Nickel-Catalyzed Reductive Cross-Electrophile-Coupling Between Aryl and Alkyl Halides

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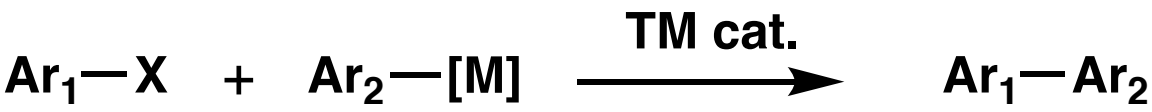
Background : Cross Coupling

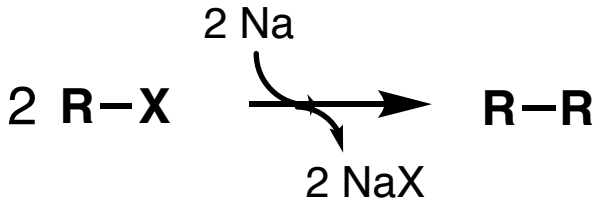


Reaction	Ar_2– [M]
Suzuki-Miyaura	Ar–$B(OH)_2$
Kumada	Ar-MgX
Negishi	Ar-ZnX
Stille	Ar-SnR_3
Hiyama	Ar-$Si(OR)_3$
Sonogashira	Alkyne-Cu

Organometallic nucleophile
- Formation requires separate step
- Moisture- and air-sensitive
- Limited FG compatibility
- May require large excess of one halide

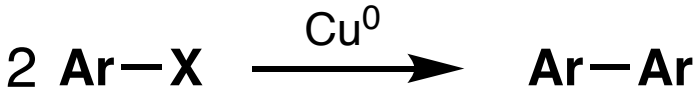
Background : Cross-Electrophile-Coupling

Wurtz Coupling (1855)



- Homocoupling of Alkyl Halides
- Side reactions : alkene formation
  hydrodehalogenation

Ullmann Coupling (1901)



- Homocoupling of Aryl Halides

Challenge

- *Cross-selectivity*
- Easy *setup*
- *Side reactions*
- *Stoichiometry* between coupling partners

Cross-coupling ***without organometallic intermediacy***

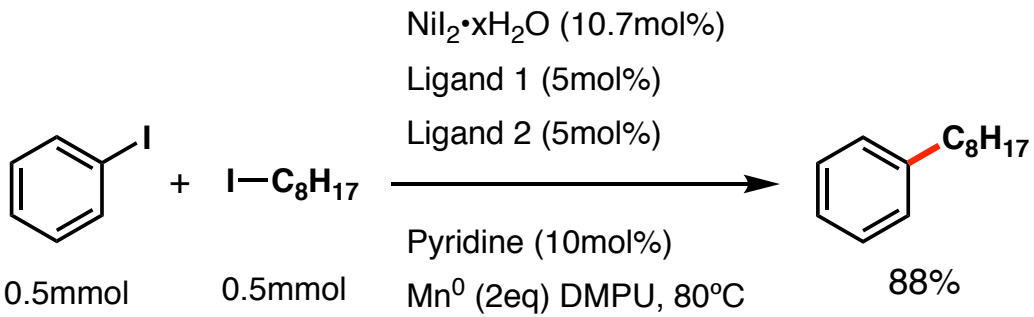
- Commercial availability
- Moisture- and air-tolerance
- Wide FG compatibility

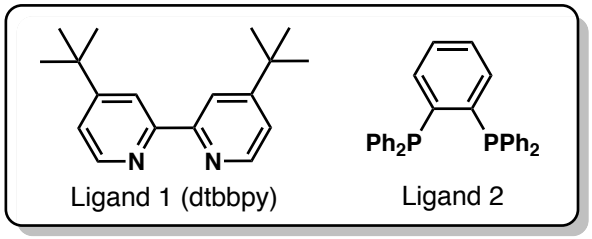
83854 Ar-I, 642185 Ar-Br <cf> 2954 Ar-$B(OH)_2$

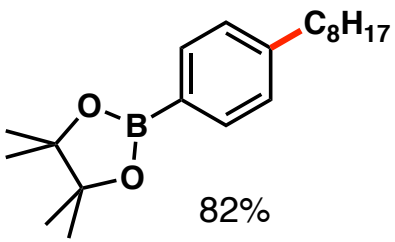
771 Alkyl-I, 9856 Alkyl-Br <cf> 183 Alkyl-$B(OR)_2$

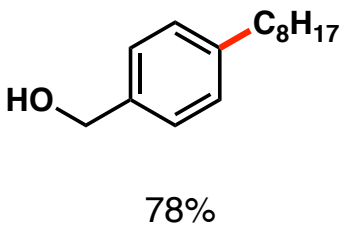
D. J. Weix *et al.*, *J. Am. Chem. Soc.*, **2010**, *132*, 920-921

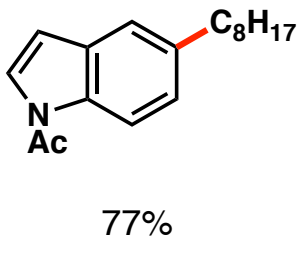
Weix's Pioneering Work

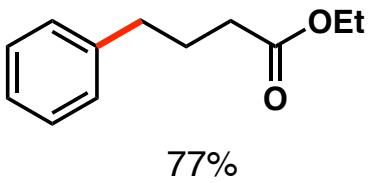


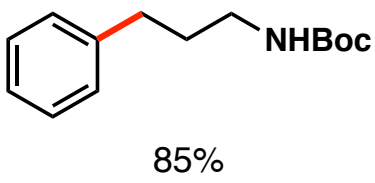


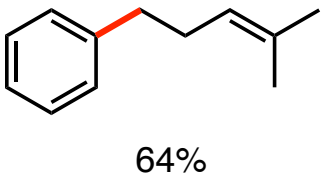


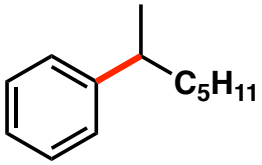












- P / Branched isomer / Linear isomer = 89 : 7: 4
- Isolated : P / Branched isomer = 95 : 5

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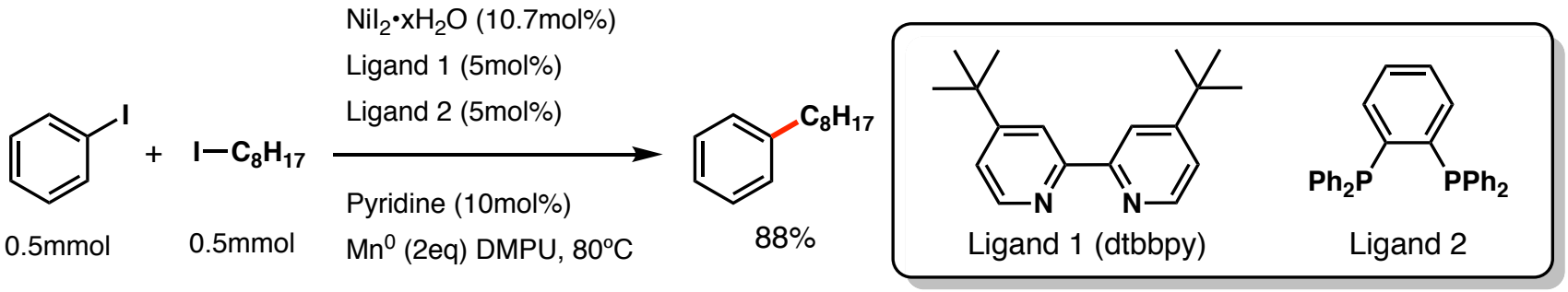
Weix's Pioneering Work



Lessons from optimization

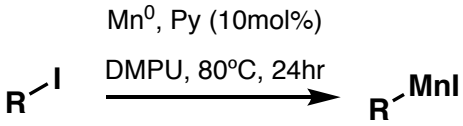
- Pyridine : less ß- hydride elimination
- Solvent : amide based solvents work (>60%)

Preliminary mechanistic studies : *Ruling out R-Mn-X intermediacy*

1) literature

2) TDAE instead of Mn : 57% yield

3) Control rxn :



