DUDOGNON Yohan

03/26/2015

Bibliography Seminar

The synthesis of cyclopropenes and their applications in cycloadditions from 2006 to nowadays

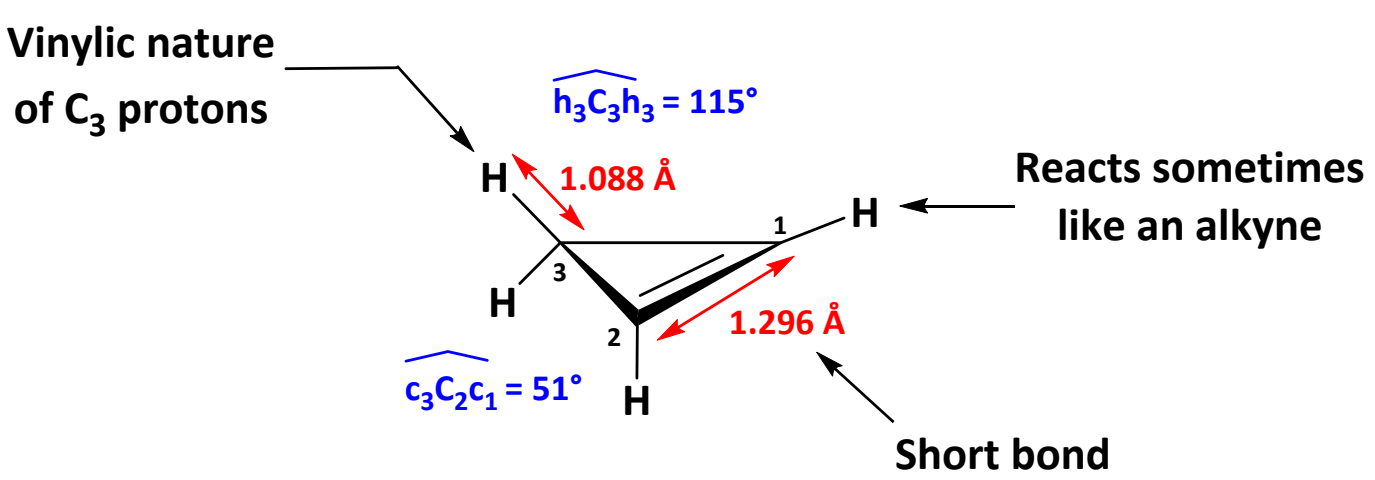
Bond lengths
Angles
Strain energy
Reactivity

(2+1) Cycloaddition
1,2-Elimination
From other cyclopropenes

(2+2+1) Pauson-Khand
(3+2+1)
(2+2)
(4+2)
(3+3)

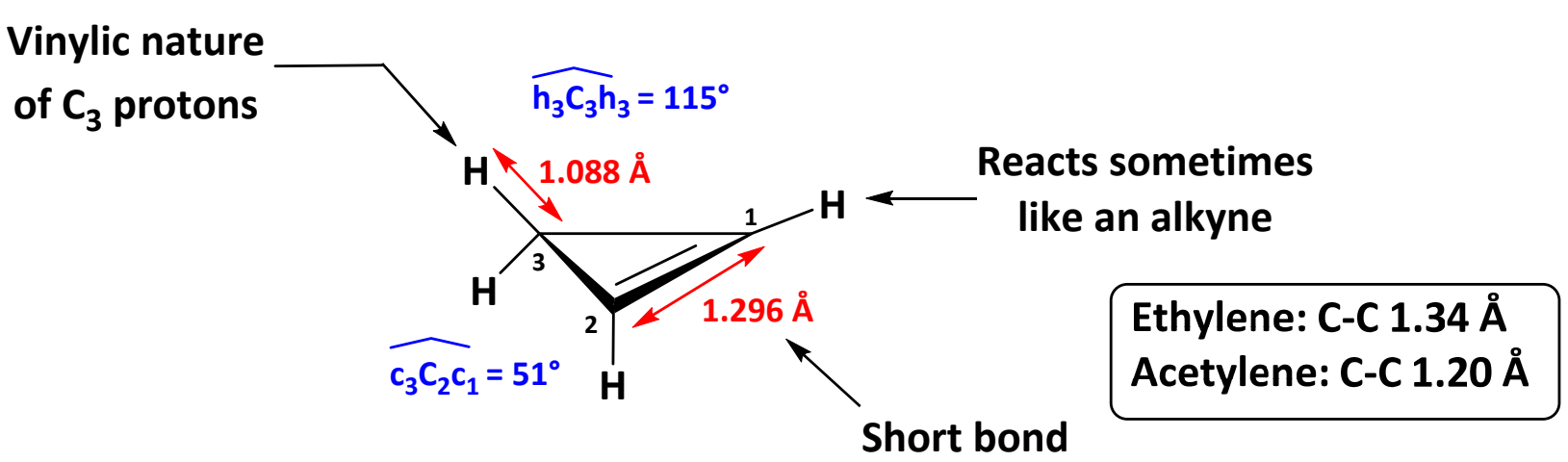
Institut des Sciences Moléculaires de Marseille
UMR 7313

General informations



F. Allen, *Tetraheddron*, **1982**, *38*, 645

General informations



F. Allen, *Tetraheddron*, **1982**, *38*, 645

General informations

Vinylic nature of C_3 protons

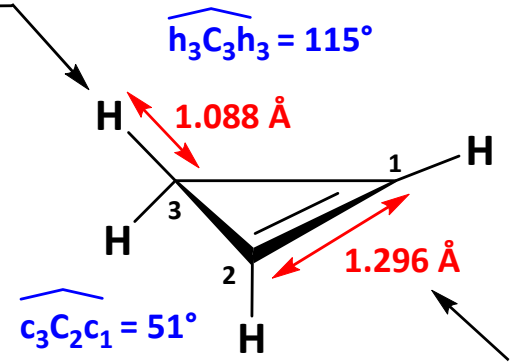
Strain Energy (kcal/mol):

Cyclohexane: 0.1

Cyclobutane: 26.3

Cyclopropane: 27.5

Cyclopropene: 54.1



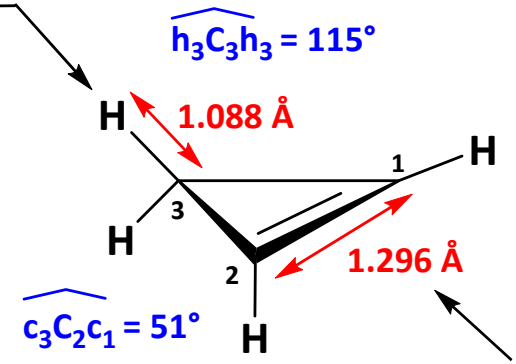
Reacts sometimes like an alkyne

Ethylene: C-C 1.34 Å
Acetylene: C-C 1.20 Å

Short bond

F. Allen, *Tetraheddron*, **1982**, *38*, 645

Vinylic nature of C_3 protons



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Strain Energy (kcal/mol):

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Cyclopropene: 54.1

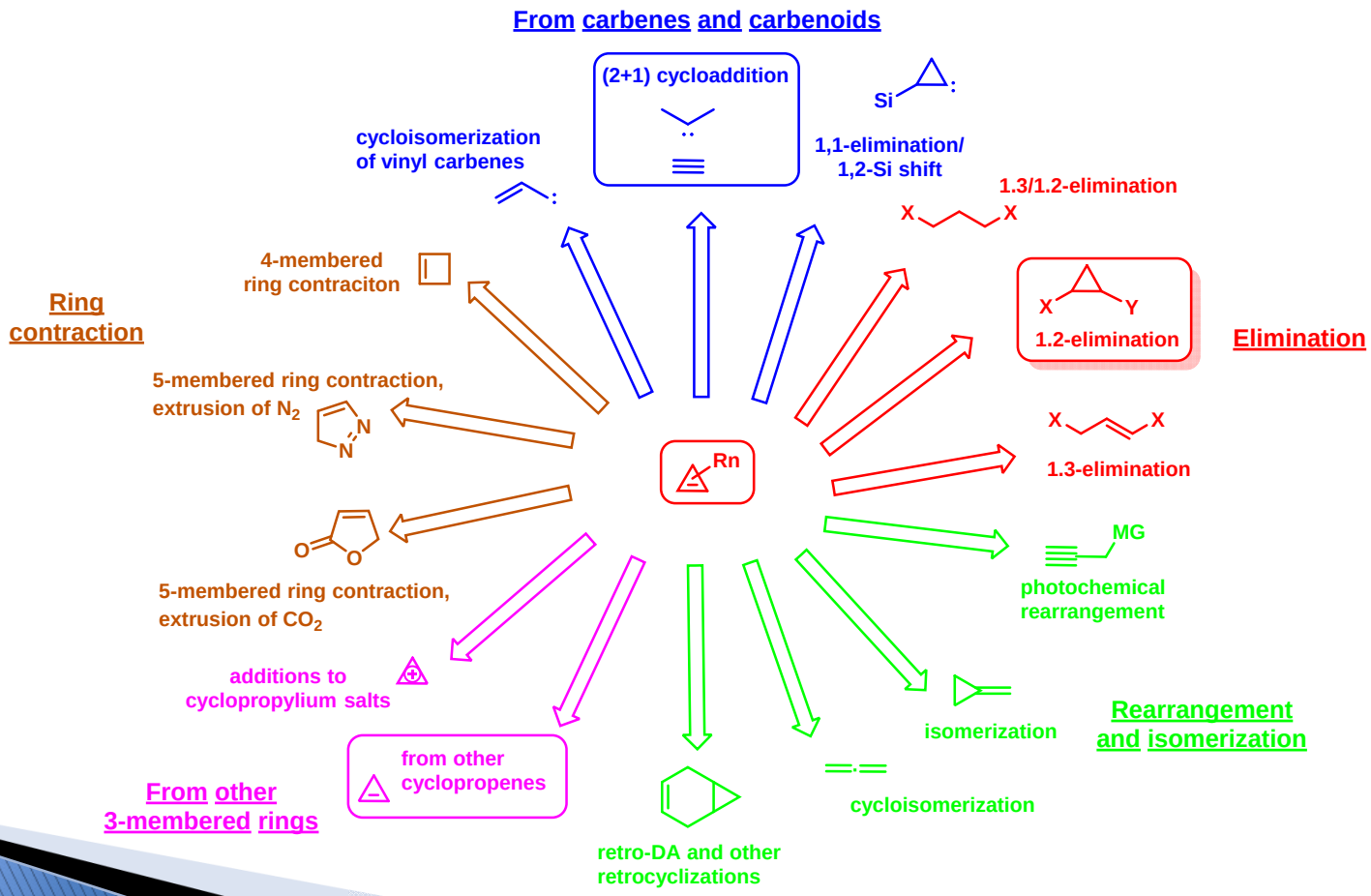
Ethylene: C-C 1.34 Å
Acetylene: C-C 1.20 Å

Because the ring is **highly strained**, cyclopropenes are both **difficult to prepare** and **interesting to study**

F. Allen, *Tetraheddron*, **1982**, *38*, 645

General informations → Synthesis →

General scheme of all the ways to synthesize cyclopropenes



M. Rubin, M.Rubina, V. Gevorgyan, *Synthesis*, **2006**, *8*, 1221

(2+1) Cycloaddition between alkynes and carbenes or carbenoids

IUPAC Nomemclature of cycloaddition

Website: http://goldbook.iupac.org/C01496.html

IUPAC Nomemclature of cycloaddition

Use **[x+y] (square brackets)** for the number of **electrons** involved in the transformation
Use **(x+y) (parenthesis)** for the number of **atoms** involved in the transformation

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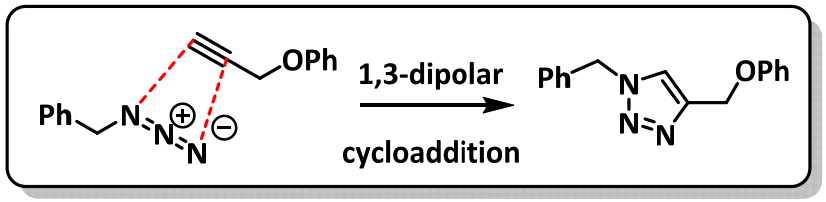
Example of a **1,3-dipolar cycloaddition**:



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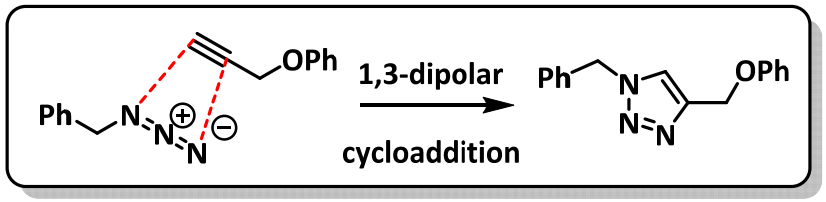

1,3-dipolar cycloadditions can be called:

(3+2) cycloaddition (number of atoms)
or **[4+2] cycloaddition** (number of electrons)

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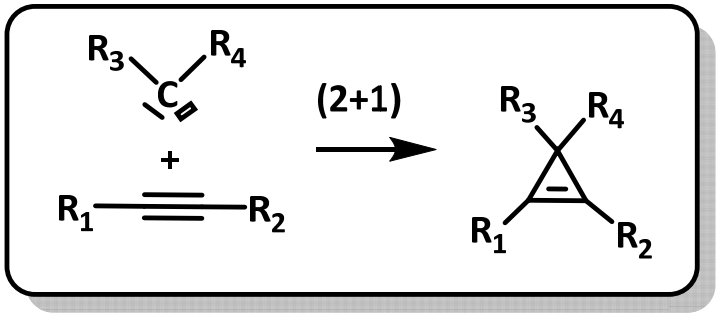
(2+1) Cycloaddition between alkynes and carbenes or carbenoids

(2+1) Cycloaddition between alkynes and carbenes or carbenoids

General scheme



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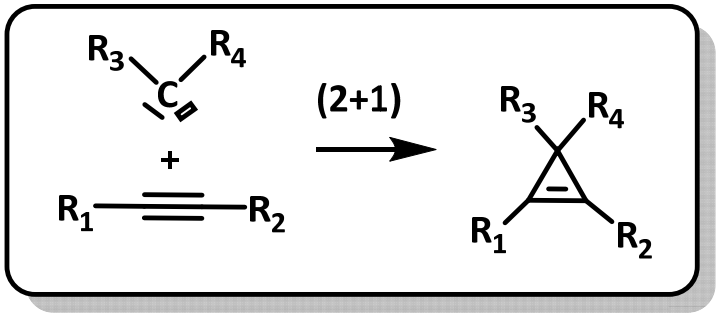

Two types of cycloadditions

(2+1) Cycloaddition between alkynes and carbenes or carbenoids

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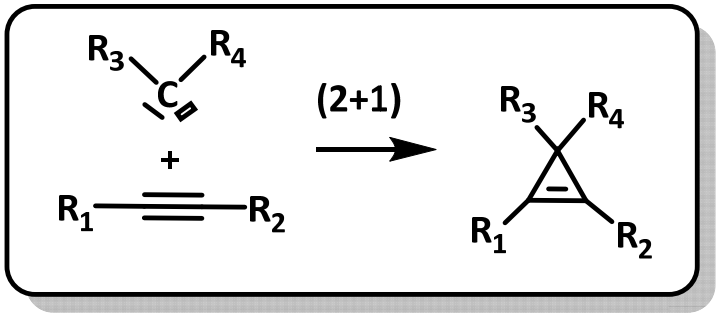


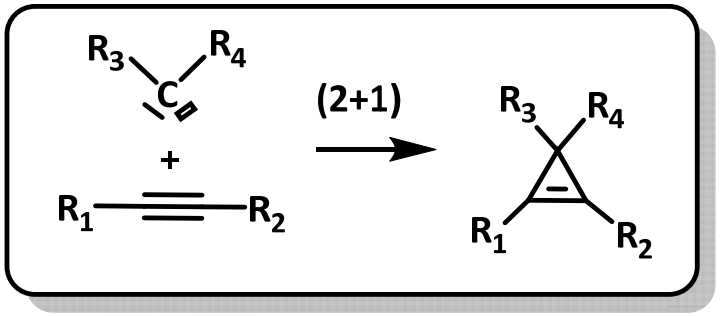
Two types of cycloadditions

Transition-Metal-Catalysed (carbenoids):

Rh Ag Ir Co Cu Zn

(2+1) Cycloaddition between alkynes and carbenes or carbenoids

General scheme



Two types of cycloadditions

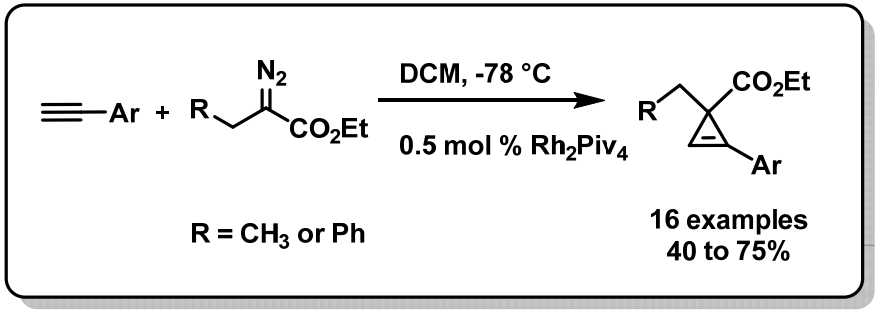
Transition-Metal-Catalysed (carbenoids):

Rh Ag Ir Co Cu Zn

Transition-Metal-Free:

In situ generated carbenes

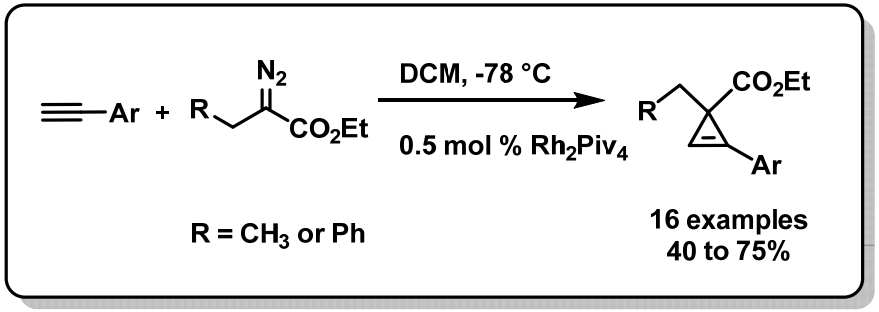
Transition-Metal-Catalysed cycloadditions



First general method for cyclopropenation that **tolerates ß-hydrogens**
Highly substituted cyclopropenes bearing an ester and different aromatics

P. Panne, J. Fox, *J. Am. Chem. Soc.*, **2006**, *129*, 22

Transition-Metal-Catalysed cycloadditions



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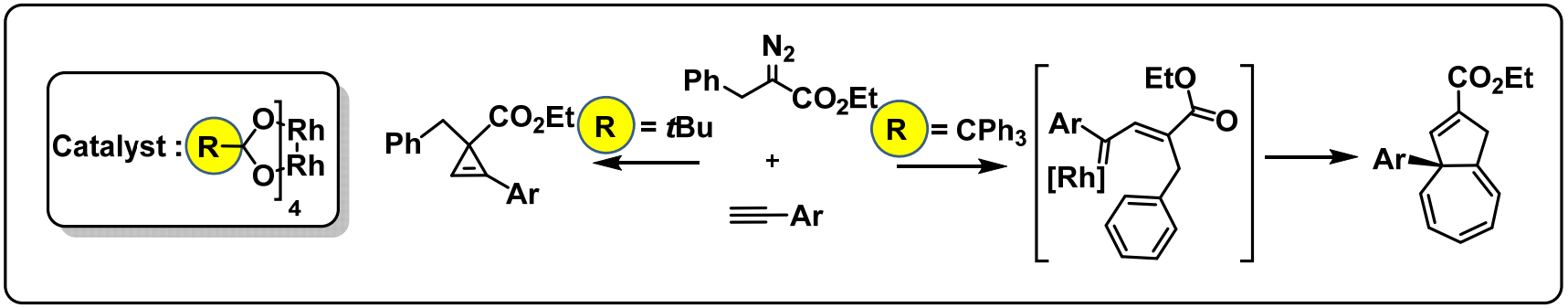
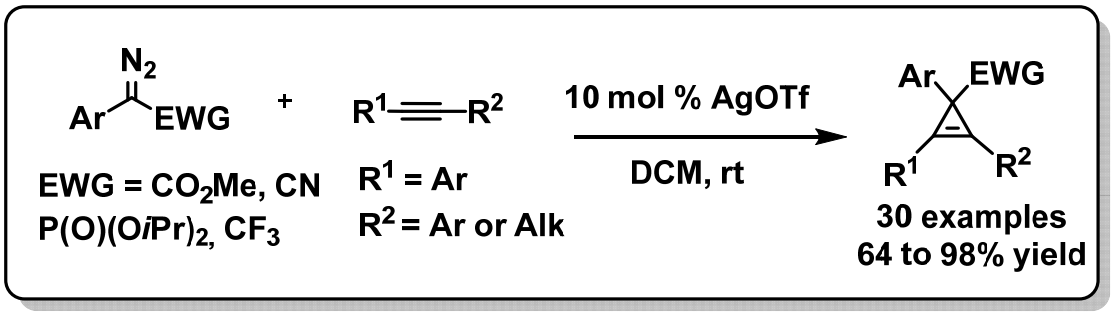


Creation of distinct types of complex molecules from identical starting materials based solely on **catalyst selection**

P. Panne, J. Fox, *J. Am. Chem. Soc.*, **2006**, *129*, 22

Transition-Metal-Catalysed cycloadditions



J.Briones, H. Davies, *Org. Let.*, **2011**, *13*, 3984

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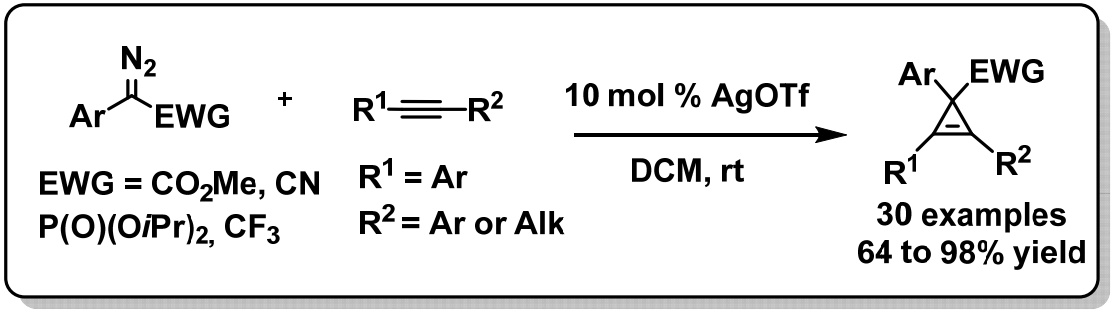

Silver triflate: efficient for the **cyclopropenation of internal alkynes** using donor-/-acceptor-substituted diazo compounds as carbenoid precursors.

