CROSS-COUPLING REACTIONS

Joesphine Eshon & Prithvi Vangal

11th November 2014

OUTLINE

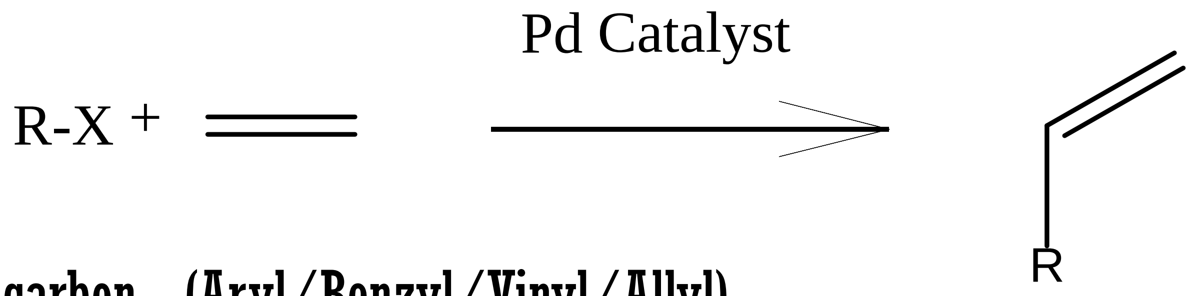
- Introduction
- Cross-coupling reactions:
  A. Negishi* Reaction
  B. Heck* Reaction
  C. Stille Reaction
  D. Suzuki* Reaction
  E. Sonogashira Reaction
  F. Buchwald-Hartwig Reaction
- Summary

INTRODUCTION TO CROSS-COUPLING REACTIONS

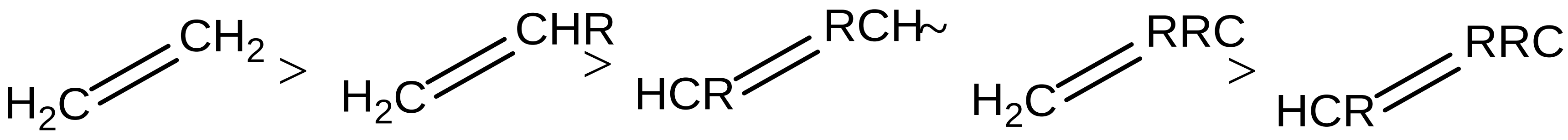
- Reactions that form (usually) carbon-carbon bonds between complex fragments
- Typically use a transition metal catalyst and an organometallic precursor
- Most involve a "transmetallation step"
- Transmetallation: Transfer of alkyl group from one metal to another
- Typical trend: Can transfer from more electropositive to less electropositive metals

HECK REACTION (OLEFINATION)

- General reaction scheme:



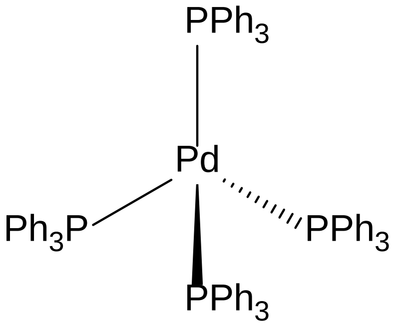
- R: Lacks a β hydrogen attached to an sp^3 carbon. (Aryl/Benzyl/Vinyl/Allyl)
- X: Typically Cl, Br, I, Otf
- Regioselectivity and rates are determined by steric hindrance at the alkene



Spessard and Meissler, Organometallic Chemistry

HECK: CATALYST AND CONDITIONS USED

- Palladium is in the 0 oxidation state in the active catalyst :



- The palladium can be reduced in situ : $PdCl_2$, $Pd(OAc)_2$ $\xrightarrow{e}$ Pd^0

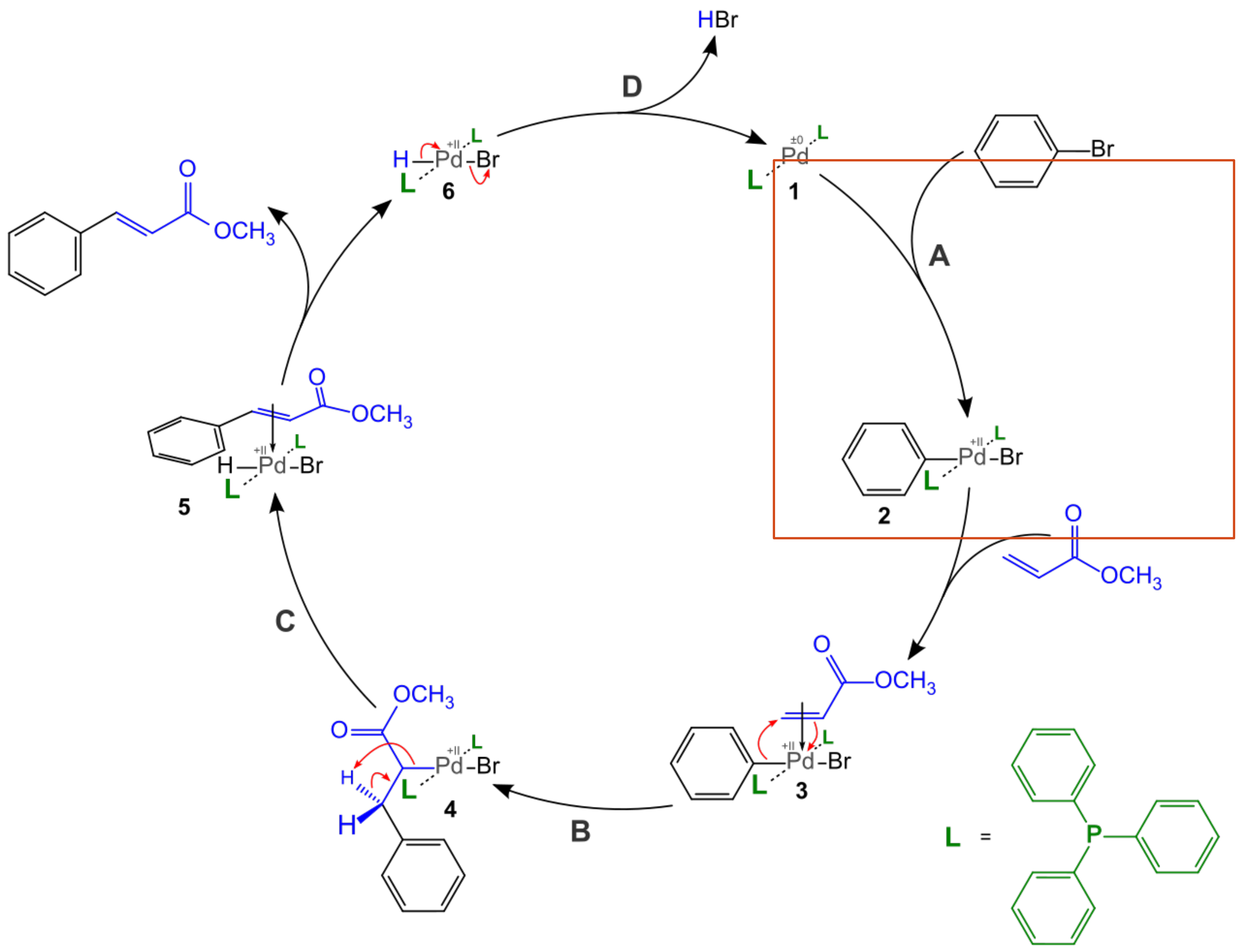
- Preferred solvent is DMF

- Increases rate, lowers temp. to from 80^0 C : $(^{n-}Bu)_4N^+ + KHCO_3$

- Two catalytic cycles are possible depending on the reaction conditions

Spessard and Meissler, Organometallic Chemistry

HECK: NEUTRAL CATALYTIC CYCLE



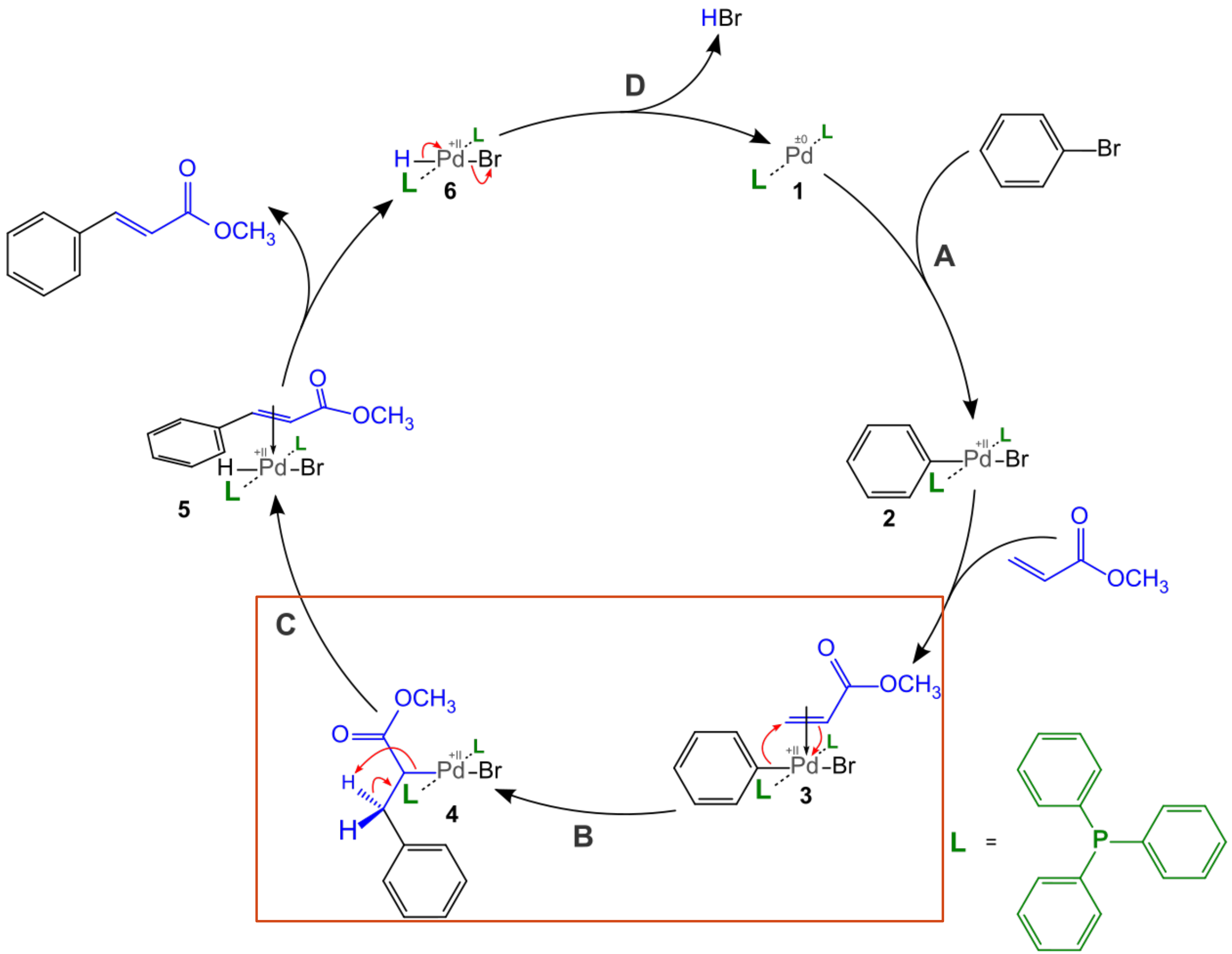
Oxidative Addition:

Pd(0) → Pd(+2)

