

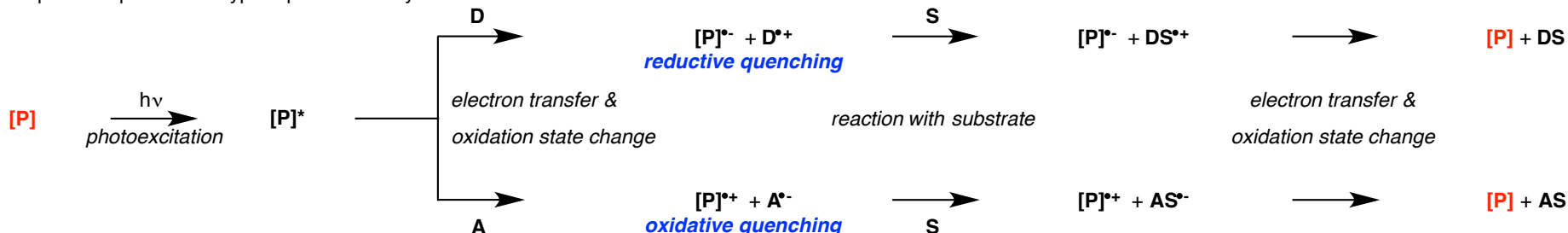
Photoredox catalysis is photoinduced electron transfer (PET) catalysis.

Photoinduced electron transfer is an excited state electron transfer process by which an excited electron is transferred from a donor to an acceptor. Since an excited state molecule has an electron in an antibonding orbital as well as a vacancy in its highest energy bonding orbital, the resultant excited state molecule is both a better oxidant and a stronger reductant than the ground state molecule. Consequently, intermolecular electron transfer is more facile. Photoredox catalysis leverages the intermediate radical species to promote novel chemical reactivity.

"Visible light photoredox catalysis"... "relies on the ability of metal complexes and organic dyes to engage in **single-electron transfer (SET)** processes with organic substrates upon **photoexcitation** with light." - MacMillan and coworkers, 2013

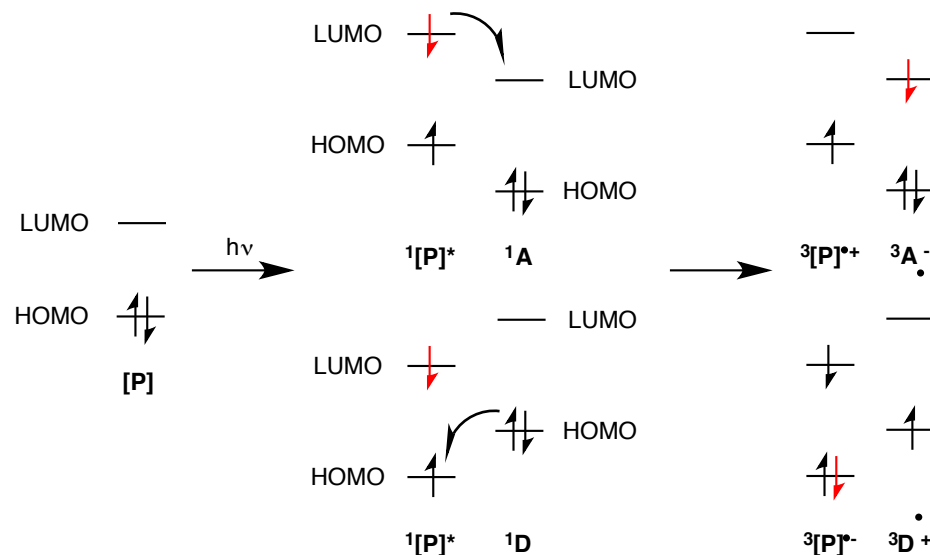
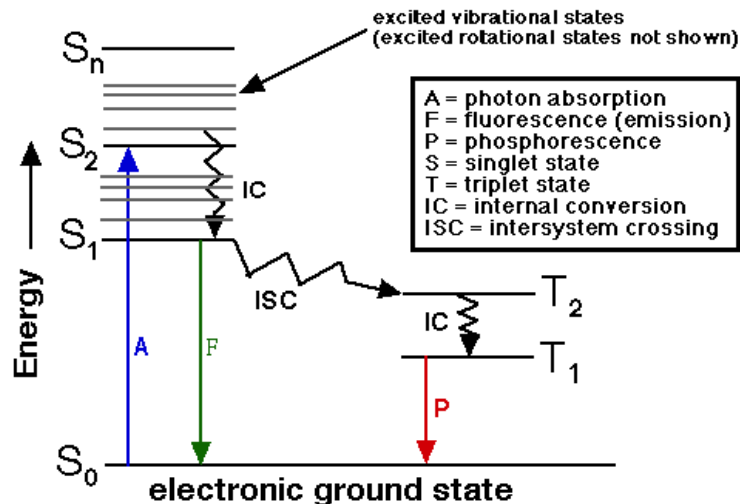
This discussion is restricted to selected transition metal mediated reactions with applications to organic synthesis post 2006, with emphasis placed on the most recent work. See http://www.scripps.edu/baran/images/grpmtgpdf/Yan_2014.pdf for Ming Yan's discussion of PET prior to 2006.

Graphical depiction of a typical photoredox cycle:



Photoredox catalysts promote SET processes via *intermolecular quenching* pathways. Consider this in the context of all possible electronic transitions:*

Graphical depiction of intermolecular quenching by PET:



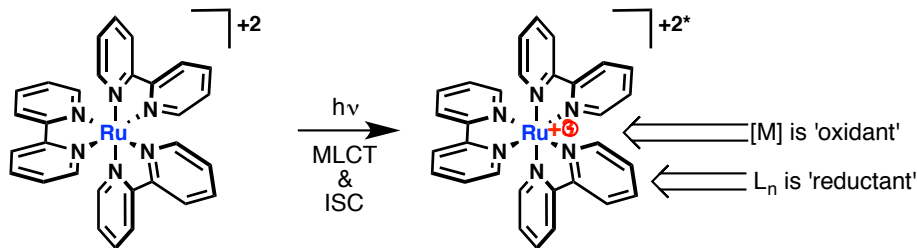
Key Reviews: Prier, C. K.; Rankic, D. A.; MacMillan, D.W.M. *Chem. Rev.* **2013**, *113*, 5322.; Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.

*Jablonski diagram taken from http://www.shsu.edu/chm_tgc/chemilumdir/JABLONSKI.html

Anslryn, E.V.; Dougherty, D.A. *Modern Physical Organic Chemistry*, University Science Books, **2006**.

Photoelectronic properties of transition metal photoredox catalysts.

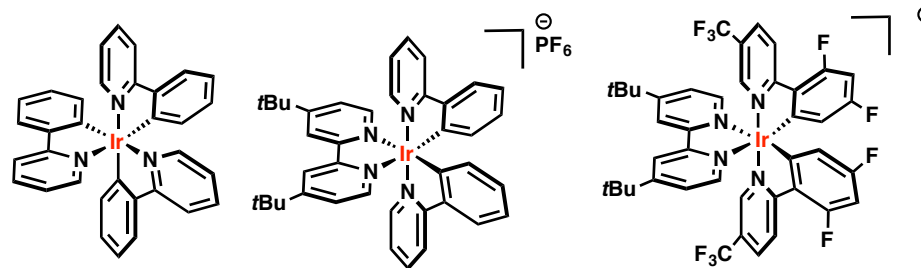
ex) The case of [Ru(bpy)₃]²⁺:



$[Ru(bpy)_3]^{2+}$
 $E(Ru^{III}/Ru^{II}) = -0.81\text{ V}$
 $E(Ru^{II}/Ru^I) = +0.77\text{ V}$
 $\tau = 1.1\ \mu\text{s}$
 $\lambda_{\text{abs}} = 452\text{ nm}$
 $\lambda_{\text{em}} = 615\text{ nm}$
 $\Phi_{\text{em}} = 0.095$

$[Ru(bpy)_3]^{2+*}$
 = reduction potential (vs. SCE)
 = oxidation potential (vs. SCE)
 = lifetime of triplet excited state
 = wavelength of max. absorption
 = wavelength of max. emission
 = quantum yield of emission

Some other common transition metal photoredox catalysts:

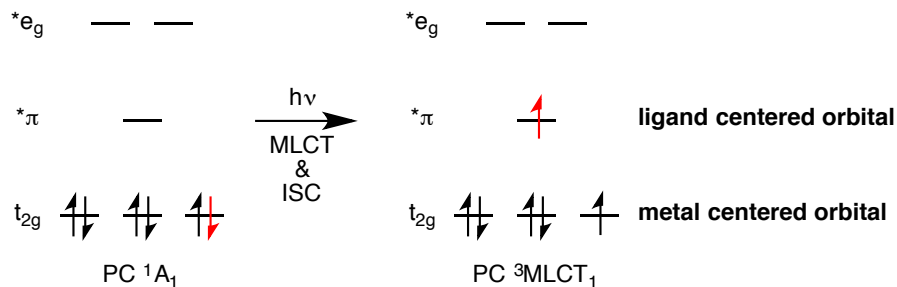


$Ir(III)(ppy)_3$
 $E(Ir^{IV}/Ir^{III}) = -1.73\text{ V}$
 $E(Ir^{III}/Ir^I) = +0.31\text{ V}$
 $\tau = 1.9\ \mu\text{s}$
 $\lambda_{\text{abs}} = 375\text{ nm}$
 $\lambda_{\text{em}} = 518\text{ nm}$
 $\Phi_{\text{em}} = 0.38$

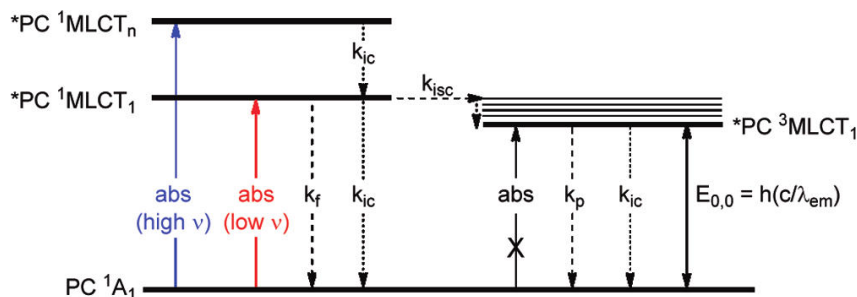
$[Ir(III)(ppy)_2(dtbbpy)]^+ PF_6^-$
 $E(Ir^{IV}/Ir^{III}) = -0.96\text{ V}$
 $E(Ir^{III}/Ir^I) = +0.66\text{ V}$
 $\tau = 0.56\ \mu\text{s}$
 $\lambda_{\text{abs}} = 410\text{ nm}$
 $\lambda_{\text{em}} = 581\text{ nm}$
 $\Phi_{\text{em}} = 0.094$

$Ir(III)[dF(CF_3)ppy]_2(dtbbpy)^+$
 $E(Ir^{IV}/Ir^{III}) = -0.89\text{ V}$
 $E(Ir^{III}/Ir^I) = +1.21\text{ V}$
 $\tau = 2.3\ \mu\text{s}$
 $\lambda_{\text{abs}} = 380\text{ nm}$
 $\lambda_{\text{em}} = 470\text{ nm}$
 $\Phi_{\text{em}} = 0.68$

Simplified molecular orbital diagram for [Ru(bpy)₃]⁺². L₆[Ru]⁺² is octahedral, d⁶, max CFSE ∴ substitutionally inert



Corresponding Jablonski Diagram



Some general trends should be noted:

- [Ir]⁺³ is a better oxidant than [Ru]⁺² (higher OS to be d⁶ ∴ more electron poor) cf. [Ru(bpy)₃]²⁺ with [Ir(bpy)₃]³⁺ ($E(M^+/M^*) = -0.88\text{ V}$ and $E(M^*/M^+) = +1.18\text{ V}$)
- [Ir]⁺³ has a larger LFSE and HOMO/LUMO gap than [Ru]⁺² and therefore requires more photonic input (needs higher energy light for excitation. This leads to a larger difference between reduction and oxidation potentials)
- As electron density of the metal center increases, the oxidative power of the complex decreases.
- As electron density of the ligand increases, the reductive power of the complex increases
- [Ir]⁺³ can support a heteroleptic ligand set, while [Ru]⁺² is better with homoleptic ligand sets. Two reasons for this include the greater charge of [Ir]⁺³, allowing it to better stabilize anionic ligands, and improved spin-orbit coupling in larger elements, which improves MLCT efficiency. Since symmetric ligands make MLCT less efficient because of lower orbital degeneracy, use of metals with better spin-orbit coupling can compensate for decreased MLCT efficiency resulting from use of heteroleptic ligand sets.

