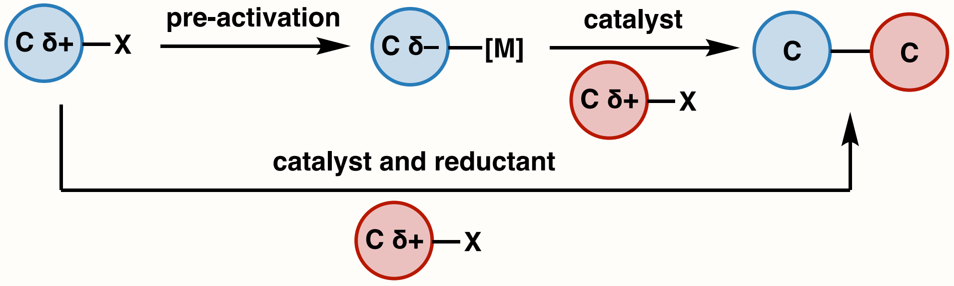
Cross electrophile coupling

Group meeting
Carl Mansson
25/01/22



Cross electrophile coupling (XEC) advantages

- Cuts down one step (making nucleophile)
- Safety (avoids pyrophoric e.g RMgX, or toxic e.g. $RSnR'_3$)
- Easier to handle
- Increased stability/easier storage
- More commercial availability
- Better FG compatibility

Commercially available (2011)	
$R{-}B(OH)_2$	~ 5500
R−I	~ 80000
R−Br	~ 700000

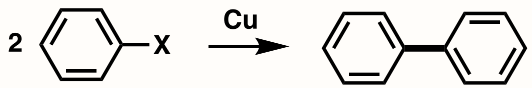
JACS **2012**, 6146

XEC Disadvantages

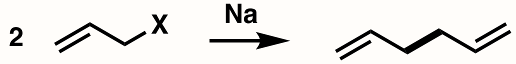
- Mostly heterogenous (elemental metals and salts)
- Sometimes sensitive to stir rates and purity and mesh size of metal
- Inherently less selective

<u>Electrophile coupling known for a long time: homodimerization</u>

Ullman coupling



Wurtz coupling



XEC strategies

- xs of one reagent (not cross selective)
- Electronic differentiation/matching
- Steric differentiation/matching
- Distinct reactivity/mechanistic pathways

$$\underset{\text{1 equiv.}}{\text{R-X}} + \underset{\text{n equiv.}}{\text{R'-X}} \xrightarrow{\text{cat.}} \underset{1}{\text{R-R}} + \underset{:\ 2n\ :}{\text{R-R'}} + \underset{n^2}{\text{R'-R'}}$$

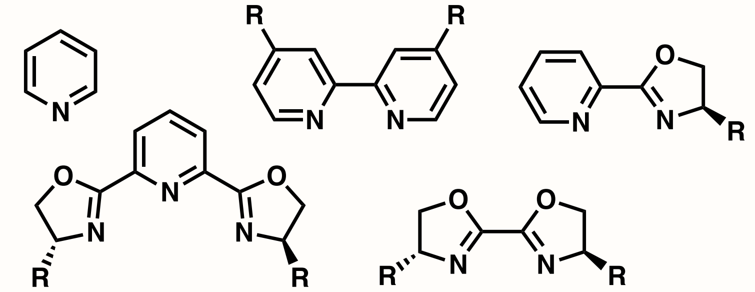
n	R-R' yield[a]	Pdt:dimers[a]
1	50%	1:1
2	80%	1:1.25
3	86%	1:1.67

[a]Assuming complete rxn reversibility

JACS **2012**, 6146

Stars of the show:

<u>Ligands</u>



<u>Reductants</u>

Zinc

Manganese

Magnesium

<u>Catalysts</u>

Nickel (NiX_2)

Outline

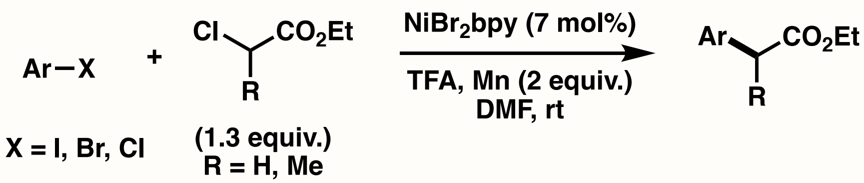
1. Aryl–alkyl
2. Allylation
3. Vinylation
4. Alkyl–alkyl
5. Aryl–aryl
6. Acylation
7. Epoxide/aziridine opening

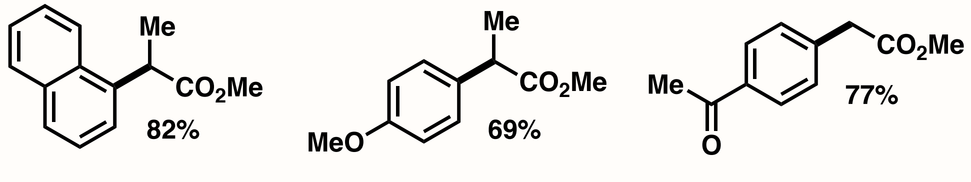
Definition of XEC (for today)

- No in situ formation of nucleophile
- Reductant acts on catalyst
- No addition into polar π systems (e.g. NHK)
- Will not be discussing electrochemical methods

Cross electrophile coupling

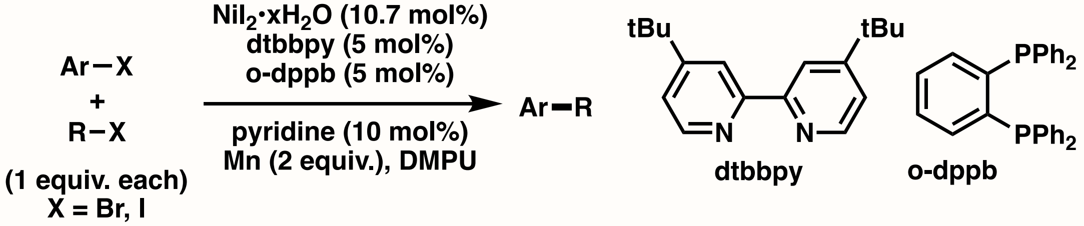
Aryl-alkyl

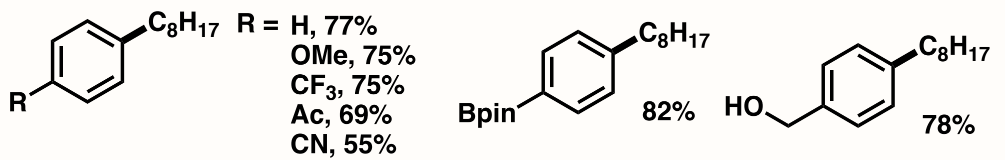




- 16 examples
- Aryl chlorides gave poor yields (20%)

Gosmini. *JACS* **2007**, 1146

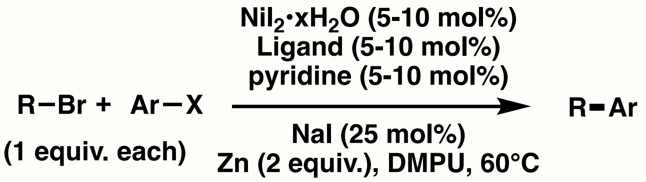


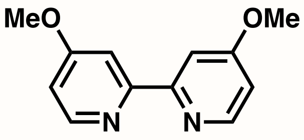


- 16 examples

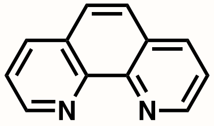
- Unexplained synergistic effects of two ligands
- Reaction postulated not to involve organomanganese species

Weix. *JACS* **2010**, 920

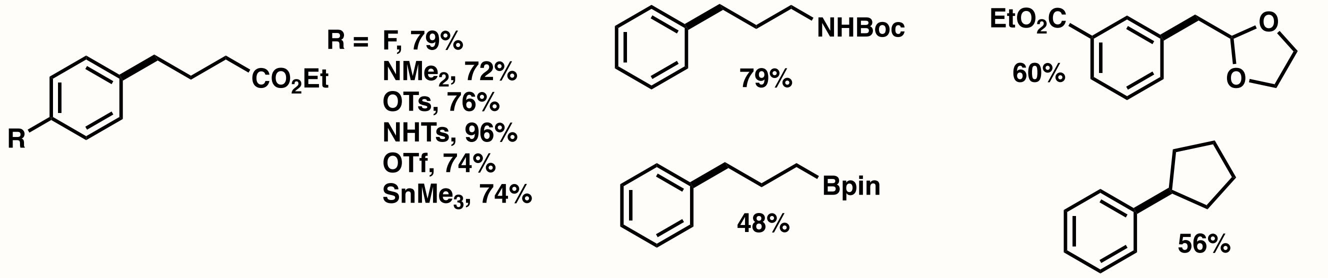


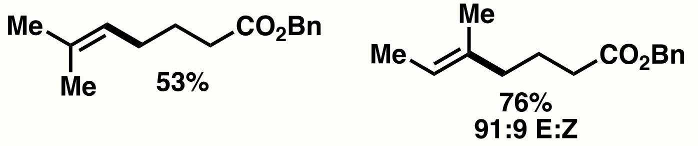


dOMebpy: better for electron-rich arenes



1,10-phenanthroline: better for electron-poor arenes

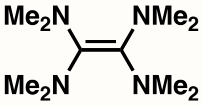




- Aryl bromides: 28 examples
- Vinyl bromides: 4 examples
- 7 examples of electron poor aryl chlorides

Mechanistic insights
- RZnX and ArZnX slow to form under rxn conditions
- TDAE instead of Zn gives 54% yield for a representative reaction

TDAE



Weix. *JACS* **2012**, 6146

Cross electrophile coupling

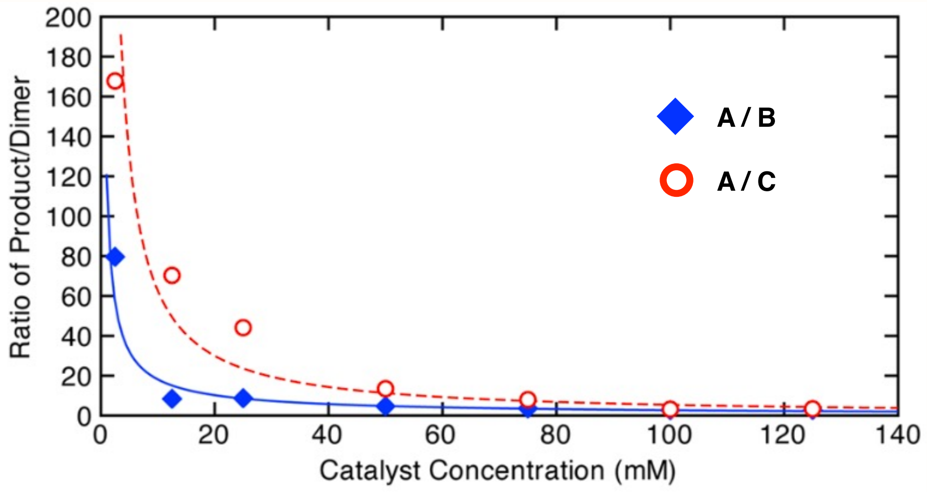
A. $R\text{-}X \xrightarrow{Mn^0} R\text{-}Mn\text{-}X \xrightarrow[R'\text{-}X]{[Ni]} R\text{-}R'$ **Traditional cross-coupling (in-situ nucleophile formation)**

B. $R\text{-}X \xrightarrow{[Ni]} R\text{-}[Ni]\text{-}X \xrightarrow{R'\text{-}[Ni]\text{-}X} R\text{-}R'$ **Ni/Ni transmetalation**

C. $R\text{-}X \xrightarrow{[Ni]} R\text{-}[Ni]\text{-}X \xrightarrow{R'\text{-}X} R\text{-}R'$ **Sequential oxidative addition**

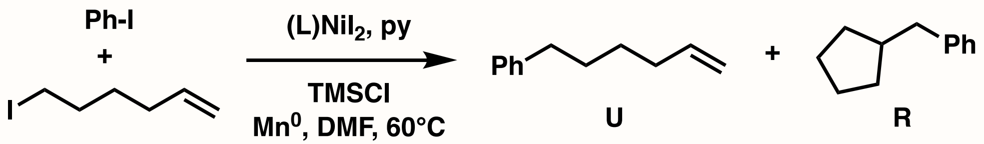
D. $R\text{-}X \xrightarrow{[Ni]} R\text{-}[Ni]\text{-}X \xrightarrow{R'\cdot} R\text{-}R'$ **Radical chain reaction**

