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Regiochemical studies for nucleophilic addition on allylic acetate cycloheptyne cobalt complexes and the progression towards the synthesis of 7,5-bicyclic ring systems containing the cobalt complex.

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Regiochemical Studies for Nucleophilic Addition on Allylic Acetate Cycloheptyne Cobalt Complexes and the Progression Towards the Synthesis of 7,5–Bicyclic Ring Systems Containing the Cobalt Complex

by
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Abstract

There are several naturally occurring compounds that have fused 7,5–bicyclic ring systems. This thesis will focus on approaches to synthesizing 7,5–bicyclic systems containing a dicobalt hexacarbonyl complex. In this context, the allylic acetate cycloheptenyne complex (**66**) was reacted with various carbon– and hetero–based nucleophiles to determine the regiochemistry of the substitution. The γ to α ratio for carbon–based nucleophiles were approximately 4:1, while hetero–based nucleophiles were 100% γ. Once the ratios were established, several of these product compounds, which contained an electrophilic site, were investigated for further reaction to form the additional ring (**Scheme 28**). Formation of a 7,5–bicyclic ketone **131**, alcohol **132** and diol **133** were observed when compound **129** was mixed with boron trifluoride (**Scheme 42**).

Dedication

This thesis is dedicated to my parents.

Acknowledgements

I would like to thank my supervisor, Dr. Jim Green, for accepting me as his graduate student. Furthermore, his guidance, encouragement and patience have been greatly appreciated. I would also like to thank Dr. Eichhorn and Dr. Zielinski for being on my committee.

Special thanks go to the Green group: Ahmed Mohamed, Yu Ding and Giancarlo Pizzuti. Their constant support and friendly attitude made it fun to be in the lab. I would also like to thank Bobby Ellis and Tracy Murray for proofreading my thesis and for their support. Thanks to Mike Fuerth, Sharon Horne, Linda Bunn and the rest of the staff at the University of Windsor.

Lastly, I would like to thank my parents for all their support and I will always be indebted to them for all the sacrifices they made for me. Also, to all my homeboys in the Peg, one love.

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Abbreviations

Ac	acetyl, $-C(O)CH_3$
α	alpha, one atom away from reference atom
β	beta, two atoms away from reference atom
Bn	benzyl, $-CH_2C_6H_5$
^{n}Bu	butyl, $-(CH_2)_3CH_3$
^{t}Bu	tertiary butyl, $-C(CH_3)_3$
CAN	ceric ammonium nitrate
δ	chemical shift in ppm
Cy	cyclohexyl, $-C_6H_{11}$
Cp	cyclopentadienyl, $-C_5H_5$
DIBALH	diisobutylaluminum hydride, $[(CH_3)_2CHCH_2]_2AlH$
DCHC	dicobalt hexacarbonyl–alkyne complex
d	doublet
dd	doublet of doublets
E	electrophile
equiv.	equivalents
Et	ethyl, $-CH_2CH_3$
γ	gamma, three atoms away from reference atom
GC	gas chromatography
η	hapto
IR	infrared
Ln	n ligands
MS	mass spectroscopy

Mes	mesityl, 2,4,6–trimethylphenyl, 2,4,6–$(CH_3)_3C_6H_2$
Ms	mesylate, $–OSO_2CH_3$
Met	metal
Me	methyl, $–CH_3$
μ	mu
mol	mole
m	multiplet
MMX	molecular mechanics X, an extension of MM2 and MMP1 force fields
NMO	N–methylmorpholine oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidation
ppm	parts per million
PKR	Pauson Khand reaction
^{i}Pr	isopropyl, $–CH(CH_3)_2$
Ph	Phenyl, $–C_6H_5$
Pr	propyl, $–(CH_2)_2CH_3$
R	alkyl or aryl group
RCM	ring closing metathesis
RT	room temperature
s	singlet
TLC	thin layer chromatography
OTf	triflate, $–OSO_2CF_3$
TES	triethylsilyl, $–Si(CH_2CH_3)_3$
TIPS	triisopropylsilyl, $–Si(CH(CH_3)_2)_3$

TMS	trimethylsilyl, $-Si(CH_3)_3$
t	triplet

1.0 Introduction

1.1 Transition Metal–Alkyne Complexes

In 1948, Reppe and co–workers was first to report the reaction of transition metal alkynes, where the alkyne was oligomerized by a nickel catalyst.[1] Transition metals can coordinate with alkyne functional groups in several ways as depicted in **Figure 1**. The mononuclear **1**, dinuclear **2** and trinuclear **3** complexes have several very important differences from the uncomplexed alkyne. Without the coordination to transition metals, alkynes have a linear geometry, whereas when alkynes are coordinated, angles of 118.5° to 177° have been observed.[2] The carbon–carbon bond length increases as the bond order is reduced through electron donation to the metal centre and electron back donation from the metal to the alkyne.[1] Both changes in geometry are a result of an increased p contribution to hybridization relative to the initial sp hybridization of the carbon atoms. Transition metals that have been complexed to the alkyne include both early and late metals: Zr,[3] Mo,[4] Re,[5] Ru,[6] Co,[7] Ni,[8] Pt.[9] Throughout this thesis cobalt will be the transition metal of primary focus.

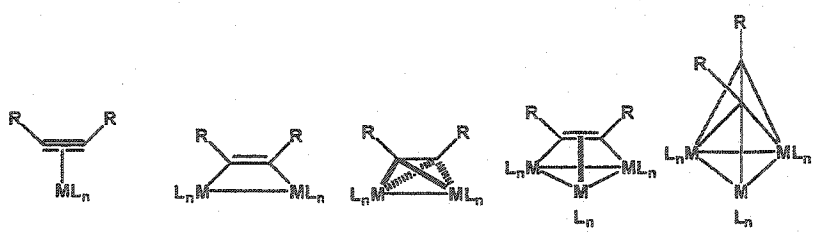


Figure 1: Coordination of the Alkyne Functional Group to the Transition Metal

1.2 The Nicholas Reaction

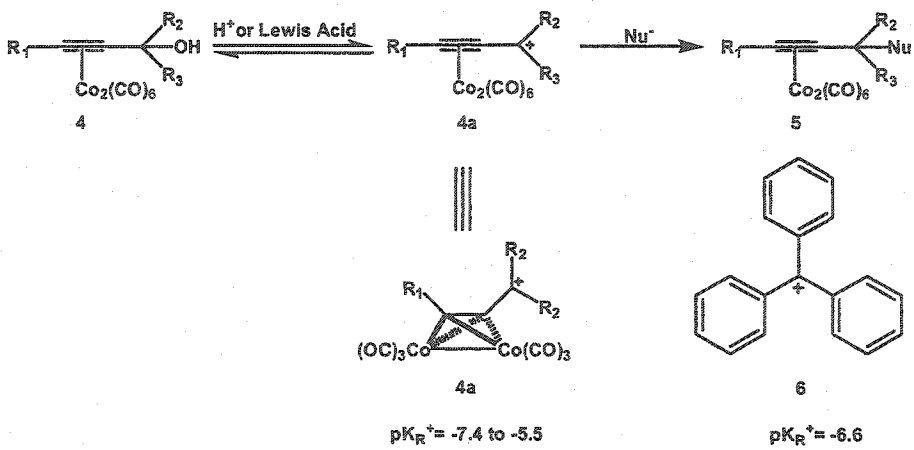
Dicobalt hexacarbonyl is coordinated by the alkyne in a dinuclear fashion as shown in **Figure 1 (2b)**; the C–C≡C angle is then decreased from 180° to 140°. In 1972, Nicholas reported the enhanced stability of the propargyl carbocation as

a dicobalt hexacarbonyl–alkyne complex or DCHC.[10] Propargyl dicobalt carbocations (**4a**) were produced by the addition of an acid to the propargyl alcohol complex. The stability of these cations has been judged by their pK_R^+, which is defined as the equilibrium constant between cation/water and alcohol/acid (**Figure 2**). As the pK_R^+ value increases, so does the stability of the cation.

$$R^+ + 2H_2O \rightleftharpoons R\text{-}OH + H_3O^+$$

$$K_R^+ = \frac{[R\text{-}OH]\,[H_3O^+]}{[R^+]}$$

Figure 2: The Cation Hydrolysis Equilibrium Constant Expression



Scheme 1

The reported propargyl dicobalt cation pK_R^+ values range from -7.4 to -5.5, which depend on the electronics and the sterics of $R_{1,2,3}$, as well as the method of measurement. The pK_R^+ value for trityl cation (**6**) is -6.6 (**Scheme 1**).[11,12] Therefore, the DCHC 2° propargyl cation is exceptionally stable and has approximately the same stability as a 3° trityl carbocation molecule. This increased stability, relative to the propargyl cation itself, is related to the interaction between the cobalt atoms and the carbocation. The complex allows for delocalization of the positive charge onto the cobalt atoms and their carbonyl ligands.[13,14] **Figure 3** reflects the possible structures of the propargyl cation delocalized onto the cobalt atoms.[15]

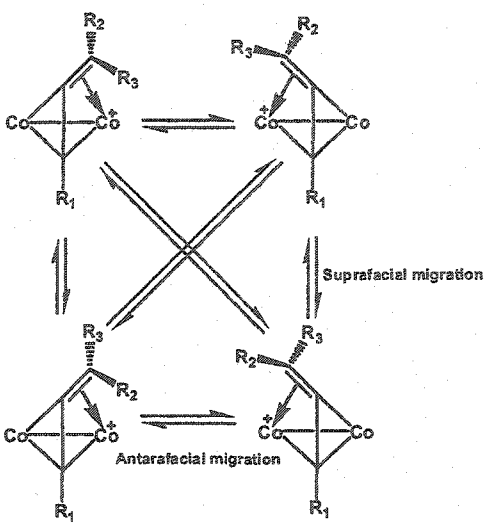
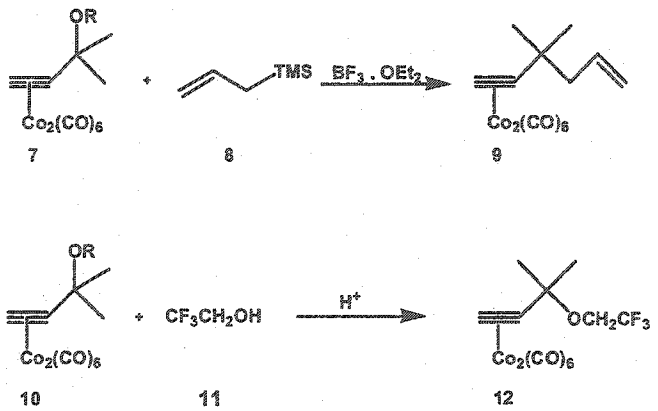


Figure 3: Suprafacial and Antarafacial Migrations of the DCHC Cation (the CO ligands have been removed for clarity)

In 1987 Schreiber and co–workers outlined the possible structures of the propargyl DCHC cation (**Figure 3**).[15] The cation bends towards one $Co(CO)_3$ unit and this structure has several possible isomers, interconverting through two types of migrations: suprafacial and antarafacial.[15] Schreiber's suggested structural features have been subsequently supported by an X–Ray crystal structure and computational studies on the cation.[16,17]

The first known reaction of **4a** was carried out by Nicholas in 1972 (**Scheme 1**); since these initial studies, many heteroatom and carbon nucleophiles have been added to the cationic complex and in all cases the nucleophiles reacted at the propargyl site.[18-20] When added with a Lewis or protic acid, a carbon–based nucleophile such as an allylsilane (allyltrimethylsilane in this particular case) attacked at the propargyl cationic site (**Scheme 2**) to give a 1,5–enyne complex. Oxygen–based nucleophiles, such as trifluoroethanol, also attacked at the propargyl site and produced propargylic ethers (in this case a trifluroethyl ether, **12**). Other appropriate nucleophiles included electron rich aromatics, β–keto esters, silyl enol ethers, enol acetates, enol borinates and amines.



Scheme 2

This contrasts with the reactivity of metal–free propargyl systems. Without the presence of the cobalt, propargyl carbocations (**13a**) often reacted via the allenic resonance form (**13b**), as depicted in **Figure 4**. However, in the presence of the DCHC, no allenic products have ever been found to have formed.

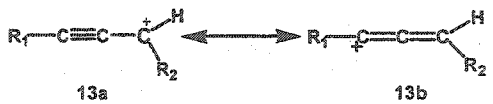


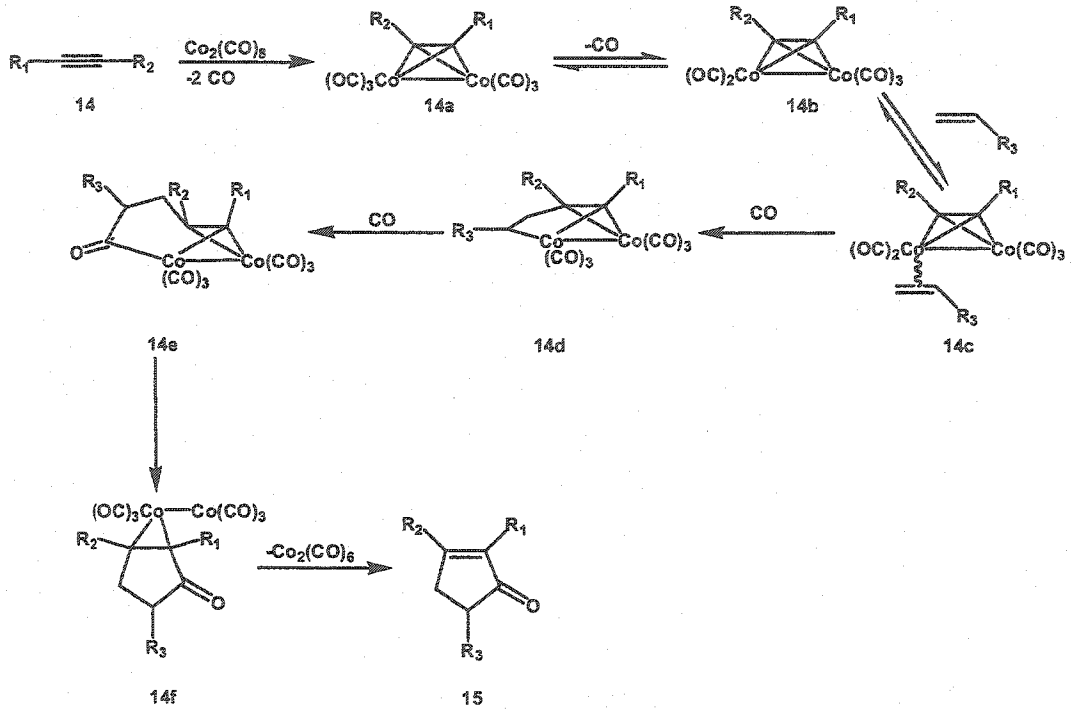
Figure 4: Resonance Structure of the Propargyl Cation

1.3 Pauson Khand Reaction

1.3.1 Intermolecular PKR

The most well known cyclization reaction of the cobalt alkyne complex is the Pauson Khand reaction (PKR), which is a [2+2+1] cycloaddition reaction. A typical PKR consists of three components: an alkyne, a dicobalt octacarbonyl and an alkene molecule (**Scheme 3**).[21] The PKR can also be carried out with an alkene and a DCHC. The generally accepted mechanism (**Scheme 3**) shows the interaction of the alkyne and alkene π bonds, and a CO from the dicobalt octacarbonyl. Normally, the dicobalt octacarbonyl is added to the alkyne to form the complex (**14a**). The alkene is then added to the solution, and complexes to one of the cobalt atoms. This is followed by an oxidative coupling of the alkene

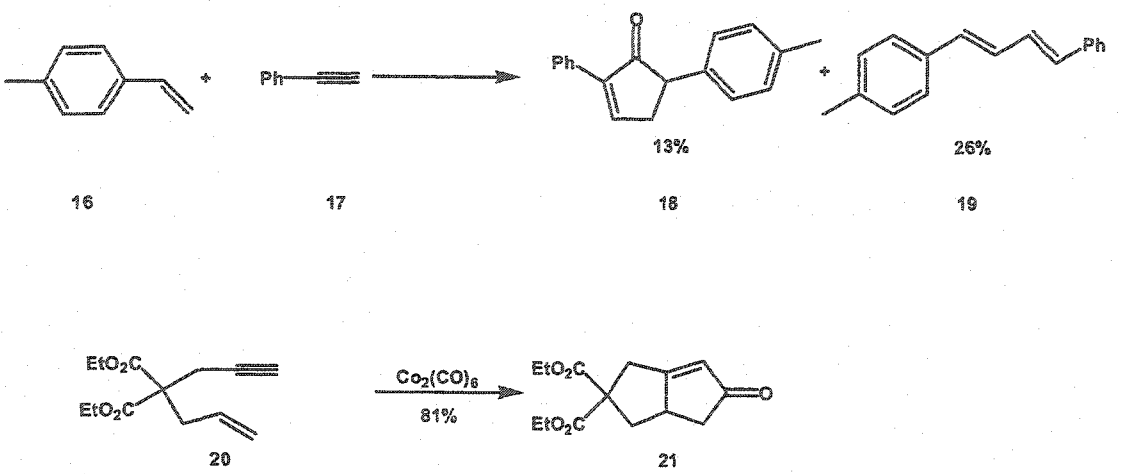
and alkyne, where one cobalt becomes Co^{II}. CO insertion then occurs (**14d–14e**), to form a Co-C sigma bond. Reductive elimination to give Co^0 and the cyclopentenone **15** follows.[21] This mechanism has only been speculated, and has not yet been fully proven.



Scheme 3

Both intermolecular and intramolecular PKR's have been observed.[22,23] For the intermolecular cases, the Pauson Khand reaction is restricted by the alkene. First of all, the metallacycles resulting from acyclic alkenes are susceptible to β–hydride elimination. Electronically, the alkene becomes more electron deficient when it is bonded to a strong electron–withdrawing group, and in such cases competing reactions occur. Furthermore, as the number of substituents on the alkene increases, it becomes more difficult for the cobalt–carbon insertion to occur since there is more steric hindrance. **Scheme 4** depicts a PKR, where the alkene has a bulky electron–withdrawing side group; the yield was very low. These restrictions do not contribute as much in the intramolecular

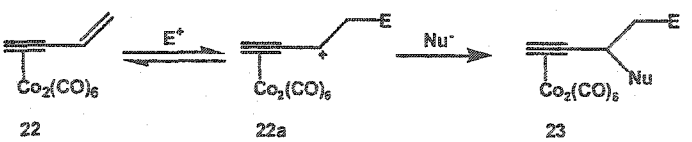
PKR since the alkene and alkyne are in the same molecule; as a result, intramolecular Pauson–Khand reactions are far more widely successful.



Scheme 4

1.3.2 Electrophilic Attack on Enyne Complexes

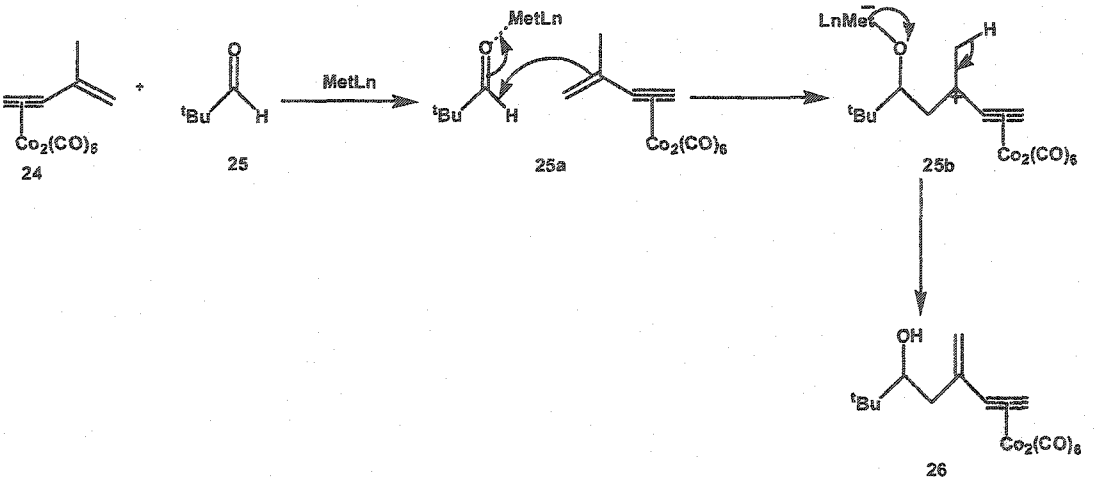
Smit and Caple generated a propargyl carbocation DCHC by an addition reaction of a double bond α to the alkyne (**Scheme 5**).[24,25] These 1,3–enynes complexes have been found to be quite electron rich, such that a wide range of electrophiles were capable of reacting with the enyne; including arylsulfenium, nitronium, acylium and carbenium ions.[24-26] The DCHC cation generated may then be trapped by a number of nucleophiles, including alcohols and enol silanes, to give 'Nicholas–type' addition products.