[Ir]⁺³ complexes therefore are generally more powerful and versatile than [Ru]⁺² complexes.

MOT is very useful for predicting the relative behaviour of different complexes.

Kinetic Parameters of electron transfer.

A favorable potential difference is a thermodynamic factor. Favorable kinetics are also requisite to successfully close a photoredox catalytic cycle. For the cases of substitutionally inert d⁶ octahedral [Ru]²⁺ and [Ir]³⁺, two outer sphere electron transfer processes must occur to close a catalytic cycle:

- 1) an electron transfer to quench the excited state
- 2) a subsequent electron transfer to regenerate the ground-state catalyst

Marcus theory relates relevant thermodynamic factors to the rate of these ET processes:

$$k_{et} = 4\pi^2/h |H_{A,B}|^2 (4\pi\lambda k_b T)^{-1/2} e^{-(\lambda + \Delta G^\circ)^2 / (4\lambda k_b T)}$$

where h = Plank's constant

$|H_{A,B}|$ represents the electronic coupling of the reaction partners
 λ = the reorganization energy. This represents the energy required for the reorganization of the precursor complex to the same configuration of the successor complex without the corresponding transfer of an electron.

k_b = Boltzmann's constant

T = absolute temperature

ΔG° = Gibb's free energy

Basically, this equation says that the rate of electron transfer between A and B depends on how well A and B are electronically coupled, how easily A and B can reorganize their structures (including the solvent cage) following ET, the absolute temperature, and the degree of exergonicity of the reaction.

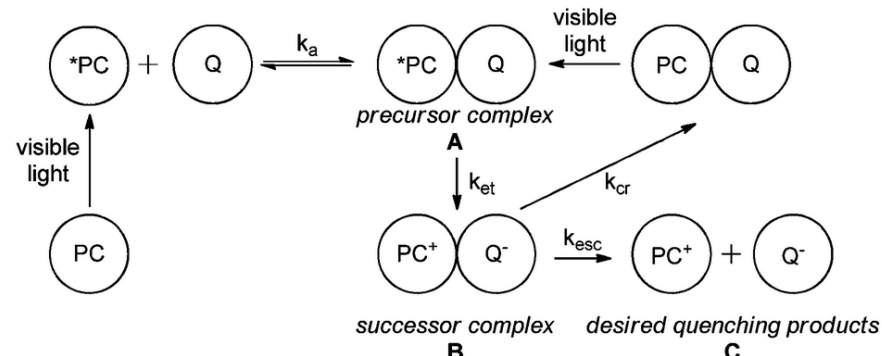
k_{et} increases when A and B...are better coupled electronically

- ...require less structural reorganization leading up to and following ET
- ...as T decreases
- ...as ΔG° increases (exergonicity increases), until the Marcus inverted region

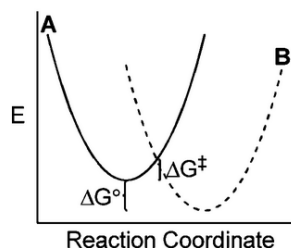
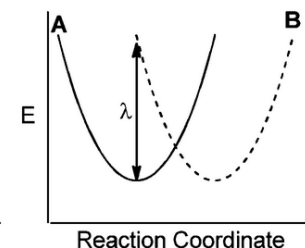
The size k_{et} relative to the other rate constants k_a , k_{cr} , k_{esc} , etc. is also crucial to have a sufficient amount of the desired quenching products for a successful reaction.

Transition metal photoredox catalysts have relatively low reorganization energies, long triplet lifetimes (improves probability of intermolecular quenching) and are fairly stable to radicals (which means cat. decomposition is slow). These factors lead to favorable k_{et} values. Quenching by ET is ~10-20% efficient with these complexes.

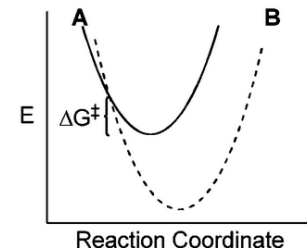
A: Example of an Electron Transfer Process: Oxidative Quenching



B: Exergonic SET

C: $\Delta G^\circ = 0$ 

D: Marcus Inversion



Selected examples of other Visible Light Photocatalysts:

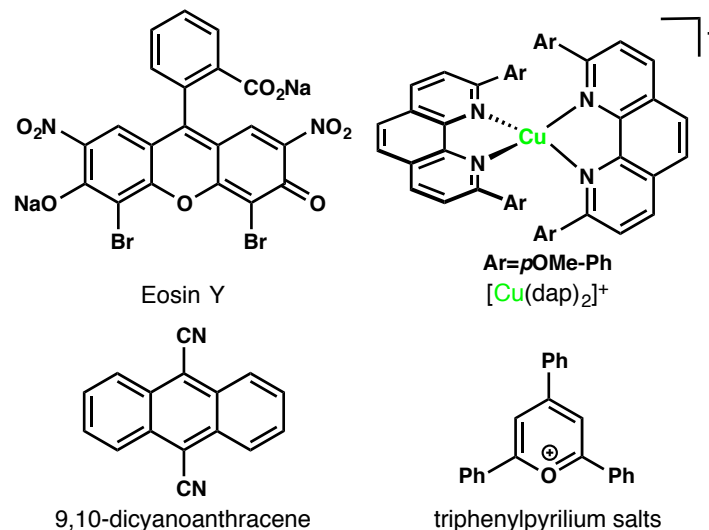


Table 1. Redox Potentials and Selected Photophysical Properties of Commonly Utilized Visible Light Photocatalysts^a

a) in Volts vs SCE; measured in MeCN at rt.
 b) determined in propylene carbonate
 c) determined in aqueous solution
 d) determined in CH₂Cl₂
 e) determined in 1:1 EtOH/MeOH glass at 77 K
 Taken from: *Chem. Rev.* **2013**, *113*, 5322.

entry	photocatalyst	$E_{1/2}$ (M ⁺ /M [*])	$E_{1/2}$ (M [*] /M ⁻)	$E_{1/2}$ (M ⁺ /M)	$E_{1/2}$ (M/M ⁻)	excited-state lifetime, τ (ns)	excitation λ_{\max} (nm)	emission λ_{\max} (nm)
1	Ru(bpm) ₃ ²⁺	-0.21	+0.99	+1.69	-0.91	131 ^b	454	639 ^b
2	Ru(bpz) ₃ ²⁺	-0.26	+1.45	+1.86	-0.80	740	443	591
3	Ru(bpy) ₃ ²⁺	-0.81	+0.77	+1.29	-1.33	1100	452	615
4	Ru(phen) ₃ ²⁺	-0.87	+0.82	+1.26	-1.36	500	422	610 ^c
5	Ir[dF(CF ₃) ppy] ₂ (dtbbpy) ⁺	-0.89	+1.21	+1.69	-1.37	2300	380	470
6	Ir(ppy) ₂ (dtbbpy) ⁺	-0.96	+0.66	+1.21	-1.51	557		581
7	Cu(dap) ₂ ⁺	-1.43		+0.62		270		670 ^d
8	fac-Ir(ppy) ₃	-1.73	+0.31	+0.77	-2.19	1900	375	494 ^e

Selected reviews, perspectives and highlights in reverse chronological order:

Recent (2010-2014) advances in asymmetric C-C bond formation: Pena-Lopez, M.; Rosas-Hernandez, A.; Beller, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 5006.

Olefin difunctionalizations via photoredox catalysts: Cau, M.-Y. *et al. Tetrahedron Lett.* **2015**, *56*, 3732.

Amine functionalization via photoredox catalysis: Beatty, J.W.; Stephenson, C.J. *Acc. Chem. Res.* **2015**, *48*, 1474.

Recent (2010-2015) advances in photoredox catalysis: Angnes, R.A. *Org. Biomol. Chem.* **2015**, *13*, 9152

C-H functionalization via photoredox catalysis: Xie, J. *et al. Tetrahedron Lett.* **2014**, *55*, 36.

Radical additions into iminium ions and cationic heterocycles: Tauber, J. *et al. Molecules* **2014**, *19*, 16190.

Recent (2010-2013) advances in organic dye mediated photoredox catalysis: Nicewicz, D.A.; Nguyen, T.M. *ACS Catal.* **2014**, *4*, 355.

[Ru] and [Ir] photoredox catalysis: Koike, T.; Akita, M. *Inorg. Chem. Front.* **2014**, *1*, 562.

Trifluoromethylation by photoredox catalysis: Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967.

Oxidative photoredox activation of aliphatic nucleophiles for C(sp³)-C(sp²) cross coupling reactions (Pd, Ni, Au): Jahn, E.; Jahn, U. *Angew. Chem., Int. Ed.* **2014**, *53*, 13326.

Dual catalysis: Photoredox plus organo-, acid, and T.M.(Pd, Ni, Cu, Au, Rh) catalysis: Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874.

Synthesis of α -alkyl substituted aldehydes (incl. photoredox): Hodgson, D. M.; Charlton, A. *Tetrahedron* **2014**, *70*, 2207.

Eosin Y in photoredox catalysis: Hari, D. P.; Koenig, B. *Chem. Commun.* **2014**, *50*, 6688.

Photoredox catalysis in flow: Garlets, Z. J.; Nguyen, J. D.; Stephenson, C. R. *J. Isr. J. Chem.* **2014**, *54*, 351.

Organic dyes as photoredox catalysts: Fukuzumi, S.; Ohkubo, K. *Org. Biomol. Chem.* **2014**, *12*, 6059.

Photocatalyst selection for desired reactivity: Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Stephenson, C. R. *J. Aldrichimica Acta* **2014**, *47*, 15.

Photoredox catalysis in carbocyclic and heterocyclic ring construction: Xuan, J.; Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Eur. J. Org. Chem.* **2013**, *2013*, 6755.

Synthetic applications of photoredox catalysis (5): Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387; Reckenthaeler, M.; Griesbeck, A. G. *Adv. Synth. Catal.* **2013**, *355*, 2727.; Koike, T.; Akita, M. *Synlett* **2013**, *24*, 2492.; Narayanam, J. M. R.; Stephenson, C. R. *J. Chem. Soc. Rev.* **2011**, *40*, 102.; Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785.

Synthetic applications of transition metal photoredox catalysis: Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

Photoredox generated amine radical cation chemistry: Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem.* **2013**, *9*, 1977.

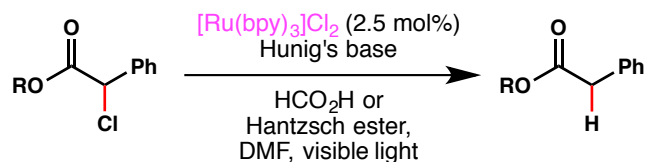
Theory and applications of photoredox catalysis: Tucker, J. W.; Stephenson, C. R. *J. J. Org. Chem.* **2012**, *77*, 1617.

α -amino C-H functionalization via photoredox catalysis: Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687.

