Ether C-O Bond Cleavage via Transition Metal Homogeneous Catalysis

BECCA LEISING

SED GROUP MEETING

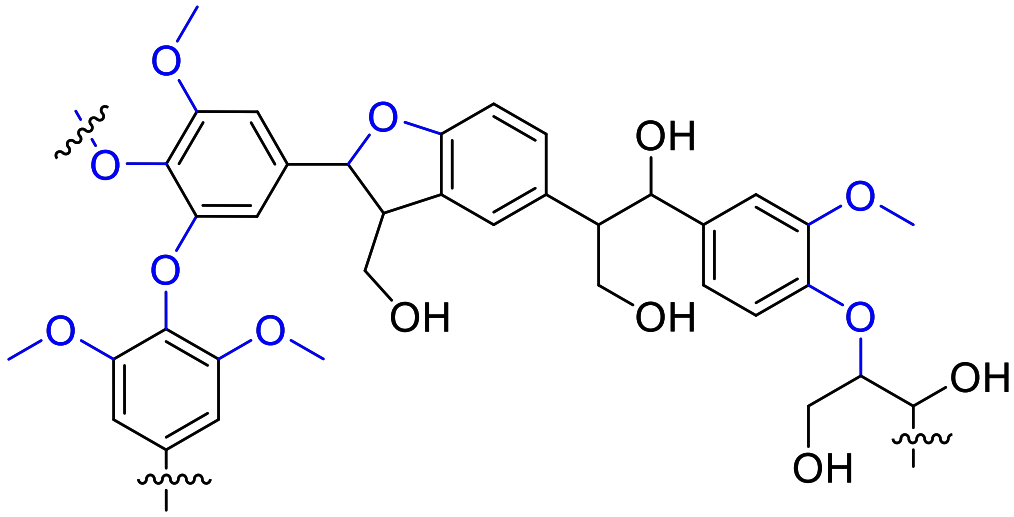
MAY 12, 2015

Overview

1. Uses of a different bond disconnection
2. Seminal work
3. Mechanistic studies
4. C-C bond forming reactions
    1. Kumada type
    2. Negishi type
    3. Heck type
    4. α-Arylation
    5. Suzuki-Miyaura type
5. Reductive coupling
6. Future directions/Conclusion

Valorization of Lignin

- Amorphous polymer which gives plants their structural integrity
- 50 million tons were extracted by paper industry
- Potential as renewable energy source
- Conversion to commercial arene feedstock
- No selective C-O bond cleavage with hydrogen

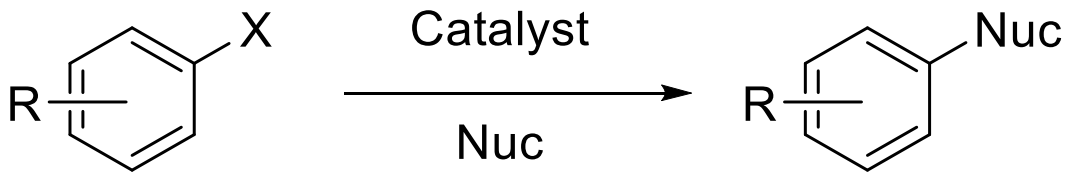


From Hardwood

Sergeev, A. G.; Hartwig, J. F. *Science*, **2011**, *332*, 439
Fedorov, A.; Toutov, A. A.; Swisher, N. A.; Grubbs, R. H. *Chem. Sci.* **2013**, *4*, 1640
Zakzeski, J.; Bruijnincx, P. C. A.; Jongerius, A. L.; Weckhuysen, B. M. *Chem. Rev.* **2010**, *110*, 3552

Environmental Impact

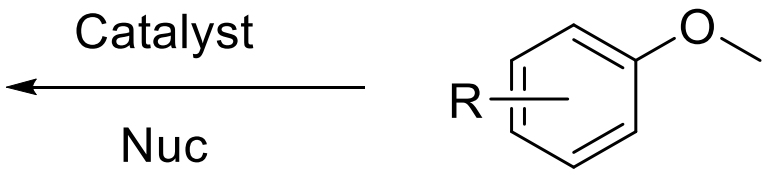
CLASSICAL CROSS-COUPLINGS



X= I, Br, OTf, OTs, Cl

- Use of Aryl halides and sulfonates
  - Halogenated and S-containing waste
- Moisture Instability
- High costs
- Low atom economy
- Low access to dense functionality

C-OMe CLEAVAGE

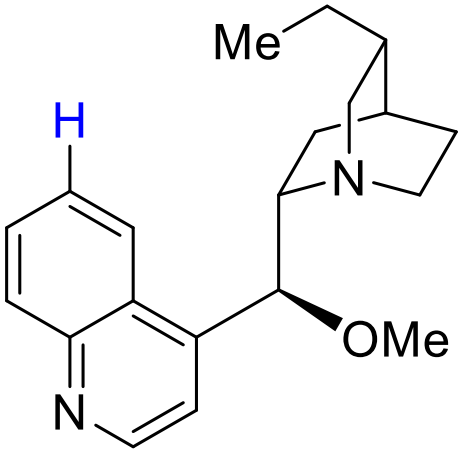


- Use of Aryl OMe
  - Reduced waste
- Highly inert, used as a directing group
- Derived from phenols
- Low cost
- No Sn reagents needed for reductive coupling

Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Late Stage Defunctionalization

QUININE DERIVATIVE

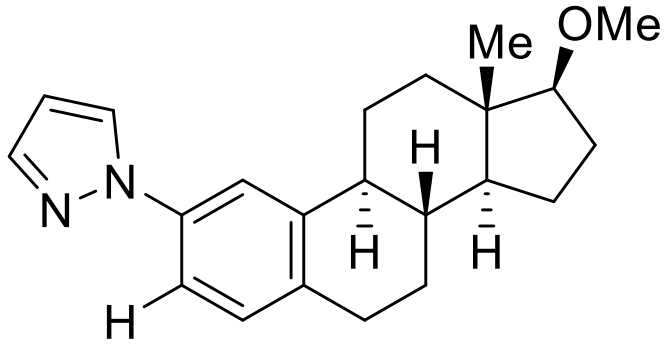


Previously used for antimalarial and antipyretic

Currently testing as a potential for an autophospholipid syndrome (APS)

- Reduce binding to phospholipid bilayers

ESTRADIOL DERIVATIVE



Prior use as a treatment for breast cancer

Used as hormone therapy

Rao, A. V. R.; Gurjar, M. K., Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135
Alvarez-Berceedo, P; Martin, R. *J. Am. Soc. Chem.* **2010**, *132*, 17352
Bezati, E.; Wu, X.-X.; Quinn, A. S.; Taatjes, D. J.; Rand, J. H. *Lupus* **2014**, *0*, 1
Molloy, M. E.; White, B. E. P.; Ghenerzghiher, T.; Michalsen, B. T.; Xiong, R.; Patel, H.; Zhao, H.; Maximov, P. Y.; Jordan, V. C.; Thatcher, G. R. J.; Tonetti, D. A. *Mol. Cancer Ther.* **2014**, *13*, OF1

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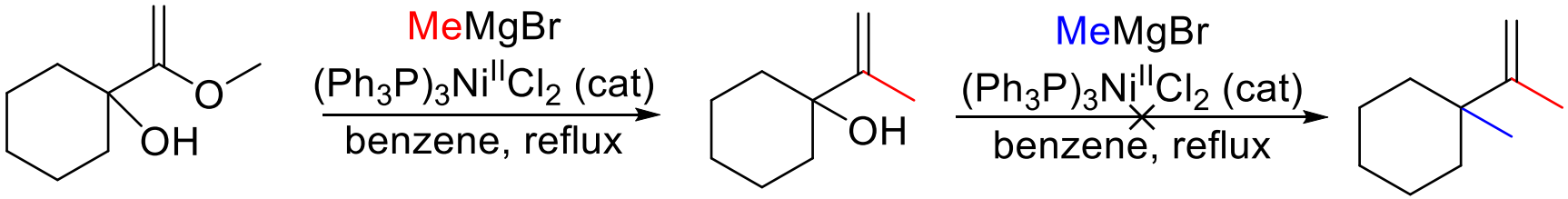
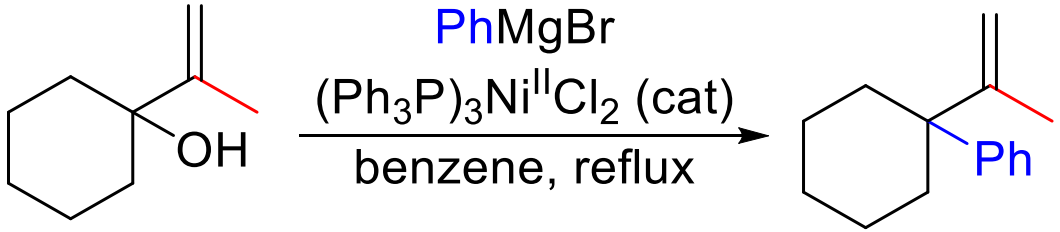
Wenkert – Seminal Work

Investigating allylic alcohols with Grignard reagents:



- Unprecedented OMe replacement
- Inert under resubmission to MeMgBr
  - Product not due to an early quench

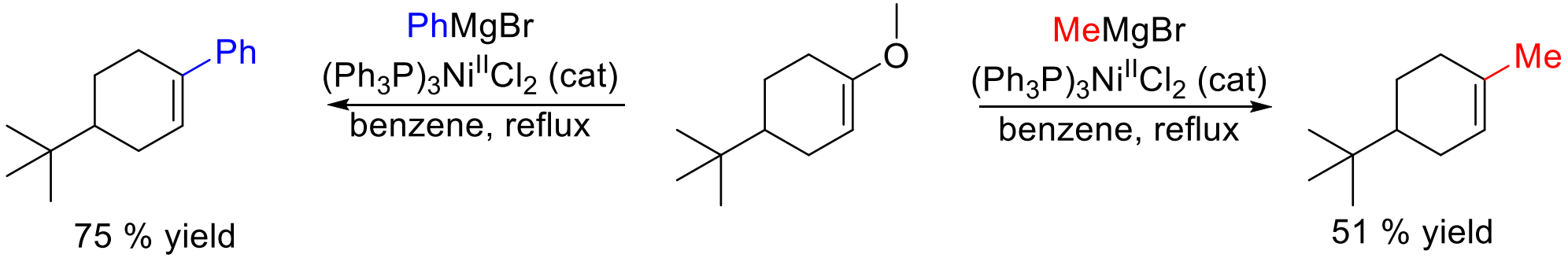


- More powerful Grignard lead to fully deoxygenated product

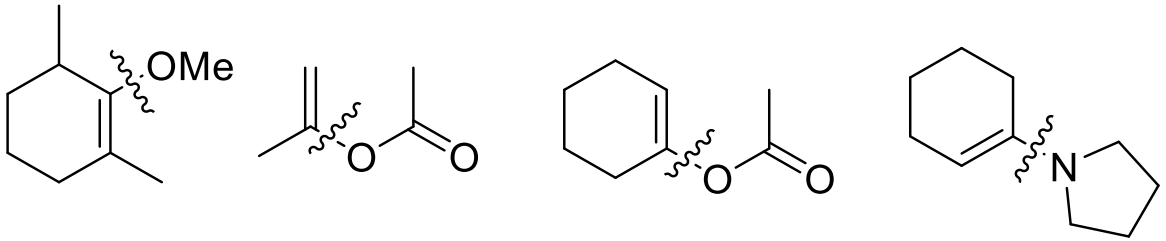
Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246
Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Am. Chem. Soc.* **1984**, *49*, 4894

Wenkert – Seminal Work

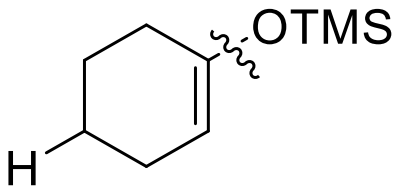
Further studies of enol ethers:



- No reaction occurred with highly substituted substrates



Silyl enol ethers proceed with low yields with PhMgBr



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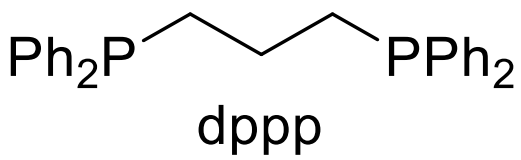
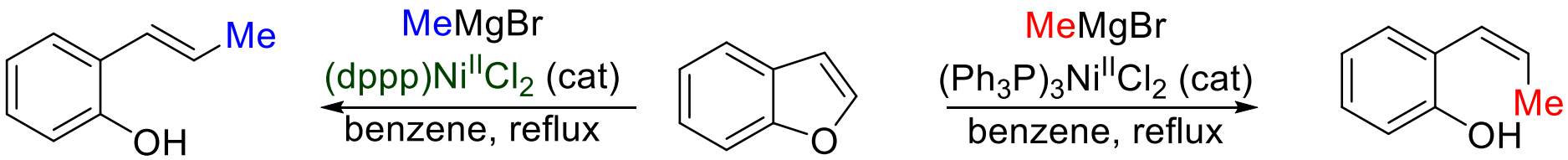
Wenkert – Seminal Work



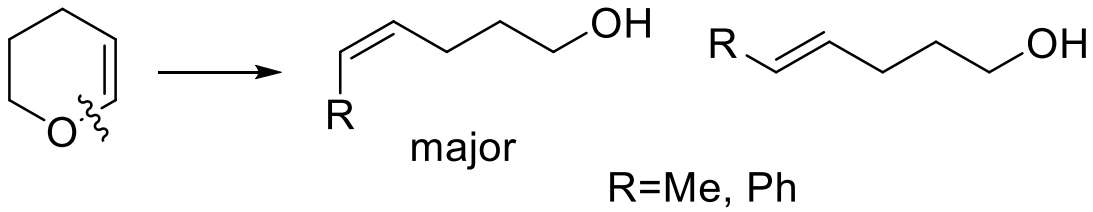
Double bond geometry dependent on the ligand

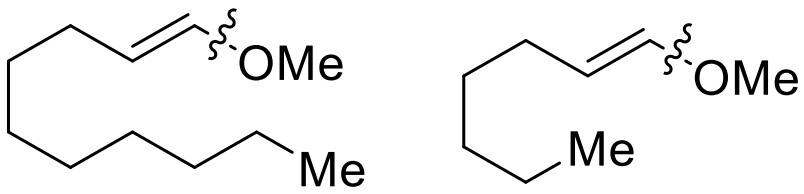


1:3 *Z*:*E*

4:1 *Z*:*E*

- Dihydropyrans gave retention of geometry
- Benzofuran gave inversion of geometry with respect to PhMgBr



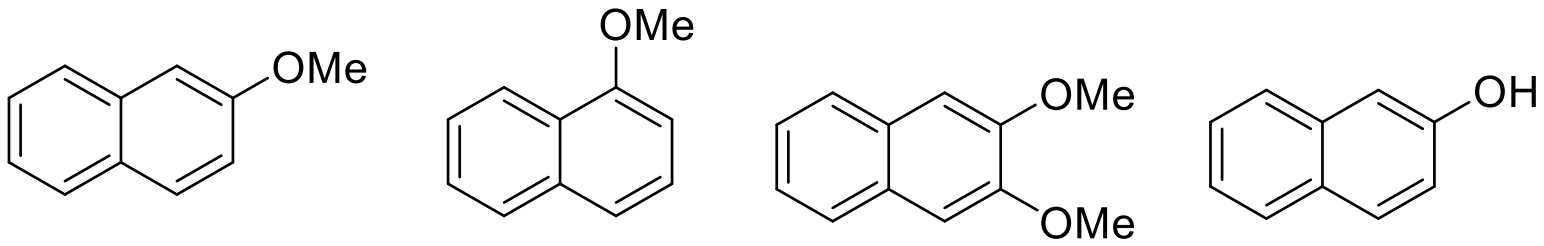


- EtMgBr gave both ethylated and reduction products
  - Grignards with β-hydrogens gave reduced products
- Linear enol ethers under went coupling with MeMgBr and PhMgBr with a retention of double bond geometry

Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246
Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Am. Chem. Soc.* **1984**, *49*, 4894

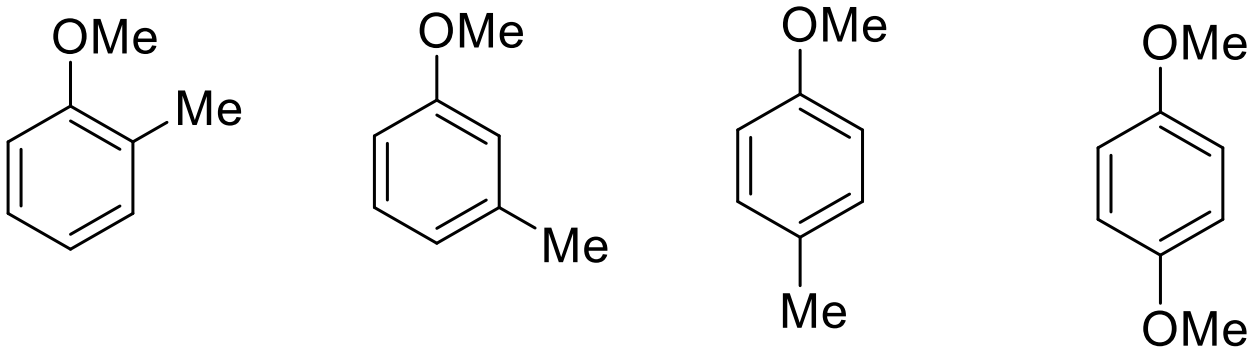
Wenkert – Seminal Work

- Extended π-system, e.g. naphthalene derivatives, afforded high yields with coupling at all the MeO positions



low yields

- Simple phenyl ethers afforded low yields and strong steric effects



  - No reaction occurred with ortho substitution
  - Enol ethers reacted at a faster rate than aryl ethers

Retention of double bond configuration, low tolerance for simple anisole derivatives, limited scope and no alkyl Grignards with β-hydrogens

Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246
Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Am. Chem. Soc.* **1984**, *49*, 4894

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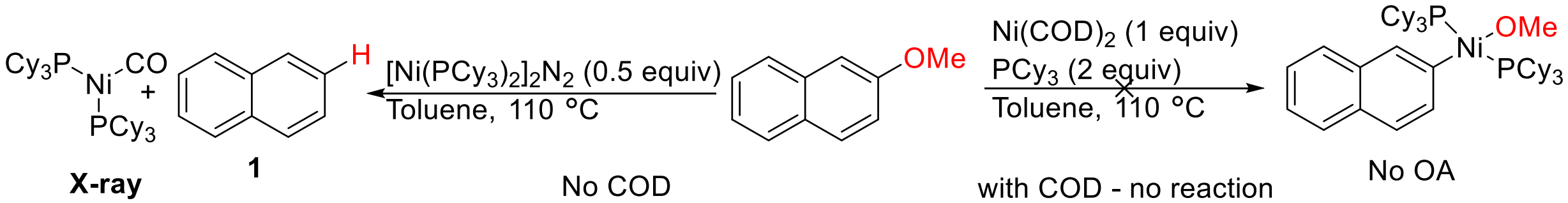
Mechanistic Studies – Reductive Cleavage

2013 – Martin reported in depth mechanistic studies on the reductive cleavage of C(sp^2) – OMe bonds under Ni catalysis



Experimentally and theoretically (B3LYP or Truhlar's M06/6-311++G(d,p)/SDD) and (6-31G(d,p)/LANL2DZ) found that "classical" oxidative addition does NOT occur up to 110 ˚C

