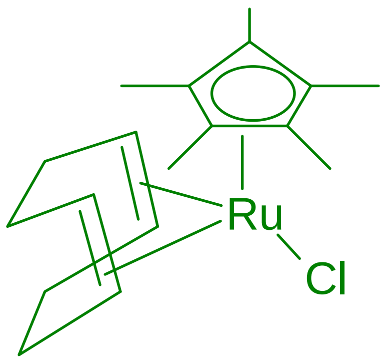
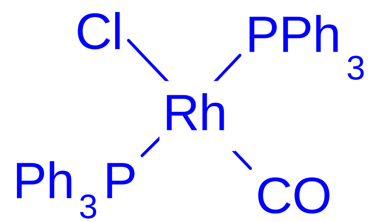
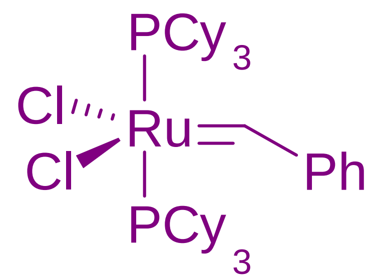
Transition Metal-Catalyzed Multicomponent Cycloadditions







Luke Zuccarello

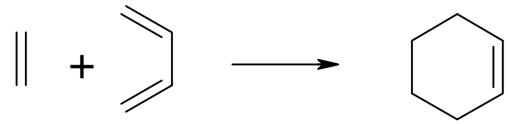
The University of North Carolina at Chapel Hill

March 5, 2004

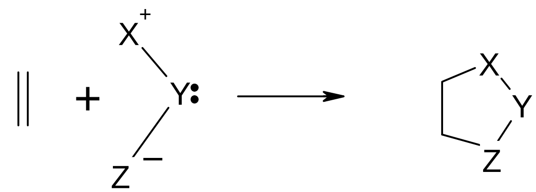
Cycloadditions: Common Versus Multicomponent

- Common pericyclic cycloadditions:

Diels-Alder [4+2]

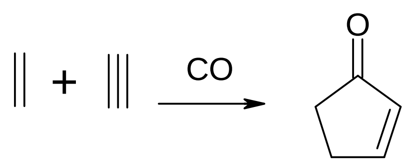


1,3-Dipolar [3+2]

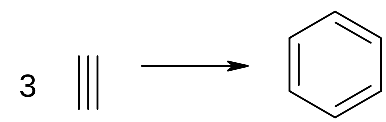


- Multicomponent cycloadditions are most commonly three - component

[2+2+1]



[2+2+2]



- Other examples: [5+2+1], [4+2+2], etc.

Murakami, M. *Angew. Chem. Int. Ed.* **2003**, *42,* 718.

Introduction: Multicomponent Cycloadditions

Multicomponent cycloadditions made possible through metal assistance/catalysis by surmounting:

- Entropic barriers
- Regio- and stereoselectivity issues
- Non-polarized/unactivated bonds

Advantages of Multicomponent Cycloadditions

- Multicomponent cycloadditions provide new, efficient routes to a variety of ring systems
- *Catalytic* multicomponent cycloadditions provide atom economy: lower costs; reduced waste; improved safety; simplified purification

Presentation Scope

I. [2+2+1] Cycloadditions: The Pauson-Khand Reaction
   - Original (non-catalytic) reaction
   - Recent, catalytic variants using Rh

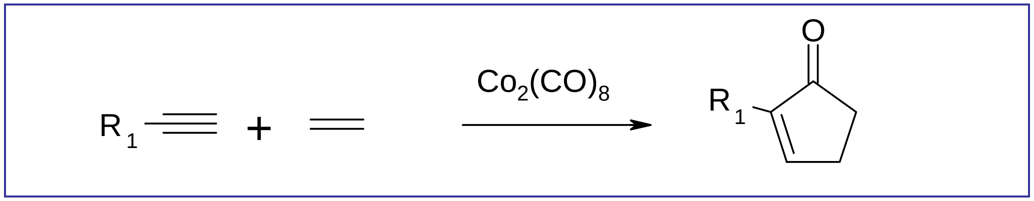
II. Metal-Catalyzed [2+2+2] Cycloadditions
   - Background
   - Ru-catalyzed metallacycle-type [2+2+2]
   - Ru-catalyzed metathesis-type [2+2+2]

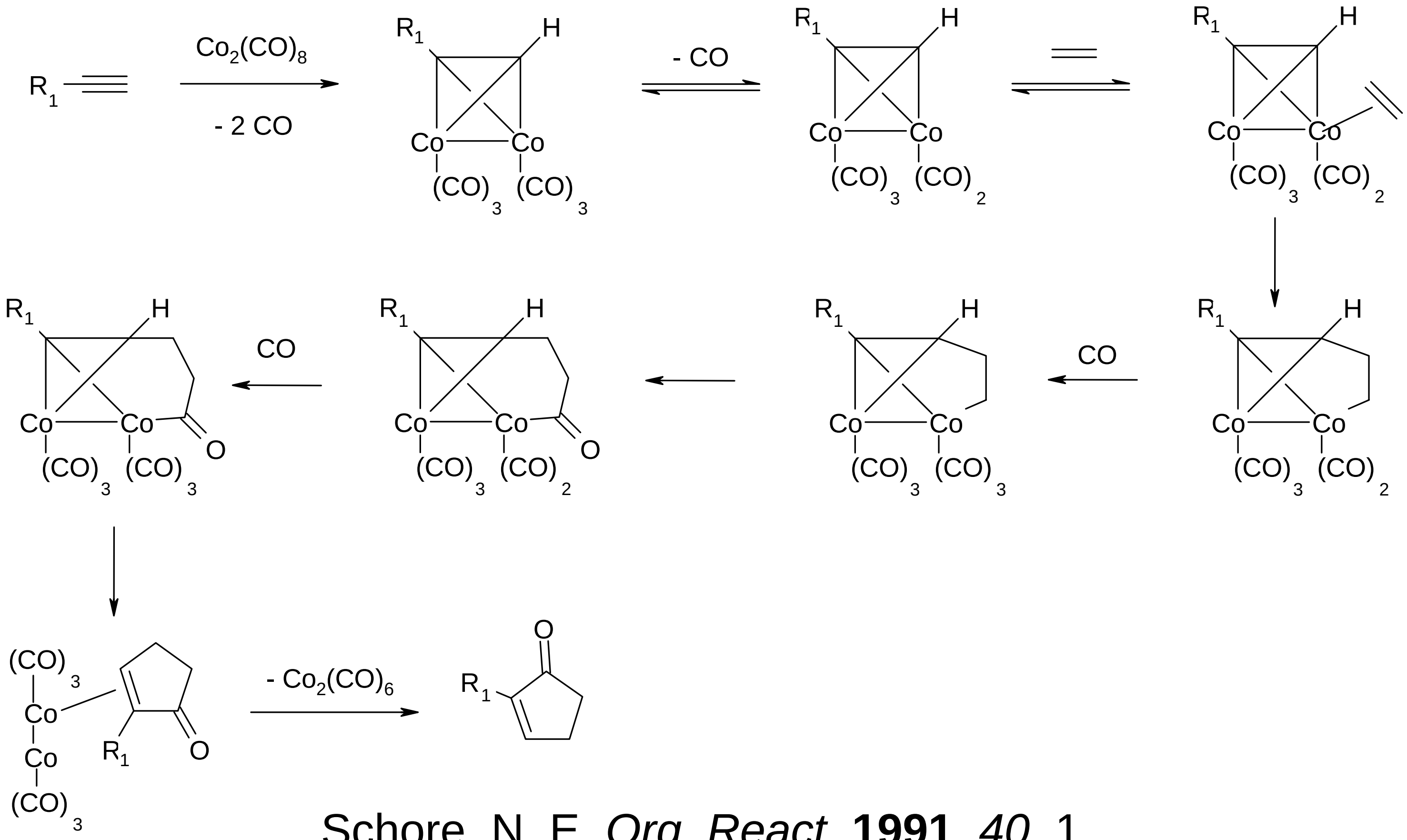
The Pauson-Khand Reaction (PKR)

- Discovered in 1971 by Peter Pauson and Ihsan Khand
- Is a formal cycloaddition incorporating an alkene, alkyne, and carbon monoxide
- Can be inter- or intramolecular
- Is stoichiometric in $Co_2(CO)_8$

Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans.* **1973**, *1,* 977.
Schore, N. E. *Org. React.* **1991**, *40*, 1.

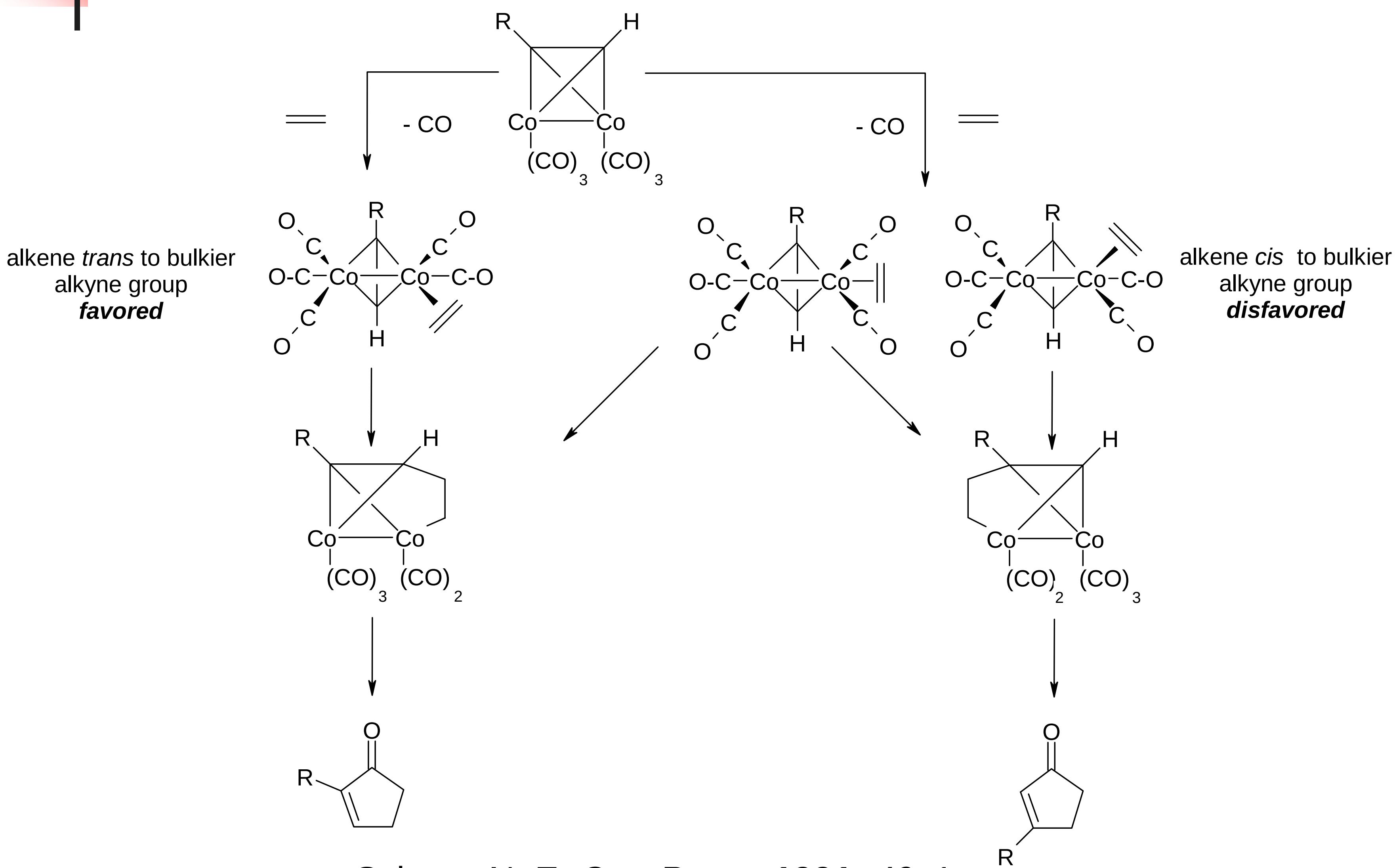
The PKR Mechanism





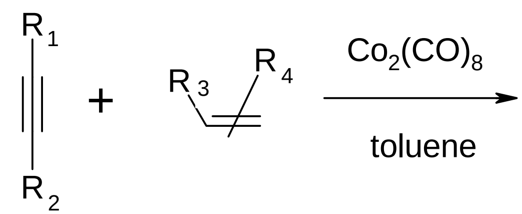
Schore, N. E. *Org. React.* **1991**, *40*, 1.

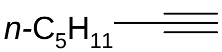
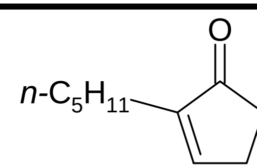
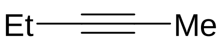
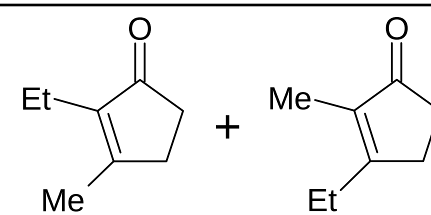
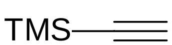
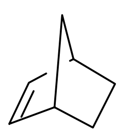
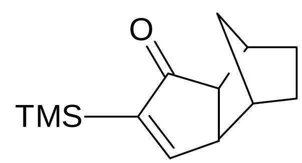
The PKR Mechanism: Regiochemistry



Schore, N. E. *Org. React.* **1991**, *40*, 1.

