# Carbon-Carbon Bond Formation by Metallophotoredox Catalysis

Vincent Kassel
January 28th, 2020

University of Illinois At Urbana-Champaign

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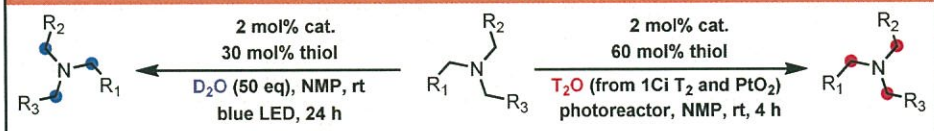
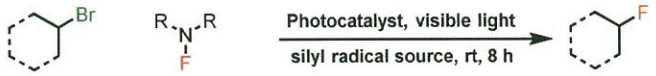
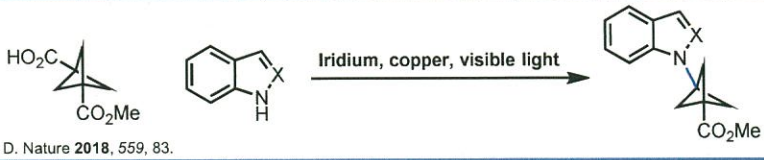
## Photoredox Applications



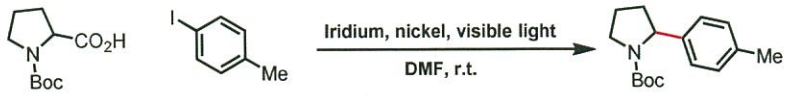

MacMillan, D. et al. *Science* **2017**, *358*, 1182.




MacMillan, D. et al. *J. Am. Chem. Soc.* **2019**, *141*, 20031.




MacMillan, D. Nature **2018**, *559*, 83.




MacMillan, D. Science **2014**, *345*, 437.

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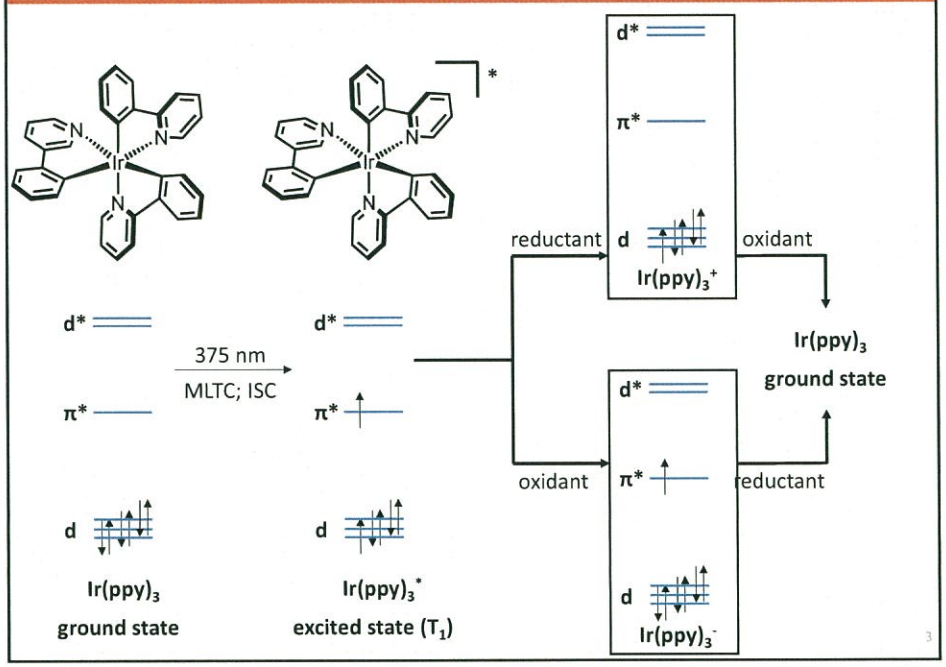
## Photophysics Primer

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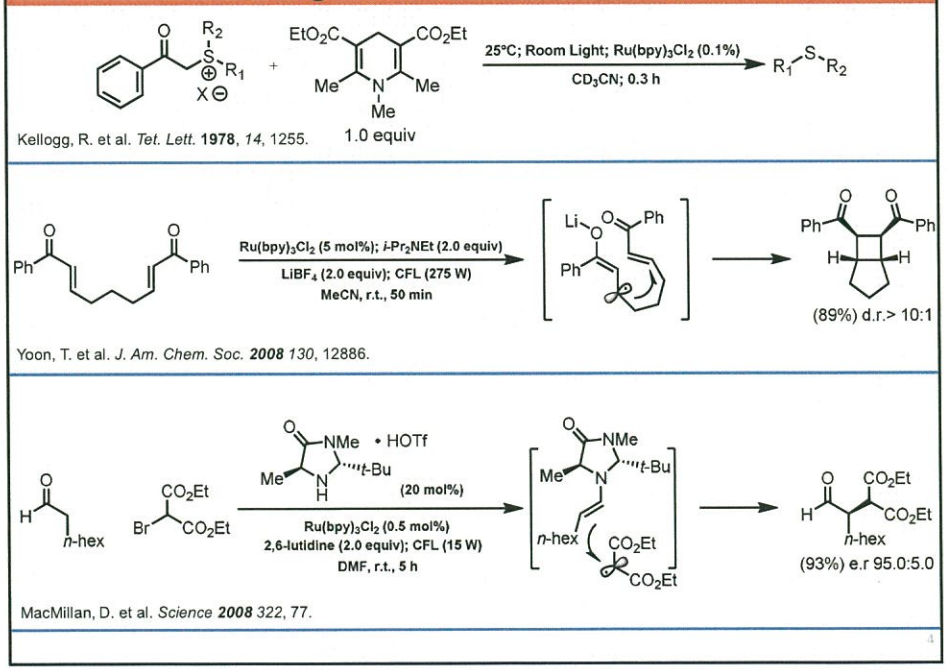
## Origins and Renaissance

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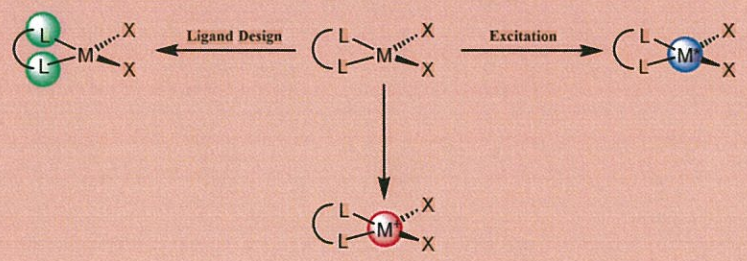
## Metallophotoredox

"We consider systems only with distinct photoredox and transition-metal catalysts; photoexcitable catalysts performing multiple types of activation are not covered. Also, the broader paradigm in which a photocatalyst and a transition-metal catalyst act in concert to enable a chemical reaction is termed 'metallophotocatalysis.' Metallophotoredox catalysis is the subset of these transformations wherein the photocatalyst performs SET. Reactions in which the photocatalyst performs other roles, such as energy transfer, are not covered."

