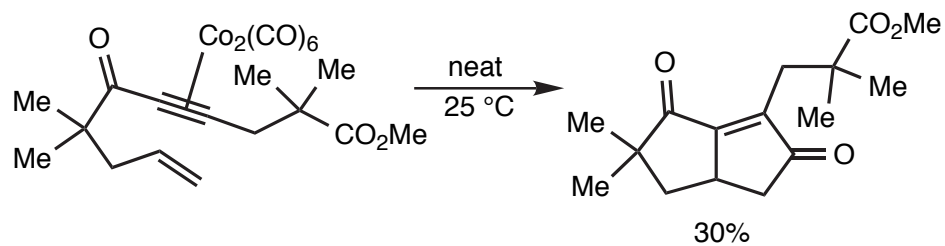
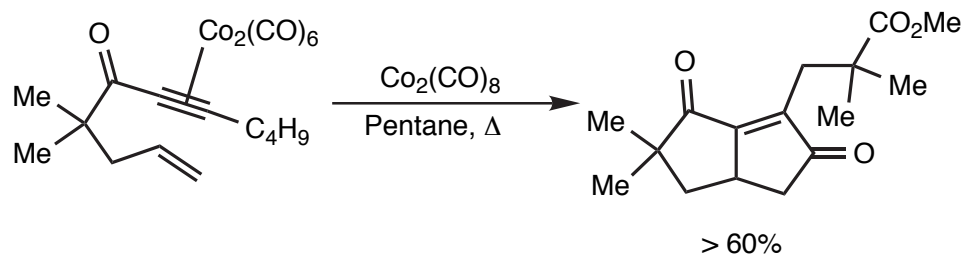


### Miscellaneous

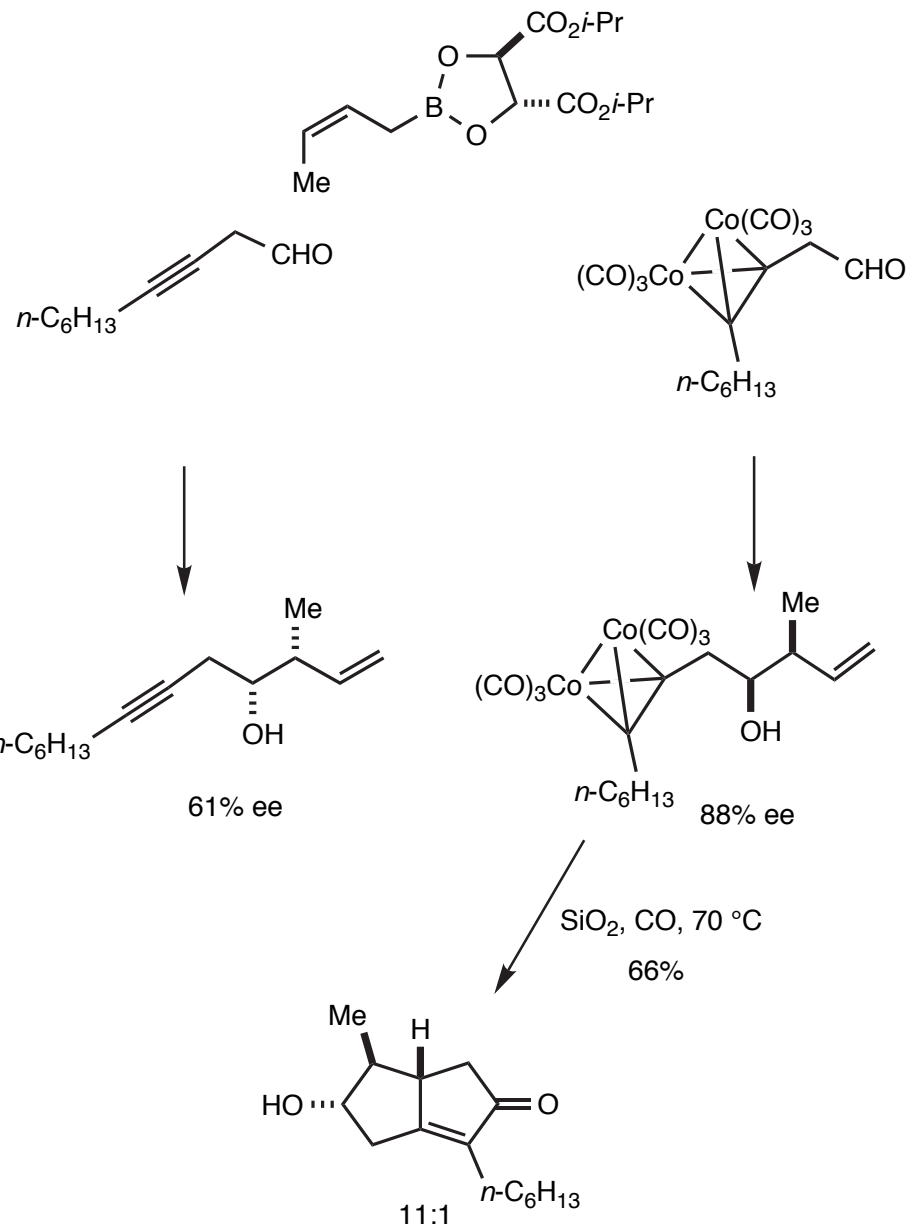


Dinsmore, C. J.; Hoye, T. R. Unpublished results



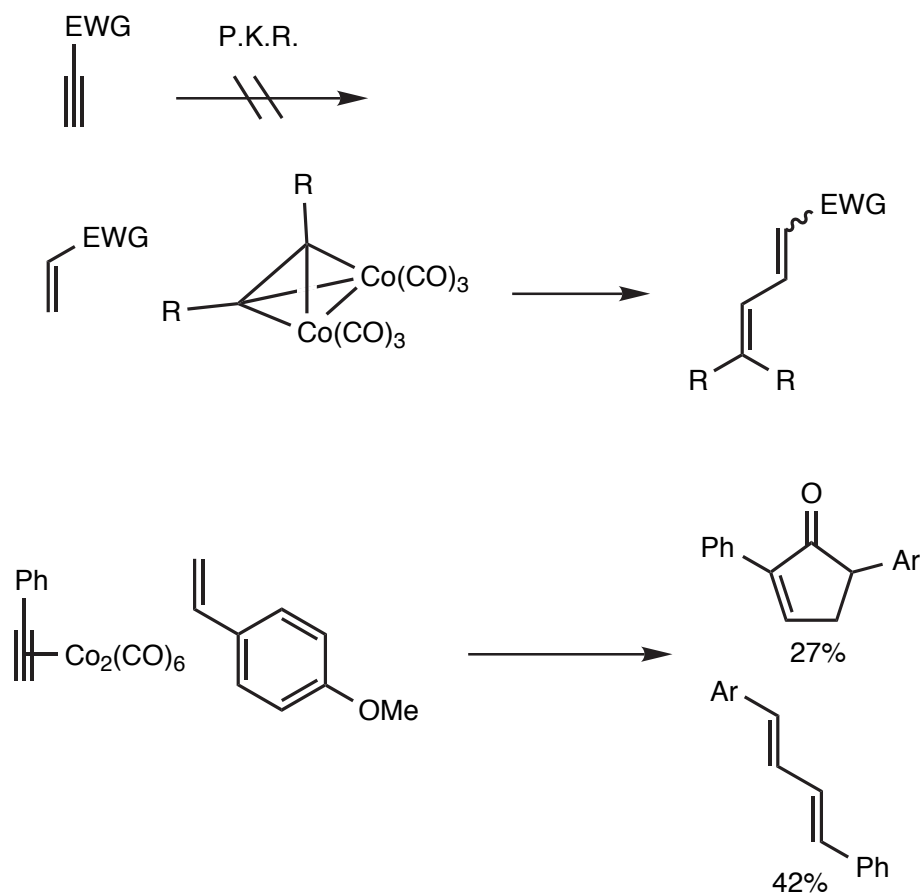
Suriano, J. A.; Hoye, T. R. Unpublished results