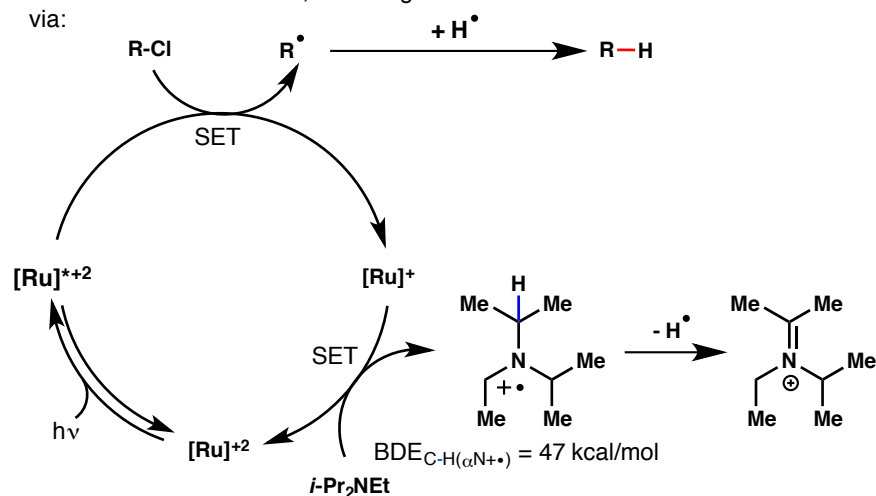
Historical roots of photoredox chemistry and chemistry of [Ru(bpy)₃]²⁺: Tepy, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859.

Asymmetric alkylation of aldehydes using photoredox catalysis: Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360.; Renaud, P.; Leong, P. *Science (Washington, DC, U. S.)* **2008**, *322*, 55.

Reductive Dehalogenations

Benzylic and α -halo carbonyls

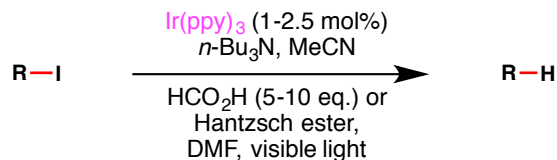
via:



- good for chlorides and bromides
- benzylic, α -carbonyl halides > aryl, vinyl halides

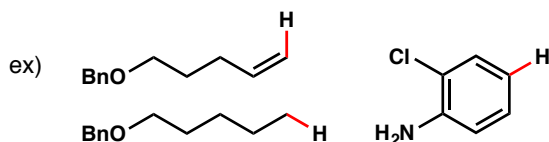
Stephenson, C.R.J. & co. *J. Am. Chem. Soc.* **2009**, *131*, 8756.

Alkyl, Alkenyl and Aryl Iodides



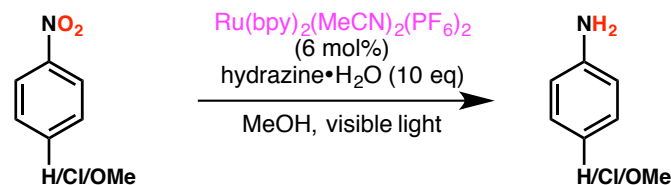
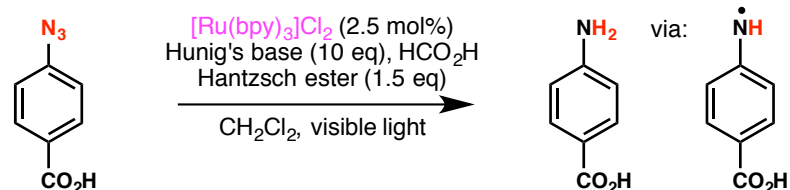
R = alkyl, alkenyl, aryl

selective for Ar-I over Ar-Br/Cl

Stephenson, C.R.J. co. *Nature Chem.* **2012**, *4*, 854.Prier, C. K.; Rankic, D. A.; MacMillan, D.W.M. *Chem. Rev.* **2013**, *113*, 5322.

Nitrogen functional group reductions

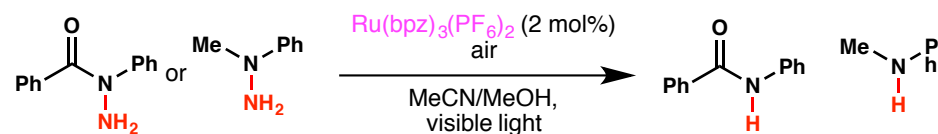
Reductions of nitro and azide functionalities

Hirao, T. *et al. Bull. Chem. Soc. Jpn.* **2004**, *77*, 1763.

- works with aryl and alkyl azides; compatible with biomolecules

Chen, Y. *et al. Nature Chem* **2011**, *3*, 146.

Reductions of hydrazide and hydrazine functionalities

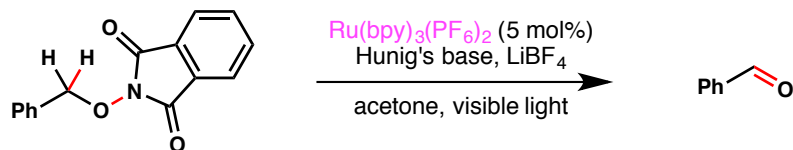


Mechanism?

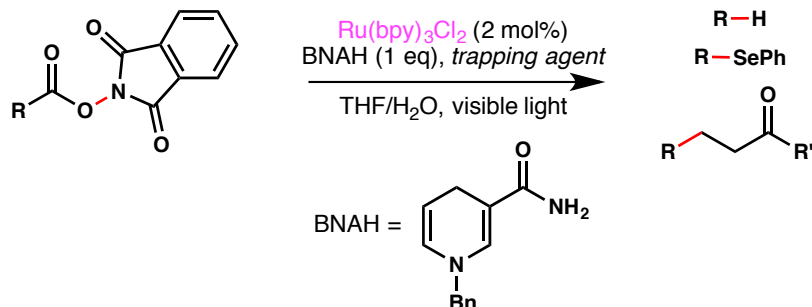
(Hint: reductive quenching, needs O₂; ONOH is a side product)Zhu, M.; Zheng, N. *Synthesis* **2011**, *14*, 2223.

Protecting group removal

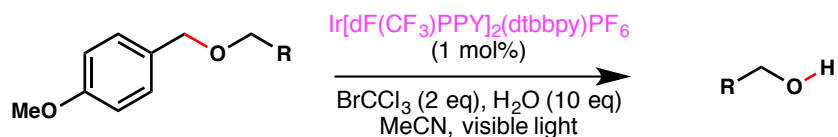
N-alkoxyphthalimides as masking groups for aldehydes

Zlotorzynska, M.; Sammis, G.M. *Org. Lett.*, **2011**, *13*, 6264.

N-(acyloxy)phthalimides as masking groups for alkyl radicals

Okada, K. *et al. J. Am. Chem. Soc.*, **1991**, *113*, 9401.

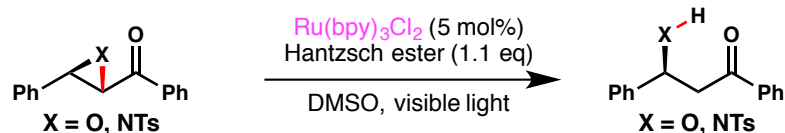
Oxidative PMB group removal



- chemoselective for PMB in the presence of olefins, Boc, Bn groups

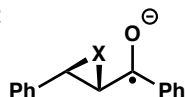
Stephenson & co. *Chem. Commun.* **2011**, *47*, 5040.

Reductive Opening of Epoxides and Aziridines

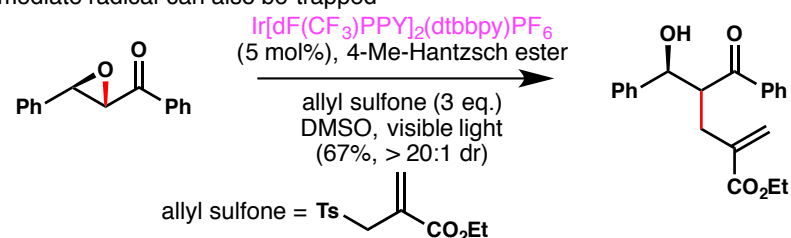


- FG needs to be adjacent to a redox-active carbonyl

via:

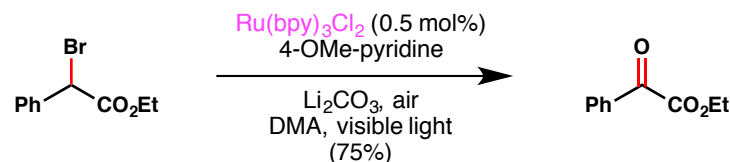


-intermediate radical can also be trapped

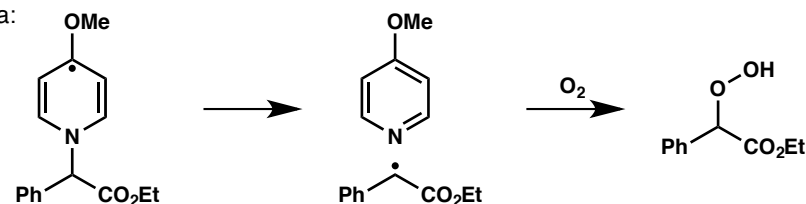
Larraufie, M.-H. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 4463.; Hasegawa, E. *et al. Tetrahedron* **2006**, *62*, 6581

Oxidations

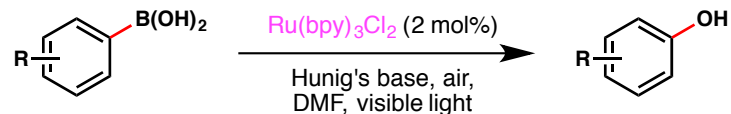
Aerobic oxidation of benzylic halides



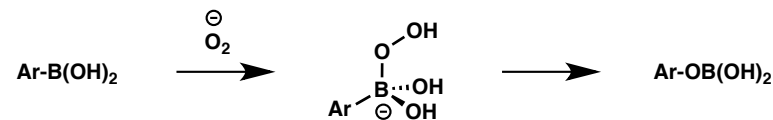
via:

Su, Y. *et al. Org. Lett.* **2011**, *13*, 2168.

Aerobic oxidative hydroxylation of aryl boronic acids

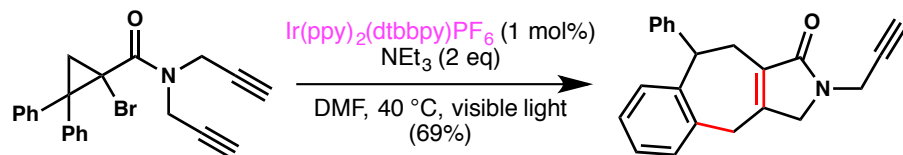
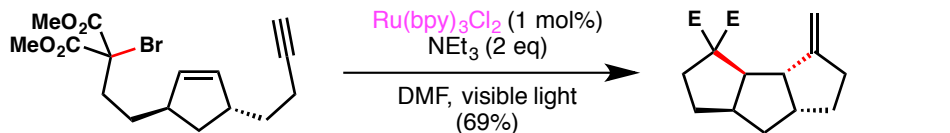


via:

Jorgensen, K.A.; Xiao, W.-J. & co. *Angew. Chem. Int. Ed.* **2012**, *51*, 784.

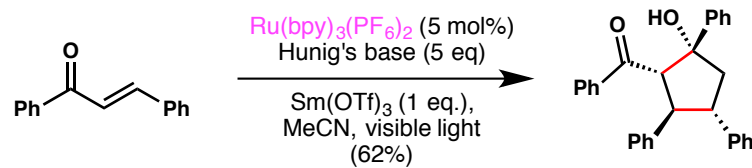
Radical cyclizations

Radical cascades

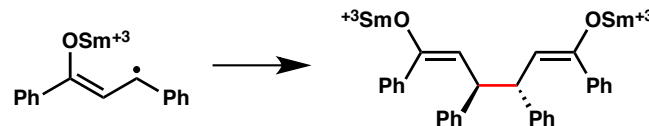


Mechanism?

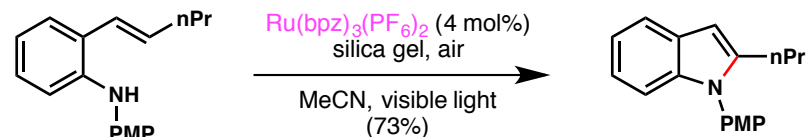
Reductive cyclization of chalcones to cyclopentanol



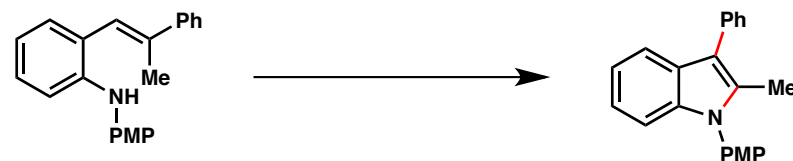
via:

Zhao, G. *et al. J. Org. Chem.* **2012**, *77*, 6307.