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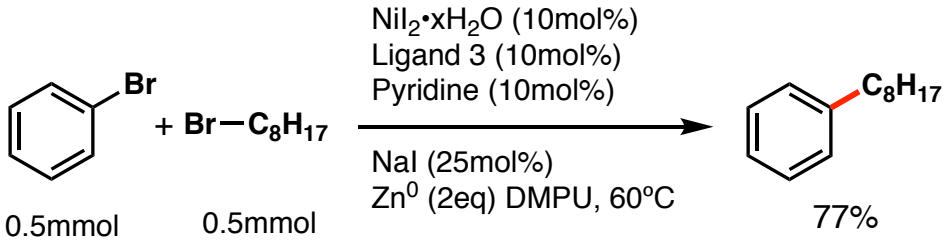
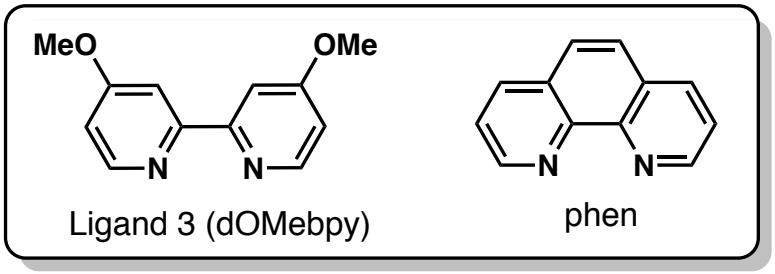
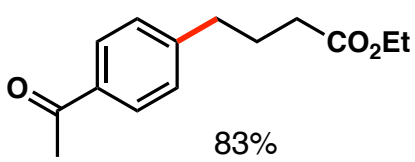
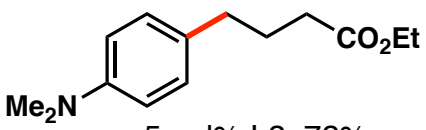
Further Development



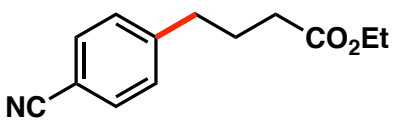




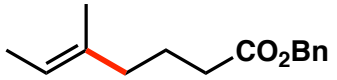
83%



5mol% L3, 72%

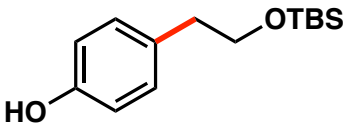


5mol% L3, 68%



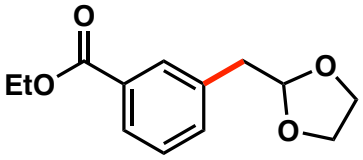
5mol% L3, 76%

E : *Z* = 9 : 1



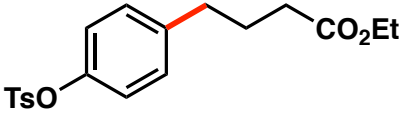
5mol% L3, 1.25eq Alk-Br

76%

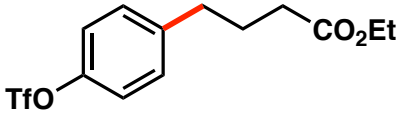


5mol% phen, 1eq NaI

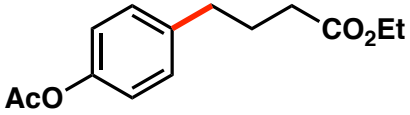
80°C, 60%



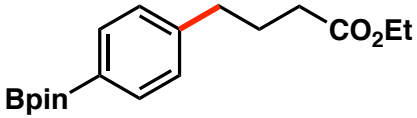
5mol% phen, 76%



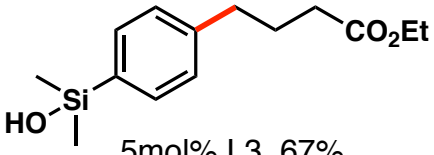
5mol% phen, 74%



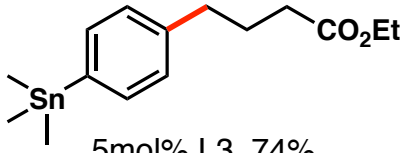
5mol% phen, 64%



5mol% phen, 76%



5mol% L3, 67%

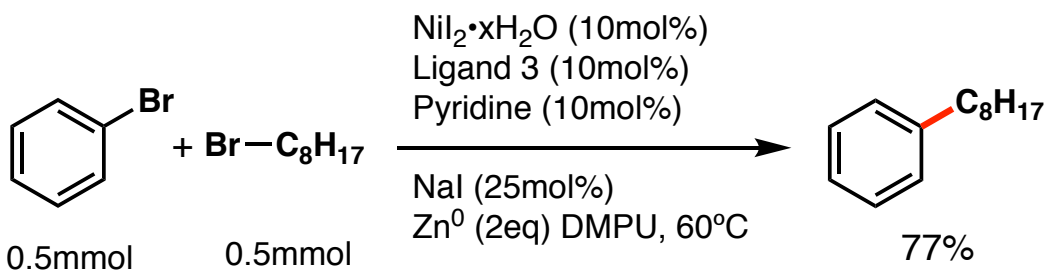


5mol% L3, 74%

D. J. Weix *et al.*, *J. Am. Chem. Soc.*, **2012**, *134*, 6146-6159

Preliminary Mechanistic Studies

1. Lessons from optimization



Role of iodide
- Facilitate reduction of Ni cat. (act as a bridging ligand)
- Form reactive nickelates
- Form alkyl-I *in situ*
- Facilitate ligand exchange

Condition	Product	Benzene	Octane
Optimized	77	6	3
70ºC	53	18	3
80ºC	49	11	6

⇨ Increased direct Zn insertion detrimental to yield

Halides	Time	GC Yield
Br-Ph + Br-R	18	77
Br-R only	53	(Dimer) 45
Br-Ph only	53	(Dimer) 24

⇨ Homocoupling significantly Slower than cross-coupling

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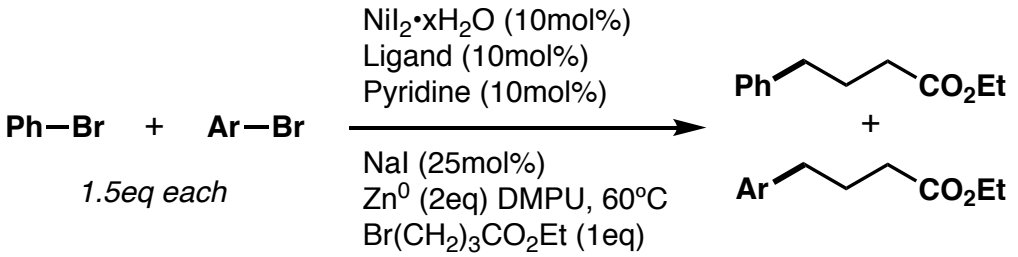
Preliminary Mechanistic Studies

2. Rate vs electronics : *Hammett analysis*



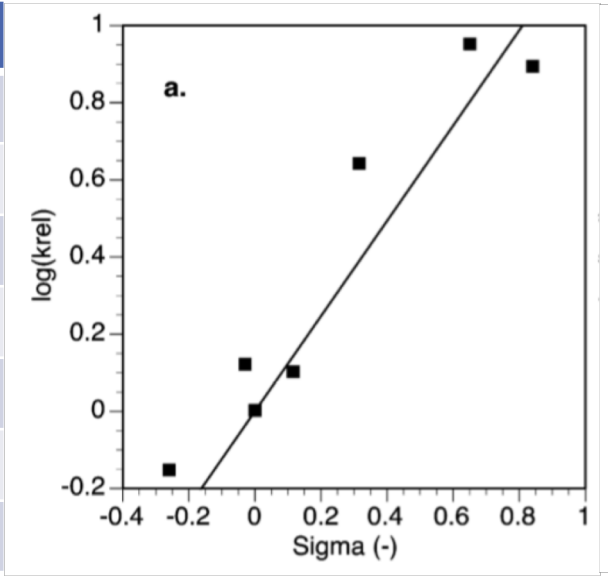
$$k_{rel} = \frac{k_{ArBr}}{k_{PhBr}} \Leftarrow \ln\frac{[ArBr]_0}{[ArBr]} = kr_{el} \cdot ln\frac{[PhBr]_0}{[PhBr]}$$

