

Nickel-Catalyzed Cycloadditions

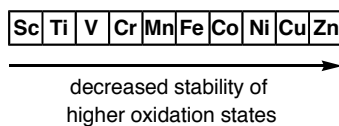
Tristan Lambert
 MacMillan Group Meeting
 January 31, 2001

- Properties of nickel
- Introduction to metal-catalyzed cycloadditions
- Nickel-catalyzed cycloadditions

Review of metal-catalyzed cycloadditions: Lautens, *Chem. Rev.*, **1996**, *96*, 49.

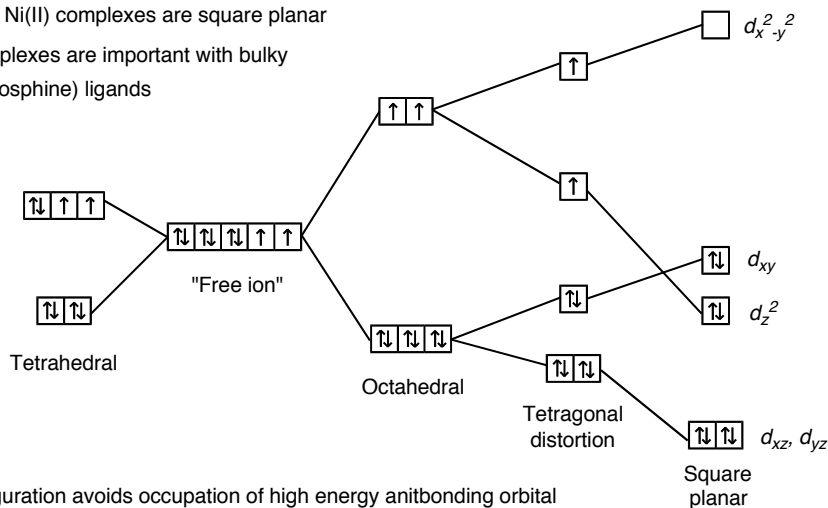
Physical Properties of Nickel

- Across the first row of transition metals, there is a trend towards decreased stability of higher oxidation states such that only Ni(II) occurs in the normal chemistry of the element



Cotton, *Advanced Inorganic Chemistry*, 6th ed.; p. 835

- The vast majority of Ni(II) complexes are square planar
- Tetrahedral Ni complexes are important with bulky (i.e. phosphine) ligands

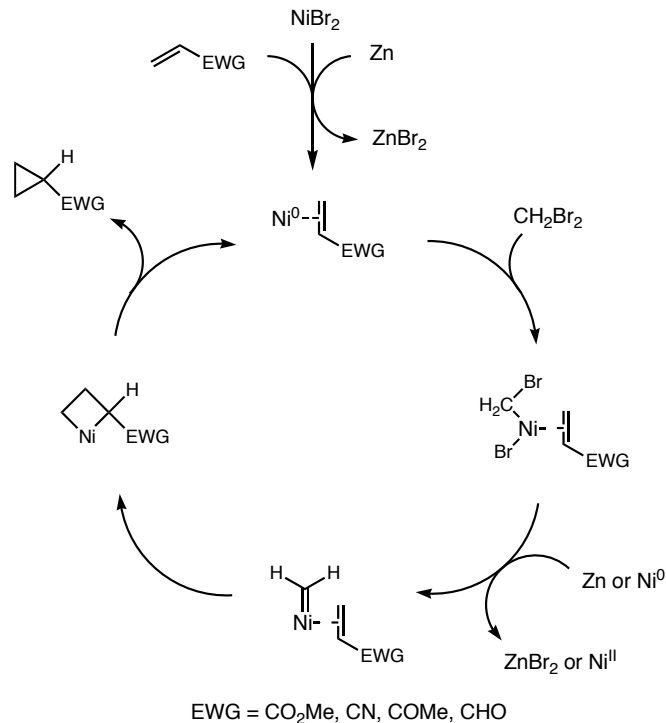


- Square planar configuration avoids occupation of high energy antibonding orbital

Greenwood, *Chemistry of the elements*; p. 1347

Catalytic Cycle of Ni(II) Catalyzed Cyclopropanation

■ Catalytic Cycle



Notes:

■ Differences with the Simmons-Smith reaction

1. Electron deficient olefins are more reactive than electron rich olefins
2. Dibromomethane is more suitable than diiodomethane
3. No cyclopropanation occurs in diethyl ether (reactions performed in THF)

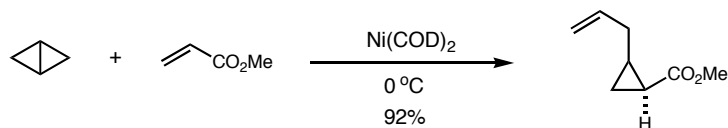
- 10-20 mol% ZnBr₂ or AlCl₃ additive dramatically increases yields. >50 mol% dramatically decreases yields. Excess NaI (4 eq) is also beneficial.

- The role of Lewis acids and solvent has not been clarified

Kanai, *Bull. Chem. Soc. Jpn.*, **1983**, 53, 1025.

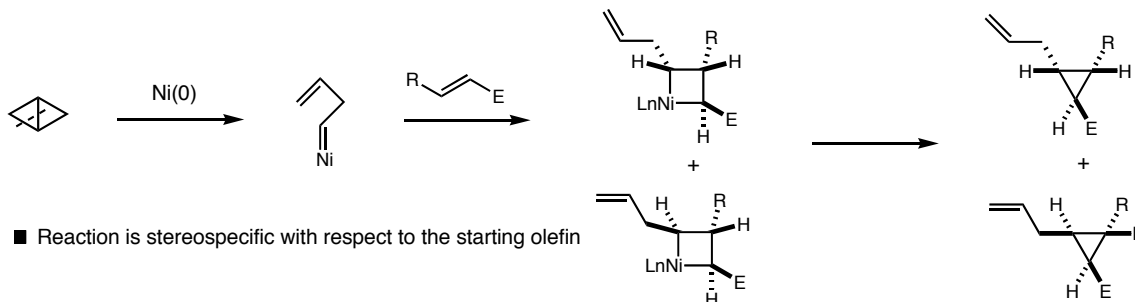
[2 + 1] Cycloadditions: Nickel Carbenes From Highly Strained Hydrocarbons

- Bicyclo[1.1.0]butane: strain energy 66 kcal/mol



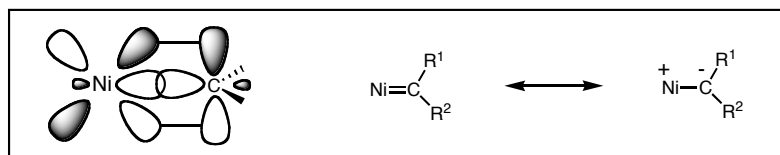
Noyori, *Tetrahedron Lett.*, **1974**, 1749.

■ Mechanism:



- Reaction is stereospecific with respect to the starting olefin

■ Nature of bonding in Ni-carbene

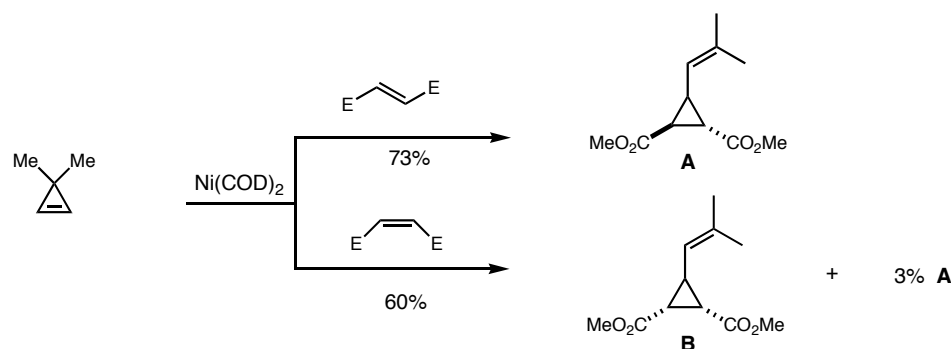


- Carbenoids involving metals with high backbonding capacity have considerable ylide character

- Nickel has low electronegativity \rightleftharpoons carbenoid carbon nucleophilic

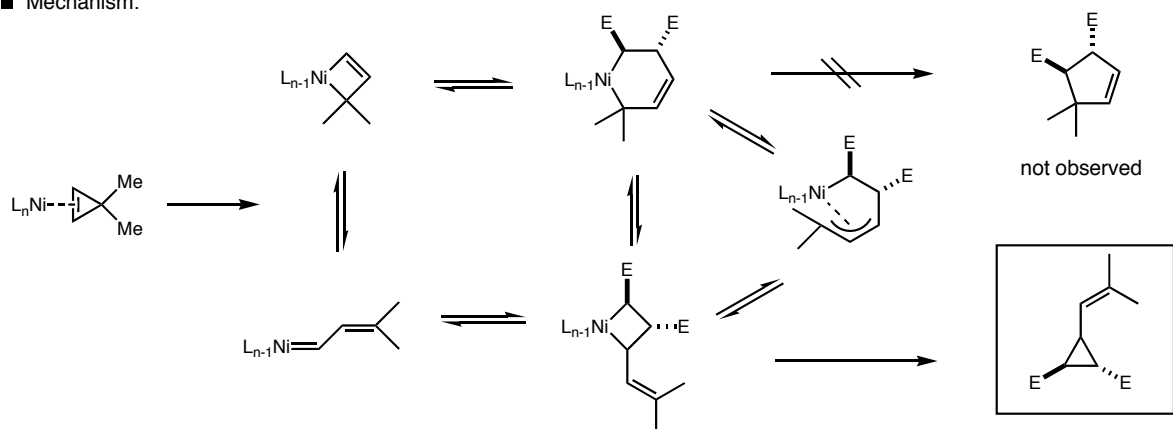
Noyori, *Tetrahedron Lett.*, **1973**, 1691.