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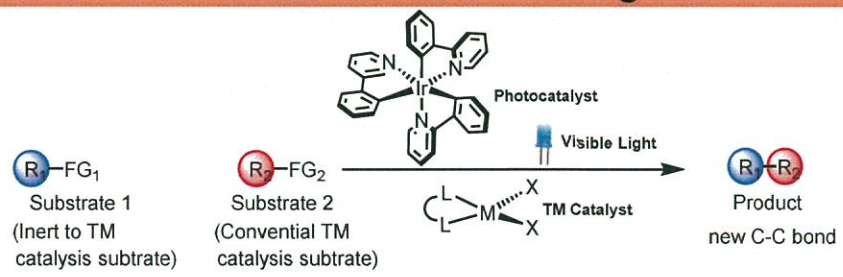
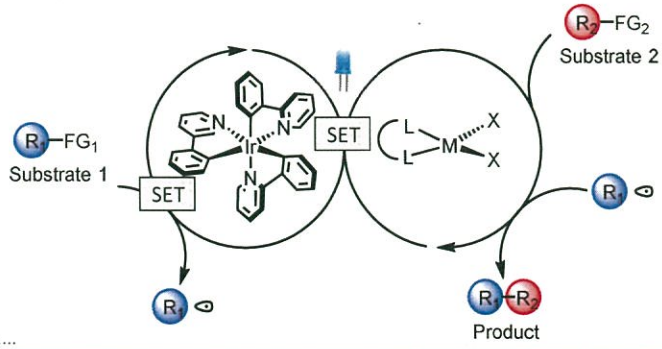
## General Mechanistic Paradigm

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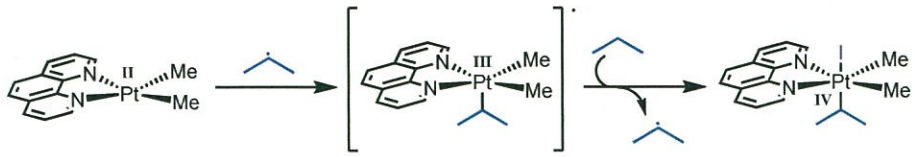
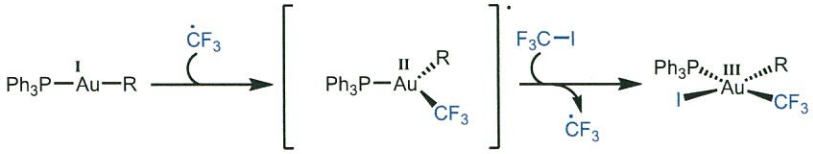
## Stoichiometric Precedent



Puddephatt, R. et al. *J. Am. Chem. Soc.* **1985** *107*, 1218.



Puddephatt, R. et al. *J. Chem. Soc., Dalton Trans.* **1976** 1360.

Toste, D. et al. *J. Am. Chem. Soc.* **2014** *136*, 7777.

Reproduced from Toste, D. et al. *ACS Cent. Sci.* **2016** *2*, 293.

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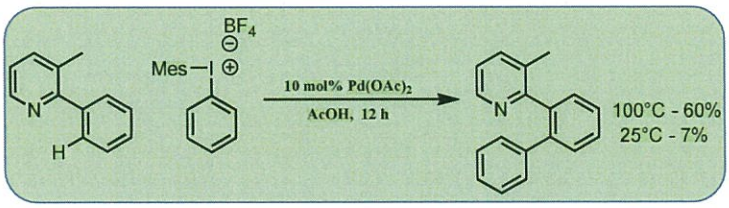
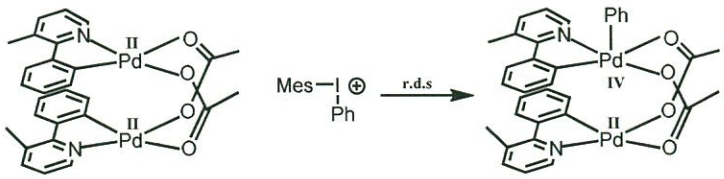
## Sanford Contributions




"This result led us to hypothesize that the rate of the reaction could be accelerated by substituting diaryliodonium salts with more kinetically reactive arylating reagents.

Sanford, M. et al. *J. Am. Chem. Soc.* **2009** *131*, 11234.

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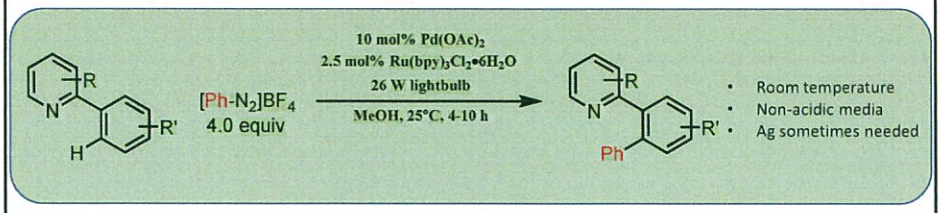
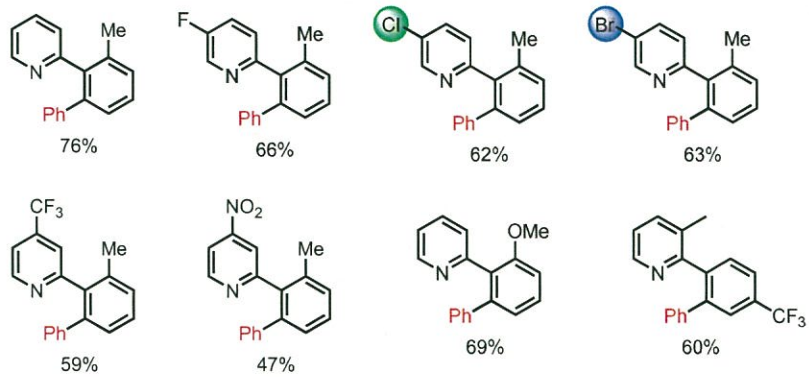
## Sanford Contributions




Sanford, M. et al. *J. Am. Chem. Soc.* **2011** *133*, 18566.