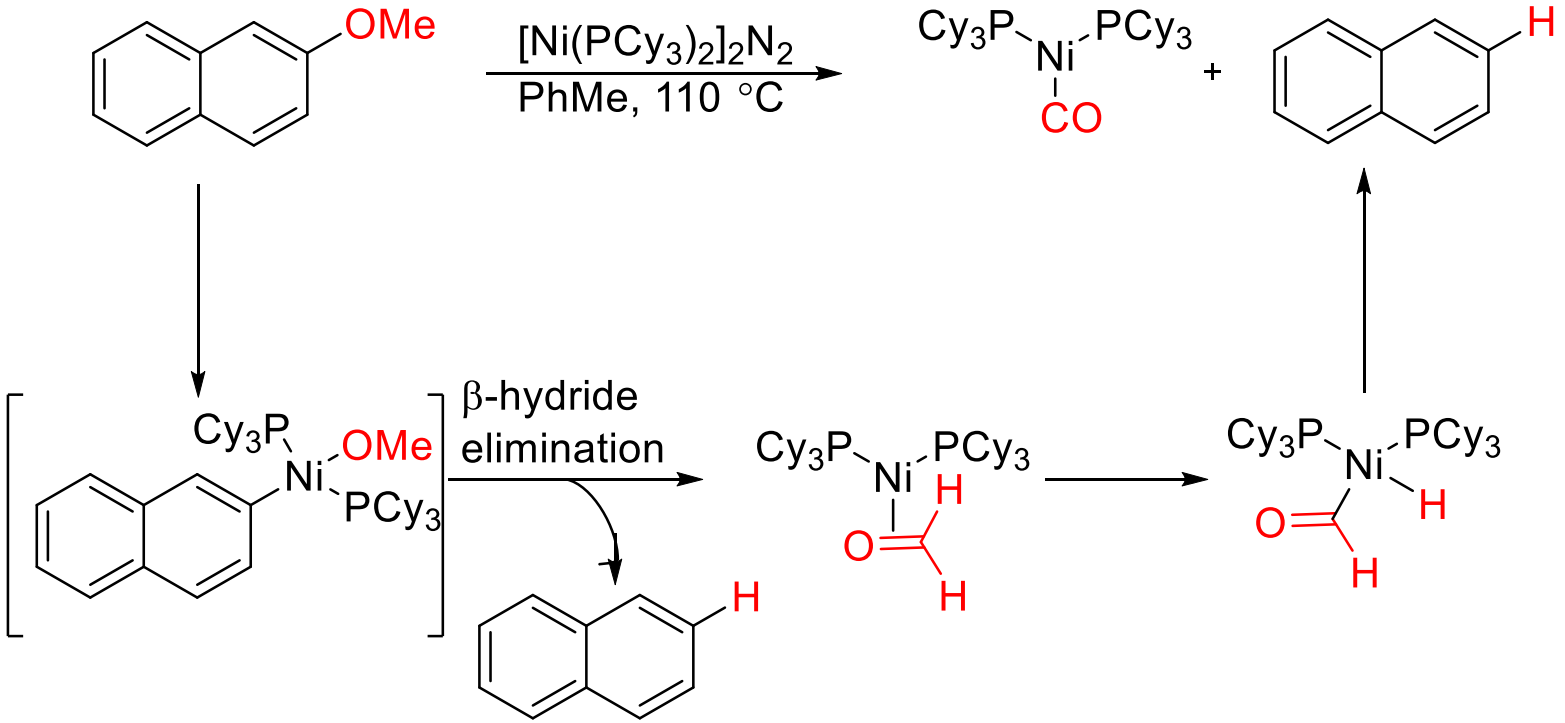
- Different outcome without COD

Cornella, J.; Gomez-Bengoz, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Mechanistic Studies – Reductive Cleavage

Mechanistic interpretation:

- Oxidative addition into the C – OMe bond
- β – hydride elimination
- C-H functionalization
- H_2 extrusion



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Mechanistic Studies – Reductive Cleavage

Isotope-labelling - β – hydride elimination occurs in the absence of silanes

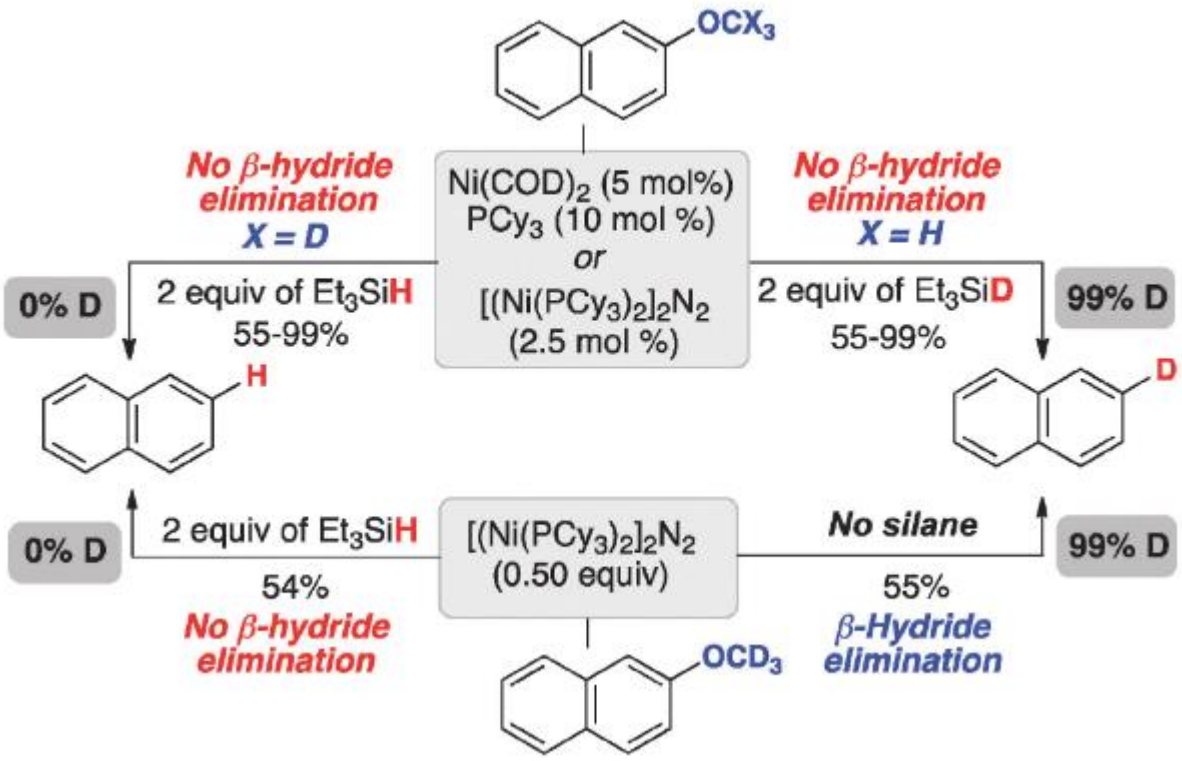
In the presence of silanes σ-bond metathesis occurs faster than β – hydride elimination

Kinetic studies showed 1st order rate dependence on Ni, substrate and silane

Ni^{i} intermediate was invoked

Confirmed Ni^{i} through high temperature ^{1}H-NMR, and low temperature electron paramagnetic resonance (EPR)

- EPR is the same as NMR, except that electron spins are excited in place of atomic nuclei



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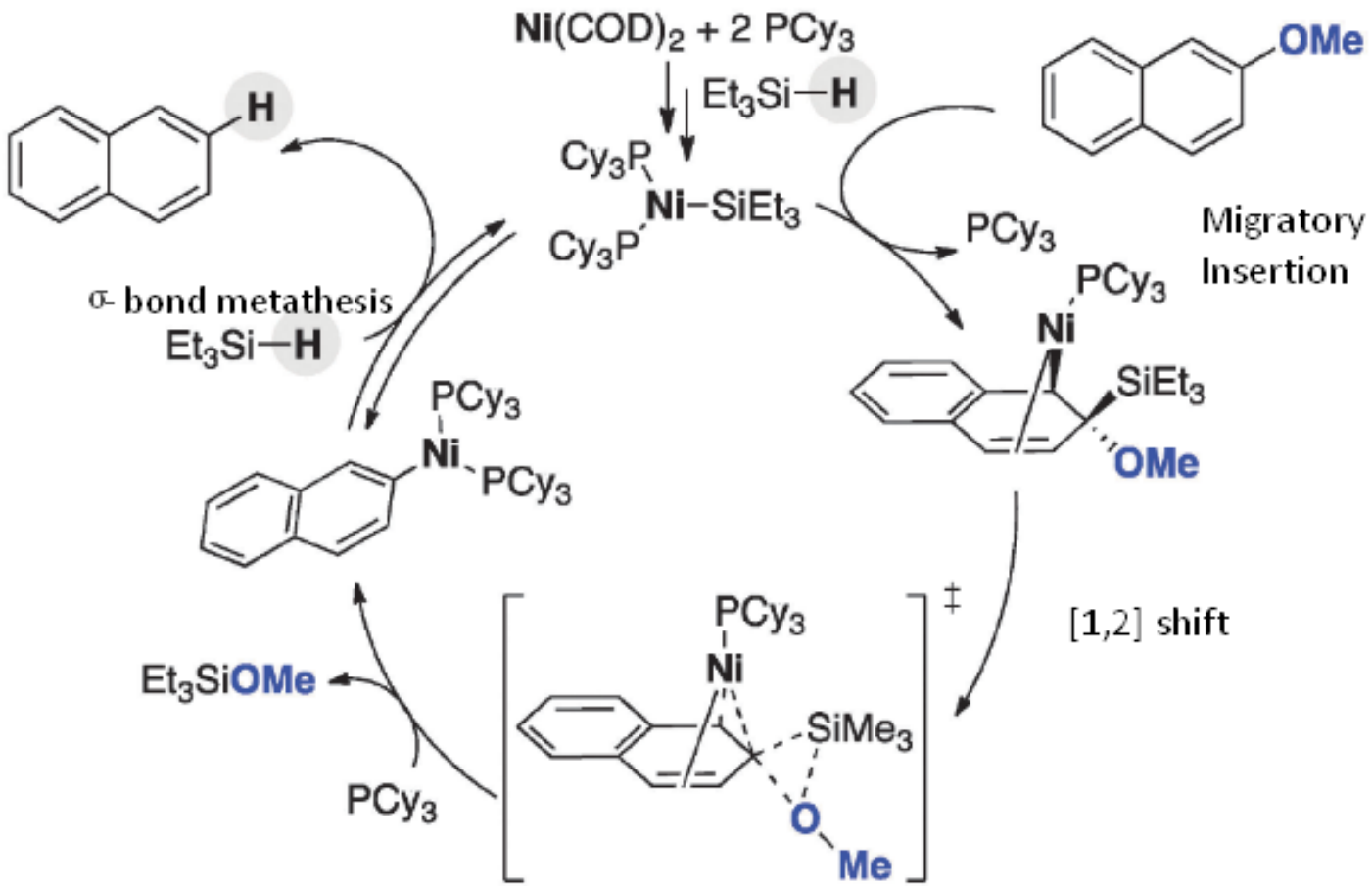
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Mechanistic Studies – Reductive Cleavage

Proposed Mech:

Intermediacy of Ni^{I}-SiR_3

- Migratory insertion
- [1,2]-shift
- σ-bond metathesis



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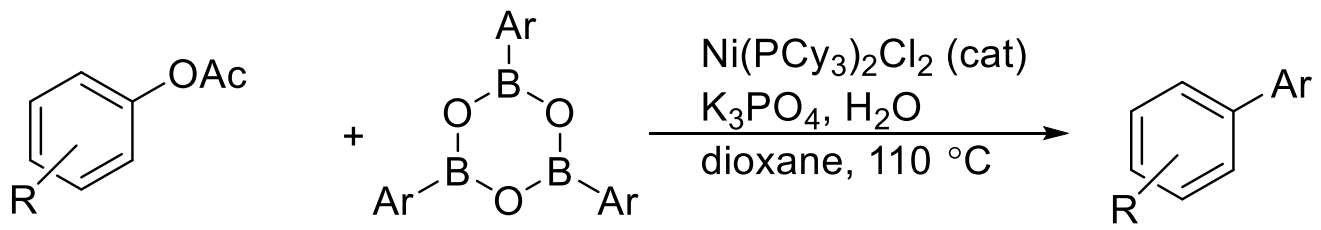
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

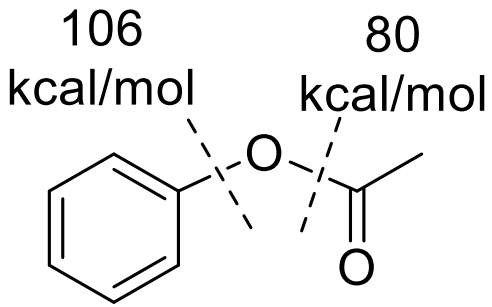
Mechanistic Studies – OA selectivity



OA of O-Ac bond is 8.7 kcal/mol lower in energy relative to Ph-O OA

O-Ac intermediate is less stable by 18.8 kcal/mol

- OA of O-Ac is reversible (14.2 kcal/mol vs. 25.7 kcal/mol); whereas Ph-O is irreversible (22.9 kcal/mol vs. 53.2 kcal/mol)

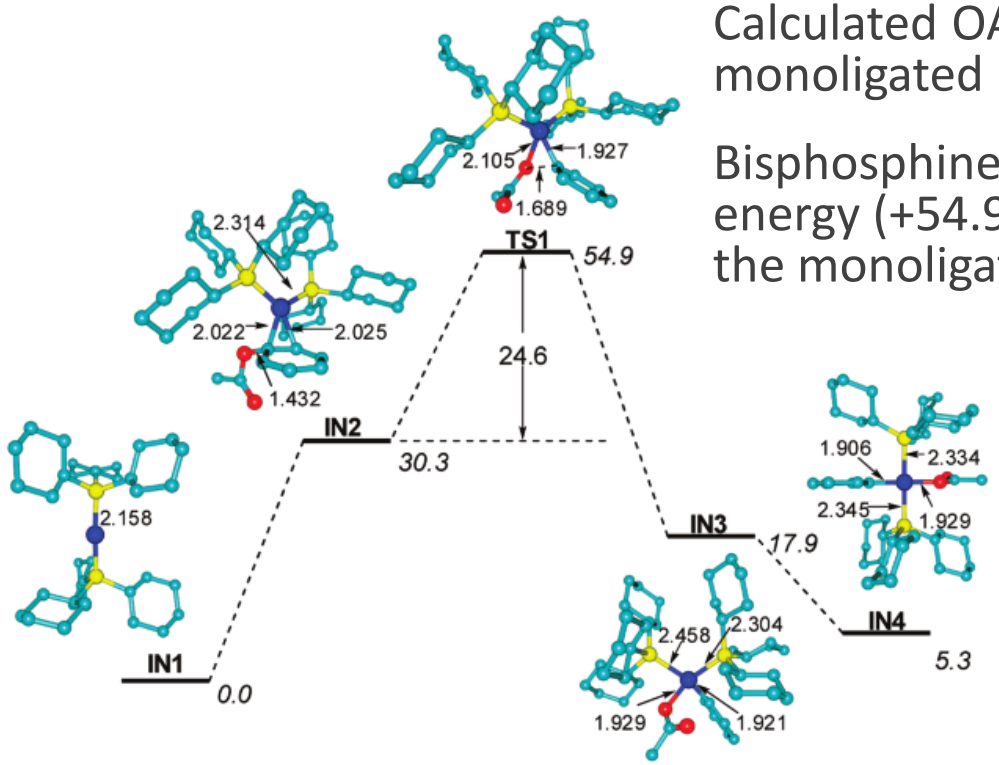


Experimentally Pd fails to activate C-O:
Ni and Pd share an η^2-complex followed by a C-X activation
Calculations of monoligated metals showed the η^2-complex between Ph-X and Ni^0 is highly exothermic (-22 to -27 kcal/mol), where Pd is less (-8 to +2 kcal/mol)
The OA energy barrier is +26.4 kcal/mol for Ni and +34.0 kcal/mol for Pd

Li., Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815
Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468

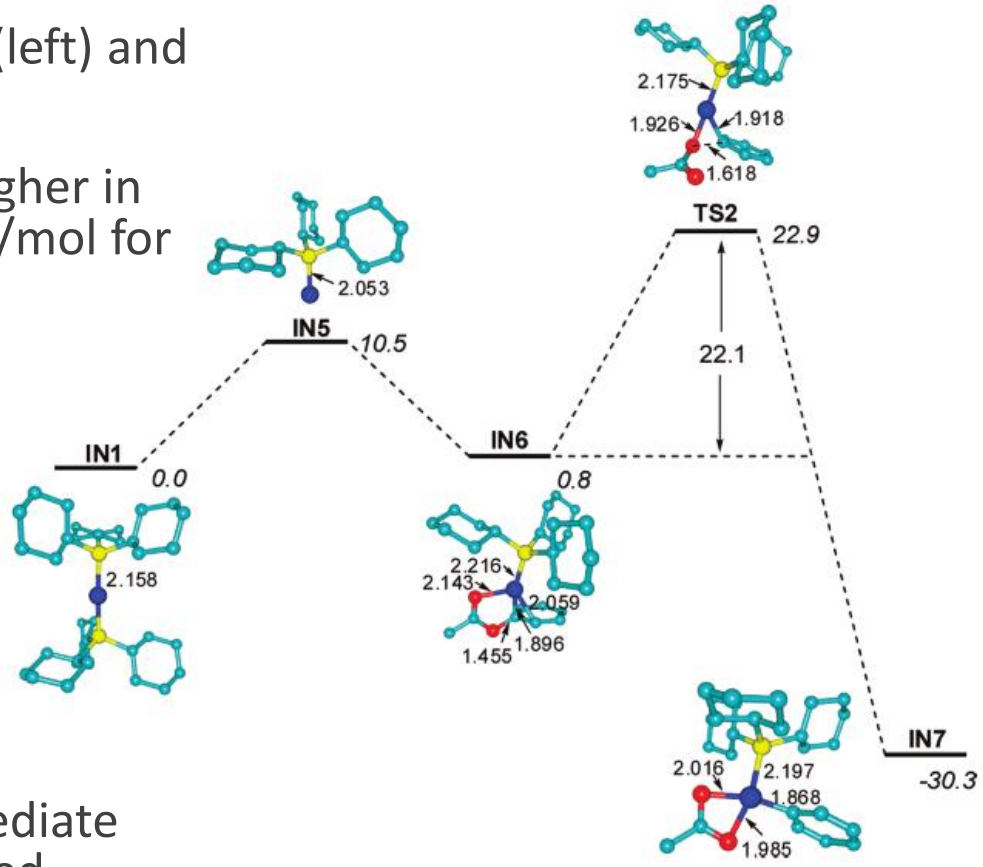
Mechanistic Studies – OA

B3Pw91/6-311+G(2d.p)/SDD for single point



Calculated OA for both bisphosphine (left) and monoligated (right) Ni^0 complex

Bisphosphine pathway significantly higher in energy (+54.9 kcal/mol) vs. +22.9 kcal/mol for the monoligated Ni

