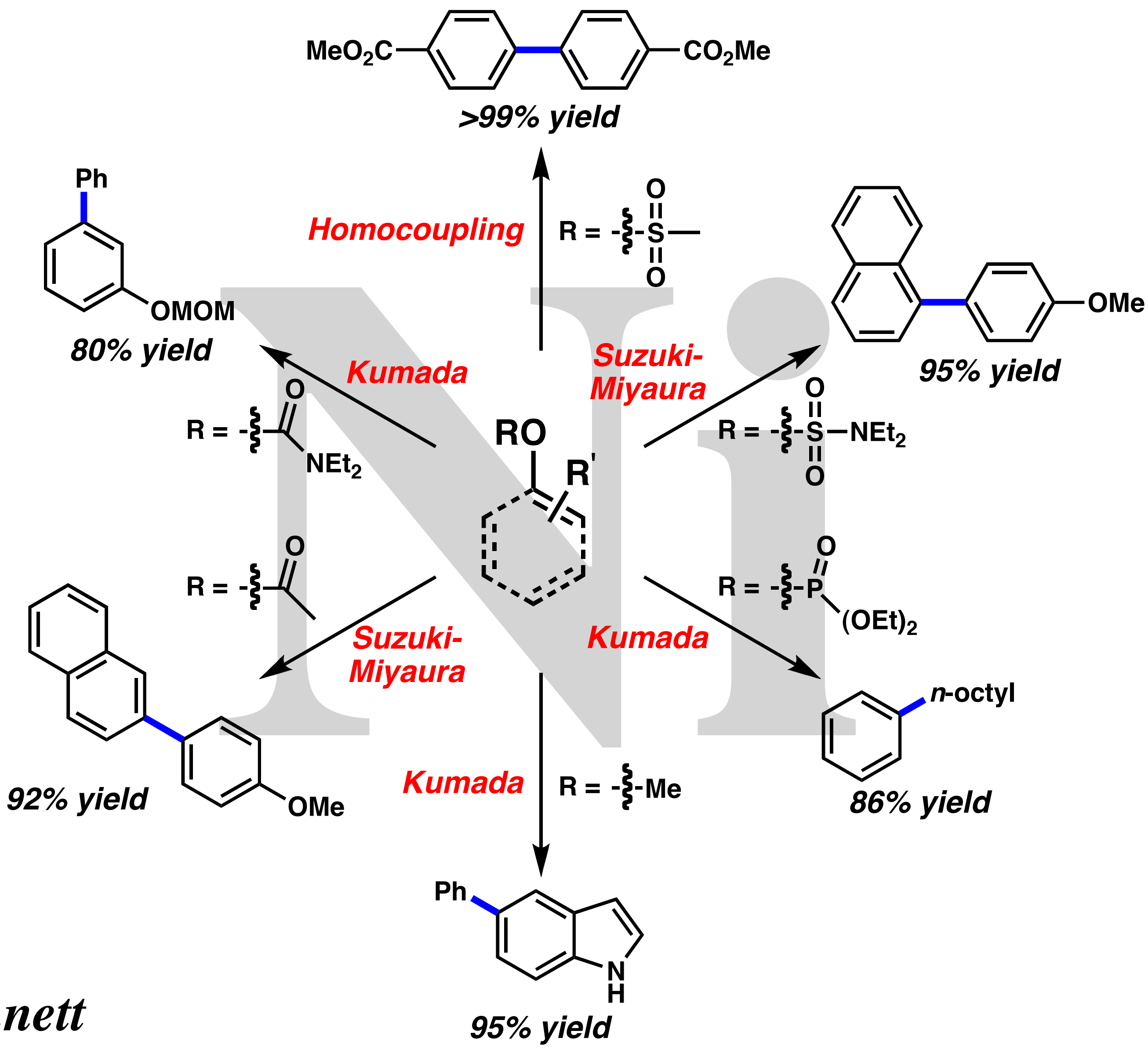
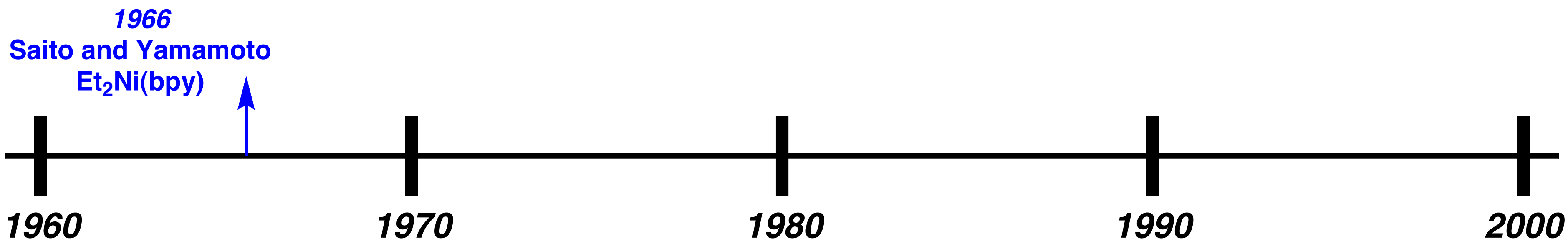
From C–O to C–C through Nickel Coupling



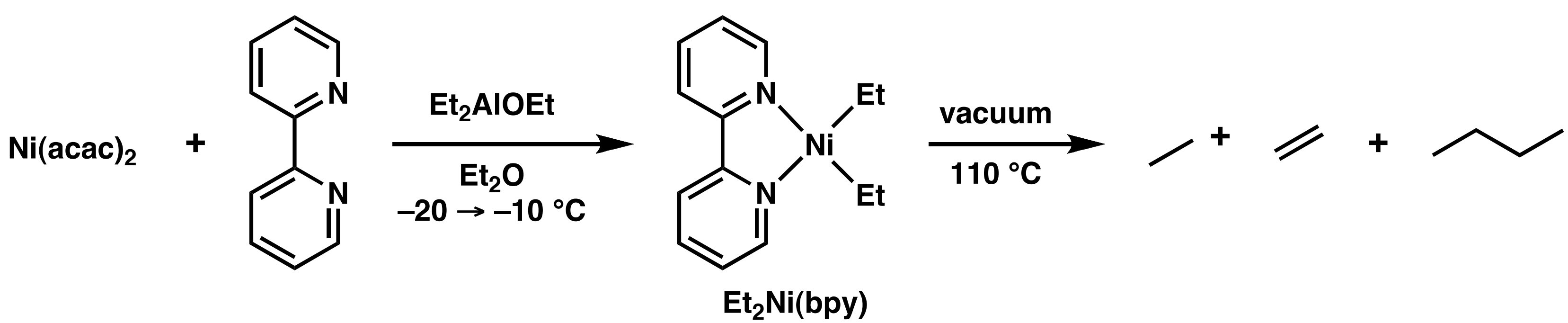
Nathan Bennett
Group Meeting

May 7, 2011

Ni Chemistry Timeline
Initial Studies



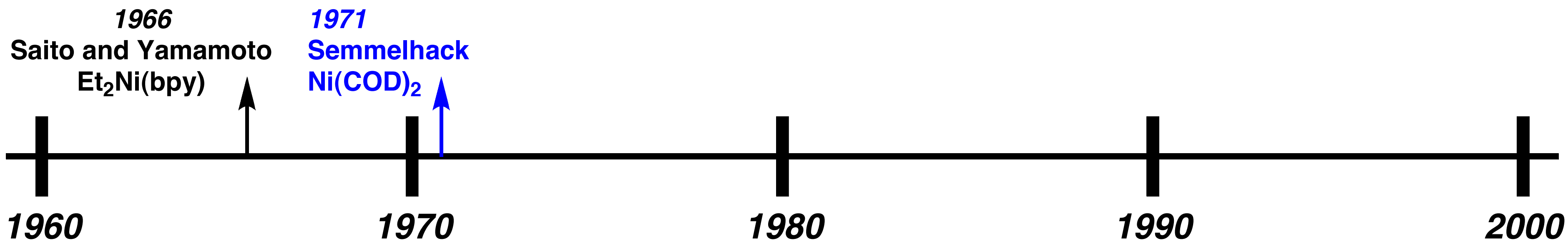
Saito, T. and Yamamoto, A.



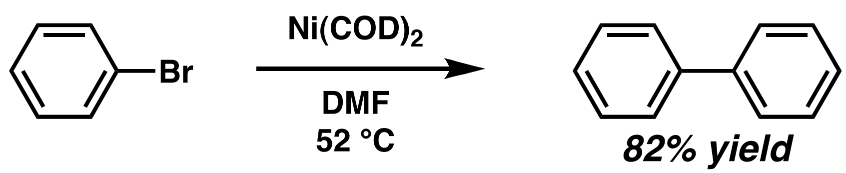
J. Am. Chem. Soc. **1966**, *88*, 5198.

Ni Chemistry Timeline

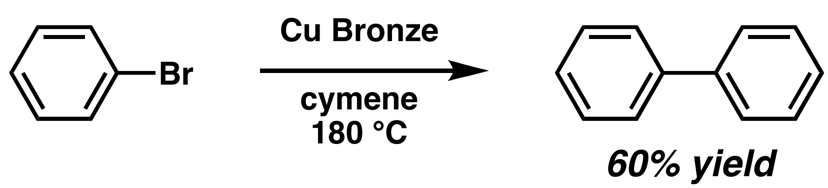
Initial Studies



Semmelhack, M. F.

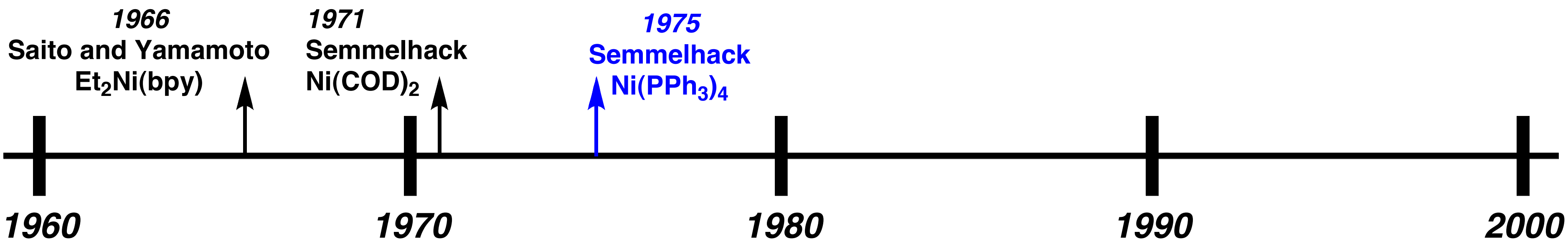


Ullmann Coupling Comparison

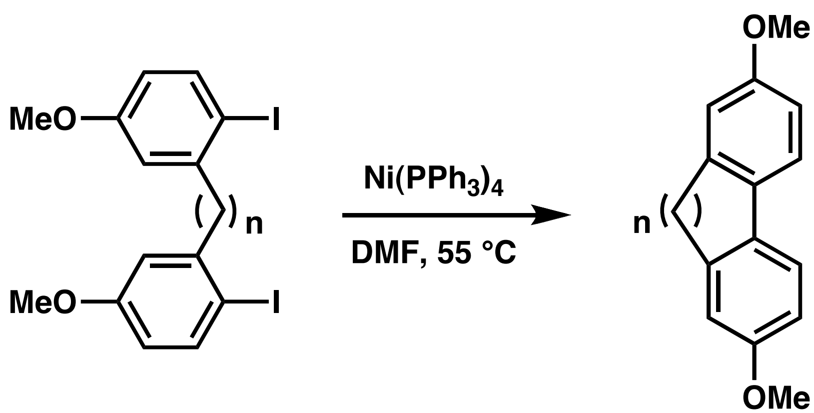


Ni: Semmelhack, M. F. *J. Am. Chem. Soc.* **1971**, *93*, 5908.
Ullmann Coupling: Fanta, P. E. *Chem. Res.* **1964**, *64*, 613.

Ni Chemistry Timeline
Initial Studies



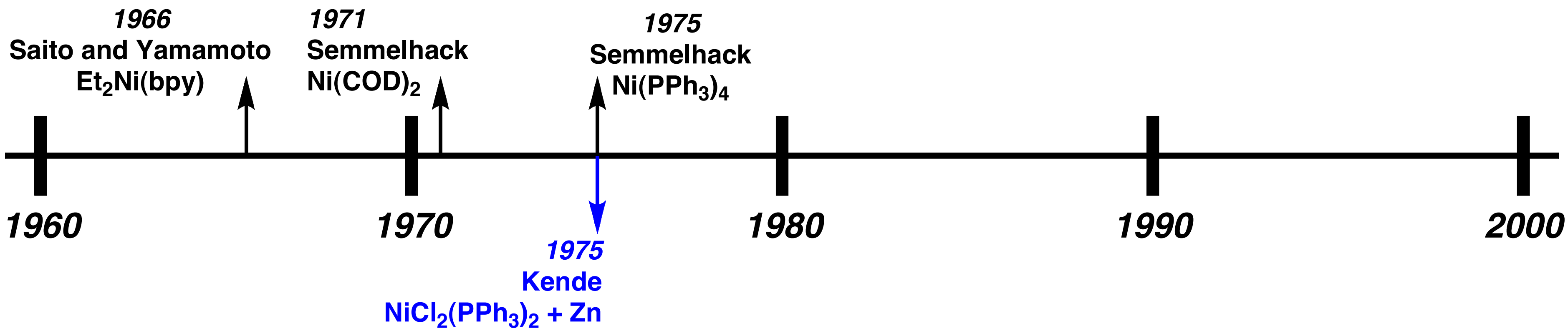
Semmelhack, M. F.



n	yield (%)
2	81
3	83
4	76
5	85
6	38

J. Am. Chem. Soc. **1975**, *97*, 3873.
J. Am. Chem. Soc. **1981**, *103*, 646.

Ni Chemistry Timeline
Initial Studies



Kende, A. S.

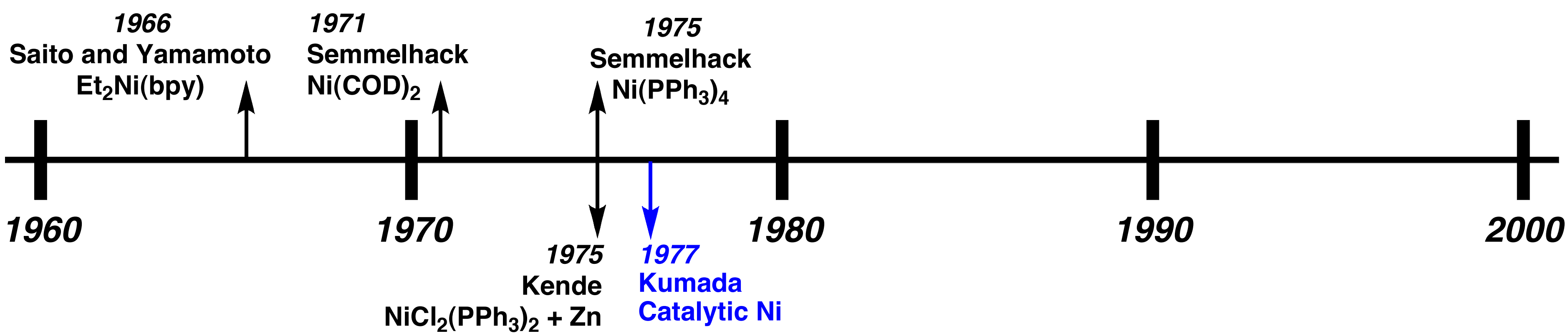
$$Ni^{II}Cl_2(PPh_3)_2 \xrightarrow[\text{DMF}]{Zn^0,\ PPh_3} \underset{\textit{in situ}}{Ni^0(PPh_3)_3}$$

— **Tolman Research: $Ni^0(PPh_3)_3$ active catalyst**
— **Kende formed *in situ***

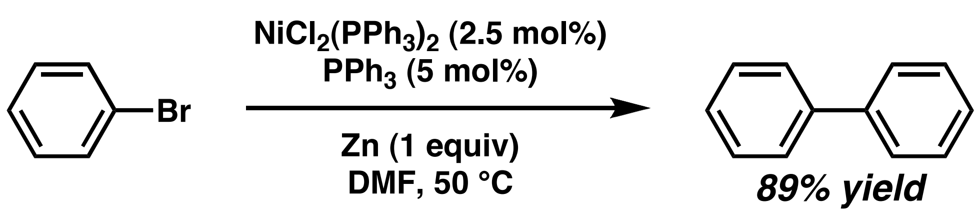
Tolman, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 53.
Kende, A. S. *Tetrahedron Lett.* **1975**, 3375.

Ni Chemistry Timeline

Initial Studies



Kumada, M.



Tetrahedron Lett. **1977**, *47*, 4089.

Why Phenol/Enol Derived Electrophiles?

Availability

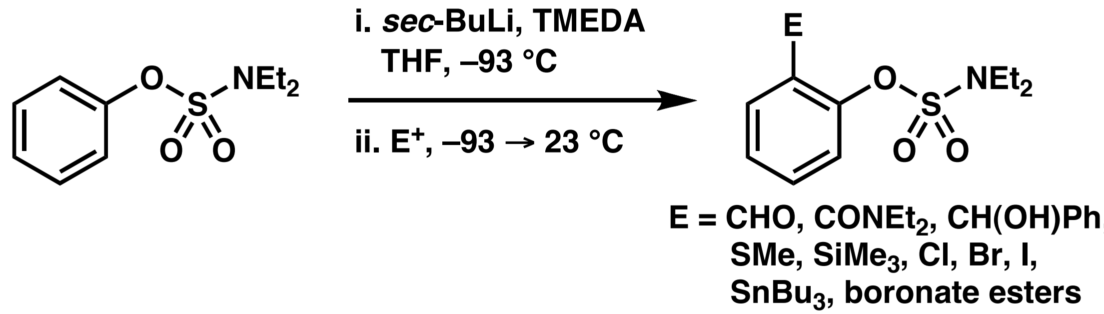
— 50,000 commercial phenol and aryl polyol

— Enol electrophile from trapping enolates

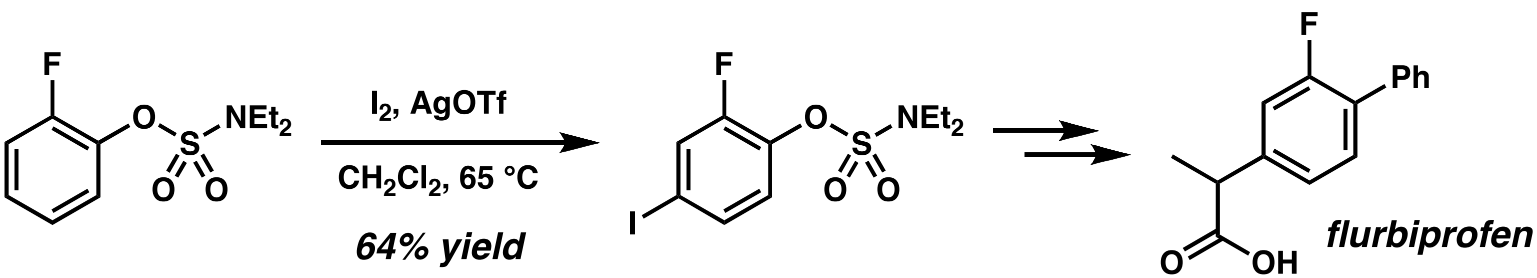
Reactivity

— Directed Ortho Metalation (DoM)

Possible with:
Sulfamates
Ethers
Esters
Carbamates



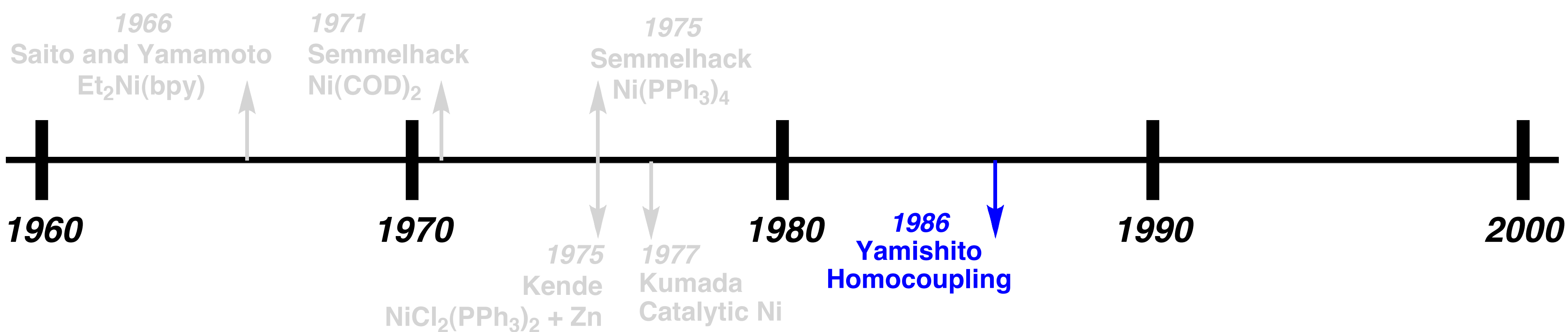
— *p*-Direction



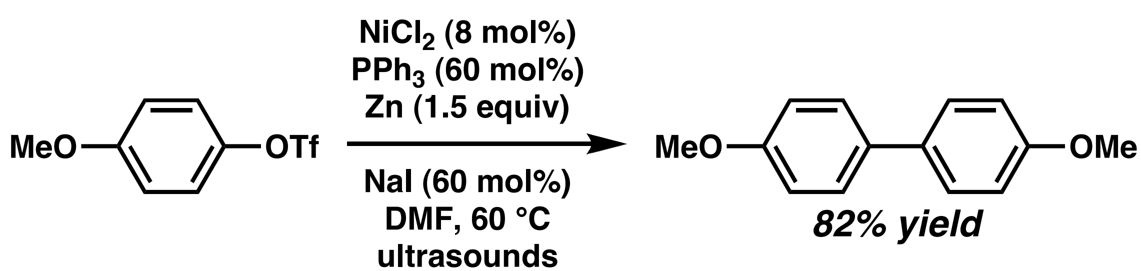
Garg, N. K. and Percec, V. *Chem. Rev.* **2011**, ASAP, *DOI: 10.1021/cr100259t.*
DoM Review: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
***p*-Direction Example:** Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748.

Ni Chemistry Timeline

Sulfonate Highlights



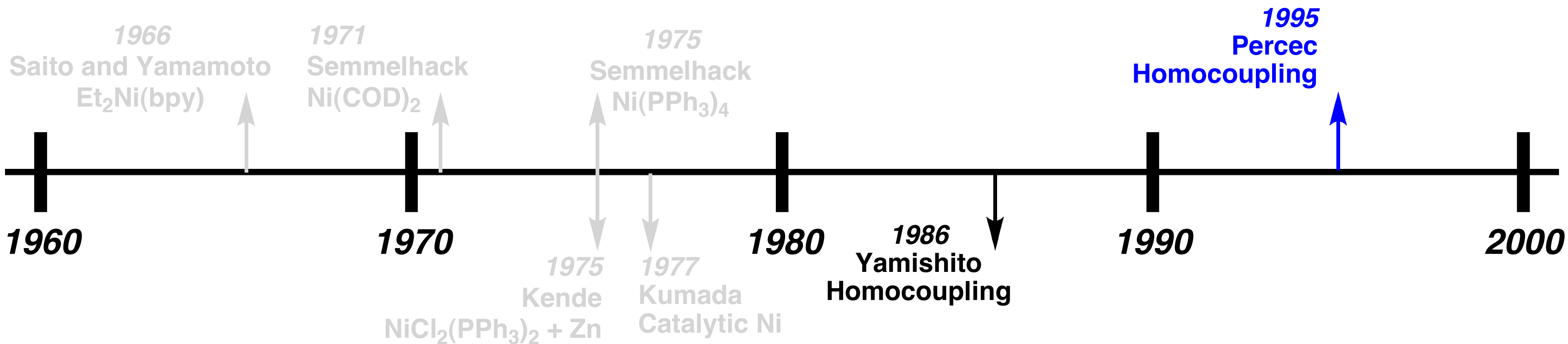
Yamishito, J.



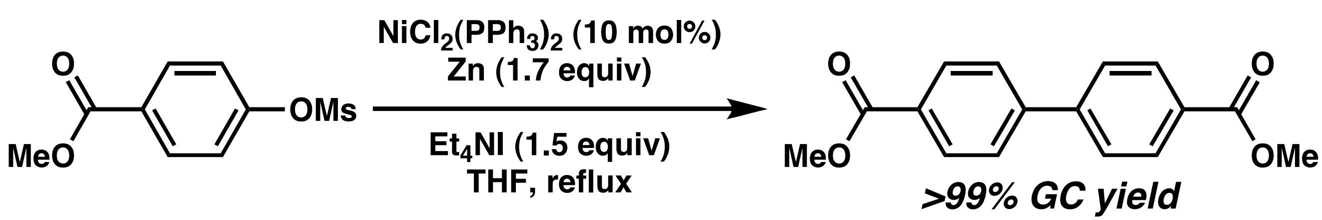
Chem. Lett. **1986**, 407.

Ni Chemistry Timeline

Sulfonate Highlights

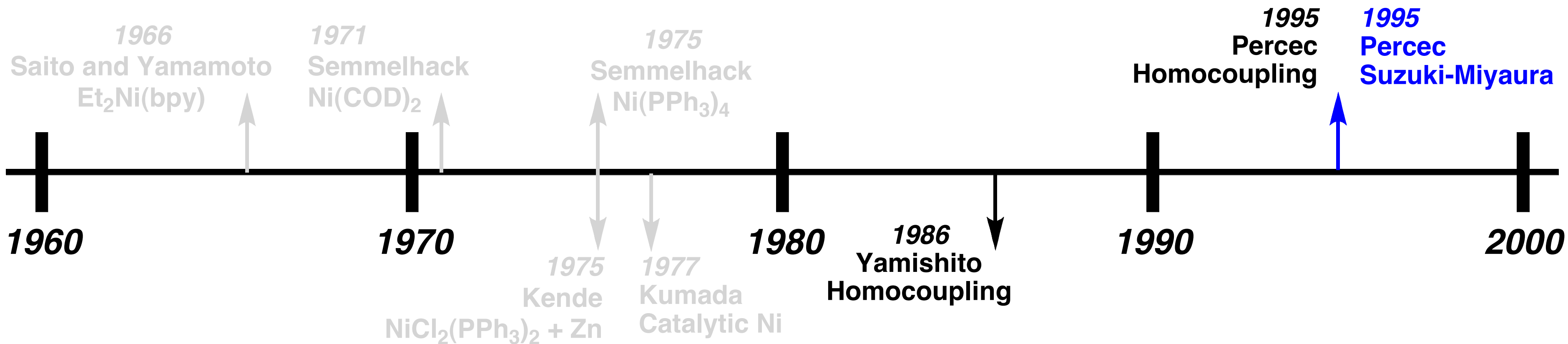


Percec, V.

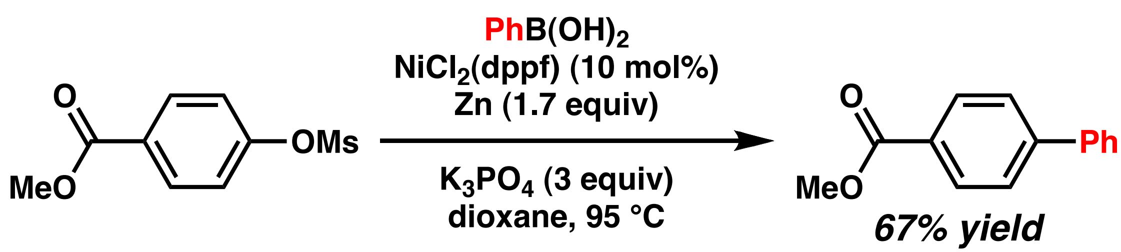


J. Org. Chem. **1995**, *60*, 176.

Ni Chemistry Timeline
Sulfonate Highlights

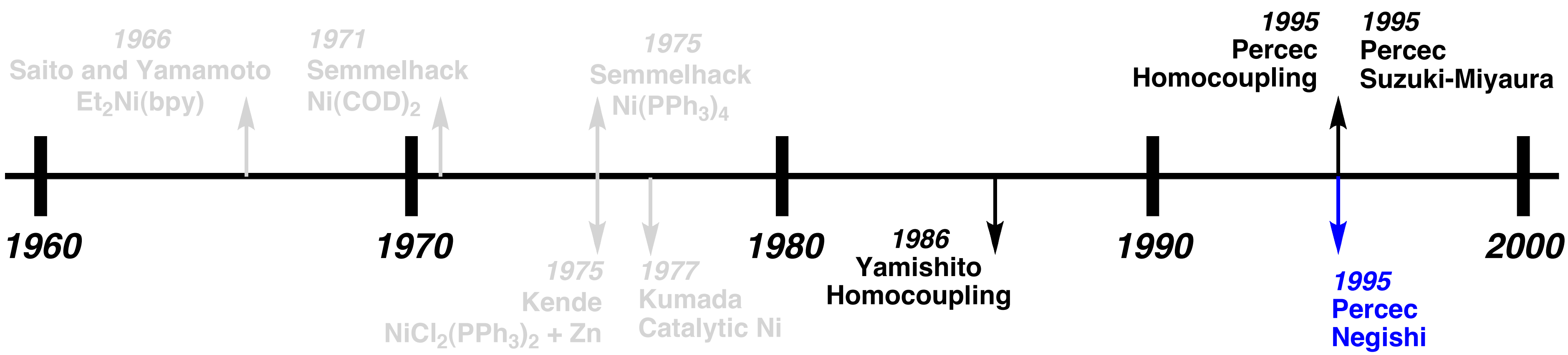


Percec, V.

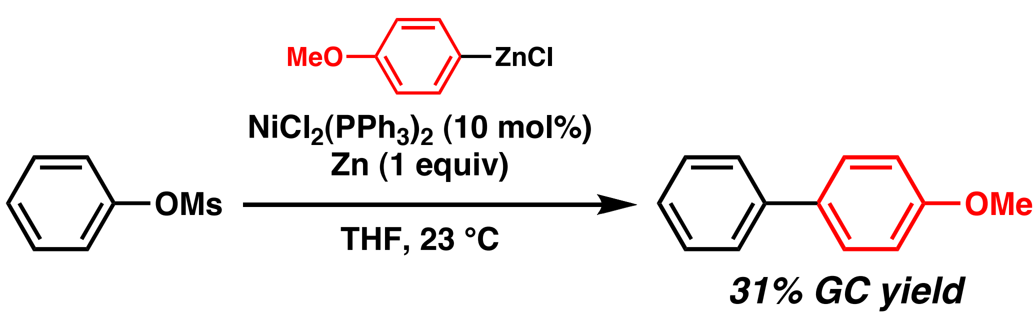


J. Org. Chem. **1995**, *60*, 1060.

Ni Chemistry Timeline
Sulfonate Highlights



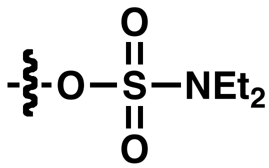
Percec, V.



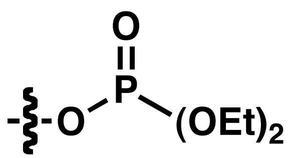
J. Org. Chem. **1995**, *60*, 6895.

