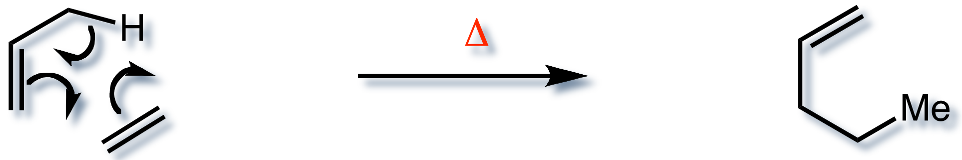
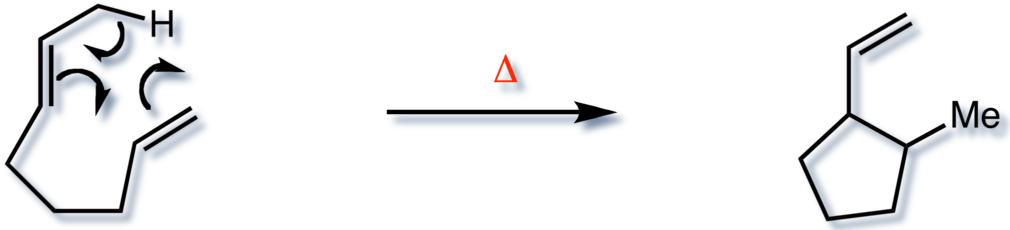
The Alder-Ene Reaction



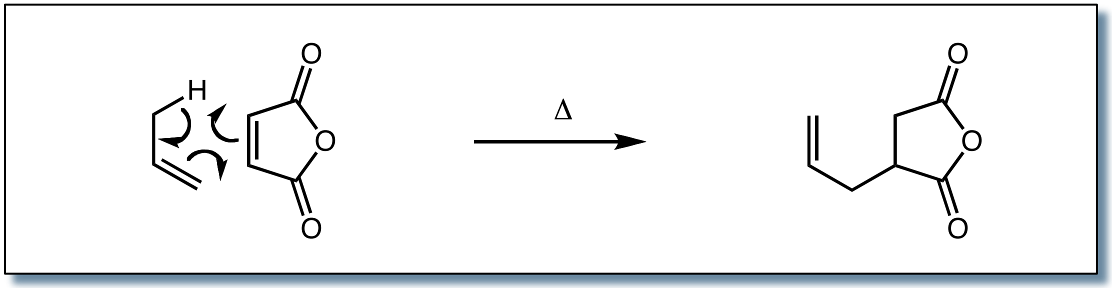


MacMillan Group Meeting
5-20-09
by
Anthony Casarez

Kurt Alder

- Born: Königshütte, Upper Silesia in southern Poland, on the 10th of July 1902.
- Education: Began chemistry at the University of Berlin in 1922 then finished his PhD in 1926 at the University of Kiel for work supervised by Otto Diels.
- Notable Award: Nobel Prize in Chemistry (1950) with Otto Diels for the 4 + 2 cycloaddition (Diels-Alder) discovered in 1928.

A Pericyclic Reaction



Alder, K.; Pascher, F.; Schmitz, A. *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 27.

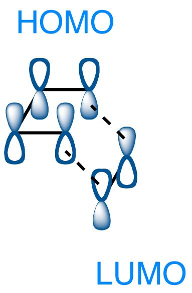
- Direct translated quote:

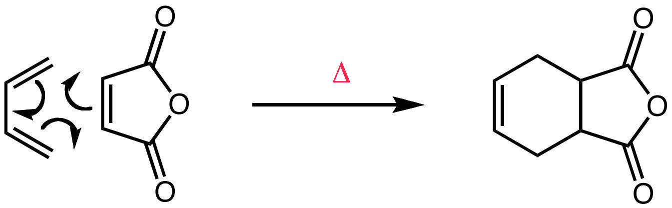
  "It is concluded that the addition occurs at the carbon atom adjacent to the double bond (ene). During the course of the reaction a hydrogen atom is detached and transposed to the region of the maleic acid anhydride (enophile)."

- Dr. Alder was unaware that his discovery was mechanistically very similar to the Diels-Alder which would later win him the Nobel Prize.

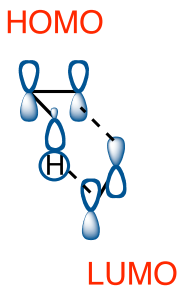
Mechanistic Comparison

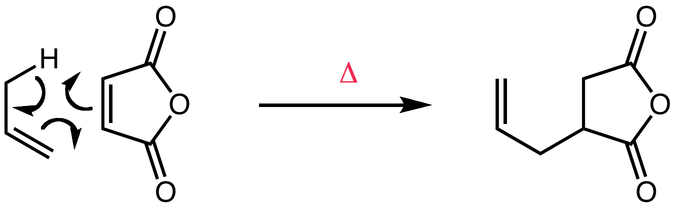
- Diels-Alder





- Alder-Ene

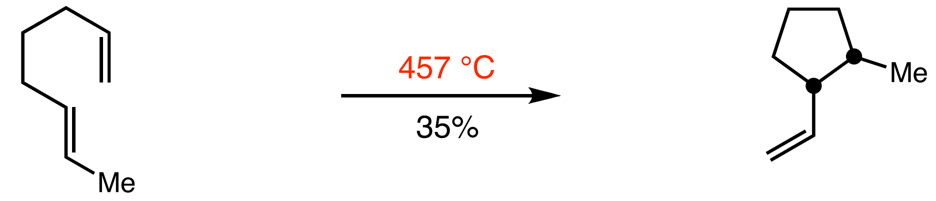


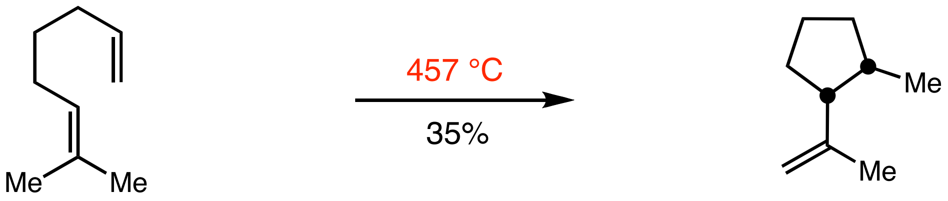


- Normally, both transformations occur with the HOMO of the diene/ene and the LUMO of the dienophile/enophile. **Lewis acids also work to catalyze the Alder-ene reaction.**

In the Beginning

- Thermal Alder-ene

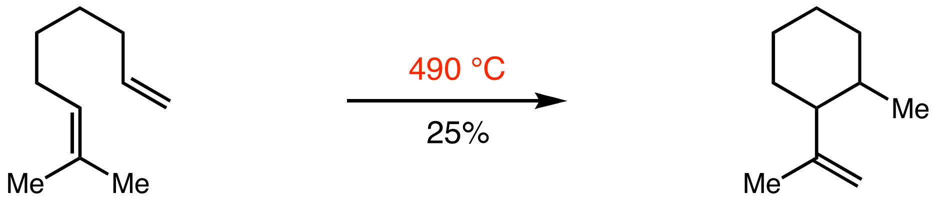


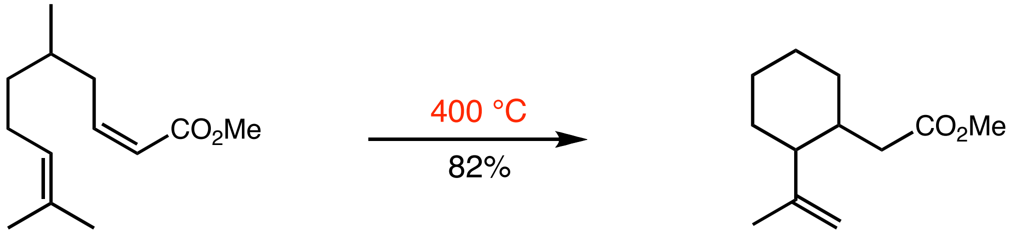


Huntsman et al. *J. Org. Chem.*, **1962**, *27*, 1983.

In the Beginning

- Thermal Alder-ene

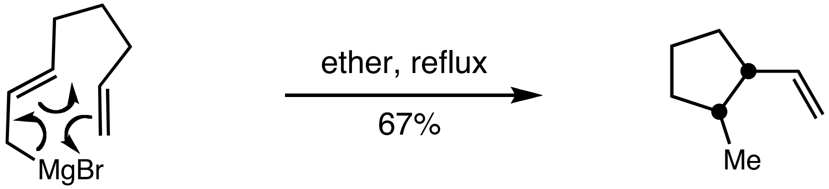




Huntsman et al. *J. Org. Chem.*, **1962**, *27*, 1983.

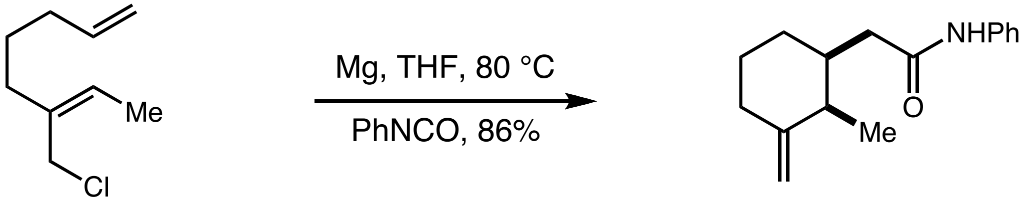
The Metallo-Ene

- Type I



Felkin et al. *Tetrahedron Lett.*, **1972**, *22*, 2285.

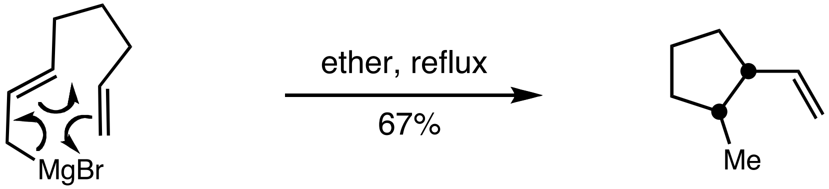
- Type II



Oppolzer et al. *J. Am. Chem. Soc.*, **1982**, *104*, 6476.

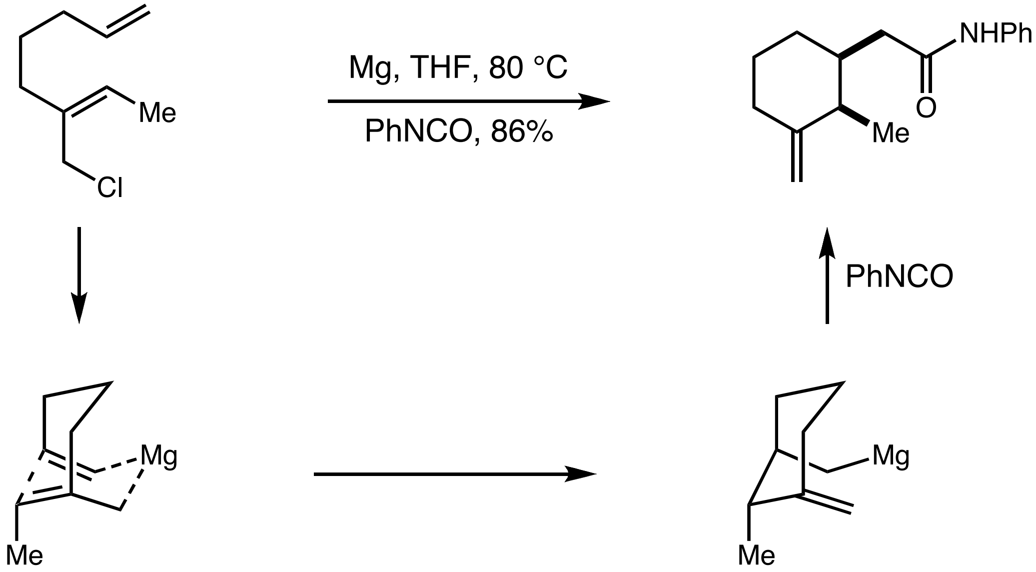
The Metallo-Ene

Type I



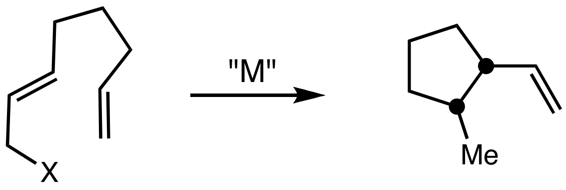
Felkin et al. *Tetrahedron Lett.*, **1972**, *22*, 2285.

Type II



The Metallo-Ene: M = Mg, Li, Zn

Type I

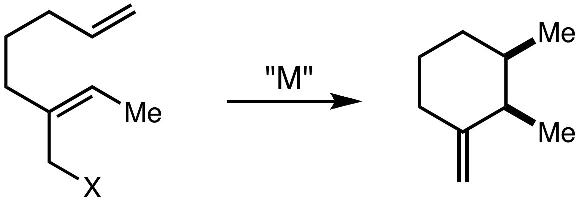


Ring formation: 5 > 6 >> 7

Selectivity: *syn* ring juncture

Heterocycles: problematic

Type II

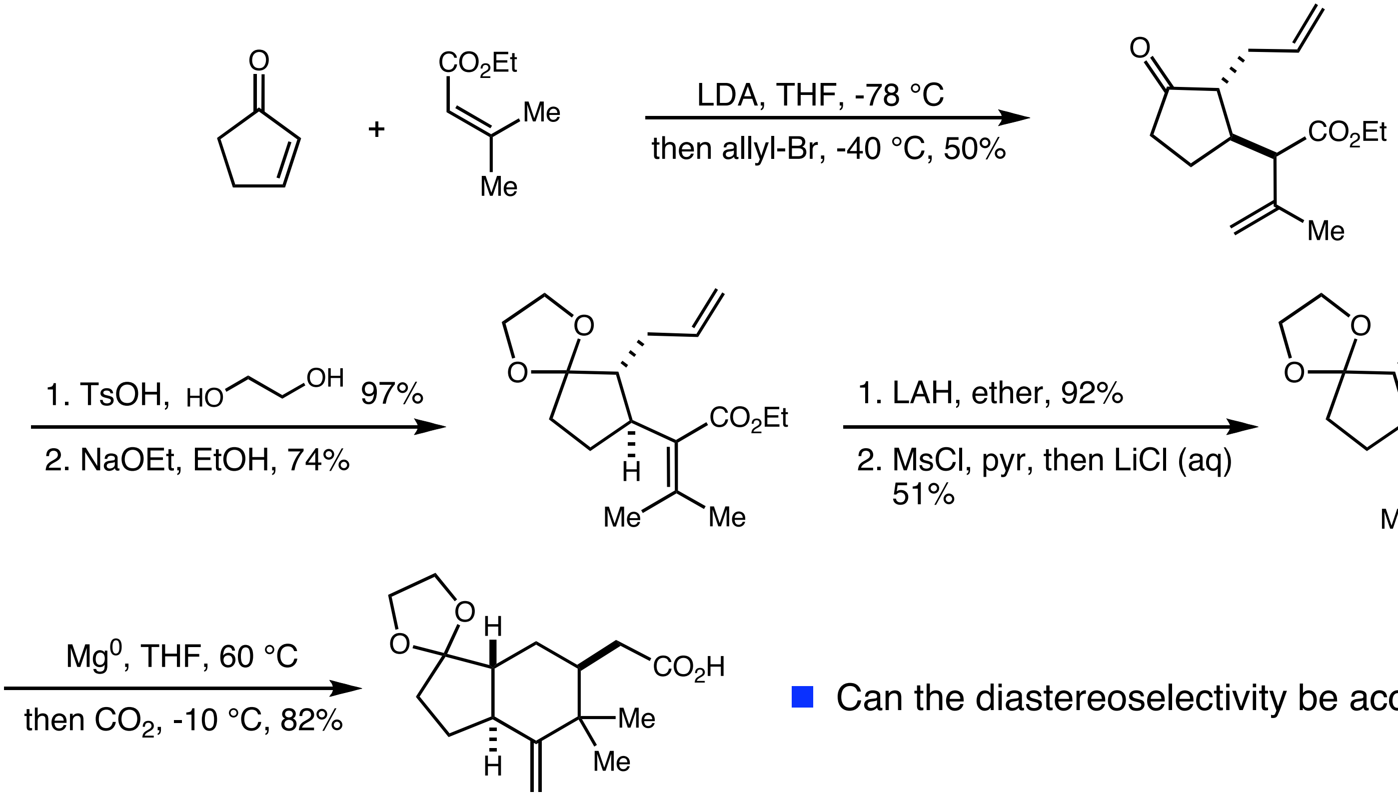


Ring formation: 6 > 5 ≈ 7 >> 8

Selectivity: *syn* ring juncture

Heterocycles: when M = Zn

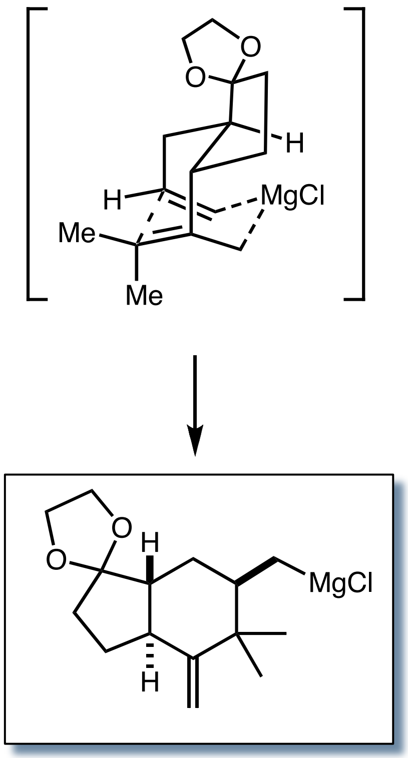
Total Synthesis of Khusimone



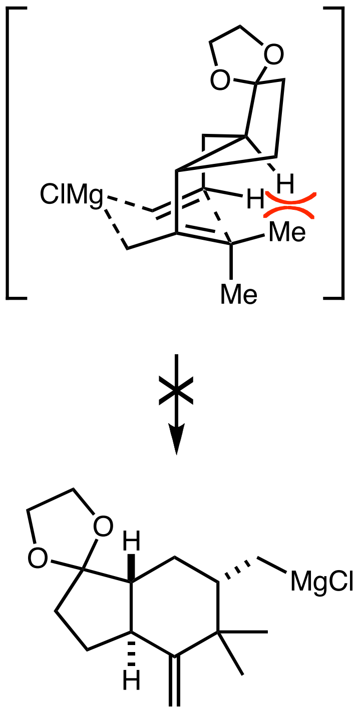
- Can the diastereoselectivity be accounted for?

Oppolzer et al. *J. Am. Chem. Soc.*, **1982**, *104*, 6478.

Transition State Analysis

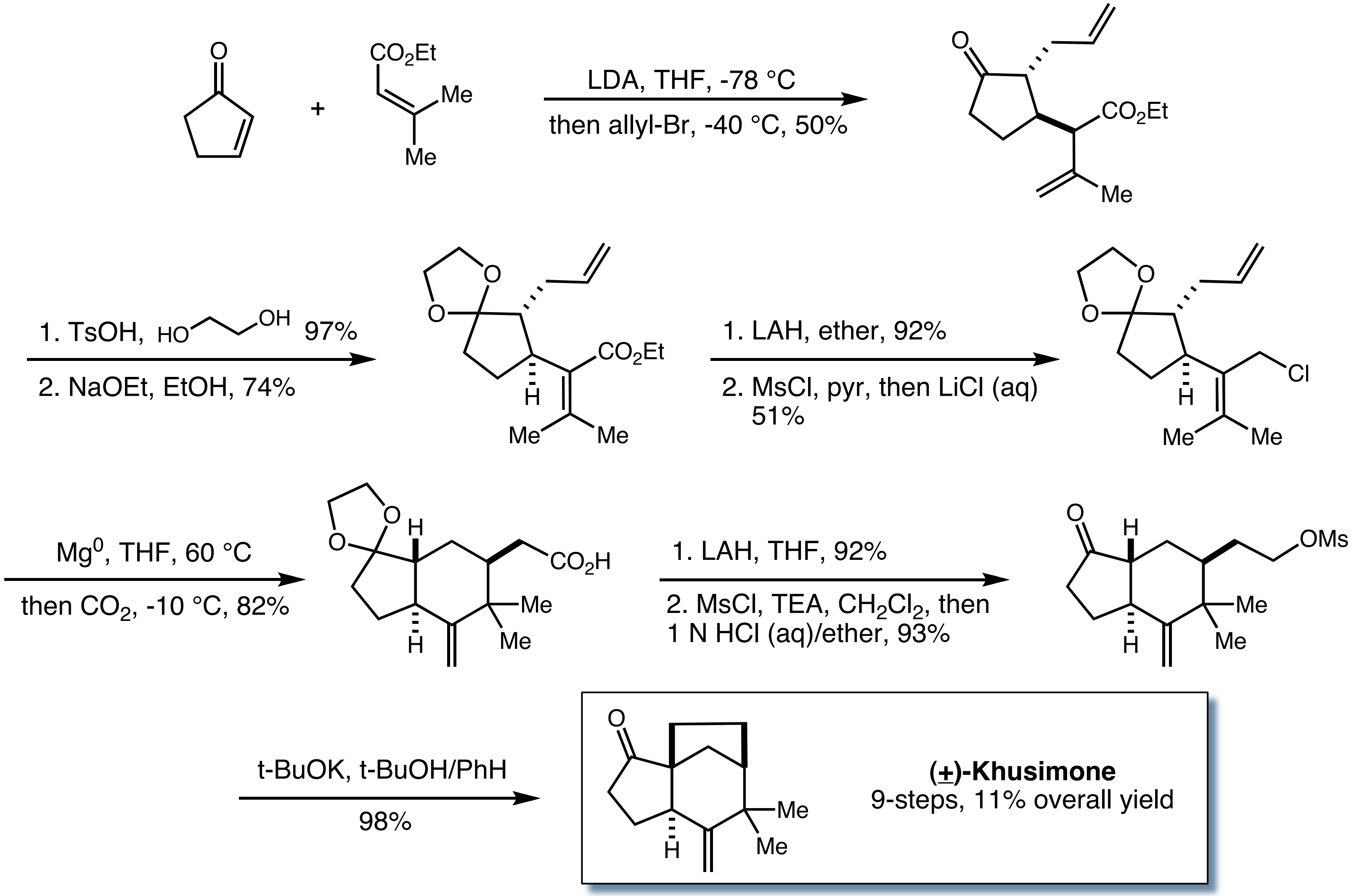


- Chair conformation experiences the least steric interaction



Oppolzer et al. *J. Am. Chem. Soc.*, **1982**, *104*, 6478.

