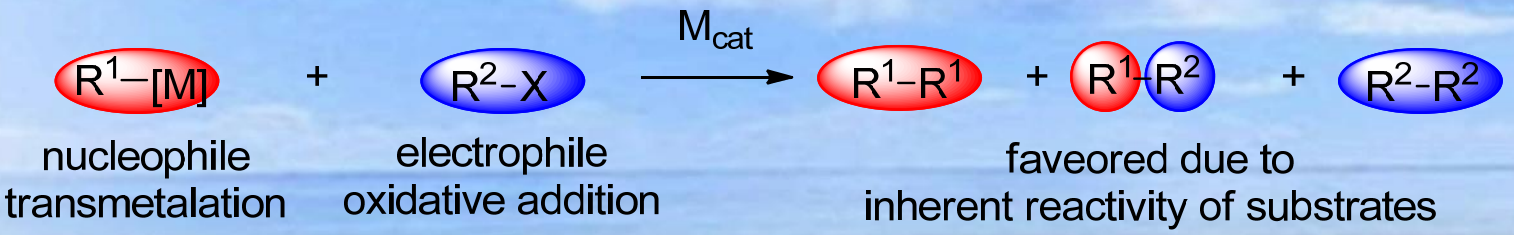
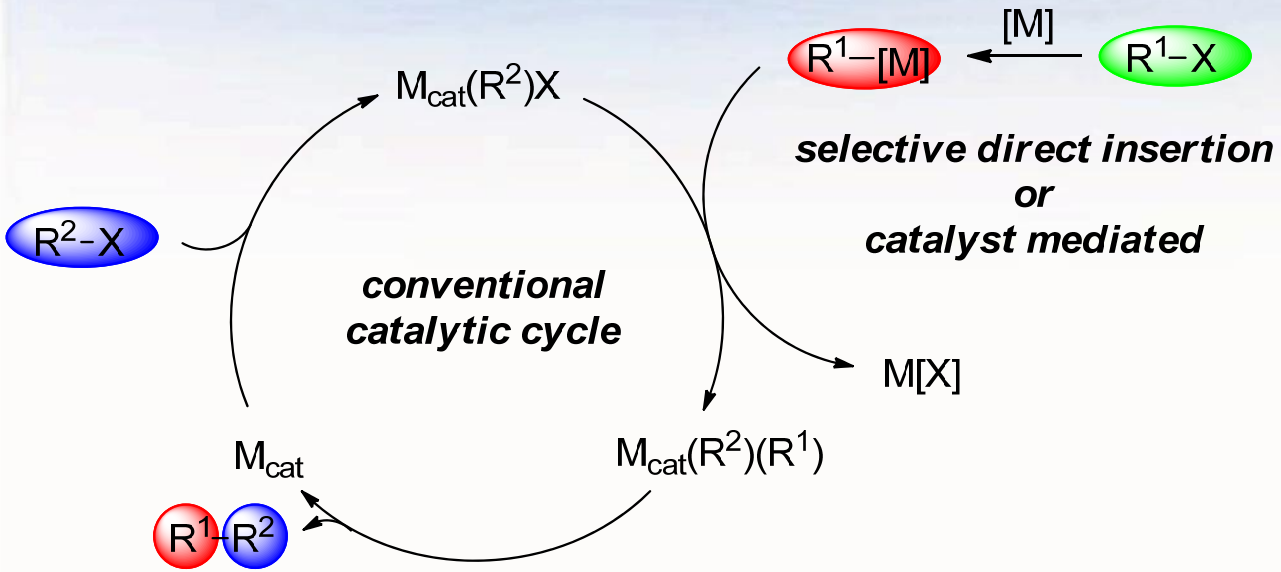
Strategy and Mechanism for Nickel-Catalyzed Selective Cross-Electrophile Coupling

Bo Xing

2016.05.09

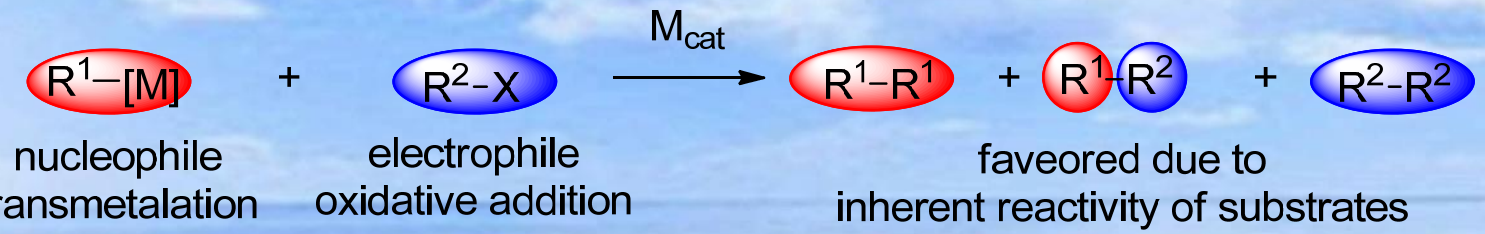
Conventional Metal Catalyzed Cross-Coupling



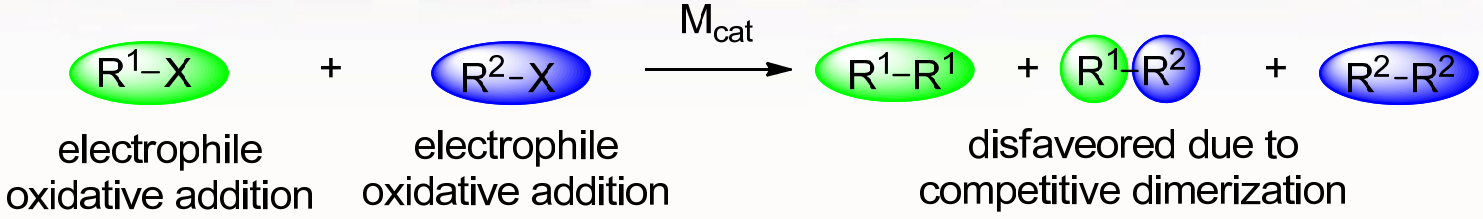


M = Mg, Zn:
air- and moisture- sensitive
M = B, Si:
additives required to fancilitate transmetalation

Conventional Metal Catalyzed Cross-Coupling

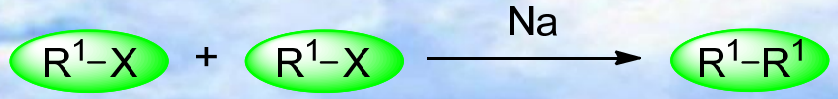


Cross Electrophile Coupling (XEC)

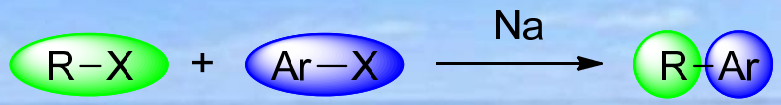


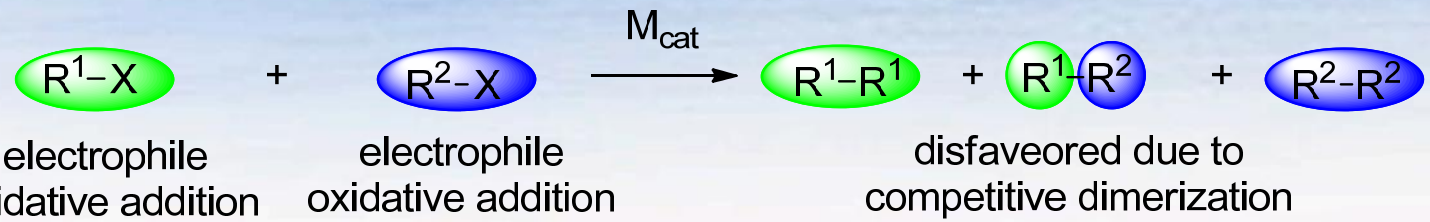
stable, easy to handle, readily available…

Wurtz coupling(1855):



Wurtz-Fittig reaction(1864):





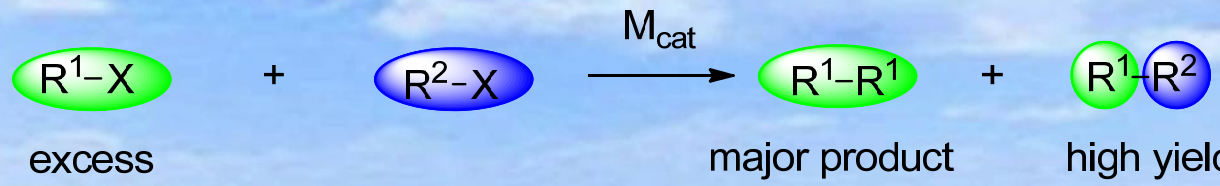
equal reactivity for substrates: statistical mixture