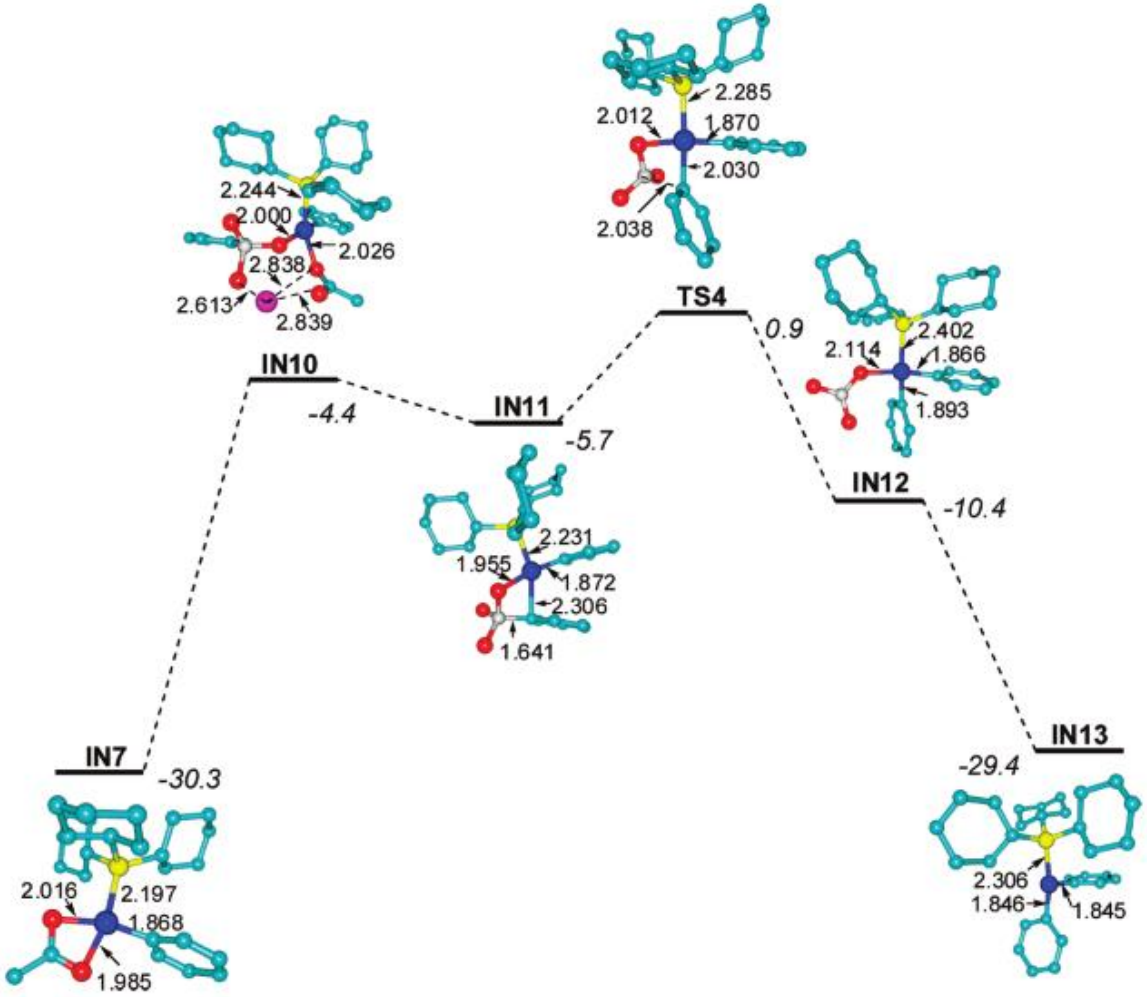


Monoligated Ni – more stable intermediate with both carboxyl oxygens coordinated

B3Pw91/D95v(d)/LANL2DZ+p for gas phase

Li., Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815

Mechanistic Studies – Transmetalation



Free base transmetalation has too high of an activation energy (54.7 kcal/mol) compared to 31.2 **cal**/mol for base-assisted transmetalation

$$K_3PO_4 + H_2O + PhB(OH)_2 \longrightarrow K[PhB(OH)_3] + K_2HPO_4$$

Organoboronic acid exists in an equilibrium

1. Coordination of $K[PhB(OH)_3]$
2. Dissociation of KOAc
3. Four centered transition state - Rate Determining Step
4. Dissociation of $B(OH)_3$

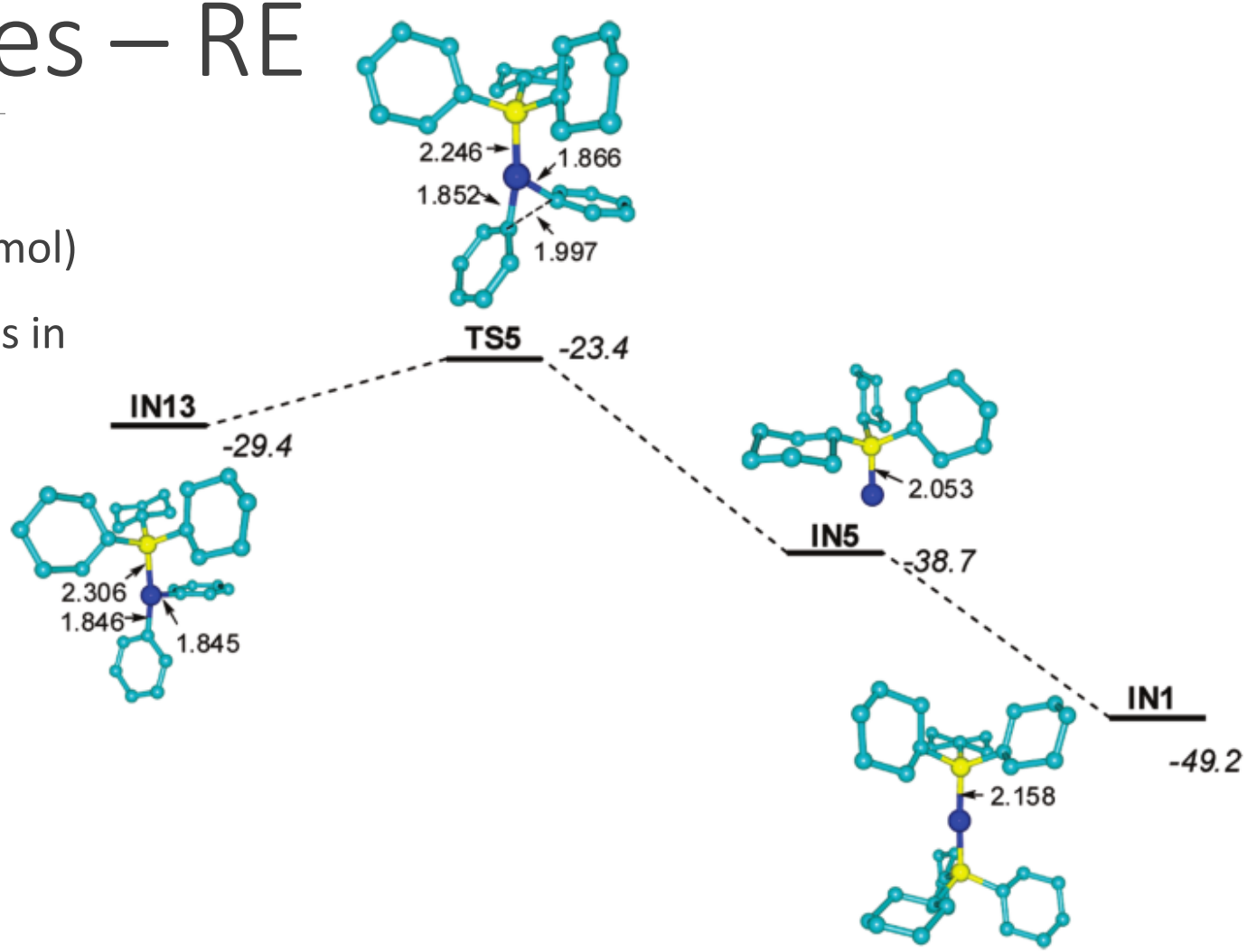
Li., Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815

Mechanistic Studies – RE

Tricoordinate transition state (+ 6.0 kcal/mol)

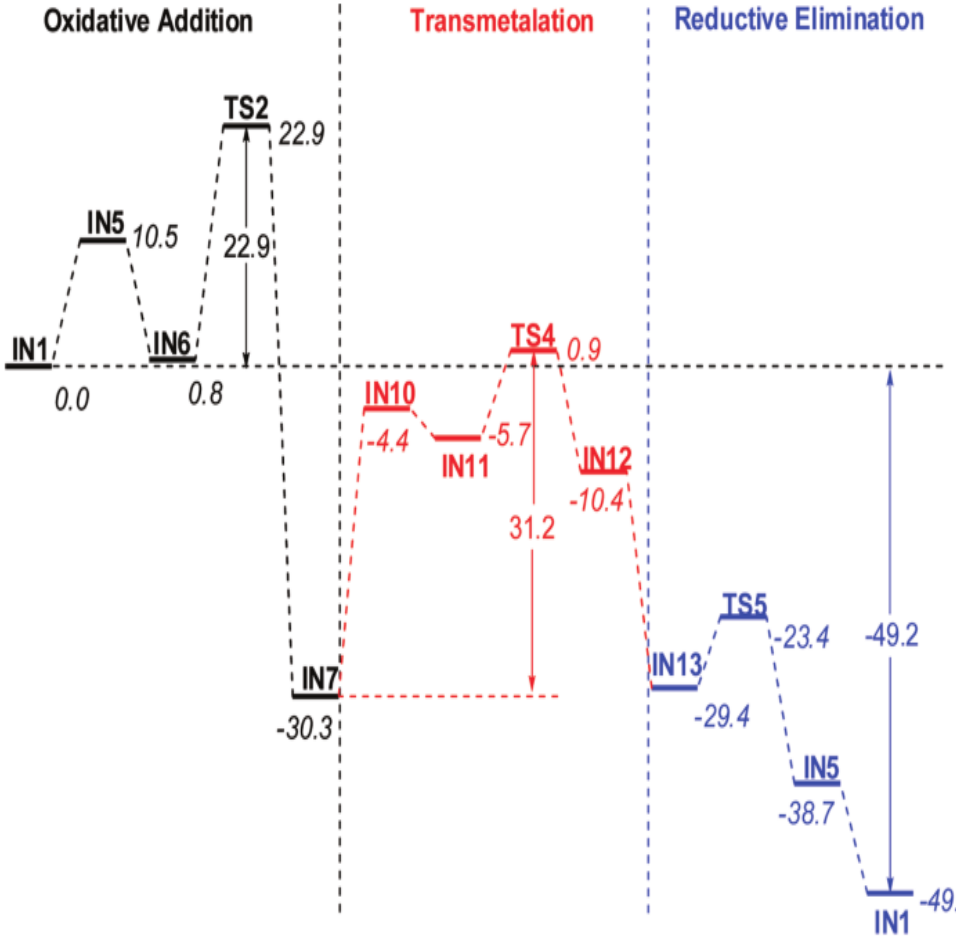
Results in a monoligated product, which is in equilibrium with the bisligated product

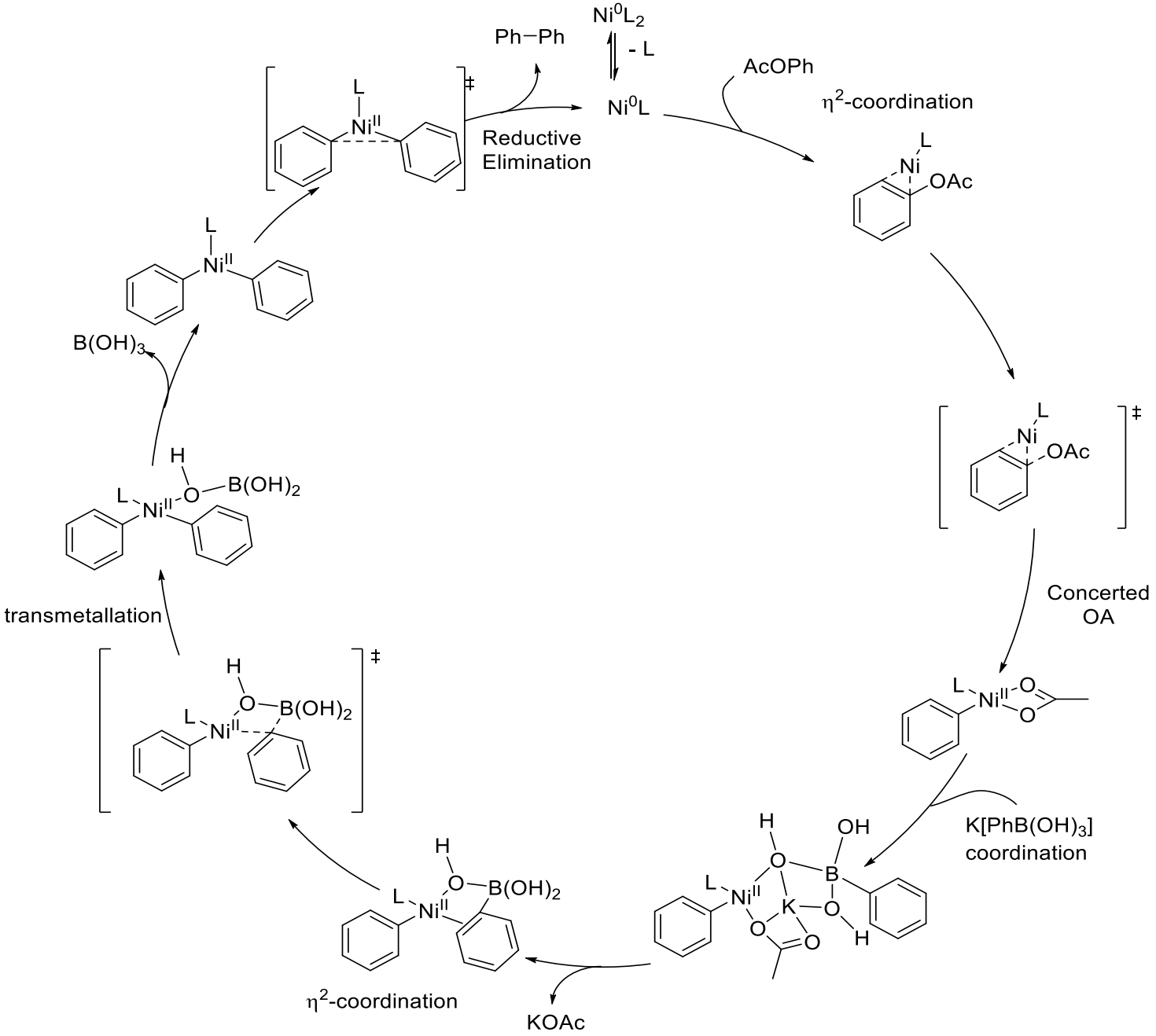
Very facile step



Li., Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815

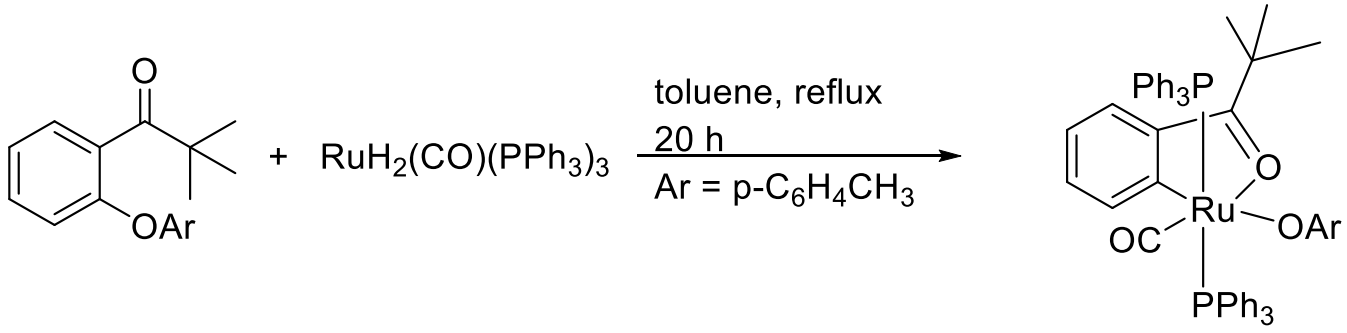
Overall Catalytic Cycle

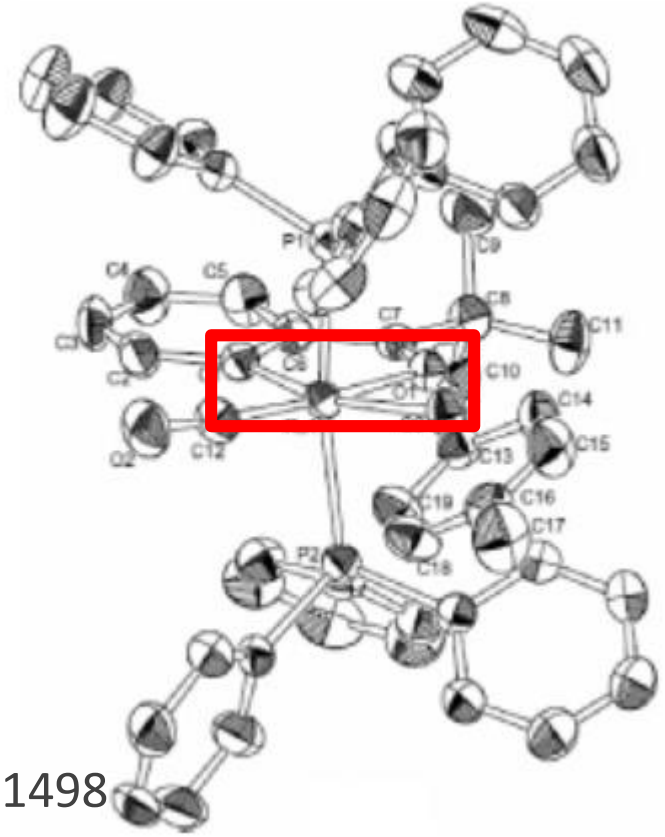




Mechanistic Studies – OA

First report of observed oxidative addition into an aryl C-O bond





Aryloxy ligand trans to aryl carbon

Five-membered ruthenacycle through ketone was coordination

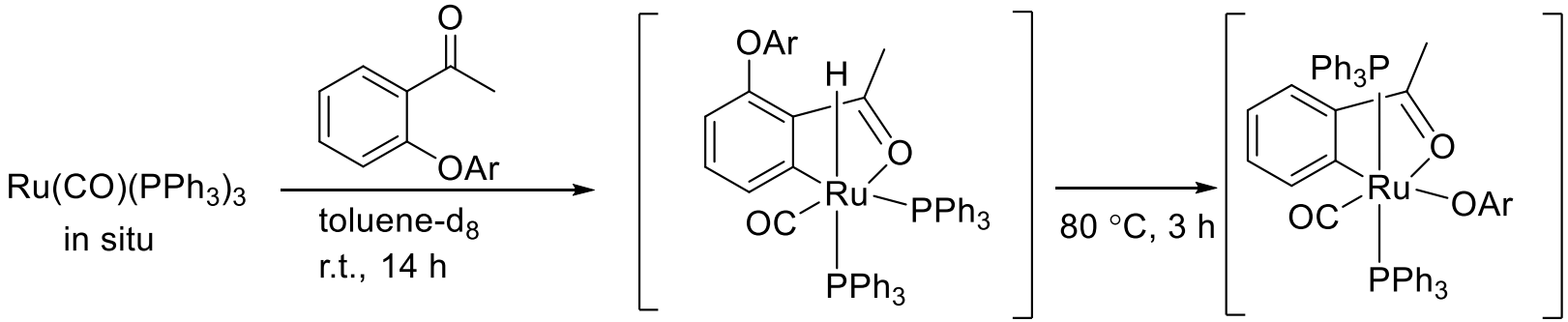
Aryl carbon cis to CO ligand

Further evidence: shift upfield of ^{31}P- and ^{1}H-NMR and IR carbonyl shift to 1498 cm^{-1}

Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516

Mechanistic Studies – OA

Relative Reactivity between aryl C-O and aryl C-H bonds



C-H oxidative addition:

One hydride signal observed at -5.97 ppm

Two signals were present in the ^{31}P-NMR

Was stable for two days

Kinetic product

C-O oxidative addition:

Deep red species

One signal in the ^{31}P-NMR

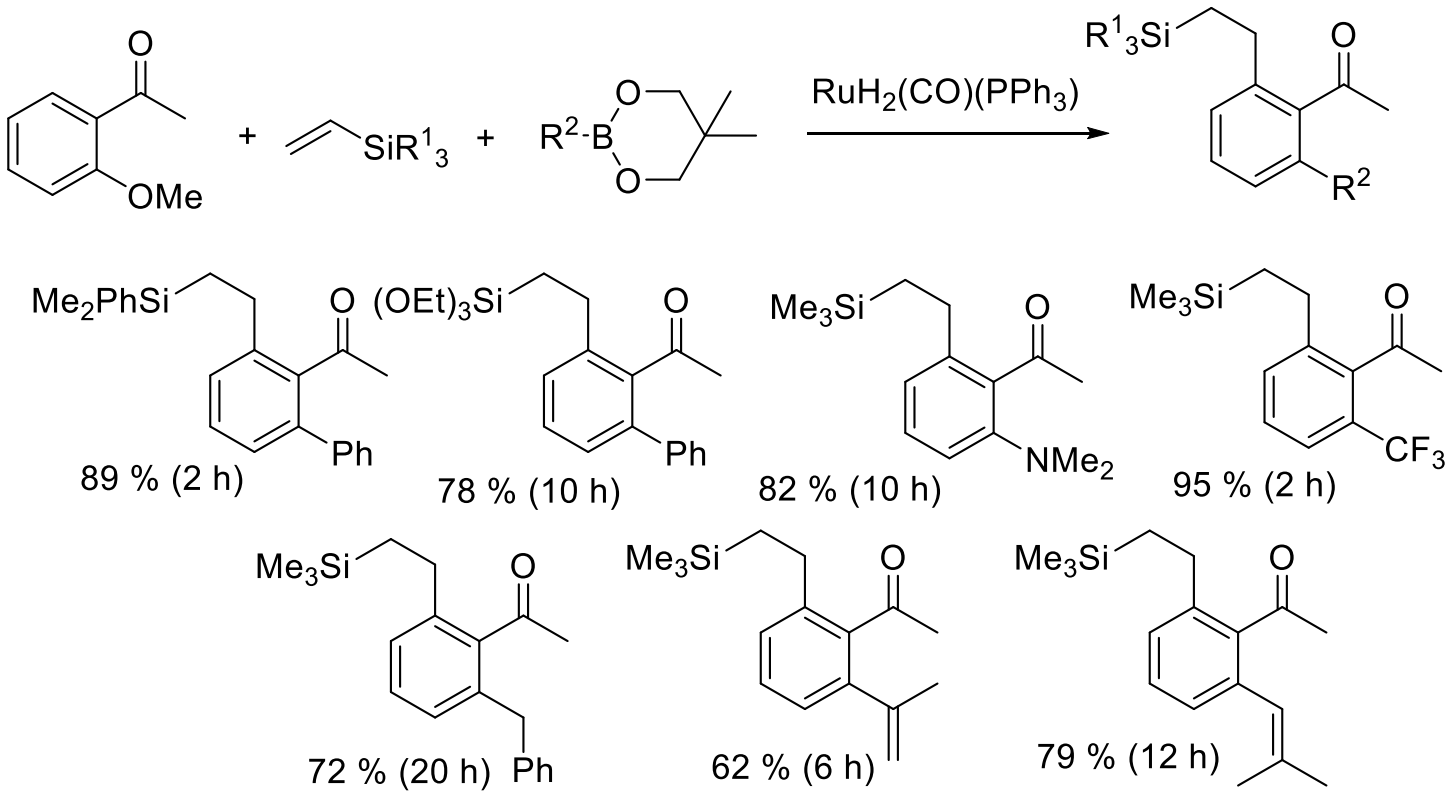
Similar to previous complex

Thermodynamic product

Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516

Mechanistic Studies – OA

Chemoselective sequential C-C bond formation (Suzuki type):



Dimethylphenyl and triethoxyvinylsilanes were tolerated under the reaction conditions

Aryl, alkyl and alkenylboronates can be used

Both electron deficient and electron rich aryls were tolerated

C-H/olefin proceeds faster than C-H/R-B-$(OR')_2$

No β-hydride elimination products observed

- Transmetalation occurs rapidly

Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516

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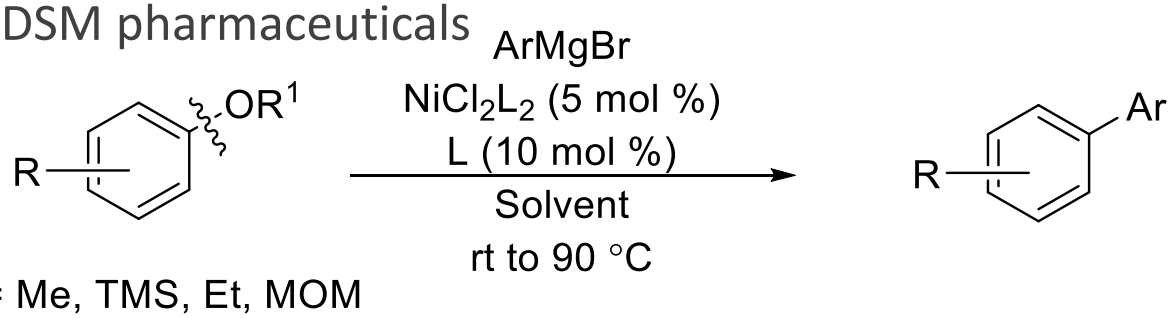
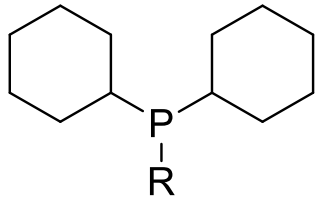
Kumada type Coupling

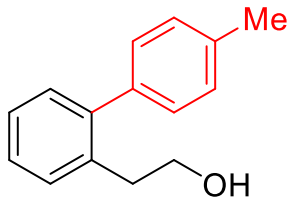
2004 - Dankwardt at DSM pharmaceuticals



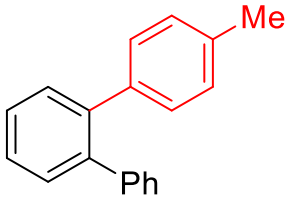
R^1= Me, TMS, Et, MOM



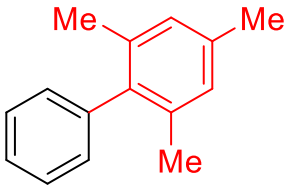
R = Cy, **L1**
R = Ph, **L2**



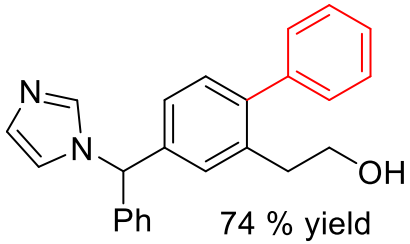
63 % yield
Et_2O, **L1**



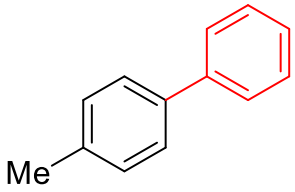
80 % yield
*t*AmOMe, **L1**



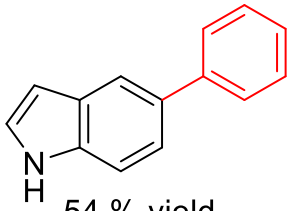
75 % yield
Et_2O, **L1**



74 % yield
*t*AmOMe, **L2**



94 % yield
*t*AmOMe, **L2**



54 % yield
Et_2O, **L2**

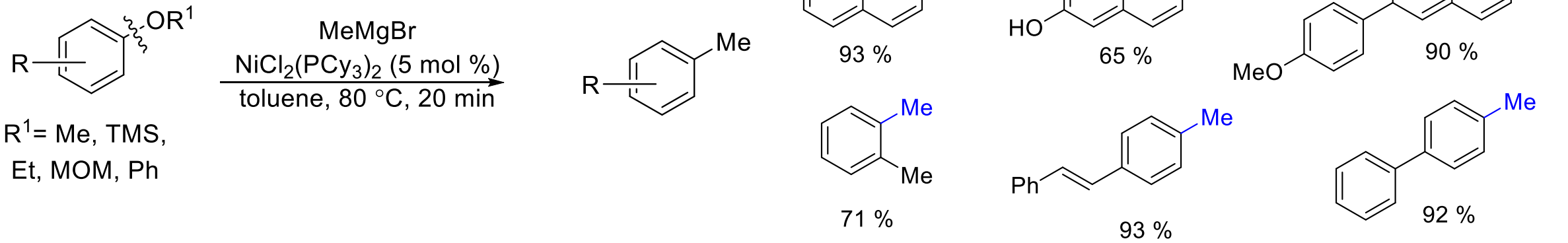
PCy_3 provided a large cone angle and an electron-rich ligand
Functional group tolerance was broadened to include:
Phenols, alcohols, enamines, amines and N-heterocycles
Ethereal solvents were noted as one of the critical factors

Broader substrate scope including non-π-extended conjugation, could not utilize alkyl or alkenyl Grignard reagents, and excess Grignard used

Dankwardt, J. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2428
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Kumada type Coupling

2008 – Shi extended the scope to cross-coupling MeMgBr



Shorter reaction times for less activated aryl alkyl ethers and diaryl ethers

Methyl ethers of an extended π-system reacted at a faster rate by competition experiments

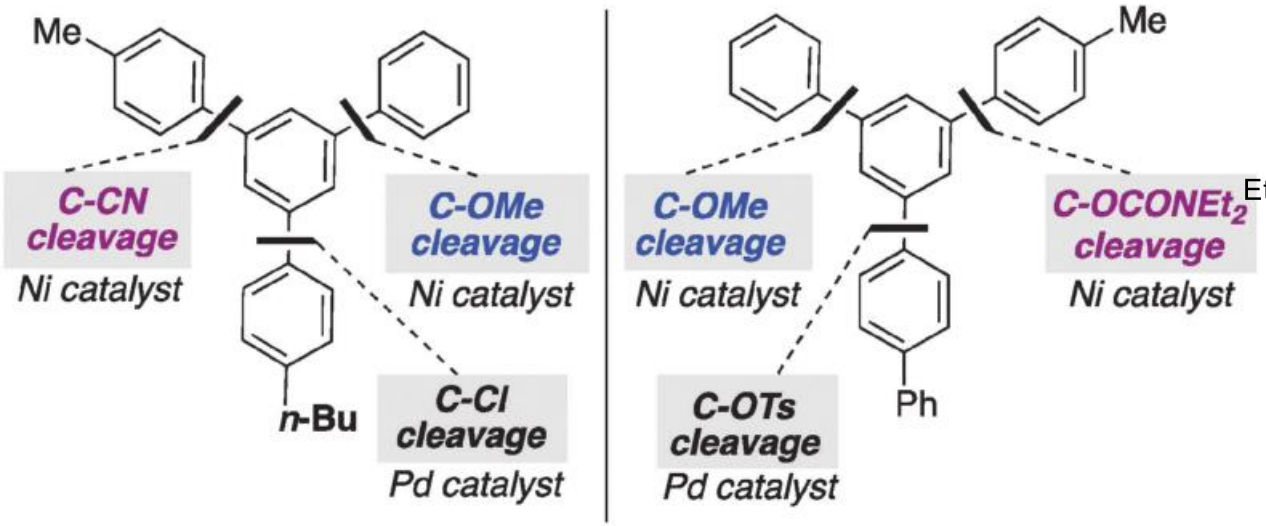
Included coupling with MeMgBr with shorter reaction times. Free alcohols were tolerated and C-F bonds could be activated.

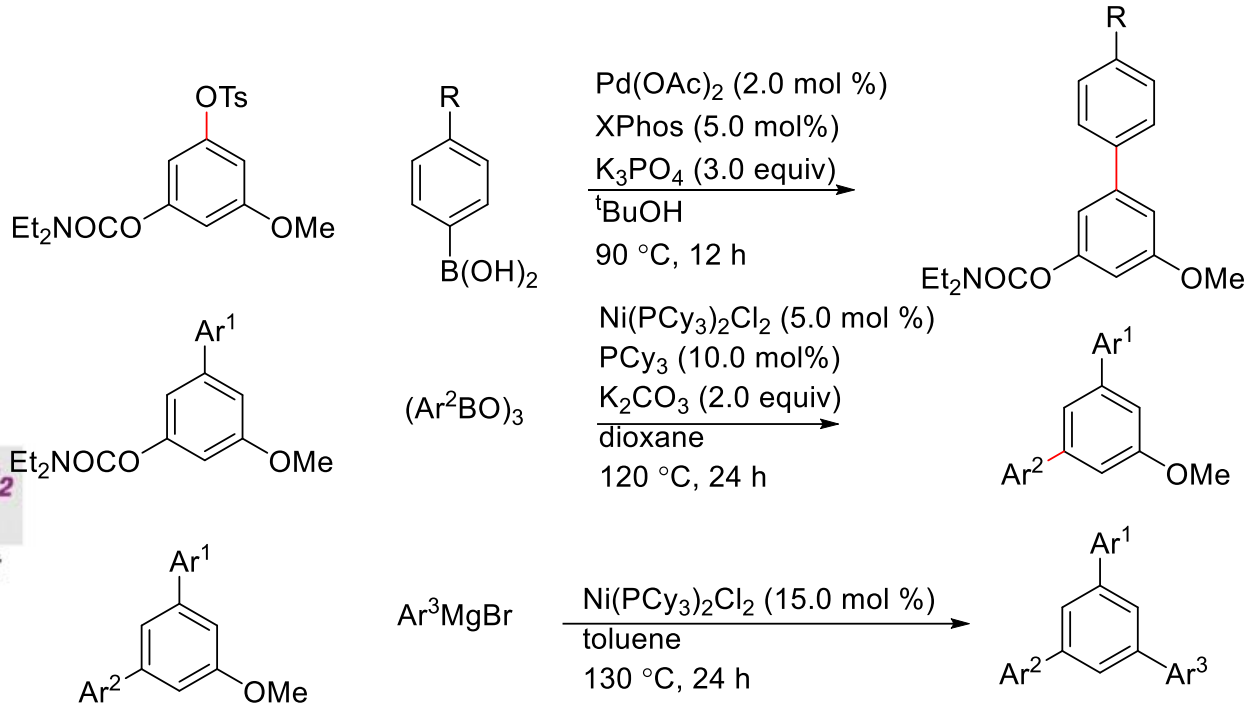
Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Application of Kumada type Coupling

2013 – Shi reported consecutive C-C bond formation

C-OMe cleavage was conducted later in the synthesis after the corresponding Suzuki-Miyaura reactions with Cl, CN, $OCONEt_2$, OTs

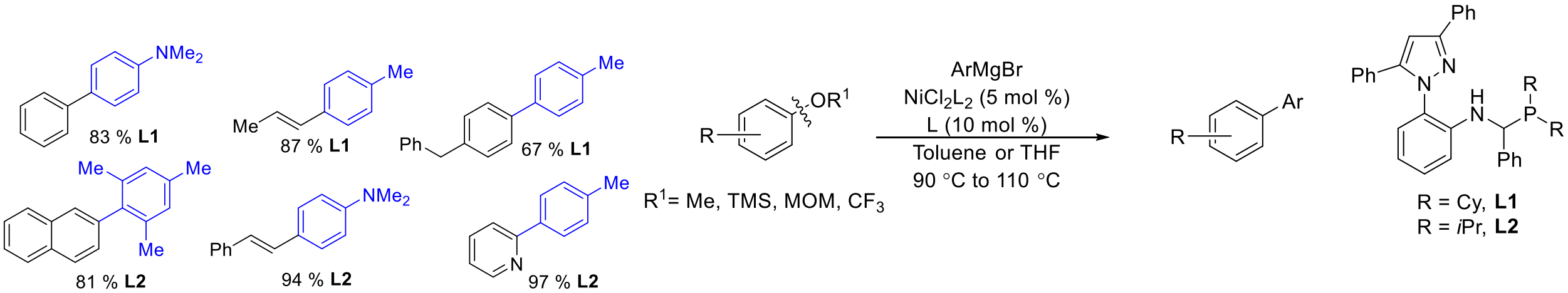




Zhao, F.; Zhang, Y.-F.; Wen, J.; Yu, D.-G.; Wei, J.-B.; Xi, Z.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 3230
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Kumada type Coupling

2010 – Wang improved the efficiency with sterically-encumbered and electron-rich pyrazolyl amino phosphines towards challenging aryl methyl ethers



Ligand originally designed for Kumada addition to C-Cl

Substrate scope:

Vinyl ethers, anisole derivatives as well as π-extended aromatic systems

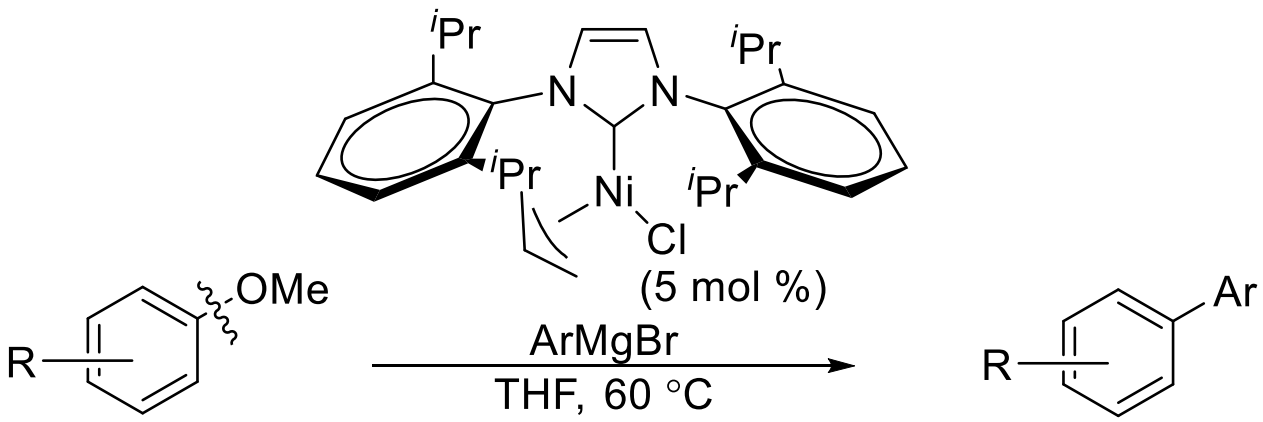
Vinyl and naphthyl ethers were shown to be more reactive than alkyl aryl ethers