### Miscellaneous



Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1991**, *32*, 6285-6288

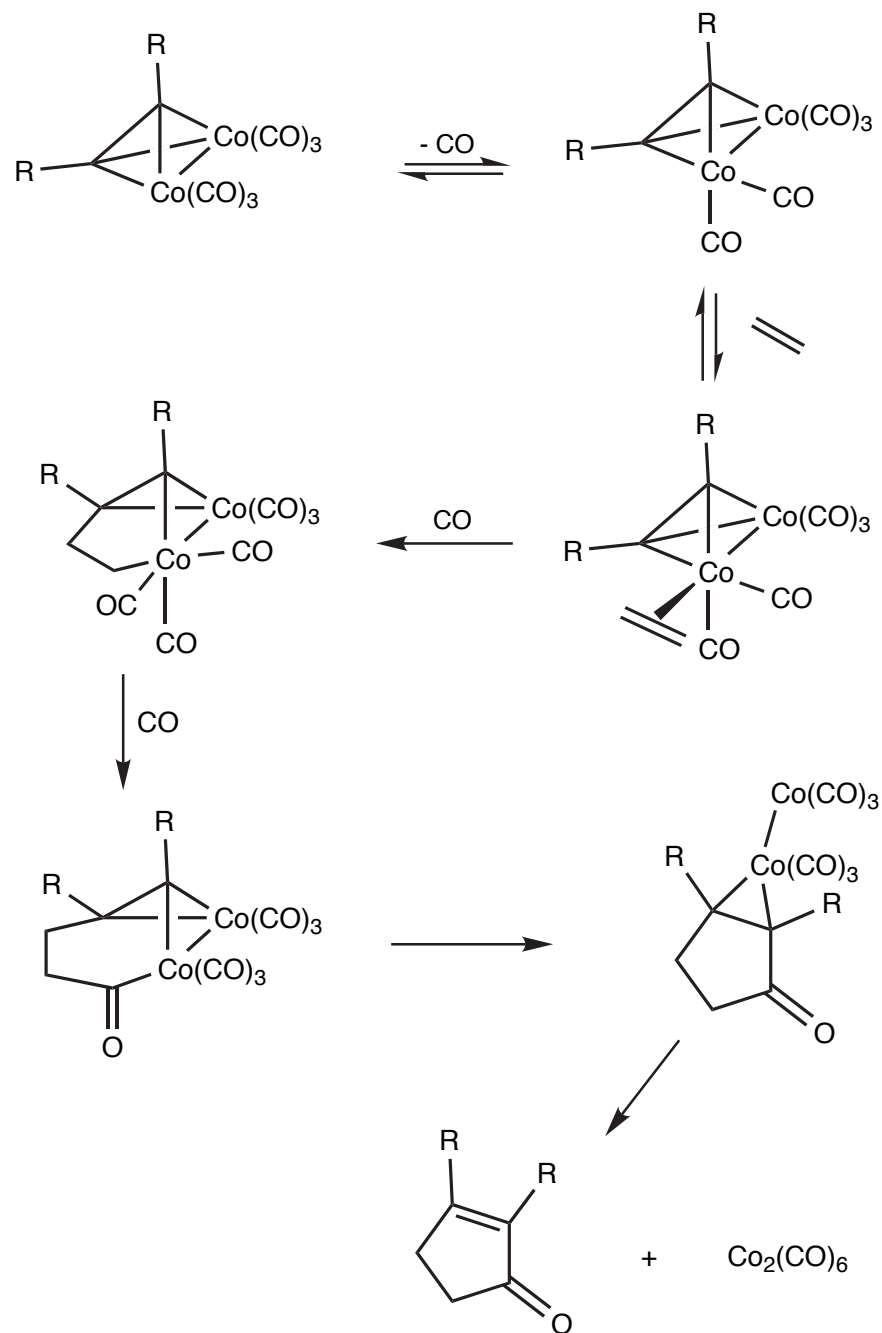
### Further Observations:



Most other functionality is well tolerated although allylic and propargylic substituents can be problematic.

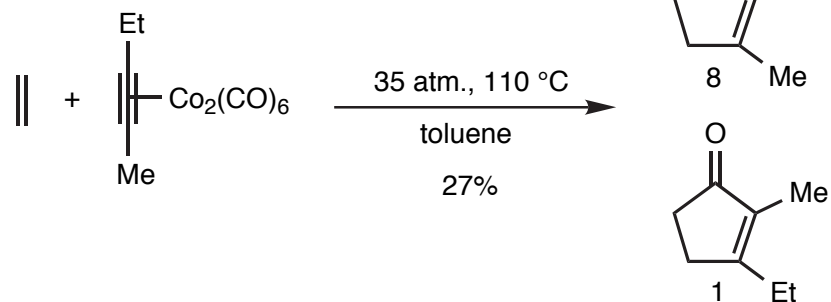
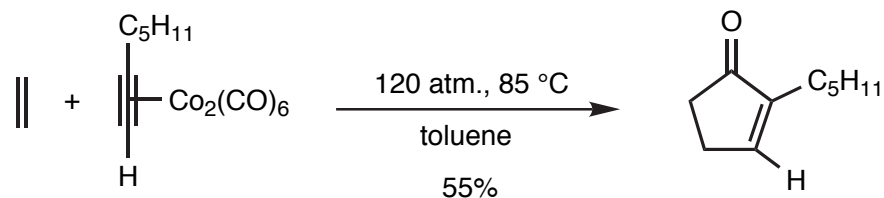
Increased steric hinderance on the alkyne or on the alkene results in lower yields.

### Proposed Mechanism:



## Intermolecular - Alkyne Regioselectivity

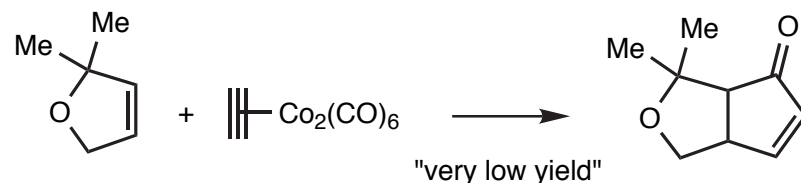
The reaction is consistently regioselective with respect to the alkyne fragment, placing the larger substituent at C-2 of the cyclopentenone



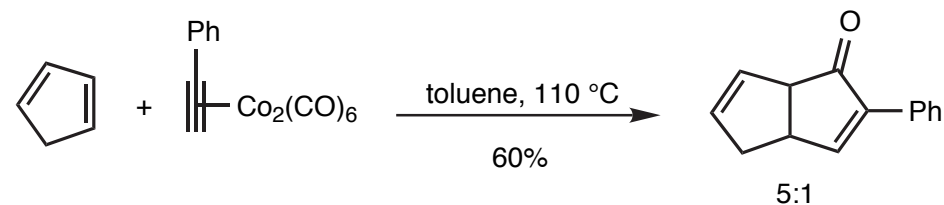
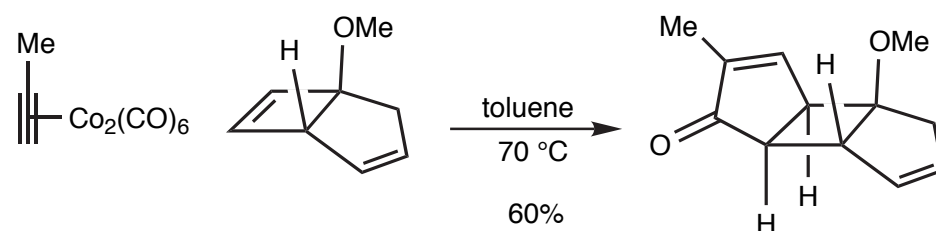
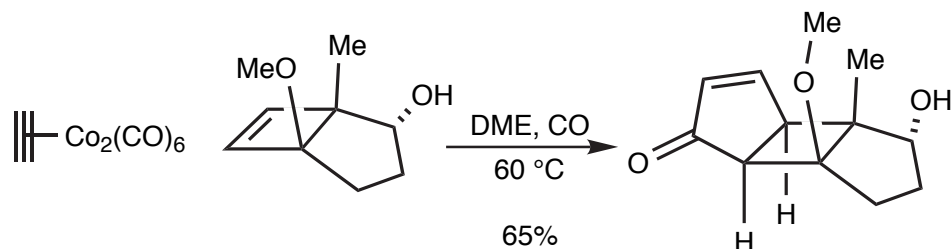
## Intermolecular - Alkene Regioselectivity

The reactions of monosubstituted alkenes with monosubstituted alkynes are non-selective

The reactions of 1,2-disubstituted olefins can be regioselective, but predictive ability is limited

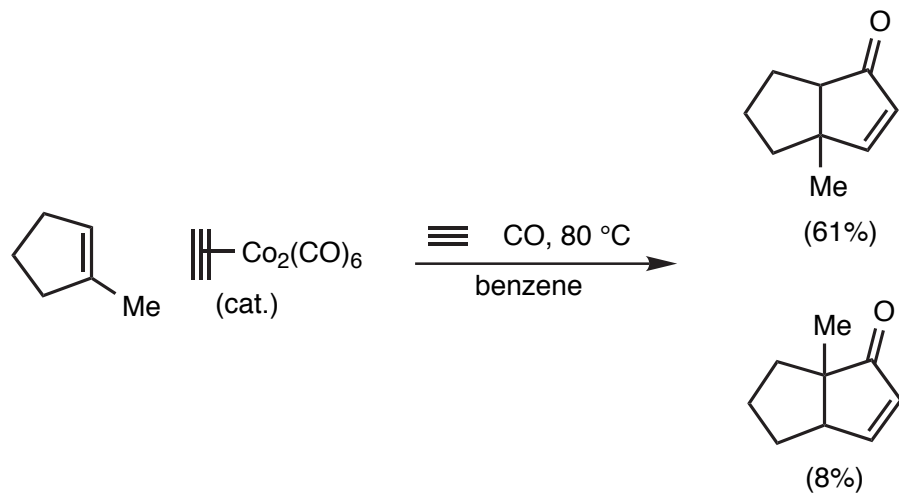
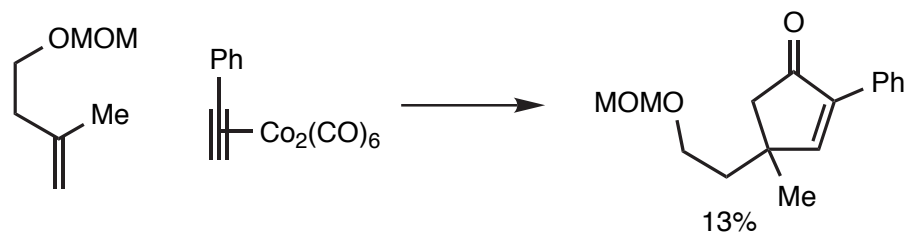
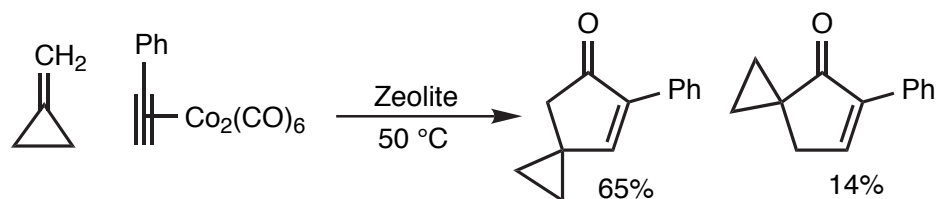


