Palladium- and Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Electrophiles

Palladium

- *Suzuki*
- *Heck*
- *Hiyama*
- *Negishi*
- *Sonogashira*
- *Stille*

Nickel

- *Negishi*
- *Suzuki*
- *Hiyama*
- *Kumada*
- *Stille*

Palladium- and Nickel-Catalyzed Cross-Coupling Reactions

$$R\text{–}X \quad + \quad M\text{–}R^1 \xrightarrow{\text{Pd or Ni catalyst}} R\text{–}R^1$$

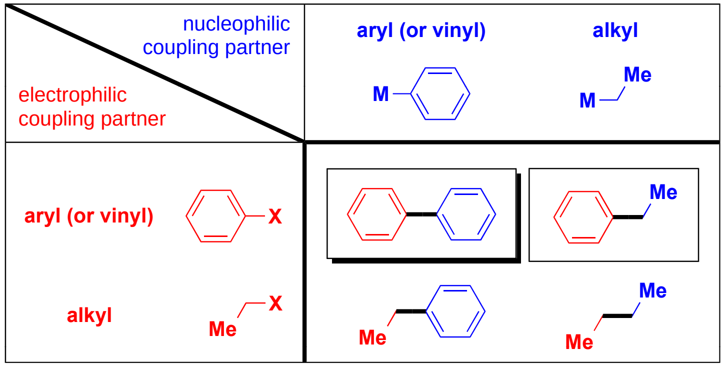
X = Cl, Br, I, OTf

M =	
B	***Suzuki-Miyaura***
Zn	***Negishi***
Sn	***Migita-Stille***
Si	***Hiyama***
Mg	***Murahashi-Kumada-Corriu***

Powerful tools for carbonŠcarbon bond formation in natural product synthesis, pharmaceutical chemistry, materials science, etc.

Palladium- and Nickel-Catalyzed Cross-Couplings: *Going Beyond the Formation of C_{sp^2}–C_{sp^2} Bonds*

Most studies have focused on carbonŠcarbon bond formation between sp^2-hybridized carbons

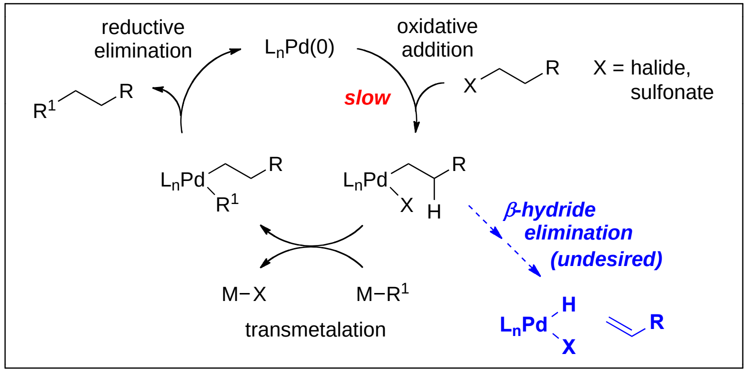


"AlkylŠalkyl cross-coupling reactions have historically been the most difficult to realize"

Metal-Catalyzed Cross-Coupling Reactions (de Meijere, Diederich; Wiley-VCH: 2004)

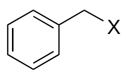
Palladium-Catalyzed Cross-Coupling of Alkyl Electrophiles: *Background*

There are relatively few reports of cross-couplings of alkyl electrophiles



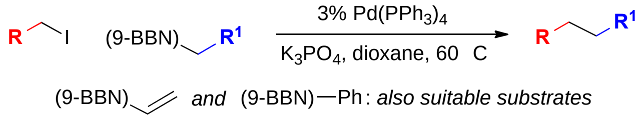
Activated electrophiles that lack β hydrogens are suitable substrates:

e.g.,



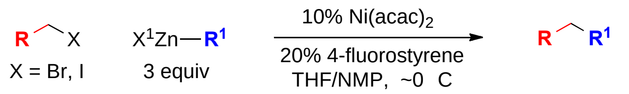
Pd- and Ni-Catalyzed Cross-Coupling of Unactivated Alkyl Electrophiles: *State of the Art in 2000*

