MAX-PLANCK-INSTITUT
FÜR KOLLOID- UND
GRENZFLÄCHENFORSCHUNG

CROSS COUPLING

Dr. Dario Cambié

Max Planck Institute of Colloids and Interfaces

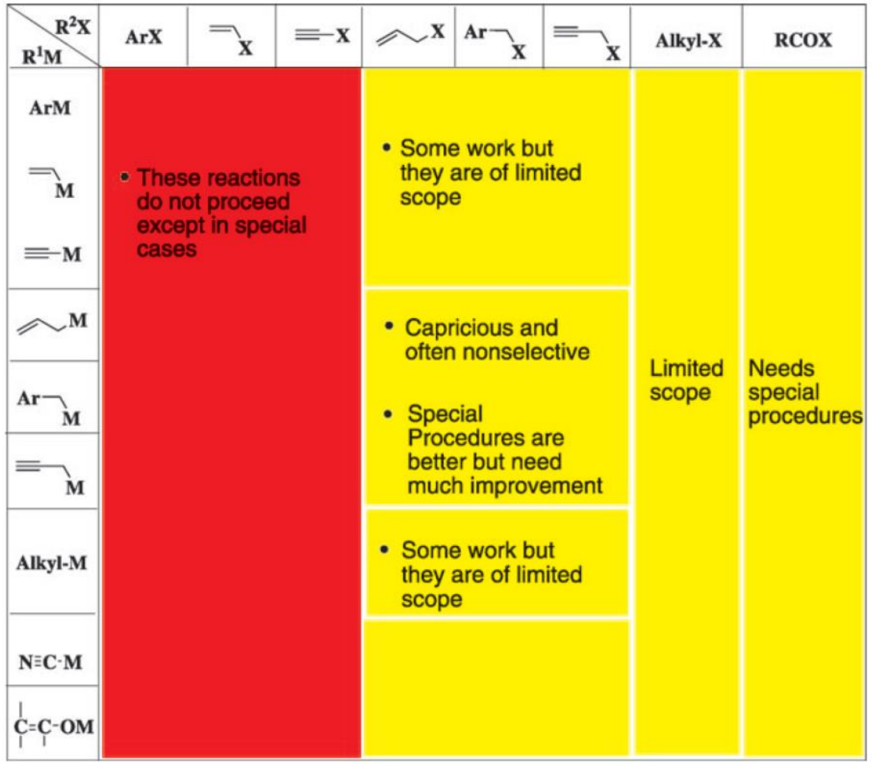
Biomolecular Systems

Dario.Cambie@mpikg.mpg.de

10.1.1 WHY CATALYTIC CROSS-COUPLING

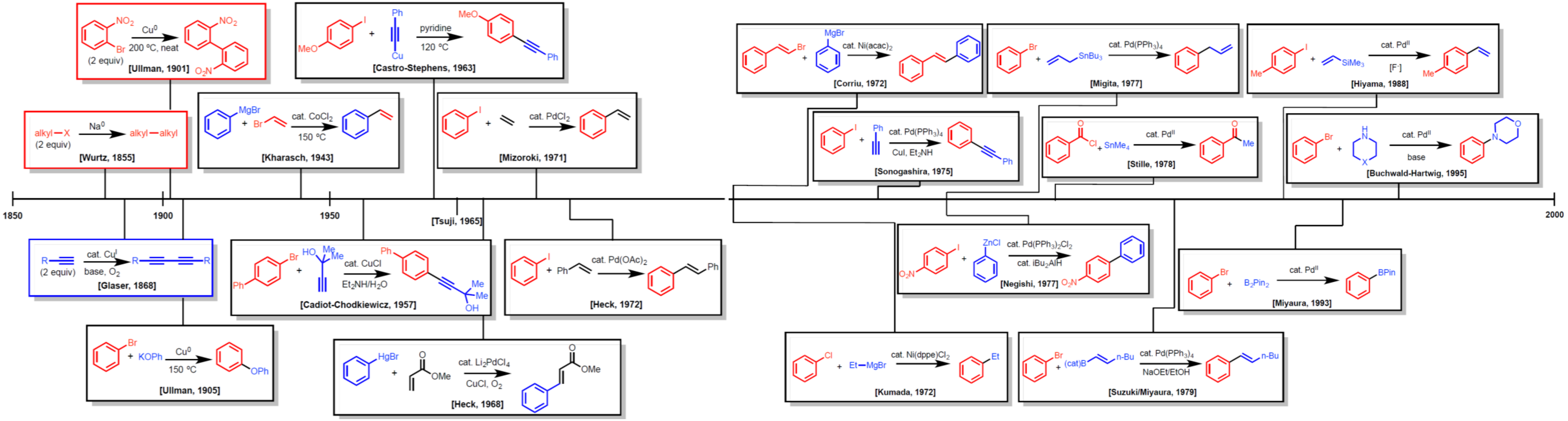
$$R^1\text{–}M + R^2\text{–}X \xrightarrow{\text{with or without catalyst}} R^1\text{–}R^2 + M\text{–}X$$

R^1, R^2: carbon groups, M: metal or metal-containing groups, X: halogens or other leaving groups

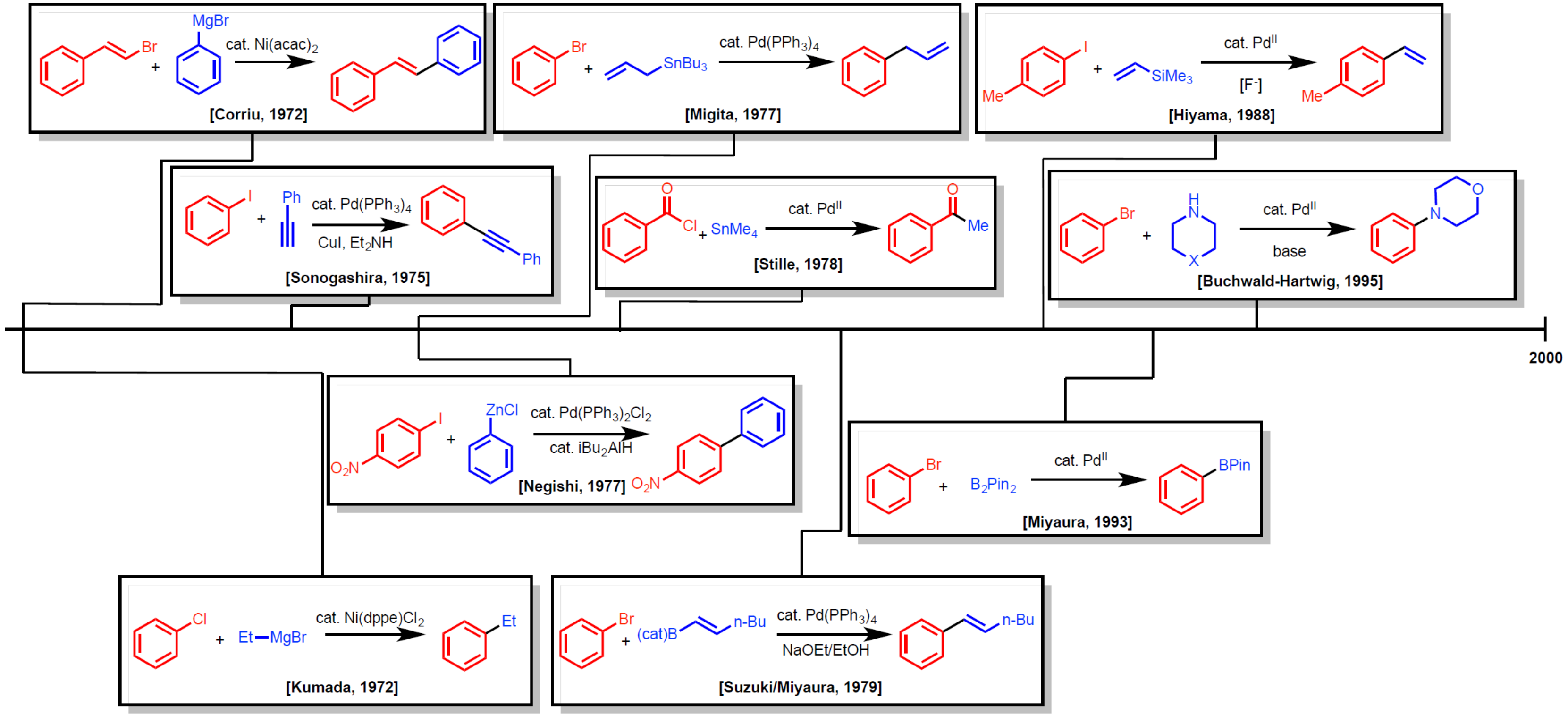


Negishi *ACIE* **2011** 50, 6738. DOI: 10.1002/anie.201101380 (Nobel lecture)

10.1.2 CROSS-COUPLING TIMELINE

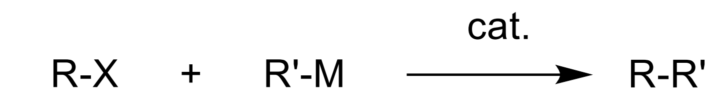


10.1.2 CROSS-COUPLING TIMELINE

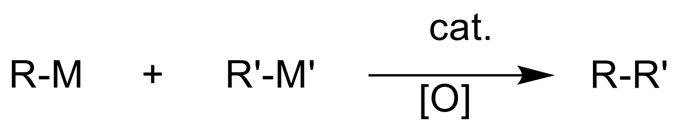


10.1.3 CATALYTIC CROSS-COUPLING OVERVIEW

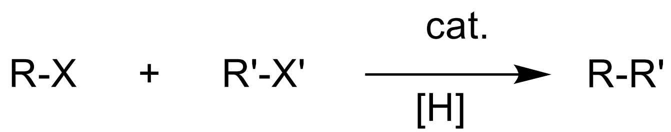
Traditional



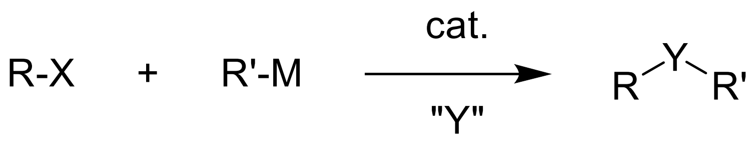
Oxidative



Reductive

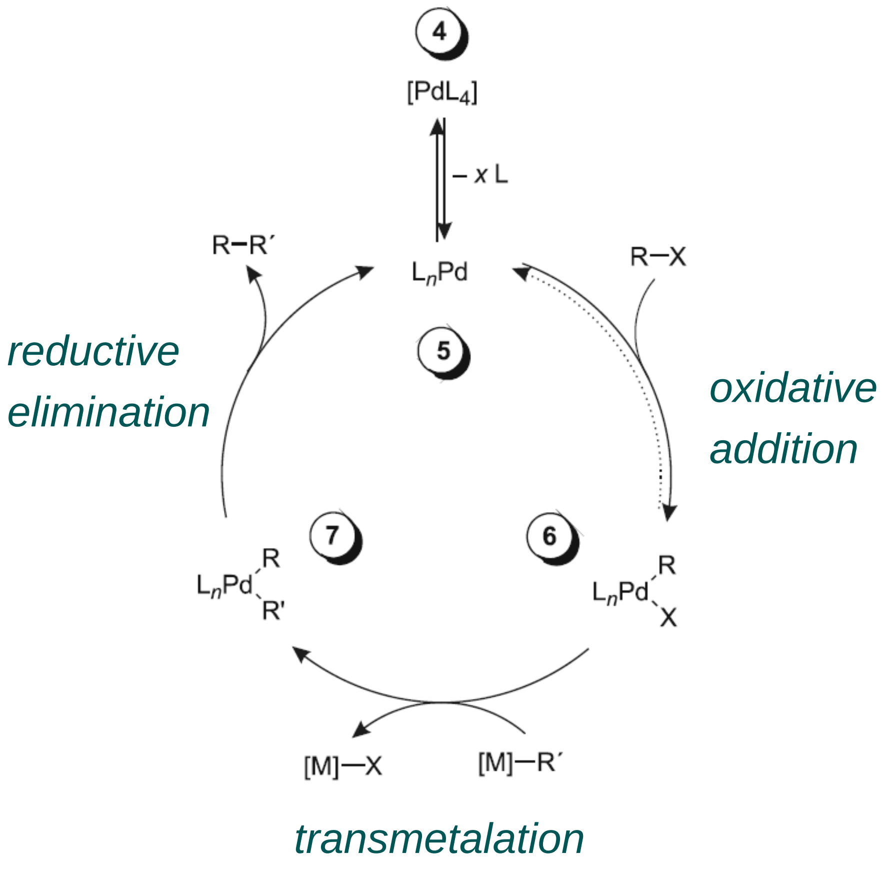


Conjunctive



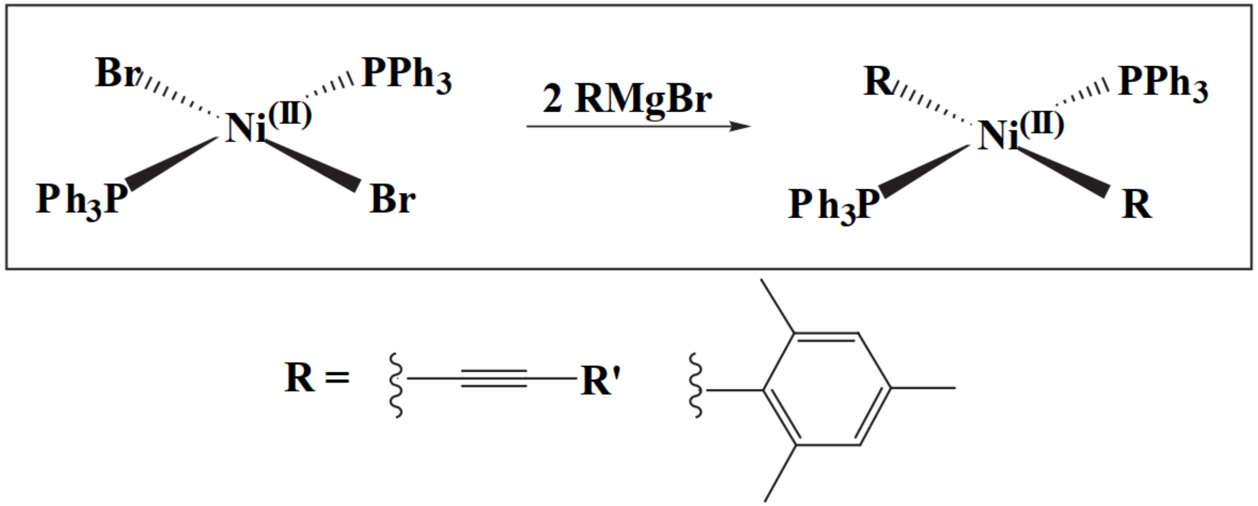
Jamison *Nature* **2014** 509, 299. DOI: 10.1038/nature13274 (Recent review Ni cross-coupling)
ACIE **2012** 51, 5062. DOI: 10.1002/anie.201107017 (historical Pd cross-coupling perspective)
Sigman *Chem Rev* **2011** 111, 1417. DOI: 10.1021/cr100327p (Recent review Pd/Ni/Fe cress-coupling)

