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UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

**NOVEL COBALT-MEDIATED REGIO- AND
STEREOSELECTIVE RADICAL CYCLIZATIONS**

A Dissertation

SUBMITTED TO THE GRADUATE FACULTY

In partial fulfillment of the requirements for the

degree of

Doctor of Philosophy

By

Karen L. Salazar

Norman, Oklahoma

1998

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**NOVEL COBALT-MEDIATED REGIO- AND
STEREOSELECTIVE RADICAL CYCLIZATIONS**

**A Dissertation APPROVED FOR
THE DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY**

BY

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LIST OF ABBREVIATIONS

AIBN	2,2'-Azobisisobutyronitrile
AMVN	2,2'-Azobis(2,4-dimethylvaleronitrile)
BuLi	<i>n</i> -Butyllithium
COSY	Correlated spectroscopy
Cp	Cyclopentadienyl
d	doublet
dd	doublet of doublets
ddd	double doublet of doublets
dq	doublet of quartets
dt	doublet of triplets
ddt	double doublet of triplets
DEPT	Distortionless enhancement by polarization transfer
DIPHOS	1,2-Bis(triphenylphosphino)ethane
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMgH	Dimethylglyoxime
EA	Elemental analysis
EIMS	Electron-impact mass spectrometry
FMO	Frontier molecular orbital
g	gram
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry

Hz	Hertz
IR	Infrared spectroscopy
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
M	Molarity
MHz	Megahertz
mmol	millimole
m/z	Charge to mass ratio
N	Normality
NMR	Nuclear magnetic resonance
Ph	Phenyl
PTC-Cl	Phenyl chlorothionoformate
PTLC	Preparatory thin layer chromatography
q	Quartet
R _f	retardation factor
s	Singlet
SOMO	Singly occupied molecular orbital
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCL	Trimethylsilyl chloride
t	Triplet

ABSTRACT

NOVEL COBALT-MEDIATED REGIO- AND STEREOSLECTIVE RADICAL CYCLIZATIONS

Initial studies of (propargyl)Co₂(CO)₆ radicals demonstrated that they dimerize with very good regio- and stereoselectivity. However, very little was known about the general reactivity of such species. For this reason, the goal of this project was to investigate the reactivity of (propargyl)Co₂(CO)₆ radicals by studying their addition to double bonds of varying electronic character, and if successful, development of their synthetic utility would be explored.

Initially efforts focused on the intermolecular additions of the radicals to electron deficient double bonds; however, these were unsuccessful. For this reason, efforts then focused on intramolecular cyclizations of 1-[(alkynyl)Co₂(CO)₆]-5-hexenyl systems. The radicals were first generated by the reduction of the (propargyl)Co₂(CO)₆ cations with zinc and underwent cyclization to produce the 5-*exo* products in low yield. Efforts to improve the reaction yields were unsuccessful. For this reason, we focused on developing a system in which the radicals could be generated by direct homolytic cleavage of a carbon-thionocarbonate bond, which was unsuccessful, and by homolytic cleavage of a carbon-bromine bond. The cyclizations employing the propargyl bromide complexes were successful, but the yields were not synthetically useful. It was serendipitously discovered that when neat samples were irradiated, halogen atom transfer occurred with novel regioselectivity (5-*exo* vs. 6-*endo*) and exceptionally high *trans* stereoselectivity in the cases where the 5-*exo* products were formed. Photochemical cyclizations were also attempted on the homologous 1-alkynyl-6-heptenyl bromide complexes. Cyclization was

observed only in one case in low yield, but with novel regioselectivity as well; the 7-*endo* product was produced.

In order to explain these findings, a mechanism has been postulated in which the reactions take place *via* a radical cyclization under kinetic control but proceed through a late transition state. While this mechanism adequately explains our results, it does not rule out the possibility that the reactions proceed by a non-radical pathway, or are thermodynamically controlled. For this reason, mechanistic studies were performed, on the propargyl bromide complexes to determine if they were proceeding by a radical pathway and if they were reversible. The results of these studies were ambiguous, but they did not discredit the proposed mechanism.

Finally, the synthetic utility of (propargyl bromides) $\text{Co}_2(\text{CO})_6$ was explored and resulted in the successful development of a tandem cyclization/allylation reaction. The product from this reaction was designed so that it could be employed in a Pauson-Khand reaction, which if successful would produce a tricyclic compound in two steps from the acyclic bromide. Unfortunately, this reaction was not successful under any of the conditions that were investigated.

CHAPTER I

AN INTRODUCTION TO THE CHEMISTRY AND SYNTHETIC UTILITY OF (PROPARGYL)Co₂(CO)₆ RADICALS

I. INTRODUCTION

A. Activation of organic ligands by complexation with metals

When a metal fragment is bound to an organic ligand, the reactivity of the ligand changes. It can become activated or deactivated towards nucleophilic or electrophilic addition depending on the electronic character of the complex.¹ For example, nucleophilic aromatic substitution occurs by an addition-elimination mechanism, for this reason aromatic compounds substituted with electron donating groups do not undergo this reaction because the anion that would be generated after addition of the nucleophile would not be stable.² However, when aromatic compounds are substituted with electron withdrawing groups, the aromatic ring is activated towards nucleophilic attack because the resulting anion will be stabilized by induction or resonance.³ Moreover, metal complexes that can act as electron withdrawing groups also activate aromatic compounds towards nucleophilic attack. For example, Semmelhack *et al.* have shown that complexation of anisole with chromium tricarbonyl (**1**) activates the aromatic ring towards nucleophilic attack by the cyano-stabilized anion to generate **3**, which is converted to **4** upon hydrolysis (Scheme 1.1).⁴

Scheme 1.1: Nucleophilic addition to anisole-chromium complex **1**

In the case of transition metal alkyne complexes, the opposite effect (i.e. stabilization/deactivation) is observed. For example, when propargyl cations are generated from uncomplexed alcohols, then treated with nucleophiles, addition occurs to give the substituted allenes.⁵ However, when $(\text{propargyl})\text{Co}_2(\text{CO})_6$ cations (Figure 1.1) are generated from the complexed alcohols, the cation is highly stabilized, isolable, and undergoes facile nucleophilic addition at the propargyl position without formation of allenic products.⁶ Many useful synthetic methodologies have been developed which employ complexes such as **5**.⁷

Figure 1.1: (propargyl)Co₂(CO)₆ cation complex, **5**

Analogous examples exist for metal complexes activating or stabilizing organic ligands towards electrophilic attack.⁸ However, the main purpose of this section is to illustrate that metal complexation can dramatically effect the reactivity of organic compounds.

B. Synthesis and study of (propargyl)Co₂(CO)₆ cations

The isolation and investigation of (propargyl)Co₂(CO)₆ cations originated from studies of the Co₂(CO)₆-fragment as a protecting group for carbon-carbon triple bonds.⁹ During the course of these studies, it was discovered that (propargyl)Co₂(CO)₆ alcohols readily undergo acid-promoted dehydration to give 1,3-enynes. This raised the suspicion that the reaction intermediates were (propargyl)Co₂(CO)₆ cations.⁷ The eventual isolation of cation complexes **5** was accomplished by treatment of the corresponding complexed alcohols **7** with acids of non-coordinating anions,¹⁰ or by treatment with Lewis acids (Scheme 1.2).¹¹

Scheme 1.2: Synthesis of (propargyl)Co₂(CO)₆ cation complexes, **5**

Subsequently, methods which have been developed to generate the cation complexes include treatment of complexed acetates¹² or ethers¹³ with Lewis acids and treatment of 1,3-enyne complexes with electrophiles for *in situ* generation.¹⁴

Once the (propargyl)Co₂(CO)₆ cations were isolated, investigation into their structure followed. Early studies employing ¹H NMR and IR spectroscopy offered evidence that the positive charge is highly delocalized and extends onto the carbonyl ligands.^{10a} In addition, pK_{R+} measurements indicated that the thermodynamic stabilities of (propargyl)Co₂(CO)₆ cations were comparable to triarylmethyl carbenium ions.¹⁵ Later studies employing low temperature ¹³C NMR spectroscopy also supported extensive delocalization of the positive charge. However, they also suggested that the cation complexes possess a fluxional behavior in which the propargylic carbon interacts dynamically with both cobalt atoms of the -Co₂(CO)₆ group.¹⁶ Very recently, further evidence for the delocalization of the positive charge was provided by the X-ray structure of **8** (Figure 1.2).¹⁷ This structure clearly showed that there is a direct interaction between one of the cobalt atoms and the propargylic carbon formally bearing the positive charge (Figure 1.2).

Figure 1.2: The first X-ray structure of a (propargyl)Co₂(CO)₆ cation, **8**

C. Reactions with nucleophiles

In addition to elucidating the structure and physical properties of (propargyl)Co₂(CO)₆ cations, studies were simultaneously undertaken to explore their synthetic utility. Efforts initially focused on reactions of the cation complexes with nucleophiles. Such reactions were of interest because it was believed that nucleophilic addition which generated the substituted allenes could be avoided in the presence of the Co₂(CO)₆-complexed triple bond. Early studies involved addition of aromatic nucleophiles such as anisole, phenol, *N,N*-dimethylaniline, and 1,2,4-trimethoxybenzene to (propargyl)Co₂(CO)₆ cations.¹⁸ These reactions take place at room temperature or below giving good to excellent yields of propargylated products. Similarly, substrates with electron-rich double bonds, β-dicarbonyl compounds,¹⁹ ketones, enol acetates, trimethylsilyl enol ethers,²⁰ and allylsilanes²¹ undergo nucleophilic addition to the cations yielding the propargylated products in good to excellent yields without rearrangement (Scheme 1.3).

Scheme 1.3: Addition of various nucleophiles to (propargyl)Co₂(CO)₆ cations

Nu = anisole, phenol, *N,N*-dimethylaniline, 1,2,4-trimethoxybenzene, β -dicarbonyl compounds, ketones, enol acetates, trimethylsilyl enol ethers, allylsilanes

As the addition of nucleophiles to (propargyl)Co₂(CO)₆ cations proved to be an extremely useful synthetic process, the potential to make these reactions diastereoselective was also recognized. For example, in the reactions employing β -diketones, diastereoselectivities of 2 : 1 to 15 : 1 were observed.¹⁹ Similarly, addition of trimethylsilyl enol ethers to α -alkoxy cations produced β -alkoxy ketone complexes with diastereoselectivities of > 10 : 1.⁷ Schreiber also reported that reactions between (propargyl ethers)Co₂(CO)₆ and both isomers of the trimethylsilyl enol ether of propiophenone were highly facial selective. In one case **12** and **13** were obtained in a syn/anti ratio of 18 : 1 (Scheme 1.4).¹³

Scheme 1.4: Lewis acid mediated addition of TMS enol ether to **10**

In this study, higher diastereoselectivities were observed when the E-isomer was employed, and the stereochemistry of the major product was highly influenced by the substituent on the terminal end of the coordinated triple bond (Me_3Si -, Ph-, or Me).

In order to rationalize the product distribution Schreiber *et al.* performed low temperature ^1H and ^{13}C NMR experiments on the cations and discovered that they were fluxional species. Based on their observations, the transition state model in Figure 1.3 was proposed.

Figure 1.3: Proposed transition state model for syn selectivity

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The synclinal arrangement of the two π -systems accounted for both the syn selectivity of the reaction and the effect of the substituent on the terminal end of the triple bond. This transition state structure also incorporated the idea that the positive charge of the cation was highly delocalized, and that one of the cobalt atoms interacts with the propargylic carbon. In addition to Schreiber's studies, many other groups have undertaken efforts to expand the chemistry of stereoselective addition of nucleophiles to (propargyl aldehydes) $\text{Co}_2(\text{CO})_6$, (propargyl ketones) $\text{Co}_2(\text{CO})_6$ and (propargyl acetals) $\text{Co}_2(\text{CO})_6$.²²

An alternative method of achieving stereoselectivity in the addition of nucleophiles to (propargyl) $\text{Co}_2(\text{CO})_6$ cations was developed by Nicholas *et al.*²³ In this method, selectivity was achieved by employing chiral clusters. The first generation of chiral clusters was prepared by treating (propargyl alcohols) $\text{Co}_2(\text{CO})_6$ with triphenylphosphine (Scheme 1.5).

Scheme 1.5: Synthesis of chiral clusters **15** and **16**

When the cations were generated from the chiral alcohols they proved to be very stable and less reactive than the corresponding hexacarbonyl analogs. This was attributed to the fact that PPh₃ is a better σ -donor and poorer π -acceptor than CO. In addition, the phosphinated cations were not as fluxional as their hexacarbonyl counterparts.

The configurational stability of the chiral clusters was further investigated and culminated in the development of a completely enantioselective addition reaction.²⁴ In this study, the enantiomerically enriched (propargyl alcohols)Co₂(CO)₆, **17**, were treated with tris(1,1,1,3,3,3-hexafluoroisopropyl) phosphite to give complex **18** and **19** in a 1.0 : 1.6 ratio in 65% yield (Scheme 1.6).

Scheme 1.6: Synthesis of chiral phosphite clusters **18** and **19**

The diastereomers were separated and **19** was treated with $\text{HBF}_4 \cdot \text{OEt}_2$ and propionic anhydride, then **20** was added (Scheme 1.7). From this reaction, compounds **21** and **21'** were produced in a 9 : 1 ratio in 77% overall yield. The major product **21** was converted to the hexacarbonyl complex, then demetallated to give **22**. Its enantiomeric purity was identical to the original alcohol, and further investigation showed that the reaction had proceeded with retention of configuration.

Scheme 1.7: Enantioselective nucleophilic addition

D. (Propargyl) $\text{Co}_2(\text{CO})_6$ -mediated cationic cyclizations

A natural progression from studying the intermolecular nucleophilic addition to (propargyl) $\text{Co}_2(\text{CO})_6$ cations was to study the corresponding intramolecular processes. The earliest of these studies was reported by Schreiber *et al.*¹³ They found that treatment of complexed ethers such as **23** with $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 gave **24** in 55% yield (Scheme 1.8). In these reactions, the (propargyl) $\text{Co}_2(\text{CO})_6$ group had been incorporated into the ring.

Scheme 1.8: Intramolecular cationic cyclization with an *endo* -Co₂(CO)₆ group

Compounds containing 6-, 7-, and 8-membered rings were also synthesized. The compounds containing the coordinated cyclooctynes were subsequently converted into polycyclic compounds through a Pauson-Khand reaction.²⁵ A cyclization reaction was also performed on compound **25**, and **26** was produced in 91% yield (Scheme 1.9). The (propargyl)Co₂(CO)₆ group was *exo* to the newly formed ring, and the product was isolated as a single diastereomer in which the substituents on the ring were *trans*. The complex was demetallated with Me₃NO to give **27** in 89% yield.

Scheme 1.9: Intramolecular cationic cyclization with an *exo* -Co₂(CO)₆ group

Another methodology, which employed $\text{Co}_2(\text{CO})_6$ -mediated cationic cyclizations, was developed by Magnus *et al.* for the synthesis of the anticancer substances Neocarzinostatin Chromophore A,²⁶ Dynemicin,²⁷ and for Esperamicin A₁ and Calicheamicin γ_1 through the development of 2-ketobicyclo[7.3.1]enediynes and 13-ketobicyclo[7.3.1]enediynes cores.²⁸ In all of the preceding syntheses, the $\text{Co}_2(\text{CO})_6$ -mediated cationic cyclization was employed to generate the 10-membered ring. An example of the cyclization in the synthesis of Dynemicin is illustrated in Scheme. 1.10. The cyclized product, **29**, was produced in 43% yield.

Scheme 1.10: Synthesis of the 10-membered ring of Dynemicin

The preceding examples have illustrated how the reactivity of alkynes is dramatically altered by the presence of the $-\text{Co}_2(\text{CO})_6$ group. The (propargyl) $\text{Co}_2(\text{CO})_6$ cations are highly stabilized yet undergo facile regioselective nucleophilic addition. As a result of the success that was achieved with employing (propargyl) $\text{Co}_2(\text{CO})_6$ cations in

synthetically useful reactions, the question arose as to whether or not comparable stabilization by the $-\text{Co}_2(\text{CO})_6$ group would be observed with (propargyl) $\text{Co}_2(\text{CO})_6$ radicals because the unpaired electron would be located in a p orbital which could interact with the orbitals of the cobalt atom. This interaction was responsible for the extensive delocalization of the positive charge in the cation complexes. Therefore, it seemed feasible that there would be similar delocalization (and hence stabilization) of the (propargyl) $\text{Co}_2(\text{CO})_6$ radical (Figure 1.4).

Figure 1.4: Comparison of (propargyl) $\text{Co}_2(\text{CO})_6$ cation, **30**, and radical, **31**

Therefore, the goal of the project was to study the reactivity of (propargyl) $\text{Co}_2(\text{CO})_6$ radicals, then try to determine whether or not the reactivity was directly related to the radical stability. If these studies were successful, efforts would then be made to explore the synthetic utility of the radicals.

E. Carbon-centered organometallic radicals

In the earlier studies, carbon-centered organometallic radicals were only reported as suspected intermediates in reactions where cations were subjected to reductive conditions and dimers or the reduced starting material was produced (*vide infra*). No efforts were made to explore the synthetic utility of carbon-centered organometallic radicals until recently. In 1963 Pettit reported that treatment of E-E-2,4-hexadien-1-ol-iron tricarbonyl **32** with perchloric acid generated the perchlorate salt, **33**, which when treated with zinc, gave a 1 : 1 mixture of two compounds which were diastereomers of **35** (Scheme 1.11).²⁹

Scheme 1.11: Synthesis of **35** as a diastereomeric mixture

It was postulated that the reaction had proceeded through the radical intermediate **34**. The exact structure of the diastereomers was not determined; however, this work was further developed and led to the generation of cyclic compounds through the intramolecular

coupling of bis-pentadienyl iron tricarbonyl radicals. The radicals were produced from the cations, which were generated from **36**, where $n = 3, 4$, and 8 , then reduced with zinc.³⁰ The yields ranged from 40-60%, and in the case where $n = 3$, a single diastereomer was produced (Scheme 1.12).

Scheme 1.12: Coupling of bis-pentadienyl iron tricarbonyl radicals

The first confirmed non-metal centered organometallic radical, **38**, was reported by Forrester.³¹ The *t*-butylferrocenylnitroxide was prepared by treating ferrocenylmagnesium bromide with 2-methyl-2-nitrosopropane followed by autoxidation of the resulting hydroxylamine. The presence of the radical was confirmed by elemental analysis, IR and ESR spectroscopy, as well as X-ray crystallography. From the spectral data, it is believed that there is extensive delocalization of the unpaired electron in **38** (Scheme 1.13).

Scheme 1.13: Delocalization of the unpaired electron in **38**

In a separate study, Horspool *et al.* reported that ferrocenyl radicals were generated by irradiating substituted ferrocenyl ethers, **39**.³² Products resulting from dimerization, **40**, hydrogen atom abstraction, **41**, and solvent exchange, **42**, were isolated (Scheme 1.14). In addition it was shown that increasing the stability of the radicals increased the yield of dimerization, and increasing the steric bulk around the radical precluded dimerization.

Scheme 1.14: Reactions of ferrocenyl radicals

Carbon-centered organometallic radicals have also been generated from chromium complexes³³ and molybdenum complexes.³⁴ When aryl tricarbonyl chromium cations were treated with *n*-BuMgBr, the reactions proceeded by both nucleophilic and radical pathways. A typical result from these studies is illustrated in Scheme 1.15. Treatment of **43** with *n*-BuMgBr gave the dimer, **44**, in 74 % yield.

Scheme 1.15: A reaction of aryl tricarbonyl chromium cation

When molybdenum complexes were employed, **46** was produced when **45** was treated with sodium amalgam. It has been postulated that **46** is the result of a coupling reaction between two radical anions (Scheme 1.16).³⁵

Scheme 1.16: Dimerization of molybdenum complex **45**

The synthetic utility of carbon-centered organometallic radicals was first explored by Pearson.³⁶ In this study, which was related to the work done by Pettit,²⁹ cyclic voltammetry was employed to prove that tricarbonyl (1-methoxycarbonylcyclohexadienyl) iron hexafluorophosphate, **47**, undergoes a 1-electron reduction to form a radical intermediate. Identical mixtures of **48** were produced when **47** was reduced with either zinc or by electrochemical means (Scheme 1.17).

Scheme 1.17: Dimerization of **47**

Once this was established, Pearson explored whether or not the radical could undergo addition to a double bond. In order to do this, compound **50** was synthesized from **49**, then the cation was generated and treated with zinc (Scheme 1.18). From this reaction, **52** was produced in 15-25% yield as a 3 : 1 mixture of diastereomers along with the reduced complex **53**.

Scheme 1.18: Synthesis and radical cyclization of 51

Aside from Pearson's study, no reports appeared concerning the synthetic utility of carbon-centered organometallic radicals until recently when Schmalz reported that $(\eta^6\text{-arene})(\text{tricarbonyl})\text{chromium}$ complexes could be used in the diastereoselective synthesis of hydrobenzindene derivatives. In this process, the radical is generated by treatment of **54** with SmI_2 , which then undergoes a 5-*endo*-trig cyclization (Scheme 1.19).³⁷ The resulting radical is reduced by a second equivalent of SmI_2 , then the anion is protonated. A racemic mixture of **55** is produced in > 99% de.

Scheme 1.19: Radical cyclization of 54

In order to explain the stereochemistry, Schmalz *et al.* presumed that the reaction was occurring through a reversible pathway, and the most stable product resulted from the radical which faced away from the sterically demanding Cr(CO)_3 group after cyclization (Scheme 1.20).

Scheme 1.20: Proposed mechanism for the cyclization of 56

One difficulty with Schmaltz's rationalization is that the radical **57** is shown as sp^3 hybridized and is not stabilized by the arene ring. Julia and Curran have each demonstrated that radicals must be highly stabilized in order to observe reversible cyclizations,³⁸ which is not the case with **57**. For this reason, an alternative explanation to the observed stereochemistry could be that cyclization is not reversible and is operating under kinetic control. Presumably, the observed product arises by virtue of having a lower energy transition state where the radical attacks the less hindered face opposite the $Cr(CO)_3$ group.³⁹

Merlic has also explored the synthetic utility of carbon-centered organometallic radicals by synthesizing spirolactones using $(\eta^6\text{-arene})(\text{tricarbonyl})\text{chromium}$ complexes.⁴⁰ The reaction involved generating the radical at the benzylic position, then trapping it with methyl acrylate. The resulting radical was reduced by samarium iodide, then the anion was quenched by *t*-BuOH. The resulting alkoxide then cyclized to produce the spirolactone. Selectivity was obtained by taking advantage of the fact that addition of the radical trap would occur to the face opposite of the sterically demanding $-Cr(CO)_3$ group. Therefore, when compounds such as **59**, were treated with SmI_2 , and methyl acrylate, **60**, the spirolactones were produced as single diastereomers in yields ranging from 33-83%.

Scheme 1.21: Merlic's synthesis of spirolactone, 61

With the advent of synthetically useful methodologies employing carbon-centered organometallic radicals, the potential for this new field of chemistry to establish itself as a viable means to accomplish the efficient, stereoselective syntheses of organic compounds is tremendous. When synthesizing compounds with reactions involving the generation of radicals, the factors which govern the outcome of the reaction are very different from those which govern polar reactions. For this reason, one must have a good understanding of the chemistry of radicals in order to be successful.

II. PRINCIPLES OF RADICAL CHEMISTRY

A. Classification of radicals

The definition of a radical is a species that contains an unpaired electron.⁴¹ Even though the existence of radicals has been known for many years, their use in synthetic organic chemistry was virtually unexplored until the late 1970's and early 1980's.⁴² Since this time, some very good reviews and books about the development and use of radical chemistry in organic synthesis have been published.⁴³

The lifetime of most radicals is very short and they will either dimerize or disproportionate upon generation in the absence of a hydrogen atom donor (Scheme 1.22).⁴⁴

Scheme 1.22: Dimerization and disproportionation of radicals

In order to control the reactivity of radicals, there are ways in which their lifetimes can be extended. One method involves substituting the carbon bearing the radical with aryl groups. By doing this, the electron can delocalize into the π -system so that dimerization and/or disproportionation are slowed down or prohibited. These radicals are referred to as stable radicals. Some examples are given in Scheme 1.23.⁴⁴

Scheme 1.23: Examples of stable radicals

Another way to extend the lifetime of a radical is to place sterically bulky groups, which have no α -protons, on the carbon bearing the odd electron. The size of the groups will hinder dimerization due to their steric bulk, and the lack of β -protons will prevent disproportionation. This is a kinetic stabilization, and radicals of this type are referred to as persistent radicals (Scheme 1.24).⁴⁴

Scheme 1.24: Examples of persistent radicals

In terms of their reactivity, radicals can be classified as nucleophilic, electrophilic, or ambiphilic. Nucleophilic radicals are generally heteroatom-substituted radicals, or vinyl, aryl, acyl and alkyl radicals. These radicals generally react readily with electron deficient double bonds (Scheme 1.25).⁴¹

Scheme 1.25: Examples of nucleophilic, electrophilic, and ambiphilic radicals

Nucleophilic radicals

$R^1, R^2, R^3 = \text{H, alkyl, vinyl, aryl}$

Electrophilic radicals

Ambiphilic radicals

Electrophilic radicals are characterized by being substituted with two or more strong electron-withdrawing groups or being perhalo-substituted.⁴⁵ They generally react readily with electron rich alkenes.

Finally, ambiphilic radicals are substituted with only one electron-withdrawing group. These radicals can react with both electron-rich and electron-poor double bonds.

B. Principles of intermolecular radical additions to double bonds

Intermolecular addition of radicals to carbon-carbon double bonds is a thermodynamically favorable reaction. In this process a C-C π -bond is replaced by a stronger C-C σ -bond; therefore, the process is very exothermic and is believed to take place through an early transition state. This transition state has been studied using molecular mechanics calculations.⁴⁶ A picture of the presumed transition state is shown in Figure 1.5.

Figure 1.5: Presumed transition state of radical addition to a double bond

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From the molecular mechanics calculations, it was postulated that the radical approaches the double bond at an angle of 109° . The forming C-C bond distance is predicted to be $> 2.0 \text{ \AA}$, and the sp^2 carbons of the double bond are slightly pyramidalized.

The observed reactivity and selectivity for addition of radicals to double bonds has been treated by Frontier Molecular Orbital (FMO) theory.⁴⁷ It explains that when nucleophilic radicals are employed, the interaction between the singly occupied molecular orbital (SOMO) of the radical and the lowest unoccupied molecular orbital (LUMO) of the double bond is the most important, while with electrophilic radicals, the interaction between the SOMO of the radical and the highest occupied molecular orbital (HOMO) of the double bond is dominant (*vide infra*).

C. Types of radical chain reactions:

One reason why reactions employing radicals are so different from reactions employing polar species is that radicals possess the ability to react with themselves while polar species do not.⁴¹ Therefore, when planning a reaction which involves the generation of a radical, one must consider the rate of each step in the reaction.

Radical reactions are generally chain reactions which consist of three steps: initiation, propagation, and termination. The reason why chain reactions are employed is that they can maintain low concentrations of radicals throughout the reaction, which is desirable because this prevents the occurrence of non-productive side reactions.⁴⁸ In addition, chain reactions fulfill the requirements for radical reactions to be synthetically useful: the radicals must be generated site-selectively, and they must have a sufficient lifetime to react, but not live so long that unwanted side-reactions take place. Therefore,

radical reactions can only be successful if the rate of the desired reaction is faster than the rates of any undesired reactions.

1. Trialkyltin hydride-mediated reactions

The most popular way to conduct a radical addition reaction is by the trialkyltin hydride method.⁴¹ The mechanism is illustrated in Scheme 1.26.

Scheme 1.26: Mechanism for the trialkyltin hydride-mediated reaction

Initiation usually takes place when compounds containing weak bonds are homolytically cleaved by heat or irradiation. Some examples of frequently used initiators (I-I) are di-*t*-butyl peroxide, 2,2'-azobisisobutyronitrile (AIBN), and triethylborane in the presence of oxygen (Et₃B/O₂). In some cases, the initiator can be ultra-violet light. When

employing a chemical initiator, it is important to know its half-life temperature because if the reaction is run below that temperature, not enough radicals will be produced to maintain the chain. However if the temperature is too high, rapid decomposition of the initiator will disrupt the chain because $I\cdot$ will be consumed too fast in non-productive side reactions.⁴¹

The propagation steps maintain the chain reaction and produce most of the product molecules. Once the initiator decomposes (step a), it reacts with HSnBu_3 to produce $\cdot\text{SnBu}_3$ (step b). The tributyltin radical reacts with the alkyl halide ($\text{R}'\text{-X}$) to generate the site-selective radical, $\text{R}'\cdot$ (step c). Once $\text{R}'\cdot$ is generated, there are two different paths by which it can react: it can add to a double-bond, then be reduced by HSnBu_3 to regenerate $\cdot\text{SnBu}_3$ (steps d and e), or it can form the unwanted dimer (step f). If steps d and e occur, $\text{R}'\cdot$ can repeat step c, which is known as the chain transfer step. In order for the reaction to be successful, the rate of step c must be faster than step d, and the rate of step d must be faster than step e. In addition, steps b, d and e must be faster than steps f and g. The termination of a chain reaction involves the coupling of two radicals (steps f and g). These are unwanted side-reactions because they disrupt the efficiency of the chain.

An example of a tributyltin hydride-mediated addition reaction is given in Scheme 1.27. The addition of **67** to acrylonitrile produced **68** in 70% yield.⁴⁹

Scheme 1.27: An example of a tributyltin hydride-mediated reaction

In order to determine the limit for which addition will occur faster than dimerization Curran performed the derivation outlined in Scheme 1.28.⁴¹

Scheme 1.28: Rate limit for which addition will occur faster than dimerization

After the rate equations for dimerization and addition were determined (steps a and b), the rate equation for addition was set greater than the rate equation for dimerization and $[\text{R}\cdot]$

was canceled from each side (step c). By knowing that the diffusion controlled rate for dimerization of radicals, k_t , is $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ and by assuming that the typical radical concentration in a chain reaction is 10^{-8} M , the rate of formation of the adduct radical must be $>10^2 \text{ s}^{-1}$. Therefore, in order to successfully conduct a radical chain reaction the rate of addition must be greater than 10^2 s^{-1} .

2. Allyltributyltin-mediated reactions

An alternative way to mediate radical addition reactions is by the fragmentation of allyltributyltin.⁴⁸ The mechanism is outlined in Scheme 1.29.

Scheme 1.29: Mechanism for the allyltributyltin-mediated reaction

Some advantages of employing the fragmentation method over the tin hydride method is that the rate of formation of the tributyltin radical, the chain transfer agent, is not dependent on abstraction of the hydrogen atom, nor are the intermediate radicals susceptible to hydrogen atom abstraction before addition to the double bond occurs. For this reason, low concentrations of radicals are not necessary.

For this reaction to be successful, $R\cdot$ must add to the allyltributyltin before it disproportionates. An example of a successful fragmentation reaction is illustrated in Scheme 1.30. The allylcyclohexane, **71**, was produced in 88% yield.⁵⁰

Scheme 1.30: An example of an allyltributyltin-mediated reaction

3. The atom transfer reaction

Another type of radical chain addition reaction is the atom transfer reaction. This process is also known as the Kharasch addition.⁴⁸ The net reaction is the addition of $R-X$ across a double or triple bond. Scheme 1.31 illustrates the net reaction as well as the general mechanism.

Scheme 1.31: Net reaction and mechanism for the atom transfer reaction

Net Reaction:

X = H, halogen

R = carbon, heteroatom

Mechanism:

Initiation takes place when $\text{I}\cdot$ reacts with R-X to generate the radical, $\text{R}\cdot$ (step a). The chain is propagated by steps b and c; $\text{R}\cdot$ adds to the alkene, then the adduct radical reacts with another molecule of R-X to produce the desired product and another molecule of $\text{R}\cdot$. After this second molecule of $\text{R}\cdot$ is generated, it can repeat step b, the chain transfer step, or it could add to the double bond, telomerize (step d), or it could dimerize (step e).

The difference between an atom transfer reaction and a reaction mediated by tributyltin hydride is that site-selective generation of the radical and chain transfer are

combined into one step. For an atom transfer reaction to be successful, it is desirable that $R\cdot$ is more stable than the adduct radical, and it must be transferred more rapidly than it dimerizes.

An example of a halogen atom transfer reaction is illustrated in Scheme 1.32.⁵¹ Compound **74** was produced in 83% yield.

Scheme 1.32: An example of halogen atom transfer addition

D. Radical cyclization reactions

The utilization of radical reactions to accomplish intramolecular additions to double bonds is well documented.⁴³ These reactions are a valuable synthetic tool because cyclic compounds are produced with very good regio- and stereoselectivity in high yields. The factors which govern the addition of the radical to the double bond in cyclizations are very similar to those of intermolecular additions. However with radical cyclizations, one must also consider the factors which determine the regio- and stereochemistry of the products in order to be successful.

The activation entropies of intramolecular reactions are less negative than in intermolecular reactions.⁴² For example, the activation entropy of cyclization of the 5-hexenyl radical ($\Delta S^\ddagger$) is -11 e.u. compared to -25 e.u. for the intermolecular addition of

an ethyl radical to 1-hexene (Scheme 1.33).⁵² These entropic differences make radical cyclizations more facile than intermolecular additions.

Scheme 1.33: Activation entropies of inter- and intramolecular reactions

The rate constant for the cyclization of the 5-hexenyl radical is approximately $1 \times 10^6 \text{ s}^{-1}$ at 20°C ⁵³ and increases when the double bond is substituted with electron withdrawing groups.⁵⁴

1. Regioselectivity of radical cyclizations

When employing a radical cyclization reaction, there is a possibility of addition occurring at either end of the multiple bond. If addition occurs to the internal carbon of the multiple bond and excludes the terminal carbon from the cyclic framework, the addition is classified as *exo*. However, if the radical adds to the terminal carbon of the multiple bond so that both carbons are incorporated within the ring that is formed, the cyclization is classified as *endo* (Scheme 1.34).⁵⁵

Scheme 1.34: *Exo* vs. *endo* cyclization

5-hexenyl radical cyclization

6-heptenyl radical cyclization

It has been experimentally determined by Beckwith *et al.* that 5-hexenyl radicals cyclize to give the *exo* product in a ratio of 98 : 2 and that 6-heptenyl radicals cyclize to give the *exo* product in a ratio of 90 : 10 (Scheme 1.34).⁵⁶ Upon initial inspection, the outcome of these cyclizations seem unusual because the less stable, primary radical is favored. This suggests that cyclization occurs through an early transition state and the products are determined by kinetics rather than thermodynamics.⁴² This reactivity is typical for most radicals; however, in cases where the radical is substituted by electron withdrawing groups, the cyclization can become thermodynamically controlled to the point that cyclization is reversible (*vide infra*).^{38a}

In order to explain why cyclization occurs through an early transition state, Beckwith postulated that the regiochemistry of the cyclizations was highly dependent on

an effective overlap between the SOMO and LUMO (π^*) orbitals in the transition state, and that the 5-*exo* and 6-*exo* transition states could achieve this overlap with less steric strain compared to the 6-*endo* and 7-*endo* transition states. This postulate was supported by molecular mechanics calculations using the MM2 force-field.⁵⁷

2. Stereochemistry of radical cyclizations

Beckwith's studies of cyclization reactions of substituted 5-hexenyl radicals also led to a deeper understanding of the factors governing stereoselectivity.⁵⁷ From his empirical studies, Beckwith determined that the major product of cyclizations employing 1- and 3- substituted-5-hexenyl radicals was *cis*, while cyclizations employing 2- and 4- substituted-5-hexenyl radicals yielded the *trans* compound as the major product. In order to account for these stereochemical outcomes, Beckwith postulated that to accommodate the necessary tetrahedral approach of the radical to the alkene, the transition state of the 5-hexenyl radical must resemble the chair conformation of cyclohexane.⁵⁸ Once this was accomplished, the relationship of the groups in the final product could be predicted by placing the substituent in the pseudo-equatorial position (Figure 1.6).

Figure 1.6: Beckwith's model to predict stereochemistry

R = location of substituent in major diastereomer
r = location of substituent in minor diastereomer

Even though his molecular mechanics calculations qualitatively predicted the observed stereochemistry, Beckwith's calculations did not reproduce the observed product ratios. In a separate paper, Houk and Spellmeyer reported molecular mechanics calculations on the substituted-5-hexenyl system using modified MM2 parameters.⁵⁹ Their calculations did reproduce the observed *cis/trans* ratios accurately, and they concluded that those ratios could only be explained by considering the contributions from a transition state in the “boat” conformation in addition to the transition state in the “chair” conformation (Figure 1.7).

Figure 1.7: Transition state conformations of 5-hexenyl radicals

The relationship between the "chair" and "boat" transition states of the 5-hexenyl radical is very different to the relationship between chair and boat cyclohexane. For example, the "boat" transition state of the 5-hexenyl radical is only 1 kcal/mol higher in energy than the "chair" transition state, while boat cyclohexane is 7 kcal/mol higher than chair cyclohexane.⁶⁰ The reason why the "boat" and "chair" transition states are close in energy for the radical is that the "boat" transition state lacks the flagpole interactions present in boat cyclohexane. Also, because the C1 and C5 carbons are nearly sp^2 hybridized, the bonds between C1-C2 and C4-C5 are partially eclipsed. This makes the eclipsing energy of the "chair" and "boat" transition states very similar because they differ only by a 180° rotation of the C4-C5 bond (Figure 1.8).⁶⁰

Figure 1.8: Comparison of “chair” vs. “boat” transition states

The Beckwith-Houk model accurately predicts the *cis* isomer to be the major product in 1-substituted-5-hexenyl radicals. For example, cyclization of the 1-methyl-5-hexenyl radical gives **88** and **89** in a *cis/trans* ratio of 66 : 34 (Scheme 1.35).⁶⁰

Scheme 1.35: Cyclization of the 1-methyl-5-hexenyl radical, **87**

It is believed that the *cis* product is favored because steric interactions between the substituent at the 1-position and the terminal methylene group are relieved as a result of a very long bond forming between C1 and C5 in the transition state (Figure 1.9).⁵⁹

Figure 1.9: “Chair” transition state of the 1-methyl-5-hexenyl radical

Because the energy difference between the “chair” and “boat” transition states is only 1 kcal/mole, if the substituent at the 1-position is very large, the length of the bond forming between C1 and C5 cannot compensate for the steric demand of the substituent and the hexenyl radical has to proceed through the “chair-axial” or the “boat”-equatorial transition state so that the *trans* isomer becomes the major product. This has been observed with the 1-*tert*-butylhexenyl radical system.⁶¹ Cyclization produces *trans*-1-*tert*-butyl-2-methyl-cyclopentane, **93**, in 85% yield and *cis*-1-*tert*-butyl-2-methyl-cyclopentane, **92**, in 15% yield as the maximum selectivity between 60 and 80 °C.⁶⁰ Even though the *trans* isomer is the major product, it is surprising that the *cis* isomer is observed at all considering the size of the *tert*-butyl group (Scheme 1.36).

Scheme 1.36: Cyclization of the 1-*tert*-butyl-5-hexenyl radical, **91**

III. PROJECT GOALS

The exhibition of a small stereochemical preference in the product ratios of radical cyclization reactions indicates that there is a need to develop new methods which increase the regio- and stereochemical outcomes of cyclization. Many examples of attempted stereoselective radical cyclization exist in the literature and have been compiled in various reviews.⁴³ However, one method that has received almost no attention is the use of carbon-centered organometallic radicals. Therefore, the overall objective of this project was to study the reactivity of (propargyl) $\text{Co}_2(\text{CO})_6$ radicals by examining whether they would undergo intermolecular and/or intramolecular addition to electron rich and electron poor double bonds. Not only would these studies help to assess their reactivity, but they would also give insight into whether or not the radicals were stabilized by the $-\text{Co}_2(\text{CO})_6$ group. In addition, efforts would be directed at exploring ways in which these radicals could be employed in synthetically useful processes. The following chapters demonstrate our success and failures in achieving these goals.

