



Development of rhodium and cobalt catalyzed cycloadditions  
by David B Belanger

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in  
Chemistry

Montana State University

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Abstract:

Initial studies on the asymmetric Rh-catalyzed [4+2] cycloaddition using cationic rhodium complexes have shown that the nature of the counterion can dramatically affect the rate of cyclization. This discovery is expected to lead to catalyst systems with improved selectivity and efficiency. The first examples of a  $\text{Co}_2(\text{CO})_8$ -catalyzed carbonylative cyclization of allenynes have been discovered. In most cases, product selectivities and yields can be improved by altering alkyne substitution. A novel rhodium-catalyzed carbonylative cyclization of allenynes at 1 atm of CO has been discovered. A novel rhodium-catalyzed cycloisomerization of allenynes has been discovered. An improved method for the catalytic photopromoted intramolecular Pauson-Khand reaction has been developed. It was discovered that careful control of the internal reaction temperature allows for efficient catalysis without photochemical activation. Additional studies on the substrate-based control of diastereoselectivity in the catalytic Pauson-Khand reaction have also been described. The development of an alternative precatalyst for the Pauson-Khand reaction has been described. This novel catalyst offers several advantages over traditional catalyst for the Pauson-Khand reaction as it is easily prepared and is stable in air.

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by

David B. Belanger

A thesis submitted in partial fulfillment  
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY  
Bozeman, Montana

November 1999

APPROVAL

D378  
B4124

of a thesis submitted by

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This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style and consistency, and is ready for submission to the College of Graduate Studies.

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## ACKNOWLEDGMENTS

I would like to thank Professor Tom Livinghouse for the opportunity to develop my skills under his advisement. I also thank Tom for his enthusiastic support of this work and for the occasional use of the "Iron Fist". I thank the Chemistry Department office staff, particularly Mary McLaughlin and Carol Thurston, for their help during my stay at MSU. I acknowledge Drs. Joe Seárs and Scott Busse for their work obtaining relevant analytical data. I would like to thank the talented individuals in the Livinghouse group that have positively affected this work. Special thanks to Brad Wolfe for reviewing the main chapters of this thesis. I thank the "truckdrivin' neighbor downstairs", Todd Meyer, for his invaluable assistance in the late stages of this endeavor. I thank Drs. Brian Pagenkopf and Donogh O'Mahony for their contribution to the science that is described in this dissertation. Special thanks to Dr. Donogh O'Mahony for his guidance and for teaching me how to find (and remove) the "yellow band of misery". Lastly, I thank my family for their boundless generosity and love. I dedicate this accomplishment to them.

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**ABSTRACT**

Initial studies on the asymmetric Rh-catalyzed [4+2] cycloaddition using *cationic* rhodium complexes have shown that the nature of the counterion can dramatically affect the rate of cyclization. This discovery is expected to lead to catalyst systems with improved selectivity and efficiency. The first examples of a  $\text{Co}_2(\text{CO})_8$ -catalyzed carbonylative cyclization of allenynes have been discovered. In most cases, product selectivities and yields can be improved by altering alkyne substitution. A novel rhodium-catalyzed carbonylative cyclization of allenynes at 1 atm of CO has been discovered. A novel rhodium-catalyzed cycloisomerization of allenynes has been discovered. An improved method for the catalytic photopromoted intramolecular Pauson-Khand reaction has been developed. It was discovered that careful control of the internal reaction temperature allows for efficient catalysis without photochemical activation. Additional studies on the substrate-based control of diastereoselectivity in the catalytic Pauson-Khand reaction have also been described. The development of an alternative precatalyst for the Pauson-Khand reaction has been described. This novel catalyst offers several advantages over traditional catalyst for the Pauson-Khand reaction as it is easily prepared and is stable in air.

## 1. INTRODUCTION

This dissertation describes the development of metal catalyzed syntheses of hetero- and carbocyclic molecules. Though the rhodium-catalyzed cycloisomerization, catalytic Pauson-Khand reaction and other related Co- and Rh-catalyzed carbonylative cyclization reactions are believed to proceed through discreet intermediates, the reactions are regarded as cycloaddition reactions.<sup>1</sup> The use of the word cycloaddition is not meant to imply a concerted reaction mechanism, but is merely used as a description of the product bond connectivity.

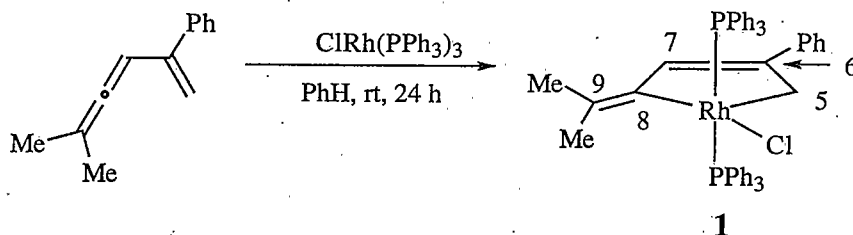
The Background Section contains a brief survey of other metal-catalyzed cycloaddition reactions that are related to the research detailed in this dissertation. The increased interest in metal-catalyzed cycloadditions is evident if one observes that most of the research described in this section has occurred within the last five years. While significant effort has been made to include all relevant chemistry, the rate of new discoveries in this area will almost surely make the review obsolete in a short time.

The Results and Discussion Section describes the original discoveries that have been made. In some cases, the contributions of others are presented to more clearly demonstrate the current scope and limitations of the described chemistry.

## 2. BACKGROUND

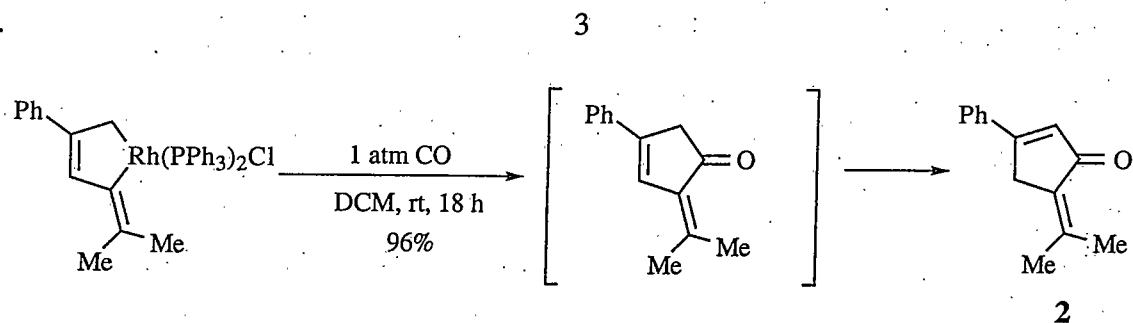
### 2.1 Rhodium-Catalyzed [4+1] Cycloadditions