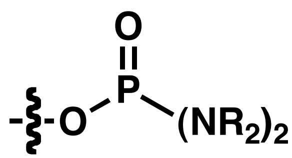
Overview

Sulfamates

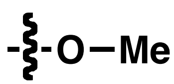


Phosphonates and Phosphoramides

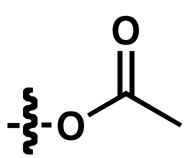


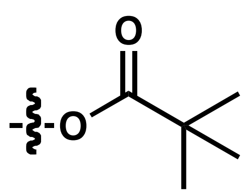


Ethers

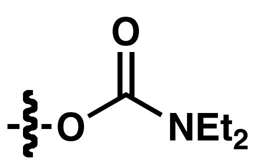


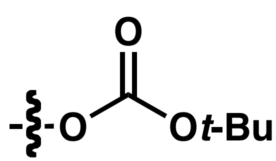
Esters





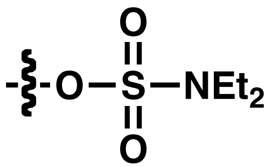
Carbamates and Carbonates





Overview

Sulfamates



Phosphonates and Phosphoramides

Ethers

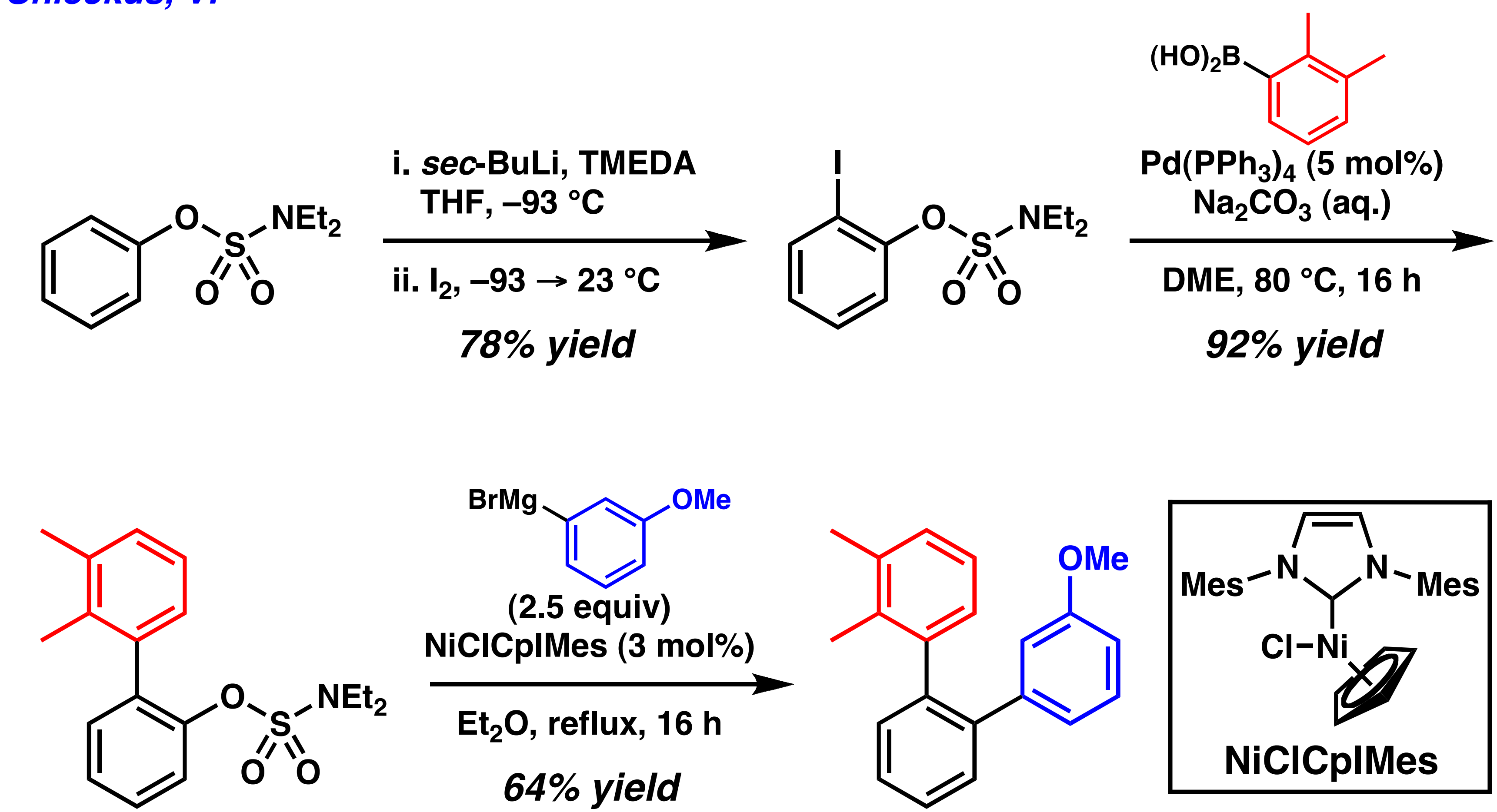
Esters

Carbamates and Carbonates

Sulfamate Ni Cross Coupling

Directed Ortho Metalation (DoM)

Snieckus, V.

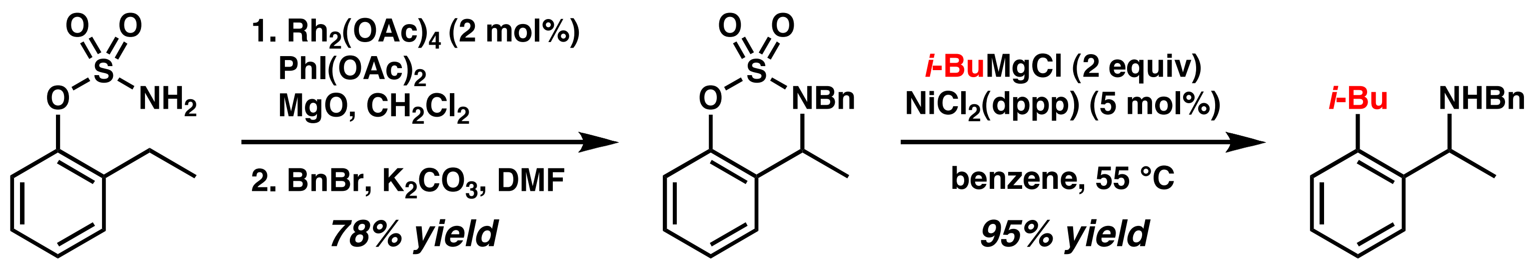


Org. Lett. **2005**, *7*, 2519.

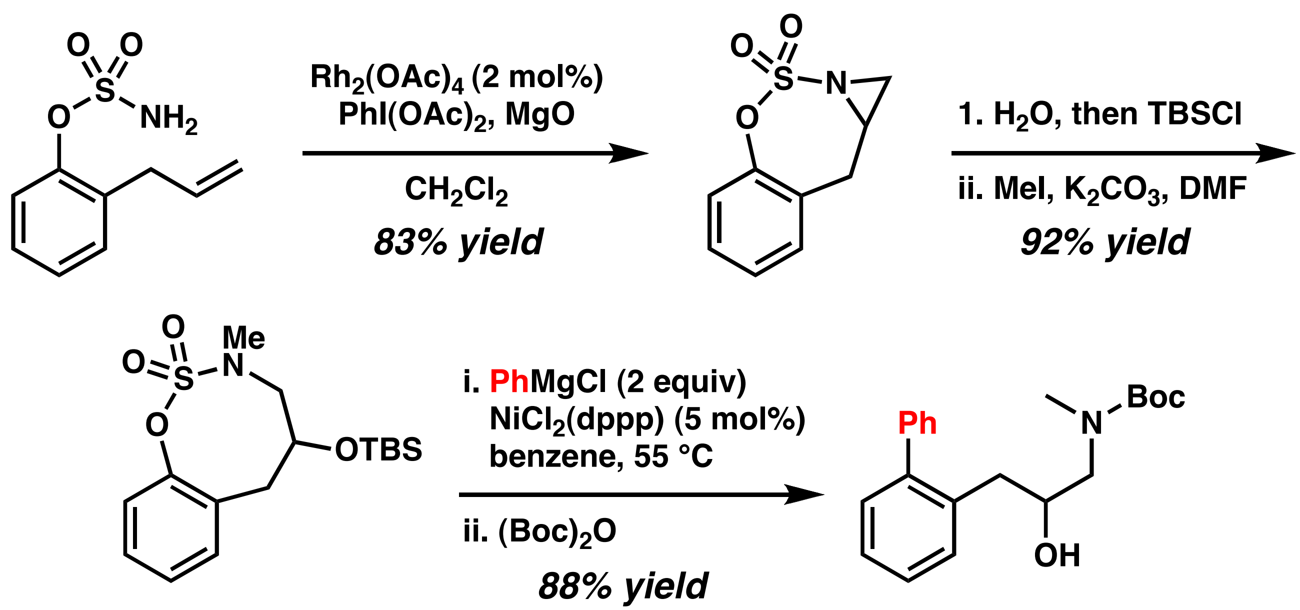
Sulfamate Ni Cross Coupling
Kumada Coupling

Du Bois, J.

C-H Insertion



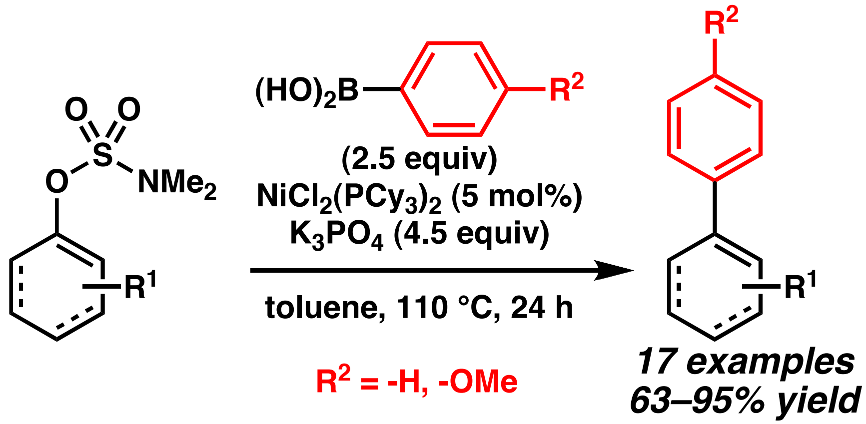
Aziridine Formation

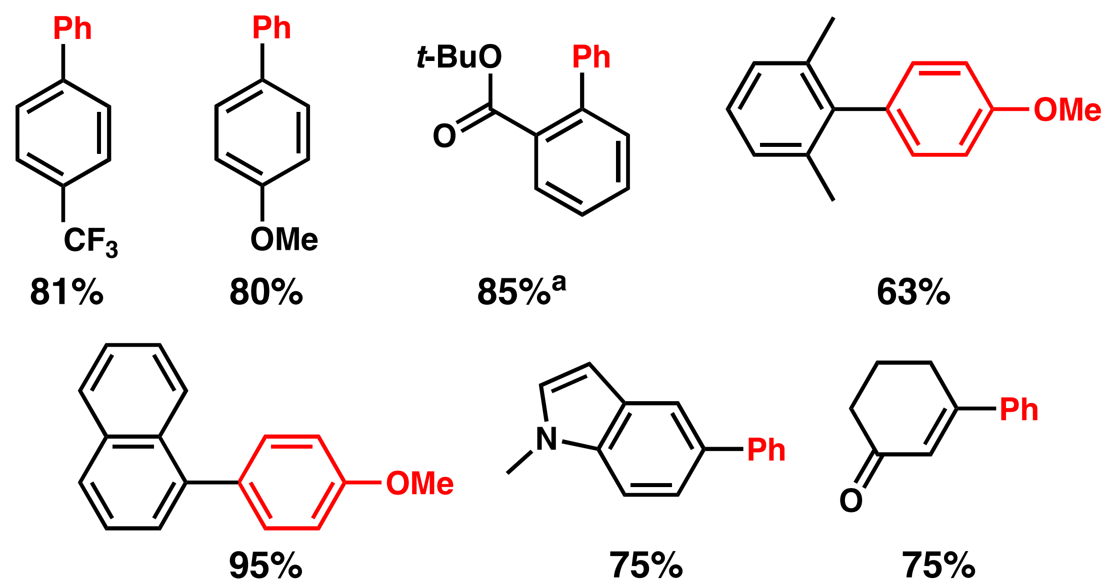


Org. Lett. **2005**, *7*, 4685.

Sulfamate Ni Cross Coupling
Suzuki-Miyaura Coupling

Garg, N. K.





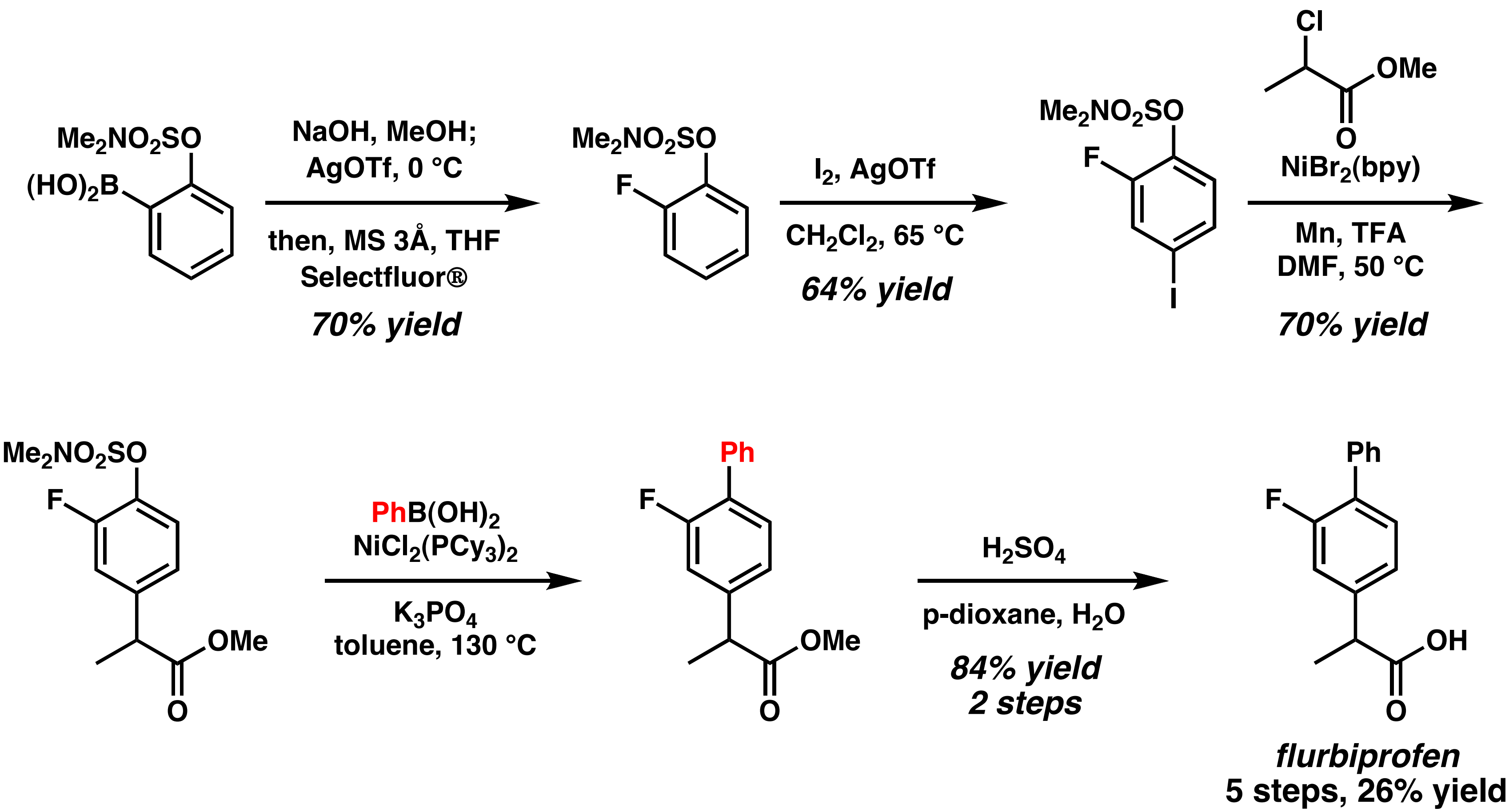
[a] 10 mol% $NiCl_2(PCy_3)_2$, 4 equiv $ArB(OH)_2$, 7.2 equiv K_3PO_4, toluene, 130 °C

J. Am. Chem. Soc. **2009**, *131*, 17748.

Sulfamate Ni Cross Coupling

Total Synthesis of Flurbiprofen

Garg, N. K.

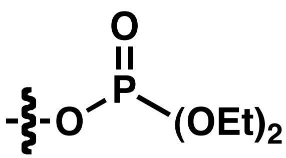


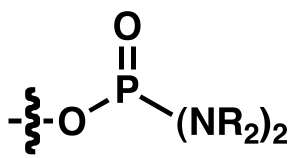
J. Am. Chem. Soc. **2009**, *131*, 17748.

Overview

Sulfamates

Phosphonates and Phosphoramides





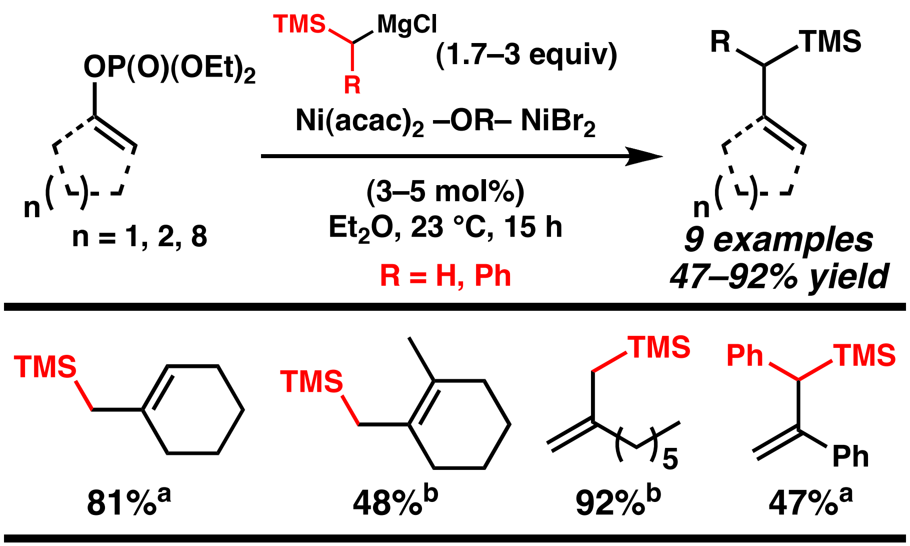
Ethers

Esters

Carbamates and Carbonates

Phosphonate and Phosphoramide Cross Coupling
Kumada Coupling: Vinyl Phosphonates

Kumada, M.



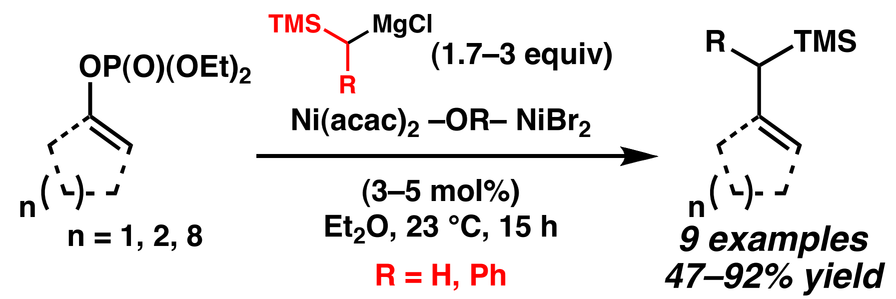
[a] $Ni(acac)_2$. [b] $NiBr_2$

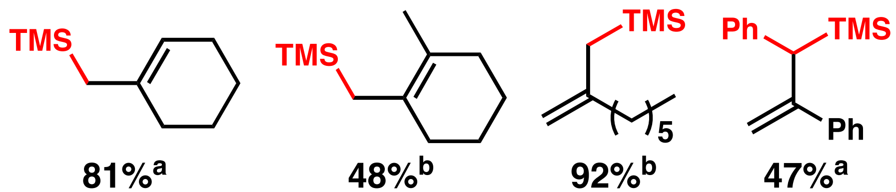
Kumada, M. *Synthesis* **1981**, 1001.
Claesson, M. *Tetrahedron Lett.* **1983**, *24*, 5137.
Nicolaou, K. C. *Chem. Commun.* **1998**, 1757.
Backvall, J.-E. *J. Org. Chem.* **1999**, *64*, 1745.

Phosphonate and Phosphoramide Cross Coupling

Kumada Coupling: Vinyl Phosphonates

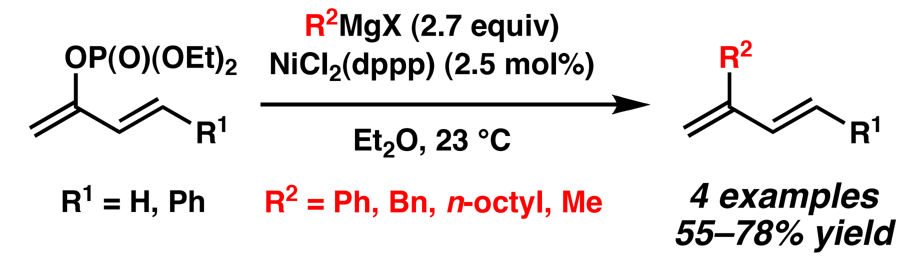
Kumada, M.

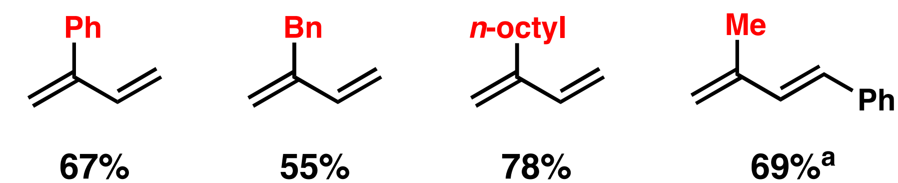




[a] Ni(acac)$_2$. [b] NiBr$_2$

Claesson, A.





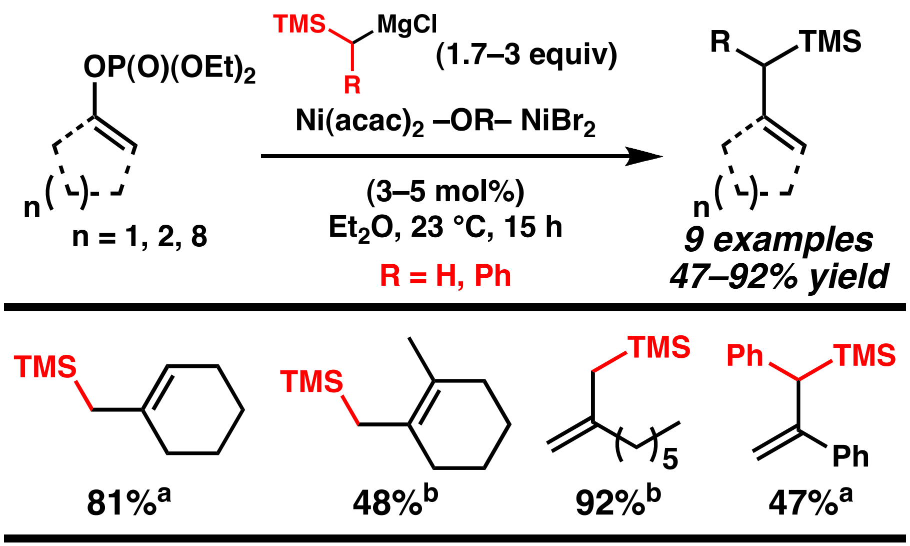
[a] NiCl$_2$(dppe).

Kumada, M. *Synthesis* **1981**, 1001.
Claesson, M. *Tetrahedron Lett.* **1983**, *24*, 5137.
Nicolaou, K. C. *Chem. Commun.* **1998**, 1757.
Backvall, J.-E. *J. Org. Chem.* **1999**, *64*, 1745.

Phosphonate and Phosphoramide Cross Coupling

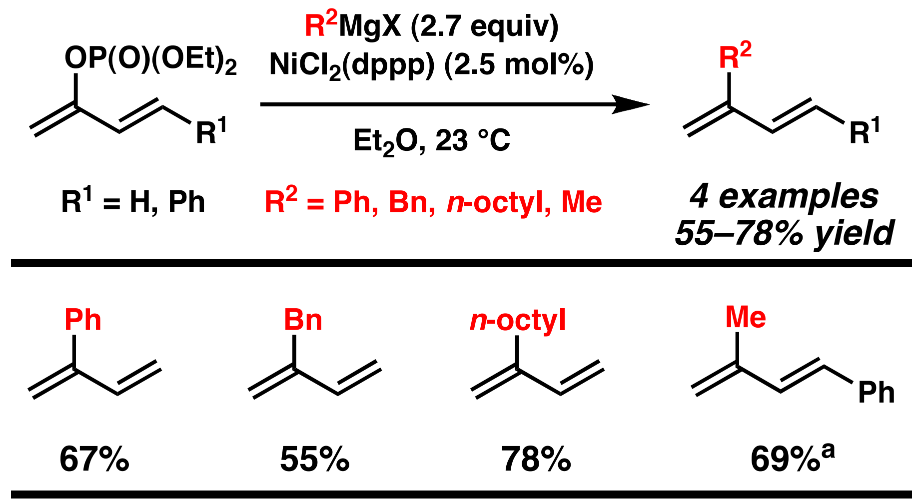
Kumada Coupling: Vinyl Phosphonates

Kumada, M.



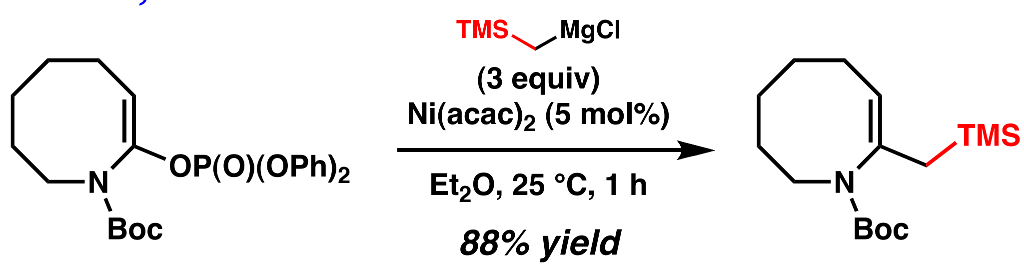
[a] Ni(acac)$_2$. [b] NiBr$_2$

Claesson, A.



[a] NiCl$_2$(dppe).

Nicolaou, K. C.

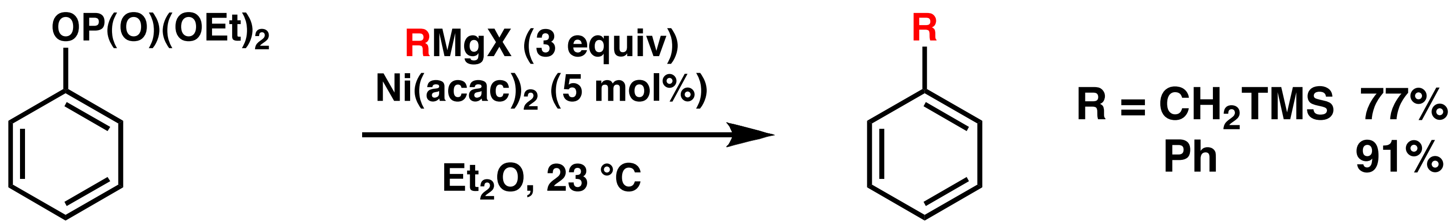


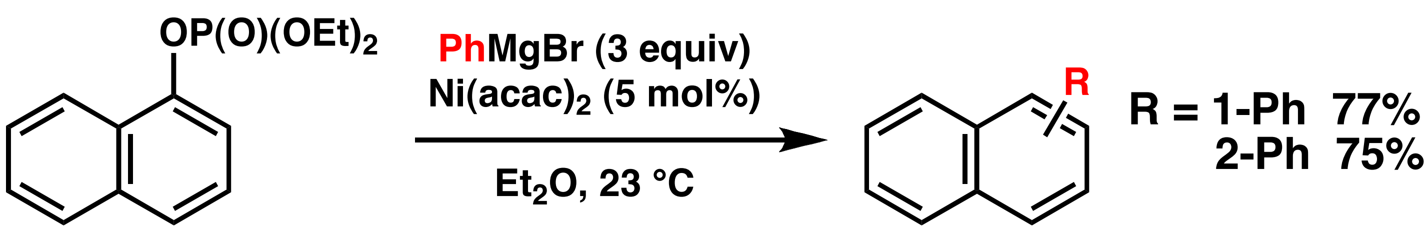
Kumada, M. *Synthesis* **1981**, 1001.
Claesson, M. *Tetrahedron Lett.* **1983**, *24*, 5137.
Nicolaou, K. C. *Chem. Commun.* **1998**, 1757.
Backvall, J.-E. *J. Org. Chem.* **1999**, *64*, 1745.

Phosphonate and Phosphoramide Cross Coupling

Kumada Coupling: Aryl Phosphonates

Kumada, M.



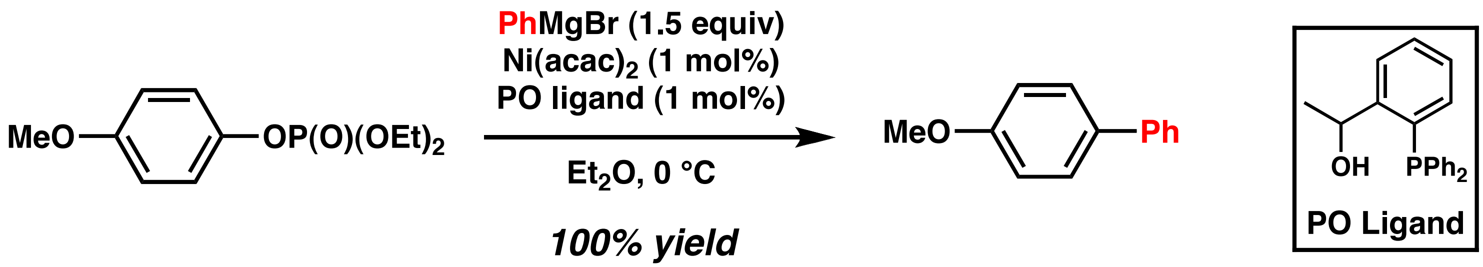


Tetrahedron Lett. **1981**, *22*, 4449.

Phosphonate and Phosphoramide Cross Coupling

Hydroxyphosphine Promoted Kumada Coupling

Nakamura, E.

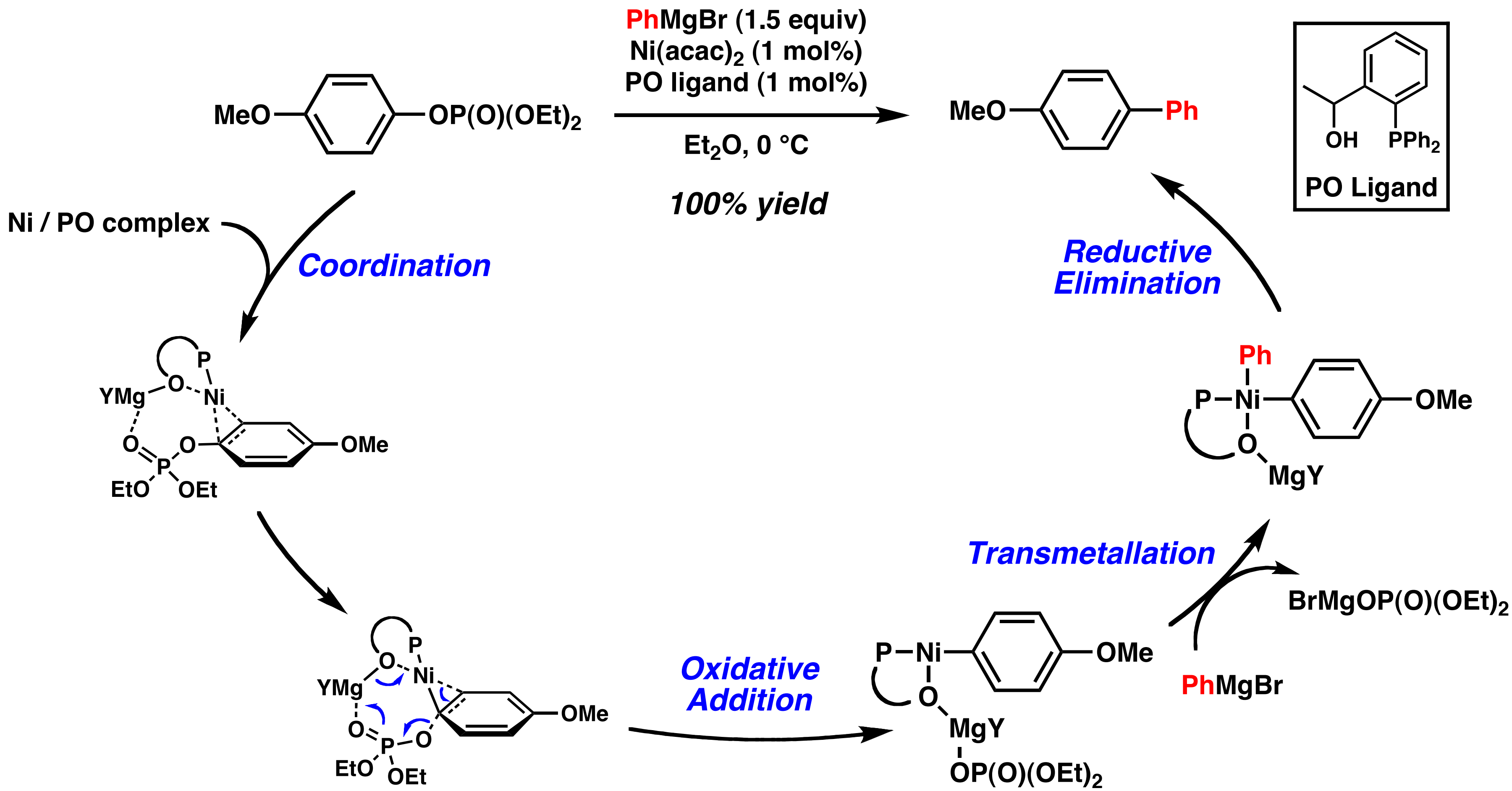


J. Am. Chem. Soc. **2009**, *131*, 9590.

Phosphonate and Phosphoramide Cross Coupling

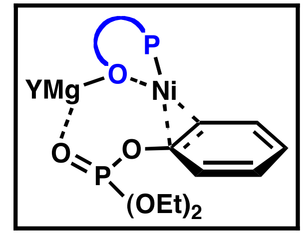
Hydroxyphosphine Promoted Kumada Coupling

Nakamura, E.