Suzuki reactions: Suzuki (1992)



(9-BBN) vinyl *and* (9-BBN)—Ph : *also suitable substrates*

Negishi reactions: Knochel (1995)

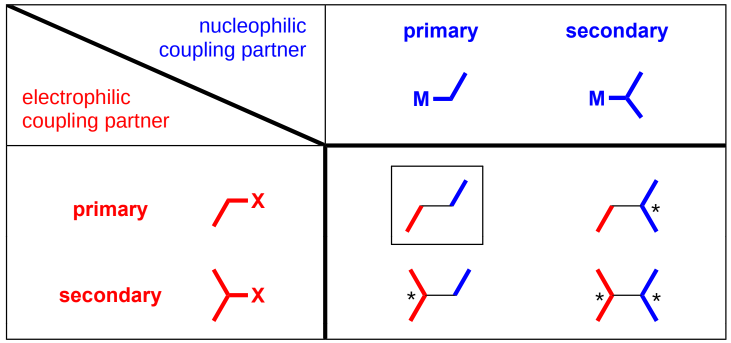


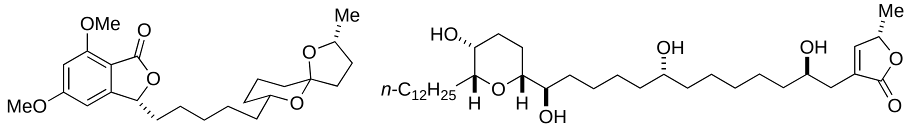
Copper-, cobalt-, and iron-catalyzed cross-couplings of alkyl electrophiles with **Grignard** reagents have been reported

For a review and leading references on progress since 2000 (by many groups), see:

Angew. Chem., Int. Ed. **2009**, *48*, 2656–2670 (Lautens)

Alkyl–Alkyl Cross-Coupling: *Some of the Challenges*

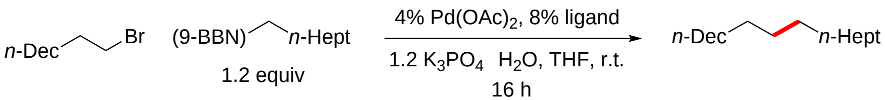




(+)-spirolaxine methyl ether

(+)-pyranicin

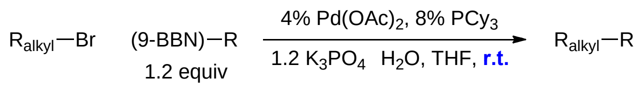
Palladium-Catalyzed Suzuki Cross-Couplings of Alkyl Bromides with Alkylboranes: *Ligand Effects on Reactivity*



Ligand	Yield
PPh_3, P(2-furyl)$_3$, P(*o*-tol)$_3$, binap, P(2,4,6-trimethoxyphenyl)$_3$	<2%
$AsPh_3$	<2%
$P(OPh)_3$	<2%
P(*t*-Bu)$_3$	**<2%**
P(*i*-Pr)$_3$	**68%**
PCy_3	**85%**
P(*n*-Bu)$_3$	**9%**

Chaoyang Dai, Matt Netherton

Suzuki Cross-Couplings of Alkyl Bromides Catalyzed by Pd/PCy$_3$ at Room-Temperature



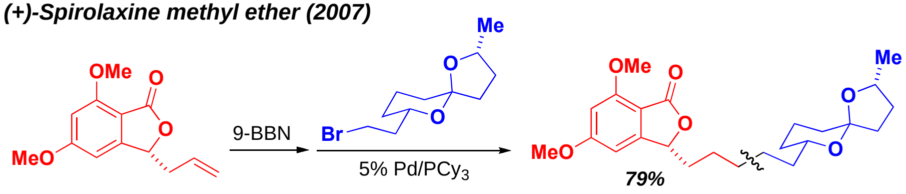
R_{alkyl}—Br	(9-BBN)—R	Yield
Me, Me, Br	(9-BBN), OTES	72%
NC ( )$_4$ Br	(9-BBN) ( )$_{10}$ O, OMe	81%
Cl ( )$_6$ Br	(9-BBN), OTES	81%
n-Dodec—Br	(9-BBN)	66%

