Tandem Reactions in Organic Synthesis: Ruthenium and Palladium Catalysis

April 20, 2006

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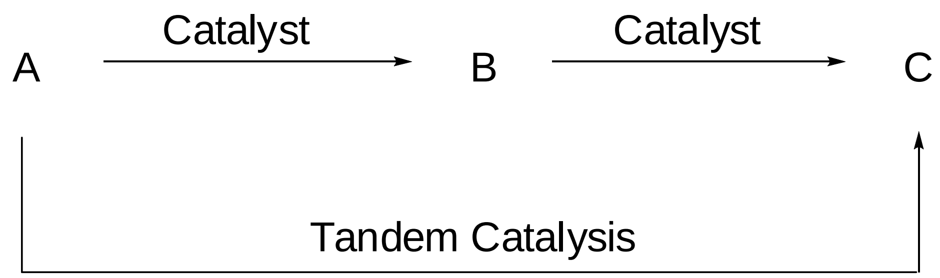
Crimmins Group

An Example of Tandem Catalysis



- -Intermediates do not require purification
    - -less purification materials used (solvent, silica, etc.)
    - -more time efficient

- -Reduces catalyst used

- -Higher yield

- -Reduces waste

Outline

1. Definitions
2. Pd-catalyzed reactions, then Pd-catalyzed tandem reactions
3. Ru-catalyzed reactions, then Ru-catalyzed tandem reactions
4. Example of tandem catalysis in natural product synthesis

What is Tandem Catalysis?

The term tandem catalysis represents processes in which "sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes."

Three types of tandem catalysis:

-Orthogonal tandem catalysis

-Auto-tandem catalysis

-Assisted tandem catalysis

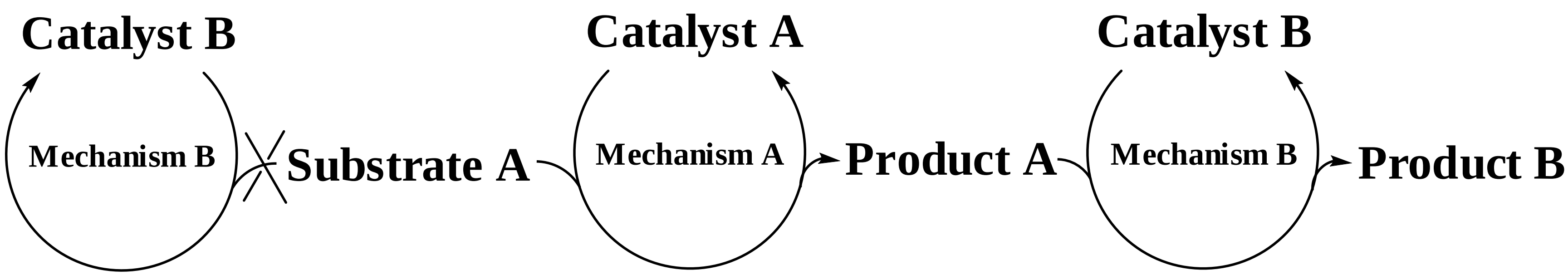
Fogg, D.E.; dos Santos, E.N.; *Coord. Chem. Rev.* **2004**, *248*, 2365.

Orthogonal Tandem Catalysis

-Two or more mechanistically distinct transformations

-Two or more functionally distinct, and ideally non-interfering, catalysts

-All catalysts present from the outset of the reaction.

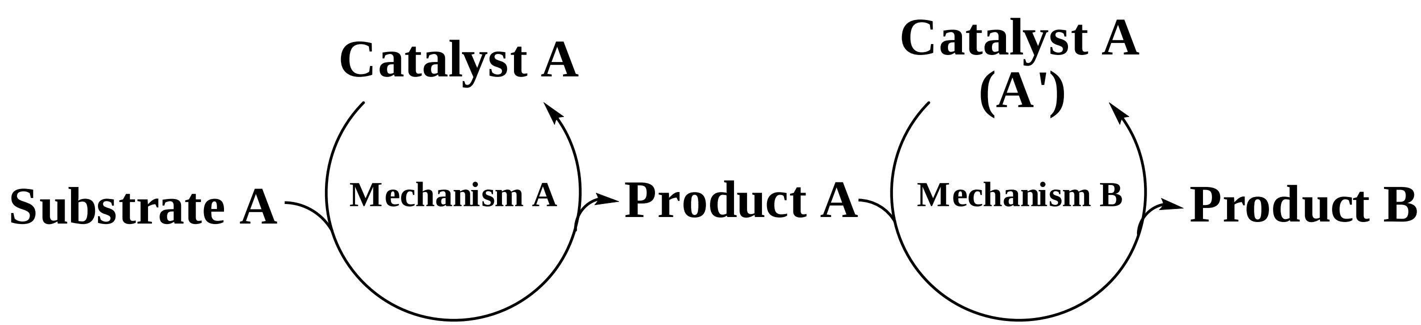


Auto-Tandem Catalysis

-Two or more mechanistically distinct transformations occur via a single catalyst precursor

-Both catalytic cycles occur spontaneously

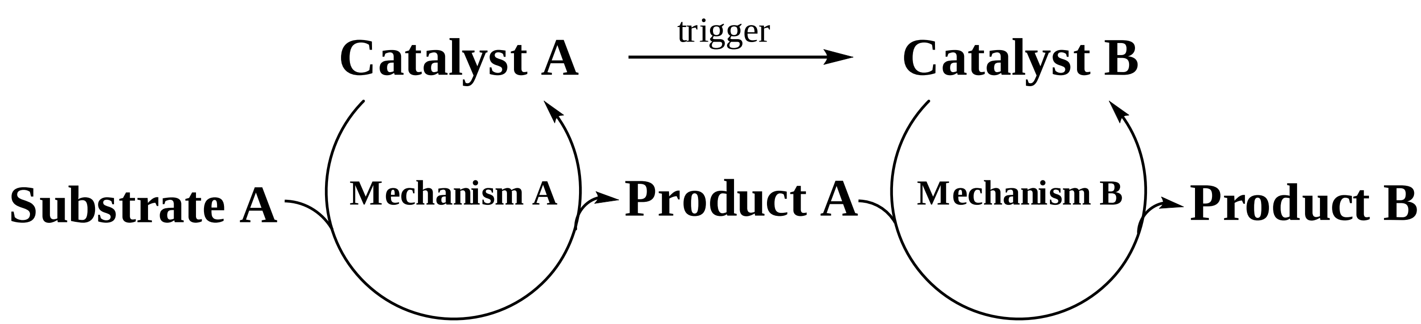
-Cooperative interaction of all species present at the outset of the reaction.



Assisted Tandem Catalysis

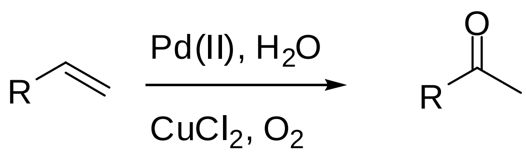
-Two or more mechanistically distinct transformations are promoted by a single catalyst species

-Addition of a reagent to trigger a change in catalyst function

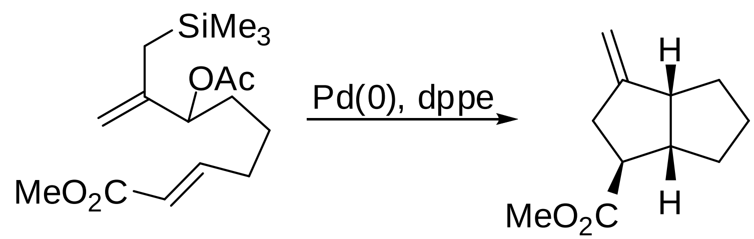


Common Pd-Catalyzed Reactions

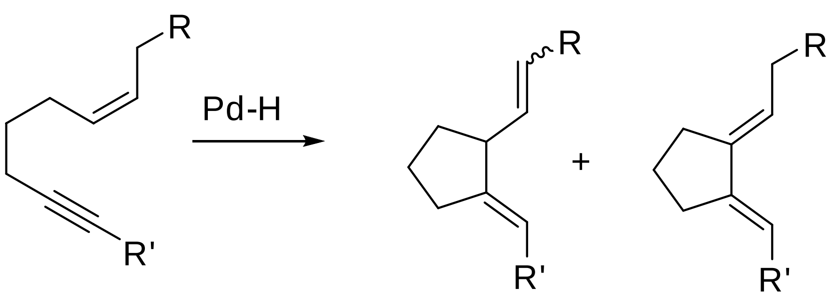
Nucleophilic addition to alkenes



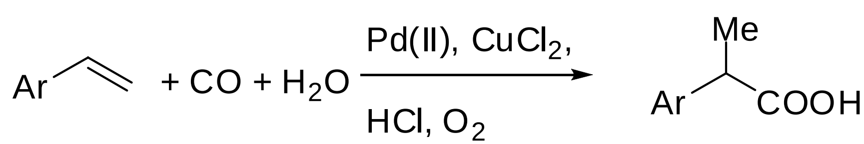
Cycloadditions



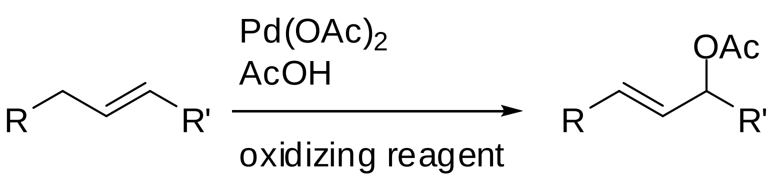
Cycloisomerization



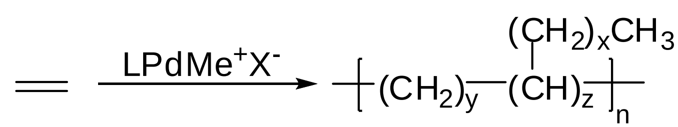
Carbonylation



Allylic oxidation



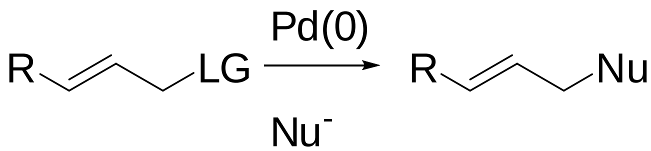
Polymerization



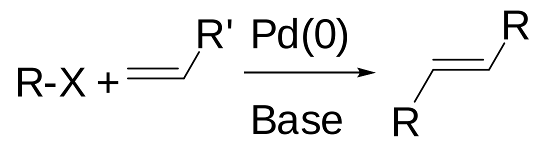
Poli, G.; Giambastiani, G.; Heumann, A.; *Tetrahedron* **2000**, *56*, 5959.

Common Pd-Catalyzed Coupling Reactions

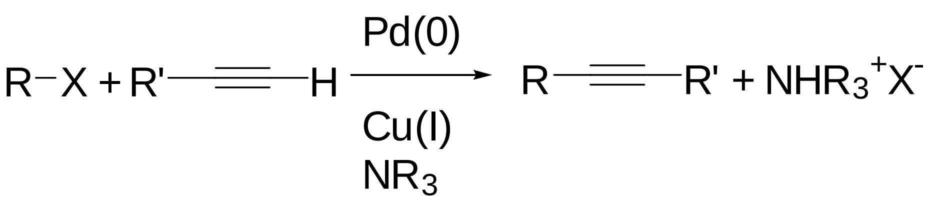
Tsuji-Trost:



Heck:



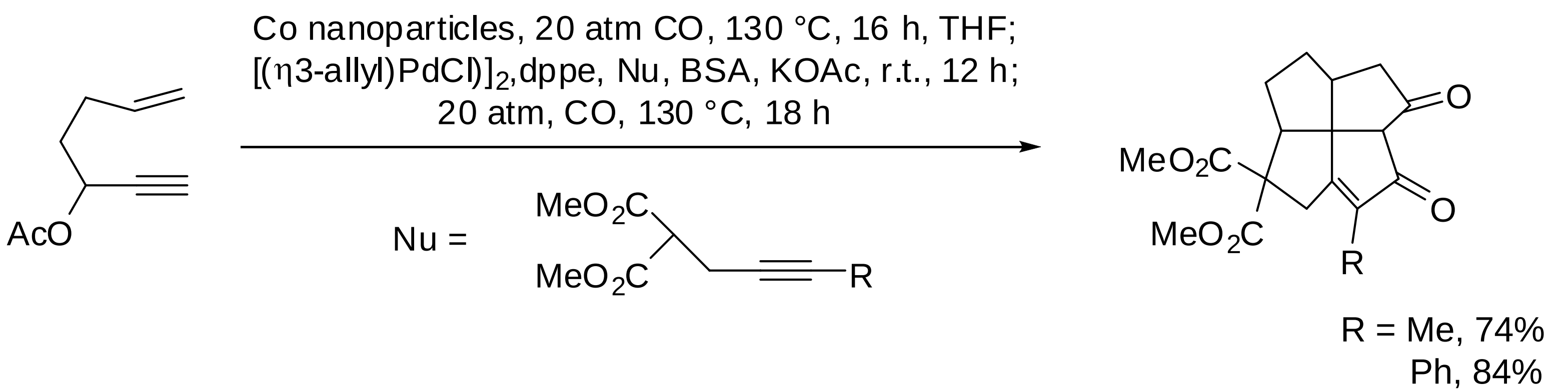
Sonogashira:



$$R\text{-}X + R'\text{-}M \xrightarrow{Pd(0)} R\text{-}R' + X\text{-}M$$

M = SnR_3	Stille
BX_2	Suzuki
MgX	Kumada
Li	
ZnX	Negishi

Pd and Co-Catalyzed Tandem Alkylation/Pauson-Khand Reaction
(Orthogonal Tandem Catalysis)

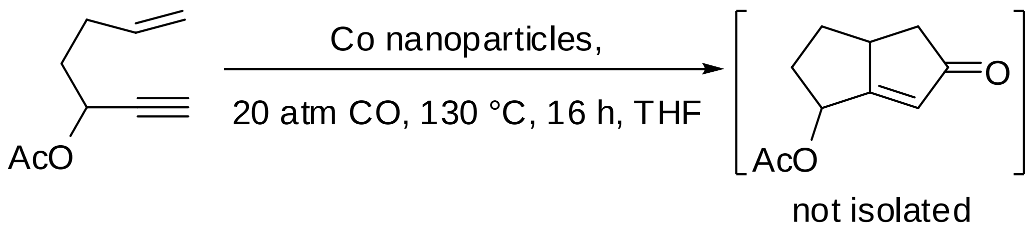


-Construction of fenestranes in one pot from simple building blocks

-Transition-metal nanoparticles used with homogeneous TM catalyst

Son, S.; Park, K.; Chung, Y.; *J. Am. Chem. Soc.* **2002**, *124*, 6838.