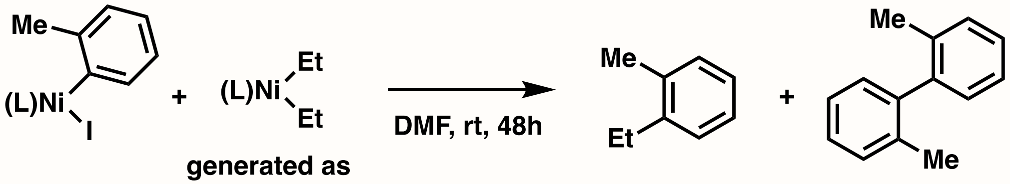
$$Ph\text{-}I + C_8H_{17}I \xrightarrow[Mn^0,\ DMPU,\ 60°C]{Ni(cod)_2,\ L,\ py} \underset{A}{Ph\text{-}C_8H_{17}} + \underset{B}{Ph\text{-}Ph} + \underset{C}{C_{16}H_{34}}$$



Quenching exp. and stoichiometric organonickel exp. supports initial ox. addn. of aryl halide, unfeasible for alkyl halide

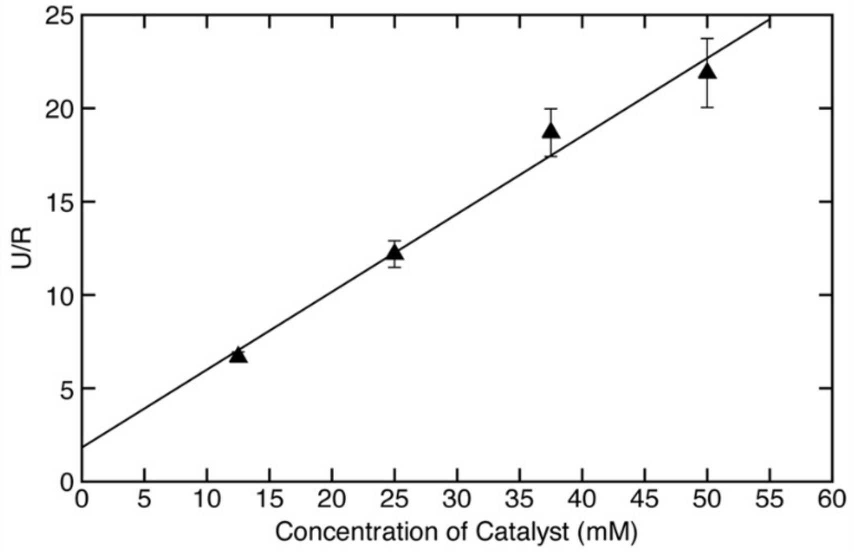
But Ni cat. biaryl formation has transmet. mechanism and is 2nd order in Ni
- *J. Organomet. Chem.* **1992**, 223

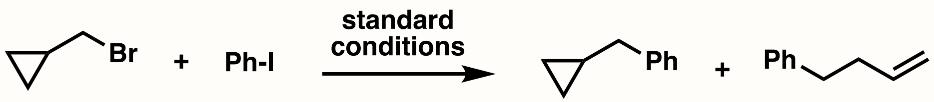




generated as
1:1 with (L)NiI$_2$

1 : 36





ND 35%

Weix. *JACS* **2013**, 16192

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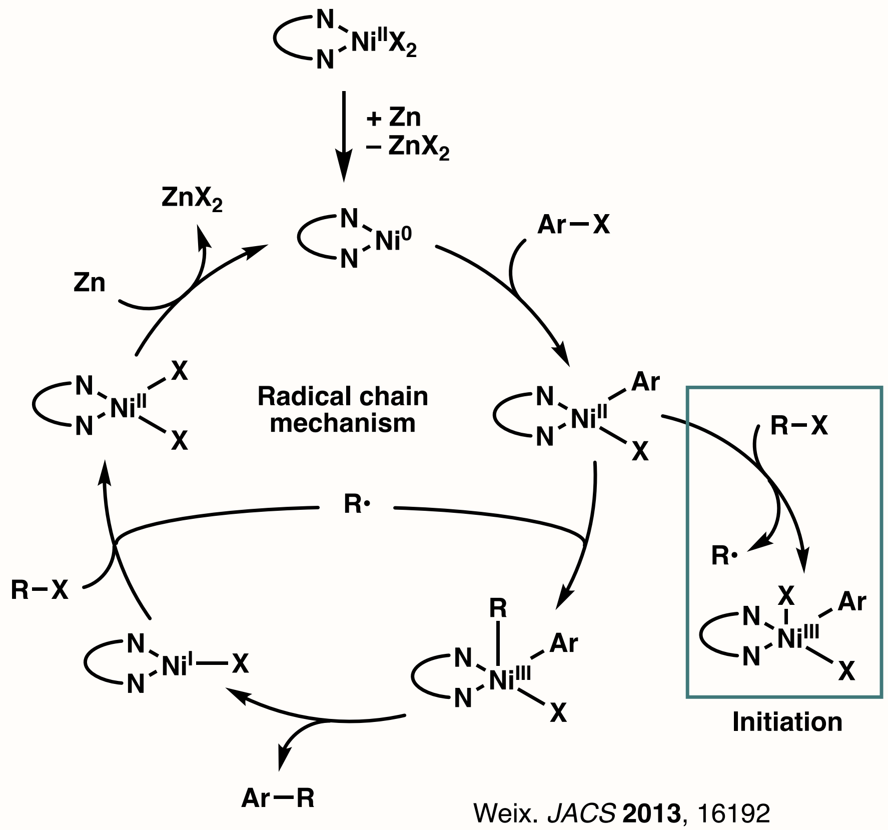
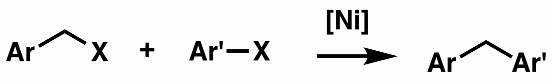
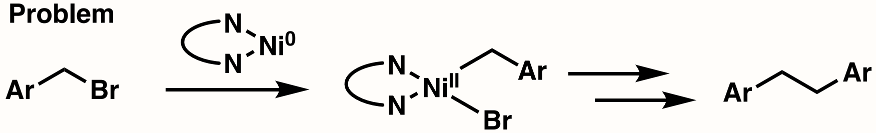


Weix. *JACS* **2013**, 16192

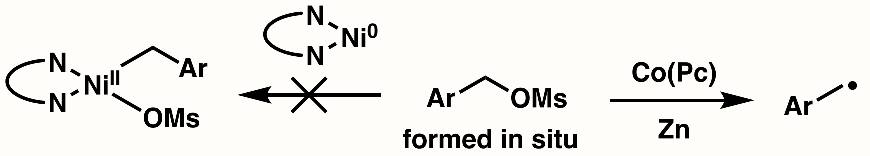
Goal

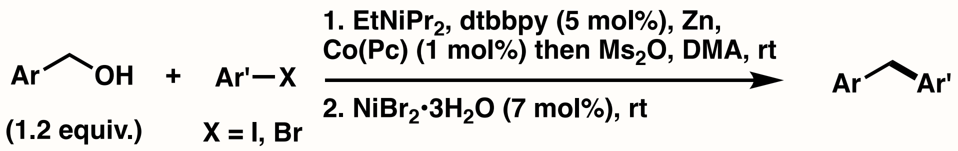


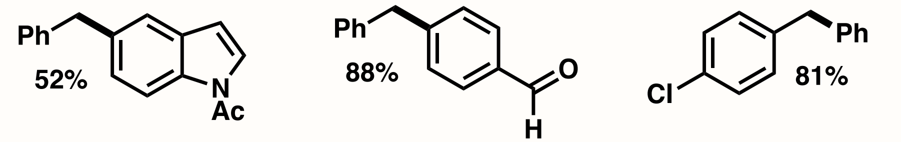
Problem



Solution





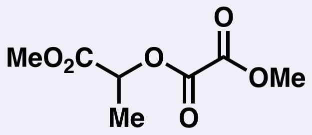


- 17 examples

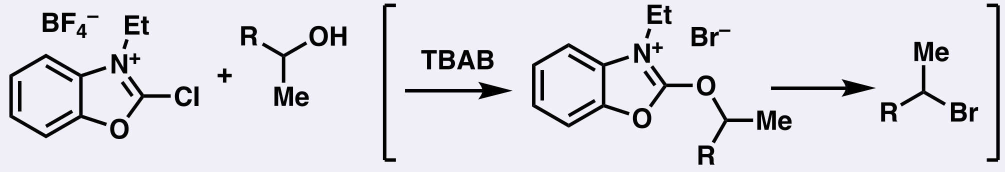
Weix. *Chem. Sci.* **2015**, 1115

Other similar alcohol coupling strategies

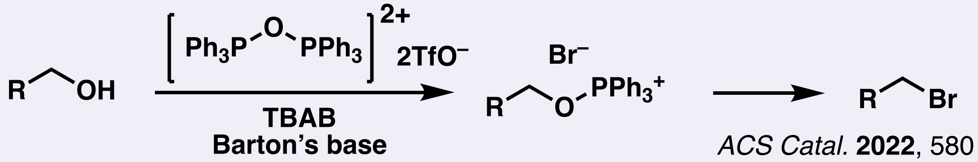
Org. Lett. **2018**, 7846



Org. Lett. **2019**, 1645

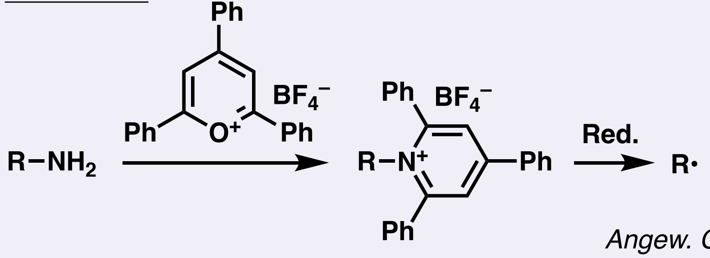


ACS Catal. **2021**, 14102



ACS Catal. **2022**, 580

For amines



Org. Lett. **2019**, 2941
Org. Lett. **2019**, 3346
Org. Lett. **2020**, 950
Sci. Adv. **2019**, eeaw9516
Angew. Chem. Int. Ed. **2020**, 13484

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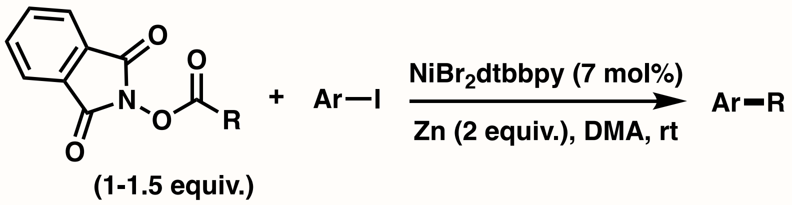
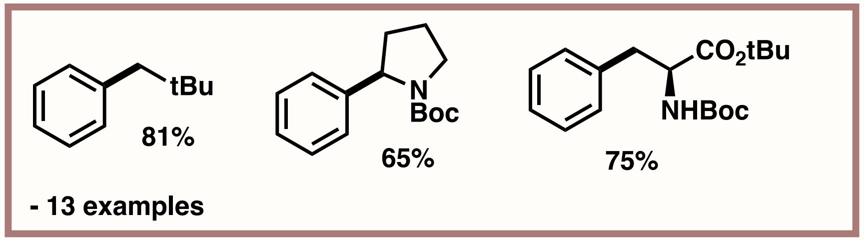
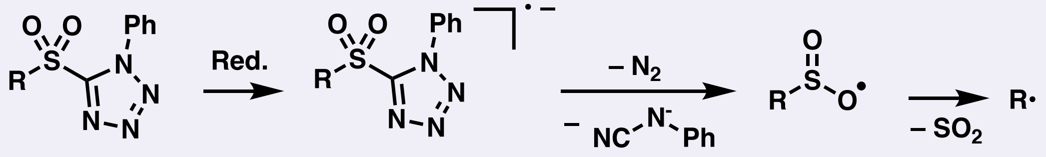
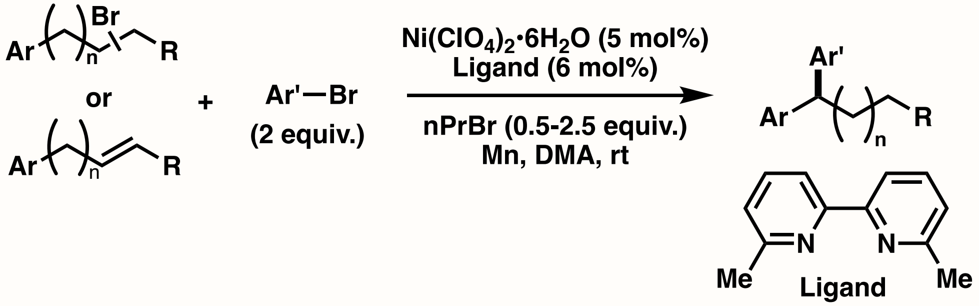