R^1-X more reactive than R^2-X: R^1-R^1 formed first, R^2-R^2 second, then incidental R^1-R^2 formed

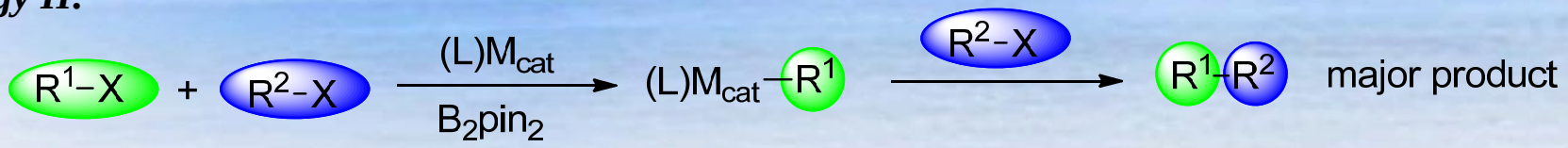
Strategies for crossing selectivity in XEC reaction

For starting materials that have identical chemical reactivity:

Strategy I:

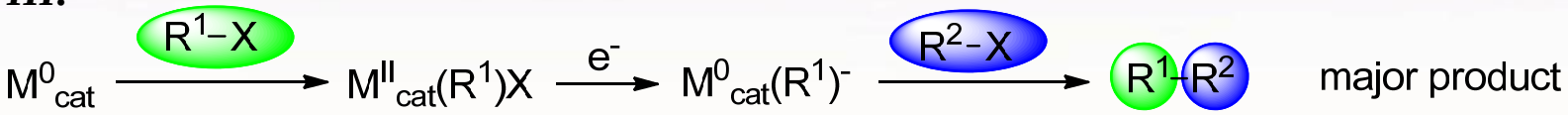


Strategy II:

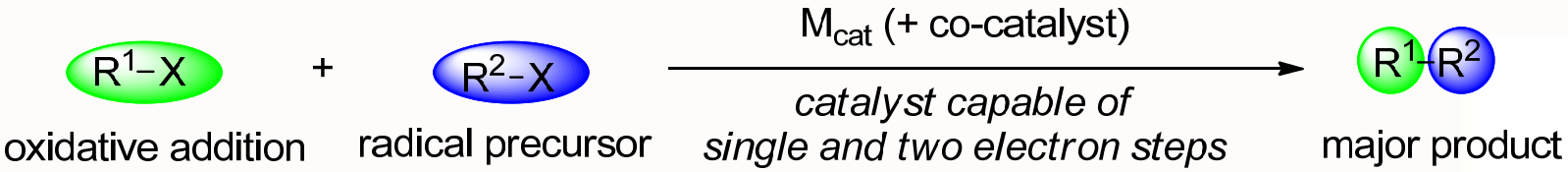


For substrates that are not so identical in chemical reactivity:

Strategy III:

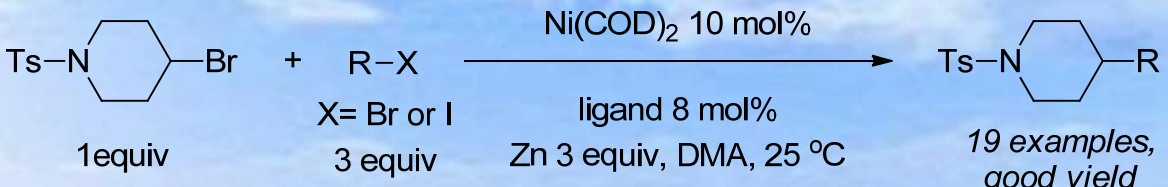


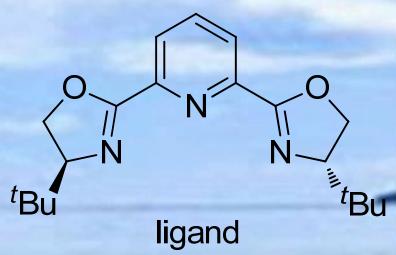
Strategy IV:



Everson, D. A.; Weix, D. J. *J. Org. Chem.*, **2014**, 79, 4793

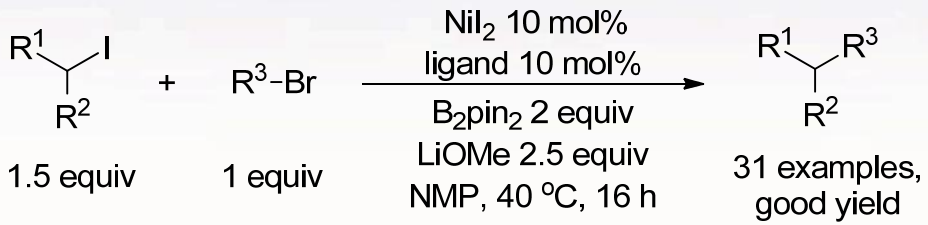
Strategy I: excess of one reagent

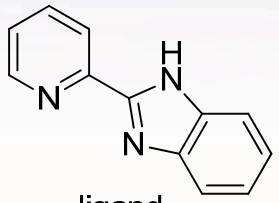




ligand

Strategy II: steric differentiation of starting materials



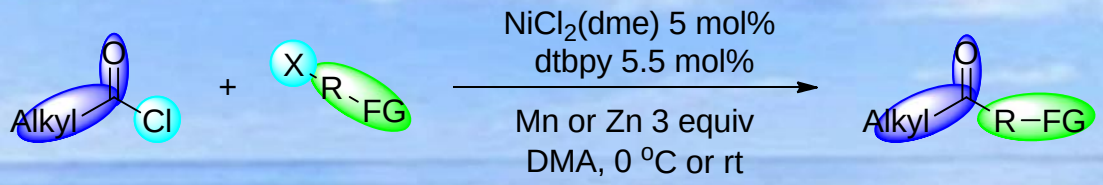


ligand

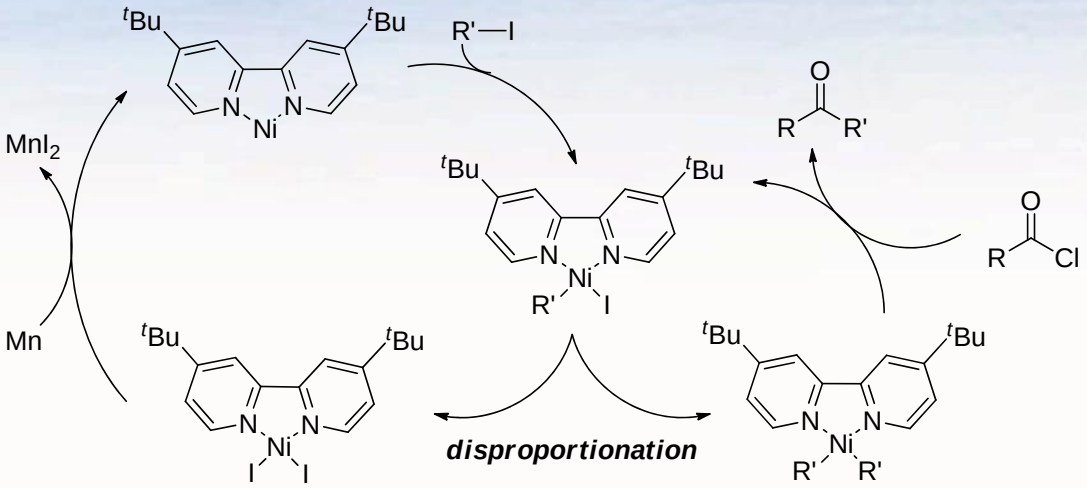
Yu, X.; Yang, T.; Wang, S.; Hu, H.; Gong, H. *Org. Lett.*, **2011**, *13*, 2138

Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. *Chem. Sci.*, **2013**, *4*, 4022

