ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Visible-Light Photocatalysis Induced C–H Functionalization for Heterocycle Synthesis

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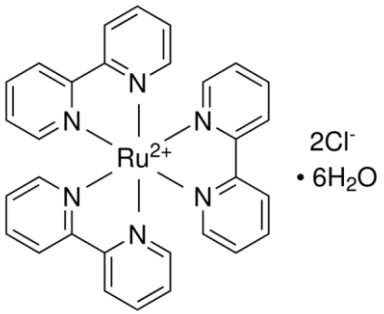
Introduction

- Heterocyclic compounds are known to occur in a wide range of biologically active compounds, including both natural products and pharmaceutical compounds.

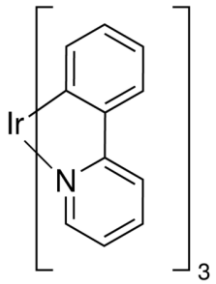
- Over the last decade, efficient heterocycle synthesis via C–H functionalization has attracted increasing attention from organic chemists, yielding materials used in applications in both medicinal and process chemistry.

- Due to its energy-conservant and environmentally friendly features, visible-light-induced photoredox catalysis has undergone rapid development over the past decade. Recently, the use of visible-light-induced photocatalytic C–H functionalization for the construction of heterocyclic systems has emerged as growing fields in synthetic organic chemistry.

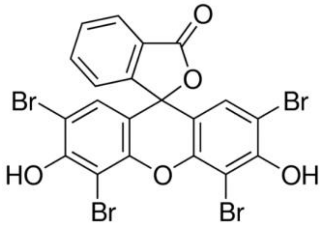
- The most commonly employed visible-light photocatalysts (PCs) are the polypyridyl complexes of ruthenium and iridium, such as $Ru(bpy)_3Cl_2$, (bpy: 2,2′-bipyridine) *fac*-$Ir(ppy)_3$, (ppy: 2-phenylpyridine) and organic dyes (i.e., Eosin Y and Rose Bengal).



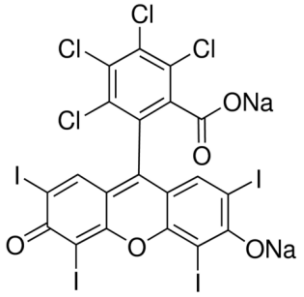
$Ru(bpy)_3Cl_2 \cdot 6H_2O$



fac-$Ir(ppy)_3$



Eosin Y



Rose Bengal

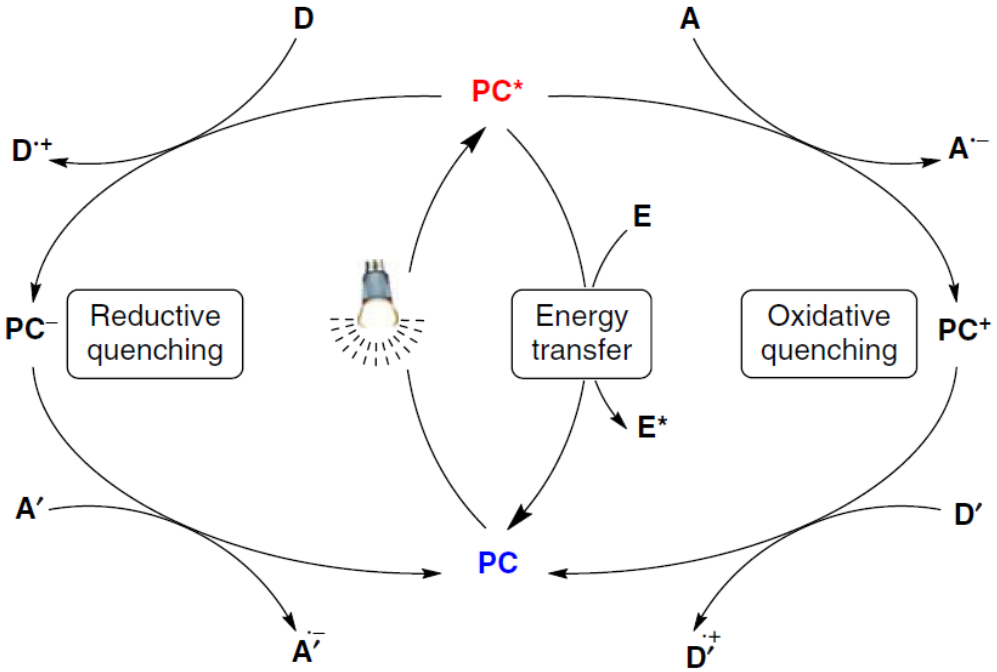
Introduction

- Three distinctive pathways, namely, reductive quenching, oxidative quenching, and energy transfer, are frequently used to describe photocatalytic mechanisms enabled by visible light.

- Reductive quenching requires the reductive quencher, such as a tertiary amine, to reduce the photoexcited catalyst to its low-valence state.

- In oxidative quenching, an oxidative quencher, such as alkyl halide, oxidizes the catalyst in the photoexcited state, yielding a high-valence state.

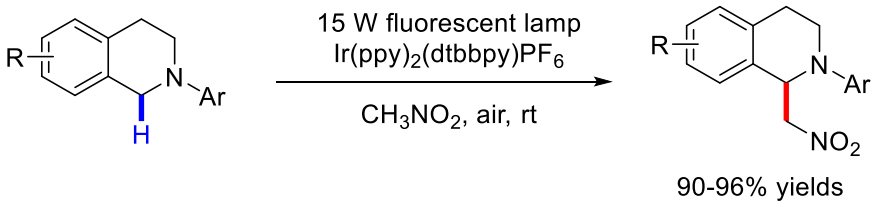
- When the energy of the photoexcited catalyst is similar to the triplet energy of the substrate, energy transfer from PC* to the substrate may occur, undergoing additional organic transformations.

