UNIVERSITY OF OXFORD

Nickel-Catalyzed Cross-Coupling Reactions

Activation of phenolic C-O bond

Felix Urbitsch
23/03/18

SBM

Nickel

• derived from mischievous spirit of German miner mythology Nickel who represeented the fact that copper-nickel ores resisted the refinement into copper

•Nickel is one of the 4 ferromagnetic elements at rt (iron, cobalt, gadolinium), alnico permanent magnets in strentgh in between iron magnets and rare earth metal magnets

• consumption: 68 % stainless steel, plating, electrodes,...

•Recently: battery industry

•Money: 50p coin 75% copper, 25 % Nickel

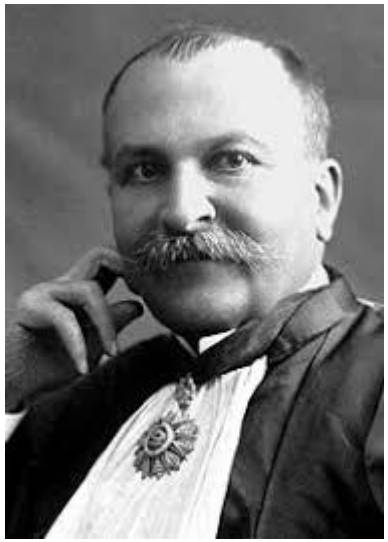
Catalysis

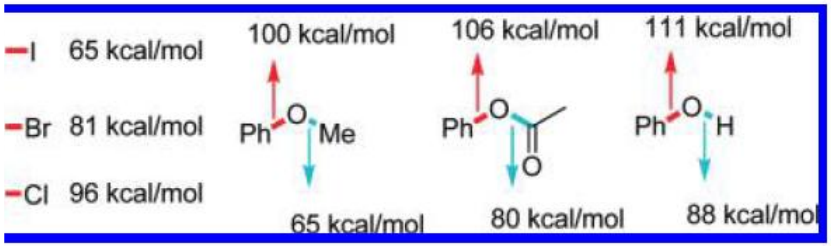
Nickel

•Isolated 1751, Cronstedt

•1912: Nobel prize Sabatier, ethylene hydrogenation Ni/H2

•Wilke: seminal contributions, reactions known: allylation, oligomerisation, cycloisomerisation, red. coupling





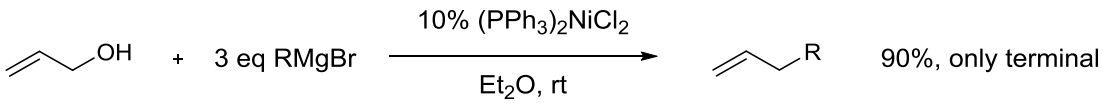
Accc .Chem. Res,, **2010**, 1486

Structure

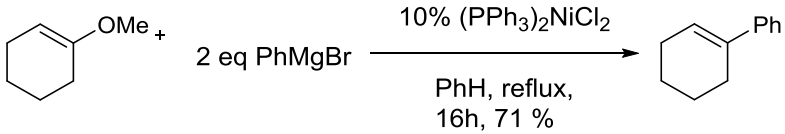
1. **Hard nucleophiles**
2. Boronic acids
3. Reductions & mechanistic discussion
4. Outlook

The Beginning

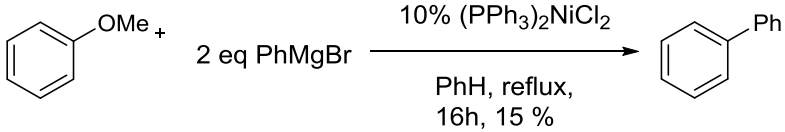
- allyllic C-O insertion known since 1977 Swierczewski



- activation of C(sp^2)-O:
  - Wenkert, 1979

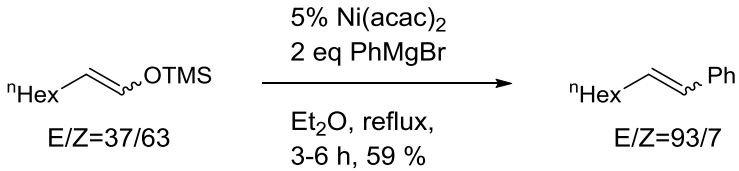


  - Wenkert, 1984



also tolerates RMgBr (lower yield)

  - Kumada, 1981

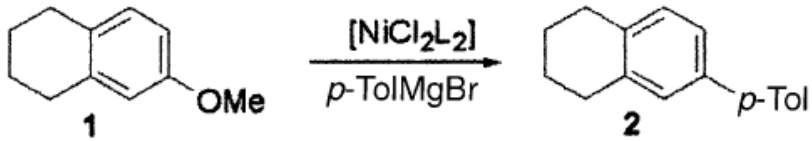


J. Organomet. Chem., **1977**,, 371
JACS, **1979**, 2246
JOC, **1984**, 4894
TL, **1980**, 3915

The Beginning

- Dankwardt, 2004

Table 3: Ni-catalyzed cross-coupling of **1**: Optimization of the phosphane.[a]



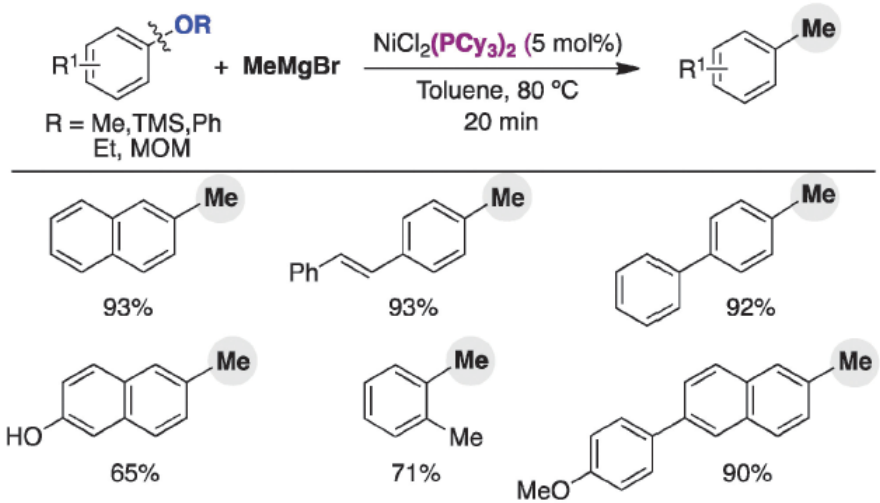
Entry	L	Recovd. **1** [%]	Conv. **2** [%]
1	PMe_3	33	33
2	PEt_3	75	7
3	$PiBu_3$	32	42
4	$PiPr_3$	<1	82
5	PCy_3	0	93
6	$PhPCy_2$	<1	92
7	Ph_2PCy	7	81
8	Ph_3P	74	15

[a] Reactions were carried out at 60 °C in iPr_2O for 15 h with 5 mol% nickel catalyst. Conversions were determined by GC analysis with tridecane as an internal standard.

ACIE, **2004**, 2428

Extension to Methyl

- Shi, 2008

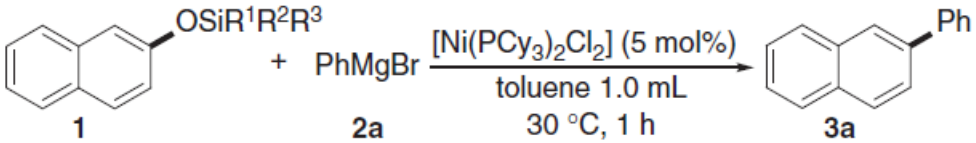


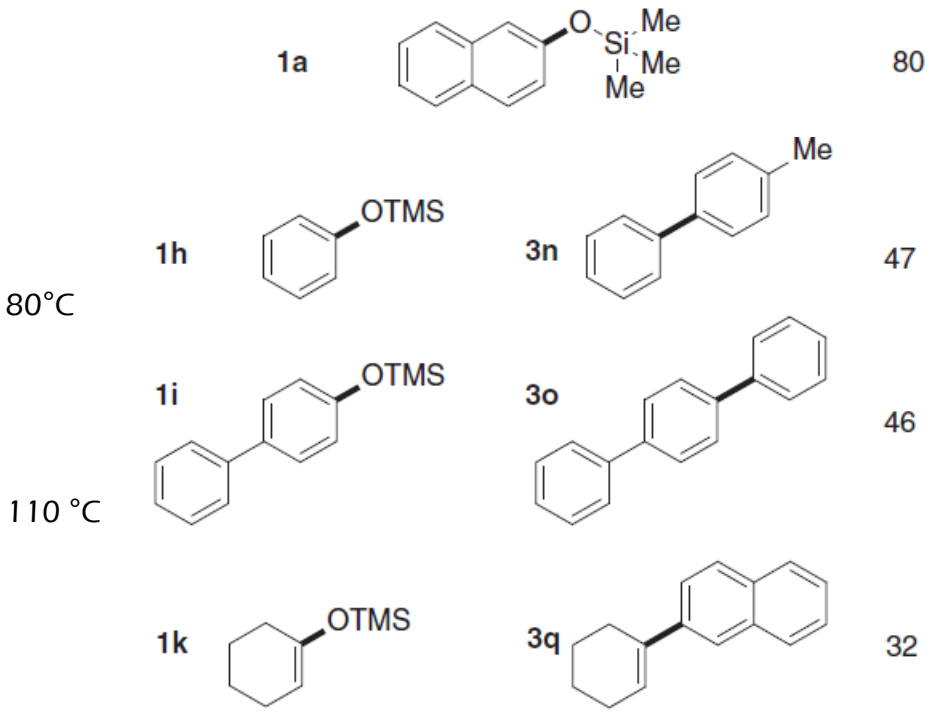
1.2 eq of MeMgBr

Chem Comm, **2008**, 1437

Extension to Aryl-Silyl-Ethers

- Shi, 2011



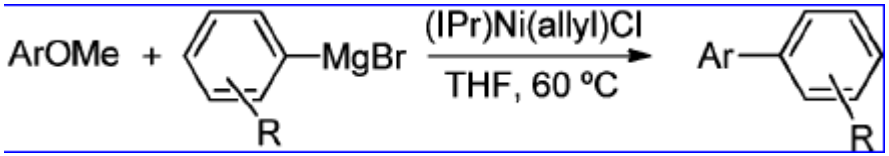


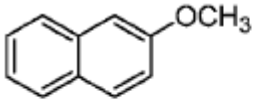
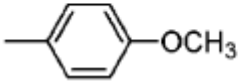
„The π-problem“
Tobisu, Chatani

CL, **2011**, 1001

Introducing NHC Ligands

- Prieto, Nicasio, 2012



aryl ether	R	time (h)	yield (%)[b]
	*p*-Me	24	94[c]
	H	24 12	76[c] 95

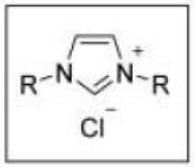
[a] Reaction conditions: aryl ether (0.5 mmol), ArMgBr (0.75 mmol), nickel complex (5 mol %), total volume of THF (1 mL). [b] Isolated yields.

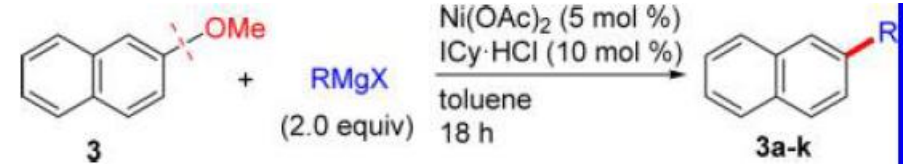
OL, **2012**, 4318

NHC Ligands – An Example

- Tobisu, Chatani, 2015

1	PCy_3	0
2	IMes·HCl (R = 2,4,6-$Me_3C_6H_2$)	0
3	IPr·HCl (R = 2,6-^{i}$Pr_2C_6H_3$)	0
4	IMe·HCl (R = Me)	4
5	I^{i}Pr·HCl (R = ^{i}Pr)	29
6	ICy·HCl (R = cyclohexyl)	62
7	I^{t}Bu·HCl (R = ^{t}Bu)	0



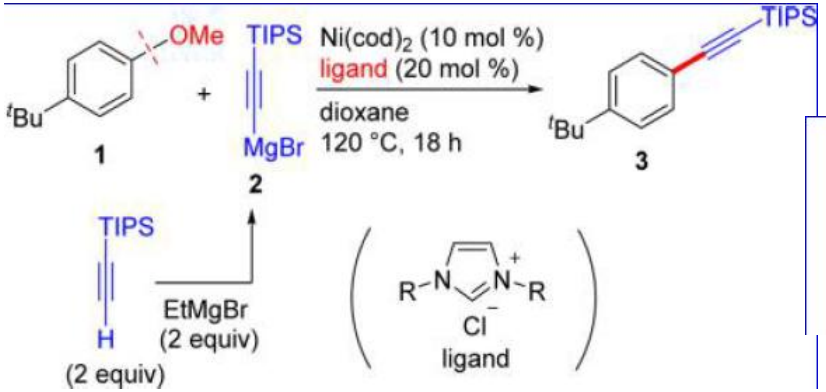


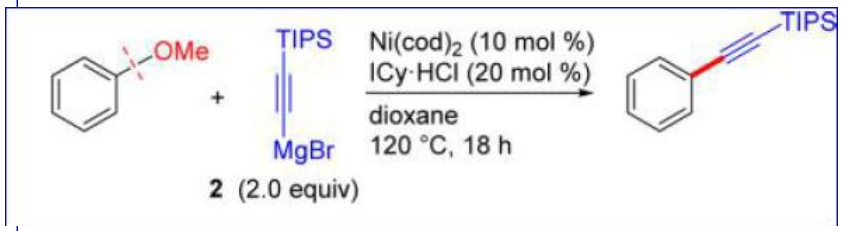
entry	Grignard reagent	temperature (°C)	yield (%)[b]
1	Me_3SiCH_2MgCl (**2a**)	rt	92
2	^{t}$BuCH_2MgBr$ (**2b**)	rt	>99
3	CH_3MgBr (**2c**)	100	96[c]
4	$PhCH_2MgBr$ (**2d**)	100	96

OL, **2015**, 4352

Alkynyl-Grignards

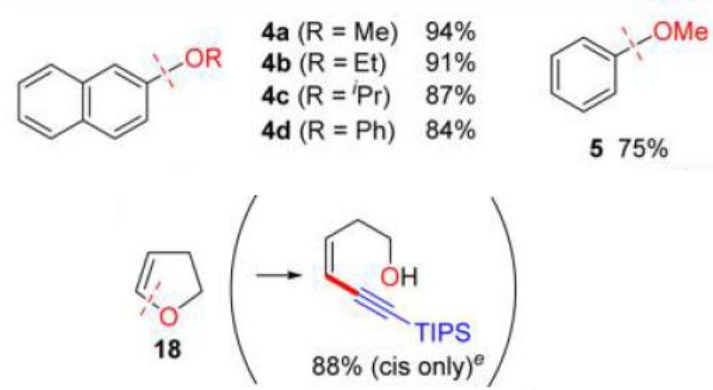
- Tobisu, Chatani, 2015





entry	ligand	GC yield of 3 (%)
1	PCy_3	0
2	IMes·HCl (R = 2,4,6-$Me_3C_6H_3$)	8
3	IPr·HCl (R = 2,6-$^iPr_2C_6H_4$)	<5
4	IMe·HCl (R = Me)	7
5	I^iPr·HCl (R = ^iPr)	38
6	ICy·HCl (R = Cy)	76 (70)[b]
7	I^tBu·HCl (R = ^tBu)	45

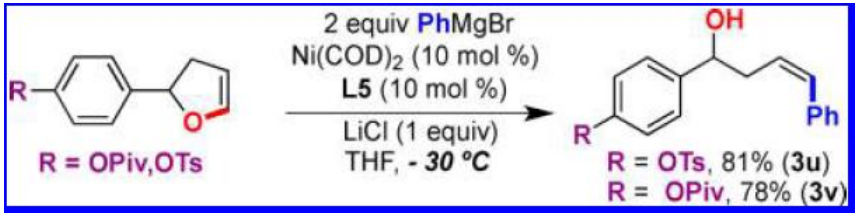
[a]Reaction conditions: 1a (0.25 mmol), 2 (0.50 mmol), $Ni(cod)_2$ (0.025 mmol), and ligand (0.050 mmol) in dioxane (0.50 mL) at 120 °C for 18 h. [b]Isolated yield.