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**THE STUDY OF ADDITION AND CYCLIZATION REACTIONS
INVOLVING (PROPARGYL)Co₂(CO)₆ RADICALS GENERATED BY
ZINC REDUCTION OF THE CATION COMPLEXES**

A. Initial Studies Involving (Propargyl)Co₂(CO)₆ Radicals

In 1994, Melikyan and Nicholas *et al.* implicated (propargyl)Co₂(CO)₆ radicals as intermediates in the Mn(OAc)₃-mediated oxidative cycloaddition reaction of complexed 1-alken-3-yne with β-dicarbonyl compounds (Scheme 2.1).³

Scheme 2.1: Mn(OAc)₃-mediated oxidative cycloaddition reactions

The mechanism is presumed to involve the selective addition of the β -dicarbonyl radical to the terminal carbon of the double bond to generate the (propargyl) $\text{Co}_2(\text{CO})_6$ radical which undergoes facile oxidation to the cation, and then cyclizes to give the substituted dihydrofuran. The reactions occur with moderate yields and exhibit a preferential *cis* stereoselectivity between the R^2 and R^3 groups (Scheme 2.1). The implication that (propargyl) $\text{Co}_2(\text{CO})_6$ radicals were generated during the $\text{Mn}(\text{OAc})_3$ -mediated reaction suggested that chemistry could be developed which utilized (propargyl) $\text{Co}_2(\text{CO})_6$ radicals in synthetically useful processes. Therefore, studies were undertaken by Nicholas and Melikyan to explore the synthesis and reactivity of these species.

In their initial study, (propargyl) $\text{Co}_2(\text{CO})_6$ cations, **5**, were treated with zinc, presumably forming a radical intermediate, **6**, which underwent dimerization to yield the *d,l* (**7a**) and *meso* (**7b**) dimer isomers in 76% yield with a *d,l/meso* ratio of 75 : 25.⁴ The radical intermediate also underwent hydrogen atom abstraction to produce the reduced complex, **8**, in 3.5% yield (Scheme 2.2).

Scheme 2.2: Production of **7a**, **7b** and **8** by reduction of **5** with zinc

The success of the dimerization reaction prompted efforts to determine the scope of this methodology. This was accomplished by comparing dimerization reactions of primary, secondary, and tertiary radicals. (Scheme 2.3).⁴

Scheme 2.3: Exploration of the scope of dimerization of **9a-c**

The reaction involving the primary radical (generated from **9a**) produced the dimer, **10a**, in 21% yield along with 3.5% of the reduced complex, **11a**. The secondary radical (generated from **9b**) produced the *d,l* and *meso* dimers in 21% yield with a ratio of 72 : 28. Coupling of the tertiary radical was unsuccessful and yielded only the reduced complex, **11c**, in 19% yield.⁴ Thus, the presence of the $-\text{Co}_2(\text{CO})_6$ group enforced a regiospecific reaction at the propargylic position upon reduction of the cation. By comparison, reactions involving the reduction of uncomplexed propargylic substrates produce regioisomeric mixtures.⁵ Also, the diastereoselectivity observed in the reactions employing **9b** is in accord with findings that radicals substituted by sterically demanding groups form dimers with high stereoselectivity.⁶

Because the results of the intermolecular reactions were so promising, reactions were investigated where coupling took place intramolecularly to form 10-membered rings (Scheme 2.4).

Scheme 2.4: Intramolecular coupling of **12** to form 10-membered rings

In general, the synthesis of larger rings is problematic due to the entropic difficulty associated with bringing the two reacting centers close enough to form a bond.⁷ However, for the reactions involving the (propargyl)Co₂(CO)₆ radicals, it was postulated that the bent geometry of the complexed triple bonds would help in overcoming entropy by placing the two radical centers in close proximity. After the alcohols were synthesized, the bis-cations were generated and treated with excess zinc in methylene chloride. The reaction produced the 3,4-diphenyl-1,5-cyclodecadiyne, **14**, in 51% yield with a *d,l/meso* ratio of 90 : 10. This method of preparation for 1,5-cyclodecadiynes improved upon previous synthetic routes in both the number of steps and the overall yield.⁸

Moreover, the intramolecular radical coupling reactions were further explored and led to the synthesis of novel cycloocta-1,5-diynes and cyclooct-3-ene-1,5-diynes.⁹ Once again, the strategy involved taking advantage of the bent geometry of the complexed starting materials to bring the reacting centers in close proximity.

Scheme 2.5: Synthesis of 3,4-diphenyl-cycloocta-1,5-diyne, **16**

The cyclization of **15** produced the *d,l* isomer of **16** in 48% yield and the *meso* isomer of **16** in 0.6% yield. Analysis of the X-ray structure of the *d,l* isomer showed that the bond angles for the sp^3 -hybridized carbons in the ring ranged from 109-115° which indicated a strain-free molecule.⁹ Another remarkable feature of this reaction was the diastereoselectivity; there is virtually complete production of the *d,l* isomer, which is in agreement with conformational analysis and molecular mechanics calculations predictions that the transition state for the cyclization of the *meso* isomer is higher in energy.⁹

The culmination of this work was the synthesis of the first cyclooct-3-ene-1,5-diyne derivative, **19** (Scheme 2.6). Complexation of the starting diol produced two diastereomers, **18a** and **18b**, which were separated by flash chromatography. Both isomers reacted (protonation/reduction) to produce a single isomer of **19** ranging from 38-42% yield and a diastereomeric excess (de) >99%. Analysis of the X-ray structure of **19** revealed that the bond angles and lengths of the sp^2 and sp^3 hybridized carbons of the ring did not deviate much from ideality. Therefore, there was very little strain energy in the molecule. A difficulty encountered in this series of reactions was that **19** could not be demetallated so as to provide the free ene-diyne.⁹

Scheme 2.6: Synthesis of 7,8-diphenyl-cyclooct-3-ene-1,5-diyne, 19

B. Results

While the previous studies had established that the (propargyl) $\text{Co}_2(\text{CO})_6$ radicals could be generated from the cations and that they exhibited extraordinary stereoselectivity in dimerization reactions, it was unknown whether these radicals could be employed in other reactions such as radical additions or cyclizations. If so, then such reactions could have the potential to be developed into synthetically useful processes. For this reason, studies were undertaken which would give more insight into the electronic character of the radicals. The initial strategy was to trap the radicals intermolecularly with electron-deficient and/or electron-rich double bonds. Arbitrarily, efforts initially focused on trapping the radicals with electron deficient double bonds. Studies were performed on compound 5 because it had previously been used in the dimerization studies. Methyl

acrylate was used as the radical trap and THF as the hydrogen atom source to terminate the reactions (Scheme 2.7).

Scheme 2.7: Initial conditions for attempted synthesis of **21**

In the first reaction, the starting material : granular zinc : methyl acrylate : THF ratio was 1 : 1 : 5 : 20 and the concentration of **5** was 0.05 M. The reaction stirred at 30 °C for 30 minutes. Analysis of the reaction mixture by TLC showed that no reaction was taking place. The flask was then warmed to room temperature and TLC indicated that the starting material was being consumed. When the reaction was complete, the only products that had formed were the *d,l* and *meso* dimers, **7a** and **7b**, as well as the reduced complex **8** (Scheme 2.8).

Scheme 2.8: Products obtained from the reduction of **5**

In general, most of the reactions performed in the intermolecular addition study were analyzed only by TLC against previously synthesized samples of **7a**, **7b**, and **8** unless a new compound was observed.

In order to try to increase the rate of addition relative to dimerization, the ratio of starting material : zinc : methyl acrylate : THF was varied to 1 : 1 : 20 : 80 with a 0.01 M concentration of **5**, and 1 : 1 : 50 : 500 with a 0.007 M concentration of **5**. However, analysis of the reactions by TLC indicated that the dimers and the reduced complex were the only compounds being produced.

Other modifications to the procedure, such as adding the complexed salt to the reaction mixture very slowly using a dropping funnel, also produced the dimers and the reduced complex as the only products.

Because our observations indicated that dimerization was proceeding faster than addition, it was postulated that addition might be observed if a more electrophilic radical

trap was employed. Therefore, a reaction was attempted using diethylmethylene malonate, **22**, as the acceptor (Scheme 2.9).

Scheme 2.9: Reaction employing a more reactive radical trap, **22**

The ratio of starting material : zinc dust : diethylmethylene malonate : THF was 1 : 1 : 17 : 80, and the concentration of **5** was 0.01 M. The reaction stirred at room temperature until the starting material was consumed. Analysis by TLC indicated that once again, only the *d,l* and *meso* dimers, as well as the reduced complex were formed. No evidence for the formation of the addition product, **23**, was observed.

Because the attempted additions employing the secondary radical were unsuccessful, it was postulated the carbon bearing the unpaired electron was too sterically crowded to undergo addition. For this reason, an experiment was performed in which a primary cation complex, **25**, was employed (Scheme 2.10).

Scheme 2.10: Reaction employing the primary radical, **26**

The ratio of starting material : zinc dust : methyl acrylate : THF was 1 : 1 : 20 : 80, and the concentration of **24** was 0.01 M. The reaction mixture stirred for 1 hour at -30 °C and was then warmed to room temperature. After purification by PTLC, two fractions were isolated, and a proton NMR spectrum was taken of each; however, neither contained the desired addition product nor could the structures be identified.

The unsuccessful attempts to trap the radicals with electron deficient double bonds prompted us to think of other ways to solve this problem. The most logical method would have been to trap the radicals with electron rich double bonds; however, a major concern of this method was that if the double bonds were too nucleophilic, they would add to the cation complexes before the radicals could be generated. For this reason, no attempts to trap the radical with electron rich double bonds were made.

C. Discussion

The studies involving the dimerization of (propargyl)Co₂(CO)₆ radicals were of significance because the observed *d, l/meso* ratios were among the highest reported for any radical system.⁴ Even though there were examples in the literature where carbon-centered organometallic radicals had undergone dimerization,¹⁰ only three of those systems were tested to see if the radicals could be trapped by intermolecular addition to a double bond.¹¹ As very little was known about the reactivity of the (propargyl)Co₂(CO)₆ radicals, it was postulated that the exploration of intermolecular addition to double bonds could lead to a novel, synthetically useful, stereoselective addition reaction. Unfortunately, the failure of these systems to undergo intermolecular addition was not anticipated.

According to our results, the rate of dimerization is extremely fast compared to the rate of addition. This was evident because most of the reactions were run in the presence of a large excess of the trapping agent in very dilute solution, and in all of these cases, only dimerization and hydrogen atom abstraction were observed. These findings were peculiar because many methods of trapping alkyl radicals intermolecularly with double bonds have been developed.¹² Therefore, it was rationalized that failure to trap the (propargyl)Co₂(CO)₆ radicals using similar methods must be due to the component of molecule that is different, i.e. the -Co₂(CO)₆ group.

The ability of the -Co₂(CO)₆ group to stabilize the positive charge of (propargyl)Co₂(CO)₆ cations is well documented.¹³ However, at the outset of this study, it was unknown if the -Co₂(CO)₆ group would affect the radical in the same way. From our observations, it appeared that the -Co₂(CO)₆ group was stabilizing the radicals similar

to the way it stabilized the cations, and at the conclusion of this study, it was postulated that failure to observe addition was due to the stabilization of the radical by the $-\text{Co}_2(\text{CO})_6$ group, which lowered its reactivity so that addition to the double bond did not occur.

In general, radicals that are stabilized by electron withdrawing groups react very slowly with electron deficient double bonds. For example, k_{rel} for the addition of **28** to acrylonitrile, **29a**, is more than one thousand times slower than addition to propene, **29b**, ($k_{\text{rel}} = 1$) and 16,000 times slower than addition to α -methylstyrene, **29c**, ($k_{\text{rel}} = 16$) (Scheme 2.11).⁷

Scheme 2.11: Addition of **28** to **29a-c**

Even though a facile addition took place between **28** and α -methylstyrene, **29c**, an electron rich double bond, a direct comparison with (propargyl) $\text{Co}_2(\text{CO})_6$ radicals could not be made because their addition to electron rich double bonds had not been studied.

However, it is possible that the (propargyl) $\text{Co}_2(\text{CO})_6$ radicals are unreactive towards electron rich double bonds as well.

Moreover, our observations can be explained by FMO theory.¹⁴ In a reaction between a radical and a double bond, the new sigma bond that forms is the result of effective overlap between the SOMO of the radical and the LUMO of the double bond (Scheme 2.12).¹⁵

Scheme 2.12: Diagram of the SOMO-LUMO interaction

The rate of the reaction depends on the energy difference of the orbitals, so that if the difference is small, the reaction is faster because there is a large stabilization of the transition state. For this reason, effects which bring the orbitals closer in energy, such as lowering the LUMO of the double bond by substituting it with electron withdrawing groups, will increase the rate. However, when the radical is stabilized to a large extent, the most important orbital interaction is the one between the SOMO and HOMO orbitals,

and effective trapping can only be accomplished by addition to an electron rich double bond (Scheme 2.13).

Scheme 2.13: Diagram for the SOMO-HOMO interaction

As only electron-deficient double bonds were employed in our studies, the observed formation of the dimers and hydrogen atom abstraction products can be understood: if the $-\text{Co}_2(\text{CO})_6$ group stabilized the radical to make the SOMO-HOMO interaction of greatest importance, then no trapping of the radical should be observed with an electron deficient double bond. Therefore, because the development of synthetically useful reactions involving intermolecular addition of carbon-centered organometallic radicals appeared to be unfeasible using this methodology, we decided to explore other types of radical addition reactions.

II. INTRAMOLECULAR CYCLIZATION STUDIES

A. Synthesis of Starting Materials

As previously stated, radical cyclizations are more facile than intermolecular additions because the entropy for cyclization is less negative than the entropy for addition. For this reason, it was believed that the best way to modify the present study was to design a system in which addition of the (propargyl) $\text{Co}_2(\text{CO})_6$ radicals could take place intramolecularly. It was also decided that the reactions should employ the 1-alkynyl-5-hexenyl system because it is the most common system that has been studied in radical cyclizations. Therefore, the focus of the project changed, and efforts centered on developing methods to synthesize the starting materials.

In designing the synthesis of the requisite starting materials, a retrosynthetic analysis was performed to determine the most efficient route. Deliberation over various options led to that outlined in Scheme 2.14.

Scheme 2.14: Retrosynthetic analysis of the starting materials

The initial strategy was to treat glutaraldehyde with phenylacetylide, then trap the resulting alkoxide anion with trimethylsilyl chloride (34 to 33). This would leave the second aldehyde available to react by Knoevenagel or Wittig reaction to generate various substituted double bonds (33 to 32). Once the double bonds were in place, the alcohol could be deprotected and the triple bond could be complexed with $\text{Co}_2(\text{CO})_8$ to give the starting materials (32 to 31).

In the first attempt to synthesize 33, phenylacetylide was prepared by treatment of phenyl acetylene with butyl lithium at $-78\text{ }^\circ\text{C}$. It was then added dropwise to a solution of glutaraldehyde in THF that had also been cooled to $-78\text{ }^\circ\text{C}$. Once all of the phenylacetylide was added, the reaction stirred at $-78\text{ }^\circ\text{C}$ for 2 hours, then TMSCl was added dropwise. The reaction was monitored by TLC until the starting material was consumed. After work-up and purification by flash chromatography, three fractions were isolated. Analysis of the proton NMR spectrum of the first fraction (least polar compound) indicated that it was trimethylsilyl phenyl acetylene. Analysis of the NMR spectrum taken for the second fraction was slightly more difficult because there appeared to be a mixture of compounds.

At the outset of this reaction, it was unknown to us that when a nucleophile, such as phenylacetylide, attacks one carbonyl of glutaraldehyde, the resulting alkoxide anion will add intramolecularly to the second carbonyl to give a hemiacetal after protonation (Scheme 2.15).

Scheme 2.15: Generation of the hemiacetal, **37**

Therefore, structures were not assigned to the compounds until *a posteriori* analysis revealed that this fraction contained cyclic structures which were diastereomers of **38**. These compounds are produced from the reaction of **36** with TMSCl (Scheme 2.16).

Scheme 2.16: Generation of the TMS-protected hemiacetal, **38a,b**

Failure to recognize the formation of **38** prompted another attempt to synthesize **33**. In this reaction the phenylacetylide and the glutaraldehyde stirred for 6 hours before

the TMSCl was added. After addition of TMSCl, the reaction stirred another 2 hours. Work-up and purification by flash chromatography gave four fractions; the major products, which were diastereomers of each other, were located in the first two fractions. Initially, it was concluded that they were diastereomers of the cyclic, TMS-protected hemiacetal, **38**, but *a posteriori* analysis of the data revealed an error. The notable resonances of the proton NMR spectrum of the first fraction were a triplet at 4.57 ppm ($\text{CH}_2\text{CH}\underline{\text{O}}\text{H}$ and $\text{CH}_2\text{CH}\underline{\text{O}}\text{TMS}$), and a singlet at 0.19 ppm ($\text{Si}(\text{CH}_3)_3$). The proton NMR spectrum of the second fraction looked very similar to the first except there were two triplets at 4.62 ppm ($\text{CH}_2\text{CH}\underline{\text{O}}\text{H}$ and $\text{CH}_2\text{CH}\underline{\text{O}}\text{TMS}$) and 4.57 ppm ($\text{CH}_2\text{CH}\underline{\text{O}}\text{H}$ and $\text{CH}_2\text{CH}\underline{\text{O}}\text{TMS}$). The spectral data were found to be more consistent with uncyclized propargylic alcohols rather than the initially proposed cyclic hemiacetal. Therefore, the compounds in the first two fractions were assigned as diastereomers of **41** (Scheme 2.17).

Scheme 2.17: Mechanistic rationale for the production of **41**

The observed products can be rationalized according to the mechanism outlined in Scheme 2.17. After addition of the first equivalent of phenylacetylide anion, the alkoxide anion is trapped by TMSCl . Addition of a second equivalent of phenylacetylide to the remaining carbonyl, followed by protonation gives the monoprotected propargylic diol, **41**.

While it was initially incorrectly concluded that the compounds in the first two fractions were diastereomers of the cyclic, TMS-protected hemiacetal, **38**, the supposition that the alkoxide could undergo intramolecular cyclization was correct. Based on the belief that a cyclic product had been obtained, it was surmised that the cyclic, unprotected

hemiacetal was as valuable as the original synthetic target because it represented both a masked propargylic alcohol and a masked aldehyde, which could be revealed by treating the hemiacetal with an equivalent of base. For this reason, the cyclic hemiacetal **37** became the new target for synthesis. It was produced in 47% yield as a 2 : 1 mixture of diastereomers according to the above procedure except that the addition of TMSCl was omitted (Scheme 2.18).

Scheme 2.18: Synthesis of **37a,b**

The distinguishing resonances in the proton NMR spectrum of **37a,b** were a doublet of doublets at 5.35 ppm ($\text{CH}_2\text{CH}(\text{OH})$), a multiplet from 5.02-4.99 ppm ($\text{CH}_2\text{CH}(\text{CCPh})$, proton), and a doublet at 2.55 ppm (OH) which belonged to the major isomer, as well as a doublet of doublets at 4.79 ppm ($\text{CH}_2\text{CH}(\text{OH})$), a doublet of doublets at 4.46 ppm ($\text{CH}_2\text{CH}(\text{CCPh})$), and a doublet at 2.86 ppm (OH) which belonged to the minor isomer.

After the successful preparation of **37a,b**, efforts focused on introducing the substituted double bond. It was arbitrarily decided to study the cyclization of a compound containing a highly electron-deficient double bond, **43**. Preparation of this compound could be accomplished by a Knoevenagel reaction between **37a,b** and diethyl malonate (Scheme 2.19).

Scheme 2.19: Proposed synthesis of **43** by the Knoevenagel reaction

Initially, Falsone's method using TiCl_4 and pyridine in THF was employed.¹⁶ However, no reaction was observed. Modifications to the procedure, which included running the reaction without TiCl_4 or using undecanoic acid/4-pyrrolidinopyridine, failed as well. When the reaction was run with TiCl_4 and pyridine in dioxane, two compounds were isolated. The major product of the reaction was compound **44**, where the acetal had undergone elimination (Scheme 2.20).

Scheme 2.20: Products obtained from the addition of **42** to **37a,b**

However, determining the structure of the minor product was more complicated; it contained a mixture of two diastereomers. The most distinct resonances in the proton NMR spectrum were a broad doublet at 4.94 ppm ($\text{CH}_2\text{CH}(\text{CCPh})$), a double doublet of

doublets at 4.59 ppm ($\text{CH}_2\text{CHCH}(\text{CO}_2\text{Et})_2$), a doublet of doublets at 4.34 ppm ($\text{CH}_2\text{CH}(\text{CCPh})$), two overlapping doublet of quartets between 4.29–4.09 ppm (OCH_2CH_3), a double doublet of doublets at 4.03 ppm ($\text{CH}_2\text{CHCH}(\text{CO}_2\text{Et})_2$), a doublet at 3.51 ppm ($\text{CH}(\text{CO}_2\text{Et})_2$), and a doublet at 3.44 ppm ($\text{CH}(\text{CO}_2\text{Et})_2$).

While it was evident that the diethyl malonate had been incorporated into the molecule, there was not a peak for a vinyl proton. Therefore, it was initially assumed that **43** had not been obtained. Fortunately, closer inspection of the proton NMR spectrum revealed that **45a,b** was the desired product masked as the cyclic compound (Scheme 2.20). Its formation can be explained by realizing that **43** contains a highly electron deficient α,β -unsaturated ester. Therefore, when the alkoxide is generated, it undergoes an extremely facile Michael addition as soon as the double bond is formed.

Even though **45a,b** was a cyclic compound, it was surmised that it could be employed to perform the radical cyclization reactions. Therefore, efforts to optimize its formation continued. The conditions which proved to be successful involved running the reaction in a NaOEt/EtOH medium. The optimum yield of 46% was obtained by having a 1 : 3 : 1.5 ratio of hemiacetal : diethylmalonate : sodium. Once **45a,b** was isolated in pure form, it was complexed according to the procedure outlined by Nicholas¹⁷ in 51% yield (Scheme 2.21).

Scheme 2.21: Complexation of **45a,b**

The presence of the $-\text{Co}_2(\text{CO})_6$ group in the molecule had a dramatic effect on only one of the isomers. The doublet at 3.44 ppm ($\text{CH}(\text{CO}_2\text{Et})_2$) in the proton NMR spectrum of the uncomplexed mixture shifted downfield and overlapped with the multiplet between 4.24-3.96 ppm, and the double doublet of doublets at 4.03 ppm ($\text{CH}_2\text{CHCH}(\text{CO}_2\text{Et})_2$) in the uncomplexed mixture shifted downfield to 4.31 ppm. The peaks of the other complexed isomer were very similar to the peaks of its uncomplexed counterpart.

B. Cyclization studies

After **46a,b** was synthesized, it was possible to study the addition of (propargyl) $\text{Co}_2(\text{CO})_6$ radicals to double bonds. Earlier work in the laboratory had demonstrated that these radicals could be generated by reduction with zinc.⁴ Therefore, the same methodology was applied to this system (Scheme 2.22).

Scheme 2.22: Generation of **48** by reduction of **47** with zinc

In the first attempt, compound **46a,b** was treated with 3.2 equivalents of propionic anhydride, and the mixture was cooled to $-45\text{ }^\circ\text{C}$. At this time, 3.2 equivalents of $\text{HBF}_4 \cdot \text{OEt}_2$ were added dropwise and the reaction mixture stirred for 45 minutes. The reaction mixture was washed with anhydrous diethyl ether in order to precipitate the salt. It was dissolved in methylene chloride, then one equivalent of zinc was added. When the reaction was complete, purification was carried out by flash chromatography. One compound, which had a mass of m/z 612 (12 eV DIP), was isolated. The resonances in the proton NMR spectrum that were most significant for structure determination were the doublet of doublets at 6.98 ppm ($\text{CH}_2\text{CH}(\text{CO}_2\text{Et})_2$), the doublet at 6.77 ppm ($\text{CHCH}(\text{CCPh})$), and the doublet of triplets at 6.17 ppm (CH_2CHCH). Based on the spectral data, the structure was assigned as **49** (Scheme 2.23).

Scheme 2.23: Observed products of the cyclization reactions

In the second attempt at cyclization, the conditions were the same as in the previous reaction except that the concentration of **46a,b** was decreased from 0.03 M to 0.01 M. After purification by flash chromatography, two products were isolated. Both compounds showed a molecular ion of m/z 614 (70 eV DIP), but the proton NMR spectra were very different. In the spectrum of the first compound the significant resonances were the doublet at 3.63 ppm ($\text{CHCH}(\text{CO}_2\text{Et})_2$), a quartet at 3.56 ppm ($\text{CHCH}(\text{CCPh})$), and a series of multiplets ranging from 2.54-1.58 ppm ($\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}$). The manner in which the methylene protons were spread out was indicative of a cyclic compound. For this reason the structure was assigned as **51** (Scheme 2.23).

In order to confirm the structure, a 1-D proton decoupling NMR experiment was performed (Table 2.1). Once the chemical shifts were assigned to each labeled proton, it was possible to assign the carbon atom to which each proton was attached. After all the

assignments were made, the data confirmed the structure of **51**, but the stereochemistry was still unknown.

Table 2.1: 1-D proton decoupling NMR experiment of **51**

Proton	Chemical Shift Assignment (ppm)	Observed decoupling (ppm)
H ^A	3.63	2.54-2.45
H ^B	2.54-2.45	3.63, 3.56, 2.12-2.00, 1.95-1.84
H ^C	3.56	2.54-2.45, 2.31-2.20, 1.67-1.58
H ^{D1}	2.31-2.20	3.56, 1.67-1.58, 1.80-1.69
H ^{D2}	1.67-1.58	3.56, 2.31-2.20, 1.80-1.69
H ^{E1}	1.80-1.69	Could Not Determine
H ^{E2}	1.80-1.69	Could Not Determine
H ^{F1}	2.12-2.00	2.54-2.45, 1.95-1.84, 1.80-1.69
H ^{F2}	1.95-1.84	2.54-2.45, 1.95-1.84, 1.80-1.69

Even though the radical cyclization was successful, the yield was only 10%. Efforts to reproduce and improve this result were troublesome because **47** was

surprisingly soluble in diethyl ether, the solvent used to precipitate it. This resulted in a huge loss of material during the course of the reaction. Efforts were made to circumvent this problem by precipitating **47** using a 1 : 1 solution of pentane : diethyl ether, and 5% solution of diethyl ether in pentane. Unfortunately, it was soluble in both cases.

An attempt was also made to regenerate **47** from the compound that had dissolved in the diethyl ether during precipitation. This red oil, which was assumed to be starting material, was treated with 4 equivalents of $\text{HBF}_4 \cdot \text{OEt}_2$ and 4 equivalents of propionic anhydride. The mixture was not rinsed with any solvent to try to precipitate **47**. Instead, methylene chloride was added directly to the flask, followed by two equivalents of zinc. Two products were isolated from this reaction: the cyclic product, **51** (7%) and the reduced product **50** (2%) (Scheme 2.23).

Because the above reaction was successful in producing the cyclic product without rinsing the reaction mixture to precipitate **47**, a reaction was attempted in which **47** was only generated once and was not rinsed before the reaction mixture was dissolved in methylene chloride and treated with zinc. Purification yielded the reduced complex, **50** as the major product in 15% yield. Compound **51** was not observed.

In order to simplify NMR spectra of the reaction products, the starting substrate was changed to the dimethyl malonate complex, **54a,b**. It was synthesized from **53a,b**, using the procedure outlined by Nicholas *et al.*¹⁷ No change in reactivity was foreseen (Scheme 2.24).

Scheme 2.24: Synthesis of complex **54a,b**

In the first reaction employing **54a,b**, **55** was not rinsed before it was dissolved in methylene chloride (Scheme 2.25). The reaction stirred at room temperature for 8 hours. Purification was carried out by PTLC, and two fractions were isolated. Each fraction contained a mixture of products. According to the 12 eV DIP mass spectrum, the product in the first fraction had a molecular ion at m/z 586 which is consistent with the acyclic, reduced complex, **50**. Beyond that, structures could not be assigned for any of the other compounds.

Due to the failure of the reaction to produce the cyclic product with this new starting compound, a reaction was run in which **55** was rinsed with diethyl ether. Unfortunately, it was still soluble. What remained in the flask after washing was dissolved in methylene chloride and was treated with one equivalent of zinc. Purification by PTLC gave one compound which was a single diastereomer of the starting material.

The procedure was further modified by treating the starting material with six equivalents each of propionic anhydride and $\text{HBF}_4 \cdot \text{OEt}_2$. While the reaction mixture was stirring, the flask was allowed to warm to room temperature, then was cooled back down to $-40\text{ }^\circ\text{C}$. The reaction mixture turned dark brown. When it was rinsed with diethyl ether a dark brown, insoluble oil formed. This oil was dissolved in methylene chloride, and treated with one equivalent of zinc. The reaction stirred at room temperature for 8 hours. Purification by PTLC gave two compounds. The proton NMR spectrum (taken in CDCl_3) for the first compound looked very similar to the cyclic compound obtained from the reaction employing the diethylmalonate analog, **51**. A doublet overlapped with one of the resonances for the methoxy methyl group at 3.65 ppm ($\text{CHCH}(\text{CO}_2\text{CH}_3)_2$ and CO_2CH_3). Also, there was a quartet at 3.52 ppm ($\text{CH}_2\text{CH}(\text{CCPh})\text{CH}$), and a series of multiplets from 2.54–1.58 ppm. For this reason, the compound was assigned structure **57a** (Scheme 2.25).

Scheme 2.25: Cyclization reactions starting from **54a,b**

Further confirmation of the structure was obtained by a 1-D proton decoupling NMR experiment performed in C_6D_6 (Table 2.2). The data supported the assigned structure.

Table 2.2: 1-D proton decoupling NMR experiment of **57a**

Proton	Chemical Shift Assignment (ppm)	Observed Decoupling (ppm)
H ^A	3.89	3.69
H ^B	2.80-2.70	3.89, 3.69, 2.19-1.97
H ^C	3.69	2.80-2.70, 2.19-1.97, 1.63-1.52
H ^{D1}	2.19-1.97	3.69, 1.63-1.52
H ^{D2}	1.63-1.52	3.69, 1.63-1.52
H ^{E1}	1.63-1.52	2.19-1.97, 1.63-1.52
H ^{E2}	1.63-1.52	2.19-1.97, 1.63-1.52
H ^{F1}	2.19-1.97	2.80-2.70, 1.63-1.52
H ^{F2}	2.19-1.97	2.80-2.70, 1.63-1.52

In order to determine the stereochemistry of the two substituents, an NOE experiment was performed in C₆D₆. Irradiation of the chemical shift assigned to H^C did not produce an enhancement of the signal between 2.80-2.70 ppm (H^B). Conversely, an enhancement was not seen at 3.69 ppm (H^C) when the multiplet between 2.80-2.70 ppm

was irradiated. Even though this evidence is not conclusive, the stereochemistry of **57a** was tentatively assigned as *trans*.

Assignment of a structure to the second compound was more difficult. The proton NMR spectrum for this compound was similar to the spectrum of the first compound. There was a doublet at 3.49 ppm, and a series of multiplets from 2.74-1.60 ppm. The chemical shifts of the methylene protons in this spectrum were not as spread out as the chemical shifts of the methylene protons in the first spectrum. However, the pattern of the resonances for the methylene protons suggested that this compound was cyclic as well. Comparison of the mass spectra for both compounds (12 eV DIP) revealed that they exhibited similar fragmentation patterns. Neither a decoupling study, nor an NOE study was performed on the second compound; however it was assigned to be the *cis* isomer, **57b**. The combined yield of the reaction was 13% (8% *trans*, 5% *cis*).

While the cyclic compounds had been successfully generated, the yield of the reaction was far from synthetically useful. Efforts were made to improve the yield. For example, the salt was rinsed at -78 °C in order to try to prevent it from dissolving in diethyl ether. From this reaction, the *trans* compound was isolated in only 7% yield, and the *cis* isomer was isolated in 1% yield.

In another attempt the procedure was modified by employing trifluoroacetic anhydride. As the starting material was a cyclic ether, the mechanism required that the oxygen react with the anhydride so the ring could open to form the double bond, then the salt could be generated (Scheme 2.26). If the coordination between the propionic anhydride and the oxygen was so weak that the starting material was not being completely converted to the ring-opened cation, **60**, then perhaps an anhydride which formed a

stronger bond to the oxygen would improve the yield. Therefore, **54a,b** was treated with 2 equivalents of trifluoroacetic anhydride and 2 equivalents of $\text{HBF}_4 \cdot \text{OEt}_2$. After stirring for 15 minutes at $-40\text{ }^\circ\text{C}$, the contents in the flask was rinsed with Et_2O . Unfortunately, the salt was soluble and we were unable to attempt a cyclization reaction.

Scheme 2.26: Mechanism for formation of **60** from **54a,b**

Finally, an attempt was made to generate the cation *in situ*. The starting material was dissolved in methylene chloride, then 1.2 equivalents of zinc were added. The reaction mixture was cooled to $-78\text{ }^\circ\text{C}$, then three equivalents of $\text{HBF}_4 \cdot \text{OEt}_2$ were added. The reaction warmed to room temperature and stirred over night. None of the desired product was isolated.

Because attempts to improve the reaction yield failed, it was decided that a different approach to generating the cations needed to be developed. After analyzing our results, we decided that working with a cyclic starting material was detrimental to the reaction yield. For this reason, efforts were made to synthesize an acyclic starting material from which the radical could be generated. The target compound became the ring opened, protected alcohol, **61** (Scheme 2.27).

Scheme 2.27: Synthesis of **61**

It was prepared by dissolving **54a,b** in acetic anhydride, cooling the solution to $-40\text{ }^{\circ}\text{C}$, then adding three equivalents of triflic acid. When the reaction was complete, the mixture was purified by flash chromatography. Two compounds were isolated. A structure could not be determined for the first compound. However, analysis of the second fraction indicated that it contained **61**. The notable resonances in the proton NMR spectrum were a doublet of doublets at 6.94 ppm ($\text{CH}_2\text{CHC}(\text{CO}_2\text{CH}_3)_2$), a doublet of doublets at 6.39 ppm ($\text{CH}_2\text{CH}(\text{OAc})$), a doublet of triplets at 2.35 ppm ($\text{CH}_2\text{CH}_2\text{CH}$), and a singlet at 2.12 ppm (CO_2CH_3). In addition, the ^{13}C NMR spectrum contained three peaks at 170.4, 165.1 and 164.1 ppm. These were assigned to the carbonyl carbons. Because **61** was

unstable to silica gel, it was immediately used in the cyclization reactions without purification.

In the first cyclization reaction employing **61**, the salt was generated by treatment with three equivalents of both propionic anhydride and $\text{HBF}_4 \cdot \text{OEt}_2$, then was dissolved in methylene chloride and treated with one equivalent of zinc. After purification by flash chromatography, two fractions were isolated. According to the proton NMR spectrum, the first fraction contained the cyclic, *trans* isomer, **57a**, in 19% yield. The proton spectrum of the second fraction showed that it contained the *cis* isomer, and an unidentified compound.

Even though cyclization was observed, the yield of the reaction was still low. In a final effort to increase the yield, **61** was converted to the cation complex, then the radical was generated by the addition of Cp_2Co . (Scheme 2.28).

Scheme 2.28: Cyclization of **61** employing Cp_2Co

The salt was isolated in 48% yield. It was then dissolved in 20 mL of methylene chloride and cooled to -78°C before adding 1.1 equivalents of Cp_2Co . The reaction stirred at -78°C until it was complete. Purification by PTLC gave four fractions. The compound in the

first fraction was determined to be the cyclic *trans* isomer. It was obtained in 8% yield. The structure of the compound in the second fraction could not be determined. The third fraction contained the *cis* isomer and an unidentified compound in 2% yield, while the fourth fraction contained the product resulting from elimination of HOAc in 1% yield.

Even though the reaction employing **61** as the starting material was not as successful as was hoped, it did provide an alternative idea: if the activity of the double bond was decreased by eliminating one of the methyl esters, then an acyclic starting material would be obtained. In turn, this could simplify the mechanism of generating the salt and improve the reaction yield. For this reason, it was decided to try a new substrate, the monoester analog, **63** (Scheme 2.29).

Scheme 2.29: Synthesis of **63**

Compound **62a,b**, was prepared by treating **37a,b** with 2 equivalents of methyl (triphenylphosphoranylidene) acetate. Both the *cis* and *trans* isomers, **62a,b**, were

produced in an overall yield of 56%. As expected, the products were not cyclic. They were separated by flash chromatography. The *trans* isomer was the major product. Some distinguishing resonances in the proton NMR spectrum were a doublet of triplets at 6.97 ppm (CH_2CHCH , $J = 15.6, 6.9$ Hz), a doublet at 5.84 ppm ($\text{CHCHCO}_2\text{CH}_3$, $J = 15.9$ Hz), a triplet at 4.60 ppm (CH_2CHOH , $J = 6.0$ Hz, proton), and a singlet at 3.71 ppm (CO_2CH_3). The distinguishing chemical shifts for the *cis* isomer were similar. There was a doublet of triplets at 6.23 ppm (CH_2CHCH , $J = 11.7, 7.5$ Hz), a doublet of triplets at 5.79 ppm ($\text{CHCHCO}_2\text{CH}_3$, $J = 11.7, 1.8$ Hz), a triplet at 4.62 ppm (CH_2CHOH , $J = 6.3$ Hz), and a singlet at 3.69 ppm (CO_2CH_3). After the isomers were separated, only the *trans* isomer was employed in the complexation reaction. The procedure used was outlined by Nicholas *et al.*,¹⁷ and the proton NMR spectrum of **63** looked very similar to the uncomplexed alcohol. The only differences between the two spectra were that the resonance at 4.62 ppm (CH_2CHOH) in the uncomplexed compound showed up as a multiplet between 5.04-5.01 ppm in the proton NMR spectrum of the complex. Also, the hydroxyl proton resonance, which was overlapping with resonances of other protons in the uncomplexed spectrum, was visible as a doublet at 2.13 ppm (CHOH , $J = 5.1$ Hz) in the spectrum of the complexed compound.

In the first cyclization reaction employing **63** (Scheme 2.30), it was dissolved in 3 equivalents of propionic anhydride, then stirred for 10 minutes, as the reaction mixture was cooled to -30 °C. At this time, 3 equivalents of $\text{HBF}_4 \cdot \text{OEt}_2$ were added. When the contents began to stick to the side of the flask, the reaction mixture was rinsed with diethyl ether that had been chilled to -78 °C. It seemed that this modification to the procedure helped in keeping the salt from dissolving. After it was isolated, the salt was

cooled to -78°C , dissolved in methylene chloride, then two equivalents of zinc were added. The reaction was allowed to warm to -45°C . Purification was attempted by flash chromatography; however, the products of the reaction decomposed on the silica gel.

Scheme 2.30: Cyclization reaction employing **63**

The procedure was modified by treating the starting alcohol with 1.5 equivalents of propionic anhydride and 3 equivalents of $\text{HBF}_4 \cdot \text{OEt}_2$. Also the reaction was run under more dilute conditions. Purification was carried out by column chromatography over alumina. Two compounds were isolated, and proton NMR spectra were taken using CDCl_3 as the solvent. This compound was suspected to be **65**; however, the chemical shifts of the most distinguishing protons were overlapping so that accurate chemical shift assignments could not be made. For this reason, a second proton spectrum was obtained in C_6D_6 . The important peaks were nicely separated which helped in confirming the

structure. In addition, a COSY NMR spectrum was taken in order to make the final proton assignments (Table 2.3).