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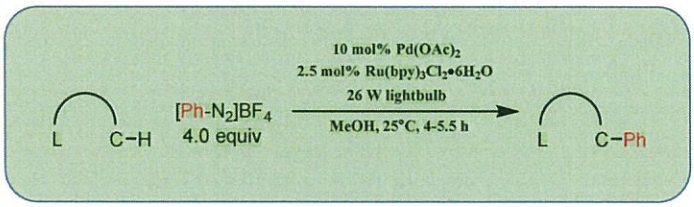
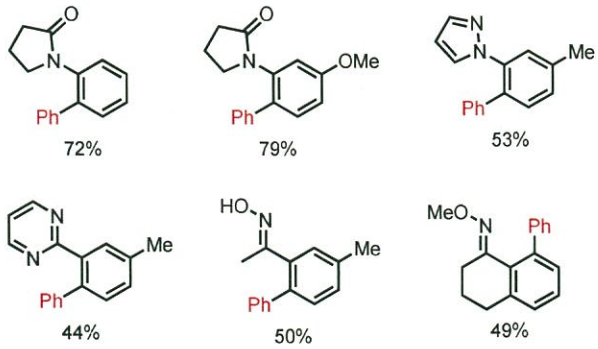
## Sanford Contributions




Sanford, M. et al. *J. Am. Chem. Soc.* **2011** *133*, 18566.

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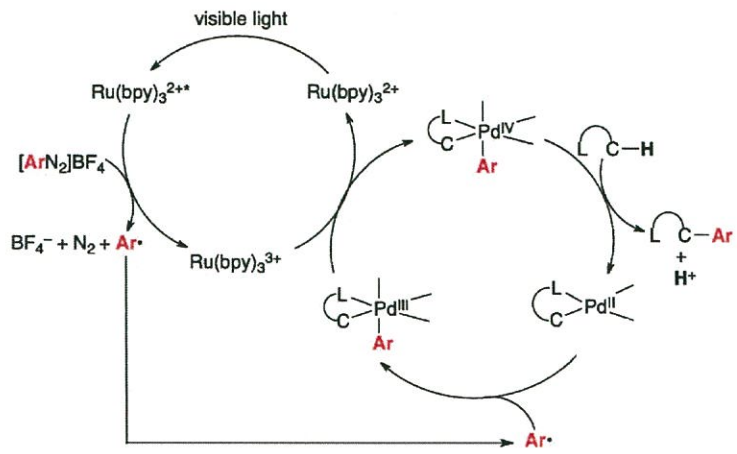
## Sanford Contributions




Sanford, M. et al. *J. Am. Chem. Soc.* **2011** *133*, 18566.

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## Single Electron Transmetalation-$BF_3K$ Salts

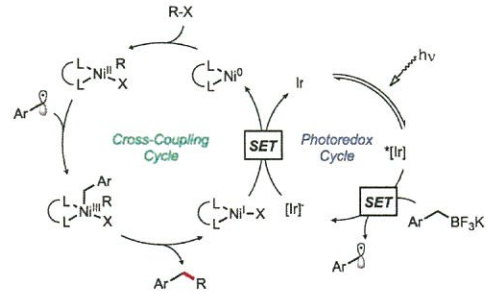
**Traditional Cross-Coupling**

- Two electron transmetalation
- TM generally rate-limiting
- Stoichiometric base
- Transmetalation rates: $C_{sp}>C_{sp2}>C_{sp3}$

**Photoredox Cross-Coupling**

- Single electron transmetalation
- Low activation energy
- Requires no base or heat
- Transmetalation rates: $C_{sp}<C_{sp2}<C_{sp3}$

*Photoredox Cross-Coupling: Single-Electron Transmetalation*




Molander, G. et al. *Science* **2014** *345*, 433.

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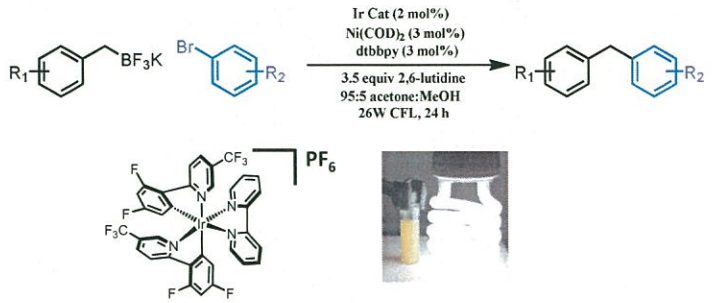
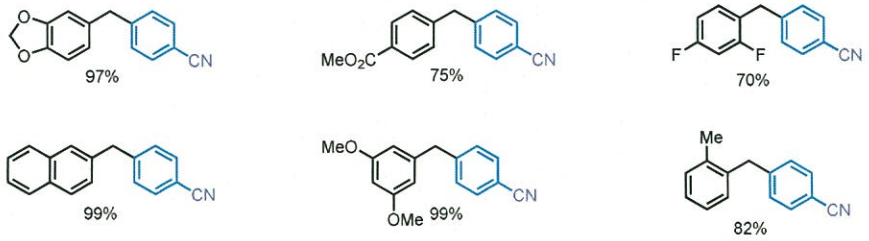
## Single Electron Transmetalation-$BF_3K$ Salts




Molander, G. et al. *Science* **2014** *345*, 433.

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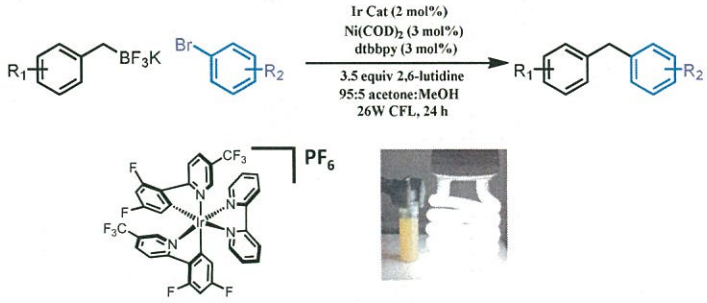
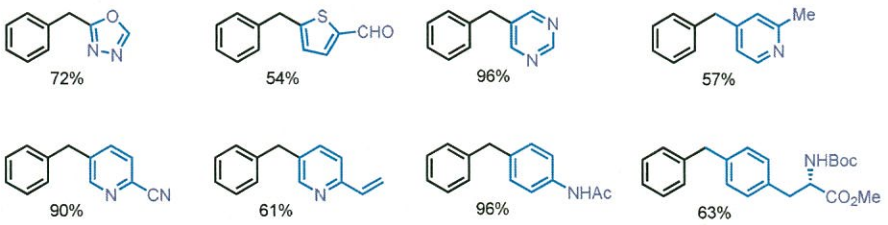
## Single Electron Transmetalation-$BF_3K$ Salts




Molander, G. et al. *Science* **2014** *345*, 433.