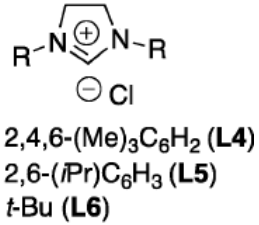


OL, **2015**, 680

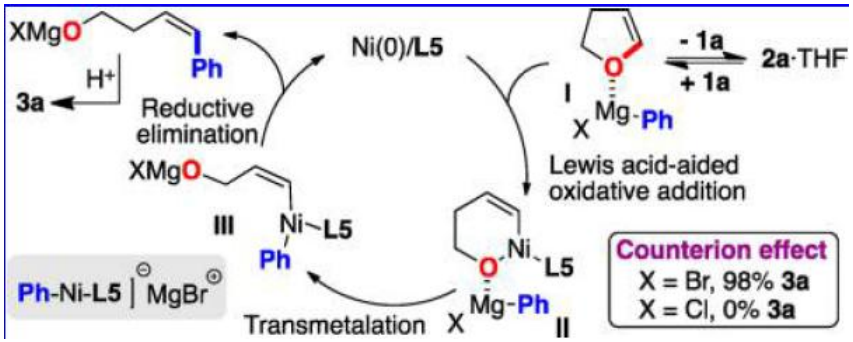
Very Low Temperature Process

- Martin, 2013





(a) reaction conducted at −40 °C;



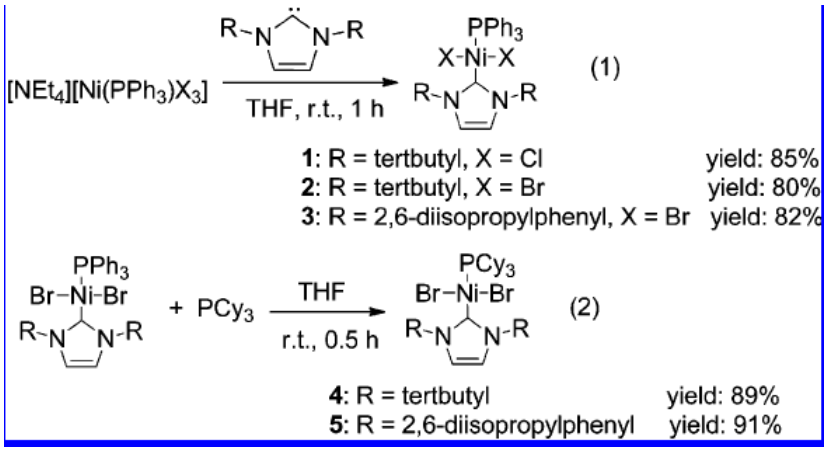
OL, **2013**, 6298

Mixed NHC-Phosphine-Ligand

- Sun, 2015

entry	complex (mol %)	T (h)	yield (%)
1	**1** (1)	10	2
2	**2** (1)	10	3
3	**3** (1)	10	10
4	**4** (1)	10	99 (98)[b]
5	**5** (1)	10	90
6	$Ni(PCy_3)_2Cl_2$ (1)	10	82
7	$Ni(PCy_3)_2Br_2$ (1)	10	86
8	$Ni(IPr)_2Br_2$ (1)	10	21

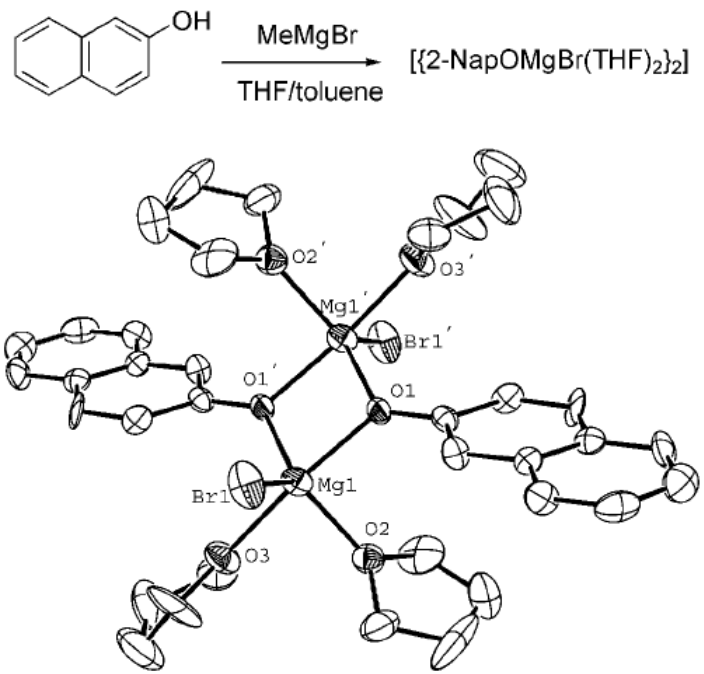
[a]Reaction conditions: 2-methoxynaphthalene (1.0 mmol), 4-MeC_6H_4MgBr (1.5 mmol, 1.0 M in THF) was added in one portion, THF (total volume: 2.0 mL), 25 °C, GC yield using *n*-hexadecane as internal standard, average of two trials. [b]Isolated yield.

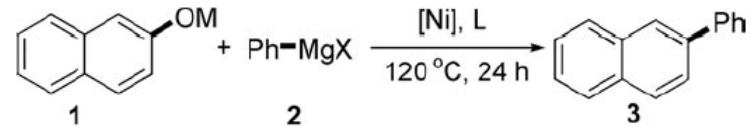


Organometallics, **2015**, 5792

You're nickel'd pal!

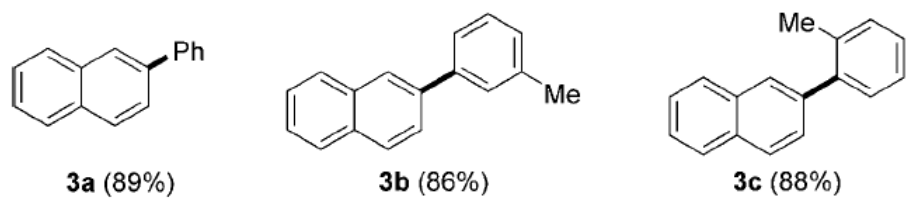
- Shi, 2010





M = Li, X = Br, 8%
M = K, X = Br, 14%
M = Mg, X = Cl, 64%
M = Na, X = Br, 81%
M = Mg, X = Br, 100%
M = Mg, X = I, 87%

Figure 3. Coupling reaction of 2-naphtholate and PhMgX (GC yield). TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.

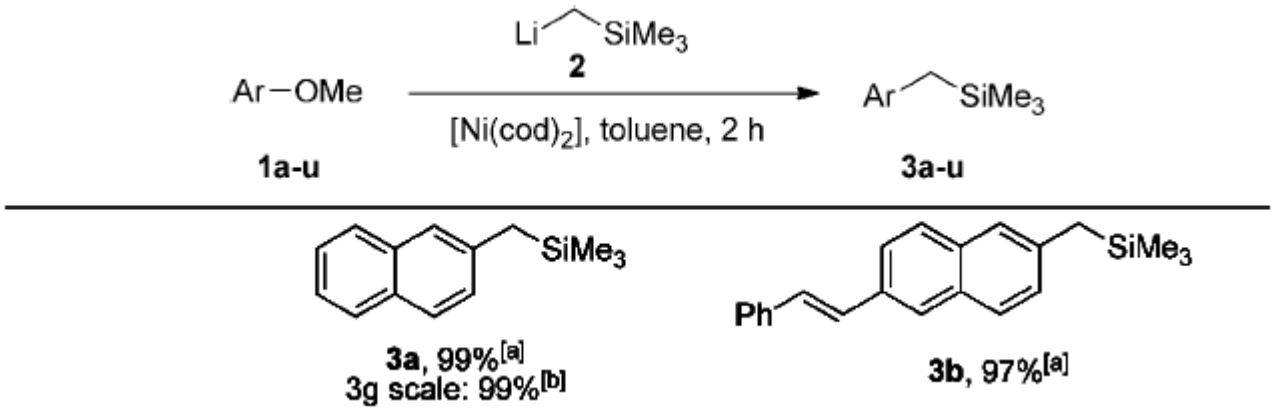


Scheme 1. Biaryl products synthesized from naphthol with various aryl Grignard reagents by nickel catalysis. Reaction conditions: **1** (0.2–0.4 mmol), NiF_2 (10 mol%), PCy_3 (40 mol%), MeMgBr (120 mol%), and ArMgBr **2** (200 mol%) in toluene (0.75 mL) and DIPE (0.25 mL), 120 °C, 24 hours. All reported yields are the avarage yields of at least two experiments.

ACIE, **2015**, 5792

Metals – How far can you push it

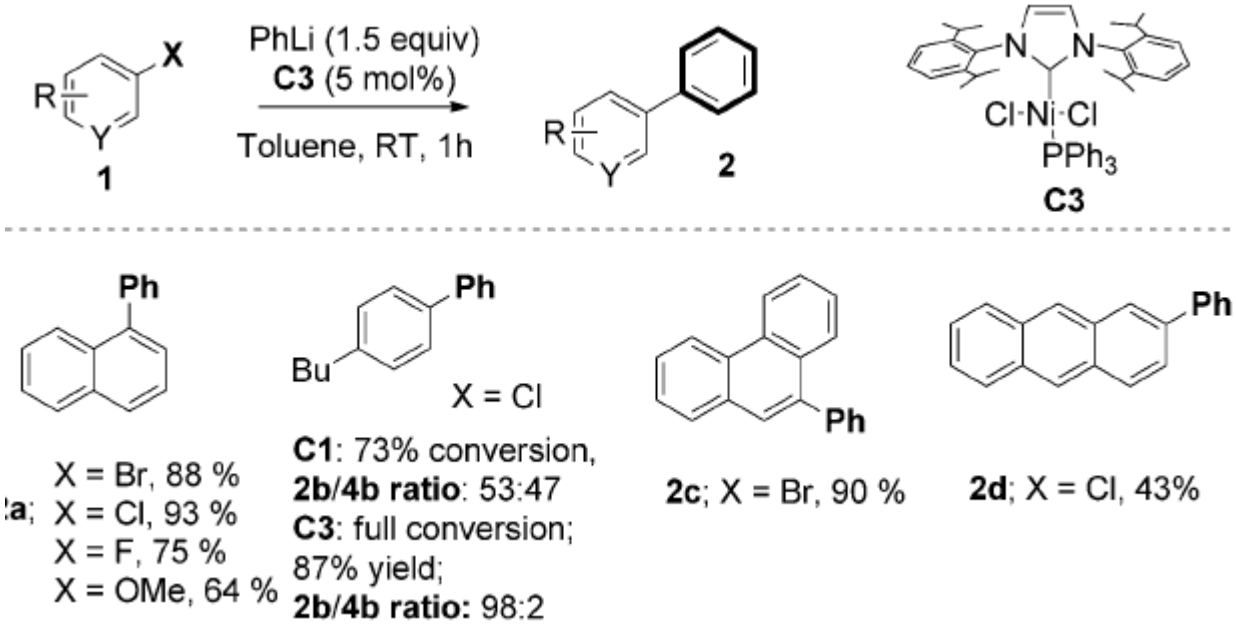
- Rueping, 2014



ACIE, **2014**, 12912

Metals – How far can you push it

- Feringa, 2016

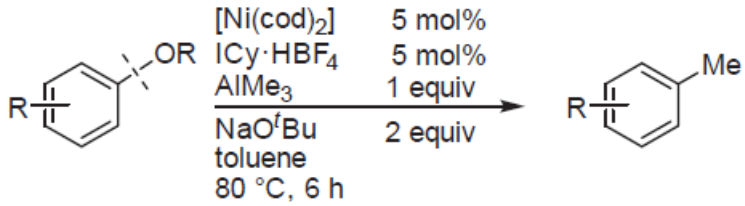


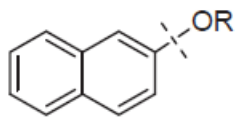
ACIE, **2016**, 3991

Metals – How far can you push it

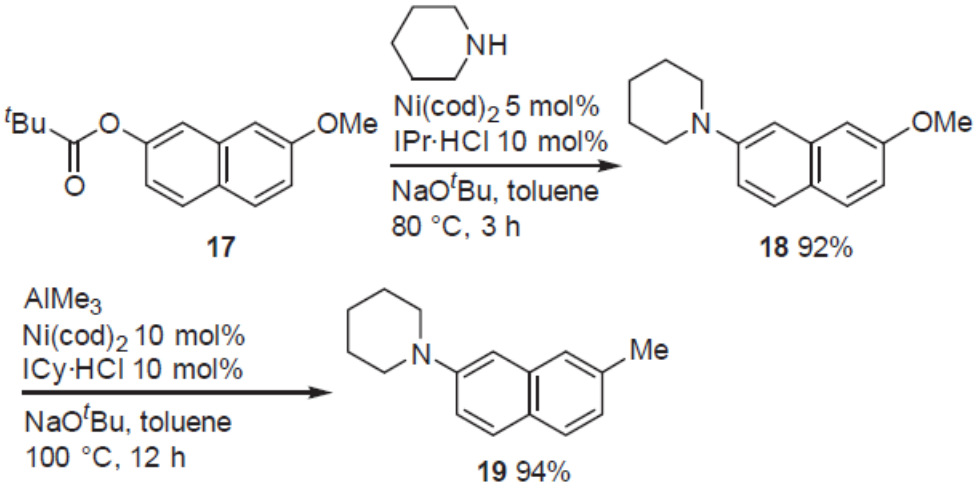
- Tobisu, Chatani, 2015

Table 2. Substrate scope[a]





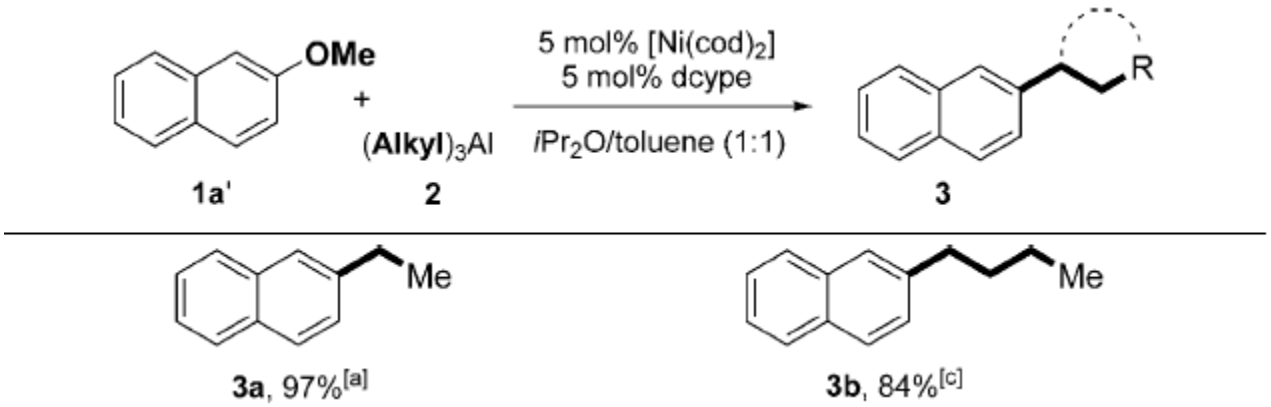
3a (R = Me) 92%[b]
3b (R = Et) 94%[b]
3c (R = $^{n}C_8H_{17}$) 96%[b]
3d (R = ^{i}Pr) 94%[b]
3e (R = Ph) 31%[b]



Organometallics, **2015**, 5792

Metals – How far can you push it

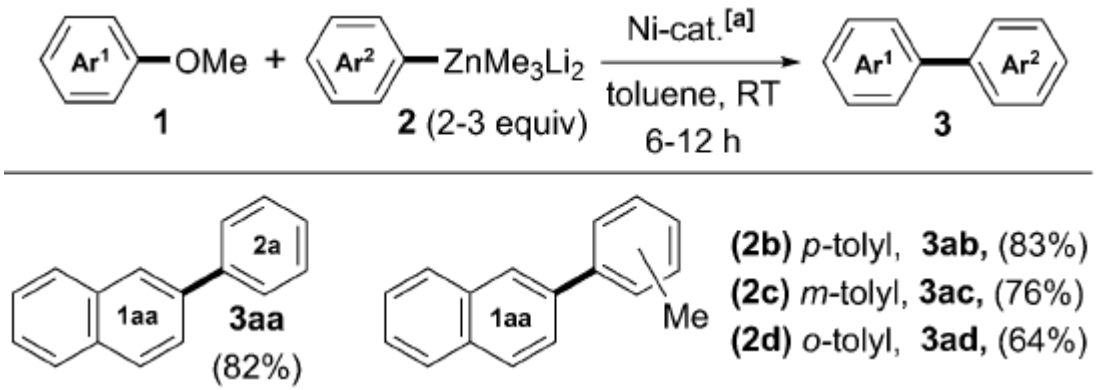
- Schoenebeck, Rueping, 2016



ACIE, **2016**, 6093

Metals – How far can you push it

- Uchiyama, 2012



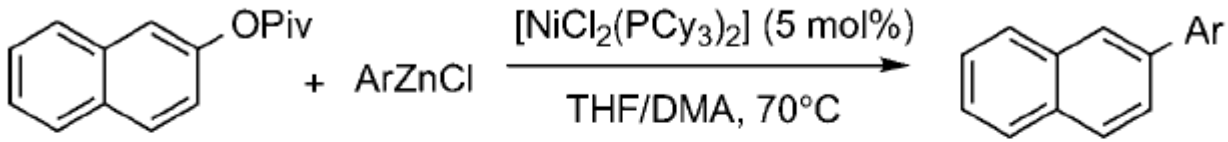
Scheme 3. Cross-coupling of aromatic ethers with aryl zincates. [a] $[NiCl_2(PCy_3)]$ (4 mol%) or $[Ni(cod)_2]$ (4 mol%)/PCy_3 (8 mol%) was used as a catalyst. Isolated product yields are given in brackets.