Alkyl ***chlorides*** *are also suitable coupling partners (90 C)*

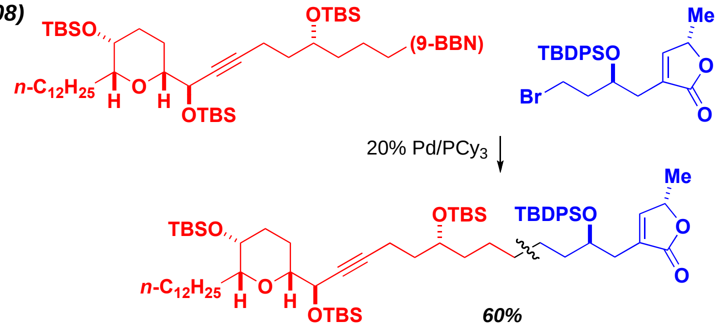
Matt Netherton, Klaus Neuschuetz

Pd/PCy$_3$-Catalyzed Suzuki Cross-Couplings of Alkyl Bromides: *Applications to Fragment Coupling in Synthesis (Phillips)*

(+)-Spirolaxine methyl ether (2007)



(+)-Pyranicin (2008)

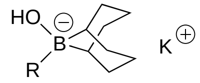


Suzuki Cross-Couplings of Alkyl Bromides: *Mechanistic Observations*

R_{alkyl}—Br (9-BBN)—R $\xrightarrow[\text{1.2 } K_3PO_4 \text{ } H_2O]{\text{4\% Pd(OAc)}_2 \text{, 8\% PCy}_3}$ R_{alkyl}—R

Reactions are not moisture-sensitive:
the presence of water leads to a faster reaction

R—(9-BBN) K_3PO_4 H_2O ⇄



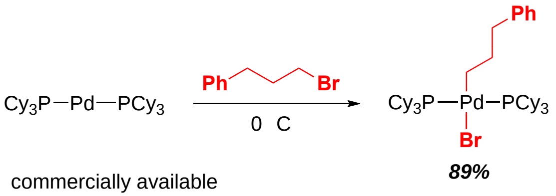
⇦ the species that participates in transmetalation? (cf. Soderquist)

identified by [11]B NMR

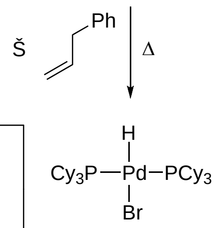
The resting state of the catalytic process appears to be Pd(PCy$_3$)$_2$

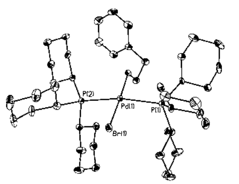
Matt Netherton

Suzuki Cross-Couplings of Alkyl Bromides: *Facile Oxidative Addition to Pd(PCy$_3$)$_2$*



commercially available
effective cross-coupling catalyst





⇧
reaction with R-(9-BBN) leads to cross-coupling

Reactivity data

⇓

oxidative addition involves PdL$_2$
β-hydride elimination involves PdL$_1$

Matt Netherton, Klaus Neuschuetz

Suzuki Cross-Couplings of Alkyl Tosylates: *Dependence of Reactivity on Phosphine Structure*

n-Dodec—**OTs** (9-BBN)—*n*-Oct $\xrightarrow[\text{1.2 NaOH, dioxane, 50 C}]{\text{4\% Pd(OAc)}_2 \text{, 16\% trialkylphosphine}}$ *n*-Dodec—*n*-Oct

For PCy$_3$: 46% yield

	R = *i*-Pr	R = Et	R = Me
PCy$_2$**R**	44%	70%	48%
P(*t*-Bu)$_2$**R**	<2%	<2%	**78%**

⇧

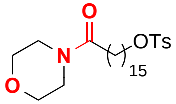
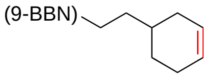
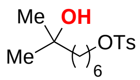
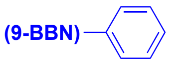
air-stable [HP(t-Bu)$_2$Me]BF$_4$ (Strem, Aldrich) can also be used

