Shedding Light on Nickel Mechanisms: Combining Photoredox and Nickel Catalysts

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Frontiers of Chemistry 02/27/16

Wipf Group

If I had a Nickel for every time …

- A silvery-white metal found in nature as a component of silicate, sulfide, or arsenide ores. Primarily combined with oxygen or sulfur as oxides or sulfides.
- Abundance in earth crust is about 0.009% (Fe >> Ni > Cu).
- Used in alloys, electroplating, batteries, coins, industrial plumbing, spark plugs, machinery parts, stainless-steel, nickel-chrome resistance wires, and catalysts.
- Nickel may not be worth a dime, but 1 mmol is!

	Common Catalyst Precursors				
	$NiCl_2$	**$PdCl_2$**	**$PtCl_2$**	**$AuCl_3$**	**$RhCl_3$**
USD/1 mmol	0.1	5.8	32.2	35.6	51.8

http://www3.epa.gov/airtoxics/hlthef/nickel.html; accessed 02/21/2016.
Review: **V. P. Ananikov**: *ACS Catal.* **2015**, *5*, 1964.

Production of Nickel

- Mined in >23 countries and smelted/refined in 25 countries.
- Primary nickel is produced and used in the form of ferro-nickel and nickel oxides.
- Also readily recycled. Large tonnages of secondary or "scrap" nickel are used to supplement newly mined metal.
- Annual global production is about 1.4 million tons of primary nickel (Cu > 10 million tons; steel > 800 million tons).

Country	Tons Mined in 2015
Philippines	440,000
Russia	260,000
Indonesia	240,000
Canada	233,000
Australia	220,000

* USA has one mine in Michigan
2014, 3,600 tons mined;
102,000 tons from recycling scraps.

http://minerals.usgs.gov/, accessed 02/22/216.

http://investingnews.com/daily/resource-investing/base-metals-investing/nickel-investing/10-top-nickel-producing-countries/, accessed 02/22/2016.
https://www.nickelinstitute.org/, accessed 02/22/2016.

U.S. Environmental Protection Agency (EPA) Hazard Statement for Nickel

- "**Nickel dermatitis**, consisting of itching of the fingers, hands, and forearms, **is the most common effect in humans** from chronic (long-term) skin contact with nickel. Respiratory effects have also been reported in humans from inhalation exposure to nickel ... EPA has classified **nickel refinery dust and nickel subsulfide as Group A**, human carcinogens, and **nickel carbonyl as a Group B2**, probable human carcinogen."

- **Group A** - Carcinogenic to Humans: Agents with adequate human data to demonstrate the causal association of the agent with human cancer.
- **Group B** - Probably Carcinogenic to Humans: Agents with sufficient evidence from animal bioassay data, but either limited human evidence (Group B1), or with little or no human data (Group B2).

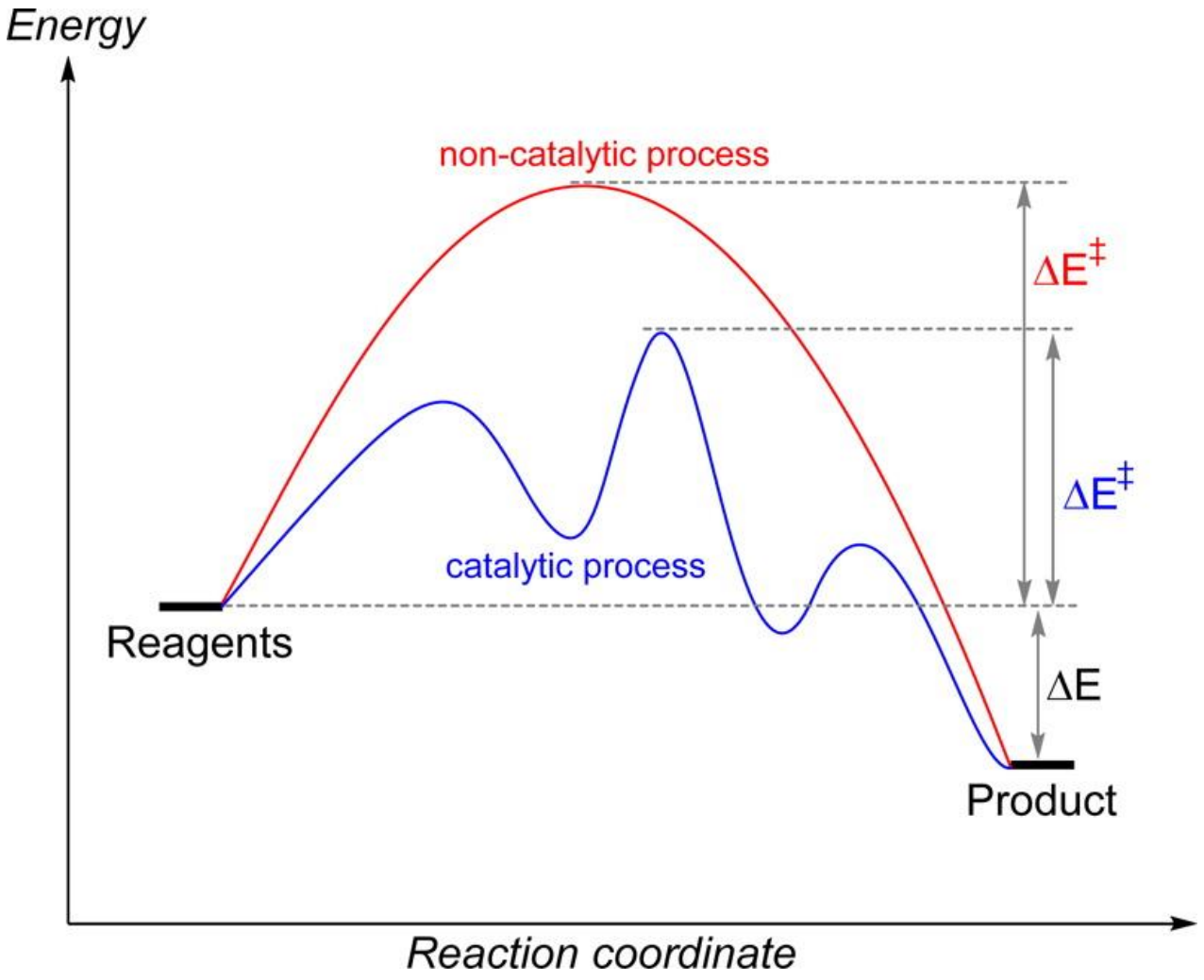
http://www3.epa.gov/airtoxics/hlthef/nickel.html; accessed 02/21/2016.

Exposure to Nickel

- Occupational: production and processing. Contact: jewelry, coins, stainless steel cooking and eating utensils.
- Average in drinking water (USA): 2 - 4.3 ppb. Soil: 4 - 80 ppm.
- An essential nutrient for some mammals, and possibly humans. A 70 kg (154 lbs) reference man contains 10 mg of nickel (body concentration of 0.1 ppm).
- Food is the major source of exposure. Daily intake: food (about 170 µg; high in chocolate, soybeans, nuts, and oatmeal); drinking water (2 µg); breathing air (0.1 - 1 µg, excluding nickel in tobacco smoke).

http://www3.epa.gov/airtoxics/hlthef/nickel.html; accessed 02/21/2016.
http://www.atsdr.cdc.gov/toxprofiles/tp15.pdf; accessed 02/21/2016.

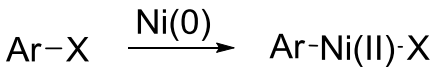
Basics of Organotransition Metal Reactions

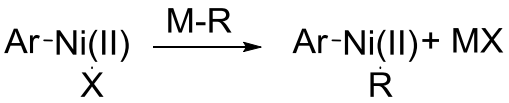


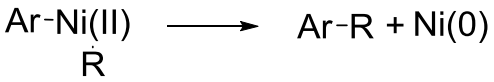
Bond	BDE (kcal/mol)
H_3C-CH_3	87.4
$L_2(X)Ni(II)$-CH_3	38.0-51.1
$L_2(X)Pd(II)$-CH_3	48.3-55.2
$L_2(X)Pt(II)$-CH_3	60.8-66.5

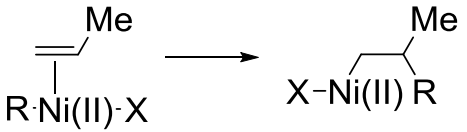
Review: **V. P. Ananikov**: *ACS Catal.* **2015**, *5*, 1964.

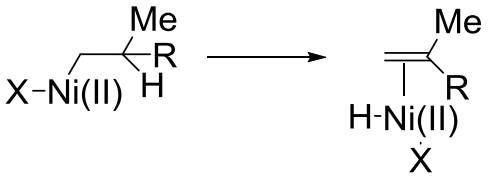
Basics of Organotransition Metal Reactions

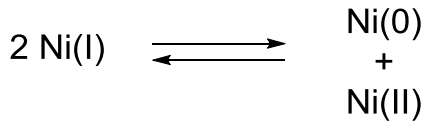
Oxidative Addition: 

Transmetalation: 

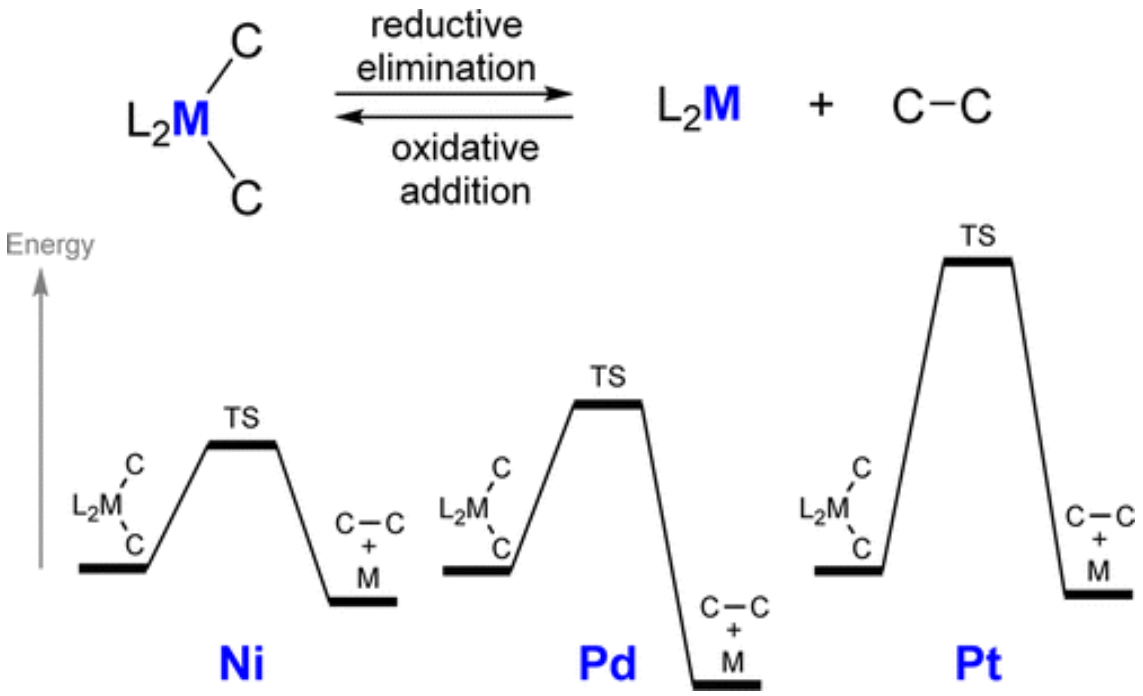
Reductive Elimination: 

β-Migratory Insertion: 

β-Hydride Elimination: 

Disproportionation/ Comproportionation: 

Basics of Organotransition Metal Reactions



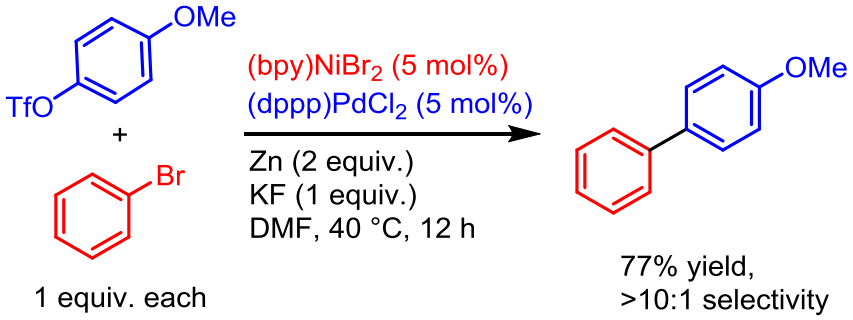
M	ΔE‡ (RE)	ΔE (RE)	ΔE‡ (OA)	ΔE (OA)
Ni-C	16.8	-4.1	20.9	4.1
Pd-C	24.9	-19.0	43.9	19.0
Pt-C	45.8	-3.5	49.3	3.5

Review: **V. P. Ananikov**: *ACS Catal.* **2015**, *5*, 1964.

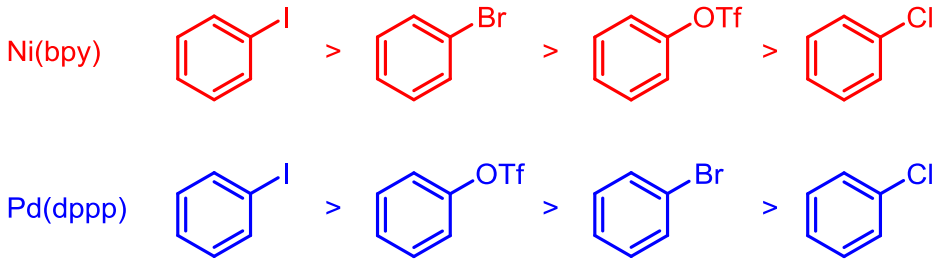
Ni vs. Pd

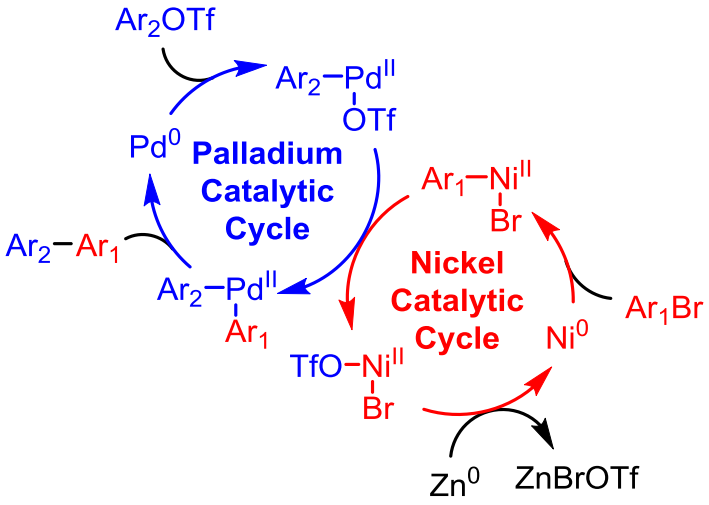
Nickel	Palladium
-1, **0**, **+1**, **+2**, **+3**, +4	**0**, +1, **+2**, +3, **+4**
Smaller atomic radius	Larger atomic radius
Less electronegative	More electronegative
Harder	Softer
Facile oxidative addition	Facile reductive elimination
Facile β-migratory insertion	Facile β-hydride elimination
Radical pathways more accessible	
Less expensive	