Scheme 5

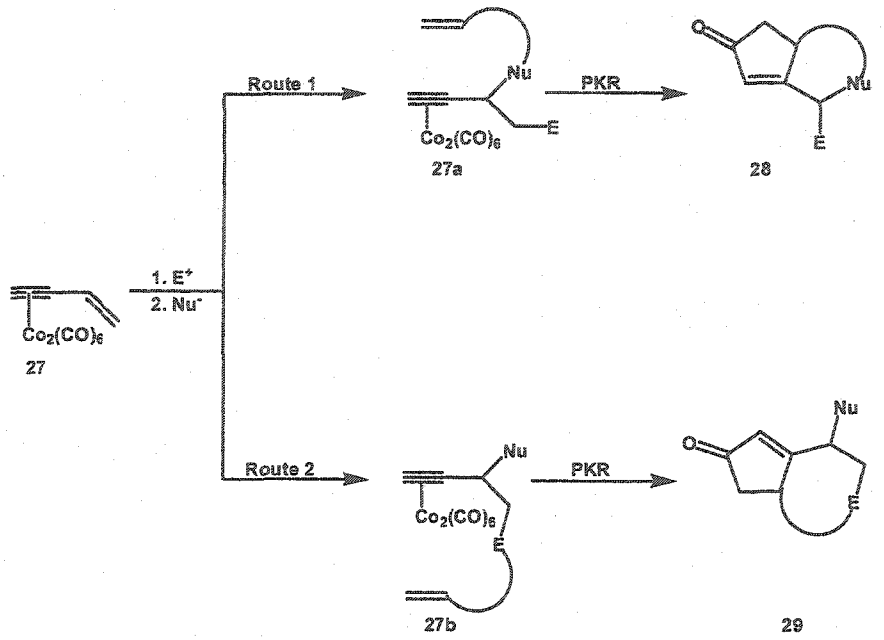
Suzuki and co–workers focused on carbonyl–ene reactions of these enyne complexes, which are important carbon–carbon bond formation processes.[27]

When an aldehyde (**25**) was mixed with compound **24** and a Lewis acid (**Scheme 6**), the oxygen coordinated the Lewis acid and the alkene attacked the carbonyl to give a positive charge at the propargyl site of the dicobalt complex (**25b**); subsequent elimination of the H^+ gave a new enyne–DCHC.[27] This reaction would not have occurred if the cobalt complex was not present, as the alkene would either have needed an electron donating group to facilitate the reaction or the aldehyde would have needed an activating group.



Scheme 6

Smit and Caple have also incorporated their enyne complex electrophilic addition process with an intramolecular Pauson–Khand cycloaddition reaction for bicyclic ring syntheses.[28] Two routes for the cycloaddition have been developed based on the position of the alkene (**Scheme 7**), which may be bonded to either the site of the electrophile (**27b**) or the nucleophile (**27a**).[26] The presence of the alkyne cobalt complex allowed both for the cyclization of the five membered ring, and stabilization of the cationic charge when the electrophile was attacked by the alkene of the complex; furthermore, it prevented the attack of the alkyne by the electrophile.[26]

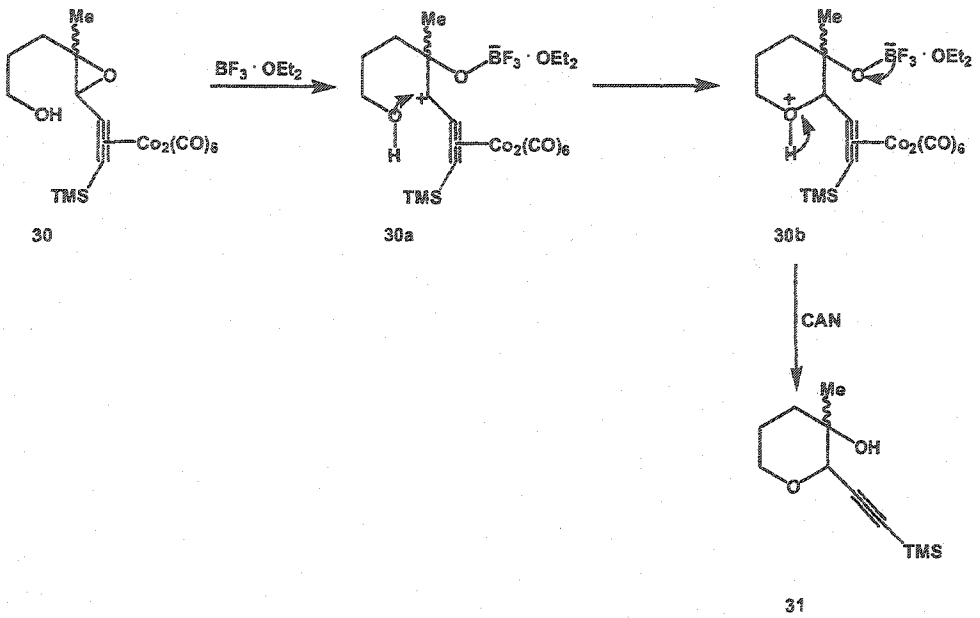


Scheme 7

1.4 Ring Formation with the Nicholas Reaction

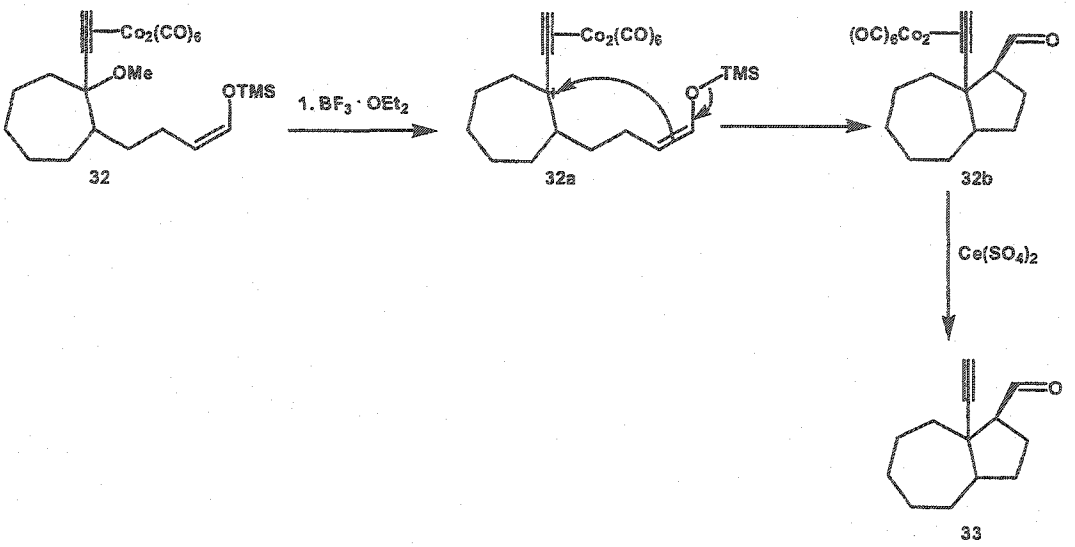
1.4.1 Ring Systems that Utilize the Stability of the Propargyl DCHC

Alkyne DCHC's allows for new methodologies to form (poly)cyclic compounds. In 1994, Mukai and co–workers synthesized 5– to 7–membered oxacyclic species containing an exocyclic dicobalt complex (**Scheme 8**).[29-31] In this case, boron trifluoride etherate was added to compound **30**, and induced ring–opening of the epoxide to form a cation at the propargyl site (**30a**). The alcohol then attacked the cation and an oxacyclic ring was produced (**31**). The transition metal fragment was then decomplexed with CAN.[25] Mukai's approach allowed for the synthesis of tetrahydropyran (the indicated case), tetrahydrofuran and oxepane systems.[30]



Scheme 8

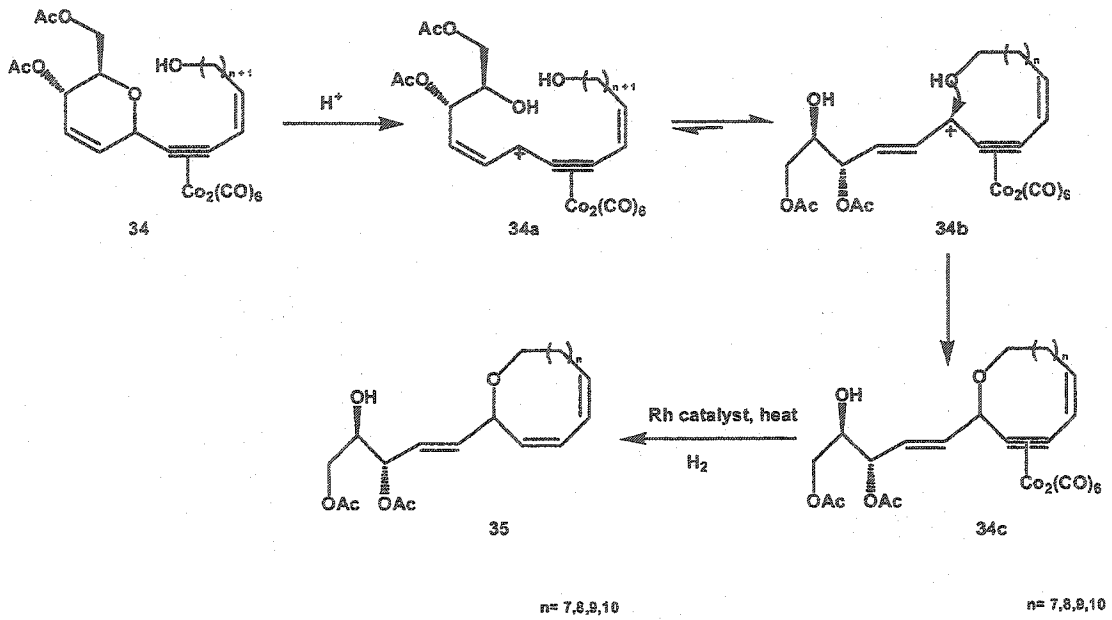
In 1993, Tyrrell and co–workers carried out numerous ring forming reactions that included an alkyne–DCHC (**Scheme 9**).[32] Tyrrell incorporated the stability of the propargyl cation species in the synthesis of medium sized polycyclic systems.[33] For example, the treatment of a propargyl ether (**32**) with boron trifluoride diethyl etherate formed the cation (**32a**), which was attacked by the alkene of enol silane to form the new ring (**32b**).[32] Decomplexation of the transition metal fragment gave the all–organic 7,5–bicyclic species.



Scheme 9

1.4.2 Ring Systems that Contain the DCHC

Isobe's group has been developing various methods to form sugars by using cobalt alkyne complexes. In 1994, Isobe reported the synthesis of 7–, 8–, 9– and 10–membered cyclic ether complexes (**Scheme 10**).[34] In this work an acid was added to compound **34**, which was then attacked by the oxygen on the six membered ring, which cleaved the ring. This formed a cationic species (**34a**) at the propargyl site of the DCHC. As mentioned earlier, this cation is extremely stable and the oxygen on the side chain of the complex then attacked the cation, which formed a ring (**34c**) that ranged from 7–10 atoms in size. After the macrocyclic ether ring was synthesized, the DCHC was then decomplexed reductively and an all–organic cyclic diene **35** formed.



Scheme 10

This general method has been incorporated repeatedly into Isobe's later total synthesis efforts, which have focused on the preparation of fragments of the naturally occurring product, ciguatoxin (**Figure 5**).[35] The synthesis of **35** constituted one of several of the fragments of the natural product, the **A** ring being the most evident.

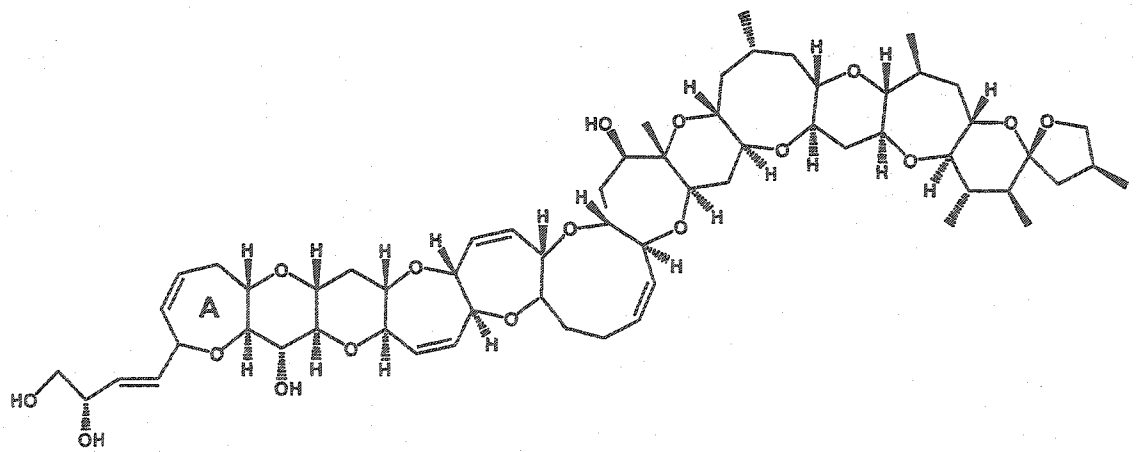
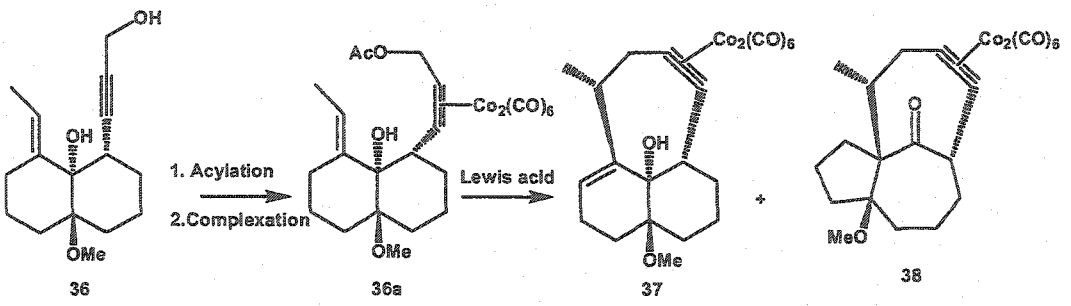


Figure 5: Structure of Ciguatoxin

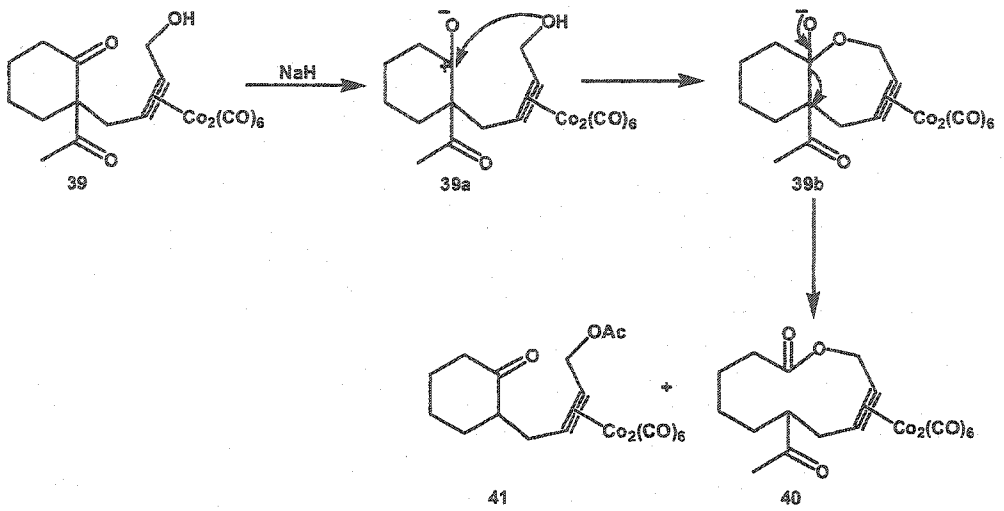
Other natural products had also been synthesized by incorporating the alkyne–DCHC. In 1997, Tanino and Kuwajima reported model studies for the synthesis of ingenol, which contained a 7,5–ring system and an additional bridged 7–membered ring.[36] The preparation of this ring system employed a cyclization that again utilized the stability of the cationic species at the propargyl site (**Scheme 11**). Compound **36** was acylated and complexed with dicobalt octacarbonyl. A Lewis acid was then added to the complex **36a**, which was attacked by the oxygen of the acetate group and formed the stable cationic species. This formed the bridged ring and either the 7,6,6–tricyclic (**37**) or the 7,7,5–tricyclic system (**38**), depending on the Lewis acid used.[36]



36 36a 37 38

Scheme 11

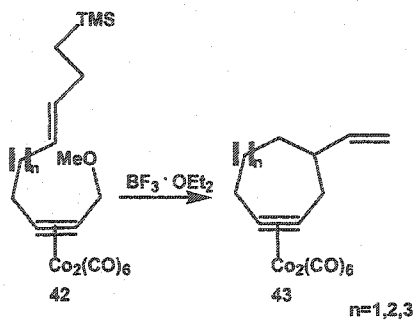
Even larger rings are possible, such as lactones containing an alkyne. Schore and co–workers carried out the synthesis of 11–membered ring lactones containing an alkyne, (**Scheme 12**) by way of a 7–membered ring intermediate.[37] The cobalt complexation allowed for the intermediate to form but the hemiacetal was still somewhat strained and as a result, there was a driving force on compound **39b** for a ring opening of the hemiacetal to the eleven–membered lactone. The smallest previously reported lactone rings, containing an alkyne, was 10– and 12– carbons in size.



