Recent Advances in Rhodium Catalyzed Asymmetric Cascade Reactions

Jason M. Stevens

01/19/2007

What Exactly is a Cascade Reaction?

Cascade, Tandem, Domino, Sequential, Multidirectional, One-pot transformation…

A cascade reaction is any bond forming reaction or chemical transformation that generates a reactive intermediate that undergoes a subsequent intra- or intermolecular reaction

or more simply…

"Any reaction that generates molecular complexity in a concise fashion"

Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

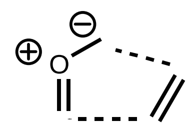
Why is Rhodium Special?

- Many Rhodium catalysts are air/moisture stable
- Metallocarbene formation
  - 1,3 dipole formation
  - C-H activation/insertion
  - Cyclopropanation
- Oxidative coupling
- Cyclopropane/cyclobutane opening
- Decarbonylation

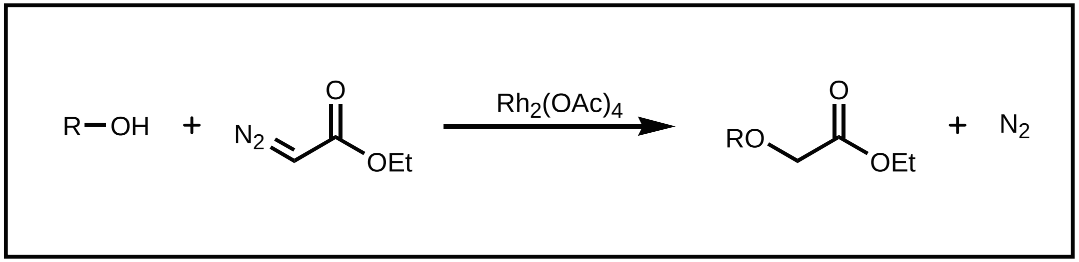
Topics for Today's Discussion

- 1,3-Dipole Generation/[3+2] Cycloadditions
- C-H Activation/Cope Rearrangement
- Formal [5+2] Cycloadditions
- Formal [2+2+1] Pauson-Khand Reactions
- Formal [2+2+2] Cycloadditions

Rhodium Catalyzed [3+2] Dipolar Cycloadditions

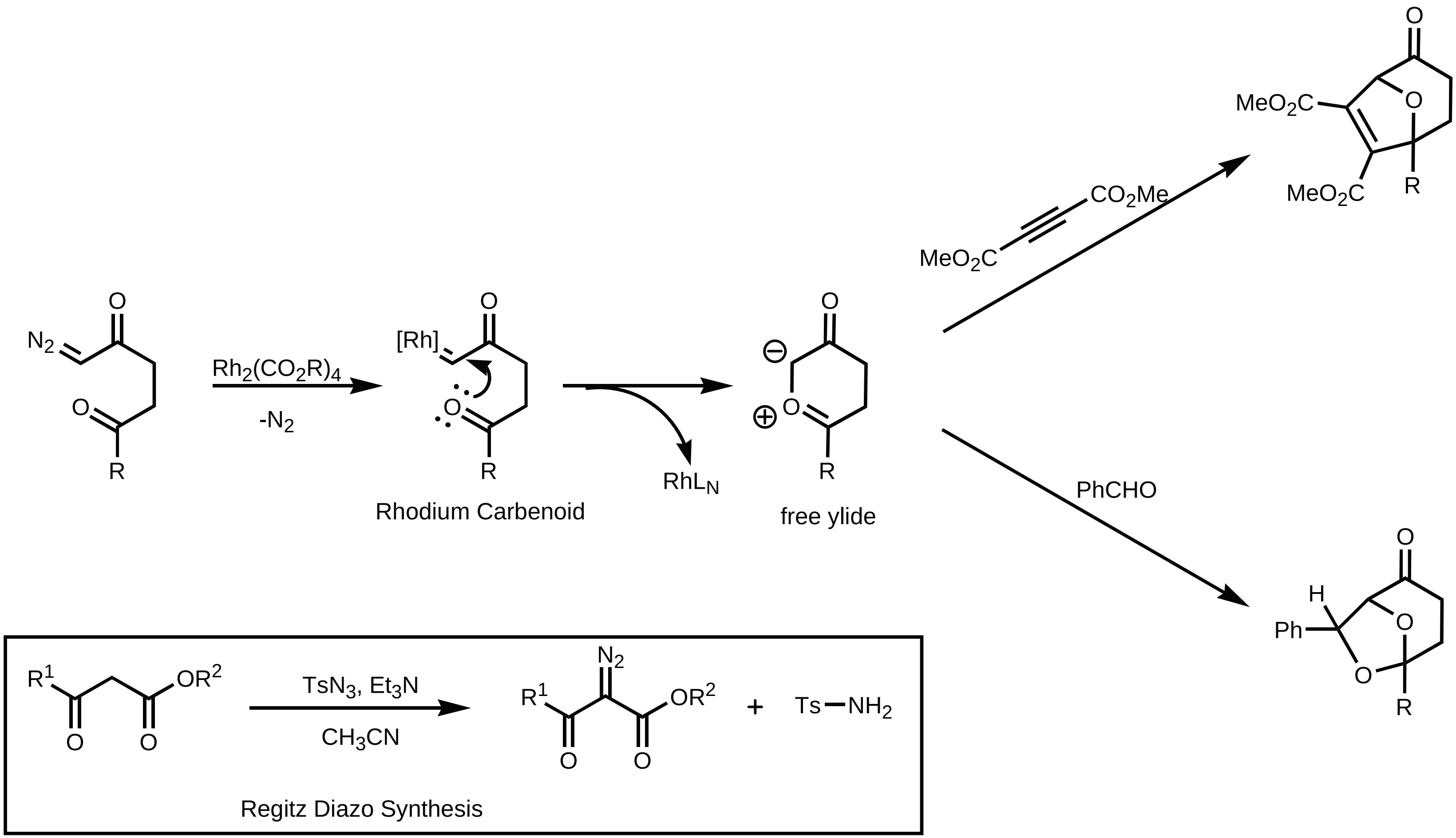


3 + 2



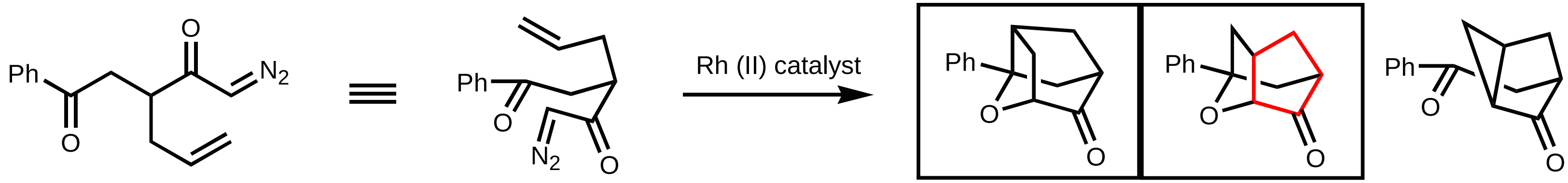
Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. Paulisson, R.; Reimlinger, H.; Hayez, A. J.; Teyssié, P. H. *Tetrahedron Lett.* **1973**, 2233.

Rhodium Catalyzed [3+2] Dipolar Cycloadditions



Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986.

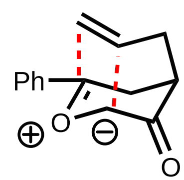
Rhodium Catalyzed Regioselective [3 + 2] Cycloadditions



5 membered product is favored

$Rh_2(OAc)_4$: 94%, **10 : 47** : 37
$Rh_2(cap)_4$: 96%, **12 : 52** : 32

$Rh_2(pfb)_4$: 87%, **33 : 12** : 42
$Rh_2(tfa)_4$: 93%, **34 : 12** : 47

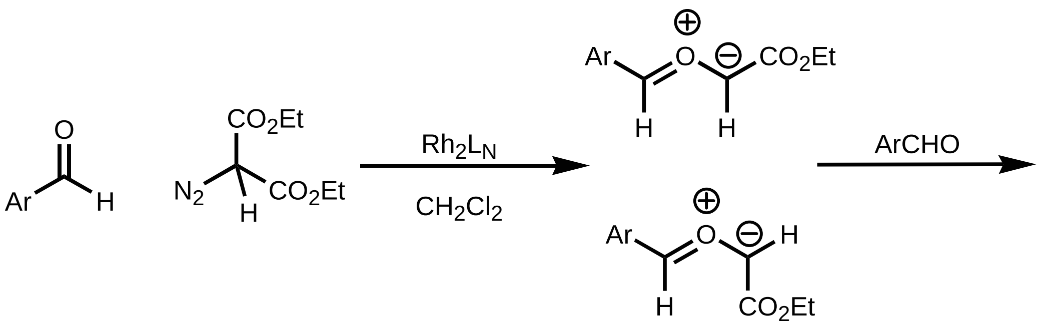


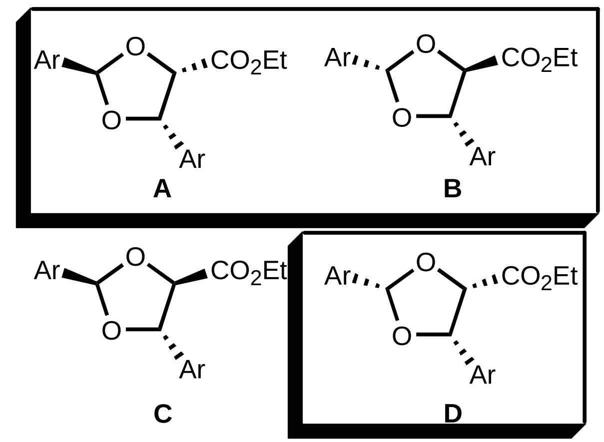
free carbonyl ylide

Changing the catalyst to rhodium(II) trifluoroacetate or to rhodium(II) perfluorobutyrate generated a significant change in the product distribution

Padwa, A.; Austin, D. F.; Hornbuckle, S. F. *J. Org. Chem.* **1995**, *61*, 63.

Rhodium Catalyzed Regioselective [3 + 2] Cycloadditions





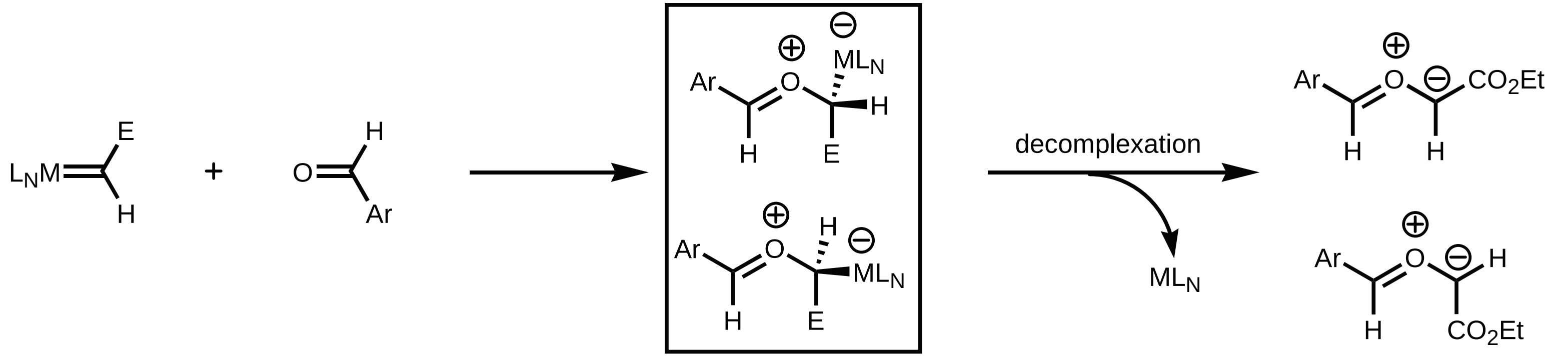
Ar = *p*-MeOC_6H_4
RhL_N =$Rh_2(OAc)_4$, **A:B = 52:48**, 15%
RhL_N =$Rh_2(cap)_4$, **A:B = 52:48**, 52%
RhL_N =Rh_2(5S-MEPY)$_4$, **A:B = 52:48**, 77%

Ar = *p*-$NO_2C_6H_4$
RhL_N =$Rh_2(pfb)_4$, **A:B:C:D** = 28:20:7:**45,** 41%

If a free ylide is formed the catalyst shouldn't influence the regiochemical outcome. Therefore, in the case of fluorinated ligands, perhaps the metal is still bound to the original site of attachment.

Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210.

Rhodium Catalyzed Regioselective [3 + 2] Cycloadditions



chiral

catalyst influences the stereochemical outcome

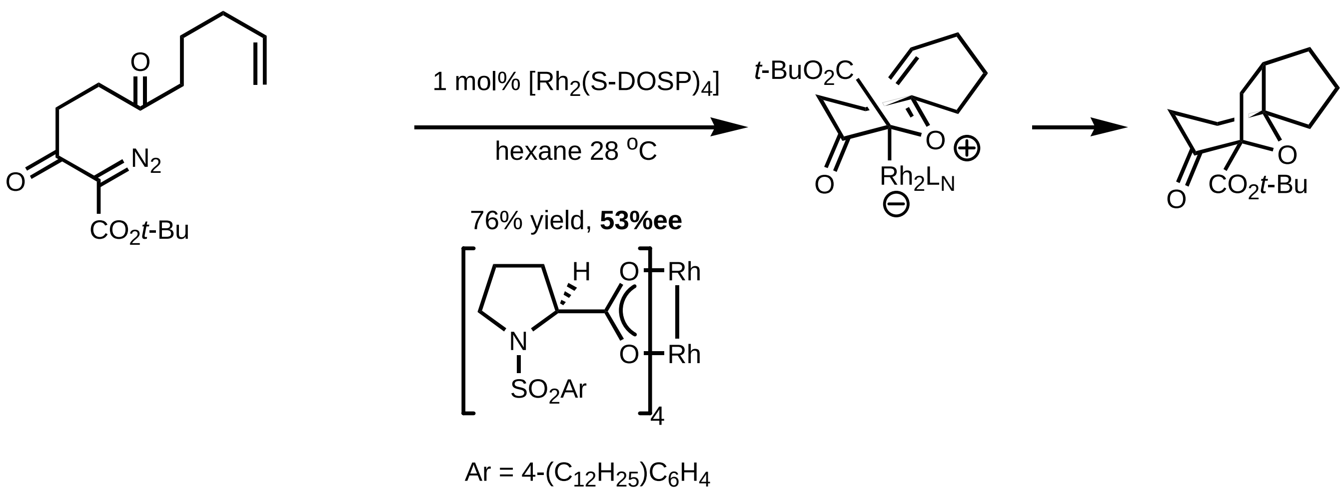
prochiral

catalyst has no influence on the stereochemical outcome

If the dipole is not fully formed and the metal is still bound to the original site of attachment, the ligands on the metal may be able to provide stereochemical communication

Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210.

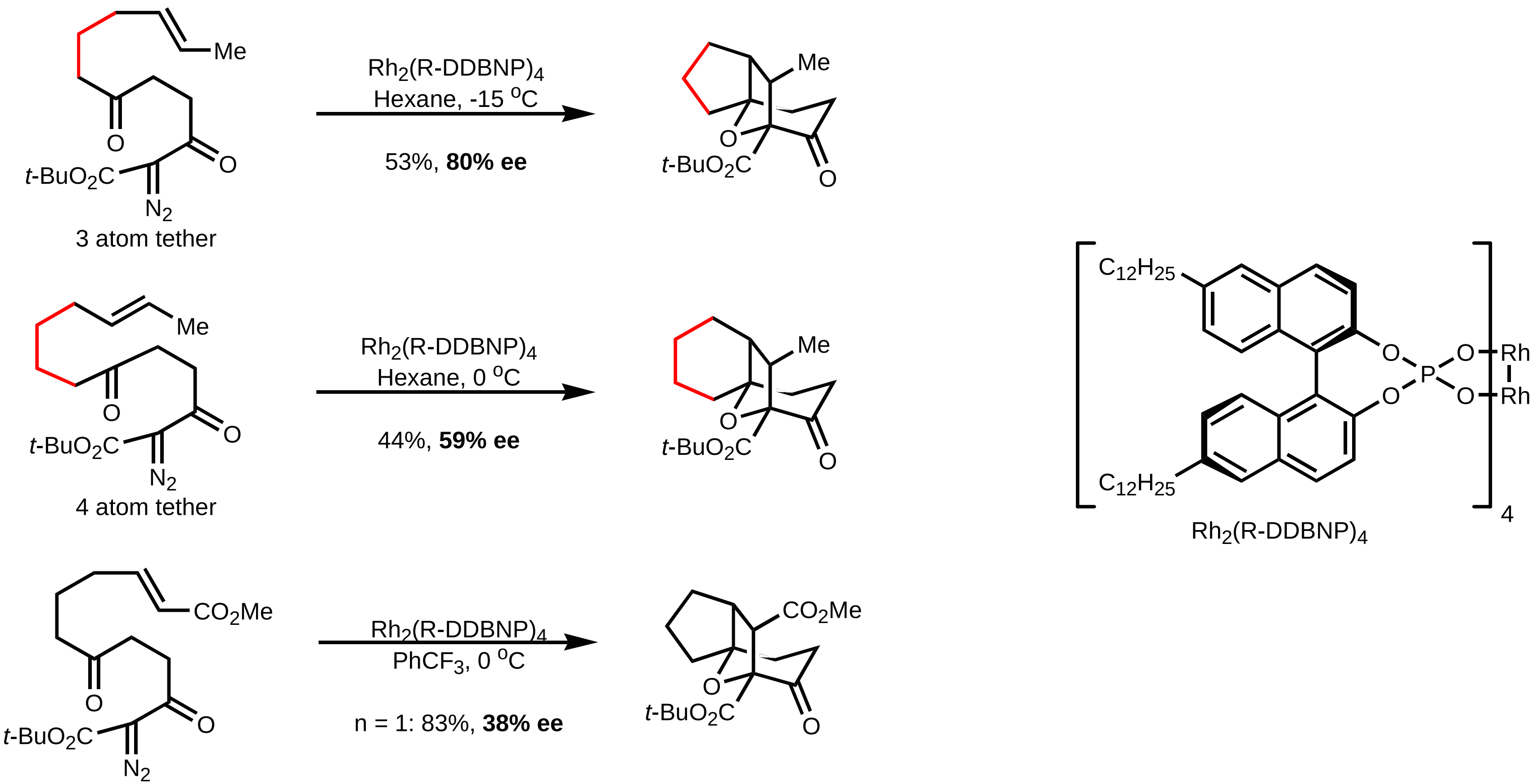
Asymmetric Catalysis of Intramolecular [3 + 2] Cycloadditions



A highly reactive dienophile is required so that the cycloaddition occurs faster than metal decomplexation

Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett*. **1997**, *38*, 6471.

