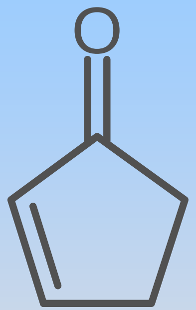
Agnès Corbères

Wednesday December 5th, 2007

THE PAUSON KHAND REACTION:

A useful synthetic tool to give cyclopentenones

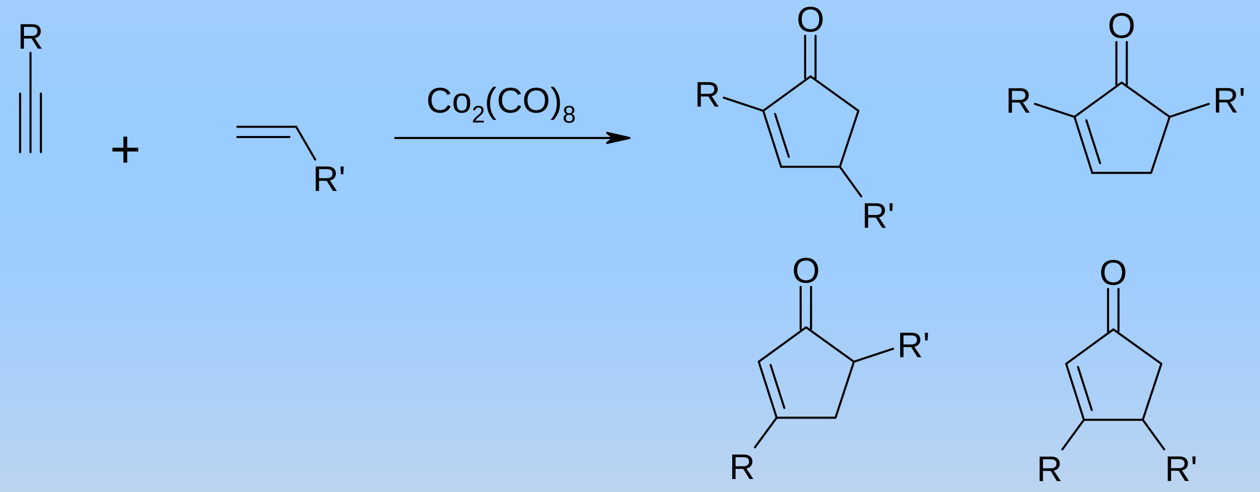


Séminaire SYMBIO

Once upon a time…Pauson Khand reaction

- First reported in detail in 1973*
- Method for making **cyclopentenones**

↪ Cycloaddition [2+2+1] of an **alkyne**, **olefin**, **carbon monoxyde** and **$Co_2(CO)_8$**



⇢**4 regioisomers**: initially, only symmetrical alkenes were used (ethylene, norbornene…)

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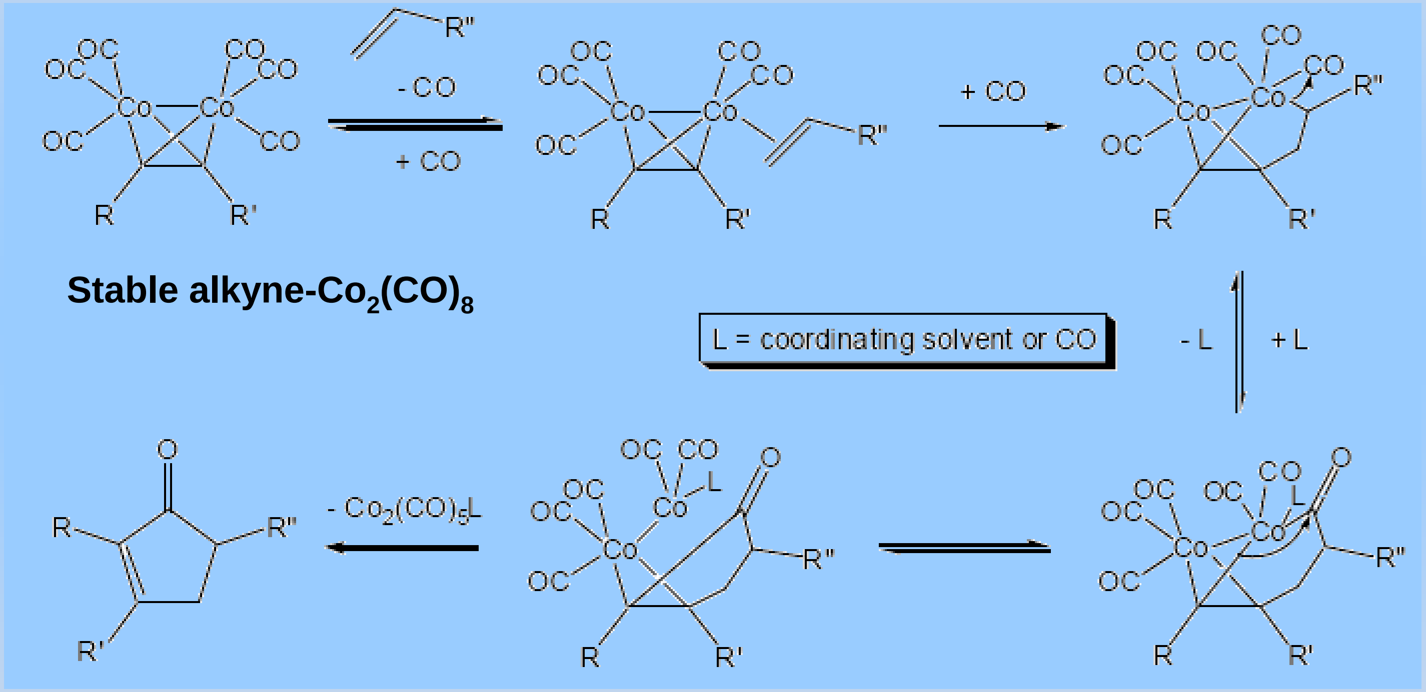
* Khand, I. U.; Knox, G.R.; Pauson, P. L.; Watts, W.E.; Foreman, M. I. *J.Chem. Soc., Perkin Trans. 1* **1973**, 977

How does Pauson Khand reaction work?

- **Proposed mechanism***: based on regio- and stereochemical observations



- **Alkene insertion** step: determines the **regioselectivity** of the product.

↳ Unsymmetrical alkyne ⇢alkene inserts at the carbon bearing the smaller substituent.

[*] Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, 26, 4851

Original Pauson Khand reaction: pros and cons…

☺ Tolerant of a wide range of functionnality: esters, ethers, thioesters, tertiary amines, amides, sulfonamides, nitriles, alcohols

⇨ **Attractive reaction for organic synthesis**

☹ Stoechiometric amount of $Co_2(CO)_8$

☹ Harsh reactionnal conditions:

High temperatures (60-110°C), high pressure of CO, long reaction time (6h-4days)

Regioselectivity

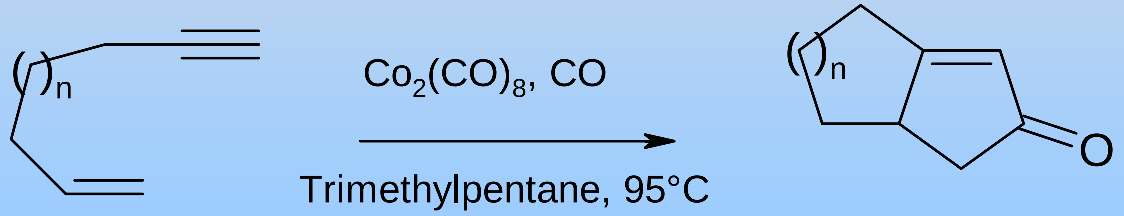
Trisubstituted alkenes unreactive

Terminal alkynes more effective than internal one

Methods were developed over the years for the promotion of the reaction….

Few promotions

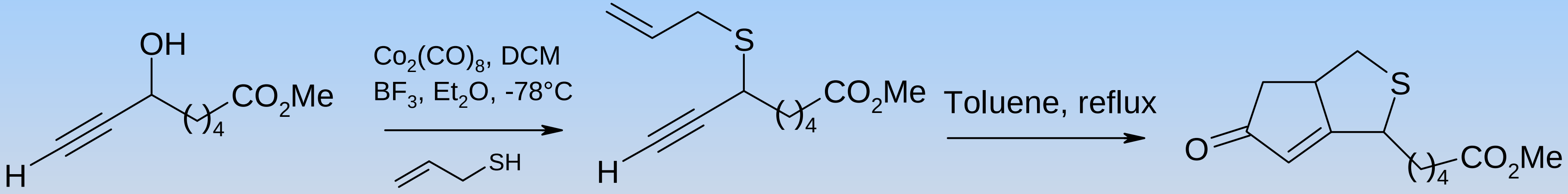
- 1981: first examples of intramolecular Pauson Khand reaction*:



n=1, 2

35-40%

- A current example**:



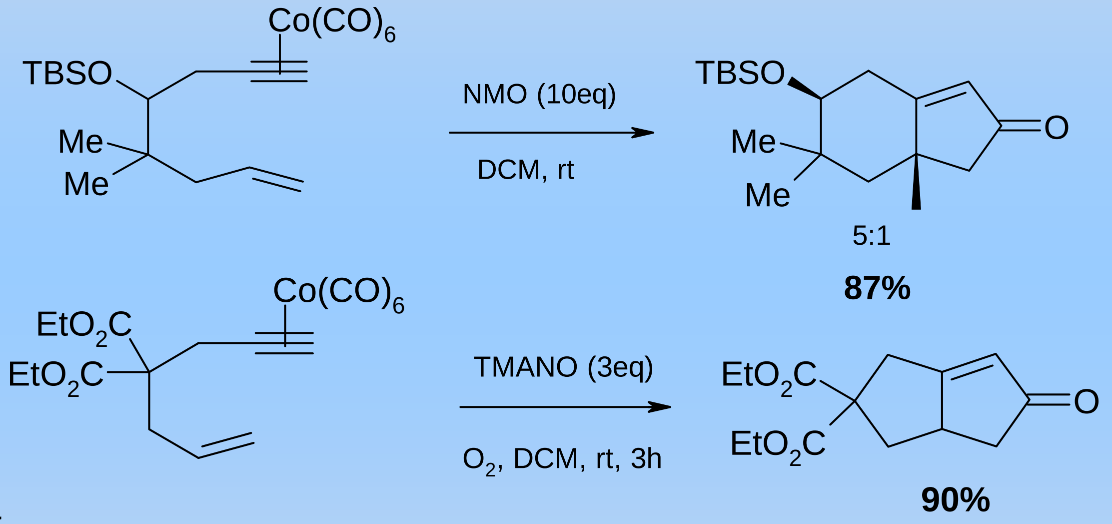
57%

* Schore, N. E., Croudace, M. C., *J. Org. Chem*. **1981**, 46, 5436-5438
McNeill, E.; Chen, I.; Ting, A. Y.; *Org. Lett*. **2006, 8(20), 4593-4595

Few promotions

- Some promoters to circumvent high temperatures and long reaction times:

NMO * or **TMANO****: room temperature, Ar, N_2 or O_2 atmosphere



Silica

Irradiation with UV

Sonication

Molecular sieves

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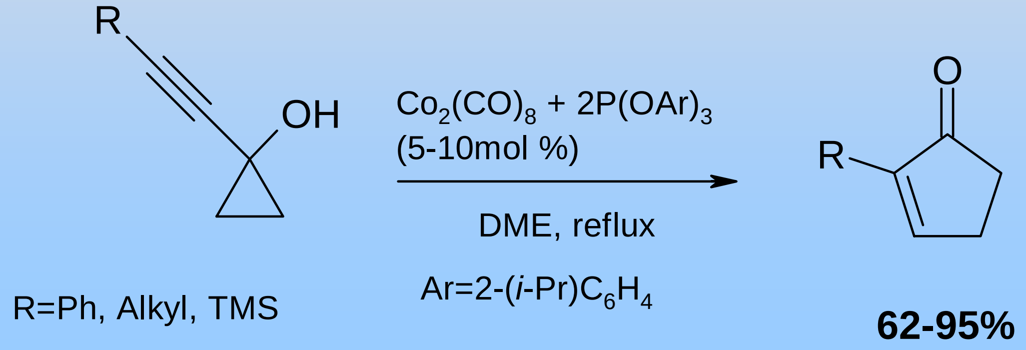
[*] Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, 31, 5289

[**] Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. E. *Synlett* **1991**, 204.

Catalytic Pauson Khand

- Use of a **co-ligand** with $Co_2(CO)_8$ is the starting point for catalytic PK reactions

⇢Triaryl phosphite*:



$Co_2(CO)_8$ + 2P(OAr)$_3$ (5-10mol %)

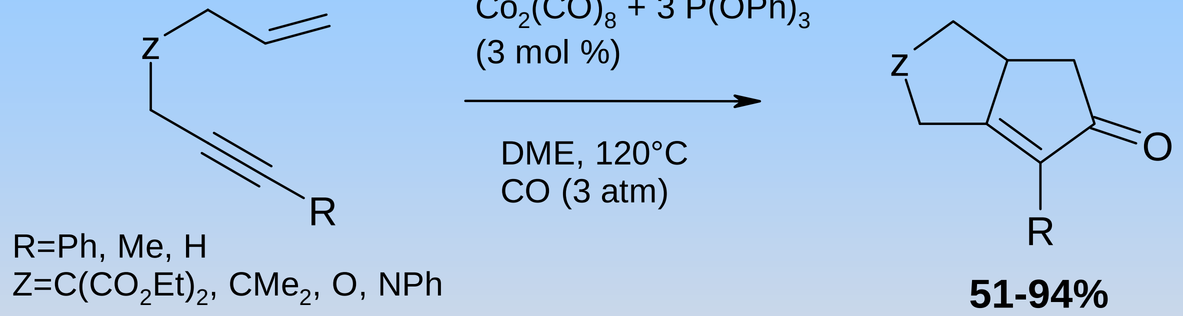
DME, reflux

Ar=2-(*i*-Pr)C_6H_4

R=Ph, Alkyl, TMS

62-95%

⇢Triphenyl phosphite**:



$Co_2(CO)_8$ + 3 P(OPh)$_3$ (3 mol %)

DME, 120°C
CO (3 atm)

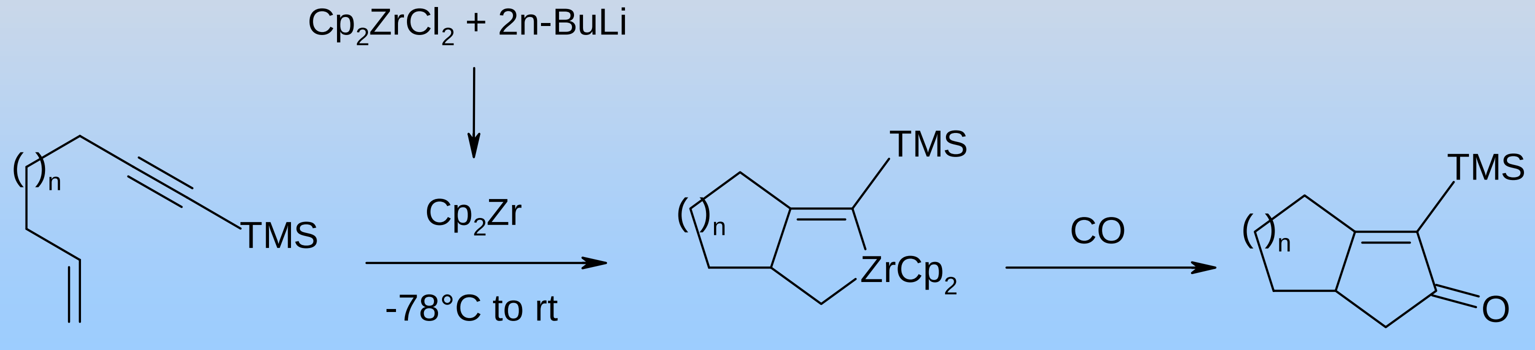
R=Ph, Me, H
Z=C(CO_2Et)$_2$, CMe$_2$, O, NPh

51-94%

* Iwazawa, N.; Matsuo, T.; *Chem. Lett.*, **1993**, 997-1000
Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994, 116, 3159

Other transition metals

- **Zr**-mediated reaction*

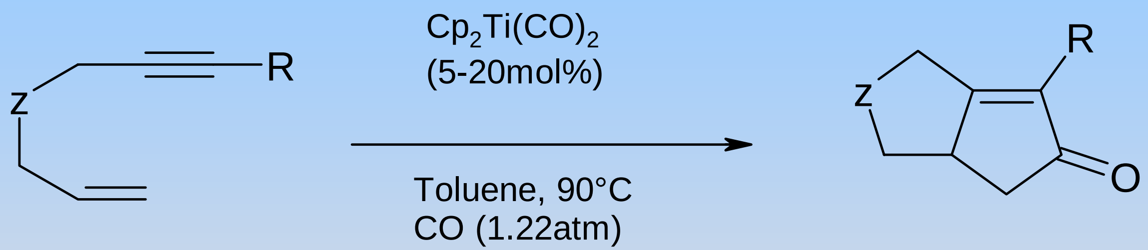


n=1, 2

90-100%

55-65%

- **Ti**-catalysed intramolecular reaction**



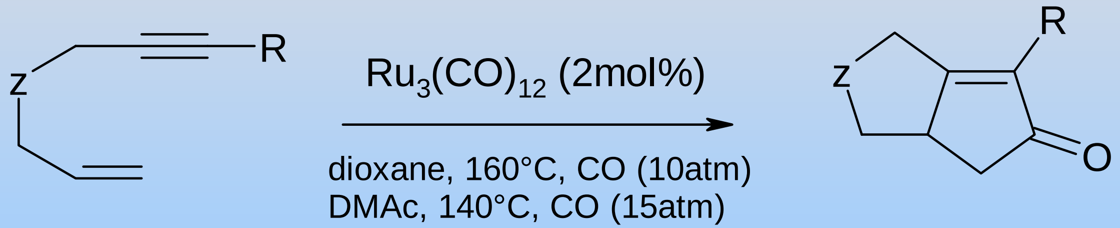
R= Ar, Me, H
Z= $C(CO_2Et)_2$, O, CH_2, NPh

72-95%

*Negishi, E.-I.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; *J. Am. Chem. Soc.* **1985**, 107, 2568-2569
** Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L.; *J. Am. Chem. Soc.* ***1996**, 118, 9450-9451*