$d^{10} \rightarrow d^{8}$

14 e → 16 e

HECK: NEUTRAL CATALYTIC CYCLE



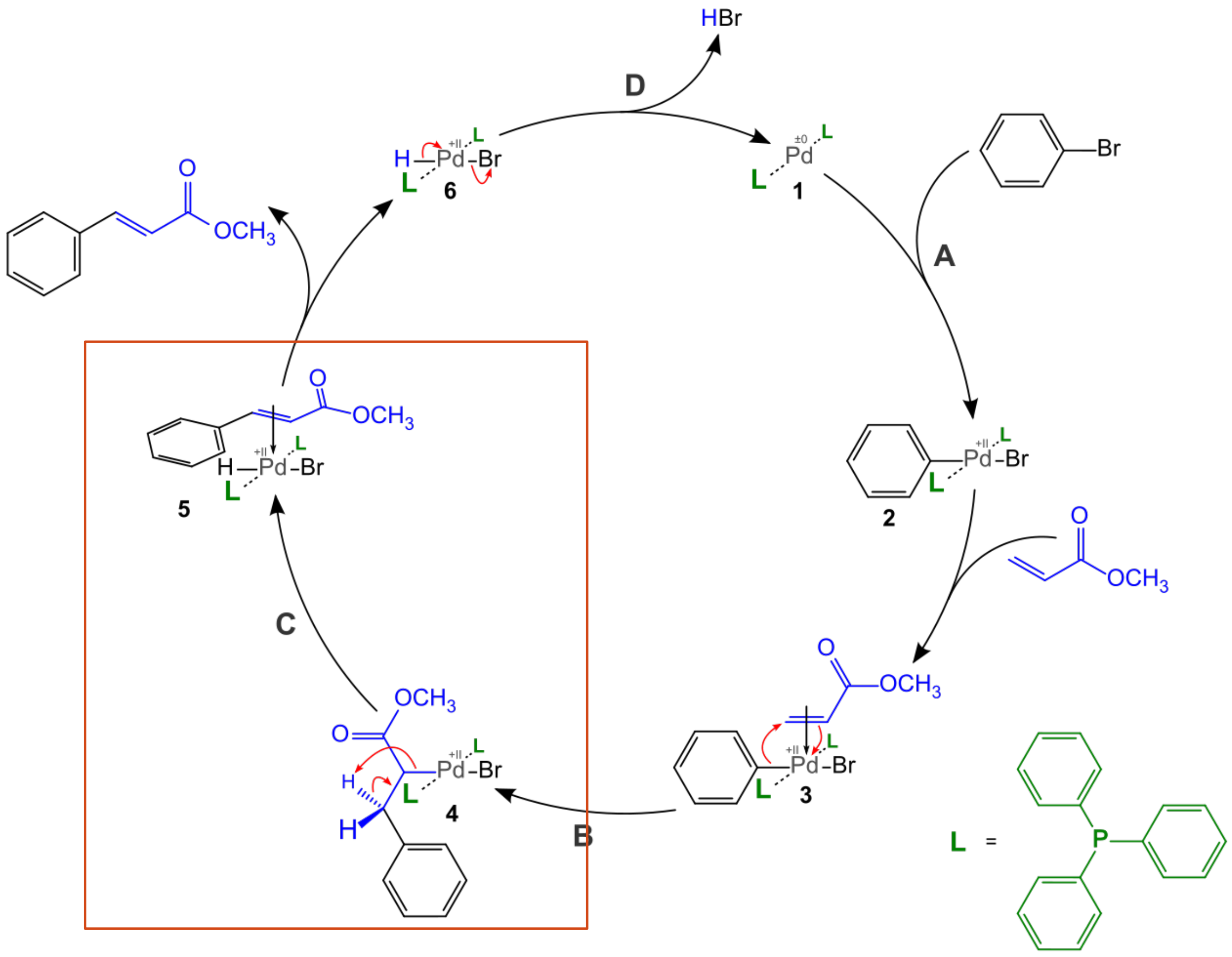
Insertion:

Pd(+2) → Pd(+2)

$d^8 \rightarrow d^8$

16 e → 16 e

HECK: NEUTRAL CATALYTIC CYCLE



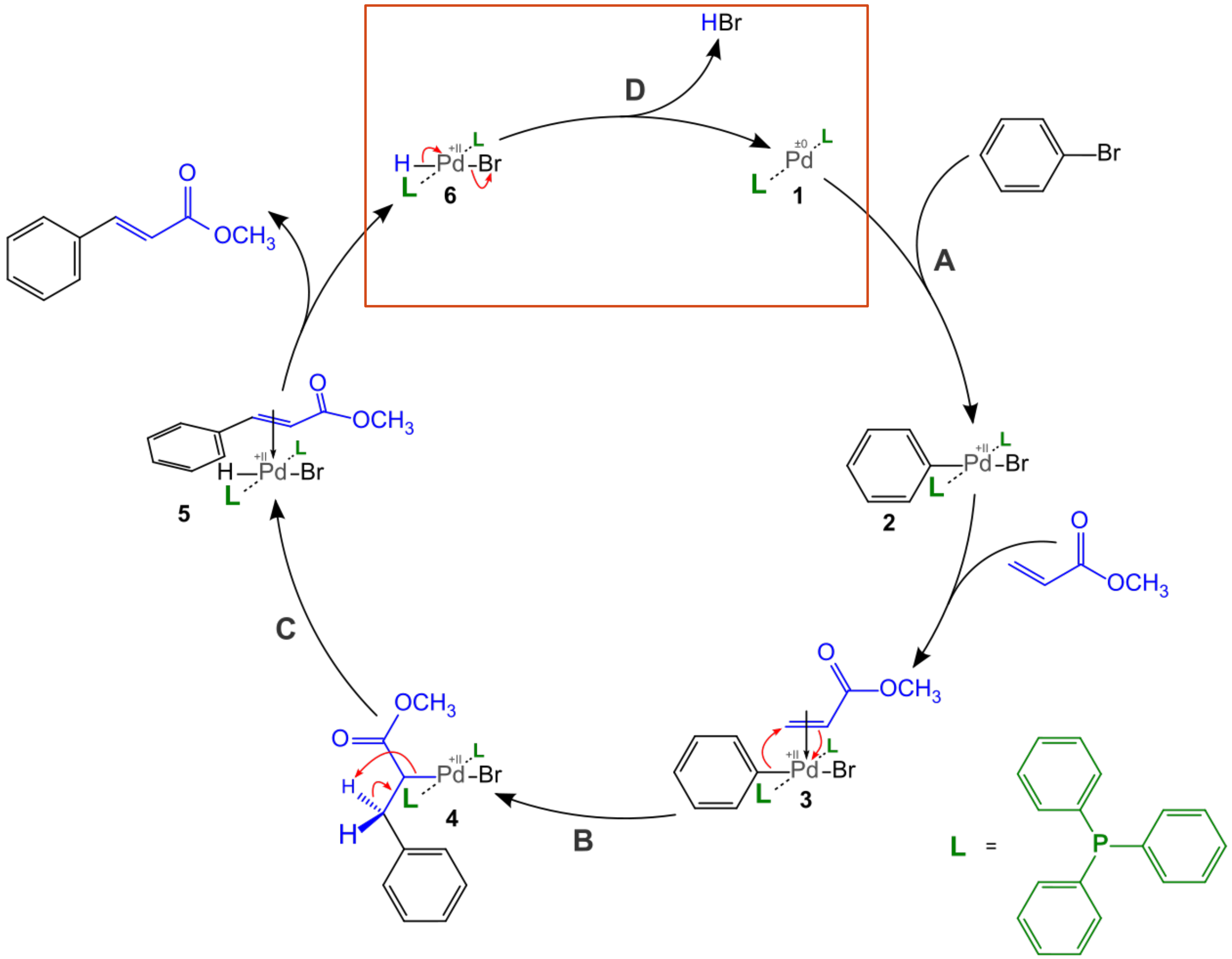
Hydride elimination:

Pd(+2) → Pd(+2)

$d^8 \rightarrow d^8$

16 e → 16 e

HECK: NEUTRAL CATALYTIC CYCLE



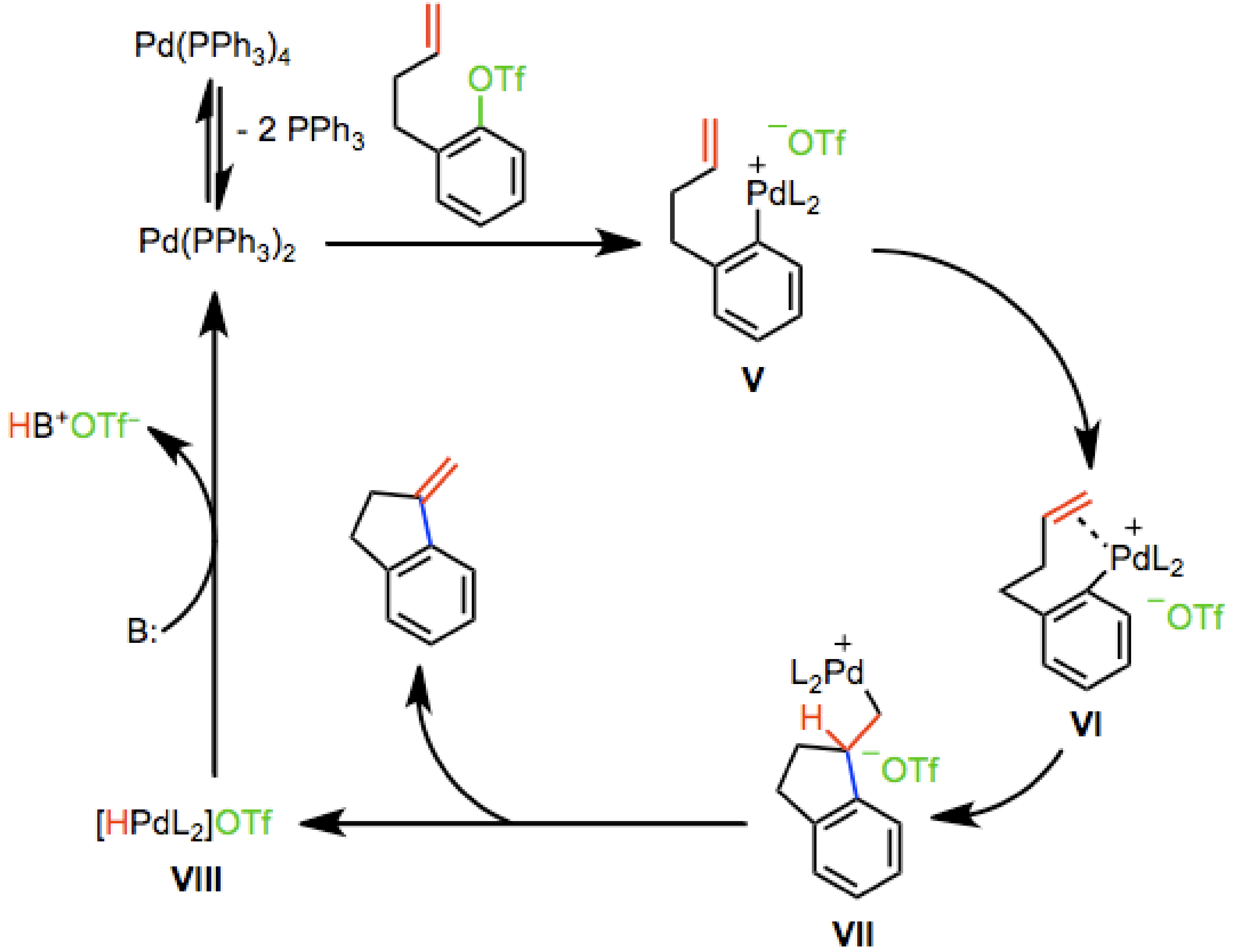
Reductive elimination:

Pd(+2) → Pd(0)