CEJ, **2012**, 3482

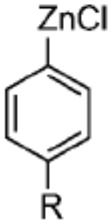
Metals – How far can you push it

- Shi, 2008

Table 2: Nickel-catalyzed C–C bond formation with various arylzinc reagents.[a]



1c **2** **3**

Entry	ArZnCl		Product (yield [%])[b]
1		R = H, **2a**	**3a** (84)
2		R = Me, **2b**	**3b** (80)
3		R = OMe, **2c**	**3c** (85)
4		R = CH_2OMe, **2d**	**3d** (66)

- 3 eq ArZnCl

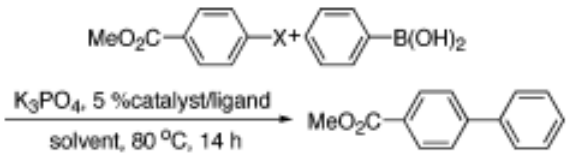
ACIE, **2008**, 10124

Structue

1. Hard nucleophiles
2. Boronic acids
3. Reductions & mechanistic discussion
4. Outlook

- Percec, 2004

TABLE 1. Influence of Leaving Group, Catalyst, Ligand, and Solvent on the Ni(II)-Catalyzed Cross-Coupling Reaction



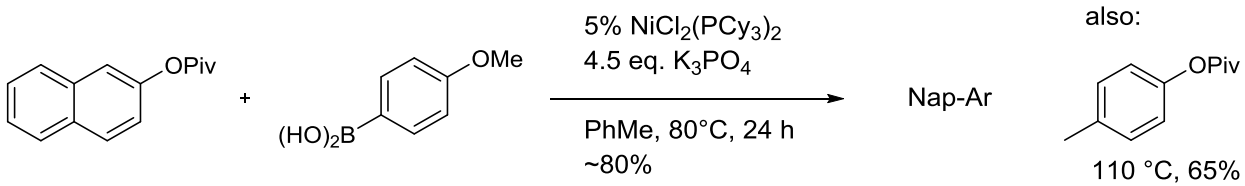
				solvent and conv (%)	
entry	X	catalyst	ligand/%	dioxane	PhMe
1	Cl	$NiCl_2(PCy_3)_2$	PCy_3/10	>95	>95
2	Cl	$NiCl_2(PPh_3)_2$	PPh_3/10	19	95
3	Cl	$NiCl_2$(dppe)	dppe/5	91	>95, 92[a]
4	Cl	$NiCl_2$(dppb)	dppb/5	80	10
5	Cl	$NiCl_2$(dppf)	dppf/5	>95	87
6	OMs	$NiCl_2(PCy_3)_2$	PCy_3/10	>95	22
7	OMs	$NiCl_2(PPh_3)_2$	PPh_3/10	18	88
8	OMs	$NiCl_2$(dppe)	dppe/5	>95	77, 70[a]
9	OMs	$NiCl_2$(dppb)	dppb/5	70	50
10	OMs	$NiCl_2$(dppf)	dppf/5	57	12
11	OTs	$NiCl_2(PCy_3)_2$	PCy_3/10	95	52
12	OTs	$NiCl_2(PPh_3)_2$	PPh_3/10	24	75
13	OTs	$NiCl_2$(dppe)	dppe/5	82	87
14	OTs	$NiCl_2$(dppb)	dppb/5	traces	50
15	OTs	$NiCl_2$(dppf)	dppf/5	20	20

[a] Reactions carried out with 1 mol % of catalyst and 1 mol % of dppe.

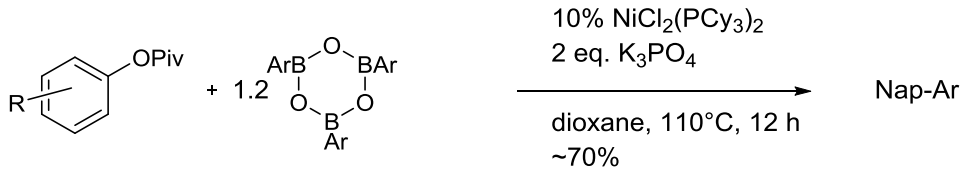
JOC, **2004**, 3447

Boron

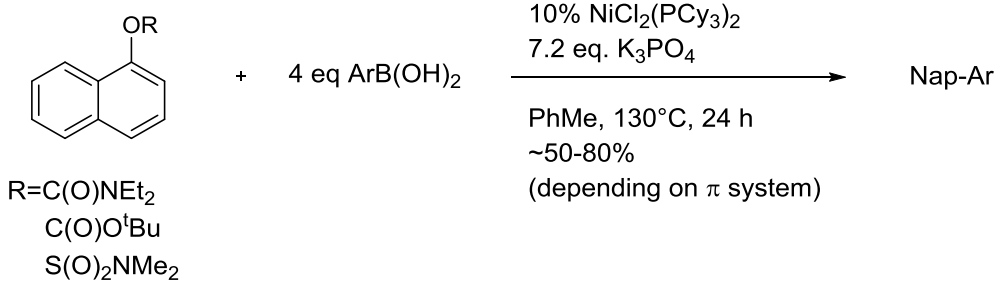
- Garg, 2008



- Shi, 2008



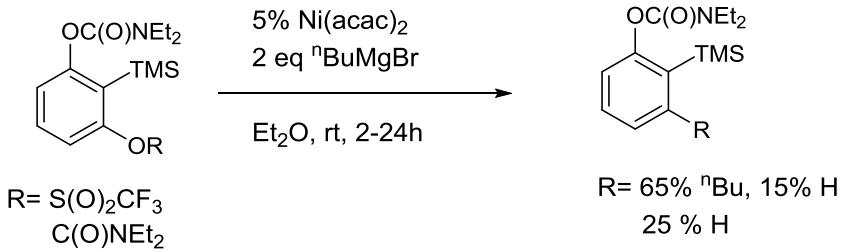
- Garg, 2009



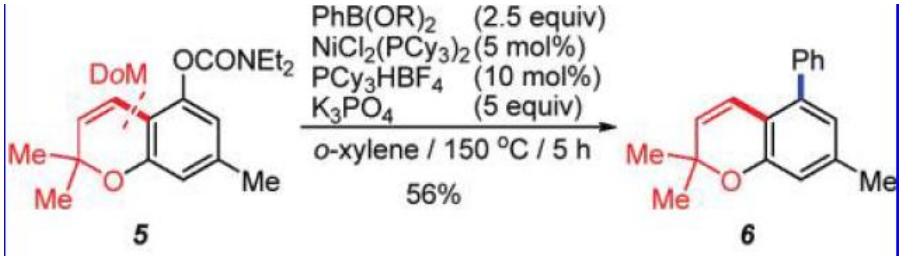
JACS, **2008**, 14422
JACS, **2008**, 14468
JACS, **2009**, 17748

DOM and beyond

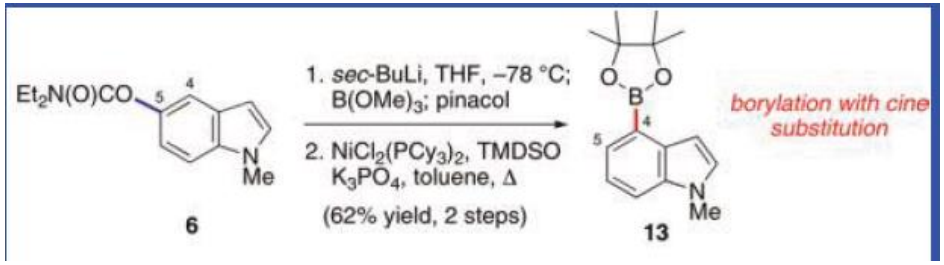
- Snieckus, 1992



- Snieckus, 2009



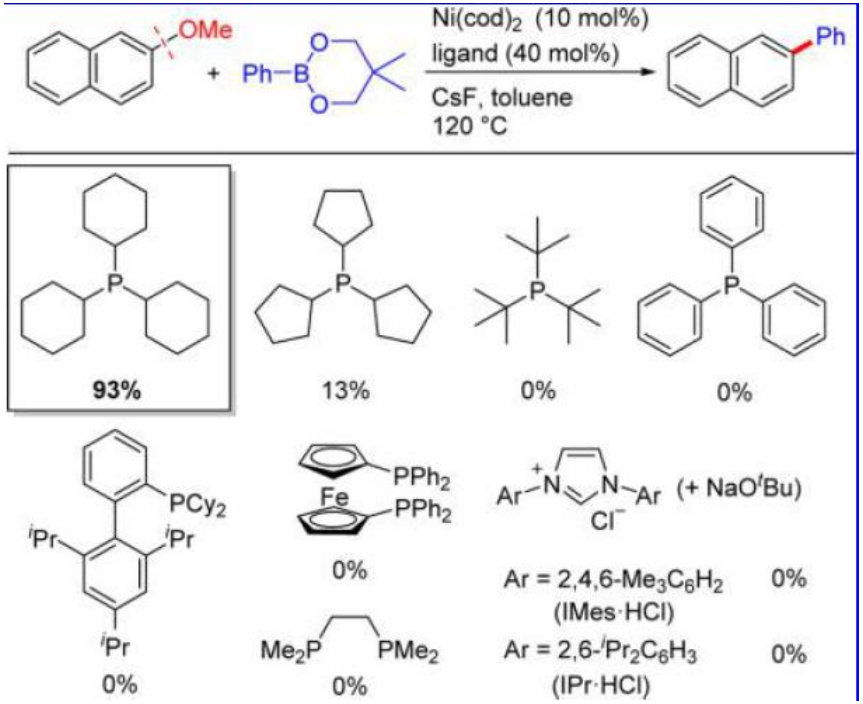
- Garg, 2012, 2918

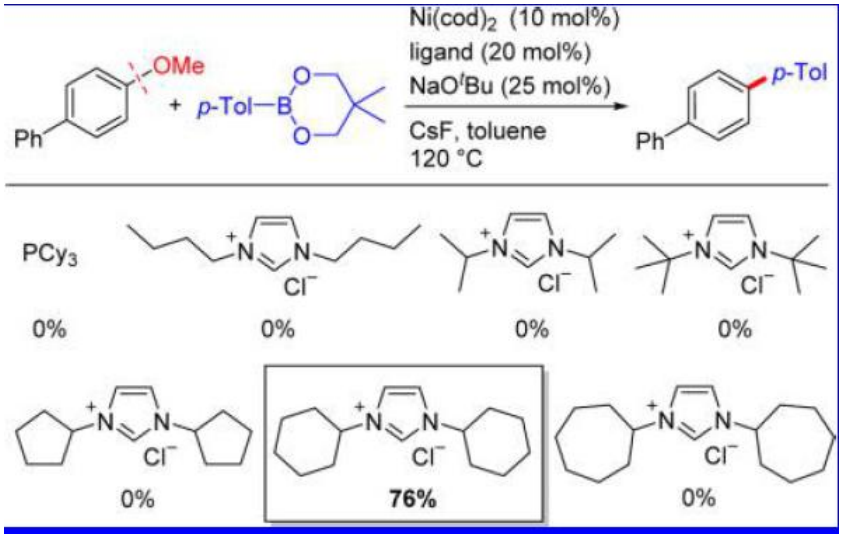


JOC, **1992**, 4006
JACS, **2009**, 17750
OL, **2012**, 2918

Ligands

- Chatani, 2008





ACIE, **2008**, 4866
Acc Chem Res, **2015**, 1717

Leaving groups

- Percec, 2012

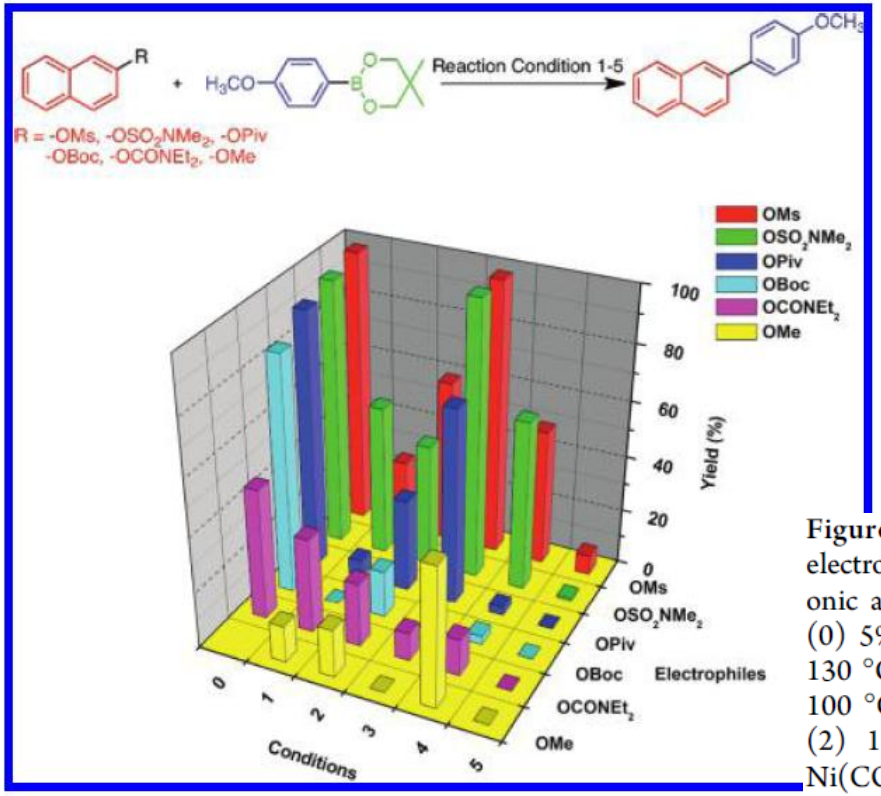
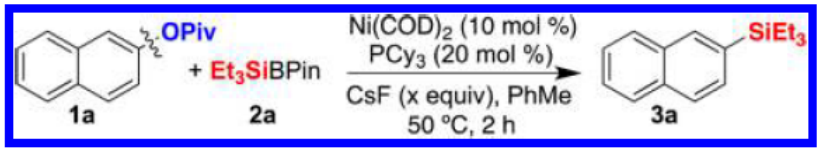


Figure 1. Comparison of the efficiency of 2-naphthyl C–O electrophiles in the cross-coupling reaction with 4-methoxyphenylboronic acid (0) and 4-methoxyphenyl neopentylglycolboronate (0–5): (0) 5%(pivalate), 10% (for the rest) $NiCl_2(PCy_3)_2/K_3PO_4$/toluene/130 °C[5a,6] except for OMs where 1% $NiCl_2(dppp)/K_3PO_4$/dioxane/100 °C was used;[3k] (1) 10% $NiCl_2(PCy_3)_2/K_3PO_4$/toluene/110 °C; (2) 10% $Ni(COD)_2$/40% PCy_3/K_3PO_4/toluene/120 °C; (3) 6% $Ni(COD)_2$/12% PCy_3/K_3PO_4/ THF/25 °C; (4) 10% $Ni(COD)_2$/40% PCy_3/CsF/toluene/120 °C; (5) 10% $NiCl_2(PCy_3)_2$/CsF/toluene/110 °C.