Other transition metals

Ru-catalysed reaction*



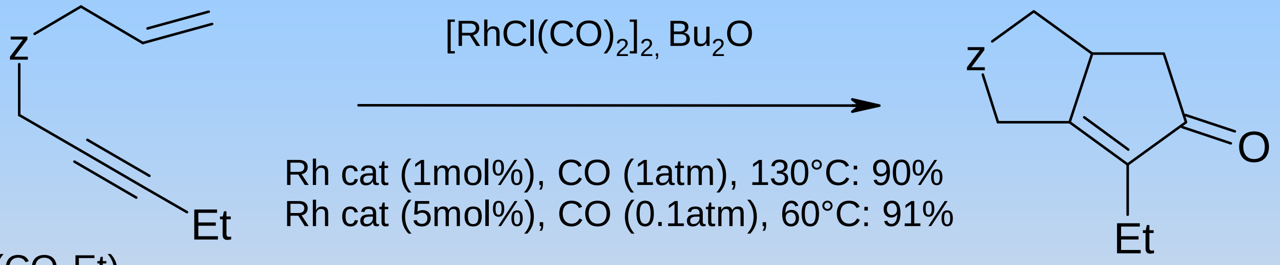
$Ru_3(CO)_{12}$ (2mol%)

dioxane, 160°C, CO (10atm)
DMAc, 140°C, CO (15atm)

R= Ar, Alkyl, TMS
Z= $C(CO_2Et)_2$, O, NTs

57-95%

Rh-catalysed reaction*



$[RhCl(CO)_2]_2$, Bu_2O

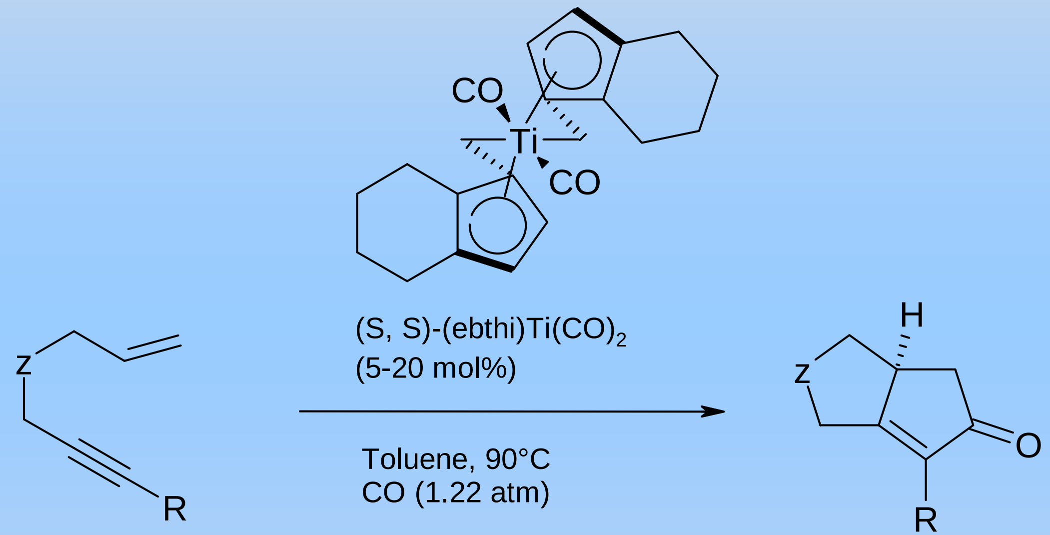
Rh cat (1mol%), CO (1atm), 130°C: 90%
Rh cat (5mol%), CO (0.1atm), 60°C: 91%

Z=$C(CO_2Et)_2$

* Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S.; *J. Org. Chem.* **1997**, 62, 3762-3765
Koga, Y.; Kobayashi, T.; Narasaka, K.; *Chem. Lett.* **1998, 249-250

Enantioselective Pauson Khand reaction

- **Chiral Ti-complex***



(S, S)-(ebthi)Ti$(CO)_2$
(5-20 mol%)

Toluene, 90°C
CO (1.22 atm)

R=Ar, Alkyl, H
Z=$C(CO_2Et)_2$, CH_2, O, NBoc

77-94% ee
50-96%

☺ Highly enantioselective intramolecular PK reaction

☺ Various enynes were transformed into chiral bicyclic cyclopentenones

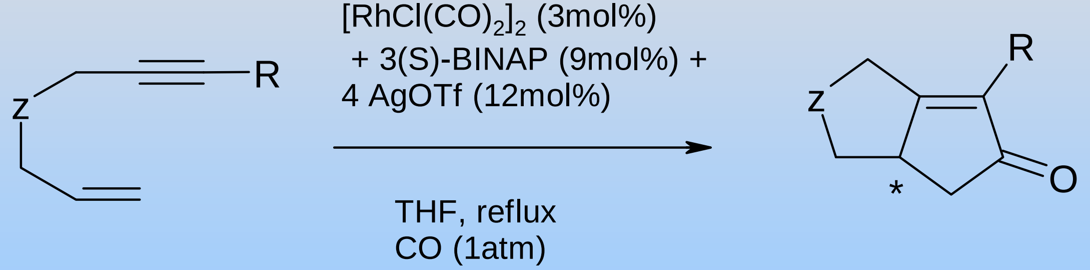
☹ Several steps needed for the synthesis of the chiral ligand

☹ Ti complex air and moisture sensitive

*Hicks, F. A.; Buchwald, S. L.; *J. Am. Chem. Soc*. **1996**, 118, 11688-11689;
Hicks, F. A.; Buchwald, S. L.; *J. Am. Chem. Soc*. **1999**, 121, 7026-7033

Enantioselective Pauson Khand reaction

- **Rh-catalysed** enantioselective PK reaction*



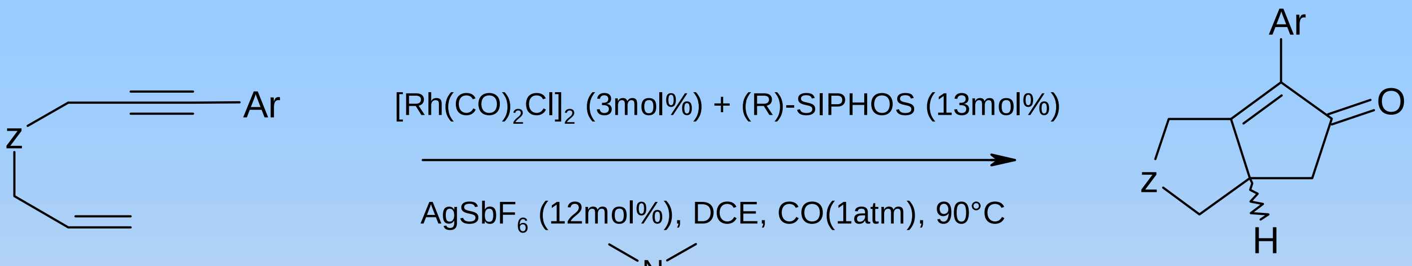
$[RhCl(CO)_2]_2$ (3mol%) + 3(S)-BINAP (9mol%) + 4 AgOTf (12mol%)

THF, reflux
CO (1atm)

R= Ph, Me
Z= $C(CO_2Et)_2$, O, NTs

61-96% ee
67-99%

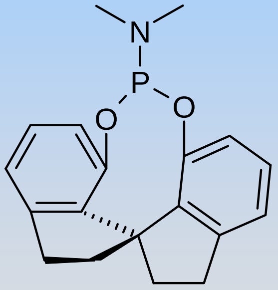
- Spiro-monophosphoramidite as a chiral ligand for the Rh catalyst**



$[Rh(CO)_2Cl]_2$ (3mol%) + (R)-SIPHOS (13mol%)

$AgSbF_6$ (12mol%), DCE, CO(1atm), 90°C

Ar= Ph, 4-MePh, 4-MeOPh, 4-NO_2Ph
Z= O, NTs, $C(CO_2Et)_2$



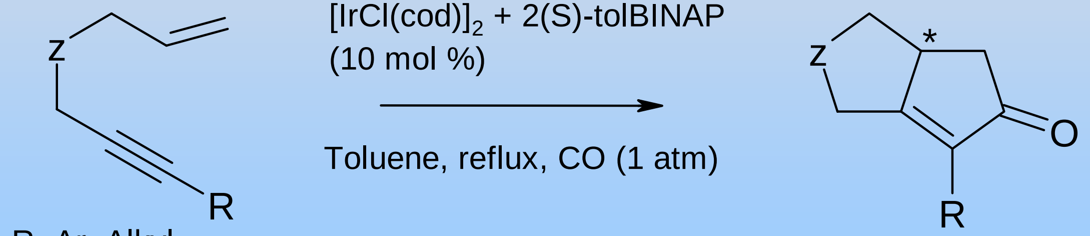
(R)-SIPHOS

47-84% ee
28-73%

*Jeong, N.; Sung, B. K.; Choi, Y. K.; *J. Am. Chem. Soc.* **2000**, 122, 6771-6772;
** Fan, B.M.; Xie, J.H.; Li, S.; Tu, Y. Q., Zhou, Q. L.; *Adv. Synth. Catal.* **2005**, 347, 759-762

Enantioselective Pauson Khand reaction

- **Chiral Ir-catalyst***



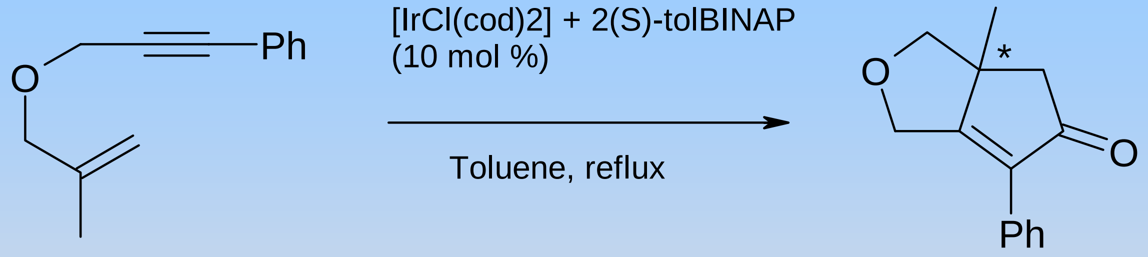
$[IrCl(cod)]_2$ + 2(S)-tolBINAP
(10 mol %)