$d^8 \rightarrow d^{10}$

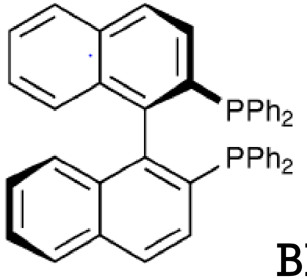
16 e → 14 e

HECK: CATIONIC CATALYTIC CYCLE



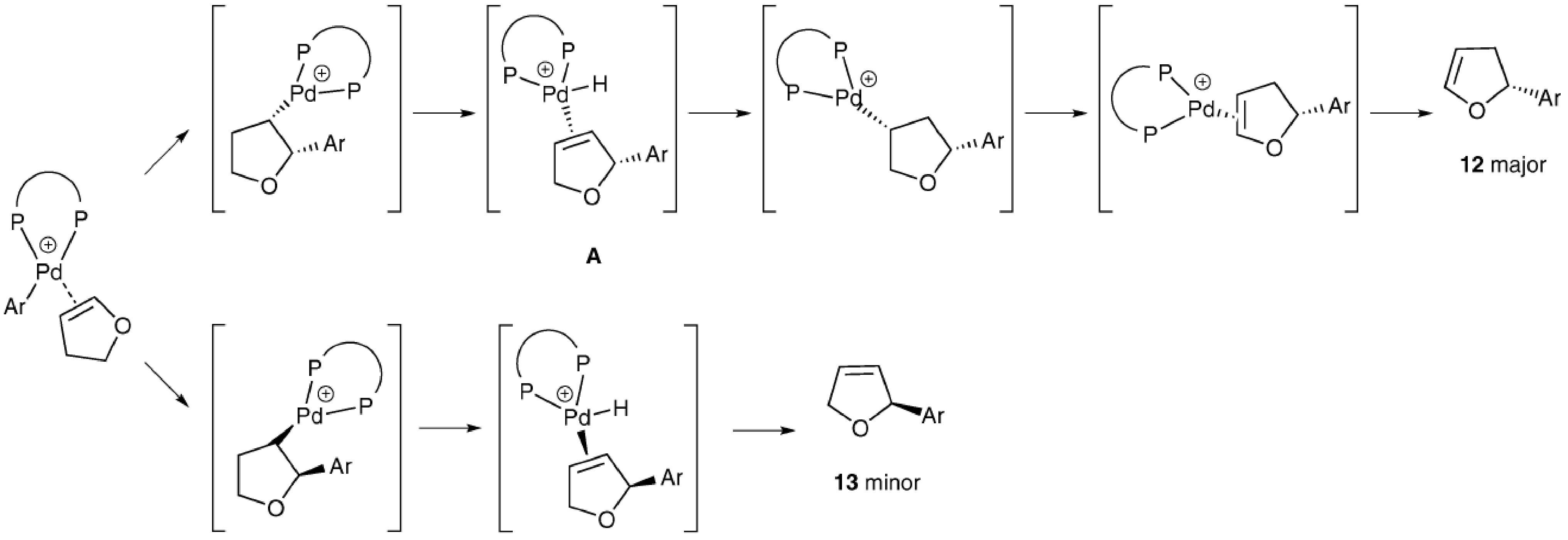
Example of an intramolecular Heck reaction

ASYMMETRIC HECK REACTIONS

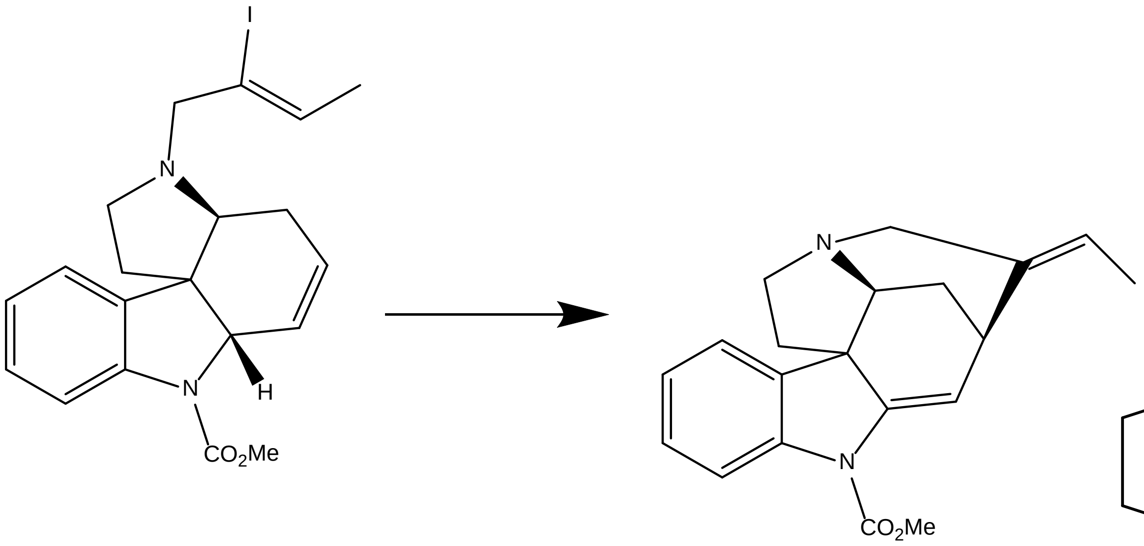


BINAP

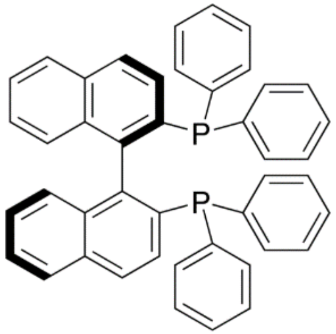
- By preventing β elimination from the new sp^3 center, an asymmetric product may be formed
- In order to do this, the hydride is anti to the Pd and chiral ligands are used

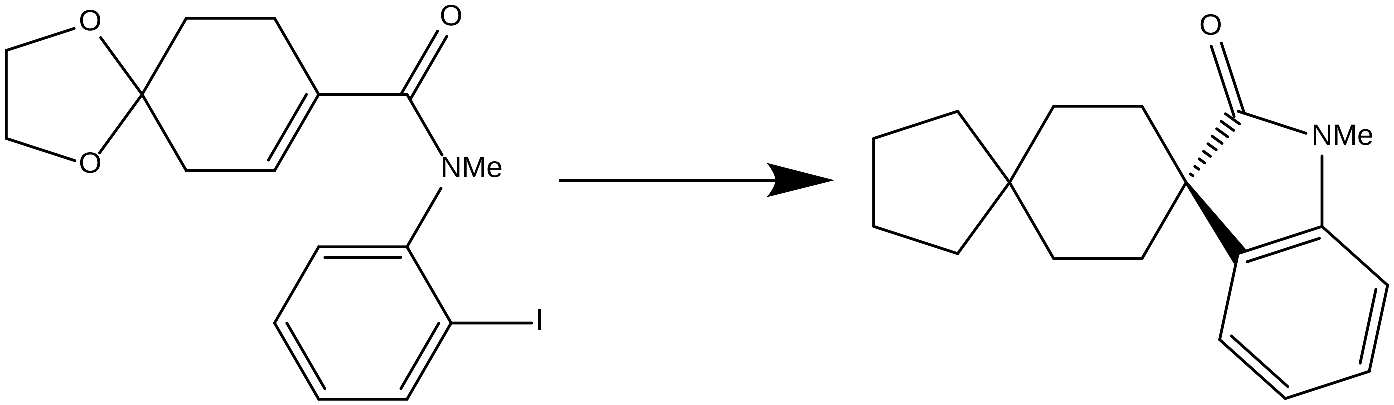


APPLICATIONS OF THE HECK REACTION



Chiral phosphine ligand





J. Org. Chem.,58,5583
J. *Org. Chem*, 57, 4571

STILLE CROSS-COUPLING

- Based on early studies by Eaborn and Kosugi.
- Stille Coupling is useful for constructing new C-C bonds because of the following:
  - Reaction conditions are highly tolerant of many organic functional groups, therefore limiting protection-deprotection steps.
  - Organotin compounds are easy to synthesize and some are commercially available.
  - Organotin compounds are more stable.
  - Organotin compounds are not moisture or air sensitive so sophisticated laboratory techniques are not needed.
  - Sn-C bond is stable with a bond energy of 50 kcal/ mol

Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D.R.M. *J. Organometal. Chem.* **1976**, 117,C55.
Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.,* **1977**, 201.
Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.,* **1977**, 1423.
Milstein, D.; Stille, J.K. *J.Chem. Soc.* **1978**, 100, 3636.

STILLE CROSS-COUPLING
GENERAL TYPE OF REACTIONS

- General reaction type:

$$R'\text{-}X + R\text{-}SnR''_3 \xrightarrow[L_nPd]{} R'\text{-}R + X\text{-}SnR''_3$$

- R'X reacts to yield Ketone.

$$R'\text{-}C({=}O)\text{-}X + R\text{-}SnR''_3 \xrightarrow[L_nPd]{} R'(CO)\text{-}R'' + X\text{-}SnR''_3$$

- R'-X reacts in the presence of CO to yield a ketone as well.

$$R'\text{-}X + R\text{-}SnR''_3 \xrightarrow[L_nPd/CO]{} R'(CO)\text{-}R'' + X\text{-}SnR''_3$$

Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

STILLE CROSS-COUPLING
REQUIREMENT FOR R'-ELECTROPHILE

- General reaction type:

$$R'\text{-}X + R\text{-}SnR''_3 \xrightarrow[L_nPd]{} R'\text{-}R + X\text{-}SnR''_3$$

- The reaction works best when R is the following:

  - [R'(C=O)]-Cl
  - [R'R"C=CR'"-CH_2]-X(allyl)
  - Aryl-X
  - Benzyl-X
  - [R'R"C=CR'"]-X
  - R'-C(H)X-CO_2R"

STILLE CROSS-COUPLING REQUIREMENT FOR R

- General reaction type:

$$R'\text{-}X + \mathbf{R}\text{-}SnR''_3 \xrightarrow[L_nPd]{} R'\text{-}R + X\text{-}SnR''_3$$

- The reaction works best when R is the following:
  - [H]-SnR'''_3
  - [R-CC]-SnR'''_3
  - [RRC=CR] -SnR'''_3
  - [Aryl]-SnR'''_3
  - [RRC=CR-CH_2]-SnR'''_3
  - [R-C(H)X-CO_2R] -SnR'''_3
  - [Ar-CH_2]-SnR'''_3
  - [Alkyl]-SnR'''_3
    - R=Methyl and Butyl

Why organotin?

Multiple alkyl groups possible.

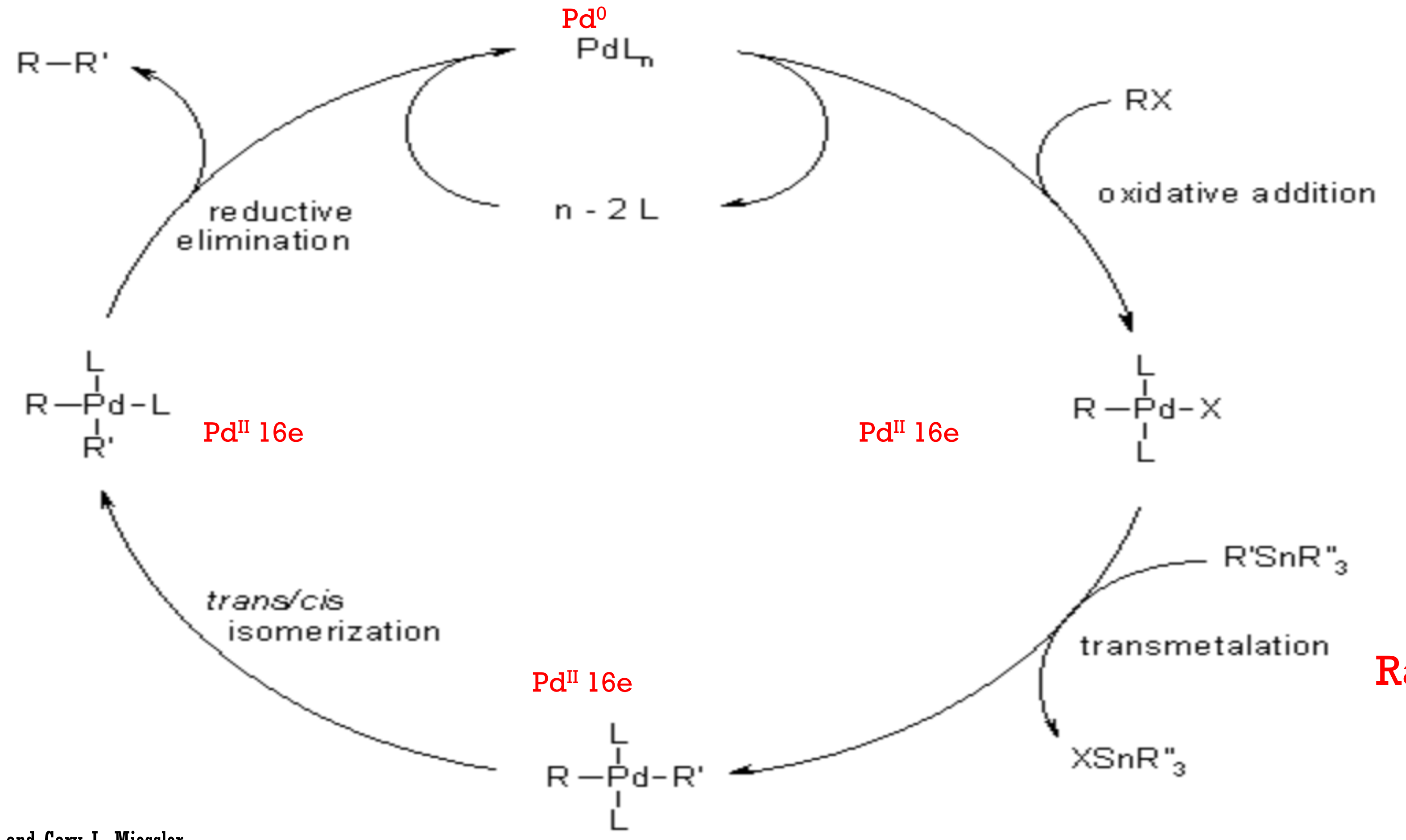
- Order of transfer

$$R\text{—}C{\equiv}C > RCH{=}CH > \text{aryl} > \text{ally-benzyl} > CH_3(C{=}O)CH_2 > \text{alkyl}$$

Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

STILLE CROSS-COUPLING REACTION MECHANISM

- Proposed reaction mechanism

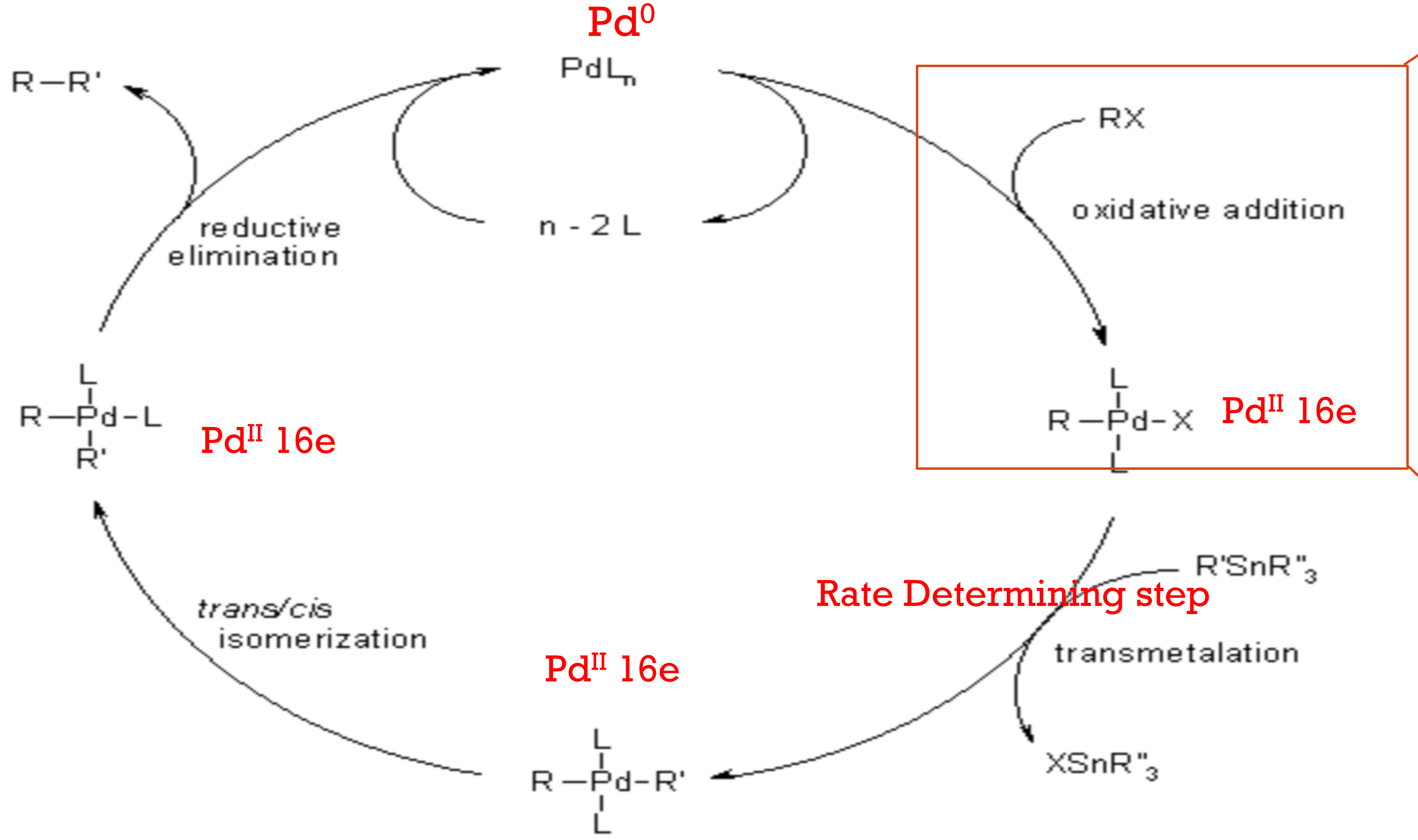


Rate Determining step

Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

STILE CROSS-COUPLING
REACTION MECHANISM-OXIDATIVE ADDITION

- Proposed reaction mechanism



R' is sp^2

Retention

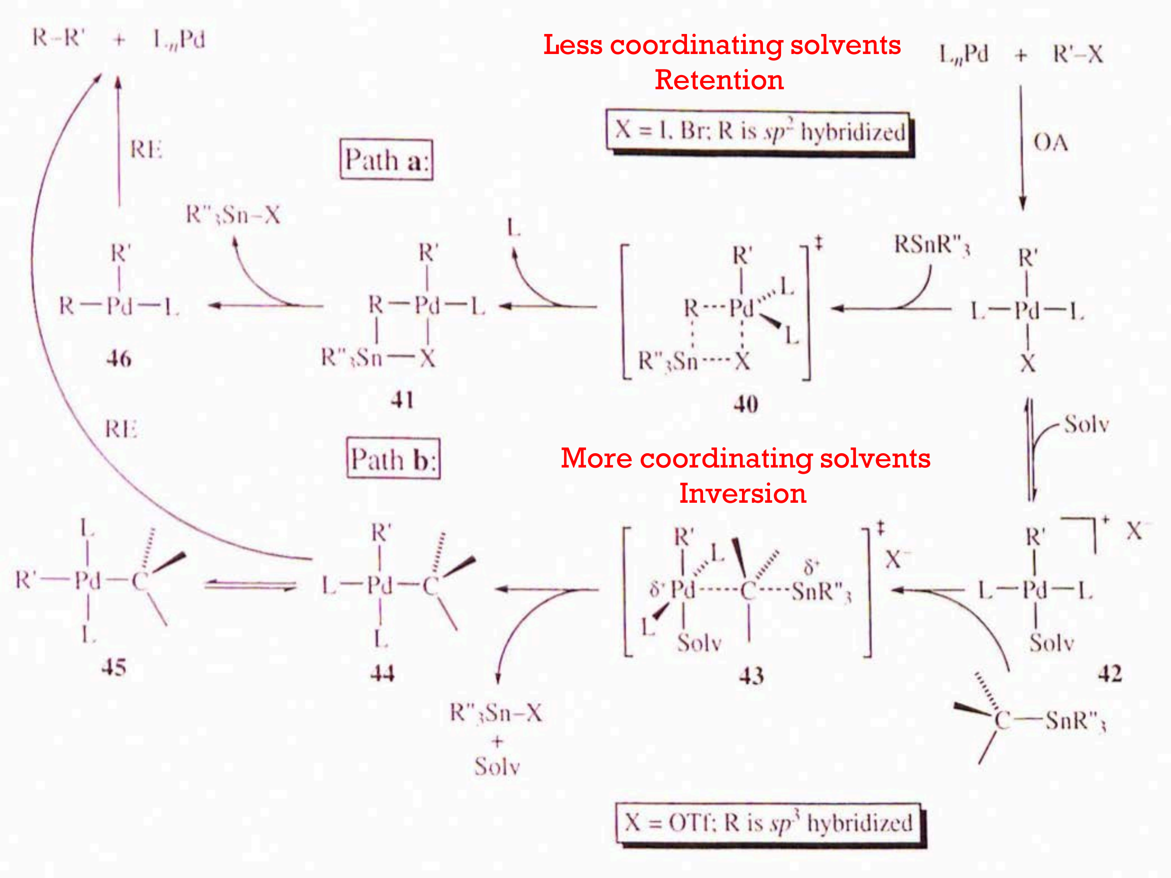
R' is sp^3

S_N2 Mechanism Inversions

Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

STILLE CROSS-COUPLING REACTION MECHANISM-TRANSMETALATION

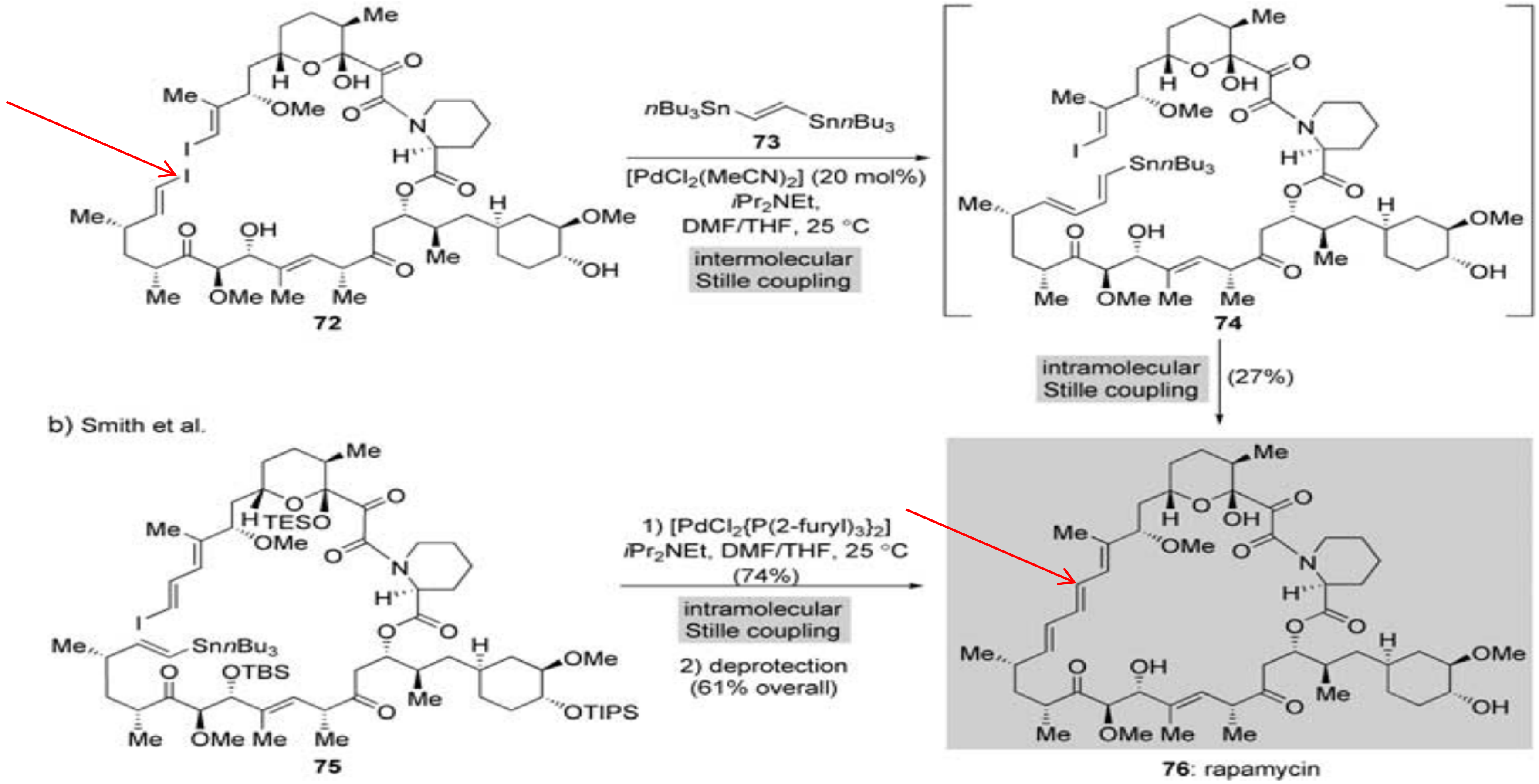
- Transmetalation



Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

STILLE CROSS-COUPLING APPLICATION AND SYNTHESIS

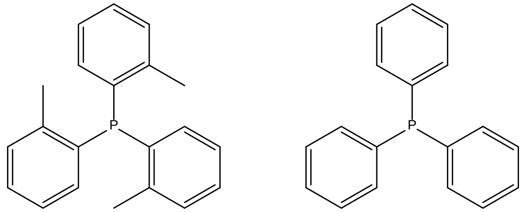
- K.C.Nicolaou synthesis of rapamycin.



Nicolaou, K.C.; Bulger, P.G. *Angew. Chem. Int. Ed.*, **2005**, 44, 4442.