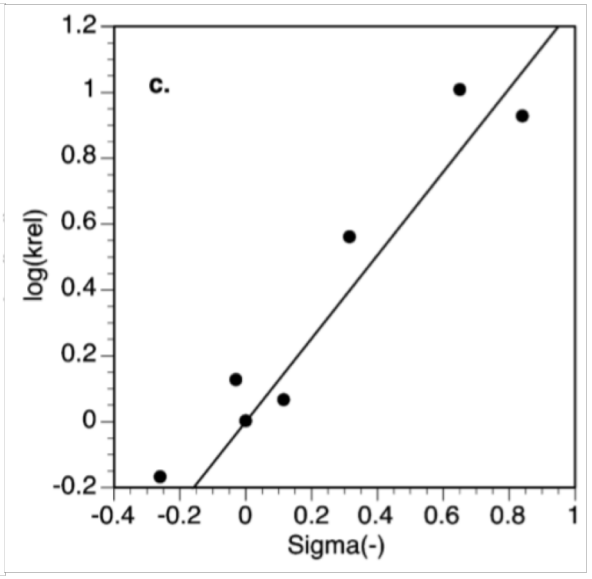
Oxidative addition of Ar-Br is **NOT TOF limiting**

Oxidative addition of aryl halides to Ni : ρ 4.4 ~ 8.8

ρ ~ 1.3

subst.	L3 [Ni]k_{rel}	phen [Ni]k_{rel}
4-H	1.00	1.00
4-OMe	0.81	0.71
4-F	1.34	1.84
3-OMe	1.15	1.19
3-CO_2Et	4.21	3.62
4-CF_3	10.06	8.42
4-C(O)Me	9.2	8.43





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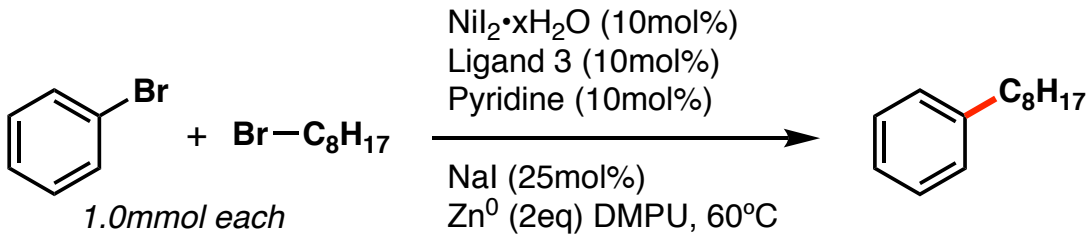
Preliminary Mechanistic Studies

3. Unravelling role of components : *concentration variation study*

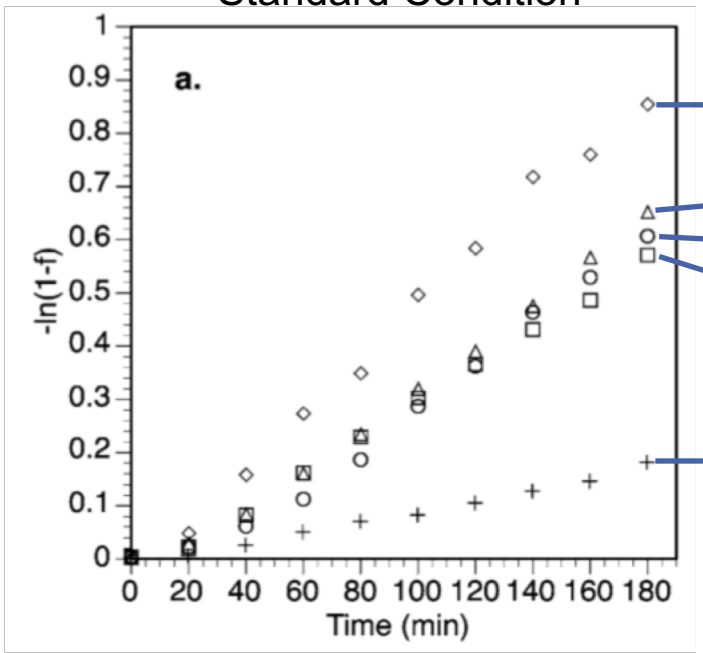


- Reduction is TOF determining
- Ph-Br slows reaction
- TMSCl, 1,2-DBE : reduction ↑

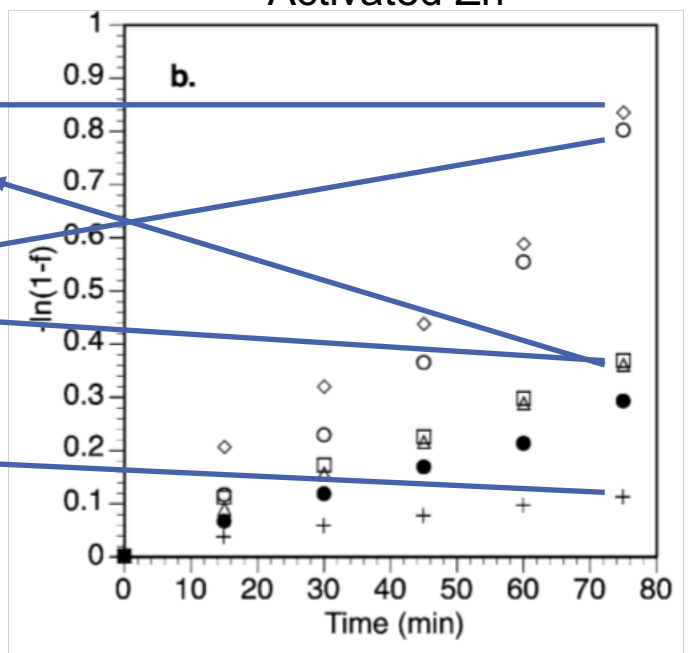
$$v \propto \frac{[R\text{–}Br]^x[Catalyst]^y}{[Ar\text{–}Br]^z}$$

$$-\ln(1-f) = mt$$

Standard Condition



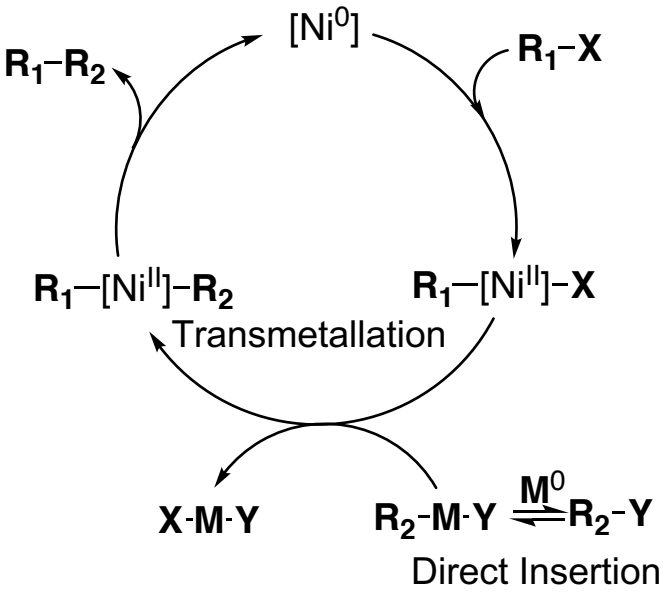
Activated Zn



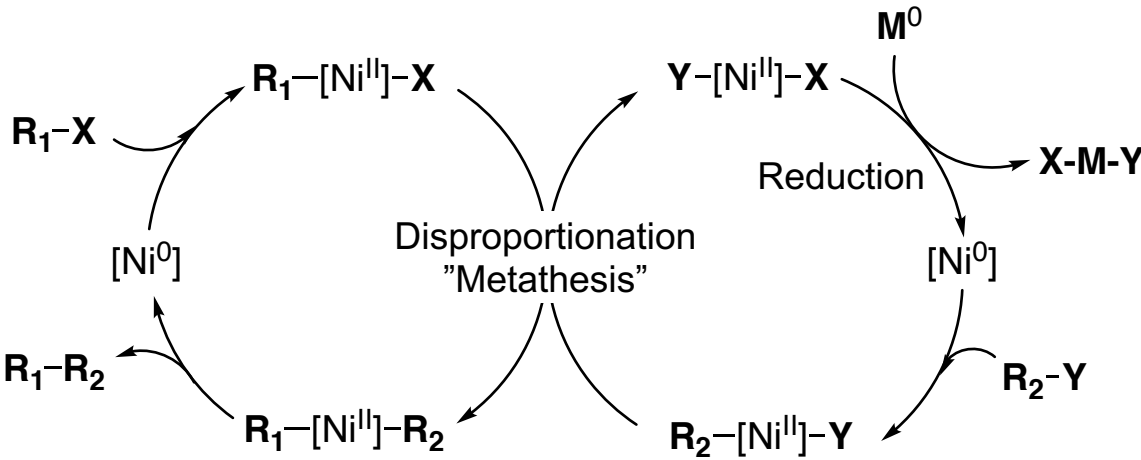
2 x cat. system
2 x Zn
2 x Alkyl-Br
standard
2 x Ph-Br