Toluene, reflux, CO (1 atm)

R=Ar, Alkyl
Z=$C(CO_2Et)_2$, O, NTs

84%-98% ee
54-85%

☺ $[IrCl(cod)]_2$ and (*S*)-tolBINAP both commercially available and air stable



[IrCl(cod)2] + 2(S)-tolBINAP
(10 mol %)

Toluene, reflux

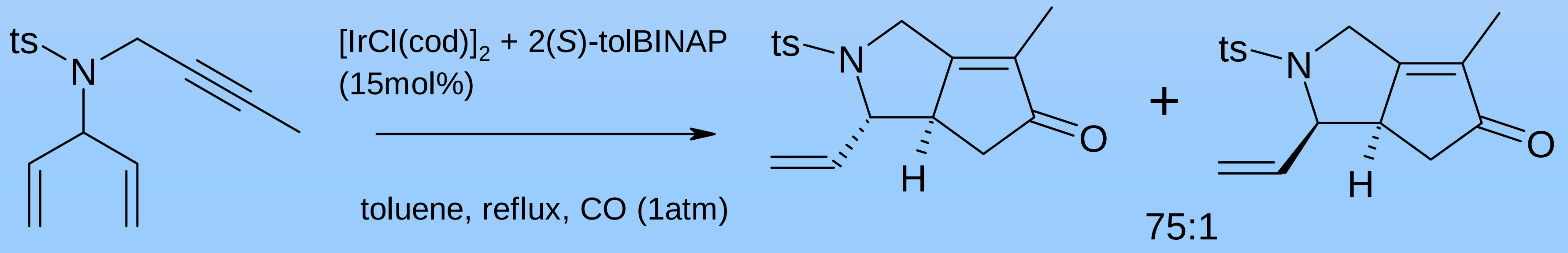
CO (1atm): 30%, 88%ee
CO (0.2atm): 86%, 93%ee

☺ CO (0.2atm) gives rise to higher yield and enantioselectivity than CO (1atm)

*Shibata, T.; Tagaki, K.; *J. Am. Chem. Soc*. **2000**, 122, 9852-9853;
Shibata, T.; Toshida, N.; Yamazaki, M.; Maekawa, S.; Takagi, K., *Tetrahedron* **2005**, 61, 9974-9979

Enantioselective Pauson Khand reaction

- **Chiral Ir-catalyst** used in desymetrization of *meso*-dienynes*



$[IrCl(cod)]_2$ + 2(*S*)-tolBINAP (15mol%)

toluene, reflux, CO (1atm)

75:1

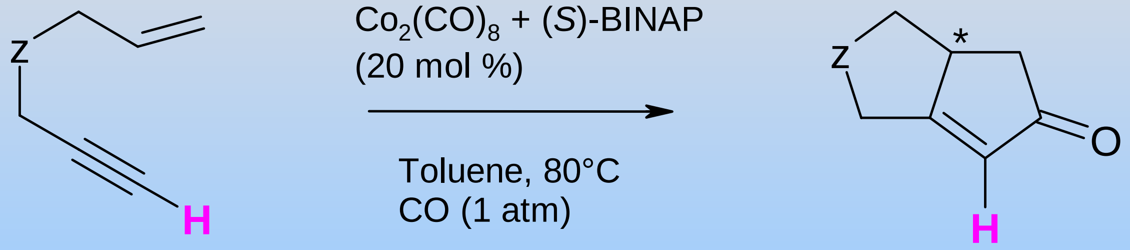
75%, 96%ee

↳ vinyl-substituted bicyclic cyclopentenones with two chiral centers

*Jeong, N.; Kim, D. H.; Choi, J. H.; *Chem. Commun*. **2004**, 1134-1135

Enantioselective Pauson Khand reaction

- **Chiral $Co_2(CO)_8$ complex catalyst***



$Co_2(CO)_8$ + (*S*)-BINAP
(20 mol %)

Toluene, 80°C
CO (1 atm)

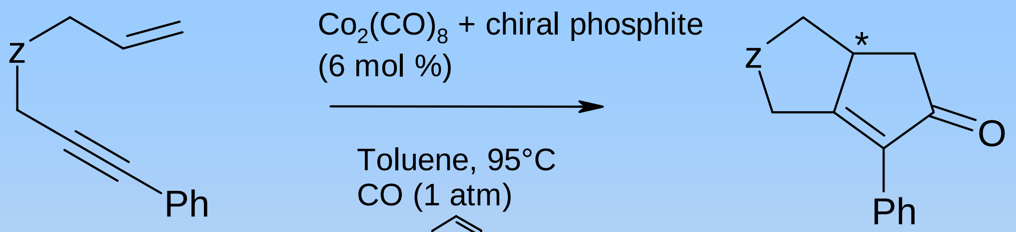
Z=$C(CO_2Et)_2$, NTs

90-93% ee
53-60%

☺ High enantioselectivity

☹ Limited to enynes with no substituent on the alkyne terminus

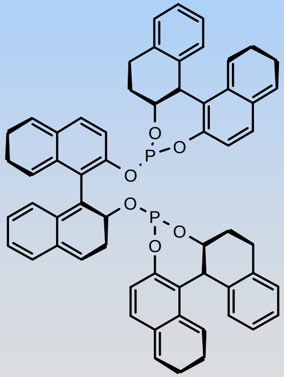
- **$Co_2(CO)_8$ chiral phosphite catalyst****



$Co_2(CO)_8$ + chiral phosphite
(6 mol %)

Toluene, 95°C
CO (1 atm)

Z=$C(CO_2Et)_2$



75% ee
75%

☹ Enantioselectivity and generality of enynes are inferior to those with Ti, Rh and Ir catalysts

*Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I.; *Tetrahedron Lett*. **2000**, 41, 891-895
Sturla, S. J.; Buchwald, S. L.; *J. Org. Chem*. **2002**, 67, 3398-3403

Aldehydes: another CO source…

- **Decarbonylation of carbonyl compounds**

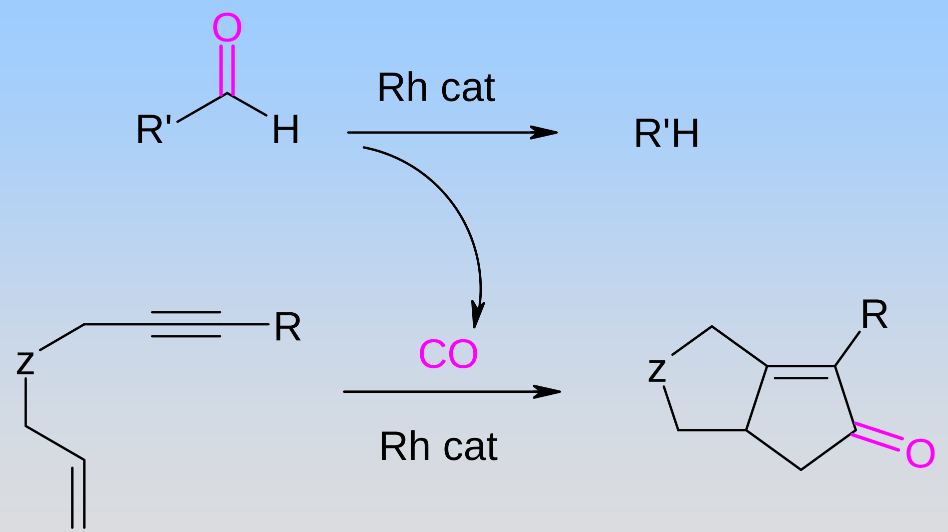
↳ Catalyzed by transition metal

= key step in transition metal catalyzed unique transformation since 1960s*

Use of generated CO by a decarbonylation step was largely neglected…

- **Carbonylative coupling of enynes**

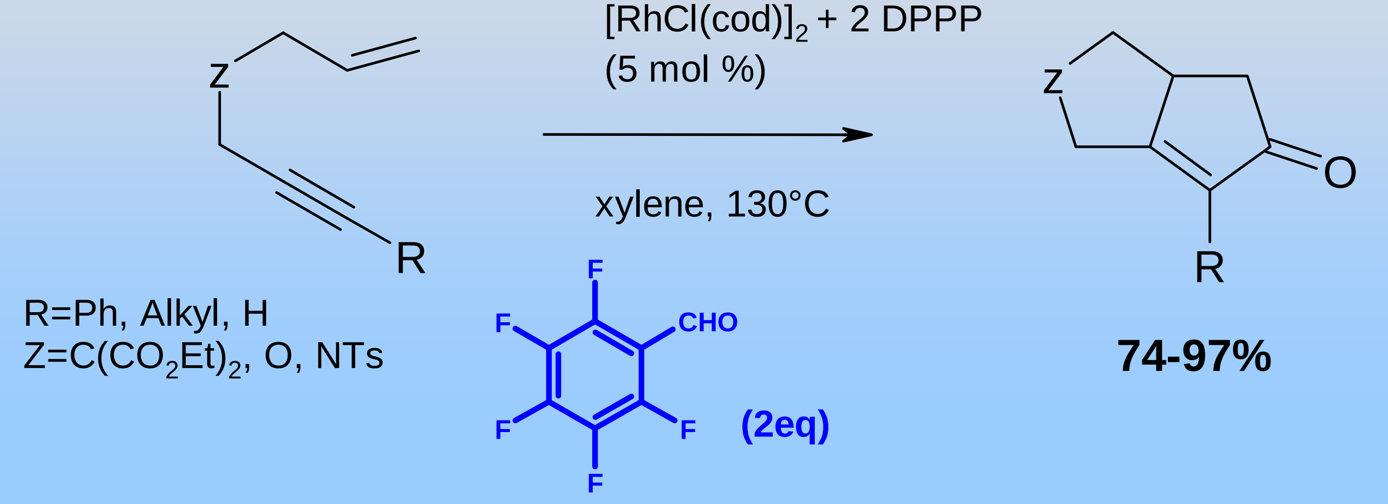
↳ Rh complexes catalyze both decarbonylation of aldehydes and PK reaction