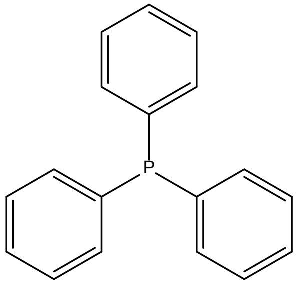
SUZUKI REACTION (SUZUKI-MIYAURA)

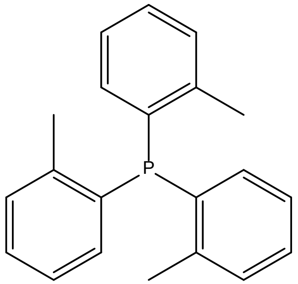
- General reaction scheme: $R'X + RBR''_2 \xrightarrow{L_nPd^0,\ Base} R'\text{-}R + X\text{-}BR''_2$
- Ligands: PY_3



- Base: NaOH, TlOH, Na_2CO_3, K_2CO_3, NaF, KF, NaOMe, etc.
- R”: Alkyl, O-alkyl, OH
- Scope is similar to that of the Stille reaction (B, Sn have similar electronegativities)
  1. Less toxic than organotin reagents
  2. More functional group tolerance
  3. Several boronic acids are commercially available

SUZUKI: CATALYST USED



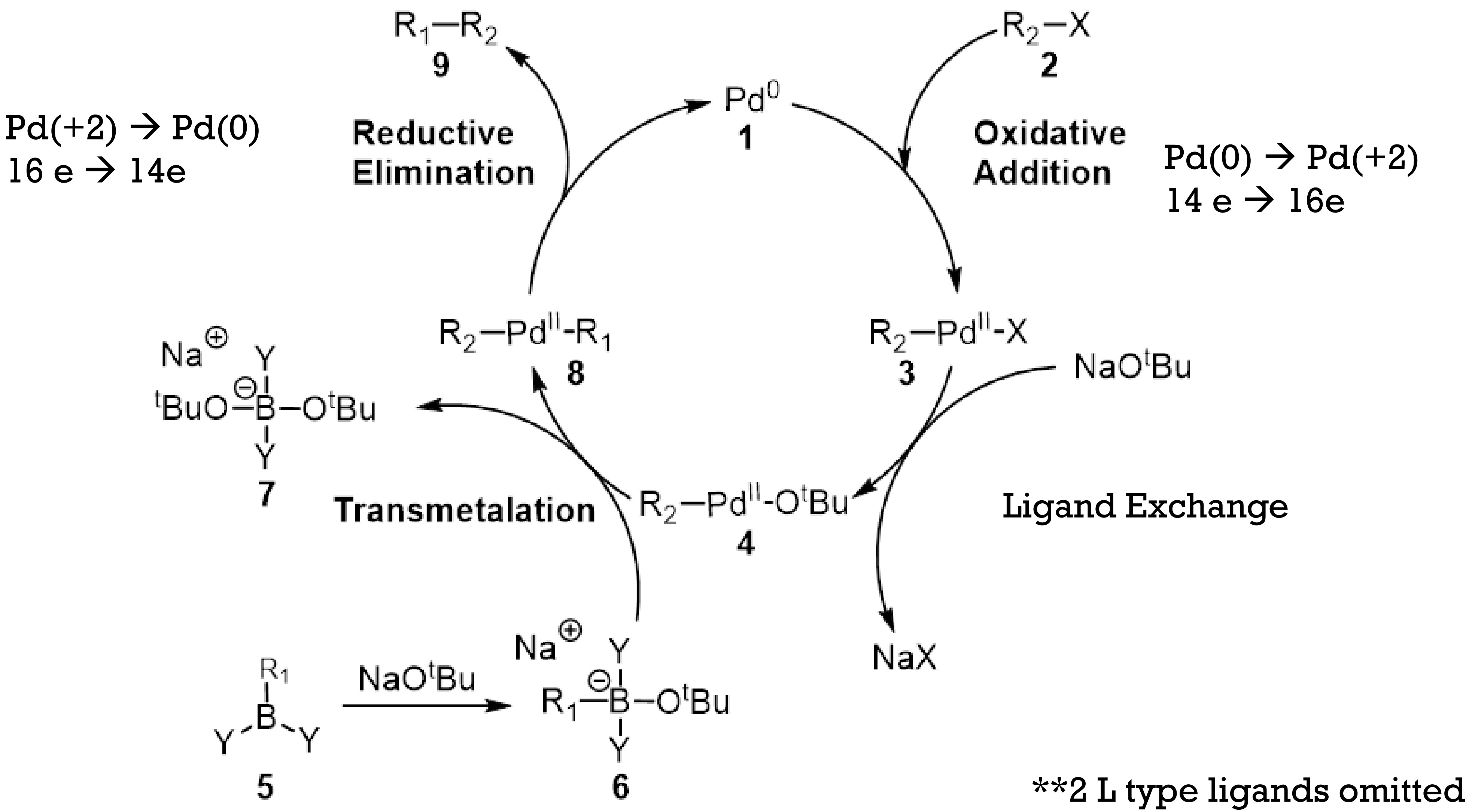


- Typically use a palladium catalyst in the 0 oxidation state:
- Phosphine Ligands: Triphenylphosphine and triorthotolylphosphine
- In recent years, Nickel catalysts have become popular:

1. Not as expensive as Pd
2. More abundant than Pd
3. Need higher catalyst loading
4. Mechanism not fully understood

- Other isolated reports use Fe and Cu as catalysts for the Suzuki reaction

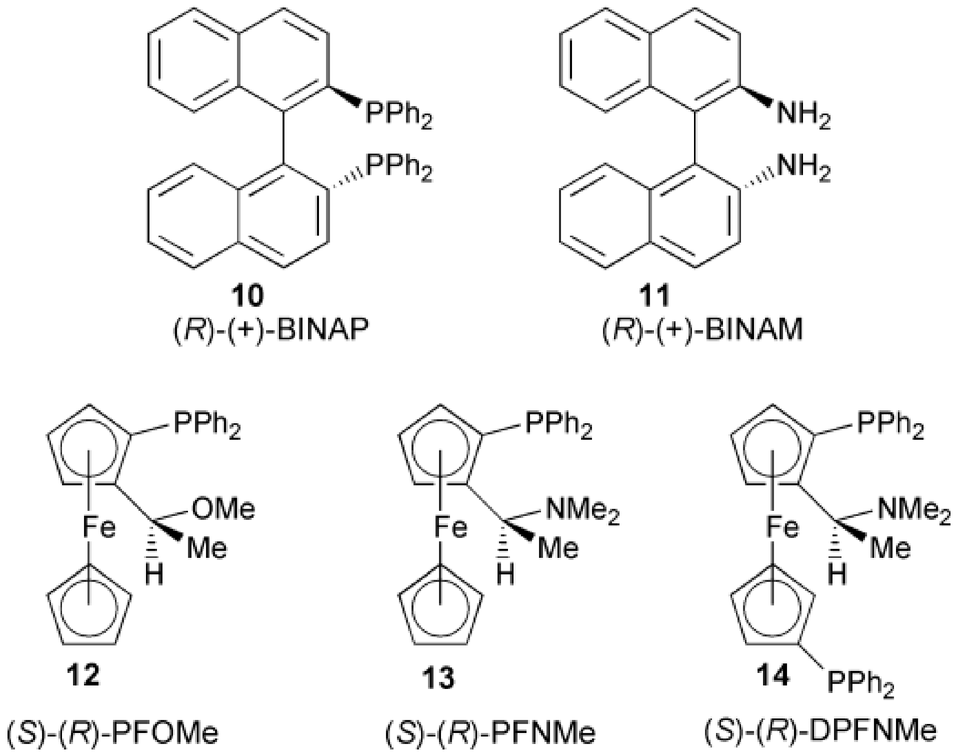
SUZUKI: CATALYTIC CYCLE WITH PALLADIUM



**2 L type ligands omitted

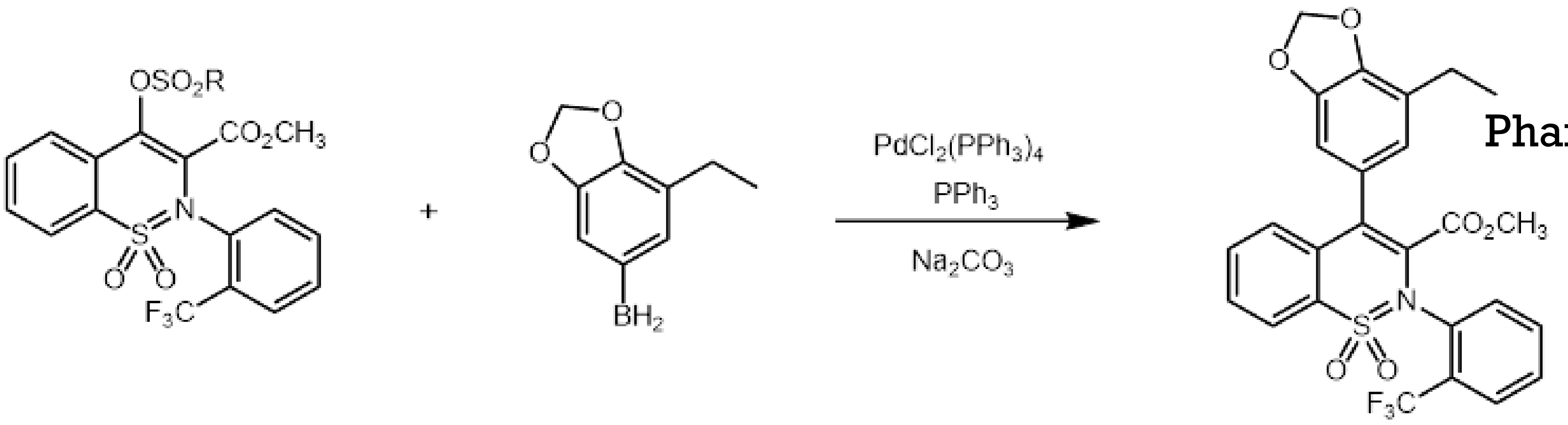
SUZUKI: ASYMMETRIC/SELECTIVE SYNTHESES

- Use chiral ligands like:



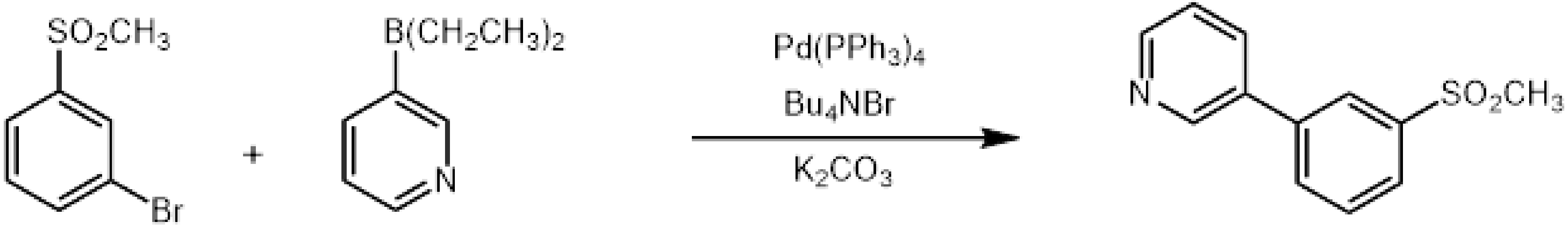
- May impart selectivity through pre-complexation with the ligand

APPLICATIONS OF THE SUZUKI REACTION



Pharmaceutical : CI:1034

CI-1034



Central nervous system agent

NEGISHI CROSS-COUPLING

- The Negishi Coupling was first published in 1977.

$$R'\text{-}X + M'\text{-}R \longrightarrow R'\text{-}R + M'\text{-}X$$

- This is the first reaction that allowed the preparation of unsymmetrical biaryls in good yields.
- Uses versatile nickel- or palladium-catalyzed coupling of organozinc compounds with various halides such as aryl, vinyl, benzyl, and allyl.
- Often used to synthesis acyclic di, tri, and higher order terpeniod systems.
- This used than Suzuki reactions.

Negishi, E.; Lious, S.Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, 4, 261.
Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

NEGISHI CROSS-COUPLING REQUIREMENTS FOR R'

- General rection

$$R'\text{-}X + M'\text{-}R \longrightarrow R'\text{-}R + M'\text{-}X$$

- The reaction works best when R' is the following:
  - Aryl
  - Vinyl
  - Alkynly
  - Acyl
  - Allyl
  - Benzyl
  - Homoallyl
  - Homobenzyl
  - Primary alkyl

Negishi, E.; Lious, S.Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, 4, 261.