Strategy III: electronic differentiation of starting materials

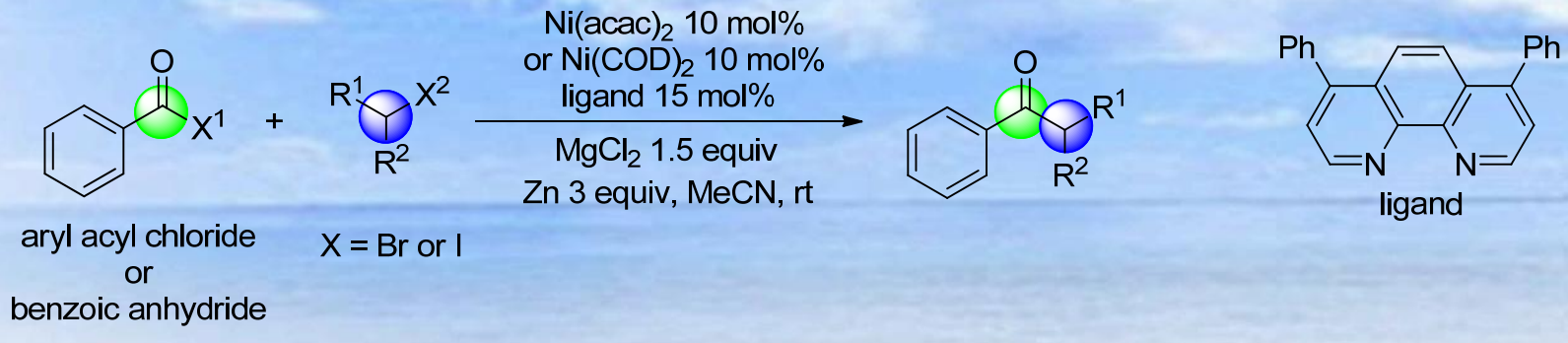


Alkyl = 1°/2°/3° FG = TIPS, alkynyl, NHBoc, NHCbz, Bpin...

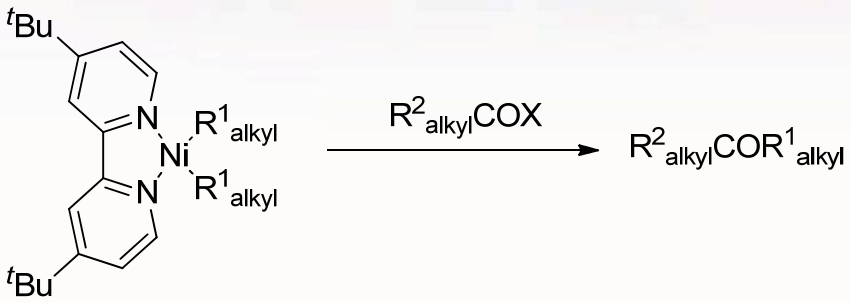


Wotal, A. C.; Weix, D. J. *Org. Lett.*, **2012**, *14*, 1476

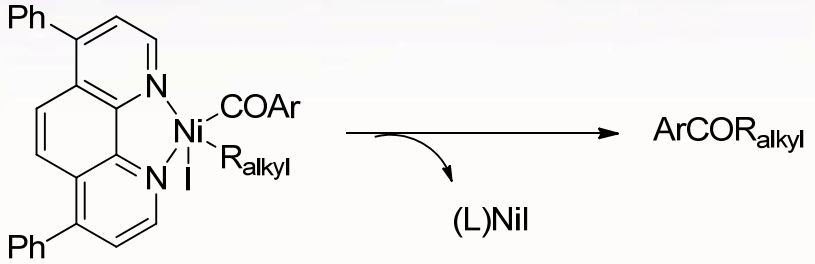
Strategy III: electronic differentiation of starting materials



Proposed Ni^0/Ni^{II} process



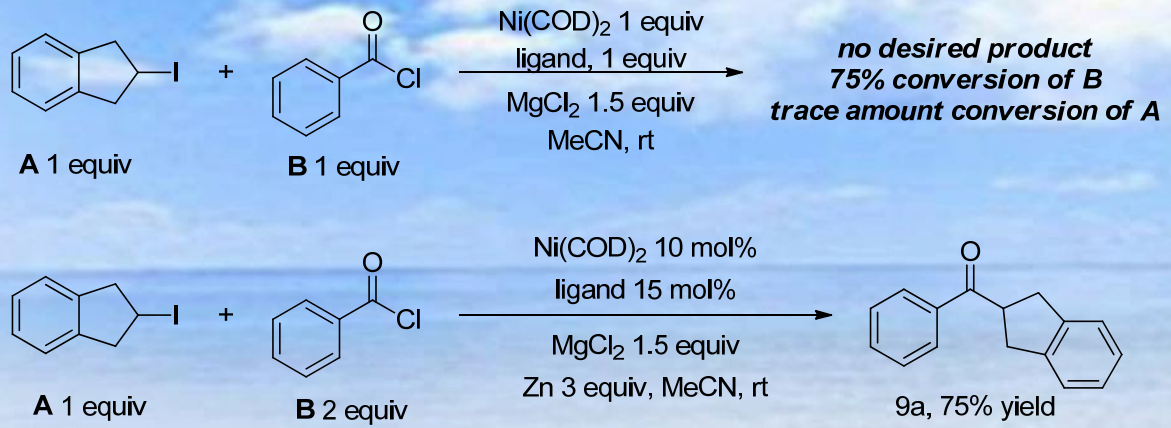
Proposed Ni^I/Ni^{III} process



Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044

Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. *Chem. Commun.*, **2012**, *48*, 7034

Strategy III: electronic differentiation of starting materials



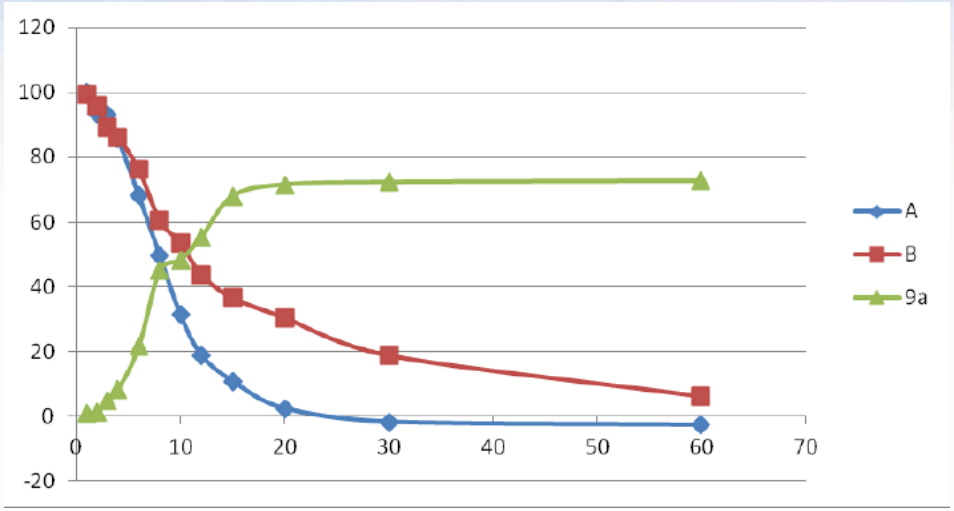
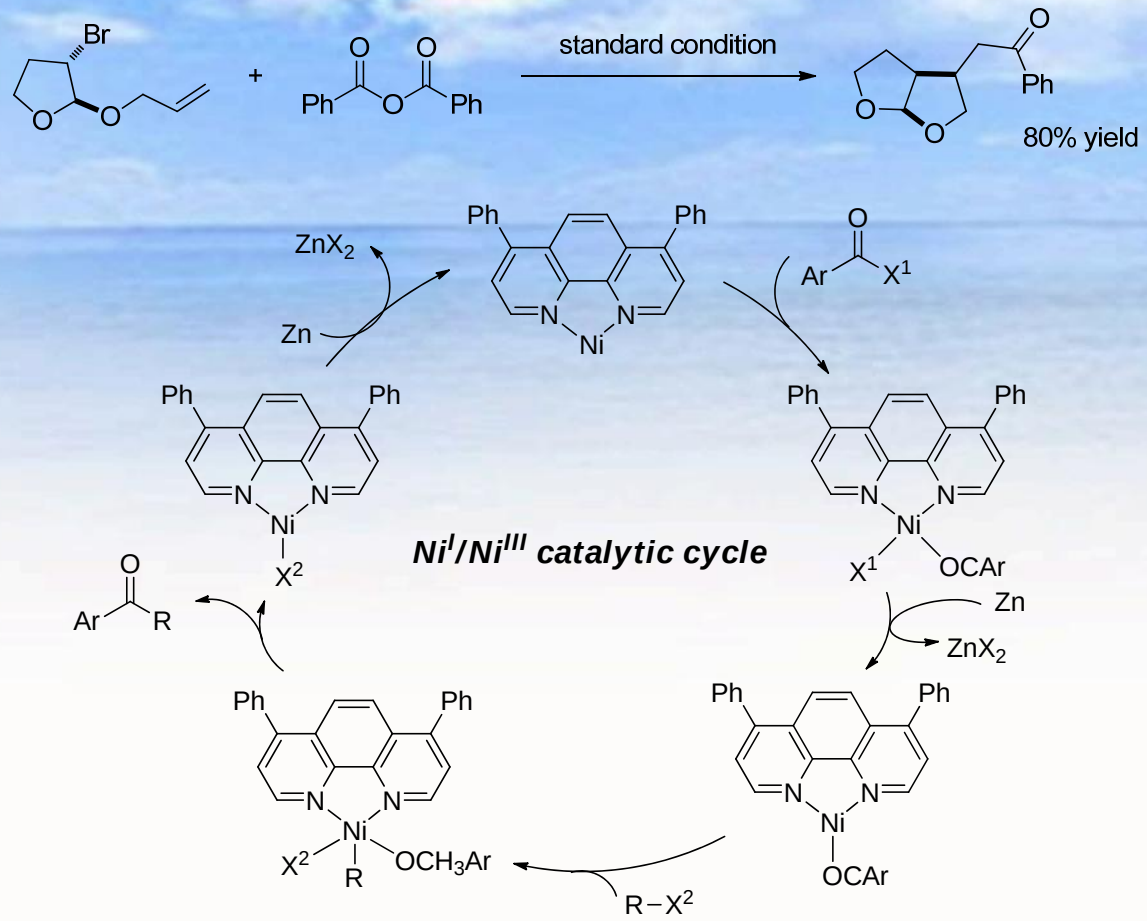