*Murukami, M.; Amii, H.; Ito, Y., *Nature* **1994**, 370, 540-541

Aldehydes: another CO source…

- **Few examples of aldehydes used as CO source***



$[RhCl(cod)]_2$ + 2 DPPP (5 mol %)

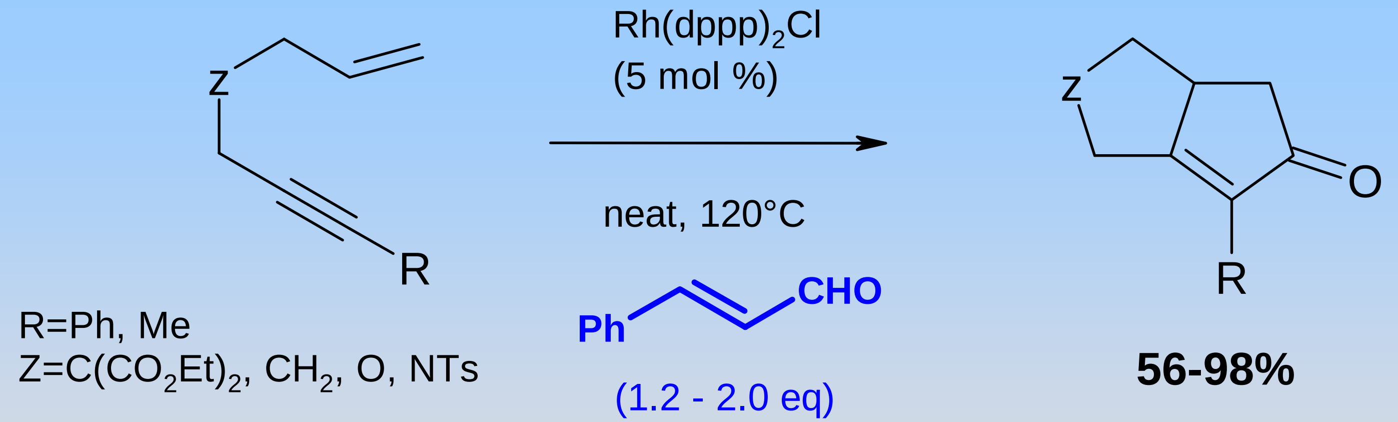
xylene, 130°C

(2eq)

R=Ph, Alkyl, H

Z=$C(CO_2Et)_2$, O, NTs

74-97%



$Rh(dppp)_2Cl$ (5 mol %)

neat, 120°C

(1.2 - 2.0 eq)

R=Ph, Me

Z=$C(CO_2Et)_2$, CH_2, O, NTs

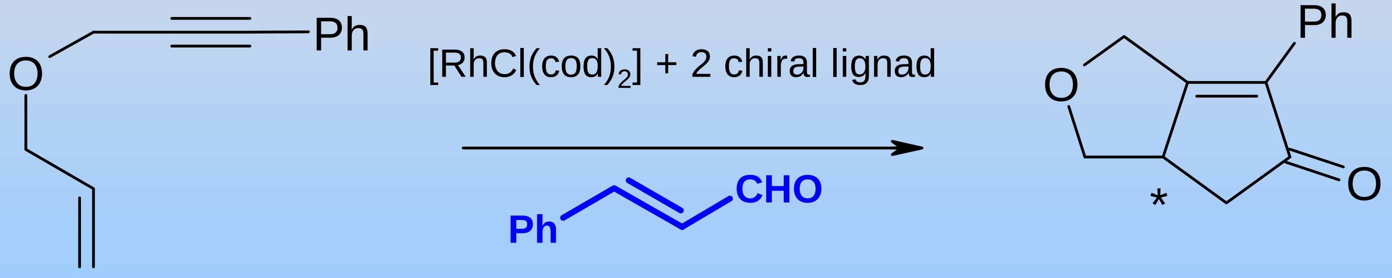
56-98%

*Moromoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K.; *J. Am. Chem. Soc*. **2002**, 124, 3806-3807

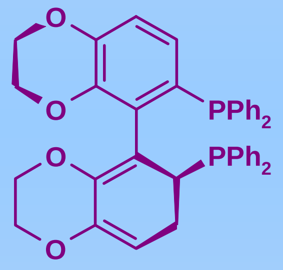
Shibata, T.; Toshida, N.; Takagi, K.; *Org. Lett*. **2002**, 4, 1619-1621

Aldehydes: another CO source…

- **Aldehydes as CO source in enantioselective reaction***



(S)-tolBINAP



neat, 120°C
89%, 82%ee

tert-amyl alcohol, 100°C
70%, 86%ee

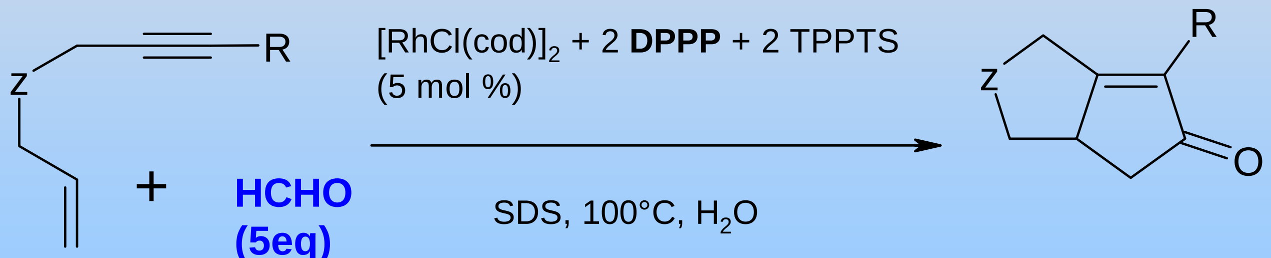
☺ New protocol for carbonylation without the use of toxic CO

☹ Atom economy (pentafluorobenzene and styrene are wasted)

*Shibata, T.; Toshida, N.; Takagi, K.; *J. Org. Chem.* **2002**, 68, 7446-7450
Kwong, F. Y.; Lee, H. W.; Qiu, L.; Lam, W. H., Li, Y. M.; Kwong, H. L.; A. S. C. Chan, *Adv. Synth. Catal.* **2005**, 347, 1750-1754

Aldehydes: atom economical CO source…

- **Use of formaldehyde under aqueous conditions***


[RhCl(cod)]$_2$ + 2 **DPPP** + 2 TPPTS (5 mol %)

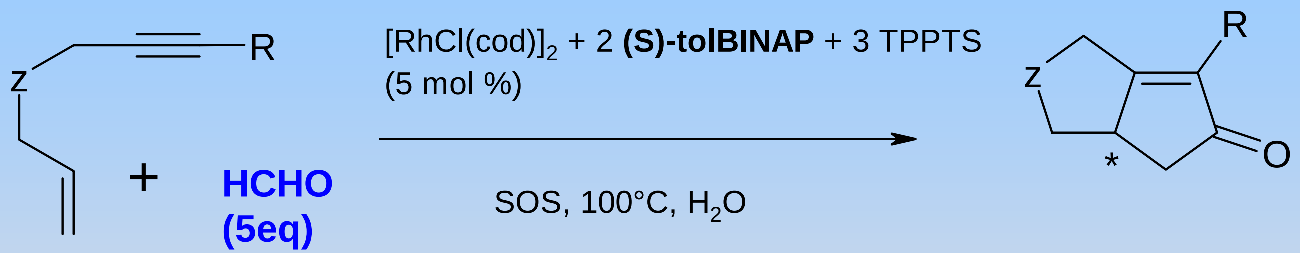
SDS, 100°C, H_2O

+ **HCHO (5eq)**

R=Ph, Alkyl
Z= $C(CO_2Et)_2$, O, NTs

81-96%

DPPP + TPPTS +SDS are essential for high yield


[RhCl(cod)]$_2$ + 2 **(S)-tolBINAP** + 3 TPPTS (5 mol %)

SOS, 100°C, H_2O

+ **HCHO (5eq)**

R=Ph, Alkyl
Z= $C(CO_2Et)_2$, O, NTs

47-83%
74-95%ee

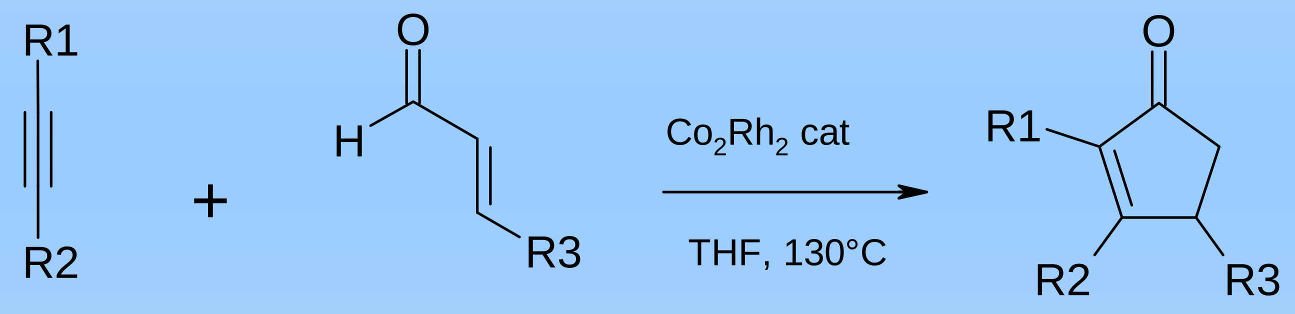
Decarbonylation takes place in aqueous phase whereas carbonylation proceeds in micellar phase