Scheme 12

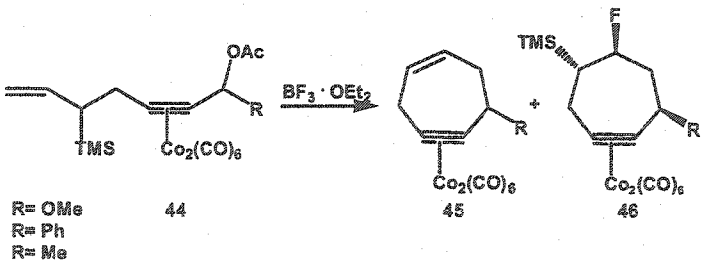
1.4.3 Cycloheptenynes Containing the DCHC

With several methods established for DCHC–containing ring formation, several research groups have carried out the formation of different medium sized rings that would be inaccessible if the alkyne was not complexed. Cycloheptynes fall under this category, as this 7–membered ring would not form under regular conditions due to the strain imposed by the angles at the triple bond. Alkynes, with sp–hybridized carbons would prefer a linear geometry, but with the complexation of the dicobalt hexacarbonyl, this strain is lessened considerably. Instead, the bond angle of 140° and the infrared absorption for the alkyne-$Co_2(CO)_6$ unit (ν_{max}= 1490–1630cm^{-1}) suggest pseudo–sp^2–hybridization.[2] The first example was reported by Schreiber and co–workers in 1986.[38] In it, a propargyl ether–dicobalt hexacarbonyl complex bearing a remote allylsilane reacted with boron trifluoride diethyl etherate to form a 7–membered ring cycloalkyne complex bearing an exocyclic vinyl group. By varying the length of the carbon chain in the complex, 8– and even 6–membered rings were formed analogously (**Scheme 13**).[38] Schreiber attempted to oxidize the cobalt to form the free cycloalkyne but the angle strain was such that the cycloalkyne decomposed.[38]



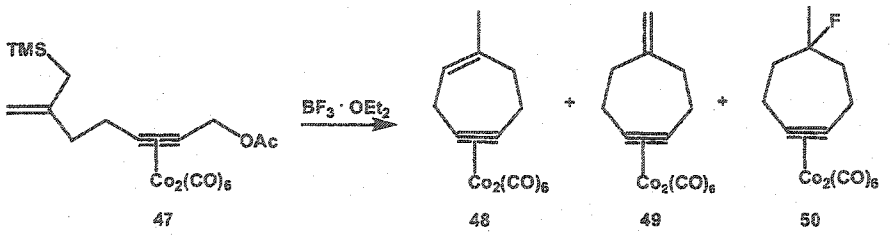
Scheme 13

The Green group has developed several methods for the synthesis of the seven membered ring alkyne–DCHC's. Their initial work covered the formation of the ring by the addition of γ–methoxyalkynoate or –alkynone dicobalt complex and a stannylsilane, with subsequent carbonyl reduction, to form **44**.[39] Boron trifluoride diethyl etherate was added to compound **44** and the Lewis acid was then attacked by the acetate group, to form a cationic propargyl species. The allylsilane then cyclized onto the cation to form two products through an intramolecular Nicholas reaction, the intended homoallylic compound **45** and a small amount of a by–product (**46**) that was a fluorinated cycloheptyne complex (**Scheme 14**).[39]



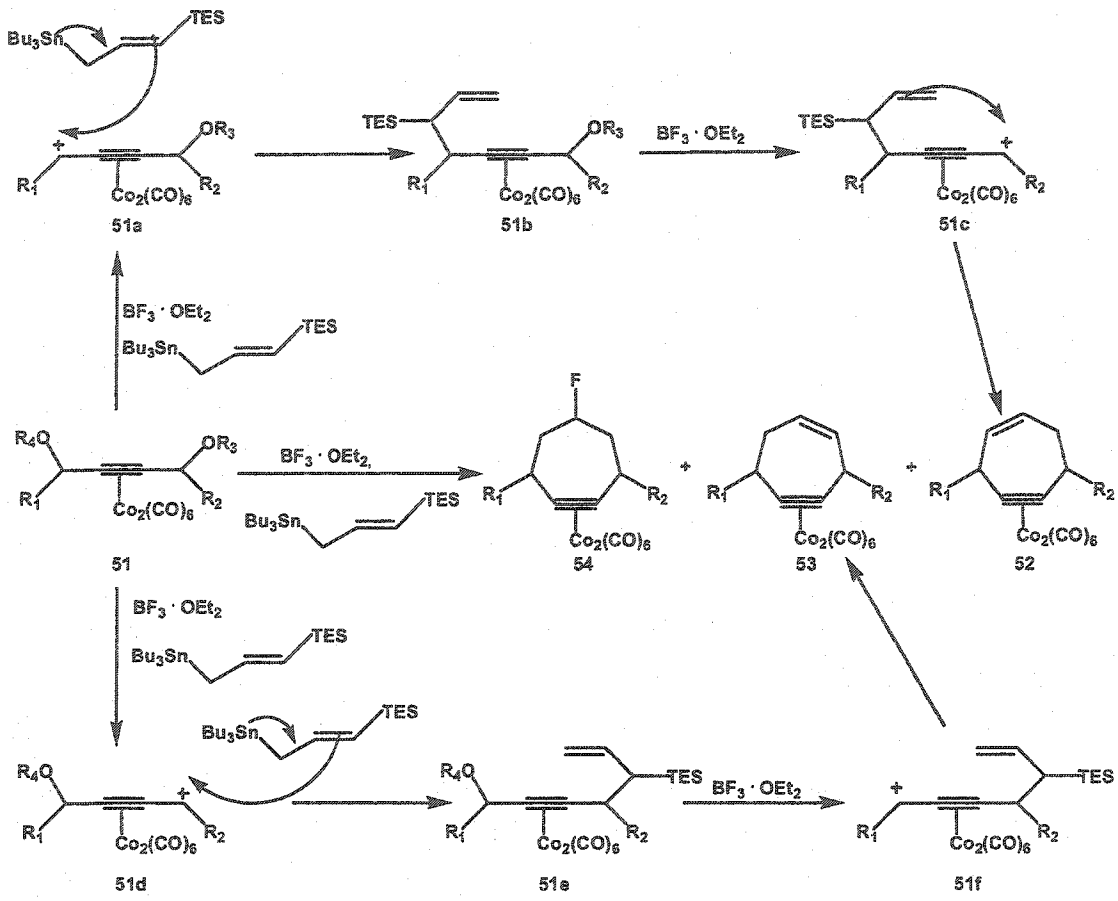
Scheme 14

Another related intramolecular Nicholas cyclization technique also was described. The addition of boron trifluoride diethyl etherate to compound **47** (**Scheme 15**) formed three cyclic materials: the methylenecycloheptyne complex (**48**), its cycloheptenyne isomer (**49**), and fluorocycloheptyne complex (**50**).[39]



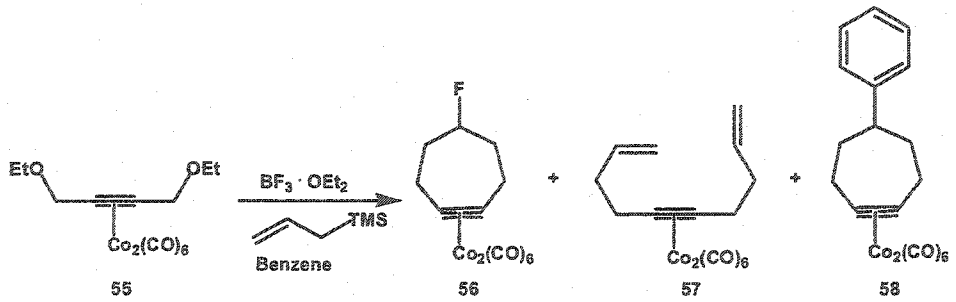
Scheme 15

In 1999, Green and co–workers developed a one–pot method for the formation of the complexed cycloheptyne.[40] The alkynyl diether complex (**51**) was added with a stannylsilane to form the cycloheptyne complexes **52** and **53** and **54**. **Scheme 16** outlines the formation of the three products. The addition of the boron trifluoride diethyl etherate formed the cationic species (**51a** or **51d**), and then the allyltin portion of the nucleophile attacked the cation and bonded at the propargyl site (**51b** or **51e**).[40] The boron trifluoride was then attacked by the other propargyl ether to form a second cationic intermediate (**51c** or **51f**), which was attacked by the allylsilane to form the cycloheptenyne.[40] This is a [4+3] cycloaddition process.



Scheme 16

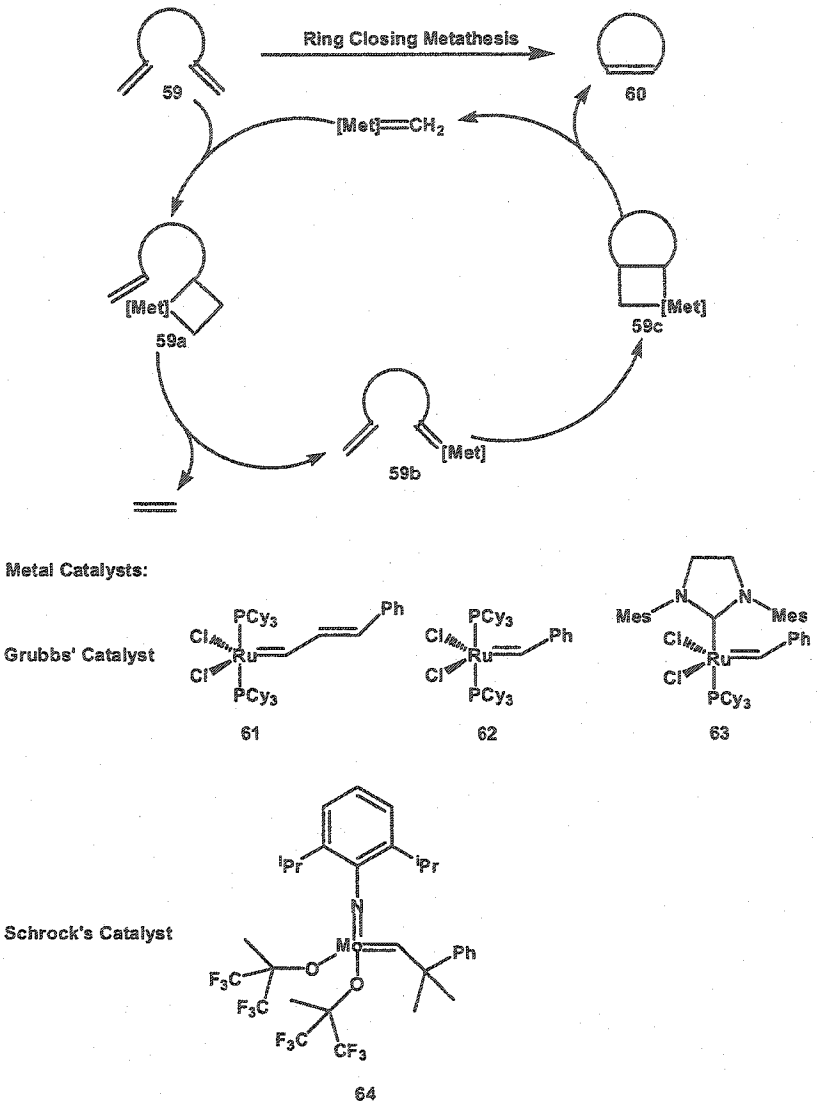
With the stannylsilane nucleophile, the fluorocycloheptyne product was only observed when the Lewis acid was added slowly to compound **51**.[40] Subsequently, it was found that if allyltrimethylsilane and boron trifluoride diethyl etherate were added to compound **55**. The fluorocycloheptyne **56** was formed more reliably, along with a diene DCHC (**57**), and compound **58** if the reaction was conducted in benzene (**Scheme 17**).[41] Though the third product (**58**) was unexpected, it was apparent that it resulted from the benzene solvent that reacted in a Friedel–Crafts fashion with a cycloheptyne complex containing an 2° alkyl cation at C–5.



Scheme 17

1.5 Ring Closing Olefin Metathesis

In addition to the synthesis of cycloheptynedicobalt complexes via [4+3] cycloaddition reactions with allylsilanes or allyldimetals, the Green group has prepared this class of compounds by way of ring closing olefin metathesis (RCM).[42] RCM is relatively new method of carbon–carbon bond formation of great importance, which utilizes a transition metal alkylidene pre–catalyst.[43] **Scheme 18** depicts the mechanism of an RCM, where the alkylidene complex attacked one of the alkenes, to form a metal alkylidene **59b** by a [2+2] cycloaddition/retrograde [2+2] cycloaddition process. This in turn underwent [2+2] cycloaddition with the remaining alkene, giving **59c**, and a further retro [2+2] cycloaddition to give a cycloalkene and the reformed transition metal alkylidene catalyst.[44]

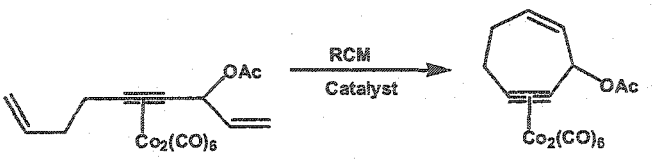


Scheme 18

There are several types of transition metal pre–catalysts that are commonly used to induce RCM reactions. The two most common classes of catalysts contain either ruthenium or molybdenum. Grubbs has done extensive work with ruthenium catalysts and has found that of all the transition metal catalysts used for RCM, the ruthenium catalysts are particularly stable and react readily with the olefinic functional group.[45] Their functional group tolerance is also very good; excellent reactivity occurs with alkenes if alcohols, aldehydes, ketones reside in the substrate, and reactions may be conducted in the presence

of water. This is far superior to metathesis catalysts based on other transition metals, such as titanium, tungsten or molybdenum.[46] Molybdenum catalyst are extremely reactive for metathesis but have poor functional group tolerance, and are very susceptible to the presence of oxygen or moisture.[47,48] There are several variations of the Grubbs' catalyst; compound **61** was the first extensively studied complex but was rapidly supplanted by **62** (first generation). Recently, there has been much interest in compound **63** (second generation); this ruthenium complex contains an *N*–heterocyclic carbene functional group and is extremely active for olefin metathesis.[49]

Green and co–workers attempted to get access to cycloheptenyne–DCHC complexes by RCM reactions with two types of pre–catalysts: Schrock's (**64**) and Grubbs' first generation (**62**).[42] In the experiments, diene complexes (ie. **65**) were treated with each pre–catalyst in order to form the cycloheptenynes (ie. **66**) depicted **Scheme 19**.[42] With the molybdenum pre–catalyst, the ring formation was not observed while with the ruthenium, successful conversion was obtained.[42] Young's group has subsequently reported success using the molybdenum pre–catalyst **64** and closely related propargylic silyl ether complexes.[50]



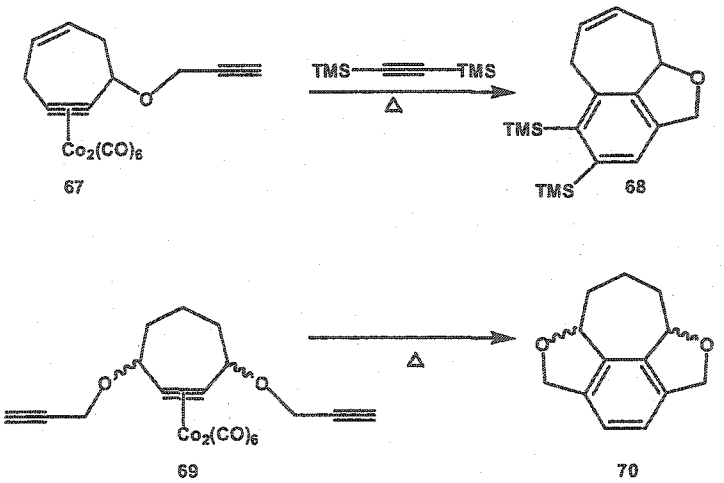
65 66

Catalyst:
$(Cy_3P)_2Cl_2Ru{=}CHPh$ (62)
$Mo(C_{10}H_{12})(C_{12}H_{17}N)[OC(CH_3)(CF_3)_2]_2$ (64)

Scheme 19

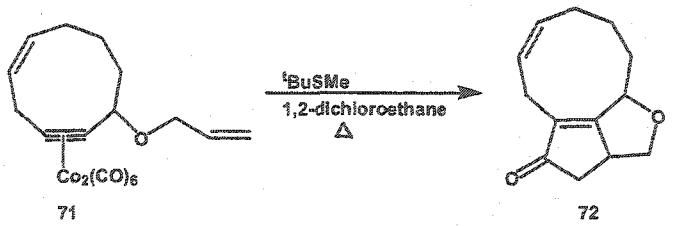
There are numerous natural products that contain 7–membered rings, with the vast majority of these being fused to cyclopentanes or cyclohexanes.[51] With the establishment of the metathesis synthetic route for cycloheptenyne complexes, these compounds could lead to the formation of multiple rings bonded to the 7–membered ring. Such studies of the synthesis of bi–, tri– or tetracyclic ring systems have been performed by the Green group. In 2003, they

reported the synthesis of a tricyclic system by using the propargylic acetate function of **66** to incorporate a propargylic ether system (**67**), and subsequent reaction with a third alkyne, which either was added separately or was present within the same molecule (**69**→ **70**) in a [2+2+2] cycloaddition process (**Scheme 20**).[52] Many examples of alkyne trimerizations [2+2+2] cycloadditions do exist and normally employ this strategy of tethering two alkynes together. Of the many reagents/catalysts known to induce this type of transformation, $CpCoL_2$ (Co^I) is the most common, although infrequent examples of the use of Co^0 complexes are known.[53]



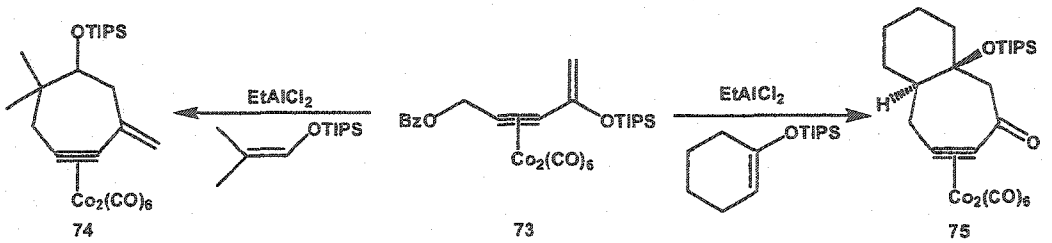
Scheme 20

Pauson Khand reactions have been carried out on medium ring alkyne DCHC complexes. Schreiber and Young have reported intramolecular PKR's on cyclooctyne– and cyclononanyne complexes, respectively, to have formed tricyclic systems. The Pauson–Khand reactions have been often carried out at very elevated temperatures, but the Schreiber version was accomplished at room temperature with NMO. The Young version was conducted under the Sugihara sulfide conditions which are known to give particularly high reaction efficiency under relatively mild conditions (**Scheme 21**).[54,55]



Scheme 21

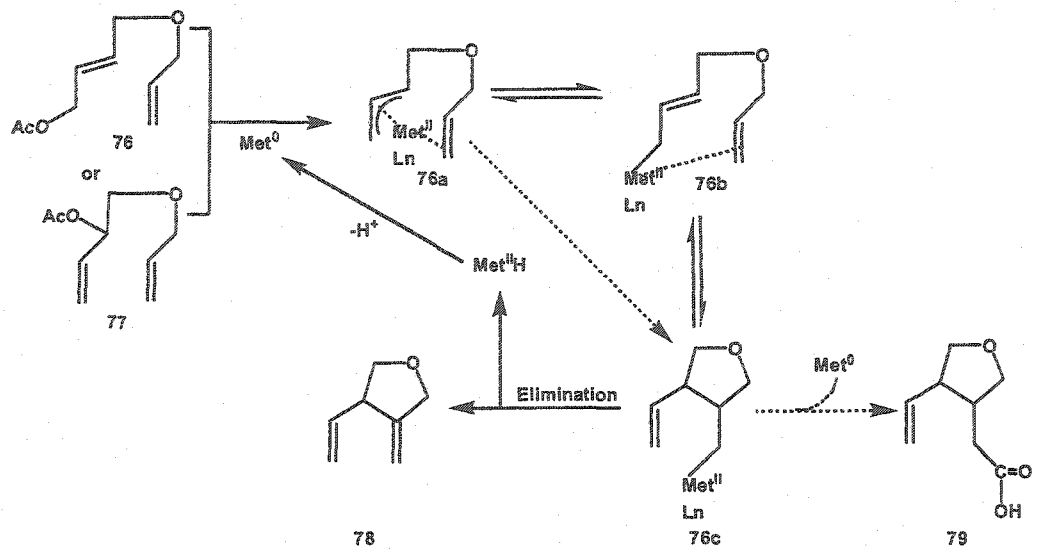
There are very few ring fusing reactions that keep the Co–alkyne intact. Tanino has examined the synthesis of cycloheptenyne complexes and bicyclic systems.[56,57] Instead of a [4+3] cycloaddition protocol, they developed a [5+2] cycloaddition which formed the cycloheptenyne complex (**Scheme 22**). Silyl enol ethers were employed to form a new ring with two different functional groups. For example, 7,6–bicyclic systems were synthesized by employing a cyclohexanone based enol silane. Futhermore, the cycloheptyne complex was oxidized in the presence of calcium carbonate, to form an additional fused anhydride.[58]