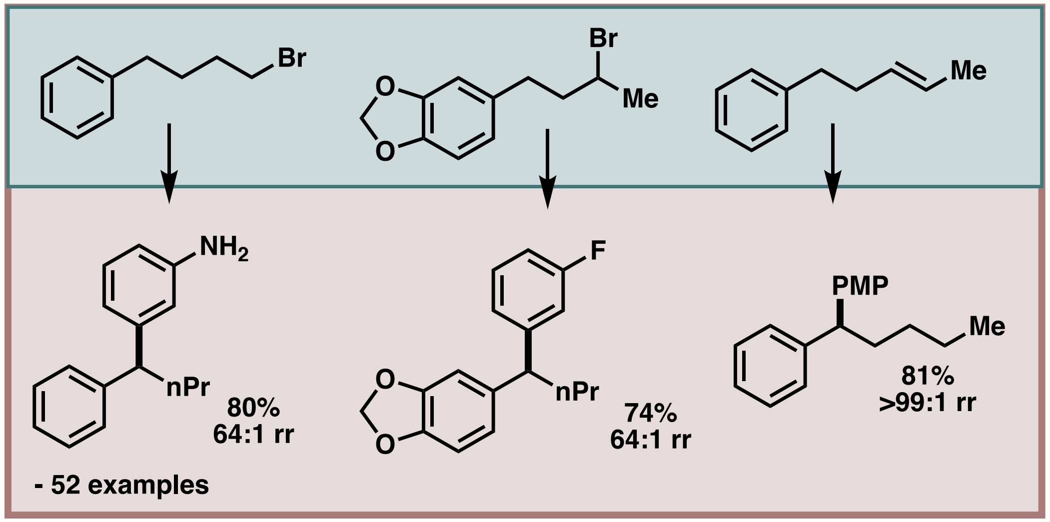


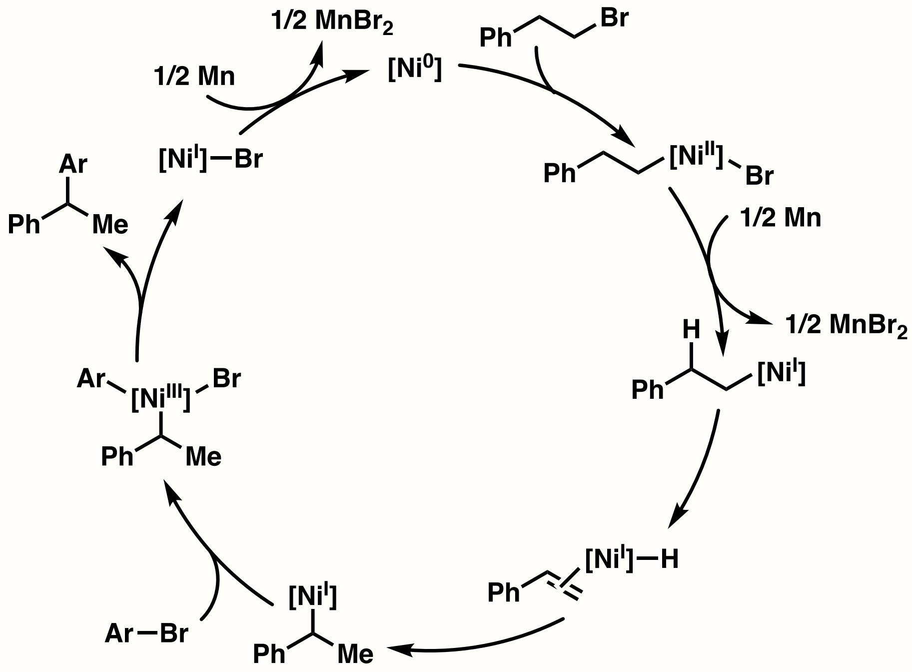
Weix. *JACS* **2016**, 5016

Similar strategy *Org. Lett.* **2019**, 5650









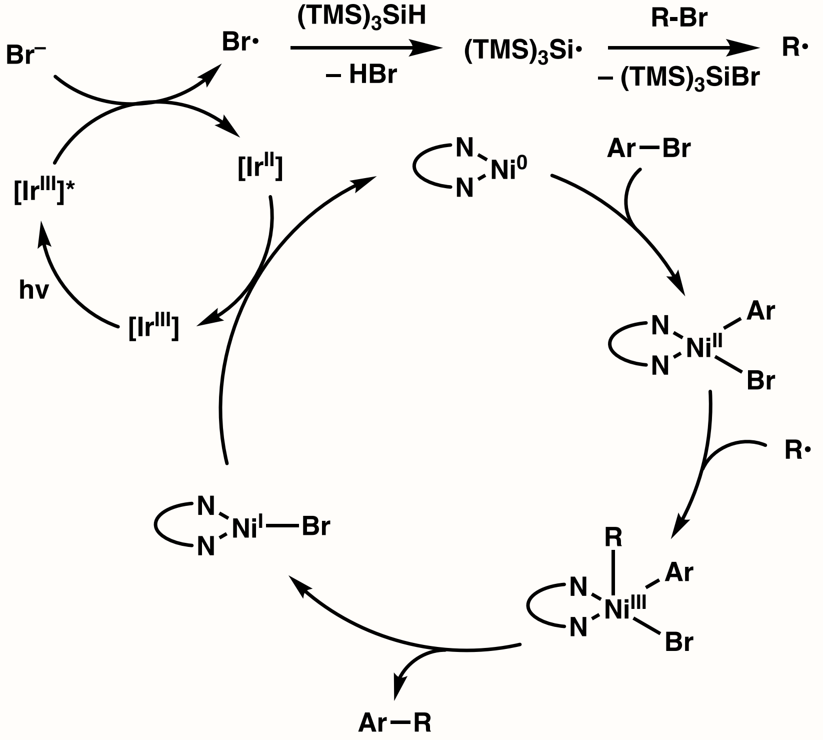
Initial oxidative addition to alkyl bromide seems unfounded

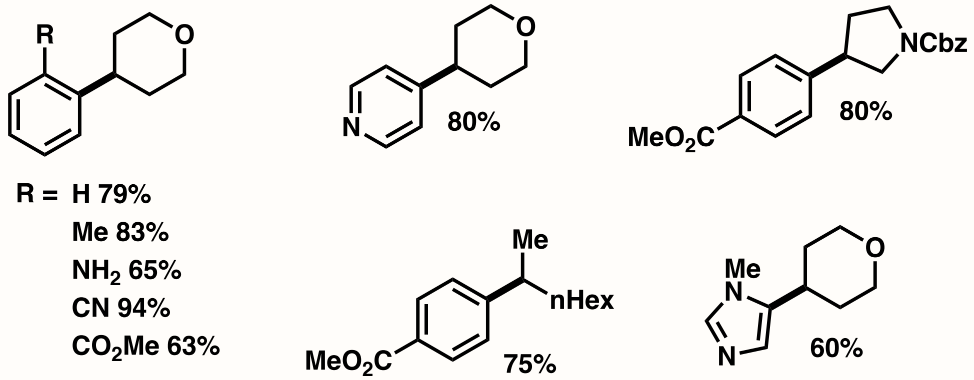
Zhu. *JACS* **2017**, 13929

Similar chain walking XECs:
JACS **2017**, 1061 **(initial report uses ArI and generates NiH with CsF and PMHS)**
ACS Catal. **2018**, 310 **(proposes initial OA to ArBr)**

Cross electrophile coupling

$$\text{Ar–Br} + \underset{\text{(1.5 equiv.)}}{\text{R–Br}} \xrightarrow[\text{TTMSS, Na}_2\text{CO}_3\text{ or LiOH; blue LEDs}]{\text{Ir[dF(CF}_3\text{)ppy]}_2\text{(dtbbpy)PF}_6\text{ (1 mol\%), NiCl}_2\cdot\text{dtbbpy (0.5 mol\%)}} \text{Ar–R}$$

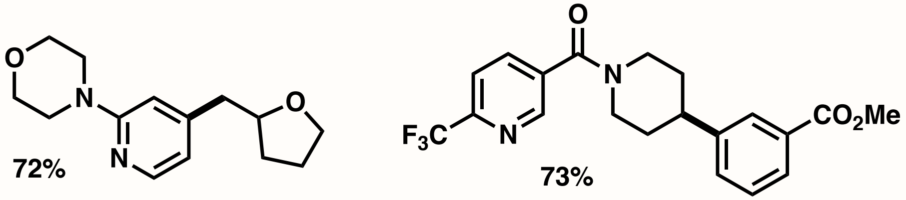




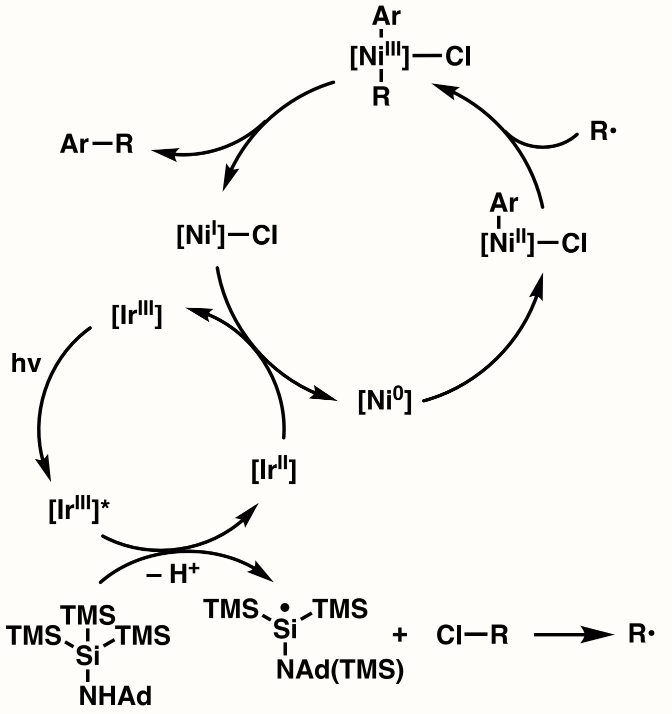
- 39 examples

MacMillan. *JACS* **2016**, 8084

$$\text{Ar–Cl} + \underset{\text{(2 equiv.)}}{\text{R–Cl}} \xrightarrow[\text{(TMS)}_3\text{SiNHAd, TMG; DMA:t-AmylOH (3:1); blue LEDs, 55°C}]{\text{Ir(ppy)}_2\text{(dtbbpy)PF}_6\text{ (1 mol\%), NiCl}_2\text{bim (5 mol\%)}} \text{Ar–R}$$



- 35 examples



MacMillan. *JACS* **2020**, 11691

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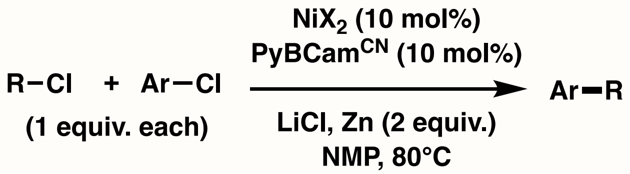
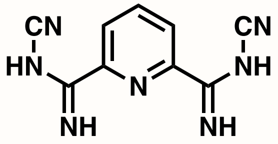


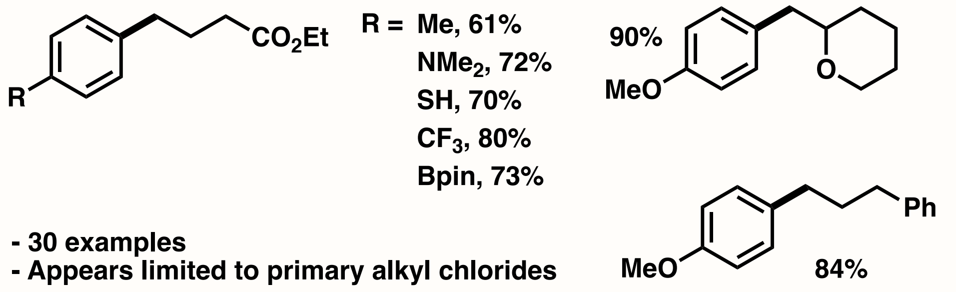
X = Br, I



PyBCam^{CN}

Crucial for reacting with both substrates at equal rate, suppressing both alkyl and aryl dimerization

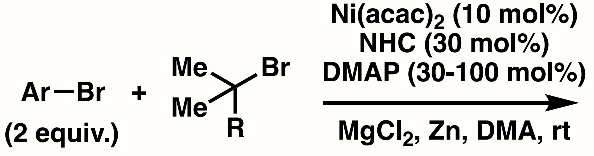
Commercially available (2020)	
R−I	< 100000
R−Br	~ 841000
R−Cl	~ 1.8M

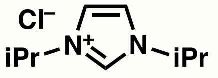


R = Me, 61%
NMe$_2$, 72%
SH, 70%
CF$_3$, 80%
Bpin, 73%

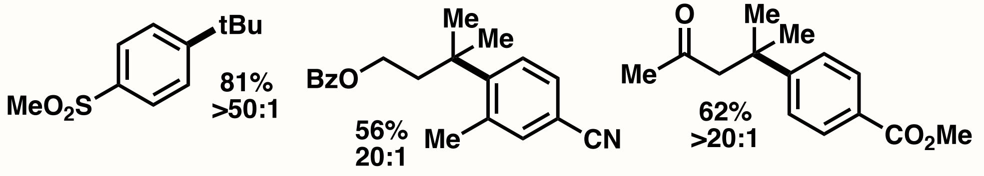
- 30 examples
- Appears limited to primary alkyl chlorides

