PHOTOCHEMICAL CONTINUOUS FLOW STRATEGIES.

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1st NSERC CREATE: Continuous Flow Science Symposium
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Montréal, Qc.

GROUP INTERESTS

Macrocyclization Strategies in Organic Synthesis

(Cosmetics, Peptides/Pharmaceuticals)
Green Chemistry/Green Solvents
Continuous Flow Chemistry

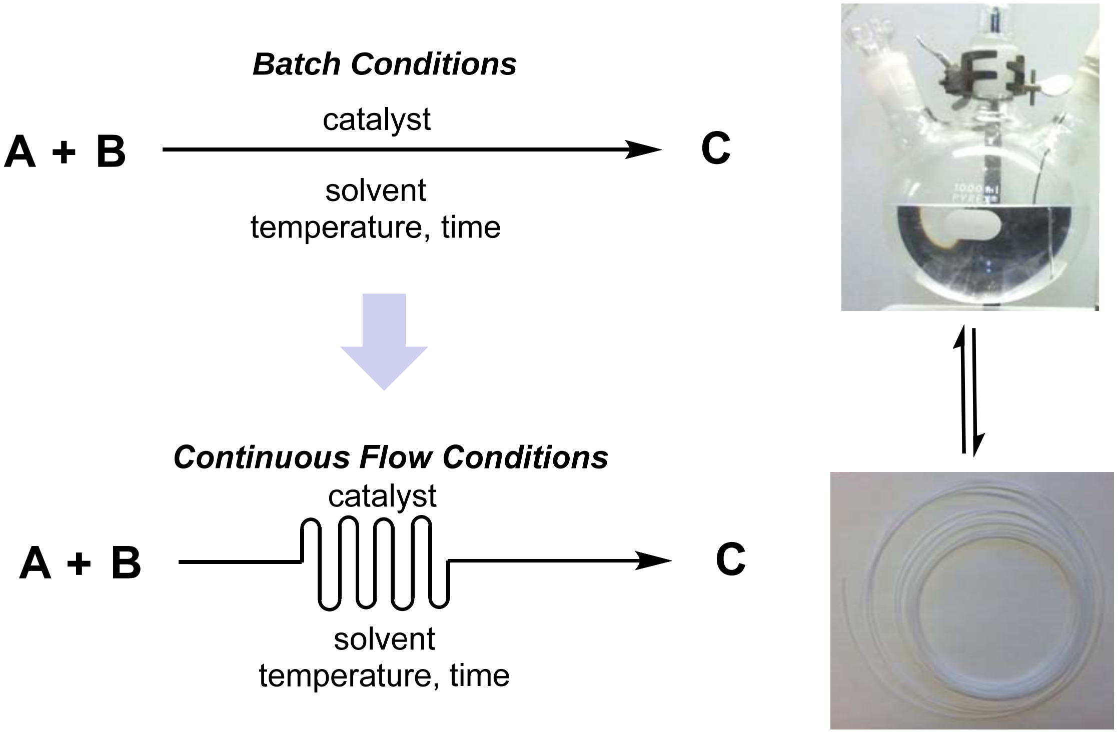
Photochemical Strategies in Organic Synthesis

(Carbon-Based Materials, Heterocyclic Materials/Pharmaceuticals)
Green Chemistry (Visible and UV Light Chemistry)
Continuous Flow Chemistry

Catalysis

Cu and Ni-based Glaser Hay Couplings
Ru-based Olefin Metathesis
Hf-based Macrolactonization
Cu-based Sonogashira Cross-Coupling
Cu and Fe-based Photoredox Cyclizations
Cu-based Cycloadditions

CONTINUOUS FLOW IN GREEN CHEMISTRY



Batch Conditions

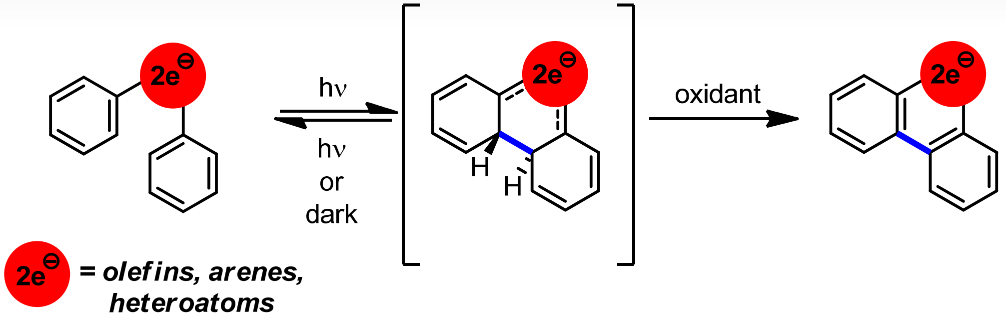
$$A + B \xrightarrow[\text{solvent, temperature, time}]{\text{catalyst}} C$$

Continuous Flow Conditions

$$A + B \xrightarrow[\text{solvent, temperature, time}]{\text{catalyst}} C$$

- Increasing reaction efficiency through expanding available reaction conditions
- Telescoping multistep reactions
- Heterogeneous catalysis/catalyst recycling
- More data using less material
- Safe access to supercritical fluids
- Safe practical use of gases/hazardous reagents
- Accessible/Scalable Photochemistry

CARBON RICH MATERIALS AND THE MALLORY REACTION.



Organic Photochemistry:

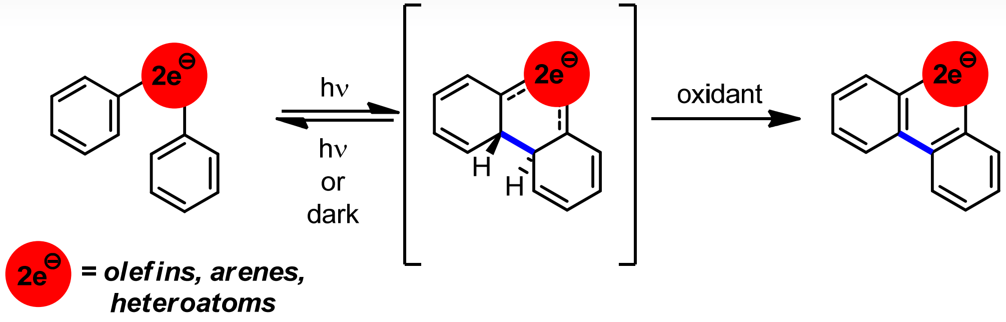
- Light as a clean and traceless reagent
- Atom economy
- Provides a “green” method for the synthesis of C_{aryl}-C_{aryl} bonds

Disadvantages:

- Often incompatibility with acid-sensitive functionalities.
- Often incompatible with various functional groups.
- Need for special (expensive) glassware
- Need for protective eye wear.
- High dilution (formation of [2+2] adducts at higher concentrations). Example: 0.1 mmol in 1L of solvent
- Lack of enantiocontrol

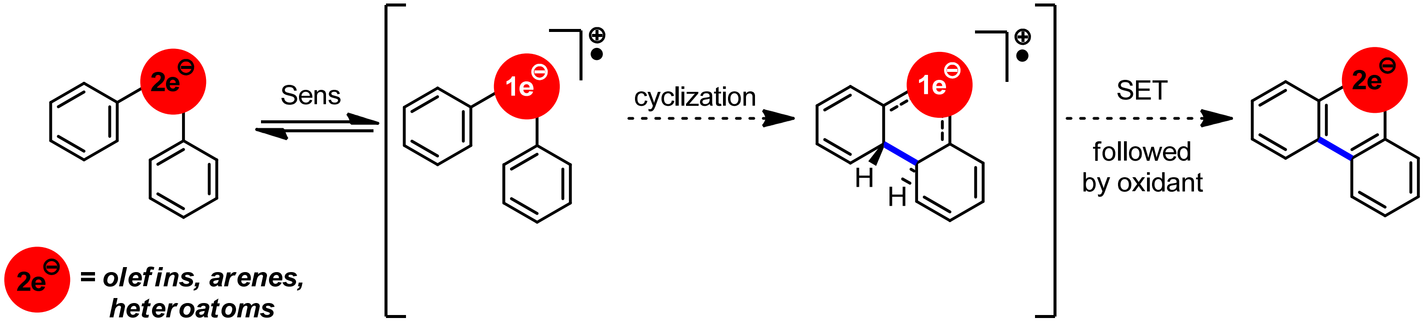
For references towards photochemistry as a green technology see: Anastas, P. T.; Warner, J. C.; Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998.

MALLORY REACTION.



2e⊖ = *olefins, arenes, heteroatoms*

Develop a new visible-light mediated synthesis based upon photoredox chemistry:

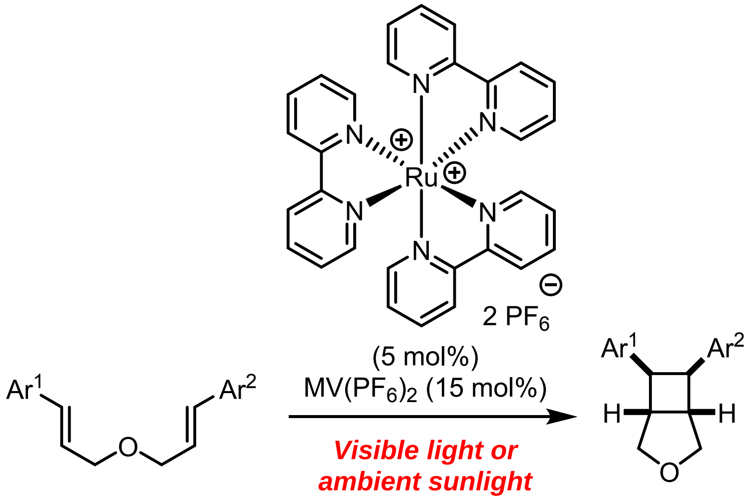


2e⊖ = *olefins, arenes, heteroatoms*

- **Large number of sensitizers available for study**
- **Use simple solar light or household lighting and regular Pyrex glassware**

For reviews see: (a) Joergensen, K. B. *Molecules* **2010**, *15*, 4334-4358. (b) Mallory, F. B.; Mallory, C. W. *Organic Reactions* **1984**, *30*, 1-456. For other early contributions to the development of this photochemical transformation see: (c) Muszkat, K. A; Fischer, E. *J. Chem. Soc. B* **1967**, 662-678. (d) Cuppen, Th. J. H. M.; Laarhoven, W. H. *J. Am. Chem. Soc.* **1972**, *94*, 5914-5915. (e) Wynberg, H.; Groen, M. B. *J. Am. Chem. Soc.* **1968**, *90*, 5339-5341.

PHOTOREDOX REACTIONS USING VISIBLE-LIGHT.

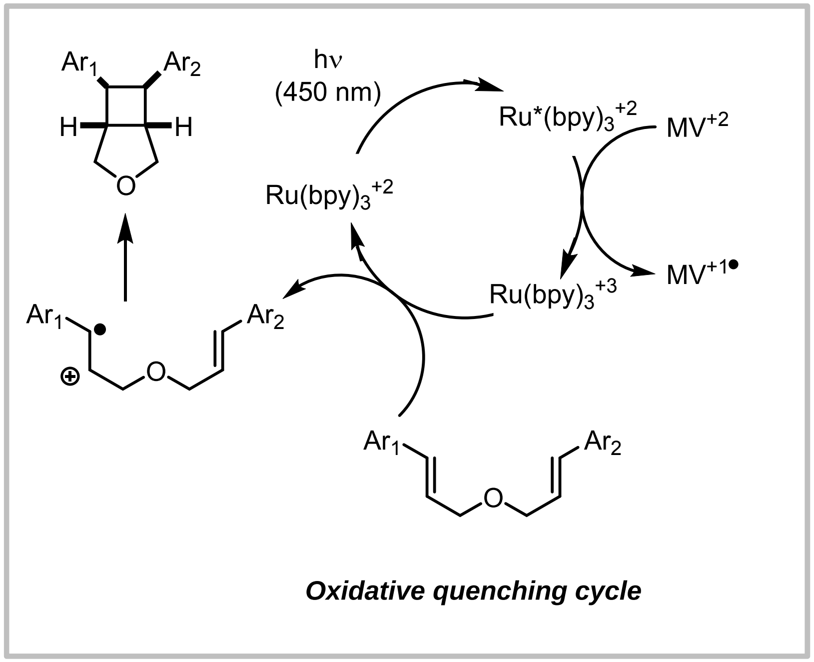


(5 mol%)
$MV(PF_6)_2$ (15 mol%)

Visible light or ambient sunlight

$MgSO_4$, $MeNO_2$
3.5 h

79-89%



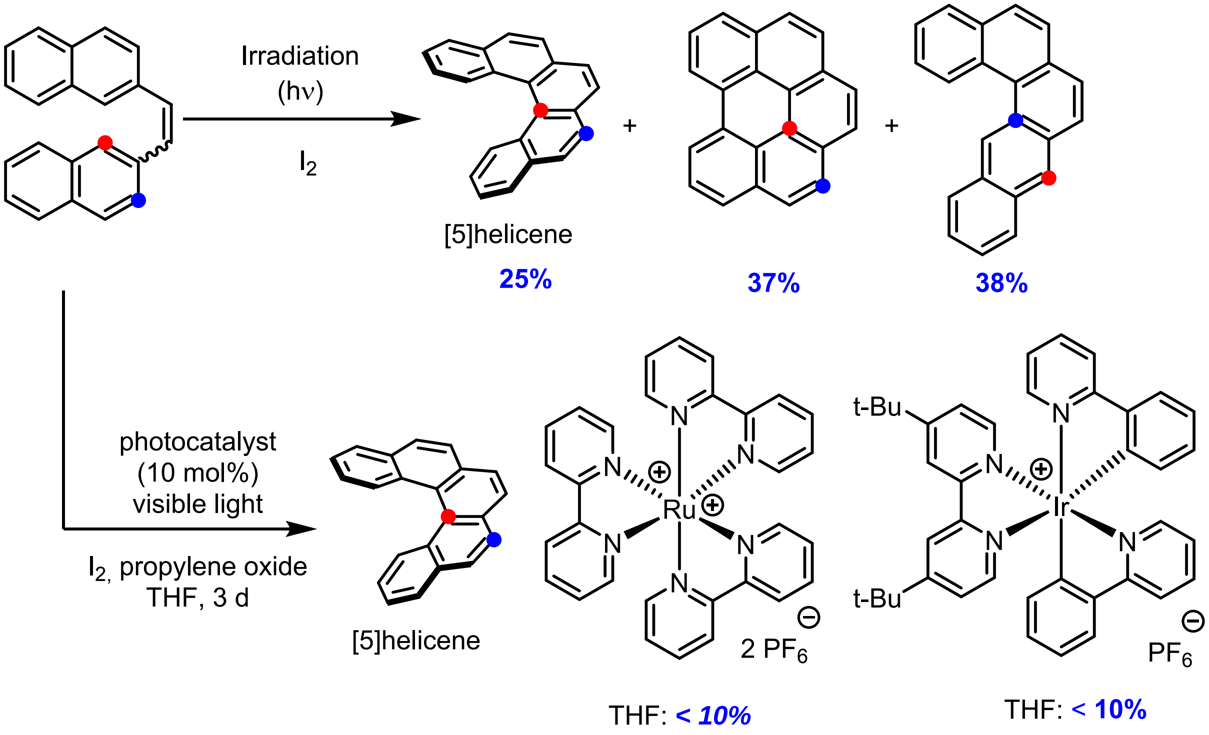
Oxidative quenching cycle

Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886 – 12887. Du, J.; Yoon,T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604 – 14605. Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572–8574.