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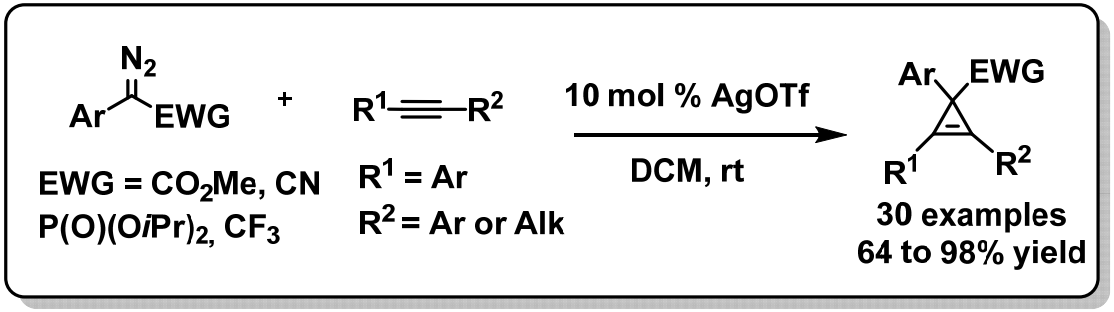

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Highly substituted cyclopropenes

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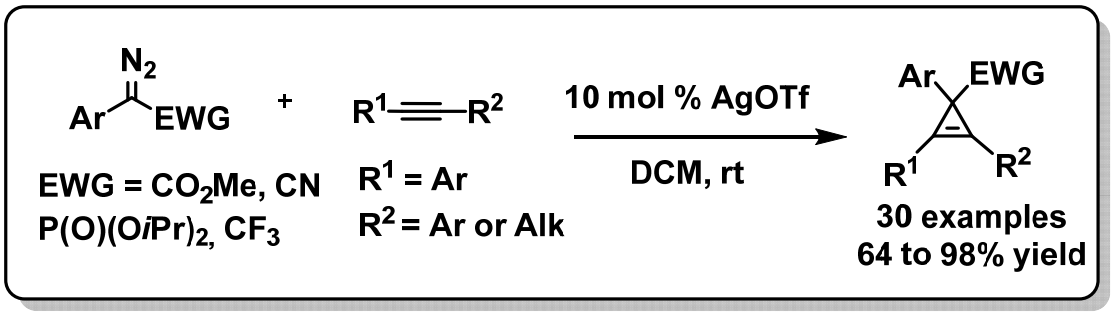

Silver triflate: efficient for the **cyclopropenation of internal alkynes** using donor-/-acceptor-substituted diazo compounds as carbenoid precursors.

Highly substituted cyclopropenes

Cannot be synthesized via Rh(II)-catalysed carbenoid chemistry (steric hindrance)

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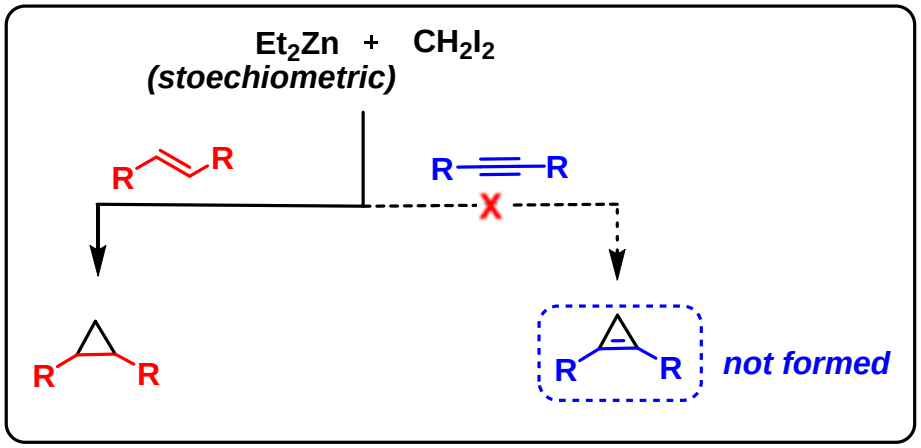
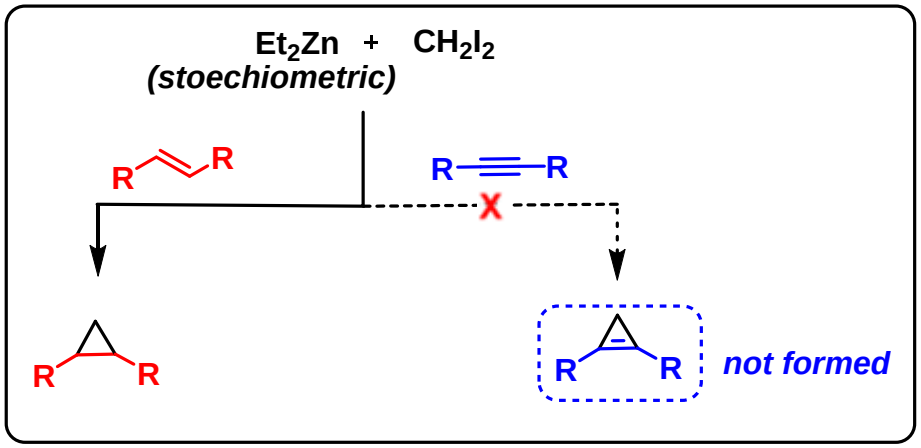
Transition-Metal-Catalysed cycloadditions



Simmons-Smith does not work with alkynes

M. Gonzalez, L. Lopez, R. Vincente, *Org. Let.*, **2014**, *16*, 5780

Transition-Metal-Catalysed cycloadditions



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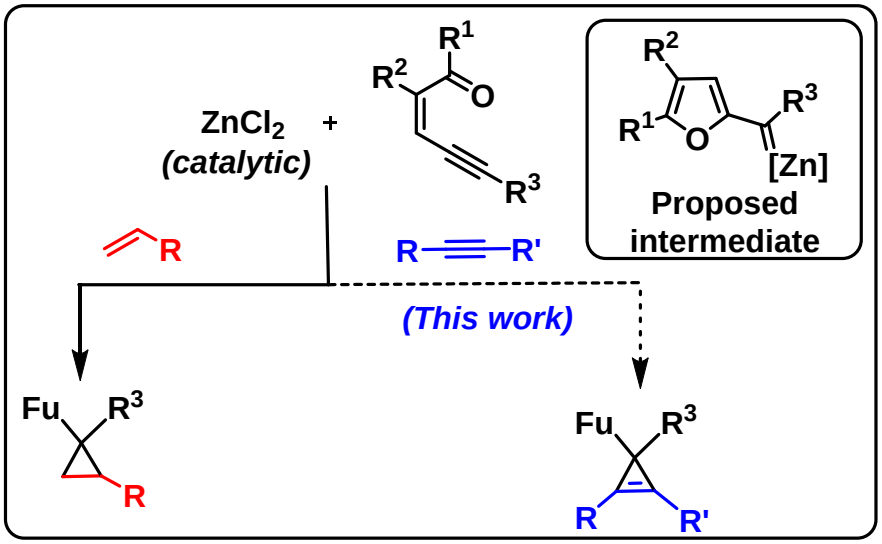
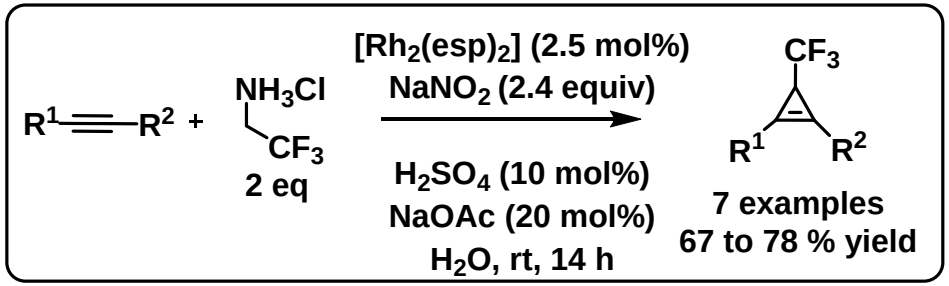


First zinc-catalyzed cyclopropenation
Inexpensive and **less toxic catalyst**
Mild conditions (25 °C, DCM, 0.5-7 h)

M. Gonzalez, L. Lopez, R. Vincente, *Org. Let.*, **2014**, *16*, 5780

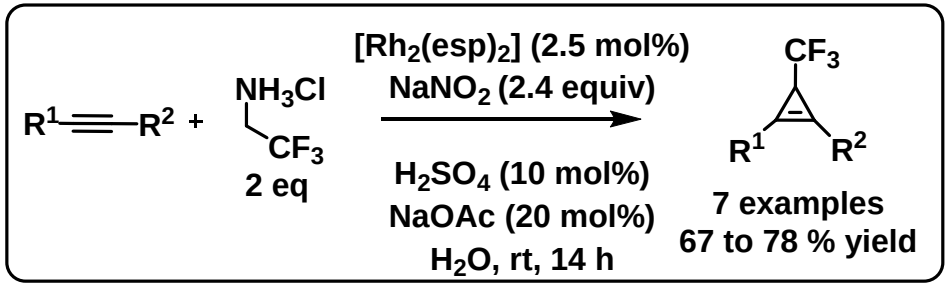
Transition-Metal-Catalysed cycloadditions



Highly useful subunits (CF_3 groups and functionalisable cyclopropenes)

B. Morandi, E. Carreira, *Angew. Chem.*, **2010**, *49*, 4294

Transition-Metal-Catalysed cycloadditions



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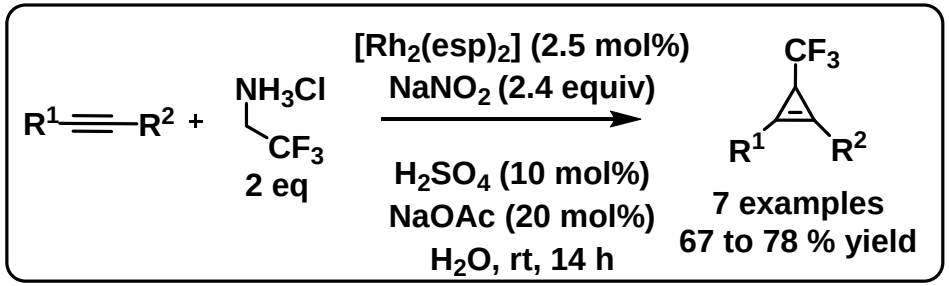


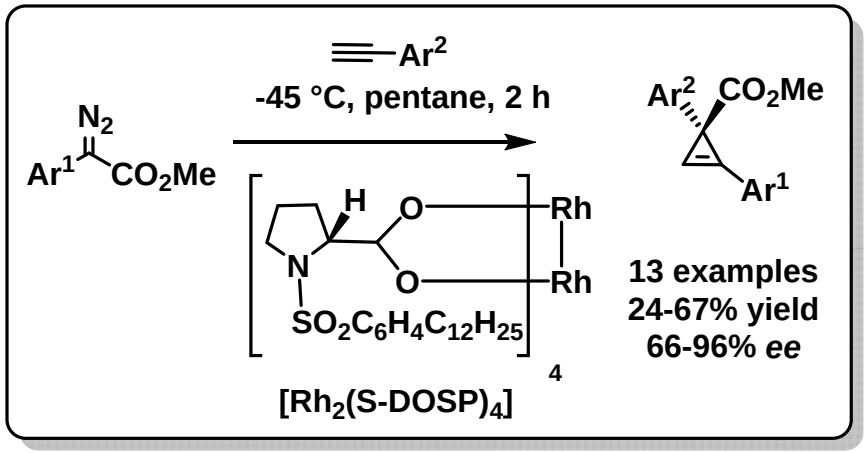
Highly useful subunits (CF_3 groups and functionalisable cyclopropenes)

First cyclopropenation of alkynes with trifluoromethyldiazomethane

Key: identification of a **robust catalyst** to support harsh conditions

B. Morandi, E. Carreira, *Angew. Chem.*, **2010**, *49*, 4294

Enantioselective Transition-Metal-Catalysed cycloadditions



$[Rh_2(S\text{-DOSP})_4]$ **effective catalyst** for highly **enantioselective cyclopropenation**

J. Briones, J. Hansen, K. Hardcastle, J. Autschbach, H. Davies; *J. Am. Chem. Soc.*, **2010**, *132*, 17211

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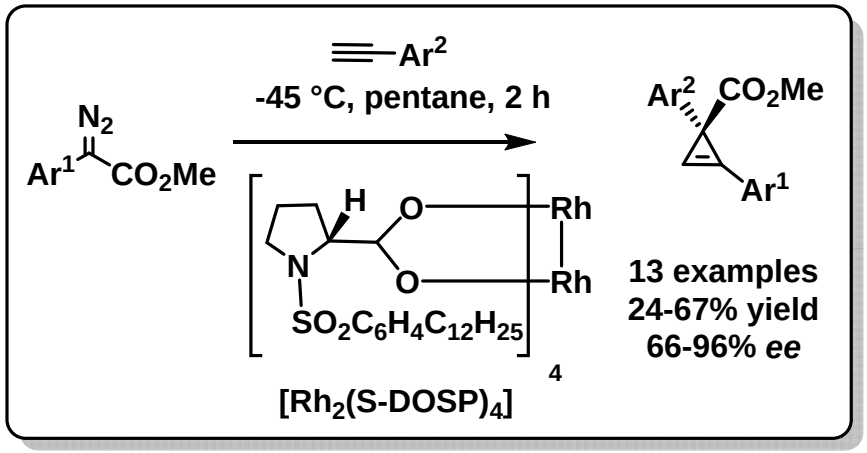

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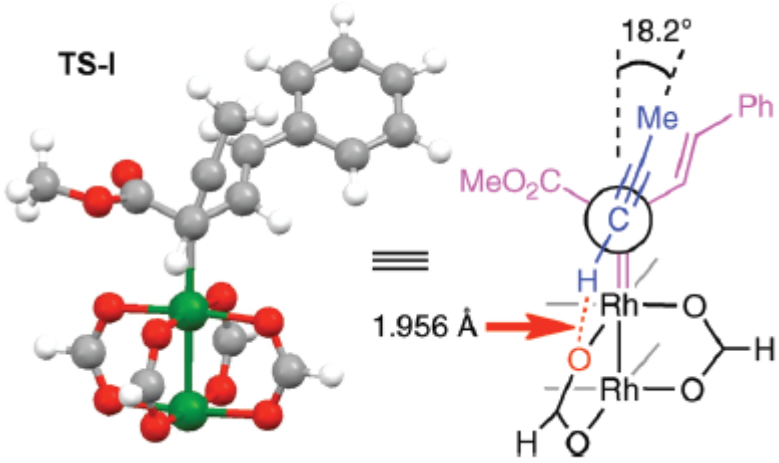

High enantioselectivity governed by: **Specific orientation** of the approach of the alkyne **due to hydrogen bonding**

J. Briones, J. Hansen, K. Hardcastle, J. Autschbach, H. Davies; *J. Am. Chem. Soc.*, **2010**, *132*, 17211

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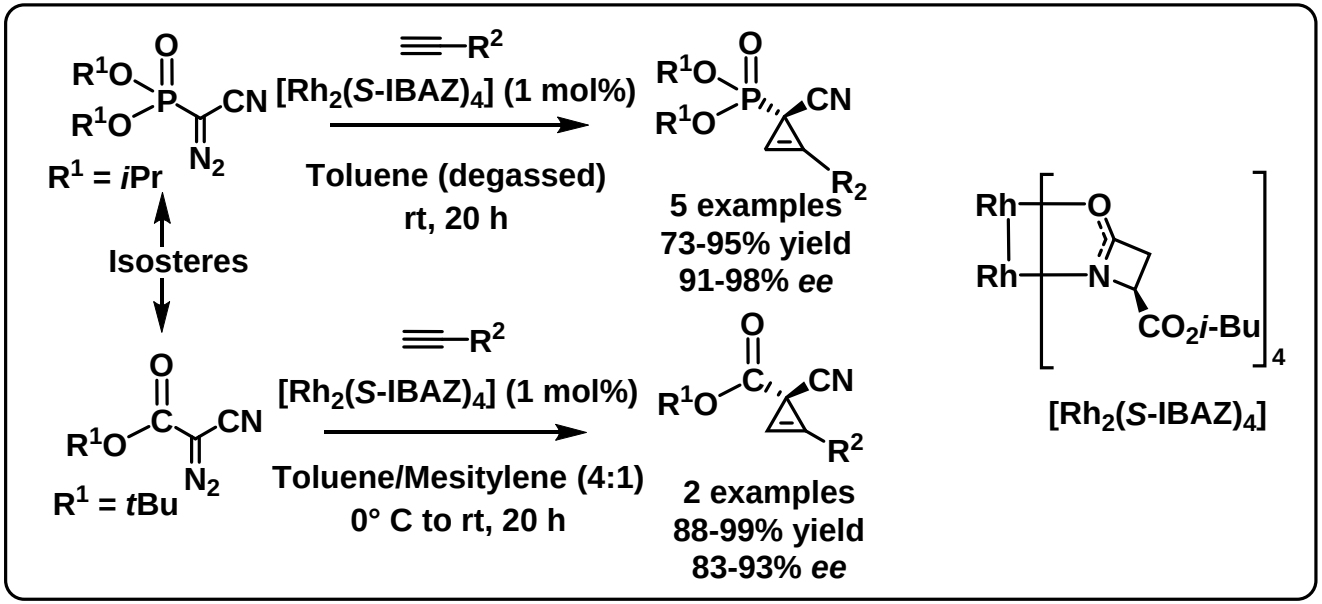
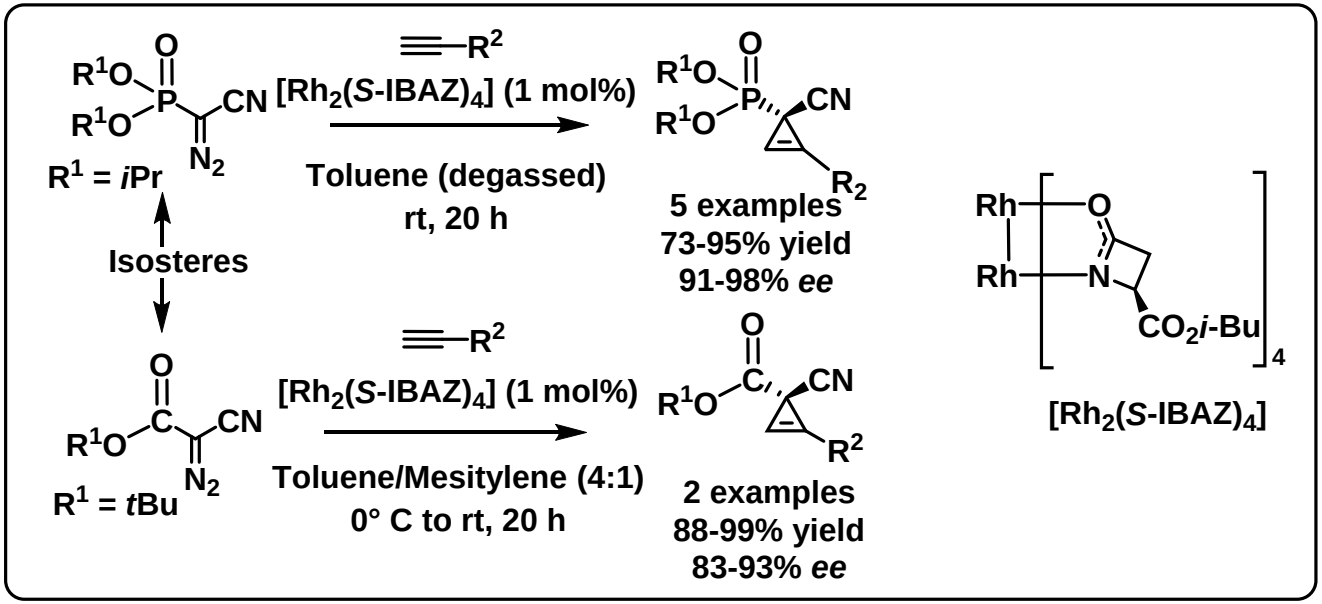
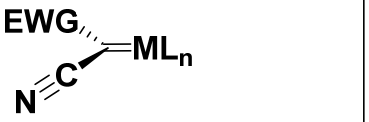


First catalytic asymmetric route to **diacceptor** cyclopropenylphosphonates

V. Lindsay, D. Fiset, P. Gritsch, S. Azzi, A. Charrette, *J. Am. Chem. Soc.*, **2013**, *135*, 1463

Enantioselective Transition-Metal-Catalysed cycloadditions





in-plane conformation
L_nM=C forced to conjugated to CN
more electrophilic carbenoid

First catalytic asymmetric route to **diacceptor** cyclopropenylphosphonates

Takes advantages of the **particuliar reactivity** of the cyanocarbenes

V. Lindsay, D. Fiset, P. Gritsch, S. Azzi, A. Charrette, *J. Am. Chem. Soc.*, **2013**, *135*, 1463

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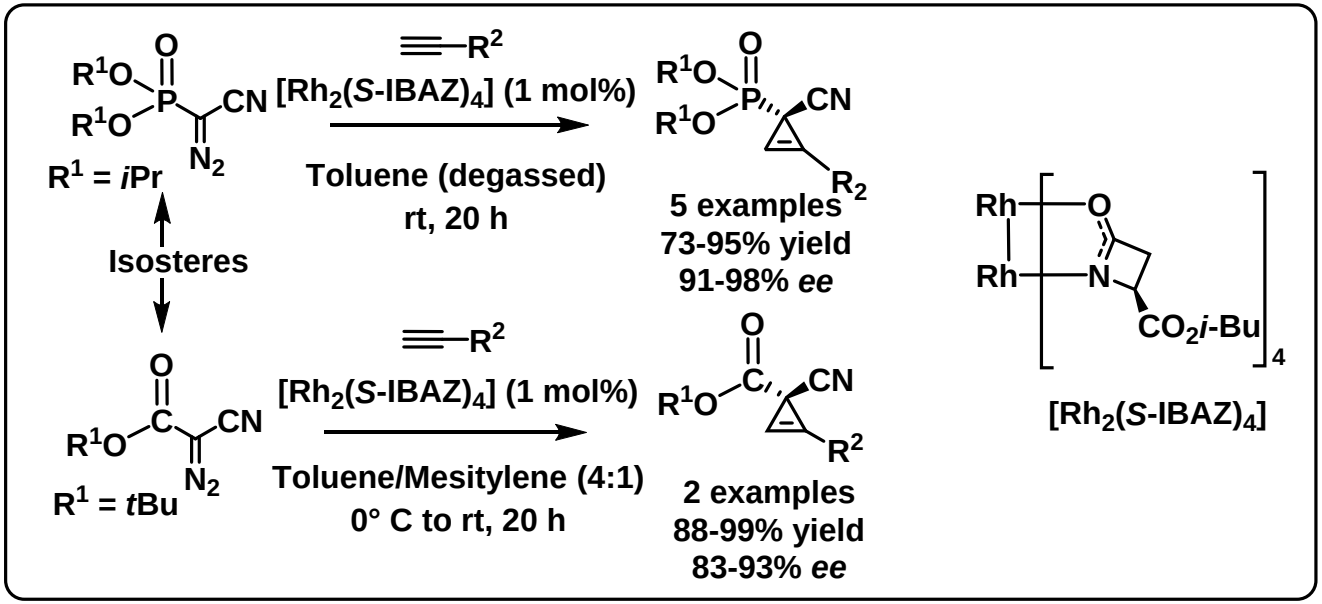

