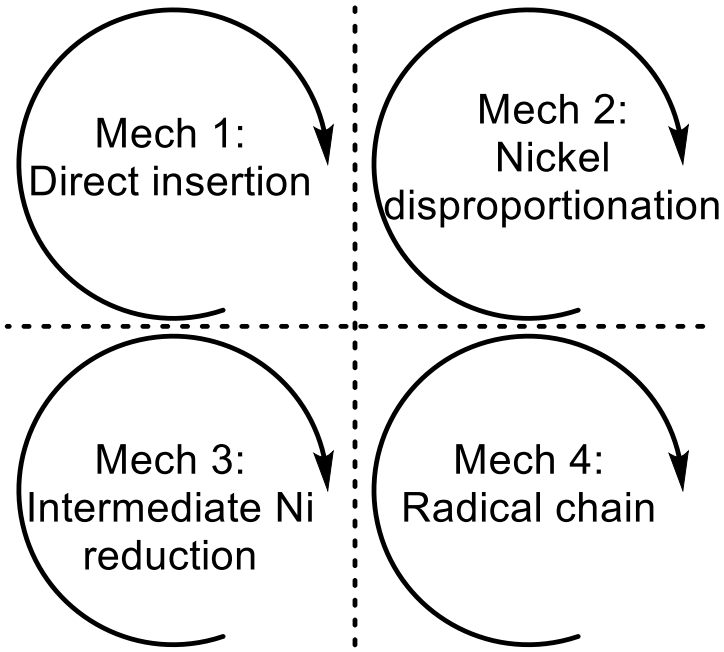
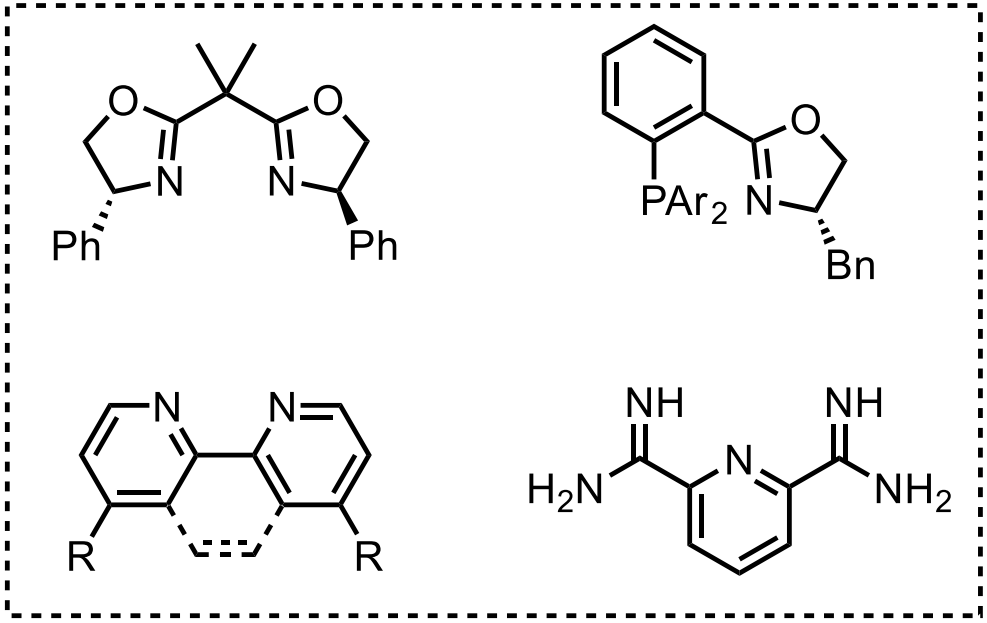




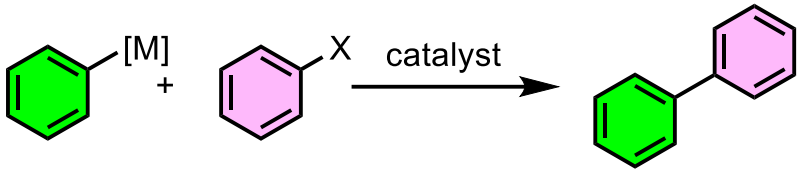
Cross Electrophile Coupling: Mechanistic Insights and Synthetic Application

Jesse Panger

28Sep2021

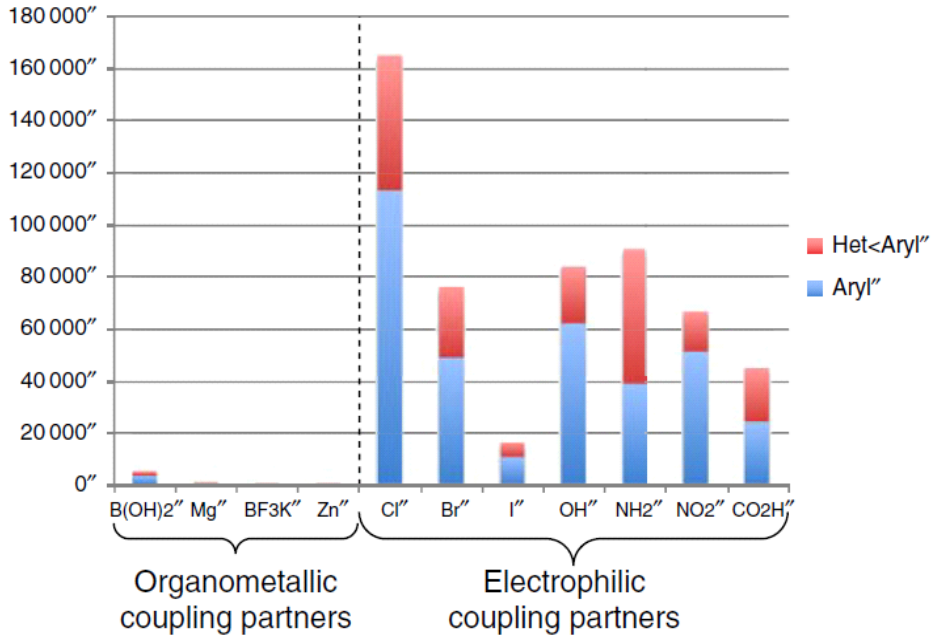
Classical TM Methods & XEC

Conventional Transition Metal Cross-Coupling



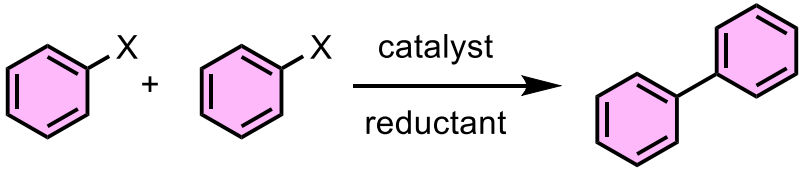
Suzuki (M = BX_2), Negishi (M = ZnX)
Kumada (M = MgX), Stille (M = SnR_3), etc.

√ Well-established
√ Robust, prolific
X Limited commercial availability
X Additional synthetic steps



Traditional TM-catalyzed cross-coupling reactions account for ~11.5% of all C–C bond forming reactions in medicinal chemistry

Cross-Electrophile Coupling



X Recently established (~10 years)
√ Robust, prolific (FG tolerant)
√ Highly commercially available
X Others...?

Note: Reductive cross-coupling (RCC) and Cross electrophile coupling (XEC) are similar but non-equivalent nomenclature.

Goldfogel, M. J.; Huang, L.; Weix, D. J. Cross-Electrophile Coupling: Principles and New Reactions. In *Nickel Catalysis in Organic Synthesis: Methods and Reactions*; Sensuki, O. Ed.; Wiley-VCH Verlag, 2020; pp 183–222.

What is XEC?

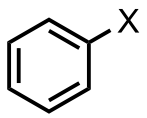
Catalytic method that couples two different carbon electrophiles under reductive conditions

Advantages include…

1) Bench stable coupling partners

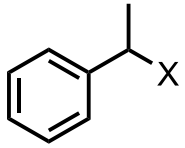
2) Large substrate pools

Aryl (pseudo)halides



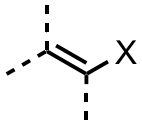
X = Br, I, OTf, OTs, CO_2H, COY

Benzyl (pseudo)halides



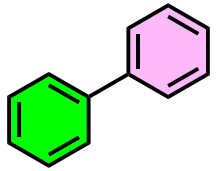
X = Cl (most often)

Vinyl/Alkynyl (pseudo)halides

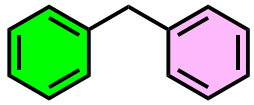


3) Functional group compatibility
   A. –OH, –NHPG, C=O, S^{6+}, β-leaving groups all tolerated
   B. $–N_3$, $–NO_2$ and other reducible functional groups not tolerated

4) Facile synthesis of $C(sp^3)–C(sp^x)$ – complementary to traditional TM methods



$C(sp^2)$-$C(sp^2)$ well-suited for traditional TM methods

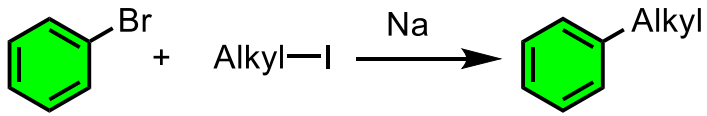


$C(sp^3)$-$C(sp^2)$ well-suited for XEC

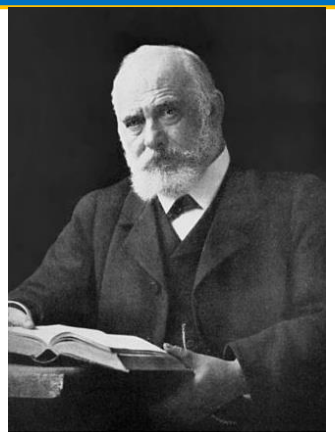
Goldfogel, M. J.; Huang, L.; Weix, D. J. Cross-Electrophile Coupling: Principles and New Reactions. In *Nickel Catalysis in Organic Synthesis: Methods and Reactions*; Sensuki, O. Ed.; Wiley-VCH Verlag, 2020; pp 183–222.

Historical RCC

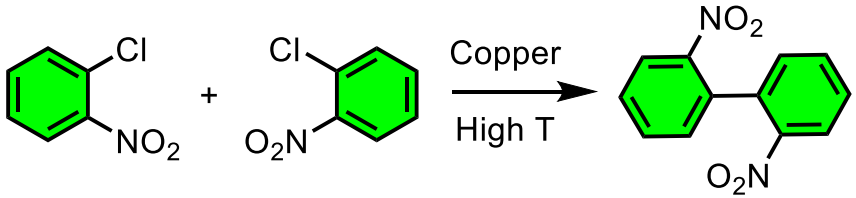
Wurtz - 1855 + Fittig - 1860s



1. Radical and polar mechanisms operative
2. Common mode of off-reactivity in the modern synthetic chemistry

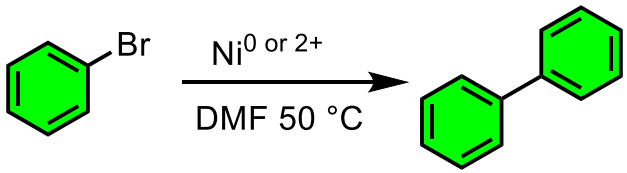


Ullman - 1901



1. Modern developments include Ni or Pd rendering the process more mild
2. Requires electron-deficient arenes

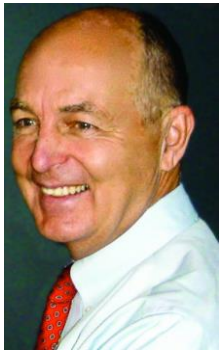
Seminal reports of Ni-Mediated Reductive Homocoupling



Semmelhack - 1971

Kende - 1975

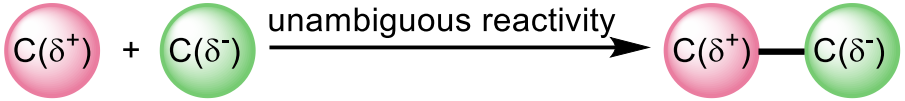
Kumada 1977

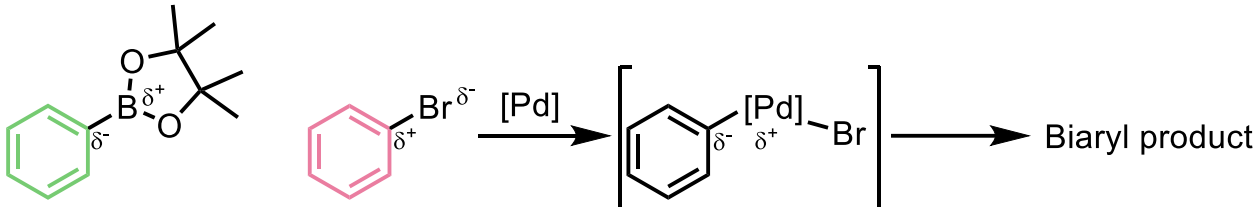


Wang, Z. Wurtz Synthesis. In *Comprehensive Organic Name Reactions and Reagents*; Wiley & Sons 2010; pp 3094–3099.
Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174–2185.

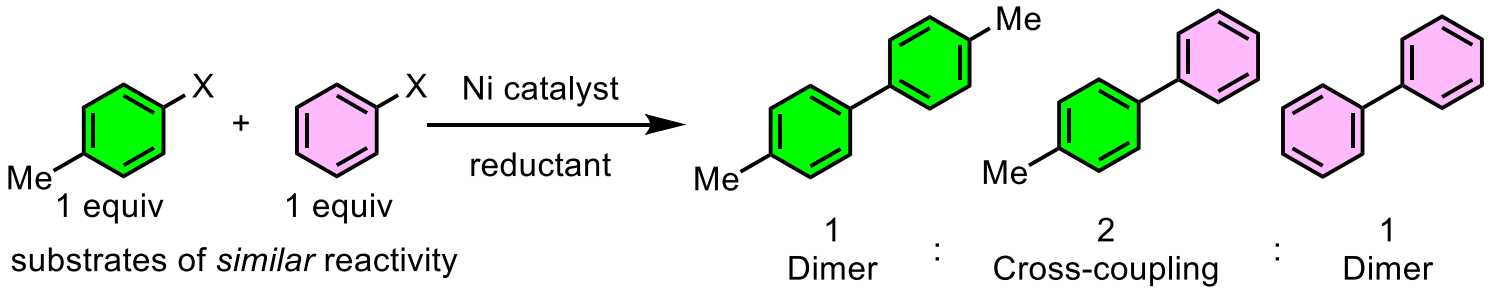
Why Has XEC Been Challenging to Develop?