Billington, D. C. *Tetrahedron Lett.* **1983**, 24, 2905

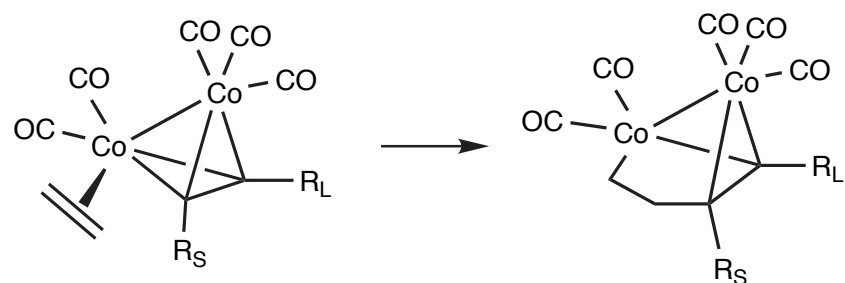


## Intermolecular - Alkene Regioselectivity

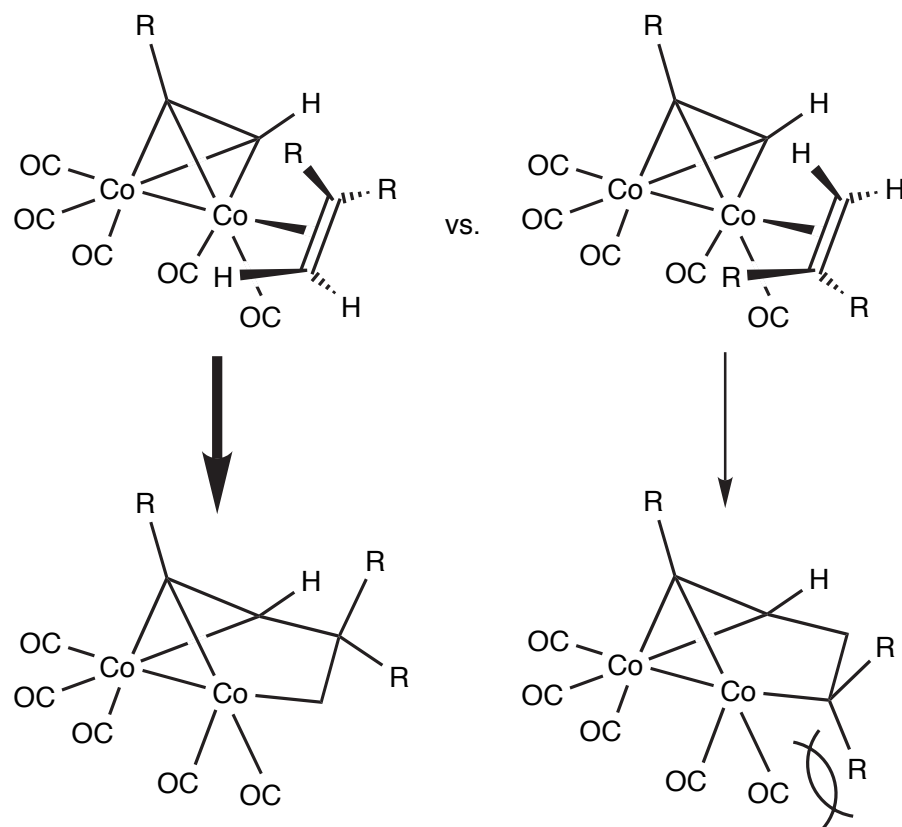
The reactions of 1,1-disubstituted and trisubstituted alkenes are regioselective with the bulkier end of the olefin incorporated at C-4 of the cyclopentenone



Rationale for alkyne regioselectivity:

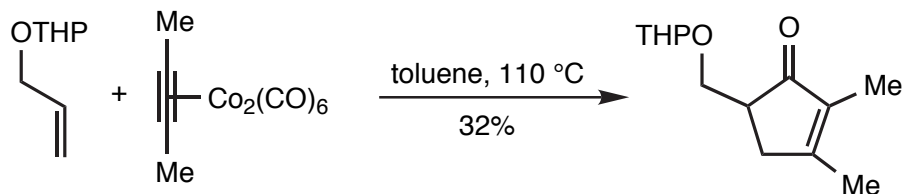


Rationale for 1,1-disubstituted and trisubstituted alkene regiochemistry:

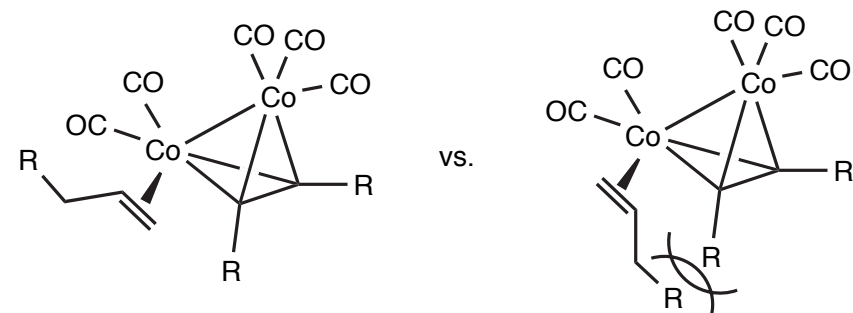
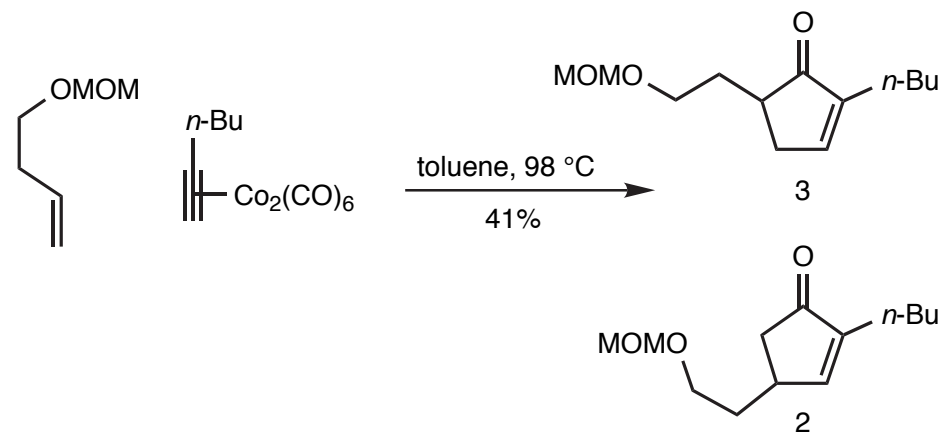
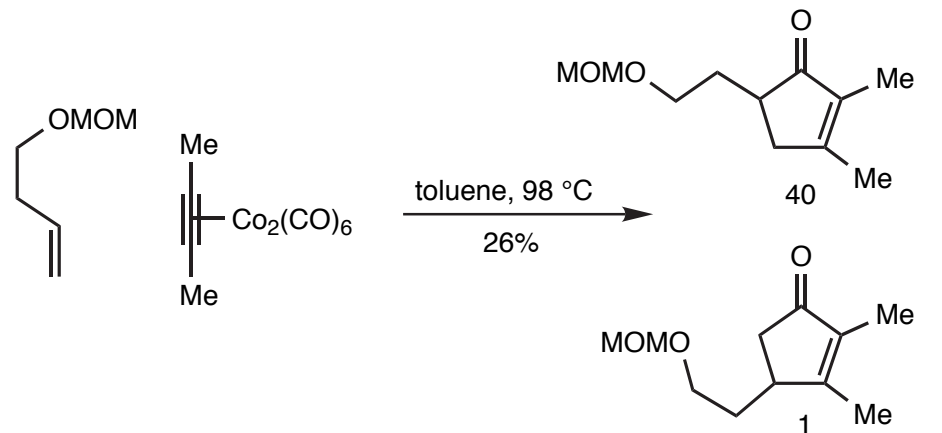
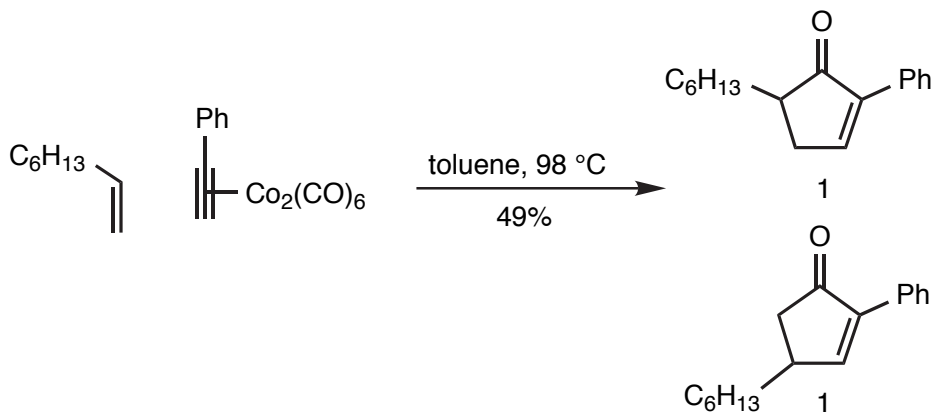
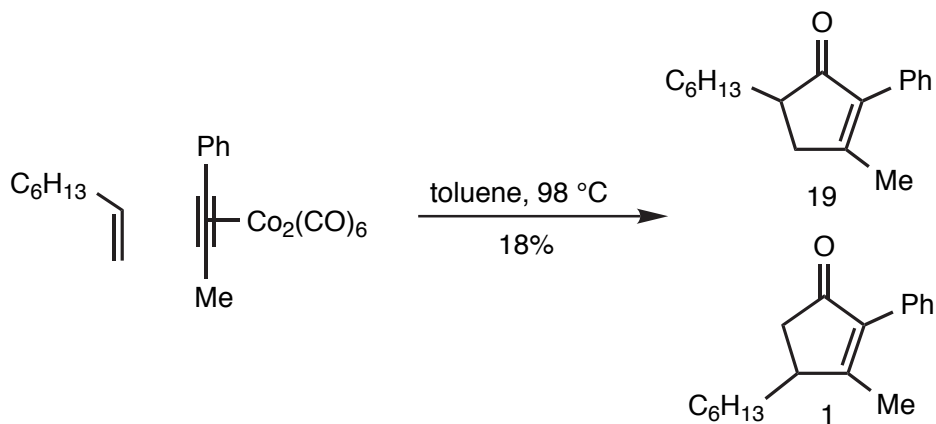


### Intermolecular - Internal Alkynes:

The use of internal acetylenes results in dramatic increases in alkene regiocontrol and diminished yields.