10.1.4 TRADITIONAL CATALYTIC CYCLE



10.1.5 FIRST LITERATURE EXAMPLES

Transmetalation step

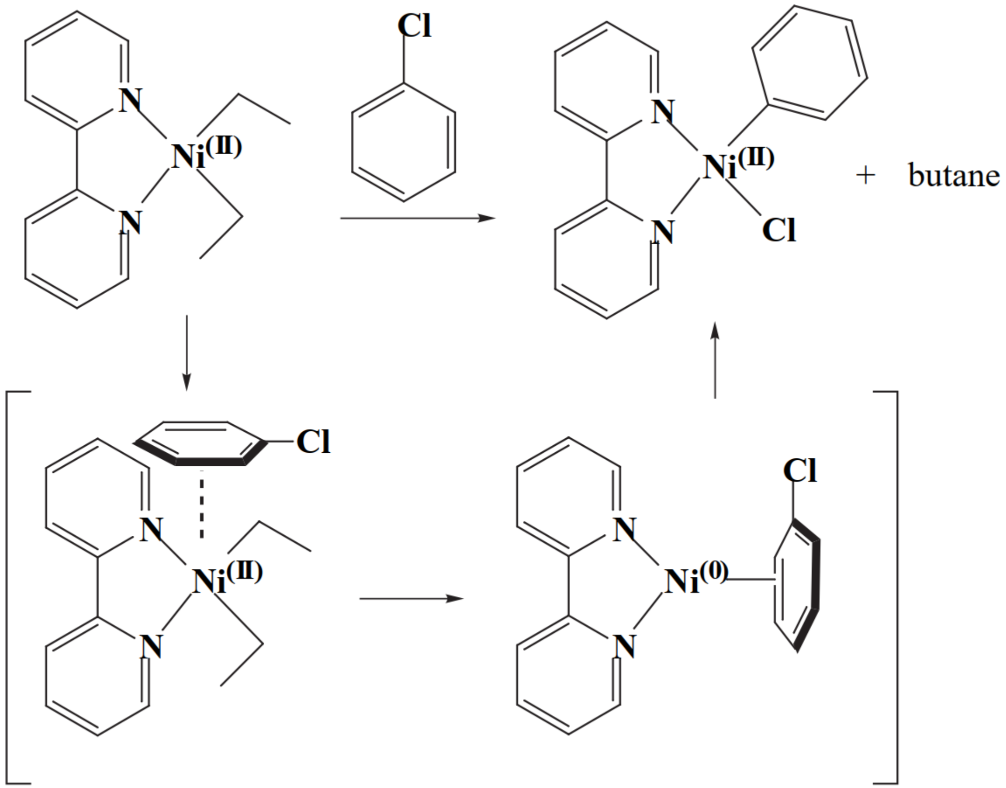


Chatt and Shaw *J. Chem. Soc.* **1960** 1718. DOI: fcffvz

10.1.5 FIRST LITERATURE EXAMPLES

Reductive elimination

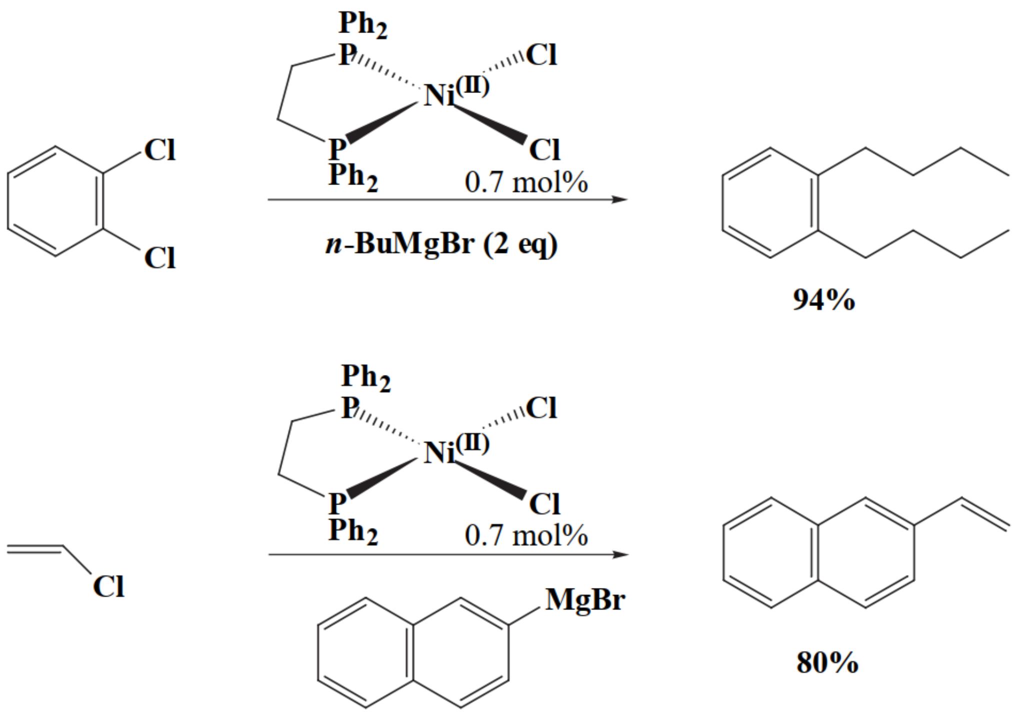
Oxidative addition



Yamamoto *JOMC* **1970** (24) C63. DOI: dpx2vq

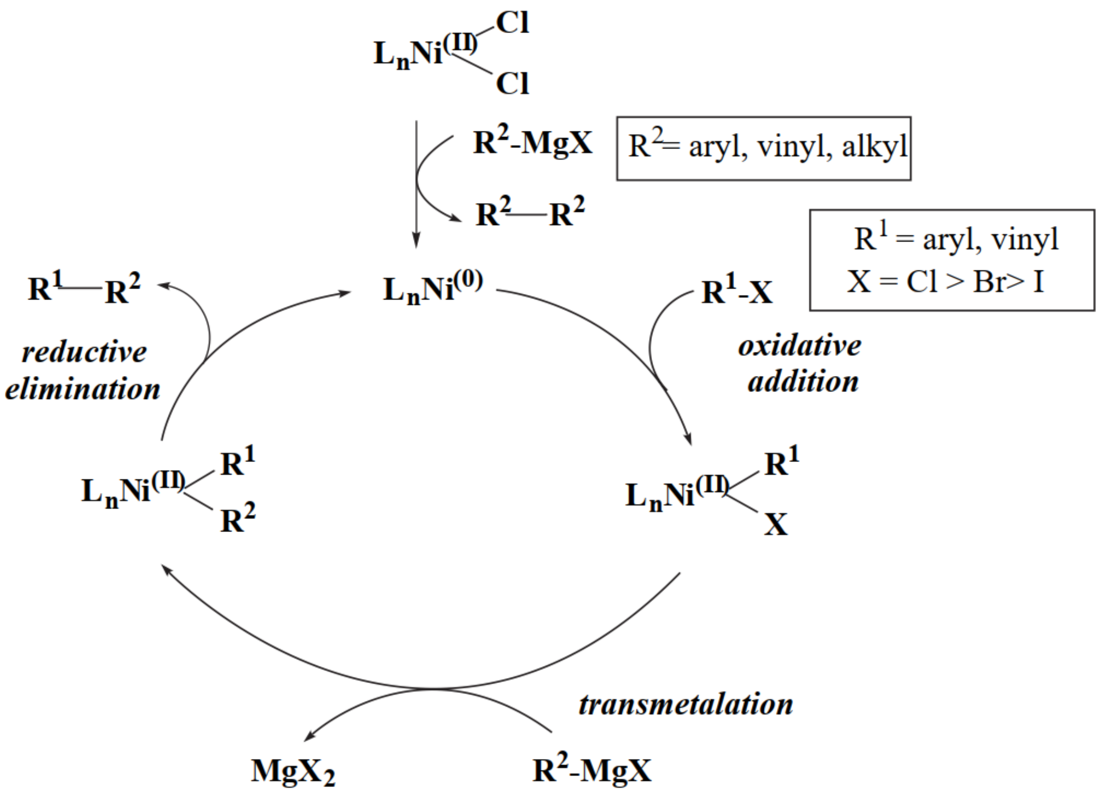
10.2.1 KUMADA-CORRIU

- Grignard as R-M (sometimes R-Li as well)
- Very fast/robust
- limited FG tolerance (due to Grignard)
- Currently used for hindered coupling partners



Kumada *JACS* **1972** 94, 4374. DOI: [10.1021/ja00767a075]

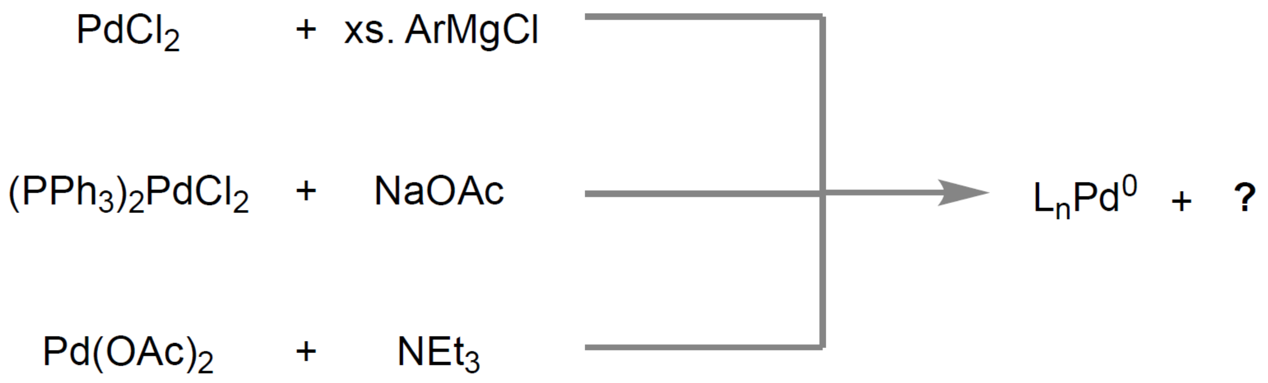
10.2.2 KUMADA-CORRIU - MECHANISM



Kumada *JACS* **1972** 94, 4374. DOI: 10.1021/ja00767a075

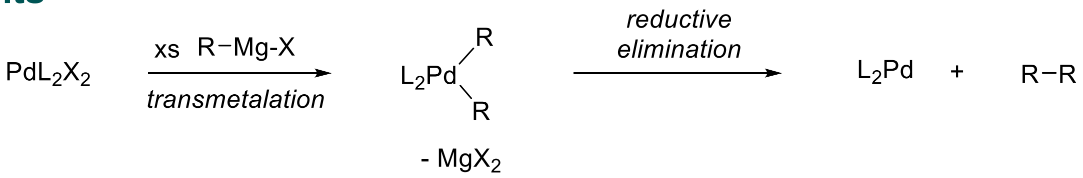
POD #1

Consider the following processes for active catalyst formation below and **provide the mechanism of generation of Pd(0).**

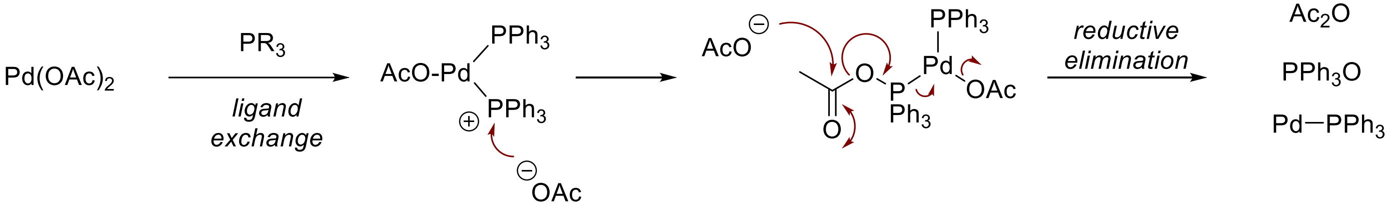


POD #1

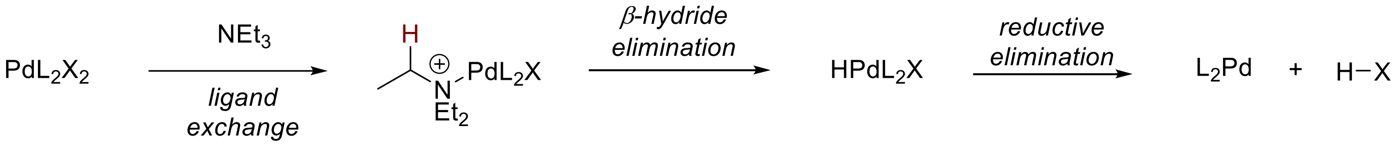
Grignard reagents



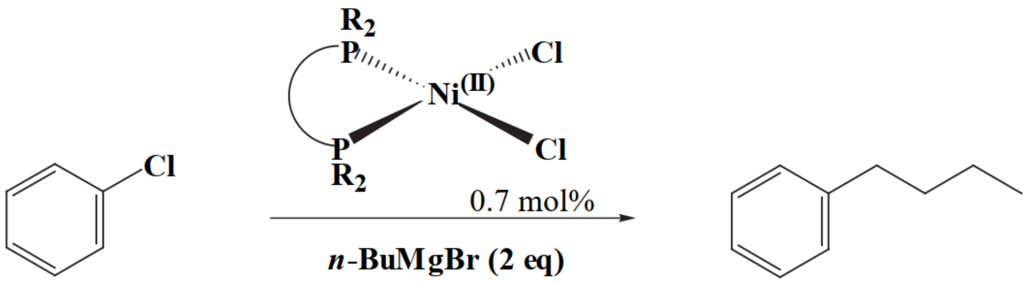
Phosphines



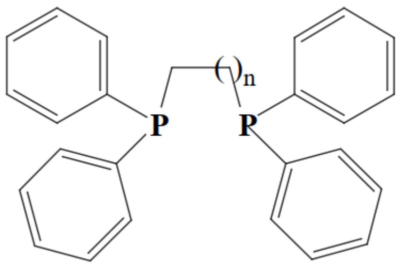
Amines



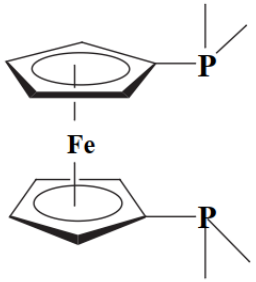
10.2.3 KUMADA-CORRIU – LIGAND EFFECT



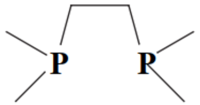
Ligand	% yield
dppp	**100**
dmpf	94
Ph_3P (2eq)	84
dppe	79
dmpe	47
dppb	28



dppm, n=0, bis(diphenylphosphino)methane
dppe, n=1, bis(diphenylphosphino)ethane
***dppp**, n=2, bis(diphenylphosphino)propane*
dppb, n=3, bis(diphenylphosphino)butane



dmpf, bis(dimethylphosphino)ferrocene

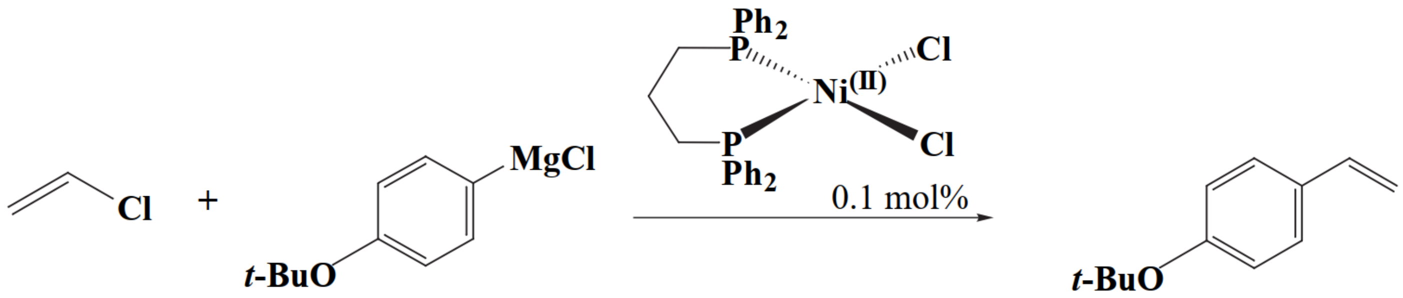


dmpe, bis(dimethylphosphino)ethane

Kumada *Bull. Chem. Soc. Jpn.* **1976** (49) 1958. DOI: 10.1246/bcsj.49.1958

10.2.3 KUMADA-CORRIU – APPLICATIONS

industrial-scale production of styrene derivatives

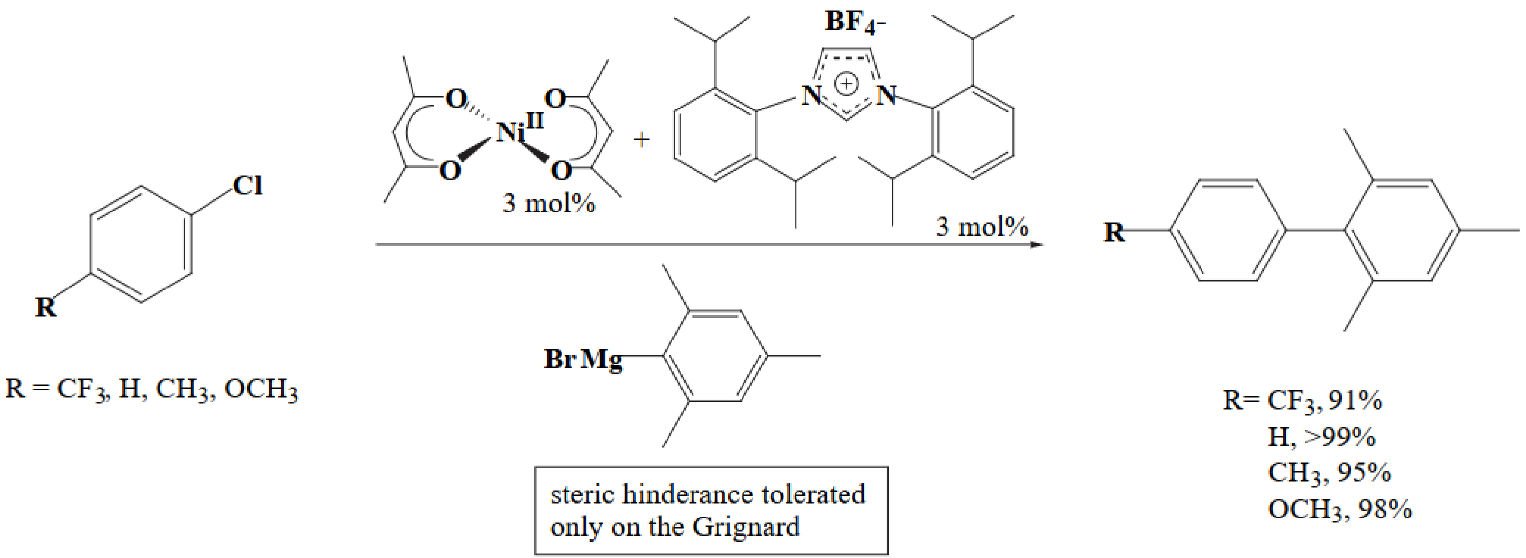


(dppp)$NiCl_2$ still relatively inexpensive (≈10 EUR/g)