Classical reactivity:



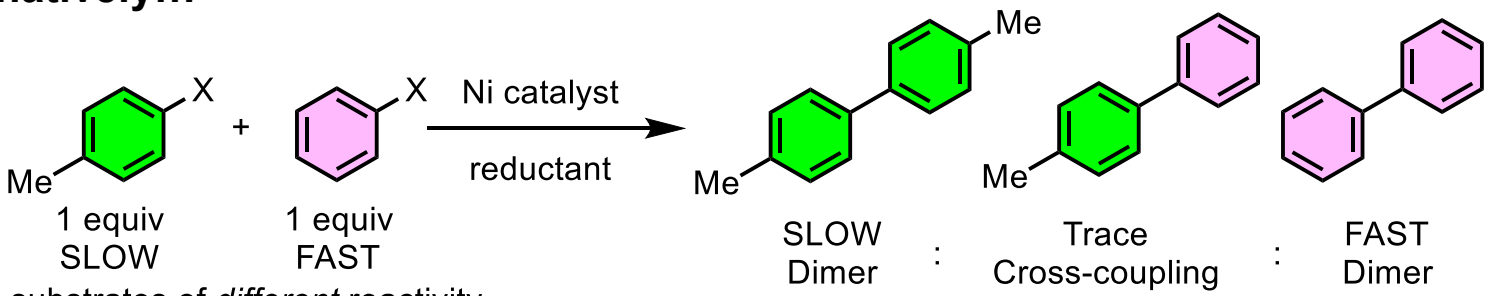


Issues with selectivity:



substrates of *similar* reactivity

Alternatively…

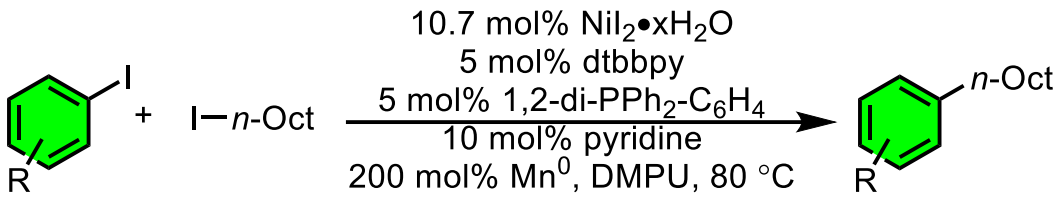


substrates of *different* reactivity

Goldfogel, M. J.; Huang, L.; Weix, D. J. Cross-Electrophile Coupling: Principles and New Reactions. In *Nickel Catalysis in Organic Synthesis: Methods and Reactions*; Sensuki, O. Ed.; Wiley-VCH Verlag, 2020; pp 183–222.

Early Work with General Application

Weix - 2010

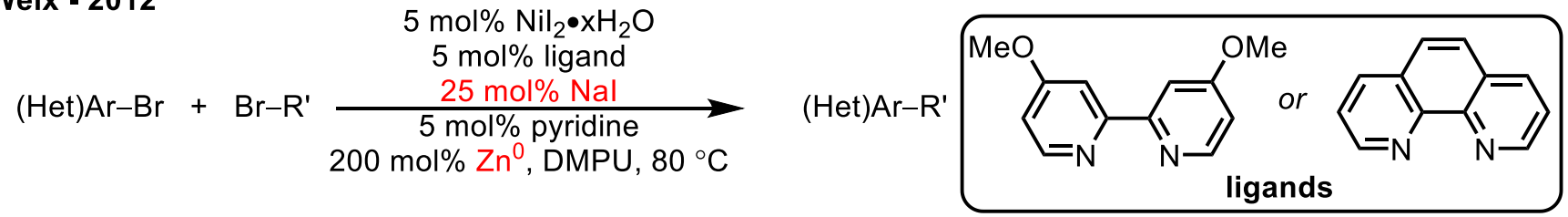


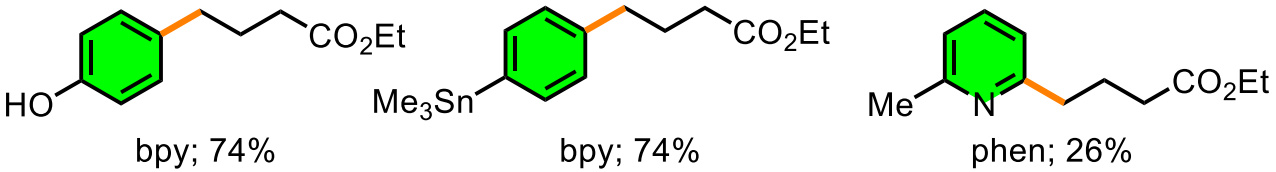
Role of...
Pyridine: mitigate β-hydride elimination
2 ligands: modulate reactivity of nickel

R = BPin, CH_2OH, CN, C(O)Me

Best selectivity when one halide is an iodide

Weix - 2012

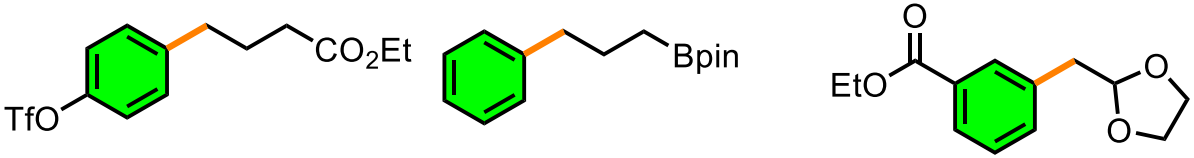




bpy; 74%

bpy; 74%

phen; 26%



phen; 74%

unspecified; 48%

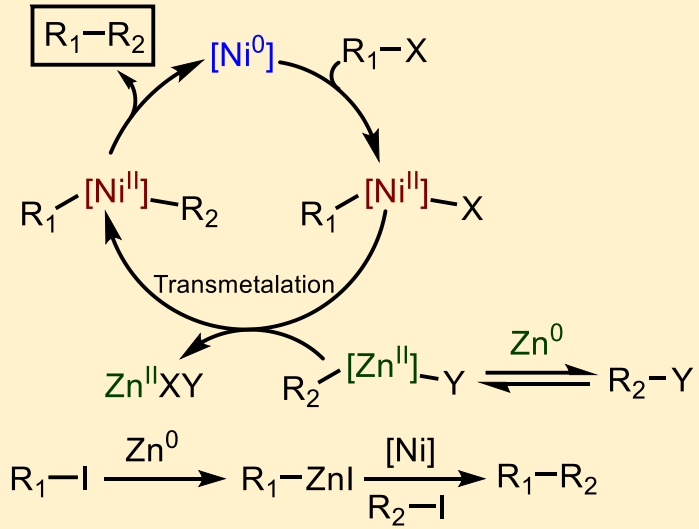
phen; 60%

What potential mechanisms are at play? Are multiple mechanisms operative?

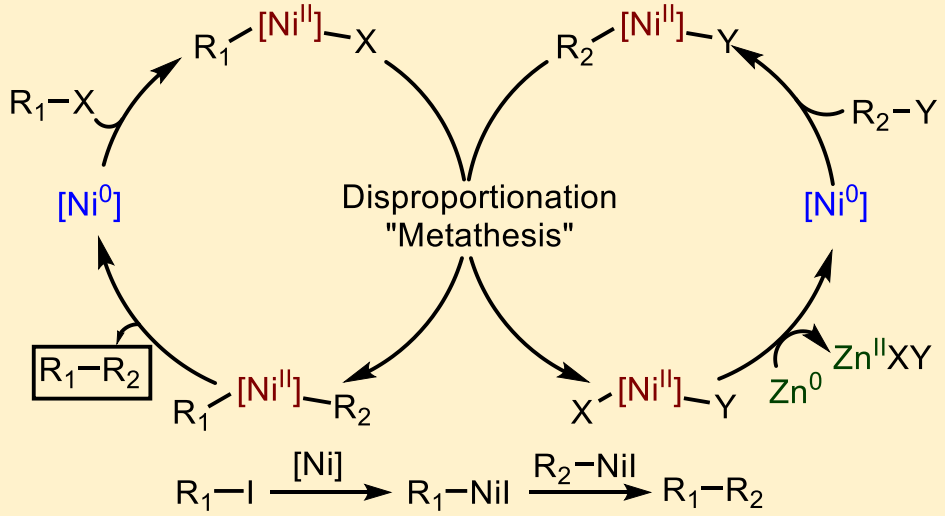
Everson, D. A.; Shrestha, R.; Weix, D. J.; *J. Am. Chem. Soc.* **2010**, *132*, 920–921.

Potential Mechanisms to Consider

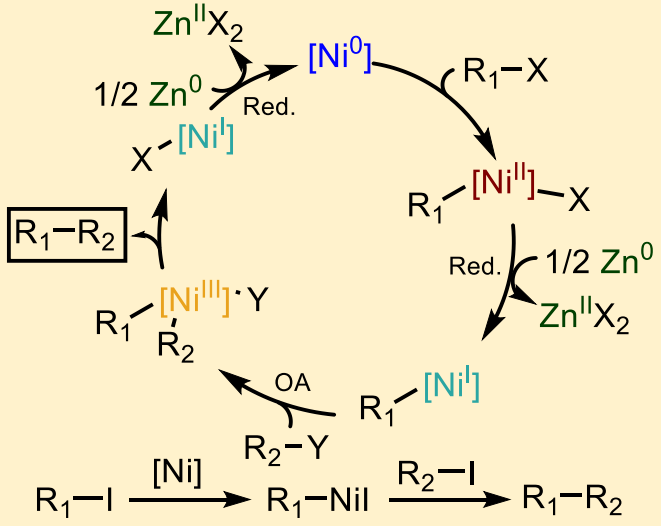
Mechanism 1: Direct Insertion of Reducing Metal



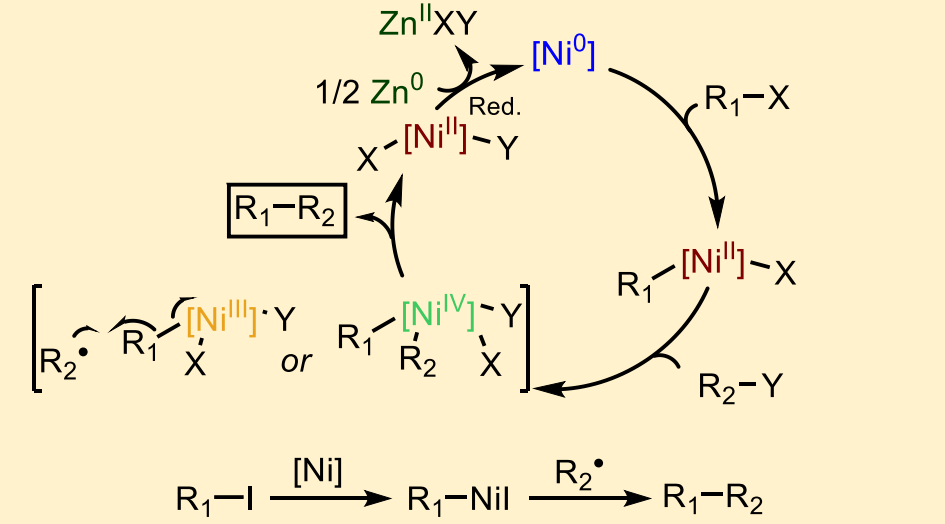
Mechanism 2: Disproportionation of Nickel Intermediates



Mechanism 3: Intermediate Reduction of Nickel



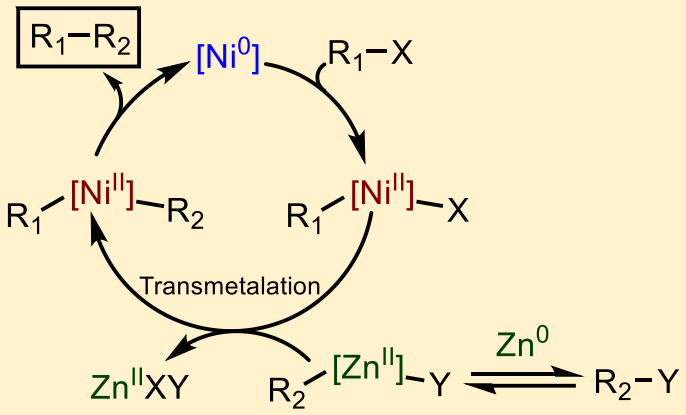
Mechanism 4: Radical Chain



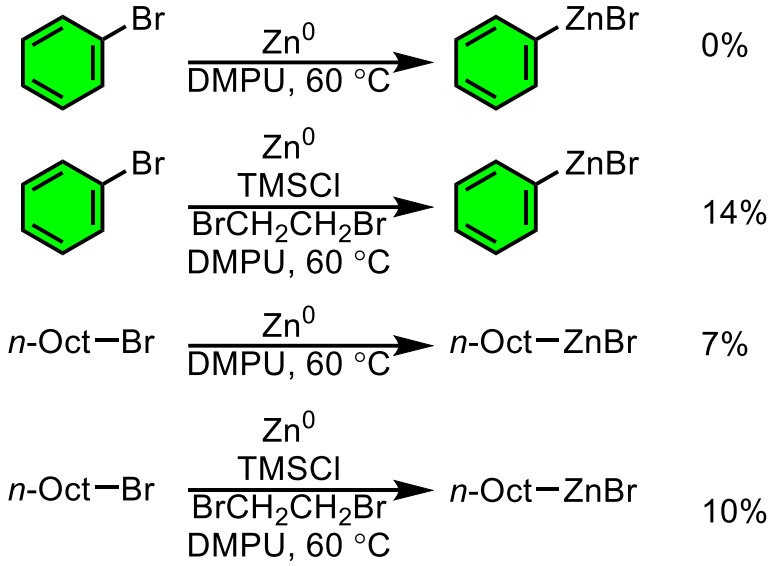
Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159.