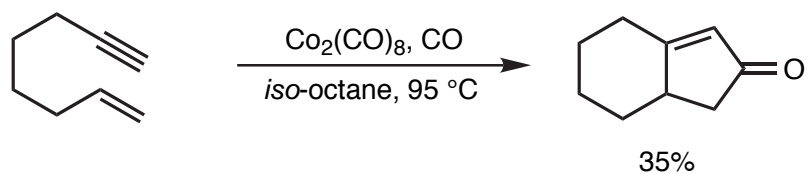
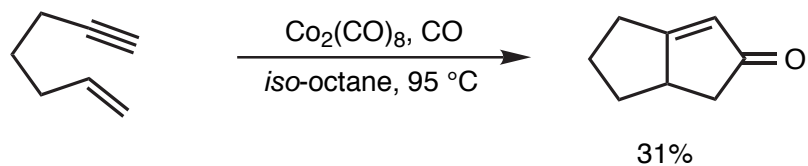


Billington, D. C.; Pauson, P. L. *Organometallics*, **1982**, 1, 1560



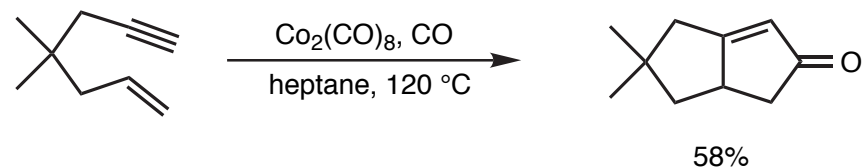
Krafft, M. E. *Tetrahedron Lett.* **1988**, 29, 999-1002

## The Intramolecular Pauson-Khand Reaction:



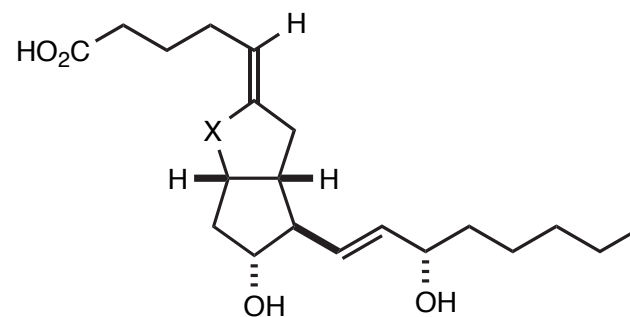
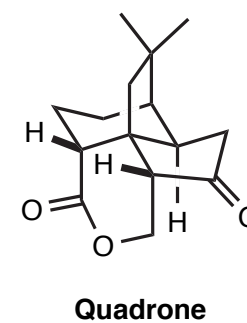
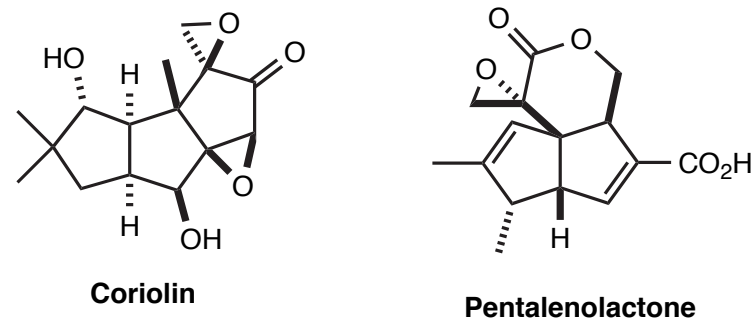
1. Conditions are milder
2. Unstrained alkenes can be used

Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, 46, 5436

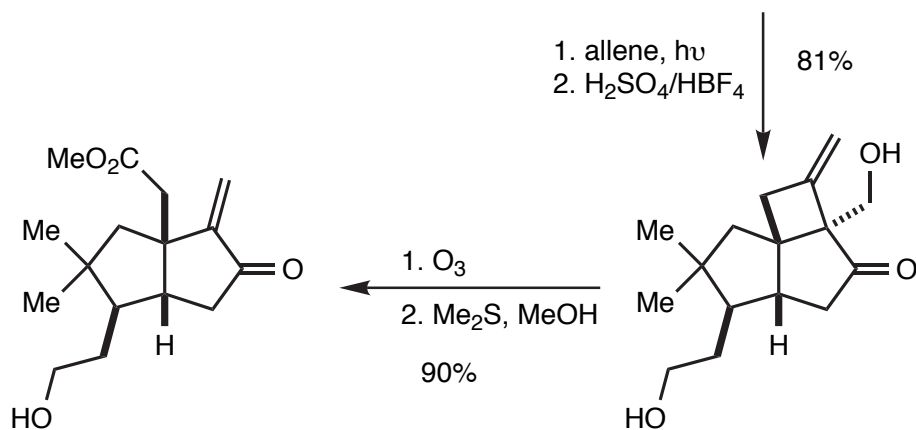
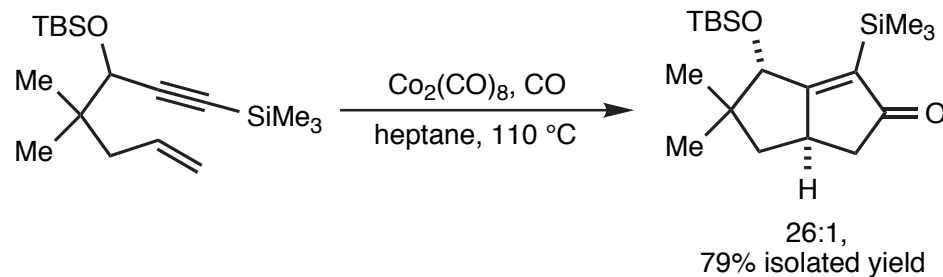
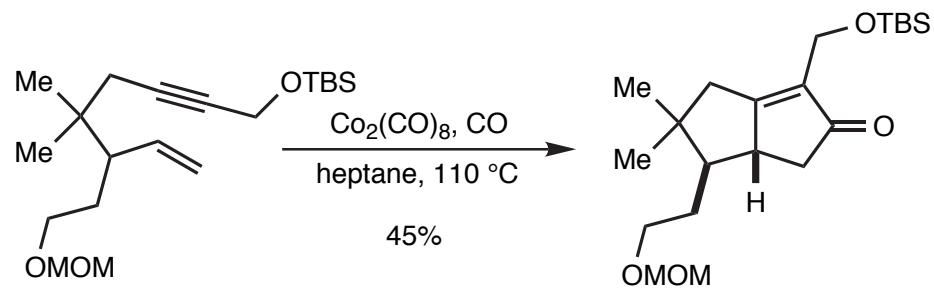
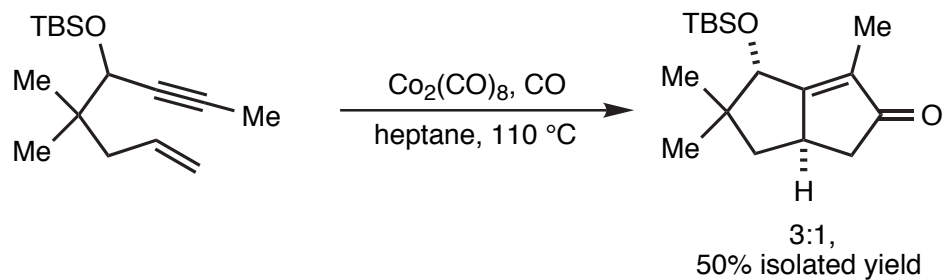
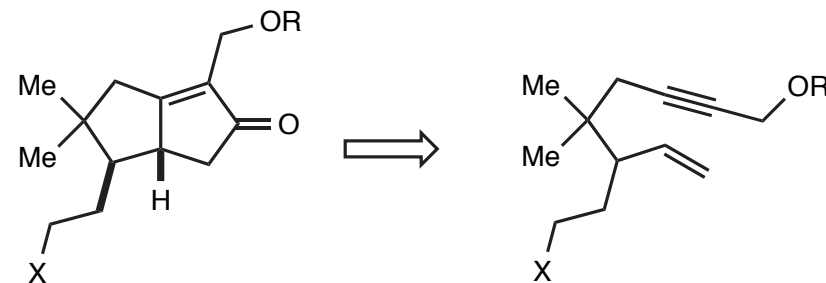
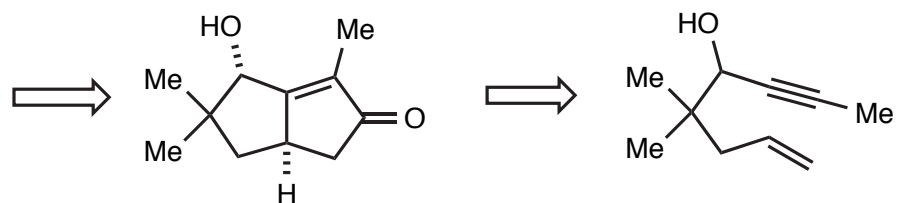
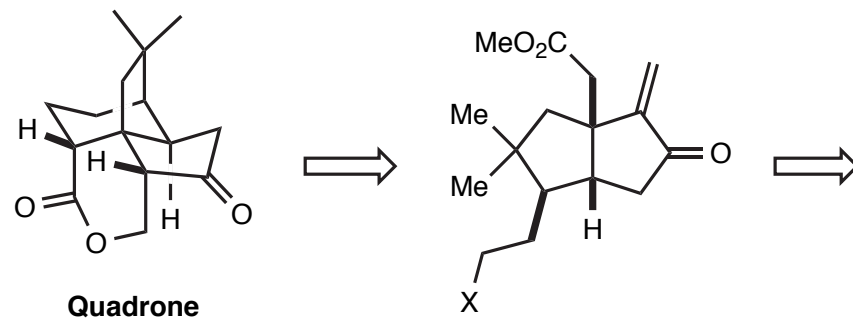
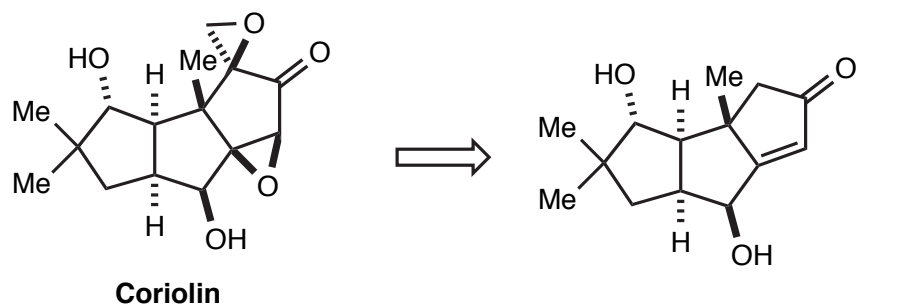