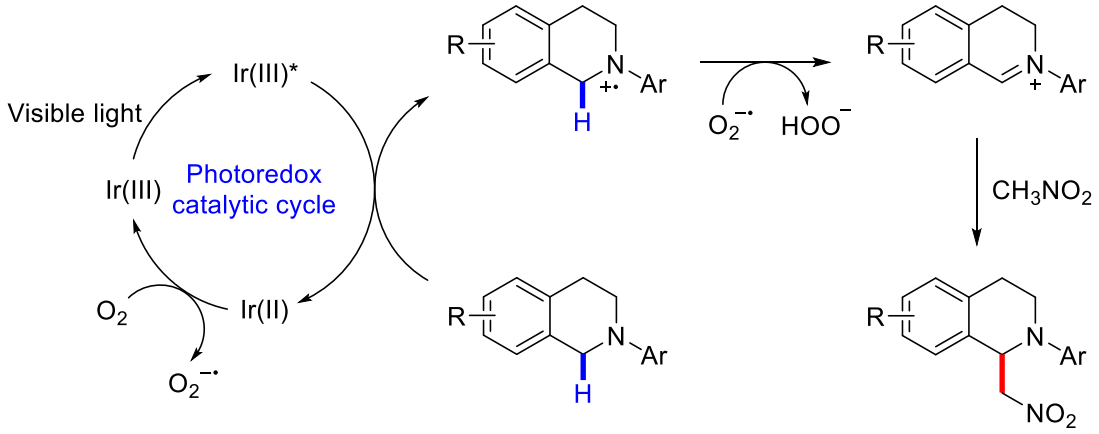


PC: photocatalyst; **D, D'**: electron donor; **A, A′**: electron acceptor

Photocatalytic sp^3 C–H Functionalization

Stephenson's work (2010): visible-light-induced α-amino C–H functionalization of tetrahydroisoquinoline



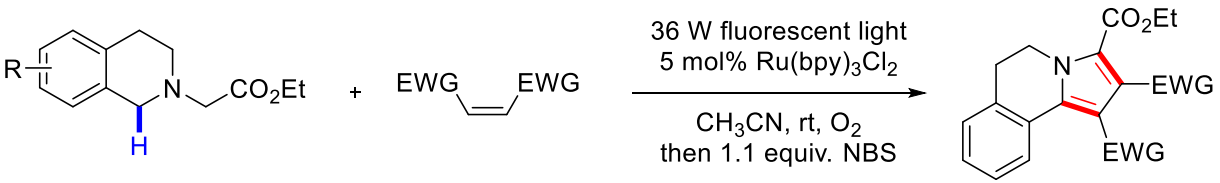


Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.

Photocatalytic sp^3 C–H Functionalization

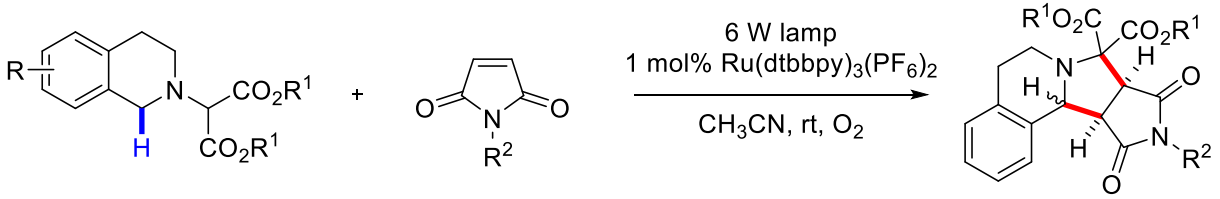
I. Trapping of iminium ion intermediates

Xiao's work (2011): synthesis of pyrrolo[2,1-*a*]isoquinolines from tetrahydroisoquinoline



51-94% yields

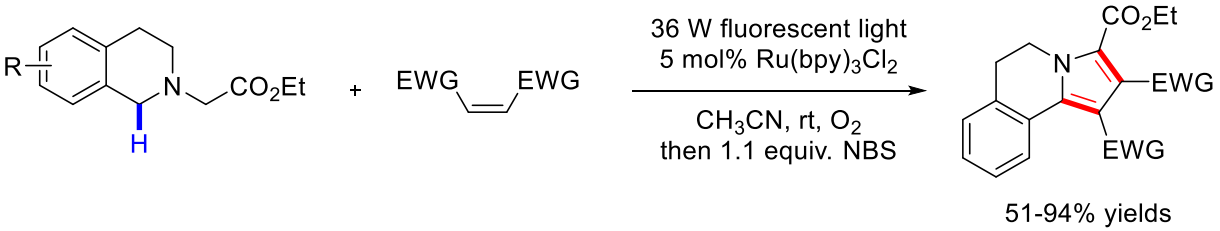
Rueping's work (2011)

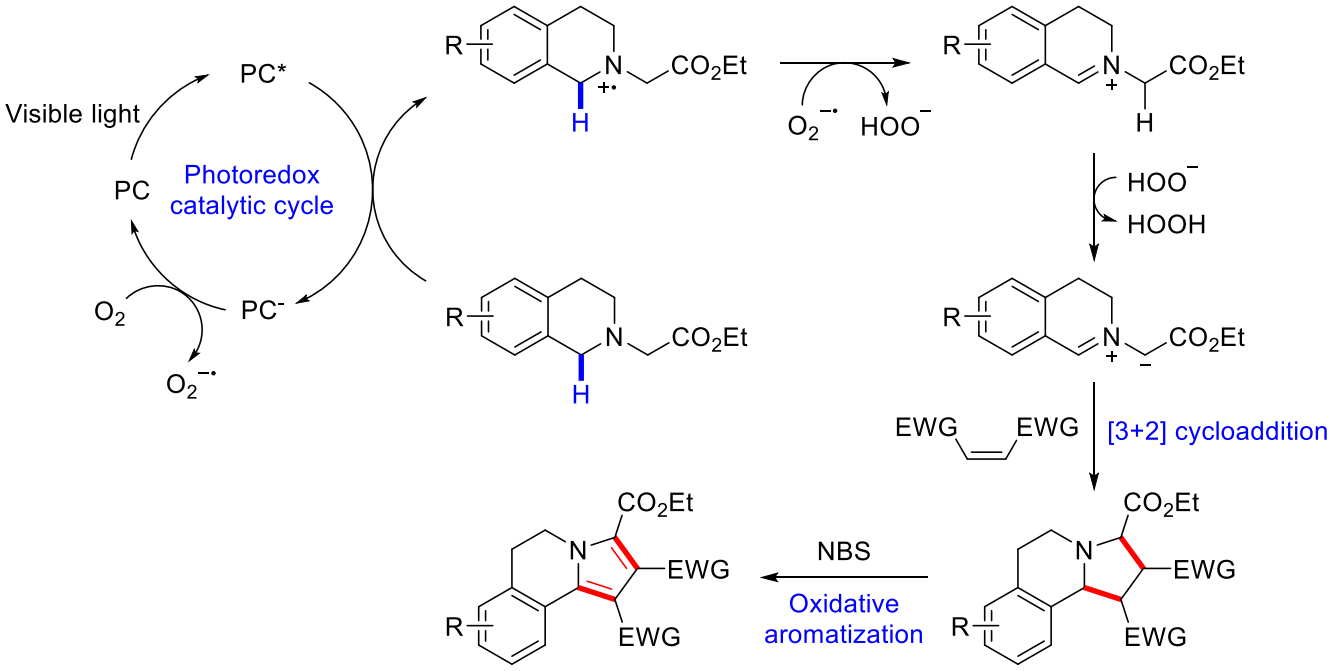


56-67% yields
3:1-5:1 dr

Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 7171–7175.
Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615–9617.