Probing Potential Mechanisms: Direct Insertion

Mechanism 1: Direct Insertion of Reducing Metal



Direct Insertion of Reducing Metal

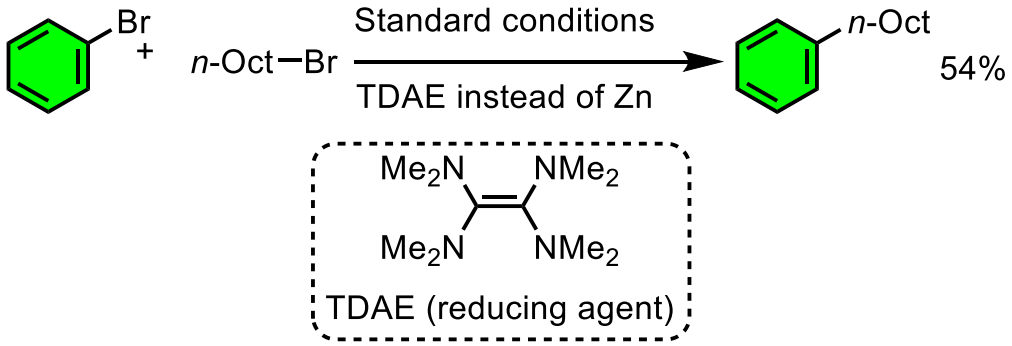


GC yields after 24 h

Further insights…

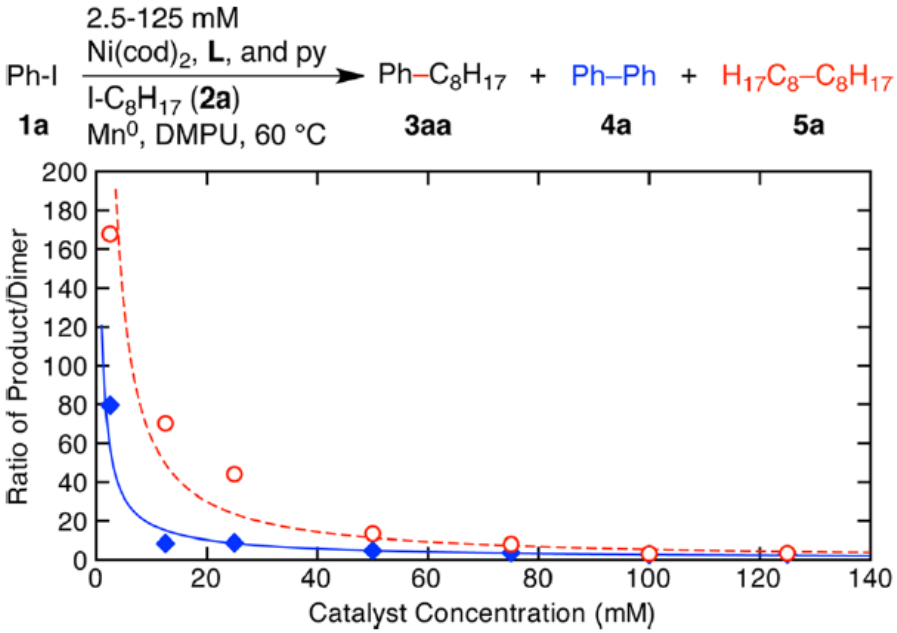
1. Induction period when air present but doesn't affect yield or selectivity
2. Over-activation of zinc leads to hydro-dehalogenated products (rapid Zn insertion)
3. Heterogeneous Zn reduction likely RDS but activated Zn did not lead to faster rate indicating new turnover-limiting step

Conclusion: RCC much faster than Zn insertion

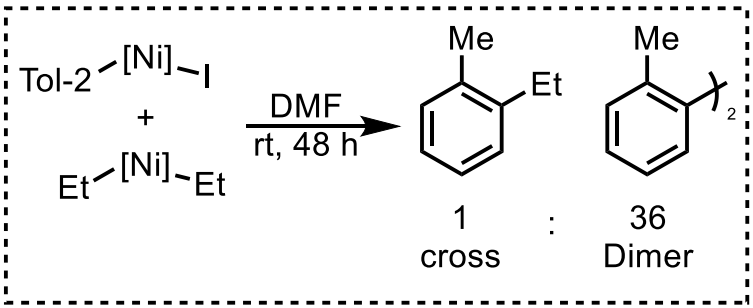


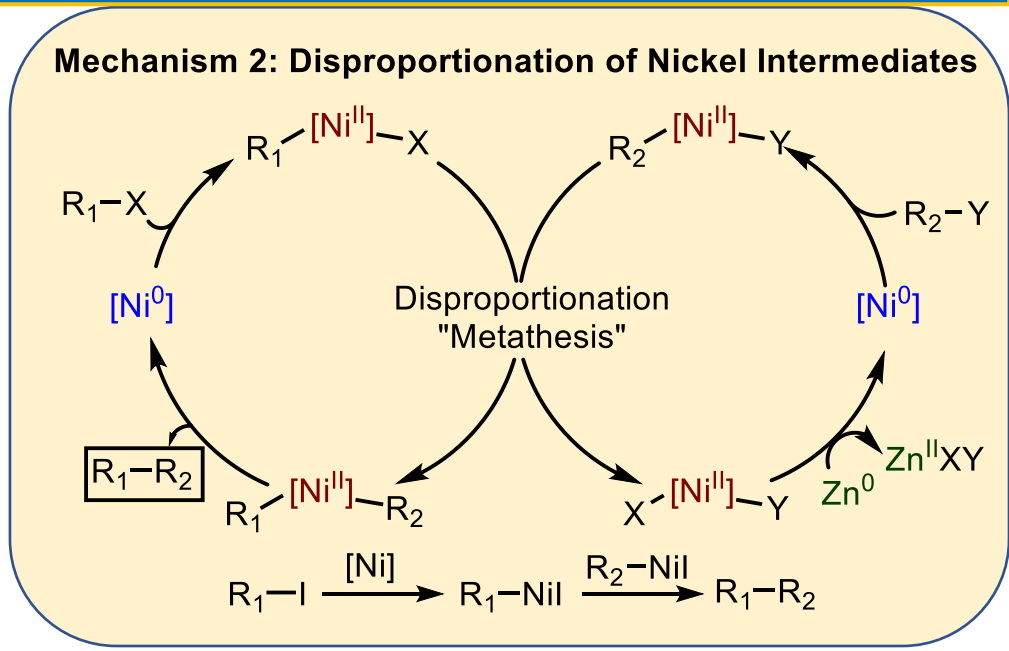
Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159.
Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.

Probing Potential Mechanisms: Disproportionation



If mechanism follows disproportionation, a molar ratio of product/dimer vs. [Ni] would give a straight, horizontal line.





Conclusions:

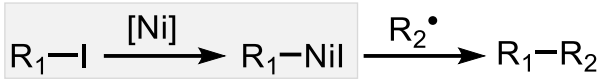
1. Preformed nickel complexes show little metathesis
2. Biaryl formation (dimer) has 2nd order dependence on [Ni]
3. Cross coupling has ~1st order dependence on [Ni]

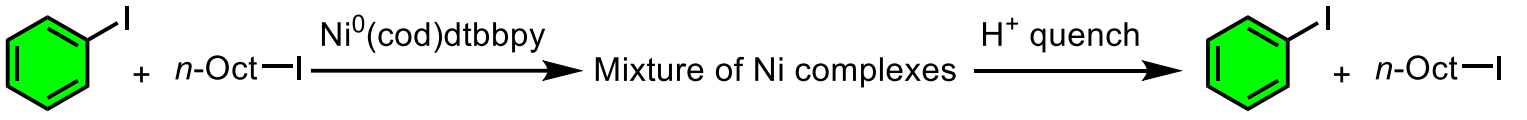
Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.

Probing Potential Mechanisms: Intermediate Reduction or Radical Chain?

Intermediate Reduction

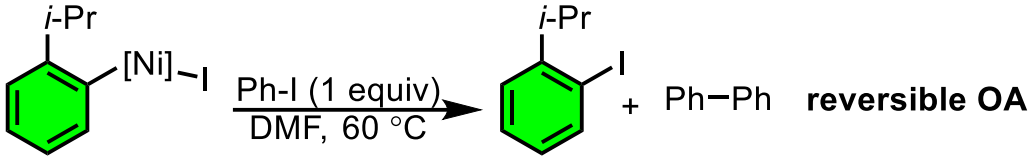
Radical Chain





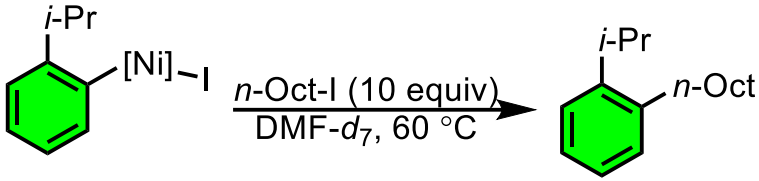
89% conv. 19% conv.

~5x rate difference



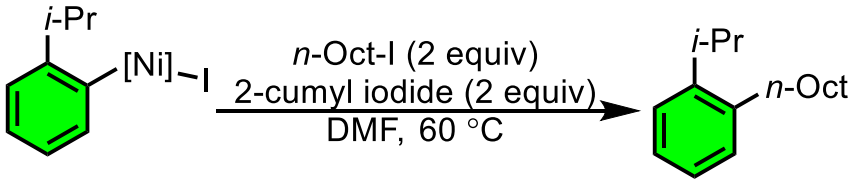
reversible OA

65% quant.



quant.; 99% cross-selective

Still can't say anything about the 2nd step



56% yield; >99% cross-selective

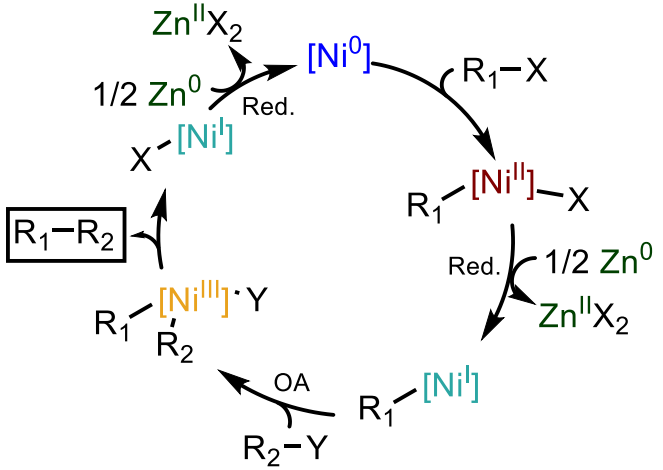
X = I	14	:	1
X = *n*-Oct	270	:	1

First step likely OA into Ar-X

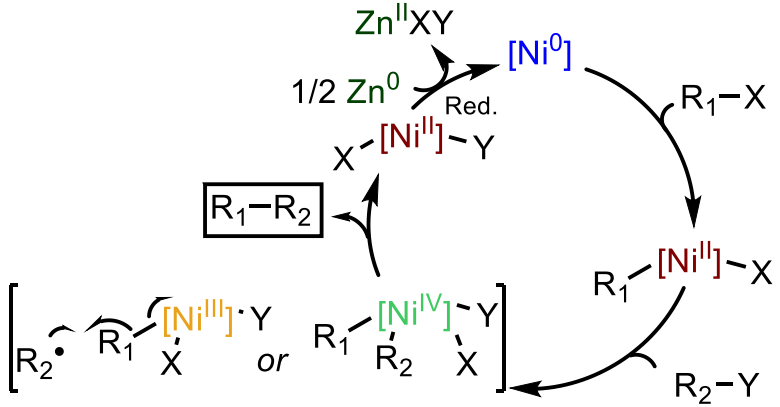
Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.

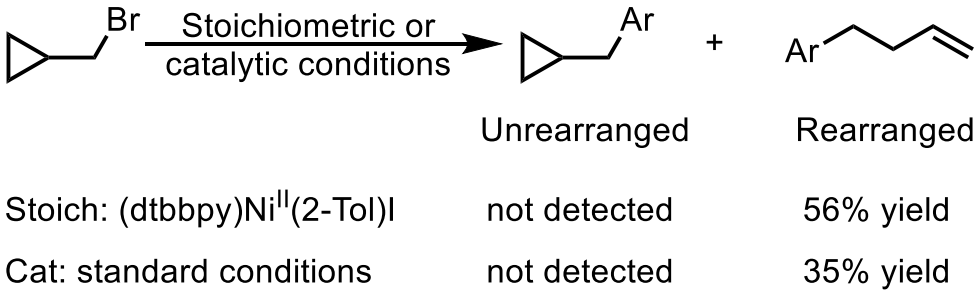
Probing Potential Mechanisms: Intermediate Reduction or Radical Chain?