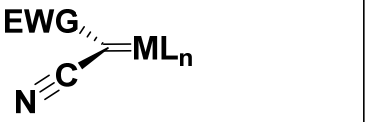

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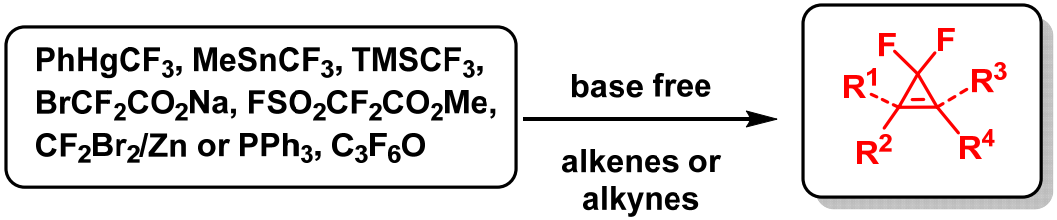
Takes advantages of the **particuliar reactivity** of the cyanocarbenes

Scope extented to **ester cyclopropenes** and substituted **allenes**

V. Lindsay, D. Fiset, P. Gritsch, S. Azzi, A. Charrette, *J. Am. Chem. Soc.*, **2013**, *135*, 1463

Transition-Metal-Free cycloadditions



Increasing demand for ***gem*-difluorocyclopropa(e)nes** and hetereoatom difluoromethyl compounds

L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem.*, **2013**, *52*, 12390

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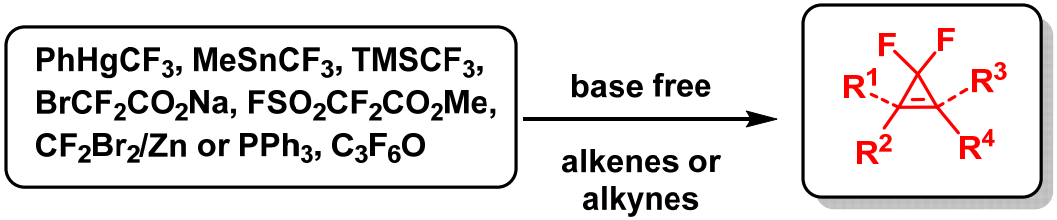

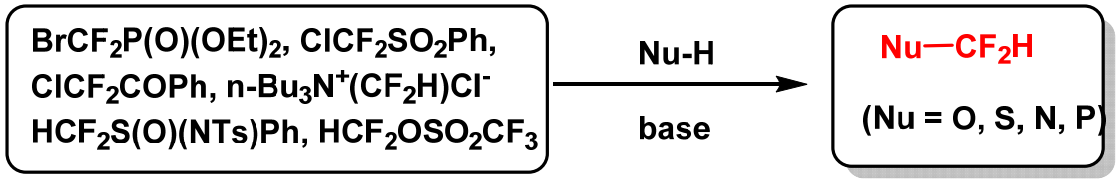

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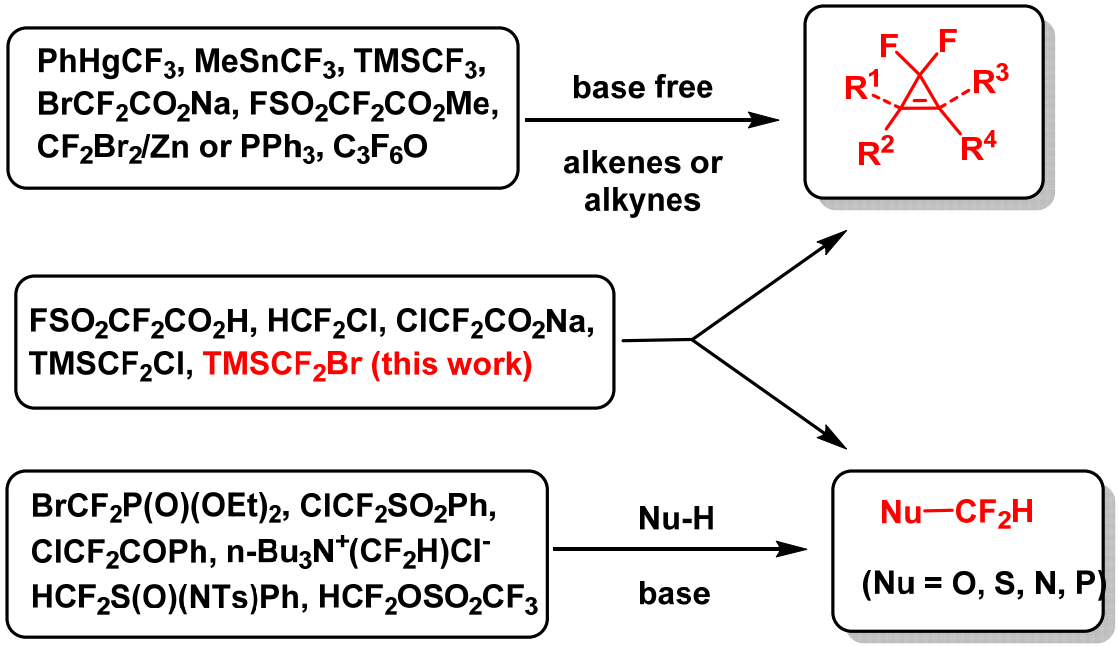

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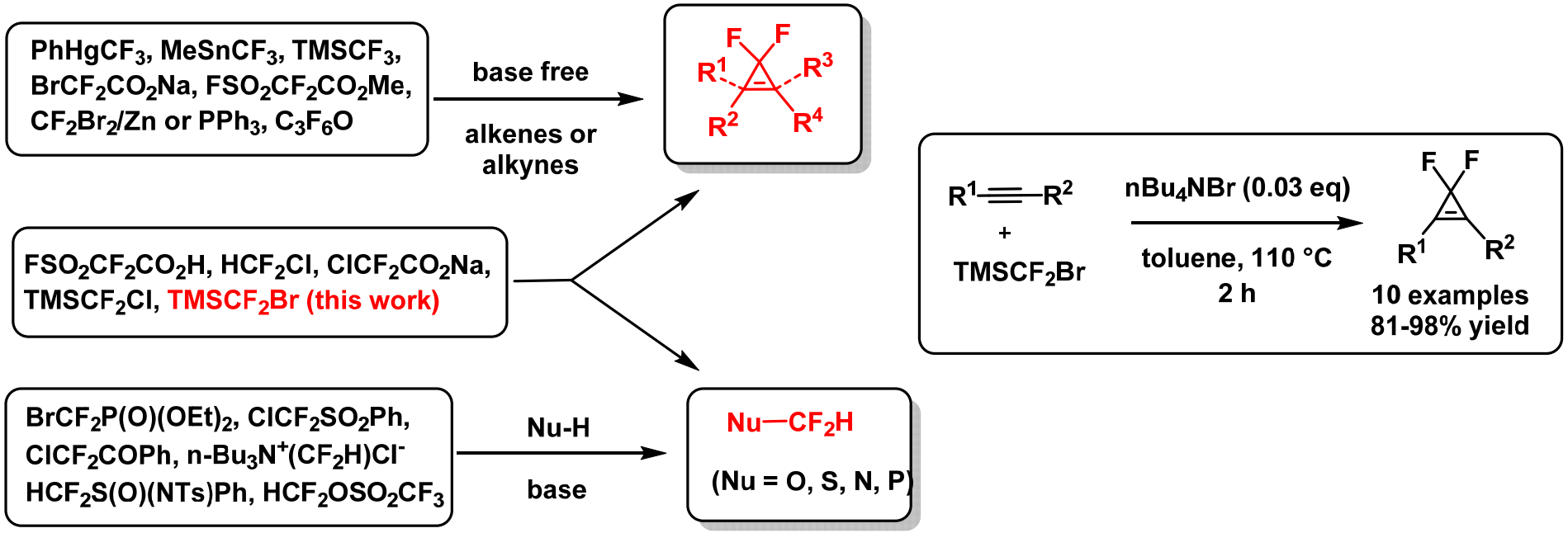

Increasing demand for ***gem*-difluorocyclopropa(e)nes** and hetereoatom difluoromethyl compounds

Highly efficient method for the **difluoromethylation**

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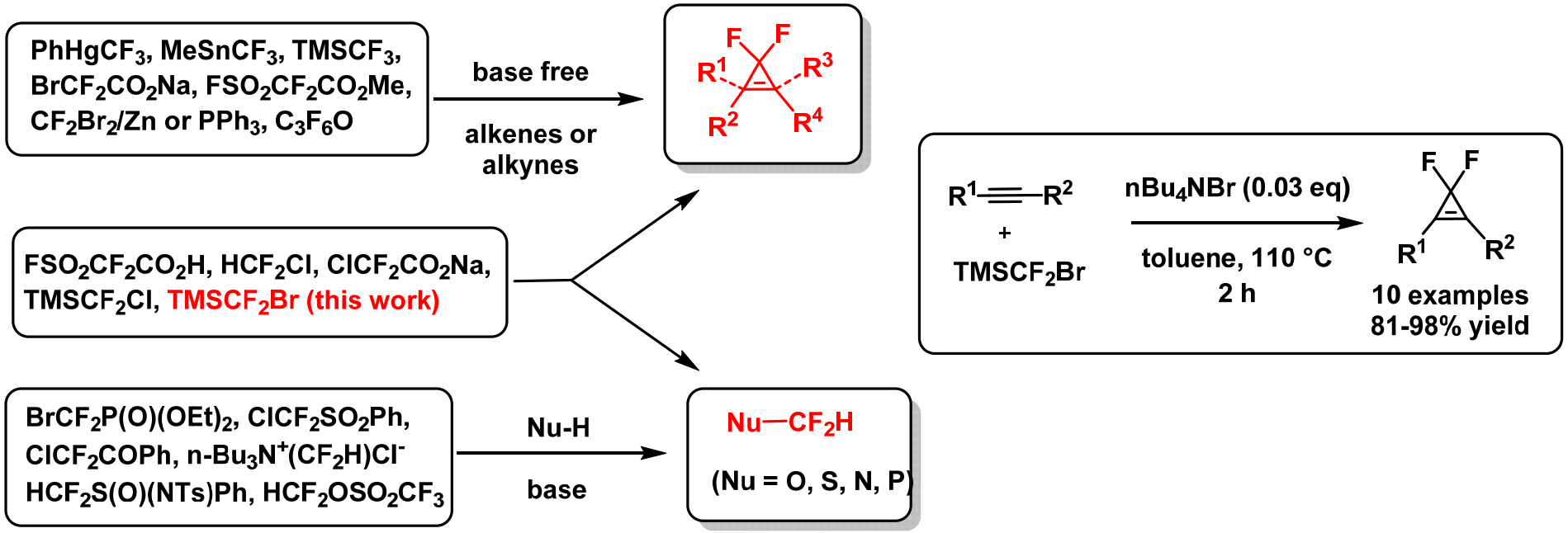

Increasing demand for ***gem*-difluorocyclopropa(e)nes** and hetereoatom difluoromethyl compounds

Highly efficient method for the **difluoromethylation**

Much safer and **more convenient** for large-scale application than other methods

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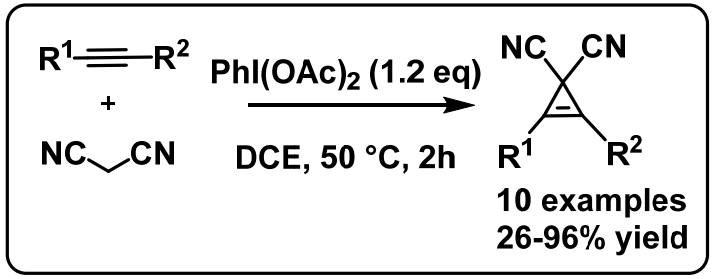
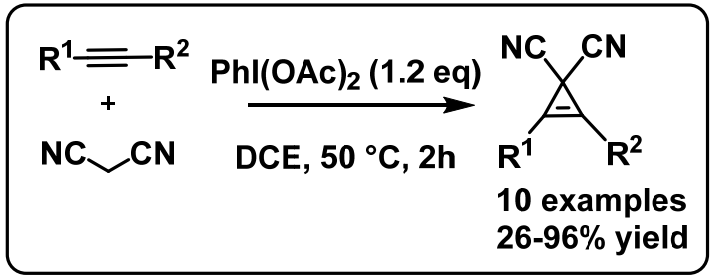


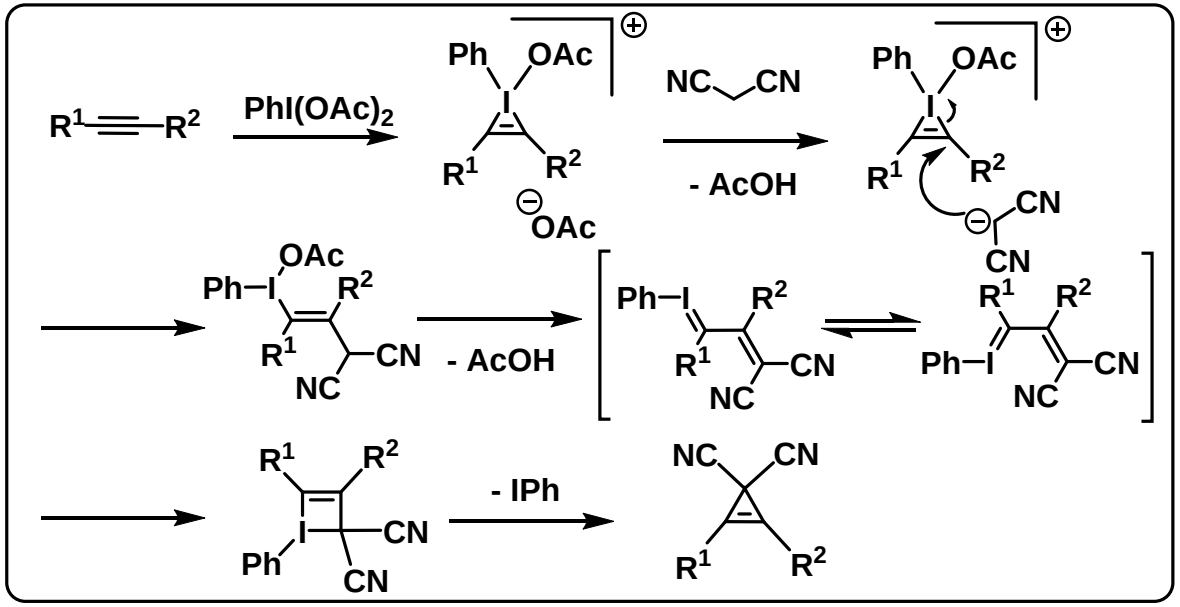
First Hypervalent iodine-mediated cyclopropenation under mild conditions

S. Lin, M. Li, Z. Dong, F. Liang, J. Zhang, *Org. Biomol. Chem.*, **2014**, *12*, 1341

Transition-Metal-Free cycloadditions



First Hypervalent iodine-mediated cyclopropenation under mild conditions



Hypervalent iodine-mediated cyclopropenation mechanism postulated by the authors

S. Lin, M. Li, Z. Dong, F. Liang, J. Zhang, *Org. Biomol. Chem.*, **2014**, *12*, 1341

1,2-Elimination - General scheme

W. Sherrill, R. Kim, M. Rubin, *Tetraheddron*, **2008**, *64*, 8610

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Limitations of the (2+1) cycloaddition:

- Poorly applicable to some substrates (i.a. aryl diazoacetates with EWG substituents)
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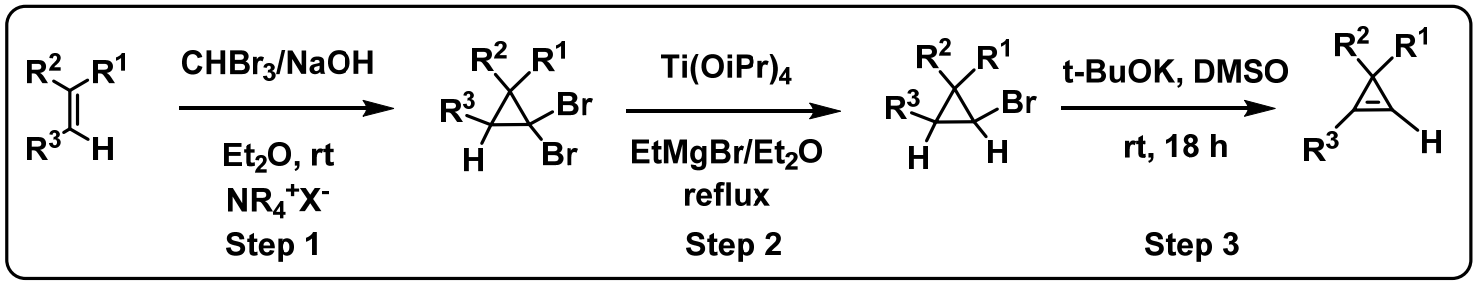
Good alternative: 1,2-Elimination



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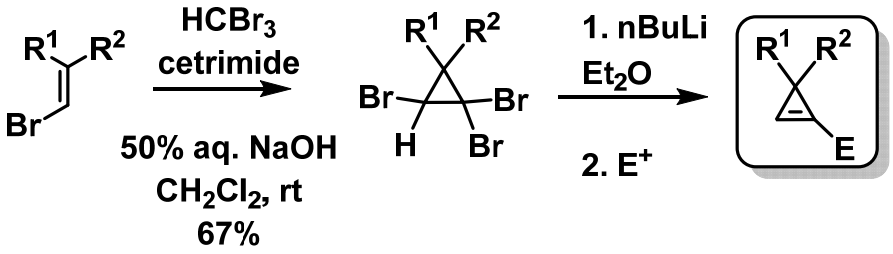

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L. Sydnes, E. Bakstad, *Acta Chem. Scand.*, **1996**, *50*, 446

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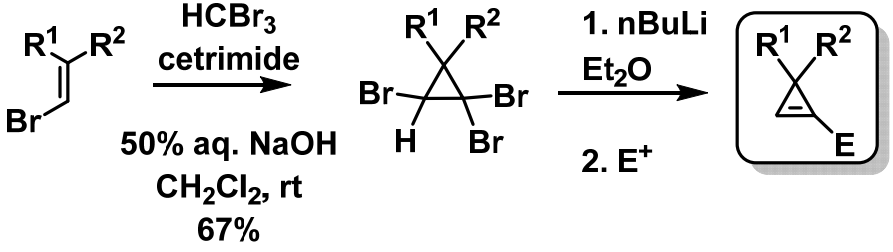

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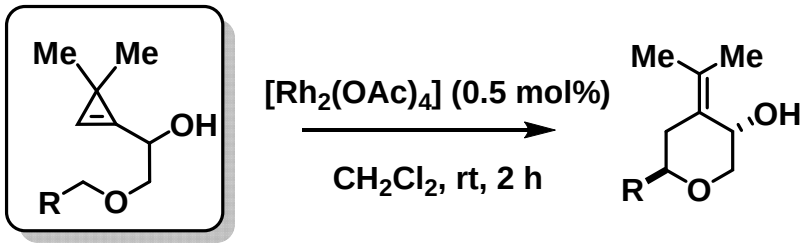

Rh-Catalyzed Stereoselective C(sp^3)H insertion

A. Archambeau, F. Miege, C. Meyer, J. Cossy
Angew. Chem., **2012**, *51*, 11540

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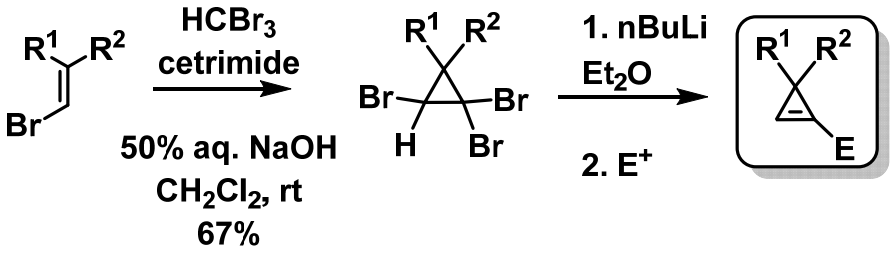

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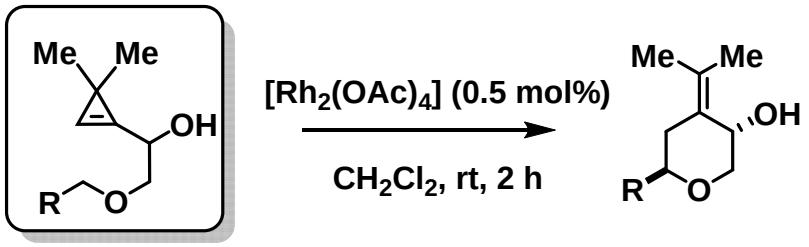

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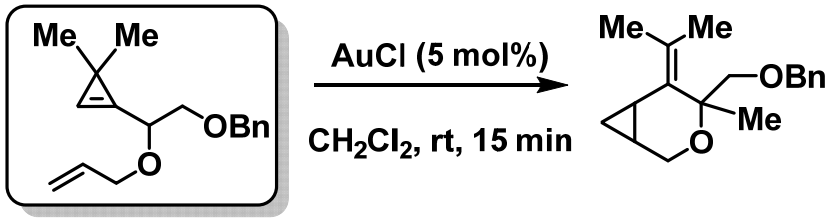

Au-Catalysed cycloisomerisation

F. Miege, C. Meyer, J. Cossy, *Chem. Eur. J.* **2012**, *18*, 7810

From other cyclopropenes

S. Chuprakov, D. Malyshev, A. Trofimov, V. Gevorgyan,
J. Am. Chem. Soc., **2007**, *129*, 14868

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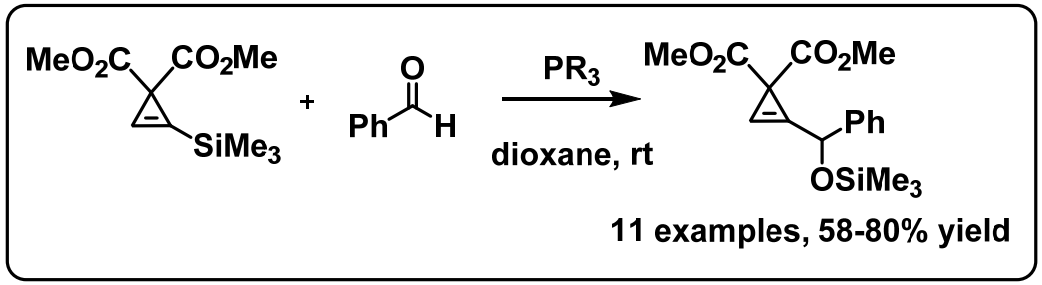

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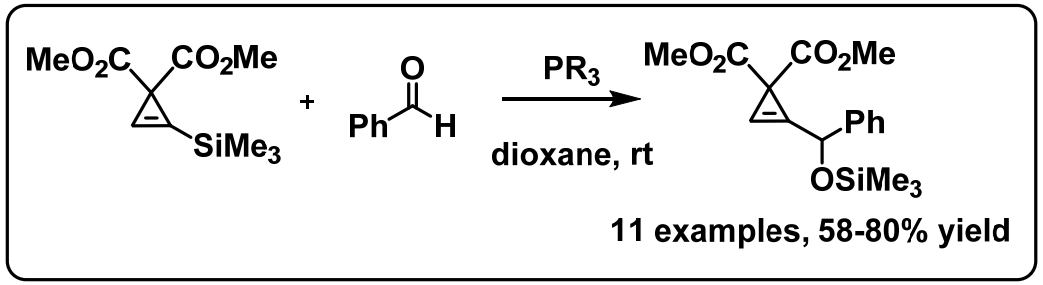