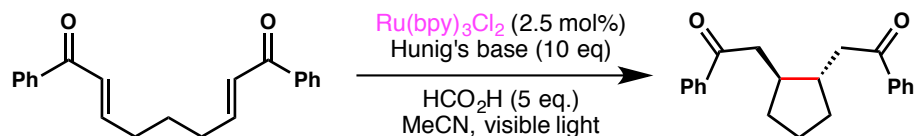
Cyclizations of aminium radical cations



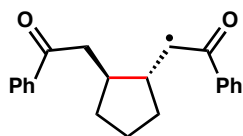
Mechanism?

Tucker, J. W.; Stephenson, C.R.J. *Org. Lett.* **2011**, *13*(20), 5468.

Reductive radical cyclizations of bis enones



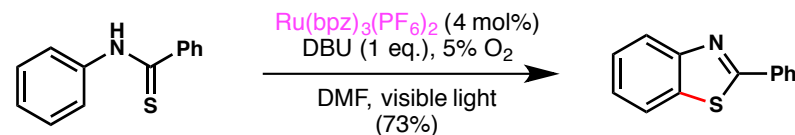
via:



- cf. with [2+2] cycloaddition
 - THF, pyrrolidine and 6-membered carbocycles can also be formed

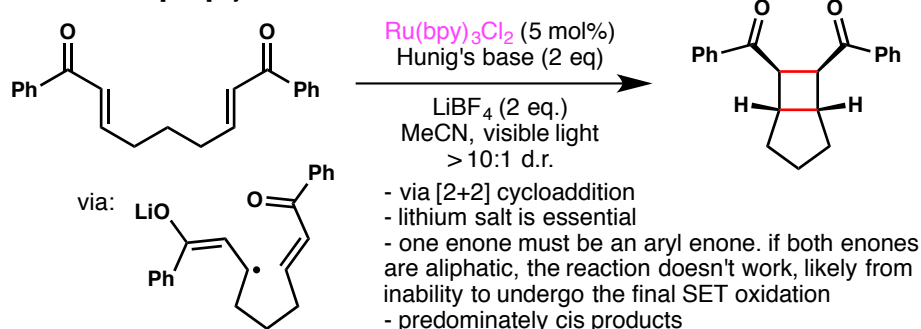
Yoon, T.P. & co. *Chem. Sci.* **2011**, *2*, 2115.Maity, S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9562.

Oxidative cyclization of thiobenzanilides to benzothiazoles

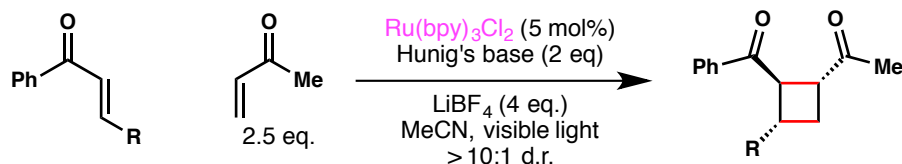
Maity, S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9562.

Cycloadditions

Intramolecular [2+2] cycloadditions

Yoon, T.P. & co. *J. Am. Chem. Soc.* **2008**, *130*, 12886.

Intermolecular [2+2] cycloadditions



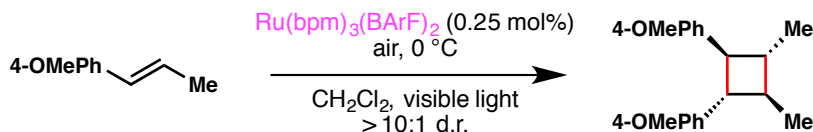
- works because homodimerization is slower than heterodimerization. Aliphatic acceptor cannot have β substituents. α substituents are ok.

- gives trans product predominately (> 10:1 d.r.)

- subsequent work has used an *N*-methylimidazolyl group as an auxiliary so that the requisite aryl ketone can be concerted to other types of ketones with an appropriate nucleophile (*Org. Lett.* **2012**, *14*, 1110.)

Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* **2009**, *131*, 14604.

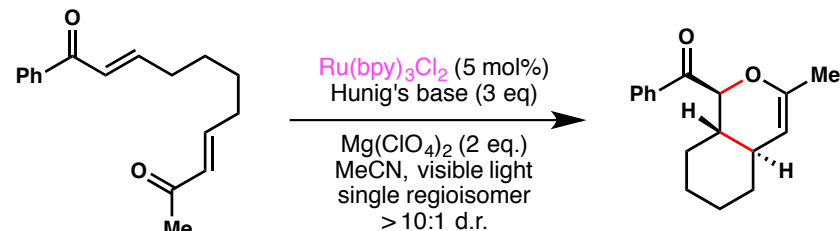
Intermolecular [2+2] cycloadditions



via: radical cation

Yoon, T.P. & co. *Chem. Sci.* **2010**, *3*, 2807.

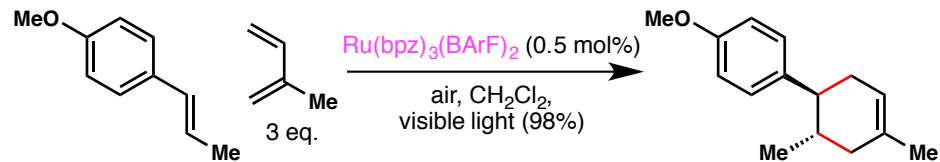
Intramolecular [4+2] cycloadditions



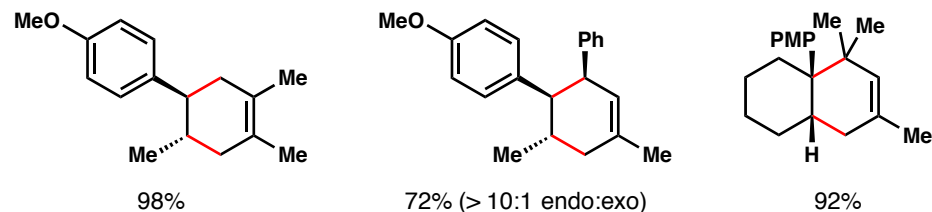
Why is only a single diastereomer formed?

Yoon, T.P. and co. *Tetrahedron* **2011**, *67*, 4442.

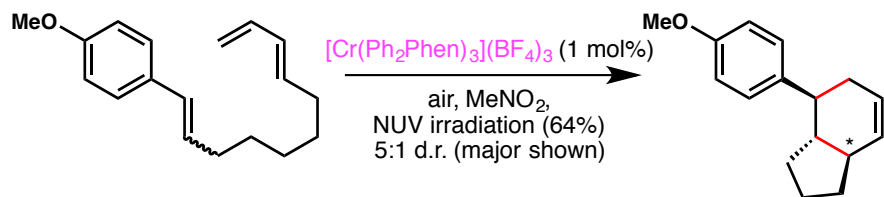
Radical cation Diels-Alder reaction



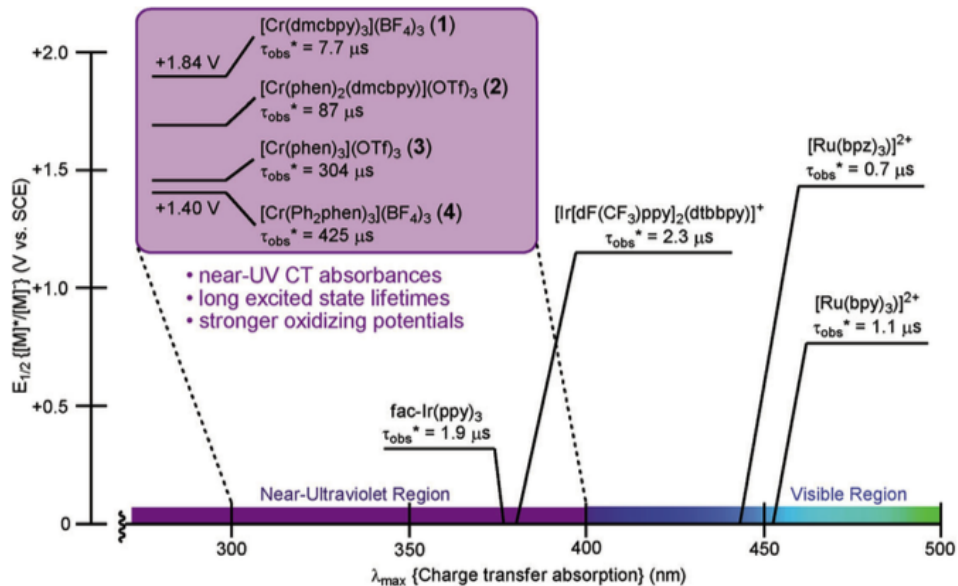
examples:

Yoon, T.P. & co. *J. Am. Chem. Soc.* **2011**, *133*, 19350.

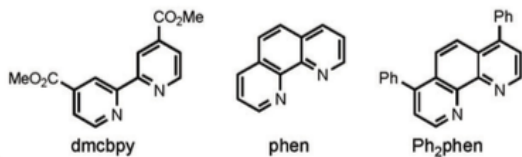
Radical cation Diels-Alder reaction



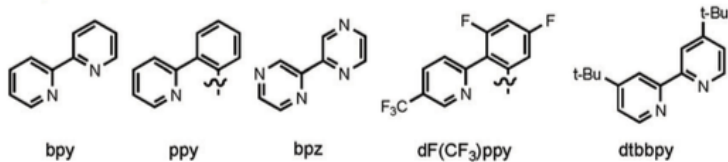
- no [2+2] products observed with unsubstituted dienes, unlike [Ru] and [Ir] reactions
- exclusively anti products formed despite E/Z mixture
- intermolecular cycloadditions work well too
- 1st row TM photoredox catalysts are a current area of research interest



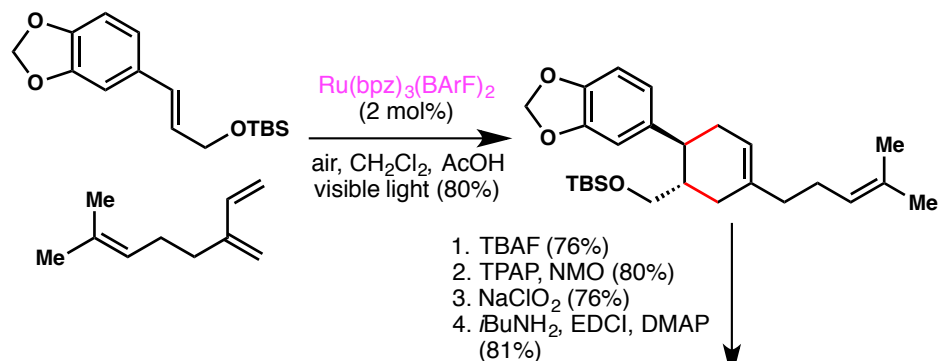
Cr ligands



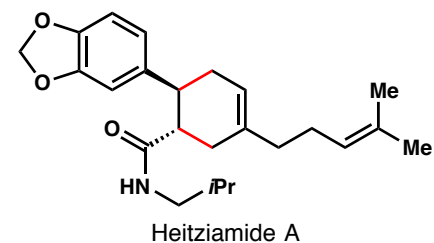
Ru/Ir ligands



Total Synthesis of Heitziamide A via a [4+2] cycloaddition



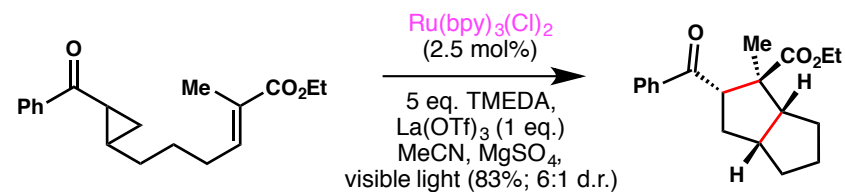
1. TBAF (76%)
2. TPAP, NMO (80%)
3. NaClO_2 (76%)
4. $i\text{BuNH}_2$, EDCI, DMAP (81%)



- opposite regioisomer is obtained under thermal conditions (150 °C, 72 hrs (60%; 2:1 d.r.))