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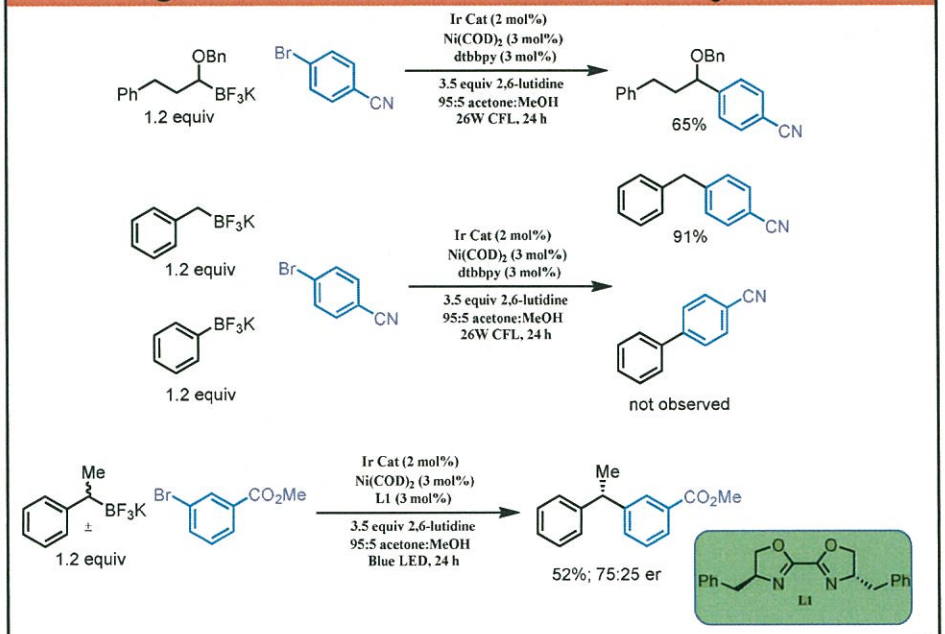
## Single Electron Transmetalation-$BF_3K$ Salts




Molander, G. et al. *Science* **2014** *345*, 433.

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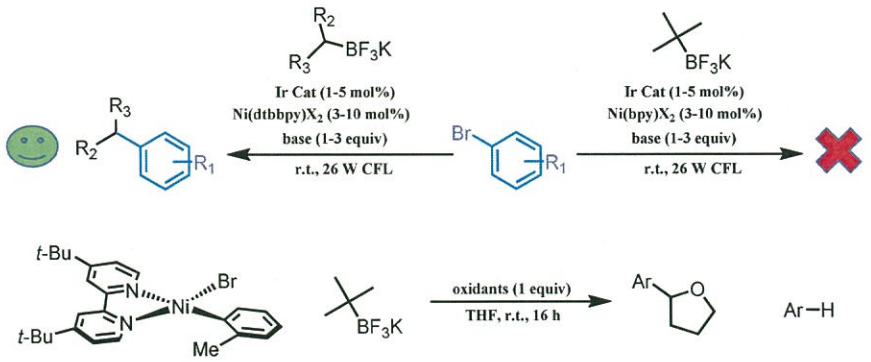
## Tertiary Boron Nucleophiles




| Oxidant | THF Adduct | Dehalogenation |
|---|---|---|
| Ir cat (10%) uv light | 10% | 3% |
| $AgNO_3$ (dark) | 0% | 15% |
| DMP (dark) | 15% | 4% |
| CAN (dark) | 17% | 6% |

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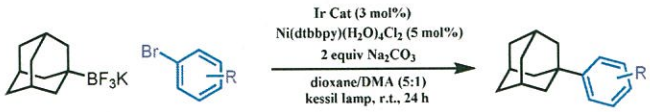
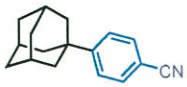
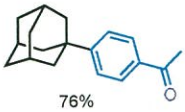
## Tertiary Boron Nucleophiles

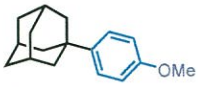


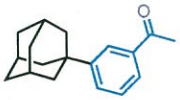

64%




76%




20% (aryl iodide)

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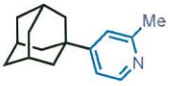
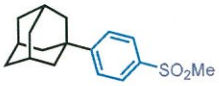



51%




91%

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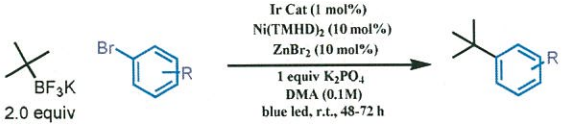
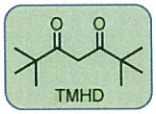
## Tertiary Boron Nucleophiles

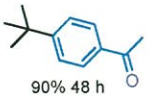


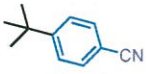

**Ligands Screened**

Phosphines, pyridines, terpyridines, amino alcohols, NHC's, olefins, 1,3-diketones

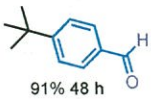
"Although these additives ($ZnBr_2$) were deemed non-essential, rate studies show that they reduce the initial induction period observed for the coupling, particularly at larger reaction scales."