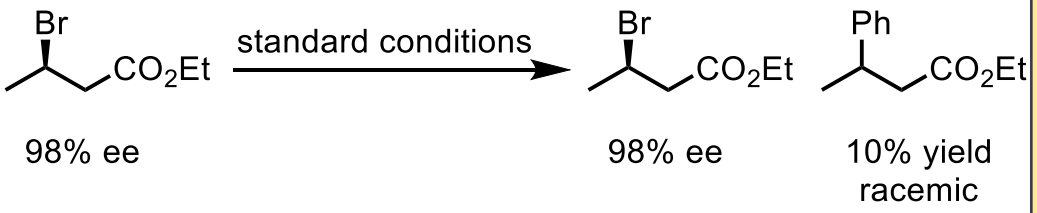
Mechanism 3: Intermediate Reduction of Nickel



Mechanism 4: Radical Chain





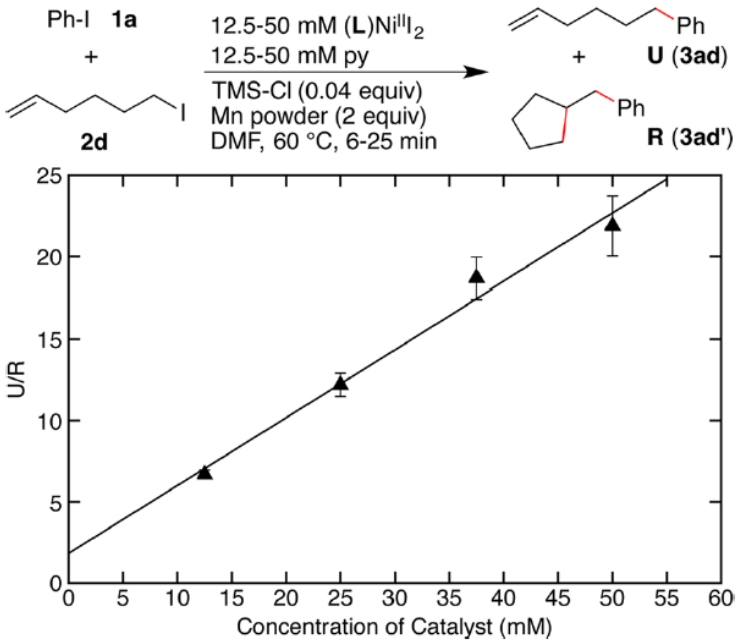


- Both mechanisms can have alkyl radical intermediates
  - In mechanism 3 the radical would be generated and consumed at the same nickel center providing a net oxidative addition.
  - In mechanism 4, the radical is generated and consumed at different nickel centers.

Only in mechanism 4 would the radical lifetime depend on nickel concentration.

Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.

Probing Potential Mechanisms: Radical Intermediates

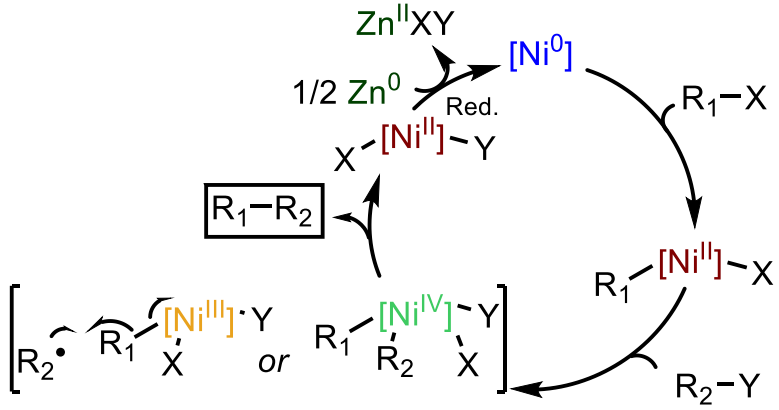


Note: 5-hexenyl radical rearranges more slowly than cylopropylmethyl radical

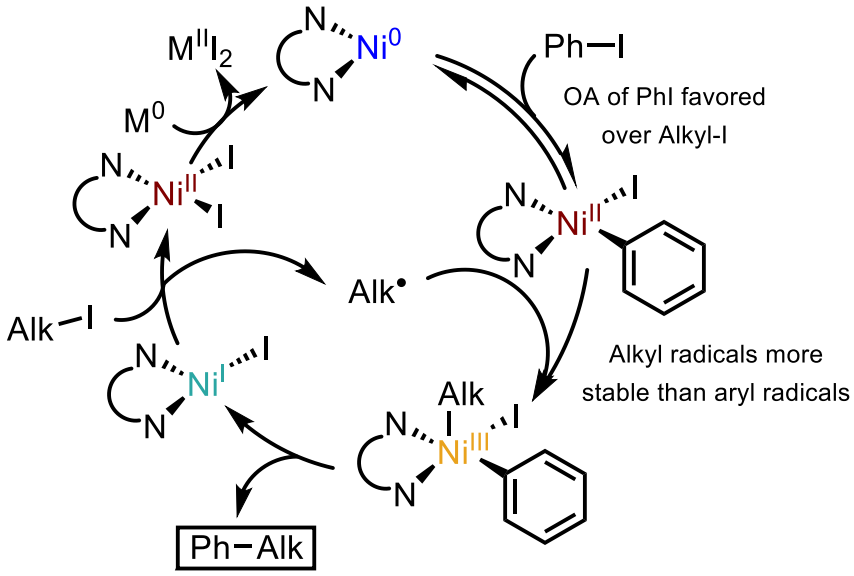
Conclusion: Data supports mechanism 4:

1. Initial OA into Ar-X
2. Alkyl-I reacts stoichiometrically with Ar-Ni^{II}-I without reductant
3. Alkyl Ni^{II} intermediate does not react with Aryl Ni^{II} intermediate
4. Alkyl radical generated with lifetime inversely dependent on catalyst concentration

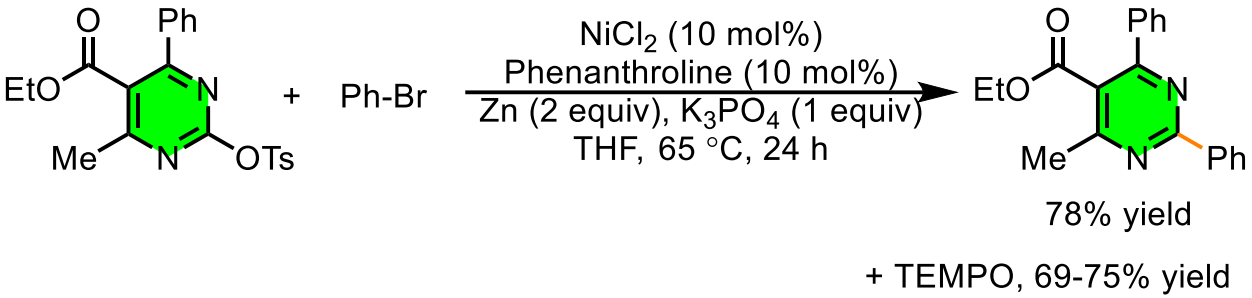
Initially proposed mechanism

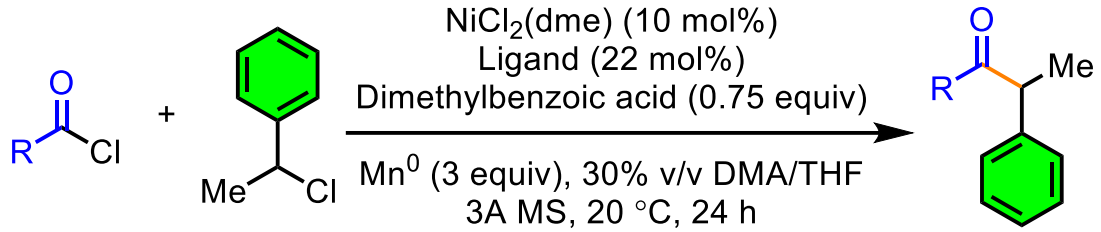


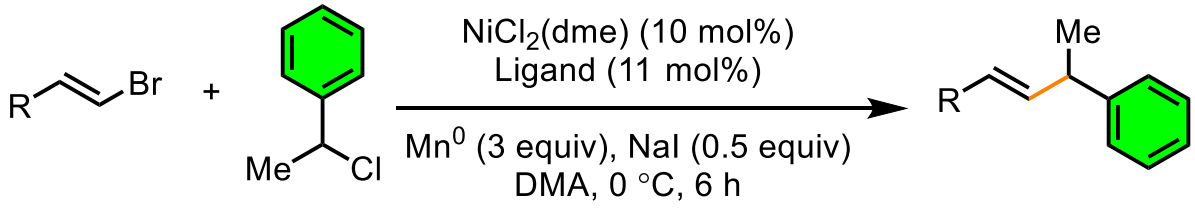
Revised mechanism

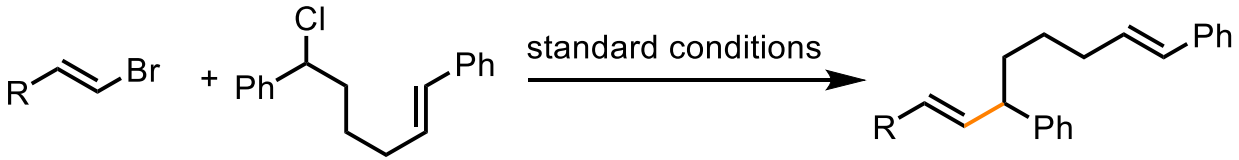


Story Shut on the Mechanism of XEC/RCC?

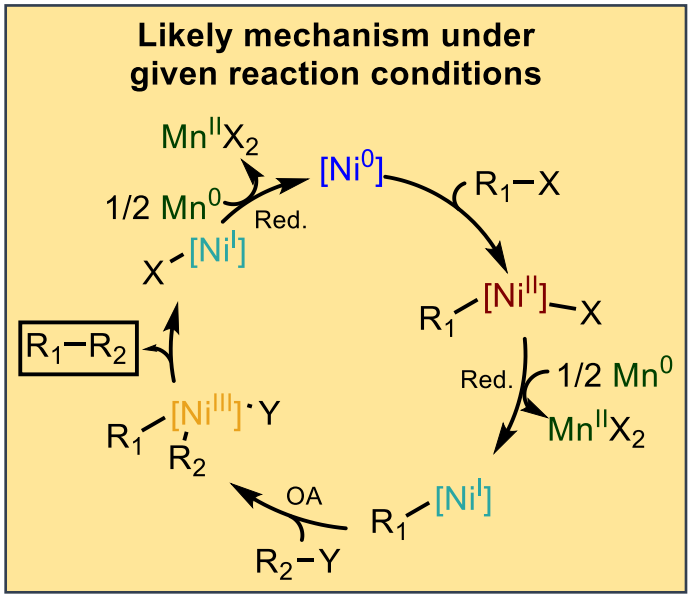






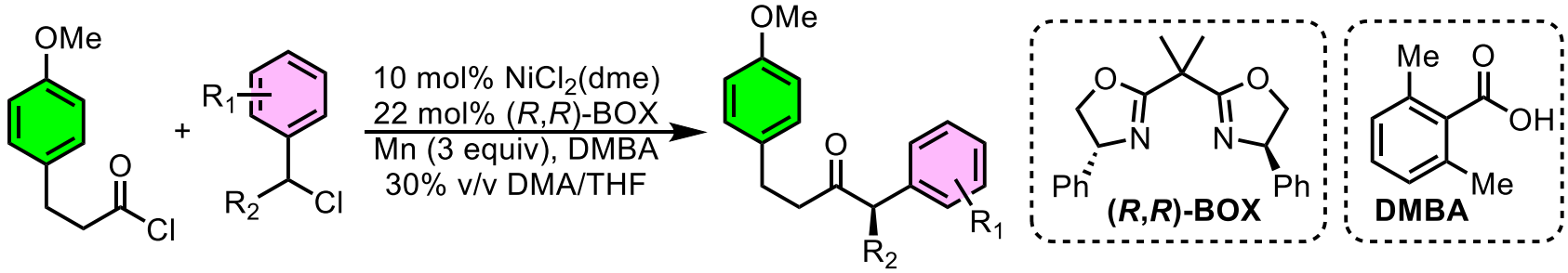


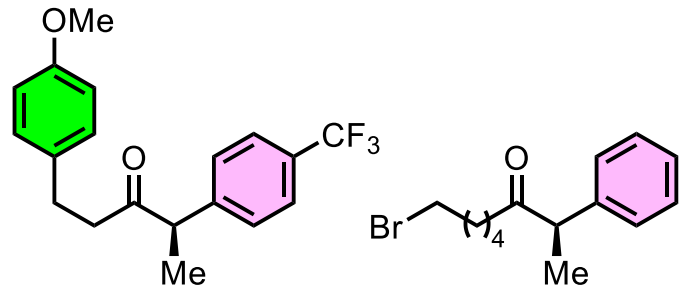
62% yield
no radical cyclization detected

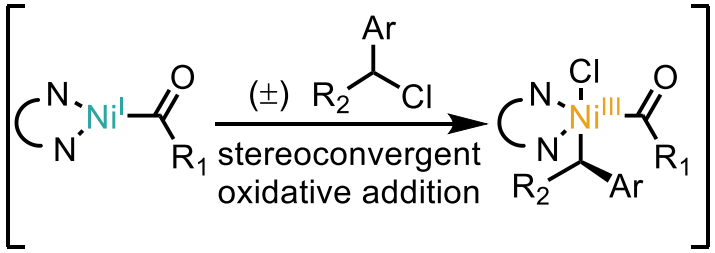


Gong, C.; Huo, C.; Wang, X.; Quan, Z. *Chin. J. Chem.* **2017**, *35*, 1366–1370. Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442–7445. Cherney, A.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, 136, 14365–14368.