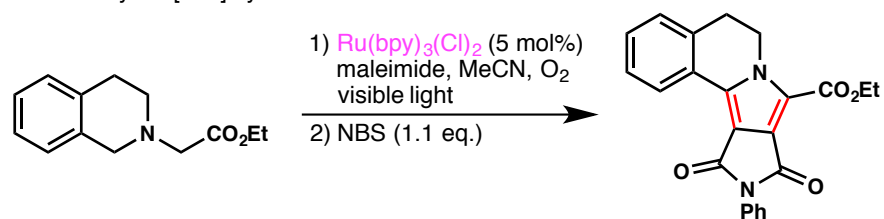
Yoon, T.P. & co. *J. Am. Chem. Soc.* **2011**, *133*, 19350.

Intramolecular [3+2] cycloadditions of cyclopropyl ketones



Mechanism?

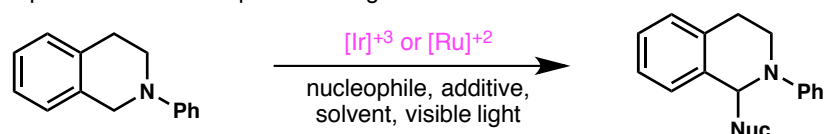
Azomethine ylide [3+2] cycloadditions



- other dipolarophiles: $\text{O}_2\text{N}-\text{CH}=\text{CH}-\text{Ph}$ $\text{CH}_2=\text{CH}-\text{CO}_2\text{Et}$ $\text{EtO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$

Zhou *et al.* *Angew. Chem. Int. Ed.* **2011**, *50*, 7171.; Rueping, M. *Chem. Commun.* **2011**, 47, 9615.

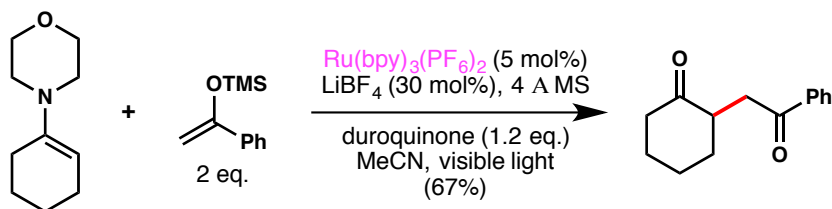
Nucleophilic additions into photoredox-generated iminiums



Nuc: nitromethane, cyanate, silyl enol ether, enamine, dialkyl phosphates, allylic silanes, indoles, alkynes, $-\text{CF}_3$, etc.

Review: Prier, C. K.; Rankic, D. A.; MacMillan, D.W.M. *Chem. Rev.* **2013**, *113*, 5322.; Tauber, J. *et al. Molecules* **2014**, *19*, 16190

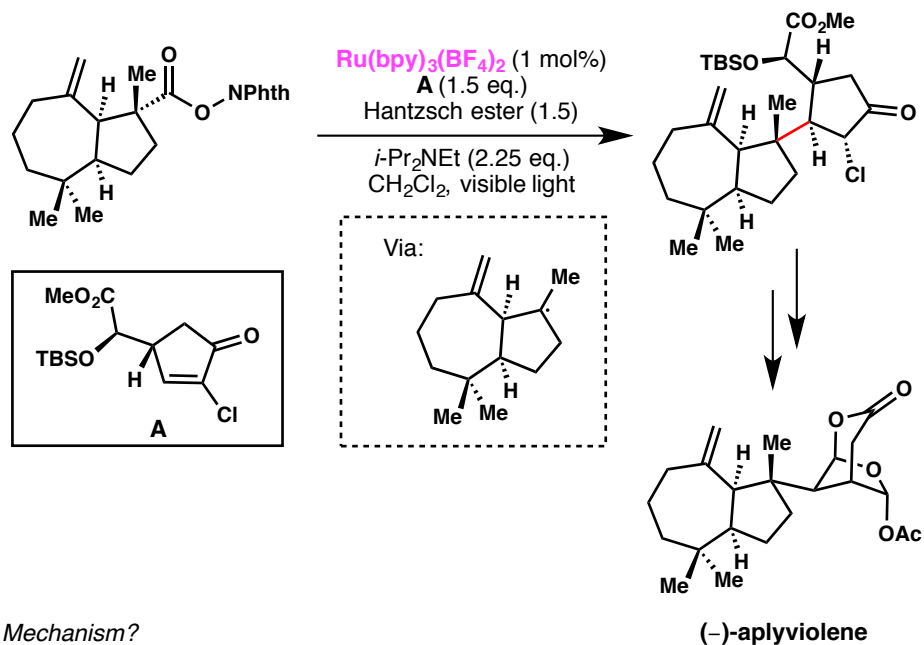
Couplings of enamines with enolsilanes (dissonant products)



Mechanism?

Akita & co. *Chem. Commun.* **2012**, 48, 5355.

Synthesis of (-)-Aplyviolene via photoredox catalyzed radical conjugate addition



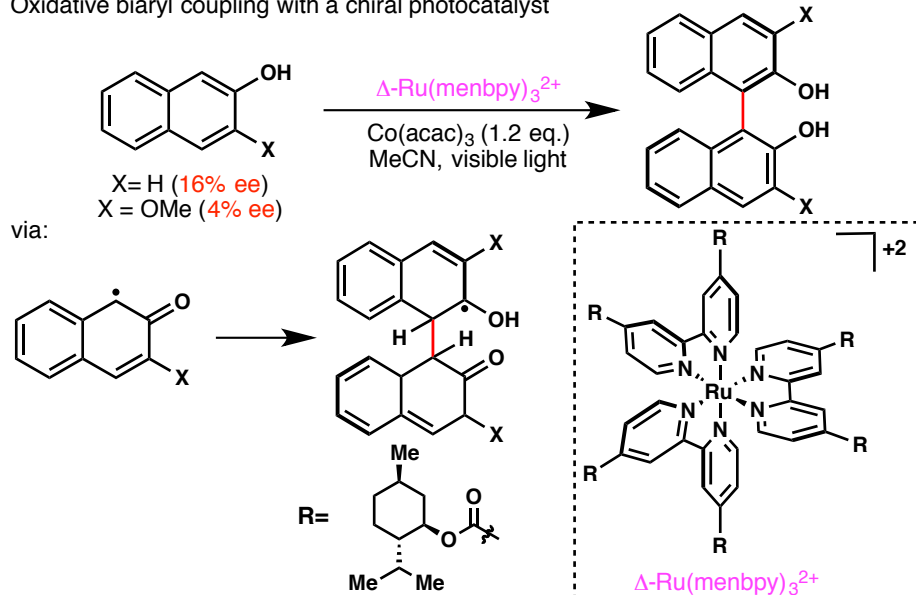
Mechanism?

Schnermann, M.J.; Overman, L.E. *Angew. Chem. Int. Ed.* **2012**, *51*, 9576.

Asymmetric C-C bond formation

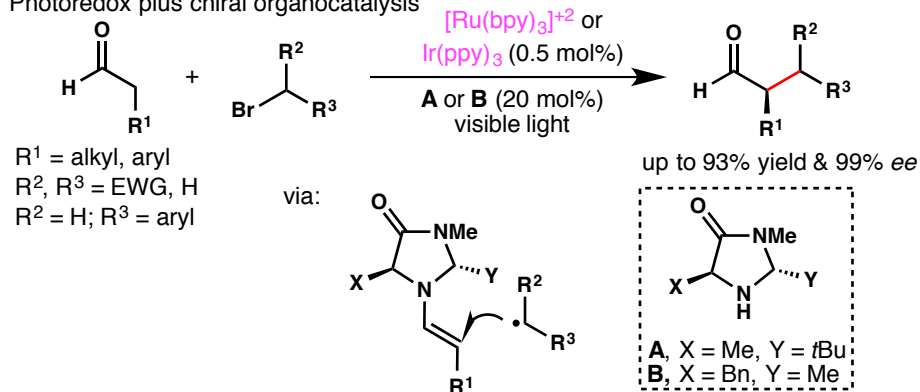
Because photoredox catalysts are primarily involved in initiating and terminating reactions via outer-sphere SET (aka generating reactive radical species), they are not usually closely associated with the reactive organic molecules and do not catalyze the bond forming step. For this reason, alongside the inherent challenge (early transition state in bond formation) of using radicals to form bonds, enantioselective bond formation has been particularly challenging. The most successful strategies to date have employed ancillary chiral catalysts.

Oxidative biaryl coupling with a chiral photocatalyst



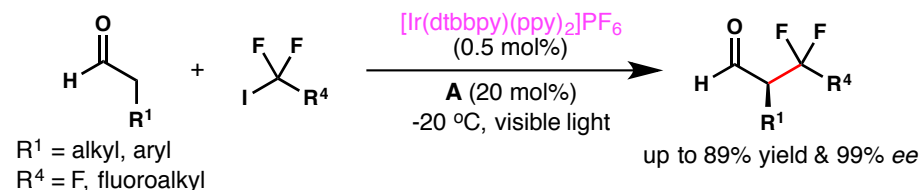
Hamada, T. *et al. J. Chem. Soc., Chem. Commun.* **1993**, 909.; Hamada, T. *et al. J. Mol. Catal.* **1994**, 88, L1.

Photoredox plus chiral organocatalysis



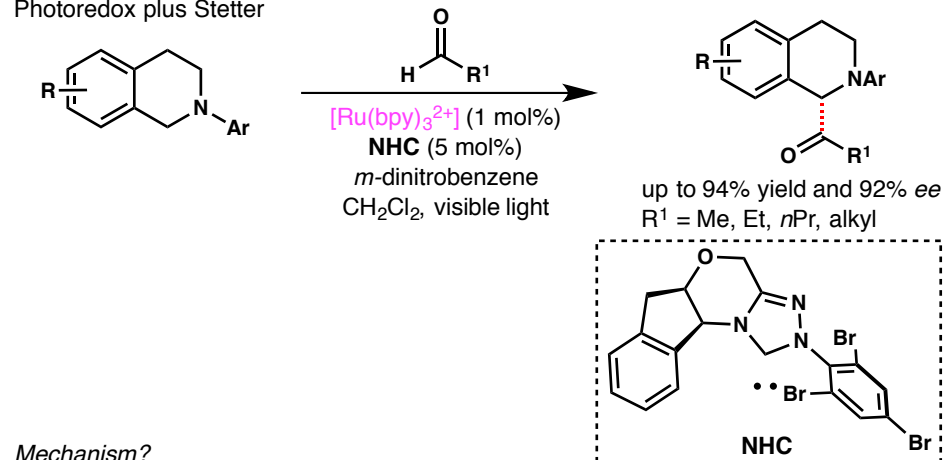
MacMillan & co. *J. Am. Chem. Soc.* **2010**, 132, 13600; *Science* **2008**, 322, 77.

Photoredox plus chiral organocatalysis



MacMillan, D.W.C. & co. *J. Am. Chem. Soc.* **2009**, 131, 10875.

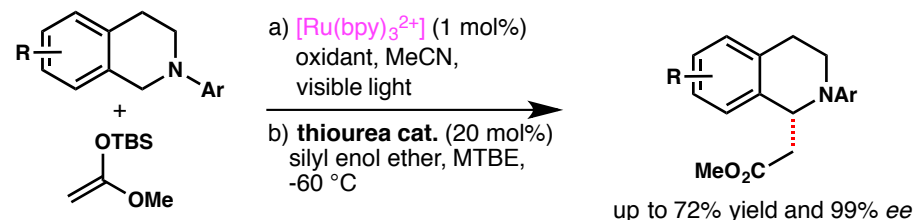
Photoredox plus Stetter



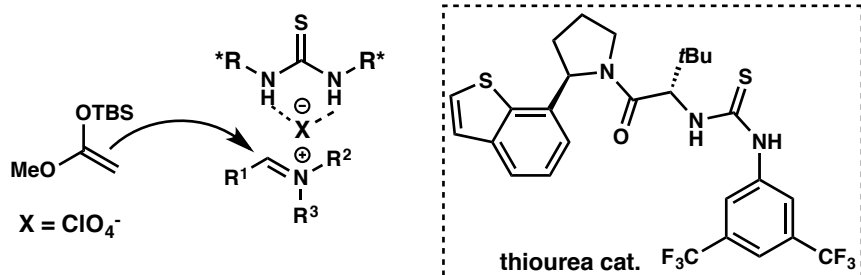
Mechanism?