Plausible Mechanisms

A. Concurrent organometallic synthesis and cross-coupling



B. Disproportionation of Ni intermediates



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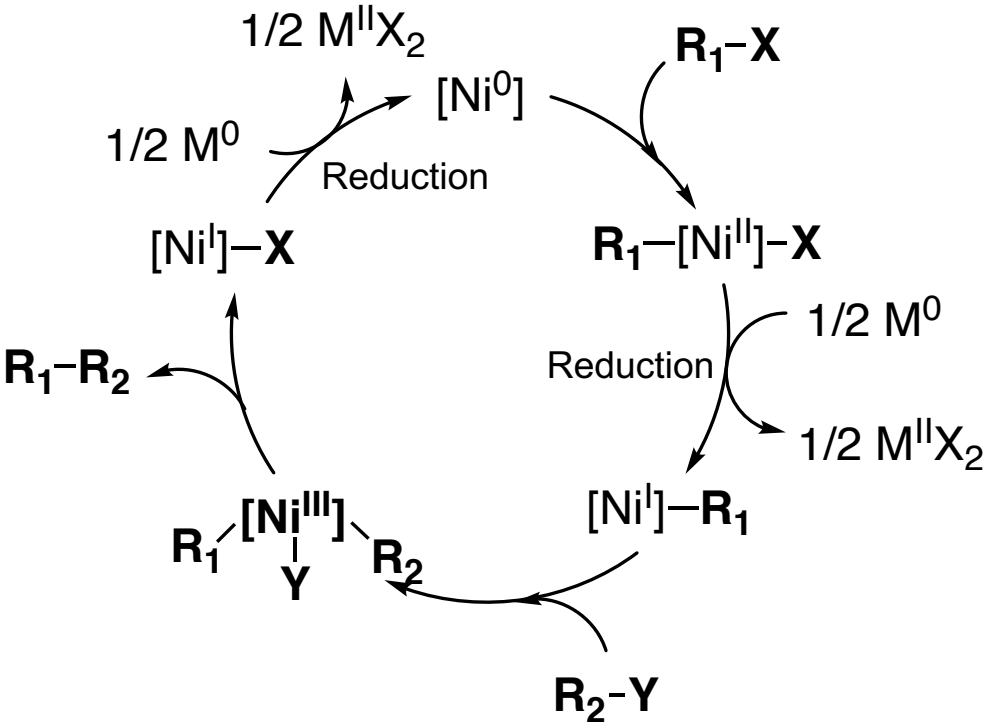
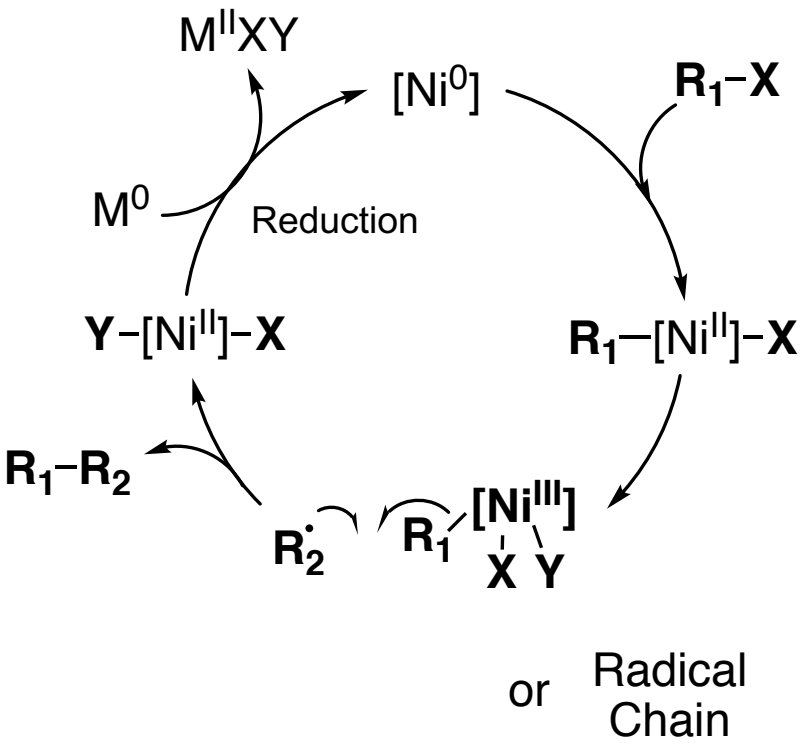
Plausible Mechanisms

C. Sequential oxidative additions



D. Radical reaction



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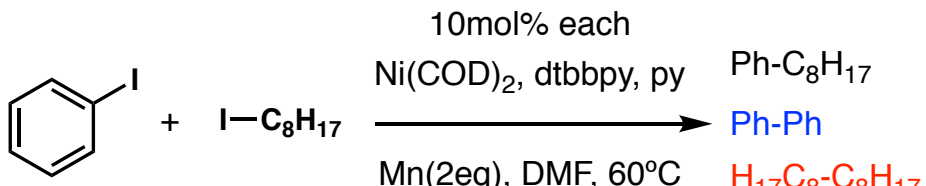
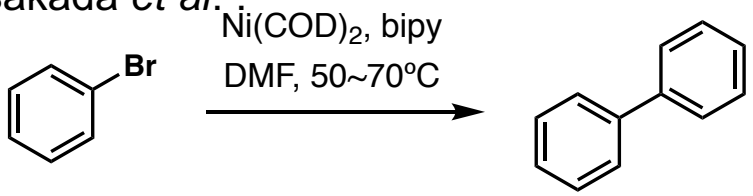
In-Depth Mechanistic Studies

1. Reaction conditions



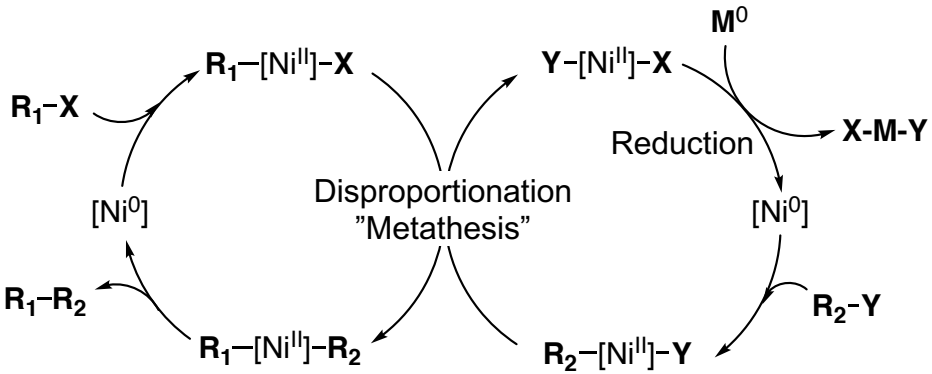
2.1 Ruling out Mechanism B : *Product / Dimer vs Ni conc.*

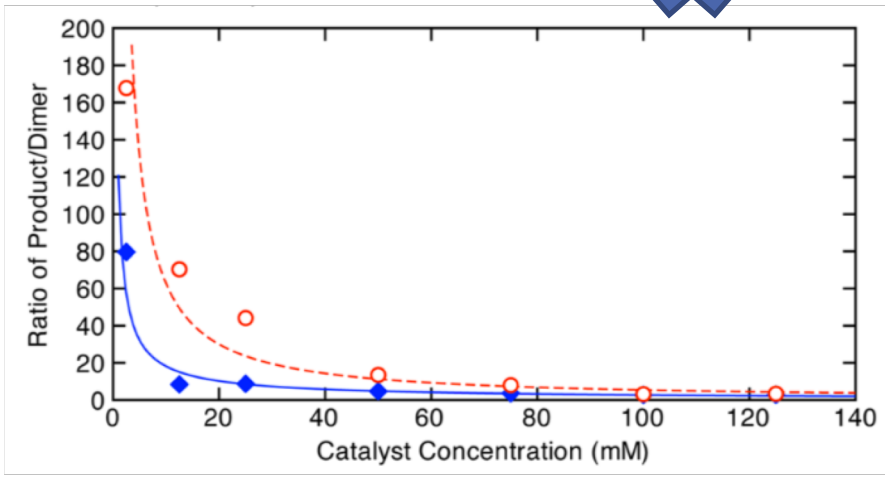
Osakada *et al.* :