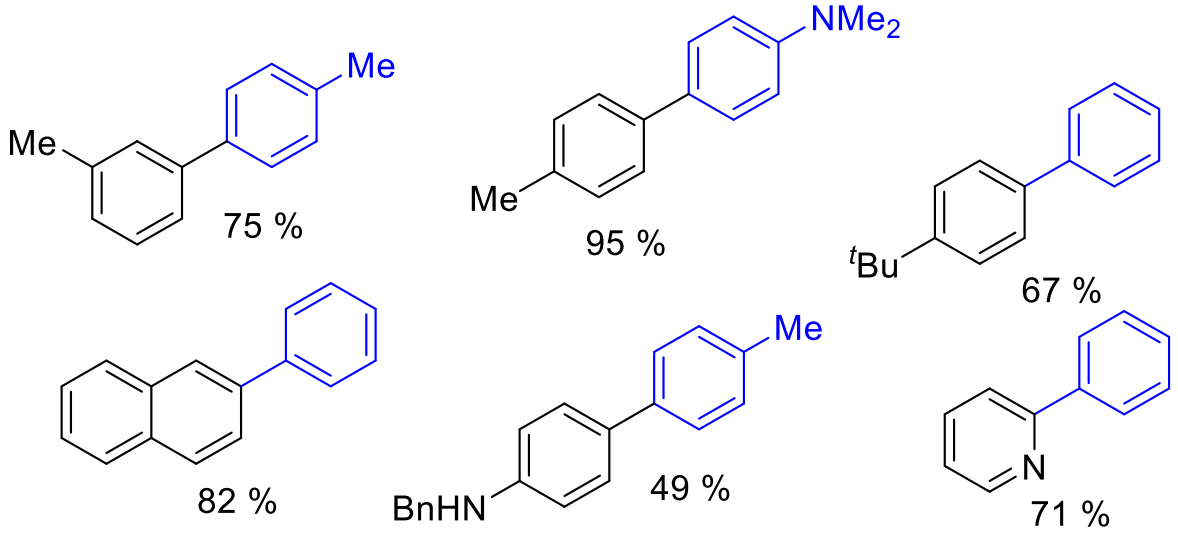
Electron rich and sterically-encumbered ligand allowed access to less activated anisole derivatives

Xie, L.-G.; Wang, Z.-X. *Chem. Eur. J.* **2011**, *17*, 4972
Xie, L.-G.; Wang, Z.-X. *Chem. Eur. J.* **2010**, *16*, 10332
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Kumada type Coupling

2012 – Nicasio used N-Heterocyclic Carbenes as a ligand alternative when coupling alkyl aryl ethers





Mild reaction conditions

Scope demonstrate both anisole derivatives and π-extended aromatics could be coupled equally as well

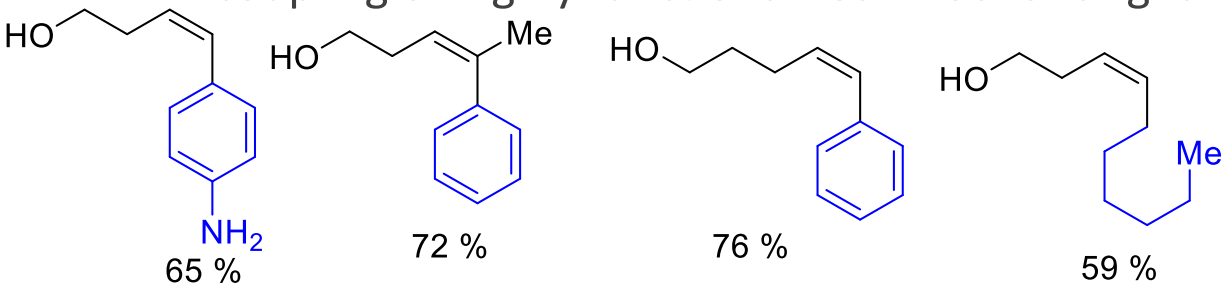
Method could not be used in the presence of sensitive functional groups

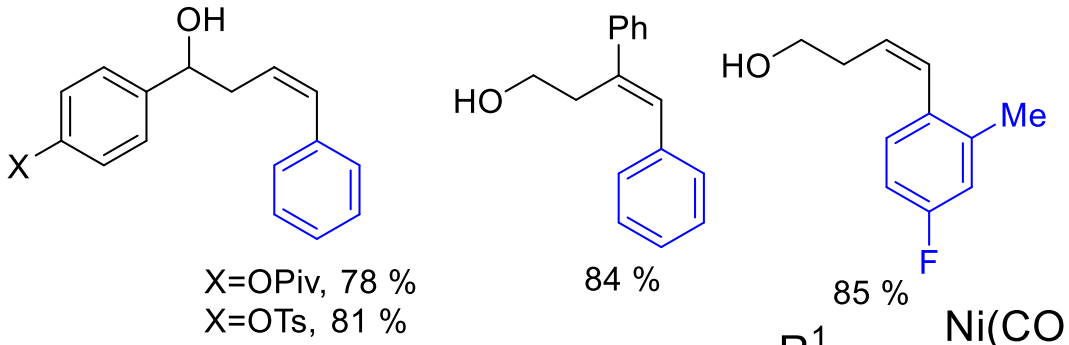
An NHC ligand increased reactivity with regular anisole derivatives at the cost of functional group tolerance.

Iglesias, M. J.; Prieto, A.; Nicasio, M. C. *Org. Lett.* **2012**, *14*, 4318
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Kumada type Coupling

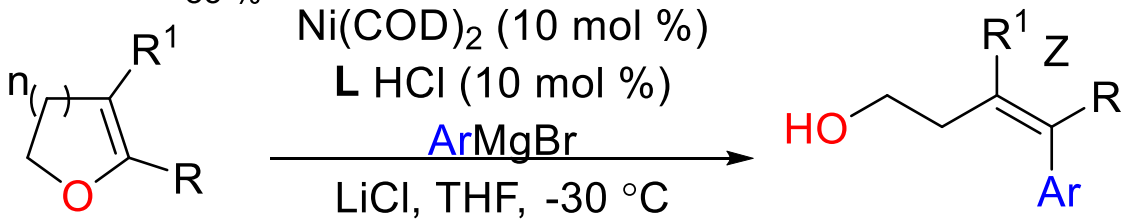
2013 – Martin increased functional group tolerance and stereoselective control for the coupling of highly functionalized Knochel Grignards at low temperatures

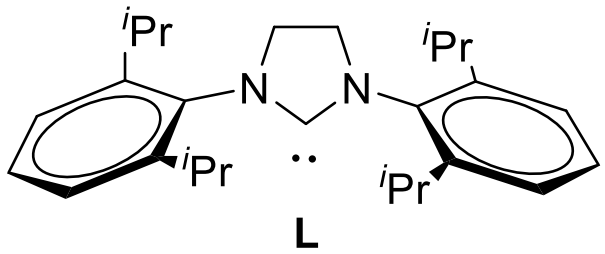




Highly functionalized Grignards used at low temperatures increased functional group tolerance with an NHC ligand

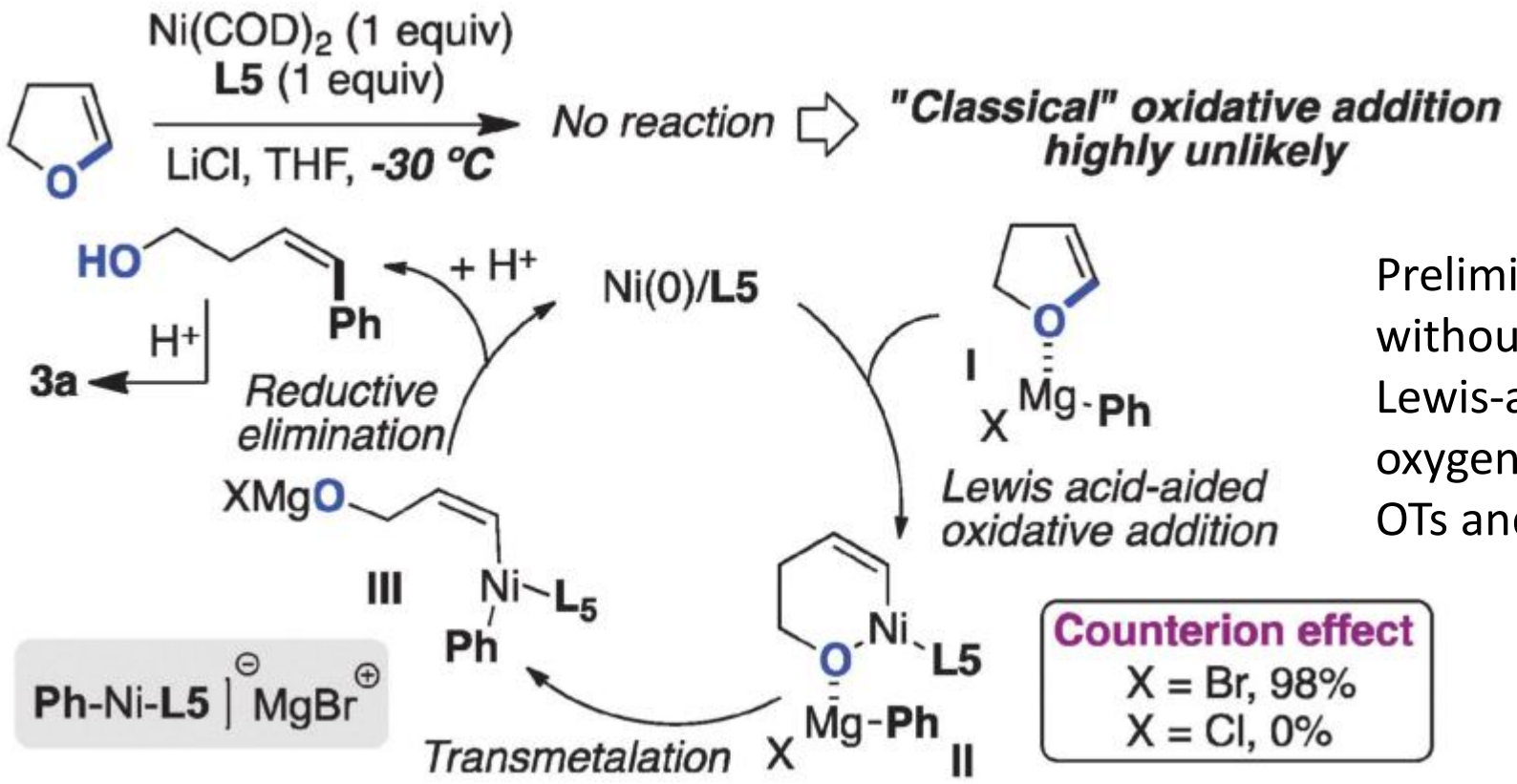
Elusive *Z*-homoallylic alcohols from cyclic vinyl ethers
Alkyl Grignards containing β-hydrogens could be used without significant reduction products (e.g. *n*-hexylMgBr)

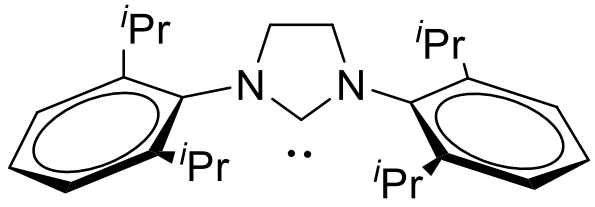




Cornella, J.; Martin, R. *Org. Lett.* **2013**, *15*, 6298
Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Kumada type Coupling – Unusual OA





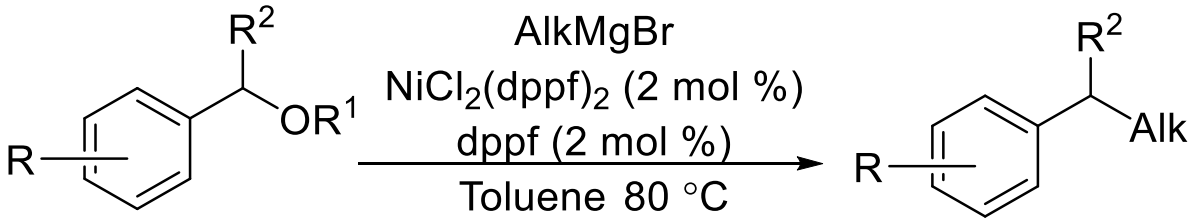
L5

Preliminary experiments with and without Grignards point towards a Lewis-acid aided OA. Lewis basic oxygens are necessary; however Aryl-OTs and –OPiv are tolerated

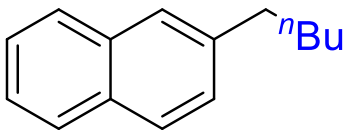
Cornella, J.; Martin, R. *Org. Lett.* **2013**, *15*, 6298
Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Kumada type Coupling – C(sp^3)–O

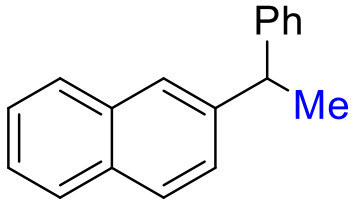
2008 – Shi described a C(sp^3)-O activation with $NiCl_2(dppf)_2$



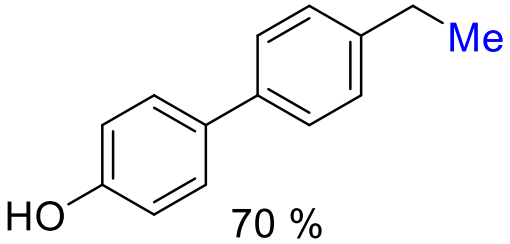
R^1= Me, TMS, Ph, Et



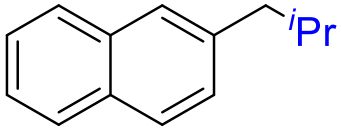
51 %



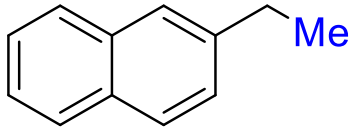
85 %



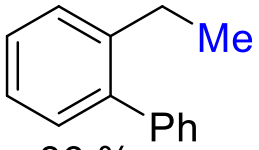
70 %



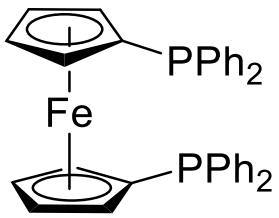
20 %



93 %



86 %



dppf

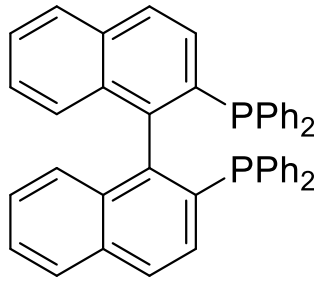
First example of C(sp^3)-O activation in a Kumada type coupling with $NiCl_2(dppf)_2$.

Activated primary and secondary benzyl alkyl ethers were utilized

The use of ^{i}PrMgBr and ^{n}BuMgBr afforded lower yields

Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Stereospecific Kumada type Coupling



BINAP

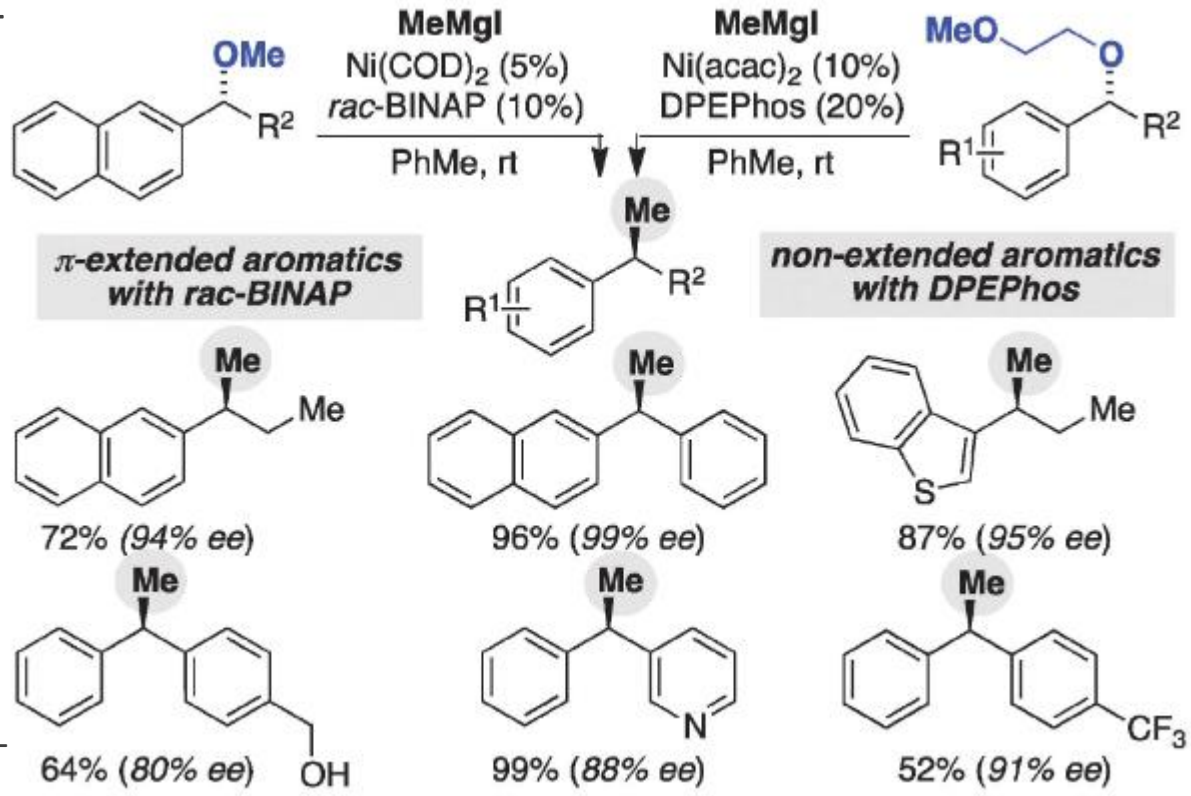
2011 – Jarvo found enantioenriched π-extended aromatic ethers reacted with MeMgBr

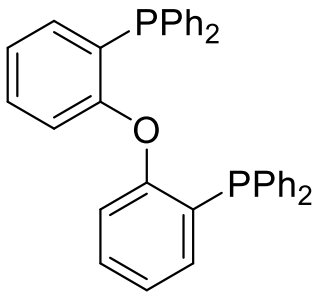
- Regular benzyl methyl ethers were found to be unreactive

2012 – Jarvo expanded the scope to include non-extended aromatics with a traceless directing group, DPEPhos, and inversion of configuration

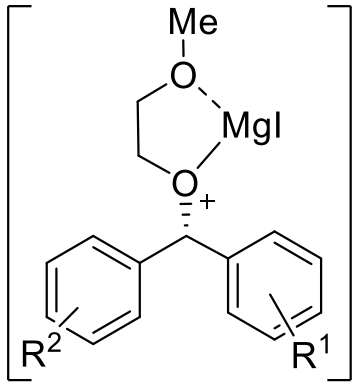
Highly enantiospecific with no background reaction for most substrates without Ni

Substrate scope: Electron- donating, electron-withdrawing groups, pendant alcohols, and protected phenols