Scheme 22

1.6 Metallo–Ene Reactions

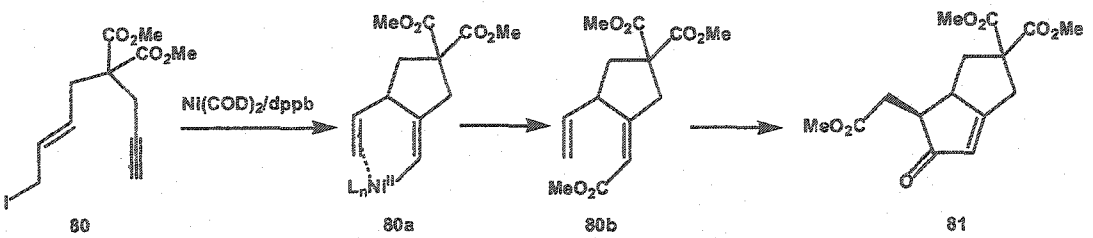
Oppolzer has developed a synthesis of carbo– and heterocycles by way of transition metal mediated cyclization reactions that utilized palladium[59-61] or nickel[62-64] based catalysts and allylic acetates, alcohols, or halides with a pendant alkene (**Scheme 23**).[62]



Scheme 23

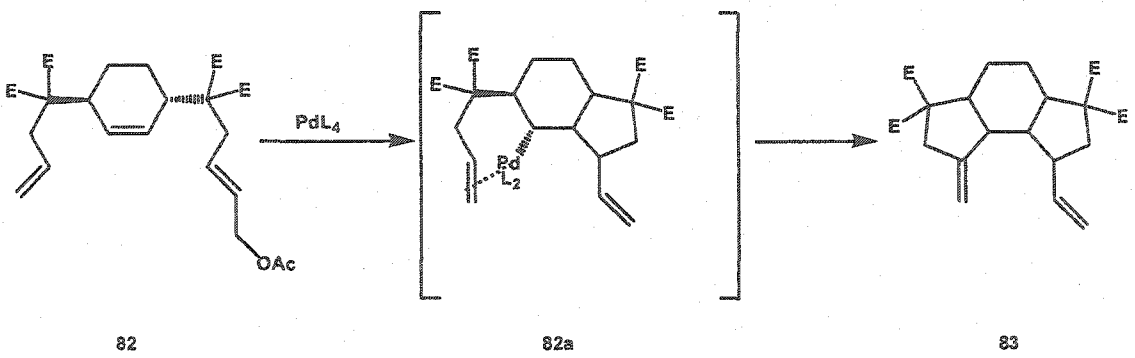
Mechanistically, the intermediate (**76a**) was accessed by an oxidative addition of the metal complex to the allylic acetate **76** or **77**. An intramolecular alkene insertion then occurred (**76b** to **76c**) and the metal fragment in the +2 oxidation state subsequently undergoes as a β–elimination to give a second carbon–carbon double bond (**78**). Compound **79** may be formed through a CO insertion/reductive elimination process in the presence of carbon monoxide to produce a carboxyl group and regenerate the catalytic metal fragment.

Of the possible catalysts, those based on nickel are preferred over those based on palladium because of the low cost and the greater reactivity to certain compounds.[65] Oppolzer has used several Ni^0–complexes and found that nickel cyclooctadiene was very efficient.[64] It was also determined that bidenate ligands, such as 1,4–bis(diphenylphosphino)butane (dppb), gave the highest conversion and yields for the cyclic material.[62] When the nickel–catalyzed carbocyclization was performed in a carbon monoxide atmosphere, a second cyclization occurred in some cases when an alkyne is the cyclization partner (**Scheme 24**).[65] In these cases, the Heck–like reaction of the acylnickel was faster than ester formation.



Scheme 24

Since the initial studies in 1987, the metallo–ene reaction has been used to synthesize polycyclic systems by Oppolzer; **Scheme 25** depicts a tandem reaction much like the **80–81** transformation.[66,67] In addition, the metallo–ene chemistry has been employed in the synthesis of several natural products.[68] Recently, intramolecular metallo–ene reactions have been carried out with a water–soluble catalyst, which is important since the reaction was performed under environmentally benign or mild conditions.[69]

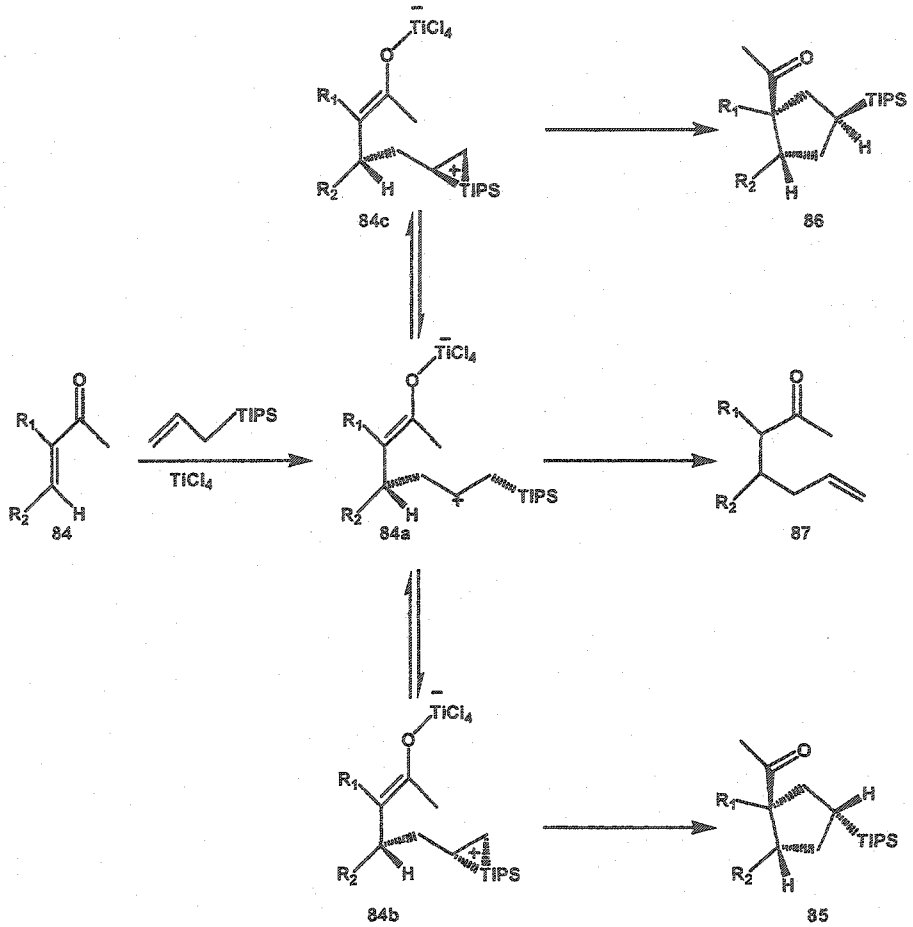


Scheme 25

1.7 Cycloadditions with Allyltriisopropylsilane

It has been found by the Knölker group found that cyclic systems may be formed by the Lewis acid mediated cycloaddition of allylsilanes with electron deficient alkenes.[70] Initial studies involved the reaction of an enone (**84**) with an allylsilane species that either had a bulky group like isopropyl or a smaller (methyl) group bound to silicon (**Scheme 26**).[71] The yields of cyclic products were much higher when the bulky group was bonded to silcon.[71] The

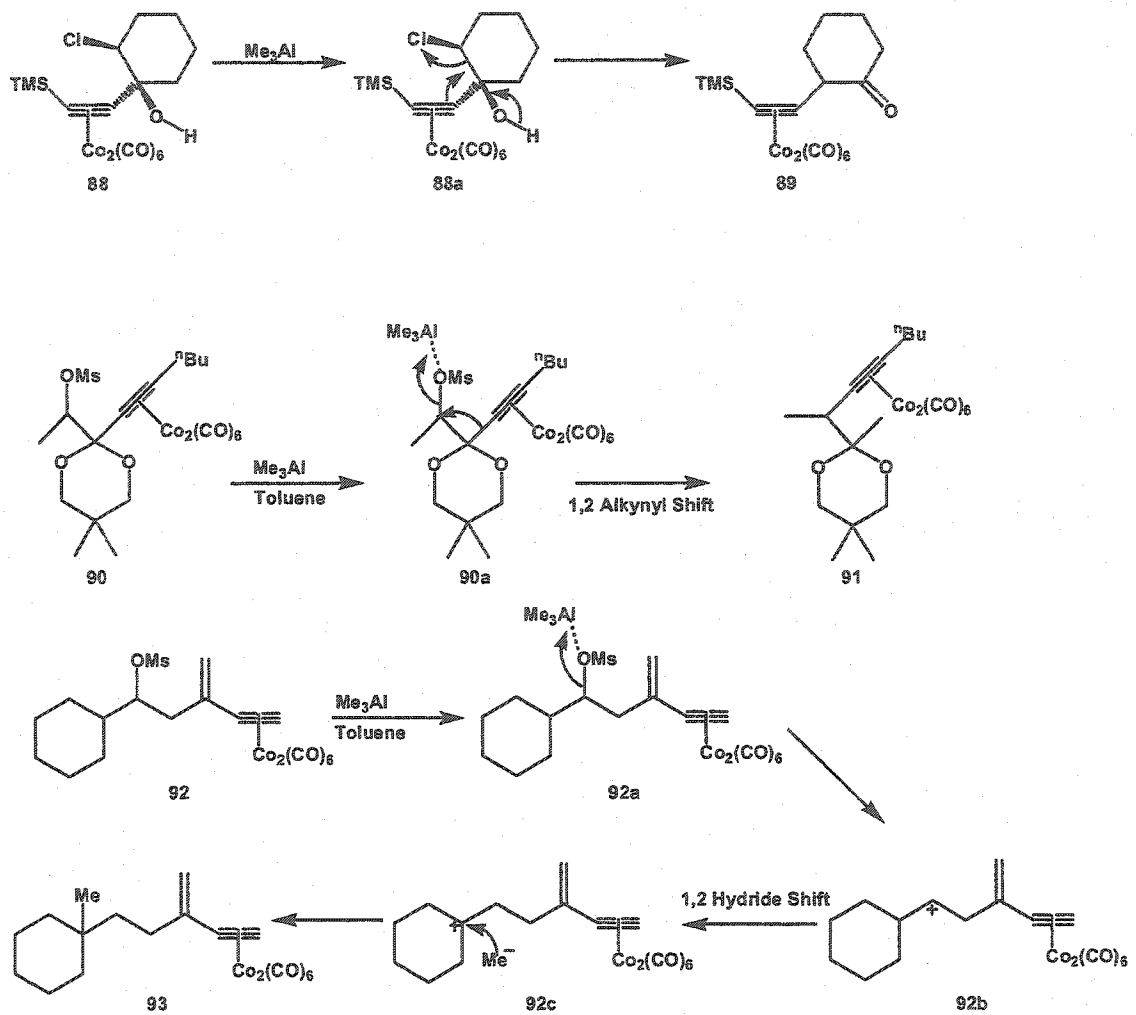
cycloaddition succeeded because the triisopropylsilyl group stabilized the cationic species (**84a** to **84b**), and the enolate double bond then attacked the cation.[71] Mechanistically, the Lewis acid ($TiCl_4$) activated the enone and allowed for attack at the β–position by the allylsilane. The cationic species was stabilized by the $^{i}Pr_3Si$ group β to it, but isomerized to a siliranium ion (**84b**). The enolate double bond then attacked the siliranium ion at the less substituted end, which gave a cyclopentane with a TIPS group still present. The overall process was a [3+2] cycloaddition. Two cycloaddition products formed, as the newly constructed ring could form in either *syn* (**86**) or *anti* (**85**) fashion.[70] The by–product was the loss of the silyl group (**87**), which is known as the Hosomi–Sakurai product; this is the predominant route of reaction with allyltrimethylsilane.[72] In other electron deficient alkenes, like alkenoates, the reaction of the enolate with **84a** was faster than isomerization to the siliranium ion, and a [2+2] cycloaddition process competed in these situations.



Scheme 26

1.8 Alkynyl or Hydride Migrations in DCHC

Rearrangements have been observed in Lewis acid mediated reactions of alkyne–DCHC's. These take the form of a 1,2–alkynyl or hydride shift in the molecule with the cobalt complex.[73-75] In a communication in 1996, Suzuki and co–workers reported the reaction of compound **88** with a Lewis acid (**Scheme 27**), which formed the ketone (**89**), by way of with a 1,2–alkynyl shift, where the cobalt complex migrated to the site where chlorine originated.[73] With the addition of the Lewis acid, a plausible by–product came from a Nicholas reaction to form the stable propargyl cationic intermediate, but this was not observed.[73]

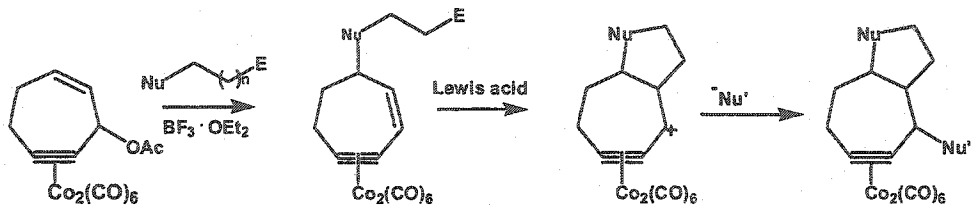


Scheme 27

The mesylate cobalt complex (**90**) underwent an analogous rearrangement with organoaluminum Lewis acids. In this reaction, a mesylate was ionized by the Lewis acid and the alkyne–DCHC underwent a 1,2–alkynyl shift, which formed compound **91** (**Scheme 27**).[74] In other work, instead of an alkynyl shift, a 1,2–hydride shift occurred (**Scheme 27**).[75] Again the mesylate was ionized by the Lewis acid (**92a**), to give a cation where the positive charge resided on the alkyl chain (**92b**); a 1,2–hydride shift then occurred to give a more stable alkylcyclohexyl (3°) cation (**92c**). This cation was then finally trapped by a nucleophile, which in this case was the methyl group from the Lewis acid (**93**).[74]

1.9 Aim of this Study

There is a need for the development of reactions for fusing rings onto the cycloheptyne without destroying the complex, so it can be used for additional ring forming reactions. Furthermore, exisiting methods of preparing cycloheptyne–DCHC complexes are not very good for putting substituents at the C–5 position. Therefore, the focus of this thesis is to study the reaction of the allylic acetate DCHC (**94**) with various nucleophiles. The ideal nucleophiles will be ones that also contain an electrophilic centre (**Scheme 28**). If the electrophilic centre is reactive enough, the double bond in **94a** is expected to attack and generate a propargylic cation. The positive charge, which is very stable due to the Co complexation, would be trapped by an additional nucleophile (**94b**). Other techniques mentioned earlier, such as the metallo–ene reaction and Knölker's [3+2] cycloaddition will also be investigated to attempt to form the bicyclic species (**95**).

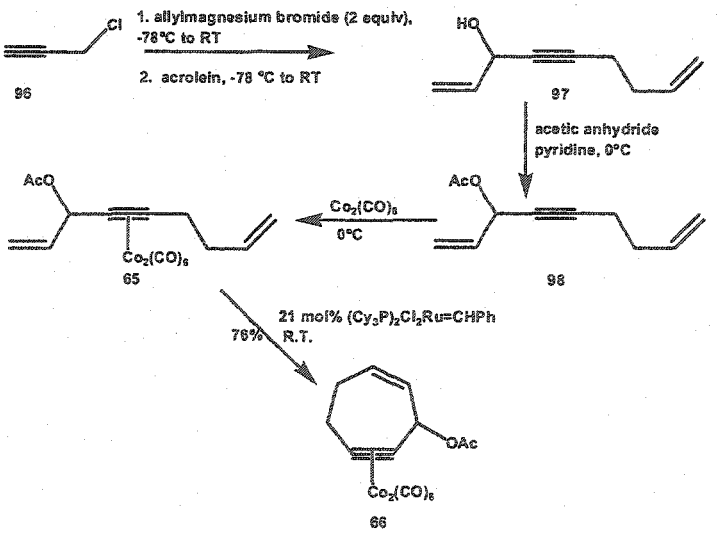


Scheme 28

2.0 Results and Discussion

2.1 Formation of the Cycloheptenyne

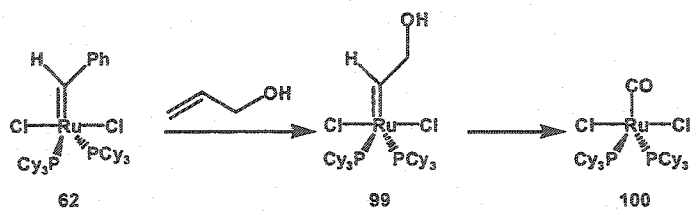
The formation of cycloheptenyne dicobalt hexacarbonyl complexes, by ring closing metathesis, has been thoroughly studied by Green and co-workers.[42] On reproducing these reactions (**Scheme 29**), the initial steps were completed with success but there were several difficulties with the ring closing metathesis reaction (RCM) in the final step. Initially 10 mol% of Grubbs' catalyst was added to compound **65**, but only a 40% conversion was observed to the desired product and starting material was still present. The amount of Grubbs' catalyst was increased to 21 mol% following this adjusted reaction, the conversion to the cycloheptenyne was determined to be 76%. Unfortunately, the residual starting material could not be removed by silica gel chromatography.