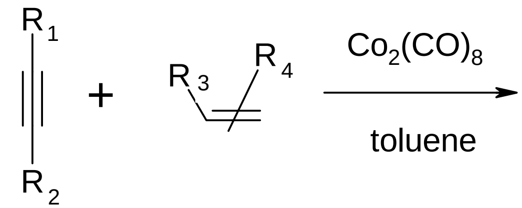
Intermolecular PKR

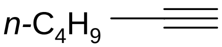
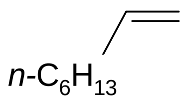
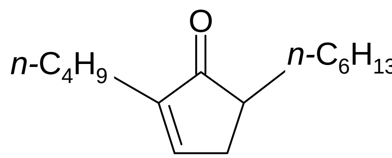
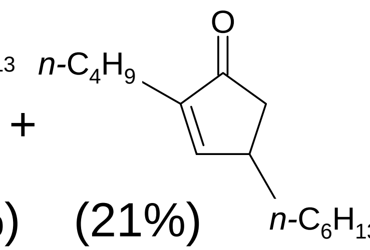
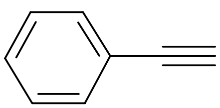
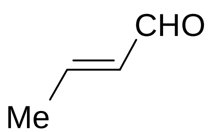
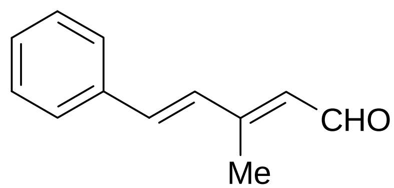


Alkyne	Alkene	Temp. (°C)	Pressure (atm)	Time (h)	Product (Yield)
		85	120	36	 (55%)
		110	35	36	 (24%) (3%)
		80-90	--	18	 (93%)

Schore, N. E. *Org. React.* **1991**, *40*, 1.

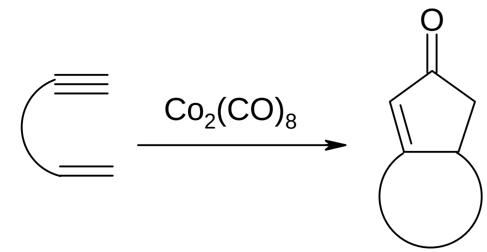
Intermolecular PKR

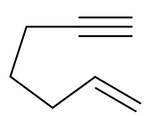
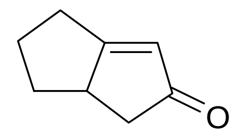
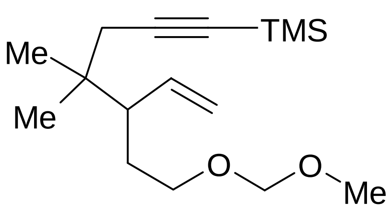
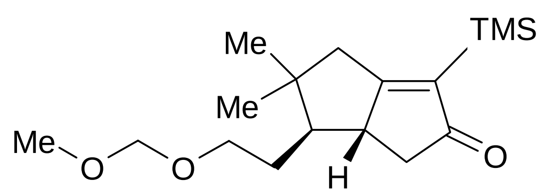


Alkyne	Alkene	Temp. (°C)	Time (h)	Product (Yield)
		95-100	48	 +  (21%) (21%)
		--	--	 (major pdt)

Schore, N. E. *Org. React.* **1991**, *40*, 1.

Intramolecular PKR



Enyne	Temp. (°C)	Time	Product (Yield)
	95	4 d	 (31%)
	115	36 h	 (78%)

Schore, N. E. *Org. React.* **1991**, *40*, 1.

Limitations and Disadvantages of PKR

- Stoichiometric in a transition metal
- High pressure/temperature often necessary
- $Co_2(CO)_8$ ignites in air
- Problematic substrates in intermolecular PKR: internal alkynes (low yield), alkenes which are acyclic (low yield, regioselectivity) or have EWG (reaction failure)
- Intramolecular PKR fails if alkyne is internal and alkene is more than disubstituted

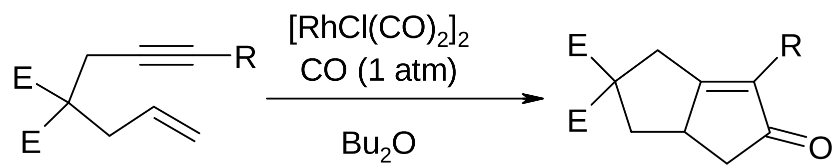
Schore, N. E. *Org. React.* **1991**, *40*, 1.
Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed. Engl*. **2003**, *42*, 1800.

The Catalyzed PKR (CPKR)

•1973: $Co_2(CO)_8$ as catalyst
•1990s: improved Co catalyst systems
•Most recent discoveries: Rh, Ru, Ir, Ti as metal catalysts

Gibson, S. E.; Stevenazzi, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1800.

$[RhCl(CO)_2]_2$ -Catalyzed PKR



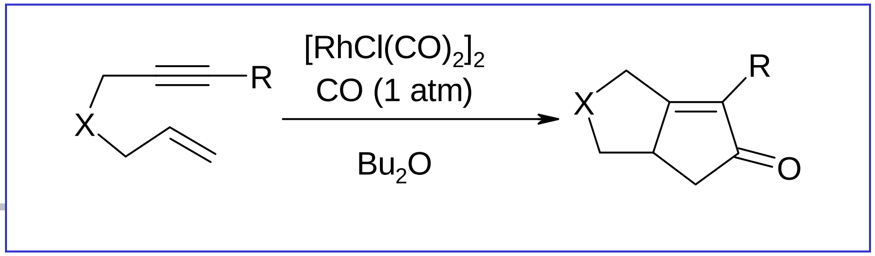
E = CO_2Et

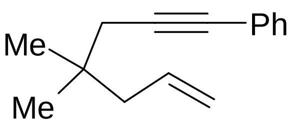
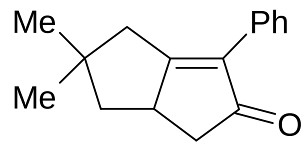
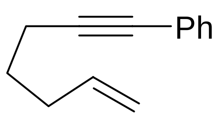
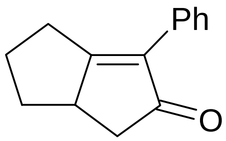
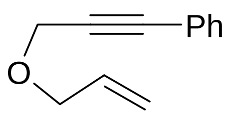
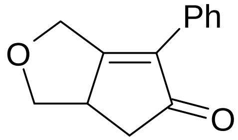
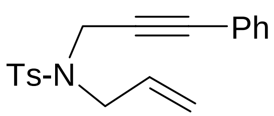
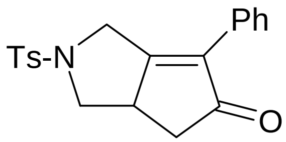
R	Cat. Mol%	Temp. (°C)	Time (h)	Yield
Et	1	130	12	91%
Ph	1	130	16	94%
$SiMe_3$	5	150	18	76% *
H	1	150	2	55%

* includes desilylation product

Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem*. **2001**, *634,* 73.

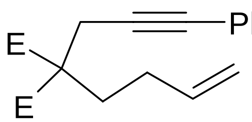
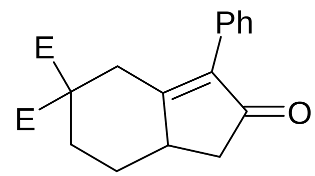
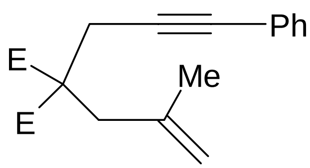
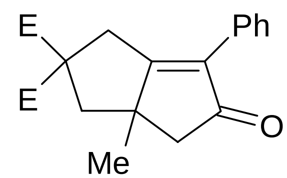
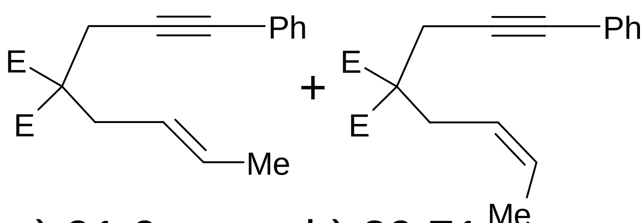
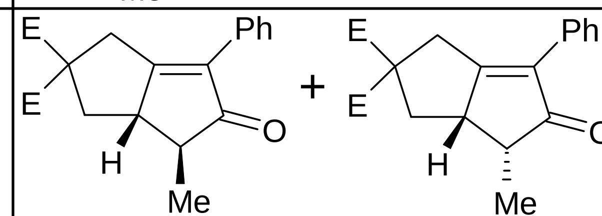
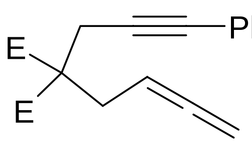
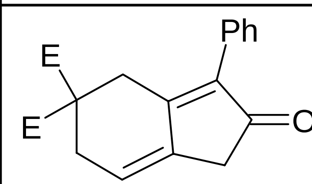
$[RhCl(CO)_2]_2$ -Catalyzed PKR



Enyne	Cat. Mol%	Temp. (°C)	Time (h)	Product (Yield)
	5	130	1	 (92%)
	1	160	12	 (81%)
	2	130	18	 (89%)
	2	130	16 h	 (92%)

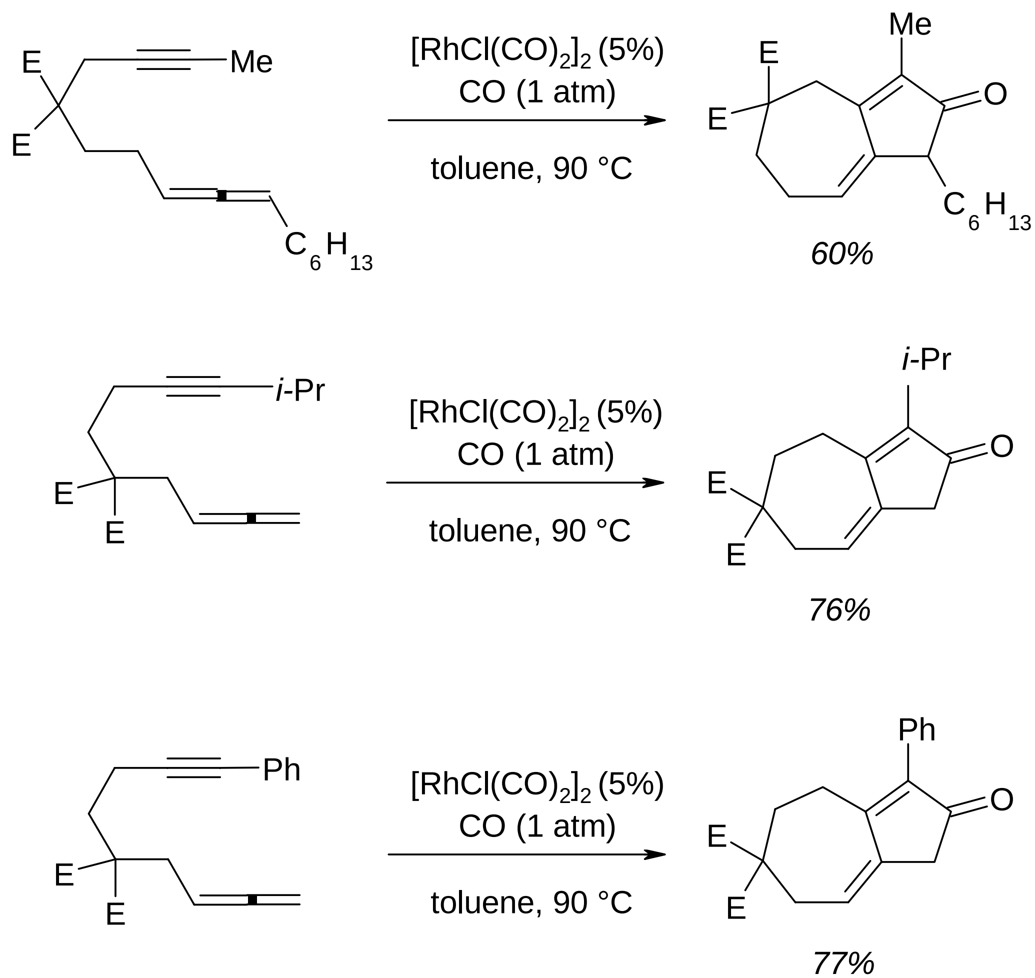
Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem*. **2001**, *634,* 73.

$[RhCl(CO)_2]_2$ -Catalyzed PKR

Substrate	Cat. Mol%	Temp. (°C)	Time (h)	Product (Yield)
	5	160	5	 (93%)
	5	160	15	 (71%)
 a) 91:9 b) 29:71	1	160	a) 6 b) 12	 a)95:5 (96%) b)31:69 (90%)
	5	r.t.	18	 (61%)

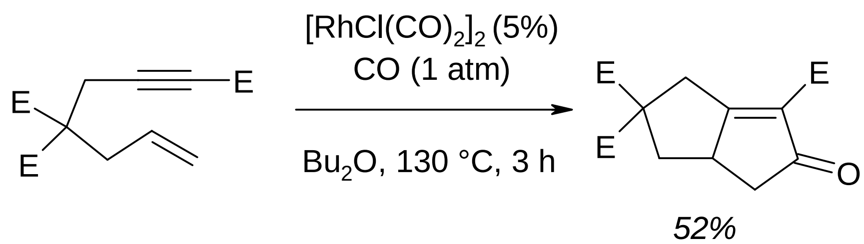
Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem*. **2001**, *634,* 73.

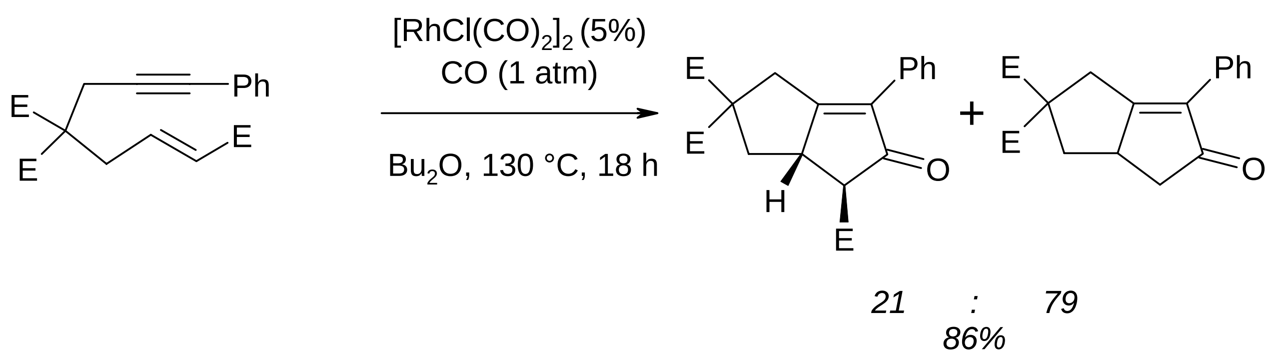
$[RhCl(CO)_2]_2$ -Catalyzed PKR: Allenynes



Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. *Org. Lett.* **2002**, *4*, 1931.