Figure. coupling under standard condition

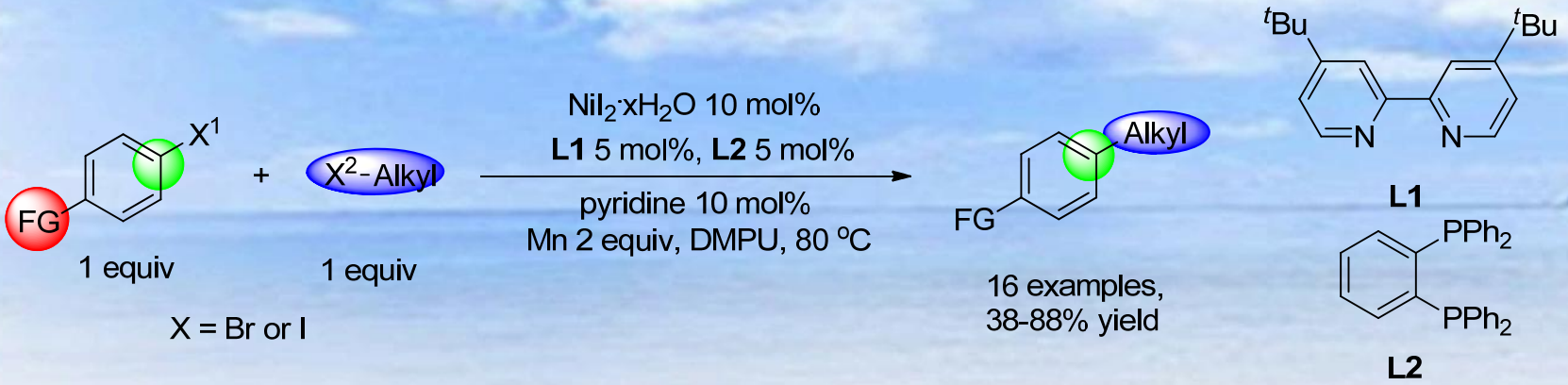
Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044

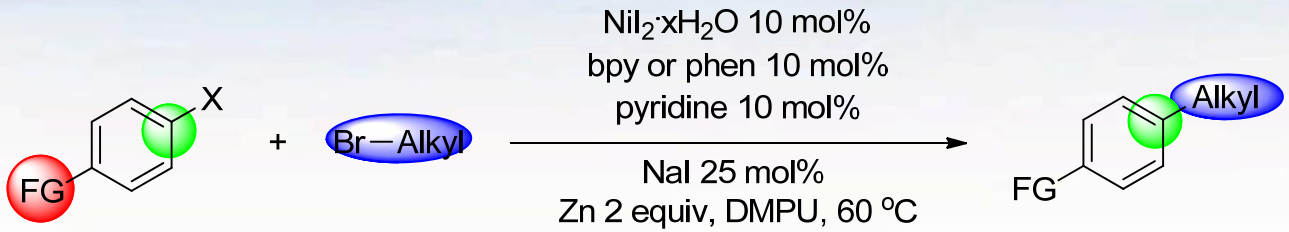
Strategy III: electronic differentiation of starting materials



Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. *Chem. Commun.*, **2012**, *48*, 7034

Strategy IV: radical chain mechanism





FG includes:

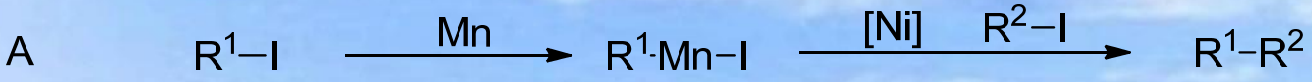
nucleophiles	**acids**	**electrophiles**
-$SnMe_3$	-NHBoc	-OAc
-Bpin	-OH	-C(O)Me
-$SiMe_2OH$	-NHTs	-OTf

X = Br or Cl
42 examples
41-96% yield

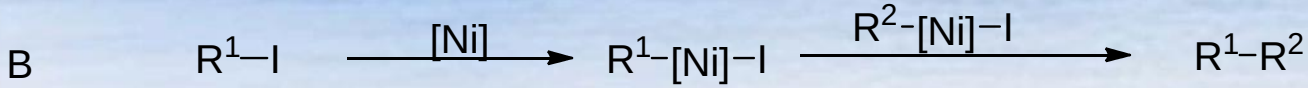
Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.*, **2010**, *132*, 920

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

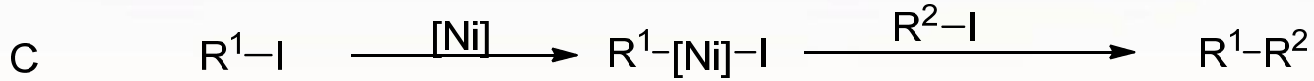
Mechanism A : organometallic reagent generated in situ



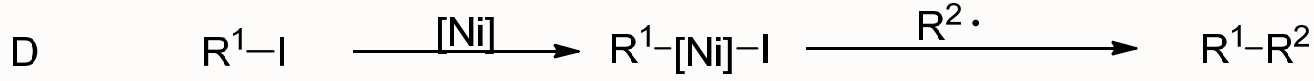
Mechanism B : disproporization methasis of two nickel centers