INITIAL ATTEMPTS AT VISIBLE-LIGHT MEDIATED SYNTHESIS OF HELICENES.

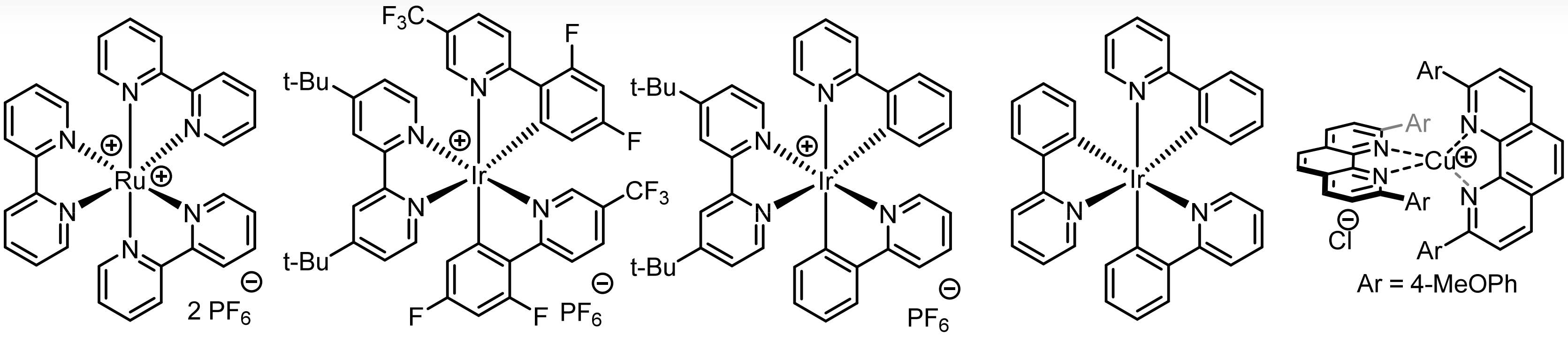
- **Traditional UV-Mediated Photocyclization Reaction**
- **Disadvantages: high dilution, need for quartz glassware and protective eye wear, lack of regiocontrol.**

Mallory Reaction: Mallory, F. B.; Mallory, C. W. *Org. React*. **1984**, *30*, 1-456.



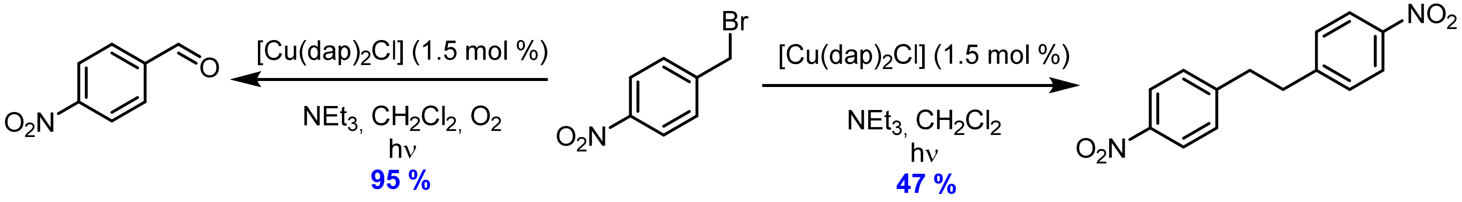
Hernandez-Perez, A. C.; Vlassova, A.; Collins, S. K. *Org. Lett.* **2012**, *14*, 2988-2991.

Cu-BASED SENSITIZERS FOR PHOTOREDOX REACTIONS.



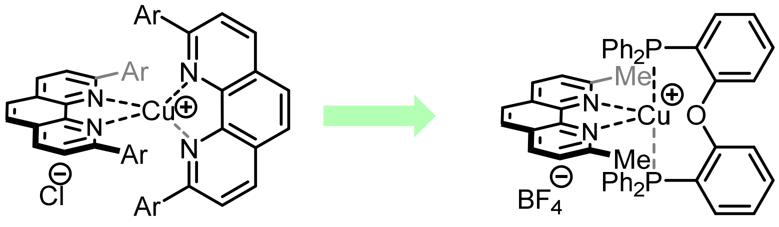
$E_{1/2}$ (M^*/M^+) =	-0.81 V	-0.89 V	-0.96 V	-1.73 V	-1.43 V
Excited state lifetime =	1100 ns	2300 ns	557 ns	1900 ns	270 ns

In contrast to the Ru and Ir complexes shown, in general Cu photocatalysts do not undergo photoredox catalysis through a reductive quenching cycle.



Kern, J.-M.; Sauvage, J.-P. *J. Chem. Soc. Chem. Commun.* **1987**, 546

Cu-BASED SENSITIZERS FOR PHOTOREDOX REACTIONS.



Ar = 4-MeOPh

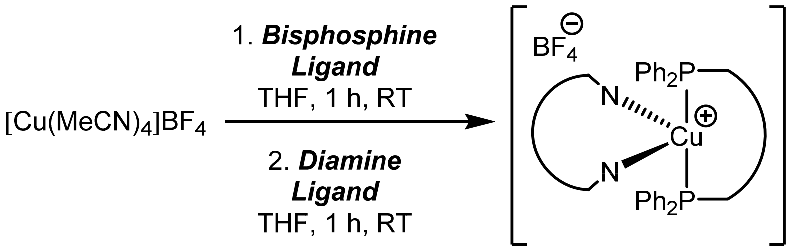
Excited state lifetime =	**270 ns**	**14300 ns**

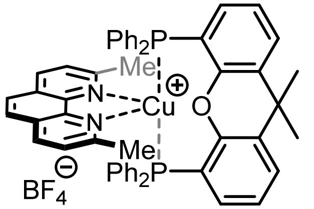
Cuttell, D. G.; Kuang, S.-M.; Fanwick, P. E.; McMillin, D. R.; Walton, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 6-7.

Cu(I) phen complexes undergo excited-state reorganization from a ground-state tetrahedral geometry to a square planar geometry. The appropriate use of a bulky chelating phosphine ligand reinforcing geometry results in an increase of the lifetime of the excited triplet state as well as photostability by preventing excited-state structural relaxation.

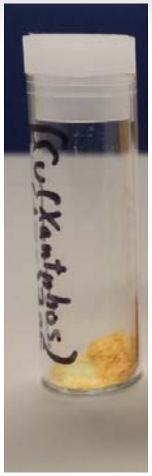
For other contributions to the development of photochemical copper (I): Deaton, J. C.; Switalski, S. C.; Kondakov, D. Y.; Young, R. H.; Pawlik, T. D.; Giesen, D. J.; Harkins, S. B.; Miller, A. J. M.; Mickenberg, S. F.; Peters , J. C. *J. Am. Chem. Soc.* **2010**, *132*, 9499-9508. Smith, C. S.; Mann, K. R. *J. Am. Chem. Soc.* **2012**, *134*, 8786-8789.

Cu-BASED SENSITIZERS FOR PHOTOREDOX REACTIONS.



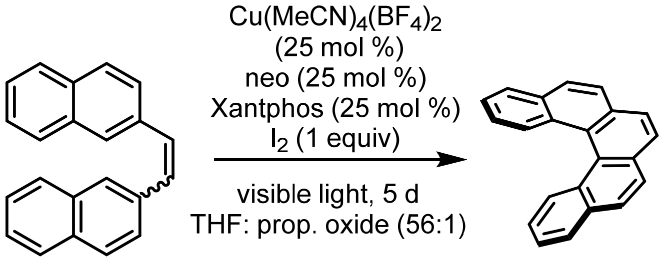


[Cu(Xantphos)(dmp)]BF$_4$



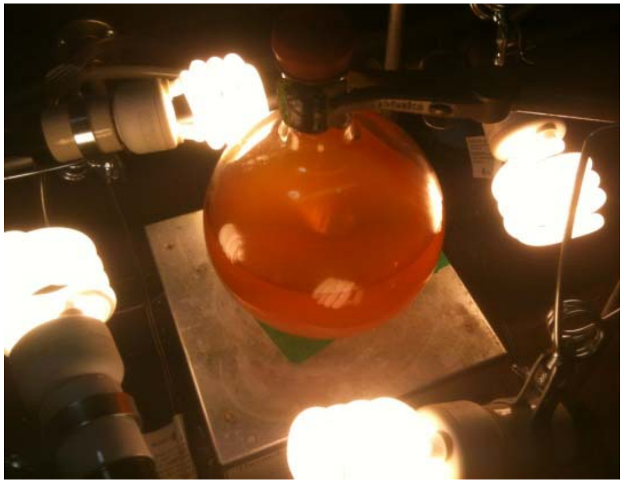
In-situ formation:

- **No isolation/purification of copper complex**
- **Rapid screening of a library of sensitizers is possible**



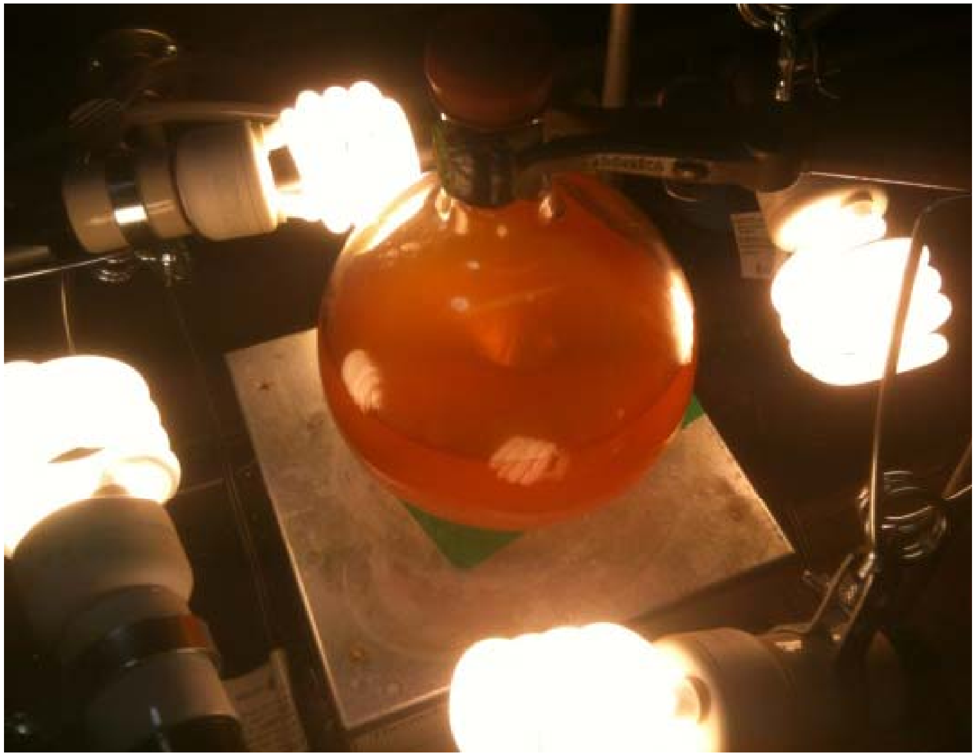
40 - 47 % (50 mg scale)

42% gram scale



Hernandez-Perez, A. C.; Vlassova, A.; Collins, S. K. *Org. Lett.* **2012**, *14*, 2988-2991.

LAMBERT-BEER LAW.



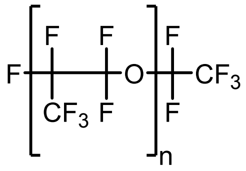
Lambert-Beer Law

$$A = -\lg\left(\frac{I}{I_0}\right) = \varepsilon_\lambda \cdot c \cdot l$$

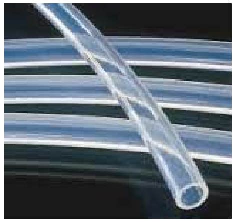
Riboflavin tetraacetate
[100 mM], MeCN/H_2O
>90 % of light absorbed
in first 1mm path length

TUBING.

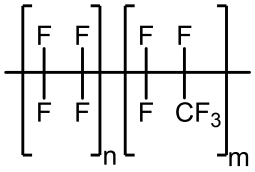
Perfluoroalkoxy alkanes (PFAs) are fluoropolymers with ether groups in the polymer backbone.