Table 2.3: Assignment according to the COSY NMR spectrum of **65**

Proton	Chemical Shift Assignment (ppm)	Observed coupling
H ^{A1}	2.07	H ^{A2} , H ^B
H ^{A2}	2.53	H ^{A1} , H ^B
H ^B	2.30-2.20	H ^{A1} , H ^{A2} , H ^C
H ^C	2.98	H ^B , H ^{D1} , H ^{D2}
H ^{D1}	1.68-1.29	H ^{D2} , H ^C
H ^{D2}	2.05-1.89	H ^C , H ^{D1} , H ^{E2}
H ^{E1}	1.68-1.29	Could not determine
H ^{E2}	1.68-1.29	H ^{D2}
H ^{F1}	2.05-1.89	H ^B , H ^{F2}
H ^{F2}	1.68-1.29	H ^{F1}

The COSY NMR spectrum helped in confirming the structure of **65**, but the stereochemistry was unknown. Fortunately, the structure was determined by X-ray crystallography, which showed that it was the *trans* isomer (Figure 2.1).

Figure 2.1: X-ray structure of **65**

The dihedral angle between C14-C15-C19-C20 was 69°, and the bond lengths between the carbon atoms in the 5-membered ring ranged from 1.51-1.54 Å, which is in the range of typical C-C bonds. The structure also showed the typical non-linearity of the coordinated triple bond where the C12-C13-C14 and the C13-C14-C15 bond angles were each 141°.

Table 2.4: Selected bond lengths [Å] and bond angles [deg] for **65**

Co1-C13	1.967(8)	C12-C13-Co1	135.9(6)
Co1-C14	1.977(8)	C12-C13-Co2	132.9(6)
Co1-Co2	2.469(2)	C15-C14-Co1	136.5(6)
Co2-C13	1.958(8)	C15-C14-Co2	133.9(6)
Co2-C14	1.979(8)	C12-C13-C14	141.2(8)
C13-C14	1.356(12)	C13-C14-C15	141.6(8)

The structure of the second compound appeared to be the acyclic, reduced complex because there was a doublet of triplets at 6.67 ppm (CH_2CHCH , $J = 15.6, 6.9$ Hz), and a doublet at 5.42 ppm ($\text{CHCHCO}_2\text{CH}_3$, $J = 15.9$ Hz) in the proton NMR spectrum. The best yield of **65** that was obtained was 38% based on the starting alcohol. Efforts to improve this yield were unsuccessful.

Table 2.5: Crystal data and structure refinement for **65**

Empirical formula	$C_{22}H_{18}Co_2O_8$
Formula weight	528.22
Temperature	233(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	$a = 8.450(6)$ Å $\alpha = 103.80(2)^\circ$ $b = 8.574(2)$ Å $\beta = 98.50(4)^\circ$ $c = 16.608(5)$ Å $\gamma = 98.03(4)^\circ$
Volume, Z	1136.4(9) Å ³ , 2
Density	1.544 mg/m ³
Absorption coefficient	1.504 mm ⁻¹
F(0 0 0)	536
Crystal size	0.4 x 0.2 x 0.1 mm
Theta range for data collection	2.48 to 20.00°
Reflections collected	2210
Independent reflections	2024
Refinement method	full-matrix least squares on F ²
Data / restraints / parameters	4375 / 0 / 317
Final R indices [I>2 sigma (I)]	R1 = 0.0715, wR2 = 0.1806
R indices (all data)	R1 = 0.0814, wR2 = 0.1945

In order to test the generality of the method, cyclization was attempted on compound **69a,b**, which contained a phenyl substituted double bond. This compound was prepared exactly as **63**, except that benzyl triphenylphosphonium bromide was used in the Wittig reaction. Both the *trans* and *cis* isomers were produced in a ratio of 2.6 : 1 in 52% yield (Scheme 2.31).

Scheme 2.31: Synthesis of **69a,b**

The isomers could not be separated. The significant resonances in the proton NMR spectrum of **68a,b** were two doublets at 6.43 ppm (CHCHPh , $J = 11.9$ Hz) and at 6.40 ppm (CHCHPh , $J = 15.9$ Hz) as well as two doublet of triplets at 6.22 ppm (CH_2CHCH , $J = 15.9, 7.9$ Hz) and 5.66 ppm (CH_2CHCH , $J = 11.9, 7.9$ Hz).

Complexation of **68a,b** with $\text{Co}_2(\text{CO})_8$ gave **69a,b** in 85% yield. The only major difference between the proton NMR spectra of the complexed and uncomplexed compounds is that the multiplet between 4.63–4.58 ppm (CH_2CHOH) resolved into two

multiplets that were shifted downfield and ranged from 5.10-5.05 ppm and 5.03-4.97 ppm.

The attempt to cyclize **69a,b** *via* generation of the cation gave interesting results. The starting material was treated with 2 equivalents of propionic anhydride, then 3 equivalents of $\text{HBF}_4 \cdot \text{OEt}_2$. Upon addition of $\text{HBF}_4 \cdot \text{OEt}_2$, the reaction mixture froze, so the temperature was raised from $-30\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$ and the reaction mixture melted. It stirred for 1 hour. When the salt was rinsed with a solution of 1 : 1 diethyl ether/pentane, all of it dissolved. The solution was concentrated and purified by flash chromatography. Two fractions were isolated.

Scheme 2.32: Cationic cyclization of **69a,b**

Analysis of the proton NMR spectrum for each compound indicated that they were both diastereomers of the cyclized compound **70a,b** (Scheme 2.32). The proton NMR spectra were very similar. The spectrum of the first compound contained a low field doublet at 5.95 ppm ($\text{CHCH}(\text{OR})\text{Ph}$, $J = 4.5\text{ Hz}$), a quartet at 2.41 ppm (COCH_2CH_3) and a triplet at 1.48 ppm (COCH_2CH_3), while the second spectrum also had a doublet at

5.55 ppm ($\text{CHCH}(\text{OR})\text{Ph}$, $J = 10.2$ Hz), a quartet at 2.12 ppm (COCH_2CH_3), and a triplet at 0.95 ppm (COCH_2CH_3). The stereochemistry between the substituents of the ring is unknown. However, comparison of both spectra to related *cis* and *trans* cyclopentanes, suggests that the groups are *trans* (*vide infra*).

To explain the formation of **70a** and **70b**, it was postulated that the reaction took place by a cationic cyclization followed by addition of the carboxylate anion to the resulting benzylic cation (Scheme 2.33).

Scheme 2.33: Mechanism for the cationic cyclization of **69a,b**

C. Discussion

In the study of intramolecular addition reactions the results were successful, but the yields were not synthetically useful. The synthesis of 1, 2-disubstituted cyclopentanes **51**, **53a,b**, and **65** by radical cyclization was achieved and **70a** and **70b** were produced by cationic cyclization. Formation of the 5-*exo* products in the radical cyclizations is in accordance with the expected regiochemistry for radical cyclizations.¹⁸ However, the stereochemical outcome of the cyclizations was rather surprising. The stereochemistry of **65** has been confirmed by X-ray crystallography to be *trans*. Based upon a comparison of the chemical shifts for the protons assigned to H^x in Table 2.6, we see that they are very similar to the chemical shift of H^x for **65**. The only resonance which does not correlate is that of **57b**. Therefore, by this indirect evidence we can conclude that the stereochemistry of **51**, **57a**, **65** and **70a,b** is *trans* while the stereochemistry of **57b** is *cis*.

Table 2.6: Rationale for stereochemical assignments

Compound	R ¹	R ²	Stereochemistry	Chemical shift of H ^x (ppm)
51	CO ₂ Et	CO ₂ Et	<i>trans</i>	3.56
57a	CO ₂ CH ₃	CO ₂ CH ₃	<i>trans</i>	3.69
57b	CO ₂ CH ₃	CO ₂ CH ₃	<i>cis</i>	2.74-2.56
65	H	CO ₂ CH ₃	<i>trans</i>	3.21
70a	C(O)Et	Ph	<i>trans</i>	3.61-3.56
70b	Ph	C(O)Et	<i>trans</i>	3.44

With the stereochemistry of the compounds established, it is interesting to note that in all cases, it is opposite to what is predicted. As previously stated, the Beckwith-Houk transition state model predicts that 1-substituted hexenyl radicals cyclize to give the *cis* product as the major isomer by proceeding through the “chair” equatorial transition state, while the *trans* isomer, the minor product, is formed by the radical going through the “chair”-axial and the “boat”-equatorial transition states.¹⁹

In the radical cyclizations of **46a,b**, **54a,b**, and **63**, the selective formation of the *trans* isomer can be interpreted as a direct indication that the -Co₂(CO)₆ group is large enough to overcome the effects of the long bond forming between C1 and C5 in an early

“chair” transition state. Alternatively, the stereochemical outcome could also be the result of cyclization occurring *via* a late transition state. In this case, the bond forming between C1 and C5 would be much shorter, and the steric interactions between C1 and C5 would be greater. Therefore, the reaction would proceed *via* the “chair”-axial or the “boat”-equatorial transition states and the *trans* compound would be preferred (Figure 2.2).

Figure 2.2: Rationale of observed stereochemistry

In the cyclization reactions of **46a,b** and **54a,b**, the results are slightly complicated by the production of small amounts of the *cis* isomer, **57b**. Even though the

trans product was the only isomer observed in the cyclization of **54a,b**, it is possible that some of the *cis* diastereomer was produced but not detected because of the low yield of the reaction. In order to explain the formation of the *cis* isomer, it is postulated that the reaction does proceed through the “chair”-axial and/or the “boat”-equatorial transition states to give the *trans* isomers, rather, the product radical that is formed after cyclization is extremely stable (two CO₂CH₃ groups). Therefore, the formation of the *cis* product could be the result of a reversible reaction (Scheme 2.34).

Scheme 2.34: Reversible reaction of **56**

The idea that cyclizations involving stabilized radicals can be reversible was illustrated by Julia.²⁰ He reported that when compound **77** was heated with benzoyl peroxide or di-*tert*-butyl peroxide in boiling cyclohexane, **78** was isolated in 70% yield while **79** was isolated in 30% yield (Scheme 2.35).

Scheme 2.35: Julia's reversible cyclization of **77**

The radical which he studied is highly stabilized as are radicals **48** and **56**. The reason why **48** and **56** do not form the 6-*endo* product may be due to the fact that the terminal carbon of the double bond is substituted with very large groups and the radical cannot add due to steric hindrance.

While we were successful in achieving intramolecular cyclization employing (propargyl)Co₂(CO)₆ radicals, the yields of the reactions remained low despite many efforts to improve them. As one of the main goals of this project was to develop the synthetic utility of these radicals, we decided that the reaction yields might improve if the radical was generated by direct homolysis of a C-X bond (X = halogen or thionocarbonate) using non-reductive methods. In addition, we believed that direct

homolysis of the C-X bond would provide a more efficient way to gauge the reactivity of the radicals; therefore, we proceeded with research in this area.

III. CONCLUSION

In our investigation of (propargyl)Co₂(CO)₆ radicals, we have found that intermolecular addition of the radicals to electron deficient double bonds are unsuccessful. One of the probable reasons why addition did not occur was that the -Co₂(CO)₆ group effects a very large stabilization of the radical which lowered the SOMO and prevented effective overlap with the LUMO of the double bond. As a result the only products we observed were the *d,l* and *meso* dimers as well as the hydrogen atom abstracted product. We did not test reactions which employed electron rich double bonds because we were concerned that the electron rich double bonds would react with the cation complexes before the radical could be generated.

On the other hand, intramolecular radical cyclization reactions were successful. Compounds **51**, **57a,b**, and **65** were synthesized in 10, 8, 5, and 38% yield respectively. The main reason why the yields could not be improved was that the precursor salts were soluble in the solvents normally employed to precipitate them. The regiochemistry of these reactions is in accordance with theoretical predictions, but the stereochemistry is not. The major products exhibit *trans* stereochemistry, which is contrary to the predicted stereochemical outcome. We believe that the radical is highly stabilized, which causes the cyclization to proceed *via* a late transition state and the steric demand of the -Co₂(CO)₆ group forces the molecule to proceed through conformations

which lead to the *trans* isomer. In the cyclization of **46a,b**, formation of the *cis* product can be explained by a reversible reaction.

IV. EXPERIMENTAL

General Methods

All of the solvents employed were freshly distilled before use. Methylene chloride and acetonitrile were distilled over CaH_2 , and diethyl ether, THF, benzene, toluene, and pentane were distilled over sodium benzophenone ketyl. Methanol and ethanol were distilled over magnesium.²¹ Preparatory TLC was performed using E. Merck silica gel (G-60PF₂₅₄₋₃₆₆) 1 mm and Whatman silica gel 60 Å, 1000 μm , with fluorescent indicator, 20 x 20 glass plates. Analytical TLC was performed using silica gel IB-F plates (Baker-flex); visualization was accomplished with UV illumination (254 nm) or by spraying with a 95 : 5 solution of phosphomolybdic acid/ethanol, then heating. Flash chromatography was performed as described by Still using E Merck silica gel (230-400 mesh) under 20 psi of N_2 .²² Organolithium reagents were standardized by titration before use.²³ Glutaraldehyde was purchased as a 50 % aqueous solution from Aldrich. For use in reactions, the water was removed by freeze-drying. For all reactions, the glassware was dried in the oven at 125 °C. NMR spectra were taken on a Varian XL-300 FT-NMR, a Varian Inova-400 FT-NMR and a Varian VXR-500 FT-NMR using CDCl_3 or C_6D_6 as solvents. Residual chloroform-H (δ 7.24) was used as internal reference for spectra measured in CDCl_3 and residual benzene (δ 7.14) was used as internal reference for C_6D_6 . ^{13}C NMR spectra were measured at 75 MHz, 100 MHz, and 125 MHz and were referenced with the δ 77.0 resonance of CDCl_3 . All J values are in Hz. IR spectra were recorded on a Bio-Rad FT-IR spectrometer; all wave numbers are given in cm^{-1} . Mass spectra were recorded on a VGZAB-E or Kratos HRMS-25 mass spectrometer. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN. X-ray

diffraction of **65** (Chapter II) **35b**, **38a**, **46** (Chapter III) were performed by Dr. M. Khan, staff crystallographer for the Department of Chemistry and Biochemistry at OU.

General procedure for the synthesis of 4 and 24:

In a 250 mL side-arm side-arm roundbottom flask containing a stir bar, 5.5 g (15 mmol) of $\text{Co}_2(\text{CO})_8$ were dissolved in 25 mL of CH_2Cl_2 . The solution stirred under a flow of N_2 , and a solution of 2.3 g (15 mmol) of the uncomplexed alcohol in 5 mL of CH_2Cl_2 was added dropwise. The reaction was monitored by TLC (1 : 1 petroleum ether/diethyl ether). After approximately 2 hours, the uncomplexed alcohol had been consumed. The reaction mixture was filtered through alumina, then concentrated. Purification was performed using flash chromatography (2 : 1 petroleum ether/diethyl ether). The yield of **4** was 5.9 g (14.2 mmol, 95%). The yield of **24** was 5.6 g (13 mmol, 90%)

General procedure for the synthesis of cation complexes 21, 23, and 27:

In a 100 mL side-arm roundbottom flask containing a stir bar, 0.21g (0.50 mmol) of complexed alcohol was dissolved in 0.21 mL (1.6 mmol) of propionic anhydride. The reaction mixture was kept under a flow of N_2 , and it was cooled to $-45\text{ }^\circ\text{C}$. At this time, 0.21 mL (1.4 mmol) $\text{HBF}_4\cdot\text{OEt}_2$ was added dropwise. The contents of the flask became very viscous. After 45 minutes the reaction mixture was rinsed with 10 mL portions of anhydrous diethyl ether. When the ether washes remained clear, the insoluble salt remained at the bottom of the flask, and the remaining solvent was removed by vacuum. Once the salt was isolated, it was dissolved in 50 mL of methylene chloride, then cooled

to -30 °C. At this time, 0.90 mL (10 mmol, 20 equivalents) of methyl acrylate, 0.03 mg (0.50 mmol) of zinc dust, and 3.0 mL (40 mmol) of THF were added. The reaction stirred under a flow of N₂ at room temperature. Analysis of the products was conducted by TLC (5 : 1 hexanes/diethyl ether). In the TLC analysis, the reaction mixture was compared against authentic samples of *the d,l* and *meso* dimers as well as the reduced product. When the reaction mixtures were purified, PTLC was employed (5 : 1 hexanes/diethyl ether); however, in all cases **7a**, **7b**, and **8** as well as the hydrolyzed cation were the only products isolated. According to the TLC and proton NMR spectra, no evidence was found that the radical had undergone addition to the radical trap (methyl acrylate or diethyl methylene malonate) .

Procedure for the synthesis of hemiacetal, 37a,b:

In a 250 mL side-arm roundbottom flask containing a stir bar, 5.5 mL (0.05 mol) of phenyl acetylene was dissolved in 70 mL of THF. The solution stirred under a flow of N₂, and was cooled to -78 °C, then 32 mL (0.05 mol) of butyl lithium (1.6 M in hexanes) were added dropwise. As the reaction stirred, the solution turned dark yellow. In a separate 500 mL side-arm roundbottom flask containing a stir bar, 5.02 g (50.2 mmol) of glutaraldehyde were dissolved in 50 mL of THF. This solution also stirred under a flow of N₂, and cooled to -78 °C. The solution of phenylacetylide was added dropwise to the solution of glutaraldehyde by cannula. The reaction mixture turned yellow and was slushy. Once all of the phenylacetylide was added, the reaction mixture was warmed to room temperature. During this time, the solution became clear and turned darker yellow. The reaction was monitored by TLC (1 : 1 petroleum ether/diethyl ether) for the

disappearance of glutaraldehyde. When the starting material was consumed, the reaction mixture was quenched with 100 mL of 1N HCl. The color of the solution lightened, and the organic layer separated from the aqueous layer. The reaction was extracted with 5 x 100 mL of diethyl ether. These extractions were combined, dried over magnesium sulfate, filtered through celite and concentrated. Purification was performed using flash chromatography with 1:1 petroleum ether/diethyl ether as the eluent. The yield of **37a,b** was 0.09 g (0.44 mmol, 47%).

Data for 37a,b (mixture of diastereomers):

Physical state: light yellow oil.

R_f = 0.43 (1 : 1 petroleum ether/ diethyl ether).

¹H NMR (mixture) (300 MHz, CDCl₃) δ 7.44-7.41 (m, 4H, Ph), 7.29-7.26 (m, 6H, Ph), 5.35 (dd, J = 6.9, 3.7 Hz, 1H, CH₂CHHOH), 5.02-4.99 (m, 1H, CH₂CHHOH), 4.79 (dd, J = 6.3, 2.0 Hz, 1H, CH₂CHH(CCPh)), 4.46 (dd, J = 12.0, 2.5 Hz, 1H, CH₂CHH(CCPh)), 2.86 (d, J = 6.0 Hz, 1H, OH), 2.55 (dd, J = 3.0, 0.9 Hz, 1H, OH) 1.98-1.24 (m, 12 H, CH₂CH₂CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 131.8, 131.7, 128.4, 128.3, 128.2, 122.6, 122.5, 96.4, 92.3, 87.9, 87.5, 85.1, 84.5, 66.8, 62.0, 32.1, 31.5, 31.3, 30.3, 21.5, 17.7.

IR (CH₂Cl₂) 3587 (m), 3427 (w), 3101 (w), 3082 (w), 3064 (w), 3045 (w), 3083 (w),

3022 (w), 2952 (m), 2232 (w), 1490 (m), 1192 (m), 1127 (m), 1071 (m), 1026 (s), 973 (s) cm^{-1} .

HRMS-FAB (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{O}_2$ 203.1072 found, 203.1063.

Procedure for the synthesis of 45a,b and 53a,b:

Sodium metal (0.243g, 10.6 mmol) was added to a 500 mL side-arm roundbottom flask containing a stir bar and kept under a flow of N_2 . The flask was cooled to $-78\text{ }^\circ\text{C}$, then 106 mL of ethanol (**45a,b**) or methanol (**53a,b**) was added very slowly. The reaction mixture was allowed to warm to room temperature, then 2.4 mL (21 mmol) of diethyl malonate (**45a,b**) or dimethyl malonate (**53a,b**) was added. The flask was fitted with a water-cooled condenser, then the reaction mixture was heated to reflux. When the sodium had dissolved, a solution of **37a,b** 1.428g (7.069 mmol) in 78 mL of ethanol (synthesis of **45a,b**) or methanol (synthesis of **53a,b**) was added dropwise by a syringe pump over 3.5 hours. After addition was complete, the reaction was monitored by TLC (1:1 petroleum ether/diethyl ether) for the disappearance of **37a,b**. The color of the reaction mixture turned bright yellow. Compound **37a,b** was consumed after 12 hours. The reaction mixture was quenched with 200 mL of 1N HCl, then was extracted with 3 x100 mL of diethyl ether. The ether extracts were combined, dried over magnesium sulfate, filtered through celite, then concentrated. Purification was performed using flash chromatography with 2 : 1 petroleum ether/diethyl ether as the eluent. The yield of **45a,b** was 0.160 g (46 mmol), 46%. The yield of **53a,b** was 0.174 g, (0.553 mmol, 78%).

Data for 45a,b (mixture of diastereomers):

Physical state: yellow oil.

$R_f = 0.74$ (1 : 1 petroleum ether/diethyl ether).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.46-7.43 (m, 2H, Ph), 7.41-7.37 (m, 2H, Ph), 7.32-7.25 (m, 6H, Ph), 4.94 (d, $J = 3.0$ Hz, 1H, $\text{CH}_2\text{CH}(\text{CCPh})$), 4.59 (ddd, $J = 11.1, 9.0, 2.1$ Hz, 1H, $\text{CH}_2\text{CHCH}(\text{CO}_2\text{Et})_2$), 4.34 (dd, $J = 9.0, 3.0$ Hz, 1H, $\text{CH}_2\text{CH}(\text{CCPh})$), 4.29-4.09 (overlapping dq, 8H, OCH_2CH_3), 4.03 (ddd, $J = 11.4, 9.6, 1.8$ Hz, 1H, $\text{CH}_2\text{CHCH}(\text{CO}_2\text{Et})_2$), 3.51 (d, $J = 9.0$ Hz, 1H, $\text{CH}(\text{CO}_2\text{Et})_2$), 3.44 (d, $J = 9.0$ Hz, 1H, $\text{CH}(\text{CO}_2\text{Et})_2$), 2.10-1.49 (m, 12H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.32-1.20 (overlapping dd, 12H, OCH_2CH_3).

IR (neat) 2937 (m), 2866 (m), 1734 (s) cm^{-1} .

EIMS (70 eV) m/z : $[\text{M}]^+$ 344 (0.4).

Data for 53a,b (mixture of diastereomers):

Physical state: light yellow oil.

$R_f = 0.50$ (1 : 1 petroleum ether/diethyl ether).

¹H NMR (mixture) (300 MHz, CDCl₃) δ 7.45-7.38 (m, 4H, Ph), 7.31-7.25 (m, 6H, Ph), 4.94 (broad d, J = 4.5 Hz, 1H, CH₂CH(CPh)), 4.59 (ddd, J = 12.9, 9.6, 1.8 Hz, 1H, CH₂CHCH(CO₂CH₃)₂), 4.18 (dd, J = 11.1, 2.1 Hz, 1H, CH₂CH(CPh)), 4.04 (ddd, J = 11.1, 9.6, 1.8 Hz, 1H, CH₂CHCH(CO₂CH₃)₂), 3.75 (s, 3H, CO₂CH₃), 3.74 (s, 3H, CO₂CH₃), 3.71 (s, 6H, CO₂CH₃), 3.56 (d, J = 9.0 Hz, 1H, CHCH(CO₂CH₃)₂), 3.49 (d, J = 9.0 Hz, 1H, CHCH(CO₂CH₃)₂), 2.18-1.61 (m, 10H, CH₂), 1.45-1.33 (m, 2H, CH₂).

¹³C NMR (mixture) (75 MHz, CDCl₃) δ 167.7, 167.5, 167.3, 167.0, 131.7, 131.6, 128.3, 128.2, 128.1, 122.7, 122.5, 87.9, 87.0, 86.7, 84.3, 76.4, 70.5, 69.1, 66.0, 57.6, 52.6, 53.5, 52.4, 32.1, 30.1, 28.8, 28.2, 22.9, 19.0.

IR (CH₂Cl₂) 3007 (w), 2954 (m), 2930 (m), 2848 (m), 2231 (w), 1760 (s), 1756 (s), 1750 (s), 1739 (s), 1733 (s), 1355 (m), 1337 (m), 1197 (m), 1153 (m), 1077 (m), 1041 (m) cm⁻¹.

HRMS-FAB (m/z): [M+H]⁺ calcd for C₁₈H₂₀O₅ 317.1389; found, 317.1384.

Procedure for the synthesis of 62a,b:

In a 50 mL side-arm roundbottom flask containing a stir bar and kept under a flow of N₂, 0.331 g (0.989 mmol) of Ph₃PCH(CO₂CH₃) were dissolved in 5 mL of THF. A solution of 0.201 g (0.995 mmol) of **37a,b** in 3 mL of THF was then added. The flask was equipped with a water-cooled condenser, and the reaction mixture was heated to

reflux. The reaction was monitored by TLC for the disappearance of **37a,b** (10% ethyl acetate in petroleum ether). When it had been consumed (after approximately 3 hours), the reaction was quenched with 20 mL of water, then extracted with 3 x 10 mL of diethyl ether. The extracts were dried over magnesium sulfate, filtered through celite, then concentrated. Purification was performed using column chromatography (10% ethyl acetate in petroleum ether). The yield of **62a,b** was 1.064 g (4.124 mmol, 56%).

Data for 62a,b:

Physical state: yellow oil.

$R_f = 0.23$ (10% ethyl acetate in petroleum ether).

¹H NMR (*cis*) (300 MHz, CDCl₃) δ 7.42-7.39 (m, 2H, Ph), 7.30-7.27 (m, 3H, Ph), 6.23 (dt, $J = 11.7, 7.5$ Hz, CH₂CHCH), 5.79 (dt, $J = 11.7, 1.8$ Hz, CHCHCO₂CH₃), 4.62 (t, $J = 6.3$ Hz, 1H, CH₂CHOH), 3.69 (s, 3H, CO₂CH₃), 2.74 (dddd, $J = 15.0, 7.0, 3.6, 1.8$ Hz, 2H, CH₂CH₂CHCH), 1.87-1.81 (m, 2H, CH₂), 1.73-1.62 (m, 2H, CH₂).

¹H NMR (*trans*) (300 MHz, CDCl₃) δ 7.42-7.36 (m, 2H, Ph), 7.31-7.27 (m, 3H, Ph), 6.97 (dt, $J = 15.6, 6.9$ Hz, 1H, CH₂CHCHCO₂CH₃), 5.84 (d, $J = 15.9$ Hz, 1H, CHCHCO₂CH₃), 4.60 (t, $J = 6.0$ Hz, 1H, CH₂CHOH), 3.71 (s, 3H, CO₂CH₃) 2.27 (q, $J = 7.2$ Hz, 2H, CH₂CH₂CHCH), 1.85-1.64 (m, 5H, CH₂CH₂ and OH).

¹³C NMR (*cis*) (75 MHz, CDCl₃) δ 166.7, 150.0, 131.6, 128.3, 128.2, 122.6, 119.6, 90.0, 84.8, 62.5, 50.9, 37.1, 29.6, 28.4, 24.5.

¹³C NMR (*trans*) (75. MHz, CDCl₃) δ 167.1, 148.9, 131.6, 128.3, 128.2, 122.5, 121.2, 89.8, 84.9, 62.4, 51.3, 37.0, 31.7, 23.6.

IR (CH₂Cl₂) 3594 (m), 3472(m), 3064(w), 3024 (w), 2999(w), 2950(m), 2865 (m), 2227 (w), 2203 (w), 1721 (s), 1658 (s), 1598 (w), 1490 (m), 1458 (m), 1438 (m), 1342 (m), 1316 (m), 1200 (m), 1181 (m), 1154 (m), 1100 (m), 1069 (m), 1027 (m), 984 (m), 917 (w) 860 (w) cm⁻¹.

HRMS-FAB (m/z): [M]⁺ calcd for C₁₆H₁₈O₃ 258.1256; found, 258.1231.

Procedure for the synthesis of 68a,b:

In a 100 mL side-arm roundbottom flask containing a stir bar and kept under a flow of N₂, 1.01 g (2.34 mmol) of the phosphonium salt, **66**, was dissolved in 5 mL of THF, then 3.1 mL (2.3 mmol) of BuLi (1.3 M in hexanes) was added. The solution immediately turned bright orange. It was stirred 15 minutes before a solution of 0.236 g (1.17 mmol) of **37a,b** dissolved in 5 mL of THF was added dropwise. The reaction was monitored by TLC (2 : 1 petroleum ether/diethyl ether) for the disappearance of **37a,b**. When **37a,b** was consumed, the reaction was quenched with 10 mL of 1N HCl, then extracted with 3 x 50 mL of diethyl ether. The combined ether extracts were dried over magnesium sulfate, filtered through celite, then concentrated. Purification was

performed using flash chromatography (1 : 1 petroleum ether/diethyl ether). The mixture of **68a,b** was isolated in a 2.6 : 1 ratio. The yield was 0.167 g (0.605 mmol, 52%).

Data for 68a,b (mixture of diastereomers):

Physical state: light yellow oil.

R_f = 0.56 (3 : 1 petroleum ether/diethyl ether).

¹H NMR (major isomer) (400 MHz, CDCl₃) δ 7.43-7.16 (m, 10H, Ph), 6.40 (d, J = 15.9 Hz, 1H, CHCH₂Ph), 6.22 (dt, 15.9, 7.9 Hz, 1H, CH₂CHCH), 4.63-4.58 (m, 1H, CH₂CHOH), 2.29 (q, J = 7.2 Hz, 2H, CH₂CH₂CH), 1.89-1.79 (m, 5H, CH₂CH₂ and OH).

¹H NMR (minor isomer) δ 7.43-7.16 (m, 10H, Ph), 6.43 (d, J = 11.9 Hz, 1H, CHCH₂Ph), 5.66 (dt, J = 11.9, 7.9 Hz, 1H, CH₂CHCH), 4.63-4.58 (m, 1H, CH₂CHOH), 2.41 (q, J = 7.0 Hz, 2H, CH₂CH₂CH), 1.76-1.66 (m, 5 H, CH₂CH₂ and OH).

¹³C NMR (mixture) (CDCl₃, 75 MHz) δ 138.0, 137.9, 132.3, 131.8, 130.6, 130.4, 129.6, 128.8, 128.5, 128.4, 128.3, 128.2, 126.9, 126.6, 126.1, 122.9, 90.3, 85.2, 63.0, 62.9, 37.6, 32.6, 28.2, 25.6, 25.1.

IR (CH₂Cl₂) 3595 (m), 3082 (w), 3026 (m), 2943 (m), 2862 (m), 2227 (w), 1598 (m), 1490 (s), 1379 (m), 1070 (m), 1025 (m), 967 (s), 917 (w) cm⁻¹.

HRMS-FAB (m/z): [M]⁺ calcd for C₂₀H₂₀O 276.1514; found, 276.1492.

General procedure for the synthesis of complexes 46a,b, 54a,b, 63, 69a,b:

In a 250 mL side-arm roundbottom flask containing a stir bar, 0.200 g (0.585 mmol) of Co₂(CO)₈ were dissolved in 10 mL of CH₂Cl₂. The solution was stirred under a flow of N₂, and a solution of 0.149 g (4.714 mmol) of **45a,b** in 5.0 mL of CH₂Cl₂ was added dropwise. The reaction was monitored for the disappearance of **45a,b** by TLC (1 : 1 petroleum ether/diethyl ether). After **45a,b** had been consumed (after approximately 2 hours), the reaction mixture was filtered through alumina, then concentrated. Purification was performed using flash chromatography with silica gel as the adsorbent (2 : 1 petroleum ether/diethyl ether). The yield of **46a,b** was 0.162 g (0.257 mmol, 51%). The yield of **54a,b** was 0.85 g (1.4 mmol, 83%). The yield of **63** was 0.201 g (0.037 mmol, 90%). The yield of **69a,b** was 1.03 g (1.83 mmol, 85%).

Data for 46a, b (mixture of diastereomers):

Physical state: red oil.

R_f = 0.76 (2 : 1 petroleum ether/ diethyl ether).

¹H NMR (mixture) (300 MHz, CDCl₃) δ 7.52 (dd, J = 6.6, 0.9 Hz, 4H, Ph), 7.35-7.26 (m, 6H, Ph), 4.99 (dd, J = 12.0, 3.0 Hz, 1H, CH₂CH(CPh)), 4.81-4.76 (m, 2H,

CH₂CH(CCPH) and CHCH(CO₂Et)₂), 4.31 (ddd, J = 11.1, 9.15, 1.8 Hz, 1H, CH₂CHCH(CO₂Et)₂), 4.24-3.96 (overlapping dq and d, 9H, OCH₂CH₃ and CHCH(CO₂Et)₂), 3.49 (d, J = 9.0 Hz, 1H, CHCH(CO₂Et)₂), 2.08-1.69 (m, 9H, CH₂), 1.62-1.38 (m, 3H, CH₂), 1.24 (m, 6H, OCH₂CH₃), 1.13 (overlapping dd, 6H, OCH₂CH₃).

¹³C NMR (mixture) (75 MHz, CDCl₃) δ 167.2, 167.1, 166.9, 166.8, 137.9, 137.8, 129.8, 129.7, 128.7, 128.6, 127.7, 127.6, 98.2, 97.1, 90.3, 90.0, 77.8, 76.4, 72.4, 71.2, 61.5, 61.4, 61.3, 58.1, 52.9, 33.7, 33.4, 28.3, 26.3, 23.3, 18.5, 14.0, 13.8.

Data for compound 54a,b :

Physical state: red solid

¹H NMR (major isomer) (300 MHz, CDCl₃) δ 7.51 (d, J = 6.9 Hz, 2H, Ph), 7.35-7.27 (m, 3H, Ph), 4.75 (dd, J = 10.8, 1.8 Hz, 1H, CH₂CH(CCPH)), 4.31 (ddd, J = 11.1, 6.9, 2.1 Hz, 1H, CH₂CHCH(CO₂CH₃)₂), 3.71 (s, 3H, CO₂CH₃), 3.58 (s, 3H, CO₂CH₃), 3.53 (d, J = 9.0 Hz, 1H, CHCH(CO₂CH₃)₂), 2.03-1.96 (m, 2H, CH₂), 1.79-1.70 (m, 2H, CH₂), 1.61-1.38 (m, 3H, CH₂).

¹H NMR (minor isomer; partial data) (300 MHz, CDCl₃) δ 4.99 (dd, J = 10.8, 2.5 Hz, CH₂CH(CCPH)), 4.81-4.78 (m, 1H), 4.19 (d, J = 11.4 Hz, 1H, CHCH(COCH₃)₂), 3.73 (s, 3H, CO₂CH₃), 3.58 (s, 3H, CO₂CH₃).

^{13}C NMR (major isomer) (75 MHz, CDCl_3) δ 167.6, 167.3, 137.8, 129.8, 128.8, 127.7, 97.1, 90.0, 77.9, 76.5, 57.8, 52.5, 52.3, 33.4, 28.4, 23.4.

^{13}C NMR (minor isomer) (75 MHz, CDCl_3) δ 167.5, 167.4, 137.8, 129.8, 128.7, 127.6, 98.0, 90.4, 72.6, 71.3, 52.5, 33.6, 26.3, 18.4.

IR (mixture) (CH_2Cl_2) 2956 (w), 2091 (s), 2055 (s), 2026 (s), 1736 (m), 1732 (m) cm^{-1} .

Data for 63:

Physical state: red solid.

R_f = 0.45 (1 : 1 petroleum ether/diethyl ether).

^1H NMR (300 MHz, CDCl_3) δ 7.50 (dd, J = 6.0, 1.5 Hz, 2H, Ph), 7.39-7.32 (m, 3H, Ph), 6.97 (dt J = 15.6, 6.9 Hz, 1H, CH_2CHCH), 5.82 (d, J = 15.6 Hz, 1H, $\text{CHCHCO}_2\text{CH}_3$), 5.05-5.01 (m, 1H, CH_2CHOH), 3.72 (s, 3H, CO_2CH_3), 2.29 (apparent q, J = 6.0 Hz, 2H, $\text{CH}_2\text{CH}_2\text{CHCH}$), 2.13 (d, 5.1 Hz, 1H, OH), 1.88-1.67 (m, 4H, CH_2CH_2).

^{13}C NMR (75 MHz, CDCl_3) δ 167.0, 148.6, 137.4, 129.4, 129.0, 128.0, 121.4, 101.5, 90.7, 72.1, 51.4, 38.9, 31.8, 24.8.

IR (CH_2Cl_2) 3047 (w), 2984 (w), 2950 (w), 2864 (w), 2846 (w), 2091 (s), 2058 (s), 2050 (s), 2028 (s), 1720 (m), 1716 (m), 1658 (w), 573 (w), 518 (w) cm^{-1} .

EA Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_9\text{Co}_2$: C, 48.53; H, 3.33; found, C, 47.67; H, 3.28.

Data for 69a,b (mixture of isomers):

Physical state: red solid.

^1H NMR (major isomer) (300 MHz, CDCl_3) δ 7.52-7.48 (m, 2H, Ph), 7.35-7.20 (m, 3H, Ph), 6.39 (d, $J = 15.9$ Hz, 1H, CHCHPh), 6.20 (dt, $J = 15.9, 6.9$ Hz, 1H, CH_2CHCHPh), 5.10-5.05 (m, 1H, CH_2CHOH), 2.32 (q, $J = 6.9$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CHCH}$), 1.93 (d, $J = 5.1$ Hz, 1H, OH), 1.96-1.69 (m, 4H, CH_2CH_2).

^1H NMR (minor isomer) (300 MHz, CDDl_3) δ 7.52-7.48 (m, 2H, Ph), 7.35-7.20 (m, 3H, Ph), 6.46 (d, $J = 11.5$ Hz, 1H, CHCHPh), 5.65 (dt, $J = 11.5, 7.2$ Hz, 1H, CH_2CHCHPh), 5.03-4.97 (m, 1H, CH_2CHOH), 2.43 (q, 6.9 Hz, 2H, $\text{CH}_2\text{CH}_2\text{CHCH}$), 1.90 (d, $J = 5.4$ Hz, 1H, OH), 1.96-1.69 (m, 4H, CH_2CH_2).

^{13}C NMR (mixture) (75 MHz, CDCl_3) δ 137.6, 137.5, 132.1, 130.5, 130.0, 129.4, 128.9, 128.7, 128.4, 128.1, 127.9, 126.9, 126.5, 125.9, 101.8, 90.7, 72.5, 72.2, 39.1, 39.0, 32.4, 28.1, 26.7, 25.9.

IR (CH_2Cl_2) 3600 (w), 3080 (w), 3025 (w), 2938 (w), 2860 (w), 2091 (s), 2058 (s), 2048 (s), 2028 (s), 1607 (w), 1072 (w), 967 (w), 631 (w), 599 (w), 573 (w), 520 (w) cm^{-1} .

EA Anal. Calcd for $\text{C}_{26}\text{H}_{20}\text{O}_7\text{Co}_2$: C, 55.54; H, 3.58; found, C, 55.33; H, 3.31.

Procedure for the synthesis of 61:

In a 25 mL side-arm roundbottom flask containing a stir bar, 0.199 g (0.315 mmol) of **54a,b** were dissolved in 1.5 mL (1.7 mmol) of acetic anhydride. The reaction mixture was kept under a flow of N_2 , and was cooled to $-40\text{ }^\circ\text{C}$. At this time, 0.01 mL (0.99 mmol) of triflic acid were added. The reaction stirred for 2 hours at $-40\text{ }^\circ\text{C}$ and was monitored by TLC (1 : 1 petroleum ether/diethyl ether) for the disappearance of starting material (approximately 2 hours). When the starting material was consumed, 0.63 mL of NEt_3 (4.5 mmol) were added, then the reaction mixture was warmed to room temperature. The reaction mixture was then poured into a 250 mL separatory funnel containing NaHCO_3 in ice water, and was extracted with 5 x 50 mL of Et_2O . The Et_2O extracts were combined, dried over magnesium sulfate, filtered over celite, then concentrated. Purification was attempted by flash chromatography (3 : 1 petroleum ether/diethyl ether). No purification was performed because the product was unstable to silica gel. The crude product was immediately used in the cyclization reaction.