Banno *JOMC* **2002** (653) 288. DOI: dxs2kd (Hokka Chemical Industry)

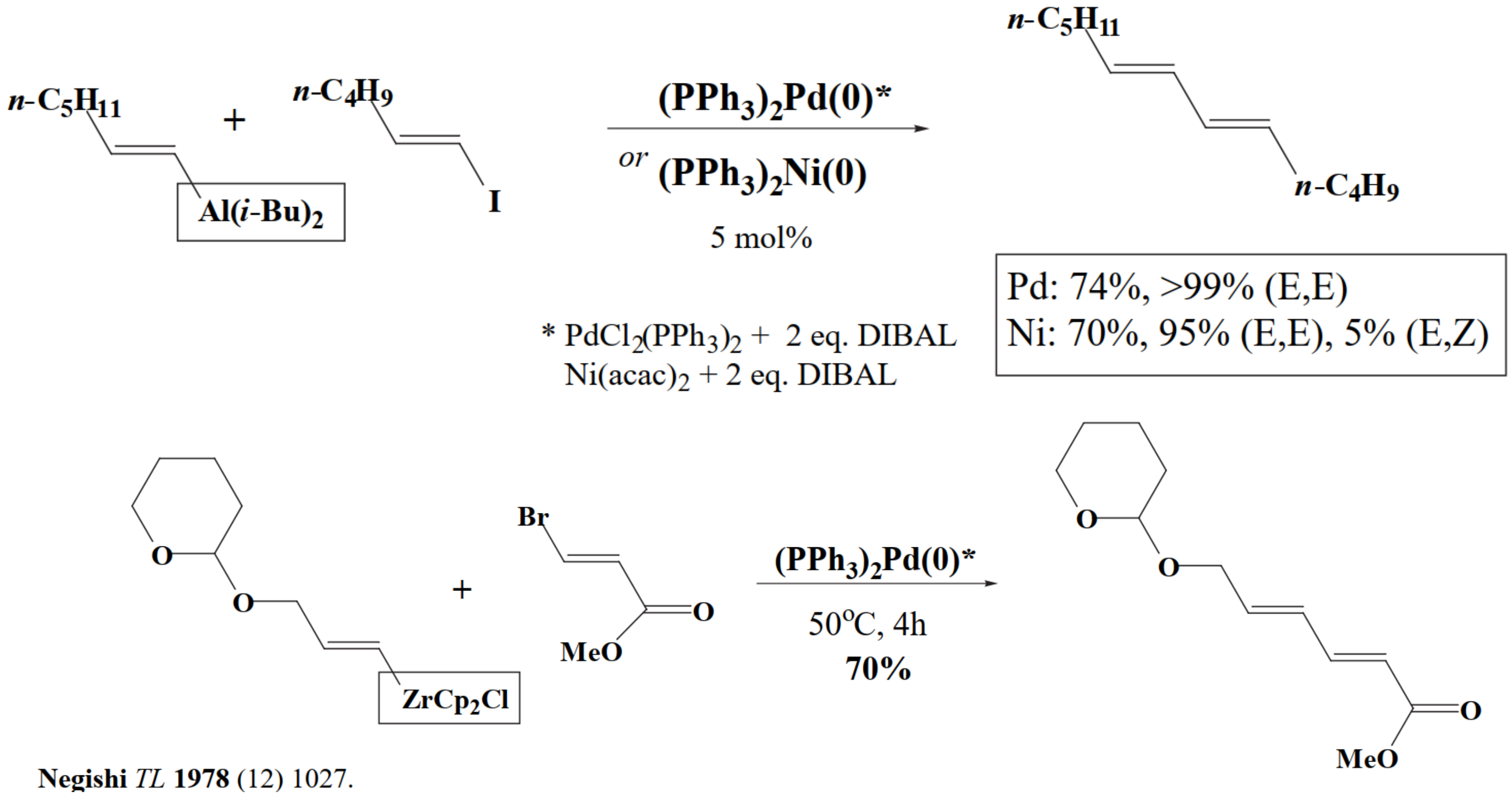
10.2.3 KUMADA-CORRIU – APPLICATIONS

Sterically hindered biaryls



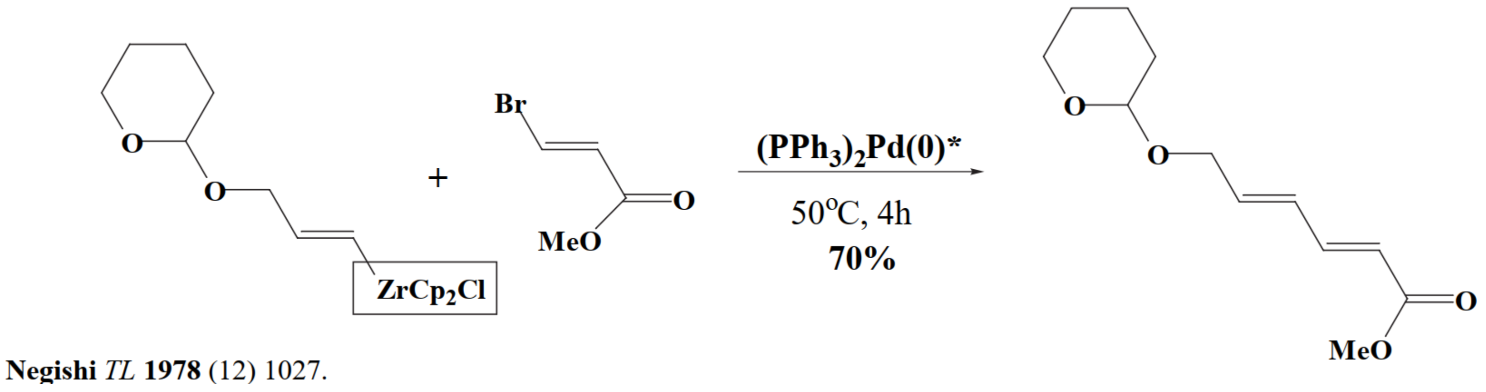
Herrmann *ACIE* **2000** (39) 1602. DOI: fg58pz

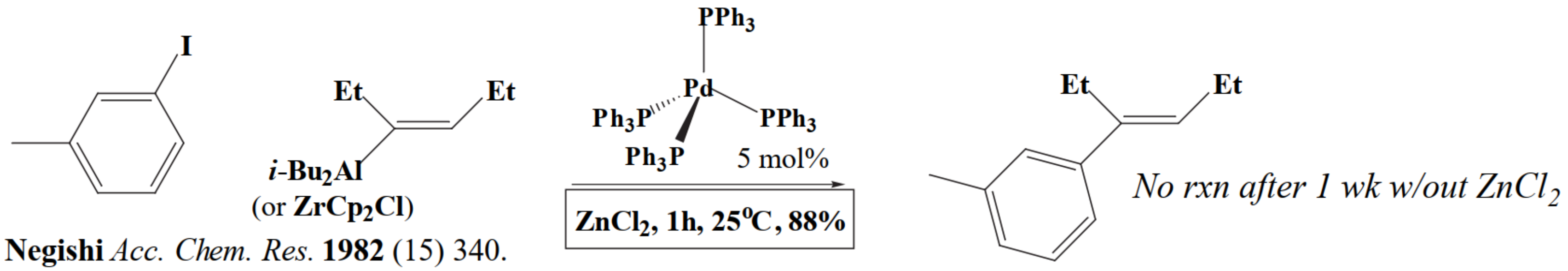
10.3.1 NEGISHI – INITIAL ATTEMPTS WITH ALANES AND Zr



Negishi *JACS* **1976** (98) 6729. DOI: 10.1021/ja00437a067
Negishi *TL* **1978** 12, 1027. DOI: ckhdhh

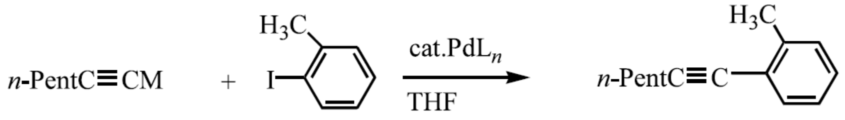
10.3.1 NEGISHI – KEY Zn TRANSMETALATION





Negishi *Acc, Chem. Res.* **1982** 15, 340. DOI: 10.1021/ar00083a001

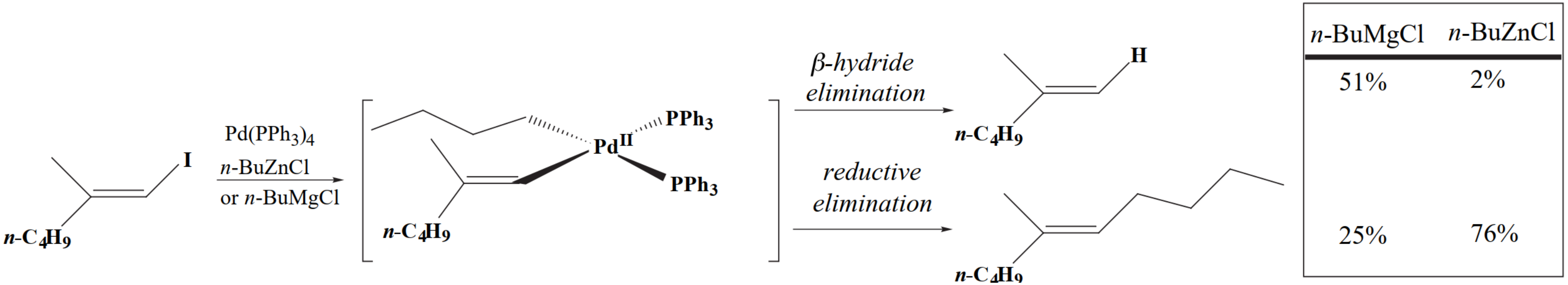
10.3.2 NEGISHI – METAL SCREENING



M	temp (°C)	time (h)	product yield (%)	starting material (%)
Li	25	1	trace	88
Li	25	24	3	80
MgBr	25	24	49	33
ZnCl	25	1	91	8
HgCl	25	1	trace	92
HgCl	reflux	6	trace	88
BBu_3Li	25	3	10	76
BBu_3Li	reflux	1	92	5
Al(Bu-*i*)$_2$	25	3	49	46
$AlBu_3Li$	25	3	4	80
$AlBu_3Li$	reflux	1	38	10
$SiMe_3$	reflux	1	trace	94
$SnBu_3$	25	1	75	14
$SnBu_3$	25	6	83	6
$ZrCp_2Cl$	25	1	0	91
$ZrCp_2Cl$	reflux	3	0	80

Negishi *JOMC* **2002** (653) 34. DOI: dxzfdm – data from 1977

10.3.3 NEGISHI – APPLICATIONS



Csp²—Csp³ coupling

R.E. faster than β–hydride elimination!

Negishi *JACS* **1980** (102) 3298. DOI: 10.1021/ja00529a091

10.3.3 CROSS-COUPLING SIDE REACTIONS

Side reactions in cross-coupling	
1	Formation of R^1-R^1
2	Formation of R^2-R^2
3	Reduction of R^2X to give R^2H
4	α-elimination to give carbenoids
5	β-elimination to give alkenes
6	Stereoisomerization
7	Regioisomerization
8	Reactions of functional substituents
9	Other undesirable reactions of substrates
10	Undesirable reactions of catalysts, ligands, solvents, added reagents, adventitious chemicals, etc

Negishi *JOMC* **2002** (653) 34. DOI: dxzfdm

10.3.4 WHY Pd?

TABLE 1. Some Fundamental Properties of Pd

Property	Value and/or Description			
Atomic number	46			
Atomic weight	106.4			
Isotopes and relative abundance[a]	^{102}Pd	0.8%	^{104}Pd	9.3%
	^{105}Pd	22.6%	^{106}Pd	27.1%
	^{108}Pd	26.7%	^{110}Pd	13.5%
Magnetic property	^{105}Pd has $I = \frac{5}{3}$, but it is of very low sensitivity.			
Electronic configuration	$1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 4p^6 4d^{10} = [Kr]4d^{10}$			
Common oxidation states and coordination numbers	Oxidation State	Electronic Configuration	Geometry	
	0	d^{10}	Tetrahedral	
	+2	d^8	Square planar	
	+4 (rare)	d^6	Octahedral	
Electronegativity[b]	2.2 (Pauling), 1.57 (Sanderson)			
Occurrence in the lithosphere[c]	0.015 ppm Some data for comparison: C (180 ppm), Ni (99 ppm), Pt (0.01 ppm), Ru and Rh (0.001 ppm each)			

Negishi, *Hanbook of Organopalladium Chemistry for Organic Synthesis.* DOI: 10.1002/0471212466

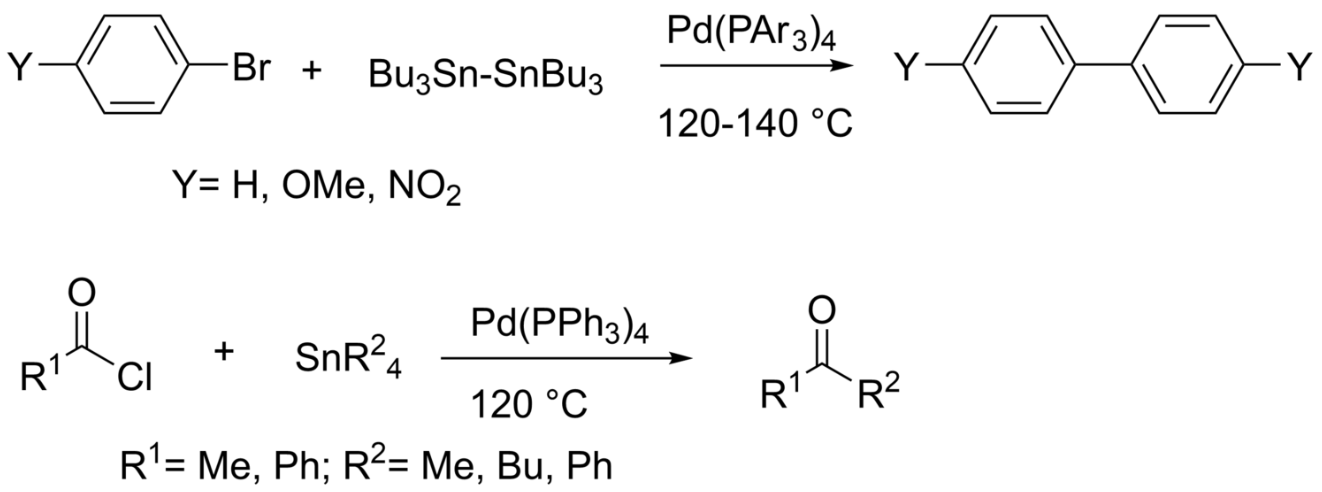
10.3.4 WHY Pd?