Mechanism C : sequential oxidative addition at a single metal center

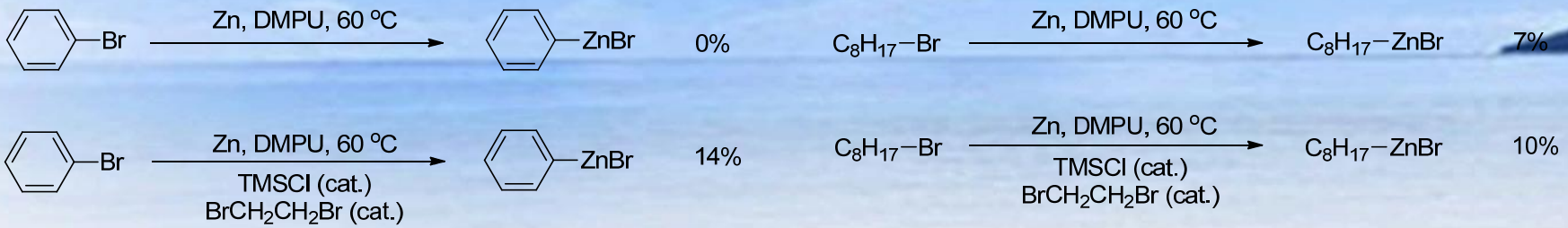


Mechanism D : radical chain mechanism

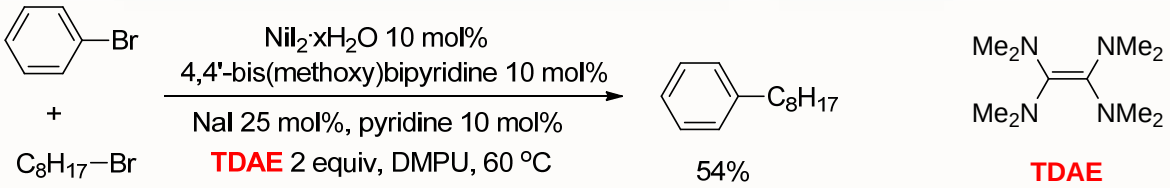


Potential intermediacy of organozinc reagents

Direct insertion of zinc or activated zinc

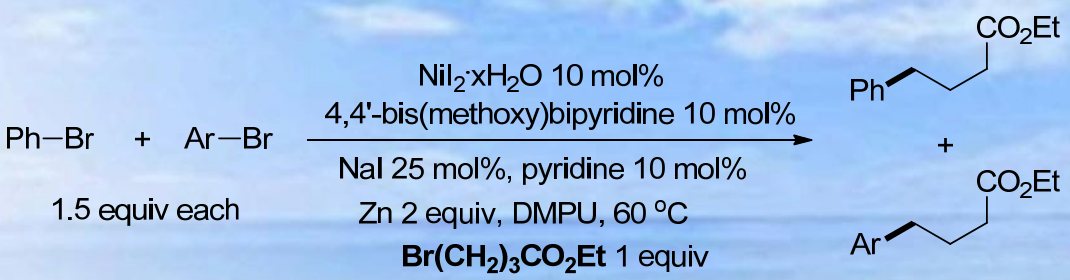


Reductive cross-coupling with a nonmetallic reducing agent

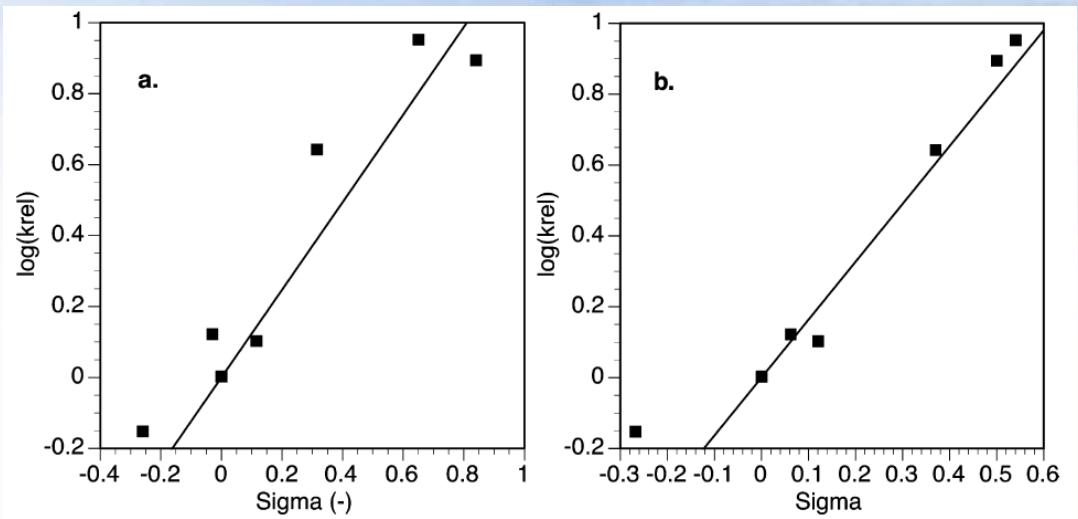


Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.*, **2012**, *134*, 6146

Turnover-frequency limiting step



entry	substituent	k_{rel}	σ	σ(–)
1	4-H	1	0	0
2	4-OMe	0.81	-0.268	-0.26
3	4-F	1.34	0.062	-0.03
4	3-OMe	1.15	0.12	0.115
5	3-CO_2Et	4.21	0.37	0.315
6	4-CF_3	10.06	0.54	0.65
7	4-C(O)Me	9.21	0.50	0.84



k_{rel} =1.235σ(-), R^2=0.9259

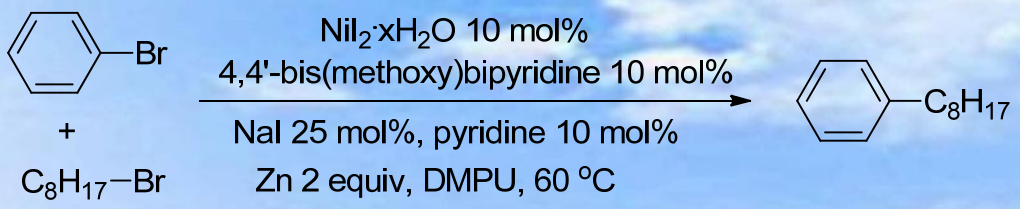
k_{rel} =1.635 σ, R^2=0.9531

slop for Ni-mediated oxidative addition of aryl halides: 4.4-8.8

Oxidative addition is not turnover-frequency limiting.

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

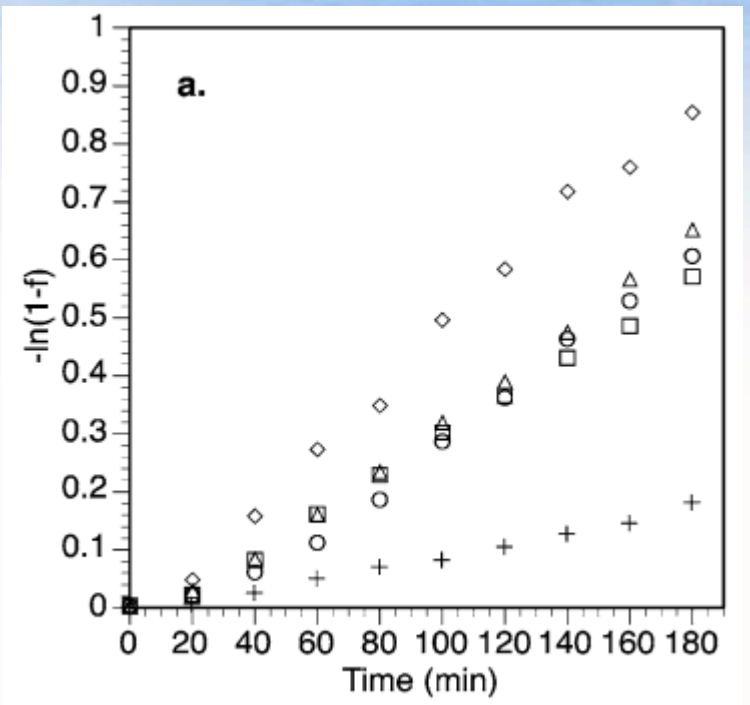
Turnover-frequency limiting step



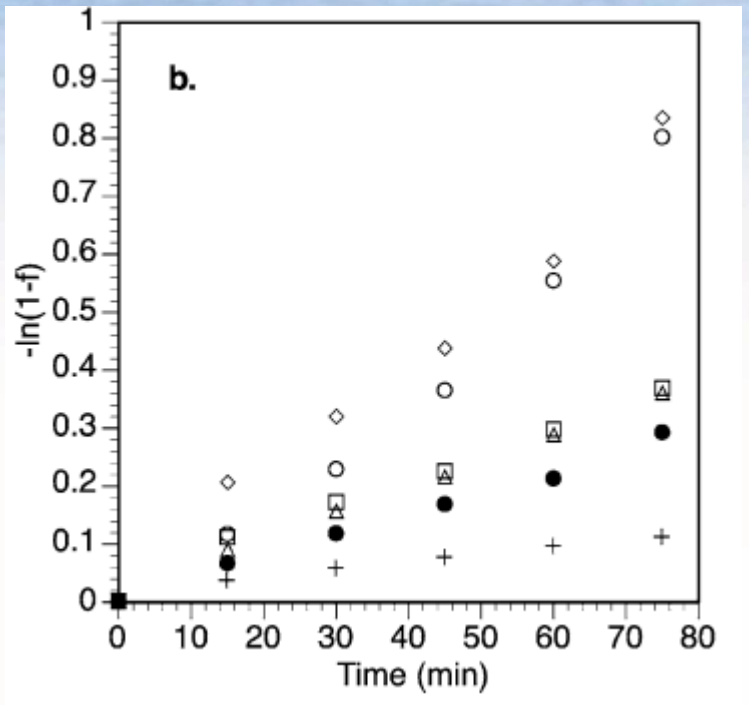
$$-\frac{d[c]}{dt} = \upsilon = k[c]$$

$$kt = -\ln\frac{c}{c_0} = -\ln(1-f)$$

standard conditions(□) 4 equiv Zn(△) 1 equiv benzene(●)
2×PhBr(+) 2×AlkylBr(○) 2×[Ni/ligand/py](◇)