Formation of the Allylacetate

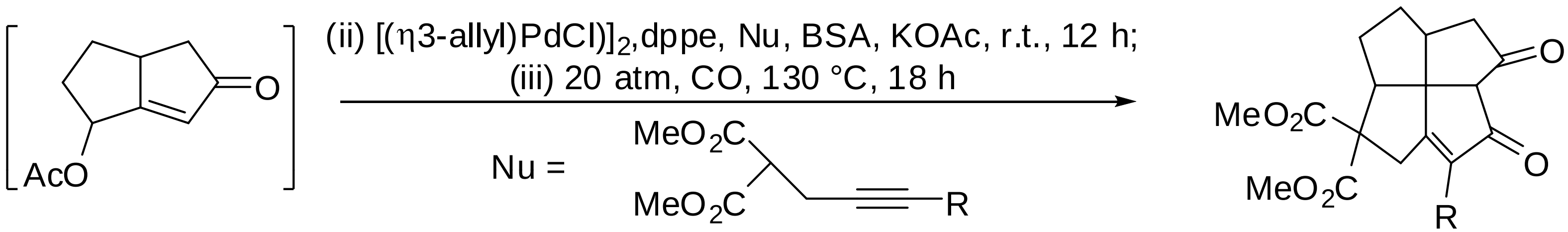


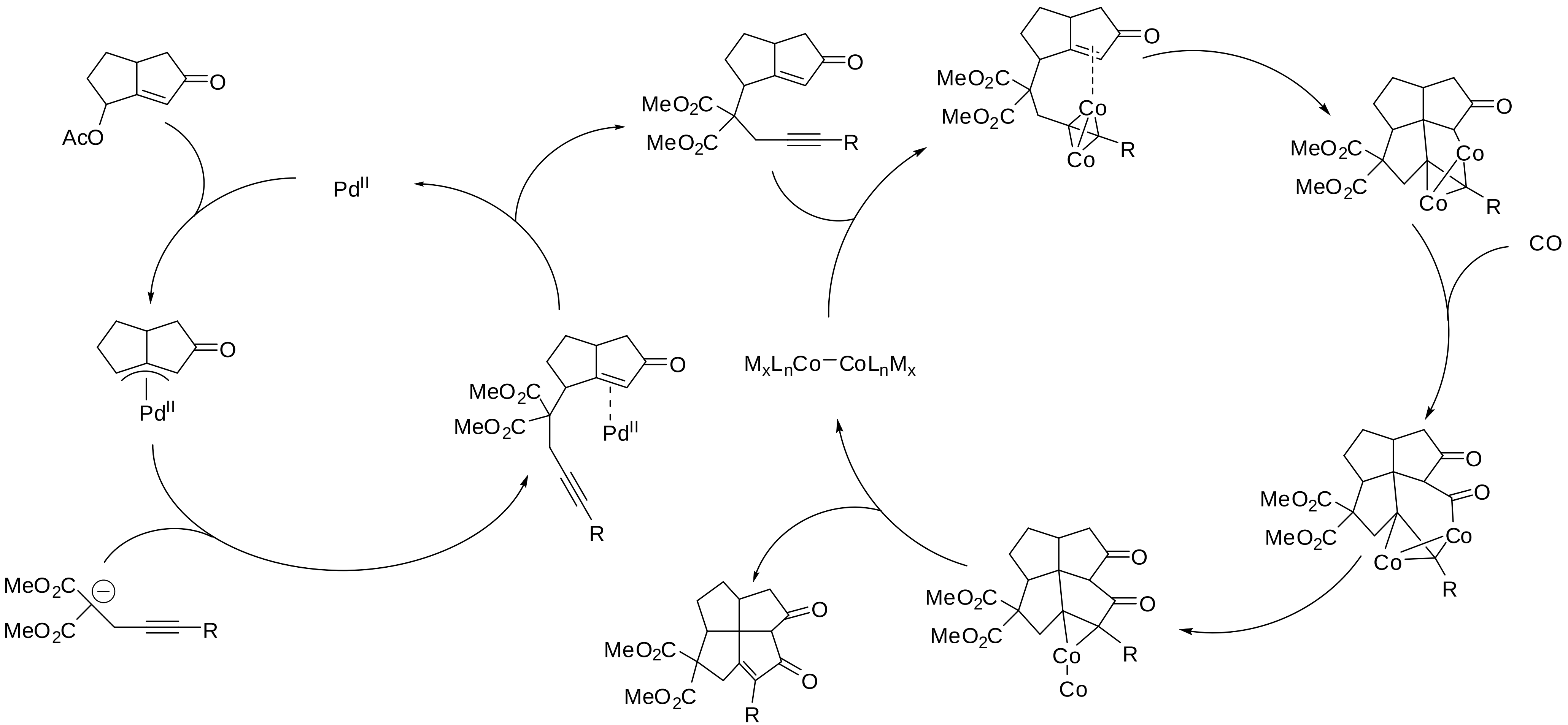
-1st Pauson-Khand reaction not tandem

-Pd has not been added

-Formation of precursor to tandem sequence

Proposed Mechanism for Tandem Alkylation/Pauson-Khand Reaction

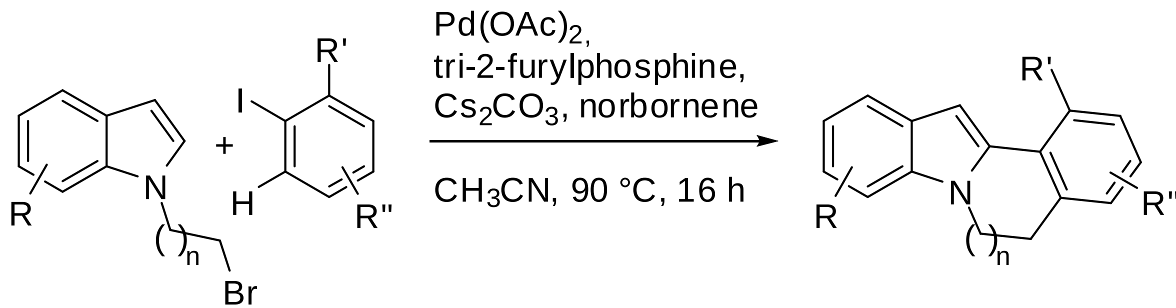




R = Me, 74%
Ph, 84%

Pd-Catalyzed Tandem Alkylation/Direct Arylation

(Auto-Tandem Catalysis)



-Two carbon-carbon bonds formed

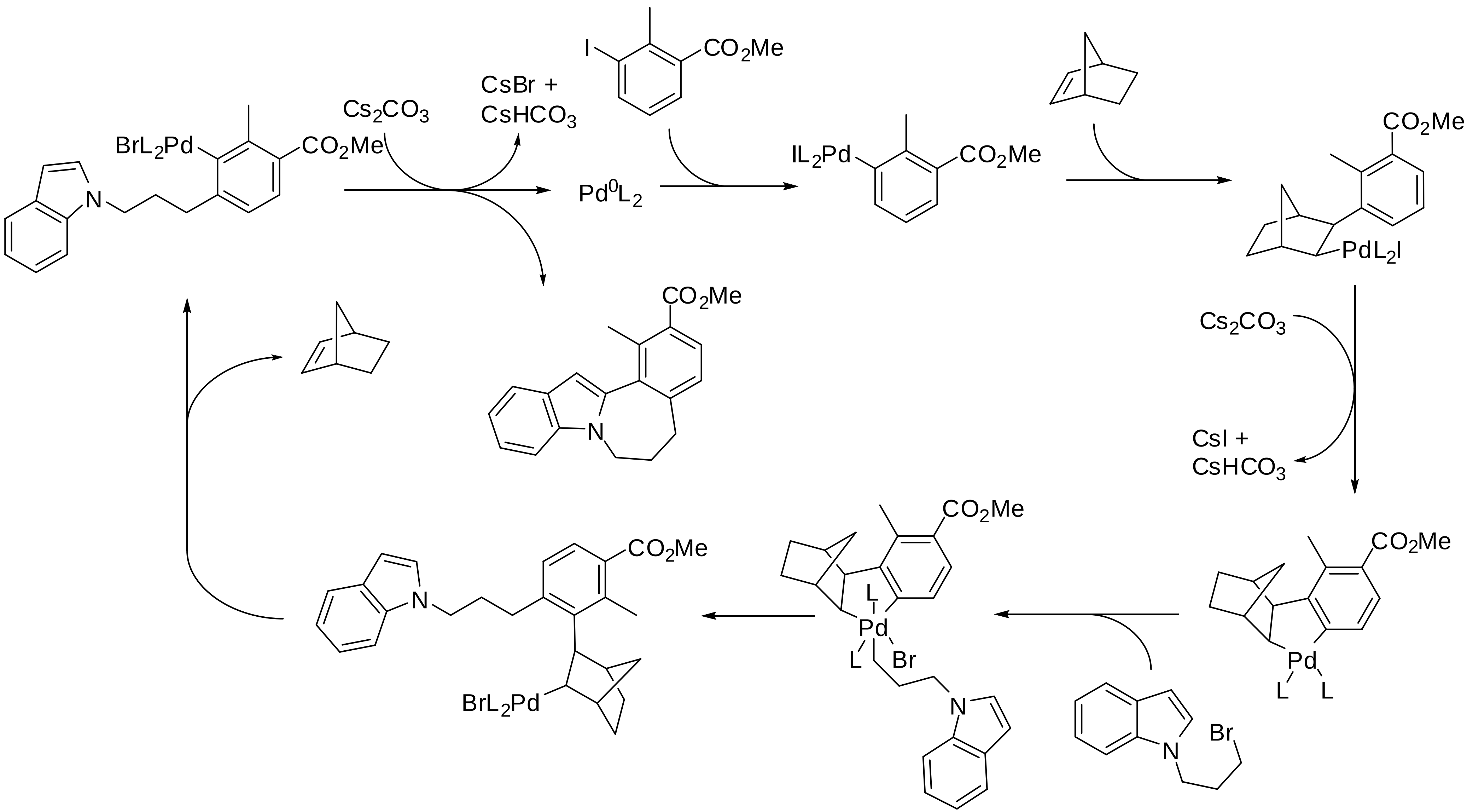
-Six and seven-membered ring formation

-Range of functionality tolerated

-No manipulation of Pd catalyst required

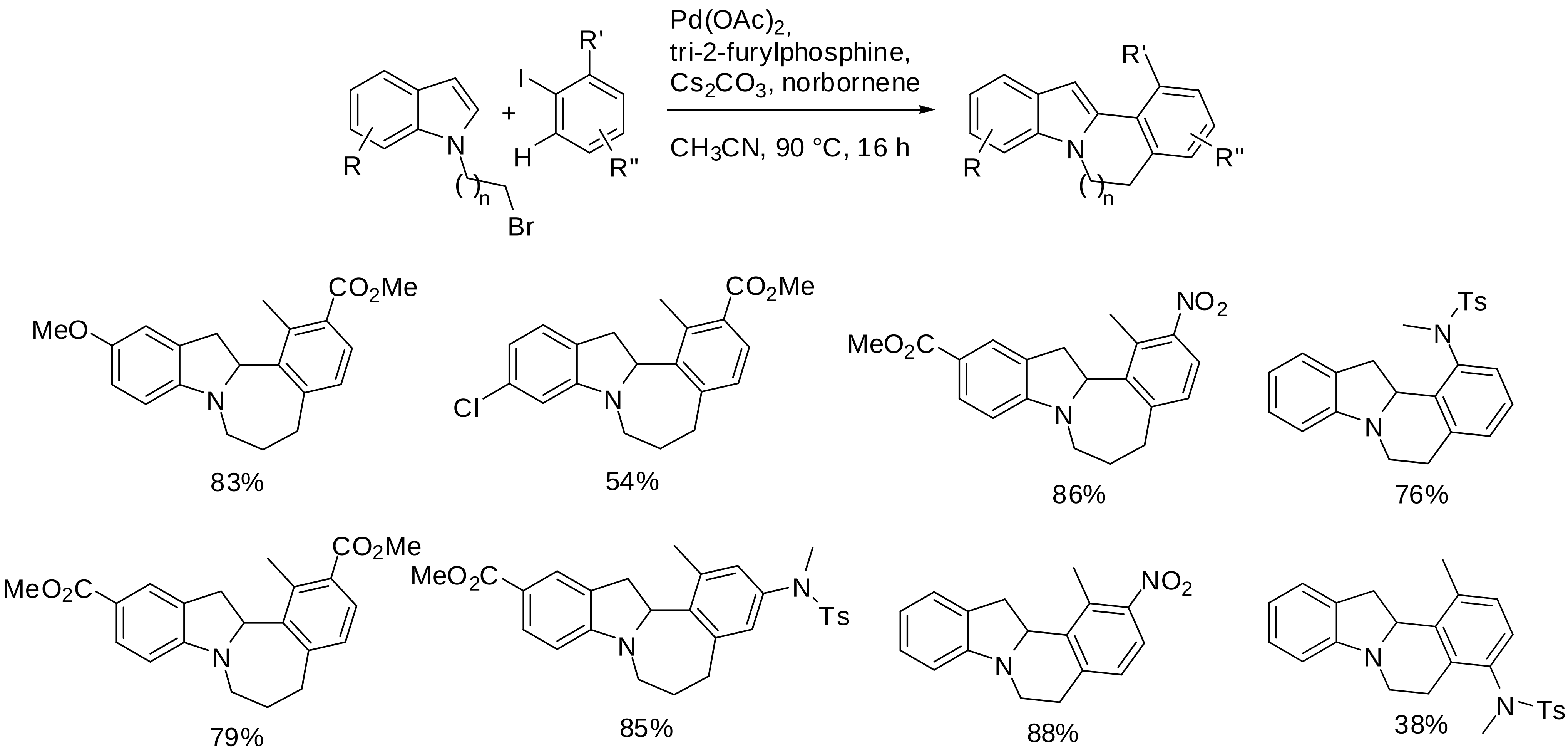
Bressy, C.; Alberico, D.; Lautens, M.; *J. Am. Chem. Soc.* **2005**, *127*, 13148.

Proposed Mechanism for Pd-Catalyzed Alkylation/Direct Arylation



Bressy, C.; Alberico, D.; Lautens, M.; *J. Am. Chem. Soc.* **2005**, *127*, 13148.

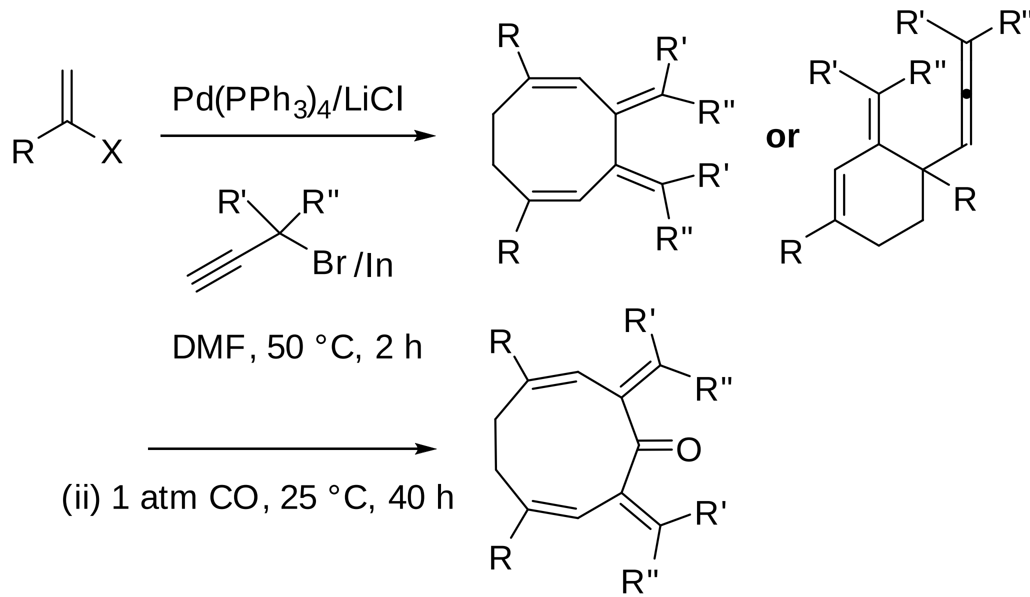
Substrate Scope for Pd-Catalyzed Tandem Alkylation/ Direct Arylation of Bromoalkyl Indoles



Bressy, C.; Alberico, D.; Lautens, M.; *J. Am. Chem. Soc.* **2005**, *127*, 13148.

Pd-Catalyzed Tandem Cross-Coupling/Cycloaddition

(Auto-Tandem Catalysis)



-Six, eight, and nine-membered rings are formed

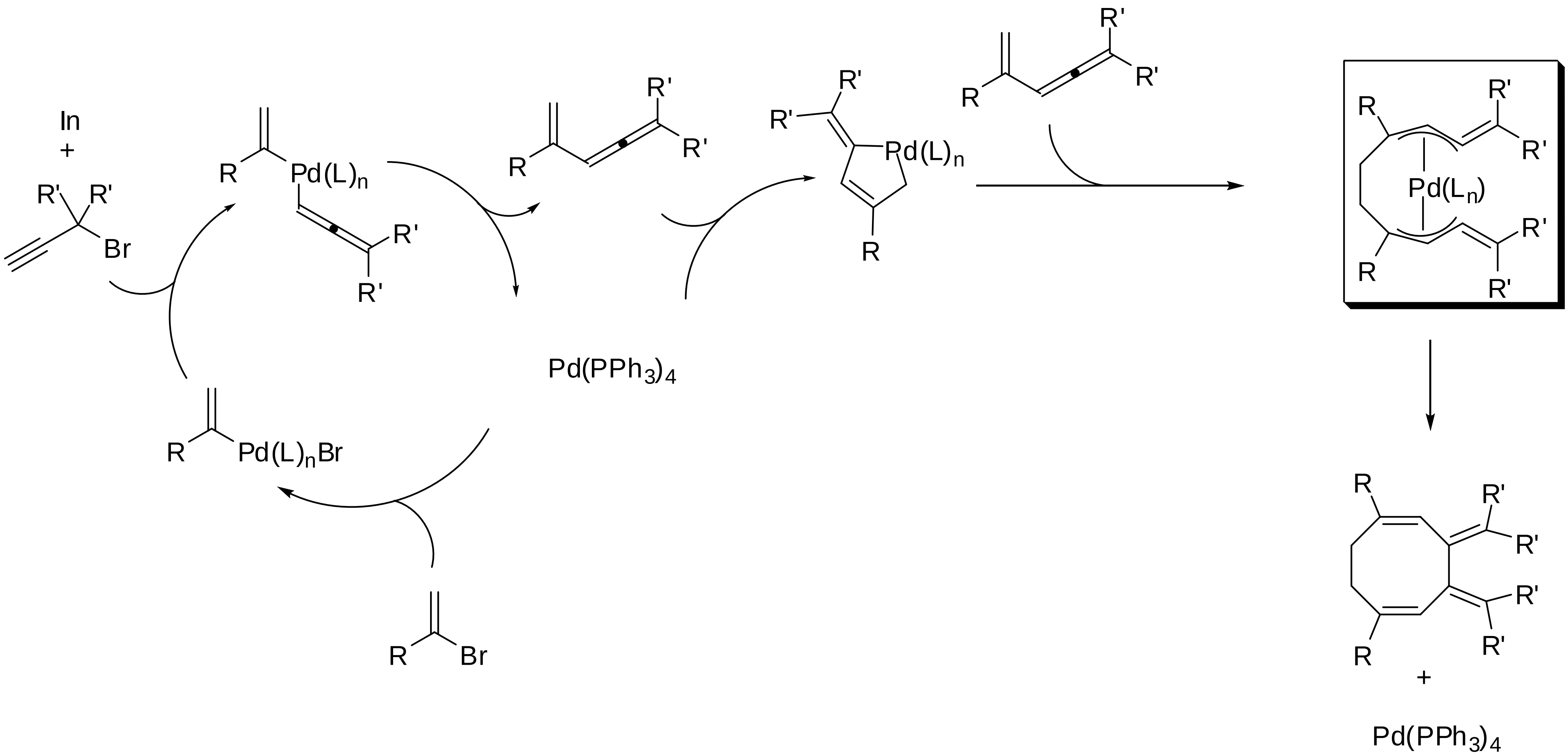
-Assembly of four or five simple compounds to a relatively complex structure

-No manipulation of Pd catalyst required

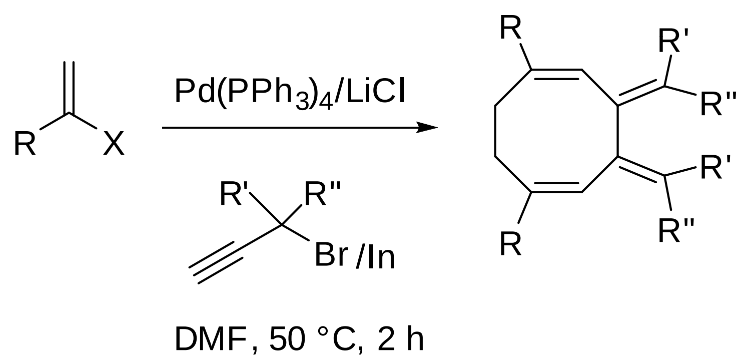
Lee, P. H.; Lee, K.; Kang, Y.; *J. Am. Chem. Soc.* **2006**, *128*, 1139.