Weix. *JACS* **2020**, 9902



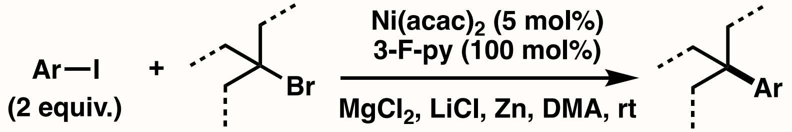


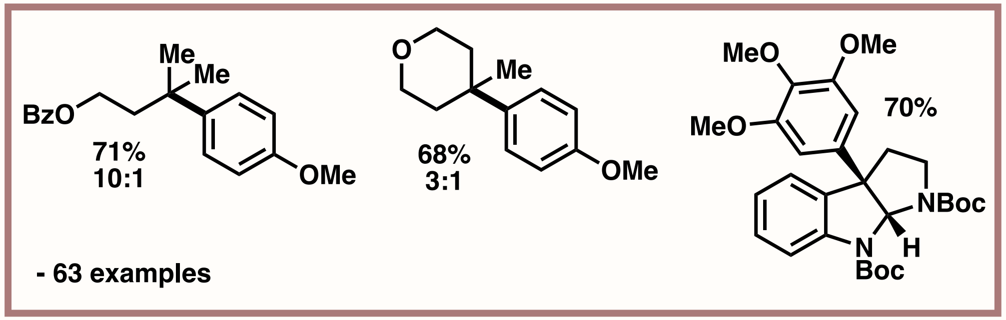
NHC



- 33 examples
- Only suitable for electron-poor arenes
- All yields within 12% of standard conditions if NHC omitted!
- Slight decrease in pdt/isomer without NHC

Gong. *JACS* **2015**, 11562





- 63 examples

Gong. *JACS* **2018**, 14490

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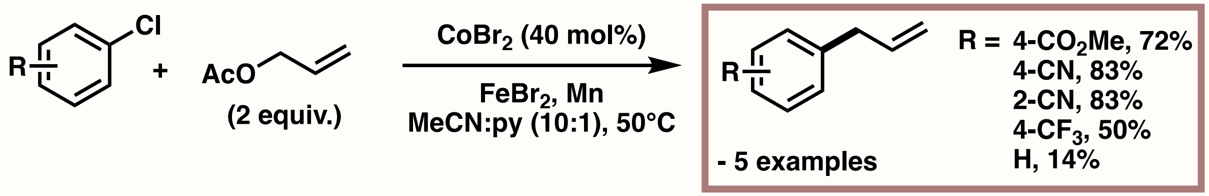
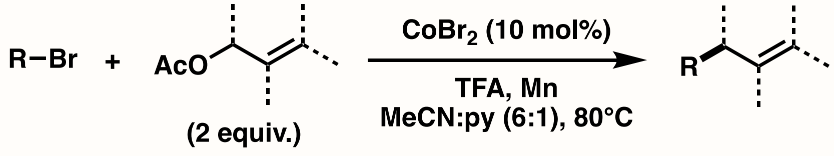


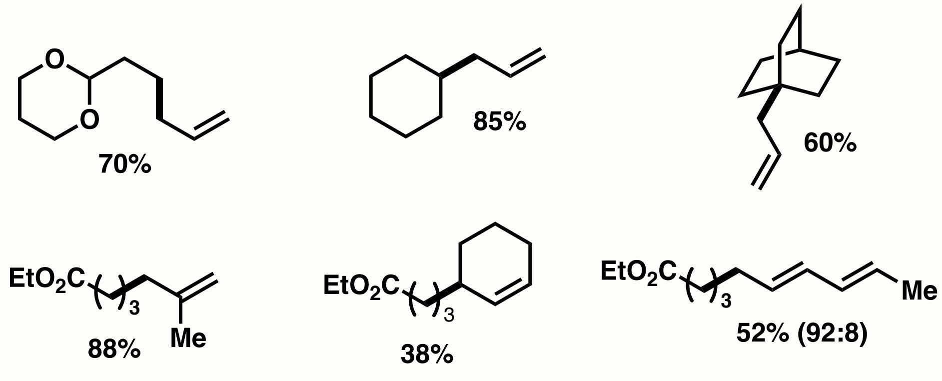
- 5 examples

Allylation

- Similar allylation with Ar-Br and Zn presumed to proceed through ArZnBr
- This allylation presumed a true XEC (no intermediate ArMnCl)
- Mechanism not speculated

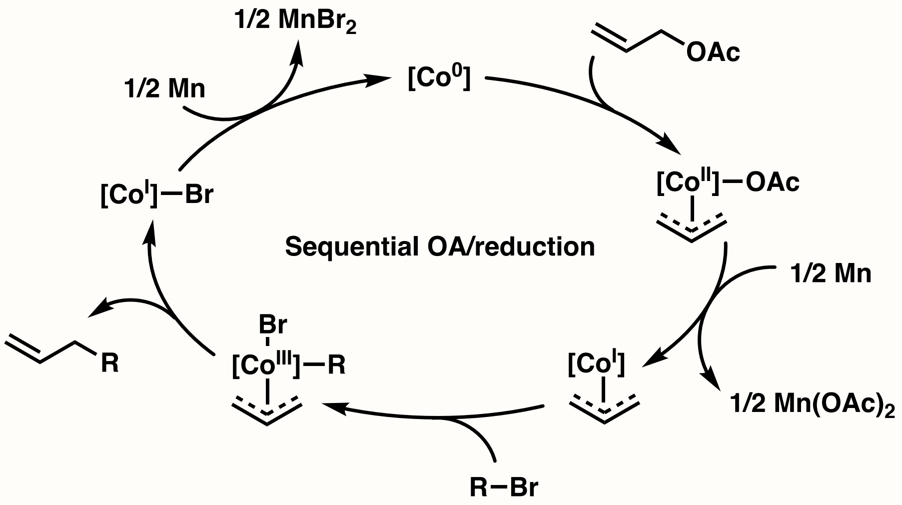
Gosmini. *Org. Lett.* **2003**, 1043

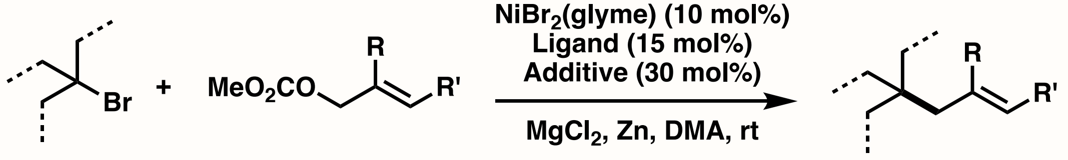


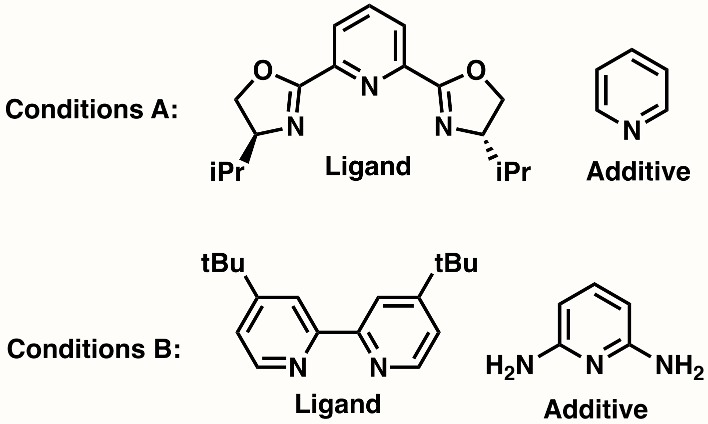


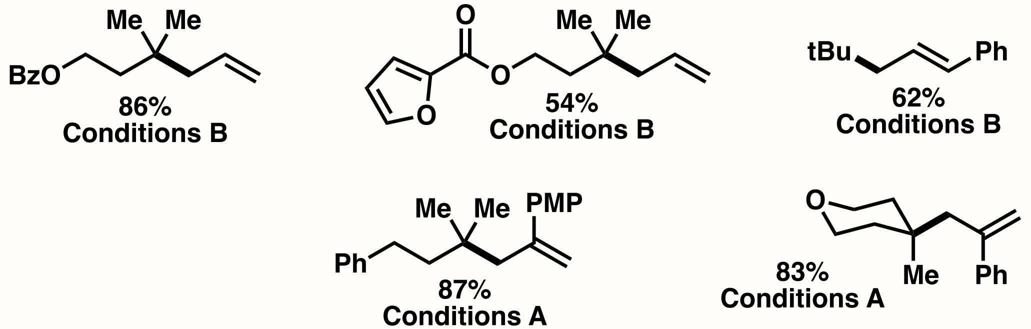
- 29 examples including one R-Cl and four allylic carbonates

Gosmini. *Angew. Chem. Int. Ed.* **2011**, 10402









- 40 examples
- Only tolerates one additional substituent and limited to Ar for 1,1 disubstitution

Gong. *Angew. Chem. Int. Ed.* **2017**, 13103

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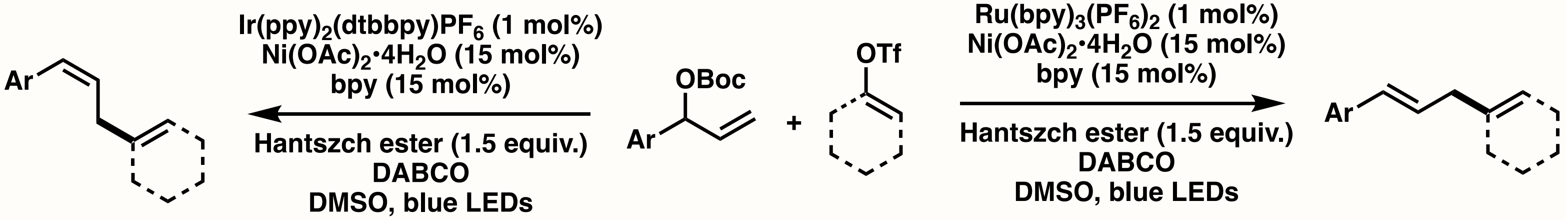
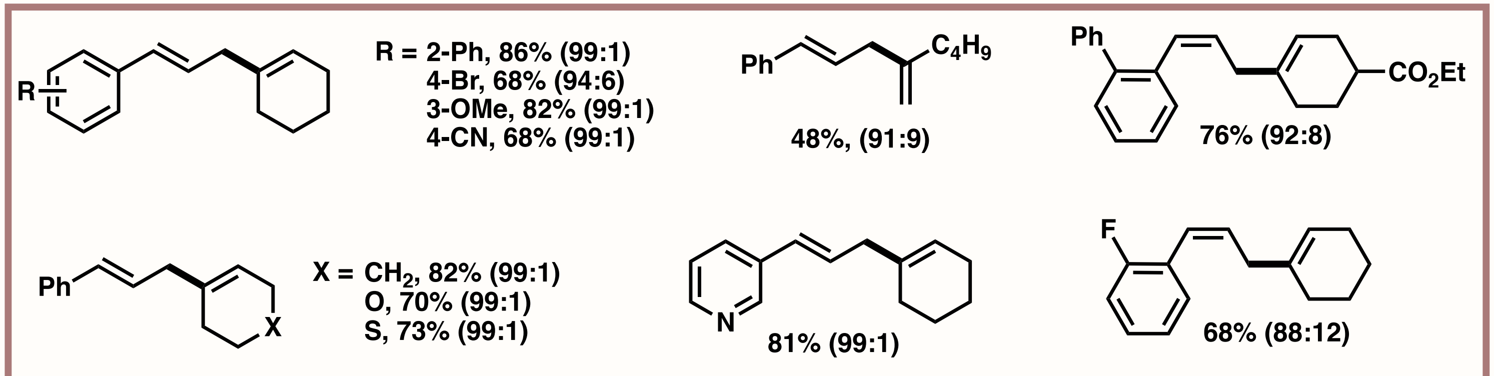
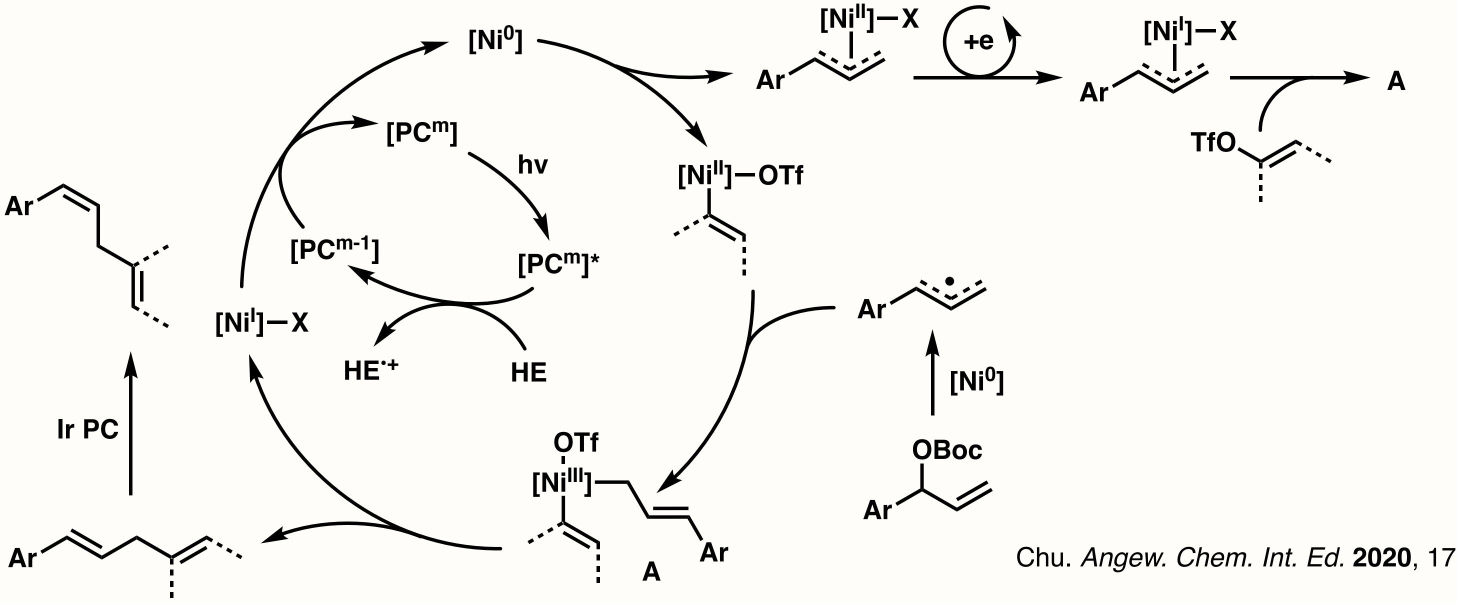
25/01/22