$F-[CF(CF_3)-CF_2-O]_n-CF_2-CF_3$



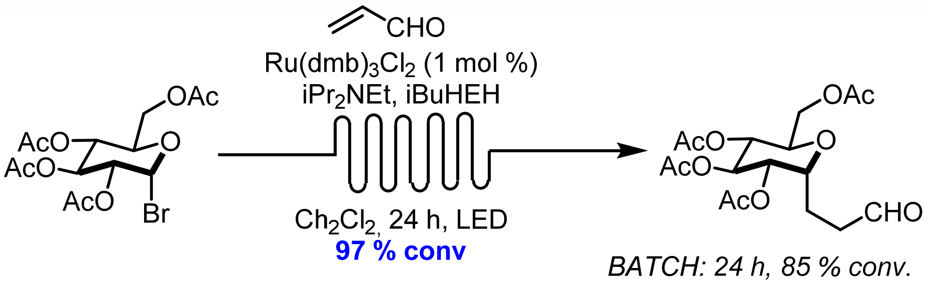
Fluorinated ethylene propylene or FEP is a co-polymer of hexafluoropropylene and tetrafluoroethylene.
Fluorinated ethylene propylene was invented by DuPont and is sold under the brandname Teflon FEP.



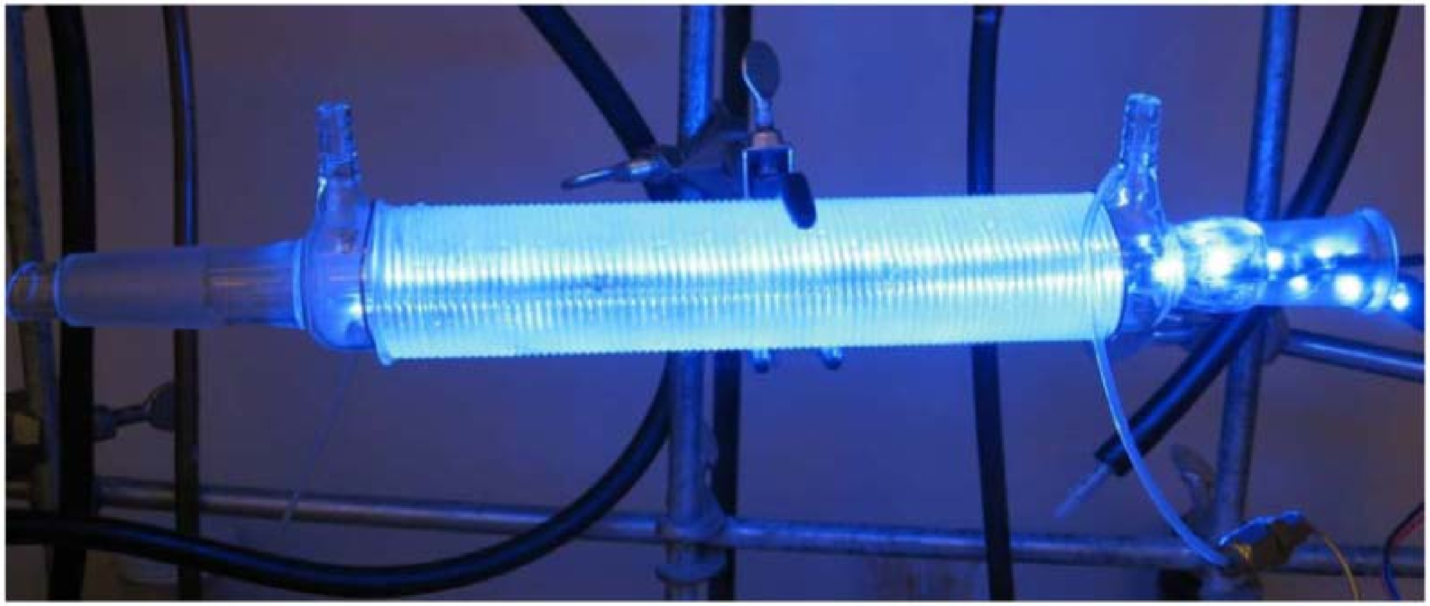
$-[CF_2-CF_2]_n-[CF_2-CF(CF_3)]_m-$

FEP and PFA both share PTFE's useful properties of low friction and non-reactivity, but are more easily formable. FEP is softer than PTFE and melts at 260 °C; it is highly transparent and resistant to sunlight.

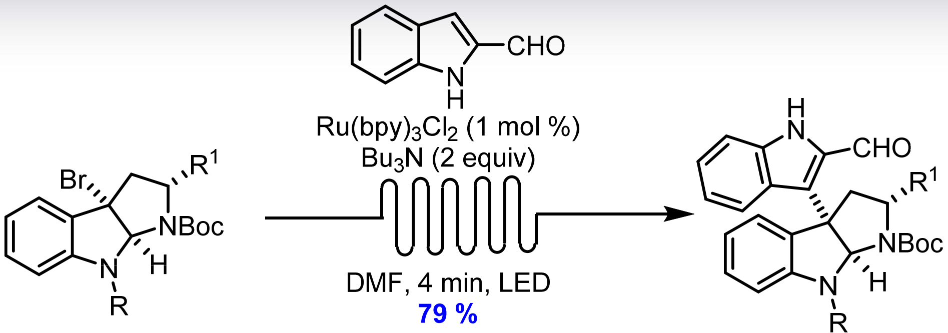
FLOW PHOTOREDOX REACTIONS.



Andrews, R. S.; Becker, J. J.; Gagne, M. R. *Angew. Chem., Int. Ed*. **2012**, *51*, 4140-4143



FLOW PHOTOREDOX REACTIONS.

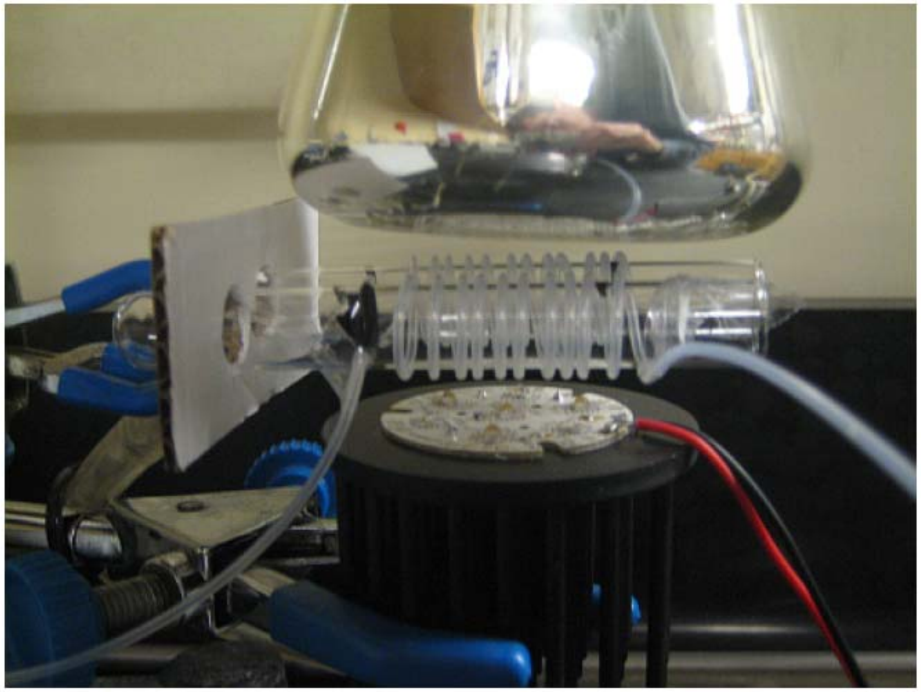


Ru(bpy)$_3$Cl$_2$ (1 mol %)
Bu$_3$N (2 equiv)

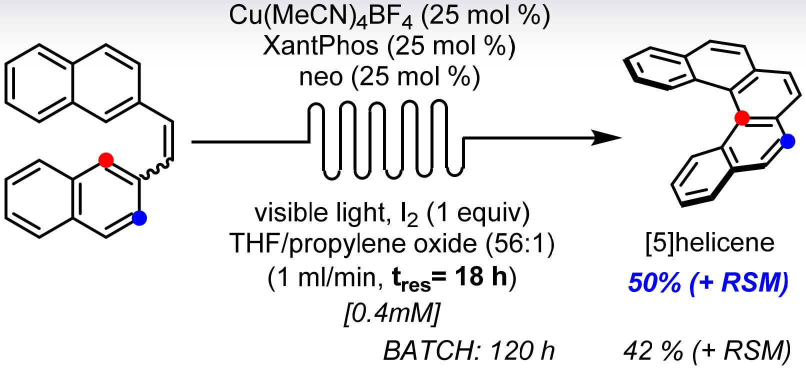
DMF, 4 min, LED
79 %
R = Boc, R^1 = H

BATCH: 12 h, 82 % conv.
R = Cbz, R^1 = C(O)NHMe

Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 4144–4147



INITIAL ATTEMPTS AT VISIBLE-LIGHT MEDIATED SYNTHESIS OF HELICENES.



$Cu(MeCN)_4BF_4$ (25 mol %)
XantPhos (25 mol %)
neo (25 mol %)

visible light, I_2 (1 equiv)
THF/propylene oxide (56:1)
(1 ml/min, **t_{res}= 18 h**)
[0.4mM]

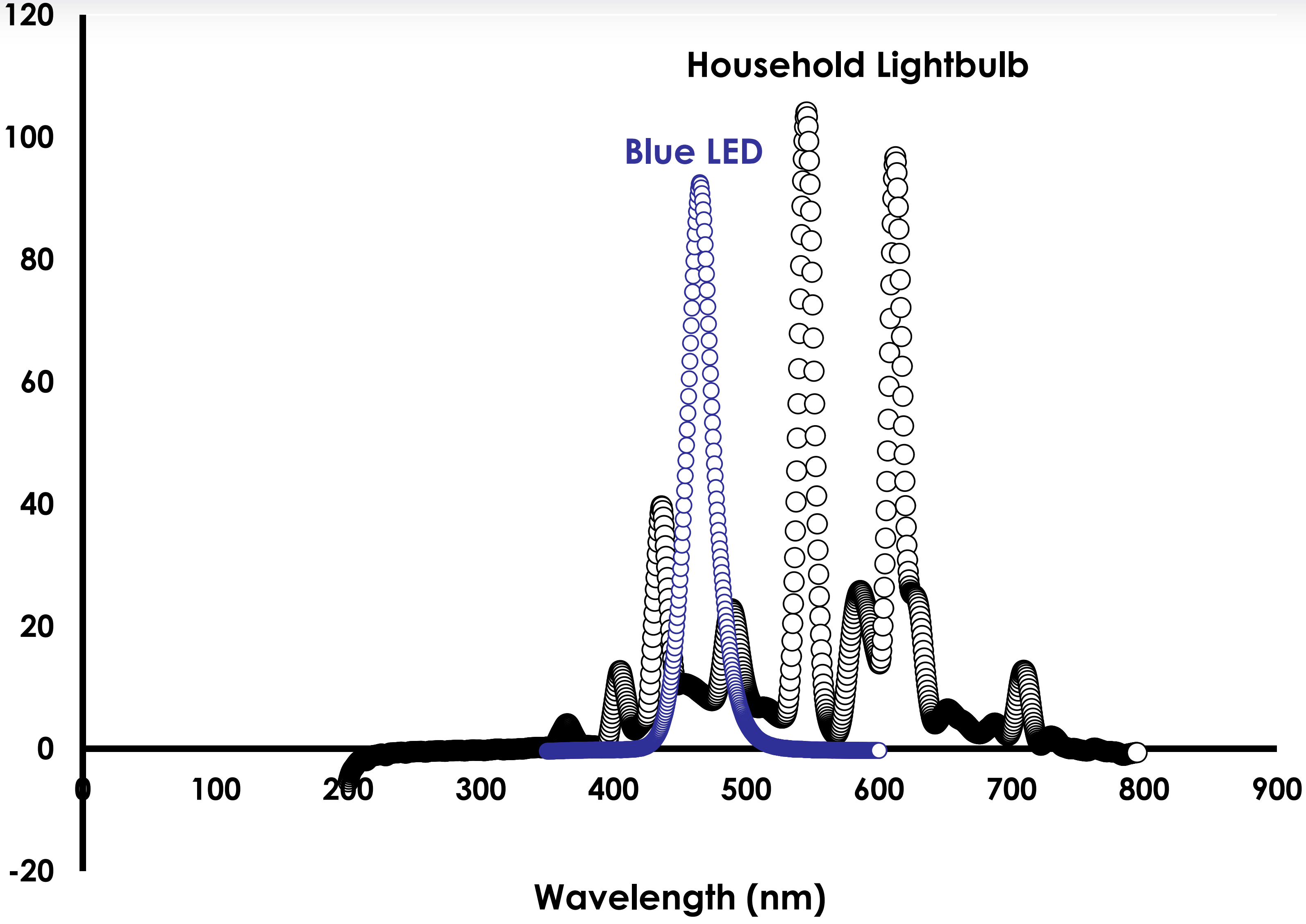
BATCH: 120 h

[5]helicene
50% (+ RSM)

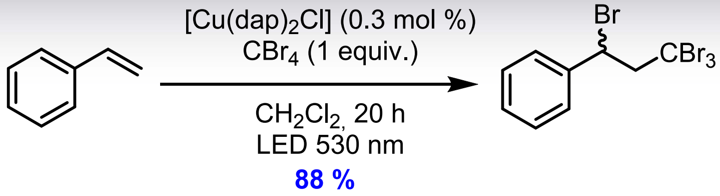
42 % (+ RSM)

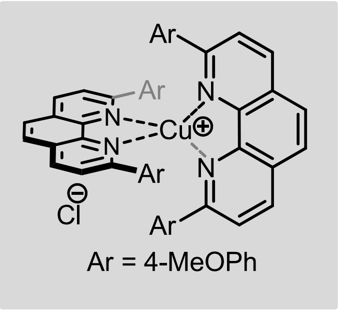
Hernandez-Perez, A. C.; Vlassova, A.; Collins, S. K. *Org. Lett.* **2012**, *14*, 2988-2991.