Few methods for the formal [4+1] cycloaddition exist despite its potential for the construction of cyclopentenones.<sup>1</sup> Ito has shown that  $\text{ClRh}(\text{PPh}_3)_3$  oxidatively adds to vinylallenes. The *pentacoordinate*, distorted octahedral Rh complex **1**, characterized by X-ray crystallography, has a unique structure as the rhodacyclopentene ring is almost planar (Scheme 2.1).<sup>2b,d</sup> Bond lengths for C6-C7 and C8-C9 were determined to be 1.33 Å



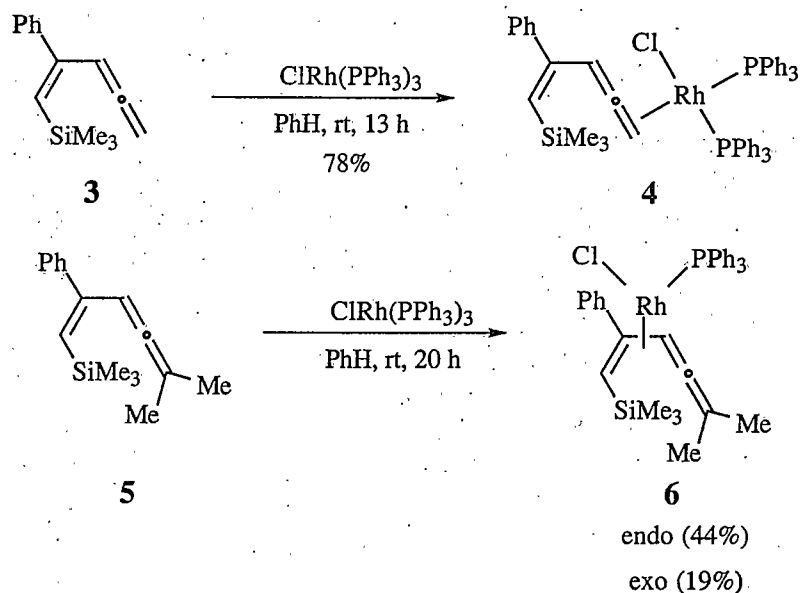
Scheme 2.1

and 1.36 Å, respectively. This suggests that no bonding is occurring between either olefin  $\pi$ -orbital and the Rh center (average bond length for a non-ligated olefin = 1.34 Å). Most notably, the C5-Rh and C8-Rh bond lengths were determined to be identical (2.05 Å), and similar to an  $\text{sp}^3$  carbon-rhodium bond (2.02 Å). The bonding characteristics of the two carbon-rhodium bonds suggest that subsequent reactions are possible. Indeed, treatment of the novel rhodium complex with CO formed the  $\alpha$ -isopropylidene cyclopentenone **2** after isomerization (Scheme 2.2).



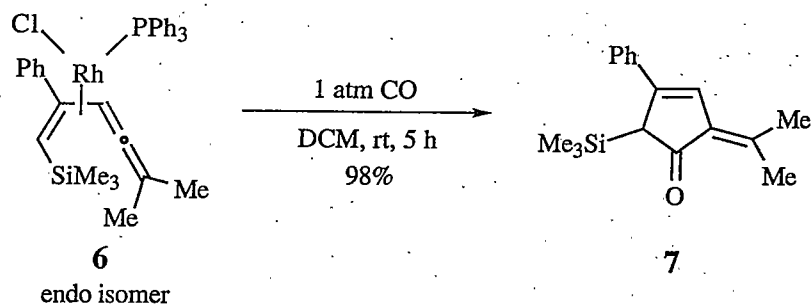
**Scheme 2.2**

It is also observed that sterically dissimilar vinylallenes ligate to  $\text{ClRh}(\text{PPh}_3)_3$  differently. While the terminally unsubstituted allene **3** ligated rhodium via  $\eta^2$ -



**Scheme 2.3**

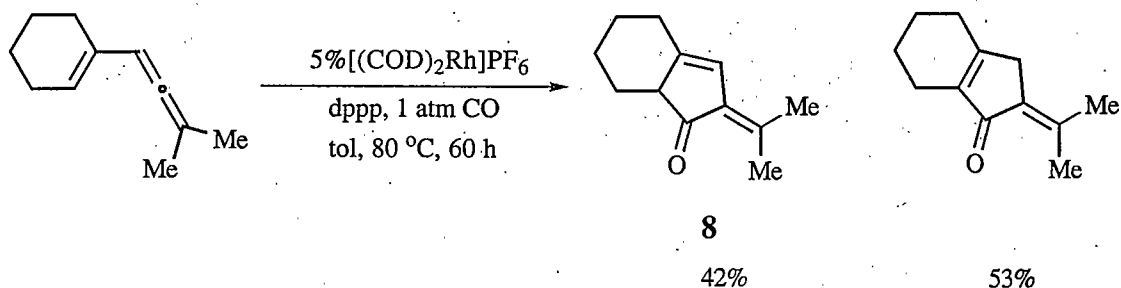
coordination, a related allene **5** bearing dimethyl-substitution ligated in an  $\eta^4$  fashion (Scheme 2.3).<sup>2a</sup> Presumably, the sterically encumbered vinyl silane moiety inhibits formation of the rhodacyclopentene. Treatment of the  $\eta^4$ -bound vinylallene rhodium complex **6** with CO led to the  $\alpha$ -isopropylidene cyclopentenone **7** in nearly quantitative



Scheme 2.4

yield (Scheme 2.4). In contrast, the  $\eta^2$ -ligated vinylallene rhodium complex 4 was unreactive under analogous conditions.

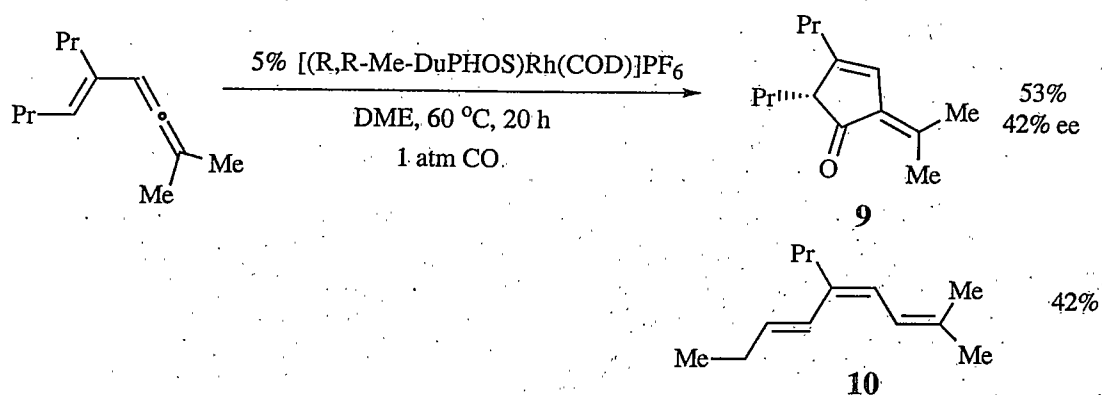
Through the elegant structural studies of vinylallene rhodium complexes, a novel catalytic [4+1] cycloaddition was discovered. Treatment of vinylallenes with Wilkinson's catalyst under 1 atm of CO afforded bicyclopentenones in good yields, though the primary