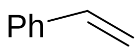
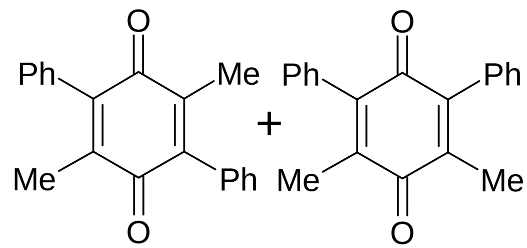
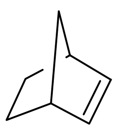
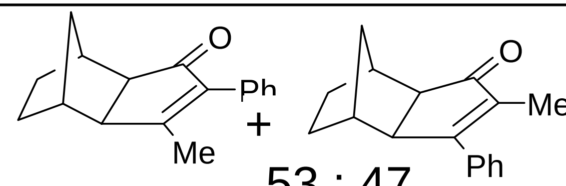
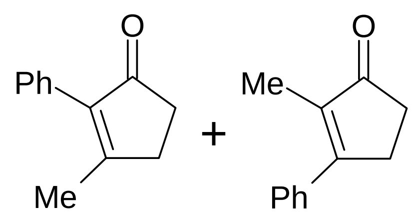
$[RhCl(CO)_2]_2$ -Catalyzed PKR Using Alkenes and Alkynes with Electron Withdrawing Groups





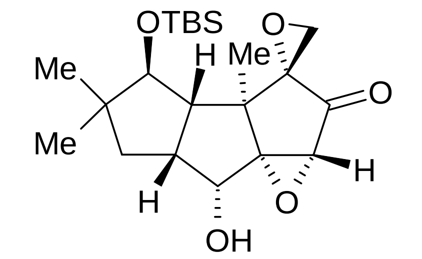
Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem*. **2001**, *634,* 73.

$[RhCl(CO)_2]_2$ -Catalyzed Intermolecular PKR

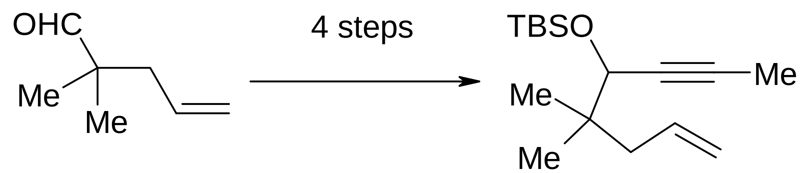
Alkyne	Alkene	Cat. Mol%	Temp. (°C)	Time (h)	Product (Yield)
Ph—≡—Me		5	130	10	 (60%)
Ph—≡—Me		5	130	60	 53 : 47 (69%)
Ph—≡—Me		5	130	60	 1 : 1 (38%)

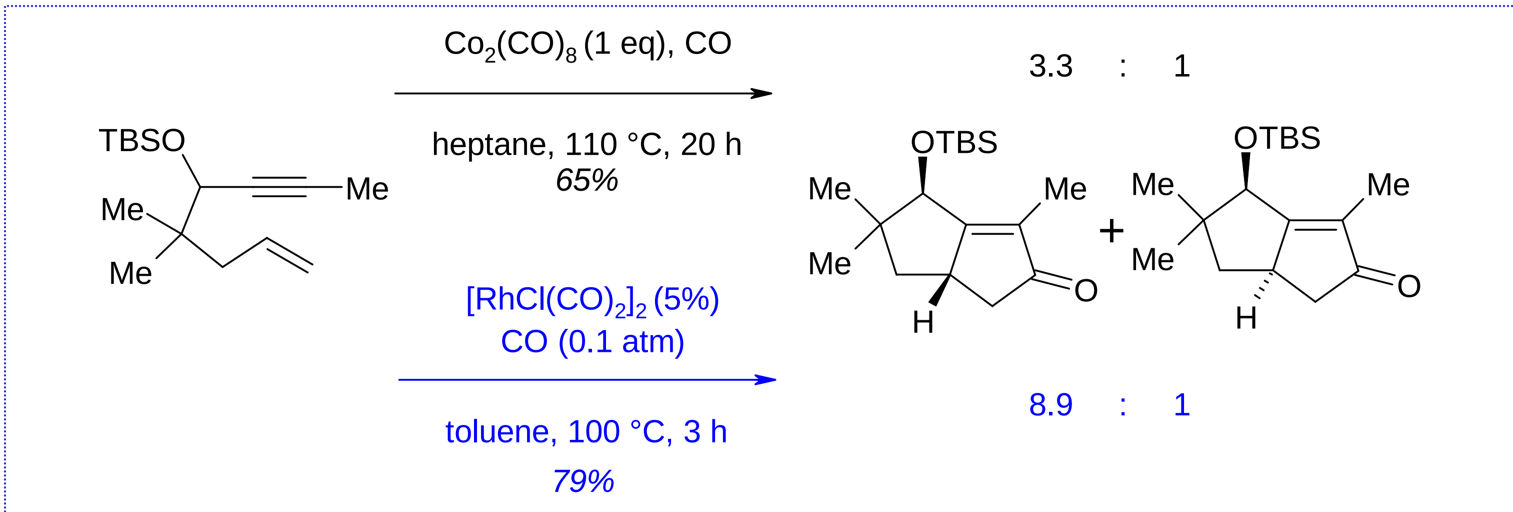
Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem*. **2001**, *634,* 73.

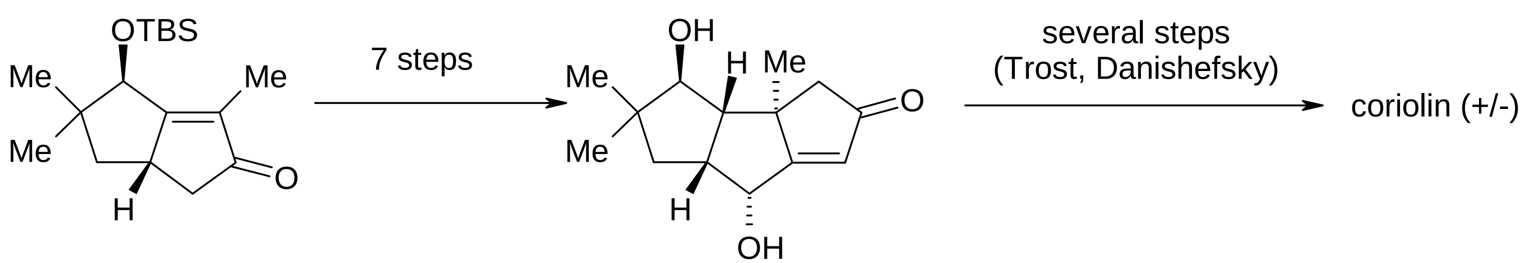
An Application in Natural Product Synthesis



coriolin (+/-)

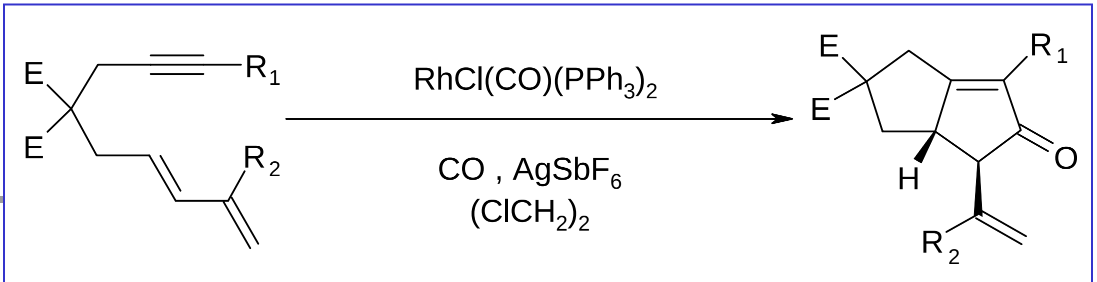


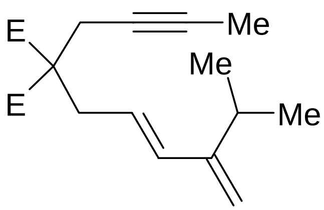
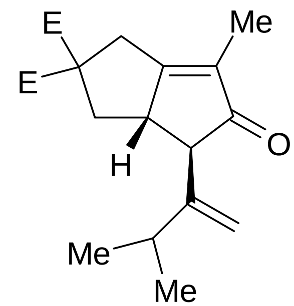
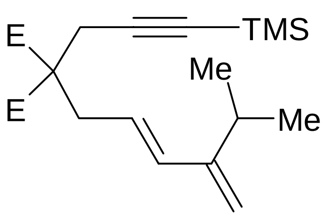
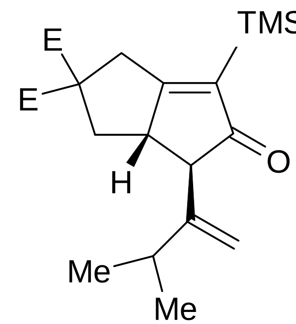




Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem*. **2001**, *634,* 73.
Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477.

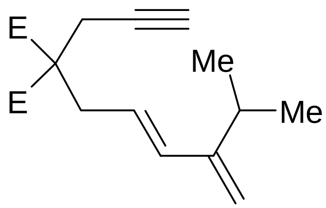
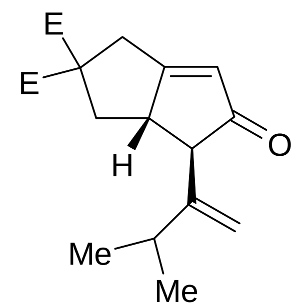
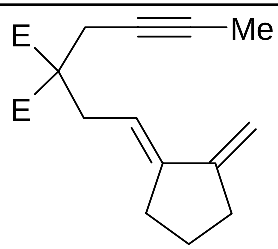
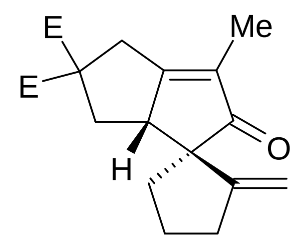
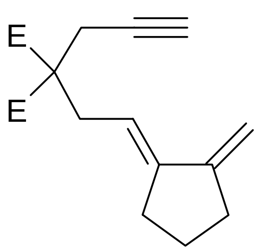
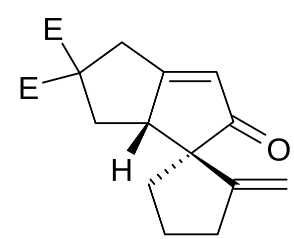
$RhCl(CO)(PPh_3)_2$ -Catalyzed PKR



Dienyne	Rh/Ag Mol%	Temp. (°C)	Press. (atm)	Time (h)	Product (Yield)
	1	r.t.	1	14	 (89%)
	2	r.t.	2	12	 (85%)

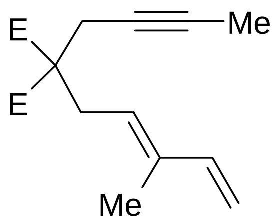
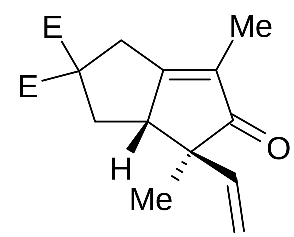
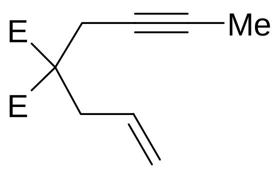
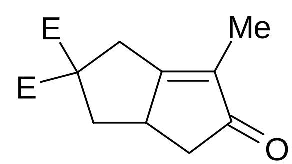
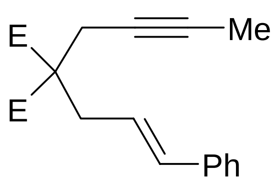
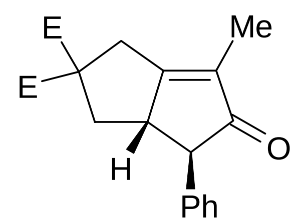
Wender, P.; Deschamps, N.; Gamber, G. *Angew. Chem. Int. Ed.* **2003**, *42,* 1853.

RhCl(CO)(PPh$_3$)$_2$ -Catalyzed PKR

Dienyne	Rh/Ag Mol%	Temp. (°C)	Press. (atm)	Time (h)	Product (Yield)
	1	r.t.	1	40	 (43%)
	1	r.t.	1	24	 (96%)
	5	r.t.	1	32	 (45%)

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

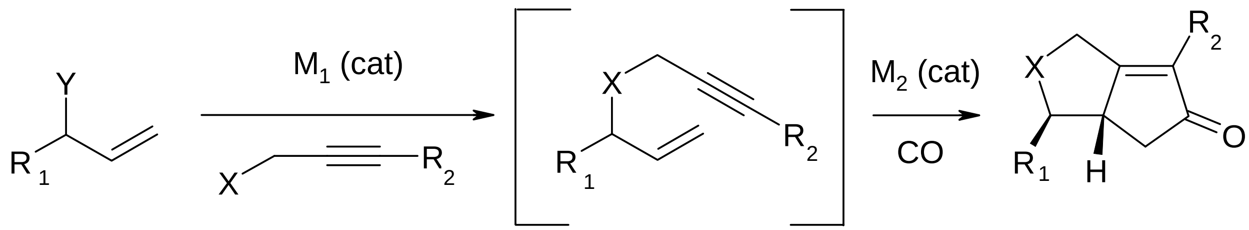
RhCl(CO)(PPh$_3$)$_2$ -Catalyzed PKR

Dienyne	Rh/Ag Mol%	Temp. (°C)	Press. (atm)	Time	Product (Yield)
	2.5	40	1	10 h	 (96%)
	5	80	1	3 d	 (71%)
	5	80	1	4 d	 (33%) *