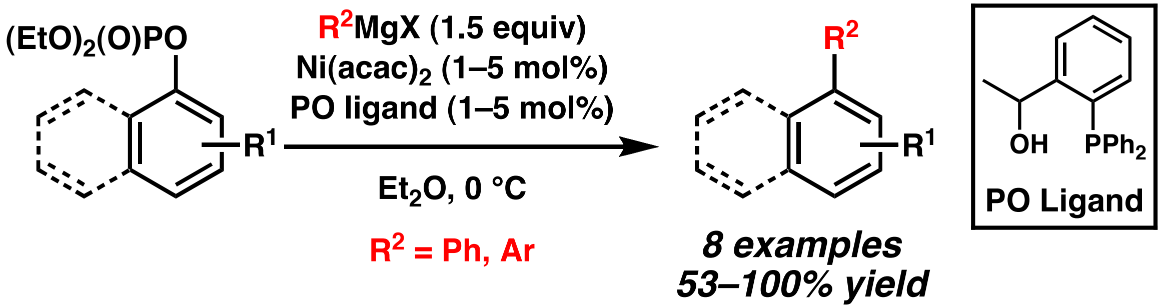


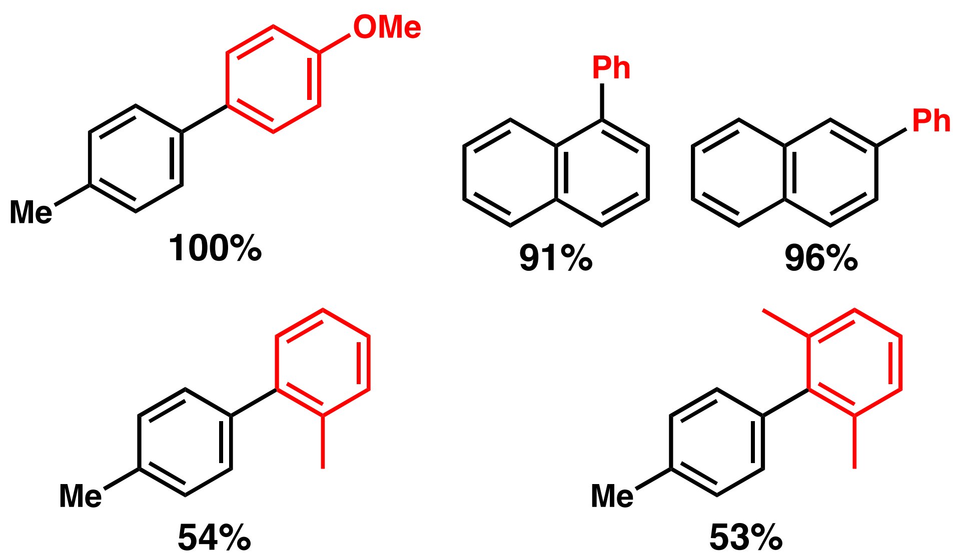
J. Am. Chem. Soc. **2009**, *131*, 9590.

Phosphonate and Phosphoramide Cross Coupling
Hydroxyphosphine Promoted Kumada Coupling



Nakamura, E.

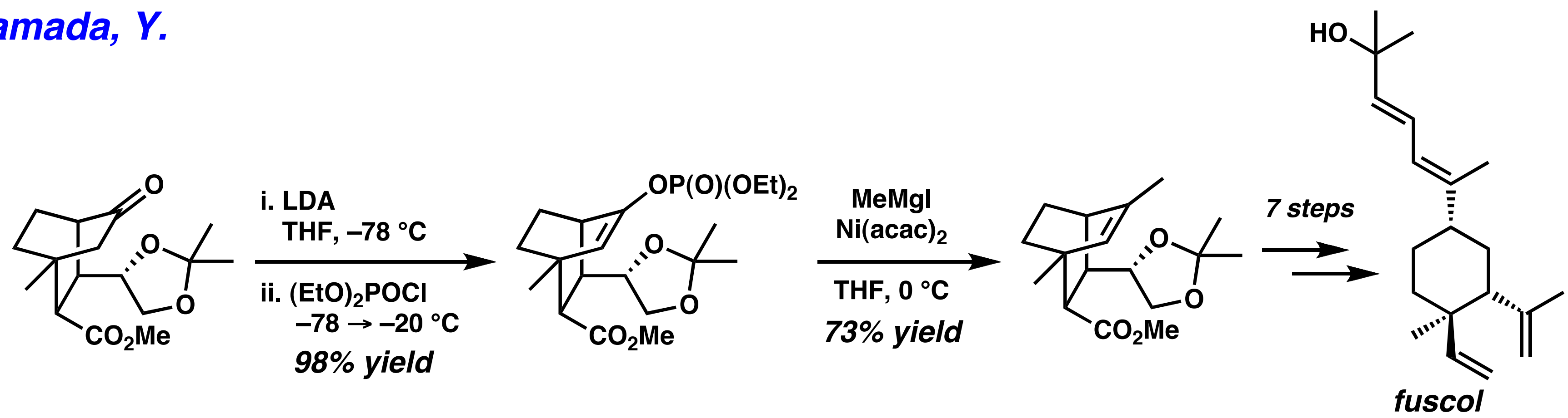




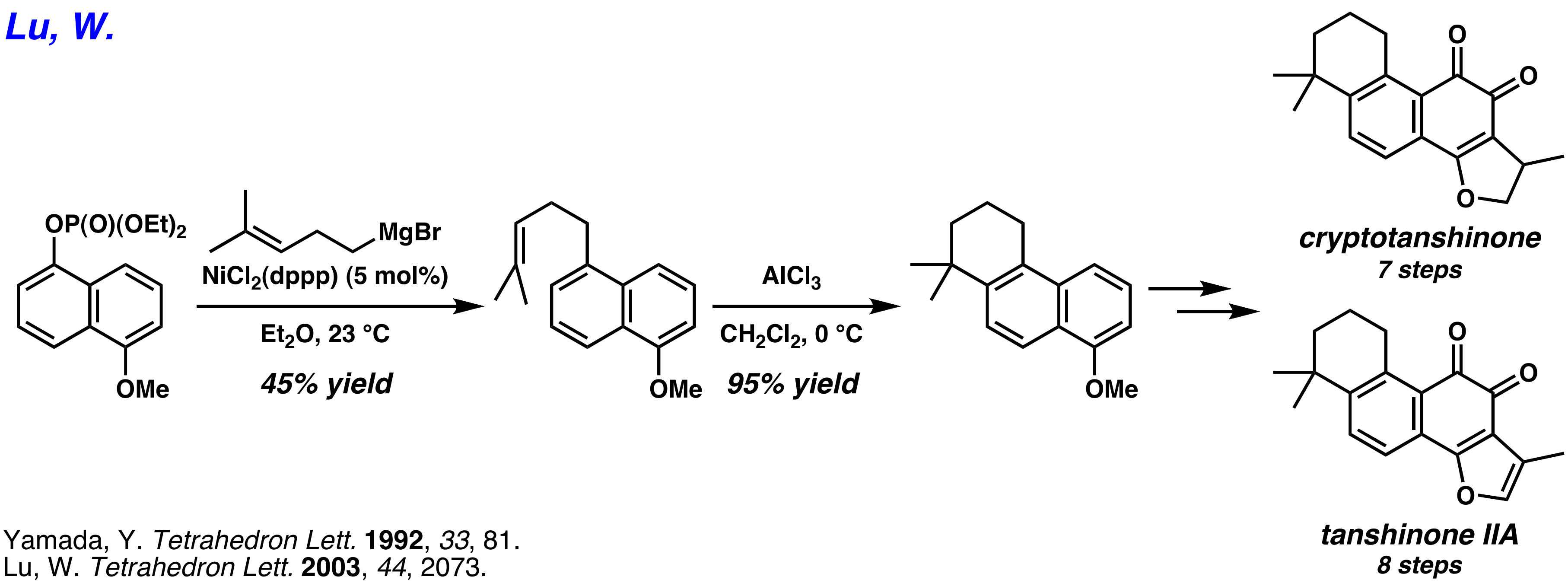
J. Am. Chem. Soc. **2009**, *131*, 9590.

Phosphonate and Phosphoramide Cross Coupling
Kumada Coupling: Total Synthesis

Yamada, Y.



Lu, W.

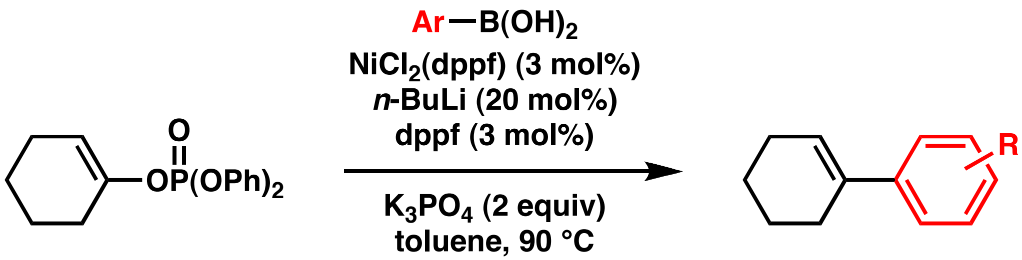


Yamada, Y. *Tetrahedron Lett.* **1992**, *33*, 81.
Lu, W. *Tetrahedron Lett.* **2003**, *44*, 2073.

Phosphonate and Phosphoramide Cross Coupling

Suzuki-Miyaura Coupling: Vinyl Phosphonates

Yang, Z.



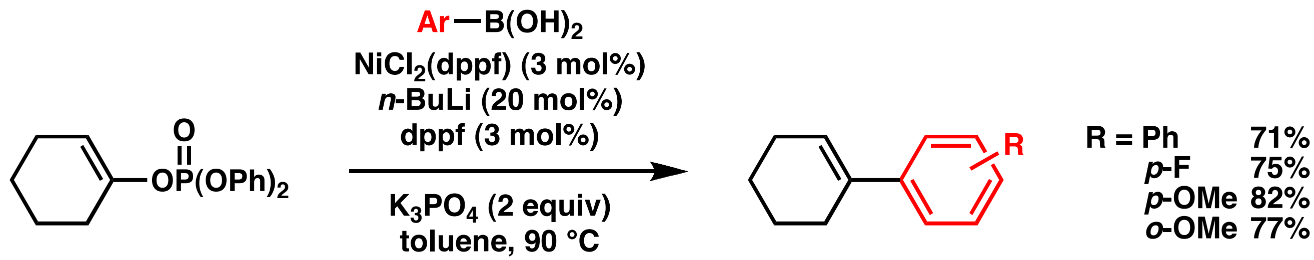
R = Ph	71%
p-F	75%
p-OMe	82%
o-OMe	77%

Yang, Z. *Tetrahedron Lett.* **1999**, *40*, 3321.
Yamada, Y. *Chem. Commun.* **2006**, 4137. Yamada, Y. *J. Org. Chem.* **2007**, *72*, 6465.

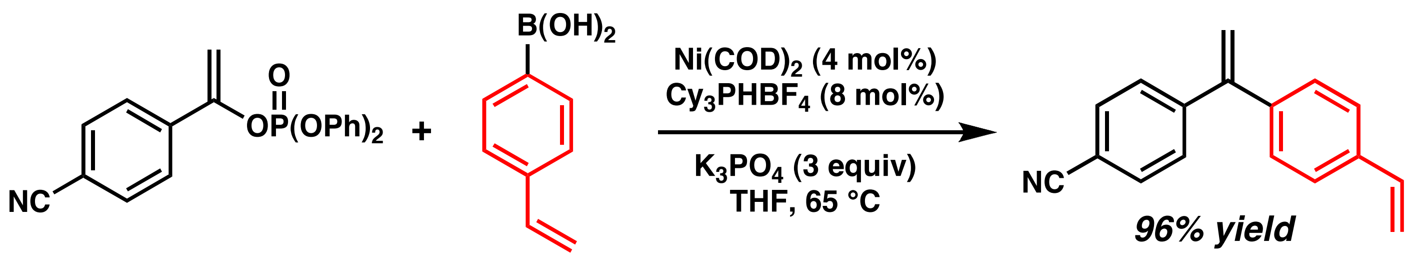
Phosphonate and Phosphoramide Cross Coupling

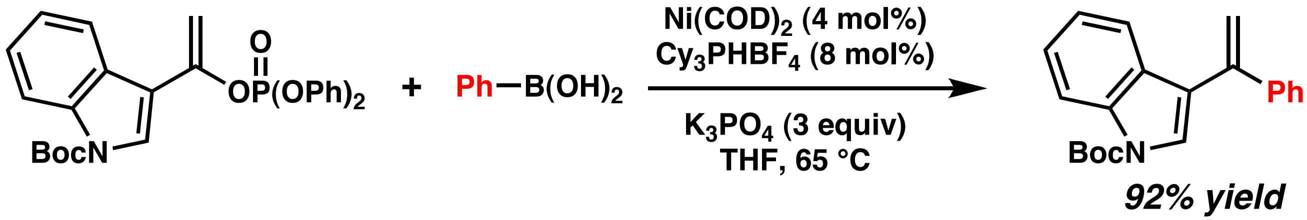
Suzuki-Miyaura Coupling: Vinyl Phosphonates

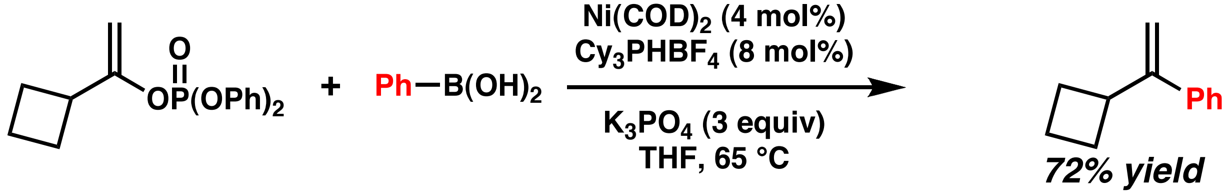
Yang, Z.



Yamada, Y.





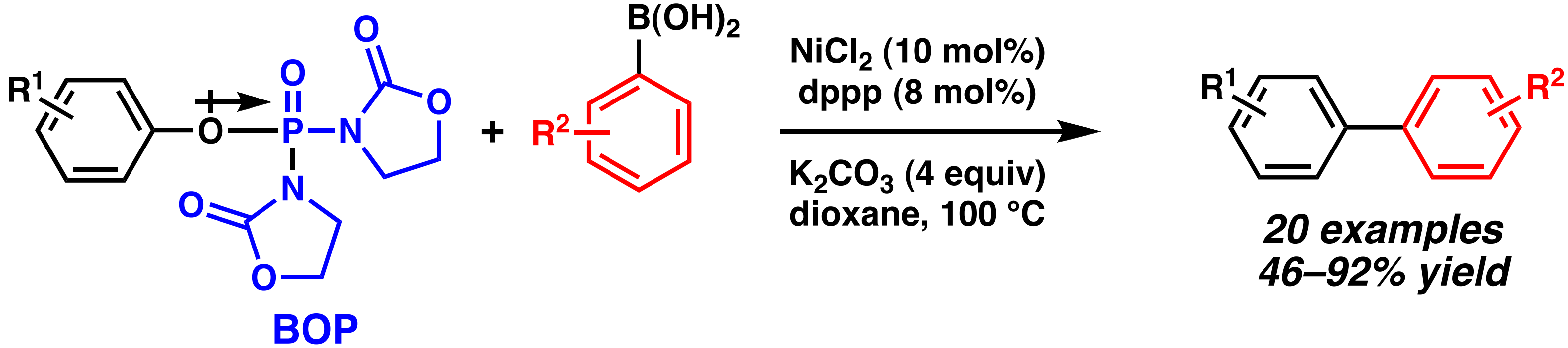


Yang, Z. *Tetrahedron Lett.* **1999**, *40*, 3321.
Yamada, Y. *Chem. Commun.* **2006**, 4137. Yamada, Y. *J. Org. Chem.* **2007**, *72*, 6465.

Phosphonate and Phosphoramide Cross Coupling

Suzuki-Miyaura Coupling: Aryl Phosphoramides

Han, F.-S.

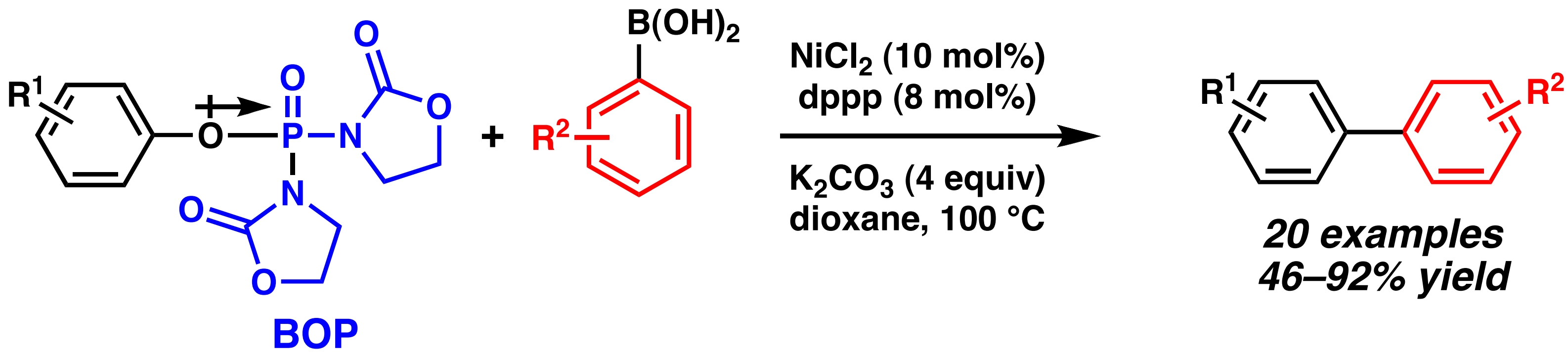


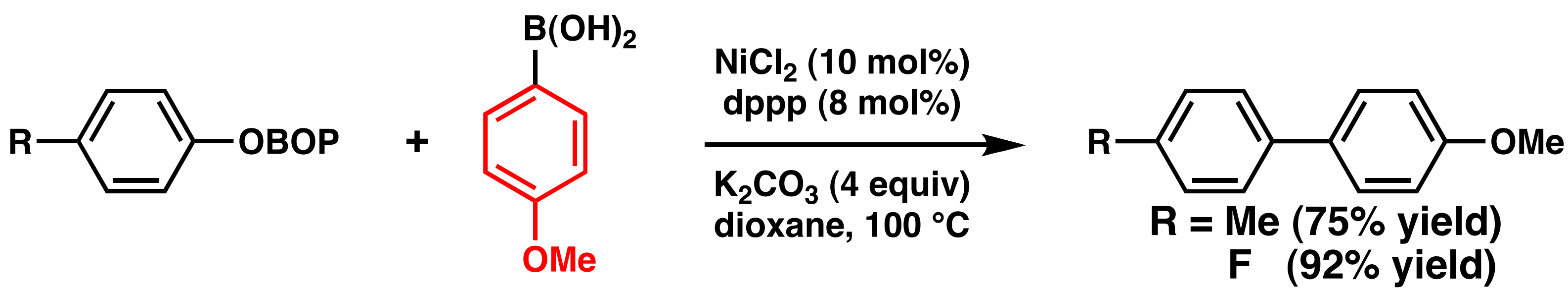
Chem. Eur. J. **2010**, *16*, 4991.

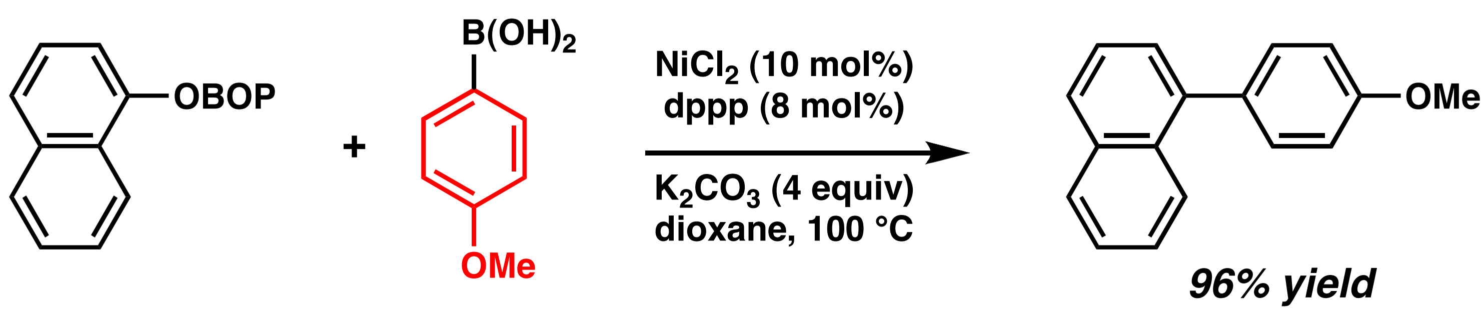
Phosphonate and Phosphoramide Cross Coupling

Suzuki-Miyaura Coupling: Aryl Phosphoramides

Han, F.-S.







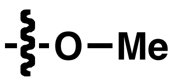
Chem. Eur. J. **2010**, *16*, 4991.

Overview

Sulfamates

Phosphonates and Phosphoramides

Ethers



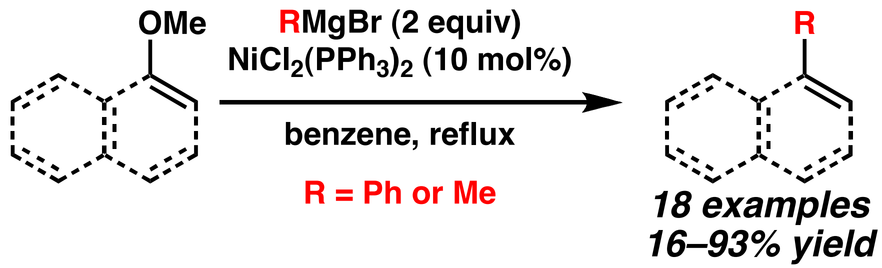
Esters

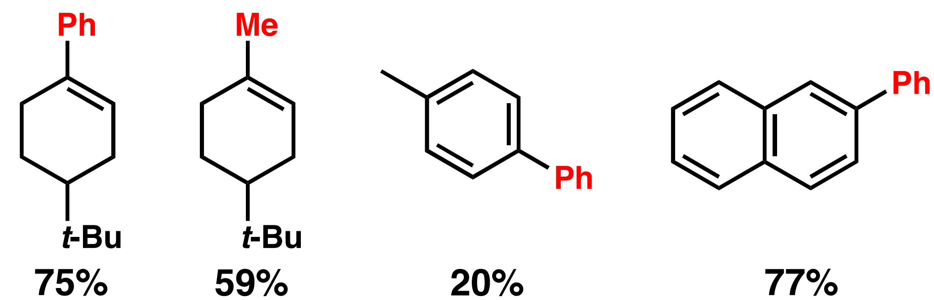
Carbamates and Carbonates

Ether Cross Coupling

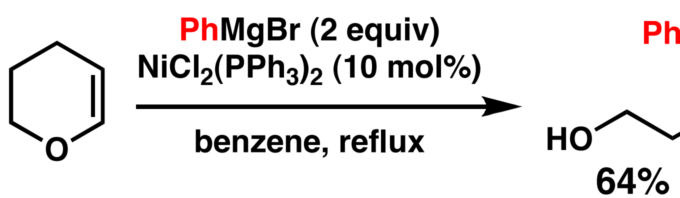
Kumada Coupling

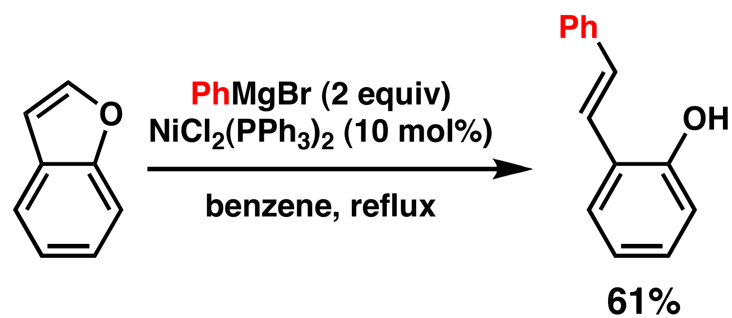
Wenkert, E.





Cyclic Ethers



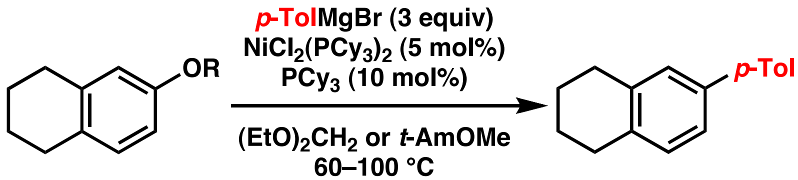


J. Am. Chem. Soc. **1979**, *101*, 2246.

Ether Cross Coupling

Kumada Coupling: Aryl and Benzyl Ether Screen

Dankwardt, J. W.

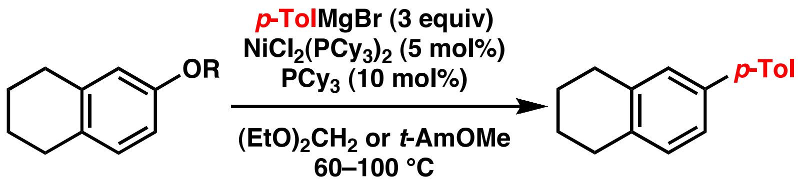


R	GC yield	R	GC yield
-Me	94%	-MOM	92%
$-(CH_2)_2OMe$	77%	-TMS	70%
$-(CH_2)_2NMe_2$	99%		

Aryl Ethers: Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428.
Aryl Ethers: Shi, Z.-J. *Chem. Commun.* **2008**, 1437.
Benzyl Ethers: Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268.

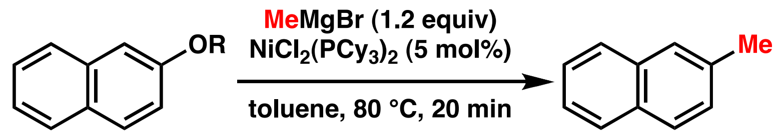
Ether Cross Coupling
Kumada Coupling: Aryl and Benzyl Ether Screen

Dankwardt, J. W.



R	GC yield	R	GC yield
-Me	94%	-MOM	92%
$-(CH_2)_2OMe$	77%	-TMS	70%
$-(CH_2)_2NMe_2$	99%		

Shi, Z.-J.

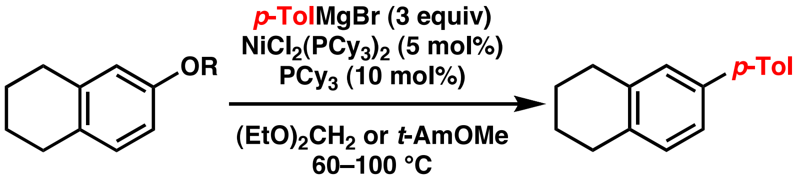


R	yield	R	yield
-Me	92%	-*t*-Bu	88%
-Et	92%	-MOM	69%
-*n*-Bu	96%	-TMS	95%
-*i*-Bu	91%	-Ph	95%

Aryl Ethers: Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428.
Aryl Ethers: Shi, Z.-J. *Chem. Commun.* **2008**, 1437.
Benzyl Ethers: Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268.

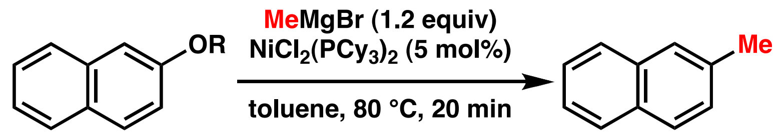
Ether Cross Coupling
Kumada Coupling: Aryl and Benzyl Ether Screen

Dankwardt, J. W.



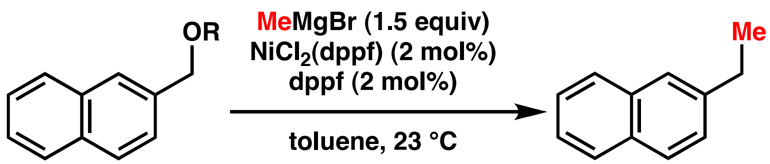
R	GC yield	R	GC yield
-Me	94%	-MOM	92%
-$(CH_2)_2$OMe	77%	-TMS	70%
-$(CH_2)_2NMe_2$	99%		

Shi, Z.-J.



R	yield	R	yield
-Me	92%	-*t*-Bu	88%
-Et	92%	-MOM	69%
-*n*-Bu	96%	-TMS	95%
-*i*-Bu	91%	-Ph	95%

Shi, Z.-J.



R	yield	R	yield
-Me	80%	-Ph	75%
-Et	73%	-TMS	76%
-*t*-Bu	79%	-Ac	18%[a]

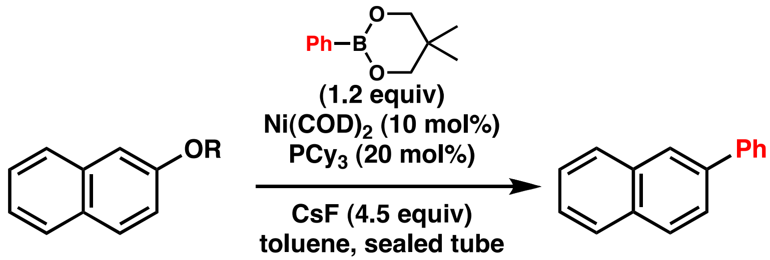
[a] GC yield

Aryl Ethers: Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428.
Aryl Ethers: Shi, Z.-J. *Chem. Commun.* **2008**, 1437.
Benzyl Ethers: Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268.

Ether Cross Coupling
Suzuki-Miyaura

Chatani, N.

Aryl Ether Screen



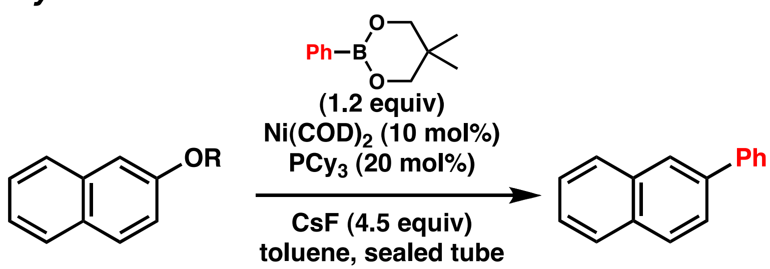
R	yield	R	yield
-Me	93%	-*i*-Pr	16%
-Et	74%	-Ac	10%

Aromatic Ethers: *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.
Vinyl Ethers: *Org. Lett.* **2009**, *11*, 4890.

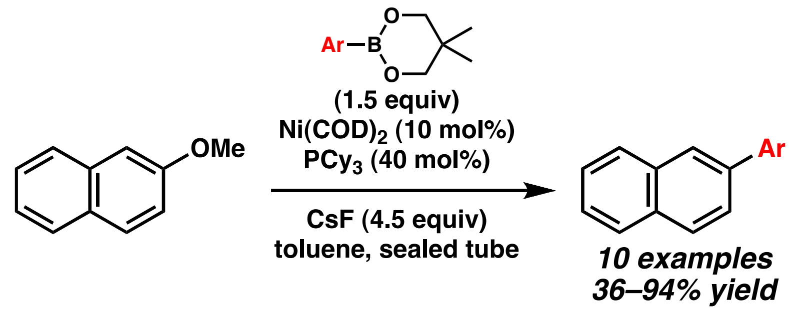
Ether Cross Coupling
Suzuki-Miyaura

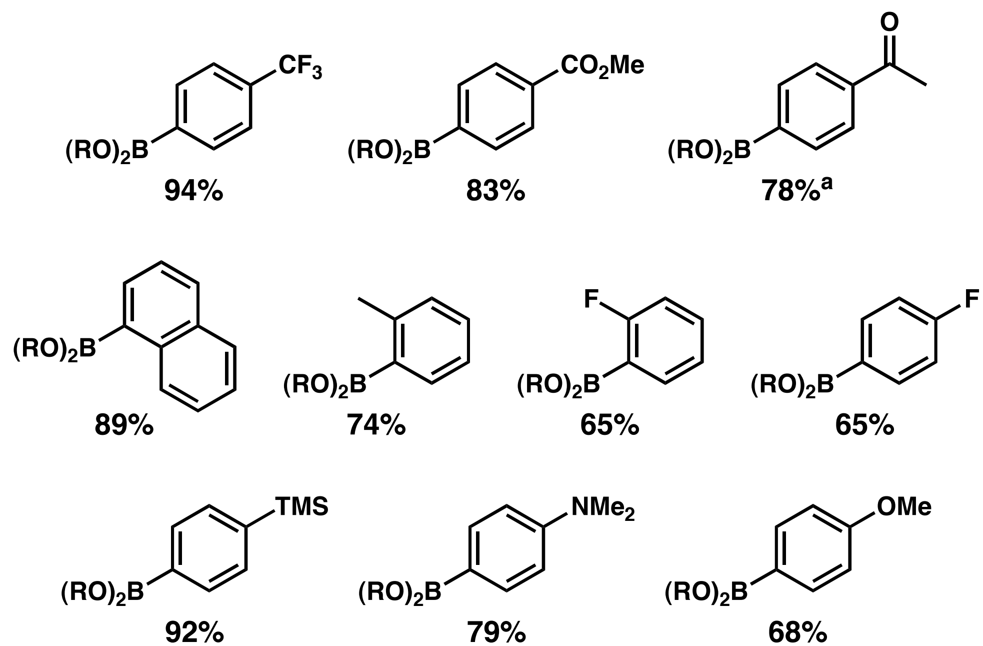
Chatani, N.