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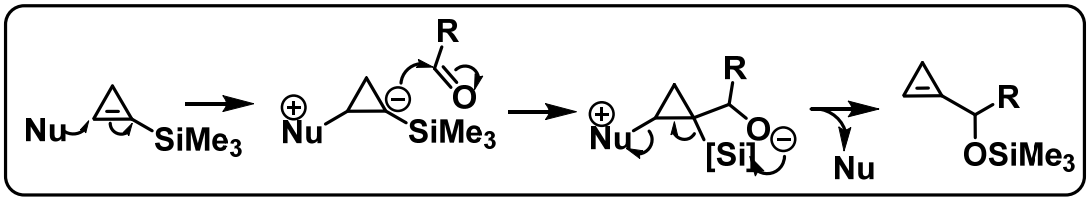

Mechanism

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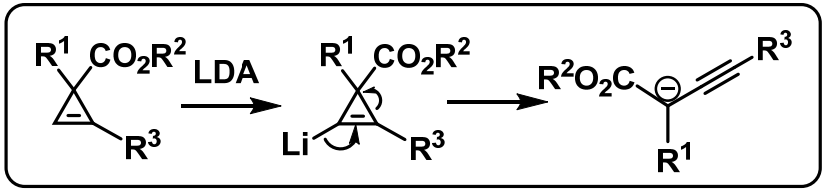
From other cyclopropenes

Stille Coupling Reactions with Base-Sensitive Cyclopropenes



Ring-opening of Cyclopenyl Lithium Species

E. Fordyce, T. Luebbers, H. W. Lam, *Org. Let.*, **2008**, *10*, 3993

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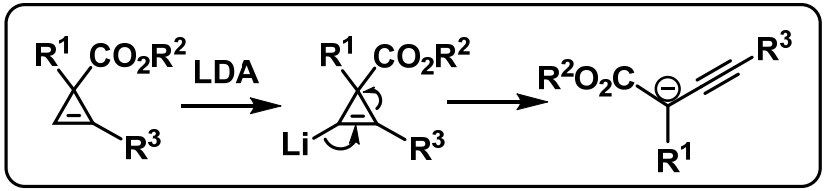

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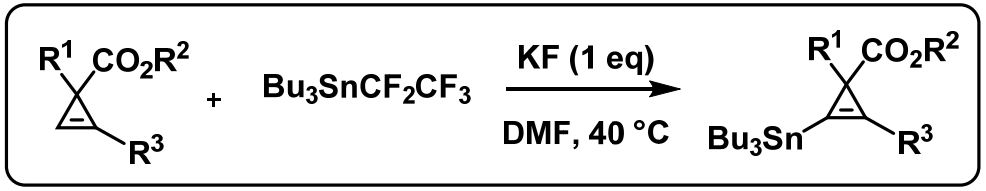

Stannylation of various cyclopropenes

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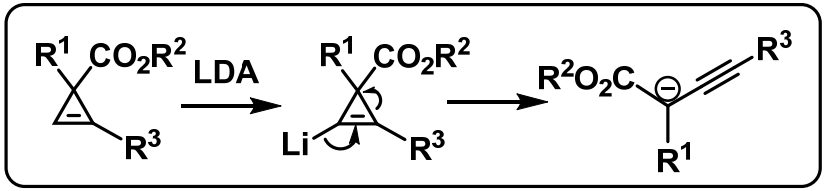

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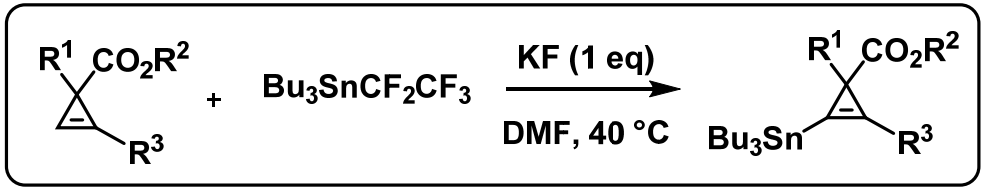

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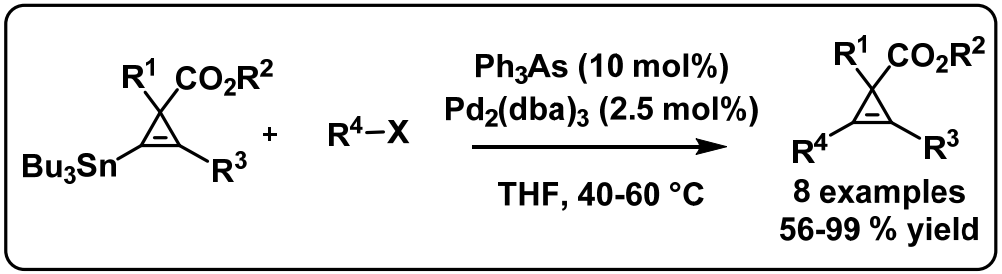

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Reactivity of cyclopropenes – General scheme

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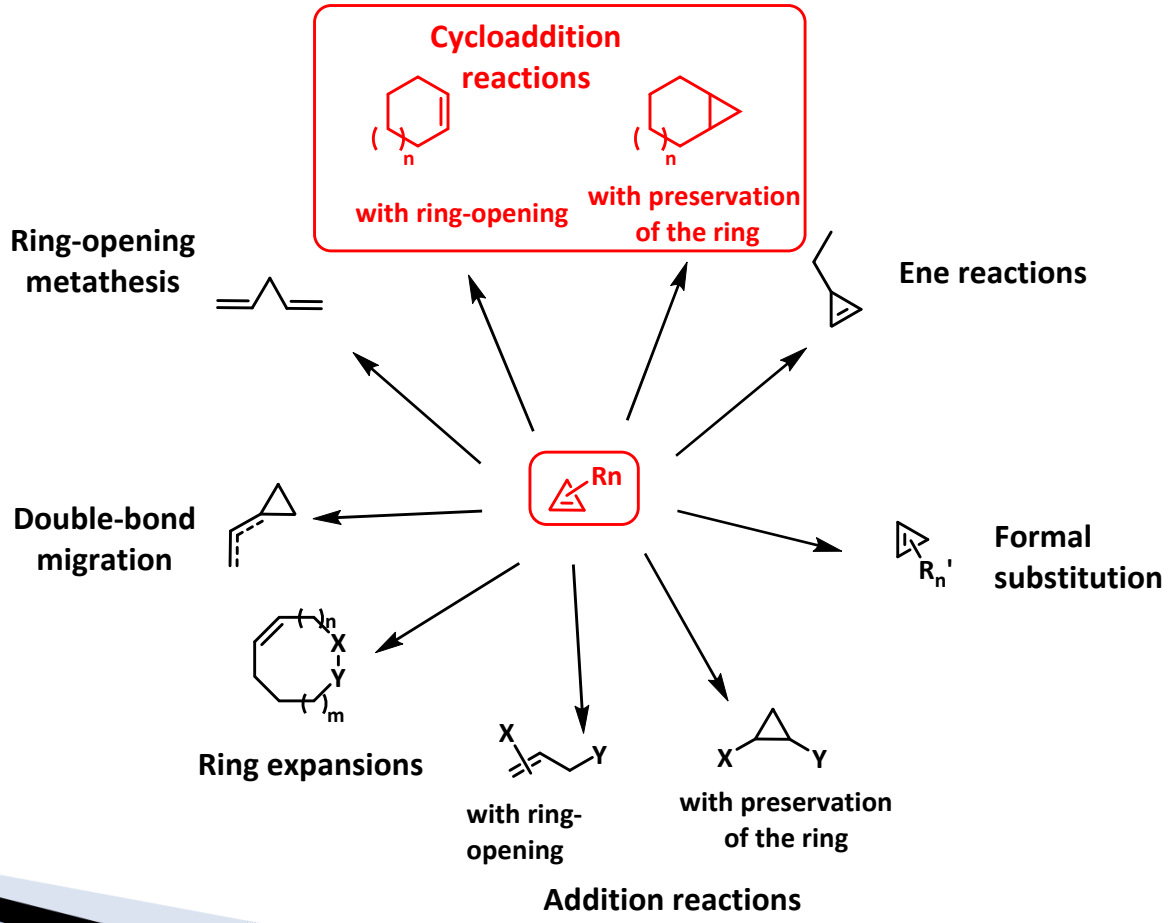

M. Rubin, M.Rubina, V. Gevorgyan, *Synthesis*, **2006**, *8*, 1221

(2+2+1) Pauson-Khand Cycloaddition

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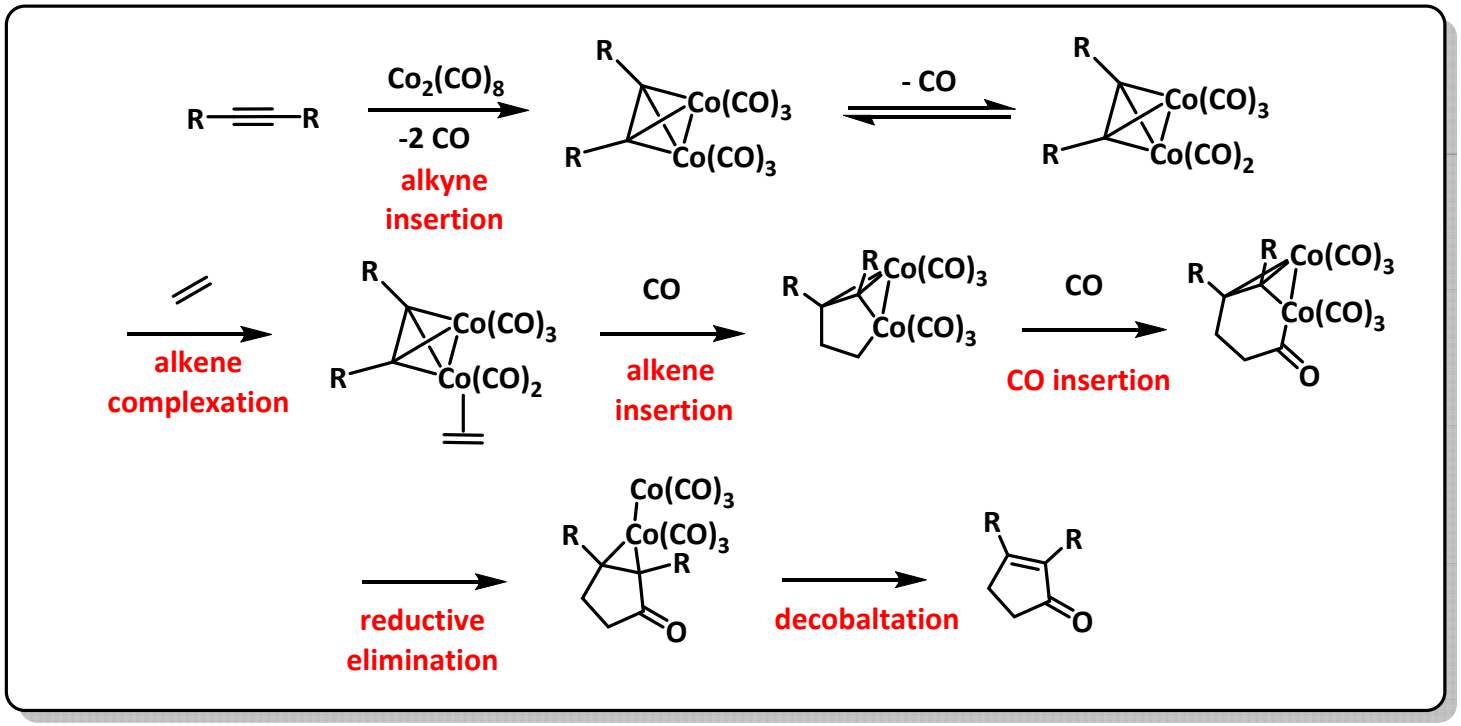

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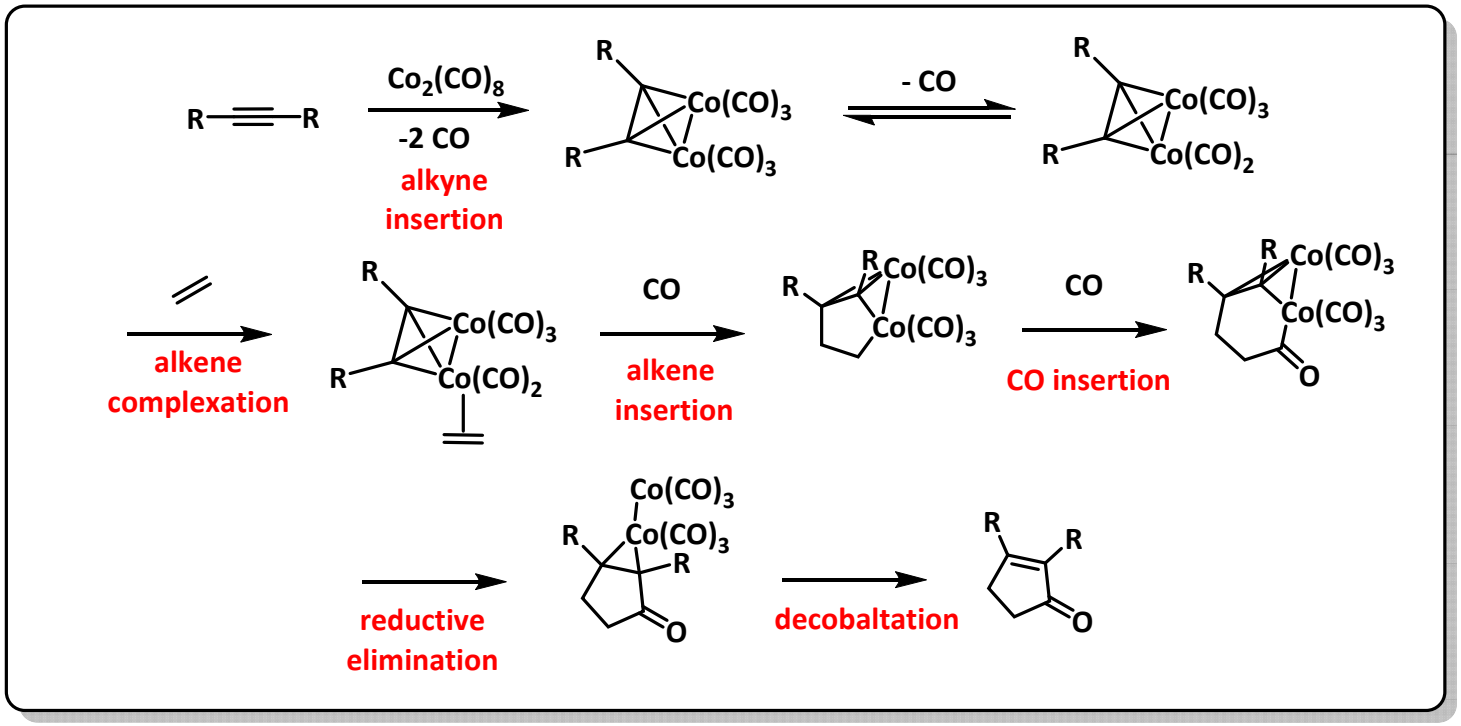


Applicable to cyclopropenes

(2+2+1) Pauson-Khand Cycloaddition - Application to cyclopropenes

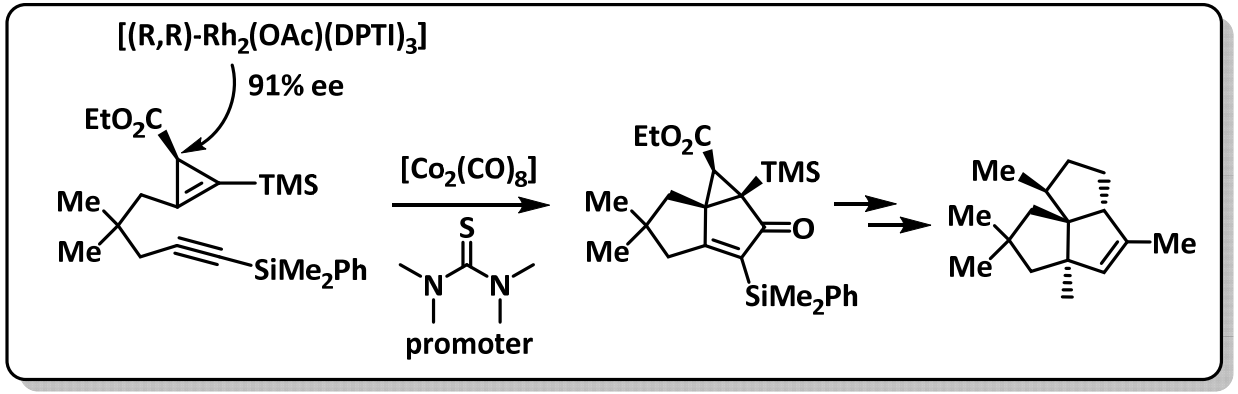
Enantioselective Synthesis of (–)-Pentalenene

M. Pallerla, J. Fox, *Org. Let.*, **2007**, *9*, 5625

(2+2+1) Pauson-Khand Cycloaddition - Application to cyclopropenes

Enantioselective Synthesis of (–)-Pentalenene

Using [2+2+1] Pauson-Khand **cycloaddition of cyclopropenes** as **key step**



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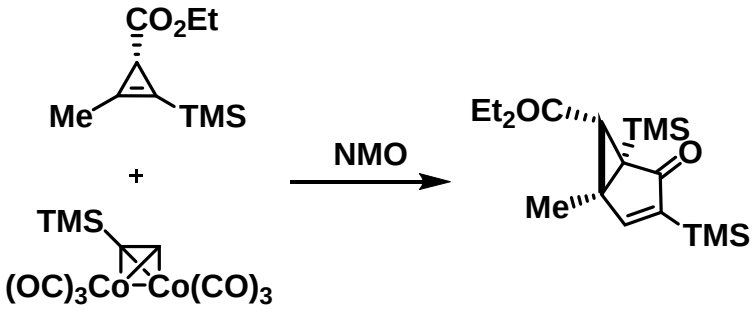
Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

An **unexpected discovery**…



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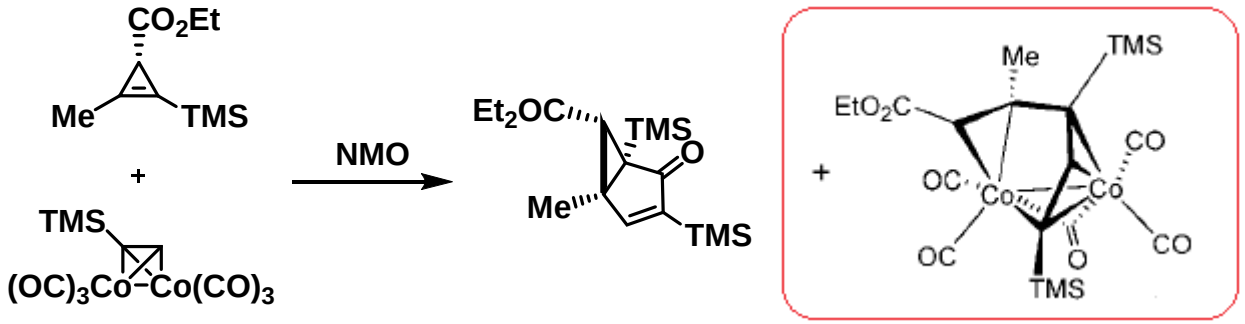

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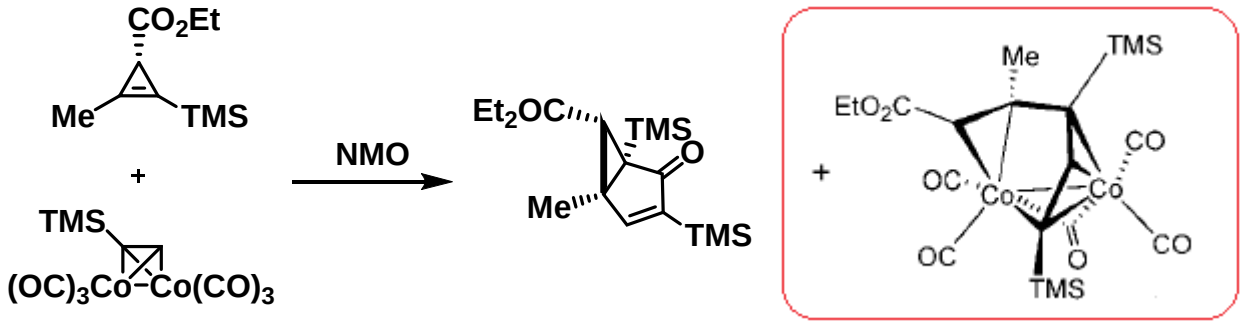

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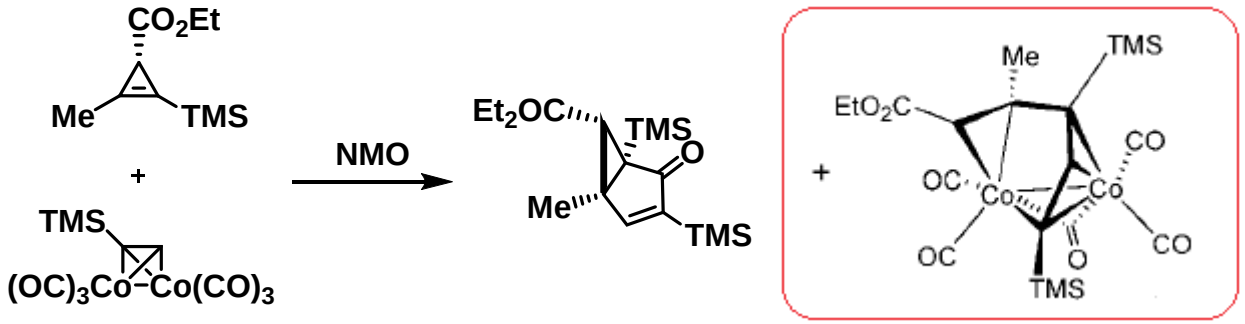

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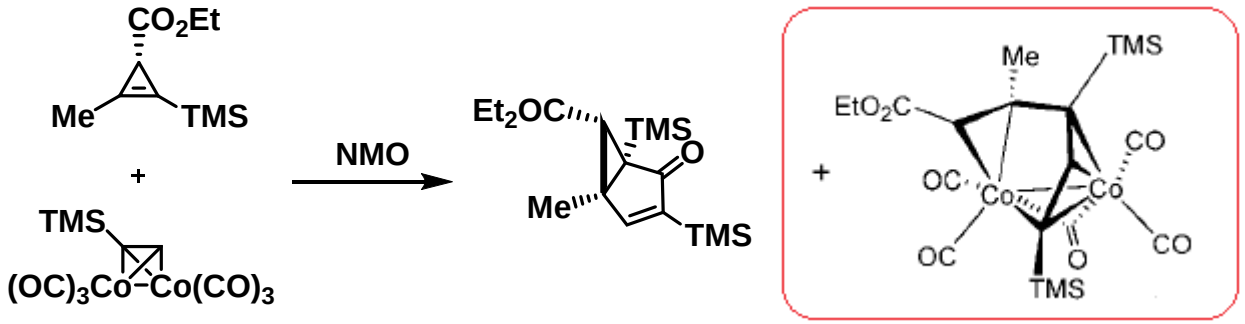