Scheme 2.5

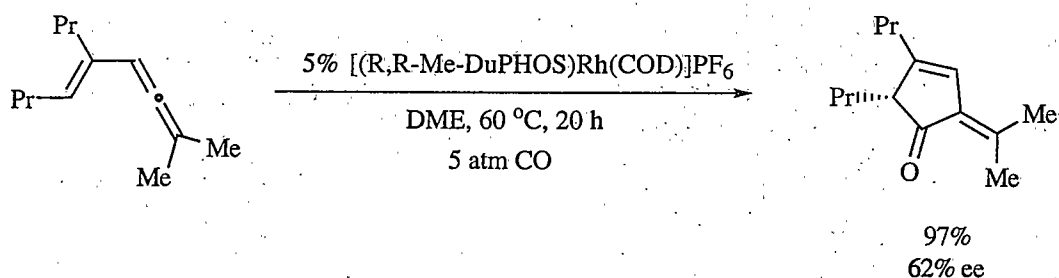
product 8 underwent significant isomerization using these reaction conditions (Scheme 2.5).<sup>2a</sup>

The enantioselective Rh-catalyzed [4+1] cycloaddition was recently described by Ito. Treatment of vinylallene with 5 mol % [(COD)Rh(R,R-Me-DuPHOS)]PF<sub>6</sub> under 1 atm CO afforded  $\alpha$ -isopropylidene cyclopentenone 9 in 53% yield and 42% ee (Scheme 2.6).<sup>2c</sup> The modest yield resulted from formation of an undesired triene 10, presumably



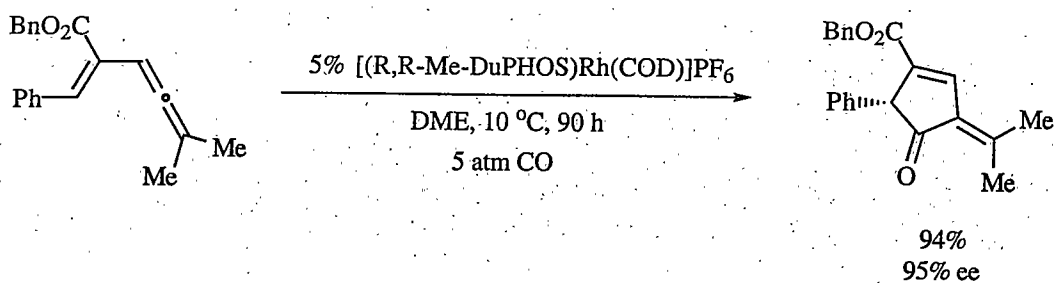
Scheme 2.6

arising through a competing  $\beta$ -hydride elimination/reductive elimination pathway. At higher CO pressures (5 atm), the yield of the expected cyclopentenone **9** was significantly improved. Interestingly, a modest improvement in asymmetric induction was observed at 5



Scheme 2.7

atm of CO (65% ee) (Scheme 2.7).<sup>2c</sup> Further increases in the CO pressure did not have a notable effect on the level of enantioselection. Carbonylative cyclization of several vinylallene substrates was performed using these conditions affording products with good

**Scheme 2.8**

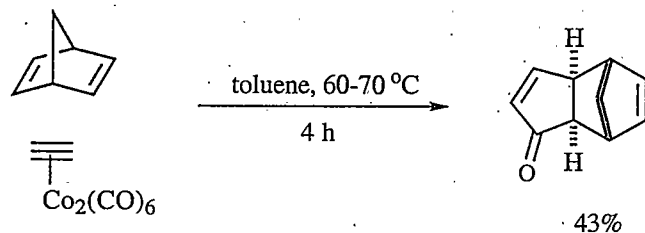
enantiomeric excess. The level of asymmetric induction was dramatically enhanced by judicious placement of an ester functional group (**Scheme 2.8**).<sup>2c</sup> These ester-modified vinylallenes appear to be more reactive demonstrated by efficient [4+1] cycloaddition at temperatures as low as 10 °C.



## 2.2 Transition Metal-Catalyzed [2+2+1] Cycloadditions

### 2.2.a Stoichiometric Pauson-Khand Reaction

Arguably, the most impressive aspect of transition-metal chemistry is the ability to promote C-C bond forming reactions which would otherwise be virtually impossible. The cobalt-mediated [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide, introduced by Khand and Pauson in 1973, is representative of the power of such metal-mediated reactions. The method introduced by Pauson required heating alkyne-cobalt

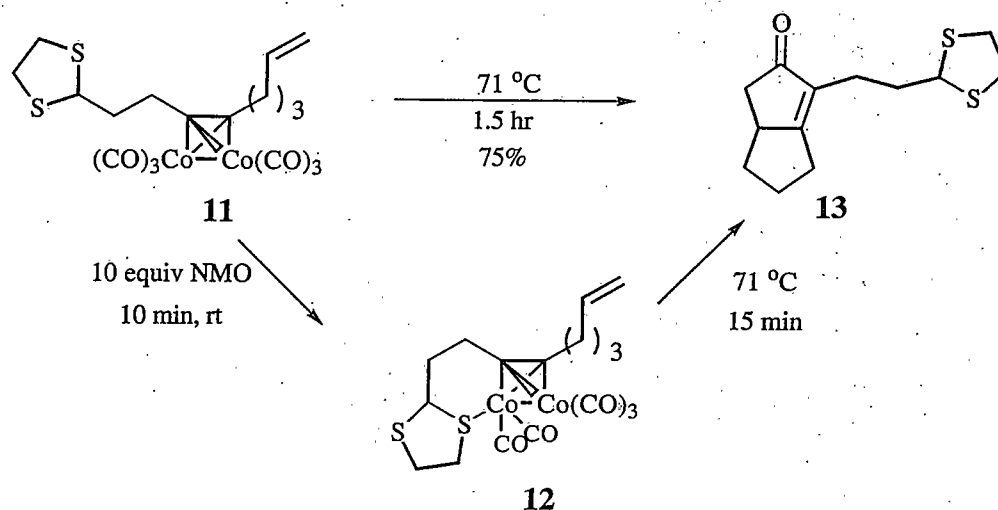


**Scheme 2.9**

complexes with reactive olefins under an atmosphere of dinitrogen (**Scheme 2.9**).<sup>3a</sup> Toluene-tetracobaltnonacarbonyl was the only other product isolated from this reaction (22%). Since this seminal discovery, the stoichiometric Pauson-Khand reaction has been well-defined in scope and both the inter- and intramolecular variations are known. The long-standing interest in the PKR has led to several comprehensive reviews.<sup>4</sup>