TABLE 2. Relationships between Some Fundamental Properties of Pd and Chemical Consequences

Fundamental Properties of Pd	Consequences
• Moderately *large size*	• *Moderate stability* of organopalladiums (Ni < Pd < Pt)
• Strong preference for the *0* and *+2 oxidation states* separated by a relatively narrow energy gap	• Relatively *rare one-electron or radical processes* (e.g., relative to Ni) • *Ready and reversible two-electron oxidation and reduction* (⟹ catalysis)
• Late transition metal favoring d^{10} *Pd(0) and* d^{8} *Pd(II)* configurations ⟹ (i) *soft,* (ii) ready availability of Pd complexes containing *both empty and filled non-bonding orbitals* (LUMO and HOMO)	• High propensity for *concerted processes* • High affinity toward *soft* π*- and n-donors* • *Selective and yet very resourceful reactivity* permitting reactions with almost any type of compounds
• Relatively *electronegative*	• Relatively *unreactive* toward *polar functional groups* • High *chemoselectivity* • Largely *complementary* with the chemistry of *Grignard reagents* and *organolithiums*

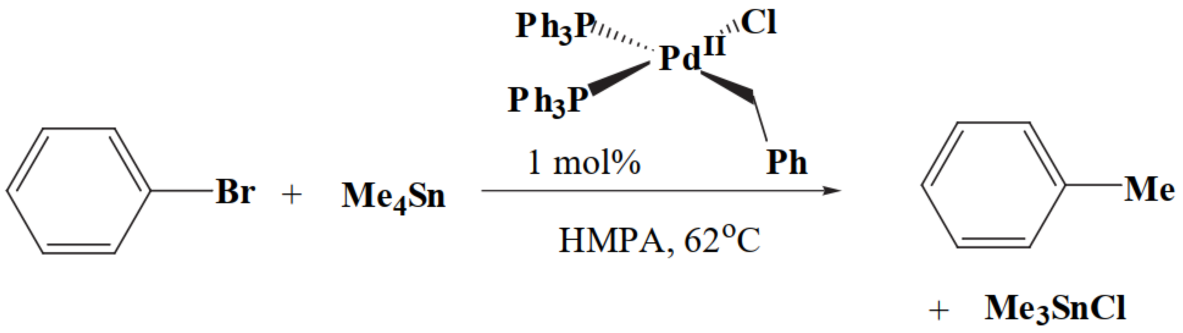
Negishi, *Hanbook of Organopalladium Chemistry for Organic Synthesis.* DOI: 10.1002/0471212466

10.4.1 MIGITA-STILLE COUPLING – EARLIER EXAMPLE



Eaborn *JOMC* **1976** 117, 55. DOI: 10.1016/S0022-328X(00)91902-8
Migita *Chem Lett* **1977** 6, 1423. DOI: 10.1246/cl.1977.1423

10.4.2 MIGITA-STILLE COUPLING

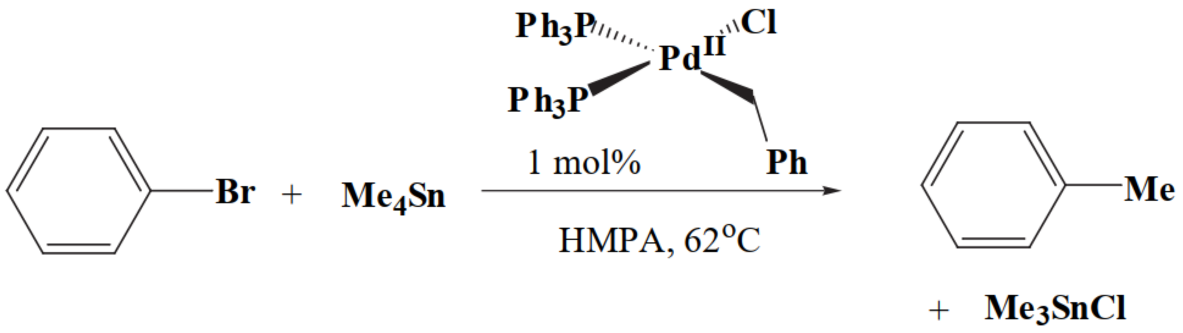


Dummy ligands ($RSnBu_3$) thanks to different rate of transfer from tin

Order: alkynyl>alkenyl>aryl>benzyl>allyl>alkyl.

Stille *JACS* **1979** (101) 4992. DOI: 10.1021/ja00511a032

10.4.2 MIGITA-STILLE COUPLING



Dummy ligands ($RSnBu_3$) thanks to different rate of transfer from tin

Order: alkynyl>alkenyl>aryl>benzyl>allyl>alkyl.

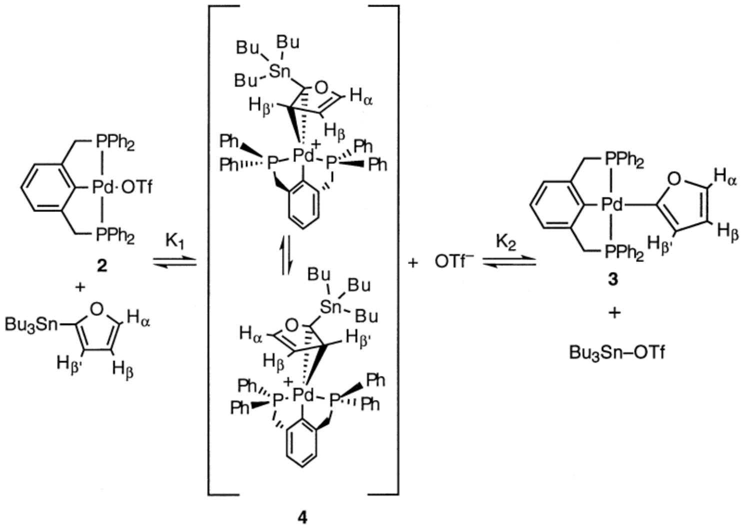
Faster rate for unsasturated groups may result from coordination to the metal prior to C-Sn bond cleavage.

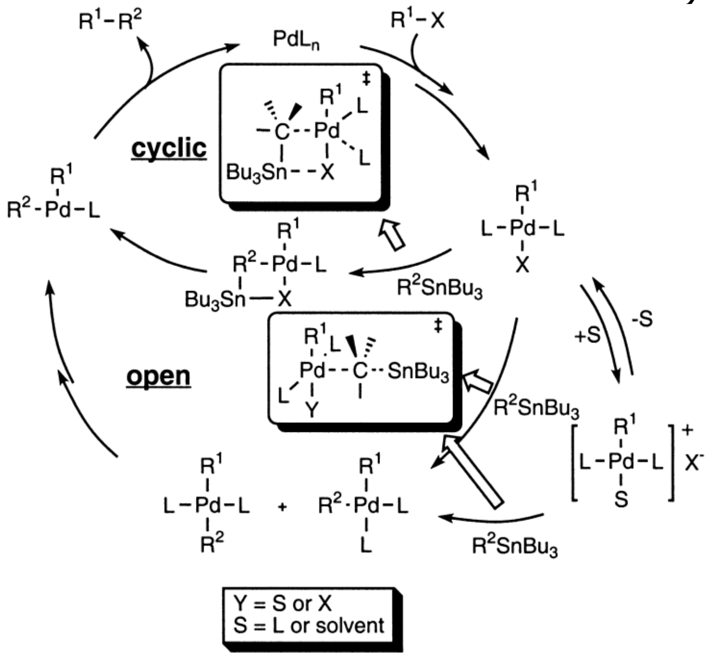
Stille *JACS* **1979** (101) 4992. DOI: 10.1021/ja00511a032

10.4.2 MIGITA-STILLE COUPLING – TRANSMETALATION

Transmetallation preceded by coordination.

Eletronic effects on the transmetalation are also counterintuitive. The reactions of benzylic stannanes are accelerated by EWG on the benzyl. This effect contradicts a view that the alkyl group is transferred to the transition metal as nucleophile.

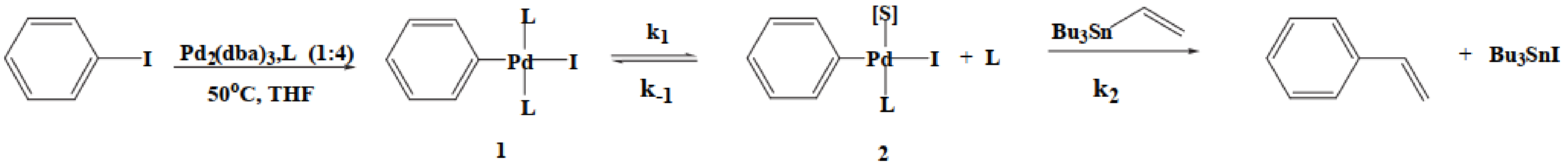




Cotter *JACS* **1998**, 120, 42, 11016. DOI: 10.1021/ja980901w (TM is preceded by coordination to Pd via the tin-substituted double bond.)
Casado *JACS* **1998**, 120, 35, 8978. DOI: 10.1021/ja9742388
Casado *JACS* **2000**, 122, 48, 11771. DOI: 10.1021/ja001511o
Stille *JACS* **1983** 105, 19, 6129. *DOI:* 10.1021/ja00357a026 (Benzyl stannanes trends)

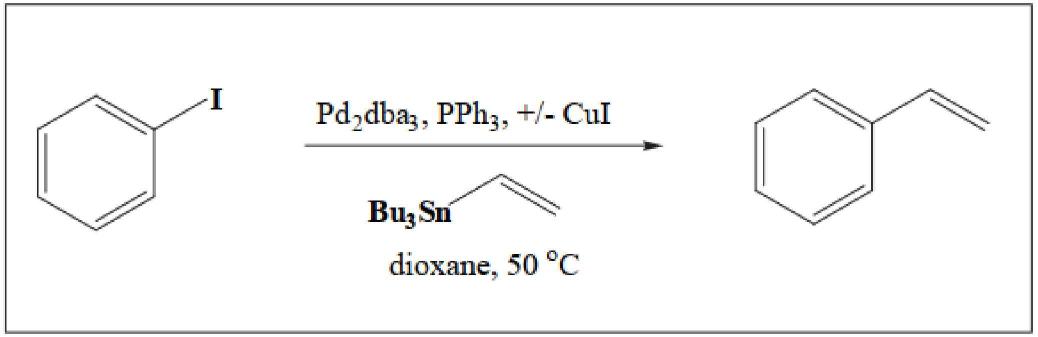
10.4.3 MIGITA-STILLE COUPLING – MECHANISM

Usually, fast OA followed by rate-determining TM requiring ligand exchange.



10.4.4 MIGITA-STILLE COUPLING – COPPER EFFECT

Copper can be used to promote ligand dissociation (or bulky phopshines/ligands)

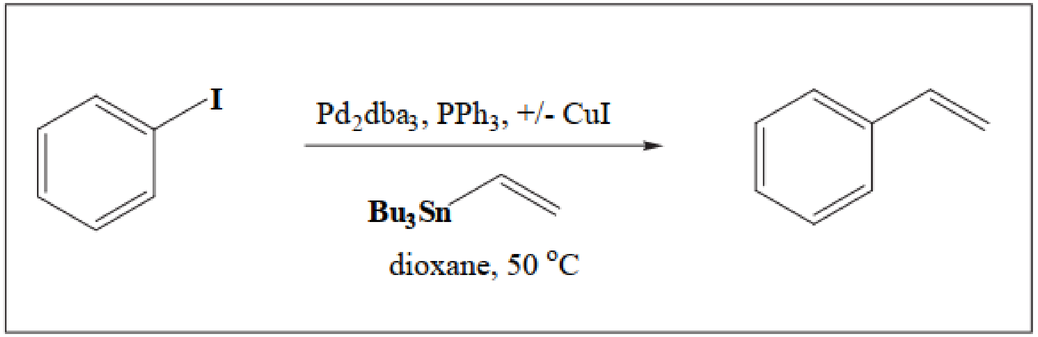


Pd:L:CuI molar ratio	Relative rate	HPLC Yield (%)
1:4:0	1	85
1:4:1	5	85
1:4:2	114	>95
1:4:4	197	45
1:2:0	64	91

Farina and Liebeskind *JOC* **1994** 59, 5905. DOI: 10.1021/jo00099a018

10.4.4 MIGITA-STILLE COUPLING – COPPER EFFECT

Copper can be used to promote ligand dissociation (or bulky phopshines/ligands)



Pd:L:CuI molar ratio	Relative rate	HPLC Yield (%)
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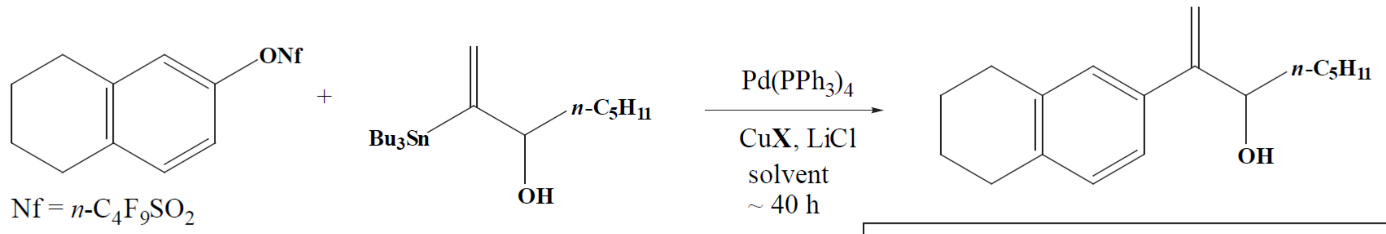
1:2:0	64	91

Farina and Liebeskind *JOC* **1994** 59, 5905. DOI: 10.1021/jo00099a018

10.4.4 MIGITA-STILLE COUPLING – COPPER EFFECT

Cu possibly also involved in intermediate transmetalation

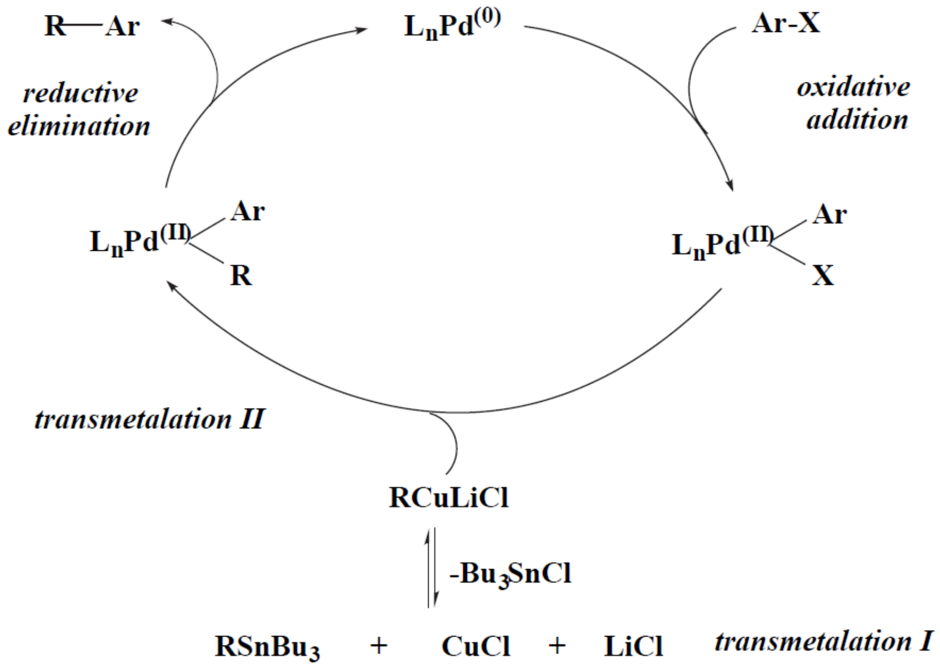


Conditions	optimized yield
X = I, solvent = DMA	38 %
X = Cl solvent = DMSO	88 %

Corey *JACS* **1999** 121, 7600. DOI: 10.1021/ja991500z

10.4.4 MIGITA-STILLE COUPLING – COPPER EFFECT

Cu possibly also involved in intermediate transmetalation



Corey *JACS* **1999** 121, 7600. DOI: 10.1021/ja991500z

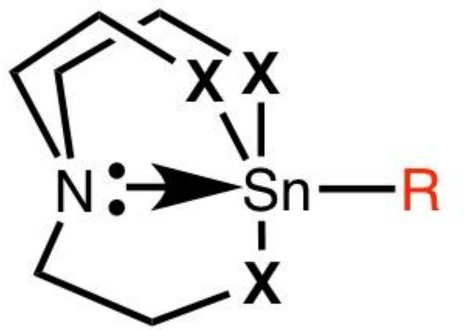
10.4.5 MIGITA-STILLE COUPLING – ORGANOTIN

Organotin reagents are compatible with:

- Chromatography
- Water
- Oxygen

But their toxicity is a significant drawback.