* at 69% conversion

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

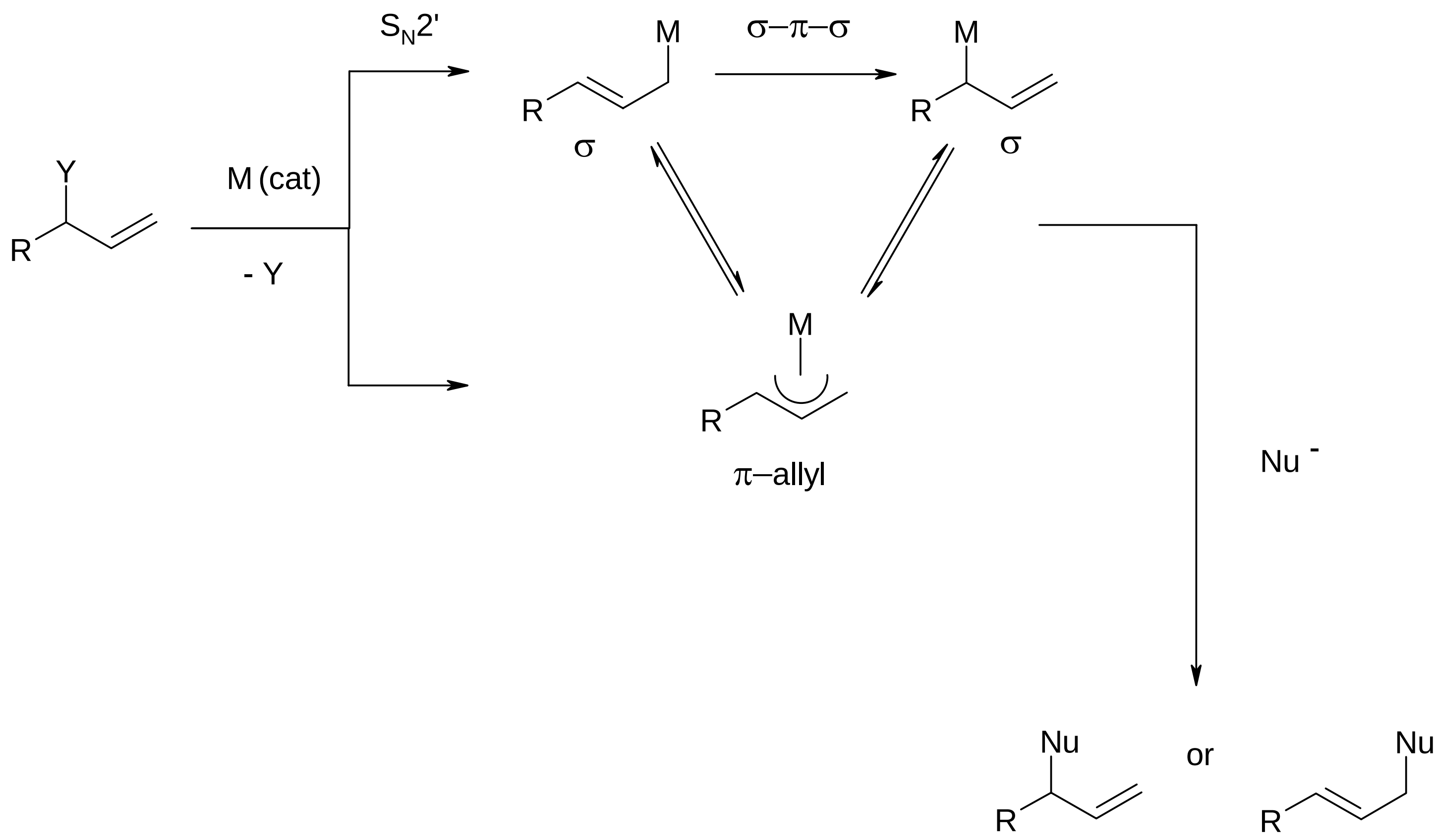
One Pot, Tandem Alkylation-PKR



- N. Jeong: M_1 = Pd, M_2 = Rh
- P. A. Evans: M_1 = M_2 = Rh

Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122,* 10220.
Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123,* 4609.

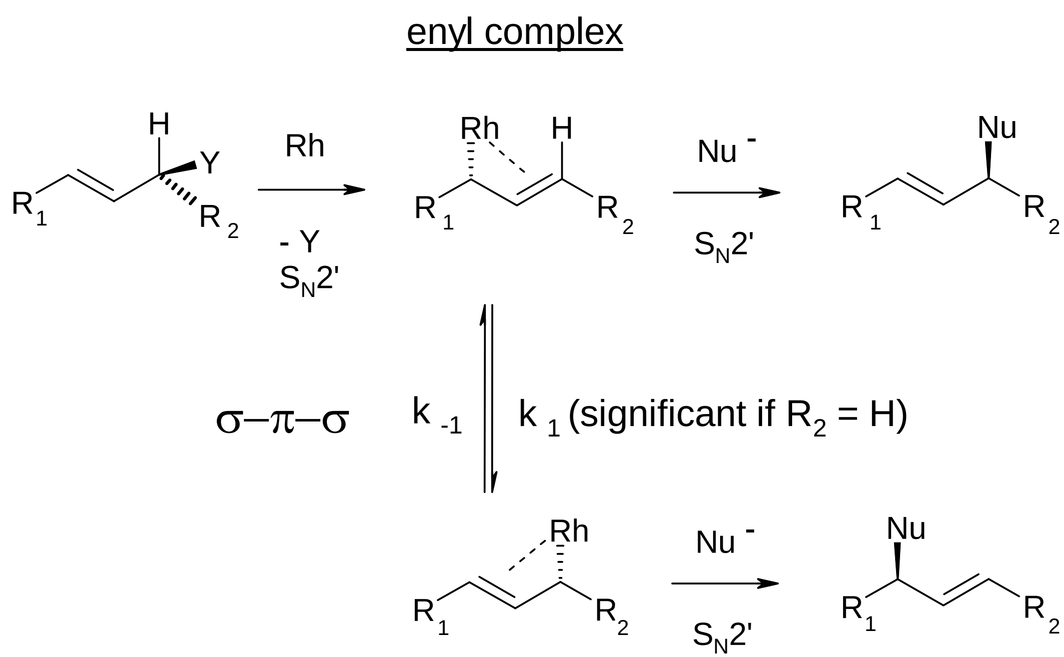
Mechanistic Possibilities for Metal-Catalyzed Allylic Alkylation



Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120,* 5581.

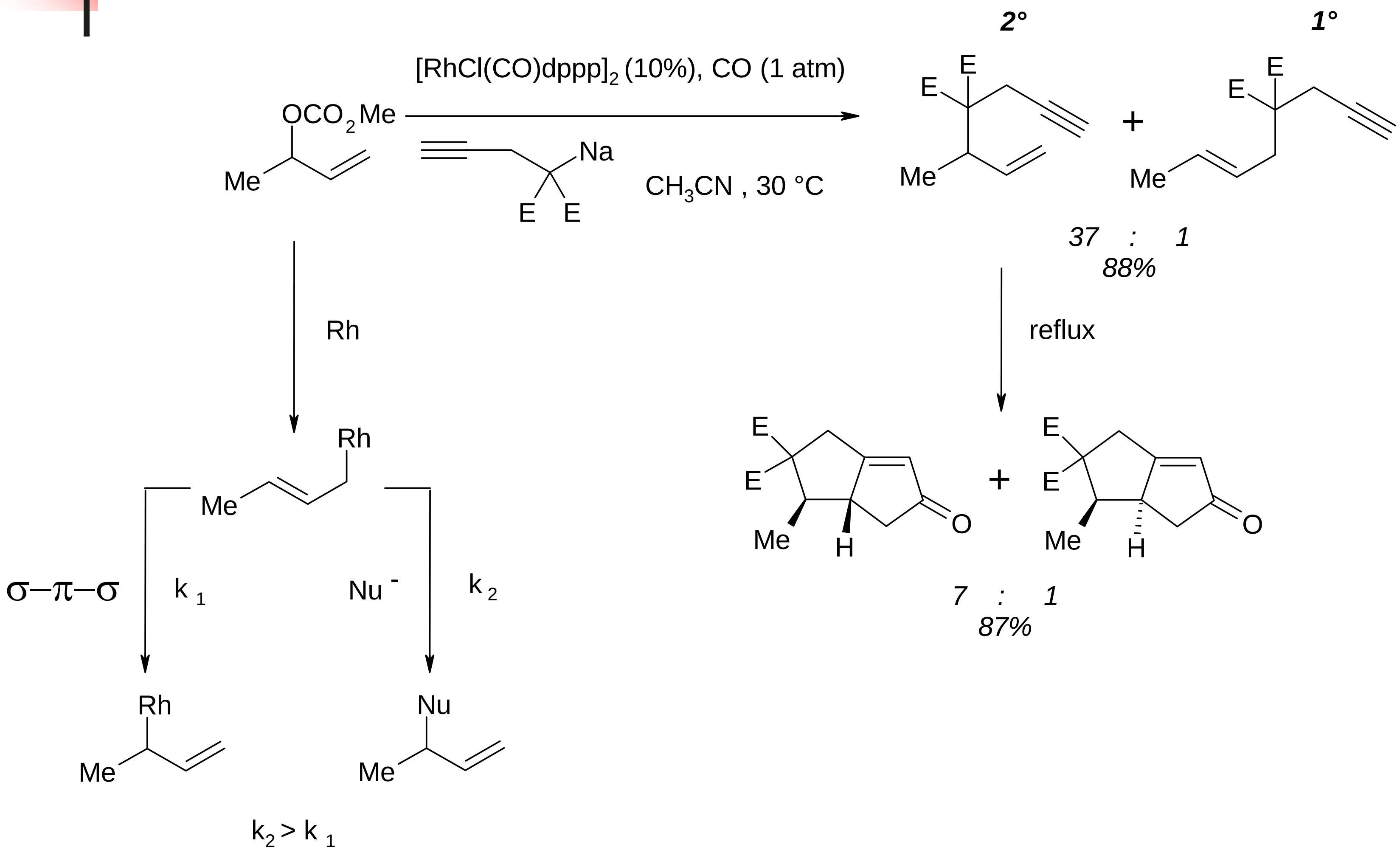
Plausible Mechanism for Rhodium-Catalyzed Allylic Alkylation

•Alkylation was observed to proceed stereospecifically with retention, even in acyclic substrates, when $R_2 \neq H$



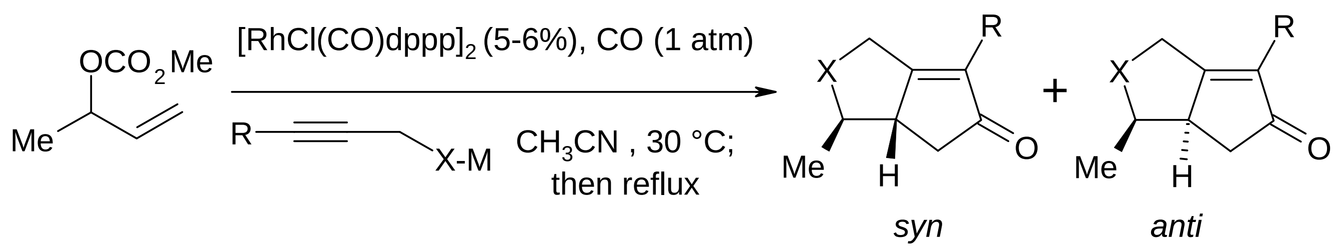
Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120,* 5581.

Tandem Rhodium-Catalyzed Alkylation-PKR



Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123,* 4609.

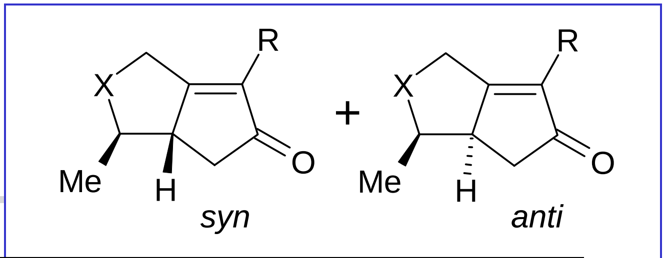
Tandem Rhodium-Catalyzed Alkylation-PKR



X	M	R	Alkylation Regioselectivity *2° : 1°*	Yield of Major Regio-isomers of Bicycle (syn:anti)
E_2C	Na	Ph	11 : 1	78% (9:1)
		Me	19 : 1	80% (6:1)
		H	27 : 1	82% (5:1)

Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123,* 4609.

Tandem Rhodium-Catalyzed Alkylation-PKR

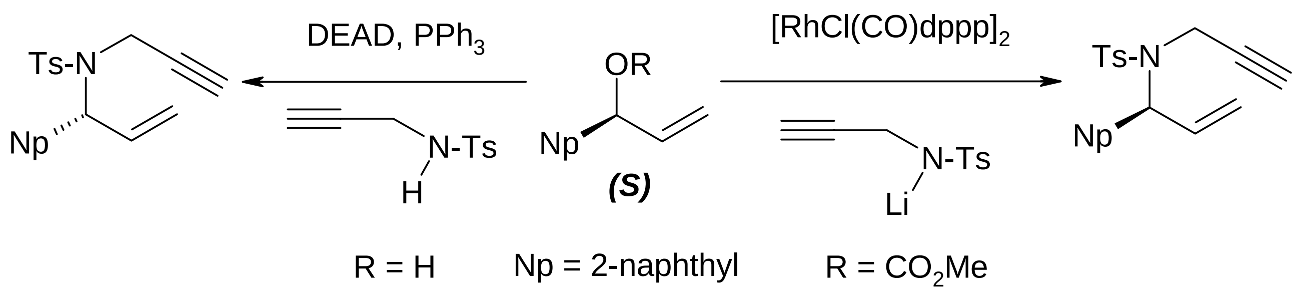


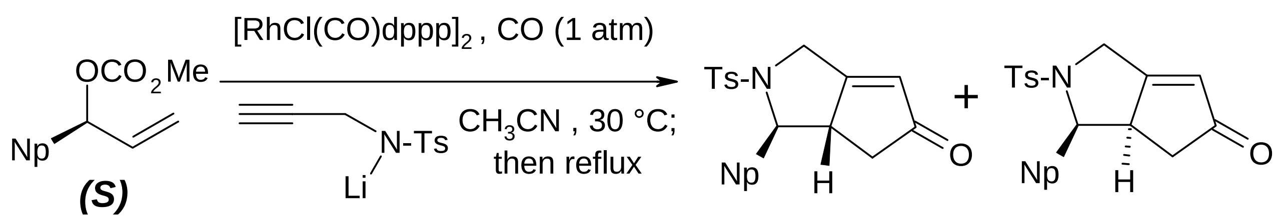
X	M	R	Alkylation Regioselectivity *2° : 1°*	Yield of Major Regio-isomers of Bicycle (syn:anti)
TsN	Li	Ph	57 : 1	81% (7:1)
		Me	32 : 1	84% (6:1)
		H	20 : 1	79% (3:1)
O	Li	Ph	8 : 1	81% (❍ 19:1)
		Me	7 : 1	73% (❍ 19:1)
		H	5 : 1	63% (❍ 19:1)

Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123,* 4609.