Total Synthesis of Khusimone

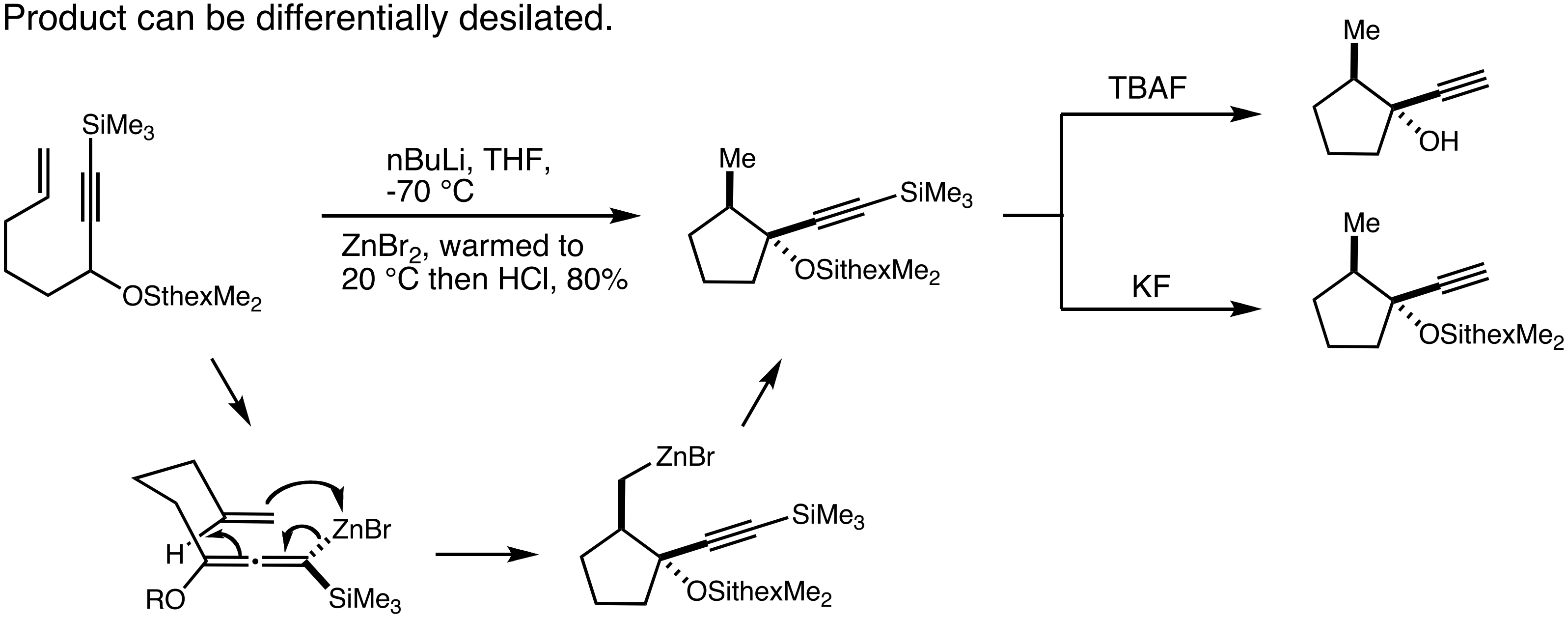


(±)-Khusimone
9-steps, 11% overall yield

Oppolzer et al. *J. Am. Chem. Soc.*, **1982**, *104*, 6478.

The Catalytic Metallo-Ene: M = Zn

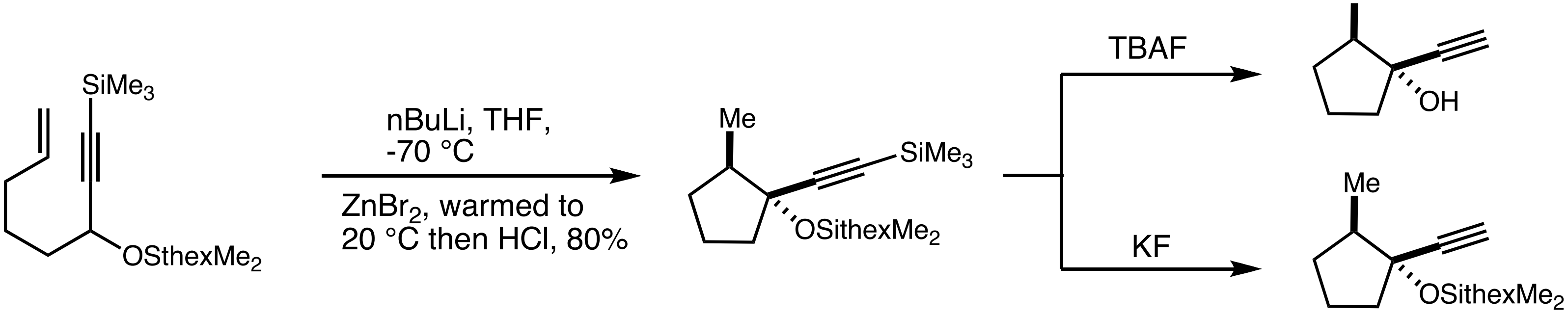
- Product can be differentially desilated.



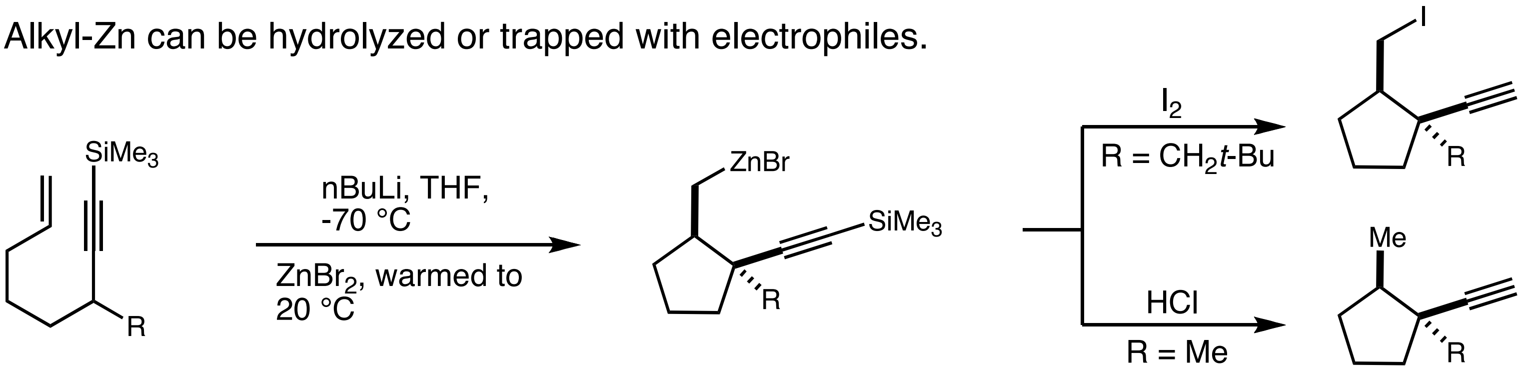
Marek et al. *J. Org. Chem.*, **1995**, *360*, 863.

The Catalytic Metallo-Ene: M = Zn

- Product can be differentially desilated.



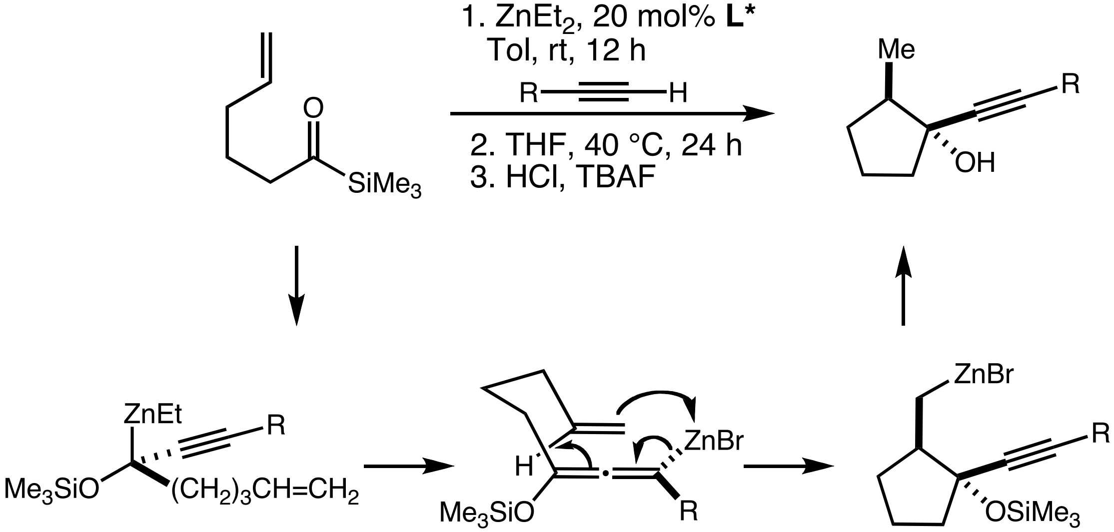
- Alkyl-Zn can be hydrolyzed or trapped with electrophiles.



- Can also be used directly in cross-coupling reactions.

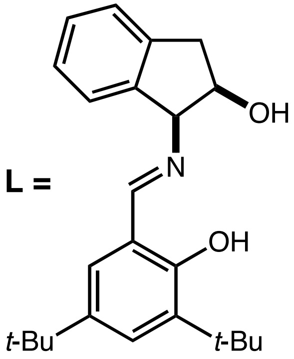
Marek et al. *J. Org. Chem.*, **1995**, *360*, 863.

Tandem Zn Promoted 1,2-Brook Rearrangement Metallo-Ene



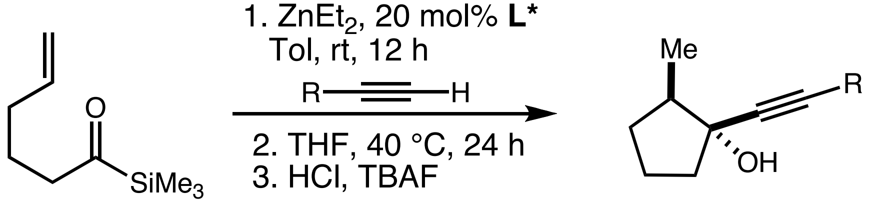
R = Ph, 92%, >99:1 dr, 81:19 er
R = Hex, 91%, >99:1 dr, 77:23 er

L =

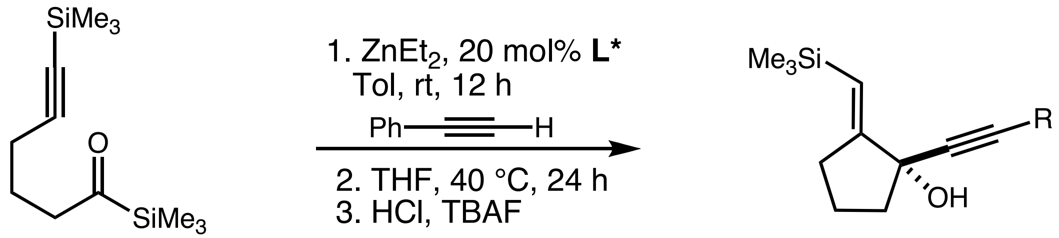


Marek et al. *Org. Lett.*, **2009**, ASAP.

Tandem Zn Promoted 1,2-Brook Rearrangement Metallo-Ene

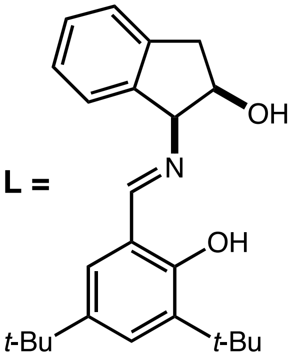


R = Ph, 92%, >99:1 dr, 81:19 er
R = Hex, 91%, >99:1 dr, 77:23 er



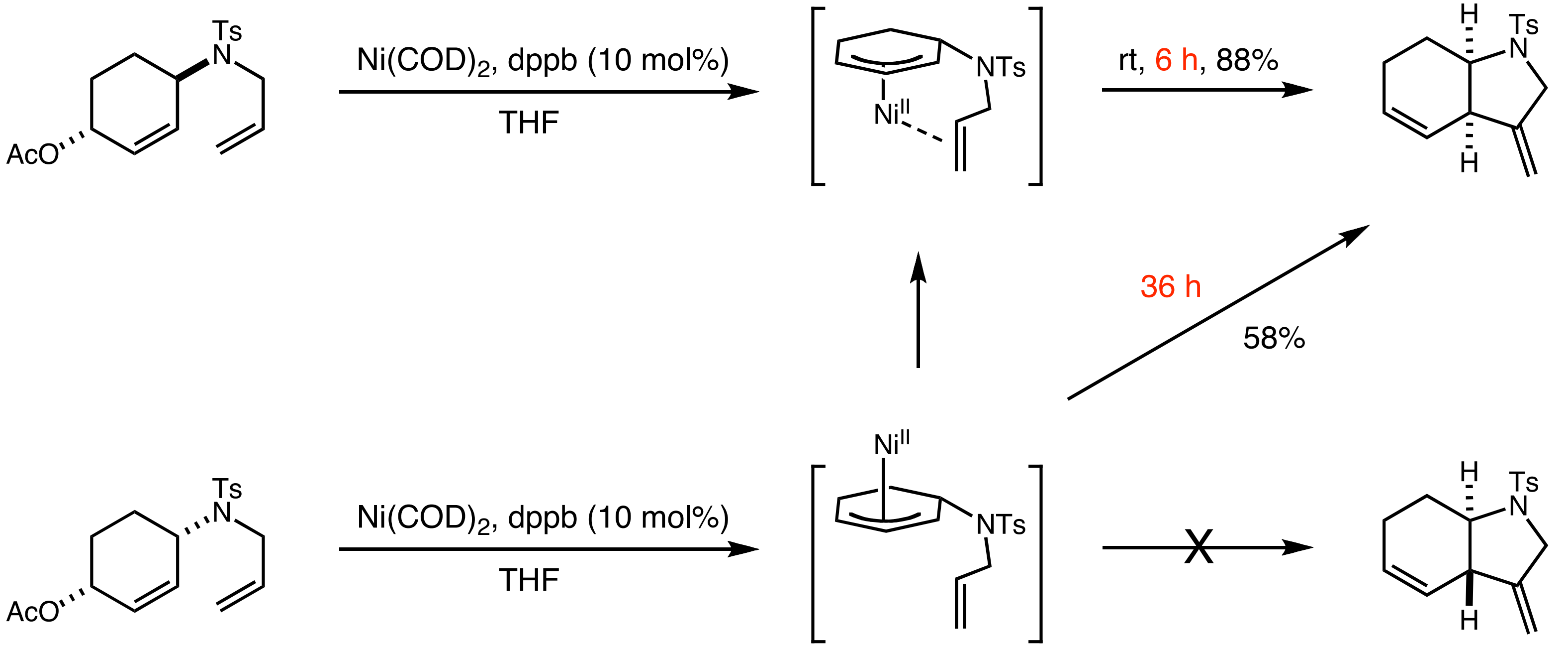
79%, 77:23 er

L =



Marek et al. *Org. Lett.*, **2009**, ASAP.

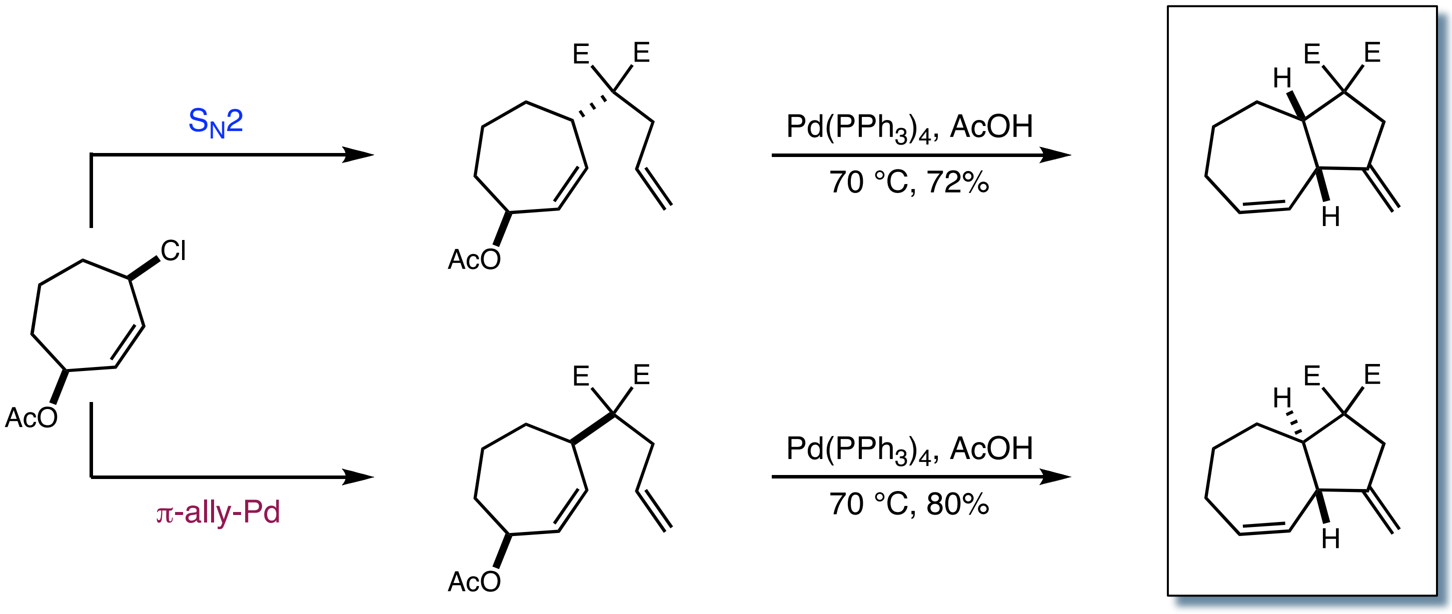
The Catalytic Metallo-Ene: M = Ni



- The same trends are observed for Pd.

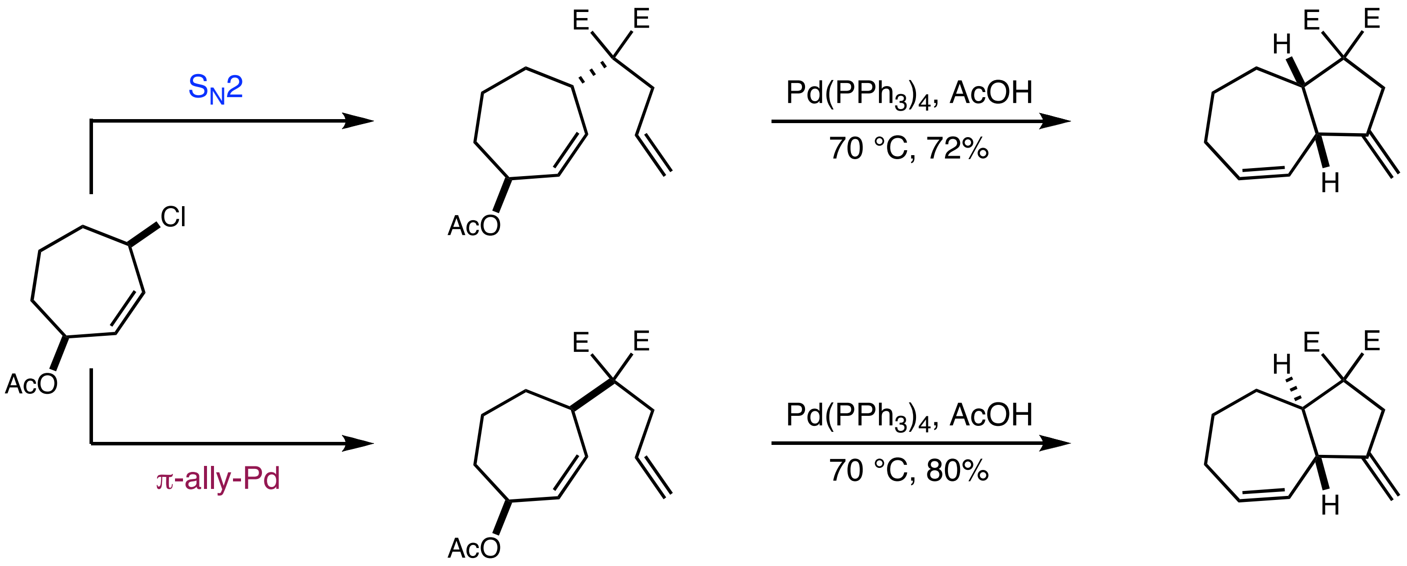
Oppolzer et al. *Tetrahedron Lett.*, **1988**, *29*, 6433.

