1,3-Diene Difunctionalization

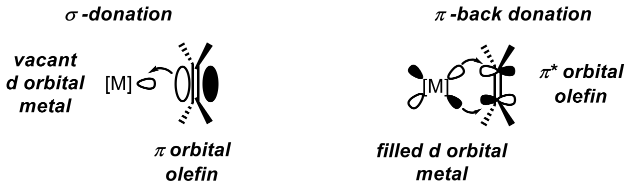
Topics Covered

1. Carbofunctionalizations with Pd^0
2. Difunctionalizations with Pd^{II}
    a. Bäckvall Difunctionalizations
        Main Reference: Bäckvall, J. E. *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH: Weinheim, 2014; Ch. 11
3. Aminofunctionalization
    a. Booker-Milburn Diamination and Carboamination with Pd^{II}
    b. Shi Diamination with Pd^0
    c. Shi Diamination with Cu^I
4. Borylations
    a. Morken Diborylation with Pt^0
    b. Morken Diborylation with Ni^0
5. Acylfunctionalizations with Ni^0

Topics Not Covered

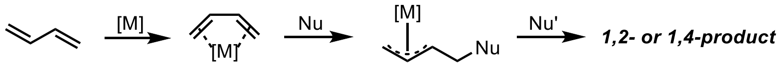
- Halogenations
- Osmium-catalyzed dihydroxylations
- Cycloadditions
- Polymerizations
- Hydrofunctionalizations

- Simple conjugated dienes like isoprene and 1,3-butadiene are readily available and more complex dienes can be prepared from common transformations: cross-coupling reactions, olefin synthesis, olefin metathesis
- Products contain an olefin which can be further functionalized to make a molecule of high functionality

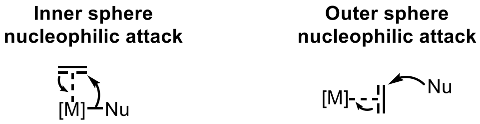


- The coordination of a metal catalyst to dienes occurs through σ-donation and π-back donation
- Stronger σ-donation to cationic or higher oxidation state metal complex activates olefin to nucleophilic attack

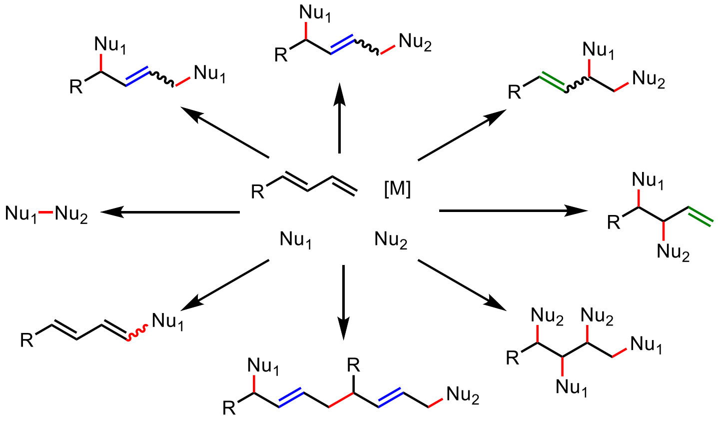
General Mechanism



- After attack by the first nucleophile, a stable π-allyl metal complex is formed
- A second nucleophile addition results in allylic substitution and elimination of the metal catalyst



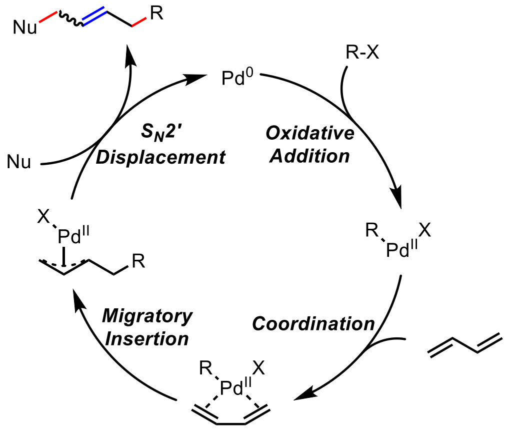
Challenges: Regioselectivity and Stereoselectivity



1,3-Diene Difunctionalization

1. Carbofunctionalizations with Pd^0

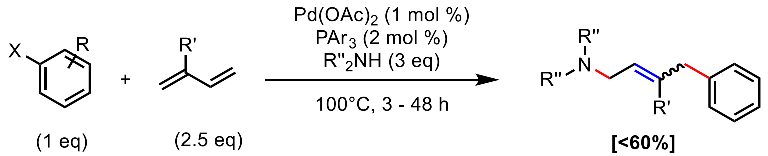
General Mechanism of Pd^0-catalyzed reactions to give 1,4-product



- Addition of the first nucleophile shares the same mechanism as the Heck reaction, but the extended conjugation gives a Pd-π-allyl complex
- Addition of the second nucleophile can occur on either end of the Pd-π-allyl species, but most examples give 1,4-product

Carboamination

Intermolecular



$Pd(OAc)_2$ (1 mol %)
PAr_3 (2 mol %)
R''_2NH (3 eq)
100°C, 3 - 48 h

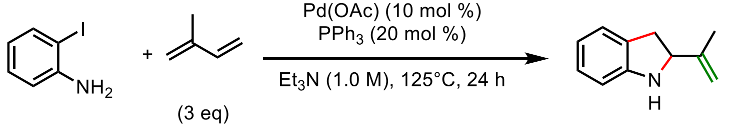
(1 eq) (2.5 eq) **[<60%]**

X = Br, I

R''_2NH = morpholine, piperidine

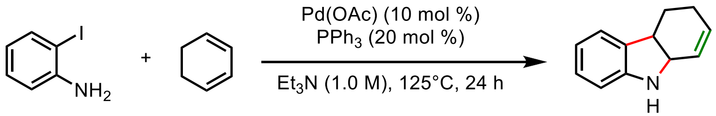
Heck. R. F. J. Org. Chem. 1978, 43, 5018-5020.

- Most substrates primarily yielded the Heck coupling product - hydrocarbon dienes gave moderate yield of difunctionalized product



Pd(OAc) (10 mol %)
PPh_3 (20 mol %)
Et_3N (1.0 M), 125°C, 24 h

(3 eq) **[72%]**



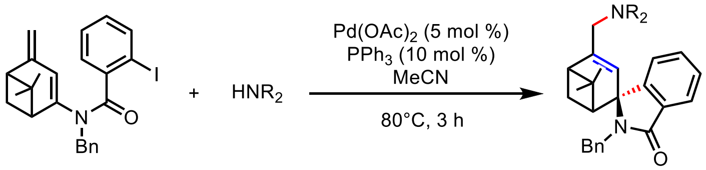
Pd(OAc) (10 mol %)
PPh_3 (20 mol %)
Et_3N (1.0 M), 125°C, 24 h

(3 eq) **[70%]**

Dieck, H. A. J. Org. Chem. 1983, 48, 807-809.

Intramolecular

Cyclization during carbopalladation

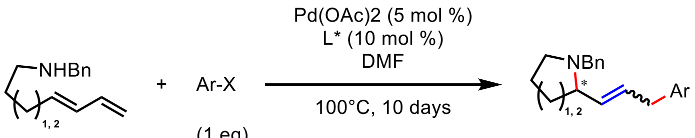


$Pd(OAc)_2$ (5 mol %)
PPh_3 (10 mol %)
MeCN
80°C, 3 h

(1 eq) (2 eq) **[40-60%]**

Grigg, R. Tetahedron Lett. 1989, 30, 1139-1142.