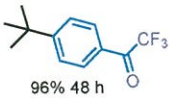

90% 48 h



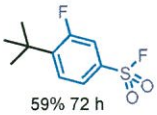

83% 24 h



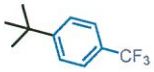

91% 48 h



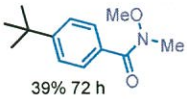

96% 48 h



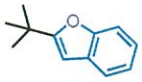

59% 72 h



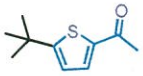

95% 48 h



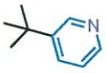

39% 72 h




53% 24 h




66% 48 h




< 5% 72h

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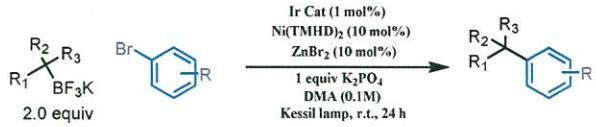
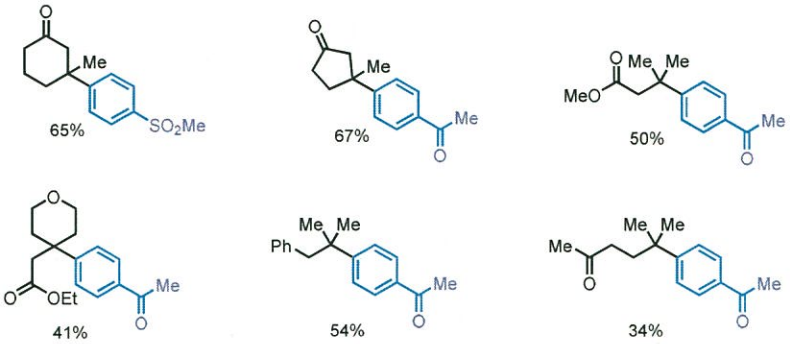
## Tertiary Boron Nucleophiles

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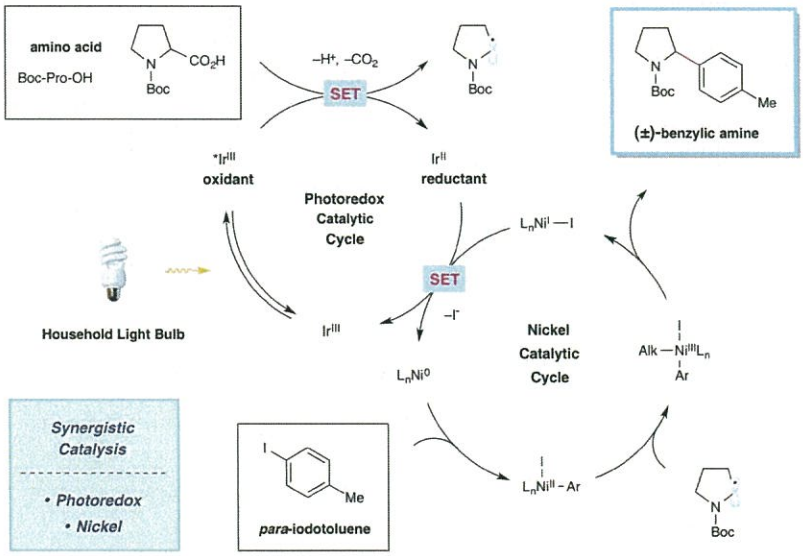
## Amino Acids




MacMillan, D., Doyle, A. et al. *Science* **2014** *345*, 437.

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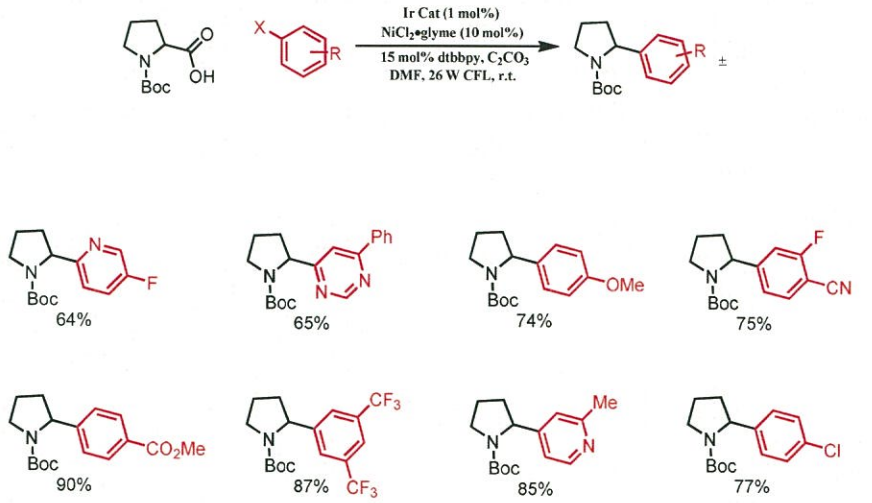
## Amino Acids




MacMillan, D., Doyle, A. et al. *Science* **2014** *345*, 437.

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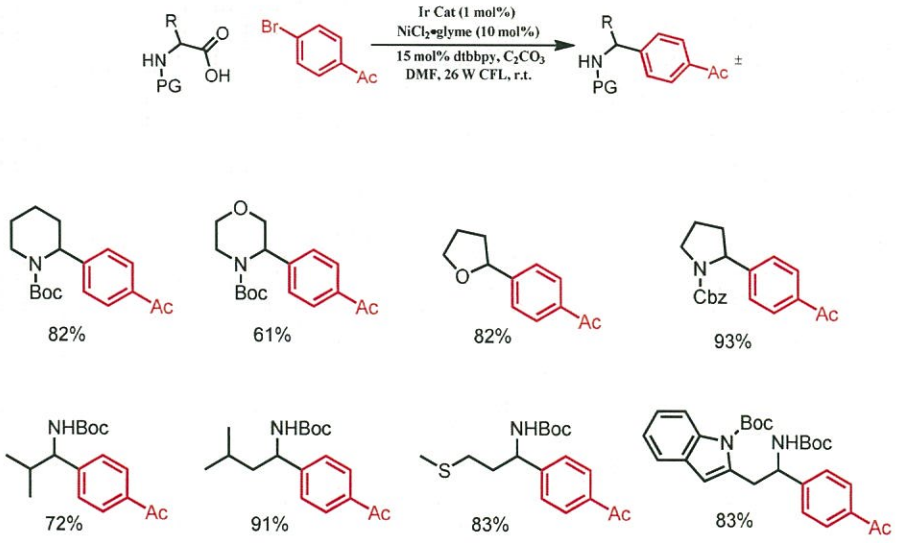
## Amino Acids




MacMillan, D., Doyle, A. et al. *Science* **2014** *345*, 437.