Data for 61:

Physical state: red oil.

¹H NMR (300 MHz, CDCl₃) δ 7.45-7.42 (m, 2H, Ph), 7.36-7.29 (m, 3H, Ph), 6.93 (t, J = 8.1 Hz, 1H, CH₂CHC(CO₂CH₃)₂), 6.38 (t, J = 6.6 Hz, 1H, CH₂CH(CCPH)), 3.77 (s, 3H, CO₂CH₃), 3.76 (s, 3H, CO₂CH₃), 2.34 (q, J = 7.5 Hz, 2H, CH₂CH₂C), 2.11 (s, 3H, OC(O)CH₃), 1.88-1.81 (m, 2H, CH₂), 1.68-1.61 (m, 2H, CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 170.4, 165.1, 164.1, 148.8, 137.2, 129.3, 128.9, 127.9, 122.9, 95.9, 90.5, 73.3, 52.3, 52.2, 36.6, 29.0, 24.6, 20.6.

General procedure for the synthesis of 51, 57a,b, 65 by reduction of the (propargyl)Co₂(CO)₆ cations:

In a 100 mL side-arm roundbottom flask containing a stir bar, 0.418 g (1.00 mmol) of complexed alcohol was dissolved in 0.41 mL (3.2 mmol) of propionic acid. The reaction mixture was kept under a flow of N₂, and it was cooled to -45 °C (CO₂ in acetone). At this time, 0.43 mL (2.9 mmol) HBF₄·OEt₂ was added dropwise. The contents of the flask became very viscous. After 45 minutes the reaction mixture was rinsed with 10 mL portions of anhydrous diethyl ether, that had been chilled to -78 °C while the reaction mixture was kept at -40 °C. When the ether washes remained clear, the insoluble salt remained at the bottom of the flask, and the remaining solvent was removed by vacuum. Once the salt was isolated, it was dissolved in 20 mL of methylene chloride, then 0.016 g (0.25 mmol) of zinc was added. The reaction stirred under a flow of N₂ at

room temperature while being monitored by TLC (1 : 1 petroleum ether/diethyl ether) for the disappearance of hydrolyzed starting material (approximately 1 hour). When it had been consumed, the solution was filtered through celite, then concentrated. Purification was performed using flash chromatography (5 : 1 petroleum ether/diethyl ether). The yield of **51** was 0.30 g (0.05 mmol, 10%). The yield of **57a** was 0.008 g (0.01 mmol, 8%). The yield for **57b** was 0.005 g (0.008 mmol, 5 %). The yield of **65** was 0.090 g (0.017 mmol, 38%).

Data for 51:

Physical state: red oil.

$R_f = 0.5$ (5 : 1 petroleum ether/diethyl ether).

^1H NMR (*trans*) (300 MHz, CDCl_3) δ 7.47 (dd, $J = 7.8, 1.5$ Hz, 2H, Ph), 7.35-7.27 (m, 3H, Ph), 4.15 (dq, $J = 20.0, 7.2$ Hz, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.63 (d, $J = 4.5$ Hz, 1H, $\text{CHCH}(\text{CO}_2\text{Et})_2$), 3.56 (q, 8.0 Hz, 1H, $\text{CH}_2\text{CHCH}(\text{CCPh})$) 2.54-2.45 (m, 1H, $\text{CHCHCH}(\text{CO}_2\text{Et})_2$), 2.31-2.20 (m, 1H, CH_2), 2.12-2.00 (m, 1H, CH_2), 1.95-1.84 (m, 1H, CH_2), 1.80-1.69 (m, 2H, CH_2), 1.67-1.58 (m, 1H, CH_2), 1.22 (dt, $J = 20.0, 7.2$ Hz, 6H, OCH_2CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ 168.9, 168.4, 138.1, 129.1, 128.8, 127.7, 103.2, 93.0, 61.2, 61.1, 53.0, 47.8, 45.7, 36.1, 28.9, 24.5, 14.0, 13.9.

EIMS (70 eV) m/z : $[M - 2(CO)]^+$ 558 (2.9), $[M - 3(CO)]^+$ 530 (13.1), $[M - 4(CO)]^+$ 502 (23.2), $[M - 5(CO)]^+$ 474 (100).

Data for 57a (*trans*) 57b (*cis*):

Physical state: red oil.

^1H NMR (*trans*) (300 MHz, C_6D_6) δ 7.56-7.54 (m, 2H, Ph), 7.06-7.00 (m, 2H, Ph), 6.97-6.91 (m, 1H, Ph), 3.89 (d, $J = 4.8$ Hz, 1H, $\text{CHCH}(\text{CO}_2\text{CH}_3)_2$), 3.69 (q, $J = 7.8$ Hz, 1H, $\text{CH}_2\text{CH}(\text{CCPh})$), 3.28 (s, 3H, CO_2CH_3), 3.25 (s, 3H, CO_2CH_3), 2.80-2.70 (m, 1H, $\text{CH}_2\text{CHCH}(\text{CO}_2\text{CH}_3)_2$), 2.19-1.97 (m, 3H, CH_2), 1.63-1.52 (m, 3H, CH_2).

^{13}C NMR (*trans*) (75 MHz, CDCl_3) δ 169.4, 168.9, 138.1, 129.1, 128.8, 127.7, 52.9, 52.3, 52.2, 47.9, 45.8, 36.0, 29.0, 24.3.

IR (*trans*) (CH_2Cl_2) 2088 (s), 2050 (s), 2024 (s), 1730 (m), 1197 (m), 935 (m), 848 (m) cm^{-1} .

EIMS (*trans*) (12 eV) m/z : $[M - 2(CO)]^+$ 530 (5.6), $[M - 3(CO)]^+$ 502 (7.8), $[M - 4(CO)]^+$ 474 (15.3).

^1H NMR (*cis*) (300 MHz, CDCl_3) δ 7.38-7.35 (m, 2H, Ph), 7.26-7.23 (m, 3H, Ph), 3.72 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 3.49 (d, $J = 7.8$ Hz, 1H,

CHCH(CO₂CH₃)₂, 2.74-2.56 (m, 2H, CHCH(CPh) and CHCHCH(CO₂CH₃)₂), 2.16-1.99 (m, 2H, CH₂), 1.83-1.58 (m, 4H, CH₂).

EIMS (*cis*) (12 eV) *m/z*: [M - 6(CO)]⁺ 300 (8.2), [M - 300]⁺ 168 (82.3).

Data for 65:

Physical state: red solid crystallized from pentane.

¹H NMR (300 MHz, C₆D₆) δ 7.49 (d, *J* = 7.8 Hz, 2H, Ph), 7.06-6.93 (m, 3H, Ph), 3.24 (s, 3H, CO₂CH₃) 2.49 (q, *J* = 8.0 Hz, 1H, CH₂CH(CPh)), 2.53 (dd, *J* = 15.3, 3.9 Hz, 1H, CHCH^ACH^BCO₂CH₃), 2.30-2.20 (m, 1H, CHCHCH₂CO₂CH₃), 2.07 (dd, *J* = 15.0, 9.9 Hz, 1H, CHCH^ACH^BCO₂CH₃), 2.05-1.89 (m, 2H, CH₂), 1.68-1.29 (m, 4H, CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 172.8, 138.2, 129.0, 128.8, 127.7, 103.1 92.4, 51.4, 48.4, 45.5, 39.1, 36.2, 32.8, 23.9.

IR (CH₂Cl₂) 3027 (w), 2954 (w), 2927 (w), 2871 (w), 2088 (s), 2051 (s), 2023 (s), 1731 (m) cm⁻¹.

X-ray Crystal Structure Determination:

Crystals of **65** were obtained by slow crystallization from pentane at -20 °C. The data were collected at -70 °C on a Siemens P4 diffractometer using monochromated

MoK α ($\lambda = 0.71073$ Å) radiation. The data were corrected for Lorentz and polarization effects; no absorption correction was applied since it was judged to be insignificant. The structure was solved by direct methods using SHELXTL5.0 (Siemens system) and refined by full matrix least squares on F^2 using all reflections. The methoxy group (C22A and C22B) was found to be disordered at two sites with unequal population. The size of the C22A and C22B atoms in the difference map, and refinement of the partial occupancy factor for these atoms, suggested 65% and 35% occupancy respectively for these atoms. Hydrogen atoms were included in the idealized positions. Details of the crystal data and refinement have been given in Table 2.5. Figures are drawn with 15% thermal ellipsoids. For the sake of clarity, C22B and all the hydrogens except H15A and H19A are omitted.

Procedure for the synthesis of 57a,b from 61 by reduction of the (propargyl)Co₂(CO)₆ cation with zinc:

In a 100 mL side-arm roundbottom flask containing a stir bar, 0.190 g (0.295 mmol) of **61** was dissolved in 0.11 mL (0.87 mmol) of propionic anhydride. The reaction mixture was kept under a flow of N₂, and it was cooled to -45 °C. At this time, 0.12 mL (0.87 mmol) HBF₄·OEt₂ was added dropwise. The contents of the flask became very viscous. After 45 minutes the reaction mixture was rinsed with 10 mL portions of anhydrous diethyl ether. When the ether washes remained clear, the insoluble salt remained at the bottom of the flask, and the remaining solvent was removed by vacuum. Once the salt was isolated, it was dissolved in 20 mL of methylene chloride, then cooled to -30 °C, then 0.014 g of zinc dust were added and the reaction stirred for 2 hours. Purification was performed by flash chromatography (1 : 1 petroleum ether/diethyl ether)

and two fractions were isolated. The compound in the first fraction was **57a**. The yield was 0.023 g (0.039 mmol, 19%). The second fraction contained a mixture of **57b** and the the compound resulting from **61** – HOAc. The combined yield was 0.006 g.

Procedure for the synthesis of 57a,b from 61 by treatment with Cp₂Co:

In a 100 mL side-arm roundbottom flask containing a stir bar, 0.171 g (0.265 mmol) of **61** was dissolved in 0.10 mL (0.81 mmol) of propionic anhydride. The reaction mixture was kept under a flow of N₂, and it was cooled to -30 °C. At this time, 0.16 mL (1.1 mmol) HBF₄·OEt₂ was added dropwise. The contents of the flask became very viscous. After 20 minutes the reaction mixture was rinsed with 10 mL portions of anhydrous diethyl ether. When the ether washes remained clear, the insoluble salt remained at the bottom of the flask, and the remaining solvent was removed by vacuum. Once the salt was isolated, it was dissolved in 20 mL of methylene chloride, then cooled to -78 °C, then a solution of 0.03 g (0.1 mmol) Cp₂Co in CH₂Cl₂ was added and the reaction stirred at -78 °C while being monitored by TLC. When the starting material had been consumed, the reaction mixture was filtered over silica gel, then concentrated. Purification was performed by PTLC (4 : 1 petroleum/diethyl ether) and three fractions were isolated. The yield of the salt was 0.085 g (0.014 mmol, 48%). The compound in the first fraction was **57a**. The yield of was 0.012 g (0.020 mmol, 8%). The compound in the second fraction was **57b**. The yield was 0.003 g (0.005 mmol, 2%). The compound in the third fraction was **61** - HOAc. The yield was 0.001 g (0.002 mmol, 1%).

Procedure for the synthesis of 70a,b

In a 100 mL side-arm roundbottom flask containing a stir bar, 0.292g (0.521 mmol) of **69a,b** was dissolved in 0.13 mL (1.0 mmol) of propionic anhydride. The reaction mixture was kept under a flow of N₂, and it was cooled to -30 °C. At this time, 0.22 mL (1.5 mmol) HBF₄·OEt₂ was added dropwise. The contents of the flask turned into a red solid. The temperature was raised to 0 °C, then the reaction mixture was stirred for 1 hour. At this time, the reaction mixture was rinsed with a 1 : 1 solution of diethyl ether/pentane and the reaction mixture dissolved. This solution was concentrated and was purified using flash chromatography. Two fractions were isolated. The first fraction contained a mixture of compounds, but no structures could be determined; however, the second compound contained a mixture of **70a,b**. The yield was 0.141g (0.262 mmol, 50%). The diastereomers, **70a** and **70b** were separated by PTLC (1 : 1 petroleum ether/diethyl ether).

Data for 70a,b:

Physical state: red oil.

¹H NMR (major) (300 MHz, CDCl₃) δ 7.43-7.40 (m, 2H, Ph), 7.34-7.18 (m, 8H, Ph), 5.95 (d, J = 4.5 Hz, 1H, CHCH(OR)Ph), 3.49-3.41 (m, 1H, CH₂CH(CCPh)), 2.41 (q, J = 7.8 Hz, 2H, COCH₂CH₃), 2.33-2.23 (m, 1H, CH₂CHCHPh), 1.92-1.84 (m, 1H, CH₂), 1.77-1.61 (m, 3H, CH₂), 1.29-1.20 (m, 2H, CH₂), 1.48 (t, J = 1.8 Hz, 3H, COCH₂CH₃).

IR (major) (CH_2Cl_2) 3045 (w), 2965 (w), 2087 (s), 2048 (s), 2023 (s), 1738 (m), 1605 (w) cm^{-1} .

^1H NMR (minor) (300 MHz, CDCl_3) δ 7.55-7.52 (m, 2H, Ph), 7.36-7.26 (m, 8H, Ph), 5.55 (d, $J = 10.2$ Hz, 1H, $\text{CHCH}(\text{OR})\text{Ph}$), 3.61-3.56 (m, 1H, $\text{CH}_2\text{CH}(\text{CCPh})$), 2.70-2.62 (m, 1H, CH_2CHCHPh), 2.42-2.30 (m, 1H, CH_2), 2.12 (q, $J = 7.2$ Hz, 2H, COCH_2CH_3), 1.73-1.63 (m, 5H, CH_2), 0.95 (t, $J = 7.2$ Hz, 3H, COCH_2CH_3).

IR (minor) (CH_2Cl_2) 3047 (w), 2979 (w), 2086 (m), 2045 (s), 2020 (s), 1734 (m), 1606 (w) cm^{-1} .

EIMS (12 eV) m/z : $[\text{M} - 2(\text{CO})]^+$ 562 (3.2), $[\text{M} - 3(\text{CO})]^+$ 534 (44.0), $[\text{M} - 4(\text{CO})]^+$ 506 (24.1), $[\text{M} - 5(\text{CO})]^+$ 478 (29.0), $[\text{M} - 6(\text{CO})]^+$ 450 (20.6).

Figure 2.3: 300 MHz ^1H NMR spectrum of **51** in CDCl_3

Figure 2.4: 300 MHz ^1H NMR spectrum of **57a** in CDCl_3

Figure 2.5: 300 MHz ^1H NMR spectrum of **57b** in CDCl_3

Figure 2.6: 300 MHz ¹H NMR spectrum of **62a** in CDCl₃

Figure 2.7: 300 MHz ^1H NMR spectrum of **63** in CDCl_3

Figure 2.8: 300 MHz ^1H NMR spectrum of **65** in C_6D_6

Figure 2.9: 300 MHz COSY NMR spectrum of **65** in C_6D_6

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CHAPTER III

ATOM-TRANSFER CYCLIZATION OF (PROPARGYL BROMIDES)Co₂(CO)₆

I. CYCLIZATION STUDIES OF 1-[(ALKYNYL)Co₂(CO)₆]-5-HEXENYL RADICALS

A. Introduction: Variations of the Barton-McCombie reaction

Despite efforts to improve the yield of the cyclization reactions starting from the cationic precursor complexes, no significant increase was seen. It became apparent that performing cyclizations by this method was not synthetically viable. For this reason other methodologies were explored in which the radical could be generated site-selectively at the propargyl position. The most common method of generating site-selective radicals is by employing the trialkyltin hydride method with alkyl halides. However, for our system this method was unattractive for two reasons: previous work involving the complexation of propargylic bromides with Co₂(CO)₈ showed that the desired complexes could not be isolated,¹ and the reaction temperatures for initiation with AIBN would likely cause decomposition of the complexes.

Perusal of the literature for milder reaction conditions led us first to a variation of the Barton-McCombie deoxygenation reaction² by Robins *et al.* which involves generating the radicals from phenoxythionocarbonates.³ This method was attractive because Oshima *et al.* found that mild conditions could be employed to generate the radical.⁴ For example, **1a** and **1b** were reduced using tributyltin hydride at 20 °C with

Et₃B/O₂ as the initiator to give the corresponding hydrocarbons in 82 and 78% yield respectively in 20 minutes (Scheme 3.1).

Scheme 3.1: Oshima's variation of the Barton-McCombie reaction

In order to effect deoxygenation, the alcohols are converted to the thionocarbonates by reaction with phenyl chlorothionocarbonate. After the thionocarbonates are isolated, they are treated with HSnBu₃ and Et₃B. The reaction is initiated by autoxidation of Et₃B (Scheme 3.2).⁵

Scheme 3.2: Autoxidation of Et₃B

For successful initiation, there must be adventitious oxygen in the system, or oxygen needs to be added directly to the reaction mixture.

been postulated.⁷

Scheme 3.3: The proposed mechanism of the Barton-McCombie reaction

When the ethyl radical is generated from Et_3B , it reacts with the HSnBu_3 , **3**, to generate the tributyltin radical, **4** (step a). This radical undergoes reversible addition to the sulfur atom of the thionocarbonate forming the adduct radical, **6** (step b). The adduct radical fragments to give **8** and the desired alkyl radical, **7** (step c), which abstracts a hydrogen atom from HSnBu_3 to produce the deoxygenated compound and the tributyltin radical, **4**

(step d). The efficiency of the reaction is highly dependent on the rate of fragmentation of the adduct radical, **6**.⁶

Most applications of the Barton-McCombie reaction and variations thereof have focused on the deoxygenation of secondary alcohols. However, Bartlett *et al.* reported that generation of the alkyl radical by this methodology could lead to cyclization reactions (Scheme 3.4).⁸

Scheme 3.4: Cyclization reactions employing Barton-McCombie reaction

The radical was generated from **9** by treatment with HSnBu_3 and AIBN, then heating to $80\text{ }^\circ\text{C}$. A mixture of **10** and **11** was obtained in a ratio of 62 : 38 in 93% overall yield.

B. Results

1. Synthesis of (propargyl thionocarbonate)Co₂(CO)₆ complexes

Because this system was amenable to the preparation of the phenyl thionocarbonate in one step from the propargylic alcohols, we decided to explore whether cyclization of (propargyl)Co₂(CO)₆ radicals would be successful using the Barton-McCombie methodology. Therefore, attempts were made to prepare the thionocarbonate from the complexed alcohol.

In the initial reaction, the alcohol was dissolved in methylene chloride and was then treated with 1 equivalent of phenyl chlorothionoformate (PTC-Cl), **13**, and 3.8 equivalents of pyridine (Scheme 3.5).³ The reaction was monitored by TLC, and it appeared as if no reaction had occurred. This was confirmed by the proton NMR spectrum of the crude reaction mixture.

Scheme 3.5: Attempted synthesis of **14** using pyridine/CH₂Cl₂

In a second experiment, the alcohol **12** was dissolved in acetonitrile then treated with 1.5 equivalents of PTC-Cl and 3 equivalents of DMAP (Scheme 3.6).

Scheme 3.6: Attempted synthesis of **14** using DMAP/CH₃CN

The reaction stirred overnight, and the color of the reaction mixture changed from red to green. An aliquot was taken from the reaction mixture and worked-up. The proton NMR spectrum indicated that the reaction mixture contained mostly starting material. It was allowed to stir for another 12 hours. A second aliquot was taken, and the proton NMR spectrum indicated that some changes had occurred to the starting material. For instance the multiplet between 5.04-5.01 ppm (CH_2CHOH) changed to a doublet or doublets, and the doublet at 2.13 ppm (CHOH) had disappeared. The rest of the spectrum looked similar to the spectrum of the starting alcohol, so it was unknown as to whether or not a reaction had actually taken place. After work-up and purification by PTLC, one compound was isolated. Its proton NMR spectrum revealed that it was starting material, which was very surprising considering that the initial NMR had indicated that a reaction had taken place. However, since **12** was the only compound isolated.

In the final attempt, the alcohol was dissolved in pyridine, then 1 equivalent of DMAP and 1 equivalent of PTC-Cl were added (Scheme 3.7). The reaction stirred for 2 days. A proton NMR spectrum of the crude reaction mixture indicated that it was composed of mostly starting material.

Scheme 3.7: Attempt at synthesizing **14** using DMAP/pyridine

It was not apparent why the synthesis of the thionocarbonate from **12** was unsuccessful. It is possible that the presence of the $-\text{Co}_2(\text{CO})_6$ group makes the hydroxyl proton less acidic so that the bases were too weak to deprotonate the alcohol. Because the $\text{p}K_{\text{a}}$ of the hydroxyl proton was unknown, and the employment of very harsh, basic conditions to effect deprotonation was undesirable, an attempt was made to synthesize the thionocarbonate from the uncomplexed propargyl alcohol, **15** (Scheme 3.8).

Scheme 3.8: Synthesis of **16** from **15**

Compound **15** was treated with 1.5 equivalents of **13** and 3 equivalents of DMAP. The reaction mixture stirred for two hours while being monitored by TLC. Once the starting material had been consumed, the reaction was worked up and purified by flash

chromatography. Compound **16** was isolated in 76% yield. Its proton NMR spectrum revealed the following characteristic resonances: a doublet of triplets at 6.99 ppm (CH_2CHCH , $J = 15.6, 6.0$ Hz), a triplet at 6.07 ppm (CH_2CHOR , $J = 6.3$ Hz), a doublet of triplets at 5.89 ppm (CH_2CHCH , $J = 15.6, 1.5$ Hz), and a singlet at 3.74 ppm (CO_2CH_3).

After **16** was isolated, it was complexed according to the procedure outlined by Nicholas (Scheme 3.9).⁹

Scheme 3.9: Complexation of **16**

The reaction mixture was purified by flash chromatography. Two fractions were isolated, and a proton NMR spectrum was taken of each. The compound in the first fraction was assigned structure **17**; it is the result of elimination of $\text{HOC}(\text{S})\text{OPh}$. This was evident by the presence of two doublets at 6.74 ppm (CHCHCCPh , $J = 14.1$ Hz) and 5.82 ppm ($\text{CHCHCO}_2\text{CH}_3$, $J = 15.6$ Hz), which each integrated for one proton, and two multiplets

between 7.01-6.88 ppm ($\text{CH}_2\text{CHCHCO}_2\text{CH}_3$) and 6.20-6.11 ppm ($\text{CH}_2\text{CHCHCCPh}$). The FAB mass spectrum was also consistent with the structural assignment as it gave an $M + 1$ peak at m/z 395.

The second compound off the column was the desired thionocarbonate complex, **14**. It was produced in 31% yield. The most distinguishing resonances were the doublet of triplets at 6.92 ppm ($\text{CH}_2\text{CHCHCO}_2\text{CH}_3$, $J = 15.6, 6.9$ Hz), the doublet at 5.79 ppm ($\text{CHCHCO}_2\text{CH}_3$, $J = 15.6$ Hz), and the doublet of doublets at 4.99 ppm (CH_2CHCOR , $J = 10.2, 4.2$ Hz). The FAB mass spectrum of **14** was also consistent with the structural assignment; there was an $M - 3(\text{CO})$ peak at m/z 512.

After **14** was synthesized, studies focused on the radical cyclization reactions. Initially, Oshima's conditions were employed where **14** was dissolved in benzene, then treated with 1.1 equivalents of tributyltin hydride and 1.1 equivalents of Et_3B .⁴ The reaction mixture stirred at room temperature for 5 hours and was monitored by TLC; however, no reaction had taken place. For this reason, the reaction mixture was heated to 40 °C and stirred another 12 hours. Again, TLC indicated that no reaction had occurred (Scheme 3.10).

Scheme 3.10: Attempted cyclization of **14** using Oshima's procedure

The second attempt to cyclize **14** employed the original Barton-McCombie conditions.² One concern about using this procedure was the reaction temperature. Typically, AIBN initiates radical reactions at 80 °C. However, because the cobalt complexes decompose at this temperature, the reaction was run at 60 °C (Scheme 3.11).

Scheme 3.11: Attempt to synthesize **18** using the original Barton-McCombie procedure

Compound **14** was dissolved in toluene, then 3 equivalents of tributyltin hydride and 0.4 equivalents of AIBN were added. The reaction was heated to 60 °C and stirred for 1 hour, then the flask was removed from the heat and the mixture stirred for another hour. TLC analysis indicated that no reaction was taking place. Therefore, 0.4 equivalents of AIBN were added and the reaction stirred at 60 °C for another 1.5 hours. Afterwards, the reaction was purified by a gravity column using alumina. Three fractions were collected, and a proton NMR spectrum was taken of each. However, the spectra showed that each fraction contained a complex mixture of compounds, and there was no evidence that cyclization had taken place.

As the original Barton-McCombie reaction conditions were unsuccessful, a modification of Oshima's conditions was attempted.⁴ One equivalent of Et₃B and 1.2 equivalents of HSnBu₃ were dissolved in toluene, then this solution was added to a

solution of **14** in toluene with a syringe pump over 1.5 hours. As addition took place, air was bubbled through the reaction mixture (Scheme 3.12). After the Et_3B and HSnBu_3 were added, the reaction stirred for 5 hours at room temperature. Analysis by TLC showed that no reaction had taken place.

Scheme 3.12: Attempted synthesis of **18** using a modification of Oshima's procedure

Finally, a different methodology by Barton was tested in which diphenylsilane, Ph_2SiH_2 , was employed as the reducing agent in reactions run at room temperature.¹⁰ The use of organosilanes in radical reactions offered an improvement over reactions employing trialkyltin hydrides because they are not as toxic, they are easier to remove during work-up, and the purity of commercially available silanes is not as questionable as it is for tributyltin hydride.¹¹ Therefore, a reaction was attempted where 1 equivalent of Et_3B and 1.2 equivalents of Ph_2SiH_2 were added to a solution of benzene containing the thionocarbonate, **14**, under a flow of oxygen. The reaction mixture stirred overnight, but TLC analysis indicated that no reaction had taken place (Scheme 3.13).

Scheme 3.13: Final attempt to synthesize **18** using Barton's modified procedure

It is unknown why the above reactions were unsuccessful. According to reports by Robins,³ Oshima,⁴ and Barton,¹² their reactions involving the phenoxy thionocarbonates were very successful. One difference between the above reactions and those reported in the literature is that we were attempting to generate a radical which is proximate to an organometallic group. Interaction with the organometallic group could affect the ability of the thionocarbonate group to fragment, and could ultimately result in no reaction taking place. However, there is no evidence to substantiate this.

2. Synthesis of (propargyl bromides)Co₂(CO)₆

Because efforts to cyclize **14** by the Barton-McCombie reaction were unsuccessful, a different method of site-selective radical generation was desired in which the radical precursor could be produced by a simple transformation of the complexed alcohols. It was decided that the best way to proceed was by generating the radical from a (propargyl halide)Co₂(CO)₆.

Even though earlier studies had demonstrated that complexation of propargyl bromides with Co₂(CO)₈ yielded dimers instead of the desired complexes,¹ there were no reports in the literature of attempts to synthesize (propargyl halides)Co₂(CO)₆ from

complexed alcohols. Uncomplexed propargyl halides had been synthesized from uncomplexed propargyl alcohols;¹³ therefore, it was postulated that the analogous complexed halides could be synthesized using the same procedure. The synthesis of (propargyl bromides) $\text{Co}_2(\text{CO})_6$ was attempted because bromides are less reactive than iodides, but more reactive than chlorides,¹⁴ and it was postulated that if the (propargyl bromides) $\text{Co}_2(\text{CO})_6$ could be isolated, they might be easier to handle than the iodides and still be reactive enough to achieve radical generation and cyclization.

The use of very mild conditions was desired for the synthesis of the bromides because their reactivity was unknown. In a report by Schmidt and Brooks, the propargyl bromide **20** was prepared using Br_2 and 1,2-bis(triphenylphosphino)ethane (DIPHOS) in 98% yield at 0 °C (Scheme 3.14).¹⁵

Scheme 3.14: Synthesis of uncomplexed propargyl halide, **20**

The reaction conditions were very mild and the bromide could be isolated without exposing it to air or moisture. Therefore the synthesis of the complexed bromide **21** was attempted according to the Schmidt/Brooks' procedure (Scheme 3.15).

Scheme 3.15: Synthesis of (propargyl bromide)Co₂(CO)₆, **21**

The DIPHOS (1.2 equivalents) was dissolved in CH₂Cl₂, then the solution was cooled to 0 °C; a solution of Br₂ (2.4 equivalents) in CH₂Cl₂ was added dropwise to the flask, then the reaction mixture stirred for 10 minutes, preforming the DIPHOS·Br₂ reagent. A solution of **12** in CH₂Cl₂ was then added dropwise to the flask. The reaction mixture stirred for one hour, then pentane and Et₂O were added to precipitate the phosphine byproducts. The solution was filtered through celite under N₂, then concentrated. Compound **21** was isolated in 88% yield. As expected, the bromide complex **21** was unstable and decomposed after approximately 2 hours if left at room temperature, so as a precaution, it was kept at 0 °C under nitrogen until it was employed in the cyclization reactions. The proton NMR spectrum of **21** was very similar to the starting alcohol. There was a doublet of triplets at 6.95 ppm (CH₂CHCHCO₂CH₃, J = 15.6, 6.9 Hz), and a doublet of triplets at 5.83 ppm (CH₂CHCHCO₂CH₃, J = 15.6, 1.5 Hz). In addition, the multiplet between 5.04–5.01 ppm (CH₂CHOH) was replaced by a doublet of doublets at 5.43 ppm (CH₂CHBr, J = 4.3 Hz). In the ¹³C NMR spectrum, the peak for C* shifted upfield to 56.2 ppm in **21** from 76.1 ppm in **12**.

3. Radical cyclization studies

Because **21** was so unstable, the cyclization reactions were set up as soon as it was isolated. Initially, the tributyltin hydride method was employed as outlined in Scheme 3.16. A solution of the starting material in benzene was heated to 40 °C, then a 0.002 M solution of HSnBu_3 and AIBN in benzene was added dropwise.

Scheme 3.16: Attempted cyclization of **21** using the tributyltin hydride method

The reaction mixture stirred for one hour, then was purified by gravity column chromatography over alumina. A proton NMR spectrum of the compound that was isolated indicated that it was neither the cyclized product, the starting bromide, nor the complexed alcohol. The compound did exhibit vinyl proton resonances (suggesting the dehydrohalogenation of **21**), but a structure could not be assigned.

Because the conditions for the tributyltin hydride method were rather harsh for this system, generation of the radical was attempted according to a variation of Oshima's procedure (Scheme 3.17).¹⁶

Scheme 3.17: Generation of the radical from **21** using Oshima's procedure

In the first reaction, a 0.023 M solution of HSnBu_3 in CH_2Cl_2 was added to a 0.023 M solution of the bromide, followed by addition of Et_3B (1 equivalent). The reaction stirred for three hours and was monitored by TLC for the appearance of the cyclized product; however, there was no evidence that it had formed. After the reaction mixture was purified by flash chromatography, three fractions were isolated. According to the proton NMR spectra, each fraction contained a mixture of compounds; however, there was evidence that the tributyltin radical may have trapped the radical before it cyclized. Therefore, the reaction was repeated, but this time the Et_3B was added very slowly and 10 ml of air was bubbled through the solution. The reaction stirred at $0\text{ }^\circ\text{C}$ for 1.5 h, then was quenched with a saturated solution of KF. Two fractions were isolated after purification by column chromatography. The proton NMR spectra of the fractions indicated that they both contained mixtures of the same compounds, but structures could not be assigned.

The reaction was repeated with modified conditions. In one case, a solution of HSnBu_3 in benzene was added to a 0.077 M solution of **21** in benzene at $-78\text{ }^\circ\text{C}$ by syringe pump over 30 minutes. In the second case, the solution of HSnBu_3 in benzene was added to a 0.004 M solution of **21** in benzene at $-78\text{ }^\circ\text{C}$ by syringe pump over a

period of six hours. For both reactions, purification was carried out using a gravity column of alumina. However, structures could not be assigned to the compounds that were isolated.

It was unknown why the above reactions were unsuccessful, but it was suspected that one of the reasons may have been due to impure HSnBu_3 .¹¹ Therefore, in order to avoid the problems associated with using HSnBu_3 , a cyclization reaction was attempted using Ph_2SiH_2 as the reducing agent (Scheme 3.18).¹⁰

Scheme 3.18: Cyclization of **21** using Ph_2SiH_2

In this reaction, **21**, 1 equivalent of Et_3B , and 1 equivalent Ph_2SiH_2 were dissolved in toluene at 0 °C. Oxygen was bubbled through the solution, then the reaction mixture was warmed to room temperature. When the starting material had been consumed, the reaction was concentrated and purified by PTLC. Two fractions were isolated, then a proton NMR spectrum was taken of each. One fraction contained a mixture of two compounds which were suspected to be cyclic because there were no resonances for vinyl protons. The compound in the second fraction also appeared to be cyclic. However, structures were not assigned until *a posteriori* analysis revealed that one of the compounds

was **18** and the other two compounds were diastereomers resulting from bromine atom transfer (*vide infra*).

In the subsequent reaction, the procedure was modified. Benzene was employed as the solvent, the ratio of starting material : Et₃B : Ph₂SiH₂ was 1 : 0.2 : 1.1, and only 0.2 equivalents of oxygen were bubbled through the solution (Scheme 3.19).

Scheme 3.19: Cyclization of **21** using modified conditions

The reaction was complete after 1 hour. Purification was carried out by passing the mixture through a gravity column of alumina. Three fractions were isolated, and a proton NMR spectrum was taken of each. The three compounds that had been observed in the reaction illustrated in Scheme 3.18 were observed in the spectra of this reaction. In addition, **18** was identified as one of the products by comparison to a proton NMR spectrum of an authentic sample that had previously been synthesized by reduction of the (propargyl)Co₂(CO)₆ cation with zinc (Scheme 2.29). An attempt was made to assign structures to the other two compounds. At this time, a mass spectrum could not be obtained, so structure determination was based solely on proton NMR data. According to the proton NMR spectra, there was a doublet at 4.59 ppm and one at 4.32 ppm. Each integrated for one proton (CHCH(CO₂CH₃)X). In addition, there were two singlets at

3.70 and 3.77 ppm which each integrated for three protons (CCO_2CH_3). Based on this data, it was concluded that the two compounds were cyclic, they were diastereomers of each other, and the protons assigned to the resonances at 4.59 and 4.32 ppm were each adjacent to a heteroatom. For these reasons, the compounds were assigned the generic structures, **22** in Figure 3.1. However, the identity of the heteroatom was unknown.

Figure 3.1: Suspected structure of the diastereomers

In a study by Nakamura *et al.*, it was reported that oxygenative cyclization reactions could be obtained by bubbling dry air through a solution of an alkyl halide and HSnBu_3 at 0 °C (Scheme 3.20).¹⁷

Scheme 3.20: Oxygenative radical cyclization of **23**

The alcohol formed as a result of the cyclized radical reacting with oxygen to generate the peroxide which was subsequently reduced in the presence of HSnBu_3 . Even though the conditions for the cyclization of **21** were not identical to the conditions outlined by Nakamura, it was postulated that it might be possible to obtain an oxygenative cyclization under the conditions that were being employed in the reaction in Scheme 3.19 and the heteroatom was tentatively assigned as being an oxygen atom (Figure 3.2). In **25a** and **25b**, the presence of the hydroxyl group in each diastereomer could explain the downfield doublets observed in the proton NMR spectra.

Figure 3.2: Tentative assignment for the cyclic compounds **25a** and **25b**

In the reaction illustrated in Scheme 3.19, the ratio of **18** to the putative diastereomers **25a** and **25b** was 1.3 : 1. However, because the objective of the study was to synthesize **18**, efforts were aimed at trying to increase its yield and decrease the formation of **25a** and **25b** by modifying reaction conditions. For example, the reaction in toluene was repeated, but the bromide decomposed. Also, a reaction was run without bubbling oxygen through the solution. Unfortunately **25a** and **25b** were still produced and the **18** : **25a** + **25b** ratio was 1 : 1.

In another reaction, the benzene was freeze-thaw degassed three times before the substrates were added. Both **25a** and **25b** were present in the product mixture and the **18** : **25a** + **25b** ratio improved slightly to 1.8 : 1. However, when the number of equivalents of Ph_2SiH_2 was increased from 1.1 to 2, the ratio improved to 2.8 : 1. In the hope of further improving the ratio, a reaction was run which employed 4 equivalents of Ph_2SiH_2 . The ratio increased to 4 : 1, but new side products were generated which could not be separated from **18**, **25a** and **25b**, and their structures could not be identified. Therefore, elimination of **25a** and **25b** from the product mixture was not possible.

Even though formation of **25a** and **25b** could not be suppressed, efforts remained focused on determining the reactivity of the (propargyl bromides) $\text{Co}_2(\text{CO})_6$. A new complexed alcohol was synthesized which contained an unsubstituted double bond. This alcohol was employed to simplify the product mixture by eliminating the formation of diastereomers in the 5-*exo* cyclization (Scheme 3.21). Compound **27** was prepared by treating **26** with BuLi, then a solution of **28a,b** in THF was added. The reaction was monitored by TLC for the disappearance of **28a,b**. After work-up and purification by flash chromatography, **29** was isolated in 83%. It was then treated with $\text{Co}_2(\text{CO})_8$ in methylene chloride to produce complex **30** in 95% yield.

Scheme 3.21: Synthesis of 30

The proton NMR spectrum of **29** aided in confirming the structure. The notable resonances were the double doublet of triplets at 5.83 ppm (CH_2CHCH_2 , $J = 17.1, 10.2, 6.6$ Hz), the doublet of doublets at 5.04 ppm (CHCHH^t , $J = 17.1, 1.6$ Hz), a double doublet of triplets at 4.98 ppm (CHCHH^c , $J = 10.2, 1.6, 1.0$ Hz) and the doublet of doublets at 4.61 ppm (CHOH , $J = 12.0, 6.6$ Hz). The proton NMR spectrum of **30** was slightly different from the spectrum of **29**. The resonance for the proton on the carbon adjacent to the hydroxyl group shifted downfield and overlapped with the resonances of the two protons on the terminal carbon of the double bond. These resonances appeared as a multiplet between 5.07–4.96 ppm. However, the most distinguishing resonance which confirmed the structure was the double doublet of triplets at 5.81 ppm (CH_2CHCH_2 , $J = 17.1, 10.2, 6.6$ Hz).

After **30** was synthesized, a cyclization reaction was attempted. For this reaction, **31** was prepared according to the procedure outlined by Schmidt and Brooks (i.e.

DIPHOS-Br₂).¹⁵ Once **31** had been isolated, a proton NMR spectrum was taken, then it was dissolved in 20 ml of benzene. The solution was cooled to 0 °C, then 0.2 equivalents of Et₃B and 1.1 equivalents Ph₂SiH₂ were added. The reaction mixture was warmed to room temperature then stirred for 4 hours (Scheme 3.22).

Scheme 3.22: First attempted cyclization of **31**

According to the TLC, a reaction had taken place and only one new spot was visible. Purification was performed using flash chromatography. One fraction was isolated, but the proton NMR spectrum showed that it was a mixture of products. Further purification was performed using PTLC, and three fractions were isolated; however, none of the compounds resembled **32**. Subsequent analysis of the proton NMR spectrum revealed that two isomers of the 6-*endo* cyclized product were produced (*vide infra*).

A cyclization reaction employing **33b,c** was also attempted (Scheme 3.23). The mixture **33b,c** was also prepared from **33a** using the procedure outlined by Schmidt and Brooks.¹⁵

Scheme 3.23: Attempted cyclization of **33b,c**

The conditions were the same as in Scheme 3.22. After stirring at room temperature for 1.5 hours, the TLC indicated the presence of starting material, so another equivalent of Et_3B was added to the reaction mixture and 10 ml of air was bubbled through the solution. The reaction mixture stirred another 5 hours, then another TLC was taken. It revealed that the bromide was still present, so another equivalent of Et_3B and 10 ml of air were added to the reaction. After 12 hours, the reaction mixture had changed color from red to brown. TLC indicated the starting material had been consumed. The reaction mixture was concentrated and purified by PTLC, and one fraction was collected. Its proton NMR spectrum looked as though the fraction contained a mixture of products.

