

Beyond Traditional Cross-Coupling Chemistry

I. Background: cross-coupling

- a. the standard mechanism(s)
- b. Nobel prize (**2010**)
- c. *Why do I care?*

II. $\text{sp}^3\text{--}\text{sp}^3$ (alkyl–alkyl) cross-couplings (attached presentation)

III. Emerging sub-fields:

Choice: nickel vs. palladium

Cross-electrophile coupling

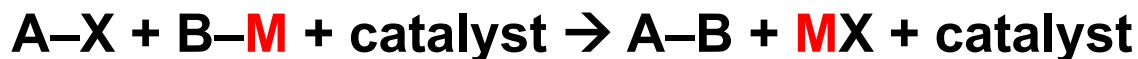
Coupling ‘unreactive’ bonds

Beyond Traditional Cross-Coupling Chemistry

Objectives

1. Understand the progression of discoveries in cross-coupling chemistry.

traditional cross-coupling



cross-electrophile



2. To introduce alternative coupling partners, new reagents and mechanistic cycles involved in transition-metal catalyzed cross-couplings.

3. Inspire you to consider alternative (yet practical) ‘non-traditional’ methods in your future research.

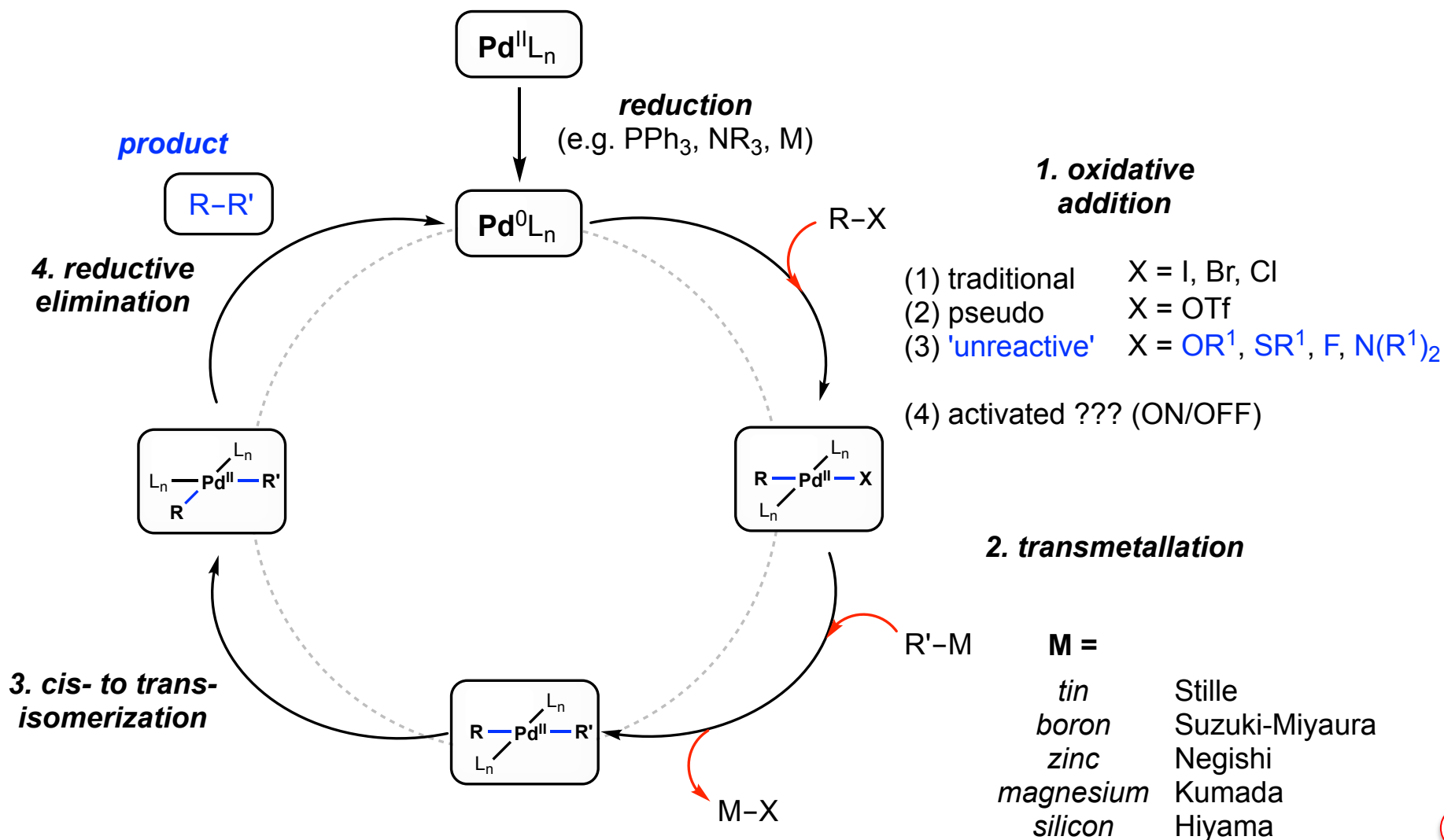
This is not a comprehensive review, check this most recent review.

Richmond, E.; Moran, J. “Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents” *Synthesis* **2018**, 50, 499.

traditional cross-coupling chemistry

I. Background (focus on C–C bond formation)

a. the standard mechanism



Beyond Traditional Cross-Coupling Chemistry

I. Background (focus on C–C bond formation)

b. Nobel prize (2010)



Richard F. Heck
University of Delaware
Newark, Delaware, USA
b. 1931 d. 2015 (84)



Professor Ei-ichi Negishi
Purdue University
West Lafayette, Indiana, USA
b. 1935 (82)



Professor Akira Suzuki
Hokkaido University
Sapporo, Japan
b. 1930 (87)

8			9	10
VIII B				
26	27	28		
Fe	Co	Ni		
Iron	Cobalt	Nickel		
55.845	58.933	58.693		
2-8-14-2	2-8-15-2	2-8-16-2		
44	45	46		
Ru	Rh	Pd		
Ruthenium	Rhodium	Palladium		
101.07	102.91	106.42		
2-8-18-15-1	2-8-18-16-1	2-8-18-18		



“This year’s Nobel Prize in Chemistry concerns the development of methods for **palladium catalyzed formation of carbon-carbon bonds** via so-called cross-coupling reactions. The formation of new carbon-carbon bonds is of central importance in organic chemistry and a prerequisite for all life on earth.”

from Scientific Background on the Nobel Prize in Chemistry (2010)

Beyond Traditional Cross-Coupling Chemistry

I. Background (focus on C–C bond formation)

c. Why do I care?

- sophomore organic chemistry covers general cross-coupling (2006)
i.e. Suzuki coupling
- my last formal class about catalysis, cross-coupling (2009)
- organize and formulate ideas / themes

what does this mean? categorize and turn into useful tools

- identify common themes, branding (e.g. cross-electrophile)
- reading papers, attending seminars, watching groups...
- consider/perform cross-coupling reactions in the lab
- understand off-cycle products that deviate from the traditional coupling mechanisms

inspiration: propose currently impossible transformations!

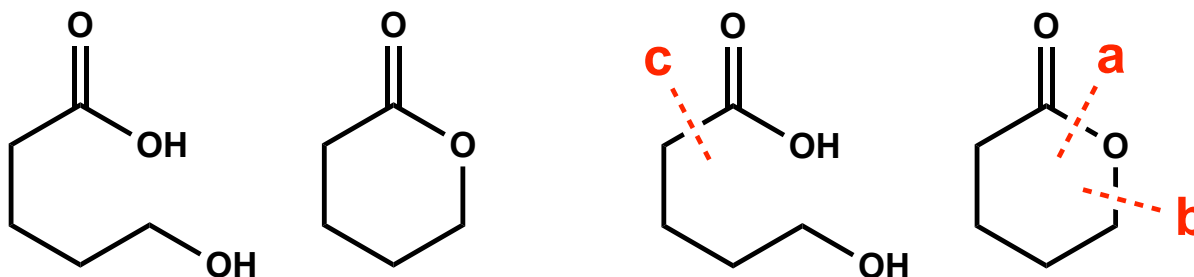
exercise

I. Background (focus on C–C bond formation)

lactone example:

what reactions do you know?

*can you cleave site **a**, **b** or **c**?*



inspiration: propose currently impossible transformations!

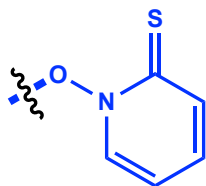
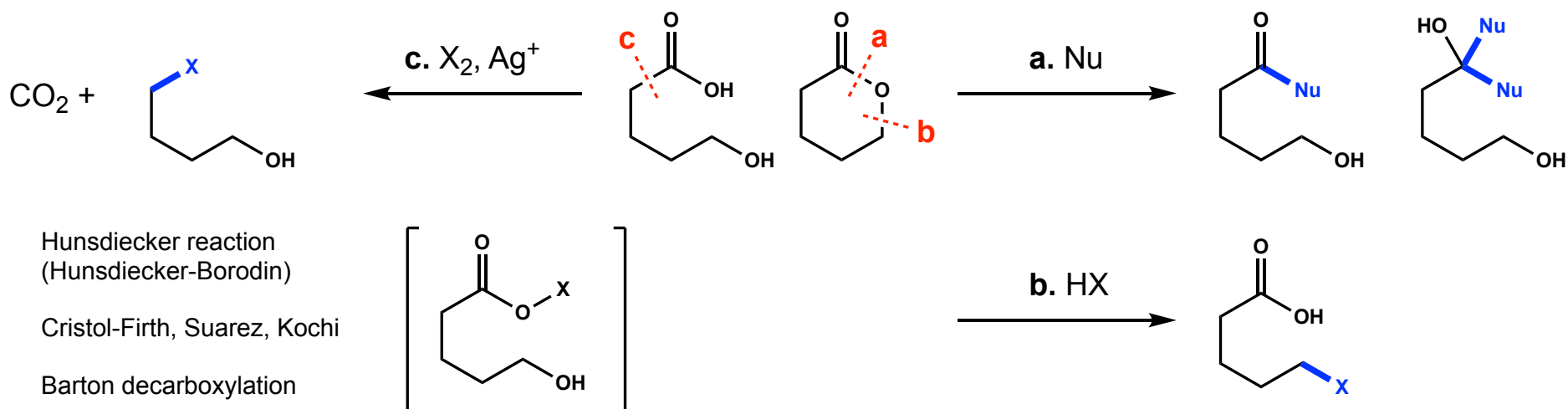
exercise

I. Background (focus on C–C bond formation)

lactone example:

*can you cleave site **a**, **b** or **c**?*

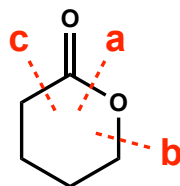
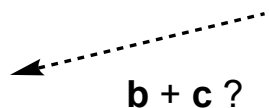
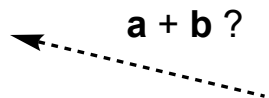
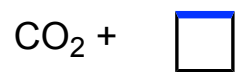
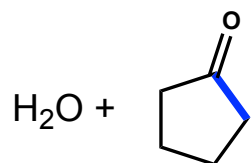
are the resultant products electrophilic?



exercise

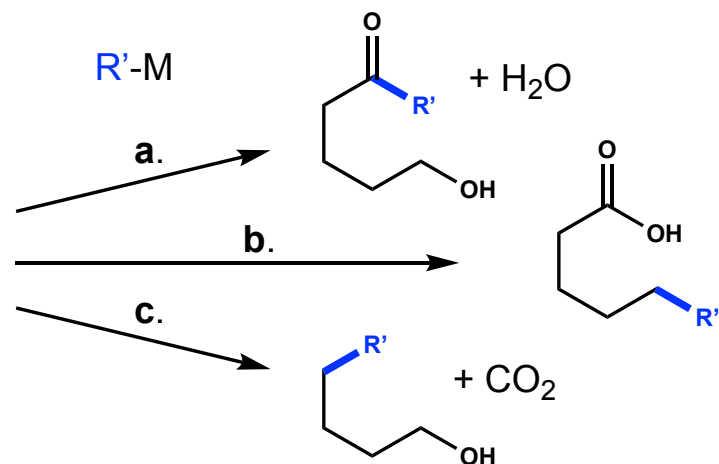
I. Background (focus on C–C bond formation)

cross-electrophile
(intramolecular)

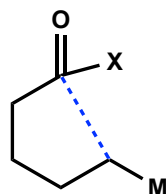


traditional
cross-coupling

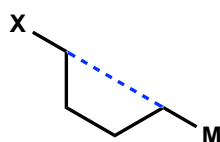
'unreactive' bonds
C–O, C–C



$\text{a} + \text{b}$



$\text{b} + \text{c}$



*not all functional groups are
compatible with stoichiometric
organometallics*

of course, prefunctionalization
is also an option

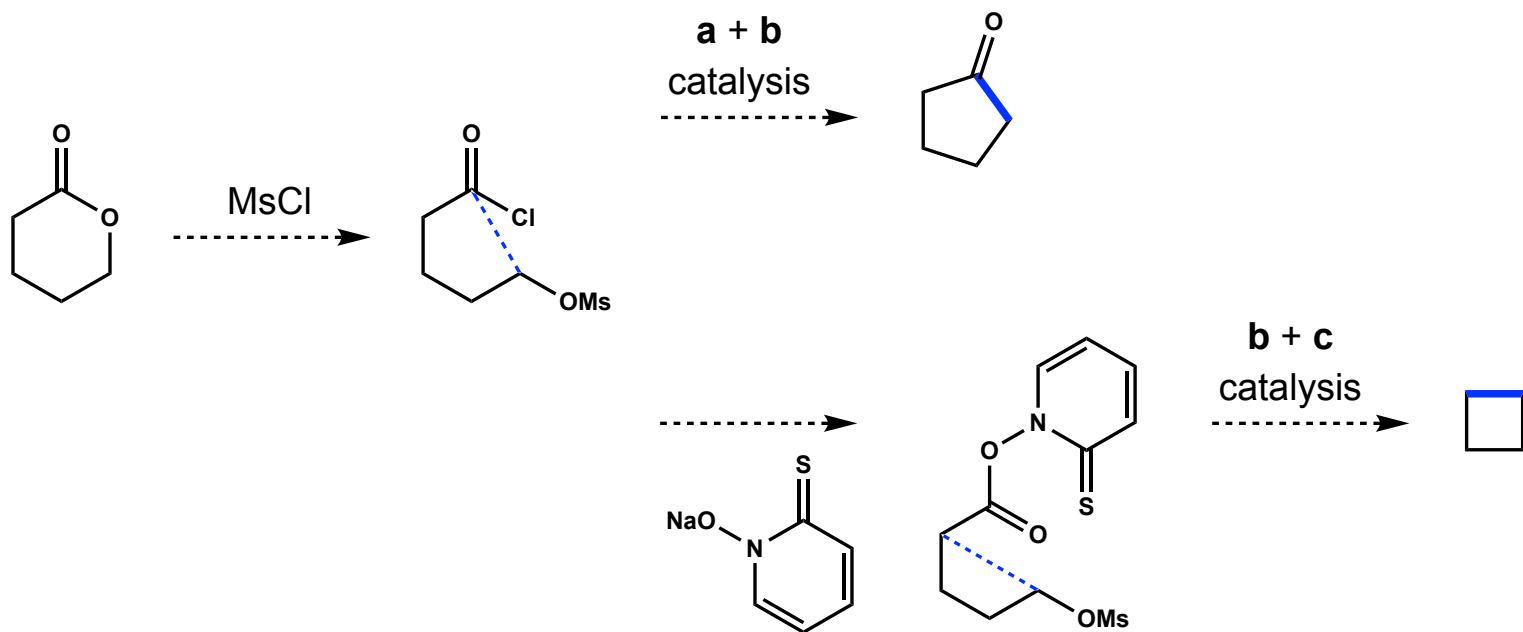
exercise

I. Background (focus on C–C bond formation)

c. Why do I care?