Scheme 29

The need to increase the amount of catalyst is not uncommon for RCM. In Werner's 2003 paper on the topic, the deactivation of ruthenium catalysts by allylic alcohols (**Scheme 30**) was discussed.[76] When Grubbs' catalyst **62** was stirred with the allylic alcohol, it forms compound **99**. However, if allowed to remain in solution, compound **100** also forms, which eventually decomposes the ruthenium catalyst. A similar process could be possible for compound **65**, as the

allylic alcohol is merely substituted with the allylic acetate which is capable of deactivating the catalyst in a similar manner. Green has also attempted the RCM containing an alcohol functional group and found that the conversion was far less then for compound **66**.[42]

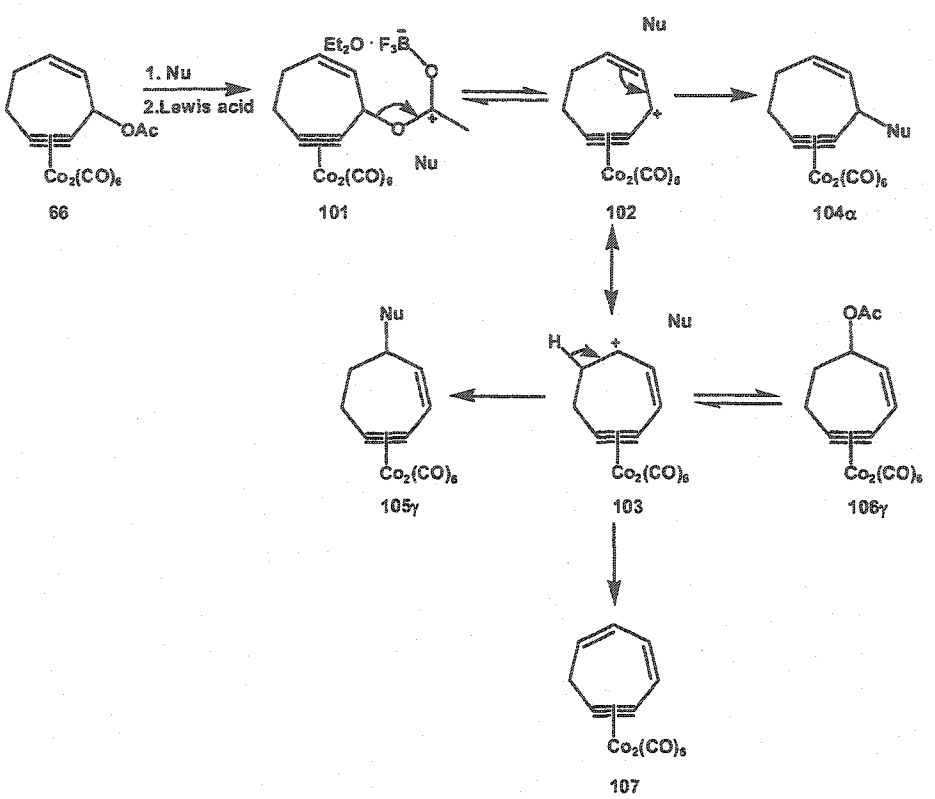


Scheme 30

2.2 Formation of α- and γ–Products from Cycloheptenyne Dicobalt Hexacarbonyl Complexes and Hetero– and Carbon–Based Nucleophiles

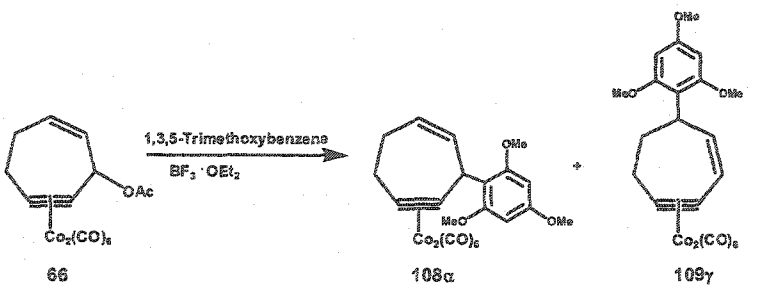
Several intriguing factors must be considered before performing a study of 7,5–ring system formation for the dicobalt alkyne complex. Firstly, upon substitution of the OAc group (compound **66**), one may form two products in a Nicholas reaction, either α– or γ–substituted. Our interest lies only with the γ–product, as it has a double bond electron rich enough for further reaction in order to fuse an additional ring onto the existing cycloheptenyne dicobalt hexacarbonyl complex. By electrophilic formation of the bicyclic system, the cationic charge is very stable since the charge is on the propargyl site (**Scheme 28**); furthermore the propargyl cation can be trapped by an additional nucleophile. **Scheme 31** shows the mechanism for both the formation of the α– and γ–products. The acetate group attacks the Lewis acid, boron trifluoride, forming species **101**. The conjugate base $(F_3B\text{-}OAc)^-$ species dissociates, leaving an allylic cation that may be described by several resonance forms, two of which have positive charge at the α (**102**) and the γ (**103**) site. The nucleophile may then attack either of the cationic sites. This type of chemistry has been attempted on acyclic molecules. Nicholas studied allylic alcohol cobalt complexes, where the Lewis acid would complex the alcohol, forming an analogous propargyl cation species.[77] The

products formed were γ–products, because of the steric hindrance of the dicobalt complex.[77] Of these routes of attack for acyclic systems, the kinetic product is that of the γ–position because sterically, it is more difficult for the nucleophiles to attack at the α–position due to the large dicobalt hexacarbonyl group. Thermodynamically, the γ–product is also favored since the γ–position is conjugated to enyne and sterically, a repulsive steric interaction with the $Co_2(CO)_6$ unit remains when the nucleophile is bonded to the α–site. This reaction would then incorporate γ nucleophiles more reliably and with greater flexibility than earlier results, where only F, Cl, or Ph groups could be incorporated in the γ–position, using [4+3] cycloaddition cation trapping reactions (**Scheme 17**).[37] Lastly, there are three additional minor products that may be obtained from **Scheme 31**: reformation of the starting material **66**, the γ–rearranged acetate product **106**, and the diene product **107**. Which of these might form depends upon the strength of the nucleophile as well as the length of time the reaction is conducted.



Scheme 31

1,3,5–Trimethoxybenzene was used as a representative nucleophile since it forms a very stable carbocationic sigma complex intermediate due to the electron donating groups on the aromatic ring. The cycloheptenyne (**66**) was mixed with 1,3,5–trimethoxybenzene (**Scheme 32**), and the Lewis acid was slowly added over thirty minutes. Electrophilic aromatic substitution occurred with the cationic species and the nucleophile. Initially, the reaction was performed at -30°C, forming products with a γ/α ratio of 3:2, with a yield that was adequate. This reaction was not optimized yet; therefore 1,3,5–trimethoxybenzene and compound **66** were mixed under several conditions (**Table 1**).

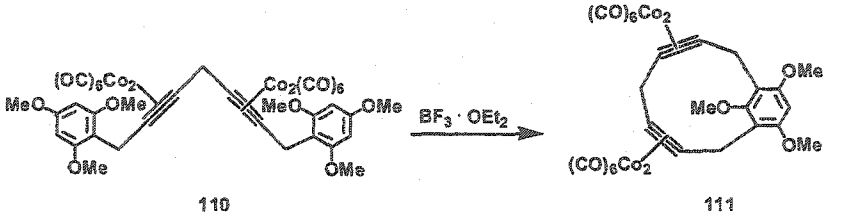


Scheme 32

Table 1: Optimization of the Nicholas Reaction with 1,3,5–Trimethoxybenzene as the Nucleophile

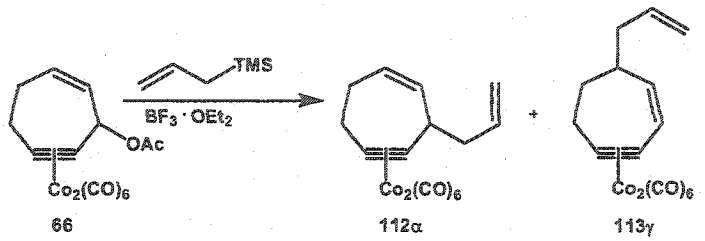
Conditions	Yield (%)	γ-product	α-product
-30°C, $BF_3 \cdot OEt_2$	70	59	41
-10°C, $BF_3 \cdot OEt_2$	86	70	30
0°C, $BF_3 \cdot OEt_2$	73	81	19
RT, $BF_3 \cdot OEt_2$	52	86	14
-10 °C, $SnCl_4$	77	76	24
-30 °C, Bu_2BOTf	Decomposition	n/a	n/a

As **Table 1** illustrates, when the temperature was increased, the γ–product increased from 59% to 86% of the condensation products, while the α–product decreased from 41% to 14%. There is a concern, however, with the possibility that are these results due to a retro–Nicholas reaction that has been observed for the 1,3,5–trimethoxybenzene (**Scheme 33**). With the addition of the boron trifluoride, a retrograde intramolecular Nicholas reaction occurred to form compound to **111**.[78] Consequently, it is possible that the **109:108** ratios in **Scheme 32** do not reflect a purely kinetic ratio.



Scheme 33

As a result, a nucleophile incapable of a retro–Nicholas reaction was investigated. Allyltrimethylsilane was therefore mixed with the cycloheptenyne and boron trifluoride etherate under different conditions (**Scheme 34**). The results depicted in **Table 2** indicate no change in the γ and α ratios when the temperature was increased.



Scheme 34

Table 2: Nicholas Reaction with Allyltrimethylsilane as the Nucleophile

Conditions	Yield (%)	γ-product	α-product
-30°C, $BF_3 \cdot OEt_2$	68	82	18
-10°C, $BF_3 \cdot OEt_2$	83	80	20
0°C, $BF_3 \cdot OEt_2$	77	81	19
RT, $BF_3 \cdot OEt_2$	56	83	17

It was also observed that the yields were notably higher at -10°C for both 1,3,5–trimethoxybenzene and allyl trimethylsilane. Therefore, reactions of the cycloheptenyne dicobalt complex with all nucleophiles were completed at -10°C. In addition, several Lewis acids were used instead of boron trifluoride diethyl etherate, such as tin tetrachloride and $^{n}Bu_2BOTf$ (**Table 1**). The best results were obtained with boron trifluoride diethyl etherate, although $SnCl_4$ is only marginally inferior, while $^{n}Bu_2BOTf$ caused extensive decomposition.

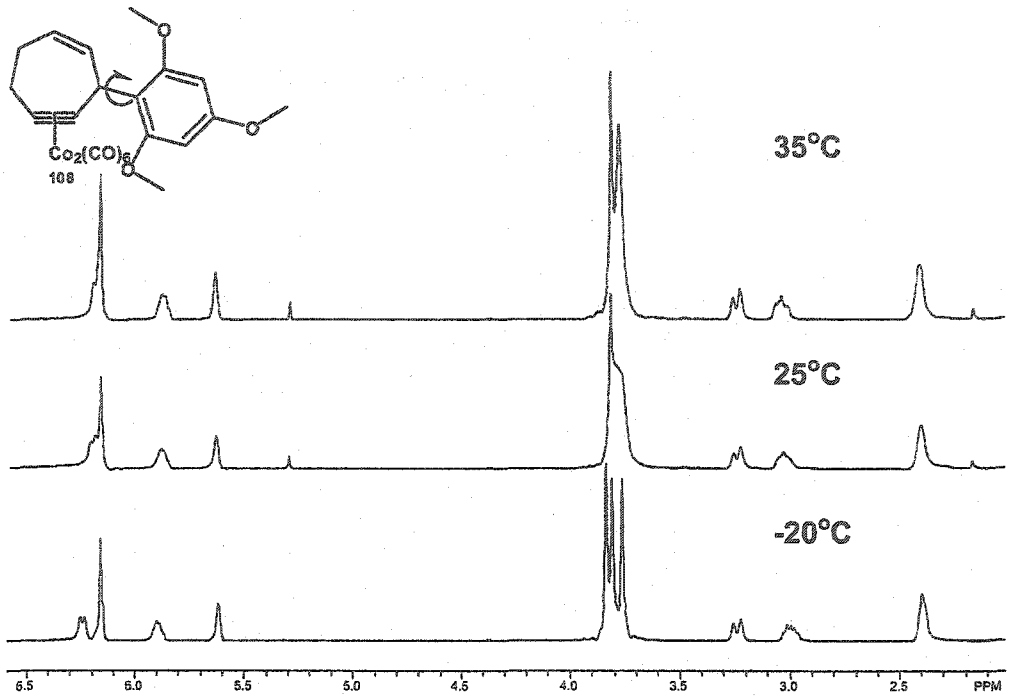


Figure 6: Variable Temperature ^{1}H NMR spectra of Compound **108**

The ^{1}H NMR spectrum of the α–product **108** exhibited a very interesting feature. There were broadened resonances at room temperature, suggesting a restricted rotation situation near its coalescence point. **Figure 6** details ^{1}H NMR spectra of the α–product at several variant temperatures, 35, 25 and -20°C. The peaks of particular interest were located around 4ppm, which are indicative of the three methyl groups on the 1,3,5–trimethoxyphenyl functional group. At the lowest temperature (-20°C) there were three distinctive peaks, which is an indication of slow exchange in the NMR time scale. As the temperature is increased, the peaks representing two of the methyl groups on the *ortho* position 'met' at 25°C; this intermediate situation is known as the coalescence point. At 35°C the three peaks shifted into two noticeably distinct peaks due to the fast exchange on the NMR time scale, as the two *ortho* methoxy groups had become indistinguishable. From the MMX calculations on **108** (PC Model®),[79] the ortho methoxys are oriented as far as possible from the carbonyls on the cobalt such that the aryl ring is aligned nearly eclipsed to the α C–H bond (**Figure 7**).

Rotation about the aryl–α carbon bond by 180° do not exactly exchange methyls on the methoxy but the rotation of the *para*–aryl carbon and the oxygen is simple, so it can be coupled to this first rotation process.

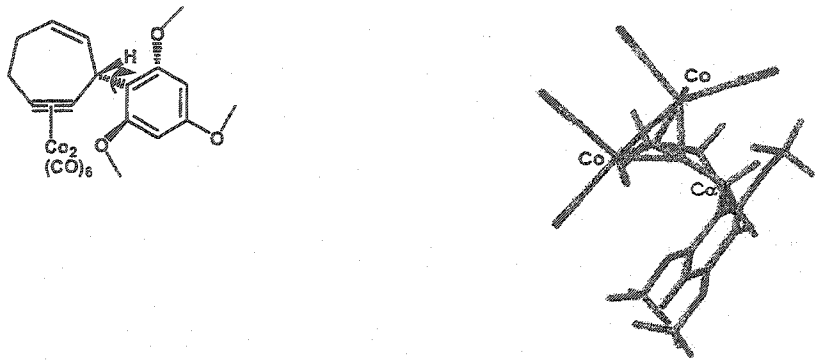


Figure 7: Minimum Energy Structure of Compound **108** (PCModel™)

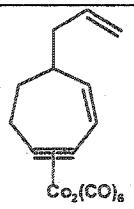
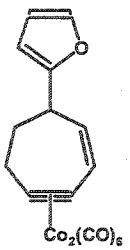
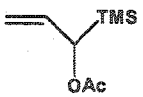
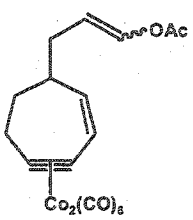
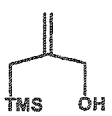
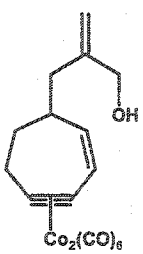
$$k_c = \pi\Delta\nu/\sqrt{2} \qquad (1)$$

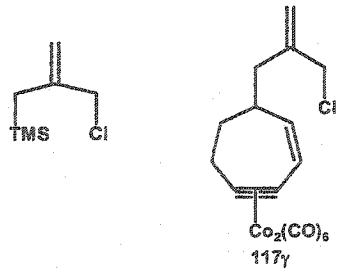
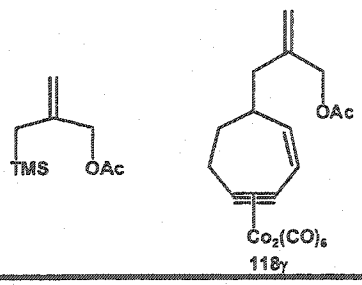
$$\Delta G_c = 2.3RT_c[10.32 + \log(T_c/k_c)] \qquad (2)$$

Equation **1** is the relationship for the rate of exchange at the coalescence point (k_c) and $\Delta\nu$ is the distance between the two peaks at slow exchange, in Hz.[79] Equation **2** is the relationship for the free energy of activation at the coalescence temperature (T_c).[80] From these equations, the activation energy of the rotational barrier (ΔG_c) of compound **108** was calculated to be 15.2 Kcal/mol.

Once the optimization was completed for the Nicholas reaction with trimethoxybenzene, several other nucleophiles were added to the allyl acetate dicobalt hexacarbonyl complex. The nucleophiles were either carbon– or heteroatom–based, with one hydride nucleophile, and were drawn from the list of nucleophiles known to participate well in the Nicholas reaction.

Table 3: Nicholas Reactions with Carbon–Based Nucleophiles

Nu	Cpd. No.	Yield (%)	γ– Product	α– Product	Rearr. Acetate (**106**)	Diene (**107**)
	 **113γ**	74	84	16	—	—
	 **114γ**	62	80	20	—	—
	 **115γ**	65	100	—	7%	7%
	 **116γ**	76	55	45	—	—

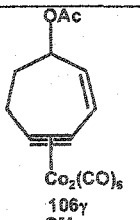
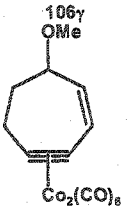
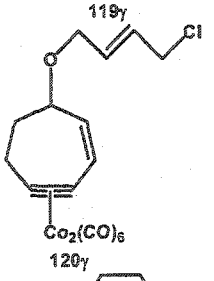
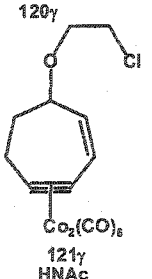
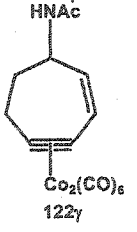
	70	62	38	—	—
	75	56	44	—	—

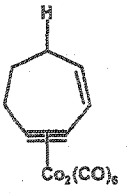
Generally, carbon–based nucleophiles gave condensation products with a ratio of approximately 4:1 in favor of the γ–product, and yields ranged from 66 to 76% (**Table 3**). Also, for most of the nucleophiles, no rearranged acetate (**106**) or diene (**107**) products were observed. The only exception for the carbon–based nucleophiles was compound **115**, where no α–product were observed, but where there were, however, minor amounts of both **106** and **107** isolated.

The effect of heteroatom–based nucleophiles on the allylic acetate dicobalt complex **66** (**Table 4**) was studied subsequently. The product ratios for the heteroatom nucleophiles were 100% γ–product and the yields ranged from 12% to 79%. The mechanisms for the reaction of the carbon and heteroatom nucleophiles are slightly different. In the case of the carbon nucleophiles, the substitution reaction is irreversible, following the carbon bond to the cycloheptenyne. In contrast, heteroatom–based products (**106**, **119–122**) are always in equilibrium with the cation, the starting material, or the γ–rearranged acetate. Therefore, there is no α–product present as the γ–products are both less sterically hindered and possessing of a conjugated enyne unit. Thus in these cases, the reactions are reversible. While all of the heteroatom–based nucleophiles gave the γ–product, the hydride nucleophile gave **123** with ca. 3 to 2 γ/α ratio. It is reasonable to propose that this ratio was unusually low because

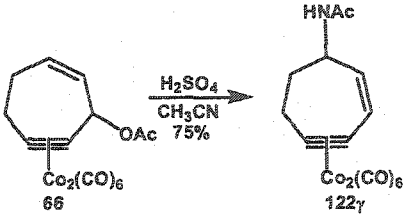
hydride attack is irreversible, and because of the small size of the hydride nucleophile, steric hindrance with the $Co_2(CO)_6$ unit therefore is not a substantial factor.

Table 4: Nicholas Reactions with Heteroatom–Based Nucleophiles and a Hydride Nucleophile

Nu	Cpd. No.	Yield (%)	γ– Product	α– Product	Rearr. Acetate (**106**)	Diene (**107**)
CH_3CO_2H	 106γ	79	100	—	—	—
MeOH	 119γ	65	100	—	—	—
	 120γ	68	100	—	13%	4%
	 121γ	59	100	—	15%	15%
H_2NAc	 122γ	12	100	—	83%	5%

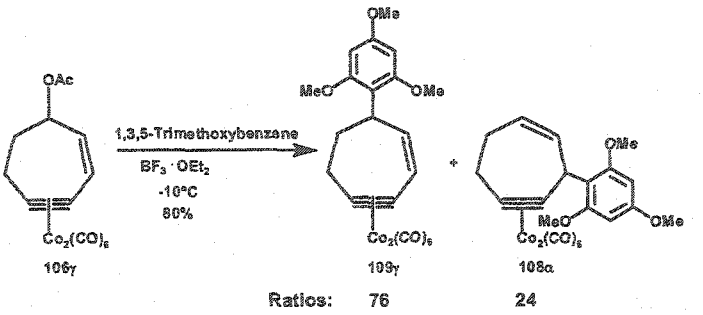
Et_3SiH	 123γ	54	63	37	—	—

An interesting result of the Nicholas reaction with acetamide (compound **122**) was that the yield is very low (12%). This is likely due to the Lewis acid not only attacking the acetate functional group on the cycloheptenyne dicobalt complex but also being complexed by the acetamide. Consequently, the nucleophile would be less reactive and as a result more of the γ–acetate rearrangement product is formed if there is more boron trifluoride than the acetamide. If there is more acetamide then the Lewis acid, the reactivity is suppressed by virtue of tying up the BF_3. The yield of compound **122** was increased from 12% to 75% by instead using a protic acid (H_2SO_4) and acetonitrile as the nucleophile, in a Ritter–type reaction (**Scheme 35**).