*Fuji, K.; Morimoto, T., Tsutsumi, K.; Kakiuchi, K.; *Angew. Chem. Int. Ed*. **2003**, 42, 2409-2411
Fuji, K.; Morimoto, T., Tsutsumi, K.; Kakiuchi, K.; *Tetrahedron Lett*. **2004**, 45, 9163-9166

Aldehydes: atom economical CO source…

- **Use of α, β unsaturated aldehydes***

= CO source and alkene moiety



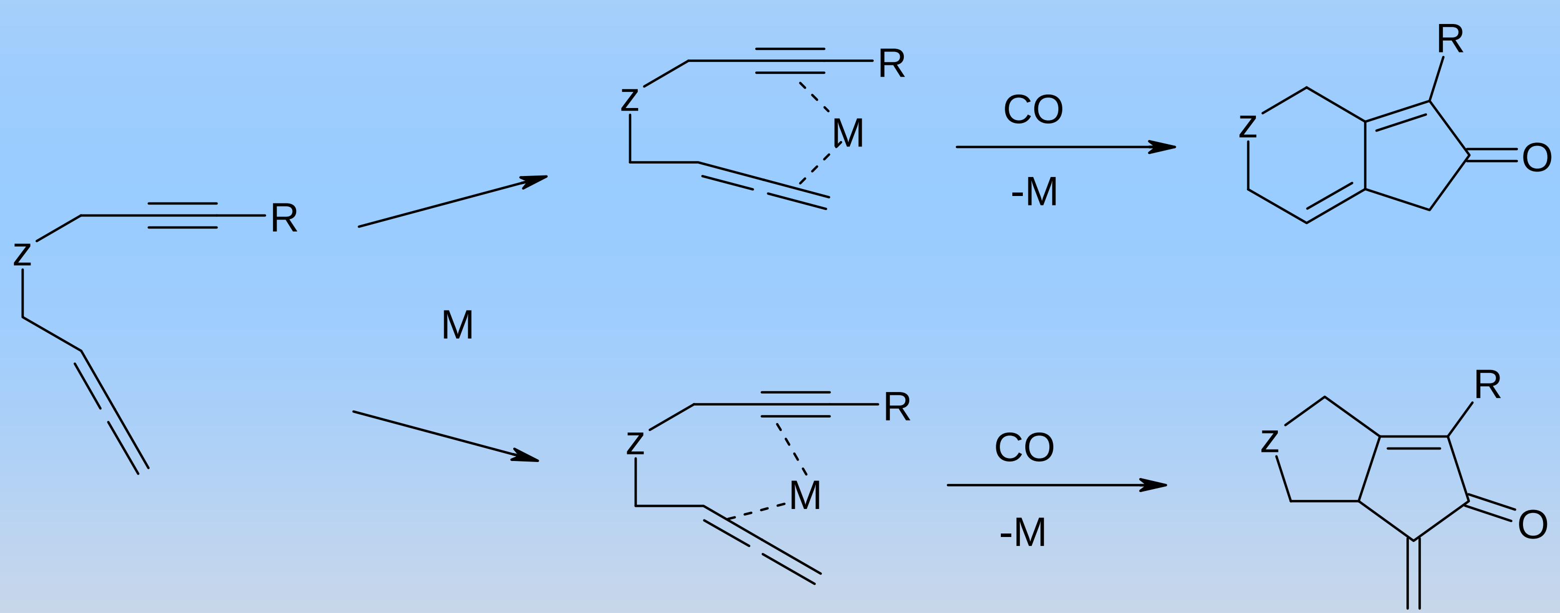
R1, R2= Ph, Me, H
R3= Ph, Alkyl, TMS

48-77%

*Park, K. H., Jung, G., Chung, Y. K.; *Org. Lett.* **2004**, 6, 1183-1186

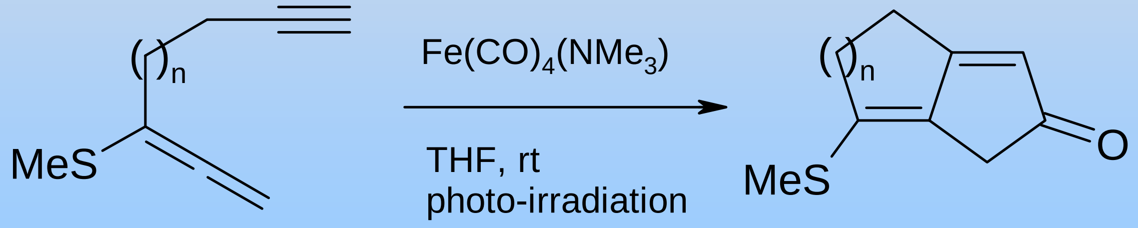
Allene moiety: another ene component

- **Intramolecular reaction of allenynes**
  - ↳ 2 possible reaction pathways



Allene moiety: another ene component

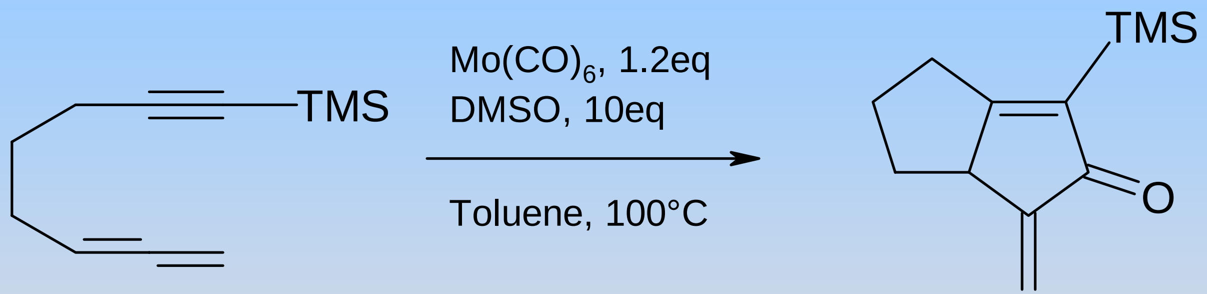
- **First reports***
  - Iron carbonyl complex*



n=1-3

47-60%

  - Molybdene mediated reaction**



68%

☹ **Stoechiometric reactions**

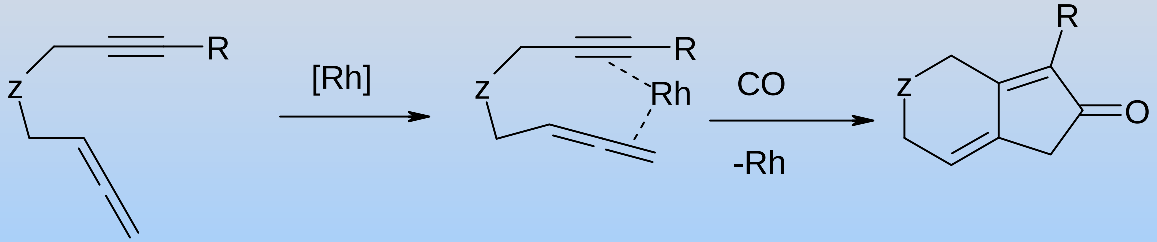
*Narasaka, K.; Shibata, T.; *Chem. Lett* **1994**, 315-318
** Kent, J. L.; Wan, H.; Brummond, K. M., *Tetrahedron Lett*. **1995**, 36, 2407-2410

Allene moiety: another ene component

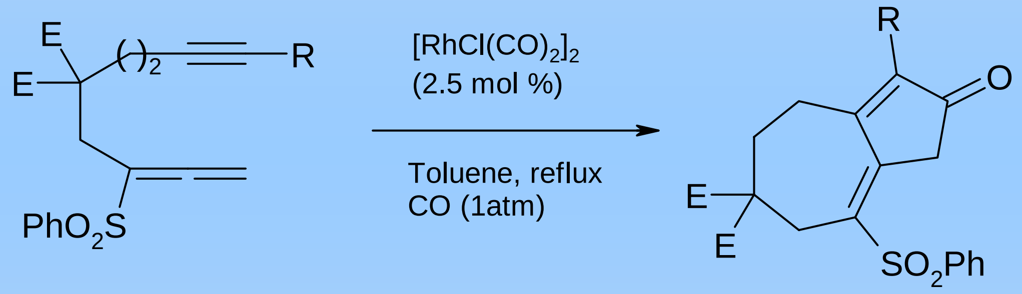
What about catalytic reaction?