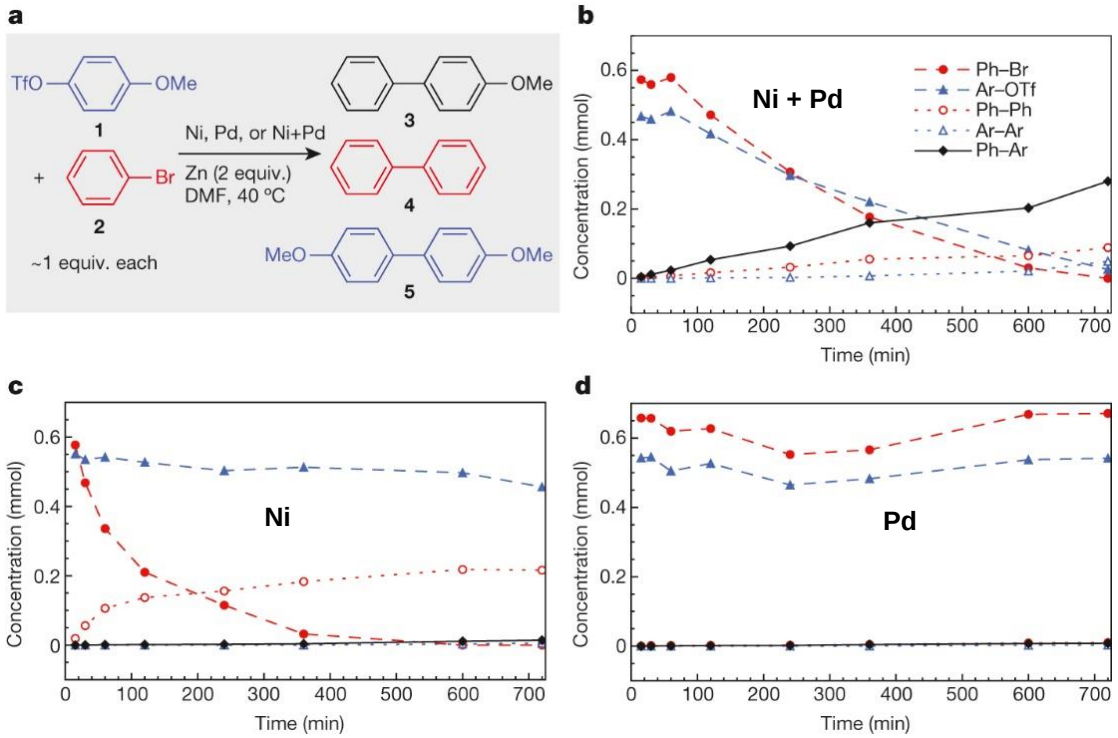
Ni/Pd Dual Catalysis



Relative Reactivity:

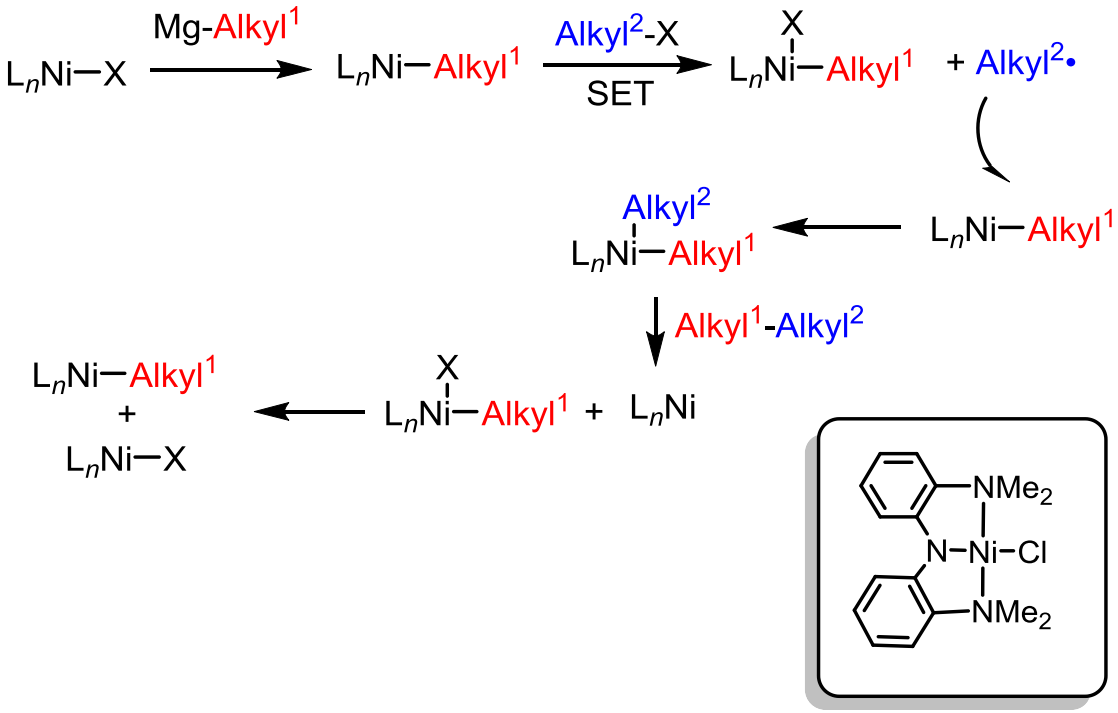






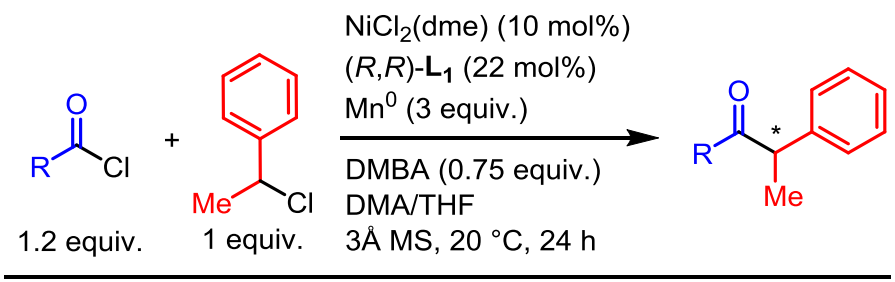
D. J. Weix: *Nature* **2015**, *524*, 454.

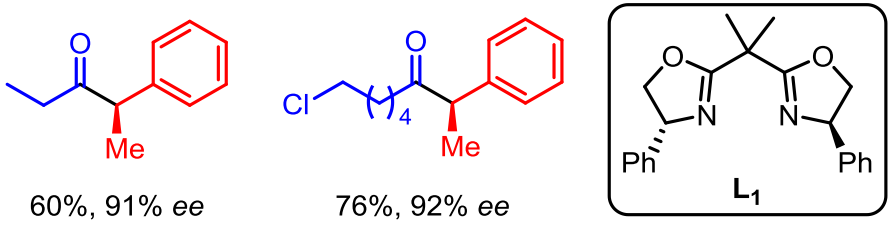
Ni/Ni Bimetallic Catalysis
Alkyl-Alkyl Kumada Coupling



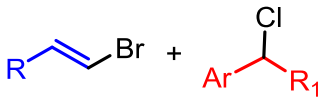
X. Hu: *J. Am. Chem. Soc*. **2013**, *135*, 12004.

Arsenal of Oxidation States: 0, I, II, III
Reductive Cross-Coupling of Electrophiles

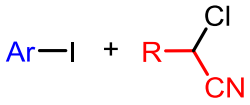




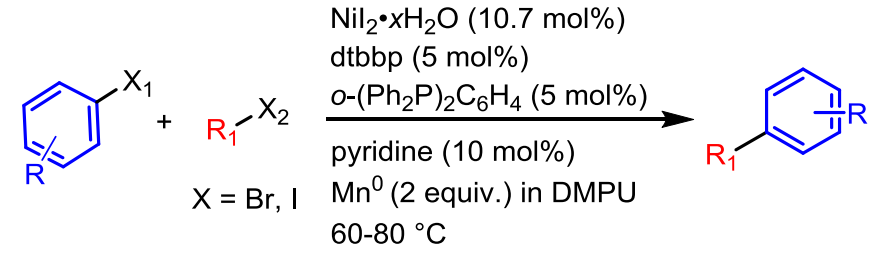
S E. Reisman: *J. Am. Chem. Soc*. **2013**, *135*, 7442.



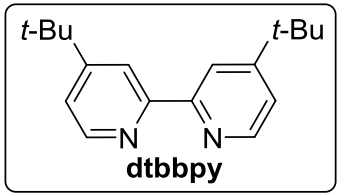
S. E. Reisman: *J. Am. Chem. Soc*. **2014**, *136*, 14365.

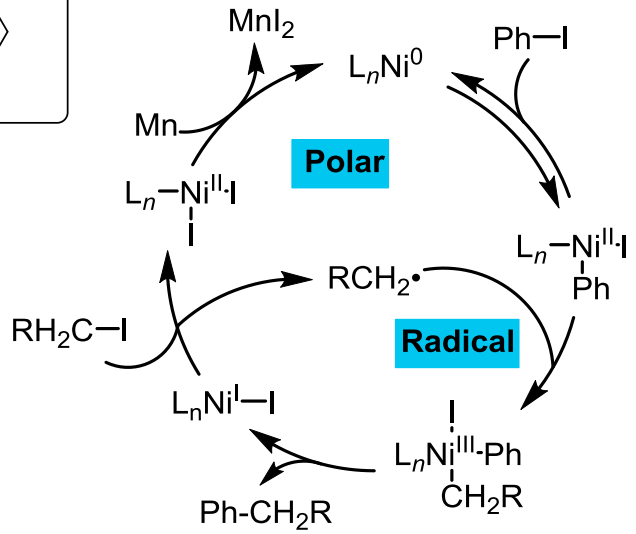


S. E. Reisman: *J. Am. Chem. Soc*. **2015**, *137*, 10480.

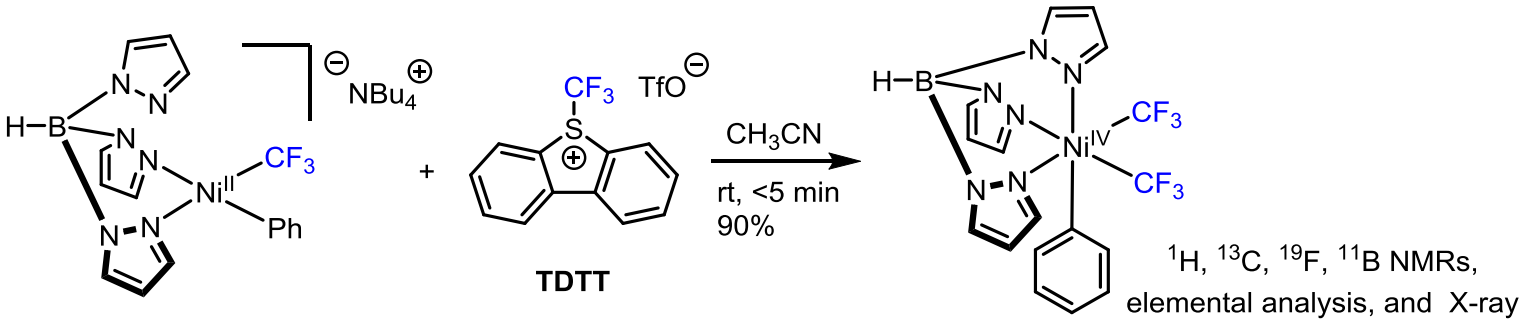


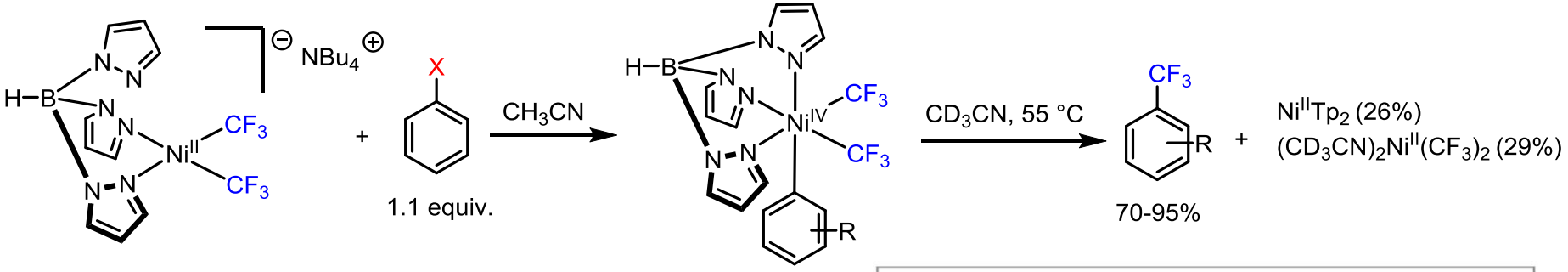
D. J. Weix: *J. Am. Chem. Soc*. **2010**, *132*, 920.



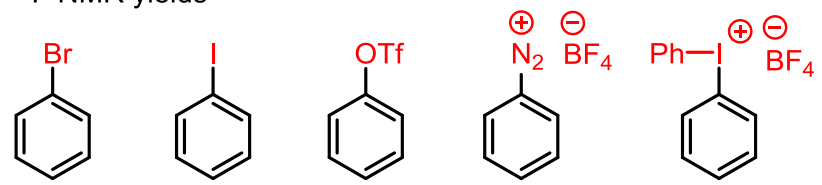


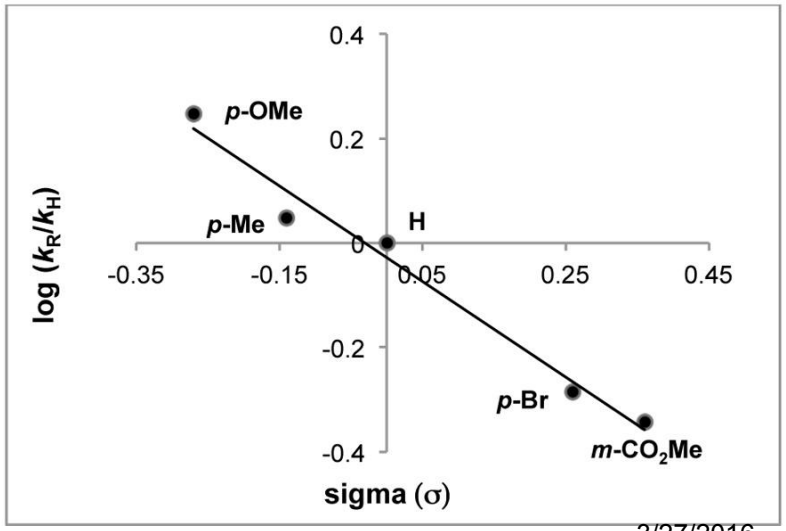
What about Ni(IV)?