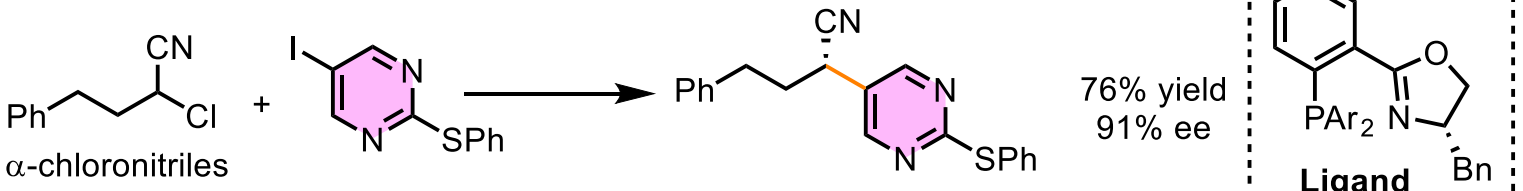
Enantioconvergent XEC



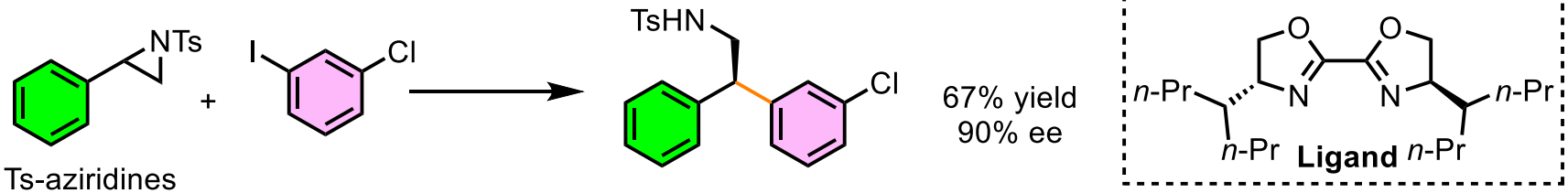




Reisman - 2015



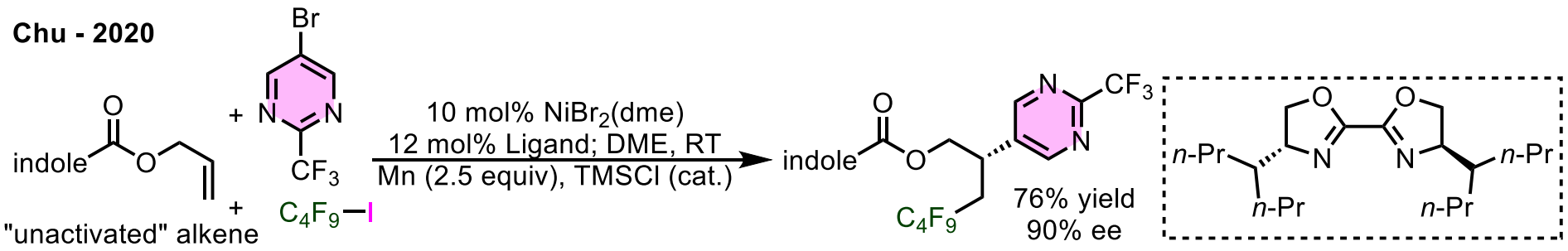
Sigman & Doyle - 2017

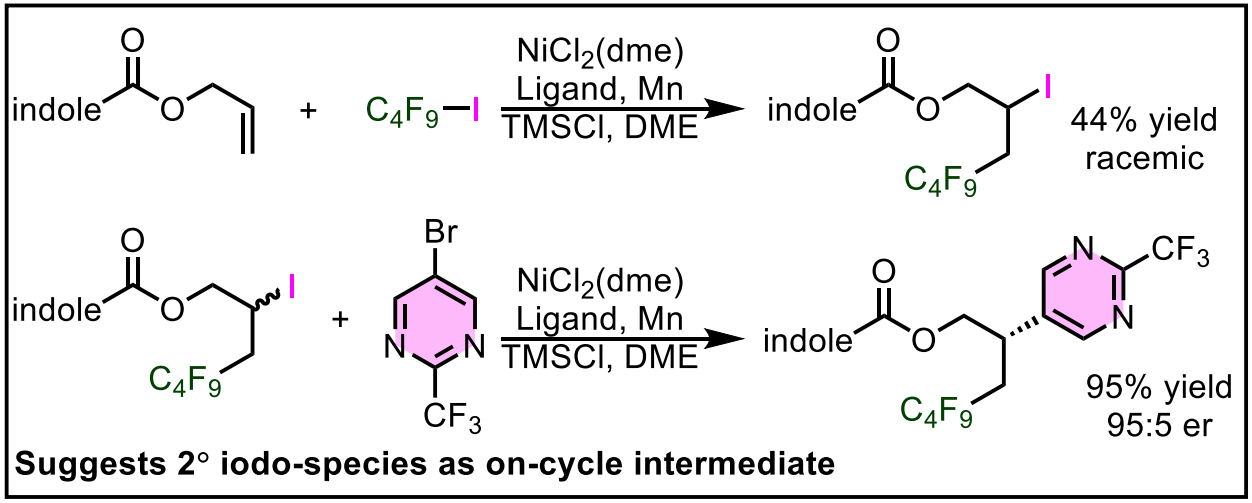


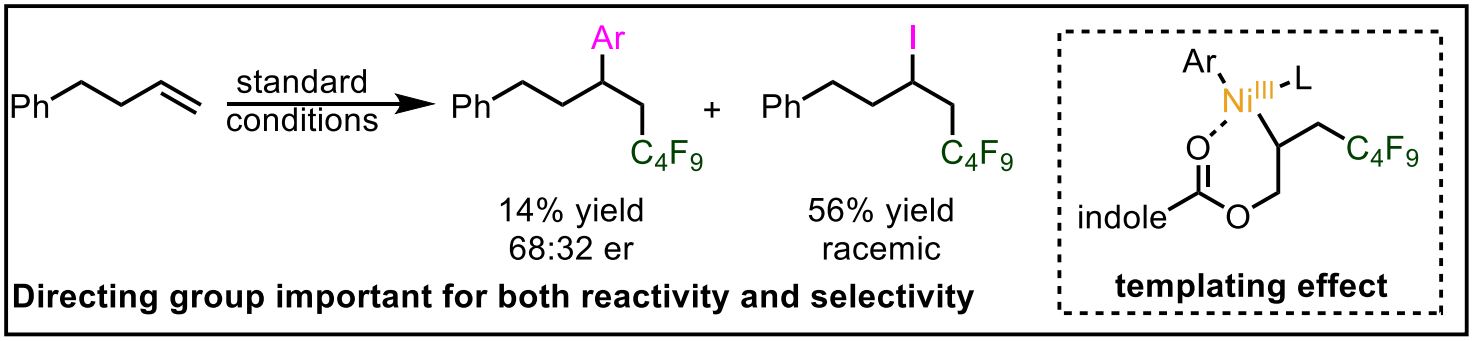
Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442–7445. Woods, B. P.; Orlandi, M.; Huang, C.-Y.; Sigman, M. S.; Doyle, A. G. *J. Am. Chem. Soc*. **2017**, *139*, 5688−5691. Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480−10483.

Enantioselective XEC: Dicarbofunctionalization

Chu - 2020

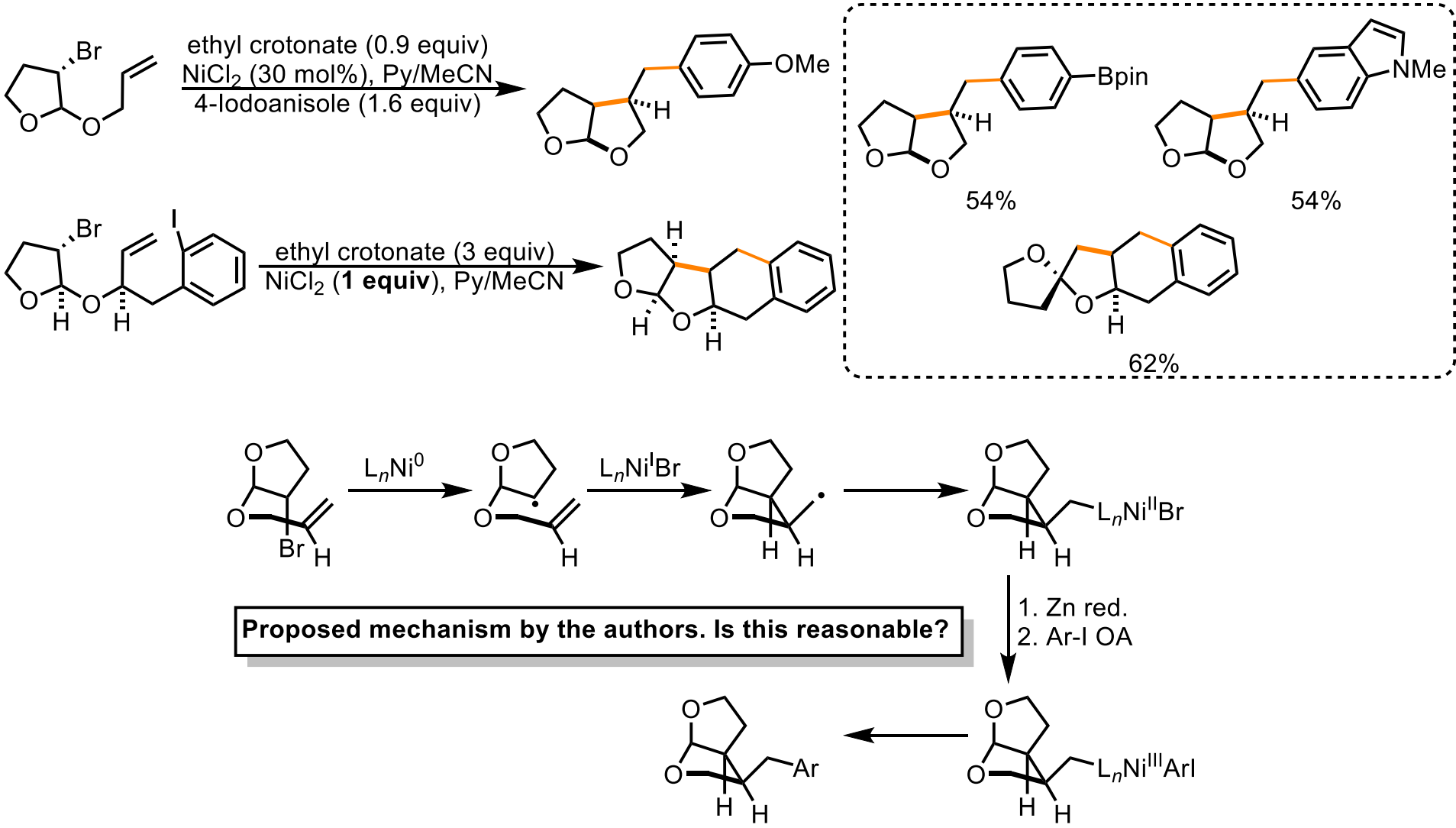






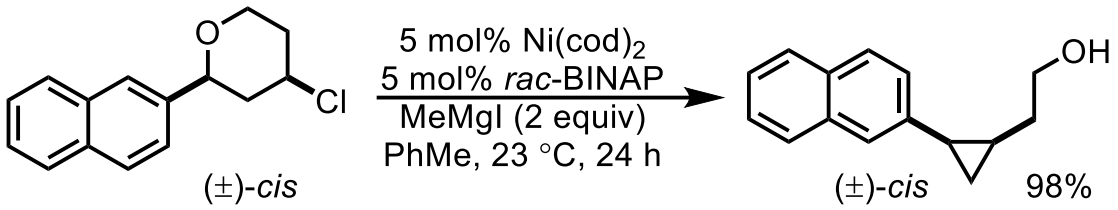
Tu, H. Y.; Wang, F.; Hou, L.; Li, Y.; Zhu, S.; Zhao, X.; Li, H.; Qing, F. L.; Chu, L. *J. Am. Chem. Soc.* **2020**, *142*, 9604−9611.

Intramolecular XEC: Limited Examples

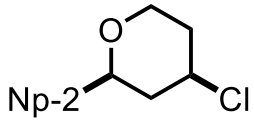


Yan, C.-S.; Peng, Y.; Xu, X.-B.; Wang, Y.-W. *Chem. Eur. J.* **2012**, *18*, 6039–6048.

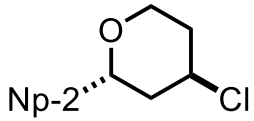
Intramolecular XEC: Stereospecific Cyclopropane Synthesis



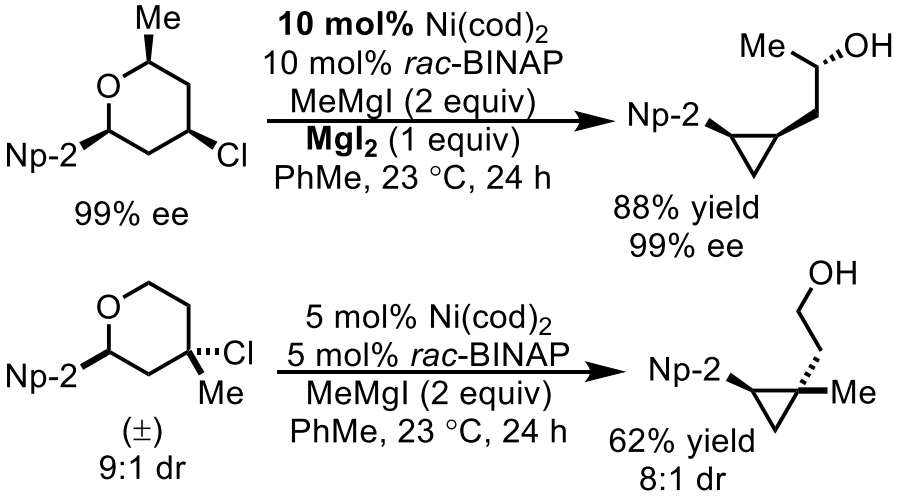
Substrate controlled stereospecificity

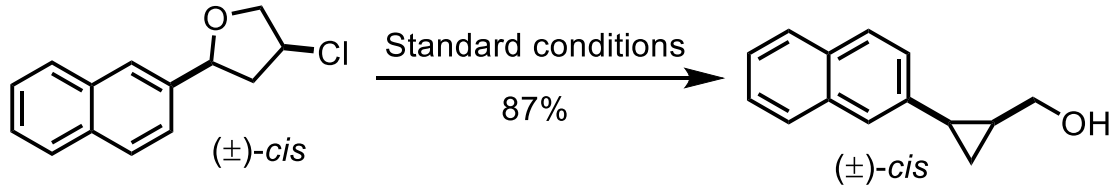


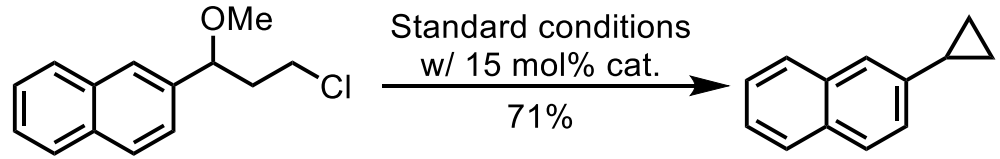
rac-BINAP
(*R*)-BINAP
(*S*)-BINAP → ≥95% yield, >20:1 dr