Rh catalysis

In general, the pathway is:



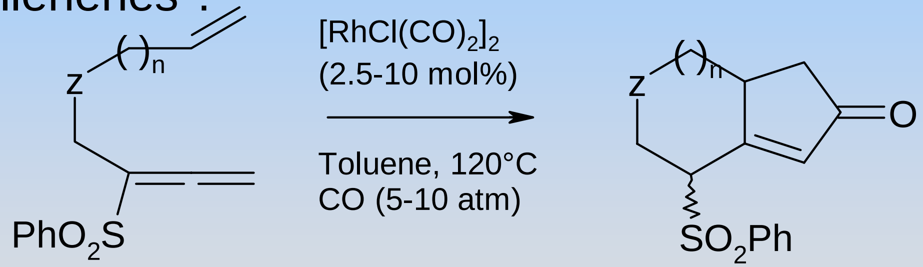
- seven-membered ring systems are also possible*:



R= Ph, H
E= CO_2Me

70-84%

- Reaction of allenenes*:



n=1, 2
Z= $C(CO_2Me)_2$, CH_2, O, NTs

33-89%

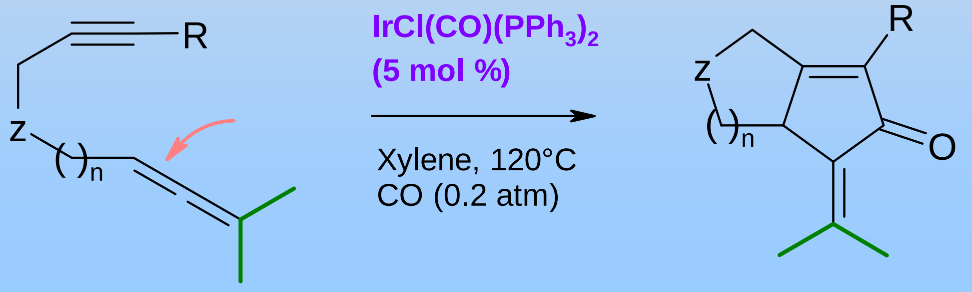
*Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M.; *Org. Lett*. **2002**, 4, 1755-1758
** Inagaki, F.; Mukai, C.; *Org. Lett*. **2006**, 8, 1217-1220

Allene moiety: another ene component

What about catalytic reaction?

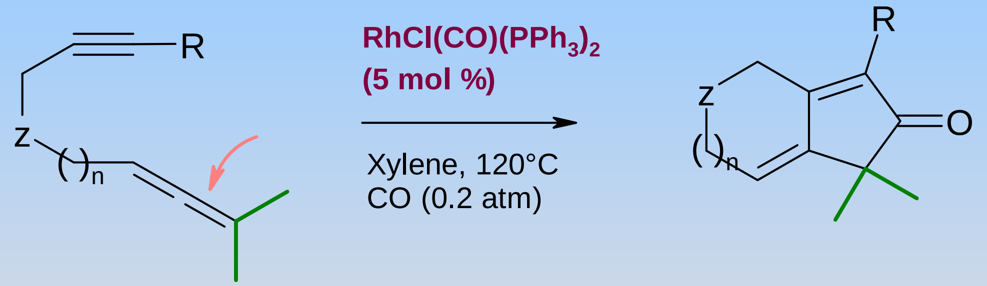
- **Ir catalysis***

↪ Different regioselectivity



n= 1, 2
R= Ar, Me, SiMe$_2$Ph
Z= C(CO$_2$Et)$_2$, O, NTs

52-91%



n= 1, 2
R= Ar, Me, SiMe$_2$Ph
Z= C(CO$_2$Et)$_2$, O, NTs

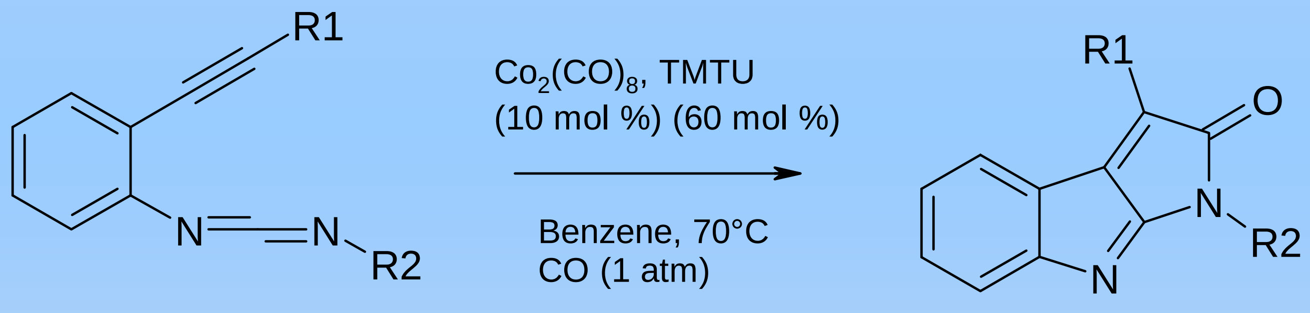
52-91%

*Shibata, T.; Kadowaki, S.; Hirase, M.; Takagi, K.; *Synlett* **2003**, 573-575

Carbodiimide: nitrogen analogue of an allene

Carbodiimide = ene moiety in a PK reaction

↳ ***Hetero-Pauson-Khand reaction****



$Co_2(CO)_8$, TMTU
(10 mol %) (60 mol %)

Benzene, 70°C
CO (1 atm)

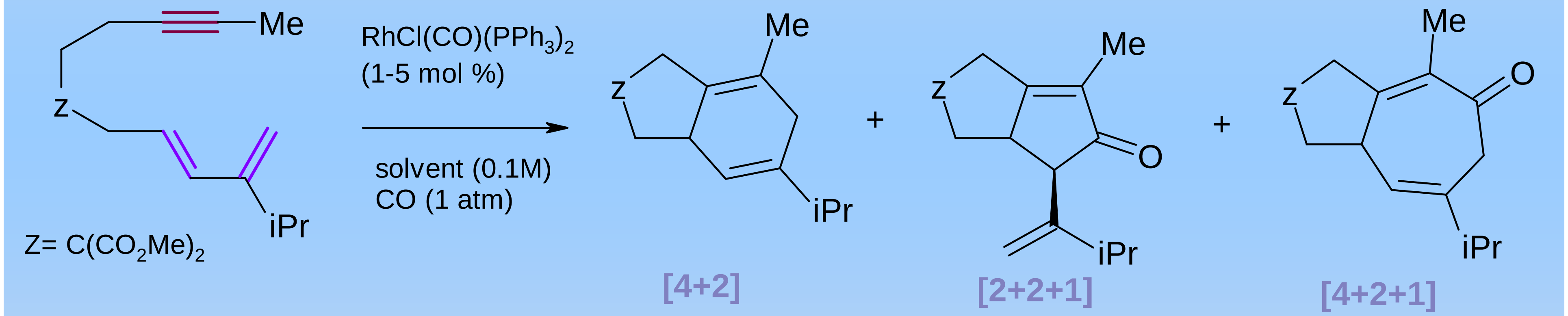
R1= alkyl, TMS
R2= Ar, Me

41-69%

*Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A.; *Org. Lett*. **2006**, 8, 83-86

Diene moiety: another ene component

- **Rh catalyzed reactions**
- **1, 3-diene-ynes***



Z= $C(CO_2Me)_2$

$RhCl(CO)(PPh_3)_2$
(1-5 mol %)

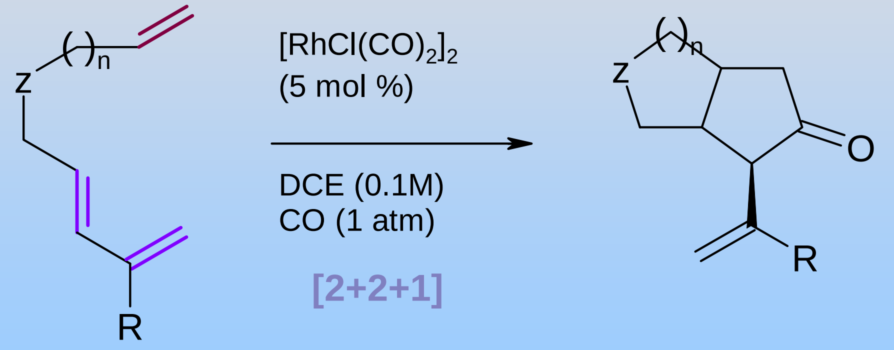
solvent (0.1M)
CO (1 atm)

	[4+2]	[2+2+1]	[4+2+1]
THF, 40°C:	**45%**	**25%**	**18%**
DCE, rt:	**7%**	**88%**	

* Wender, P. A.; Deschamps, N. M.; Gamber, G. G.; *Angew. Chem. Int. Ed.* **2003**, 42, 1853-1857

Diene moiety: another ene component

- **1, 3-diene-enes***



[RhCl(CO)$_2$]$_2$
(5 mol %)

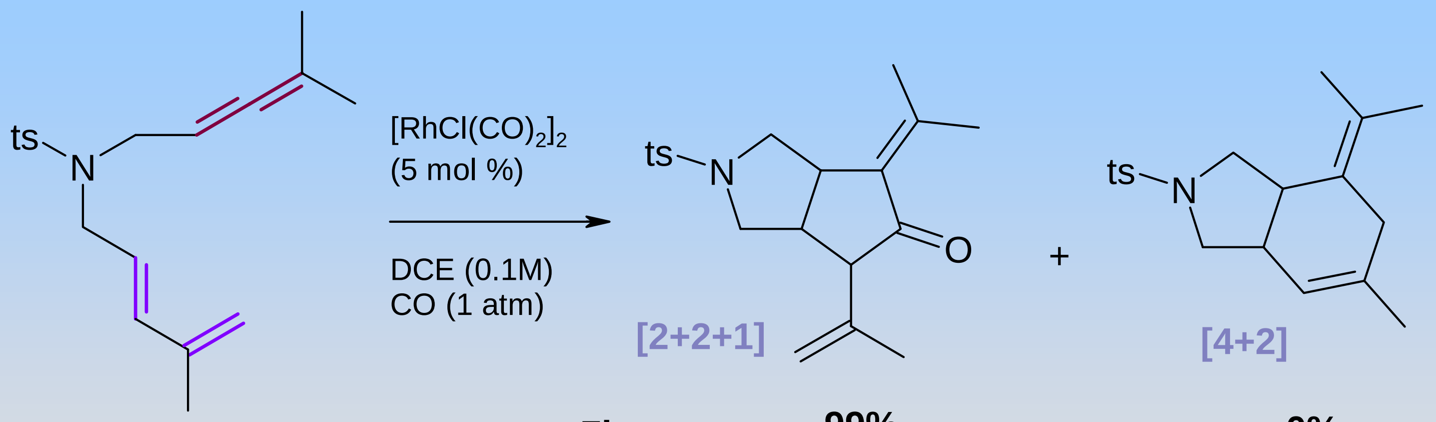
DCE (0.1M)
CO (1 atm)