The Catalytic Metallo-Ene: M = Pd

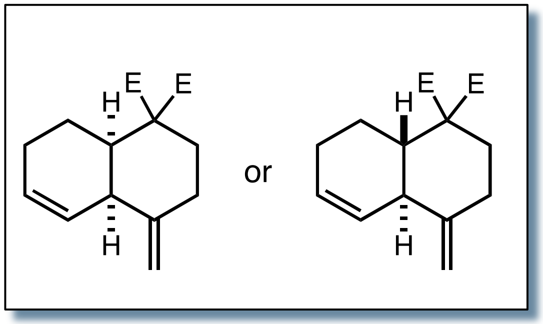


Oppolzer et al. *Tetrahedron Lett.*, **1988**, *29*, 4705.

The Catalytic Metallo-Ene: M = Pd



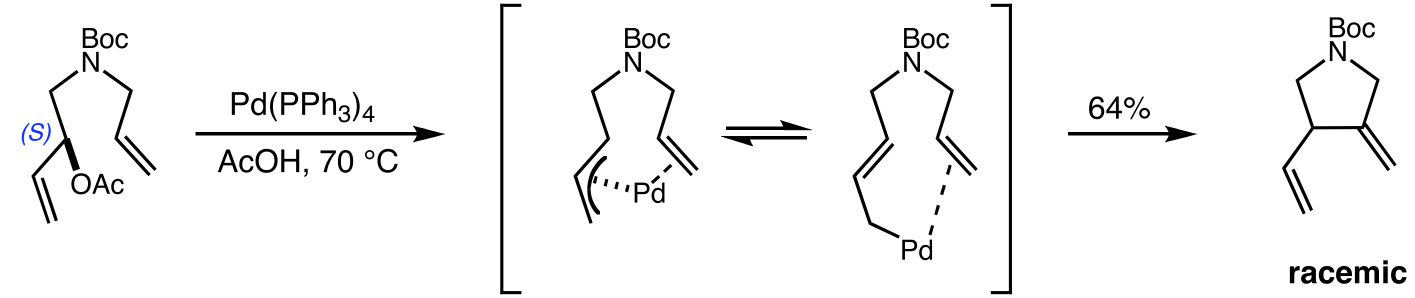
- Also works to form *cis* or *trans* decalin systems:



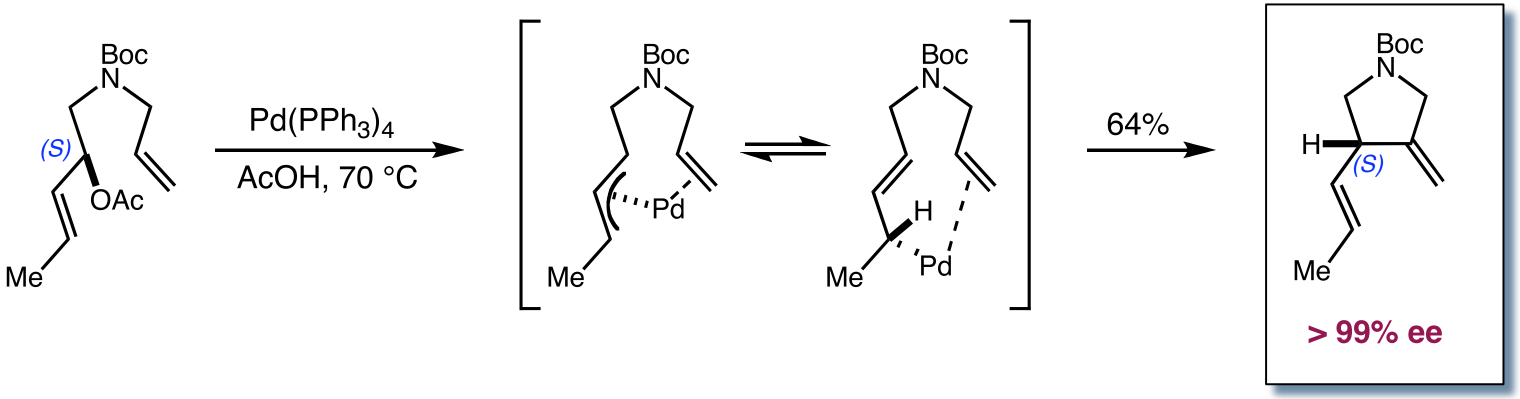
Oppolzer et al. *Tetrahedron Lett.*, **1988**, *29*, 4705.

Stereochemistry of Pd-Catalzed Metallo-Ene

- Terminal olefin results in loss of stereochemical integrity.



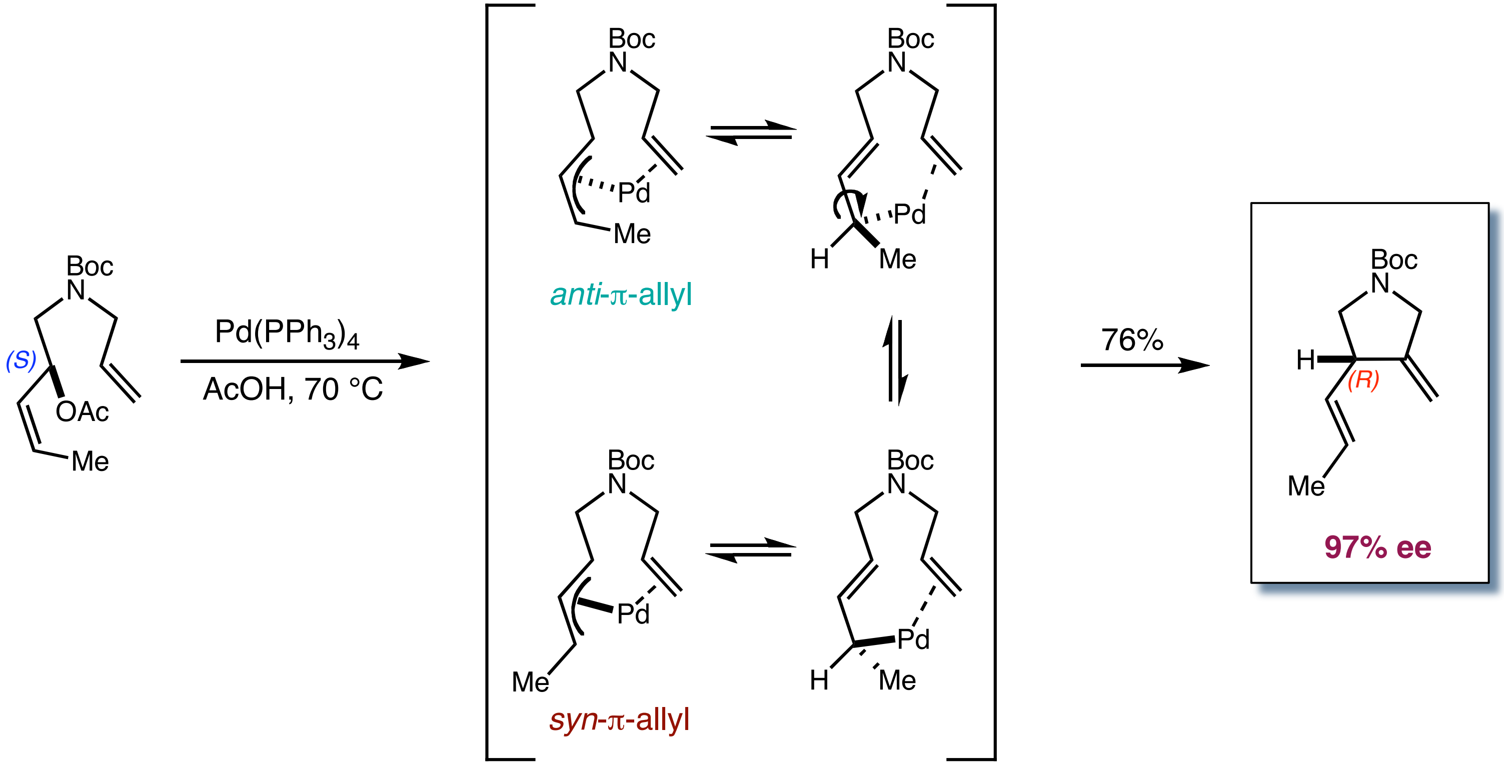
- *E*-alkene allows for transfer of stereochemistry.



Oppolzer, W. *Pure & Appl. Chem.* **1990**, *62*, 1941.

Stereochemistry of Pd-Catalzed Metallo-Ene

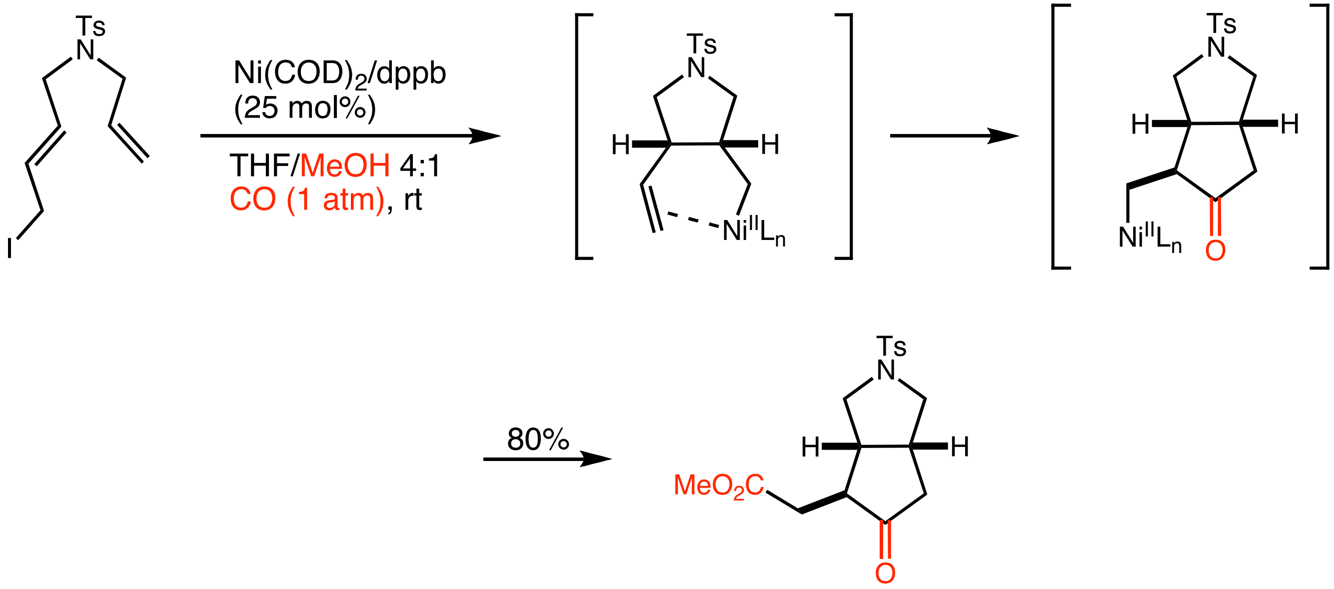
- Alkene geometry impacts expected outcome.



Oppolzer, W. *Pure & Appl. Chem.* **1990**, *62*, 1941.

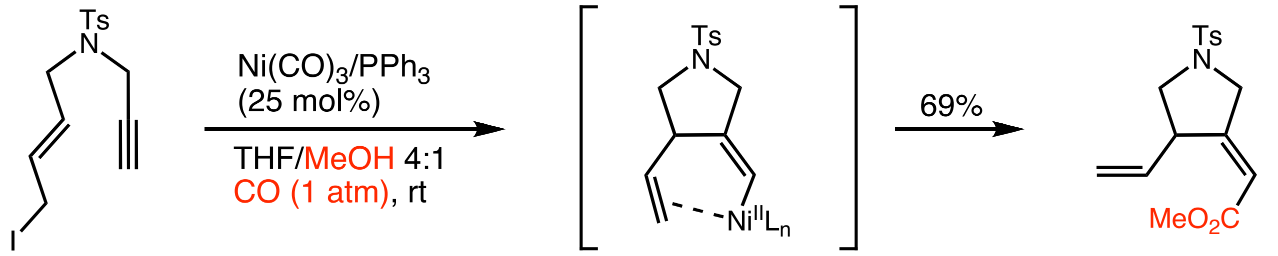
Doing More in One Step

- CO-insertion happens at both alkyl-Ni stages

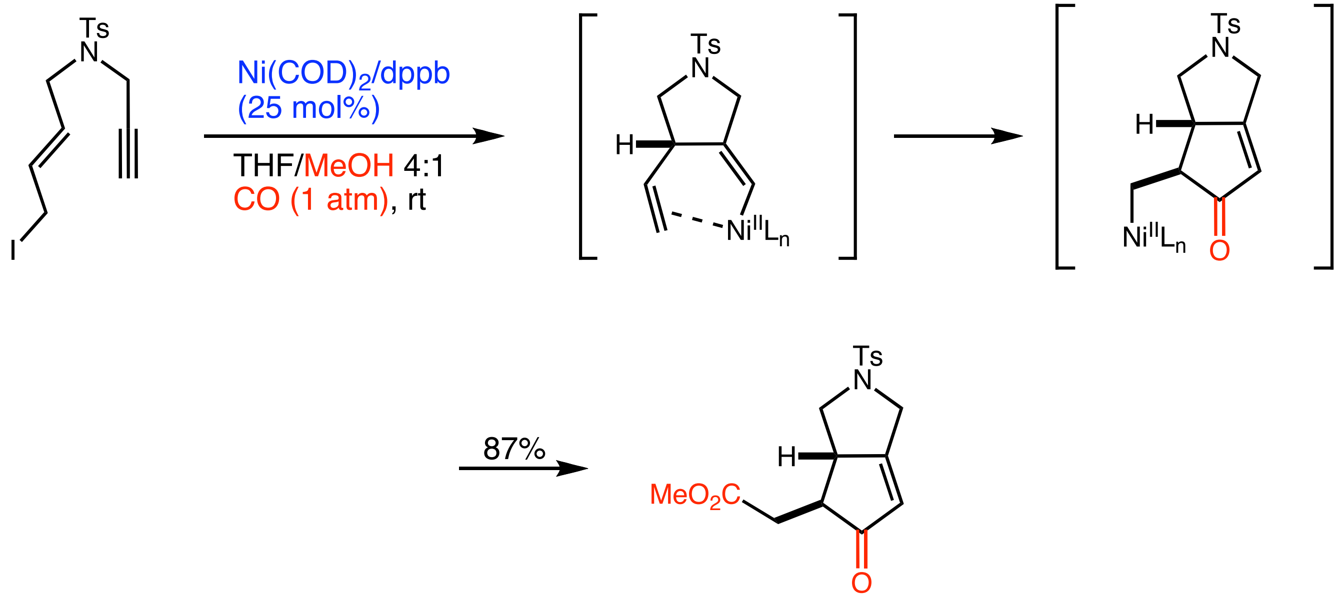


Oppolzer et al. *Tetrahedron Lett.* **1989**, *30*, 5883.

Doing More in One Step



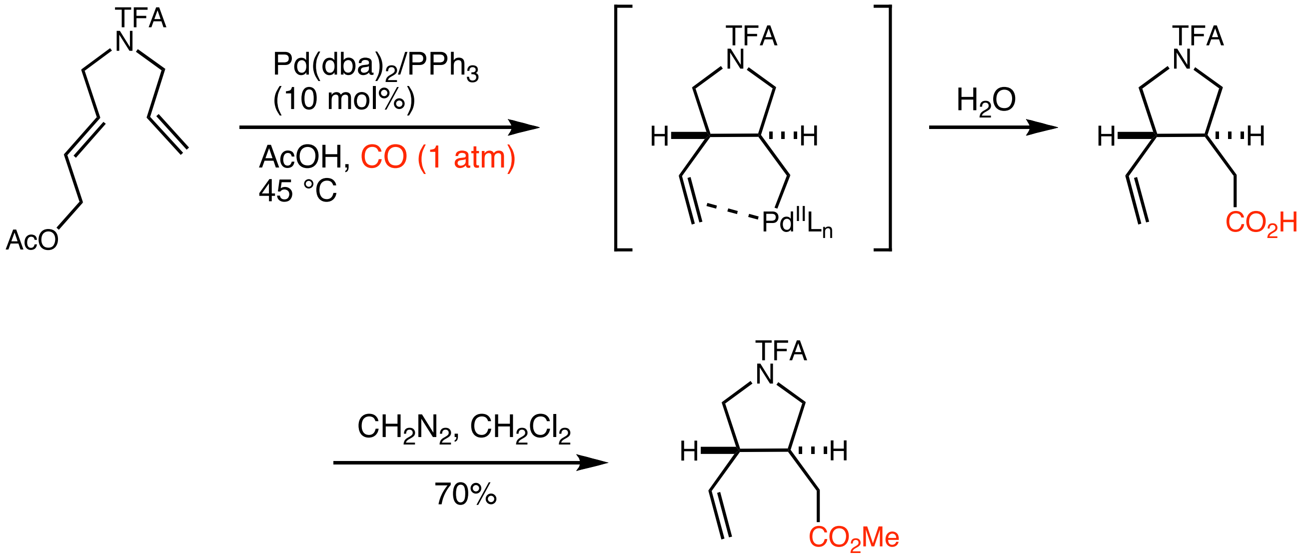
- Changing the ligand allows for control of CO-insertion.



Oppolzer et al. *Tetrahedron Lett.* **1989**, *30*, 5883.

Doing More in One Step

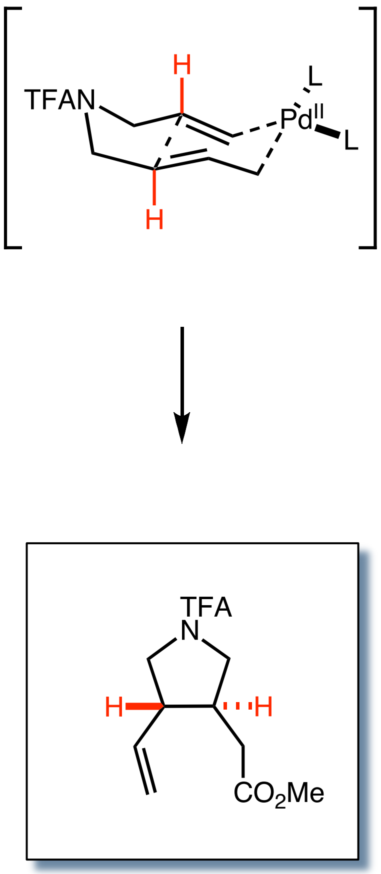
- Pd-affords the *trans*-ring juncture.



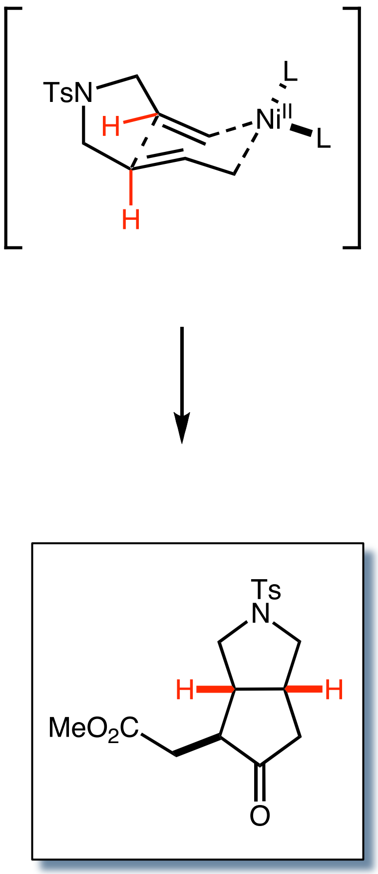
Oppolzer et al. *Tetrahedron Lett.* **1989**, *30*, 5883.

Models for Diastereoselectivity

- *Endo*

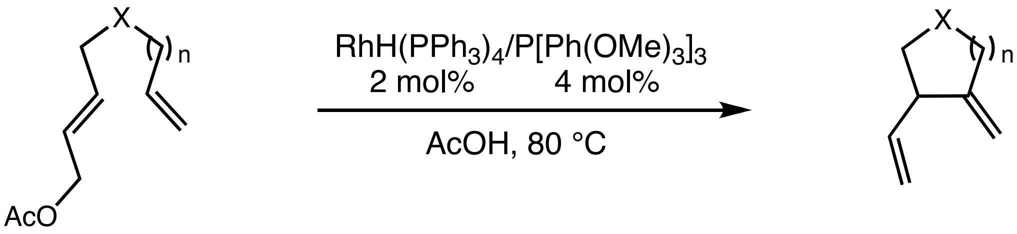


- *Exo*



Oppolzer et al. *Tetrahedron Lett*. **1990**, *31*, 1265.