Scheme 35

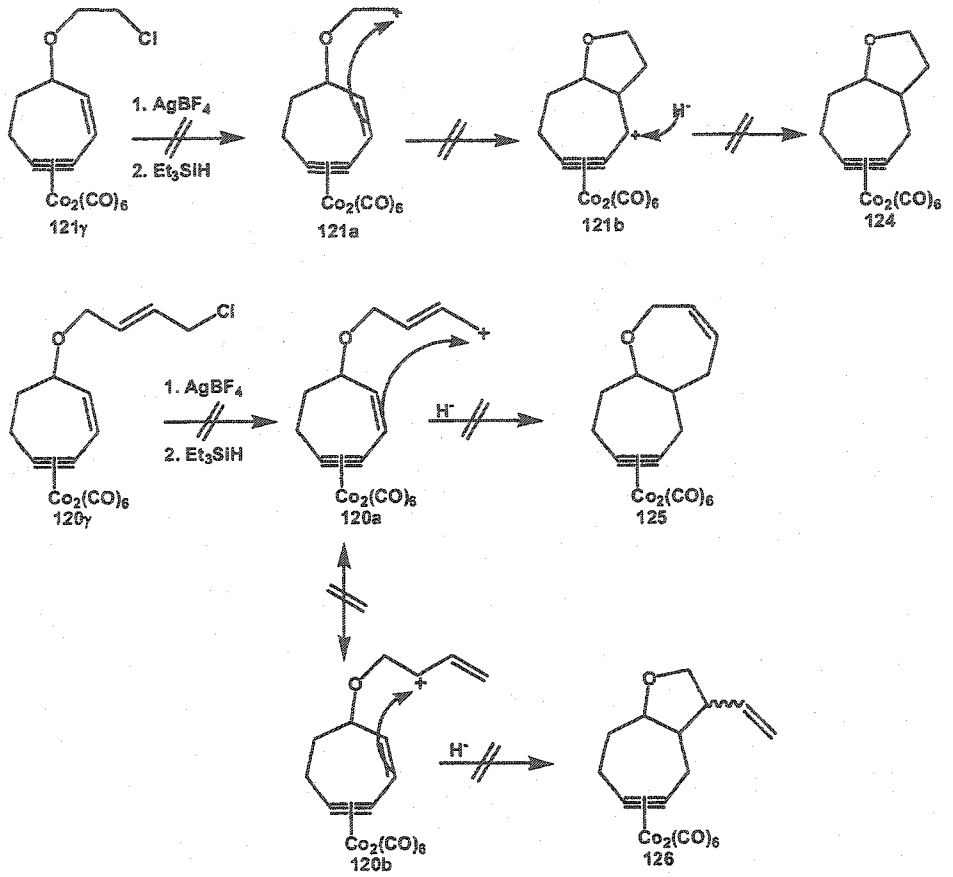
Since the allylic cation **103–104** is in principle obtainable from either **66** or **106**γ, we decided to test this concept. As a result, the γ–acetate **106**γ was subjected to a reaction with 1,3,5–trimethoxybenzene under reaction conditions identical to that of **66** (**Scheme 36**). In the experiment, condensation occurred in similar yield (80%) to afford the same products in a similar but not identical ratio (**109**γ:**108**α = 76:24). Therefore, if any of the reactions formed rearranged acetate, this product could then be re–reacted to form the α– and/or γ–condensation product.



Scheme 36

2.3 Progression to the Formation of 7,5–Bicyclic Rings

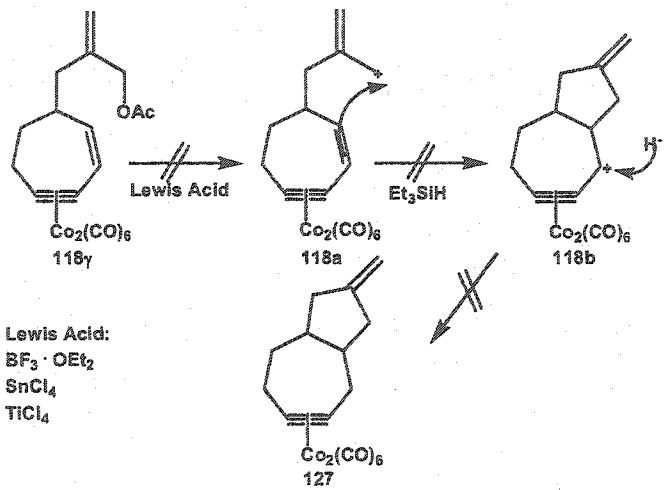
After concluding that attack at the γ–position was the predominant reaction pathway for both carbon and heteroatom nucleophiles, several of the γ–products were reacted further in attempts to form an additional ring fused to the cycloheptenyne dicobalt hexacarbonyl complex. Compound **121**γ was investigated first and the anticipated route of reaction involved the removal of the chloride, forming a 1° carbocation and attack of the double bond to form the ring (**Scheme 37**). The resultant **121b** would then be further reacted with a hydride source to quench the propargyl cation. Therefore, compound **121**γ was added to silver tetrafluroborate and triethylsilane. The reaction mixture was stirred for several hours and then further left to stir overnight. From the ^{1}H NMR data there was no reaction, as only starting material was present. Furthermore, when the reaction was stirred overnight no conversion to the bicyclic ring occurred, but there was a great deal of decomposition observed. The reaction likely did not form product **124** as the necessary 1° carbocation was not stable enough for its facile formation. Therefore, allylic chloride **120**γ was also reacted with silver tetrafluoroborate, which would form a monosubstituted allyl cation instead of forming the 1° cation. Again, no productive reaction and gradual decomposition was observed. From the literature, it is apparent that further stabilization was required for the effective generation of a 2° allylic cation.[81]



Scheme 37

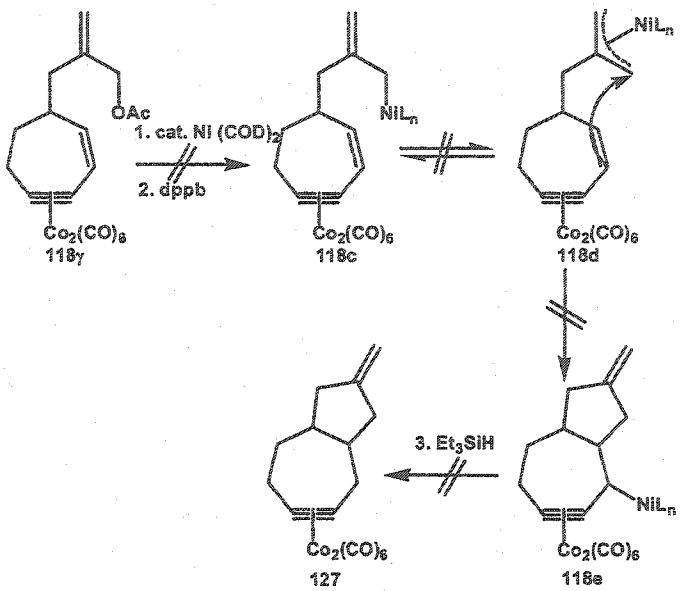
While the reaction for compound **120γ** did not proceed, another allylic cationic synthetic strategy was attempted. Compound **118γ** was stirred with several Lewis acids: boron trifluoride diethyl etherate, tin tetrachloride and titanium tetrachloride (**Scheme 38**). It was thought that the Lewis acid would remove the acetate functional group by ionization to give the allyl cation **118a**. The double bond would then react with the cation, but there was no reaction observed. The reaction was stirred for an additional eight hours, however still no formation was found to have occurred. Again, this reaction did not form the five membered ring. This was likely due to the necessary 1° allyl carbocation, which is not quite stable enough for easy formation. It has been observed by several groups that the carbon–carbon formation would not form if the allylic alcohol was not 2° or tertiary.[81-83] In 1992, Grieco and co–workers reacted a 2° allylic alcohol with

lithium perchlorate, and found that the reaction would only proceed if there was a γ–disubstitution.[81,82] The Lewis acid mediated generation of allyl cation from allyl acetates usually needs one additional substituents and a γ–disubstitution.[81-83]



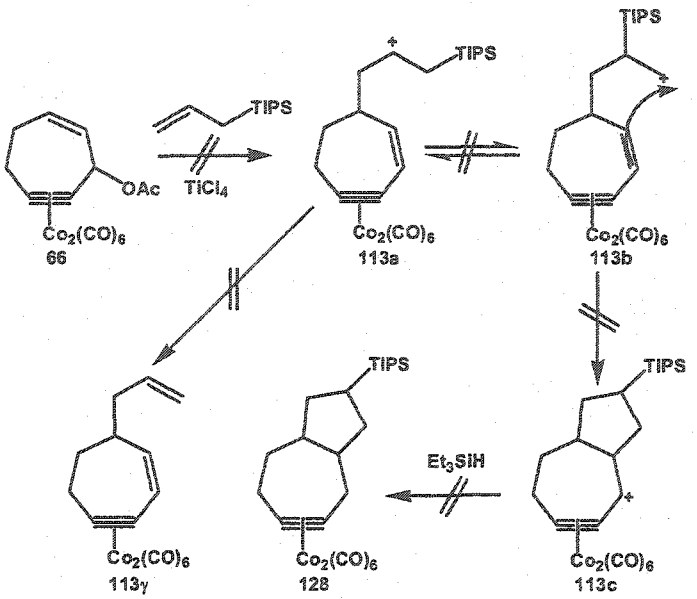
Scheme 38

As has been described in the Introduction, Oppolzer has examined carbocyclization reactions of allyl acetate on alkenes with nickel and palladium catalysts.[54] Of the common catalyst systems, the literature suggests that, with palladium based catalysts, the reaction mixture would need to be heated to 70°C, which with **118γ** would likely decompose the dicobalt complex. Conversely, the nickel catalyzed reactions, however, are often conducted at room temperature. With **118γ** one could envision an oxidative addition of the nickel complex to the acetate, coupling with the alkene to give allylnickel **118e**, with Et_3SiH induced reduction of the nickel–carbon bond (**127**). In the attempt, compound **118γ** was stirred with nickel 1,5–cyclooctadiene and 1,4–bis(diphenylphosphinobutane); no reaction was observed and when the solution was stirred overnight, there was only slow decomposition and recovered starting material **118γ**. Finally, the mixture was stirred at 30°C, and greater amounts of decomposition were observed.



Scheme 39

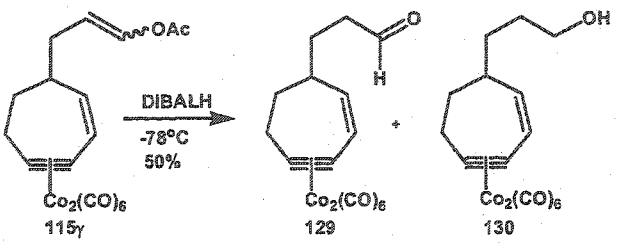
Finally, an attempt to modify Knölker's allyltriisopropylsilane [3+2] cycloaddition process was made (**Scheme 40**).[66] It was believed that with the cation derived from **66**, allyltriisopropylsilane would form cation **113a**, which would rearrange to **113b**. This latter cation would be capable of attack by the alkene unit to form a cyclopentane. In the experiment, compound **66** was mixed with allyltriisopropylsilane and $TiCl_4$, with Et_3SiH also present in order to reduce the propargyl cation **113c** to **128**. After the addition, the reaction was allowed to stir for nineteen hours, but no product was formed. The ^1H NMR data showed what appeared to be only starting material and some decomposition, even though the reaction was kept at -20°C. This result was surprising as even if the cycloaddition did not occur, it was thought that compound **113γ** would still be formed. It is clear that allyltriisopropylsilane is a less reactive nucleophile than allyltrimethylsilane.



Scheme 40

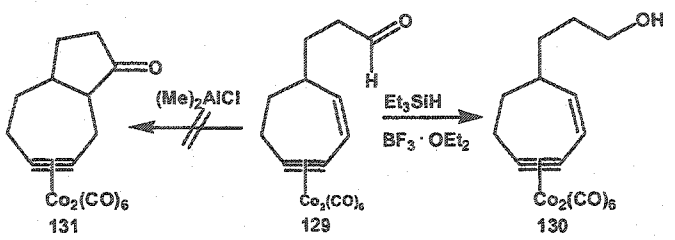
2.4 Reaction of Cycloheptenyne Dicobalt Hexacarbonyl Complexes Leading to Bicyclic Systems

The enol acetate in **115**γ can serve as a masked aldehyde function, which is a much more reliable electrophilic carbon source than those of allyl or alkyl cation precursors. Therefore, compound **115**γ was mixed with DIBALH, which reduced the enol acetate to an aldehyde functional group attached to the cycloheptenyne dicobalt complex (**Scheme 41**). The overall yield for the reduction was 50%. One of the reasons for the modest yield is that compound **129** could also get further reduced to form compound **130**; evidence of the alcohol (**130**) was present in the crude reaction mixture.



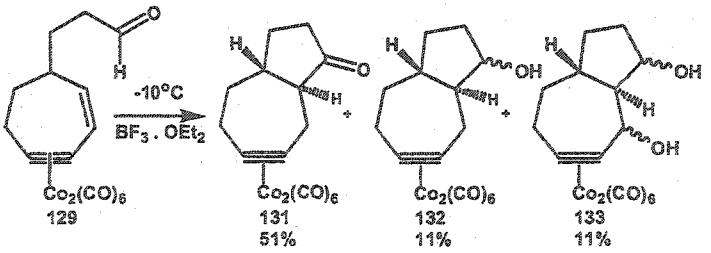
Scheme 41

Aldehyde **129** was mixed with Me_2AlCl in order to initiate cyclization (**Scheme 42**), in the presence of Et_3SiH for propargyl cation reduction with the intent of forming **131**. Surprisingly no reaction of any fashion occurred. Replacing Me_2AlCl with $BF_3 \cdot OEt_2$ (with Et_3SiH) did result in consumption of **129** but afforded only reduction product **130**.



Scheme 42

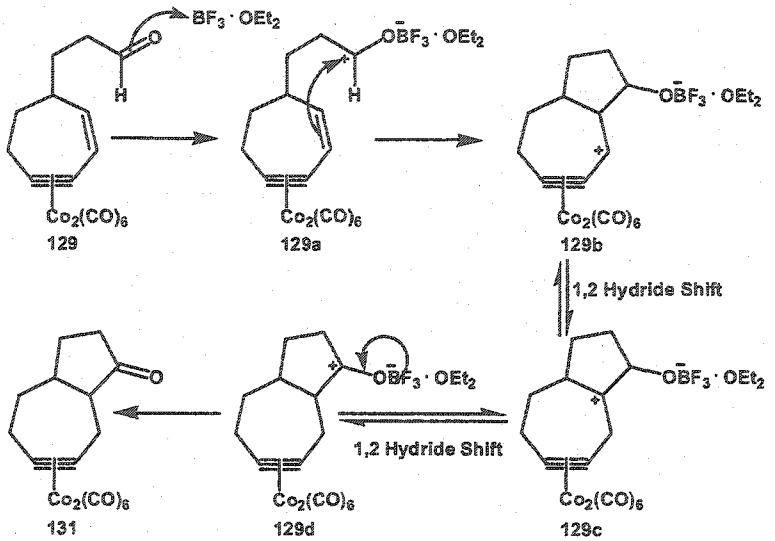
Seeing as the cyclization was surprisingly slow relative to hydride attack, compound **129** was reacted with boron trifluoride diethyl etherate alone. At long reaction times, there was a significant amount of decomposition, but cyclization did occur (**Scheme 43**). Three products were formed: the bicyclic ketone (compound **131**), an alcohol (compound **132**) and a diol (compound **133**). The initial yields when the reaction was stirred overnight were 30% for the ketone, and 5% for both the alcohol and diol functional groups. These yields increased when the reaction time was decreased; at two hours the yields of the three products increased to 51%, 11% and 11% respectively.



Scheme 43

For the 7,5–bicyclic dicobalt complex containing the ketone, the formation likely proceeded through two 1,2–hydride shifts (**Scheme 44**). The boron trifluoride would be complexed by the lone pair electrons on the oxygen. The

double bond would then attack the highly electron deficient carbonyl carbon of **129a**, forming the cyclopentane ring (**129b**). Hydride would migrate to the positive charge, forming a new positive charge in the β position (**129c**) and a subsequent second hydride migration to give a cation next to the O atom (**129d**). The positive charge would then be lost when the Lewis acid dissociates from the oxygen atom, forming the ketone (**131**).



Scheme 44

The diol (**133**) is essentially the expected reaction of **129b** quenched with $NaHCO_{3(aq)}$. Water would attack the cation (**129b**) forming the alcohol and would offer an additional proton source on the alcohol. The alcohol (**132**) would form if there was an intermolecular hydride shift from another aldehyde molecule via a Cannizzaro–like reaction. The resulting acid by–product is likely very polar and was not isolated.

The stereochemistry for the bicyclic ketone (**131**) is trans (H_3 and H_4) at the ring juncture as evident by the 11 Hz (axial–axial) coupling constant (**Figure 8**). The remaining coupling constant for H_3 were 4 Hz (H_1) and 11 Hz (H_2), further confirming the axial nature of H_3. The stereochemistry of the diol (**133**) was assumed to be trans at the ring juncture also. Since the $J_{H2\text{-}H1}$ is small (2 Hz), an axial orientation for the propargylic OH (trans to H_2) is assigned. For the alcohol

in the cyclopentane unit in **132** and **133**, the stereochemistry was assigned based on the presumed preferred reactive conformation of the aldehyde in **129**. Orienting the aldehyde carbonyl away from the substituent at C5 on the cycloheptenyne complex (**Figure 9**) results in the orientation of the alcohol cis to the C5 substituent in **132** and **133**.

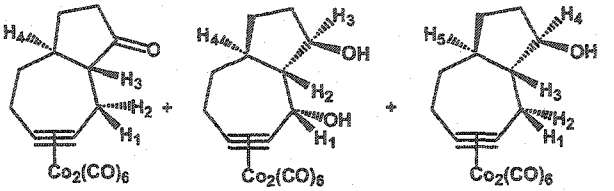


Figure 8: Stereochemistry of the Bicyclic Compounds

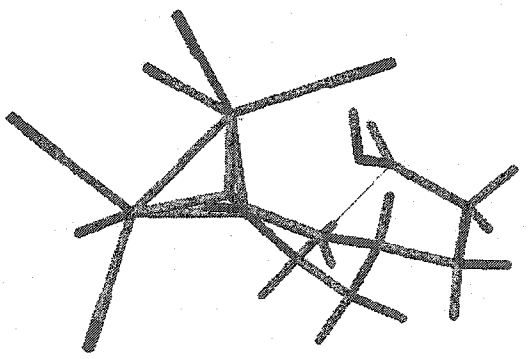


Figure 9: MMX Minimized Energy Structure of Compound **129**–H^+

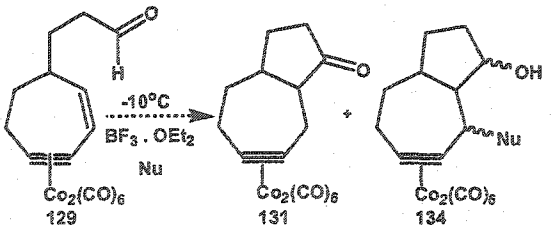
3.0 Conclusion and Future Work

3.1 Conclusion

In this study, carbon– and heteroatom–based nucleophiles were mixed with the cycloheptenyne allylic acetate complex (**66**). In the case of the carbon–based nucleophiles, the ratios of the γ to α products were 4:1, while the heteroatom–based nucleophiles were 100% γ. Several attempts were made to form a 7,5–bicyclic system; success was only observed with the reaction of compound **129** with boron trifluoride diethyl etherate (**Scheme 43**). Three bicyclic products were formed: a ketone (**131**), an alcohol (**132**) and a diol (**133**).