JOC, **2012**, 1018

Silylation

- Martin, 2014

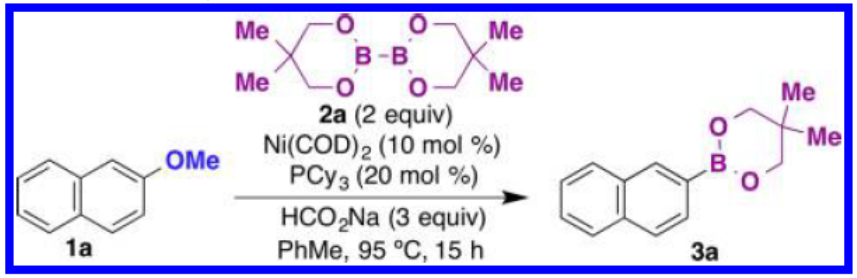


entry	Ni catalyst	CsF (x)	additive (mol %)	3a (%)[b]
1	$Ni(PCy_3)_2(C_2H_4)$	0	–	1
2	$NiCl_2(PCy_3)_2$	0	–	0[c]
3	$Ni(COD)_2$	0	–	11
4	$Ni(COD)_2$	0	CsF (30)	10
5	$Ni(COD)_2$	0	CsF (100)	10
6	$Ni(COD)_2$	0	AgF (30)	20
7	$Ni(COD)_2$	0	CuF_2 (30)	10
8	$Ni(COD)_2$	0	CuF_2 (50)	18[d]
9	$Ni(COD)_2$	0	CuF_2 (30)	0[e], 1[f], 24[g]
10	$Ni(COD)_2$	1	CuF_2 (30)	94(90)[h]
11	$Ni(COD)_2$	1	CuF_2 (30)	88 (85)[h,i]
12	$Ni(COD)_2$	1	AgF (30)	21
13	$Ni(COD)_2$	1	$CuBr_2$ (30)	0

JACS, **2014**, 1062

Borylation

- Martin, 2015



entry	deviation from standard conditions	yield 3a (%)[b]
1	none	88 (80)[c]
2	without $Ni(COD)_2$	0
3	without PCy_3	0
4	without HCO_2Na	42
5	PCy_2Ph instead of PCy_3	0
6	IPrHCl instead of PCy_3[d]	0
7	ICy-HBF_4 instead of PCy_3[d]	48
8	$NiCl_2(PCy_3)_2$ instead of $Ni(COD)_2/PCy_3$	0
9	$Ni(PCy_3)_2(C_2H_4)$ instead of $Ni(COD)_2/PCy_3$	61
10	$[Ni(PCy_3)_2]_2(N_2)$ instead of $Ni(COD)_2/PCy_3$	64
11	$PhCO_2Na$ instead of HCO_2Na	73
12	CsF instead of HCO_2Na	65
13	$B_2(pin)_2$ (2b) instead of $B_2(nep)_2$ (2a)	2

[a]Conditions: 1a (0.50 mmol), 2a (1.00 mmol), $Ni(COD)_2$ (10 mol %), PCy_3 (20 mol %), and HCO_2Na (1.50 mmol) in PhMe (2.0 mL) at 95 °C, 15 h. [b]GC yields using decane as internal standard. [c]Isolated yield. [d]+NaO*t*Bu (25 mol%).

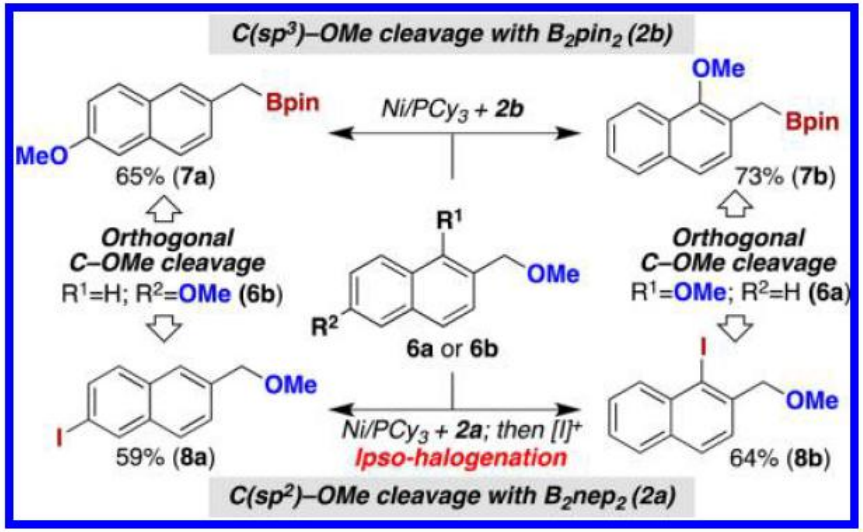


Figure 1. Orthogonal borylation via C–OMe cleavage. Conditions for $C(sp^3)$–OMe cleavage: **6a** or **6b** (0.50 mmol), **2b** (1.00 mmol), $Ni(COD)_2$ (10 mol %), PCy_3 (20 mol %), and CsF (1.50 mmol) in PhMe (2.0 mL) at 120 °C. Conditions for $C(sp^2)$–OMe cleavage: as for Table 1 (entry 1), followed by NaI (1.50 mmol) and chloramine T·$3H_2O$ (1.50 mmol) in 4 mL of THF/H_2O (1:1) at rt (1h). For **8a**, borylation was conducted at 120 °C. For **8b**, borylation was conducted with HCO_2Na (0.15 mmol).

JACS, **2015**, 6754

Quiz

A When heating o-Bromonitrobenzene with finely dispersed copper powder, one noticed that the latter lost its shine and got converted into a flat, grey mass. Upon work-up it became apparent that most of the copper got converted into cuprous bromide...

B In a study on Cyclopentadienequinone Albrecht reports the addition of cyclopentadiene to p-quinone. The resulting compounds which he names “Cyclopentadienequinone” and “Di-Cyclopentadienequinone” are assigned the following structural formula.

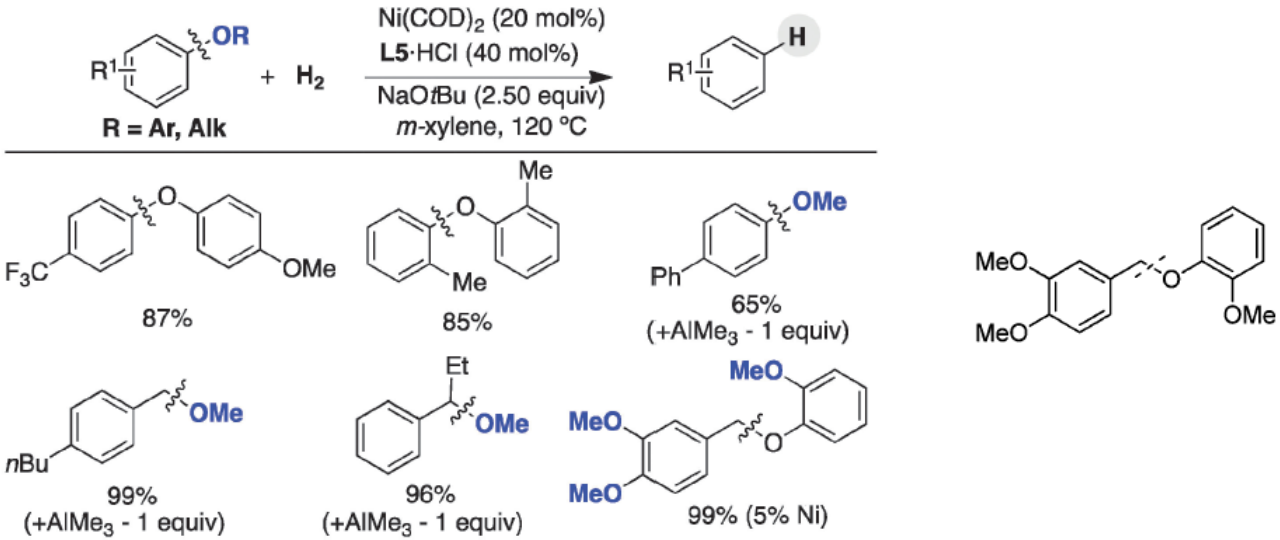
C This study presents a simplified route predicated on simple C–H functionalization logic that is enabled by a Cu-mediated oxidative phenol coupling that mimics the putative biosynthesis. This operationally simple macrocyclization is the largest of its kind and can be easily performed on gram scale

D Pyridinium chlorochromate, $C_5H_5NHCr0_3Cl$, a readily available, stable reagent, oxidizes a wide variety of alcohols to carbonyl compounds with high efficiency. It is easily and safely prepared by the addition of pyridine to a solution of chromium Rioxide in 8 g HCl followed by filtration to obtain the yellow-orange, air-stable solid.

1. Hard nucleophiles
2. Boronic acids
3. Reductions & mechanistic discussion
4. Outlook

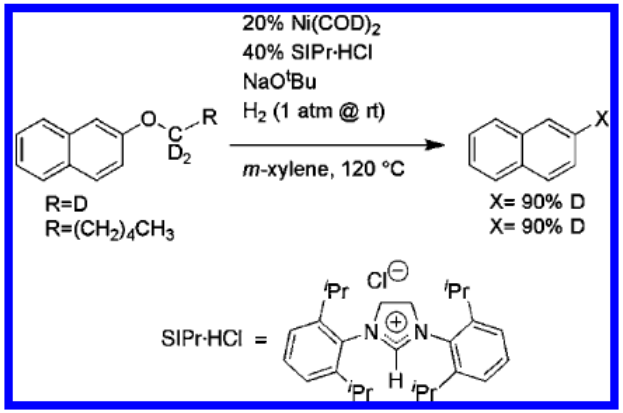
Reduction with H_2

- Hartwig, 2011



Scheme 26 Hartwig's Ni-catalyzed reductive cleavage of aryl or benzyl ethers.

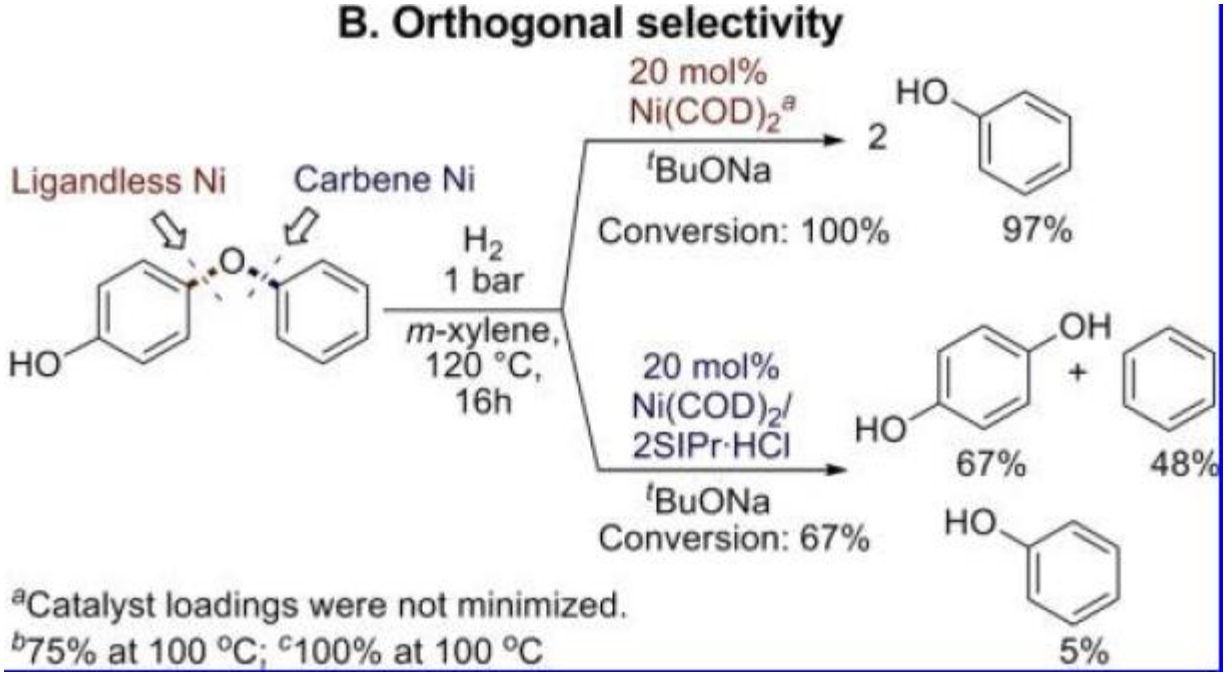
- Agapie, 2012



Science, **2011**, 439
JACS, **2012**, 5480

Reduction with H_2

- Hartwig, 2012

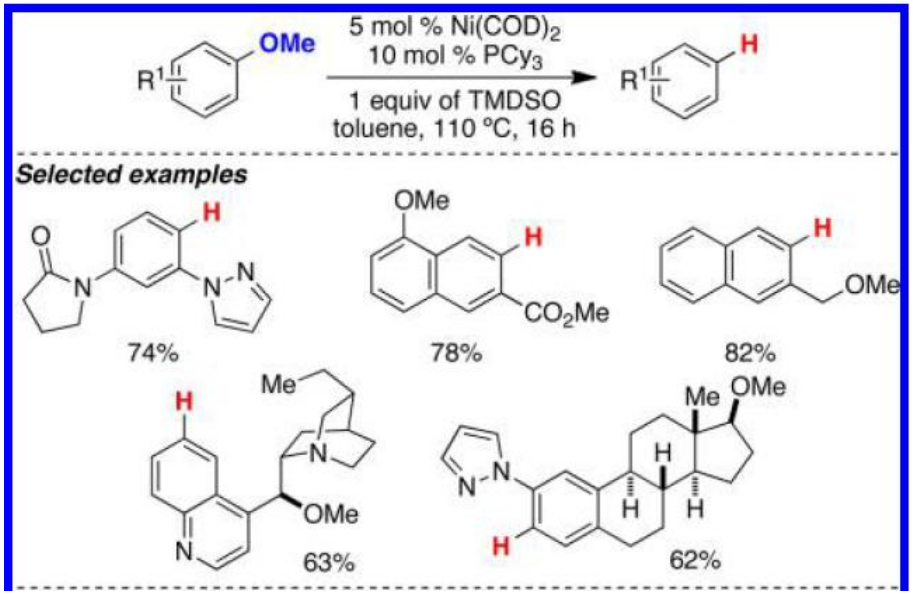


- Hartwig, 2016
  - Ni/C at 180 °C much higher performanc

JACS, **2012**, 20226
ACIE, **2016**, 1474

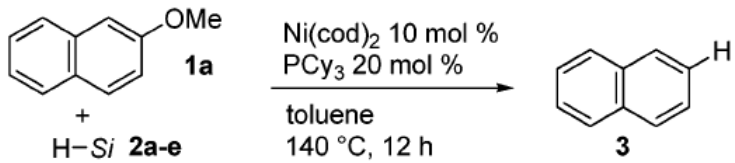
Reduction with Silane

- Martin, 2010



- Tobisu, 2011

Table 1 Optimization of reaction conditions[a]



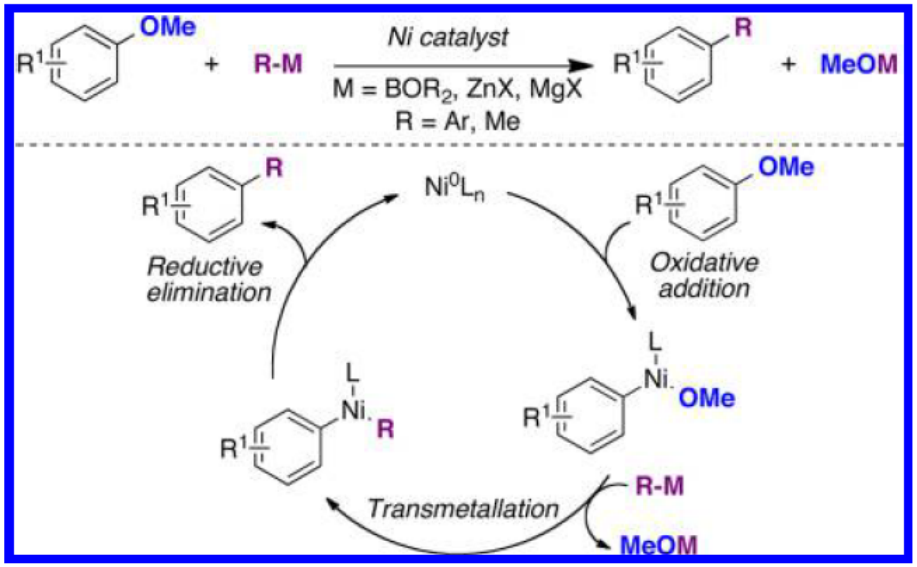
Entry	H–*Si*	Yield[b] (%)
1	$HSiEt_3$ (**2a**)	67 (49)[c]
2	$HSiMe_2tBu$ (**2b**)	12
3	$HSiMe_2Ph$ (**2c**)	46
4	$HSi(OEt)_3$ (**2d**)	91 (3)[c]
5	$HSiMe(OMe)_2$ (**2e**)	96 (95)[c]