[2 + 1] Cycloadditions: Vinyl Carbenes



■ Cis maleate undergoes Ni-catalyzed isomerization leading to small amounts of trans product

■ Mechanism:

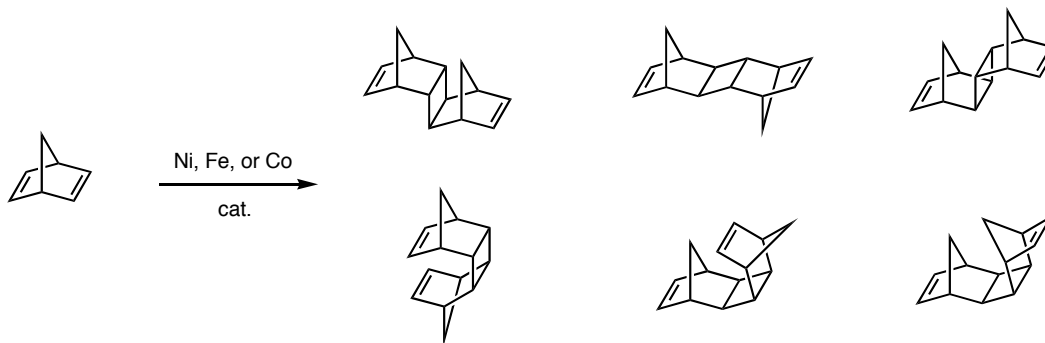


Binger, *Chem. Ber.*, 117, 1984, 1551.

[2 + 2] Cycloadditions: Catalysis of Thermally Forbidden Processes

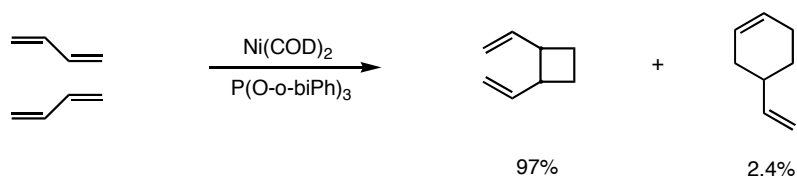
Early Examples

■ Dimerization of Norbornadiene



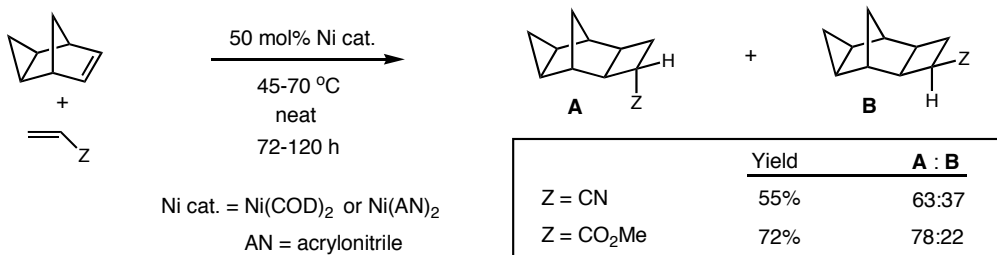
Vallerino, *J. Chem. Soc.*, 1957, 2287.

■ Dimerization of 1,3-butadiene



Heimbach, *ACIEE*, 1967, 6, 800.

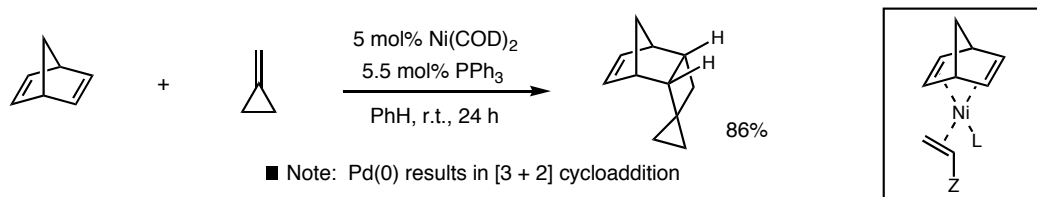
[2 + 2] Cycloadditions: Strained Alkenes and Electron Deficient Olefins



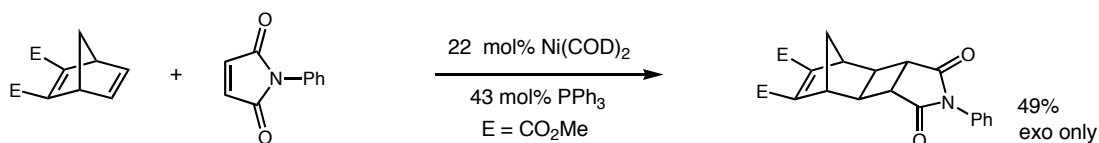
Noyori, *Bull. Chem. Soc. Jpn.*, 55, **1982**, 852.

■ Ni(0) catalyzed reaction of electron deficient olefins with norbornadienes usually gives [2 + 2 + 2] homo-Diels-Alder adducts

■ Certain strained or highly reactive enophiles undergo exclusive [2 + 2] pathway



■ Note: Pd(0) results in [3 + 2] cycloaddition
Noyori, *J. Am. Chem. Soc.*, **1973**, 95, 1674.

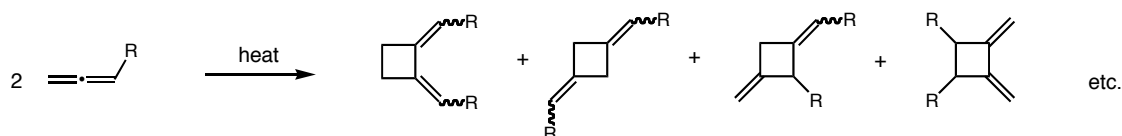


■ When E = electron donating \rightleftharpoons endo products observed (5-12 : 1)

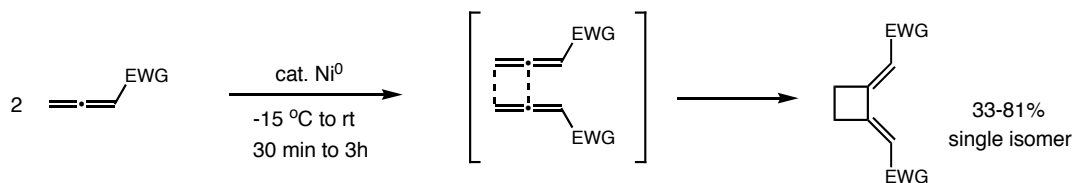
Lautens, *J. Am. Chem. Soc.*, 117, **1995**, 10276.

[2 + 2] Cycloadditions: Electron-Deficient Allenes

■ Thermal [2 + 2] with allenes gives mixture of regioisomers

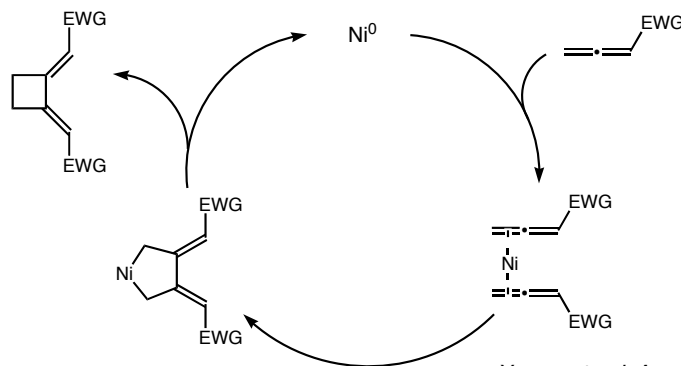


■ Nickel-catalyzed reaction is highly selective



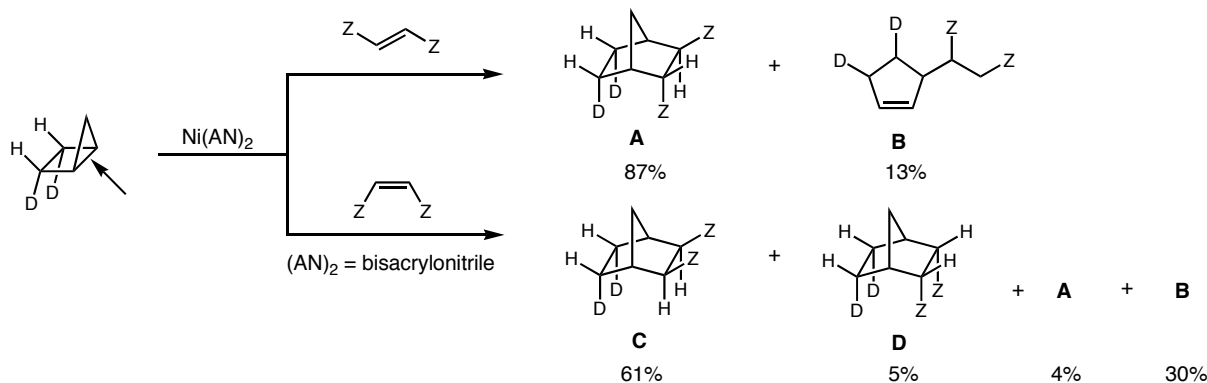
EWG = n-C₆F₁₃, C₆F₅, CO₂Et, CON(Me)Ph, COEt, COPh, SO₂Ph

■ Catalytic cycle

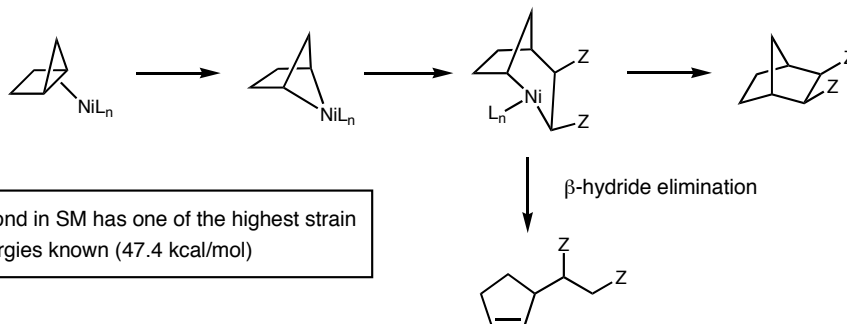


Yamamoto, *J. Am. Chem. Soc.*, **2000**, 122, 10776.