There were resonances in the vinyl region which suggested that at least one of the compounds contained a double bond, and there was a doublet at 5.30 ppm which suggested that the putative cyclic oxygenated compound had been generated.

Because it appeared as though cyclization was occurring using **33b,c**, the reaction was repeated. While the bromide was being concentrated, the trap attached to the vacuum line became clogged with solvent, and the reaction flask was moved to a different vacuum line so the trap could be unclogged. During this time (approximately 30 minutes), the reaction mixture was inadvertently exposed to direct sunlight, and the color changed from red to brown. It was apparent that a reaction had taken place, and a proton NMR spectrum was taken of the crude residue. Surprisingly, the most notable resonances were the two doublets at 5.30 and 4.89 ppm. The compounds were suspected of being cyclic, and diastereomers. They were separated by PTLC, and a FAB mass spectrum was taken of each. The mass spectra revealed that each compound contained a bromine atom. Both spectra showed a $M-1(\text{CO})$ peak at m/z 596 and an $M+2-1(\text{CO})$ peak at m/z 598. At this point, it was apparent that **33b,c** had undergone a bromine atom transfer reaction to form two diastereomers of the cyclic bromide, **35a** and **35b**, and the idea that the reactions were undergoing oxygenative cyclization was dismissed (Scheme 3.24).

Scheme 3.24: Halogen atom transfer reaction of **33b,c**

The proton NMR spectrum of the major isomer, **35a**, contained a doublet at 5.30 ppm ($\text{CHCH}(\text{Ph})\text{Br}$, $J = 2.7$ Hz), and a double of doublet of doublets at 3.66 ppm ($\text{CH}_2\text{CH}(\text{CCPh})\text{CH}$, $J = 7.5, 7.5, 7.5$ Hz). The proton NMR spectrum of the minor isomer, **35b**, contained a doublet at 4.89 ppm ($\text{CHCH}(\text{Ph})\text{Br}$, $J = 10.8$ Hz), a multiplet between 3.90–3.88 ppm ($\text{CH}_2\text{CH}(\text{CCPh})\text{CH}$), and a multiplet between 3.06–3.01 ppm ($\text{CHCH}(\text{CHBr})\text{CH}_2$). The overall yield for this reaction was 83% and **35a** and **35b** were further characterized by ^{13}C NMR and IR spectroscopy. In addition the structure of **35b** was confirmed by X-ray crystallography (Figure 3.3).

According to this structure, the relative stereochemistry of **35b** is (S^* , S^* , S^*). The dihedral angle between C14–C15–C19–C20 is 123° , which is indicative of the two substituents being *trans*, and the typical non-linearity of the coordinated triple bond is illustrated by the 142° bond angle between C12–C13–C14 and the 140° bond angle between C13–C14–C15. These and other selected bond lengths and angles are listed in Table 3.1.

Figure 3.3: X-ray structure of 35b

Table 3.1: Selected bond lengths [Å] and bond angles [°] of **35b**

Co1-C13	1.957(4)	C12-C13-Co1	132.7(3)
Co1-C14	1.967(9)	C12-C13-Co2	134.5(3)
Co1-Co2	2.4624(9)	C15-C14-Co1	134.9(3)
Br1-C20	1.989(5)	C15-C14-Co2	136.4(3)
C13-C14	1.344(6)		

Table 3.2: Crystal data and structure refinement for **35b**

Empirical formula	$C_{26}H_{19}BrCo_2O_6$
Formula weight	625.18
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	$a = 24.862(5)$ Å $\alpha = 90^\circ$ $b = 8.691(2)$ Å $\beta = 92.03(3)^\circ$ $c = 23.130(5)$ Å $\gamma = 90^\circ$
Volume, Z	$4995(2)$ Å ³ , 8
Density	1.663 mg/m ³
Absorption coefficient	2.967 mm ⁻¹
F(0 0 0)	2496
Crystal size	0.42 x 0.36 x 0.28 mm
Theta range for data collection	2.36 to 24.97°
Reflections collected	4491
Independent reflections	4381
Absorption correction	semi-empirical from psi-scans
Max. and min. transmission	0.1726 and 0.1452
Refinement method	full-matrix least squares on F ²
Data / restraints / parameters	4375 / 0 / 317
Final R indices [$I > 2$ sigma (I)]	R1 = 0.0607, wR2 = 0.1461
R indices (all data)	R1 = 0.0705, wR2 = 0.1587
Extinction coefficient	0.00019(12)

After determining that **33b,c** was cyclizing to form **35a** and **35b**, reexamination of the proton NMR spectra taken of the compounds isolated from the cyclization reaction illustrated in Scheme 3.19 indicated that cyclized bromides were being produced in that reaction as well. In order to confirm this, FAB mass spectra were obtained of the three compounds that were isolated, and they confirmed the presence of bromine in two of the compounds and the presence of the reduced product, **18**. As a result, it was possible to assign the correct structures to the observed products (Scheme 3.25).

Scheme 3.25: Cyclization of **21** with proper structural assignments

In a subsequent reaction, a neat sample of **21** was irradiated for 45 minutes, then purified by flash chromatography. Three fractions were isolated and a proton NMR spectrum was taken of each. The first fraction contained a mixture of **36a** and **36b** in 56% yield. The distinguishing chemical shifts of the major isomer was the doublet at 4.59 ppm (CHCH₂(Ph)Br, *J* = 3.2 Hz), the singlet at 3.70 ppm (CO₂CH₃), and the quartet

at 3.51 ppm ($\text{CHCH}(\text{CCPh})\text{CH}_2$, $J = 8.0$ Hz). The characteristic resonances of the minor isomer were a doublet at 4.32 ppm ($\text{CHCH}(\text{Ph})\text{Br}$, $J = 8.0$ Hz), and a singlet at 3.77 ppm (CO_2CH_3), and a multiplet at 3.63 ppm ($\text{CHCH}(\text{CCPh})\text{CH}_2$). The resonances at 3.51 and 3.63 ppm suggest that the stereochemistry of the groups is *trans*.

The second fraction appeared to contain two isomers of an uncyclized compound. It was isolated in 4% yield, but structures could not be assigned. The third fraction contained **12** (Scheme 3.15). It was isolated in 2% yield. The presence of the compounds in these two fractions can be explained by the fact that the reaction mixture was unstable to silica gel, and either decomposed or hydrolyzed during purification.

To explore the scope of this atom transfer reaction, another cyclization reaction was attempted employing **31** (Scheme 3.22). This time, a neat sample was irradiated for 45 minutes, and the reaction mixture changed color from red to brown. Purification was performed using flash chromatography where the silica gel that had been treated with 2% of NEt_3 . Three fractions were isolated from the column and a proton NMR spectrum was taken of each. The first fraction appeared to contain decomposed material, but the second and third fractions each contained one compound. A FAB mass spectrum was obtained for each compound. They confirmed the presence of bromine, each had an $M-2(\text{CO})$ peak at m/z 520, and an $M+2-2(\text{CO})$ peak at m/z 522, and that the compounds in the two fractions were diastereomers. The NMR spectra of these compounds were very similar as well, but the peaks were not characteristic of the 5-*exo* product, **37** (Scheme 3.26).

Scheme 3.26: Expected 5-*exo* product from the cyclization of **31**

Had cyclization yielded **37**, two doublet of doublets should have been observed for H^{A} and H^{B} between 4–5 ppm, and a double doublet of doublets should have been observed for H^{C} between 3–4 ppm. Instead, the spectrum of the compound in the second fraction contained a broad singlet at 4.80 ppm, and an apparent triplet of triplets at 3.60 ppm, which both integrated for one proton. Similarly, the proton NMR spectrum of the compound in the third fraction contained an apparent triplet of triplets at 4.14 ppm and an apparent triplet of triplets at 3.02 ppm, which each integrated for one proton. These features were compared to the proton spectrum of cyclohexyl bromide.¹⁸ Surprisingly, in the proton NMR spectrum of cyclohexyl bromide, there was an apparent triplet of triplets at 4.20 ppm. This led us to conclude that cyclization had yielded the 6-*endo* product exclusively. Subsequently, the products were assigned structures **38a** and **38b** (Scheme 3.27).

Scheme 3.27: Cyclization of 31

In order to confirm these structural assignments, a DEPT NMR experiment was performed on the compound in the first fraction. This spectrum would distinguish whether the carbon adjacent to the bromine atom was a methylene or a methine carbon ($\text{CH}_2\text{CHBrCH}_2$, 6-*endo* or CHCH_2Br , 5-*exo*). The peak at 53.6 ppm was assigned to C2 (Table 3.1). In the DEPT NMR spectrum of **38a**, this peak pointed up, which indicated that it was a methine carbon and thereby confirmed the structures of **38a** and **38b**. Analysis of the spectrum is provided in Table 3.3.

Table 3.3: DEPT NMR experiment of **38a**

Chemical Shift (ppm)	Direction of peak	Assignment
53.6 (C2)	up	CH
43.0 (C1)	down	CH ₂
36.2 (C6)	up	CH
34.7	down	CH ₂
34.0	down	CH ₂
21.0 (C4)	down	CH ₂

A COSY NMR spectrum was also taken of **38a** and **38b**. The data in these spectra (see Experimental Section) also supported the conclusion that **38a** and **38b** were the cyclohexyl bromides.

Determination of the relative stereochemistry of the two substituents was sought by X-ray crystallography. Compound **38a** was crystallized from heptane; however assignment of the stereochemistry was not possible because the crystals seemed to be internally twinned. However, the presence of the six-membered ring was confirmed (Figure 3.4).

Figure 3.4: X-ray structure of **38a**

Tentative assignment of stereochemistry has been made for the isomers based on the NMR splitting patterns of the resonances at 4.80 and 4.14 ppm. In the spectrum of **38a**, the splitting pattern of the resonance at 4.80 ppm appears as a broad singlet. This is indicative that the coupling constants are not large, which according to the Karplus

correlation, occurs when the dihedral angle between two protons is very close to 90° .¹⁹ This situation is possible if the proton assigned to this peak ($\text{CH}_2\text{CHBrCH}_2$) is in the equatorial position. Therefore, the stereochemistry has been assigned as *trans*. Similarly, in the proton NMR spectrum of **38b**, the resonance at 4.14 ppm is an apparent triplet of triplets with a coupling constant of 11.8 Hz. According to the Karplus correlation, when the dihedral angle between two protons is 180° , the coupling constant should be approximately 10 Hz. This situation can be attained if the proton assigned to this peak is in the axial position. For this reason, the stereochemistry has been assigned as *cis*. The yield of the cyclization was 73% and the **38a/38b** ratio was 2 : 1. In addition, the compounds were further characterized by ^{13}C NMR and IR spectroscopy, as well as elemental analysis.

The generality of the cyclization reaction was further explored by examining the cyclization of **39**, which contained a methyl-substituted double bond. It was prepared by the same series of reactions that had been used to synthesize the other complexed alcohols, only **40** was employed as the ylide in the Wittig reaction (Scheme 3.28).

Scheme 3.28: Synthesis of 42a,b

The inseparable mixture of *cis* and *trans* isomers, **41a,b**, was obtained in 78%. In the proton NMR spectrum of the mixture, there was a multiplet between 5.48-5.35 ppm ($\text{CH}_2\text{CHCHCH}_3$) which represents the overlapping resonances of the vinyl protons of both isomers, and there were two overlapping doublet of doublets between 4.61-4.57 ppm (CH_2CHOH). When the mixture **41a,b** was complexed with $\text{Co}_2(\text{CO})_8$, the mixture, **42a,b** was produced in 96% yield. Again, the *cis* and *trans* isomers could not be separated. In the proton NMR spectrum of **42a,b**, the resonances for the vinyl protons of both isomers overlapped between 5.52-5.33 ppm ($\text{CH}_2\text{CHCHCH}_3$), and the resonances for the protons adjacent to the hydroxyl group overlapped between 5.06-5.00 ppm (CH_2CHOH). In addition, there were two doublets at 1.93 ppm (CHOH , $J = 5.1$ Hz) and at 1.60 ppm (CHOH , $J = 6.3$ Hz). The mixture was further characterized by ^{13}C NMR and IR spectroscopy as well as elemental analysis.

The mixture **42a,b** was converted to **43a,b** by Schmidt/Brooks' procedure,¹⁵ then a neat sample of **43a,b** was irradiated for an hour (Scheme 3.29). The color changed from red to brown. Purification was performed using PTLC, and two fractions were isolated. The proton NMR spectrum of the first fraction indicated the presence of two compounds. One compound was characterized by a double doublet of doublets at 5.82 ppm and two doublets at 5.02 and 4.93 ppm as well as a quartet at 3.51 ppm. The second compound was characterized by a doublet of quartets at 4.38 ppm (CHCHBrCH_3 , $J = 6.8, 2.4$ Hz), a quartet at 3.53 ppm ($\text{CH}_2\text{CH}(\text{CCPh})\text{CH}$, $J = 8.4$ Hz) and a doublet at 1.65 ppm (CHBrCH_3 , $J = 6.8$ Hz). In addition the FAB mass spectrum exhibited a $M-1(\text{CO})$ peak at m/z 533 and an $M+2-1(\text{CO})$ peak and m/z 535, which indicated that at least one of the compounds contained bromine. Based on this data, the structure of the bromine-containing compound was assigned as one of the isomers of **44a,b**, while the other compound was assigned structure **45**. It was postulated that the formation of **45** is due to the dehydrohalogenation of **44a,b** when exposed to silica gel during purification (Scheme 3.29).

Scheme 3.29: Cyclization of **43a,b**

The structure of **44a** was confirmed by a 1-D proton decoupling NMR experiment (Table 3.4).

Table 3.4: 1-D proton decoupling NMR experiment of **44a**

Irradiated Proton	Chemical Shift (ppm)	Result
H ^A	3.53	Change in H ^E
H ^C	4.38	H ^D appears as a singlet
H ^D	1.65	H ^C appears as a doublet
H ^E	2.28-2.21	Change in H ^A No change in H ^C

Irradiation at the resonance frequency for the methyl protons H^D, changed the coupling pattern of the resonance for the H^C proton to a doublet. Conversely, irradiation at the resonance frequency for H^C changed the coupling pattern of the resonance for the methyl protons to a singlet. The multiplet at 2.28-2.21 was assigned to H^E because irradiation of the resonance of H^E affected the resonance for H^A, but the multiplet resonance for H^C was not affected.

For the second fraction off the column, the proton NMR spectrum indicated that it consisted of two major compounds in a 1 : 1 ratio along with some minor compounds. The FAB mass spectrum revealed that at least one of the compounds contained bromine and was an isomer of **44a,b**. However, the proton NMR spectrum was very intriguing

because there were two doublets at 1.03 and 1.68 ppm. For this reason, it was postulated that the other major compound was **46**, which resulted from the 6-*endo* cyclization. In order to confirm this, a 1-D proton decoupling NMR experiment was performed on the mixture. For clarity, the data for **44b** is given in Table 3.5, and the data for **46** is given in Table 3.6.

Table 3.5: 1-D proton decoupling NMR experiment of **44b**

Irradiated Proton	Chemical Shift (ppm)	Result
H ^A	3.41	Change in H ^E
H ^B	overlapping	Could not determine
H ^C	4.24	Change in H ^D
H ^D	1.68	Change in H ^C
H ^E	2.31-2.60	No change in H ^A No change in H ^C

Irradiation at the resonance frequency of H^C showed a change in the splitting pattern of the H^D resonance. Conversely, irradiation at the resonance frequency of H^D showed a change in the splitting pattern of the H^C resonance. From this data the structure of the

second isomer of **44b** was confirmed; however the relative stereochemistry is unknown, but is expected to be *trans* because the resonance assigned to H^A is at 3.41 ppm.

The notable resonances of the proton NMR spectrum are assigned as follows: a doublet of quartets at 4.24 ppm (CHCHBrCH₃, J = 6.4, 6.0 Hz), a double doublet of doublets at 3.41 ppm (CH₂CH(CCPh)CH, J = 7.2, 7.2, 7.2 Hz) and a doublet at 1.68 ppm (CHBrCH₃, J = 6.4 Hz).

Table 3.6: Data from the 1-D proton decoupling NMR experiment of **46**

Irradiated Proton	Chemical Shift (ppm)	Result
H ^A	3.16	Change in H ^B
H ^B	2.49-2.45	Change in H ^A Change in H ^C Change in H ^D
H ^C	1.03	Change in H ^B
H ^D	2.31-2.60	Change in H ^B

According to the crystallographic data, the cyclohexyl ring is in the chair conformation, and the stereochemistry between the bromine atom and the alkynyl group is *cis*. These substituents are located in the equatorial positions. The methyl group is *trans* to the bromine atom and the alkynyl group, and it is in the axial position. The bond lengths between the carbon atoms of the cyclohexyl ring are in the normal range for C-C single bonds (1.50-1.53 Å). The non-linearity of the substituents on the coordinated triple bond is demonstrated by the C15-C14-C13 bond angle of 145° and a C14-C13-C12 bond angle of 143°. The dihedral angle between C21-C16-C15-C14 and C21-C16-C17-Br are -57 and 58° respectively.

Table 3.7: Selected bond lengths [Å] and bond angles [deg] for **46**

Co1-C14	1.978(3)	C14-Co1-Co2	51.42(9)
Co1-C13	1.986(3)	C13-Co1-Co2	51.08(9)
Co1-Co2	2.4623(9)	C13-Co2-Co1	51.82(9)
Co2-C13	1.965(3)	C14-Co2-Co1	51.51(9)
Co2-C14	1.975(3)	C14-C13-C12	143.4(3)
Br1-C17	1.983(3)	C12-C13-Co2	136.5(2)
C13-C14	1.340(4)	C12-C13-Co1	130.9(20)
		C13-C14-C15	145.6(3)
		C15-C14-Co2	133.5(2)
		C15-C14-Co1	131.9(2)

The structure of the minor isomers in the second fraction could not be determined. The optimized yield for the reaction was 60% and the ratio of 5-*exo* to 6-*endo* was 2 : 1.

Table 3.8: Crystal data and structure refinement for **46**

Empirical formula	C ₂₁ H ₁₇ BrCo ₂ O ₆
Formula weight	563.12
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.8064(9) Å alpha = 87.281(5)° b = 9.9550(8) Å beta = 83.053(6)° c = 14.8795(12) Å gamma = 71.994(7)°
Volume, Z	1091.6(2) Å ³ , 2
Density	1.713 mg/m ³
Absorption coefficient	3.384 mm ⁻¹
F(0 0 0)	560
Crystal size	0.12 x 0.38 x 0.22 mm
Theta range for data collection	2.15 to 26.34°
Reflections collected	4154
Independent reflections	3828
Absorption correction	integration
Max. and min. transmission	0.6718 and 0.3991
Refinement method	full-matrix least squares on F ²
Data / restraints / parameters	3826 / 0 / 272
Final R indices [I>2 sigma (I)]	R1 = 0.0324, wR2 = 0.0790
R indices (all data)	R1 = 0.0429, wR2 = 0.0859

C. Discussion

In the previous cyclization studies, several intriguing observations were made:

- When neat samples of (propargyl bromides) $\text{Co}_2(\text{CO})_6$ are irradiated, they undergo facile bromine atom transfer cyclizations in good yields (56-83%).
- Cyclization of **33b,c** yielded unprecedented exclusive formation of the 6-*endo* product.
- Cyclization of **43** yielded both 5-*exo* and 6-*endo* products.
- The stereochemistry of the 5-*exo* products, **35a,b**, **36a,b**, and **44a,b**, is *trans*; formation of the *cis*-isomers was not observed.

The proposed halogen atom transfer mechanism for the cyclization reactions of **21**, **31**, **33b,c**, and **43a,b** is outlined Scheme 3.30.

Scheme 3.30: Halogen atom transfer mechanism for **21**, **31**, **33b,c**, and **43a,b**

The contrasts between the halogen atom transfer cyclizations of **21**, **31**, **33b,c** and **43a,b** (Schemes 3.24, 3.25, 3.27 and 3.29) are striking when compared to halogen atom transfer reactions studied by Curran.²⁰ For example, in the atom transfer cyclizations of α -iodo and α -bromoesters, Curran found that **48a**, **48b** and **48c** were formed an ratio of 50 : 40 : 10 in an overall yield of 42% after **47** was irradiated for 24 h in the presence of $\text{Bu}_3\text{SnSnBu}_3$ (Scheme 3.31). Initiation by 10% AIBN or

$\text{Me}_3\text{SnSnMe}_3/\text{heat}$ gave comparable ratios in 78 and 83% yields respectively, but the reaction times were still 24 and 16 hours. When **49** was irradiated in the presence of 10% $\text{Bu}_3\text{SnSnBu}_3$ for 24 hours, **50a**, **50b** and **50c** were produced in an unspecified ratio in a combined yield of 42%, and unreacted bromide was still present in the reaction mixture. (Scheme 3.31).

Scheme 3.31: Curran's halogen atom transfer of **47** and **49**

A comparison of Curran's cyclizations with the cyclizations of the cobalt complexes **21**, **31**, **33b,c** and **43a,b** illustrates that **47** and **49** yielded the *cis* and *trans* isomers of the 5-*exo* products, **48a,b**, and **50a,b** as well as 6-*endo* products, **48c** and **50c** for every set of conditions Curran employed (Scheme 3.31); however, **21** and **33b,c** cyclized to give exclusive formation of the 5-*exo* products, and **31** cyclized to give exclusive formation of the 6-*endo* products. Only the cyclization of **43a,b** gave both the 5-*exo* and 6-*endo* products. In addition, **21**, **33b,c** and **43a,b** yielded only the *trans*-cyclopentyl bromides.

In general, the radical cyclizations of 5-hexenyl systems favor the formation of the 5-*exo* products when the double bond is unsubstituted or has a substituent on the terminal

carbon, while the 6-*endo* product is favored when there is a substituent located on the internal carbon of the double bond or the compound is conformationally biased.²⁰ Therefore, the exclusive formation of the 6-*endo* product from the cyclization of **31** was unexpected and is unprecedented.

Furthermore, the cyclization reactions of **21**, **31**, **33b,c** and **43a,b** were unique because they were initiated from the bromide. As previously stated, alkyl bromides are not good candidates for halogen atom transfer reactions because initiation is not efficient.²⁰ This was illustrated in Scheme 3.30, and by our attempts to cyclize the uncomplexed bromide, **51**, by irradiating a neat sample for 3 hours, in the absence of an initiator, to mimic the cyclizations of **21**, **31**, **33b,c** and **43a,b**, and also by irradiating a 0.3 M solution of **51** in benzene in the presence of 10% $\text{Bu}_3\text{SnSnBu}_3$ for 24 hours, to mimic Curran's cyclization procedure. In both cases only the starting material was recovered (Scheme 3.32).

Scheme 3.32: Attempted halogen atom transfer reactions employing **51**

The reactions in Scheme 3.32 support the idea that the $-\text{Co}_2(\text{CO})_6$ group exhibits a stabilizing effect on the generated radical because homolytic cleavage of the C-Br bond

occurs only when the triple bond is complexed, and when the bromine atom is in the propargylic position.

In order to explain the observed regioselectivity from the cyclizations of **21**, **31**, **33b,c** and **43a,b**, it is necessary to compare our results to those of Julia²¹ and Curran.²² As previously stated, Julia demonstrated that 1-substituted-5-hexenyl radical cyclizations became reversible when solutions of **52** in cyclohexane were heated in the presence of di-*tert*-butyl peroxide (Scheme 3.33).²¹

Scheme 3.33: Reversibility studies of **52** by Julia

Subsequently, Curran expanded upon Julia's studies and found that iodo(pent-4-enyl) malononitriles underwent reversible cyclization as well. In this study, solutions of **55** and **58** in benzene yielded the products shown in Scheme 3.34, in the indicated yields and ratios, after being heated to 80 °C in the dark between 8-10 hours.

Scheme 3.34: Halogen atom transfer of stabilized radicals

In order to gain more insight into the factors which make reactions reversible, a solution of **56** in benzene with 10% $\text{Bu}_3\text{SnSnBu}_3$ was irradiated for 50 minutes. Analysis of the reaction mixture showed that **56** and **57** were present in a ratio of 78 : 22 (Scheme 3.35).

Scheme 3.35: Reversibility study of **56** by irradiating in the presence of $\text{Bu}_3\text{SnSnBu}_3$

In reactions where **56** and **57** were reduced by HSnBu_3 , **56** yielded **60**, **61** and **62** in a ratio of 52 : 41 : 7, while **57** yielded **60** (Scheme 3.36).

Scheme 3.36: Studying the reduction of **56** and **57**

From these observations, Curran concluded that the cyano groups stabilize the radical to the extent that cyclization occurs under thermodynamic control, and this stabilization can facilitate the reverse cyclization (ring-opening) by shifting the equilibrium towards **64** when the radical is generated from **56** (Scheme 3.37).

Scheme 3.37: Stabilization of **64** facilitates ring-opening from **63**

In addition, it was postulated that reduction of **57** yielded only **60** because the radical is trapped before it can ring-open. Despite these observations, Curran remained uncertain as to whether or not true thermodynamic control (i.e. complete equilibration) was operating.

In a thermodynamically controlled process, the product composition is governed by the equilibrium thermodynamics of the system, and in a kinetically controlled process, the composition of the products reflects the competing rates of their formation.²³ In addition, Hammond's postulate relates the structure of the transition state to the structures of the reactants, intermediates, and products of the reaction by a comparison of their energies, so that in a reaction which proceeds through an early transition state, the transition state structure will most likely resemble the reactants. Conversely, in a reaction which proceeds through a late transition state, the transition state structure will most likely resemble the products.²³ According to the cyclization reactions of **21**, **31**, **33b,c** and **43a,b**, the results can be interpreted in two ways: the cyclizations could be occurring by a radical mechanism under kinetic control *via* a late transition state or the cyclizations could be occurring by a radical mechanism under thermodynamically control where cyclization is reversible. Based on our observations, we believe the former to be the case

and that the cyclizations proceed through a late transition state because the radical is highly stabilized by the $-\text{Co}_2(\text{CO})_6$ group

Several observations provide evidence to suggest that the reaction is proceeding by a radical mechanism. For example, the cyclizations of **21**, **31**, **33b,c** and **43a,b** were very efficient either when neat samples of the bromides were employed or when the bromides were dissolved in a non-polar solvent (benzene). This suggests that the reactions are not affected by solvents and is supportive of a radical mechanism because unlike polar reactions, solvents have very little effect on the rate or efficiency of radical reactions.²⁴

Additional support for a radical mechanism was provided by the fact that the cyclization reactions were very efficient regardless of the electronic character of the double bond. For example, if the cyclization was proceeding by a carbocation mechanism, the cyclization of **43a,b** should have been much more efficient than the cyclization of **21**; however, both cyclization reactions were complete after 45 minutes and the yields were comparable. Furthermore, in the cyclization of **21**, if the reaction had proceeded by a cationic mechanism, the observed 5-*exo* product would have required the generation of a very unstable cation compared to the cation from which the 6-*endo* product would have formed (Scheme 3.38).

Scheme 3.38: Evidence against a cationic cyclization mechanism for **21**

Considering that only the 5-*exo* product was observed, it is highly unlikely that **36a,b** were produced from cation **66**.

Further evidence for the radical mechanism was provided by the fact that **31** underwent cyclization to give exclusive formation of the 6-*endo* products employing two common methods of radical initiation: Et₃B/O₂ (Scheme 3.22), and photochemical initiation (Scheme 3.27).

Finally, irradiation of 1-(propargyl bromide)Co₂(CO)₆-6-heptenyl systems produced dimeric compounds which can best be explained by the reactions occurring *via* a radical mechanism (*vide infra*).

In addition to the reactions occurring by a radical process, we believe that they are also operating under kinetic control *via* a late transition state in which the regioselectivities observed in the cyclizations of **21**, **31**, **33b,c**, and **43a,b** reflect a product-like transition state structure with significant C-C bond making (and breaking) as well as

development of radical character at the olefinic carbons in which the resulting products represent formation of the most stable radicals, which are generated faster than the unstable radicals (Scheme 3.39).

Scheme 3.39: Mechanistic rationale for cyclizations of **21**, **31**, **33b,c**, and **43a,b**

For example, in the cyclizations of **21** and **33b,c** ($R = \text{CO}_2\text{CH}_3$ and Ph) exclusive formation of the 5-*exo* products can be rationalized by the presence of groups on the terminal carbon which stabilize the developing radical by delocalization. Similarly, in the cyclization of **31** ($R = \text{H}$), formation of the 6-*endo* product reflects greater stabilization of the developing secondary radical over the developing primary radical. Finally, the seemingly reversible cyclization of **43a,b** ($R = \text{CH}_3$) can also be explained by the mechanism in Scheme 3.38 because there is developing secondary radical character in both the 5-*exo* and 6-*endo* cyclizations, which are presumably very close in energy. Therefore there should be a distribution between the two products. This is in complete agreement with our observations.

The cyclization of **43a,b** also offers an indirect comparison of the stability of the (propargyl) $\text{Co}_2(\text{CO})_6$ radical versus the stability of Curran's malononitrile stabilized radicals (Scheme 3.34) as well as evidence that the cyclizations of **21,31**, **33b,c**, and **43a,b** are occurring *via* a late transition state. In Curran's study, only the 5-*exo* product was observed from the cyclization of **58**, while **43a,b** yielded both the 5-*exo* and the 6-*endo* products. Because the two systems are exactly the same with the exception of the group(s) stabilizing the radical, it can be concluded that the (propargyl) $\text{Co}_2(\text{CO})_6$ radical is stabilized to a greater extent than the malononitrile radical. Furthermore, Curran has reported that the cyclization of **58** is operating by thermodynamic control, yet none of the 6-*endo* product is observed. This suggests that the cyclization is actually proceeding by kinetic control, and that while **55** can undergo reversible radical cyclizations in the presence of an unsubstituted double bond, when the substitution (and hence the electronic character) of the double bond changes (**58**), the reaction appears to proceed by kinetic

control. Therefore, the production of 5-*exo* and 6-*endo* compounds from the cyclization of the highly stabilized radical **43a,b** does not necessarily have to be explained by a reversible cyclization; the results can also be explained by the cyclization occurring under kinetic control *via* late transition state.

In addition to explaining the regiochemical outcome of the reactions, this mechanism also explains the stereochemistry observed in the 5-*exo* cyclizations: in a late transition state, the bond forming between C1 and C5 will be much shorter and the substituents will experience greater steric interactions. For this reason they will be arranged *trans* to each other in order to relieve the steric strain.

The stereochemistry for **46** (Scheme 3.29) can be rationalized in the same way, but the situation may not be as simple because the cyclization was carried out using a mixture of diastereomers. Compounds **43a** and **43b** might cyclize with different regiochemistry, and it is impossible to know if one or both lead to the 6-*endo* product **46**. Therefore, a definitive explanation of the observed stereochemistry cannot be offered.

II. CYCLIZATION STUDIES OF 1-[(ALKYNYL)Co₂(CO)₆]-6-HEPTENYL RADICALS

A. Synthesis of starting materials

As we had established that cyclizations of (propargyl)Co₂(CO)₆ radicals were facile reactions which provided products with very high regio- and stereoselectivities, we decided to further explore their synthetic utility. One manner in which this was done was by attempting cyclizations employing the homologous 1-[(alkynyl)dicobalt hexacarbonyl]-6-heptenyl systems. We decided that the complexed alcohols for use in the cyclizations

should be synthesized using the same procedure that was employed in the 5-hexenyl cyclizations because it was very efficient and required few steps. In order to do this, it was necessary to prepare adipaldehyde, **69**, (Scheme 3.40). This was done by dissolving *trans*-1,2-cyclohexane diol, **68**, in water, then treating it with 1 equivalent of NaIO₄ (Scheme 3.40).²⁵

Scheme 3.40: Synthesis of adipaldehyde

The adipaldehyde was isolated in 29% yield, after purification by vacuum distillation. An attempt was then made to generate the propargyl alcohol by treating the adipaldehyde with 1 equivalent of phenylacetylide (Scheme 3.41). The reaction mixture stirred at -78 °C until **69** was consumed. After work-up and purification by flash chromatography, one fraction was isolated and proton NMR, IR, and mass spectra were taken. According to this data, the adipaldehyde had undergone diaddition. None of the monoadduct could be detected.

Scheme 3.41: Diaddition of phenylacetylide to **69**

In order to circumvent the problem of diaddition, 6,6-dimethoxyhexanal, **72**, was synthesized according to Schreiber's procedure.²⁶ It was isolated in 60% yield. (Scheme 3.42).

Scheme 3.42: Synthesis of **72**

After **72** was isolated, the propargyl alcohol, **73**, was synthesized in 24 % yield according to Scheme 3.43.

Scheme 3.43: Synthesis of 73

The most characteristic resonances in the proton NMR spectrum of **73** were a singlet at 9.76 ppm ($\text{CH}\underline{\text{O}}$), the triplet at 6.8 ppm ($\text{CH}_2\text{CH}\underline{\text{C}}(\text{CCPh})\text{OH}$, $J = 6.8$ Hz) and a broad singlet at 1.91 ppm ($\text{CHO}\underline{\text{H}}$). The presence of the downfield singlet indicated that when the aldehyde was deprotected in the final step, the molecule did not cyclize. Therefore in order to confirm the presence of a carbonyl group in the molecule, an IR spectrum was taken and it contained a peak at 1723 cm^{-1} .

With the successful synthesis of **73**, preparation of the other complexed alcohols was straightforward. Alcohol complex **75** was prepared in 91% from **74** starting from **73** via a Wittig reaction followed by complexation with $\text{Co}_2(\text{CO})_8$ (Scheme 3.44).

Scheme 3.44: Synthesis of 75

Some notable resonances from the proton NMR spectrum of **74** were a double doublet of triplets at 5.48 ppm ($\text{CH}_2\text{CHCH}^i\text{H}^c$, $J = 17.0, 10.2, 6.8$ Hz), two broad doublets at 4.99 ppm ($\text{CH}_2\text{CHCH}^i\text{H}^c$, $J = 17.0$ Hz), and 4.93 ppm ($\text{CH}_2\text{CHCH}^i\text{H}^c$, $J = 10.2$ Hz), and a multiplet between 4.60–4.55 ppm ($\text{CH}_2\text{CH}(\text{CCPh})\text{OH}$).

Upon complexation of **74** to form **75**, the multiplet between 4.60–4.55 ppm in the spectrum of **74** shifted downfield to a multiplet between 5.02–4.90 ppm, the double doublet of triplets in the spectrum of **74** shifted downfield to 5.76 ppm ($\text{CH}_2\text{CHCH}^i\text{H}^c$, $J = 17.0, 10.7, 6.8$ Hz), and there was a doublet at 1.90 ppm (CHOH , $J = 4.8$ Hz).

The alcohol, **78**, was also prepared analogously in 51% yield from **77** (Scheme 3.45).

Scheme 3.45: Synthesis of 78

The proton NMR spectrum of **77** exhibited a doublet of triplets at 6.90 ppm ($\text{CH}_2\text{CHCHCO}_2\text{CH}_3$, $J = 15.6, 6.9$ Hz), a doublet at 5.76 ppm ($\text{CHCHCO}_2\text{CH}_3$, $J = 15.6$ Hz), a multiplet between 4.57–4.86 ppm (CH_2CHOH), and a singlet at 3.64 ppm (CO_2CH_3). The proton NMR spectrum of **78** was very similar with a doublet of triplets at 6.95 ppm ($\text{CH}_2\text{CHCHCO}_2\text{CH}_3$, $J = 15.6, 6.9$ Hz), a doublet of triplets at 5.76 ppm ($\text{CHCHCO}_2\text{CH}_3$, $J = 15.6, 1.0$ Hz), a multiplet between 5.05–4.99 ppm (CH_2CHOH), a singlet at 3.64 ppm (CO_2CH_3), and a doublet at 1.96 ppm (CHOH , $J = 5.1$ Hz).

One problem that was encountered during the synthesis of the complexed alcohols was the preparation of **73** from **72** (Scheme 3.43); the yield of this reaction was very low. It was postulated that the conditions which were used to deprotect the acetal were too harsh for this compound because it contained the acid-sensitive propargyl alcohol. Therefore, attempts were made to deprotect it using milder conditions such as Amberlyst resin,²⁷ or silica gel;²⁸ however, these methods were unsuccessful. For this reason, the

synthetic procedure was modified by reversing the order of the Wittig reaction and the addition of phenylacetylide in the preparation of **86a,b** and **87a,b** (Scheme 3.46).

Scheme 3.46: Synthesis of **86a,b** and **87a,b**

The overall yields after the Wittig reaction and hydrolysis of the acetal were 35% for **82a,b** and 42% for **83a,b**. In both cases, the *cis* and *trans* isomers could not be separated. The most notable resonances in the proton NMR spectrum of **82a,b** were the singlets at 9.76 and 9.72 ppm (CH_2CHO), a doublet at 5.64 ppm (CH^cCHPh , $J = 11.7$

Hz) and 6.37 ppm (CH^tCHPh , $J = 16.0$ Hz), a doublet of triplets at 6.35 ppm (CH_2CHCH^t , $J = 16.0, 6.6$ Hz) and a doublet of triplets at 5.62 ppm (CH_2CHCH^c , $J = 11.7, 7.2$ Hz).

The proton spectrum for **83a,b** contained a singlet at 9.74 ppm (CH_2CHO); however, all of the resonances for the vinyl protons in both isomers overlapped in a multiplet ranging from 4.45-5.33 ppm.

After addition of phenyl acetylide, **84a,b** and **85a,b** were produced in 73 and 70% yield respectively from the aldehyde precursors. The notable changes in the proton NMR spectra of these compounds were the disappearance of the downfield singlets and the appearance of a multiplet between 4.61-4.52 ppm (CH_2CHOH) for **84a,b** and a multiplet between 4.55-4.50 ppm (CH_2CHOH) for **85a,b**. In addition the proton NMR spectrum of **84a,b** contained a doublet at 6.38 ppm (CH_2CHCH^c , $J = 11.5$ Hz) and at 6.36 ppm (CH_2CHCH^t , $J = 16.0$ Hz), a doublet of triplets at 6.18 ppm (CH_2CHCH^t , $J = 16.0, 7.0$ Hz) and at 5.63 ppm (CH_2CHCH^c , $J = 11.5, 7.0$ Hz). The spectrum of **85a,b** contained a multiplet between 5.42-5.30 ppm which was assigned to the overlapping vinyl protons of both isomers.

The complexed alcohols **86a,b** and **87a,b** were produced in 74 and 95% respectively. In the proton NMR spectrum of **86a,b**, the most notable change was that the upfield peaks of the methylene protons converged from three multiplets between 1.95-1.91, 1.82-1.76, and 1.57-1.52 ppm into two multiplets between 1.89-1.63 and 1.59-1.45 ppm. In addition there were two doublets at 1.91 ppm (CHOH , $J = 5.4$ Hz), and 1.88 ppm (CHOH , $J = 5.1$ Hz). The effect was similar for compound **87a,b**. The

multiplets between 2.06-1.93, 1.77-1.71, 1.62-1.54, 1.52-1.43 and 1.41-1.32 ppm converged into one multiplet between 3.07-1.34 ppm.

B. Cyclization studies

The cyclization reactions were carried out using the procedure that was employed for the cyclization of the 5-hexenyl systems. Initially, **75** was converted to the bromide according to the method of Schmidt and Brooks (Scheme 3.47).¹⁵

Scheme 3.47: Synthesis of **88**

The proton NMR spectrum of **88** was not well resolved, but a double doublet of triplets, and two overlapping doublets could be distinguished at 5.79 ppm and between 5.00-4.92 ppm as well as an apparent triplet at 5.44 ppm (CH_2CHBr).