^{19}F NMR yields





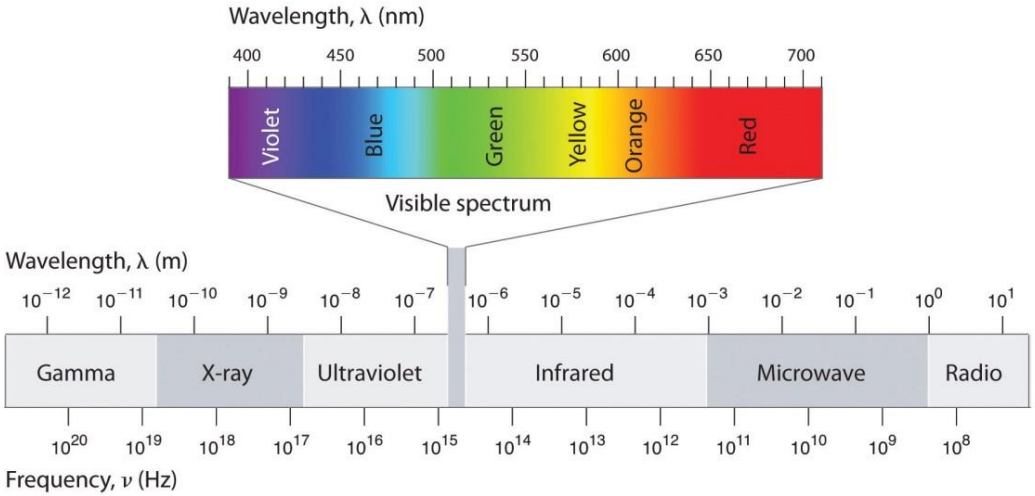
M. S. Sanford: *Science* **2015**, *347*, 1218;
J. Am. Chem. Soc. **2015**, *137*, 8034.

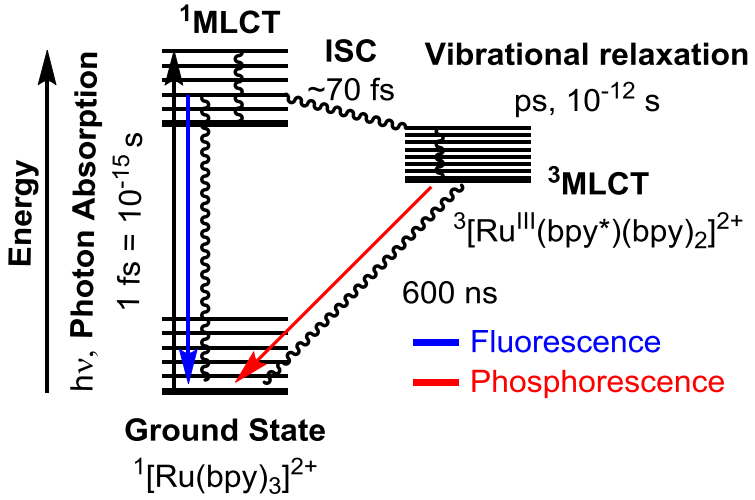
Photoredox/Ni Dual Catalysis

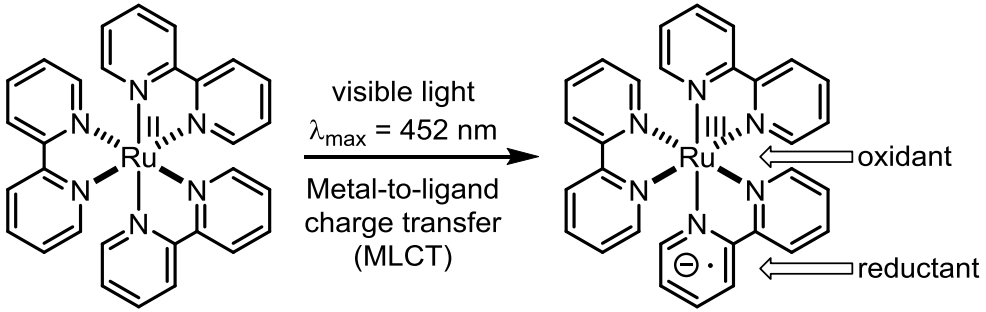
- **Publication History** (Original Research Articles)**:**
  - **2013:** 1
  - **2014:** 2
  - **2015:** 11
  - **2016:** 9 (as of 02/22/2016)

Journal	# of Publications	Journal	# of Publications
J. Am. Chem. Soc.	8	*Nature*	1
Angew. Chem. Int. Ed.	3	*Proc. Natl. Acad. Sci. U.S. A.*	1
Org. Lett.	3	*Chem. Sci.*	1
Science	2	*J. Org. Chem.*	1
Chem. Eur. J.	2	*Org. Chem. Front.*	1

Basics of a Photoredox Catalyst





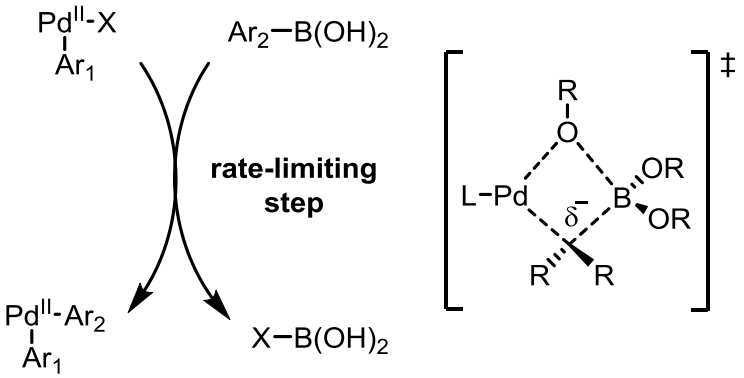


Metal = low oxidation potential; e^- rich
Ligand = low-lying LUMO (acceptor orbital)

A. Cannizzo: *Angew. Chem. Int. Ed.* **2006**, *45*, 3174.
Review: **C. R. J. Stephenson**: *J. Org. Chem.* **2012**, *77*, 1617.

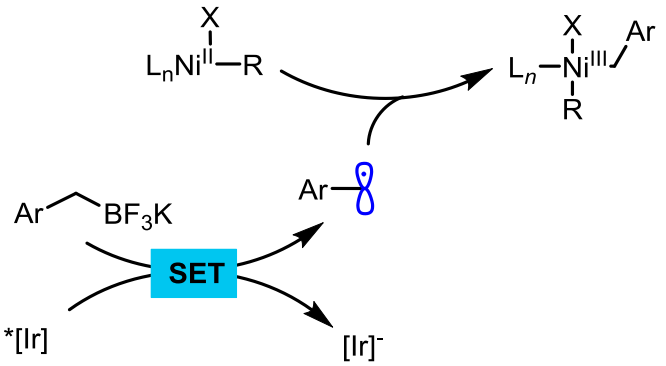
Single-Electron Transmetalation in Organoboron Cross-Coupling

Two-Electron Transmetalation



- High activation energy.
- Rate-limiting step in most Suzuki cross–couplings.
- Requires stoichiometric base, and high temperature.
- Transmetalation rate:
  $C_{sp} > C_{sp2} > C_{sp3}$

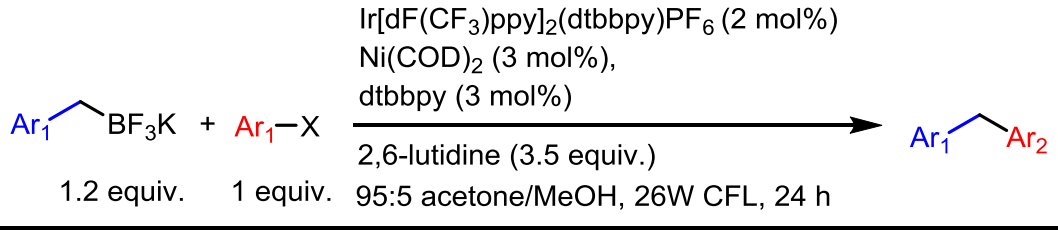
Single-Electron Transmetalation

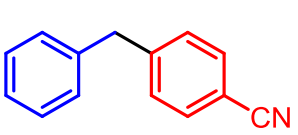


- Low activation energy.
- Reactivity dictated by measurable redox potentials.
- Requires no base or heat.
- SET rate:
  $C_{sp3} > C_{sp2} > C_{sp}$

G. A. Molander: *Science* **2014,** *345*, 433.

Single-Electron Transmetalation in Organoboron Cross-Coupling





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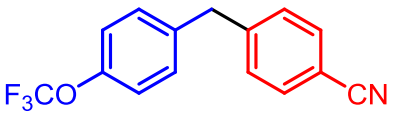

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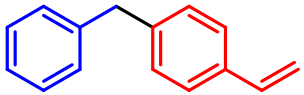

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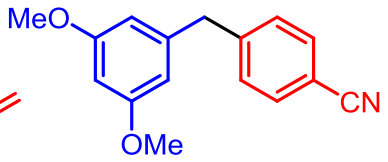

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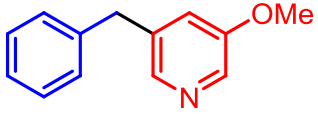

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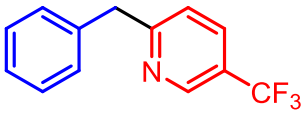

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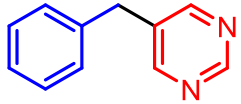

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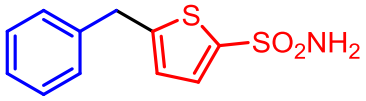

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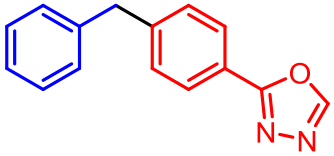

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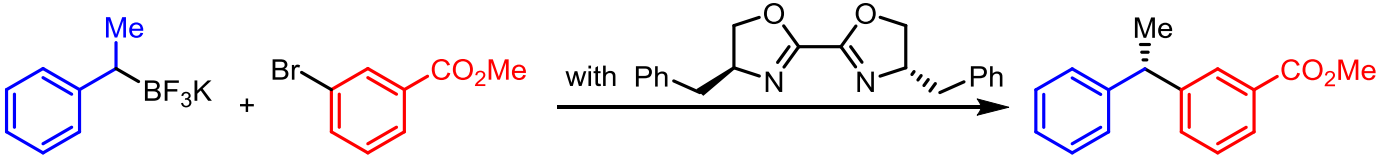
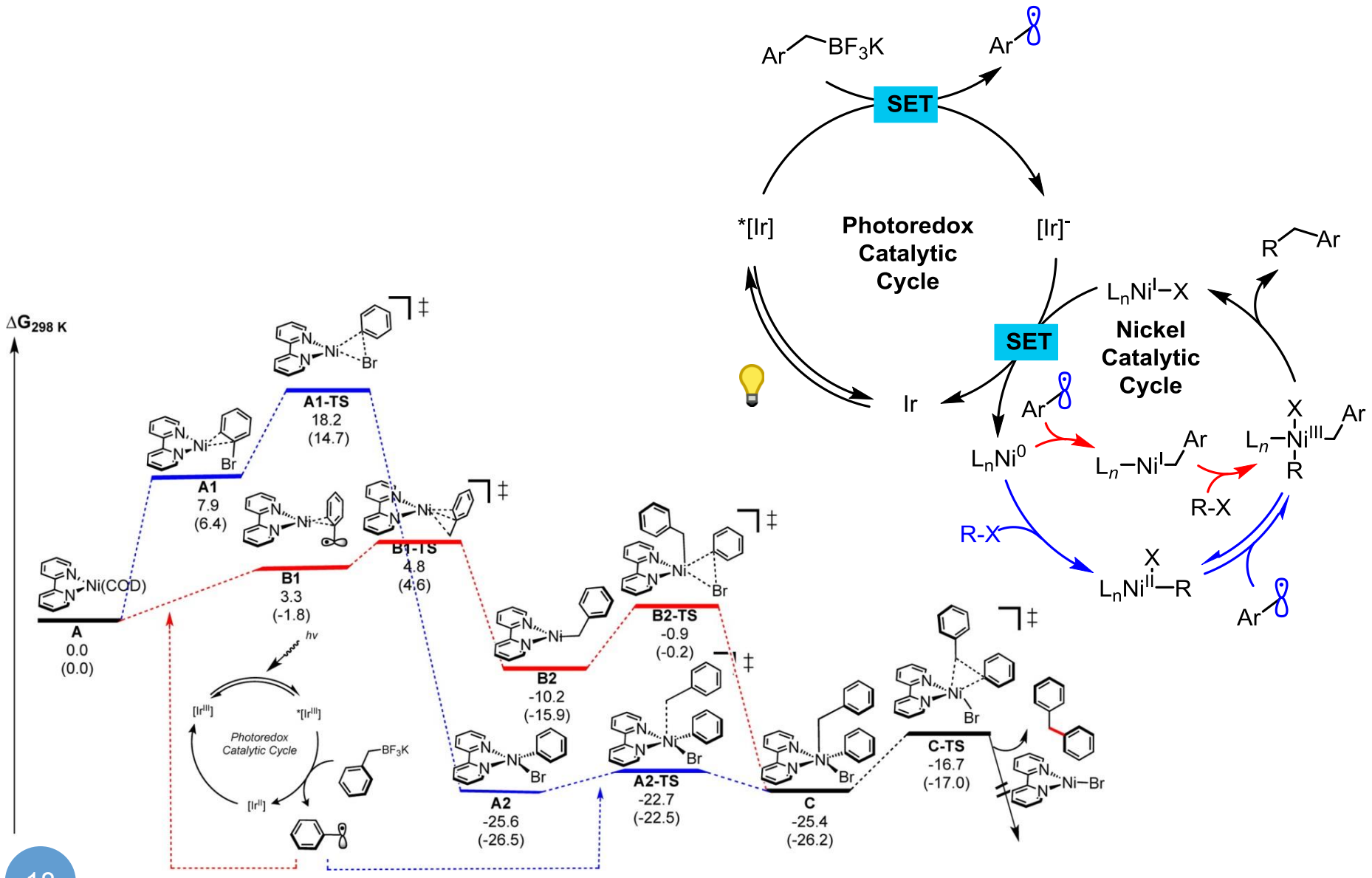


52%, 75:25 *er*

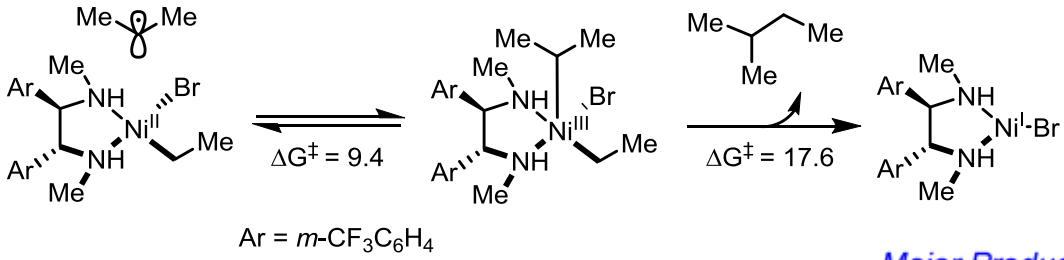
G. A. Molander: *Science* **2014,** *345*, 433; *J. Am. Chem. Soc.* **2015**, *137*, 2195; *Chem. Eur. J.* **2016**, *22*, 120.