Aryl Ether Screen



R	yield	R	yield
-Me	93%	-*i*-Pr	16%
-Et	74%	-Ac	10%





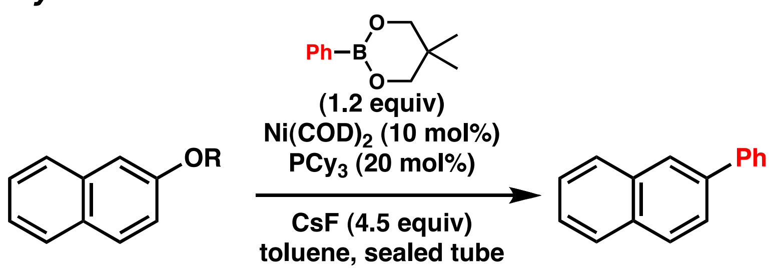
[a] 20 mol% $Ni(COD)_2$, 80 mol% PCy_3.

Aromatic Ethers: *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.
Vinyl Ethers: *Org. Lett.* **2009**, *11*, 4890.

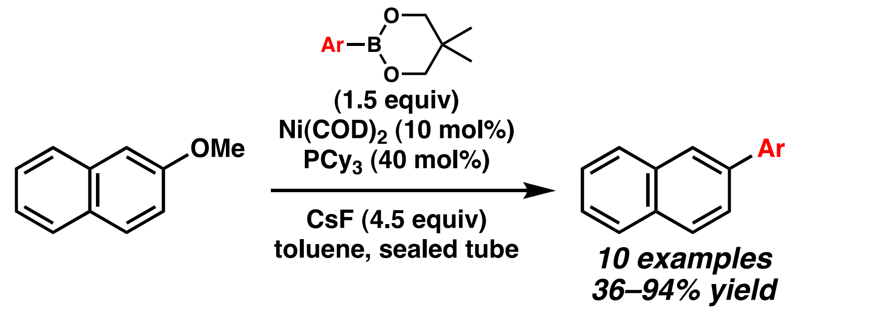
Ether Cross Coupling
Suzuki-Miyaura

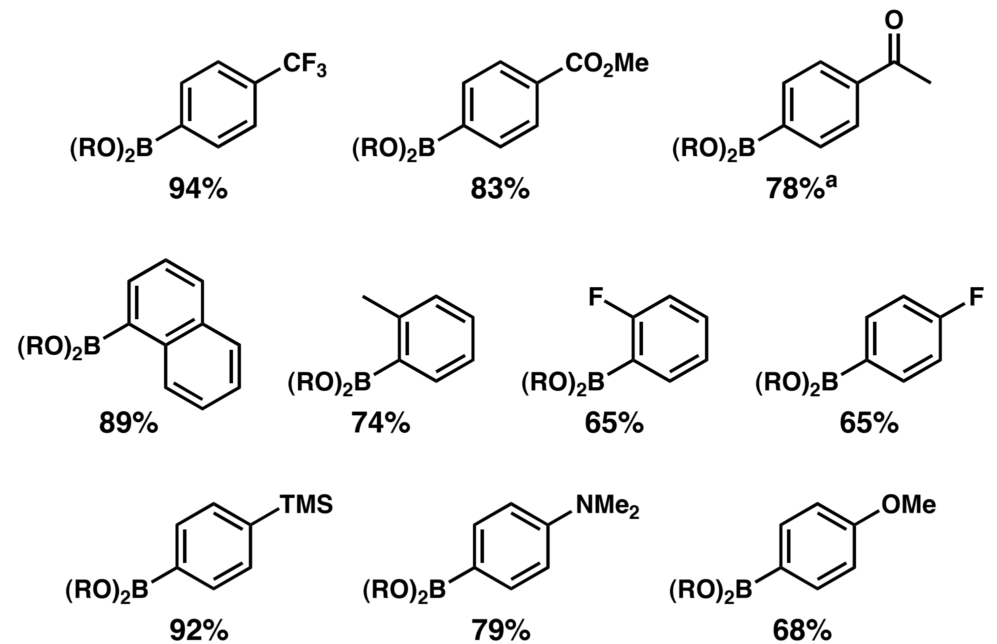
Chatani, N.

Aryl Ether Screen



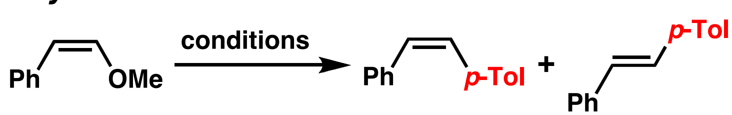
R	yield	R	yield
-Me	93%	-*i*-Pr	16%
-Et	74%	-Ac	10%





[a] 20 mol% Ni(COD)$_2$, 80 mol% PCy$_3$.

Vinyl Ethers



2 h	66 / 34
24 h	5 / 95

Aromatic Ethers: *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.
Vinyl Ethers: *Org. Lett.* **2009**, *11*, 4890.

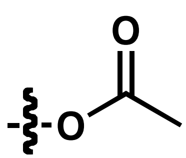
Overview

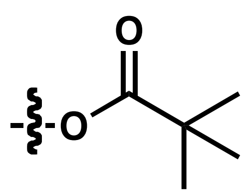
Sulfamates

Phosphonates and Phosphoramides

Ethers

Esters



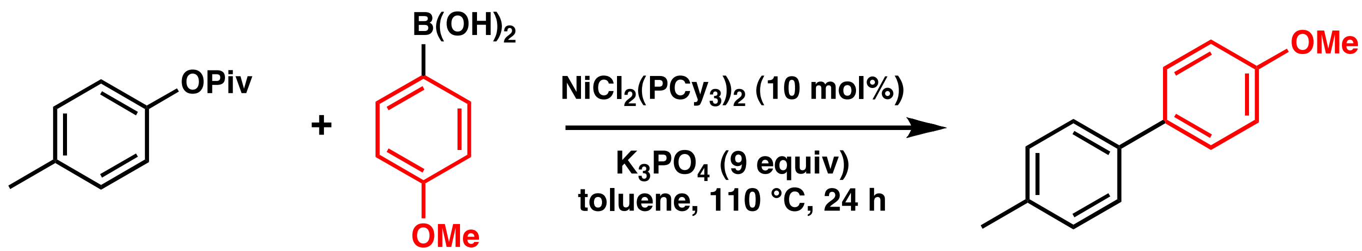


Carbamates and Carbonates

Ester Cross Coupling

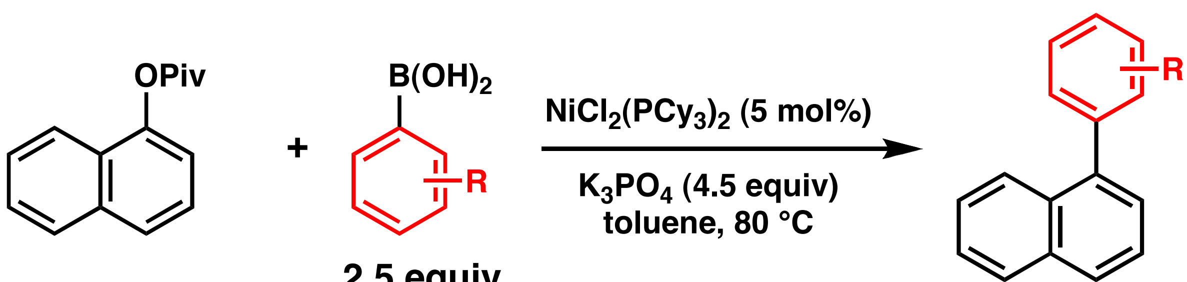
Suzuki-Miyaura Coupling: Aryl Esters

Garg, N. K.



5 equiv

65% yield



2.5 equiv

Electronics

R = *p*-OMe 95%

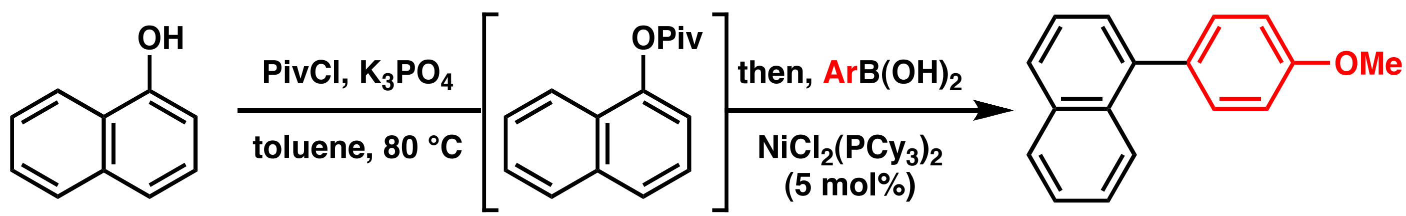
***p*-CF_3 77%**

Sterics

R = *p*-Me 91%

***m*-Me 99%**

***o*-Me 58%**



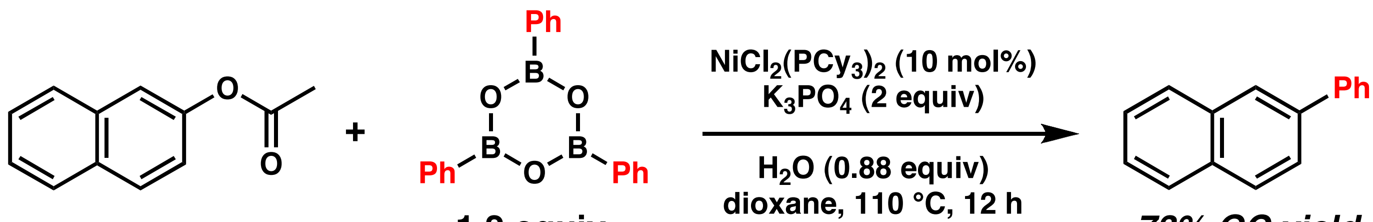
86% yield

J. Am. Chem. Soc. **2008**, *130*, 14422.

Ester Cross Coupling

Suzuki-Miyaura Coupling: Aryl Esters

Shi, Z.-J.



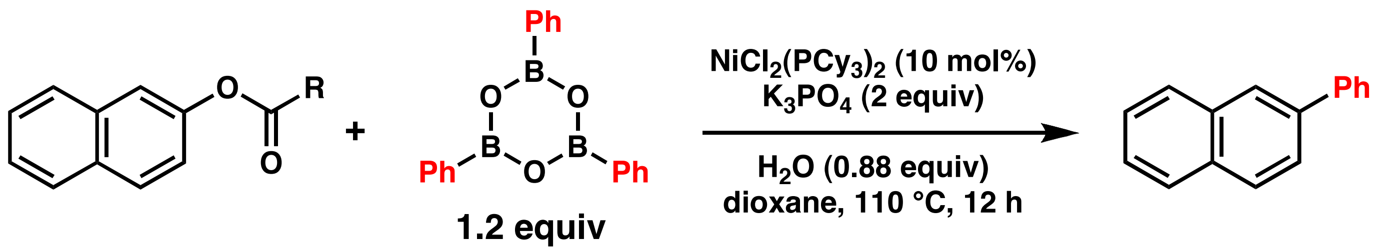
1.2 equiv

73% GC yield

J. Am. Chem. Soc. **2008**, *130*, 14468.

Ester Cross Coupling
Suzuki-Miyaura Coupling: Aryl Esters

Shi, Z.-J.



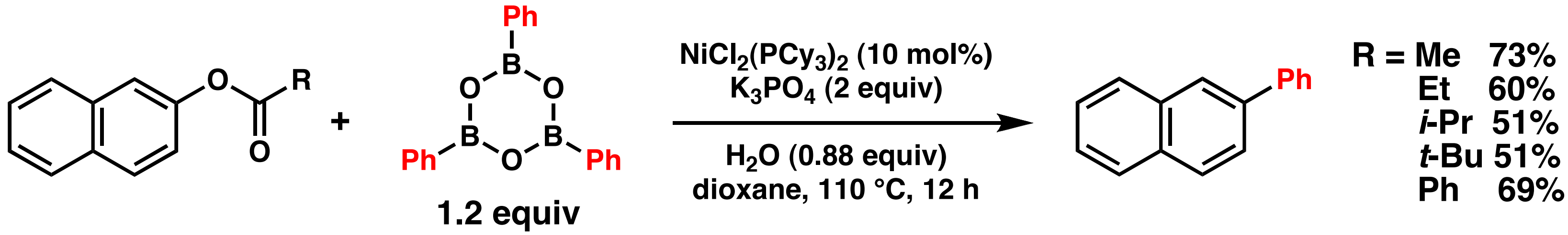
R =	Yield
Me	73%
Et	60%
i-Pr	51%
t-Bu	51%
Ph	69%

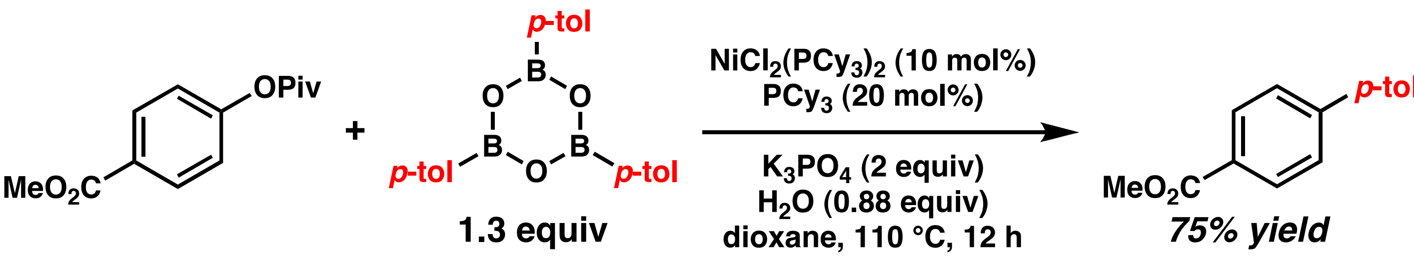
J. Am. Chem. Soc. **2008**, *130*, 14468.

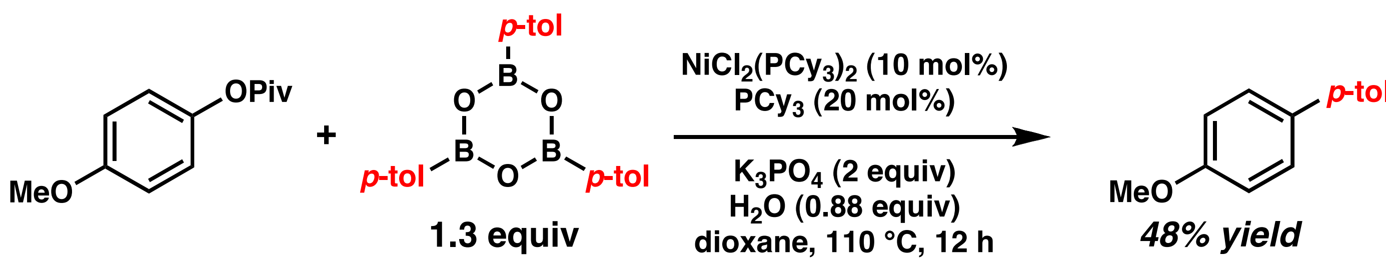
Ester Cross Coupling

Suzuki-Miyaura Coupling: Aryl Esters

Shi, Z.-J.





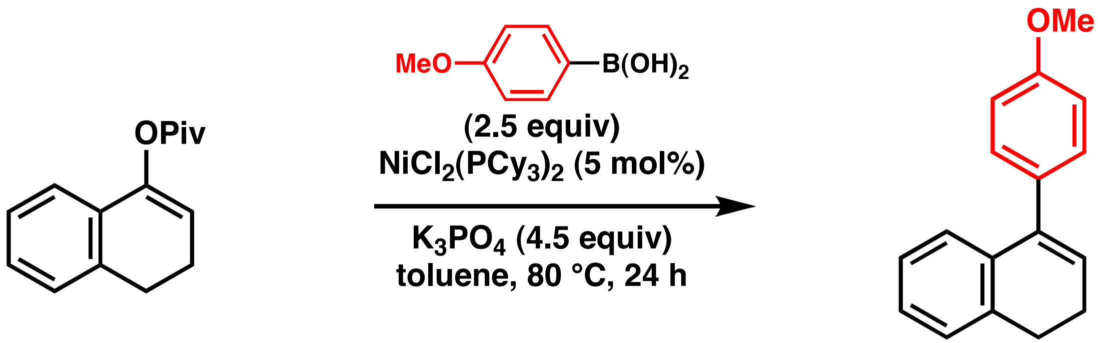


J. Am. Chem. Soc. **2008**, *130*, 14468.

Ester Cross Coupling

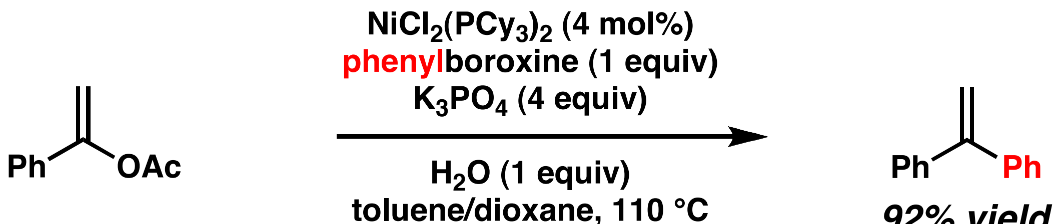
Suzuki-Miyaura Coupling: Vinyl Esters

Garg, N. K.

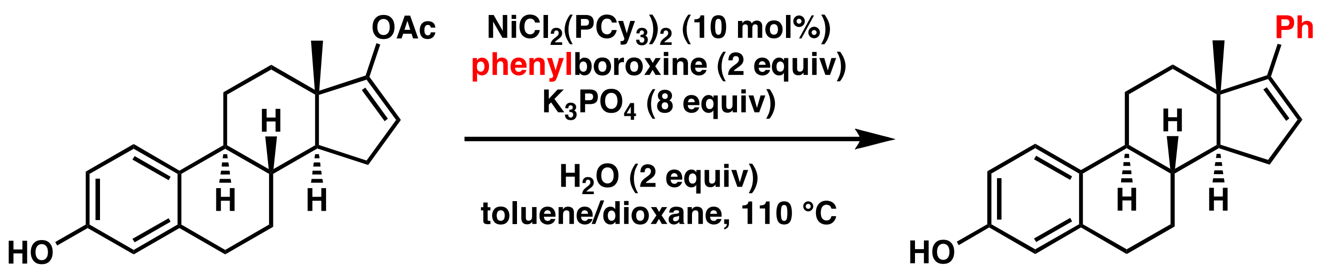


79% yield

Shi, Z.-J.



92% yield



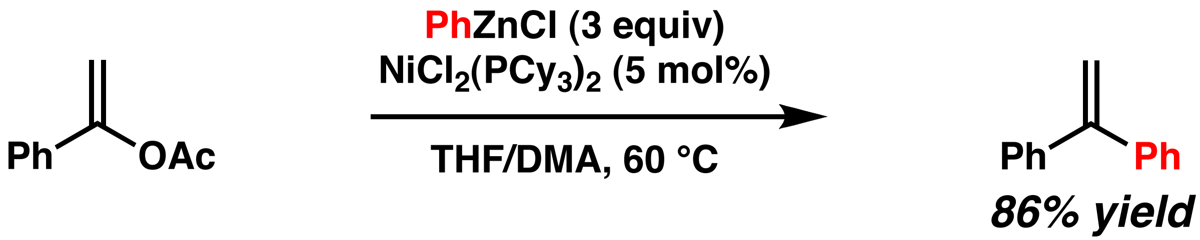
43% yield

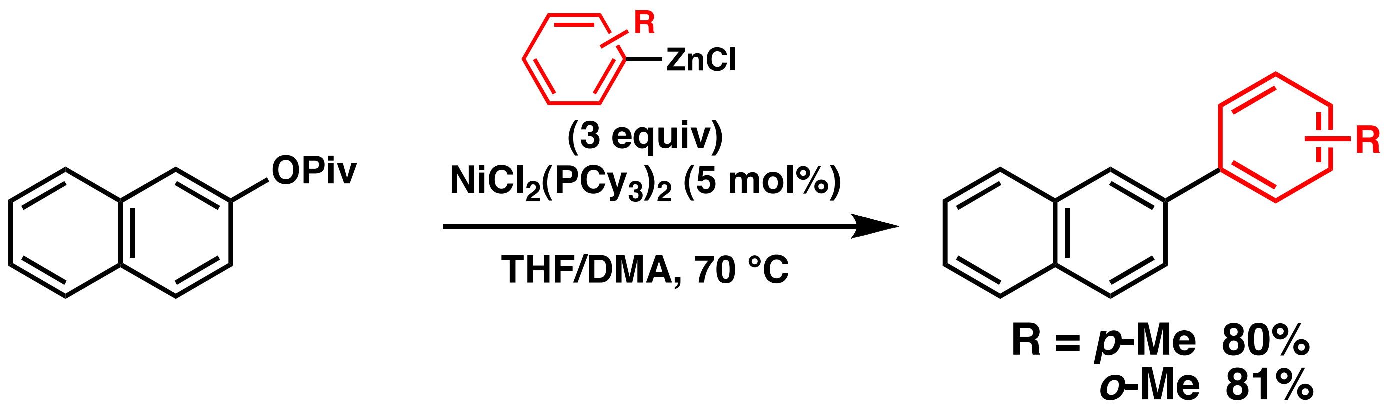
Garg, N. *J. Am. Chem. Soc.* **2008**, *130*, 14422.
Shi, Z.-J. *Chem. Eur. J.* **2010**, *16*, 5844.

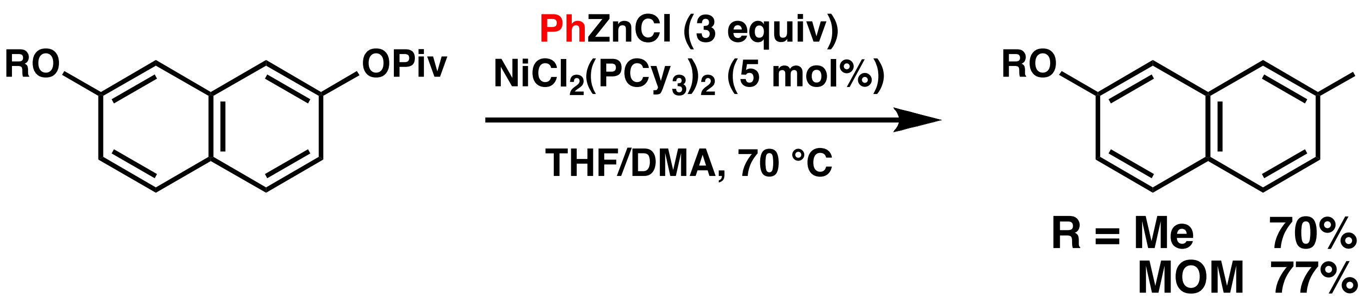
Ester Cross Coupling

Negishi Coupling

Shi, Z.-J.







Angew. Chem., Int. Ed. **2008**, *47*, 10124.
Chem. Eur. J. **2010**, *16*, 5844.

Overview

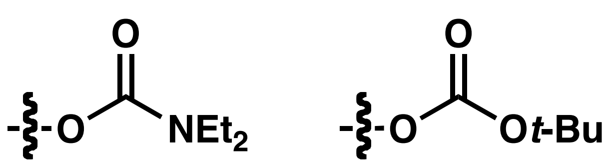
Sulfamates

Phosphonates and Phosphoramides

Ethers

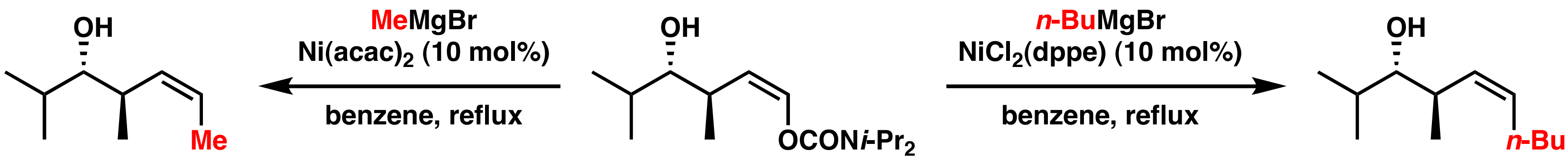
Esters

Carbamates and Carbonates



Carbamate and Carbonate Cross Coupling
Kumada Coupling: Vinyl Carbamate

Kocienski, P.

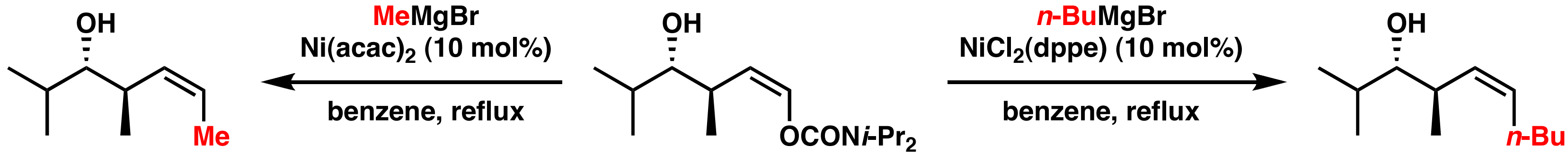


Kocienski, P. *Sylett* **1989**, 52.
Betzer, J.-F. *Tetrahedron Lett.* **2003**, *44*, 7553.

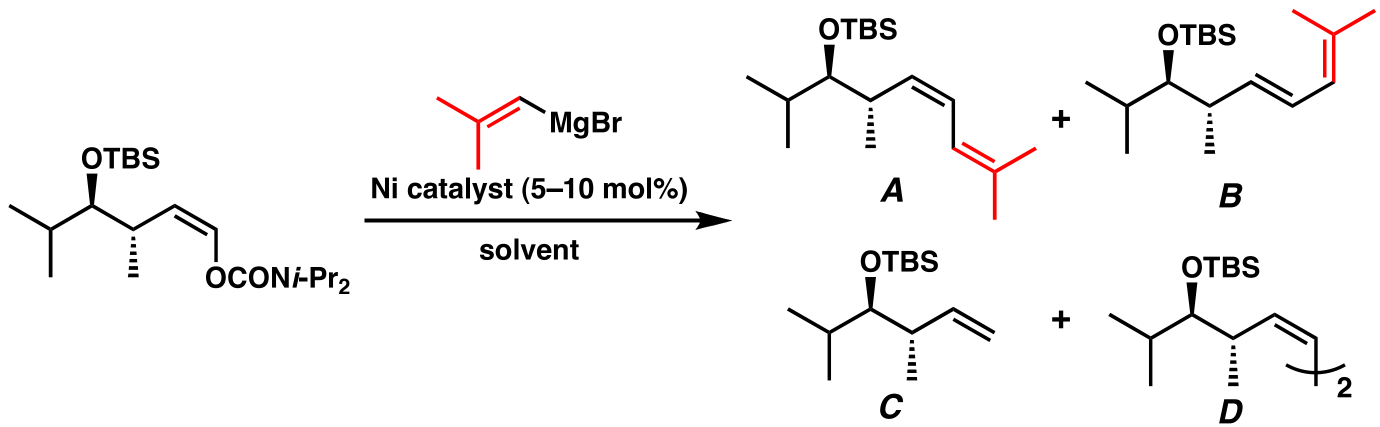
Carbamate and Carbonate Cross Coupling

Kumada Coupling: Vinyl Carbamate

Kocienski, P.



Betzer, J.-F.



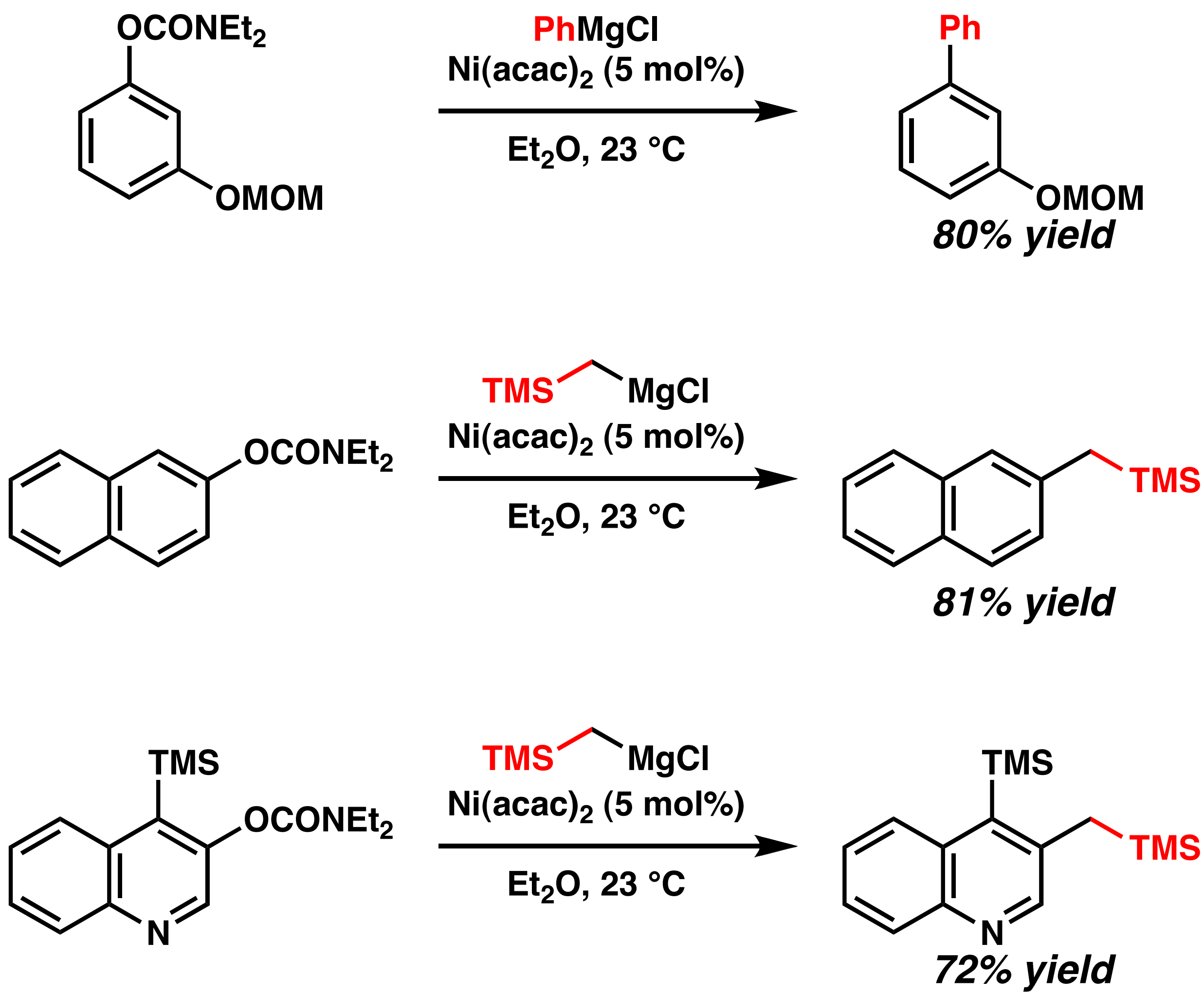
Ni catalyst	solvent	yield	A	B	C	D
Ni(acac)$_2$	Et$_2$O	57%	100	0	0	0
Ni(acac)$_2$	toluene	63%	89	5	0	6
NiCl$_2$(dppp)	toluene	56%	89	7	4	0

Kocienski, P. *Sylett* **1989**, 52.
Betzer, J.-F. *Tetrahedron Lett.* **2003**, *44*, 7553.

Carbamate and Carbonate Cross Coupling

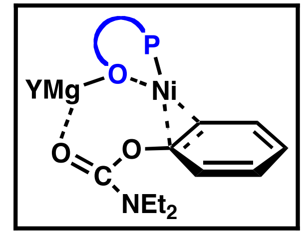
Kumada Coupling: Aryl Carbamate

Snieckus, V.