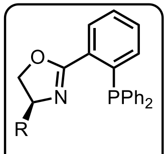
Cyclization during amination



Pd(OAc)2 (5 mol %)
L* (10 mol %)
DMF
100°C, 10 days

(1 eq) (1 eq)

Ar = Ph or 2,6-Me_2Ph



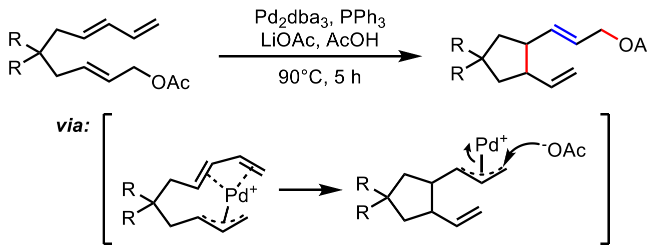
PHOX ligands

Helmchen, G. Tetrahedron Lett. 1999, 40, 3867-3868.

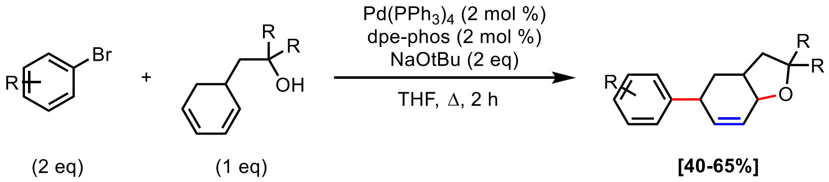
- *e.e.* ranged from 59-80% under optimized conditions

1,3-Diene Difunctionalization

Carbooxygenation

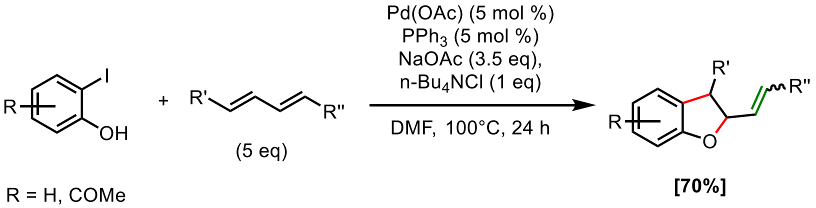


Trost, B.M. J. Am. Chem. Soc. 1988, 110, 8239-8241.



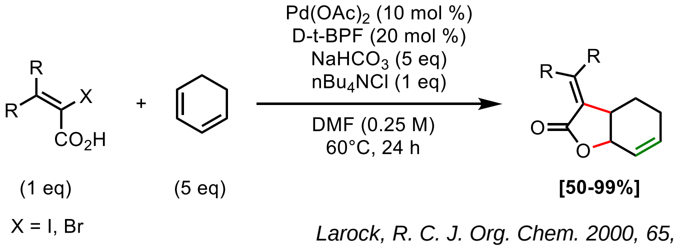
Yeh, M. P. Organometallics, 2005, 24, 5909-5915.

- Linear dienes gave 1,2-product – hydroxyl-directed regioselectivity



Larock, R. C. J. Org. Chem. 1990, 55, 3447-3450.

- Linear and cyclic diene-containing hydrocarbons, and hydroxyl-containing isoprene included in substrate scope
- Mixtures of products with asymmetrical dienes

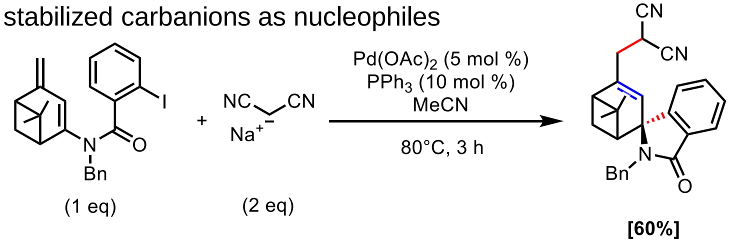


Larock, R. C. J. Org. Chem. 2000, 65, 1525-1529.

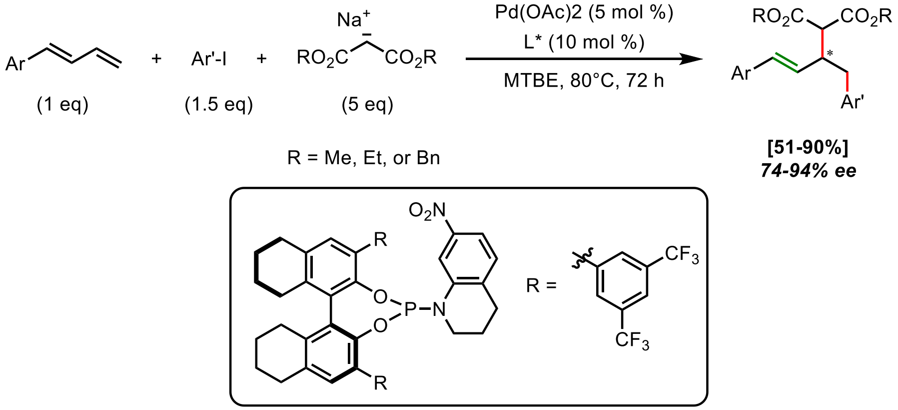
- 1-substituted acyclic and cyclic dienes used
- 2-substituted dienes gave mixtures of regioisomers

Arylalkylation

With stabilized carbanions as nucleophiles



Grigg, R. Tetrahedron Lett. 1989, 30, 1139-1142.



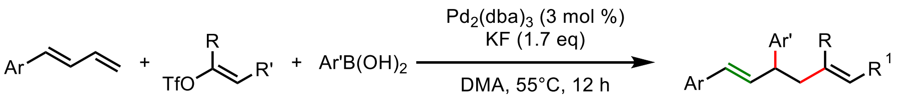
Gong, L. J. Am. Chem. Soc. 2015, 137, 13476-13479.

- Bulky Ar’ = lower yields, but higher *e.e.*
- *Ortho*-methyl groups on either Ar or Ar’ results in diminished regioselectivity

1,3-Diene Difunctionalization

Vinylarylation

1,2-Regioselectivity

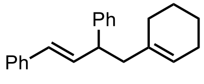


> 20:1 regioselectivity

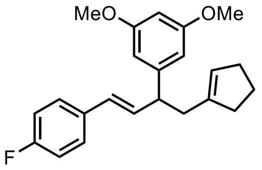
Ar = Ph, p-$MeOC_6H_4$, p-FC_6H_4

Sigman, M. S. J. Am. Chem. Soc. 2011, 133, 5784-5787.

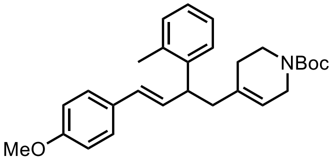
Selected examples:



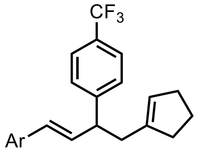
[84%]



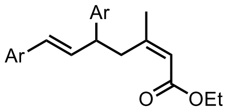
[96%]



[91%]

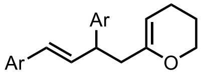


[97%]

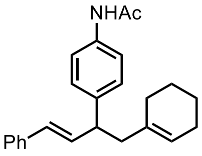


[50%]

Ar = p-$MeOC_6H_4$



[46%]



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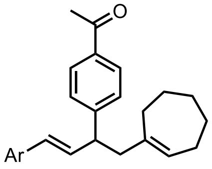
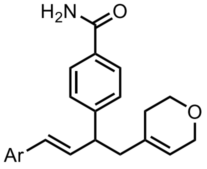


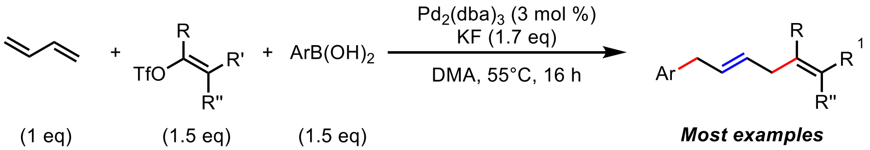
[64%]



[60%]

- Vinyl triflates were used rather than halides to generate a more electrophilic palladium species, resulting in faster migratory insertion to the diene than transmetallation of the aryl boronic acid
- Use of phosphine ligands promoted Suzuki, Heck, and hydroarylation product formation

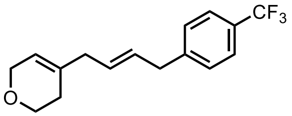
1,4-Regioselectivity - affords skipped dienes



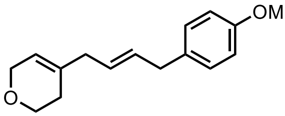
Most examples
>20:1 regioselectivity
9:1 E/Z ratio

Sigman, M. S. J. Am. Chem. Soc. 2013, 135, 4167-4170.