Xiao's work (2011)



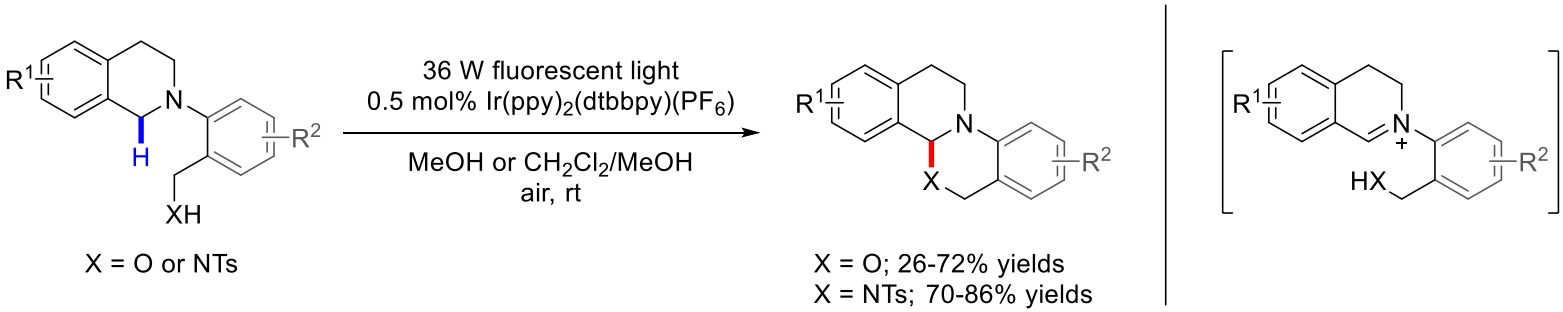


Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Chen, J.-R.; and Xiao, W.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 7171–7175.

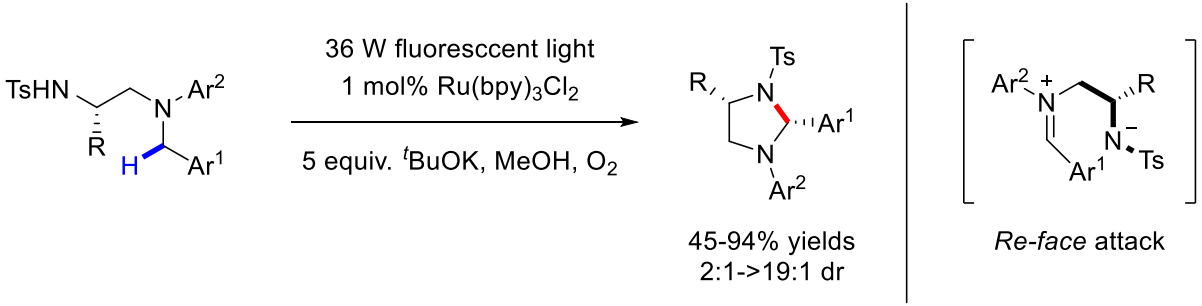
Photocatalytic sp^3 C–H Functionalization

I. Trapping of iminium ion intermediates

Xiao's work (2012)

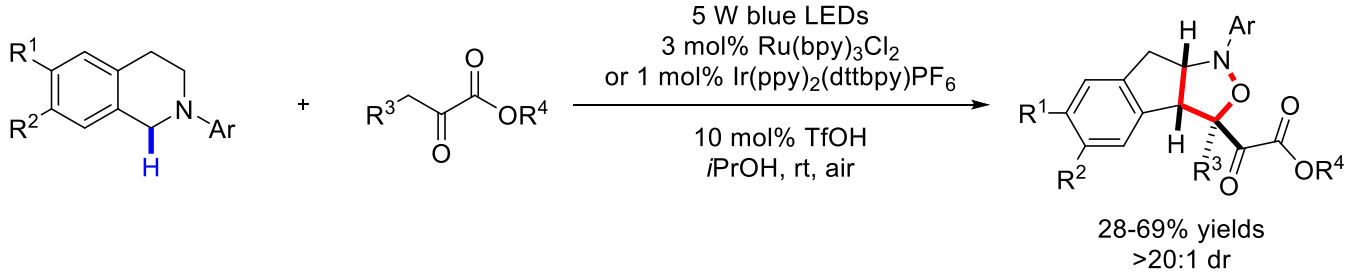


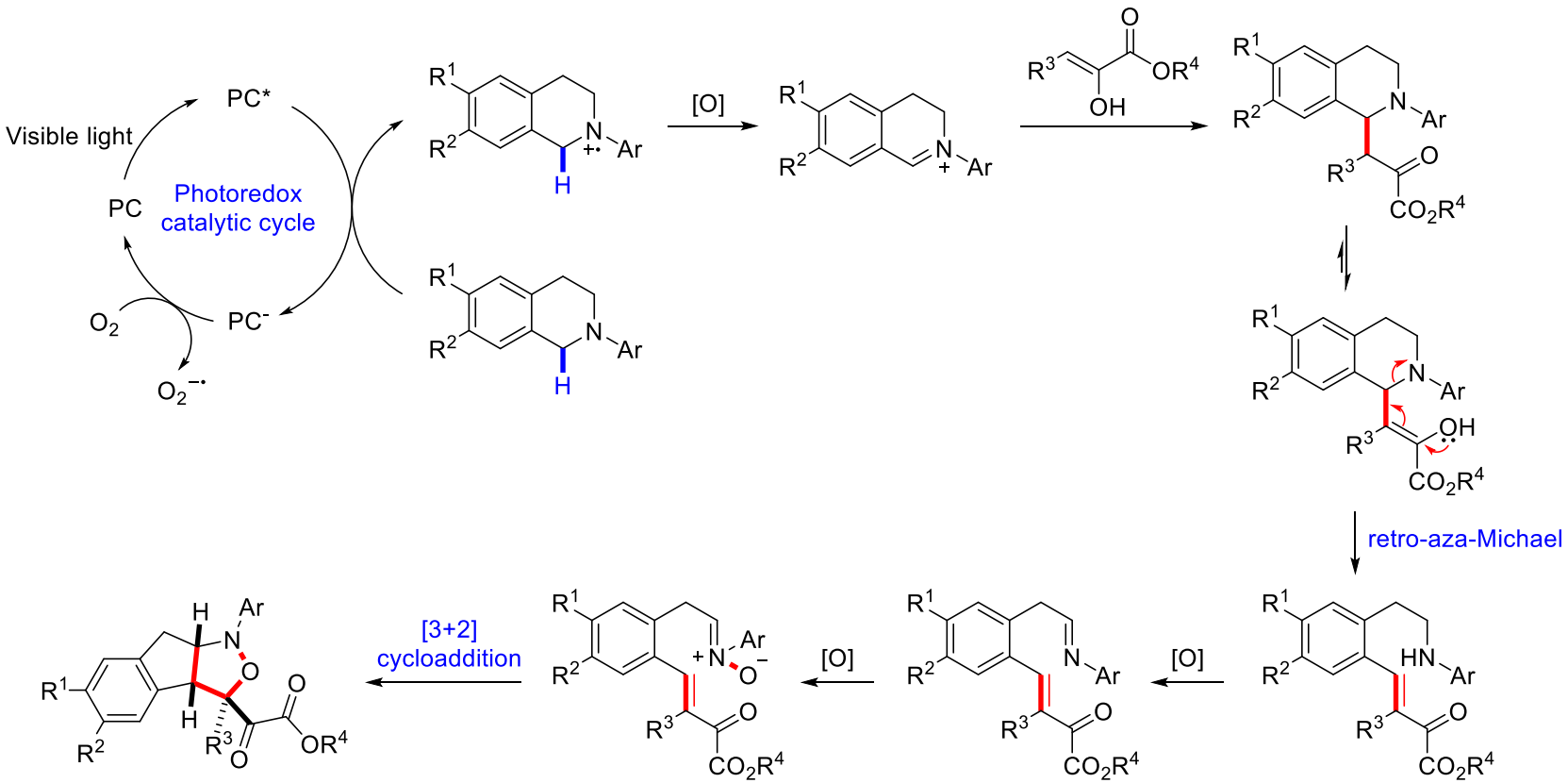
Xiao's work (2011): synthesis of tetrahydroimidazole from diamine