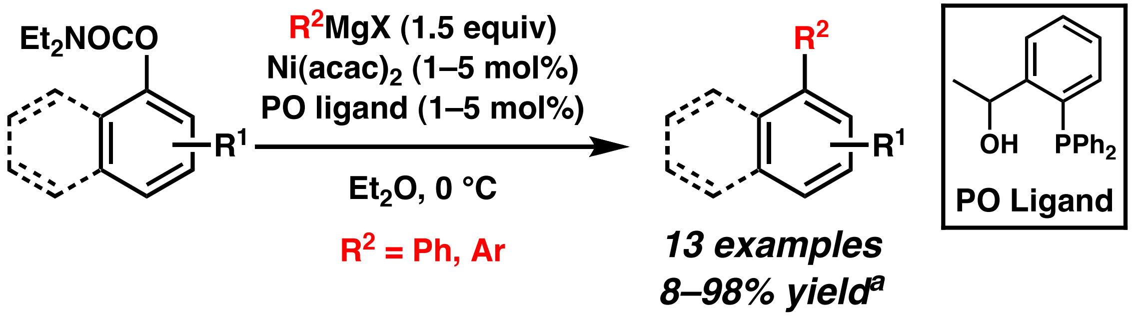


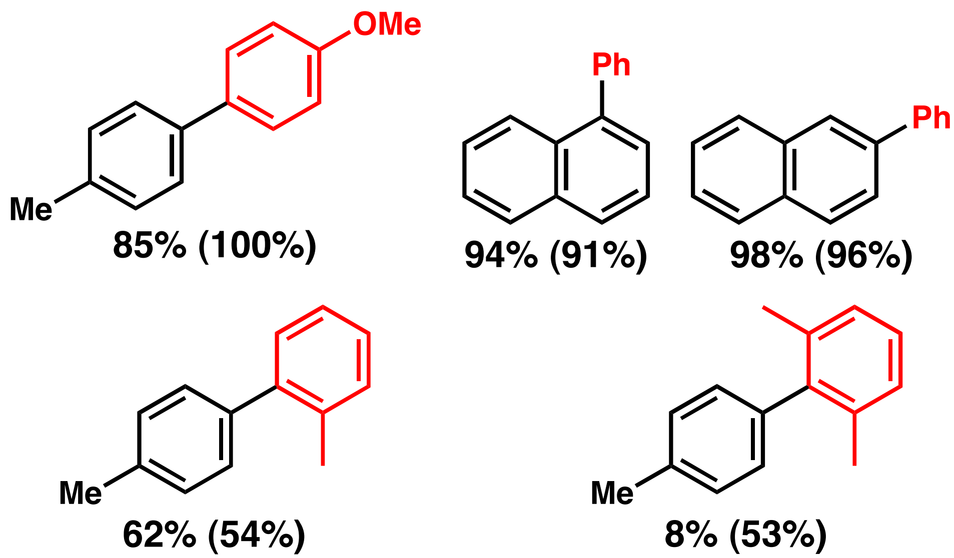
J. Org. Chem. **1992**, *57*, 4067.

Carbamate and Carbonate Cross Coupling
Hydroxyphosphine Promoted Kumada Coupling



Nakamura, E.





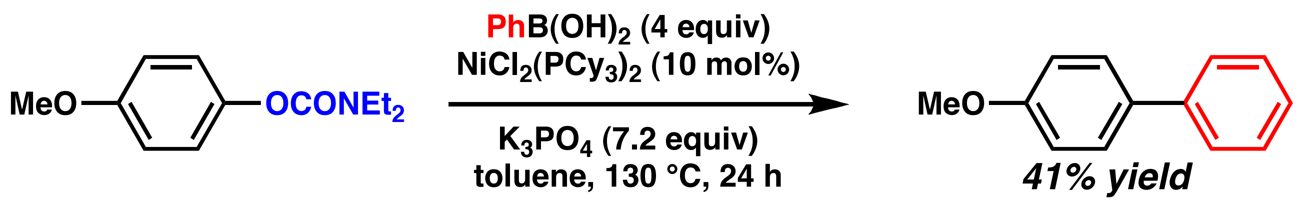
[a] Phosphonate comparison in parentheses.

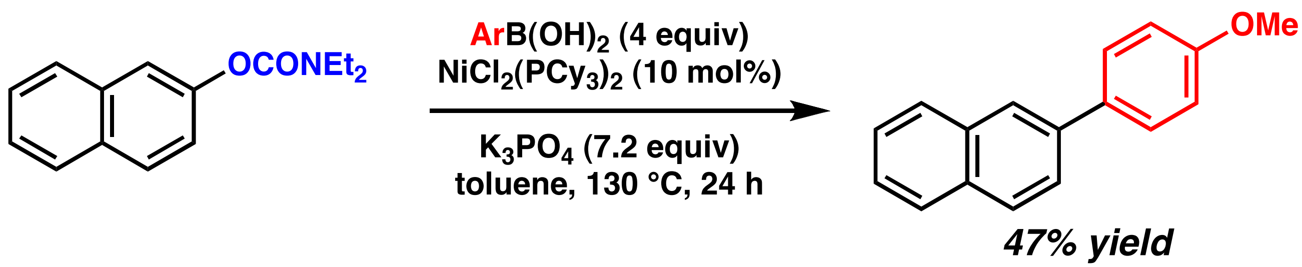
J. Am. Chem. Soc. **2009**, *131*, 9590.

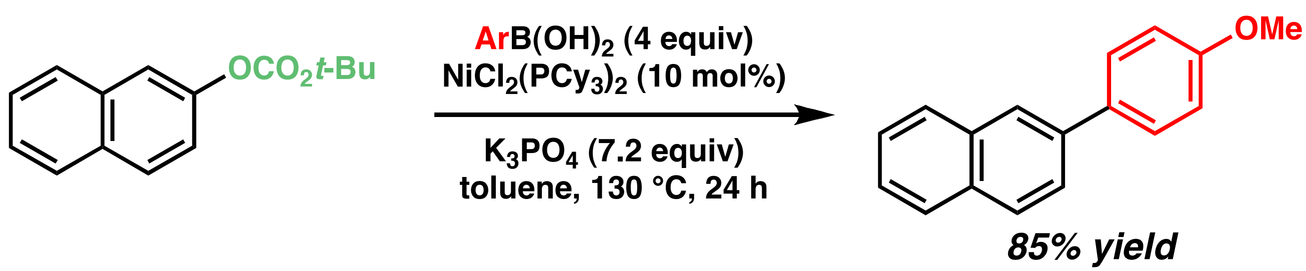
Carbamate and Carbonate Cross Coupling

Suzuki-Miyaura Coupling: Aryl Carbamates and Carbonates

Garg, N. K.





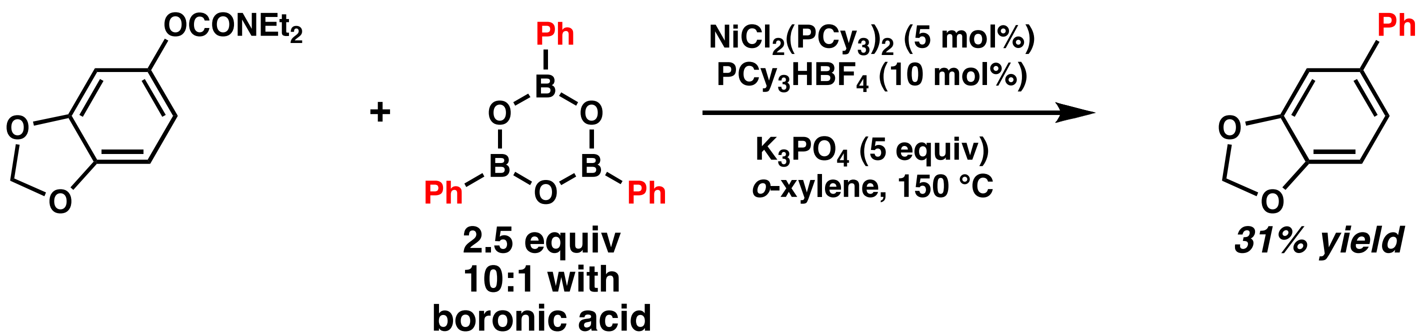


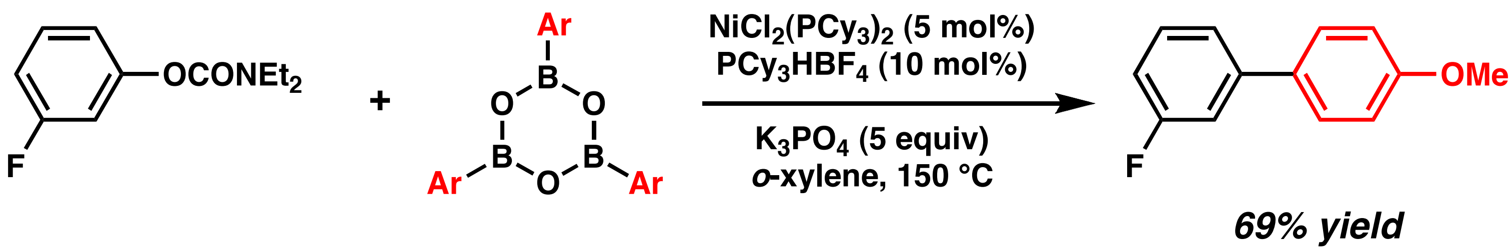
J. Am. Chem. Soc. **2009**, *131*, 17748.

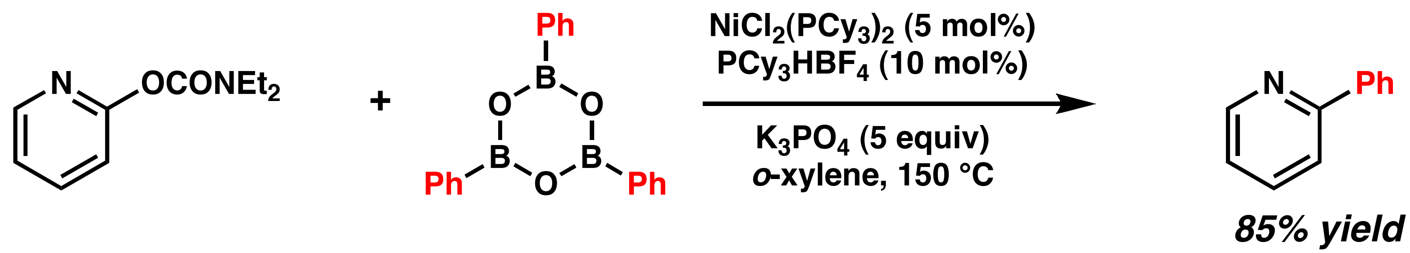
Carbamate and Carbonate Cross Coupling

Suzuki-Miyaura Coupling: Aryl Carbamates

Snieckus, V.





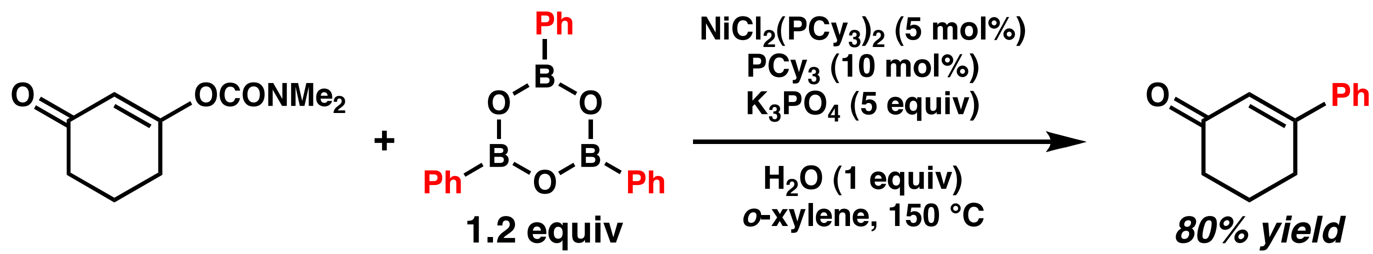


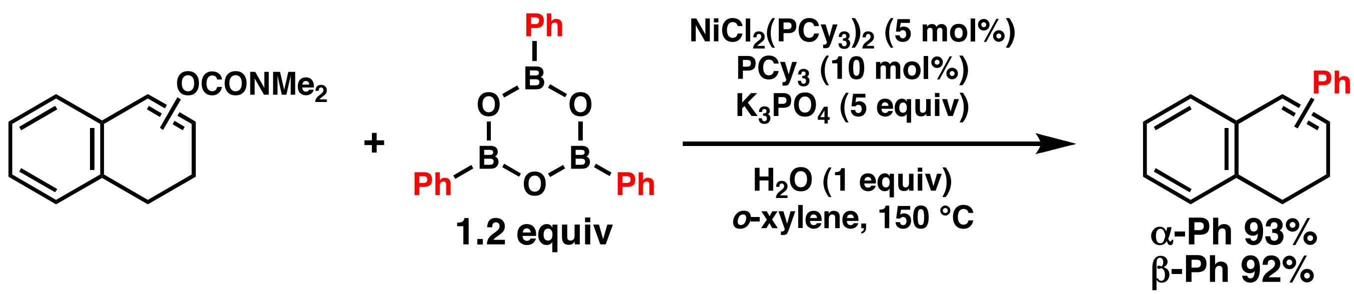
J. Am. Chem. Soc. **2009**, *131*, 17750.

Carbamate and Carbonate Cross Coupling

Suzuki-Miyaura Coupling: Vinyl Carbamates

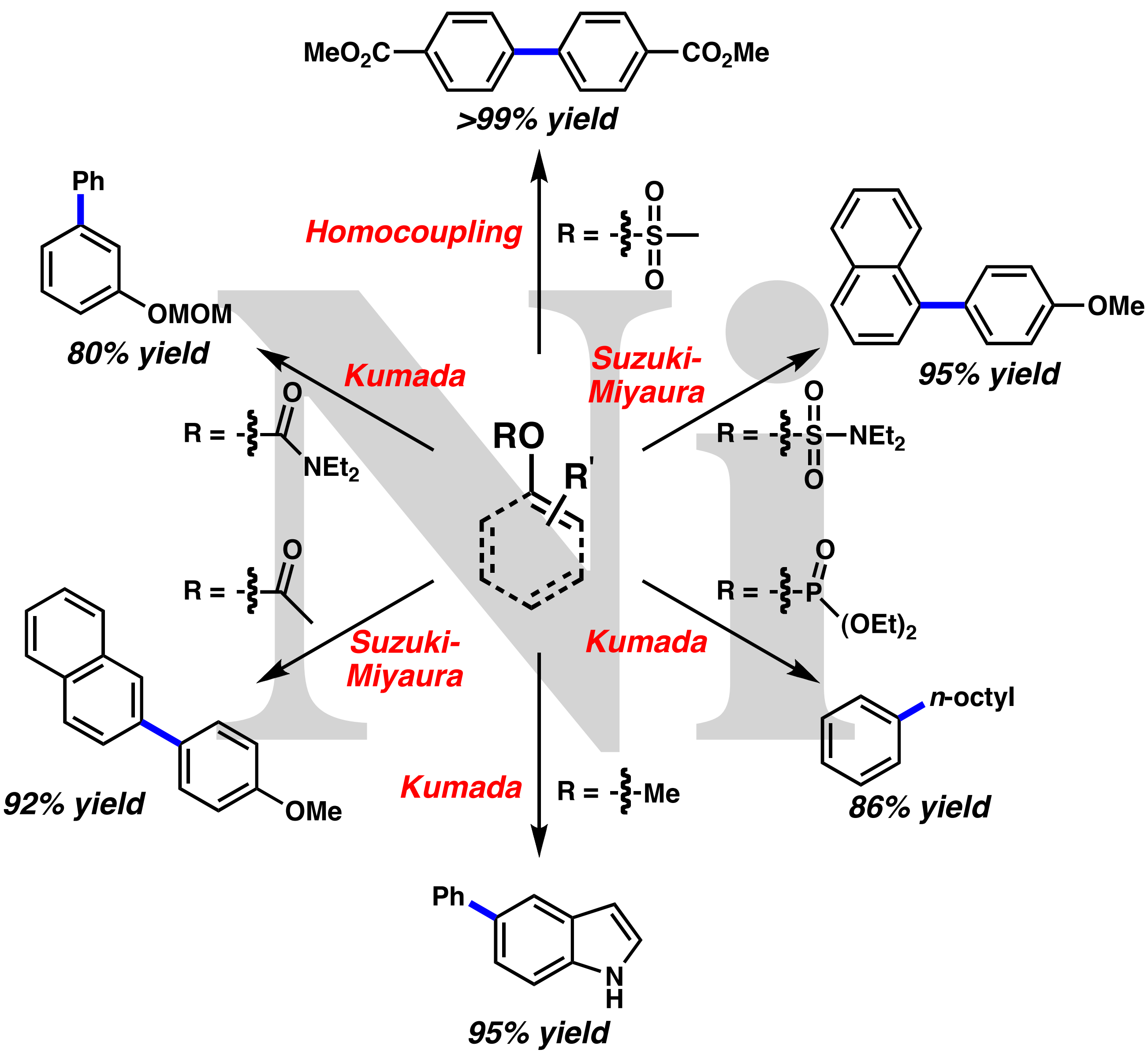
Shi, Z.-J.





Org. Lett. **2010**, *12*, 884.

Summary

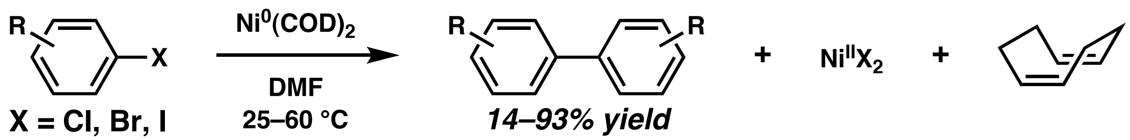


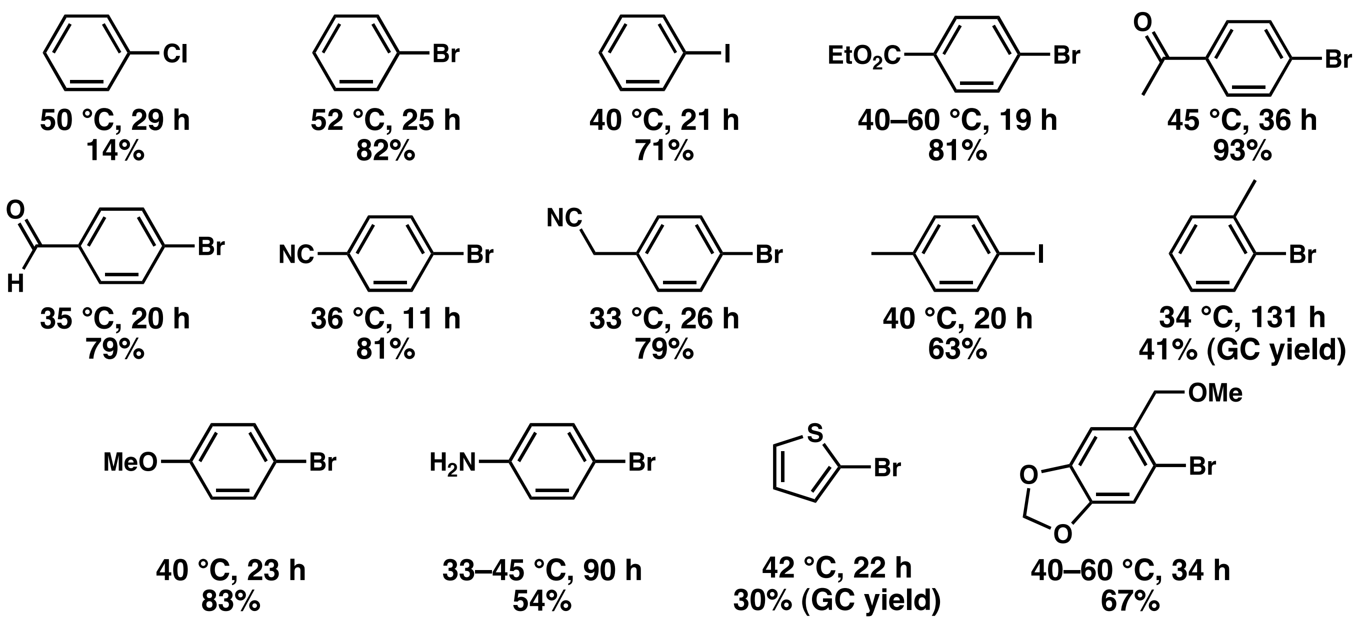
MeO$_2$C
CO$_2$Me
>99% yield
Homocoupling
R =
O
S
O
Ph
OMOM
80% yield
Kumada
R =
O
NEt$_2$
Suzuki-
Miyaura
OMe
95% yield
R =
O
S
NEt$_2$
O
RO
R'
R =
O
Suzuki-
Miyaura
92% yield
OMe
R =
O
P
(OEt)$_2$
Kumada
n-octyl
86% yield
Kumada
R = -Me
Ph
N
H
95% yield

History of Nickel Coupling

First Ni Homocoupling

Semmelhack, M. F.





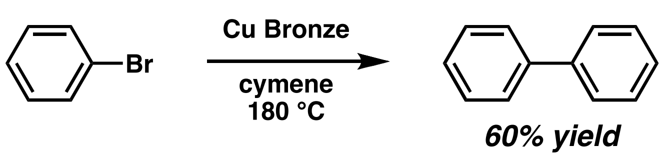
Reactivity

- **I > Br > Cl**
- **EWG > EDG**
- ***o*-substitution not well tolerated**
- **-NO_2, -OH, -CO_2H not tolerated**
  - **Reduction products with protic substrates**

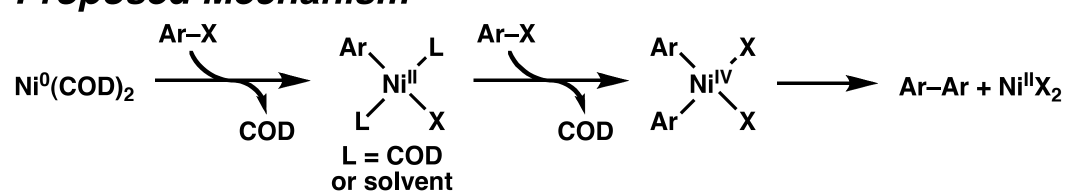
Limitations

- **Stiochiometric Ni**
- **Substrate issues**
- **Ni decomposition @ high temp**
- **DMF only solvent**

Ullmann Coupling Comparison



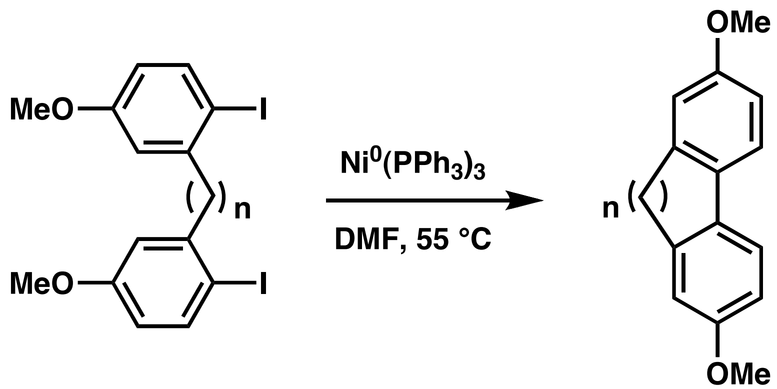
Proposed Mechanism



Ni: Semmelhack, M. F. *J. Am. Chem. Soc.* **1971**, *93*, 5908.
Ullmann Coupling: Fanta, P. E. *Chem. Res.* **1964**, *64*, 613.

History of Nickel Coupling
Transition to Other Ni Sources

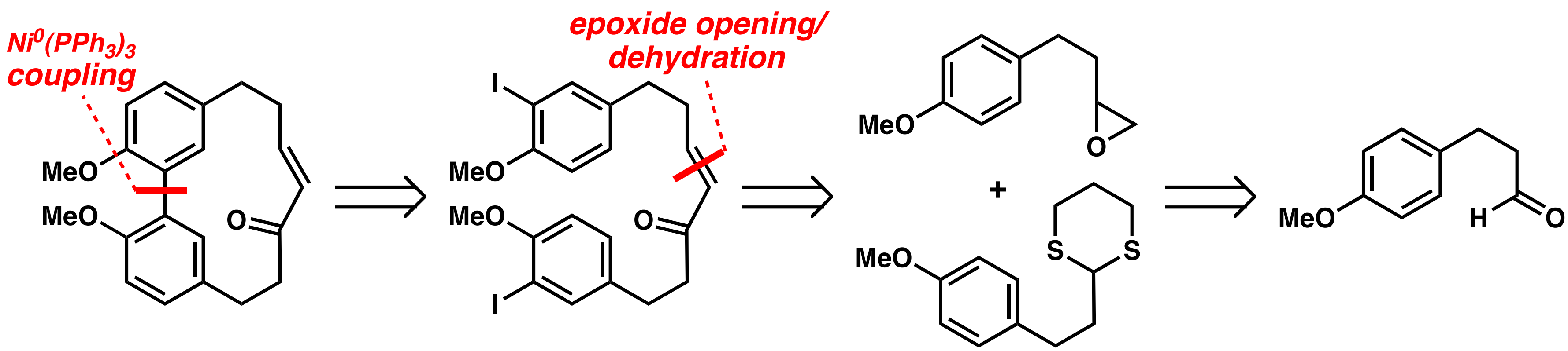
Semmelhack, M. F.



n	yield (%)
2	81
3	83
4	76
5	85
6	38

— **Stiochiometric Ni**
— **$Ni^0(PPh_3)_3$ necessary**
— **$Ni^0(COD)_2$ alone or with PPh_3 or PEt_3 resulted in no coupling**

Synthesis of Dimethyl Ether Alnusone



Kende, A. S.

$$Ni^{II}Cl_2(PPh_3)_2 \xrightarrow[\text{DMF}]{Zn^0,\ PPh_3} Ni^0(PPh_3)_3$$
in situ

— **Tolman Research: $Ni^0(PPh_3)_3$ active catalyst**
— **Kende formed *in situ***

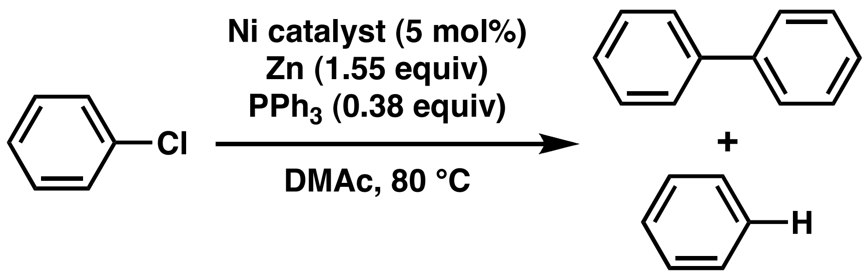
Semmelhack, M. F. *J. Am. Chem. Soc.* **1975**, *97*, 3873.
Semmelhack, M. F. *J. Am. Chem. Soc.* **1981**, *103*, 6460.
Tolman, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 2669.
Tolman, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 53.
Kende, A. S. *Tetrahedron Lett.* **1975**, 3375.

History of Nickel Coupling

Ni^{II} Catalyst and Reducing Metal Analysis

Colon, I.

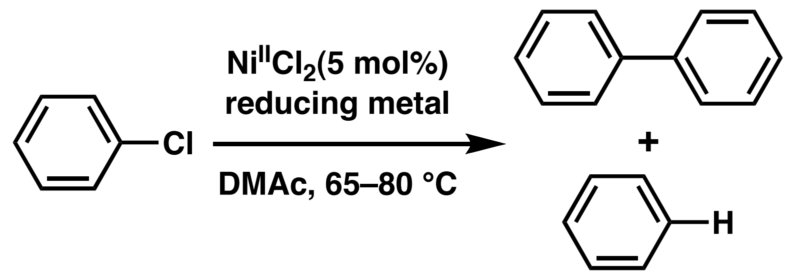
Ni Catalyst Screen



		GC yield (%)	
Ni catalyst	time (h)	biphenyl	benzene
$NiCl_2$	2	99	1
$NiBr_2$	2	99	1
$NiI_2 \cdot 6H_2O$	2	58	42
$Ni(OOCMe)_2 \cdot 4H_2O$	17	66	34
$Ni(acac)_2 \cdot 2H_2O$	17	82	18
$Ni(NO_3)_2 \cdot 6H_2O$	24	0	0
NiO	24	0	0
NiF_2	24	0	0

Strem: $NiCl_2$ = $34 / 50 g
$NiBr_2$ = $78 / 50 g

Reductant Screen



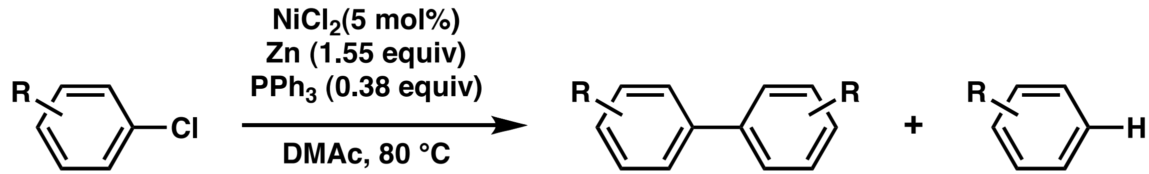
			GC yield (%)	
metal	E^0 (V)	time (h)	biphenyl	benzene
Fe	–0.44	24	0	0
Zn	–0.76	2	99	1
Mn	–1.18	24	>99	0
Al	–1.66	5	22	76
Mg	–2.37	2	96	4
Na	–2.71	24	6	6
Ca	–2.87	6	22	77

— Zn essential for reactivity
- $Ni(PPh_3)_4$ + ArCl → stalls
- Add Zn → completion

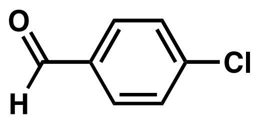
J. Org. Chem. **1986**, *51*, 2627.

History of Nickel Coupling

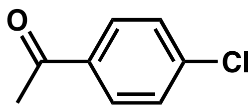
Homocoupling of Aryl Chlorides



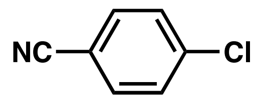
25–100% GC yield ***reduction***



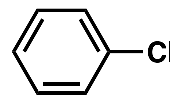
94%



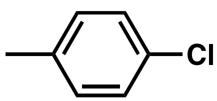
100%



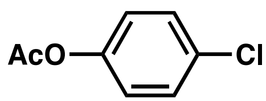
98%



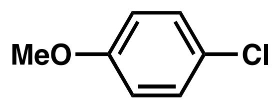
99%
1% reduction



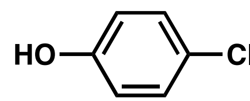
90%
3% reduction



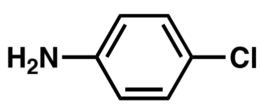
90%[a]
5% reduction[a]



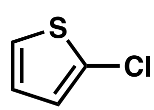
96%[a]
3% reduction



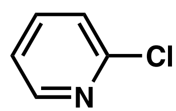
25%
62% reduction



31%
26% reduction
31% biphenyl



98%



70%[b]

[a] 5 mol% bpy added. [b] Isolated yield.

Reactivity

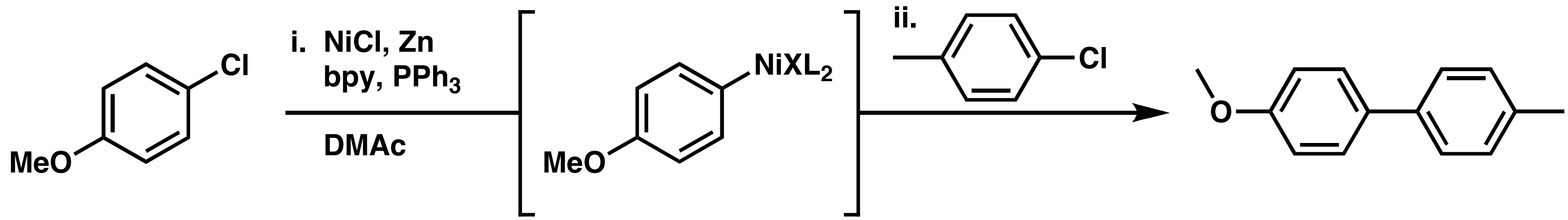
- **Aryl Cl best substrates**
- **Aryl I and Br produce more reduction and are slower**
- **EWG > EDG**
- **$-NO_2$, $-CO_2H$ not tolerated**

Colon, I. *J. Org. Chem.* **1986**, *51*, 2627.

History of Nickel Coupling

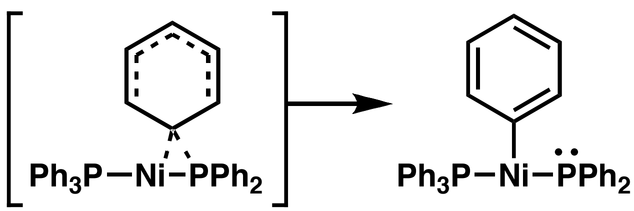
Impact of Other Additives

First Cross Coupling



Phosphines

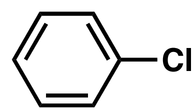
— PAr_3 best
— $P(alkyl)_3$ slower and lower yields
— dppe ineffective
— Ph from PPh_3 transferred for e^- rich substitutents



o-insertion ruled out due PAr_3 use

Halide Ions

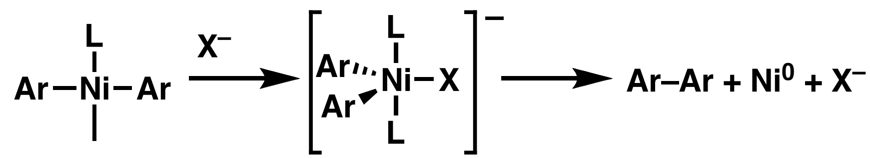
— $I^- > Br^- >> Cl^- > F^-$
— Accelerates reaction substatially:



with NaI

completely homocoupled in 2 min!