'unreactive' bonds

cross-electrophile coupling (reductive)



C–N bond cleavage: an example

I. Background (focus on C–C bond formation)

c. Why do I care?

'unreactive' bonds

alkyl transfer from nitrogen?

three problems

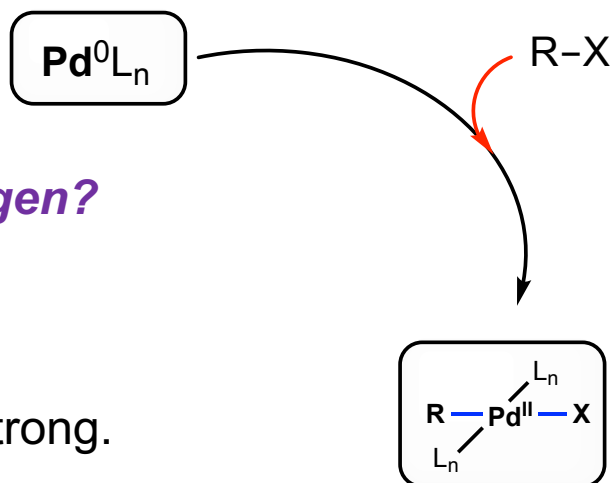
1. The C–N bond is strong.

–F > –H > –OR (ether) > –C (carbon) > –NR₂ (amine) >

–Cl > –OTf > –Br > –SR (sulfide) > –I

2. Amines are coordinating, can poison or slow catalysis.
Both before and after cleavage.

3. Selectivity. (multiple, up to three C–N bonds in substrate)



1. oxidative addition

- (1) traditional $\text{X} = \text{I}, \text{Br}, \text{Cl}$
- (2) pseudo $\text{X} = \text{OTf}$
- (3) 'unreactive' $\text{X} = \text{OR}^1, \text{SR}^1, \text{F}, \text{N}(\text{R}^1)_2$
- (4) activated?

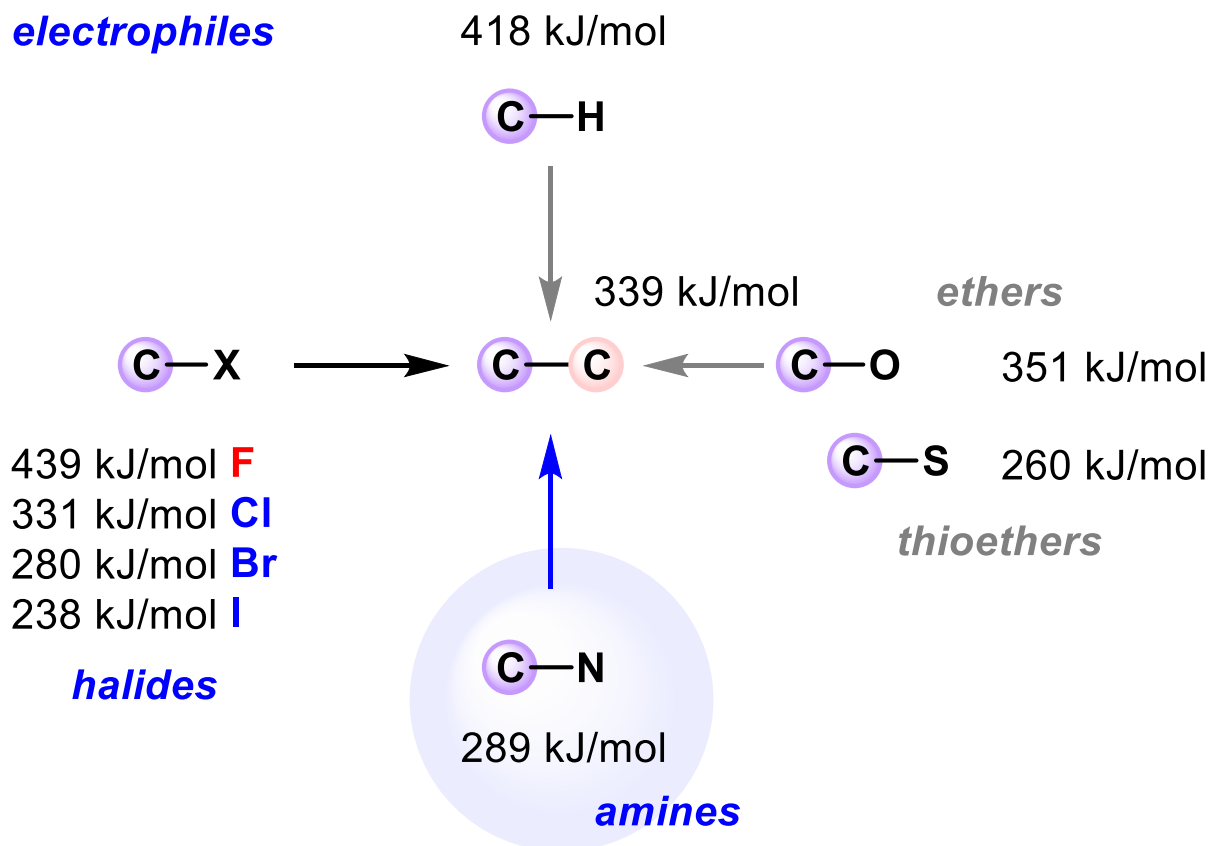
C–N bond cleavage: an example

I. Background (focus on C–C bond formation)

c. Why do I care?

compatible electrophiles for oxidative addition?

electrophiles



<u>C--X</u>	<u>kJ/mol</u>	<u>kcal/mol</u>
C--F	439	104.9
C--H	418	99.9
C--OR	351	83.9
C--C	339	81.0
C--Cl	331	79.1
C--N	289	69.1
C--Br	280	66.9
C--SR	260	62.1
C--I	238	56.9

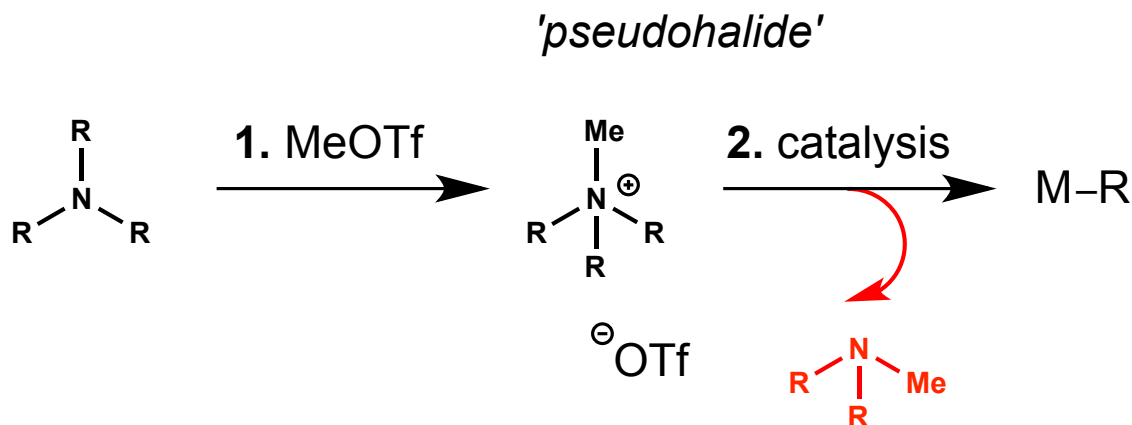
C–N bond cleavage: an example

I. Background (focus on C–C bond formation)

alkyl transfer from nitrogen?

2. Amines are coordinating, can poison or slow catalysis.
Both before and after cleavage.

the most common method of activation is peralkylation (quaternization)



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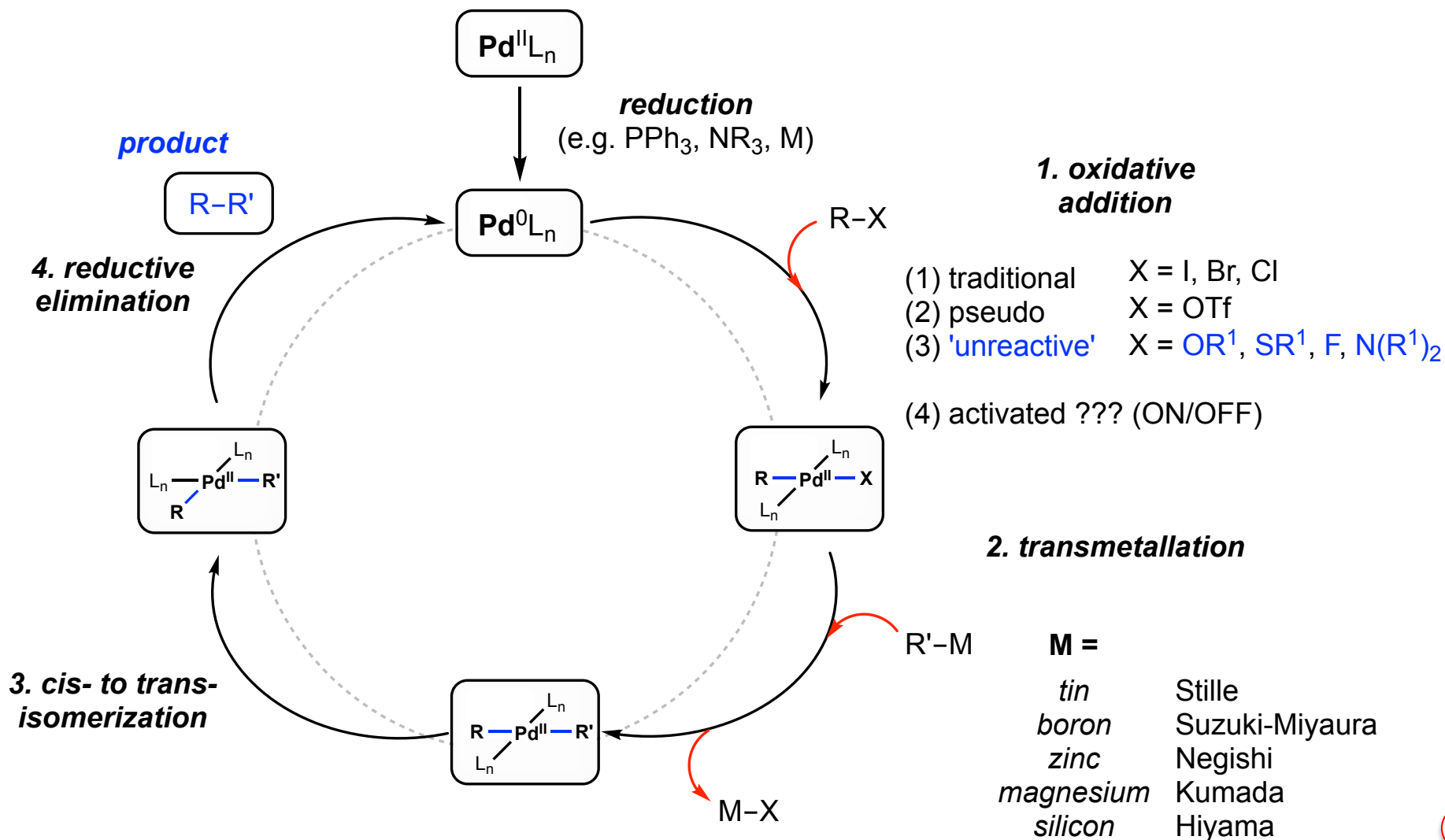
Cross-electrophile coupling

Coupling ‘unreactive’ bonds

standard cross-coupling mechanism

II. Transition metal catalyzed cross-coupling

sp^3 – sp^3 cross-couplings (see attached presentation, 2013)

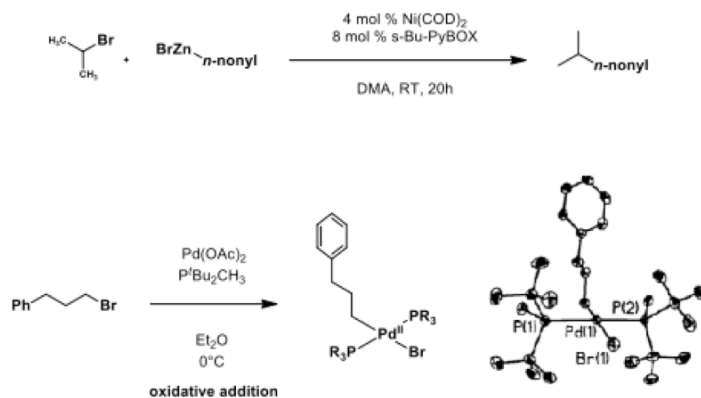


another presentation...

II. Transition metal catalyzed cross-coupling

sp^3 – sp^3 cross-couplings (see attached presentation, 2013)

Palladium and Nickel Cross Coupling *Focus: sp^3 – sp^3 (alkyl) coupling*



March 7, 2013

Roberts, Group Meeting

University of California Los Angeles



50 slides

highlights: sp^3-sp^3

II. Transition metal catalyzed cross-coupling

sp^3-sp^3 cross-couplings (see attached presentation, **2013**)

highlights

palladium methods

1. *B-alkyl* Suzuki (RI and R⁹BBN – recent advances)
2. Suzuki based sp^3-sp^3 cross-couplings
3. Negishi and Kumada based sp^3-sp^3 cross-couplings (Prof. Greg Fu)

nickel methods and mechanisms

1. Negishi and Kumada based sp^3-sp^3 cross-couplings (Prof. Greg Fu)
2. Demonstrated a unique ligand mechanism for Ni cross couplings
3. Several practical reductive homo/heterocouplings (cross-electrophile)

Cobalt cross couplings are also general (in parallel to Ni) although there are fewer examples with ligand control.

additional literature

Nickel Catalysis for $\text{sp}^3\text{--sp}^3$ Cross Coupling (alkyl–alkyl)

1999_JOC_Knochel_New Efficient Nickel-Catalyzed Cross-Coupling Reaction between Two Csp^3 Centers

2001_JOC_Knochel_Nickel-Catalyzed Cross-Coupling between Functionalized Primary or Secondary Alkylzinc Halides and Primary Alkyl Halides

2005_ACIEE_Beller_Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides

2006_JACS_Vicic_Ligand Redox Effects in the Synthesis, Electronic Structure, and Reactivity of an Alkyl–Alkyl Cross-Coupling Catalyst

2011_ChemRev_Sigman_Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-coupling Reactions using Alkyl-organometallics as Reaction Partners

2013_JACS_Hu_Bimetallic Oxidative Addition Involving Radical Intermediates in Nickel-Catalyzed Alkyl–Alkyl Kumada Coupling Reactions

2016_JACS_Cook_Manganese-Catalyzed Borylation of Unactivated Alkyl Chlorides

2016_Science_Baran_A general alkyl–alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents

2017_Science_Fu_Transition metal–catalyzed alkyl-alkyl bond formation: Another dimension in cross-coupling chemistry

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Choice: nickel vs. palladium

Cross-electrophile coupling

Coupling ‘unreactive’ bonds

Beyond Traditional Cross-Coupling Chemistry

III. Emerging subfields within cross-coupling (7+ fields!)

Which of these sub-fields apply to your coupling of interest?