Despite the intensive study of the Pauson-Khand reaction, very little is known about the reaction mechanism.<sup>4e</sup> Aside from the initial formation of the alkyne- $\text{Co}_2(\text{CO})_6$  complex, few of the intermediate complexes have either been isolated or observed experimentally. In 1993, Krafft found that treatment of certain enyne-cobalt complexes **11**

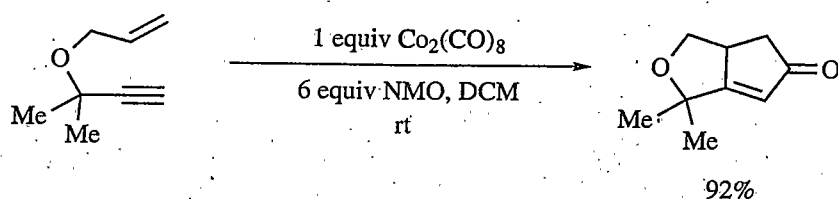
with excess *N*-methyl morpholine *N*-oxide (*vide infra*) afforded isolable complexes **12** in which one of the CO ligands was replaced by a sulfur-cobalt bond (Scheme 2.10).<sup>5</sup>



Scheme 2.10

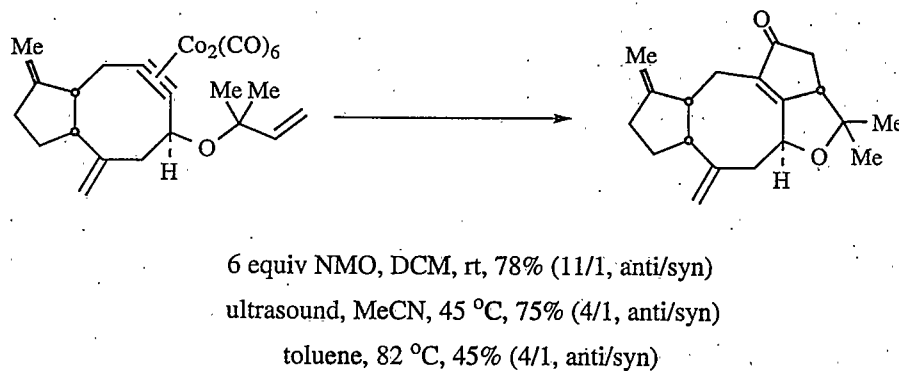
Warming a solution of complex **12** produced the desired pentalenone **13** in only 15 minutes (yield was not reported). In comparison, the corresponding enyne cobalt complex **11** required heating for 1.5 hours to form the same pentalenone **13** (75% yield) (Scheme 2.10). This result suggests that initial loss of carbon monoxide from the enyne-hexacarbonylcobalt complex **11** and subsequent coordination of the pendant olefin provides an intermediate structure that may lie on the mechanistic pathway that leads to product formation.

Though details of the reaction mechanism remain unclear, several groups have introduced procedural modifications that facilitate the stoichiometric Pauson-Khand reaction. In 1990, Schreiber disclosed that excess *N*-methyl morpholine *N*-oxide had a



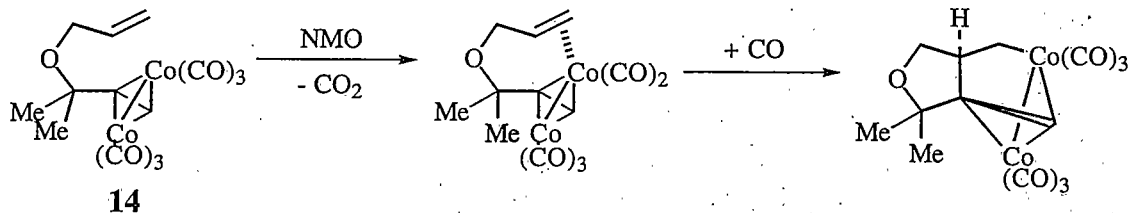
Scheme 2.11

significant rate-accelerating effect on the reaction.<sup>6</sup> Good yields of bicyclopentenones were isolated using this room temperature procedure (Scheme 2.11). These considerably milder conditions offered improved selectivities when compared to other known methods of that time (Scheme 2.12). It had been known since 1959<sup>7</sup> that pyridine-*N*-oxide



Scheme 2.12

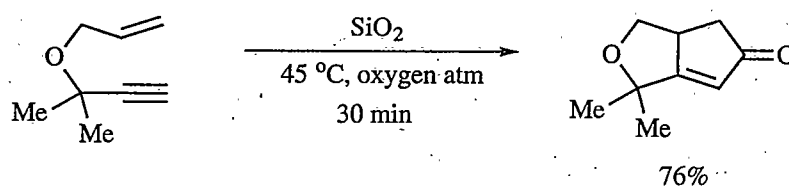
facilitated the removal of CO from metal carbonyl complexes (e.g.,  $\text{Fe}(\text{CO})_5$ ), but Schreiber's method is the first example applied to the formation of C-C bonds. Presumably, oxidative decomplexation of CO from the enyne cobalt complex 14 allows



Scheme 2.13

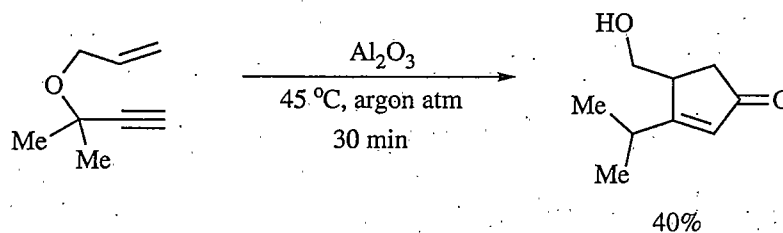
olefin coordination and subsequent oxidative cyclization (**Scheme 2.13**). It is not clear, however, whether NMO has a rate accelerating effect on bond forming events subsequent to olefin coordination.