— Two Suggested Explinations for Results
- Pentacoordinate anionic complex



- Accelerated Ni Reduction
  — Bridges Zn and Nickel
  — Increase dielectric properties of solvent

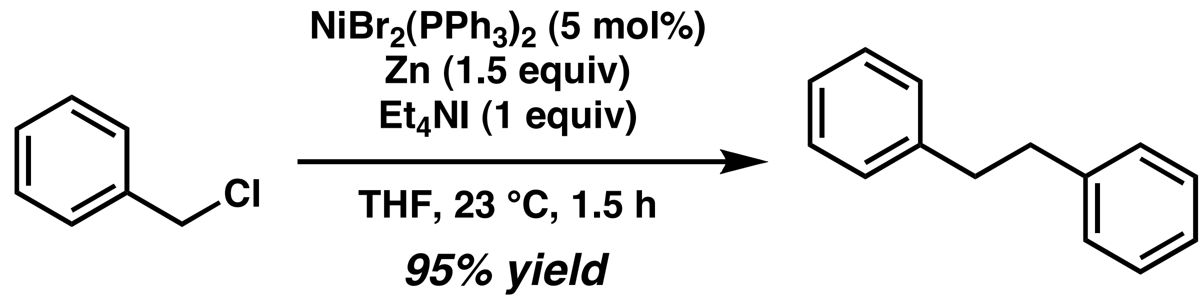
Colon, I. *J. Org. Chem.* **1986**, *51*, 2627.
Phosphine Pentacoordinate Intermediate: Favero, G. *J. Organomet. Chem.* **1978**, *149*, 395.

History of Nickel Coupling

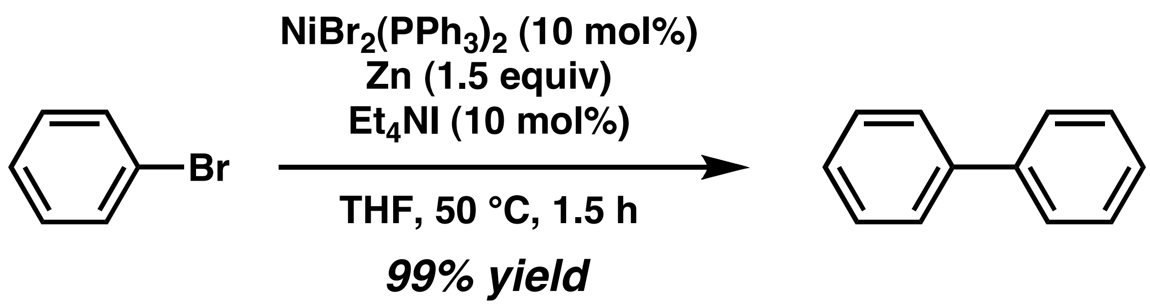
Et_4NI: A More Soluble Halogen Source

Iyoda, M.

Benzyl Halide Couplings



Aryl Halide Couplings



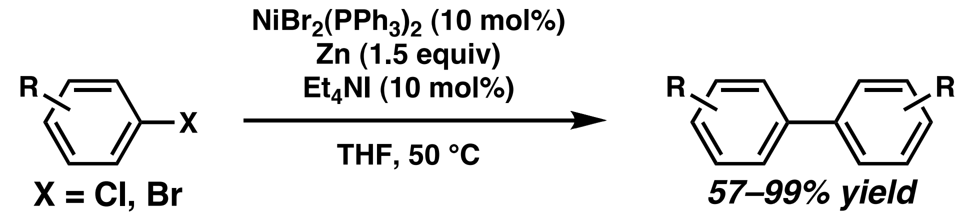
Conditions Screened

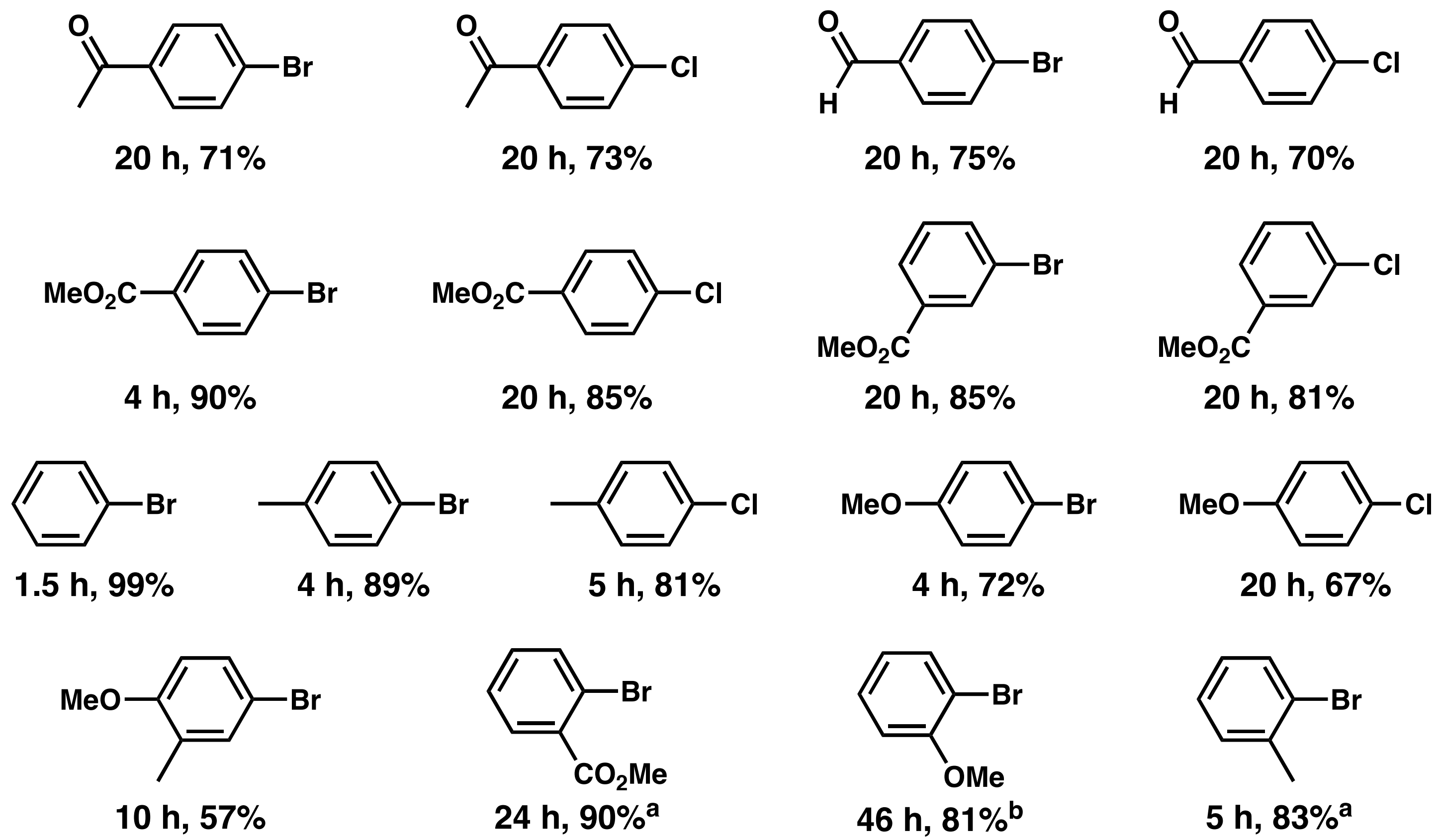
- **Ni Sources: $NiCl_2(PPh_3)_2$, $NiBr_2(PPh_3)_2$, $NiI_2(PPh_3)_2$**
- **Solvents: THF, DMF, CH_3CN, Acetone**
- **Loadings of Et_4NI: 10 mol% *p*- & *m*-substituted; 1 equiv for *o*-substituted**
- **Excess PPh_3 not neccesary**

Benzyl Coupling: Iyoda, M. *Chem. Lett.* **1985**, *51*, 2627.
Aryl Coupling: Iyoda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80.

History of Nickel Coupling

Aryl Halide Homocoupling





Notes

- **I >> Br > Cl**
- **Aryl I do not require Et_4NI**
- **o-substituted require high Ni loadings**

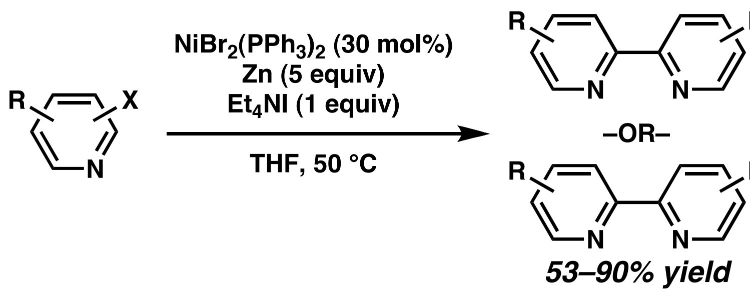
[a] 20 mol% $NiBr_2(PPh_3)_2$, 1 equiv Et_4NI. [b] 50 mol% $NiBr_2(PPh_3)_2$.

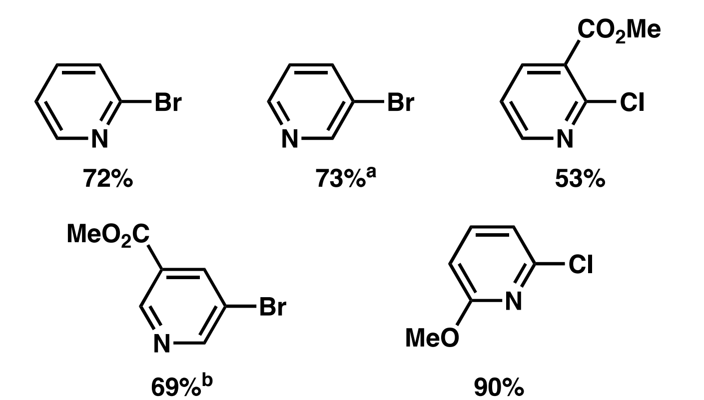
Iyoda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80.

History of Nickel Coupling

Heteroaromatic Homocoupling

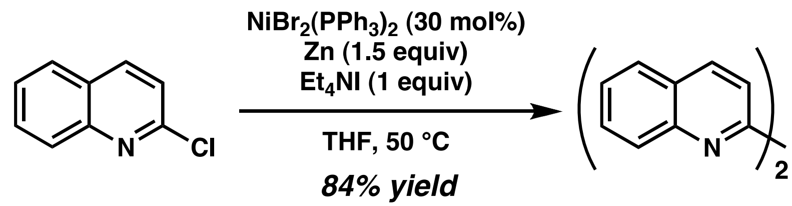
Pyridines

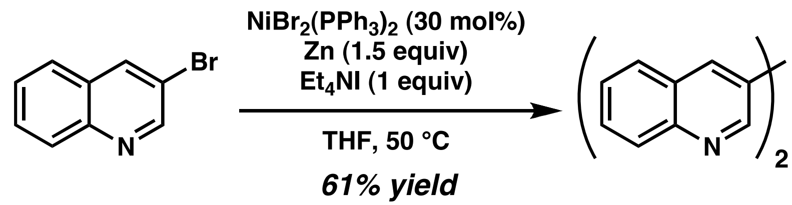


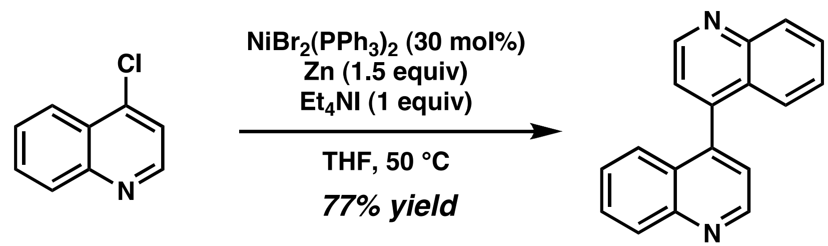


[a] 3 equiv Et_4NI. [b] 30 mol% Et_4NI.

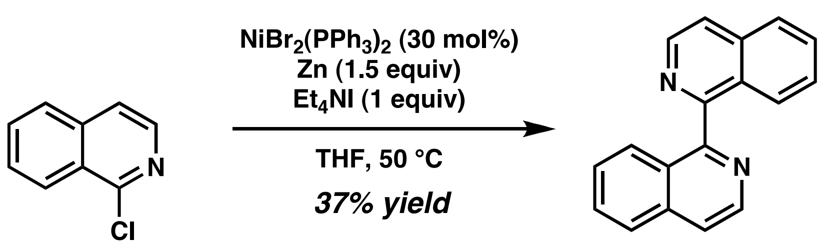
Quinolines

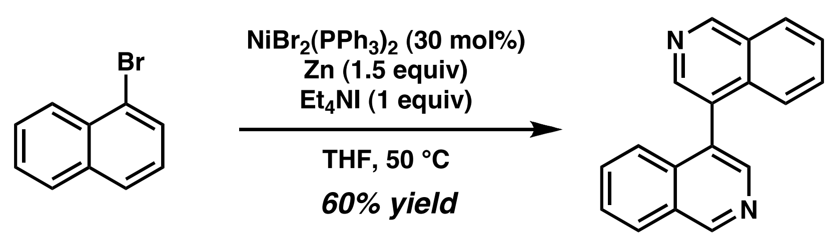






Isoquinolines

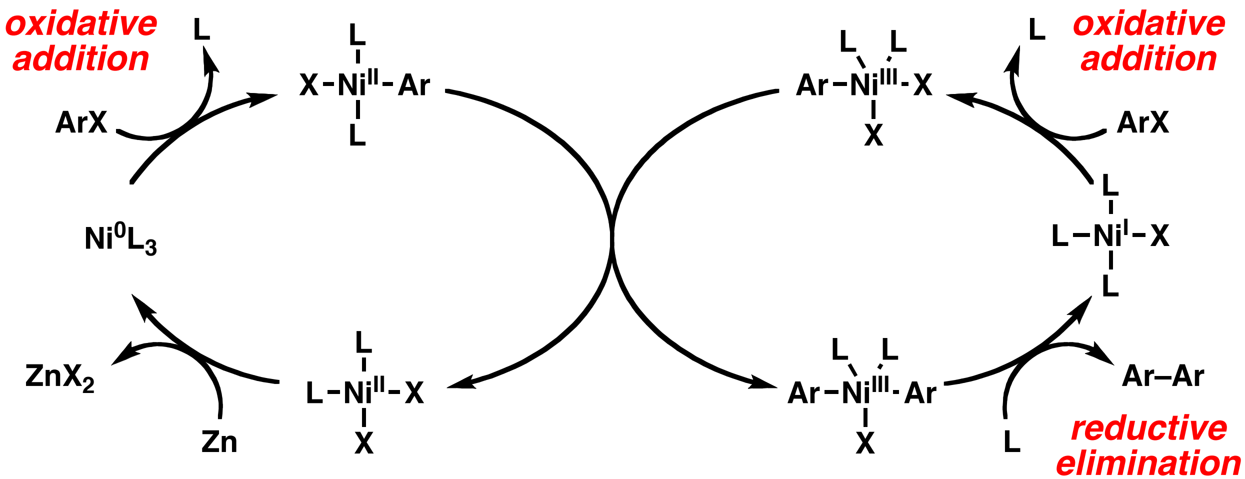




Iyoda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80.

History of Nickel Coupling
Proposed Mechanisms

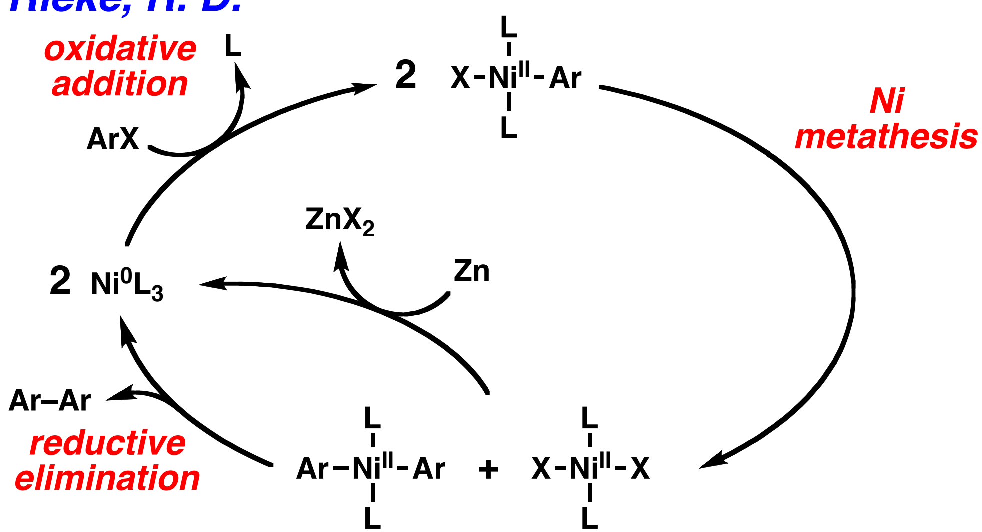
Tsou, T. T. and Kochi, J. K.



Performed in PhMe, THF, hexanes with $Ni^{0}(PEt_3)_4$

J. Am. Chem. Soc. **1979**, *101*, 6319. *J. Am. Chem. Soc.* **1979**, *101*, 7547.

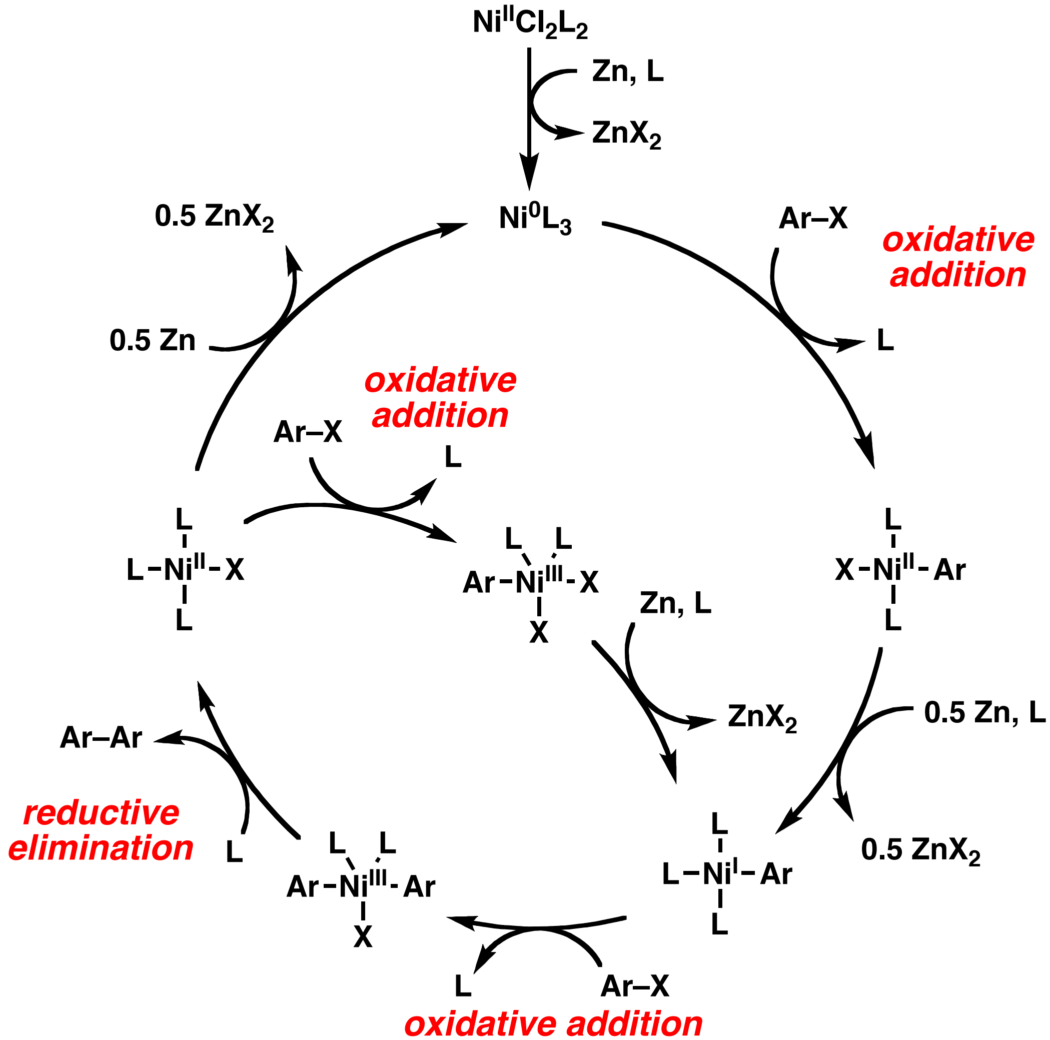
Rieke, R. D.



J. Am. Chem. Soc. **1977**, *99*, 4089. *J. Org. Chem.* **1983**, *48*, 840.

History of Nickel Coupling
Proposed Mechanisms

Bontempelli, G.



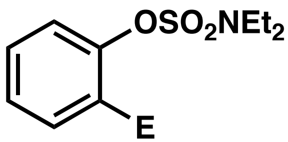
J. Chem. Soc., Dalton Trans. **1981**, 1074.

Sulfamate Ni Cross Coupling

Kumada Coupling

Snieckus, V.

Directed o-Metalation (DoM)



E = CHO, $CONEt_2$, CH(OH)Ph, SMe, $SiMe_3$, Cl, Br, I, $SnBu_3$, boronate esters

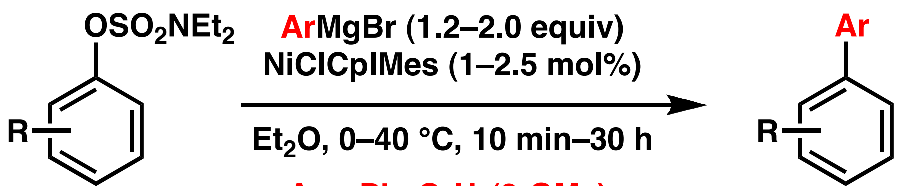
— Sulfamate is orthogonal functionality to Suzuki-Miyaura coupling with halides

Ni Catalyst Screen

— $Ni(acac)_2$, $NiCl_2$, $NiCl_2/P(t\text{-}Bu)_3$, $NiCl_2$/dppf, $NiClCpPPh_3$, NiClCpIMes
— Cp Complexes provided best yields
— NHC bulky ligands likely accelerate reductive elimination
— NiClCpIMes air stable

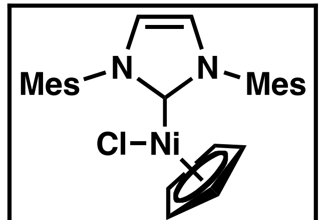
Solvent Screen

— PhMe, Et_2O, THF

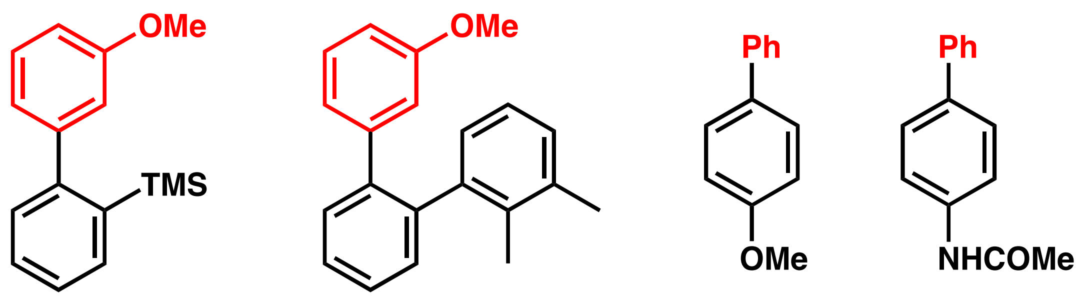


Ar = Ph, C_6H_4(3-OMe), 2-Mes, *p*-Tol

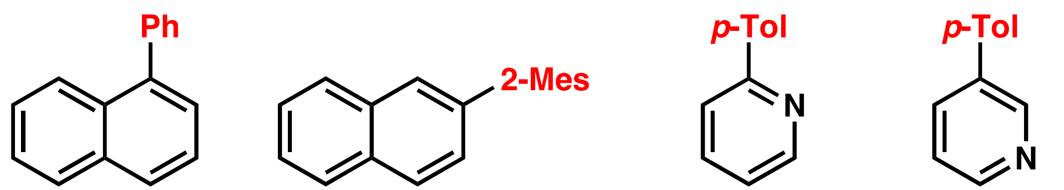
13 examples
47–86% yield



NiClCpIMes



40 °C, 12 h	40 °C, 30 h	40 °C, 19 h	23 °C, 1 h
76%	**64%**	**47%**	**50%**



0 °C, 10 min	40 °C, 18 h	23 °C, 18 h	23 °C, 8 h
84%	**69%**	**71%**	**82%**

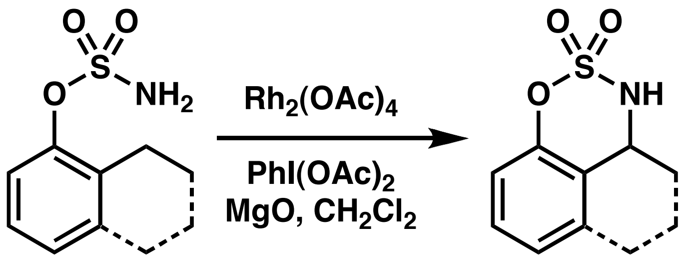
Org. Lett. **2005**, *7*, 2519.

Sulfamate Ni Cross Coupling

Kumada Coupling

Du Bois, J.

C-H Insertion to Form Sulfamate



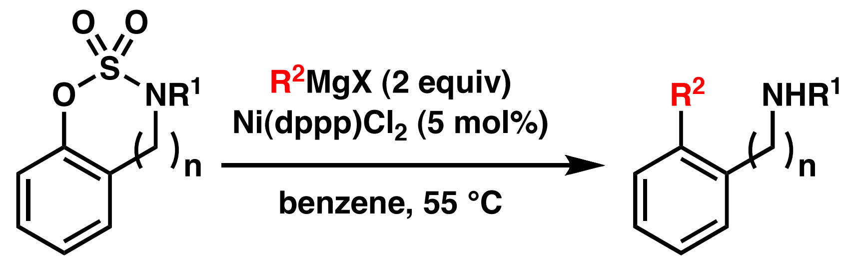
— NH → NR to allow Kumada coupling
— NH under Kumada conditions results acyl moiety cleavage

Ni Catalyst Screen

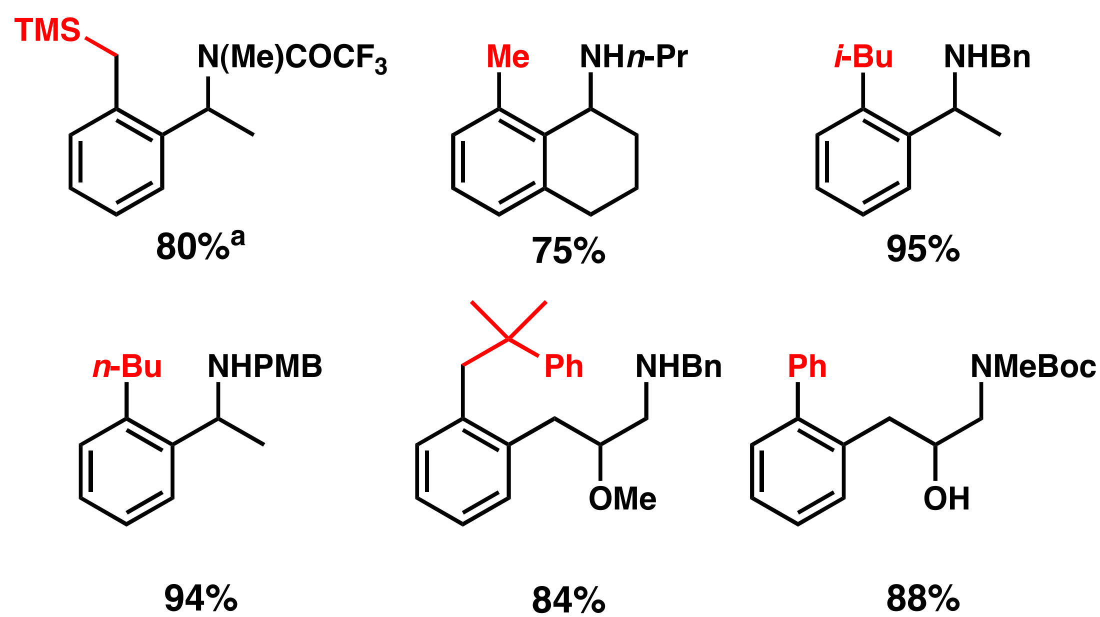
— Ni(dppe)Cl_2, Ni(PPh_3)Cl_2, Ni(acac)$_2$, Ni(dppf)Cl_2, Ni(dppp)Cl_2, Ni(COD)+dppp
— Ni(dppp)Cl2 optimal
— Other Ni^{II} phosphine left starting material

Solvent Screen

— benzene, $CF_3C_6H_5$, Et_2O, THF, DME, dioxane
— THF, DME, dioxane inhibit reaction



11 examples
72–95% yield



[a] 10 mol % Ni(dppp)Cl_2.

Org. Lett. **2005**, *7*, 4685.

Sulfamate Ni Cross Coupling

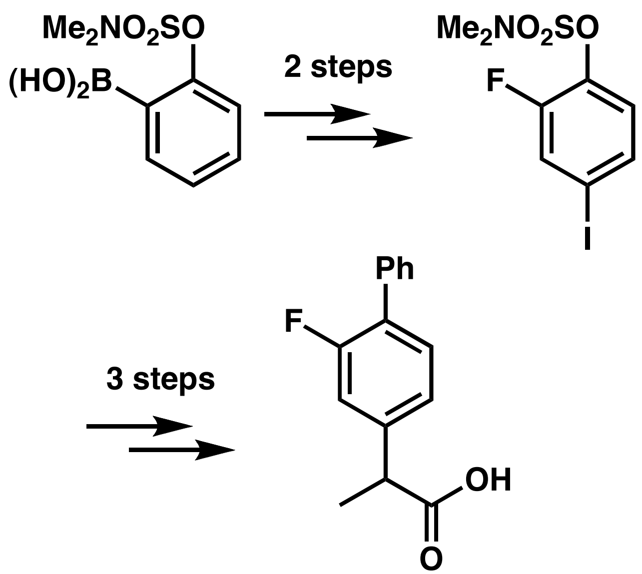
Suzuki-Miyaura Coupling

Garg, N. K.

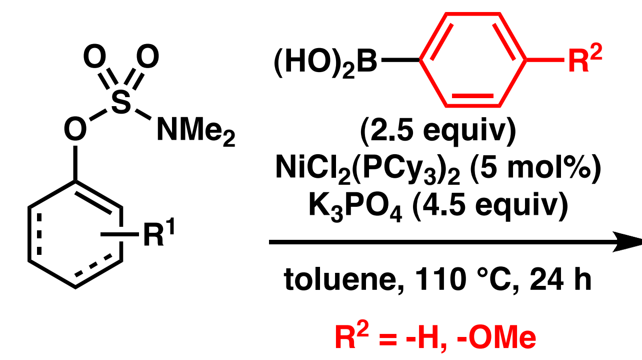
Functionalization of Aryl Sulfamates

— **Directed *o*-Metalation (DoM)**
— ***p*-directed electrophilic aromatic substitution**

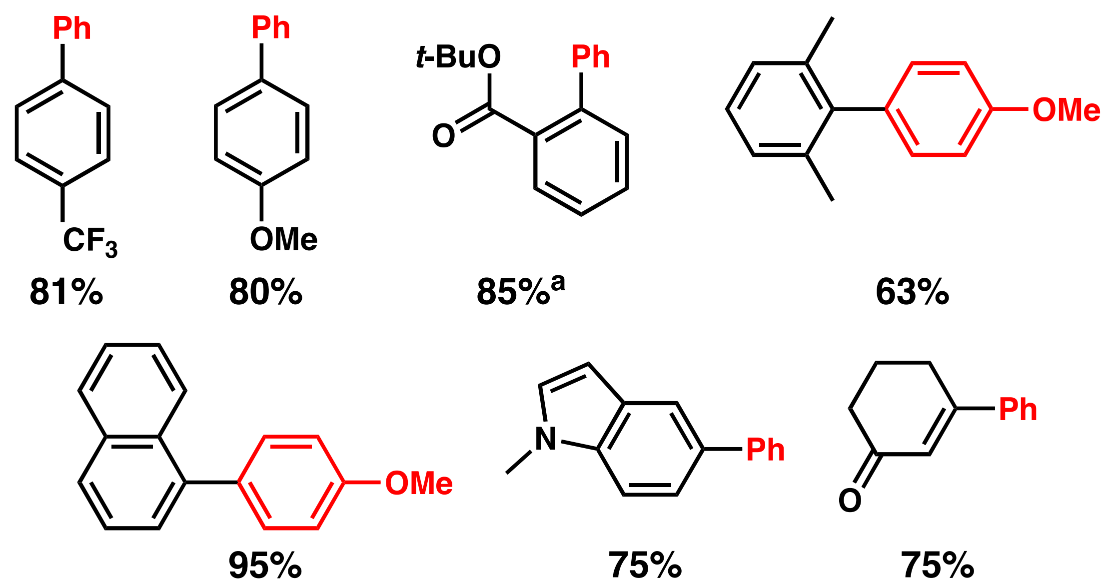
Total Synthesis of Flurbiprofen



flurbiprofen
5 steps, 26% yield



17 examples
63–95% yield



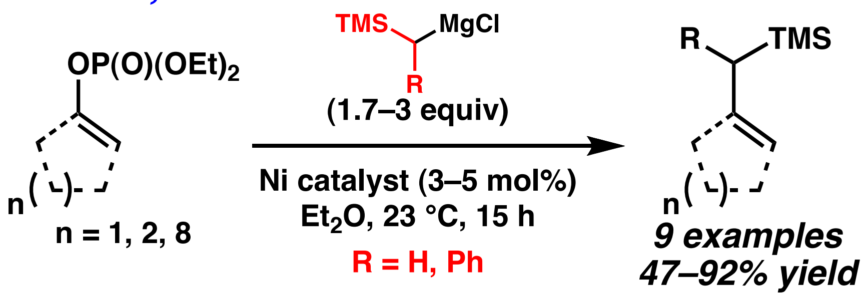
[a] 10 mol% $NiCl_2(PCy_3)_2$, 4 equiv $ArB(OH)_2$, 7.2 equiv K_3PO_4, toluene, 130 °C

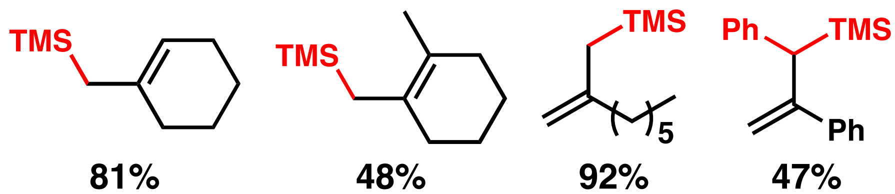
J. Am. Chem. Soc. **2009**, *131*, 17748.