Xuan, J.; Feng, Z.-J.; Duan, S.-W.; Xiao, W.-J. *RSC Adv.* **2012**, *2*, 4065–4068.
Xuan, J.; Cheng, Y.; An, J.; Lu, L. Q.; Zhang, X. X.; Xiao, W.-J. *Chem. Commun*. **2011**, *47*, 8337–8339.

Zhu's work (2013): formation of isoxazolidine ring from tetrahydroisoquinoline and α-ketoester



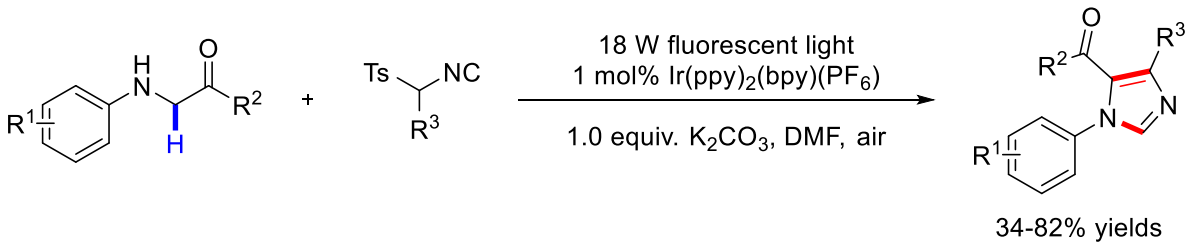


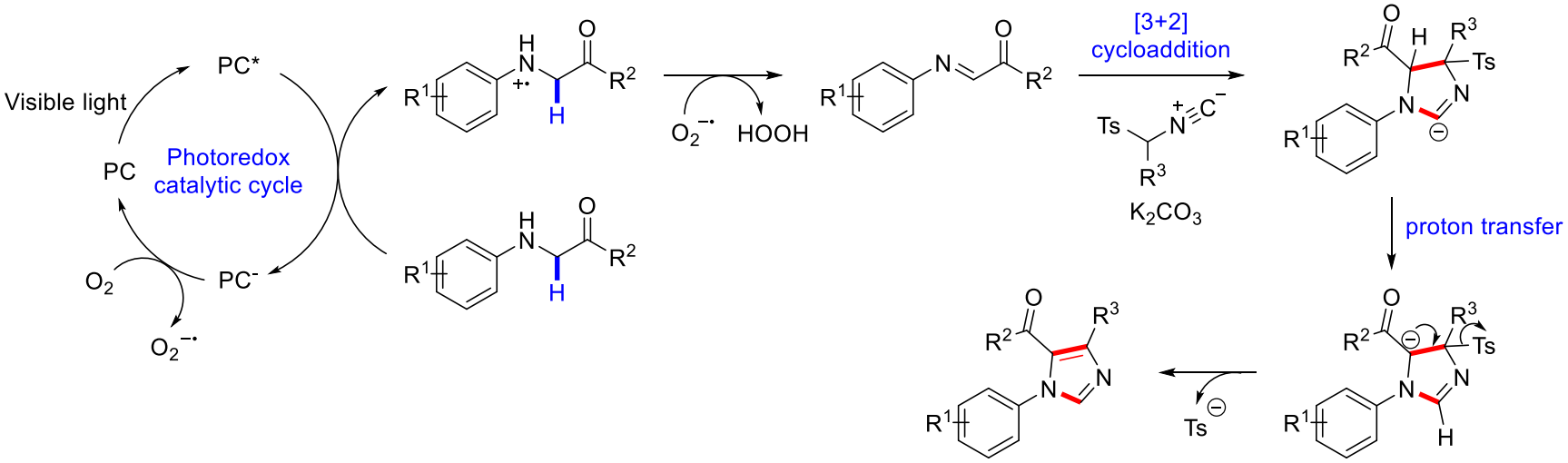
Xie, J.; Xue, Q.; Jin, H.; Li, H.; Cheng, Y.; Zhu, C. *Chem. Sci.* **2013**, *4*, 1281–1285.

Photocatalytic sp^3 C–H Functionalization

II. Trapping of imine intermediates

Xiao's work (2014): synthesis of imidazole from aniline and isonitrile derivatives