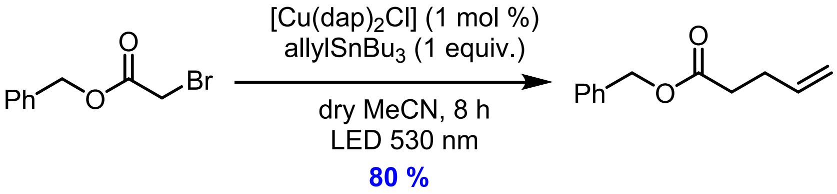
HOUSEHOLD LIGHTBULD *vs* THE LED

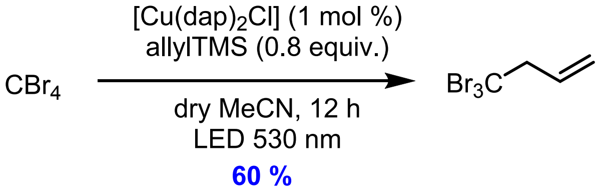


Cu-BASED SENSITIZERS FOR PHOTOREDOX REACTIONS.

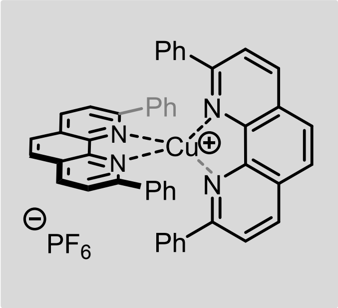


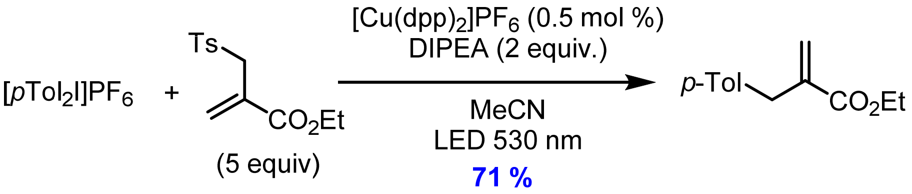






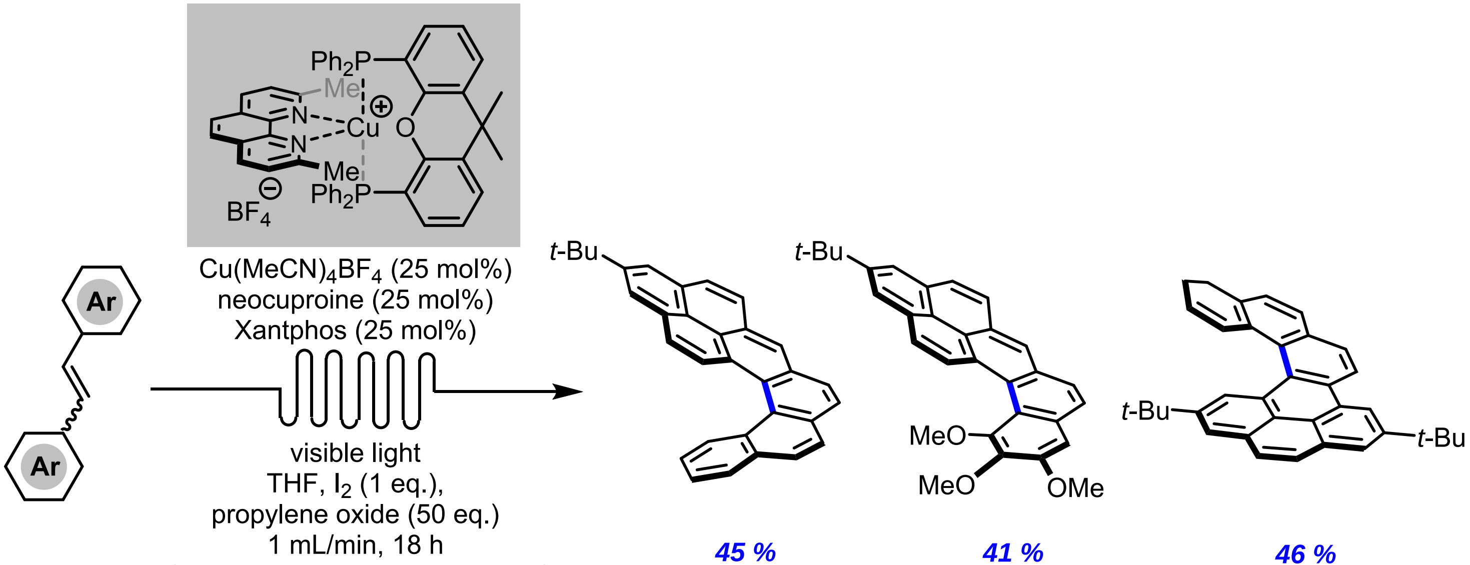
Pirtsch, M.; Paria, S.; Matsumo, Isobe, H.; T.; Reiser, O. *Chem Eur-J*. **2012**, *18*, 7336-7340.





Baralle, A.; Fensterbank, L.; Goddard, J.P.; Ollivier, C. *Chem. Eur.-J*. **2013**, *19*, 10809–10813.

PYRENE-HELICENE HYBRIDS IN CONTINUOUS FLOW



$Cu(MeCN)_4BF_4$ (25 mol%)
neocuproine (25 mol%)
Xantphos (25 mol%)

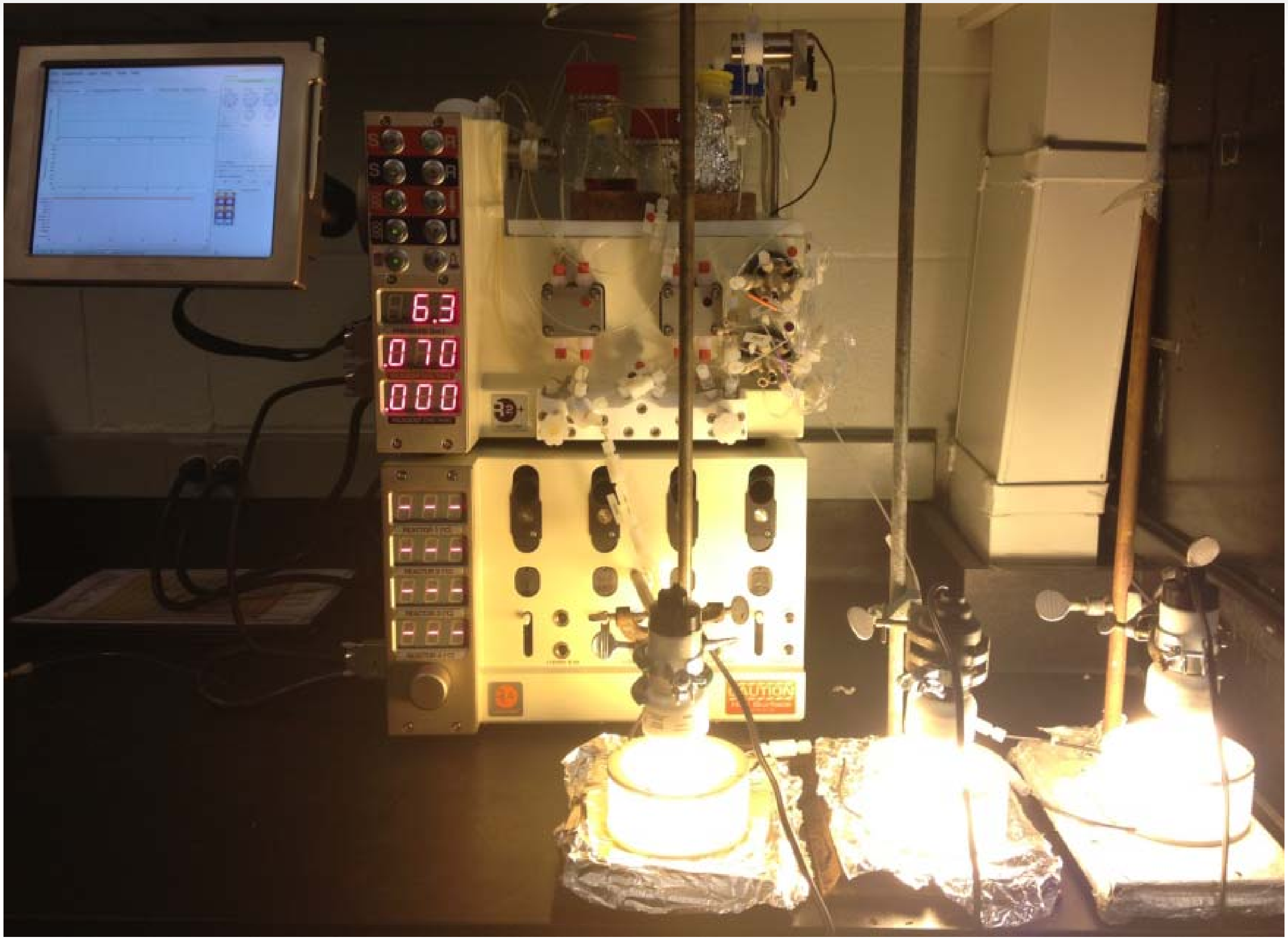
visible light
THF, I_2 (1 eq.),
propylene oxide (50 eq.)
1 mL/min, 18 h
(solution is recycled three times)

45 % **41 %** **46 %**

ALL BATCH YEILDS = 12-23 %, 120 h

Bédard, A.-C.; Vlassova, A.; Hernandez-Perez, A. C.; Bessette, A.; Hanan, G. S.; Heuft, M., Collins, S. K. *Chem. Eur J.* **2013**, *19*, 19295-19302.

PYRENE-HELICENE HYBRIDS IN CONTINUOUS FLOW



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PYRENE-HELICENE HYBRIDS IN CONTINUOUS FLOW

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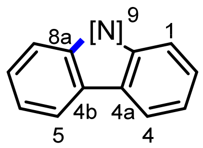
CARBAZOLE SYNTHESIS.

Oxidative C-N Formation

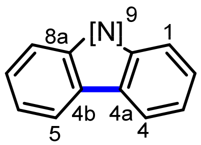


Typical Reactions Conditions:

- [N] = NAc: $Pd(OAc)_2$ (5 mol %) $Cu(OAc)_2$ (5 eq.)
- [N] = NBn: $Pd(OAc)_2$ (10 mol %) $PhI(OAc)_2$ (1 eq.)
- [N] = NSO_2tol: $Cu(OTf)_2$ (5 mol %) $PhI(OAc)_2$ (1.5 eq.)
- [N] = N_3: $Rh_2(O_2CC_3F_7)_4$ (5 mol %)

Significant recent interest
Variety of catalytic systems available
Wide substrate scope

Oxidative C-C Formation



Typical Reactions Conditions:

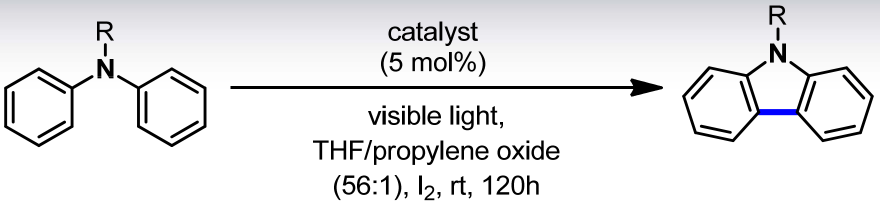
- [N] = NMe: UV-light, air
- [N] = NH: Pt/C (5 mol %), H_2O, 250°C
- [N] = NH: $Pd(OAc)_2$ (2-10 mol %) PivOH, 110 °C

Few synthetically useful protocols
High temperatures, harsh conditions
Often limited substrate scope

Goals: **Cu catalyzed photoredox catalysis (5 mol %), visible light, O_2 or I_2 (1 eq.)**

Tsang, P. W. C.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*,14560–14561. Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186. Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996–6005. Liégault, B.; Lee, D.; Huetis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022-5028.

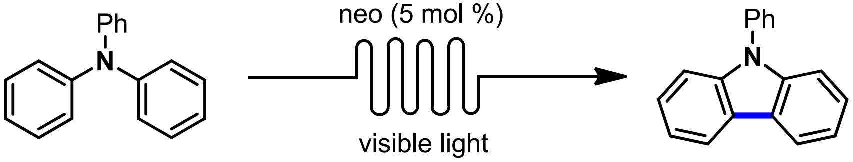
CARBAZOLE SYNTHESIS.



catalyst
(5 mol%)

visible light,
THF/propylene oxide
(56:1), I_2, rt, 120h

entry	R	catalyst		yield (%)	recovered SM (%)
1	H	$Ru(bpy)_3(PF_6)_2$		0	>99
2	H	$[Cu(XantPhos)(neo)]BF_4$		0	>99
3	Ph	$Ru(bpy)_3(PF_6)_2$		27	69
4	Ph	Eosin Y		32	63
5	**Ph**	**$[Cu(XantPhos)(neo)]BF_4$**	**in situ**	**56**	**44**
6	Ph	$[Cu(XantPhos)(neo)]BF_4$		52	34
7	Ph	$[Cu(DPEPhos)(neo)]BF_4$		14	61
8	Ph	$[Cu(XantPhos)(bpz)]BF_4$	in situ	32	40
9	Ph	$[Cu(DPEPhos)(bpz)]BF_4$	in situ	30	47

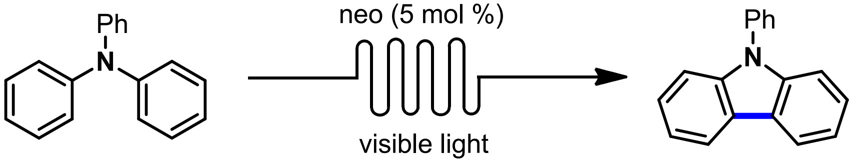


$Cu(MeCN)_4BF_4$ (5 mol %)
XantPhos (5 mol %)
neo (5 mol %)

visible light
I_2 (1 equiv)
THF/propylene oxide (56/ 1)
(0.5 mL/min, 10 h residence time)
75 %

Hernandez-Perez, A. C.; Collins, S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 12696-12700.