Tandem Rhodium-Catalyzed Alkylation-PKR

Rhodium-catalyzed alkylation-PKR was found to proceed stereospecifically with retention





82%

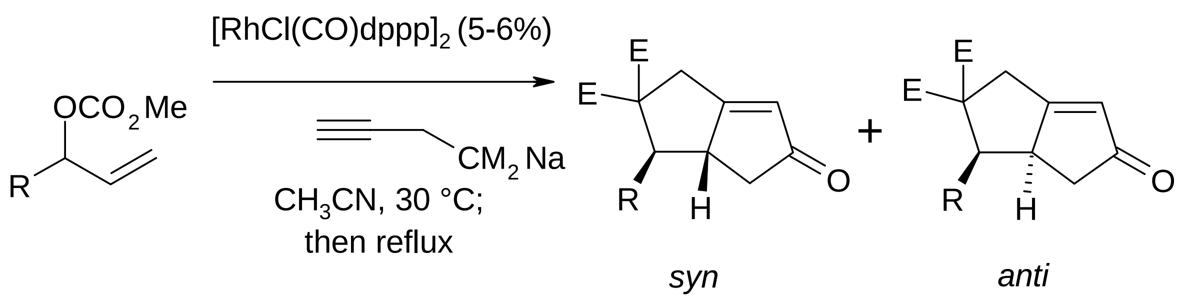
43 : 1

98% conservation of ee

Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123,* 4609.

Tandem Rhodium-Catalyzed Alkylation-PKR

- Increasing size of R from Me to Np increased selectivity for *syn* diastereomer

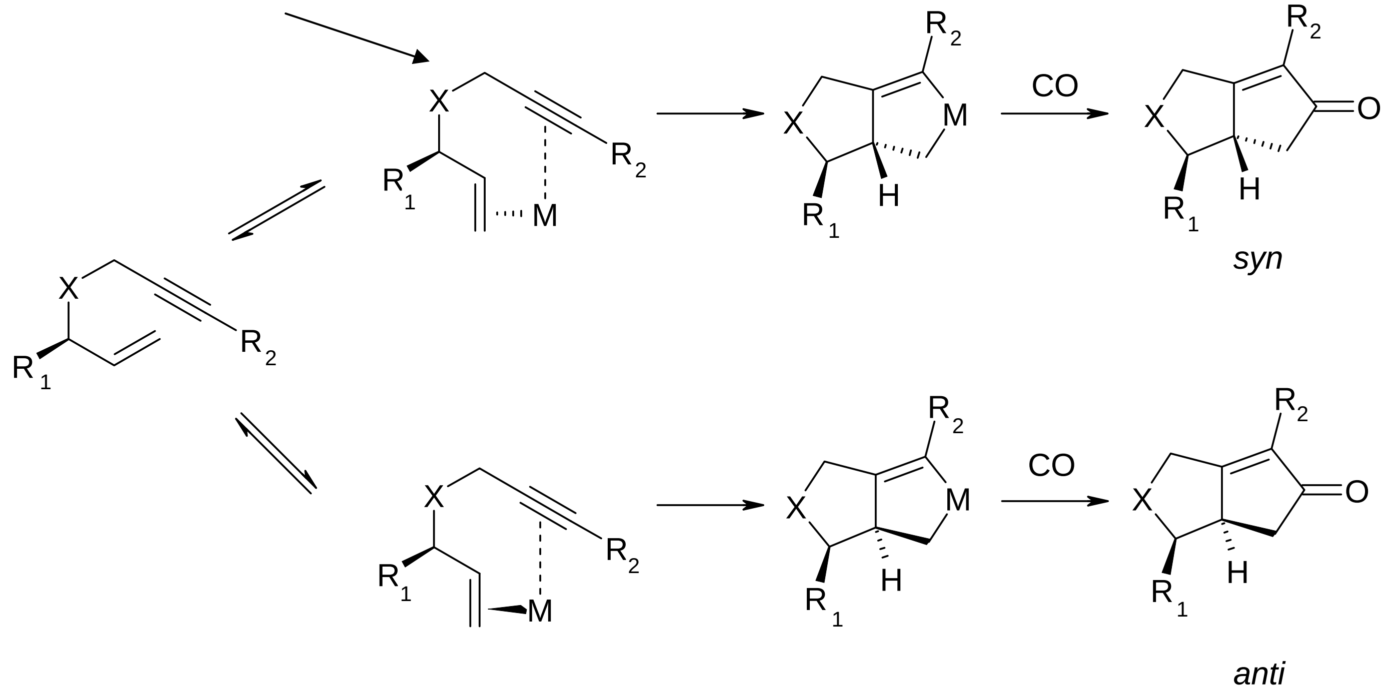


	syn	:	anti
R = Me	5	:	1
Np	43	:	1

Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123,* 4609.

Mechanistic Hypothesis

Larger R_1 will favor this intermediate diastereomer, leading to enriched *syn* product



Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123,* 4609.

Conclusions

Rhodium-Catalyzed PKR:

- is an efficient, atom economical route to fused bicyclic cyclopentenone derivatives
- is tolerant of polar functions including EWGs, dienes, allenes, aryl groups, and alkyl substituents
- typically provides improved yields and selectivities over previous, stoichiometric methods
- often requires only ambient pressure and mild temperature
- can be exploited in tandem, one-pot, stereospecific allylic alkylation-cycloadditions

Conclusions

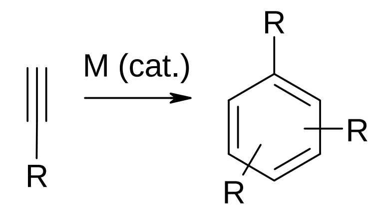
Areas of the Rh-catalyzed PKR needing most improvement:

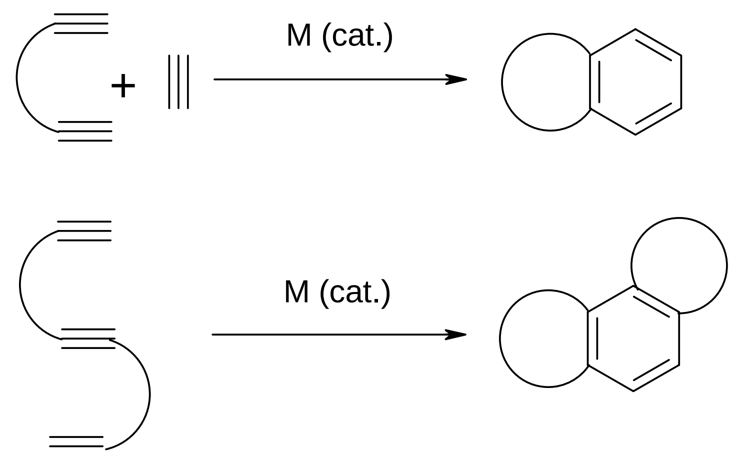
•Regio- and chemoselectivity of intermolecular reactions
•Asymmetric catalysis

N . Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771.

Metal-Catalyzed [2+2+2] Cycloaddition Route to Substituted Benzene Derivatives: Background

- First example: Reppe et al. (Ni), 1948
- Useful metals for catalysis:
  Co > Rh, Ni > Pd



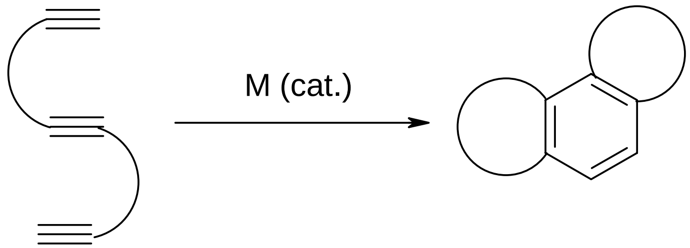


- Control of regio- and chemo-selectivity remains a challenge; intramolecularity is one solution:

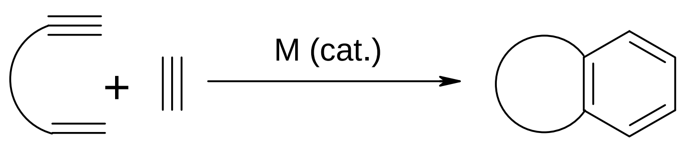
Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem*. **1948**, *560*, 104.
Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100,* 2901.
Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

Metal-Catalyzed [2+2+2] Cycloaddition Route to Substituted Benzene Derivatives: Background

•Completely intramolecular [2+2+2] cycloadditions offer complete regiocontrol



•Regio- and chemoselectivity of diyne-monoalkyne templates (Vollhardt; Grigg; Chiusoli) still need further evaluation

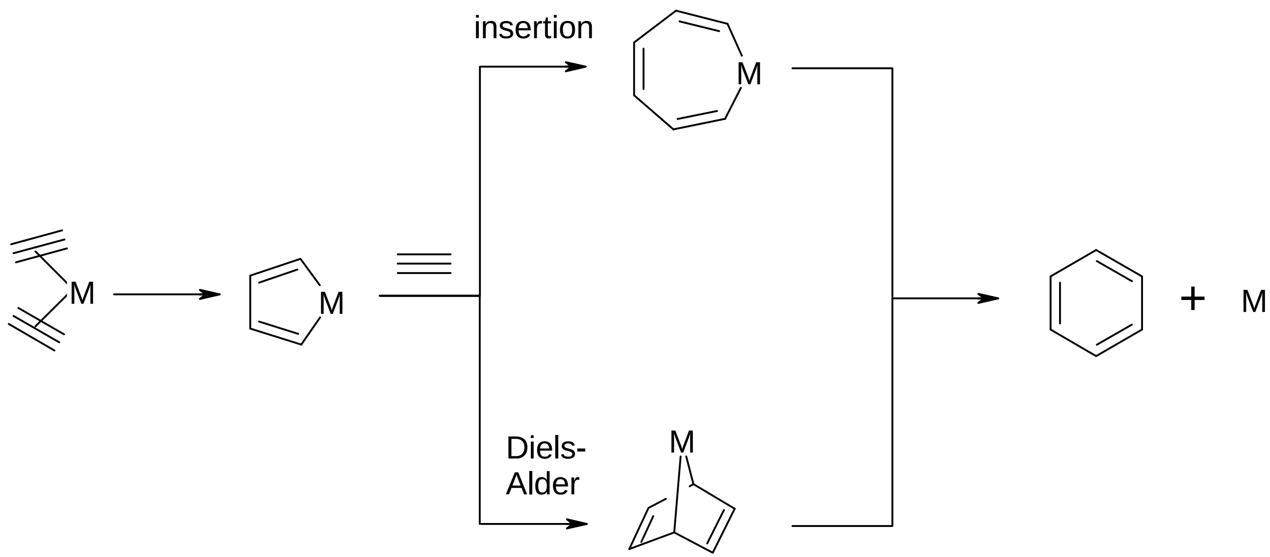


•Protocols usually require heating or irradiation

Vollhardt, K. P. C.; Bergman, R. G. *J. Am. Chem. Soc.* **1974**, *96,* 4996.
Grigg, R.; Scott, R.; Steveson, P. *Tetrahedron Lett.* **1982**, *23,* 2691.
Chiusoli, G. P.; Pallini, L.; Terenghi, G. *Transition Met. Chem.* **1983***, 8,* 189.
Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

Mechanisms of [2+2+2] Cycloadditions

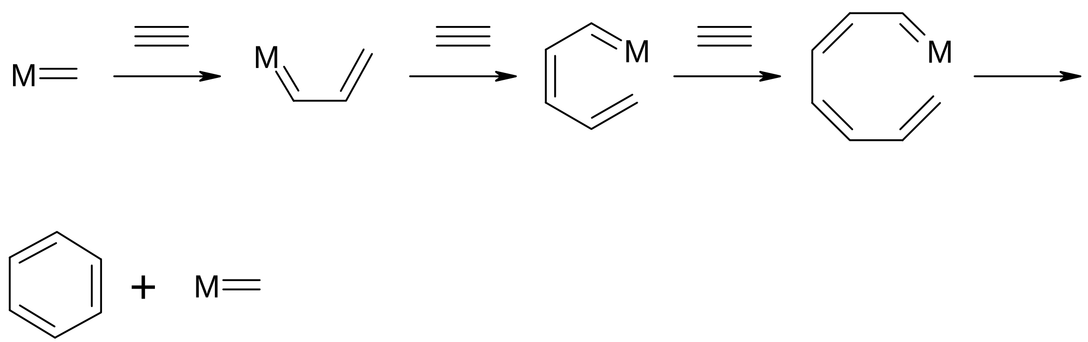
I. Metallacycle (Common) Mechanism



Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

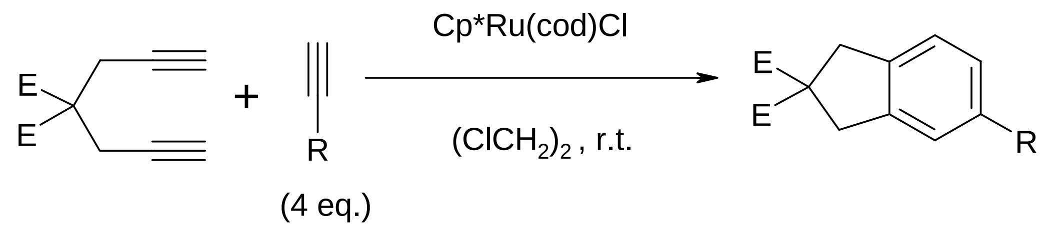
Mechanisms of [2+2+2] Cylcoadditions

II. Metathesis Cascade Mechanism



Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

Ruthenium-Catalyzed [2+2+2] Cycloadditions

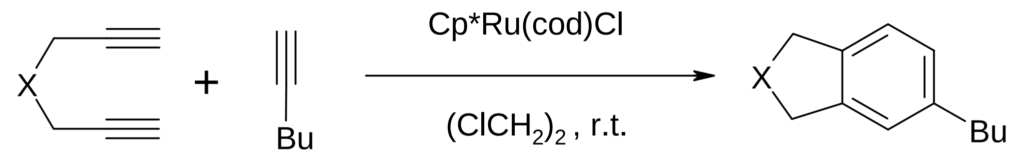


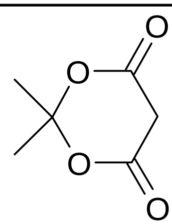
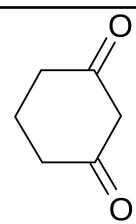
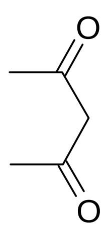
R	Mol% Cat.	Time (h)	Yield
n-Bu	1	0.25	94%
CH_2OMe	1	0.25	83%
CH_2OH	5	4	92%
CH_2NMe_2	1	1	77%
Ph	5	0.25	90%
H *	1	1	84%
$(CH_2)_3Cl$	2	1	96%
t-Bu	1	1.5	34%