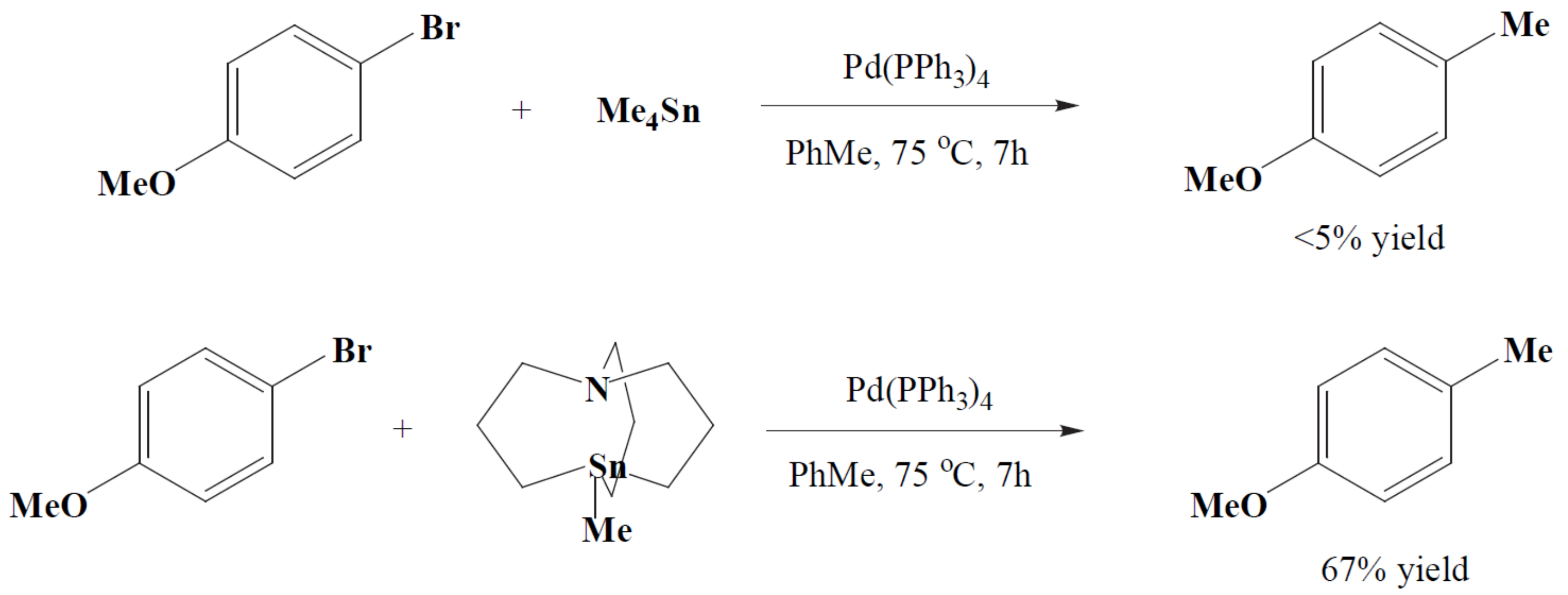
Another way to accelerate TM are carbastannatrane (also, less toxic)



stannatrane

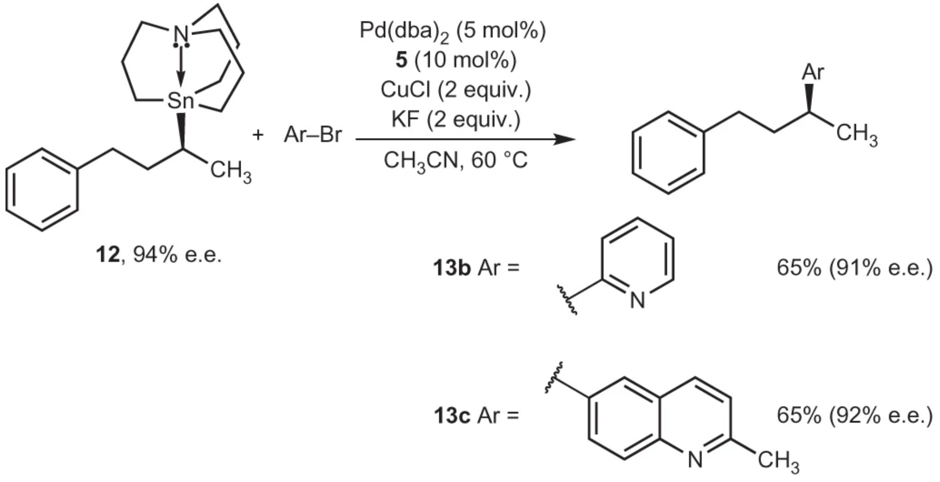
Vedejs *JACS* **1992** 114, 6556. DOI: 10.1021/ja00042a044

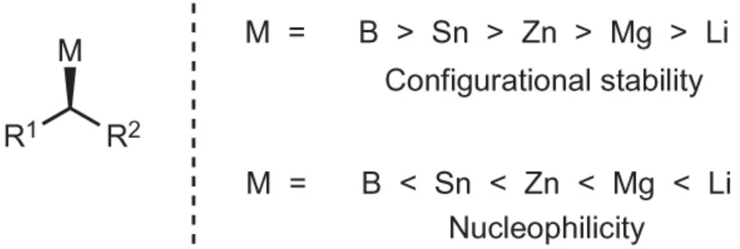
10.4.5 MIGITA-STILLE COUPLING – ORGANOTIN



Vedejs *JACS* **1992** 114, 6556. DOI: 10.1021/ja00042a044

10.4.6 STEREORETENTIVE MIGITA-STILLE COUPLING

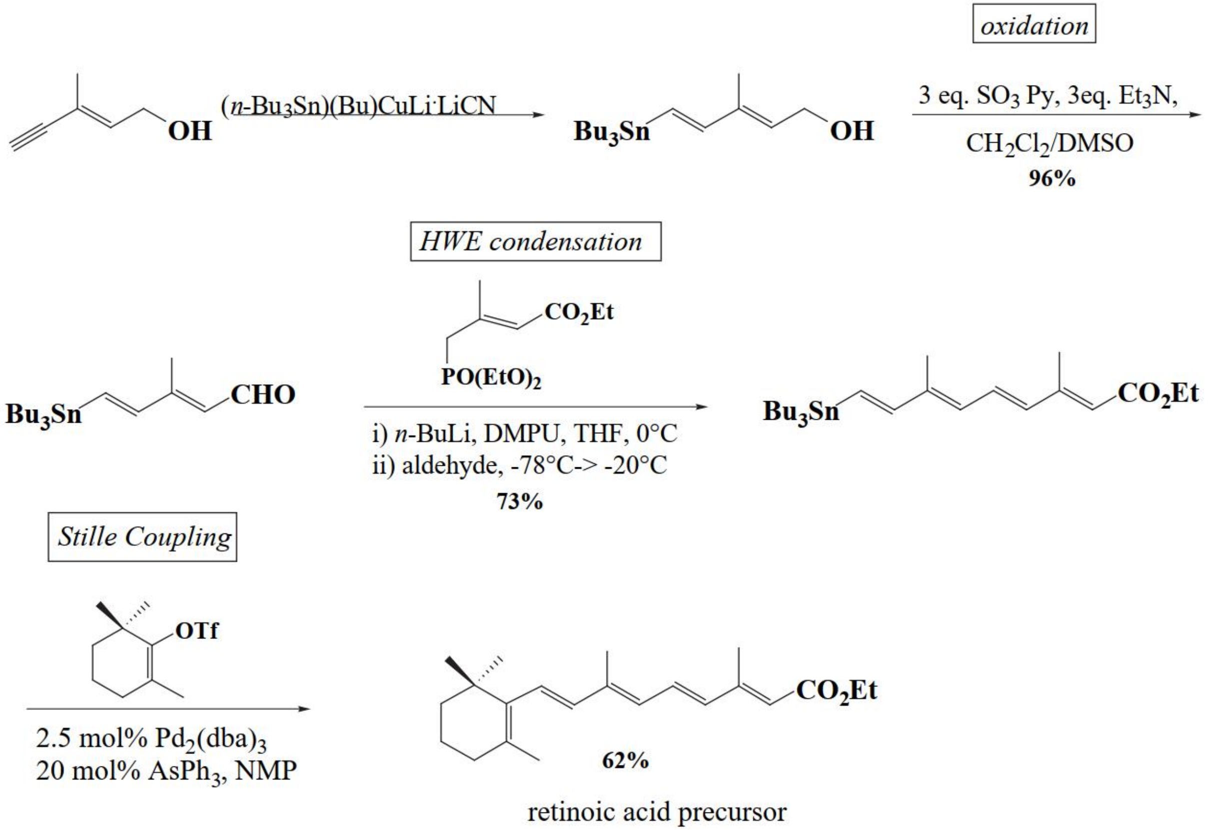




Secondary alkyltin and alkylboron reagents are configurationally stable and isolable

Biscoe *Nat Chem* **2013** 5, 607. DOI: 10.1038/nchem.1652

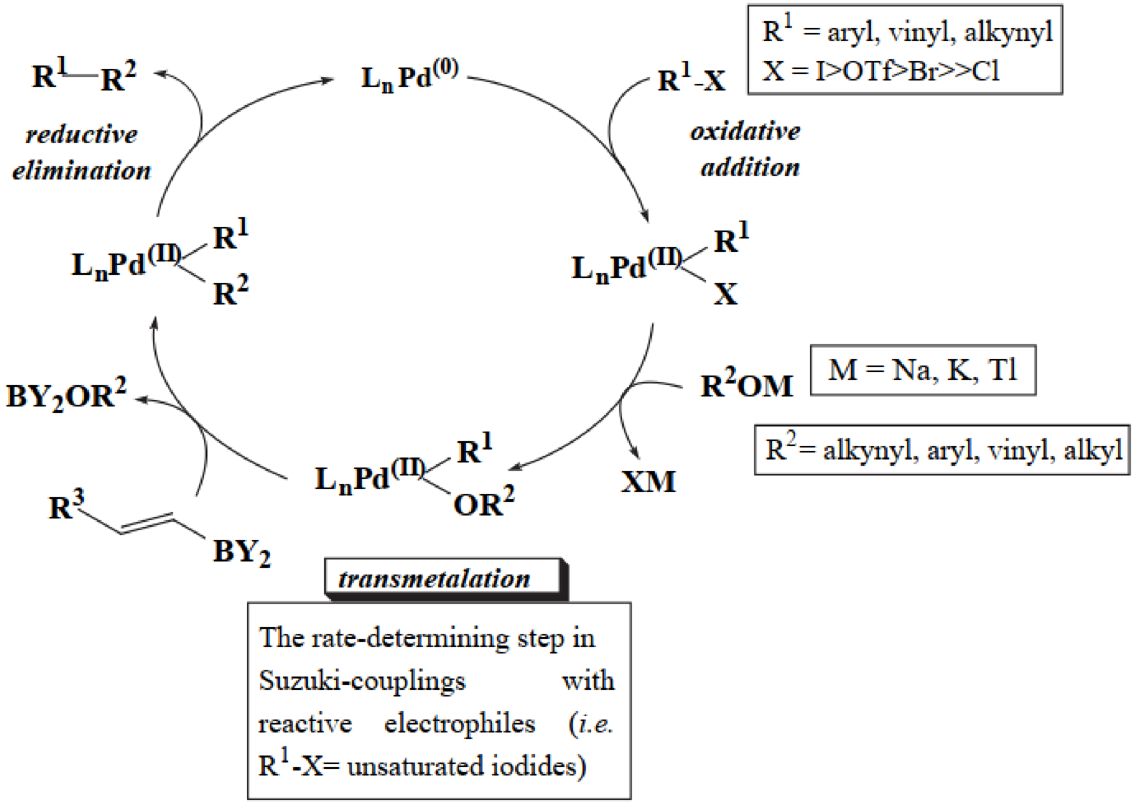
10.4.7 MIGITA-STILLE COUPLING – APPLICATIONS



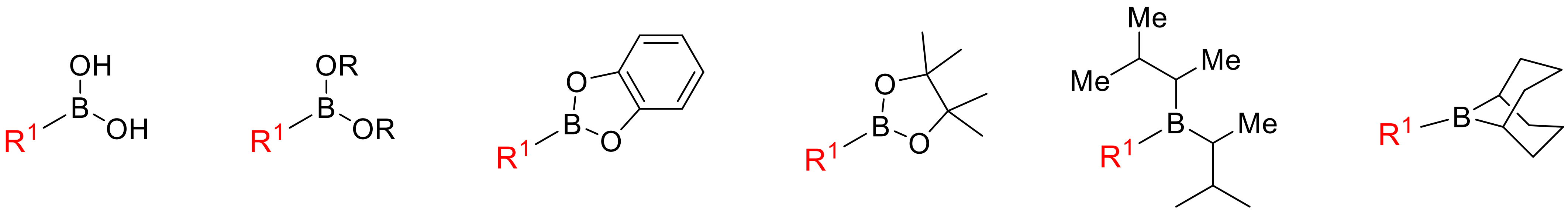
Dominguez *Tet* **1999** (55) 15071. DOI: 10.1016/S0040-4020(99)00962-X

10.5.1 SUZUKI-MIYAURA – MECHANISM

Unlike other cross-coupling, a base is required



10.5.1 SUZUKI-MIYAURA



boronic acids | boronic esters | boronic esters (catechol) | boronic esters (pinacolate) | alkyl borane | 9-BBN

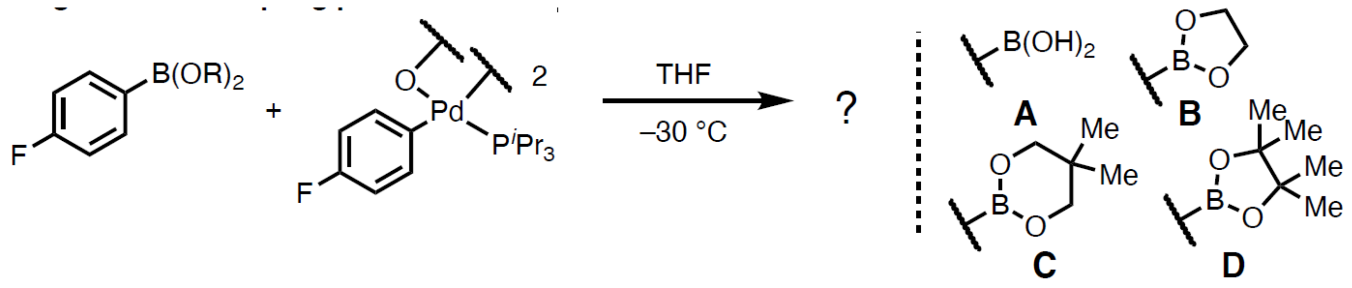
Identity of organoborn affects TM rate

A variety of different organoboron reagents can be used to effect transfer of the R2 group via transmetalation. Generally, electron rich unhindered organoboranes are most reactive towards transmetalation. Organoboranes are non-toxic and air and moisture stable

Lennox and Lloyd-Jones *Chem Soc Rev* **2014** 43, 412. DOI: 10.1039/C3CS60197H (boron reagents for Suzuki)

POD #2

For the reaction depicted below, provide the product and **predict the relative rates of the different organoboron coupling partners shown**.

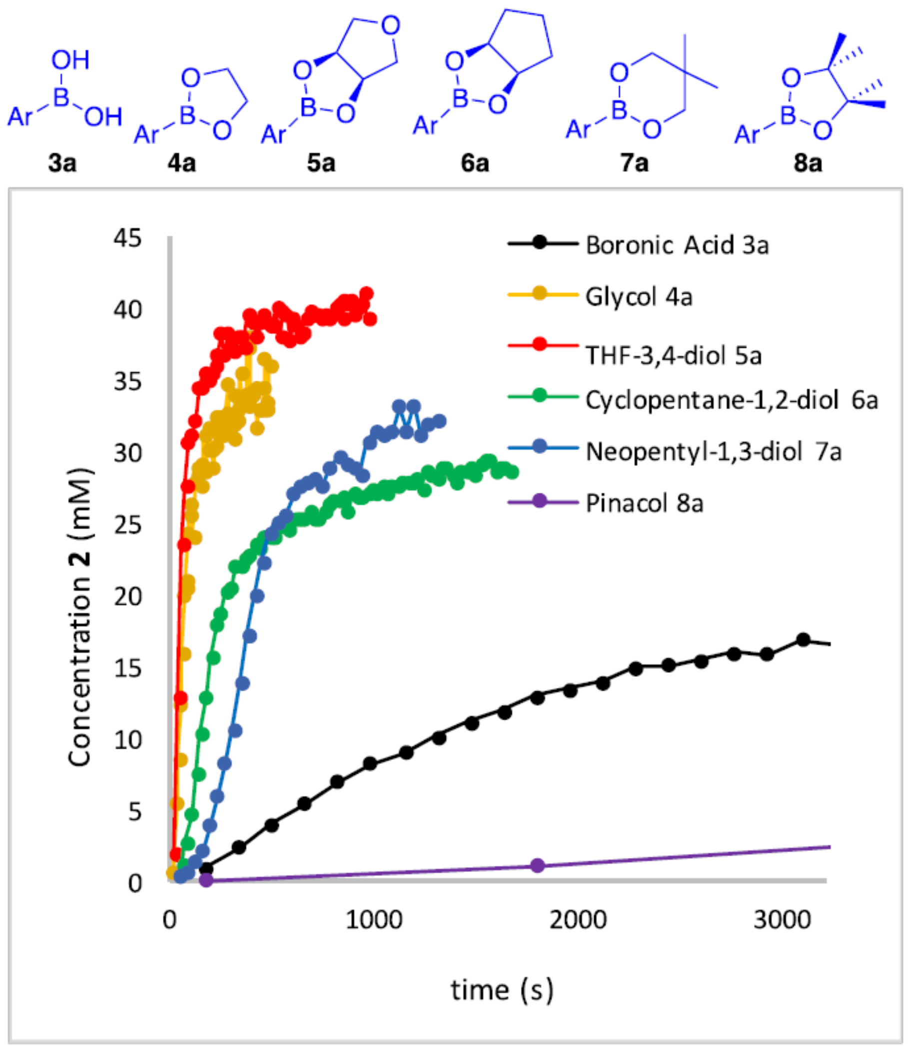


Denmark ACS Catal 2020 10, 73. DOI: 10.1021/acscatal.9b04353 (data)
Denmark JACS 2018, 140, 12, 4401. DOI: 10.1021/jacs.8b00400 (rationale)

