other properties. There are many reasons for total synthesis of organic molecules. Nevertheless, many compounds that are commercially available and inexpensive are also small, containing five or fewer carbon atoms. Therefore, organic chemists are interested in reactions which form new carbon-carbon (C-C) bonds in order to synthesize larger, complicated molecules from smaller, simple fragments. Name reactions such as Grignard and Friedel-Craft alkylation are examples of such processes.

The purpose of this project is to develop a new C-C bond forming reaction based upon $Br^{\bullet}$ chemistry. The proposed mechanism of this reaction is illustrated in scheme 1-1. Decomposition of a small amount of initiator forms two radicals ($In^{\bullet}$). The resultant radical ($In^{\bullet}$) should attack the double bond of the allyl bromide. The new radical undergoes β-scission and generates a bromine atom. The initiation stage provides a radical ($Br^{\bullet}$) which will be the chain carrier for the proposed allylation reactions under study.



Scheme 1-1. Initiation reaction with substituted allyl bromide

The proposed mechanism for the propagation stage of this reaction is illustrated in scheme 1-2. Bromine atom starts the propagation stage by abstracting hydrogen from a hydrocarbon. The resultant carbon-centered radical ($R^{\bullet}$) should add to the double bond of the allyl bromide forming a β-bromo adduct radical. Subsequently the β-bromo alkyl radical should go through a β-scission yielding the product and regenerating $Br^{\bullet}$ (Scheme 1-2).



Scheme 1-2. Propagation stage for allyl transfer reaction of a hydrogen atom donor

In order to study the scope and limitations of this reaction, different substituents on the allyl bromide (Y= H, Ph, COOEt, CN) and different substrates ($PhCH_3$, $PhCH(CH_3)_2$, *i*-PrOH, Ph(*c*-C_3H_5)) were tested. In addition, experiments to establish the mechanism of the reactions were performed.

In the following sections, a literature review will provide information pertaining to each step of the propagation stage. The literature precedent related to $Br^{\bullet}$ reactivity towards hydrocarbons, requirements for radical additions to olefins and the β-cleavage step will be considered. In addition, literature pertaining to chain transfer agents, which include addition-fragmentation steps, will be reviewed. Lastly, a review of other free radical addition-fragmentation reactions in organic synthesis provides an overview for the type of reactions to be discussed or dealt with.

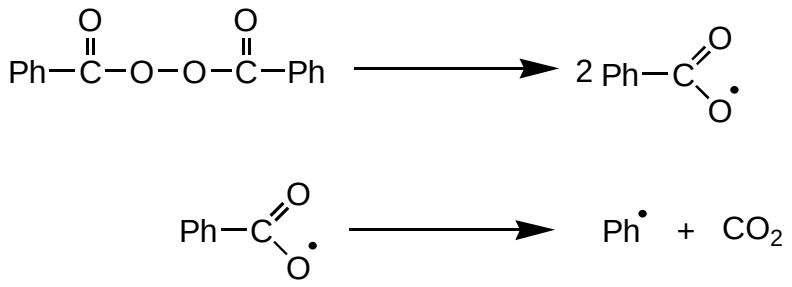
1.2 Free radical initiators

As explained earlier, before starting a chain reaction, a chain carrier should be produced. In most cases, decomposition of a small amount of initiator (thermally or photochemically) will initiate the chain reaction and produce the chain carrier as depicted (Scheme 1-1). Compounds which have weak bonds are good initiators (i.e., peroxides and azo compounds). Other than weak bonds, a functional group which can stabilize the radical is important to have a longer lived radical (i.e., CN or Ph group). In these experiments, three different thermal initiators were used: benzoyl peroxide $(BzO)_2$, *t*-butyl peroxide (*t*-$BuO)_2$, and azobisisobutyronitrile (AIBN).

1.2.1 Benzoyl peroxide

The products obtained from decomposition of benzoyl peroxide are those which would be expected from the reaction of both benzoyloxy and phenyl radicals. Benzoyloxy radicals result from the one-bond cleavage of O-O in the

peroxide and phenyl radicals form through a decarboxylation of the benzoyloxy radical (Scheme 1-3).

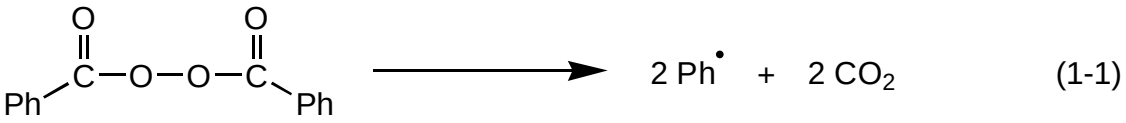


Scheme 1-3. Decomposition of benzoyl peroxide

Decomposition in the absence of solvent gives CO_2, biphenyl and small amounts of phenyl benzoate and benzene.[1]

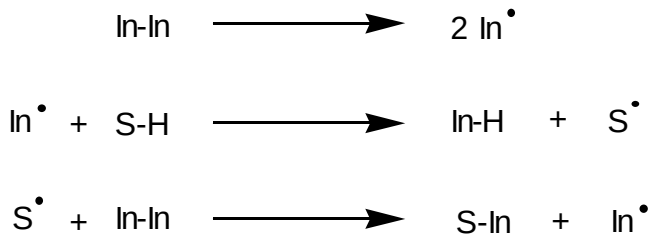
The evidence for a two step decomposition as illustrated in the scheme (1-3) vs. a concerted two bond cleavage mechanism was provided by different researchers.[2-4] In the first step, only O-O bond is cleaved. The one-bond cleavage mechanism was established for benzoyl peroxide decomposition in CCl_4 by Hammond, et. al.[2] Adding iodine and moisture trapped 100% of the benzoyloxy groups as benzoic acid without affecting the decomposition rate. When benzoyl peroxide is decomposed in styrene, the one-bond cleavage mechanism was established by study of the end groups in the polystyrene produced.[3] The phenyl rings of the peroxide were labeled with ^{14}C. The proportion of benzoyloxy and phenyl end groups was determined by counting the radioactive carbon in the polymer both before and after removing all of the benzoyloxy end groups by hydrolysis. At high styrene concentration, no phenyl radical formation was detected which means that the second step is required for formation of this radical. However, Fischer argued that a small amount of the concerted reaction (two bond cleavage mechanism) contributes to the decomposition of benzoyl peroxide (Eq. 1-1).[4] He cites the isolation of small

amounts of phenyl benzoate as support for his claim. If there is any concerted reaction, $Ph^{\bullet}$ which is readily formed, may attack the benzoyloxy radicals and form phenyl benzoate.



(1-1)

One problem regarding the kinetics studies of initiators is called “induced decomposition”. Induced chain decompositions refer to the extent to which a potential initiator is destroyed by chain reactions. The importance of induced chain decomposition of benzoyl peroxide was deduced by Nozaki and Bartlett[5a] and by Cass.[5b] The rate of decomposition of benzoyl peroxide was found to be reduced when scavengers were added and the rate law was greater than first order in some cases. The unimolecular rate constant for decomposition increased with peroxide concentration, and the rate was increased by added radical sources. These observations are consistent with the chain sequence shown in scheme 1-4.



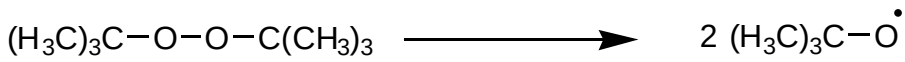
Scheme 1-4. Induced decomposition of peroxide in the presence of a hydrogen atom donor (S-H)

The effect of one or more of these radical-induced reactions can seriously affect the magnitude of the observed activation parameters.

The thermolysis of benzoyl propanoyl and benzoyl acetyl peroxides gives the corresponding benzoate esters and alkyl benzenes. From the CIDNP signals of those products, the rate constants for the decarboxylation of the benzoyloxy radical is estimated to be approximately 1×10^8 s^{-1} at 130 ^oC,[6a] at 100 ^oC,[6b] and at 90 ^oC[6c] (Scheme 1-3). Ingold et. al.[6d] also reported rate constants of 10^5 s^{-1} for the decarboxylation of benzoyloxy radical at 55 ^oC using spin-trapping procedure.

1.2.2 *t*-Butyl peroxide

t-Butyl peroxide decomposes by a first-order process in the gas phase independent of pressure.[7] Between 116-350 ^oC in the gas phase, the activation parameters for the decomposition of $(t\text{-BuO})_2$ were found to be 38 kcal (E_a) and 7×10^{15} s^{-1} (pre-exponential factor).[8] The rate constants in solution are essentially the same as in the gas phase, suggesting a simple unimolecular process as a rate determining step which has a minimum induced (chain) reaction effect in solution (Eq. 1-2).[7]



(1-2)

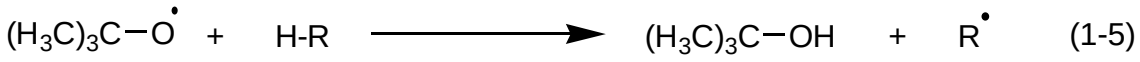
However, the overall course of the decomposition is complicated by decomposition of *t*-butoxy radical to acetone and methyl radicals (Eq. 1-3).

(1-3)

In the gas phase, the resulting methyl radicals dimerize to yield ethane (Eq. 1-4).

(1-4)

In solution however, attack on solvent (e.g., by hydrogen abstraction) may compete with reaction (1-3) (Eq. 1-5).



(1-5)

Because reaction (1-3) is a radical decomposition which would be expected to occur at a constant rate at a given temperature and be independent of the medium, the *t*-butyl alcohol/acetone ratio will depend on the hydrogen-donating ability of the solvent.[9]

In general, values of the *t*-butyl alcohol/acetone ratio in a given system decrease with temperature, indicating a considerable activation energy for the *t*-butoxy radical decomposition (Eq. 1-3), higher than that for hydrogen abstraction. An estimate for the activation energy of the β-scission step is 11-16 kcal/ mol.[10] Thus, *t*-butoxy radical decomposition is easy to circumvent and almost any hydrogen donor will divert this intermediate away from acetone to *t*-butyl alcohol.

Rates and activation parameters for the solution and gas phase decomposition of *t*-butyl peroxide indicate that unlike $(BzO)_2$ the effect of induced decomposition in solution is insignificant (Table 1-1). [9,11] In other words, the decomposition of $(t\text{-BuO})_2$ is not complicated by chain-induced pathways.

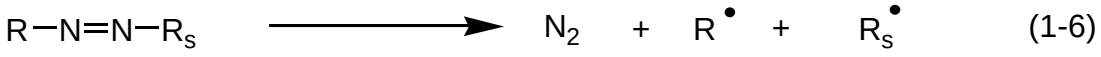
Table 1-1. Activation parameters for *t*-butyl peroxide decomposition

Reaction condition	E_a (kcal/mol)	log A (s^{-1})
Gas phase	37.4	15.6
In *t*-butyl benzene	38.0	16
In Cumene	37.5	15.8

The activation enthalpy varies from a low of 31 kcal/mol in acetonitrile to a high of 40.8 kcal/mol in cyclohexane. There is not very much difference in the rates because of compensation in the apparent activation entropies.[12]

1.2.3 Azobisisobutyronitrile

Although the thermolysis of azoalkanes ultimately gives two alkyl radicals, the mechanism can range from a completely concerted two bond cleavage (Eq. 1-6) to a stepwise one bond cleavage (Scheme 1-5).



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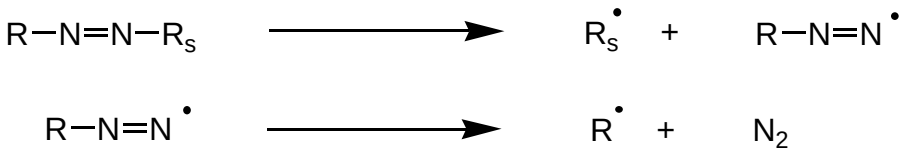
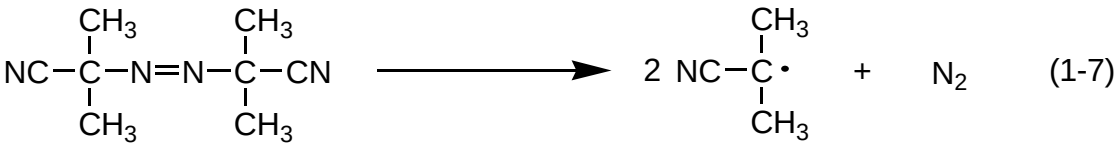


Scheme 1-5. Concerted and Stepwise mechanisms for thermal decomposition of azo compounds

It is probable that symmetrical azoalkanes decompose by the concerted mechanism, with equal stretching of both bonds. Simple aliphatic azo compounds, (e.g., azomethane), decompose appreciably only at temperatures near 400 ^{o}C.[12+1] However, suitably substituted azo compounds, in which C-N bond dissociation energies are lowered by the stability of the resulting radicals, dissociate at much lower temperatures. Azobisisobutyronitrile (AIBN) is an example of a disubstituted azo acetonitrile which breaks down to 2-cyano isopropyl radical and N_2 (Eq. 1-7).



(1-7)

Azobisisobutyronitrile decomposes by strictly first order kinetics at essentially the same rate in a variety of solvents. Therefore, the possibility of the induced chain decomposition of AIBN is ruled out (Table 1-2).[13] In other words, the decomposition of AIBN proceeds by reaction 1-7 and is not complicated by solvent molecules or any radical interference.

Table 1-2[13]. Decomposition of azobisisobutyronitrile in various solvents at 80^{o}

Solvent	k ($\times 10^{4}$) (s^{-1})
Xylene	1.53
Dimethylaniline	1.83
Aniline	1.68
Toluene	1.55

Decomposition rates may be followed by nitrogen evolution[13a] or spectrophotometrically.[13b]

1.3 Relative reactivities of 1^{o}-, 2^{o}-, 3^{o}- hydrogen atoms in alkylaromatics

Because the first step of the propagation stage of the reaction under study (Scheme 1-2) involves hydrogen abstraction by a bromine atoms, the reactivity of the bromine atom towards different types of hydrogens is an important consideration for this project. Alkylaromatics are one type of substrate which has been tested. The benzylic radical resulting from H-abstraction is stabilized by

resonance interactions with the aromatic ring. Therefore, comparing the reactivity of bromine atom towards different alkylaromatics is important.

The bond strengths and relative reactivities of a number of alkyl and alkylaromatic hydrogen atoms are summarized in Table 1-3. The bond strength of HBr is 87 kcal/mole.[14] Consequently, hydrogen atom abstraction by $Br^{\bullet}$ from simple alkanes is substantially endothermic and occurs at a slow rate. In contrast to alkanes, abstraction of a benzylic hydrogen is more facile and occurs at a significantly greater rate (The rate constant for $Br^{\bullet} + PhCH_3 \rightarrow PhCH_2^{\bullet} + HBr$ is on the order of 10^5 $M^{-1}s^{-1}$)[15], and the reaction is thermoneutral. Therefore, $Br^{\bullet}$ shows an especially high reactivity for benzylic hydrogens. Moreover, benzylic radical stability increases with increasing alkyl substitution. For example, cumyl radical is more stable than benzyl radical. Consequently, for alkylaromatics, the relative reactivities of the hydrogens towards $Br^{\bullet}$ are 3^o- benzylic (59)> 2^o-benzylic (25)> 1^o-benzylic (1.0).[16]

Table 1-3. Bond dissociation energy (BDE) and relative reactivities (k_{rel}) of alkyl and aralkyl hydrogen atoms towards bromine atom

R-**H**	BDE[1] (kcal/mole)	k_{rel}[16] at 77 ^oC (per hydrogen)
$CH_3C\mathbf{H}_3$	98.2	1
$(CH_3)_2C\mathbf{H}_2$	95.1	220
$(CH_3)_3C\mathbf{H}$	93.2	19,400
$C_6H_5C\mathbf{H}_3$	88.0	64,000
$C_6H_5C\mathbf{H}_2CH_3$	85.4	1,600,000
$C_6H_5C\mathbf{H}(CH_3)_2$	84.4	3,800,000

1.4 Addition of C-centered radicals to C=C

The second step of the proposed reaction involves the addition of a carbon-centered radical to the double bond of the allyl bromide (Scheme 1-2). This type of addition is one of the most important free radical reactions and is widely used in polymer and organic synthesis. There are several factors which affect the rate of addition and the nature of the transition state. These factors include: polar, steric and enthalpic effects of the radical and the alkene substituents. There is some controversy about the importance of the role of each factor in the mechanism of addition of the C-centered radicals to the double bond of an olefin.

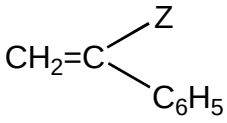
According to the experimental results, the rate of alkyl radical addition to alkenes is controlled by steric and polar effects. The rate of addition of C-centered radicals to β-substituted alkenes increases by increasing the electron-withdrawing ability of the substituent (Table 1-4).[17]

Table 1-4.[17] Relative rate constants (k_{rel}) for the addition of radicals to substituted olefins

$$\dot{R} + H_2C{=}CHZ \xrightarrow{k_{rel}} RCH_2\text{-}\dot{C}HZ$$

Z \ R•	•CH_3 (65 °C)	•C_2H_5 (100 °C)	•C_6H_{11} (20 °C)
CN	2.2	5.1	24
CO_2CH_3	1.3	1.9	6.7
C_6H_5	≡1.0	≡1.0	≡1.0

Similar results have been obtained for the addition reaction of cyclohexyl radical ($^{\bullet}C_6H_{11}$) to substituted styrenes (**1**), methyl acrylates (**2**), and acrylonitriles (**3**) (Table 1-5). A Hammett plot of the relative reactivities of the cyclohexyl radical against $\sigma^{\cdot-}$ and σ-values, gives a straight line with correlation coefficients of 0.91-0.99. The ρ-values calculated from the gradients lie between 3.1 and 3.8 at 20 ^{o}C.[17c] The positive sign of these ρ-values indicates that alkyl radicals are nucleophilic.



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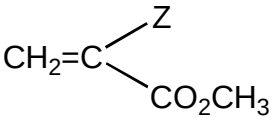

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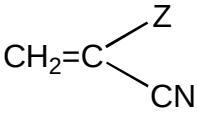

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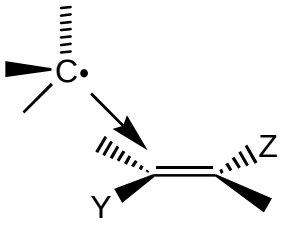
Table 1-5.[17c] Relative rate of addition of cyclohexyl radical to styrenes (**1**), methyl acrylates (**2**), and acrylonitriles (**3**) at 20 ^{o}C

Z \ Alkenes	**1**	**2**	**3**
CO_2CH_3	6.4	150	310
C_6H_5	0.51	6.4	66
H	0.15	≡1.0	3.6
CH_3	0.14	0.75	2.0

These results provide evidence for a polar effect of the β-substituent on the alkenes for the alkyl radical addition reactions.

Addition of alkyl radicals to alkenes is strongly exothermic, since a σ-bond is formed and a π-bond is broken.[18] According to Hammond's postulate, [19] the transition state should lie very early on the reaction coordinate. The measured

enthalpy of activation (3 and 8 kcal/mol)[20] and theoretical calculations for the distance between methyl radical and ethylene (*ca.* 230 pm) support these predictions.[21] All calculations favor an unsymmetrical transition state (**4**) in which the distances between the attacking radical and the two vinylic carbon atoms of the alkene are unequal.[21,22]



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Because of the early transition state and the lack of steric β-effects, frontier orbital theory can explain the substituent effect in the free radical addition to olefins. The singly occupied orbital (SOMO) of the radical interacts with the lowest unoccupied orbital (LUMO) or the highest occupied orbital (HOMO) of the olefin. Alkyl radicals are nucleophilic in addition reactions towards olefins. Consequently, alkyl radicals have high lying SOMO and the SOMO-LUMO interaction is decisive for the alkyl radical addition to double bonds of alkenes. Electron-withdrawing substituents lower the LUMO energy. Therefore, the SOMO-LUMO energy difference decreases which result in an increase in the rate of free radical addition (Figure 1-1).

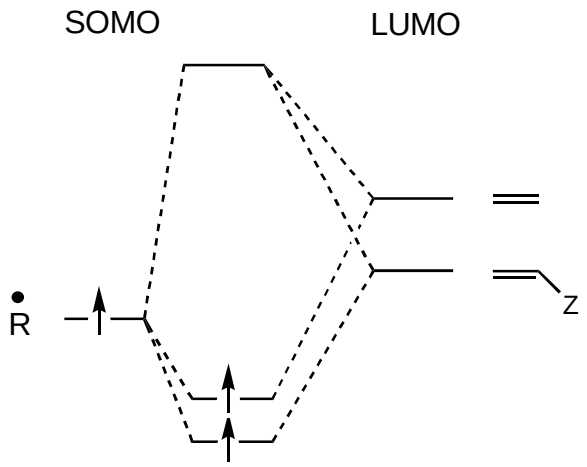


Figure 1-1. Substituent effects in the free radical addition to olefins by frontier orbitals

Recently, high level *ab initio* calculations have been carried out for the addition reactions of methyl radicals to a few substituted alkenes (CH_2=CHX) where X= F, H, OH, CH_3, NH_2, SiH_3, Cl, CHO, NO_2, CN.[23] The result of these calculations indicate that exothermicity is the main factor that dominates the reactivity of the addition reaction. Polar contributions to the transition state are minor. In addition, an early transition state with reactant like structure for the reactions of methyl radical plus ethylene and methyl radical plus formaldehyde has been predicted.[24]

Absolute rate constants for the addition of benzyl ($PhCH_2^{\bullet}$) and cumyl ($PhC(^{\bullet})Me_2$) radicals to substituted alkenes in solution have been reported.[25] The rate constant for addition is dependent on the substitution on the double bond of the alkene. The more electronegative the substituent is, the faster the addition reaction is (Table 1-6).

Table 1-6.[25] Absolute rate constants for $PhCH_2^{\bullet}$ and $PhC(^{\bullet})Me_2$ addition to alkenes ($H_2C=CXY$) in $M^{-1}s^{-1}$

X	Y	$PhCH_2^{\bullet}$	$PhC(^{\bullet})Me_2$
H	CO_2Me	430	800
H	Ph	1100	1200
H	CN	2200	2200

Comparing the reactivity of benzyl and cumyl radicals towards substituted alkenes reveals a similar trend for both radicals (Table 1-6).

In conclusion, one would expect that the same considerations would pertain to addition of $PhCH_2^{\bullet}$ and $PhC(^{\bullet})Me_2$ radicals to double bonds in general will also pertain to allyl bromides. If the substituents on the allyl bromide are varied in analog to those illustrated in Table (1-6), an increased rate of addition may result in a faster reaction overall and higher product yield.

2-Propanol was another substrate which was used for the allyl transfer reaction under study. Because of a low ionization potential of 6.48 ev,[26] 2-hydroxy-2-propyl radical is expected to be very reactive in additions to the double bonds. Absolute rate constants for the addition of the 2-hydroxy-2-propyl radical to alkenes in solution were reported by Fischer, et. al in 1993 by time-resolved CIDNP spectroscopy.[27] The correlation of the rate constants with the alkene electron affinities provided evidence that the 2-hydroxy-2-propyl radical is very nucleophilic, and its addition rates are highly governed by polar effects. Recently,[28] rate constants for the addition of the 2-hydroxy-2-propyl radical to alkenes in solution studied by laser flash photolysis were reported. The results which are listed in Table (1-7) support the earlier findings.

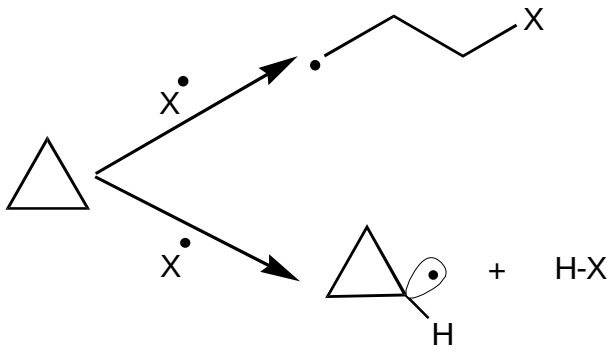
Table (1-7).[28] Rate constants for the addition of the 2-hydroxy-2-propyl radical to alkenes

Alkene	k ($\times 10^{-5}$) $[M^{-1}s^{-1}]$
α-Methyl styrene	2.0
Styrene	4.1
Methyl methacrylate	160
Methacrylonitrile	310
Methyl acrylate	400
Acrylonitrile	1100

As is listed in Table 1-7, the more electronegative the substituent on the double bond is, the faster the rate of reaction is. It is noteworthy that acrylonitrile shows an exceptionally high rate of addition compared with the other alkenes.

1.5 Addition of $Br^{\bullet}$ to cyclopropane

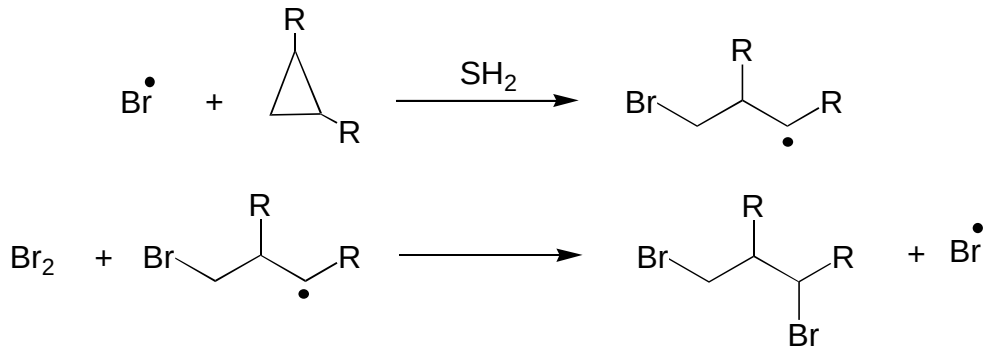
The reaction of a free radical with cyclopropane occurs via two different pathways: hydrogen abstraction and/or ring opening (Scheme 1-6).



Scheme 1-6. Free radical reactions with cyclopropane

The observed chemoselectivity depends on the identity of the attacking radical ($X^{\bullet}$) and the nature of the substitution on the cyclopropane. It has been observed that bromine atom produces ring-opened products in the reactions of alkyl cyclopropanes and most arylcyclopropanes.[29]

The free radical bromination of alkylcyclopropane involves the backside attack of bromine atom on the least-hindered position of the cyclopropane with inversion of configuration (Scheme 1-7).[29]



Scheme 1-7. Propagation steps for the bromination of alkylcyclopropane

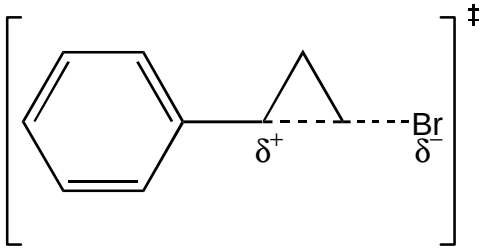
For arylcyclopropanes, free radical bromination results in ring opening in most cases.[30,31] For systems where the aryl moiety is phenyl or α- or β-naphthyl, the bimolecular homolytic substitution is the leading pathway and ring cleavage products were observed.

In the case of 9-cylcopropylanthracene, however, the observed product is the result of a hydrogen atom abstraction reaction. The chemoselectivity of these reactions were related to the conformational energy and the magnitude of the barrier to conformational interconversion. For the 9-cyclopropylanthracene, the lowest energy perpendicular conformation finds the α-C-H bond aligned with the π-system, and consequently hydrogen abstraction is facile (Scheme 1-8).

Perpendicular ($\theta = 90^{o}$) Bisected ($\theta = 0^{o}$)

Scheme 1-8. Conformations of cyclopropylarenes

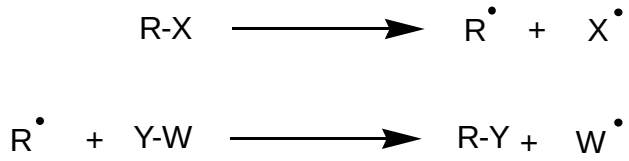
A study of substituent effects in the free radical bromination of substituted phenylcyclopropanes gave a linear Hammett plot with σ^{+} (ρ = -1.84).[30c] The interpretation of the resultant data was that transition state had some charge separation:



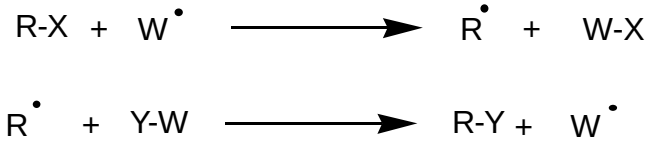
This substituent effect is similar to that found in hydrogen abstraction from substituted toluenes by bromine atom (correlation to σ^+, ρ = -1.76). The similarity of the substitution effects for the free radical bromination of phenylcyclopropane and toluene is due to the formation of a benzylic radical via a polar transition state for both compounds.

1.6 β-Bromoalkyl radicals

Free radical substitution reactions can be carried out by a cleavage (Scheme 1-9) or an abstraction as first step to form $R^{\bullet}$ (Scheme 1-10).



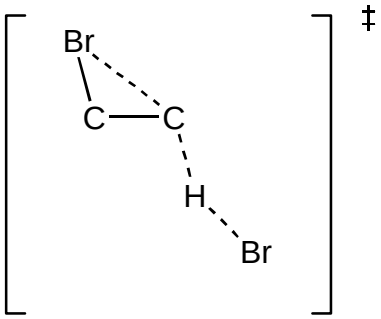
Scheme 1-9. Free radical substitution via cleavage



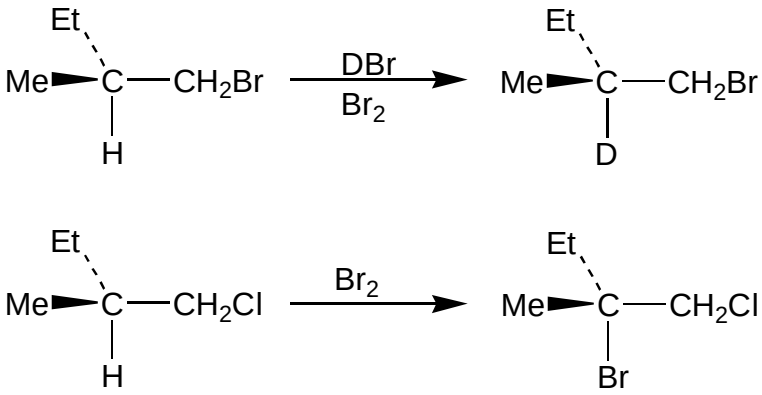
Scheme 1-10. Free radical substitution via abstraction

In a few cases, it has been shown that the cleavage and abstraction steps are accelerated by the presence of neighboring groups. In 1962, Thaler reported 1,2-dibromobutane as the principal product of bromination of 1-bromobutane.[32] The reactivity of C-2 was 5.78 times that of C-3. Since then, a variety of kinetic and

stereochemical studies noted the unusual high reacitvity of β hydrogens of bromo alkanes for free radical bromination.[33] These results have been interpreted in terms of anchimeric assistance by the neighboring bromine substitution in the rate limiting hydrogen abstraction step.

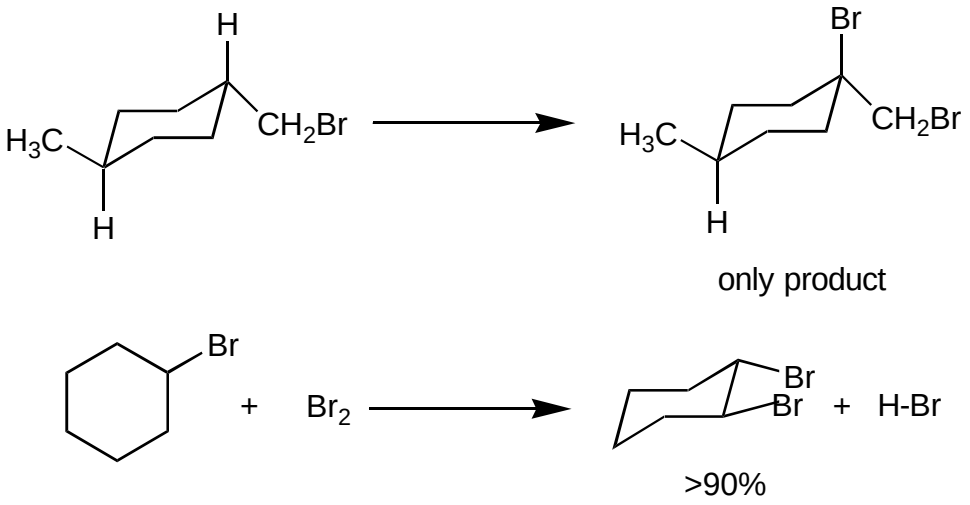


Reactions creating bridged radicals afford experimental evidence for restricted rotation about the C-C bond and control of configuration at both carbon centers. Some examples of extensive retention of enantiomeric purity at a center undergoing radical substitution are illustrated in scheme 1-11.[33d]



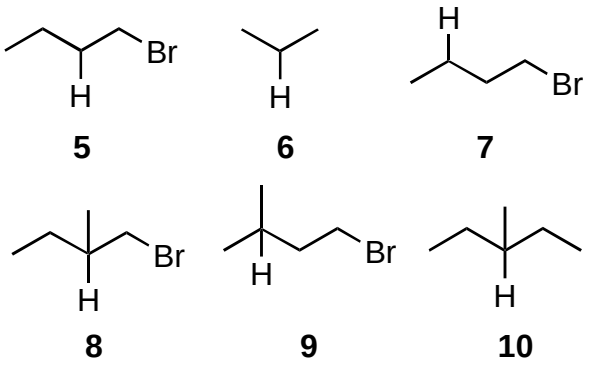
Scheme 1-11. Dis symmetry retained in β-bromosubstituted radicals

Electronegative groups usually deactivate the vicinal position relative to other positions of the same classification in halogenation reactions, thereby favoring substitution at the more remote positions. However, there are numerous reports that in radical brominations the position vicinal to a bromo substituent undergoes substitution more readily than does a similar position in the corresponding hydrocarbon or elsewhere in the bromo-substituted substrate (Scheme 1-12).[34]



Scheme 1-12. Rate enhancement of bromination of bromo alkanes due to bromine neighboring effect

The effect of the bromo substituent on the activation energy and entropy for hydrogen abstraction from alkanes has been studied through competition reactions. A favorable effect on the activation energy and an unfavorable effect on the activated entropy for radical attack at a secondary or tertiary position β to a bromo substituent compared to attack to a similar position γ to the bromo substituent or at one in unsubstituted alkane was observed (Scheme 1-13).[35]



5 **6** **7**

8 **9** **10**

Competition	ΔE_a (kcal/mol)	$\Delta\Delta S^{\neq}$ (eu)
5 vs. **6**	-3	-7
5 vs. **7**	-3	-7
8 vs. **9**	-3	-4
8 vs. **10**	-0.9	-2

Scheme 1-13.[35] Comparative activation parameters for hydrogen abstraction from different alkanes

These differences reflect the expected effect of a bridged transition state in vicinal hydrogen abstraction, namely lower E_a (more resonance stabilization) and more negative $\Delta S^{\neq}$ (loss of rotational freedom). Therefore, according to the experimental evidence, a β-bromo substituent provides substantial neighboring group participation in radical bromination, facilitating hydrogen abstraction and constraining configuration at the vicinal site.

In the proposed system (Scheme 1-2), the β-bromo alkyl radical intermediate is involved in the addition or elimination steps. Forming a bridged radical may accelerate addition of $R^{\bullet}$ to the double bond of the allyl bromide. Because of acceleration in rate of addition, the substitution effect which was observed in the rates of addition to the alkenes (section 1-4) might not be as significant in the current system. On the other hand, a bromo-bridged radical is more resonance stabilized and may retard the rate of the β-scission step of the reaction.

1.7 β-Scission

The third step of the propagation stage is β-scission of the β-bromo alkyl radical (scheme 1-2). In this step, a C-Br bond is being cleaved and a new C=C bond is formed. Based upon bond dissociation energies, formation of a new π-bond is energetically equivalent to the cleavage of a C-Br bond.[14] Therefore, the last step of the propagation in this reaction is thermoneutral.

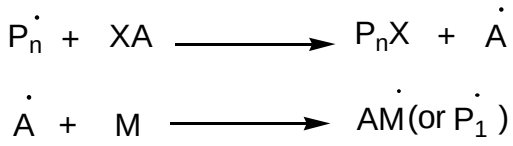
1.8 Free Radical Addition-Fragmentation Reactions In Organic Synthesis

Carbon-carbon bond formation through free radical addition to an unsaturated system has become one of the most important methods for the synthesis of simple and complicated organic and polymer structures.[36] After construction of a C-C bond by addition, the radical adduct can be transformed to a non-radical product by intermolecular trapping reactions, or expulsion of a radical, (i.e., β-cleavage). The following review examines C-C bond formation via addition-fragmentation processes.

1.8.1 Chain transfer reactions

1.8.1.1 Introduction

Chain transfer involves the reaction of a polymer radical $P_n^{\bullet}$ with species XA, known as the transfer agent, which is present in the polymerization. An atom or group of atoms is transferred from XA to $P_n^{\bullet}$, with the generation of a new radical $A^{\bullet}$. The resultant radical ($A^{\bullet}$) may then reinitiate polymerization by reaction with monomer M (Scheme 1-14).



Scheme 1-14. Reinitiation of polymerization by reaction of $A^{\bullet}$ with monomer M

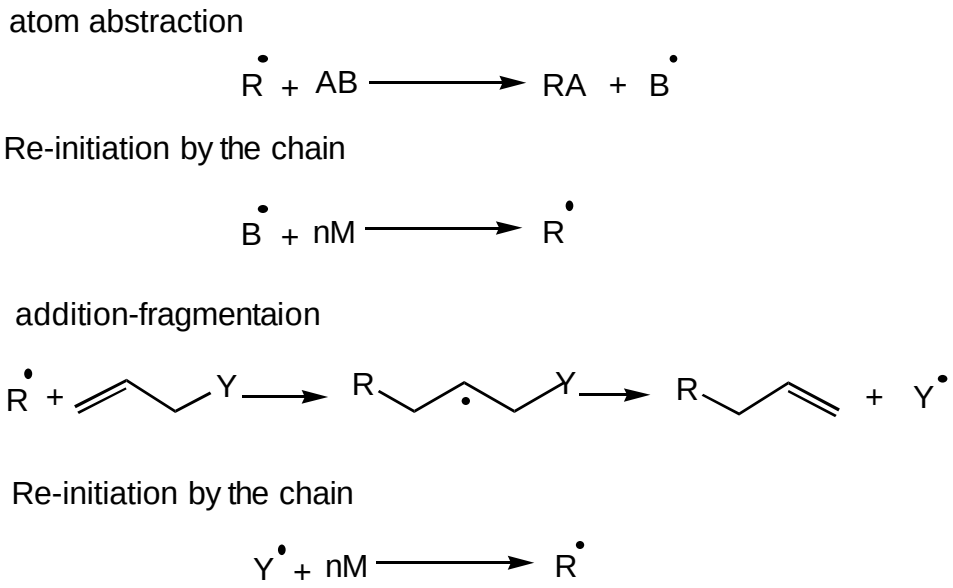
XA can be monomer, initiator, and solvent, as well as dissolved additive or terminated polymer. Although the kinetic chain is continued by the preservation of a radical center, the molecular chain is terminated. If the transfer proceeds according to the scheme 1-14, the kinetic chain is continued. Therefore, the overall rate of polymerization remains constant. This process is regarded as conventional transfer.

When the reactivity of $A^{\bullet}$ with monomer molecules is less than that of $P_n^{\bullet}$, the concentration of $A^{\bullet}$ increases. Therefore, the chance of terminating the polymerization increases, which leads to a decrease in the rate of polymerization. In addition, the kinetic-chain length is decreased. This type of reaction is known as degradative chain transfer.[37]

An addition-fragmentation process in free radical polymerization occurs whenever a growing polymer chain reacts with a compound bearing both an activated site of unsaturation and a weak bond located elsewhere in the molecule. The intermediate radical formed by the addition of the propagating radical to the transfer agent undergoes fragmentation involving the weak bond, generating another radical which can enter the polymerization cycle.[38]

The control of the molar mass in free radical polymerization is usually achieved by the addition of a chain transfer agent in the polymerization medium. When a chain-carrying radical is trapped by another specific compound XY, a radical ($Y^{\bullet}$) is produced which is also reactive. This radical ($Y^{\bullet}$) can reinitiate a new radical chain. In this case, the compound XY is called a chain transfer agent (CTA).

There are two kinds of chain transfer agents: Atom or group transfer agents and addition-fragmentation chain transfer agents (Scheme 1-15).

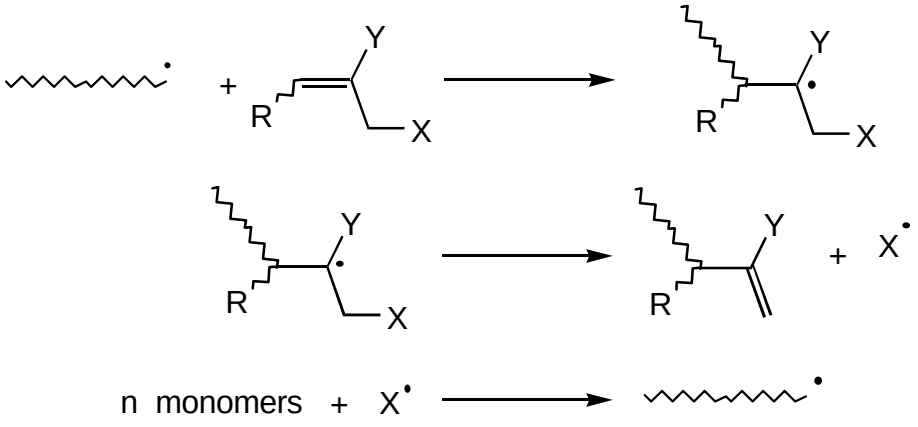


Scheme 1-15. Mechanisms of two different kinds of chain transfer agents

The chain transfer agents, which follow the addition-fragmentation mechanism, are of particular interest in organic and polymer chemistry. Recently, many studies have shown that allyl, acrylyl and allenyl transfers to alkyl halides represent powerful synthetic tools to prepare sophisticated molecules. Such a process was also identified as an effective means for controlling the molar mass of vinyl polymers, avoiding the use of conventional chain transfer agents based on thioderivatives.

1.8.1.2 Chain transfer agents involving exclusively addition-fragmentation

In 1988, Meijs reported that the allylic *tert*-butyl sulfides activated by phenyl, ethoxycarbonyl or cyano groups, respectively, are efficient chain transfer agents in the free radical polymerization of methyl methacrylate (MMA) and styrene (St).[39] The lowering of the molecular weight in polymerization by addition of the allylic sulfides is consistent with a radical addition-fragmentation mechanism. The effectiveness of the allylic sulfides in chain transfer reactions is because of the presence of an active double bond. The substitution and the presence of a weak carbon-sulfur bond in a β-position of double bond ready to undergo fragmentation are reasons for the activity of the double bond (Scheme 1-16).



Y: CO_2H, CO_2R, CN, Ph
R: H, Ph
X: SR, S(O)R, SO_2Ph, $P(O)(OR)_2$, $SnBu_3$, I, Br, Cl, F, CH(CN)SR

Scheme 1-16. Mechanism of addition-fragmentation chain transfer agents

Similarly, 2-(substituted) acrylic esters including 2-bromomethyl propenoate as well as the corresponding 2-(substituted) styrenes and acrylonitriles have been reported acting as chain transfer agents for the polymerization of methyl

methacrylate or styrene through the addition of the polymer radical to the unsaturated fragment and subsequent β-scission of the resultant radical.[40,41]

Recently,[42] Colombani and Chaumont reported the reactivity of a variety of 2-(substituted) cinnamates as chain transfer agents in the polymerization of vinyl monomers. These olefins are activated towards free radical addition and contain a homolytic leaving group in the allylic position. The compounds studied include bromide, iodide, sulfone, mercaptan, and peroxide derivatives. Cinnamic iodide, however, exhibits degradative chain transfer activity.

Viehe et. al.[43] studied 15 new compounds with allylic or pentadienic structure carrying potential radical leaving groups in an addition-fragmentation reaction (Table 1-8 and Table 1-9). Their experimental evaluation, as chain-transfer agents (CTA), was achieved in radical polymerization of ST and MMA.

Table 1-8. $CH_2=C(Y)CR_1R_2X$ as an effective chain transfer agent[43]

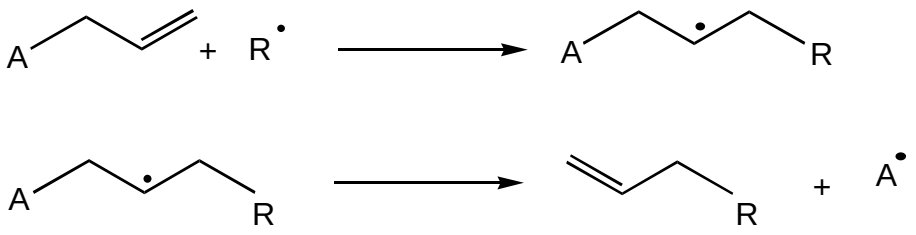
Y	R_1	R_2	X
H	CH_3	CH_3	$C(NMe_2)COPh$
H	Ph	H	$C(NMe_2)COPh$
CH_3	CH_3	CH_3	$C(NMe_2)COPh$
H	H	H	C(CN)SEt
CO_2Et	H	H	OCOPh
CO_2Et	H	H	$OCOCH_2Ph$
CO_2Et	H	H	$C(CN)NMe_2$
CO_2Et	H	H	C(CH)SEt
CO_2Et	H	H	C(CN)SMe
CO_2Me	Ph	H	$C(NMe_2)COPh$
CO_2Me	Ph	H	$OCOCH_2Ph$

Table 1-9. CH_2=CY(CH=CY')CH_2X as an effective chain transfer agent[43]

Y	Y'	X
H	H	S*t*Bu
H	H	C(SMe)CN
CH_3	CO_2Me	S*t*Bu

1.8.2 Allyl Transfer Reactions

Radicals can readily attack the double bond of a β-substituted allyl compound. The β substituent (e.g., Br, SO_2R, S (O) R, SiR_3, SnR_3, P (O)R_2) leaves the radical adduct homolyticaly with concomitant formation of a double bond (Scheme 1-17).

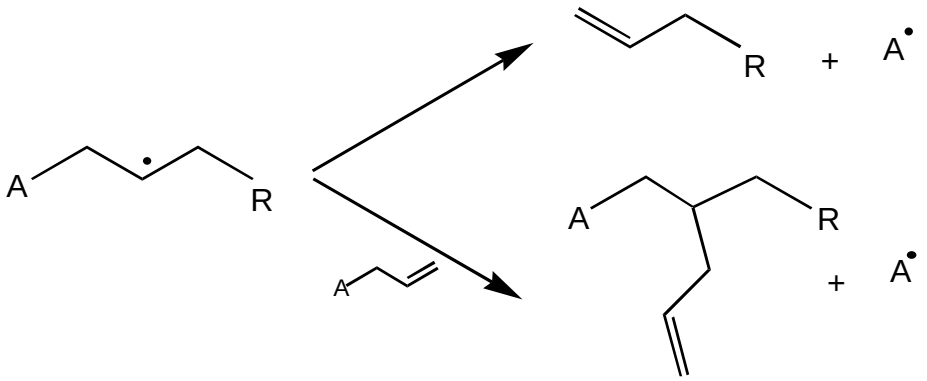


A = Br, SO_2R, S(O)R, SiR_3, SnR_3, P(O)R_2

Scheme 1-17. Mechanism of allyl transfer reactions

The radical fragmentation, which is called β-scission, can compete with the radical addition to an alkene (Scheme 1-18). Therefore, the rate of formation of

the product and the percent yield depend on the relative rate of these two competing reactions.

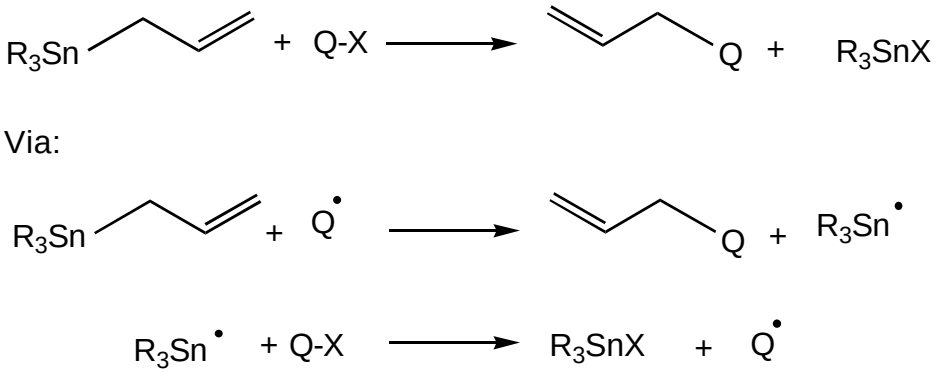


Scheme 1-18. Competition of β-scission with the radical addition to alkene in radical fragmentation step

If the rate of the β-cleavage is faster than addition in a system, the reaction has synthetic potential. Various synthetic methods have been developed during the last years in which different radicals are expelled during the propagation stage. The following is a review of allyl transfer reactions by addition-fragmentation, which have been organized based on the β-bond cleavage.

1.8.2.1 Carbon-tin bond cleavage

Allyl transfer reactions from allylic organotin compounds were discovered originally by Pereyre and Migita (Scheme 1-19).[44]



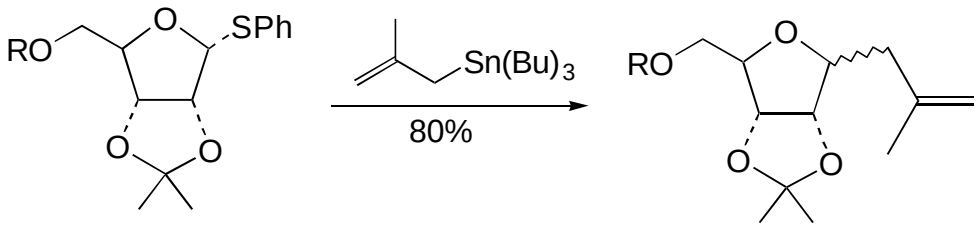
Q = CCl_3, $CHCl_2$, MeO_2CCH_2, $MeCCl_2$, $CH_2=CH(CH_2)_4$

X = halogen

Scheme 1-19. Allyl transfer reaction through carbon-tin bond cleavage

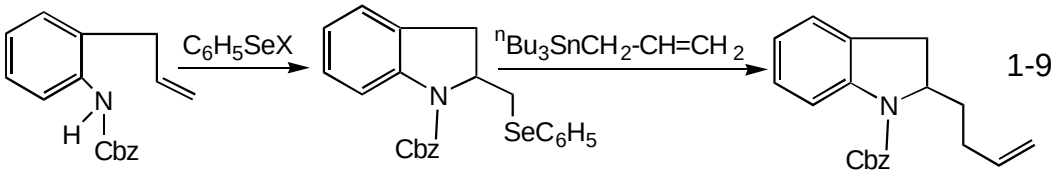
In this type of reaction, C-Sn bond cleaves readily and forms a trisubstituted tin radical. The tin radicals abstract the substituent X from the substrate Q-X and form $Q^{\bullet}$ radical. Therefore, $Q^{\bullet}$ radical is the chain carrier in these types of reactions. The substrate Q-X can be a halide, xanthate, thioether, or selenide. The radical chain is initiated by thermolysis of AIBN or irradiation. A variety of precursors Q-X, including carbohydrate derivatives can be used.

Keck and Danishefsky have used this methodology for the synthesis of a variety of molecules.[45] One application is the stereoselective conversion of thiophenyl glycosides to C-glycosides by a reaction with allyl or methallyltri-n-butylstannane (Eq. 1-8).[45a]



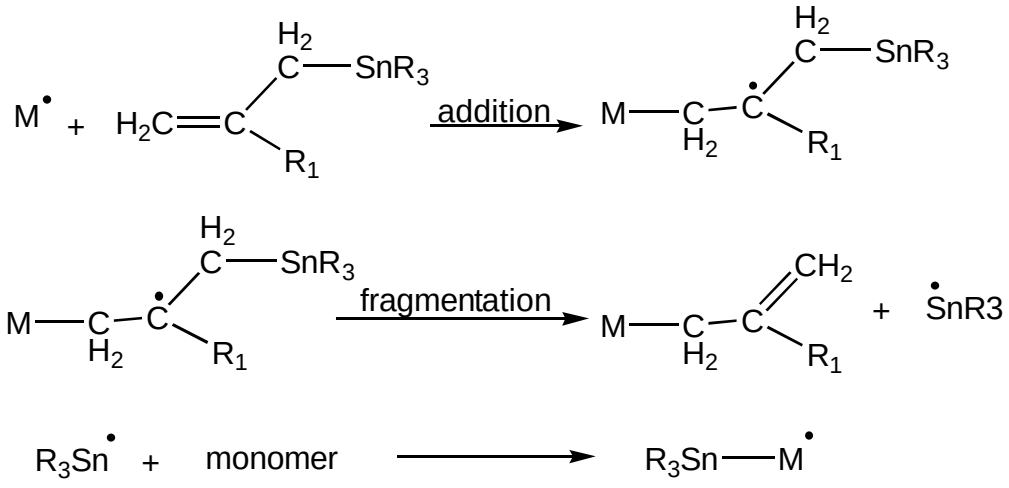
1-8

Another application is in the synthesis of alkaloids by intramolecular addition of a nitrogen-based group to an unactivated double bond followed by attachment of an allyl group (Eq. 1-9).[45b]



1-9

Recently,[41] allylic tin compounds have been used as chain transfer agents in free radical polymerization reactions. These compounds function by a radical addition-fragmentation mechanism (Scheme 1-20).



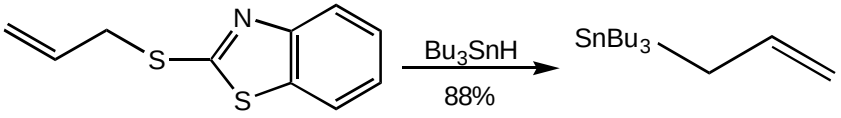
Scheme 1-20. Allylic tin compounds as chain transfer agents

Addition of the propagating radical to the double bond of the allyl compound gives a new adduct radical which readily fragments (β-scission) to an olefin-

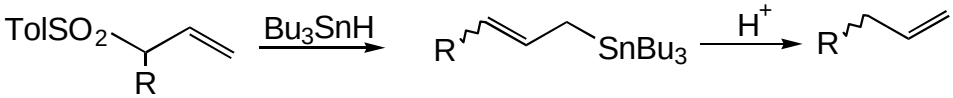
terminated polymer and tin radical. The latter species initiates formation of a new polymer chain. The rate of the first step (addition) is enhanced by the selection of an appropriate activating group R_1, while the driving force for the rapid fragmentation is believed to be provided by formation of a relatively stable tin-centered radical.

1.8.2.2 Carbon-sulfur bond cleavage

Similar to allyl stannane , S_H2' reactions are known for allylic sulfides or sulfones. In 1973, the capability of allyl sulfides for addition-fragmentation reactions by phenyl radicals was reported by Migita.[46] Later, Ueno et.al. Reported the stannylation of allylic sulfides and sulfones (Eq. 1-10 and 1-11).[47]



1-10



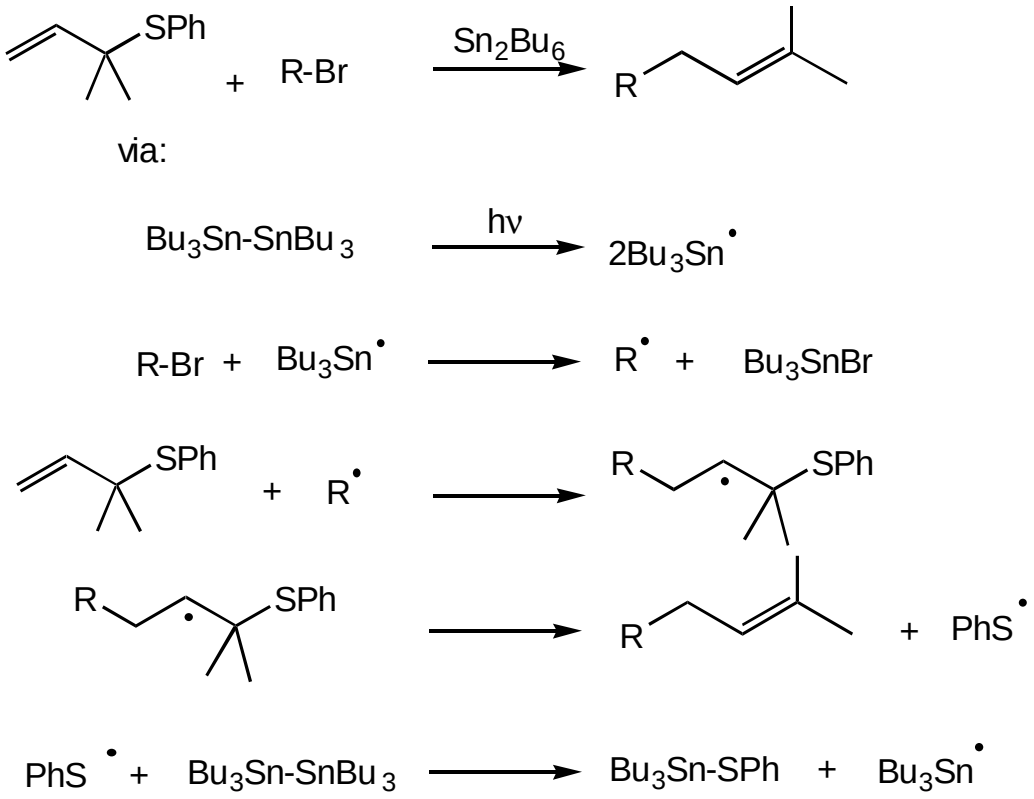
1-12

R = C_4H_9 80%

R = C_6H_{13} 80%

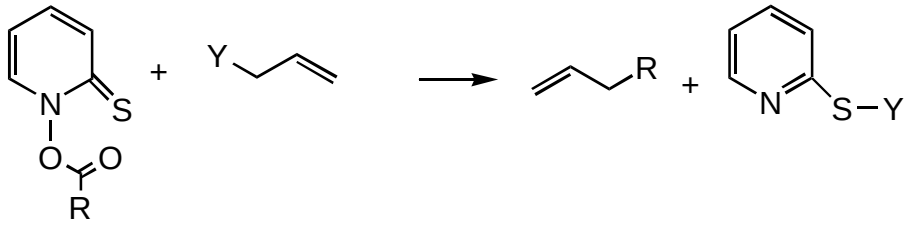
R = $C_6H_5CH_2$ 84%

Another type of initiator is hexabutyldistannane (Bu_3Sn-$SnBu_3$) which decomposes to tributyltin radical ($Bu_3Sn^{\bullet}$) by irradiation (Scheme 1-21). The tributyltin radical thus formed can react with an alkyl halide generating the starting radical ($R^{\bullet}$). The evidence for the role of phenylthio radical as a chain carrier is provided by the formation of $Bu_3SnSC_6H_5$ which is a trapped adduct through the reaction of hexabutyldistannane and $PhS^{\bullet}$.[48]

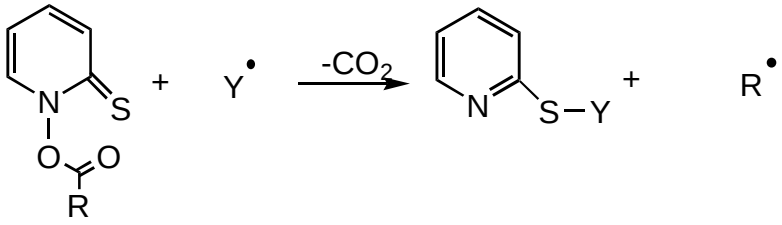


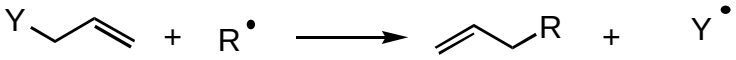
Scheme 1-21. Allyl transfer reaction through carbon-sulfur bond cleavage

In an attempt to unveil the mechanism of an allyl transfer reaction, Barton et.al.[49] carried out a series of reactions using esters of *N*-hydroxy-2-thiopyridone (Scheme 1-22).



via:





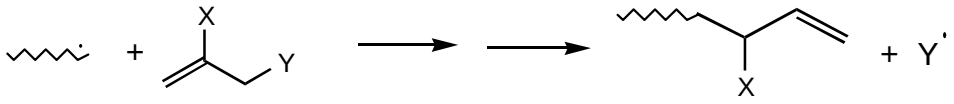
R = $Me(CH_2)_{14}$

Y = $SCMe_3$, $SCEt_3$, SPh, $SC_6H_4NO_2$-*p*, $SO_2C_6H_4Me$-*p*

Scheme 1-22. Allyl transfer reaction using N-hydroxy-2-thiopyridone

Allyl transfer occurs through an addition of a carbon centered radical ($R^{\bullet}$) to the double bond of an allyl sulfide or sulfoxide molecule followed by cleavage of a C-S bond and formation of a new alkene. Improved yields are obtained if the allyl compounds carry an electron withdrawing group on the β-position.

Similar to allylic stannanes, allylic sulfides, sulfones and sulfoxides are effective chain transfer agents. A new series of chain transfer agents which operate by a radical addition-fragmentation mechanism was introduced when the reactions of allylic *tert*-butyl sulfides activated by phenyl, ethoxycarbonyl or cyano groups was reported (Eq. 1-12).[41]



1-12

X = C_6H_5, $CO_2C_2H_5$, CN

Y = $S(O)(CH_2)_3CH_3$, $S(CH_2)_3CH_3$, $S(O)_2Ph$

The addition step is enhanced by an electron withdrawing substituent on the α position of the olefin (e.g. C_6H_5, $CO_2C_2H_5$, and CN) and the fragmentation occurs due to the weak C-S bond on the β position of the adduct radical.

1.8.2.3 Carbon-halogen bond cleavage

Reactions of allyl halides with thiols were studied by Hall in 1967.[50] It is postulated that formation of 2-halopropyl isomers in these additions is the result of an addition-fragmentation followed by an ionic hydrogen halide readdition to the allylic sulfide formed (Scheme 1-23).

$$H_2C{=}C(R)CH_2X + C_6H_5SH \longrightarrow C_6H_5SH_2C\text{-}C(X)(R)\text{-}CH_3$$

via:

$$C_6H_5S^{\bullet} + H_2C{=}C(R)CH_2X \longrightarrow C_6H_5SH_2C\text{-}C(R){=}CH_2 + X^{\bullet}$$

$$C_6H_5SH + X^{\bullet} \longrightarrow C_6H_5S^{\bullet} + HX$$

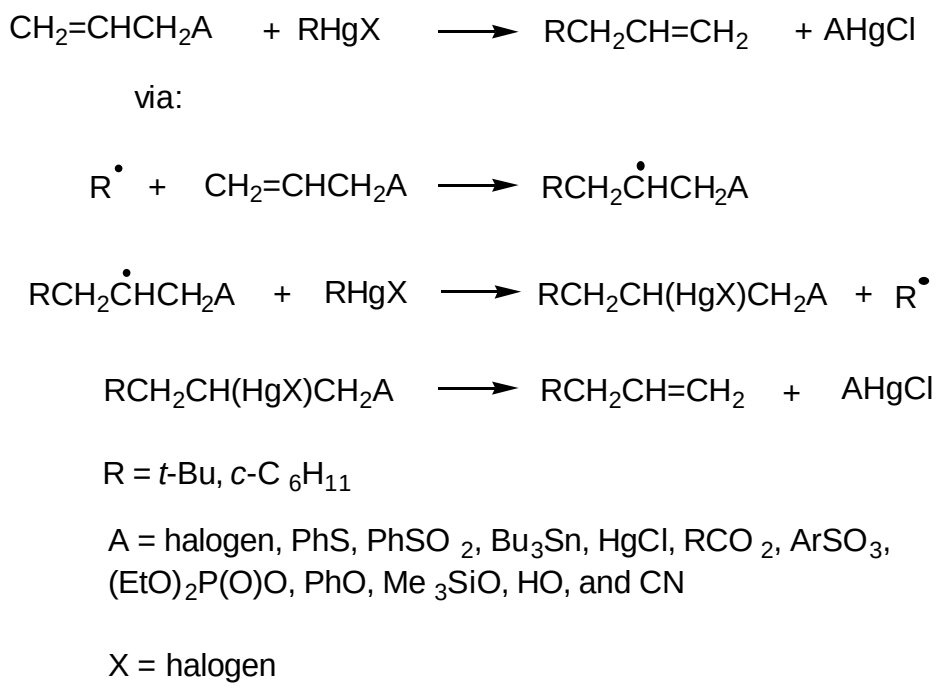
$$C_6H_5SH_2C\text{-}C(R){=}CH_2 + HX \longrightarrow C_6H_5SH_2C\text{-}C(X)(R)\text{-}CH_3$$

X = halogen

R = H, CH_3

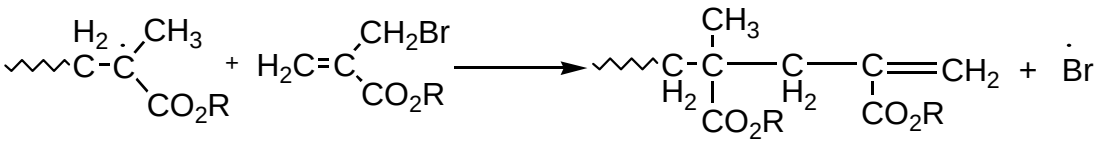
Scheme 1-23. Allyl transfer reactions through carbon-halogen bond cleavage using thiols

Free radical allyl transfer reactions of allylhalides involving radicals generated from alkylmercury halides have been studied by Russell et. al.[51] The reaction involves an addition step of $R^{\bullet}$ to the double bond of the allyl compound. Then the adduct radical undergoes an S_H2 process at Hg releasing $R^{\bullet}$. The last step of this propagation stage is elimination, forming a new allyl compound (Scheme 1-24).



Scheme 1-24. Allyl transfer reactions through carbon-halogen bond cleavage using alkylmercury halides

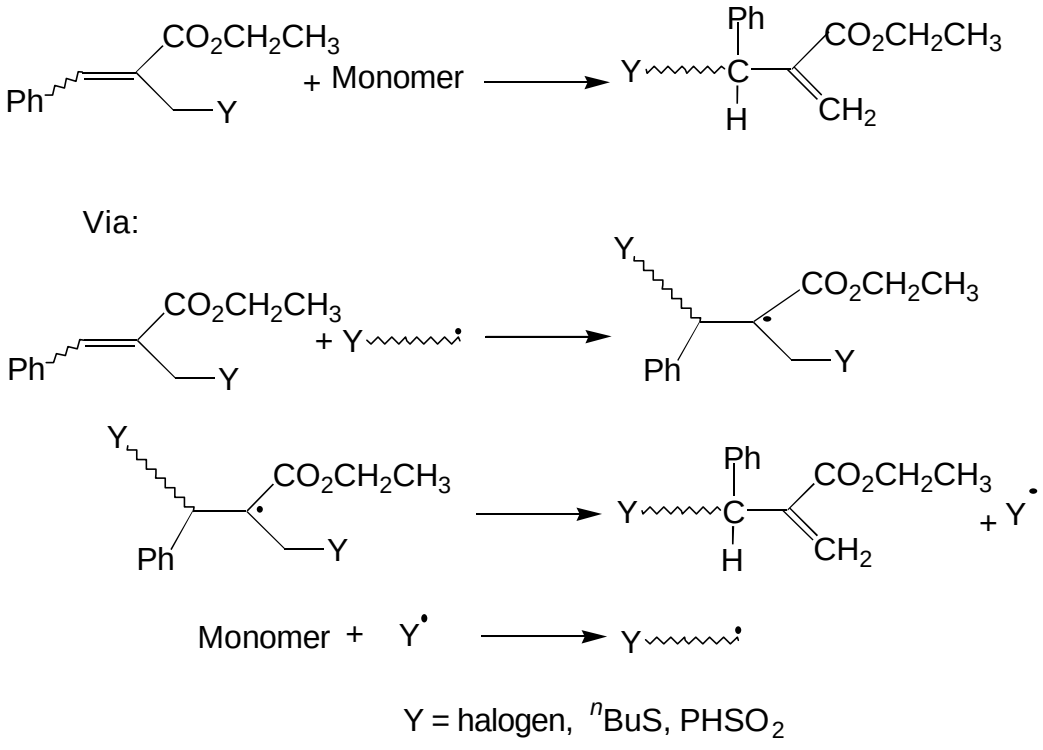
Allyl bromide as well as methyl α-bromomethyl acrylate (MBMA) function as effective chain transfer agents through an addition-fragmentation process in the radical polymerization of ethyl and methyl methacrylate and methyl acrylate (Scheme 1-25).[52a]



Scheme 1-25. Allyl transfer reaction using methyl α-bromomethyl acrylate as a chain transfer agent

According to the study done by Yamada et. al., no MBMA unit was incorporated in the main chain of the product. Consequently, the rate determining step of the addition-fragmentation reaction in this example is considered the addition step (Scheme 1-25).[52b]

Ethyl 2-bromomethyl cinnamate is another chain transfer agent which has been introduced recently (Scheme 1-26).[42] A series of 2-(substituted) cinnamate derivatives were tested as new chain transfer agents (CTA) in the bulk polymerization of styrene, methyl methacrylate, butylacrylate, and vinyl acetate by Colombani and Chaumont.[42] According to the reported monomer conversion and the number-average molar masses of the polymers obtained at various concentrations of CTA, they all show low reactivities. However, the fragmentation step is a dominating process in the 2-(substituted) cinnamate derivatives. The relative stabilities of the radicals generated by the fragmentation process appear to be a key factor in controlling the addition-fragmentation chain transfer process. For example, a bromo compound (Y=Br) is a more efficient CTA compared to iodo compound (Y=I). Increasing ethyl 2-(butylthiomethyl) cinnamate (Y=*n*BuS) concentration also shows very little decrease in the molar mass of polymers. But in cases of phenylsulfonylmethyl substituent (Y=$PhSO_2$) the resultant polymers were markedly lower molar masses compared with those prepared in the absence of this CTA (Scheme 1-23).



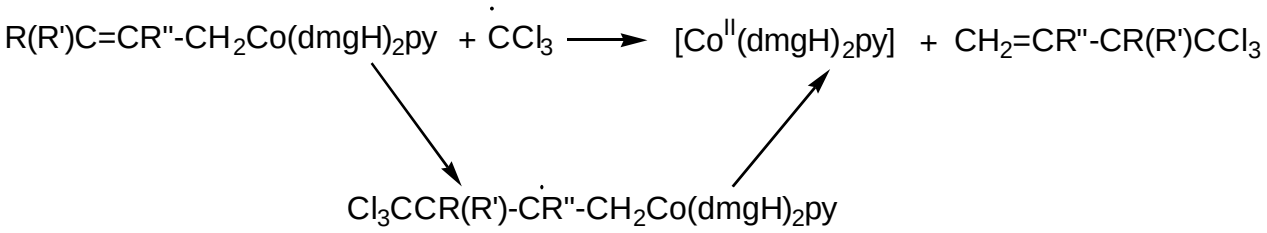
Scheme 1-26. Ethyl 2-bromomethyl cinnamate as a chain transfer agent for allyl transfer reactions

1.8.2.4 Carbon-transition metal bond cleavage

The first example of homolytic displacement of a transition metal from carbon was described by Johnson et.al. in 1976.[53] The reaction involves allyl- and substituted-allyl-bis (dimethylglyoximato) pyridine cobalt (III)[RCo^{III} $(dmgH)_2L$] complexes, which have been attacked by conventional organic radicals generated from polyhalogenomethanes, such as bromotrichloromethane (Eq.1-13).

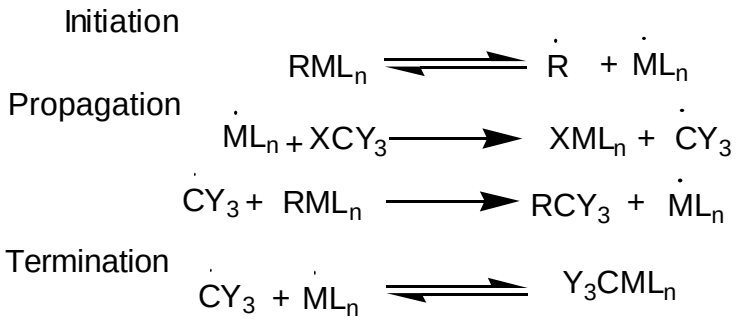
$$R(R')C{=}CR''\text{-}CH_2Co(dmgH)_2py + XCCl_3 \longrightarrow XCo(dmgH)_2py + CH_2{=}CR''\text{-}CR(R')CCl_3 \qquad 1\text{-}13$$

Evidence for a radical chain mechanism has been collected by studying the influence of initiators, inhibitors, and the nature of the reagent on the rates of the above reactions. A key step in the propagation stage of this reaction involves the attack of a C-centered radical ($R^{\bullet}$) on the double bond of the organic ligand of the complex [$RCo^{III}(dmgH)_2L$], with the synchronous or subsequent displacement of the metal as a cobaloxime (II) complex. The cobaloxime (II) complex is also effective in the generation of the radical ($R^{\bullet}$) from the reagent (RY) (Scheme 1-27).[54]



Scheme 1-27. Propagation stage of the reaction of $^{\bullet}CCl_3$ with [$RCo^{III}(dmgH)_2L$]

Organometallic complexes of rhodium and iridium similarly undergo a homolytic displacement of a low-valent metal complex by an attack from a polyhalogenomethyl radical at unsaturated carbon of an organic ligand.[55] The overall reaction sequence is illustrated in Scheme 1-28.



ML_n = Ir(CO)P $_2X_2$, Rh(CO)P $_2X_2$, $Co(dmgH)_2L'$

X = Br, Cl

P = PPh_3, PMe_2Ph

L' = pyridine, imidazole

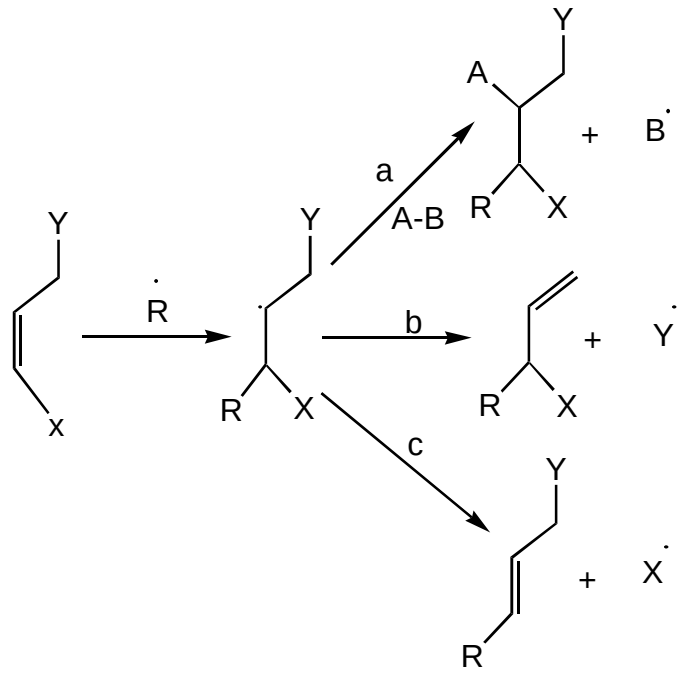
R = allyl, 2- or 3-methylallyl, 3,3-dimethylallyl

CY_3 = CCl_3, CHBrCN, CCl_2CN, CCl_2CHO, CCl_2CO_2R, etc.

Scheme 1-28. Homolytic displacement of a low-valent metal complex by a polyhalogenomethyl radical

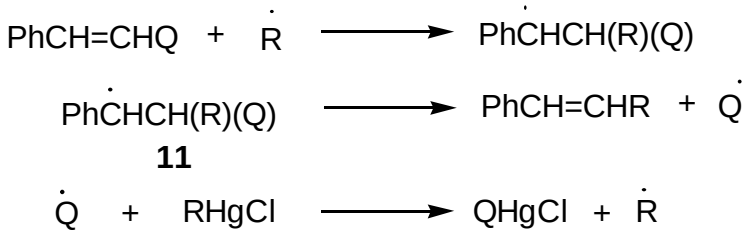
1.8.3 Vinyl transfer reactions

When a carbon radical attacks an alkene, there are two possible pathways from the radical adduct to the product: 1) reaction with a radical donor (i.e., tri-*n*-butyltin hydride, pathway a, Scheme 1-29) or 2) elimination of a radical off the adduct. Elimination may occur in two ways: distal to the attacking radical (S_H' reaction,(pathway b) or proximal (pathway c). In this section, the focus is on the proximal elimination from radical adduct.



Scheme 1-29. Mechanism of vinyl transfer reactions

Russell and co-workers have demonstrated that a variety of substituted alkenes including PhCH=CHQ and Ph_2C=CHQ with Q= HgCl, Bu_3Sn, SO_2Ph, SOPh, I or SPh react with alkylmercury halides (RHgX) by a free radical chain process to form PhCH=CHR or Ph_2C=CHR (Scheme 1-30).[56]



Scheme 1-30. Propagation stage in free radical chain reaction of PhCH=CHQ with R•

The carbon centered radical, $R^{\bullet}$, attacks C_1 of the vinylation reagent to generate a benzylic radical (**11**). This intermediate radical can then undergo β-scission to form the vinylated product and $Q^{\bullet}$, which in turn propagates the chain process.

Evidence for the free radical chain reaction follows from the observed photostimulation, initiation by AIBN or Bz_2O_2, the inhibitory effect of di-*tert*-butyl nitroxide, and the rearrangement of R= Δ^5-hexenyl to cyclopentylcarbinyl (Table 1-10).[56a]

Table 1-10.[56] Results of reaction of $PhHC{=}CHSnBu_3$ and RHgCl

$$PhHC{=}CHSnBu_3 + RHgCl \rightarrow PhHC{=}CHR$$

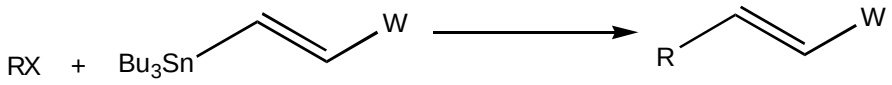
R	Conditions[a]	% product
i-Pr	PhH, S, 18 h	86
i-Pr	PhH, AIBN, 80 ^{o}C, 16 h	73
i-Pr	PhH, dark, 50 ^{o}C	0
i-Pr	PhH, S, DTNO, 16 h	35
Δ^5-C_6H_{11}	PhH, R, 48 h	52[b]

[a] S = radiation by a 275-W sunlamp; R = radiation in a Rayonet reactor at 350nm; AIBN = azobisisobutyronitrile; DTNO = 10 mol% di-*tert*-butyl nitroxide.

[b]Only cyclopentylcarbinyl product observed.

A free radical addition-fragmentation chain process has been reported which can be used for the preparation of vinyl sulfones and phosphine oxides.[57] The reactions involve irradiation of appropriate precursors to produce carbon-

centered radicals with β-tri-*n*-butylstannyl α,β-unsaturated sulfones or phosphine oxides in the presence of AIBN(Eq. 1-14).



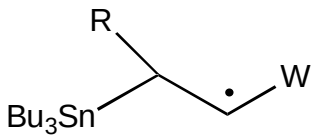
1-14

R = *c*-C_6H_{11}, C_6H_5, C_7H_{15}

X = Br, I

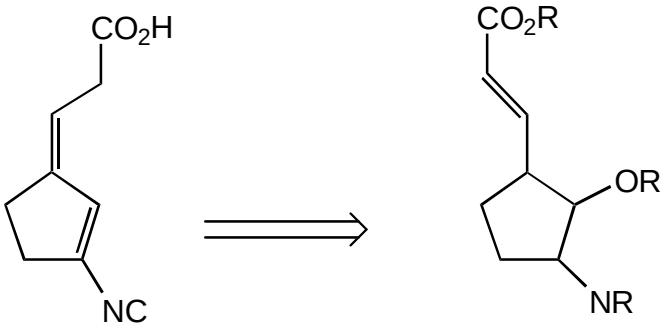
W = SO_2Ph, $PO(Ph)_2$

It is important to note that reactions of this type do not appear to proceed without some functional group stabilization (W) of the intermediate radical (**12**). For example, upon attempted reaction of vinyl tri-*n*-butyl stannane with a variety of carbon-centered radicals, none of the desired vinylated products could be obtained.[57]



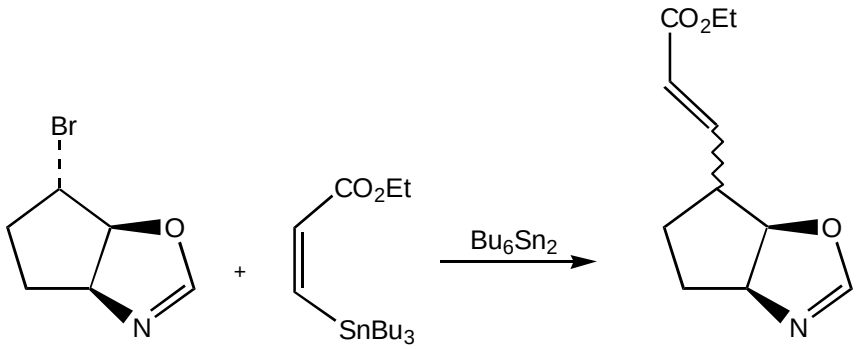
12

The vinyl transfer methodology has been used in the synthesis of fungel dienyl isonitrile antibiotic (structure **13**, Scheme 1-31).[58] The key step of carbon-carbon coupling in this synthesis is the reaction of β-stannyl acrylates with carbon radicals, generated from the corresponding bromides (Eq. 1-15).



13

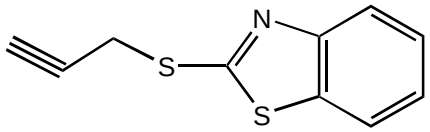
Scheme 1-31. Retrosynthesis of fungel dienyl isonitrile antibiotic



1-15

1.8.4 Allene transfer reactions

Allene transfer reactions were reported the first time in 1979 by Ueno et.al. Through the S_H' (addition-fragmentation) reaction of an organo tin radical (attacking group) and an organosulfur-centered radical (eliminating group) (Eq. 1-16).[59]



$$\xrightarrow[\text{AIBN, } 100\,^{o}\text{C}\\ \text{or } h\nu]{Bu_3SnH} Bu_3SnCH{=}C{=}CH_2 \qquad \text{1-16}$$

Later, reactions of propargyltriphenylstannane, which undergo free radical addition-fragmentation with different precursors to form allenic substitution products were studied (Eq. 1-17).[60]

$$RC{\equiv}CCH_2SnPh_3 \xrightarrow[h\nu]{QY} QC(R){=}C{=}CH_2 + Ph_3SnY \qquad \text{1-17}$$

R= H, CH_3

Q= alkyl, $PhSO_2$, *n*-$PrSO_2$, CCl_3, $CHCl_2$, PhSe, PhS

Y = halide, PhS, SO_2Cl, SCH_2Ph, PhSe

The procedure appears to be compatible with most standard protecting groups and good to reasonable yields are obtained.

Other than tin derivatives, addition of alkyl radicals to substituted propargyls (e.g., Halogen, PhS, $PhSO_2$, or HgCl substituents) can undergo β-elimination to form the alkyl-substituted allene and an eliminated radical which regenerates the alkyl radical by displacement (Scheme 1-32).[61]

$$\dot{R} + HC{\equiv}CCH_2A' \longrightarrow RCH{=}\dot{C}CH_2A'$$

$$RCH{=}\dot{C}CH_2A' + RHgX \longrightarrow RCH{=}C(HgCl)CH_2A' + \dot{R}$$

$$RCH{=}C(HgCl)CH_2A' \longrightarrow RCH{=}C{=}CH_2 + A'HgCl$$

Scheme 1-32. Addition of alkyl radicals to substituted propargyls

CHAPTER 2. RESULTS

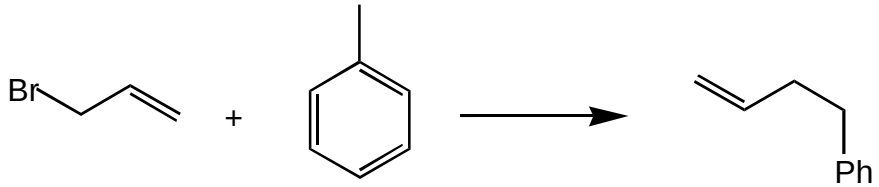
2.1 Synthesis

Reactions of several allyl bromides with different substrates were studied. For each allyl bromide/substrate system the desired product was isolated and identified spectroscopically. Afterward, the reaction conditions (i.e., initiator, reaction time, temperature, and concentration of starting compounds) were varied in order to optimize the yield. The maximum yield and the corresponding conditions for each system are reported in following sections.

2.1.1 Reactions of allyl bromides with toluene

a. Allyl bromide (CH_2=$CHCH_2Br$)

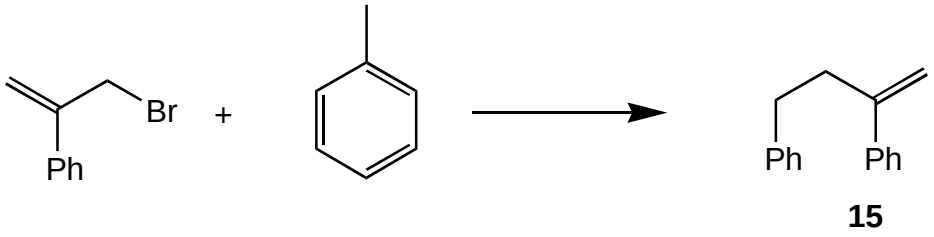
The reaction of allyl bromide and toluene was conducted in neat toluene (Eq. 2-1). The yield of product (**14**) is about 45% in the presence of (*t*-$BuO)_2$ using K_2CO_3 or 1,2-epoxy butane as HBr scavenger. The amount of the remaining allyl bromide at the end of the reaction was not determined.



14 (2-1)

b. α-Bromomethyl styrene

The reaction of toluene and α-bromomethyl styrene (Eq. 2-2) was studied thoroughly, using different reaction conditions and initiators. The results are illustrated in Table 2-1.



15 (2-2)

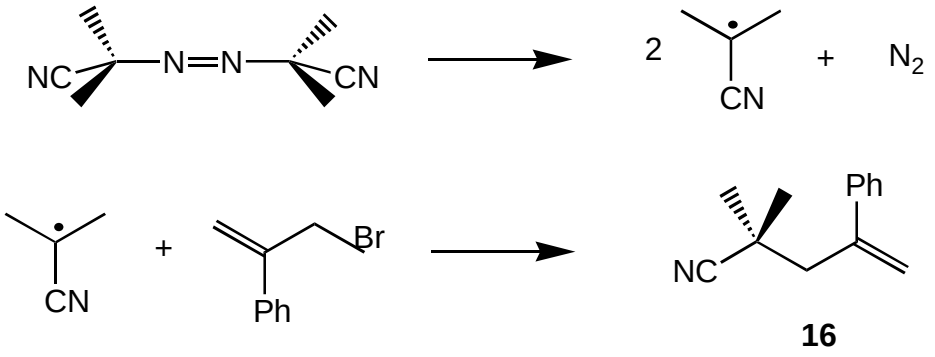
Table 2-1. Reactions of α-bromomethyl styrene (αBMS) and toluene

Initiator	Conditions[a]	Product (**15**)	Remaining αBMS	Mass balance
AIBN	85 °, 20 h neat $PhCH_3$	61%	16%	77%
(*t*-BuO)$_2$	120 °, 20 h neat $PhCH_3$	92%	10%	102%
(BzO)$_2$	80 °, 21 h neat $PhCH_3$	42%	67%	109%
(*t*-BuO)$_2$	120 °, 94 h, in PhH 0.56 M $PhCH_3$	24%	20%	44%

[a] $[\alpha BMS]_i = 0.14$ M

The optimum yield for this reaction was obtained in the presence of (t-BuO)$_2$ as initiator (yield: 92%).

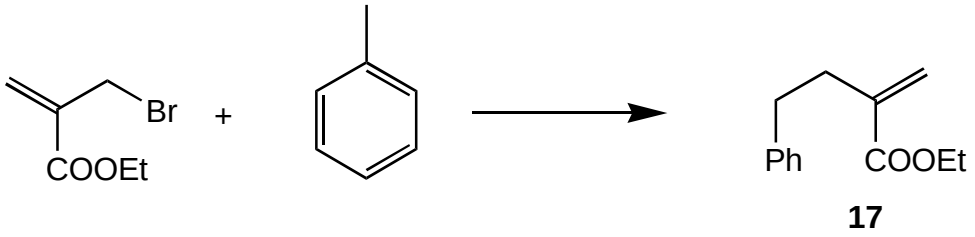
The 2- cyano-2-propyl radical, resulting from the decomposition of AIBN, has a tendency to undergo addition to the double bonds. Formation of a side product (4-cyano-4-methyl-2-phenyl-1-pentene, **16**) was observed during the course of the reaction of toluene and α-bromomethylstyrene in the presence of AIBN (yield~ 13%). This product is the result of addition of 2-cyano-2-propyl radical to the double bond of the allyl bromide followed by fragmentation (Scheme 2-1).



Scheme 2-1. Reaction of 2-cyano-2-propyl radical with α-bromomethyl styrene

c. Ethyl α-bromomethylacrylate

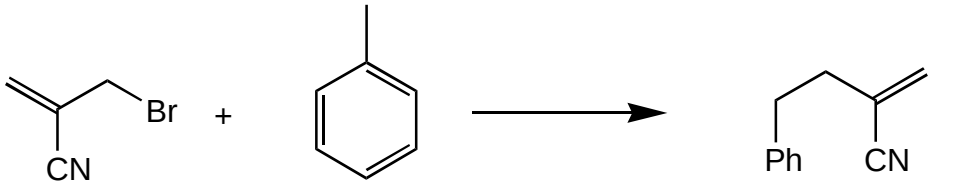
The optimum yield of the reaction of toluene and ethyl α-bromomethylacrylate was obtained in the presence of (t-BuO)$_2$ (Eq. 2-3). The yield of the desired product (**17**) was 58%. The yield of product in the presence of (t-BuO)$_2$ in dilute toluene (solvent: PhH) was negligible.



17 (2-3)

d. α-Bromomethylacrylonitrile

The reaction of toluene and α-bromomethylacrylonitrile (αBMCN) is the fastest one in this series (Eq. 2-4). Product (**18**) yield was 66%. The optimum yield was obtained after heating the reaction mixture for 2 h in the presence of $(BzO)_2$ as the initiator. Increasing the time of the reaction did not affect the product yield, but decreased the concentration of allyl bromide (Table 2-2).



18 (2-4)

Table 2-2. Reaction of toluene and α-bromomethylacrylonitrile (αBMCN) in the presence of $(BzO)_2$[a]

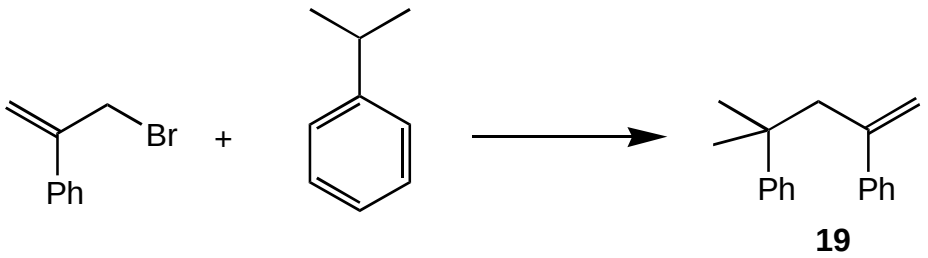
Reaction time(min)	Product (**18**)	Unreacted αBMCN	Mass balance
30	49%	63%	112%
61	59%	42%	101%
121	66%	31%	97%
300	68%	21%	89%
1212	68%	21%	89%

[a][αBMCN]= 0.19 M, neat $PhCH_3$, $[(BzO)_2]$=0.038 M, 120 ^oC

2.1.2 Reactions of allyl bromides with cumene

a. α-Bromomethylstyrene (αBMS)

The reaction of cumene and α-bromomethylstyrene was the most efficient one of these series (Eq. 2-5). Product (**19**) yield was 100%. The results of different reactions are illustrated in Table 2-3.



19 (2-5)

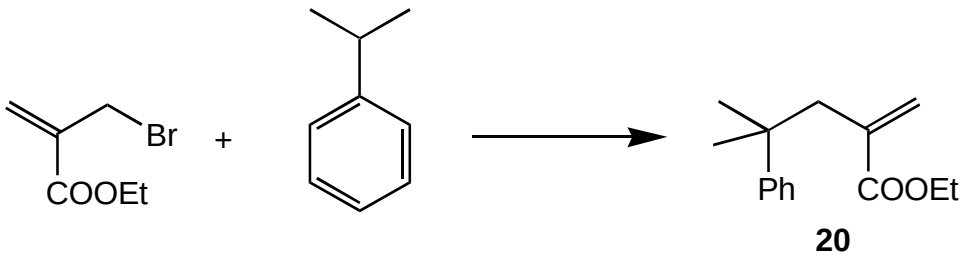
Table 2-3. Reactions of α- bromomethylstyrene (αBMS) and cumene[a]

Initiator	Conditions	Product (**19**)	Unreacted αBMS	Mass balance
AIBN	85 °, 22 h neat $PhCH(CH_3)_2$	55%	31%	86%
(*t*-BuO)$_2$	110 °, 94 h neat $PhCH(CH_3)_2$	100%	0%	100%
(*t*-BuO)$_2$	120 °, 94 h 0.28 M $PhCH(CH_3)_2$ in PhH	66%	7%	73%

[a] [αBMS]=0.14 M, [initiator]=0.028 M

b. Ethyl α-bromomethylacrylate [EαBMA]

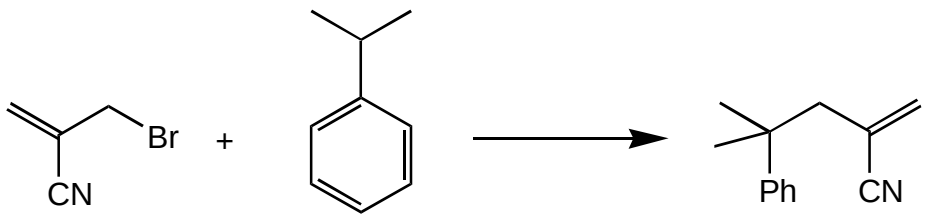
The maximum product yield of **20** in the reaction of ethyl α-bromomethylacrylate with cumene was 48% in the presence of $(BzO)_2$ (Eq. 2-6). None of the allyl bromide was left at the end of the reaction after 94 h heating at 80 °C. It is assumed some polymerization occurred in the course of reaction which could not be detected by GC.



20 (2-6)

c. α-Bromomethylacrylonitrile (αBMCN)

The maximum yield of the reaction of cumene and α-bromomethylacrylonitrile was obtained in the presence of (*t*-BuO)$_2$ (Eq. 2-7). The yield of product (**21**) was 80%.



21 (2-7)

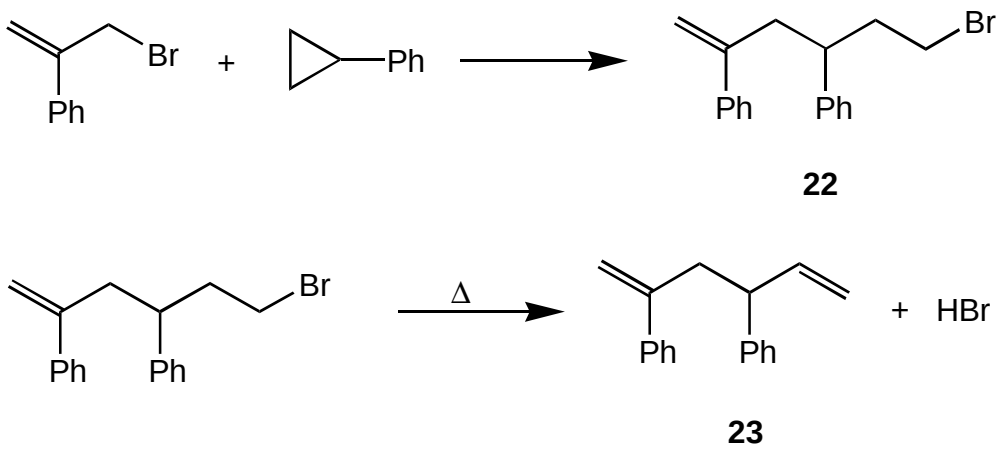
The reaction was conducted in neat cumene, using 20% of [αBMCN] for initiator. Maximum yield was obtained after 2h heating at 120 ^{o}C. Since the cumene signal on the GC trace overlapped with the signal related to α-bromomethylacrylonitrile, the remaining allyl bromide at the end of the reaction could not be measured.

2.1.3 Reactions of allyl bromides with phenylcyclopropane

a. α-Bromomethylstyrene (αBMS)

The initial product of the reaction between α-bromomethylstyrene and phenylcyclopropane (**22**) undergoes elimination of HBr at high temperatures

(>100^{o}) (Scheme 2-2). The elimination product (**23**) was identified by GC-MS. Maximum yield (57%) of the reaction product (**22**) was obtained in the presence of $(BzO)_2$ after about 10 h heating at 80 ^{o}C. Increasing the reaction time did not have a significant effect on the product yield but decreased the concentration of αBMS (Table 2-4).



Scheme 2-2. Reaction of α-bromomethylstyrene (αBMS) and phenylcyclopropane

Table 2-4. Reaction of α-bromomethylstyrene (αBMS) and phenylcyclopropane in the presence of $(BzO)_2$[a]

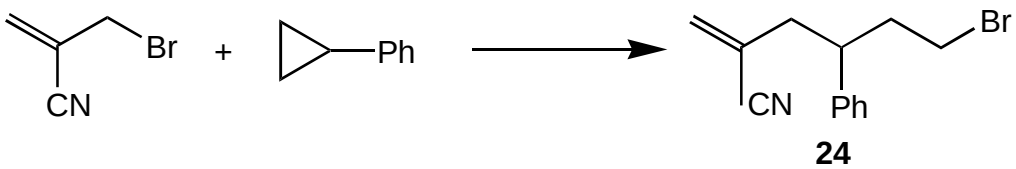
Reaction time (min)	Product (**22**)	Unreacted αBMS	Mass balance
60	16%	95%	111%
300	44%	54%	98%
644	57%	39%	96%
2402	55%	34%	89%

[a] $[\alpha BMS]_i$=0.14 M, $[(BzO)_2]$=0.028 M, neat Ph(*c*-C_3H_5), 80 ^oC

Dilute reaction of phenylcyclopropane (1.4 M) and α-bromomethylstyrene (0.14 M) in benzene was conducted in the presence of $(BzO)_2$ (0.028 M). The yield of **22** after heating at 80 ^oC for 40 h is 42%. (unreacted αBMS=44%)

b. α-Bromomethylacrylonitrile

The reaction of phenylcyclopropane and α-bromomethylacrylonitrile was the most efficient one in this series (Eq. 2-8). The reaction was conducted in neat phenylcyclopropane in the presence of $(BzO)_2$. After 3 h of heating at 80 ^oC, a quantitative yield of the desired product (**24**) was obtained.



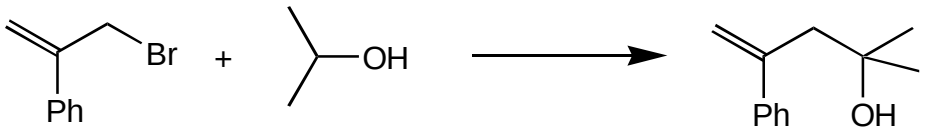
(2-8)

24

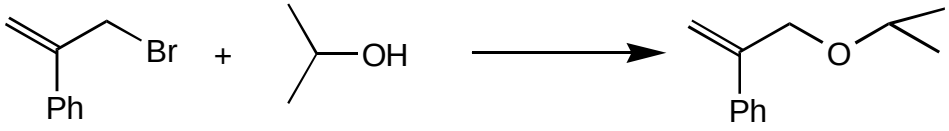
2.1.4 Reactions of allyl bromides with 2- propanol

a. α-Bromomethylstyrene

Reaction of α-bromomethylstyrene and 2- propanol at 120 ^{o}C yielded 21% of the desired product (**25**) (Eq. 2-9). A side product was detected (**26**, 46%) which was the result of a nucleophilic substitution reaction (Eq. 2-10). A quantitative yield of **26** was obtained without initiator under the same reaction conditions (Table 2-5).



25 (2-9)



26 (2-10)

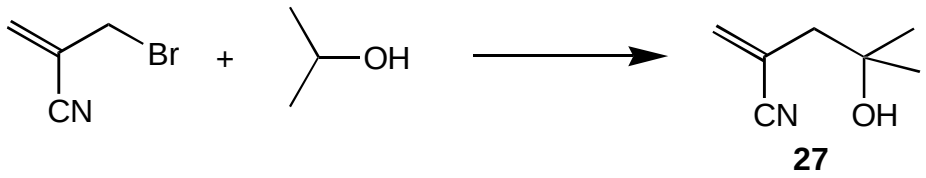
Optimizing the reaction condition gave a 59% yield of the desired product (**25**) (Table 2-5). (Unreacted αBMS=36%)

Table 2-5. Reactions of isopropanol and α-bromomethylstyrene

initiator	condition	**25** (%)	**26** (%)
(*t*-BuO)$_2$	120 ^{o}C, 95 h, K_2CO_3 neat *i*-PrOH	21%	46%
None	120 ^{o}C, 94 h, K_2CO_3 neat *i*-PrOH	2%	99%
(BzO)$_2$	80 ^{o}C, 40 h, K_2CO_3 0.14 M αBMS, 1.56 M *i*-PrOH in PhH	59%	0%

b. α-Bromomethylacrylonitrile

The optimum yield for the reaction of α-bromomethylacrylonitrile and isopropanol was obtained after 3 h heating at 80 ^{o}C in the presence of (BzO)$_2$ (Eq. 2-11). The yield of the desired product (**27**) was 54% while 37% of αBMCN remained unreacted.



27

(2-11)

2.2 Mechanistic study

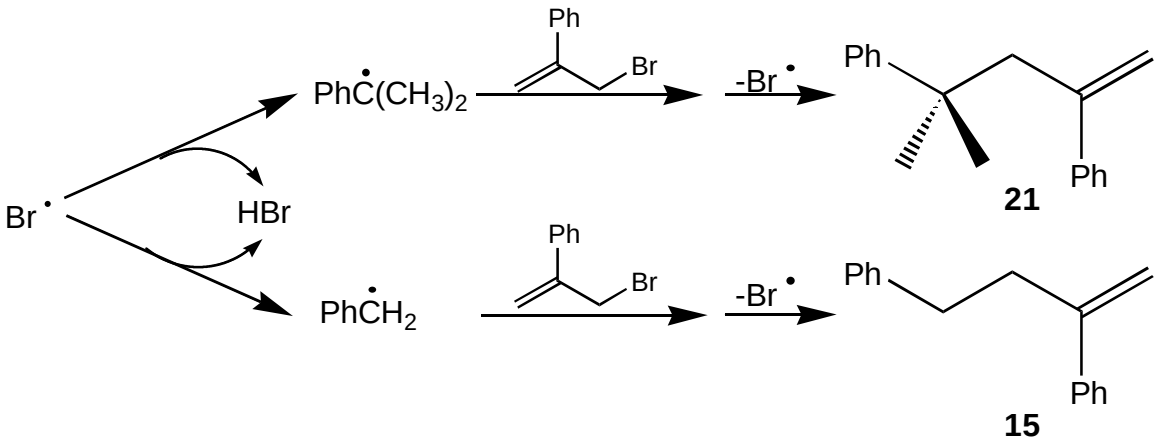
2.2.1 Competition experiments

Two sets of competition reactions were performed. The first set was the study of the competition of two hydrogen atom donors (i.e., toluene and cumene) which have different reactivities in hydrogen atom abstractions. In order to confirm the role of the bromine atom as the hydrogen atom abstractor and the chain carrier, competitions of two alkyl aromatics were conducted using α-bromomethyl styrene as $Br^{\bullet}$ source. The selectivity measured from this reaction was compared to the selectivity measured using Br_2 as the $Br^{\bullet}$ source.

The other set of competition experiments were designed to compare the relative reactivities of different allyl bromides towards the same alkyl aromatic (i. e., toluene). The results were compared to the measured literature trend for the addition of benzylic radical to the substituted alkenes.

2.2.1.1 Reaction of α-bromomethylstyrene with toluene and cumene

The selectivity of α-bromomethylstyrene towards tertiary vs. primary hydrogen abstraction ($r(3^o/1^o)$) was measured by a competition reaction of toluene and cumene (Scheme 2-3).



$$r(3^o/1^o) = \frac{[\,\mathbf{21}\,]_f}{[\,\mathbf{15}\,]_f} \; X \; \frac{[\,PhCH_3\,]_i}{[\,PhCH(CH_3)_2\,]_i} \; X \quad 3$$

Scheme 2-3. Selectivity of $3^o/1^o$ hydrogen atom abstraction by $Br^{\bullet}$

Abstraction of hydrogen by $Br^{\bullet}$ is a reversible process (Eq. 2-12), and this reversibility may result in a distorted measurement of $r(3^{o}/1^{o})$. In order to prevent this reaction 1,2-epoxybutane was used as an HBr scavenger.[62] The selectivity as a function of the concentration of 1,2-epoxybutane is summarized in Table 2-6. The concentration of the HBr scavenger was increased to the point that it did not have any effect on $r(3^{o}/1^{o})$, which is an indication that HBr reversal is minimized. Therefore, the selectivity of α-bromomethyl styrene towards tertiary to primary hydrogen atom abstraction was measured to be 25.

$$RH + Br^{\bullet} \rightleftharpoons R^{\bullet} + HBr \qquad (2\text{-}12)$$

Table 2-6. Competition reactions of toluene vs. cumene using α-bromomethylstyrene (αBMS) and Br_2 as bromine atom source

$Br^{\bullet}$ source	1,2-epoxybutane (equiv.)	r($3^o/1^o$) at 80 ^oC
αBMS[a]	0.05	50
αBMS	0.10	48
αBMS	0.50	34
αBMS	1.10	25
αBMS	2	25
Br_2[b]	1.1	26

[a] 41 mmol $PhCH_3$, 5.0 mmol $PhCH(CH_3)_2$, 0.7 mmol αBMS, 0.77mmol 1,2-epoxy butane, 0.14 mmol $(BzO)_2$, 80 ^oC for 1 h

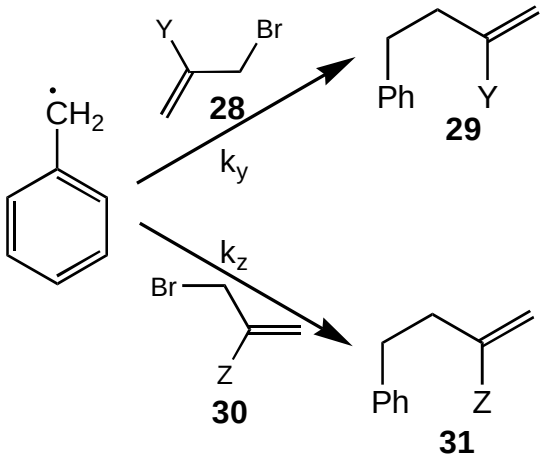
[b] 0.2 mmol $PhCH_3$, 0.2 mmol $PhCH(CH_3)_2$, 0.2 mmol 1,2-epoxy butane, 0.02 mmol (*t*-$BuO)_2$, 5 mL PhH, 0.2 mmol Br_2, 80 ^oC for 5 min

In order to compare these results, the selectivity was measured using liquid bromine as bromine atom source. The measured selectivity at 80 ^oC was 26 (Table 2-6). Since the selectivities for αBMS and Br_2 are nearly identical, $Br^{\bullet}$ is likely the chain carrier and the hydrogen abstractor for the system under study.

2.2.1.2 Reactions of allyl bromides with toluene

a. Unsubstituted allyl bromide and α-bromomethylstyrene

The relative reactivity of allyl bromide and α-bromomethylstyrene ($k_{\alpha BMS}/k_{ALLB}$) was measured by using toluene as a benzyl radical source (Scheme 2-4).



$$k_y/k_z = \frac{\ln\{\mathbf{28}_o/(\mathbf{28}_o-\mathbf{29})\}}{\ln\{\mathbf{30}_o/(\mathbf{30}_o-\mathbf{31})\}}$$

Scheme 2-4. Competition reactions of various allyl bromides towards benzyl radical

The competition was conducted in neat toluene in the presence of $(BzO)_2$ and 1,2-epoxy butane. ($[ALLB]_i$=0.7 M, $[\alpha BMS]_i$=0.14 M) The measured relative reacitvity for the competition reaction of unsubstituted allyl bromide and α-bromomethylstyrene ($k_{\alpha BMS}/k_{ALLB}$) was 65 at 80 ^oC.

b. α-Bromomethylstyrene and ethyl α-bromomethylacrylate

Relative reactivity of α-bromomethylstyrene and ethyl α-bromomethylacrylate towards benzyl radical was measured in a similar manner as described in Scheme 2-4. The reaction was conducted in neat toluene in the presence of $(BzO)_2$ and 1,2-epoxy butane. ($[\alpha BMS]_i$= 0.7 M, $[E\alpha BMS]_i$=0.15 M) The measured relative reactivity for the competition reaction of the title compounds ($k_{E\alpha BMA}/k_{\alpha BMS}$) was 1.7 at 80 ^oC.

c. Ethyl α-bromomethylacrylate and α-bromomethylacrylonitrile

The relative reacitvity of ethyl α-bromomethylacrylate and α-bromomethylacrylonitrile towards $PhCH_2^\bullet$ was measured in a similar manner as in section a (Scheme 2-2). The reaction was conducted in neat toluene in the presence of $(BzO)_2$ and 1,2-epoxy butane. ($[E\alpha BMS]_i$= 0.7 M, $[\alpha BMCN]_i$= 0.15 M) The measured selectivity ($k_{\alpha BMCN}/k_{E\alpha BMA}$) was 1.6 at 80 ^oC.

Results of the competition reactions of various allyl bromides towards toluene are summarized in Table (2-7).

Table (2-7). Relative reactivities of various allyl bromides towards benzyl radical at 80 ^oC (for reactions see Scheme 2-4)

Y	Z	k_y/k_z
Ph	H	65
COOEt	Ph	1.7
CN	COOEt	1.6

2.2.2 Chain length measurement

2.2.2.1 Reactions of allyl bromides with toluene

a. Allyl bromide

The reaction of allyl bromide [ALLB] and toluene was studied in the presence of $(t\text{-BuO})_2$ (20% of allyl bromide) at different time intervals in neat toluene (Table 2-8).

Table 2-8. Reactions of toluene and allyl bromide in the presence of $(t\text{-BuO})_2$[a]

Reaction time (min)	Product (**14**) (mmol)	$t\text{-BuO}^\bullet$ ($\times 10^3$) (mmol)
18	0.005	0.4
31	0.009	0.7
65	0.02	2
180	0.05	4
303	0.07	7
600	0.1	14
1200	0.2	26
5647	0.3	126

[a]$[ALLB]_i$= 0.14 M, 4 ml $PhCH_3$, 0.028 M $(t\text{-BuO})_2$, 0.16 M [1,2-epoxy butane], 120 ^oC

Due to the early retention time of allyl bromide on the GC trace, the amount of the remaining allyl bromide at the end of reaction could not be calculated. The amount of $t\text{-BuO}^\bullet$ was calculated based upon rate constant ($k_{(t\text{-BuO})2} = 1.72 \times 10^-$

[6] s^{-1} at 120 ^{o}C) and the initial concentration of the initiator (A_o) (See Scheme 2-5).

$$A \xrightarrow{k} 2R^{\bullet}$$

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

$$[R^{\bullet}] = 2 \times ([A]_o - [A]_t)$$

Scheme 2-5. Produced radical calculation

In order to measure the initial chain length of this reaction, the amount of product was divided by the total amount of radical produced from the initiator (P/R) as a function of time. Then the log(P/R) was plotted against time. Using the first three data points (less than an hour reaction time), the equation for linear regression approximation was derived (Figure 2-1).

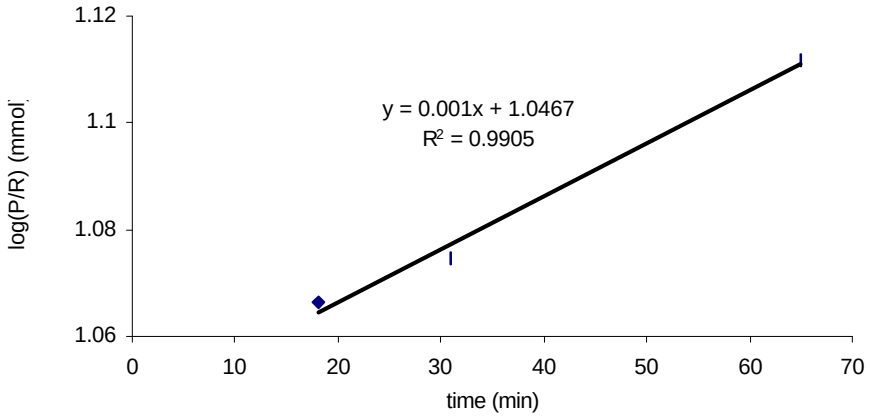


Figure 2-1. Plot of log(P/R) vs. time for the reaction of unsubstituted allyl bromide and toluene

By extrapolating the regression line to t=0, the intercept (1.0467) is assumed to be the log of the initial chain length. Therefore, the initial chain length for the reaction of unsubstituted allyl bromide and toluene was 11 ($=10^{1.0467}$).

b. α-Bromomethylstyrene

Reaction of α-bromomethylstyrene [αBMS] and toluene was studied in the presence of (*t*-BuO)$_2$ (20% of αBMS) in neat toluene in different time intervals (Table 2-9).

Table 2-9. Reaction of toluene and α-bromomethylstyrene in the presence of $(t\text{-BuO})_2$[a]

Reaction time (min)	Unreacted αBMS (mmol)	Product (**15**) (mmol)	$t\text{-BuO}^{\bullet}$ ($\times 10^3$) (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

[a] $[\alpha BMS]_i$=0.14, 4 ml $PhCH_3$, 0.028 M $(t\text{-BuO})_2$, 0.16 M [1,2-epoxy butane], 120 ^{o}C

The calculation of the total amount of $t\text{-BuO}^{\bullet}$ produced is the same as described in previous section (Scheme 2-5). According to the results of these experiments, the product of the reaction is being consumed during the course of the reaction (Figure 2-2).

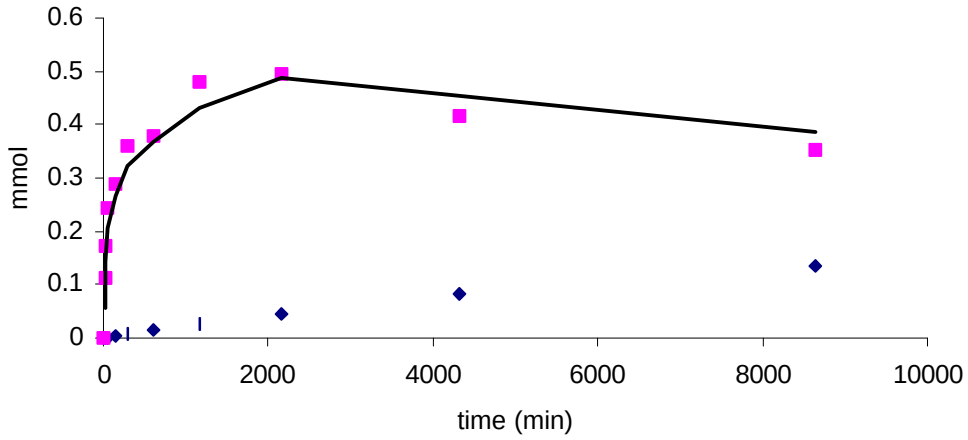
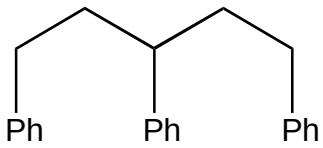


Figure 2-2. Product (**15**) and radical (*t*-BuO$^{\bullet}$) yield vs. time for the reaction of toluene and α-bromomethylstyrene in the presence of (*t*-BuO)$_2$

According to GC-MS, the concentration of a high molecular weight product (MW=300 g/mol) increased while the concentration of the product decreased. Based on the fragmentation of the GC-mass spec, structure **32** was assigned to the side product which is the result of a second addition of the benzylic radical to the double bond of the product.



32

In order to measure the initial chain length of this reaction, a linear regression analysis was performed similar to that described in section a (Figure 2-3).

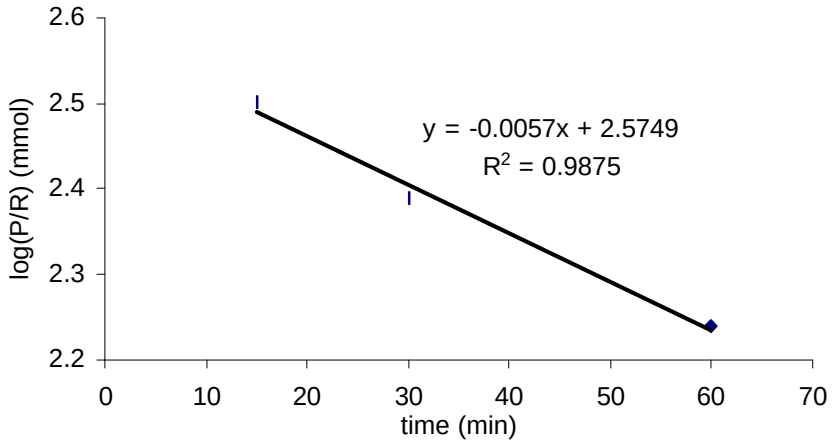


Figure 2-3. Plot of log(P/R) vs. time for the reaction of α-bromomethylstyrene and toluene

By extrapolating the line to t=0, the intercept 2.5749 was obtained. Therefore, the initial chain length of the reaction of toluene and α-bromomethylstyrene was 376 (=$10^{2.5749}$).

c. Ethyl α-bromomethylacrylate

Reaction of toluene and ethyl α-bromomethylacrylate (EαBMA) was studied in the presence of (*t*-BuO)$_2$ (20% of EαBMA) in neat toluene and at different time intervals (Table 2-10).

Table 2-10. Reaction of toluene and ethyl α-bromomethylacrylate in the presence of (*t*-BuO)$_2$[a]

Reaction time (min)	Unreacted EαBMA (mmol)	Product (**17**) (mmol)	*t*-BuO$^\bullet$ ($\times 10^3$) (mmol)
15	0.30	0.22	0.4
30	0.19	0.30	0.7
60	0.13	0.33	1.4
120	0.14	0.30	2.8
180	0.021	0.27	4.2

[a] 0.14 M [EαBMA]$_I$, 4 mL toluene, 0.028 M (*t*-BuO)$_2$, 0.16 M (1,2-epoxy butane), 120 ^{o}C

Calculation of the total amount of *t*-BuO$^\bullet$ produced is the same as that described in section 2.2.2.1.a (Scheme 2-5).

The reduction in concentration of the product for this reaction was observed to be similar to the result of the reaction of toluene and α-bromomethylstyrene. A linear regression analysis was performed in order to measure the initial chain length (Figure 2-4).

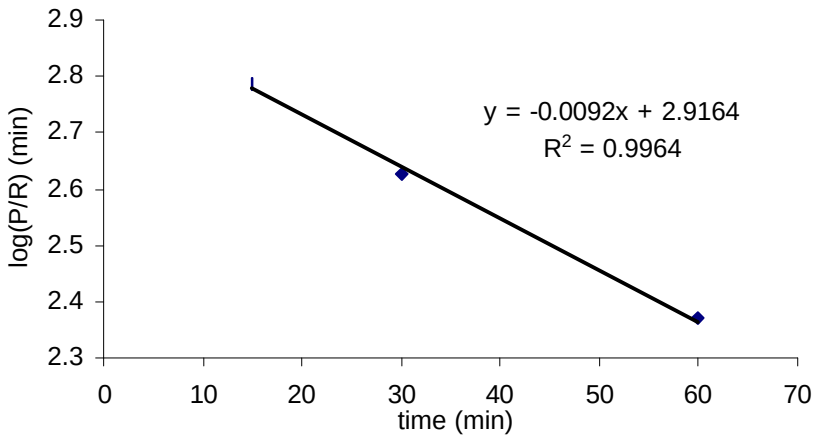


Figure 2-4. Plot of log(P/R) vs. time for the reaction of ethyl α-bromomethylacrylate and toluene

By using a similar calculation as described in section 2.2.2.1.a, the initial chain length for the reaction of toluene and ethyl α-bromomethylacrylate is 825 ($=10^{2.9164}$).

d. α-Bromomethylacrylonitrile

The reaction of α-bromomethylacrylonitrile [αBMCN] and toluene was studied in the presence of $(BzO)_2$ (20% of [αBMCN]) in neat toluene at different time intervals (Table 2-11).

Table 2-11. Reaction of toluene and α-bromomethylacrylonitrile in the presence of $(BzO)_2$[a]

Reaction time (min)	Unreacted αBMCN (mmol)	Product (**18**) (mmol)
5	0.74	0.12
10	0.73	0.20
16	0.57	0.27
30	0.49	0.37
47	0.37	0.42
61	0.32	0.45
121	0.24	0.50
300	0.17	0.52
588	0.16	0.51
1212	0.16	0.52

[a] 0.19 M $[\alpha BMCN]_i$, 4 mL $PhCH_3$, 0.016 M $(BzO)_2$, 0.21 M (1,2-epoxy butane), 80 ^oC

As illustrated in Figure 2-5, the product concentration reaches its maximum in a very short time (~2h at 80 ^oC). After that, the product yield did not change significantly while concentration of allyl bromide decreased.

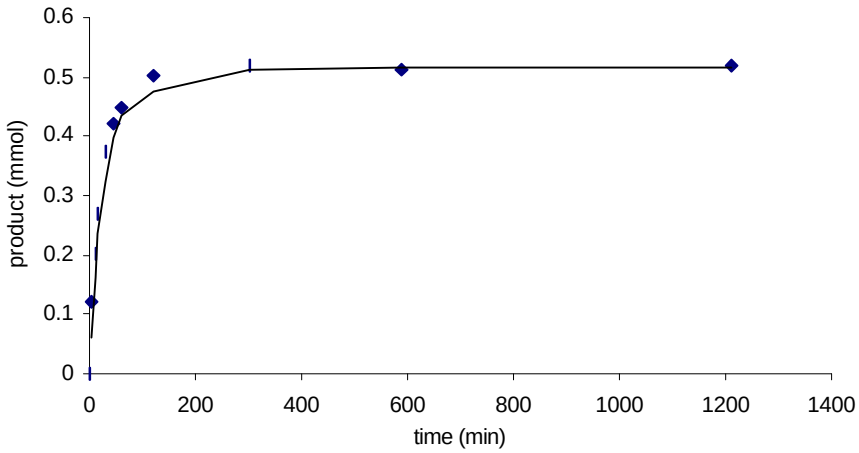


Figure 2-5. Product (**18**) yield vs. time for the reaction of toluene and α-bromomethylacrylonitrile in the presence of $(BzO)_2$

The reaction of α-bromomethylacrylonitrile and toluene was studied in the presence of $(t\text{-BuO})_2$ (20% of [αBMCN]) in order to compare the measured initial chain length with other allyl bromide reactions (Table 2-12).

Table 2-12. Reaction of toluene and α-bromomethylacrylonitrile in the presence of (*t*-BuO)$_2$[a]

Reaction time (min)	Unreacted αBMCN (mmol)	Product (**18**) (mmol)	*t*-BuO$^\bullet$ ($\times 10^3$) (mmol)
10	0.64	0.19	0.32
21	0.52	0.30	0.66
47	0.38	0.39	1.48

[a] 0.19 M [αBMCN]$_i$, 4 mL $PhCH_3$, 0.038 M (*t*-BuO)$_2$, 0.2 M 1,2-epoxy butane, 120 ^oC

The resulting radical concentration was calculated as in Scheme 2-5, section 2.2.2.1.a. Running a similar calculation as in section a, resulted in an initial chain length of 737 for the reaction of toluene and α-bromomethylacrylonitrile (Figure 2-6).

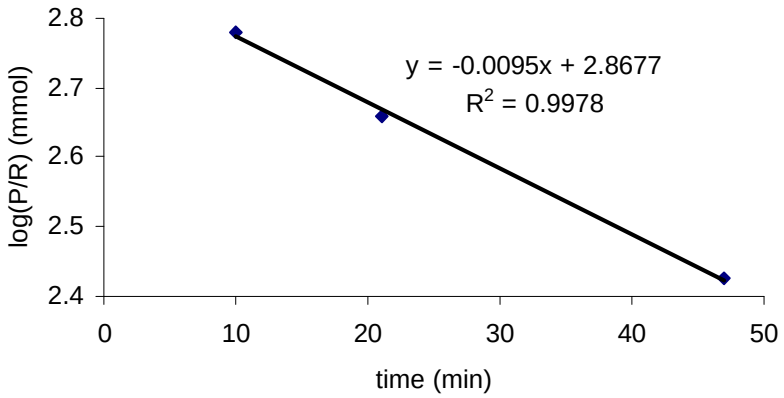


Figure 2-6. Plot of log(P/R) vs. time for the reaction of α-bromomethylacrylonitrile and toluene

2.2.2.2 Reactions of allyl bromides with cumene

a. α-Bromomethyl styrene

Reaction of α-bromomethylstyrene and cumene was studied in neat cumene in the presence of (*t*-BuO)$_2$ (20% of αBMS) (Table 2-13). Calculation for the produced radical concentration is the same as described in 2.2.2.1.a (Scheme 2-5).

Table 2-13. Reaction of cumene and α-bromomethylstyrene in the presence of (t-BuO)$_2$[a]

Reaction time (min)	Unreacted αBMS (mmol)	Product (**19**) (mmol)	t-BuO$^\bullet$ ($\times 10^3$) (mmol)
15	0.55	0.02	0.036
30	0.56	0.04	0.070
60	0.50	0.07	1.4
152	0.46	0.14	3.5
300	0.34	0.24	6.9

[a] 0.14 M [αBMS]$_i$, 4 mL PhCH(CH$_3$)$_2$, 0.028 M (t-BuO)$_2$, 0.16 M 1,2-epoxy butane, 120 ^{o}C

Linear regression analysis as described in 2.2.2.1 resulted in an initial chain length of 59 for the reaction of cumene and α-bromomethylstyrene (Figure 2-7).

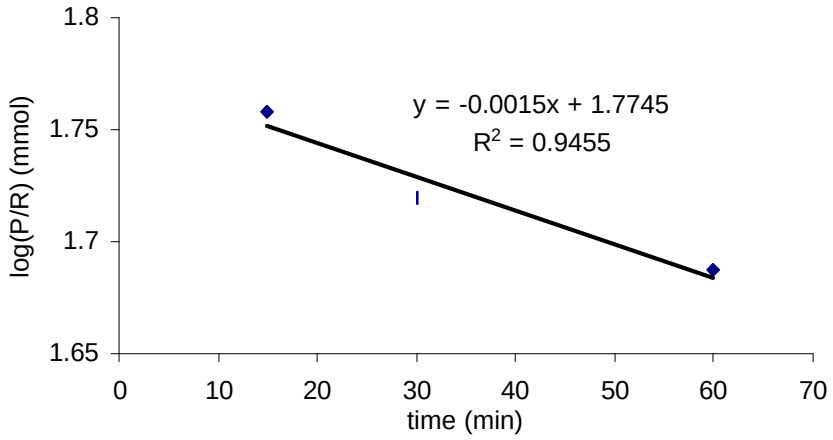


Figure 2-7. Plot of log(P/R) vs. time for the reaction of α-bromomethyl styrene and cumene

b. Ethyl α-bromomethyl acrylate

The reaction of cumene and ethyl α-bromomethylacrylate was studied in neat cumene at different time intervals in the presence of $(t\text{-BuO})_2$ (Table 2-14). The resulting radical concentration was calculated similarly as described in section 2.2.2.1.a (Scheme 2-5).

Table 2-14. Reaction of cumene and ethyl α-bromomethylacrylate in the presence of (*t*-BuO)$_2$[a]

Reaction time (min)	Unreacted EαBMA (mmol)	Product (**20**) (mmol)	*t*-BuO$^\bullet$ ($\times 10^3$) (mmol)
15	0.50	0.022	0.36
60	0.39	0.083	1.4
180	0.22	0.16	4.2
300	0.12	0.21	6.9

[a] 0.14 M $[E\alpha BMA]_i$, 4 mL $PhCH(CH_3)_2$, 0.028 M (*t*-BuO)$_2$, 0.16 M 1,2-epoxy butane, 120 ^oC

Figure 2-8 illustrates the linear regression analysis of the first two data points of this reaction. According to a similar calculation as described in 2.2.2.1.a, the initial chain length for the reaction of ethyl α-bromomethylacrylate and cumene is 64 (=$10^{1.8069}$).

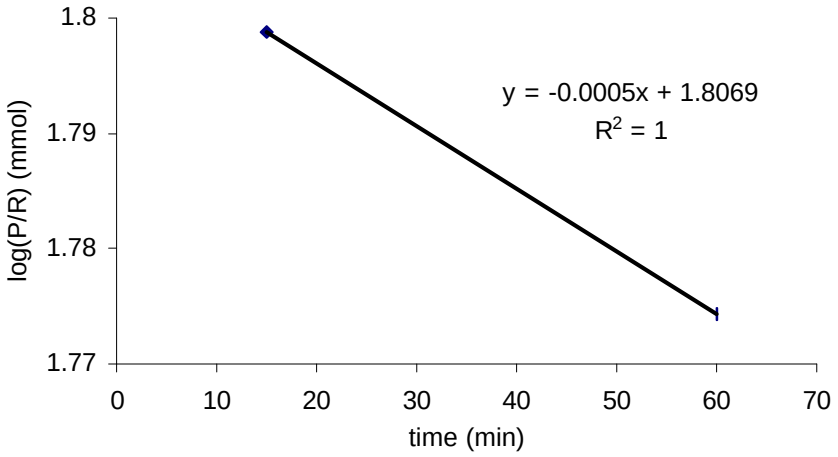


Figure 2-8. Plot of log(P/R) vs. time for the reaction of ethyl α-bromomethylacrylate and cumene

c. α-Bromomethylacrylonitrile

The reaction of cumene and α-bromomethylacrylonitrile was studied in neat cumene in the presence of (*t*-BuO)$_2$ (20% of αBMCN) at various time intervals (Table 2-15). The calculation for resulting radical concentration was similar to that described in 2.2.2.1.a. (Scheme 2-5) Since the peaks related to cumene and α-bromomethylacrylonitrile overlapped on the GC trace, the amount of remaining αBMCN could not be calculated.

Table 2-15. Reaction of cumene and α-bromomethylacrylonitrile in the presence of $(t\text{-BuO})_2$[a]

Reaction time (min)	Product (**21**) (mmol)	$t\text{-BuO}^{\bullet}$ ($\times 10^3$) (mmol)
10	0.12	0.31
20	0.25	0.63
30	0.36	0.94
63	0.53	0.17
120	0.62	0.38

[a] 0.19 M $[\alpha BMCN]_i$, , 4 mL $PhCH(CH_3)_2$, 0.038 M $(t\text{-BuO})_2$, 0.21 M 1,2-epoxy butane, 120 ^oC

The linear regression analysis was similar as described in 2.2.2.1.a and resulted in an initial chain length of 427 (Figure 2-9).

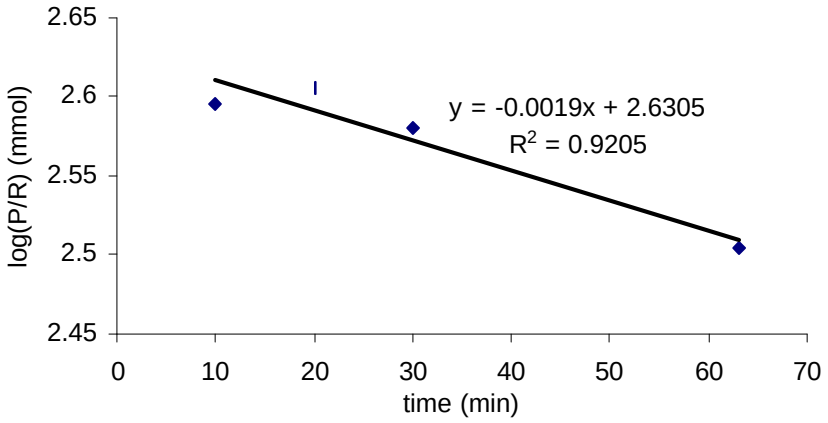


Figure 2-9. Plot of log (P/R) vs. time for the reaction of α-Bromomethylacrylonitrile and cumene

2.2.2.3 Reactions of allyl bromides and phenylcyclopropane

a. α-Bromomethyl styrene

The reaction of α-bromomethylstyrene and phenylcyclopropane was studied in the presence of $(BzO)_2$ (20% of [αBMS]) and neat toluene at different time intervals (Table 2-16). The resulting radical concentration was calculated similarly as that described in 2.2.2.1.a (Scheme 2-5).

Table 2-16. Reaction of phenylcyclopropane and α-bromomethylstyrene in the presence of $(BzO)_2$[a]

Reaction time (mmol)	Unreacted αBMS (mmol)	Product (**22**) (mmol)	$BzO^{\bullet}$ ($\times 10^3$) (mmol)
15	0.66	0.030	7.2
30	0.59	0.056	1.4
60	0.50	0.10	27
180	0.35	0.20	77
300	0.30	0.28	108
644	0.22	0.32	169
1203	0.21	0.30	208
2402	0.19	0.31	224

[a] 0.14 M $[\alpha BMS]_i$, , 4 mL Ph(*c*-C_3H_5), 0.028 M $(BzO)_2$, 80 ^oC

After the formation of the product reached its maximum (~10 h at 80 ^{o}), the change in the product concentration was insignificant (Figure 2-10).

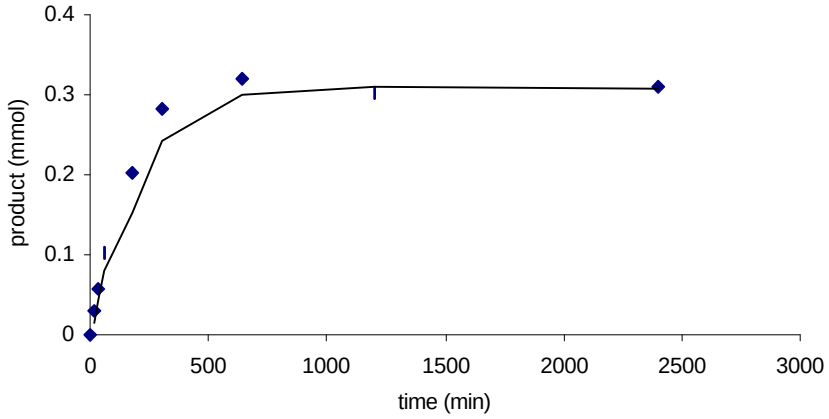


Figure 2-10. Product (**22**) vs. time for the reaction of phenylcyclopropane and α-bromomethylstyrene in the presence of $(BzO)_2$

Linear regression analysis was performed as described earlier. The initial chain length which was measured for the reaction of α-bromomethylstyrene and phenylcyclopropane was 4 (Figure 2-11).

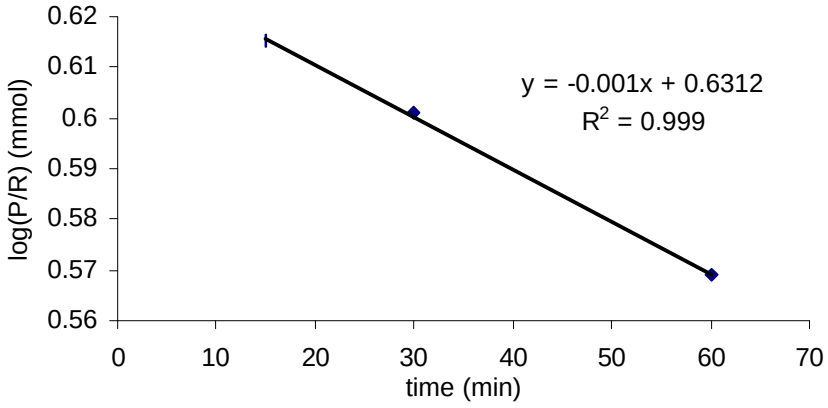


Figure 2-11. Plot of lot (P/R) vs. time for the reaction of α-bromomethylstyrene and phenylcyclopropane

b. α-Bromomethylacrylonitrile

Reaction of phenylcyclopropane and α-bromomethylacrylonitrile was studied in neat phenylcyclopropane using $(BzO)_2$ (20% of αBMCN) as initiator in various time intervals (Table 2-17). The calculation for the produced radicals was similar as described in 2.2.2.1.a (Scheme 2-5). This resulted in an initial chain length of 26 (Figure 2-12).

Table 2-17. Reaction of phenylcyclopropane and α-bromomethylacrylonitrile in the presence of $(BzO)_2$[a]

Reaction time (min)	Unreacted αBMCN (mmol)	Product (**24**) (mmol)	$BzO^{\bullet}$ ($\times 10^3$) (mmol)
15	0.57	0.22	9.7
30	0.41	0.37	19
60	0.40	0.53	37
180	0.22	0.77	98
300	0.15	0.81	145

[a] 0.19 M $[\alpha BMCN]_i$, , 4 mL Ph(*c*-C_3H_5), 0.038 M $(BzO)_2$, 80 ^oC

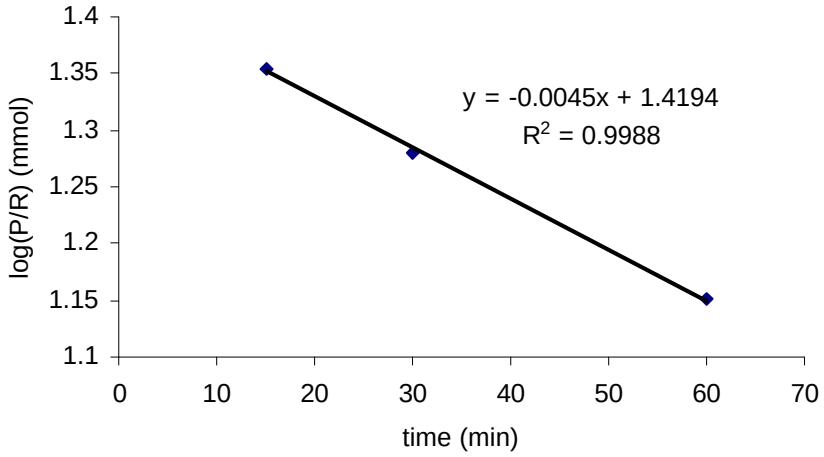


Figure 2-12. Plot of log(P/R) vs. time for the reaction of α-bromomethylacrylonitrile and phenylcyclopropane

2.2.2.4 Reactions of allyl bromides with isopropanol

a. α- Bromomethylstyrene

The reaction of α- bromomethylstyrene and isopropanol was studied in the presence of $(BzO)_2$ (20% of [αBMS]) in benzene at various time intervals (Table 2-18). The produced radical calculation was accomplished as described in 2.2.2.1.a.

Table 2-18. Reaction of isopropanol and α- bromomethylstyrene in the presence of $(BzO)_2$[a]

Reaction time (min)	Unreacted αBMS (mmol)	Product (**25**) (mmol)	$BzO^{\bullet}$ ($\times 10^3$) (mmol)
15	0.56	0.062	7.2
30	0.47	0.078	1.4
66	0.41	0.14	2.7
180	0.37	0.18	7.2
300	0.37	0.18	11
600	0.40	0.19	16
906	0.39	0.19	19
1200	0.41	0.19	21
2400	0.38	0.20	22

[a] 0.14 M $[\alpha BMS]_i$, 1.5 M [*i*-PrOH], 4 mL PhH, 0.028 M $(BzO)_2$, 0.16 M 1,2-epoxy butane, 80 ^{o}C

As is illustrated in Figure 2-13, the product yield reached a maximum then leveled off.

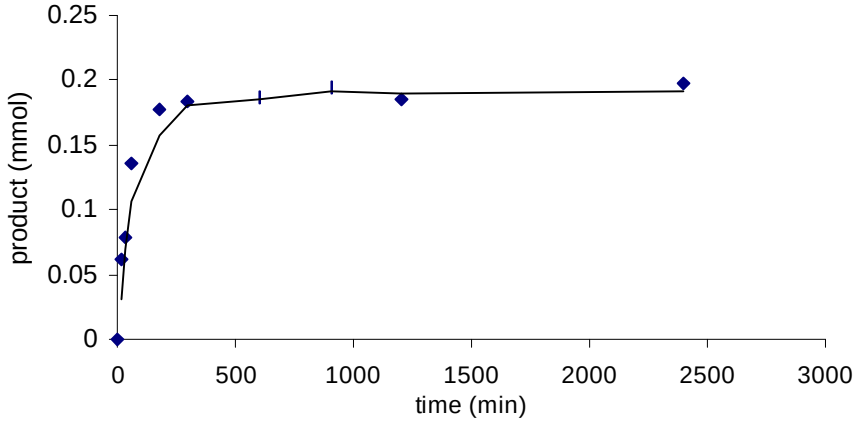


Figure 2-13. Product (**25**) yield vs. time for the reaction of isopropanol and α-bromomethylstyrene in the presence of $(BzO)_2$

The linear regression analysis was similar as described in 2.2.2.1.a and resulted in an initial chain length of 9 for the reaction of α-bromomethylstyrene and isopropanol (Figure 2-14).

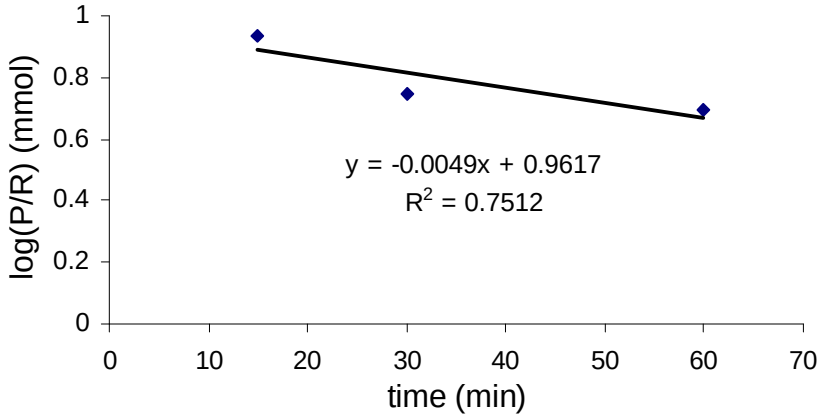


Figure 2-14. Plot of log(P/R) vs. time for the reaction of α-bromomethylstyrene and isopropanol

b. α-Bromomethylacrylonitrile

The reaction of isopropanol and α-bromomethylacrylonitrile was studied in the presence of $(BzO)_2$ in benzene at various time intervals (Table 2-19). The calculation for the produced radical was similar as that described in 2.2.2.1.a.

Table 2-19. Reaction of isopropanol and α-bromomethylacrylonitrile in the presence of $(BzO)_2$[a]

Reaction time (min)	Unreacted αBMS (mmol)	Product (**27**) (mmol)	$BzO^{\bullet}$ ($\times 10^3$) (mmol)
30	0.71	0.24	0.020
63	0.38	0.29	0.041
180	0.25	0.15	0.10
300	0.16	0.11	0.15
600	0.016	0	0.24

[a] 0.19 M $[\alpha BMCN]_i$, 2.0 M [*i*-PrOH], 4 mL PhH, 0.1 M $(BzO)_2$, 0.2 M 1,2-epoxy butane, 80 ^oC

The change in product consumption was so fast that after 10 h of reaction time there was no detectable product in the solution. The initial chain length of the reaction of isopropanol and α-bromomethylacrylonitrile was calculated to be 18 as described in 2.2.2.1.a (Figure 2-15).

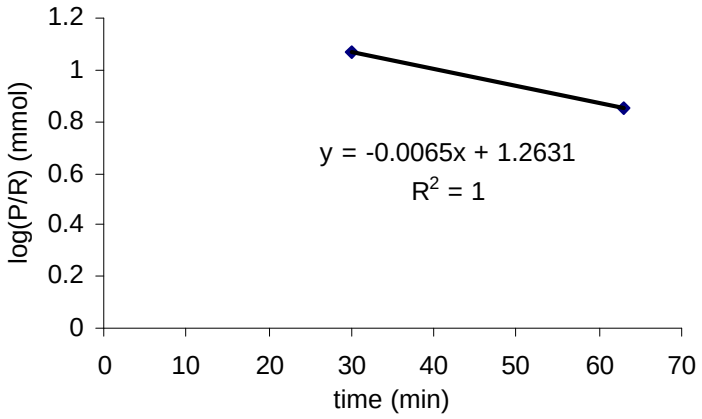


Figure 2-15. Plot of log(P/R) vs. time for the reaction of isopropanol and α-bromomethylacrylonitrile

CHAPTER 3. DISCUSSION

3.1 Introduction

The goal of this research is to develop a new allylation reaction based upon $Br^{\bullet}$ chemistry (Scheme 1-2). The results in chapter 2 demonstrate that the reaction of allyl bromides with a variety of substrates is a viable method of C-C bond formation. In this chapter, several experiments to elucidate the mechanism of these reactions are discussed. Among these experiments are: (1) competition experiments to provide evidence for bromine atom as chain carrier, (2) study of the effect of substituents on the reactivity of allyl bromides, and (3) measurement of chain length of each of these reactions. The chapter concludes with a discussion of the potential application and limitation of this new allylation pathway in organic synthesis.

3.2 Evidence for $Br^{\bullet}$ as the chain carrier

Measurement of the selectivity of $3^{o}/1^{o}$ hydrogen atom abstraction by bromine atom in a competition reaction of toluene and cumene with α-bromomethyl styrene provided evidence for the chain carrier of the allylation reaction under study. 1,2- Epoxy butane was employed as an HBr scavenger for these competition reactions. As illustrated in Table 2-6, the concentration of the scavenger was increased (from 0.05 to 2 equivalent of αBMS). By increasing the concentration of 1,2-epoxy butane, the selectivity decreased which indicates the reversibility of hydrogen abstraction by $Br^{\bullet}$ (Eq. 2-12). At very high scavenger concentration (>1.10 eq.) the reverse reaction is effectively eliminated and a constant value of selectivity was measured ($r(3^{o}/1^{o})=25$).

The selectivity of similar competition reaction using liquid bromine as the bromine atom source was measured to be 26 (Table 2-6). The fact that the selectivities of 3^{o} to 1^{o} hydrogen atom abstraction for the two systems are

identical confirms the role of $Br^{\bullet}$ as the chain carrier in accordance with scheme (1-2).

3.3 Relative reactivities of different allyl bromides

Absolute rate constants for the addition of benzyl ($PhCH_2^{\bullet}$) radical to substituted alkenes have been measured.[25] The evidence for irreversible addition of $PhCH_2^{\bullet}$ and other benzylic radicals to alkenes was provided by Fischer. Since these radicals are resonance-stabilized, the exothermicity of their addition is very low compared to other alkyl radicals. Low ionization potential could be a reason for the nucleophilic polar effect of these radicals.

In general, electron-withdrawing groups on the alkene increase the rate of radical addition as was discussed earlier (Chapter 1, Section 1.4). Absolute rate constants of addition of benzylic radical to some of the di- and mono-substituted alkenes are listed in Table 3-1.

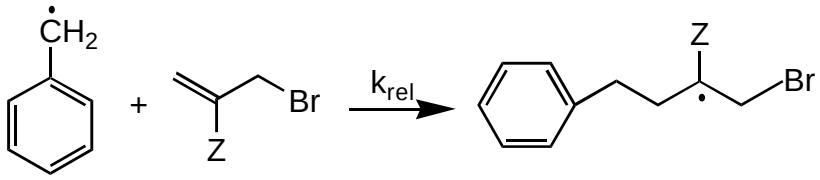
Table 3-1.[25] Rate constants for the addition of benzyl ($PhCH_2^{\bullet}$) radical to alkenes ($H_2C=CXY$) in $M^{-1}s^{-1}$

X	Y	k_{296}
H	CO_2Me	430
Me	Ph	850
H	Ph	1100
Me	CO_2Me	2100
H	CN	2200
Me	CN	6600

According to Table 3-1, the rate constant of addition from styrene to acrylate increased for disubstituted alkenes and decreased for monosubstituted alkenes. In either case (mono or di-substituted olefins), acrylonitrile has the highest rate constant. Although we can sort these data according to an electron deficiency trend in disubstituted olefins, apparently the electron-withdrawing property of the substituent is not the only factor in the rate of addition of radical to the double bond.

The relative rate constants for addition of $PhCH_2^{\bullet}$ to several allyl bromides were determined via competition experiments (Table 3-2).

Table 3-2. Relative reactivities of various allyl bromides towards benzyl radical



Z	k_{rel} at 80 ^{o}C
H	1.0
Ph	65 ± 10
COOEt	110 ± 10
CN	180 ± 10

The results reveal that the observed substituent effect is very similar to that reported by Fischer for disubstituted alkenes. According to Fischer's conclusion, the nucleophilicity of the benzyl radical is dominant and an early transition state is expected for this type of reactions. Log of the relative rate constant of the benzyl radical addition to the double bond of the substituted allyl bromide (log k_{rel}) and log of the absolute rate constant of benzyl radical addition to the double bond of the di-substituted alkenes (log k) are listed in Table 3-3. Plot of log k_{rel} vs. log k is illustrated in Figure 3-1. According to the linear regression analysis, the slope is about 0.49. The slope of less than one is suggestive of a faster (less selective) reaction by benzylic radical to the double bond of the allyl bromide. The reason for this finding is the anchimeric assistance by the β-bromo substituent. As explained earlier in chapter 1, the β-bromo substituent on the double bond of the allyl bromide can stabilize the adduct radical by forming a bridged radical. Therefore, the β-bromoalkyl radical intermediate in the reaction

under study is being stabilized and because of neighboring group assistance the reaction proceeds faster (and less sensitive to the effects of substituent) than with the simple alkenes which were reported by Fischer.

Table 3-3. Log of k_{rel} for $PhCH_2^{\bullet}$ addition to $CH_2=C(Z)CH_2Br$ vs. log k for $PhCH_2^{\bullet}$ addition to $H_2C=CXY$

Z[a]	Log k_{rel}[b]	X, Y[c]	Log k[d]
Ph	1.8	Me, Ph	2.9
COOEt	2.0	Me, COOMe	3.3
CN	2.3	Me, CN	3.8

[a] Reaction illustrated in Table 3-2

[b] k_{rel} from Table 3-2

[c] Reaction illustrated in Table 3-1

[d] k from Table 3-1

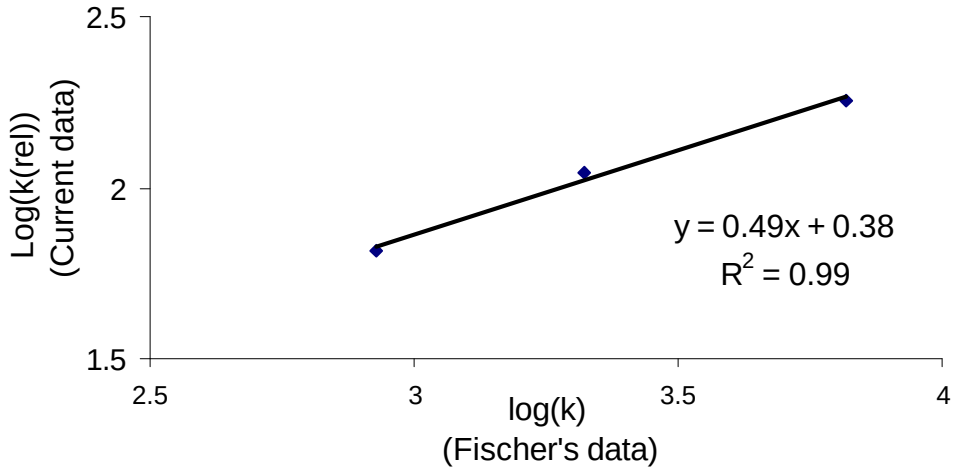


Figure 3-1. Plot of Log of k_{rel} for $PhCH_2^{\bullet}$ addition to $CH_2=C(Z)CH_2Br$ vs. log k for $PhCH_2^{\bullet}$ addition to $H_2C=CXY$ (from Table 3-3)

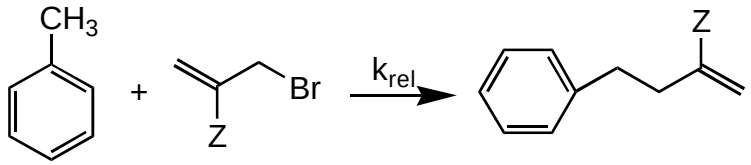
3.4 Chain length discussion

It was observed that by conducting the reaction over an extended period, the product yield decreased during the course of the reaction (Figure 2-2). Due to product consumption, the apparent chain length of reaction varies with time. Since an over all chain length measurement was not possible, an initial chain length was measured by extrapolating the regression line of log(P/R) vs. time. Although this technique of measurement is crude, the gross extracted data fit into some trends for the reactivity of different systems.

3.4.1 Reactions of allyl bromides with toluene

Initial chain length and relative chain length of the reaction of toluene and different allyl bromides are listed in Table 3-4.

Table 3-4. Initial chain lengths for the reaction of toluene (neat) with allyl bromides at 120 ^{o}C



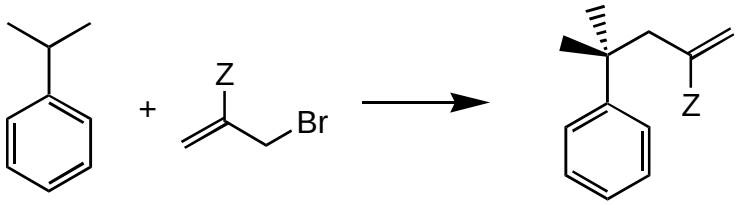
Z	Initial concentration of allyl bromide	Initial chain length	Relative chain length
H	0.14 M	10 ± 2	1
Ph	0.14 M	400 ± 100	40
COOEt	0.14 M	800 ± 120	80
CN	0.19 M	700 ± 100	70

A large effect on chain length of the reaction of toluene with allyl bromides was observed when there was a substituent on the allyl bromide compared with the unsubstituted allyl bromide. On the other hand, within substituted allyl bromides the difference in chain length of reactions was not very significant. While the chain length of the reaction of αBMS (Z=Ph) is slightly different than the other two substituents, acrylate (Z=COOEt) and acrylonitrile (Z=CN) have almost identical chain lengths. The overall trend confirms the assumption that the electron-withdrawing substitution on the double bond increased the rate of reaction.

3.4.2 Reactions of allyl bromides with cumene

The results of initial chain length measurement and their relative values for the reaction of substituted allyl bromides with cumene are illustrated in Table 3-5.

Table 3-5. Initial chain lengths for the reaction of cumene (neat) with allylbromides at 120 ^{o}C



Z	Initial concentration of allyl bromide	Initial chain length	Relative chain length
Ph	0.14 M	60 ± 10	1
COOEt	0.14 M	60 ± 10	1
CN	0.19 M	400 ± 100	7

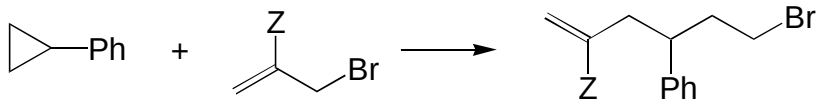
The values for the initial chain length for cumene reactions with allyl bromides are lower compared with the corresponding toluene reactions. Apparently, the rate of reaction is much smaller in the case of cumene reactions which can be related to existence of two bulky methyl groups on the radical center which diminish the rate of addition to the C=C of allyl bromide. Higher exothermicity of the reaction and lower ionization potential (IP) for PhC($^{\bullet}$)Me_2 compared with toluene reactions are also factors for a difference in chain length between two reactions. The chain length for acrylonitrile (Z=CN) is significantly different from

the other two substituents (Z=Ph, COOEt). Although this difference can be related to the higher nucleophilicity of the cumyl radical in the former reactions, this value is too high for this reaction since the cumyl radical should encounter some additional loss of entropy by a hindrance of methyl group rotation in the transition state. The error in measuring the chain length for the reaction of acrylonitrile can be related to the experimental difficulties in this type of reaction.

3.4.3 Reactions of allyl bromides with phenyl cyclopropane

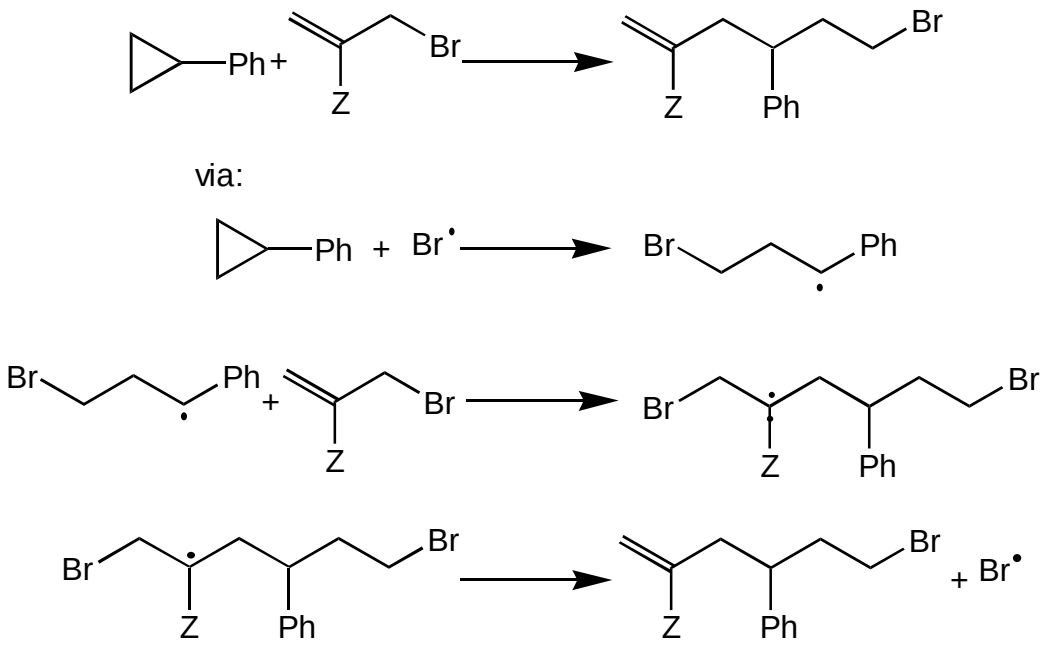
The initial chain lengths and the relative values for the reaction of phenyl cyclopropane and allyl bromides are listed in Table 3-6.

Table 3-6. Initial chain length for the reaction of phenyl cyclopropane (neat) with allyl bromides at 80 ^{o}C



Z	Initial concentration of allyl bromide	Initial chain length	Relative chain length
Ph	0.14 M	5 ± 1	1
CN	0.14 M	30 ± 5	6

Although $Br^{\bullet}$ is the chain carrier for the reaction of phenyl cyclopropane with allyl bromide, the first step of the propagation stage is attack of $Br^{\bullet}$ at the least hindered carbon of cyclopropane resulting in ring opening (Scheme 3-1).



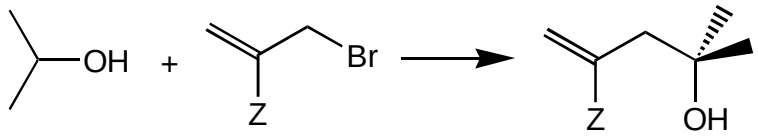
Scheme 3-1. Reaction of allyl bromides with cyclopropanes

Benzoyl peroxide was the most effective initiator used for the reaction of phenyl cyclopropane and allyl bromides. It is not known whether benzoyl peroxide is effective for the opening ring of cyclopropane. Therefore, the low chain length measurements of the reaction of phenyl cyclopropane and allyl bromide is likely attributed to the fact that the initiation process is inefficient.

3.4.4 Reactions of allyl bromides with isopropanol

The initial chain lengths measured for the reactions of isopropanol and allyl bromides along with their relative values are listed in Table 3-6.

Table 3-7. Initial chain lengths for the reaction of isopropanol and allyl bromides



Z	Initial concentration of allyl bromide	Initial chain length	Relative chain length
Ph[a]	0.14 M	10 ± 2	1
CN[b]	0.14 M	20 ± 4	2

[a] [*i*-PrOH]$_i$= 1.5 M, solvent: PhH

[b] [*i*-PrOH]$_i$= 2.0 M, solvent: PhH

These experiments were performed at 80 ^{o}C using benzoyl peroxide for initiation in order to avoid formation of the nucleophilic substitution product (See Table 2-5). Fischer reported that the addition of 2-hydroxy-2-propyl radical to substituted alkenes at room temperature was very fast (Table 3-7).

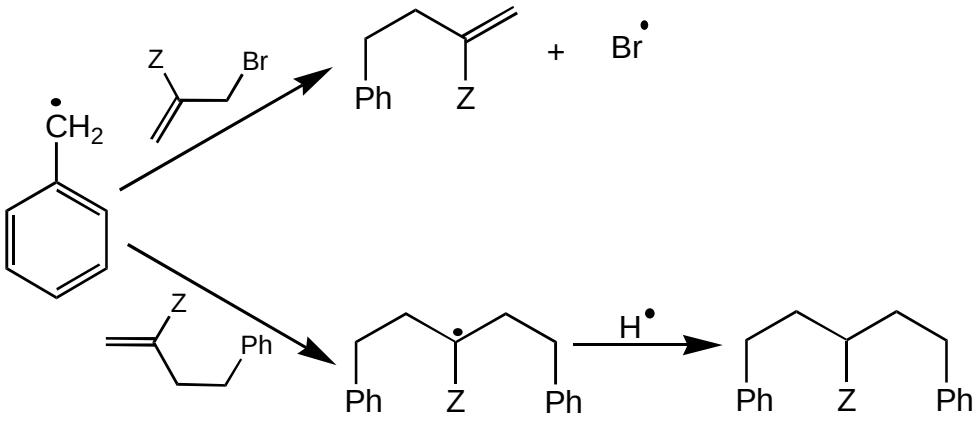
Table 3-8. Rate constants for the addition of the 2-hydroxy-2-propyl radical to alkenes

alkene	k ($\times 10^{-5}$) $[M^{-1}s^{-1}]$
α-Methyl styrene	2.0
Methyl acrylonitrile	310

Addition of $(CH_3)_2C(^{\bullet})OH$ to alkenes are two degree of magnitude faster than benzylic radical addition to the similar alkenes (Table 3-1). The fact that the chain lengths for *i*-PrOH reaction are low merits further discussion. One explanation for this discrepancy can be attributed to the difference in temperature of the reaction. Even though isopropanol reactions were monitored at 80 ^{o}C, similar alkyl aromatic reactions were monitored at 120 ^{o}C. Another reason for this discrepancy can be due to using two different initiators for two systems. For isopropanol reactions, benzoyl peroxide was used as an initiator, while *t*-butyl peroxide was used for alkyl aromatic systems. Benzoyl radicals which are products of the decomposition of the initiator can go through a competition for addition to the double bond of the allyl bromide and cause an experimental error which lead to the above discrepancy. Lastly, the main reason may be related to the difference in concentration of the substrate in two different systems. While the isopropanol reactions are run in dilute condition using benzene as solvent, the alkyl aromatic reactions were conducted in neat solution of substrates (i.e. cumene, toluene).

3.5 Limitation of the synthetic pathway

During our study for measuring the chain length of these reactions, we observed that the produced product is being consumed during the course of the reaction. (i.e., Figure 2-2) According to GC-MS spectra, a new higher molecular weight compound (i.e., MW: 300 g/mol for toluene/αBMS reaction) is formed while the concentration of product decreased. Based on the fragmentation and GC-MS results, the structure of this new product was assigned as **5** (see section 2.2.2.1.b). This result revealed the limitation of this allyl transfer reaction as illustrated in Scheme 3-2.



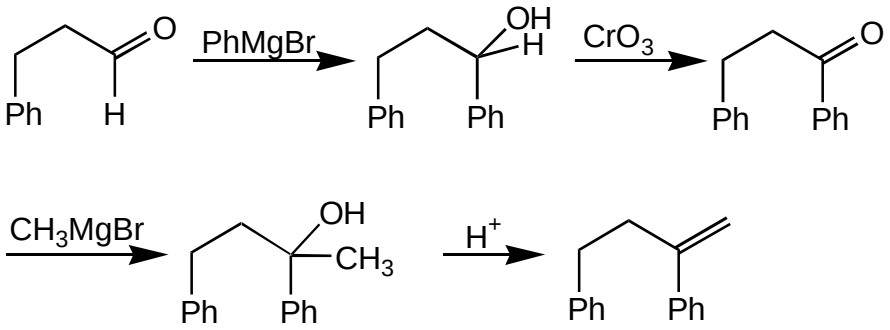
Scheme 3-2. Product competes with allyl bromide in radical addition step

The product of the allylation, which also has a double bond, goes through a competition with the allyl bromide for the addition step. This limits our reaction condition optimization. In other words, the reaction yield can not be increased by running the reaction for a long time, although it would be helpful due to the small chain length of the reaction. The reaction conditions were optimized for each system in order to obtain the highest yield of the desired product and the lowest yield of the oligomer product. For most systems, the oligomer was identified via

GC-MS. In phenyl cyclopropane/αBMS reaction, it was assumed that due to the high molecular weight of oligomer, it does not go through the GC column and could not be observed.

3.6 Synthetic prospects

In summary, the free radical chain reactions which have been discussed provide powerful tools for synthetic organic chemists. The C-C bond formation occurs through free radical addition to an unsaturated system followed by a fragmentation step. In addition to achieving the desired C-C bond formation, important functional group transformations are possible under mild conditions in one step reaction. Brevity is another characteristic of these synthetic pathways which is the result of chain mechanism. Synthesis of similar compounds using other routs requires several steps while current allyl transfer reaction provides one step synthesis (i.e., **15** was synthesized through a four step reaction, see Scheme 3-3).



15

Scheme 3-3.[68] Using another rout for the synthesis of 2,4-diphenyl-1-butene (**15**)

Other than brevity and high yield in a successful synthesis, using relatively non toxic and easily handled reagents are important factors. In fact, all of the

free radical addition-fragmentation reactions which have been used in organic synthesis involve organo-metalic (R_1-M) reagents. These reagents result in the formation of an organo-metalic salt through the course of the reaction. For this reason, environmental concerns have given impetus to avoid such reagents. In these synthetic pathways, alkyl radicals are formed through halogen abstraction of alkyl halides (R-X). Consequently, one functional group (C=C) is formed at the price of sacrificing two others (-M, -X). On the other hand, allyl bromides which are being used for the functionalization of alkanes, are less harmful and easily handled compounds. In the novel allyl transfer reaction which was introduced, alkanes are the source of alkyl radicals. Using alkanes which can be the starting compounds for the synthesis of alkyl halides, a significant shortening of the synthetic sequence is achieved.

3.7 Conclusion

The reaction of allyl bromides and substrates is a newly developed C-C bond formation reaction which is believed to proceed via a chain mechanism (Scheme 1-2). The evidence for the chain mechanism was provided by measuring chain length for all of the systems under study. Although some systems showed poor chain length, all of them provided a chain length larger than 1. These reactions likely involve $Br^{\bullet}$ as the chain carrier, which abstracts hydrogen from hydrocarbon (R-H) to yield alkyl radical ($R^{\bullet}$). The competition experiments provide evidence related to this hypothesis. By using two different $Br^{\bullet}$ source (αBMS and Br_2) and measuring comparable selectivity for the hydrogen abstraction, it was concluded that $Br^{\bullet}$ is the chain carrier and involves hydrogen abstraction in the reaction. As has been discussed in chapter 1, the substituent on the allyl bromide is an effective factor to improve the reaction rate. The competition reactions of various allyl bromides provided evidence for this effect. The trend of relative reactivities of different substituted and unsubstituted allyl bromides (Table 3-2) is in favor of substituted allyl bromide and the electronegativity trends matched what was discussed by Fischer, et.al.[25] The

chain length measurement also reveals reasons for the low efficiency of some reactions. Although the reaction has a limitation due to addition of the produced radical to the double bond of product, optimization of reaction conditions resulted in good to excellent yield for all the systems. This new allylation reaction is unique in that it accomplishes a C-C bond transformation in a single step through high yields and selectivities. Lastly, by using different substituted allyl bromides, this synthetic pathway could be particularly suitable for the synthesis of polyfunctional molecules.

CHAPTER 4. EXPERIMENTAL

4.1 GENERAL

4.1.1 Instrumentation Description

NMR spectra were recorded in $CDCl_3$ (unless other wise stated) on a Bruker WP -200, Bruker WP-270, or Bruker AM-360. Coupling constants are given in Hertz; chemical shifts are given in ppm downfield from TMS. GC/MS was performed on Fisons 8060 GC with VG Quattro Ms or on a Hewlett Packard model 5890 gas chromatograph with an HP methylsilicone capillary column interfaced with an HP 5097B EI mass spectrometer and an HP series computer. GC was performed on a Hewlett Packard HP 5890A instrument equipped with FID detector, and an HP 3393A reporting integrator. Infrared spectra were recorded on a Niclolet Impact 400 FT-IR spectrometer. IR bands were reported in wave numbers (cm^{-1}). UV spectra were obtained on a Hewlett Packard HP 8452A diode array spectrophotometer. HPLC was performed on a Beckman instrument using a Microsorb C-18 reverse phase preparative column (5 um, 21.4 mm ID $\times$ 25 cm L) with acetonitrile/ water solvent mixture. 240 nm detector wavelength and 15 ml/min flow rate of solvent were used in a normal prep HPLC separation. Flash Chromatography[64] was performed on silica gel (grade 60, 230-400 mesh). Thin layer chromatography was performed on Whatman silica gel plates, (250 μm layer, UV_{254}; prep: Analtech, silicagel G & GF preparative UNIPLATES, 20 $\times$ 20 cm, Thickness: 500, 1000 and 1500 μm) were performed using a ethylacetate/ hexane solvent mixture.

4.1.2 Materials and Purification

Toluene (Fisher) and benzene (Fisher) were rinsed with H_2SO_4 several times followed by simple distillation.[65] Purification of cumene was similar except it was done under an Argon atmosphere followed by vacuum distillation. Phenylcyclopropane (Aldrich, 98%) was purified by bubbling Cl_2 in order to remove alkene impurities followed by vacuum distillation. Methylene chloride was distilled over P_2O_5. All of the above reagents were stored over molecular sieves under Ar.

The following reagents were used without purification: hexanes, acetonitrile (HPLC grade), water (HPLC grade), ethyl acetate, carbon tetrachloride, α-methylstyrene, NBS, 2-propanol, formaldehyde (33% w/w), allyl bromide, ammonium chloride, potassium carbonate, triethyl phosphonoacetate, ether, phosphorus tribromide, sodium chloride, magnesium sulfate, and diethyl cyanomethylphosphonate.

4.1.3 Reaction Solution Preparation

Except for the synthesis of the starting materials, solution mixtures were measured into a pressure tube. After degassing through freeze-pump-thaw, the mixture was heated at the desired temperature while stirring.

4.2 Synthesis of starting materials

a. α-bromomethylstyrene[66]

Mixture of α-methylstyrene (250 mL, 1.92 mol), NBS (100 g, 0.56 mol) and carbon tetrachloride (40 mL) was heated just to boiling, and the flask was then quickly immersed in an ice bath. Unreacted NBS was precipitated by pentane (100 mL) and was separated by filteration. Unreacted α-methylstyrene was removed by means of vacuum distillation. An additional 100ml pentane was added to the residue in order to precipitate the remaining succinimide and the

solid was filtered. Crude (103 g) was purified by flash chromatography (hexane: solvent). Each 5mL portion of the crude which was used for purification yielded 3 g (15 mmol) of pure product. If the crude were kept for an extended time, a vacuum distillation would have been necessary after chromatography in order to remove the polymer product.

b. Ethyl α-bromomethyl acrylate[67]

Ethyl α-hydroxymethyl acrylate was prepared by mixing triethyl phosphonoacetate (10 mL, 50 mmol) and 33% aqueous solution of formaldehyde (20.2 mL, 222 mmol). A saturated solution of potassium carbonate (7.3 mL, 88 mmol) was added dropwise to the mixture in 30 min while stirring. At the end of addition, the temperature reaches 30-35 ^{o}C and stirring is continued for 1 h. Then a saturated solution of ammonium chloride (18.9 mL) was added. Product was extracted by ether (3×6.3 mL) and dried over magnesium sulfate. The solvent was evaporated. Crude (5.94 g) was purified by vacuum distillation; yield: 3.74 g (57%); b.p. 65-75 ^{o}C/ 2 torr. According to the GC trace, the purity of the product was 80% which was used for the synthesis directly.

Phosphorus tribromide (1.3 mL, 14 mmol) was added dropwise to the mixture of ethyl α-hydroxymethyl acrylate (3.7 g, 28 mmol) in dry ether (28 mL) at –10 ^{o}C while stirring. The solution was stirred at room temperature for 3 h. Water (16.5 mL) was added at –10 ^{o}C and the mixture was extracted by hexane (3 × 5.5 ml) and washed with a saturated solution of sodium chloride (2 × 5.5 mL). After drying the organic layer over magnesium sulfate, the solvent was evaporated and the crude product (4.7 g) was purified by vacuum distillation; yield: 4.1 g (74%); b.p. 54-58 ^{o}C/ 2 torr. ^{1}H-NMR δ= 4.16 (s), 5.9 (s), 6.3 (s); ^{13}C-NMR: δ= 14.1, 29.4, 61.3, 128.9, 137.6, 164.8.

c. α-Bromomethyl acrylonitrile[67,42]

α-Hydroxymethyl acrylonitrile was prepared by mixing diethyl cyanomethyl phosphonate (30 mL, 190 mmol) and 37% aqueous solution of formaldehyde (75

mL, 2.6 mmol). Then adding a saturated potassium carbonate solution (27 mL, 330 mmol) dropwise in 30 min while the temperature was kept under 20 ^{o}C. After one hour of stirring, 70 mL of a saturated solution of ammonium chloride was added. The alcohol product was extracted by ether (3×24 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue was distilled under vacuum; yield: 3.29 g (21%); b.p. 78-86 ^{o}C/8 torr. According to the GC, the product is 80% pure which was then used for synthesis of the title compound.

α-Bromomethyl acrylonitrile was prepared by adding phosphorus tribromide (6.8 mL, 71 mmol) to the solution of α-hydroxymethyl acrylonitrile(12.6 g, 151 mmol) in CH_2Cl_2 (144 mL) at –10 ^{o}C under Ar atmosphere. Then 83 mL of ice-cold water was added and the solution was neutralized by 25% sodium hydroxide solution (3×83 mL). The organic layer was washed by saturated sodium chloride solution (2×83 mL), dried over magnesium sulfate and concentrate under vacuum. The crude product (11.49 g) was distilled under vacuum. The yield was not calculated: b.p. 52-54 ^{o}C/ 8torr. ^{1}H-NMR: δ= 6.06 (s, 1H), 6.03 (s, 1H), 4.01 (s, 2H).

4.3 Reactions

4.3.1 General

a. Synthesis

All of the product syntheses were run in 20 mL pyrex pressure tubes. After degassing the mixture by freeze-pump-thaw, they were heated at the appropriate temperature and time while stirring. The temperature fluctuation was $\pm$5 ^{o}C and the time of the reaction run has the accuracy of $\pm$1 min. At the end of each reaction, the pressure tube was cooled down under tap water. All of the reaction mixtures were first filtered, then washed with a saturated solution of sodium hydrogen carbonate, except in the case of phenyl cyclopropane as the substrate.

Concentration of the solution was performed under vacuum followed by purification. Each synthesis has its own purification procedure which will be described accordingly in the following sections.

b. Reaction

Reaction yield was optimized by changing different factors (initiator, temperature, and time). All of the reactions were run in pressure tubes and preparation is the same as previous section. At the end of the reaction, diphenyl methane (10 μL, 0.06 mmol) was added as an internal standard. Quantitative analysis was done by GC.

4.3.2 Reaction of unsubstituted allyl bromide

4.3.2.1 Toluene

a. Reaction

Allyl bromide (0.14 M), *t*-butyl peroxide (0.03 M), 1,2-epoxybutane (0.15 M), and toluene (15 mL) were measured into a pressure tube. After degassing the solution, it was heated at 120 ^{o}C for 94 h. Yield of product **14** :33%.

4.3.3 Reactions of α-bromomethyl styrene

4.3.3.1 Toluene

a. Synthesis

In a pressure tube, toluene (15 mL), α-bromomethylstyrene (300 μL, 2.20 mmol), benzoyl peroxide (26 mg, 0.1 mmol) and potassium carbonate (450 mg, 2.4 mmol) were measured. After degassing the mixture, it was heated at 120 ^{o}C

for 20 h. At the end of the reaction 375 mg crude product was obtained which was purified by prep HPLC (80% CH_3CN/H_2O solvent mixture). ^{1}H-NMR δ= 5.29 (s, 1H), 5.06 (s, 1H), 2.77 (m, 4H); ^{13}C-NMR δ= 34.7, 34.3, 112.7, 125.8, 126.1, 127.4, 128.3, 128.35, 128.4, 141.09, 141.95, 147.8; GC-MS (EI) m/e 208(M), 193 (M-15), 165, 152, 130, 115, 104, 91, 65, 51 ; UV λ_{max}= 248 nm, ε= 7.1688×10^3 $M^{-1}cm^{-1}$.

b. Reaction

α-Bromomethyl styrene [αBMS] (0.14 M), toluene (5 mL), K_2CO_3 (0.75 mmol) and 20% of the initiator (AIBN, (*t*-BuO)$_2$ or (BzO)$_2$) were measured into a pressure tube. Results are illustrated in table 2-1.

4.3.3.2 Cumene

a. Synthesis

In a pressure tube, cumene (10 mL), α-bromomethylstyrene (200 μL), K_2CO_3 (300 mg, 1.5 mmol), and *t*-butyl peroxide (260 μL, 1.4 mmol) were mixed. After degassing the mixture, it was heated at 110 ^oC for 20 h. After evaporating the solvent, the crude was purified by prep HPLC (90% acetonitrile/water solvent mixture). The purified compound (255 mg) included 10% bicumyl. Further purification was performed by prep HPLC using the following solvent program: 90% (CH_3CN/ H_2O; 5 min) → 60% (5 min) → 90%. Yield: 33mg. ^{1}H-NMR δ= 1.2 (s, 6H), 2.8 (s, 2H), 4.79 (t, 1H, J=0.9), 5.14 (d, 1H, J=1.89), 7.25 (m, 10H); ^{13}C-NMR δ= 28.7, 38.7, 49.6, 116.9, 125.4, 125.9, 126.5, 126.8, 127.8, 127.99, 143.4, 146.7, 149.4; UV λ_{max}= 236 nm, ε= 1.9923×10^{-4} $M^{-1}cm^{-1}$; Elemental analysis: actual (%C 91.77, %H 8.53); theoretical (%C 91.53, %H 8.47); GC-MS (EI) m/e 236(M), 202, 180, 145, 119, 91,51.

b. Reaction

α- Bromomethyl styrene [αBMS] (0.14 M), cumene, K_2CO_3 (0.15 M) and 20% of initiator (AIBN, (*t*-BuO)$_2$) were measured into a pressure tube. Results are illustrated in table 2-3.

4.3.3.3 Phenyl cyclopropane

a. Synthesis

In a pressure tube, α- bromomethyl styrene (200 μL, 1.43 mmol), benzoyl peroxide (70 mg, 0.3 mmol), and phenyl cyclopropane (10 mL) were measured. After degassing the solution, it was heated at 80 ^{o}C for 9 h. The crude (530 mg) was purified by HPLC (90% CH_3CN/H_2O (3min) $\rightarrow$ 70% (1 min) $\rightarrow$ 95%) followed by PTLC (solvent: hexane). Yield: 89 mg. ^{1}H-NMR, δ= 2.2 (m, 2H), 2.8 (m, 3H), 3.0 (m, 1 H), 3.2 (m, 1 H), 4.95 (s, 1 H), 5.2 (d, 1 H, J=1.4), 7.3 (m, 10 H); ^{13}C-NMR, δ= 31.7, 38.7, 42.5, 42.8, 114.7, 126.3, 126.6, 127.5, 127.6, 128.3, 128.5, 140.8, 143.2, 146.2; GC/MS (EI), m/e 316 (M+1), 314 (M-1), 223, 199, 197, 180, 118, 91,77; IR: 3055, 3024, 2955, 1948, 1872, 1797, 1646, 1494, 1450, 1419, 1211, 1155, 928, 896, 859, 764, 689, 588.

b. Reaction

α-Bromomethyl styrene (0.14 M), 20% benzoyl peroxide and phenyl cyclopropane (neat) were measured into a pressure tube. After degassing the solution, they were heated at 80 ^{o}C for 10 h. The yield of this reaction was 57% ([αBMS]$_f$= 39%). In a dilute condition of phenylcyclopropane (1.4 M, solvent: PhH), the yield of the similar reaction was 42% (Unreacted αBMS= 44%).

4.3.3.4 Isopropanol

a. Synthesis

In a pressure tube, 2-propanol (1.2 mL, 14 mmol), α-bromomethylstyrene (200 μL, 1.43 mmol), benzoyl peroxide (176 mg, 0.700 mmol), potassium carbonate (300 mg, 1.6 mmol), and benzene (8.6 mL) were measured. After degassing the mixture, it was heated at 80 ^{o}C for 40 h. The crude product was purified by PTLC (10% ethylacetate/hexane solvent mixture). ^{1}H-NMR δ= 1.1 (s, 6H), 1.5 (s, 1H), 2.7(s, 2H), 5.1(s, 1H), 5.4(s, 1H), 7.3(m, 5H); ^{13}C-NMR δ= 145.8, 142.3, 128.4, 127.5, 126.5, 117.3, 70.8, 48.7, 29.7; GC-MS(EI) m/e 176 (M), 161 (M-15), 133, 118, 105, 91, 77, 51.

b. Reaction

In a pressure tube, α-bromomethyl styrene (0.14 M), isopropanol (1.4 M), benzoyl peroxide (0.07 M), potassium carbonate (0.75 mmol) and benzene (4.3 mL) were measured. After degassing the solution, it was heated at 80 ^{o}C for 40 h. The yield of the reaction product (**25**) is 59% (Unreacted αBMS= 36%).

4.3.4 Reactions of ethyl α-bromomethyl acrylate

4.3.4.1 Toluene

a. Synthesis

In a pressure tube, toluene (15 mL), ethyl α-bromomethyl acrylate (300 μL, 2.30 mmol), *t*-butyl peroxide (140 μL, 2.30 mmol), and potassium carbonate (351 mg, 2.50 mmol) were measured. After degassing the mixture, it was heated at 120 ^{o}C for 8 h. The crude (483 mg) was purified by prep HPLC (70% CH_3CN/ H_2O solvent mixture) which yielded 72 mg of the desired product. Small amount of the polymer in the product was removed by PTLC (10% ethyl acetate/hexane solvent mixture). After extracting the product by methylene chloride and drying

over magnesium sulfate, 31 mg of the pure product was obtained. ^{1}H-NMR δ= 1.28 (t, 3H, J=7.1), 2.6 (t, 2H, J= 8.3, 7.3), 2.77 (t, 2H, J= 7.1, 8.5), 4.18 (q, 2H, 7.1), 5.48 (s, 1H), 6.14 (s, 1H), 7.2 (m, 5H); ^{13}C-NMR δ= 14.2, 33.89, 34.9, 60.6, 125.1, 125.9, 128.3, 128.5, 134.3, 140.1, 141.5, 167.1; GC/MS (EI) m/e 204(M), 175 (M-29), 159 (M-45), 131, 91, 77, 65; Elemental analysis: actual (%C 76.38, %H 7.94), theoretical (%C 76.47, H% 7.84).

b. Reaction

In a pressure tube, ethyl α-bromomethyl acrylate [EαBMA] (0.15 M), (*t*-BuO)$_2$ (0.03 M), K_2CO_3 (0.85 mmol) and toluene (4 mL) were measured. After degassing the mixture, it was heated at 120 ^{o}C for 1 h. The yield of the reaction was 58% (Unreacted EαBMA= 22%).

4.3.4.2 Cumene

a. Synthesis

In a pressure tube, cumene (15 mL), ethyl α-bromomethyl acrylate (300 μL, 2.30 mmol), potassium carbonate (351 mg, 2.50 mmol), and benzoyl peroxide (111 mg, 0.500 mmol) were measured. After degassing the mixture, it was heated at 80 ^{o}C for 18.5 h. The crude product (228 mg) was purified by PTLC (10% ethyl acetate/ hexane solvent mixture) followed by HPLC (70% CH_3CN/H_2O). After drying and evaporating the solvent, 61 mg pure product was obtained. ^{1}H-NMR δ= 1.18 (t, 3H, J=7.0), 1.3 (s, 6H), 2.63 (s, 2H), 4.0 (q, 2H, J=7.0), 5.1 (s, 1H), 6.0 (s, 1H), 7.3 (m, 5H); ^{13}C-NMR δ= 14.1, 27.96, 38.4, 45.1, 60.6, 125.69, 126.1, 127.1, 127.9, 138.2; GC/MS (EI) m/e: 232(M), 187(M-45), 143, 119, 91, 51; Elemental analysis, actual (C% 77.49, H% 8.80), theoretical (C% 77.59, H% 8.6).

b. Reaction

In a pressure tube, ethyl α-bromomethyl acrylate (0.15 M), (*t*-BuO)$_2$ (0.03 M), potassium carbonate (0.85 mmol) and cumene (5 mL) were measured. After degassing the solution, it was heated at 120 ^{o}C for 94 h. The yield of the reaction product (**21**) was 48% (Unreacted EαBMA= 0).

4.3.5 Reactions of α-bromomethyl acrylonitrile

4.3.5.1 Toluene

a. Synthesis

In a pressure tube, toluene (15 mL), α-bromomethyl acrylonitrile (300 μL, 3.1 mmol), potassium carbonate (474 mg, 3.40 mmol), and benzoyl peroxide (150 mg, 0.600 mmol) were measured. After degassing the mixture, it was heated at 80 ^{o}C for 40 h. The crude (660 mg) was purified by PTLC (10% ethyl acetate/hexane solvent mixture) followed by HPLC (90% CH_3CN/H_2O solvent mixture). After drying and evaporating the solvent, 149 mg of the pure product was obtained. ^{1}H-NMR δ= 2.56 (t, 2H, J=7.3, 8.0), 2.9 (t, 2H, J=8.2, 7.2), 5.6 (s, 1H), 5.9 (s, 1H); ^{13}C-NMR δ= 47.0, 52.5, 139.8, 141.7, 141.9, 144.3; GC/MS (EI) m/e 157(M), 91, 65, 51; Elemental analysis, actual (C% 83.96, N% 8.52, H% 6.89), theoretical (C% 84.08, N% 8.92, H% 7.01).

b. Reaction

In a pressure tube, α-bromomethyl acrylonitrile [αBMCN] (0.19 M), benzoyl peroxide (0.04 M), 1,2-epoxybutane (0.2 M) and toluene (4 ml) were measured. After degassing the solution, it was heated at 80 ^{o}C for 2 h. The yield of the reaction product (**18**) is 66% (unreacted αBMCN= 31%).

4.3.5.2 Cumene

a. Synthesis

In a pressure tube, α-bromomethyl acrylonitrile (300 μL, 3 mmol), potassium carbonate (474 mg, 3.30 mmol), benzoyl peroxide (150 mg, 0.600 mmol) and cumene (15 mL) were measured. After degassing the mixture, it was heated at 80 ^{o}C for 40 h. The crude (590 mg) was purified by PTLC (10% ethyl acetate/hexane solvent mixture) followed by HPLC (80% CH_3CN/H_2O). Yield: 78.50 mg. ^{1}H-NMR: δ= 1.4 (s, 6H), 2.5 (s, 2H), 5.38 (d, 1H, J=0.86), 5.8 (s, 1H), 7.3 (m, 5H); ^{13}C-NMR: 29.2, 47.9, 134.6; elemental analysis: actual (C% 84.26, H% 8.38, N% 7.52), theoretical (C% 84.32, H% 8.11, N% 7.57).

b. Reaction

In a pressure tube, α-bromomethyl acrylonitrile [αBMCN] (0.19 M), (*t*-BuO)$_2$ (0.04 M), 1,2-epoxybutane (0.2 M) and cumene (4 ml) were measured. After degassing the solution, it was heated at 120 ^{o}C for 2 h. The yield of the reaction product (**20**) is 80%.

4.3.5.3 Phenylcyclopropane

a. Synthesis

In a pressure tube, α-bromomethyl acrylonitrile (300 μL, 3 mmol), benzoyl peroxide (150 mg, 0.600 mmol), and phenyl cyclopropane (15 mL) were measured. After degassing the solution, it was heated at 80 ^{o}C for 12 h. The crude (1.26 g) were purified by twice PTLC (1st solvent: hexane, 2nd solvent: 20% ethyl acetate/hexane) followed by HPLC (95% CH_3CN/H_2O (2 min) → 50% (3 min) → 95%), then PTLC (20% ethyl acetate/hexane). Yield: 104.5 mg. ^{1}H-NMR: 2.15 (m, 4H), 2.5 (m, 2H), 3.2 (m, 4H), 5.5 (s, 1H), 5.7(d, 1H,

J=12), 7.3(m, 10H); ^{13}C-NMR: 31.4, 39.0, 42.1, 43.2, 127.9, 128.2, 129.1, 132.9 ; GC/MS (EI) m/e 263 (M), 197, 169, 154, 117, 91, 51.

b. Reaction

In a pressure tube, α-bromomethyl acrylonitrile (0.19 M), benzoyl peroxide (0.04 M), and phenyl cyclopropane (4 mL) were measured. After degassing, the solution were heated at 80 ^{o}C for 3 h. The yield of the reaction product (**24**) is quantitative.

4.3.5.4 2-Propanol

a. Synthesis

In a pressure tube, α-bromomethyl acrylonitrile (300 μL, 3 mmol), isopropanol (2.4 mL, 31 mmol), benzoyl peroxide (368 mg, 1.500 mmol), potassium carbonate (465 mg, 3.30 mmol), and benzene (13 mL) were measured. After degassing the mixture, it was heated at 85 ^{o}C for 3 h. The reaction mixture was extracted by water (3 × 10 mL) and CH_2Cl_2 after filteration. The organic layer was washed with saturated solution of NaCl (2 × 10 mL) and dried over $MgSO_4$. Crude (320 mg) was purified by PTLC (20% ethyl acetate/hexane). Yield: 77 mg, ^{1}H-NMR: δ= 1.31(s, 6H), 1.4(s, 1H), 2.4(s, 2H), 5.8 (s, 1H), 6.0 (s, 1H); ^{13}C-NMR: δ=29.2, 47.9, 134.6.

b. Reaction

In a pressure tube, α-bromomethyl acrylonitrile (0.2 M), isopropanol (2 M), benzoyl peroxide (0.1 M), K_2CO_3 (1.1 mg) and benzene (4.3 mL) were measured. After degassing, the mixture was heated at 80 ^{o}C for 3 h. Yield of the reaction product (**27**) was 54% (unreacted EαBMCN = 37%)

4.4 Competition Reactions

4.4.1 General

In a normal run, all of the reagents were measured into a pressure tube. After degassing the mixture by freeze-pump-thaw, it was heated at appropriate time and temperature. At the end of the reaction, the pressure tube was cooled down and diphenyl methane (10 μL, 0.06 mmol) was added as an internal standard. Quantitative analysis has been done by GC.

4.4.2 Reactions of α-bromomethyl styrene with toluene and cumene

In a pressure tube, toluene (4.4 mL, 41 mmol), cumene (700 μL, 5.00 mmol), α-bromomethylstyrene (100 μL, 0.70 mmol), 1,2-epoxybutane (68 μL, 0.77 mmol), and benzoyl peroxide (35 mg, 0.14 mmol) were measured. After degassing the solution, it was heated at 80 ^{o}C for 1 h. According to GC, relative selectivity of two substrates (r($3^{o}/1^{o}$)) was 26.

For the comparison purpose, r($3^{o}/1^{o}$) was measured using bromine as a bromine atom source. Toluene (21 μL, 0.20 mmol), cumene (28 μL, 0.20 mmol), *t*-butyl peroxide (3.6 μL, 0.020 mmol), 1,2-epoxybutane (18 μL, 0.20 mmol), and benzene (5 mL) were measured into a pressure tube. After degassing the solution, bromine (10 μL, 0.2 mmol) was distilled into the pressure tube. The solution was warmed up to room temperature at dark, then heated at 80 ^{o}C in an oil bath for 5 min. r($3^{o}/1^{o}$)=26.

4.4.3 Reactions of allyl bromides with toluene

4.4.3.1 Allyl bromide and α-bromomethyl styrene

In a pressure tube, toluene (5 mL), α-bromomethyl styrene [αBMS] (100 μL, 0.72 mmol), allyl bromide [ALLB] (300 μL, 3.50 mmol), 1,2 epoxy butane (68 μL, 0.79 mmol), and benzoyl peroxide (35 mg, 0.14 mmol) were measured. After degassing the solution, it was heated at 80 ^{o}C for 1 h. According to GC, relative reactivity of these two allyl bromides ($k_{\alpha BMS}/k_{ALLB}$) was 65.

4.4.3.2 α-Bromomethyl styrene and ethyl α-bromomethyl acrylate

In a pressure tube, toluene (2.6 mL), α-bromomethyl styrene [αBMS] (270 μL, 1.9 mmol), ethyl α-bromomethyl acrylate [EαBMA] (50 μL, 0.38 mmol), 1,2-epoxy butane (36 μL, 0.42 mmol), and benzoyl peroxide (19 mg, 0.080 mmol) were measured. After degassing the solution, it was heated at 80 ^{o}C for 1 h. According to GC, the relative reactivity of these two allyl bromides ($k_{E\alpha BMA}/k_{\alpha BMS}$) was 1.7.

4.4.3.3 Ethyl α-bromomethyl acrylate and α-bromomethyl acrylonitrile

In a pressure tube, toluene (2.6 mL), ethyl α-bromomethyl acrylate [EαBMA] (250 μL, 1.9 mmol), α-bromomethyl acrylonitrile [αBMCN] (37 μL, 0.39 mmol), 1,2- epoxy butane (37 μL, 0.43 mmol), and benzoyl peroxide (19 mg, 0.080 mmol) were measured. After degassing the solution, it was heated at 80 ^{o}C for 10 min. According to GC, the relative reactivity of these two allyl bromides ($k_{\alpha BMCN}/k_{E\alpha BMA}$) was 1.6.

4.5 Initial chain length measurement

4.5.1 General

In a typical reaction preparation, a stock solution was prepared in a 25 mL volumetric flask. A 4 mL portion of the stock solution was measured into a pressure tube. After degassing each solution by freeze-pump-thaw, it was

heated in an oil bath. The temperature accuracy is ±0.1 ^{o}C. At the end of the reaction, the pressure tube was cooled down under tap water and diphenyl methane (10 μL, 0.06 mmol) was added as an internal standard. Quantitative analysis was accomplished by GC. The initial chain length has been calculated using linear regression of the product yields and produced radicals.

4.5.2 Reaction of unsubstituted allyl bromide

a. Toluene

In a 25 ml volumetric flask, 1,2-epoxy butane (330 μL, 3.9 mmol), *t*-butyl peroxide (130 μL, 0.700 mmol), and allyl bromide (300 μL, 3.50 mmol) were measured. Using toluene as solvent, the volumetric flask was filled up to the line. After degassing, each pressure tube was heated at 120 ^{o}C for the appropriate time. The measured initial chain length for this reaction was 15.

4.5.3 Reactions of α-bromomethyl styrene

a. Toluene

In a 25 ml volumetric flask, 1,2-epoxy butane (300 μL, 3.90 mmol), *t*-butyl peroxide (130 μL, 0.700 mmol), and α-bromomethyl styrene (490 μL, 3.50 mmol) were measured. Then the flask was filled up to the line using toluene as solvent. After degassing each pressure tube, it was heated at 120 ^{o}C for the appropriate time. The measured initial chain length for this reaction was 380.

b. Cumene

In a 25 mL volumetric flask, 1,2-epoxy butane (300 μL, 3.90 mmol), *t*-butyl peroxide (130 μL, 0.700 mmol), and α-bromomethyl styrene (490 μL, 3.50 mmol) were measured. Using cumene as solvent, the flask was filled up to the line.

Each pressure tube was heated at 120 ^{o}C after degassing for the appropriate time. The initial chain length for this reaction was measured to be 70.

c. Phenyl cyclopropane

In a 25 mL volumetric flask, α-bromomethyl styrene (490 μL, 3.50 mmol) and benzoyl peroxide (170.3 mg, 0.7000 mmol) were measured. The flask was filled up to the line with phenyl cyclopropane. Each pressure tube was heated at 80 ^{o}C for the appropriate time after degassing. According to the measurement, the initial chain length for this reaction was 105.

d. Isopropanol

In a 25 mL volumetric flask, 1,2-epoxy butane (300 μL, 3.90 mmol), benzoyl peroxide (168.25 mg, 0.70000 mmol), α-bromomethyl styrene (490 μL, 3.50 mmol) and 2-propanol (2.8 mL, 37 mmol) were measured. The flask was filled up to the line by benzene. After degassing, each pressure tube was heated at 80 ^{o}C for the appropriate time. The initial chain length for this reaction was measured to be 210.

4.5.4 Reactions of ethyl α-bromomethyl acrylate

a. Toluene

In a 25 ml volumetric flask, 1,2- epoxy butane (330 μL, 3.90 mmol), t-butyl peroxide (130 μL, 0.700 mmol) and ethyl α-bromomethyl acrylate (460 μL, 3.50 mmol) were measured. The flask was filled up to the line by using toluene as solvent. After degassing each pressure tube, it was heated at 120 ^{o}C for the appropriate time. The measured initial chain length for this reaction was 735.

b. Cumene

In a 25 mL volumetric flask, 1,2-epoxy butane (330 μL, 3.90 mmol), *t*- butyl peroxide (130 μL, 0.700 mmol), and ethyl α-bromomethyl acrylate (460 μL, 3.50 mmol) were measured. The flask was filled up to the line by cumene. After degassing each pressure tube, it was heated at 120 ^{o}C for the appropriate time. The measured initial chain length for this reaction was 75.

4.5.5 Reactions of α-bromomethyl acrylonitrile

a. Toluene

In a 25 mL volumetric flask, α-bromomethyl acrylonitrile (460 μL, 4.80 mmol), *t*-butyl peroxide (175 μL, 0.950 mmol), and 1,2-epoxy butane (455 μL, 5.30 mmol) were measured. Then the flask was filled up to the line with toluene. After degassing each pressure tube, it was heated at 120 ^{o}C for the appropriate time. The measured initial chain length was 643.

b. Cumene

In a 25 mL volumetric flask, α-bromomethyl acrylonitrile (460 μL, 4.80 mmol), *t*-butyl peroxide (175 μL, 0.950 mmol), and 1,2-epoxy butane (455 μL, 5.30 mmol) were measured. Using cumene as solvent, the flask was filled up to the line. After degassing each pressure tube, it was heated at 120 ^{o}C for the appropriate time. The measured initial chain length for this reaction was 413.

c. Phenyl cyclopropane

In a 25 mL volumetric flask, α-bromomethyl acrylonitrile (460 μL, 4.80 mmol), and benzoyl peroxide (230.90 mg, 0.95000 mmol) were measured. The flask was filled up to the line with phenyl cyclopropane. After degassing each pressure

tube, it was heated at 80 ^{o}C for the appropriate time. The measured initial chain length was 735.

d. 2- Propanol

In a 25 ml volumetric flask, α-bromomethyl acrylonitrile (490 μL, 5.10 mmol), benzoyl peroxide (613 mg, 2.50 mmol), 1,2-epoxy butane (440 μL, 5.70 mmol), and 2- propanol (3.9 mL, 51 mmol) were measured. Then the flask was filled up to the line with benzene. After degassing the solution, it was heated at 80 ^{o}C for the appropriate time. The measured initial chain length was 390.

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Vita

Mitra Sadeghipour

Mitra Sadeghipour was born in August 11, 1965 in Abadan, Iran to Parvin and Mohammad Taghi Sadeghipour. She graduated from Bahonar (Hadaf) High School in 1983.

In Fall of 1985, she enrolled at Sharif (Aryamehr) University of Technology in Tehran, Iran majoring in applied chemistry. She received her Bachelor of Science in chemistry in Fall 1989. Afterward, she started working in Industrial Chemical Research Company (ICRCo.) in Tehran for a few months, until she was admitted to the Masters program at Ball State University, Muncie, IN, in August of 1990. She received her Masters degree in August 1996. In spring 1993, she entered the graduate program at Virginia Polytechnic Institute and State University, Blacksburg, VA where she worked under the supervision of Prof. James Tanko in the area of physical organic chemistry. She received a Doctor of Philosophy in chemistry in July, 1998.

She will begin her postdoctoral research under the guidance of Prof. Lawrence Sayre in the Chemistry Department at Case Western Reserve University, Cleveland, OH, USA.