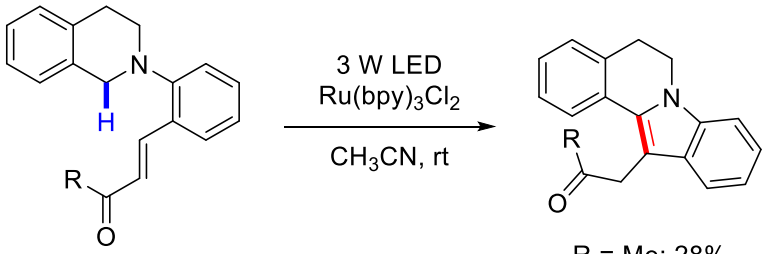


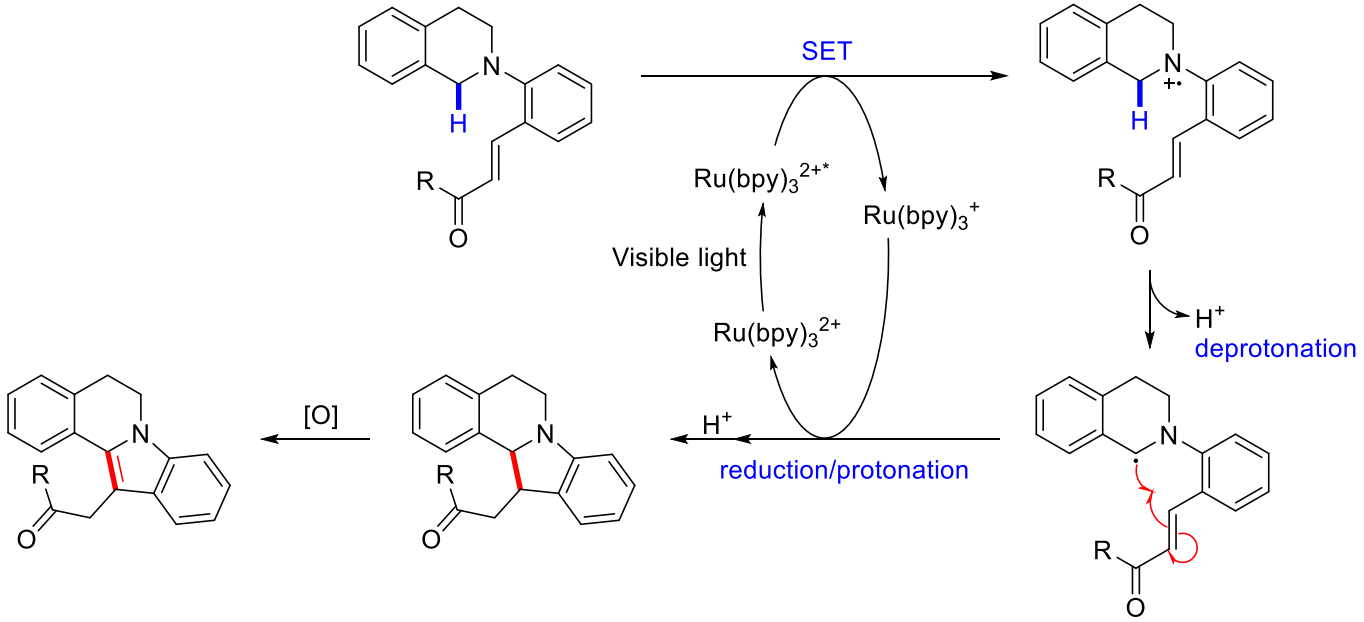
Deng, Q.-H.; Zou, Y.-Q.; Lu, L.-Q.; Tang, Z.-L.; Chen, J.-R.; Xiao, W.-J. *Chem. Asian J.* **2014**, *9*, 2432–2435.

Photocatalytic sp^3 C–H Functionalization

III. Coupling of *α*-aminoalkyl radicals

Reiser's work (2012): visible-light-induced coupling of α-aminoalkyl radical and unsaturated moities



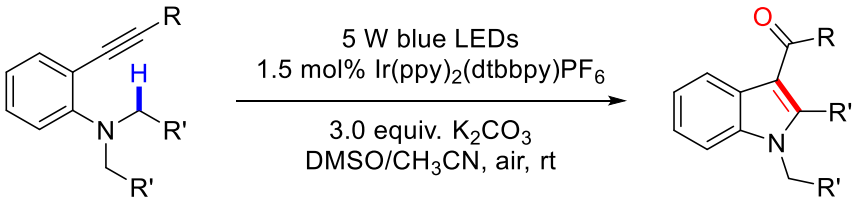


Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672–675.

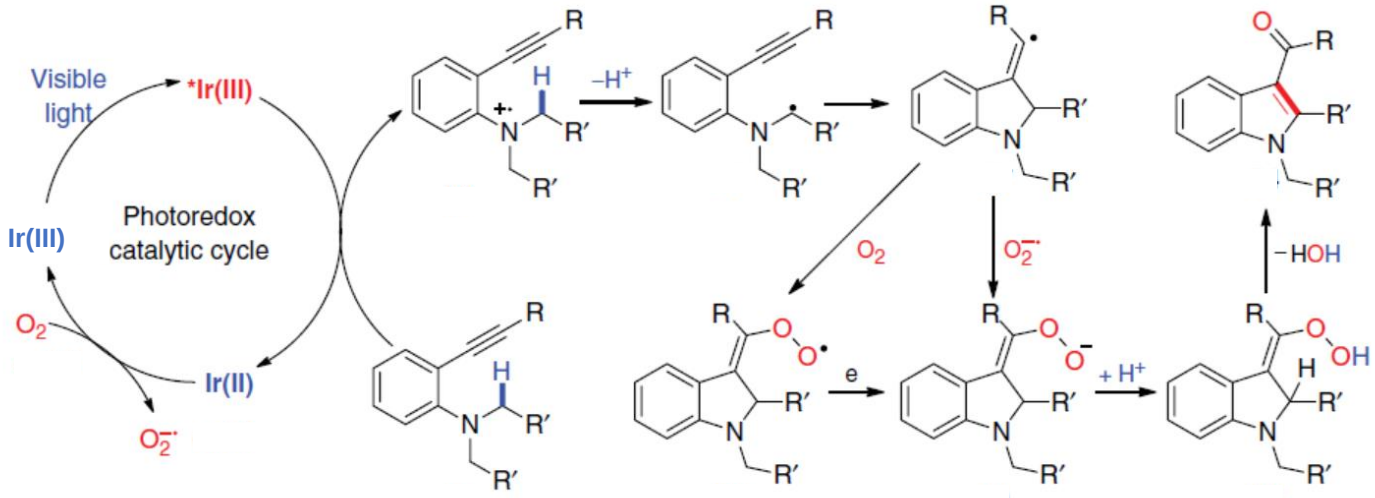
Photocatalytic sp^3 C–H Functionalization

III. Coupling of *α*-aminoalkyl radicals

Zhou's work (2014): synthesis of indole from *ortho*-alkynylated *N*,*N*-dialkylamine



51-80% yields

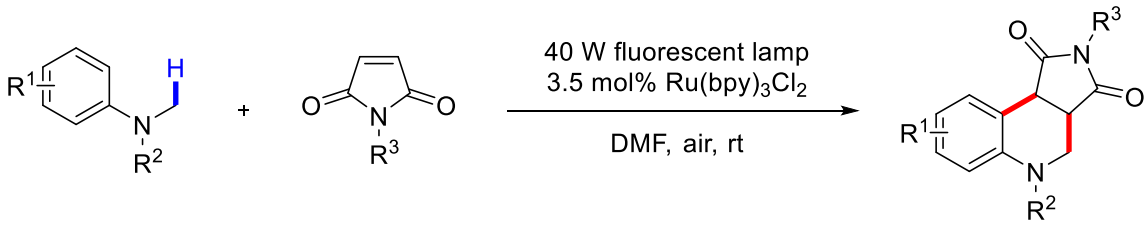


Zhang, P.; Xiao, T.; Xiong, S.; Dong, X.; Zhou, L. *Org. Lett.* **2014**, *16*, 3264–3267.