Utility of non-traditional palladium (II, III, IV) cycles

(Sanford, Ritter, Yu, Doyle, ...)

C–H functionalization (CCHF)

Photoredox catalysis (and the merge with transition metals)

(Yoon, Stephenson, Macmillan, Doyle, Molander, Baran, ...)

Radicals and electrochemical intermediates intercepted by transition metals

Choice: nickel vs. palladium

Cross-electrophile couplings

(Corey, Montgomery, Semmelhack, Knochel, Hu, Gong, **Weix**, ...)

Functionalization of unreactive bonds (interest in C–N bond cleavage)

(Chatani, Jarvo, Jamison, Doyle, Watson, Garg, Szostak, ...)

nickel & palladium: how to decide

Choice: nickel vs. palladium

always consider the overall cost (metal + ligand)

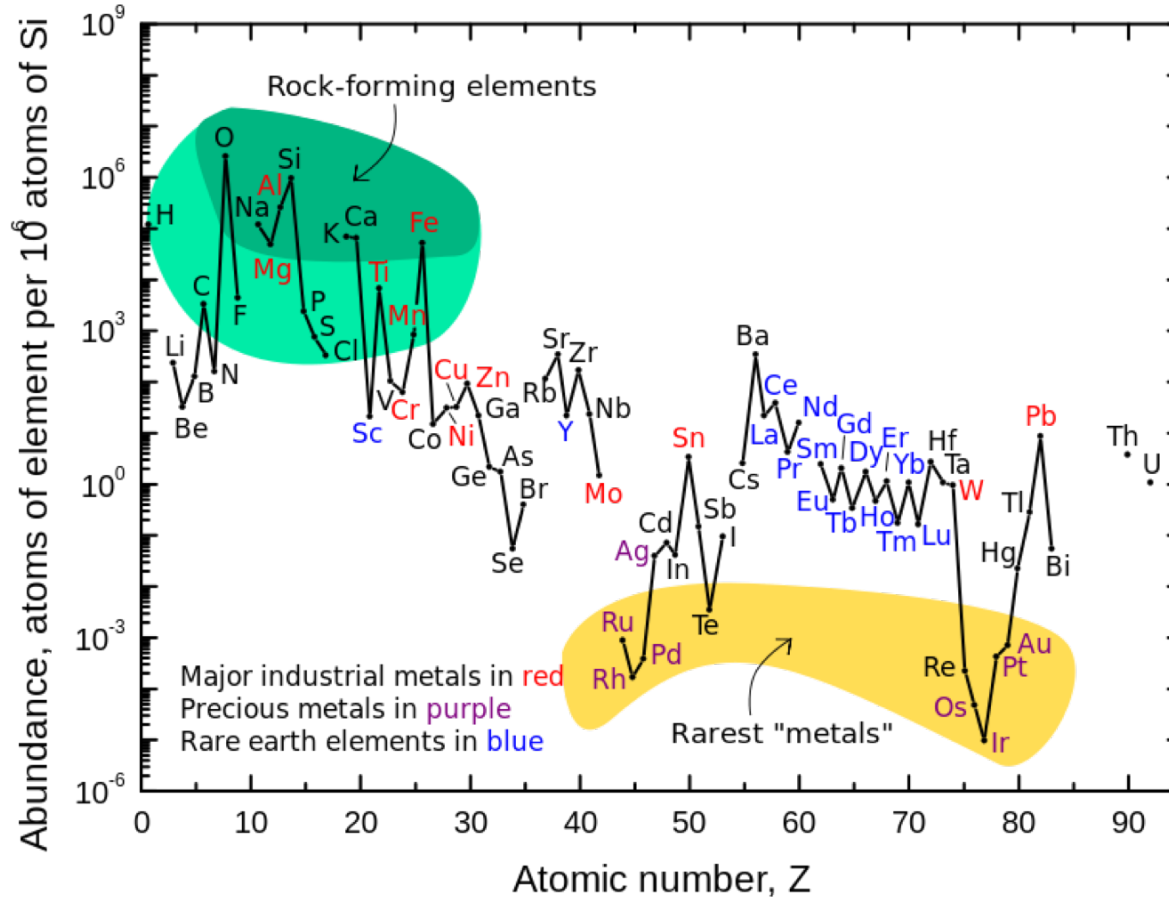


image: Relative abundance of elements in the Earth's upper crust (2003)
U.S. Geological Survey (<http://pubs.usgs.gov/fs/2002/fs087-02>)

nickel & palladium: how to decide

Choice: nickel vs. palladium

How do you choose between nickel and palladium?

- cost:** quoted at 2,000 × cheaper than Pd, 10,000 × cheaper than Pt
(mole-for-mole basis, but...always consider loading and the ligand price!)
- consider either privileged catalyst for alkene/alkyne coordination, reductive coupling conditions (standard cross-couplings vs cyclization, cascade reactions, oligomerization)
- consider available/required oxidation states and cycle
- nickel is more electropositive, radicophilic (*often stated but what does it mean?*)
oxidative-addition is more likely, but reductive elimination is more difficult
- metal to ligand and metal to substrate electron donation
the radical character of Ni is more dynamic (dynamic kinetic resolution)
- beta-hydride elimination is slower:** due to higher energy of Ni–C bond rotation vs. Pd–C (key for difficult sp^3 or alkyl–alkyl cross-couplings)

nickel & palladium: how to decide

Choice: nickel vs. palladium

Articles that discuss nickel vs. palladium and the emergence of nickel.

***1985_JACS_Morokuma_Role of Agostic Interaction in Beta-Elimination of Pd and Ni Complexes**

2004_Organometallics_Guo_Comparing Nickel- and Palladium-Catalyzed Heck Reactions

2011_ChemRev_Percec_Nickel-Catalyzed Cross-Couplings Involving Carbon–Oxygen Bonds

2014_Nature_Jamison_Recent advances in homogeneous nickel catalysis

2015_CJC_Liu_Recent advances in mechanistic studies on Ni catalyzed cross-coupling reactions

2015_ACSCat_Ananikov_Nickel: The “Spirited Horse” of Transition Metal Catalysis

2015_ACR_Jamison_Nickel Catalysis: Synergy between Method Development and Total Synthesis

2015_ACR_Shi_Exploration of Earth-Abundant Transition Metals (Fe, Co, and Ni) as Catalysts in Unreactive Chemical Bond Activations

2015_ChemRev_Resiman_Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C–C Bonds

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Cross-electrophile coupling

Coupling ‘unreactive’ bonds

the Wurtz reaction (homodimerization)

Electrophile homocouplings + electrochemical (not discussed)

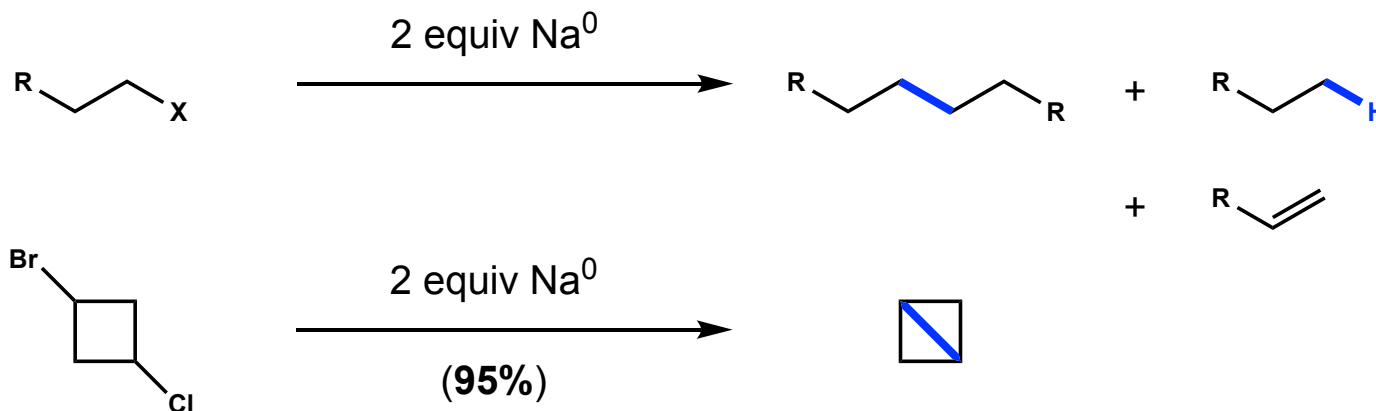
(Corey, Semmelhack, Kochi, Knochel, Hu, Gong, Weix)

inspiration: homocoupling of alkyl halides

First, you must know the Wurtz Reaction (1855)

Ueber eine neue Klasse organischer Radicale;
nach A. Wurts.

On a New Class of Organic Radicals



can there be control?

Cross-electrophile couplings

can there be control? proposed (Weix, 2008)

heterocoupling ('cross-electrophile') of aryl and alkyl halides
assume identical reactivity and no organometallic intermediates



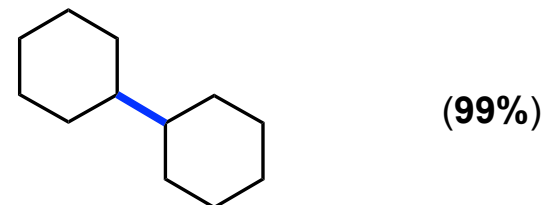
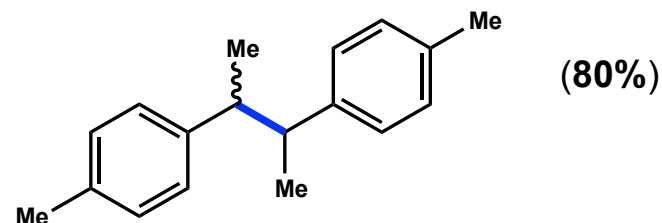
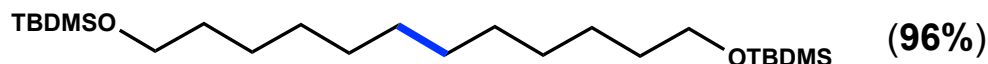
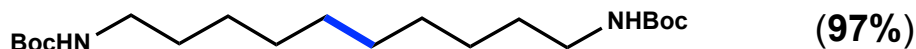
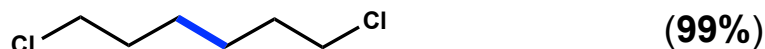
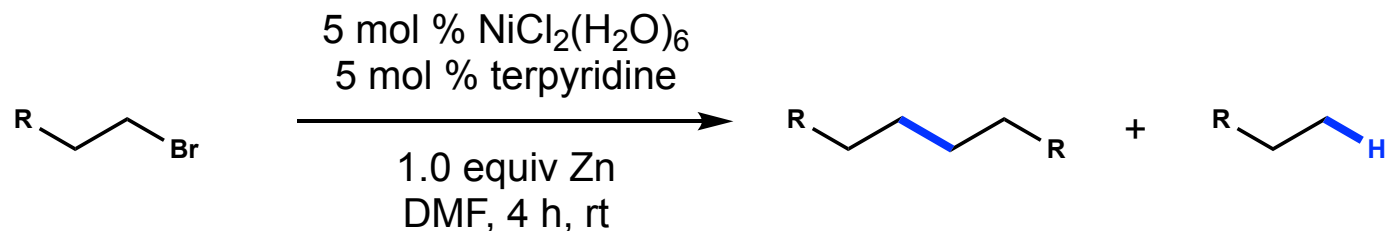
$n = 1$ 50% max. statistical yield, **1:1** **product** : dimers

$n = 2$ 80% max. statistical yield, **1:1.25** **product** : dimers

$n = 3$ 86% max. statistical yield, **1:1.67** **product** : dimers

a new homocoupling method: substrate scope

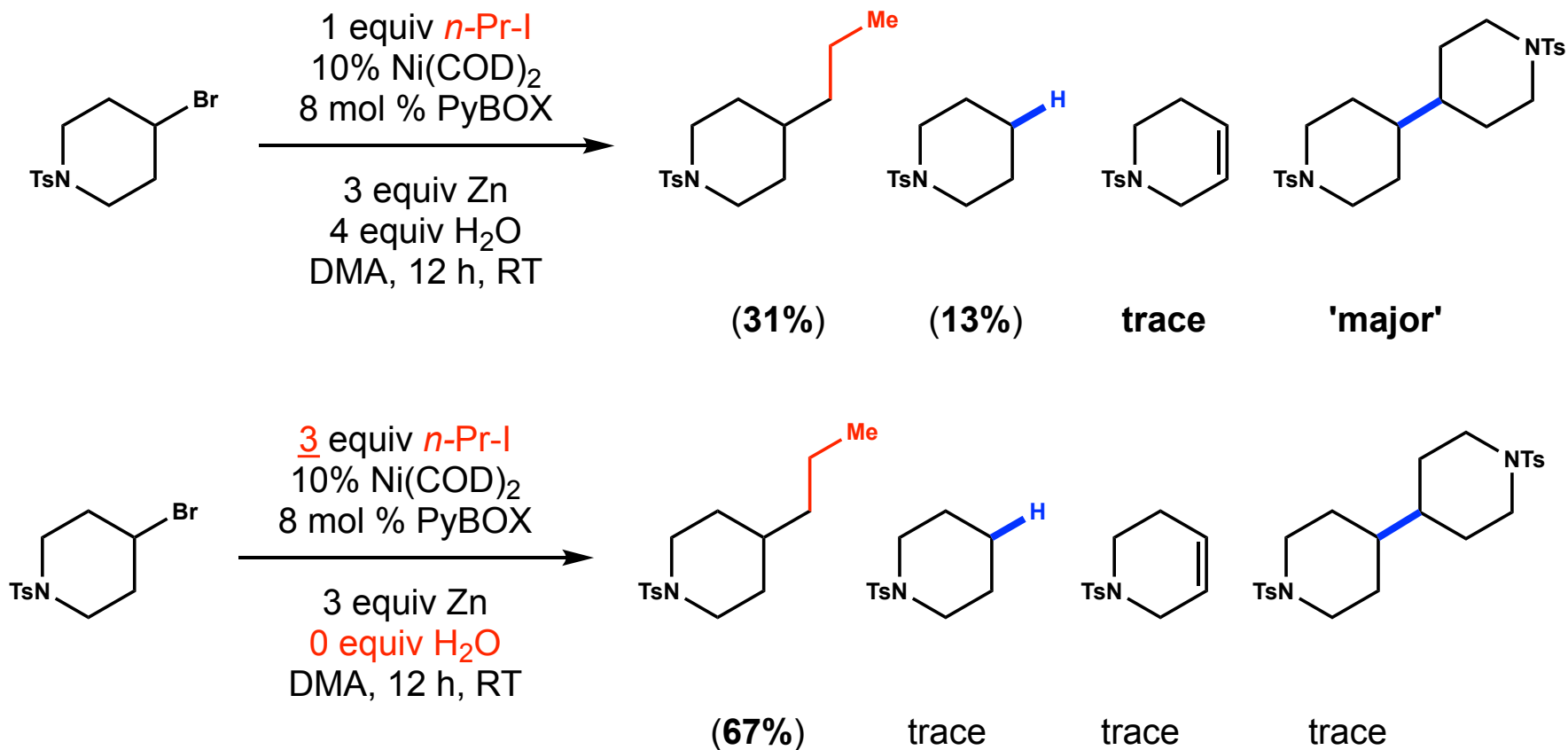
Electrophile homocouplings (Weix, 2010)