rac-BINAP
(*R*)-BINAP
(*S*)-BINAP → ≥96% yield, 1:20 dr

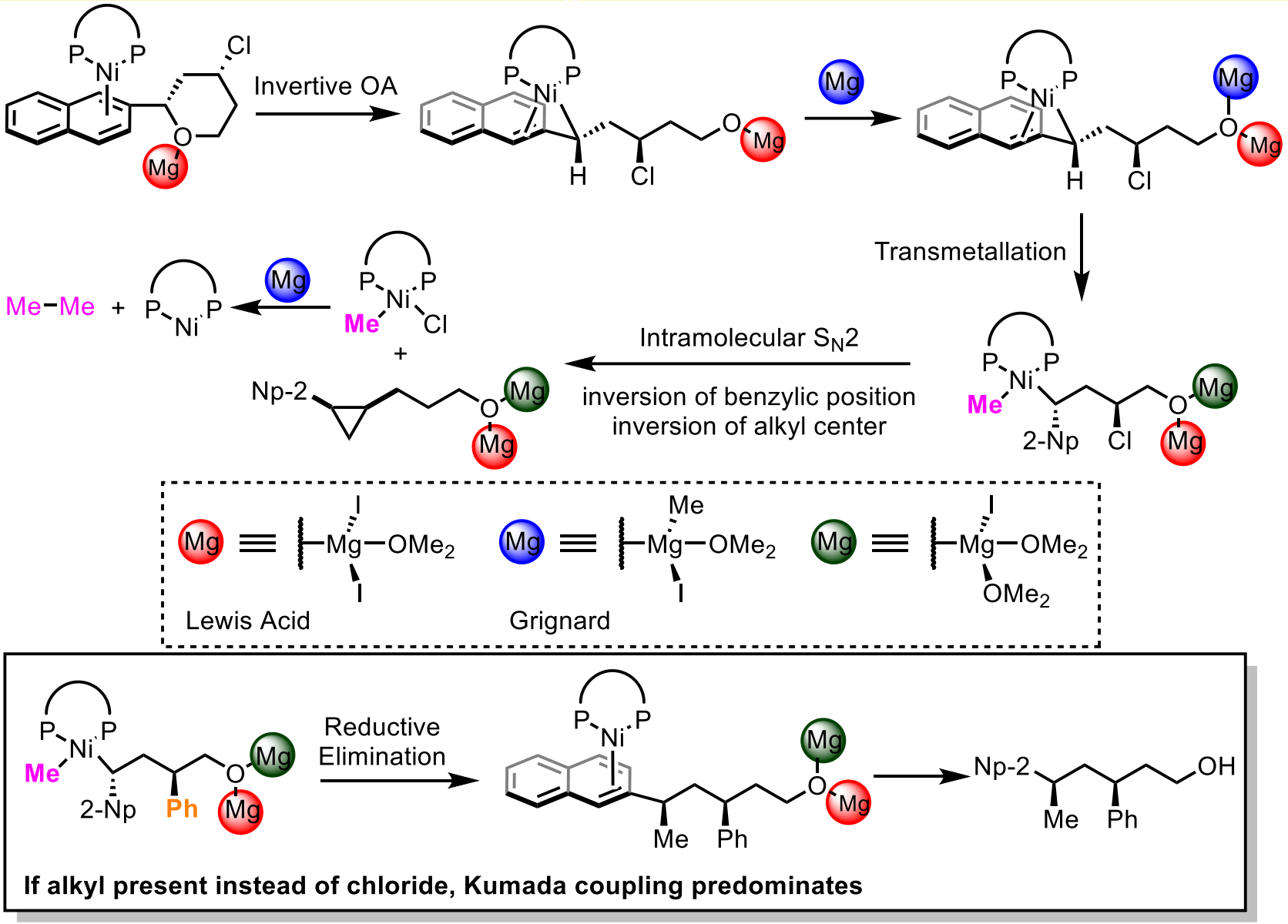






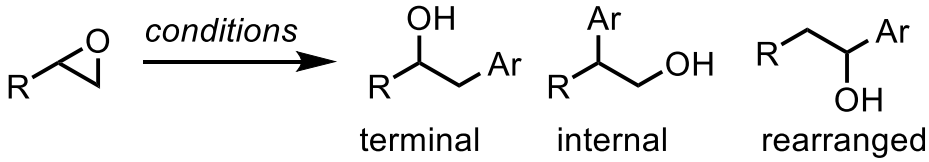
Tollefson, E. J.; Erickson, L. W.; Jarvo, E. R. *J. Am. Chem. Soc.* **2015**, *137*, 9760–9763. Chen, P.-P.; Lucas, E. L.; Greene, M. A.; Zhang, S.-Q.; Tollefson, E. J.; Erickson, L. W.; Taylor, B. L. H.; Jarvo, E. R.; Hong, X. *J. Am. Chem. Soc.* **2019**, *141*, 5835–5855.

Intramolecular XEC: Stereospecific Cyclopropane Synthesis

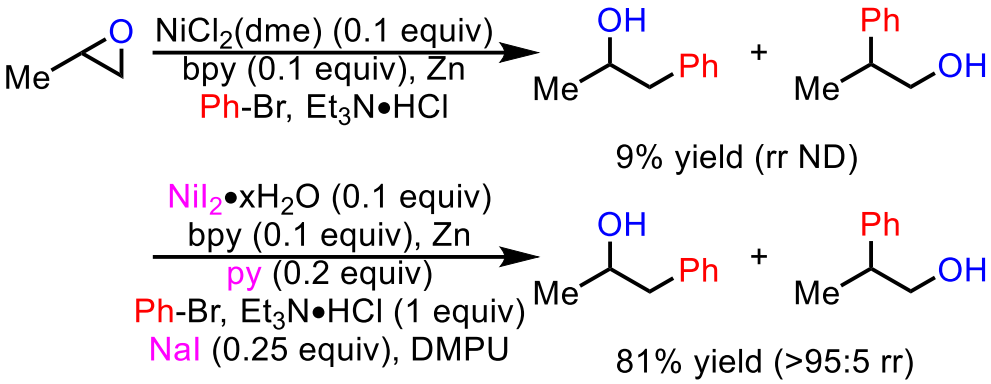


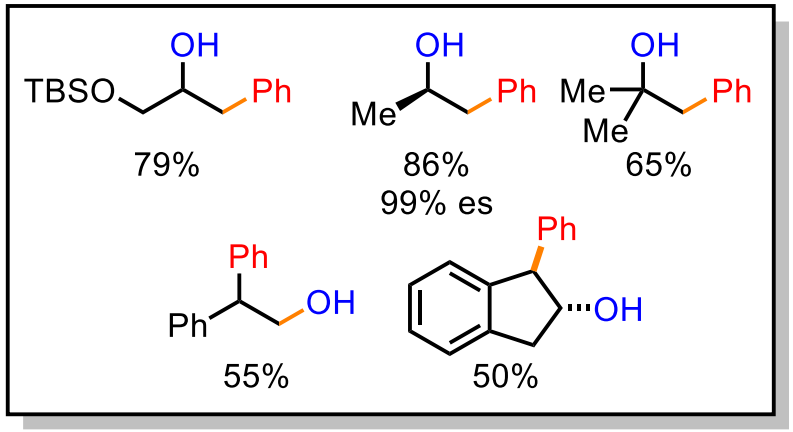
Tollefson, E. J.; Erickson, L. W.; Jarvo, E. R. *J. Am. Chem. Soc.* **2015**, *137*, 9760–9763. Chen, P.-P.; Lucas, E. L.; Greene, M. A.; Zhang, S.-Q.; Tollefson, E. J.; Erickson, L. W.; Taylor, B. L. H.; Jarvo, E. R.; Hong, X. *J. Am. Chem. Soc.* **2019**, *141*, 5835–5855.

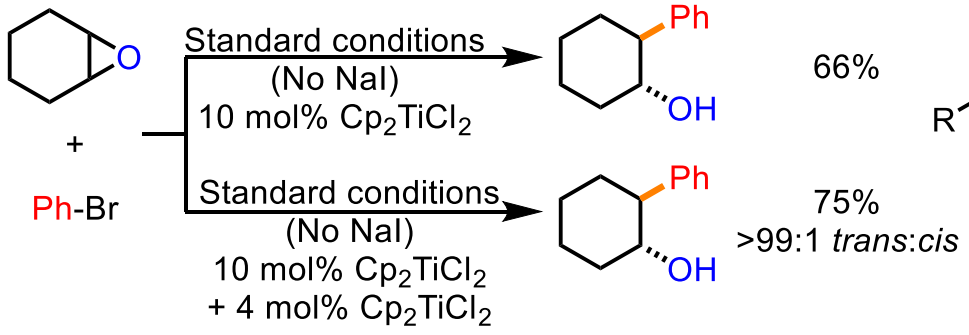
Epoxides as Electrophiles in XEC

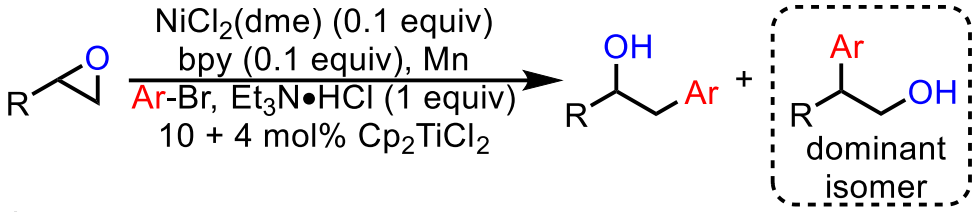


Coupling of simple aryl groups less precedented than one might imagine







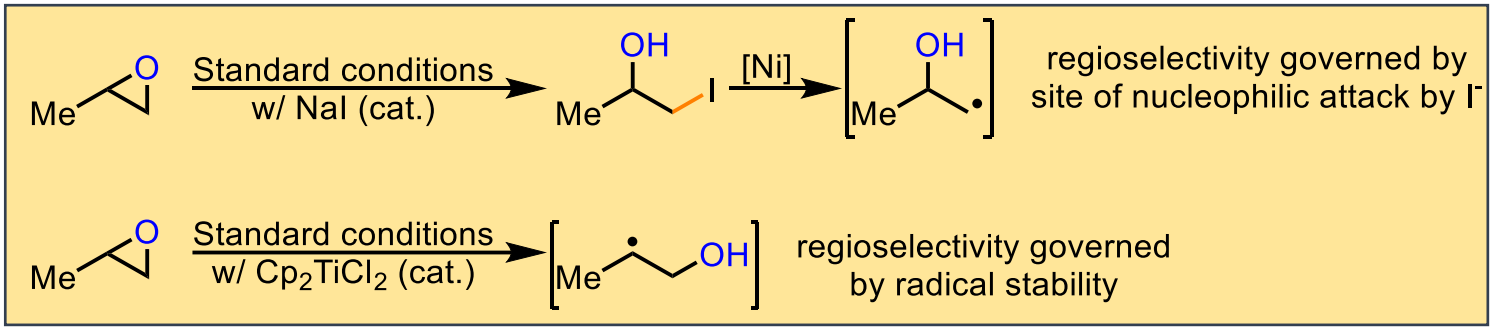


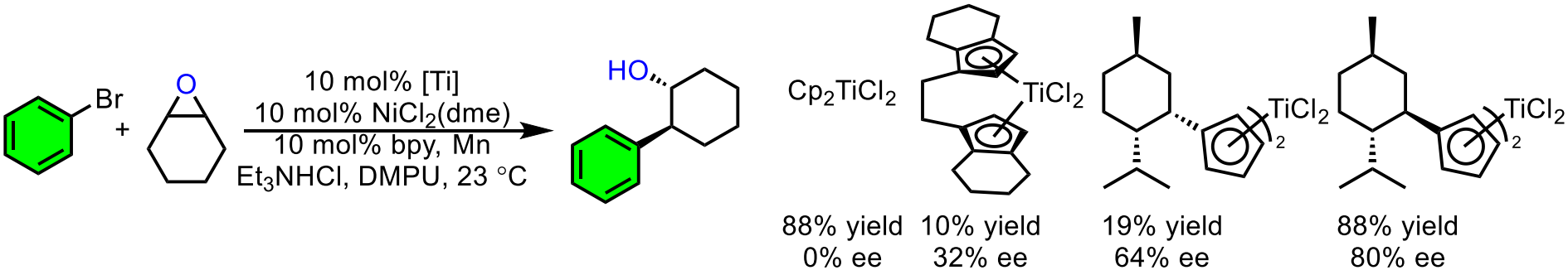
Between 3.3:1 and 99:1 selectivity for linear product

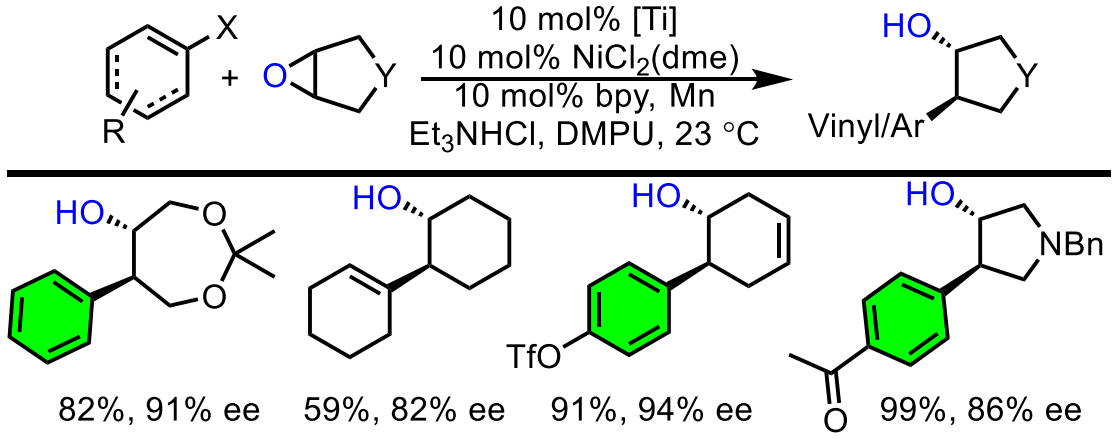
How does this process become regiodivergent depending on co-catalyst?