3.2 Future Work

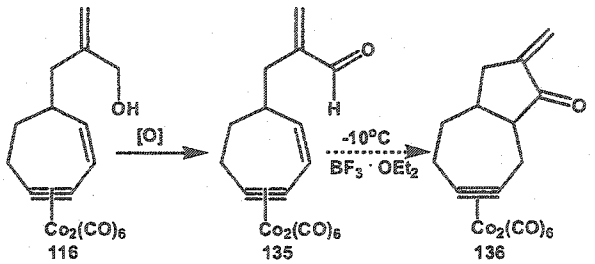
Once the optimization for **Scheme 43** is completed, several other reactions should be attempted. When boron trifluoride was added by itself, the dominant product was the bicyclic ketone (**131**). If a nucleophile was added to compound **129** during the cyclization process, it would be very interesting to see if the bicyclic ketone would still be the major product or if the nucleophile can trap the cationic charge before the 1,2–hydride shifts (**Scheme 45**).



Scheme 45

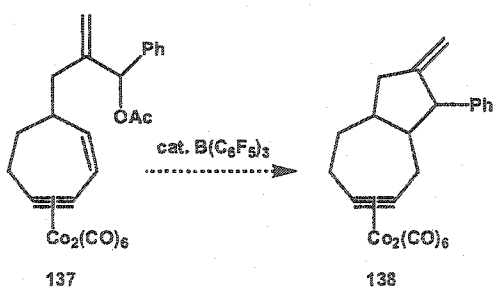
Another alternative route to form the 7,5–bicyclic system is to oxidize compound **116** and then add boron trifluoride (**Scheme 46**). Manganese dioxide was added to the allylic alcohol cycloheptenyne complex (**116**) but the yield of

135 was only 10% and therefore only a very small amount of material is yet available. Once the yield of the oxidation is optimized, the final step of this reaction is analogous to compound **129** in **Scheme 45**.



Scheme 46

As mentioned in Section 2.3, generation of an 1° allylic cation to react further to form a carbon–carbon bond could not be accomplished but if the allylic cation was 2° or 3°, reaction would be expected to occur. Therefore, if compound **118** had an additional functional group (**137**) the cation is more stable and cyclization is likely to occur (**Scheme 47**). If the bicyclic system does not form, different Lewis acids would be used, such as tris(pentafluorophenyl)borane. In a recent paper by Gevorgyan, a catalytic amount of $B(C_6F_5)_3$ was mixed with a benzyl acetate and an allylsilane. The Lewis acid attacks the acetyl functional group to form the cation and the allylsilane would then attack the charge to form a new carbon–carbon bond.[84]



Scheme 47

4.0 Experimental

4.1 General Methods

All chemicals were purchased from Aldrich. All solvents were purified with a 'Grubbs' type' solvent purification system, which was manufactured by Innovative Technology. Boron trifluoride diethyl etherate was distilled before it was used, while all the other compounds were used as they were received.

All reactions were conducted under a nitrogen atmosphere. The term -78°C refers to a bath containing CO_2 and acetone. The term -30°C refers to a solution containing CO_2 and 50% ethanol. The term -10°C refers to a solution containing ice water and sodium chloride, while 0°C refers to an ice bath.

Analytical thin layer chromatography (TLC) was done using Merck precoated silica gel 60 F_{254} sheets, while preparative TLC's were performed on Aldrich silica gel GF 1000 micron plates. In addition, Still's method for flash chromatography was utilized.[85] A typical workup consisted of extracting the aqueous phase three times with diethyl ether or dichloromethane. The product was then dried with anhydrous magnesium sulphate, followed by vacuum filtration. The excess solvent was evaporated under reduced pressure, yielding the crude product.

^1H NMR spectra were completed on either a Bruker Avance 300 or 500 spectrometer in $CDCl_3$ at room temperature; coupling constants are given in Hertz. $^{13}C\{^1H\}$ NMR spectra were completed on the Bruker Avance 300 spectrometer at 75MHz in $CDCl_3$ at room temperature. Chemical shifts are given in ppm with respect to tetramethylsilane, with higher frequency taken as positive. IR spectra were acquired on a Bruker Vector 22 FT–IR spectrophotometer, using KBr plates and are reported as wavenumber (cm^{-1}) maxima. Low resolution mass spectra were completed on a Varian Saturn 1200 MS using the electron impact mode.

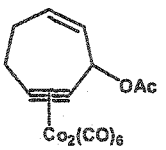
4.2 Procedure A: Synthesis of the Cycloheptenyne Dicobalt Complex and Nucleophiles

Hexacarbonyl[μ–η⁴–(acetoxy–1–vinyl–hept–6–en–2–ynyl ester)] dicobalt (Co–Co) (65)

65

Compound **65** was prepared by the procedure of Green.[42]

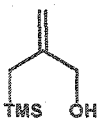
Hexacarbonyl[μ–η⁴–(3–acetoxy–cyclohept–1–en–4–yne)] dicobalt (Co–Co) (66)



66

To a solution of **65** (0.511 g, 1.10 mmol) in 31 mL of dichloromethane, of Grubbs' catalyst [$Cl_2(Cy_3P)_2Ru{=}CHPh$] (0.06 g, 7 mol%) was added over a period of 30 min. The solution was stirred for 3 h, the Grubbs' catalyst was filtered through a plug of silica gel and concentrated under reduced pressure. The residue was redissolved in dichloromethane (31 ml) and Grubbs' catalyst (0.06 g, 7 mol%) was again added. After stirring 3 h, the solution was filtered through a plug of silica and concentrated under reduced pressure. This step was repeated again before the crude product was collected. Flash chromatography (10:1 petroleum ether: diethyl ether) afforded **66** (0.389 g, 76%), which was spectroscopically identical to the literature report.[42]

2-(Trimethylsilylmethyl)-2-propen-1-ol



2-(Trimethylsilylmethyl)-2-propen-1-ol was prepared by the method of Trost and co–workers.[86]

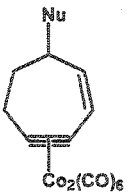
1-(Trimethylsilyl)allyl acetate

1-(Trimethylsilyl)allyl acetate was prepared by the method of Prock and co-workers.[87]

4–Chloro–2–buten–1–ol

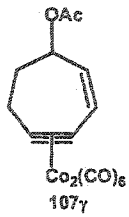
4-chloro-2-buten-1-ol was prepared by the method of Ravikumar and co-workers.[88]

4.3 Procedure B: Reactions of the Cycloheptenyne Dicobalt Complex with Carbon– and Heteroatom–Based Nucleophiles (Nu)



The nucleophile (1.5 equiv) was added to the cycloheptenyne **66** in dichloromethane (0.05 M). Then boron trifluoride diethyl etherate (10 equiv) was added over 30 min in dichloromethane (1.0 M) at -10°C. The solution was stirred for 1 h and followed by addition of aqueous sodium bicarbonate. A typical workup was performed. The crude product was purified by flash chromatography.

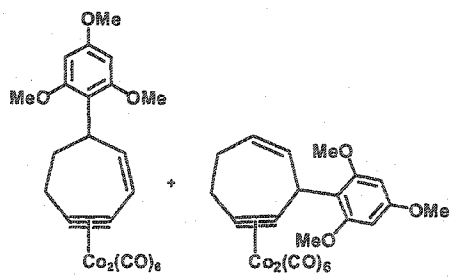
Hexacarbonyl[μ–η^4–(7–acetoxy–cyclohept–1–en–3–yne)] dicobalt (Co–Co) (107γ)



107γ

The cycloheptenyne **66** (0.0540 g, 0.124 mmol), in dichloromethane (2.5 mL), was stirred with glacial acetic acid (0.0149 g, 0.248 mmol) via **Procedure B**. The crude product was purified by flash chromatography (10:1 petroleum ether: diethyl ether) to yield the **107γ** (0.0427 g, 79%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2923, 2850, 2092, 2051, 2021, 1740, 1238; ^1H NMR δ: 6.68 (d, *J* = 9.9, 1H), 6.06 (dd, *J* = 4.6, 10.0, 1H), 5.48 (m, 1H), 3.30 (m, 1H), 3.22 (m, 1H), 2.12 (m, 1H), 2.09 (s, 3H), 2.00 (m, 1H); $^{13}C\{^1H\}$ NMR δ: 199.6, 170.3, 133.5, 128.9, 98.0, 89.0, 72.6, 30.5, 30.4, 21.3. MS EI m/e: 436 (M^+), 408 (M^+ -1CO), 380 (M^+ -2CO), 352 (M^+ -3CO), 324 (M^+ -4CO), 296 (M^+ -5CO), 268 (M^+ -6CO).

Hexacarbonyl[μ–η^4–(7–trimethoxyphenylcyclohept–1–en–3–yne)] dicobalt (Co–Co) (109γ) and Hexacarbonyl[μ–η^4–(3–trimethoxyphenylcyclohept–1–en–4–yne)] dicobalt (Co–Co) (108α)

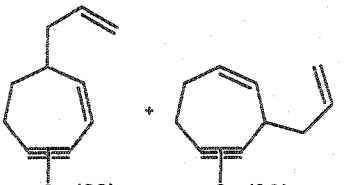


109γ 108α

The cycloheptenyne **66** (0.0385 g, 0.0883 mmol), in dichloromethane (2 mL), was stirred with 1,3,5–trimethoxybenzene (0.0297 g, 0.1766 mmol) via **Procedure B**. The product was purified by flash chromatography (25:1 petroleum ether: diethyl ether) the **109γ** and **108α** were separated (0.0328g, 86%) as a red–

brown oil. IR (neat, KBr, cm^{-1}) γ–product: 2925, 2851, 2087, 2017, 1609, 1385; ^1H NMR γ–product δ: 6.46 (d, *J* = 9.8, 1H), 6.14 (s, 2H), 5.97 (dd, *J* = 2.7, 9.9, 1H), 4.03 (m, 1H), 3.79 (s, 9H), 3.35 (m, 1H), 3.16 (m, 1H), 2.19 (m, 1H), 1.82 (m, 1H); ^{13}C {^1H} NMR γ–product δ: 200.0, 159.0, 143.1, 123.7, 116.0, 99.3, 91.5, 89.7, 55.8, 55.5, 38.0, 35.9, 31.4, 24.3; IR (neat, KBr, cm^{-1}) α–product: 2926, 2085, 2043, 2014, 1733, 1609; ^1H NMR α–product δ: 6.22 (m, 1H), 6.17 (s, 2H), 5.88 (m, 1H), 5.63 (s, 1H), 3.83 (s, 9H), 3.24 (m, 1H), 3.03 (m, 1H), 2.41 (m, 2H); $^{13}C\{^1H\}$ NMR α–product δ: 200.3, 160.4, 137.4, 128.4, 111.0, 101.0, 100.2, 91.2, 90.2, 55.5, 54.3, 38.5, 34.5, 27.3. MS EI *m/e*: for α– and γ–products: 544 (M^+), 516 (M^+ -1CO), 488 (M^+ -2CO), 460 (M^+ -3CO), 432 (M^+ –4CO), 404 (M^+-5CO), 376 (M^+-6CO). HRMS m/e for $C_{22}H_{18}Co_2O_9$ calcd (M^+) 543.9615, found 543.9609.

Hexacarbonyl[μ–η⁴–(5–allylcyclohept–1–en–3–yne)] dicobalt (Co–Co) (113γ) and Hexacarbonyl[μ–η⁴–(3– allylcyclohept–1–en–4–yne)] dicobalt (Co–Co) (112α)

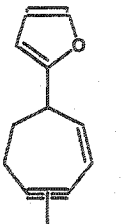


113γ 112α

The cycloheptenyne **66** (0.0817 g, 0.187 mmol), in dichloromethane (3.7 mL), was stirred with allyltrimethylsilane (0.0297 mL, 0.187 mmol) via **Procedure B**. Flash chromatography (25:1 petroleum ether: diethyl ether) resulted in the co–elution of **113γ** and **113α** (0.0782 g, 83%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 3015, 2926, 2854, 2089, 2046, 2017, 1641, 1582; ^1H NMR γ–product δ: 6.52 (d, *J* = 9.9, 1H), 5.95 (dd, *J* = 4.3, 9.9, 1H), 5.78 (m, 1H), 5.08 (m, 2H), 3.25 (m, 1H), 3.10 (m, 1H), 2.46 (m, 1H), 2.26 (m, 2H), 2.21 (m, 1H), 1.88 (m, 1H); ^1H NMR α–product δ (incomplete): 5.94 (m, 1H), 5.65 (m, 1H), 5.13 (m, 2H), 3.75

(m, 1H), 3.2 (m, 1H), 2.95 (m, 1H), 2.65 (m,1H), 2.40 (m, 1H); ^{13}C {^{1}H} α– and γ–mixture NMR δ: 200.1, 139.7, 136.3, 136.1, 131.5, 126.4, 117.2, 98.1, 87.5, 41.0, 40.6, 33.4, 30.3. MS EI m/e: 418 (M^+), 390 (M^+ -1CO), 362 (M^+ -2CO), 334 (M^+ -3CO), 306 (M^+-4CO), 278 (M^+ -5CO), 250 (M^+ -6CO).

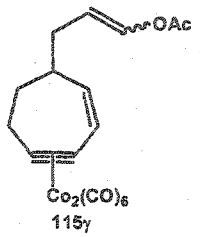
Hexacarbonyl[μ–η^4–(2–cyclohept–2–en–4–ynylfuran)] dicobalt (Co–Co) (114γ)



114γ

The cycloheptenyne **66** (0.0540 g, 0.124 mmol), in dichloromethane (2.5 mL), was stirred with furan (0.136 g, 0.186 mmol) via **Procedure B**. The crude product was purified by flash chromatography (100 % petroleum ether) to yield the **114γ** (0.0341 g, 62%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2927, 2089, 2048, 2017, 1622, 1428; ^{1}H NMR δ: 7.35 (d, *J* = 1.4, 1H), 6.71 (d, 9.9, 1H), 6.28 (dd, *J* = 1.8, 3.1, 1H), 6.15 (dd, *J* = 3.1, 9.9, 1H), 6.03 (d, *J* = 3.2, 1H), 3.89 (m, 1H), 3.17 (m, 1H), 2.98 (m, 1H), 2.23 (m, 1H), 2.08 (m, 1H); $^{13}C\{^{1}H\}$ NMR δ: 200.1, 156.0, 141.9, 133.9, 128.0, 110.3, 106.5, 98.3, 87.0, 41.4, 32.4, 30.3. MS EI m/e: 444 (M^+), 416 (M^+ -1CO), 388 (M^+ -2CO), 360 (M^+-3CO), 332 (M^+ -4CO), 304 (M^+ -5CO), 276 (M^+ -6CO).

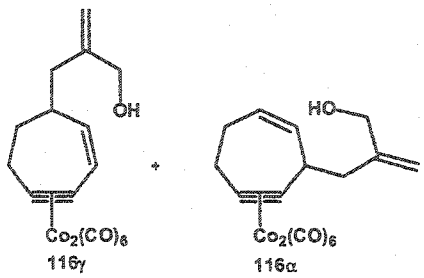
Hexacarbonyl[μ–η^4–(10–acetoxypropenyl–cycloheptˉ1–en–3–yne)] dicobalt (115γ)



115γ

The cycloheptenyne **66** (0.0524 g, 0.120 mmol), in dichloromethane (2.4 mL), was stirred with 1-trimethylsilylallylacetate (0.0384 g, 0.240 mmol) via **Procedure B**. The crude product was purified by flash chromatography (25:1 petroleum ether: diethyl ether) to yield the **115γ** (0.0349g, 65%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2926, 2089, 2047, 2016, 1760, 1673, 1217; ^{1}H NMR δ: 7.15 (d, *J* = 5.4, 1H), 6.54 (d, *J* = 9.9, 1H), 5.95 (m, 1H), 4.89 (m, 1H), 3.28 (m, 1H), 3.12 (m, 1H), 2.34 (m, 2H), 2.19 (m, 1H), 2.13 (s, 3H), 1.86 (m, 1H), 1.73 (m, 1H); ^{13}C{^{1}H} NMR δ: 200.1, 168.1, 139.3, 139.1, 126.9, 126.7, 112.3, 111.4, 98.3, 87.0, 41.3, 41.1, 20.9. MS EI m/e: 476 (M$^+$), 448 (M$^+$ -1CO), 420 (M$^+$ -2CO), 392 (M$^+$ -3CO), 364 (M$^+$ -4CO), 336 (M$^+$ -5CO), 308 (M$^+$ -6CO).

Hexacarbonyl[μ–η^4–(2–cyclohept–2–en–4–ynylmethyl–prop–2–en–1–ol)] dicobalt (Co–Co) (116γ) and Hexacarbonyl[μ–η^4–(2–cyclohept–2–ynyl–methyl–prop–2–en–1–ol)] dicobalt (Co–Co) (116α)

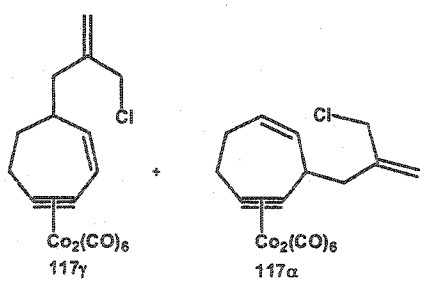


116γ 116α

The cycloheptenyne **66** (0.0776 g, 0.178 mmol), in dichloromethane (3.6 mL), was stirred with 2-(trimethylsilylmethyl)-2-propen-1-ol (0.0384 g, 0.267

mmol) via **Procedure B**. Flash chromatography (3:1 petroleum ether: diethyl ether) resulted in the isolation of **116**α and **116**γ (0.0607g, 76%) as a red–brown oil. IR (neat, KBr, cm^{-1}) γ–product 3354, 2923, 2086, 2047, 2021, 1608, 1435, 1384; ^{1}H NMR γ–product δ: 6.54 (d, *J* = 10.0, 1H), 5.96 (dd, *J* = 3.8, 9.9, 1H), 5.17 (s, 1H), 4.94 (s, 1H), 4.09 (s, 2H), 3.28 (m, 1H), 3.12 (m, 1H), 2.61 (m, 1H), 2.28 (m, 2H), 1.91 (m, 1H), 1.75 (m, 1H), 1.51 (s, 1H); $^{13}C\{^{1}H\}$ NMR γ–product δ: 200.0, 146.4, 139.5, 126.6, 112.5, 98.3, 87.8, 65.9, 39.7, 39.5, 33.5, 31.1. IR (neat, KBr, cm^{-1}) α–product 3385, 2925, 2088, 2046, 2016, 1608, 1506, 1093; ^{1}H NMR for the α–product δ: 5.95 (m, 1H), 5.67 (m, 1H), 5.23 (s, 1H), 5.05 (s, 1H), 4.18 (s, 2H), 3.92 (m, 1H), 3.24 (m, 1H), 3.01 (m, 1H), 2.35 (m, 4H), 1.59 (s, 1H);. MS EI m/e α– and γ–products: 448 (M^{+}), 420(M^{+} -1CO), 392 (M^{+} -2CO), 364 (M^{+} -3CO), 336 (M^{+} -4CO), 308 (M^{+} -5CO), 280 (M^{+} -6CO).