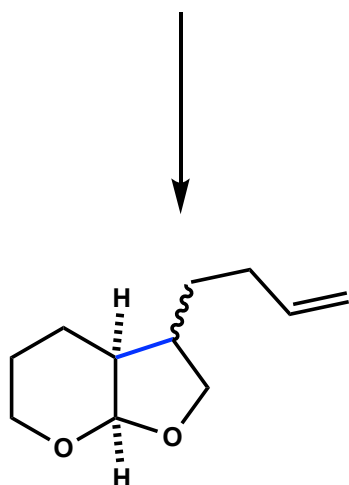
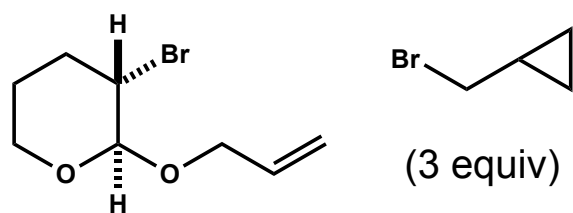
control?... 'loaded' cross-electrophile couplings

'Loaded' cross-electrophile couplings (Gong, 2011)

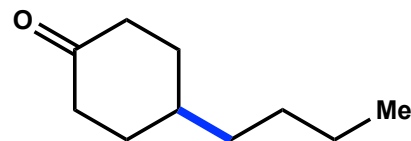
inspiration: homo- and hetero-coupling of aryl/alkyl halides



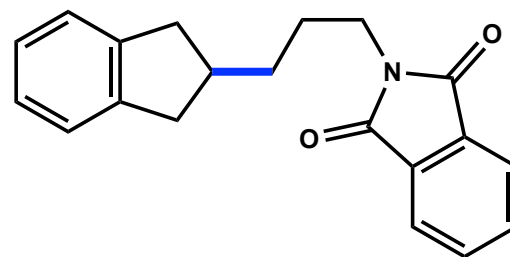
Gong: substrate scope and mechanism



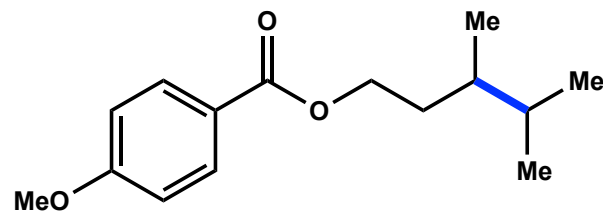
(68%)
d.r. 20:1



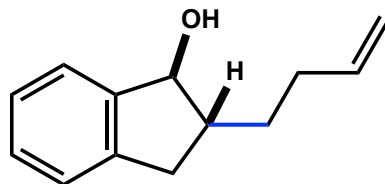
(65%) *n*-Bu-I
(57%) *n*-Bu-Br



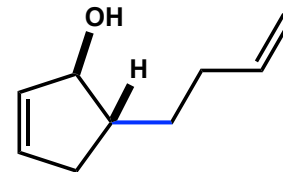
(45%)



(55%)



(65%)
d.r. 4:1

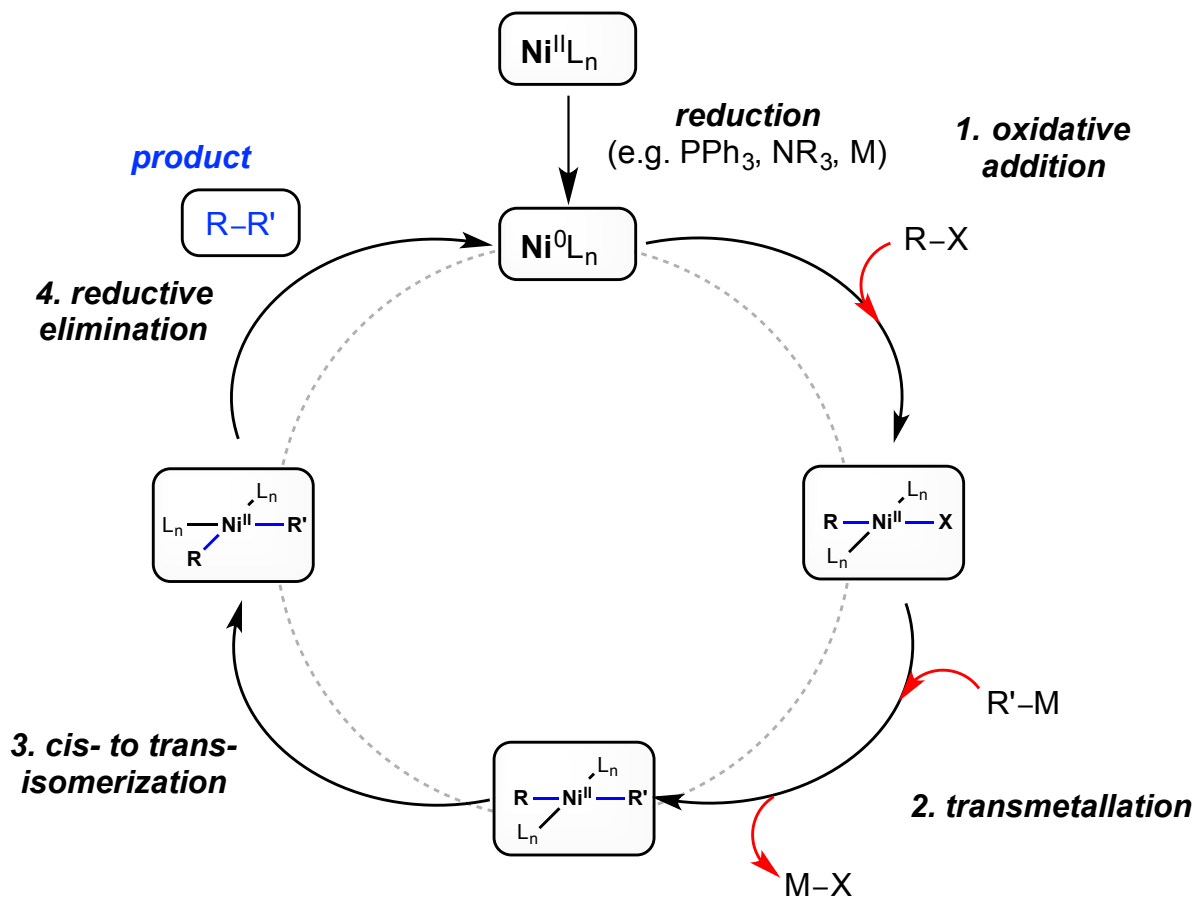


(60%)
d.r. 6:1

a simple explanation? concurrent mechanisms

Homo- or cross-electrophile couplings

traditional-path: nickel mechanism (simplest explanation)



cross-coupling of alkyl halides

Cross-electrophile couplings

Nickel-catalyzed reductive dimerizations

Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chem. Sci.* **2010**, 1, 383.

Prinsell, M. R.; Everson, D. A.; Weix, D. J. "Nickel-catalyzed, sodium iodide-promoted reductive dimerization of alkyl halides, alkyl pseudohalides, and allylic acetates," *Chem. Commun.* **2010**, 46, 5743.

Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. "Nickel-Catalyzed Reductive Cross-Coupling of Unactivated Alkyl Halides," *Org. Lett.* **2011**, 13, 2138.

Hu, X. "Nickel-catalyzed cross coupling of non-activated alkyl halides: a mechanistic perspective," *Chem. Sci.* **2011**, 2, 1867.

Electrochemical methods

Durandetti, M.; Nédélec, J.-Y.; Périchon, J. "Nickel-Catalyzed Direct Electrochemical Cross-Coupling between Aryl halides and Activated Alkyl Halides" *J. Org. Chem.* **1996**, 61, 1748.

can there be control? Yes.

Cross-electrophile couplings

can there be control? proposed (Weix, 2008)

Prof. Daniel Weix, Univ. of Rochester (2008 – 2017)

- a. heterocoupling of aryl halide + alkyl halide ('cross-electrophile')
- b. utilize the untapped potential of combining radicals with transition metals

Accomplished:

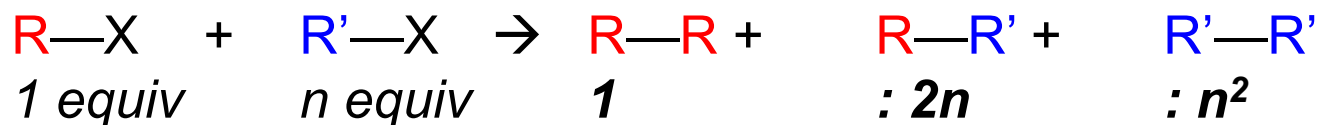
1. the coupling of an organic radical with an organometallic intermediate
(concept: cross-electrophile coupling, understanding reactivity)
2. the generation of allyl nickel intermediates from enones that proceed to react with electrophiles (paraphrased from Stahl, 2017)

can there be control?

Cross-electrophile couplings

can there be control? proposed (Weix, 2008)

heterocoupling ('cross-electrophile') of aryl and alkyl halides
assume identical reactivity and no organometallic intermediates



$n = 1$ 50% max. statistical yield, **1:1** **product** : dimers

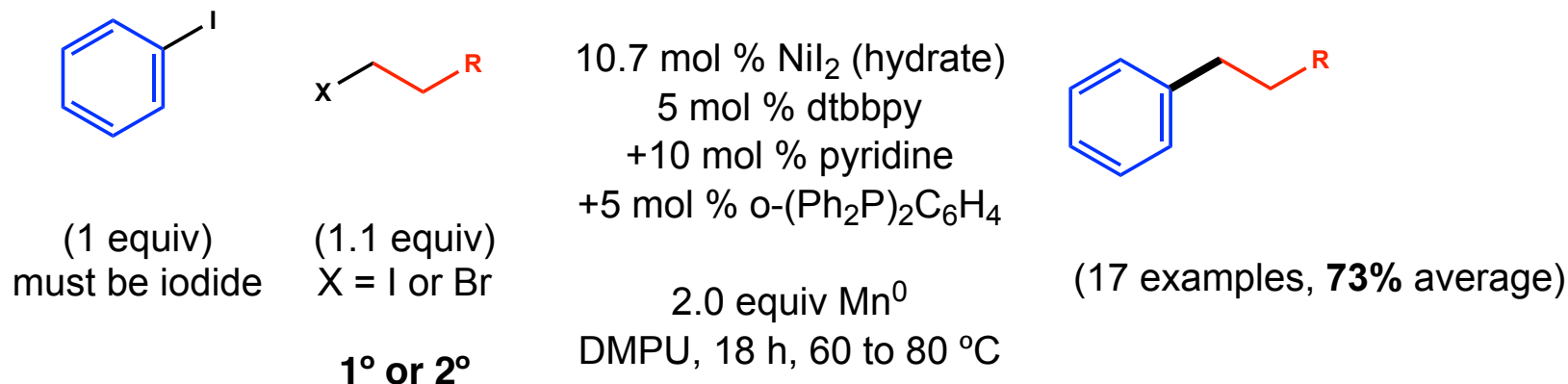
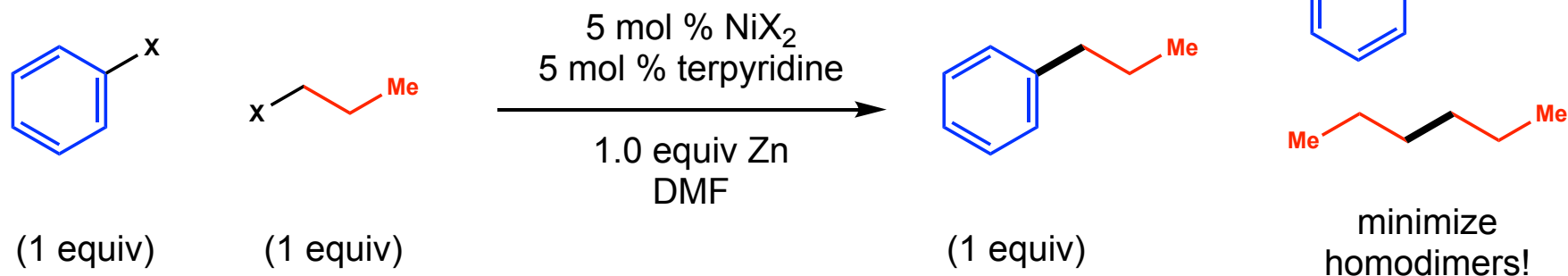
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aryl iodide + alkyl halide (rate / reactivity control)

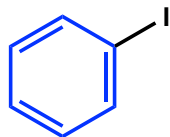
Cross-electrophile couplings

can there be control? proposed (Weix, 2008)



optimization

Cross-electrophile couplings

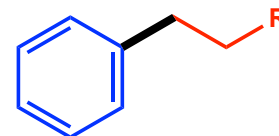


(1 equiv)
must be iodide

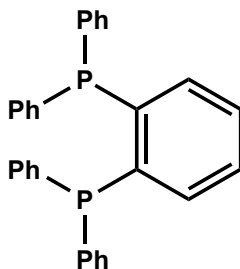
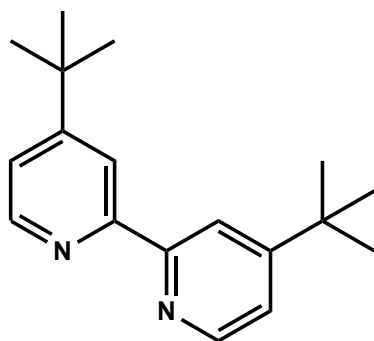


(1.0 equiv)
X = I

10.7 mol % NiI_2 (hydrate)
5 mol % dtbbpy
+10 mol % pyridine
+5 mol % o-(Ph_2P) $_2\text{C}_6\text{H}_4$
2.0 equiv Mn^0
DMPU, 18 h, 60 to 80 °C



(88%)



deviation

88%

no change

81%

5 mol % dtbbp (no phosphine)

83%

10 mol % dtbbp (no phosphine)

19%

10 mol % phosphine (no dtbbp)