DiRocco, D.A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, 134, 8094.

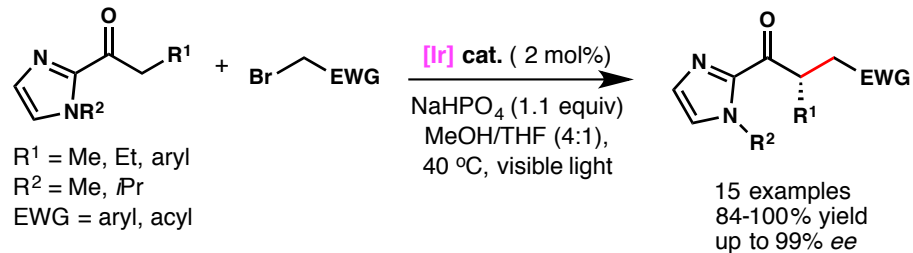
Photoredox plus anion binding catalysis



via:

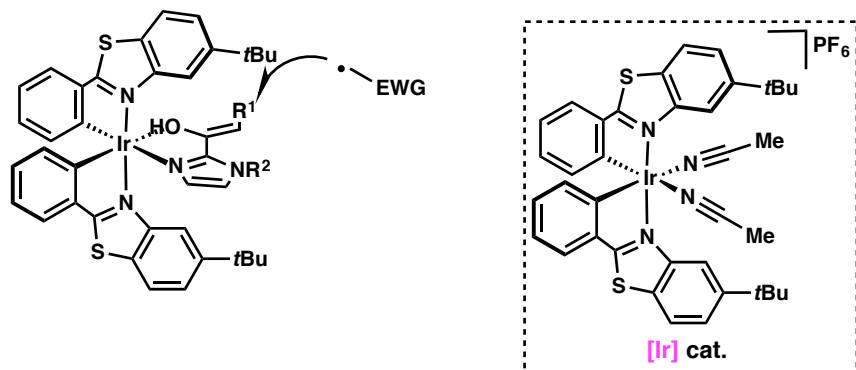
Jacobsen, E.N.; Stephenson, C.R.J. & co. *Chem. Sci.* **2014**, *5*, 112.

Chiral photoredox catalysis

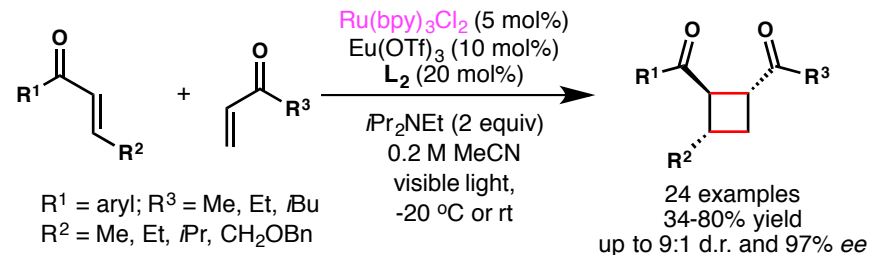


$\text{R}^1 = \text{Me, Et, aryl}$
 $\text{R}^2 = \text{Me, } i\text{Pr}$
 EWG = aryl, acyl

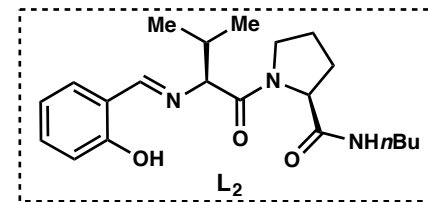
via:

Meggers, E. & co. *Nature* **2014**, *515*, 100.

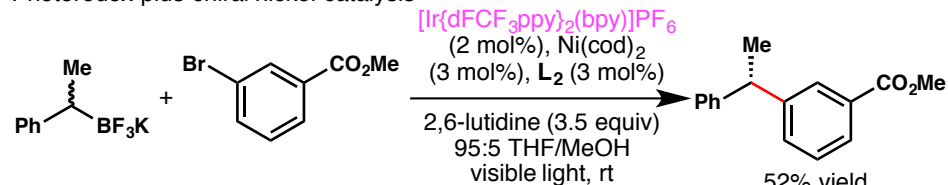
Photoredox plus chiral lewis acid catalysis



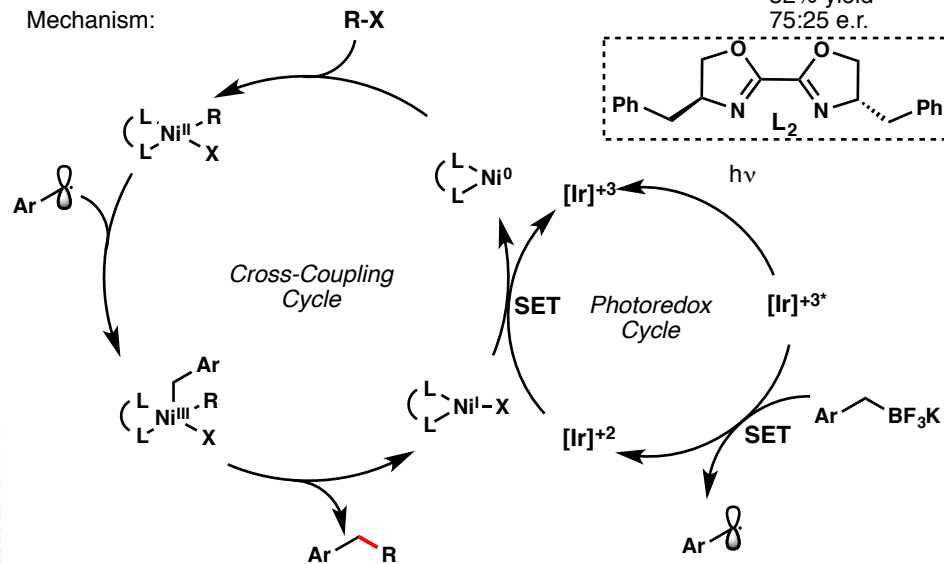
- cf. prior racemic reaction used lithium as the cation (*supra infra*)
 - LA coordination is necessary for the first reduction, therefore a chiral environment is afforded to each reactive radical

Yoon, T.P. & co. *Science* **2014**, *344*, 392.

Photoredox plus chiral nickel catalysis

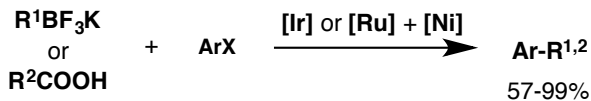


Mechanism:

Molander, G. & co. *Science* **2014**, *344*, 392.

Dual catalysis with another transition metal

Photoredox catalysts have been used in concert with other transition metals in at least two general ways. One is through the generation of reactive intermediates for another metal's catalytic cycle. The second is as an active participant in the redox cycle of the other transition metal.

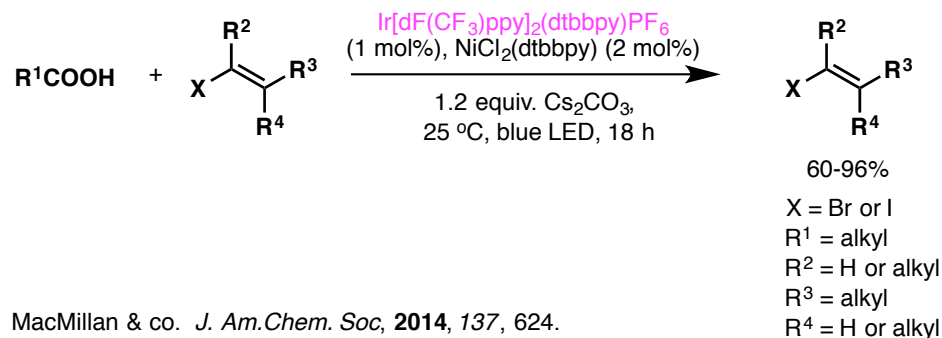
Dual catalysis with nickel ($Ni^{0/1/2/3}$ cycle)

Molander & co. R^1BF_3K $X = Br$
 MacMillan, Doyle, & co. R^2COOH $X = Cl, Br, I$



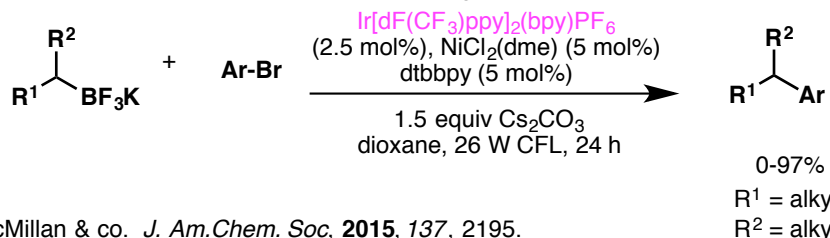
Molander, G. & co. *Science* **2014**, *345*, 433.; Doyle, A.G.; MacMillan, D.W.M. & co. *Science*, **2014**, *345*, 437

Decarboxylative Heck coupling with [Ni]



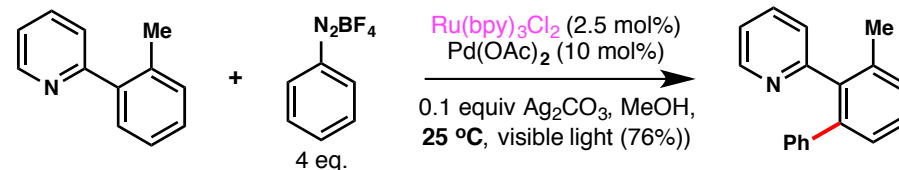
MacMillan & co. *J. Am. Chem. Soc.*, **2014**, *137*, 624.

Secondary alkyl boronates in aryl cross-coupling

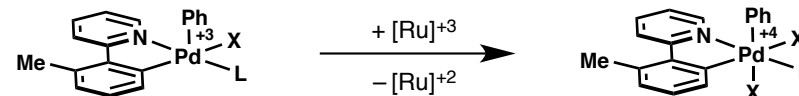


MacMillan & co. *J. Am. Chem. Soc.*, **2015**, *137*, 2195.