* 1 atm, 0 °C

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

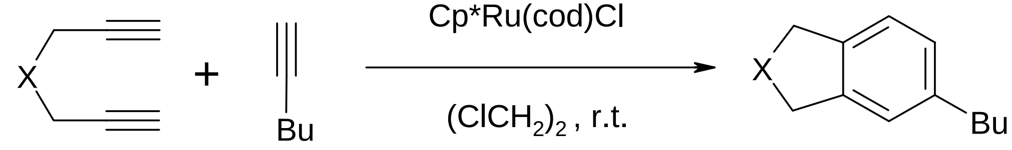
Ruthenium-Catalyzed [2+2+2] Cycloadditions



X	Mol% Cat.	Time (h)	Yield
E_2C	1	0.25	94%
	1	0.25	83%
	1	0.25	88%
	1	0.25	90%

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

Ruthenium-Catalyzed [2+2+2] Cycloadditions

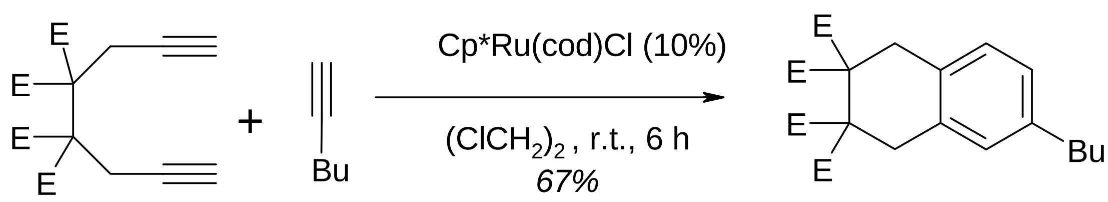


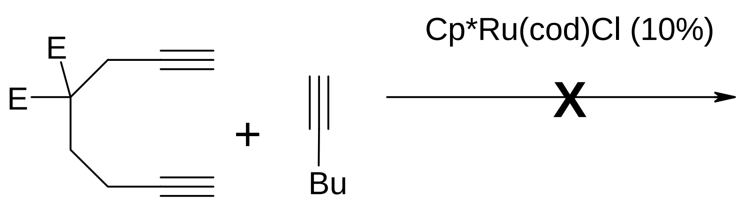
X	Mol% Cat.	Time (h)	Yield
$(CN)_2C$	1	0.25	85%
BnN	1	0.25	91%
TsN	1	0.25	96%
O	5	6	64%
S	5	1	68%

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

Formation of [4.4.0] Ring Systems

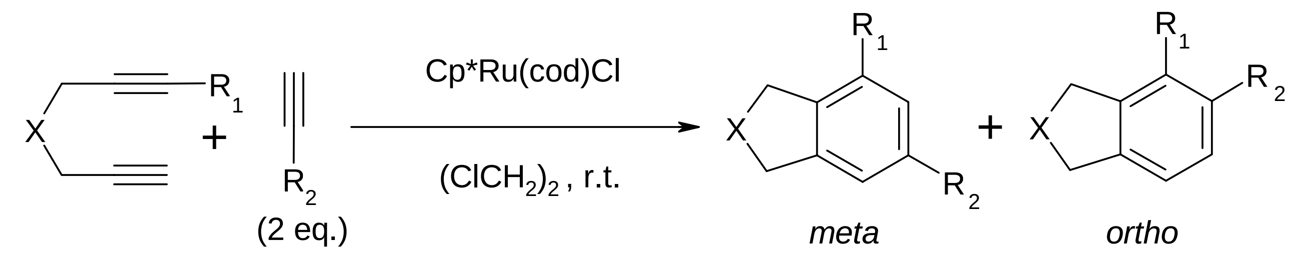
•Increasing tether length lowered reactivity, and required Thorpe-Ingold effect





Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.
Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113,* 224.

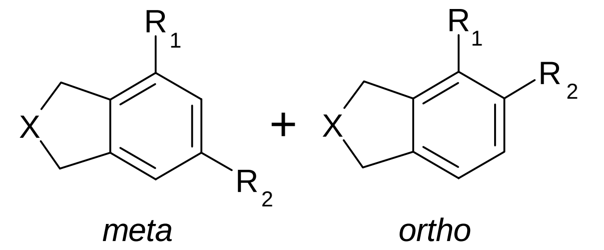
Ru-Catalyzed Cycloaddition of Unsymmetrical Diynes with Terminal Monoalkynes



X	R_1	R_2	Mol% Cat.	Time (h)	Yield (meta : ortho)
E_2C	Me	*n*-Bu	1	1	85% (93 : 7)
	Me	CH_2OH	1	3	86% (94 : 6)
	Me	Ph	3	24	82% (88 : 12)

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

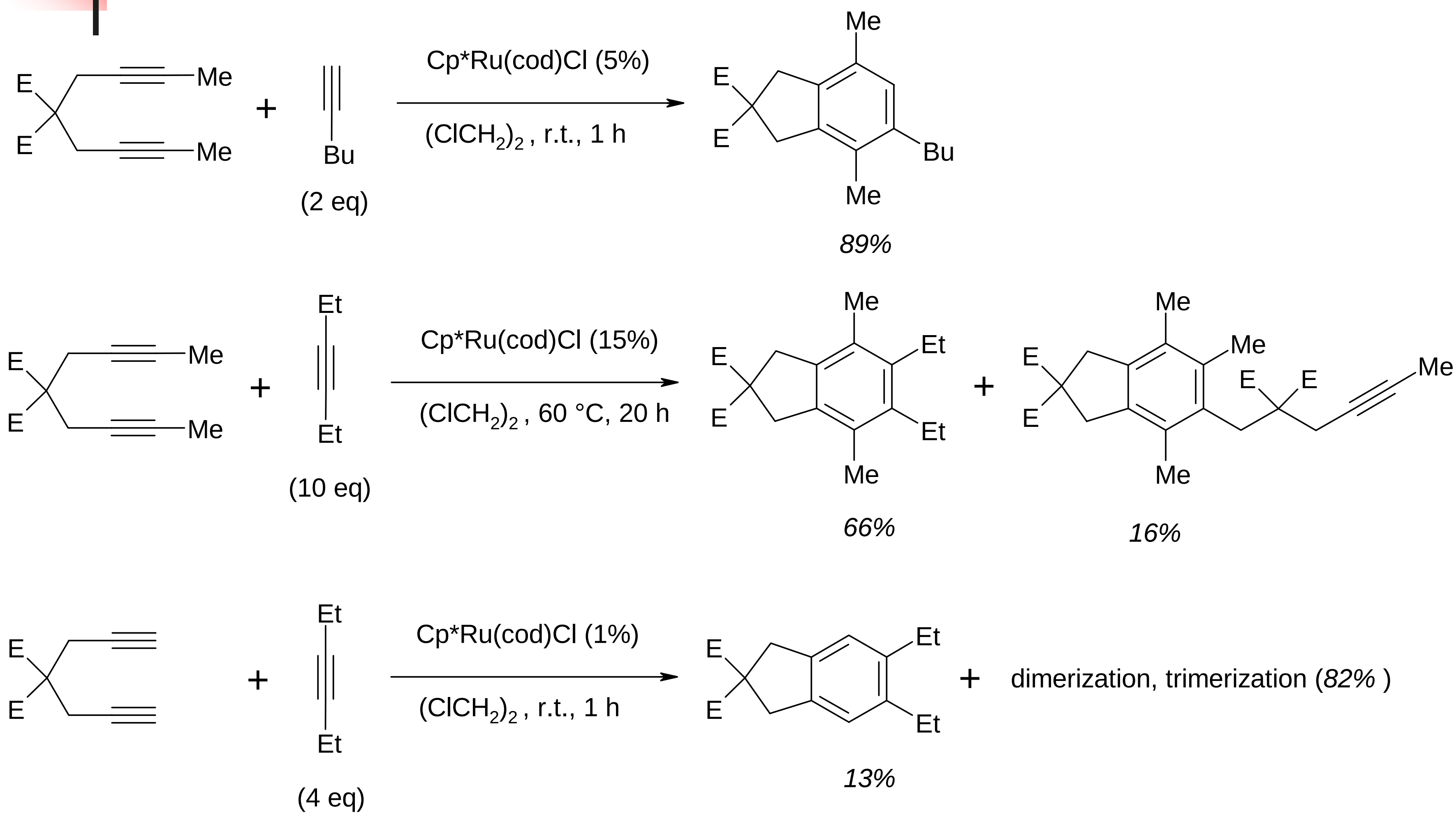
Ru-Catalyzed Cycloaddition of Unsymmetrical Diynes with Terminal Monoalkynes



X	R_1	R_2	Mol% Cat.	Time	Yield (meta : ortho)
E_2C	Me	Me (1 atm)	3	18 h	80% (94 : 6)
	CH_2OMe	*n*-Bu	3	12 h	78% (92 : 8)
	Ph	*n*-Bu	10	24 h	80% (95 : 5)
	$SiMe_3$	*n*-Bu	5	7 h	94% (98 : 2)
TsN	Me	*n*-Bu	1	10 min	82% (93 : 7)
O	Me	*n*-Bu	1	30 min	75% (95 : 5)

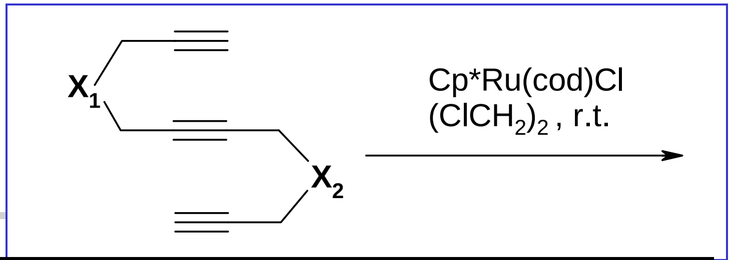
Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

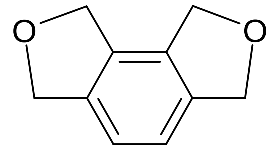
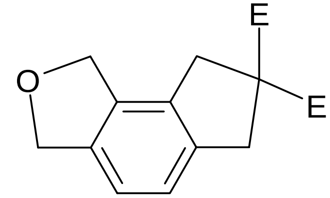
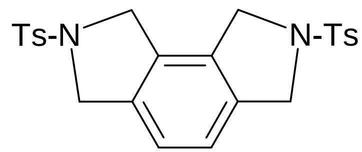
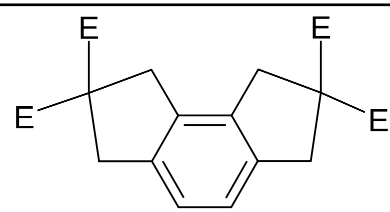
Ru-Catalyzed [2+2+2] Cycloadditions with Internal Alkynes



Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

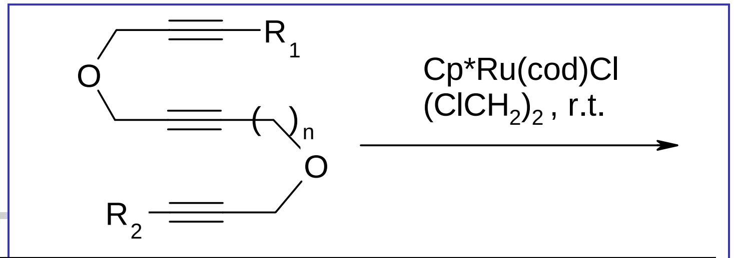
Ru-Catalyzed Cycloaddition of Triynes

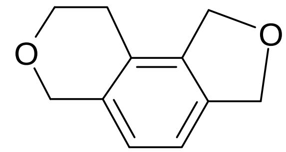
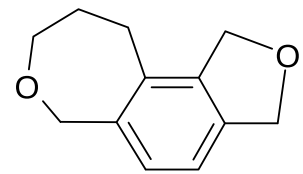
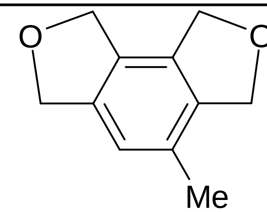
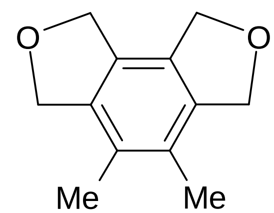


X_1	X_2	Cat. Mol%	Time (h)	Product (Yield)
O	O	1	2	 (82%)
O	CE_2	5	3	 (82%)
TsN	TsN	1	5	 (87%)
CE_2	CE_2	5	6	 (89%)