The Catalytic Metallo-Ene: M = Rh

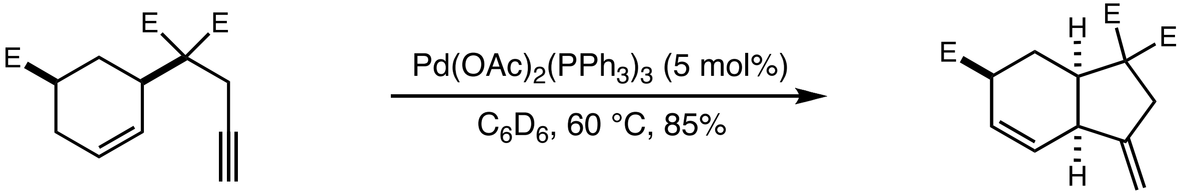


X	n	Yield (%)
NTs	1	80
NTFA	1	83
NCbz	1	63
$C(CO_2Me)_2$	1	75
$C(SO_2Ph)_2$	1	88
NTs	2	65
$C(SO_2Ph)_2$	2	55

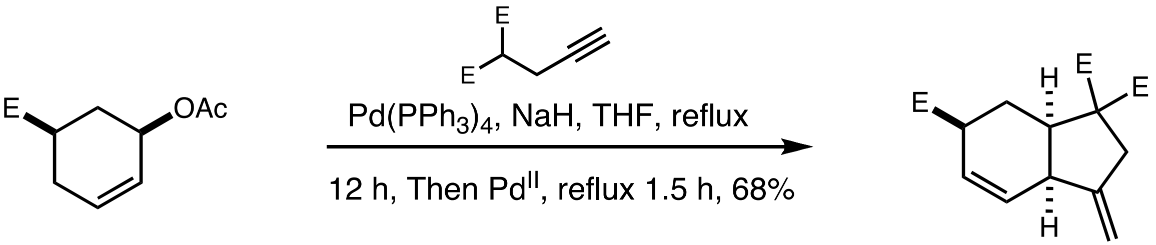
Oppolzer, W.; Furstner, A. *Helv. Chim. Acta* **1993**, *76*, 2329.

Pd^{II}-Catalyzed Formal Alder-Ene

- Pd^{II} is necessary for catalysis.



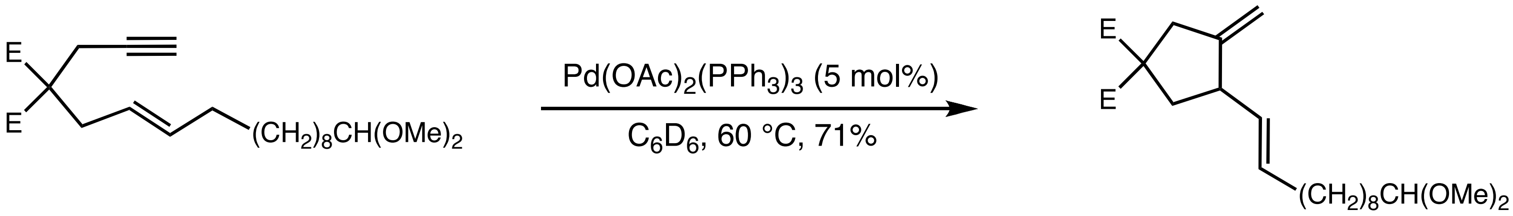
- Can be performed in one pot.



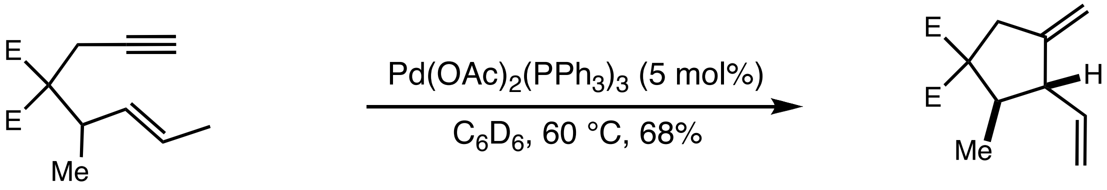
Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.

Pd^{II}-Catalyzed Formal Alder-Ene

- 1,4-Diene observed with no allylic substitution outside of pendant ring.

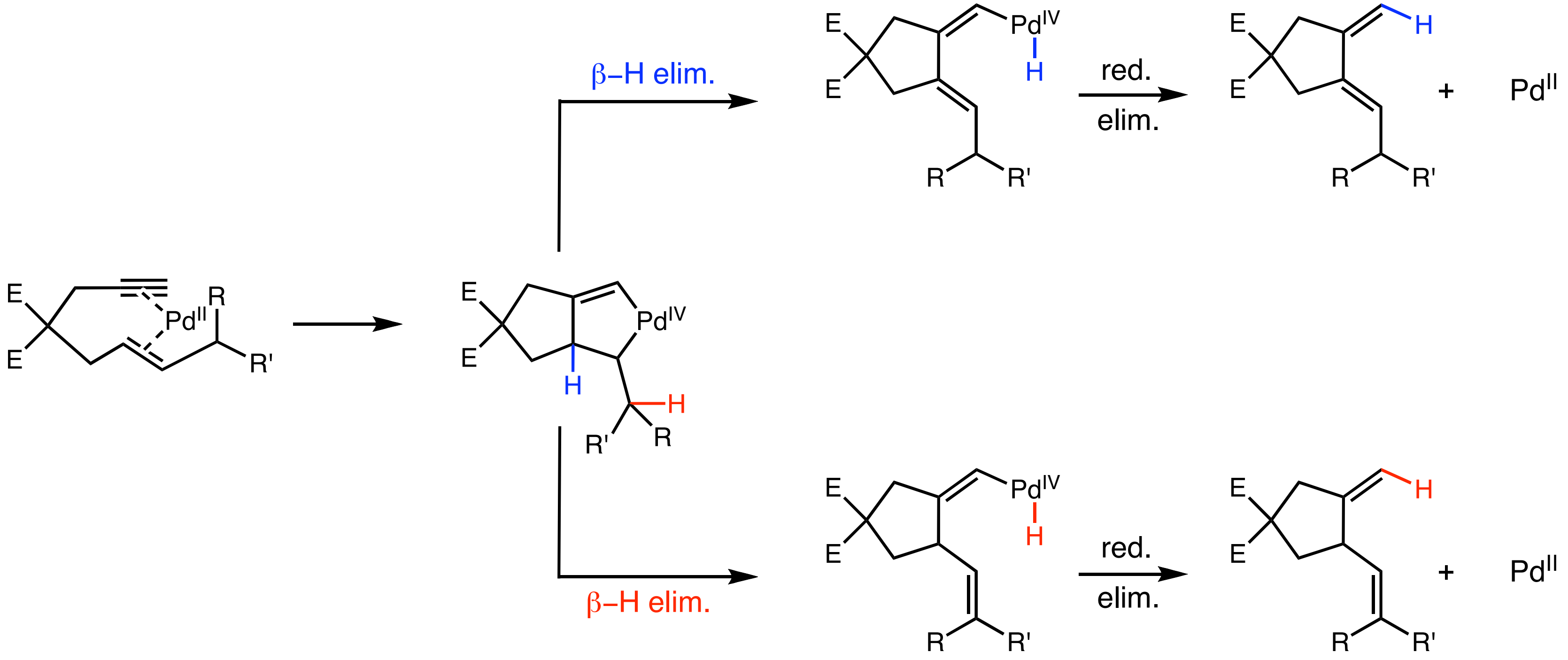


- A *trans*-relationship results when allylic substitution exists inside the pendant ring.



Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.

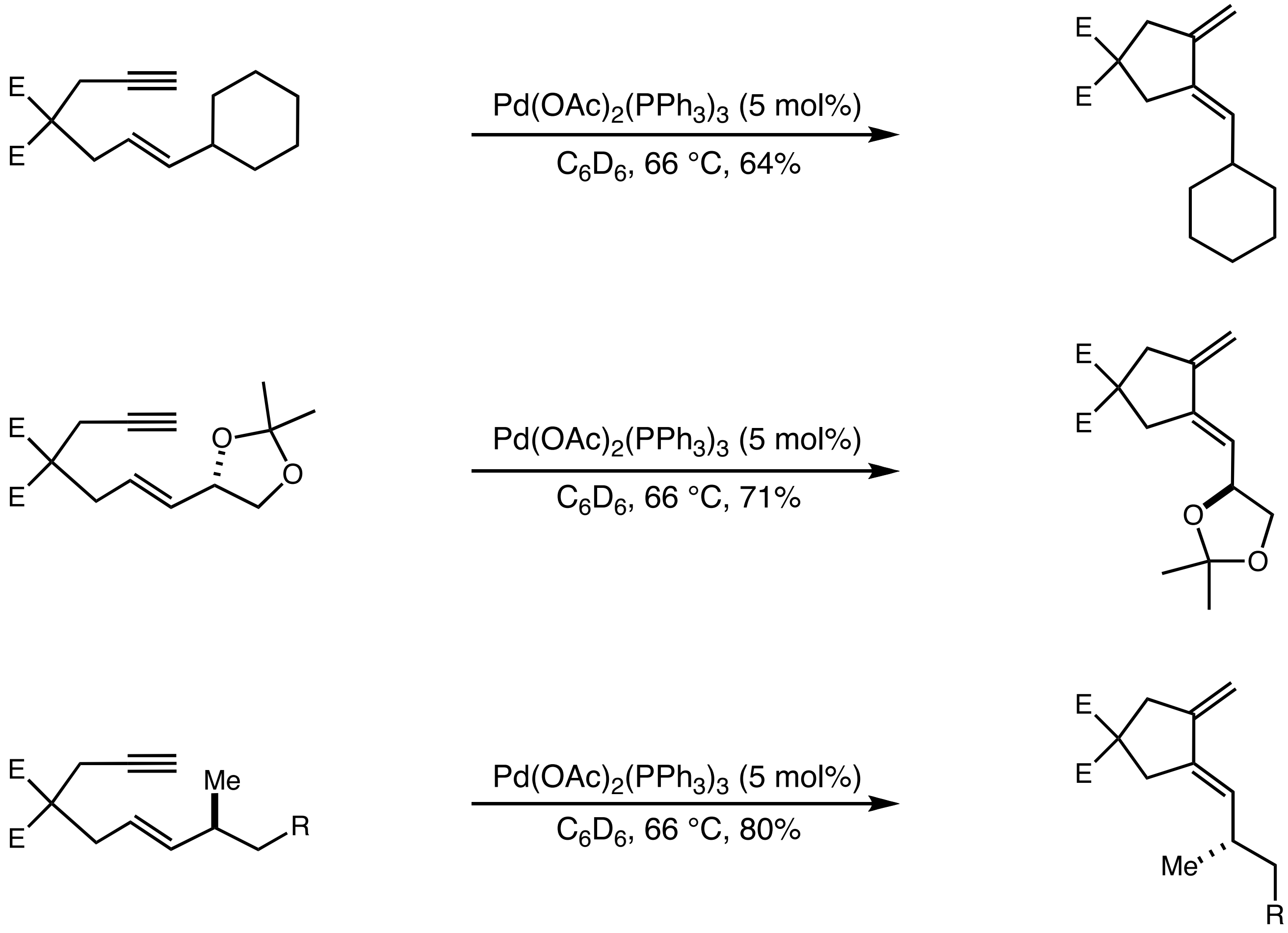
Mechanistic Proposal



Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.

Pd^{II}-Catalyzed Formal Alder-Ene

- 1,3-Diene observed with allylic substitution outside of pendant ring.



$Pd(OAc)_2(PPh_3)_3$ (5 mol%)

C_6D_6, 66 °C, 64%

$Pd(OAc)_2(PPh_3)_3$ (5 mol%)

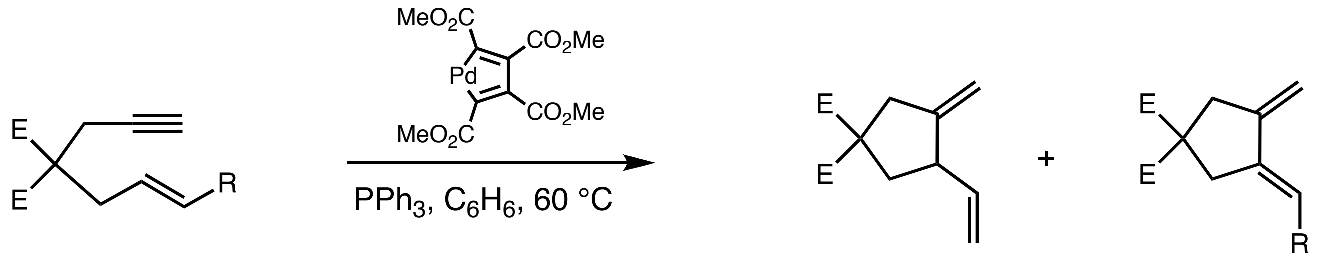
C_6D_6, 66 °C, 71%

$Pd(OAc)_2(PPh_3)_3$ (5 mol%)

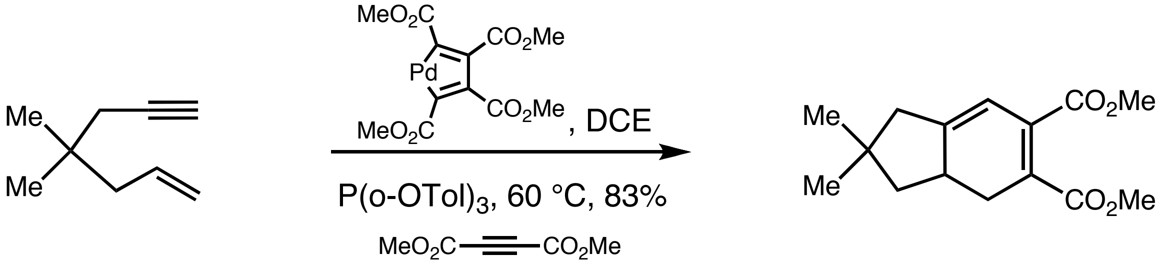
C_6D_6, 66 °C, 80%

Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.

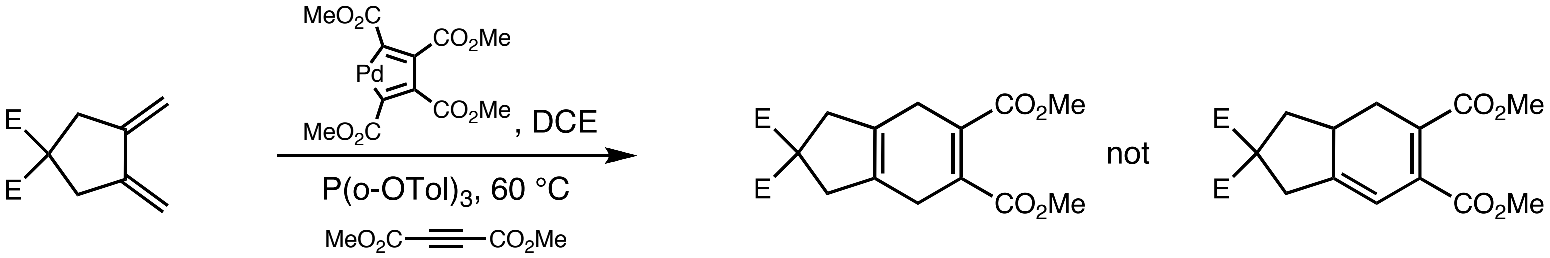
Mechanistic Support for Palladacycle Pathway



R = Me, 59%, 2 : 3
R = H, 54%

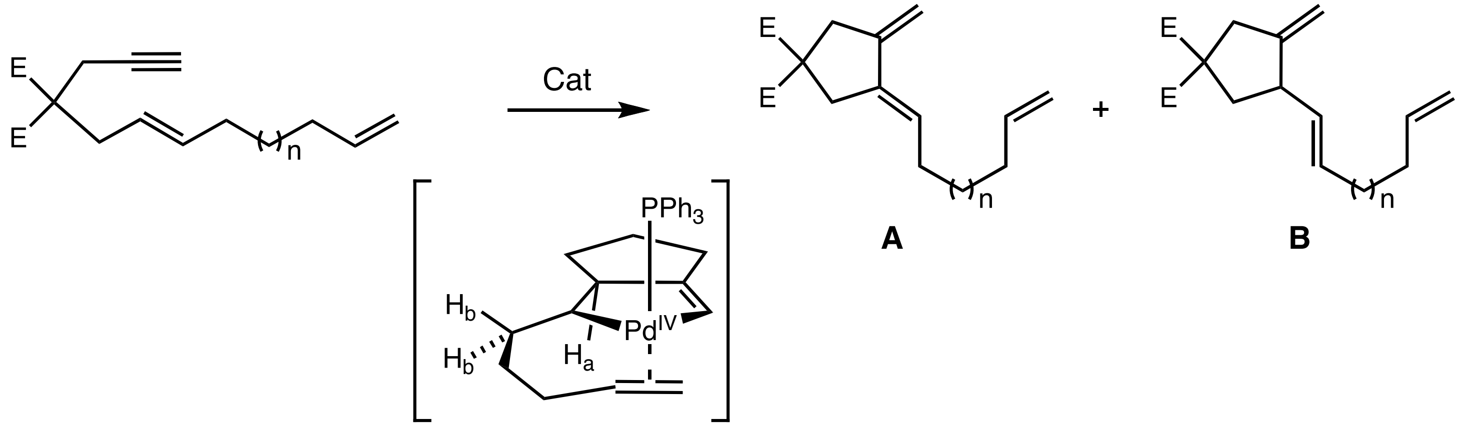


Crossover expmt with $EtO_2C{\equiv}CO_2Et$ shows only acetylene incorporation.



Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753.

Mechanistic Support for Palladacycle Pathway: Remote Binding

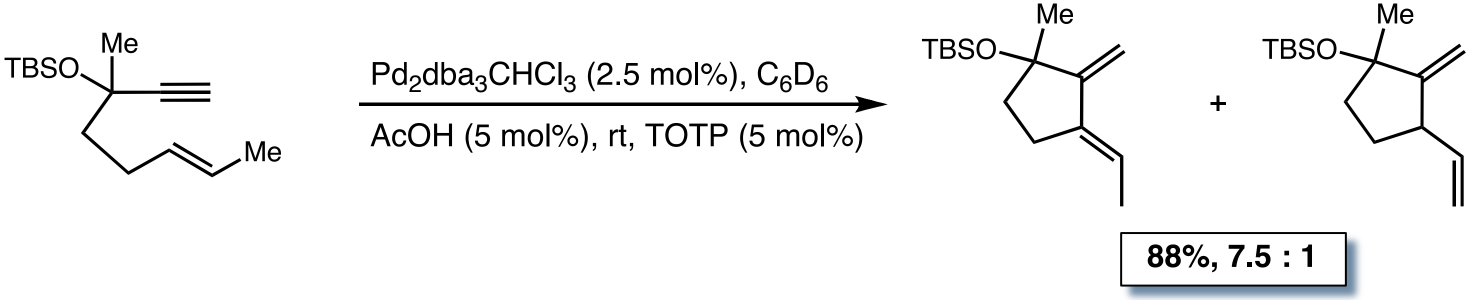


Cat	n = 1 **A:B**	Yield	n = 2 **A:B**	Yield
$Pd(OAc)_2$	21:1	76	1.1:1	75
$Pd(OAc)_2[P(o\text{-}Tol)_3]_2$	>20:1	nd	1:1.6	74
$Pd(OAc)_2(PPh_3)_2$	2.7:1	nd	1:4.6	81
$Pd(OAc)_2(PPh_3)_3$	1:2.3	24		

Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4255.

Pd^{II}-Catalyzed Formal Alder-Ene

- No reaction observed w/o AcOH



$Pd_2dba_3CHCl_3$ (2.5 mol%), C_6D_6

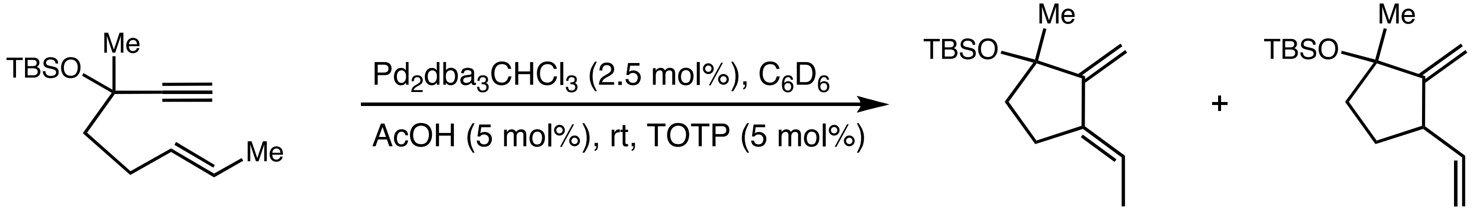
AcOH (5 mol%), rt, TOTP (5 mol%)

88%, 7.5 : 1

Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4268.