Another effective method for the promotion of the stoichiometric Pauson-Khand reaction was introduced by Smit and Caple. It was found that adsorption of ether-linked enynes onto silica gel, followed by evaporation of solvent and heating the dry silica gel



**Scheme 2.14**

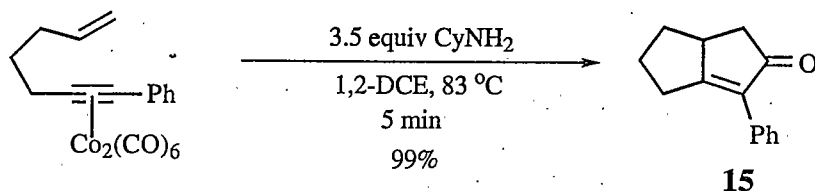
under a slow stream of air led to bicyclopentenones in modest to good yields (**Scheme 2.14**).<sup>8</sup> While the reason for the improved yields using this method is not entirely evident, one possible explanation is that the conformation of the enyne substrate bound to silica gel is positioned so that the reactive ends are in closer proximity. This manifestation of the reactive rotamer effect appears to be limited to ether-derived enyne substrates. Interestingly, a similar protocol performed on alumina under an argon atmosphere afforded hydroxymethyl cyclopentenones (**Scheme 2.15**).<sup>8</sup> While the mechanistic origin of these



**Scheme 2.15**

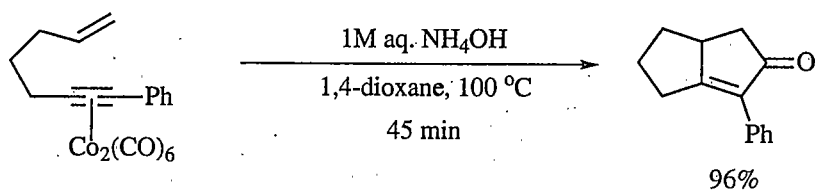
compounds is uncertain, the ease with which the propargyl C-O bond is ruptured is notable as this substrate class often gives reduced yields in the PKR relative to structurally related analogs.<sup>82</sup>

Recently, certain amines have been used to facilitate the stoichiometric Pauson-Khand reaction. Sugihara discovered that heating enyne cobalt complexes with cyclohexylamine (3.5 to 6 equiv) rapidly afforded bicyclopentenones in excellent yield (Scheme 2.16).<sup>9</sup> Without the amine additive, the reaction required 10 hours for complete



**Scheme 2.16**

consumption of starting material and afforded the pentalenone **15** in reduced yield (62%). Sugihara also found that 2M aqueous NH<sub>4</sub>OH in 1,4-dioxane (1:3 v/v; dioxane/aq NH<sub>4</sub>OH) had a similar rate-accelerating effect though a slightly higher reaction temperature was required (Scheme 2.17).<sup>9</sup> This is the first example of a Pauson-Khand reaction using water as co-solvent.<sup>10</sup> Several intra- and intermolecular Pauson-Khand reactions



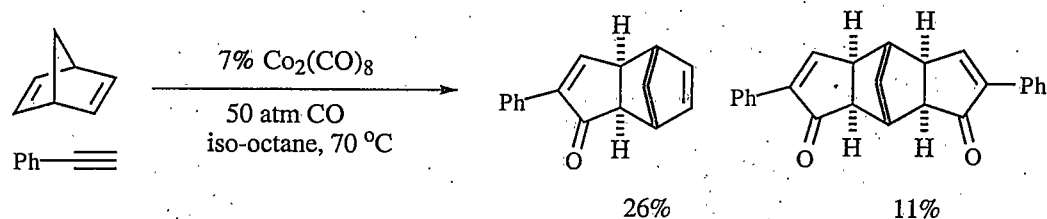
**Scheme 2.17**

were successfully performed using the procedures developed by Sugihara. While the exact role of the amine remains to be determined, Sugihara suggests that coordinated

cyclohexylamine may facilitate the dissociation of CO and, in turn, promote subsequent ligand substitution reactions. A similar amine-induced rate-accelerating effect has been observed in the ligand substitution chemistry of  $\text{Mo}(\text{CO})_5(\text{amine})$  complexes.<sup>11</sup>

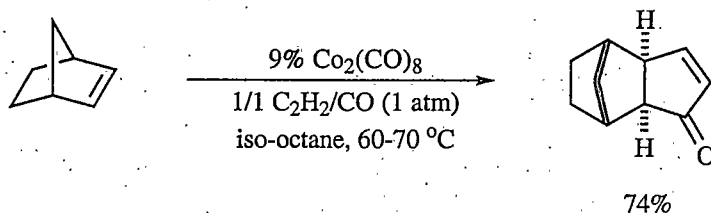
### 2.2.b Catalytic Pauson-Khand Reaction

Since the discovery of the Pauson-Khand reaction over 25 years ago, only scattered reports of a catalytic variation of the reaction have appeared. This is quite surprising considering that Pauson initially disclosed that catalytic  $\text{Co}_2(\text{CO})_8$  was able to achieve



**Scheme 2.18**

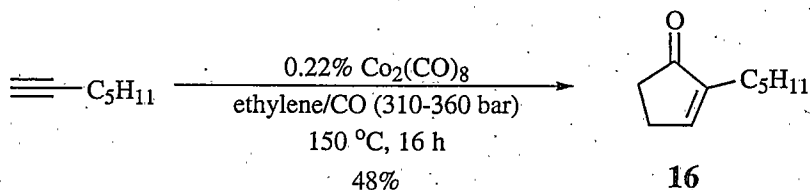
cyclopentenone formation (Scheme 2.18).<sup>3b</sup> While the intermolecular PKR involving a monosubstituted alkyne required elevated CO pressure (50 atm), the use of a gaseous



**Scheme 2.19**

alkyne, such as acetylene, allowed for product formation in good yield at *only 1 atm of CO* (Scheme 2.19).<sup>3b</sup> The inherent instability of  $\text{Co}_2(\text{CO})_8$  may reflect, in part, why general catalytic methods have remained elusive until very recently.