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

Ru-Catalyzed Cycloaddition of Triynes

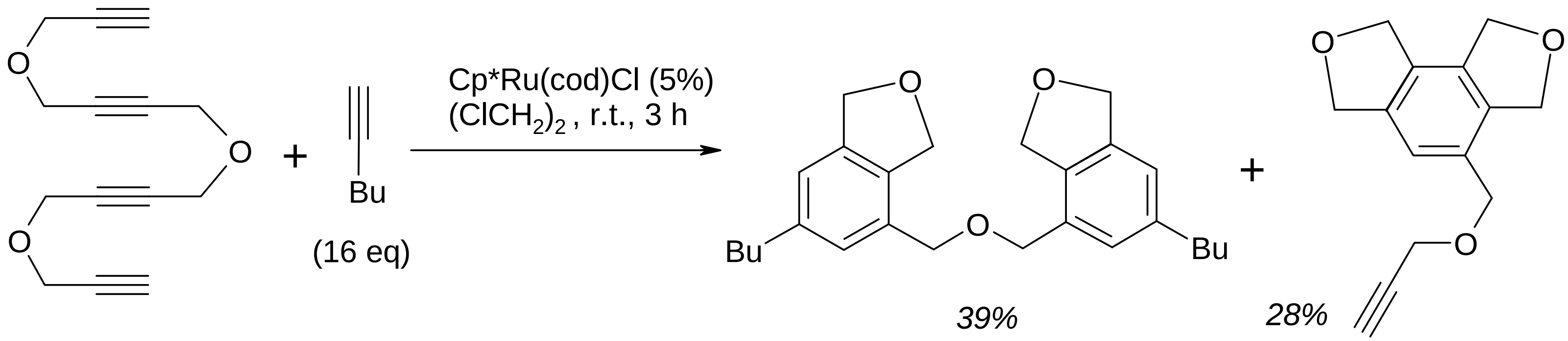


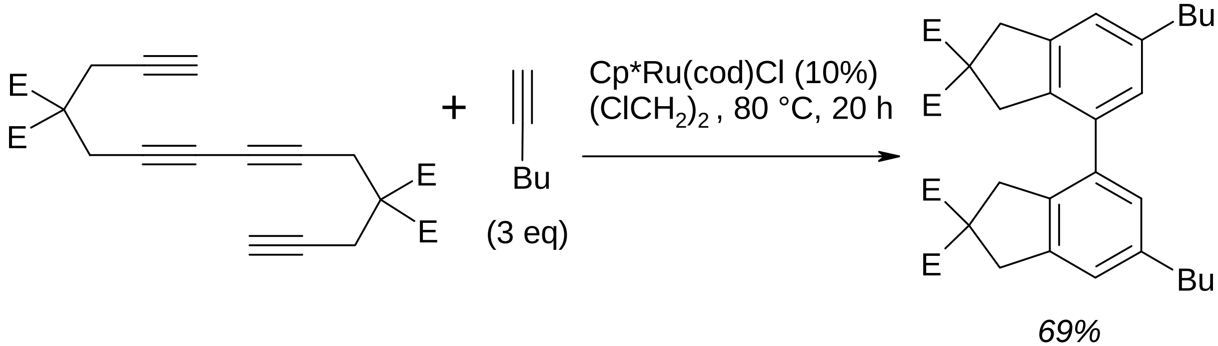
R_1	R_2	n	Cat. Mol%	Time (h)	Product (Yield)
H	H	2	5	18	 (89%)
H	H	3	5	20	 (53%)
H	Me	1	1	18	 (84%)
Me	Me	1	5	24 *	 (60%)

* In refluxing PhCl

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

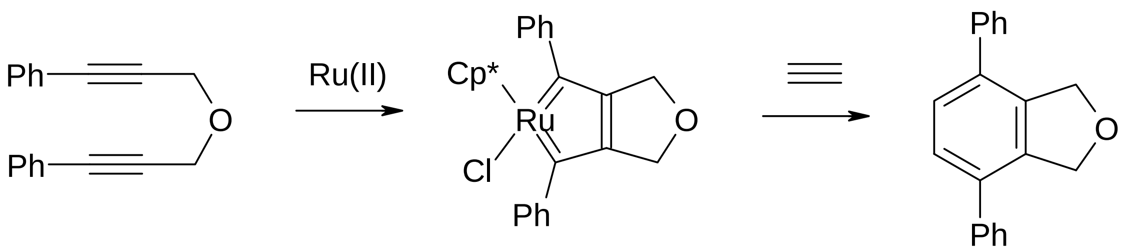
Ru-Catalyzed [2+2+2] Cycloaddition in Biphenyl Synthesis





Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

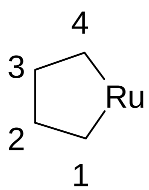
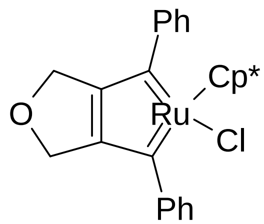
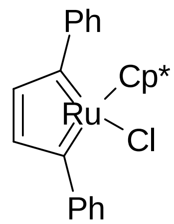
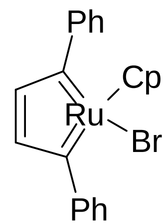
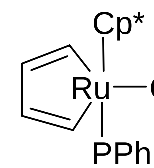
An Isolated Intermediate



isolated as crystals

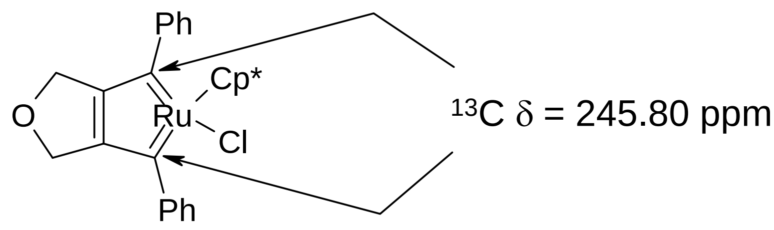
Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

Bond Lengths Determined by X-ray Diffraction (Å)

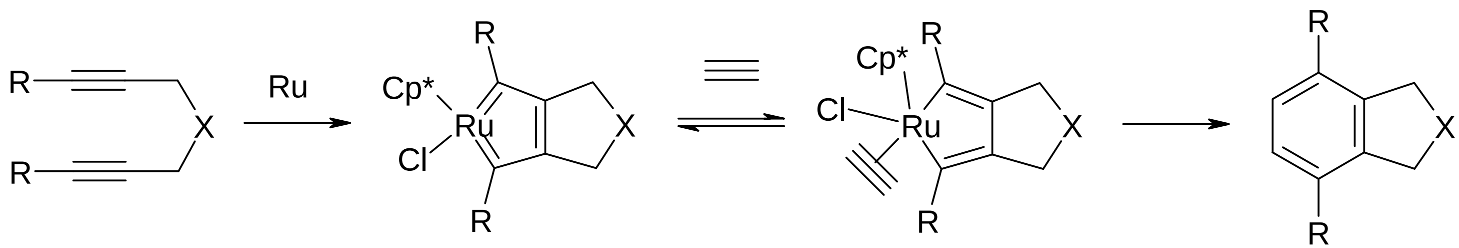
				
Ru-C1 (Ru-C4)	1.995 (1.985)	1.969	1.942	2.059 (2.092)
C1-C2 (C3-C4)	1.425 (1.412)	1.402	1.403	1.338 (1.321)
C2-C3	1.387	1.37	1.377	1.414

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.
Enrst, C.; Walter,O.; Dinjus, E. *J. Prakt. Chem*. **1999**, *341*, 801.
Albers, M. O.; de Wall, D. J. A.; Liles, D. C.; Robinson, D. J.; Singleton, E.; Wiege, M. B. *J. Chem. Soc., Chem. Commun*. **1986**, 1680.
Yi, C. S.; Torres-Lubian, J. R.; Liu, N.; Rheingold, A.; Guzei, I. *Organometallics* **1998**, *17*, 1257.

Insights into Mechanism



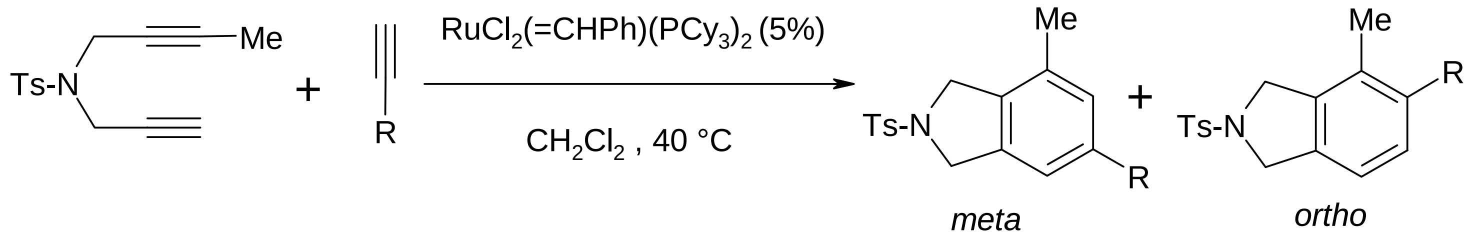
- C-Ru bonds have double bond character (bis-carbene)
- Metallacycle appears aromatic
- Possible mechanistic conclusion:



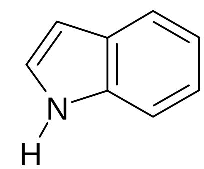
- Density functional calculations predict the insertion pathway to be lower energy than the Diels-Alder pathway

Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125,* 12143.

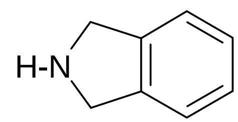
[2+2+2] Cycloadditions with Grubbs Catalyst: Isoindoline Synthesis



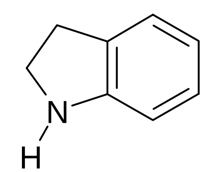
R	Meta : Ortho	Yield
Ph	5 : 1	82%
C_3H_7	6 : 1	92%
CH_2OH	6 : 1	81%
$(CH_2)_2OH$	6 : 1	89%



indole



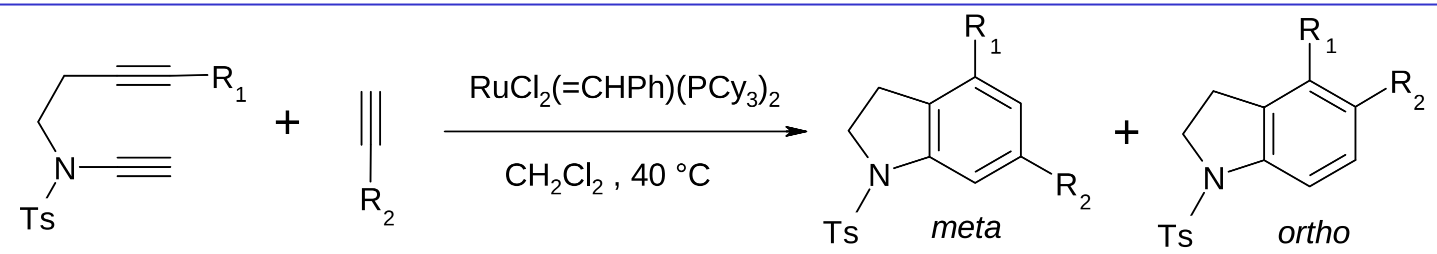
isoindoline



indoline

Witulski, B.; Stengel, T.; Fernandez-Hernandez, J. M. *Chem. Comm.* **2000**, 1965.

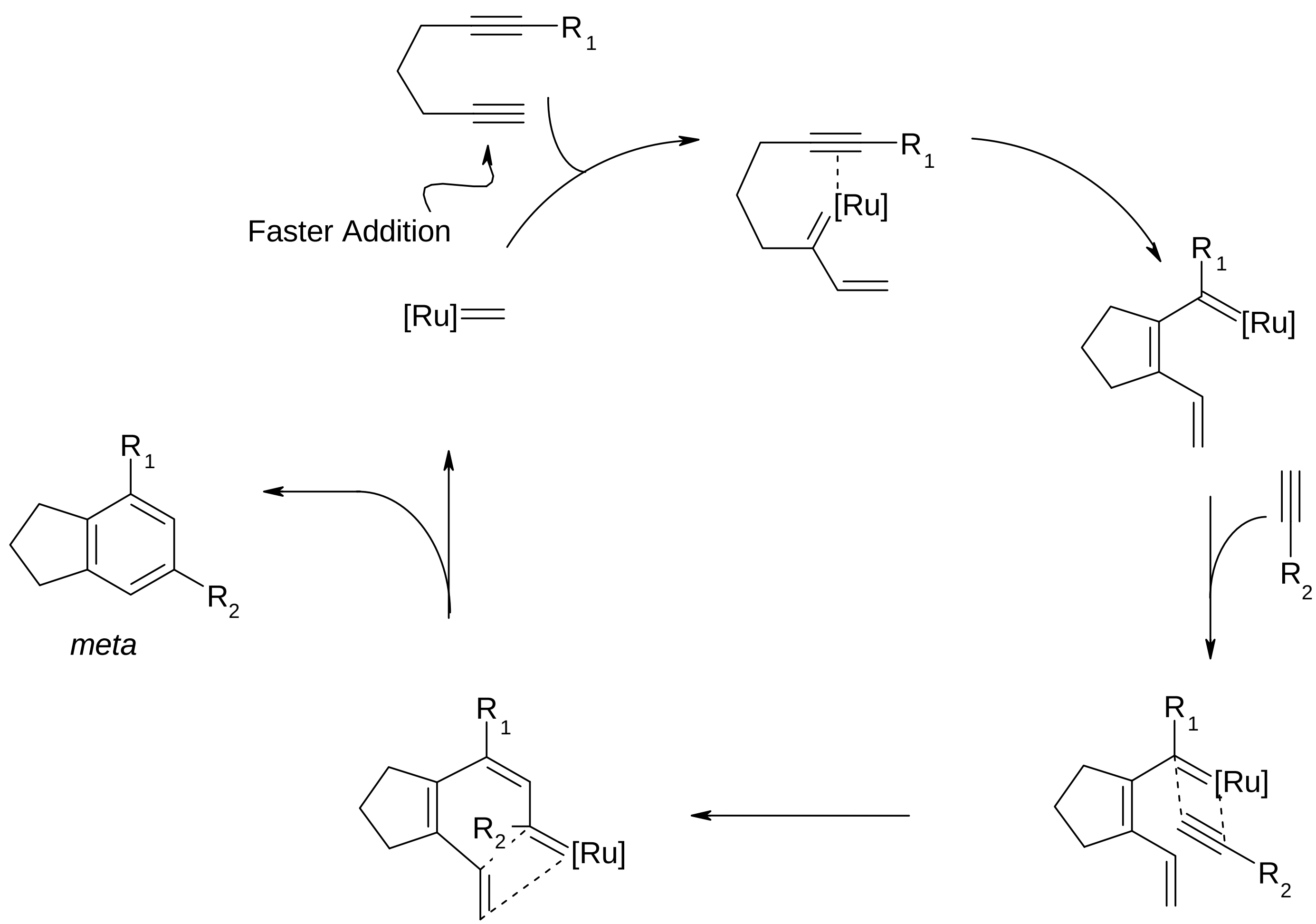
[2+2+2] Cycloadditions with Grubbs Catalyst: Indoline Synthesis



R_1	R_2	Mol% Cat.	Meta : Ortho	Yield
Me	CH_2OH	5	9 : 1	70%
Me	$(CH_2)_2OH$	10	9 : 1	51%
Me	$(CH_2)_3OH$	10	9 : 1	57%
Ph	CH_2OH	10	9.5 : 1	60%

Witulski, B.; Stengel, T.; Fernandez-Hernandez, J. M. *Chem. Comm.* **2000**, 1965.