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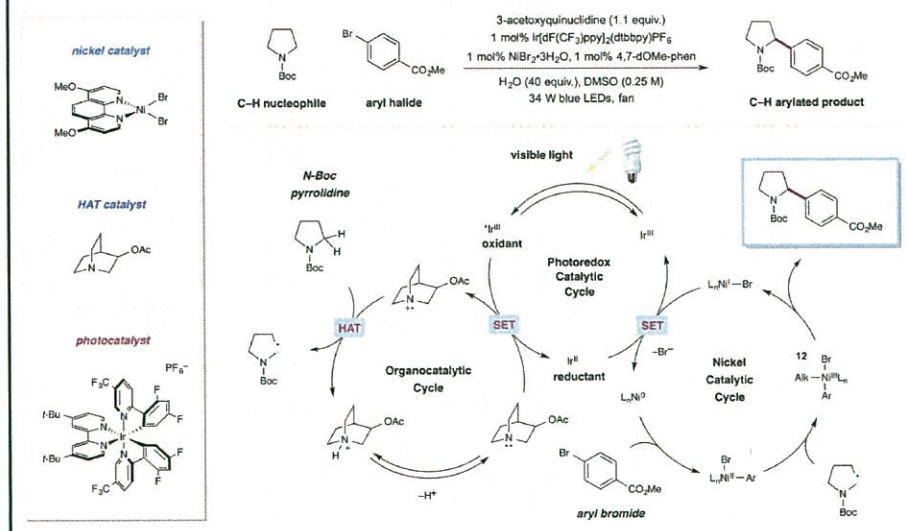
## Triple Catalysis-HAT




MacMillan, D., Doyle, A. et al. *Science* **2016** *352*, 1304.

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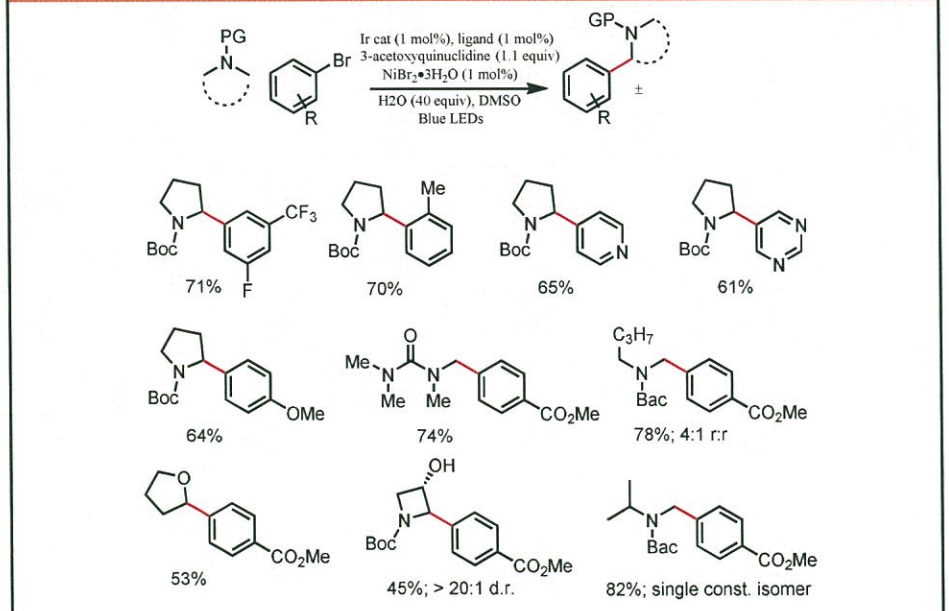
## Triple Catalysis-HAT




MacMillan, D., Doyle, A. et al. *Science* **2016** *352*, 1304.

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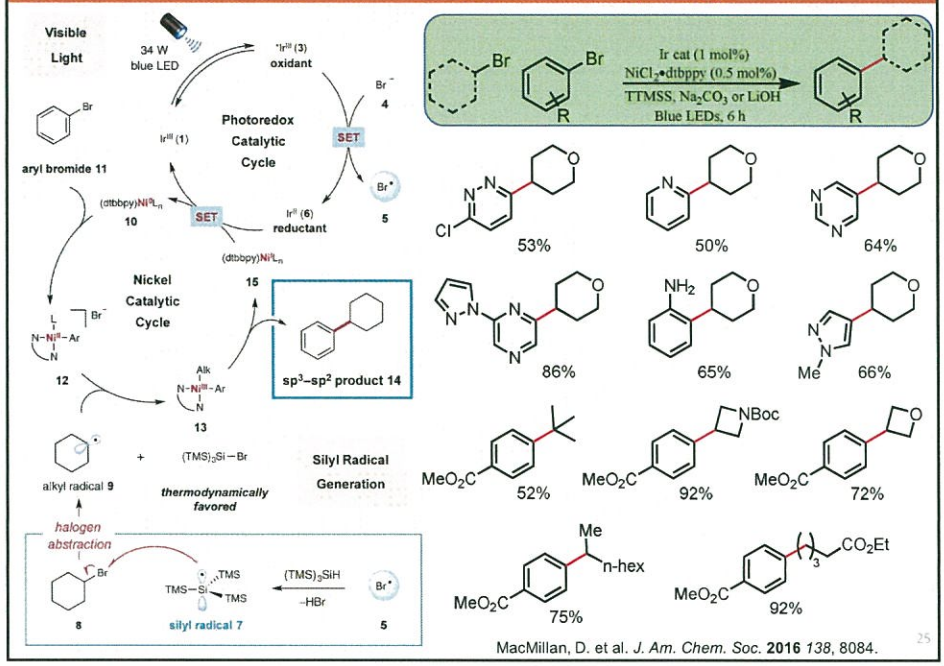
## Cross-Electrophile Coupling




MacMillan, D. et al. *J. Am. Chem. Soc.* **2016** *138*, 8084.

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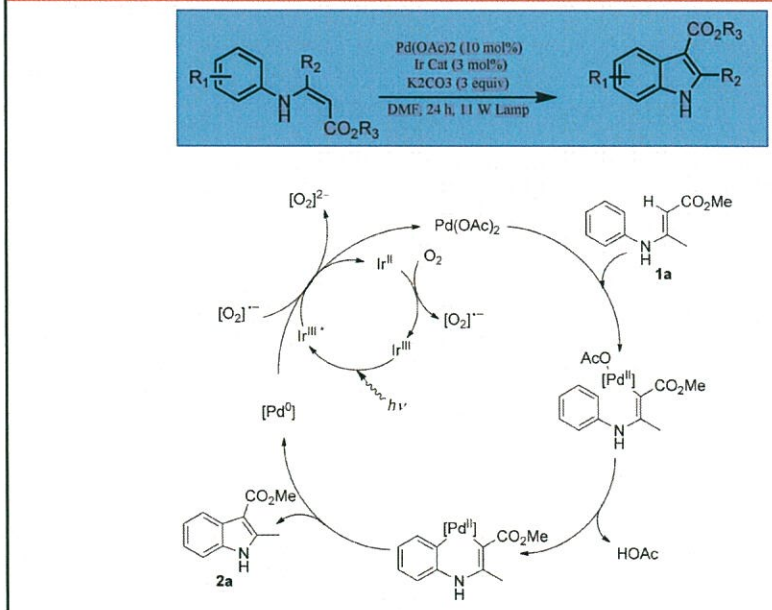
## C-H Activation (Indoles)




Sanford, M. et al. *J. Am. Chem. Soc.* **2012**, *134*, 9034.