Photocatalytic sp^3 C–H Functionalization

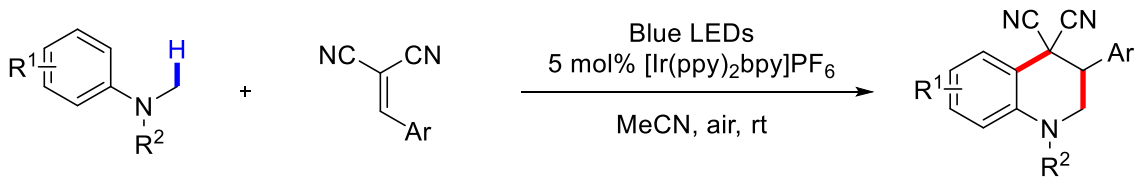
III. Coupling of *α*-aminoalkyl radicals

Bian's work (2012)



20-98% yields

Rueping's work (2013)

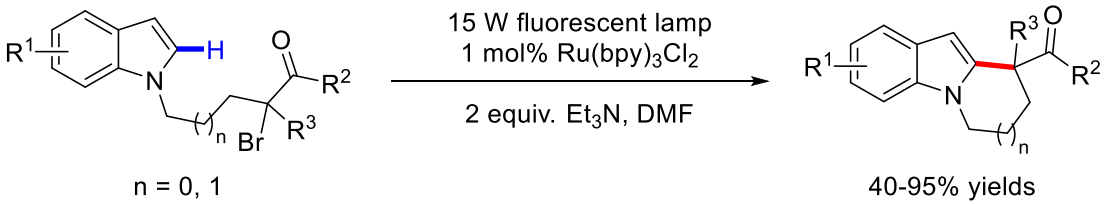


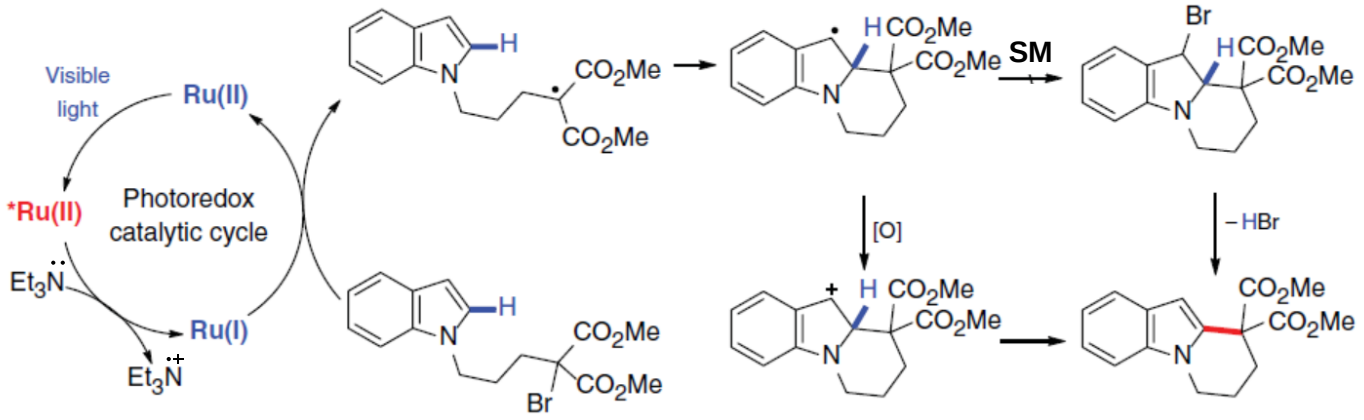
40-71% yields

Ju, X.; Li, D.; Li, W.; Yu, W.; Bian, F. *Adv. Synth. Catal.* **2012**, *354*, 3561–3567.
Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013**, *135*, 1823–1829.

Photocatalytic sp^2 C–H Functionalization

Stephenson's work (2010): reductive dehalogenation of activated carbon–halogen bond via visible-light photoredox catalysis

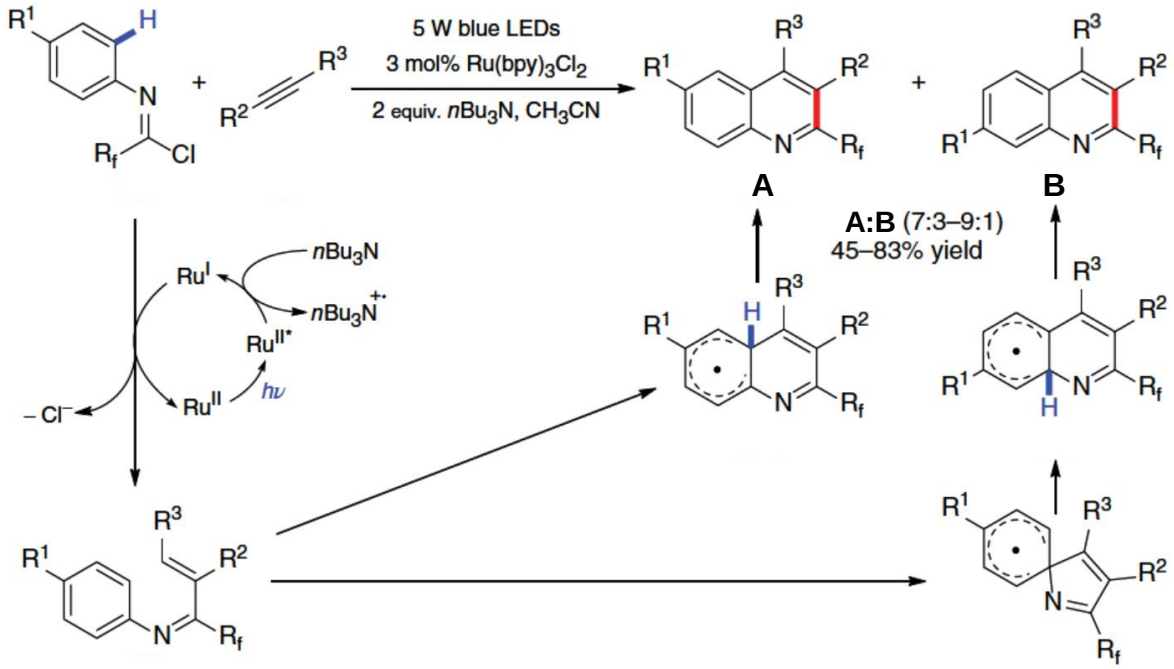




Tucker, J. W.; Narayanam, J. M.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368–371.