POD #2

Several factors influence TM of organoboron reagents:

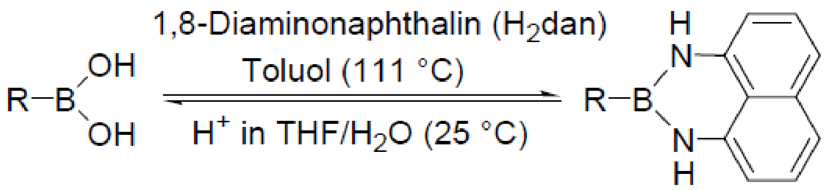
- the ability to access a coordinatively unsaturated palladium atom
- the nucleophilic character of the B-*ipso* carbon
- sp^2 / sp^3 hybridization ratio
- steric effects



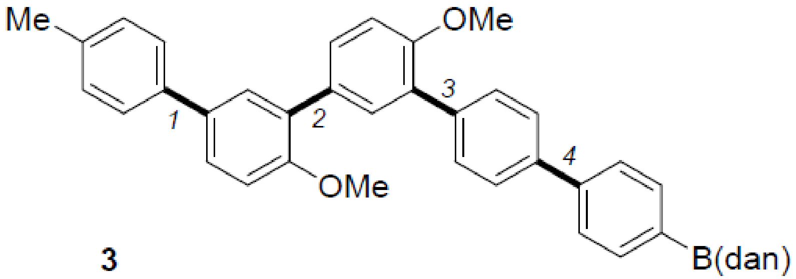
Denmark ACS Catal 2020 10, 73. DOI: 10.1021/acscatal.9b04353 (data)
Denmark JACS 2018, 140, 12, 4401. DOI: 10.1021/jacs.8b00400 (rationale)

POD #3

A strategy to complex molecules by successive Suzuki is the use of “masked” (or “protected”) bornoic acid, such as MIDA esters or R-B-(dan). **Propose a synthesis of compound 3 involving only Suzuki couplings.**

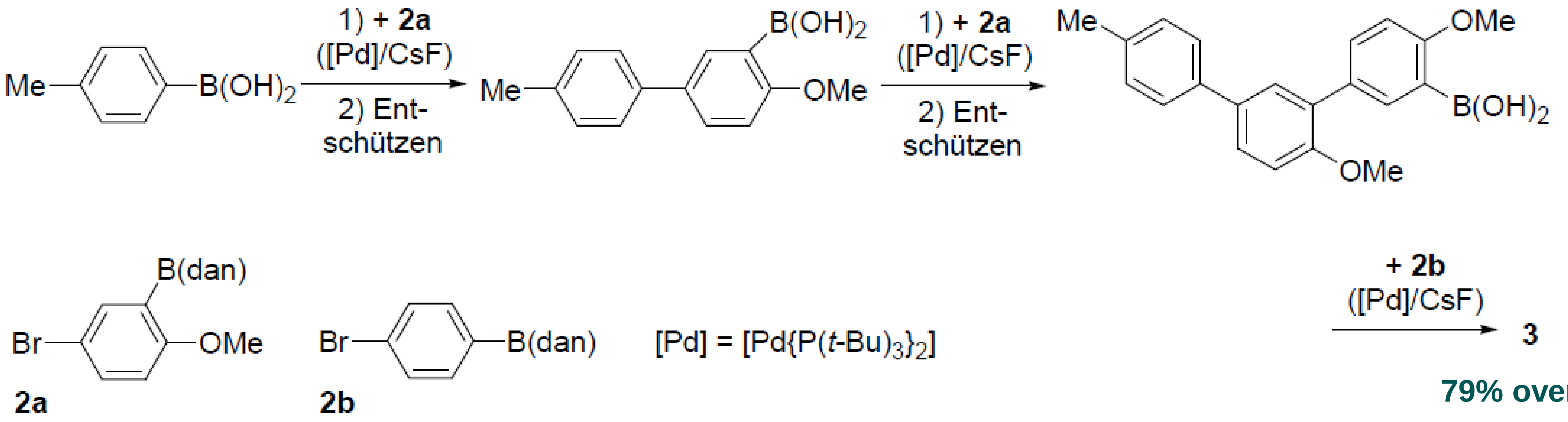


1 2



3

POD #3



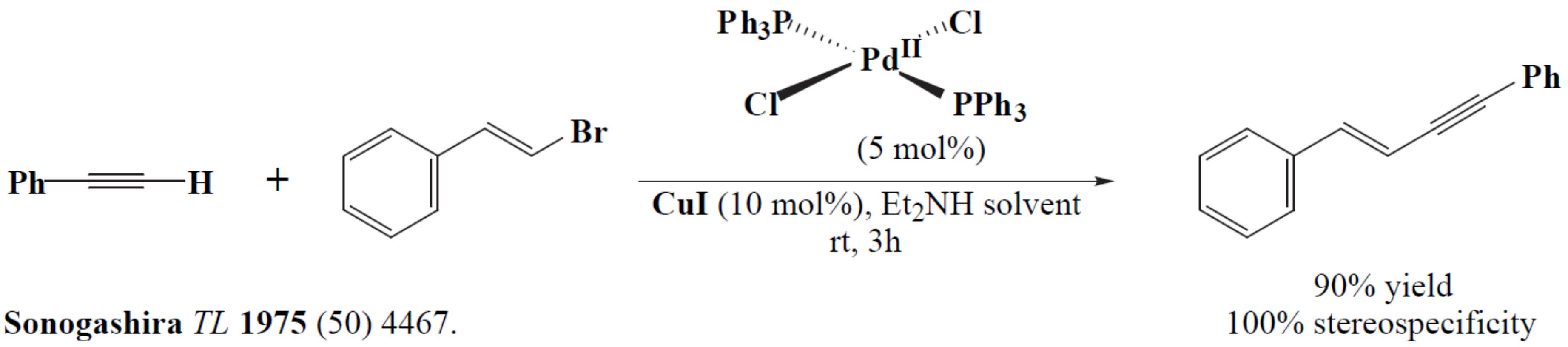
79% overall yield!

Tobisu *ACIE* **2009** 48, 3565. DOI: [10.1002/anie.200900465](https://doi.org/10.1002/anie.200900465)
Glorius *ACIE* **2009** 48, 5240. DOI: [10.1002/anie.200901680](https://doi.org/10.1002/anie.200901680)

10.6 HIYAMA

See seminar presentation :)

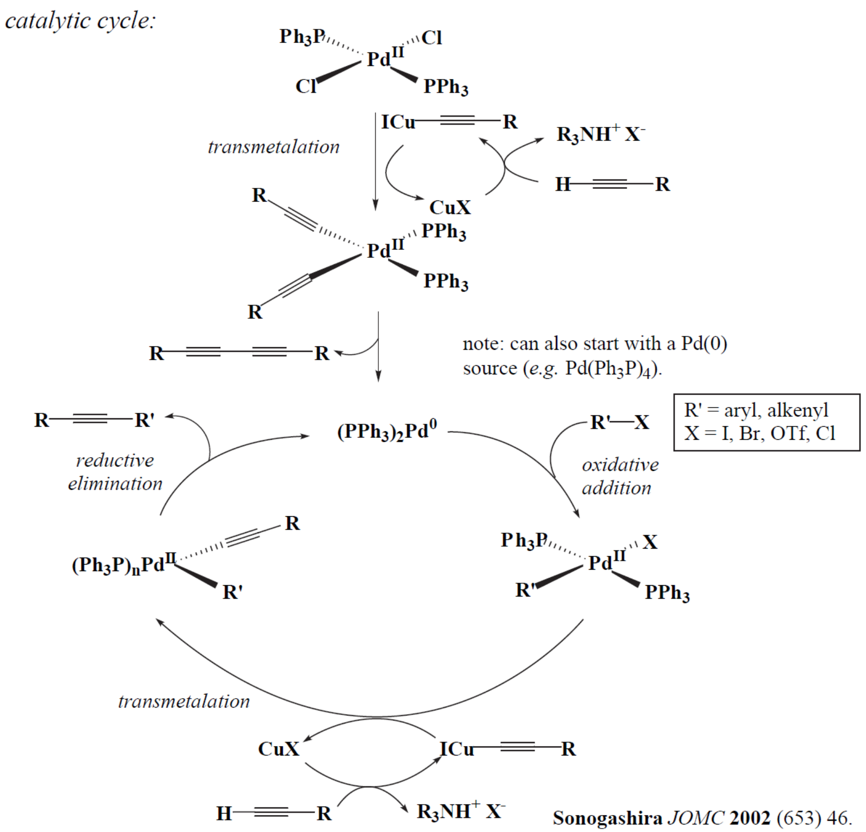
10.7.1 SONOGASHIRA – ORIGINAL REPORT



Sonogashira *TL* **1975** (50) 4467.

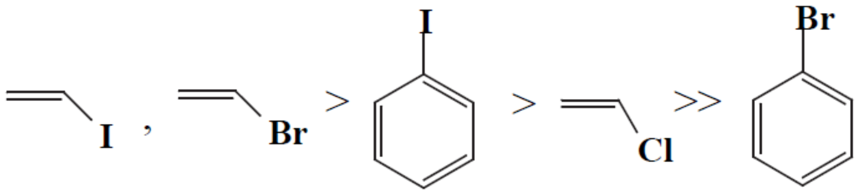
Sonogashira *Tet Lett* **1975** 16, 4467. DOI: bphsxq

10.7.2 SONOGASHIRA – MECHANISM



Sonogashira *JOMC* **2002** 653, 46. DOI: dd7dd6

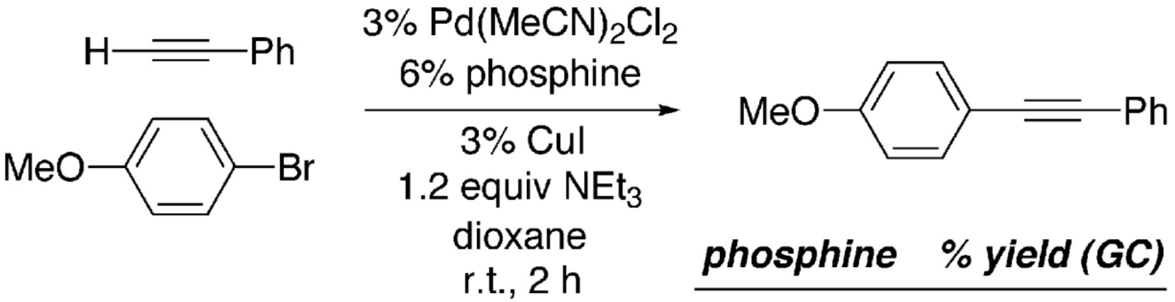
10.7.3 SONOGASHIRA – Csp^2 REACTIVITY ORDER



Sonogashira, Metal-Catalyzed Cross-Coupling Reactions, Ch. 5 DOI: 10.1002/9783527612222.ch5

10.7.3 SONOGASHIRA – LIGANDS

Instead of PPh_3 more basic and starically hindered phosphines give a more effective $12e^-$ PdL cycles instead of PdL_2

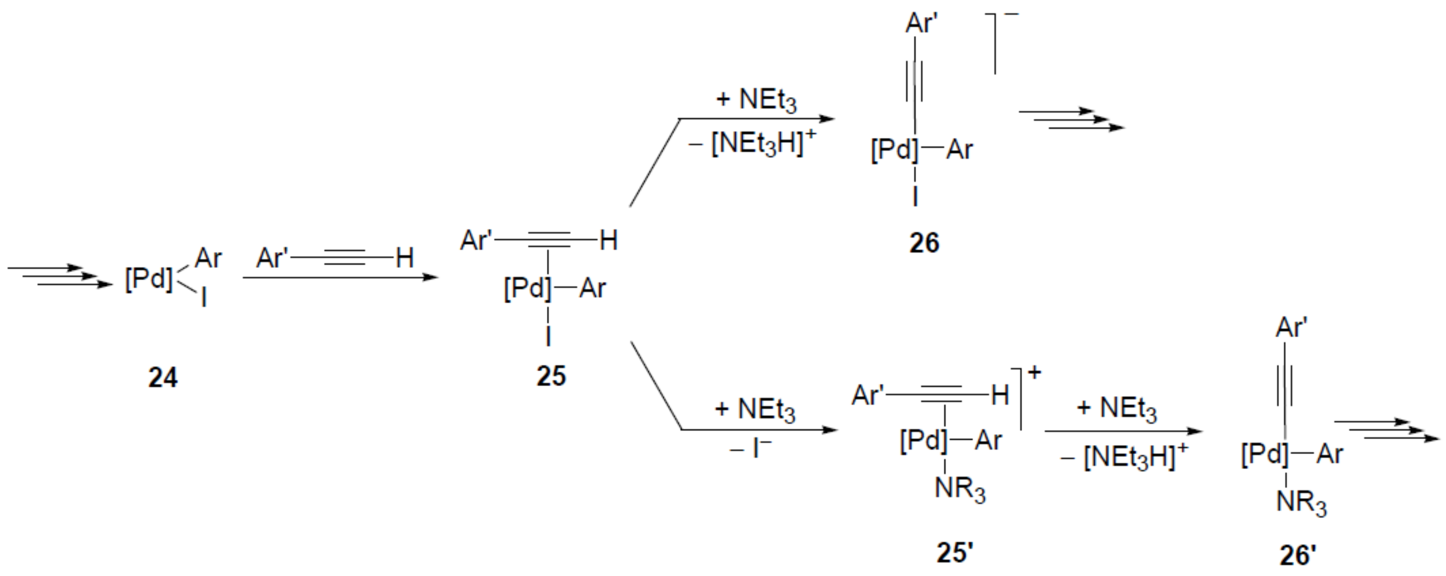


phosphine	*% yield (GC)*
PPh_3	<2
P(*o*-tolyl)$_3$	<2
dppf	<2
PCy_3	<2
P(*t*-Bu)$_3$	96

Buchwald *Org Lett* **2000** 2, 1729.