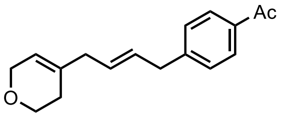
Selected examples:



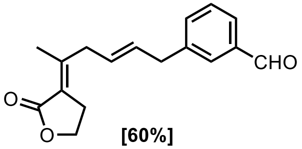
[59%]
***E:Z* 90:10**



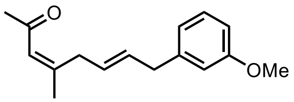
[56%]
***E:Z* 91:9**



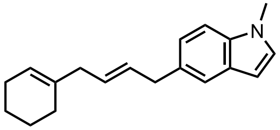
[62%]
***E:Z* 90:10**



[60%]
***E:Z* 89:11**

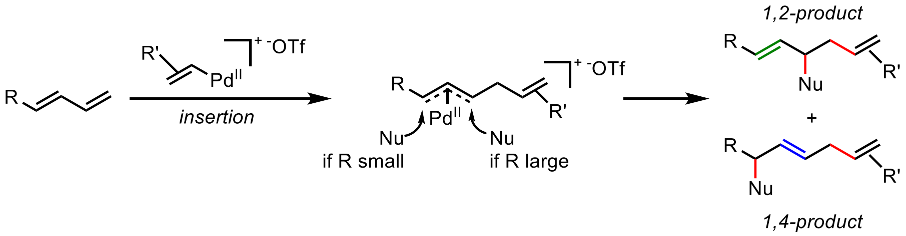


[44%]
***E:Z* 91:9**



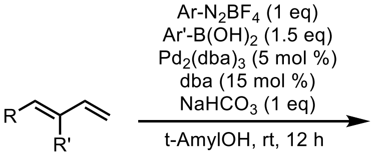
[85%]
***E:Z* 94:6**

- Boronic acids with heteroaryl groups containing Lewis basic heteroatoms give little to no product
- 1,4-regioselectivity is thought to arise from steric effects

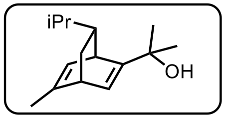


1,3-Diene Difunctionalization

Diarylation

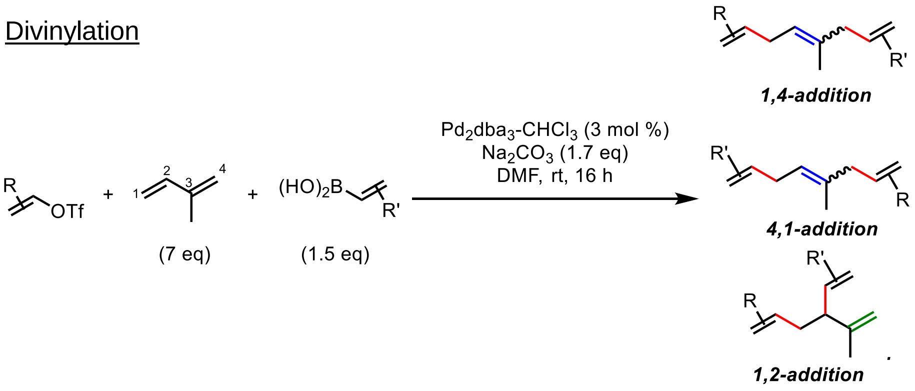


Sigman, M. S. Org. Lett. 2014, 16, 4666-4669.



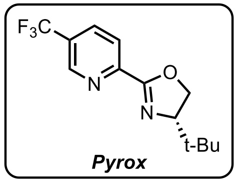
- Use of phosphine, NHC, and amine ligands gave Suzuki and Heck coupling products
- Use of chiral diene ligands gave maximum of 83% *e.e.*, but yield of 10% by GC
- Electron-poor and -rich coupling partners, as well *ortho*-, *meta*-, and *para*- substituents give comparable yields
- Bromo- and iodoaryl diazonium salts tolerated

Divinylation



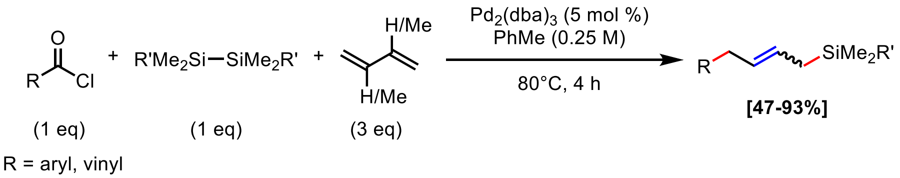
Sigman, M. S. Chem. Sci. 2015, 6, 1355-1361.

- Ligand-less reaction gives mostly (*E*)-1,4 addition product (ratios <3:1) but limited substrate scope
- Yields of mixture of isomers ranged from 50% to 89%
- Use of pyrox ligand gave higher selectivities of (*E*)-1,4 addition product (<2:1) for more challenging substrate



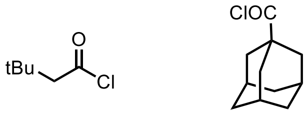
Pyrox

Carbosilylation

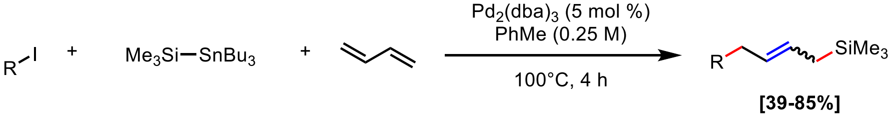


Tsuji, Y. J. Am. Chem. Soc. 1993, 115, 10414-10415.

- Decarbonylative coupling of acyl chloride and silyl group
- Acyl bromides, aryl iodides, aryl triflates failed to give desired product
- 4-Bromobenzoyl chloride coupled only at acyl position
- Complete decarbonylation of acyl chlorides occurred for most substrates – bulky substrates did not undergo any decarbonylation:



- Use of phosphine and phosphite ligands reduced yields



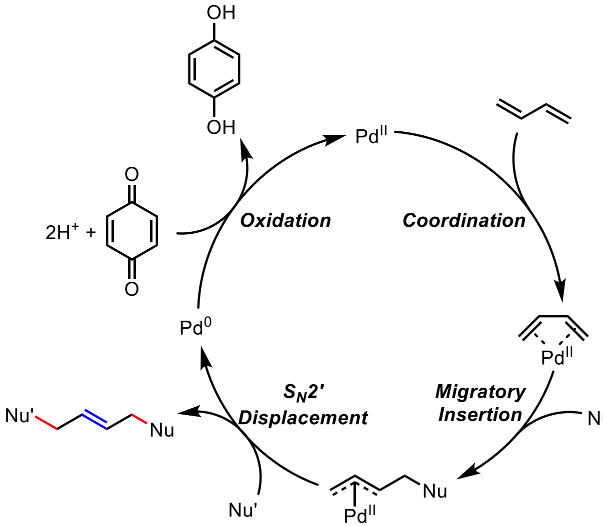
Tsuji, Y. J. Am. Chem. Soc. 1995, 117, 9814-9821.