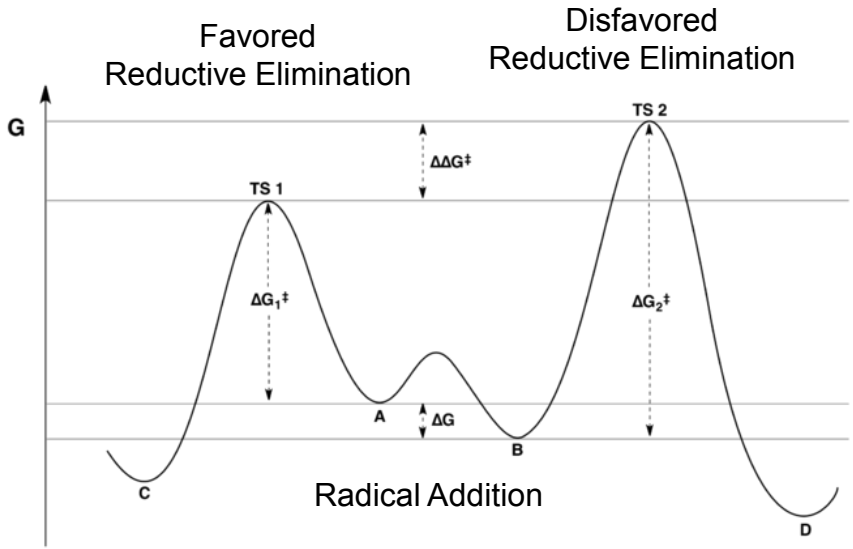
Mechanistic Considerations

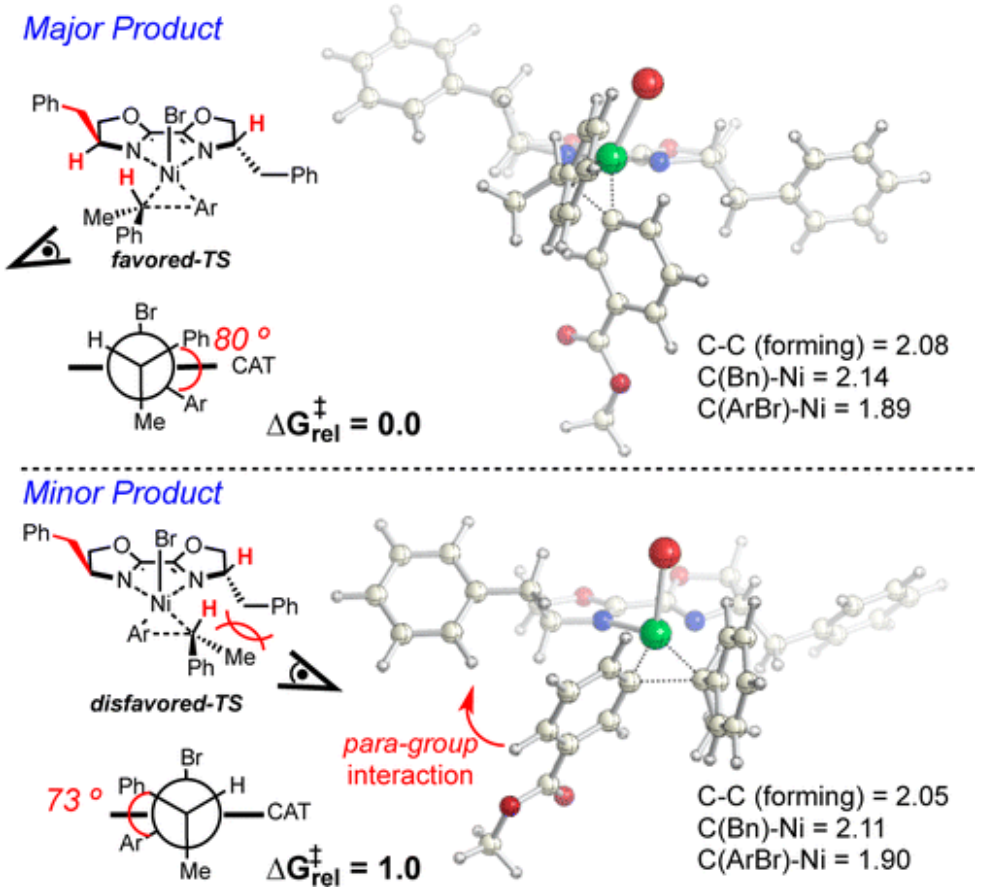


G.A. Molander and **M. C. Kozlowski**: *J. Am. Chem. Soc*. **2015**, *137*, 4896.

Dynamic Kinetic Resolution

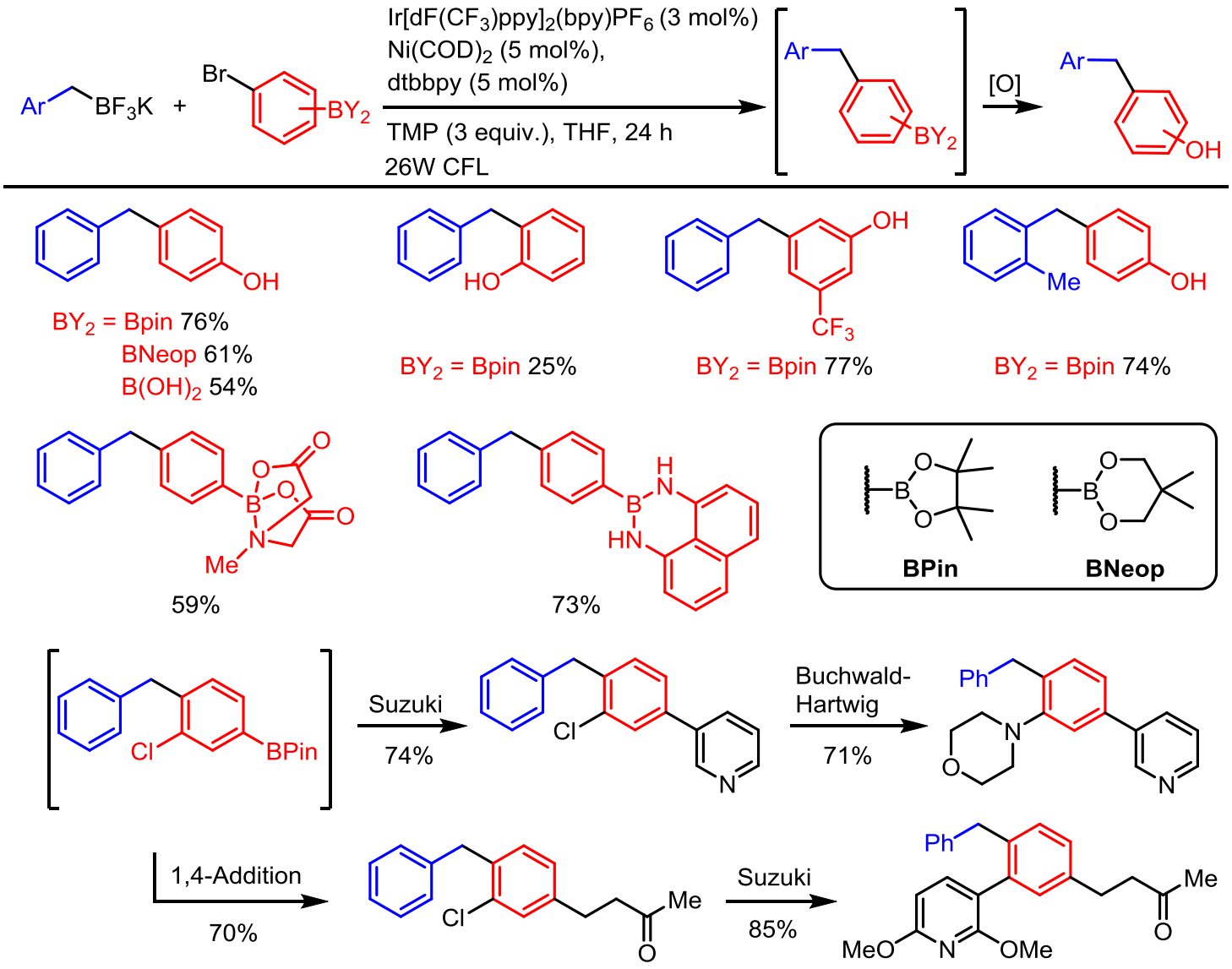






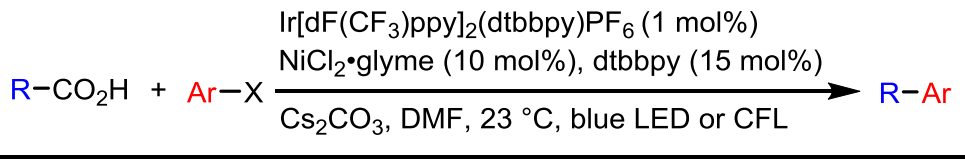
G.A. Molander and **M. C. Kozlowski**: *J. Am. Chem. Soc*. **2015**, *137*, 4896.

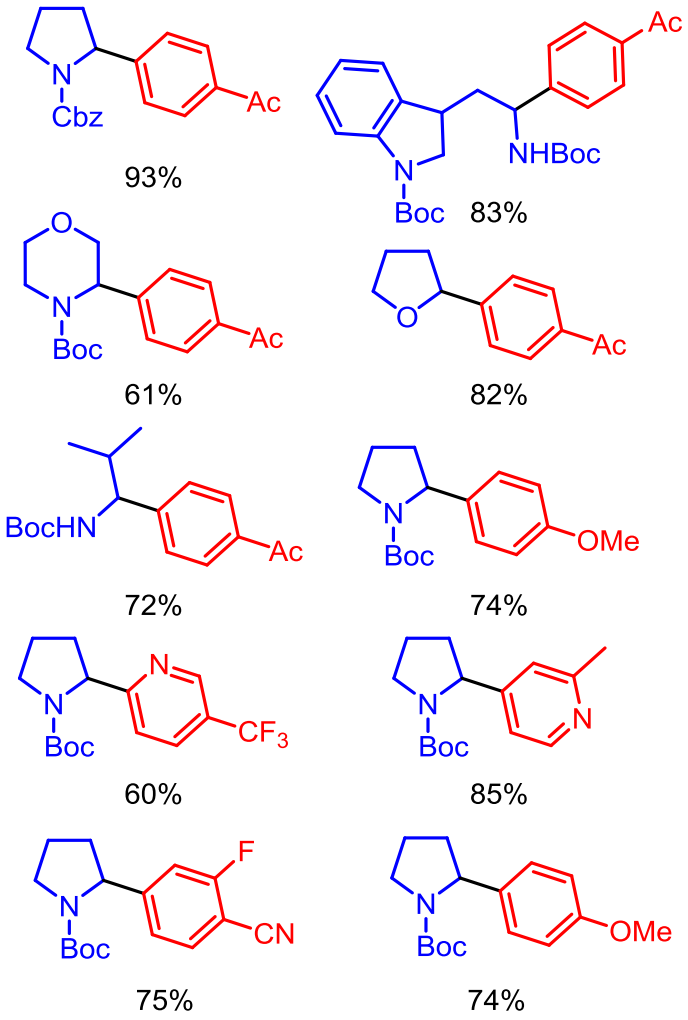
Trifluoroborates and Borylated Aryl Bromides

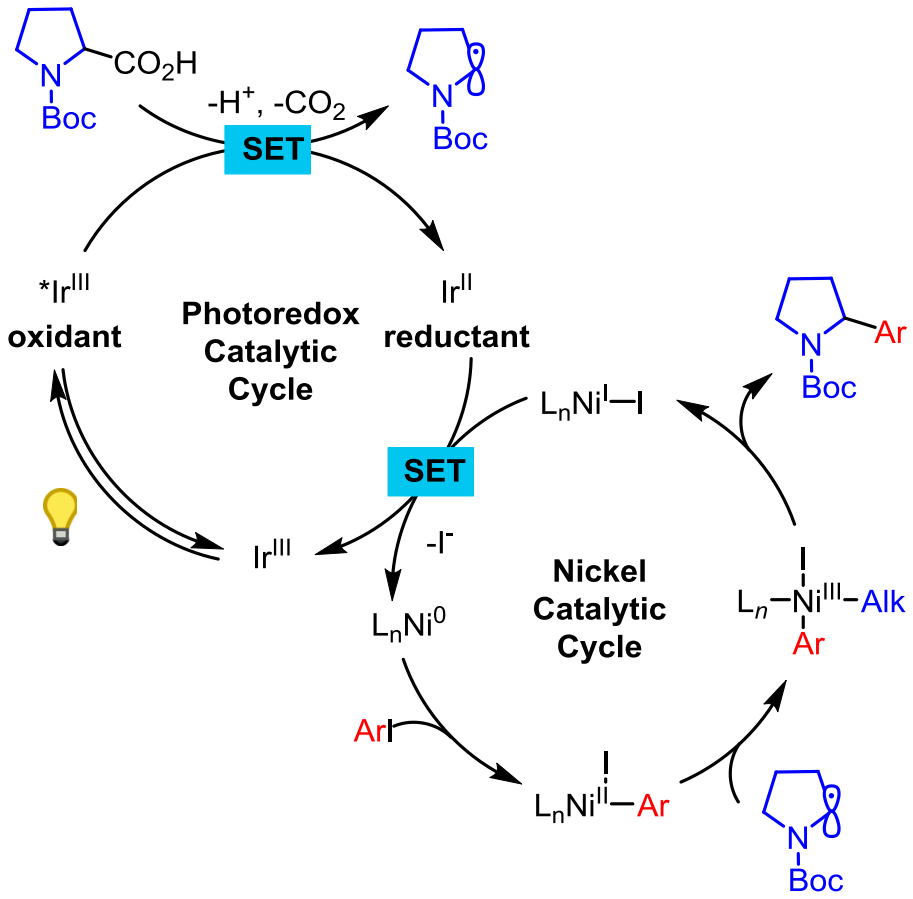


G.A. Molander: *Proc. Natl. Acad. Sci. U.S. A.* **2015**, *112*, 12026.

Coupling of α-Carboxyl C(sp^3) with Aryl Halides

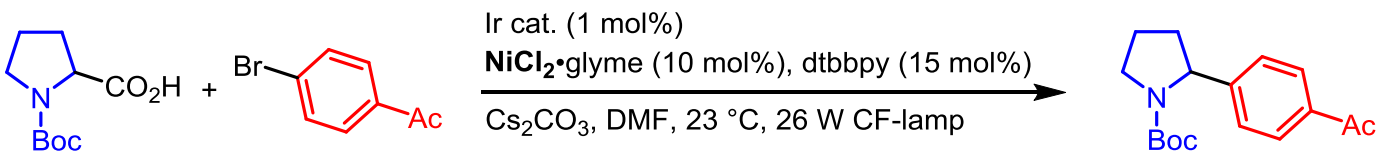




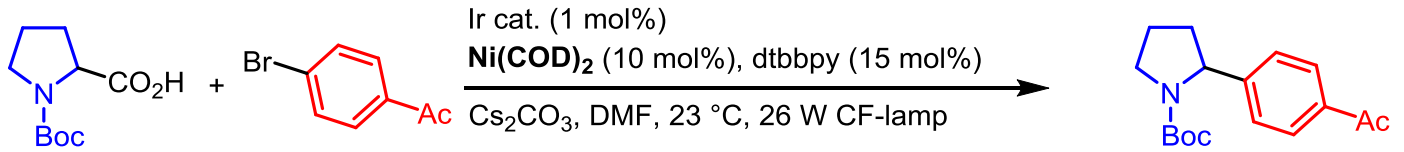


D. W. C. MacMillan and **A. G. Doyle**: *Science* **2014**, *345*, 437.

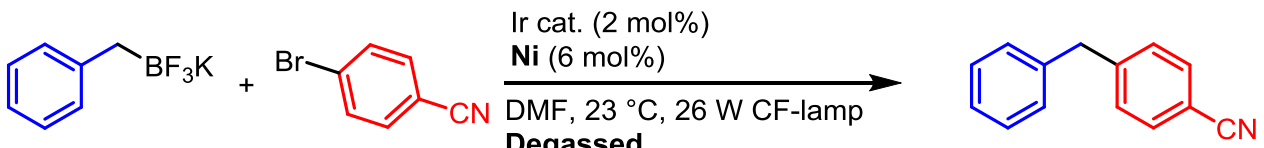
The Minor Procedural Details with Major Impact