6%

no ligands

67%

no pyridine

1%

no Mn^0

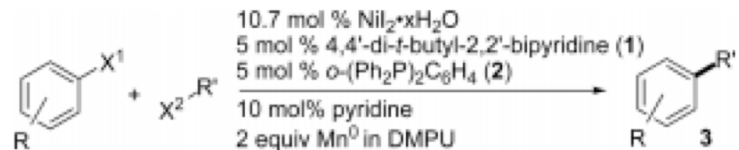
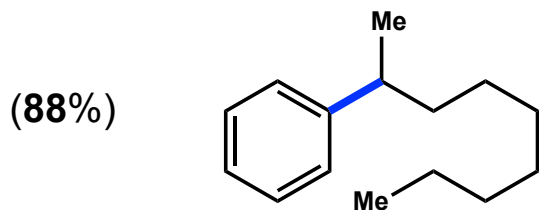
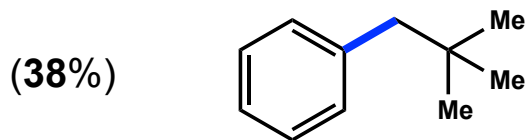
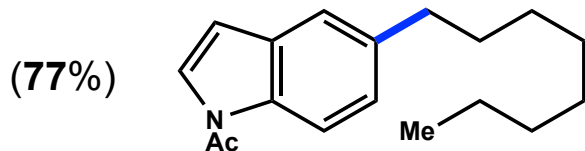
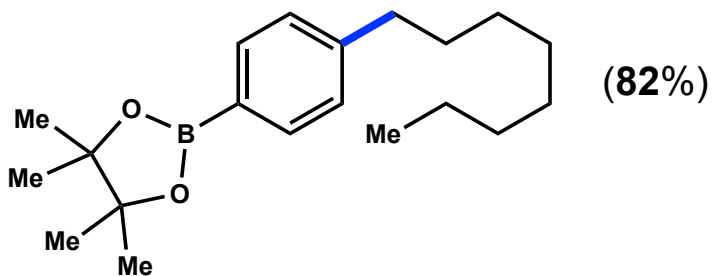
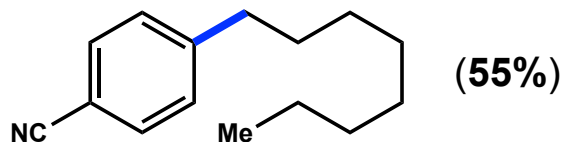
77%

aryl bromide

65%

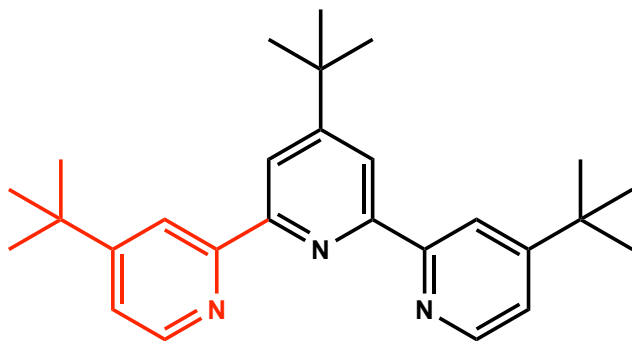
aryl bromide + alkyl bromide

substrate scope

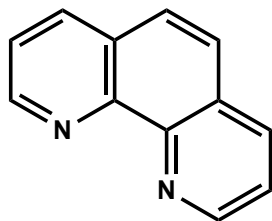


Entry	Product	X ¹	X ²	T (°C)	Yield (%) ^b	
1	R = H	3a	I	I	80	77
2	R = OMe	3b	I	I	80	75
3	R = CF ₃	3c	I	I	80	75
4	R = C(O)Me	3d	I	I	80	69
5	R = CN	3e	I	I	80	55
6	R =	3f	Br	I	60	82
7		3g	Br	I	80	82
8		3h	I	I	80	78
9 ^c		3i	Br	I	60	77
10	Y = CH ₂ CO ₂ Et	3j	I	Br	80	77
11	Y = CH ₂ NHBoc	3k	I	Br	60	85
12	Y = CH ₂ NHCbz	3l	I	Br	60	65
13 ^d	Y = CH=CMe ₂	3m	I	Br	60	64
14		3n	I	Br	80	75
15		3o	I	I	80	38
16 ^{d,e,f}		3p	I	Br	60	88 ^g

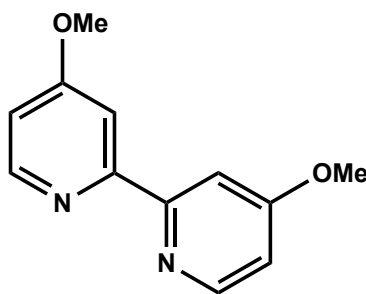
common conditions (this report and the literature)



4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (**ttbtpy**)
4,4'-di-tert-butyl-2,2'-bipyridine (**dtbpy**)



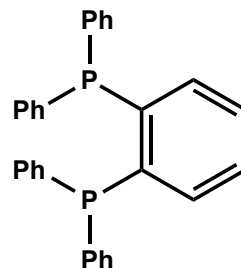
1,10-phenanthroline



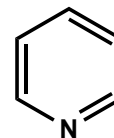
4,4'-di-methoxy-2,2'-bipyridine (**dmbpy**)

NiX_2
 NiI_2 (hydrate)

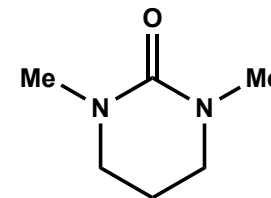
literature (related)
 NiBr_2 (glyme)



not essential
(+5%)



useful
additive
(+21%)



DMPU (bp 247 °C)
(best yields)

literature (related)
DMF, DMA,
THF, dioxane

Mn^0 vs Zn^0
(check or try)

fresh Zn^0
(superior to old)

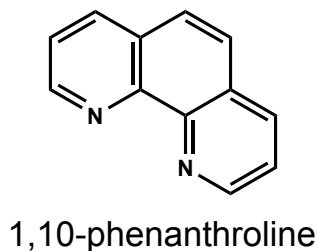
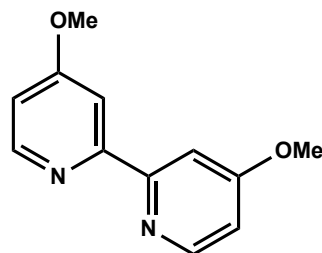
glovebox
(not necessary)

Beyond Traditional Cross-Coupling Chemistry

update, full-paper (2012): aryl and vinyl halides! lower metal / ligand loadings
sodium iodide (NaI) improves yield and enables general use of alkyl bromides
chloroarenes react, but slowly...require higher temp and superior with EWGs

from aryl / vinyl bromides
21 examples!

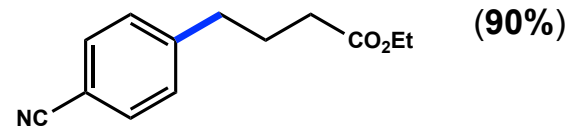
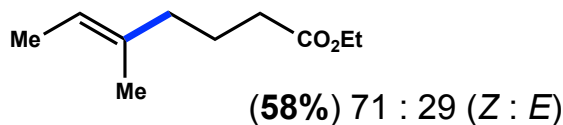
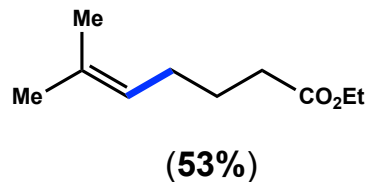
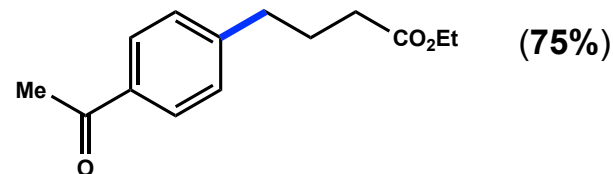
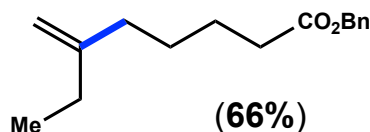
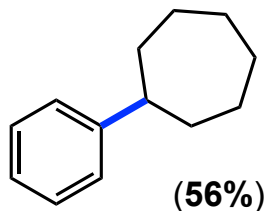
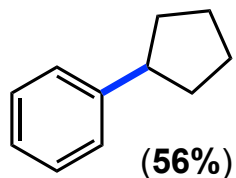
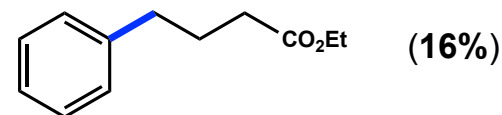
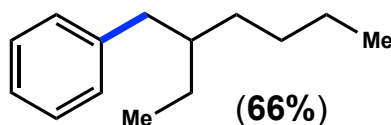
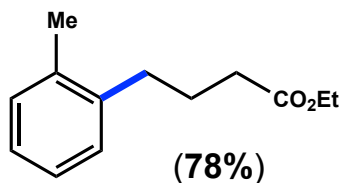
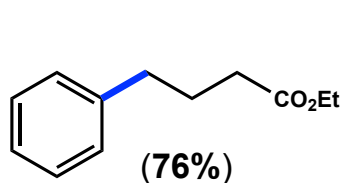
add NaI, 60 °C
lowered loadings
improved ligand



1,10-phenanthroline

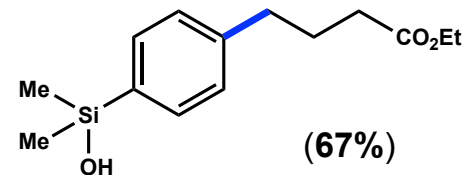
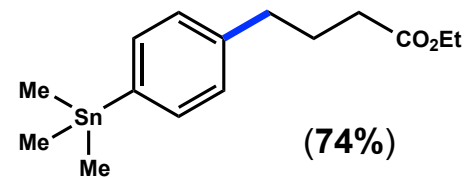
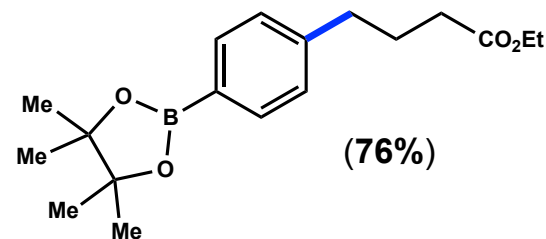
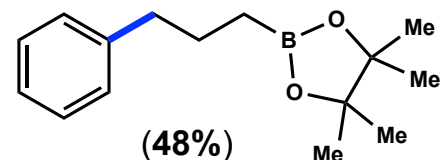
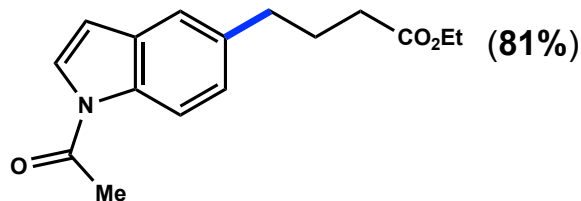
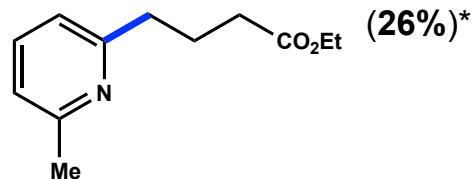
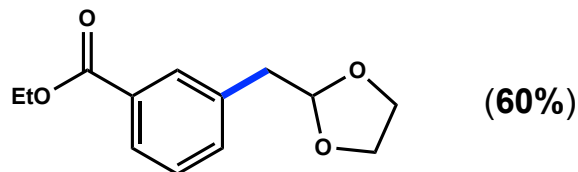
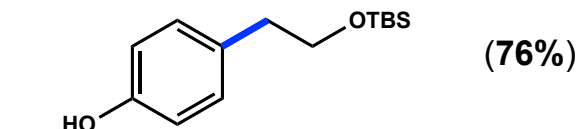
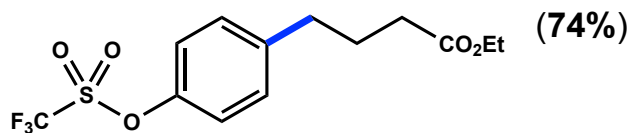
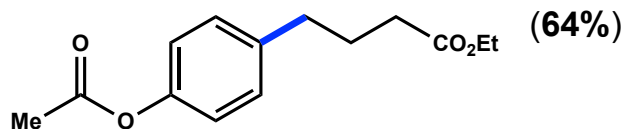
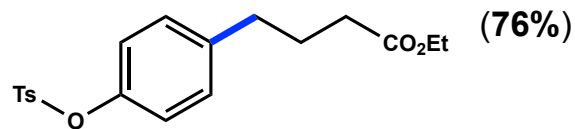
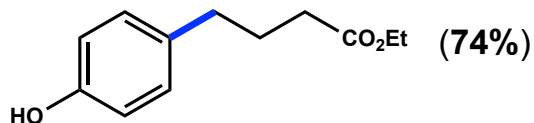
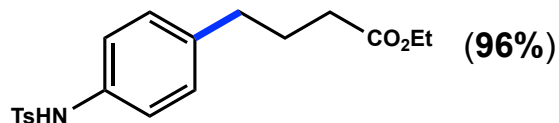
from chloroarenes

80 °C, 1.25 equiv alkyl halide



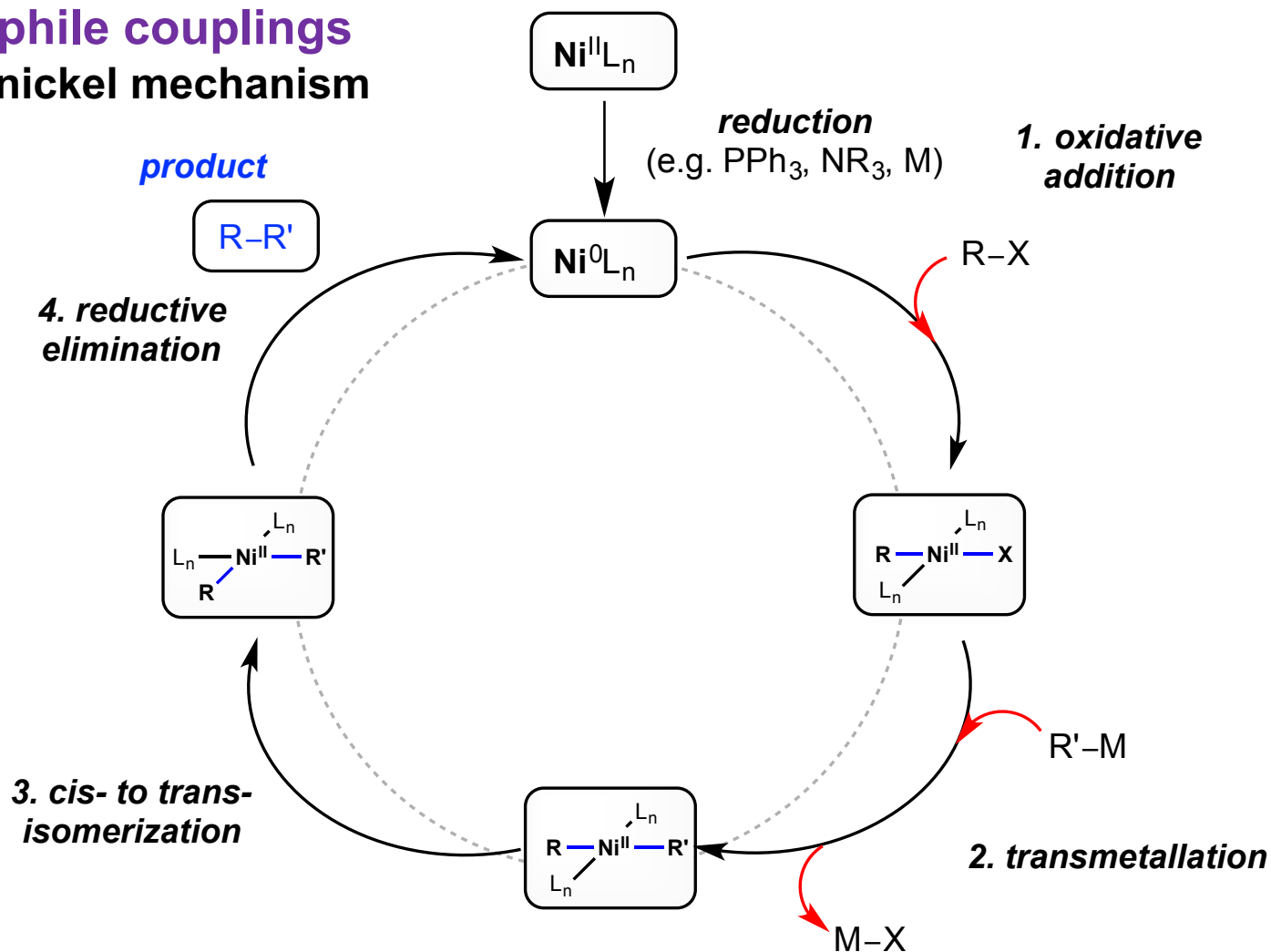
complementarity: most impressive!

complementarity, orthogonal reactivity to other functional groups



what is the mechanism?