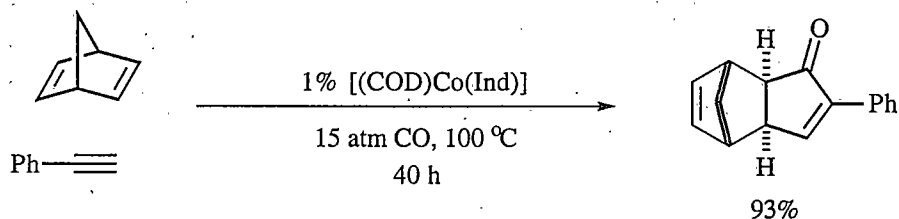
In 1990, Rautenstrauch demonstrated that catalytic  $\text{Co}_2(\text{CO})_8$  was effective for the formal [2+2+1] cycloaddition of *n*-heptyne, ethylene and CO under very high pressures of CO and ethylene (initial partial pressures of ethylene and CO at rt were 40 and 100 bar, respectively; total pressure at 150 °C was ca. 310-360 bar) (Scheme 2.20).<sup>12</sup> Although



**Scheme 2.20**

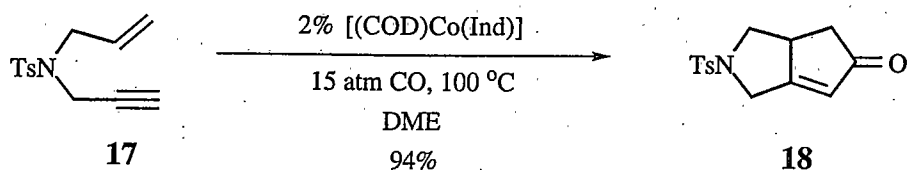
the desired cyclopentenone **16** was obtained in modest yield, this example demonstrates that only catalytic  $\text{Co}_2(\text{CO})_8$  could be used for the Pauson-Khand reaction of alkynes and *unstrained* alkenes. Unfortunately, Rautenstrauch found that the method was somewhat irreproducible.<sup>12</sup>

Subsequently, Jeong reported that  $(\text{COD})\text{Co}(\text{Ind})$  was a very effective catalyst for the intermolecular Pauson-Khand reaction of strained olefins and terminal alkynes (Scheme 2.21).<sup>13</sup> The intermolecular PKR of norbornadiene with nonterminal alkynes



**Scheme 2.21**

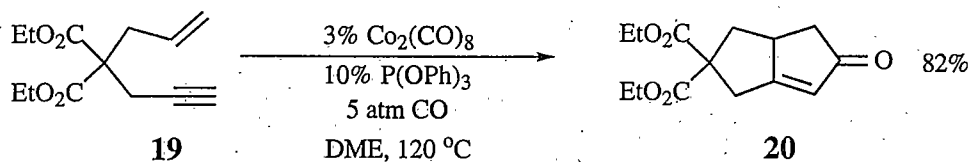
led to markedly reduced yields. In contrast, the enyne **17** bearing a terminal alkyne afforded excellent yield of bicyclopentenone **18** using (COD)Co(Ind) as catalyst precursor (Scheme 2.22).<sup>13</sup> Interestingly, complexes CpCo(CO)<sub>2</sub> and CpCo(COD) failed to



**Scheme 2.22**

promote bicyclopentenone formation suggesting that  $\eta^5$  to  $\eta^3$  ring slippage of the indenyl ligand in [(COD)Co(Ind)] may be necessary for catalytic activity. It is not clear whether Co<sub>2</sub>(CO)<sub>8</sub> is formed under the reaction conditions or if a mononuclear cobalt species is the active catalyst. Nevertheless, the development of the first reasonably general catalytic PKR is an important milestone in the long history of this reaction. Though [(COD)Co(Ind)] is described as moderately air-stable, its synthesis requires several steps and is low yielding.<sup>14</sup> In addition, this method may not be attractive to practicing synthetic chemists as it is effective only at very high CO pressures (15 atm).

A more practical method using Co<sub>2</sub>(CO)<sub>8</sub> for the catalytic Pauson-Khand reaction was subsequently developed by Jeong. It was discovered that the addition of a coligand, (P(OPh)<sub>3</sub>), increased the catalytic turnover to acceptable levels. Specifically, treatment of substrate **19** with Co<sub>2</sub>(CO)<sub>8</sub>, followed by addition of triphenyl phosphite, then heating allowed for the formation of bicyclopentenone **20** in good yield (Scheme 2.23).<sup>15</sup> Jeong

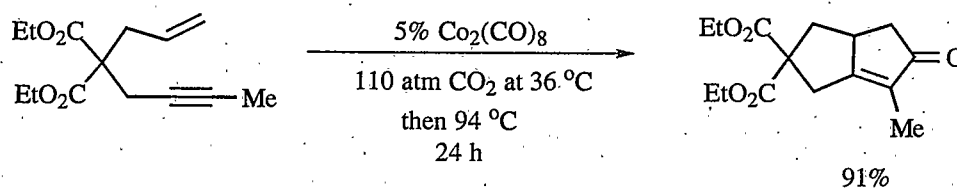


**Scheme 2.23**





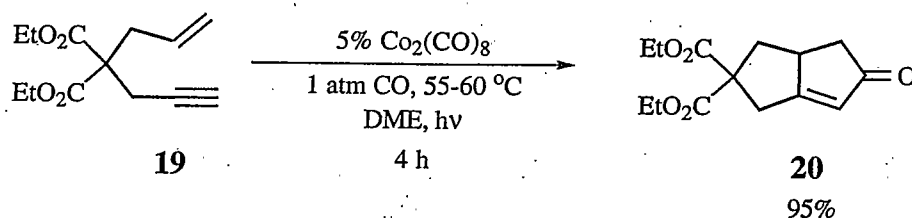
Jeong has recently reported that supercritical CO<sub>2</sub> (Sc CO<sub>2</sub>) is a useful medium for the catalytic Pauson-Khand reaction. The perceived advantages of Sc CO<sub>2</sub> are the ease of product isolation, catalyst separation and recovery, the ability to remove and recycle the solvent (CO<sub>2</sub>) and the increased solubility of carbon monoxide. Optimal conditions required initial pressurization with carbon monoxide (30 atm at room temperature), subsequent pressurization with CO<sub>2</sub> (110-120 atm at ca. 38 °C) and then heating at 90 °C for 24 hours. A homogeneous supercritical phase was achieved at 40 °C. Modest to



**Scheme 2.26**

excellent yields of bicyclopentenones were achieved using this procedure (**Scheme 2.26**).<sup>17</sup> One shortcoming of this method is the potential solubility problems of certain substrates in neat Sc CO<sub>2</sub>. Jeong noted that several substrates were found to be unreactive towards carbonylative cyclization due to this limitation.<sup>17</sup>

In 1996, Pagenkopf and Livinghouse reported an improved procedure for the catalytic Pauson-Khand reaction. It was discovered that efficient cyclization could be achieved using high-purity Co<sub>2</sub>(CO)<sub>8</sub> in the presence of high-intensity visible light (Q-Beam irradiation) at *only 1 atmosphere of CO*. Irradiation of a solution of enyne **19** and 5 mol % Co<sub>2</sub>(CO)<sub>8</sub> with a 10<sup>6</sup> candlepower spotlight rapidly formed the desired pentalenone **20** in high yield (**Scheme 2.27**).<sup>18</sup> While the photo-induced dissociation of CO from