$[3_{2\sigma} + 2_{2\pi}]$ Cycloadditions: Metallocyclobutanes



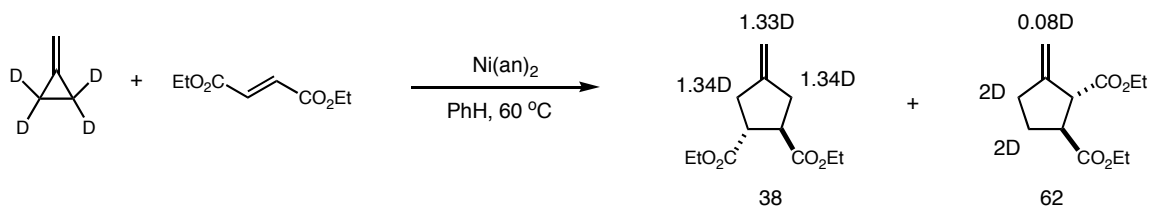
■ Mechanism:



■ Indicated bond in SM has one of the highest strain energies known (47.4 kcal/mol)

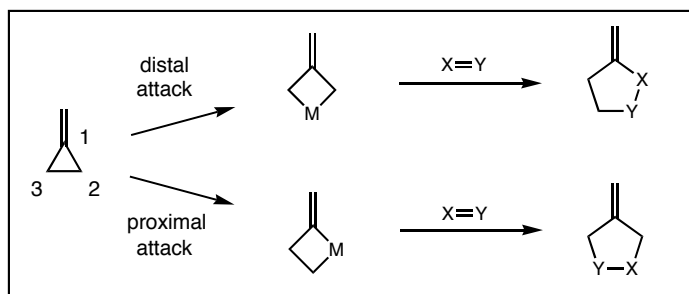
Noyori, *J. Am. Chem. Soc.*, 96, 1974, 634.

$[3_{2\sigma} + 2_{2\pi}]$ Cycloadditions: Methylene cyclopropane



■ Two possible pathways

Noyori, *Tetrahedron Lett.*, 1978, 4823.



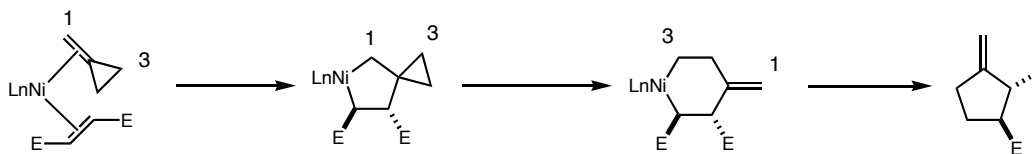
■ "Naked" nickel catalysts such as $\text{Ni}(\text{COD})_2$ favor proximal ring opening

■ Phosphine ligands result in a preference for distal ring opening

■ Palladium reacts exclusively at the distal position

Binger, *Top. Curr. Chem.*, 1987, 135, 77.

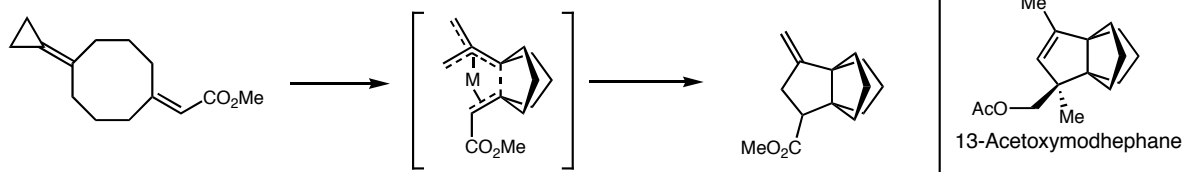
■ Mechanism (proximal attack):



Binger, *Top. Curr. Chem.*, 1983, 116, 1.

Intramolecular $[3_{2\sigma} + 2_{2\pi}]$ Cycloadditions With Methylene-cyclopropanes

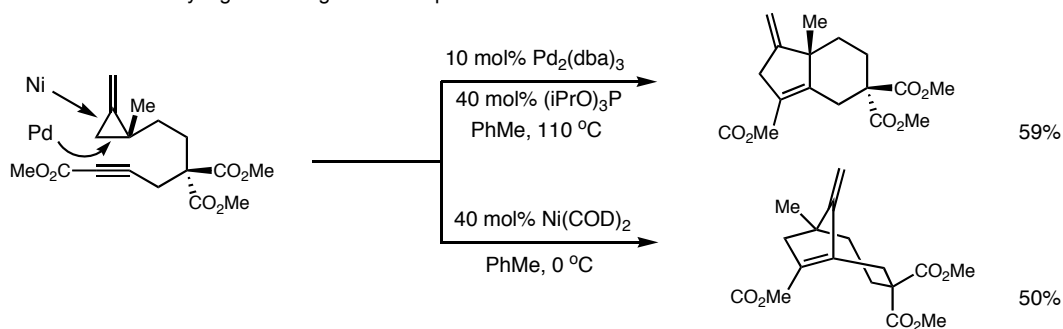
■ Synthesis of 13-Acetoxy-modhephane



catalyst (20 mol%)	temp.	yield
Ni(COD) ₂ , PPh ₃	110 °C	74%
(PPh ₃) ₂ PdCl ₂ , DIBAL	130 °C	98%

Nakamura, *J.Chem. Soc., Chem. Comm.*, **1988**, 1112.

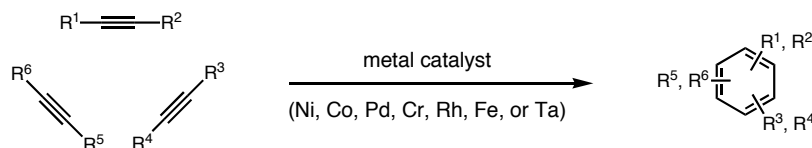
■ Selection of metal catalyst governs regiochemical product



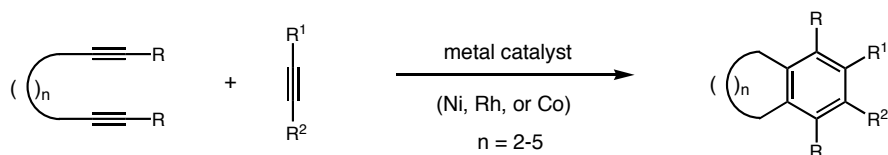
Motherwell, *Tetrahedron Lett.*, **1989**, 7107.

$[2_{2\pi} + 2_{2\pi} + 2_{2\pi}]$ Cycloadditions: Alkyne Cyclotrimerizations

- Although in principle thermal $[2 + 2 + 2]$ cycloadditions are symmetry allowed, the entropic barriers associated with bringing three reaction partners together and enthalpic activation energy contributions mitigate against such processes
- The use of a transition metal catalyst enables entropic constraints to be circumvented by coordination of the reaction partners to the metal complex in a stepwise process



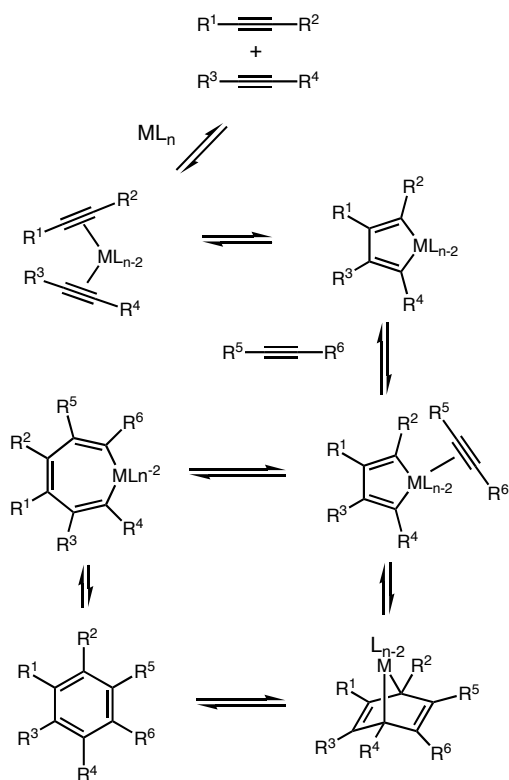
- Intermolecular reaction suffers from chemo- and regioselectivity problems \Rightarrow complex product mixture