[2+2+1]

n= 1, 2
Z= C(CO2Me)2, O, NTs
R= Me, iPr, H

84-94%

- **1, 3-diene-allenes****



[RhCl(CO)$_2$]$_2$
(5 mol %)

DCE (0.1M)
CO (1 atm)

[2+2+1]

[4+2]

rt, 7h	**99%**	**0%**
80°C, 1h	**43%**	**52%**

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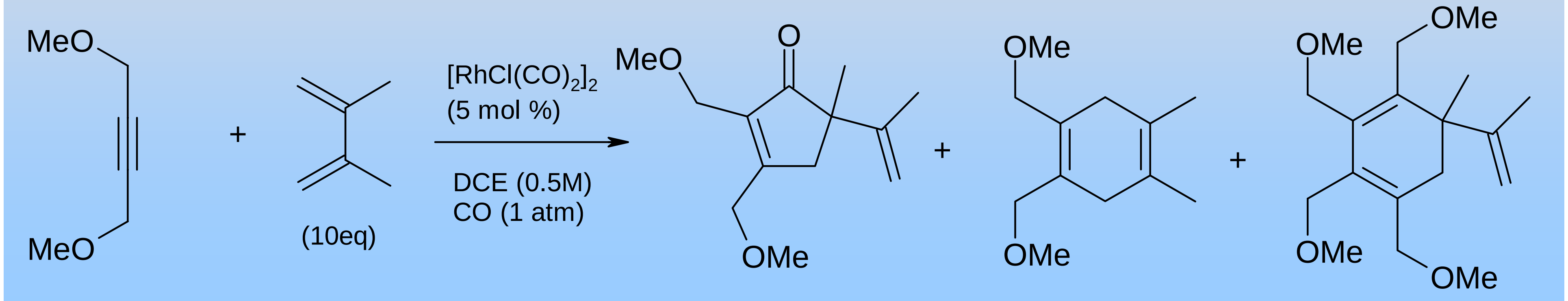
* Wender, P. A.; Deschamps, N. M.; Croatt, N. M.; *J. Am. Chem. Soc* **2004**, 126, 5948-5949

** Wender, P. A.; Deschamps, N. M.; Croatt, N. M.; *Angew. Chem. Int. Ed.* **2006**, 45, 2459-2462

Diene moiety…Heading for intermolecular PK reaction



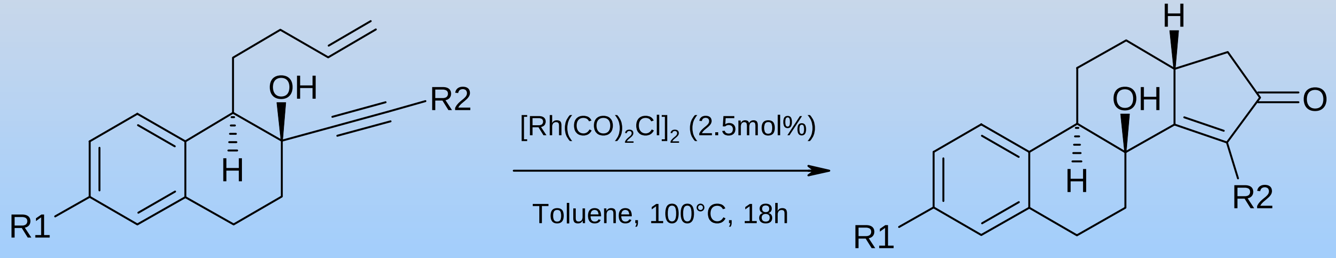
60°C	**>99%**		
80°C	**11%**	**42%**	**29%**

⇨ The choice of the reaction temperature is crucial

* Wender, P. A.; Deschamps, N. M.; Williams, T. J.; *Angew. Chem. Int. Ed.* **2004**, 43, 3076-3079

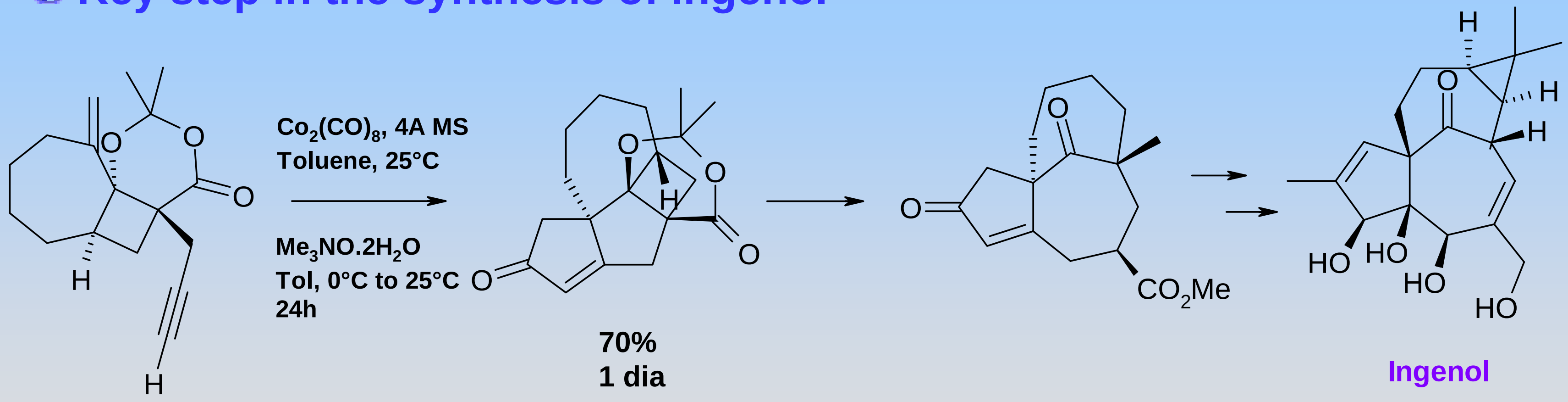
Pausan-Khand in total synthesis

A facile synthesis of the basic steroidal skeleton*



R1=H, R2=Ph, 63%
R1=H, R2=tolyl, 82%
R1=H, R2=nBu, 46%
R1=H, R2=TMS, 29%
R1=OMe, R2=Ph, 80%

Key step in the synthesis of ingenol**



•Kim, D. H.; Kim, K.; Chung, Y.K.; *J. Org. Chem*. **2006**, 71, 8264-8267
** Winkler, J. D.; Lee, E. C.; Nevels, L. I.; *Org. Lett*. **2005**, 7(8), 1489-1491

In summary…

☹ Limitation of alkynes and alkenes

☹ Intermolecular PK reaction needs to be developped

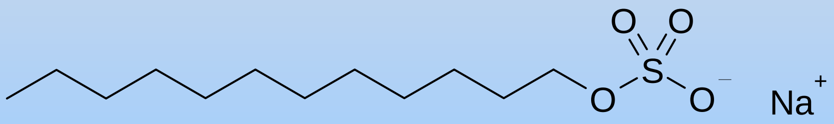
☺ Various transition metal catalysts + chiral species

☺ New types of substrates

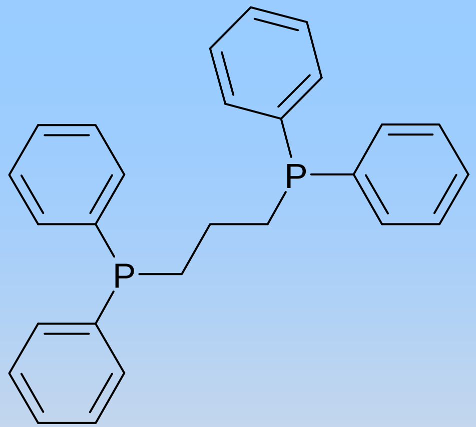
☺ Powerful synthetic route still used in total synthesis

For more details, see: *Adv. Synth. Catal*. **2006**, 348, 2328-2336

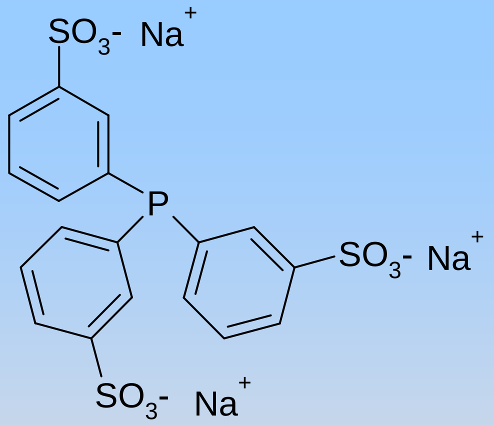
More informations



Sodium Dodecyl sulfate



1,3-bis(diphenylphosphino)propane, DPPP



Triphenylphospholane trisulfonic acid trisodium salt, TPPS