Phosphate Cross Coupling

Kumada Coupling: Vinyl Phosphates

Kumada, M.



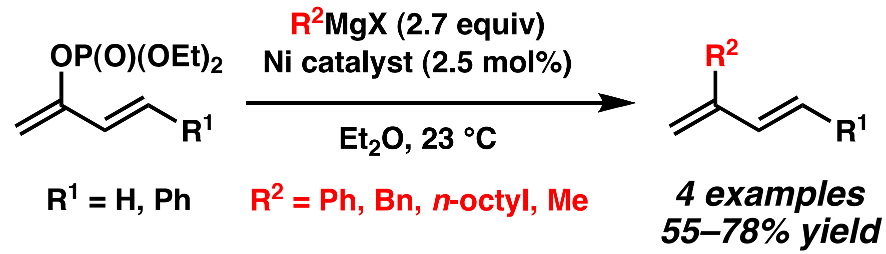


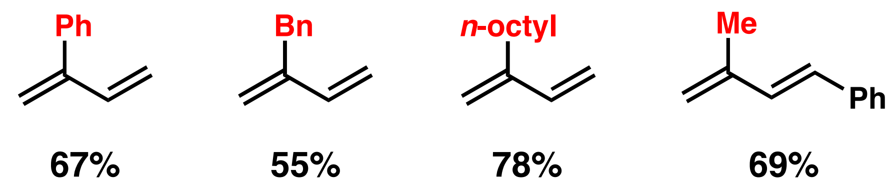
Notes

— Ni Catalysts: Ni(acac)$_2$, NiBr$_2$

— Ni^{II} + Phophines also work (no examples)

Claesson, A.



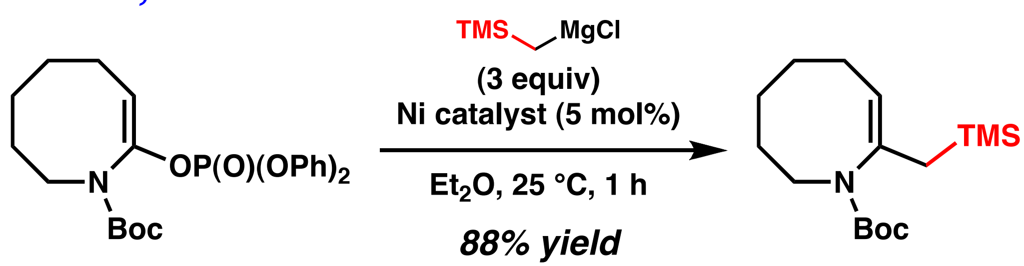


Notes

— Ni Catalysts: NiCl$_2$(dppe), NiCl$_2$(dppp)

— 2° Grignards inoperable: CyMgBr and 1-methylbutylMgBr

Nicolaou, K. C.



Kumada, M. *Synthesis* **1981**, 1001.

Claesson, M. *Tetrahedron Lett.* **1983**, *24*, 5137.

Nicolaou, K. C. *Chem. Commun.* **1998**, 1757.

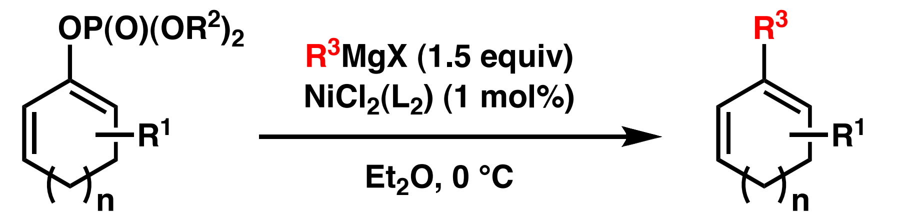
Phosphate Cross Coupling

Kumada Coupling: Vinyl Phosphates

Bäckvall, J.-E.

Notes

— Ni Catalyst: $NiCl_2$(dppe) and $NiCl_2$(dppp)
— 2° Grignard reagents possible for cyclic vinyl phosphates with longer coupling times
— No product from 2-octylMgBr



R^2 = Et or Ph
n = 1,2

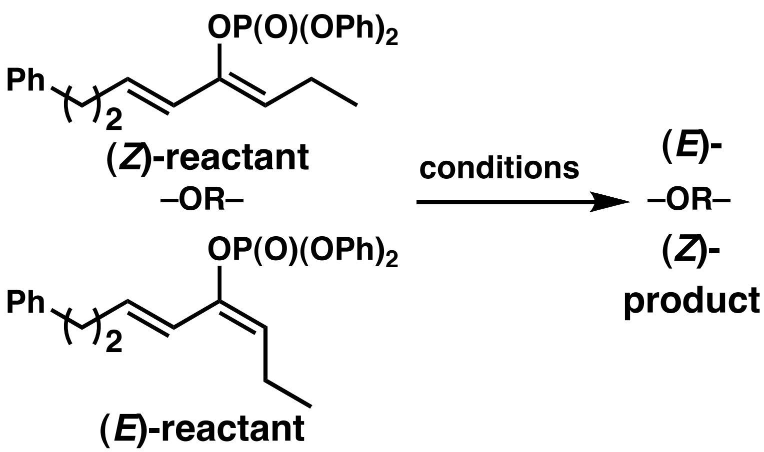
R^3 = Me, *n*-Bu, *sec*-Bu, *n*-octyl, Ph, Ar

12 examples
40–92% yield

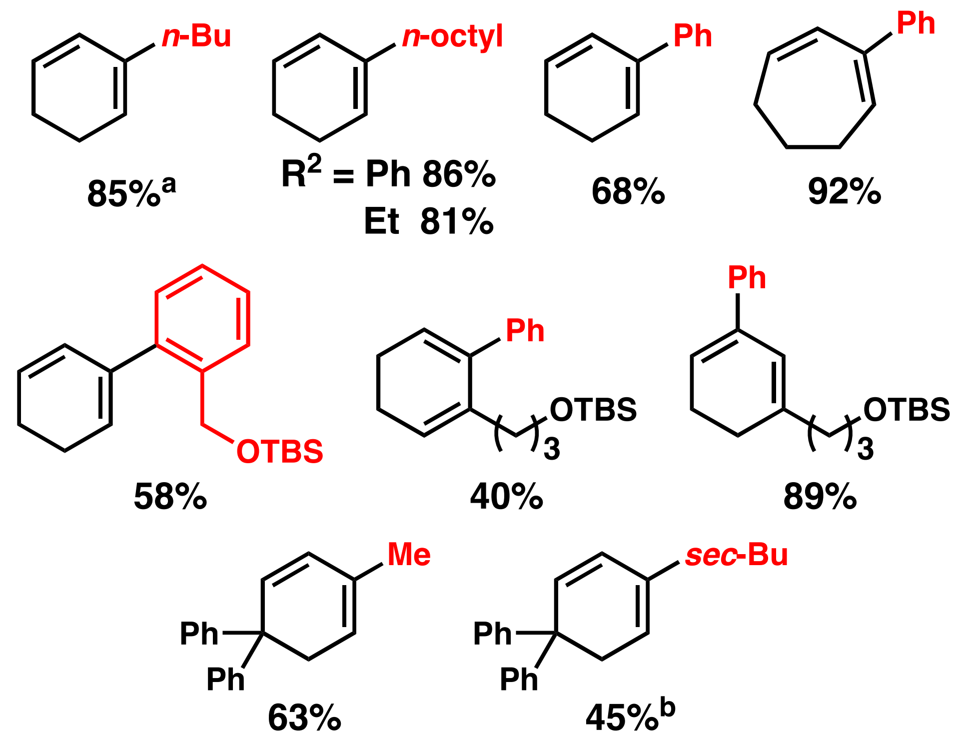
Acyclic Diene

— Yield similar to Claesson report
— 2° Grignard reagents inoperable

E/Z Selectivity Study



— Both reactant isomers favor (*E*)-product
— (E)-reactant → (Z)-product (5:95 = E:Z)
— (Z)-reactant → (E)-product (57:43 = E:Z)



[a] GC yield. [b] THF, 40 °C.

J. Am. Chem. Soc. **1979**, *101*, 2246.

Phosphate Cross Coupling

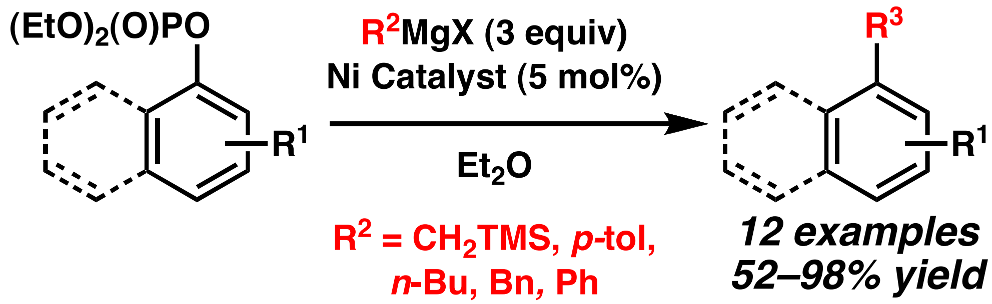
Kumada Coupling: Aryl Phosphates

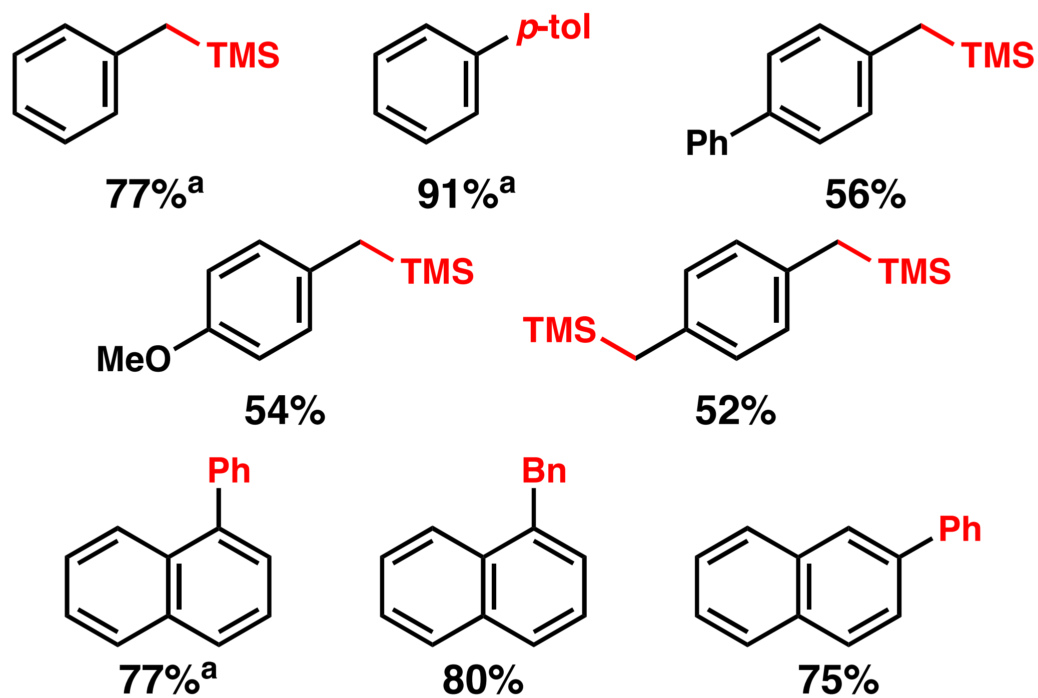
Kumada, M.

Catalyst Screen

— Ni Catalyst: Ni(acac)$_2$, NiCl$_2$(PPh$_3$)$_2$, and NiCl$_2$(dppp)

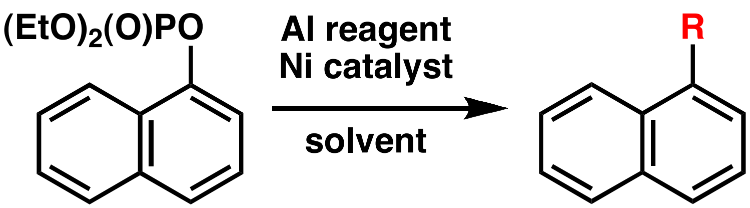
— Inoperable Catalysts: Pd(PPh$_3$)$_4$, PdCl$_2$, CoCl$_3$, Fe(acac)$_3$, CuBr

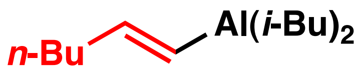




[a] GC yield.

Aluminum Reagents



Al reagent	solvent	yield
Et_3Al	Et_2O	95%
 n-Bu ... Al(i-Bu)$_2$	THF	99%

Tetrahedron Lett. **1981**, *22*, 4449.

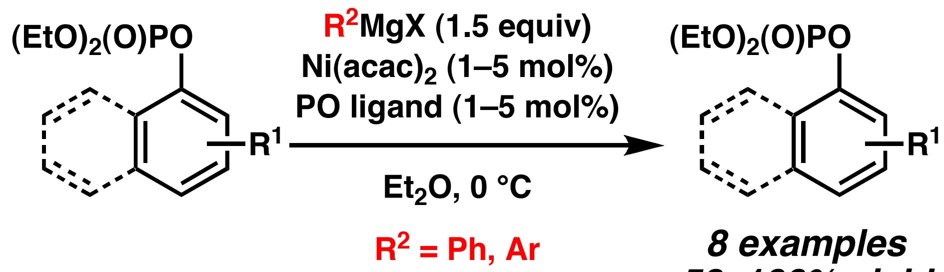
Phosphate Cross Coupling

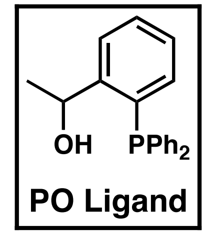
Kumada Coupling: Aryl Phosphates

Nakamura, E.

Notes

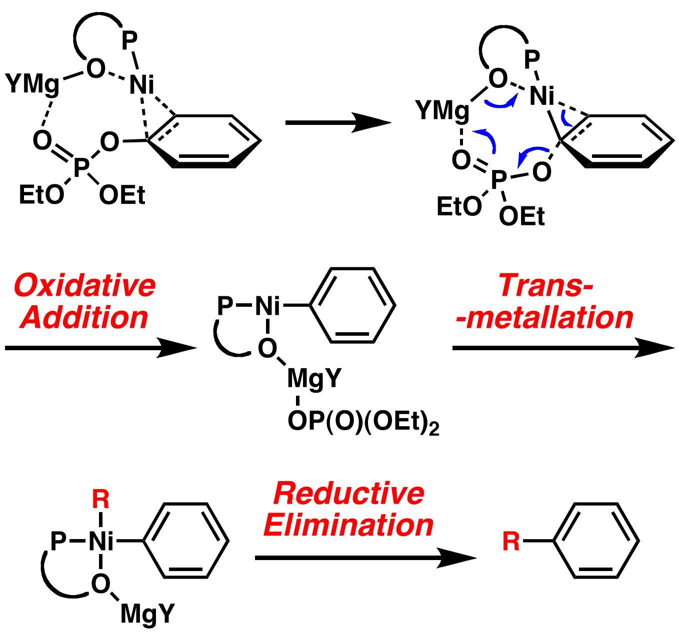
— Ligand provides cooperative effect
— 12 ligands screened
— Effective for aryl F, Cl, Br, I, OTf, OCONEt$_2$

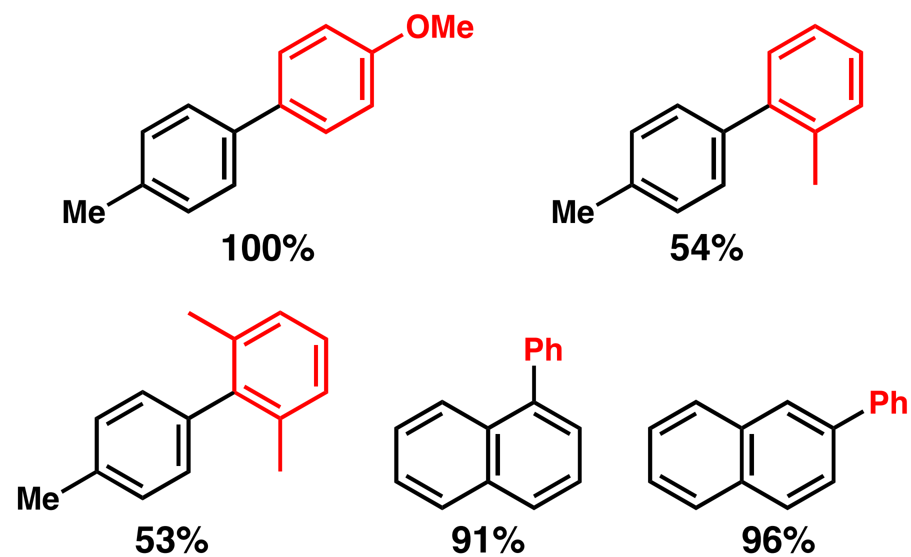




8 examples
53–100% yield

Push-Pull Mechanism





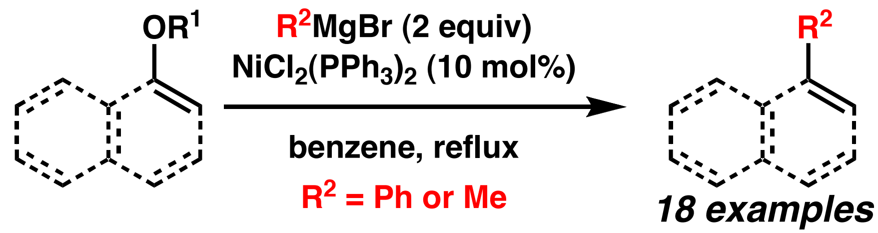
[a] GC yield. [b] THF, 40 °C.

J. Am. Chem. Soc. **2009**, *131*, 9590.

Aryl and Vinyl Ether Cross Coupling

Kumada Coupling

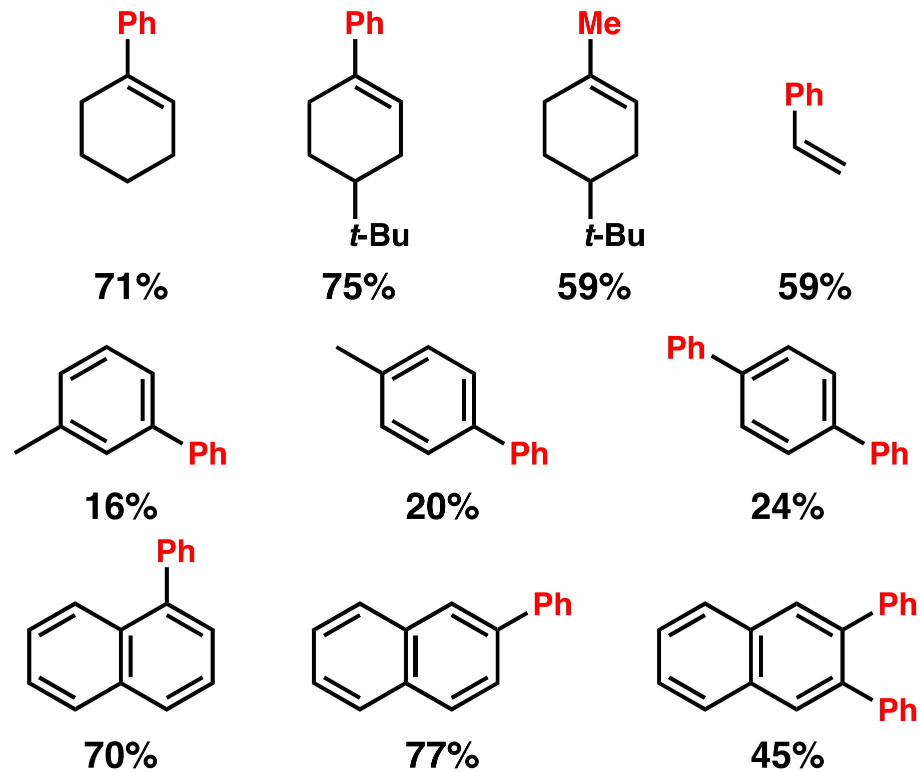
Wenkert, E.



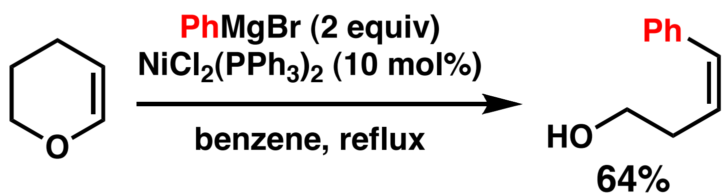
18 examples
16–93% yield

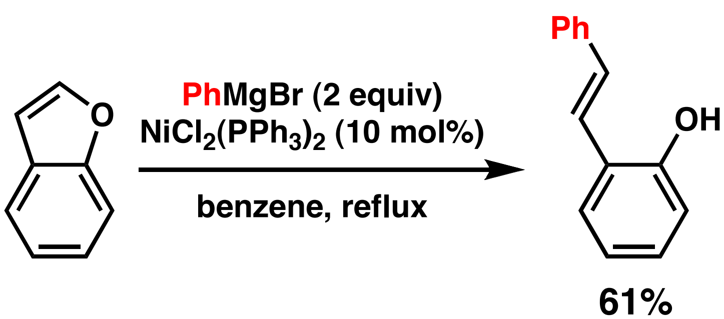
Grignard Effects

— PhMgBr effective with vinyl and aryl ethers
— MeMgBr is unreactive with aryl ethers



Cyclic Ethers



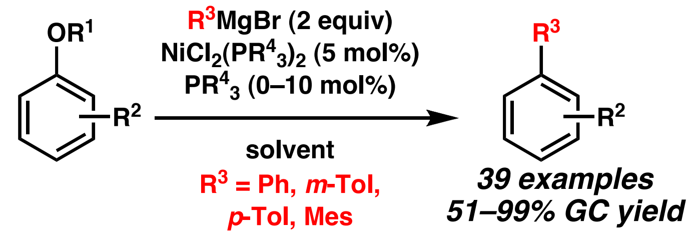


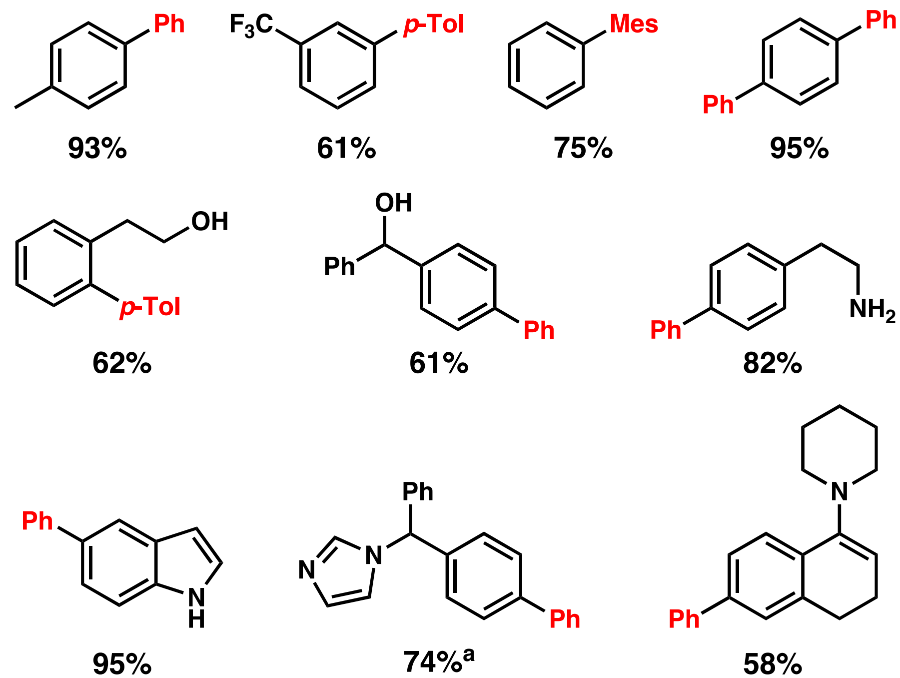
J. Am. Chem. Soc. **1979**, *101*, 2246.

Aryl and Vinyl Ether Cross Coupling

Kumada Coupling: sp^2–sp^2 C–C Formation

Dankwardt, J. W.





[a] Isolated yield.

Ni Catalyst Screen

- Numerous Ni^{II} catalysts investigated
- $Ni(acac)_2$/2 PCy_3 and $Ni(acac)_2$/2 $PPhCy_2$ are best

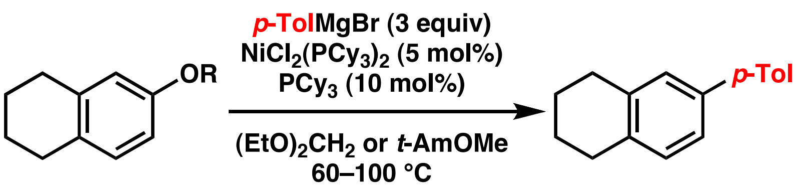
Ligand Screen

- PMe_3, PEt_3, P*i*-Bu_3, P*i*-Pr_3, PCy_3, $PPhCy_2$, PPh_2Cy, PPh_3
- PCy_3 and $PPhCy_2$ are best
- Intermediate cone angle and good σ-donating

Solvent Screen

- DME, THF, toluene, *i*-Pr_2O, $(EtO)_2CH_2$, *t*-AmOMe, *n*-Bu_2O
- Non-polar ethers or toluene preferred
- MgBr(OMe) (catalyst poison) crashes out in non-polar solvents

Aryl Ether Screen



R	GC yield	R	GC yield
-Me	94%	-MOM	92%
$-(CH_2)_2OMe$	77%	-TMS	70%
$-(CH_2)_2NMe_2$	99%		

Angew. Chem., Int. Ed. **2004**, *43*, 2428.

Reaction Scope Notes

- Amenable to functionalized benzene, napthalene, imidazole, pyridines, and indoles
- Tolerant of free alcohols and amines
- Limited to aryl Grignard reagents

Aryl and Vinyl Ether Cross Coupling
Kumada Coupling: sp^3–sp^2 C–C Formation

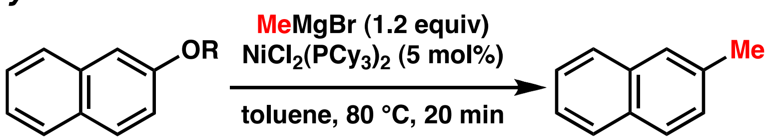
Shi, Z.-J.

Catalyst Screen
— Fe, Co, Ni, Pd catalysts investigated
— $NiCl_2(PCy_3)_2$ and $Ni(acac)_2$/2 PCy_3 are best

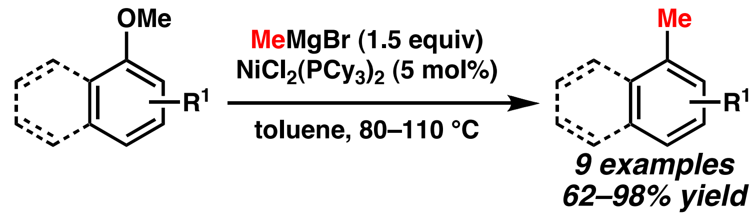
Ligand Screen
— PCy_3, PPh_3, dppe, dppf
— PCy_3 best

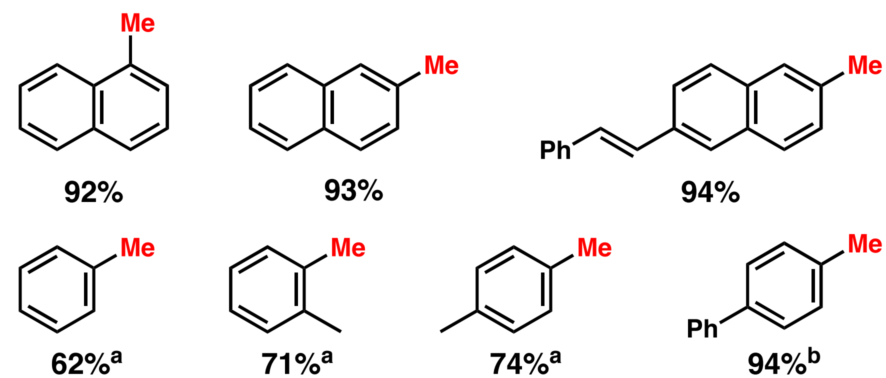
Solvent Screen
— Dioxane, THF, toluene, Et_2O
— Toluene and Et_2O are best solvents

Aryl Ether Screen



R	yield	R	yield
-Me	92%	-*t*-Bu	88%
-Et	92%	-MOM	69%
-*n*-Bu	96%	-TMS	95%
-*i*-Bu	91%	-Ph	95%

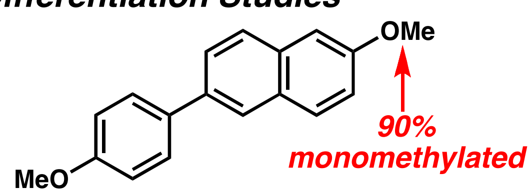


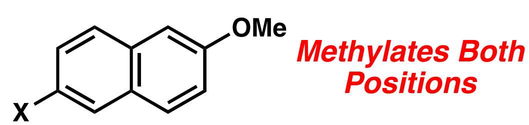


[a] GC yield. [b] t-butyl phenyl ether

Reaction Scope Notes
— More favorable for napthalene and biphenyl
— Only MeMgBr explored

Differentiation Studies





X = -Br, -OMe, -O*n*-Bu,
-O*i*-Pr, -O*t*-Bu, -OPh

Chem. Commun. **2008**, 1437.

Aryl and Vinyl Ether Cross Coupling
Kumada Coupling: sp^3–sp^3 C–C Formation

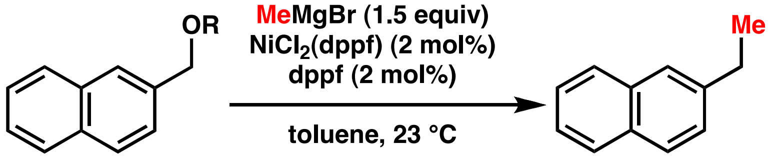
Shi, Z.-J.

Catalyst Screen
— Fe, Ni, Pd catalysts investigated
— $NiCl_2$(dppf)/dppf and $Ni(acac)_2$/dppf are best

Ligand Screen
— PCy_3, PPh_3, dppe, dppf, dppb, dppp, dppe
— PCy_3 best

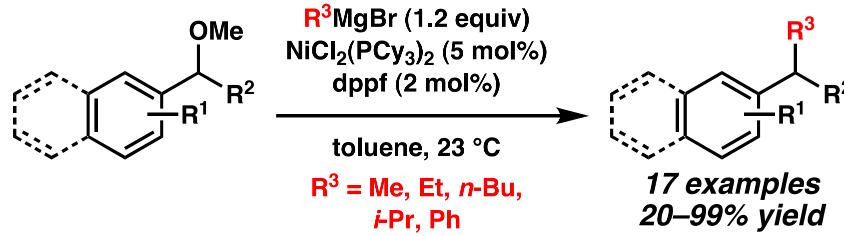
Solvent Screen
— THF, toluene, Et_2O
— Toluene and Et_2O are best solvents

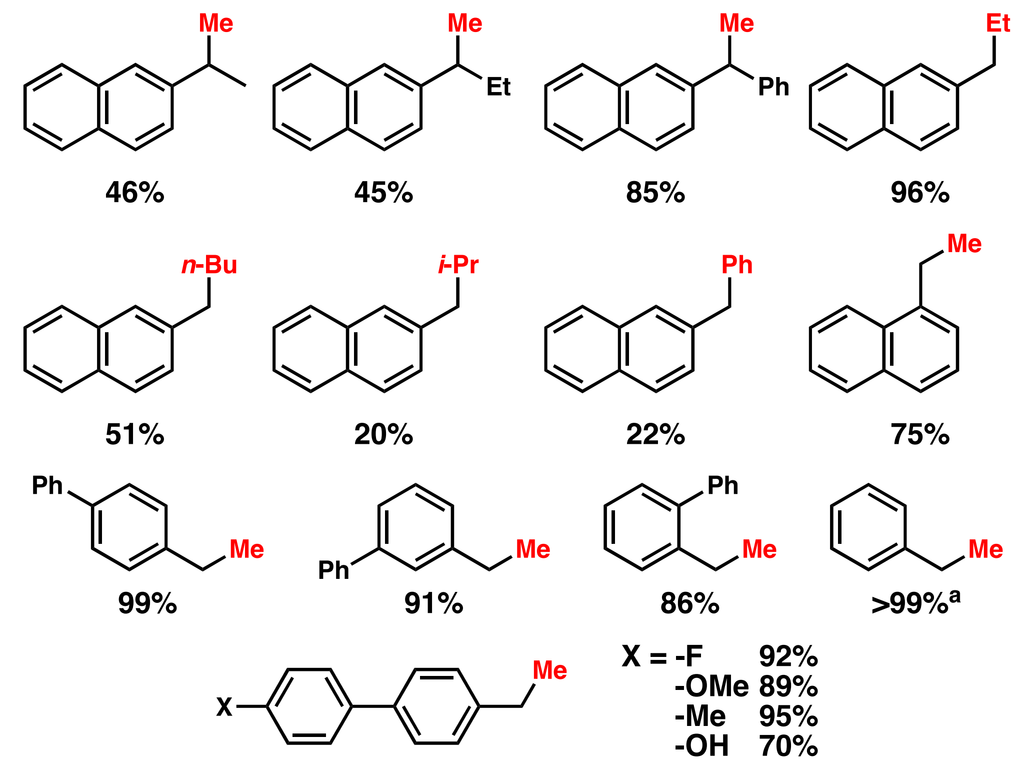
Ether Screen



R	yield	R	yield
-Me	80%	-Ph	75%
-Et	73%	-TMS	76%
-*t*-Bu	79%	-Ac	18%[a]

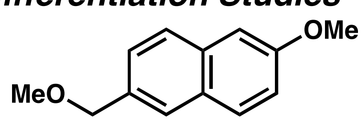
[a] GC yield





[a] GC yield.