A neat sample of **88** was irradiated for 1.5 hours, then purification was performed using flash chromatography. Six fractions were collected, and a proton NMR spectrum was taken of each. The spectrum of the third fraction was the only one which indicated the presence of a cyclic compound. Its proton NMR spectrum showed a multiplet from 4.70-4.68 ppm ($\text{CH}_2\text{CHBrCH}_2$), an apparent triplet at 3.57 ppm ($\text{CH}_2\text{CH}(\text{CCPh})\text{CH}_2$, $J = 9.5$ Hz), and a broad doublet at 2.57 ppm ($\text{BrCHCHHCH}(\text{CCPh})$). The NMR

spectrum lacked a doublet between 4–5 ppm, and the downfield multiplets each integrated for one proton. In addition, the FAB mass spectrum gave an $M - 1(\text{CO})$ peak at m/z 534, and an $M+2 - 1(\text{CO})$ peak of equal intensity at m/z 536. Based on the spectral data, it was postulated that this fraction contained a single stereoisomer of the cycloheptyl bromide complex, **89** (Scheme 3.48).

Scheme 3.48: Cyclization of **88**

Further confirmation of the structure was achieved by a 1-D proton decoupling NMR experiment. The analysis is shown in Table 3.9.

Table 3.9: Data for 1-D proton decoupling NMR experiment of **89**

Irradiated Proton	Chemical Shift (ppm)	Result
H ^A	4.70-4.68	Change in H ^{B1} Change in H ^{B2}
H ^{B1}	2.57	Change in H ^A Change in H ^C Change in H ^{B2}
H ^{B2}	2.68-2.19	Change in H ^A Change in H ^C Change in H ^{B1}
H ^C	3.57	Change in H ^{B1} Change in H ^{B2}

Both H^{B1} and H^{B2} are coupled to H^A and H^C. These interactions would not be possible in the cyclohexyl bromide because H^{B1} and H^{B2} would be on different carbons and neither would couple to both H^A and H^C at the same time. While the regiochemistry of cyclization has been confirmed, the relative stereochemistry has not been determined.

Compound **89** was isolated in 8% yield. However, none of the compounds in the other fractions could be identified. For this reason, efforts focused on improving the yield. Some modifications to the procedure included dissolving **88** in benzene, then irradiating for 7 hours at room temperature, and irradiating for 22 hours while keeping the flask at 5 °C. In both cases, **88** decomposed and no cycloheptyl bromide complex was isolated. Finally, **88** was dissolved in benzene and the reaction was initiated by Et₃B. The reaction mixture stirred for 8 hours and the color changed from red to brown. Purification was carried out using a gravity chromatography with alumina as the adsorbent. Two fractions were isolated, but neither was **89**. The structure of the compound in the first fraction could not be identified, and the compound in the second fraction was the alcohol, **75**, which most likely resulted from the hydrolysis of unreacted bromide during chromatography.

The unsuccessful attempts to improve the yield of **89**, prompted us to move ahead and study the cyclization of the bromide, **90**, in which the double bond was substituted with an electron-withdrawing group (Scheme 3.49).

Scheme 3.49: Synthesis of **90**

Compound **90** was prepared by the procedure outlined by Schmidt and Brooks,¹⁵ then the neat compound was irradiated for 30 minutes. At this time, a proton NMR spectrum was taken of the reaction mixture which indicated that only **90** was present. The reaction mixture was irradiated for another 30 minutes, but it looked as though the reaction mixture was decomposing because a green solid had formed. The reaction mixture was filtered through celite and a proton NMR spectrum was taken of the filtrate, and it showed that the isolated compound was the alcohol, **78**.

The reaction was repeated; only this time, a neat sample of **90** was irradiated for 4 hours. The color of the reaction mixture changed from red to brown, then it was purified by gravity chromatography using alumina. Three fractions were isolated and a proton NMR spectrum as well as a FAB mass spectrum were taken of each (Scheme 3.50).

The proton NMR spectrum of the compound in the first fraction contained a multiplet between 7.00-6.92 ppm ($\text{CH}_2\text{CHCH}(\text{CCPh})$), a doublet at 6.72 ppm ($\text{CHCH}(\text{CCPh})$), a multiplet from 6.21-6.15 ppm ($\text{CH}_2\text{CHCH}(\text{CO}_2\text{CH}_3)$), and a broad doublet at 5.82 ppm ($\text{CHCHCO}_2\text{CH}_3$). In addition the FAB mass spectrum gave an $\text{M}-2(\text{CO})$ peak at m/z 502. Based on this data, the structure of the compound was assigned as **92** (Scheme 3.50).

Scheme 3.50: Cyclization of 90

The proton NMR spectrum of the second fraction looked as though it contained the dimer. There was a multiplet between 6.95-6.92 ppm, a multiplet between 6.90-6.67 ppm, and two overlapping doublets at 5.60 ppm and 5.56 ppm. The FAB mass spectrum gave an $\text{M}-3(\text{CO})$ peak at m/z 998. This was consistent with the compound being a dimer, and it was assigned structure **91**. The compound in the third fraction was the alcohol **78**. It must be noted that even though cyclization of **90** was not successful, the formation of **91** implies that radicals are being generated when **90** is irradiated.

In order to try to circumvent dehydrohalogenation and dimerization, the reaction was repeated, only the bromide was dissolved in benzene and initiation was done with Et_3B . The reaction stirred for 1.5 hours and was then purified by gravity column using alumina. Four fractions were collected and a proton NMR and FAB mass spectrum was taken of each. The structure of the compound in the first fraction could not be determined; however, the compound in the second fraction appeared to be the dimer, **91**. The FAB mass spectrum gave an $\text{M}-2(\text{CO})$ peak at m/z 998. The compound in the third and fourth fractions was the alcohol **78**.

Because cyclization of **90** was unsuccessful, we decided to move on rather than continue to modify the procedure hoping to observe cyclization. Therefore, cyclization was attempted with **93a,b** (Scheme 3.51)

Scheme 3.51: Attempted cyclization of **93a,b**

After the bromide **93a,b** was prepared from **86a,b**, it was irradiated for 2 hours, then purified by chromatography using alumina. Four fractions were collected and a proton NMR and FAB mass spectrum were taken of each. The compound in the first fraction was **94a,b**. It resulted from dehydrohalogenation of **93a,b**. The FAB mass spectrum gave an $M-3(\text{CO})$ peak at m/z 474. Structures for the compounds in the second and third fractions could not be determined, and the compound in the fourth fraction was the alcohol, **86a,b** (Scheme 3.51). There was no evidence that cyclization had occurred.

The final attempt to observe cyclization with these systems employed **95a,b** (Scheme 3.52).

Scheme 3.52: Attempted cyclization of **95a,b**

The bromide **95a,b** was prepared from **87a,b**, then was irradiated for 4 hours, and the color of the reaction mixture changed from red to brown. Purification was performed

using column chromatography using alumina. Four fractions were isolated and proton NMR and FAB mass spectra were taken of each. The FAB mass spectrum of the compound in the first fraction gave an $M-1(CO)$ at m/z 468. However, a structure could not be assigned to the compound. One of the compounds in the second fraction was the dimer, **96**. Its FAB mass spectrum contained an $M-3(CO)$ peak at m/z 910. A structure for the compound in the third fraction could not be assigned, and the compound in the fourth fraction was the alcohol, **87a,b** (Scheme 3.52). There was no evidence that cyclization had occurred.

C. Discussion

Radical cyclizations of 6-heptenyl systems can be synthetically useful. In most cases, cyclization favors the 6-*exo* product, but the rate of cyclization is much slower than the rate of cyclization in 5-hexenyl systems for entropic reasons.²⁹ Also, when the rate of cyclization is very slow, the rates for 7-*endo* cyclization and intramolecular 1,5-allylic hydrogen transfer can compete (Scheme 3.53).²⁹

Scheme 3.53: Rate of cyclization for 7-heptenyl systems

In his studies of halogen atom transfer reactions of iodo(hept-6-enyl)malononitriles, Curran found that solutions of **102** and **105** in benzene cyclized to give the products in Scheme 3.54 when heated at 80 °C in the presence of 5% AIBN.²² The overall yield for the cyclization of **102** was 95% and the yield for the cyclization of **105** was 95%.

Scheme 3.54: Halogen atom transfer of **102** and **105**

In the attempted cyclization reactions of **88**, **90**, **93a,b**, and **95a,b**, the only compound which cyclized was **88**, but the yield was low. In the other reactions the only compounds that could be identified were the dimer, the compound resulting from dehydrohalogenation, or the alcohol, which is most likely produced by hydrolysis of the bromide when it is placed on alumina or silica gel. There was no evidence in any of the reactions that 1,5-allylic hydrogen transfer was taking place. These results contrast greatly with those of Curran's. However, one important difference in the reaction conditions was that neat samples of the bromides were irradiated, whereas Curran's procedure involved heating the iodides to 80° C in benzene. Even when **88** was irradiated in a solution of benzene kept at 5 °C, there was no evidence for cyclization. Therefore, we can only speculate that the higher reaction temperatures help to overcome the entropic barriers associated with heptenyl cyclizations. Also, it must be noted that even though

cyclization did not occur in the reactions involving **90**, **93a,b**, and **95a,b**, evidence for the radical mechanism was obtained by the formation of the dimeric products.

In the cyclization of **88**, one important feature of the reaction is that only the thermodynamically favored *7-endo* product was isolated. In the cyclization of the analogous system, Curran observed both the *6-exo* and the *7-endo* products in an *exolendo* ratio of 85 : 15 (Scheme 3.54). This gives further evidence for the greater stability of (propargyl)Co₂(CO)₆ radicals, and that the cyclizations proceed *via* a late transition state (Scheme 3.55).

Scheme 3.55: Mechanistic rationale for the formation of **89**

III. CONCLUSION

In our investigation of homolytic methods for the generation of (propargyl) $\text{Co}_2(\text{CO})_6$ radicals, the failure we encountered employing the thionocarbonate complexes and the success we encountered in the synthesis of (propargyl

bromides) $\text{Co}_2(\text{CO})_6$ were unexpected. We believe that cyclizations employing the thionocarbonates were unsuccessful because of inefficient fragmentation of the adduct radical **6** (Scheme 3.3). However, we did not investigate it further because generation of the radicals from the propargyl bromide complexes was very successful.

The cyclization reactions employing the 5-hexenyl radicals, which were generated by irradiation of the complexed bromides, gave very interesting results. According to our studies, the 1-[(alkynyl) $\text{Co}_2(\text{CO})_6$]-5-hexenyl radicals undergo a facile bromine atom transfer cyclization reaction to give products with novel regio- and stereoselectivities; compounds **21** and **33b,c** cyclized with exclusive formation of the 5-*exo* product, **31** cyclized with exclusive formation of the 6-*endo* product, and **43a,b** cyclized to give both the 5-*exo* and 6-*endo* products. In the cases where the 5-*exo* product was produced, the relative stereochemistry of the groups was *trans*. In order to explain our results we have postulated that the reaction is proceeding by kinetic control *via* a late transition state, where the products reflect the formation of the most stable developing radical in the transition state. This work has been published.³⁰

In reactions employing the 6-heptenyl systems, only **88** cyclized to give the 7-*endo* product in very low yield. Even though the yield of this reaction could not be improved, exclusive formation of the 7-*endo* product gave further evidence that the cyclization is kinetically controlled and proceeds via a late transition state. One reason why **90**, **93a,b**, and **95a,b** did not cyclize could be that the conditions employed in the cyclizations were too mild to overcome the entropic barriers associated with cyclization.

Also, even though we have not conclusively proved that the reaction is proceeding by a radical mechanism, the following evidence is offered in support:

- Cyclizations of **21**, **31**, **33b,c** and **43a,b** occurred efficiently in good yields and were insensitive to the electronic character of the double bond acceptor.
- Cyclizations occurred in the absence of solvent or in non-polar benzene.
- If the cyclization of **21** was occurring by a cationic mechanism, the 6-*endo* product would be favored (Scheme 3.38); however only the 5-*exo* product is observed.
- Compound **33b,c** underwent cyclization to give exclusive formation of the 6-*endo* product in two reactions which employed common methods of radical initiation (i.e. Et₃B/O₂ and photochemical irradiation)
- Irradiation of **90** and **95 a,b** produced dimers, **91** and **96**; their formation can best be explained by the formation of radicals.

Finally, even though we propose that the reaction is proceeding *via* kinetic control through a late transition state, we have not disproved that the reaction is under thermodynamic control. For this reason, additional studies were undertaken to address whether the cyclizations are kinetically or thermodynamically controlled and whether they are polar or radical; our results will be discussed in the following chapter.

IV. EXPERIMENTAL

Attempt to synthesize 14 from 12 using pyridine:

In a 25 mL side-arm roundbottom flask equipped with a stirring bar, 0.135 g (0.248 mmol) of **12** was dissolved in 5 mL of CH_2Cl_2 , then 0.04 mL (0.27 mmol) of PTC-Cl and 0.07 mL (0.95 mmol) of pyridine was added. The reaction mixture was stirred for 12 h at room temperature under N_2 , but TLC (1 : 1 petroleum ether/diethyl ether) indicated no reaction had taken place. For this reason, 0.2 mL of pyridine was added to the flask and the reaction mixture stirred another 12 h. At this time an aliquot was taken from the reaction mixture and diluted with 5 mL of methylene chloride, then it was washed with 5 mL each of 1 N HCl, 0.5 M NaHCO_3 , and saturated brine. The methylene chloride solution was dried over magnesium sulfate, filtered through celite, and then concentrated. A proton NMR spectrum was taken of the crude product residue, but it indicated that no reaction had taken place.

Attempt to synthesize 14 from 12 using DMAP:

In a 50 mL side-arm roundbottom flask equipped with a stirring bar, 0.137 g (0.561 mmol) of **12** was dissolved in 20 mL of CH_3CN , then 0.05 mL (0.37 mmol) of PTC-Cl and 0.091 g (0.746 mmol) of DMAP was added. The reaction stirred at room temperature under N_2 for 12 h. The color changed from red to green. An aliquot was taken from the reaction mixture and concentrated. It was then dissolved in 10 mL of CH_2Cl_2 and washed with 3 x 5 mL of water, then dried over MgSO_4 . The proton NMR spectrum indicated that a reaction may have taken place, so the reaction stirred another 12 h, then was worked up as above. The crude mixture was purified by PTLC (3 : 1

petroleum ether/diethyl ether). One fraction was isolated, but the proton NMR spectrum indicated that it was starting material. No reaction had taken place.

Attempt to synthesize 14 from 12 using DMAP/pyridine:

In a 50 mL side-arm roundbottom flask equipped with a stirring bar, 0.062 g (0.113 mmol) of **12**, 0.013 g (0.109 mmol) of DMAP, and 0.02 mL (0.11 mmol) of PTC-Cl were dissolved in 20 mL of pyridine. The reaction stirred under N₂ at room temperature for 48 h. An aliquot was taken, then concentrated. A proton NMR spectrum was taken of the crude residue which indicated that a reaction may have taken place, but starting material was still present in the reaction mixture. For this reason, 0.02 mL (0.11 mmol) of PTC-Cl was added to the flask and the reaction mixture stirred another 12 h. Another aliquot was taken from the reaction mixture. It was concentrated, then filtered through silica gel. The proton NMR spectrum indicated that no reaction had taken place.

Procedure for the synthesis of 16:

In a 50 mL side-arm roundbottom flask equipped with a stirring bar, 0.257 g (0.996 mmol) of **15** was dissolved in 20 mL of CH₃CN. Subsequently, 0.19 mL (1.4 mmol) of PTC-Cl; and 0.352 g (2.88 mmol) of DMAP was added. The reaction stirred under a flow of N₂ at room temperature while being monitored by TLC for the disappearance of **15**. After 1.5 h, the reaction mixture was concentrated, dissolved in CH₂Cl₂, washed with 3 x 10 mL of water, dried over magnesium sulfate, then

concentrated. Purification was performed by flash chromatography (3 : 1 petroleum ether/diethyl ether/silica gel). The yield of **16** was 0.298 g (0.758 mmol, 76%).

Data for 16:

Physical state: yellow oil.

$R_f = 0.51$ (3 : 1 petroleum ether/diethyl ether).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.49-7.40 (m, 4H, Ph), 7.36-7.30 (m, 4H, Ph), 7.15-7.13 (m, 2H, Ph), 6.99 (dt, $J = 15.6, 6.9$ Hz, 1H, CH_2CHCH), 6.07 (t, $J = 6.3$ Hz, 1H, CH_2CHOR), 5.89 (dt, $J = 15.6, 1.5$ Hz, 1H, $\text{CH}_2\text{CHCHCO}_2\text{CH}_3$), 3.74 (s, 3H, CO_2CH_3), 2.34 (q, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CHCH}$), 2.13-2.05 (m, 2H, CH_2), 1.85-1.75 (m, 2H, CH_2).

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z : 395 $[\text{M} + \text{H}]^+$.

Synthesis of 14:

In a 100 mL side-arm roundbottom flask equipped with a stirring bar, 0.12 g (0.34 mmol) of $\text{Co}_2(\text{CO})_8$ were dissolved in 5 mL of CH_2Cl_2 . The solution was kept under a flow of N_2 . A solution of 0.125 g (0.317 mmol) of **16** in 5 mL of CH_2Cl_2 was added dropwise to the flask. The reaction was monitored by TLC for the disappearance of **16**. When it had been consumed (after approximately 1.5 h), the reaction mixture was filtered through alumina. The filtrate was concentrated, then purified by flash

chromatography (3 : 1 petroleum ether/diethyl ether/silica gel). Two fractions were isolated. The yield of **17** was 0.034 g (0.065 mmol, 20%). The yield of **14** was 0.069 g (0.101 mmol, 31%).

Data for 14:

Physical state: red oil.

$R_f = 0.34$ (3 : 1 petroleum ether/diethyl ether).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.50-7.43 (m, 2H, Ph), 7.38-7.30 (m, 5H, Ph), 7.25-7.21 (m, 1H, Ph), 7.07 (d, $J = 7.8$ Hz, 2H, Ph), 6.91 (dt, $J = 15.6, 6.9$ Hz, 1H, $\text{CH}_2\text{CHCHCO}_2\text{CH}_3$), 5.79 (d, $J = 15.6$ Hz, 1H, $\text{CH}_2\text{CHCHCO}_2\text{CH}_3$), 4.99 (dd, $J = 10.2, 4.2$ Hz, 1H, CH_2CHOR), 3.70 (s, 3H, CO_2CH_3), 2.34-2.19 (m, 2H, CH_2CHCH), 2.16-2.05 (m, 1H, CH_2), 1.99-1.66 (m, 3H, CH_2).

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z : 595 $[\text{M} - 3(\text{CO})]^+$, 568 $[\text{M} - 4(\text{CO})]^+$, 539 $[\text{M} - 5(\text{CO})]^+$, 527 $[\text{M} - \text{PhOC(S)O}]^+$, 512 $[\text{M} - 6(\text{CO})]^+$.

Data for 17:

Physical state: red oil.

$R_f = 0.47$ (3 : 1 petroleum ether/diethyl ether).

¹H NMR (300 MHz, CDCl₃) δ 7.51-7.48 (m, 2H, Ph), 7.36-7.29 (m, 3H, Ph), 7.01-6.88 (m, 1H, CHCH(CCPh)), 6.74 (d, J = 14.1 Hz, 1H, CHCH(CCPh)), 6.20-6.11 (m, 1H, CHCHCO₂CH₃), 5.84 (d, J = 15.6 Hz, 1H, CHCHCO₂CH₃), 3.69 (s, 3H, CH₃), 2.40-2.38 (m, 4H, CH₂CH₂).

Attempted cyclization of 14:

In a 50 mL side-arm roundbottom flask equipped with a stirring bar, 0.052 g (0.076 mmol) of **14** were dissolved in 5 mL of benzene, then 0.02 mL (0.08 mmol) of HSnBu₃ and 0.08 mL (0.08 mmol) of Et₃B (1M in hexanes) were added. The reaction stirred at room temperature under N₂ for 5 h. TLC indicated that no reaction occurred. The reaction mixture was then heated to 40 °C, and stirred another 12 h, but **14** had begun to decompose and TLC indicated that no reaction had occurred.

Attempted cyclization of 14 using AIBN and HSnBu₃ at 60 °C:

In a 50 mL side-arm roundbottom flask equipped with a stirring bar, 0.033 g (0.049 mmol) of **14** were dissolved in 20 mL of toluene, then 0.04 mL (0.16 mmol) of HSnBu₃ and 0.003 g (0.018 mmol) of AIBN were added. The reaction stirred at 60 °C under N₂ for 1 hour. TLC showed a faint spot above the starting material, so the reaction was cooled to room temperature and stirred for another hour. Another TLC was taken, which showed the presence of a large amount of starting material; therefore 0.003 g (0.018 mmol) of AIBN was added to the flask and it was again heated to 60 °C with stirring for another 1.5 h. At this time, the reaction mixture was concentrated, then purified by chromatography over alumina. Three fractions were isolated. The proton

NMR spectra showed that each fraction contained a complex mixture of products, but there was no evidence that the cyclized product was present in any of the fractions.

Attempted cyclization of 14 using Et₃B/air and HSnBu₃ at room temperature:

In a 200 mL side-arm roundbottom flask equipped with a stirring bar, 0.042 g (0.058 mmol) of **14** was dissolved in 10 mL of toluene. In a separate 25 mL side-arm roundbottom flask equipped with a stirring bar, 0.058 mL (0.058 mmol) of Et₃B (1M in hexanes) and 0.02 mL (0.08 mmol) of HSnBu₃ were dissolved in 10 mL of toluene. This solution was then added to the solution of **14** by syringe pump over 1.5 h. As it was being added, air was bubbled through the solution. When addition was complete, the reaction stirred at room temperature under N₂. After 5 h, TLC indicated that no reaction had taken place.

Attempted cyclization of 14 using Et₃B/O₂ and Ph₂SiH₂ at room temperature:

In a 100 mL side-arm roundbottom flask equipped with a stirring bar, 0.167 g (0.246 mmol) of **14** was dissolved in 5 mL of benzene, then 0.056 mL (0.306 mmol) Ph₂SiH₂ and 0.25 mL (0.25 mmol) of Et₃B (1M in hexanes) were added. The reaction mixture stirred under a flow of O₂ and was monitored by TLC. After 12 h, TLC indicated that no reaction had occurred.

Synthesis of 73:

In a 250 mL side-arm roundbottom flask equipped with a stirring bar, 1.0 mL (9.4 mmol) of phenylacetylene was dissolved in 25 mL of THF. The solution was kept

under a flow of N₂ and was cooled to 0 °C, then 5.9 mL (9.4 mmol, 1.6 M in hexanes) of BuLi was added dropwise. The solution turned bright yellow. In a separate 250 mL side-arm roundbottom flask equipped with a stirring bar, 1.507g (9.421 mmol) of **72** was dissolved in 30 mL of THF. This flask was also kept under N₂ and was cooled to 0 °C, then the phenylacetylide was added using a dropping funnel over 45 minutes. The reaction was monitored by TLC for the disappearance of **72** (about 2 h). The reaction stirred for 1 hour, then 50 mL of 1N HCl was added and the reaction stirred another hour. The solution was then transferred to a separatory funnel containing brine, and was extracted with 5 x 20 mL of diethyl ether. Afterwards the combined extracts were washed with 50 mL NaHCO₃, dried over MgSO₄, filtered through celite, then concentrated. The proton NMR spectrum of the crude product showed that the acetal had not completely hydrolyzed, so the reaction mixture was dissolved in 50 mL of diethyl ether, then 50 mL of HCl was added. The reaction mixture was stirred another 3 h until hydrolysis was complete. It was worked up as above, then purification was performed by flash chromatography (1 : 1 petroleum ether/ diethyl ether/silica gel). The yield of **73** was 0.485 g (2.24 mmol, 24%).

Data for 73:

Physical state: yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H, C(O)H), 7.41-7.39 (m, 2H, Ph), 7.29-7.24 (m, 3H, Ph), 4.59 (t, J = 6.8 Hz, 1H, CH₂CHOH), 2.46 (t, J = 6.8 Hz, 2H, CH₂CH₂COH), 1.91 (s broad, 1H, OH), 1.83-1.73 (m, 2H, CH₂), 1.72-1.66 (m, 2H,

CH_2), 1.59-1.53 (m, 2H, CH_2).

IR (CH_2Cl_2 3598 (m), 3054 (m), 2986 (m), 2946 (m), 2865 (m), 2305 (m), 1723 (s), 1599 (w) cm^{-1} .

EIMS (12 eV) m/z : $[\text{M}]^+$ 216

General procedure for the synthesis of hexenyl and heptenyl alcohols 29, 41a,b, 74, 77, 84ab, 85a,b:

In a 100 mL side-arm roundbottom flask equipped with a stirring bar under a flow of N_2 , 1.01 g (2.34 mmol) of the phosphonium salt was dissolved in 5 mL of THF, then 3.1 mL (2.3 mmol) of BuLi (1.3 M) was added. The solution immediately turned bright orange. It stirred for 15 minutes before a solution of 0.236 g (1.17 mmol) of **28a,b** (or **73**) dissolved in 5 mL of THF was added dropwise. The reaction was monitored by TLC (2 : 1 petroleum ether/diethyl ether) for the disappearance of **28a,b** (or **73**). When it was consumed, the reaction was quenched with 10 mL of 1N HCl, then extracted with 3 x 50 mL of diethyl ether. The combined ether extracts were dried over magnesium sulfate, filtered through celite, then concentrated. Purification was performed using flash chromatography (1 : 1 petroleum ether/diethyl ether/silica gel). The yield of **29** was 0.651 g (3.25 mmol, 83%). The yield of **41a,b** was 1.024 g (4.785 mmol, 78%). The yield of **74** was 0.251g (1.17 mmol, 52%). The yield for **84a,b** was 1.387g (4.783 mmol, 70%). The yield for **85a,b** was 1.011g (4.434 mmol, 73%).

Data for 29:

Physical state: light yellow oil.

$R_f = 0.89$ (3 : 1 petroleum ether/diethyl ether).

$^1\text{H NMR}$ (300MHz, CDCl_3) δ 7.45-7.41 (m, 2H, Ph), 7.32-7.26 (m, 3H, Ph), 5.83 (ddt, $J = 17.1, 10.2, 6.6$ Hz, 1H, CH_2CHCH_2), 5.04 (dd, $J = 17.1, 1.6$ Hz, 1H, CHCHH'), 4.98 (ddt, $J = 10.2, 1.6, 1.0$ Hz, 1H, CHCHH''), 4.61 (dd, $J = 12.0, 6.6$ Hz, 1H, CHOH), 2.14 (q, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 1.94 (d, $J = 5.4$ Hz, 1H, OH), 1.86-1.78(m, 2H, CH_2), 1.68-1.58 (m, 2H, CH_2).

$^{13}\text{C NMR}$ (100MHz, CDCl_3) δ 138.4, 131.6, 128.3, 128.2, 122.5, 114.8, 90.0, 84.8, 62.7, 37.2, 33.2, 24.4.

IR (CH_2Cl_2) 3594 (s), 3447 (m), 3080 (m), 2930 (s), 2863 (s), 2229 (w), 1640 (m), 1598 (m), 1490 (s), 1379 (m), 1070 (s), 1027 (s), 997 (s), 917 (s) cm^{-1} .

HRMS-FAB (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{O}$ 201.1279; found, 201.1265.

Data for 41a,b (mixture of isomers):

Physical state: light yellow oil.

$R_f = 0.8$ (1 : 1 petroleum ether/ diethyl ether).

¹H NMR (mixture) (400 MHz, CDCl₃) δ 7.41-7.19 (m, 10H, Ph), 5.49-5.36 (m, 4H, CH₂CHCHCH₃ and CH₂CHCHCH₃), 4.61-4.57 (m, 2H, CH₂CHOH), 2.13-2.02 (m, 4H, CH₂CH₂CH), 1.84-1.73 (m, 4H, CH₂), 1.63-1.54 (m, 16H, CH₃, CH₂, OH).

¹³C NMR (major isomer) (100 MHz, CDCl₃) δ 131.6, 130.1, 128.3, 128.2, 124.3, 122.6, 90.1, 84.8, 62.8, 37.3, 26.4, 25.1, 12.8.

¹³C NMR (minor isomer) δ 131.6, 130.8, 128.3, 128.2, 125.3, 122.6, 90.1, 84.8, 62.8, 37.3, 32.1, 25.1, 17.5.

IR (CH₂Cl₂) 3593 (s), 3452 (m), 3082 (w), 3014 (m), 2938 (s), 2862 (s), 2228 (w), 1654 (w), 1598 (m), 1490 (s), 1457 (m), 1443 (m), 1378 (s), 1069 (s), 1026 (s), 971 (S), 917 (m) cm⁻¹.

HRMS-FAB (m/z): [M + H]⁺ calcd for C₁₅H₁₉O 215.1436; found, 215.1426.

Data for 74:

Physical state: light yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.41-7.39 (m, 2H, Ph), 7.29-7.28 (m, 3H, Ph), 5.48 (ddt, J = 17.0, 10.3, 6.8 Hz, 1H, CH₂CHCH₂), 4.99 (d, J = 17.0 Hz, 1H, CH₂CHCH'H^c), 4.93 (d, J = 10.2 Hz, 1H, CH₂CHCH'H^c), 4.60-4.55 (m, 1H, CH₂CHOH), 2.10-2.04 (m, 2H,

$\text{CH}_2\text{CH}_2\text{CH}$), 1.94 (s broad, 1H, OH), 1.82-1.76 (m, 2H, CH_2), 1.56-1.41 (m, 4H, CH_2CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 138.7, 131.6, 128.3, 128.2, 122.5, 114.4, 90.0, 84.8, 62.9, 37.6, 33.6, 28.5, 24.6.

IR (CH_2Cl_2) 3596 (s), 3080 (w), 2931 (s), 2360 (m), 2228 (m), 1639 (m), 1599 (m), 1490 (s) cm^{-1} .

EIMS (12eV) m/z: $[\text{M}]^+$ 214.

Data for 84 a.b

Physical state: yellow oil.

^1H NMR (mixture) (500 MHz, CDCl_3) δ 7.40-7.38 (m, 4H, Ph), 7.37-7.32 (m, 6H, Ph), 5.42-5.30 (m, 4H, $\text{CH}_2\text{CHCHCH}_3$ and $\text{CH}_2\text{CHCHCH}_3$), 4.55-4.50 (m, 2H, CH_2CHOH), 2.06-1.93 (m, 6H, CH_2 and OH), 1.77-1.71 (m, 4H, CH_2), 1.62-1.54 (m, 6H, CH_3), 1.52-1.43 (m, 4H, CH_2), 1.41-1.32 (m, 4H, CH_2).

^{13}C NMR (mixture) (125 MHz, CDCl_3) δ 131.7, 131.2, 130.4, 128.3, 128.2, 124.9, 123.9, 122.8, 90.3, 84.9, 63.0, 37.9, 32.4, 29.2, 26.7, 24.8, 24.7, 17.7, 12.6.

IR (CH_2Cl_2) 3595 (m), 3391 (w), 3052 (m), 3013 (m), 2937 (s), 2860 (s), 2305 (w), 1599 (m) cm^{-1} .

HRMS-FAB (m/z): calcd. for $\text{C}_{16}\text{H}_{20}\text{O}$ 228.1514; found, 228.1552.

Data for 85a,b

Physical state: yellow oil

^1H NMR (mixture) (500 MHz, CDCl_3) δ 7.41-7.11(m, 20H, Ph), 6.38 (d, $J = 11.5$ Hz, 1H, CH_2CHCHPh), 6.36 (d, $J = 16.0$ Hz, 1H, CH_2CHCHPh), 6.18 (dt, $J = 16.0, 7.0$ Hz, 1H, CH_2CHCHPh), 5.63 (dt, $J = 11.5, 7.0$ Hz, 1H, CH_2CHCHPh), 4.61-4.52 (m, 2H, CH_2CHOH), 2.36-2.31 (m, 2H, $\text{CH}_2\text{CH}_2\text{CHCH}$), 2.34-2.19 (m, 2H, $\text{CH}_2\text{CH}_2\text{CHCH}$), 1.95-1.91 (m, 2H, OH), 1.82-1.76 (m, 4H, CH_2), 1.57-1.52 (m, 8H, CH_2).

^{13}C NMR (mixture) (125 MHz, CDCl_3) δ 137.9, 137.8, 132.6, 131.6, 130.6, 130.1, 129.1, 128.7, 128.4, 128.3, 128.2, 128.1, 126.7, 126.4, 125.9, 122.7, 90.2, 84.9, 62.9, 37.7, 32.8, 29.6, 29.0, 28.4, 24.9, 24.7.

IR (CH_2Cl_2) 3593 (w), 3381 (w), 2931 (s), 2862 (s), 1652 (w), 1063 (s) cm^{-1} .

HRMS-FAB (m/z): $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{21}\text{H}_{22}\text{O}$ 290.1670; found 290.1655.

Procedure for the synthesis of 83:

In a 50 mL side-arm roundbottom flask equipped with a stirring bar, and kept under a flow of N₂, 2.929 g (8.819 mmol) of Ph₃PCH(CO₂CH₃) was dissolved in 20 mL of THF. A solution of 0.946 g (4.37 mmol) of **79** in 5 mL of THF was then added. The flask was equipped with a water-cooled condenser, and the reaction mixture was heated to reflux. The reaction was monitored by TLC for the disappearance of **79** (10% ethyl acetate in petroleum ether). When it had been consumed (after approximately 3 h), the reaction was quenched with 20 mL of water, then extracted with 3 x 10 mL of diethyl ether. The extracts were dried over magnesium sulfate, filtered through celite, then concentrated. Purification was performed using column chromatography (10% ethyl acetate in petroleum ether). The yield of **83** was 0.930g (3.42 mmol, 78%).

Data for 83:

Physical state yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.49-7.30 (m, 2H, Ph), 7.28-7.20 (m, 3H, Ph), 6.90 (dt, J = 15.6, 6.9 Hz, 1H, CH₂CHCHCO₂CH₃), 5.76 (d, J = 15.6 Hz, 1H, CH₂CHCHCO₂CH₃), 4.57-4.86 (m, 1H, CH₂CHOH), 3.64 (s, 3H, CO₂CH₃), 2.21-2.15 (m, 2H, CH₂CH₂CH), 1.82 (d, J = 4.2 Hz, 1H, OH), 1.78-1.67 (m, 2H, CH₂), 1.54-1.40 (m, 4H, CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 166.9, 149.2, 131.4, 128.1, 128.0, 122.4, 120.8, 90.0, 84.6, 62.5, 51.3, 37.4, 32.0, 27.6, 24.7.

IR (CH_2Cl_2) 3594 (m), 3320 (m), 2940 (m), 2862 (m), 2223 (w), 1721 (s), 1712 (s), 1657 (m) cm^{-1} .

MS (FAB, matrix: 3-nitrobenzyl alcohol) m/z : 273 $[\text{M} + \text{H}]^+$, 255 $[(\text{M} + \text{H}) - \text{H}_2\text{O}]^+$, 195 $[\text{M} - 77]^+$.

General procedure for the synthesis of 30 and 42a,b, 75, 78, 86a,b, 87a,b

In a 250 mL side-arm roundbottom flask equipped with a stirring bar, 0.200g (0.585 mmol) of $\text{Co}_2(\text{CO})_8$ was dissolved in 10 mL of CH_2Cl_2 . The solution was stirred under a flow of N_2 , and a solution of 0.618g (3.09 mmol) of **29** in 5.0 mL of CH_2Cl_2 was added dropwise. The reaction was monitored for the disappearance of **29** by TLC (1 : 1 petroleum ether/diethyl ether). When it had been consumed (after approximately 2 h), the reaction mixture was filtered through alumina, then concentrated. Purification was performed using flash chromatography (2 : 1 petroleum ether/diethyl ether/silica gel). The yield of **30** was 1.423 g (2.93 mmol, 95%). The yield of **42a,b** was 2.204 g (4.272 mmol, 96%). The yield of **75** was 0.489 g (0.978 mmol, 91%). The yield of **78** was 0.855 g (1.53 mmol, 51%). The yield of **86a,b** was 2.047 g (3.553 mmol, 74%). The yield of **87a,b** was 1.95 g (3.81 mmol, 95%).

Data for 30:

Physical state: red liquid.

¹H NMR (300MHz, CDCl₃) δ 7.53 (dd, J = 6.0, 1.5 Hz, 2H, Ph), 7.39-7.32 (m, 3H, Ph), 5.81 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H, CH₂CHCH₂), 5.07-4.96 (m, 3H, CH₂CHCH₂, CH₂CHOH), 2.18-2.12 (m, 2H, CH₂CH₂CHCH₂), 1.92 (d, J = 5.1 Hz, 1H, CHOH), 1.90-1.61 (m, 4H, CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 138.1, 137.5, 129.5, 128.9, 127.9, 115.0, 101.8, 90.7, 72.2, 39.1, 33.3, 25.5.

IR (CH₂Cl₂) 3599 (w), 3078 (w), 3061 (w), 3048 (w), 2929 (w), 2860 (w), 2091 (s), 2059 (s), 2048 (s), 2028 (s), 2015 (s), 1611 (w), 1073 (w), 999 (w), 918 (w), 573 (w), 520 (w) cm⁻¹.

EA Anal. calcd for C₂₀H₁₆O₇Co₂: C, 49.40; H, 3.31 found: C, 51.12; H, 3.48.

Data for 42a,b:

Physical state: red oil.

¹H NMR (major isomer) (300 MHz, CDCl₃) δ 7.53 (dd, J = 7.8, 1.7 Hz, 2H, Ph), 7.39-7.32 (m, 3H, Ph), 5.52-5.33 (m, 2H, CH₂CHCHCH₃, and CH₂CHCHCH₃), 5.06-5.00 (m, 1H, CH₂CHOH), 2.14 (q, J = 6.6 Hz, 2H, CH₂CH₂CH), 1.93 (d, J = 5.1 Hz, 1H, OH), 1.89-1.69 (m, 4H, CH₂CH₂), 1.60 (d, J = 6.3 Hz, 3H, CH₃).

¹H NMR (minor isomer) (300 MHz, CDCl₃) δ 7.53 (dd, J = 7.8, 1.7 Hz, 2H, Ph), 7.39-7.32 (m, 3H, Ph), 5.52-5.33 (m, 2H, CH₂CHCHCH₃, and CH₂CHCHCH₃), 5.06-5.00 (m, 1H, CH₂CHOH), 2.09-2.04 (m, 2H, CH₂CH₂CH), 1.92 (d, J = 5.1 Hz, 1H, OH), 1.89-1.69 (m, 4H, CH₂CH₂), 1.64 (d, J = 4 Hz, 3H, CH₃).

¹³C NMR (major isomer) (75 MHz, CDCl₃) δ 137.6, 129.8, 12.5, 128.9, 127.9, 124.5, 101.9, 90.7, 72.4, 39.2, 26.4, 26.2, 12.7.

¹³C NMR (minor isomer) (75 MHz, CDCl₃) δ 137.6, 130.6, 129.5, 128.9, 127.9, 125.6, 101.9, 90.7, 72.3, 39.1, 32.1, 26.1, 17.8.

IR (neat) 3596 (m), 3558 (m), 3481 (br), 3078 (m), 3014 (s), 2934 (s), 2860 (s), 2090 (s), 2051 (s), 2020 (s), 1615 (m) cm⁻¹.

EA Anal. calcd for C₂₁H₁₈O₇Co₂C: 50.42; H, 3.63; found: C, 50.44; H, 3.50.

Data for 75:

Physical state: red oil.

¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, J = 6.8 Hz, 2H, Ph), 7.36-7.29 (m, 3H, Ph), 5.76 (ddt, J = 17.1, 10.7, 6.0 Hz, 1H, CH₂CHCH₂), 5.02-4.90 (m, 3H, CH₂CHCH₂, CH₂CHOH), 2.04 (q, J = 6.8 Hz, 2H, CH₂CH₂CHCH₂), 1.90 (d, J = 4.8 Hz, 1H, OH), 1.85-1.42 (m, 6H, CH₂CH₂CH₂).

^{13}C NMR (125 MHz, CDCl_3) δ 138.3, 137.6, 129.5, 128.9, 127.9, 114.6, 101.9, 90.9, 72.5, 39.7, 33.6, 28.6, 25.9.