POD #1

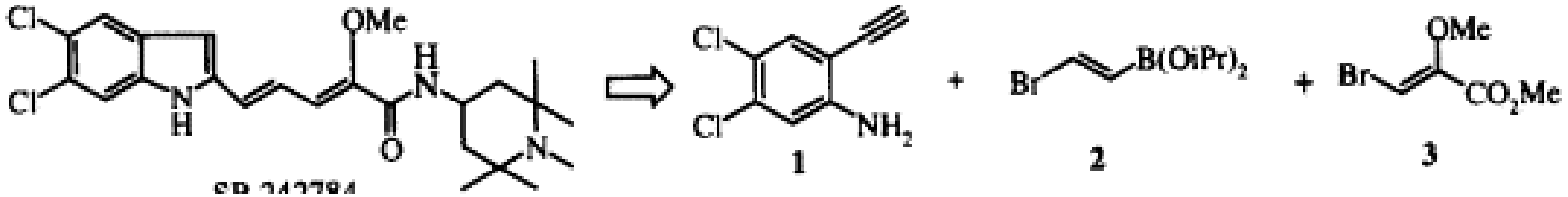
A copper-free variant of Sonogashira exists, for which the following mechanism is proposed: after OA of Ar-I to the Pd^0 complex, the terminal alkyne is coordinated (24->25). For phenylacetylenes with EWG, this is followed by a base-assisted deprotonation (25->26) as r.d.s. while for phenylacetylenes with EDG there are evidence for a 25’:25à’:26à reaction path. **Why does the mechanism change?**

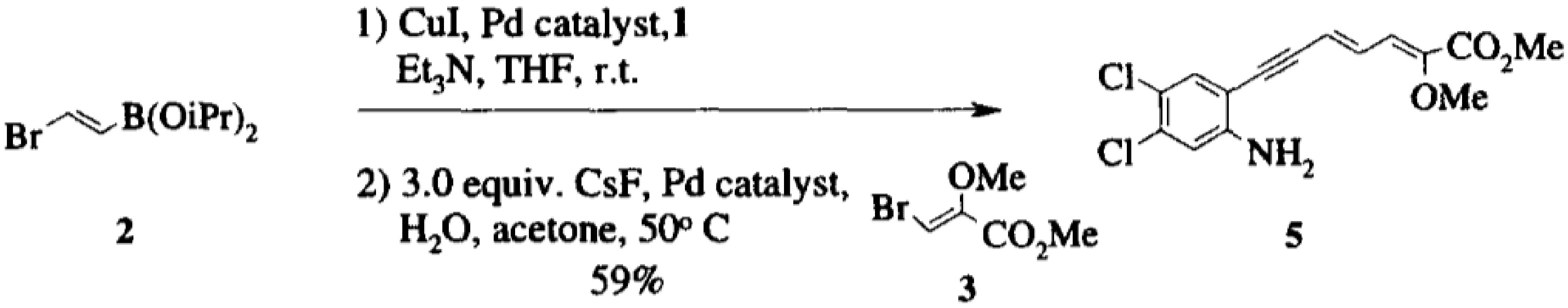


Mårtensson *Organometallics* **2008** 11, 2490. DOI: 10.1021/om800251s

POD #2

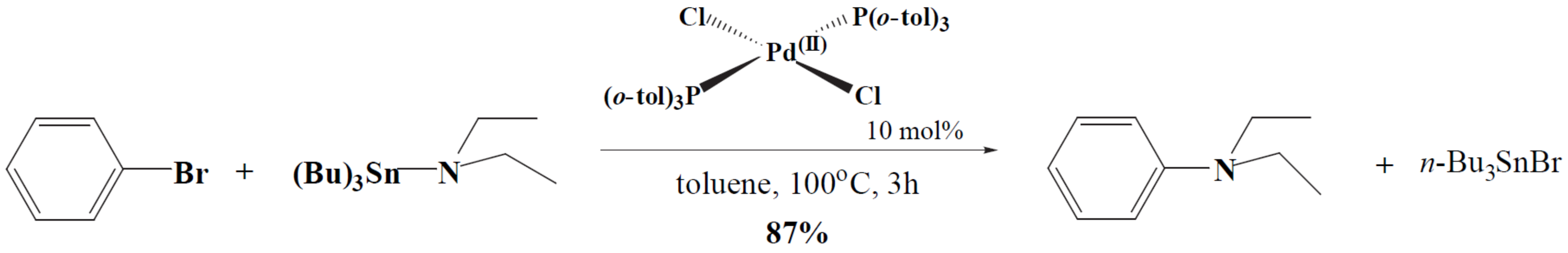
Provide a cross-coupling-based retrosynthesis of the following molecule:





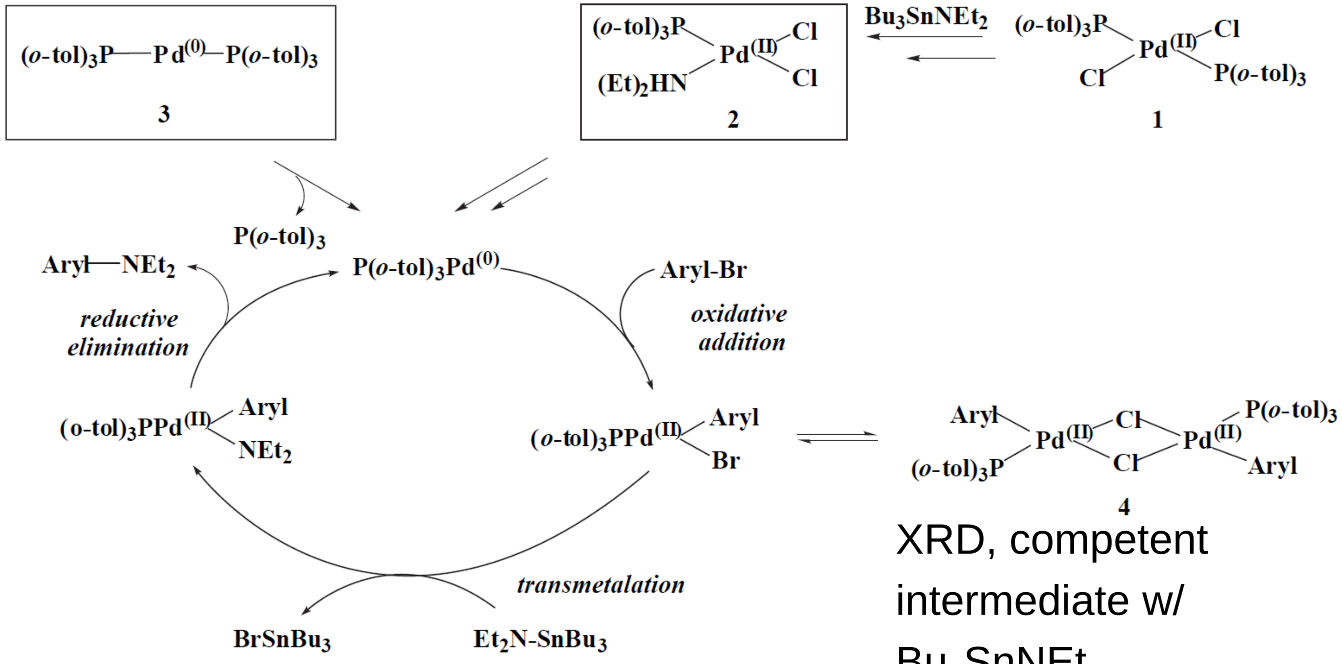
Yu *Tet* Lett **1998** 39, 9347DOI: cbr3rx

10.8.1 C-N CROSS-COUPLINGS - MIGITA



Migita *Chem Lett* **1983** 927. DOI: [10.1246/cl.1983.927](10.1246/cl.1983.927)

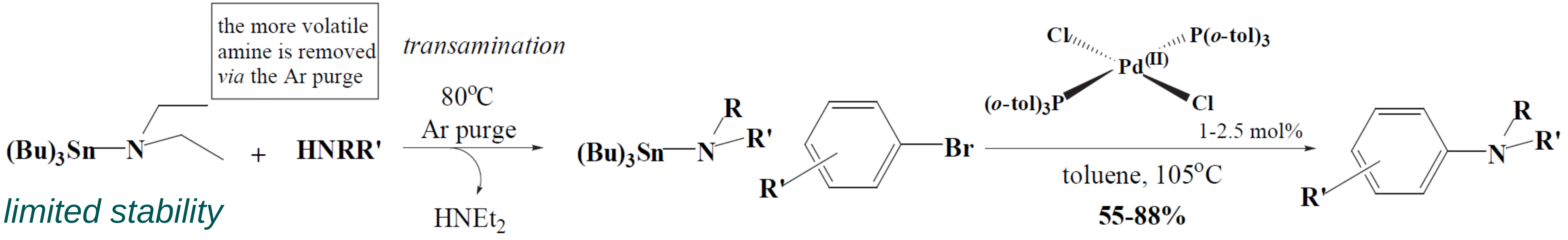
10.8.1 C-N CROSS-COUPLINGS – HARTWIG



XRD, competent intermediate w/ Bu_3SnNEt_2

Hartwig JACS **1994** 116, 5969. DOI: [10.1021/ja00092a058]

10.8.2 C-N CROSS-COUPLINGS – BUCHWALD



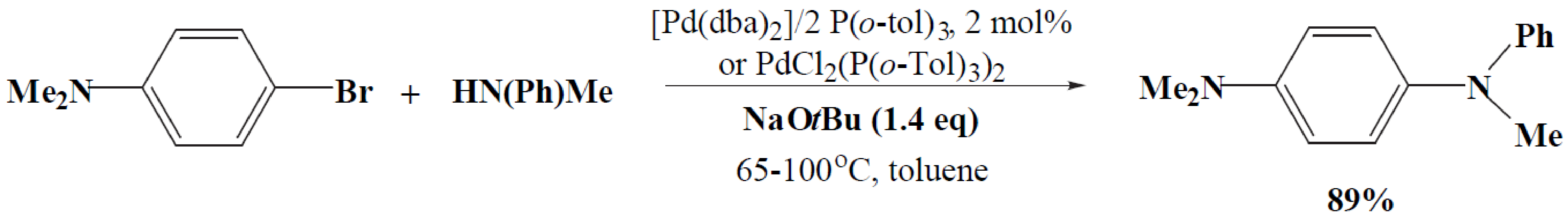
limited stability

aminostannanes

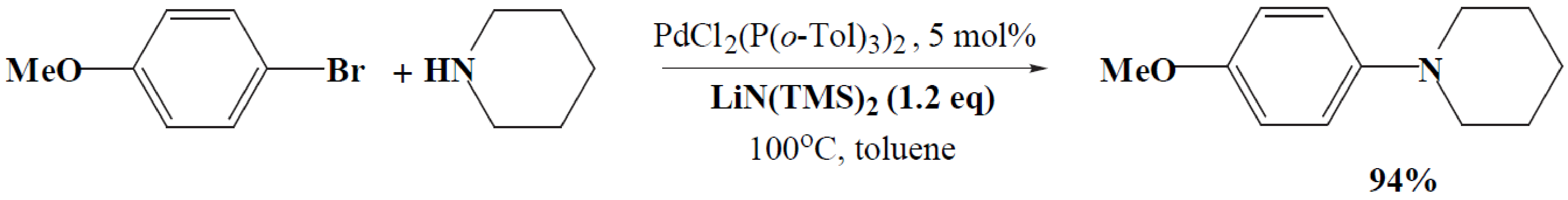
Buchwald *JACS* **1994** 116 7901. DOI: 10.1021/ja00096a059

10.8.3 C-N CROSS-COUPLINGS – BUCHWALD-HARTWIG

Buchwald 1995

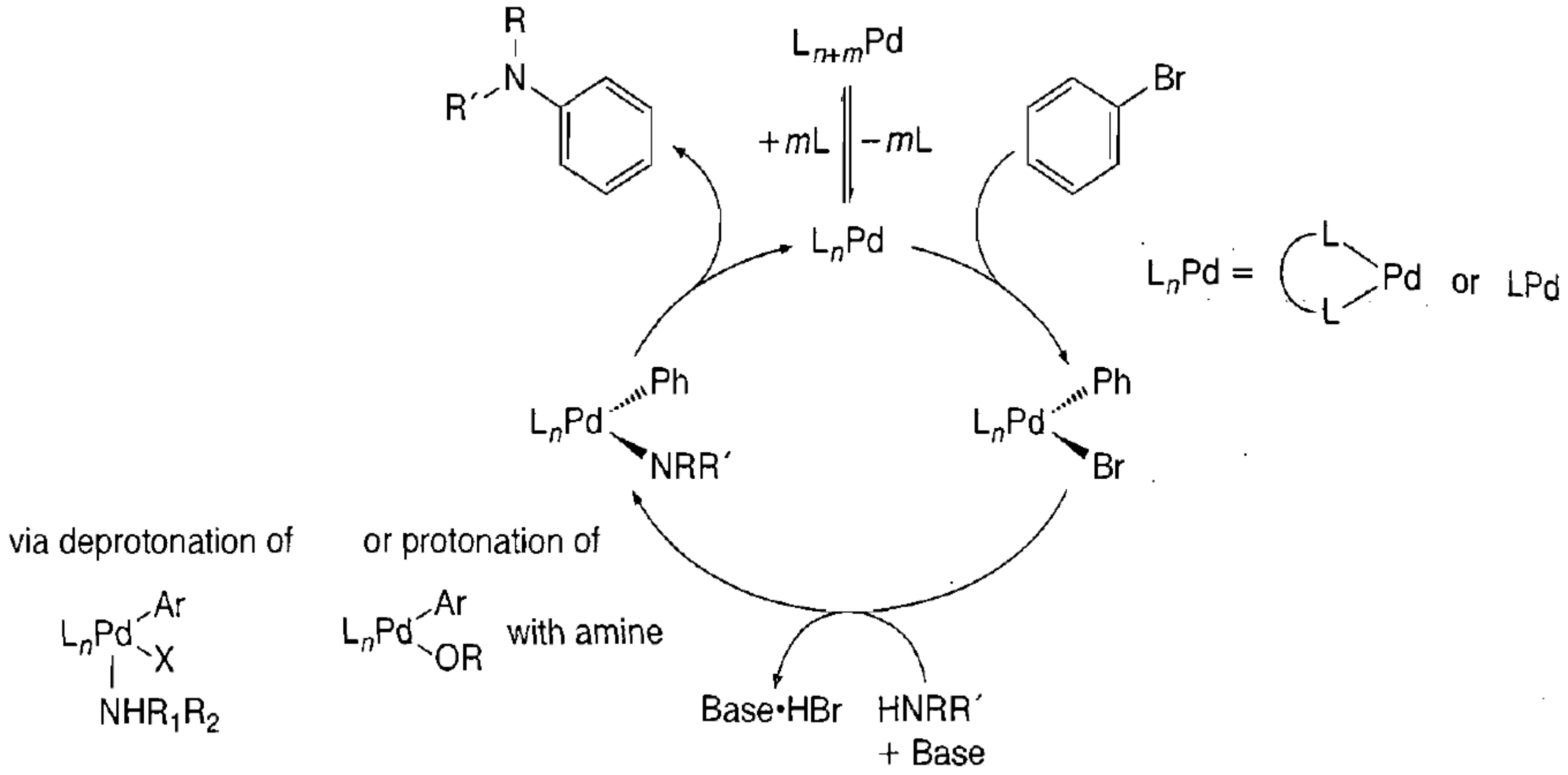


Hartwig 1995



Buchwald *ACIE* **1995** 34, 1348. DOI: 10.1002/anie.199513481
Hartwig *Tet Lett* **1995** 36, 3609. DOI: dpdwns

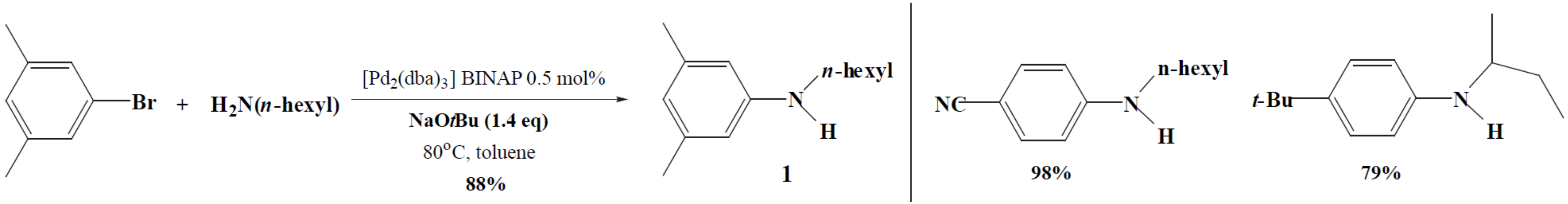
10.8.4 C-N CROSS-COUPLINGS – MECHANISM



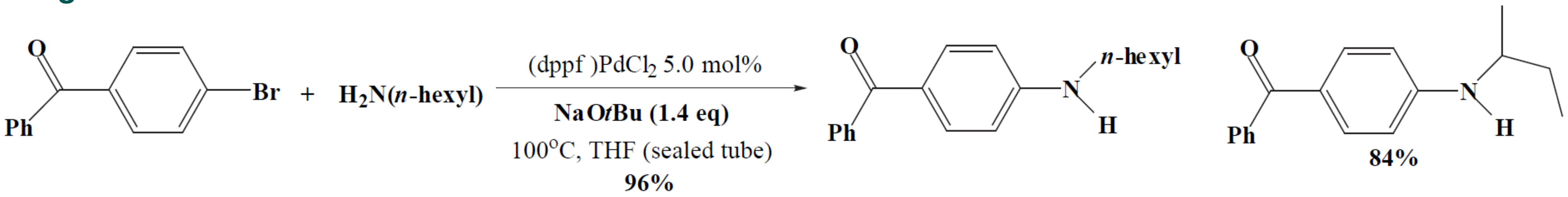
Buchwald *OM* **1996** 15, 3534 DOI: 10.1021/om9603169

10.8.5 BUCHWALD HARTWIG – PRIMARY AMINES

Buchwald 1996

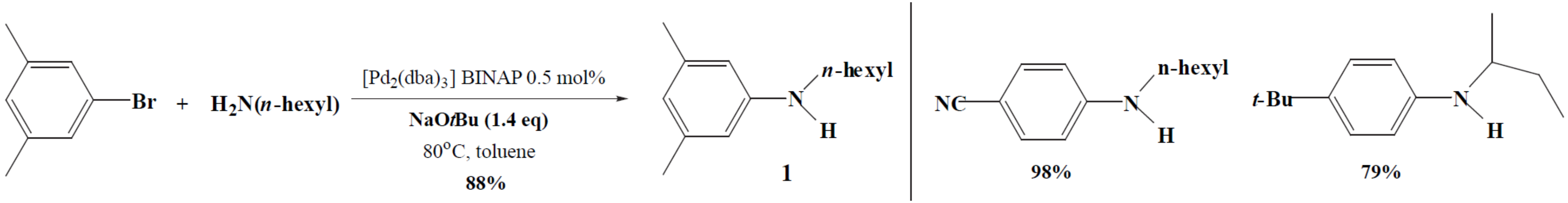


Hartwig 1996



Buchwald *JACS* **1996** 118, 7215. DOI: 10.1021/ja9608306
Hartwig *JACS* **1996** 118, 7217. DOI: 10.1021/ja960937t

10.8.5 BUCHWALD HARTWIG – PRIMARY AMINES



Ligand	% Conversion	ratio of **1** to aryl-H	ratio of **1** to doubly arylated amine	isolated yield of **1**
BINAP	100 %	40/1	39/1	88%
P(o-tol)$_3$	88 %	1.5/1	7.6/1	35%
dppe	7%	1.5/4	---	---
dppp	>2%	---	---	---
dppb	18%	1/1.6	---	---
dppf	100%	13.2/1	2.2/1	54%

BINAP is thought to:

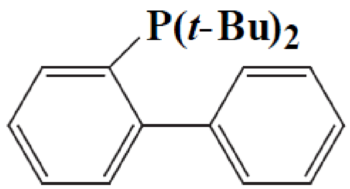
- effectively prevents β-hydride elimination pathway by blocking *cis* coordination sites.
- inhibit formation of catalytically inactive bis(amine)aryl halide complexes
- inhibit formation of bridging amido complexes that resist reductive elimination.