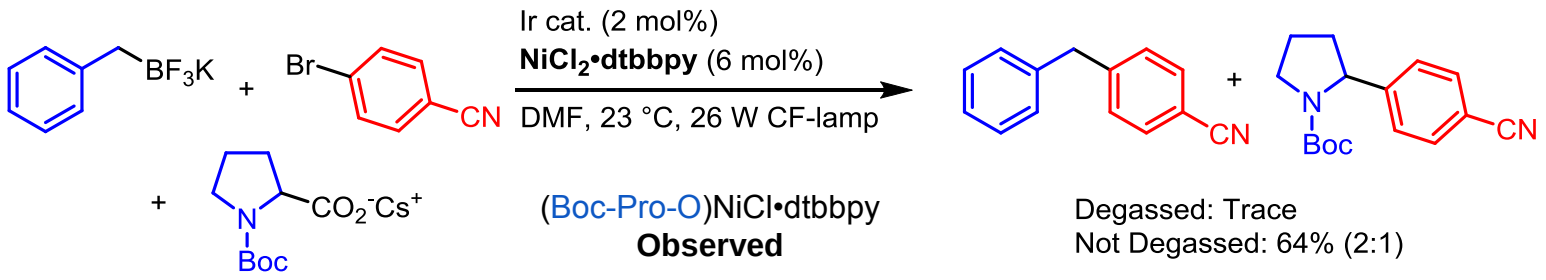
Degassed: 0%
Not Degassed: > 95%



Degassed: > 95%
Not Degassed: > 95%



$NiCl_2$•dtbbpy: 43%
$Ni(COD)_2$•dtbbpy: 49%

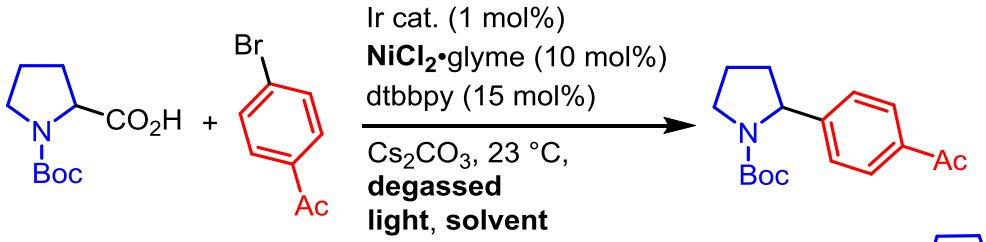


(Boc-Pro-O)NiCl•dtbbpy
Observed

Degassed: Trace
Not Degassed: 64% (2:1)

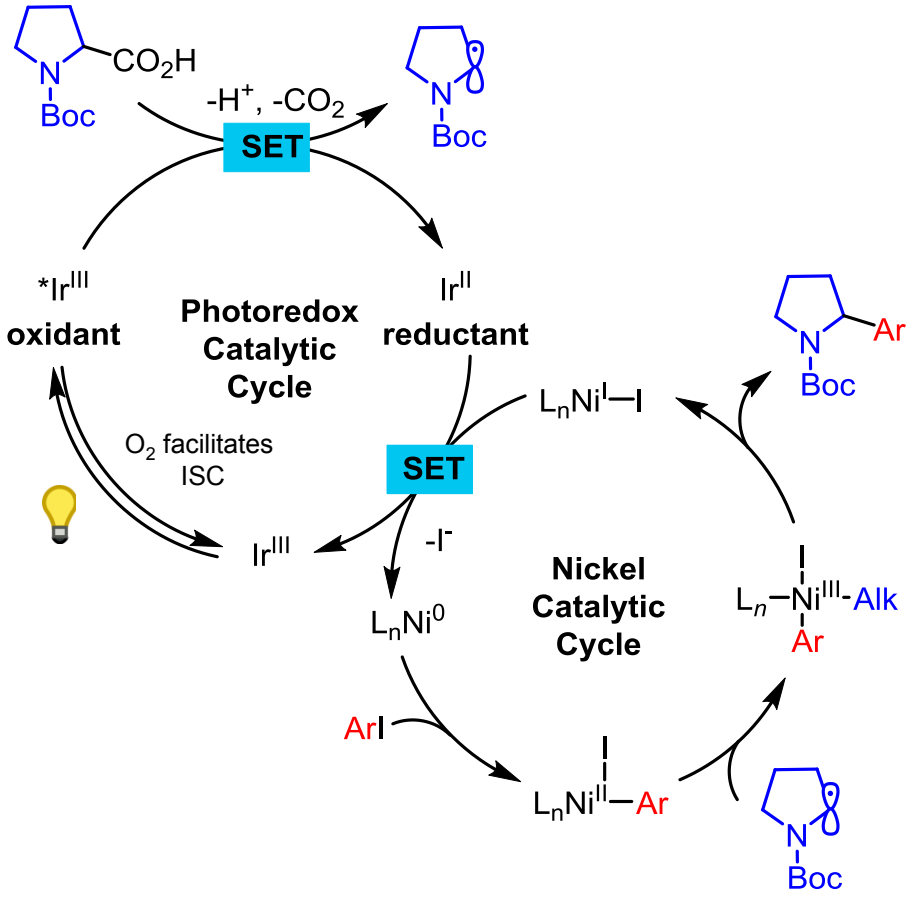
M. S. Oderinde, J. W. Johannes: *J. Org. Chem.* **2015**, 80, 7642.

The Minor Procedural Details with Major Impact



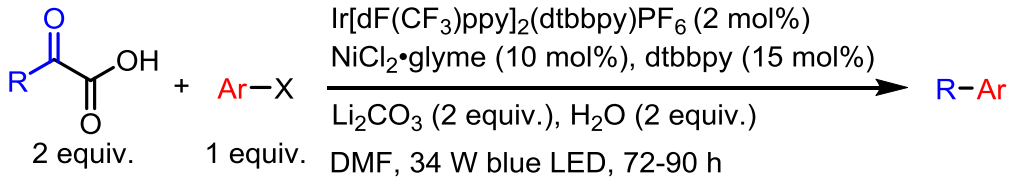
light source	solvent	reaction time	% yield
26 W CFL	DMF	20 h	0
26 W CFL	MeCN	20 h	68
26 W CFL	MeCN/DMF	20 h	90
34 W LED	DMF	5 h	>95

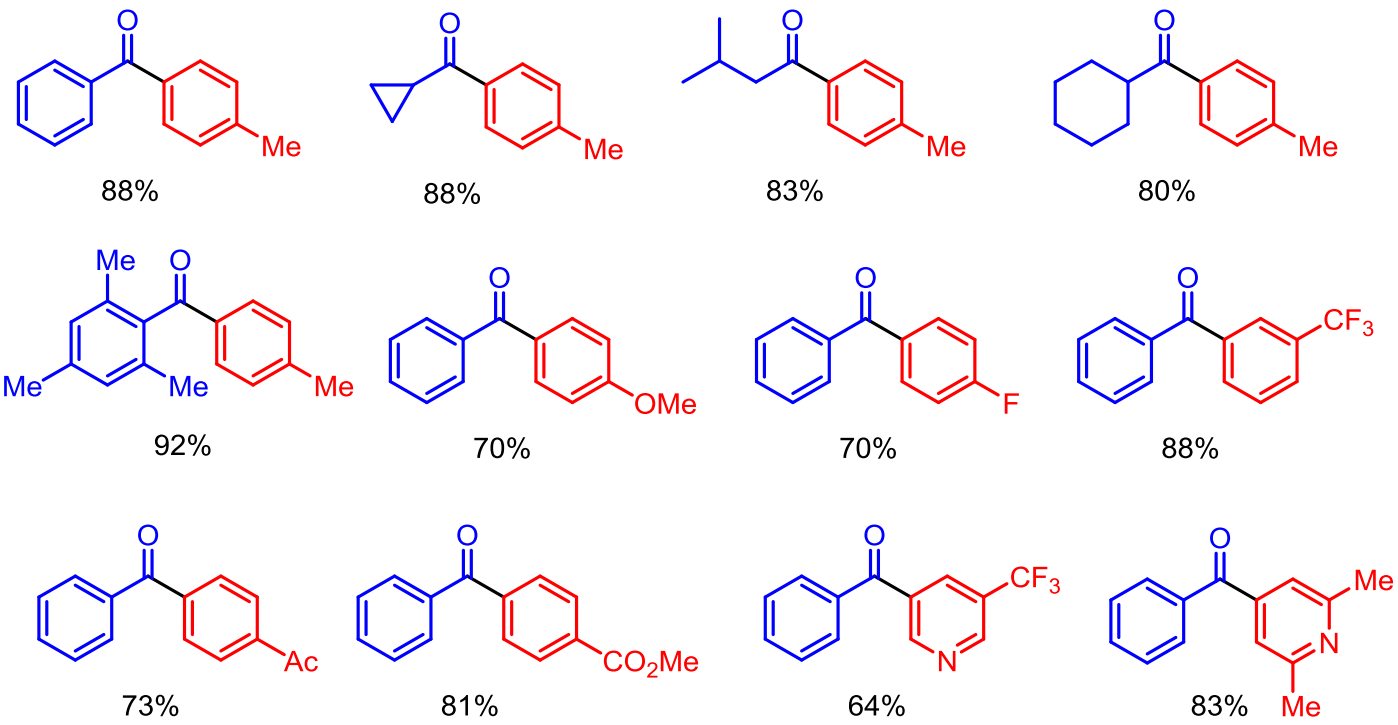
* All >95% yield when not degassed.



M. S. Oderinde, J. W. Johannes: *J. Org. Chem.* **2015**, 80, 7642.

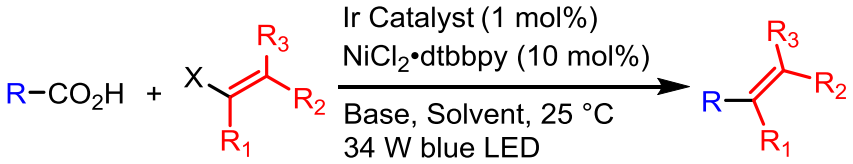
Decarboxylative Arylation of α-Oxo Acids





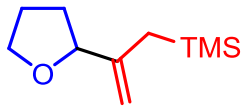
D. W. C. MacMillan: *Angew. Chem. Int. Ed.* **2015,** *54*, 7929.

Coupling of Carboxylic Acid with Vinyl Halides

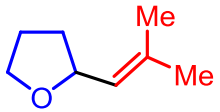


Ir Catalyst
$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$
$Ir[dF(Me)ppy]_2(dtbbpy)PF_6$

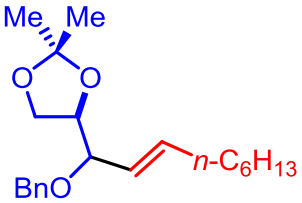
Solvent	Base
DMF	Cs_2CO_3
DMSO	DBU



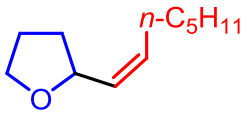
60%



71%

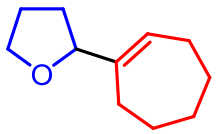


79% (1.4:1.0 dr)

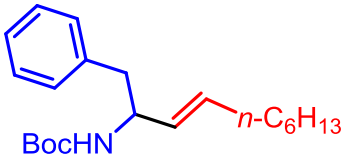


84%

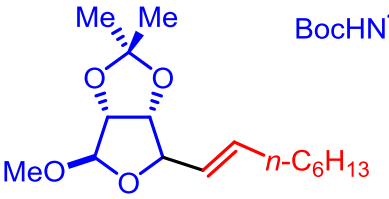
68%



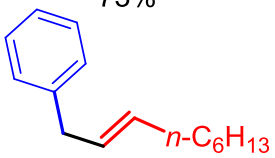
73%



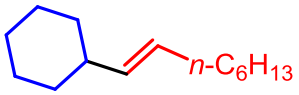
96%



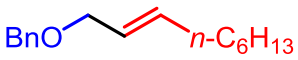
89% (18:1 dr)



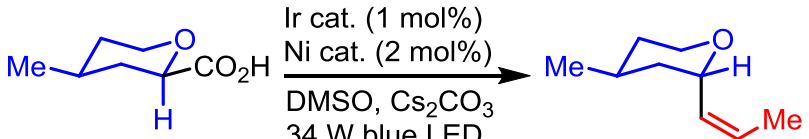
84%



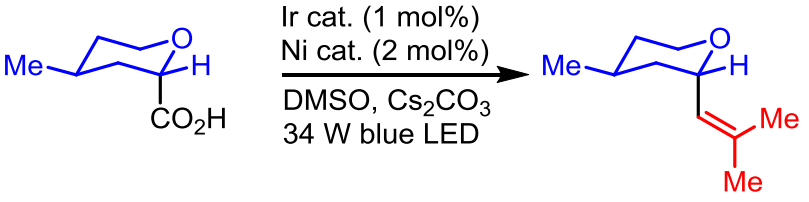
78%



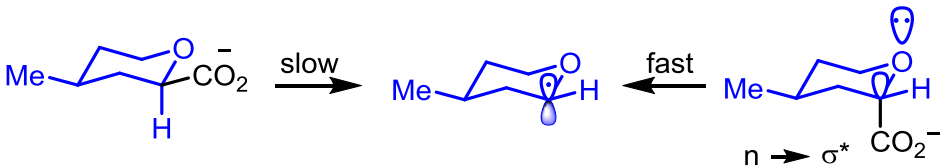
77%



10%

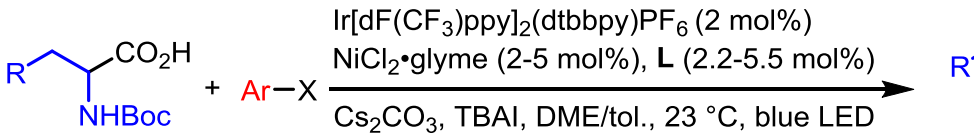


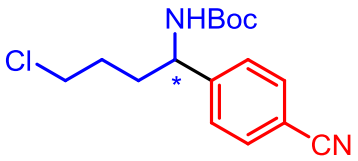
79%



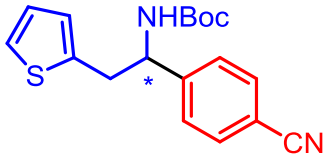
D. W. C. MacMillan: *J. Am. Chem. Soc.* **2015**, *137*, 624.