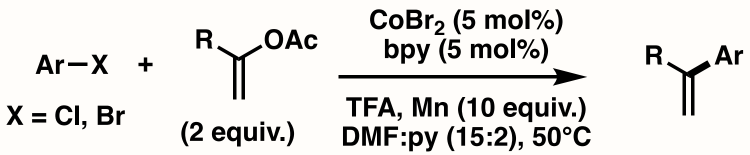
- 51 examples

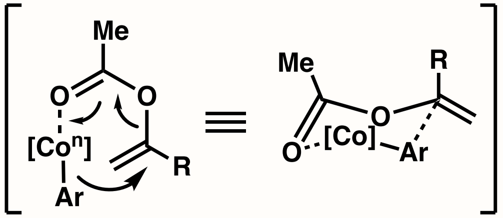


Chu. *Angew. Chem. Int. Ed.* **2020**, 177

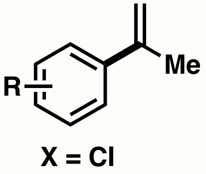
Cross electrophile coupling

Vinylation

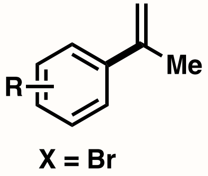




- Proposed coupling TS following OA of aryl halide to cobalt
- Resulting Co^{II} or Co^{III} reduced by Mn



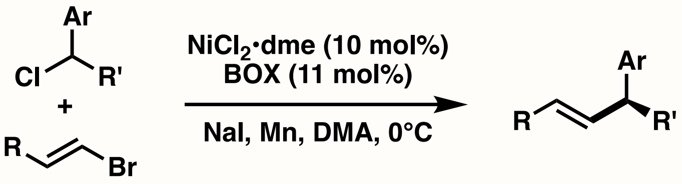
R = p-CO_2Me, 75%
p-COMe, 65%
p-CN, 76%
o-CO_2Me, 0%
o-COMe, 27%
o-CN, 73%

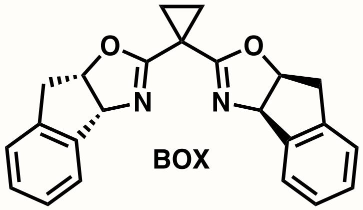


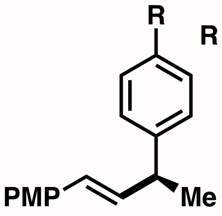
R = p-CO_2Me, 75%
p-OMe, 78%
p-CN, 42%
o-CO_2Et, 0%
o-OMe, 48%
o-CN, 16%

- 27 examples
- No clear trend in reactivity
- A few examples using vinyl- and cyclopentenyl acetate with varied success

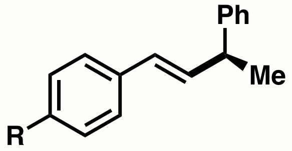
Gosmini. *Eur. JOC* **2005**, 989



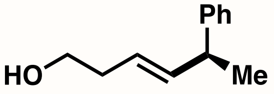




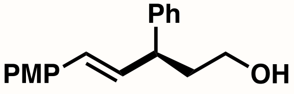
R = H, 91%, 93% ee
Me, 82%, 94% ee
OMe, 64%, 93% ee
F, 81%, 89% ee
Br, 59%, 90% ee



R = Me, 83%, 96% ee
CF_3, 49%, 94% ee
OH, 86%, 93% ee
Bpin, 59%, 94% ee



56%, 94% ee



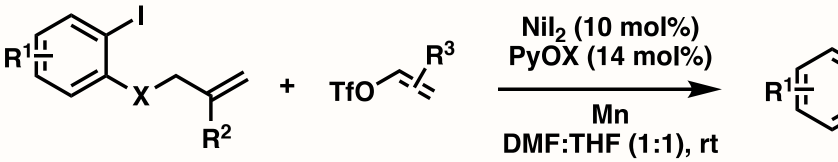
81%, 96% ee

- 32 examples

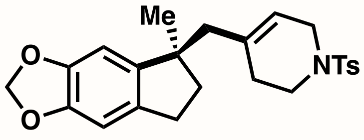
Reisman. *JACS* **2014**, 14365

Cross electrophile coupling

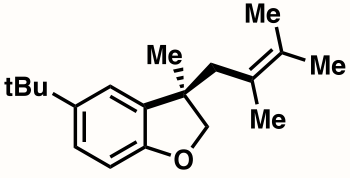
Group meeting
Carl Mansson
25/01/22



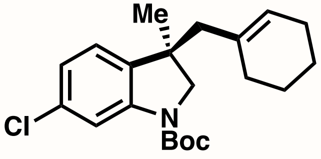
PyOX



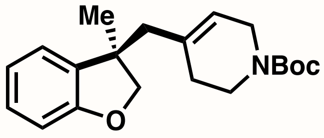
50%, 94% ee



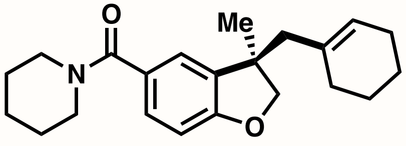
43%, >99% ee



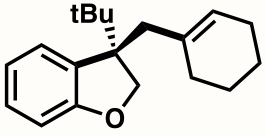
58%, 96% ee



79%, 98% ee

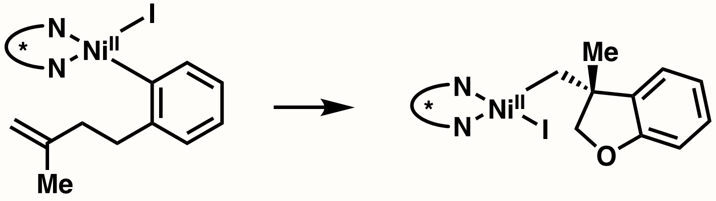


45%, 92% ee
CB2 receptor agonist analogue



65%, 98% ee

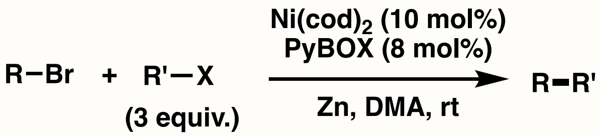
- 55 examples
- Consistently excellent ee’s
- Linker length cannot be varied
- Only 1,1 disubstitution tolerated

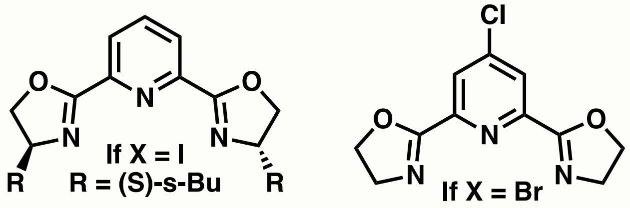


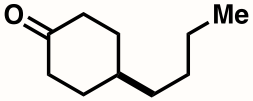
Sequential OA/reduction mechanism intercepted by migratory insertion

Shu. *JACS* **2019**, 7637

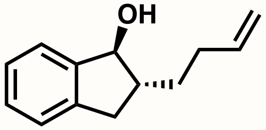
Alkyl-alkyl



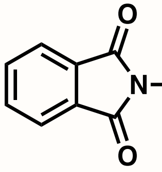




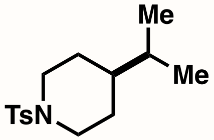
X = Br, 57%
I, 65%



X = Br, 65% (4:1 dr)



X = Br, 72%
I, 65%

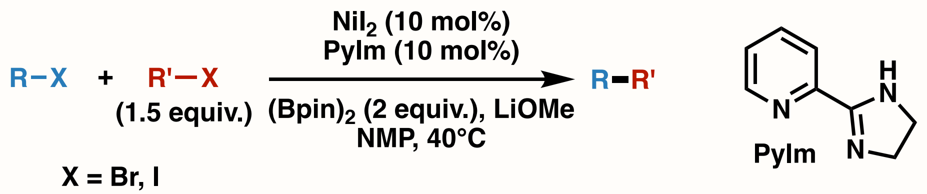


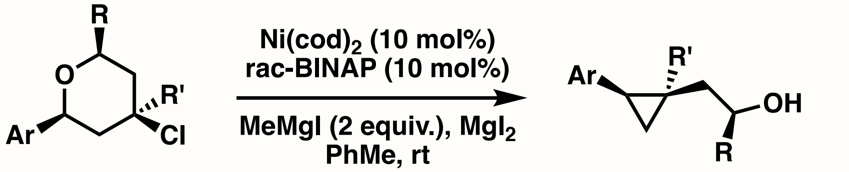
X = Br, 72%

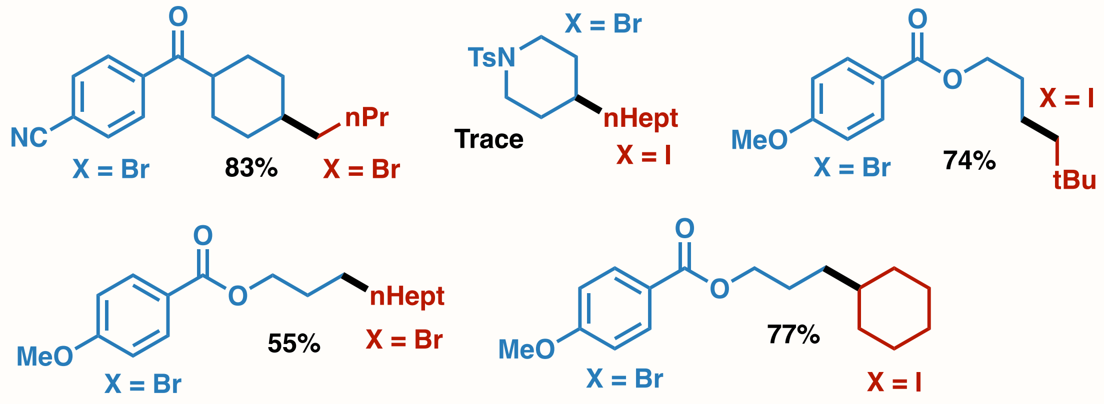
- 36 examples
- Mostly selective for coupling secondary with primary alkyl halides