JACS, **2010**, 17352
Chem Comm, **2011**, 2946

Mechanism of Silane Reduction

- Martin, 2013

Scheme 2. Accepted Mechanism for C–OMe Cleavage

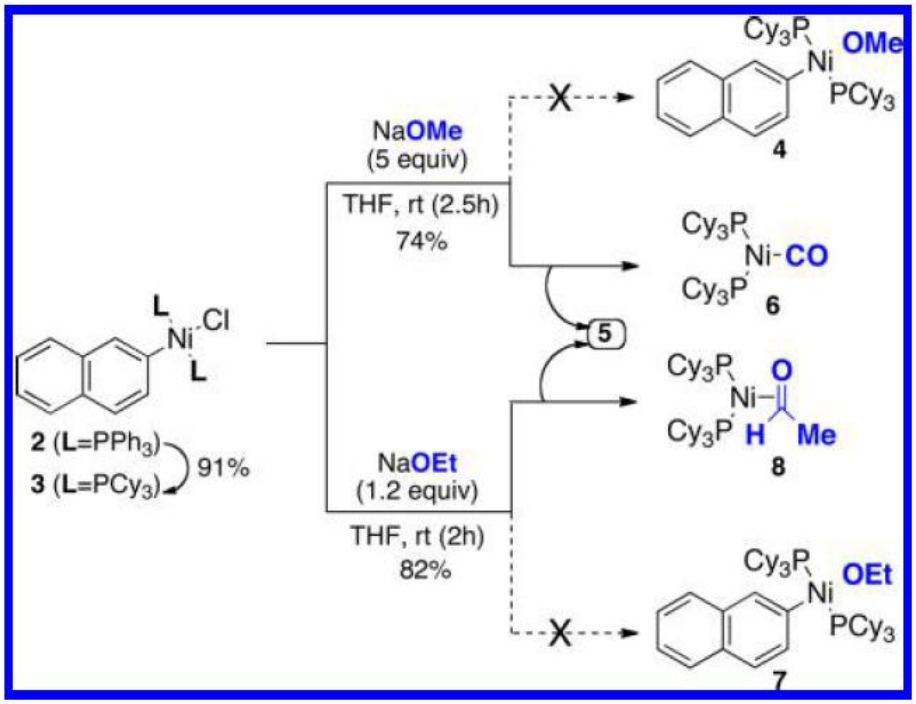


JACS, **2013**, 1997

Mechanism of Silane Reduction

- Martin, 2013

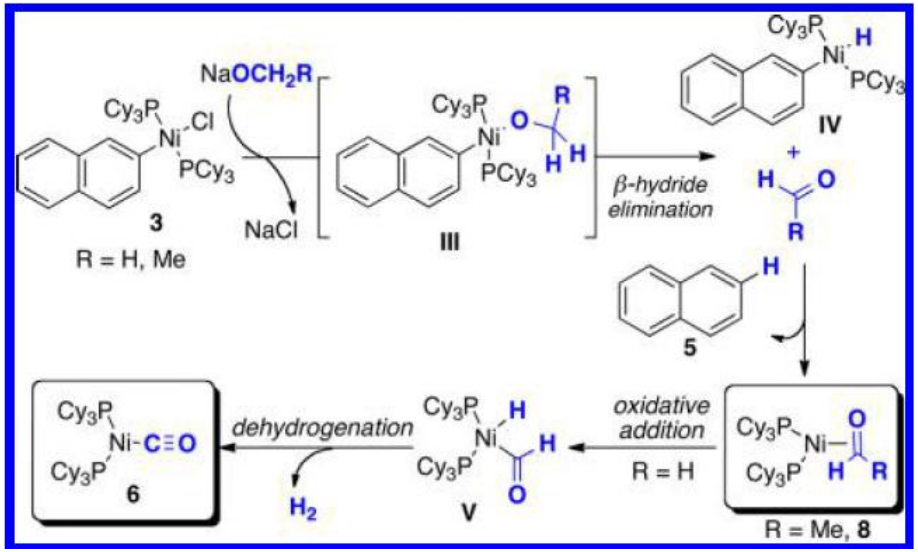
$$PCy_3 + Ni(cod)_2 \rightleftharpoons Ni(PCy_3)_2 + 2\ cod$$



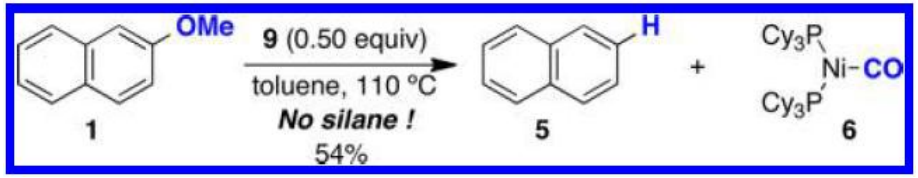
JACS, **2013**, 1997

Mechanism of Silane Reduction

- Martin, 2013



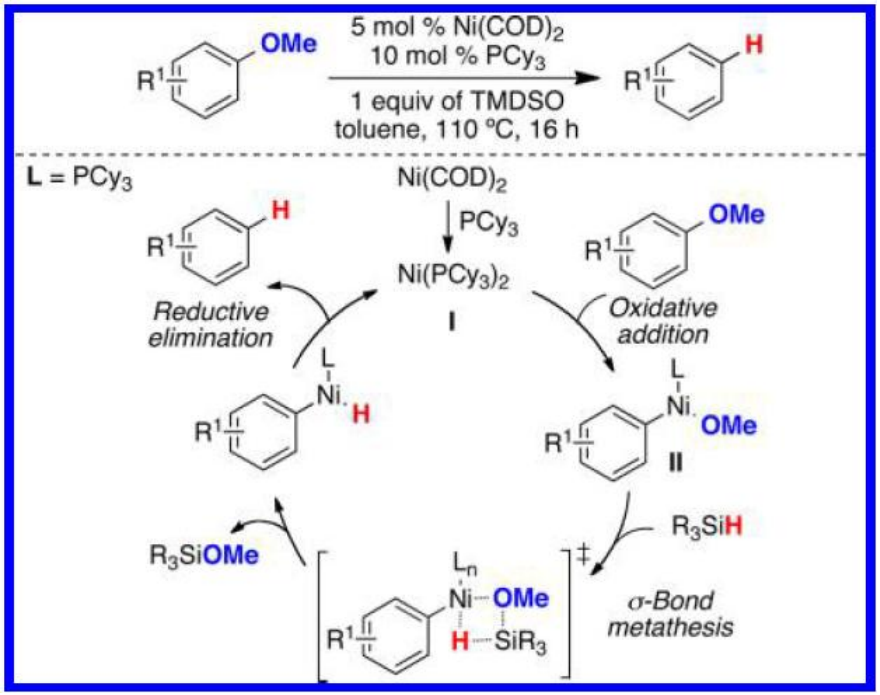
$[Ni(PCy_3)_2]_2N_2$



JACS, **2013**, 1997

Mechanism of Silane Reduction

- Martin, 2013
  - Problem: no conversion until silane added
  - Isotope labeling: σ bond metathesis faster than β hydride elimination (labeled both silane and Me)
  - No KIE Et_3Si-H/ Et_3Si-D→ Si-H not irreversibly cleaved during rds



JACS, **2013**, 1997

Mechanism of Silane Reduction

- Martin, 2013
  - Induction period by FTIR
  - ^{29}Si: only Et_3SIH signal → paramagnetic species present?

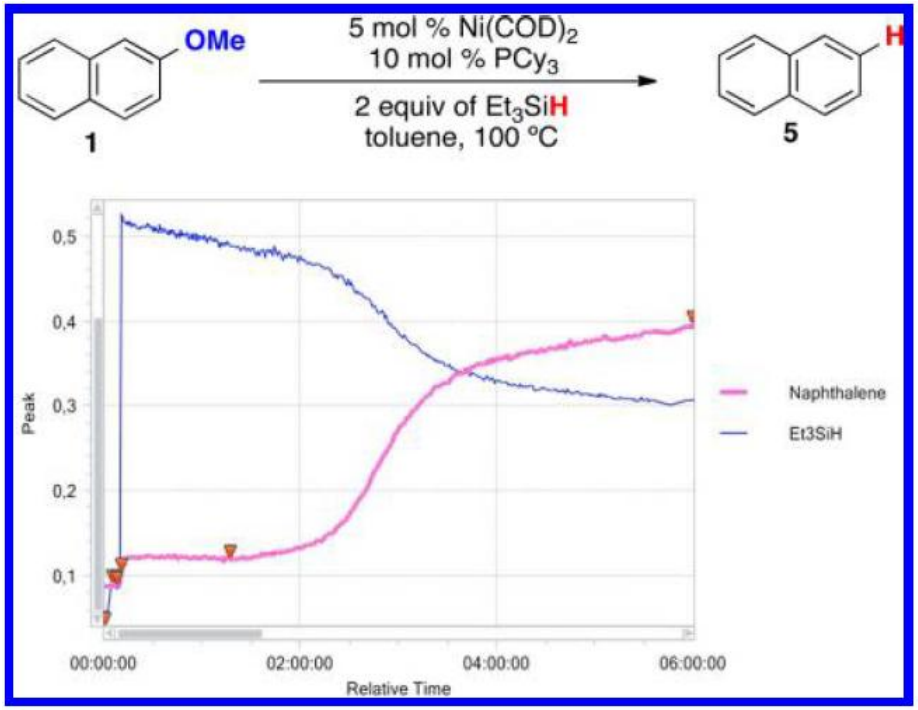
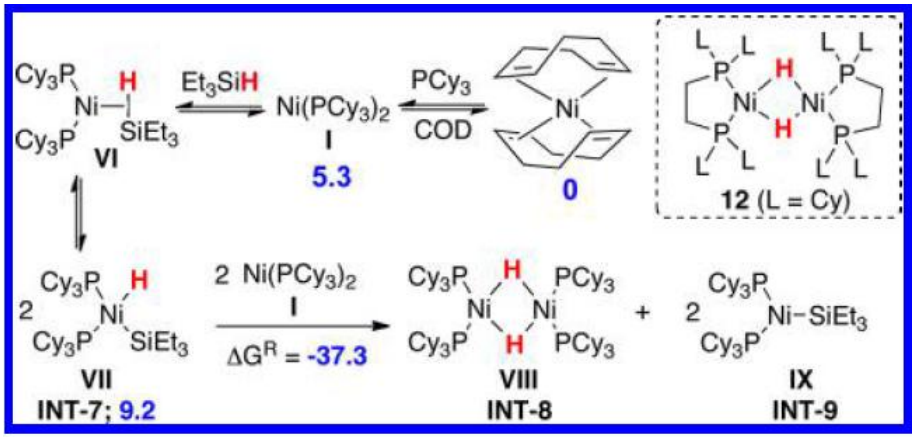


Figure 8. In-situ monitoring by FTIR spectroscopy.

JACS, **2013**, 1997

Mechanism of Silane Reduction

- Martin, 2013

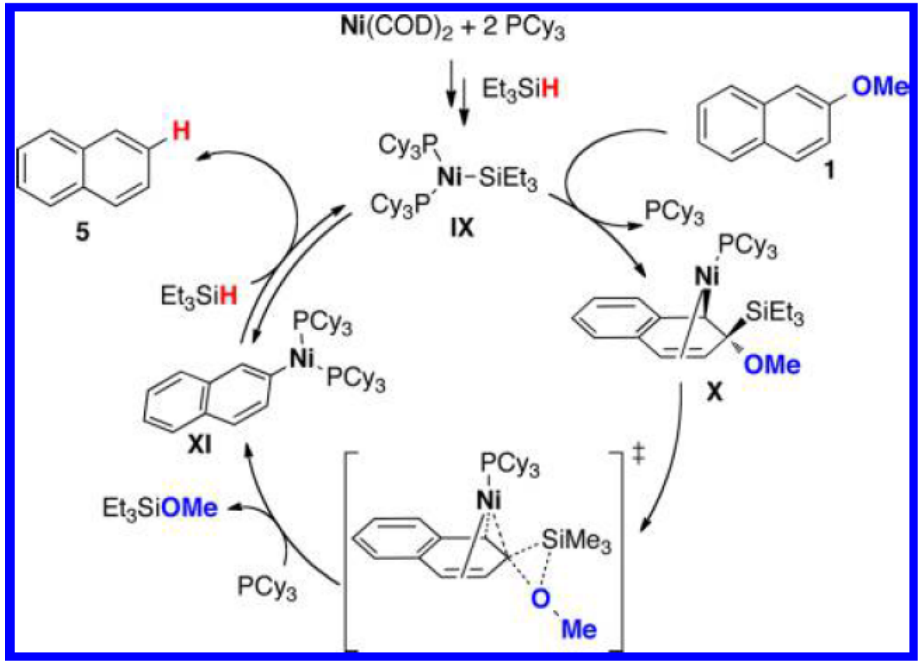


[a]Gibbs free energies computed at M06/6-311++(d,p) (SDD) (blue).

JACS, **2013**, 1997

Mechanism of Silane Reduction

- Martin, 2013



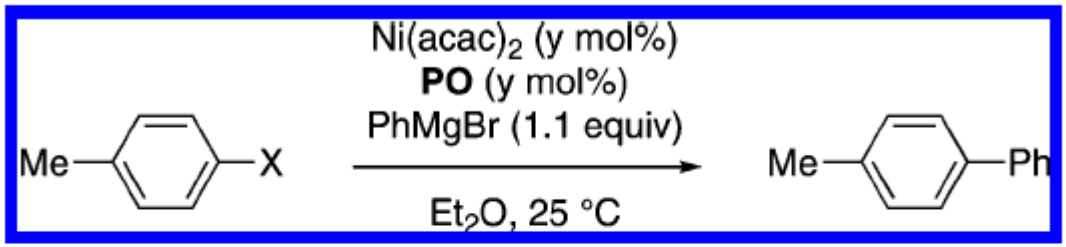
JACS, **2013**, 1997

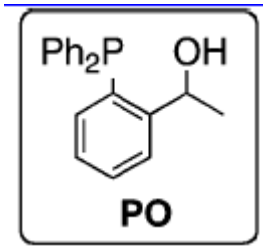
Very Active Ligand

- Nakamura, 2009

O cat. Cu/**PON-pro** Ph_2P OH

Table 2. Ni/**PO**-Catalyzed Cross-Coupling of *p*-Tolyl Halide or Pseudohalide and Phenylmagnesium Bromide