P(t-Bu)$_2$Me (available from Strem, Aldrich) provides the best catalyst

Matt Netherton

Suzuki Cross-Couplings of Alkyl Tosylates

R_{alkyl}—OTs (9-BBN)—R ⟶ R_{alkyl}—R

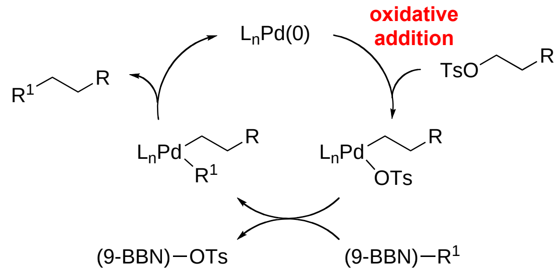
R_{alkyl}—OTs	(9-BBN)—R	Yield
n-Dodec—OTs	(9-BBN)Š*n*-Oct	80%
	(9-BBN)Š*n*-Oct	76%
NC$(CH_2)_8$OTs		64%
TsO$(CH_2)_{12}$OTs	(9-BBN)Š*n*-Oct	73%
		63%

Conditions:

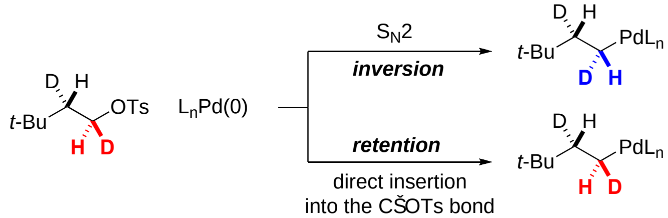
4% $Pd(OAc)_2$
16% $P(t\text{-}Bu)_2Me$
1.2 NaOH
dioxane, 50 C

Matt Netherton

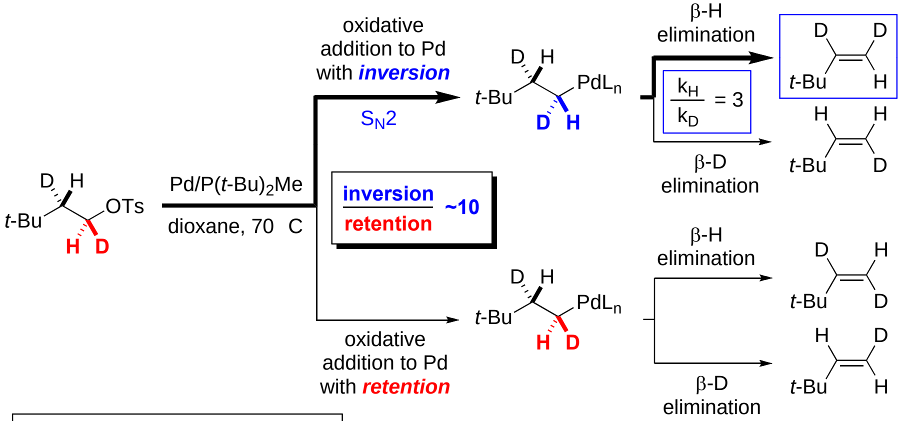
Suzuki Cross-Couplings of Alkyl Tosylates: *Mechanism*



What is the stereochemistry of the oxidative addition step?



Suzuki Cross-Couplings of Alkyl Tosylates: *Mechanism of Oxidative Addition*

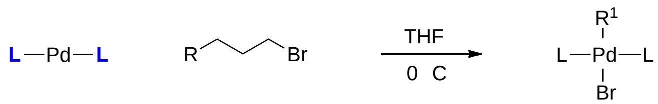


In the absence of a coupling partner, β-H/β-D elimination occurs

Reactions of alkyl bromides also proceed with predominant inversion of configuration