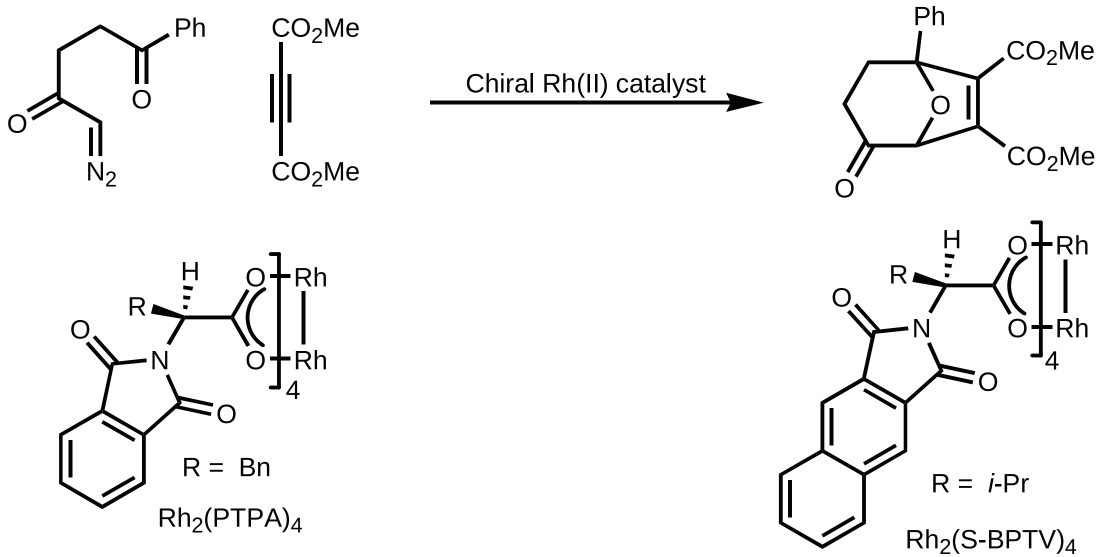
Substituted Alkene Tethers



The rate of the reaction is slower for the 4 atom tether. Therefore, the catalyst has more time to decomplex and form a free carbonyl ylide, resulting in lower ee's.

Hodgson, D. M.; Labande, A. H.; Pierard, F.; Expósito Castro, M. A. *J. Org. Chem.* **2003**, *68*, 6153.

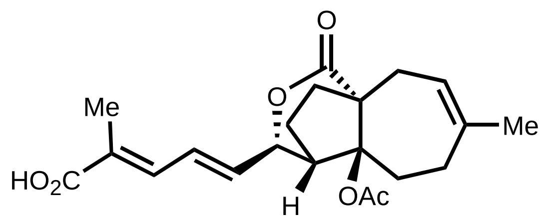
Asymmetric Catalysis of Intermolecular [3 + 2] Cycloaddition



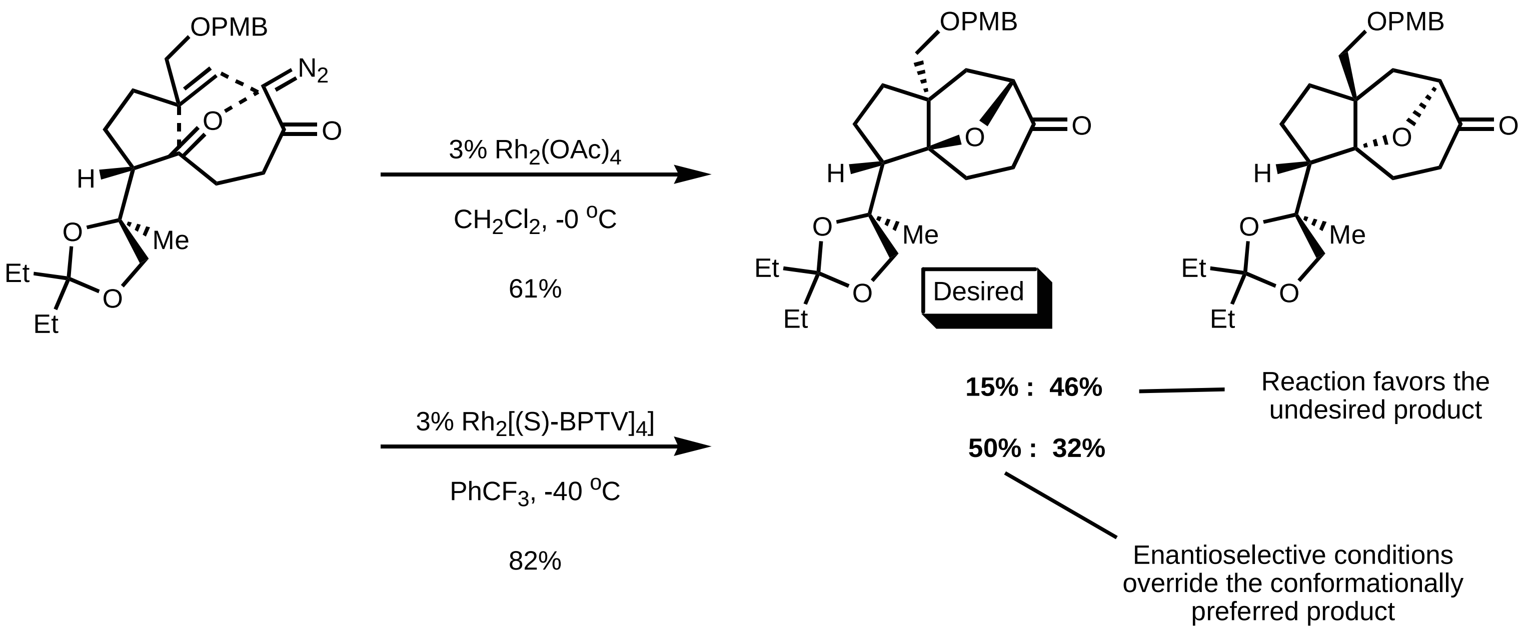
Rh(II) catalyst	**Solvent**	**Yield (%)**	**% ee**
$Rh_2(PTPA)_4$	$CF_3C_6H_5$	81	60
$Rh_2(PTPA)_4$	C_6H_6	64	59
$Rh_2(PTPA)_4$	CH_2Cl_2	79	20
$Rh_2(PTV)_4$	$CF_3C_6H_5$	79	59
$Rh_2(BPTV)_4$	$CF_3C_6H_5$	79	90

Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931.

Enantioselective [3 +2] Cycloaddition Cascade in Total Synthesis

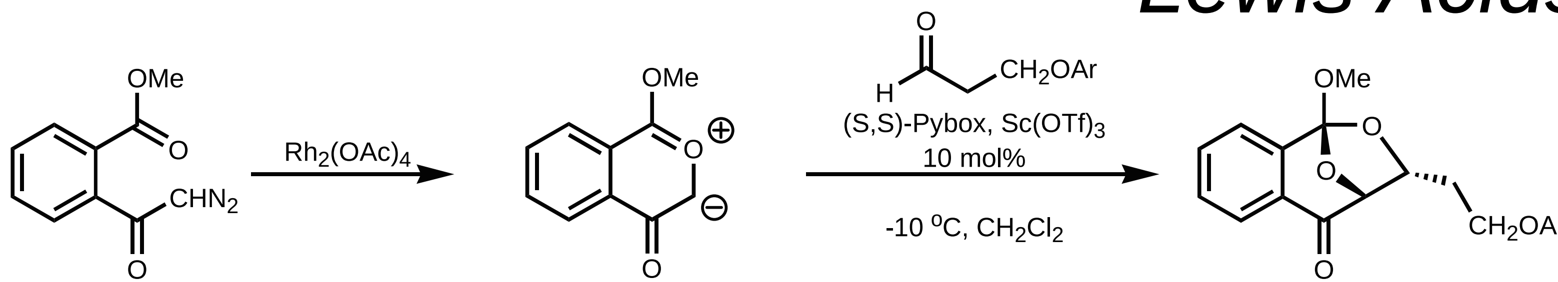


pseudolaric acid A



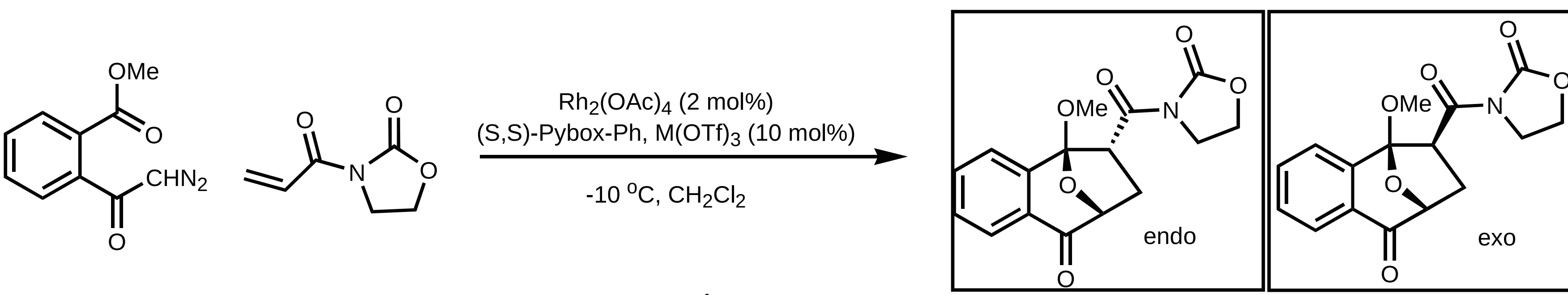
Geng, Z.; Chen, B.; Chiu, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6197.

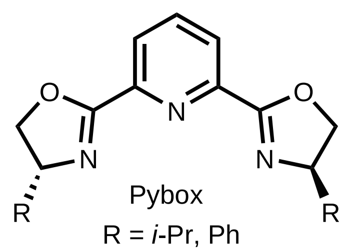
Enantioselectivity Using Chiral Lewis Acids



77 - 97%,
70 - 90% endo, 82 - 93%ee

Ar: *p*-OMeC_6H_5, *o*-OMeC_6H_5, *p*-FC_6H_5, *p*-ClC_6H_5, *p*-BrC_6H_5





M = Sc: 89 : 11

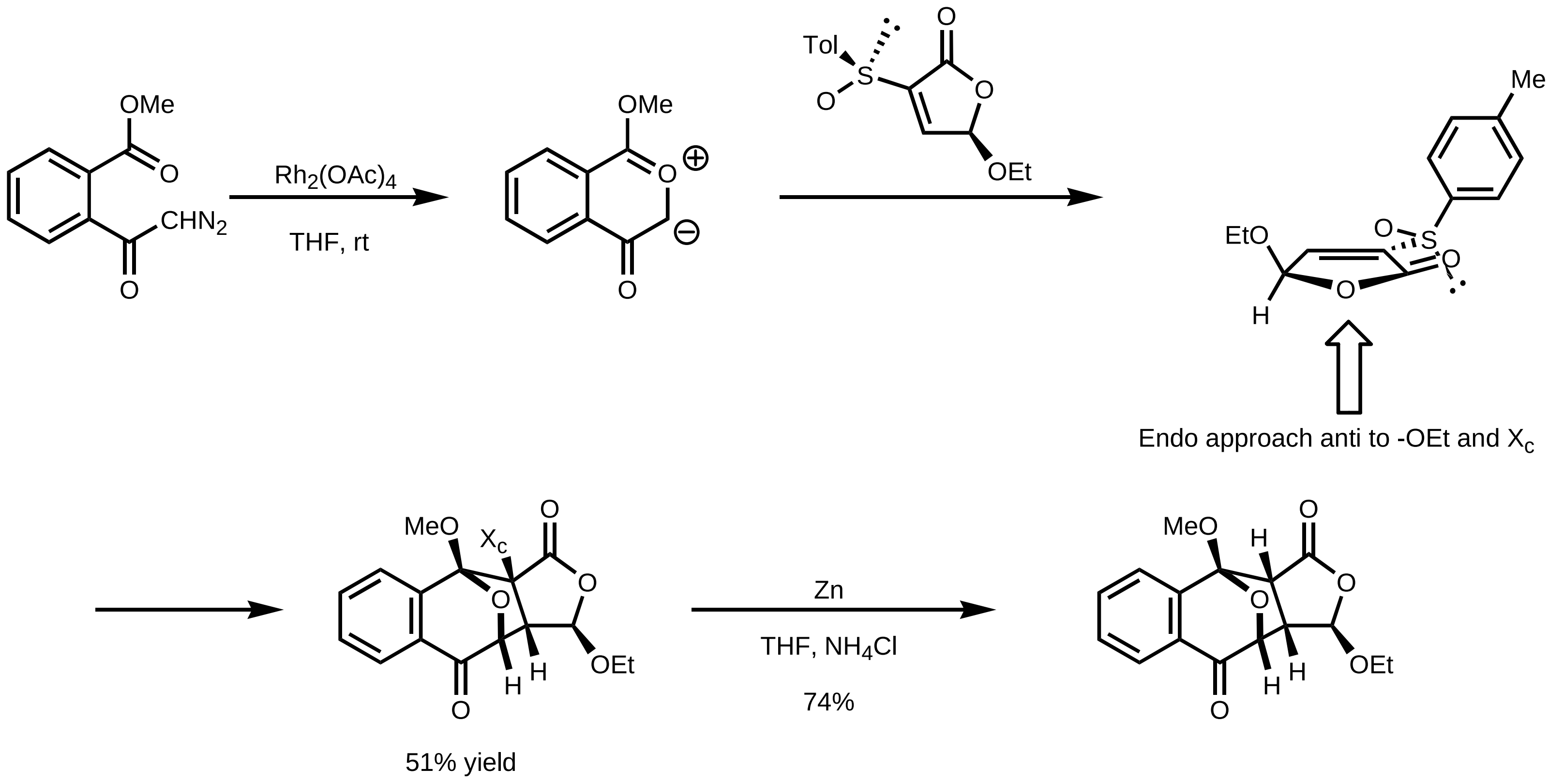
endo adduct is favored
86%, 7% ee

M = Yb : 12 : 88

exo adduct is favored
89%, 91% ee

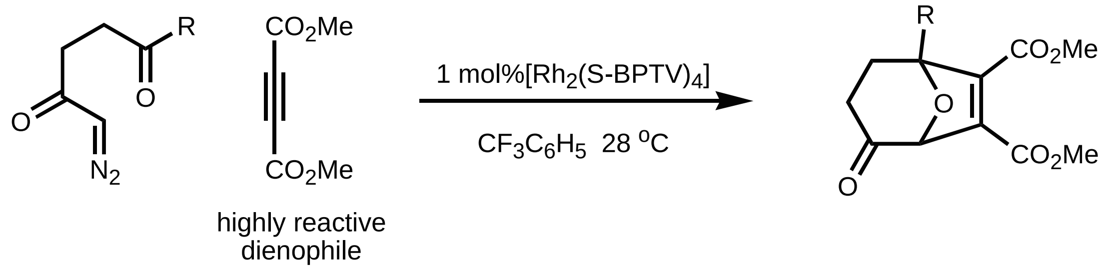
Suga, H.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836.

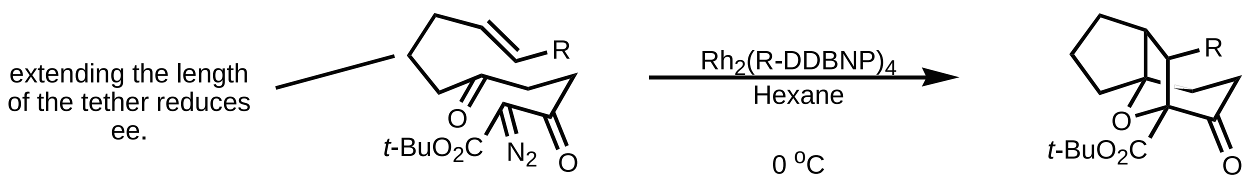
An Effective Chiral Auxiliary for [3 + 2] Cycloadditions

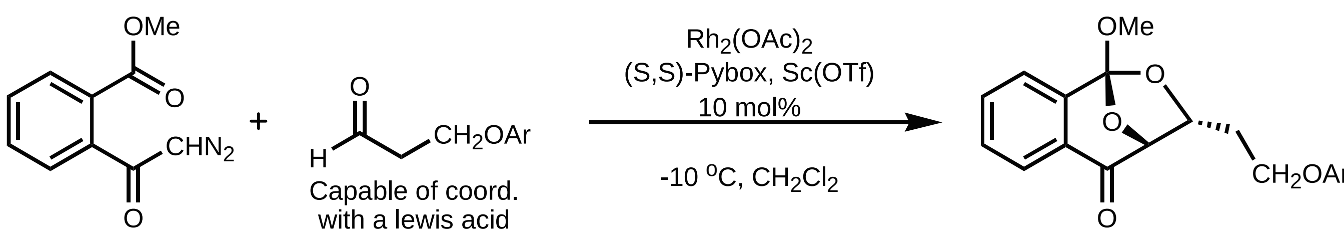


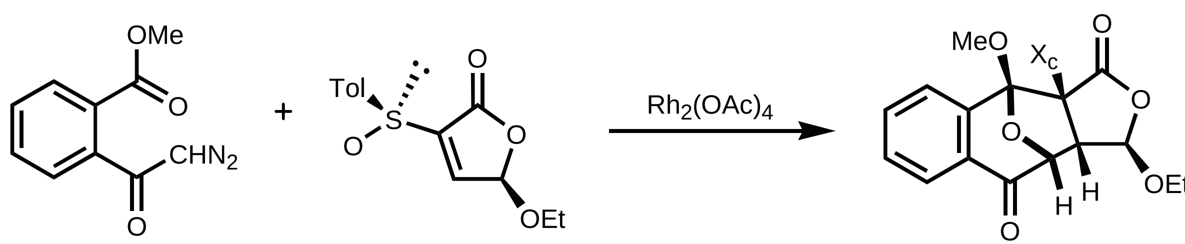
García Ruano, J. L.; Fraile, A.; Martín, R.; Núñez, A. *J. Org. Chem.* **2006**, *71*, 6536.