Enantioselective Arylation of α-Amino-Acids

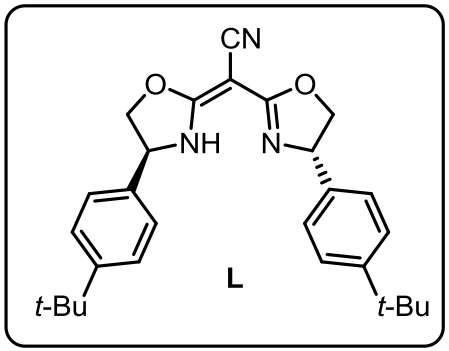


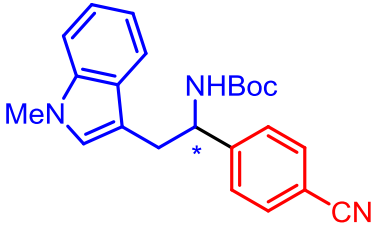


71%, 85% *ee*



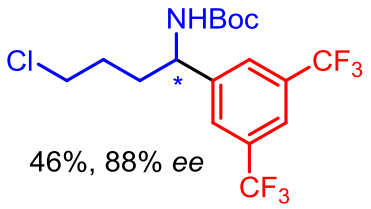
72%, 91% *ee*



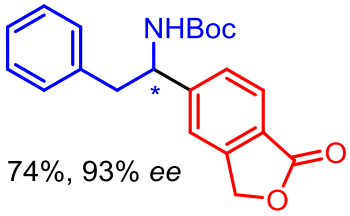


51%, 84% *ee*

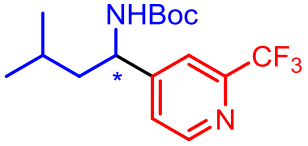
N-Boc-Pro and *N*-Boc-Val, < 10%



46%, 88% *ee*



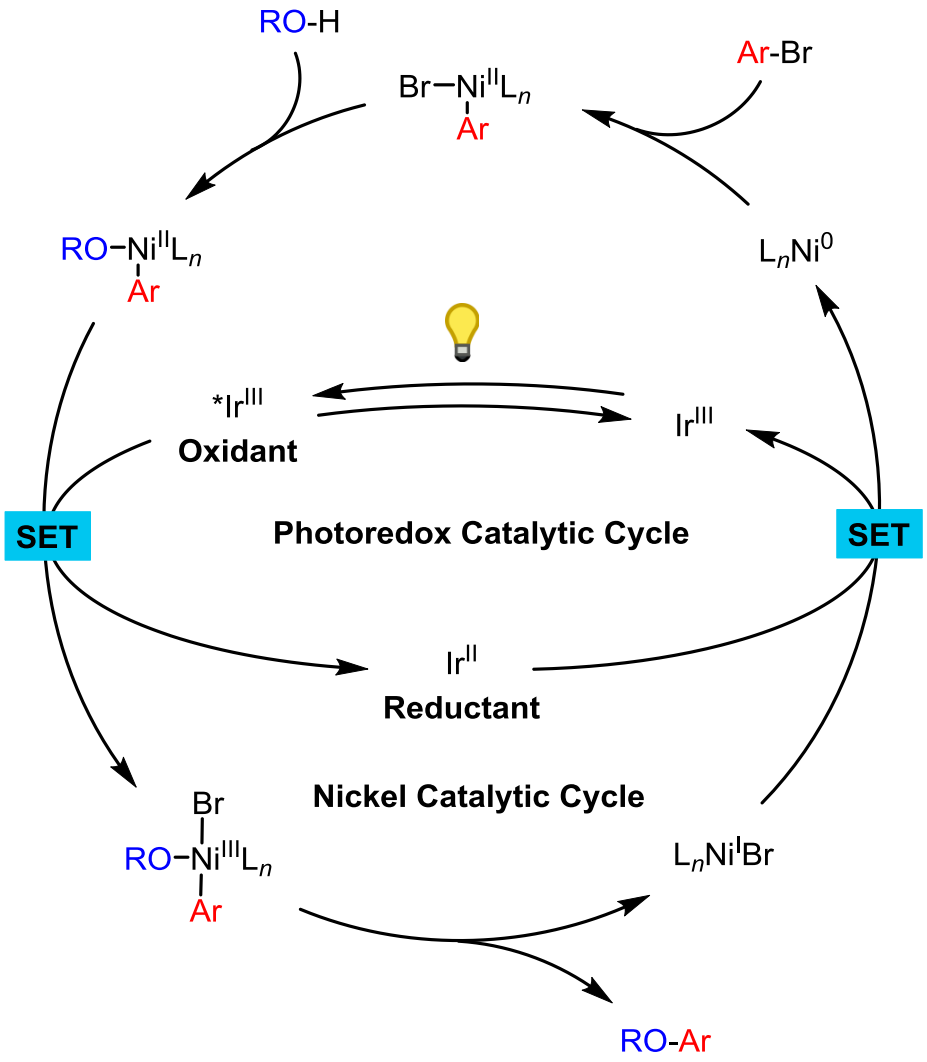
74%, 93% *ee*

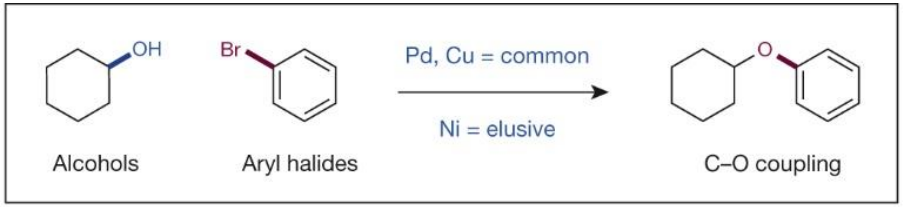


70%, 92% *ee*

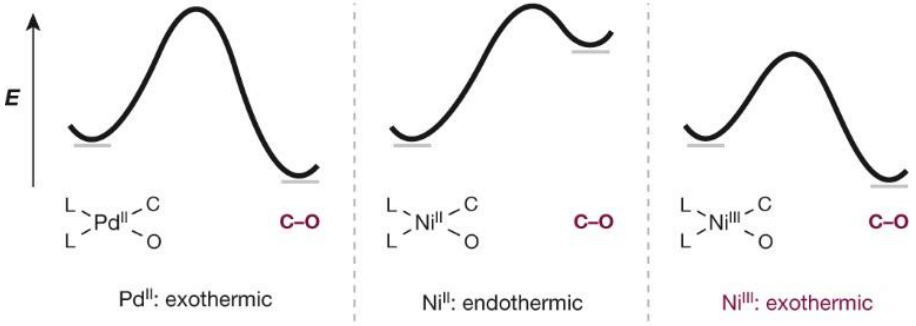
G. C. Fu and **D. W. C. MacMillan**: *J. Am. Chem. Soc.* **2016**, *138*, 1832.

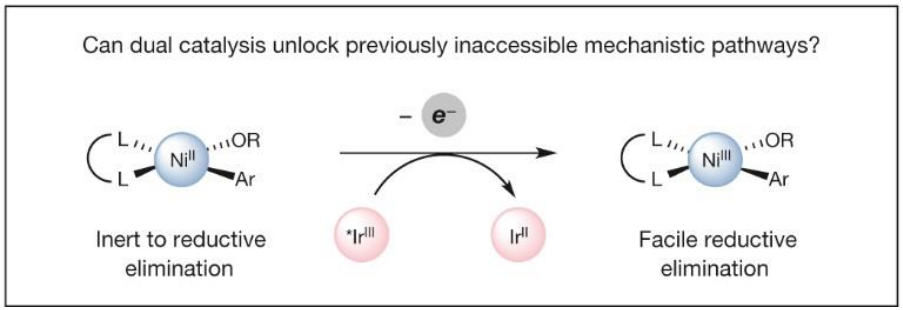
Alcohols to Ethers





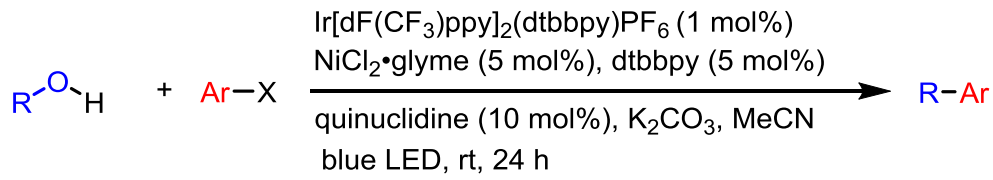
Energetic profiles of reductive elimination reactions to form C–O bonds

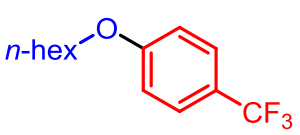




D. W. C. MacMillan: *Nature* **2015**, *524*, 330.

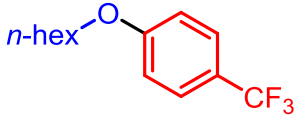
Alcohols to Ethers





90%

88%



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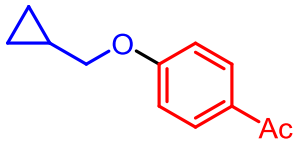

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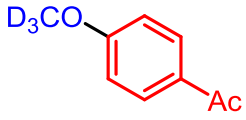
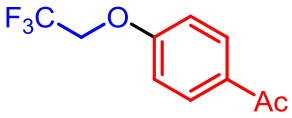
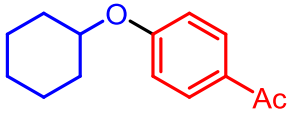


81%

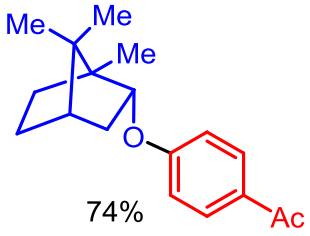


77%



86%

82%



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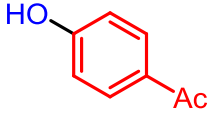

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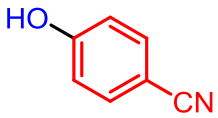
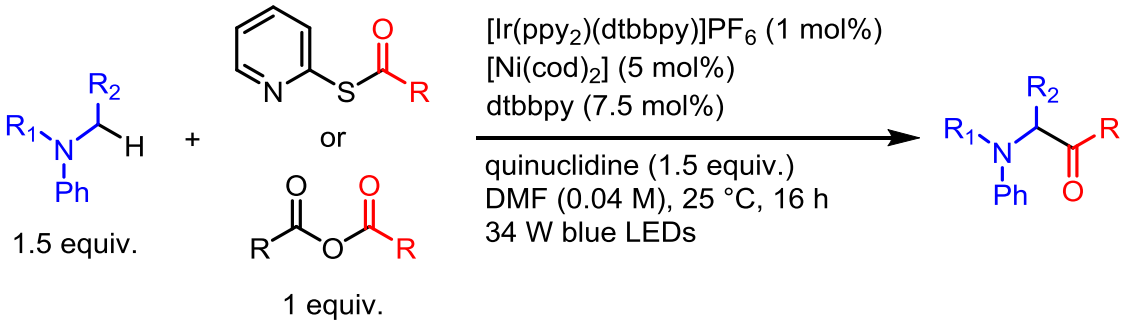
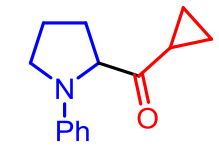


62%

D. W. C. MacMillan: *Nature* **2015**, *524*, 330.

Direct Acylation of C(sp^3)-H Bonds





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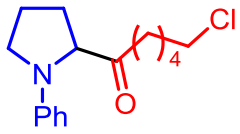

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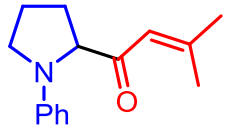

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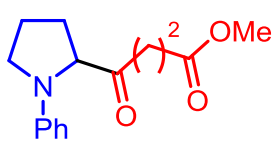

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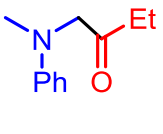

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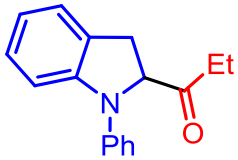

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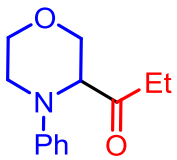

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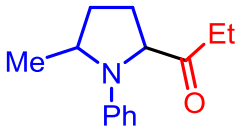

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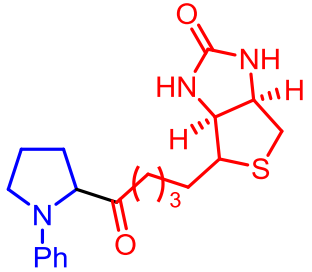

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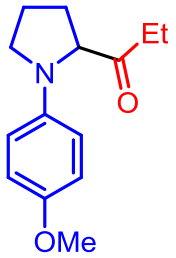

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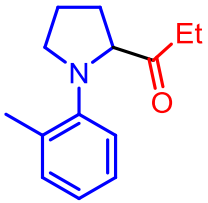

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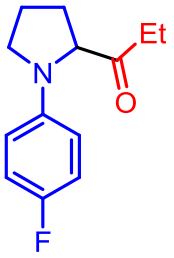

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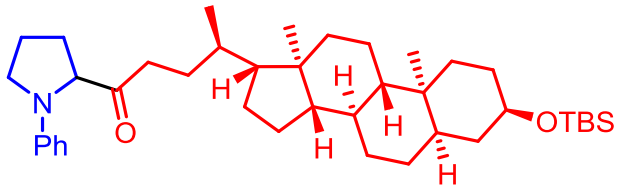

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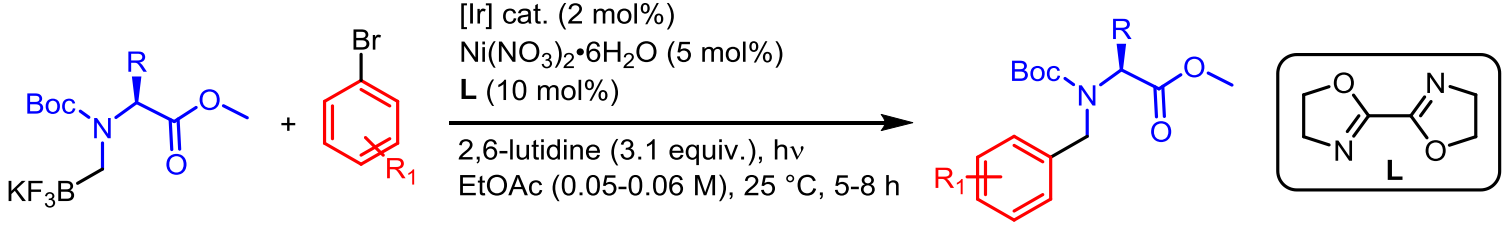
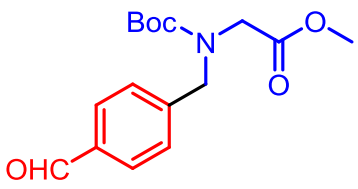
A. G. Doyle: *Angew. Chem. Int. Ed.* **2016,** DOI:10.1002/anie.201511438.