$v \propto [Ni]^2$

Selectivity (Ph-C_8H_{17} vs Ph-Ph) $\propto [Ni]^0$





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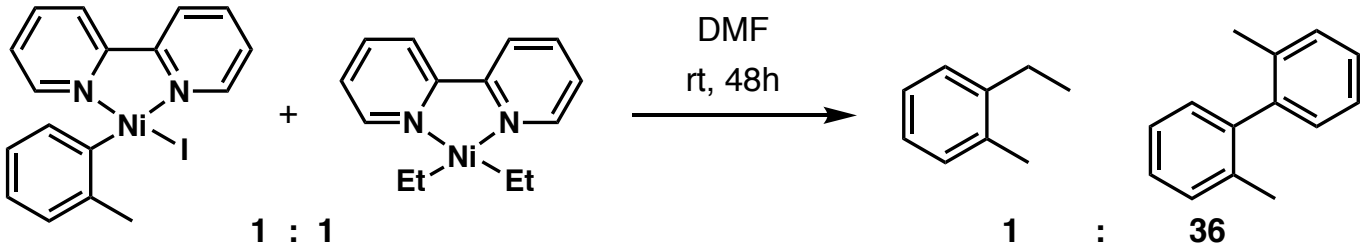
In-Depth Mechanistic Studies

2.2 Ruling out Mechanism B : *Stoichiometric experiment*

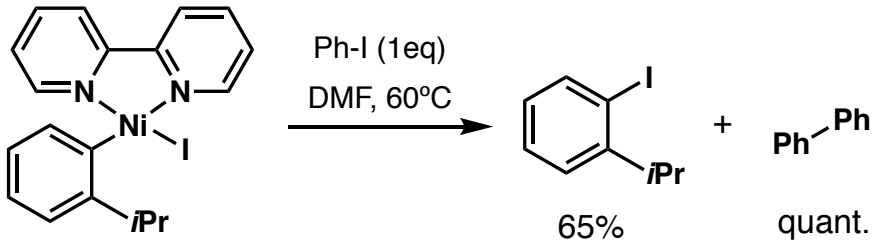


3. Evaluation of oxidative addition for C & D

3.1 *Competitive experiment*

Substrate	conv (%)
Ph-I	89
$H_{17}C_8$-I	19

3.2 *Reversibility experiment*



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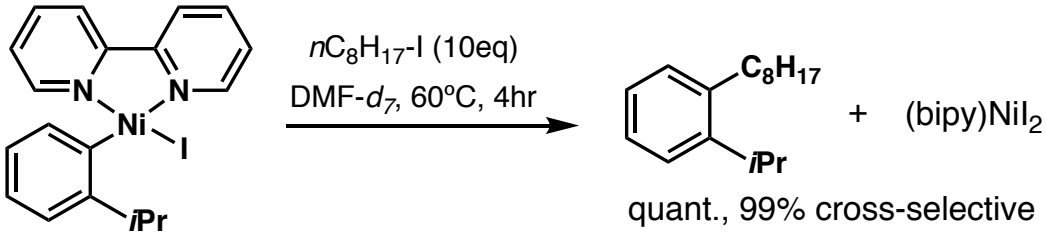
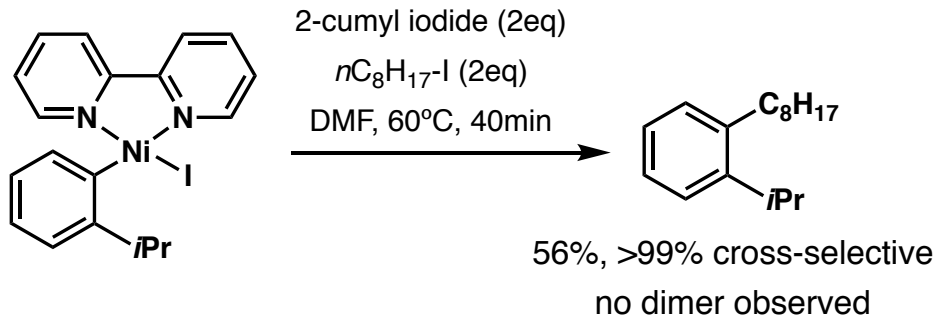
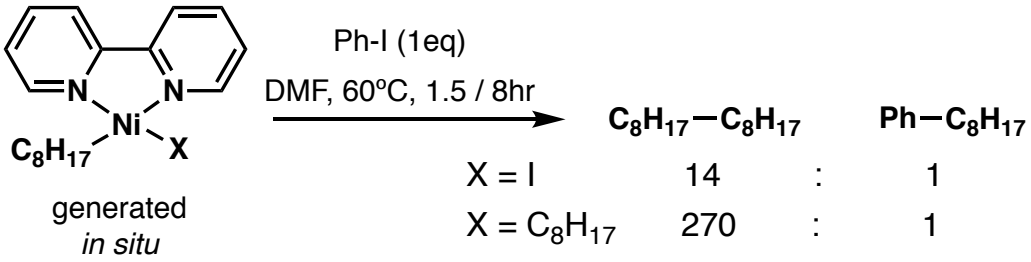
In-Depth Mechanistic Studies

3.3 *Stoichiometric experiments*





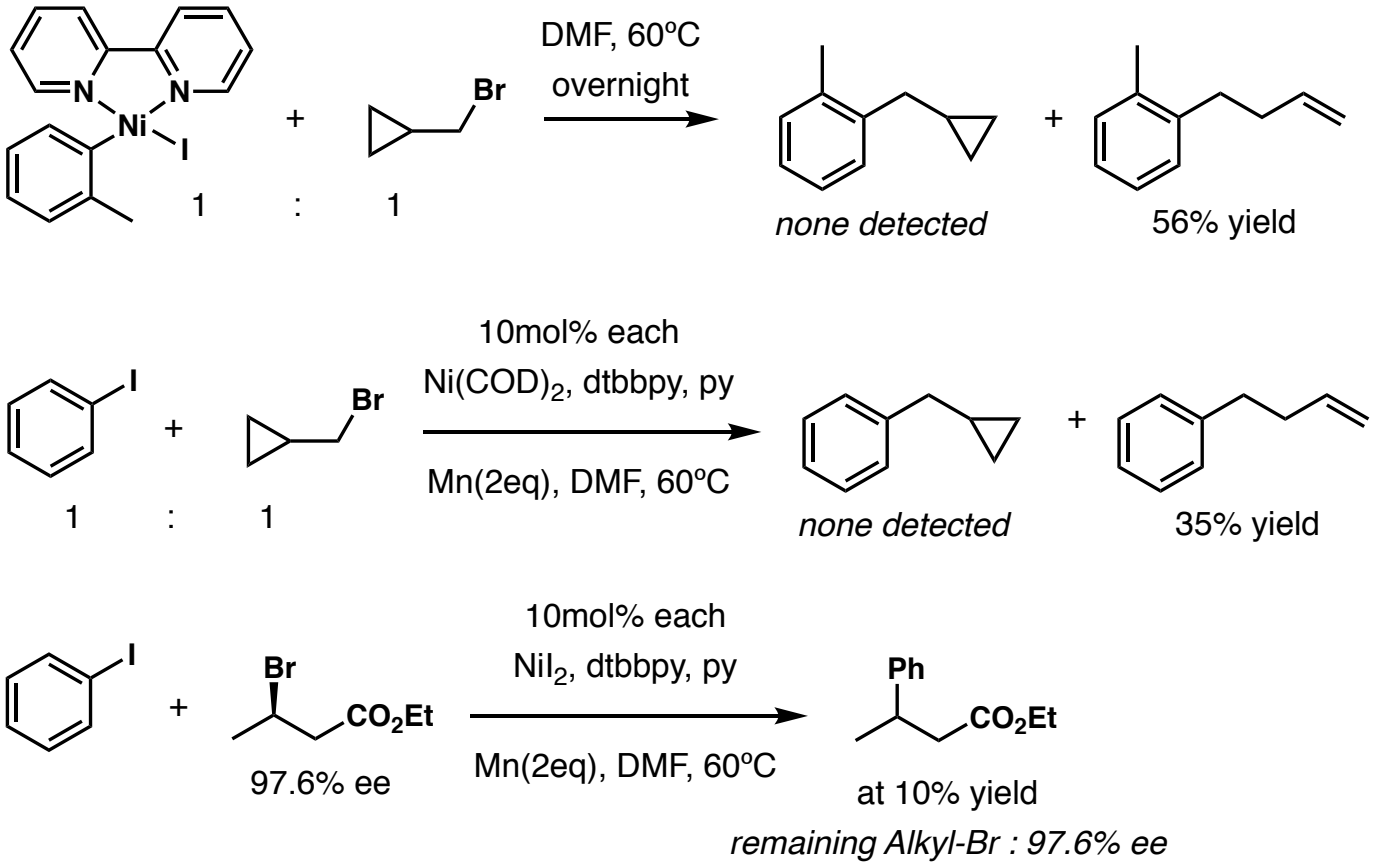
Initial oxidative addition
Ar-I to Ni(0)