Summary of Enantioselective [3 + 2] Cycloaddition Cascade's

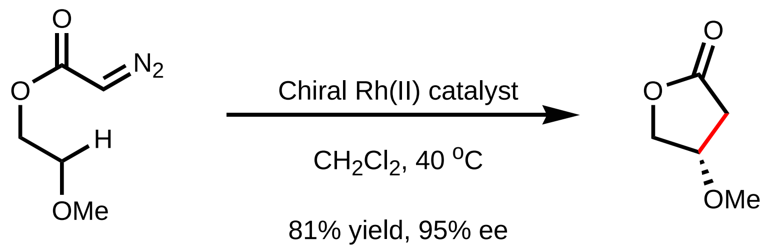




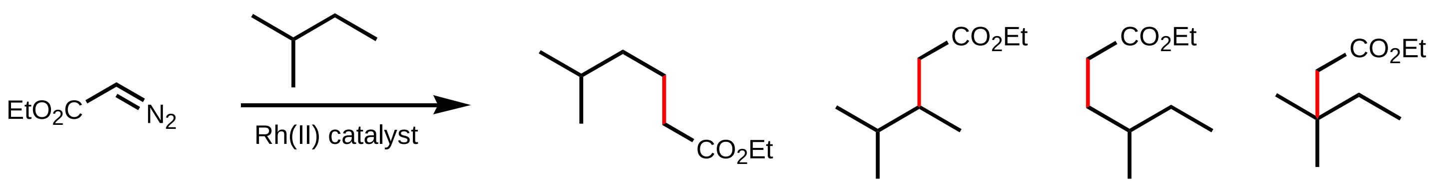


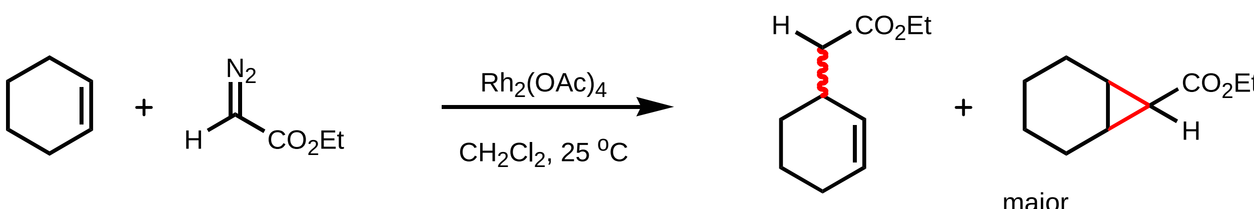


C-H Activation/Insertion



5 membered ring formation is preferred
for intramolecular C-H activation





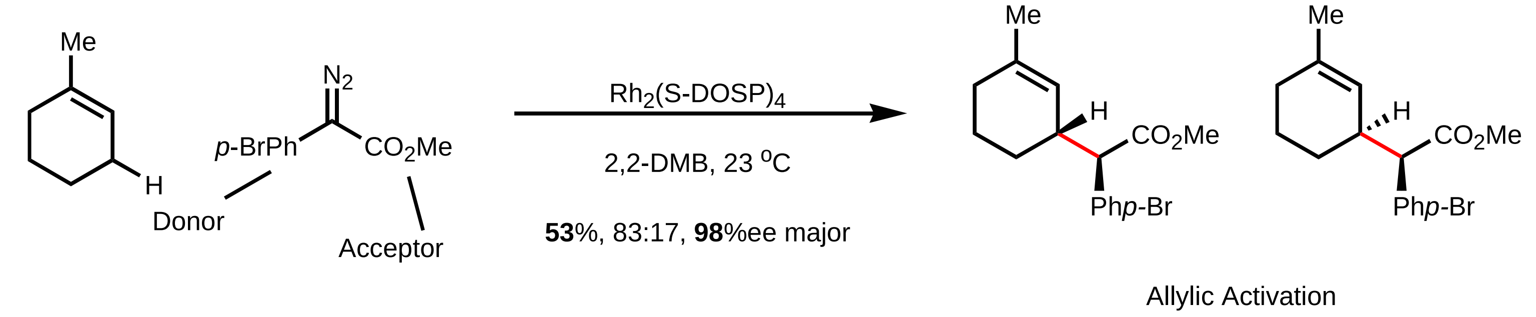
80%, **1:4**

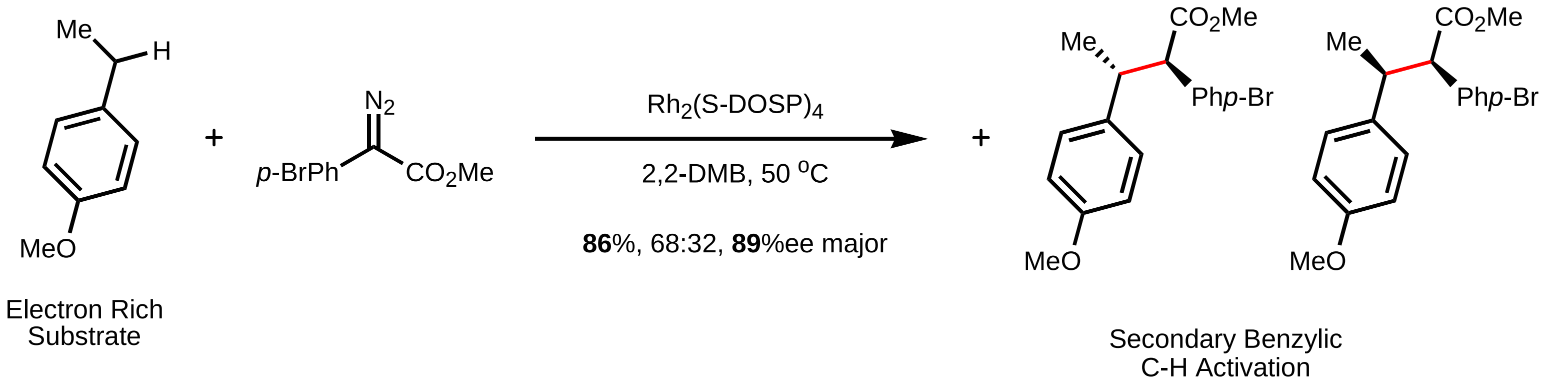
Cyclopropanation is
preferred over
C-H Activation/Insertion

Regio- and chemoselectivity for the intermolecular reaction can be difficult

Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

C-H Activation/Insertion

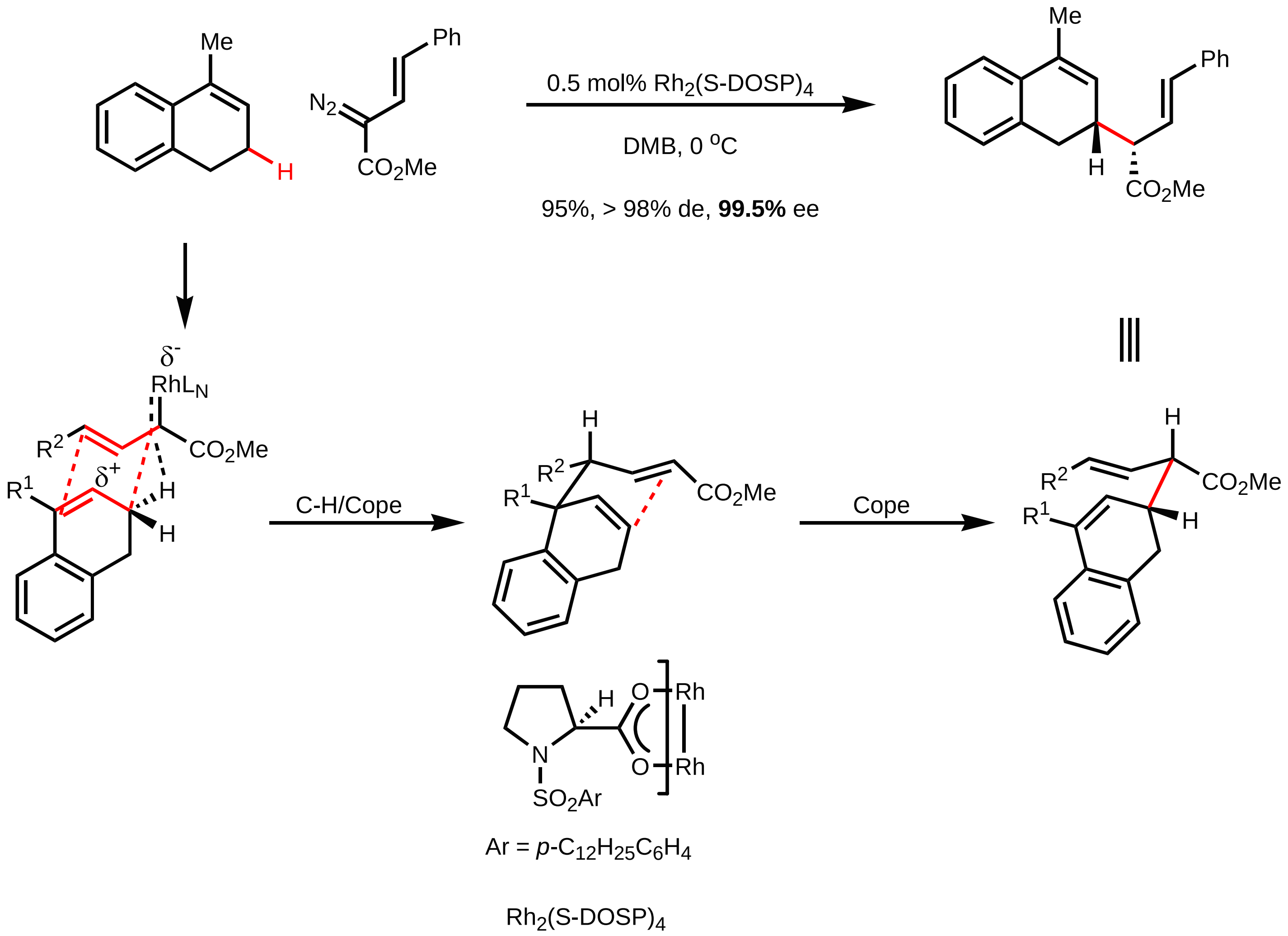




Donor/Acceptor carbenoids paired with electron rich substrates allows for intermolecular C-H activation with diminished cyclopropane byproducts

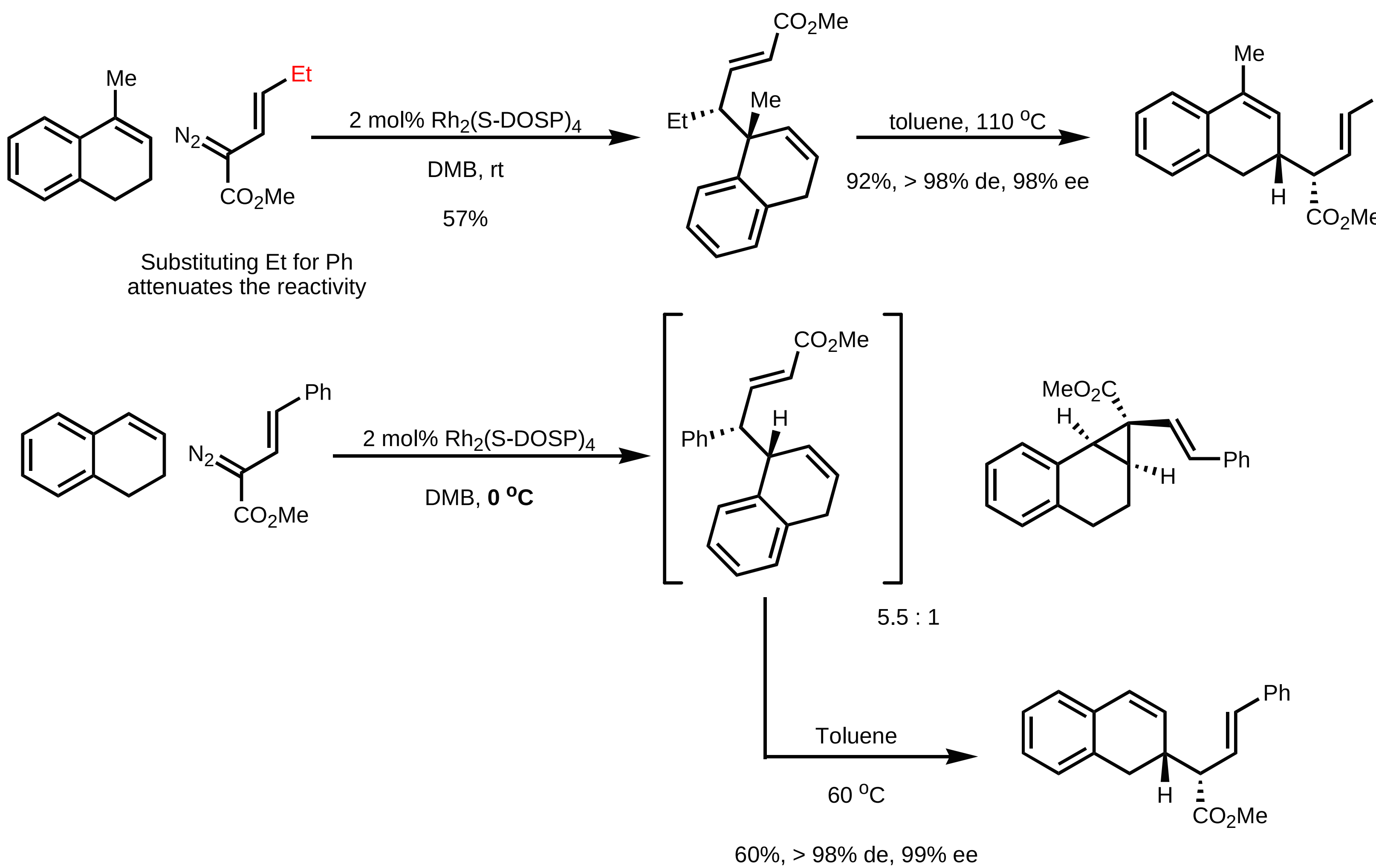
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

C-H Activation/Cope Rearrangement



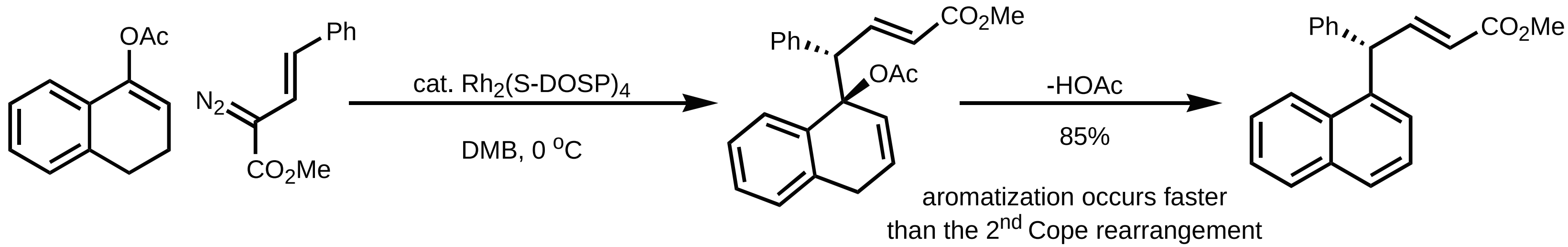
Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862.

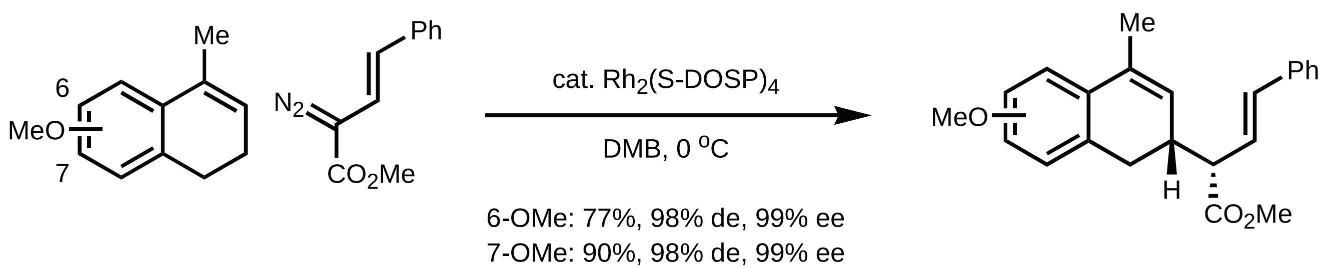
Support for the Proposed Mechanism

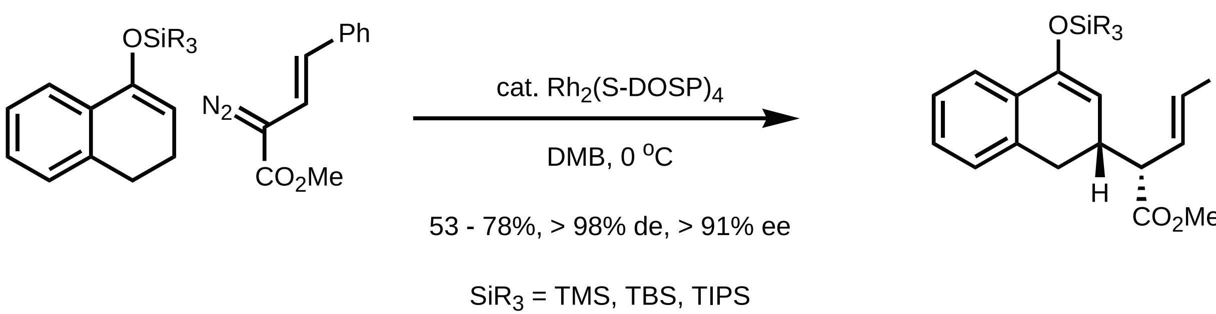


Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862.