a.Reaction with unactivated zinc

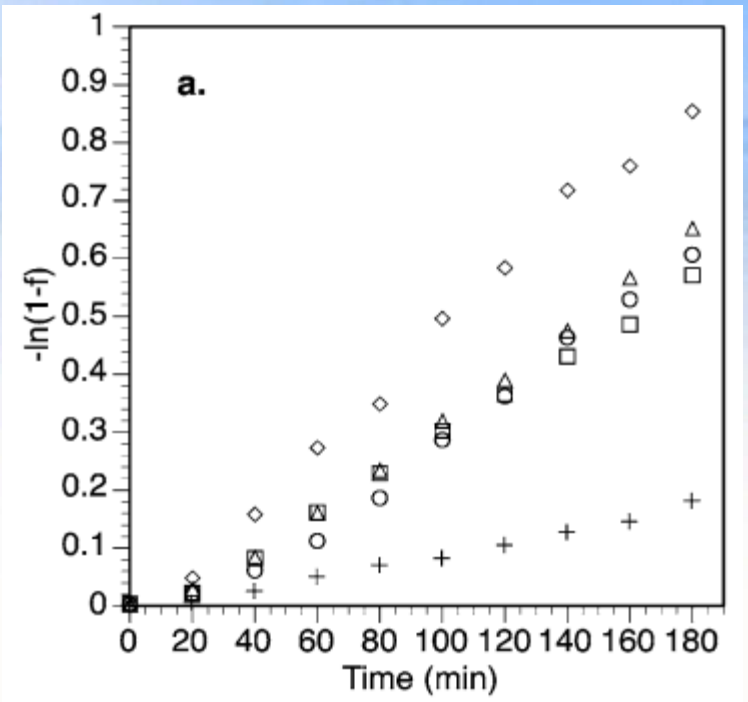


b.Reaction with activated zinc

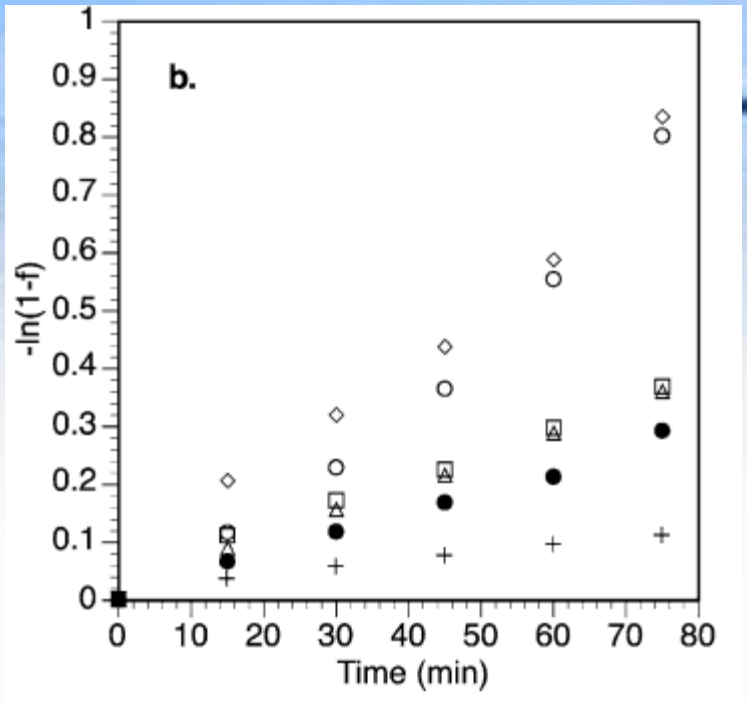
Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.*, **2012**, *134*, 6146

Turnover-frequency limiting step

standard conditions(□) 4 equiv Zn(△) 1 equiv benzene(●)
2×PhBr(+) 2×AlkylBr(○) 2×[Ni/ligand/py](◇)



a.Reaction with unactivated zinc

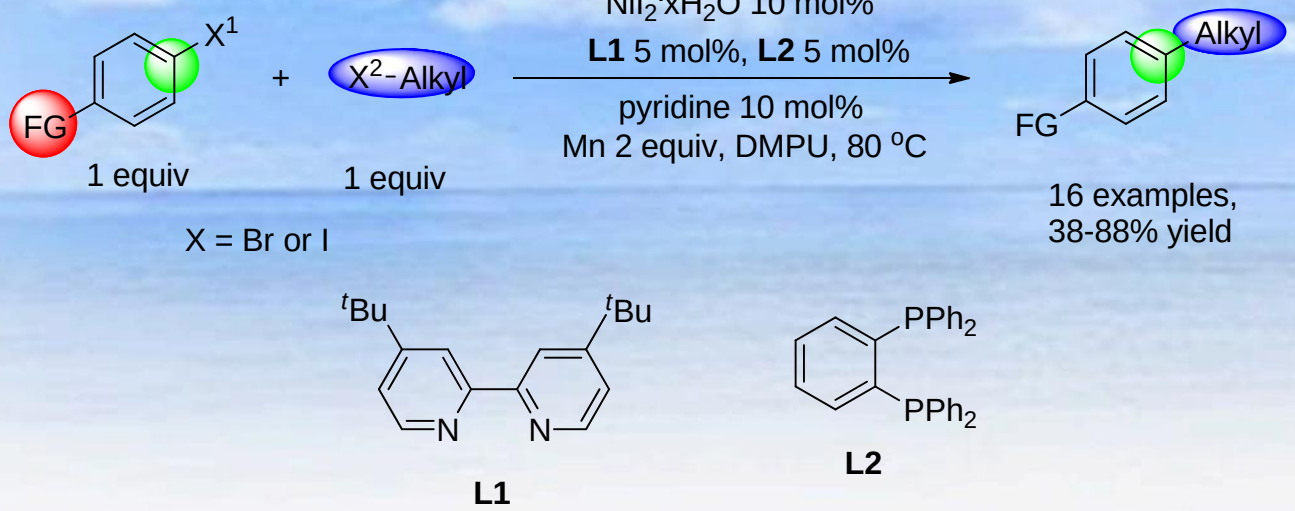


b.Reaction with activated zinc

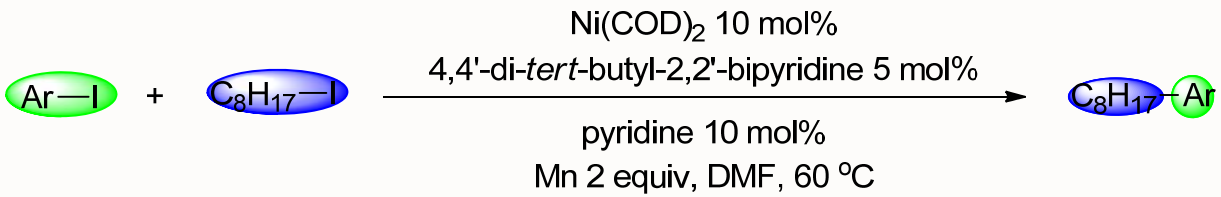
The rate of product formation is proportional to [bromoalkane]^{x}[Ni]^{y}/[bromoarene]^{z}