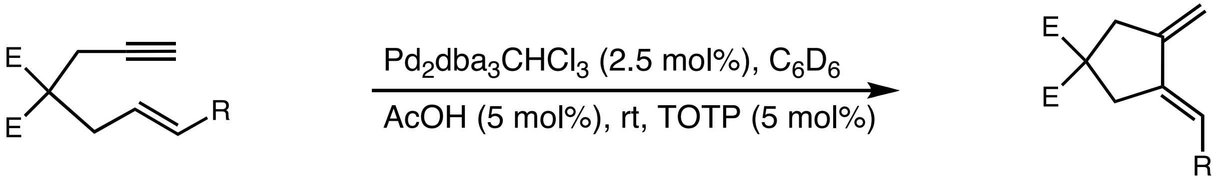
Pd^{II}-Catalyzed Formal Alder-Ene

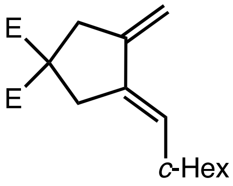
- No reaction observed w/o AcOH



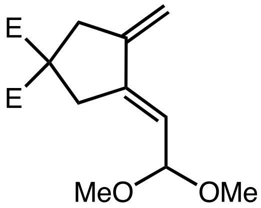
88%, 7.5 : 1

- Sensitive functional groups also tolerated

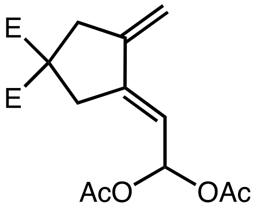




95%



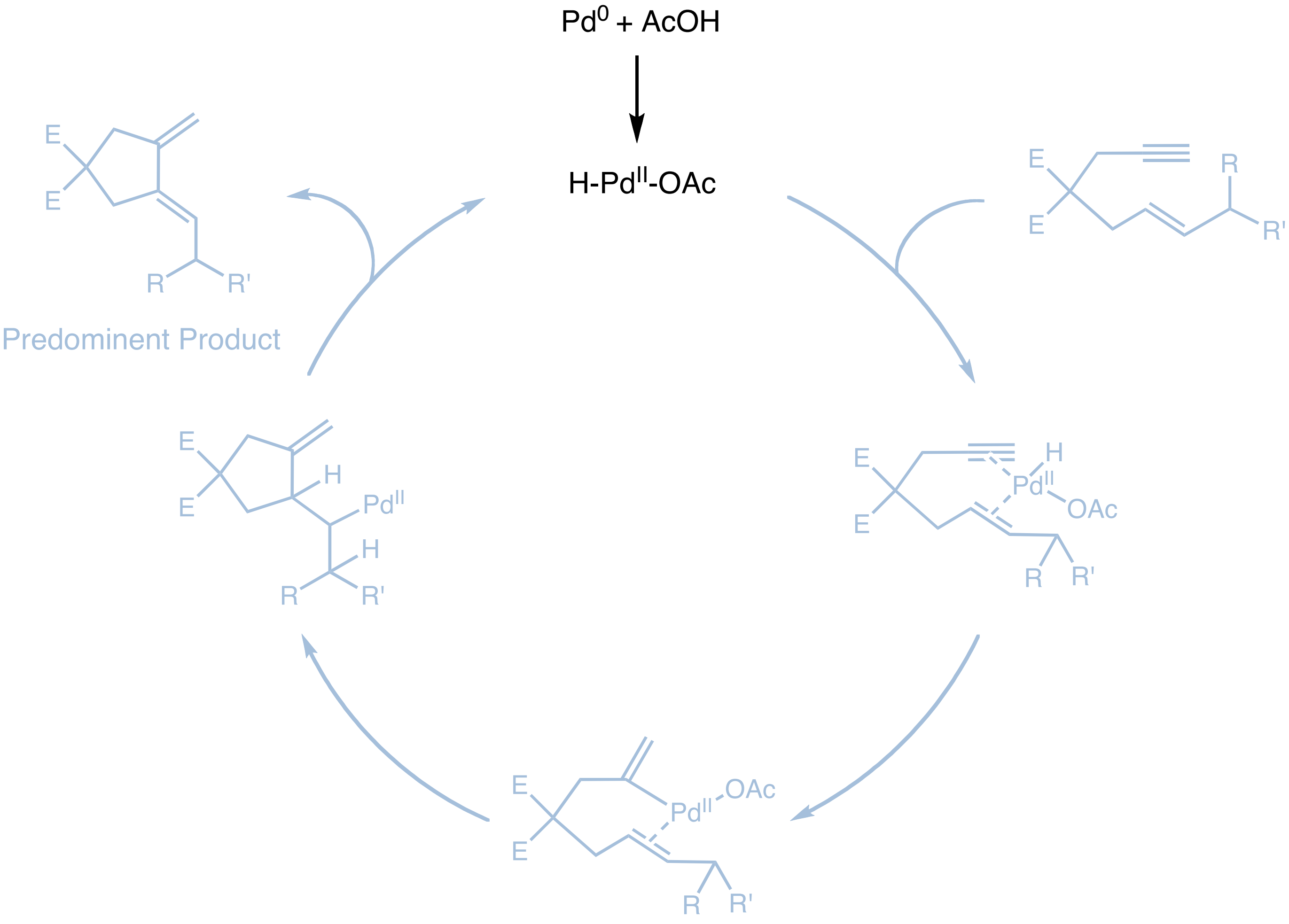
86%



75%

Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4268.

Mechanistic Proposal



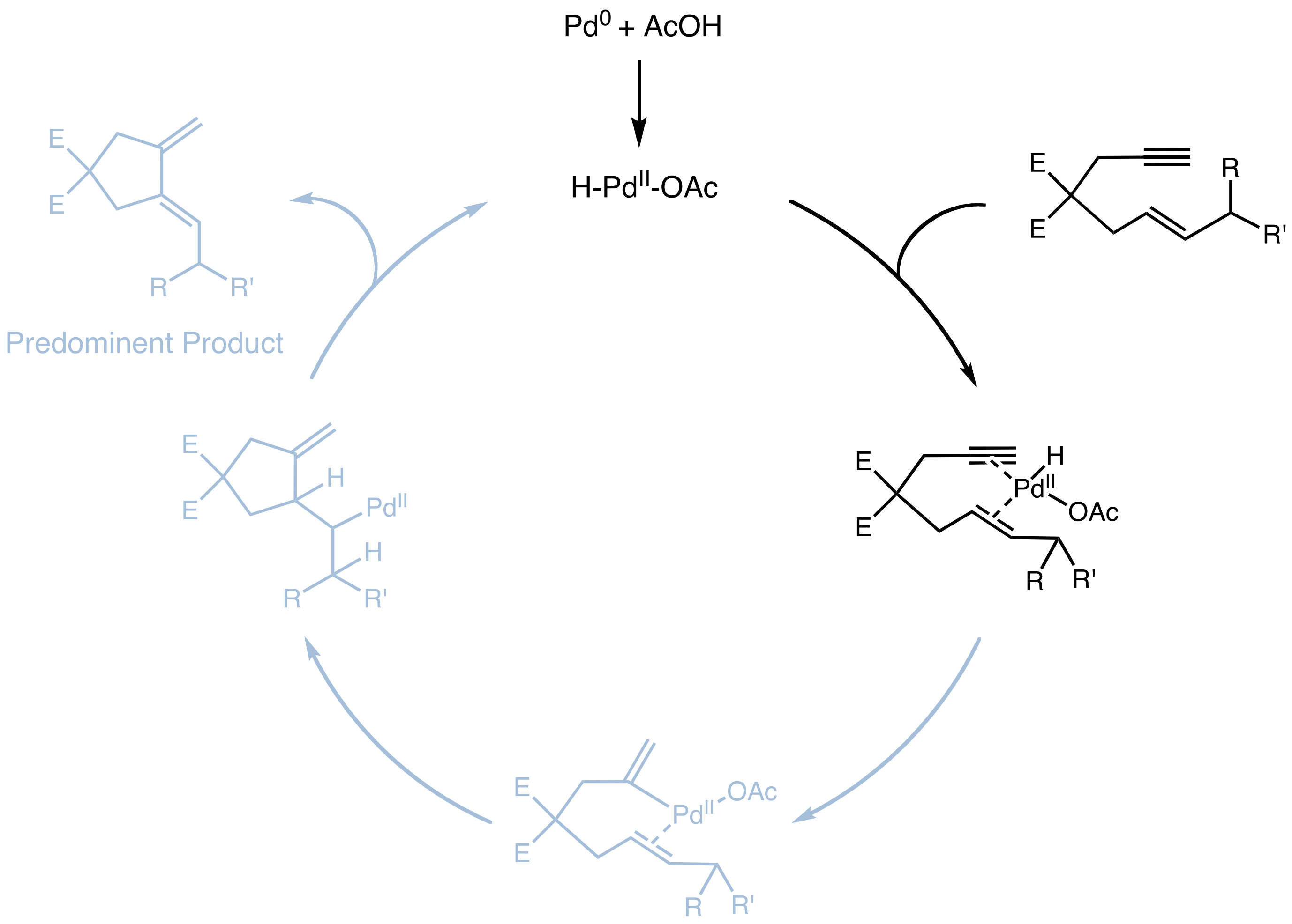
$Pd^0 + AcOH$

$H\text{-}Pd^{II}\text{-}OAc$

Predominent Product

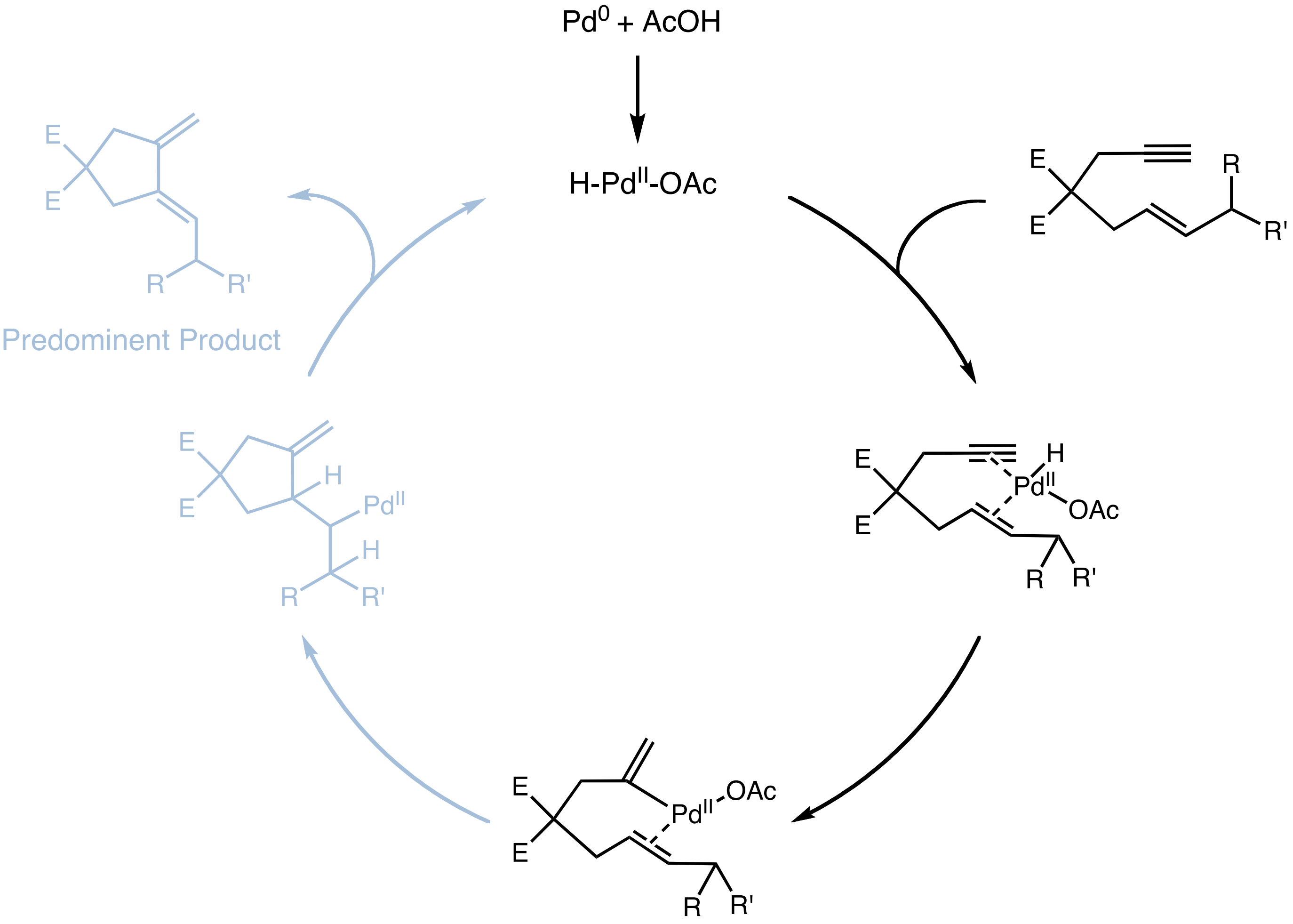
Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4268.

Mechanistic Proposal



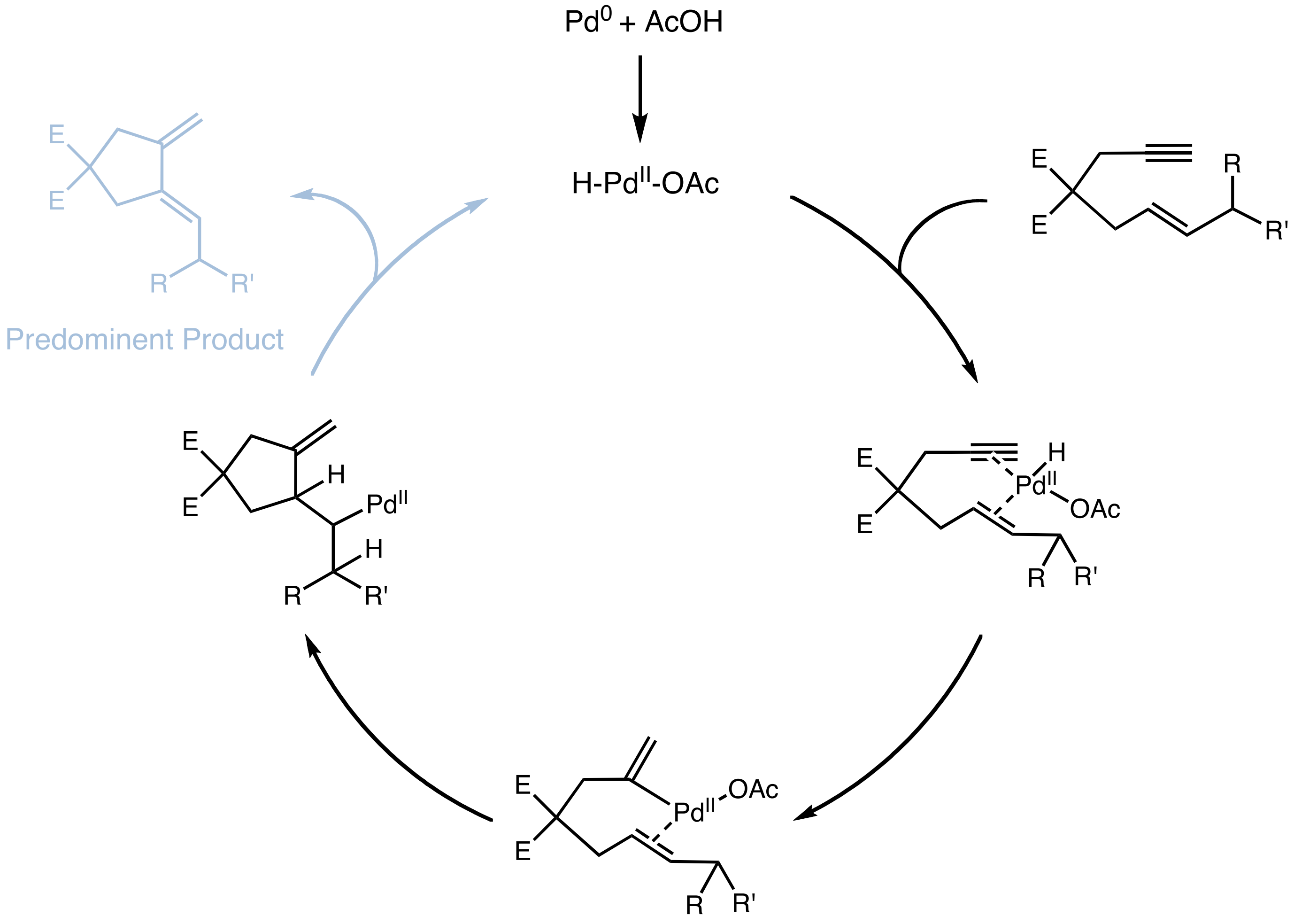
Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4268.

Mechanistic Proposal



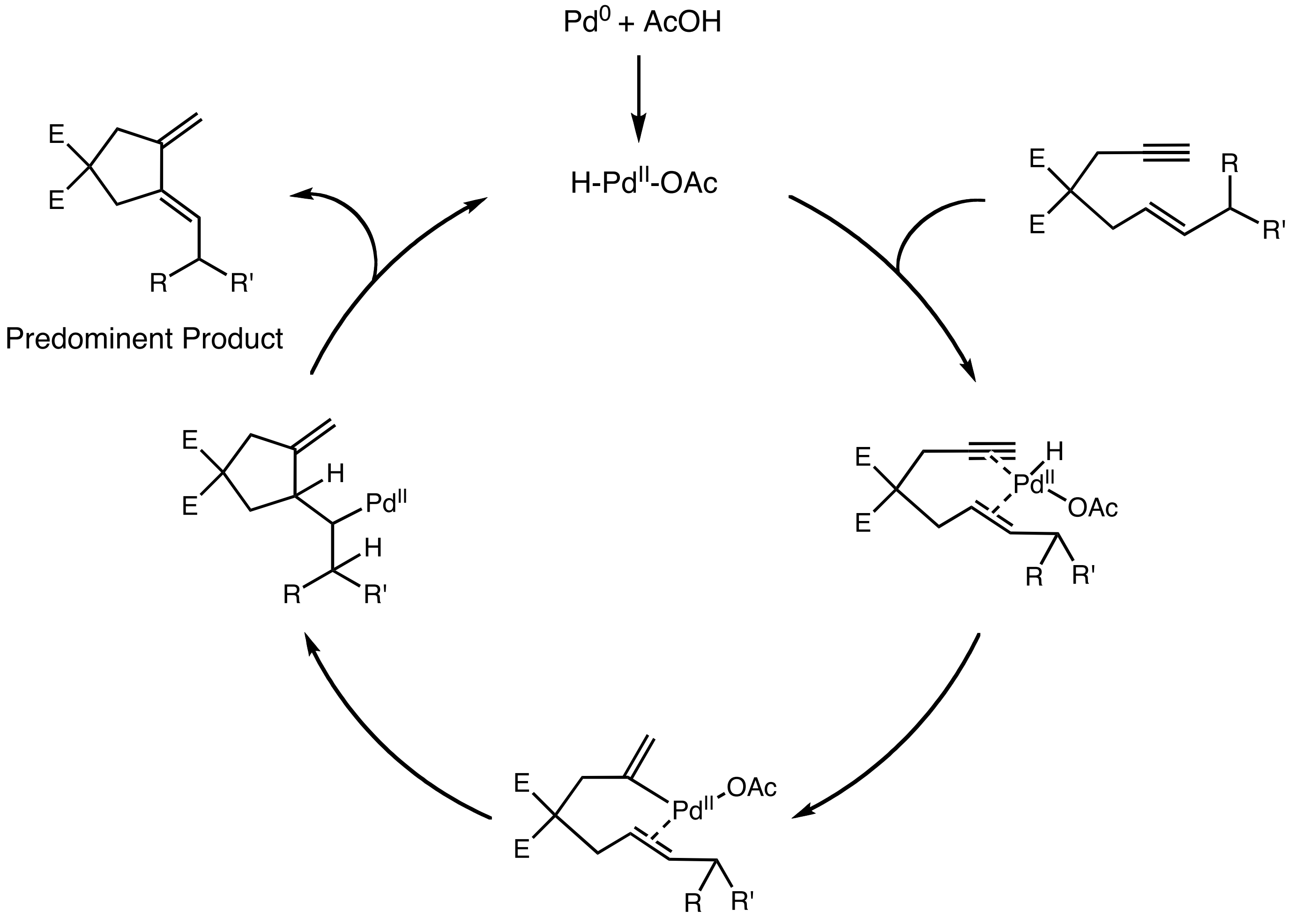
Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4268.

Mechanistic Proposal



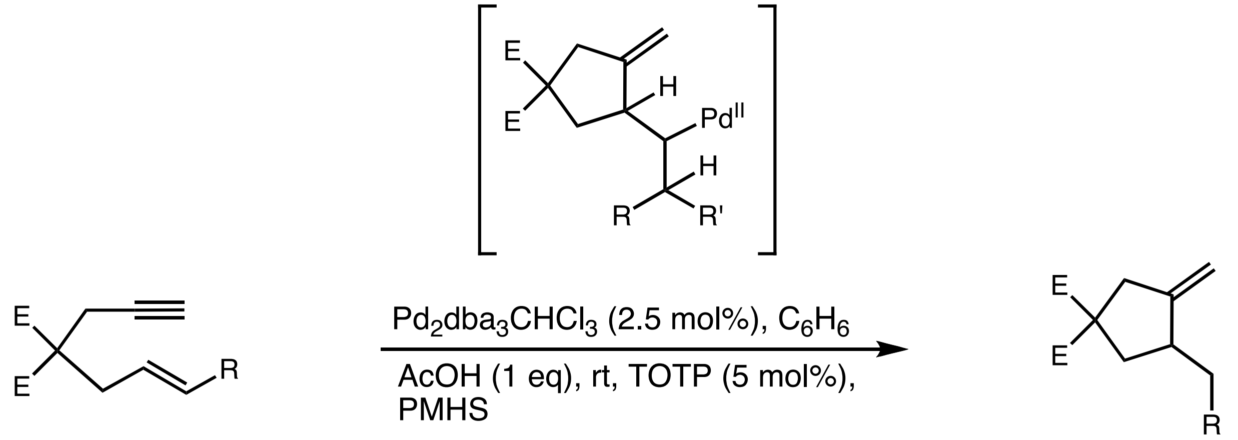
Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4268.