NEGISHI CROSS-COUPLING REQUIREMENTS FOR R

- General reaction:

$$R'\text{-}X + M'\text{-}R \longrightarrow R'\text{-}R + M'\text{-}X$$

- The reaction works best when R is the following:
  - Aryl
  - Vinyl
  - Alkynly
  - Allyl
  - Benzyl
  - Primary alkyl

Negishi, E.; Lious, S.Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, 4, 261.

NEGISHI CROSS-COUPLING REQUIREMENTS FOR X

- General reaction

$$R'\text{-}X + M'\text{-}R \longrightarrow R'\text{-}R + M'\text{-}X$$

- The reaction works best when X is the following:
  - I
  - OTF
  - Br
  - Cl-work but often sluggishly

Negishi, E.; Lious, S.Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, 4, 261.

NEGISHI CROSS-COUPLING
REQUIREMENTS FOR ORGANOZINC REAGENTS

- General reaction

$$R'\text{-}X + M'\text{-}R \longrightarrow R'\text{-}R + M'\text{-}X$$

- The organozinc reagent may be used as the following:
  - R_2Zn
  - RZnX (X=Cl, Br, I)
  - RZnX generated *in situ* by reaction R-X with Zn dust

Negishi, E.; Lious, S.Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, 4, 261.

NEGISHI CROSS-COUPLING REQUIREMENTS FOR METAL

- General reaction

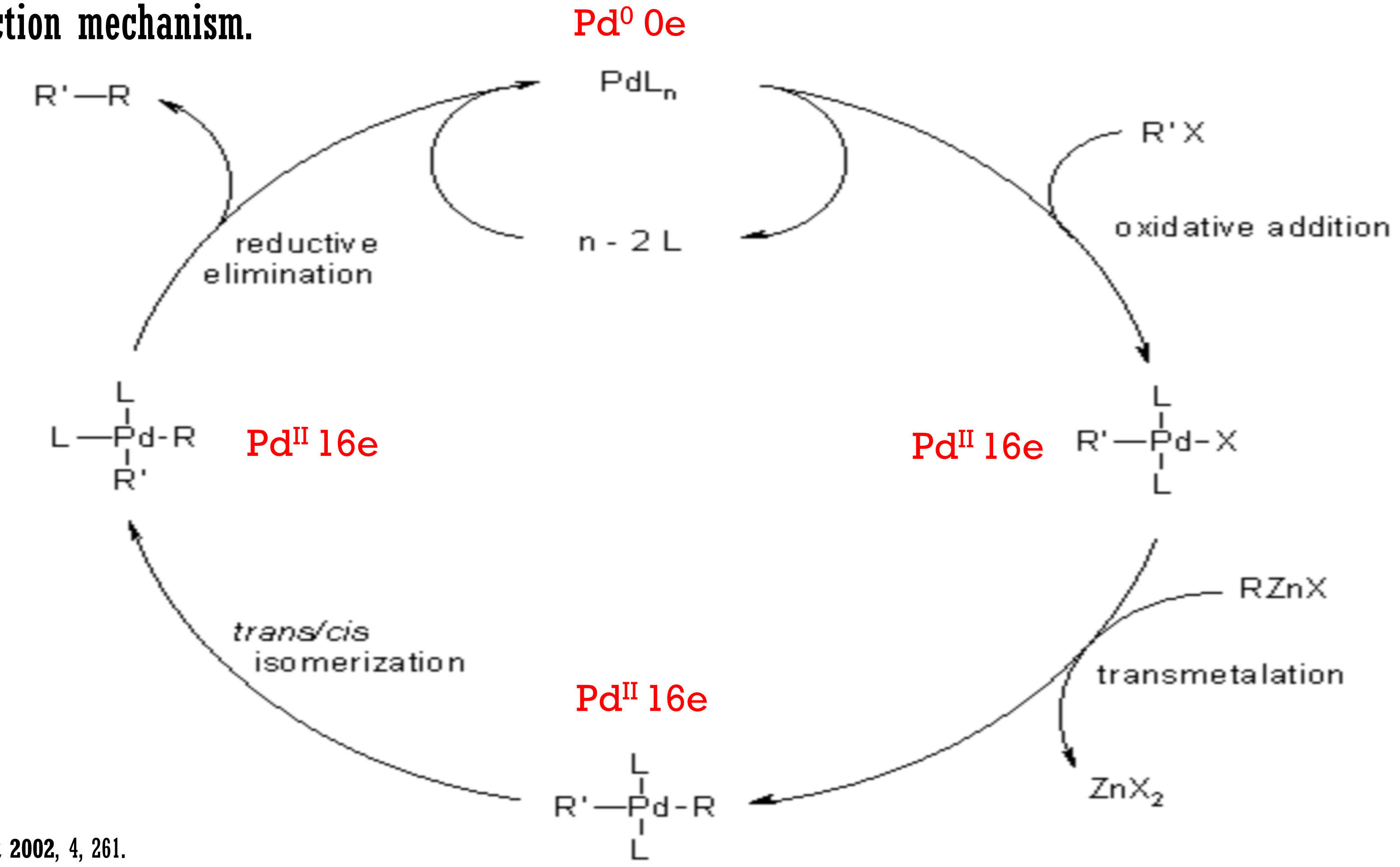
$$R'\text{-}X + M'\text{-}R \longrightarrow R'\text{-}R + M'\text{-}X$$

- The reaction works best with the following metals:
  - Palladium
    - Palladium-phosphine give the best yield
  - Nickel

Negishi, E.; Lious, S.Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, 4, 261.

NEGISHI CROSS-COUPLING REACTION MECHANISM

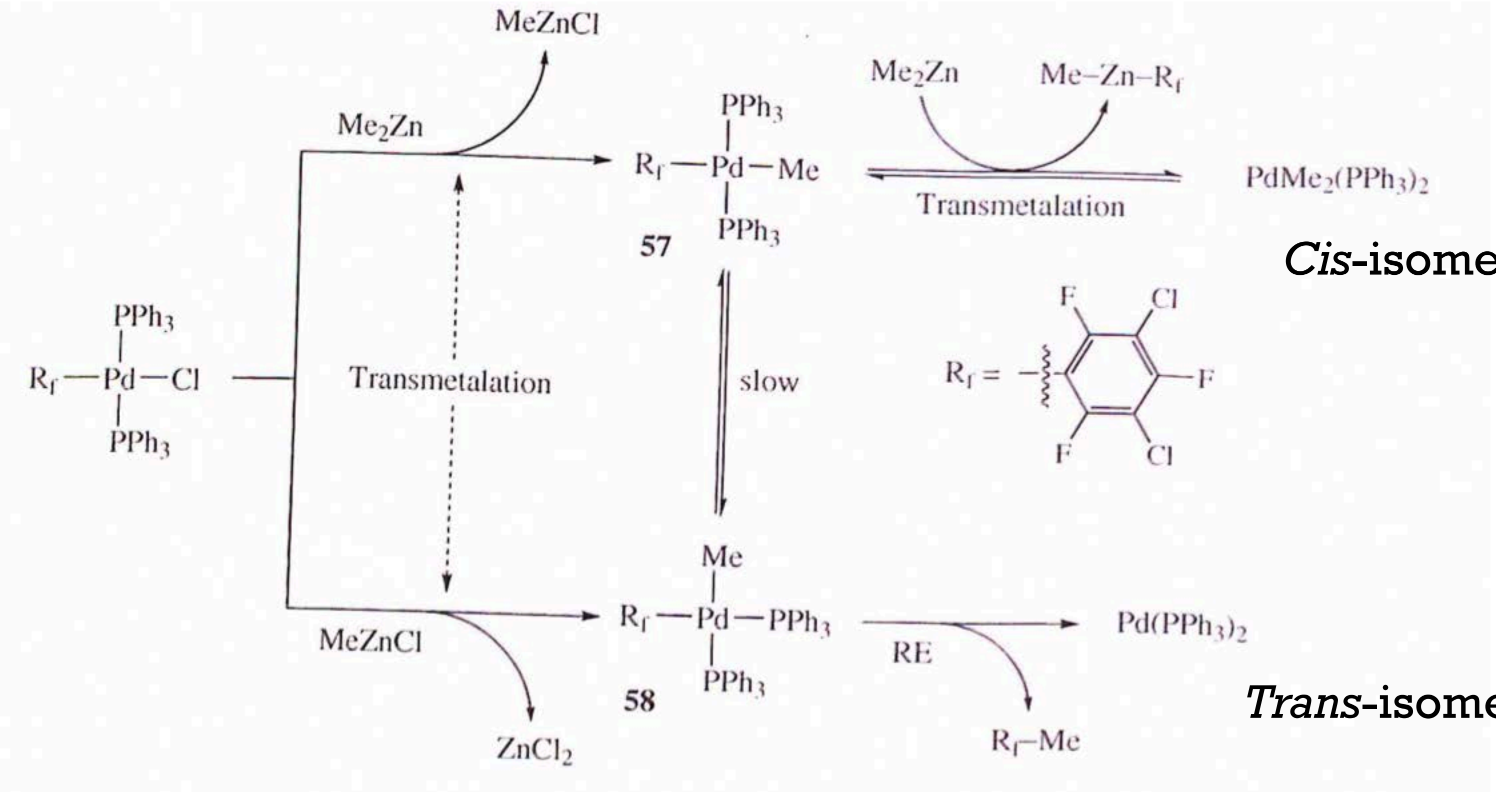
Proposed reaction mechanism.



Negishi, E.; Lious, S.Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, 4, 261.

NEGISHI CROSS-COUPLING REACTION MECHANISM-TRANSMETALATION

- Formation of different sterochemical outcomes for transmetalation as a function of the style of organozinc reagent.

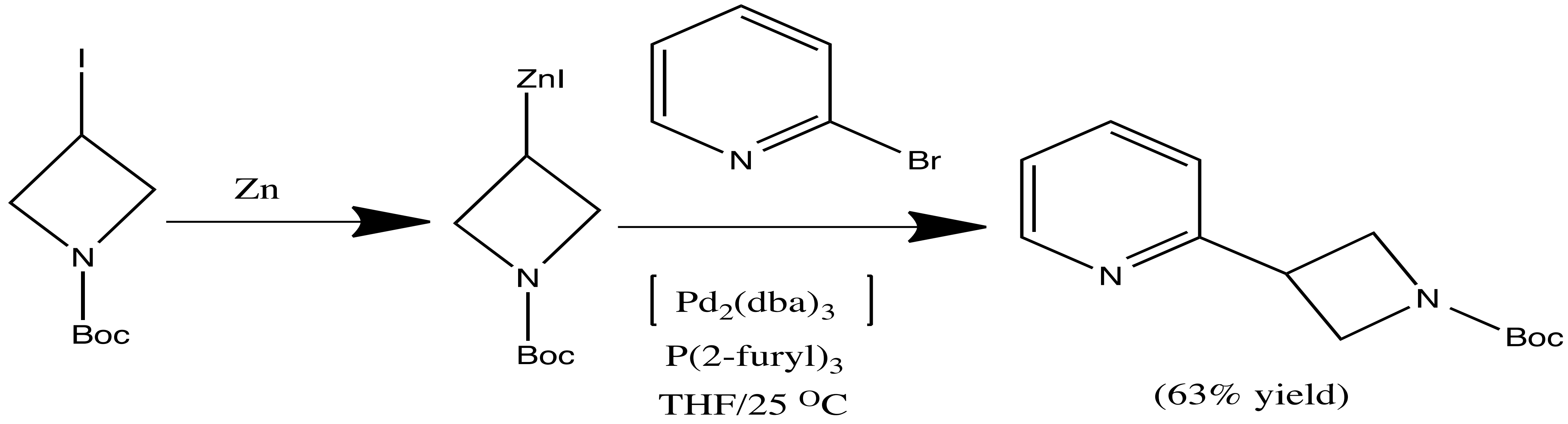


Cis-isomer

Trans-isomer

Casares, J.A.; Espinet, P.; Fuentes, B.; Salas, G. *J. Chem. Soc.* **2007**, 129, 3508.