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

Initial work



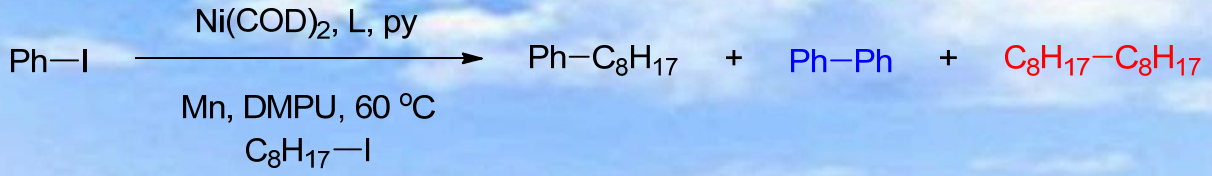
Modification

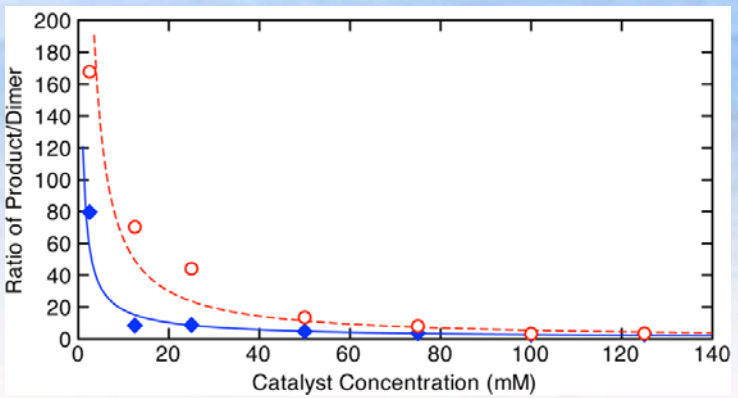


Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.*, **2010**, *132*, 920

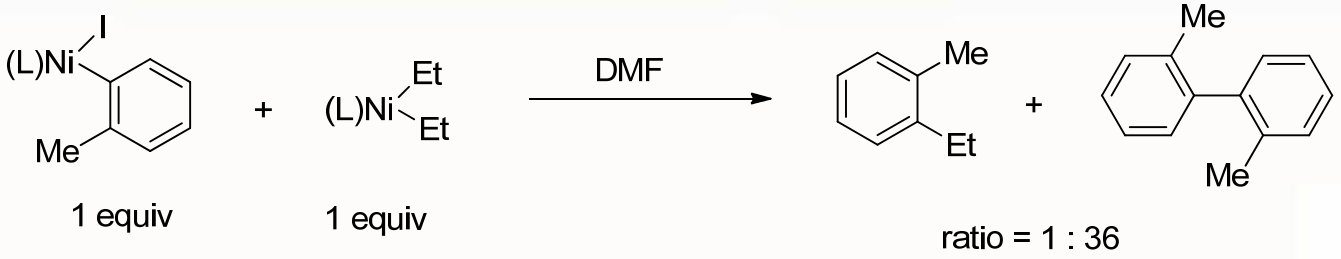
Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.*, **2012**, *134*, 6146

To rule out the disproportional mechanism :





"The rate of Ph-Ph formation has a second-order dependence on nickel concentration", shown by Osakada and Yamamoto.



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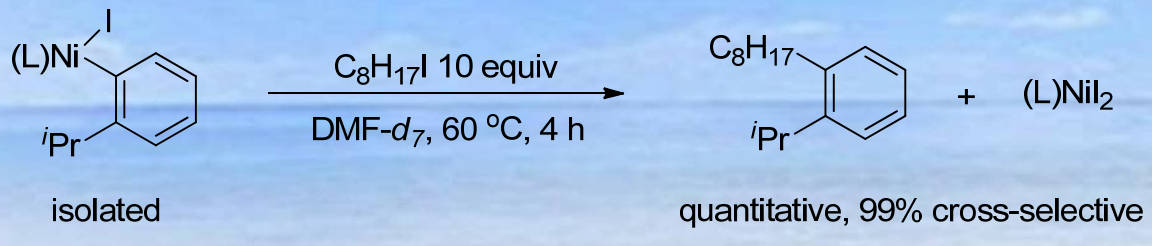
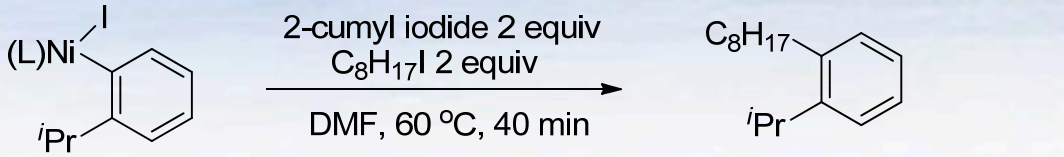
Sequence of oxidative addition:

Selectivity in oxidative addition to Ni^0



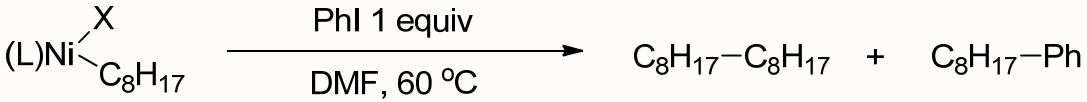
isolated

quantitative, 99% cross-selective



isolated

56% yield, 99% cross-selective



generated *in situ*

X = I	14	:	1
X = C_8H_{17}	270	:	1

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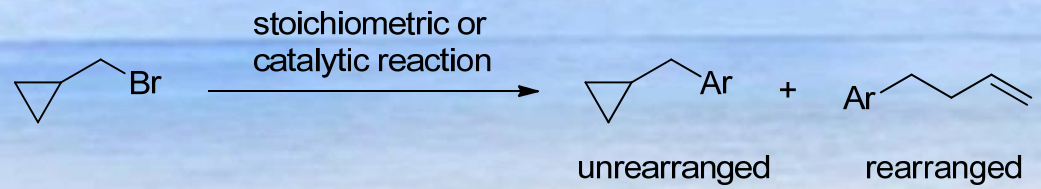
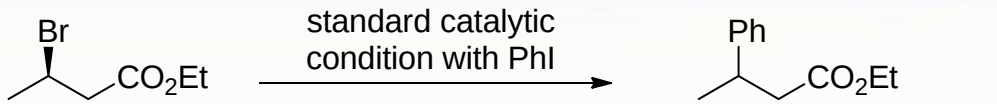
Sequence of oxidative addition:

Radical clock experiments



	unrearranged	rearranged
stoichiometric reaction with (L)Ni^{II}(2-tol)I	ND	56% yield
standard catalytic reaction with PhI	ND	35% yield



(R), 98% ee

10% yield, racemic
remaining material is 98% ee

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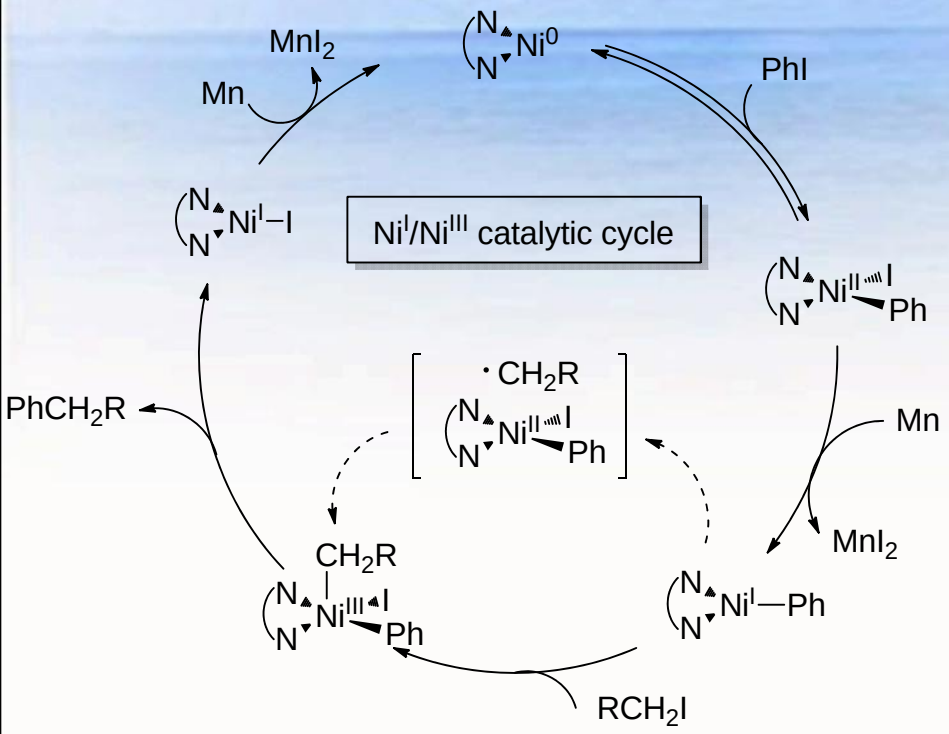
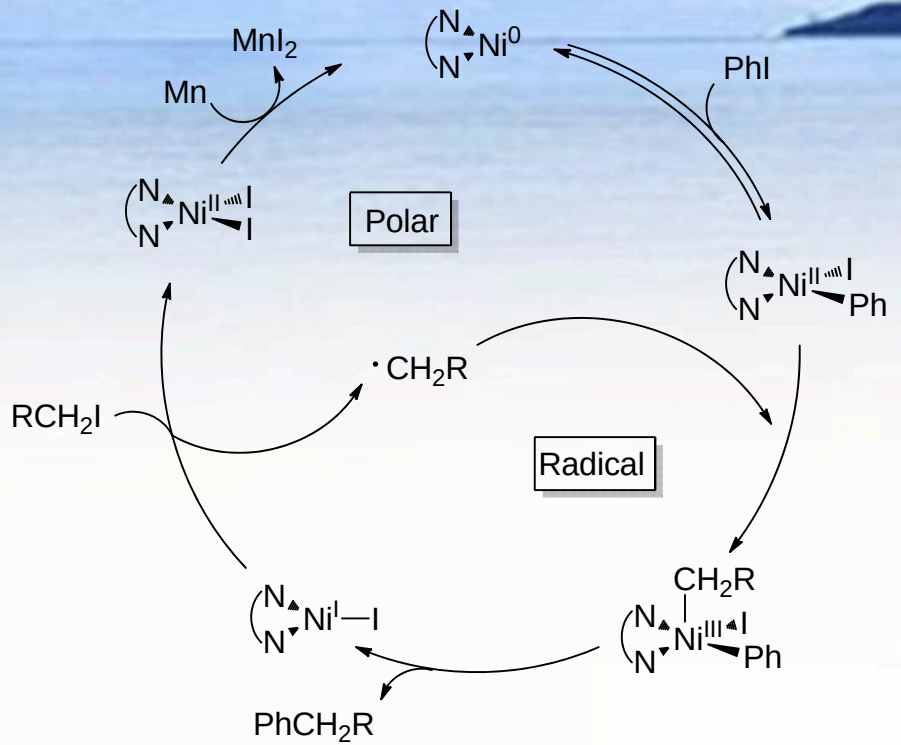
Mechanism C : Sequential oxidative