Gong. *Org. Lett.* **2011**, 2138

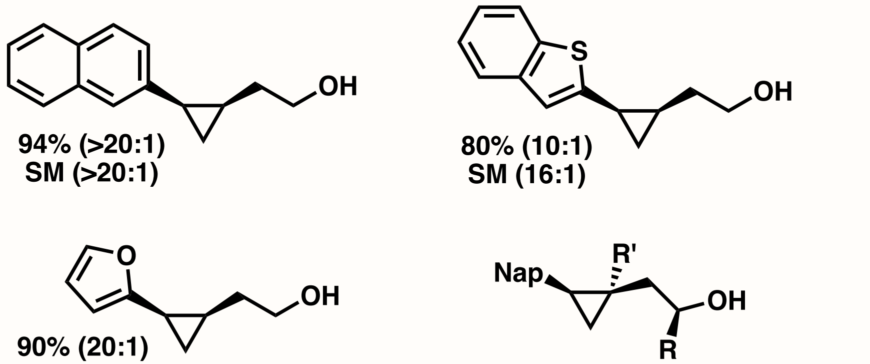
Cross electrophile coupling







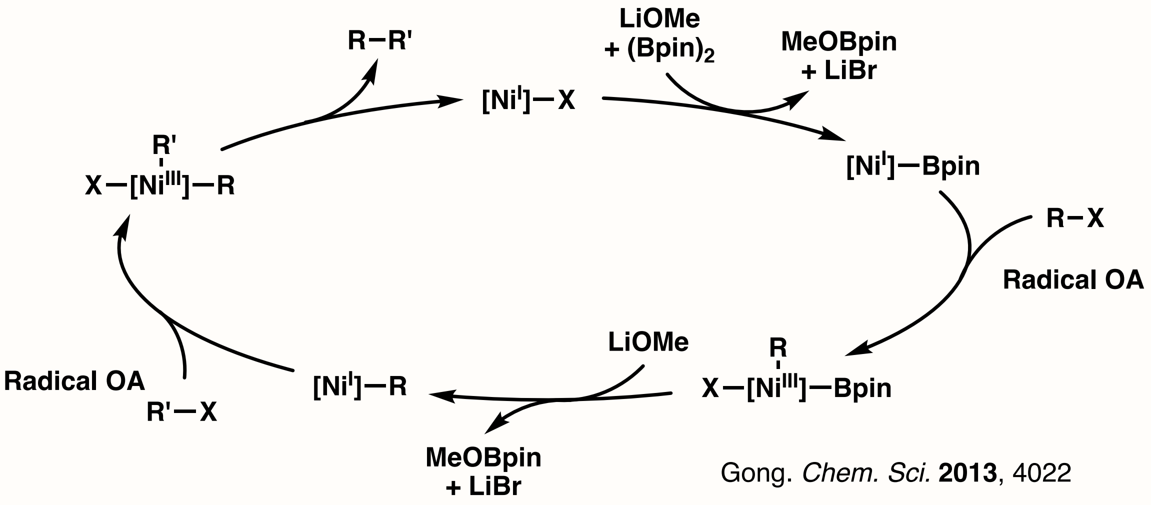
- 32 examples
- Selective for: 1° Alk-Br with 2° Alk-Br; 1° Alk-Br with 2° Alk-I and hindered 1° Alk-I
- Two 1° Alk-Br give moderate yields
- Two 2° Alk-X give v. poor yields
- Unhindered 1° Alk-I give trace yields with all Alk-Br



R = Me, R’ = H, 88% (20:1); SM (13:1)
R = Bn, R’ = H, 85% (20:1); SM (10:1)
R = H, R’ = Me, 62% (8:1), SM (9:1)

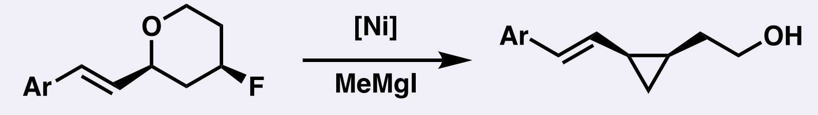
- 12 Examples
- Stereospecific, intramolecular S_N2-like mechanism

Jarvo. *JACS* **2015**, 9760

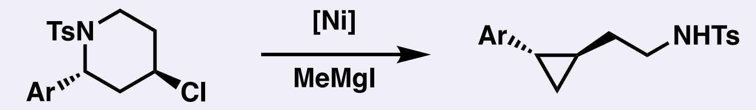


Gong. *Chem. Sci.* **2013**, 4022

<u>Similar methods by Elizabeth Jarvo</u>



JACS **2016**, 14006

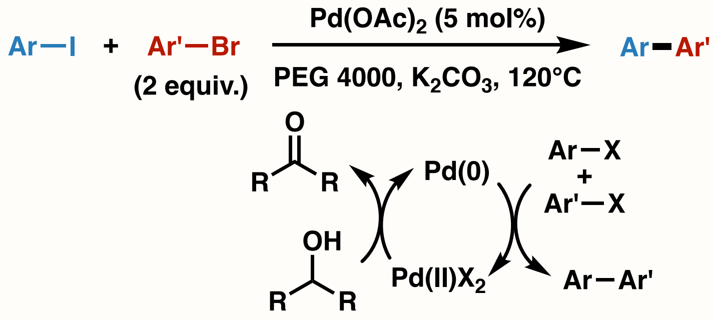


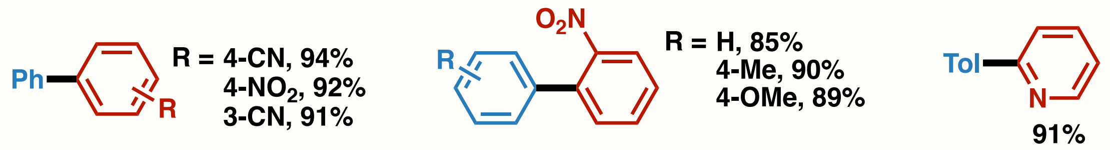
JOC **2020**, 1775

Cross electrophile coupling

Group meeting
Carl Mansson
25/01/22

Aryl-aryl

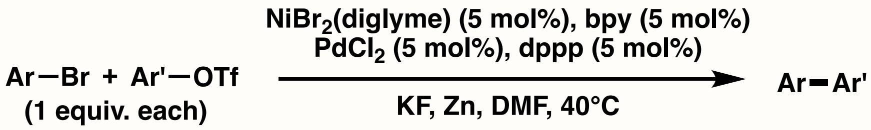


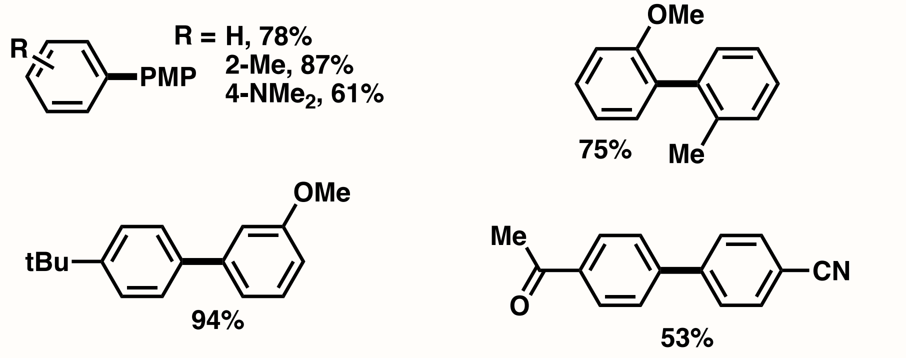


(using 4 equiv. of Ar'-Br)

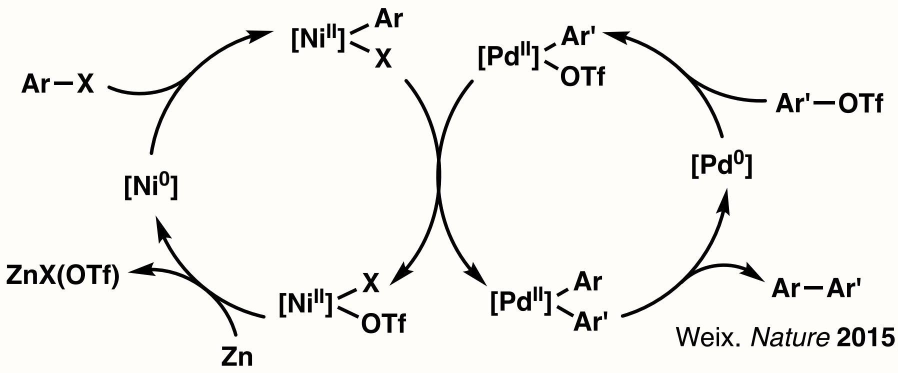
- 16 examples
- Selective for electron rich/neutral Ar-I with electron poor Ar'-Br
- Terminal PEG hydroxyl groups act as reductant
- PEG phase can be recycled up to 6 times without loss in reactivity

Wang. *JOC* **2006**, 1284

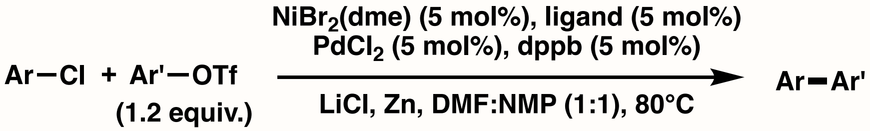




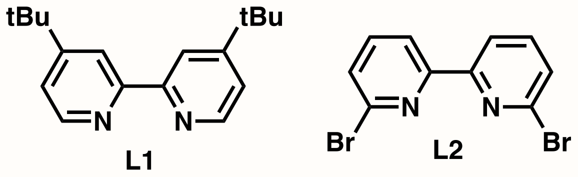
- 21 examples including 5 where Ar-I or Ar-Cl were used in place of Ar-Br

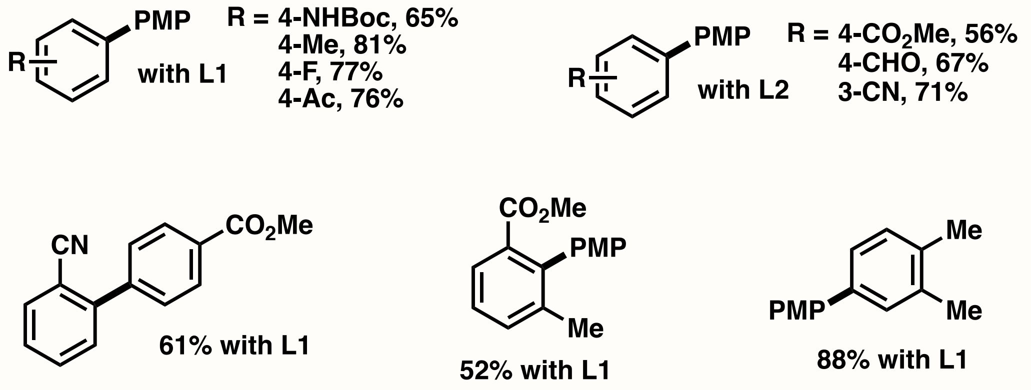


Weix. *Nature* **2015**, 454



LiCl crucial for Ni(II)X$_2$ reduction at Zn surface



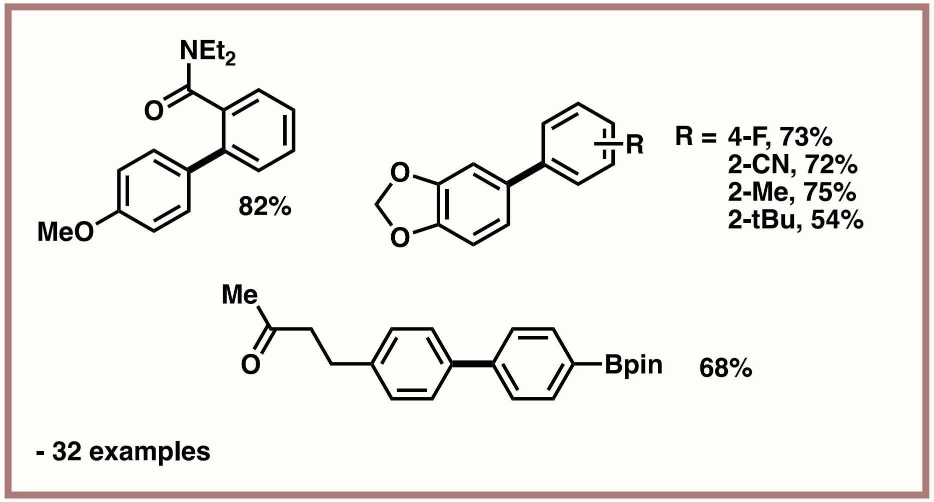


- 35 examples

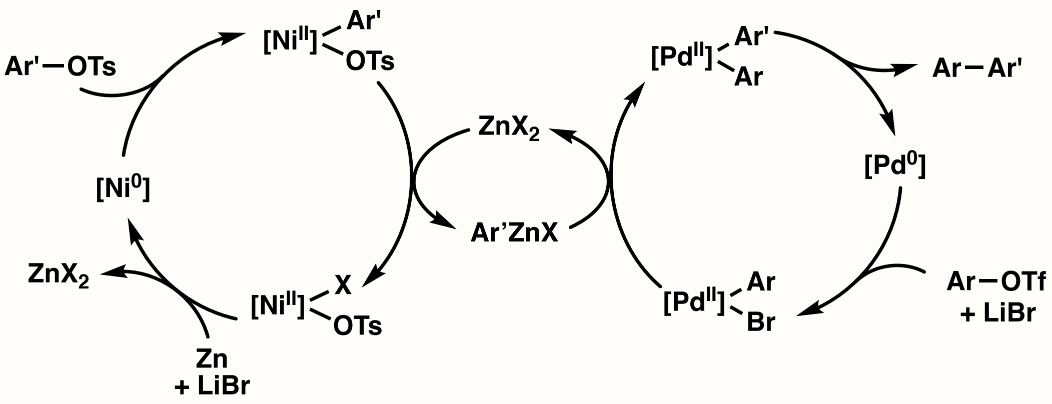
Weix. *JACS* **2019**, 10978

Cross electrophile coupling

$$\text{Ar—OTf} + \underset{(1\text{-}1.5\text{ equiv.})}{\text{Ar'—OTs}} \xrightarrow[\text{LiBr, Zn, DMF, 40-60°C}]{\text{NiCl}_2\text{(dme) (1 mol\%), dPhbpy (1.2 mol\%)}\\ \text{PdCl}_2\text{ (1 mol\%), dppb (1.2 mol\%)}} \text{Ar—Ar'}$$