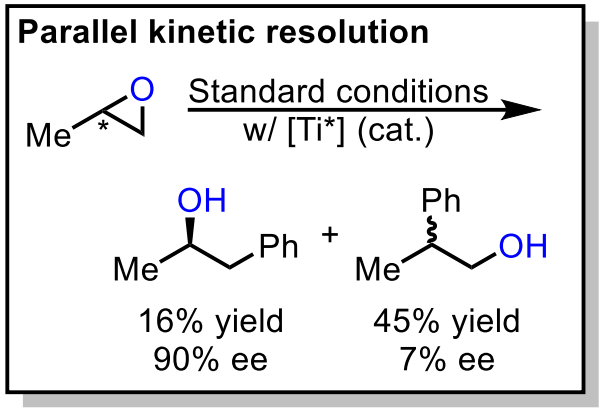
Zhao, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 48–51.

Regiodivergency & Parallel Kinetic Resolution



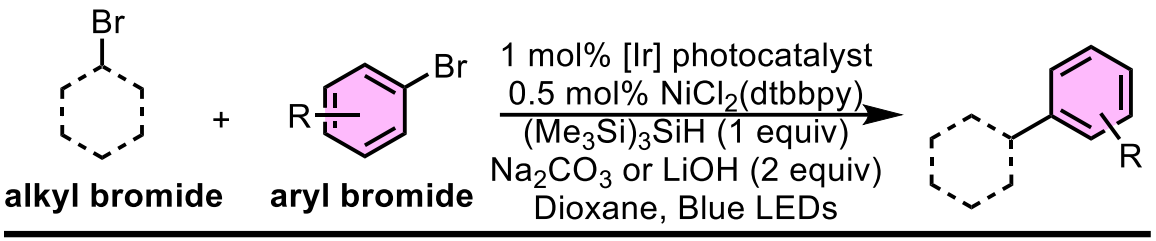


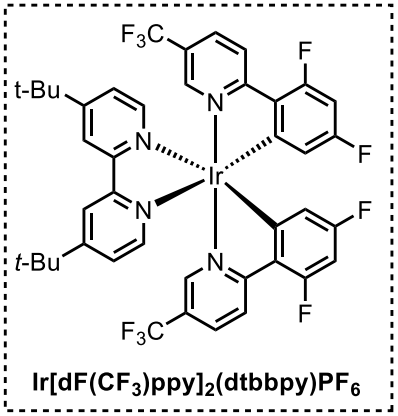


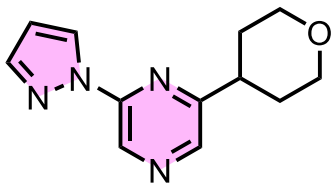


Zhao, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 3237–3240.
Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584–2585.

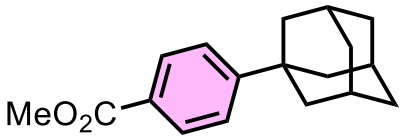
Photocatalytic Reductions



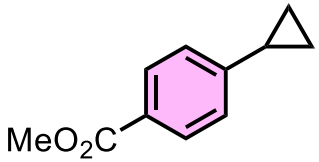




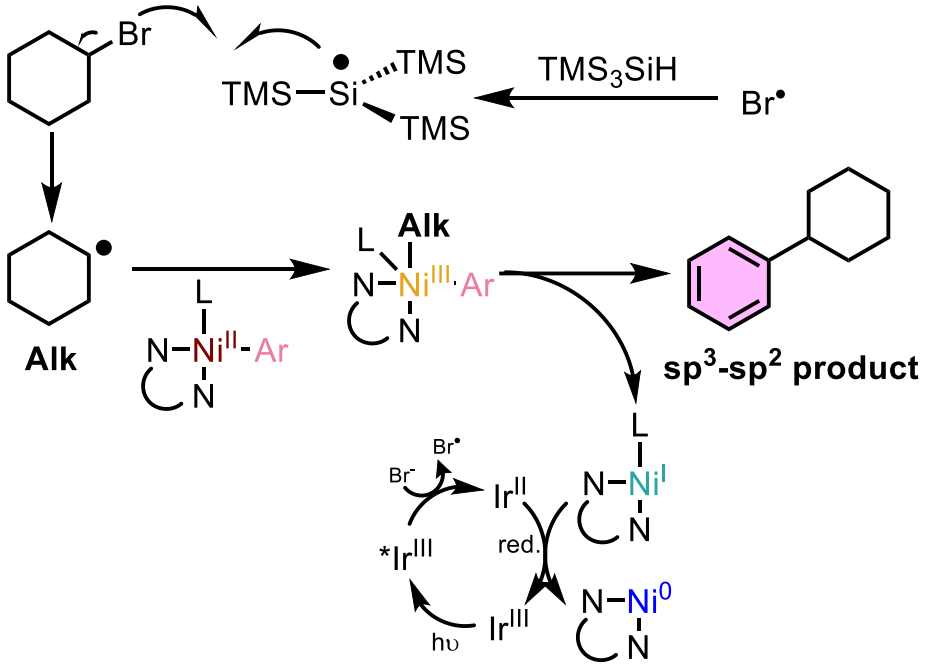
86%



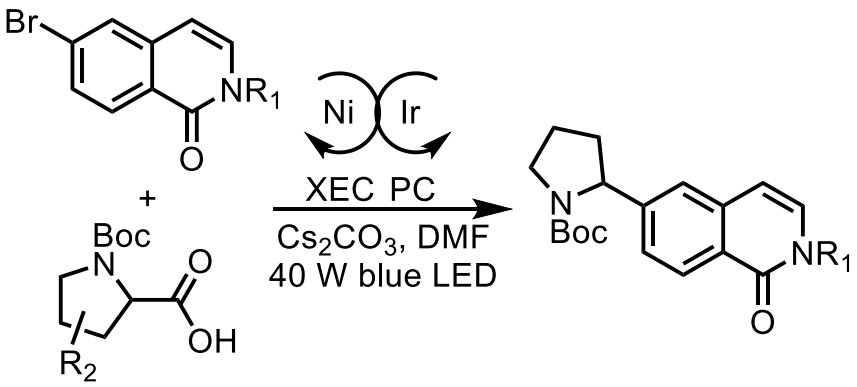
62%



32%

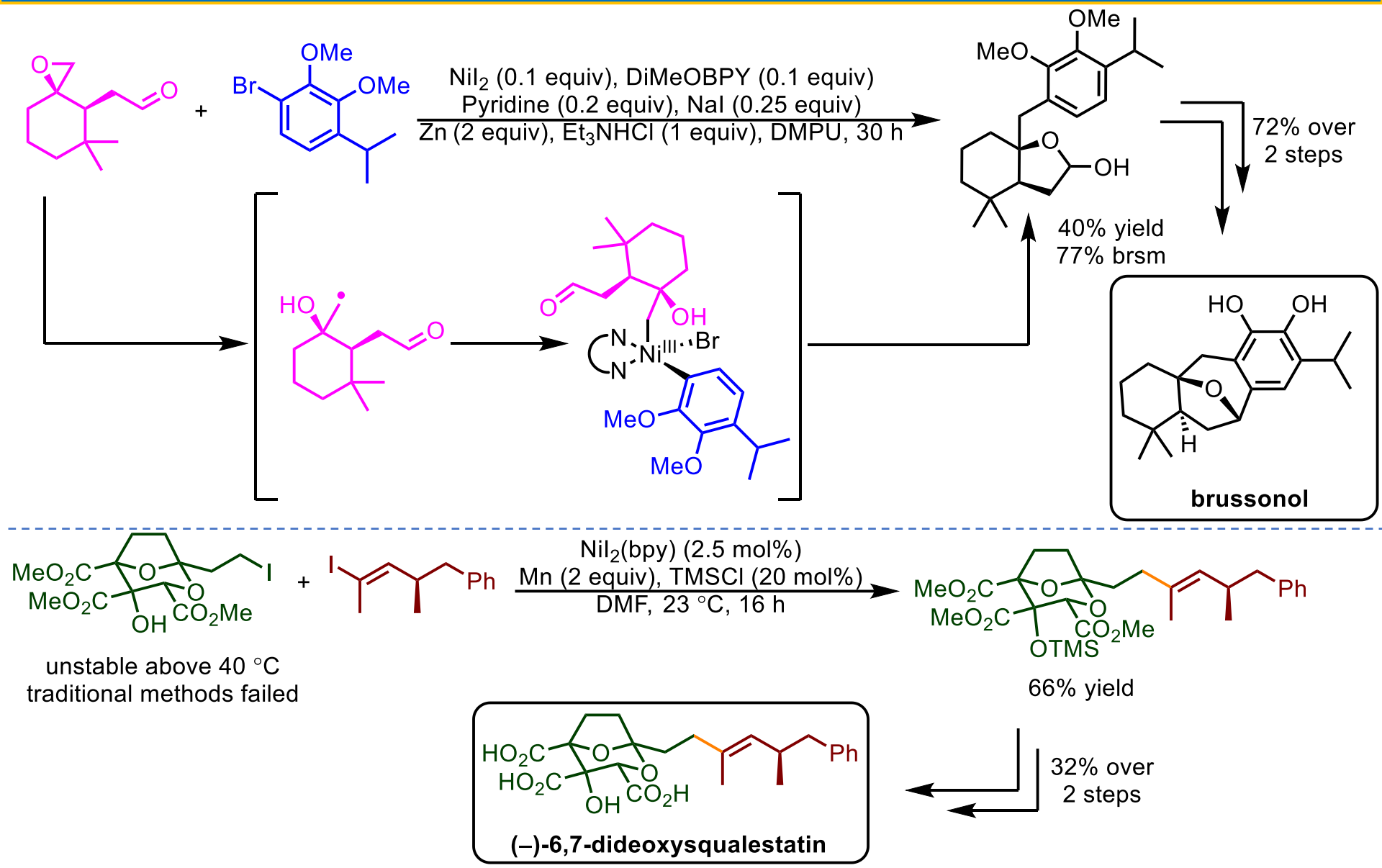


Similar conditions have been developed with concomitant decarboxylation



Zhang, P.; Le, C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 8084–8087.
Dumas, A.; Garsi, J.-B.; Poissonnet, G.; Hanessian, S. *ACS Omega* **2020**, *5*, 27591–27606.

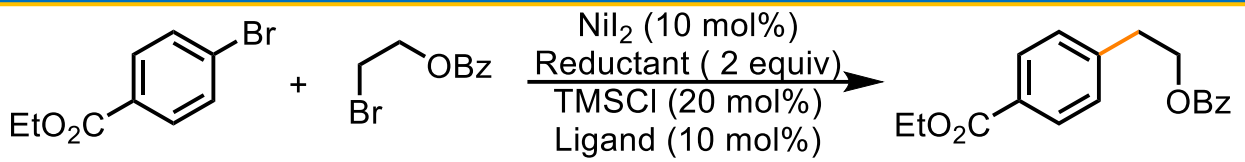
XEC in Total Synthesis



Ahmad, A.; Burtoloso, A. C. B. *Org. Lett.* **2019**, *21*, 6079–6083.

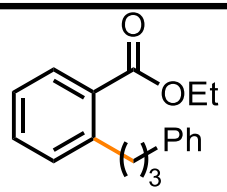
Fegheh-Hassanpour, Y.; Arif, T.; Sintim, H. O.; Al Mamari, H. H.; Hodgson, D. M. *Org. Lett.* **2017**, *19*, 3540–3543.

Unique Ligand Design for Challenging Couplings

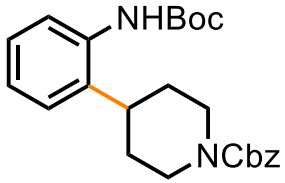


Screened with 45 commercial amines, phosphines, and carbenes under standard conditions

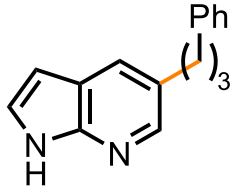
dmbpy = 82% yield
all screened ligands ≤52%



39%



1%



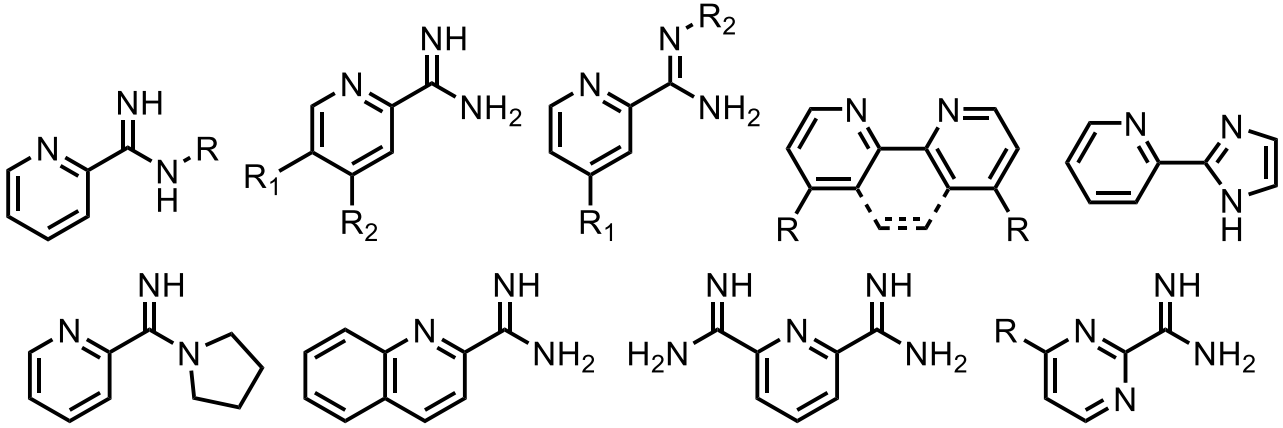
20%

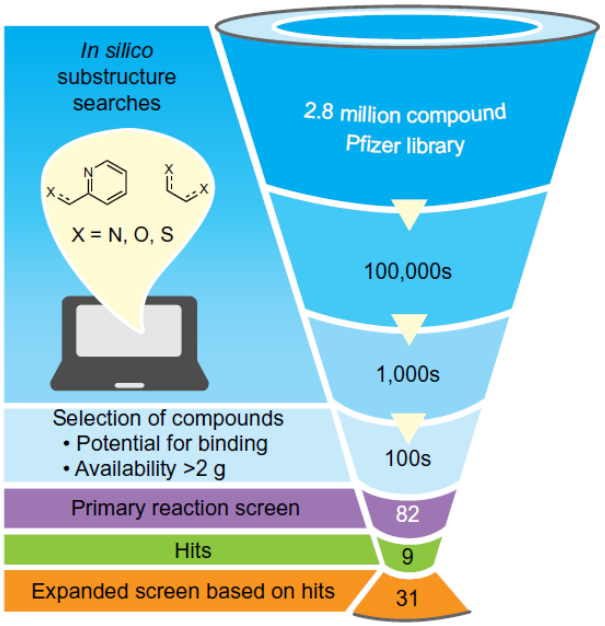
dmbpy does not provide significant product formation