Mechanistic Proposal



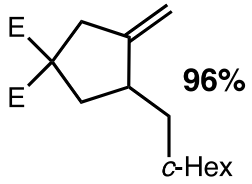
Trost et al *J. Am. Chem. Soc.* **1994**, *116*, 4268.

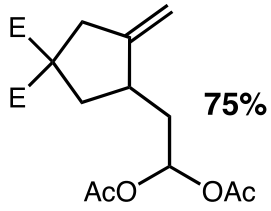
Mechanistic Support for Hydro-Palladation Pathway

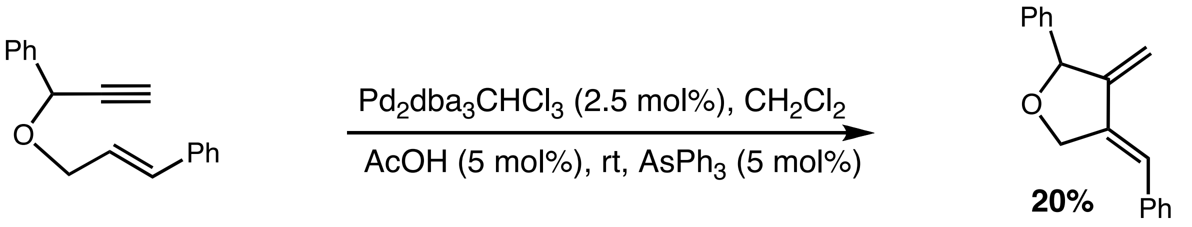


$Pd_2dba_3CHCl_3$ (2.5 mol%), C_6H_6

AcOH (1 eq), rt, TOTP (5 mol%), PMHS





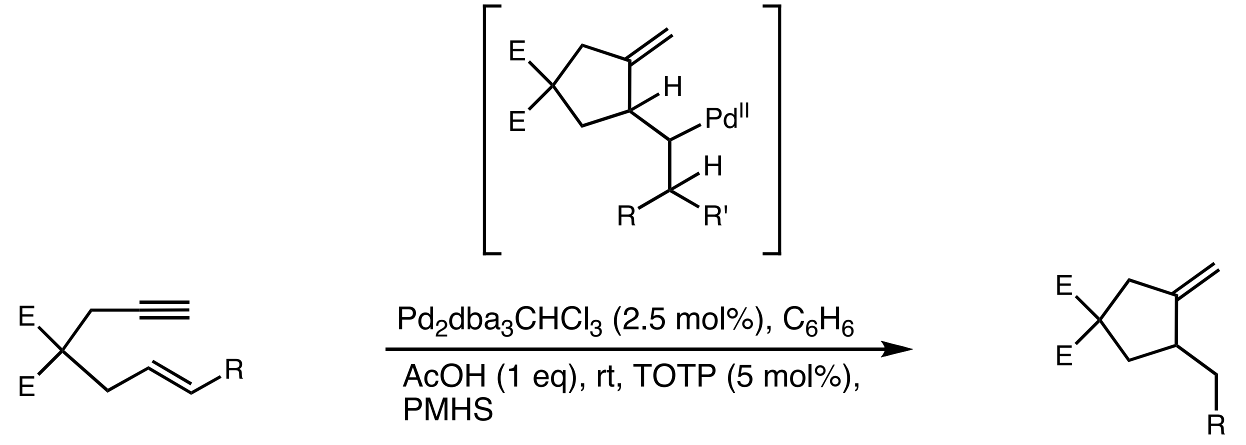


$Pd_2dba_3CHCl_3$ (2.5 mol%), CH_2Cl_2

AcOH (5 mol%), rt, $AsPh_3$ (5 mol%)

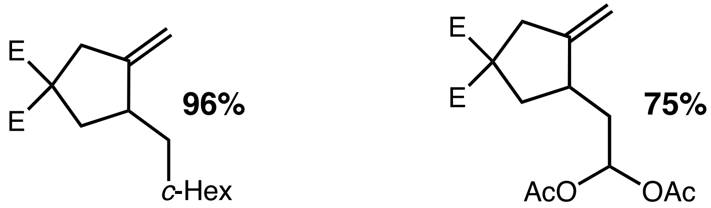
Trost et al *J. Am. Chem. Soc.* **1987**, *109*, 3161.

Mechanistic Support for Hydro-Palladation Pathway



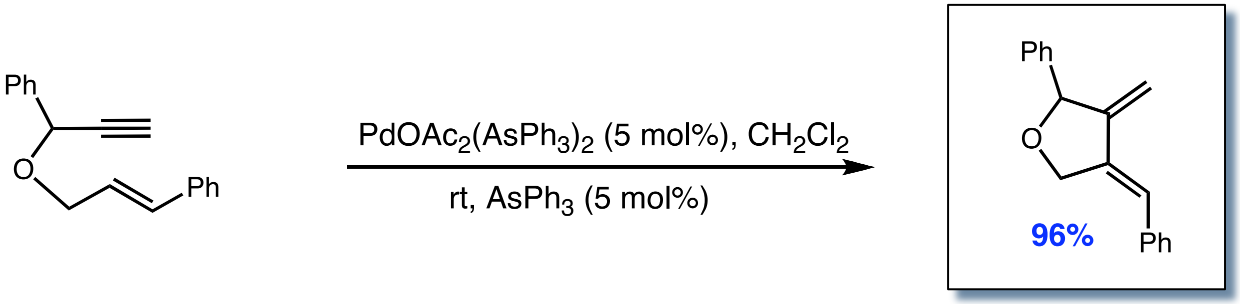
$Pd_2dba_3CHCl_3$ (2.5 mol%), C_6H_6

AcOH (1 eq), rt, TOTP (5 mol%), PMHS



96%

75%



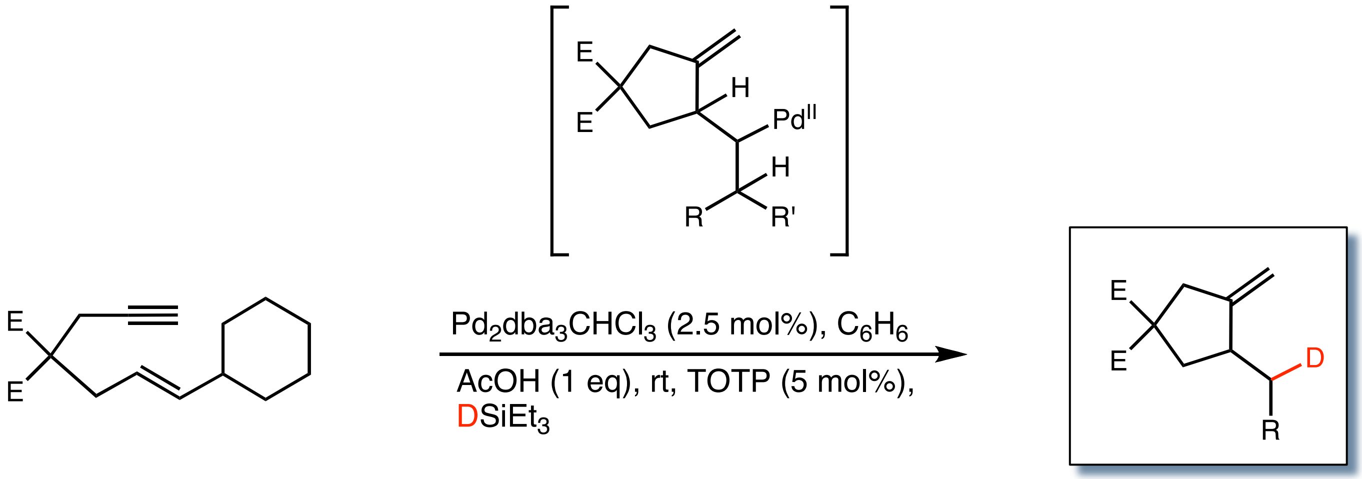
$PdOAc_2(AsPh_3)_2$ (5 mol%), CH_2Cl_2

rt, $AsPh_3$ (5 mol%)

96%

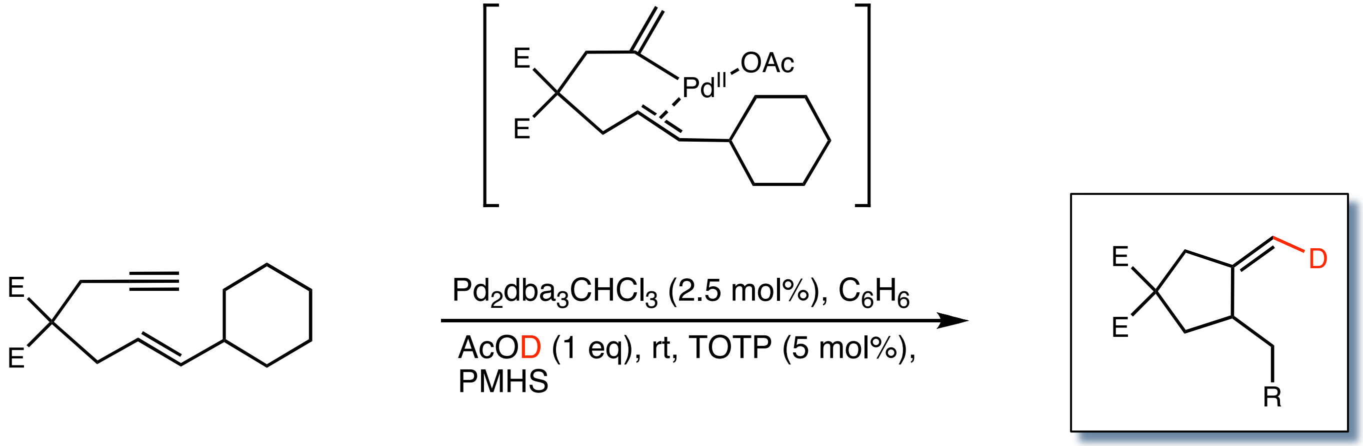
Trost et al *J. Am. Chem. Soc.* **1987**, *109*, 3161.

Mechanistic Support for Hydro-Palladation Pathway



$Pd_2dba_3CHCl_3$ (2.5 mol%), C_6H_6

AcOH (1 eq), rt, TOTP (5 mol%),
D$SiEt_3$

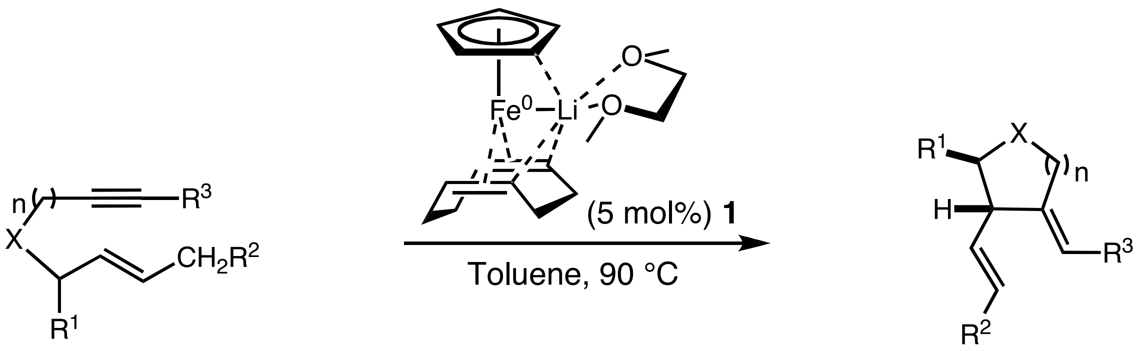


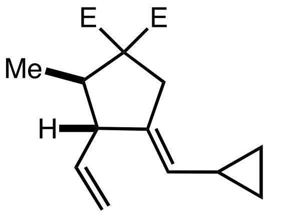
$Pd_2dba_3CHCl_3$ (2.5 mol%), C_6H_6

AcOD (1 eq), rt, TOTP (5 mol%),
PMHS

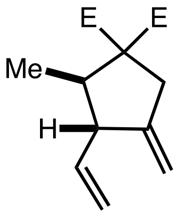
Trost et al *J. Am. Chem. Soc.* **1987**, *109*, 3161.

A Much Cheaper Alternative: Fe

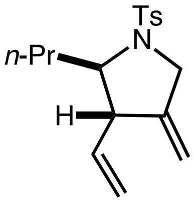




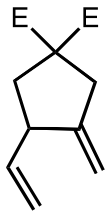
97%, 6:1 *trans/cis*



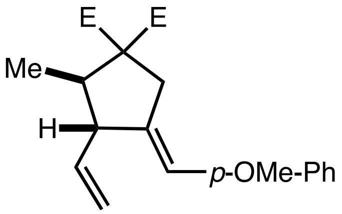
93%, 5.8:1 *trans/cis*
5 mol% **2**



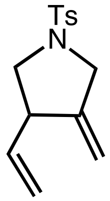
90%, 7.9:1 *trans/cis*



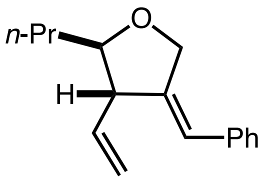
80%



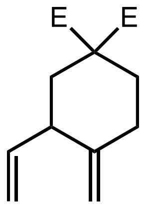
97%, 6.3:1 *trans/cis*
5 mol% **2**



79%



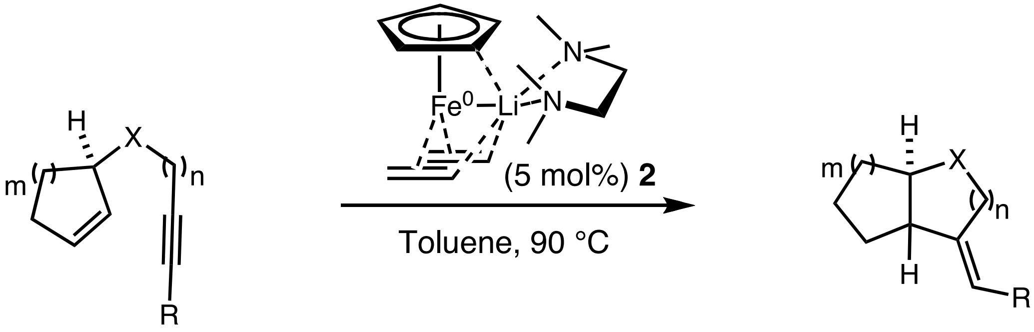
82%, 20:1 *trans/cis*
20 mol% **2**



79%,
15 mol% **1**

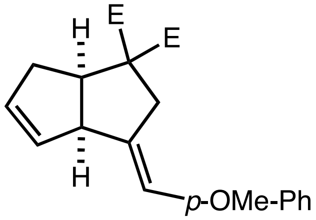
Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

A Much Cheaper Alternative: Fe

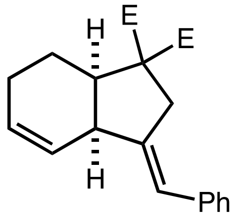


(5 mol%) **2**

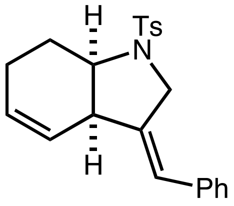
Toluene, 90 °C



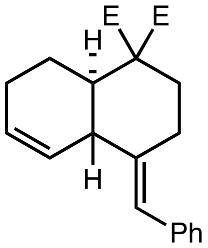
50%, 10 mol% **2**



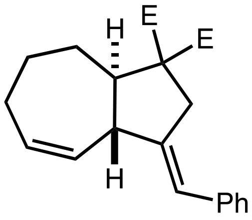
93%



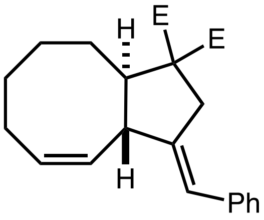
60%, 10 mol% **2**



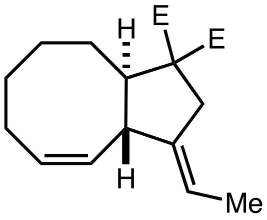
68% 2.5:1 *cis/trans*
10 mol% **2**



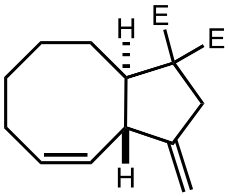
63



95%



93%

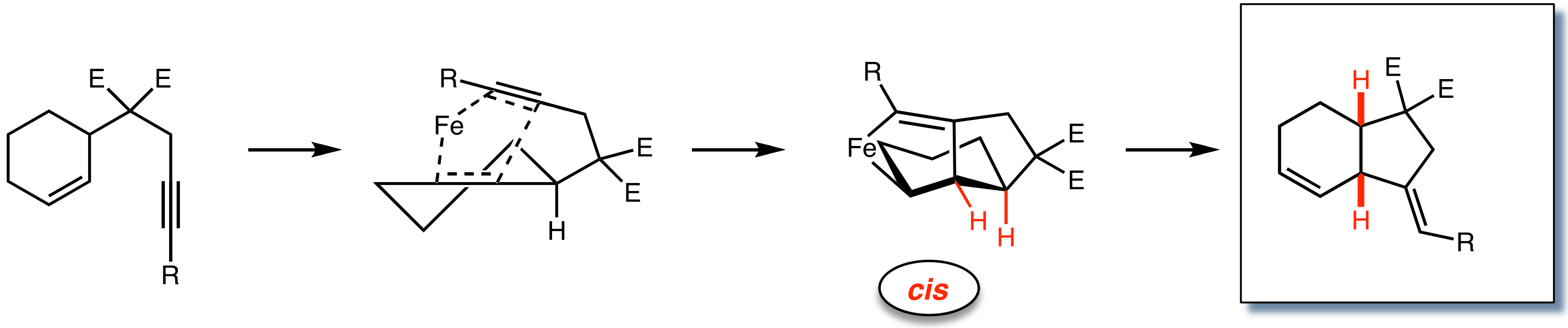


93%

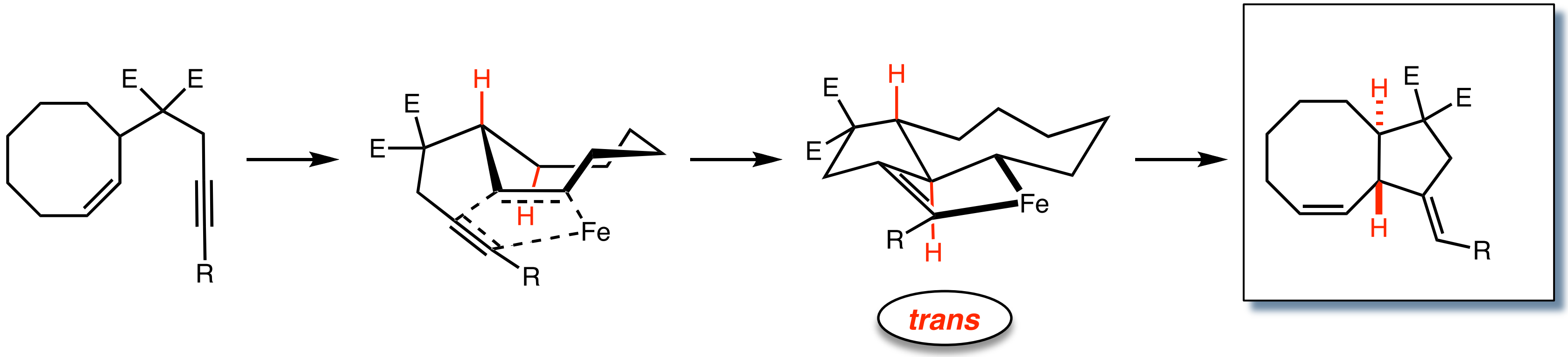
Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