DEPPhos



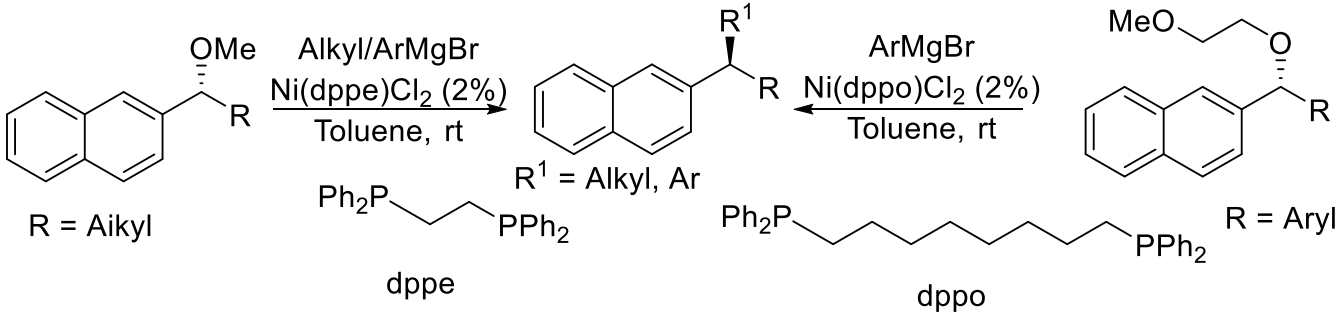
C-O bond activation

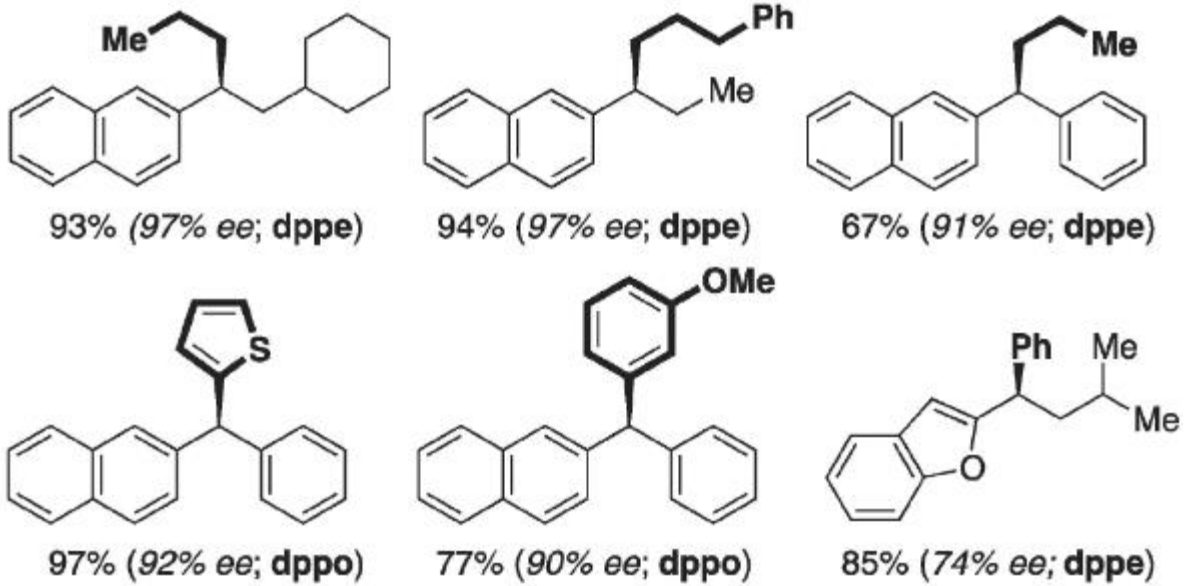
Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389
Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Stereospecific Kumada type Coupling

2012 – Jarvo reported a subsequent report detailing the reaction of ArMgBr with diaryl benzyl ethers

- Bidentate ligands with a large bite angle resulted in the highest yields





2014 – Jarvo expanded the scope to include secondary benzyl ethers with alkyl substituents through the use of dppe

- Coupling could occur with Grignard reagents possessing β-hydrogens

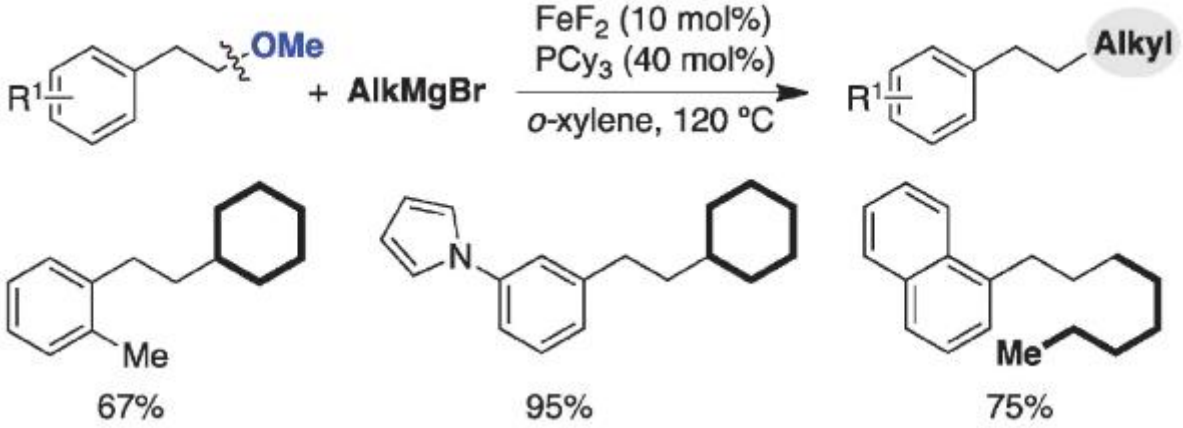
Aryl alkyl benzyl ethers were coupled with dppe. Diaryl benzyl ethers were coupled with dppo.

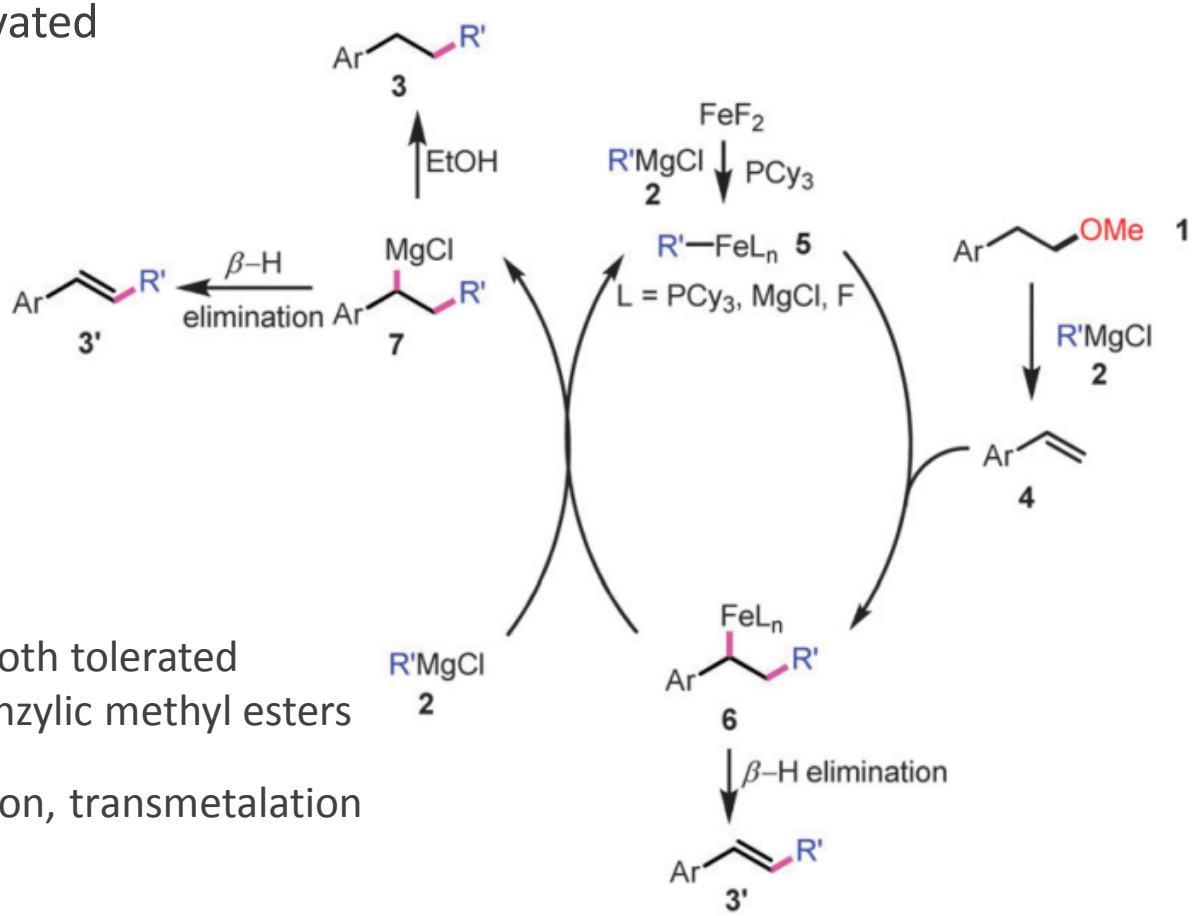
Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7790
Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2014**, *53*, 2422
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Kumada type Coupling – with Iron

2013 – Shi demonstrated the reactivity of slightly activated homobenzylic methyl ethers

- Alkyl Grignards possessed β-hydrogens





Regular aromatic and π-extended aromatic systems were both tolerated

Substrates containing β-hydrogens and secondary homobenzylic methyl esters were not tolerated

Proposed mechanism: Dehydroalkoxylation, carbometallation, transmetalation followed by termination

Luo, S.; Yu, D.-G.; Zhu, R.-Y.; Wang, Y.; Wang, L.; Shi, Z.-J. *Chem. Commun.* **2013**, *49*, 7794
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

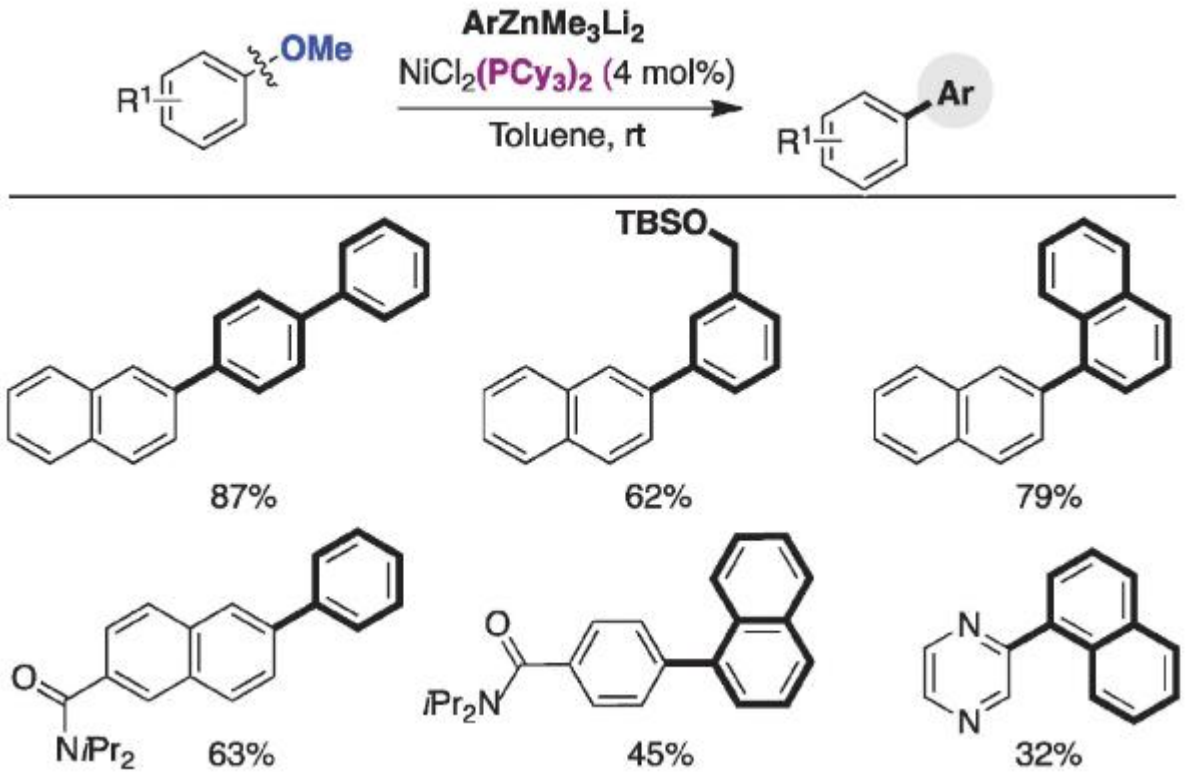
Overview

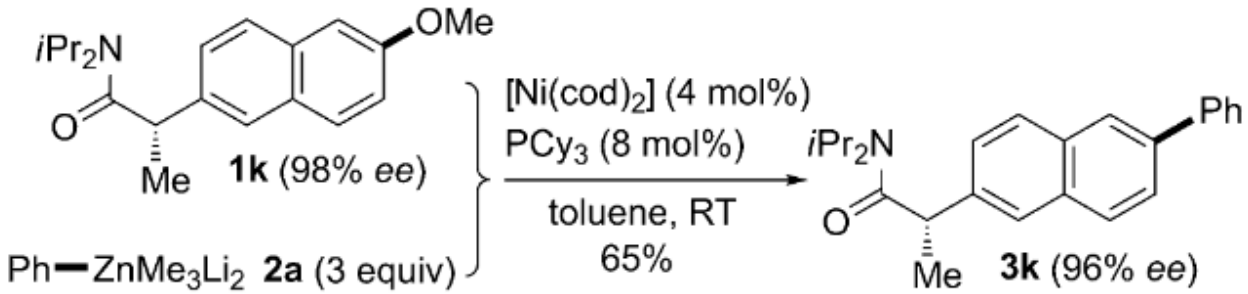
1. Uses of a different bond disconnection
2. Seminal work
3. Mechanistic studies
4. C-C bond forming reactions
   1. Kumada type
   2. **Negishi type**
   3. **Heck type**
   4. **α-Arylation**
   5. Suzuki-Miyaura type
5. Reductive coupling
6. Future directions/Conclusion

Negishi type Coupling

First example of an organozinc organometallic species. Simple anisole and C(sp^3)-O activation were not tolerated.

2012 – Wang and Uchiyama demonstrate the first negishi type coupling with C(aryl)-OMe activation





(+)-naproxen amide - Aleve

Aryl and diaryl organozinc reagents gave low product conversion

Dianion-type organozincates generated from Me_4ZnLi_2 were found to give high reactivity

Aryl groups with were well suited coupling partners

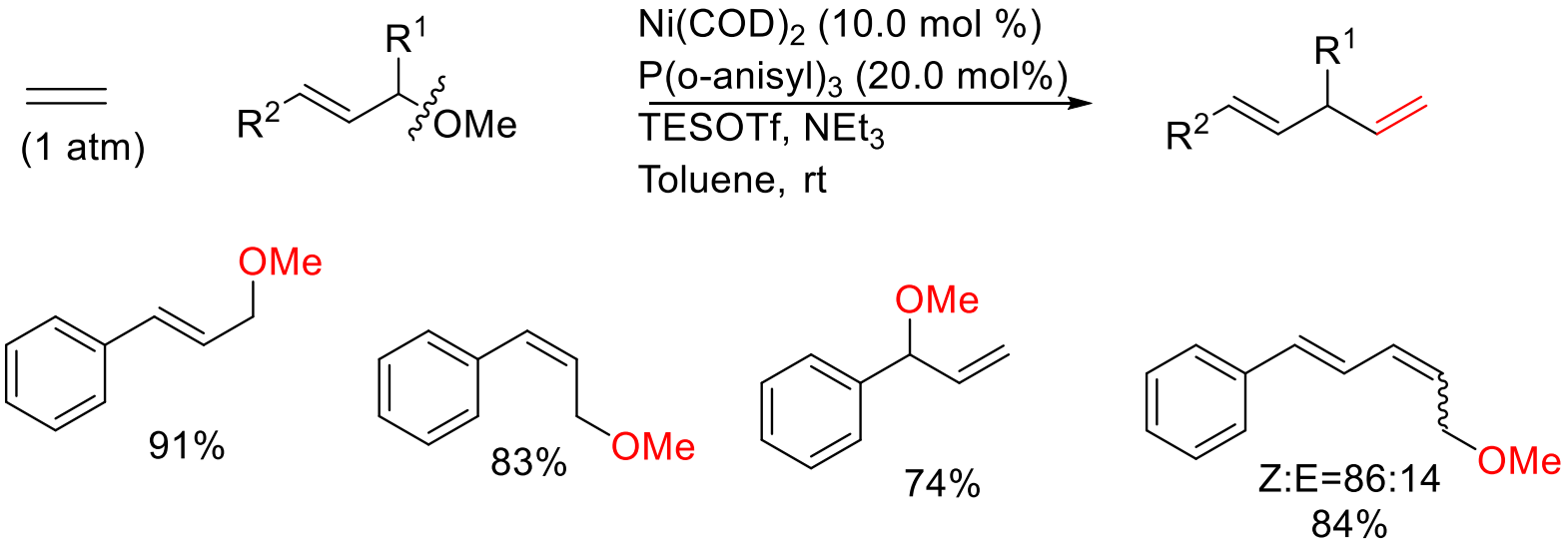
Scope included: activated anisole derivatives, aromatic extended π-systems, alkoxy, silyloxy, amino, silyl, amide, and heterocyclic

No mechanistic studies have been done

Wang, C.; Ozaki, T.; Takita, R.; Uchiyama, M. *Chem. – Eur. J.* **2012**, *18*, 3482
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Heck type Coupling

2010 – Jamison formed skipped dienes from ethylene and allyl ethers



TESOTf was necessary possibly to help facilitate a π-allyl Ni complex

Linear *Z*- and *E*-allyl ethers afforded the same *E* - isomer

1,1-Disubstituted olefins could be obtained; however the allyl carbonate was needed

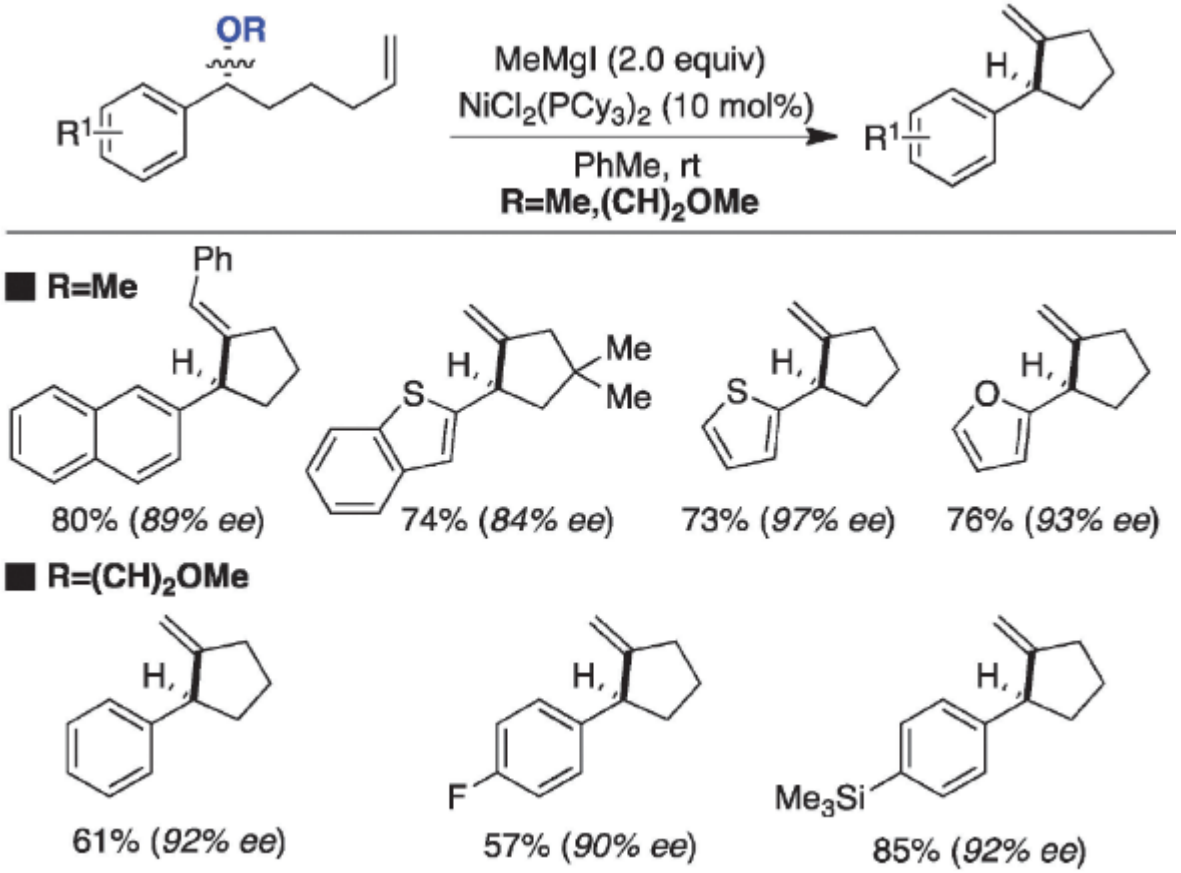
Ethylene was used as an olefin source. Thermodynamic product observed. Scope limited to alkyl substitution and protected alcohols

Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 6880
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Stereospecific Heck type Coupling

2014 – Jarvo expanded the scope to secondary benzyl alkyl ethers with an intramolecular Heck

Stoichiometric Grignard needed to regenerate the active Ni^0 cat. Intramolecular Heck was limited to formation of five-membered rings



Best selective found with PCy_3 and stoichiometric MeMgI to regenerate the Ni^0 cat

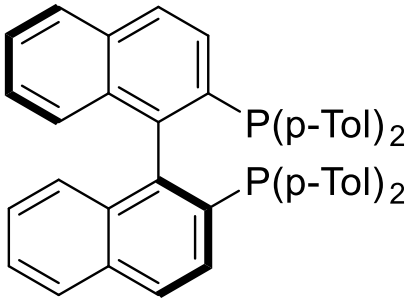
Inversion of configuration the only products seen

Scope: Different substitution patterns on the side chain and heteroaromatics

A traceless directing group was needed for benzyl alkyl ethers

Limited to five-membered ring formation

Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081



L2

α-Arylation

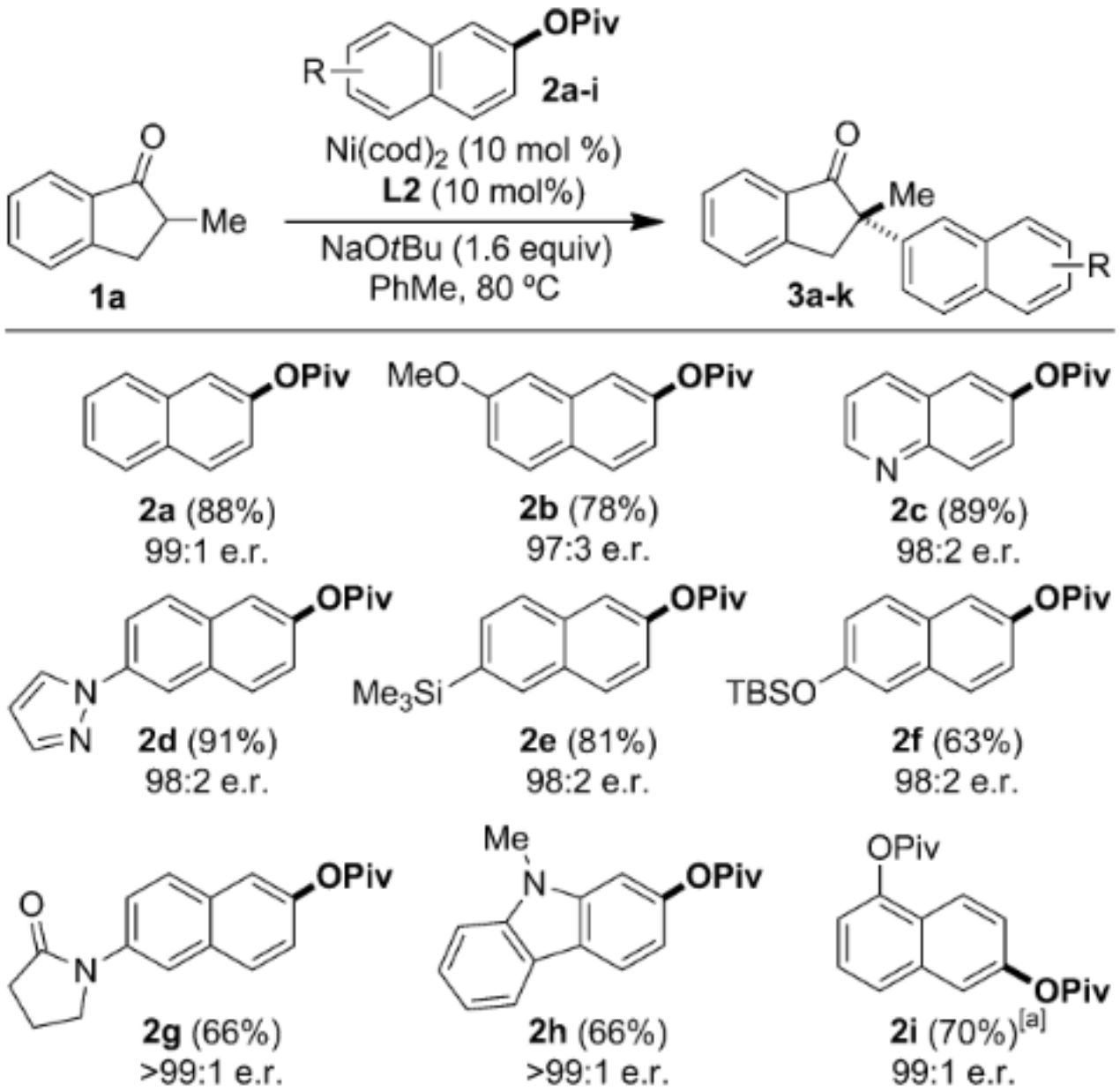
2015 – Martin reported the first enantioselective C-C bond formation with C-O bond cleavage

No preexisting stereogenic center was needed

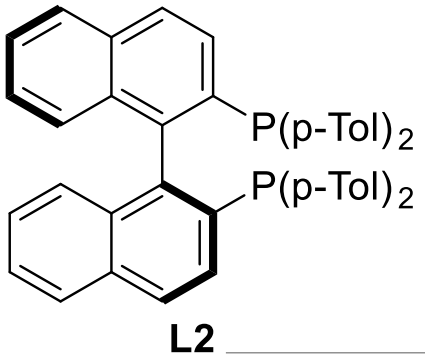
in situ generation of prochiral ketone enolates

Chiral bidentate ligand with a biaryl axis was critical for high asymmetric induction

Scope: pyrazoles, quinolones, silanes, silyl ethers, amides, esters and carbazoles



Cornella, J.; Jackson, E. P.; Martin, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 4075
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

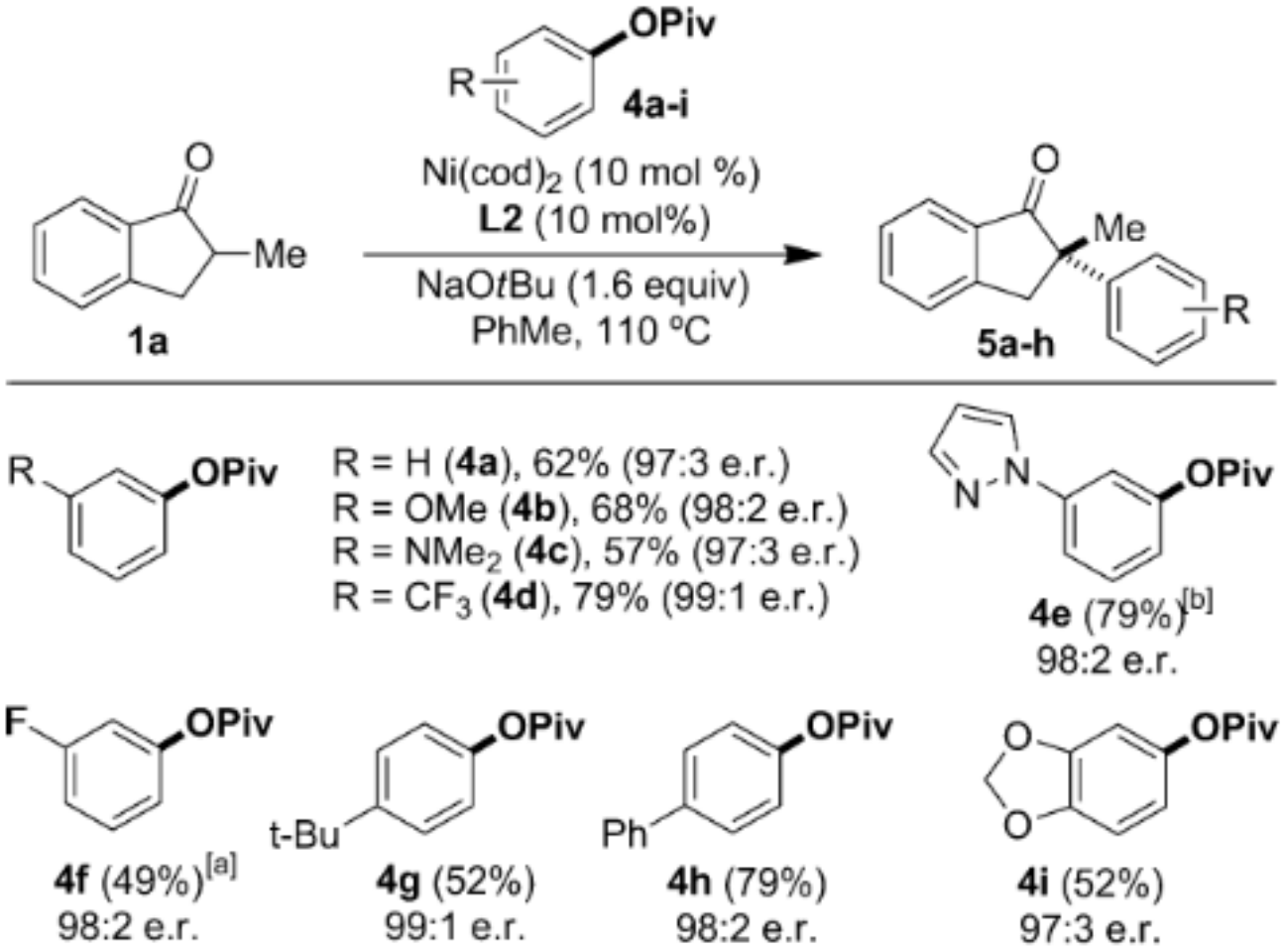


α-Arylation

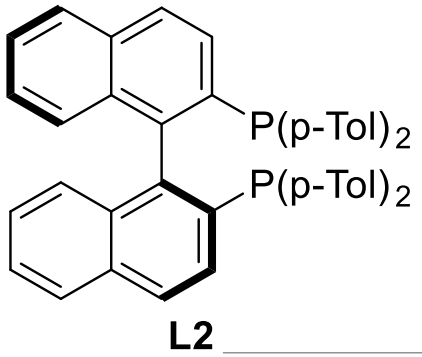
2015 – Martin

No *ortho* substitution could be included

Scope: nitrogen-containing heterocycles, acetals, aryl fluorides, and amines



Cornella, J.; Jackson, E. P.; Martin, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 4075
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

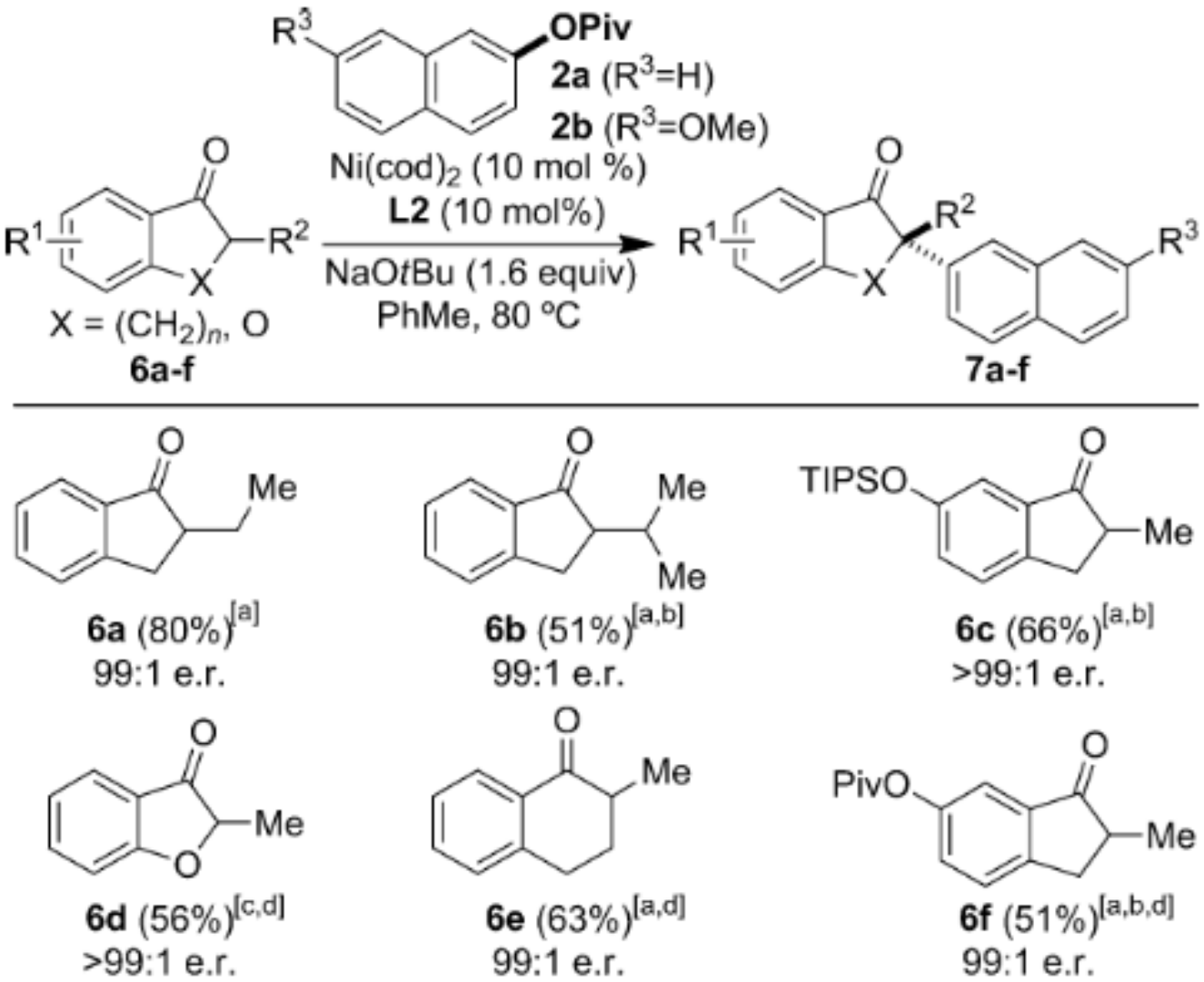


α-Arylation

2015 – Martin

Bulkier substitution at the α-position

Scope: medium rings, silyl ethers, and pivalate motifs



Cornella, J.; Jackson, E. P.; Martin, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 4075
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

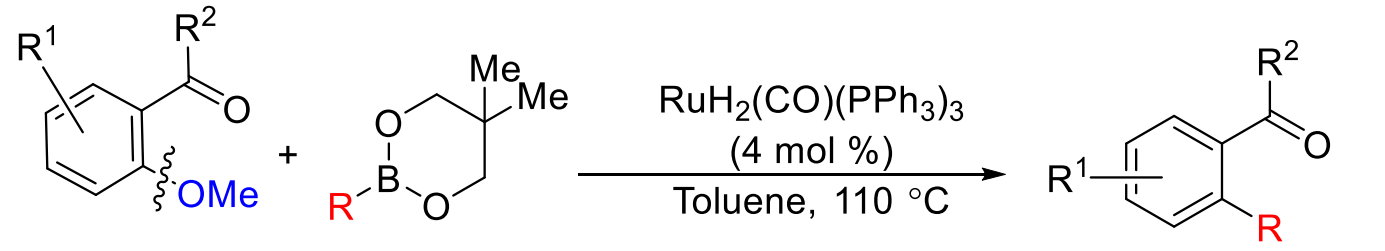
Overview

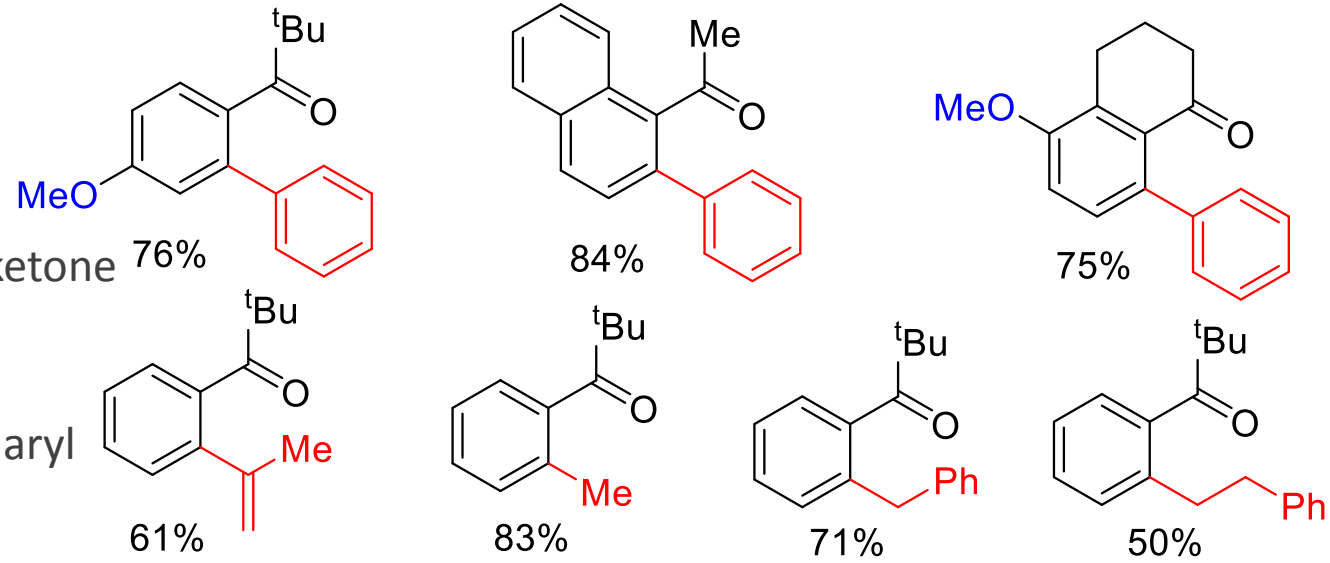
1. Uses of a different bond disconnection
2. Seminal work
3. Mechanistic studies
4. C-C bond forming reactions
   1. Kumada type
   2. Negishi type
   3. Heck type
   4. α-Arylation
   5. **Suzuki-Miyaura type**
5. Reductive coupling
6. Future directions/Conclusion

Suzuki type Coupling – Ru

2004 – Kakiuchi, Chatani and Murai demonstrated the Ru catalyzed coupling with chelating assistance of aryl methyl ethers and boronic esters

Ortho-ketone is essential; therefore the scope of the substrate is limited. Neopentyl boronates had the fastest rates.