Cross-electrophile couplings traditional nickel mechanism



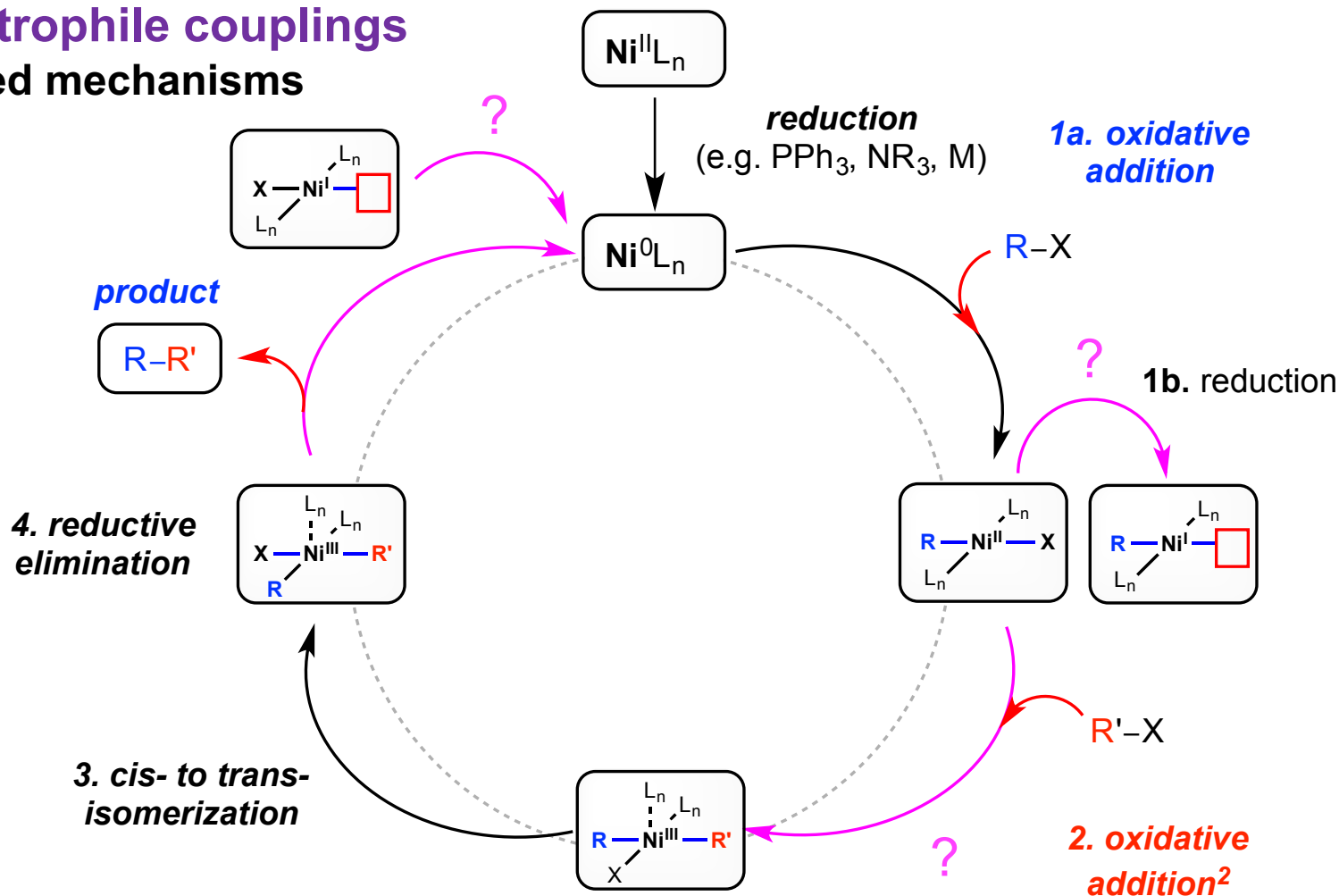
two oxidative additions? distinguish substrates?

Cross-electrophile couplings proposed mechanisms

questions?

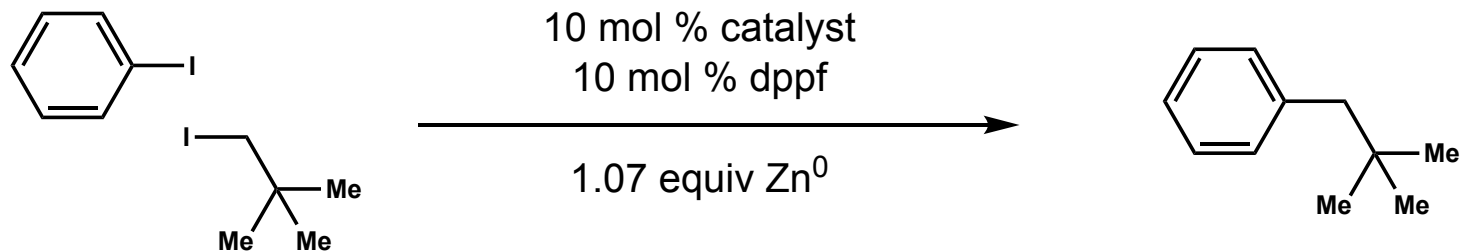
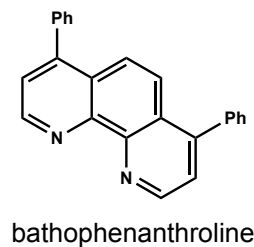
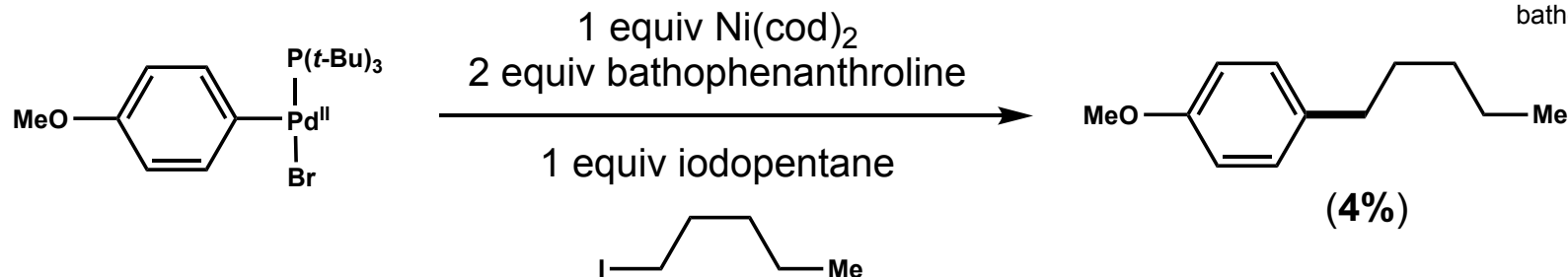
control?

order?



mechanism and questions

early experiments



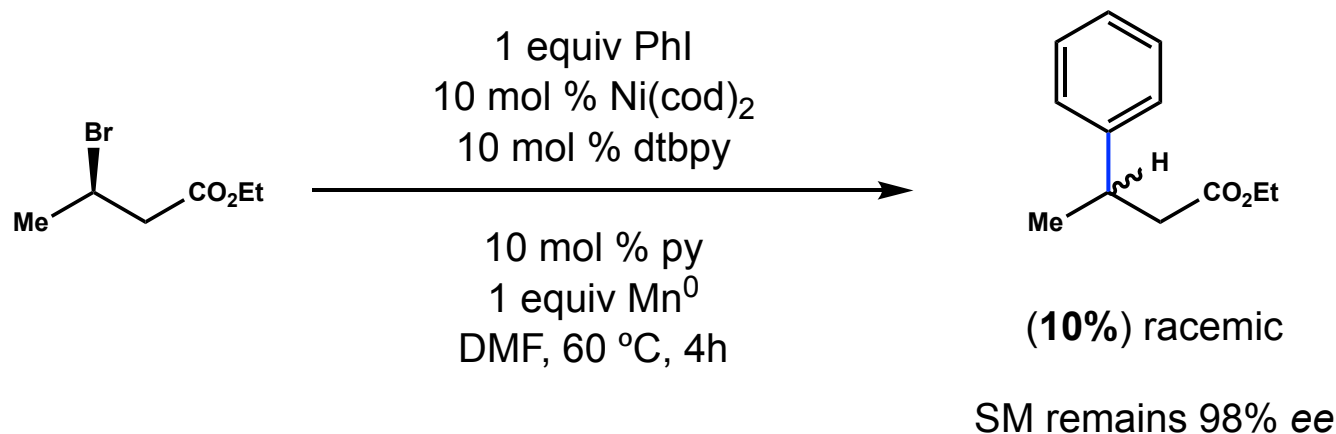
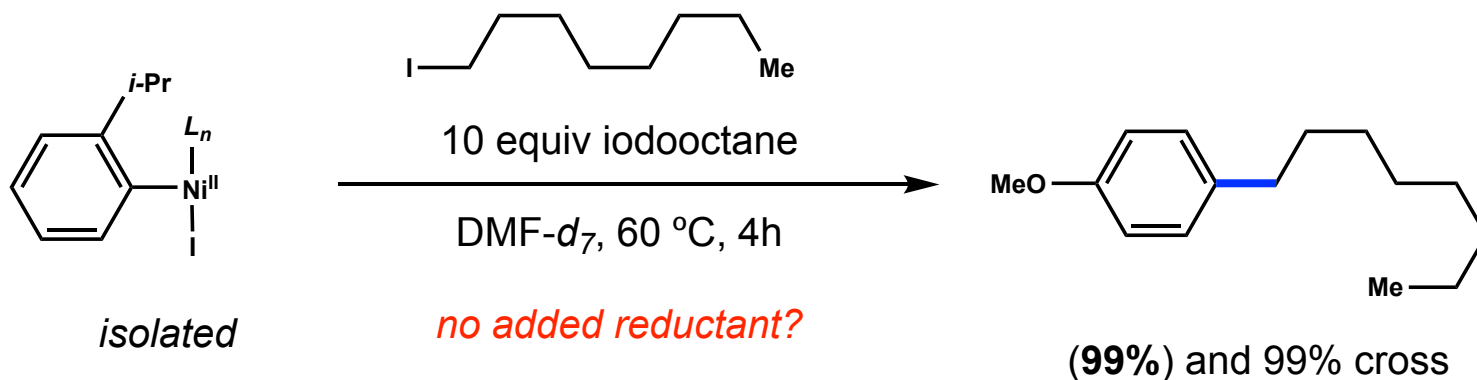
(10%) with 5 mol % each, $\text{Pd}(\text{dba})_2$ / $\text{Ni}(\text{cod})_2$