Matt Netherton

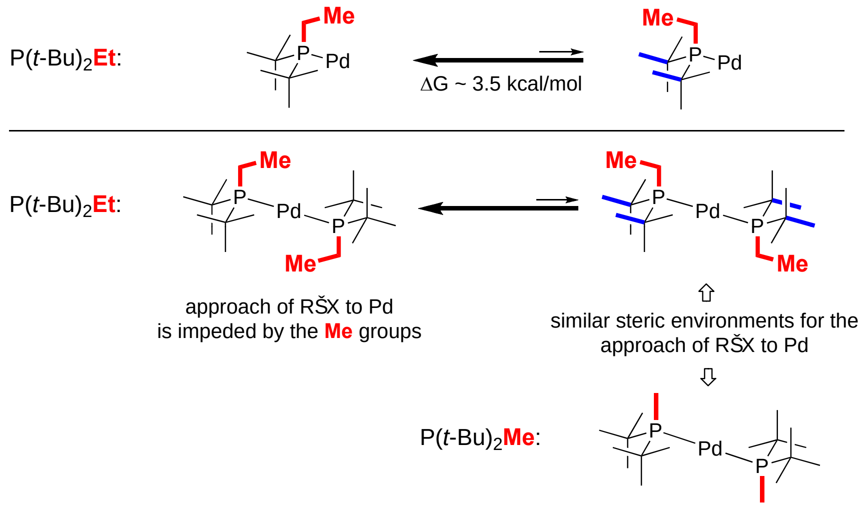
Oxidative Addition to PdL_2: *Rate as a Function of the Trialkylphosphine*



L	Conversion after 1.0 h	2.0 h	3.0 h	ΔG^a (kcal/mol)
$P(t\text{-}Bu)_2$**Me**	30%	47%	57%	**19.5** (0 C)
PCy_3	8%	12%	15%	20.0 (0 C)
$P(t\text{-}Bu)_2$**Et**	0%	0%	0%	**25.4** (60 C)
$P(t\text{-}Bu)_3$	0%	0%	0%	>28.4 (60 C)

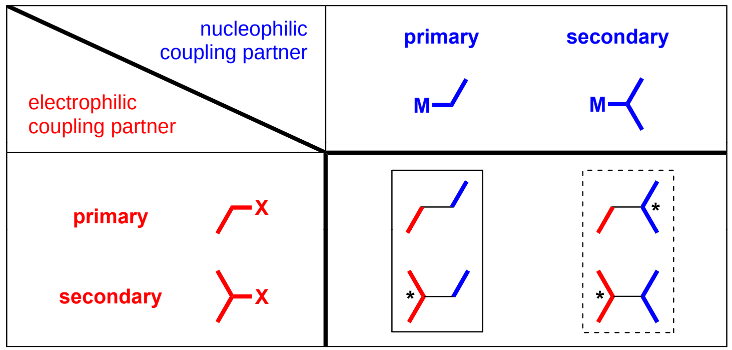
Ivory Hills

DFT Calculations (B3LYP):
The Difference Between P(t-Bu)$_2$Et and P(t-Bu)$_2$Me

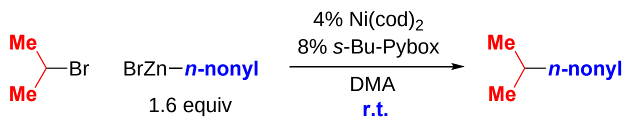


Ivory Hills

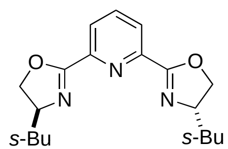
Nickel-Catalyzed Cross-Couplings of Alkyl Electrophiles:
Broader Scope and Asymmetric Reactions



Nickel-Catalyzed Cross-Couplings of Secondary Alkyl Bromides:
Negishi Reactions at Room Temperature



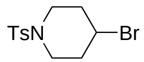
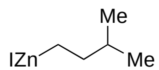
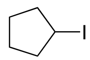
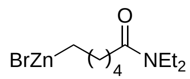
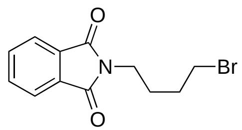
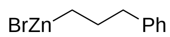
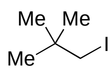
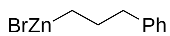
Change from above conditions	Yield
none	91%
no Ni(cod)$_2$	<5%
no *s*-Bu-Pybox	<5%
Pd(OAc)$_2$ or Pd$_2$(dba)$_3$	<5%
P(*t*-Bu)$_3$, P(*t*-Bu)$_2$Me, PCy(1-pyrrolidinyl)$_2$, 1,3-bis(1-adamantyl)imidazol-2-ylidene	<5%