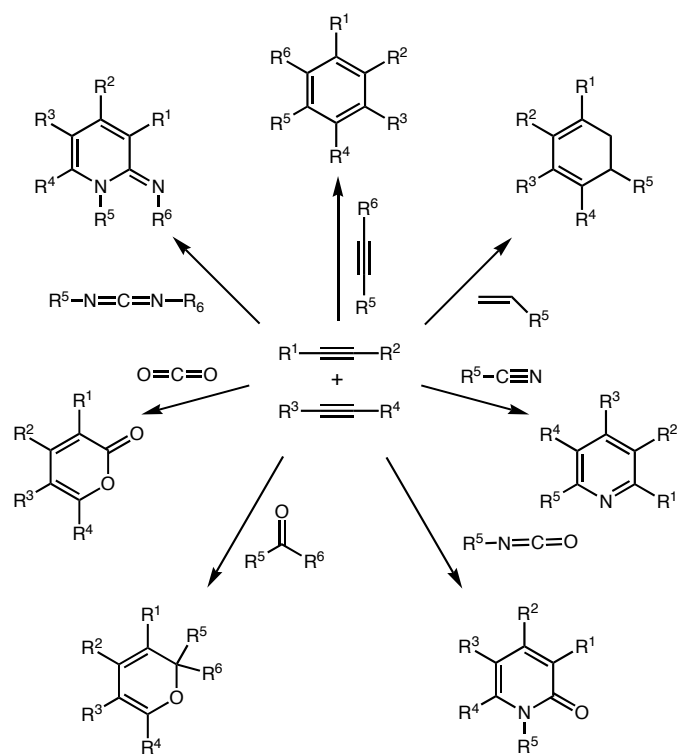
- Partially intramolecular cyclotrimerization has become a very useful synthetic procedure

[2_{2π} + 2_{2π} + 2_{2π}] Cyclotrimerizations: Mechanism and Scope

General Mechanism:

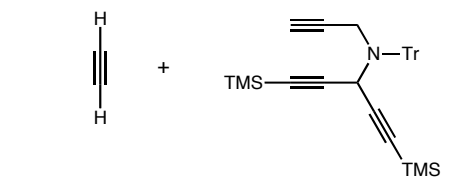


Modifications of Cyclotrimerization

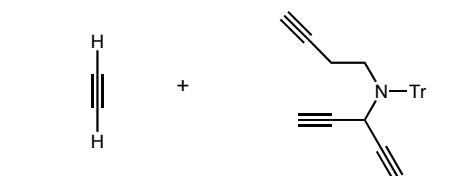
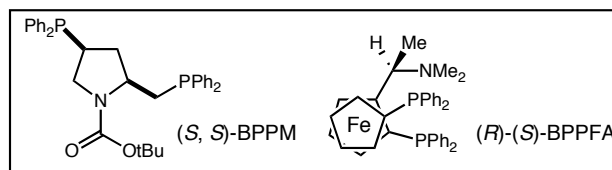
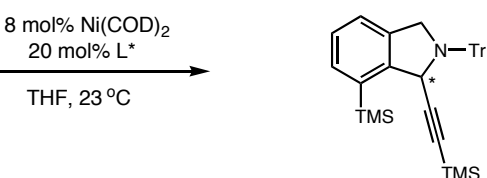


Lautens, *Chem. Rev.*, 96, 1996, 49.

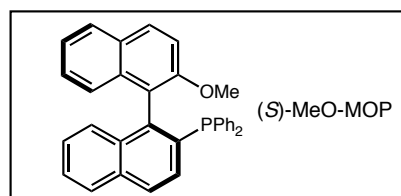
[2_{2π} + 2_{2π} + 2_{2π}] Cycloadditions: Semi-Intramolecular Alkyne Cyclotrimerizations Asymmetric Synthesis of Isoindoline and Isoquinoline Derivatives



L*	Yield	ee
(S, S)-BPPM	92%	60%
(R)-(S)-BPPFA	52%	73%



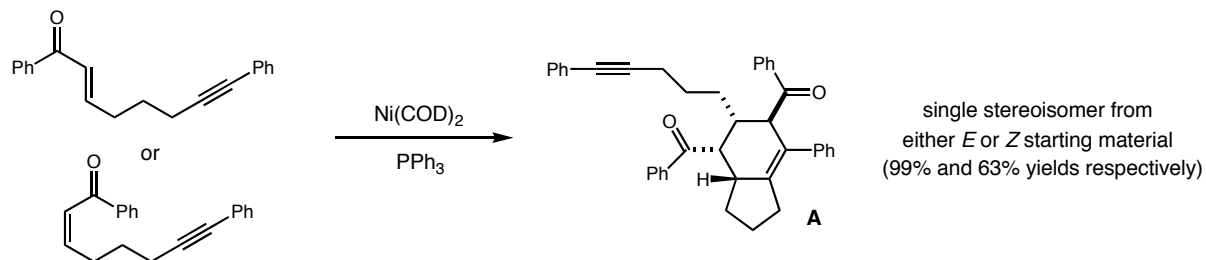
L*	Yield	ee
(S, S)-BPPM	42%	6%
(S)-MeO-MOP	62%	54%



Mori, *J. Org. Chem.*, 59, 1994, 6133.

[2 + 2 + 2] Cycloadditions: Alkynyl Enone / Alkene Cyclotrimerizations

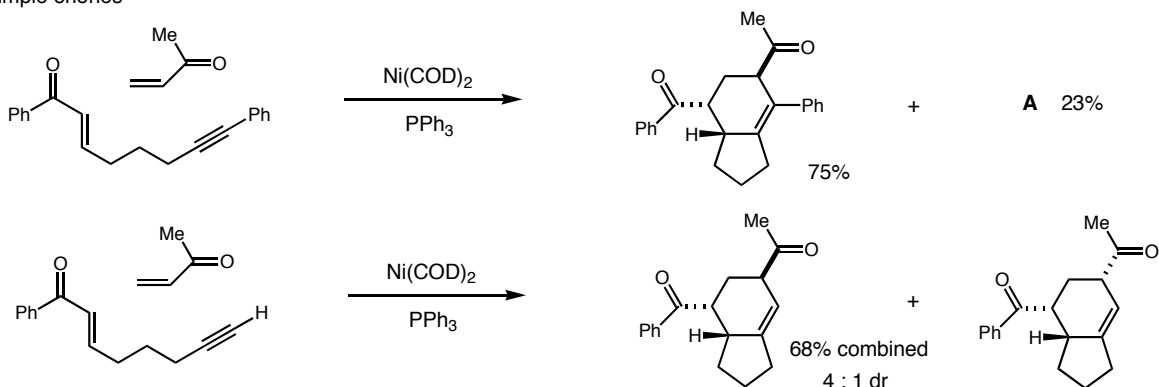
■ Montgomery (w/ Jeongbeob Seo)



■ Reaction sets two rings and four contiguous stereocenters with complete stereoselectivity

■ Unusual chemoselectivity for alkene over alkyne in [2 + 2 + 2] cyclotrimerization

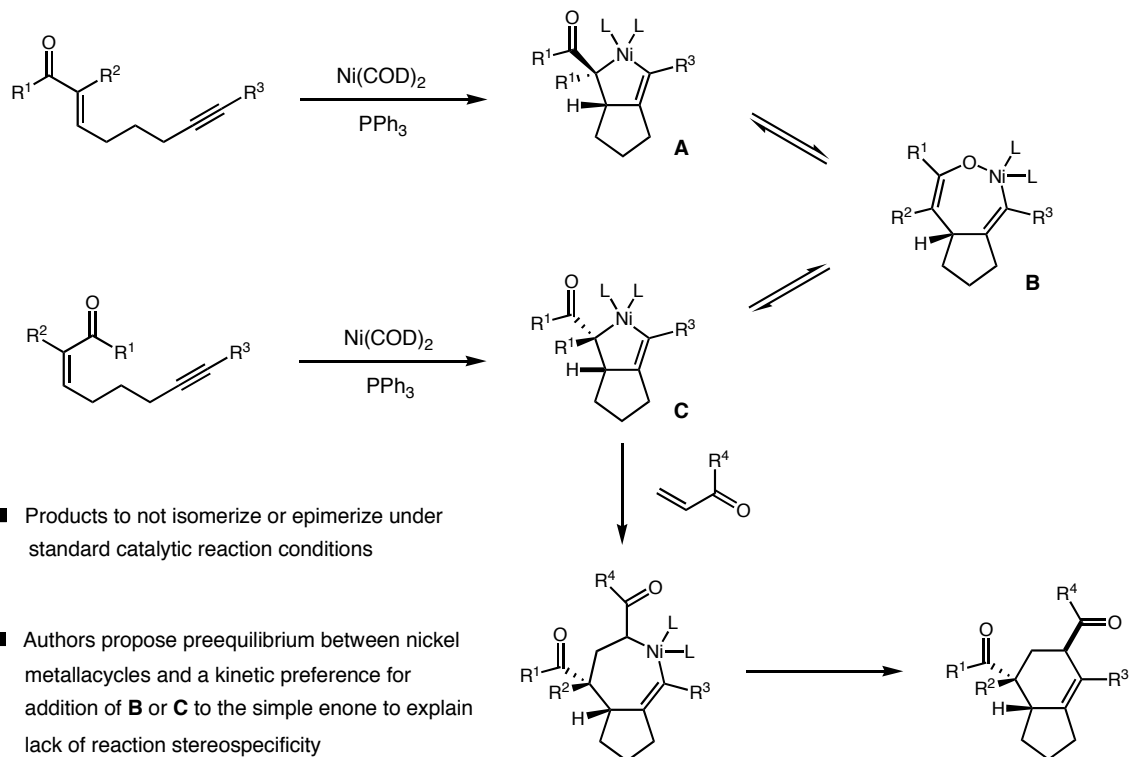
■ Simple enones



Montgomery, *J. Am. Chem. Soc.*, **1999**, 121, 477.

[2 + 2 + 2] Cycloadditions: Alkynyl Enone / Alkene Cyclotrimerizations

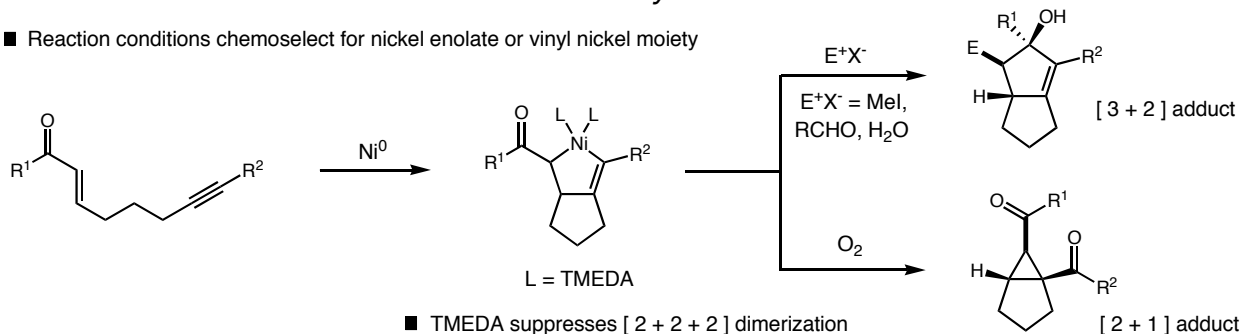
Mechanism



Montgomery, *J. Am. Chem. Soc.*, **1999**, 121, 477.

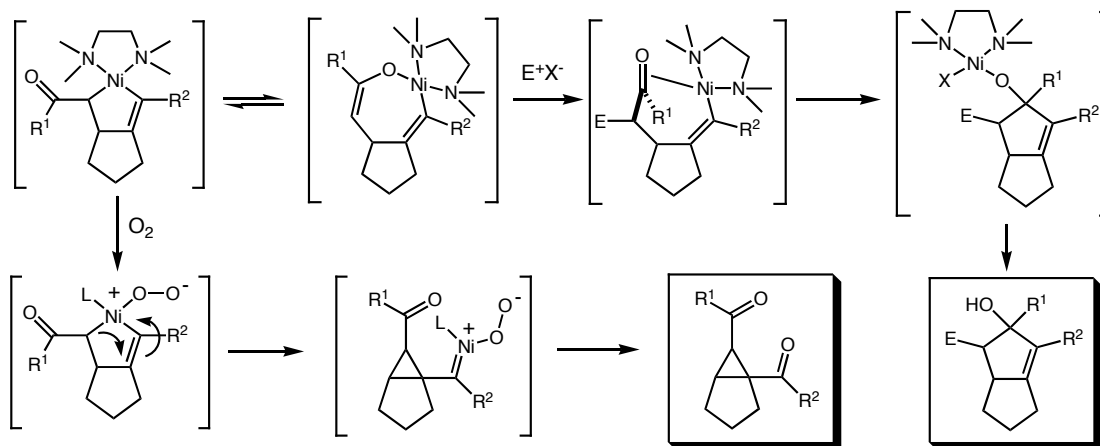
[3 + 2] and [2 + 1] Cycloadditions: Diverse Reaction Manifolds From a Common Nickel Metallocycle

- Reaction conditions chemoselect for nickel enolate or vinyl nickel moiety



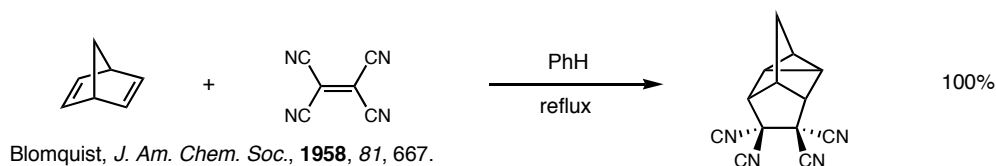
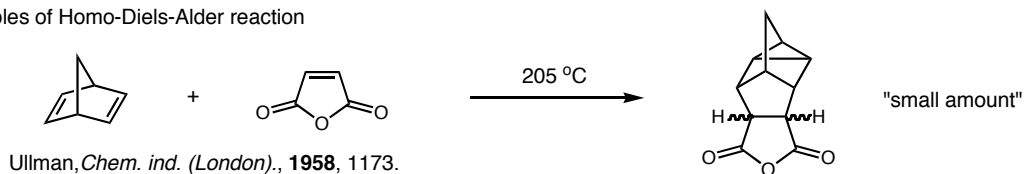
- TMEDA suppresses [2 + 2 + 2] dimerization
Montgomery, *J. Am. Chem. Soc.*, **2000**, *122*, 6775.

- Mechanisms



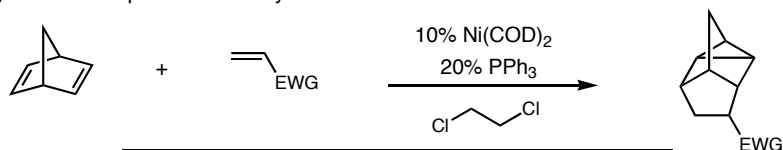
[2_{2π} + 2_{2π} + 2_{2π}] Homo-Diels-Alder Cycloadditions

- First examples of Homo-Diels-Alder reaction



- Less activated olefins result in greatly diminished yields—acrylonitrile and norbornadiene (200 °C, 12h) gives only 12% yield

- Nickel catalysts greatly broaden scope and efficiency of HDA

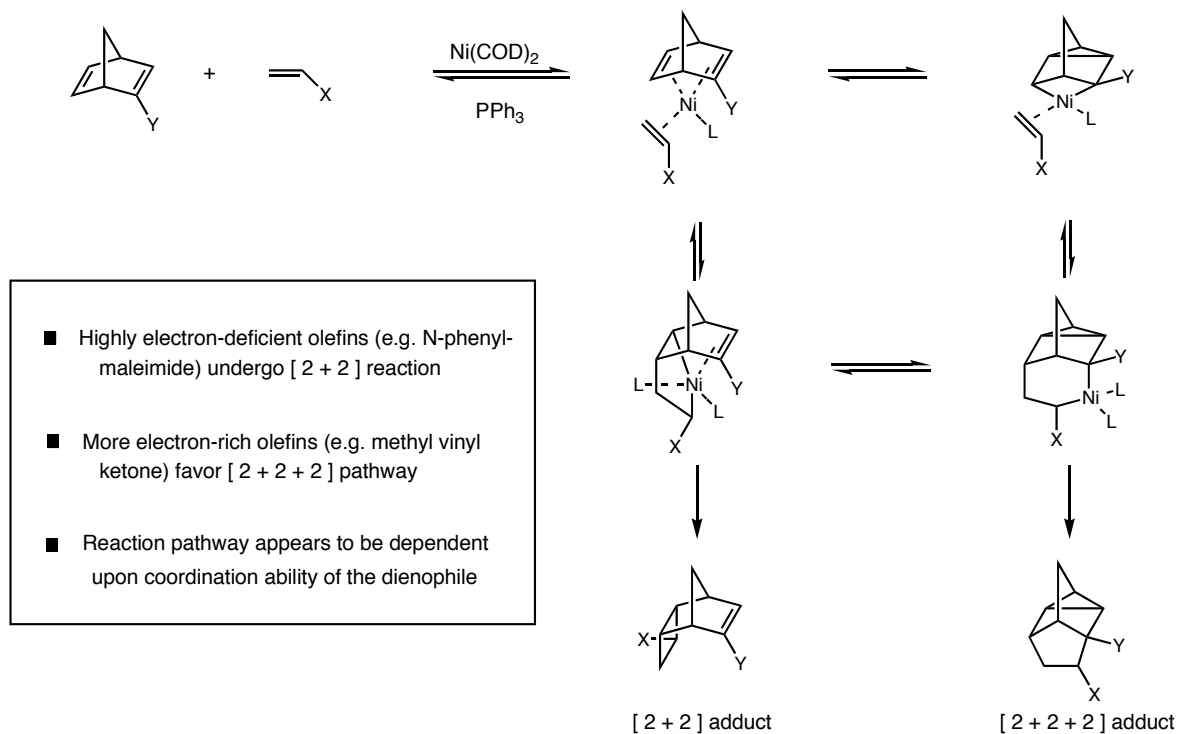


EWG	Temp.	Yield	exo : endo
COMe	80 °C	99%	>20 : 1
CHO	r.t.	58%	3 : 1
CN	80 °C	82%	4 : 1
SO ₂ Ph	r.t.	75%	1 : 1
SOPh	r.t.	73%	>19 : 1 ^a

a: P(OPh)₃ used instead of PPh₃

Lautens, *J. Am. Chem. Soc.*, **1995**, *117*, 10276.

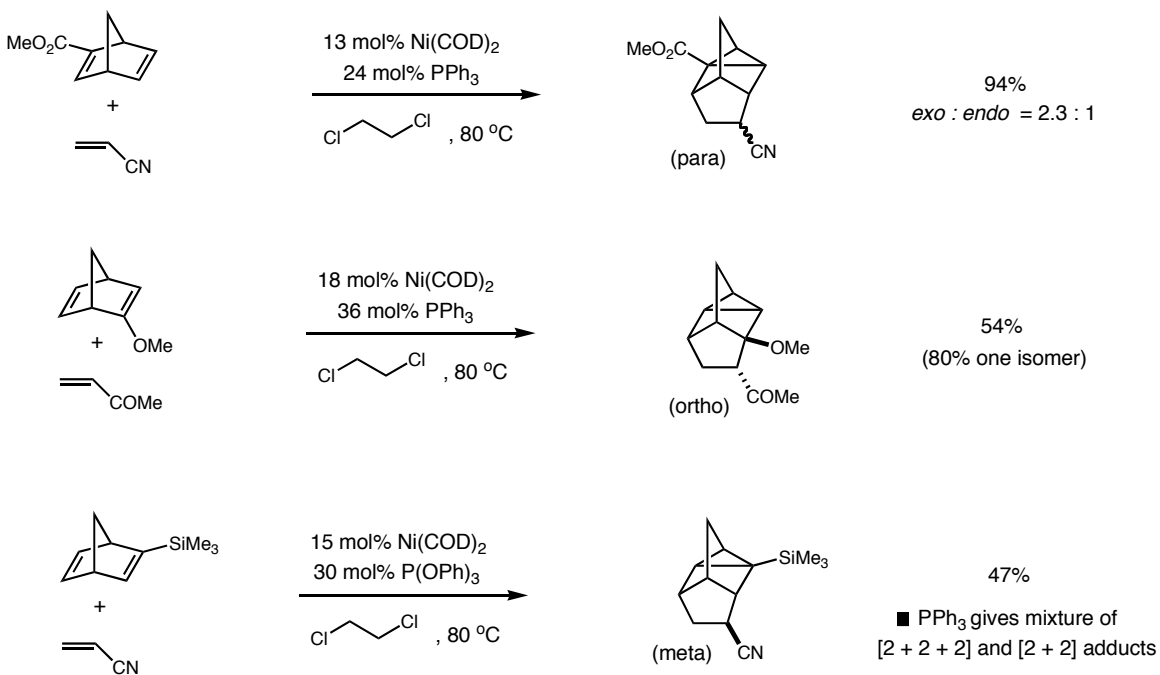
Norbornadienes: [2 + 2 + 2] Vs. [2 + 2]



Lautens, *J. Am. Chem. Soc.*, **1995**, *117*, 10276.

[2_{2π} + 2_{2π} + 2_{2π}] Homo-Diels-Alder Cycloadditions : Regio- and Stereoselectivity

2-Substituted Norbornadienes

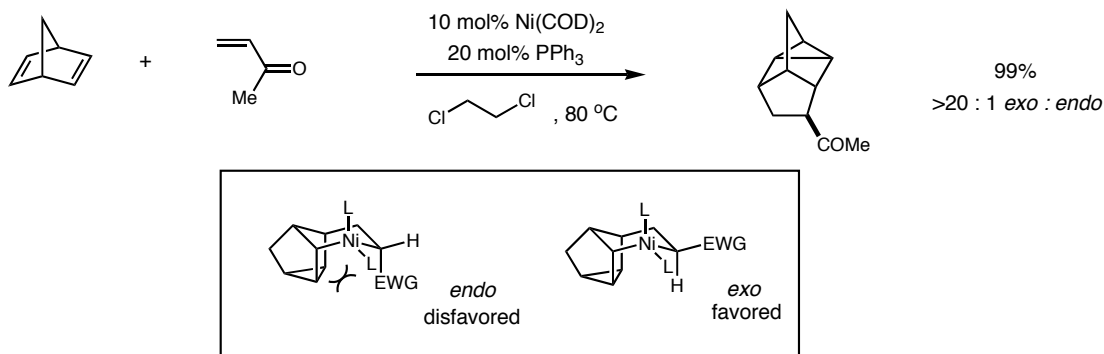


■ Diene and dienophile substituents as well as ligands shown to have dramatic effect on selectivities

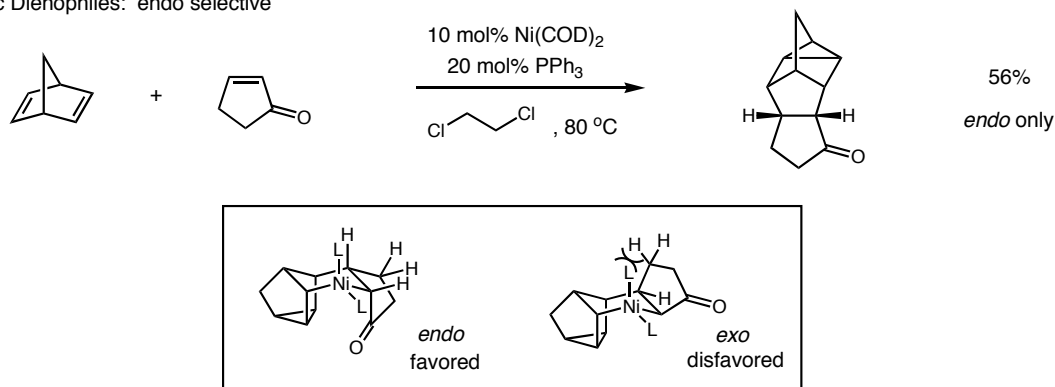
Lautens, *J. Am. Chem. Soc.*, **1995**, *117*, 10276.

$[2_{2\pi} + 2_{2\pi} + 2_{2\pi}]$ Homo-Diels-Alder: Cyclic Vs. Acyclic Dienophiles

■ Acyclic Dienophiles: exo-selective

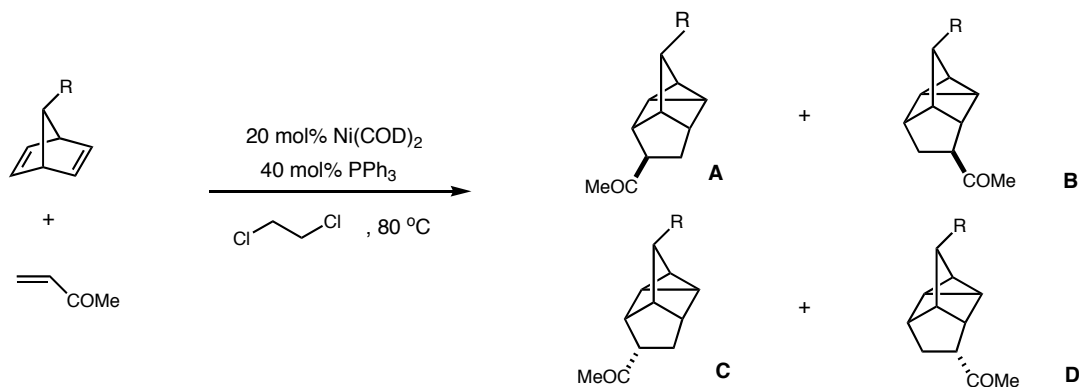


■ Cyclic Dienophiles: endo selective



Lautens, *J. Am. Chem. Soc.*, **1995**, 117, 10276.

$[2_{2\pi} + 2_{2\pi} + 2_{2\pi}]$ Homo-Diels-Alder: 7-Substituted Norbornadienes



R	Yield	A : B : C : D	<i>anti</i> : <i>syn</i>	<i>exo</i> : <i>endo</i>
n-hexyl	83%	40 : 58 : 1.6 : 0.4	42 : 58	98 : 2
Ph	84%	54 : 45 : 0.8 : 0.2	55 : 45	99 : 1
Cl	60%	71 : 28 : 0.8 : 0.2	72 : 28	99 : 1
OCOPh	97%	80 : 20 : 0 : 0	80 : 20	100 : 0
OTIPS	90%	90 : 9 : 1 : 0	91 : 9	99 : 1
OMEM	89%	88 : 9 : 3 : 0	91 : 9	97 : 3
OtBu	95%	95 : 5 : 0 : 0	95 : 5	100 : 0

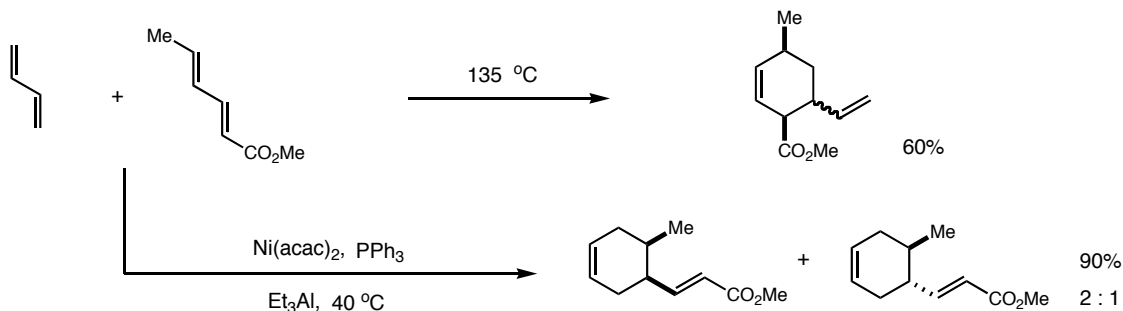
■ *Anti* : *syn* selectivity increases as group electronegativity of 7-substituent increases

■ *Ab initio* calculations indicate a shift of electron density from the anti- π olefin to the syn- π olefin as electronegativity increases

Lautens, *J. Am. Chem. Soc.*, **1995**, 117, 6863.

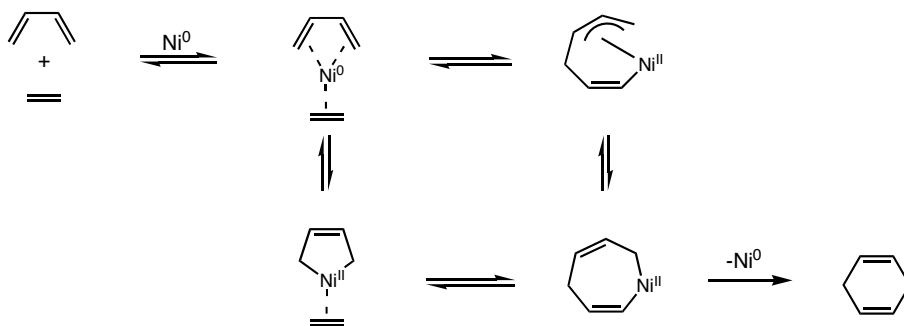
[4_{4π} + 2_{2π}] Cycloadditions: Nickel-Catalyzed Diels-Alder Reactions

■ Reversal of thermal reactivity



Garratt, *J. Chem. Soc., Chem. Comm.*, **1974**, 251.

■ Mechanism:

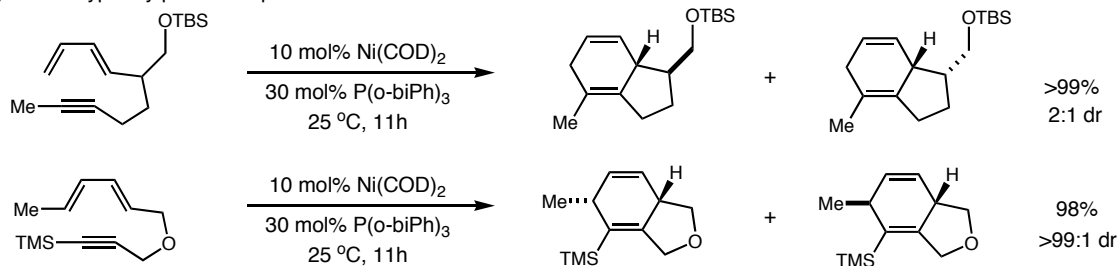


Wender, *J. Am. Chem. Soc.*, **1989**, *111*, 6432.

[4_{4π} + 2_{2π}] Cycloadditions: Nickel-Catalyzed Intramolecular Diels-Alder Reactions

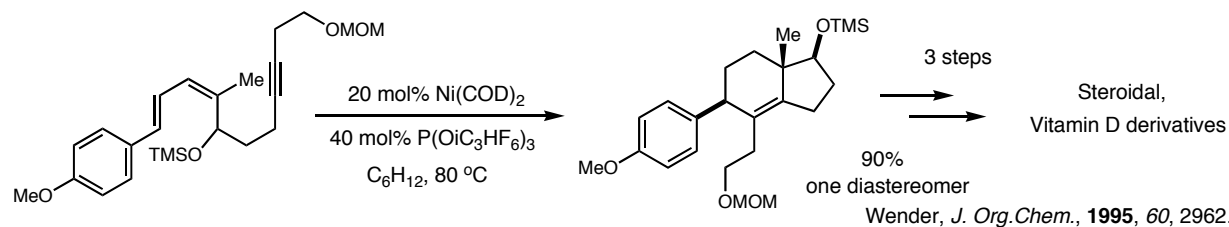
Alkyne and Allene Dienophiles

■ Alkynes are typically poor dienophiles in the Diels-Alder reaction

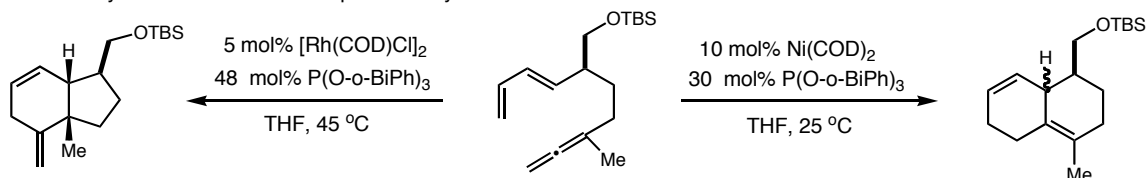


Wender, *J. Am. Chem. Soc.*, **1989**, *111*, 6432.

■ Transition metal catalysts make these processes facile and synthetically useful



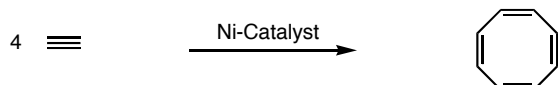
■ Allenes: Catalyst-controlled chemocomplementarity



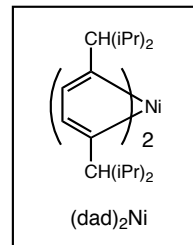
Wender, *J. Am. Chem. Soc.*, **1995**, *117*, 1843.

$[2_{2\pi} + 2_{2\pi} + 2_{2\pi} + 2_{2\pi}]$ Cycloadditions: Cyclooctatetraene Synthesis

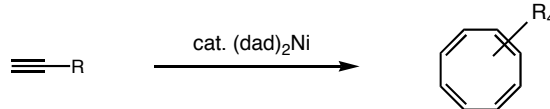
- First example by Reppe, has been used on an industrial scale



Ni-Catalyst = $\text{NiBr}_2 / \text{CaC}_2$, $\text{Ni}(\text{acac})_2$, $\text{Ni}(\text{COT})_2$
 Reppe, *Leibigs Ann. Chem.*, **1948**, 560, 1.



- tom Dieck developed first method for regioselective cycloadditions with monosubstituted alkynes



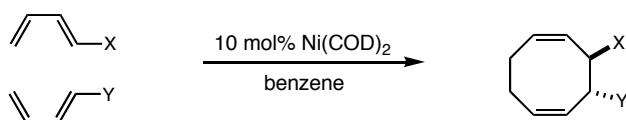
R	major product	R	major product
CH_2OH		CH_2OTol	
$\text{CH}(\text{CH}_3)\text{OH}$		$\text{CH}_2\text{CO}_2\text{Me}$	

tom Dieck, *Chem. Ber.*, **1985**, 118, 428.

$[4_{4\pi} + 4_{4\pi}]$ Cycloadditions: Cyclooctadiene Synthesis

Intermolecular

- Substituted butadiene dimerization

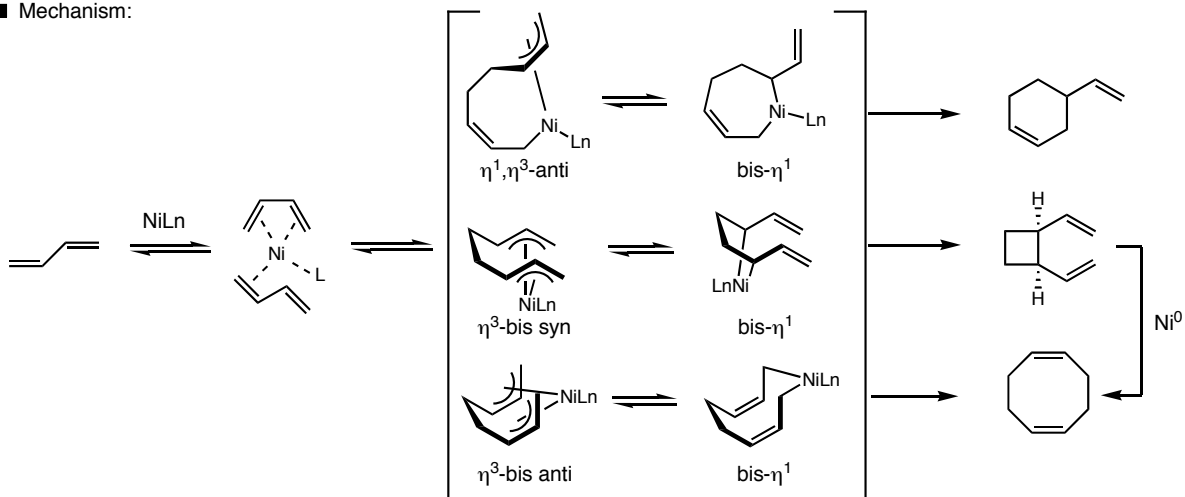


X, Y = OSiMe ₃ (18d)	90%
X, Y = CO ₂ Me (24h)	70%
X = H, Y = CO ₂ Me (72h)	33%

- Use of butadiene results in significant $[4 + 2]$ adduct

Waegell, *Tetrahedron Lett.* **1983**, 24, 385.

- Mechanism:

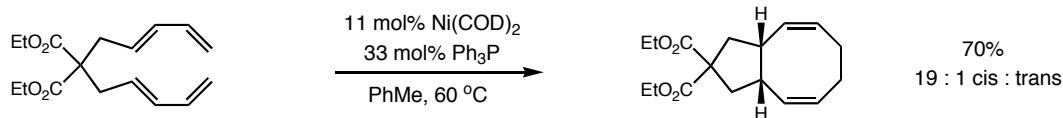


- Conditions can be optimized to minimize vinylcyclohexene and divinylcyclobutane formation

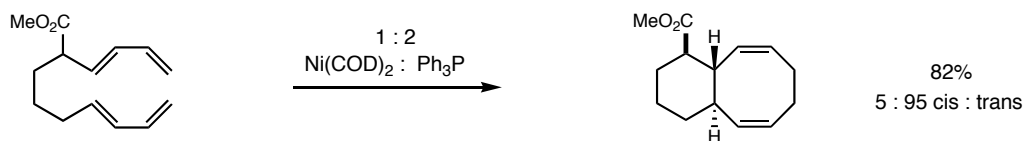
Wilke, *ACIEE*, **1988**, 27, 185.