S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, **2013**, *135*, 16192-16197

In-Depth Mechanistic Studies

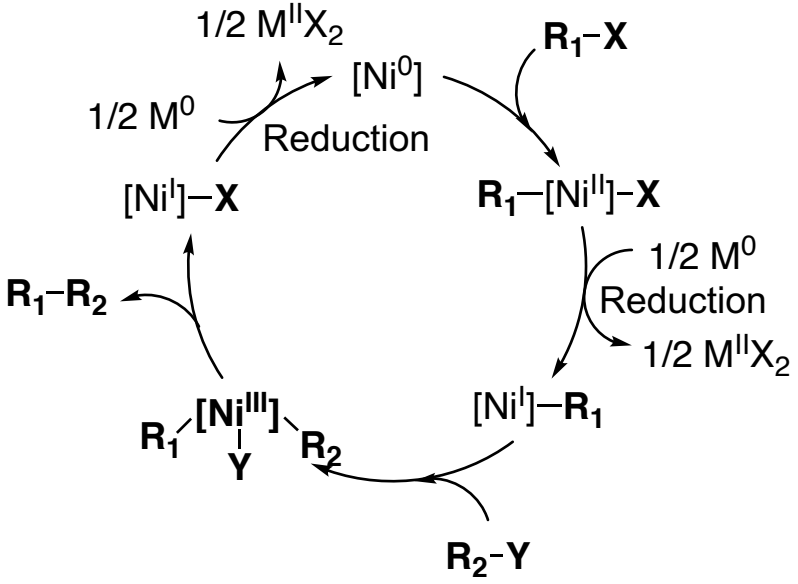
4.1 Evaluation of radical intermediacy for C & D : *radical clock experiment*



S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, **2013**, *135*, 16192-16197

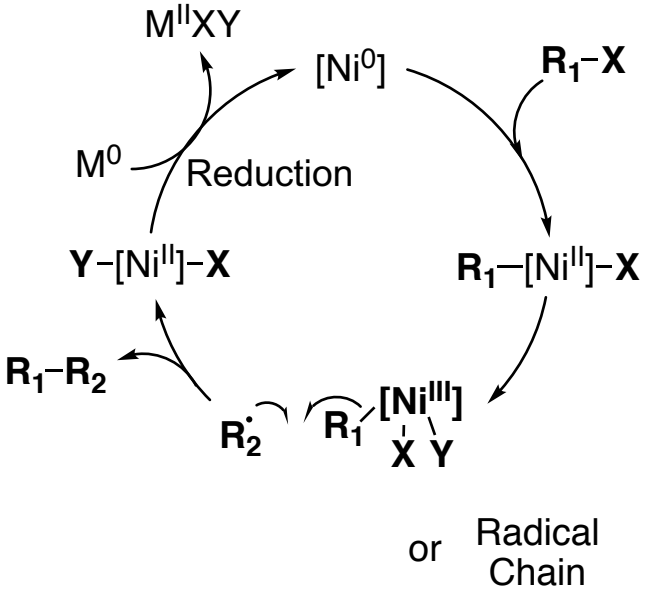
Plausible Mechanisms

C. Sequential oxidative additions



R_2 radical generated & consumed at ***same Ni***

D. Radical reaction

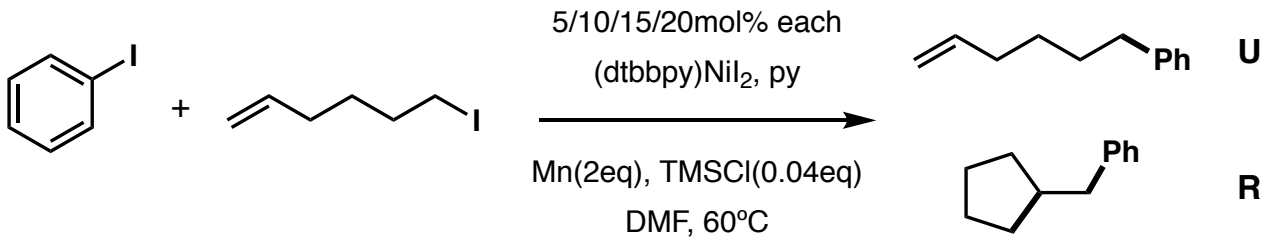


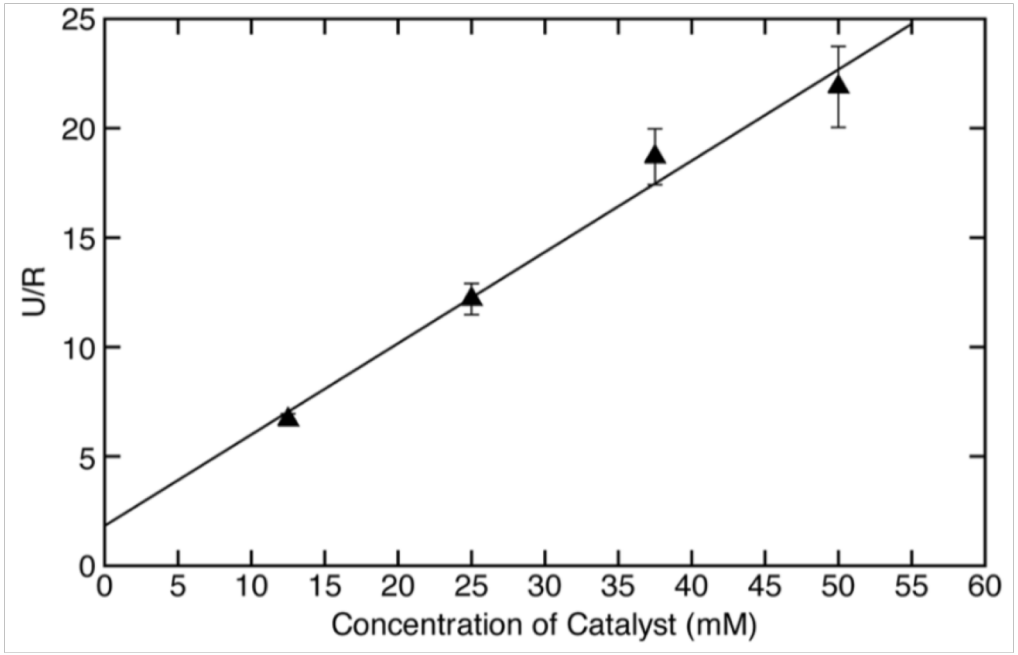
R_2 radical generated & consumed at ***different Ni***

D. J. Weix *et al.*, *J. Am. Chem. Soc.*, **2012**, *134*, 6146-6159

In-Depth Mechanistic Studies

4.1 Evaluation of radical intermediacy for C & D : *radical clock experiment*

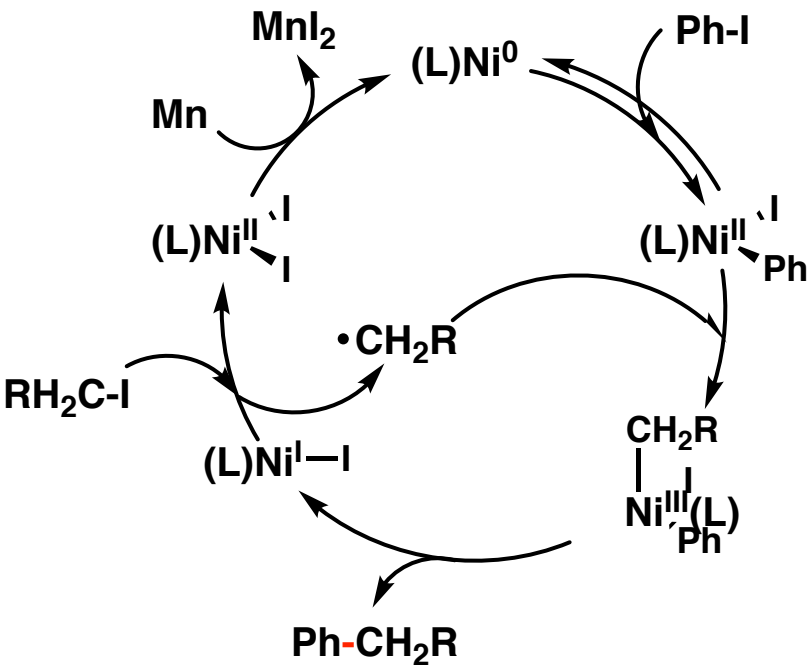




S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, **2013**, *135*, 16192-16197