Applicable Substrates

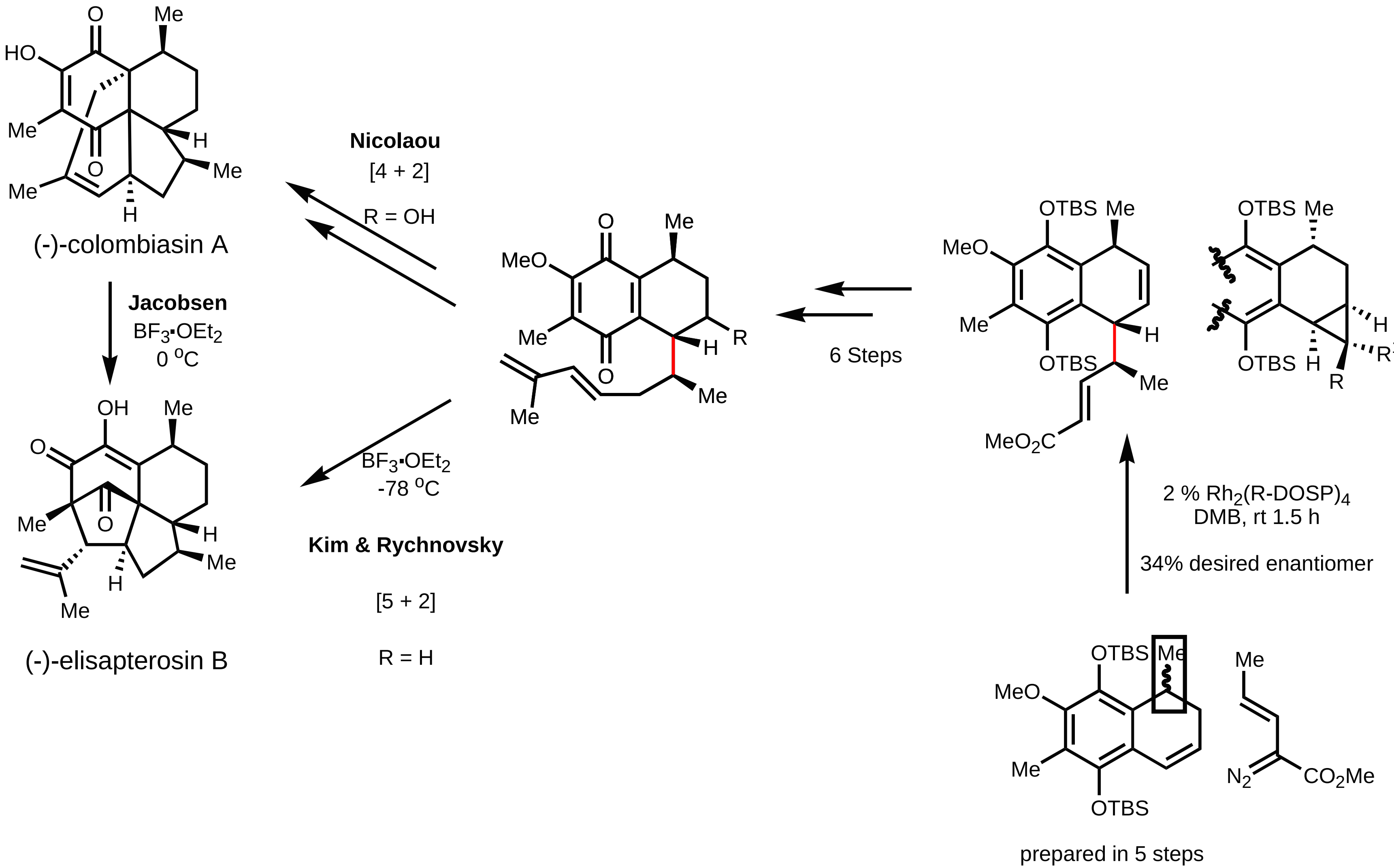






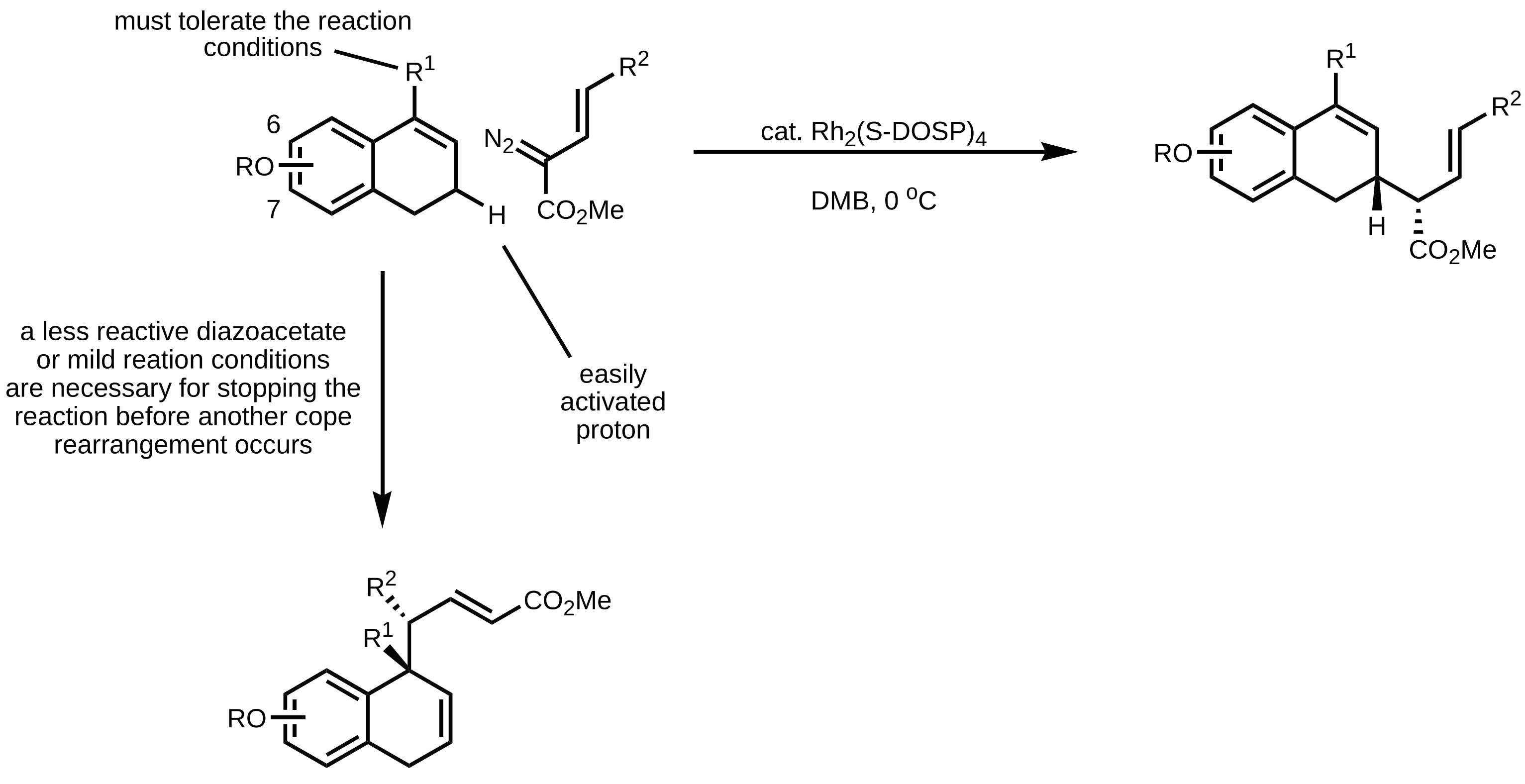
Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862.

Total Synthesis of (-)-Colombiasin A and (-)-Elisapterosin B



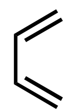
Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2005**, *128*, 2485.

Summary of Enantioselective C-H Activation/Cope Cascades

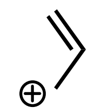


[5 + 2] Cycloadditions

[4 + 3]

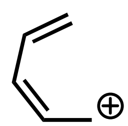


4 C
4 e^-

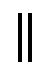


3 C
2 e^-

[5 + 2]

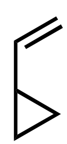


5 C
4 e^-



2 C
2 e^-

[5 + 2]

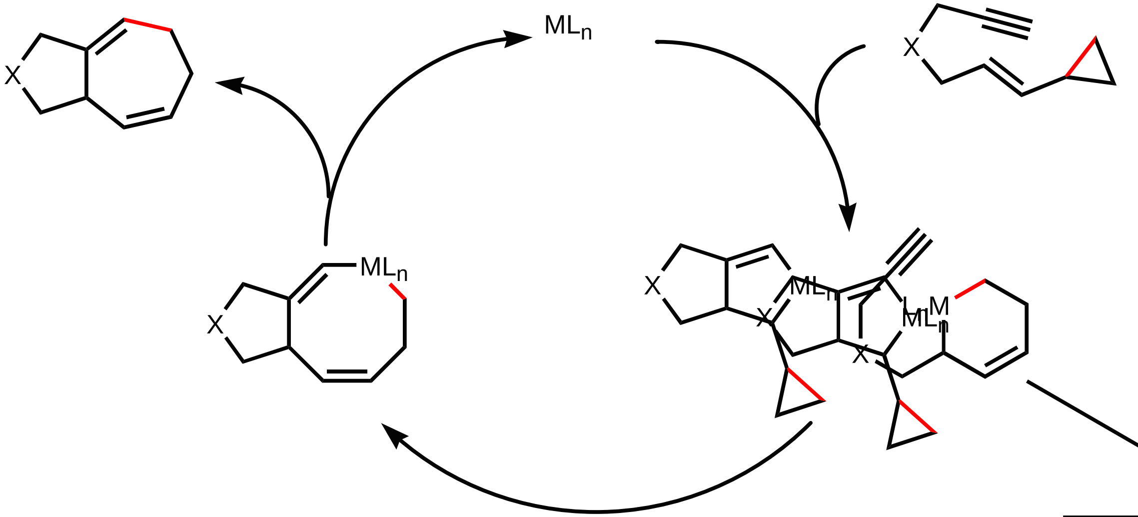


5 C
4 e^-

2 C
2 e^-

Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, 54, 7203.

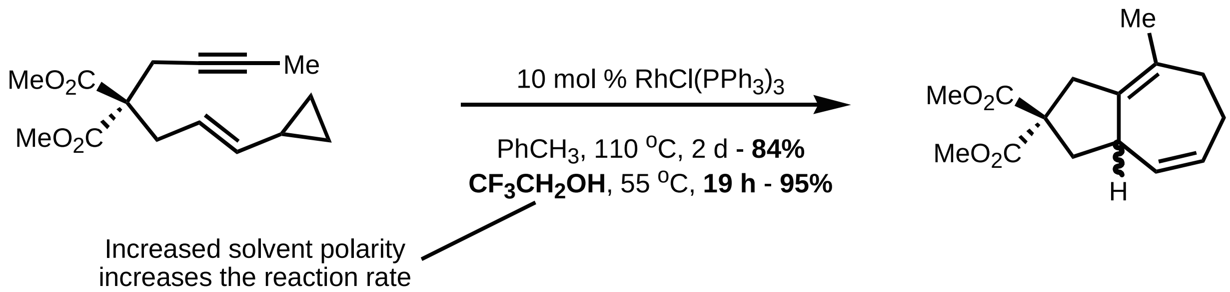
Concept



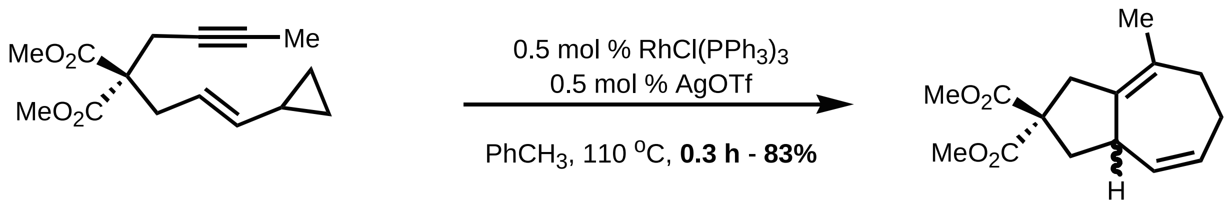
Calculated to be the energetically favored pathway

Yu, Z.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154.

Reaction Development



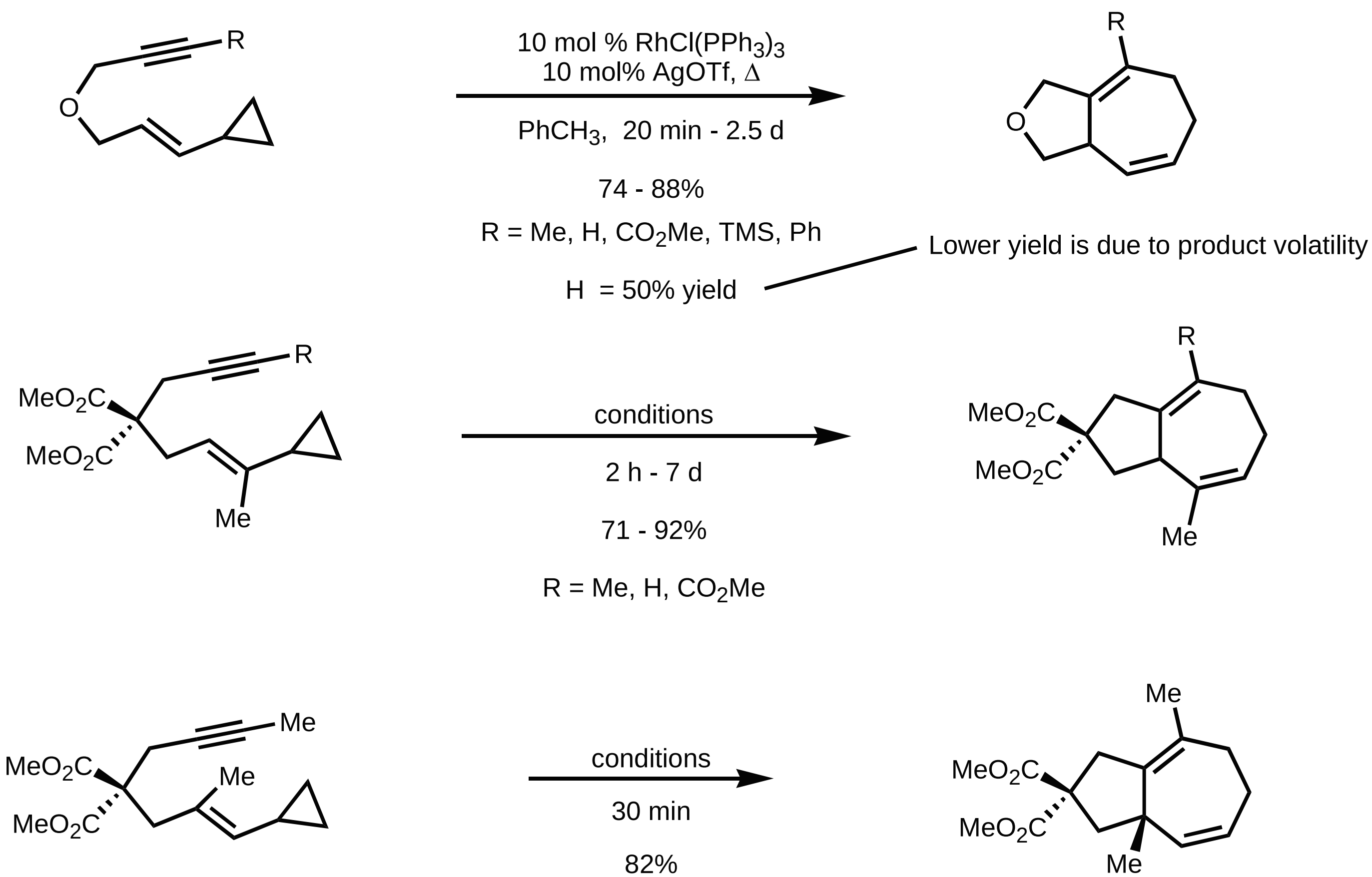
The increased solvent polarity is believed to favor formation of a cationic rhodium species through loss of chloride ligand



The silver additive irreversibly forms a cationic rhodium(I) species, opening up a vacant coordination site on the metal, through removal of the chloride ligand

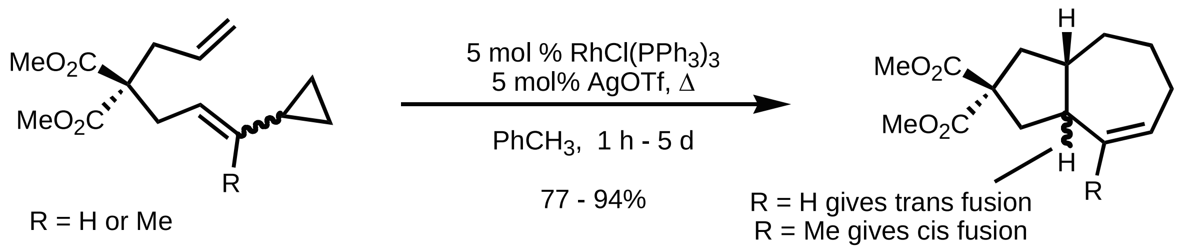
Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, 117, 4720. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203.

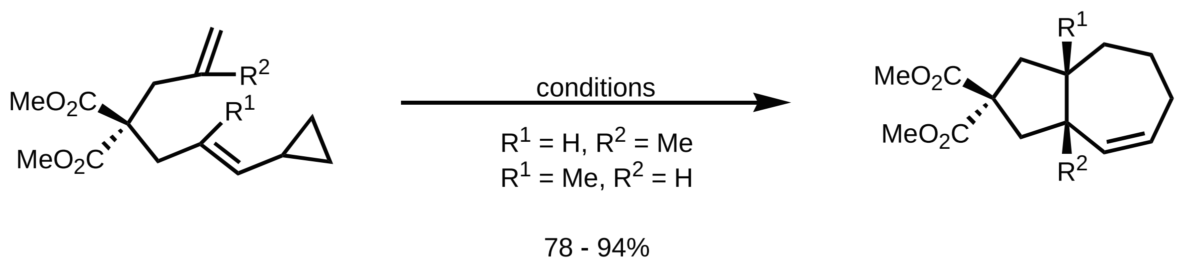
Intramolecular [5 + 2] Cycloadditions VCP's and Alkynes



Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, 117, 4720. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203.

Intramolecular [5 + 2] Cycloadditions VCP's and Alkenes

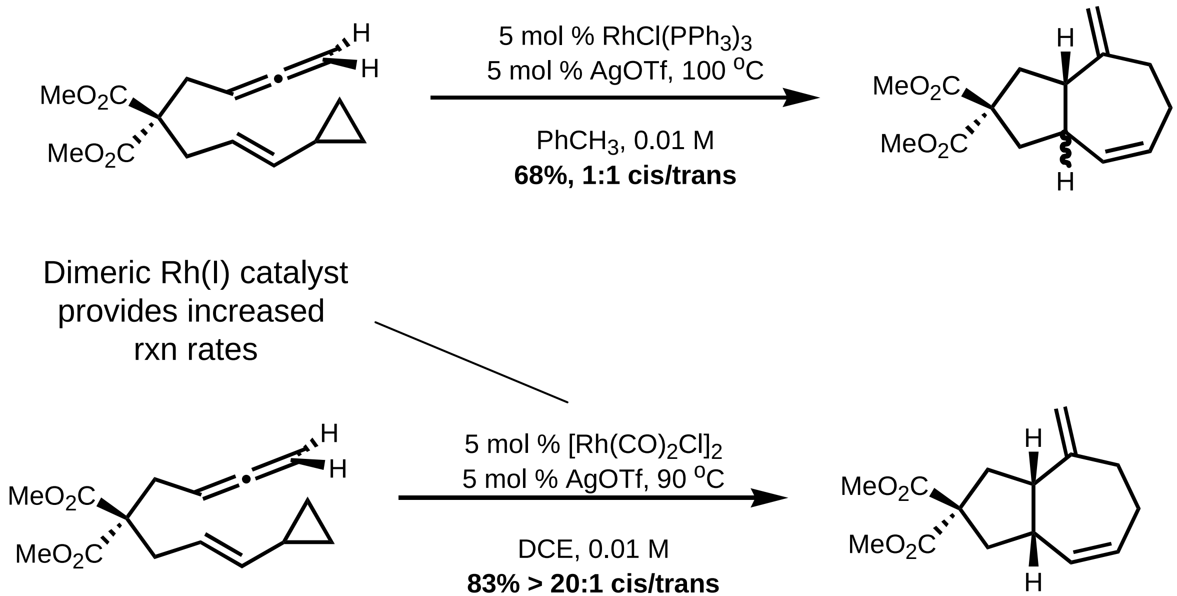




A terminal olefin is required as substituted alkenes produce mainly β-elimination products

Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; *J. Am. Chem. Soc.* **1998**, *120*, 1940.
Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203.