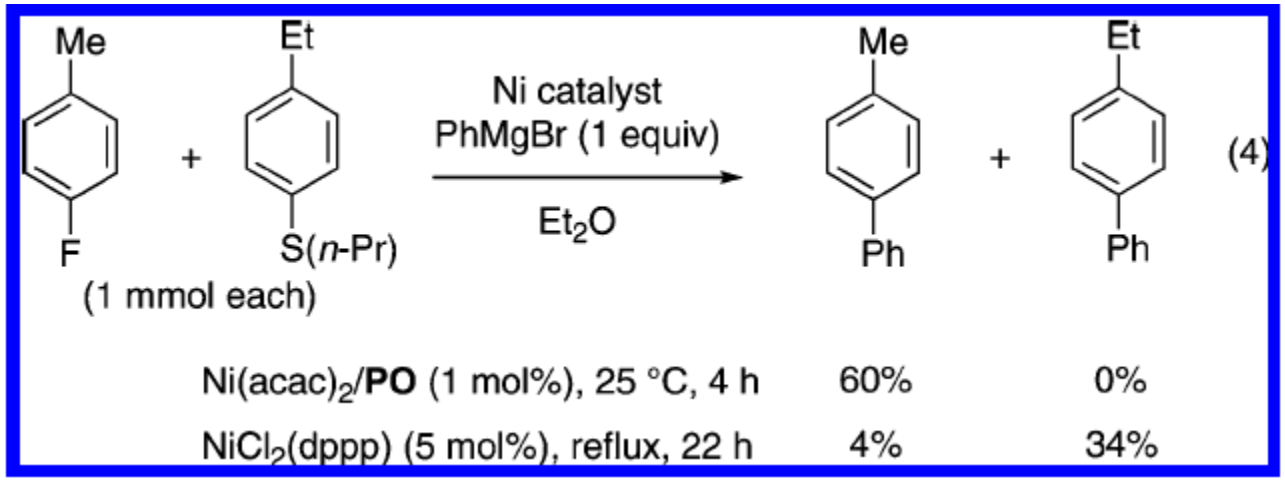


entry	X	y	time (h)	yield (%)[a]
1	F	1	1	94[b]
2	Cl	1	1/3	97
3	Br	0.2	3	91
4	I	0.05	2	98
5	OTf	1	2	95
6	SMe	1	1	5
7	SMe	5	24	62

JACS, **2009**, 9590

Very Active Ligand

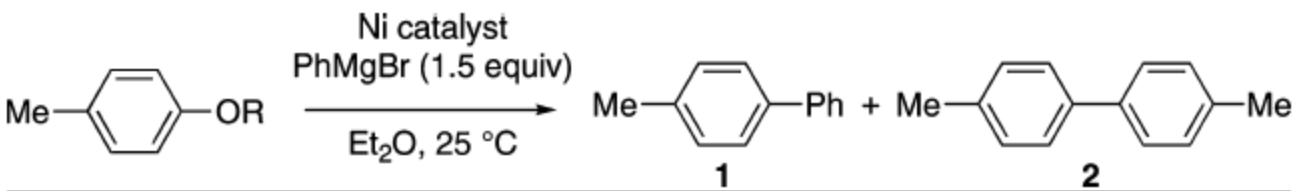
- Nakamura, 2009



JACS, **2009**, 9590

Very Active Ligand

- Nakamura, 2009



entry	R	Ni catalyst	time (h)	yield (%)[a] 1	yield (%)[a] 2
1	SO_2CF_3	$Ni(acac)_2$/PO (1 mol %)	2	95	0
2	$P(O)(OEt)_2$	$Ni(acac)_2$/PO (1 mol %)	2	92	0
3	$P(O)(OEt)_2$	$Ni(acac)_2$ (1 mol %)	2.5	9	0
4	$CONEt_2$	$Ni(acac)_2$/PO (3 mol %)	1	95	4
5	$CONEt_2$	$Ni(acac)_2$ (5 mol %)	2.5	64	27
6	$CONEt_2$	$NiCl_2$(dppp) (5 mol %)	1	10	4

JACS, **2009**, 9590

Very Active Ligand

- Nakamura, 2009

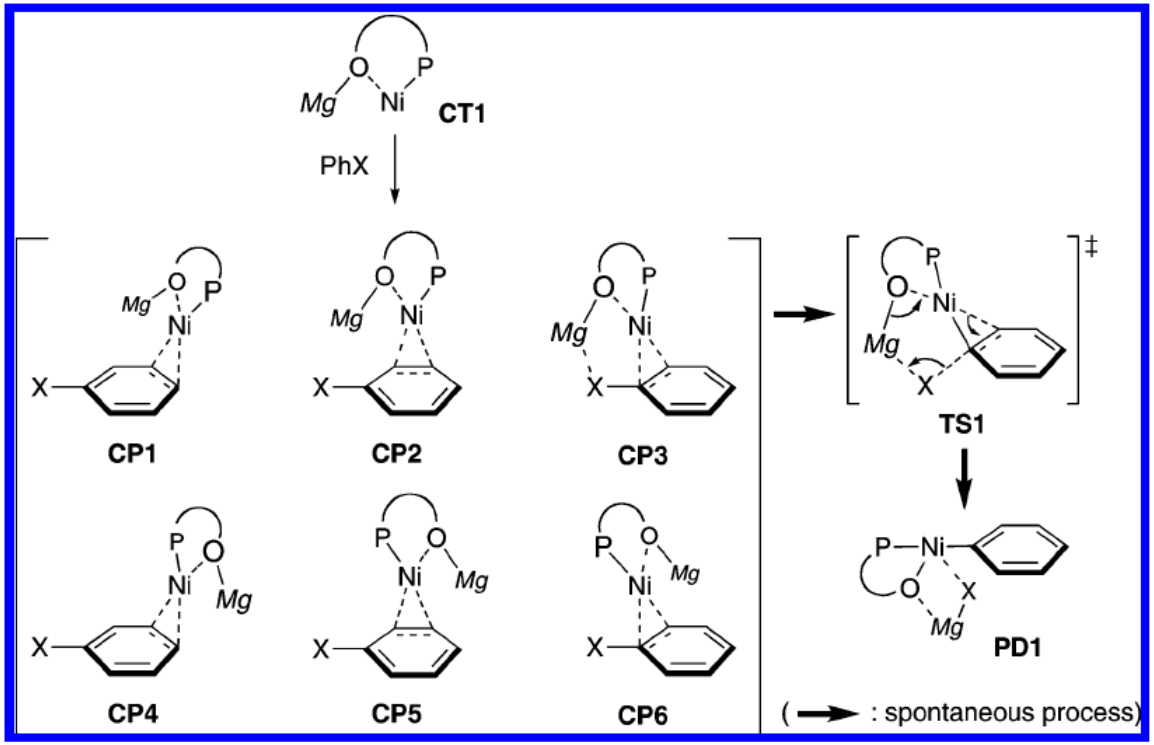


Table 7. Relative Potential Energies and Gibbs Free Energies (kcal/mol) of Ni/Mg Complexes in Scheme 1[a]

X	CP1	CP2	CP3	CP4	CP5	CP6	TS1	PD1
F	−24.4 (−13.0)	−33.3 (−20.7)	N/A[b]	−25.0 (−13.9)	−30.6 (−17.7)	−27.6 (−15.5)	N/A[b]	−52.8 (−40.8)
Cl	−24.8 (−13.0)	−27.1 (−14.3)	N/A[b]	−25.8 (−13.9)	−28.7 (−16.7)	−30.3 (−17.6)	N/A[b]	−54.0 (−41.7)
Br	−25.0 (−13.0)	−27.9 (−15.3)	N/A[b]	−26.0 (−14.3)	−28.8	−32.1 (−19.2)	N/A[b]	−56.2 (−44.0)

[a] Calculated at the B3LYP level using LANL2DZ for Ni, Ahlrichs SVP for Br, and 6-31G(d) for the rest. Gibbs free energies are shown in parentheses. [b] The structures could not be located because of spontaneous C−X bond cleavage during the geometry optimization (see Figure 2).

JACS, **2009**, 9590

Very Active Ligand

- Nakamura, 2009

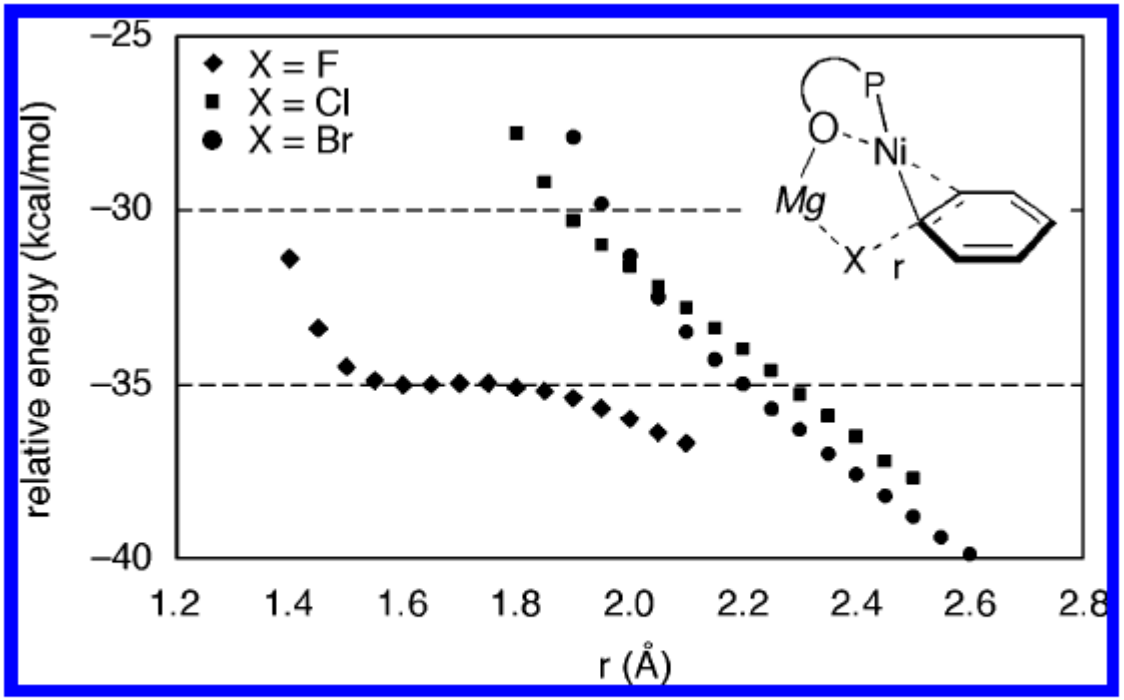
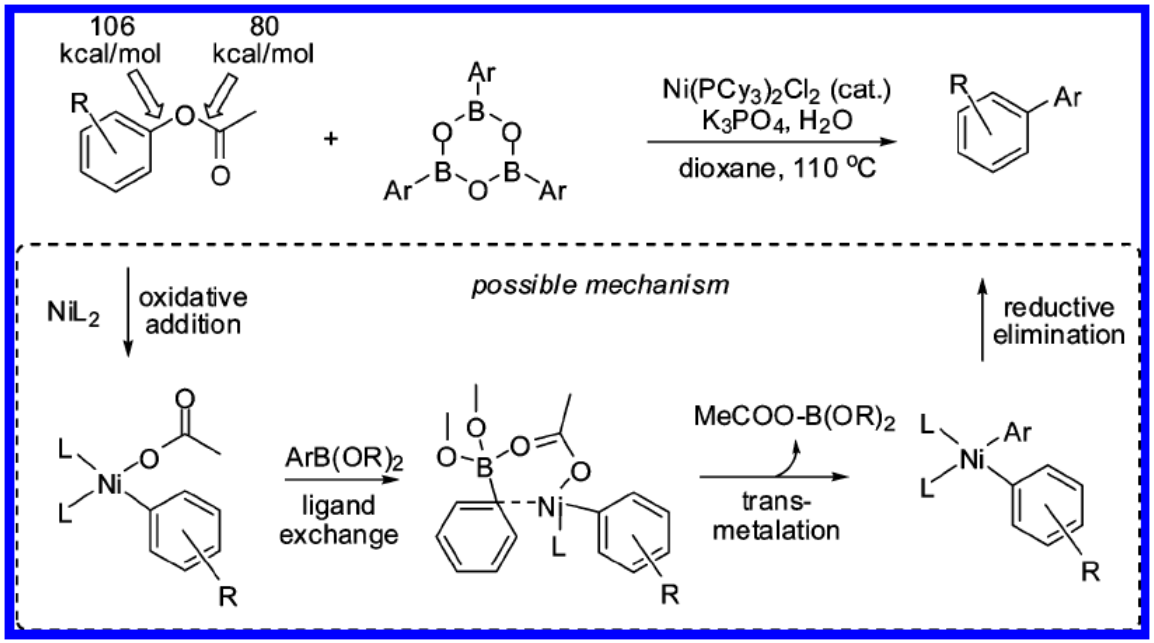


Figure 2. Change in potential energy of the **CT1**−halobenzene complex (shown in the upper-right corner) with elongation of the C−X bond length *r*.