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First insight of what happens after the alkene insertion

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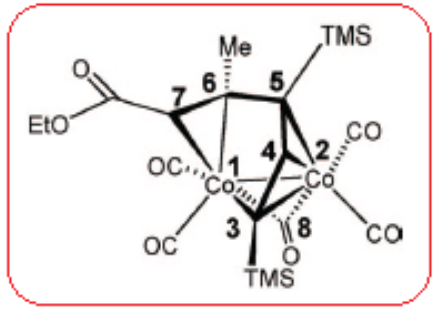

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By **silica gel chromatography**
Only **13% yield** due to partial decomposition during the purification

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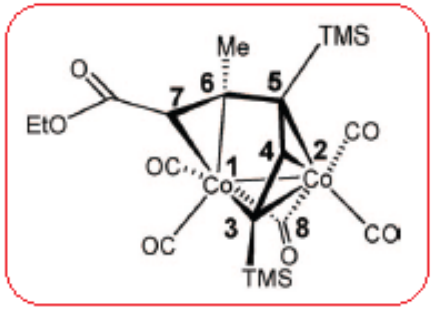

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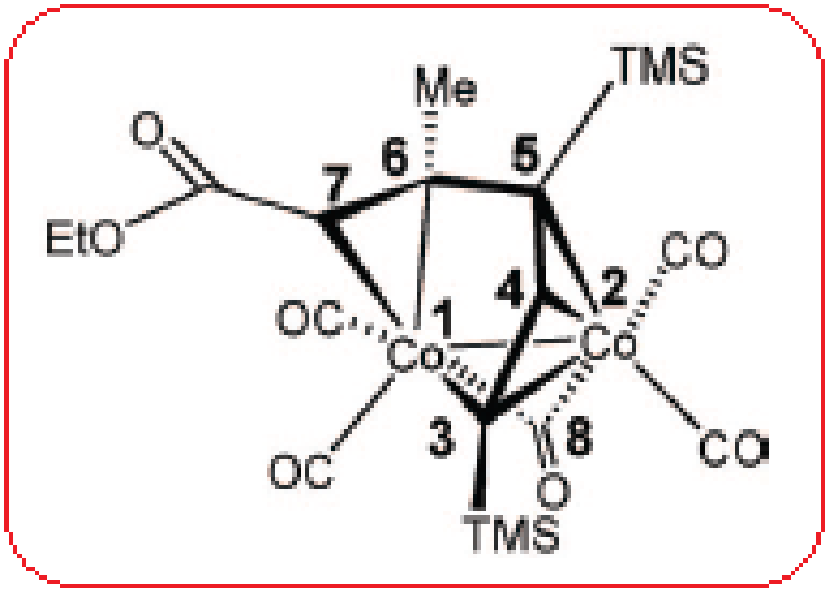

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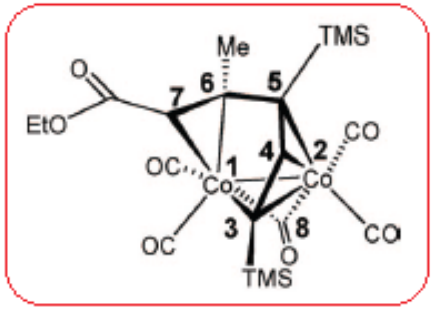

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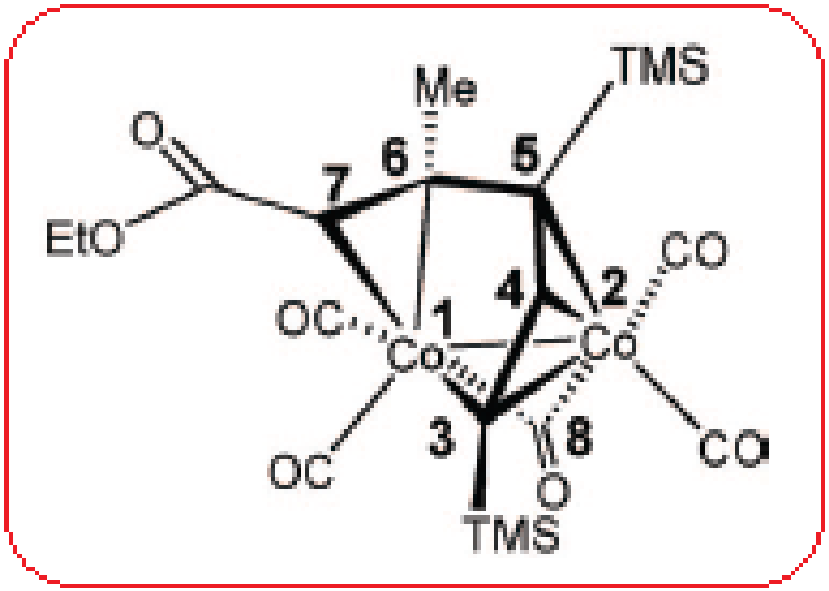

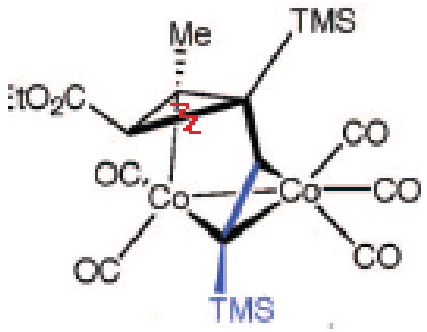

From the Fragmentation of cyclopropane

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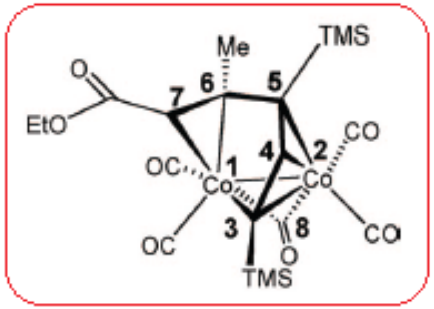

IR Analysis

υ = 4 external carbonyls: 2067, 2038, 2008 (I= 2)
υ(free CO) = 2170 cm^{-1} **(retro donation of Co)**

υ = 1 bridging carbonyl: 1853 cm^{-1}
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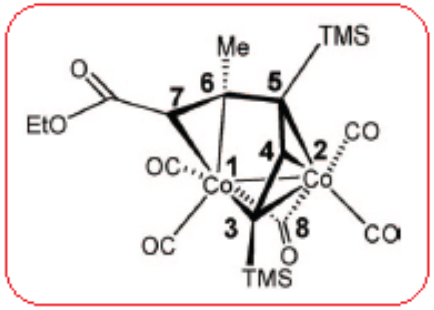

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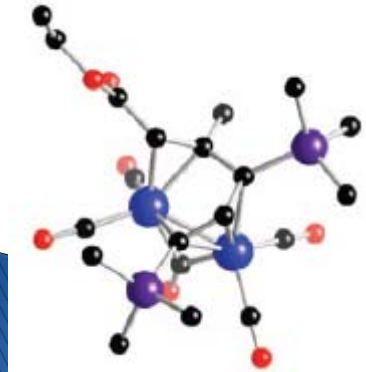

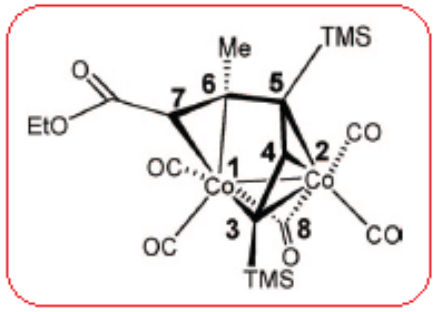

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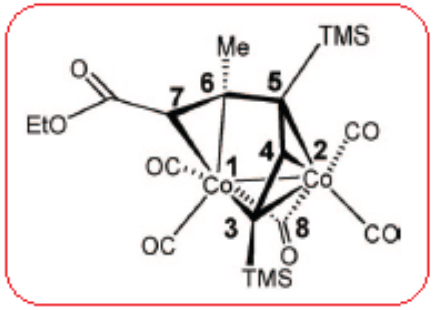

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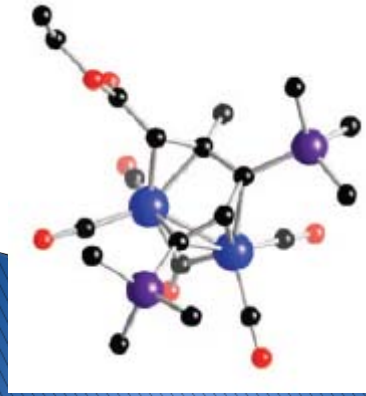

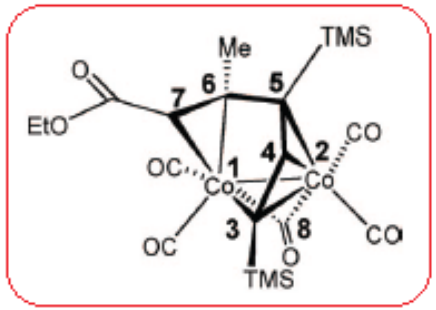

Selected bond lengths:

Co^1-Co^2 2.469 Å
Co^2-C^5 2.183 Å (longest Co-C bond)
Co^2-C^8 1.884 Å (smallest Co-C bond)

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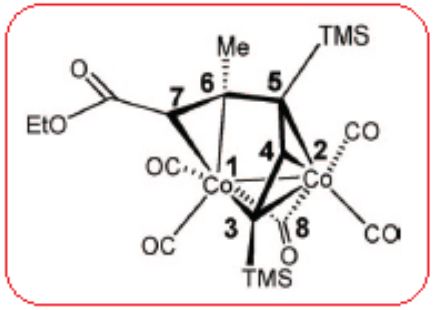

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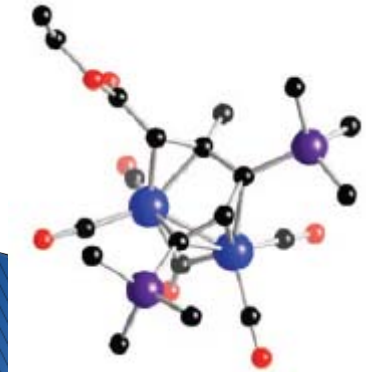
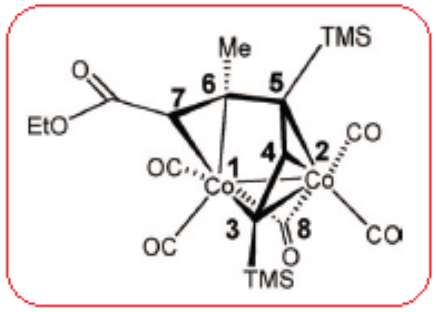


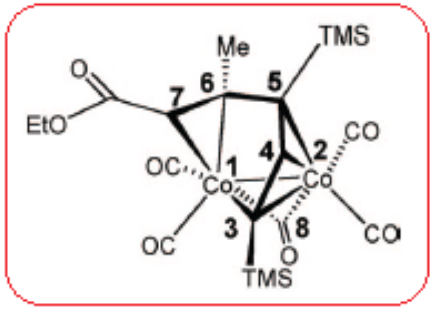


Selected bond lengths:
Co^1-Co^2 2.469 Å
Co^2-C^5 2.183 Å (longest Co-C bond)
Co^2-C^8 1.884 Å (smallest Co-C bond)

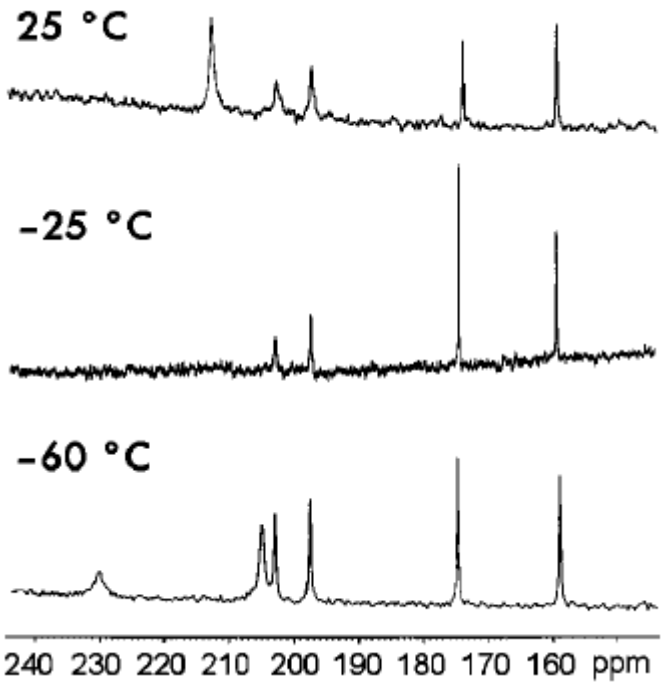
Selected angles:
Co^1-C^3-Co^2 76.22 °
Co^1-C^8-Co^2 79.31 ° (very small C(sp^2) angle)

M. Pallerla, G. Yap, J. Fox, *J. Org. Chem.*, **2008**, *73*, 6137

Serendipity in the (2+2+1) Pauson-Khand Cycloaddition



^{13}C NMR Analysis



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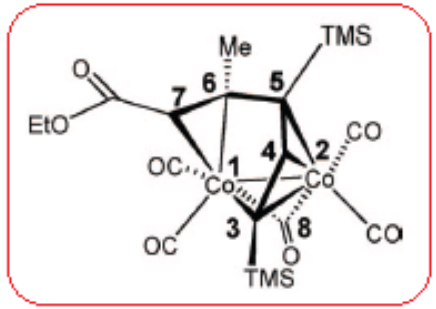

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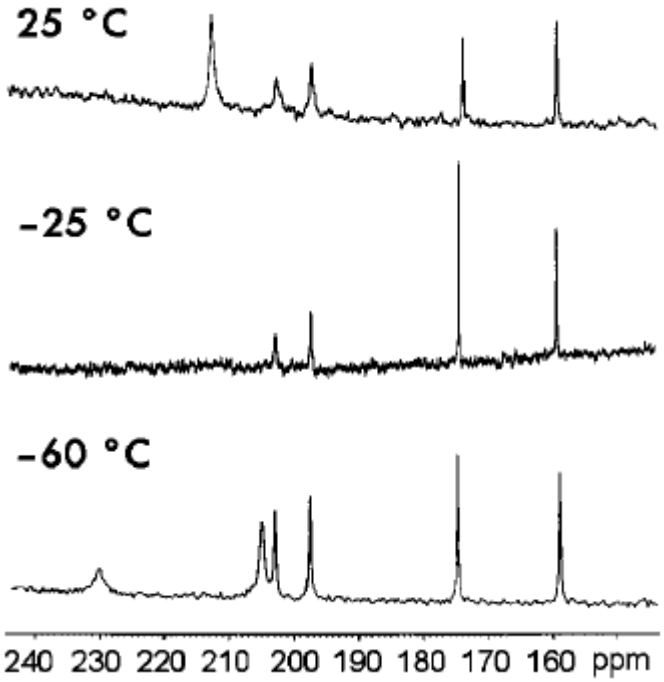
At 25°C: Three picks at 197, 202 and 212 ppm (I= 3) for the 5 carbonyls



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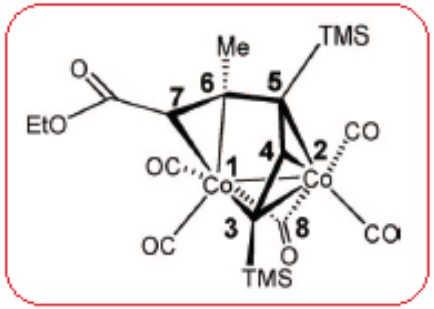

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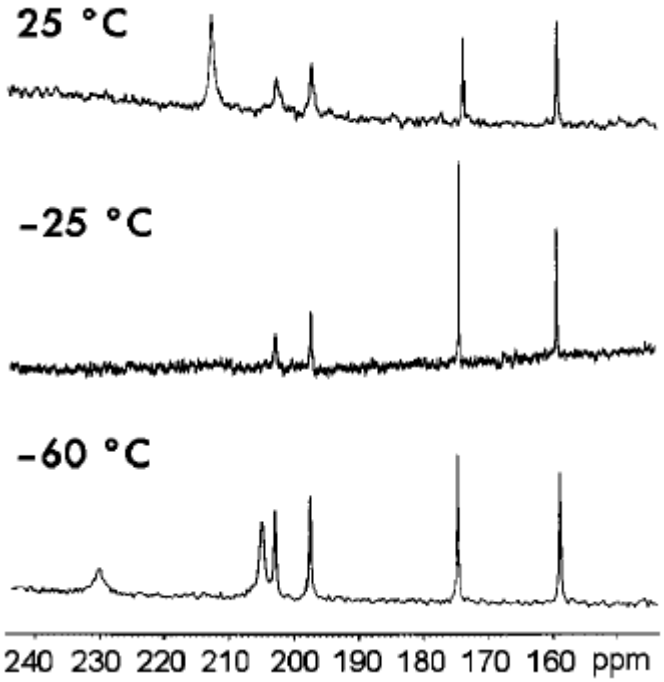

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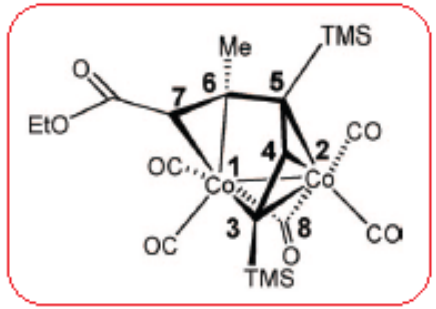

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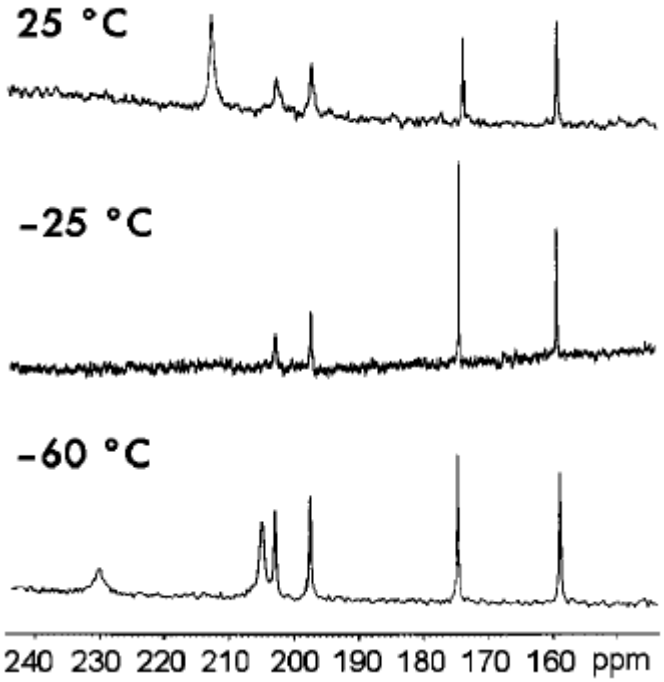

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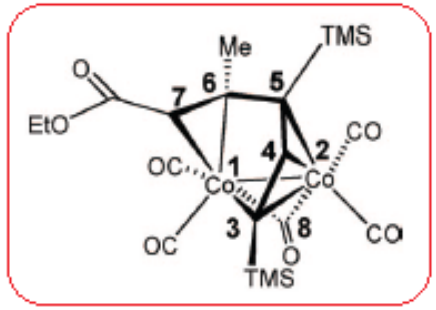

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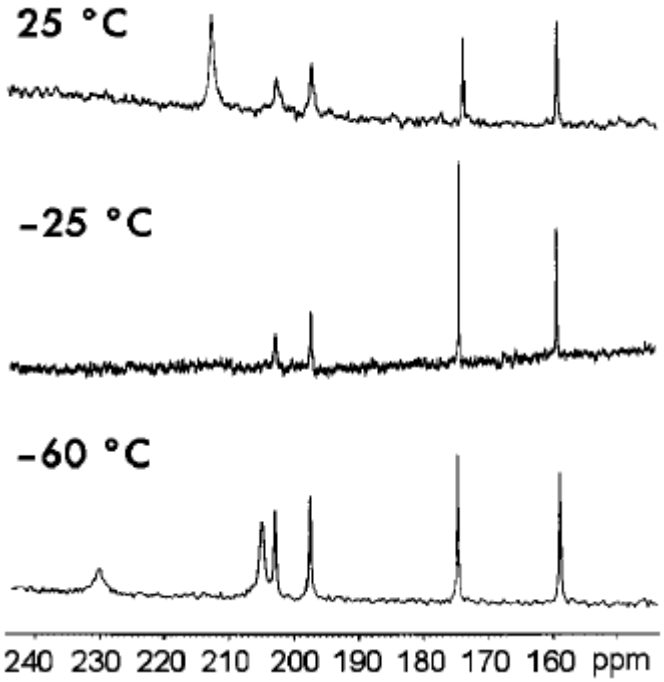
Interpretation:

Slow exchange between bridging and terminal carbonyls **at - 60 °C**



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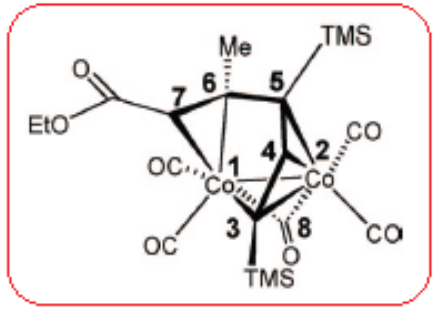

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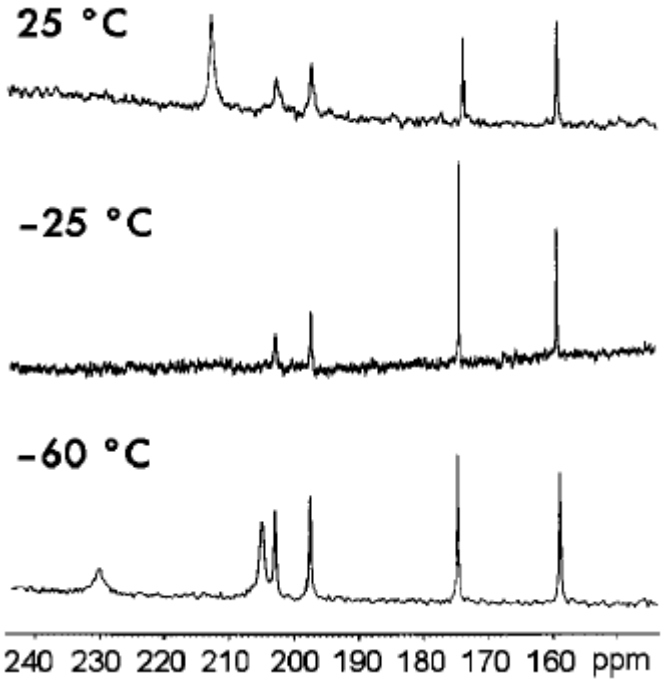

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Fast exchange on the NMR time scale **at 25 °C**

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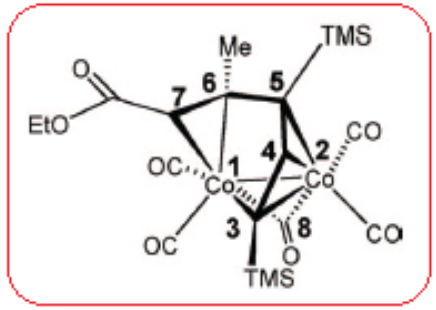