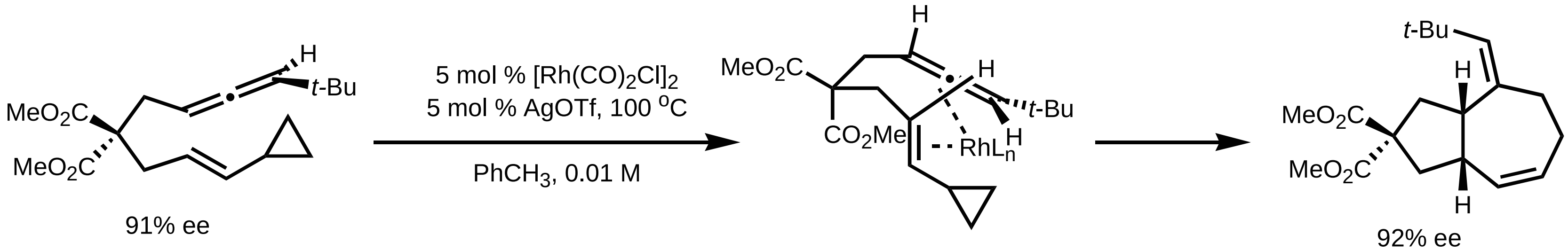
New Selective Catalyst



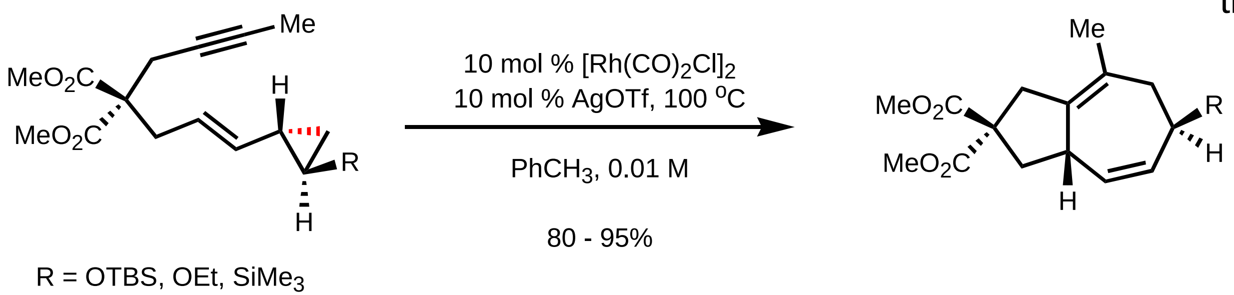
The active catalyst, presumed to be $Rh(CO)_2Cl$, is thought to be more active as the lower ligand count facilitates coordination to the metal

Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. Love, J. A.; *J. Am. Chem. Soc.* **1999**, *121*, 5348.

Stereochemical Information

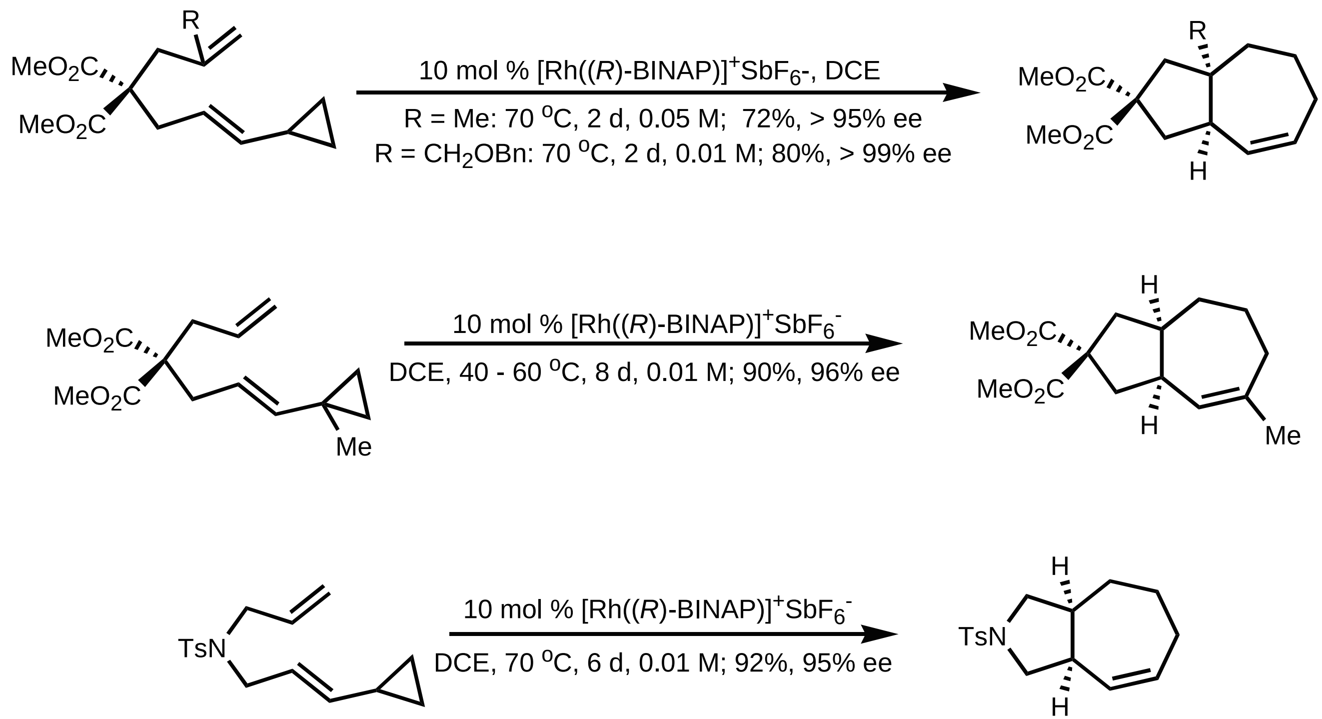


Complete chirality transfer



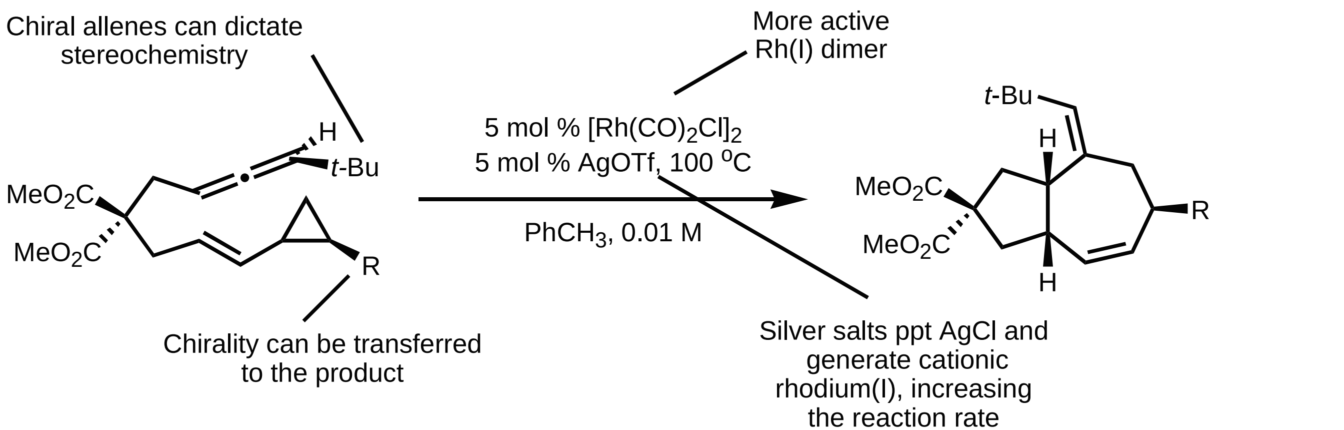
Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; *J. Am. Chem. Soc.* **1999**, *121*, 5348. Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Reick, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442.

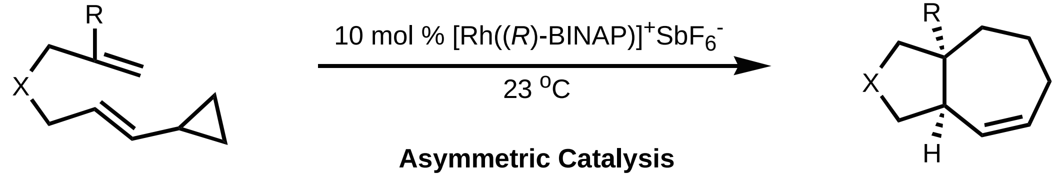
Asymmetric Catalysis of the [5 + 2] Cycloaddition



Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Williams, T. J.; Yoon, J. *J. Am. Chem. Soc.* **2005**, *128*, 6302.

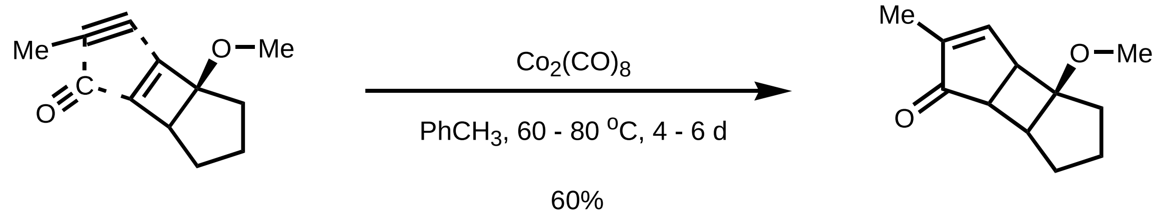
Summary of Enantioselective [5 + 2] Cycloaddition Cascades

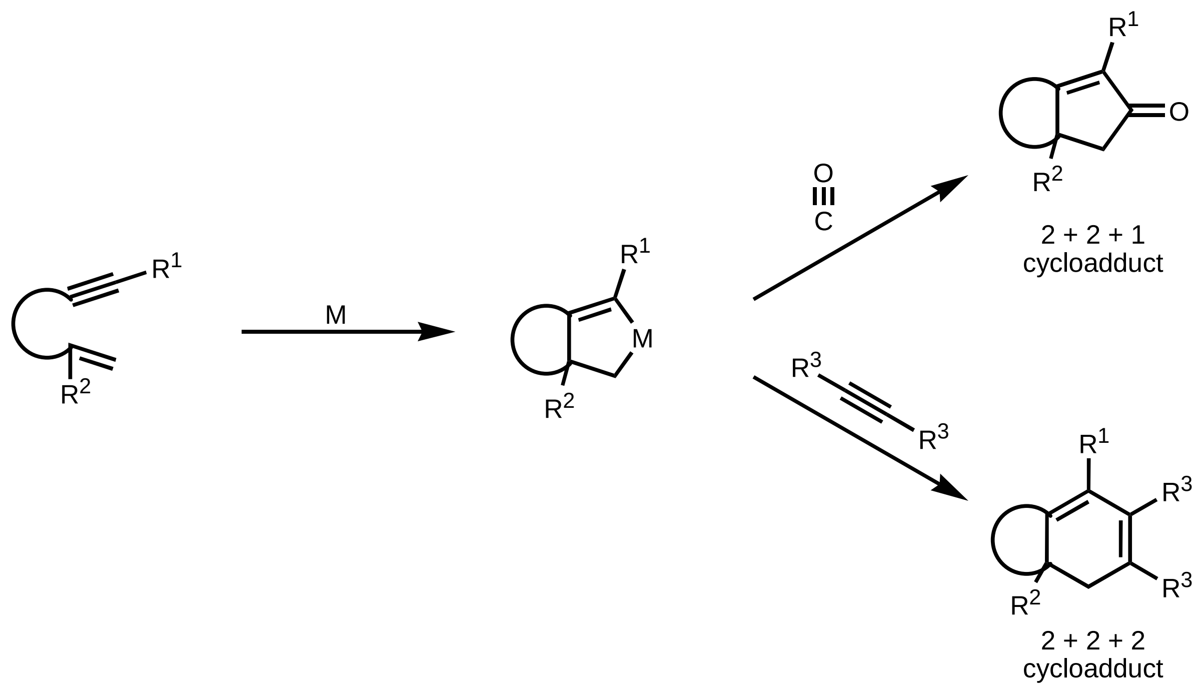




X = $(CO_2Me)_2C$, O, NTs

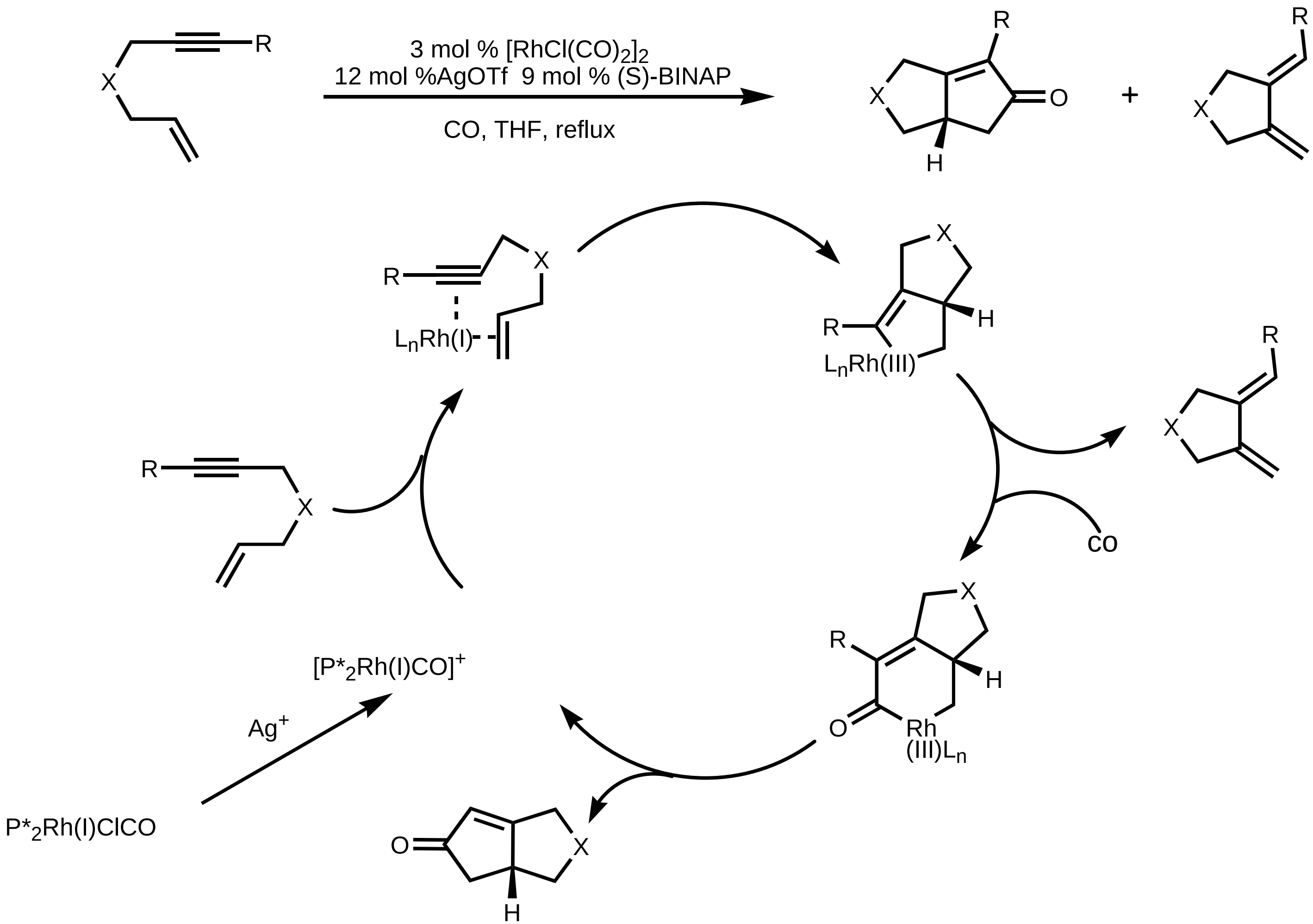
Three Component Cycloadditions





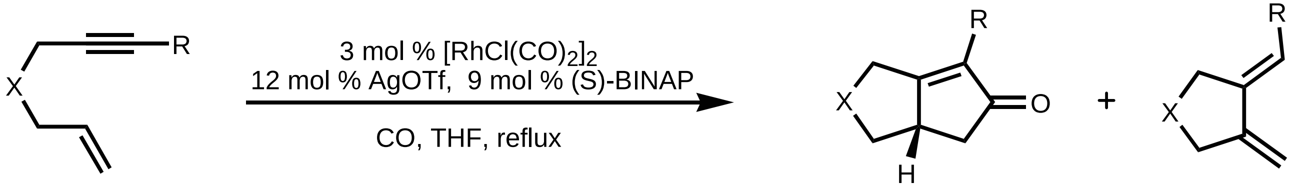
Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2. Pauson, P. L.; *Tetrahedron*, **1985**, *41*, 5855. Schore, N. E.; *Chem. Rev.* **1988**, *88*, 1081.