- Yields lower than acyl chlorides
- Selectivity of (*E*) and (*Z*)-products low
- When 2-phenylbutadiene or 2-methyl butadiene used, low selectivity
  - Mixture of (*E*) and (*Z*)-1,4 and 4,1 products

1,3-Diene Difunctionalization

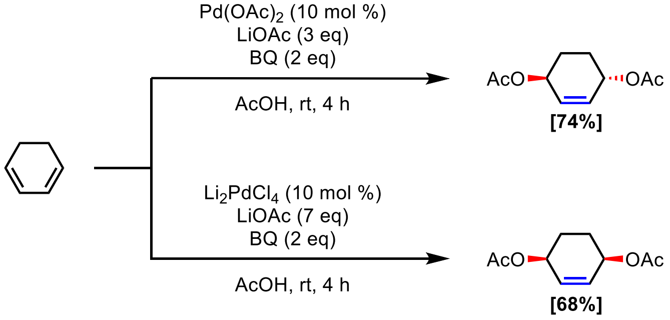
2. Bäckvall Difunctionalization with Pd^{II}

General Mechanism of Pd^{II}-catalyzed reactions to give 1,4-product



Bäckvall 1,4-Difunctionalizations

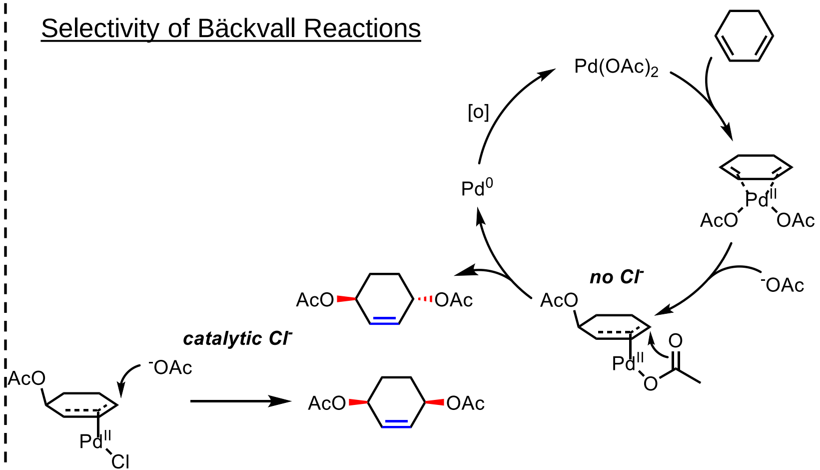
Bis-acyloxylation

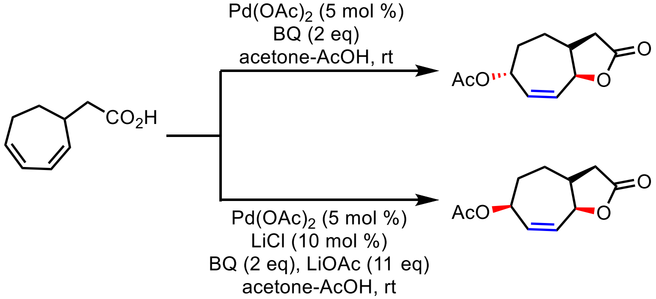


Bäckvall, J. E. J. Am. Chem. Soc. 1981, 103, 4959-4960.

- *Cis*- or *trans*- product dependent on the concentration of Cl$^-$
- Cl$^-$ is a stronger ligand than $^-$OAc
- 1,3-Cyclohexadiene used a model system, substrate scope includes cyclic and acyclic 1,3-diene-containing hydrocarbons

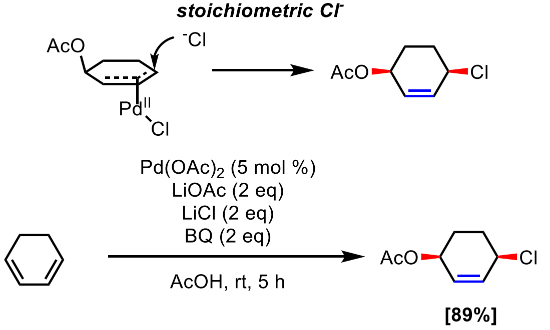
Selectivity of Bäckvall Reactions





Bäckvall, J. E. Tetrahedron Lett. 1989, 30, 137-140.

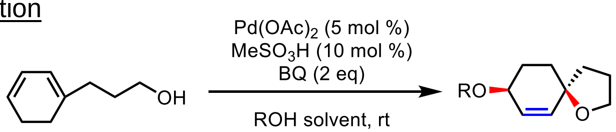
Haloacyloxylation



Bäckvall, J. E. J. Am. Chem. Soc. 1985, 107, 3676-3686.

1,3-Diene Difunctionalization

Dialkoxylation

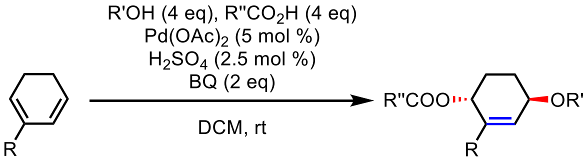


[73%]
***Z/E* >97:3**

Bäckvall, J. E. Tetrahedron, 1998, 54, 5375-5384.

- Reaction with strong acid prevents acetate from coordinating to Pd – no acetoxy transfer onto substrate
- Solvents: MeOH, EtOH, tBuOH, BnOH

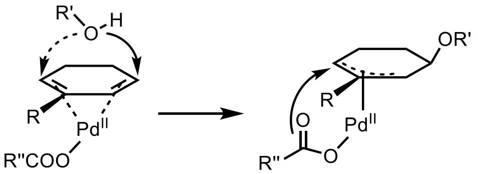
Acyloxyalkoxylation



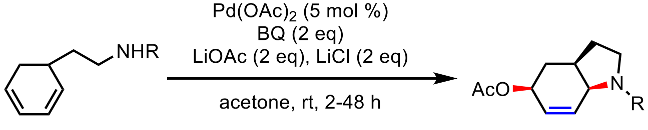
[54-60%]

Bäckvall, J. E. Tetahedron Lett. 1998, 39, 1223-1226.

- Challenge here is to avoid dialkoxylation, diacyloxylation products, and regioisomers



Aminofunctionalization



R = Ts, COMe,
CO$_2$Bn, CONHBn

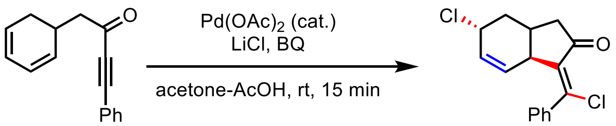
[65-97%]
***cis/trans* control > 93%**

Bäckvall, J. E. J. Am. Chem. Soc. 1990, 112, 3683-3685.

- R groups on amine decrease nucleophilicity

C-C bond formation

Alkynes

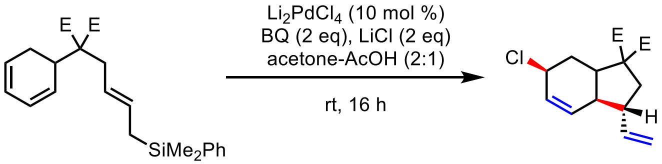


[51%]
***Z/E* > 93%**

Bäckvall, J. E. Tetrahedron Lett. 1994, 35, 5713-5716.

- Chloropalladation of alkyne, followed by vinyl palladation across diene

Allylsilane

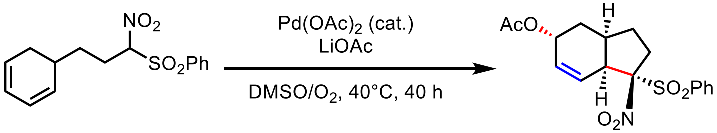


[68%]
***α/β* = 3:1**

Bäckvall, J. E. J. Am. Chem. Soc. 1995, 117, 560-561.