Merging Pd and photoredox catalysis for C-H arylations

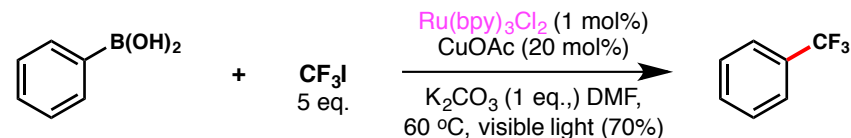


- occurs via a $[Pd]^{+2/+3/+4}$ cycle; c.f. normal $[Pd]^{+2/+4}$ cycle with hypervalent $[I]^{+3}$ via:

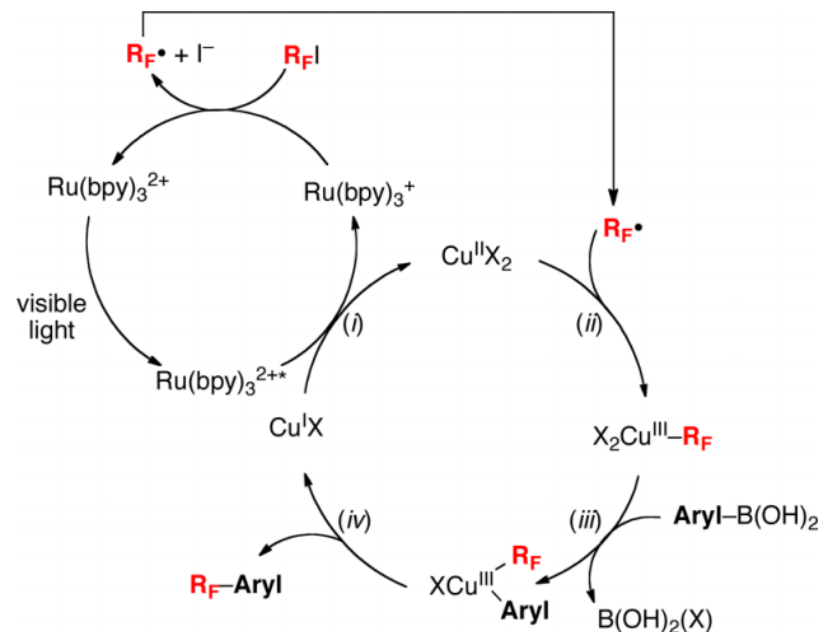


Sanford & co. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

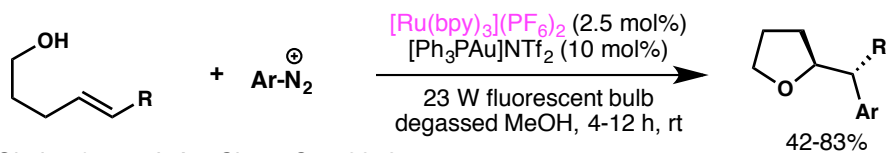
Photoredox and [Cu] for trifluoromethylation



Proposed mechanism:

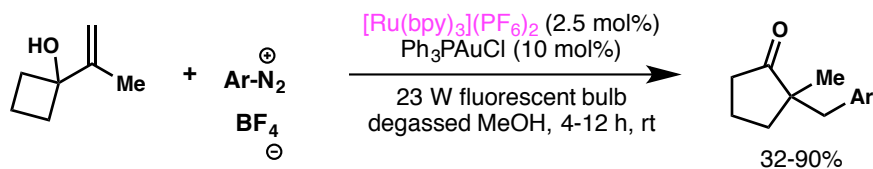


Oxy- and amino-arylation of alkenes via a $[\text{Au}]^{+1/+2/+3}$ cycle



Glorius & co. *J. Am.Chem. Soc.*, **2013**, *135*, 5505.

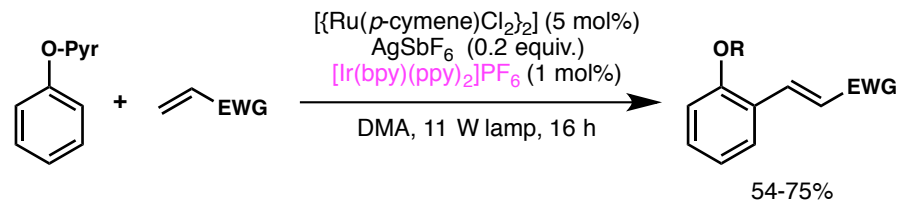
Aylative ring expansion with $[\text{Au}]^{+1/+2/+3}$



- mechanistic studies propose formation of $\text{Ar}-[\text{Au}]^{+2}$ prior to olefin coordination

Mechanism?

Photoredox as oxidation promoter in oxidative couplings



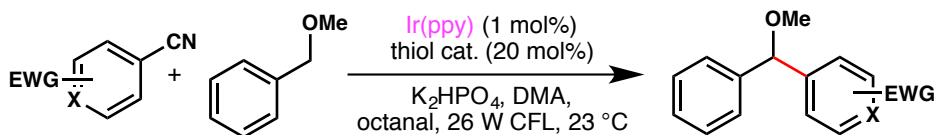
-[Ir] reoxidizes [Ru] to regenerate the active cat and is in turn oxidized by O_2

-[Ag] activated [Ru] precatalyst by chloride anion abstraction

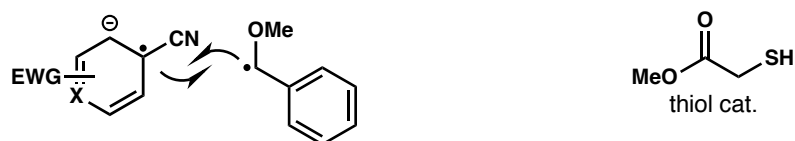
Rueping & co. *Angew. Chem. Int. Ed.*, **2015**, *54*, 2801.

Functionalization of weak aliphatic C-H bond via thiol based HAT catalysis

Benzylic ether functionalization + addition into very electron deficient arenes



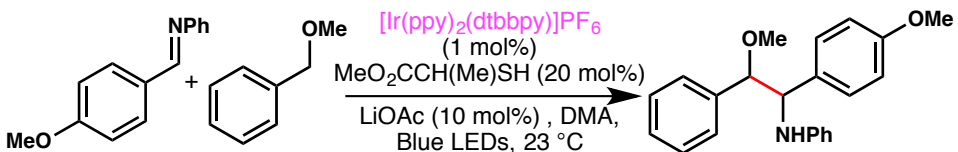
via:



- SET reduction of arene by $[\text{Ir}]^{+3}$ gives radical anion
- PCET oxidation of thiol by $[\text{Ir}]^{+4}$ gives -S centered radical which abstracts benzylic ether C-H bond
- radical recombination gives the product
- octanal may sequester eliminated CN anion

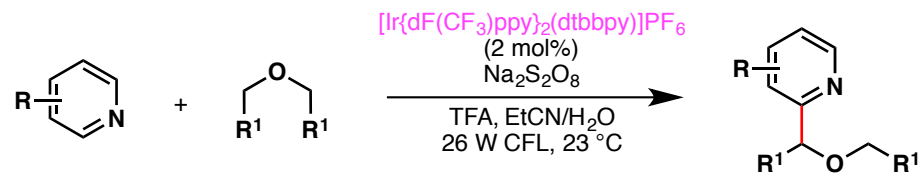
Qvortrup, K.; Rankic, D.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2014**, *136*, 16986.

Benzylic ether functionalization + addition into benzylic imines



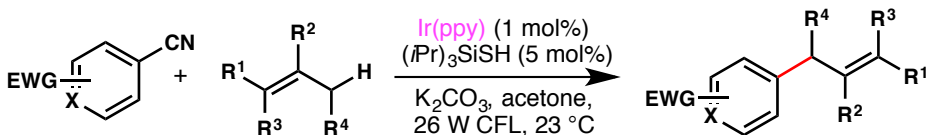
Hager, D.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2014**, *136*, 16986.

Photoredox Minisci reaction with symmetric α -alkoxy ethers



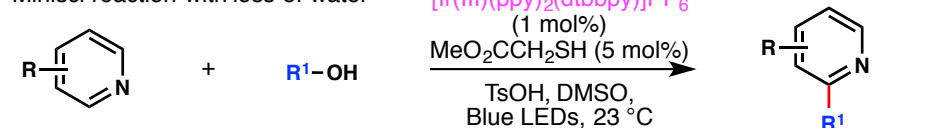
Jin, J.; MacMillan, D.W.C. *Angew. Chem. Int. Ed.* **2015**, *54*, 1565.

Allylic radical addition into very electron deficient arenes

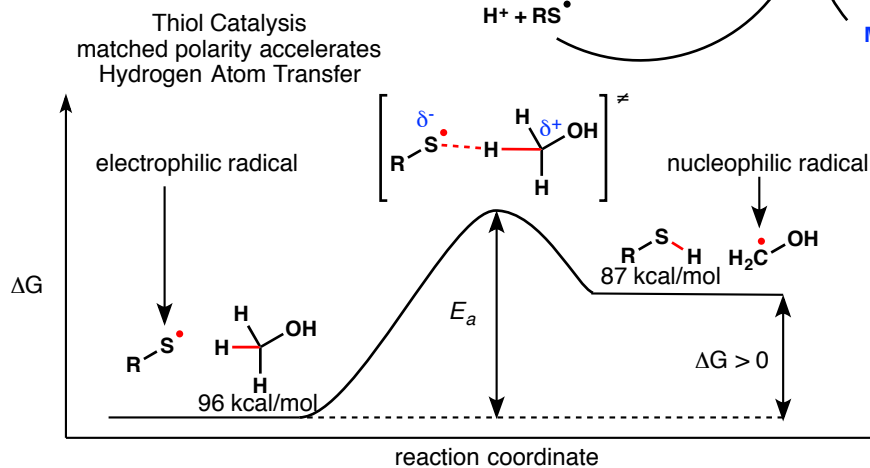
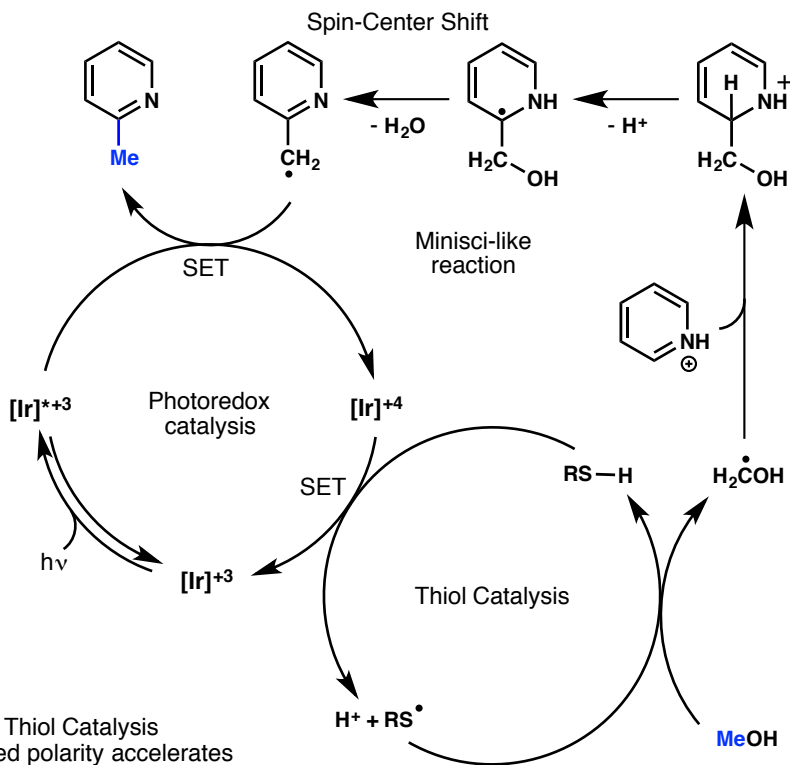


Cuthbertson, J.D.; MacMillan, D.W.C. *Nature* **2015**, *519*, 74.

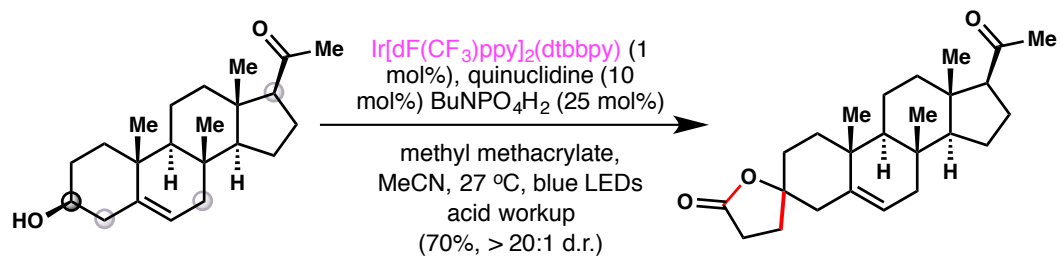
Minisci reaction with loss of water



Mechanism:



Jin, J.; MacMillan, D.W.C. *Nature* **2015**, *525*, 87.

State of the art: Selective functionalization of α -alkoxy C-H bonds

Concept:

Can we activate strong C-H bonds in the presence of weaker C-H bonds?