CARBAZOLES: CONTINUOUS FLOW SYNTHESIS

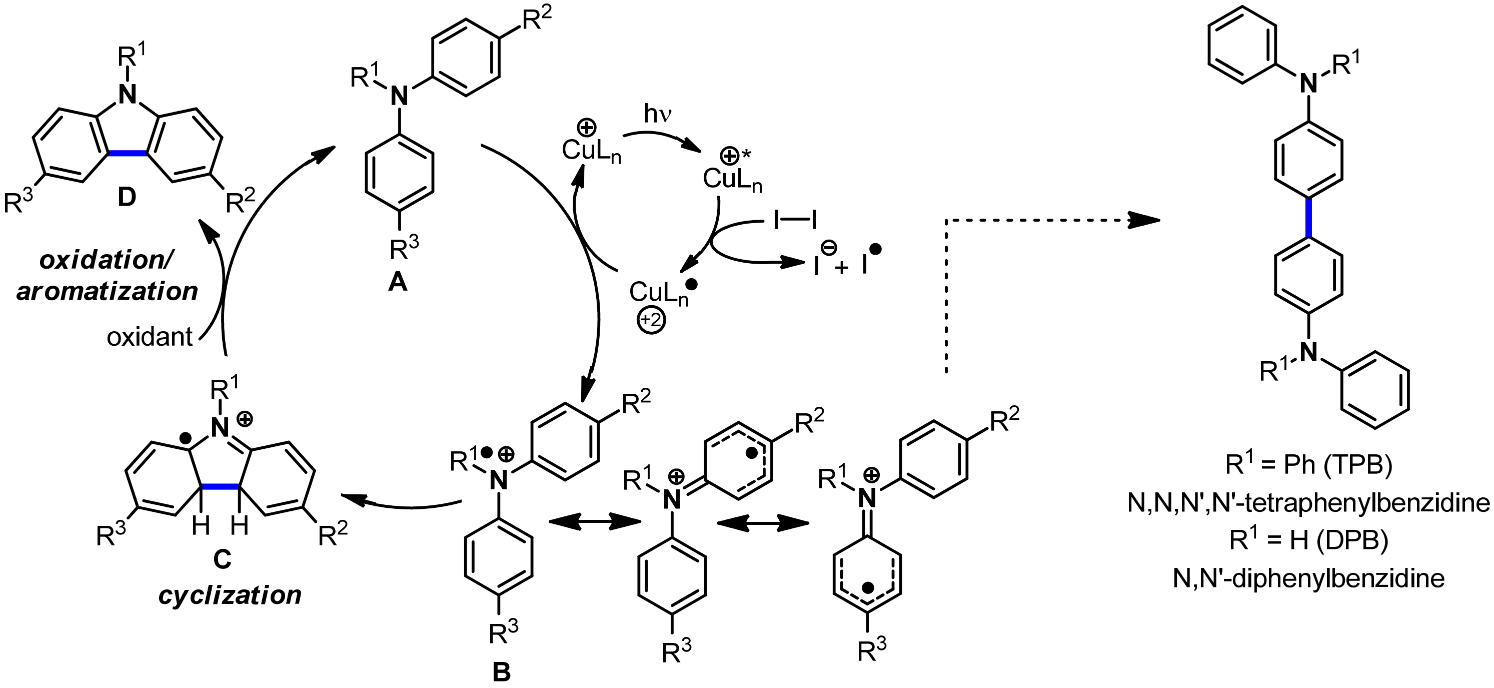


$Cu(MeCN)_4BF_4$ (5 mol %)
XantPhos (5 mol %)
neo (5 mol %)

visible light
I_2 (1 equiv)
propylene oxide (50 equiv)
THF, 10 h residence time, rt

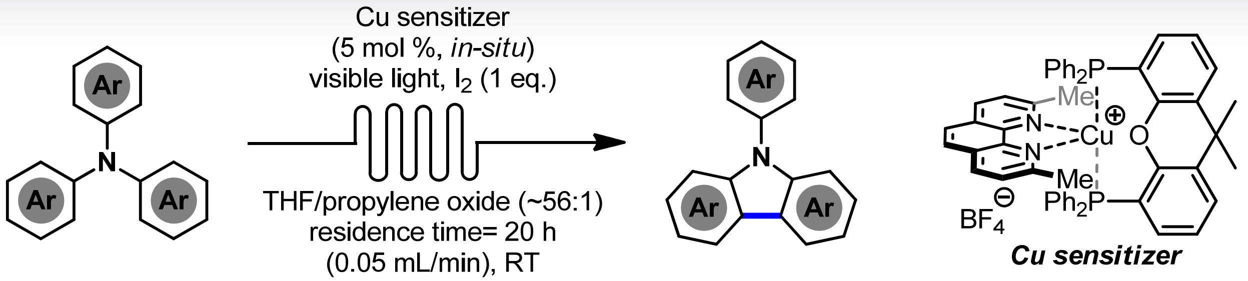
	Entry	Conditions	Yield (%)	Rec SM (%)
	1	No change	75	0
	2	No light	0	94
	3	O_2 (1 atm)	55	3
	4	$MV(PF_6)_2/O_2$ (1 atm)	17	61
$Ru(bpy)_3Cl_2$ (5 mol %) visible light I_2 (1 equiv) propylene oxide (50 equiv) THF, 10 h residence time, rt	5	No change	53	14
	6	O_2 (1 atm)	16	27
	7	$MV(PF_6)_2/O_2$ (1 atm)	22	21

CARBAZOLES: POSSIBLE MECHANISM

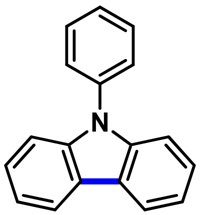


R^1 = Ph (TPB)
N,N,N',N'-tetraphenylbenzidine
R^1 = H (DPB)
N,N'-diphenylbenzidine

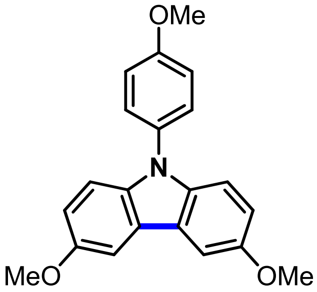
CARBAZOLES: CONTINUOUS FLOW SYNTHESIS



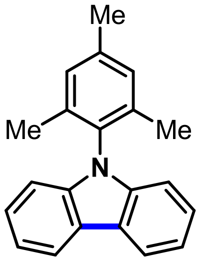
Cu sensitizer



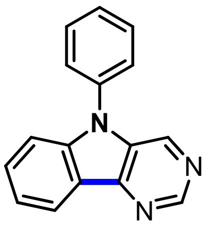
75 % (10 h)



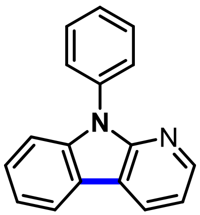
55 %



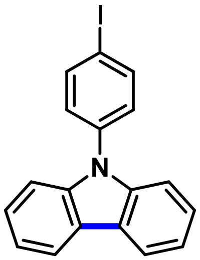
95 %



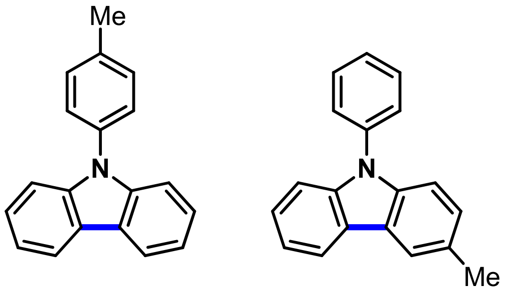
60 %



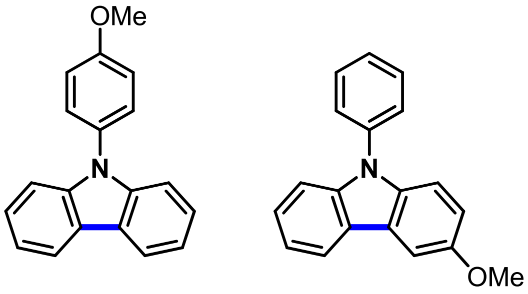
55 %



50 %

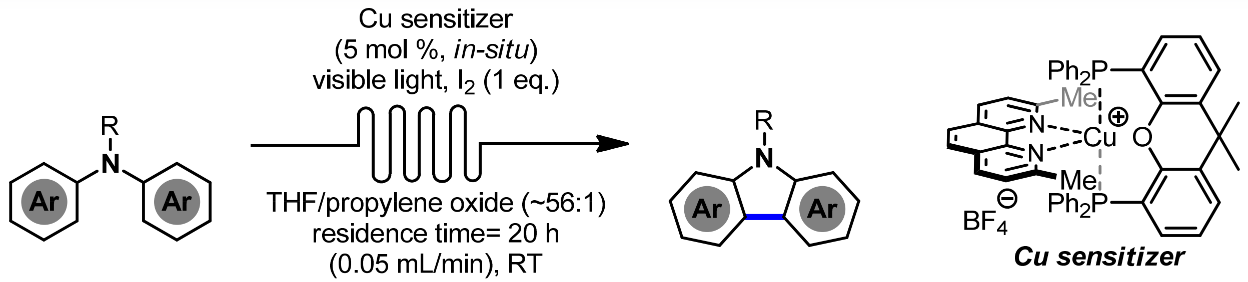


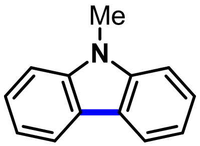
70 % (7:1)



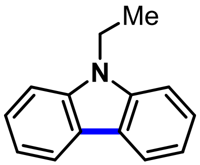
70 % (9:1)

N-ALKYL CARBAZOLES: CONTINUOUS FLOW SYNTHESIS

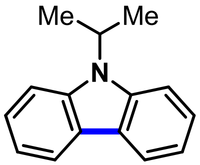




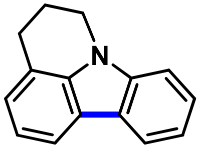
66 %



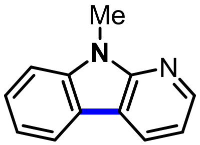
79 %



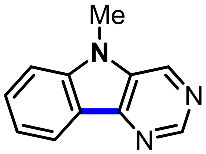
65 %



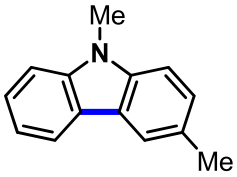
64 %



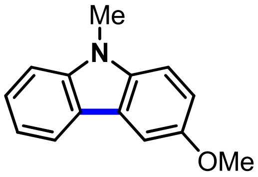
51 %



53 %



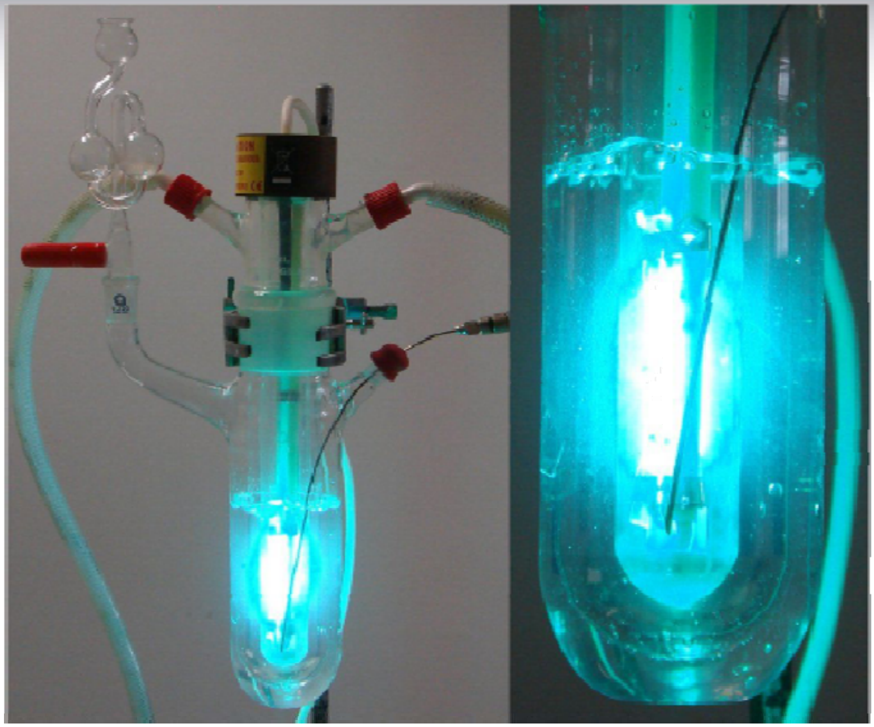
60 %



63 %

- **No dealkylated products observed**

UV LIGHT SYNTHESIS



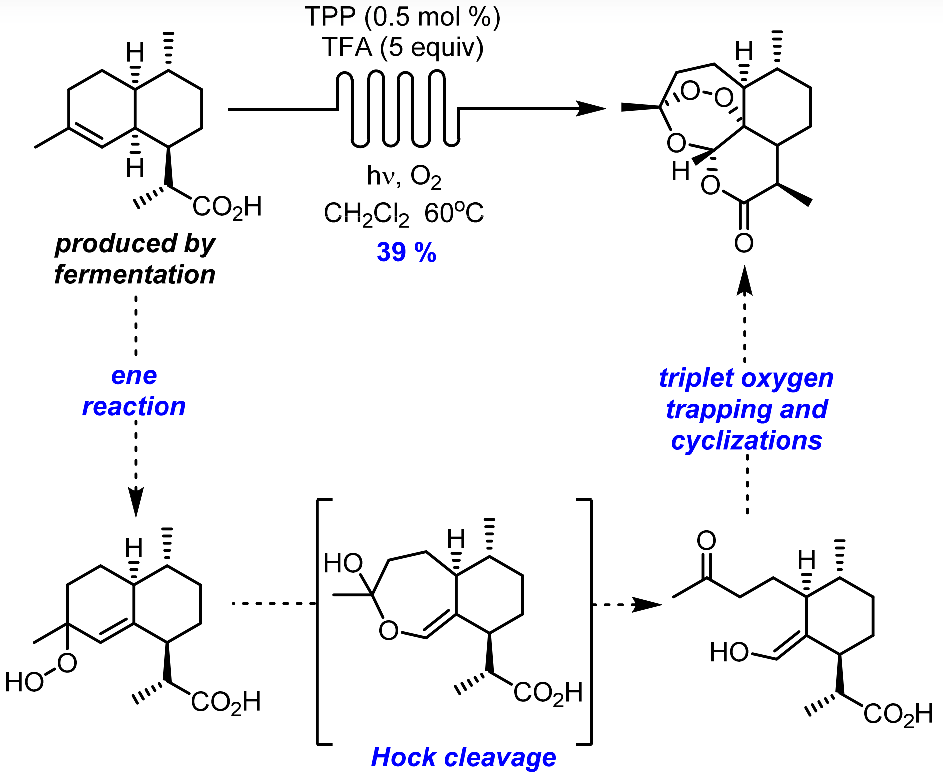
Low pressure: Everyday fluorescent lamps, 6 to 300 W, large (1–2 metres in length) and not suited to general laboratory use. Emit the bulk (90%) at 254 nm (UVC, suited to carbonyl, arene and halogenation photochemistry)

Medium pressure: Industrial lamps, 125 W to 60 kW lamps, powerful UV output in the 300–370 nm region. Strong emissions in the IR region (high operating temperatures). Used for general-purpose photochemistry with chromophores absorbing strongly in the 290–400 nm region.