IR (CH_2Cl_2) 3599 (w), 3411 (w), 2935 (m), 2089 (s), 2060 (s), 1640 (w), 1611 w) cm^{-1} .

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z : 483 $[(\text{M} + \text{H})-18]^+$, 472 $[\text{M} - \text{CO}]^+$, 444 $[\text{M} - 2(\text{CO})]^+$, 416 $[\text{M} - 3(\text{CO})]^+$, 388 $[\text{M} - 4(\text{CO})]^+$, 360 $[\text{M} - 5(\text{CO})]^+$, 332 $[\text{M} - 6(\text{CO})]^+$.

Data for 78

Physical state: red oil.

^1H NMR (300 MHz, CDCl_3) δ 7.52-7.48 (m, 2H, Ph), 7.39-7.29 (m, 3H, Ph), 6.95 (dt, $J = 15.6, 6.9$ Hz, 1H, $\text{CH}_2\text{CHCHCO}_2\text{CH}_3$), 5.80 (dt, $J = 15.6, 1.5$ Hz, 1H, $\text{CH}_2\text{CHCHCO}_2\text{CH}_3$), 5.02 (m, 1H, CH_2CHOH), 3.72 (s, 3H, CO_2CH_3), 2.55-2.52 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 1.95 (d, $J = 5.1$ Hz, 1H, OH), 1.88-1.65 (m, 2H, CH_2) 1.60-1.52 (m, 2H, CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 199.3, 167.0, 149.1, 137.4, 129.4, 128.9, 127.9, 121.1, 101.6, 90.7, 72.3, 51.4, 39.4, 32.0, 27.7, 26.0.

IR (CH_2Cl_2) 3606 (w), 2904 (m), 2862 (m), 2091 (S) 2026 (s), 1720 (m), 1657 (w) cm^{-1} .

MS (FAB, matrix: 3-nitrobenzyl alcohol) m/z : 541 $[(M + H) - H_2O]^+$, 502 $[M - 2(CO)]^+$, 474 $[M - 3(CO)]^+$, 446 $[M - 4(CO)]^+$, 390 $[M - 6(CO)]^+$.

Data for 86a,b:

Physical state: red oil.

1H NMR (mixture) (300 MHz, $CDCl_3$) δ 7.49 (dd, $J = 6.0, 2.3$ Hz, 4H, Ph), 7.37-7.26 (m, 6H, Ph), 5.45-5.29 (m, 4H, $CH_2CHCHCH_3$, and $CH_2CHCHCH_3$), 5.03-4.97 (m, 2H, CH_2CHOH), 2.03 (q, $J = 6.9$ Hz, 2H, CH_2CH_2CH), 1.91 (d, $J = 5.1$ Hz, 1H, OH), 1.89-1.34 (m, 21H, OH and CH_2).

^{13}C NMR (mixture) (125 MHz, $CDCl_3$) δ 137.6, 131.0, 130.2, 129.5, 128.9, 127.9, 125.0, 124.0, 102.0, 90.8, 72.4, 39.7, 32.4, 29.2, 26.6, 26.0, 25.9, 17.8, 12.6.

IR (CH_2Cl_2) 3599 (w), 3416 (w), 2997 (m), 2937 (s), 2863 (s), 2686 (w), 2306 (w), 2090 (s), 2049 (s), 2026 (s), 1611 (w) cm^{-1} .

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z : 497 $[(M + H) - 18]^+$, 458 $[M - 2(CO)]^+$, 430 $[M - 3(CO)]^+$, 402 $[M - 4(CO)]^+$, 374 $[M - 5(CO)]^+$, 346 $[M - 6(CO)]^+$.

Data for 87a,b:

Physical state: red oil.

¹H NMR (mixture) (300 MHz, CDCl₃) δ 7.51-7.13 (m, 20H, Ph), 6.4 (d, J = 11.4 Hz, 1H, CH₂CHCHPh), 6.34 (d, J = 15.9 Hz, 1H, CH₂CHCHPh), 6.17 (dt, J = 15.9, 6.9 Hz, 1H, CH₂CHCHPh), 5.62 (dt, J = 11.4, 7.2 Hz, 1H, CH₂CHCHPh), 5.04-4.96 (m, 2H, CH₂CHOH), 2.33 (q, J = 5.7 Hz, 2H, CH₂CH₂CH), 2.21 (q, J = 6.3 Hz, 2H, CH₂CH₂CH), 1.91 (d, J = 5.4 Hz, 1H, OH), 1.88 (d, J = 5.1 Hz, 1H, OH), 1.84-1.63 (m, 6H, CH₂), 1.59-1.51 (m, 6H, CH₂).

¹³C NMR (mixture) (125 MHz, CDCl₃) δ 137.8, 137.6, 132.5, 130.4, 130.2, 129.4, 129.2, 128.9, 128.7, 128.4, 128.1, 127.9, 126.8, 126.4, 125.9, 101.9, 90.8, 72.4, 39.7, 32.8, 29.6, 29.1, 28.4, 26.1, 26.0.

IR (CH₂Cl₂) 3600 (w), 3080 (w), 3026 (w), 2936 (3), 2858 (w), 2091 (s), 2052 (s), 2025 (s), 1608 w) cm⁻¹.

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z: 559 ([M + H] - H₂O)⁺, 520 [M - 2(CO)]⁺, 492 [M - 3(CO)]⁺, 464 [M - 4(CO)]⁺, 436 [M - 5(CO)]⁺, 408 [M - 6(CO)]⁺.

General procedure for the synthesis of 21, 31, 33a,b, 43a,b, 88, 90, 93a,b, 95a,b:

In a 500 mL side-arm roundbottom flask equipped with a stir bar and kept under a flow of N₂, 0.079 g (0.200 mmol) of DIPHOS was dissolved in 15 mL of CH₂Cl₂. The solution was cooled to 0 °C, then a solution of 0.021 mL (0.409 mmol) of Br₂ in 2.5 mL of CH₂Cl₂ was added dropwise to the solution then the solution stirred for 10 minutes and a solution of 0.091 g (0.168 mmol) of **21** in 2.5 mL of CH₂Cl₂ was added.

The reaction then stirred for an additional hour under N₂ at 0 °C. At this time, 35 mL of diethyl ether and 70 mL of pentane was added to the flask. A white precipitate formed. The reaction mixture was filtered through celite under N₂, then was concentrated on the vacuum line. The yield of the **21** was 0.089 g (0.147 mmol, 88%). The yields for the other bromides were not taken.

Data for 21:

Physical state: red oil.

¹H NMR (300 MHz, CDCl₃) δ 7.62 (dd, J = 7.6, 1.7 Hz, 2H, Ph), 7.41-7.33 (m, 3H, Ph), 6.97 (dt, J = 15.7, 6.9 Hz, 1H, CH₂CHCHCO₂CH₃), 5.85 (dt, J = 15.7, 1.5 Hz, 1H, CH₂CHCHCO₂CH₃), 5.46 (dd, J = 9.3, 4.5 Hz, 1H, CH₂CHBr) 3.73 (s, 3H, CO₂CH₃), 2.36-2.26 (m, 2H, CH₂CH₂CH), 2.23-2.15 (m, 2H, CH₂), 2.05-1.90 (m, 1H, CH₂), 1.84-1.69 (m, 1H, CH₂).

¹³C NMR (75MHz, CDCl₃, partial) δ 148.0, 129.5, 128.8, 128.0, 121.7, 56.2, 51.4, 40.6, 31.1, 26.5.

Data for 31

Physical state: red oil.

¹H NMR (mixture) (300MHz, CDCl₃, partial) δ 7.61 (d, J = 6.0 Hz, 2H, Ph), 7.51-7.17 (m, 3H, Ph), 5.79 (ddt, J = 16.6, 10.2, 6.3 Hz, 1H, CH₂CHCH¹H'), 5.46 (dd, J = 10.2, 3.3

Hz, 1H, CH₂CHCH[⋄]H'), 5.02 (d overlapping, J = 16.6 Hz, 1H, CH₂CHCH[⋄]H'), 4.98 (d overlapping, J = 10.2 Hz, 1H, CH₂CHBr).

Data for 33a,b

Physical state: red oil.

¹H NMR (major isomer) (300 MHz, CDCl₃) δ 7.61-7.56 (m, 2H, Ph), 7.34-7.18 (m, 8H, Ph), 6.39 (d, J = 15.7 Hz, 1H, CH₂CHCHPh), 6.19 (dt, J = 15.7, 6.7 Hz, 1H, CH₂CHCHPh), 5.50 (dd, J = 9.6, 3.5 Hz, 1H, CH₂CHBr), 2.45-2.10 (m, 4H, CH₂), 2.02-1.88 (m, 1H, CH₂), 1.81-1.69 (m, 1H, CH₂).

¹H NMR (minor isomer) (300 MHz, CDCl₃) δ 7.61-7.56 (m, 2H, Ph), 7.34-7.18 (m, 8H, Ph), 6.45 (d, J = 13.5 Hz, 1H, CH₂CHCHPh) 5.68-5.60 (m, 1H, CH₂CHCHPh) 5.42 (dd, J = 9.0, 4.5 Hz, 1H, CH₂CHBr) 2.45-2.10 (m, 4H, CH₂), 2.02-1.88 (m, 1H, CH₂), 1.81-1.69 (m, 1H, CH₂).

Data for 43a,b

Physical state: red oil

¹H NMR (mixture) (400 MHz, CDCl₃) δ 7.64-7.31 (m, 10H, Ph), 5.53-5.38 (m, 6H, CH₂CHCHCH₃ and CH₂CHCHCH₃ and CH₂CHBr) 2.26-2.24 (m, 8H, CH₂CH₂CHCH and CH₂), 6.94-1.78 (m, 2H, CH₂), 1.70-1.60 (m, 8H, CH₂).

General procedure employed in the cyclization of 21, 31, 33a,b and 43a,b, and 88, and the attempted cyclizations of 90, 93a,b, and 95a,b:

Once the bromides were concentrated, they were placed in direct sunlight or under a 300 W halogen floodlight for 45 minutes to an hour for **21, 31, 33a,b, and 43a,b** and between 1.5 and 4 h for **88, 90, 93a,b, and 95a,b**. After they were irradiated, purification was performed by chromatography using activity III alumina (3 : 1 petroleum ether/diethyl ether). The yield of **35a,b** was 0.103 g (0.164 mmol), 86% . The yield of **36a,b** was 0.064 (0.106 mmol), 56%. The yield of **38a,b** was 0.092 g (0.167 mmol, 73%). The yield of **44a,b + 46** was 1.04 g (1.84 mmol, 60%).

Data for 35a,b:

Physical state: red solid (crystallized from heptane).

¹H NMR (major isomer) (300 MHz, CDCl₃) δ 7.54 (d, J = 6.3 Hz, 2H, Ph), 7.41-7.30 (m, 8H, Ph), 5.30 (d, J = 2.7 Hz, 1H, CHCHBrPh), 3.66 (q, J = 7.5 Hz, 1H, CHCH(CCPh)), 2.39-2.15 (m, 3H, CH₂ and CHCHCHBr), 2.02-1.67 (m, 4H, CH₂).

¹H NMR (minor isomer) (400 MHz, CDCl₃) δ 7.53 (d, J = 7.6 Hz, 2H, Ph), 7.33-7.27 (m, 8H, Ph), 4.89 (d, J = 10.8 Hz, 1H, CHCHBrPh), 3.90-3.88 (m, 1H, CHCH(CCPh)), 3.06-3.01 (m, 1H, CHCHCHBr), 2.41-2.35 (m, 1H, CH₂), 1.83-1.59 (m, 4H, CH₂), 1.42-1.36 (m, 1H, CH₂).

¹³C NMR (major isomer) (100MHz, CDCl₃) δ 199.6, 141.3, 138.1, 103.4, 93.5 61.1, 55.7, 35.7, 29.1, 24.1.

¹³C NMR (minor isomer) (100MHz, CDCl₃) δ 199.6, 141.0, 138.3, 105.8, 93.0, 59.7, 55.7, 48.3, 35.4, 30.5, 25.2.

IR (CH₂Cl₂) 3027(w), 2957 (w), 2873 (w), 2088 (s), 2046 (s), 2028 (s), 1605 (w), 603 (w), 577 (w), 520 (w) cm⁻¹.

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z: 598 [M+2 – 1(CO)]⁺, 596 [M – 1(CO)]⁺, 542 [M+2 – 3(CO)]⁺, 540 [M – 3(CO)]⁺, 514 [M+2 – 4CO]⁺, 512 [M – 4(CO)]⁺, 486 [M+2 – 5CO]⁺, 484 [M – 5(CO)]⁺, 458 [M+2 – 6(CO)]⁺, 456 [M – 6(CO)]⁺.

X-ray crystal structure determination of 35b:

Crystals of **35b** were obtained by slow crystallization from pentane at –20 °C. The data were collected at –70 °C on a Siemens P4 diffractometer using Lorentz and polarization effects; no absorption correction was applied since it was judged to be insignificant. The structure was solved by direct methods using SHELXTL5.0 (Siemens system) and refined by full matrix least squared on F² using all reflections. The methoxy group (C22A and C22B) was found to be disordered at two sites with unequal population. The size of the C22A and C22B atoms in the difference map, and refinement of the partial occupancy factor for these atoms, suggested 65% and 35%

occupancy respectively for these atoms. Hydrogen atoms were included in the idealized positions. Details of the crystal data and refinement are given in Table 3.2. Figures are drawn with 15% thermal ellipsoids. For the sake of clarity, C22B and all the hydrogens except H15A and H19A are omitted.

Data for 36a,b:

Physical state: red oil.

¹H NMR (major isomer) (400 MHz, CDCl₃) δ 7.53-7.48 (m, 2H, Ph), 7.39-7.31 (m, 3H, Ph), 4.59 (d, J = 3.2 Hz, 1H, CHCHBrCO₂CH₃), 3.70 (s, 3H, CO₂CH₃), 3.51 (q, J = 8.0 Hz, 1H, CHCH(CPh)), 2.38-2.23 (m, 3H, CHCHBrCO₂CH₃ and CH₂), 2.01 (q, apparent, J = 6 Hz, 2H, CH₂) 1.85-1.69 (m, 2H, CH₂).

¹H NMR (minor isomer) (400 MHz, CDCl₃) δ 7.53-7.48 (m, 2H, Ph), 7.39-7.31 (m, 3H, Ph), 4.32 (d, J = 8.0 Hz, 1H, CHCHBrCO₂CH₃), 3.77 (s, 3 H, CO₂CH₃), 3.63 (m, 1H, CHCH(CPh)), 2.76-2.68 (m, 1H, CHCHBrCO₂CH₃), 2.38-2.23 (m, 2H, CH₂), 2.14-2.06 (m, 2H, CH₂), 1.85-1.69 (m, 2H, CH₂).

¹³C NMR (major isomer) (100 MHz, CDCl₃) δ 199.4, 169.3, 137.8, 129.0, 128.9, 127.9, 101.8, 92.8, 53.0, 52.2, 50.9, 46.5, 36.1, 28.9, 24.4.

¹³C NMR (minor isomer) (400 MHz, CDCl₃) δ 199.4, 169.3, 138.1, 129.1, 128.8, 127.7, 103.9, 94.4, 52.9, 52.2, 48.7, 46.9, 36.4, 30.2, 24.9.

IR (CH_2Cl_2) 2955 (w), 2928 (w), 2873 (w), 2089 (s), 2050 (s), 2025 (s), 1745 (m), 1738 (m) cm^{-1} .

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z : 580 $[\text{M}+2 - 1(\text{CO})]^+$, 552 $[\text{M}+2 - 2(\text{CO})]^+$, 550 $[\text{M} - 2(\text{CO})]^+$, 524 $[\text{M}+2 - 3(\text{CO})]^+$, 522 $[\text{M} - 3(\text{CO})]^+$, 496 $[\text{M}+2 - 4(\text{CO})]^+$, 494 $[\text{M} - 4(\text{CO})]^+$, 468 $[\text{M}+2 - 5(\text{CO})]^+$, 466 $[\text{M} - 5(\text{CO})]^+$, 440 $[\text{M}+2 - 6(\text{CO})]^+$, 438 $[\text{M} - 6(\text{CO})]^+$.

Data for 38a (*trans*) and 38b (*cis*);

Physical state: both are a red solid crystallized from heptane.

^1H NMR (*trans*) (400 MHz, CDCl_3) δ 7.50 (d apparent, $J = 7.2$ Hz, 2 H, Ph), 7.36-7.27 (m, 3H, Ph), 4.80 (s broad, 1H, CH_2CHBr), 3.60 (tt, $J = 11.6, 3.0$ Hz, 1H, $\text{CH}_2\text{CH}(\text{CCPh})$), 2.44 (d broad, $J = 14.0$ Hz, 1H, CH_2), 2.15-2.01 (m, 3H, CH_2), 1.85-1.74 (m, 3H, CH_2), 1.38 (ddd, $J = 24.8, 12.8, 3.6$ Hz, 1H, CH_2).

^{13}C NMR (*trans*) (100 MHz, CDCl_3) δ 199.6, 138.1, 129.2, 128.9, 127.7, 104.3, 91.1, 53.6, 43.0, 36.2, 34.7, 34.0, 21.0.

^1H NMR (*cis*) (400 MHz, CDCl_3) δ 7.45 (d apparent $J = 7.6$ Hz, 2H, Ph), 7.36-7.27 (m, 3H, Ph), 4.14 (tt, $J = 11.8, 4.0$ Hz, 1H, CH_2CHBr), 3.02 (tt, $J = 11.8, 3.4$ Hz, 1H, $\text{CH}_2\text{CH}(\text{CCPh})$), 2.66 (d apparent, $J = 12.4$ Hz, 1H, CH_2), 2.38 (d, apparent, $J = 12.8$

Hz, 1H, $\underline{\text{CH}_2}$), 2.11 (d apparent, $J = 12.8$ Hz, 1H, $\underline{\text{CH}_2}$), 1.95-1.74 (m, 3H, $\underline{\text{CH}_2}$), 1.54 (m, 1H, $\underline{\text{CH}_2}$), 1.37 (m, 1H, $\underline{\text{CH}_2}$).

^{13}C NMR (*cis*) (100 MHz, CDCl_3) δ 199.6, 138.0, 129.1, 128.9, 127.5, 102.8, 91.2, 49.7, 46.2, 42.6, 37.7, 33.8, 26.8.

IR (CH_2Cl_2) 3025 (w), 2958 (w), 2930 (w), 2860 (w), 2089 (s), 2051 (s), 2024 (s), 1096 (w), 1013 (w) 811 (w) cm^{-1} .

EA Anal. Calcd for $\text{C}_{20}\text{H}_{15}\text{O}_6\text{BrCo}_2$: C, 43.75; H, 2.75 found: C, 44.16; H, 2.75.

Data for 44a:

Physical state: red oil.

^1H NMR (400MHz, CDCl_3) δ 7.56-7.54 (m, 2H, Ph), 7.39-7.30 (m, 3H, Ph), 4.38 (dq, $J = 7.0, 2.4$ Hz, CHCHBrCH_3), 3.54 (q, $J = 8.0$ Hz, 1H, $\text{CHCH}(\text{CCPh})$), 2.29-2.21 (m, 1H, CHCHBrCH_3), 1.97-1.69 (m, 6H, $\underline{\text{CH}_2\text{CH}_2\text{CH}_2}$), 1.65 (d, $J = 6.8$ Hz, 3 H, $\underline{\text{CH}_3}$).

Data for 44b and 46 :

Physical state: 44b red oil; 46 red solid crystallized from CH_3CN .

¹H NMR (44b) (400MHz,CDCl₃) δ 7.46-7.25 (m, 5H, Ph), 4.24 (dq, J = 6.5, 6.4 Hz, 1H, CHCHBrCH₃), 3.41 (q, J = 6.0 Hz, 1H, CHCH(CCPh)), 2.31-2.60 (m, 2H, CH₂ and CHCHBrCH₃), 2.07-1.52 (m, 5H, CH₂), 1.68 (d, J = 6.8 Hz, 3H, CH₃).

¹H NMR (46) (400MHz,CDCl₃) δ 7.46-7.25 (m, 5H, Ph), 4.40 (dt, J = 11.6, 4.4 Hz, 1H, CHCHBr), 3.16 (dt, 11.6, 3.6 Hz, 1H, CHCH(CCPh)), 2.49-2.45 (m, 2 H, CH₂ and CHCH₃), 2.07-1.52 (m, 5H, CH₂) 1.03 (d, 6.8 Hz, 3H, CH₃).

IR (mixture) (CH₂Cl₂) 3059 (w), 2946 (w), 2868 (w), 2088 (s), 2048 (s), 2025 (s), 2016 (s), 578 (w), 520 (w) cm⁻¹.

MS (mixture of **44b** and **46**) (FAB, matrix: 3-nitrobenzylalcohol) m/z: 565 [M + H]⁺, 536 [M+2 – 1(CO)]⁺, 534 [M – 1(CO)]⁺, 508 [M+2 – 2(CO)]⁺, 506 [M – 2(CO)]⁺, 452 [M+2 – 4(CO)]⁺, 450 [M – 4(CO)]⁺, 424 [M+2 – 5(CO)]⁺, 422 [M – 5(CO)]⁺, 396 [M+2 – 6(CO)]⁺, 394 [M – 6(CO)]⁺.

X-ray crystal structure determination of 46:

Crystals of **46** were obtained by slow crystalization from pentane at –20 °C. The data were collected at –70 °C on a Siemens P4 diffractometer using MoKα (λ = 0.7107 Å) The data were corrected by Lorentz and polarization effects and an analytical absorption correction was applied . The structure was solved by direct methods using SHELXTL (Siemens system) and refined by full matrix least squared on F² using all reflections. Hydrogen atoms were included in the idealized positions. Details of the

crystal data and refinement are given in Table 3.8. Figures are drawn with 50% thermal ellipsoids.

Data for 89:

Physical state: red oil.

¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, J = 6.4 Hz, 2H, Ph), 7.35-7.27 (m, 3H, Ph), 4.70-4.68 (m, 1H, CH₂CHBr), 3.57 (t, J = 6.0 Hz, 1H, CH₂CH(CPh)), 2.57 (d broad, J = 12.0 Hz, 1H, CH₂), 2.68-2.19 (m, 4H, CH₂), 1.85-1.71 (m, 2H, CH₂), 1.62-1.40 (m, 3H, CH₂).

¹³C NMR (125 MHz, CDCl₃) δ 199.7, 138.1, 129.3, 128.8, 127.7, 54.6, 46.5, 39.1, 38.5, 37.3, 27.7, 24.4.

IR (CH₂Cl₂) 3054 (w), 2986 (w), 2932 (w), 2858 (w), 2305 (w), 2088 (s), 2050 (s), 2022 (s) cm⁻¹.

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z : 536 [M+2-1(CO)]⁺, 534 [M - 1(CO)]⁺.

Attempted cyclization of 21 using AIBN and HSnBu₃ at 40 °C:

The bromide **21**, prepared from 0.273 g (0.502 mmol) of alcohol **12** was concentrated in a 250 mL roundbottom flask equipped with a stir bar and kept under a flow of N₂, then dissolved in 20 mL of benzene. The reaction mixture was slowly

heated to 45 °C as a solution of 0.04 mL (0.01 mmol) of HSnBu_3 and 0.003 g (0.017 mmol) of AIBN in 5 mL of benzene was added. When addition was complete, a TLC was taken which indicated that the bromide had been consumed. The reaction mixture was poured over alumina, then concentrated. A proton NMR spectrum was taken of the crude residue, but there was no evidence for the formation of **18**.

Attempted cyclization of 21 using $\text{Et}_3\text{B}/\text{O}_2$ and HSnBu_3 at 0 °C:

The bromide **21**, prepared from 0.153 g (0.283 mmol) of alcohol **12** was concentrated in a 250 mL roundbottom flask equipped with a stir bar and kept under a flow of N_2 , then dissolved in 20 mL of CH_2Cl_2 . Next, 0.3 mL (0.3 mmol Et_3B (1M in hexanes) was added and 10 mL of air was bubbled through the solution. The reaction mixture was cooled to 0 °C and a solution of HSnBu_3 (0.08 mL, 0.28 mmol) in 10 mL of CH_2Cl_2 was added dropwise over a period of 20 min. The reaction stirred at 0 °C for 1.5 h. It turned cloudy and a green solid could be seen. The reaction was quenched with saturated KF, then the organic layer was isolated with a separatory funnel. It was dried over MgSO_4 and concentrated. Purification was performed using column chromatography (2 : 1 petroleum ether/diethyl ether/alumina). Two fractions were isolated. They both contained mixtures of the same compounds, but structures could not be determined.

Attempted cyclization of 21 using $\text{Et}_3\text{B}/\text{O}_2$ and Ph_2SiH_2 in toluene at 0 °C:

The bromide **21** prepared from 0.194 g (0.361 mmol) of alcohol **12** was concentrated in a 250 mL roundbottom flask equipped with a stir bar and kept under a

flow of N₂, then dissolved in 5 mL of toluene. The flask was cooled to 0 °C and 0.06 mL (0.33 mmol) of Ph₂SiH₂ and 0.3 mL (0.3 mmol, 1M in hexanes) of Et₃B were added. Oxygen was bubbled through the solution, and the reaction was warmed to room temperature. The reaction was monitored by TLC (4 : 1 petroleum ether/diethyl ether). After a hour **21** had been consumed. The reaction mixture was purified by PTLC (5 % ethyl acetate in hexanes). Two fractions were isolated and a proton NMR spectrum was taken of each. The first fraction contained **18** and **36a**. The second contained **36b**.

Attempted cyclization of 21 using Et₃B/O₂ and Ph₂SiH₂ in benzene at room temperature:

The bromide **21**, prepared from 0.105 g (0.193 mmol) of alcohol **12** was concentrated in a 250 mL roundbottom flask equipped with a stir bar and kept under a flow of N₂, then dissolved in 5 mL of benzene. The Ph₂SiH₂ (0.04 mL, 0.20 mmol) and Et₃B (0.04 mL, 0.04 mmol, 1M in hexanes) were added, then 0.9 mL of oxygen were bubbled through the solution. The color of the reaction mixture changed from red to brown and **21** was consumed after 1 h (monitored by TLC 4 : 1 petroleum ether/diethyl ether). The reaction mixture was filtered over celite then concentrated. Purification was performed using column chromatography (10% diethyl ether in petroleum ether/silica gel). Two fractions were collected and a proton NMR spectrum was taken of each. The first contained **36a**. The second contained **18** and **36b**.

Attempted cyclization of 31 using Ph_2SiH_2 and Et_3B in benzene at room temperature:

The bromide **31** prepared from 0.11 g (0.23 mmol) of alcohol **30** was concentrated in a 250 mL roundbottom flask equipped with a stir bar and kept under a flow of N_2 , then dissolved in 20 mL of benzene. The reaction stirred for 4 h while being monitored by TLC (2 : 1 petroleum ether/diethyl ether). When **31** had been consumed, the reaction mixture was filtered through silica gel. Purification was done by PTLC (10 % ethyl acetate in petroleum ether). Three fractions were collected and a proton NMR spectrum was taken of each. The structure of the first compound could not be determined, but the second fraction contained an isomer of **38a**, and the third fraction contained both **38a** and **38b**.

Synthesis of 51:

In a 250 mL side-arm roundbottom flask equipped with a stir bar and kept under a flow of N_2 , DIPHOS (0.501 g, 1.26 mmol) was dissolved in 12 mL of CH_2Cl_2 . The reaction mixture was cooled to 0 °C, then a solution of Br_2 (0.013 mL, 2.52 mmol) in 2.5 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to stir for 5 minutes, then a solution of **29** (0.211 g, 1.05 mmol) in 2.5 mL of CH_2Cl_2 was added. The reaction stirred at 0 °C for an hour, then was warmed to room temperature. The reaction stirred another 1.5 h while being monitored by TLC for the disappearance of **29** (3 : 1 petroleum ether/diethyl ether). After **29** had been consumed, 70 mL of pentane and 35 mL of diethyl ether were added. A white precipitate formed. The solution was filtered through celite and concentrated. Purification was performed by flash

chromatography (3 : 1 petroleum ether/diethyl ether/silica gel). The yield of **51** was 0.273 g (1.04 mmol, 99%).

Data for 51:

Physical state: yellow oil

¹H NMR (400MHz, CDCl₃) δ 7.43-7.36 (m, 2H, Ph), 7.30-7.25 (m, 3H, Ph), 5.81 (ddt, J = 17.1, 10.0, 6.0 Hz, 1H, CH₂CHCH[⋄]H'), 5.04 (d, 17.1 Hz, 1H, CH₂CHCH[⋄]H'), 4.98 (d, 10.0 Hz, 1H, CH₂CHCH[⋄]H'), 4.76 (t, J = 6.0 Hz, 1H, CH₂CHBr) 2.15-2.07 (m, 3H, CH₂), 1.73-1.65 (m, 3H, CH₂).

¹³C NMR (100MHz, CDCl₃) δ 137.8, 131.7, 128.7, 128.2, 122.1, 115.1, 87.9, 86.9, 39.1, 37.7, 32.7, 26.5.

IR (CH₂Cl₂) 3082 (w), 2974 (m), 2933 (m), 2867 (m), 2226 (w), 1640 cm⁻¹.

MS (FAB, matrix: 3-nitrobenzyl alcohol) m/z: 183 [M - 79]⁺, 185 [(M + 2) - 81]⁺.

Attempt to cyclize 51 by irradiation:

Compound **51** (0.058 g, 0.221 mmol) was placed in a 25 mL roundbottom flask equipped with a stir bar and kept under a flow of N₂, then was irradiated under a 300 W halogen floodlight for 3 h. A proton NMR spectrum was taken of the residue after irradiation; it showed that **51** had not reacted.

Attempt to cyclize 51 by irradiating in the presence of $\text{Bu}_3\text{SnSnBu}_3$:

In a 25 mL roundbottom flask equipped with a stir bar and kept under a flow of N_2 , **51** (0.117 g, 0.448 mmol) was dissolved in 1.5 mL of benzene, then 0.023 mL (0.045 mmol) of $\text{Bu}_3\text{SnSnBu}_3$ was added. The reaction mixture was irradiated under a 300 W halogen floodlight for 2 h while being monitored by TLC (10% diethyl ether in petroleum ether); however, there was no indication that cyclization had taken place. The reaction mixture stirred another 12 h. A proton NMR spectrum was taken of the crude residue, but it revealed that only **51** was present.

Figure 3.6: 300 MHz ¹H NMR spectrum of **21** in CDCl₃,

Figure 3.7: 400 MHz ¹H NMR spectrum of **35b** in CDCl₃

Figure 3.8: 400 MHz ^1H NMR spectrum of **36a,b** in CDCl_3

Figure 3.9: 400 MHz ¹H NMR spectrum of **38a** in CDCl₃

Figure 3.10: 400 MHz COSY NMR spectrum of **38a** in CDCl₃

Figure 3.11: 400 MHz ^1H NMR spectrum of **38b** in CDCl_3

Figure 3.12: 400 MHz COSY NMR spectrum of **38b** in CDCl_3

Figure 3.13: 400 MHz ^1H NMR spectrum of **44a** in CDCl_3

Figure 3.14: 400 MHz ^1H NMR spectrum of **44b** and **46** in CDCl_3

Figure 3.15: 300 MHz ^1H NMR spectrum of **89** in CDCl_3

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CHAPTER IV

FURTHER INVESTIGATIONS INTO THE MECHANISM AND SYNTHETIC UTILITY OF CYCLIZATION

I. MECHANISTIC STUDIES

A. Introduction

As previously stated, the results from our studies of 5-hexenyl and 6-heptenyl bromide complexes suggest that the cyclizations of the propargyl bromide complexes occur by a radical mechanism under kinetic control, but proceed *via* a late transition state so that formation of the most stable product radicals is favored. However, the possibility remains that these reactions could be proceeding by a non-radical mechanism or by a radical mechanism under thermodynamic control, especially considering the fact that **1a,b** cyclized to give both **3a,b** and **4**, while **2** gave exclusive formation of **5a,b** (Scheme 4.1).

Scheme 4.1: Cyclization of **1a,b** and **2**

A method that is used to test whether or not a reaction operates by a radical mechanism is to run the reaction in the presence of a radical scavenger such as 1,3-dinitrobenzene,¹ TEMPO,² or 1,1,3,3-tetramethylisoindoline-2-oxyl³ in order to suppress product formation. A method that is generally used to test whether or not a radical cyclization is reversible involves regeneration of the radical from the 5-*exo* (or 6-*endo*) product to see if it will ring-open and re-close to give the 6-*endo* (or 5-*exo*) product (Scheme 4.2).⁴

Scheme 4.2: The test for the reversibility of **6**

In order to unequivocally determine whether the cyclizations of the propargyl bromide complexes were operating by a radical mechanism under kinetic control, or whether a different mechanism was operating, several experiments were performed to try to suppress radical cyclization, and to induce reversibility. Our results are outlined below.

B. Results

1. Testing whether the cyclizations proceed by a radical mechanism

In order to test if the reaction was operating by a radical mechanism, several attempts were made to suppress the cyclization of **1a,b** by running the reaction in the presence of a radical scavenger. In the first reaction 1,3-dinitrobenzene was employed as the radical scavenger.¹ Hence, 1.5 equivalents of 1,3-dinitrobenzene were added to a solution of **1a,b** in benzene then the reaction mixture was irradiated for an hour (Scheme 4.3).

Scheme 4.3: Attempt to inhibit cyclization of **1a,b** using 1,3-dinitrobenzene

After purification by PTLC, four fractions were isolated and proton NMR spectra were taken of each. From these spectra, the compounds in the fractions were identified as the cyclization products **3a,b** and **4**. It was evident that cyclization had not been inhibited. One reason why cyclization was not inhibited could have been that the rate of inhibition (radical reaction of **1a,b** with DNB) was slower than cyclization.⁵ For this reason, a second reaction was attempted in which a solution of **2** in benzene containing 1.5 equivalents of THF was irradiated for 1 hour (Scheme 4.4).

Scheme 4.4: Attempt to inhibit cyclization of **2** with THF

The THF was employed as a potential hydrogen atom donor so that if the radical was generated, the expected product(s) would be either **5c** and/or **9**. After purification by flash chromatography, two fractions were isolated, and a proton NMR spectrum was taken of each. The compound in the first fraction appeared to be acyclic because it contained resonances for vinyl protons; however, there was a doublet of doublets at 5.33 ppm, which suggested that **2** had undergone nucleophilic attack by THF. The compound in the second fraction was the alcohol, which resulted from the hydrolysis of **2**. Further confirmation of the structure in the first fraction was not obtained because there was no evidence the radical had been generated or that the THF had acted as a hydrogen atom donor.

Finally, an attempt to trap the radical was made by employing the stable nitroxide TEMPO (2,2,6,6-tetramethylpiperidineoxyl) (Scheme 4.5).⁶

Scheme 4.5: First attempt to inhibit cyclization of **10** using TEMPO

In the first reaction, 1 equivalent of TEMPO was added to a solution of **10** in benzene, which was then irradiated for 1 hour. A control experiment was also run at the same time in which a solution of the same concentration of **10** in benzene, without TEMPO, was

irradiated for 1 hour. After the reaction mixtures were purified by gravity column chromatography using alumina, a proton NMR spectrum was taken of each. The spectrum of the fraction isolated from the control experiment indicated that cyclization had taken place; however, the spectrum of the fraction isolated from the reaction run in the presence of TEMPO looked as though it contained a 1 : 1 mixture of two new compounds. There were two doublet of triplets at 6.98 and 6.75 ppm (both for $\text{CH}_2\text{CHCH}'\text{CO}_2\text{CH}_3$), two doublets at 5.84 and 5.51 ppm (both for $\text{CHCH}'\text{CO}_2\text{CH}_3$), two multiplets between 5.18-5.16 and 4.66-4.63 ppm (both for CH_2CHOR), and two singlets at 3.70 and 3.67 ppm (both for CO_2CH_3). The fact that the spectrum contained resonances for vinyl protons, suggested that cyclization had been inhibited and two diastereomers **11a,b** had been produced (Scheme 4.5). This was confirmed by mass spectrometry where both the FAB and 12 ev DIP spectra gave an M-5(CO) peak at m/z 515 and a peak at m/z 156, which was assigned as the TEMPO fragment.

Even though the evidence seemed conclusive that the acyclic radical had been trapped by the TEMPO, there was a question as to whether this really was the case because the TEMPO could have reacted with the bromide before irradiation *via* nucleophilic substitution. For this reason, a second experiment was performed in which TEMPO was added to a solution of **10**, then the reaction mixture stirred for an hour without being irradiated. An aliquot was taken, and the contents left in the flask were irradiated for an hour. The proton NMR spectrum of the aliquot clearly indicated the presence of **11a,b**. In addition, the proton NMR spectrum of the fraction isolated from the reaction mixture after it had been irradiated for an hour was very similar to the sample that had not been irradiated. From this evidence, it could only be concluded that the

bromide was attacked prior to irradiation. However, one peculiar finding was that in the initial experiment, where **10** had been irradiated in the presence of TEMPO, the ratio of products was 1 : 1, but in the experiment where **10** was not irradiated in the presence of TEMPO, the ratio was 7 : 1. This could be an indication that the reaction operates under two different mechanisms depending on whether or not the reaction mixture is irradiated, but at present, it remains unknown. According to our observations from these experiments, we were unable to conclusively prove that the reaction is proceeding by a radical mechanism; however, we still believe that a radical mechanism is operating based on the indirect evidence that has been cited (Chapter II, p. 191-192).

2. Testing the reversibility of 5-hexenyl cyclization

In our studies to determine if cyclization was reversible, the uncyclized bromide, **10**, was first employed as the initiator in the reaction outlined in Scheme 4.6.

Scheme 4.6: Testing reversibility of **12a,b** using **10** as the initiator

A solution of **10** and **12a,b** was prepared, then the mixture was concentrated and irradiated for an hour. A separate proton NMR spectrum was taken of each compound

before the reaction, then one was taken of the mixture after irradiation. There was no evidence for the formation of the 6-*endo* product.

After the attempted ring-opening employing **10** failed, it was decided to proceed using **3a** because it had been generated in the only reaction which produced both the 5-*exo* and 6-*endo* compounds. In the first reaction, hexabutylditin ($\text{Bu}_3\text{SnSnBu}_3$) was employed as the initiator (Scheme 4.7). It was added to a 0.5 M solution of **3a** in benzene, then the reaction mixture was irradiated for 1.5 hours. Purification was performed using gravity column chromatography. One fraction was isolated, and the proton NMR spectrum indicated that the compound was **3a**.

Scheme 4.7: Testing the reversibility of **3a** using $\text{Bu}_3\text{SnSnBu}_3$ as the initiator

In order to check if the above reaction was unsuccessful because of impurities in the $\text{Bu}_3\text{SnSnBu}_3$, a reaction was run employing the mixture **12a,b**, where $\text{Bu}_3\text{SnSnBu}_3$ was the initiator and HSnBu_3 was the hydrogen atom source (Scheme 4.8).

Scheme 4.8: Generation of the radical from **12a,b** using $\text{Bu}_3\text{SnSnBu}_3$

Both $\text{Bu}_3\text{SnSnBu}_3$ and HSnBu_3 were added to a 1.5 M solution of **12a,b** in benzene, then the reaction was irradiated for 2.5 hours. An aliquot was taken from the solution, and the proton NMR spectrum showed that some of the bromide had been reduced to **13**. More $\text{Bu}_3\text{SnSnBu}_3$ was added to the reaction mixture and it stirred another 7 hours, while being irradiated. Purification was performed using PTLC. Two fractions were isolated, and proton NMR spectra were taken of each. The first fraction contained one isomer of **12a,b**, and the second fraction contained a mixture of the other isomer of **12a,b** and **13**. The ratio of **12a,b**/**13** was 1 : 3. Even though the reaction did not go to completion, it showed that the difficulties encountered with generating the radical from **3a** were not due to impure $\text{Bu}_3\text{SnSnBu}_3$. In addition, this reaction illustrated that even though the radical could be generated from **12a,b**, the rate of ring-opening was slow compared to the rate of reduction, and therefore offered more evidence that the cyclizations employing (propargyl) $\text{Co}_2(\text{CO})_6$ radicals are not operating under thermodynamic control. Subsequently, the reaction in Scheme 4.4 was repeated; however, after irradiating for 2 hours, only **3a** could be detected in the reaction mixture.