Differentiation Studies



— Methylate Sequentially: sp^3–sp^2 then sp^2–sp^2
— Methylate Simulatenously: Use dppf + PCy_3

J. Am. Chem. Soc. **2008**, *130*, 3268.

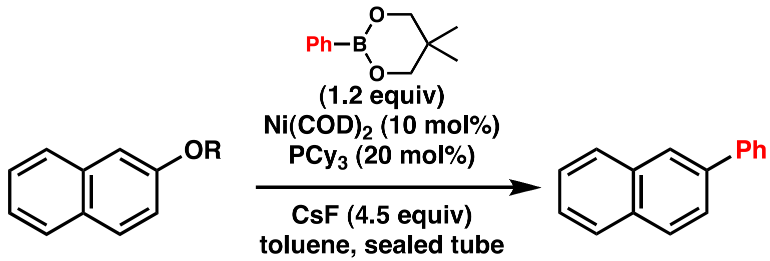
Aryl and Vinyl Ether Cross Coupling
Suzuki-Miyaura

Chatani, N.

Organoboron Screen

— $PhB(OH)_2$, $PhBF_3K$, $NaBPh_4$

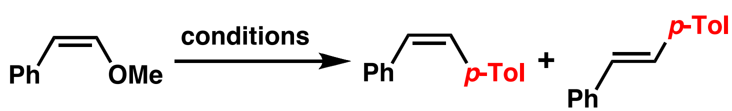
Aryl Ether Screen



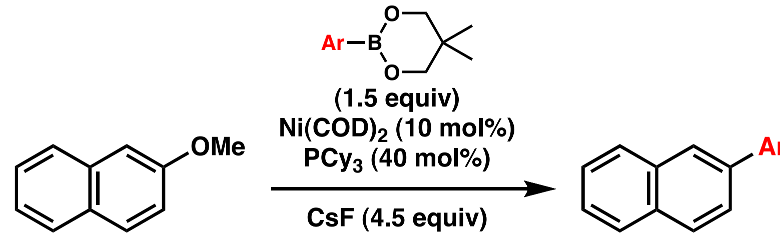
R	yield	R	yield
-Me	93%	-*i*-Pr	16%
-Et	74%	-Ac	10%

Electrophile Screen

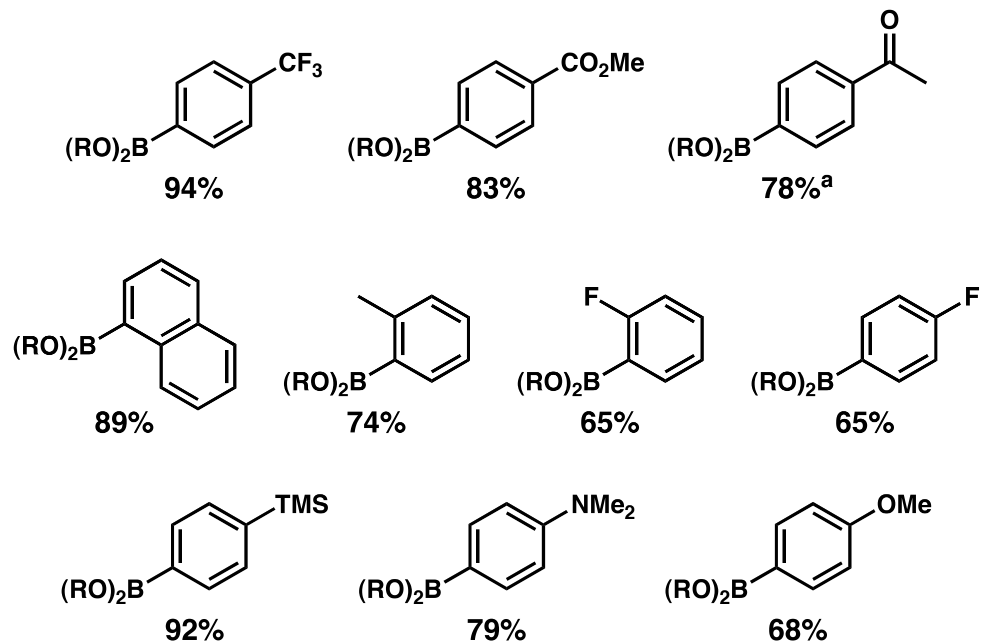
— Napthalene and phenanthrene good electrophilic substrates (57–93%)
— Only EWG functionalized benzene couple (14–55%)
— Olefins couple with poor E/Z selectivity



2 h	66 / 34
24 h	5 / 95



10 examples
36–94% yield

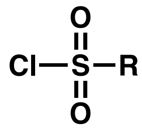


[a] 20 mol% $Ni(COD)_2$, 80 mol% PCy_3.

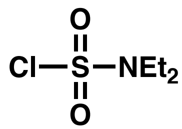
Aromatic Ethers: *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.
Vinyl Ethers: *Org. Lett.* **2009**, *11*, 4890.

Price Comparison

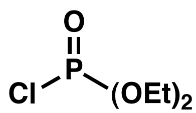
By Functional Group



R = CF_3 $310 / mol
p-tol $70 / mol
Me $20 / mol

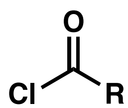


$180 / mol

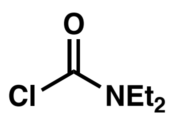


$130 / mol

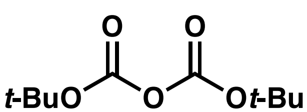
I—Me $20 / mol



R = *t*-Bu $10 / mol
Me $7 / mol



$40 / mol

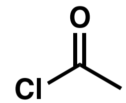


$220 / mol

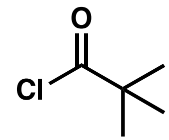
Approximate Cost from Sigma-Aldrich
see also Garg, N. *J. Am. Chem. Soc.* **2008**, *130*, 14422.

By Price

Increasing Price

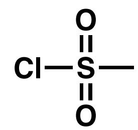


$7 / mol

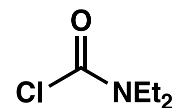


$10 / mol

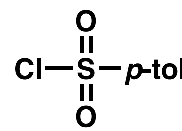
I—Me $20 / mol



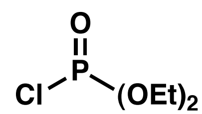
$20 / mol



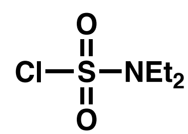
$40 / mol



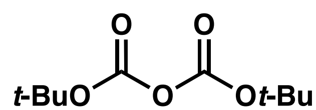
$70 / mol



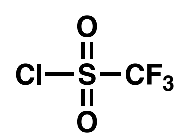
$130 / mol



$180 / mol



$220 / mol

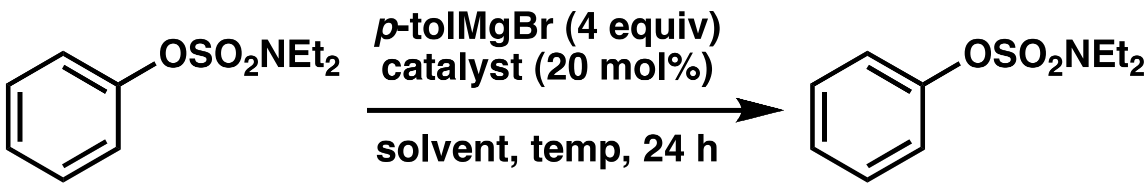


$310 / mol

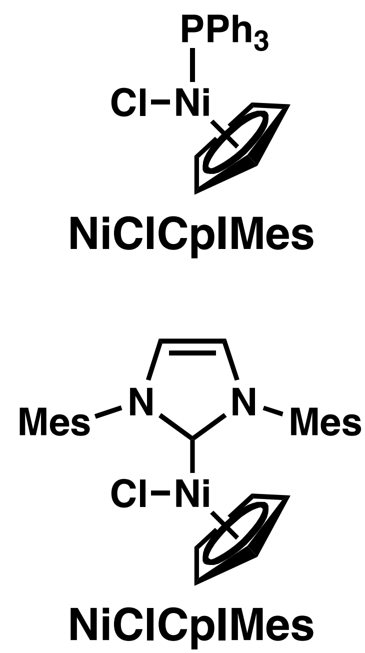
Sulfamate Ni Cross Coupling

Kumada Ni Catalyst Screen

Snieckus, V.



entry	catalyst	solvent	temp (°C)	GC yield (%)
1	$Ni(acac)_2$	PhMe	120	29
2	$NiCl_2$	PhMe	120	72
3	$NiCl_2$ / P(*t*-Bu)$_3$	PhMe	120	63
4	$NiCl_2$ / dppf	PhMe	120	74
5	NiClCpPPh$_3$	PhMe	120	91
6	NiClCpIMes	PhMe	40	85
7	NiClCpIMes	Et_2O	40	>99

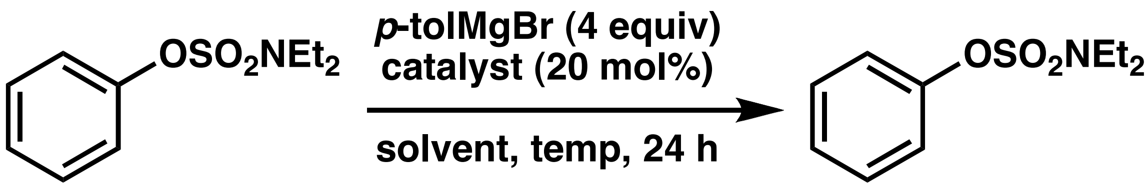


Org. Lett. **2005**, *7*, 2519.

Sulfamate Ni Cross Coupling

Kumada Ni Catalyst Screen

Snieckus, V.



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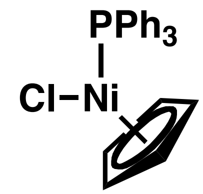
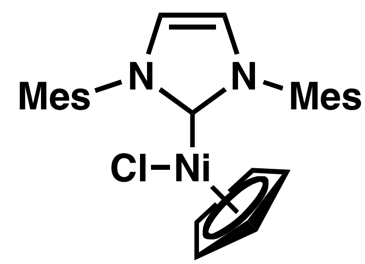


NiClCpIMes



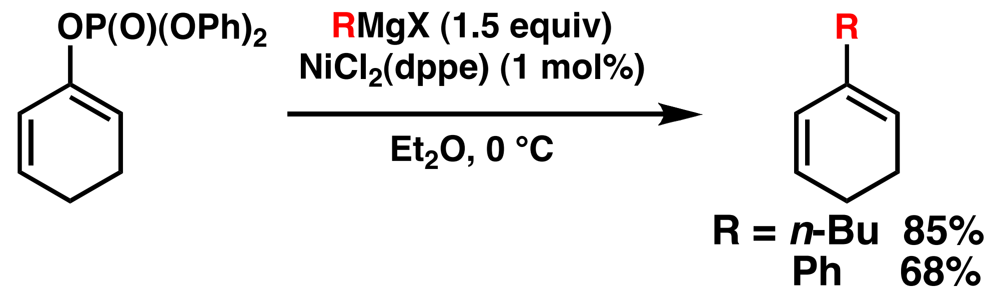
NiClCpIMes

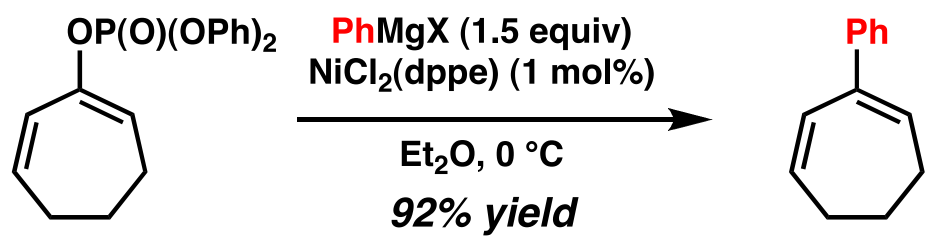
Org. Lett. **2005**, *7*, 2519.

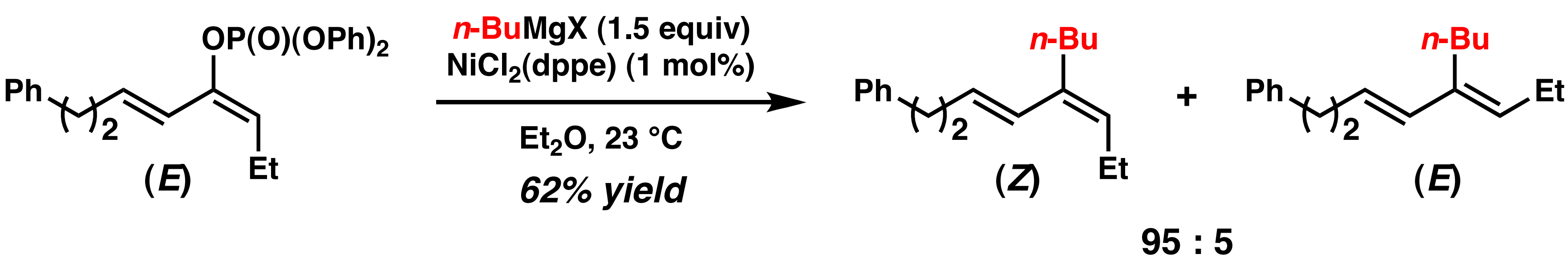
Phosphonate and Phosphoramide Cross Coupling

Kumada Coupling: Vinyl Phosphonates

Bäckvall, J.-E.





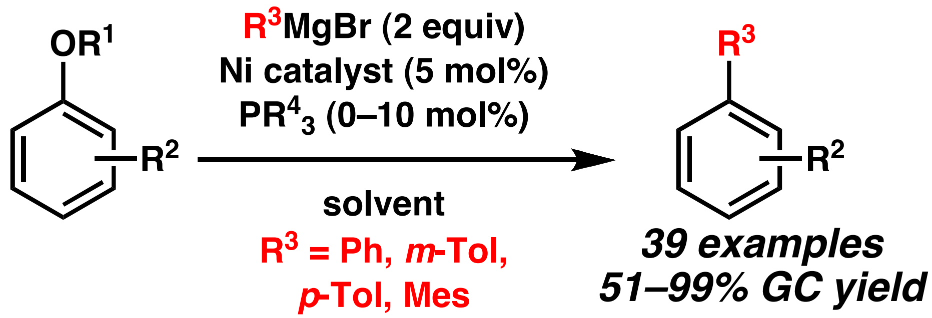


J. Org. Chem. **1999**, *64*, 1745.

Ether Cross Coupling

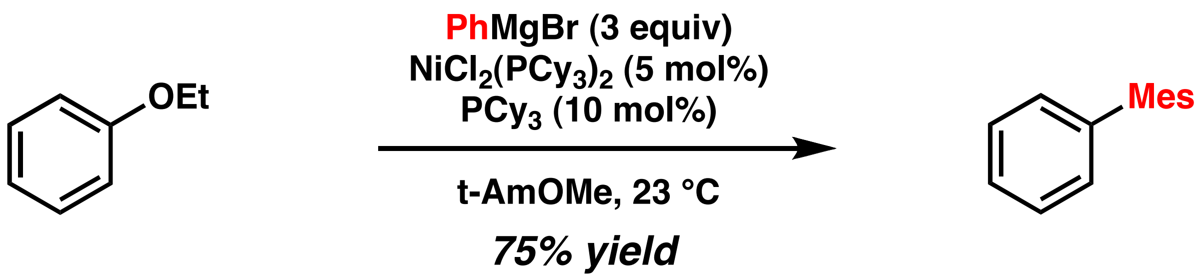
Kumada Coupling: sp^2–sp^2 C–C Formation

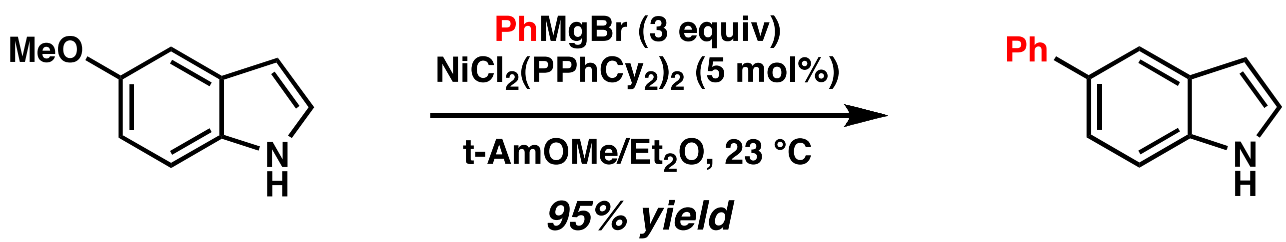
Dankwardt, J. W.



— $NiCl_2(PCy_3)_2$, $NiCl_2(PPhCy_2)_2$, –OR– $NiCl_2(PPh_2Cy)_2$

— Toluene, *i*-Pr_2O, $(EtO)_2CH_2$, *t*-AmOMe, *n*-Bu_2O



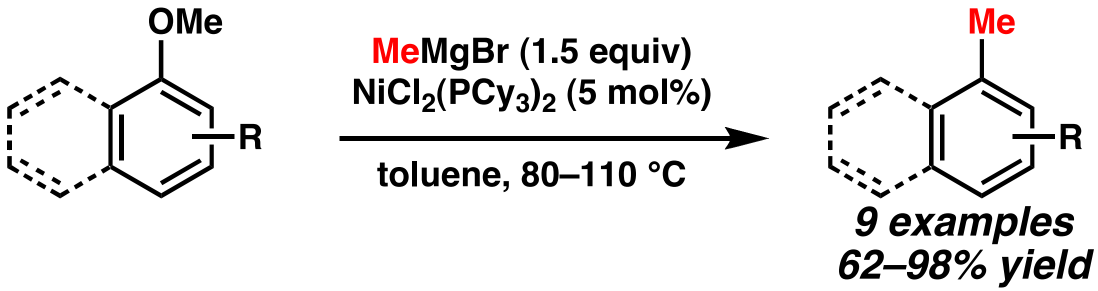


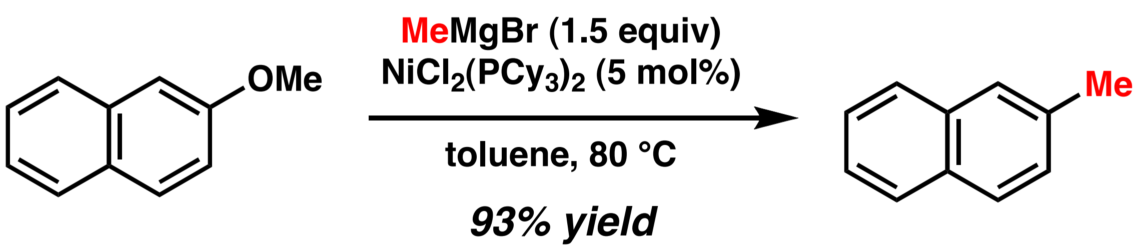
Angew. Chem., Int. Ed. **2004**, *43*, 2428.

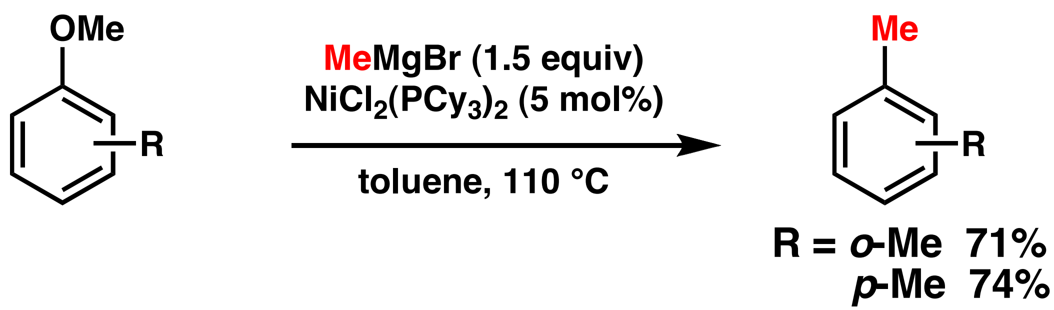
Ether Cross Coupling

Kumada Coupling: sp^3–sp^2 C–C Formation

Shi, Z.-J.





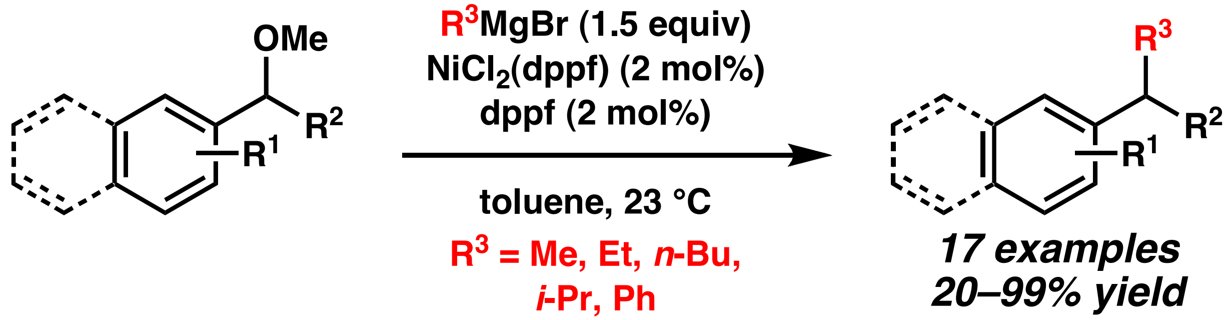


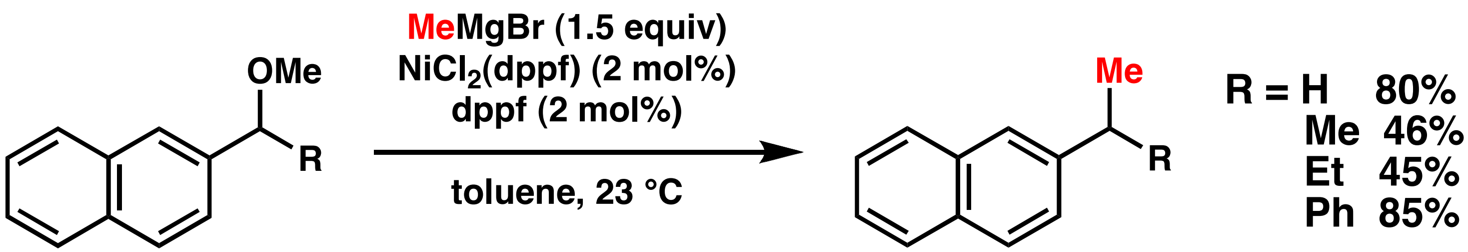
Chem. Commun. **2008**, 1437.

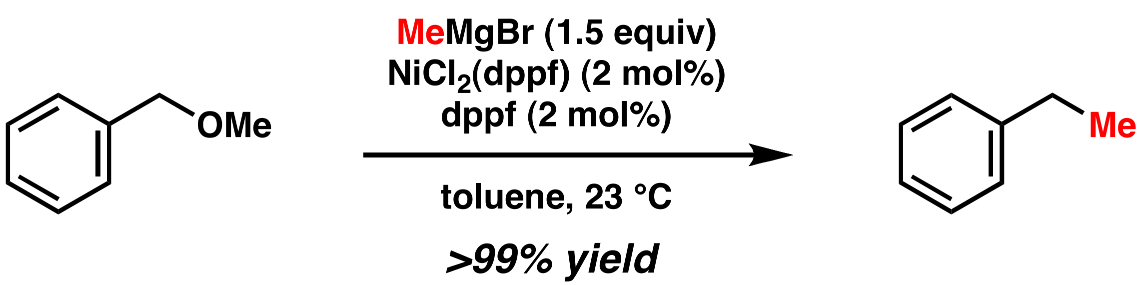
Ether Cross Coupling

Kumada Coupling: sp^3–sp^3 C–C Formation

Shi, Z.-J.





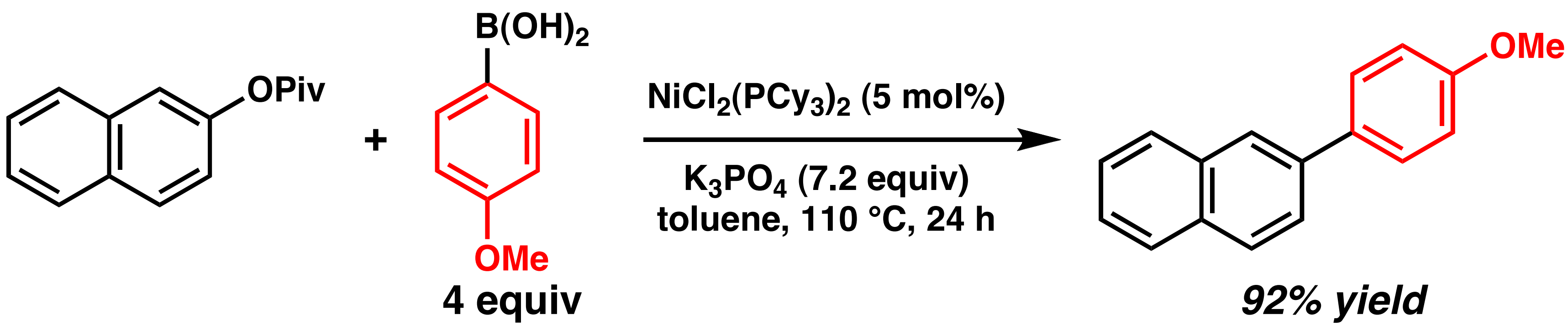


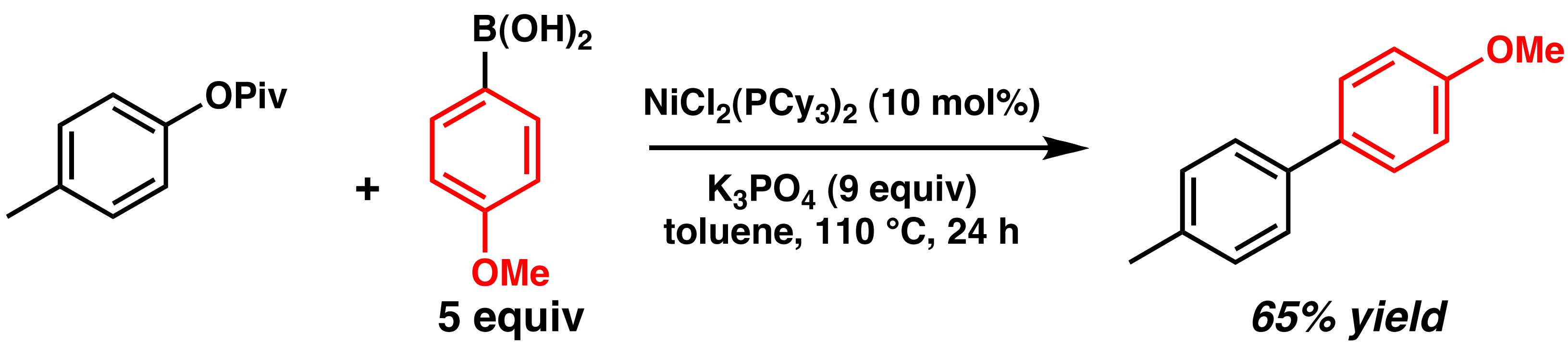
J. Am. Chem. Soc. **2008**, *130*, 3268.

Ester Cross Coupling

Suzuki-Miyaura Coupling: Aryl Esters

Garg, N. K.



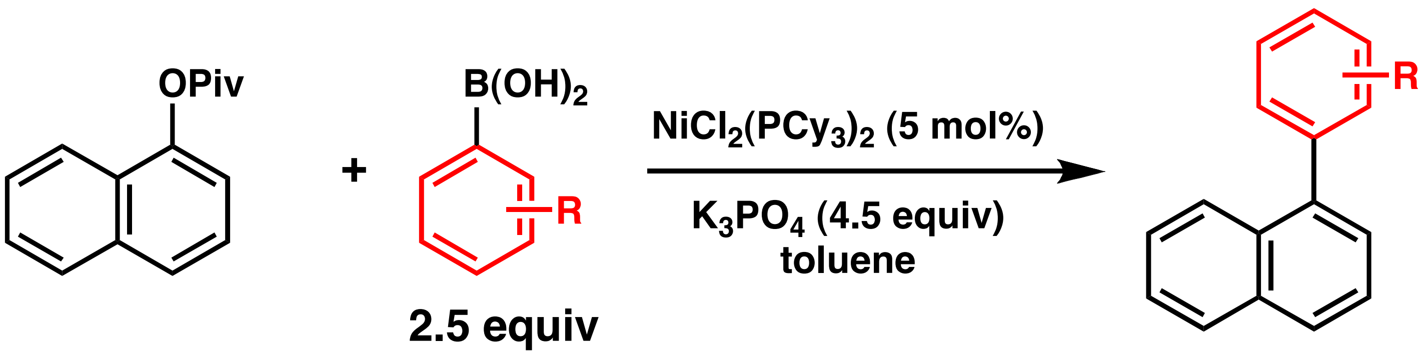


J. Am. Chem. Soc. **2008**, *130*, 14422.

Ester Cross Coupling

Suzuki-Miyaura Coupling: Aryl Esters

Garg, N. K.



Electronics

R = OMe 95%

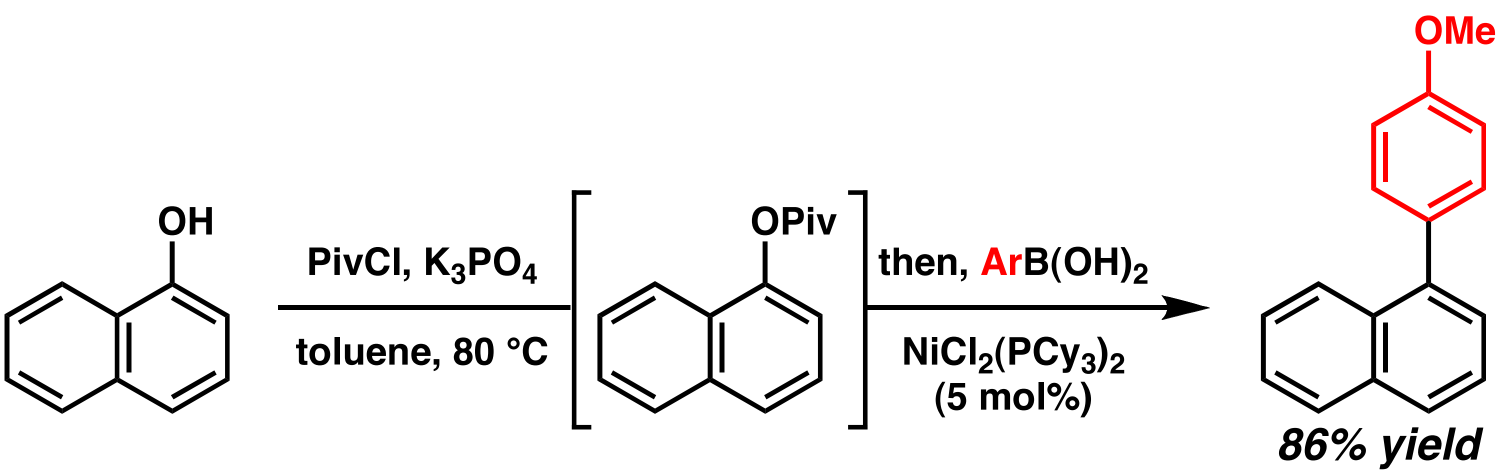
CF_3 77%

Sterics

R = *p*-Me 91%

m-Me 99%

o-Me 58%



J. Am. Chem. Soc. **2008**, *130*, 14422.