Screen refinement initially parametrized by 2-pyridyl-C(X)

- Strem has 25 commercial ligands with this motif
- Pfizer has >1,500 compounds (>2 grams)

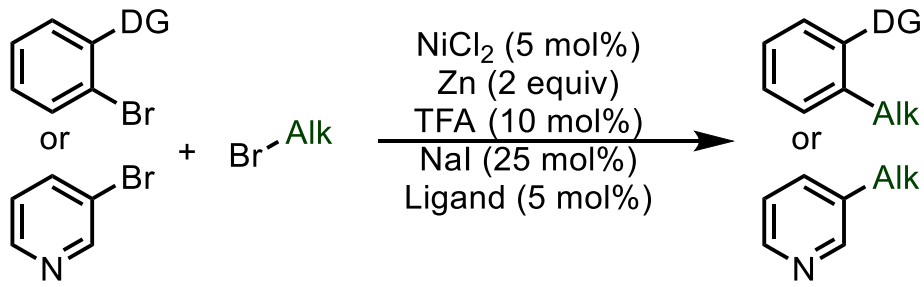
Prioritized low MW, non-proprietary compounds with different steric and electronic properties (82 compounds)

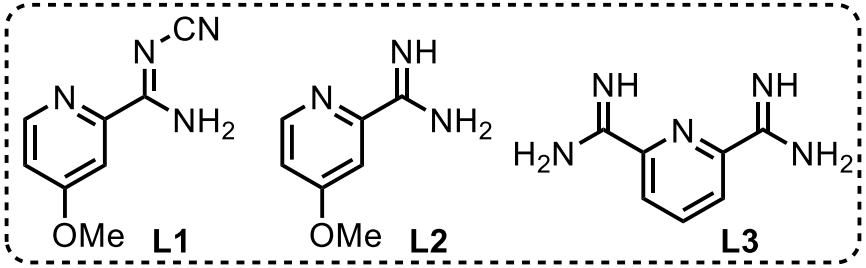


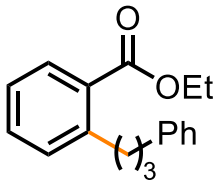


Hansen, E. C. (Pfizer); Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. *Nat. Chem.* **2020**, 8, 1126–1130.

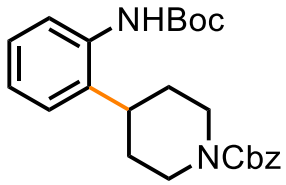
Unique Ligand Design: Pyridine (Bis)Carboxamidines



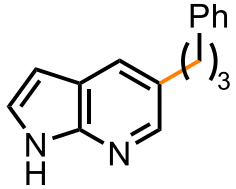




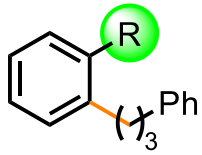
L1 = 85%



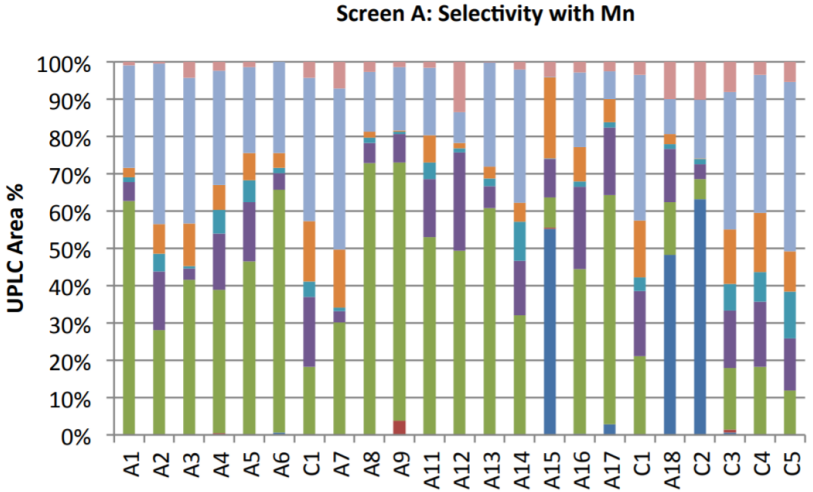
L2 = 63%

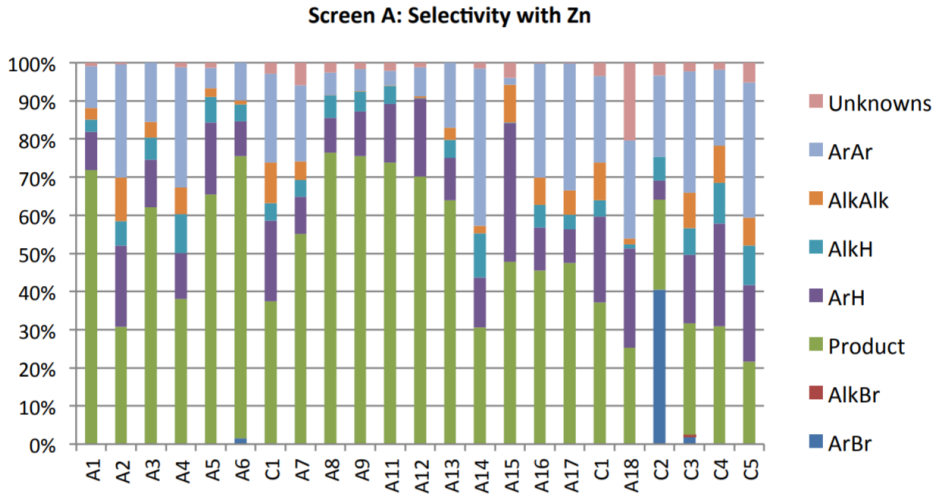


L3 = 76%



R = $B(OH)_2$ **L2** = 57%
R = SO_2NEt_2 **L2** = 55%
R = $CONH_2$ **L2** = 79%, **L1** = 62%

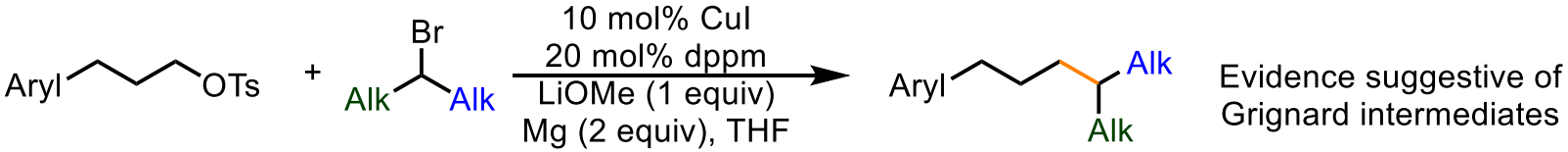




Hansen, E. C. (Pfizer); Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. *Nat. Chem.* **2020**, 8, 1126–1130.

What About Metals Beside Nickel?

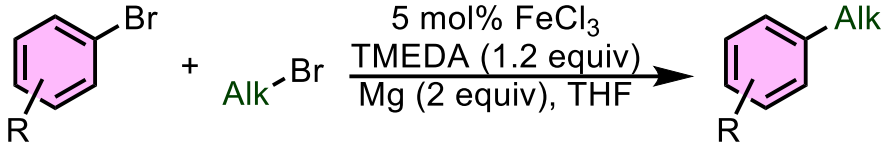
Cu-catalyzed sp^3-sp^3 coupling



Evidence suggestive of Grignard intermediates

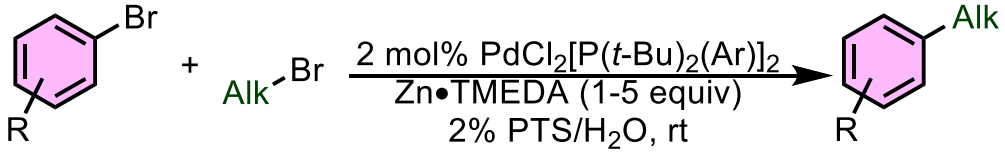
Features uncommon reducing agent (Mg), ligand (phosphine), and solvent (THF)

Fe-catalyzed sp^2-sp^3 coupling



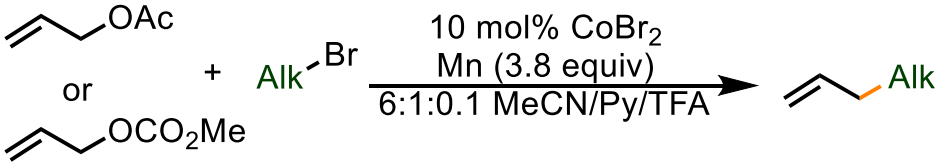
Evidence suggestive of Grignard intermediates

Pd-catalyzed sp^2-sp^3 coupling



via Alkyl-Zn intermediates
Zn powder gives no insertion

Co-catalyzed sp^3-sp^3 allylation



only other "true" reductive cross coupling

I only encountered Co and Ni to undergo truly XEC/RCC process. Nickel is uniquely suitable for XEC.

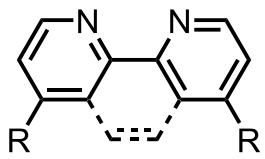
Liu, J.-H., Yang, C.-T., Lu, X.-Y.; Zhang, Z.-Q.; Xu, L.; Cui, M.; Lu, X.; Xiao, B.; Fu, Y.; Liu, L. *Chem. Eur. J.* **2014**, *20*, 15334–15338. Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. *Angew. Chem. Int. Ed*. **2009**, 48, 607–610. Krasovskiy, A.; Duplais, C.; Lipshutz, B. H.; *J. Am. Chem. Soc*. **2009**, *131*, 15592–15593. Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. *Angew. Chem. Int. Ed*. **2011**, *50*, 10402–10405.

Experimental Considerations

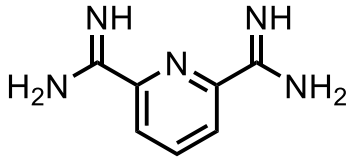
"I want to perform XEC to access a target, what conditions are most suitable?"

Nickel sources: NiX_2 (not worthwhile to try β-diketonate precats.)

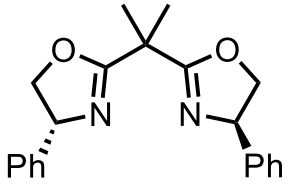
Ligands:



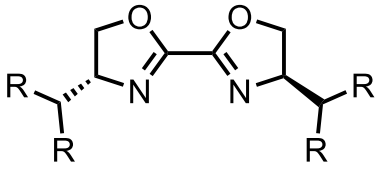
R = OMe, *t*-Bu



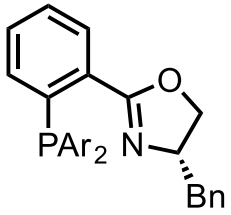
Enantioselective?:



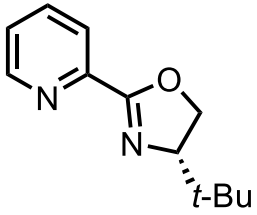
BOX-type



BiOX-type



PHOX-type



PyOX-type

Reductants: Zn, Mn, hv [Ir] and 3˚ amines, electrochemical (sacrificial anode), TDAE

Solvents: Amides (DMF, DMA), or urea (DMPU), ethereal (THF, DME, dioxane)

1st Electrophile: Aromatic/Vinylic (pseudo)halides

2nd Electrophile: Alkyl (pseudo)halides

Additives: Acids (DMBA, Et_3NHCl) reduce dimerization; NaI facilitates ligand exchange and metal reduction.

XEC and its Future in the Synthetic Toolbox

Advantages of Cross-Electrophile Coupling

Electrophile is…

- Abundant, stable, & commercially available
- Avoids preparation of organometallic reagents

Reaction conditions are…

- Functional group tolerant
  - Reducible functionality is a notable exception
- Generally low temperature (<60˚C)
- Stereoselective/Stereospecific reactions are broad and diversifiable
- $C(sp^3)$–$C(sp^x)$ are highly viable
- Use of air-stable Ni^{II} precatalysts

Challenges of Cross-Electrophile Coupling

- General mechanisms are established, and new methods often cite them, but detailed studies are rare.
- Heterocycles are underexplored and access to nitrogen (nitriles, nitro, amines) electrophiles is limited
- Stoichiometric (often heterogeneous) reductant
- Limited examples of intramolecular and tandem cross-electrophile couplings
- Disincentivized ligand developments
- Nearly all catalysts formed *in situ*

Relevant + Helpful Citations

For synthetic applications see:

Goldfogel, M. J.; Huang, L.; Weix, D. J. Cross-Electrophile Coupling: Principles and New Reactions. In *Nickel Catalysis in Organic Synthesis: Methods and Reactions*; Sensuki, O. Ed.; Wiley-VCH Verlag, 2020; pp 183–222.

Poremba, K. E.; Dibrell, S. E.; Reisman, S. E. *Acc. Chem. Res*. **2020**, *10*, 8237–8346.

For mechanistic insights see:

Biswas, S.; Weix, D. J. *J. Am. Chem. Soc*. **2013**, *135*, 16192–16197.

Weix, D. J. *Acc. Chem. Res*. **2015**, *48*, 1767–1775.

Chen, P.-P.; Lucas, E. L.; Greene, M. A.; Zhang, S.-Q.; Tollefson, E. J.; Erickson, L. W.; Taylor, B. L. H.; Jarvo, E. R.; Hong, X *J. Am. Chem. Soc.* **2019**, *141*, 5835–5855.