Divergent Pathways to Observed Sterochemistry

- Pseudo-axial approach affords *cis*-diastereomer

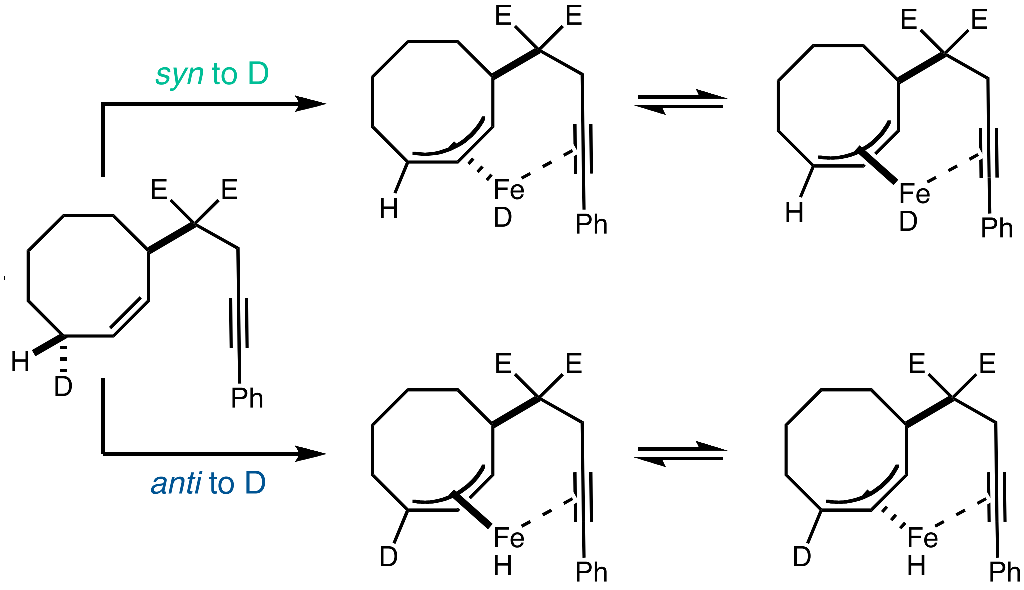


- Pseudo-equatorial approach affords *trans*-diastereomer



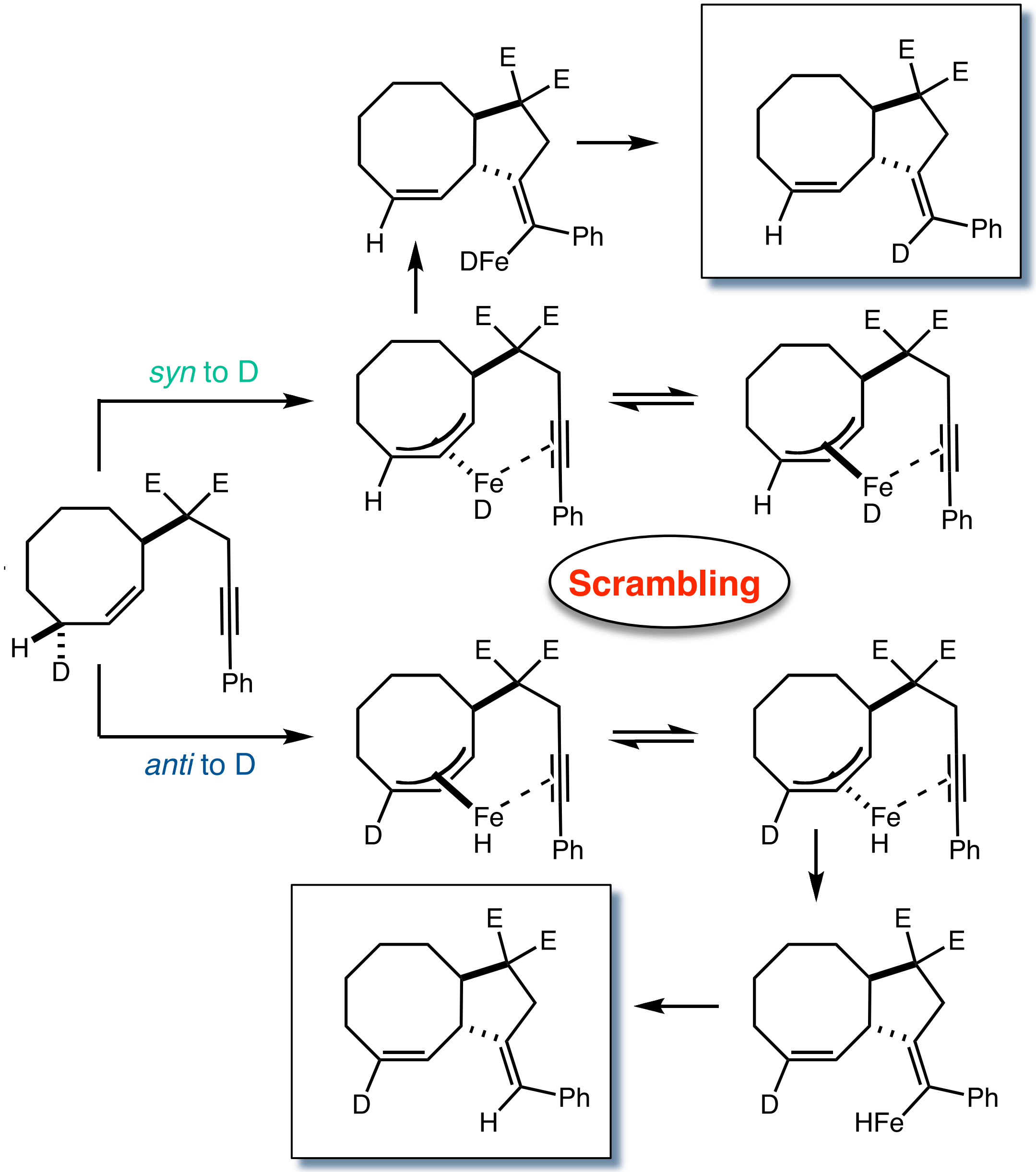
Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

Expectation of D-Labeling Study



Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

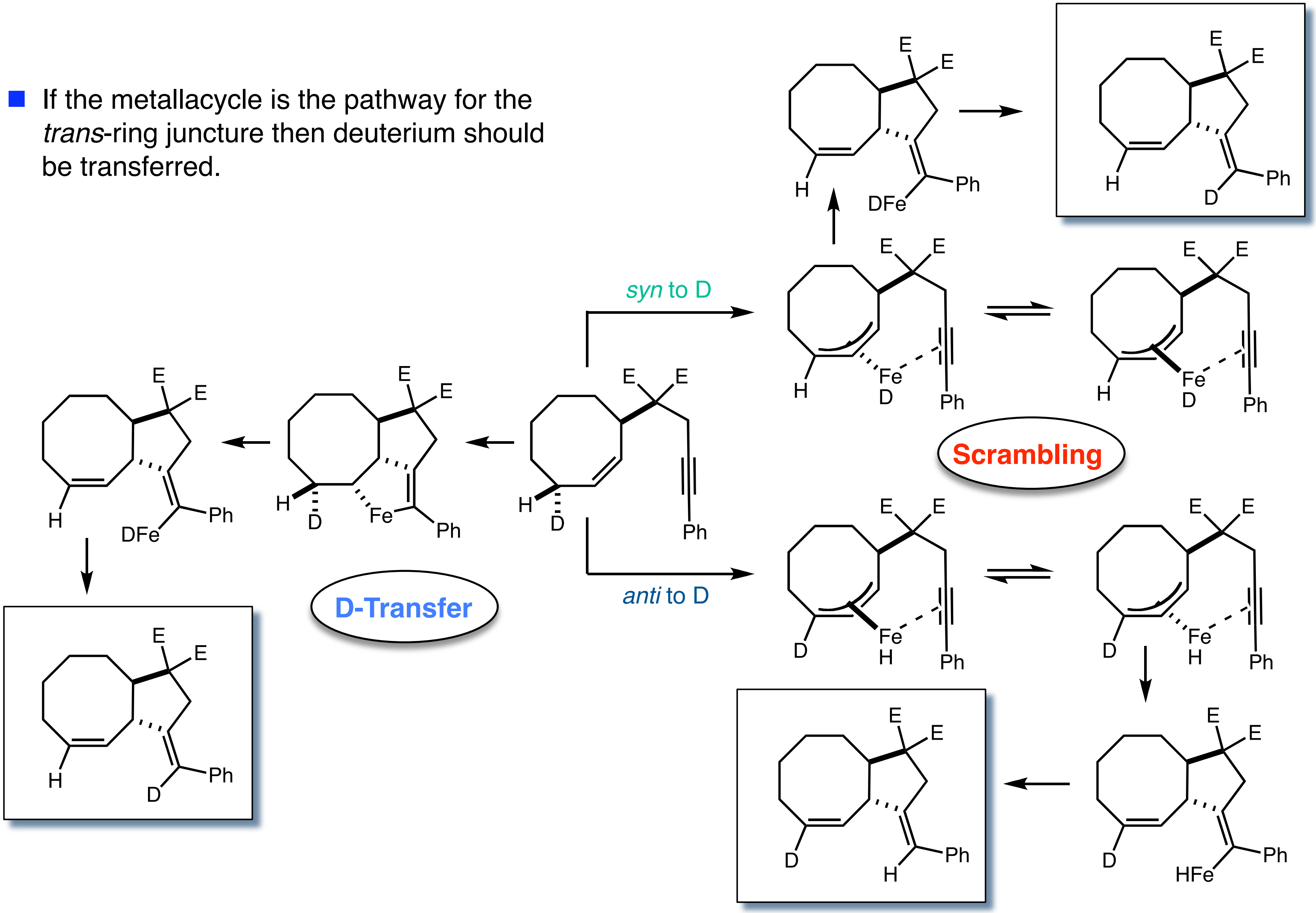
Expectation of D-Labeling Study



Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

Expectation of D-Labeling Study

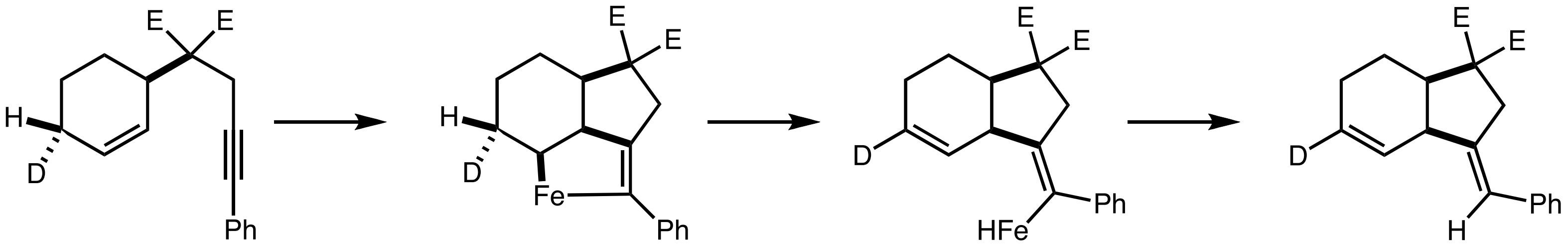
- If the metallacycle is the pathway for the *trans*-ring juncture then deuterium should be transferred.



Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

Expectation of D-Labeling Study

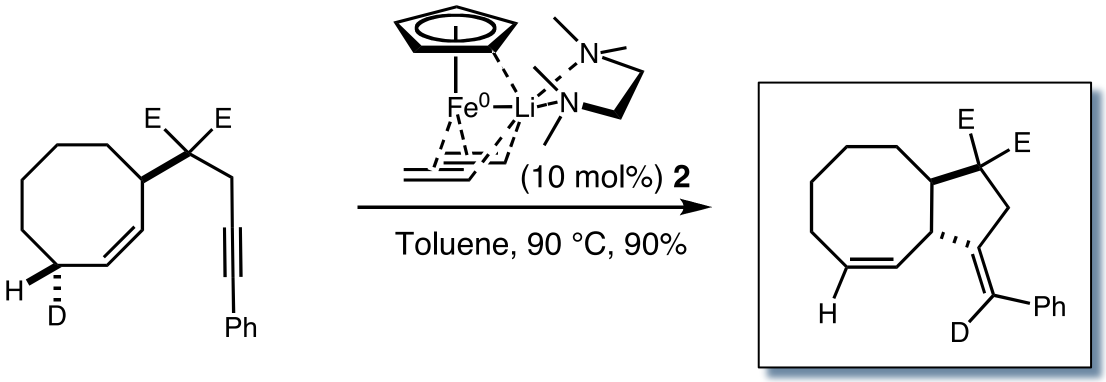
- If the metallacycle is the pathway for the *cis*-ring juncture then hydrogen should be transferred.



Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

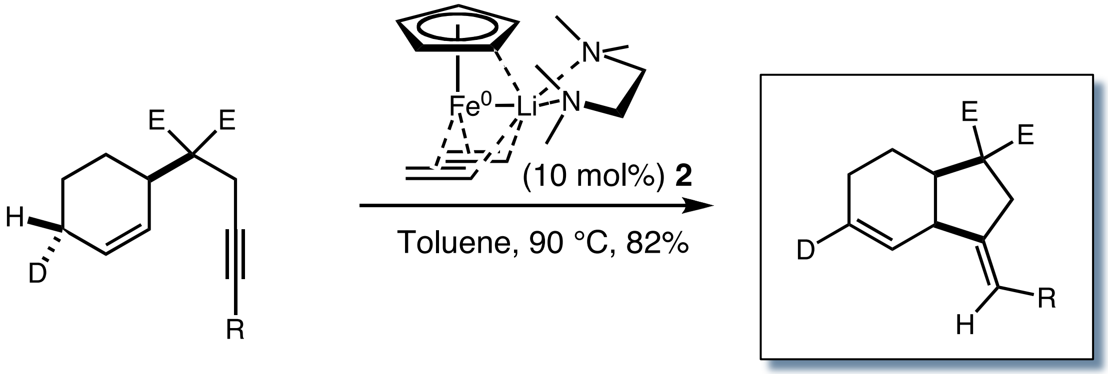
The Dramatic Conclusion

- Deuterium labeling study supports a metallacyle intermediate.



(10 mol%) **2**

Toluene, 90 °C, 90%



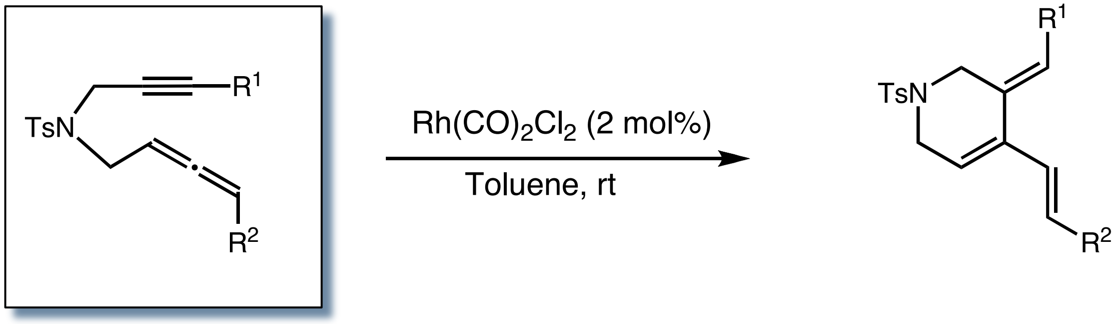
(10 mol%) **2**

Toluene, 90 °C, 82%

Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

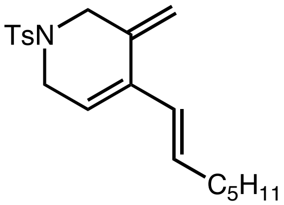
Intermolecular Rh-Catalyzed Alder-Ene

- First report of high yield and selectivity to form cross-conjugated trienes.

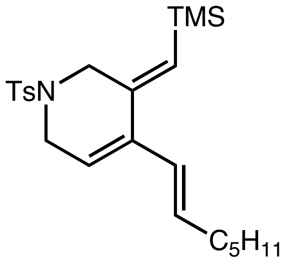


$Rh(CO)_2Cl_2$ (2 mol%)

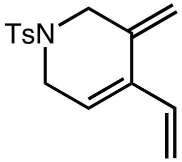
Toluene, rt



90%, 6:1 *E/Z*



85%, 5:1 *E/Z*

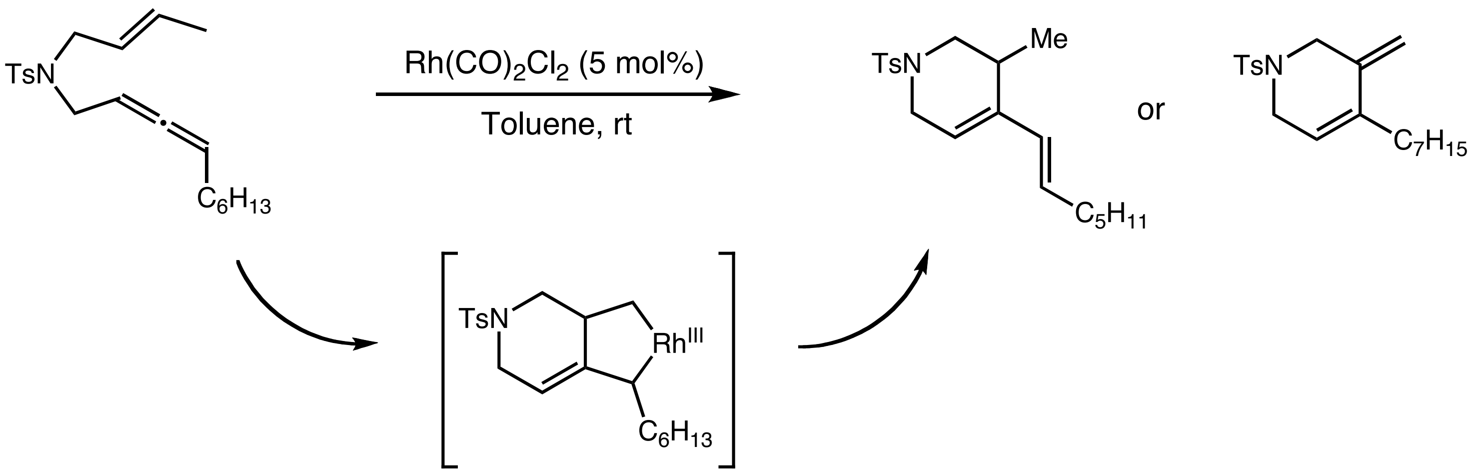


93%

Brummond et al *J. Am. Chem. Soc.* **2002**, *124*, 15186.

Intermolecular Rh-Catalyzed Alder-Ene

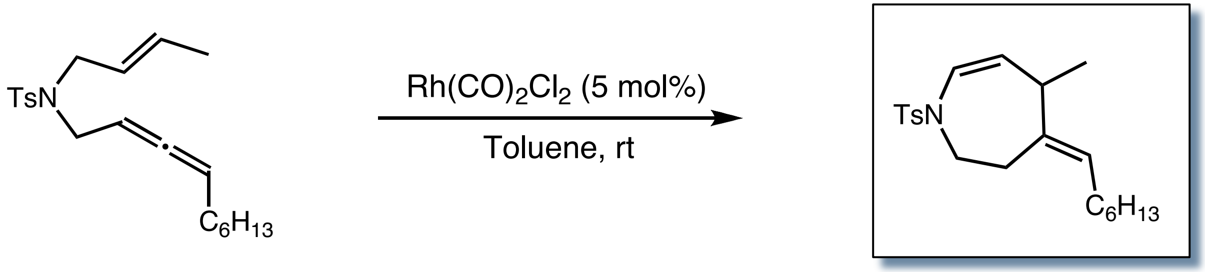
- Will This work with ene-allenes?



Brummond et al *J. Am. Chem. Soc.* **2002**, *124*, 15186.

Intermolecular Rh-Catalyzed Cycloisomerization

- Tetrahydroazepines are formed instead.

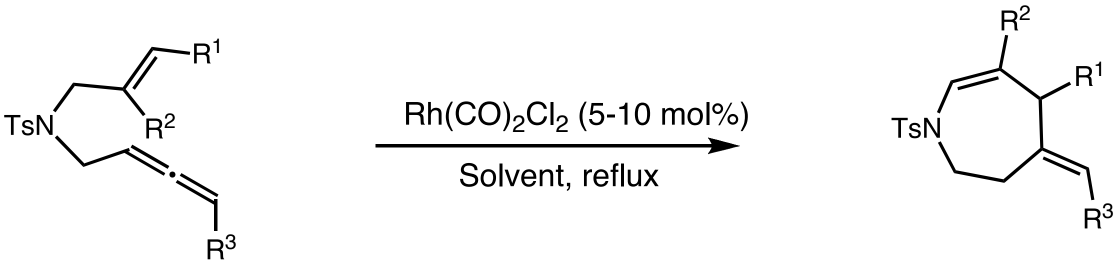


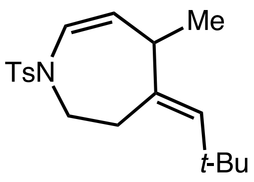
- Product possessed interesting unsaturation for further functionalization.

Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, 6, 2161.