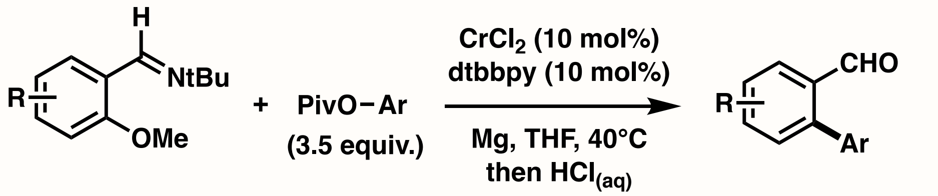


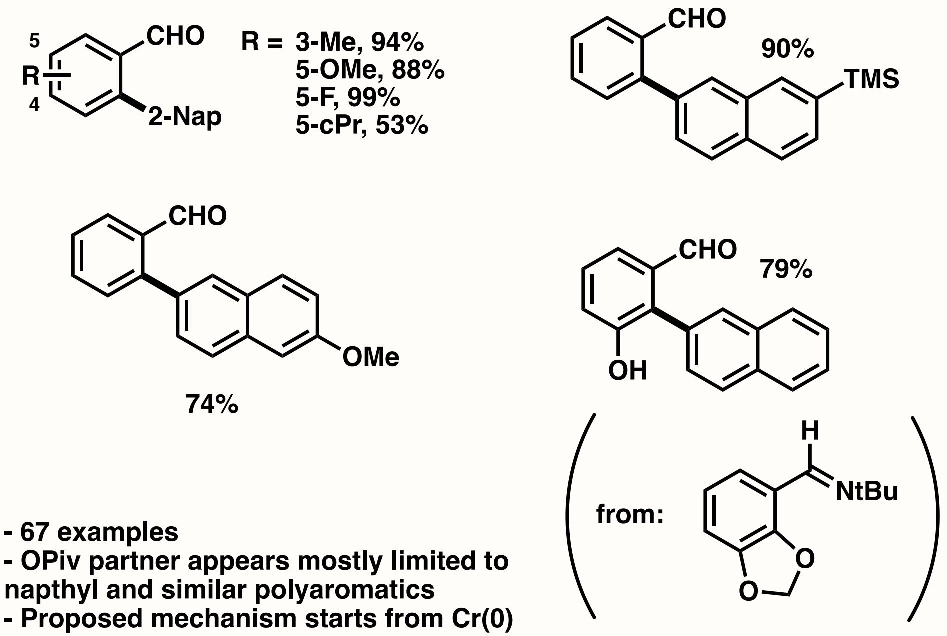
- 32 examples



- XEC proceeds in diminished yield with Ni only (58% vs 76%)
- Inverted OA selectivity for Ni cat.
- Pd helps to consume Ar'ZnX and improves cross selectivity

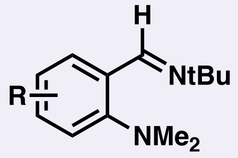
Weix. *JACS* **2020**, 10634





- 67 examples
- OPiv partner appears mostly limited to napthyl and similar polyaromatics
- Proposed mechanism starts from Cr(0) and proceeds by sequential OA/reduction

Zeng. *JACS* **2020**, 7715

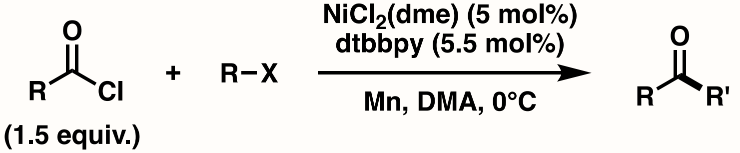


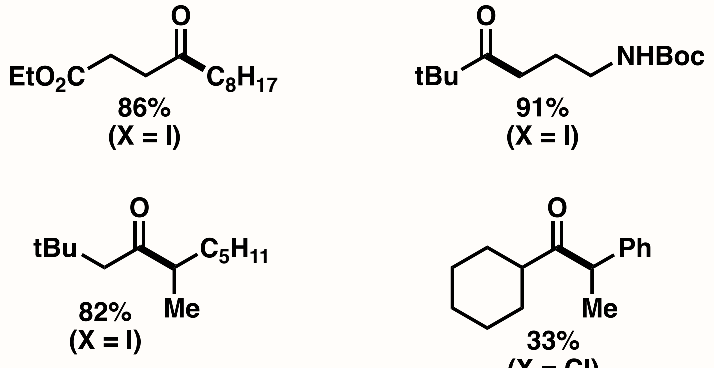
- Follow up report couples dimethyl anilines (C-N bond activation) with pivalates
- Identical conditions
- Similar substrate scope

JACS **2020**, 12834

Cross electrophile coupling

Acylation





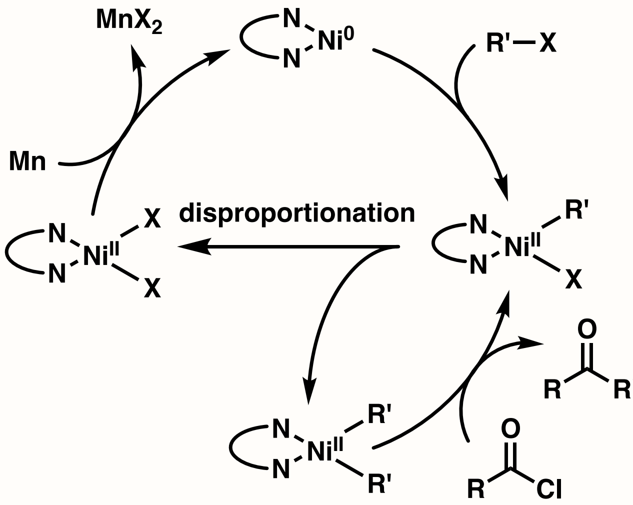
86% (X = I)

91% (X = I)

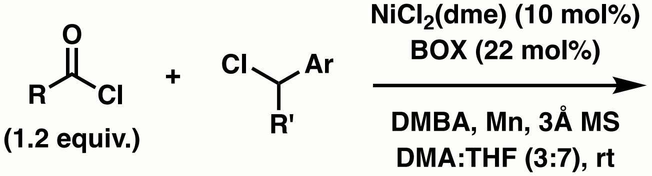
82% (X = I)

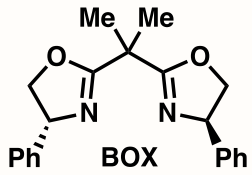
33% (X = Cl)

- 16 examples

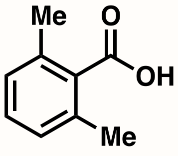


Weix. *Org. Lett.* **2012**, 1476

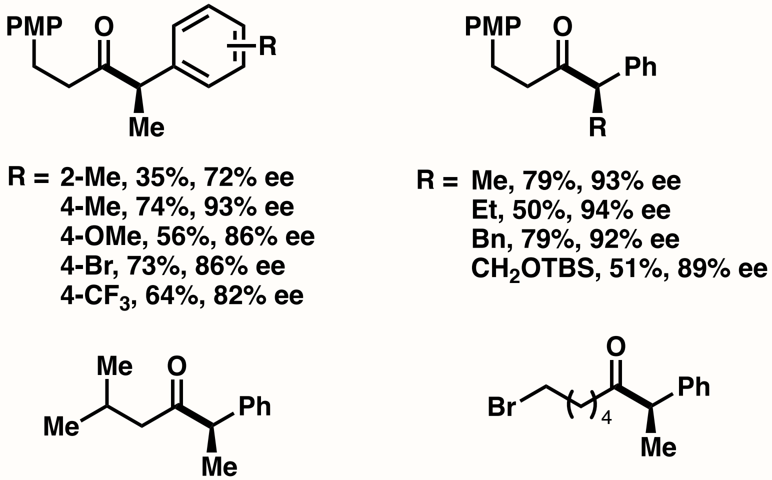




BOX



DMBA



R = 2-Me, 35%, 72% ee
4-Me, 74%, 93% ee
4-OMe, 56%, 86% ee
4-Br, 73%, 86% ee
4-CF$_3$, 64%, 82% ee

R = Me, 79%, 93% ee
Et, 50%, 94% ee
Bn, 79%, 92% ee
CH$_2$OTBS, 51%, 89% ee

73%, 88% ee

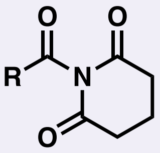
72%, 86% ee

- 23 examples

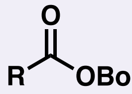
Reisman. *JACS* **2013**, 7442

Sequential OA/reduction mechanism satrting with OA of acid chloride

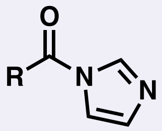
Other activated acyl groups used in XEC



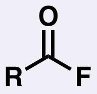
Org. Lett. **2017**, 2536



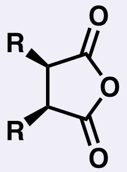
Chem. Commun. **2012**, 7034



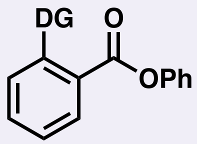
ACS Catal. **2020**, 3895



Angew. Chem. Int. Ed. **2020**, 13484



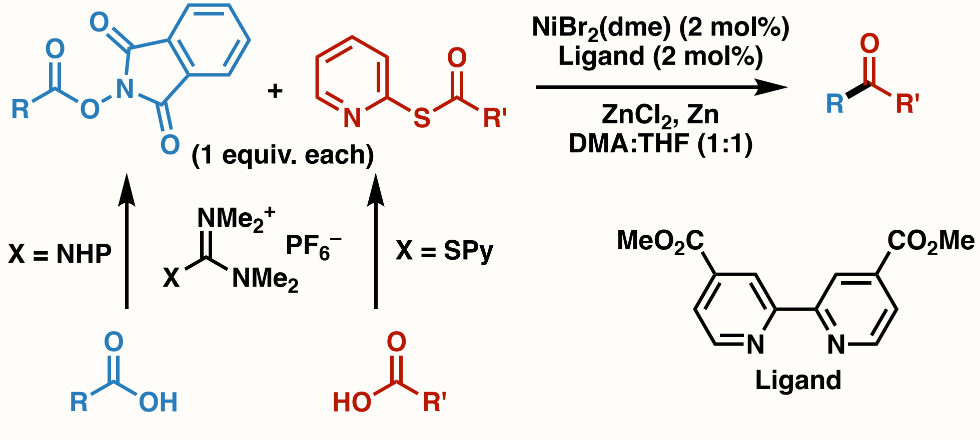
Org. Lett. **2018**, 1191



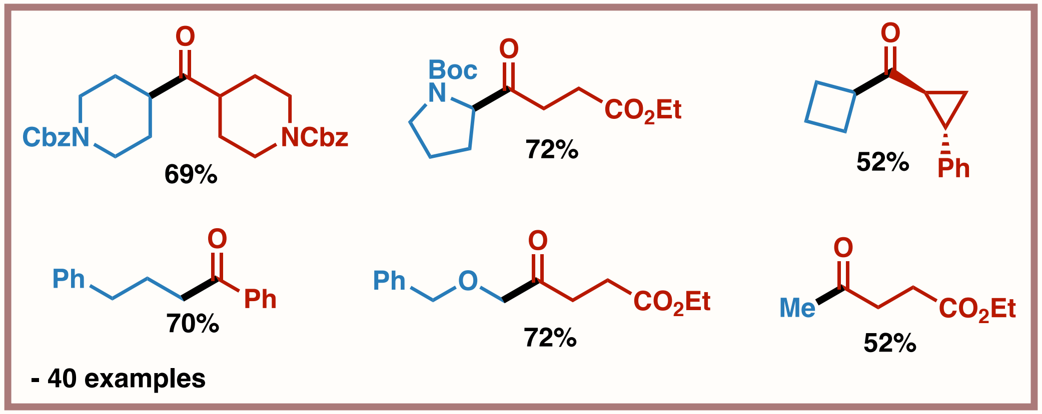
Org. Lett. **2020**, 9203

Cross electrophile coupling

Group meeting
Carl Mansson
25/01/22

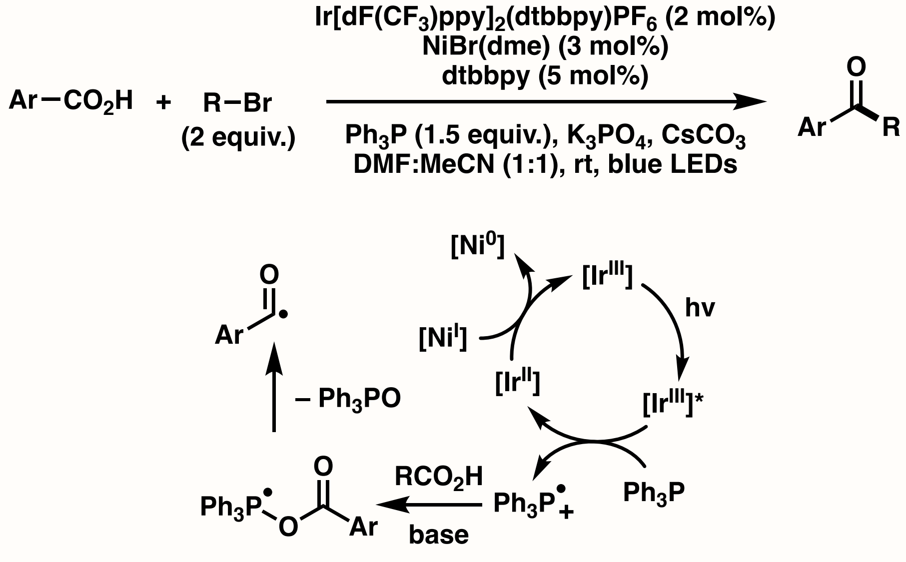


Filtration (SiO_2) and concentration gives minimal yield loss in XEC vs. purified reagents