In Summary…

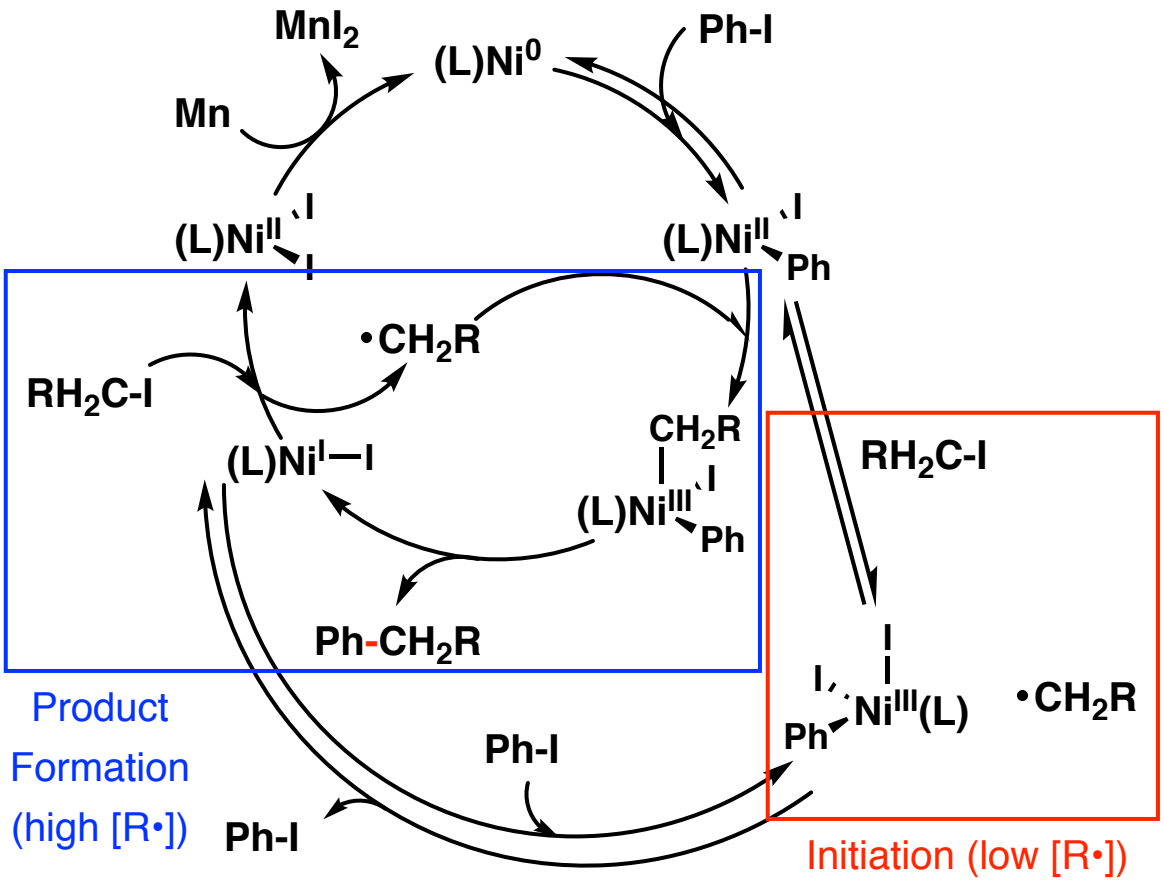
Proposed Mechanism



S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, **2013**, *135*, 16192-16197

In Summary…

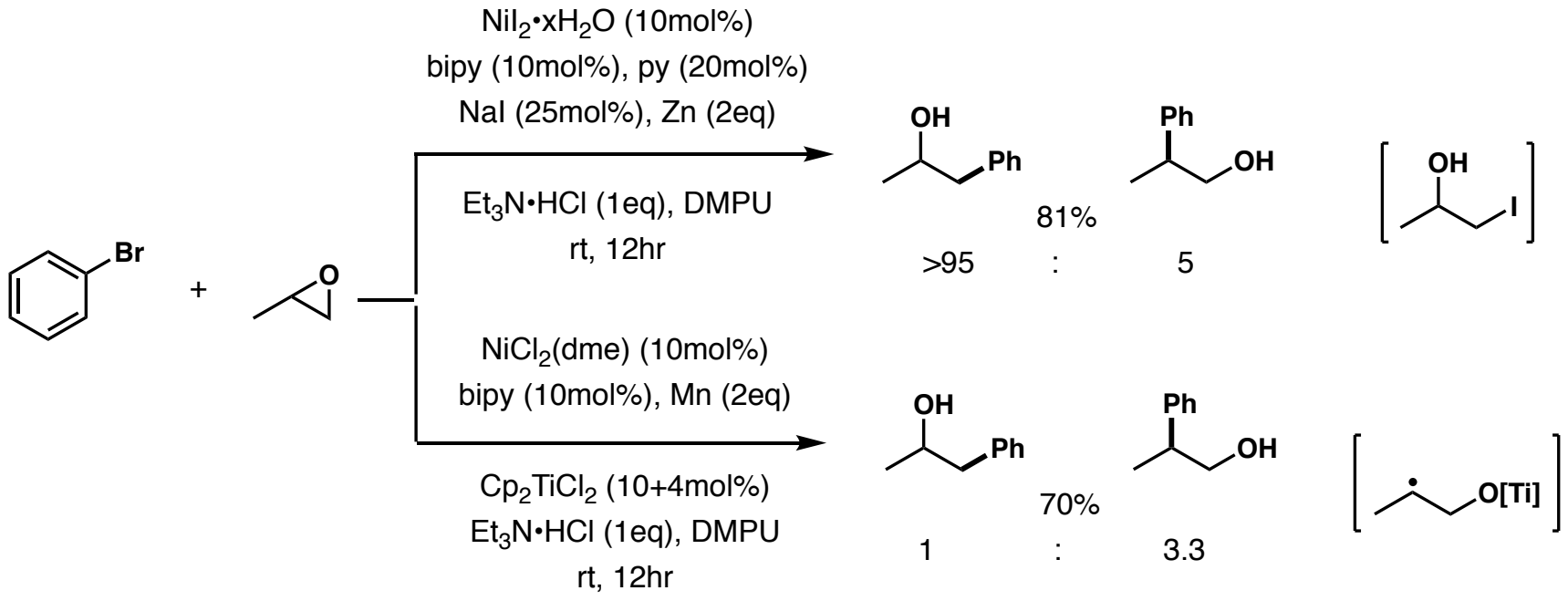
Proposed Mechanism

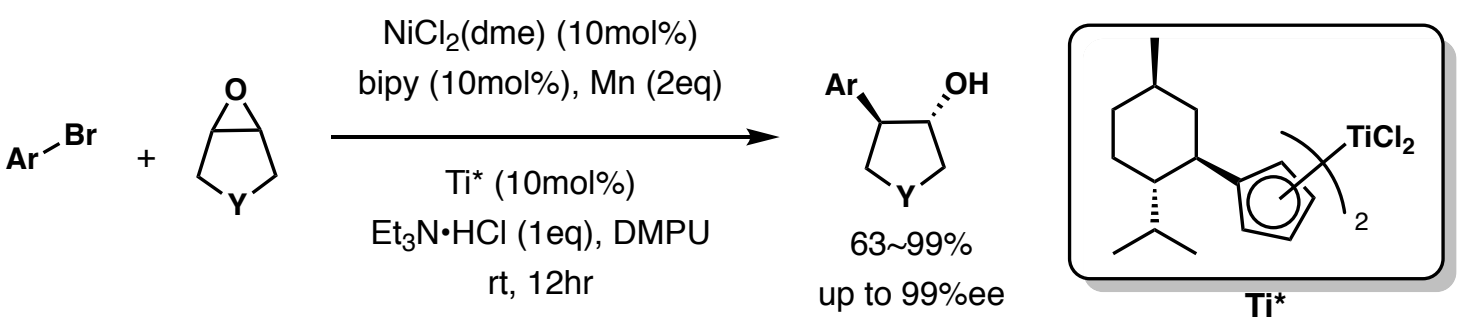


S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, **2013**, *135*, 16192-16197