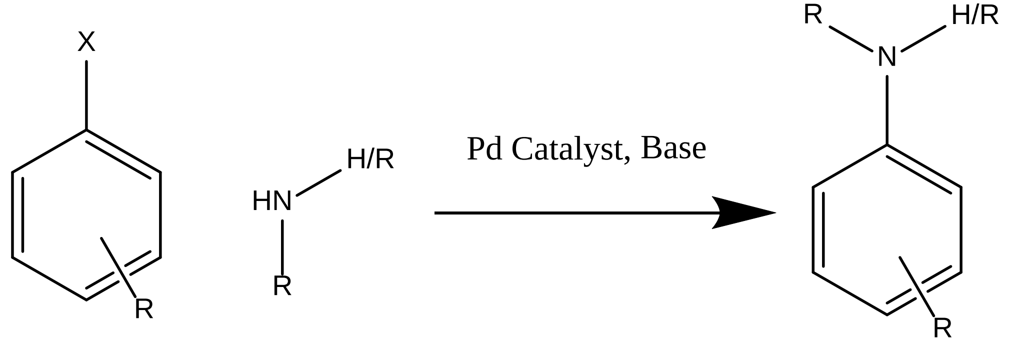
NEGISHI CROSS-COUPLING APPLICATION AND SYNTHESIS



Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

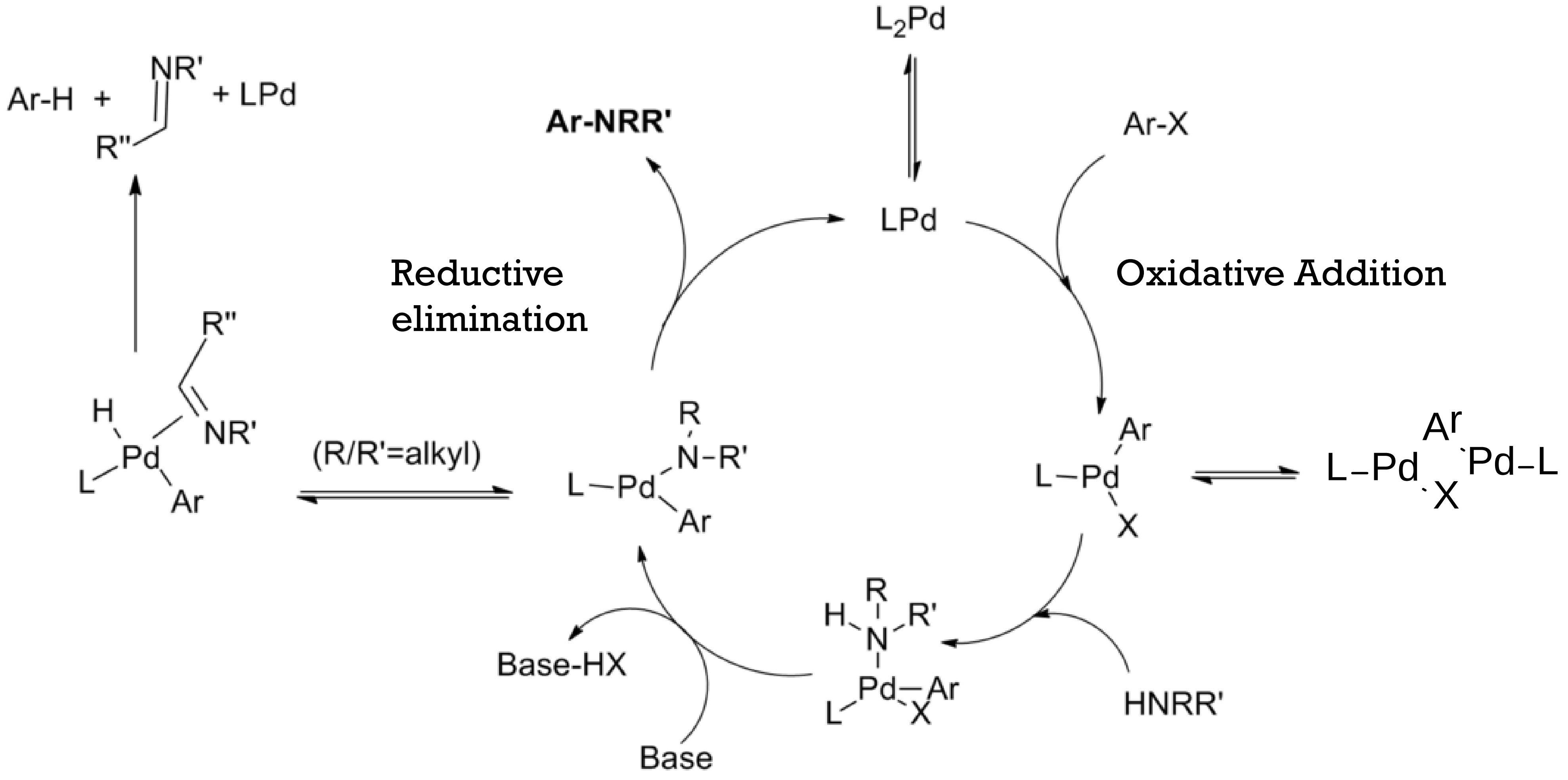
BUCHWALD-HARTWIG REACTION (AMINATION)

- General reaction scheme:

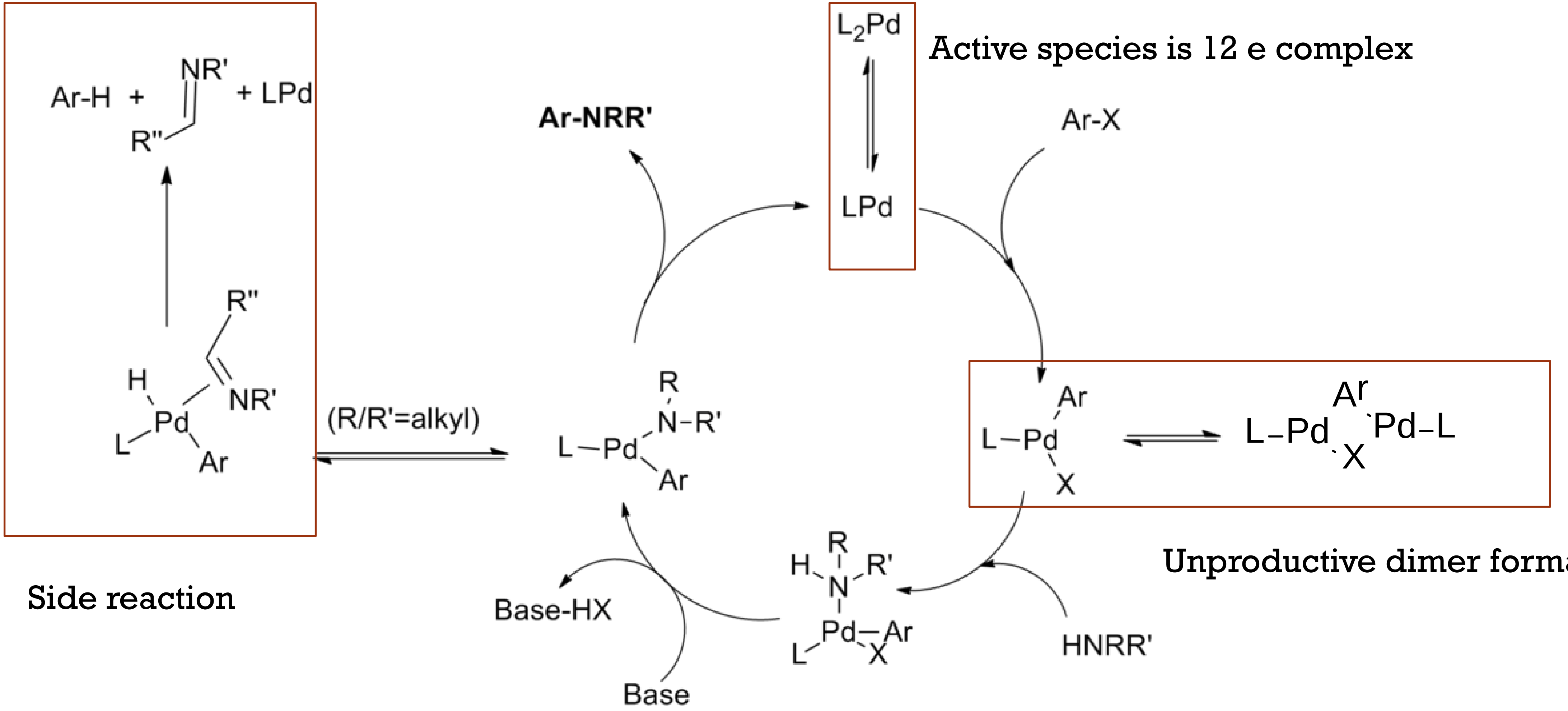


- X: Cl, Br, I
- A variety of amines can be used depending on the ligand chosen
- Can be run at room temperature using mild bases

BUCHWALD-HARTWIG: CATALYTIC CYCLE



BUCHWALD-HARTWIG: CATALYTIC CYCLE

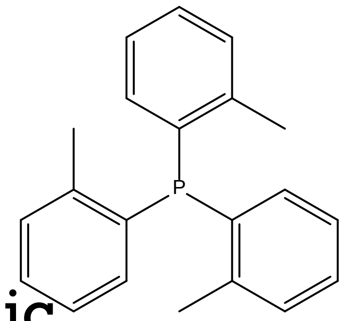


Active species is 12 e complex

Unproductive dimer formation

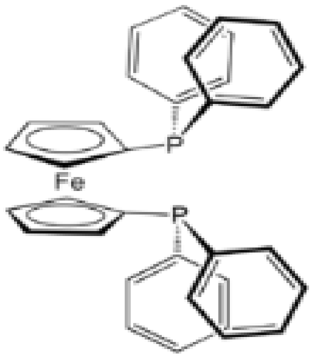
Side reaction

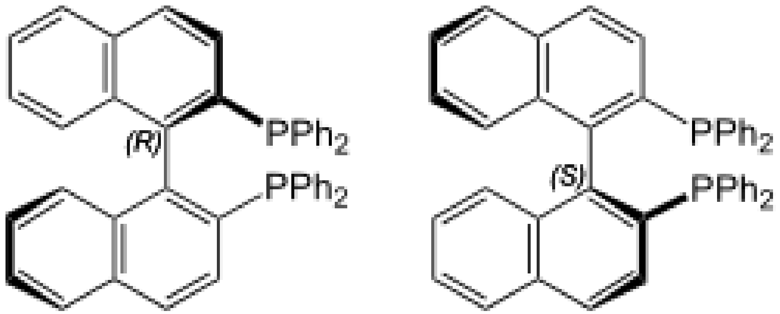
SCOPE OF AMINES



- Original catalyst (with o-tolylphosphine ligand) worked with cyclic and acyclic secondary amines

- 2nd generation, bidentate ligands enabled the use of primary amines:





- Ammonia cannot be used in these coupling reactions (yet)

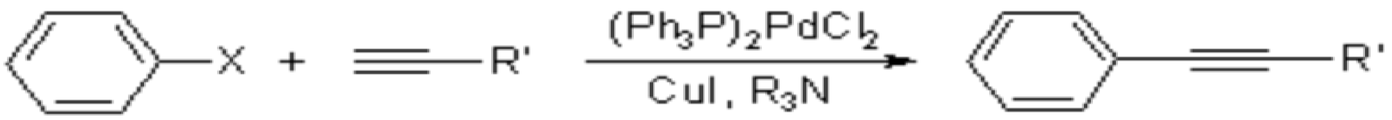
REDUCTIVE ELIMINATIONS

- Favored by electron rich X type ligands (like R^-, H^- , etc.)
- Favored by electron poor metal centers (bonded to backbonding ligands)
- Geometry is necessarily cis
- Aided by steric hindrance of ligands (C-C > C-H > H-H)
- Mechanisms may be polar, concerted or radical (principle of microscopic reversibility).

http://chemwiki.ucdavis.edu/Inorganic_Chemistry/Organometallic_Chemistry/Fundamentals/Reductive_Elimination%3A_General_Ideas

SONOGASHIRA CROSS-COUPLING

- First synthetically useful transfer of terminal alkynes to sp^2 hybridized.



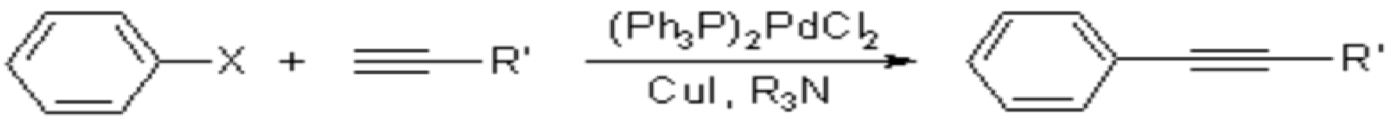
- Uses palladium catalyst, cupper catalyst and an amine base.