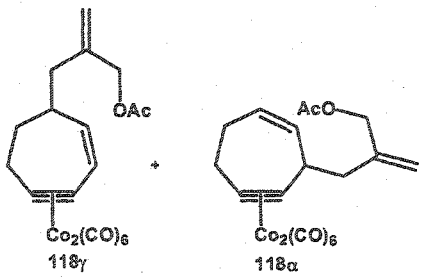
Hexacarbonyl[μ–η^4–(7-(2–chloromethylallyl)cyclohept-1-en-3-yne)] dicobalt (Co–Co) (117γ) and Hexacarbonyl[μ–η^4–(3-(2–chloromethylallyl)cyclohept-1-en-4-yne)] dicobalt (Co–Co) (117α)



The cycloheptenyne **66** (0.0477 g, 0.109 mmol), in dichloromethane (2.5mL), was stirred with 2-chloromethyl-3-trimethylsilyl-1-propene (0.030 mL, 0.164 mmol) via **Procedure B**. Flash chromatography (25:1 petroleum ether: diethyl ether) resulted in the co–elution of **117**γ and **117**α (0.0358 g, 70%) as a red–brown oil. IR (neat, KBr, cm^{-1}) α/γ–product: 2927, 2090, 2047, 2016, 2017, 1506, 1430; ^{1}H NMR γ–product δ: 6.55 (d, *J* = 11, 1H), 5.97 (m, 1H), 5.27 (s, 1H), 5.02 (s, 1H), 4.05 (s, 2H), 3.28 (m, 1H), 3.18 (m, 1H), 2.68 (m, 1H), 2.37 (m, 2H), 1.89 (m,1H), 1.87 (m, 1H); $^{13}C\{^{1}H\}$ NMR δ: 200.1, 142.7, 139.0, 126.9, 117.3,

96.3, 86.2, 48.2, 39.8, 38.7, 33.5, 30.3; ^{1}H NMR α–product δ: 5.97 (m, 1H), 5.75 (m, 1H), 5.31 (s, 1H), 5.14 (s, 1H), 4.13 (s, 2H), 3.26 (m, 2H), 3.14 (m, 1H), 2.45 (m, 1H), 2.33 (m, 2H), 1.71 (m, 1H); ^{13}C {^{1}H} NMR δ: 200.1, 135.7, 133.2, 117.1, 96.3, 86.2, 48.0, 40.3, 39.3, 34.3, 27.2, 26.2. MS EI m/e α– and γ–products: 466 (M^+), 438 (M^+ -1CO), 410 (M^+ -2CO), 382 (M^+ -3CO), 354 (M^+-4CO), 326 (M^+ -5CO), 298 (M^+ -6CO).

Hexacarbonyl[μ–η^4–(acetic acid 2-cyclohept-2-en-4-ynylmethylallyl ester)] dicobalt (Co–Co) (118γ) and Hexacarbonyl[μ–η^4–(acetic acid 2-cyclohept-2-en-6-ynylmethylallyl ester)] dicobalt (Co–Co) (118α)

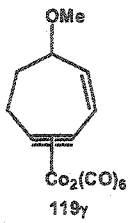


118γ 118α

The cycloheptenyne **66** (0.0653 g, 0.178 mmol), in dichloromethane (3.0 mL), was stirred with 2-(trimethylsiloxymethyl)allyltrimethylsilane (0.011 g, 0.225 mmol) via **Procedure B**. Flash chromatography (25:1 petroleum ether: diethyl ether) resulted in the isolation of **118α** and **118γ** (0.0628g, 75%) as a red–brown oil. IR (neat, KBr, cm^{-1}) γ–product: 2927, 2089, 2048, 2018, 1747, 1053; ^{1}H NMR γ–product δ: 6.54 (d, *J* = 10.0, 1H), 5.94 (dd, *J* = 4, 10, 1H), 5.18 (s, 1H), 5.01 (s, 1H), 4.55 (d, *J* = 13, 2H), 3.28 (m, 1H), 3.13 (m, 1H), 2.61 (m, 1H), 2.27 (m, 2H), 2.22 (s, 3H), 2.09 (m, 1H), 2.06 (m, 1H); ^{13}C{^{1}H} NMR γ–product δ: 200.1, 170.9, 156.3, 141.4, 139.1, 126.7, 115.6, 98.1, 87.6, 66.8, 39.9, 38.8, 33.4, 30.3. IR (neat, KBr, cm^{-1}) α–product 2928, 2090, 2048, 2018, 1740, 1026; ^{1}H NMR for the α–product δ: 5.91 (m, 1H), 5.65 (m, 1H), 5.23 (s, 1H), 5.12 (s, 1H), 4.63 (s, 2H), 3.87 (m, 1H), 3.27 (m, 1H), 3.22 (m, 1H), 2.71 (m, 1H), 2.33 (m, 2H), 2.28 (m, 1H), 2.11 (s, 3H); ^{13}C{^{1}H} NMR α–product δ: 200.1, 170.9, 141.5, 133.4, 131.7,

128.9, 96.7, 85.4, 72.6, 43.3, 39.3, 34.3, 30.5, 27.2. MS EI m/e α– and γ–products: 462 (M^+), 434(M^+ -1CO), 406 (M^+ -2CO), 378 (M^+ -3CO), 350 (M^+ -4CO), 322 (M^+ -5CO), 294 (M^+ -6CO).

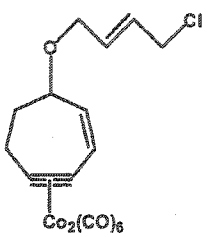
Hexacarbonyl[μ–η^4–(7–methoxy–cyclohept–1–en–3–yne)] dicobalt (Co–Co) (119γ)



119γ

The cycloheptenyne **66** (0.0623 g, 0.143 mmol), in dichloromethane (2.9 mL), was stirred with methanol (0.007 mL, 0.179 ml) via **Procedure B**. The crude product was purified by flash chromatography (10:1 petroleum ether: diethyl ether) to yield the **119γ** (0.0379 g, 65%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2923, 2090, 2048, 2017, 1615, 1430; ^{1}H NMR δ: 6.61 (d, *J* = 10.0, 1H), 6.17 (dd, *J* = 3.9, 10.0, 1H), 3.95 (m, 1H), 3.37 (s, 3H), 3.34 (m, 1H), 3.12 (m, 1H), 2.04 (m, 2H); ^{13}C{^{1}H} NMR δ: 199.7, 136.8, 127.5, 97.4, 86.3, 80.0, 56.5, 31.0, 30.3. MS EI m/e: 408 (M^+), 380 (M^+ -1CO), 352 (M^+ -2CO), 324 (M^+ -3CO), 296 (M^+ -4CO), 268 (M^+ -5CO), 240 (M^+ -6CO).

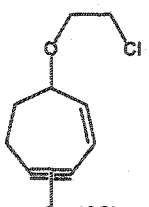
Hexacarbonyl[μ–η^4–(7-(4-chlorobut-2-enyloxy)-cyclohept–1–en–3–yne)] dicobalt (Co–Co) (120γ)



120γ

The cycloheptenyne **66** (0.0589 g, 0.135 mmol), in dichloromethane (2.7 mL), was stirred with 4-chloro-2-buten-1-ol (0.022 g, 0.203 mmol) via **Procedure B**. The crude product was purified by flash chromatography (25:1 petroleum ether: diethyl ether) to yield the **120**γ (0.044g, 68%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2925, 2091, 2051, 2021, 1457, 1054; ^1H NMR δ: 6.65 (d, *J* = 10, 1H), 6.15(dd, *J* = 4, 10, 1H), 5.76 (m, 2H), 4.18 (d, *J* = 6, 2H), 4.18 (d, *J* = 7, 3H), 3.34 (m, 1H), 3.12 (m, 1H), 2.04 (m, 2H); $^{13}C\{^1H\}$ NMR δ: 199.9, 136.3, 131.2, 128.3, 128.1, 97.3, 86.1, 70.1, 48.6, 41.1, 30.6, 30.8. MS EI m/e: 482 (M^+), 454 (M^+ -1CO), 426 (M^+ -2CO), 398 (M^+ -3CO), 370 (M^+ -4CO), 342 (M^+ -5CO), 314(M^+ -6CO).

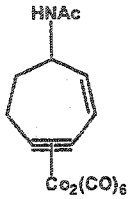
Hexacarbonyl[μ–η^4–(7–(2–chloroethoxy)–cyclohept–1–en–3–yne)] dicobalt (Co–Co) (121γ)



121γ

The cycloheptenyne **66** (0.0571 g, 0.117 mmol), in dichloromethane (2.3 mL), was stirred with 2-chloroethanol (0.0100 ml, 0.175 mmol) via **Procedure B**. The crude product was purified by flash chromatography (20:1 petroleum ether: diethyl ether) to yield the **121**γ (0.0315g, 59%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2927, 2856, 2091, 2050, 2021, 1612; ^1H NMR δ: 6.63 (d, *J* = 9.9, 1H), 6.16 (dd, *J* = 4.0, 10.0, 1H), 4.13 (m, 1H), 3.78 (m, 2H), 3.62 (t, *J* = 5.9, 2H), 3.36 (m, 1H), 3.14 (m, 1H), 2.06 (m, 2H); $^{13}C\{^1H\}$ NMR δ: 199.6, 136.1, 128.0, 97.3, 86.0, 79.0, 69.1, 43.2, 30.8, 14.3. MS EI m/e: 456 (M^+), 428 (M^+ -1CO), 400 (M^+ -2CO), 372 (M^+ -3CO), 344 (M^+ -4CO), 316 (M^+ -5CO), 288 (M^+ -6CO).

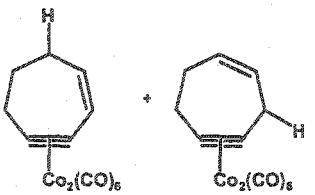
Hexacarbonyl[μ–η^4–(cyclohept–2–en–4–ynyl–acetamide)] dicobalt (Co–Co) (122γ)



122γ

Concentrated sulfuric acid was added dropwise (10 drops) to a solution of cycloheptenyne **66** (0.0481 g, 0.110 mmol) in acetonitrile (5 mL). After ten minutes the aqueous sodium bicarbonate was added and a typical workup proceeded. The crude reaction product was purified by flash chromatography (25:1 petroleum ether: diethyl ether) to yield the **122γ** (0.0360 g, 75%) as a red–brown oil. IR (neat, KBr, cm^{-1}) 2927, 2091, 2048, 2021, 1651, 1548, 1431; ^1H NMR δ: 6.59 (d, *J* = 10.1, 1H), 6.17 (dd, *J* = 3.8, 10.0, 1H), 4.05 (m, 1H), 3.35 (m, 1H), 3.11 (m, 1H), 2.04 (m, 2H), 1.31 (m, 1H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR δ: 199.9, 169.1, 135.0, 128.6, 97.3, 85.6, 50.7, 49.9, 31.2, 23.6. MS EI m/e: 436 (M^+), 408 (M^+ -1CO), 380 (M^+ -2CO), 352 (M^+ -3CO), 324 (M^+ -4CO), 296 (M^+ -5CO), 268 (M^+ -6CO).

Hexacarbonyl[μ–η^4–(cyclohept–1–en–3–yne)] dicobalt (Co–Co) (123γ) and Hexacarbonyl[μ–η^4–(cyclohept–1–en–4–yne)] dicobalt (Co–Co) (123α)

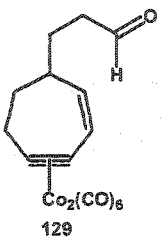


123γ 123α

The cycloheptenyne **66** (0.0500 g, 0.115 mmol), in dichloromethane (2.3 mL), was stirred with triethylsilane (0.0200 g, 0.173 mmol) via **Procedure B**. After flash chromatography (100% petroleum ether) **123α** and **123γ** could not be

separated (0.0235g, 54%). IR (neat, KBr, cm^{-1}) for α– and γ–product: 2928, 2089, 2046, 2016, 1581, 1385; ^1H NMR γ–product δ: 6.54 (d, *J* = 9.7, 1H), 6.10 (m, 1H), 3.20 (t, *J* = 5.6, 2H), 2.41 (m, 2H), 1.87 (m, 2H); $^{13}C\{^1H\}$ NMR γ–product δ: 199.7, 135.3, 127.3, 98.1, 89.6, 35.9, 31.1, 25.1; ^1H NMR α–product δ: 5.97 (m, 1H), 5.88 (m, 1H), 3.10 (m, 2H), 2.41 (m, 2H), 2.33 (m, 2H); $^{13}C\{^1H\}$ NMR α–product δ: 199.7, 130.2, 132.4, 98.1, 89.6, 34.5, 33.6, 27.2. MS EI m/e: 378 (M^+), 350 (M^+ -1CO), 322 (M^+ -2CO), 294 (M^+ -3CO), 266 (M^+ -4CO), 238 (M^+ -5CO), 210 (M^+ -6CO).

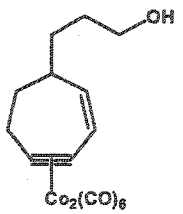
Hexacarbonyl[μ–η^4–(3–cyclohept–2–en–4–ynylpropanol)] dicobalt (Co–Co) (129)



129

DIBALH (2.3 mL, 1.5 M in toluene, 2.3 mmol) was added over 1 h to a solution containing compound **115**γ (0.100 g, 0.230 mmol) in diethyl ether (11.5 mL) at -78°C. 1M HCl was added with the -78°C solution, 15 min after the DIBALH addition. The solution was then warmed up to room temperature. A typical work up was done and the crude product was purified by flash chromatography (3:1 diethyl ether: petroleum ether) to yield the **129** (0.0500 g, 50%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2926, 2854, 2720, 2090, 2023, 1727, 1581; ^1H NMR δ: 9.8 (s, 1H), 6.57 (d, *J* = 9.9, 1H), 5.93 (dd, *J* = 4.6, 9.9, 1H), 3.27 (m, 1H), 3.26 (m, 1H), 2.55 (m, 2H), 2.46 (m, 1H), 1.54 (m, 4H); $^{13}C\{^1H\}$ NMR δ: 201.9, 200.1, 138.6, 127.3, 98.0, 87.5, 41.4, 40.4, 33.0, 32.2, 27.3. MS EI m/e: 434 (M^+), 406 (M^+ -1CO), 378 (M^+ -2CO), 350 (M^+ -3CO), 322 (M^+ -4CO), 294 (M^+-5CO), 266 (M^+ -6CO).

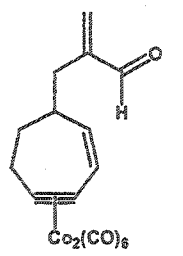
Hexacarbonyl[μ–η⁴–(3–cyclohept–2–en–4–ynyl–propan–1–ol)] dicobalt (Co–Co) (130)



130

Compound **129** (0.030 g, 0.0689 mmol) in dichloromethane (1.5 mL) was stirred with triethylsilane (0.016 mL, 0.138 mmol). Boron trifluoride diethyl etherate (0.039 g, 0.345 mmol) was then added over 30 min in dichloromethane (1 mL). The reaction was stirred for 4 h and sodium bicarbonate was then added. A typical work up was done and the crude product was purified by flash chromatography (3:1 diethyl ether: petroleum ether) to yield the **130** (0.014 g, 45%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 3355, 2926, 2855, 2089, 2048, 2019, 1581, 1384, 1056; ^{1}H NMR δ: 6.53 (d, J = 9.8, 1H), 6.01 (dd, J = 4.7, 9.8, 1H), 3.67 (m, 2H), 3.23 (m, 1H), 3.14 (m, 1H), 2.48 (m, 1H), 1.83 (m, 3H), 1.69 (m, 2H), 1.54 (m, 1H), 0.95 (m, 1H); $^{13}C\{^{1}H\}$ NMR δ: 200.2, 140.0, 128.8, 98.4, 87.9, 63.2, 40.9, 33.0, 32.1, 30.3, 28.1. MS EI m/e: 436 (M^+), 408 (M^+ -1CO), 380 (M^+ -2CO), 352 (M^+ -3CO), 324 (M^+ -4CO), 296 (M^+-5CO), 268 (M^+ -6CO).

Hexacarbonyl[μ–η⁴–(2–cyclohept–2–en–4–ynylmethyl-propenal)] dicobalt (Co–Co) (135)



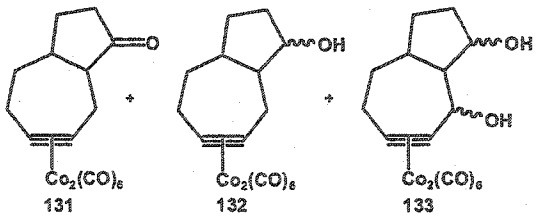
135

Manganese dioxide (0.0233g, 0.268mmol) was added to a solution containing compound **116**γ (0.060 g, 0.134 mmol) in dichloromethane (2 mL) at

RT. The reaction was stirred for 8 h; the manganese dioxide was filtered off through Celite® and the crude product was concentrated under reduced pressure. The crude product was purified by flash chromatography (3:1 diethyl ether: petroleum ether) to yield the **135** (0.006 g, 10%) as a red–brown oil. IR (neat, KBr, cm^{-1}): 2925, 2091, 2047, 2017, 1523, 1262; ^1H NMR δ: 9.58 (s, 1H), 6.53 (d, *J* = 10, 1H), 6.30 (s, 1H), 5.90 (s, 1H), 5.88 (dd, *J* = 4.0, 10, 1H), 4.23 (m, 1H), 3.31 (m, 1H), 3.13 (m, 1H), 2.40 (m, 2H), 1.28 (m, 2H); MS EI m/e: 446 (M^+), 418 (M^+ -1CO), 390 (M^+ -2CO), 362 (M^+ -3CO), 334 (M^+ -4CO), 306 (M^+-5CO), 278 (M^+ -6CO).

4.4 Procedure C: 7, 5–Bicyclic Ring Formation

Synthesis of Compounds 131,132 and 133



131 132 133

A solution of boron trifluoride diethyl etherate (0.0142 g, 0.124 mmol) in dichloromethane (1 mL) was added to compound **129** (0.0414 g, 0.0954 mmol) in dichloromethane (9 mL) at 0°C. The solution was stirred for 2 h and aqueous sodium bicarbonate was then added. A conventional workup was performed and crude product was purified by flash chromatography (5:1 petroleum ether: diethyl ether) to yield three products: compound **131** (0.0211 g, 51%) compound **132** (0.0046 g, 11%) compound **133** (0.0047 g, 11%) as red–brown oils. IR (neat, KBr, cm^{-1}) for compound **131**: 2924, 2853, 2090, 2048, 2027, 1742, 1600; ^1H NMR for compound **131**δ: 3.62 (m, 1H), 3.27 (m, 1H), 2.86 (m, 1H), 2.38 (m, 1H), 2.20 (m, 3H), 2.0 (dt, *J* = 4.0, 11.0, 11.0, 1H), 1.85 (m, 1H), 1.63 (m, 2H), 0.88 (m, 1H); $^{13}C\{^1H\}$ NMR for compound **131** δ: 218.7, 199.6, 100.0, 97.0, 57.2, 46.9, 36.7, 36.3, 35.0, 33.0, 14.3. MS EI m/e for compound **131**: 434 (M^+), 406 (M^+ -1CO), 378 (M^+ -2CO), 350 (M^+ -3CO), 322 (M^+ -4CO), 294 (M^+ -5CO), 266 (M^+-

6CO). IR (neat, KBr, cm^{-1}) for compound **132**: 3354, 2925, 2090, 2050, 2020, 1456, 1084; ^1H NMR for compound **132** δ: 4.30 (d, *J* = 2.0, 1H), 3.17 (m, 2H), 3.12 (m, 1H), 3.02 (m, 1H), 2.91 (m, 1H), 2.49 (m, 1H), 2.38 (m, 1H), 2.15 (m, 2H), 2.03 (m, 2H), 1.93 (m, 1H), 1.87 (m, 1H). MS EI m/e for compound **132**: 436 (M^+) 408 (M^+ -1CO), 380 (M^+-2CO), 352 (M^+-3CO), 324 (M^+-4CO), 296 (M^+ -5CO), 268 (M^+ -6CO). IR (neat, KBr, cm^{-1}) for compound **133**: 3441, 2925, 2855, 2360, 2342, 2091, 2049, 2025, 1593; ^1H NMR for compound **133** δ: 5.44 (s, 1H), 4.63 (s, 1H), 4.06 (s, 1H), 3.27 (m, 1H), 2.92 (m, 1H), 2.63 (s, 1H), 2.37 (m, 2H), 2.11 (m, 2H), 1.87 (m, 2H), 1.77 (m, 1H). MS EI m/e for compound **133**: 452 (M^+) 424 (M^+ -1CO), 396 (M^+ -2CO), 368 (M^+ -3CO), 340 (M^+ -4CO), 312 (M^+ -5CO), 284 (M^+ -6CO).

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