Scheme 2.27

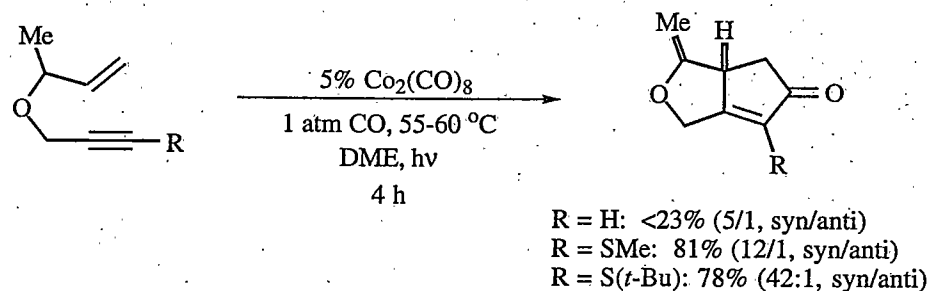
metal carbonyl complexes has been used to facilitate substitution reactions in other metal carbonyl complexes<sup>19</sup>, this is the first example that has been applied to the Pauson-Khand reaction. The method has proven to be general as seen in the following examples (Table 2.1).<sup>18</sup>

Table 2.1. Catalytic Photopromoted Pauson-Khand Reaction<sup>a</sup>

Entry	Substrate	Product	Yield
1			74
2			81
3			91
4			67

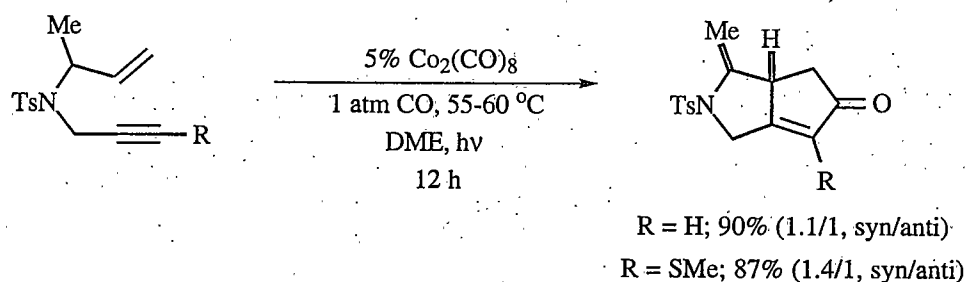
a. All reactions were performed in DME at 55 °C with 5%  $\text{Co}_2(\text{CO})_8$ , unless otherwise noted. b. 10%  $\text{Co}_2(\text{CO})_8$ .

Despite these advances, some substrates, such as 1,6-enynes bearing trimethylsilyl-substituted alkynes, failed to undergo carbonylative cyclization using the photopromoted conditions. In addition, it was found that several ether-linked substrates failed to give good yields of bicyclopentenones (Scheme 2.28).<sup>20</sup> Modification of substrates bearing terminal alkynes with a thioalkyl moiety allowed for efficient



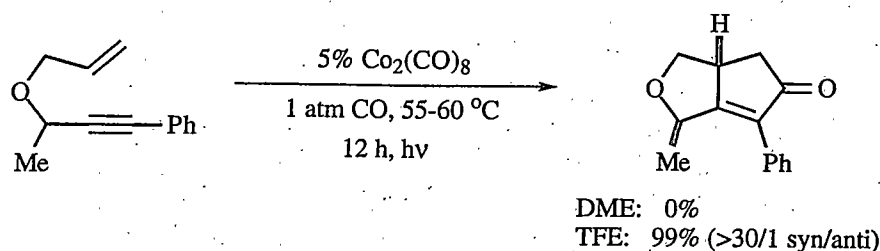
Scheme 2.28

carbonylative cyclization with increased diastereoselectivity. Increasing the steric size of the thioalkyl unit also had a positive effect on the diastereoselectivity (Scheme 2.28).<sup>20</sup> Interestingly, the "thiomethyl effect" did not lead to significant increases in the diastereoselectivity of all substrates tested (Scheme 2.29).<sup>20</sup> Alternatively, the use of



Scheme 2.29

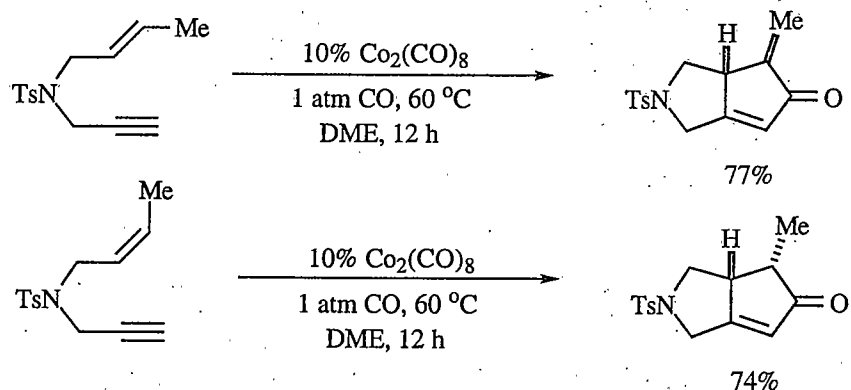
trifluoroethanol as co-solvent was shown to positively affect the cyclization efficiency of ether-linked enynes containing nonterminal alkynes (Scheme 2.30).<sup>20, 22</sup> This solvent



Scheme 2.30

effect may originate from the increased solubility of CO in the highly polar, fluorinated solvent. In addition, hydrogen bonding of the ether-linked enyne to the protic solvent may be of importance.

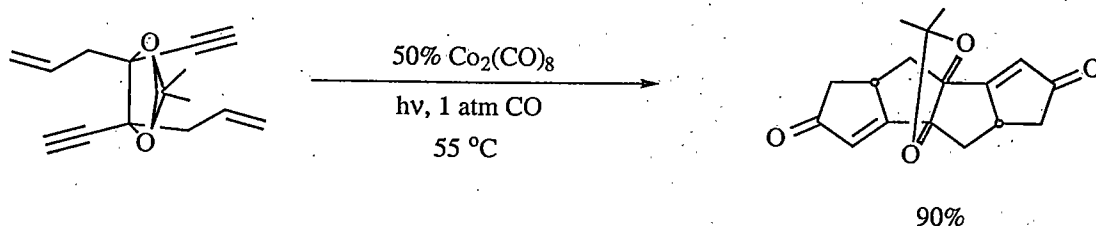
In a study concurrent with the investigations described in this dissertation, O'Mahony and Livinghouse have found that 1,6-enynes bearing substituted alkenes undergo catalytic carbonylative cyclization with complete control of initial olefin geometry (Scheme 2.31).<sup>23</sup> This important discovery may allow for the synthesis of complex



Scheme 2.31

molecules using the catalytic Pauson-Khand reaction. These findings are in direct contrast to the Ru- and Ti-catalyzed [2+2+1] cycloaddition where the stereointegrity of the alkene in the precyclization substrate was compromised in the product (*vide infra*).