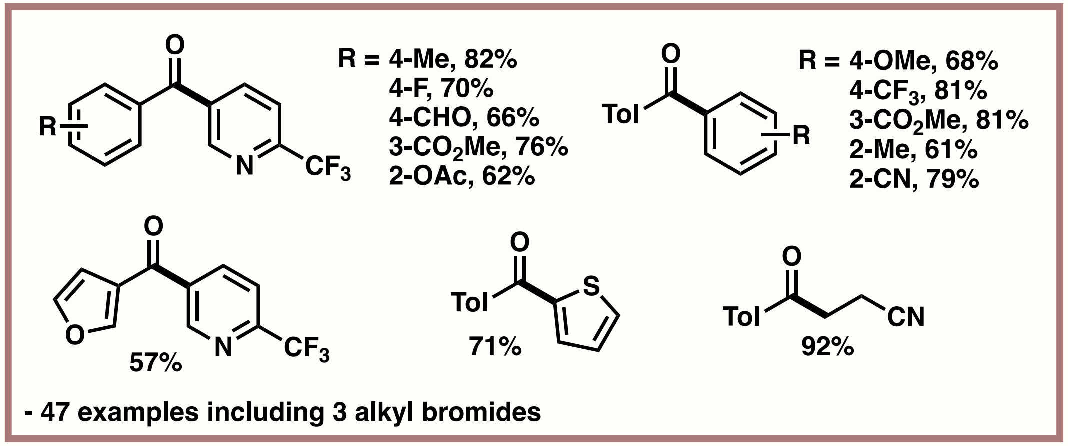


- 40 examples

Weix. *Angew. Chem. Int. Ed.* **2019**, 12081



Radical chain mechanism

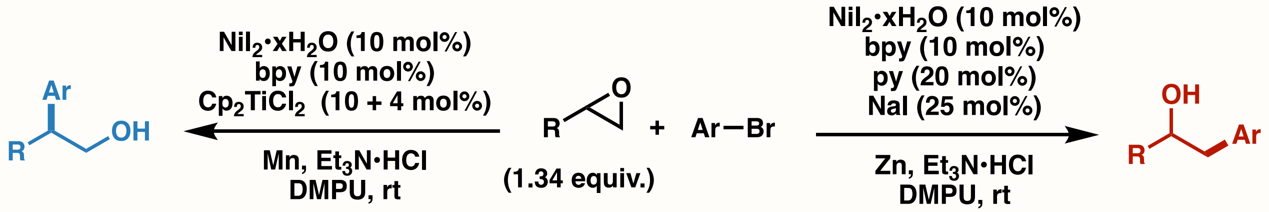


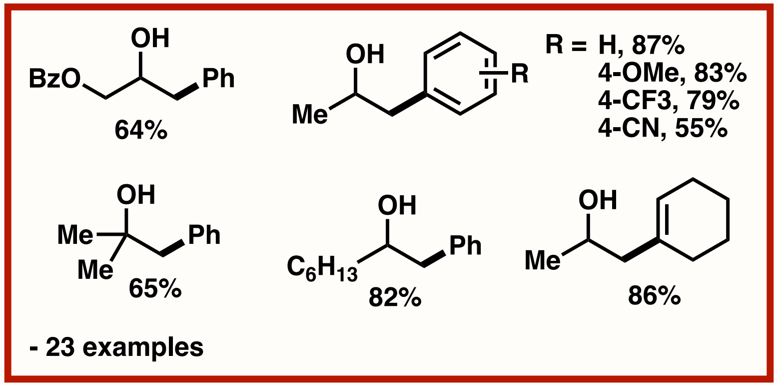
- 47 examples including 3 alkyl bromides

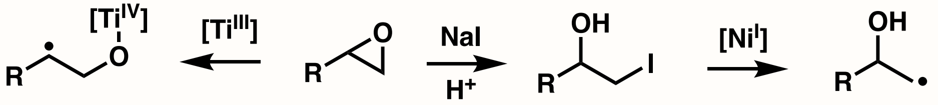
Xie. *Nat. Commun.* **2020**, 3312

Cross electrophile coupling

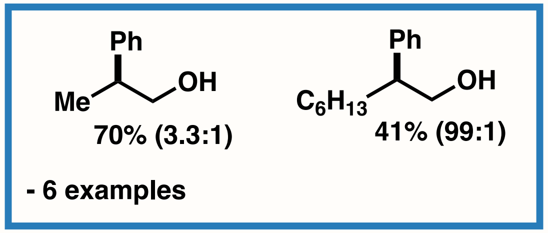
Epoxide/aziridine opening

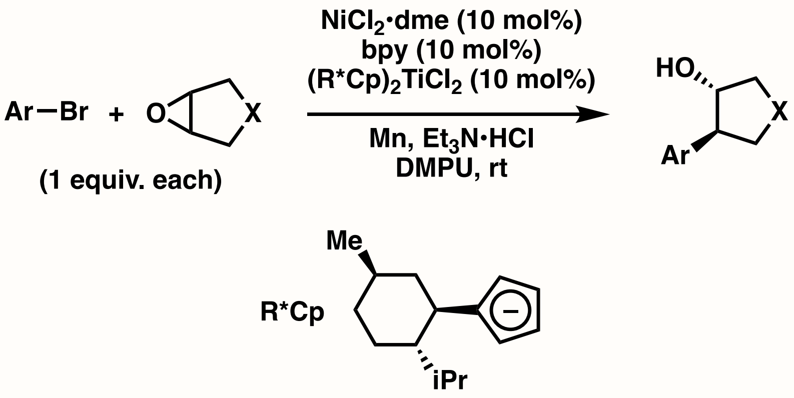


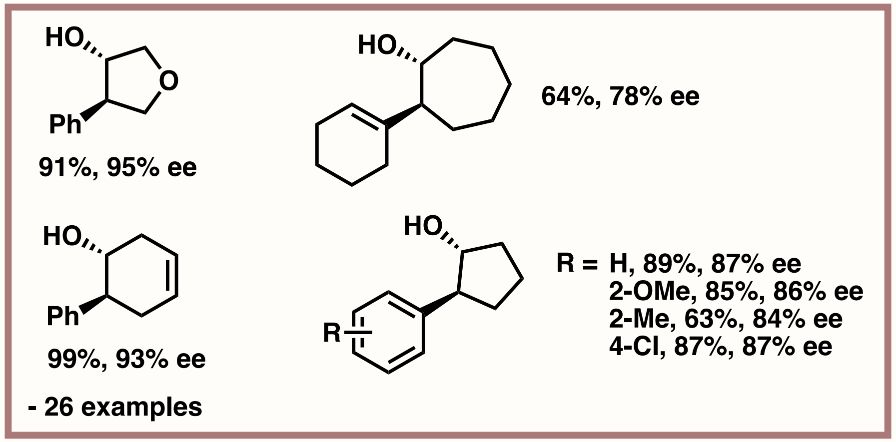




Weix. *JACS* **2014**, 48

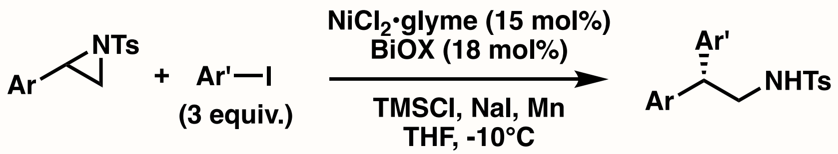


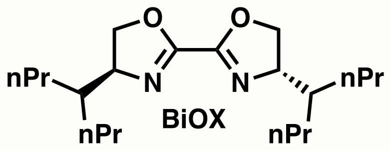




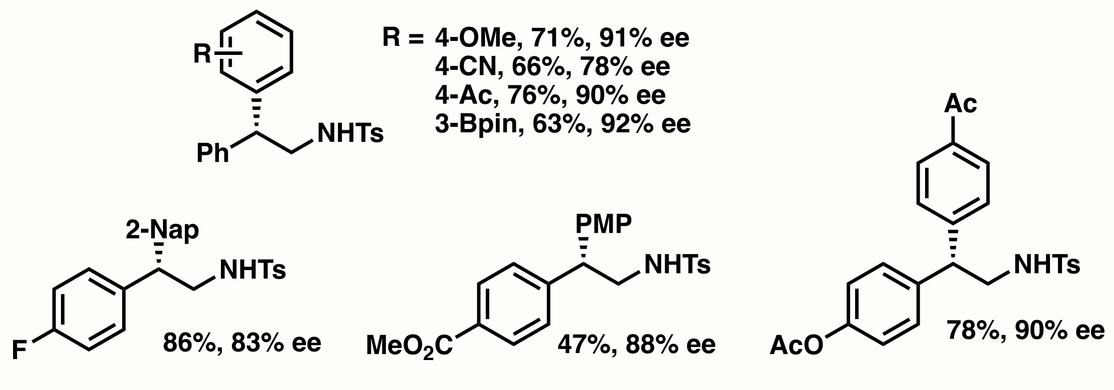
Weix. *JACS* **2015**, 3237

Cross electrophile coupling





Novel BiOx ligand developed by Reisman lab for asymmetric XEC of benzylic chlorides and aryl iodides
- *JACS* **2017**, 5684



- 21 examples

Simpler, racemic version run at rt also disclosed

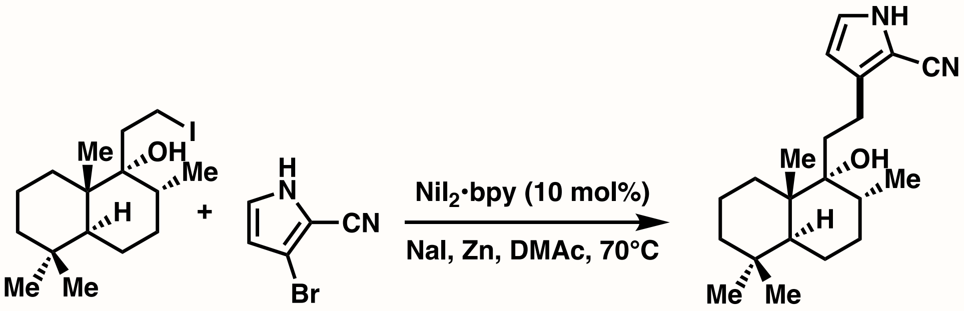
Doyle. *JACS* **2017**, 5688

Conclusions and outlook

XEC is field that has exploded in the last decade

Holds many advantages of traditional cross coupling, mainly ubiquity of substrates and orthogonality of scope

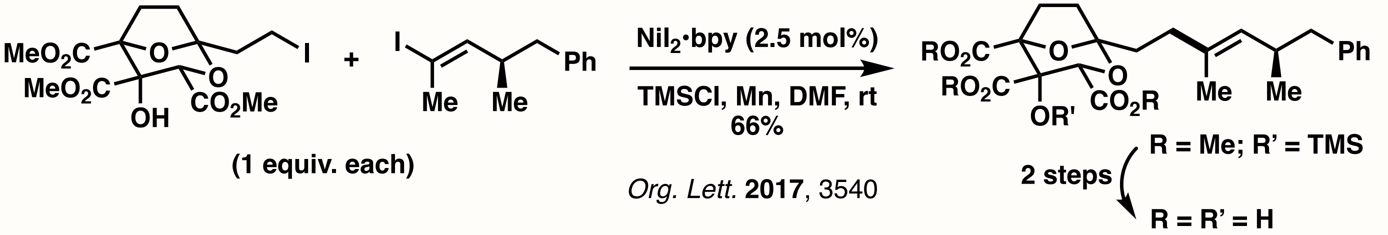
Main challenge is selectivity
- **xs reagent can be employed**
- **stereoelectronic matching**
- **selective mechanistic pathways: radical chain and sequential OA/reduction**



JOC **2018**, 6793

vitepyrroloid A

Future work
- **engage more chloride substrates**
- **make more hindered bonds (3° with 2°; 3° with 3°)**
- **lower equivalency of substrate (approaching 1:1)**
- **different metal catalysts**
- **use in total synthesis (currently limited)**
- **more intramolecular couplings/cyclizations**



Org. Lett. **2017**, 3540

6,7-Dideoxysqualestatin H5