Arylation of α-Aminomethyltrifluoroborates

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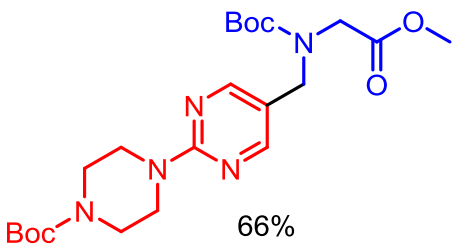
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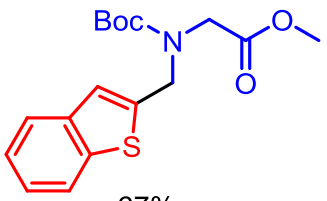
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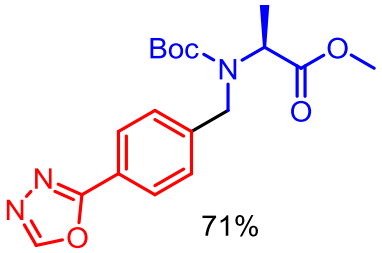
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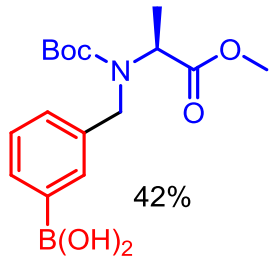
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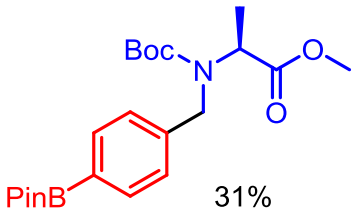
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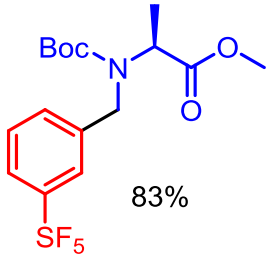
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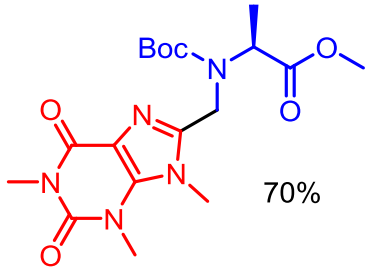
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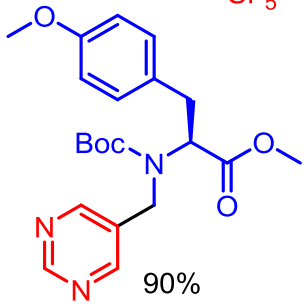
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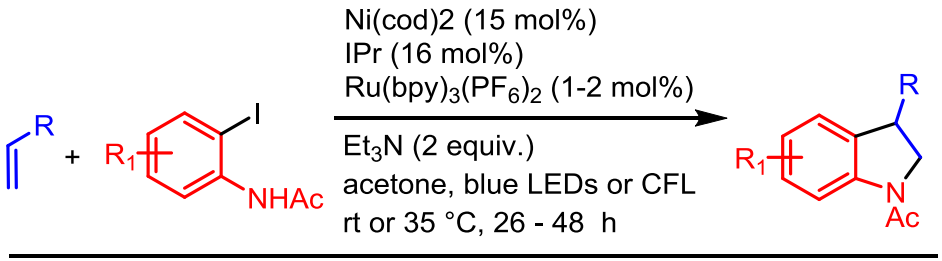
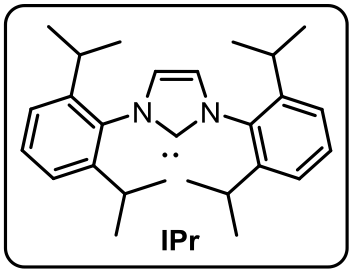
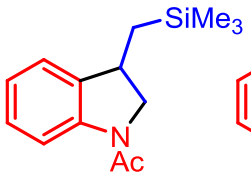
G. A. Molander: *Angew. Chem. Int. Ed.* **2016**, *55*, 254.

Regioselective Indoline Synthesis







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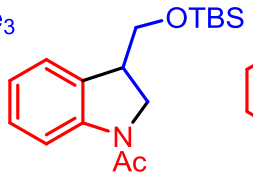

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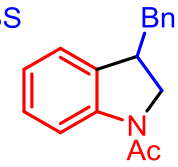

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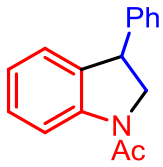

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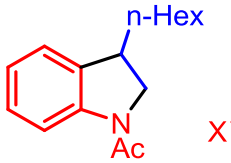
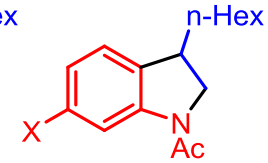
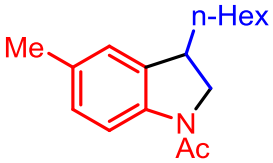


Ar-I, 88%
Ar-Br, 27%



X = Cl, 86%
X = OMe, 41%
X = F, 69%



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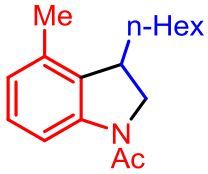

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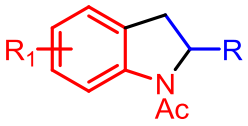
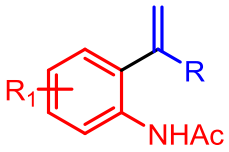
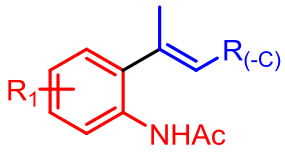
Side Products:







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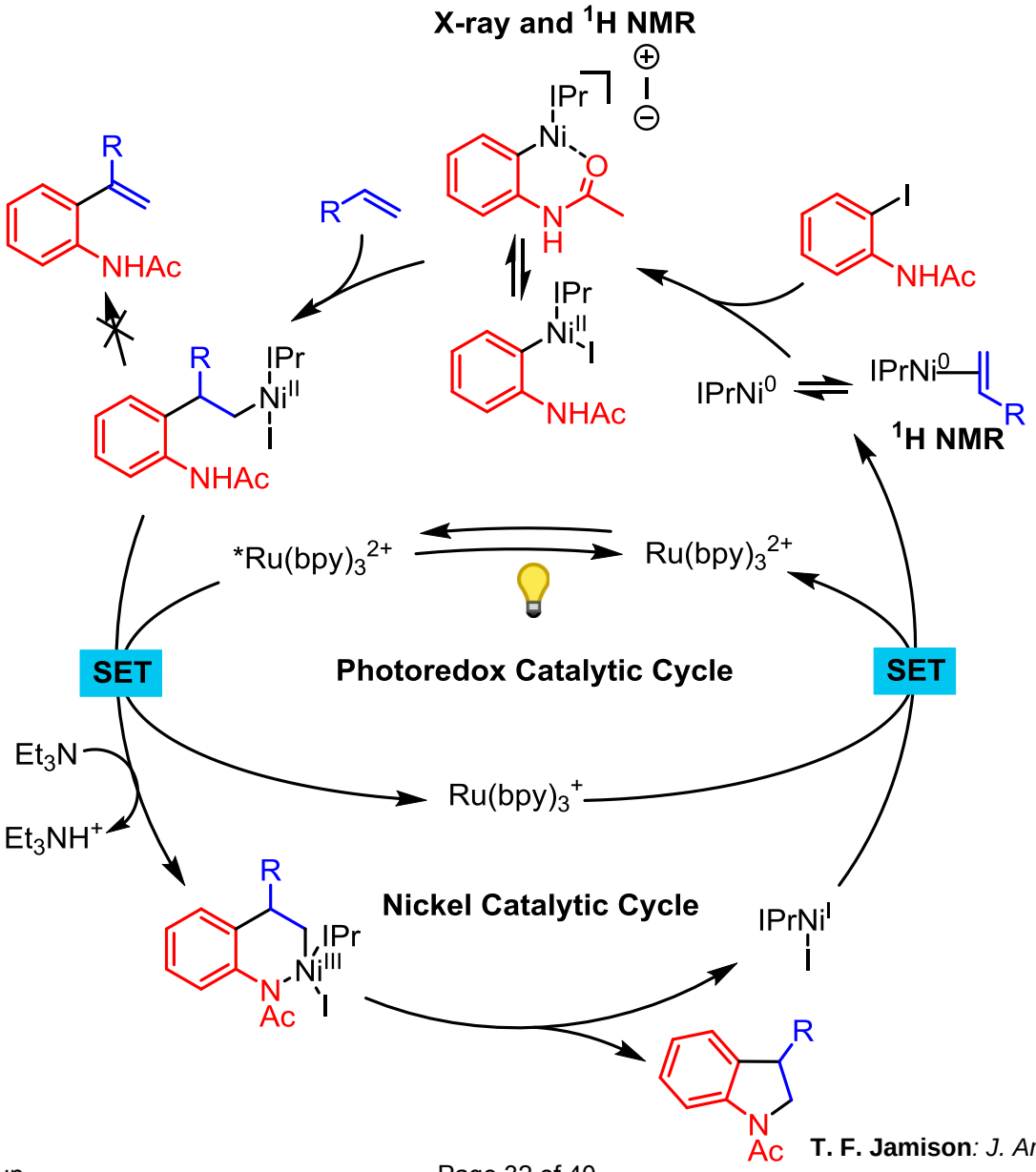
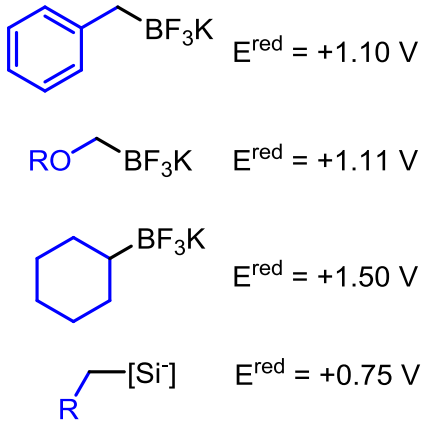
T. F. Jamison: *J. Am. Chem. Soc.* **2015**, *137*, 9531.

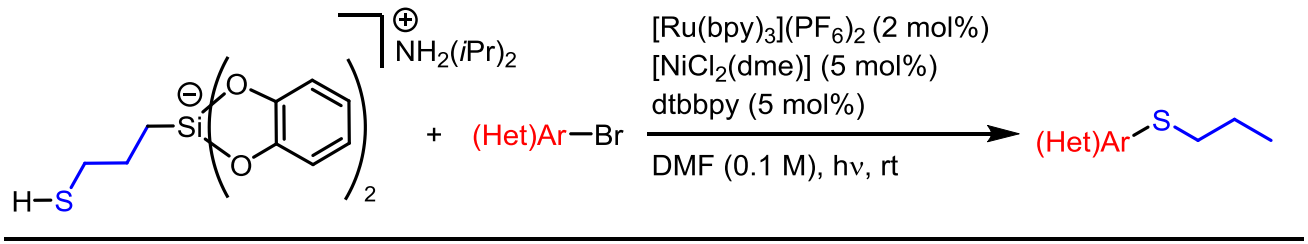
Regioselective Indoline Synthesis Mechanism

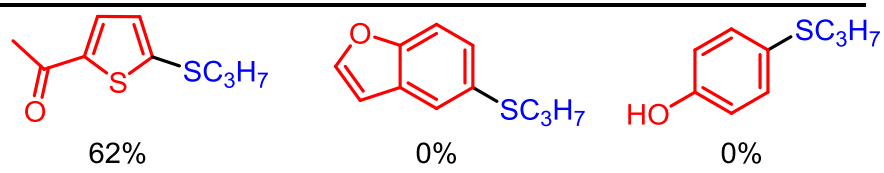


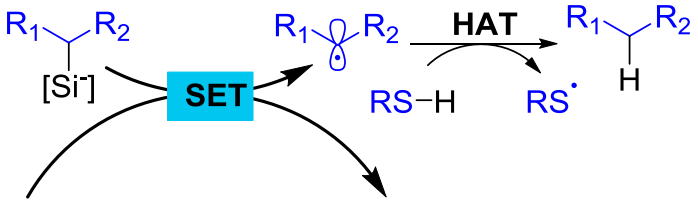
T. F. Jamison: *J. Am. Chem. Soc.* **2015**, *137*, 9531.