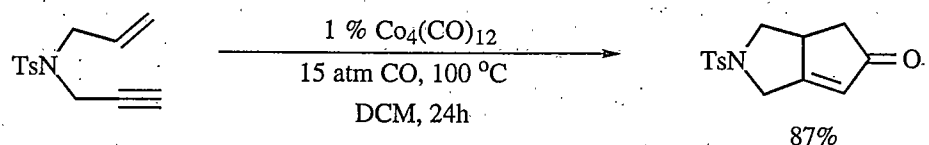
A recent example of the photopromoted catalytic Pauson-Khand reaction has been used by Cook to assemble the tetracyclic core of dicyclopenta[*a,f*]pentalene and dicyclopenta[*a,e*]pentalene (Scheme 2.32).<sup>24</sup> While the catalyst loading in each case was



Scheme 2.32

quite high (50 mol %), excellent yields were obtained in the synthesis of these complex ring systems. Interestingly, poor yields were obtained when the PKR was performed using a modification of Schreiber's NMO protocol. Cook noted that the use of substoichiometric amounts of  $\text{Co}_2(\text{CO})_8$  simplified purification and may account for the improved yields. The often overlooked challenge of product isolation from reactions employing stoichiometric  $\text{Co}_2(\text{CO})_8$  further demonstrates the synthetic importance of the catalytic Pauson-Khand reaction.

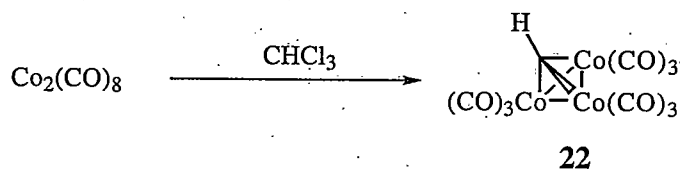
The catalytic Pauson-Khand reaction of enynes using  $\text{Co}_4(\text{CO})_{12}$  has very recently been introduced by Chung. Chung found that  $\text{Co}_2(\text{CO})_8$  could be generated *in situ* from  $\text{Co}_4(\text{CO})_{12}$  at 15 atm CO. Carbonylative annulation of several substrates was achieved in



Scheme 2.33

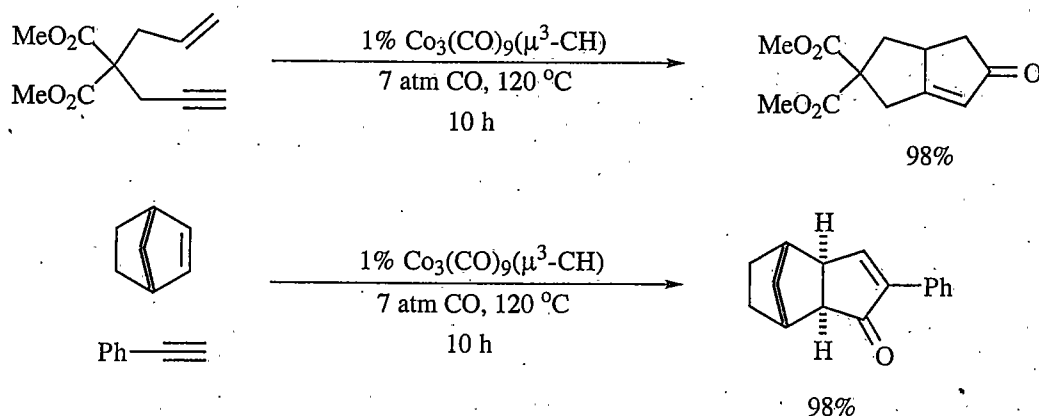
good yield using this procedure (Scheme 2.33).<sup>25</sup> There are no apparent advantages to this method as  $\text{Co}_4(\text{CO})_{12}$  is more expensive than  $\text{Co}_2(\text{CO})_8$  and displays similar stability problems.

In 1999, Sugihara has discovered that methylenetricobalt nonacarbonyl **22** was a highly effective catalyst for the inter- and intramolecular PKR.<sup>26</sup> Alkylidenetricobalt nonacarbonyl complexes are easily prepared from  $\text{Co}_2(\text{CO})_8$  and trihaloalkanes (Scheme 2.34).<sup>27</sup> Most importantly, these complexes, which are structurally-similar to alkyne-



Scheme 2.34

cobalt complexes, are air stable. Optimal reaction conditions required modest CO pressure and elevated temperatures, but provided excellent yields of product in both the inter- and intramolecular PKR (Scheme 2.35).<sup>26</sup> Importantly, with  $\text{Co}_2(\text{CO})_8$  as catalyst under

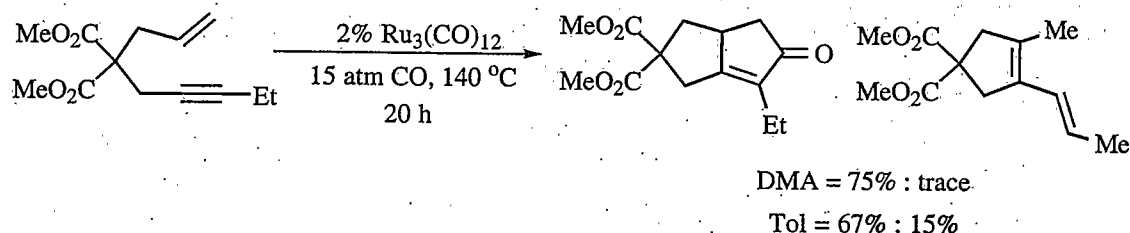


Scheme 2.35

identical reaction conditions (120 °C, 7 atm CO) very poor conversion to product was observed (12%). That  $\text{Co}_2(\text{CO})_8$  failed to exhibit similar catalytic activity as  $\text{Co}_2(\text{CO})_9(\mu^3\text{-CH})$  suggests it is not being formed *in situ*.

### 2.2.c Ruthenium-Catalyzed [2+2+1] Cycloaddition

Mitsudo has developed the first example of a ruthenium-catalyzed [2+2+1] cycloaddition. Good yields of bicyclopentenones were obtained using only 2 mol %  $\text{Ru}_3(\text{CO})_{12}$  under 15 atm CO at 140 °C. The use of dimethyl acetamide was found to suppress the formation of an undesired diene side product (Scheme 2.36).<sup>28</sup> The PKR



Scheme 2.36

of a 1,6-enyne **23** bearing a 2-substituted alkene led to a good yield of the angularly-substituted pentalenone **24**, while a similar substrate **25** with a *trans*-crotyl moiety resulted in product **26** with significant epimerization (Scheme 2.37).<sup>28</sup>

















































































































































































































































































































































































































































































































































































































































































































































































































































































































