Photocatalytic sp^2 C–H Functionalization

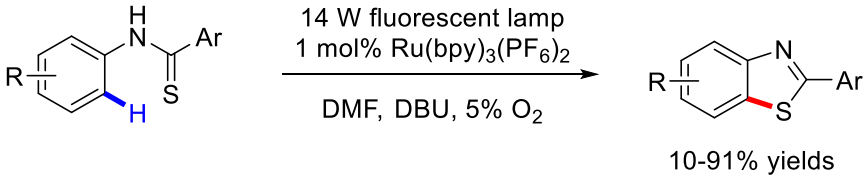
Zhou's work (2013): radical cyclization of trifluoroacetimidoyl chloride with alkyne, forming 2-trifluoromethyl quinolones

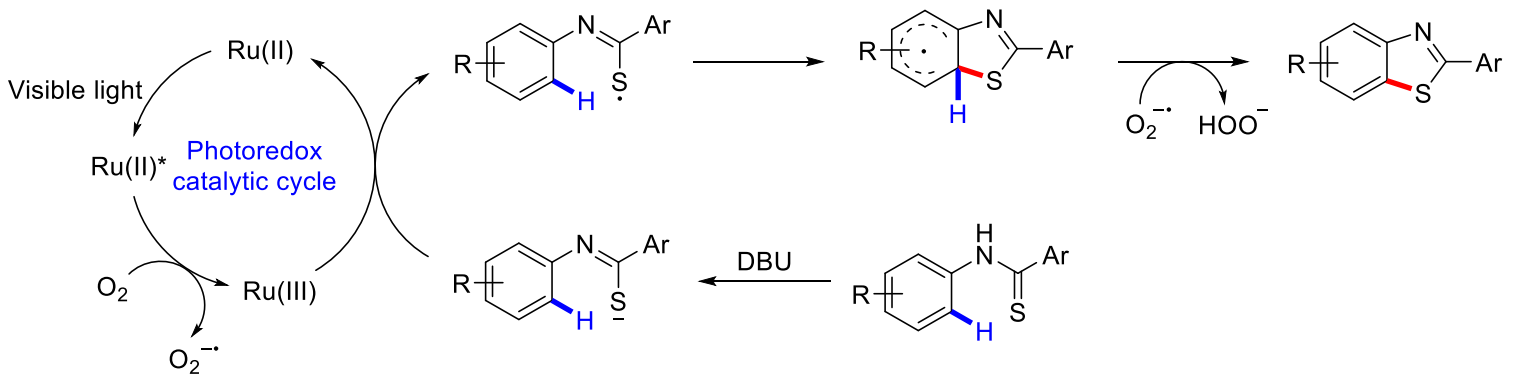


Dong, X.; Xu, Y.; Liu, J. J.; Hu, Y.; Xiao, T.; Zhou, L. *Chem. Eur. J.* **2013**, *19*, 16928–16933.

Photocatalytic sp^2 C–H Functionalization

Li's work (2012): formation of 2-substituted benzothiazole from thioamide

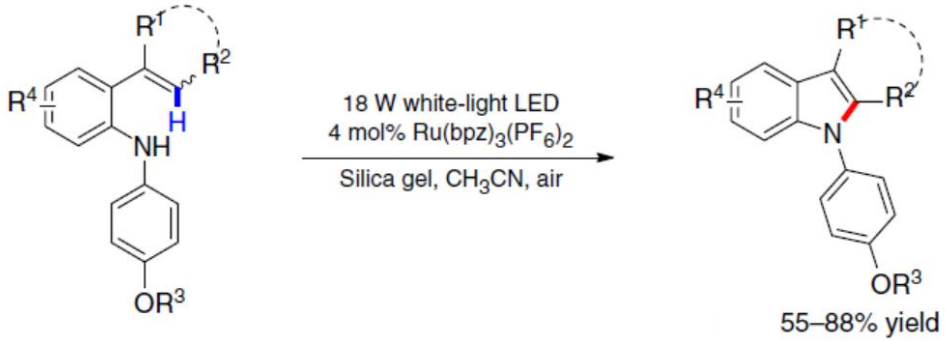


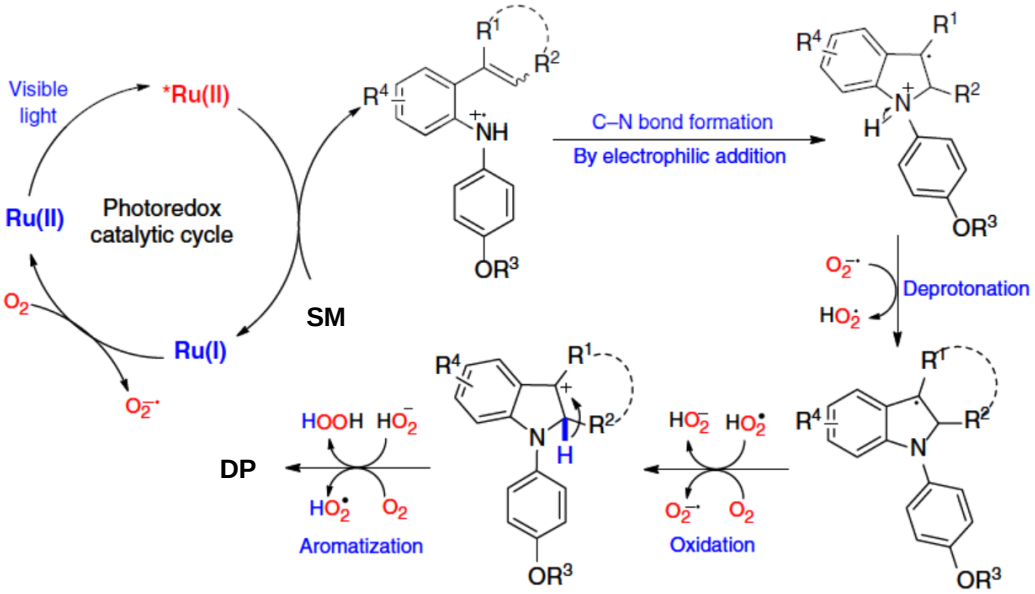


Cheng, Y.; Yang, J.; Qu, Y.; Li, P. *Org. Lett*. **2012**, *14*, 98–101.