(—%) with 10 mol % $\text{Pd}(\text{dba})_2$

(15%) with 10 mol % $\text{Ni}(\text{cod})_2$

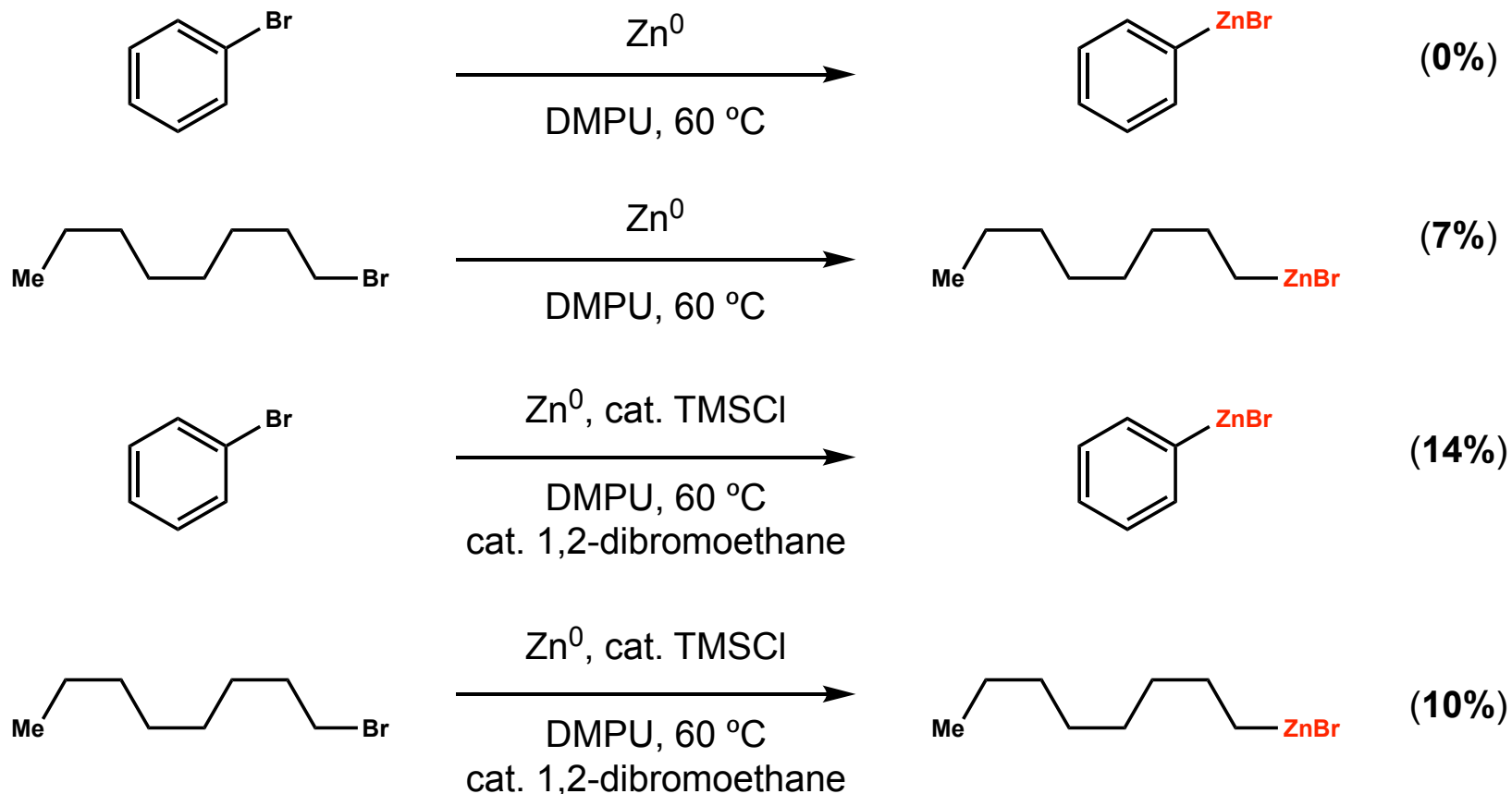
mechanism and questions

early experiments



mechanism and questions

organozinc(manganese) intermediates are unlikely

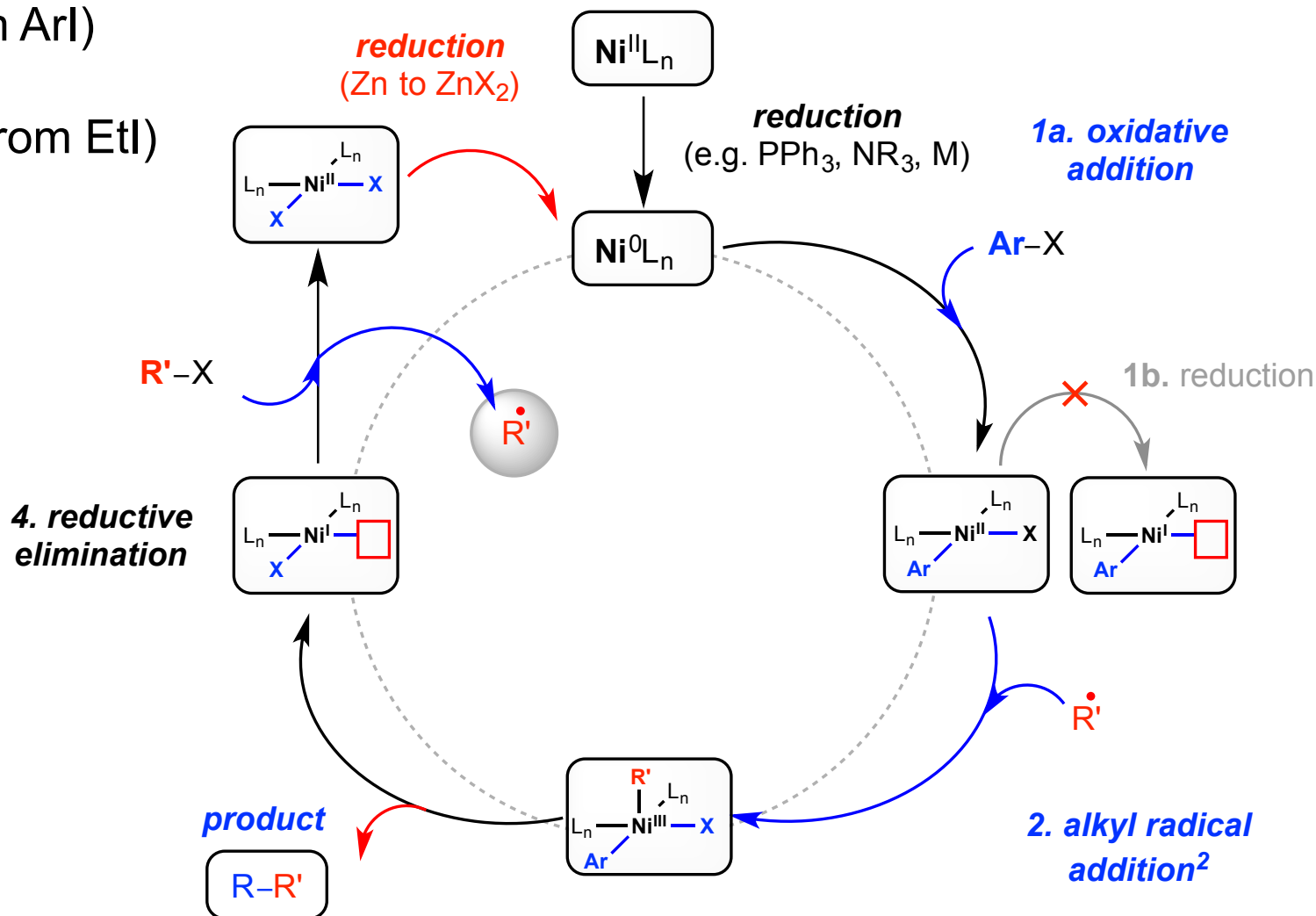


*GC yield based on unreacted SM after 24 hours
 Zn^0 or Mn^0 can be replaced with an organic reducing agent (TDAE)

Cross-electrophile mechanisms

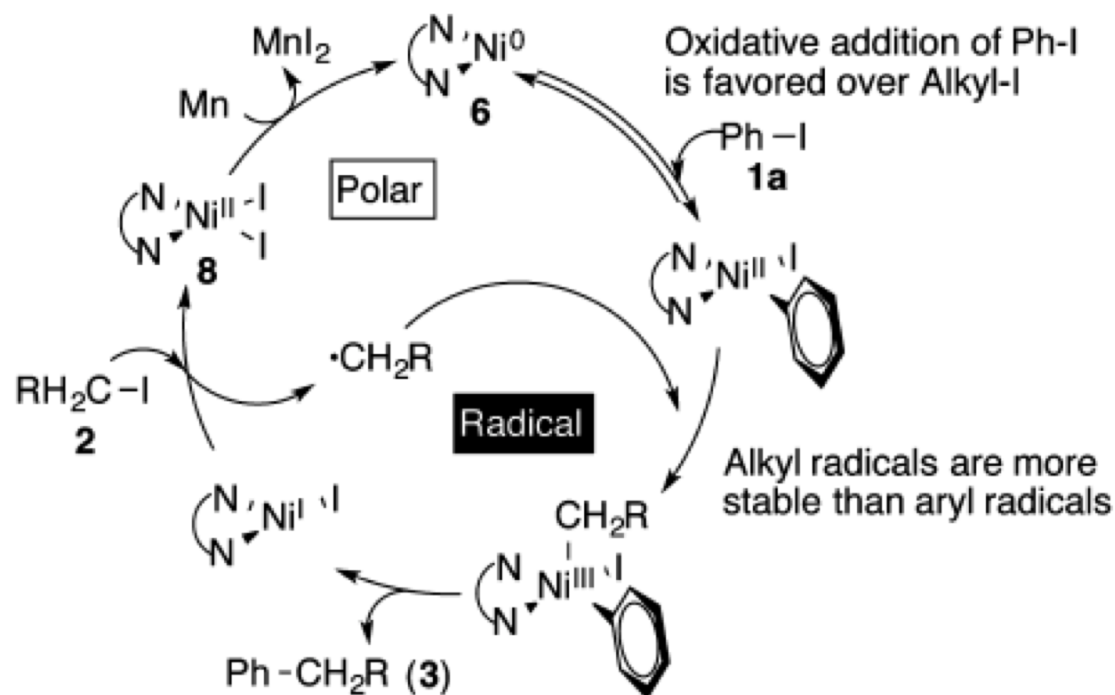
R = Ar (from ArI)

R' = alkyl (from EtI)



proposed mechanisms (as presented)

Scheme 4. Proposed Mechanism for Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides



a. the oxidative addition of aryl iodide is favored

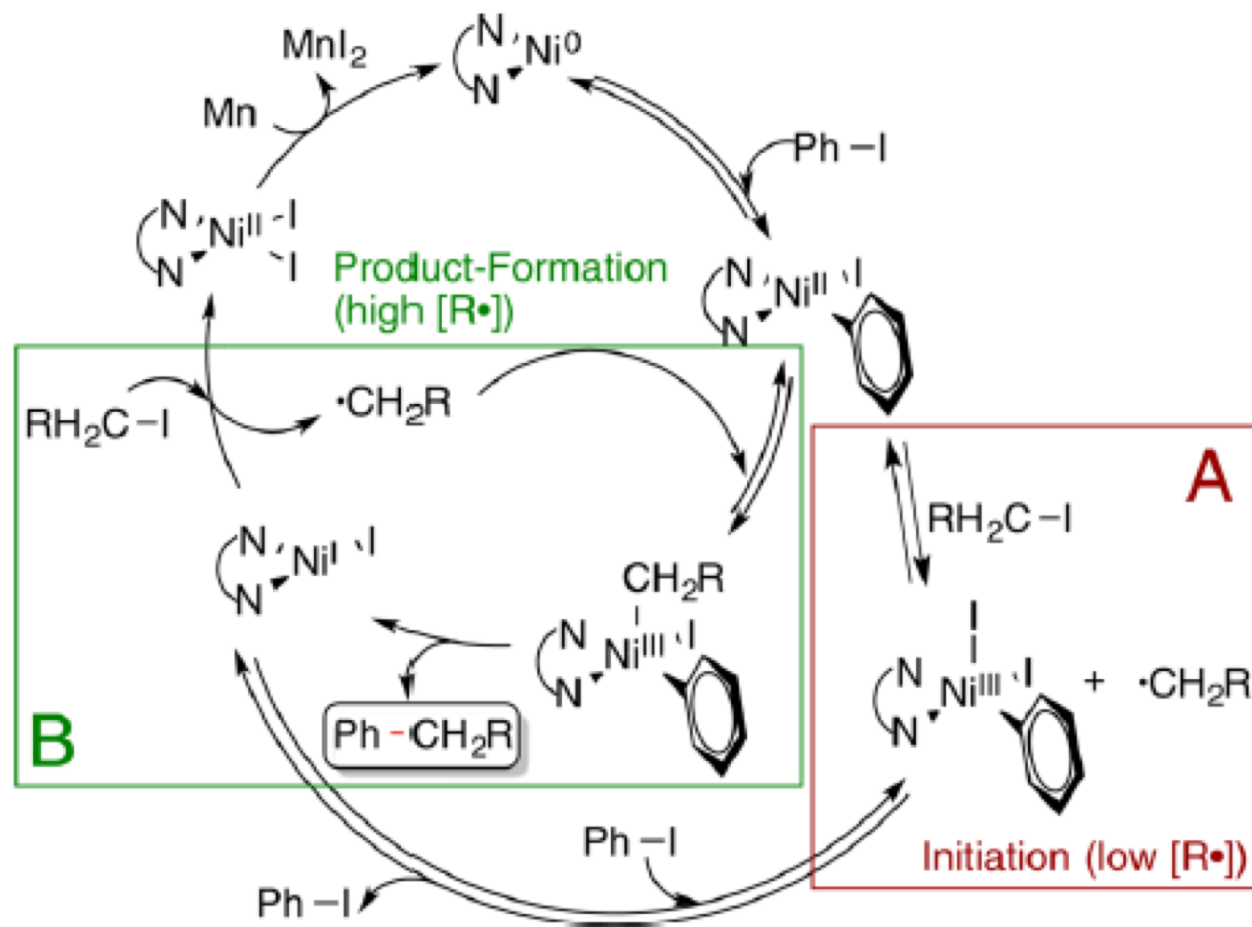
(Hammett study: use an electron rich ligand with electron poor aryl halide)

b. alkyl radicals are more stable than aryl

how is the alkyl radical formed?

proposed mechanisms (to be continued)

Scheme 5. Hypothesis for Self-Initiation



literature: cross-electrophile coupling and mechanism

Cross-electrophile couplings

Cross-Electrophile Couplings and Mechanisms

Everson, D. A.; Shrestha, R.; Weix, D. J. "Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides," *J. Am. Chem. Soc.* **2010**, 132, 920.

Everson, D. A.; Jones, B. A.; Weix, D. J. "Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides," *J. Am. Chem. Soc.* **2012**, 134, 6146.

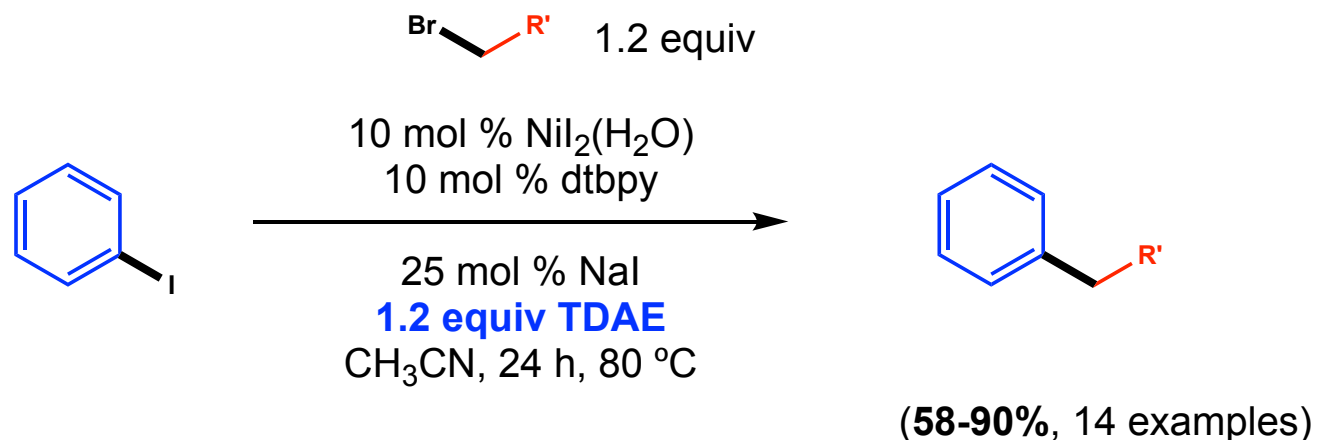
Biswas, S.; Weix, D. J. "Mechanism and Selectivity in Nickel-Catalyzed Cross- Electrophile Coupling of Aryl Halides with Alkyl Halides," *J. Am. Chem. Soc.* **2013**, 135, 16192.