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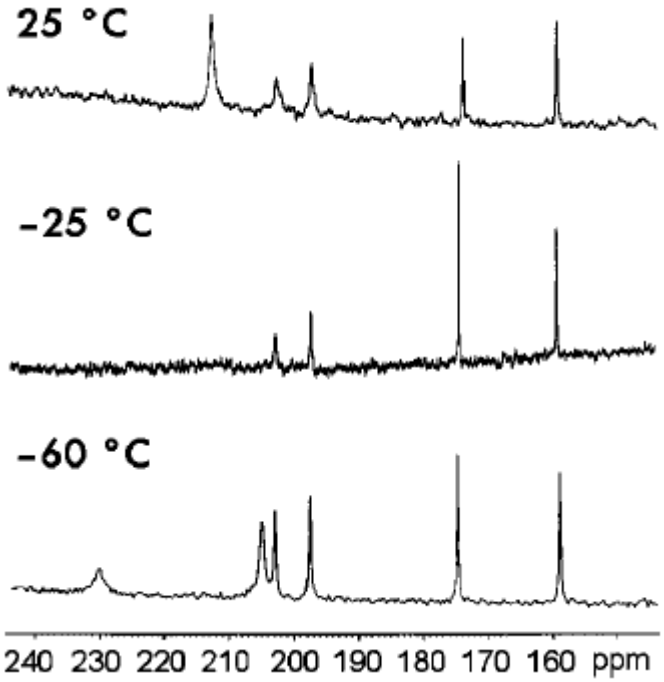

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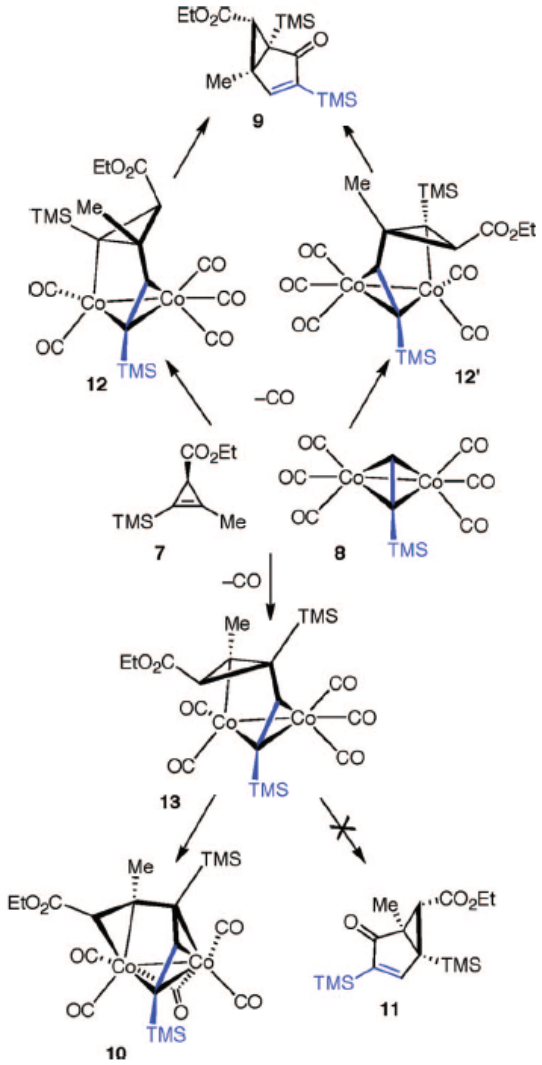
Coalescence observed at **- 25 °C** (signals too broad to be seen)

M. Pallerla, G. Yap, J. Fox, *J. Org. Chem.*, **2008**, *73*, 6137

Regioselectivity of the Pauson-Khand cycloaddition

High regioseletivity
Opposite regioselectivity between cyclopentenone **9** and complex **10**



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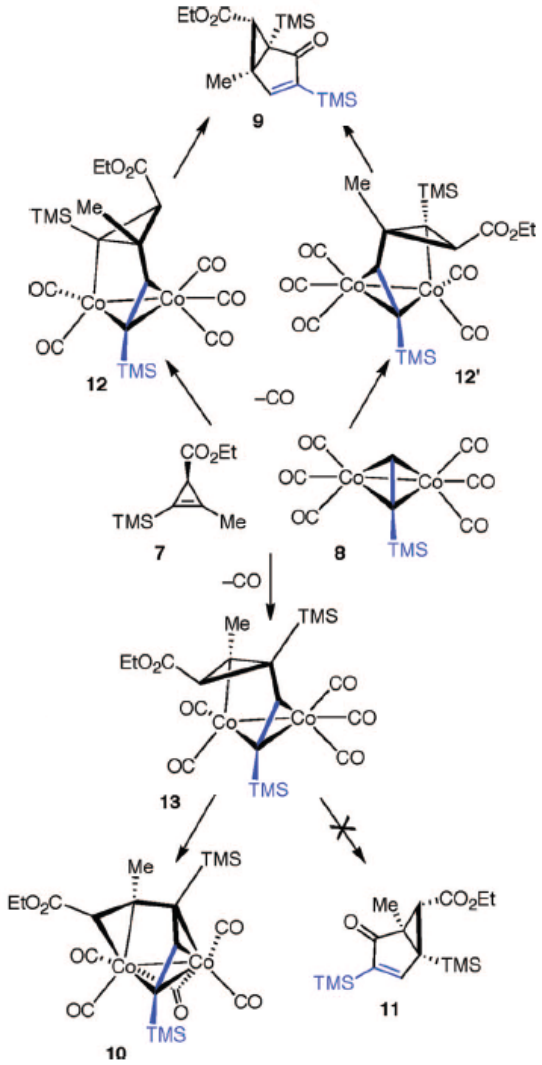
Selectivity in **alkene insertion**
Kinetic discrimination after alkene insertion



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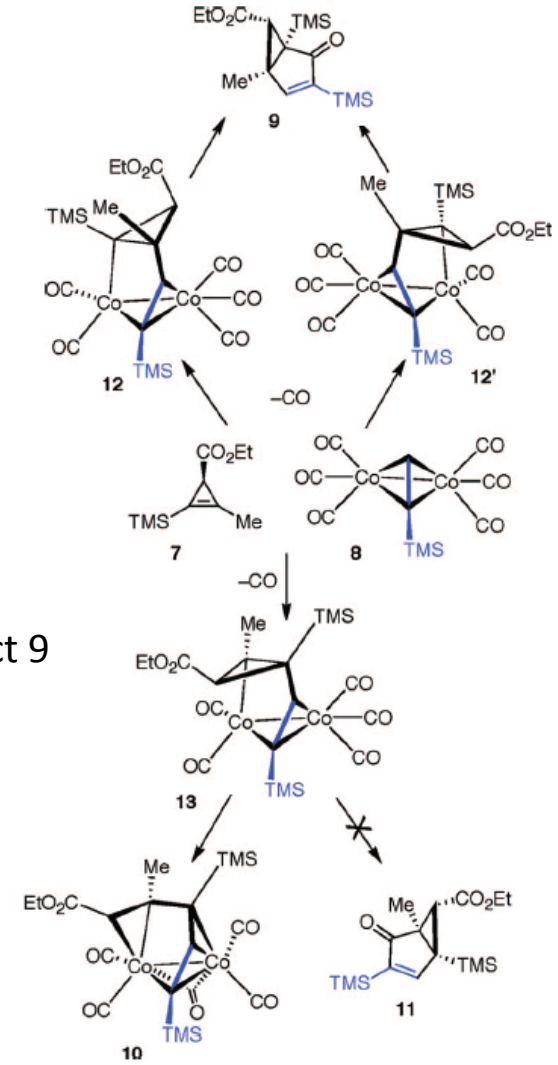

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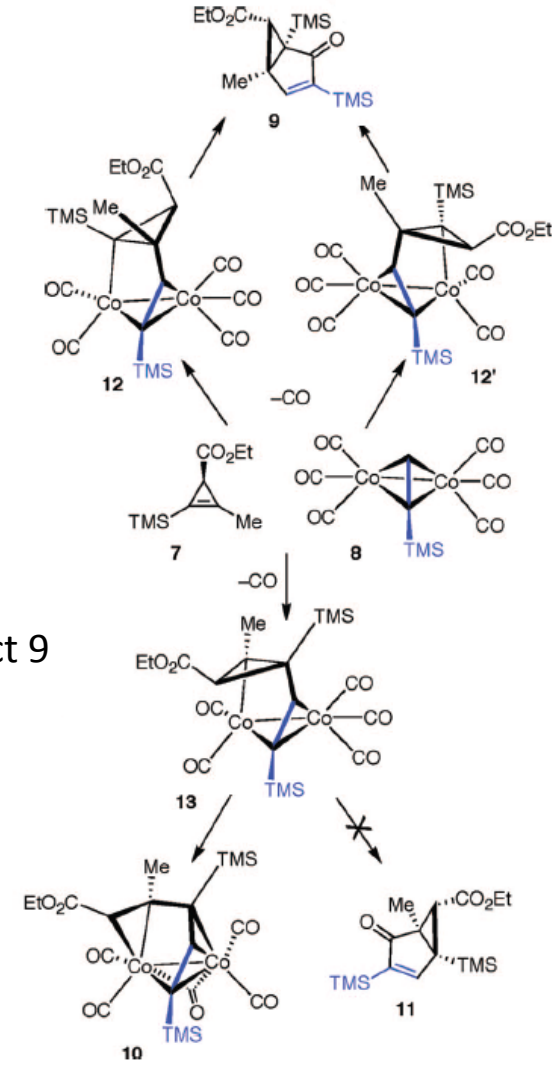
Possible explanations:
- **Stabilisation** of the α-carbon-metal bond by Si
- **Steric interactions**



(3+2+1) Cycloaddition

Much less developed than other carbonylative cycloadditions

C. Li, H. Zhang, J. Feng, Y. Zhang, J. Wang, *Org. Let.*, **2010**, *12*, 3082

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Difficulty to introduce the required **three-carbon component …**

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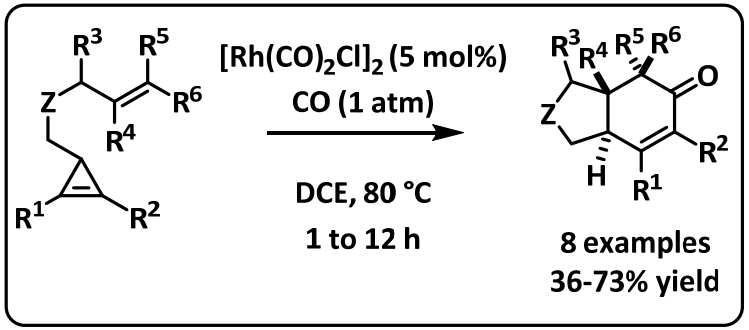

ene-cyclopropene

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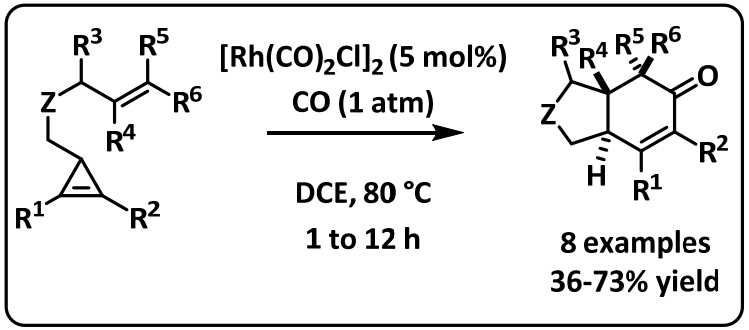

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Stereochemistry confirmed by **NOESY experiment**
Trans configuration of the fused rings

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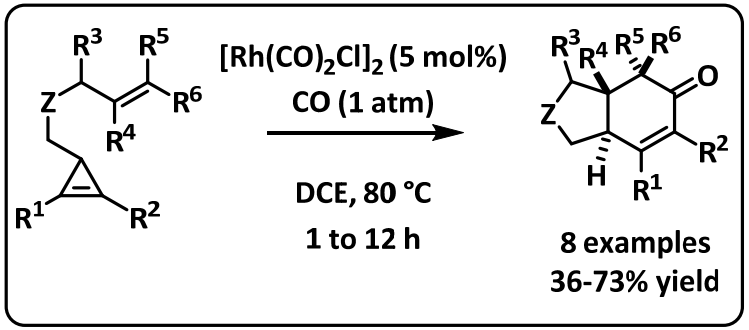

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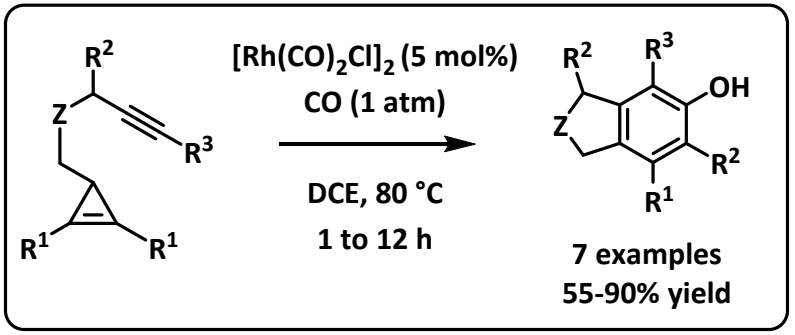

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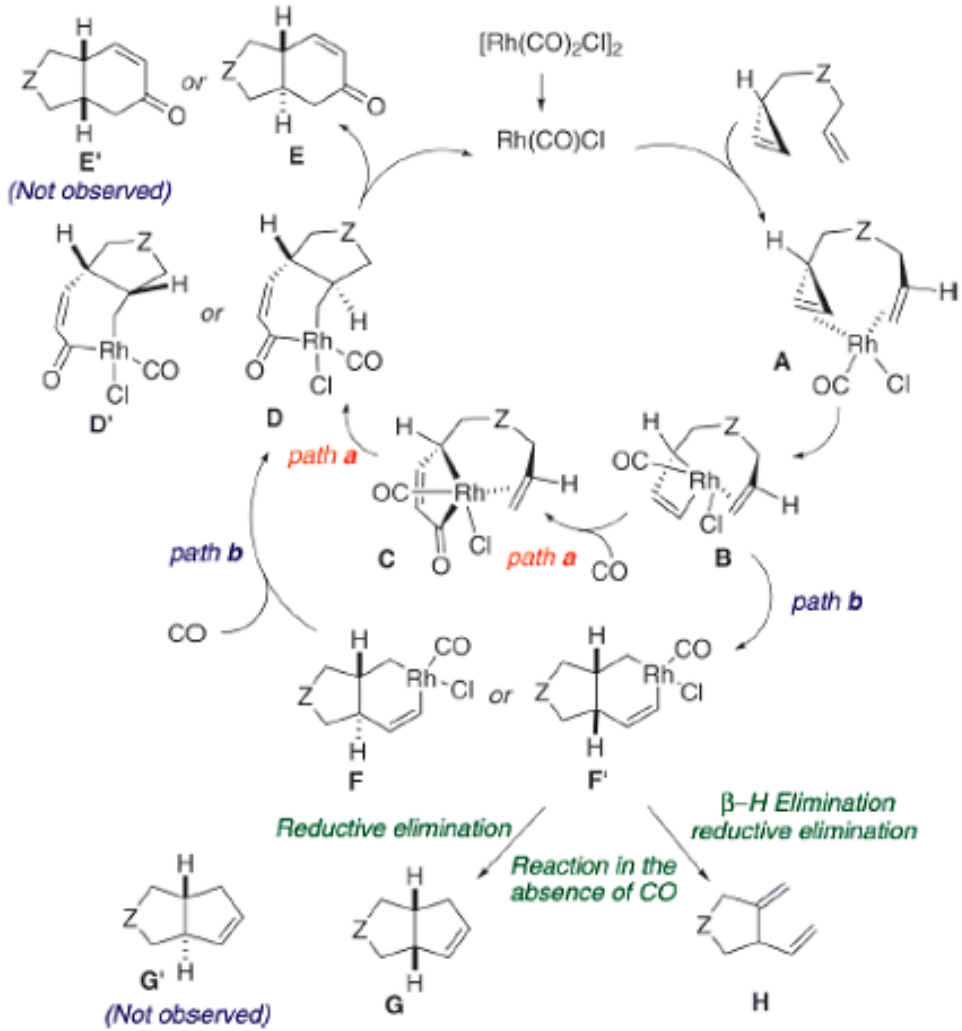

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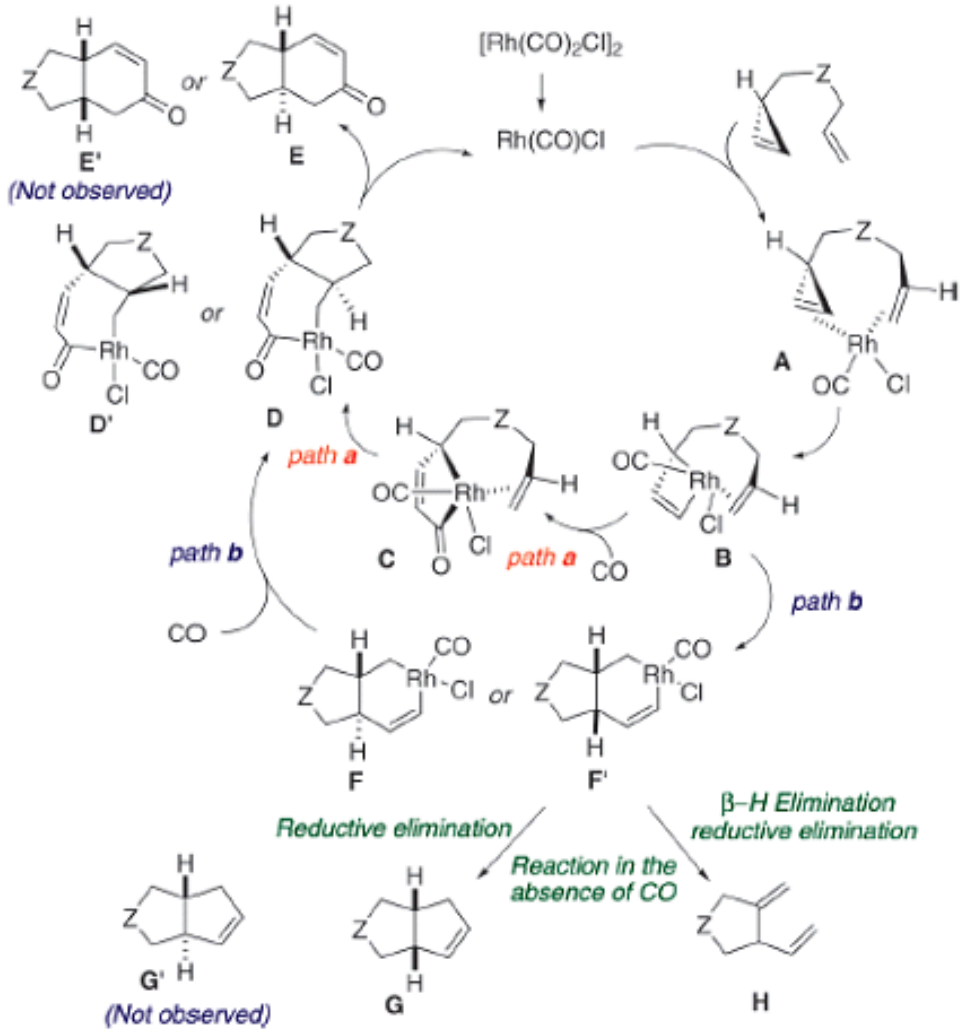
Steps of the mecanism:

A: complexation of Rh(I)



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(3+2+1) Cycloaddition

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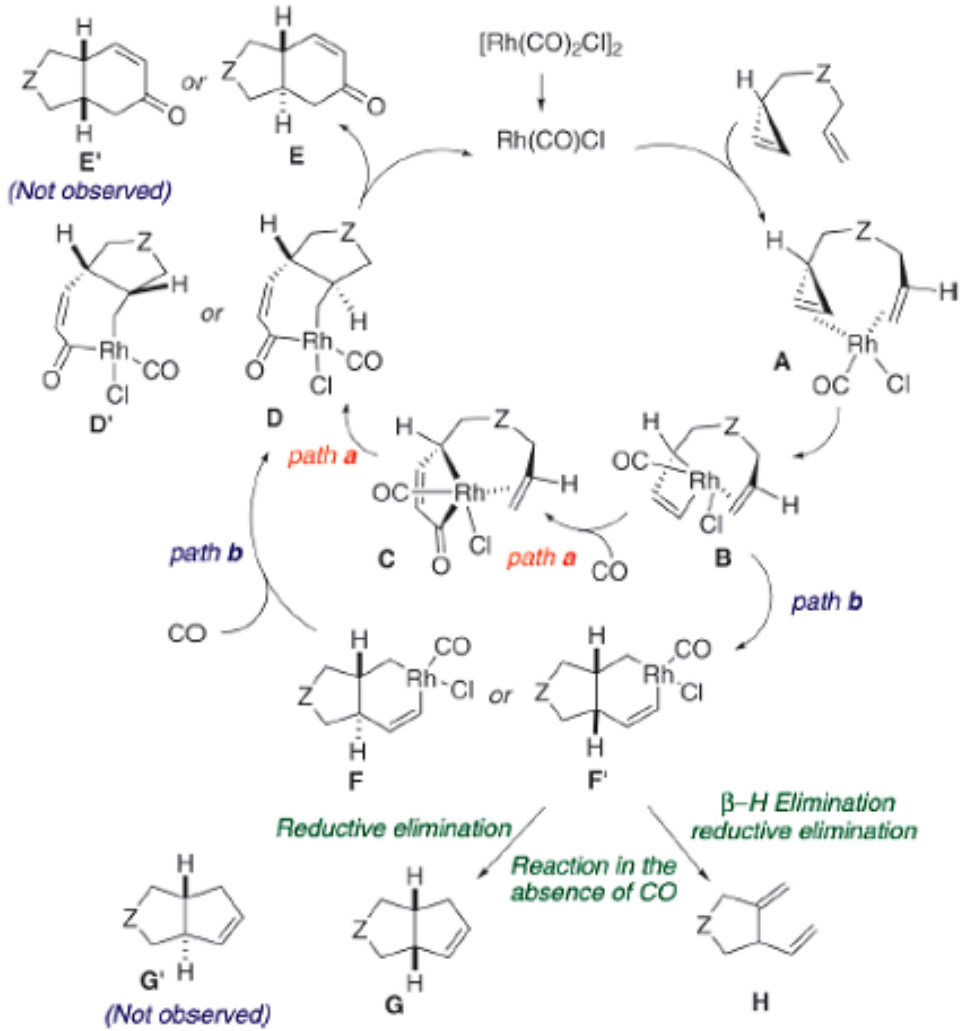