- Sakurai-like *anti*-attack of allylsilane to give Pd-π-allyl complex

Stabilized Carbanions



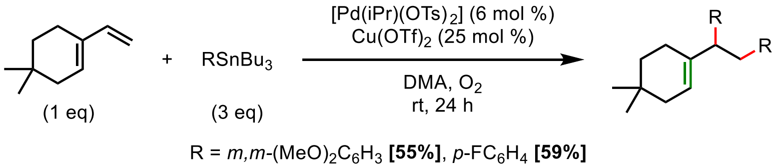
[50%]
mixture of acetate and eliminated product

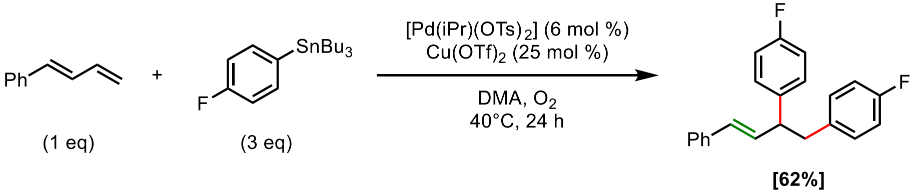
Bäckvall, J. E. Tetrahedron Lett. 1997, 38, 3603-3606.

- Generally challenging as Bäckvall reactions are run in acetic acid – protic solvent

1,3-Diene Difunctionalization

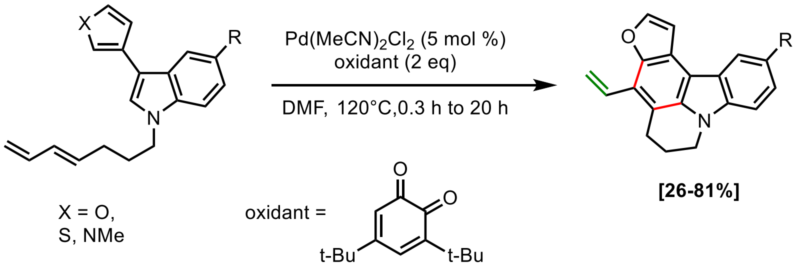
Diarylation





Sigman, M. S. Angew. Chem. Int. Ed. 2009, 48, 3146-2149.

- Reaction optimized for terminal olefin diarylation – 2 examples of dienes
- Cationic catalyst gave preference for diarylated product over Heck and hydroarylated products



Booker-Milburn, K. I. Angew. Chem. Int. Ed. 2015, 54, 6496-6500.

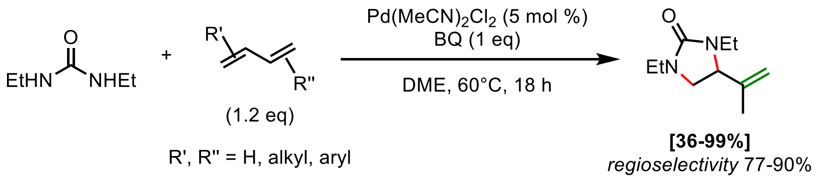
- Addition of oxidant turned catalyst over but oxidized the 1,2-addition product

1,3-Diene Difunctionalization

3. Aminofunctionalization

Booker-Milburn

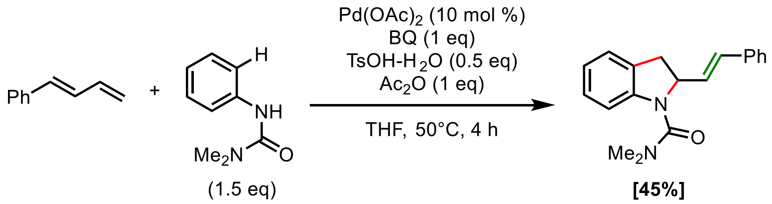
Diamination



Booker-Milburn, K. I. J. Am. Chem. Soc. 2005, 127, 7308-7309.

- Good yields with isoprene, 2,3-dimethylbutadiene (81-82%)
- Excellent yields with terminal styrenes (p-C_6H_4OMe, p-$C_6H_4CF_3$, Ph)

Carboamination

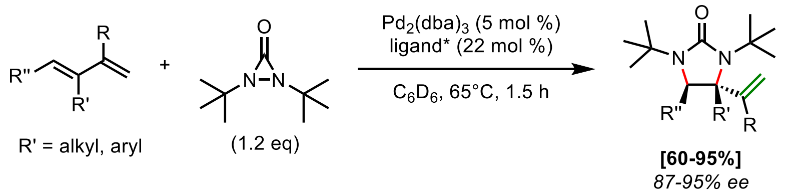


Booker-Milburn, K. I. J. Am. Chem. Soc. 2008, 130, 10066-10067.

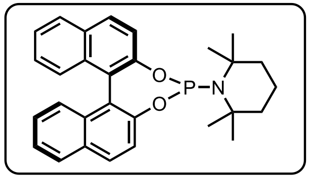
- Urea-directed C-H insertion
- Suggested TsOH generation of electrophilic $(TsO)_nPd$ species as active catalyst
- Most substrates in scope used vinylogous Michael acceptor as diene

Shi

Palladium-catalyzed Diamination

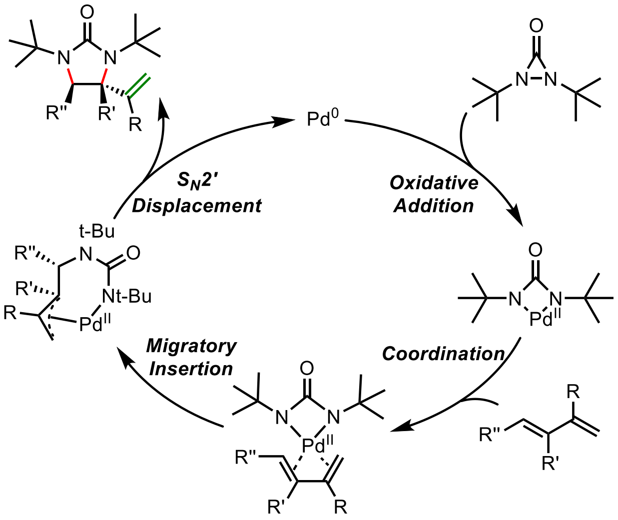


Shi, Y. J. Am. Chem. Soc. 2007, 129, 11688-11689.



- Use of phosphoramidite ligand gave high enantioselectivities
- Diamination of terminal conjugated, (*E*)- and (*Z*)-diene and trienes on internal olefin
- Tertiary amines, thiophenes, ester, ethers were tolerated
- NHC-Pd complexes have been used with similar substrate scope and comparable yields

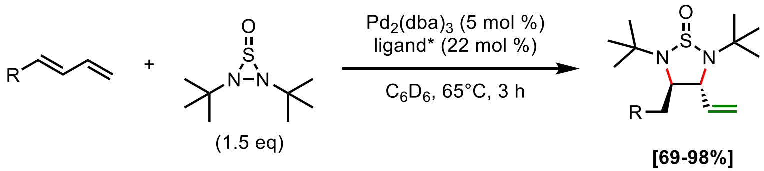
Shi, Y. J. Org. Chem. 2007, 72, 7038-7041.



Shi, Y. J. Am. Chem. Soc. 2010, 132, 3523-3532

- Proposed mechanism based on NMR studies

1,3-Diene Difunctionalization



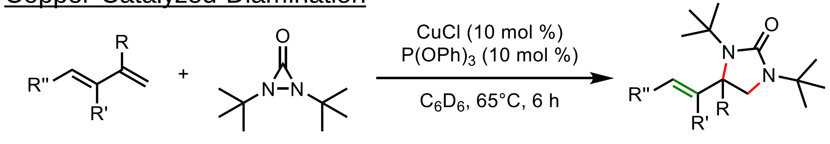
[69-98%]

90-93% ee

Shi, Y. Org. Lett. 2013, 15, 796-799.