- Unlike Stille and Suzuki reactions, Sonogashira reactions requires very limited coupling partner.

Sonogashira, K.; Tohda, J.; Hagihara, *Tetrahedron.Lett.* **1975**, 4467.

SONOGASHIRA CROSS-COUPLING REQUIREMENT FOR R'

- General Reaction:

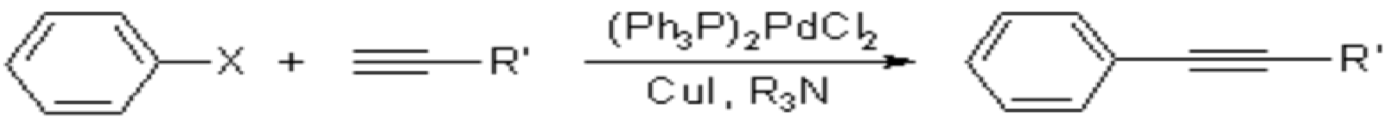


- The reaction works best when R' is the following:
  - Aryl
  - Heteroaryl
  - vinyl

Sonogashira, K.; Tohda, J.; Hagihara, *Tetrahedron.Lett.* **1975**, 4467.

SONOGASHIRA CROSS-COUPLING REQUIREMENT FOR ALKYNE

- General Reaction:

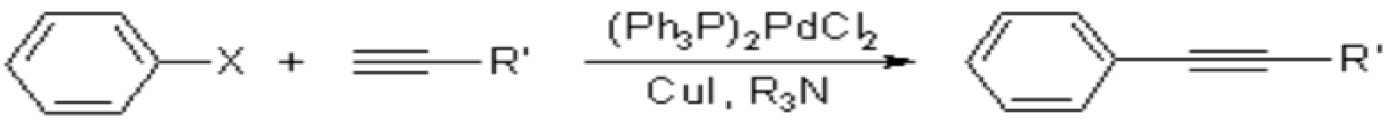


- The reaction works best when alkyne is the following:
  - Terminal alkyne

Sonogashira, K.; Tohda, J.; Hagihara, *Tetrahedron.Lett.* **1975**, 4467.

SONOGASHIRA CROSS-COUPLING REQUIREMENT FOR X

- General Reaction:

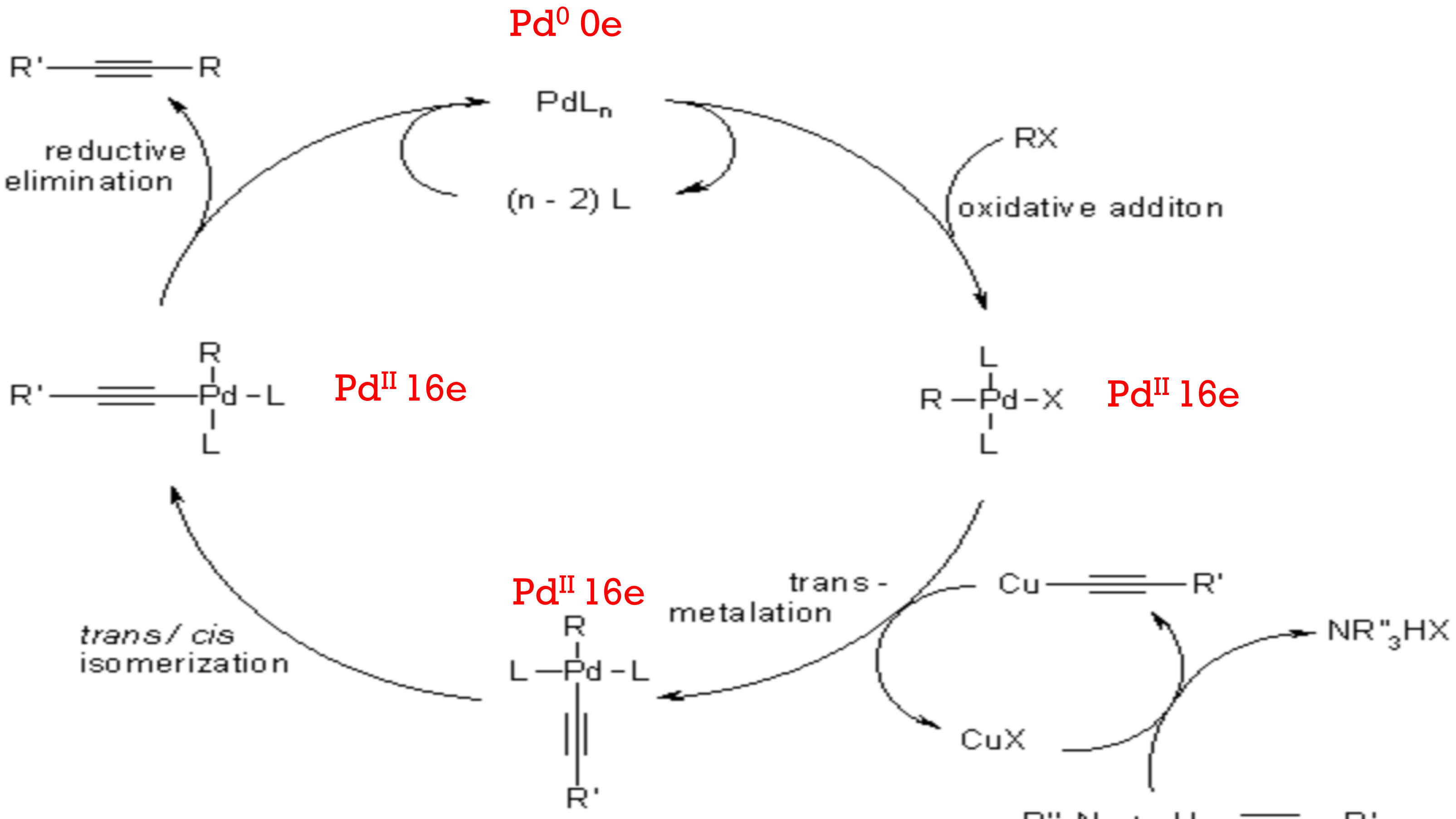


- The reaction works best when X is the following:
  - I
  - OTf
  - Br

Sonogashira, K.; Tohda, J.; Hagihara, *Tetrahedron.Lett.* **1975**, 4467.

SONOGASHIRA CROSS-COUPLING REACTION MECHANISM

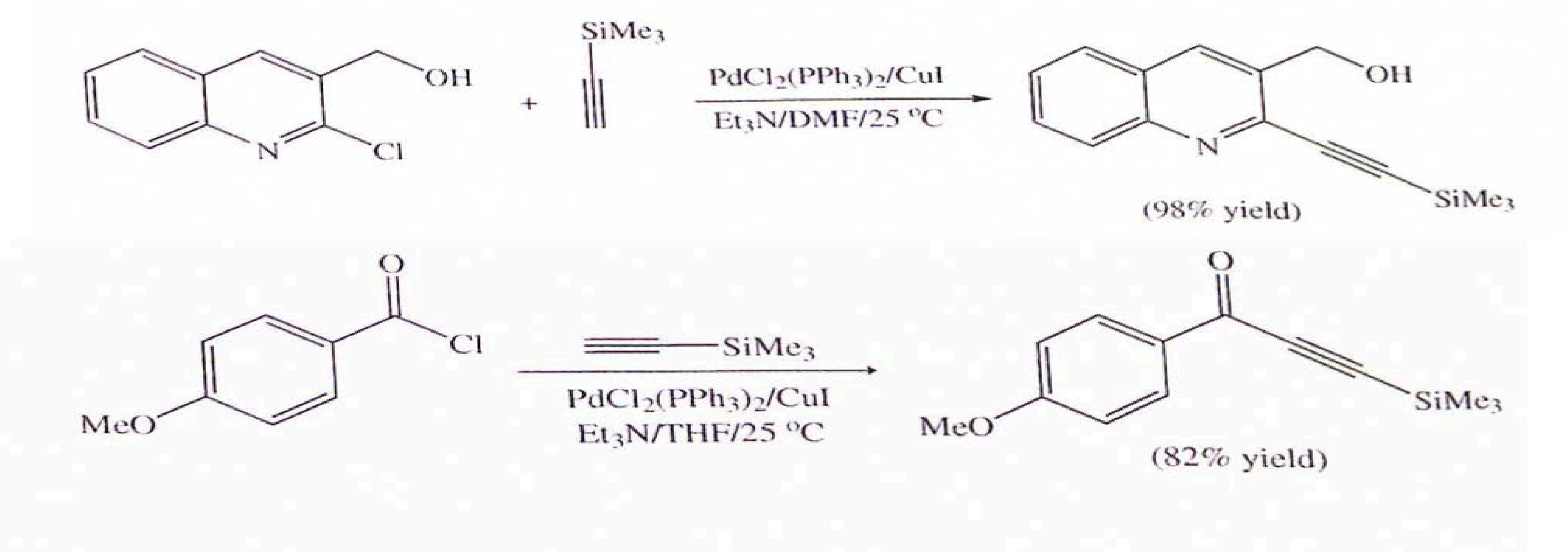
- Proposed Reaction Mechanism



Organometallic Chemistry. Gary O. Spessard and Gary L. Miessler

SONOGASHIRA CROSS-COUPLING APPLICATION AND SYNTHESIS

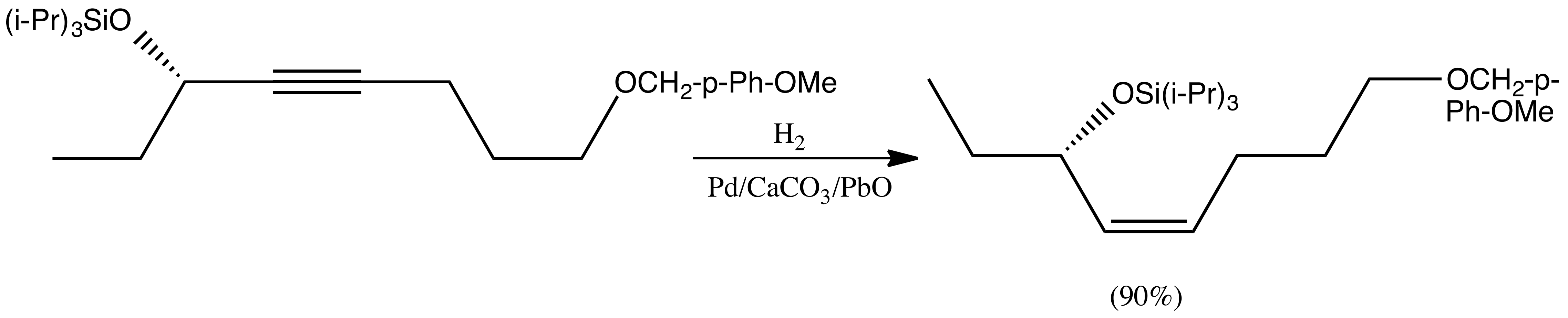
- Some useful reaction synthesis.



Rothenberg, G.; Hoefsloot, C.J. *Chem. Eur. J.* **2008**, 14, 2857.

SONOGASHIRA CROSS-COUPLING APPLICATION AND SYNTHESIS

- Useful applications.



Coffey, D.S.; Mcdonald, A.I.; Overman, L.E. *J. Am. Chem. Soc.* **2000**, 122, 4893

CONCLUSION

- Introduction to synthesis, mechanistic investigation, application of cross-coupling reaction such the following:
  - Negishi cross coupling reaction
    - Nickel or Palladium catalyzed.
    - First synthesis of unsymmetrical biaryls in good yield.
  - Heck cross coupling reaction
    - Palladium catalyzed C-C coupling between aryl halides and vinyl halides.
    - Activated alkenes in the presence of base.
  - Suzuki cross coupling reaction
    - Palladium catalyzed between organoboronic acid and halides.
  - Stille cross coupling reaction
    - Palladium catalyst with Organotin
    - Useful to construct new carbon-carbon bonds
  - Sonogashira cross coupling reaction
    - Palladium catalyzed
    - Copper (I) cocatalyst
    - Amine base
    - Coupling of terminal alkynes with aryl or vinyl halides.
  - Buchwald-Hartwig cross coupling reaction
    - Palladium catalyzed synthesis of aryl amines
    - Used aryl halides or pseudohalides and primary or secondary amines.