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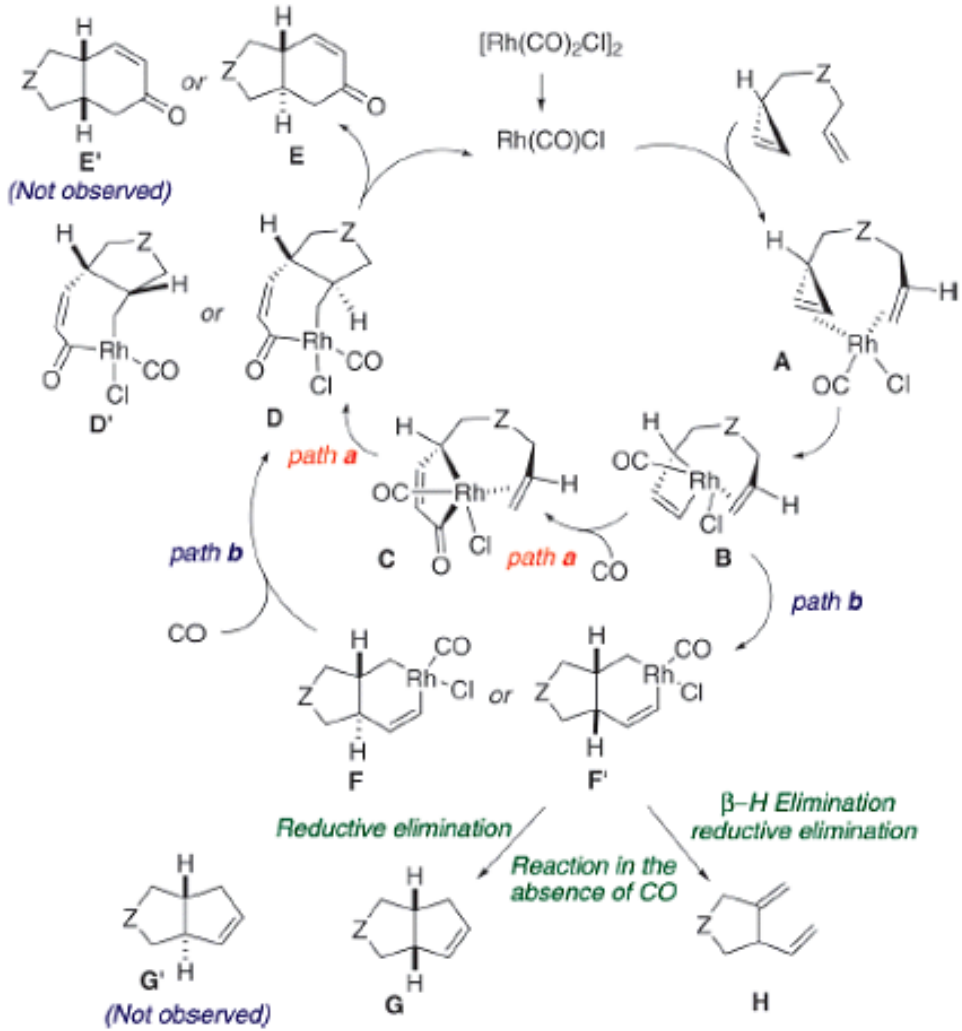

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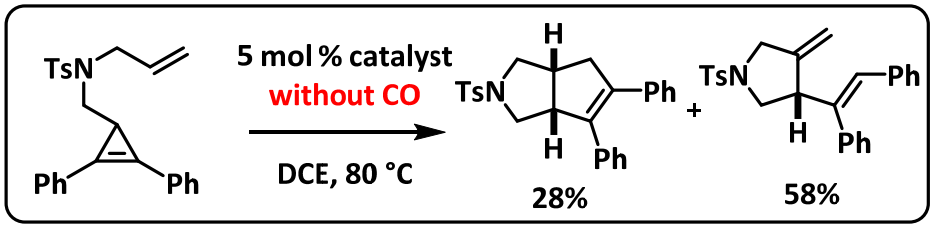

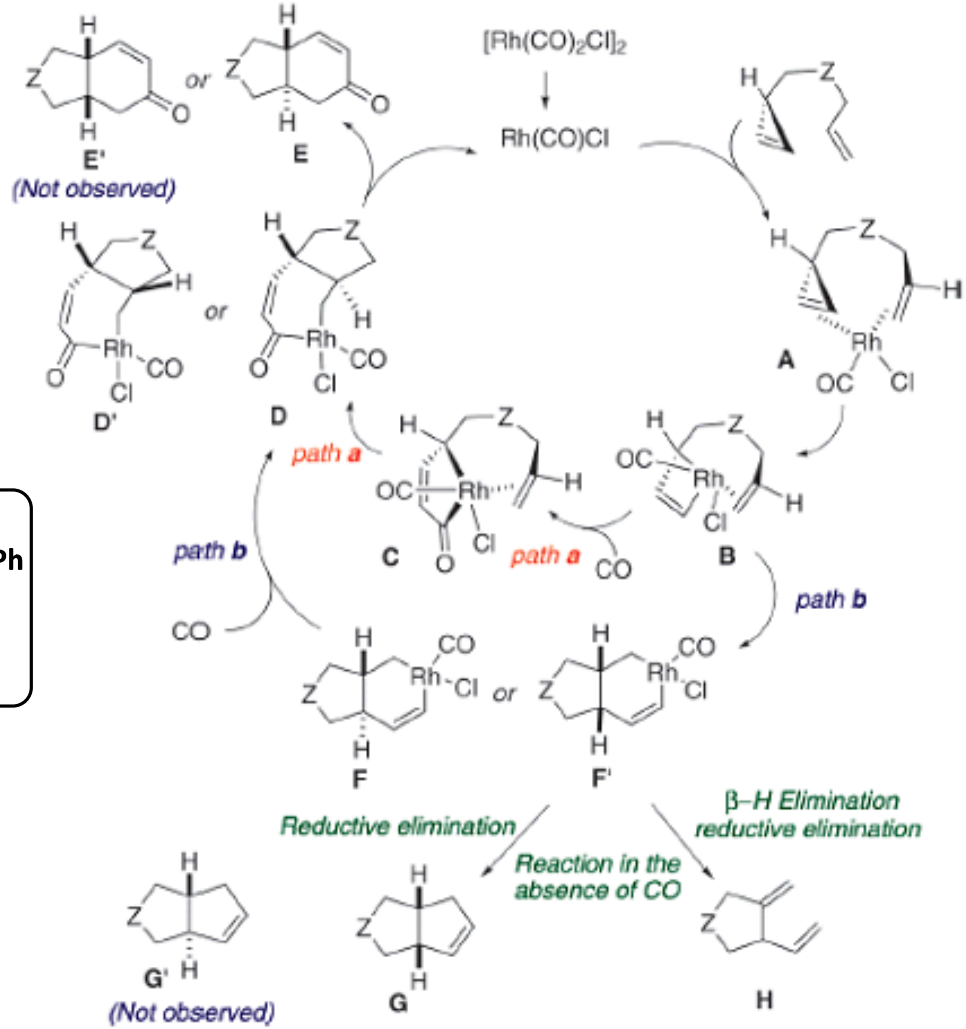

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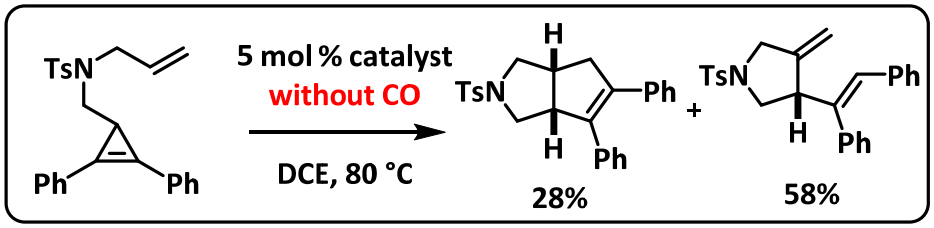
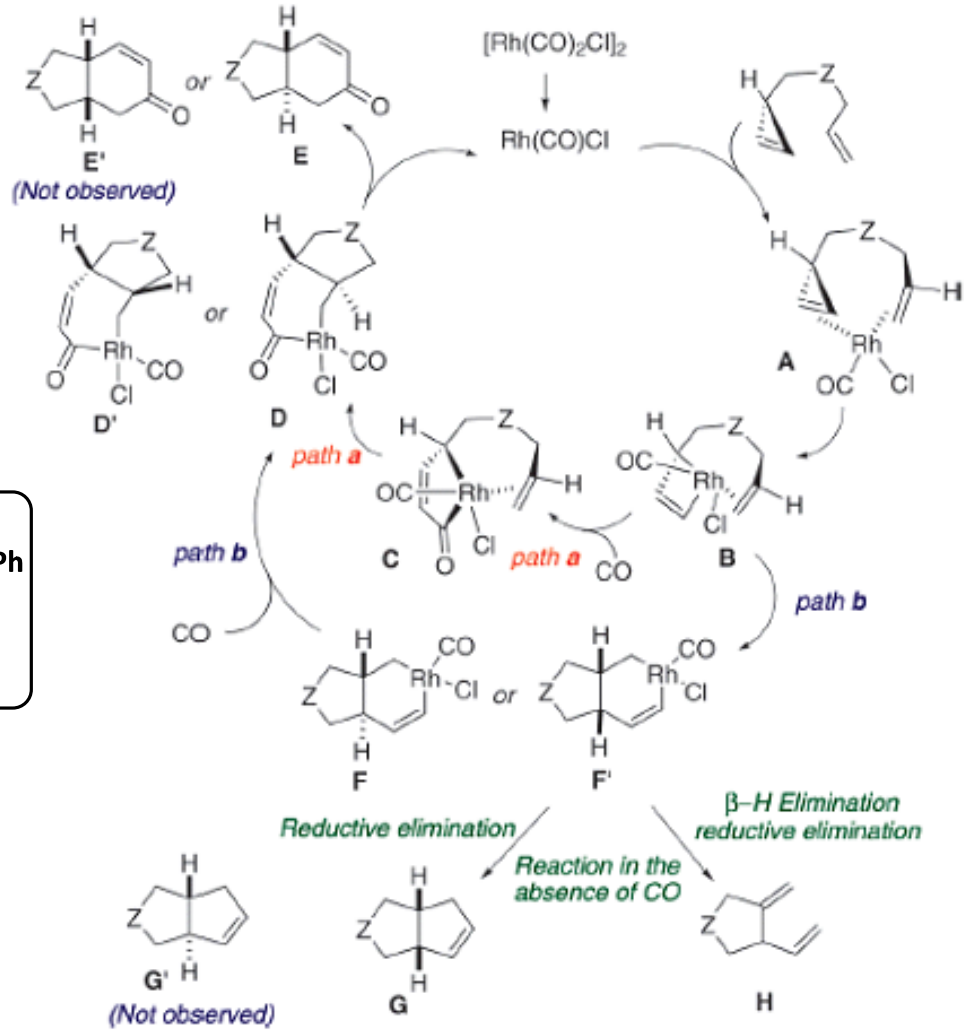


E' *cis*-fused not observed
only *cis*-fused cycloadduct G



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General informations → Synthesis → Applications

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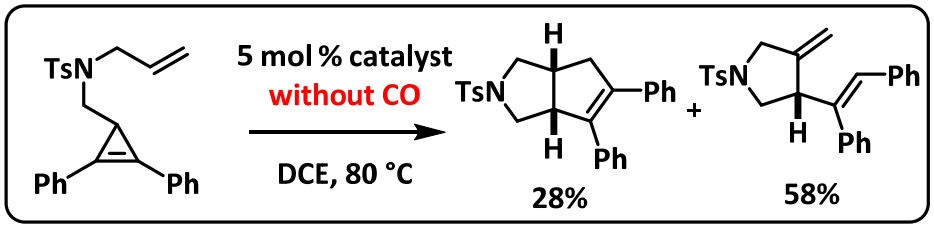

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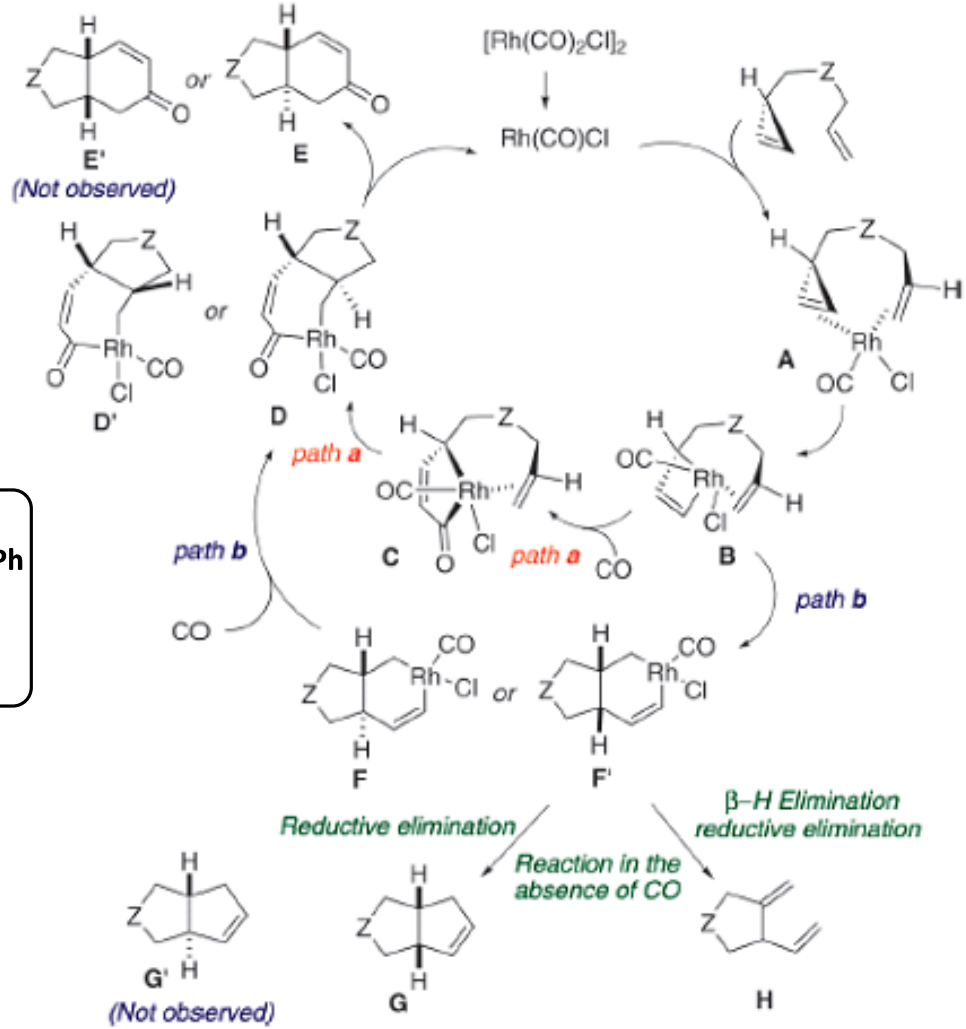
Conclusion: likely **Path a**



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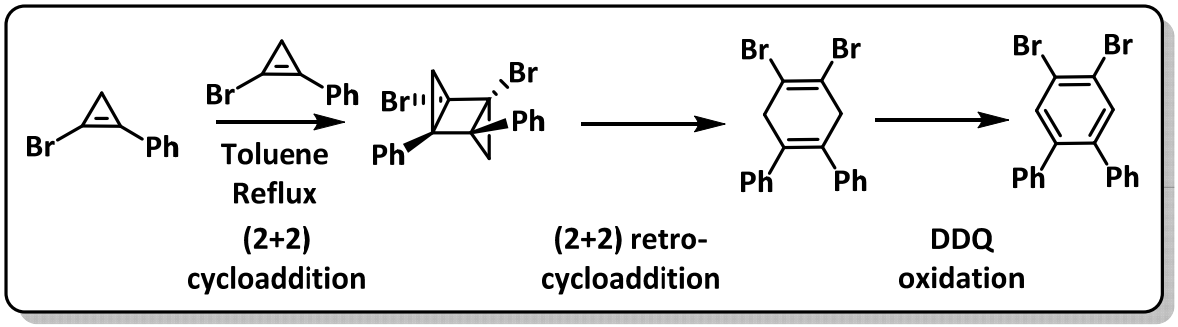
(2+2) Cycloaddition - Original formation of substituted benzene



G. Lee, W. Wang, S. Jiang, C. Chang, R. Tsai, *J. Org. Chem.* , **2009**, *74*, 7994

L. Fisher, N. Smith, J. Fox, *J. Org. Chem.*, **2013**, *78*, 3342

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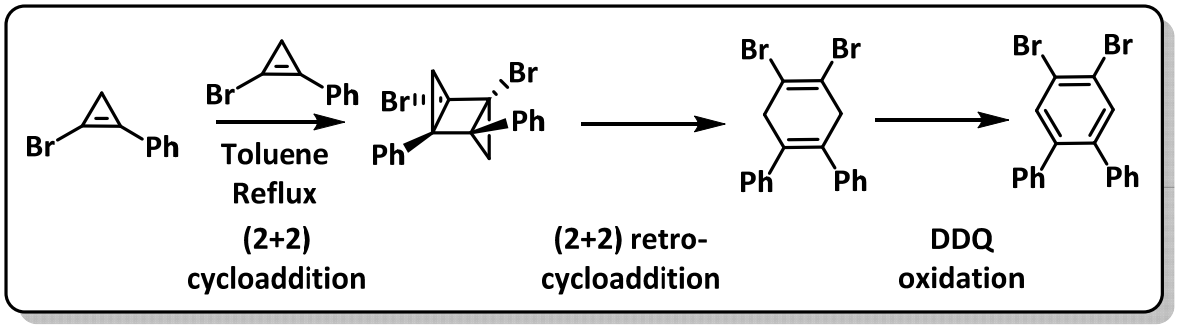

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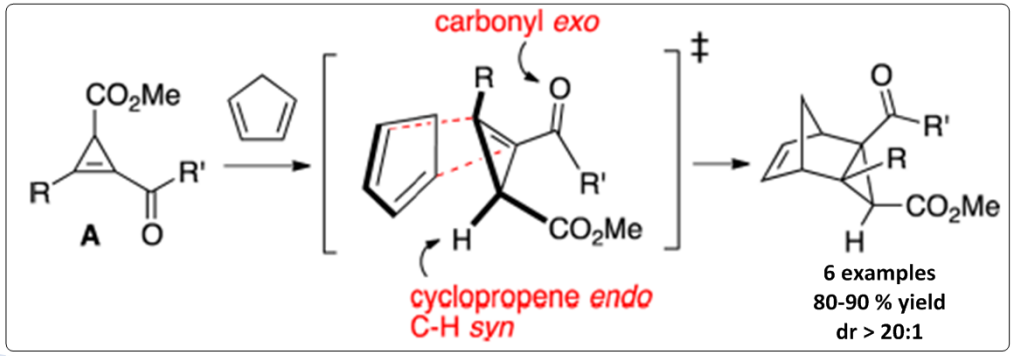
(4+2) Cycloaddition - Cyclopropenes as Reactive and Selective Dienophiles



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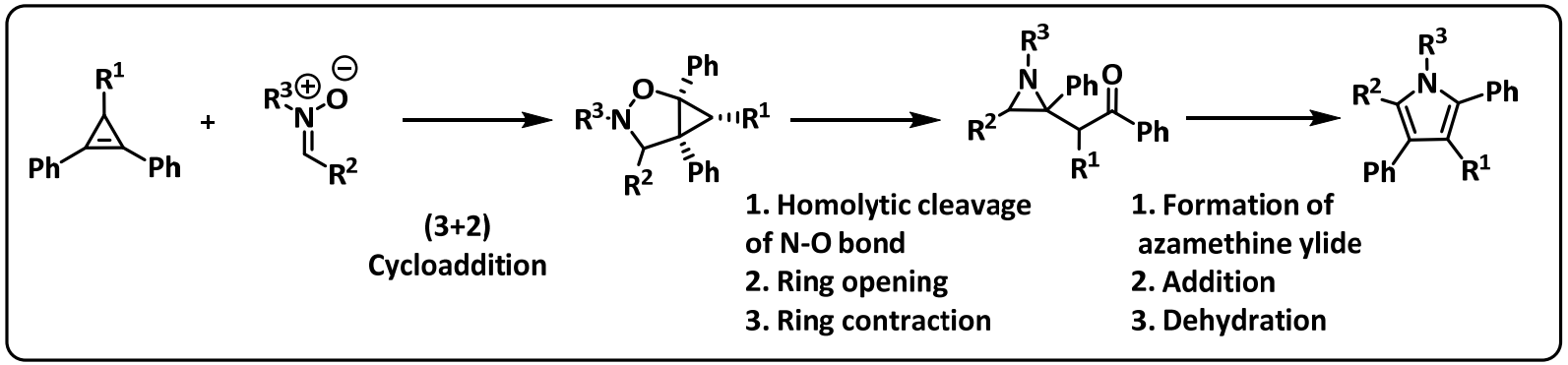
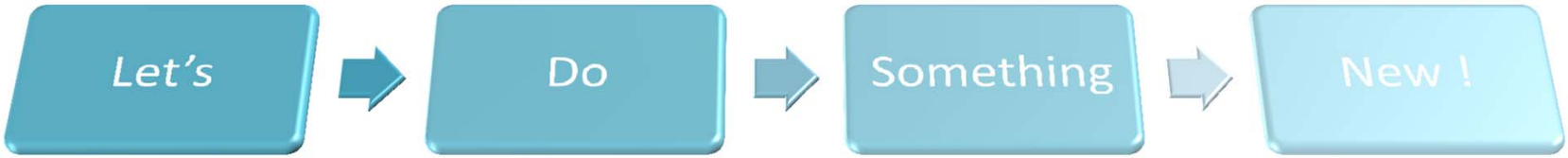
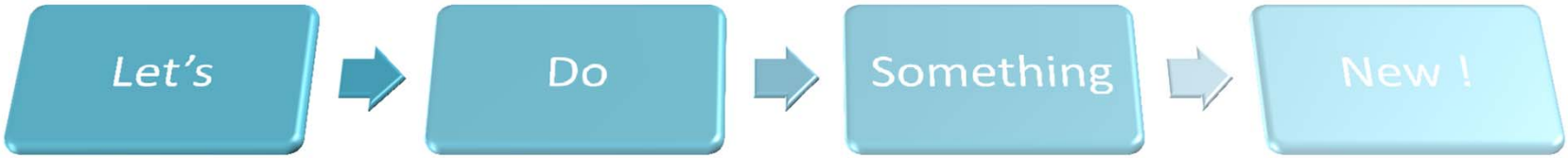


Formation of **Isoxazolidines**, **aziridines** and **pyrroles** thermically controlled

V. Diev, O. Stetsenko, T. Tung, J. Kopf, R. Kostikov, A. Molchanov, *J. Org. Chem*, **2008**, *73*, 2396



Before i thank you for your kind attention …

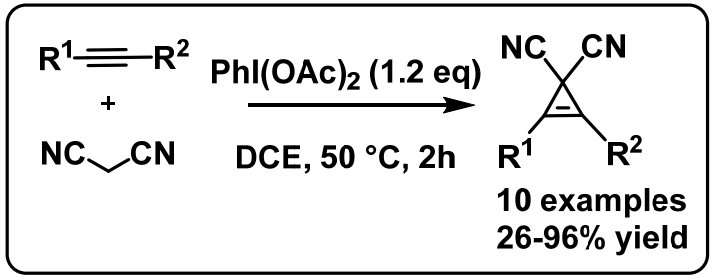


Before i thank you for your kind attention …

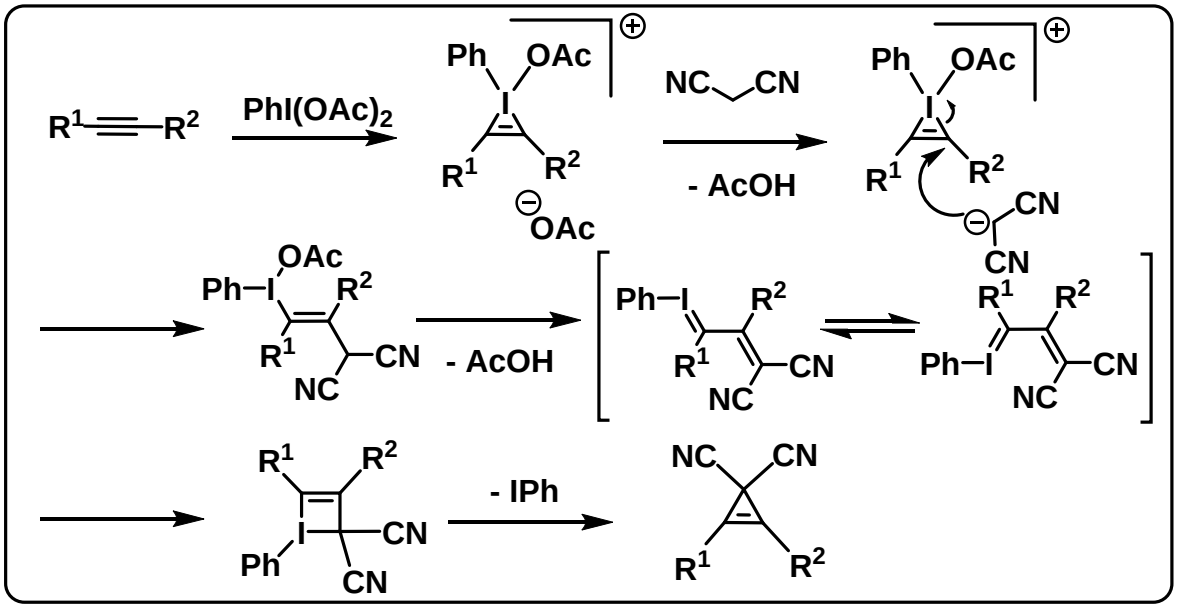
Let's go back to the Hypervalent iodine mechanism described before …

Find what could be wrong → Find a better solution → Let's find out if you were right !