Steve Zhou

Nickel-Catalyzed Negishi Cross-Couplings
of Secondary and Primary Alkyl Bromides and Iodides

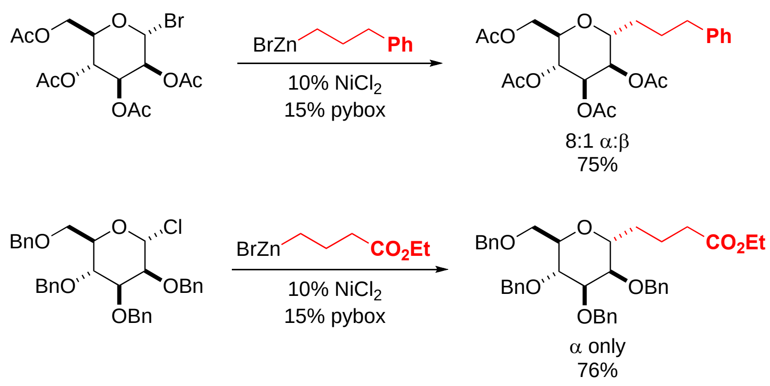
R−X + YZn−R^1 (1.6 equiv) → R−R^1 (4% Ni(cod)$_2$/8% *s*-Bu-Pybox, DMA, r.t.)

R−X	YZn−R^1	Yield
		66%
		78%
		65%
		73%

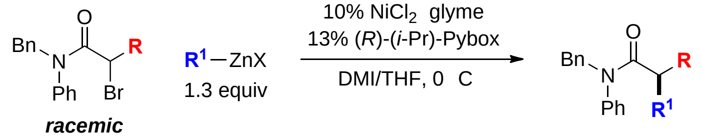
Steve Zhou

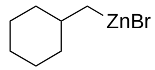
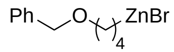
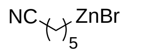
Nickel-Catalyzed Negishi Reactions of Secondary Alkyl Halides: *Use by Others*

Synthesis of C-alkyl glycosides (Gagne, 2007)



Asymmetric Cross-Couplings of Secondary Alkyl Halides: *Stereoconvergent Negishi Reactions of α-Bromoamides*

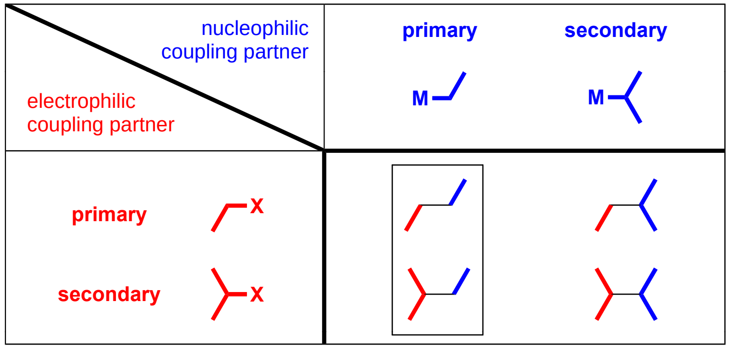


R	R^1–ZnX	Yield	ee
Et	Hex–ZnBr	90%	96%
Et		58%	92%
i-Bu	MeZnI	78%	87%
Et		77%	96%
Et		70%	93%