[4_{4π} + 4_{4π}] Cycloadditions: Intramolecular Cyclooctadiene Synthesis

■ 3-atom tethers \Rightarrow cis-fused



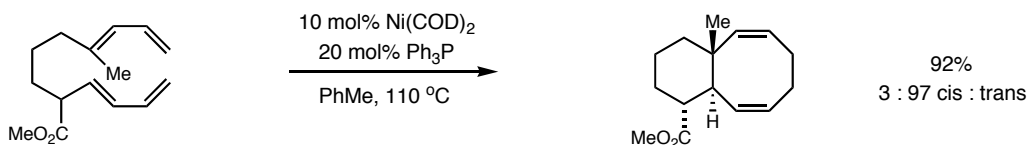
■ 4-atom tethers \Rightarrow trans-fused



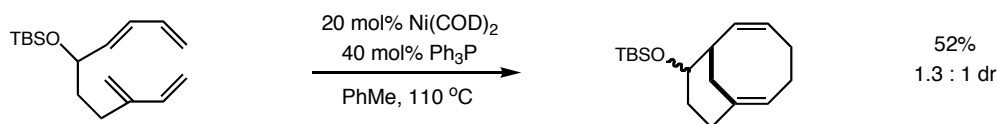
■ Note: other substrates give much lower selectivities

Wender, *J. Am. Chem. Soc.*, **1986**, *108*, 4678.

■ Type I



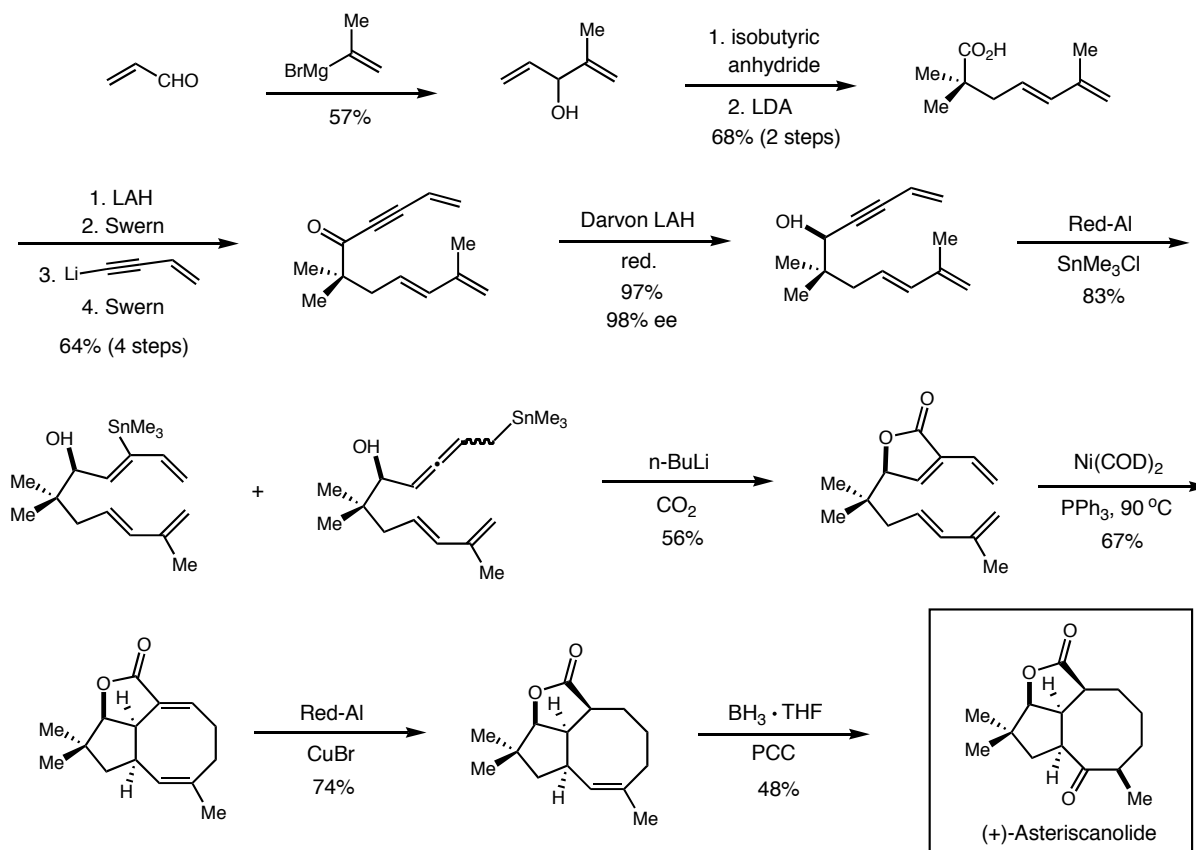
■ Type II



■ Towards taxane skeleton

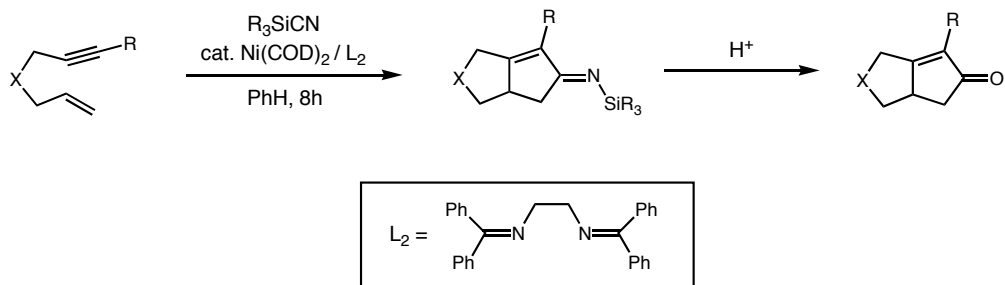
Wender, *Tetrahedron Lett.*, **1987**, *28*, 2221.

[4_{4π} + 4_{4π}] Cycloadditions: Enantioselective Total Synthesis of (+)-Asteriscanolide

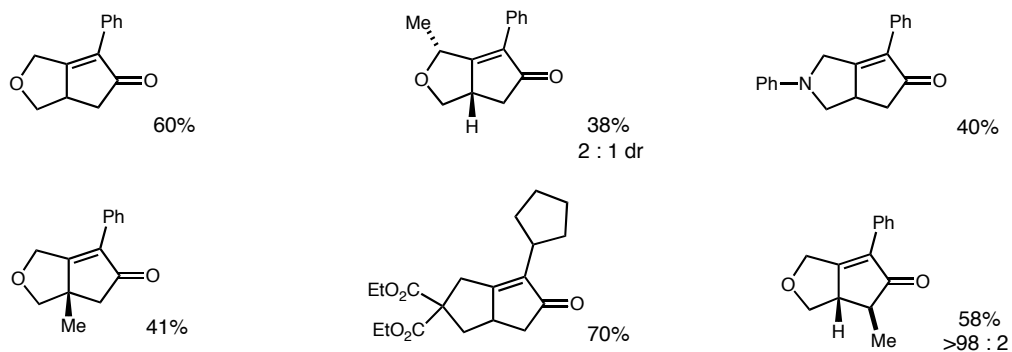


Wender, *J. Am. Chem. Soc.*, **1988**, *110*, 5904.

[2 + 2 + 1] Cycloadditions: Cyclopentenone Synthesis

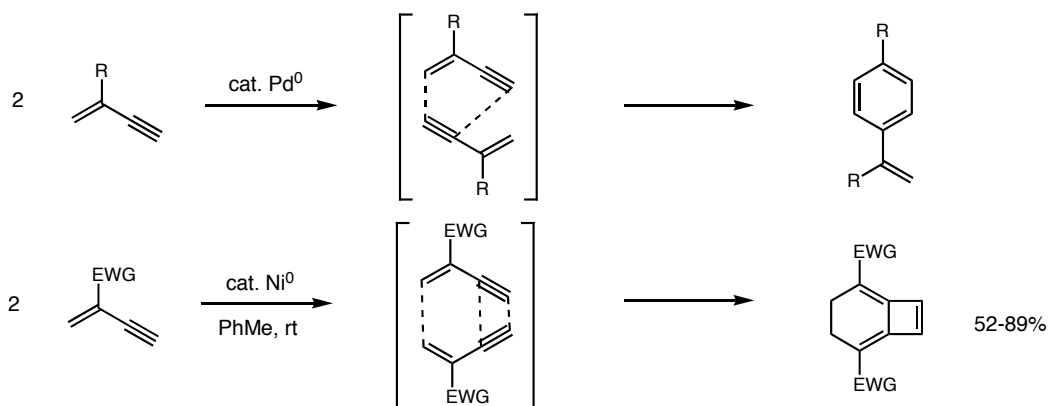


Representative examples



Buchwald, *J. Org. Chem.*, **1996**, *61*, 4498.

Nickel-Catalyzed "Zipper Annulation" of Conjugated Enynes



EWG = $n\text{-C}_6\text{F}_{13}$, PhCF_2 , $n\text{-C}_6\text{H}_{13}\text{CF}_2$ Yamamoto, *J. Am. Chem. Soc.*, **2000**, *122*, 1810.

Catalytic cycle