- Used thiadiaziridine as nitrogen source
- Phosphoramidite ligand used
- Improved yields, enantioselectivity under similar reaction conditions

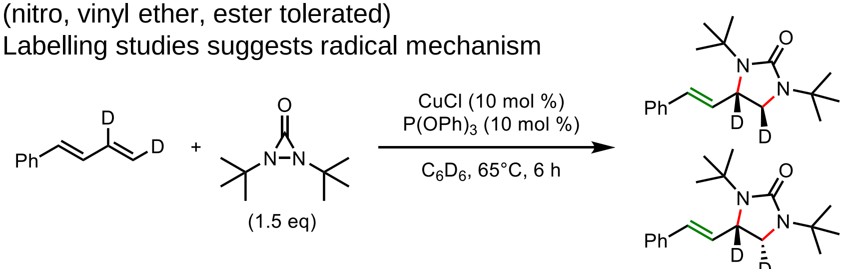
Copper-Catalyzed Diamination



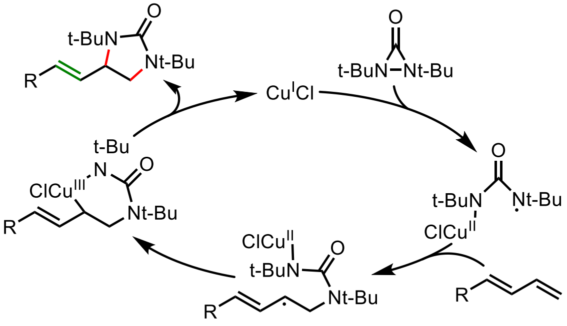
[50-89%]

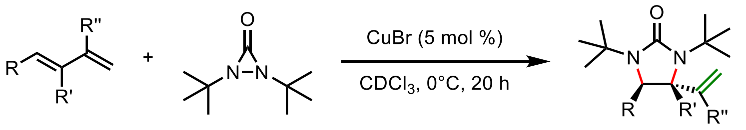
Shi, Y. Org. Lett. 2007, 9, 2589-2591.

- Diamination of terminal conjugated dienes and trienes on terminal olefin
- Substrate scope does not include many functional groups on dienes (nitro, vinyl ether, ester tolerated)
- Labelling studies suggests radical mechanism



65:35

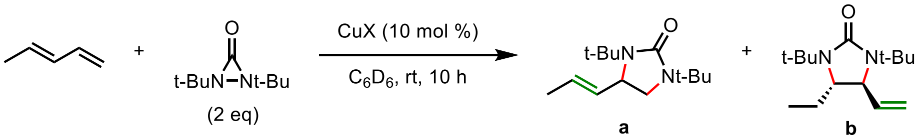




[81-99%]

Shi, Y. J. Am. Chem. Soc. 2010, 132, 11009-11011.

- Diastereoselective – no isomerization when deuterium-labelled diene difunctionalized – implies 2 electron mechanism
- Diamination of internal olefin is a result of ligandless catalyst

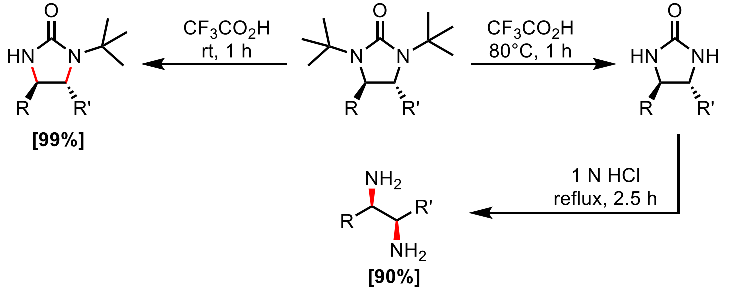


catalyst	a:b
CuCl-$P(OPh)_3$ (1:1.2)	34:66
CuCl-$P(OPh)_3$ (1:2)	42:58
CuCl-PCy_3 (1:1.2)	78:22
CuCl-PCy_3 (1:1.5)	97:3
CuCl	17:83
CuBr	1:99

- Mechanistic studies show internal diamination with copper goes through Cu^{III} species in a 2 electron process that resembles Pd^0 catalytic cycle

Shi, Y. J. Am. Chem. Soc. 2011, 133, 20890-20900.

- Cleavage of the imidazolidinone product



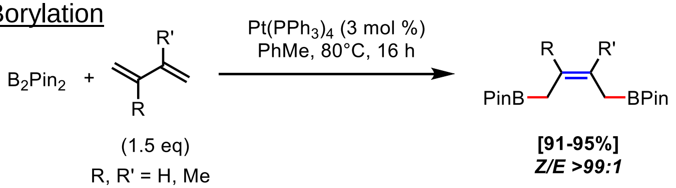
Shi, Y. J. Am. Chem. Soc. 2007, 129, 11688-11689.

1,3-Diene Difunctionalization

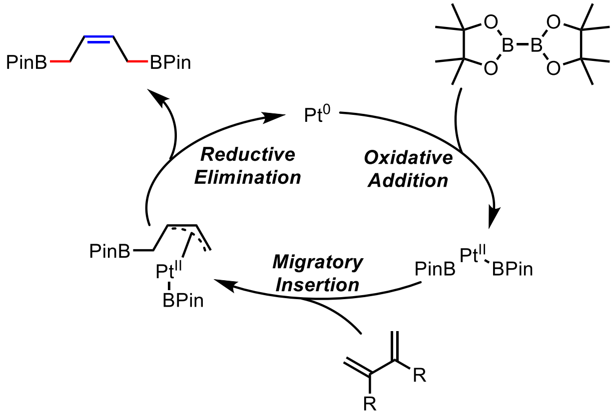
4. Borylation

Platinum-Catalyzed Borylation

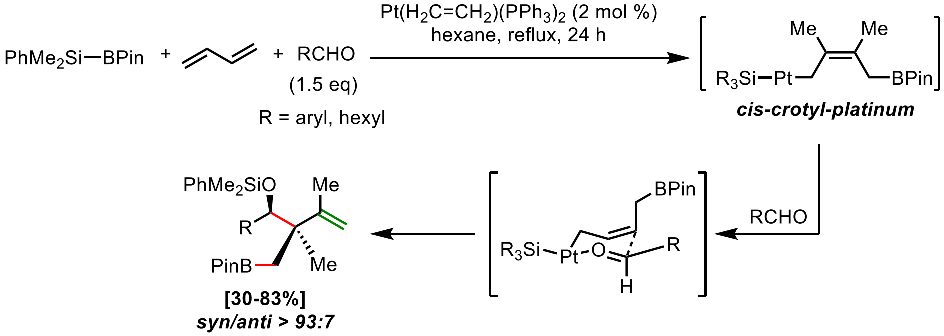
1,4-Borylation



Miyaura, N. Chem. Commun. 1996, 2073-2074.

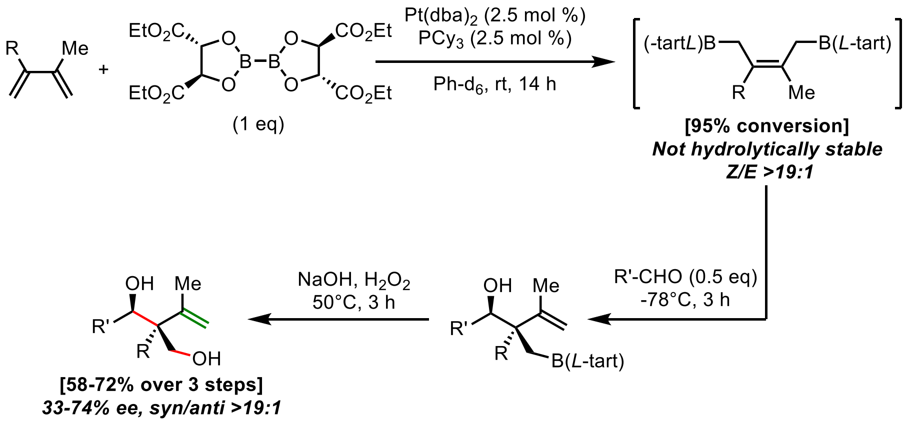


- Reductive elimination faster than *syn-anti* isomerization



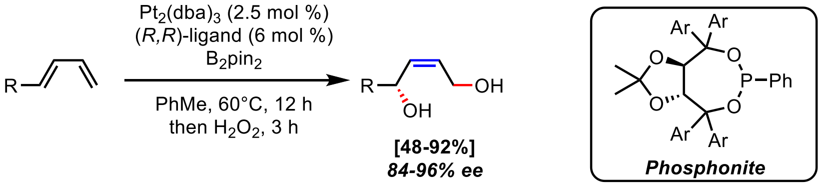
Ito, Y. J. Am. Chem. Soc. 1998, 120, 4248-4249.