Other Methodologies

1. Epoxide opening with aryl bromides

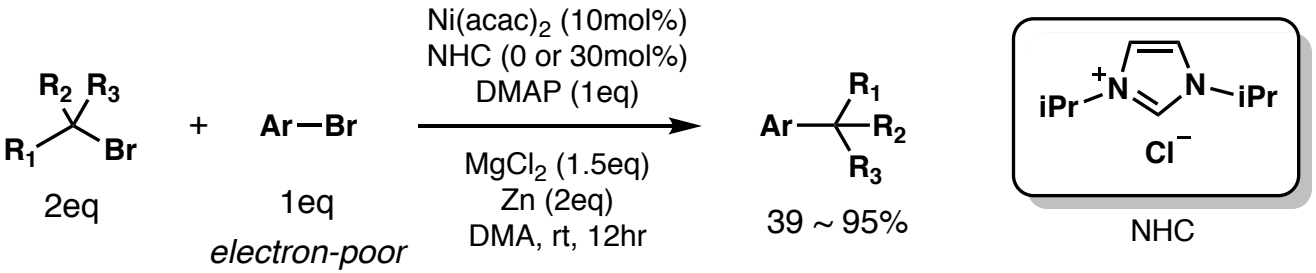


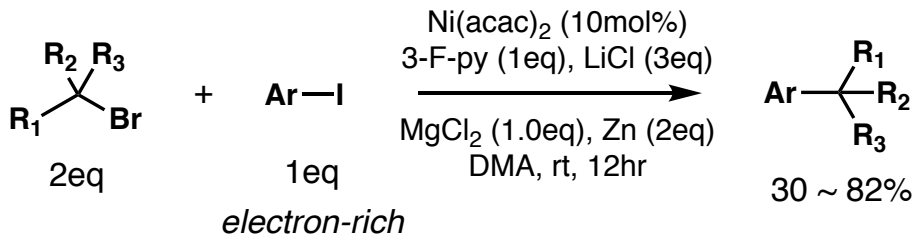


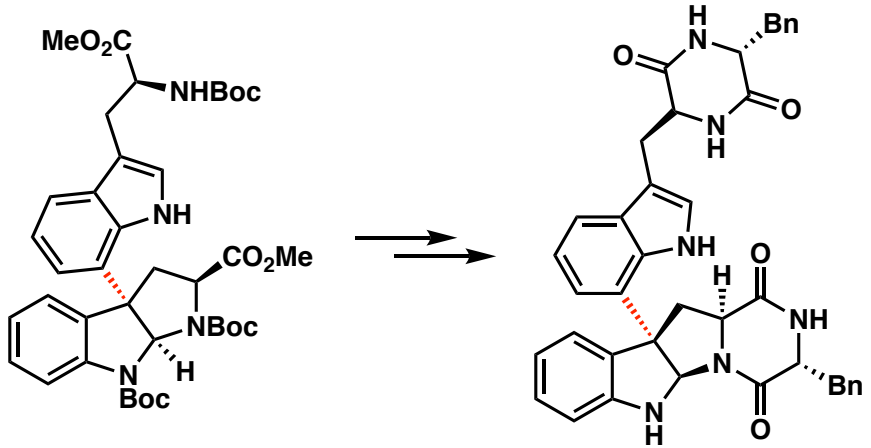
Y. Zhao and D. J. Weix, *J. Am. Chem. Soc.*, **2014**, *136*, 48-51
Y. Zhao and D. J. Weix, *J. Am. Chem. Soc.*, **2015**, *137*, 3237-3240

Other Methodologies

2. Coupling of aryl halides with *tertiary alkyl halides*





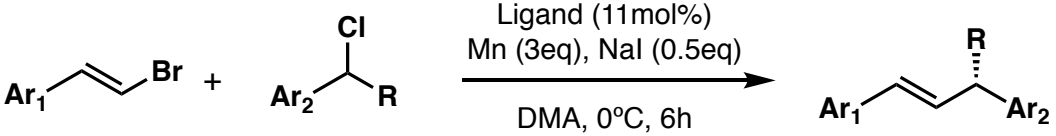


Formal synthesis of (+)-Asperazine

H. Gong *et al.*, *J. Am. Chem. Soc.*, **2015**, *137*, 11562-11565
H. Gong *et al.*, *J. Am. Chem. Soc.*, **2018**, *140*, 14490-14497

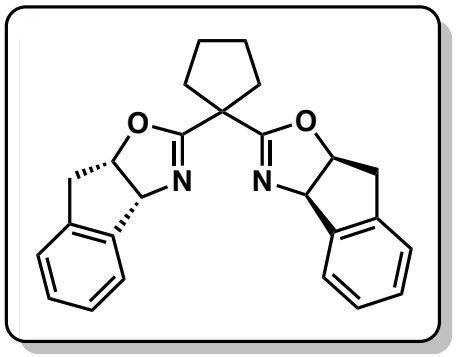
Other Methodologies

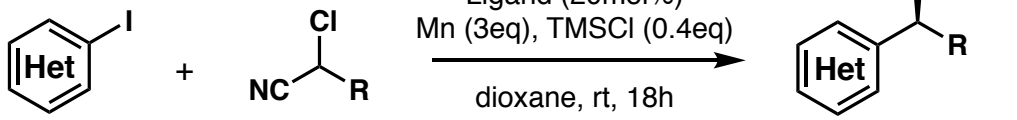
3. Enantioconvergent coupling



0.2mmol scale, 1 : 1

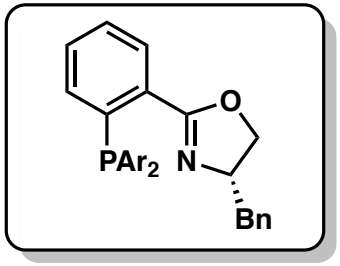
49 ~ 91% yield
88 ~ 97% ee



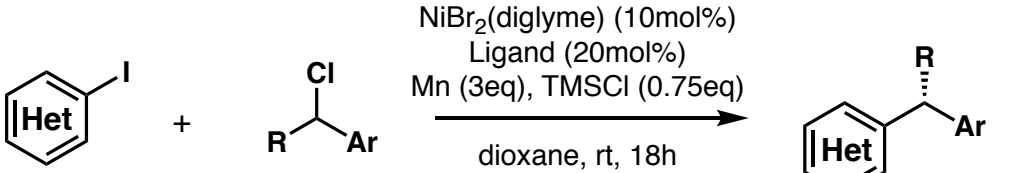


0.2mmol scale, 1 : 1

41 ~ 87% yield
79 ~ 91% ee

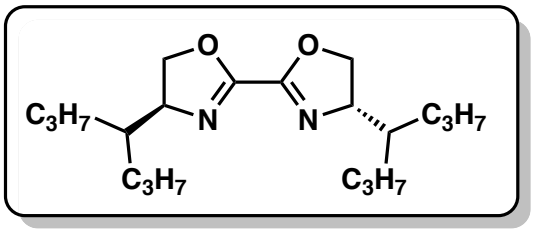


DMMB-PHOX
(Ar = 3,5-dimethyl-
4-methoxyphenyl)



0.2mmol scale, 1 : 1

42 ~ 88% yield
81 ~ 94% ee



BiOX type Ligand

S. E. Reisman *et al.*, *J. Am. Chem. Soc.*, **2014**, *136*, 14365
S. E. Reisman *et al.*, *J. Am. Chem. Soc.*, **2015**, *137*, 10480
S. E. Reisman *et al.*, *J. Am. Chem. Soc.*, **2017**, *139*, 5684

Outlook

1. Application in convergent total synthesis
   - Potential demonstrated in formal syntheses
   (Gong : (+)-Asperazine, Reisman : sertraline)

2. Further methodology development
   - Progress : acyl - alkyl coupling / allyl – alkyl coupling
   alkyne – alkyl coupling / multimetallic catalysis
   - Multicomponent reactions?

Thanks for your attention !