Reaction



Postulated mechanism



S. Lin, M. Li, Z. Dong, F. Liang, J. Zhang, *Org. Biomol. Chem.*, **2014**, *12*, 1341

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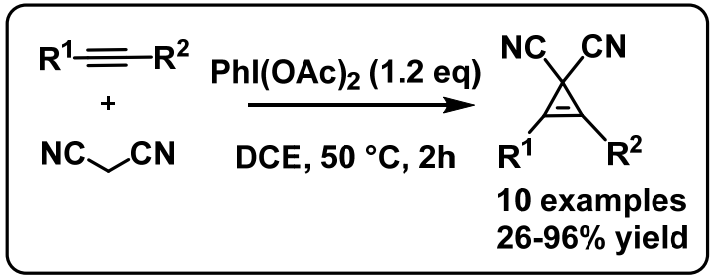
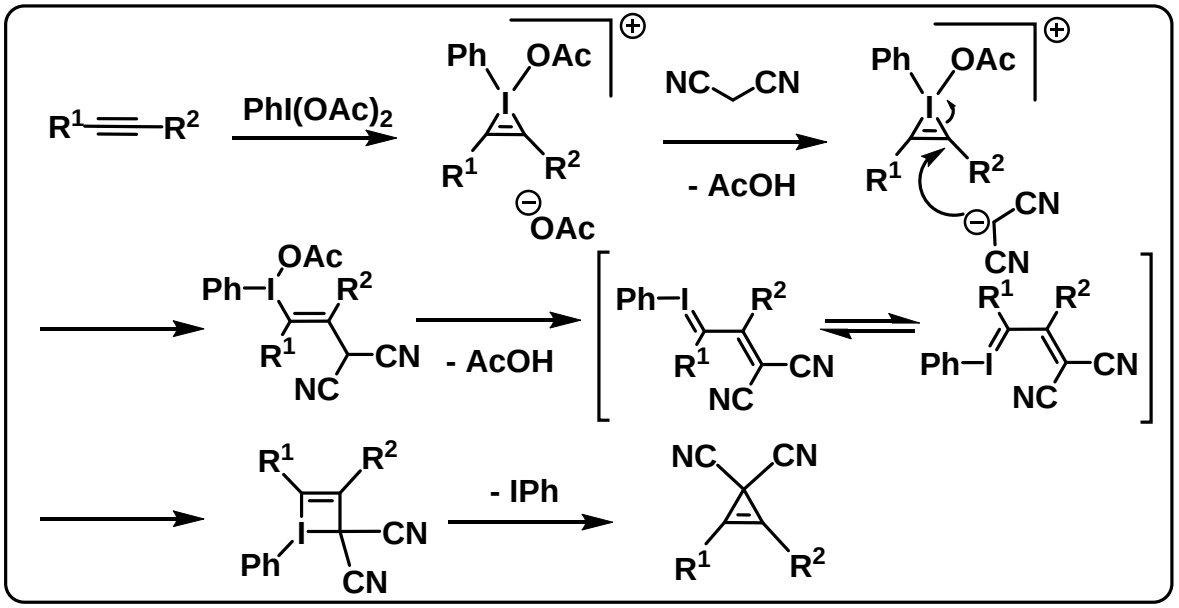
Reaction



Postulated mechanism



Exercise: Find 2 possibles flaws of the mechanism

Which electrophile is the strongest in the medium ?

How this electrophile could react with hypervalent iodine ? Write a mechanism.

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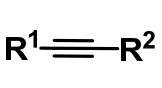
What is the strongest electrophile in the medium ?

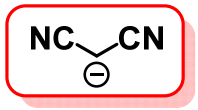
S. Lin, M. Li, Z. Dong, F. Liang, J. Zhang,
Org. Biomol. Chem., **2014**, *12*, 1341

Find what could be wrong → Find a better solution → Let's find out if you were right !

What is the strongest electrophile in the medium ?



or



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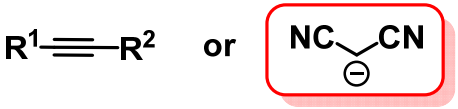

Possible flaws of mechanism:

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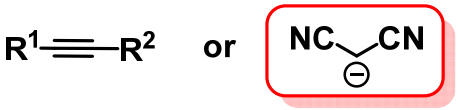
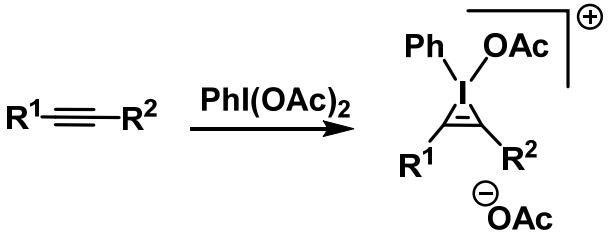
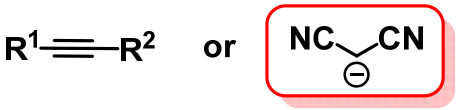
What is the strongest electrophile in the medium ? 

Possible flaws of mechanism: 

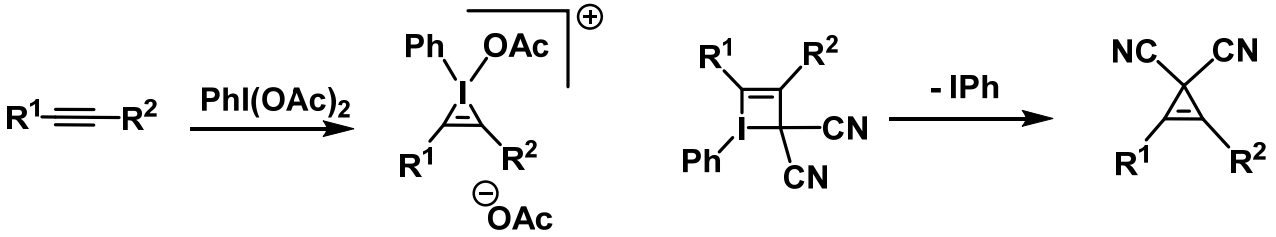
Why would the weakest electrophile react first ?

Find what could be wrong → Find a better solution → Let's find out if you were right !

What is the strongest electrophile in the medium ?



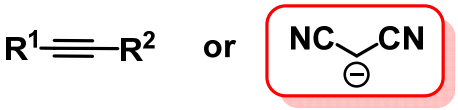
Possible flaws of mechanism:

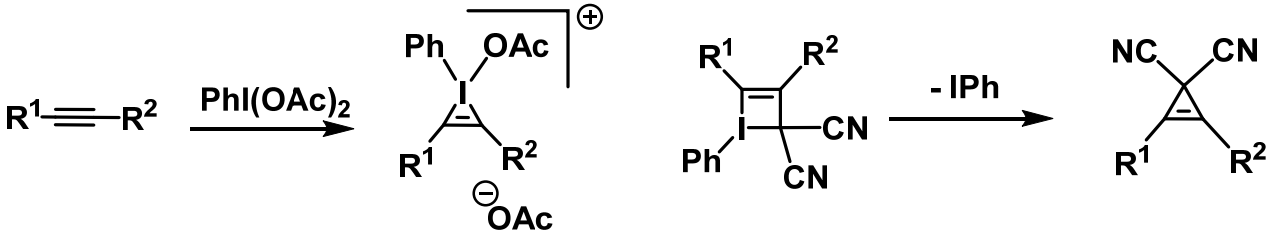


Why would the weakest electrophile react first ?

Reductive elmination to create an even more strained cycle

Find what could be wrong → Find a better solution → Let's find out if you were right !

What is the strongest electrophile in the medium ? 

Possible flaws of mechanism: 

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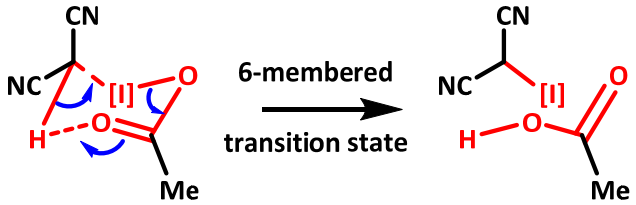
Reductive elmination to create an even more strained cycle

Sir XB's approved postulated Concerted Deprotonation-Electrophilic Iodination Mechanism:



[I] : I(OAc)Ph

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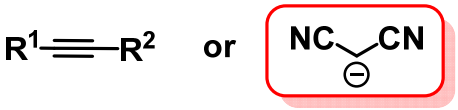
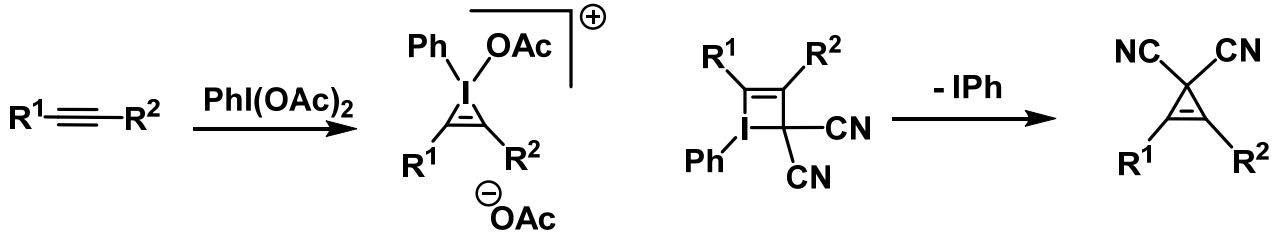
What is the strongest electrophile in the medium ?  or

Possible flaws of mechanism: 

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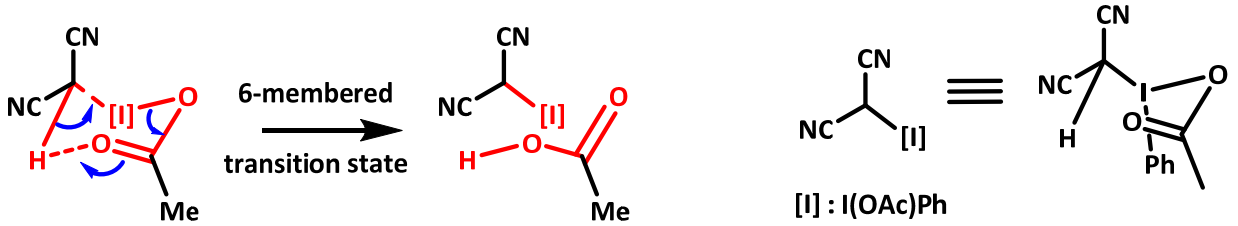

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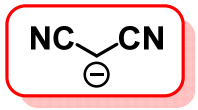
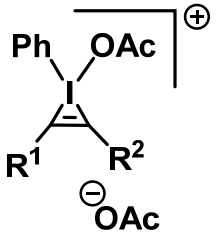
What is the strongest electrophile in the medium ? $R^1{-}{\equiv}{-}R^2$ or 

Possible flaws of mechanism: $R^1{-}{\equiv}{-}R^2$ $\xrightarrow{PhI(OAc)_2}$ 

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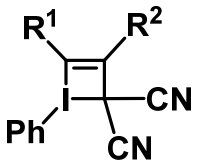
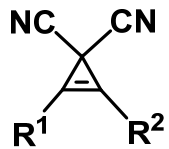
 $\xrightarrow{-\,IPh}$ 

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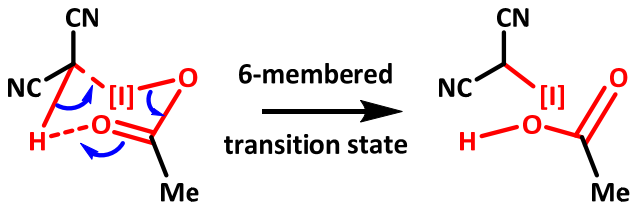

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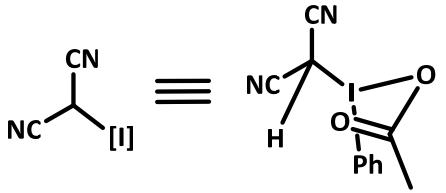

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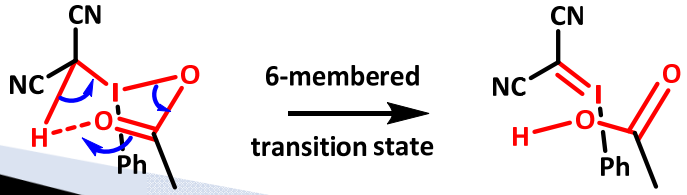

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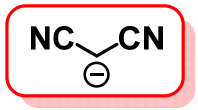
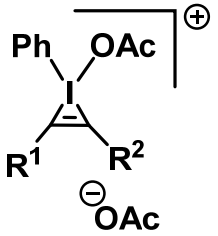
What is the strongest electrophile in the medium ? $R^1{-}{\equiv}{-}R^2$ or 

Possible flaws of mechanism: $R^1{-}{\equiv}{-}R^2$ $\xrightarrow{PhI(OAc)_2}$ 

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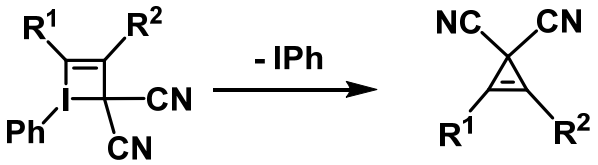

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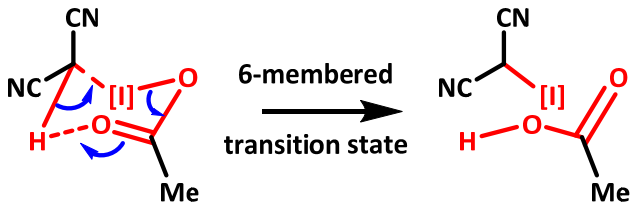

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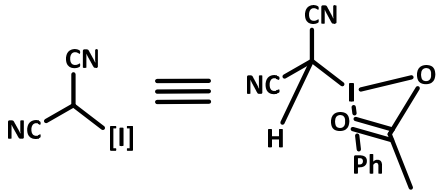

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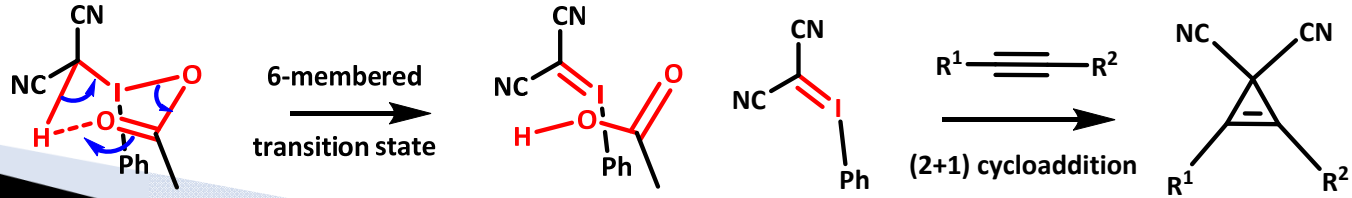
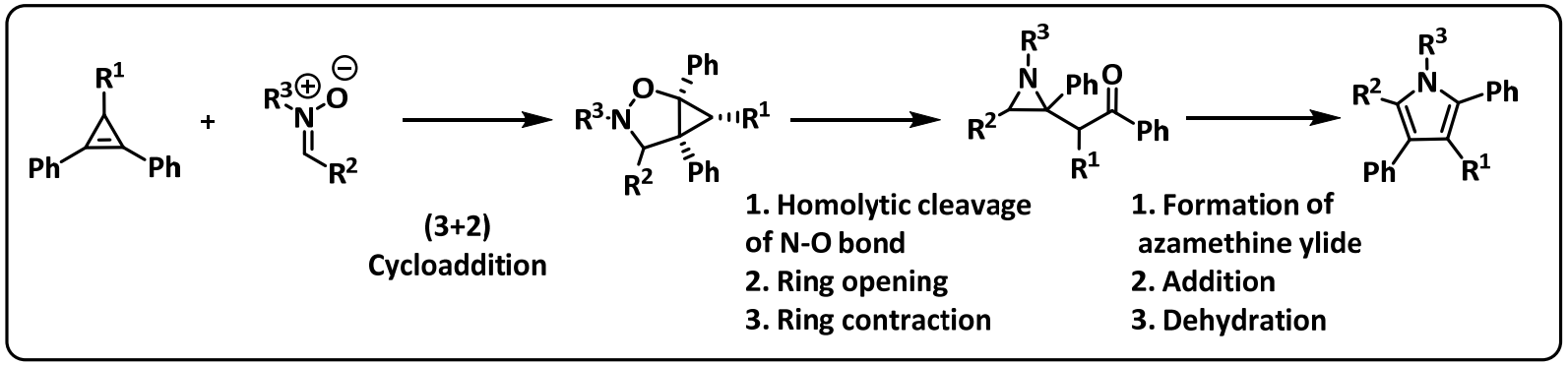
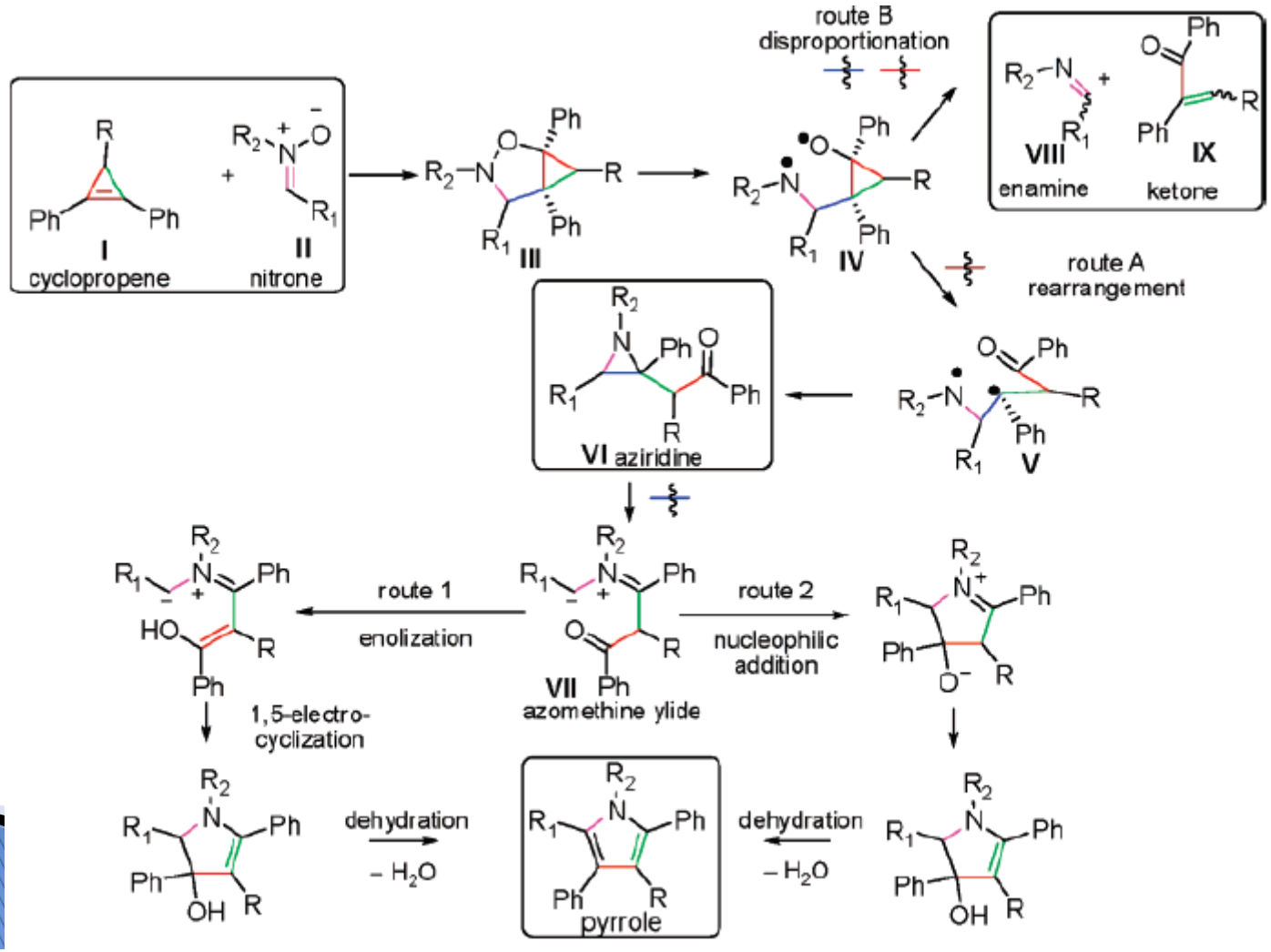


Thank → You → Very Much !

Now i can thank you

for your kind attention


(3+2)
Cycloaddition
1. Homolytic cleavage of N-O bond
2. Ring opening
3. Ring contraction
1. Formation of azamethine ylide
2. Addition
3. Dehydration


I cyclopropene
II nitrone
III
IV
route B disproportionation
VIII enamine
IX ketone
route A rearrangement
V
VI aziridine
route 1 enolization
route 2 nucleophilic addition
VII azomethine ylide
1,5-electro-cyclization
dehydration – H2O
dehydration – H2O
pyrrole