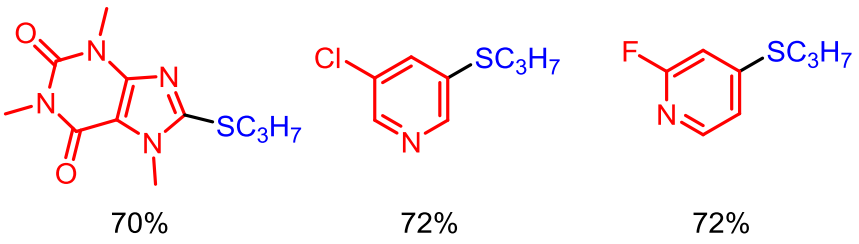
Cross-Coupling Involving Heteroatoms

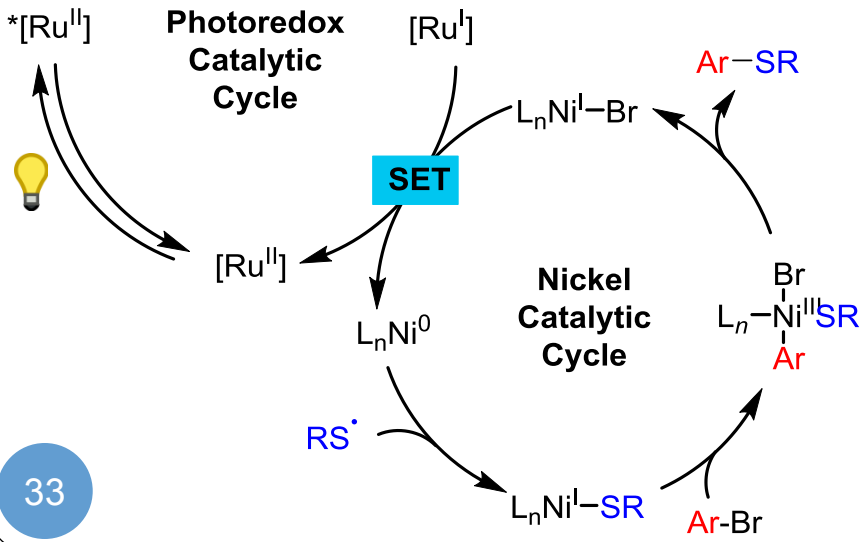


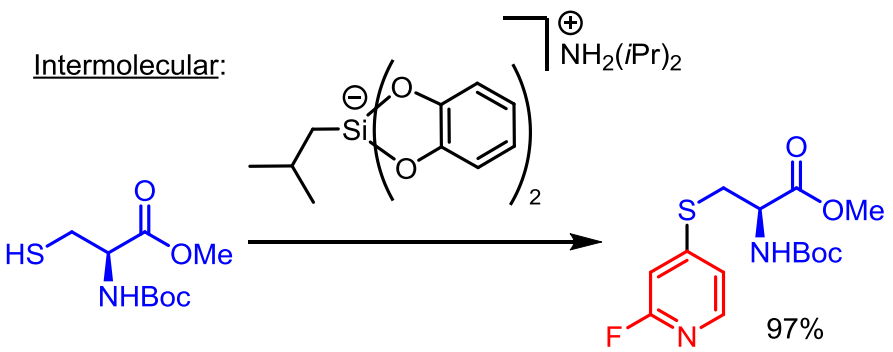






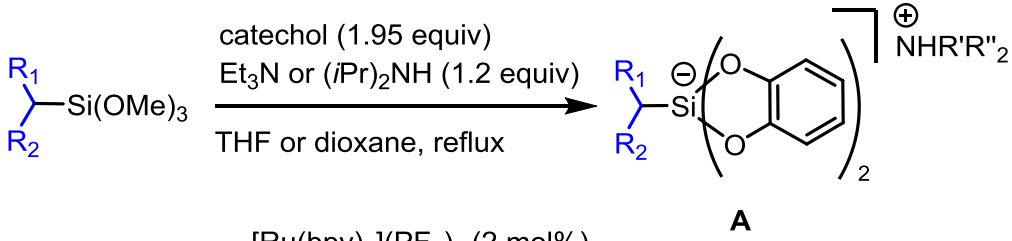


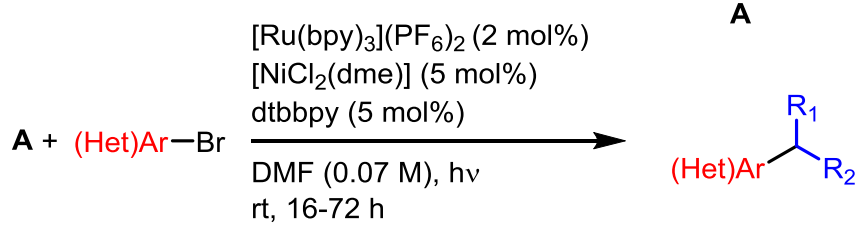


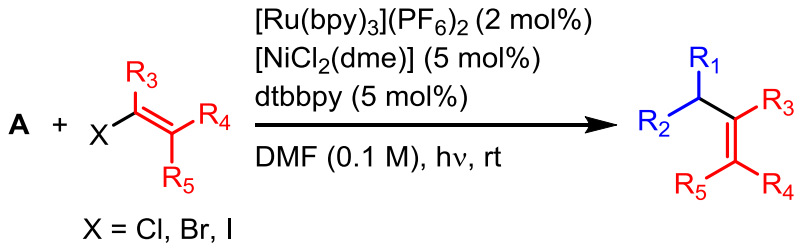


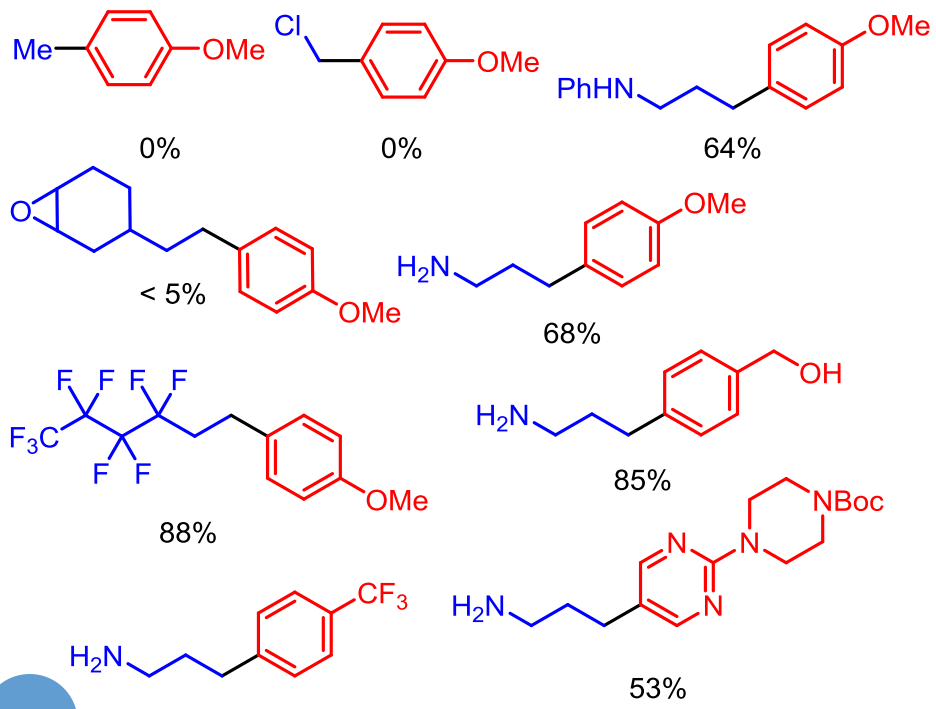
G. A. Molander: *Org. Lett.* **2016**, *18*, 876.

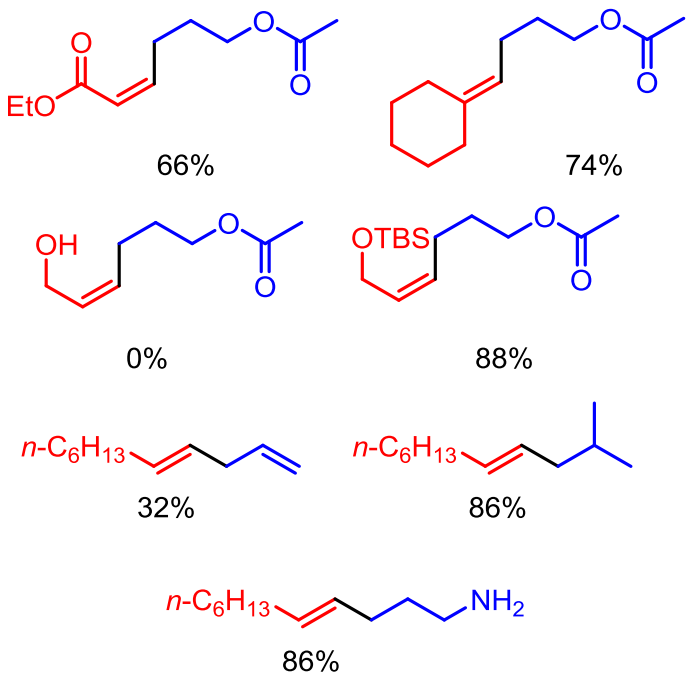
Cross-Coupling Involving Heteroatoms







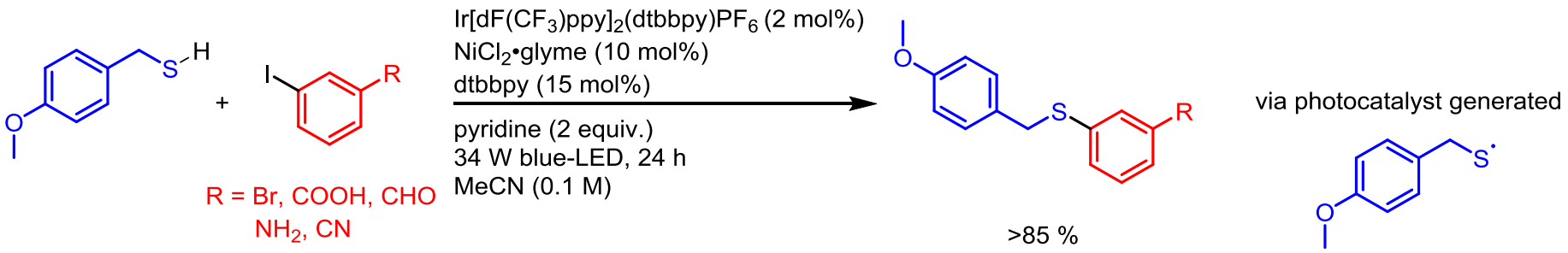




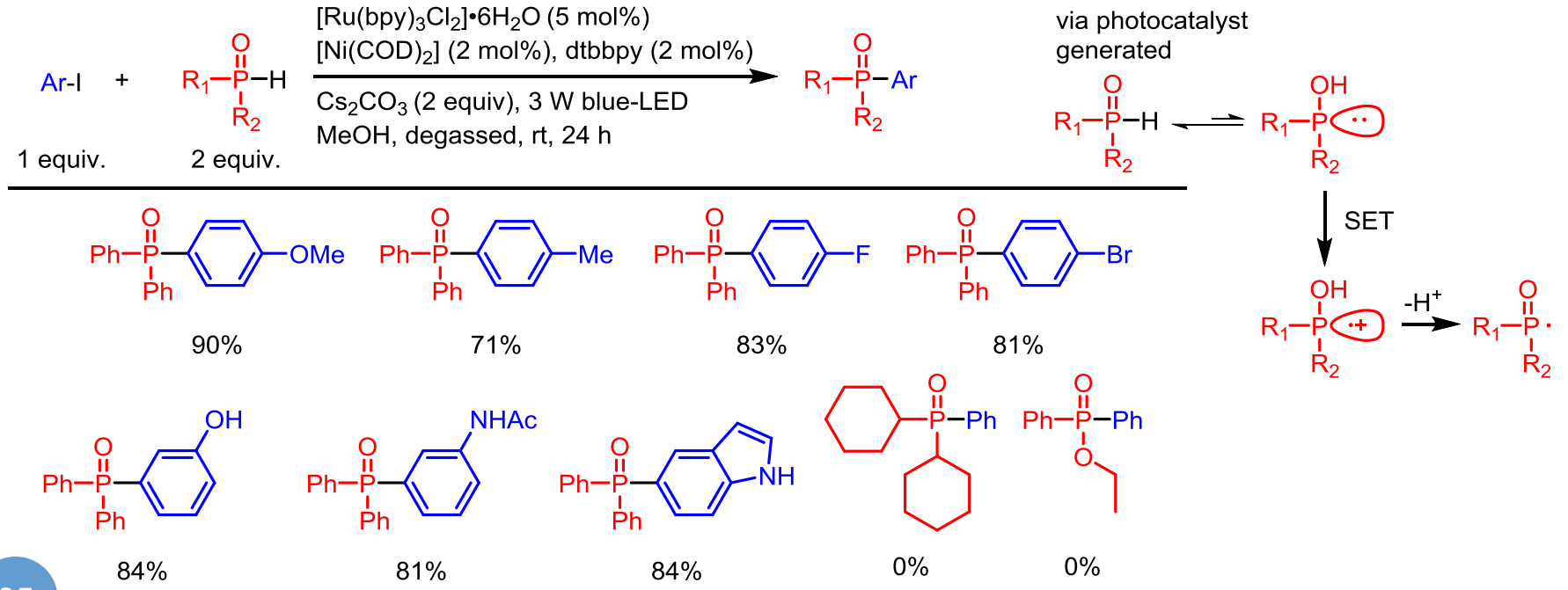
G. A. Molander: *J. Am. Chem. Soc.* **2016**, *138*, 475.

G. A. Molander: *Org. Lett.* **2016**, *18*, 764.

Cross-Coupling Involving Heteroatoms

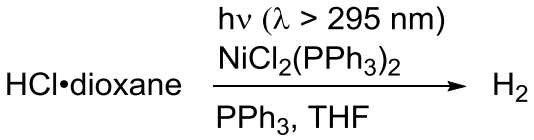


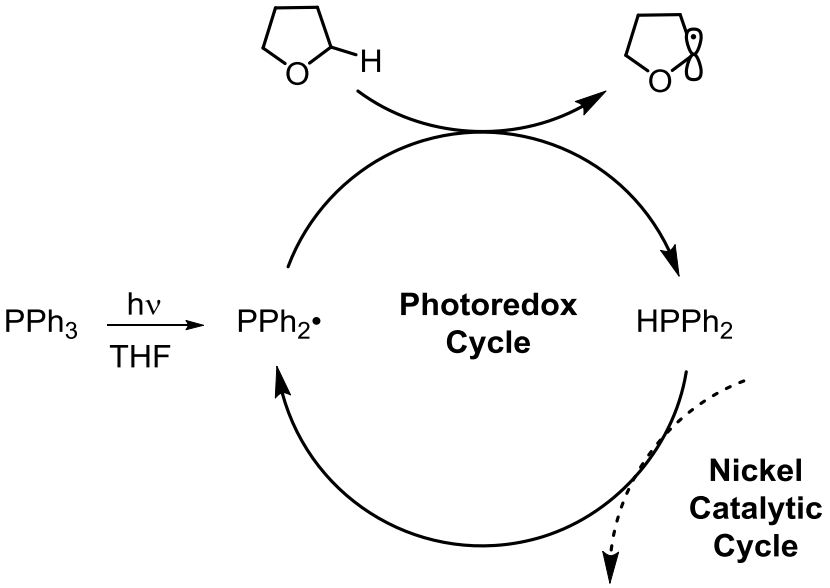
M. S. Oderinde, **J. W. Johannes**: *J. Am. Chem. Soc.* **2016**, *138*, 1760.

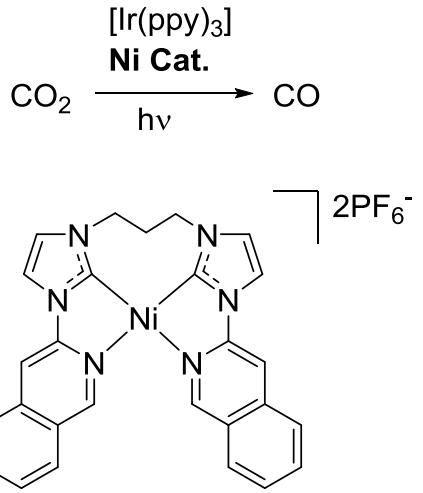


L-Q Lu, W-J Xiao: *Chem. Eur. J.* **2015**, *21*, 4962.

H_2 Generation/CO_2 reduction to CO





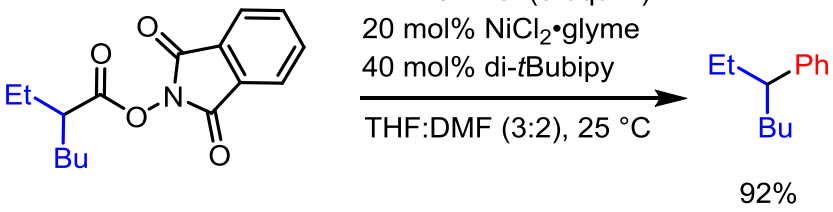


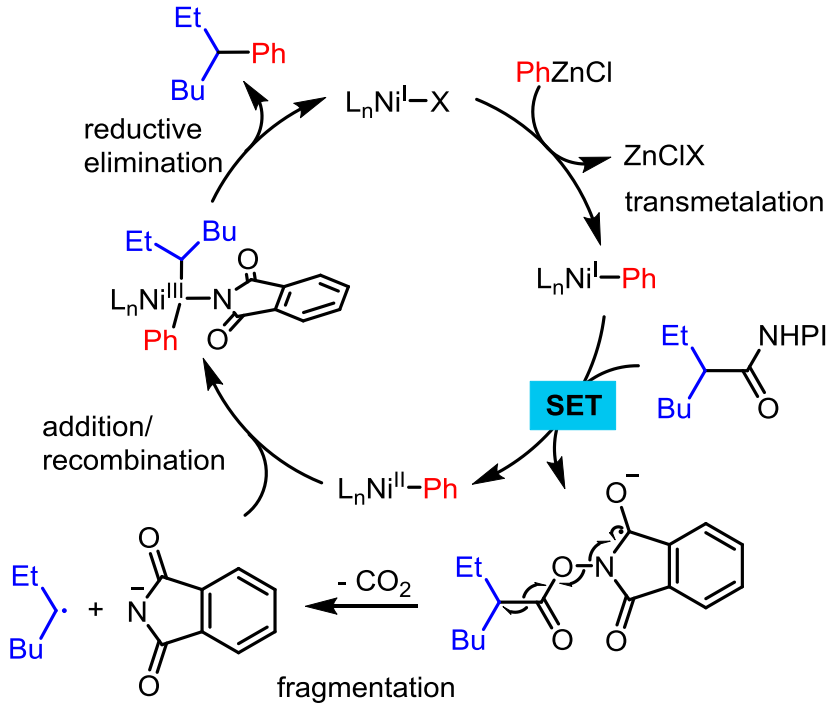
D. G. Nocera: *Chem. Sci.* **2015**, *6*, 917.

C. J. Chang: *J. Am. Chem. Soc.* **2013**, *135*, 14413.

Some Considerations

- **1. Photocatalyst**
  - cheaper catalysts needed.
  - scale limitations? (light permeability issues)
    - batch v. flow photoreaction.
  - alternative SET/radical generation conditions
    - redox-active esters





P.S. Baran: *J. Am. Chem. Soc.* **2016**, *138*, 2174.

Some Considerations

- **2. Nickel Catalyst**
  - ligand scope? Most examples use the same ligand.
  - more examples of stereo-induction via chiral ligands. Or substrate-controlled (difficult when dealing with radicals).
  - in some cases, high catalyst loadings.
  - long reaction times (but most reactions run at RT).

- **3. Coupling Partners/Non-Coupling Reagents**
  - more examples of intramolecular
  - applications in synthesis of complex molecules.
  - more examples of C-heteroatom coupling (F, B).
  - in many cases, atom economy is poor.

Future Outlook

- This methodology is in its (very) early stages and will expand rapidly in the next 5-10 yrs. 2016 is on track for 60 publications!
- So far, very nice display of different coupling partners and novel mechanisms … but the methodology is not yet practical:
  - poor atom economy
  - expensive photocatalyst (can photocatalyst be replaced?)
  - scale limitations
  - not yet demonstrated on complex molecules
- Lots of room for growth and improvement makes for exciting proposal topics!

Acknowledgments

- Prof. Peter Wipf
- Wipf Group Past and Present
- Caffeine