$NiCl_2$ glyme and (R)-(i-Pr)-Pybox: commercially available
Can be run under air

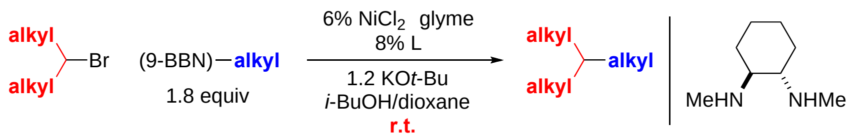
Christian Fischer

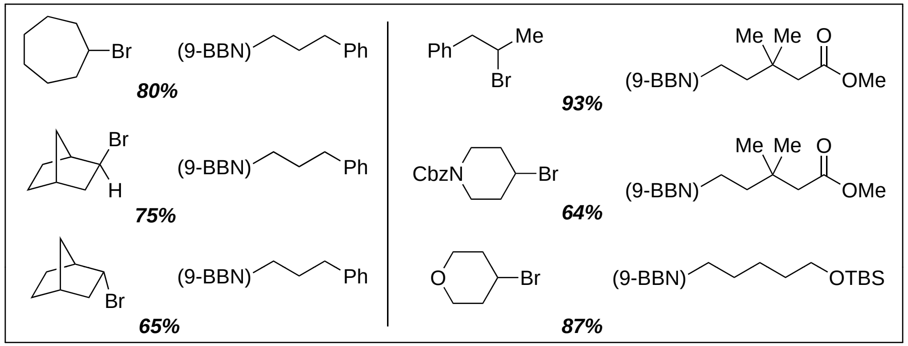
Nickel-Catalyzed Suzuki Cross-Couplings of Primary and Secondary Alkyl Electrophiles



M = *boron ??*

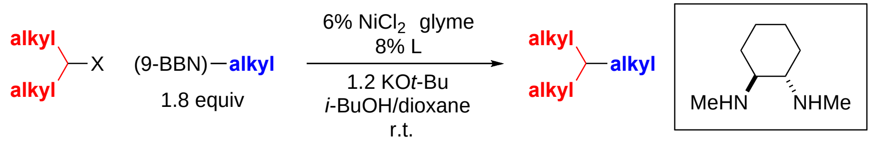
Nickel-Catalyzed Suzuki Reactions of Secondary Alkyl Bromides

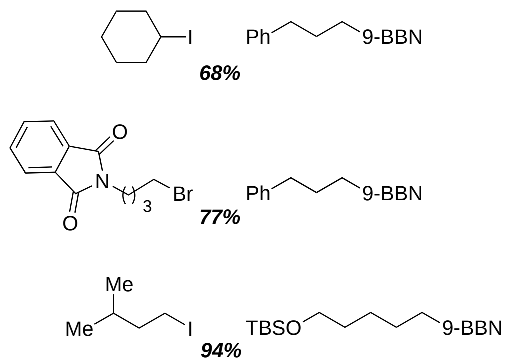


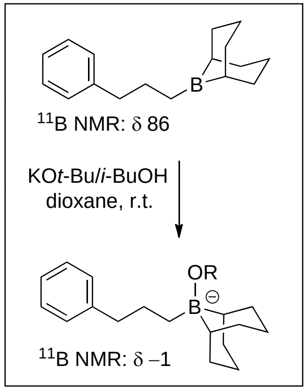


Bunnai Saito

Suzuki Reactions of Secondary and Primary Alkyl Electrophiles

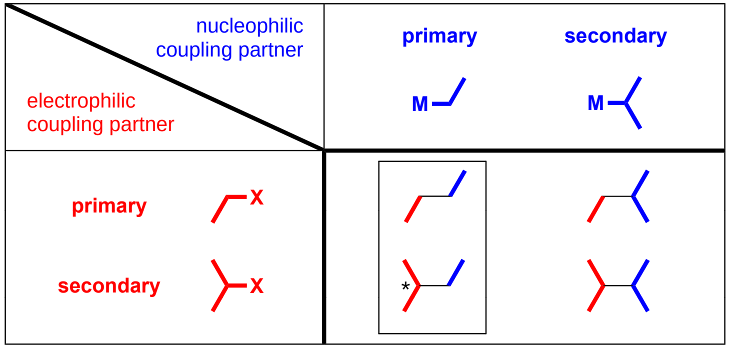






Bunnai Saito

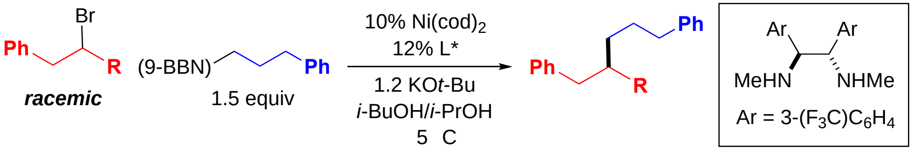
Asymmetric Suzuki Cross-Couplings: *Unactivated Secondary Alkyl Electrophiles as Substrates?*