Buchwald *JACS* **1996** (118) 7215. DOI: 10.1021/ja9608306

10.8.6 BUCHWALD HARTWIG - CHLORIDES

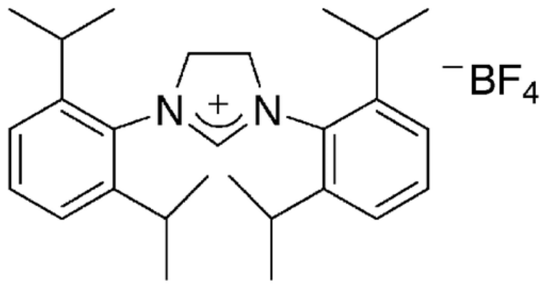
Buchwald 2000

Buchwald-type ligands



Hartwig 2000

In-situ NHC

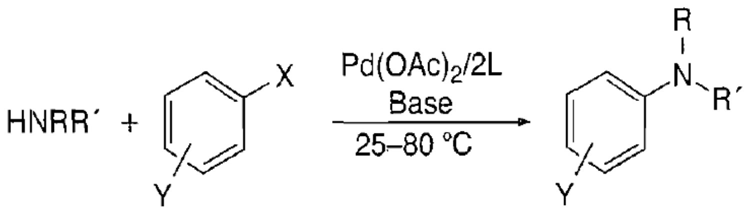


1

Buchwald *JOC* **2000**, 65, 4, 1144. DOI: 10.1021/jo9916986
Hartwig *OL* **2000** 2, 1423. DOI: 10.1021/ol005751k

10.8.8 SELECTIVE C-N BOND FORMATION

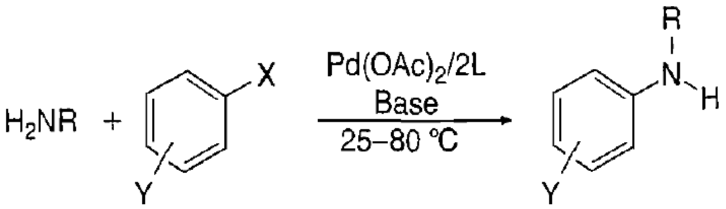
Secondary amines



(19.65)

X = Cl, Br, I, OTf, or OTs
L = Hindered monodentate ligands:
P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$, Ph_5FcP(*t*-Bu)$_2$ (Q-phos), heterocyclic carbenes, (Biaryl)PR_2, −OP(*t*-Bu)$_2$, and Verkade's proazaphosphatranes
L = Chelating bidentate ligands:
dppf, BINAP, Xantphos, and Josiphos ligands

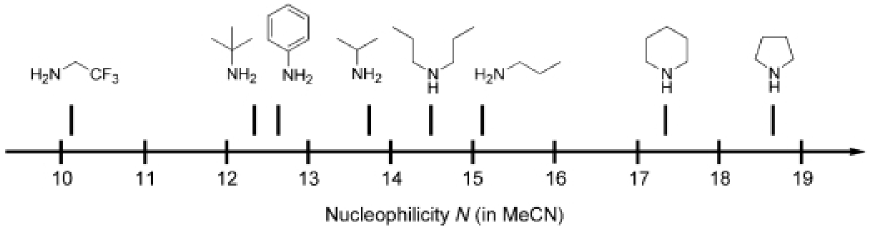
Primary amines



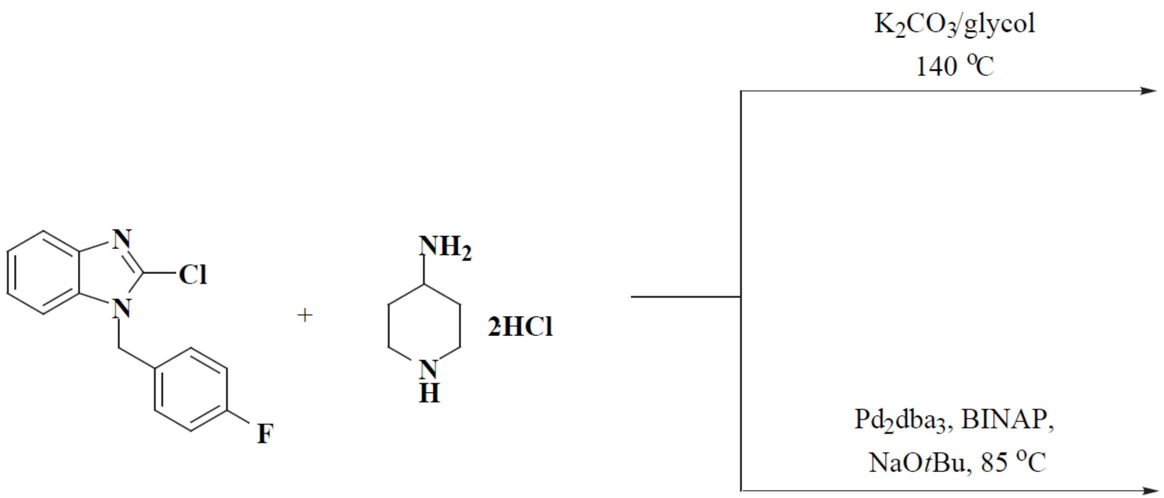
(19.66)

X = Cl, Br, I, OTf, or OTs
Base = NaO-*t*-Bu, Cs_2CO_3, or K_3PO_4
L = ligands of Eq. 19.65

POD #3



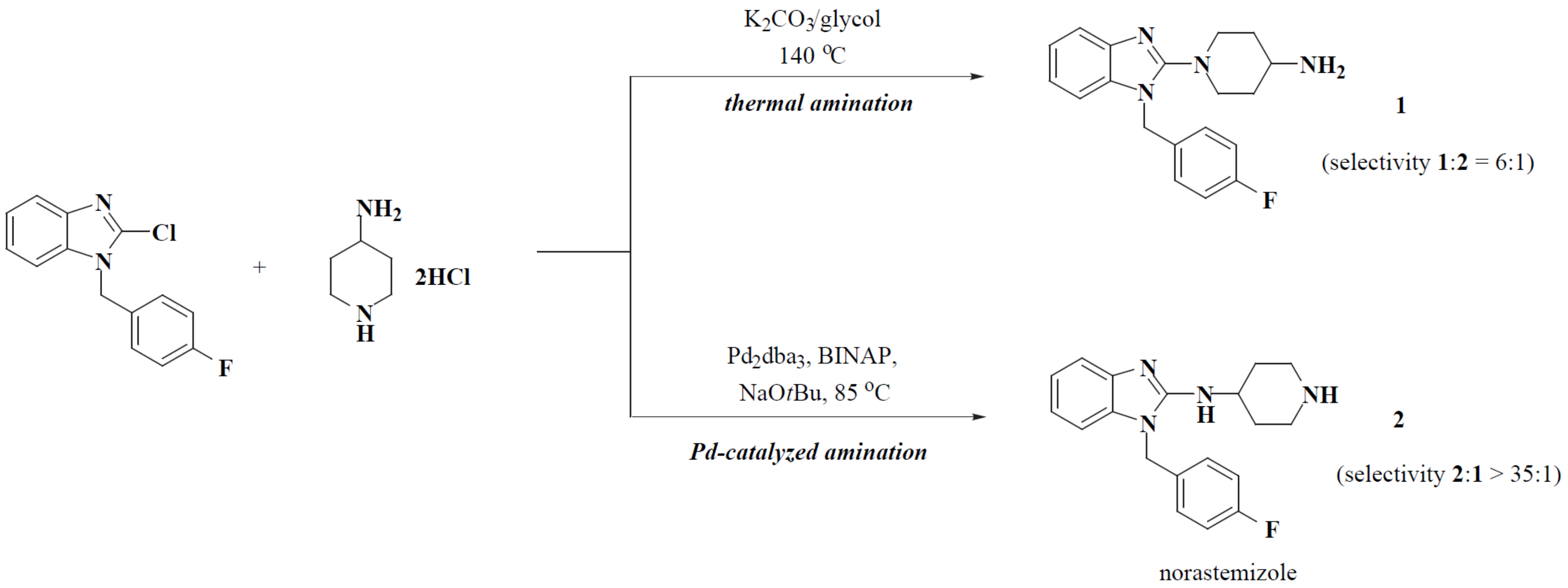
Predict the product of the following reactions:



Senanayake *Tet Lett* **1998**, *39*, 3121. DOI: cxfqgr

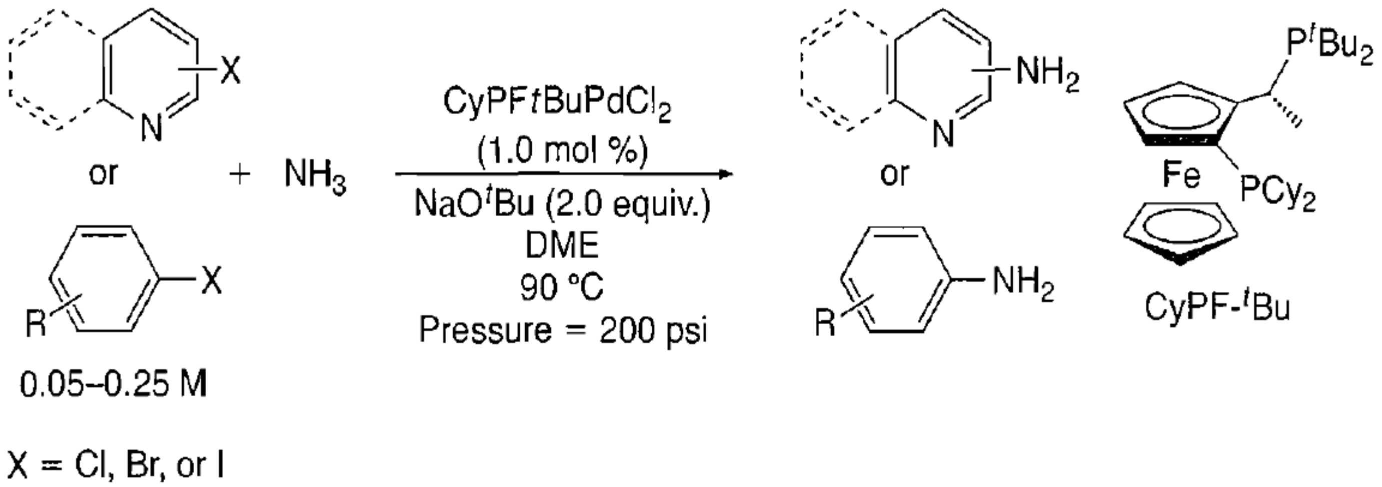
POD #3

Predict the product of the following reactions:



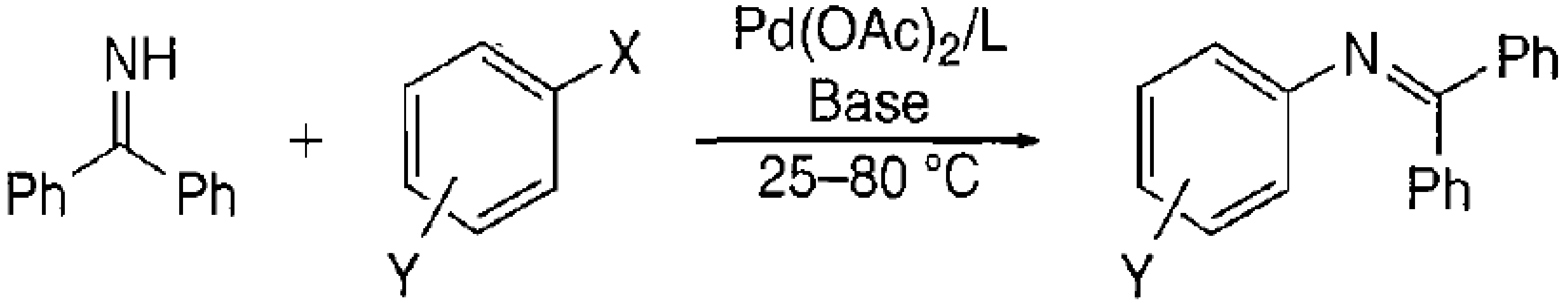
Senanayake *Tet Lett* **1998**, *39*, 3121. DOI: cxfqgr

10.8.9 AMMONIA AND AMMONIA EQUIVALENTS



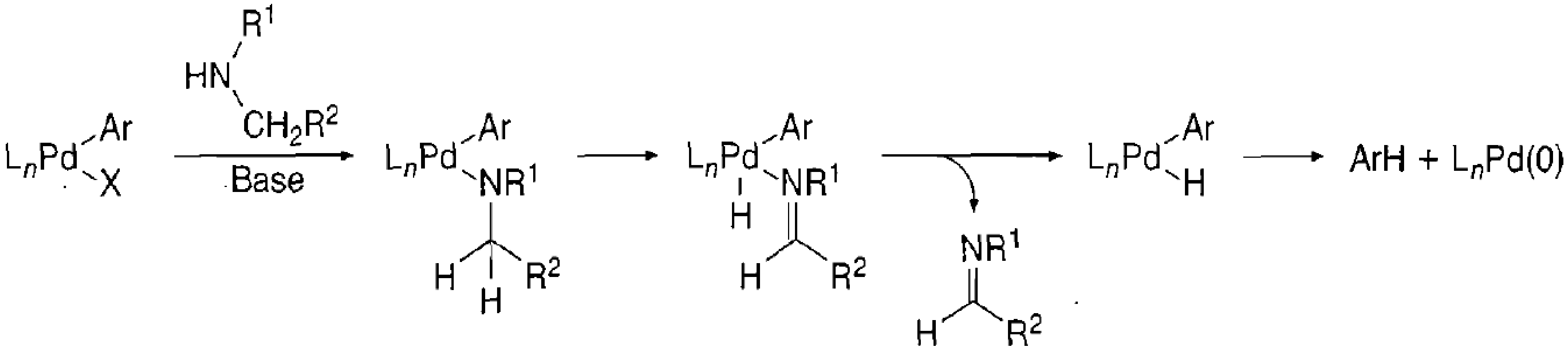
(19.67)

10.8.9 AMMONIA AND AMMONIA EQUIVALENTS



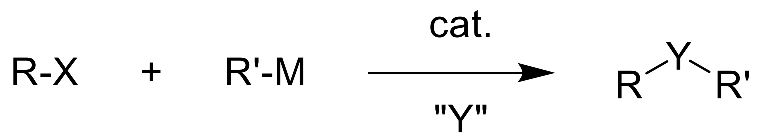
X = Cl, Br, I, or OTf
Base = NaO-*t*-Bu or Cs_2CO_3
L = dppf or BINAP, *N*-heterocyclic carbene
CyPPF-*t*-Bu (a hindered Josiphos ligand)

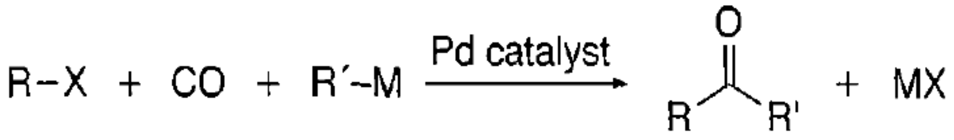
10.8.10 SIDE-REACTIONS



10.9 CARBONYLATIVE STILLE

Conjunctive cross-coupling





R = Ar, vinyl, benzyl, or alkyl
M = SnR''_3, BR''_2, or ZnX

10.9 CARBONYLATIVE STILLE