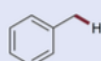
88.0 kcal/mol



88.8 kcal/mol



89.4 kcal/mol



89.8 kcal/mol

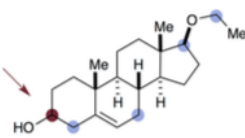


92.0 kcal/mol



92.0 kcal/mol

selectivity for strong bond = elusive

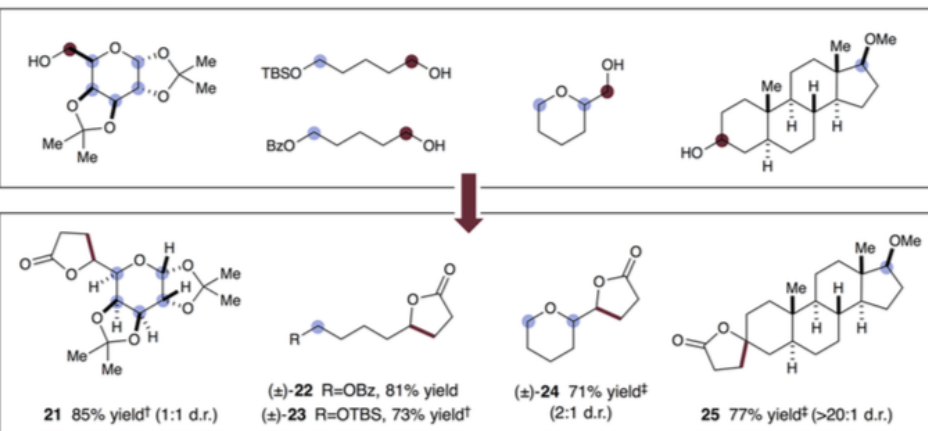


● = strong C-H bond, activated
 ● = weaker C-H bond, not activated

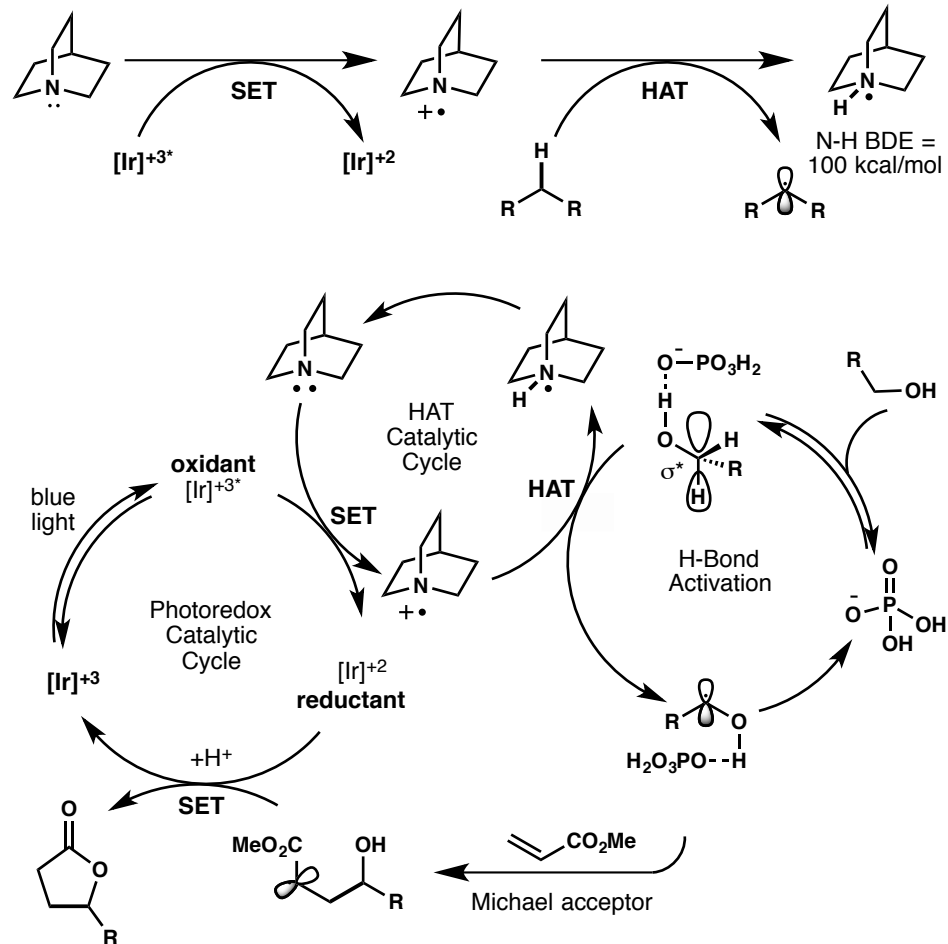
Examples from substrate scope:

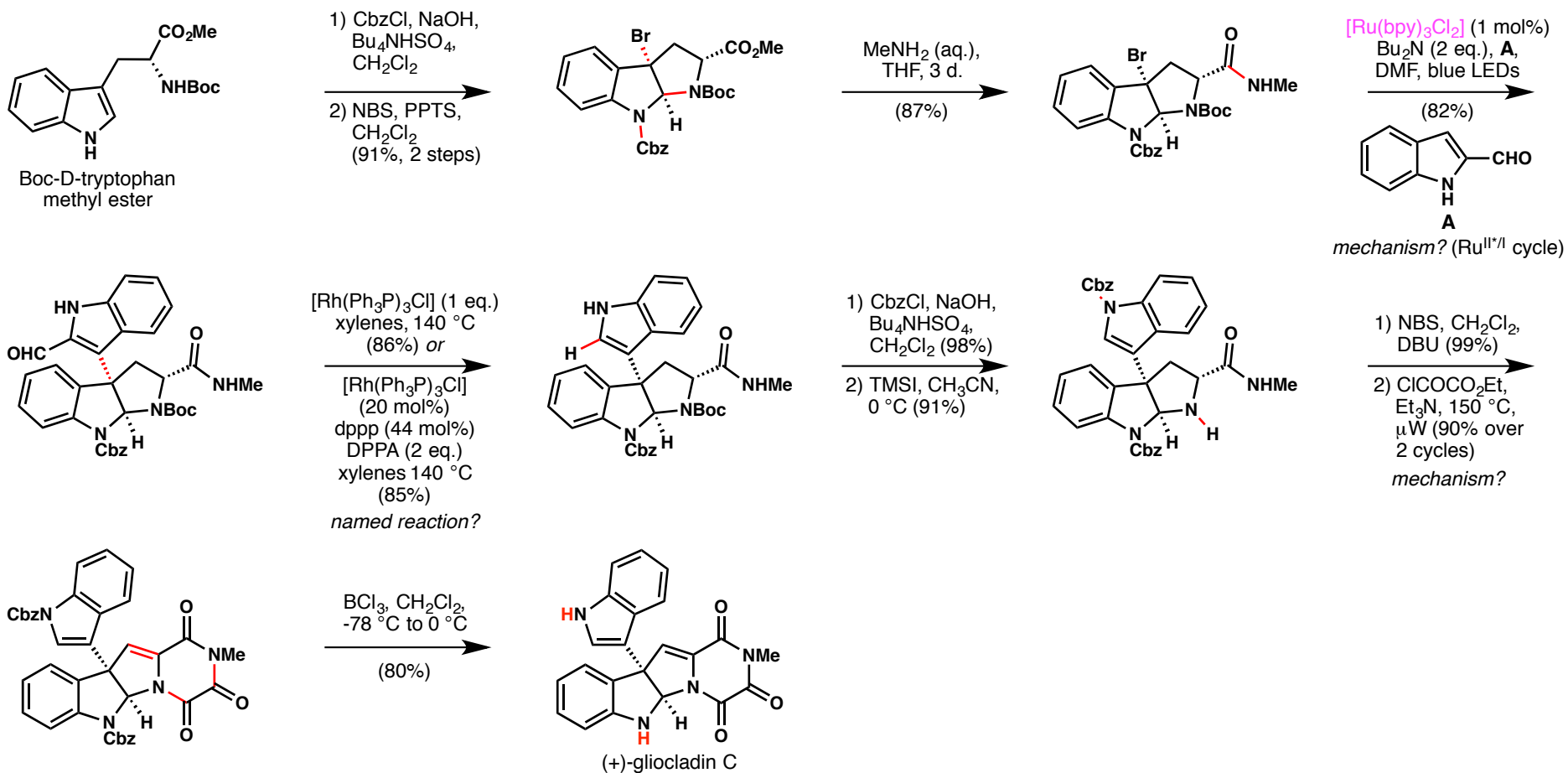
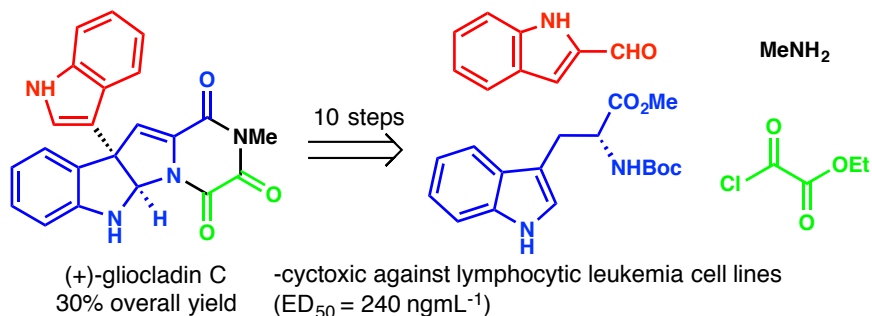
Selective alkylation of alcohol C-H in the presence of ether C-H

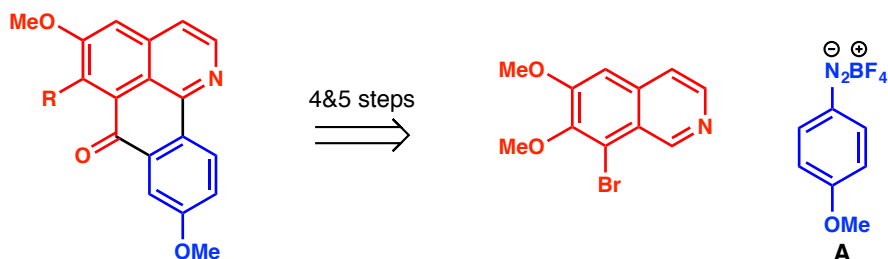
● = strong C-H ● = weaker C-H



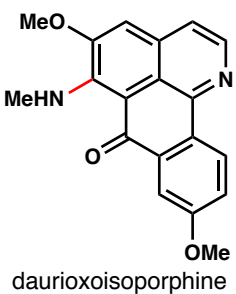
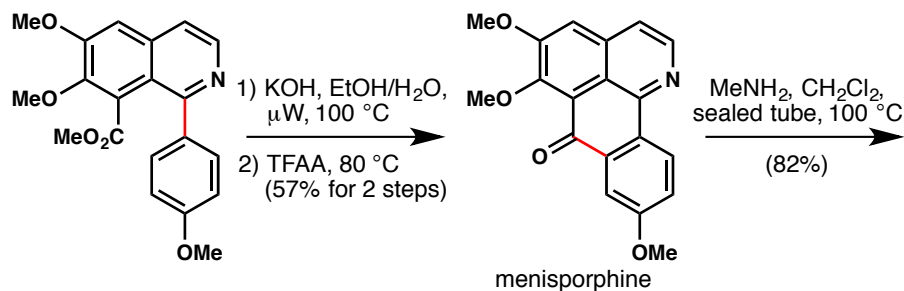
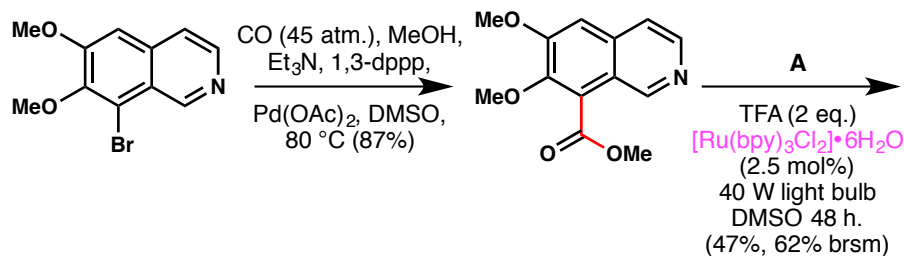
Mechanism:







Menisporphine (R=OMe) (an antiangiogenic agent)
Daurioxoisoporphine C (R=NHMe)



Proposed mechanism:

