Concentration Studies on the Radical Cyclizations of Enol acetates and Enol carbonates and the Possible Formation of 4-Hydrindanones via an Uncommon Acyl Radical Fragmentation

by

Tiffany Renee Turner

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FACULTY OF ARTS AND SCIENCES

This thesis was presented

by

Tiffany Renee Turner

It was approved by

Dr. Kay Brummond, Associate Professor, Department of Chemistry

Dr. Peter Wipf, Professor, Department of Chemistry

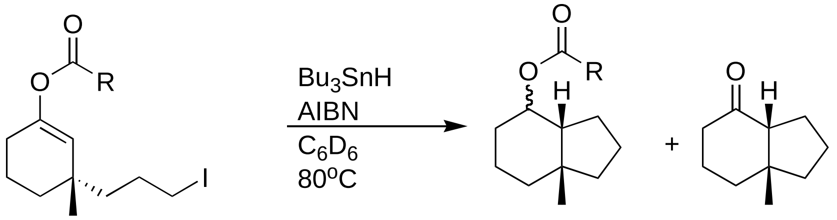
Dr. Dennis Curran, Distinguished Service Professor of Chemistry and Bayer Professor,

Department of Chemistry

Concentration Studies on the Radical Cyclizations of Enol acetates and Enol carbonates and the Possible Formation of 4-Hydrindanones via an Uncommon Acyl Radical Fragmentation

Tiffany Renee Turner, M.S.

Recently, Uta Wille and coworkers proposed a novel non-chain, self-terminating, oxidative radical cyclization that ends with the uncommon homolytic cleavage of an acyl-oxygen bond to give a ketone and an acyl radical (*J. Amer. Chem. Soc.* **2002**, *124* (1), 14-15). We present the results of our study into this type of unusual radical fragmentation. Our focus was on initiating radical intermediates **53a,b** thru thermal means using Bu_3SnH to produce ketone **54** as opposed to photo-induced methods used by Wille. In our work, we were unable to produce **54** in sufficient yields, but we were able to isolate carbonyl compounds **62-63α,β**. Based on these results, we cannot rule out an alternative polar fragmentation.



53a,b
a: R = Me
b: R = OMe

62α,β: R = Me
63α,β: R = OMe

54

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PREFACE

I am dedicating this thesis to my family, friends and colleagues who have supported me and continue to support me throughout my graduate career. I would have failed miserably if it hadn't been for the constant urging, pushing and encouragement to succeed. First, to my family for supporting my return to school after three years in industry- your love can't be measured and the financial support was much needed. You continue to support me and understand that more years of school will allow me to attain my career goals, even when you wonder if I will ever finish school.

Second, to my friends in and out of the Chemistry Department who have kept me sane, given me a shoulder to cry on, a ear to listen and the many cheers and beers for our accomplishments. A very special thanks to Andre Lapierre and Jon Tripp for being the best group members and the best friends a girl could ever have. You helped me excel, made me laugh and lit the fire when I needed it lit. To Marc, Jose and Mancuso, thanks for helping out a lowly grad student when you were the great post docs. To Bobbie, my partner in GK-12 you are a great friend, a great mentor and a great teacher. The Carmalt students are lucky to have you as a science teacher and a role model. To Marv, you are a great friend and I am glad I met you so many years ago. You keep it real and keep my feet planted and pointed in the right direction. To past and present Curran group members, you have provided knowledge, friendship and some unwanted competition and aggravations but it was all worth it- I am who I am because of you.

I cannot thank Drs. Joe Grabowski and George Bandik enough for seeing and promoting my desire to teach chemistry. Your insight and mentorship has been invaluable and will never be forgotten. Without your guidance, I would not have had the opportunities to expand my teaching skills and fall in love with teaching undergraduates the ins and outs of chemistry. I hope to one day be as confident in front of a class and as knowledgeable as you.

Finally, I would like to thank my committee and my advisor for your wisdom and teachings during my time in Pittsburgh. You pushed me to work harder and to realize I will always have more to learn.

1. Introduction

1.1. Self-terminating Oxidative Radicals

There are three general types of reactions for oxygen-centered radicals: hydrogen abstraction, B-C-C fission and C-O bond formation.[1] Dr. Uta Wille has recently demonstrated a new use of oxygen-centered inorganic radicals as oxygen atom donors upon addition to alkyne triple bonds. In a typical example, treatment of cyclodecyne **1** with •OC(O)Me , in benzene or acetonitrile at room temperature, gave *cis*-fused bicylic ketones **2** and **3** in 25% combined gc yield (1:1) (Figure 1a). When **1** is in 2-3 fold excess, the combined yield of **2** and **3** increases to 66%. The acyloxyl radical **5** was formed by the photolysis of its precursor, Barton ester thiopyridone **4** (Figure 1b).

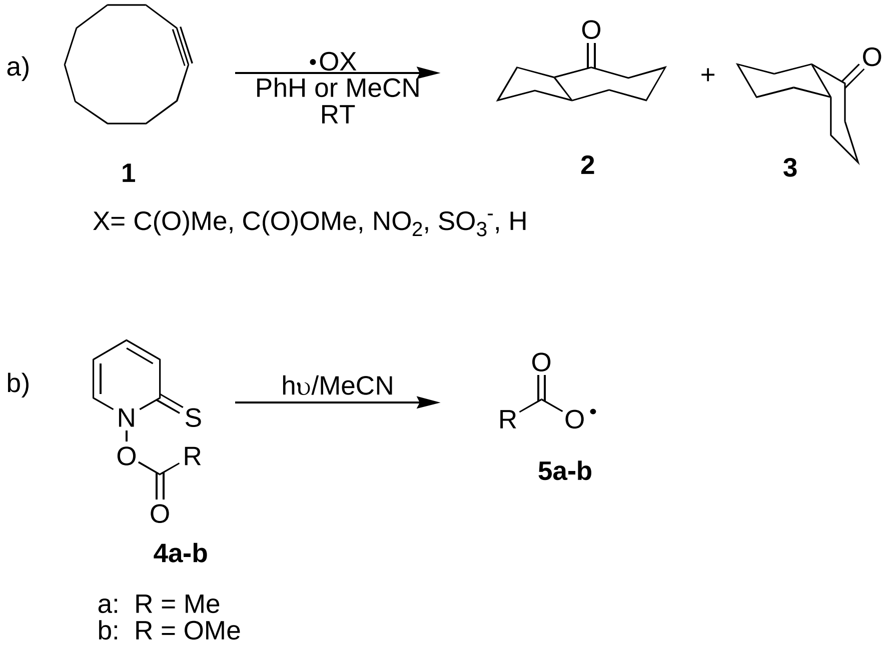


Figure 1 a) Reaction of 1 with •OX; b) photolysis of 4

Table 1 Combined Yields of 2 and 3 from cyclodecyne with •OX

X	Yield (%)[a,b]
NO_2[c]	70[d]
SO_3^{-}[e]	79[f]
H[g]	21[f]
C(O)Me[h]	25[f] (66)[i]
C(O)OMe[h]	94[i]

[a] Combined yield of *cis*-2 and *cis*-3.
[b] Reaction conditions: Benzene/MeCN at RT.
[c] Electrogenerated NO_3•. [d] Isolated Yield.
[e] Fenton redox generation of SO_4•$^-$. [f] GC Yield with internal standard (*n*-hexadecane).
[g] generated from photolysis of thiopyridinone.
[h] generated from photolysis of corresponding Barton ester.
[i] **1** in 2-3 fold excess, yield based on Barton ester precursor.

When the (alkoxycarbonyl)oxyl radical •OC(O)OMe is used, the combined yield of **2** and **3** is 94% (1:1) (Table 1, entry 5). These results are consistent with the reaction of **1** with inorganic radicals NO_3• (Table 1, entry 1), SO_4•$^-$ (Table 1, entry 2) and •OH (Table 1, entry 3). Dr. Wille has also demonstrated the synthetic application of this novel radical cyclization with various cyclic and open chain alkynes.[2]

Based on these results, a novel self-terminating, oxidative radical cyclization has been proposed by Wille.[3] The mechanism starts with addition of an oxygen-centered radical (•OX) to the alkyne to form vinyl radical intermediate **6**. 1,5 transannular hydrogen atom transfer (HAT) of Hα forms **7a** and is followed by 5-*exo* cyclication to form **8a**. 1,6 transannular HAT of Hβ forms **7b** and is followed by 6-*exo* cyclication to form **8b**. Finally, termination of the cascades via β-scission of the α-oxygen radicals forms ketones **2** and **3**, from **8a** and **8b,** respectively. During the β-scission, unreactive inorganic radicals, in the case of X = NO_2• and SO_3•$^-$, are formed. The same pathways are proposed for the reactions of acyloxyl (•OC(O)Me), (alkoxycarbonyl)oxyl (•OC(O)OMe), and hydroxyl (•OH) radicals where the reactive acyl (•C(O)Me), alkoxycarbonyl (•C(O)OMe), and hydrogen (•H) radicals are formed upon fragmentation.

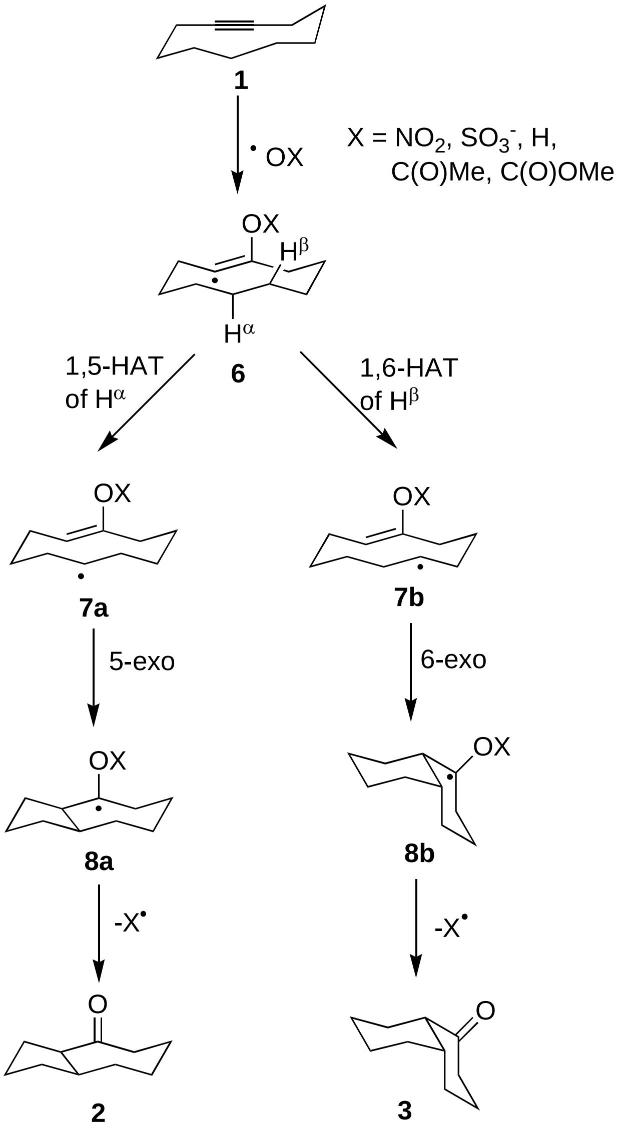


Figure 2 Mechanism for self-terminating, oxidative radical cyclization proposed by Wille

Known reactions of acyloxyl radicals include decarboxylation of diacyl peroxides,[4] hydrogen atom abstraction,[5] and addition to aliphatic C-C double bonds.[6]

We find Wille's proposed mechanism interesting because it suggests an uncommon radical fragmentation as the terminating step in the cascade shown in **Figure 2**. The homolytic cleavage of the acyl-oxygen bond and alkoxycarbonyl-oxygen bond in the radical intermediates **8a,b** is uncommon.

1.2. Reactions and Formation of Acyl Radicals

There are three common methods for formation of acyl radicals: (a)homolytic cleavage of RC(O)-X bonds, (b) carbonylation of carbon-centered radicals with CO, and (c) fragmentation of C-C bond or CO-C bonds (Figure 3).[7]

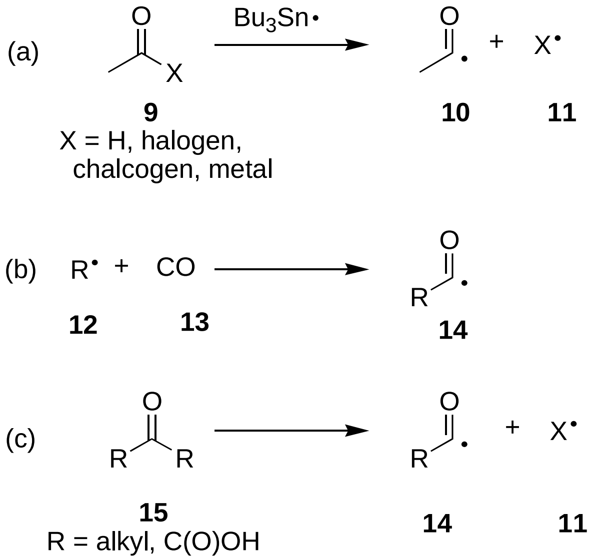


Figure 3 Common methods for acyl radical formation

β-Scission reactions to form acyl radicals are known but uncommon. Anson and Montana proposed the formation of acyl radical intermediates when deprotecting benzyl ester **16** with *N*-bromosuccinimide under neutral conditions (Figure 4).[8] The initially formed benzyl radical **18** collapses to give the acyl radical **19** that is trapped by N-bromosuccinimide to give the acyl bromide **21**, which is hydrolyzed upon workup. The radical reaction is then propagated by the released Br•. Formation of the acyl bromide via a radical mechanism has been reported by Herman and coworkers but the pathway was found to be a minor one.[9] Anson and Montana did not do a complete study of the mechanism and therefore could not rule out an ionic fragmentation. Benzyl radical **18** is brominated by NBS to form the benzylic brominated intermediate **22**. Fragmentation of **22** forms **23** which becomes **21** after reaction with Br^- (Figure 5). This ionic mechanism has been proposed before in the NBS promoted cleavage of benzylidene acetals.[10]

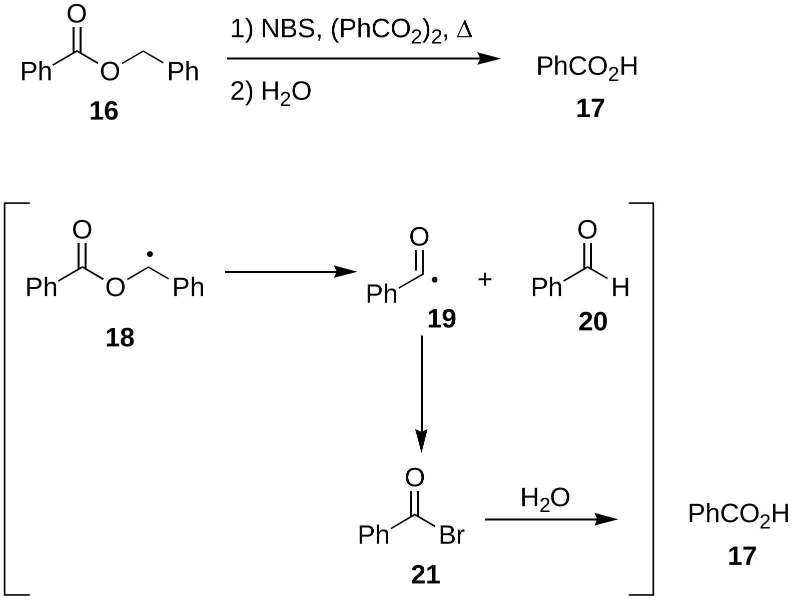


Figure 4 β-scission of carboxybenzyl radical

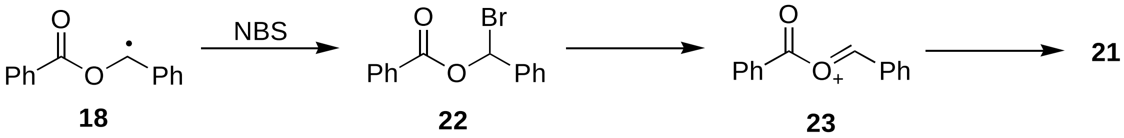
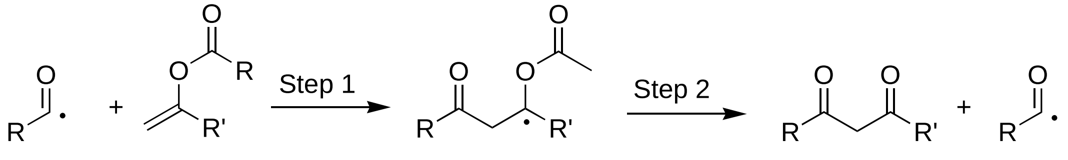


Figure 5 Brominated benzylic ionic fragmentation

If Wille's proposed radical fragmentation of intermediates **8a,b** is correct (Figure 2), we can imagine a possible chain mechanism for a radical isomerization of enol esters to 1,3 diketones (Figure 6). Upon addition of the acyl radical **14** to the enolester **23**, we propose the α-oxygen intermediate **24**. Homolytic fragmentation of the radical will form a 1,3 diketone **25** and the acyl radical **14** that can propagate the reaction.



14 **23** **24** **25** **14**

Figure 6 Proposed radical addition-fragmentation reaction of electron rich alkenes with acyl radicals

Additions of acyl radicals to electron rich alkenes are known (Step 1)[11] and Wille's work suggests the fragmentation in Step 2 is plausible. The ability to propagate the radical chain by an acyl radical would eliminate the use of toxic chain propagators such as Bu_3SnH.

1.2.1. Radical Addition/Fragmentation Reactions

Roberts recently reported the reactions of halogen atom donor **26** with O-*tert*-alkyl enols **27a-c** to give 1,4-dicarbonyl compounds **28a-c** under tin free conditions (Figure 7a).[12] The C-C bond formation occurs by a radical-addition fragmentation, as illustrated in **Figure 7b**.

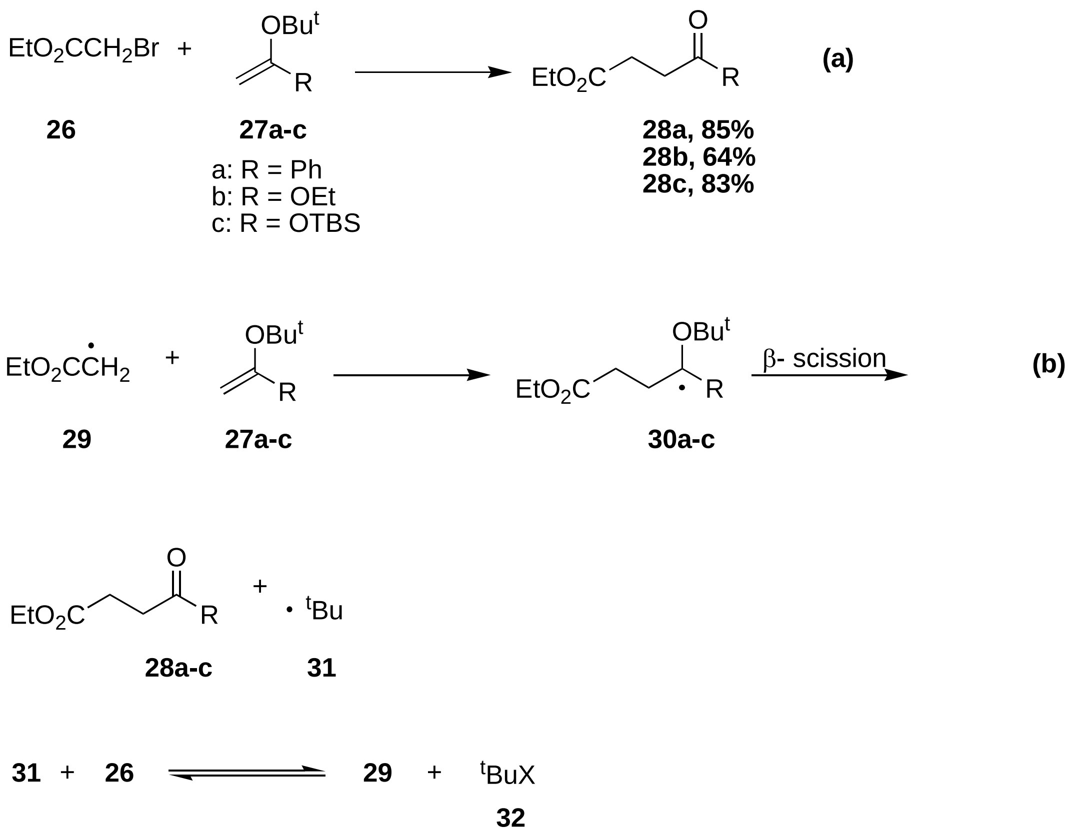


Figure 7 (1) Reaction of O-tert-alkyl enols with elthyl bromoacetate under tin free conditions (2) Proposed mechanism for radical addition-fragmentation of O-tert-alkyl enols to carbonyl compounds

At the same time, Roepel reported the radical reactions of α-phenylselenyl-malonitrile **33a** and –malonic ester **33b** with *O*-benzyl enols **34a,b** (Figure 8, Table 2).[13]

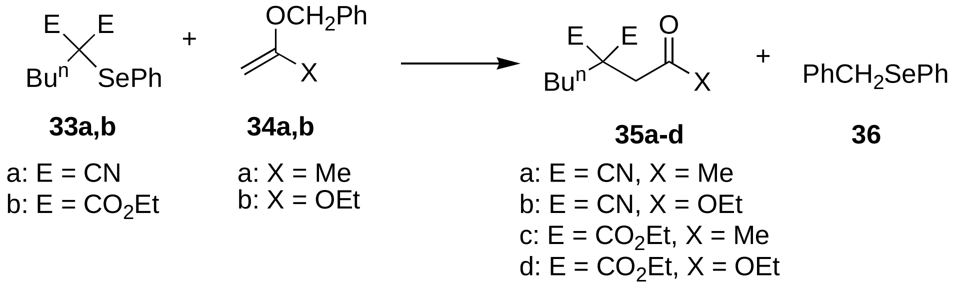


Figure 8 Reactions of -phenylselenyl malonic esters and malonitriles with *O*-benzyl enols

Table 2 Yields of 35a-d from reactions of α-phenylselenyl-malonitiles and –malonic esters 33a,b and *O*-benzyl enols 34a,b

SePh substrate	enol	Product	Yield (%)[a]
31a	32a	33a	50[b]
31a	32b	33b	69[c]
31b	32a	33c	71[c]
31b	32b	33d	62[c]

[a] Isolated Yields. [b] AIBN, refluxing benzene, 16h.
[c] hυ, $CHCl_3$, 12-17h

1.3. Radical Fragmentation on Model System

As an alternative to Wille's proposed radical fragmentation, we envision an oxidative fragmentation to form ketone **2 (Figure 9)**. After radical cyclization, oxidation of the radical intermediate **6a** to the cationic intermediate **37** would be followed by polar fragmentation to the corresponding ketone **2** and the acyl cation. An alternate pathway is addition of H_2O to give the same results.

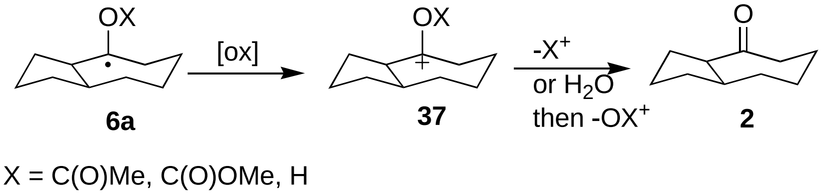


Figure 9 Alternate oxidative fragmentation mechanism

In the example of a hydroxyl radical (•OH) acting as the oxygen donor, under oxidative cleavage a proton (H^+) would be formed as opposed to a highly reactive hydrogen radical (•H).

We chose to study the radical cyclization and fragmentation of acyl enols **38a-d** under the reducing conditions of Bu_3SnH to probe the mechanism and the possibility of competitive fragmentation **(Figure 10)**.

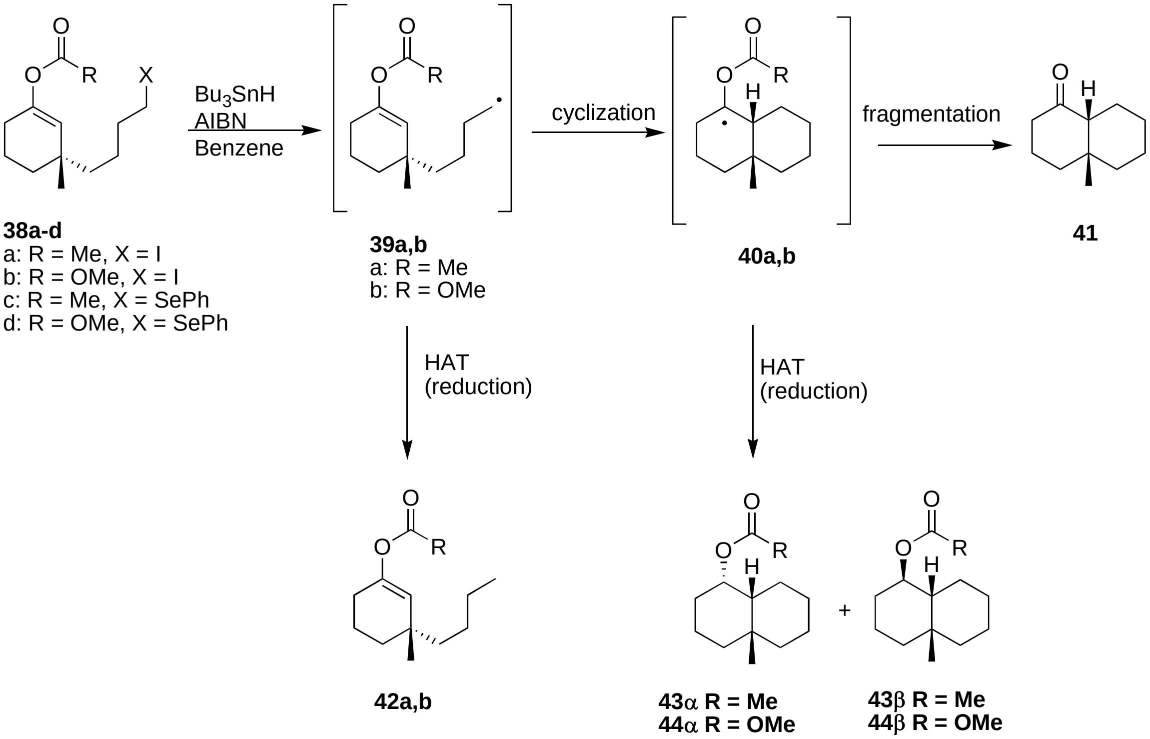


Figure 10 Proposed acyl and alkoxycarbonyl enols for fragmentation studies

Under the reducing conditions of Bu_3SnH, the possibility of the alternative oxidative fragmentation could be explored. If ketone **41** is observed at high concentrations of Bu_3SnH, then serial dilutions should produce more **41** because radical fragmentation is independent of Bu_3SnH concentration. At high concentrations, the bimolecular HAT of intermediates **39a,b** with Bu_3SnH to form the reduced products **42a,b** should compete with cyclization to form radical intermediates **40a,b**. The same competition of HAT and radical fragmentation should be observed in intermediates **40a,b** with increased formation of **43α,β** and **44α,β** and decreased formation of ketone **41**. At lower concentrations, the amounts of reduced products **42-44** should decrease because the reduction is dependent on the Bu_3SnH concentration. If ketone formation does not increase with decreasing Bu_3SnH concentration, then the radical pathway proposed by Wille cannot be the only mechanism responsible for fragmentation. Therefore, an alternative oxidative mechanism cannot be ruled out.

We decided not to study the fragmentation of the exact compounds in Wille's experiments due to the possibility of competing 1,5 HAT. We expected the formation of products, **48a,b** from precursors **45a,b** would compete with the formation of ketones **2** and **3 (Figure 11)**. We chose to incorporate a methyl substituent into substrates **38a-d** to eliminate the competing 1,5 HAT.

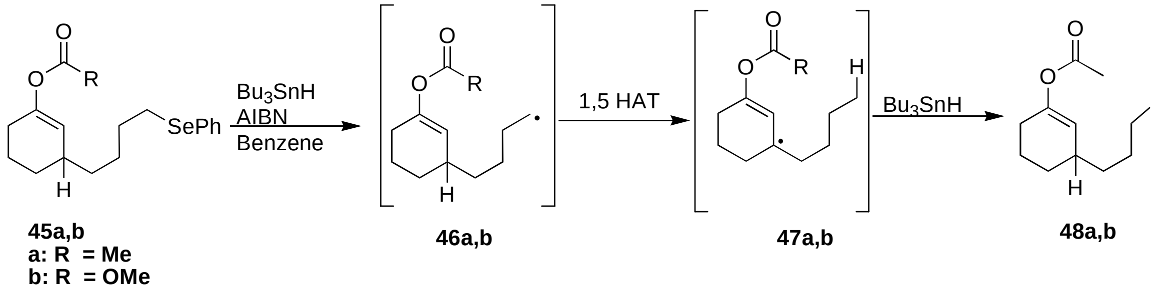


Figure 11 Competing HAT with radical precursor

2. Results

2.1. Synthesis and fragmentation studies of phenylselenide precursors

Our initial goal was the synthesis of radical precursor **38** via Copper-catalyzed conjugate addition of butenyl magnesium bromide to enone **49** followed by quenching with acetyl chloride gave known enol acetate **50** in 50% yield **(Figure 12)**.[14] Acyl enone **50** can also be synthesized in a two-step procedure by forming the enol carbonate **51** via conjugate addition of butenyl magnesium bromide to **49** followed by quenching with methyl chloroformate. Reacting **51** with nBuLi, HMPA and acetyl chloride gave **50** in 62% yield over 2 steps. Even though this path gave a higher yield overall of **50**, a significant amount of ketone **52** (15%) was formed, and thus was difficult to separate from **50** by conventional methods. We wanted to avoid the use of HMPA for safety reasons and the formation of ketone **52**, so the one-step procedure was used. Anti-Markovnikov addition of HX to the terminal alkene in **50**[15] proved unsuccessful under various conditions.

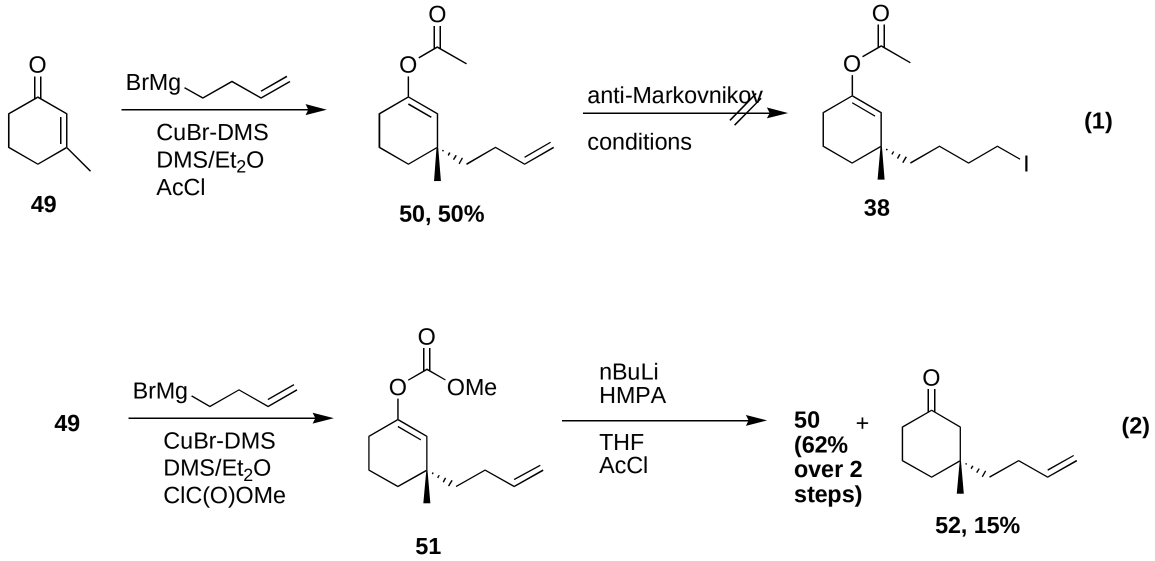
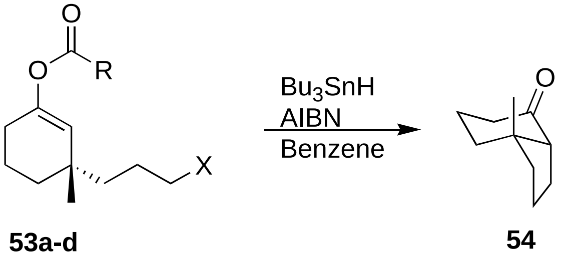


Figure 12 (1) Synthesis of 52 and potential formation of 38 (2) Alternate two-step procedure for synthesis of 52

To circumvent the difficulty in making **38**, we decided instead to synthesize targets **53a-d**. By shortening the alkyl chain by one carbon, hydroindenone **54** should be accessible and still a viable precursor for the concentration studies. Like ketones **2** and **3**, **54** should be formed in exclusively the *cis* orientation during radical cyclization **(Figure 13)**.[16]



53a-d
a: R = Me X = I
b: R = OMe X = I
c: R = Me X = SePh
d: R = OMe X = SePh

54

Figure 13 Hydroindenone formation

Dihydroxylation of the terminal alkene of **50** with AD mix-α[17] produced an intermediate diol that was subsequently cleaved via $NaIO_4$ oxidation[18] in THF/H_2O to give aldehyde **55** in 75% yield over 2 steps. The aldehyde was reduced with $NaBH_4$ in MeOH to the corresponding alcohol **56** in 78% yield.[19] Mesylation of alcohol **56** followed by phenylselenide displacement produced the radical precursor **53c** in 46% yield over 2 steps **(Figure 14)**.[20]

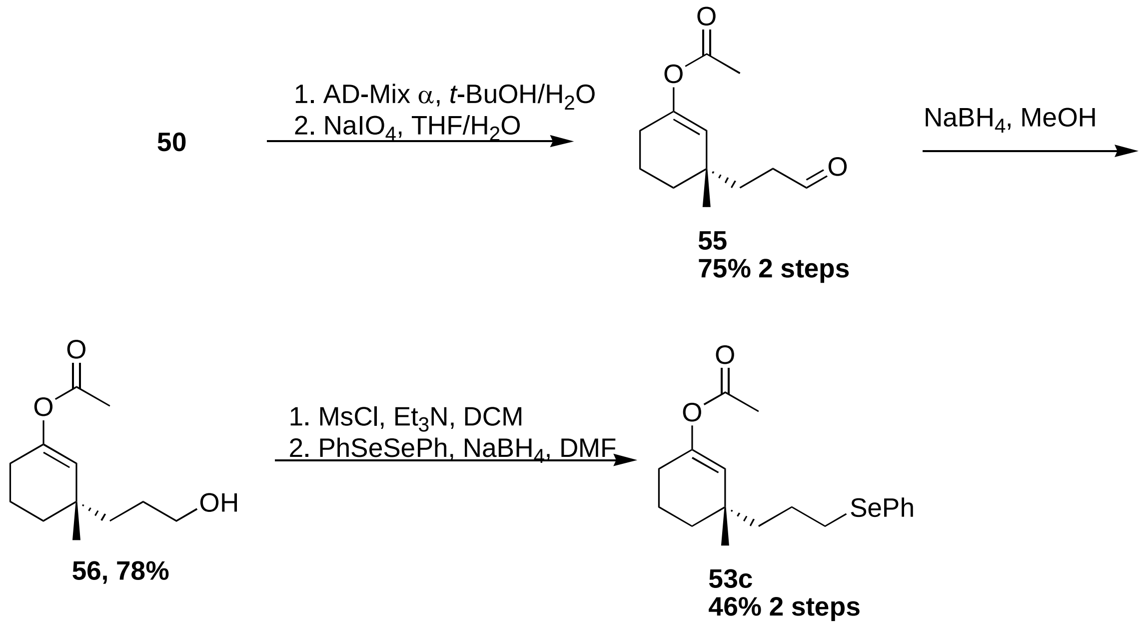


Figure 14 Synthesis of phenylselenide 53c

Phenyl selenide **53d**, was synthesized in 15% overall yield by following the same procedure with enol carbonate **51 (Figure 15)**.

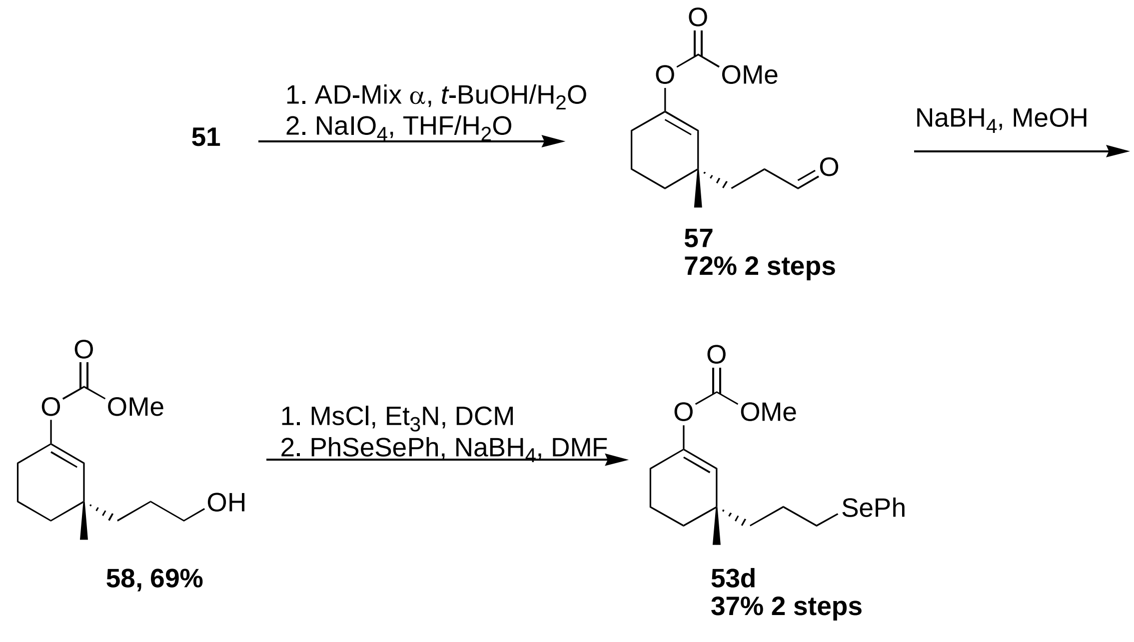


Figure 15 Synthesis of phenyl selenide 53d

Compounds **38c,d** were also synthesized in a similar manner from **50** and **51** respectively. If the hydroindenone precursors proved worthwhile, then we could expand the study to to look at fragmentations that follow 6-exo cyclization v. 5-exo cyclizations. **50** was hydroborated with 9-BBN and H_2O_2 to produce **59** in 59% yield. Mesylation of **59** followed by phenylselenide displacement gave selenyl ether **38c** in 56% yield over 2 steps. Selenyl ether **38d** was synthesized in same manner as **38d** from **51** in 30% overall yield **(Figure 16)**.

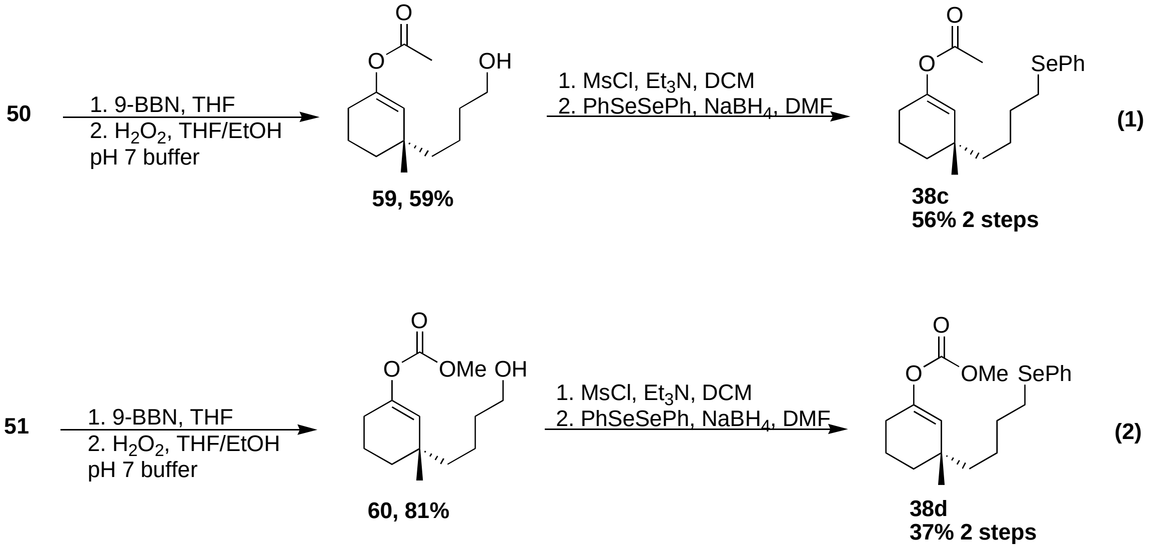


Figure 16 Synthesis of phenyl selenides 38c,d

Authentic samples of potential side products from the reaction of **53c,d** with Bu_3SnH were synthesized independently to aid in analysis **(Figure 17)**. Directly reduced acyl enols **61a,b** were synthesized by copper-catalyzed conjugate addition of propyl Grignard to enone **49** and trapping with the corresponding acid chloride in eqn 1. Acetates **62α,β** (1.5:1 dr α:β, 95% combined yield) and carbonates **63 α,β** (2:1 dr α:β, 68% combined yield) were synthesized by a preparative scale reactions of **38c,d** with Bu_3SnH at 0.1 M in eqn 2. The diastereomeric ratios were determined by 1H NMR.

Reduction of the 1.5:1 dr mixture of **62α,β** with LAH in Et_2O gave a 1.5:1 dr mixture of alcohols **64α,β** in 50% combined yield after chromatography. Alcohols **64α,β** were oxidized with DMP[21] to produce ketone **54** in 50% yield **(Figure 17 eqn 3)**.

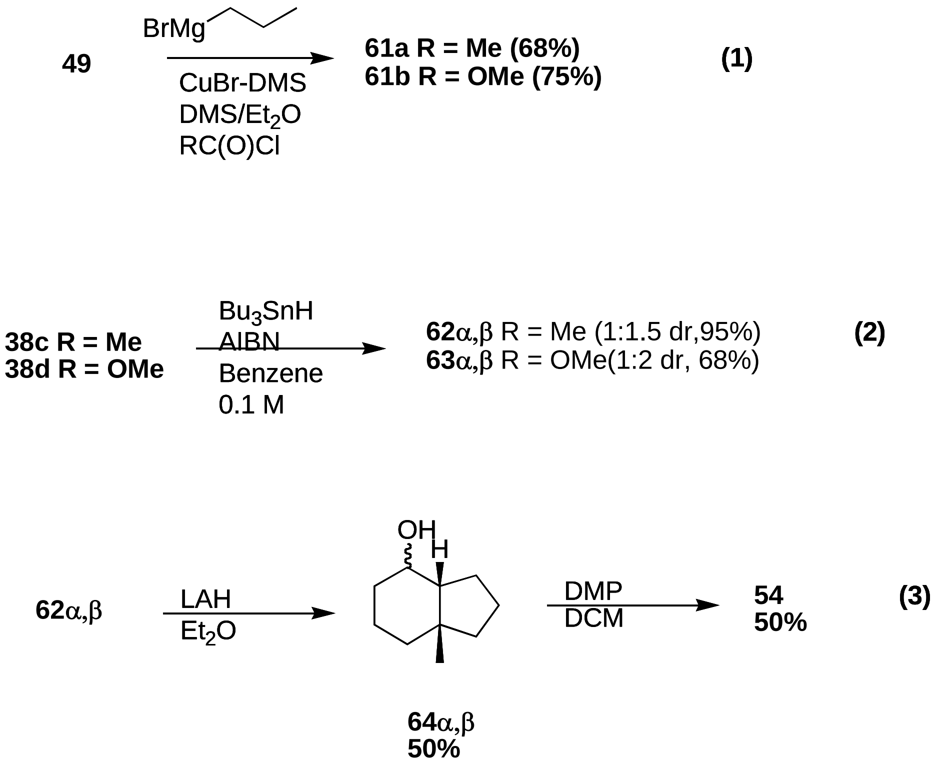


Figure 17 Synthesis of authentic samples 61-64 and 54

With phenylselenyl precursors **38c,d** and **53c,d** and likely products **61-64** and **54** in hand, concentration studies were carried out for the radical cyclizations under reducing conditions. Reactions with each precursor **53c,d** were run in triplicate and analyzed by ^{1}H NMR spectroscopy and GC before and after submission to reaction conditions with *p*-dimethoxy benzene as an internal standard. Aliquots of precursors **53c,d** in C_6D_6 were added to a sealed tube followed by aliquots of internal standard in C_6D_6. After stirring for 30 min, AIBN and Bu_3SnH were added and the reaction tube was sealed and placed in a preheated 80°C oil bath. In the reaction at 0.1 M with **53c**, a diasteromeric mixture of cyclized esters **62α,β** were seen (dr 1.5:1) along with directly reduced enol acetate **61a** and a diastereomeric mixture of alcohols **64α,β** (dr 1.5:1), but no significant evidence of ketone **54** was observed by ^{1}H NMR spectroscopy or GC **(Figure 18, Table 3)**.[22]

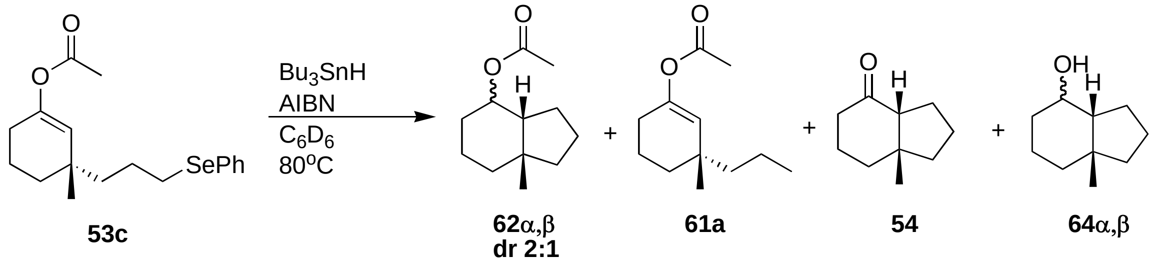


Figure 18 Reaction of 53c under reducing conditions

Table 3 GC and ^{1}H NMR Yields from reaction with 53c

Conc. (M)	**Yields (%)**[a]								
	62α,β		**54**[b]	**64α,β**[b]	**61a**		**53c**[e]		
	GC	**^{1}H NMR**	**GC**	**GC**	**GC**	**^{1}H NMR**	**GC**	**^{1}H NMR**	**Total GC Yield**
0.1	97.4	91.7	0.3	2.0	0.8	1.3	0	0	100.5
0.01[c]	52.4	56.7	0.7	2.6	0.2	1	7.5	5.3	63.4
0.001[d]	0	0	0	0	0	0	49.9	50	49.9

[a]Yields are the averages of 3 runs at each concentration and based on the internal standard, *p*-dimethoxy benzene. [b]^{1}H NMR yields were not determined due to overlapping resonances. [c]5% of an unidentified compound was detected. Uncorrected yield based on assumed chemical structure. [d]10% of an unidentified compound was detected. Uncorrected yield based on assumed chemical structure. [e]Yields are the % of **53c** detected.

By lowering the concentration to 0.01M, significant formation of **54** was not observed. In the reaction at 0.001M did not allow the reaction to proceed with the major component **53c** being observed by ^{1}H NMR and GC. The formation of an unidentified product was observed at the lower concentrations. Neither the ketone **54** nor the directly reduced product **61a** was observed at the lower concentrations. Similar results were seen with radical precursor **53d (Figure 19 and Table 4)**.[23] In the reaction at 0.1M, entire consumption of **53d** was observed, but a low yield of **63α,β** was seen by ^{1}H NMR and GC. Lowering the concentration to 0.01M showed significant detection of **53d** and a slight increase in **63α,β**. At the lowest concentration of 0.001M, only detection of **53d** was observed. At all three concentrations, ketone **54** was not observed in significant amounts by ^{1}H NMR or GC.

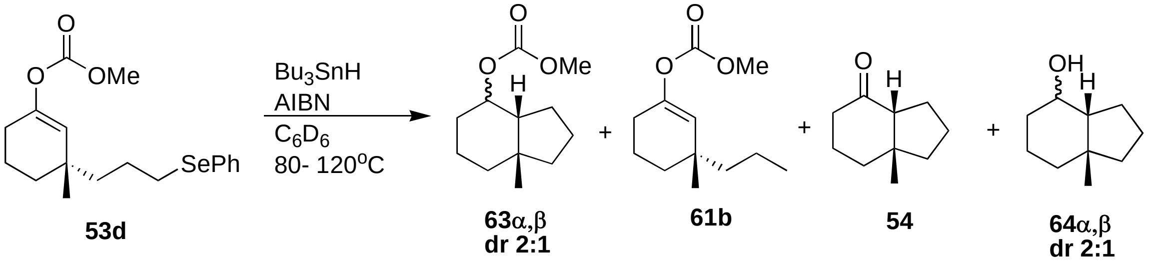


Figure 19 Reaction of 53d under reducing conditions

Table 4 GC and ^{1}H NMR Yields from reaction with 53d

Conc. (M)	**Yields**[a]								
	63α,β		**54**[b]	**64α,β**[b]	**61b**		**53d**[e]		
	GC	**^{1}H NMR**	**GC**	**GC**	**GC**	**^{1}H NMR**	**GC**	**^{1}H NMR**	**Total GC Yield**
0.1	45.5	47.7	0	0.7	1.6	2.3	0	0	47.8
0.01[c]	51.5	54	0.8	1.3	10.8	9.3	20.1	20.7	84.5
0.001[d]	0	0	0	0	0	0	45.9	39.7	45.9

[a]Yields are the averages of 3 runs at each concentration and based on the internal standard, *p*-dimethoxy benzene. [b]^{1}H NMR yields were not determined due to overlapping resonances. [c]6.7% of an unidentified compound was detected. Uncorrected yield based on assumed chemical structure. [d]7.7% of an unidentified compound was detected. Uncorrected yield based on assumed chemical structure. [e]Yields are the % of **53d** detected.

Based on these findings, the rates of cyclization for radical precursors **38c,d** were faster than the rates of hydrogen abstraction to form **61a,b**, respectively. The rate constant of H abstraction by radical **65** from Bu$_3$SnH was calculated to be less than 4.3 x 10^6 M^{-1}s^{-1} at 80°C in benzene using the determined Arrhenius parameters for the rate of

H abstraction from Bu_3SnH of primary C radical **65 (Figure 20)**.[24] The rate constant was calculated based on a primary C radical because an appropriate value for a tertiary C radical next to an ester could not be found. The actual rate is probably slower due to the increased stability of a tertiary radical over a primary radical.

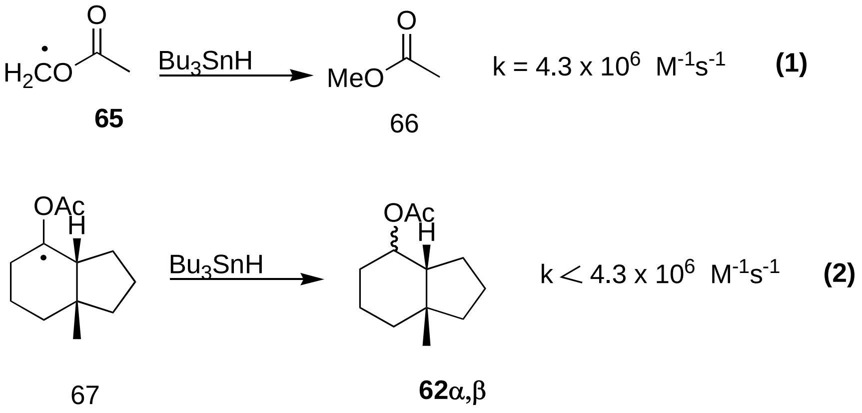
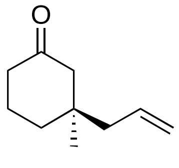


Figure 20 H abstraction rate constants

Formation of the alcohols **64α,β** can potentially be explained by reduction of the **54** with HSePh, a side product in the reaction. The unidentified product formed at lower concentrations was assumed to be **68 (Figure 21)**. This assumption was based on ^1H NMR and GCMS data of the crude reaction mixture. ^1H NMR spectrum shows a multiplet between 5.70 and 5.83 ppm (integrates for 1 H) that is coupled to a multiplet between 4.92 and 5.03 ppm (integrates for 2 H). The pattern is similar to the ^1H NMR spectrum of olefin **50**. GCMS data shows an ion peak at 152 which is consistent with the molecular weight of **68**. A fragment peak is seen at 111 which can correspond to the loss of C_3H_5. Unfortunately, an authentic sample of **68** was never successfully synthesized or isolated from the reaction mixture. Instead of forming the primary radical under the conditions, trace amounts of O_2 can promote selenoxide elimination to form the olefin. This result was confirmed by a model reaction of dodecyl phenylselenide **69** at 0.001 M under standard reducing conditions and formation of dodecene **70** by ^1H NMR and GC.



68

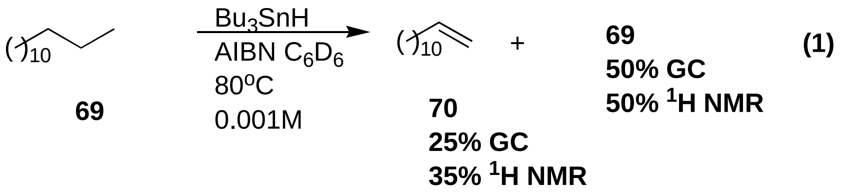


Figure 21 Olefin formation at low concentration of Bu_3SnH

2.2. Synthesis and fragmentation Studies of iodo precursors

Since we felt the presence of PhSeH or PhSeOH might compromise the results, precursors **38c,d** were not subjected to the reaction conditions. We decided instead to change the radical precursor to iodides **53a,b** to eliminate the problems seen with the phenylselenide precursors. Starting with alcohol **56**, mesylation followed by displacement gave iodide **53a** in 73% yield over 2 steps. The same procedure was used to produce iodide **53b** from alcohol **58** in 68% yield over 2 steps **(Figure 22)**.

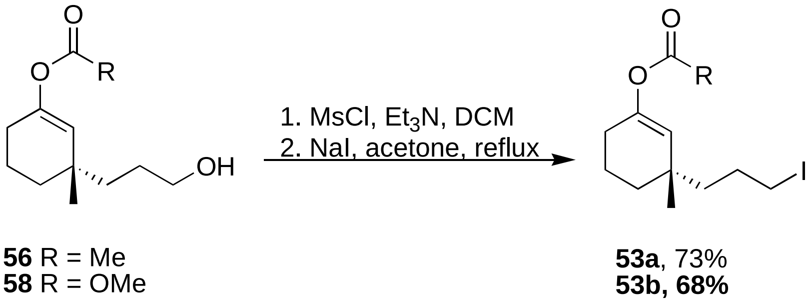
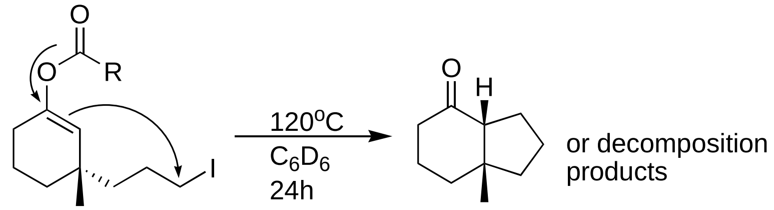


Figure 22 Formation of iodides 53a,b

Primary iodides **53a,b** have the potential to cyclize by a polar pathway upon heating under the reaction conditions instead of a radical pathway so both iodides were heated to 120°C in C_6D_6 for 24 h at 0.1M to observe any decomposition or cyclization **(Figure 23, Table 5)**. After 24 h, neither ketone **54** nor decomposition of iodides **53a,b** was observed and iodides **53a,b** were observed in >99% yield by ^{1}H NMR and GC.



53a,b **54**

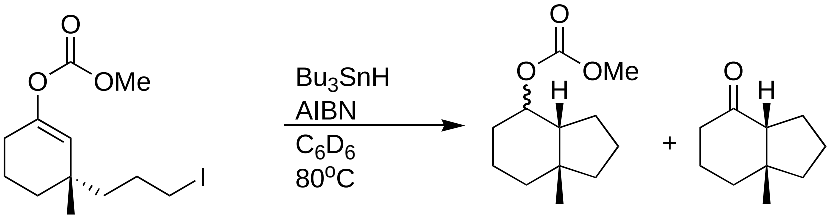
Figure 23 Possible polar cyclization of 53a,b to give ketone 54

Table 5 Yields of decomposition or cyclization of 79 and 80 via a polar pathway conditions

Yield[a]			
Substrate **Iodide**	**54[b]** **GC**	**SM** **GC**	**^{1}H NMR**
53a	0	>99	>99
53b	0	>99	>99

[a] Yields based on internal standard, *p*-dimethoxybenzene. [b] ^{1}H NMR yields were not determined due to overlapping resonances.

Following the same protocol for the reaction of **38c,d** under Bu_3SnH reducing conditions, iodides **53a,b** were monitored by ^{1}H NMR spectroscopy and GC for formation of ketone **54**.



53b **63α,β** **6:1 dr** **54**

Figure 24 Reaction of 53b to produce 63α,β and 54

Table 6 GC and ^{1}H NMR Yields from reaction with 53b

Conc. (M)	**Yields[a]**					
	63α,β GC	**^{1}H NMR**	**54[b] GC**	**53b GC**	**^{1}H NMR**	**Total GC Yield**
0.1	80	73	2	0	0	82
0.01	70	80	1	0	0	71
0.001	60	55	1	25	30	86

[a]Yields are based on the internal standard, p-dimethoxy benzene. [b]^{1}H NMR yields were not determined due to overlapping resonances.

Yields are the % of **53b** detected.

For **53b**, the reactions were not run in triplicate because the initial reactions at each concentration only produced the diastereomeric mixture of cyclized carbonates, **63α,β** and very little **54 (Figure 24, Table 6)**.[25] The directly reduced enol carbonate **61b** and alcohols **64α,β** were not observed. **Figure 25** and **26** show representative spectra of the reaction at 0.1M.

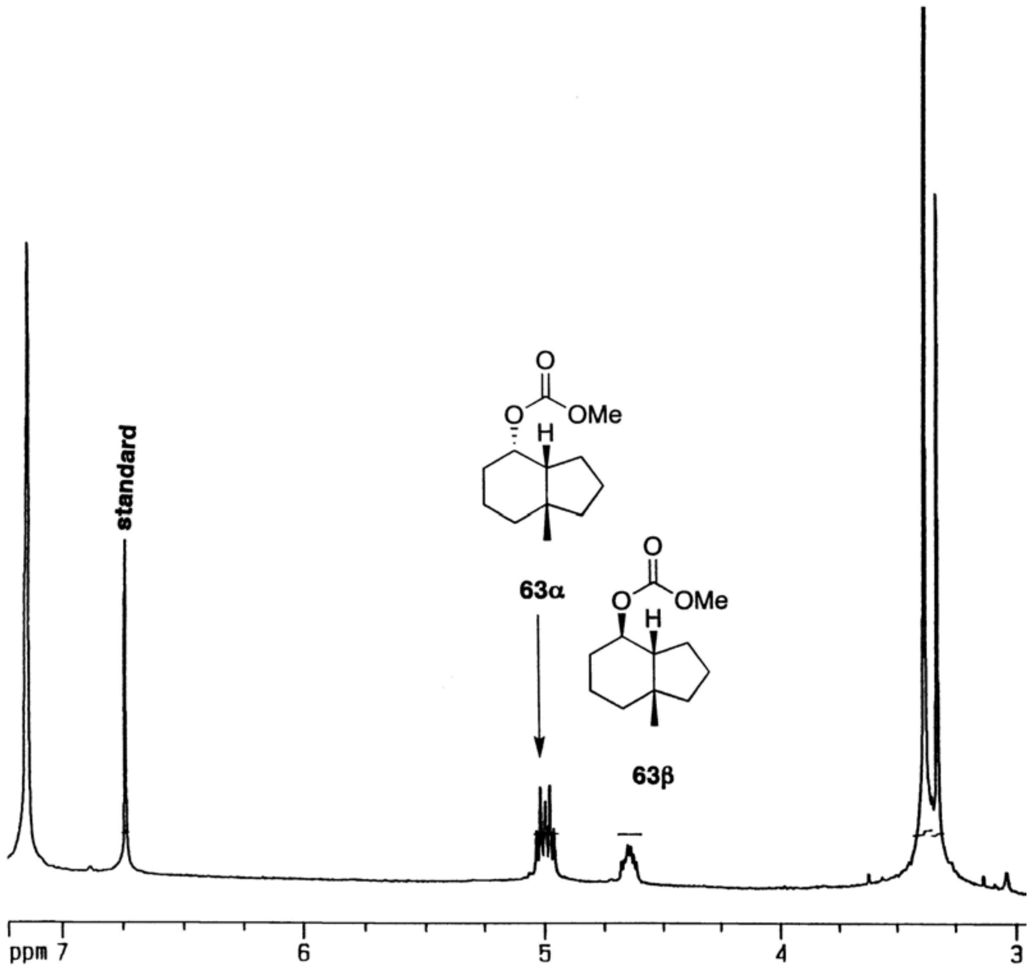


Figure 25 1H NMR spectrum of 63α,β

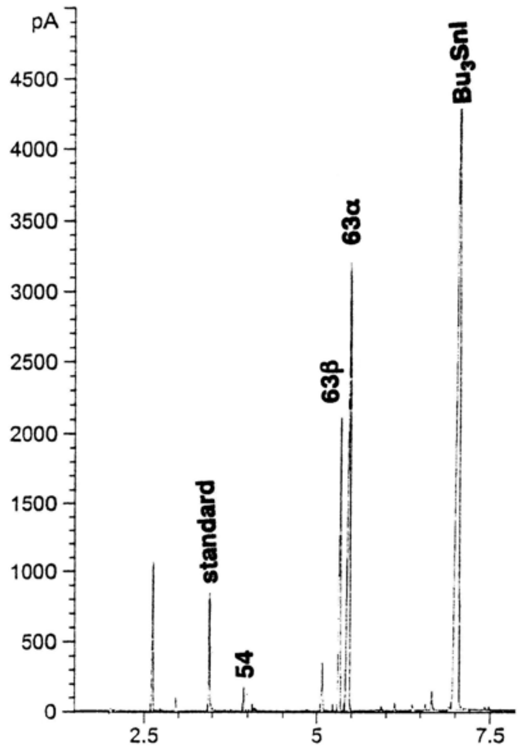


Figure 26 GC spectrum of 63α,β **and 54**

With iodide **53a**, an additional concentration of 0.005 M was added because an appreciable amount of ketone **54** was observed by GC **(Figure 27, Table 7)**.[26] Again, the cyclized acetates **62α,β** (dr 3:1) were formed as the major products and directly reduced **61a** and alcohols **64α,β** were not observed with this system. **Figure 28** and **29** show representative spectra of the reaction at 0.1M.

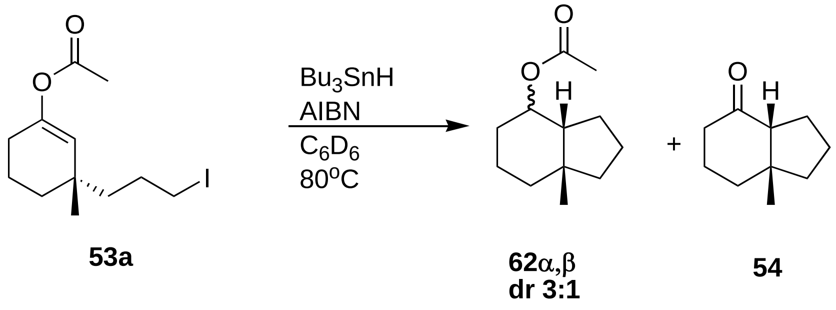


Figure 27 Reaction of 53a to produce 62α,β and 54

Table 7 GC and ^{1}H NMR Yields from reaction with 53a

Conc. (M)	**Yields**[a]					
	62α,β		**54**[b]	**53a**[c]		
	GC	**^{1}H NMR**	**GC**	**GC**	**^{1}H NMR**	**Total GC Yield**
0.1	94.8	95.3	2.4	0	0	97.2
0.01	73	73	7.5	0	0	80.5
0.005	28.3	30	15.6	42.1	38.7	86.0
0.001	1.2	0	15.6	42.9	41	59.7

[a] Yields are the averages of 3 runs at each concentration and based on the internal standard, *p*-dimethoxy benzene. [b] ^{1}H NMR yields were not determined due to overlapping resonances. [c] Yields are the % of **53a** detected.

Decreasing the concentration of Bu$_3$SnH did show an increase in the formation of **54** with 7.5% at 0.01M to 15.6% at 0.005M and 0.001M. This increase was not enough to rule in favor of the radical fragmentation pathway proposed by Wille or the alternative oxidative pathway proposed by us.

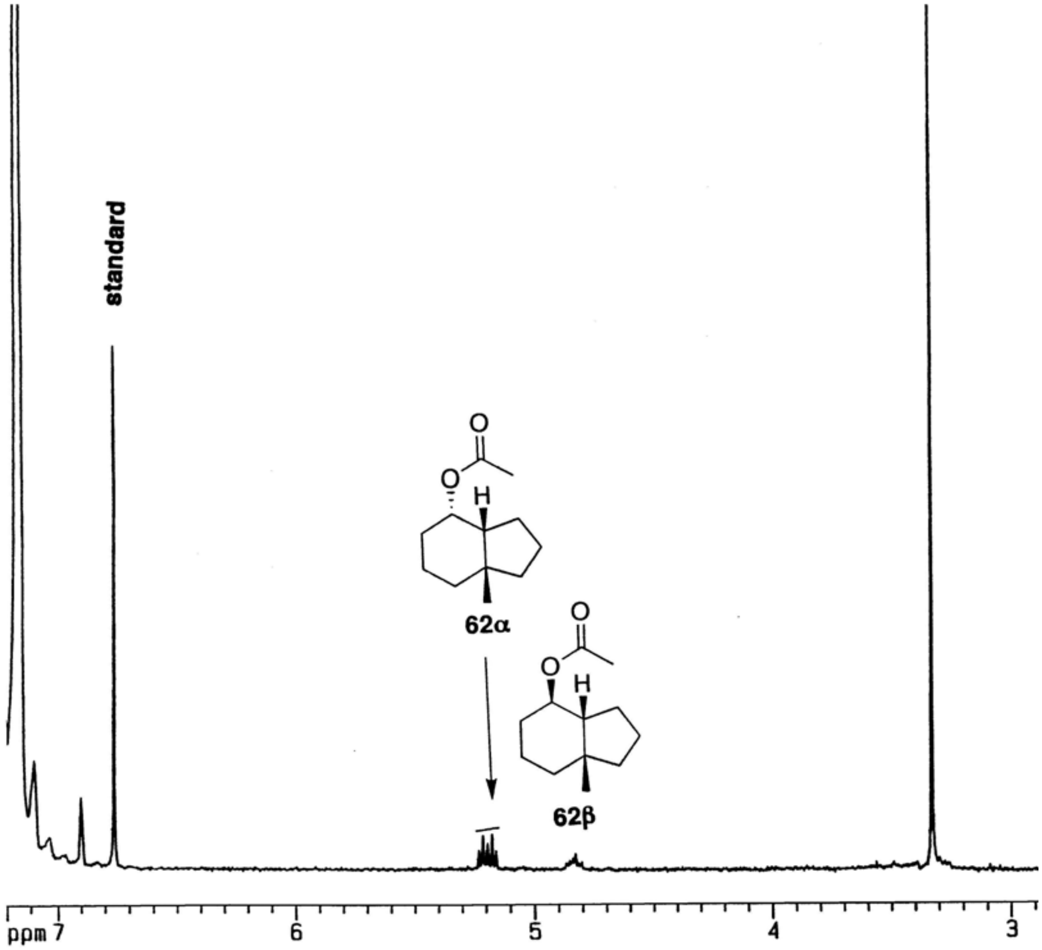


Figure 28 1H NMR spectrum of 62α,β

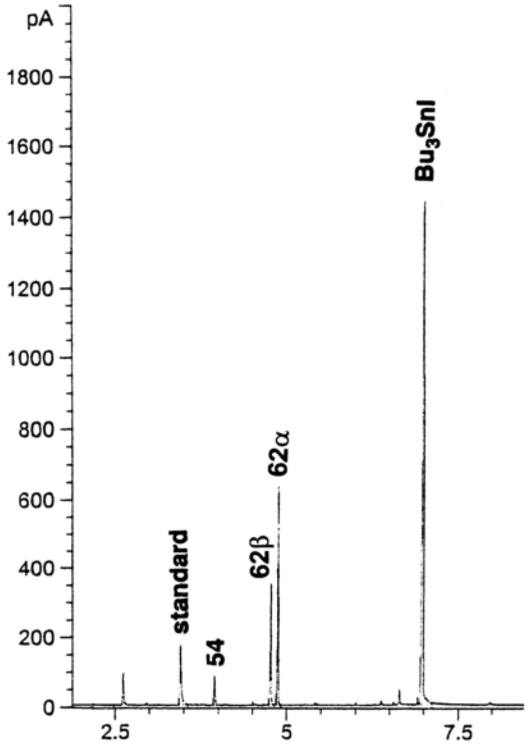


Figure 29 GC spectrum of 62α,β and 54

2.3. Oxidation in a reducing environment

The question arose during our studies, how does oxidation occur in a reducing environment? Studies have been done that probe this question but the mechanism is still not thoroughly understood.[27] One explanation can be the initiator, AIBN, acting as the oxidant.[28] To probe this possibility, varying equivalents of AIBN were added to the reaction of **53a** at 0.01M and monitored by ^{1}H NMR and GC **(Figure 27)**. Instead of an increase in ketone formation, we noticed a slight decrease in yield of the ketone **54** with increasing amounts of AIBN **(Table 8)**. From this we can conclude that AIBN is not the oxidant during the reaction.

Table 8 GC and ^{1}H NMR Yields from reaction with 53a

AIBN (equiv)	**Yields[a]**			
	62α,β		**54[b]**	
	GC	**^{1}H NMR**	**GC**	**Total GC Yield**
0.25	73.1	69.0	12.4	85.5
0.5	71.4	73	14.7	86.1
.75	76.4	73.3	10.1	86.5
1.00	76.6	71.1	7.8	84.4
2.00	71.0	69.0	8.7	79.7

[a] Yields are based on the internal standard, *p*-dimethoxy benzene.

[b] ^{1}H NMR yields were not determined

2.4. Conclusions

After our studies were completed, Sigmung, Schiesser and Wille published their findings of a theoretical and experimental investigation of the terminating homolytic fragmentation of the O-X bond in **71** where X is alkyl, aromatic or allyl as seen in **Figure 30**.[29] They wanted to provide insight into the energetic requirements and driving forces of the final fragmentation step.

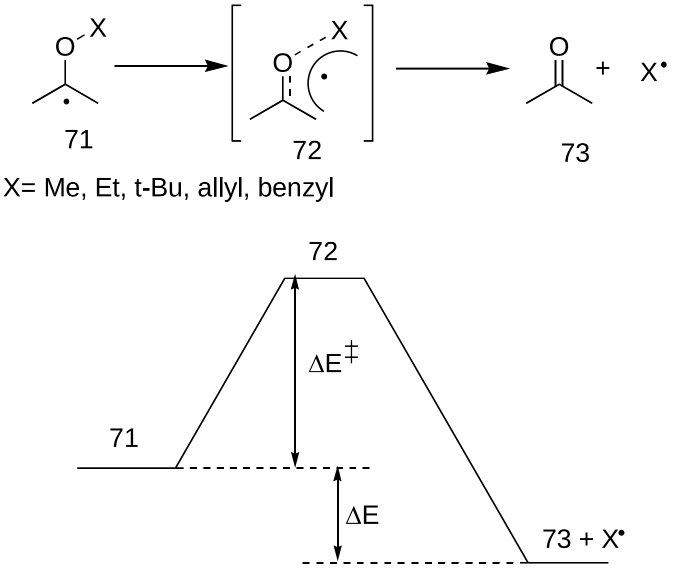


Figure 30 homolytic fragmentation of the O-X bond

For the experimental portion of the study, the alkoxy radicals were generated in the presence of cyclodecyne **1** by the photolysis of the dithiocarbamate precursors **75 (Figure 31, Table 9)**.

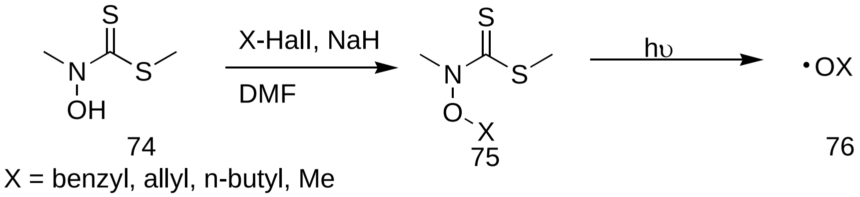


Figure 31 Formation of alkoxyl radicals from corresponding dithiocarbamate precursors

Table 9 Experimental Conditions and Results for the Reaction of cyclodecyne (1) with the alkoxyl radicals

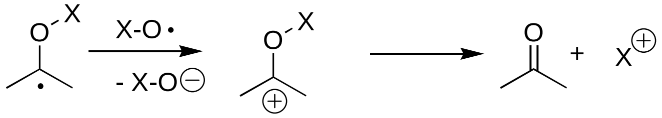
Alkoxyl radical (OX) X=	Yield (%)[abc]
benzyl	52
allyl	32
n-butyl	45

[a] Combined yield of 5/6, determined by GC using n-hexadecane as internal standard. [b] Conditions: Rayonet photoreactor at λ = 300 nm for 120 min. [c] Syringe addition of radical precursor.

Unlike previous studies, the solvent was switched from benzene to acetone and the ratio of radical precursor to alkyne was increased from 3:1 to 2:1. Acetone was found to be a superior solvent to benzene and it was speculated that the acetone diradical formed upon UV irradiation could either add to or transfer its triplet character to the radical precursor, initiating formation of the alkoxyl radicals. This hypothesis is supported by the absence of initiator AIBN in the reaction. The yields were similar to the yields when using the inorganic nitrate radicals and sulfate radical anions but they were surprised that alkoxyl allyl radical had a lower yield than the n-butyl alkoxl radical. One would expect the alkoxyl radical with a stabilized leaving group (allyl) upon scission would be better than the nonstabilized n-butyl fragment.

The theoretical calculations were carried out for the simplified model reaction shown in **Figure 30**. Representative groups were investigated using various methods: methyl, ethyl (non-stabilized radicals), *t*-butyl (inductive effect stabilized radicals), allyl and benzyl (resonance stabilized radicals). Trends were observed for $\Delta E^{\ddagger}$ and ΔE depending on the stabilization of the radical and were opposite to the observed experimental yields.[30] Resonance stabilized radicals make the hemolytic scission thermodynamically and kinetically favorable whereas inductive stabilzation only lowers the activation barrier. The non-stabilized radicals were seen to be both kinetically and thermodynamically unfavorable as one would expect. The following explanations were presented to account for the discrepancies between the experimental and theoretical data:

1. The theoretical investigations are calculated in the gas phase and the experimental investigations are in solution and therefore can be directly compared.
2. The homolytic O-X fragmentation is only one of several steps in the pathway, which may be all of similar importance for the overall success of the reaction.
3. The homolytic bond cleavage may be an ionic fragmentation **(Figure 32)**. Even though the cleavage of O-NO_2 was theoretically verified, the same mechanism may not be favored for reactive radicals (allyl, benzyl, acyl). The nature of the oxidant is unknown and photoexcited acetone cannot be excluded.



71 77 73

Figure 32 Oxidative fragmentation of 71

Based on our findings, we also conclude the terminating step of the mechanism is more than likely not the homolytic cleavage of O-X but an oxidative fragmentation of the a-oxygen radical or a combination of the two. As in Wille's observations and ours, the nature of the oxidant is unknown.

3. Experimental

General Procedures:

All reactions were performed under an atmosphere of argon unless the reaction solvent contained water. The reaction times reported are dictated by TLC analysis of the reaction mixture in comparison to the starting material. Reaction solvents were dried either by distillation or passing through an activated alumina column. Methylene chloride was distilled from CaH_2 and toluene, benzene, diethyl ether and THF were distilled from Na/benzophenone. Solvents dried by activated alumina were done according to Pangborn, A.B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518-1520.

^{1}H and ^{13}C NMR spectra were taken on a Bruker models Avance DPX 300 (300 MHz), Avance 300 (300 MHz), Avance DRX 500 (500 MHz), or Avance 600 (600 MHz) NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of $CDCl_3$ (7.27 ppm) or central $CDCl_3$ carbon peak (77.0 ppm) as an internal standard or C_6D_6 (7.15 ppm for ^{1}H and 128.0 ppm for ^{13}C). In reporting spectral data the format (δ) chemical shift (multiplicity, *J* values in Hz, integration) was used with the following abbreviations: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, sext = sextet, m = complex multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublets of doublets.

Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film or neat deposition on NaCl plates. Peaks are reported in wavenumbers (cm^{-1}). Low and high resolution electron impact mass spectra were obtained on a Micromass Inc, Autospec with an E-B-E geometry. Chemical ionization spectra were taken on the same instrument using methane as the carrier gas. All peaks reported are in units of *m/e*.

Gas chromatograms (GC) were run on an Agilent 6850 Series GC System with an HP-1 Methyl Siloxane column (Agilent 19091Z-413E, Capillary 30.0 m x 320 µm x 0.25µm). The initial temperature of the program was 150 °C with a temperature ramp of 5°C/min up to 250 °C a helium flow of 2 mL/min and 8.68 PSI was applied. *p*-dimethoxybenzene was used as internal standard and C_6D_6 or benzene was used as solvent. GC data are reported with a retention time and % area of the total integrated area.

Thin layer chromatography was performed on silica gel 60 F_{254} glass backed plates with a layer thickness of 0.25 mm manufactured by E. Merck. TLC visualization was performed by illumination with a 254 nm UV lamp or by staining with phosphomolybdic acid or permangenate solution and subsequent heating. Flash chromatography was performed on silica gel (230 – 400 mesh ASTM) purchased from Sorbtech or Bodman.

Acetic acid 3-but-3-enyl-3-methylcyclohex-1-enyl ester (50).[14]

Preparation of the Grignard reagent: Magnesium (0.40 g, 16.3 mmol) and a crystal of iodine were placed in a dry three-neck 50 mL round bottom flask attached to a reflux condensor and addition funnel. The contents were flame dried and cooled under argon. 4-Bromo-1-butene (1.38 mL, 13.62 mmol) in dry Et_2O (20 mL) was added dropwise over 10 min via addition funnel and the mixture was refluxed for an additional 10-15 min and then cooled.

To a dry three-neck 125 mL round bottom flask, attached to a reflux condensor and addition funnel, was added CuBr•DMS (0.19 g, 0.91 mmol), **49** (1.03 mL, 9.08 mmol) and dry DMS/ether (40 mL, 50:50) under argon. The solution was cooled to 0°C and the Grignard reagent was transferred via cannula to the addition funnel and added dropwise over 1 h. The mixture was warmed to RT after addition for 1 h and then recooled to 0°C. Acetyl chloride (3.20 mL, 45.4 mmol) was added and the mixture was then allowed to stir at RT overnight under argon. The reaction mixture was quenched with sat'd NH_4Cl (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (20 mL), the combined organic layers were washed with sat'd NH_4Cl (4 x 20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by column chromatography (98:2 Hexanes:EtOAc) to give **50** (0.95 g) as clear oil in 50% yield. Characterization data matches literature values. ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (dddd, *J* = 17.3, 13.1, 10.1, 6.8 Hz, 1H), 5.11 (s, 1H), 4.94 (dd, *J* = 17.3, 1.9 Hz, 1H), 4.90 (dd, *J* = 10.1, 1.9 Hz, 1H), 1.95-2.16 (m, 4H), 2.06 (s, 3H), 1.69-1.77 (m, 2H), 1.30-1.55 (m, 4H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 147.2, 138.8, 122.3, 133.7, 41.6, 34.4, 33.8, 28.2, 27.0, 26.6, 20.6, 19.1; IR (neat) 1755, 1686, 1363 cm^{-1}; LRMS (EI) (M — CH_3) 193, 151. 111, 84 *m/e*; HRMS (EI) cal'd for 193.122183, found 193.122185.

Acetic acid 3-methyl-3-(3-oxopropyl)cyclohex-1-enyl ester (55).[17,18]

To a 50 mL round bottom flask equipped with a stirrer was added H_2O (10 mL), *t*-butanol (10 mL), and AD mix-α (3.36 g) and the mixture stirred vigorously at RT for 0.5 h until 2 clear layers were formed. The mixture was cooled to 0°C and **50** (0.50 g, 2.23 mmol) was added neat and the mixture was stirred at RT overnight. Solid sodium sulfite

(3.60 g) was added to the mixture and stirred for an additional 30 min. The suspension was diluted with DCM (25 mL) and layers separated. The aqueous layer was extracted with DCM (3 x 15 mL), dried over $MgSO_4$ and concentrated in vacuo to give the diol as a clear yellow oil that was used in the next step without further purification. **Diol:** ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 1H), 3.56-3.59 (m, 2H), 3.37-3.41 (m, 1H), 2.9 (bs, 2H), 2.04-2.12 (m, 2H), 2.08 (s, 3H), 1.71-1.75 (m, 2H), 1.26-1.40 (m, 6H), 0.91 (s, 3H). To a 50 mL round bottom flask was added the diol, $NaIO_4$ (0.51 g, 2.36 mmol) and THF/H_2O (16 mL, 3:1 ratio) and the reaction mixture was stirred at RT overnight. The resulting mixture was poured into H_2O (10 mL) and extracted with Et_2O (5 x 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash chromatography (80:20 Hexanes: EtOAc) to give aldehyde **55** as a clear oil (0.35 g) in 75% yield over 2 steps. Characterization data matches literature values. ^1H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 4.88 (s, 1H), 2.29 (t, J = 7.8 Hz, 1H), 1.79-2.00 (m, 2H), 1.91 (s, 3H), 1.45-1.62 (m, 4H), 1.28-1.39 (m, 2H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 168.6, 147.8, 121.4, 38.9, 34.0, 33.6, 33.3, 27.0, 26.4, 20.5, 18.9.

Acetic acid 3-(3-hydroxypropyl)-3-methylcyclohex-1-enyl ester (56).[19]

To a stirred solution of aldehyde **55** (0.40 g, 1.77 mmol) in MeOH (2.5 mL) at 0°C was added $NaBH_4$ (63.0 mg, 1.68 mmol) portionwise. The mixture was allowed to stir under argon for 1 h at 0°C and then diluted with H_2O (6 mL) and extracted with DCM (4 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was chromatographed (80:20 Hexanes:EtOAc) to give alcohol **56** as a clear oil (314 mg, 78% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 5.02 (s, 1H), 3.48 (t, J = 6.1 Hz, 2H), 2.58 (bs, 1H), 2.00 (s, 3H), 1.90-2.02 (m, 2H), 1.65 (q, J = 5.8 Hz, 2H), 1.22-1.48 (m, 6H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 147.2, 122.7, 66.0, 38.4, 34.3, 33.8, 27.2, 27.1, 26.6, 20.9, 19.2; IR (neat) 3368, 1754 cm^{-1}; LRMS (EI) (M- C_2H_2O) 170, 153, 137, 111 *m/e*; HRMS (EI) cal'd for $C_{10}H_{18}O_2$ 170.13068, found 170.12998.

Acetic acid 3-methyl-3-(3-phenylselanylpropyl)cyclohex-1-enyl ester (53c).

To a solution of alcohol **56** (314 mg, 1.29 mmol) and Et_3N (0.27 mL, 1.94 mmol) in DCM (5 mL) at 0°C was added mesyl chloride (0.13 mL, 1.64 mmol). The solution was allowed to stir at 0°C under argon for 3 h then poured into a mixture of H_2O (5 mL) and Et_2O (12 mL). The aqueous layer was separated and extracted with Et_2O (3 x 12 mL). The organic layers were combined and washed with H_2O (10 mL), brine (10 mL) and then dried over $MgSO_4$ and concentrated in vacuo to give the mesylate as a yellow oil. The crude mesylate was used in the following step without further purification. **Mesylate:** ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.10 (t, *J* = 6.5 Hz, 2H), 2.91 (s, 3H), 1.96-2.03 (m, 2H), 2.00 (s, 3H), 1.61-1.68 (m, 4H), 1.26-1.41 (m, 4H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 147.5, 121.8, 59.9, 37.8, 36.7, 33.4, 26.9, 26.4, 23.7, 20.6, 18.9, 13.8.

To a solution of diphenyldiselenide (842 mg, 2.4 mmol) in dry DMF (10 mL) at 0°C was added $NaBH_4$ (184 mg, 4.8 mmol) portionwise. After the evolution of hydrogen ceased, the mesylate (327 mg, 1.13 mmoL) in DMF (20 mL) was added dropwise and the mixture was stirred at RT under argon for 4 h. The reaction was quenched with H_2O (20 mL) and extracted with EtOAc (5 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. Chromatography (gradient elution 100% Hexanes-10% EtOAc) gave selenyl ether **53c** (238 mg, 46 % yield over 2 steps) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.54 (m, 2H), 7.28-7.31 (m, 3H), 5.15 (s, 1H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.13-2.16 (m, 2H), 2.15 (s, 3H), 1.70-1.85 (m, 4H), 1.30-1.55 (m, 4H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 147.4, 132.3 (2C), 130.5, 128.8 (2C), 126.5, 122.5, 42.6, 34.6, 33.9, 28.5, 27.1, 26.7, 24.6, 20.9, 19.2; IR (neat) 2933, 1436 cm^{-1}; LRMS (EI) 352, 310, 111 *m/e*; HRMS cal'd for $C_{18}H_{24}O_2Se$ 352.09415, found 352.09378.

Acetic acid 3-(3-iodopropyl)-3-methylcyclohex-1-enyl ester (53c).

Following the procedure to form mesylate, alcohol **56** (540 mg, 2.55 mmol) gave the mesylate (740 mg, 2.55 mmol). To a solution of mesylate in acetone (36 mL) was added NaI (384 mg, 2.56 mmol) and the mixture was allowed to reflux under argon for 2.5 h.

The mixture was cooled to RT and the acetone was evaporated *in vacuo*. The solid mixture was dissolved in H_2O (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (90:10 Hexanes:EtOAc) gave iodide **53c** (593 mg, 73% yield 2 steps).
^{1}H NMR (300 MHz, C_6D_6)
δ [illegible], 1.10-1.03 (m, 4H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, C6D6) δ 168.4, 148.2, 122.5, 43.5, 34.5, 34.1, 28.8, 27.4, 27.2, 20.6, 19.6, 7.38; IR (neat) 1754, 1218 cm^{-1}.

Carbonic acid 3-but-3-enyl-3-methylcyclohex-1-enyl ester methyl ester (51).

Carbonate **51** was prepared in the same manner as acetate **50** using methyl chloroformate (3.51 mL, 45.4 mmol). The crude mixture was purified by column chromatography (98:2 Hexanes:EtOAc) to give 1.2 g of the carbonate in 58% yield. Characterization data matches literature values.
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 16.5, 13.5, 10.5, 6.8 Hz, 1H), 5.23 (s, 1H), 5.05 (dd, *J* = 16.5, 1.5 Hz, 1H), 4.95 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.82 (s, 3H), 2.15-2.21 (m, 2H), 2.03-2.11 (m, 2H), 1.75-1.85 (m, 2H), 1.36-1.61 (m, 4H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 147.8, 139.2, 122.8, 114.1, 54.8, 41.8, 34.8, 34.0, 28.6, 27.2, 26.5, 19.2; IR (neat) 1759, 1441 cm^{-1}; LRMS (EI) 224, 169, 125, 84 *m/e*; HRMS (EI) cal'd for $C_{13}H_{20}O_3$ 224.14125, found 224.14119.

Carbonic acid methyl ester 3-methyl-3-(3-oxopropyl)cyclohex-1-enyl ester (57).

Aldehyde **57** (0.73 g) was prepared in 72% yield over 2 steps in the same manner as aldehyde **55** using carbonate **51** (1.0 g, 4.46 mmol). Characterization data matches literature values. **Diol:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 1H), 3.74 (s, 3H), 3.53-3.57 (m, 2H), 3.32-3.38 (m, 1H), 2.06-2.10 (m, 2H), 1.68-1.71 (m, 2H), 1.26-1.47 (m, 6H), 0.95 (s, 3H). **57:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 5.17 (s, 1H), 3.78 (s, 3H), 2.40-2.46 (m, 2H), 2.11-2.14 (m, 2H), 1.73-1.77 (m, 2H), 1.62-1.67 (m, 2H), 1.38-1.42 (m, 2H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 153.3, 147.9, 121.2, 54.2, 38.6, 33.8, 33.4, 33.0, 26.6, 25.8, 18.7.

Carbonic acid 3-(3-hydroxypropyl)-3-methylcyclohex-1-enyl ester methyl ester (58).

Alcohol **58** (508 mg, 69 % yield) was prepared in the same manner as alcohol **56** from aldehyde **57** (0.73 g, 3.23 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (s, 1H), 3.56 (s, 3H), 3.34 (t, *J* = 6.3 Hz, 2H), 1.91-1.94 (m, 2H), 1.53-1.57 (m, 2H), 1.11-1.35 (m, 6H), 0.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 147.1, 122.4, 62.4, 54.3, 38.1, 34.0, 33.4, 26.8, 26.6, 25.9, 18.8; IR (neat) 3345, 2938, 1441 cm^{-1}; LRMS (EI) (M-CH_3) 213, 195, 169, 125 *m/e*; HRMS (EI) cal'd for $C_{11}H_{17}O_4$ 213.1268, found 213.11282.

Carbonic acid methyl ester 3-methyl-3-(3-phenylselanylpropyl)cyclohex-1-enyl ester (53d).

Selenyl ester **53d** (253 mg) was prepared in 37% yield over 2 steps in the same manner as **53c** using alcohol **58** (430 mg, 1.77 mmol). **Mesylate:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.61 (s, 3H), 2.86 (s, 3H), 1.94-1.99 (m, 2H), 1.55-1.61 (m, 4H), 1.19-1.34 (m, 4H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 147.7, 121.7, 70.3, 54.3, 37.6, 36.6, 34.0, 33.2, 26.7, 25.9, 23.6, 18.8.

53d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.48 (m, 2H), 7.25-7.22 (m, 3H), 5.19 (s, 1H), 3.78 (s, 3H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.12-2.11 (m, 2H), 1.74-1.64 (m, 4H), 1.46-1.34 (m, 4H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 147.5, 132.1 (2C), 130.3, 128.7 (2C), 126.3, 122.4, 54.5, 42.4, 34.5, 33.7, 28.3, 26.9, 26.1, 24.4, 19.1; IR (neat) 2934, 2860, 1689, 1439 cm^{-1}; LRMS (EI) 368, 326, 169, 135, 125 *m/e*; HRMS (EI) $C_{19}H_{24}O_3Se$ cal'd for 368.08907, found 368.08959.

Carbonic acid 3-(3-iodopropyl)-3-methylcyclohex-1-enylester methyl ester (53b).

Iodo **53b** (739 mg) was prepared in 68% yield in the same manner as **53a** using alcohol **58** (585 mg, 2.56 mmol). ^{1}H NMR (300 MHz, C_6D_6) δ [illegible] 3.32 (s, 3H), [illegible], 1.09-0.98 (m, 4H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 153.8, 148.7, 123.0, 55.6, 44.1, 35.0, 34.7, 29.3, 27.9, 27.7, 19.9, 8.0; IR (neat) 1750, 1220 cm^{-1}.

Acetic acid 3-(4-hydroxybutyl)-3-methyl-yclohex-1-enyl ester (59).

To a solution of alkene **50** (50mg, 0.22 mmol) in THF (0.5 mL) was added 1M solution of 9-BBN in THF (0.56 mL, 0.28 mmol) and the mixture was allowed to stir at RT under argon for 24 h. The mixture was treated with pH 7 phosphate buffer (0.25 mL), a 1:1 solution of THF/EtOH (0.5 mL total), and 30% H_2O_2 solution (0.5 mL) and allowed to stir for 24h. The reaction mixture was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the crude mixture (80:20 Hexanes:EtOAc) gave **59** (32.4 mg) as a yellow oil in 59 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.07 (s, 3H), 2.00-2.06 (m, 2H), 1.67-1.71 (m, 2H), 1.41-1.51 (m, 4H), 1.25-1.33 (m, 4H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 147.3, 122.9, 62.7, 42.4, 34.7. 33.9, 33.3, 27.2, 26.7. 21.0, 20.2, 19.3; IR (neat) 3375, 1745 cm^{-1}; LRMS (EI) (M- C_2H_2O) 184 *m/e*.

Acetic acid 3-methyl-3-(4-phenylselanylbutyl) cyclohex-1-enyl ester (38c).

Selenyl ester **38c** (535 mg) was prepared in 56% yield over 2 steps in the same manner as **53c** using alcohol **59** (550 mg, 2.6 mmol). **Mesylate:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.06 (t, *J* = 6.5 Hz, 2H), 2.85 (s, 3H), 1.95 (s, 3H), 1.89-1.93 (m, 2H), 1.54-1.60 (m, 4H), 1.16-1.33 (m, 6H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 147.1, 122.1, 69.8, 41.6, 36.6, 4.3, 33.5, 29.3, 26.8, 26.4, 20.6, 19.6, 18.9.
38c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.48 (m, 2H), 7.25-7.22 (m, 3H), 5.09 (s, 1H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.11 (s, 3H), 2.06-2.09 (m, 2H), 1.63-1.72 (m, 4H), 1.26-1.44 (m, 6H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 147.0, 131.9 (2C), 130.3, 128.5 (2C), 126.2, 122.4, 41.8, 34.3, 33.7, 30.5, 27.3, 26.9, 26.5, 23.9, 20.6, 19.0; LRMS (EI) 366, 213, 111 *m/e*; HRMS (EI) $C_{19}H_{26}O_2Se$ cal'd for 366.10980, found 366.11052.

Carbonic acid 3-(4-hydroxybutyl)-3-methylcyclohex-1-enyl ester methyl ester (60).

Alcohol **60** (435 mg, 80.5 % yield) was prepared in the same manner as alcohol **59** from alkene **51** (0.5 g, 2.23 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (s, 1H), 3.70 (s, 3H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.01-2.07 (m, 2H), 1.64-1.70 (m, 2H), 1.37-1.44 (m, 4H), 1.20-1.35 (m, 4H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 147.3, 122.9, 62.4, 54.6, 42.3, 34.6, 33.7, 33.2, 26.9, 26.2, 20.1, 19.2; LRMS (EI) (M-CH_3) 227, 169, 125 *m/e*; HRMS (EI) cal'd for $C_{12}H_{19}O_4$ 227.12833, found 227.12841.

Carbonic acid methyl ester 3-methyl-3-(4-phenylselanylbutyl) cyclohex-1-enyl ester (38d).

Selenyl ester **38d** (253 mg) was prepared in 37% yield over 2 steps in the same manner as **38c** using alcohol **60** (430 mg, 1.77 mmol). **Mesylate:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (s, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.67 (s, 3H), 2.89 (s, 3H), 1.99-2.02 (m, 2H), 1.60-1.68 (m, 4H), 1.21-1.40 (m, 6H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 147.5, 122.2, 69.9, 59.6, 41.6, 36.6, 34.4, 33.5, 29.3, 26.7, 25.9, 19.6, 18.9.
38d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.53 (m, 2H), 7.28-7.30 (m, 3H), 5.28 (s, 1H), 3.85 (s, 3H), 2.96 (t, *J* = 7.2 Hz, 2H), 1.18-2.02 (m, 2H), 1.75-1.79 (m, 4H), 1.37-1.42 (m, 6H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 147.5, 132.3 (2C), 130.4, 128.8 (2C), 126.5, 122.8, 54.7, 42.9, 34.6, 33.9, 30.8, 27.7, 26.9, 26.3, 24.2, 19.3; LRMS (EI) 3.82, 213, 169, 125 *m/e*; HRMS (EI) $C_{19}H_{26}O_3Se$ cal'd for 382.10471, found 382.10539.