Medium pressure lamps use quartz glassware (essentially transparent from 200 nm to Visible); Pyrex >300 nm.

Knowles, J. P.; Elliott , L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.

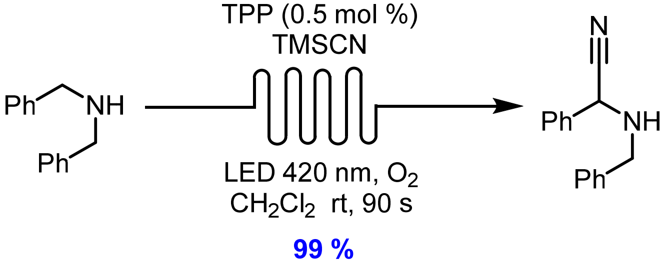
UV LIGHT SYNTHESIS



“Based on this result, we calculate that this particular set-up could produce 200 g of artemisinin per day. Estimating that roughly 225 million doses (number of cases of malaria estimated by the WHO; in 2009 the number of ACT treatment courses procured was 158 million) of the anti- malarial medication are needed per year, approximately 1500 efficient, simple, and productive photoreactors could meet this demand.”

Lévesque, F.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706 –1709

UV LIGHT SYNTHESIS



Ushakov, D. B.; Gilmore, K.; Kopetzki, D.; McQuade, D. T.; Seeberger, P. H. *Angew. Chem., Int. Ed*. **2014**, *53*, 557 –561

UV-150

Multiple gram / hour scale-up

High intensity UV light source

User selectable UV power

Light source wavelength filtering

Temperature control -5°C to 80°C

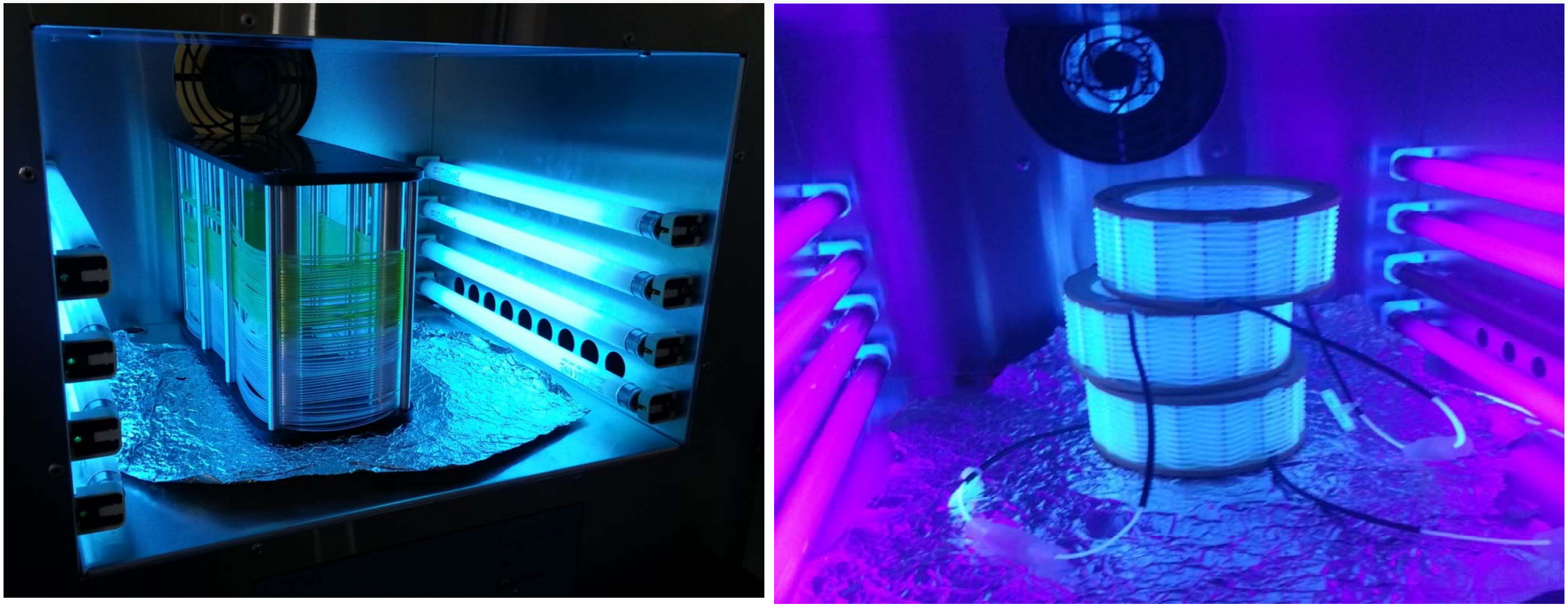
Easily changed reactors

Space saving compact design

Interlocks ensure safe operation

Optional spectrometer for real time monitoring of transmission spectra

UV LIGHT CONTINUOUS FLOW SYNTHESIS

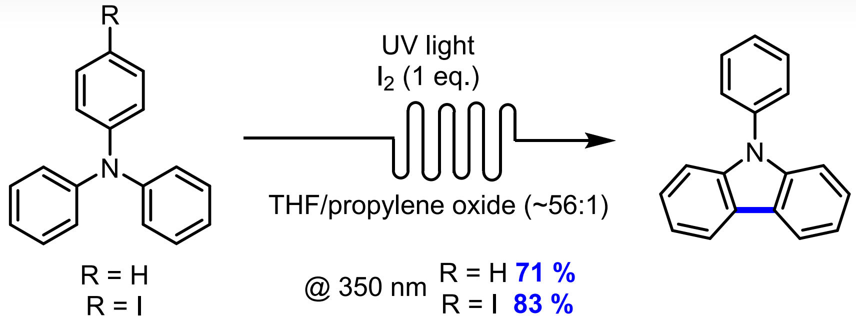


UV reactor/continuous flow set-up assembled from commercially available flow modules (Vapourtec/Uniqsis) and photoreactors (Luzchem LZC-5)

Allows large reactor volumes and modular control of the UV wavelength of irradiation.

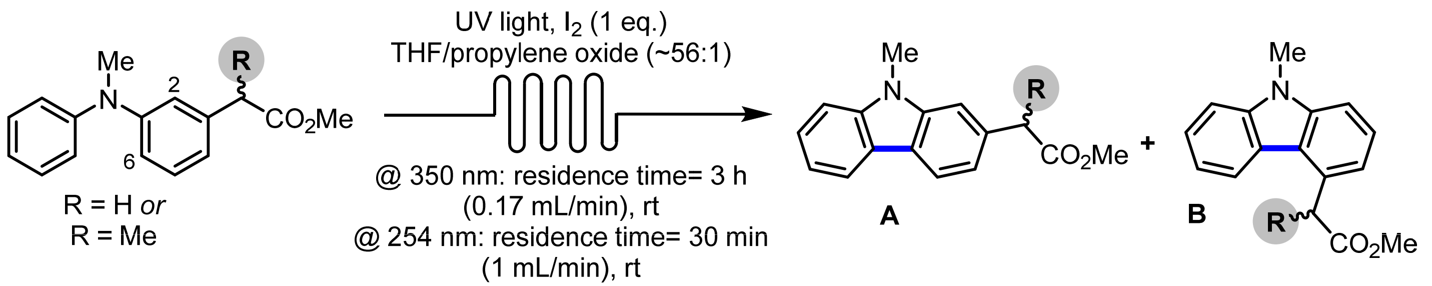
Caron, A.; Hernandez-Perez, A. C.; Collins, S. K.*Org. Process Res. Dev.*, **2014**, *18*, 1571–1574.

UV LIGHT CONTINUOUS FLOW SYNTHESIS



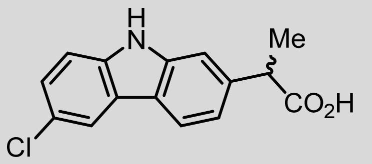
@ 350 nm R = H **71 %**
R = I **83 %**
residence time= 3 h
(0.17 mL/min), rt

@ 254 nm R = H **93 %**
residence time= 30 min
(1 mL/min), rt



@ 350 nm: residence time= 3 h
(0.17 mL/min), rt
@ 254 nm: residence time= 30 min
(1 mL/min), rt

For R = Me	@ 350 nm (1 : 2, **A : B**) ***80 %***	@ 254 nm (1 : 1.35, **A : B**) ***not determined***
For R = H	@ 350 nm (1 : 2.8, **A : B**) ***81 %***	@ 254 nm (1 : 2.3, **A : B**) ***70 %*** (30 min)



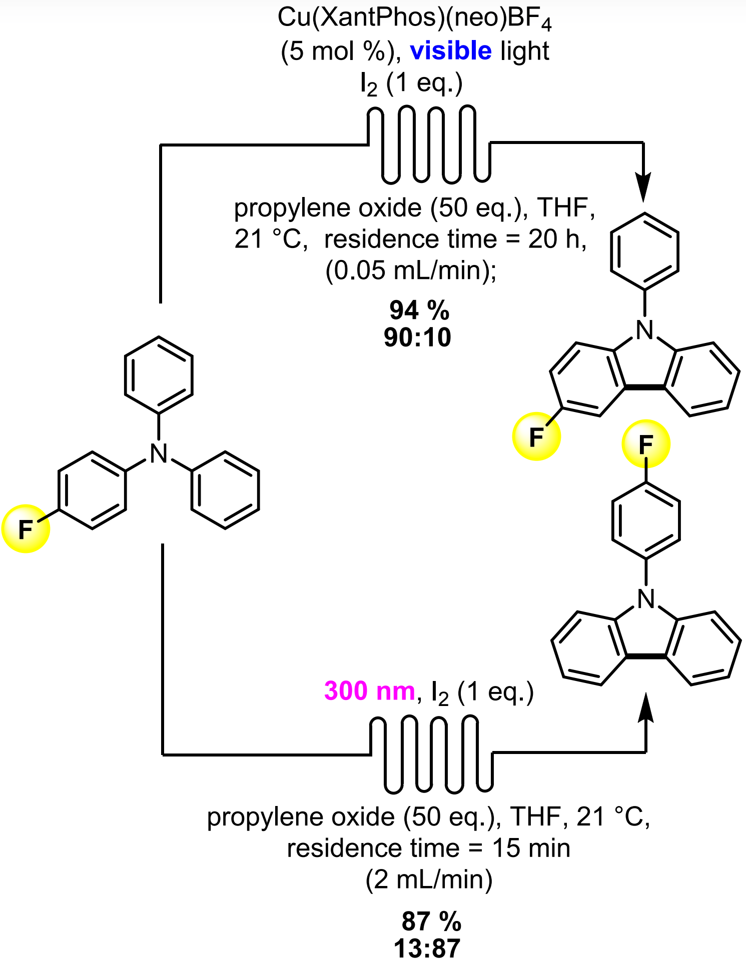
carprofen

Non-steroidal anti-inflammatroy drug
Veternarian use only
COX-2 inhibitor

Caron, A.; Hernandez-Perez, A. C.; Collins, S. K.*Org. Process Res. Dev.*, **2014**, *18*, 1571–1574.

UV LIGHT CONTINUOUS FLOW SYNTHESIS

Vapourtec R2+ Reactor



Cu(XantPhos)(neo)BF_4
(5 mol %), **visible** light
I_2 (1 eq.)

propylene oxide (50 eq.), THF,
21 °C, residence time = 20 h,
(0.05 mL/min);

94 %
90:10

300 nm, I_2 (1 eq.)

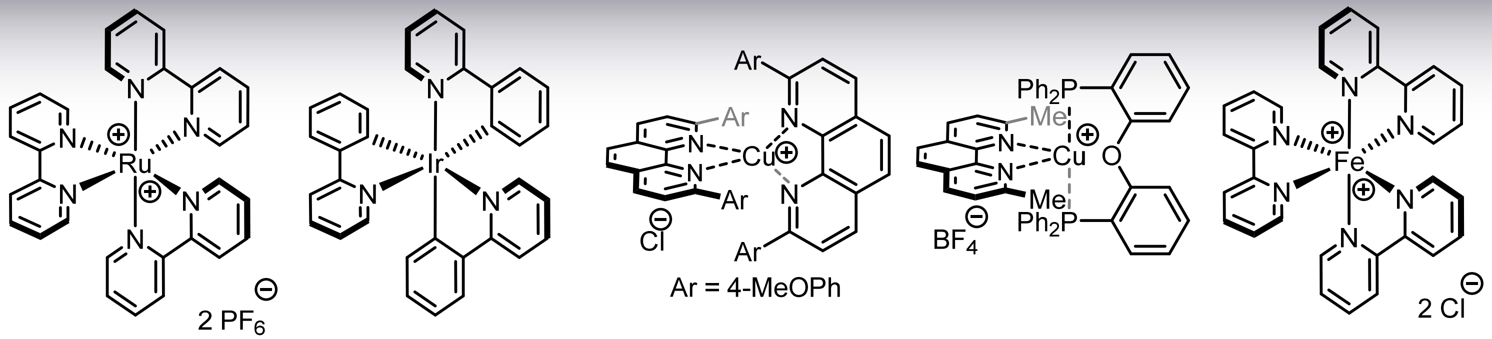
propylene oxide (50 eq.), THF, 21 °C,
residence time = 15 min
(2 mL/min)

87 %
13:87

(Vapourtec/Uniqsis) + photo-reactors (Luzchem LZC-5)

Hernandez-Perez, A. C.; Collins, S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 12696-12700.
Hernandez-Perez, A. C.; Caron, A.; Collins, S. K. *Chem Eur-J.* **2015**, *In Press.*
Caron, A.; Hernandez-Perez, A. C.; Collins, S. K. *Org. Process Res. Dev.* **2014**, *18*, 1571–1574.

Fe-BASED SENSITIZERS FOR PHOTOREDOX REACTIONS ???



$E_{1/2}$ (M*/M$^+$) =	-0.81 V	-1.73 V	-1.43 V	-1.35 V*	-1.54 V*
Excited state lifetime =	1100 ns	1900 ns	270 ns	14300 ns	0.80 ns

---

In general oxidation-reductions of *FeL$_3^{2+}$ are expected to be slow. Due to short excited state lifetimes, photoinduced electron transfer is expected only when the electron acceptor is highly reactive and present in high concentration.

Creutz, C.; Chou, M,; Netzel, T. L.; Okumura, M.; Sutin, N. *J. Am. Chem. Soc.* **1980**,*102*, 1309-1319.

Polymer nanocapsules encapsulating Fe(bpy)$_3^{+2}$ for visible light-induced photosensitized decomposition of organic pollutants (production of hydroxyl radicals)

Shiraishi , Y.;Manabe, K.; Hirai, T. *Appl Catal B: Environ* **2010**, *93*, 292–298.

Photodegradation of dyes. Production of [Fe(IV)=O] species.

Rakibuddin, S. G., Rajakumar A. *Catal. Commun*. **2015**, *58*, 53–58.

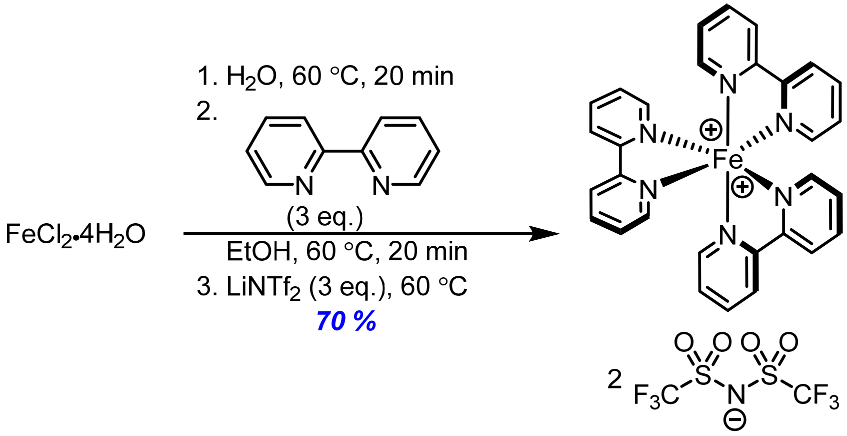
Electron rich Fe-complexes that are theoretically capable of electron transfer:
Pyridyl-Carbene Iron Complexes

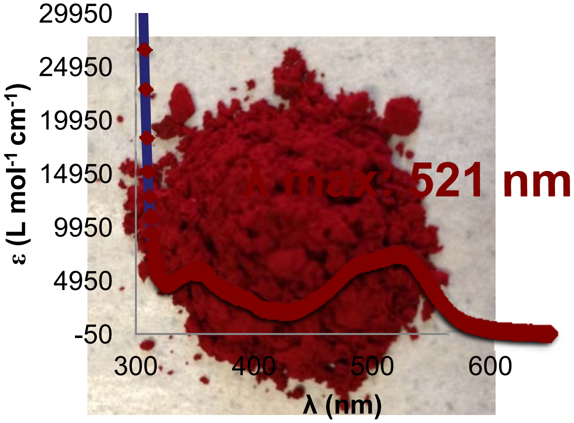
Duchanois, T.; Etienne, T.; Beley, M.; Assfeld, X.; Perpète, E. A.; Monari, A.; Gros, P. C. *Eur. J. Inorg. Chem.* **2014**, 3747–3753

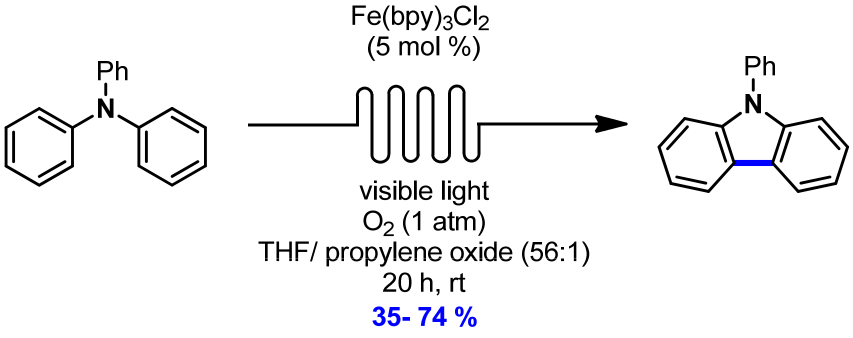
Cyclometalated Iron Complexes as Sensitizers

Mukherjee, S.; David N. Bowman, D. N.; Jakubikova, E. *Inorg. Chem*. **2015**, *54*, 560−569

PRELIMINARY Fe INVESTIGATIONS





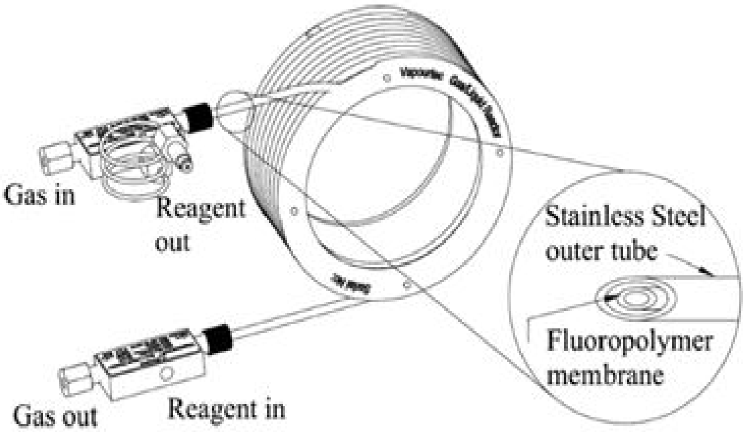


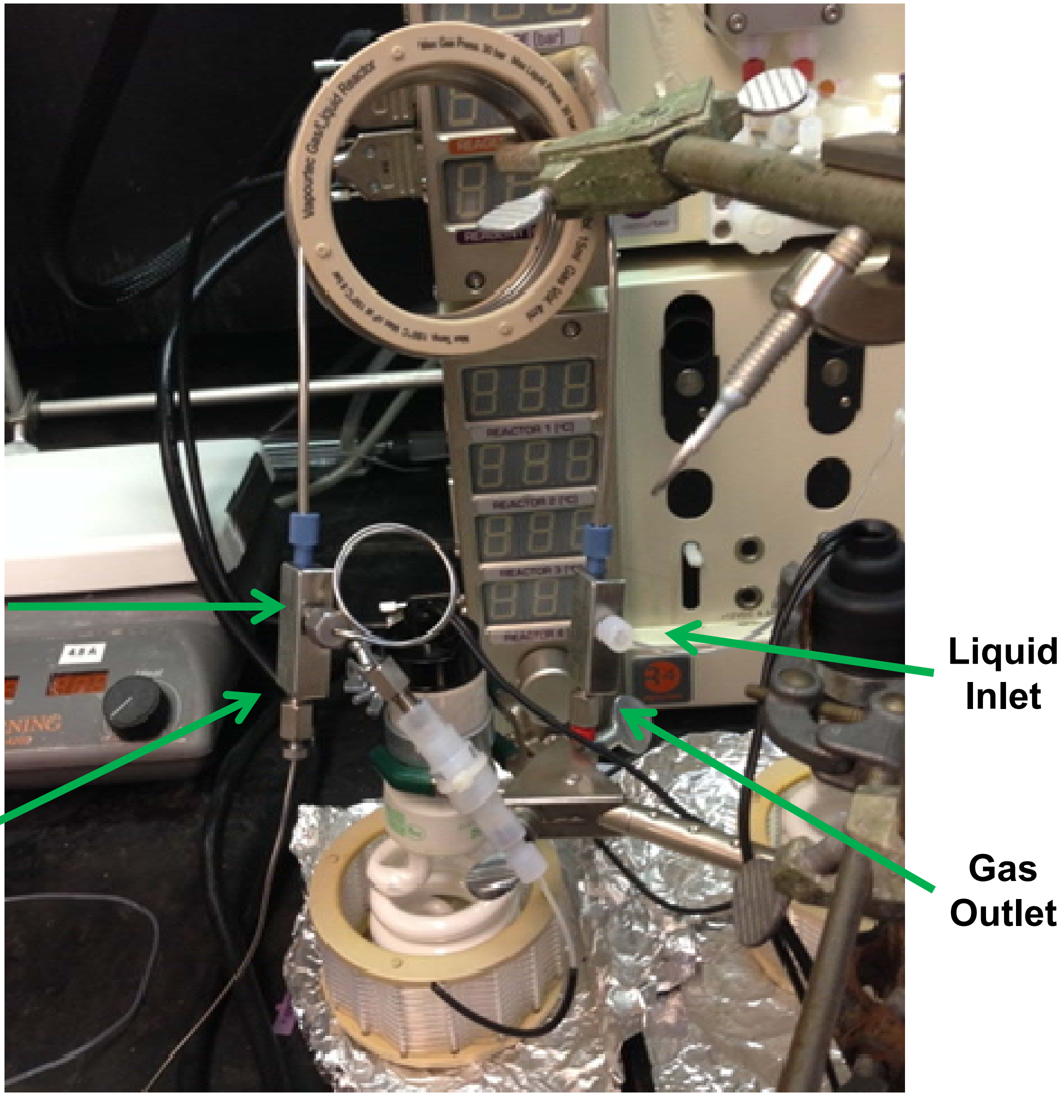
- **Initial Fe catalysts not very soluble. O_2 saturation unreliable.**

TUBE-IN-TUBE REACTORS

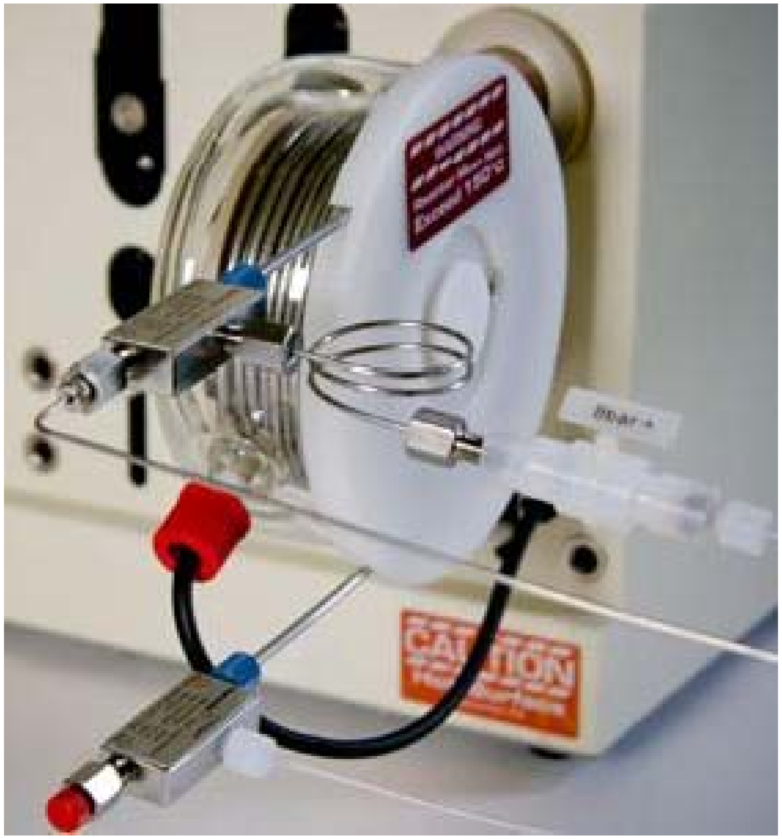
Liquid-gas reactor in continuous-flow:

- Initially developed by Ley and co-workers
- Gas diffuses to liquid via a porous membrane





TUBE-IN-TUBE REACTORS



NH_3: Cranwell, P. B.; O'Brien, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Pena-Lopez, M.; Ley, S. V. *Org. Biomol. Chem*. **2012**,*10*, 5774-5779

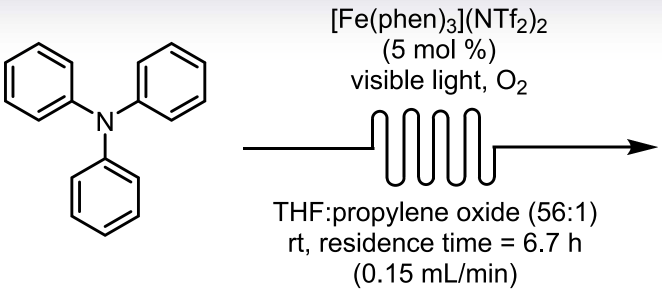
H_2: Newton, S.; Ley, S. V.; Casas Arcé, E.; Grainger, D. M. *Adv. Synth. Catal.* **2012,** *354*,1805–1812