Because there was no evidence that the $\text{Bu}_3\text{SnSnBu}_3$ was successfully initiating the reactions employing **3a**, a reaction was performed using AIBN as the initiator (Scheme 4.9). The reaction was heated to 80 °C and stirred for one hour. TLC indicated that a reaction had taken place. After purification by PTLC, three fractions were isolated. A proton NMR spectrum was taken of each fraction. The first fraction contained the starting material. The compound in the second fraction was not a cobalt complex. The spectrum showed two overlapping doublets at 6.44 ppm (CHCHPh), a doublet of doublets at 6.04 ppm (CHCHCH^iPh , $J = 15.6, 8.7$ Hz), and a doublet of doublets at 11.4 ppm (CHCHCH^cPh , $J = 11.4, 10.2$ Hz). A 12 eV DIP mass spectrum was obtained, and it gave an molecular ion at m/z 278 and an $M + 2$ peak at m/z 280. The data is consistent with a compound having the structure of **14**. The *cis* and *trans* isomers were isolated together in 18% yield (Scheme 4.9).

Scheme 4.9: Attempt to initiate the radical from **3a** using AIBN

The compound in the third fraction was not a cobalt complex either. The proton NMR spectrum contained a doublet of quartets at 4.52 ppm and a doublet at 1.77 ppm ($J = 6.9$ Hz). A 12 eV DIP mass spectrum was taken and it had a molecular ion at m/z 276 and an $M + 2$ peak at m/z 278. The data of this spectrum was consistent with the compound

having structure **15**. It was isolated in 16% yield. This result was interesting because it illustrated the difficulties associated with initiating radical reactions using alkyl bromides. In this example, **3a** undergoes demetallation/reduction rather than initiation.

Finally, a reaction was run employing 2,2'-azobis(2,4-dimethylvaleronitrile), AMVN, as the initiator. This compound operates by the same mechanism as AIBN, only it can initiate reactions at room temperature (Scheme 4.10).

Scheme 4.10: Attempt to initiate the radical from **3a** using AMVN

The initiator and HSnBu_3 were added to a 0.01 M solution of **3a** in benzene, then heated to $35\text{ }^\circ\text{C}$. The reaction mixture was stirred for 12 hours then was purified by PTLC. Two fractions were isolated and a proton NMR spectrum was taken of each. The first fraction contained **14**, while the second fraction contained **15**. Hence even in the presence of a low-temperature initiator, demetallation/reduction occurred in preference to initiation.

It was only slightly surprising that our attempts to initiate the radical from **3a** were unsuccessful. In his study of halogen atom transfer reactions employing α -bromoesters, Curran found that the reactions were difficult to effect because the bromides did not

undergo efficient initiation.⁷ This was also illustrated by the reaction in Scheme 4.8. Even though some of the reduced compound, **13**, had been produced, the starting material was not completely converted even after stirring for 7 hours. However, the fact that the radical was produced also indicates that α -bromoesters are more reactive than alkyl halides, since none of the reactions employing **3a** gave evidence that radicals had been generated.

C. Discussion

While our evidence clearly suggests that the cyclization reactions are proceeding by a radical mechanism under kinetic control which goes through late transition state, our efforts to trap the radicals and to test the reversibility of cyclization were inconclusive. A radical scavenger could not be found which trapped the radical, but did not undergo nucleophilic attack of the (propargyl bromide) $\text{Co}_2(\text{CO})_6$, nor could proper conditions be found to efficiently initiate radicals from the cyclized bromides. The results from our efforts to trap the radical with TEMPO were inconclusive because it appears that **10** reacts with TEMPO by a non-radical mechanism. However, in our reversibility studies, a notable exception in our study was when **12a,b** was irradiated in the presence of $\text{HSnBu}_3/\text{Bu}_3\text{SnSnBu}_3$ (Scheme 4.8). The fact that the radical was generated and the reduced 5-*exo* product, **13**, was isolated indicates that the rate of reduction is faster than the rate of ring-opening. However, because the rate of ring-opening is very slow, it supports our belief that cyclization is irreversible. Also interesting in this study was that when the initiators AIBN and AMVN were employed as initiators, **3a** underwent demetallation/reduction instead of radical initiation.

At present, it is unknown why the radicals were not generated from **3a**, but two reasons have been postulated: the first is in accordance with Curran's findings that it is difficult to generate radicals from alkyl bromides because initiation is not efficient.⁷ The second is that the $-\text{Co}_2(\text{CO})_6$ group is an excellent chromophore, and it could be absorbing the photons that are necessary to cleave the Sn-Sn bond. Nevertheless, our data remain consistent with an irreversible radical cyclization unless and until conditions can be found which prove that the cyclization of (propargyl) $\text{Co}_2(\text{CO})_6$ radicals is reversible. For these reasons, we remain in search of a method which definitively proves or disproves our postulate.

II. SYNTHETIC STUDIES

A. Allylation and the Pauson-Khand reaction

In addition to studying the reactivity and mechanistic aspects of cyclizations involving (propargyl) $\text{Co}_2(\text{CO})_6$ radicals, another goal of the project was to develop their synthetic utility, and the unexpected formation of the cyclopentyl and cyclohexyl bromides offered such an opportunity. We proposed that if the acyclic bromides were irradiated in the presence of a radical allylating reagent, halogen atom transfer could be suppressed and compounds such as **17a,b** and **18a,b** could be generated through a tandem cyclization/allylation reaction (Scheme 4.11).

Scheme 4.11: Proposed method of cyclization/allylation reactions using **10** and **16a,b**

The desire to synthesize **17a,b** and **18a,b** stemmed from an interest to explore whether or not further cyclization transformations could be performed on them. For example, if **17a,b** and **18a,b** could be synthesized, then the enyne system would be in the correct arrangement for a Pauson-Khand reaction (Scheme 4.12).⁸

Scheme 4.12: Proposed Pauson-Khand reaction

Such a transformation would be very valuable because it would produce a tricyclic compound from the acyclic bromide in two steps.

The use of allyltri-*n*-butylstannane as an effective radical trap in reactions employing alkyl halides was first demonstrated by Keck *et al.* when they reported that heating alkyl halides in the presence of AIBN and allyltri-*n*-butylstannane at 80 °C gave the allylated products in very good yield.⁹ For example, **21** was converted to **22** in 76% yield after heating for 8 hours (Scheme 4.13).

Scheme 4.13: Keck's allylation procedure

For our allylation reactions, only **10** and **16a,b** were employed because they produced the 5-*exo* cyclization products exclusively. We wanted to avoid extra steps to separate the 5-*exo* and the 6-*endo* products, and we postulated that the Pauson-Khand cyclization of the cyclohexyl bromide would not be possible because the resulting product would be very strained. In the initial attempt to allylate **16a,b**, the procedure outlined by Keck *et al.* was employed.⁹ Therefore, 1.3 equivalents of allyltri-*n*-butylstannane was added to a 0.03 M solution of **16a,b** in benzene (Scheme 4.14).

Scheme 4.14: Attempted allylation employing Keck's procedure

The reaction mixture was then irradiated for 1 hour, and the color changed from red to brown. Six fractions were isolated after purification by PTLC, and a proton NMR spectrum was taken of each. The compounds in the first two fractions were identified as the cyclopentyl bromides (the diastereomers had been separated), and the compound in the sixth fraction was identified as the hydrolyzed bromide. However, the compounds in the third through fifth fractions could not be identified. It appeared as though they resulted from decomposition of **16a,b** when it was placed on the PTLC plate.

The reaction was repeated with the following modifications (Scheme 4.14): the concentration was 0.003 M and 10 equivalents of allyltri-*n*-butylstannane were used. The reaction mixture was irradiated for an hour, and two fractions were collected after purification by PTLC. A proton NMR spectrum was taken of each. The spectra showed that both fractions contained the cyclic bromides; however, there was no evidence that **18a,b** was present in either fraction.

As the allylation reactions employing the uncyclized bromides were unsuccessful, attempts were made to allylate the cyclized bromides. The reaction in Scheme 4.8 had demonstrated that the radical could be generated from **12a,b** because the reduced complex **13** had been isolated. Based on that result, it was postulated that the presence of

the phenyl group might aid in generating the radical because it would be highly stabilized once it was formed. Therefore, 2.5 equivalents of allyltri-*n*-butylstannane and 0.2 equivalents of $\text{Bu}_3\text{SnSnBu}_3$ were added to a 0.02 M solution of **23a,b** in benzene, and the reaction mixture was irradiated for 3 hours, while being monitored by TLC, which gave no evidence that reaction had occurred (Scheme 4.15).

Scheme 4.15: Attempted allylation of **23a,b** and **12a,b**

In a similar reaction, 2.5 equivalents of allyltri-*n*-butylstannane and 0.2 equivalents of $\text{Bu}_3\text{SnSnBu}_3$ were added to a 0.02 M solution of **12a,b**. The reaction was irradiated for an hour; however, the TLC showed that no reaction occurred.

Further efforts to allylate **12a,b** by irradiating it in the presence of allyltri-*n*-butylstannane without an initiator, and irradiating **23a,b** and **12a,b** in the presence of allyltri-*n*-butylstannane using AIBN as an initiator were unsuccessful as well. This prompted the search for other initiators which had been employed to achieve allylation, and led to a procedure involving the use of Vitamin $\text{B}_{12\text{a}}$.¹⁰ In this reaction, 0.05 equivalents of Vitamin $\text{B}_{12\text{a}}$ were added to a solution of **23a,b** and 2 equivalents of

allyltri-*n*-butylstannane in DMF. Nitrogen was bubbled through the solution for 15 minutes, then 2.5 equivalents of activated zinc were added. The sample was irradiated; however, after fifteen minutes, the starting material (**23a,b**) demetallated (Scheme 4.16).

Scheme 4.16: Attempted allylation employing Vitamin B_{12a} as the initiator

Another method that was found involved the employment of a related compound, allylpyridinatocobaloxime, (py)Co(DMgH)₂(allyl) as the allylating agent.¹¹ This compound was prepared according to Schrauzer's procedure.¹² However, when it was added to a 0.02 M solution of **10** in benzene, **10** demetallated after 15 minutes (Scheme 4.17).

Scheme 4.17: Attempted allylation of **10** employing (py)Co(DMgH)₂(allyl)

Finally, a reaction was performed which employed $\text{Fe(allyl)(CO)}_2\text{Cp}$ as the allylating reagent. It had previously been reported by Giering *et al.* that $\text{Fe(allyl)(CO)}_2\text{Cp}$ reacts with CCl_4 at 25 °C to give **25** in 85% yield after two days (Scheme 4.18).¹³

Scheme 4.18: Study employing $\text{Fe(allyl)(CO)}_2\text{Cp}$ as a radical allylating reagent

In addition to **25**, other byproducts such as allyl chloride, hexachloroethane, 1,5-hexadiene, and propene were produced in trace amounts. After a detailed mechanistic inquiry, Giering *et al.* concluded that the reaction was proceeding by a radical mechanism. Based on this study, we decided to employ $\text{Fe(allyl)(CO)}_2\text{Cp}$ as the allylating reagent.

In this reaction a solution of **10** (0.05 M) in benzene was treated with 1.2 equivalents of $\text{Fe(allyl)(CO)}_2\text{Cp}$ (Scheme 4.19). The $\text{Fe(allyl)(CO)}_2\text{Cp}$ was prepared by the procedure outlined by Rosenblum *et al.*,¹⁴ and **10** was employed because the previous allylation reactions employing **12** and **23a,b**, gave no evidence that the radical had been generated; therefore, the only way to insure formation of the cyclic radical was to start from the acyclic bromide.

Scheme 4.19: Allylation employing $\text{Fe(allyl)(CO)}_2\text{Cp}$

The reaction stirred for 3 hours at room temperature without being irradiated. After the starting material was consumed, the mixture was purified by flash chromatography, and six fractions were isolated. In addition a red-brown solid remained in the reaction flask. A proton NMR spectrum was taken of each fraction; however, only the compounds in the first fraction could be positively identified. They were a mixture of **17a,b** and **13** in a **17a,b/13** ratio of 4 : 1. The proton NMR spectra of the compounds in the other fractions contained resonances for vinyl protons, which indicated that the compounds were acyclic. Furthermore, when the procedure was modified and 5 equivalents of $\text{Fe(allyl)(CO)}_2\text{Cp}$ were employed, the formation of **13** was suppressed and **17a,b** was isolated as a mixture of two inseparable diastereomers in 23% yield. The assigned structure was supported by a FAB mass spectrum which gave a $\text{M}-3(\text{CO})$ peak at m/z

484. The characteristic resonances in the proton NMR spectrum were the double doublet of triplets at 5.62 ppm ($\text{CH}_2\text{CHCH}^{\text{c}}\text{H}^{\text{t}}$), two sets of overlapping doublet of doublets ranging from 5.02–4.91 ppm ($\text{CHCH}^{\text{c}}\text{H}^{\text{t}}$), and two singlets at 3.65 and 3.58 ppm (CO_2CH_3). In addition, an IR spectrum was taken of the red-brown solid that was left in the flask. It was determined to be $\text{FeBr}(\text{CO})_2\text{Cp}$ by comparing the carbonyl stretching frequencies to the values found in the literature.¹⁵ The concomitant formation of $\text{FeBr}(\text{CO})_2\text{Cp}$ with **17a,b** strongly suggests that the allylation reaction occurs *via* a radical mechanism. Therefore, because the acyclic bromide, **10**, is employed in this reaction, this result offers further evidence that **10** cyclizes *via* a radical mechanism

Once compounds **17a,b** had been synthesized, the Pauson-Khand reaction was attempted. The first reaction was run according to the procedure outlined by Schreiber *et al.*¹⁶ In this reaction, 1.6 equivalents of N-methylmorpholine N-oxide, NMO, was added to a solution of **17a,b** in CH_2Cl_2 . The reaction mixture stirred for 3 hours, then it was purified by flash chromatography. Four fractions were collected, and a proton NMR and FAB mass spectrum was taken of each. According to the data, the first fraction contained starting material. The FAB mass spectrum of the second fraction gave an $\text{M} + 1$ peak at m/z 283, and the NMR spectrum exhibited resonances similar to those of the starting material; therefore the compound was assigned as **27a,b**, in which the starting material had been demetallated. The mixture was isolated in 36% yield. The compounds in the third and fourth bands could not be identified (Scheme 4.20).

Scheme 4.20: Attempted Pauson-Khand reaction employing Schreiber's procedure

In the second attempt of the Pauson-Khand reaction, the procedure developed by Smit and Caple, was employed.¹⁷ The mixture **17a,b** was adsorbed onto silica gel and then heated to 45 °C under a flow of oxygen for 2 hours. The silica gel changed color from pink to blue. It was then rinsed with diethyl ether, which yielded a yellow oil after the solution was concentrated. The oil was purified by PTLC. One fraction was isolated, and a proton NMR spectrum was taken, which showed that the demetallated compound, **27a,b**, had been produced again (Scheme 4.21).

Scheme 4.21: Attempted Pauson-Khan reaction employing Smit and Caple's procedure

The final attempt to synthesize **19a,b** followed the procedure of Sugihara *et al.*¹⁸ In this reaction, **17a,b** was dissolved in 1,4-dioxane which was followed by addition of NH₄OH (2 M). The reaction mixture was heated to 100 °C and stirred for 1 hour. During this time, the reaction mixture changed color from red to black. Purification was performed using PTLC, and one fraction was isolated. The proton NMR spectrum indicated that the fraction was composed of a mixture of compounds, but there was no indication that **19a,b** had been generated (Scheme 4.22).

Scheme 4.22: Pauson-Khand reaction employing Sugihara's procedure

B. Discussion

In the attempts to allylate **16a,b** by irradiating it in the presence of allyltri-*n*-butylstannane it was somewhat surprising that allylation did not occur. Keck *et al.* had previously determined that when **28** was heated to 80 °C in the presence of allyltri-*n*-butylstannane and AIBN for 15 hours, **30** was the only detectable product by GC (Scheme 4.23).⁹

Scheme 4.23: Keck's cyclization/allylation study of **28** and **29**

He also found that when the analogous iodides, **29**, were heated under the same conditions, halogen atom transfer competed with allylation, and at 20% conversion the **32/33** ratio was 1 : 5. This example illustrates that halogen atom transfer reactions involving typical alkyl bromides cannot compete with allylation; however if the rate of halogen atom transfer is increased, then it will suppress allylation; therefore, in the allylation reactions involving **16a,b**, the radical stabilization by the $-\text{Co}_2(\text{CO})_6$ group may have increased the rate of the halogen atom transfer so that it occurred faster than allylation.

In the attempts to allylate **12a,b** and **23a,b**, there was never any evidence that the radicals were generated, and in the case where Vitamin B_{12a} and $(\text{py})\text{Co}(\text{DMgH})_2(\text{allyl})$ were employed, it appeared as if the Co^{II} complexes were strong enough reducing agents to demetallate **23a,b**.

In the reactions which employed $\text{Fe}(\text{allyl})(\text{CO})_2\text{Cp}$, the evidence clearly suggests that cyclization/allylation occurs *via* a radical mechanism. Despite our success with synthesizing **17a,b**, the yield of the reaction was low. Many side-reactions occurred during the allylation, and while increasing the ratio of $\text{Fe}(\text{allyl})(\text{CO})_2\text{Cp}$ to **10** suppressed

the formation of **13**, it did not eliminate the formation of the other byproducts. Clearly, efforts towards the optimization of the reaction need to be made.

Finally, the failure of **17a,b** to undergo a Pauson-Khand reaction was also surprising because when a hand-held model was built of the predicted product, it appeared to be strain free. In addition, Brummond *et al.* have reported that a related compound **35a** was produced from **34a** (R = H) in a **35a/36a** ratio of 7 : 1 in 73% overall yield when it was heated to 100 °C in the presence of Mo(CO)₆, and DMSO. In the cyclization of compound **34b** (R = TMS), **35b** was the only product observed in 50% yield. (Scheme 4.24).²⁰

Scheme 4.24: Brummond's synthesis of **35a** and **35b**

There is no obvious reason why **17a,b** did not cyclize given Brummond's results. One reason why the cyclizations of **34a** and **34b** were successful could be that the allene is more reactive than **17a,b**, so the driving force for cyclization is greater. Also, in **34a** and **34b** the orientation of the groups may be more amenable toward cyclization because the sp²-hybridization of C* could aid in the approach of the two groups, while in **17a,b**,

the approach of the two groups could be prevented because they are *trans* to each other. Such a situation would favor demetallation over cyclization.

III. CONCLUSION

Our attempts to inhibit radical cyclization were complicated by the fact that TEMPO appeared to be reacting with **10** by nucleophilic substitution. At present, we remain in search of a method to unequivocally prove the mechanism of the reaction.

The results from our efforts to test whether or not the cyclization reaction of (propargyl)Co₂(CO)₆ radicals is reversible were also inconclusive. The greatest difficulty experienced with our studies was the generation of the radical from the cyclic bromides. Evidence that the radical had been generated was only observed when **12a,b** was irradiated in the presence of HSnBu₃/Bu₃SnSnBu₃. In this example, reduction occurred faster than ring-opening which was indicative that the reaction is not reversible under these conditions. In addition when **3a** was heated in the presence of AIBN or AMVN, demetallation/reduction of the complexes were observed in lieu of radical initiation, which demonstrates the difficulty associated with initiating radicals from alkyl bromides and also offers evidence that the cyclizations are not reversible.

In our efforts to explore the synthetic utility of cyclizations employing (propargyl bromides)Co₂(CO)₆, the cyclization/allylation of **10** was successful when Fe(allyl)(CO)₂Cp was employed as the allylating agent. Efforts need to focus on improving the yield of the reaction; however this result offers strong evidence that cyclization of **10** occurs via a radical mechanism. Finally, even though our attempts to further cyclize **17a,b** by the Pauson-Khand reaction, were unsuccessful, this compound

is amenable to other transformations which have the potential to extend the synthetic scope of (propargyl) $\text{Co}_2(\text{CO})_6$ radicals.

IV. EXPERIMENTAL

Attempt to inhibit cyclization of 1a,b using 1,3-dinitrobenzene:

The bromide **1a,b** (prepared from 0.127g, 0.254 mmol of alcohol (**42a,b**, Chapter III)) was isolated in a 500 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N₂. It was dissolved in 10 mL of benzene, then 0.06 g (0.37 mmol) of 1,3-dinitrobenzene was added. The mixture was irradiated under a 300 W halogen floodlight for 1 h. The reaction mixture was concentrated, then purified by PTLC (3 : 1 petroleum ether/ diethyl ether). Four fractions were isolated, and the proton NMR spectra indicated that the compounds in these fractions were the products resulting from the cyclization of **1a,b**.

Attempt to inhibit cyclization of 2 by irradiating in the presence of THF:

The bromide **2** (prepared from 0.095 g, 0.195 mmol of alcohol (**30**, Chapter III)) was isolated in a 500 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N₂. It was dissolved in 10 mL of benzene, then 0.024 mL (0.296 mmol) of THF was added and the reaction was stirred for one hour while being irradiated under a 300 W halogen floodlight. The reaction mixture was concentrated and purified using flash chromatography (10% ethyl acetate in petroleum ether/silica gel). Two fractions were isolated and a proton NMR spectrum was taken of each. The compound in the first fraction appeared to be an acyclic compound which could have resulted from **2** undergoing nucleophilic attack by THF. The compound in the second fraction was the alcohol which resulted from hydrolysis of **2**.

Attempt to inhibit cyclization of 10 using TEMPO:

The bromide **10** (prepared from 0.081g, 0.149 mmol of alcohol (**12**, Chapter III)) was isolated in a 500 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N₂. It was dissolved in 6 mL of benzene, then 3 mL was withdrawn and placed in another 25 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N₂. The first flask was immediately irradiated under a 300 W halogen floodlight, while 0.028 g (0.139 mmol) of TEMPO was added to the second flask before it was irradiated. Both reactions stirred for 4 h. They were each concentrated, then purified using gravity column chromatography (10% diethyl ether/petroleum ether/activity III alumina). One fraction was isolated from each purification. The spectrum for the control experiment indicated that cyclization had occurred, while the spectrum for the reaction containing TEMPO showed the presence of **11a,b**. The yield of **11a,b** was 0.037g (0.053 mmol, 17%).

Data for **11a,b**:

Physical state: red oil.

¹H NMR (mixture) (400 MHz, CDCl₃) δ 7.39-7.37 (m, 4H, Ph), 7.31-7.25 (m, 6H, Ph), 6.98 (dt, J = 15.7, 6.9 Hz, 1H, CH₂CHCHCO₂CH₃), 6.75 (dt, J = 15.7, 6.9 Hz, 1H, CH₂CHCHCO₂CH₃), 5.84 (d, J = 15.7 Hz, 1H, CH₂CHCHCO₂CH₃), 5.51 (d, J = 15.7 Hz, 1H, CH₂CHCHCO₂CH₃), 5.18-5.16 (m, 1H, CH₂CHOR), 4.64 (t, J = 5.9 Hz, 1H, CH₂CHOR), 3.70 (s, 3H, OCH₃), 3.67 (s, 3H, OCH₃), 2.76-2.70 (m, 1H),

2.26 (q, $J = 6.9$ Hz, 2H, CH_2CHCH), 2.15-2.02 (m, 2H), 1.87-1.81 (m, 2H), 1.77-1.66 (m, 2H), 1.55-1.80 (m, 37H), 0.87-0.49 (m, 2H).

^{13}C NMR (mixture) (100 MHz, CDCl_3) δ 199.7, 167.1, 166.9, 149.2, 148.6, 138.2, 131.3, 129.0, 128.7, 128.1, 127.8, 127.5, 123.3, 121.0, 120.7, 99.1, 91.3, 90.4, 86.3, 80.6, 75.0, 61.1, 60.4, 59.4, 51.3, 51.2, 40.8, 40.5, 40.0, 36.7, 34.9, 34.6, 34.4, 33.7, 32.0, 31.7, 24.8, 23.7, 20.8, 20.6, 20.4, 20.2, 17.3, 17.1.

IR (CH_2Cl_2) 3003 (w), 2933 (m), 2871 (m), 2090 (s), 2050 (s), 2026 (s), 1720 (s), 1716 (s), 1658 (m) cm^{-1} .

MS (FAB, matrix: 3-nitrobenzyl alcohol) m/z : 543 $[\text{M}-5(\text{CO})]^+$, 527 $[\text{M}-\text{TEMPO}]^+$, 515 $[\text{M}-6(\text{CO})]^+$.

Attempt to observe reversible cyclization of 12 using 10 as the initiator:

The bromide **10** (prepared from 0.081 g, 0.149 mmol of alcohol (**12**, Chapter III)) was isolated in a 500 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N_2 . In a separate 25 mL side-arm flask which contained a stir bar and was kept under N_2 , 0.33 g (0.06 mmol) of **12** was placed, then a solution of 0.01 g (0.02 mmol) of **10** in 1 mL of diethyl ether was transferred to the flask containing **12**. The mixture was concentrated, dissolved in 10 mL of benzene, then irradiated for 1 h under a 300 W halogen floodlight. A proton NMR spectrum was taken of the crude residue, but there was no evidence that the 6-*endo* product had formed.

Attempt to observe reversible cyclization of 3a using Bu₃SnSnBu₃ as the initiator:

In a 25 mL side-arm flask which contained a stir bar and was kept under a flow of N₂, 0.072 g (0.127 mmol) of **3a** was dissolved in 0.24 mL of benzene, then 0.006 mL (0.012 mmol) of Bu₃SnSnBu₃ was added and the reaction mixture was irradiated under a 300 W halogen floodlight for 1.5 h. A TLC was taken; however because the bands barely separated, it was difficult to tell if a reaction had taken place. The reaction mixture was concentrated, then purified using gravity column chromatography (petroleum ether/silica gel). One fraction was isolated. The proton NMR spectrum gave no evidence of crossover to the 6-*endo* product. Only **3a** was present.

Attempt to observe reversible cyclization of 12a,b using Bu₃SnSnBu₃ as the initiator:

In a 25 mL side-arm flask which contained a stir bar and was kept under a flow of N₂, 0.055 g (0.090 mmol) of **12a** was dissolved in 5.7 mL of benzene, then 0.008 mL (0.016 mmol) of Bu₃SnSnBu₃ and 0.029 mL (0.107 mmol) of HSnBu₃ were added and the reaction mixture was irradiated under a 300 W halogen floodlight for 2.5 h. TLC (5 : 1 petroleum ether/diethyl ether) indicated that a reaction was occurring. An aliquot was removed from the reaction mixture and filtered through a pipet column of silica gel (petroleum ether). The filtrate was concentrated, then a proton NMR spectrum was taken. It indicated that some of **12a,b** had been reduced to **13**. In order to see if the reaction would go to completion, 0.01 mL (0.04 mmol) of HSnBu₃ was added and the reaction stirred another 5 h. The reaction mixture was concentrated, then purified by PTLC (5 : 1

petroleum ether/diethyl ether). Two fractions were isolated. The proton NMR of the first fraction indicated that it contained one isomer of **12a,b**. The second fraction contained the other isomer of **12a,b** and **13**.

Attempt to observe reversible cyclization of 3a using AIBN as the initiator:

In a 25 mL side-arm flask which contained a stir bar and was kept under a flow of N₂, 0.014 g (0.025 mmol) of **3a** was dissolved in 1.5 mL of benzene, then 0.008 mL (0.029 mmol) of HSnBu₃ and 0.001 g (0.008 mmol) of AIBN were added. The reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated, then purified on an analytical TLC plate (petroleum ether). Three fractions were isolated and a proton NMR spectrum was taken of each. The first fraction contained **3a**. The second and third fractions were not cobalt complexes, but according to the proton NMR spectra they were both cyclic. A 12 ev DIP mass spectrum was obtained for each, and from these spectra, it was determined that the compound in the second fraction was **14** and the compound in the third fraction was **15**. The yield of **14** was 0.001g (0.003 mmol, 18%) The yield of **15** was 0.001 g (0.003 mmol, 16%).

Data for 14:

Physical state: colorless oil.

¹H NMR (mixture) (300 MHz, CDCl₃) δ 7.35-7.17 (m, 10H, Ph), 6.43 (two overlapping d, 2H, CHCHCHPh), 6.04 (dd, J = 15.6, 8.7 Hz, 1H, CHCHCHPh), 5.47

(dd, $J = 11.4, 10.2$ Hz, 1H, CHCHCHPh), 4.38-4.31 (m, 1H, CHCHBrCH_3), 4.19-4.10 (m, 1H, CHCHBrCH_3), 2.94-2.84 (m, 1H, CHCHBrCH_3), 2.54-2.47 (m, 1H, CHCHBrCH_3), 2.10-1.40 (m, 20H, CHCHCHPh , $\text{CH}_2\text{CH}_2\text{CH}_2$, and CH_3).

EIMS (12 eV) m/z : $[\text{M} + 2]^+$ 280 (30.8), M^+ 278 (32.1).

Data for 15:

Physical state: colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.38-7.35 (m, 2H, Ph), 7.24-7.20 (m, 3H, Ph), 4.56-4.85 (m, 1H, CHCHBrCH_3), 2.71-2.68 (m, 1H, CHCHBrCH_3), 2.13-1.96 (m, 2H, $\text{CH}(\text{CCPh})$, and CH_2), 1.76 (d, $J = 6.9$ Hz, 3H, CH_3), 1.86-1.58 (m, 5H, CH_2).

EIMS (12 eV) m/z : $[\text{M} + 2]^+$ 278 (99.5), M^+ 276 (100).

Attempt to observe reversible cyclization of 3a using AMVN as the initiator:

In a 25 mL side-arm flask which contained a stir bar and was kept under a flow of N_2 , 0.011 g (0.020 mmol) of **3a** was dissolved in 1.5 mL of benzene, then 0.007 mL (0.026 mmol) of HSnBu_3 and 0.002 g (0.007 mmol) of AMVN were added. The reaction mixture was heated at 35 °C and stirred 12h. The reaction mixture was concentrated, then purified by PTLC (petroleum ether). Three fractions were isolated and

a proton NMR spectrum was taken of each. The first fraction contained **3a**. The compound in the second fraction was **14**, and the compound in the third fraction was **15**.

Attempted allylation of 16a,b by photochemical initiation using allyltri-*n*-butylstannane:

The bromide **16a,b** (prepared from 0.100 g, 0.179 mmol of alcohol (**33a**, Chapter III)) was isolated in a 500 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N₂. It was dissolved in 10 mL of benzene, then 0.56 mL (1.8 mmol) of allyltri-*n*-butylstannane was added. The reaction mixture was irradiated under a 300 W halogen floodlight for 1 h, then it was concentrated and filtered through a pipet column of silica gel in order to remove the excess HSnBu₃. The filtrate was concentrated, then purified by PTLC (5% diethyl ether in petroleum ether). Two fractions were isolated, but they contained mixtures of products. No structures could be determined.

Attempted allylation of 23a,b and 12 a,b by photochemical initiation using allyltri-*n*-butylstannane and Bu₃SnSnBu₃:

In a 25 mL side-arm flask which contained a stir bar and was kept under a flow of N₂, 0.064 g (0.102 mmol) of **23a,b** was dissolved in 5 mL of benzene, then 0.077 mL (0.248 mmol) of allyltri-*n*-butylstannane and 0.01 mL (0.02 mmol) of Bu₃SnSnBu₃ were added. The reaction mixture was irradiated for 3 h under a 300 W halogen floodlight; however, TLC analysis (1 : 1 petroleum ether/diethyl ether) revealed that no reaction had taken place. The reaction mixture was concentrated and filtered through a pipet column of

silica gel (petroleum ether), then concentrated. The proton NMR spectrum confirmed that only **23a,b** was present in the crude residue.

Attempted allylation of 23a,b by photochemical initiation using allyltri-*n*-butylstannane and Vitamin B_{12a}:

In a 25 mL side-arm flask which contained a stir bar and was kept under a flow of N₂, 0.150 g (0.240 mmol) of **23a,b** was dissolved in 10 mL of DMF, then 0.016 mL (0.012 mmol) of Vitamin B_{12a}, and 0.15 mL (0.48 mmol) allyltri-*n*-butylstannane were added. The flask was wrapped in foil and N₂ was bubbled through the solution for 15 minutes. Afterwards, the foil was removed, then 0.39 g (5.9 mmol) of activated zinc was added. The reaction was irradiated under a 300 W halogen floodlamp. After 5 minutes, the color began to change from red to orange. A TLC was taken after 15 minutes (petroleum ether/alumina). Compound **23a,b** had been consumed, but there were no cobalt complexes present in the reaction mixture. The reaction stirred another hour, then was worked up by pouring the reaction mixture into 10 mL of water and extracting with 5 x 10 mL portions of pentane. The pentane extracts were combined and washed with 2 x 20 mL of water, dried over MgSO₄, filtered through celite, then concentrated to a dark-orange oil. Purification was done by PTLC (10% diethyl ether in petroleum ether). Four fractions were isolated, none were cobalt complexes and none could be identified.

Attempted allylation of 10 by using (py)Co(DMgH)₂allyl:

The bromide **10** (prepared from 0.116g, 0.214 mmol of alcohol (**12**, Chapter III)) was isolated in a 500 mL side-arm roundbottom flask which contained a stir bar and

was kept under a flow of N_2 . It was dissolved in 10 mL of benzene, then 0.085 g (0.207 mmol) of $(py)Co(DMgH)_2allyl$ was added. The reaction was stirred while being irradiated for 15 minutes under a 300 W halogen floodlight, but it appeared as if **10** had been demetallated. No purification was attempted.

Attempted allylation of 10 by using $Fe(allyl)(CO)_2Cp$:

The bromide **10** (prepared from 0.411 g, 0.757 mmol of alcohol (**12**, Chapter III)) was isolated in a 500 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N_2 . It was dissolved in 10 mL of benzene, then a solution of 0.787 g (3.75 mmol) of $Fe(allyl)(CO)_2Cp$ in 10 mL of benzene was added via cannula (after addition the flask was rinsed with 10 mL of benzene, which was added to the reaction flask *via* cannula). The reaction stirred for 3 h without being irradiated. When **10** had been consumed, the reaction was filtered through silica gel, then concentrated. Purification was performed using flash chromatography (5 : 1 petroleum ether/diethyl ether/silica gel). Six fractions were isolated and a proton NMR spectrum was taken of each. The first fraction contained **17a,b**; however the structures for the compounds in the other fractions could not be determined. The yield of **17a,b** was 0.100 g (0.177 mmol, 23%).

Data for 17a,b:

Physical state: red oil.

¹H NMR (500 MHz, CDCl₃) δ 7.47-7.43 (m, 4H, Ph), 7.34-7.26 (m, 6H, Ph), 5.62 (ddt, J = 17.0, 9.9, 8.0 Hz, 2H, CH₂CHCH^cH'), 5.02-4.91 (m, 4H, CH₂CHCH^cH'), 3.65 (s, 3H, CO₂CH₃), 3.58 (s, 3H, CO₂CH₃), 3.46 (q, J = 6.7 Hz, 1H, CHCH₂(CCPh)), 3.36 (q, J = 6.5 Hz, 1H, CHCH₂(CCPh)), 2.80-2.76 (m, 1H, CHCHCO₂CH₃), 3.28-2.59 (m, 1H, CHCHCH₂(CCPh)), 2.50-2.42 (m, 2H, CH₂), 2.33-2.06 (m, 6H, CH₂), 1.92-1.82 (m, 4H, CH₂), 1.80-1.56 (m, 6H, CH₂).

¹³C NMR (125 MHz, CDCl₃) δ 199.7, 175.0, 174.2, 138.4, 135.6, 135.4, 129.2, 129.1, 128.8, 128.7, 127.5, 116.6, 116.5, 104.9, 104.7, 93.4, 93.2, 51.2, 50.6, 50.1, 47.3, 47.2, 46.3, 46.0, 36.5, 36.1, 31.7, 28.4, 28.1, 24.8.

IR (CH₂Cl₂) 3078 (w), 2999 (w), 2952 (w), 2871 (m), 2087 (s), 2047 (s), 2024 (s), 1730 (m), 1641 (w), 1605 (w) cm⁻¹.

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z: 512 [M - 2(CO)]⁺, 484 [M - 3(CO)]⁺, 456 [M - 4(CO)]⁺, 428 [M - 5(CO)]⁺, 400 [M - 6(CO)]⁺.

Attempted Pauson-Khand reaction of 17a,b employing NMO:

In a 100 mL side-arm roundbottom flask which contained a stir bar and was kept under a flow of N₂, 0.042 g (0.075 mmol) of **17a,b** was dissolved in 10 mL of CH₂Cl₂, then 0.053 g (0.045 mmol) of NMO was added and the reaction was stirred at room temperature. After two hours, TLC indicated a reaction had occurred, but **17a,b** was still present in the reaction mixture. The reaction mixture was filtered through silica gel,

then concentrated and purified by PTLC (5 : 1 petroleum ether/diethyl ether). Four fractions were isolated. A proton NMR spectrum was taken of each fraction. The compound in the first fraction was **17a,b**. The second fraction contained **27a,b**. This was confirmed by FAB mass spectrometry. The compounds in the third and fourth bands could not be identified. The yield of **27 a,b** was 0.007 g (0.026 mmol, 36%)

Data for 27a,b:

Physical state: yellow oil.

¹H NMR (partial) (300 MHz, CDCl₃) δ 7.37-7.35 (m, 2H, Ph), 7.30-7.23 (m, 3H, Ph), 5.83-5.68 (m, 2H, CHCHCH₂), 5.05 (d, J = 17.4 Hz, 2H, CHCHCH^cCH'), 4.98 (d, J = 9.9 Hz, 2H, , CHCHCH^cCH'), 3.64 (s, 3H, CO₂CH₃), 3.60 (s, 3H, CO₂CH₃).

MS (FAB, matrix: 3-nitrobenzylalcohol) m/z: 283 [M + H]⁺, 223 [M - CO₂CH₃]⁺

Attempted Pauson-Khand reaction employing silica gel/O₂:

In a 100 mL side-arm roundbottom flask, compound **17a,b** (0.067 g, 0.118 mmol) was adsorbed onto 4 g of silica gel. The flask was connected to a rotary evaporator through which O₂ flowed, and was heated to 45 °C for 2 h. The silica gel changed color from pink to blue. The silica gel was washed with diethyl ether, then the solution was concentrated to a yellow oil. Purification was performed using PTLC (5 : 1 petroleum ether : diethyl ether). One fraction was isolated. The proton NMR spectrum indicated that it was **27a,b**. The yield of **27a,b** was 0.019 g (0.068 mmol, 57%).

Attempted Pauson-Khand reaction employing NH_4OH :

In a 100 mL side-arm roundbottom flask that contained a stir bar, 0.122 g (0.215 mmol) of **17a,b** was dissolved in 5 mL of 1,4-dioxane, then 2 mL of NH_4OH (2M) was added. A water-cooled condenser was attached to the flask, then the reaction mixture was heated to 100 °C for an hour. The reaction mixture turned black, and most of the solvent and water had evaporated. The contents in the flask was diluted with diethyl ether and transferred to a separatory funnel, then the solution was washed with 2 x 10 mL of water, 2 x 10 mL of 1N HCL, and 1 x 10 mL of saturated NaHCO_3 . The solution was then dried over MgSO_4 and filtered through celite. Purification was carried out by PTLC (5 : 1 petroleum ether/diethyl ether). One fraction was isolated. The proton NMR spectrum showed that the fraction contained a mixture of products. None of the structures could be determined.

Figure 4.2: 500 MHz ¹H NMR spectrum of 17a,b in CDCl₃

Figure 4.1: 400 MHz ^1H NMR spectrum of **11a,b** in CDCl_3

V. BIBLIOGRAPHY

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IMAGE EVALUATION TEST TARGET (QA-3)

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