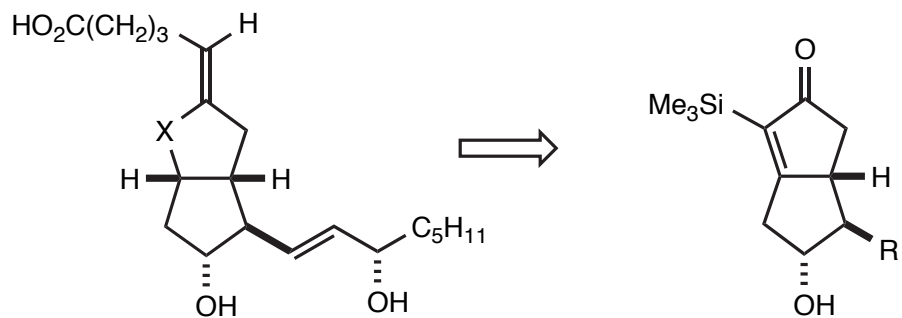
3. Thorpe-Ingold effect results in dramatic increases in yields

Hua, D. H. *J. Am. Chem. Soc.* **1986**, 108, 3835

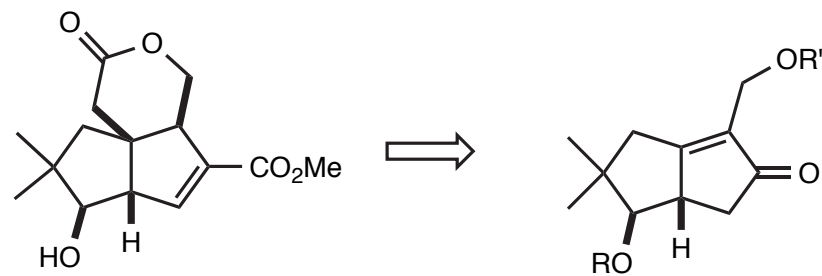
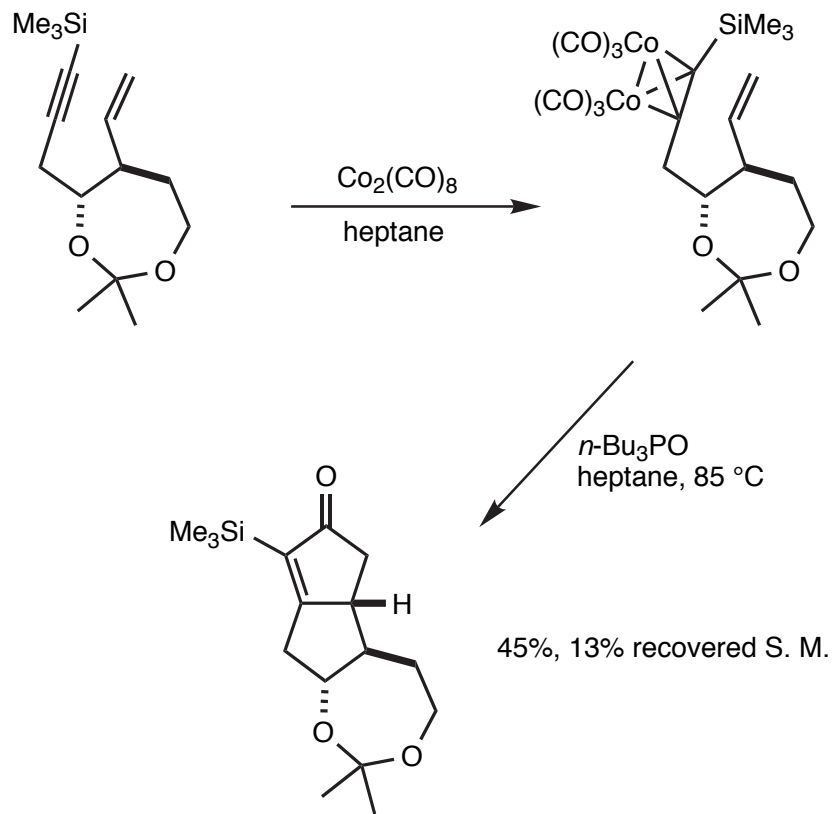