JACS, **2009**, 9590

Mechanism with Boron

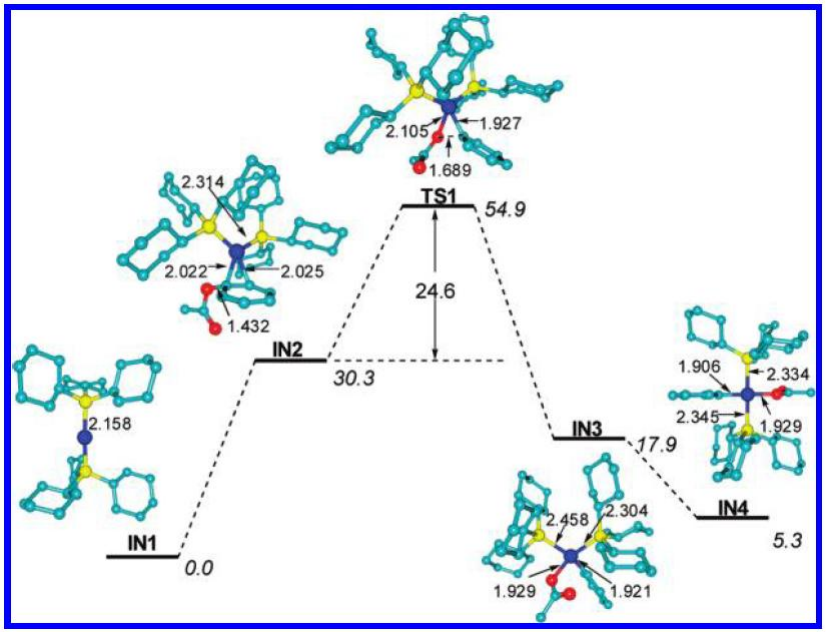
- Liu, 2009

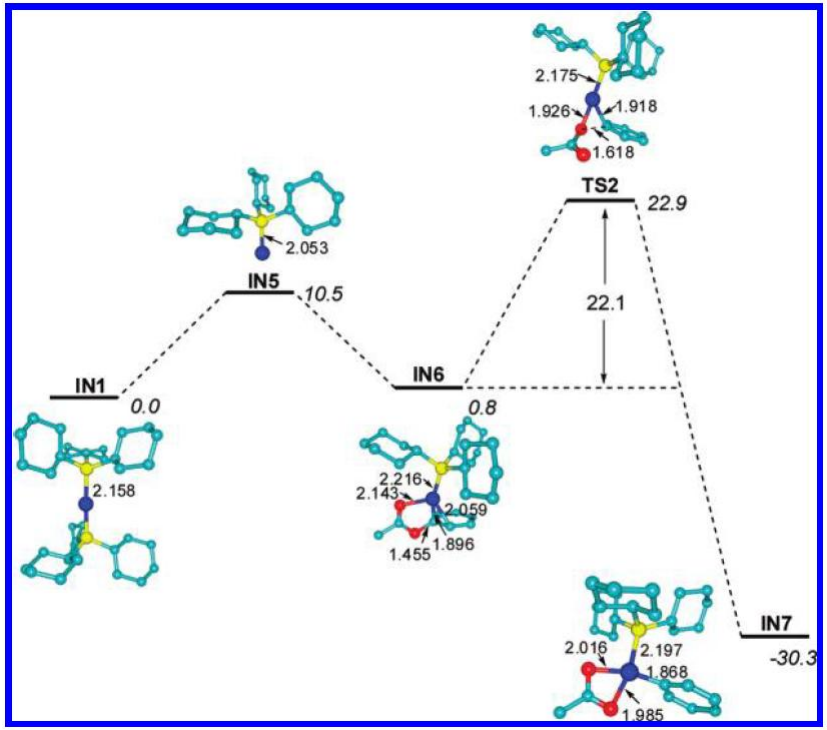


JACS, **2009**, 8815

Bisphosphine or Monophosphine

- Liu, 2009

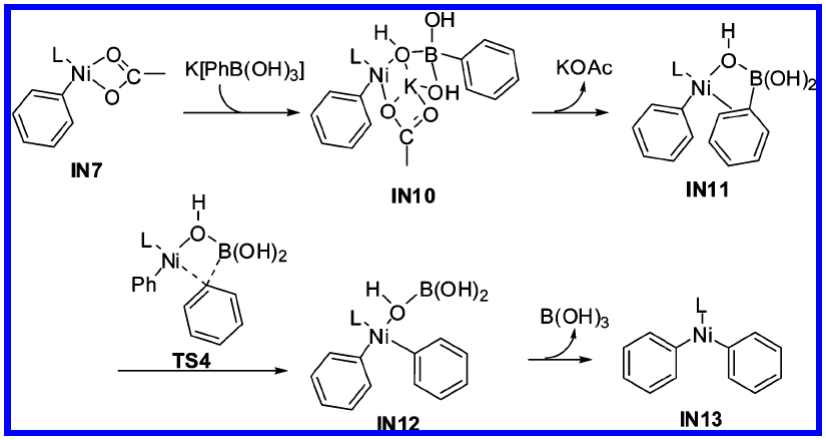


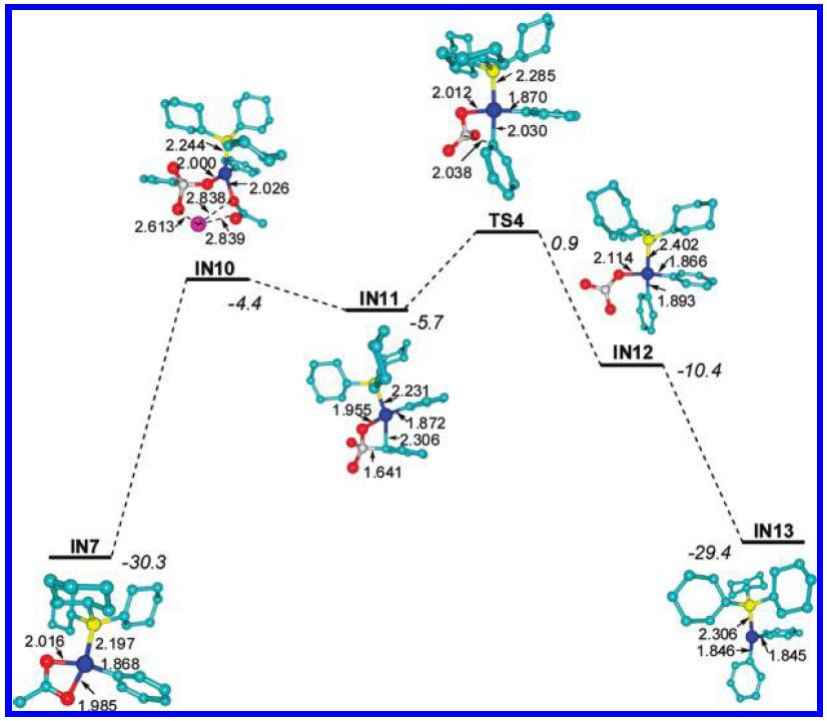


JACS, **2009**, 8815

Mechanism with Boron

- Liu, 2009

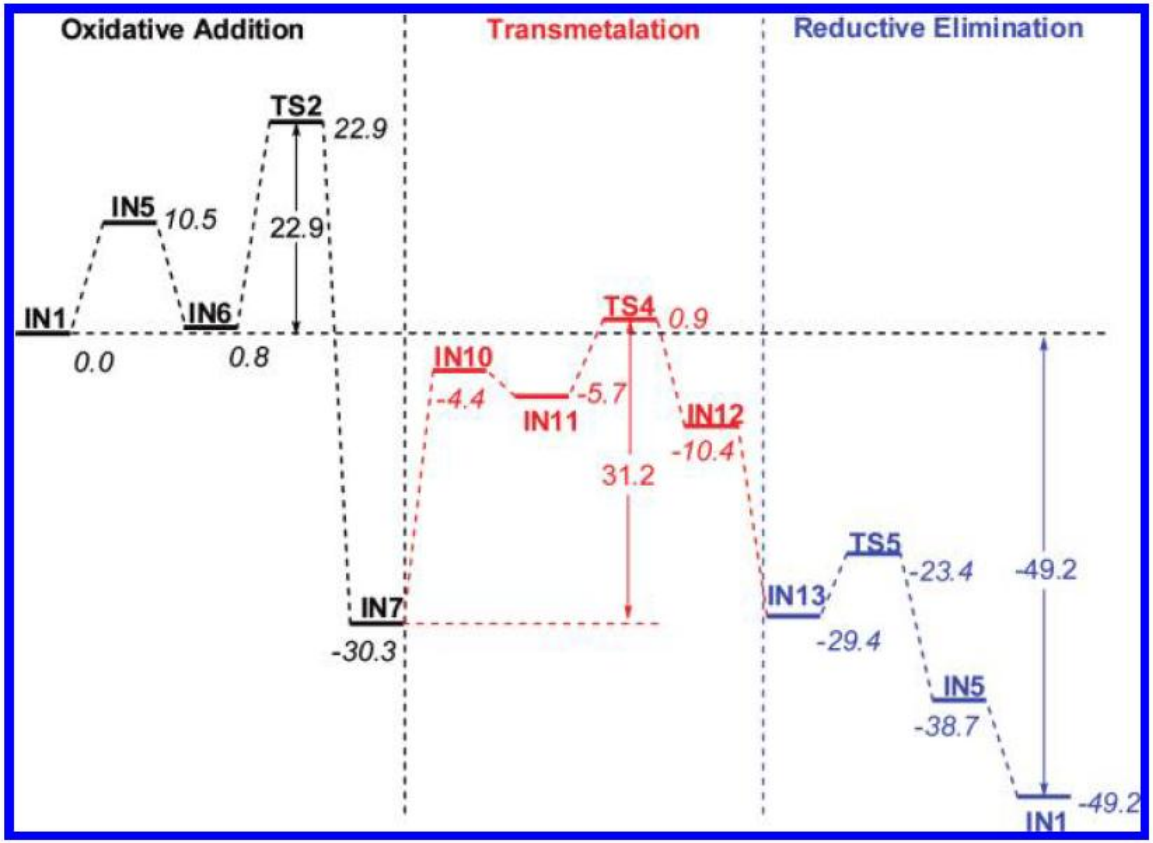




JACS, **2009**, 8815

Mechanism with Boron

- Liu, 2009

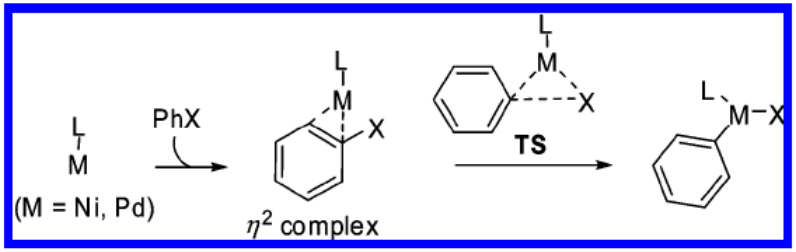


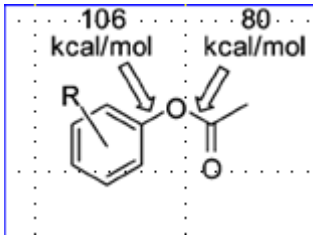
JACS, **2009**, 8815

Ni vs Pd

- Liu, 2009

Table 1. Oxidative Addition of Various Ph−X bonds to Ni(0)PMe_3 and Pd(0)PMe_3 (Unit: kcal/mol)



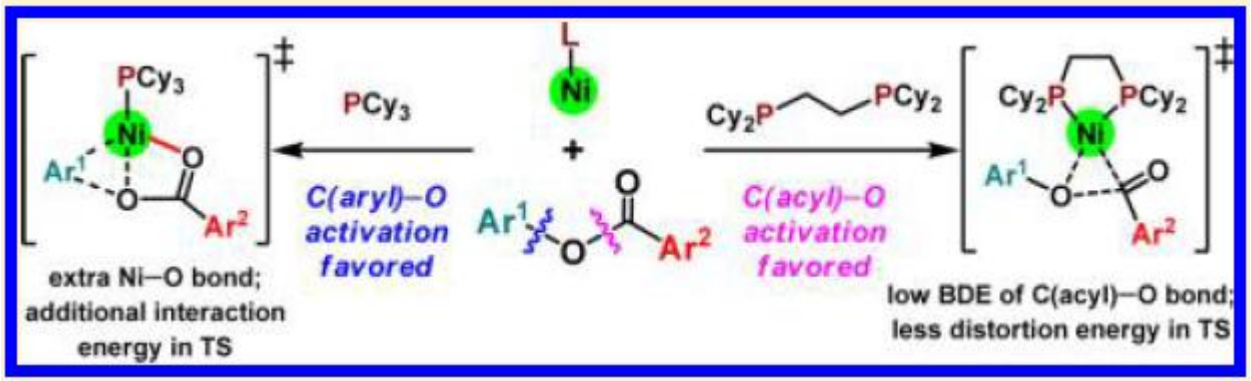


	Ni(0)PMe_3			Pd(0)PMe_3		
Ph−X	η^2 complex	TS	barrier	η^2 complex	TS	barrier
Ph−Br	−24.5	−21.2	3.3	−8.2	−4.8	3.4
Ph−Cl	−26.1	−16.5	9.6	−5.5	9.3	14.8
Ph−F	−25.9	1.8	27.7	−6.3	28.0	34.3
Ph−SAc	−26.7	−16.1	10.6	−1.9	9.5	11.4
Ph−OTf	−25.1	−20.6	4.5	−4.6	21.2	25.9
Ph−OMs	−26.1	−0.1	26.0	−3.9	24.5	28.4
Ph−OTs	−24.4	−1.0	23.4	−3.9	25.5	29.4
Ph−OAc	−23.7	2.7	26.4	−4.8	29.2	34.0
Ph−OMe	−25.4	4.2	29.5	−6.8	35.2	42.0
Ph−NHAc	−22.4	1.9	24.2	2.1	31.4	31.4

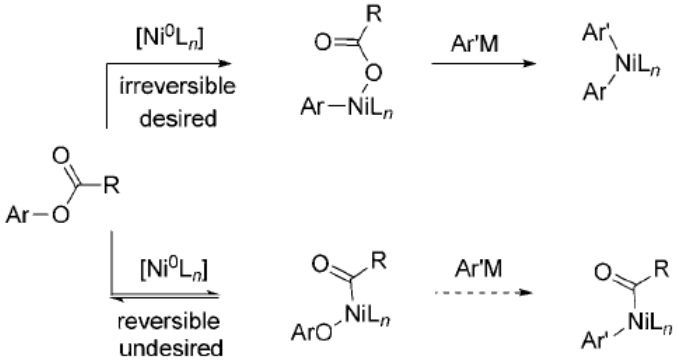
JACS, **2009**, 8815

Where does the Phosphine insert?