(*cis*) Acetic acid 7-methyloctahydroinden-4-(S)-yl ester (62α, major).
(*cis*) Acetic acid 7-methyloctahydroinden-4-(R)-yl ester (62β, minor).
Iodide **53a** (1.06 g, 3.13 mmol mmol) was added to a sealed tube equipped with magnetic stir bar and diluted with benzene to 34 mL. AIBN (100 mg, 0.06 mmol) was added to the solution followed by Bu_3SnH (0.99 mL, 3.44 mmol) via syringe and placed in a preheated oil bath and allowed to stir at 80°C for 2 h. The reaction was cooled to RT then the benzene was removed in vacuo. Chromatography (100% Hexanes followed by gradient 5-10% Et_2O) of the crude mixture gave a 584 mg mixture of inseparable diastereomers (1.5:1) **62α** and **62β** in 95% combined yield. **62α:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (dt, J = 10.9, 4.8 Hz, 1H), 1.98 (s, 3H), 1.24-1.86 (m, 12H), 1.03 (s, 3H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 72.9, 47.9, 42.8, 41.3, 31.5, 25.7, 24.8, 24.0, 21.3, 20.8, 20.3; IR (neat) 1736.7, 1245.8 cm^{-1}; GC-MS last eluting (M-OAc) 136, 121 *m/e*.
62β: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (dt, J = 11.9, 4.8 Hz, 1H), 2.00 (s, 3H), 1.24-

1.86 (m, 12H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 73.9, 49.7, 42.2, 41.4, 36.5, 34.1, 29.2, 28.3, 27.1, 20.7, 19.1; IR (neat) 1736, 1245 cm^{-1}; GC-MS first eluting (M-OAc) 136, 121 *m/e*.

(*cis*)-Carbonic acid methyl ester 7-methyloctahydroinden-4-(S)-yl ester (63α, major).

(*cis*).-Carbonic acid methyl ester 7-methyloctahydroinden-4-(R)-yl ester (63β, minor).

Diastereomers **63α** and **63β** (2:1) were prepared in 68% yield (422 mg) in the same manner as **63α** and **63β** using iodide **53b** (723 mg, 2.14 mmol). **63α**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (dt, J = 11.0, 5.2 Hz, 1H), 3.77 (s, 3H), 1.26-1.87 (m, 12H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 78.4, 54.4, 48.0, 43.1, 41.5, 31.4, 25.7, 24.7, 23.9, 20.8, 20.4; IR (neat) 1747.1 cm^{-1}; GC-MS last eluting ($M-C_2H_3O_3$) 136, 121 *m/e*. **63b**: ^{1}H NMR (300 MHz, $CDCl_3$) □ 4.80 (m, 1H), 3.76 (s, 3H), 1.26-1.87 (m, 12H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 155.4, 78.4, 54.4, 49.7, 42.3, 36.5, 33.7, 29.2, 28.3, 27.1, 20.5, 19.0; IR (neat) 1747.1 cm^{-1}; GC-MS first eluting ($M-C_2H_3O_3$) 136, 121 *m/e*.

Acetic acid 3-methyl-3-propylcyclohex-1-enyl ester (61a).

Acetate **61a** was made in the same manner as **50** using 1-bromopropane when preparing the Grignard reagent in 68% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 1H), 1.98-2.08 (m, 2H), 2.02 (s, 3H), 1.64-1.71 (m, 2H), 1.39-1.46 (m, 2H), 1.15-1.29 (m, 4H), 0.92 (s, 3H), 0.79-.084 (m, 3H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 147.1, 122.9, 45.1, 34.6, 34.0, 27.1, 26.7, 20.9, 19.3, 17.1, 14.7; IR (neat) 1760 cm^{-1}; LRMS (EI) ($M-CH_3$) 181 *m/e*.

Carbonic acid methyl ester 3-methyl-3-propylcyclohex-1-enyl ester (61b).

Carbonate **61b** was made in the same manner as **51** using 1-bromopropane when preparing the Grignard reagent in 75% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 1H), 3.71 (s, 3H), 1.97-2.15 (m, 2H), 1.57-1.84 (m, 2H), 1.36-1.45 (m, 2H), 1.13-1.31 (m, 4H), 0.92 (s, 3H), 0.79-0.83 (m, 3H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 147.3, 122.9, 54.5, 45.0, 34.7, 33.9, 26.9, 26.2, 19.2, 17.0, 14.7; IR (neat) 1756 cm^{-1}; LRMS (EI) 212 *m/e*.

(*cis*)-7-Methyloctahydroinden-4-(S)-ol (64α, major)

(*cis*)-7-Methyloctahydroinden-4-(R)-ol (64β, minor)

To a 10 mL round bottom flask was added a mixture of **62α,β** (0.50 mmol) in dry Et_2O (10 mL) and cooled to 0°C under argon. LAH (0.75 mmol) was added portionwise to the solution and allowed to stir for 30 min. The reaction mixture was quenched with H_2O (5 mL) and the aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. Chromatography (80:20 Hexanes:EtOAc) gave a 1.5:1 mixture of **64α,β**, a clear oil in 50% yield. Data matches literature values. **64α:** ^{1}H NMR (300 MHz, C_6D_6) δ 3.68 (dt, *J* = 10.6, 4.6 Hz, 1H), 1.11-1.71 (m, 12H), 0.93 (s, 3H); ^{13}C NMR (C_6D_6) δ 69.3, 51.6, 41.1, 31.9, 30.2, 25.0, 23.7, 21.5, 20.7, 18.4; IR (neat) 3340.2 cm^{-1}; GC-MS last eluting (M-H) 153, 136, 121 *m/e*. **64β:** ^{1}H NMR (300 MHz, C_6D_6) δ 3.07 (ddd, *J* = 17.6, 9.3, 3.9 Hz, 1H), 1.11-1.71 (m, 12H), 0.90 (s, 3H); ^{13}C NMR (C_6D_6) δ 71.1, 54.0, 42.6, 35.7, 34.8, 34.1, 29.3, 27.3, 20.9, 20.1; IR (neat) 3340 cm^{-1}; GC-MS first eluting (M-H) minor 153, 136, *m/e*.

7-Methyloctahydroinden-4-one (54).[21]

To a 1.5:1 mixture of **64α,β** (50 mg, 0.32 mmol) in dry DCM (5 mL) was added Dess-Martin periodane (276 mg, 0.8 mmol) and allowed to stir at RT under argon for 1 h. The reaction was diluted with H_2O (2 mL) and then extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give **54** in 50% yield. Data matches literature values. ^{1}H NMR (300 MHz, C_6D_6) δ 2.00-2.14 (m, 2H), 1.92-1.98 (m, 2H), 1.53-1.60 (m, 2H), 1.38-1.44 (m, 2H), 1.21-1.26 (m, 2H), 0.8 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 60.9, 47.8, 40.4, 39.0, 33.9, 27.4, 27.0, 21.9, 21.4; IR (neat) 1708.3 cm^{-1}; LRMS (EI) 151 *m/e*.

3.1. Procedures for Radical Cyclizations

Stock solutions of iodides **53a,b**, selenyl ethers **53c,d** and internal standard, *p*-dimethoxybenzene, were made in C_6D_6 and kept under argon and frozen when not in use. Reactions were run in triplicate at each concentration for **53a,c,d**. Aliquots from each solution were taken for a ^{1}H NMR and GC sample before and after the allotted reaction time to determine yields. Gas chromatograms (GC) were run on an Agilent 6850 Series GC System with an HP-1 Methyl Siloxane column (Agilent 19091Z-413E, Capillary 30.0 m x 320 µm x 0.25µm). The initial temperature of the program was 150 °C with a temperature ramp of 5°C/min up to 250 °C a helium flow of 2 mL/min and 8.68 PSI was applied. *p*-dimethoxybenzene was used as internal standard and C_6D_6 or benzene was used as solvent. GC data is reported with a retention time and % area of the total integrated area. GC yields were determined by calculating the response factors (RF) of each compound to the internal standard using:

$$\text{RF} = \frac{\text{mmol standard x area compound}}{\text{mmol compound x area standard}}$$

Response factors for each compound is as follows:

53c: 3.1391 **53d:** 3.3183 **64β (minor), 64α (major):** 2.6296 **62β (minor), 62α (major):** 1.2347 **63β (minor), 63α (major):** 2.8085

53a: 1.4241 **53b:** 3.0488 **54:** 1.3677 **61a:** 1.2691 **61b:** 3.6176

Retention times for each compound is as follows (min):

standard: 3.45 **54:** 4.00 **64β (minor), 64α (major):** 4.15. 4.04

40: 4.55 **62β (minor), 62α (major):** 4.93, 4.82 **61b:** 5.12

63β (minor), 63α (major): 5.48, 5.36 **53a:** 7.03 **53b:** 9.40

53c: 9.67 **53d:** 10.08

3.2. Concentration studies

Aliquots of radical precursors **53a-d** (1 equiv) and internal standard, *p*-dimethoxybenzene (0.1 to 0.2 equiv) were added to sealed tubes equipped with magnetic stir bars and diluted with C_6D_6 to the proper concentration. AIBN (0.2 equiv) was added to the solutions followed by Bu_3SnH (1.1 equiv) via syringe and were placed in a preheated oil bath and allowed to stir at 80°C for a predetermined amount of time.

Table 10 Reaction yields of 53c with varying concentrations of Bu_3SnH

[Rxn] (M)	**Time (h)**	**Vol (mL)**	**Yields**					
53c			**GC/NMR**	**GC**	**GC**	**GC/NMR**	**NMR**	**GC/NMR**
			62α,β	**54**	**64α,β**	**61a**	**76**	**53c**
0.1	2	0.8	94.6/90	0	0	1.1/2		
0.1	2	0.8	101/95	0.9	6	0.8/1		
0.1	2	0.8	90/90	0.9	0	0.6/1		
Avg			**97.4/91.7**	**0.3**	**2.0**	**0.8/1.3**	**0**	**0/0**
0.01	12	8	50.3/55	0.5	4.5	0.2/1	5	8.2/6
0.01	12	8	54.1/59	0.9	1.8	0.2/1	5	7.3/5
0.01	12	8	52.8/56	0.8	1.6	0.2/1	5	7.1/5
Avg			**52.4/56.7**	**0.7**	**2.6**	**0.2/1**	**5**	**7.5/5.3**
0.001	24	40					10	49.7/50
0.001	24	40					10	49.7/50
0.001	24	40					10	50.2/50
Avg			**0/0**	**0**		**0/0**	**10**	**49.9/50**

Table 11 Reaction yields of 53d with varying concentrations of Bu_3SnH

[Rxn] (M)	**Time (h)**	**Vol (mL)**	**Yields**					
53d			**GC/NMR**	**GC**	**GC**	**GC/NMR**	**NMR**	**GC/NMR**
			63α,β	**54**	**64α,β**	**61b**	**76**	**53d**
0.1	2	0.8	46.2/48		1	2/3		
0.1	2	0.8	45.1/47		1	2/3		
0.1	2	0.8	45.2/48		0	0.9/1		
Avg			**45.5/47.7**	**0**	**0.7**	**1.6/2.3**		**0**
0.01	12	8	52.5 /55	1	1	11.5/9	5	20.5/19
0.01	12	8	52.6/57	0.5	1.8	12.4/12	10	18.6/18
0.01	12	8	49.5/50	0.8	1.2	8.5/7	5	23.5/23.5
Avg			**51.5/54**	**0.8**	**1.3**	**10.8/9.3**	**6.7**	**20.1/20.7**
0.001	24	40					5	46.3/40
0.001	24	40					8	47.9/41
0.001	24	40					10	43.4/48
Avg			**0/0**	**0**		**0/0**	**7.7**	**45.9/39.7**

Table 12 Reaction yields of 53a with varying concentrations of Bu_3SnH

[Rxn] (M)	**Time (h)**	**Vol (mL)**	**Yields**		
53a			**GC/NMR**	**GC**	**GC/NMR**
			62α,β	**54**	**53a**
0.1	2	1.2	96.3/97	2.2	
0.1	2	1.2	92.1/93	1.8	
0.1	2	1.2	95.9/96	3.1	
Avg			**94.8/95.3**	**2.4**	**0/0**
0.01	12	12	74.9/76	6.9	
0.01	12	12	74.9/73	9.3	
0.01	12	12	69.1/70	6.2	
Avg			**73/73**	**7.5**	**0/0**
0.005	24	30	29.4/30	17.8	41.2/37
0.005	24	30	28.2/31	14	39.8/39
0.005	24	30	27.4/29	14.9	45.4/40
Avg			**28.3/30**	**15.6**	**42.1/38.7**
0.001	24	30	3.2	14.3	40.5/40
0.001	24	30	0	17.4	46.8/41
0.001	24	30	0.47	15	40.9/42
Avg			**1.2/0**	**15.6**	**42.9/41**

Table 13 Reaction yields of 53b with varying concentrations of Bu_3SnH

[Rxn] (M)	Time (h)	Vol (mL)	Yields		
53b			**GC/NMR**	**GC**	**GC/NMR**
			63α,β	**54**	**53b**
0.1	2	1.1	80/73	2	
0.01	12	11	70/80	1	
0.001	24	33	60/55	1	25/30

AIBN Concentration Studies

Aliquots of iodide **53a** (0.124 mmol) and *p*-dimethoxybenzene (0.05 mmol) were added to sealed tubes equipped with magnetic stir bars and diluted with C_6D_6 to 13.6 mL. AIBN (varying eqs.) was added to each solution followed by Bu_3SnH (0.037 mL, 0.136 mmol) via syringe and were placed in a preheated oil bath and allowed to stir at 80°C for 12 h. AIBN amounts were 0.25 eq (5 mg), 0.5 eq (10 mg), 0.75 eq (15 mg), 1 eq (20 mg), 2 eq (40 mg).

Table 14 Reaction yields of 62α,β with varying concentrations of AIBN

AIBN	GC/NMR	GC
equiv	**62α,β**	**54**
0.25	73.1/69	12.4
0.5	71.4/67.1	14.7
0.75	76.4/73.3	10.1
1	76.6/71.1	7.8
2	71.0/69	8.7

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