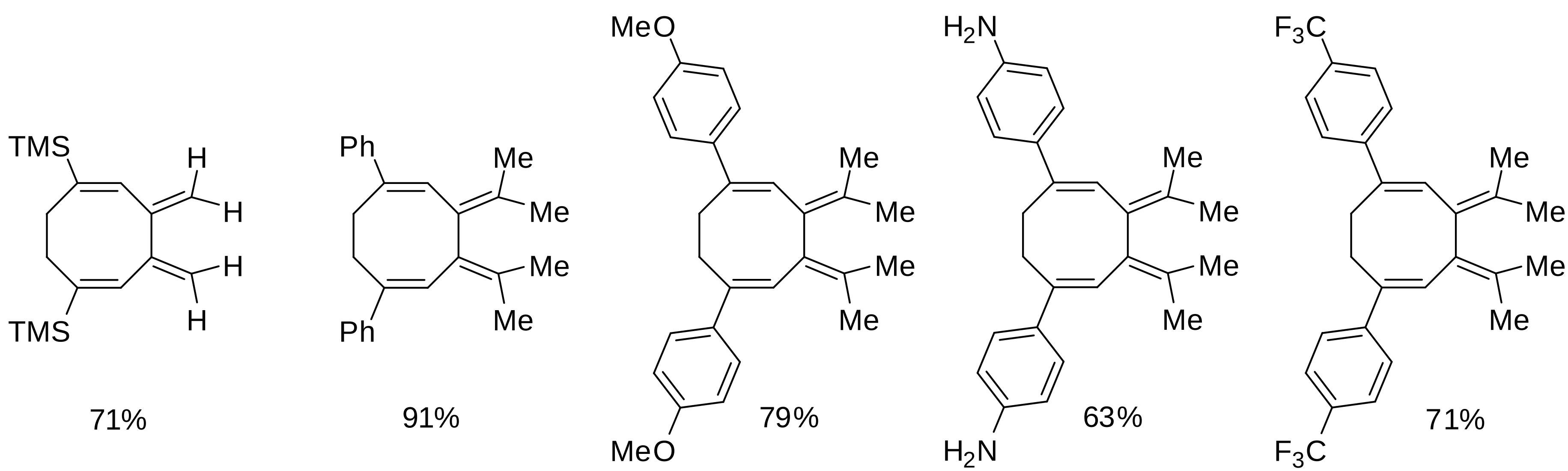
Lee, P. H.; Lee, K.; *Angew. Chem. Int. Ed.* **2005**, *44*, 3253.

Proposed Mechanism for Pd-Catalyzed Cross-Coupling/[4 + 4]Cycloaddition

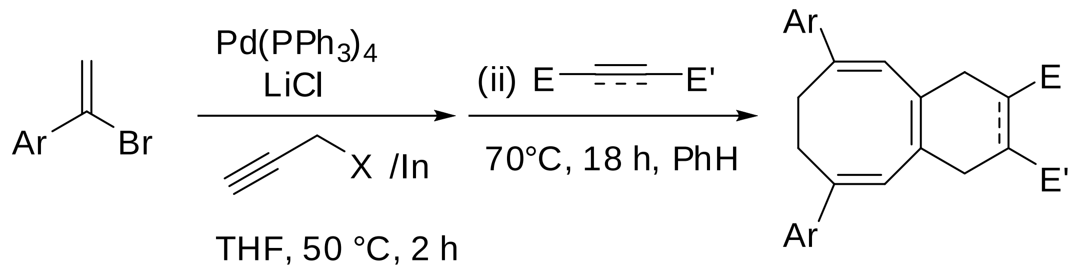


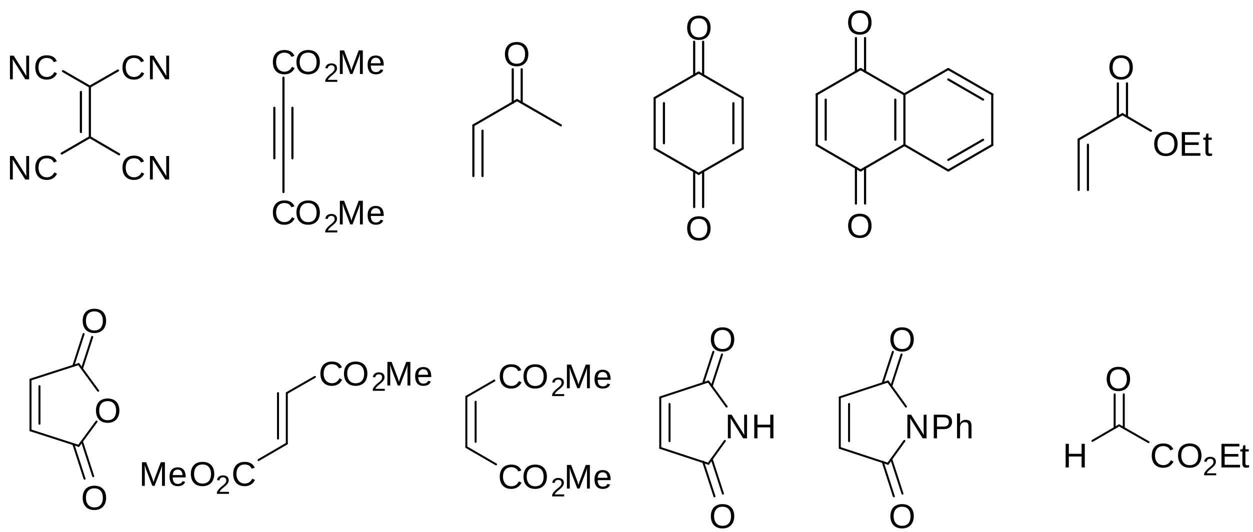
Substrate Scope for Pd-Catalyzed Tandem Cross-Coupling/[4 + 4] Cycloaddition



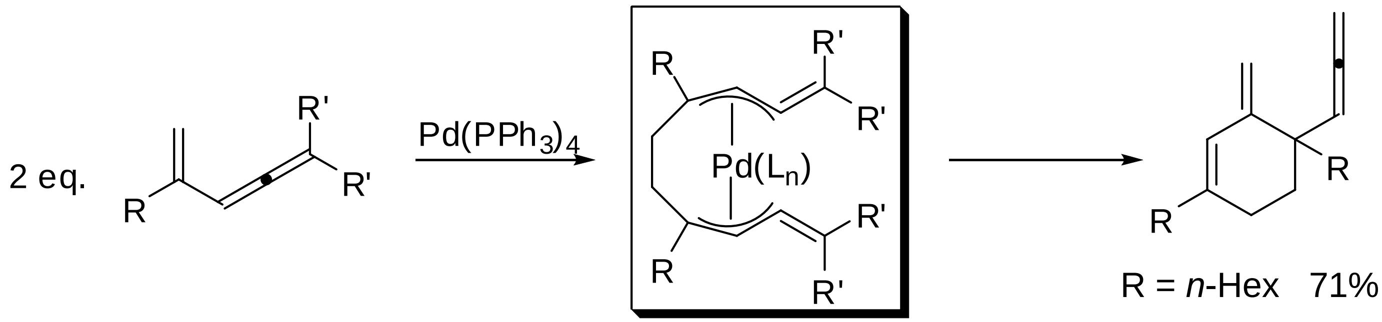


Substrate Scope for Dienophile for in [4 + 2] Cycloaddition

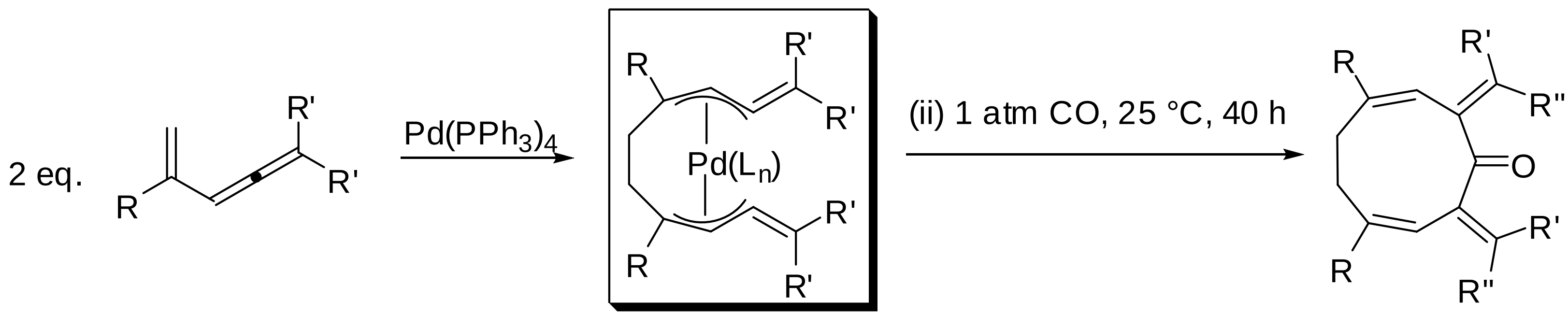


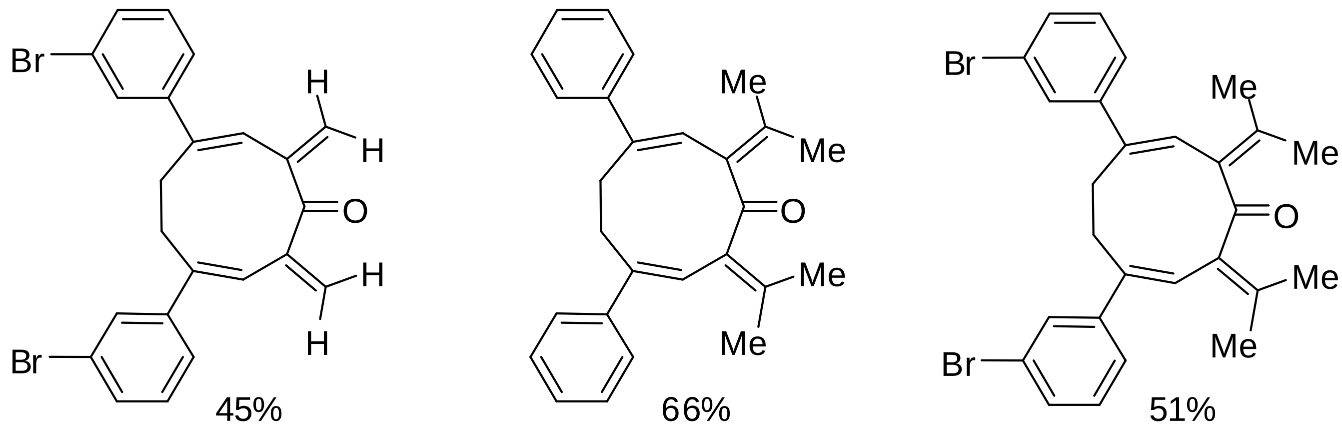


Pd-Catalyzed Cross-Coupling/[4 + 2]Cycloaddition



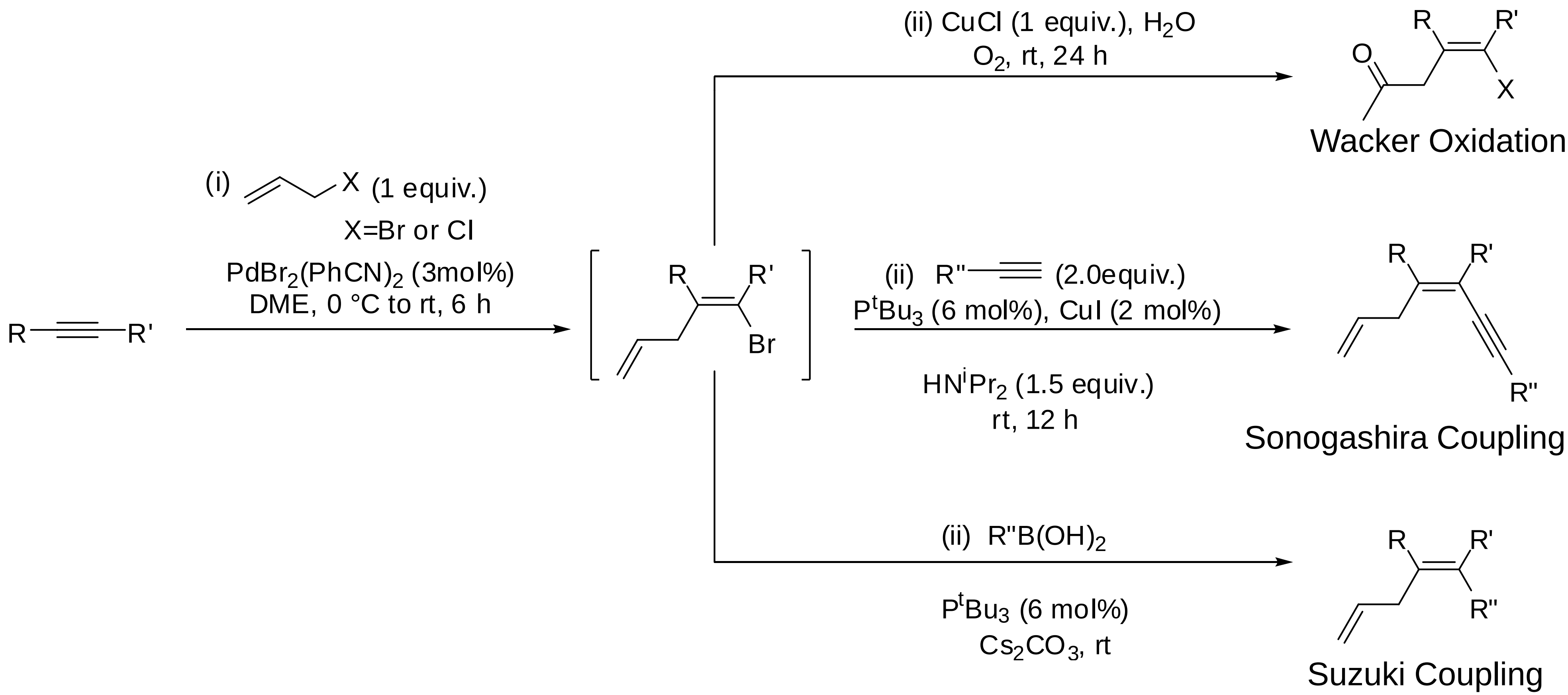
Pd-Catalyzed Cross-Coupling/[4 + 4 + 1]Cycloaddition





Pd-Catalyzed Tandem Allylation/Wacker-Tsuji Oxidation or Cross-Coupling

(Assisted Tandem Catalysis)



-Synthesis of tetrasubstituted skipped dienes

-Three reactions possible in tandem with allylation

-Rxn conditions may be modified in between transformations

Thadani, A.; Rawal, V.; *Org. Lett.* **2002**, *4*, 4317.
Thadani, A.; Rawal, V.; *Org. Lett.* **2002**, *4*, 4321.

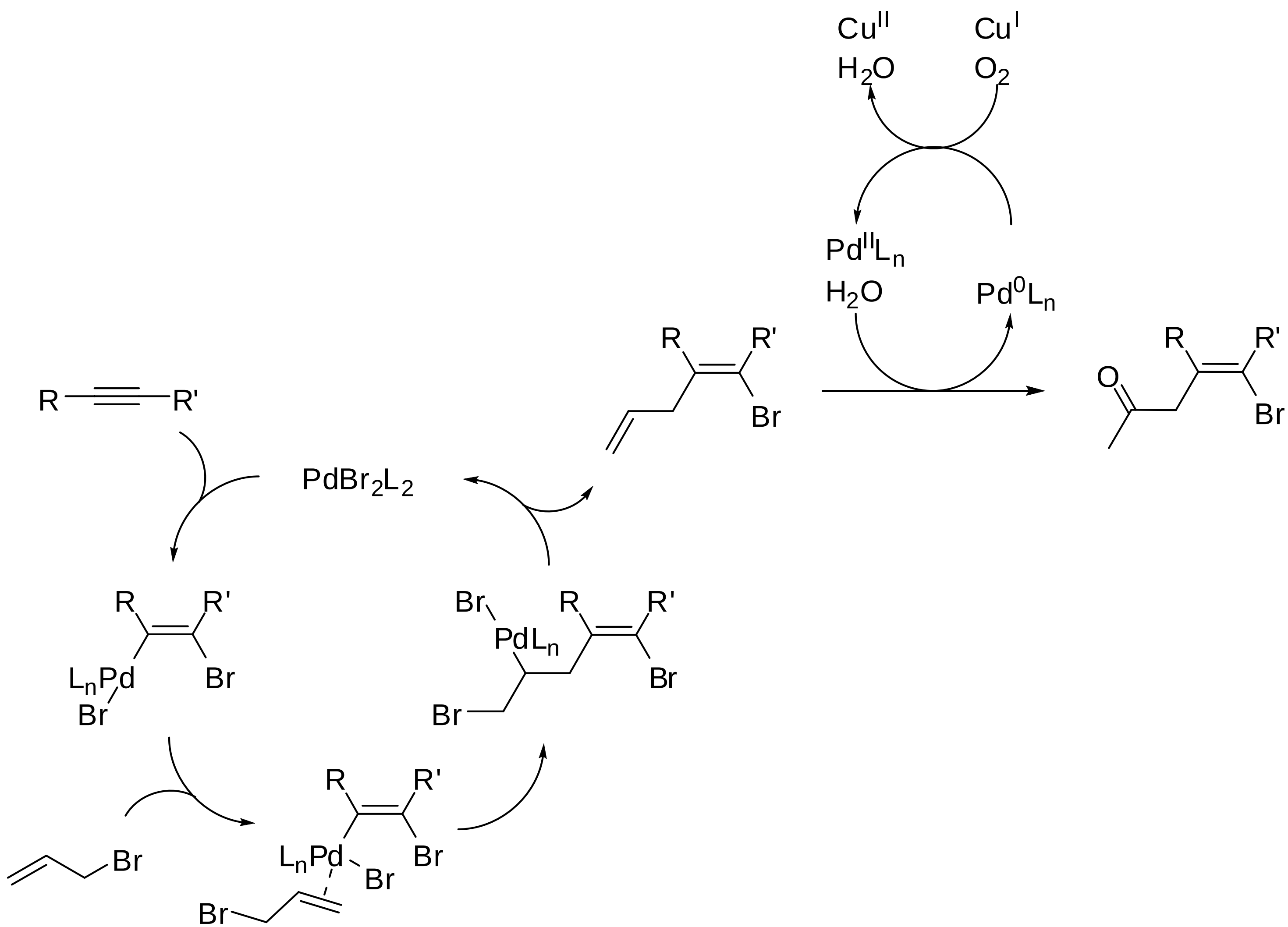
Catalyst Triggered Change

Allylation Catalyst: $PdBr_2(PhCN)_2$ —trigger→ New Catalyst: $Pd^*(L)_n$

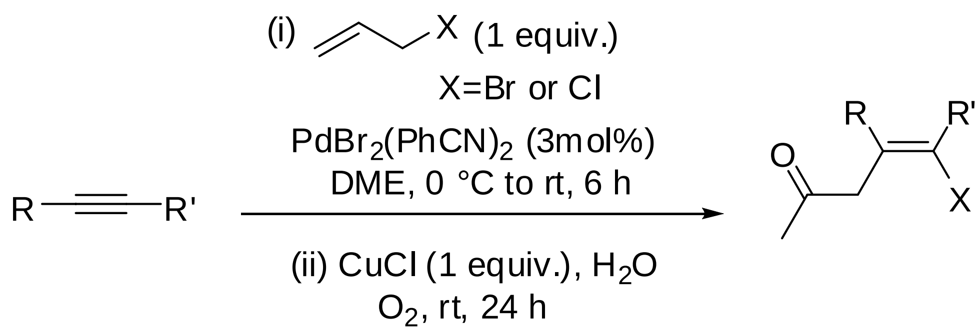
Reaction Tandem to Haloallylation:		Catalyst Triggers:		New Active Catalyst
Oxidation	+	CuCl, O_2	→	Regenerates active $Pd^{II}(L)_n$ catalyst
Suzuki	+	$RB(OH)_2$, P^tBu_3	→	$Pd^0(P^tBu_3)_2$
Sonogashira	+	R''—≡, P^tBu_3, CuI, HN^iPr_2	→	$Pd^0(P^tBu_3)_2$

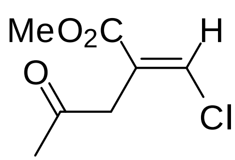
Thadani, A.; Rawal, V.; *Org. Lett.* **2002**, *4*, 4317.
Thadani, A.; Rawal, V.; *Org. Lett.* **2002**, *4*, 4321.

Pd-Catalyzed Allylation/Wacker-Tsuji Oxidation

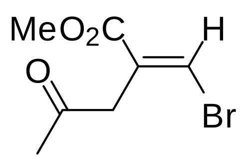


Substrate Scope for Pd-Catalyzed Tandem Allylation/ Wacker-Tsuji Oxidation

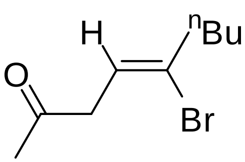




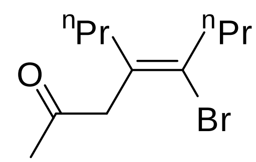
75%



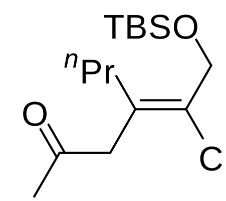
74%



70%

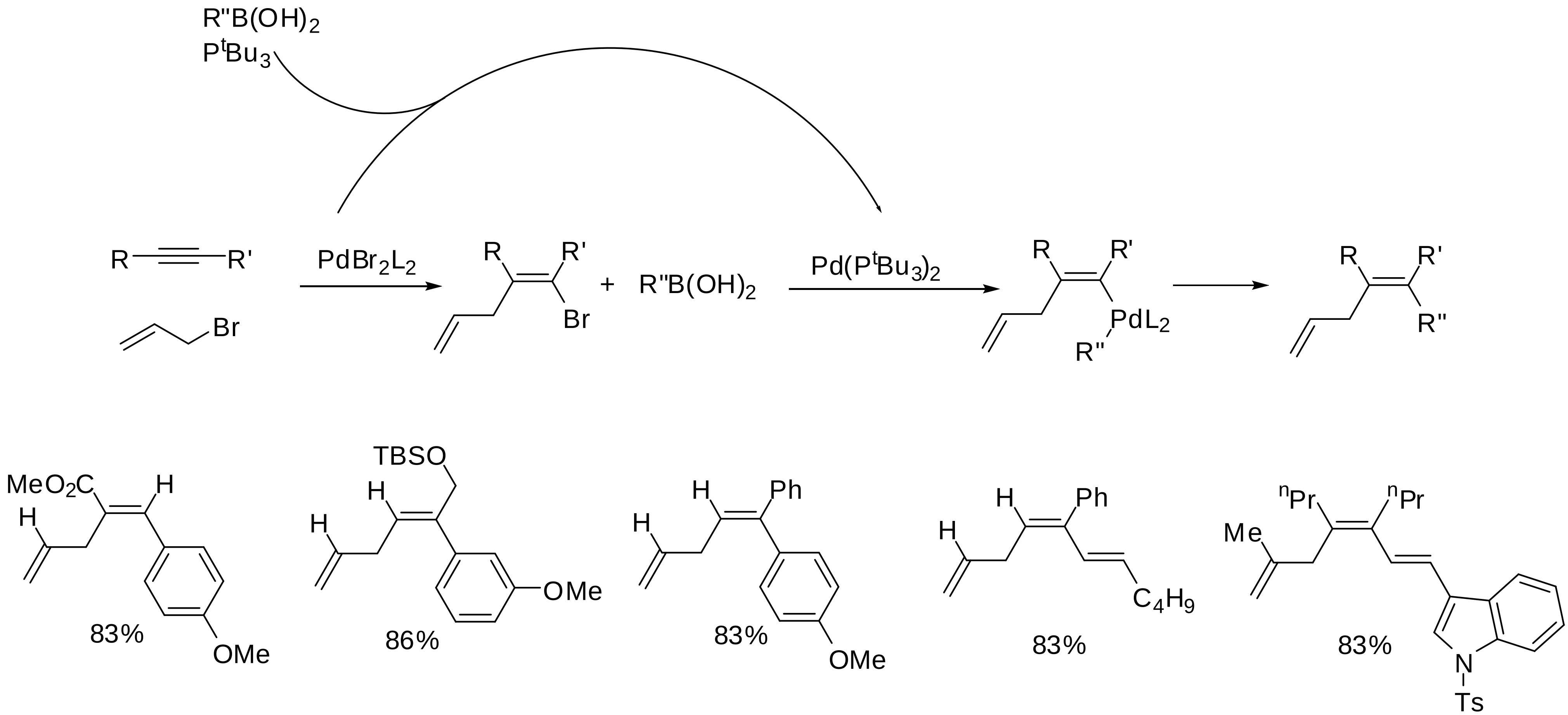


80%

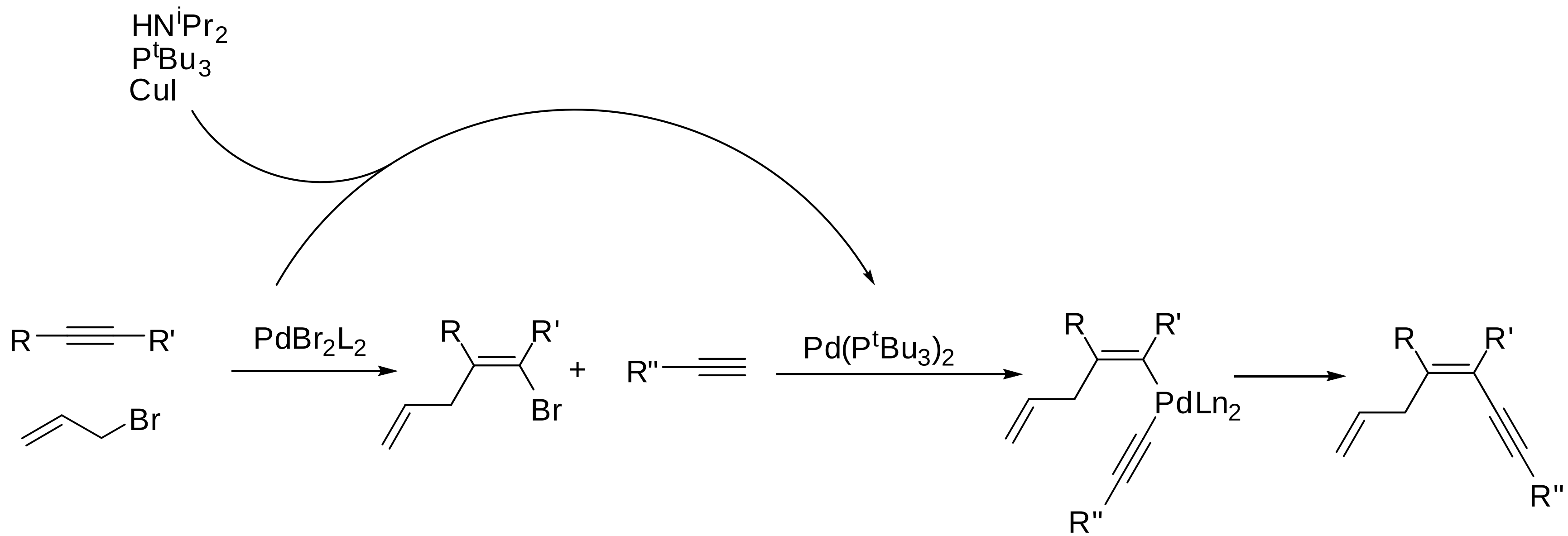


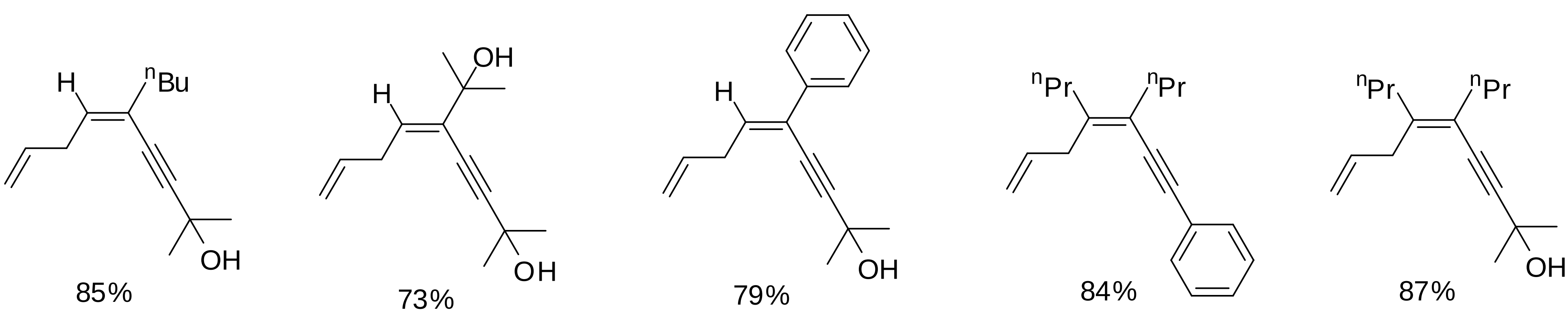
66%

Pd-Catalyzed Allylation/Suzuki Cross-Coupling



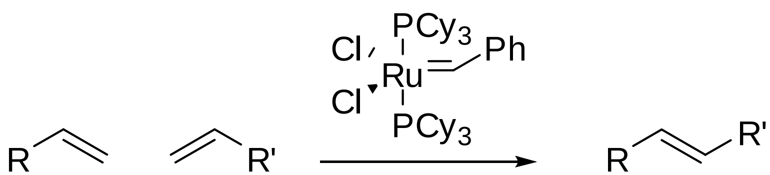
Proposed Mechanism for Pd-Catalyzed Allylation/Sonogashira Cross-Coupling



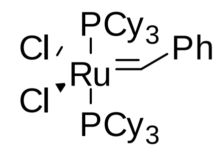


Ru-Catalyzed Metathesis Reactions and Catalysts

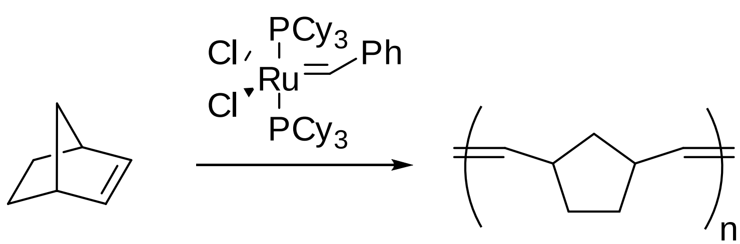
Cross metathesis



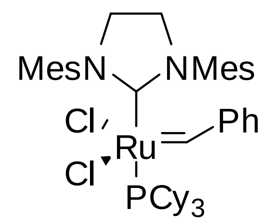
Grubbs first gen. catalyst



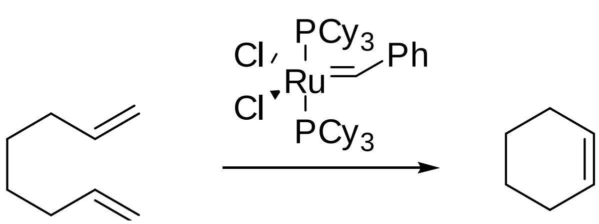
Ring opening metathesis polymerization



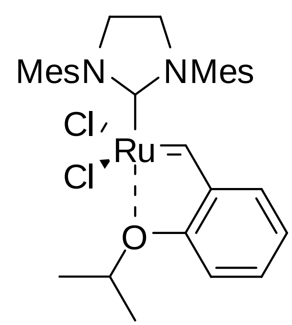
Grubbs second gen. catalyst



Ring closing metathesis

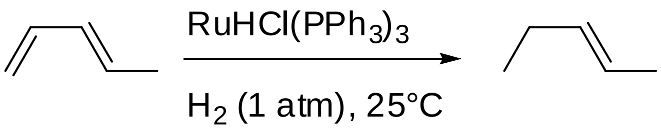


Grubbs-Hoveyda catalyst

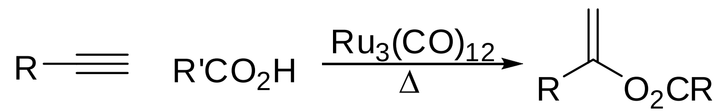


Individual Ru-Catalyzed Reactions

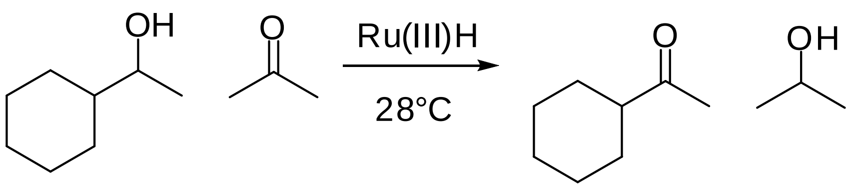
Hydrogenation



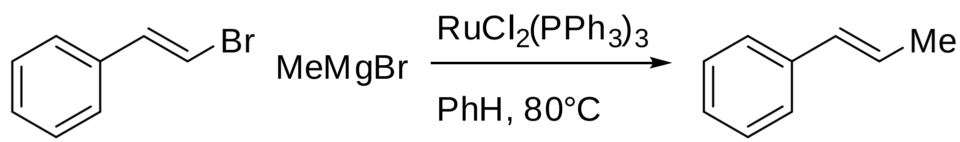
Nucleophilic attack of an alkyne



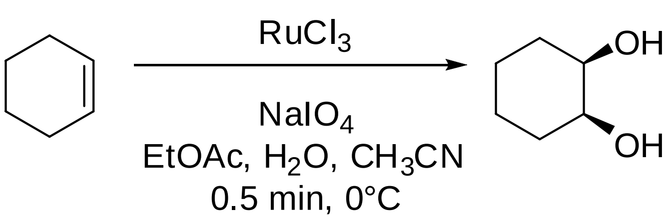
Oxidation of an alcohol



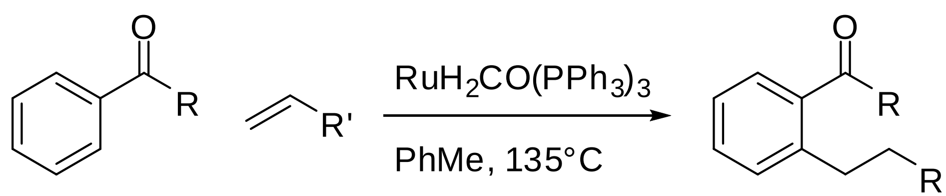
Cross-coupling



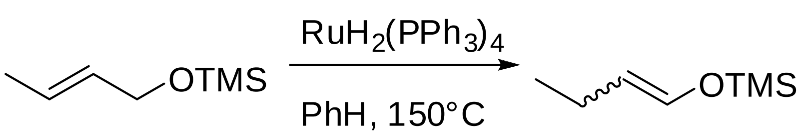
Dihydroxylation of an alkene



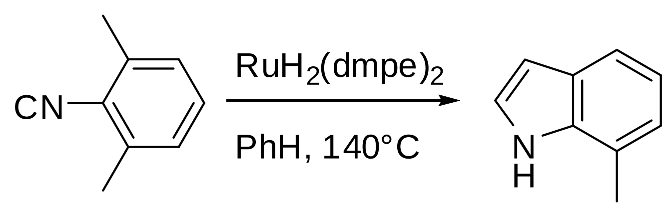
sp^{2-}C-H activation



Olefin isomerization

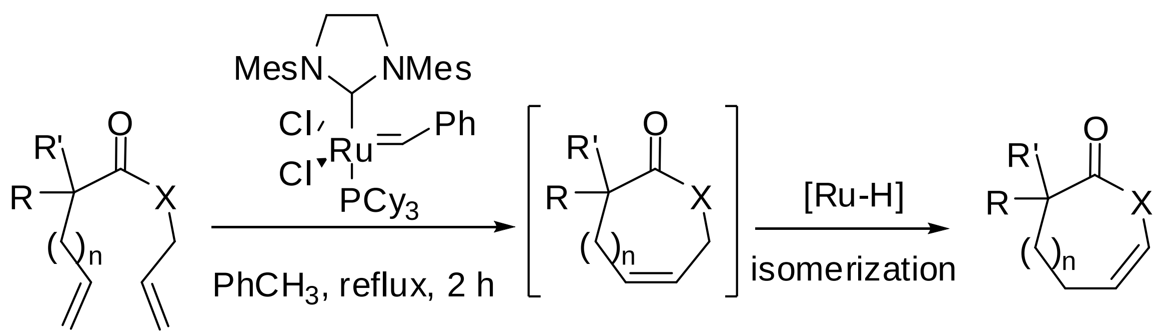


sp^3-C-H activation



Ru-Catalyzed Tandem Ring-Closing Metathesis/ Olefin Isomerization

(Auto-Tandem Catalysis)

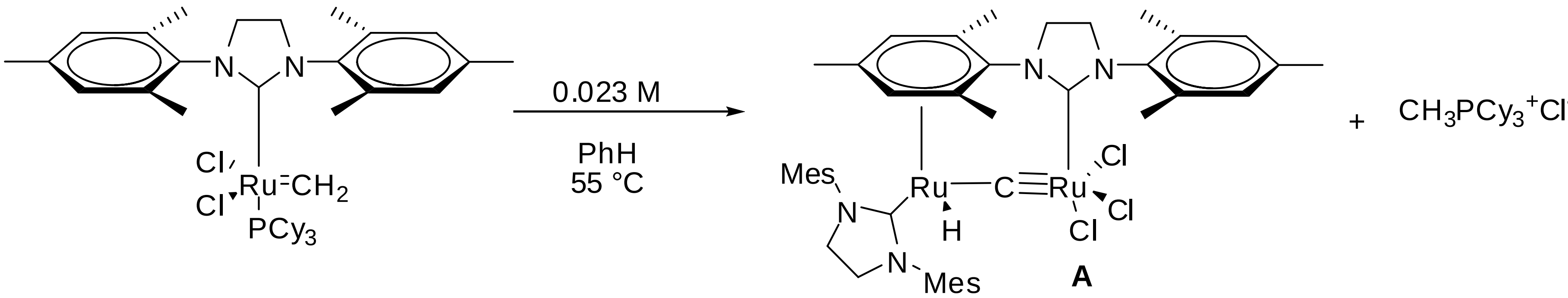


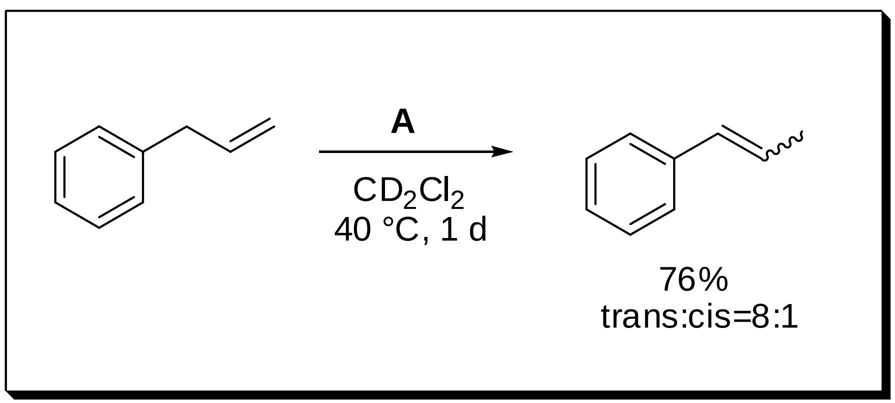
-Rapid formation of unsaturated carbo- and heterocycles

-Five, six, and seven-membered rings formed

Fustero, S.; Sanchez-Rosello, M.; Jimenez, D.; Sanz-Cervera, J.; del Pozo, C.; Acena, J.; *J. Am. Chem. Soc.* **2005**, *127*, 13148.

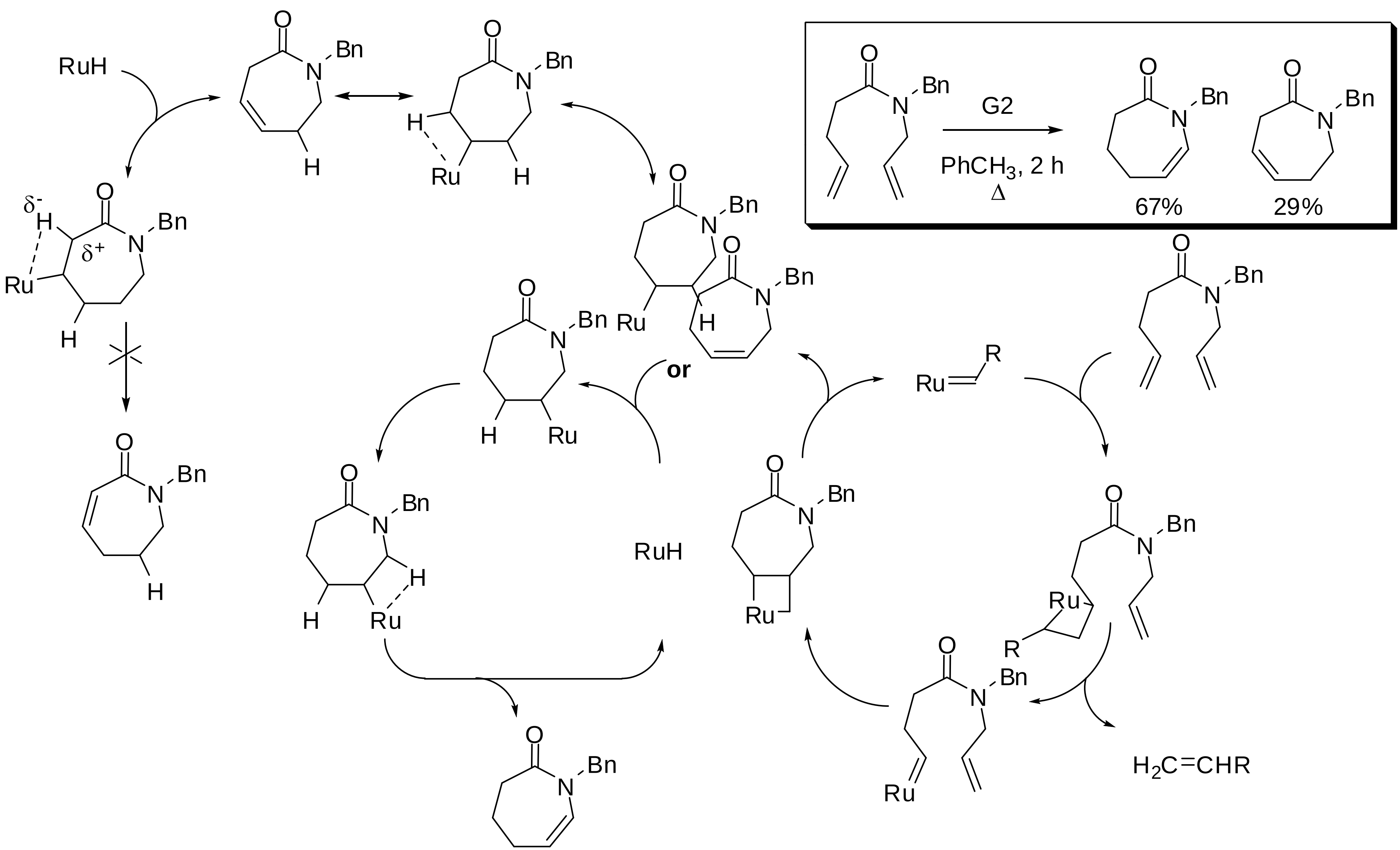
Ru-H Species formation from G2





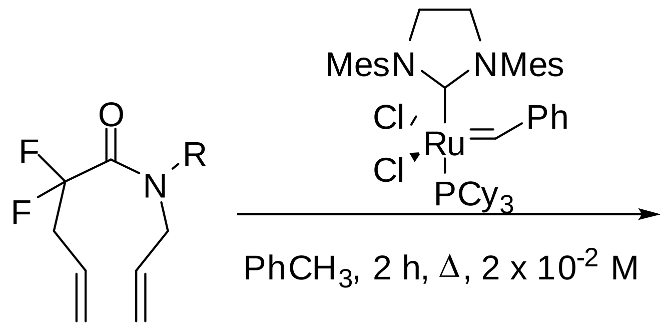
Hong, S.; Day, M.; Grubbs, R.; *J. Am. Chem. Soc.* **2006**, *124*, 7414.

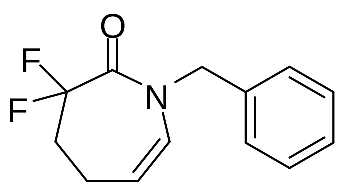
Proposed Mechanism for Ru-Catalyzed RCM/Olefin Isomerization



Fustero, S.; Sanchez-Rosello, M.; Jimenez, D.; Sanz-Cervera, J.; del Pozo, C.; Acena, J.; *J. Am. Chem. Soc.* **2005**, *127*, 13148

Substrate Scope for Ru-Catalyzed Ring-Closing Metathesis/ Olefin Isomerization





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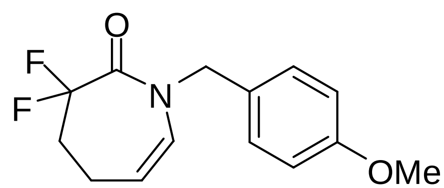

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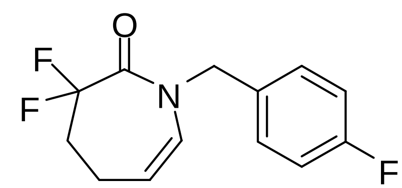

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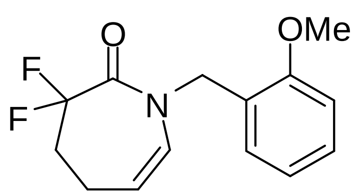

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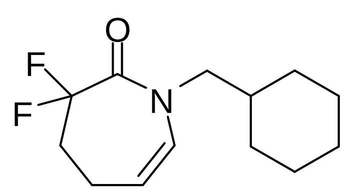

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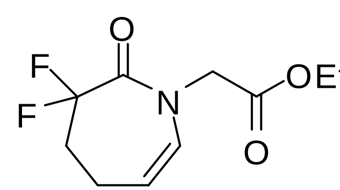
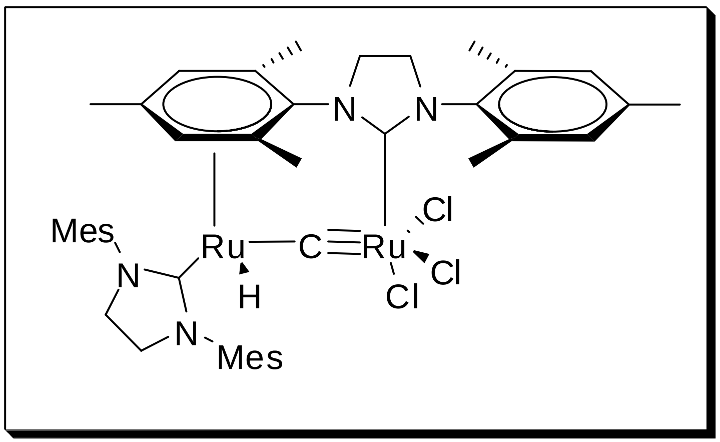
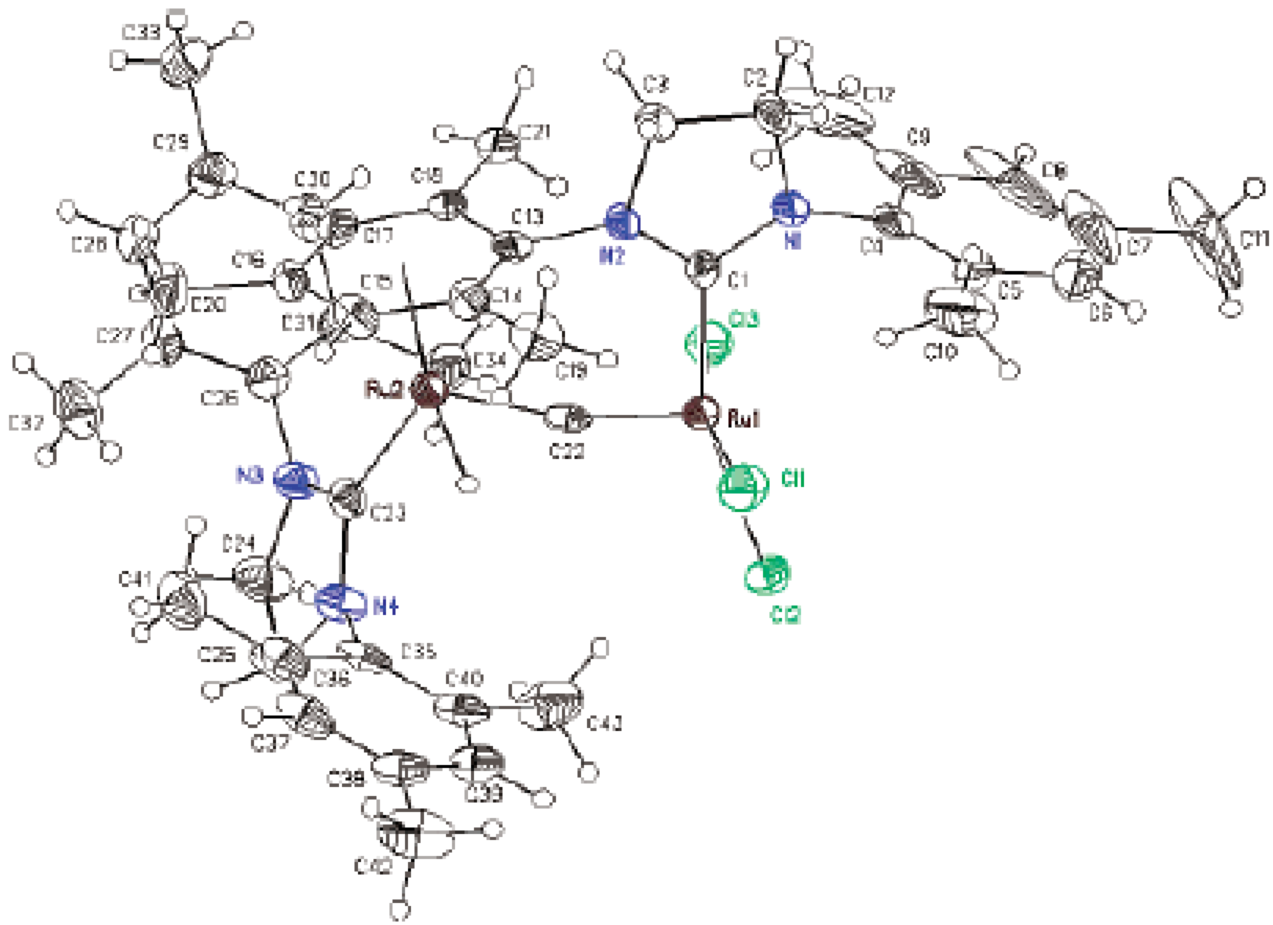


91%

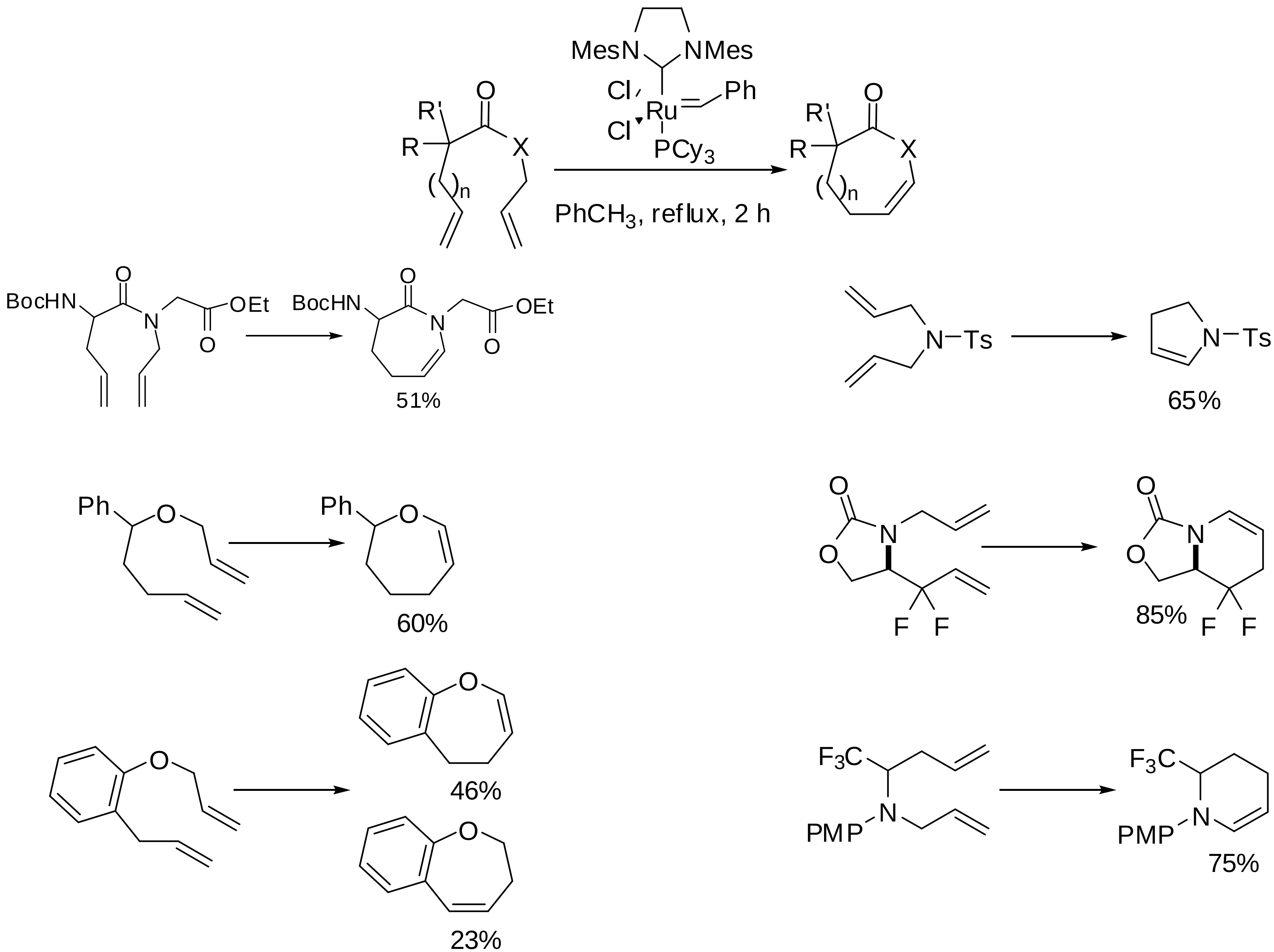
Fustero, S.; Sanchez-Rosello, M.; Jimenez, D.; Sanz-Cervera, J.; del Pozo, C.; Acena, J.; *J. Am. Chem. Soc.* **2005**, *127*, 13148.

Ru-H Catalyst Structure

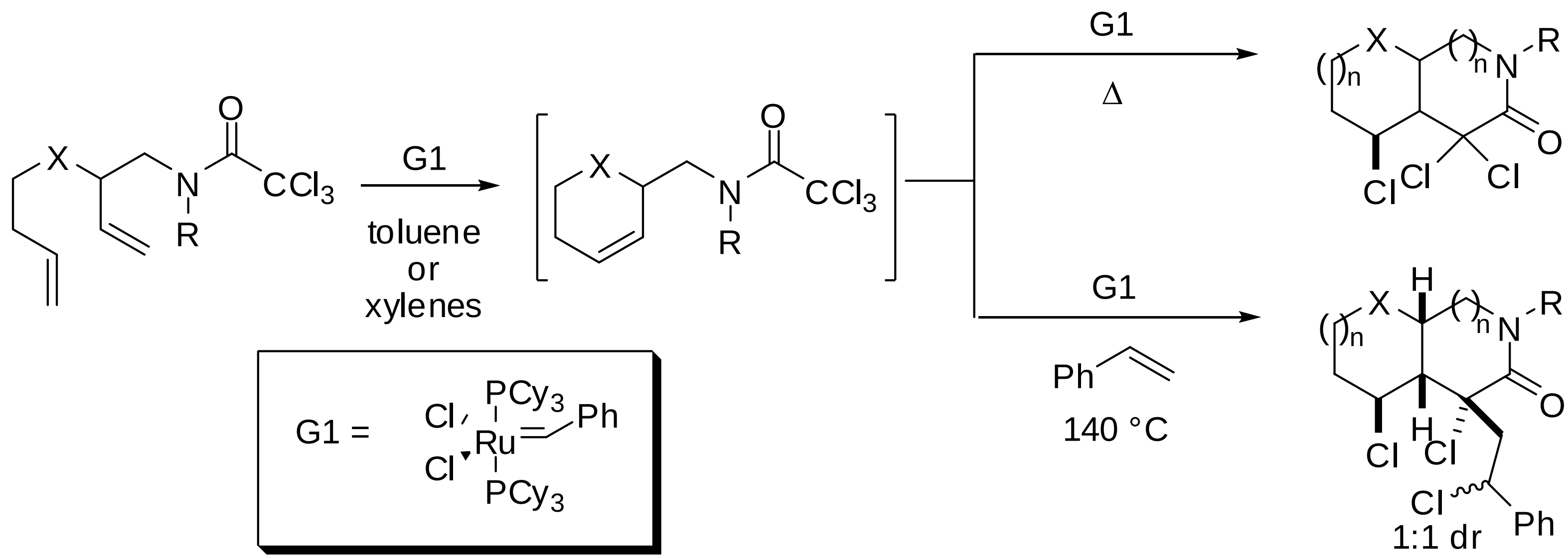




Substrate Scope for Ru-Catalyzed Ring-Closing Metathesis/ Olefin Isomerization



Ru-Catalyzed Tandem Ring-Closing Metathesis/ Kharasch Addition
(Auto-Tandem Catalysis)



-Up to three new C-C bonds and two new C-X bonds

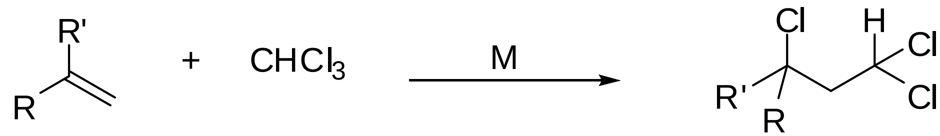
-Substrate set up for further functionalization

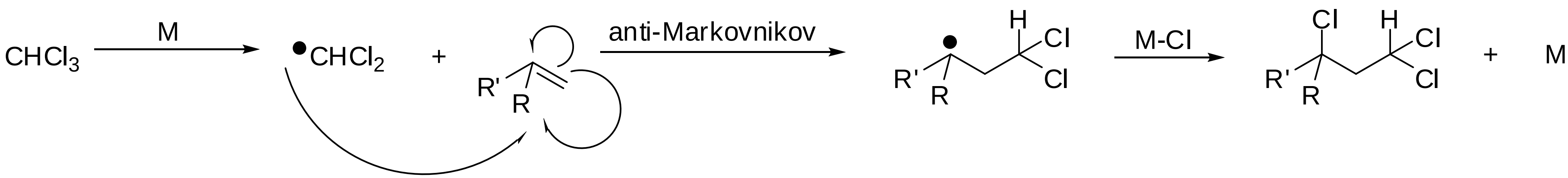
-Two rings formed from linear structure

-No manipulation of Ru catalyst required

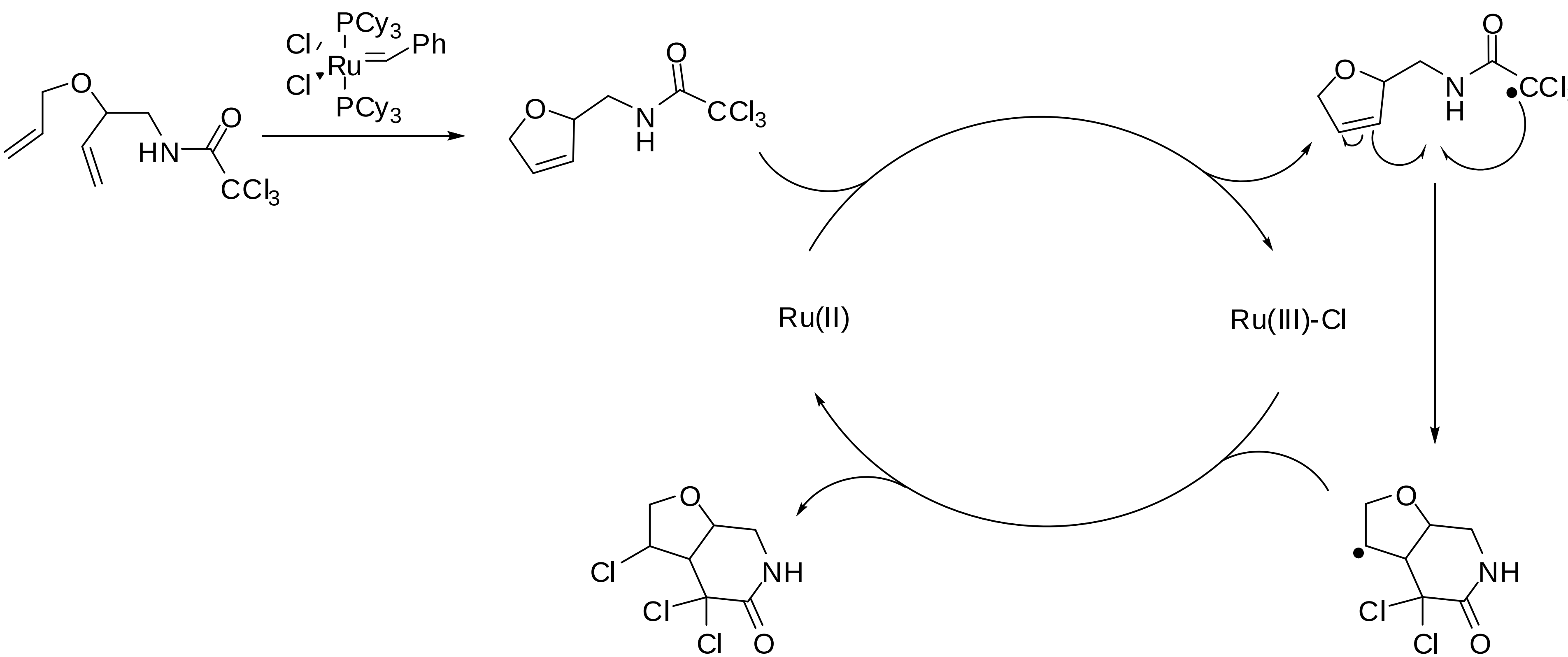
Seigal, B.; Fajardo, C.; Snapper, M.; *J. Am. Chem. Soc.* **2005**, *127*, 16329.
Schmidt, B.; Pohler, M.; *J. Am. Chem. Soc.* **2005**, *690*, 5552.

Kharasch Addition



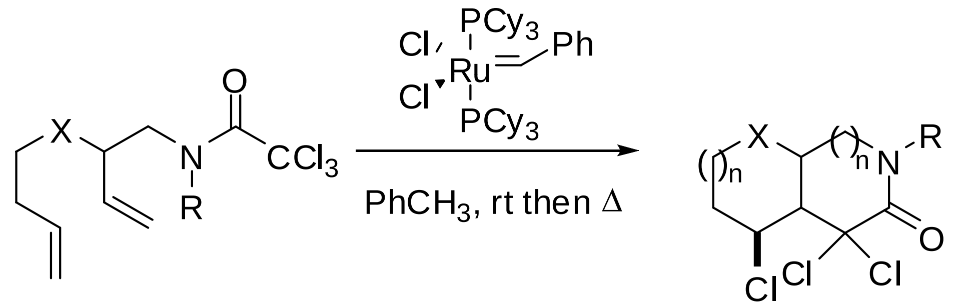


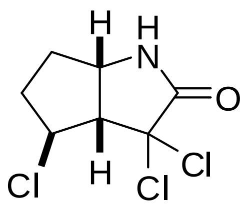
Proposed Mechanism for Ru-Catalyzed RCM/Kharasch Addition



Nagashima, H.; *et al.* *J. Org. Chem.* **1992**, *57*, 1682.

Substrate Scope for Ru-Catalyzed Ring-Closing Metathesis/ Intramolecular Kharasch Addition





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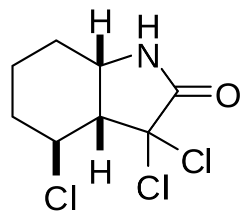

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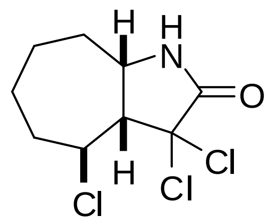

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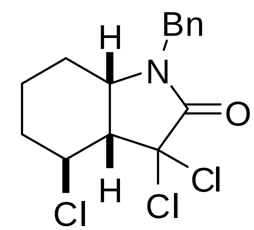

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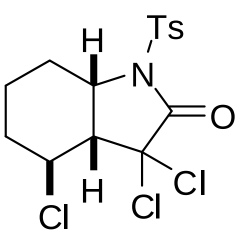

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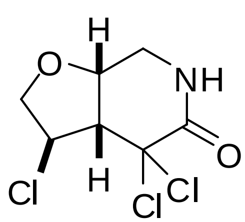

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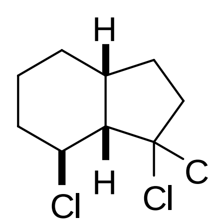

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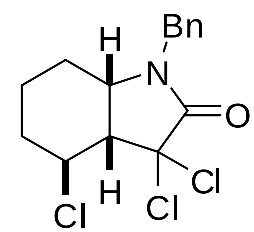
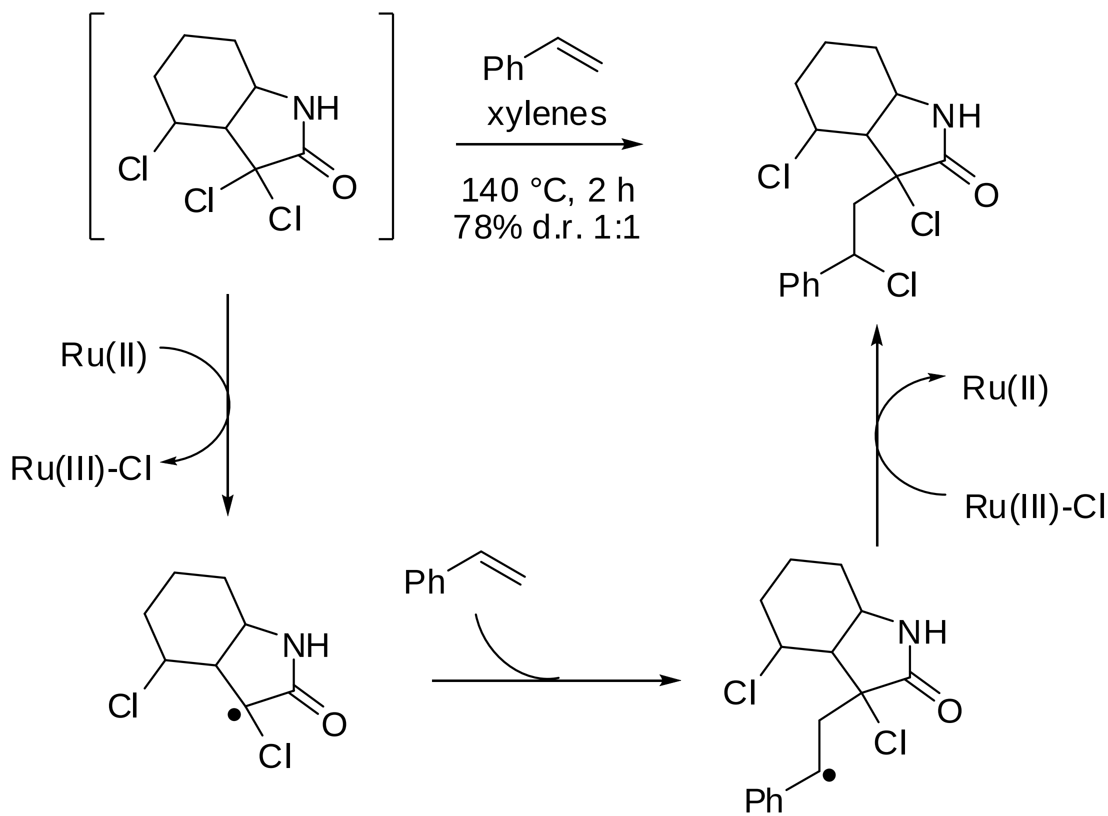


50%

Seigal, B.; Fajardo, C.; Snapper, M.; *J. Am. Chem. Soc.* **2005**, *127*, 16329.

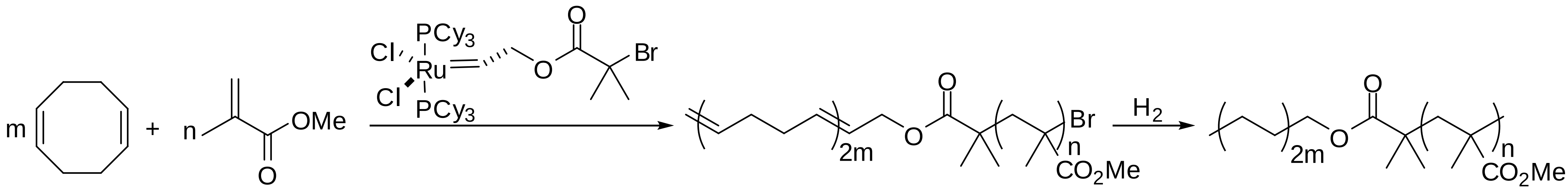
Proposed Mechanism for Second Tandem Kharasch Addition

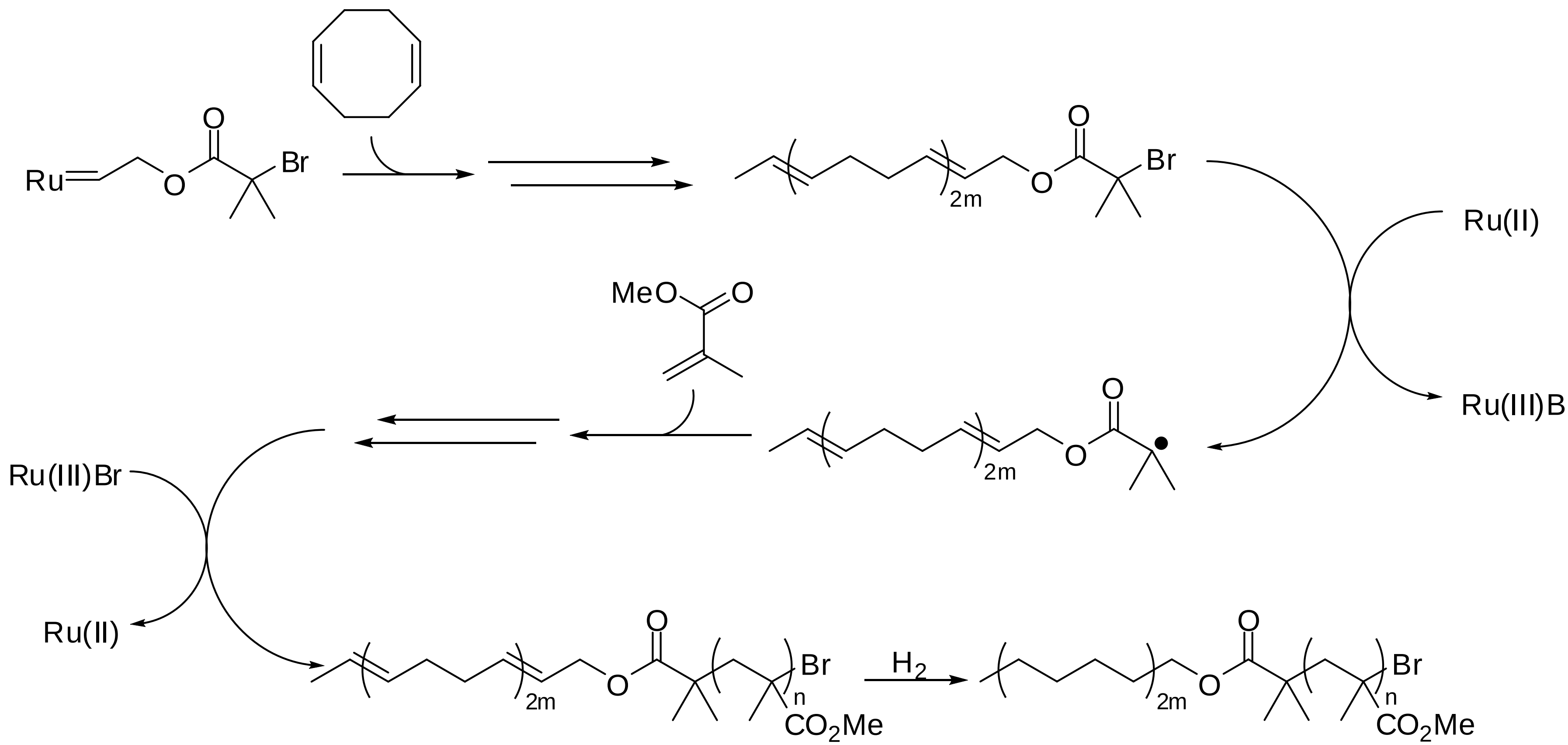


Seigal, B.; Fajardo, C.; Snapper, M.; *J. Am. Chem. Soc.* **2005**, *127*, 16329.

Ru-Catalyzed Tandem ROMP/ATRP/Olefin Hydrogenation

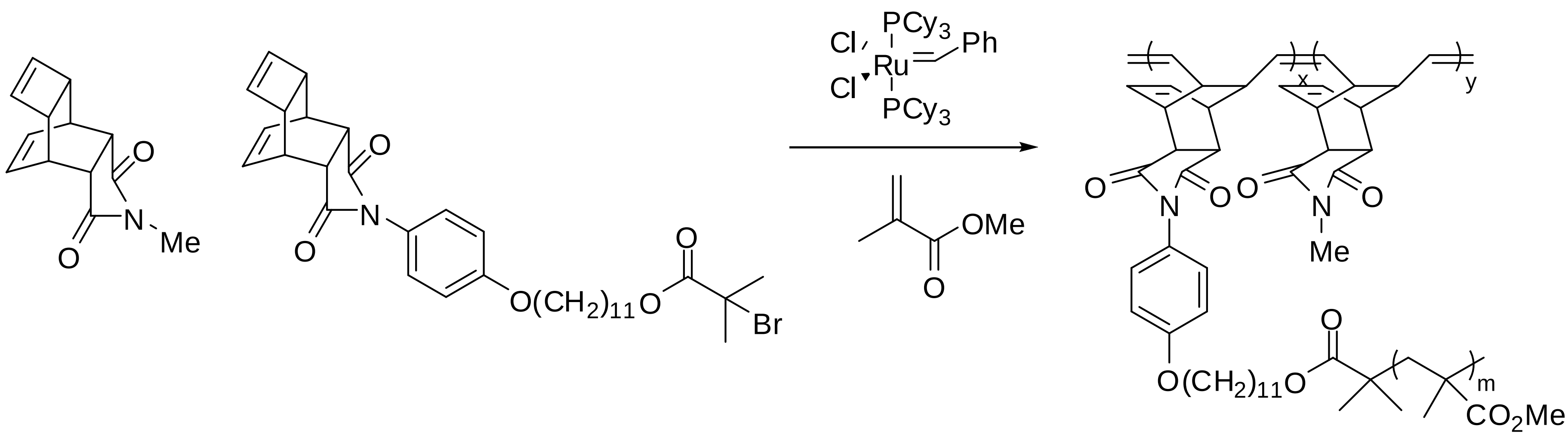
(An Extension of the G1 Kharasch Reactivity)





Bielawski, C.; Louie, J.; Grubbs, R.; *J. Am. Chem. Soc.* **2000**, *122*, 12872.

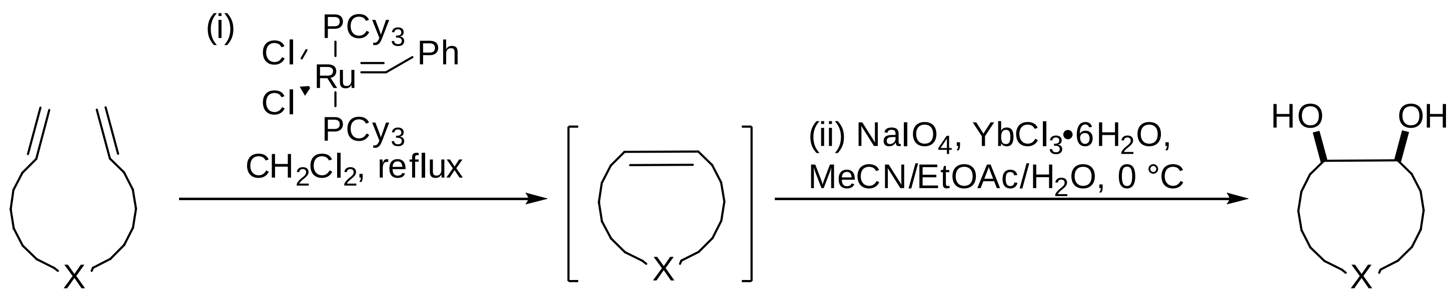
A Similar Approach



Charvet, R.; Novak, B. *Macromolecules*, **2004**, *37*, 8808.

Ru-Catalyzed Tandem Ring Closing Metathesis/Dihydroxylation

(Assisted Tandem Catalysis)



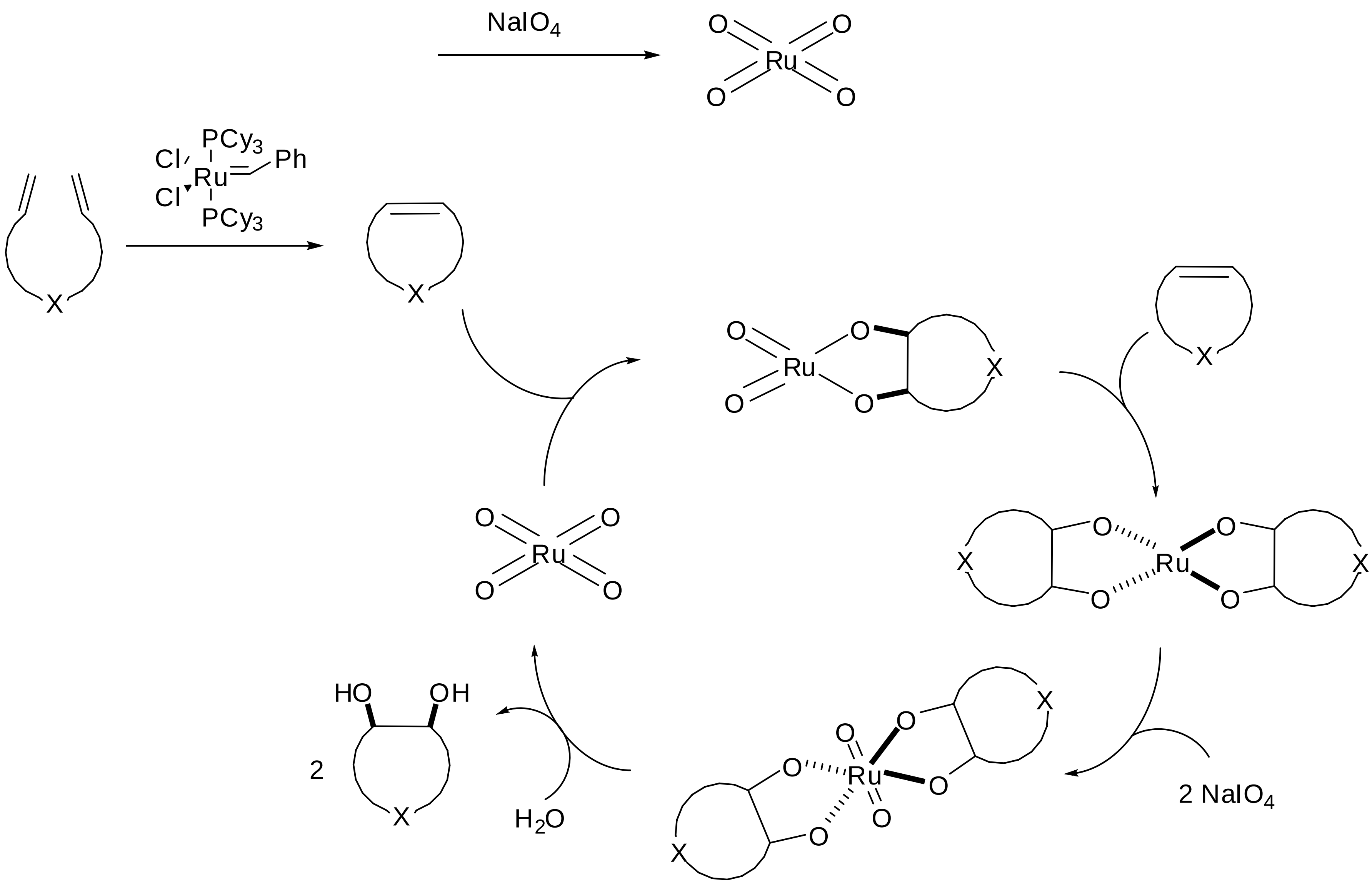
-One new C-C bond and two new C-O bonds formed

-Rapid reaction times

-Low catalyst loading

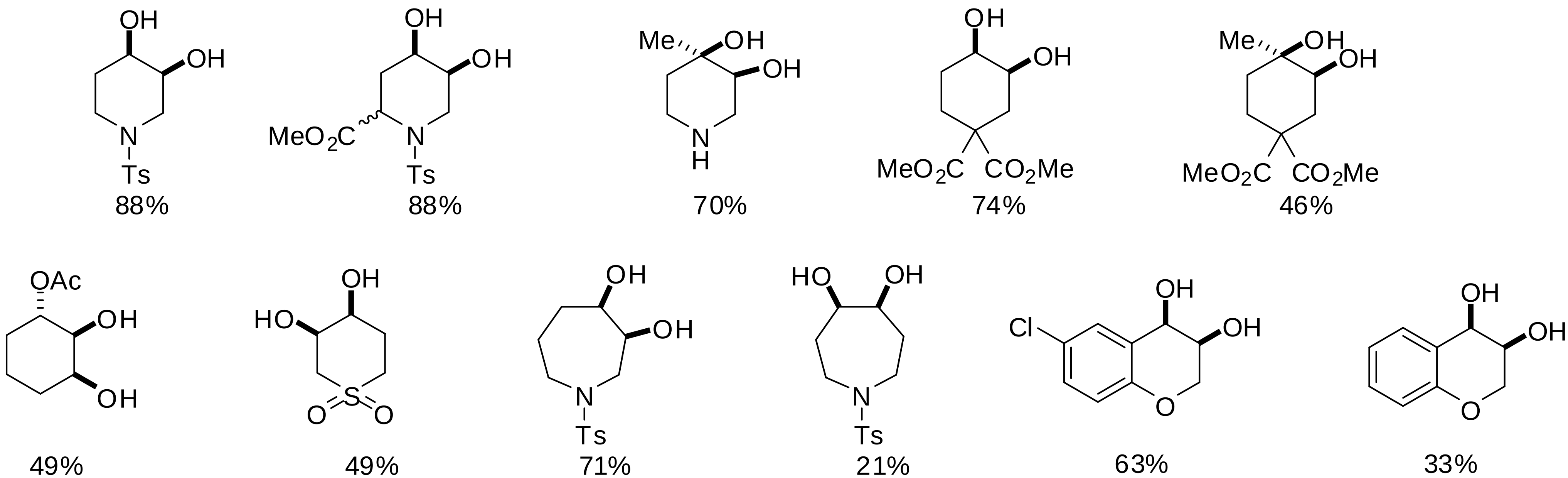
Beligny, S.; *et al*. *Angew. Chem. Int. Ed.* **2006**, *45*, 1900.

Proposed Mechanism of Ru-Catalyzed RCM/Dihydroxylation

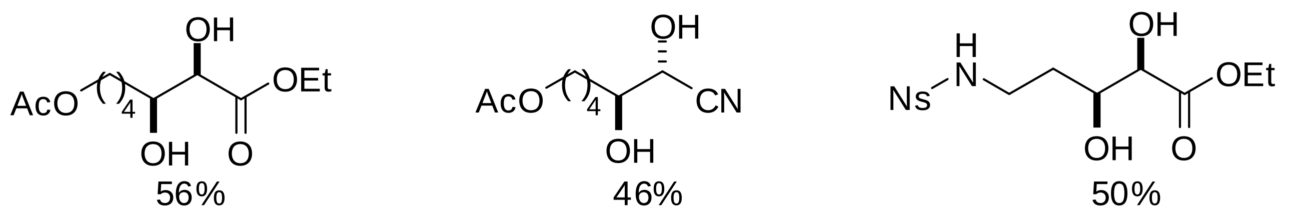


Frunzke, J.; Loschen, C.; Frenking, G.; *J. Am. Chem. Soc.* **2003**, *126*, 3642.

Substrate Scope for Ru-Catalyzed RCM/Dihydroxylation

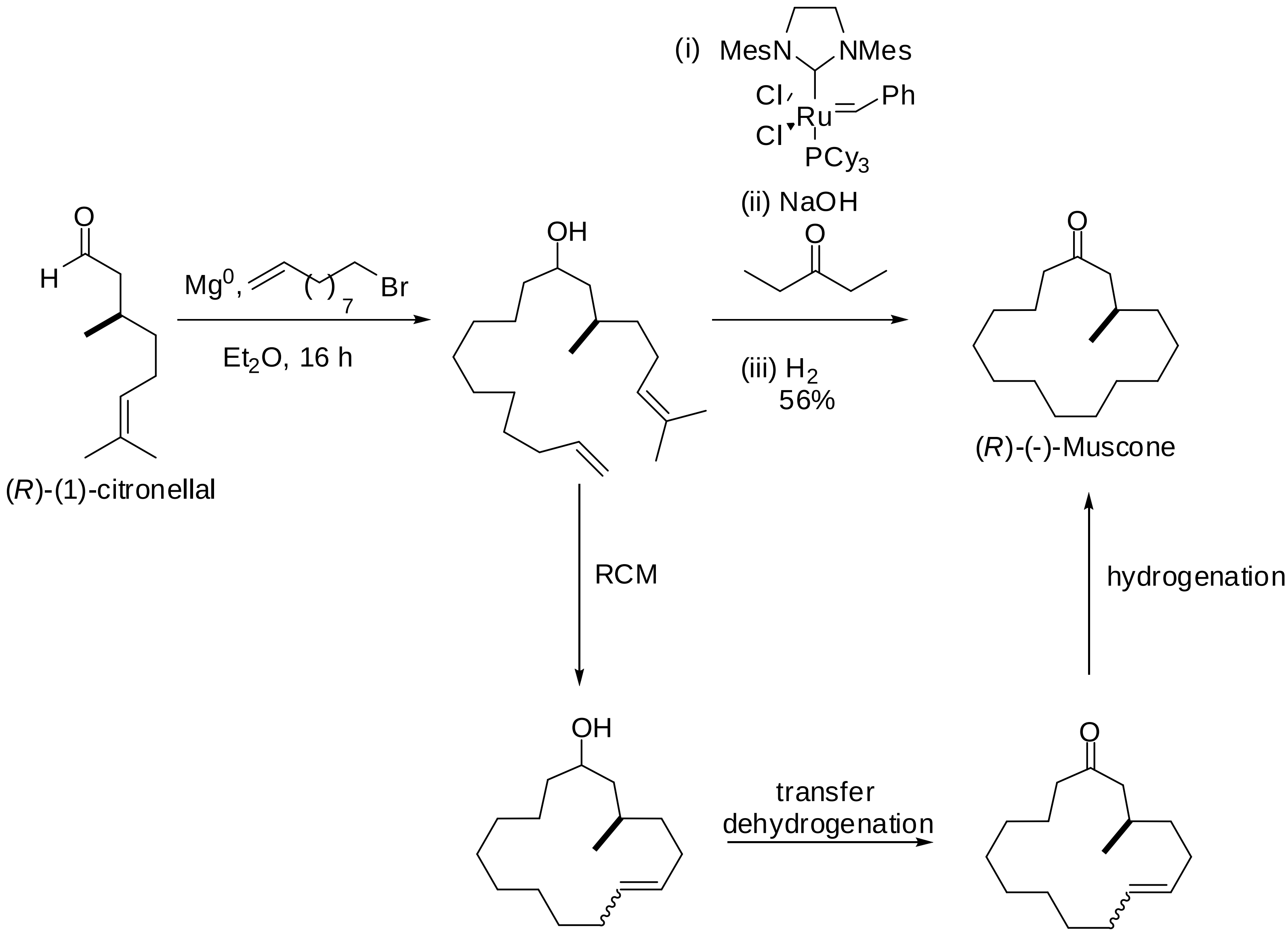


Tandem Cross-Metathesis/Dihydroxylation:



Beligny, S.; *et al*. *Angew. Chem. Int. Ed.* **2006**, *45*, 1900.

Synthesis of (*R*)-(-)-Muscone



Louie, J.; Bielawski, C.; Grubbs, R.; *J. Am. Chem. Soc.* **2001**, *123*, 11312.
Kamat, V.; *et al*.; *Tetrahedron* **2000**, *56*, 4937.

Summary

-Tandem catalysis is more cost and time efficient

-Multiple bonds in one flask

-Pd and Ru have further potential in tandem reactions

-Organic chemists have only begun to explore tandem catalysis

Acknowledgements

Professor Michael T. Crimmins

Crimmins Group:

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Amran Gowani
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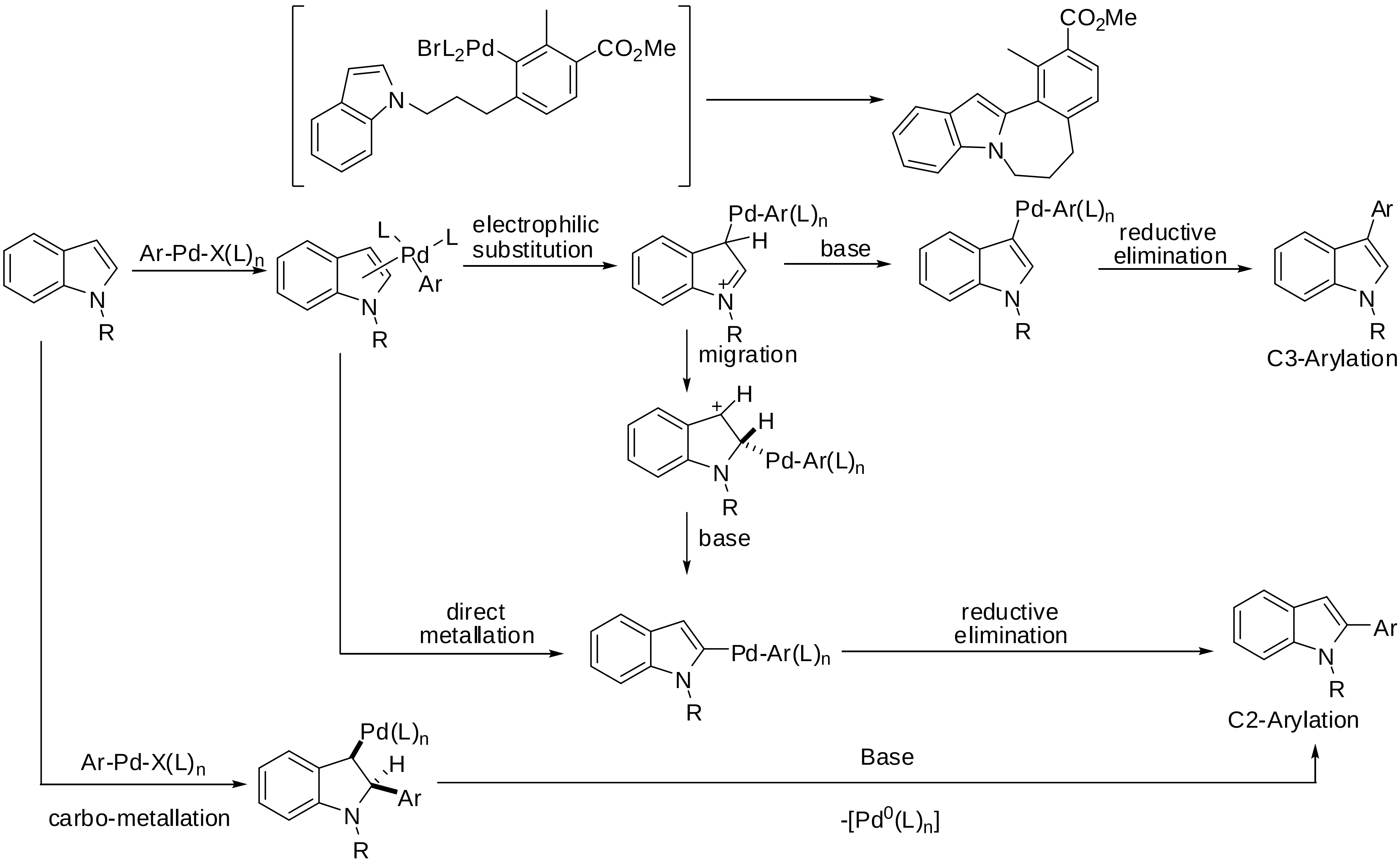
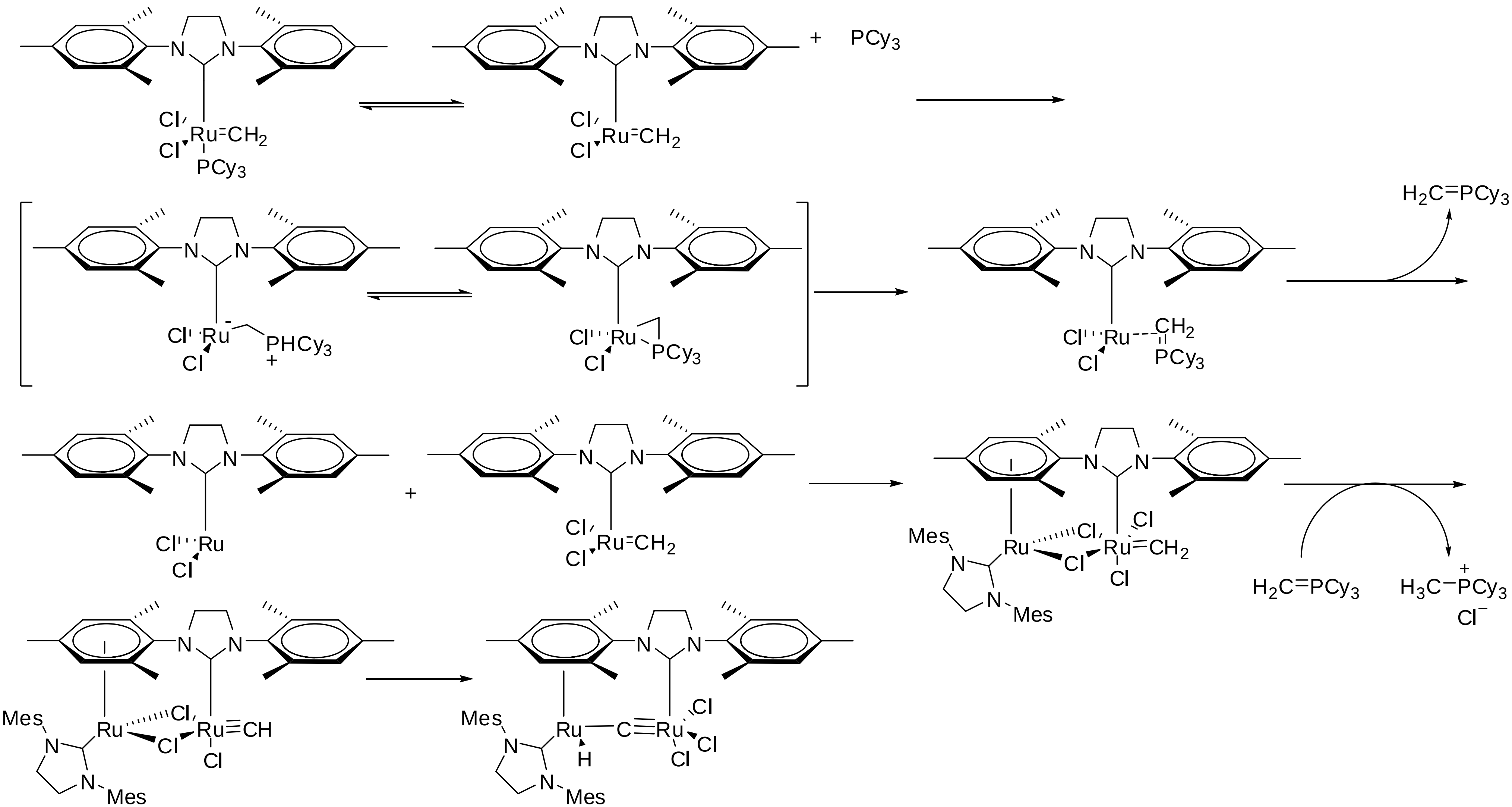
Erin Milner
Dr. Greg Schaaf
Mariam Shamszad
Todd Showalter
Aaron Smith
Yan Zhang
Luke Zuccarello
Adam Azman
Jay Stevens

Possible Mechanisms for C-2 Indole Substitution



Lane, B.; Brown, M.; Sames, D.; *JACS* **2005**, *127*, 8050.

Proposed Mechanism of Ru-Hydride Formation



Hong, S.; Day, M.; Grubbs, R.; *J. Am. Chem. Soc.* **2006**, *124*, 7414.