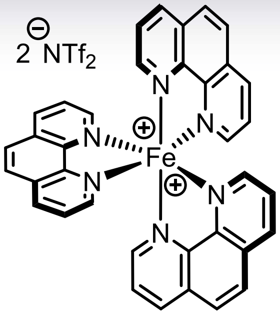
CH_2N_2: Mastronardi, F.; Gutmann, B.; Kappe, C. O. *Org. Lett.* **2013**, *15*, 5590–5593

O_2: Ley, S. V. et al. *ChemSusChem*, **2012**, *5*, 274–277

CO: Gross, U.; Koos,P.; O'Brien, M.; Polyzos, A.; Ley, S. V. *Eur. J. Org. Chem*. **2014**, 6418–6430

$Fe(Phen)_3(NTf_2))_2$

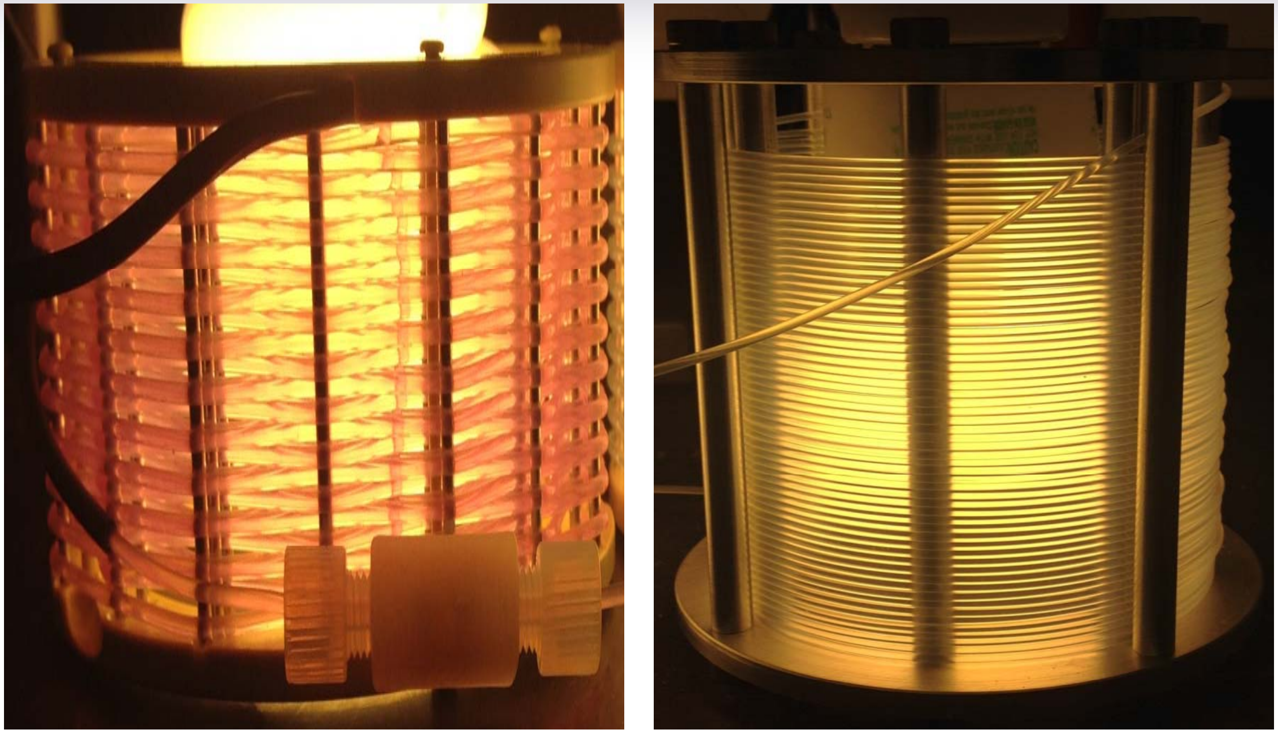


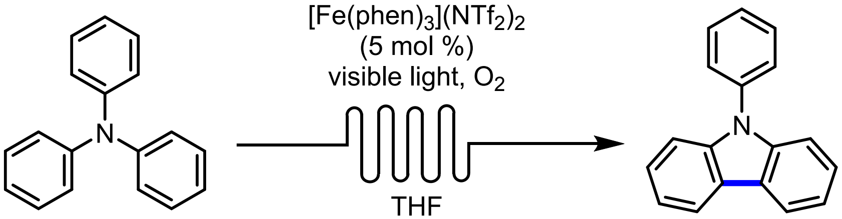


Conditions	Yield (%)	RSM (%)
-	74	0
no light; 72 h	0	90
6.7 h; reflux	0	80
No Fe	13	65
No propylene oxide	91	0

- Ru, Ir and Cu-based sensitizers all gave inferior yields
- BATCH: 80 % recovered starting material, no desired product
  DARK: 90 % recovered starting material, no desired product

REACTOR ENGINEERING ?





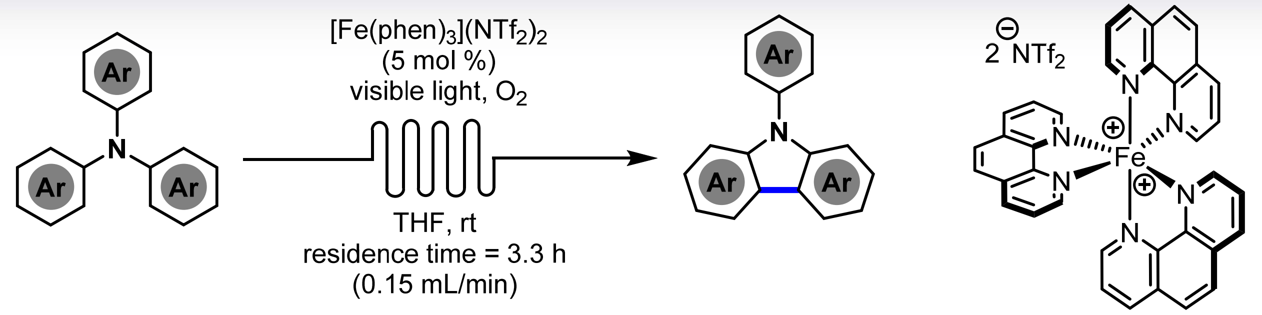
$[Fe(phen)_3](NTf_2)_2$
(5 mol %)
visible light, O_2

THF

New Coil: residence time= 3.33h,
91 %

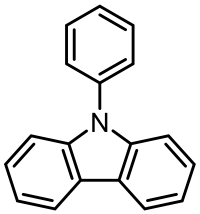
Vapourtec: residence time = 6.7 h,
95 %

CARBAZOLES: USING Fe-BASED CATALYSTS

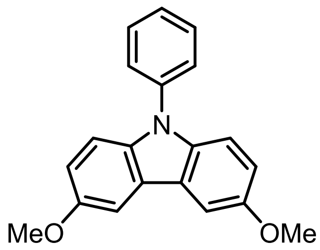


[Fe(phen)$_3$](NTf$_2$)$_2$
(5 mol %)
visible light, O$_2$

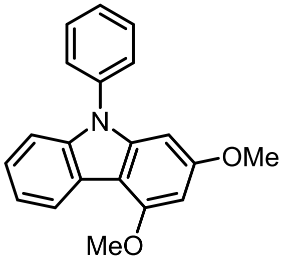
THF, rt
residence time = 3.3 h
(0.15 mL/min)



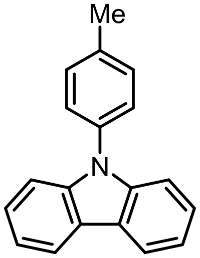
90 %



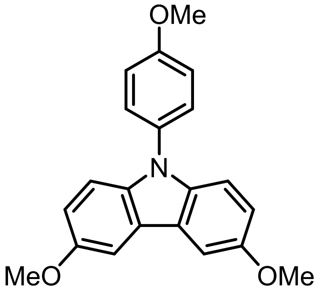
50 %
exo*:*endo
1:1



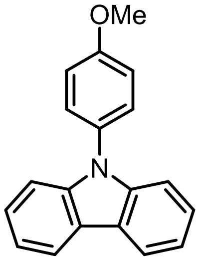
55 %
exo*:*endo
1:2



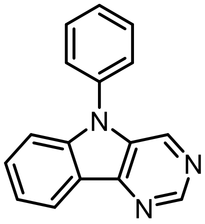
75 %
***exo*:*endo* 2:1**
14 % RSM
(Cu 70 %, 7:1)



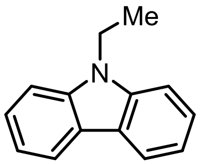
63 %
(Cu 54 %)



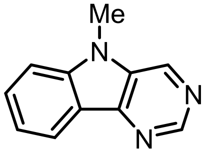
85 %
***exo*:*endo* 11:89**
14 % RSM
(Cu 70 %, 90:10)



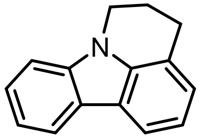
91 %
(Cu 53 %)



80 %
(Cu 79 %)



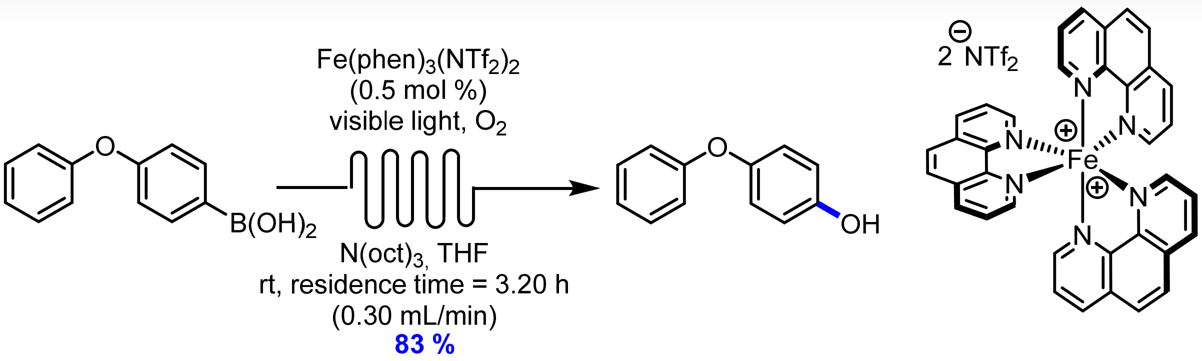
80 %
(Cu 53 %)



67 %
(Cu 64 %)

Parisien-Collette, S.; Hernandez-Perez, A. C.; Collins, S. K. *Unpublished Work.*

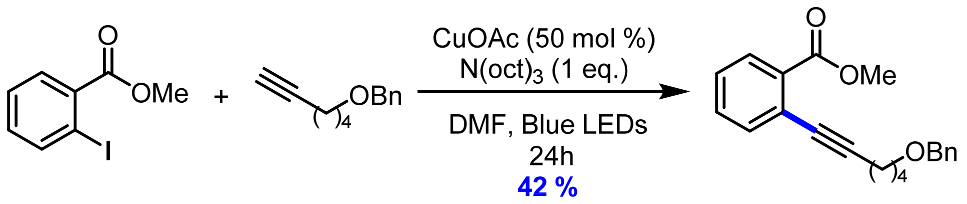
Fe-BASED CATALYSTS: OXIDATION REACTIONS



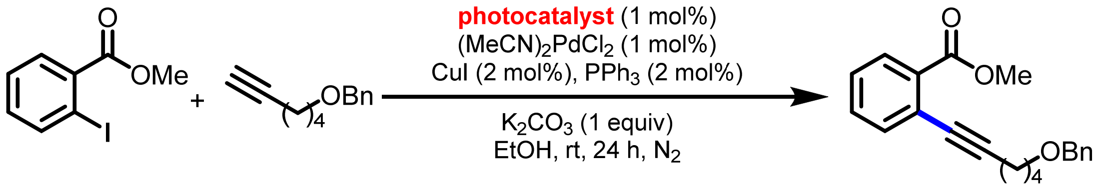
For conversion of phenylboronic acid: Ru(bpy)$_3$Cl$_2$: 58 %, methylene blue 94 % (1 mol %, DIPEA (5 eq.), 355 nm, MeCN:H$_2$O (4:1), 7 h

Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *J. Am. Chem. Soc*. **2013**,*135*, 13286-13289.

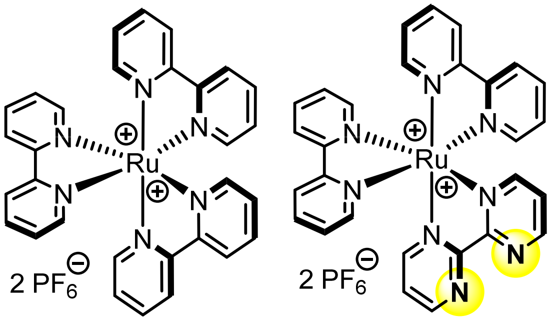
FUTURE WORK: PHOTOCATALYTIC CROSS COUPLING



- Inorganic bases afford heterogenous mixtures
- Highly insoluble Cu(I)OAc
- Existing photochemical Sonogashira:
- Limited substrate scope and scalability



None



Visible light: **14%**
No light: 12 %

Visible light: **28 %**
No light: 11 %

Visible light: **86 %**
No light: 0 %

Santandrea, J.; Minozzi, C.; Collins, S. K. *Unpublished Results…*

SUMMARY

- Developed copper-based sensitizers can promote the synthesis of C_{aryl}-C_{aryl} bonds.
- Pyrene/helicene hybrids have been prepared via a visible light photoredox cyclization employing copper-based photoredox catalyst and continuous flow techniques.
- New synthesis of carbazoles from both triaryl and diaryl amines using a copper-based sensitizer (operationally simple).
- Continuous flow synthesis significantly accelerates the reactions and reduces the reaction time

FUTUREAPPLICATIONS ?

- Photochemical transformations have significant potential to simplify multistep flow synthesis by limiting downstream complications.
- Commercial systems to help chemists replicate results are not available or still in their infancy.
- Heterogeneous photochemistry (at least in academic settings) is still challenging, but has significant "green" impact

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