Rhodium Catalyzed Asymmetric PKR



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

Reaction Conditions

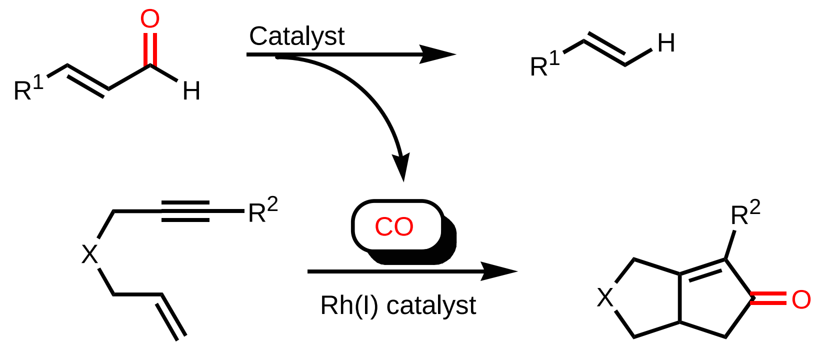


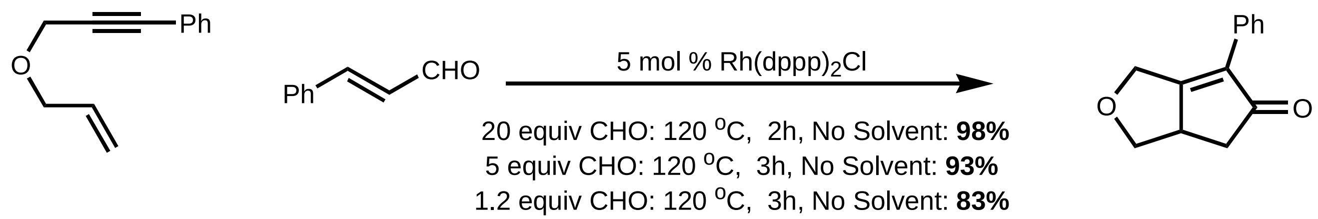
X	R	CO (atm)	temp (C)	time (h)	yield (%)	ee (%)
O	Me	2	130	20	85	86
O	Me	1	90	5	40	96
O	Ph	1	90	5	88	81

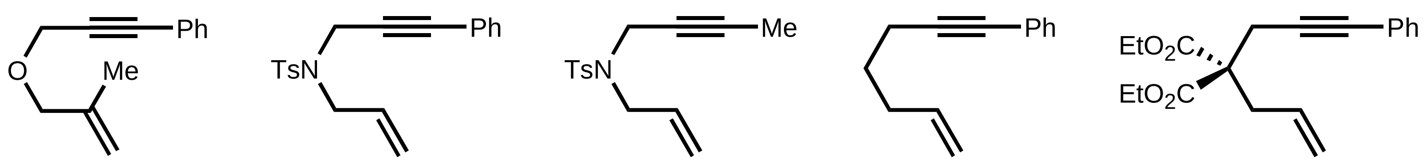
- High temperature and pressure increases yield and decreases ee
- Low temperature and pressure increases ee and decreases yield

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

Rhodium Catalyzed Decarbonylation / APKR





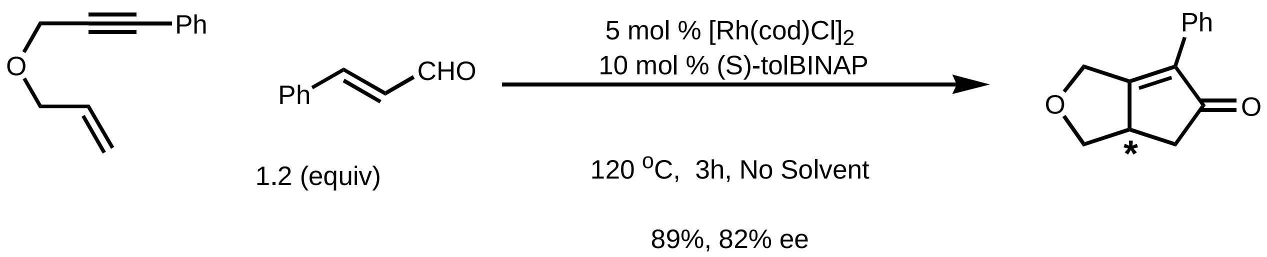


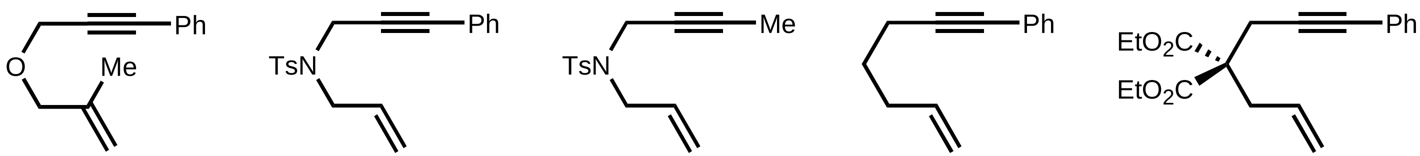
58 - 85% yield

- Aromatic and α, β-unsaturated aldehydes work best for decarbonylation

Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* **2002**, *67*, 7446.

Enantioselective Conditions

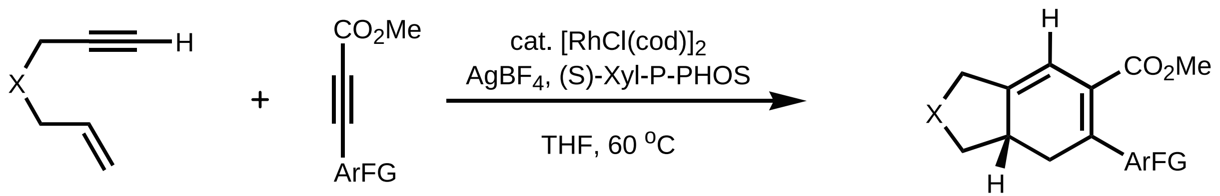




60 - 99%, 70 - 90% ee

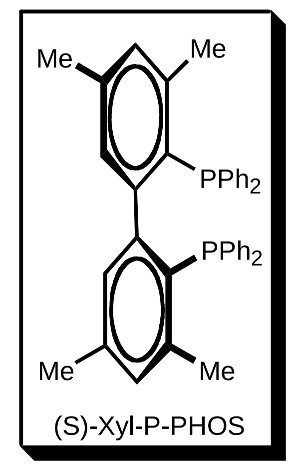
Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* **2002**, *67*, 7446.

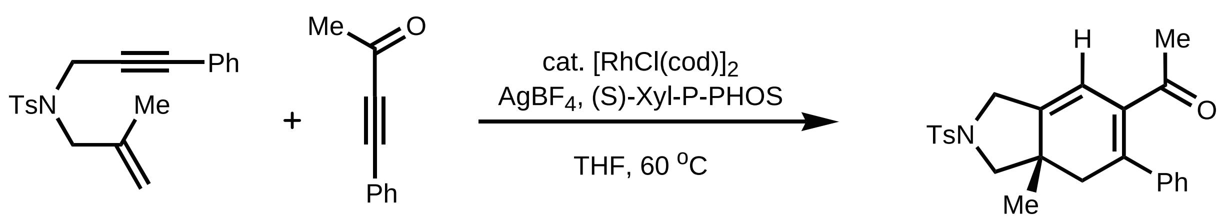
Regioselective [2 + 2 + 2] Cycloadditions



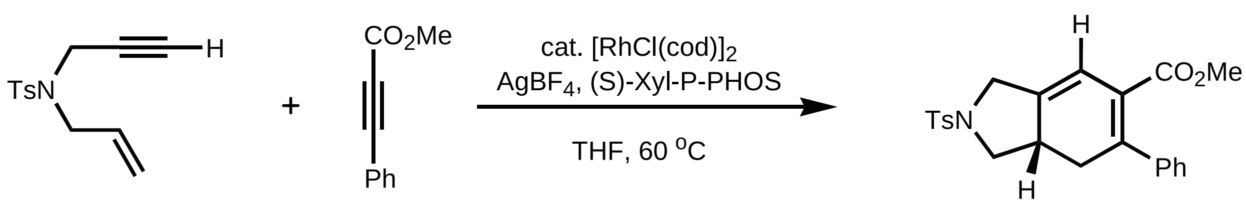
75 - 95%
regioselectivity: 5 - 19/1
95 - 99% ee

X = NTs, O, $C(CO_2Me)_2$
FG = *p*-H, *p*-OMe, *p*-Me, *p*-F, *p*-CF_3,





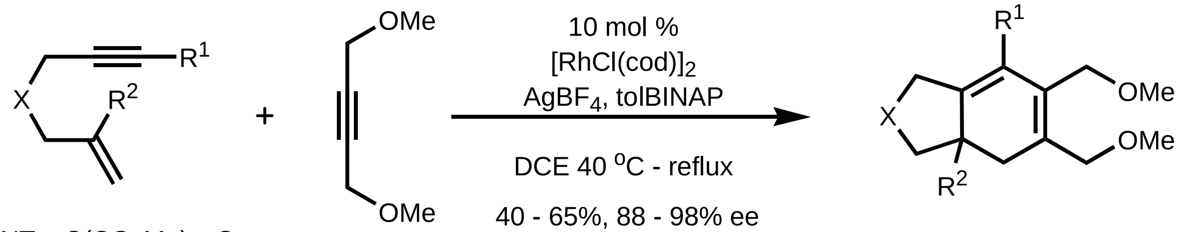
84%
regioselectivity: 10/1
> 99% ee



98%
regioselectivity: 10/1
97% ee

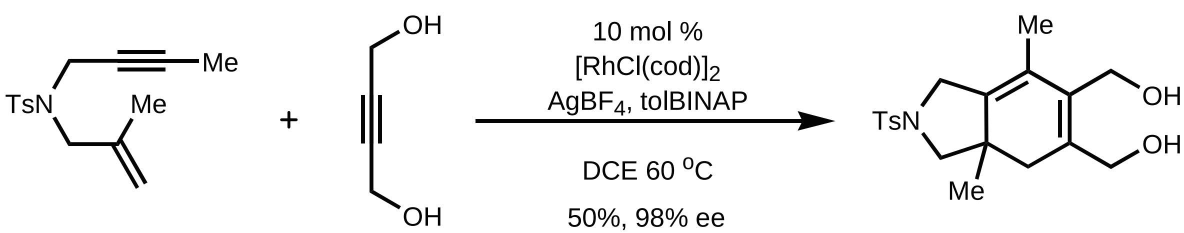
Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, 127.

Reaction Conditions



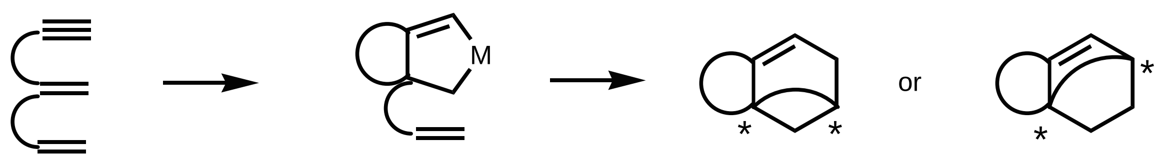
X = NTs, $C(CO_2Me)_2$, O

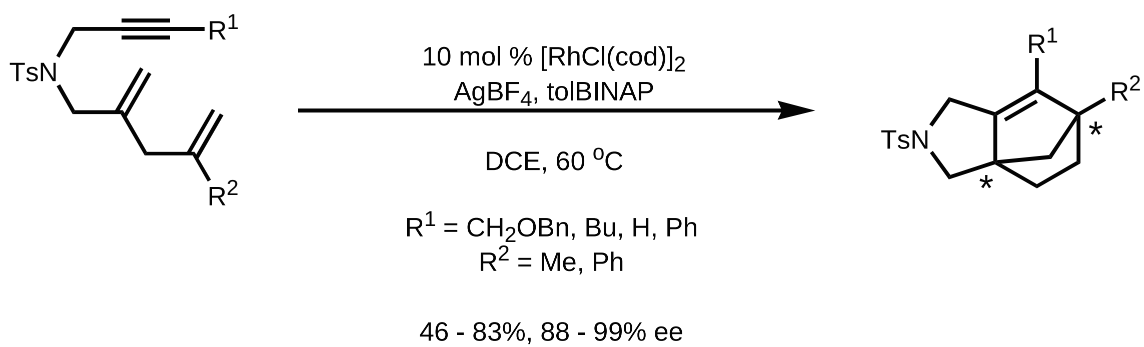
R^1 = Ph, Me, H
R^2 = Ph, Me



Shibata, T.; Arai, Y.; Tahara, Y. *Org. Lett.* **2005**, *7*, 4956.

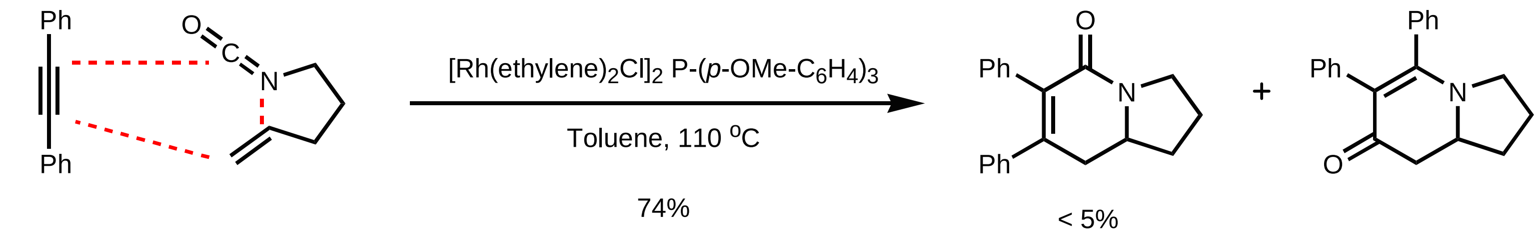
Enantioselective Intramolecular [2 + 2 + 2]'s

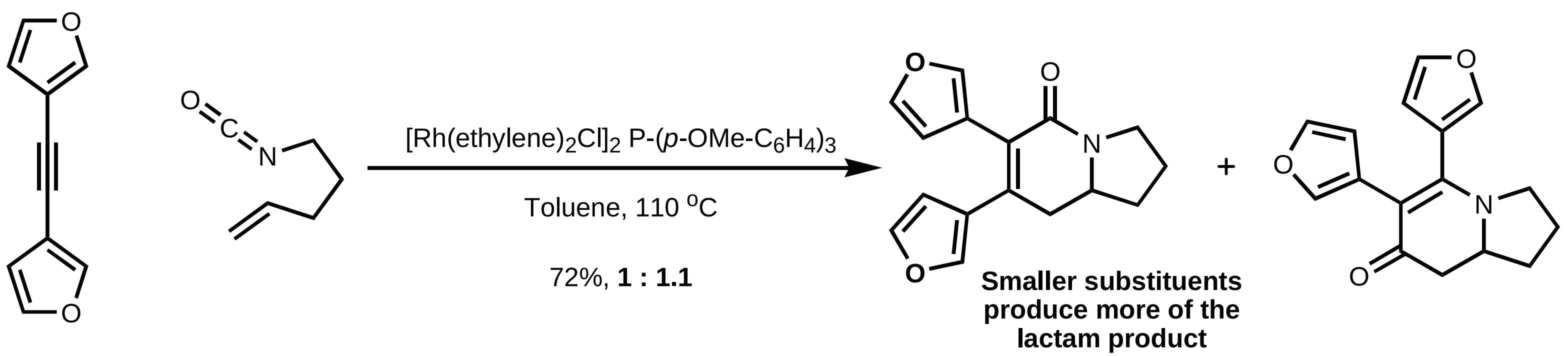


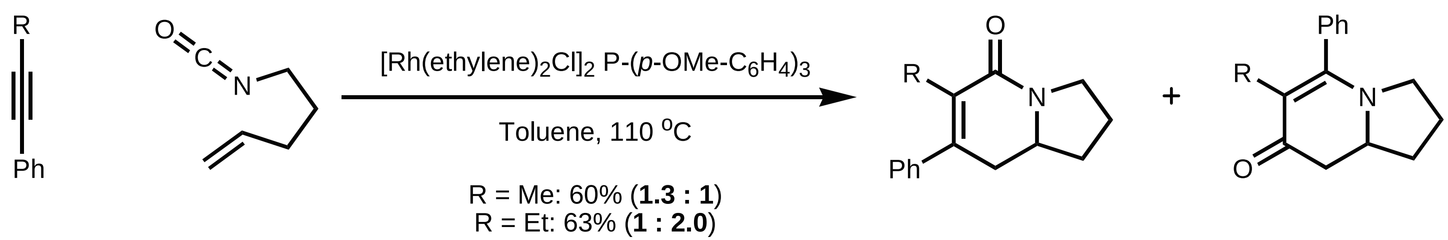


Shibata, T.; Tahara, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11766.

[2 + 2 + 2]'s with Isocyanates



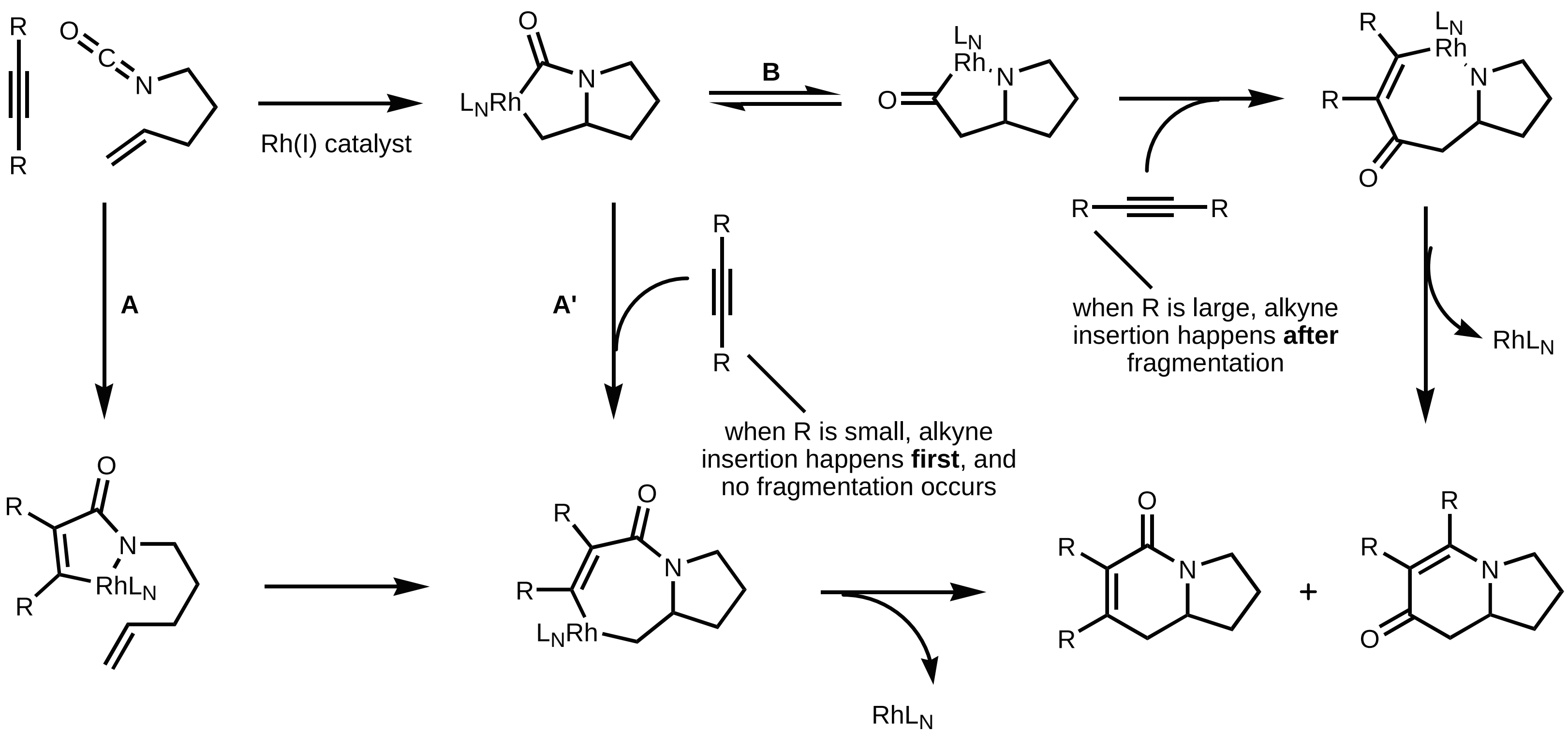




One extra carbon
reverses selectivity

Rovis, T.; Yu, R. T. *J. Am. Chem. Soc.* **2005**, *128*, 2782.