Mechanism D : Radical chain



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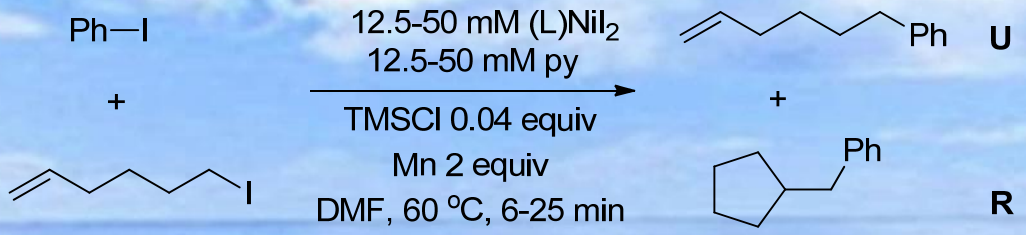
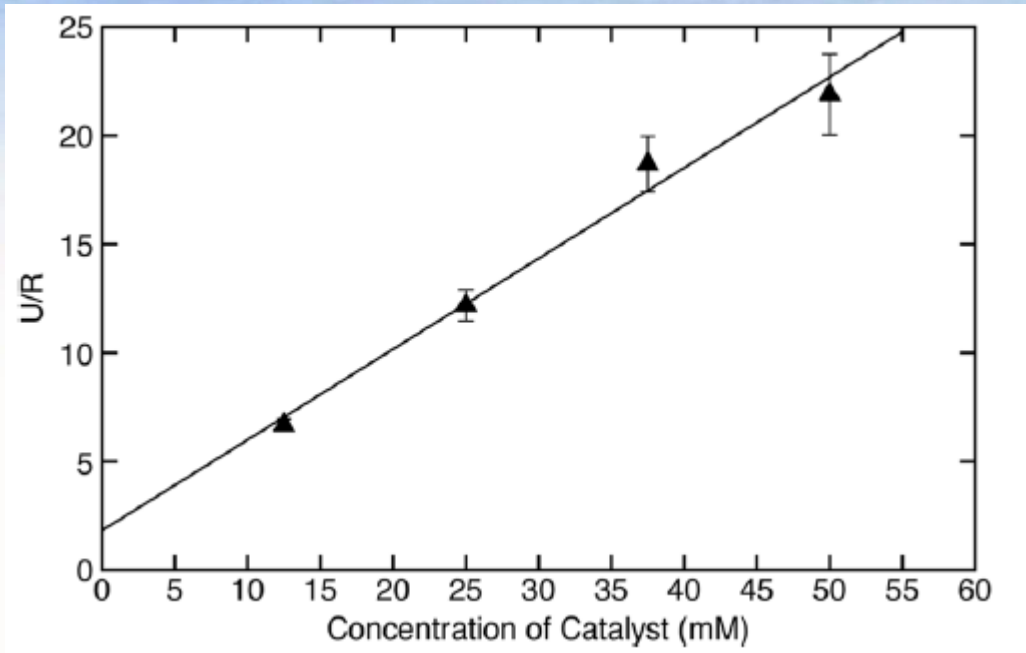
Product ratio on nickel concentration:





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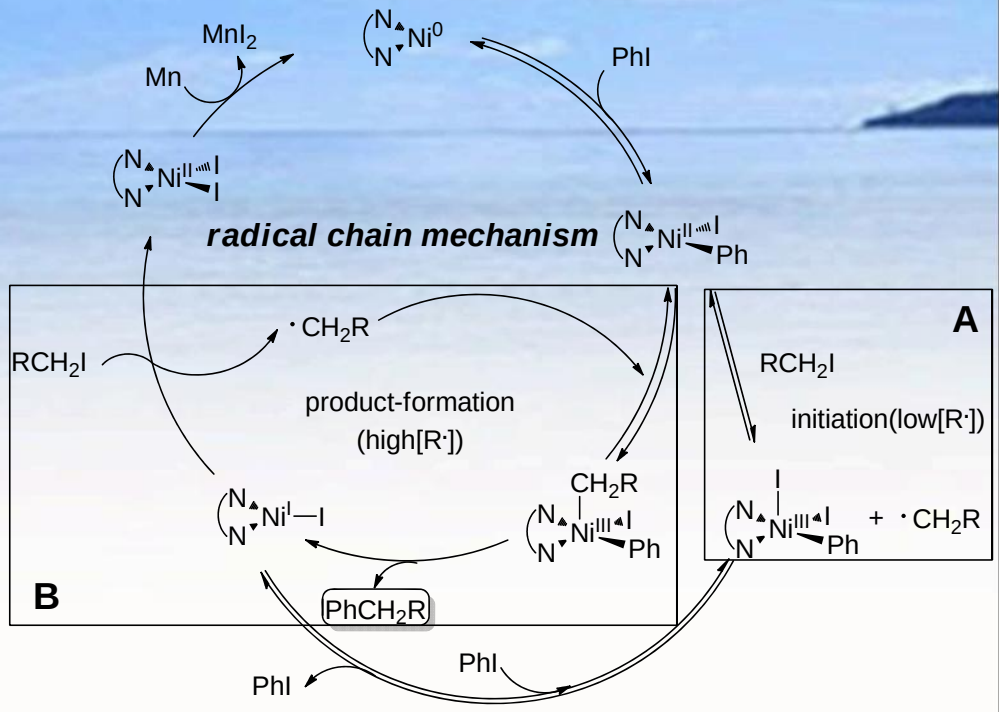
Radical chain mechanism

- ***Proportional to [bromoalkane]^{x}[Ni]^{y}/[bromoarene]^{z}***
- ***PhI oxidative addition first***
- ***Alkyl iodide transferred to alkyl radical***
- ***Unrearranged/rearranged ratio dependent on nickel concentration***



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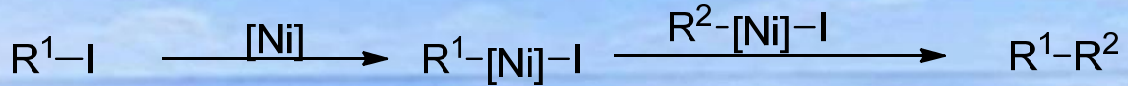
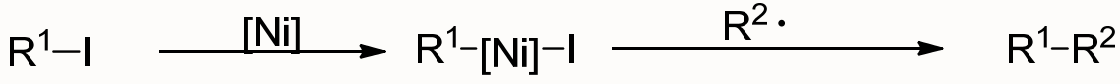
Summary

C_{sp3}-$C_{carbonyl}$, *without reduction of intermediate*



$C_{carbonyl}$-C_{sp3}, C_{sp3}-C_{sp3}, *reduction of intermediate*

C_{sp2}-C_{sp3}, *reduction of intermediate*




Thanks!