Chelation assistance necessary with an *ortho*-ketone

Fastest rates found with neopentyl boronates

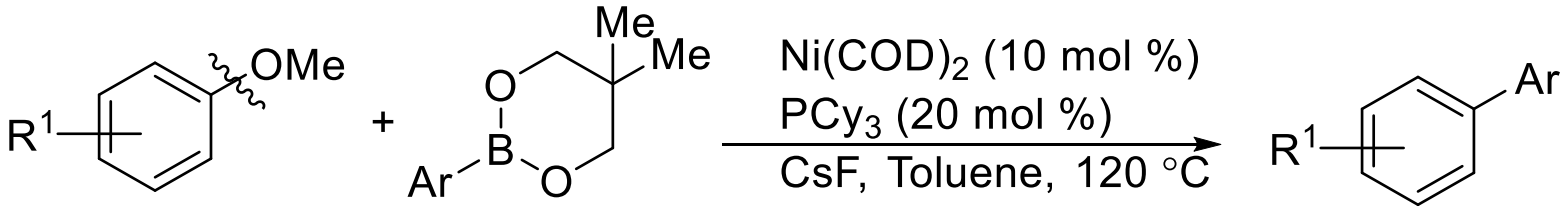
Scope of boronates included alkyl, alkenyl and aryl

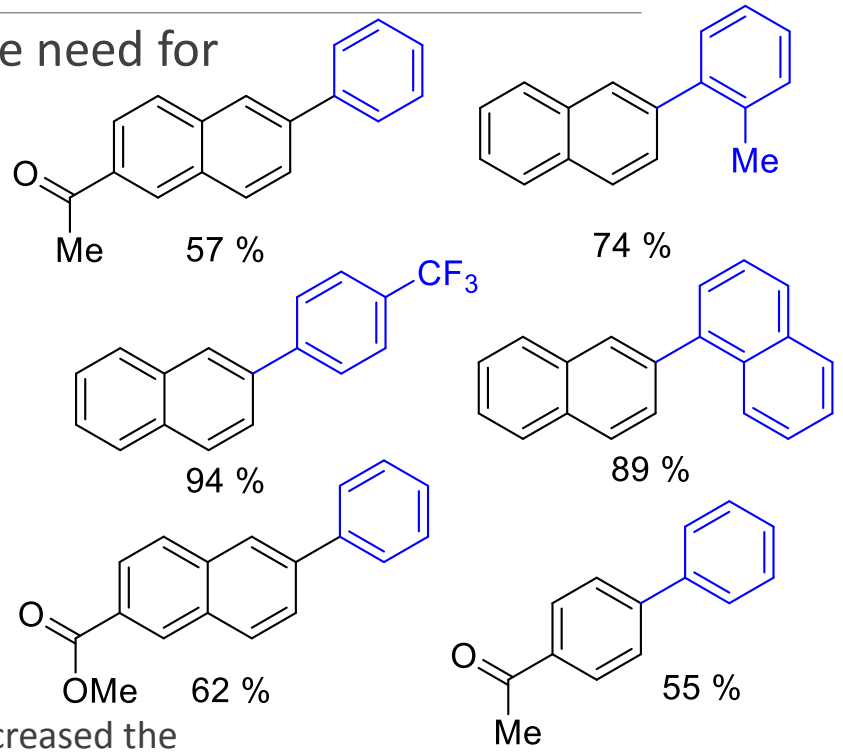
OA confirmed (refer to previous slides)

Kakiuhi, F.; Usui, M.; Ueno, S.; N. Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Suzuki type Coupling – Ru

2008 – Chatani and Tobisu extended the substrate scope by eliminating the need for an *ortho*-directing group





Aryl methyl ethers were coupled with neopentyl boronates

A base (CsF) was essential as well as a bulky and electron-rich phosphine ligand (PCy_3)

Aromatics with an extended π-system were more reactive; however EWG on anisole derivatives increased the rate

The nature of the ether profoundly had an effect on the reaction (primary was superior)

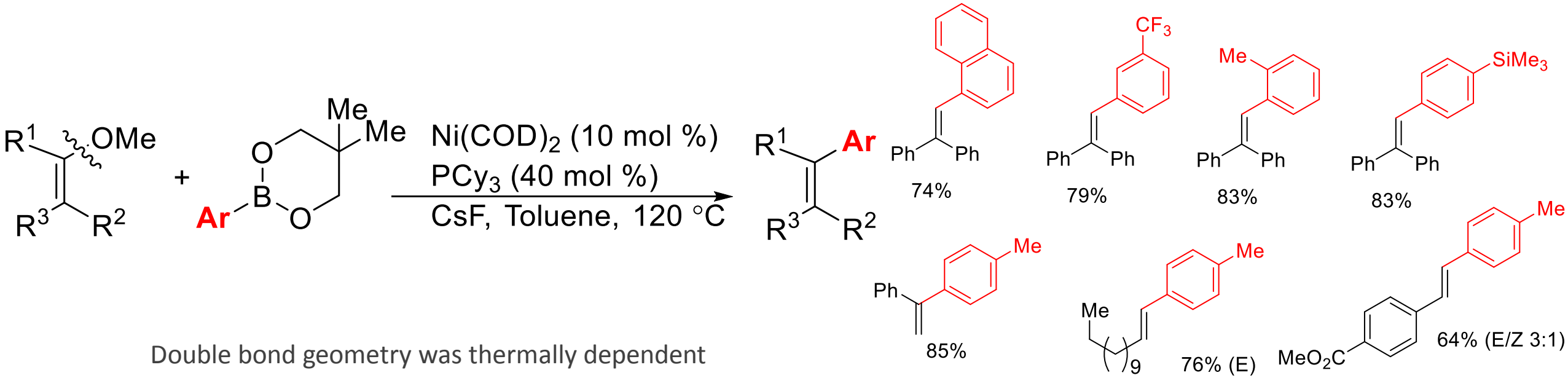
Proposed Mech: OA, TM through a four-coordinate organoboron species, and RE

Limitation of an *ortho*-directing group had been solved.

Smiasaki, T.; Tobisu, M.; N. Chatani, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4866
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Suzuki type Coupling

2009 – Chantani extended the substrate scope to include vinyl ethers



Double bond geometry was thermally dependent

Z-selectively as high as 88:12 *Z*:*E* at 50 ˚C, with a loss in yield

E-selectivity found when reaction was run at 120 ˚C

Preferential reactivity with vinyl terminus in extended π-aromatics

Scope included steric and electronic variations on both coupling partners.

Smiasaki, T.; Konno, Y.; Tobisu, M.; N. Chatani, N. *Org. Lett.* **2009**, *11*, 4890
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Overview

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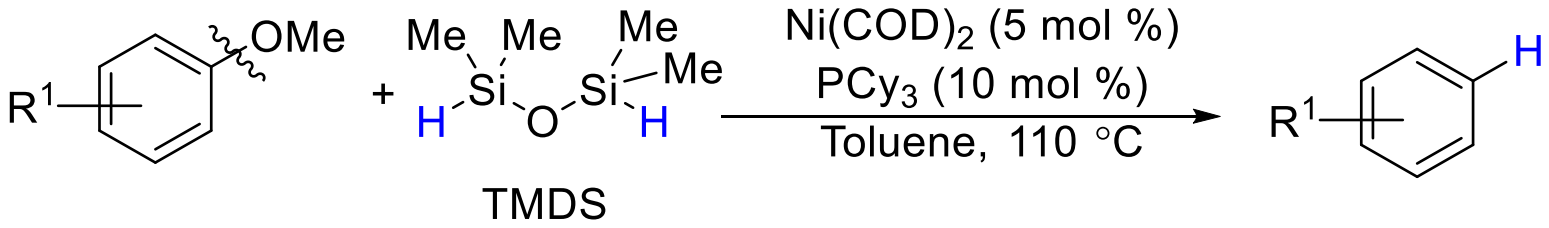
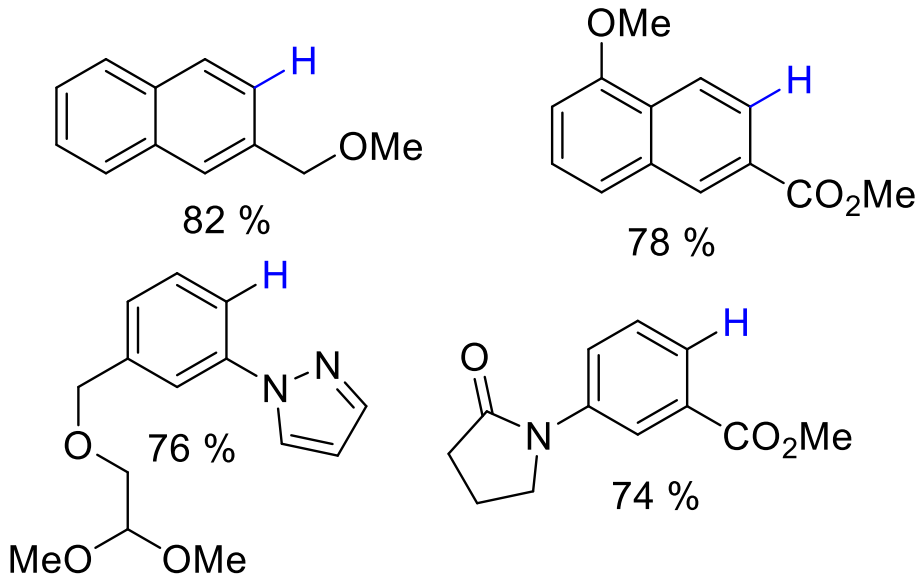
Reductive Coupling

2010 – Martin demonstrated Ni catalyzed reductive cleavage with C (aryl) – OMe and TMDSO as the reducing agent





An alternative to alkali metals

Anisole derivatives needed an *ortho*-directing group (esters, pyrazoles, pyridines or oxazolines)

- Competitive experiment demonstrated no reaction with *meta*- or *para*- directing group

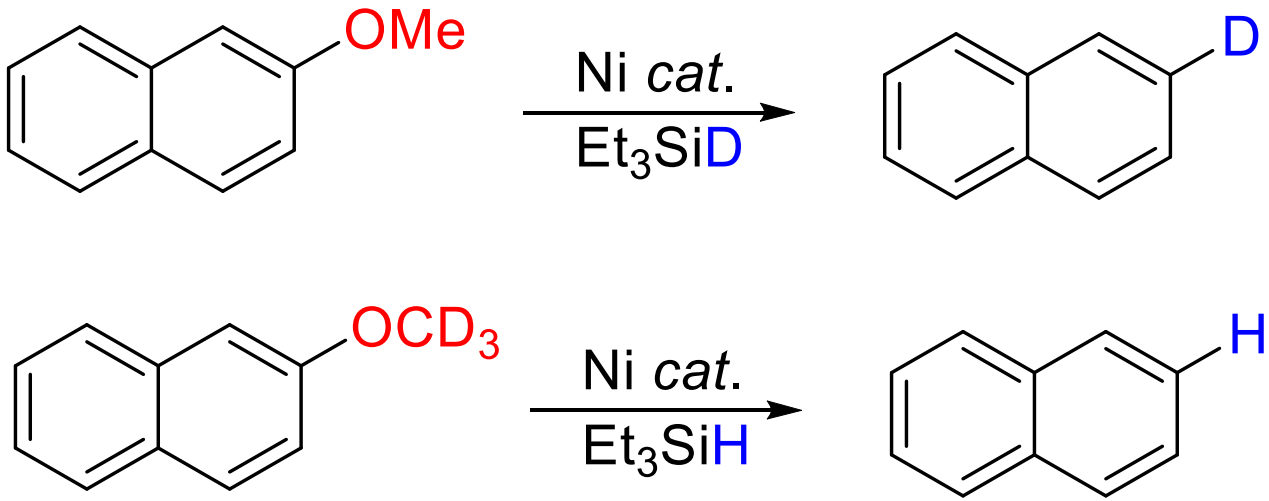
C(sp^2) – OMe bonds were functionalized selectively in the presence of benzylic C(sp^3) – OMe

Directing groups necessary for benzyl methyl ethers.

Alvarez-Bercedo, P.; ;Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Reductive Coupling

2010 – Martin



Deuterium studies rule out β-hydride elimination. Potential for temporary directing groups.

Deuterium-labeling of the reducing agent showed exclusive deuterium

- Protocol for introducing deuterium

Plausible Mech: C-O Oxidative Addition, σ-bond metathesis, Reductive Elimination

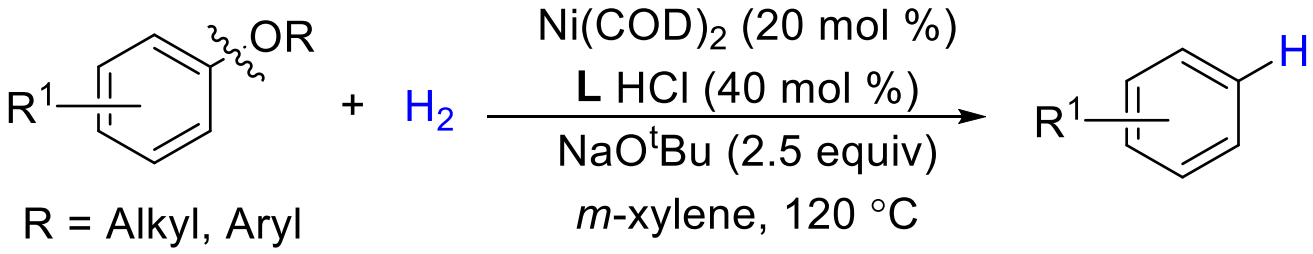
Substrate scope: silyl groups, esters, acetals, amides, tertiary amines, and nitrogen containing heterocycles

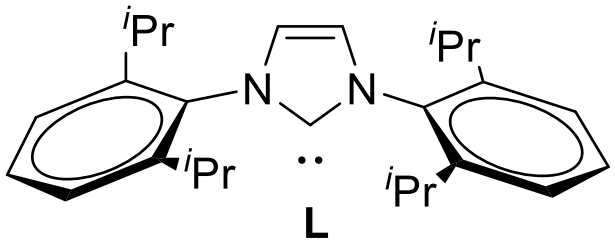
Alvarez-Bercedo, P.; ;Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Reductive Coupling

PCy_3 ligand showed no product formation. A NHC ligand in conjunction with H_2 reductively coupled C-OR bonds. $AlMe_3$ needed in C – O(sp^3) activation.

2011 – Hartwig used hydrogen as a reducing agent in the hydrogenolysis of C-OR bonds





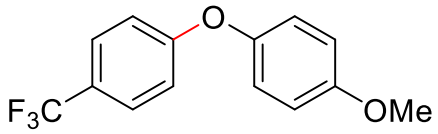
PCy_3 ligand showed only traces of composed ligand

Excess base needed for desired reactivity

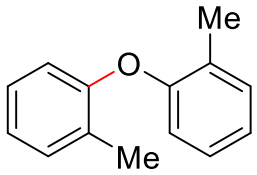
LA ($AlMe_3$) needed to activate C – O (alkyl)

Competition experiments unraveled relative reactivities: Ar-OAr>>Ar-OMe>$ArCH_2$-OMe

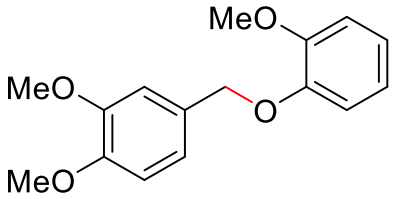
Homogeneity of the catalyst was determined through no decrease in conversion or yields in the presence of 300 fold excess of mercury



87 %

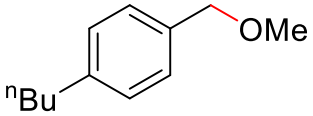


85 %

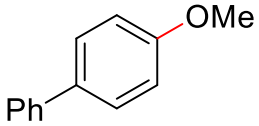


99 % (5% Ni)

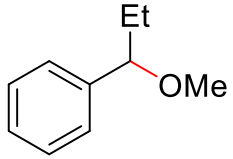
Addition of $AlMe_3$ (1 equiv):



99 %



65 %

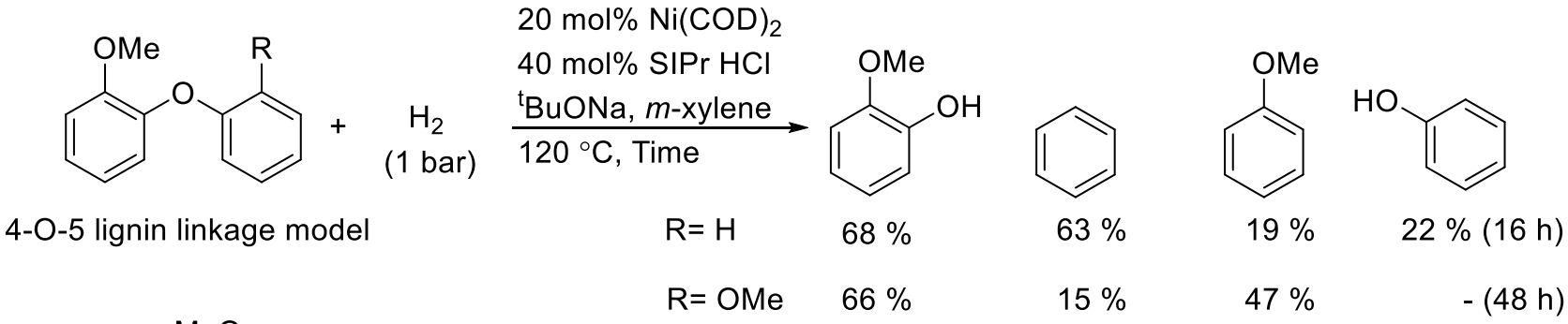


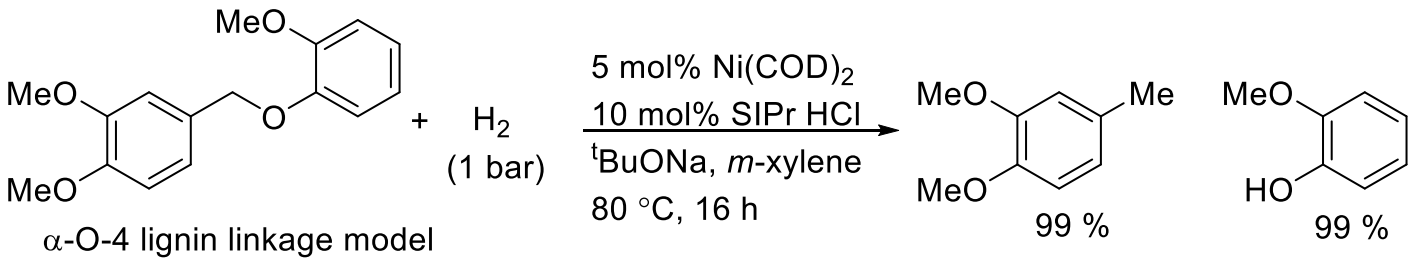
96 %

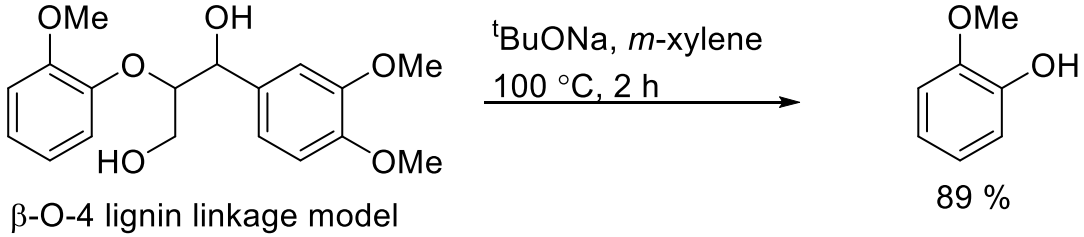
Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Reductive Coupling – Lignin Models

2011 – Hartwig validated the synthetic utility on depolymerization of lignin models







Proved the methodology could be used in transforming lignin into useful compounds.

Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439
Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

Future Directions/Conclusion

Kumada, Negishi, Heck and Suzuki couplings have been developed through C – O activation

Methodology can be used as traceless directing groups or coupling in the late stage of synthesis

C-N coupling has been shown with secondary amines

Mechanistic studies are necessary before more asymmetric methodologies can be investigated

Benzylic and homobenzylic start demonstrate cleavage of C(sp^3) – O bonds; however this is still a significant challenge

Most reactions have been found to not be functional group tolerant

Cornella, J; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081