**X = O, Prostacyclin (PGI<sub>2</sub>)**  
**X = CH<sub>2</sub>, Carbacyclin**

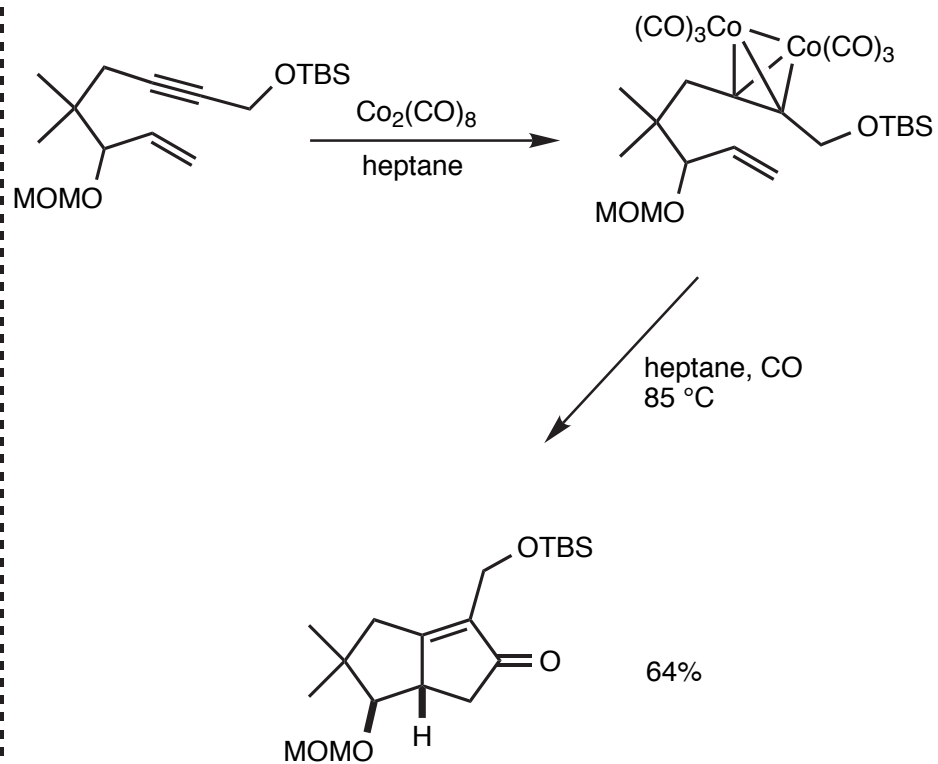




**X = O, Prostacyclin (PGI<sub>2</sub>)**  
**X = CH<sub>2</sub>, Carbacyclin**

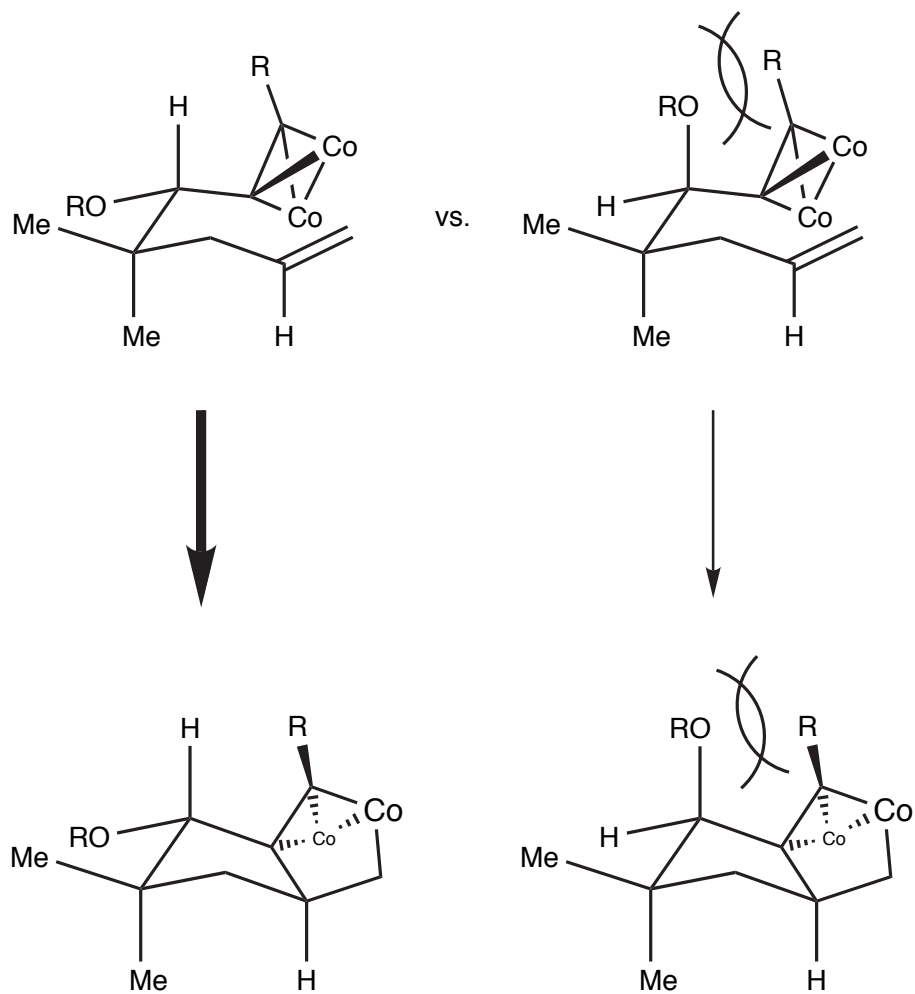


**Methyl Deoxynor-**  
**pentalenolactone H**

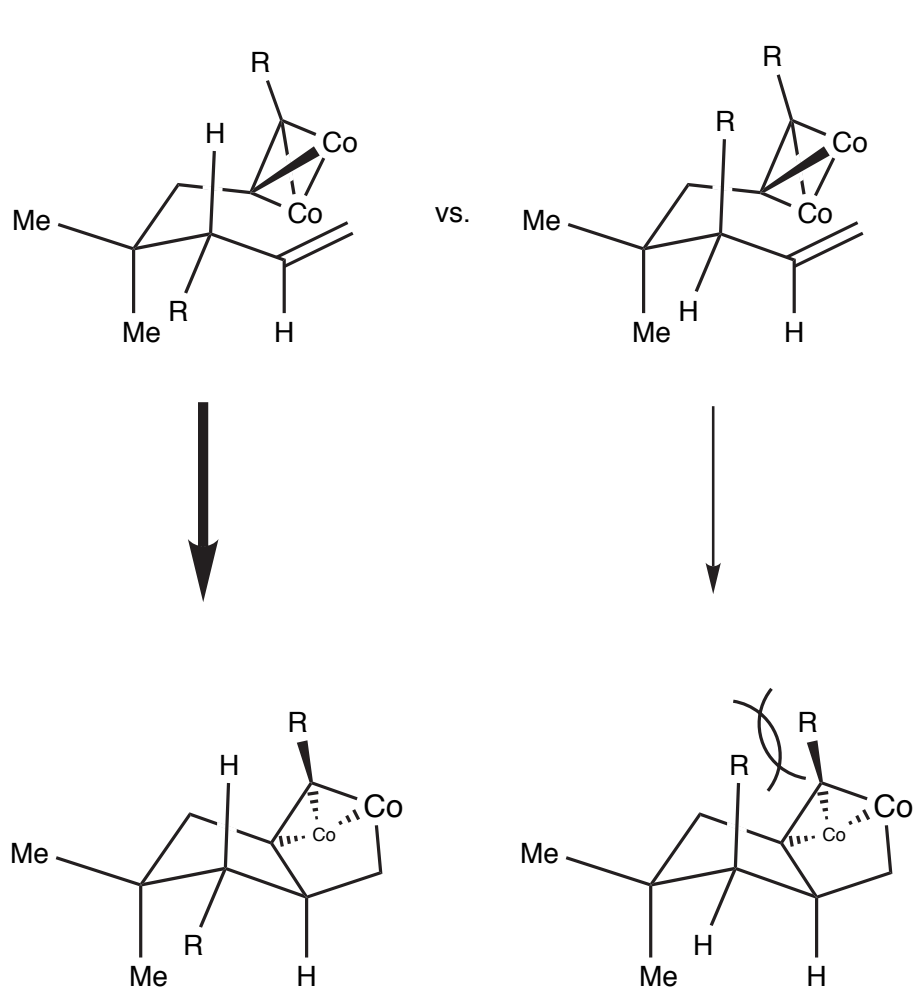




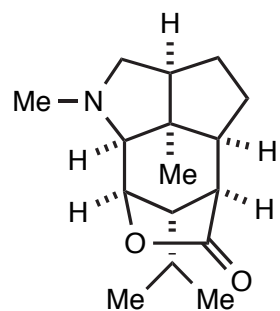
### Magnus' Explanation for Selectivity - Propargylic:



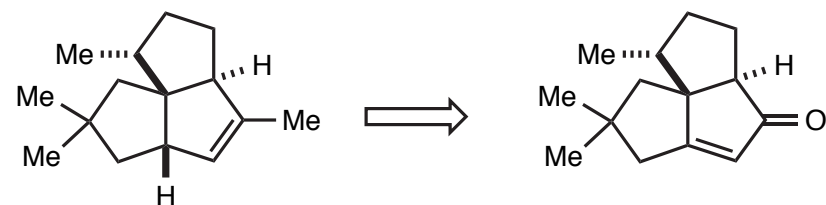
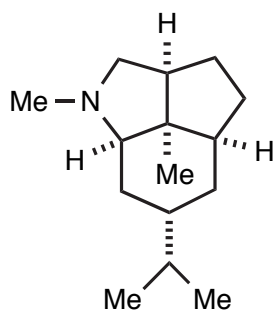
### Magnus' Explanation for Selectivity - Allylic:



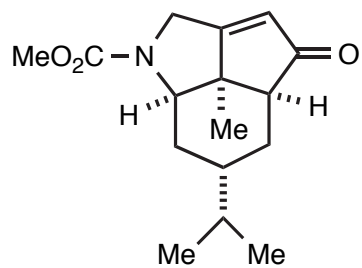
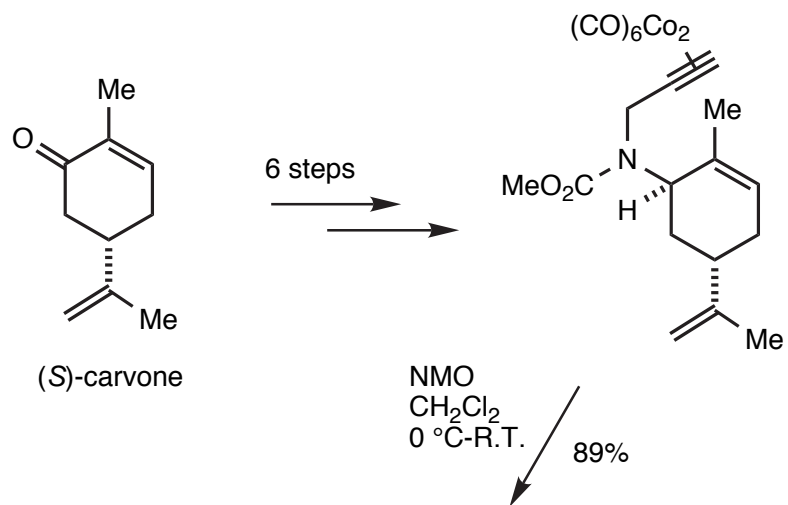
**Other Notable Intramolecular Examples:**