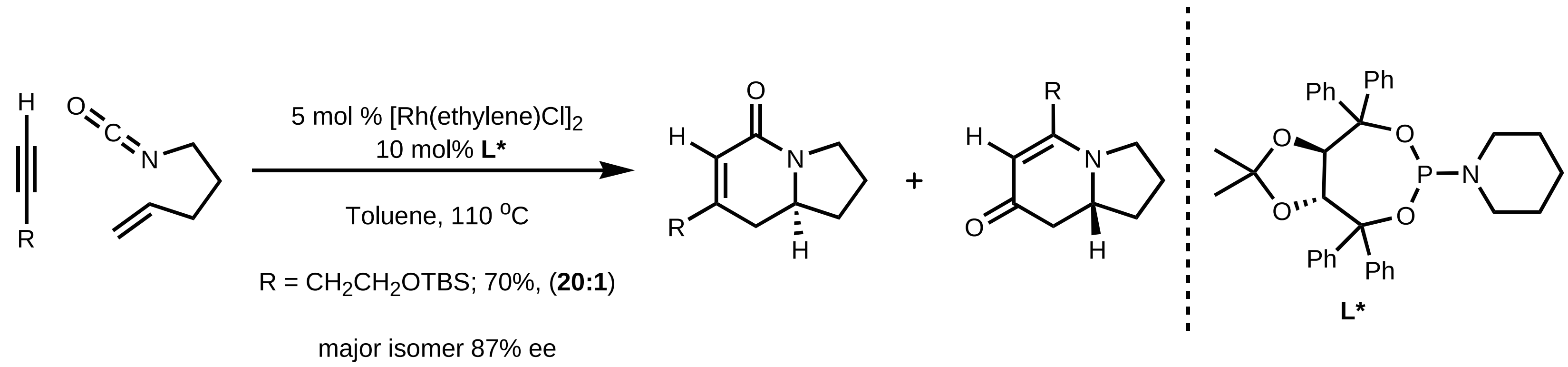
Possible Mechanism

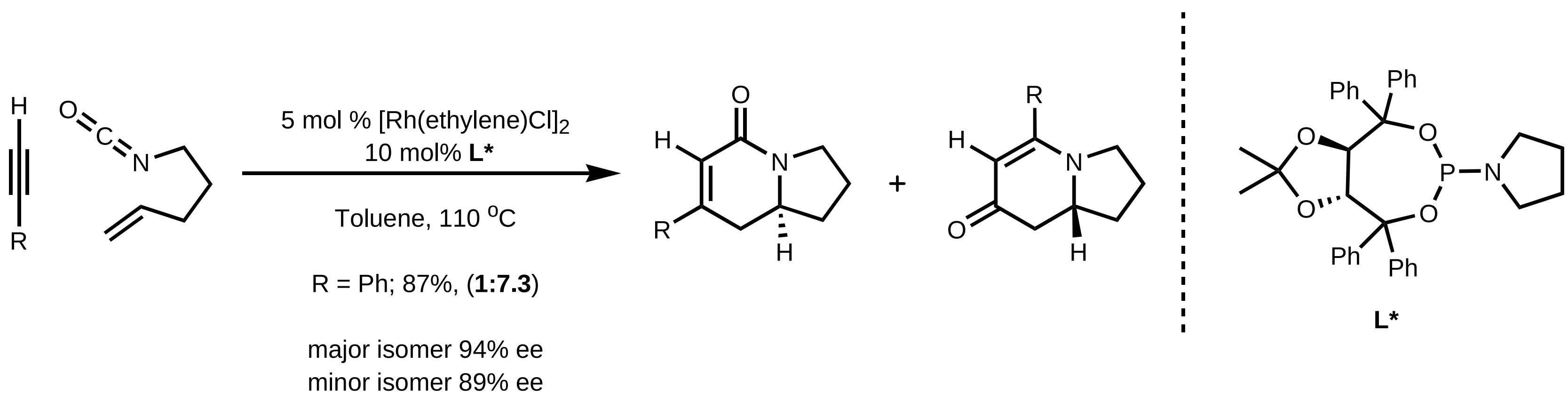


In pathway B CO migration is believed to occur faster than insertion of bulky alkynes. Thus smaller more reactive alkynes give products via pathway A'.

Rovis, T.; Yu, R. T. *J. Am. Chem. Soc.* **2005**, *128*, 2782.

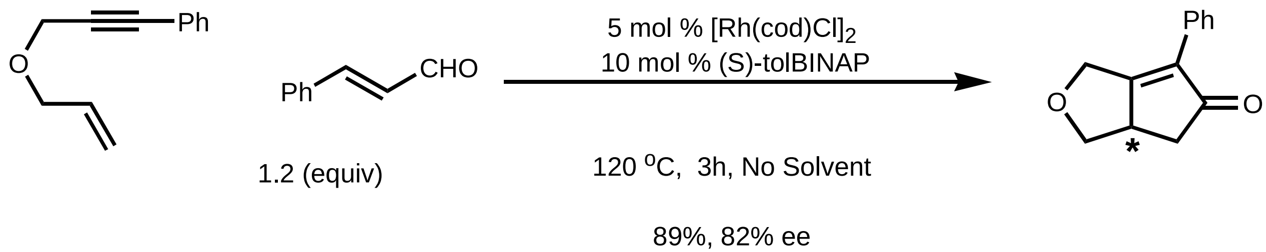
Asymmetric [2 + 2 + 2] Cycloaddition with Isocyanates

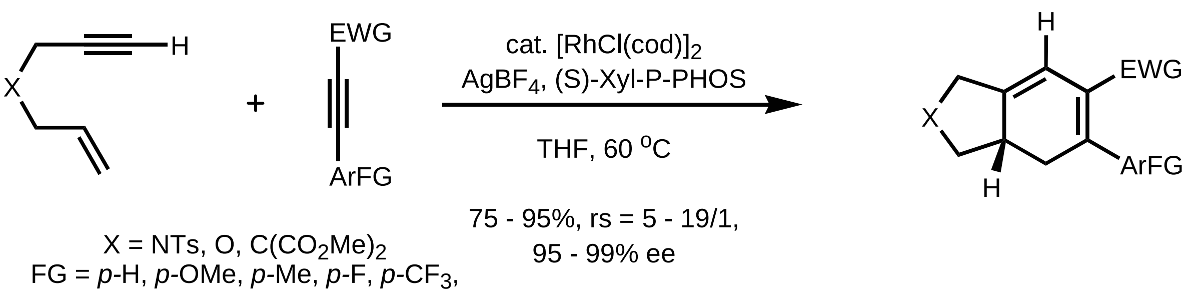


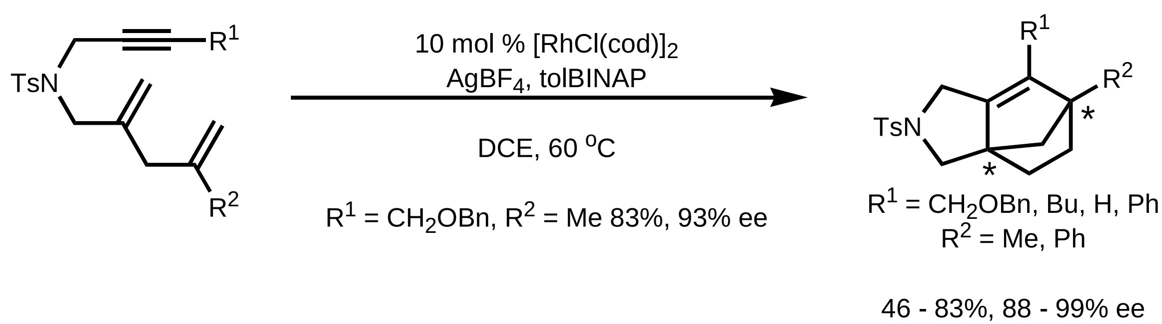


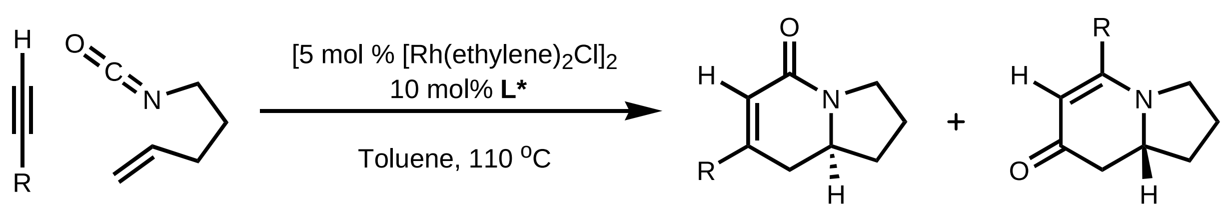
Rovis, T.; Yu, R. T. *J. Am. Chem. Soc.* **2006**, *128*, 12370.

Summary of Enantioselective Three Component Cycloadditions









In Conclusion

- The unique reactivity of Rhodium has allowed for the realization of impressive reaction cascades that generate molecular complexity in a concise fashion.
- The continuous development of new chiral Rhodium catalysts has allowed for the development of efficient methods of asymmetric catalysis.
- Rhodium has shown the ability to catalytically effect complex reaction cascades in an enantioselective fashion, which continues to expand the boundaries of modern synthetic organic chemistry.

Acknowledgments: The Crimmins Group

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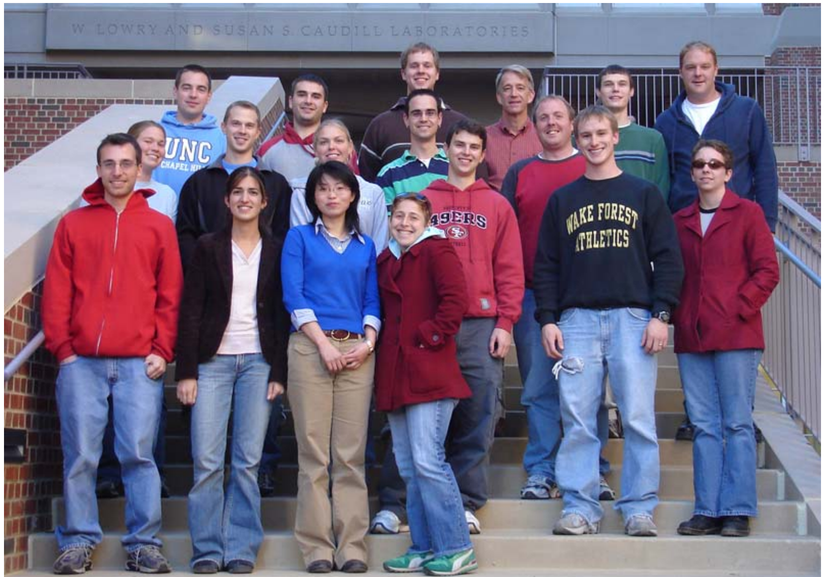
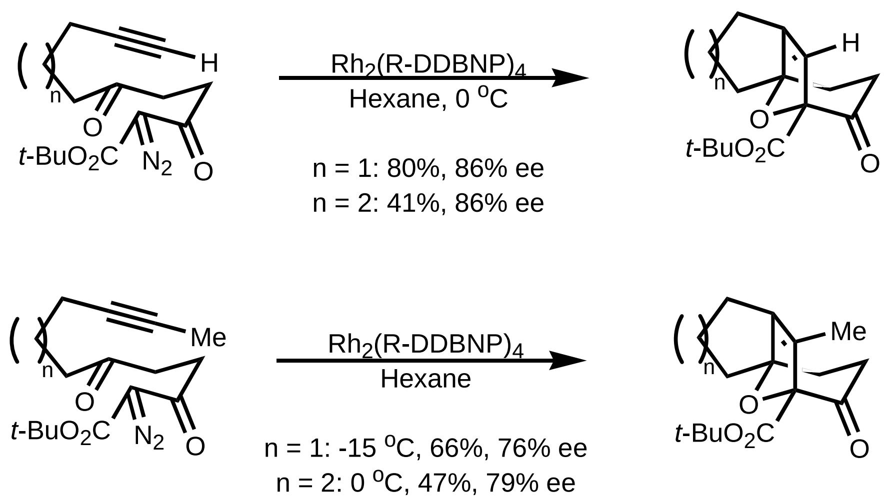
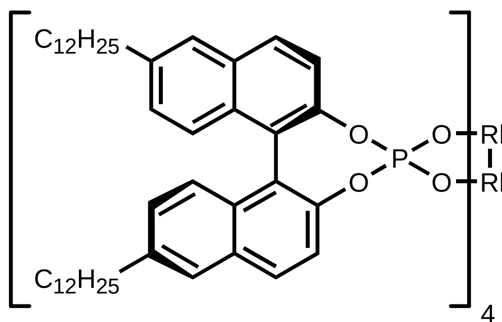
- Matthew Haley
- Mariam Shamszad
- Adam Azman
- Colin Hughes
- Philip Williams
- Mark Mans
- Tim
- Liz
- Anne Marie



Substituted Alkyne Tethers

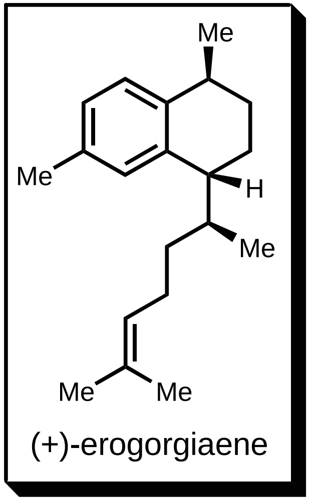


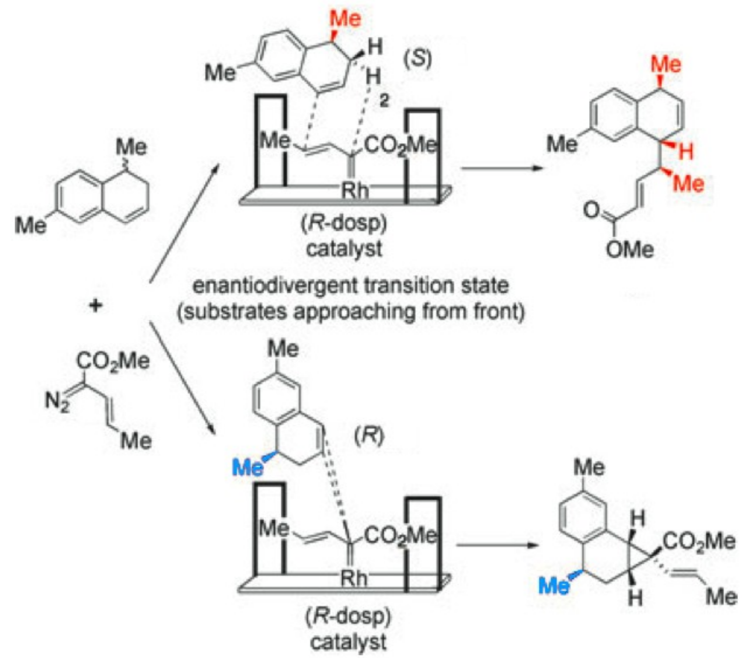


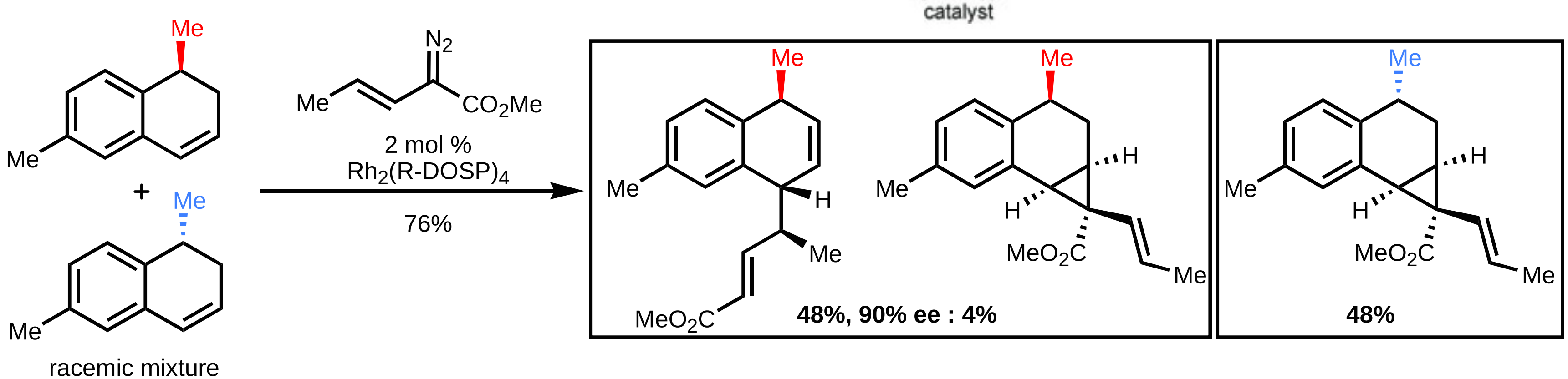
Rh_2(R-DDBNP)$_4$

Hodgson, D. M.; Labande, A. H.; Pierard, F.; Expósito Castro, M. A. *J. Org. Chem.* **2003**, *68*, 6153.

Kinetic Enantiodivergence

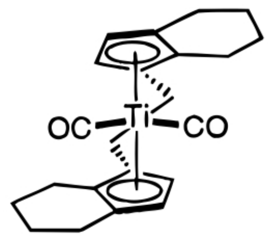




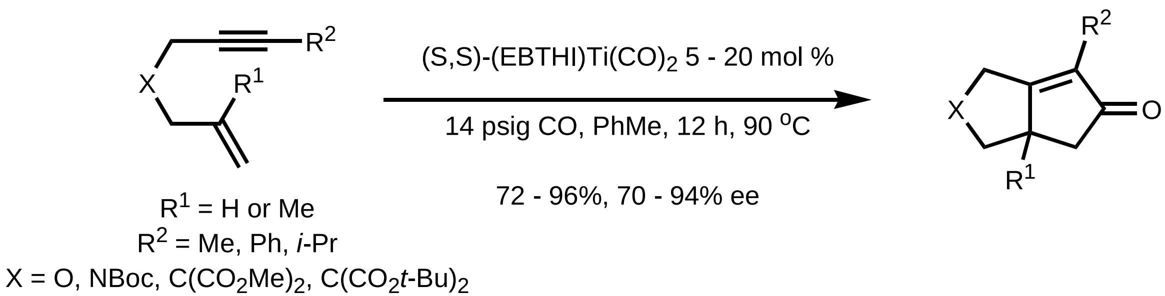


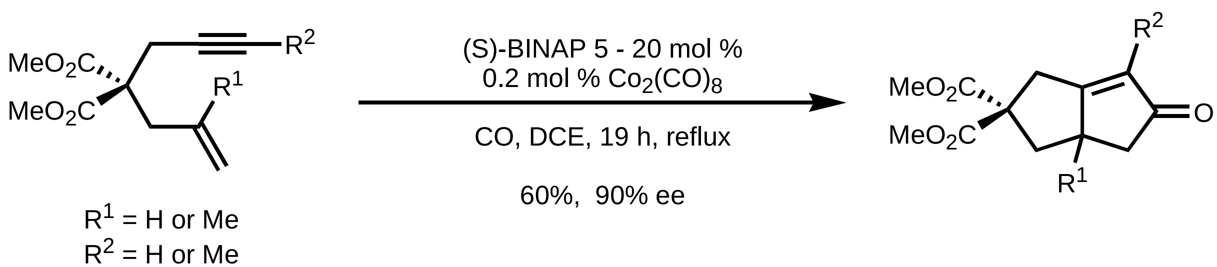
Davies, H. M. L.; Walji, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1733.