- Yields lower with aliphatic aldehydes



Morken, J. P. Org. Lett. 2003, 5, 2573-2575.

- PCy_3 ligand gave high (*Z*) ratio and conversion – bulky monodentate ligand which opens coordination site of Pt after oxidative addition
- Increased size of R group gave higher enantioselectivity
- Electron deficiency of R lowered *e.e.* by 30%

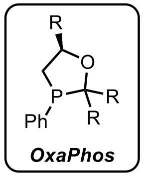


Morken, J. P. J. Am. Chem. Soc. 2009, 131, 9134-9135.

- TADDOL-like phosphonite ligand used to induce enantioselectivity
- Cyclic, acyclic terminal dienes, 1,2,3-substitution tolerated
- *Cis*-dienes gave no reaction suggesting only dienes able to give *S-cis* conformation can undergo diborylation

1,3-Diene Difunctionalization

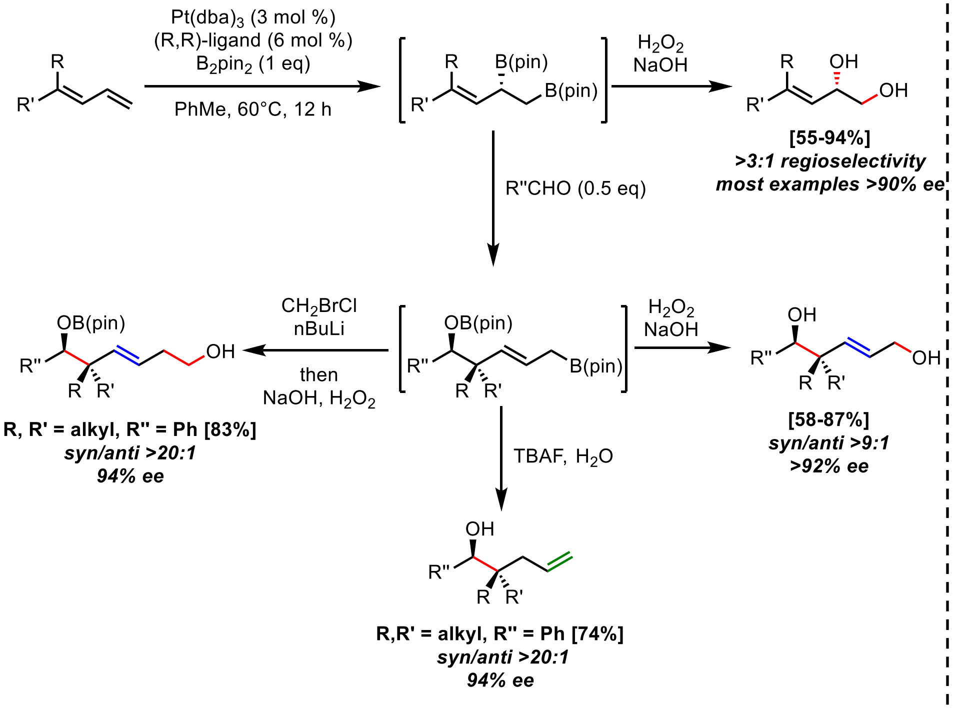
- Oxaphospholane ligands also used to access same transformation
- 1,4-diborylation products with high enantioselectivity
- Similar scope as phosphonite ligands



OxaPhos

Morken, J. P. Angew. Chem. Int. Ed. 2011, 50, 7906-7909.

1,2-Diborylation



[55-94%]
>3:1 regioselectivity
most examples >90% ee

R, R' = alkyl, R'' = Ph [83%]
syn/anti >20:1
94% ee

[58-87%]
syn/anti >9:1
>92% ee

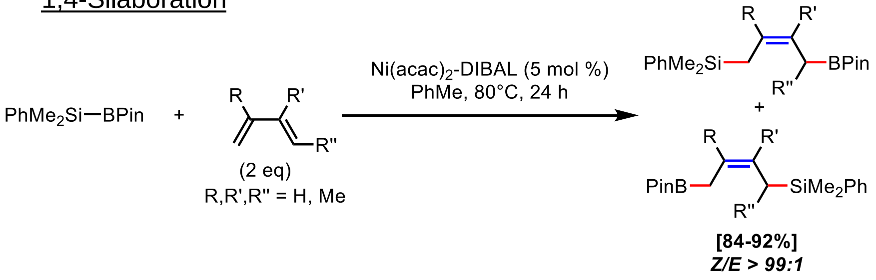
R,R' = alkyl, R'' = Ph [74%]
syn/anti >20:1
94% ee

Morken, J. P. Angew. Chem. Int. Ed. 2012, 51, 521-524.

- Chiral phosphonite ligands used to induce stereoselectivity
- Use of *cis*-dienes gave 1,2-selectivity
- Scope includes aliphatic alkyl dienes, silyl protected alcohols, olefins
- No endocyclic dienes

Nickel-Catalyzed Borylation

1,4-Silaboration

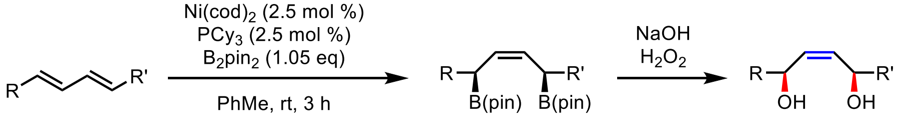


[84-92%]
Z/E > 99:1

Ito, Y. Org. Lett. 1999, 1, 1567-1569.

- Asymmetrical dienes (isoprene) gave mixture of regioisomers

1,4-Diborylation

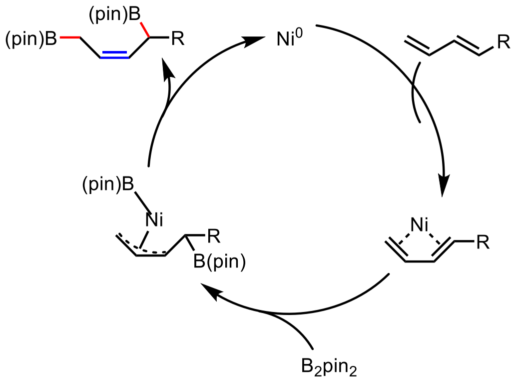


[44-77%]

Morken, J. P. Org. Lett. 2010, 12, 4348-4351.