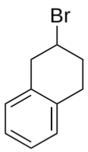
For **M = Zn** (Negishi):  = ***activated*** electrophile for asymmetric reactions:

α-halocarbonyl
allylic halide
benzylic halide

Asymmetric Suzuki Reactions of Unactivated Alkyl Halides: *Homobenzylic Bromides as Electrophiles*



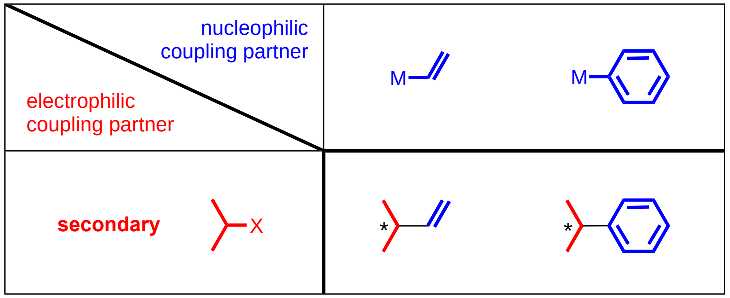
	Yield	ee
R = Me	79%	**90%**
n-Bu	62%	**94%**
i-Pr	59%	**83%**
CH_2CH_2Ph	68%	**90%**
CH_2**O**Bn	69%	**40%**



<5% ee

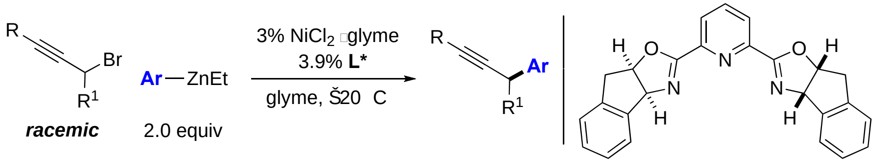
Bunnai Saito

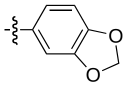
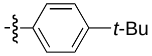
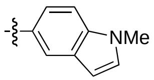
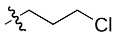
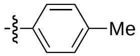
Asymmetric Cross-Couplings of Secondary Electrophiles with Vinyl- and Arylmetal Reagents



Negishi (Zn)
Hiyama
Kumada
Negishi (Zr)
Suzuki
Stille

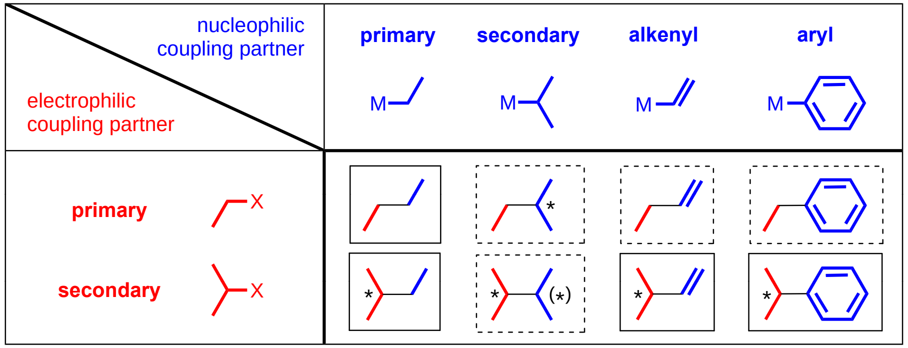
Catalytic Asymmetric Negishi Reactions: *Arylations of Propargylic Bromides*



R	R1	Ar	Yield	ee
TMS	*i*-Bu		71%	**93%**
TIPS	Et		81%	**93%**
Me	Et		78%	**89%**
t-Bu			81%	**92%**

Sean Smith

Palladium- and Nickel-Catalyzed Cross-Couplings of Alkyl Electrophiles



Current efforts: *more versatile catalysts*
asymmetric processes
mechanism studies