**Dendrobine**

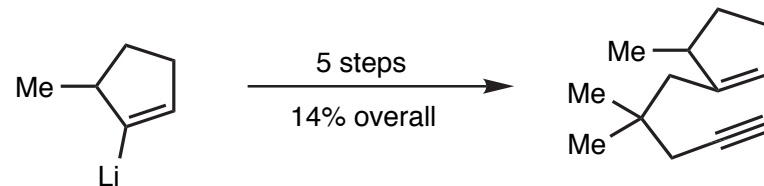


**Pentalenene**

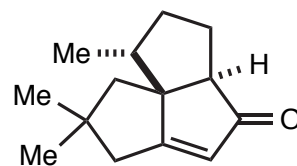


NMO  
 $\text{CH}_2\text{Cl}_2$   
 $0^\circ\text{C}-\text{R.T.}$

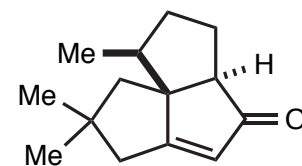
89%



$\text{Co}_2(\text{CO})_8$   
 heptane,  $110^\circ\text{C}$

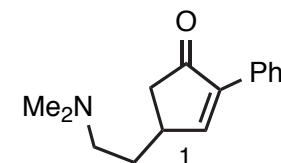
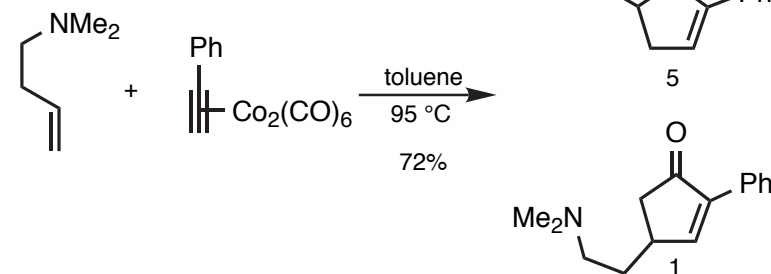
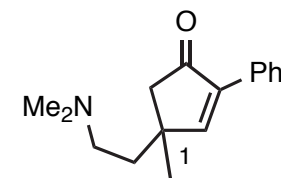
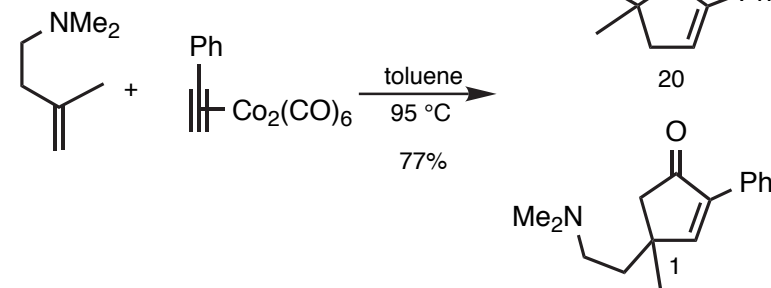
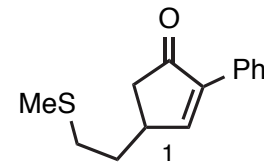
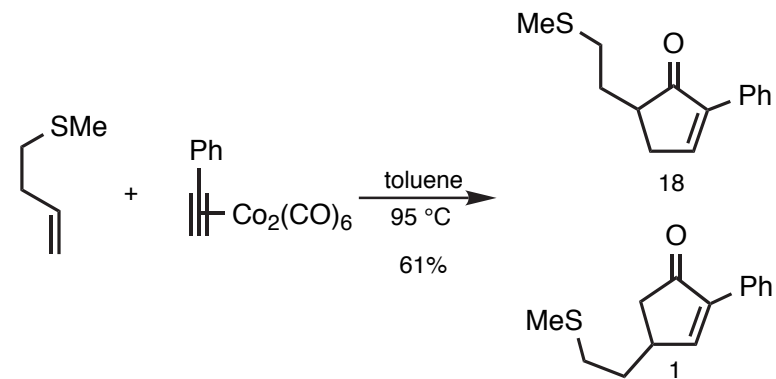
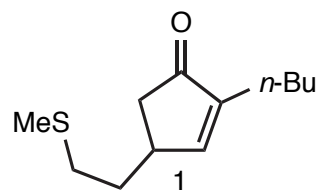
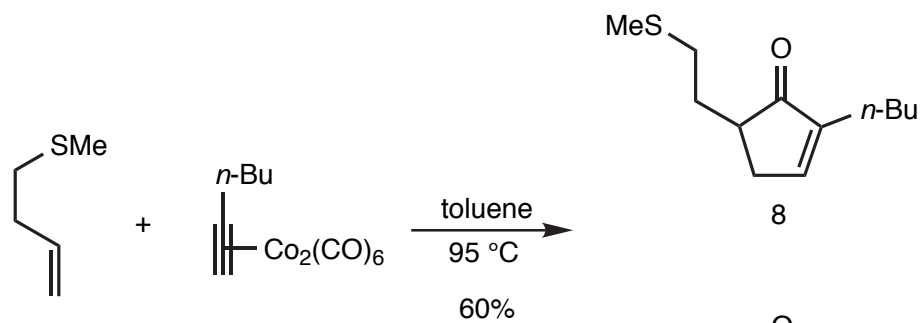
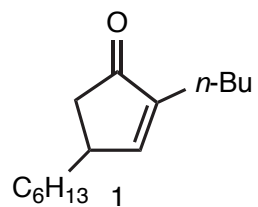
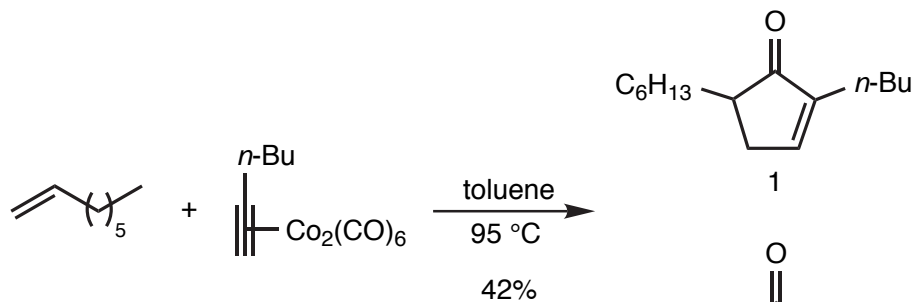


45%



6%

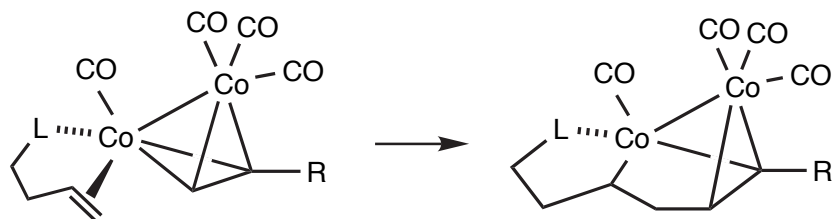
### The Directed Pauson-Khand Reaction:



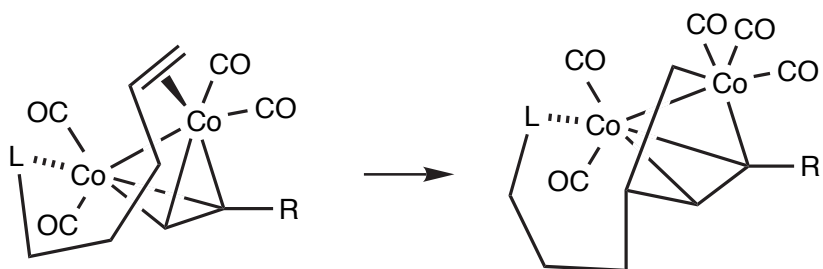
## The Directed Pauson-Khand Reaction:

### Observations:

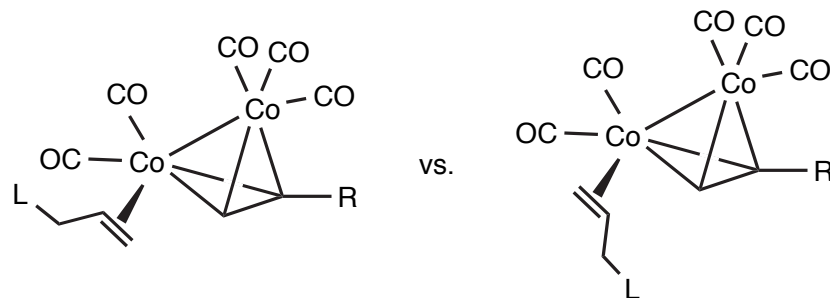
1. Homoallylic sulfides and amines (soft) work best.
2. Homoallylic ethers (hard) do not participate in a directed reaction.
3. Allylic and bishomoallylic sulfides and amines give low levels of selectivity - ca. 2-3:1.



Homoallylic tether long enough for chelation, but too short for binuclear binding

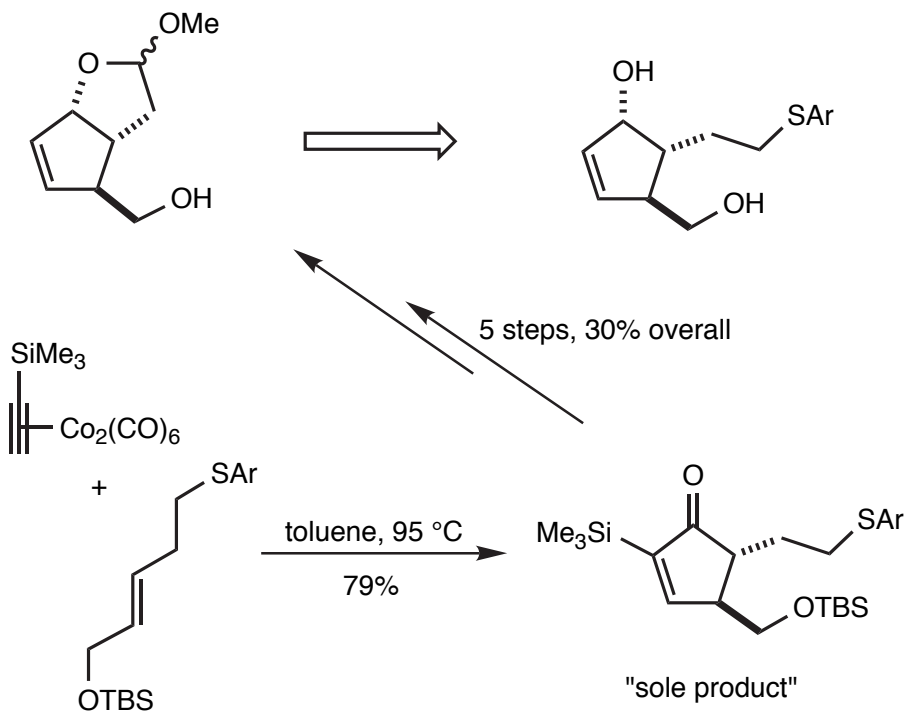


Possible side reaction leading to an erosion in regioselectivity in the bishomoallylic series



Allylic tether too short for bidentate binding, leading to poor levels of regiocontrol

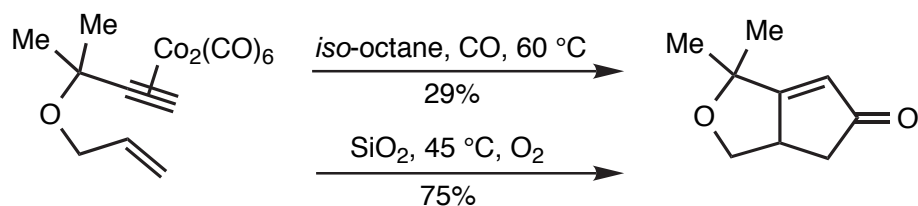
Krafft, M. E.; Juliano, C. A.; Scott, I. L.; Wright, C.; McEachin, M. D.  
*J. Am. Chem. Soc.* **1991**, *113*, 1693-1703



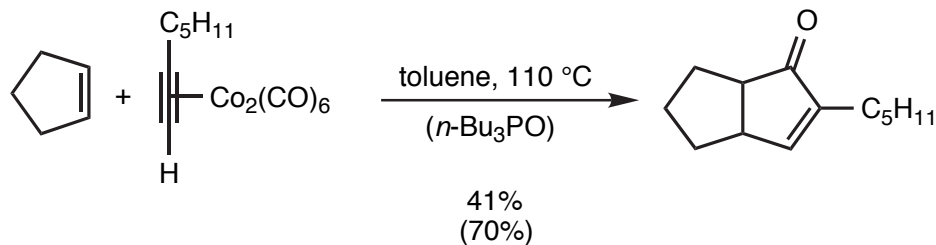
Krafft, M. E.; Wright, C. *Tetrahedron Lett.* **1992**, *33*, 151-152

## Improvements in Reaction Efficiency

- Ultrasound.** Sonication of the reaction mixture can lead to faster rates at lower temperatures.
- Solid supports.** Pre-adsorption of the cobalt complex onto one of several solid supports - silica, alumina, Zeolite NaX - can result in dramatic improvements in yields.