- Houk, 2014



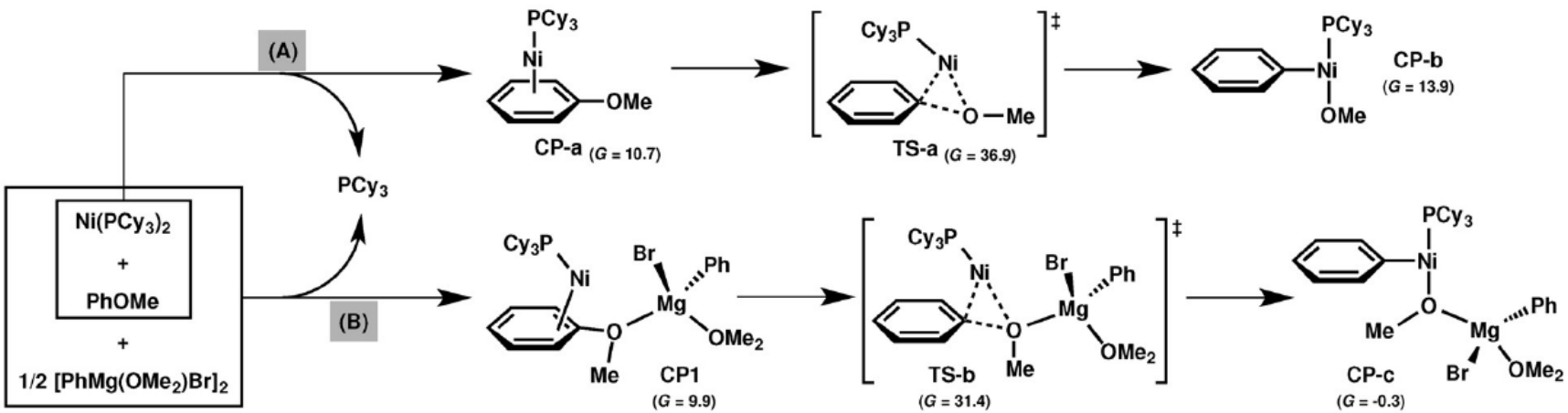
- Liu, 2009



JACS, **2014**, 2017
JACS, **2009**, 8815

Mechanism with Grignard

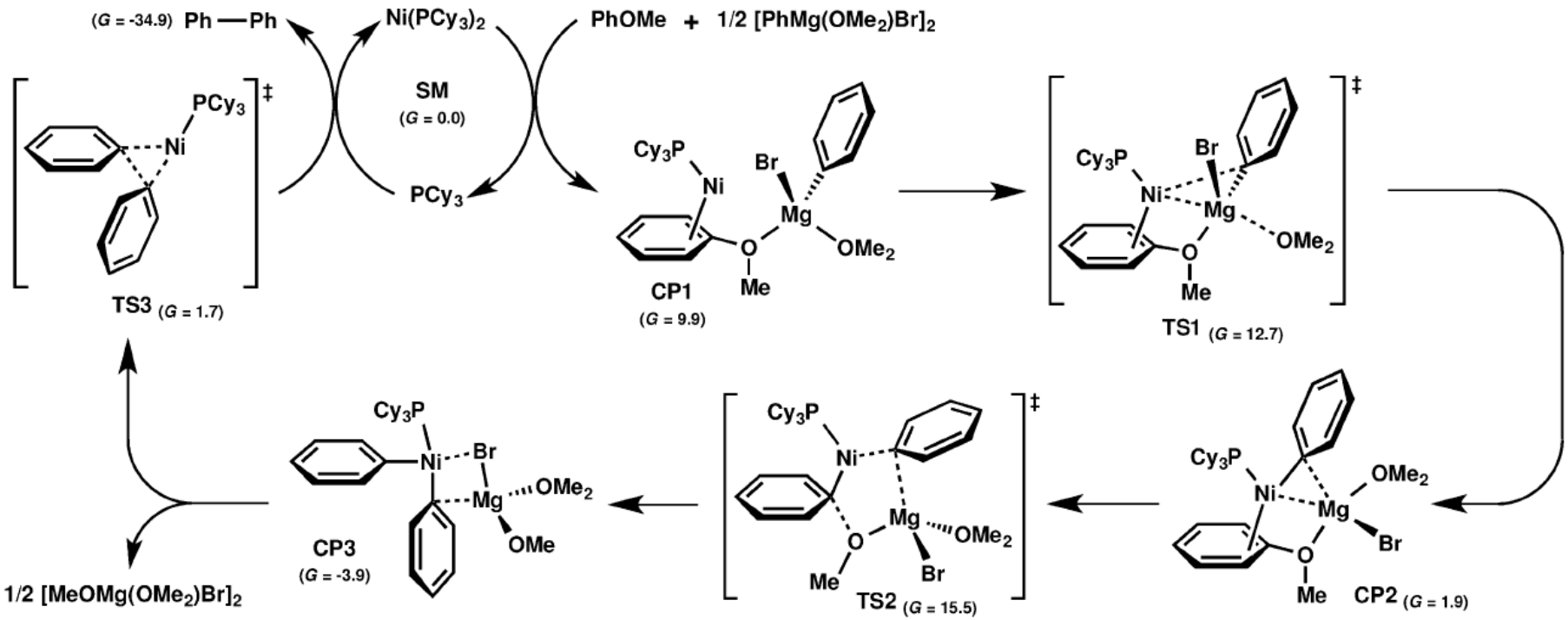
- Wang, Uchiyama, 2015



CEJ, **2015**, 13094

Nickel-ate complex

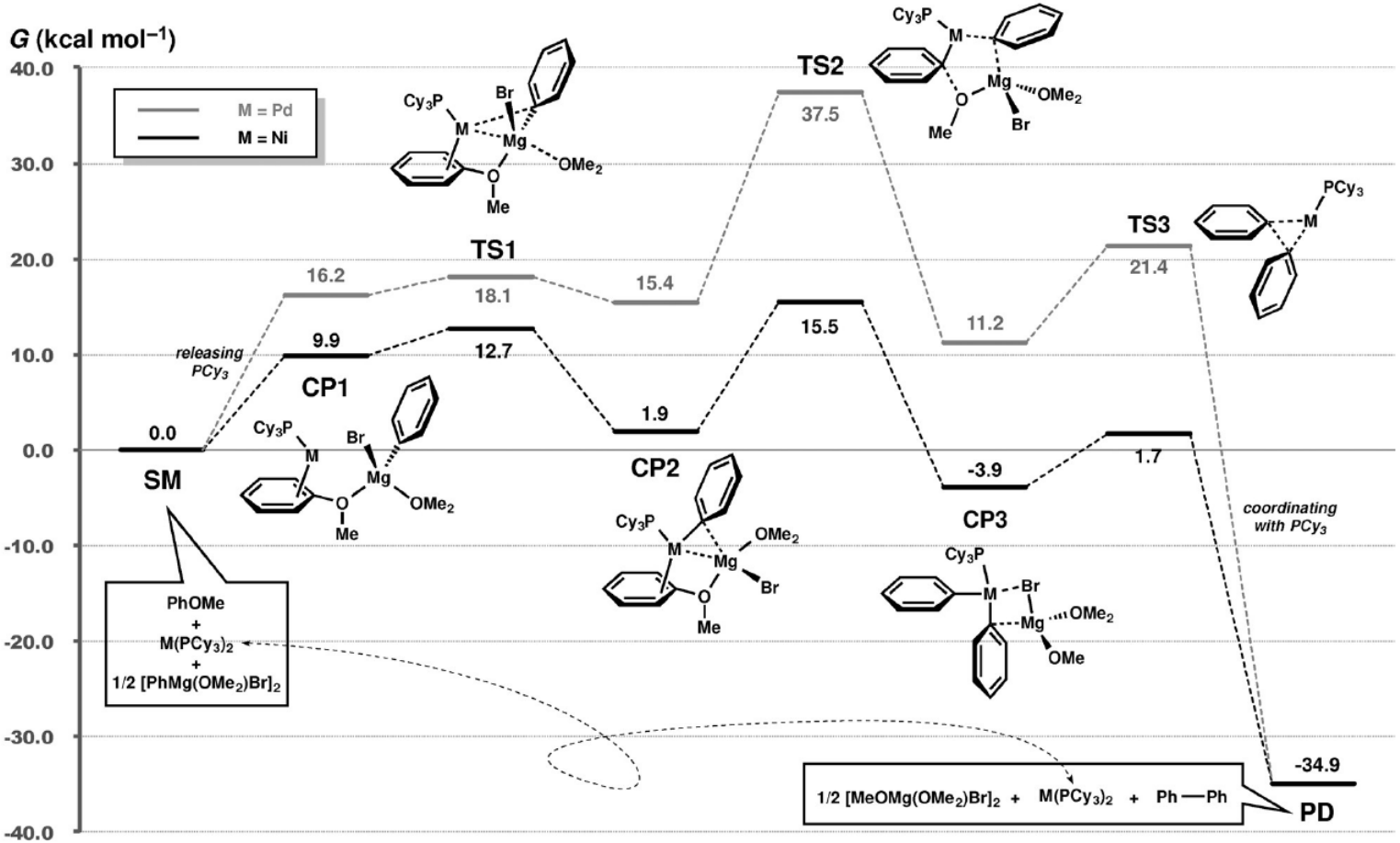
- Wang, Uchiyama, 2015



CEJ, **2015**, 13094

Nickel vs Palladium

- Wang, Uchiyama, 2015

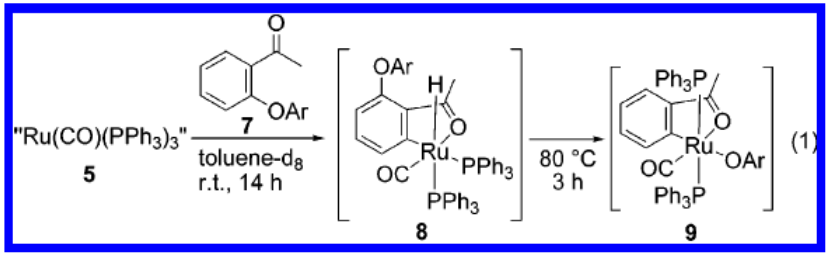


CEJ, **2015**, 13094

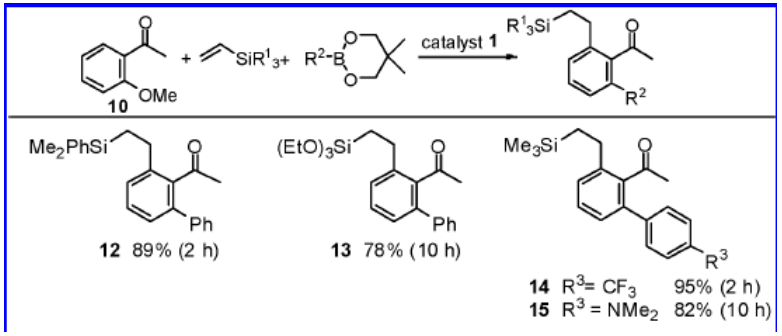
1. Hard nucleophiles
2. Boronic acids
3. Reductions & mechanistic discussion
4. Outlook

Ruthenium

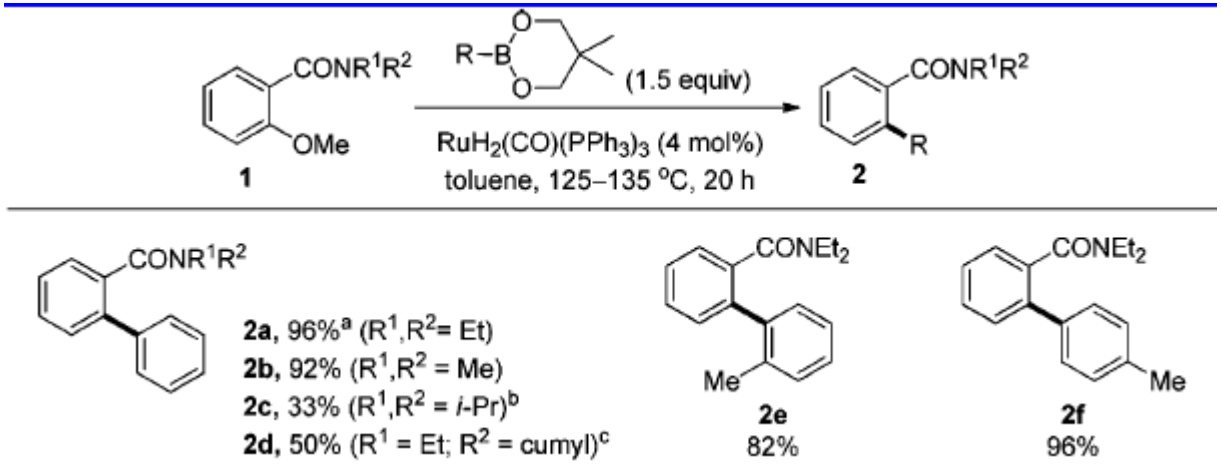
- Kakiuchi, 2006



$RuH_2(CO)(PPh_3)_3$ (**1**)

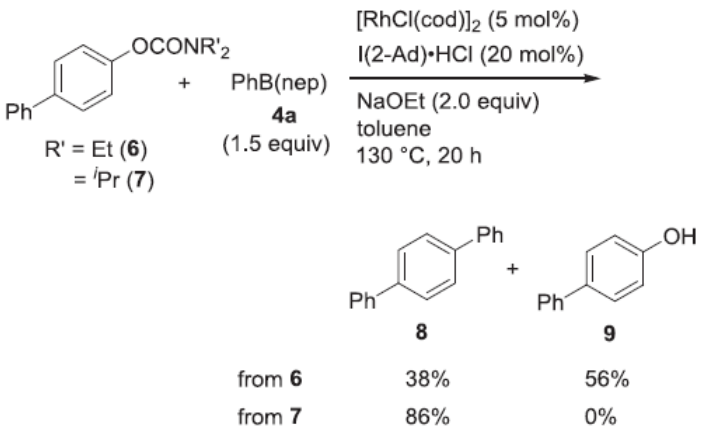


- Snieckus, 2014



JACS, **2006**, 16516
JACS, **2014**, 11224

- Tobisu, Chatani, 2015

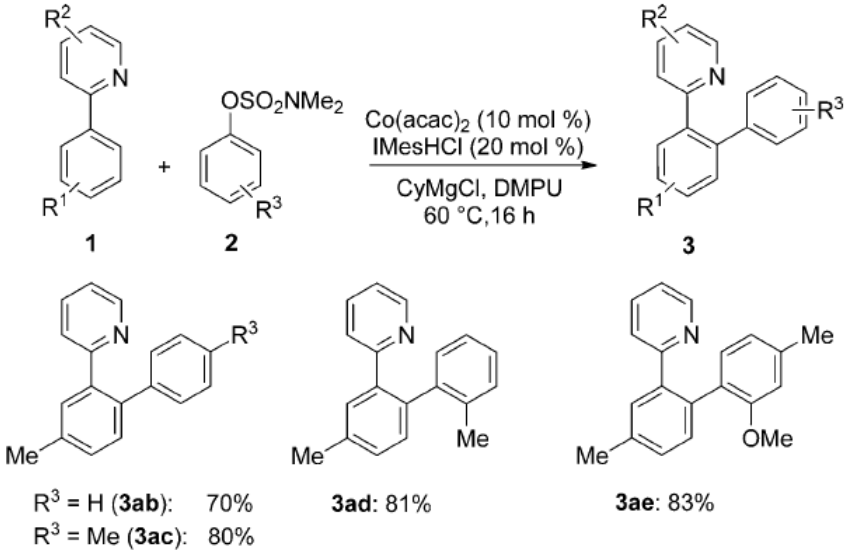


Scheme 2. Effect of the substituent of the carbamoyl group.

Tetrahedron, **2015**, 4484

Cobalt

- Ackermann, 2012

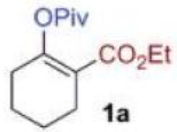
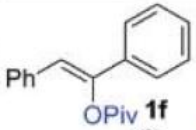
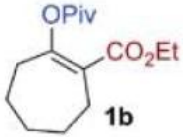
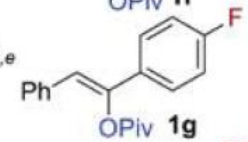
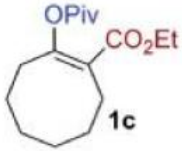
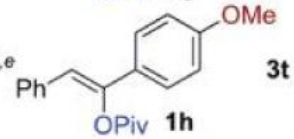
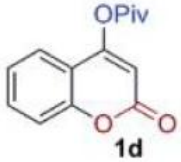
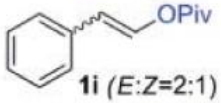
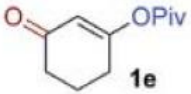
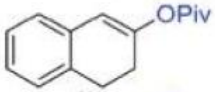
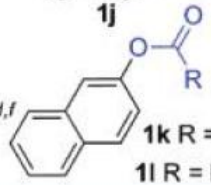


ACIE, **2012**, 8251

Iron

- Shi, 2009

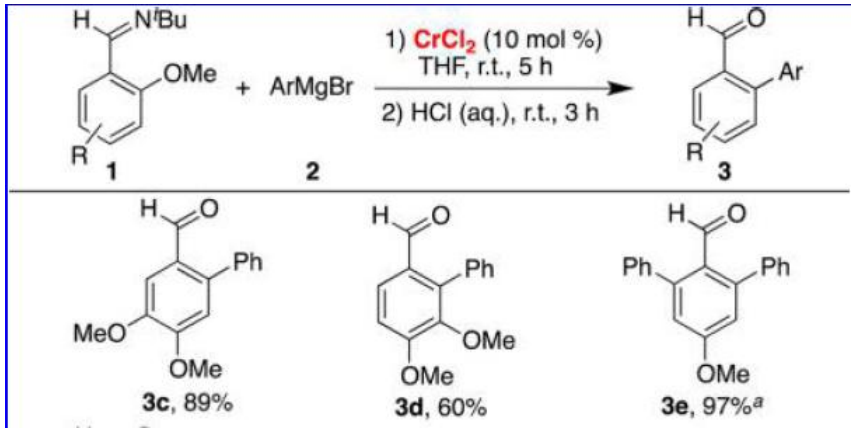
Table 3. Substrate Scope of Alkenyl/Aryl Carboxylates[a]

Entry	1	3(%)[b]	Entry	1	3(%)[b]
1	 1a	3a (93)	6[d,e]	 1f	3r (91)
2	 1b	3n (78)	7[d,e]	 1g	3s (85)
3	 1c	3o (87)	8[d,e]	 1h	3t (70)
4	 1d	3p (90)	9[e]	 1i (E:Z=2:1)	3u (71)
5[c]	 1e	3q (65)	10	 1j	3v (87)
			11[d,f]	 1k R = tBu 1l R = NMe2	3w (40) (80)

JACS, **2009**, 14656

Chromium

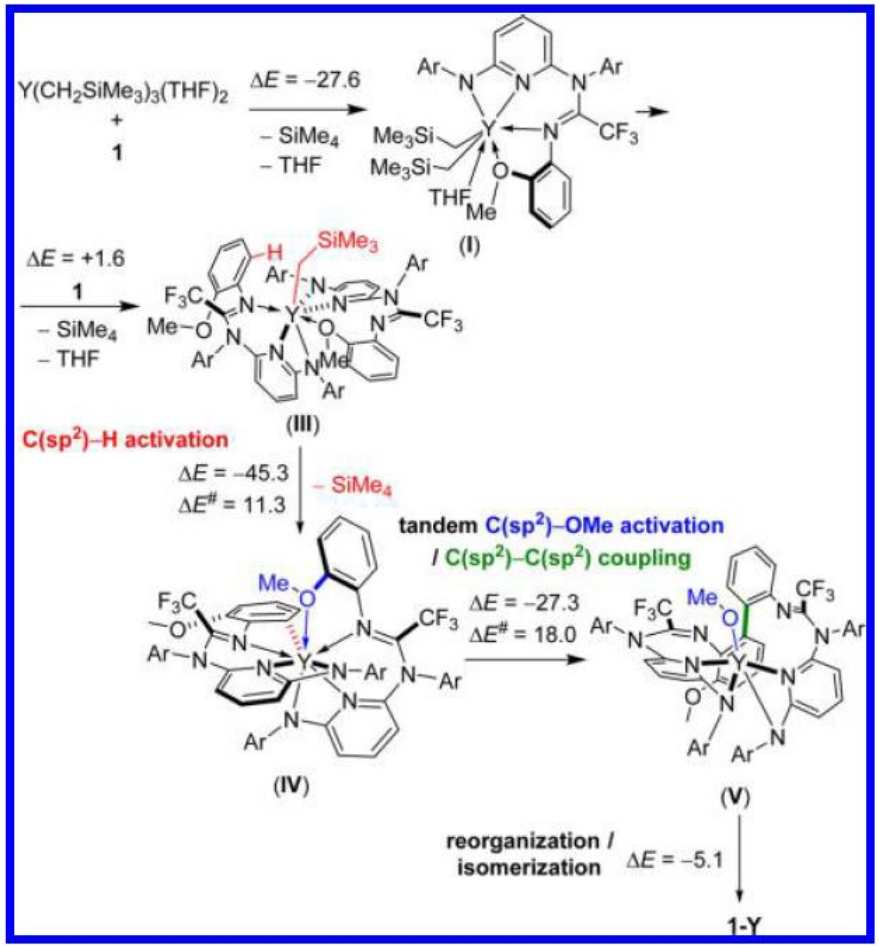
- Zeng, 2015



JACS, **2015**, 14367

Yttrium

- Carpentier, Kirillov, 2016



JACS, **2016**, 4350

Conclusion

C-O bonds are „inert“ according to at least 120 papers

Reviews

General Reviews:

Tobisu, Chatani, Top Curr Chem, **2016**, *374*, 41
Jamison, Nature, **2014**, *509*, 299
Shi, Acc. Chem. Res., **2010**, *43*,1486
Jarvo, Acc. Chem. Res., **2015**, *48*, 2344
Shi, CEJ, **2011**, *17*, 1728
Percec, Chem. Rev., **2011**, *111*, 1346
Garg, OPRD, **2013**, *17*, 29
Itami, EJOC, **2013**, *2013*, 19
Martin, Chem. Soc. Rev., **2014**, *43*, 8081
Tobisu, Chatani, , Acc. Chem. Res., **2015**, *48*, 1717