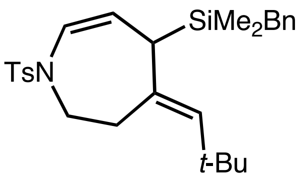
Intermolecular Rh-Catalyzed Cycloisomerization

- Selected azepine products

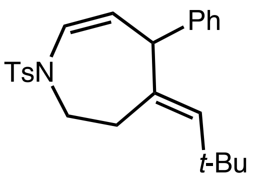




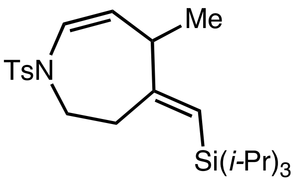
95%, DCE



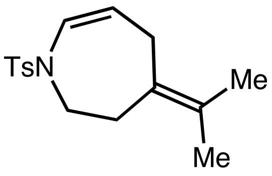
97%, DCE



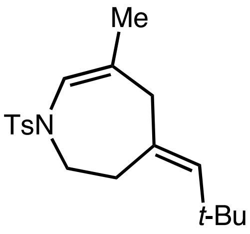
95%, 1,4-Dioxane



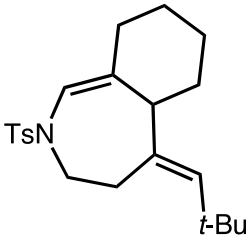
69%, 1,4-Dioxane



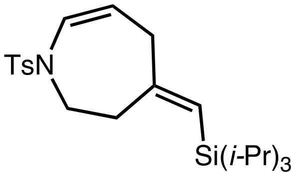
85%, 1,4-Dioxane



86%, 1,4-Dioxane



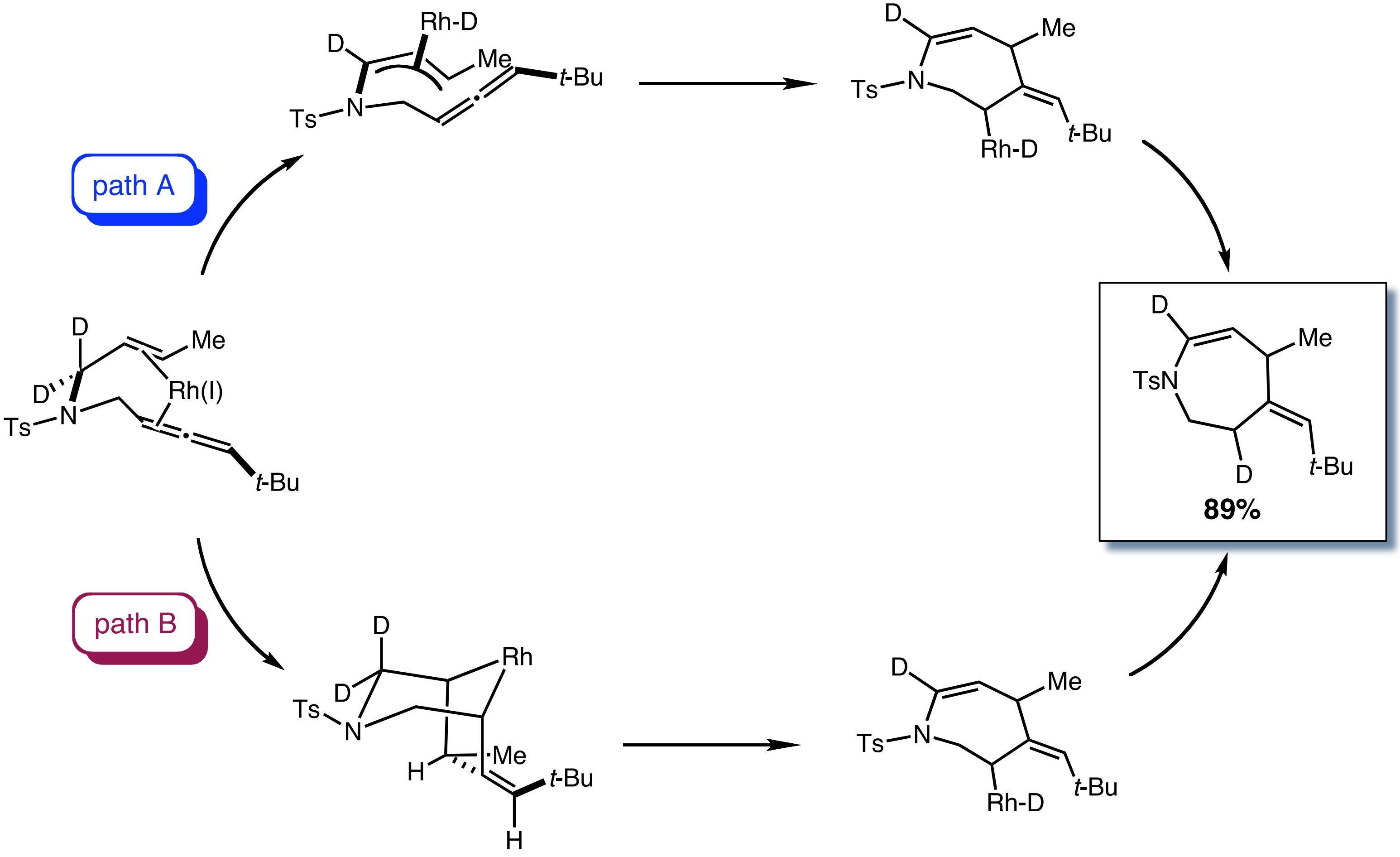
78%, 1,4-Dioxane



73%, 5.8:1 *E/Z*, 1,4-Dioxane

Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, 6, 2161.
Brummond, K. M.; Casarez, A. D*. unpublished work*.

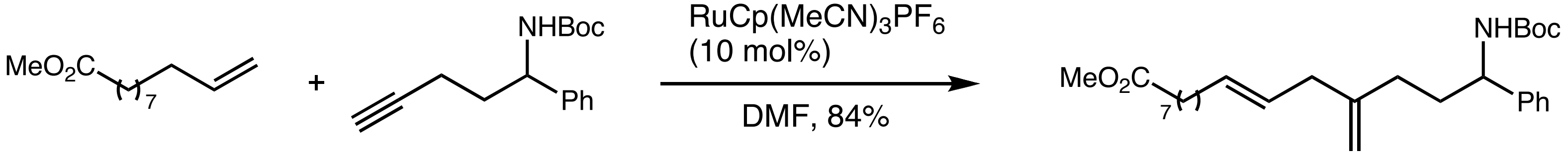
Two Plausible Mechanisms



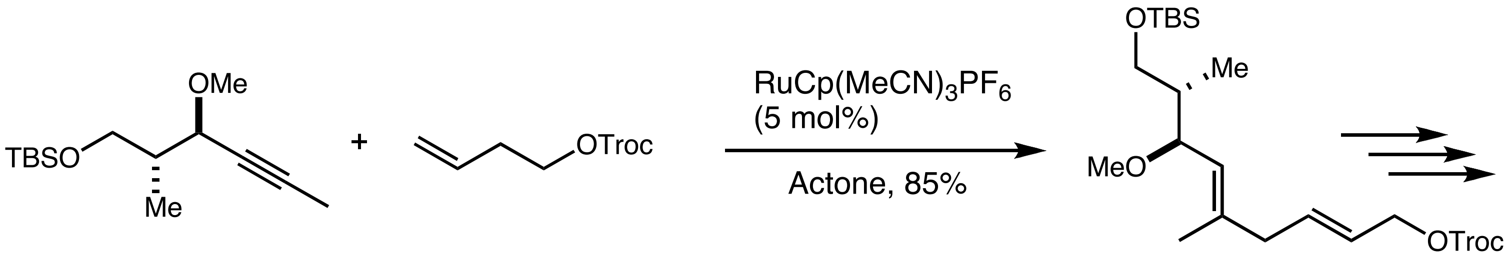
Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, 6, 2161.

Intermolecular Ru-Catalyzed Alder-Ene

- Selectivity for the branched diene can be high depending on substrate



- Selectivity for the branched diene can be high depending on substrate

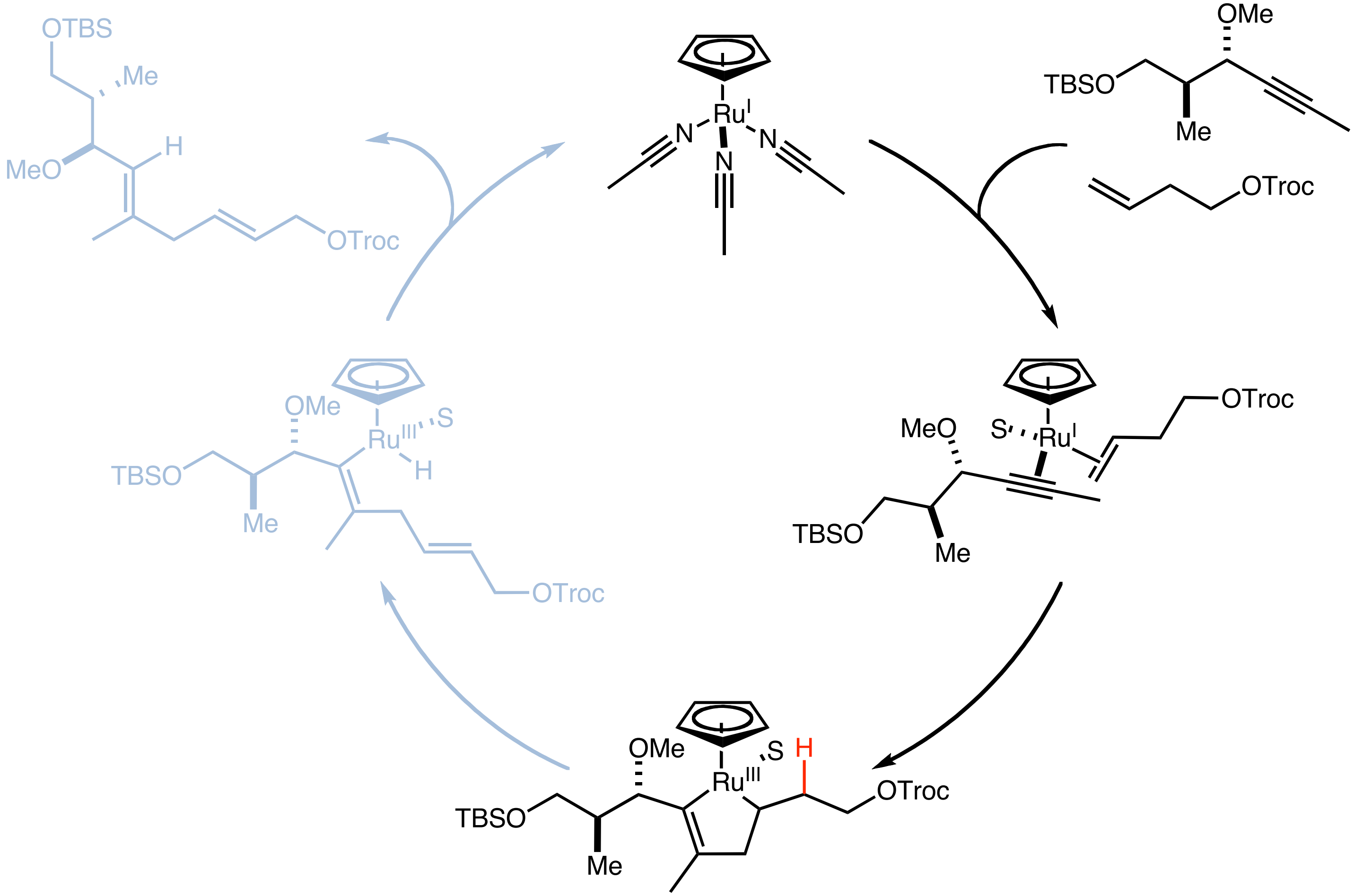


Callipeltoside A

22 longest linear
46 overall steps

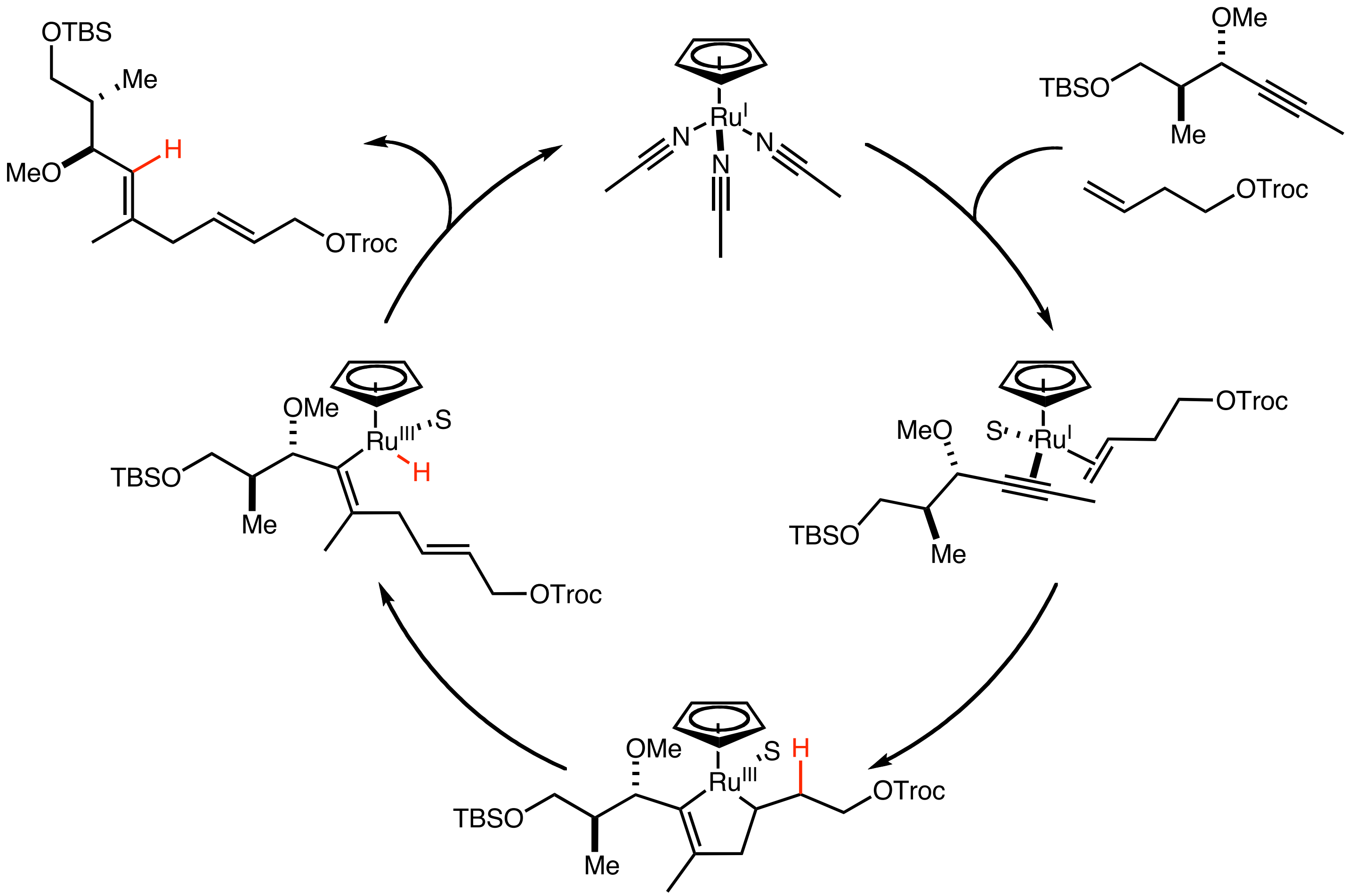
Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, 40, 7739.
Trost et al *J. Am. Chem. Soc.* **2002**, *124*, 10396.

The Catalytic Cycle



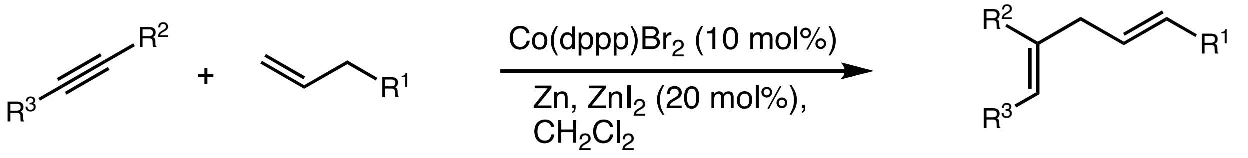
Trost et al *J. Am. Chem. Soc.* **2002**, *124*, 10396.

The Catalytic Cycle



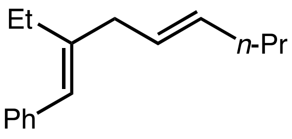
Trost et al *J. Am. Chem. Soc.* **2002**, *124*, 10396.

Intermolecular Co-Catalyzed Alder-Ene

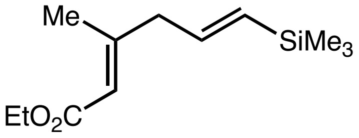


$Co(dppp)Br_2$ (10 mol%)

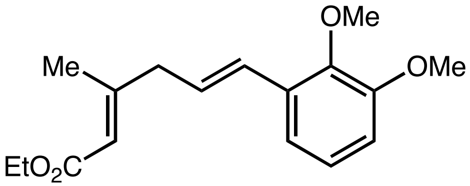
Zn, ZnI_2 (20 mol%), CH_2Cl_2



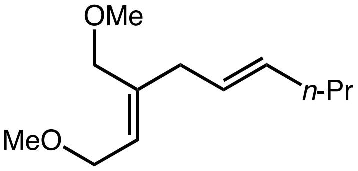
89%, 8:1 *E/Z*



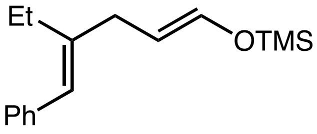
99%, 99:1 *E/Z*



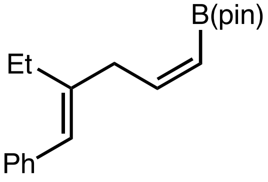
95%, 8:1 *E/Z*



99%, 99:1 *E/Z*



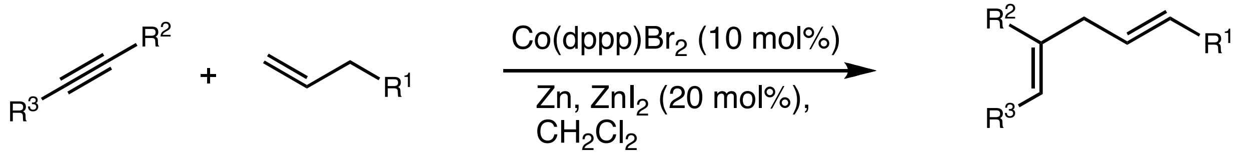
95%, *E only*

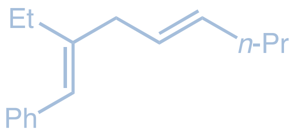


80%, 4:1 *E/Z*

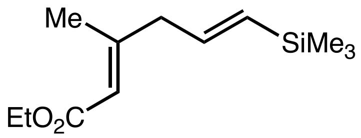
Hilt, G.; Treutwein, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8500.

Intermolecular Co-Catalyzed Alder-Ene

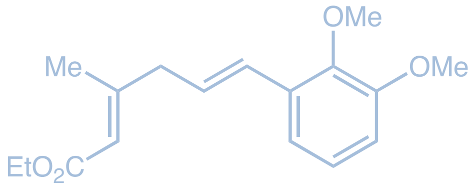




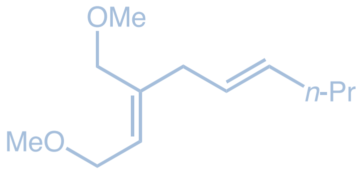
89%, 8:1 *E/Z*



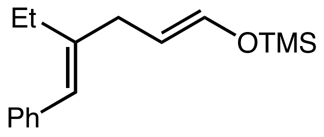
99%, 99:1 *E/Z*



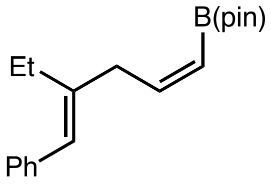
95%, 8:1 *E/Z*



99%, 99:1 *E/Z*



95%, *E only*

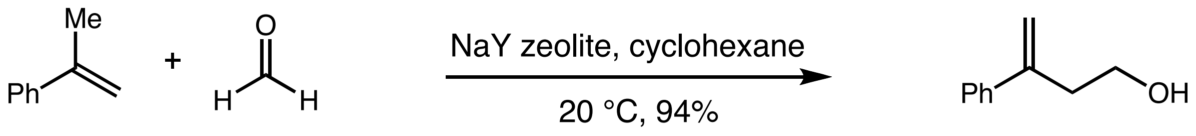


80%, 4:1 *E/Z*

Hilt, G.; Treutwein, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8500.

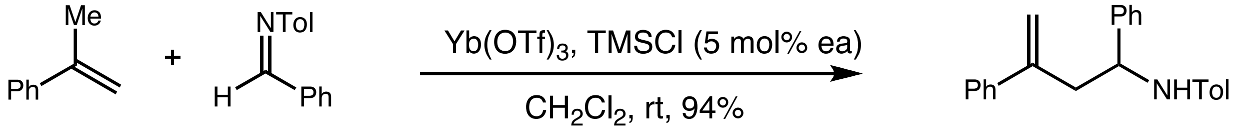
Other Ene Reactions

The Carbonyl-ene



Okachi, T.; Onaka, M. *J. Am. Chem. Soc.* **2004***, 126,* 2306.

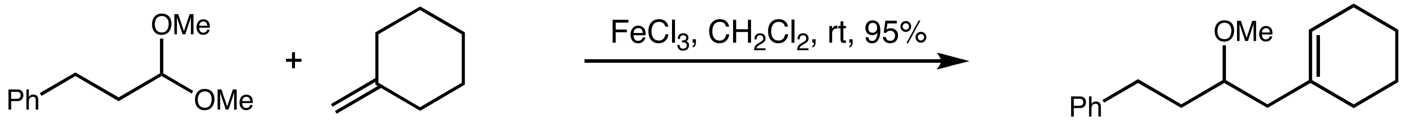
The Imino-ene



Nakagawa et al. *Org. Lett.*, **2000**, *2*, 159.

Other Ene Reactions

The Acetal-ene



Ghosez et al., *Synthesis,* **2004**, 1375.

The Arynyl-ene