Non-Rhodium APKR's



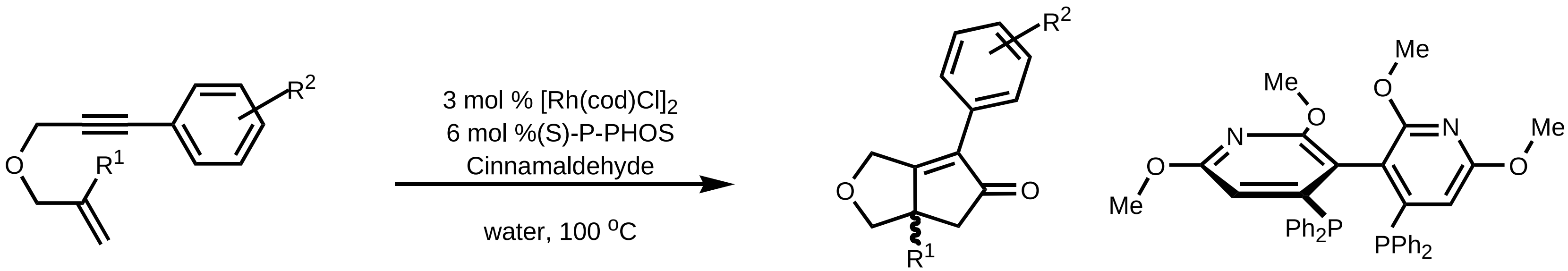
(S,S)-(EBTHI)Ti(CO)$_2$





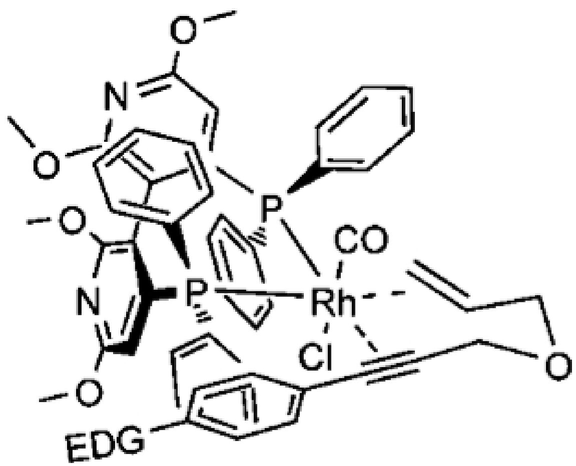
Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7026. Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron Lett.* **2000**, *41*, 891. Derdau, V.; Laschat, S.; Dix, I.; Jones, P. G. *Organometallics* **1999**, *18*, 3859.

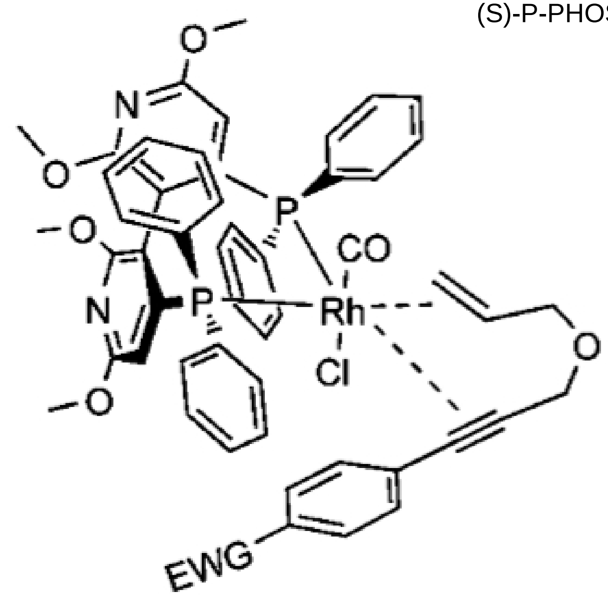
APKR - Electronic Effects



R = H, Me

(S)-P-PHOS

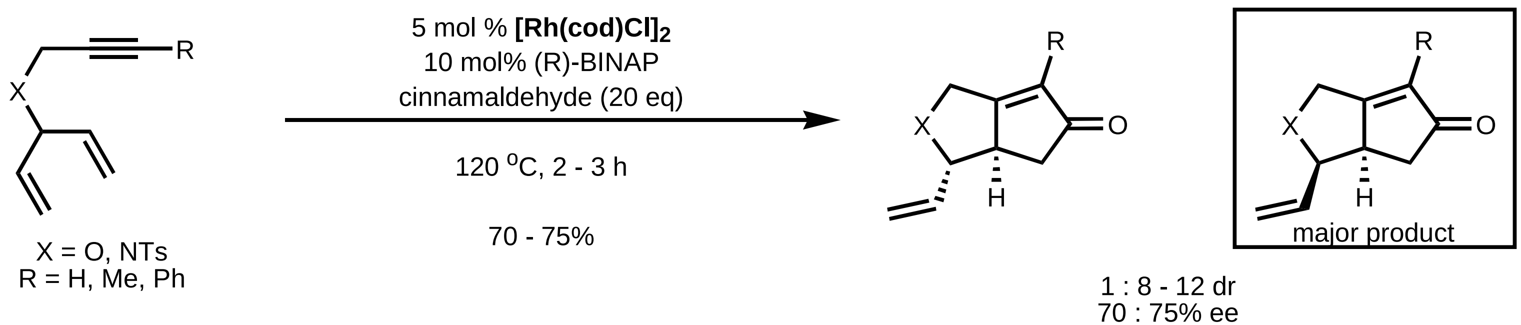


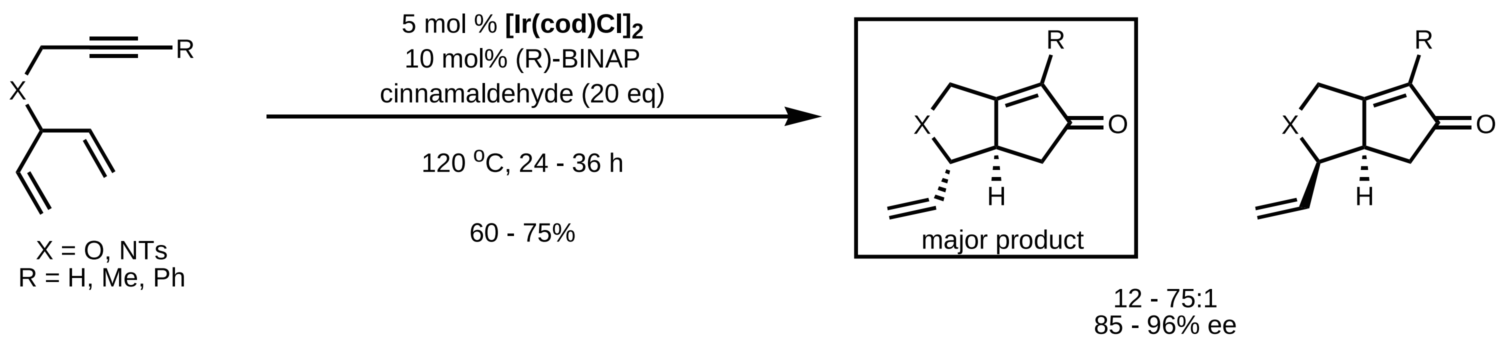


Electron donating groups give higher ee's by drawing the metal and its chiral ligands closer to the electron rich alkyne, allowing for better stereocommunication

Kwong, F. Y.; Li, Y. M.; Lam, H. L.; Qiu, L.; Lee, H. W.; Yeung, C. H.; Chan, K. S.; Chan, A. *Chem. Eur. J.* **2005**, *11*, 3872.

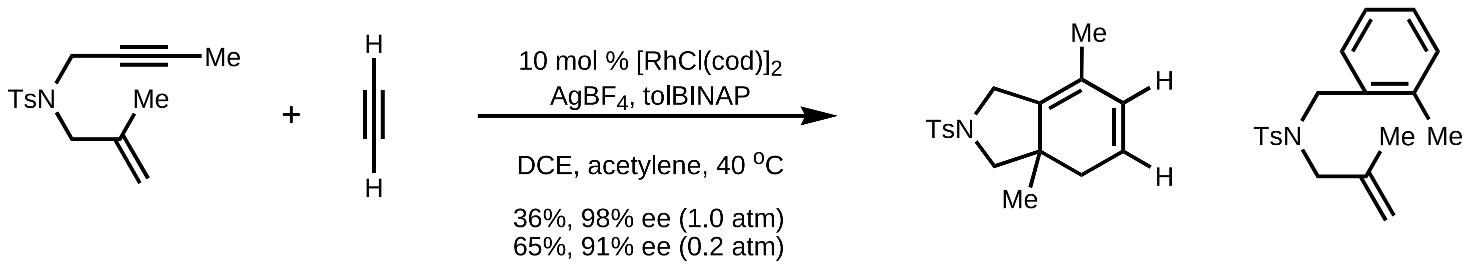
Catalyst Dependent APKR's

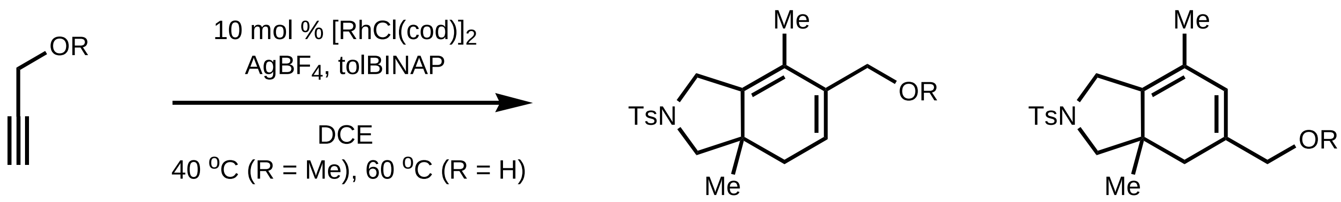




Jeong, N.; Kim, D.; Choi, J. *Chem. Commun.* **2004**, 1134.

[2 + 2 + 2]'s with Acetylene and Unsymmetrical Alkynes

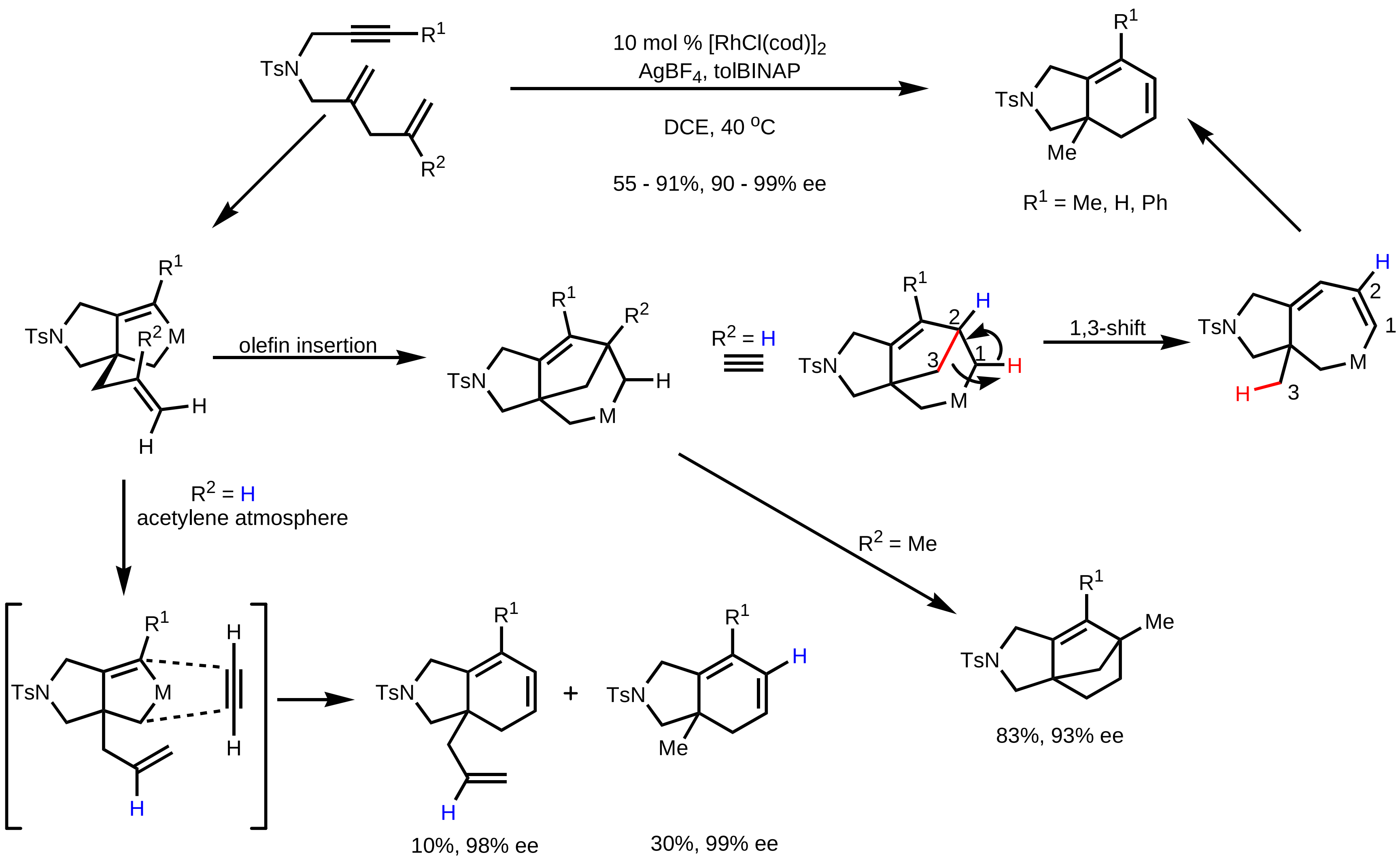




R = Me: 83%4/1 (92% / 95% ee)
R = H: 63% 7/1 (98% / 97% ee)

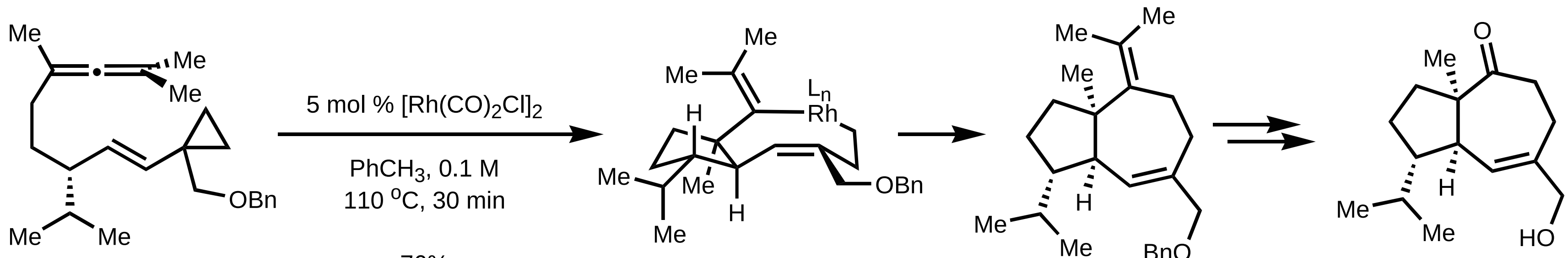
Shibata, T.; Arai, Y.; Tahara, Y. *Org. Lett.* **2005**, *7*, 4956.

1,3-Hydride Shift



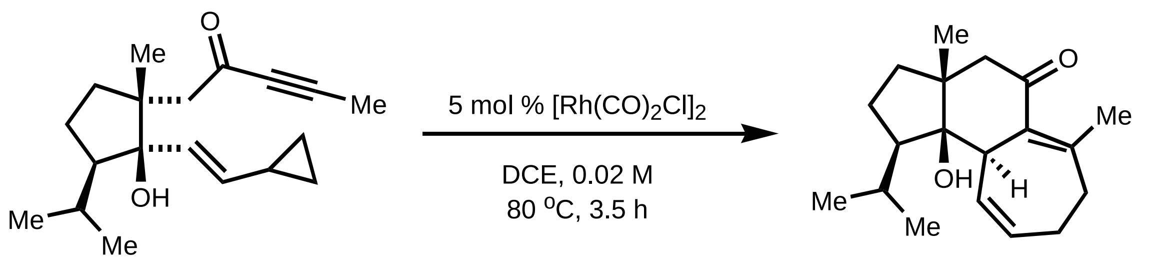
Shibata, T.; Tahara, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11766.

[5 + 2] Cycloaddition in Natural Products Synthesis



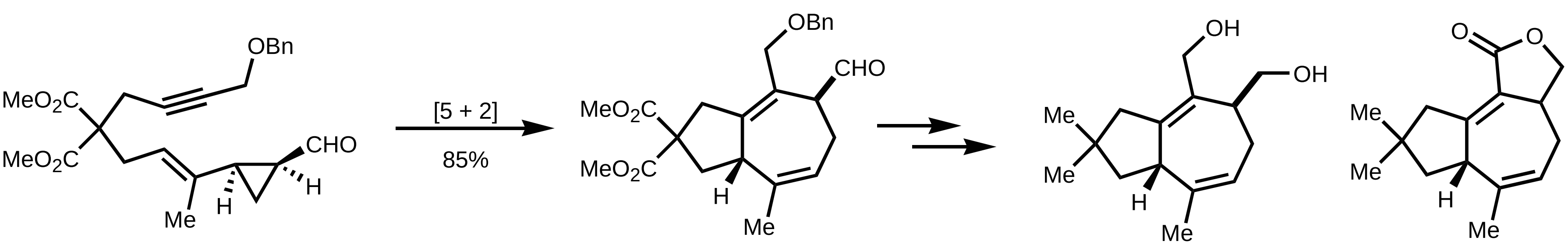
(+)-aphanamol

Wender, P. A.; Zhang, L. *Org. Lett.*, **2000**, *2*, 2323.



tricyclic core of cyathane diterpenes

Wender, P. A.; Bi, C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105.



Ashfield, B. L.; Martin, S. F. *Org. Lett*. **2005**, *7*, 4536.

tremulenediol A

tremulenolide A