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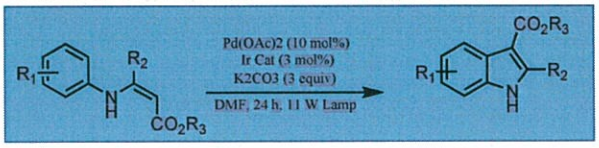
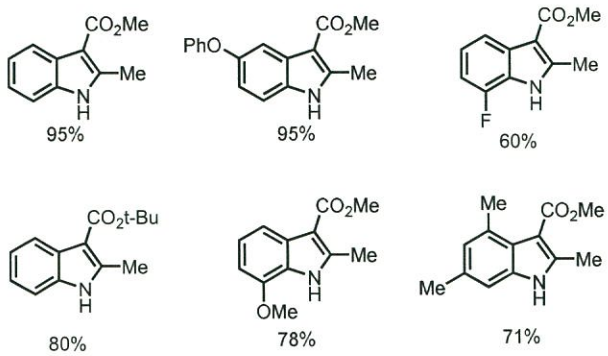
## C-H Activation (Indoles)




Sanford, M. et al. *J. Am. Chem. Soc.* **2012**, *134*, 9034.

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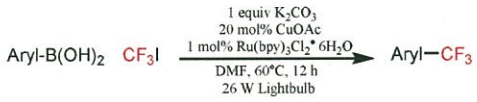
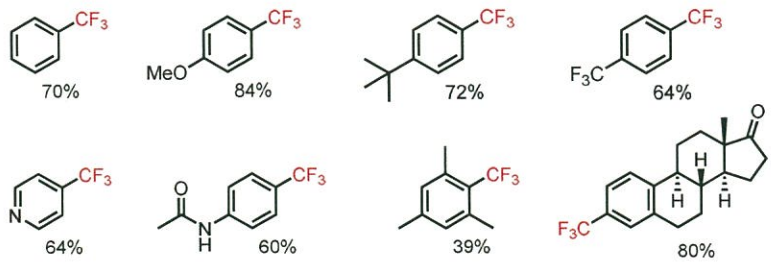
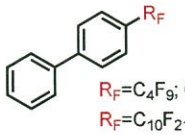
## Copper Catalyzed Trifluormethylation




- Milder than many existing protocols
- Pefluorination possible (Togni's analogues not commercial)



$R_F$=$C_4F_9$; 67%
$R_F$=$C_{10}F_{21}$; 71%
* 50 - 100 mol% Cu

Sanford, M. et al. *J. Am. Chem. Soc.* **2012**, *134*, 9034.

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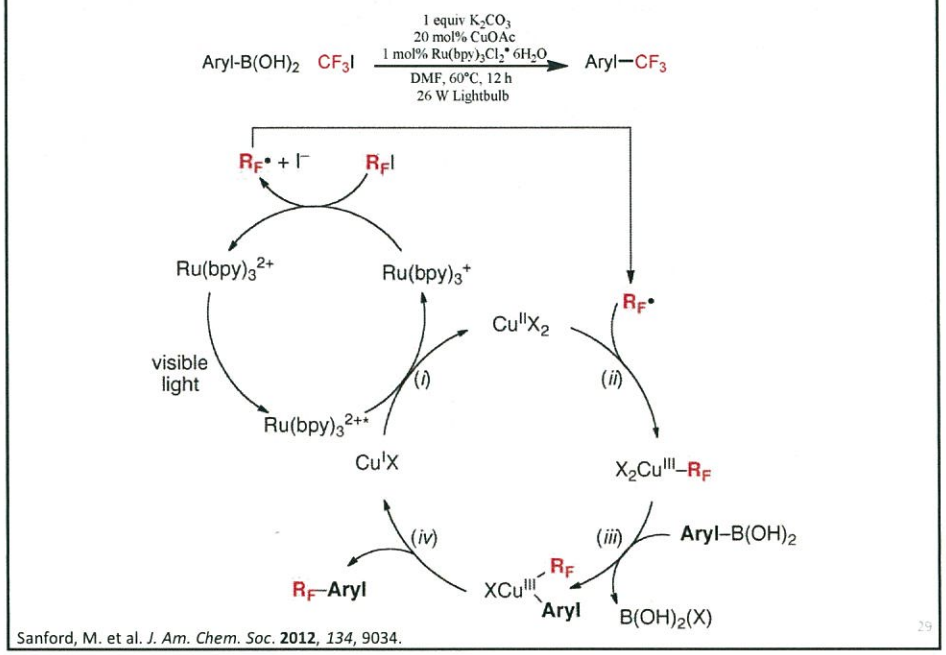
## Copper Catalyzed Trifluormethylation




Sanford, M. et al. *J. Am. Chem. Soc.* **2012**, *134*, 9034.

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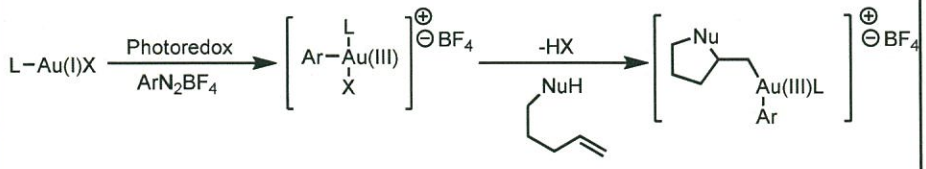
## Gold-Catalyzed Arylative Ring Expansion

"We envisioned that these reactions might proceed through a pathway in which photoredox catalysis occurs first, providing an entry into a cationic arylgold(III) intermediate that subsequently reacts with the alkene to induce intramolecular heteroarylation.




Toste, D. et al. *J. Am. Chem. Soc.* **2012**, *134*, 9034.