- Phosphine oxides.** Addition of phosphine oxides to the reaction mixture can result in higher yields.

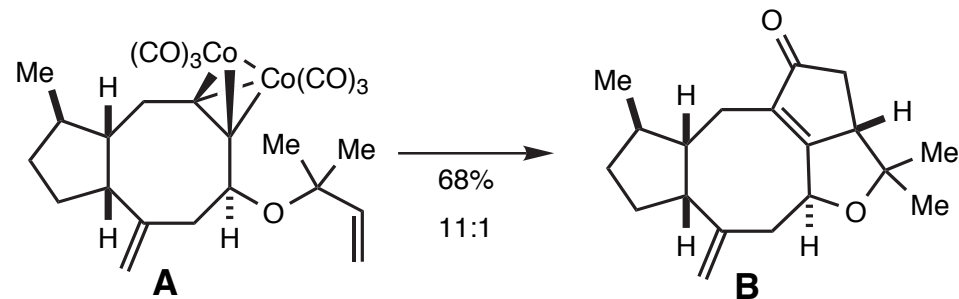
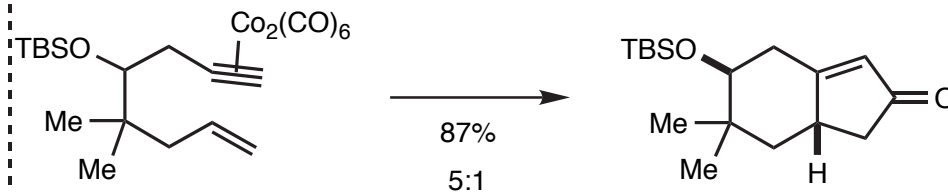
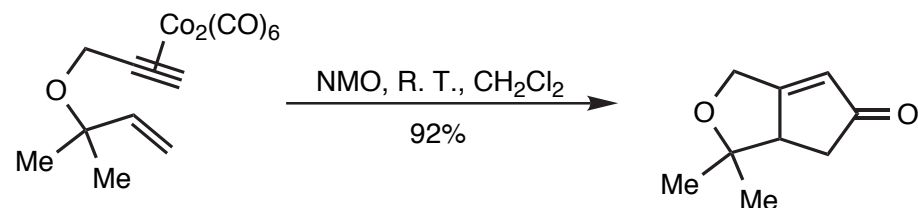


1. and 3. Billington, D. C.; Helps, I. M.; Pauson, P. L.; Thomson, W.; Willison, D. *J. Organometal. Chem.* **1988**, 354, 233-242

2. Simonian, S. O.; Smit W. A. *et al. Tetrahedron Lett.* **1986**, 27, 1245  
 Smit, W. A. *et al. Tetrahedron Lett.* **1989**, 30, 4021

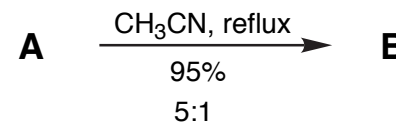
## Improvements in Reaction Efficiency

- Amine Oxides.** The use of amine oxides in intramolecular Pauson-Khand reactions has been shown to consistently give higher yields at lower reaction temperatures.



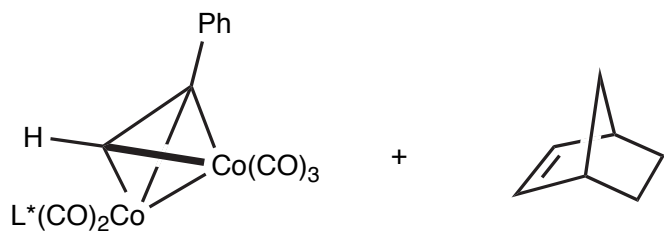
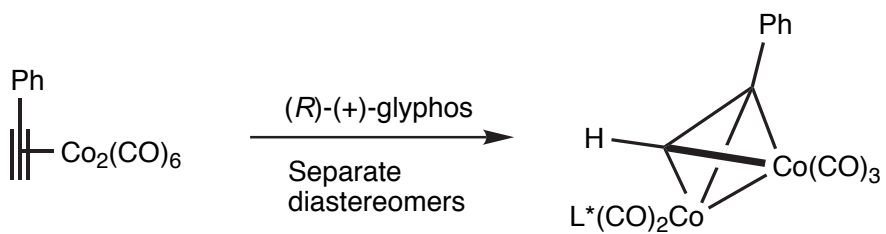
Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, 31, 5289-5292

- Acetonitrile.** The use of acetonitrile as solvent can lead to increased reaction efficiency at reduced temperatures.



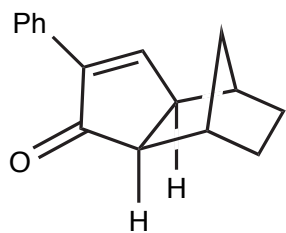
Shambayati, S. Personal communication

## Enantioselective Pauson-Khand Reaction



toluene, 45 °C

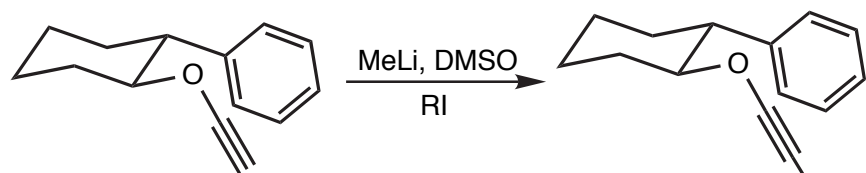
)))



31%

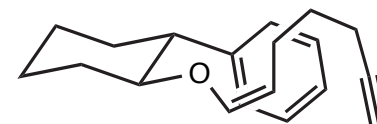
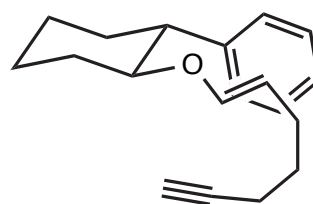
100% ee

## Chiral Auxiliary Controlled Pauson-Khand Reaction



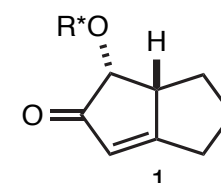
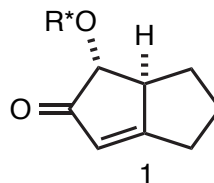
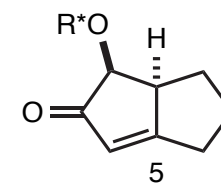
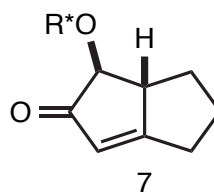
Red-Al

Red-Al-ROH

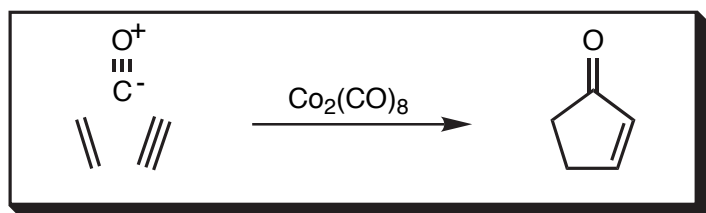


$\text{Co}_2(\text{CO})_8$   
*iso*-octane, 95 °C  
 55%

$\text{Co}_2(\text{CO})_8$   
*iso*-octane, 95 °C  
 20%



## The Pauson-Khand Reaction

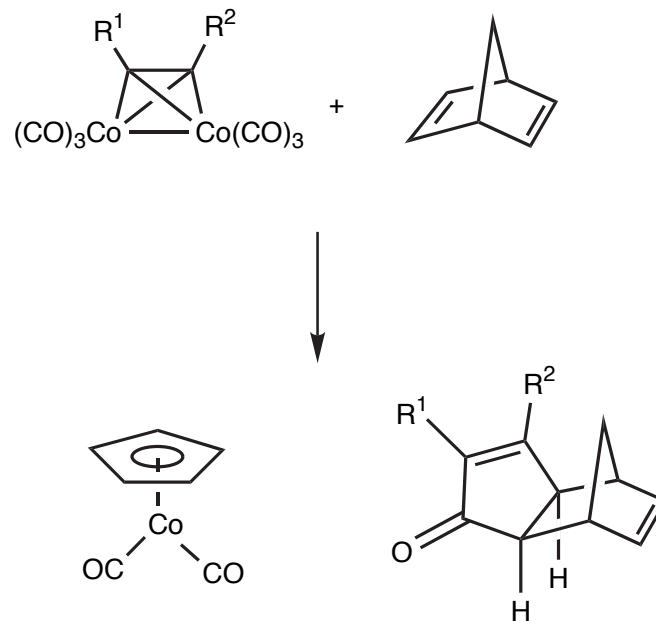


James L. Leighton

May 26, 1992

Review: Schore, N. E. *Org. Reactions*, **1991**, 40, 1-90

## Discovery:



## Initial Observations:

1. The reaction works best with strained alkenes
2. The reaction is stereospecific, giving only *exo* products
3. The reaction is regioselective with respect to an unsymmetrical alkyne, placing the large substituent at C-2 of the cyclopentenone
4. The reaction can be run *catalytic* in cobalt (< 10 turnovers)

Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 977