Proposed Mechanism of [2+2+2] Cycloadditions with Grubbs Catalyst



Witulski, B.; Stengel, T.; Fernandez-Hernandez, J. M. *Chem. Comm.* **2000**, 1965.

Conclusions

Ru-catalyzed [2+2+2] cycloadditions:

- lead to a variety of ring systems *via* diyne-monoalkyne and triyne templates
- are efficient, atom economical
- offer useful alternatives to standard electrophilic aromatic substitution routes to substituted benzenes

Conclusions on Ruthenium-Catalyzed [2+2+2] Cycloadditions

The reactions typically:

- require mild conditions, low catalyst loadings
- display high tolerance of various functional groups
- are reliably selective for *meta* substitution, though metallacycle-type seem more selective than metathesis-type

Areas which need most improvement:

- Access to fused bicyclic benzene derivatives with aliphatic rings larger than five carbons
- Selectivity and scope of intermolecular reaction
- Reliable access to *ortho* substitution

Acknowledgements

Dr. Michael T. Crimmins

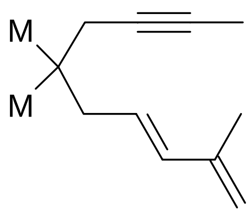
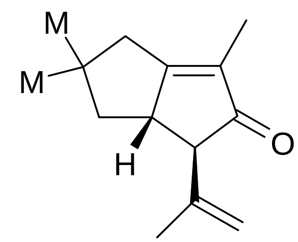
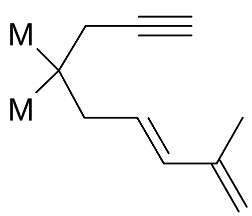
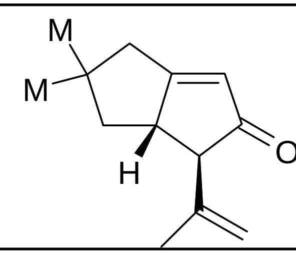
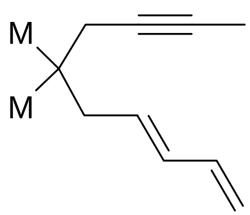
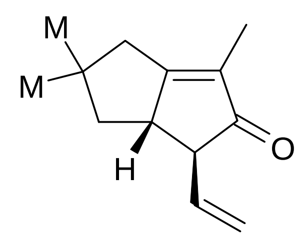
Current Group Members

Dr. Alan Long
Dr. Jon Parrish
Dr. Joe Perales
Dr. Hamish Christie
Brandon Brown
Jin She
Amy DeBaille
Amran Gowani
Dee Jacobs
David Slade
Grace Smalley
Aaron Smith
Patrick McDougall
Joyce Kung
Erin Milner
Mike Ellis
Adam Samuelson
Yan Zhang

Previous Group Members

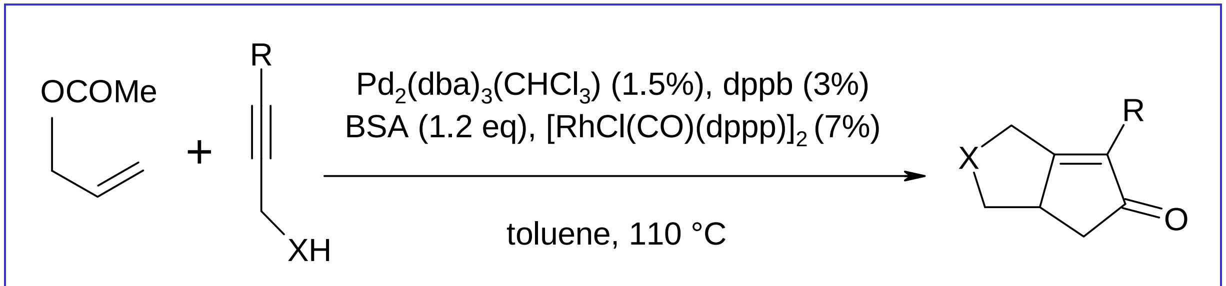
Dr. Pamela Cleary
Dr. Frank Diaz
Dr. Kleem Chaudhary
Dr. Tiffany Heady
Dr. Phieng Siliphaivanh

$RhCl(CO)(PPh_3)_2$ -Catalyzed PKR

Dienyne	Rh/Ag Mol%	Temp. (°C)	Press. (atm)	Time (h)	Product (Yield)
	2.5	40	2	12	 (42%)
	1	r.t.	1	30	 (86%)
	2.5	40	1	12	 (90%)

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

Tandem Two-Catalyst Alkylation-PKR

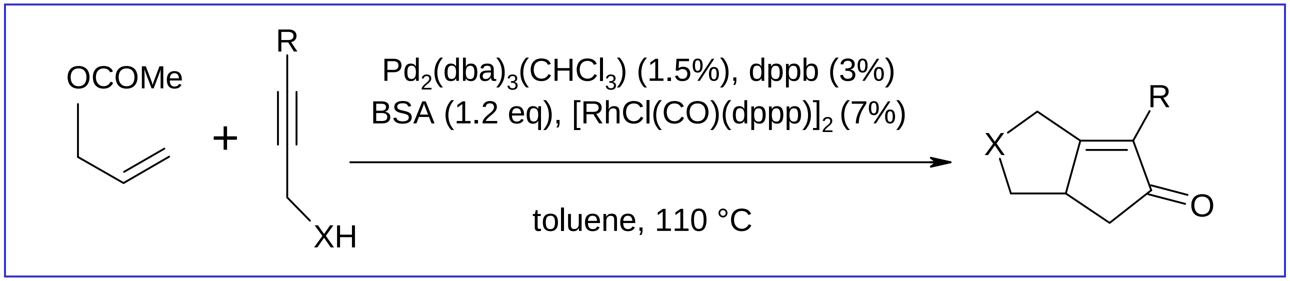


X	R	Time (h)	Yield
E_2C	Ph	25	92%
	Me	25	73%
	H	25	0%

dba = $(PhCH{=}CH)_2CO$

Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122,* 10220-10221.

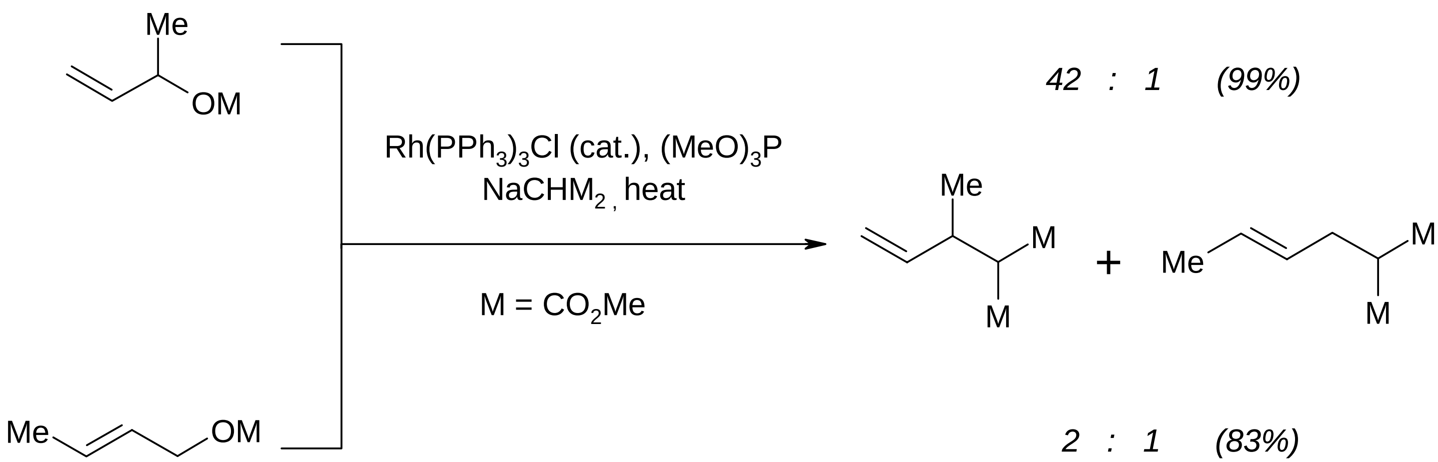
Tandem Two-Catalyst Alkylation-PKR

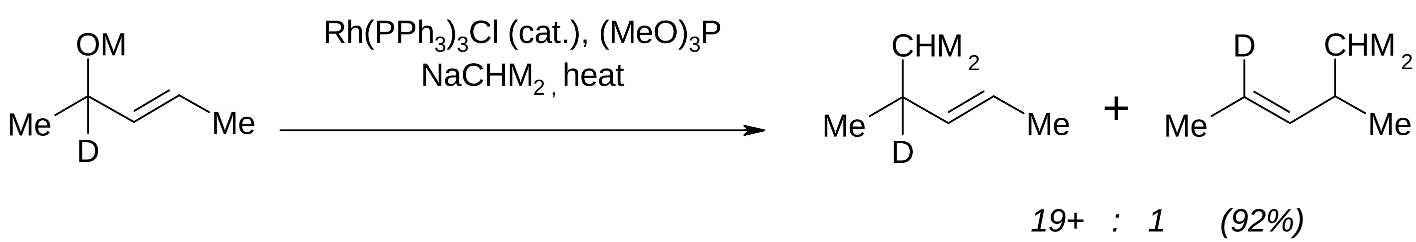


X	R	Time (h)	Yield
TsN	Ph	10	90%
	Me	10	91%
	H	6	92%
O	Ph	17	0%
	Me	17	0%

Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220-10221.

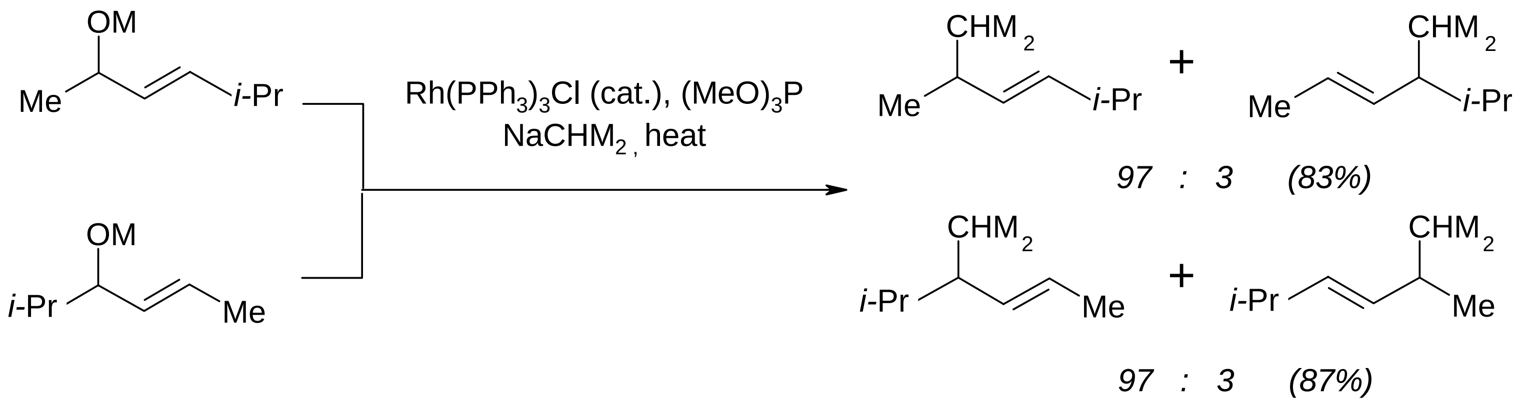
Rhodium-Catalyzed Allylic Alkylation

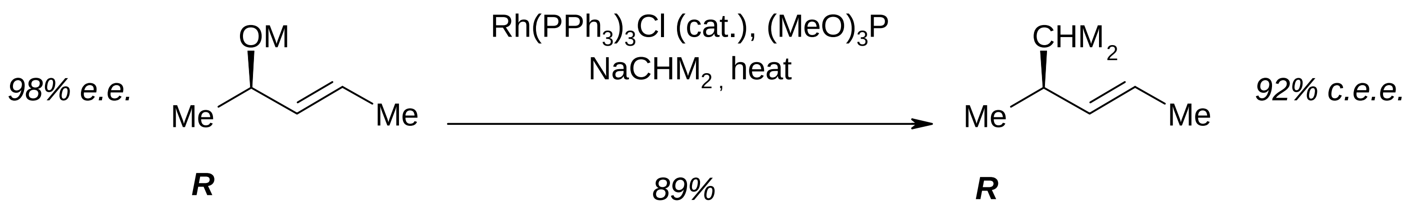


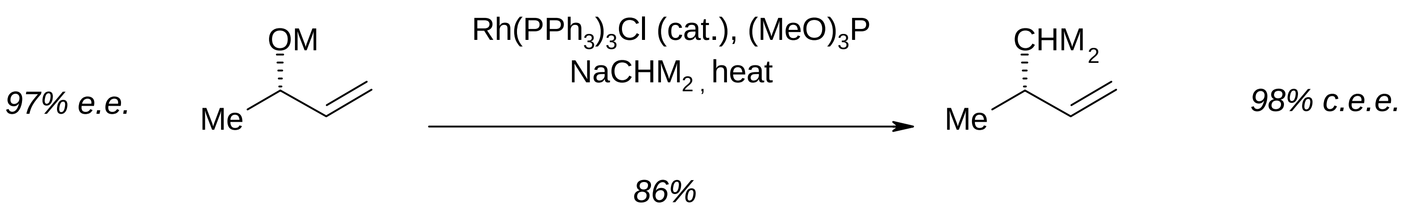


Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120,* 5581-5582.

Rhodium-Catalyzed Allylic Alkylation







Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581-5582.