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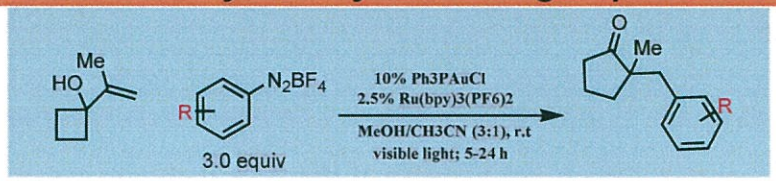
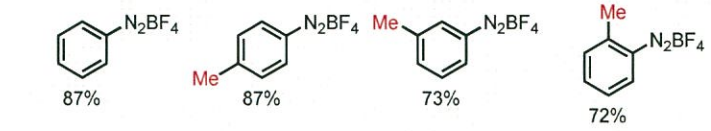
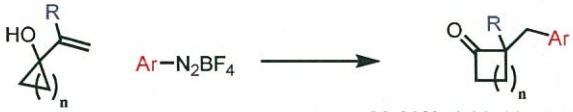
## Gold-Catalyzed Arylative Ring Expansion




32-90% yield; 11 examples

Toste, D. et al. *J. Am. Chem. Soc.* **2014**, *136*, 5844.

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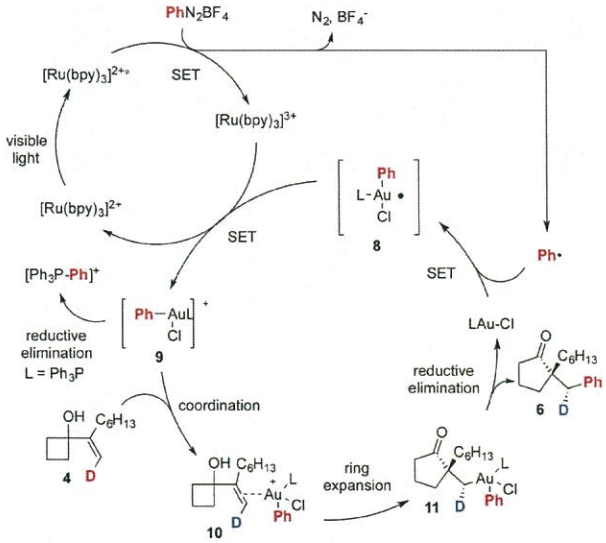
## Gold-Catalyzed Arylative Ring Expansion




Toste, D. et al. *J. Am. Chem. Soc.* **2014**, *136*, 5844.

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## Future Directions

- Novel organometallic reactivity to be discovered.
- Asymmetric Hurdles:
  "Currently, no catalyst systems control the relative configuration of the new carbon-carbon bond when other stereocenters are present in either coupling partner."

- Scale-up Hurdles: Photon penetration of reaction medium.

**Process-scale photoredox flow reactor at Merck**

*J. Org. Chem.* **2016**, *81*, 6898.

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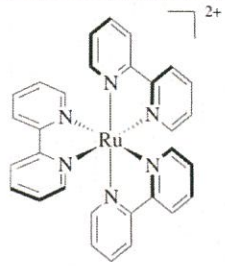
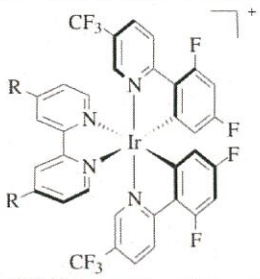
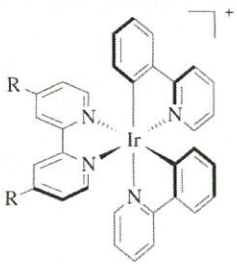


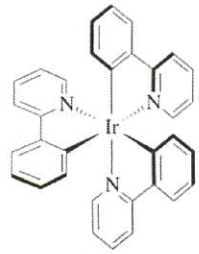
**$Ru(bpy)_3^{2+}$**
*Ref 24*



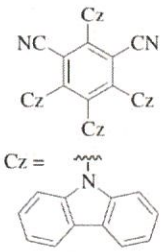
**$Ir[dF(CF_3)ppy]_2(bpy)^+$** (R = H)
*Refs 25 and 26*
**$Ir[dF(CF_3)ppy]_2(dtbbpy)^+$** (R = *t*-Bu)
*Ref 27*



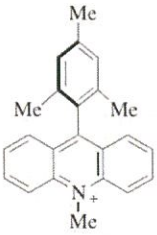
**$Ir(ppy)_2(bpy)^+$** (R = H)
*Ref 28*
**$Ir(ppy)_2(dtbbpy)^+$** (R = *t*-Bu)
*Refs 27 and 28*



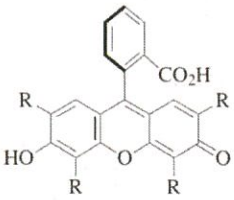
**$Ir(ppy)_3$**



**4CzIPN**



**$MesAcr^+$**



**fluorescein** R = H
**eosin Y**, R = Br

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## Stereoconvergence

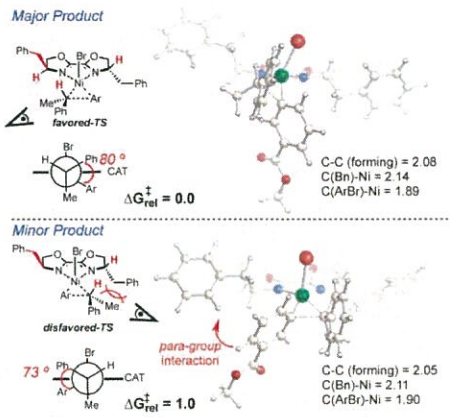


**Figure 3.** Competing diastereomeric transition states in the reductive elimination. Relative free energies (kcal/mol) are computed using SMD-water-(U)M06/6-311+G(d,p)//UB3LYP/6-31G(d).

However, if homolytic equilibration of the Ni(III)/Ni(II) pair is faster than reductive elimination, as these calculations indicate, then the origin of stereoselectivity should be found in the reductive elimination step.7a Thus, we propose that enantioselectivity arises from a process best described as a dynamic kinetic resolution (DKR)13 of Ni(III) complex C′. 14 In other words, addition of the secondary radical to the Ni center operates under Curtin-Hammett conditions15 furnishing two equilibrating diastereomeric Ni(III) complexes, one of which reductively eliminates at a faster rate, leading to the major enantiomer. Stereoconvergence then results via stereochemical scrambling of the secondary alkyl subunit through dissociation and recombination.

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