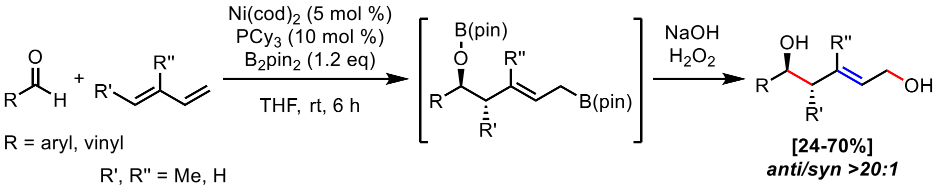
- Cyclic dienes gave 30% lower yields than acyclic
- Styrene was unreactive under these conditions implying Ni^0 does not undergo oxidative addition of B$_2$Pin$_2$

Proposed Mechanism:



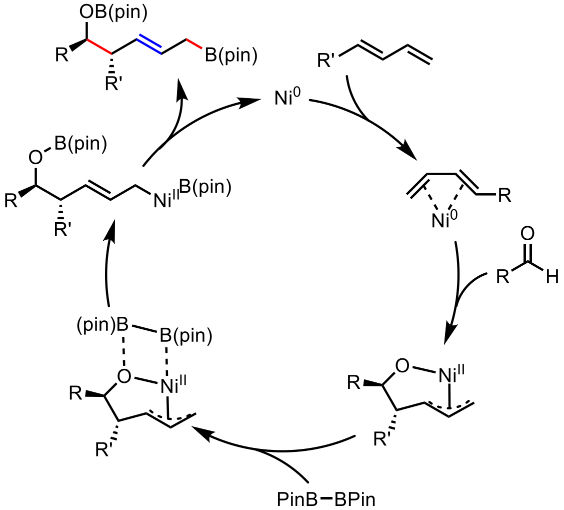
1,3-Diene Difunctionalization

1,4-Borylative Coupling



Morken, J. P. J. Am. Chem. Soc. 2008, 130, 16140-16141.

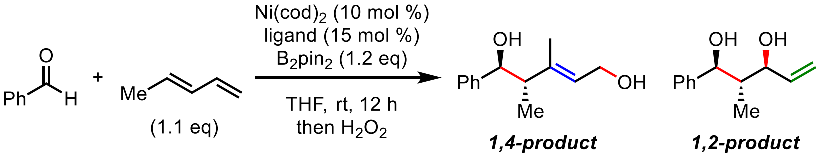
- Complementary stereochemistry to platinum-catalyzed 1,2-diborylation followed by allylboration of aldehyde
- Scope includes aryl and vinyl aldehydes and simple terminal dienes



- Nickel has been shown to be oxophilic and prefer to form the metallocycle over oxidative addition into B-B bond

Tamaru, J. Am. Chem. Soc. 2005, 127, 201-209.

1,2-Borylative Coupling



ligand	1,4:1,2 ratio	yield (%)
none	>20:1	39
PCy$_3$	>20:1	69
PEt$_3$	1:2	34
P(SiMe$_3$)$_3$	1:12	45

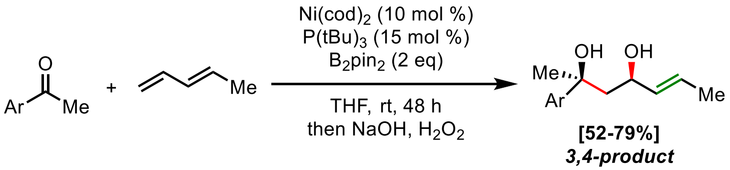
dr >20:1

Morken, J. P. J. Am. Chem. Soc. 2010, 132, 7576-7577.

- Aryl, heteroaryl, and aliphatic aldehydes can be used
- Reports of P(SiMe)$_3$ as a ligand may act as an electron acceptor – reductive elimination is faster than π-allyl isomerization

J. Organomet. Chem. 1984, 272, 29; J. Chem. Crystallogr. 2006, 36, 271.

3,4-Borylative Coupling

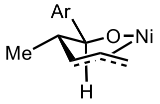


Morken. J. P. Org. Lett. 2011, 13, 5267-5269.

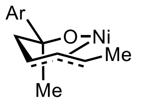
- Borylative coupling of ketones gives 3,4-product

Model to Explain Regio- and Stereochemical Outcome

non-hindered carbonyls

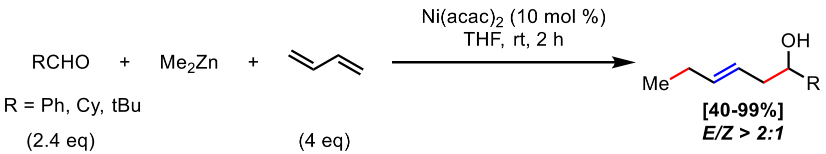


hindered carbonyls



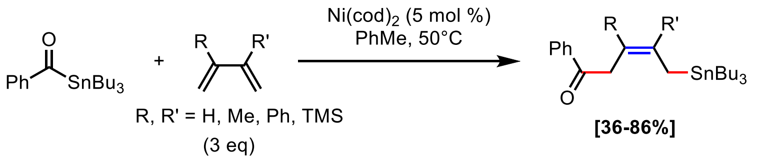
1,3-Diene Difunctionalization

5. Other Acylfunctionalizations with Ni^0



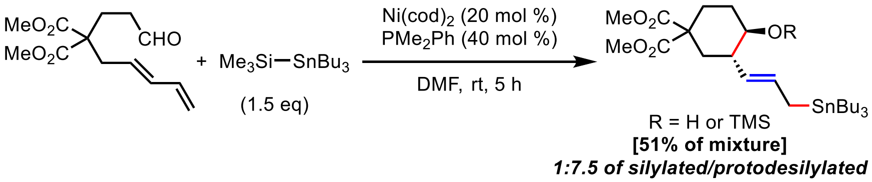
Tamaru, Y. Angew. Chem. Int. Ed. 1999, 38, 3386-3388; Tet. Lett. 2000, 41, 6789-6793.

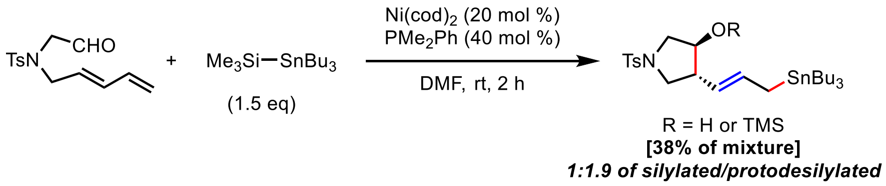
- Me_3B can be used instead of Me_2Zn



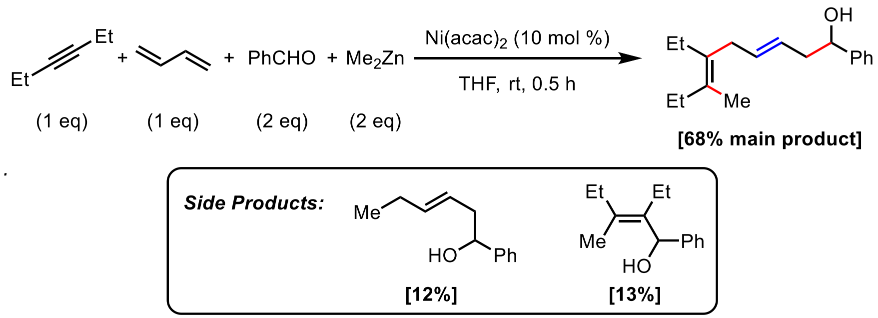
Hiyama, T. J. Am. Chem. Soc. 2000, 122, 9030-9031.

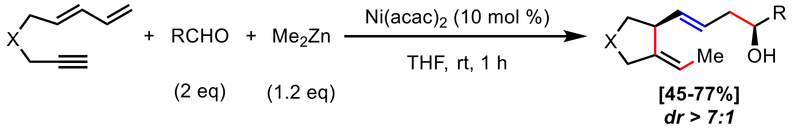
- Asymmetrical dienes give mixture of regioisomers





Mori, M. Chem. Lett. 2002, 31, 18-19.





Tamaru, Y. J. Am. Chem. Soc. 2005, 127, 201-209.

- X = $C(CO_2Et)_2$, NTs, O, $C(Ph)_2$
- R = PhEt, Cy, tBu
- Ketones instead of aldehydes have been used, giving moderate yields