Everson, D. A.; Weix, D. J. "Cross-Electrophile Coupling: Principles of Reactivity and Selectivity," *J. Org. Chem.* **2014**, 79, 4793.

recent examples: organic reductants, aryl + benzyl

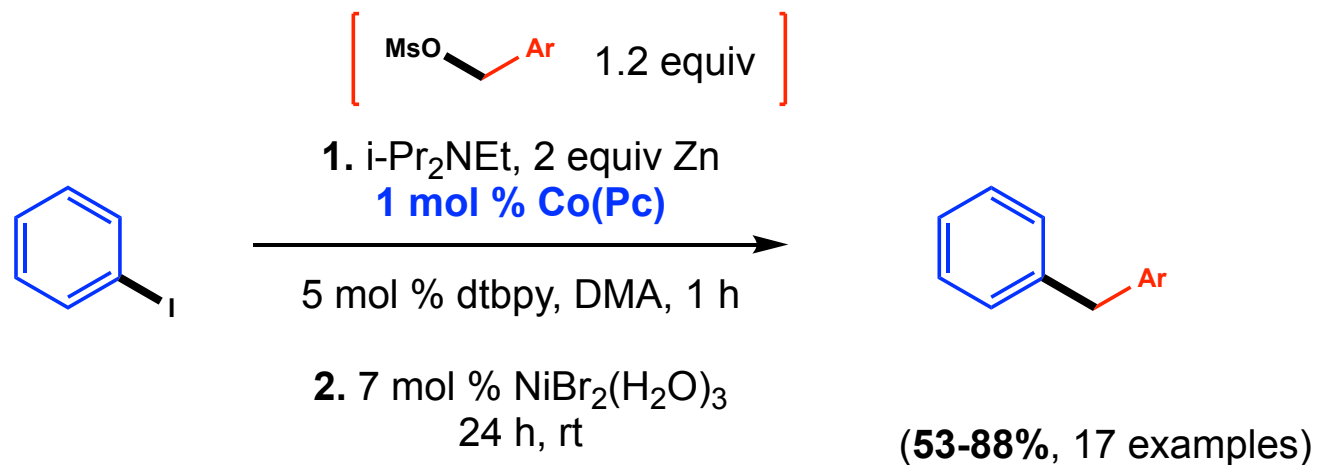
1. Anka-Lufford, L. L *et al.* *J. Chem.–Eur. J.* **2016**, 22, 11564-11567.

"Nickel-Catalyzed Cross-Electrophile Coupling with Organic Reductants in Non-Amide Solvents"



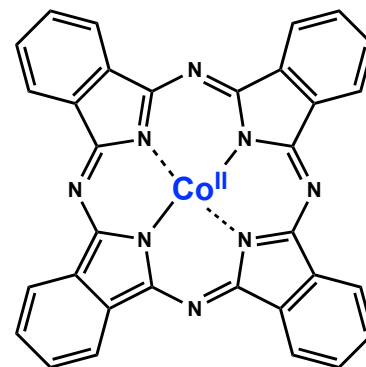
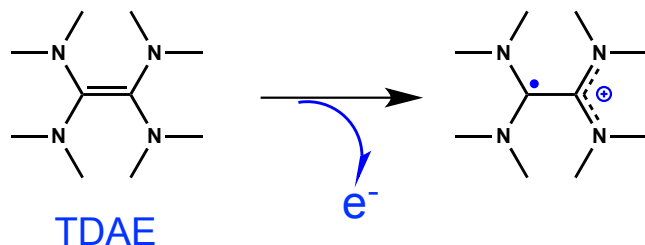
2. Ackerman, L. K. G. *et al.* *Chem. Sci.* **2015**, 6, 1115-1119.

"Cobalt co-catalysis for cross-electrophile coupling: diarylmethanes from benzyl mesylates and aryl halides"



alternative reductants (TDAE, Co(Pc))

<u>reductant</u>	<u>potential</u>		
Co ⁰	– 0.28 V	(2 ⁺ to 0)	
Zn ⁰	– 0.76 V	(2 ⁺ to 0)	
TDAE	– 0.78 V		
Co(Pc)	– 0.89 V	(2 ⁺ to 1 ⁺)	(1976_CanJChem_Wilshire)
Mn ⁰	– 1.18 V	(2 ⁺ to 0)	
"Sm ^{II} "	– 1.6 to – 3.4 V	(3 ⁺ to 2 ⁺)	(2014_JOC_Proctor)
Mg ⁰	– 2.37 V	(2 ⁺ to 0)	
Na ⁰	– 2.71 V	(2 ⁺ to 0)	



Co(Pc) = cobalt (II) phthalocyanine

samarium iodide reductions

https://www.princeton.edu/chemistry/macmillan/group-meetings/AC_SamariumIodide.pdf

organic electron donors (reductants)

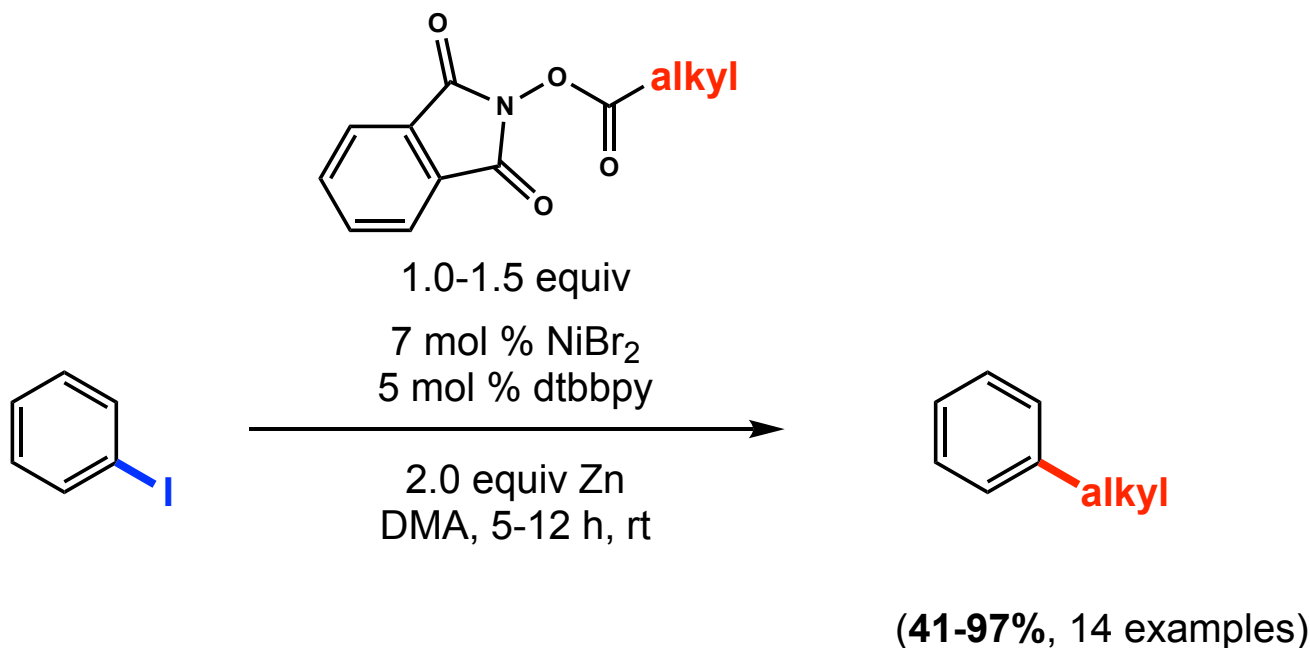
https://www.scripps.edu/baran/images/grpmtgpdf/Lo_01_2015.pdf

aryl + alkyl radicals from decarboxylation

Cross-electrophile couplings (Weix, 2016) *use alkyl esters instead of alkyl halides*

1. Huihui, K. M. M. *et al. J. Am. Chem. Soc.* **2016**, 138, 5016–5019.

"Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides
Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides"



literature: cross-electrophile coupling and mechanism

Cross-electrophile couplings

Articles on cross-electrophile couplings and nickel catalysis under reductive conditions

2004_ACIEE_Montgomery_Nickel-Catalyzed Reductive Cyclizations and Couplings

2010_JACS_Weix_Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides

2011_JACS_Flowers_Catalytic Ni(II) in Reactions of SmI_2 : Sm(II)- or Ni(0)-Based Chemistry?

2012_JACS_Weix_Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Aryl Chlorides

Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. “Nickel-catalyzed cross-coupling of unactivated alkyl halides using bis(pinacolato)diboron as reductant” *Chem. Sci.* 2013, 4, 4022 (for another seminar!, check out the research of Prof. Gong)

2015_ACR_Weix_Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles

2015_OCF_Gong_Nickel-catalyzed reductive coupling of alkyl halides with other electrophiles: concept and mechanistic considerations

2016_JACS_Diao_Bimetallic C–C Bond-Forming Reductive Elimination from Nickel

2016_TCC_Gong_Nickel-Catalyzed Reductive Couplings

summary

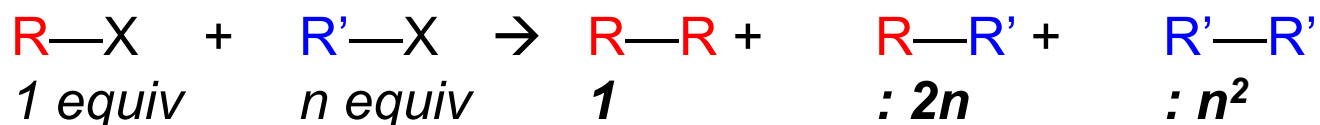
as more methods become available:

read and consider how you categorize reactivity / mechanism

think about sub-fields, what interests you?

it is not unrealistic to think that other (more difficult) cross-electrophile reactions can be developed and may ultimately lead to the replacement of preformed organometallic intermediates

consider 'unreactive' (strong bonds) and orthogonality to tradition coupling
control of two alkyl halides? asymmetry? how? (similar rates...)



$n = 1$ 50% max. statistical yield, **1:1** **product** : dimers

$n = 2$ 80% max. statistical yield, **1:1.25** **product** : dimers

$n = 3$ 86% max. statistical yield, **1:1.67** **product** : dimers

Beyond Traditional Cross-Coupling Chemistry

photoredox + C–N bond (amide) + alkyl borates (Molander, 2017)

Synergistic Visible-Light Photoredox/Nickel-Catalyzed Synthesis of Aliphatic Ketones via N–C Cleavage of Imides

Javad Amani, Rauful Alam, Shorouk Badir, and Gary A. Molander* 

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

Org. Lett., 2017, 19 (9), pp 2426–2429

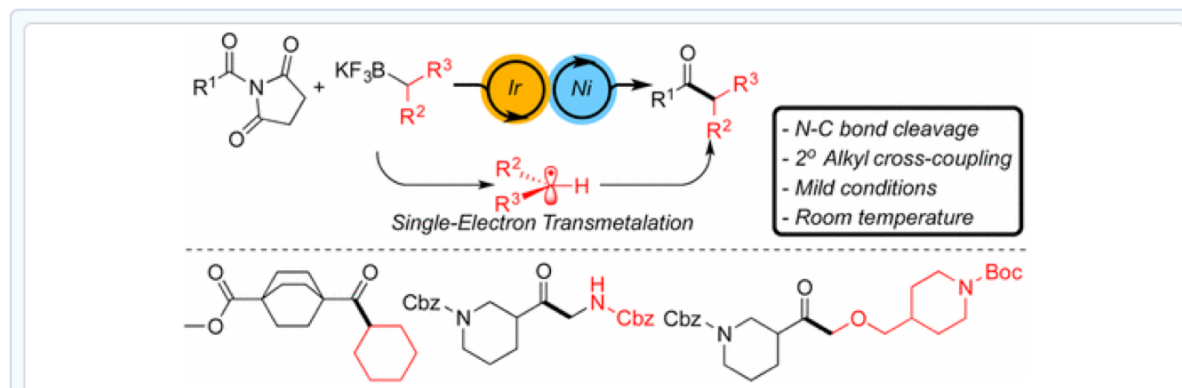
DOI: 10.1021/acs.orglett.7b00989

Publication Date (Web): April 26, 2017

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*gmolandr@sas.upenn.edu

Abstract



An electrophilic, imide-based, visible-light-promoted photoredox/Ni-catalyzed cross-coupling reaction for the synthesis of aliphatic ketones has been developed. This protocol proceeds through N–C(O) bond activation, made possible through the lower activation energy for metal insertion into this bond due to delocalization of the lone pair of electrons on the nitrogen by electron-withdrawing groups. The operationally simple and mild cross-coupling reaction is performed at ambient temperature and exhibits tolerance for a variety of functional groups.

Beyond Traditional Cross-Coupling Chemistry

C–N bond (amide) + aryl halide (cross-E⁺) + reduction (Han, 2017)



Letter

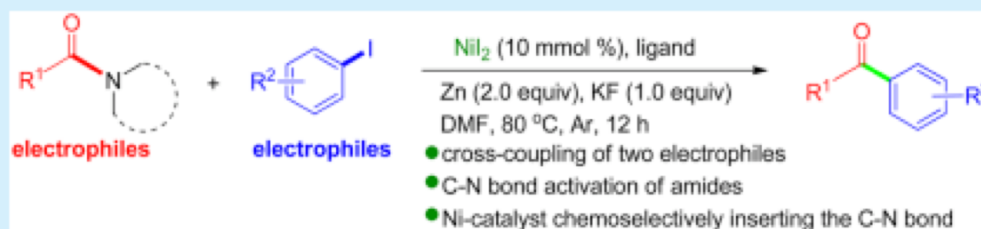
pubs.acs.org/OrgLett

Ni-Catalyzed Reductive Cross-Coupling of Amides with Aryl Iodide Electrophiles via C–N Bond Activation

Shengyang Ni, Wenzhong Zhang, Haibo Mei, Jianlin Han,*¹⁰ and Yi Pan

School of Chemistry and Chemical Engineering, State Key laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Nanjing University, Nanjing 210093, China

S Supporting Information




ABSTRACT: A Ni-catalyzed reductive cross-coupling reaction between two electrophiles, amides and aryl iodides, has been developed. This work is the first example using amide as an electrophile to couple with another electrophile, instead of using highly basic and pyrophoric nucleophiles. Furthermore, the Ni catalyst chemoselectively inserting the C–N bond of amide triggered the reductive cross-coupling reaction, which solves the problem that the Ni catalyst preferentially inserts the more reactive C–I bond to form a self-coupling product.

Beyond Traditional Cross-Coupling Chemistry

C–N (aziridine) + aryl halide (cross-E⁺) + reduction (Sigman & Doyle, 2017)

Nickel-Catalyzed Enantioselective Reductive Cross-Coupling of Styrenyl Aziridines

Brian P. Woods[†], Manuel Orlandi[‡], Chung-Yang Huang[†], Matthew S. Sigman^{*‡} , and Abigail G. Doyle[†]

[†] Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

[‡] Department of Chemistry, University of Utah, 315 S 1400 E, Salt Lake City, Utah 84112, United States

J. Am. Chem. Soc., 2017, 139 (16), pp 5688–5691

DOI: 10.1021/jacs.7b03448

Publication Date (Web): April 13, 2017

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Abstract



A Ni-catalyzed reductive cross-coupling of styrenyl aziridines with aryl iodides is reported. This reaction proceeds by a stereoconvergent mechanism and is thus amenable to asymmetric catalysis using a chiral bioxazoline ligand for Ni. The process allows facile access to highly enantioenriched 2-arylphenethylamines from racemic aziridines. Multivariate analysis revealed that ligand polarizability, among other features, influences the observed enantioselectivity, shedding light on the success of this emerging ligand class for enantioselective Ni catalysis.