Photocatalytic sp^2 C–H Functionalization

Zheng's work (2012): formation of 2,3-disubstituted indole from gem-di-substituted styryl aniline

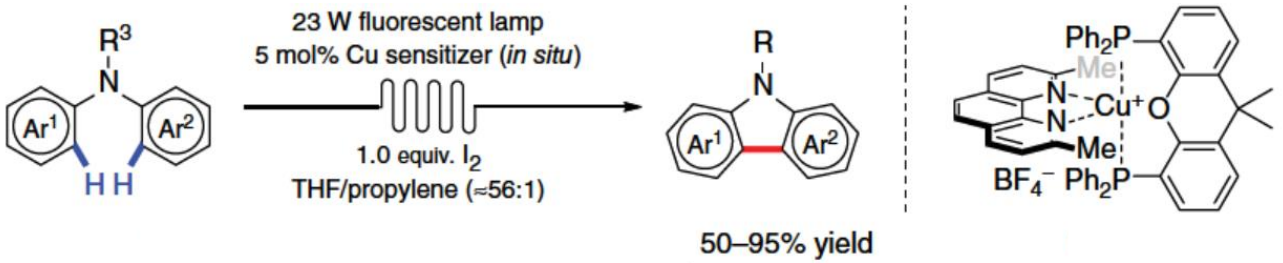


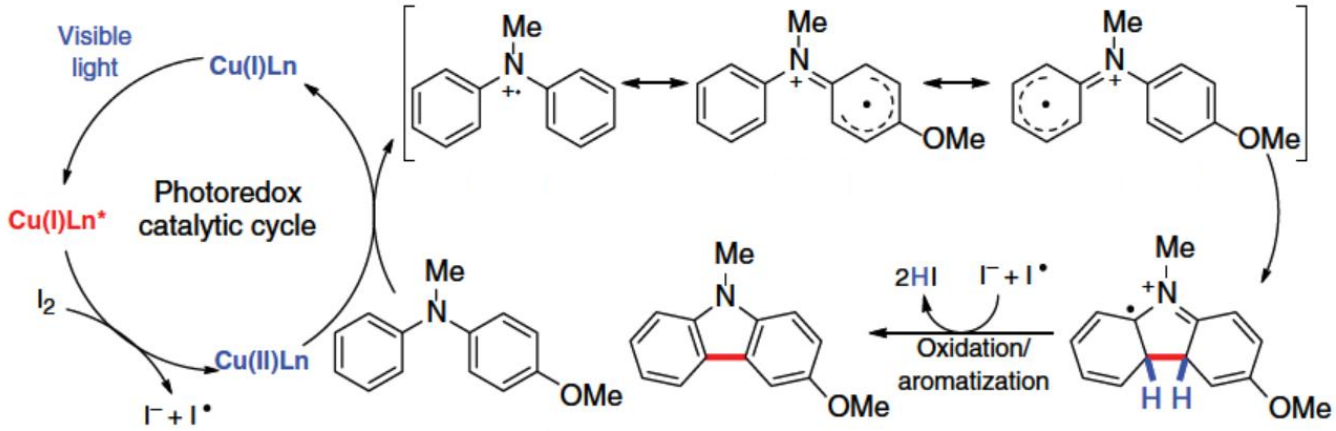


Maity, S.; Zheng, N. *Angew. Chem. Int. Ed*. **2012**, *51*, 9562–9566.

Photocatalytic sp^2 C–H Functionalization

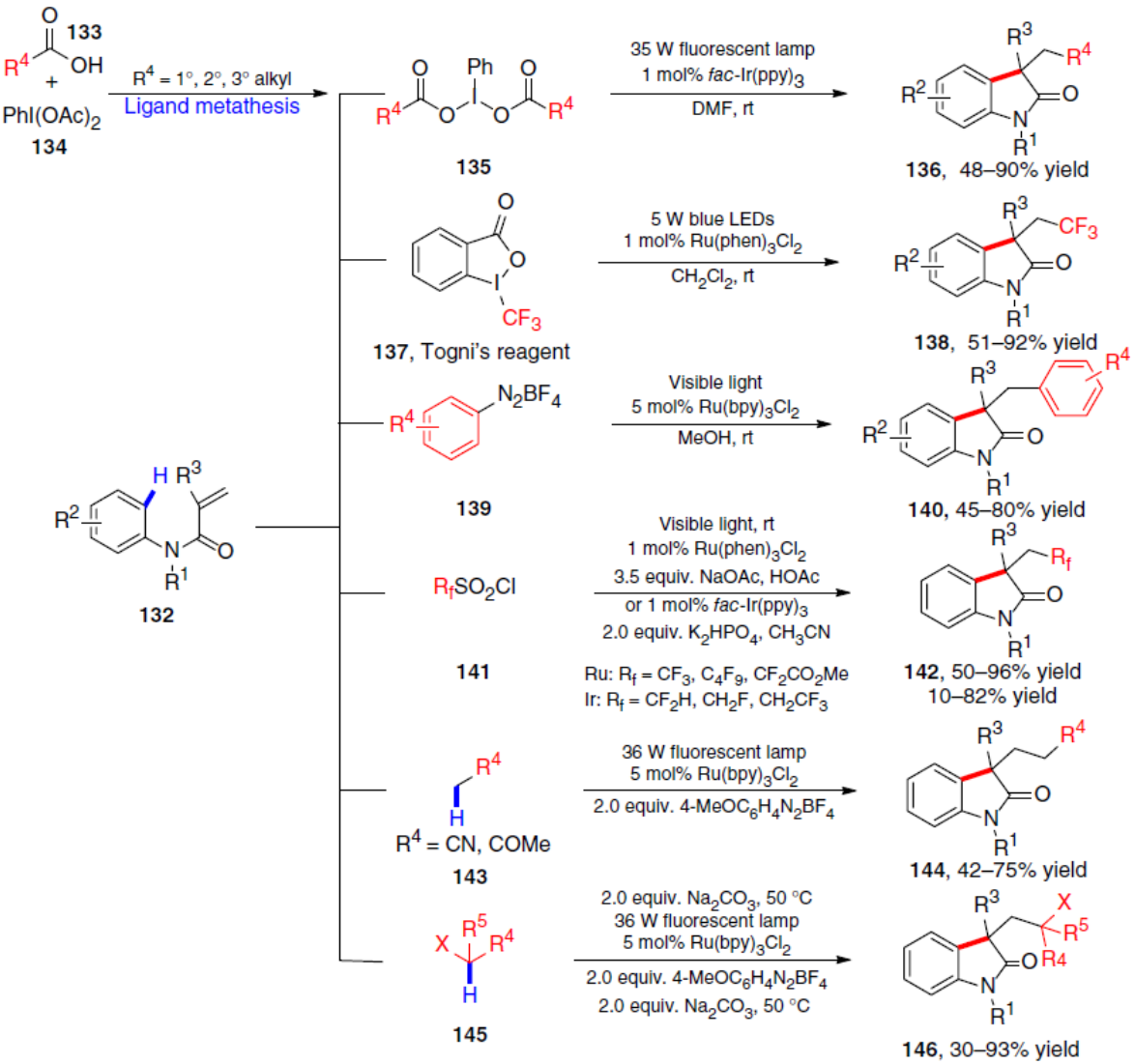
Collins' work (2013): formation of carbazole from diarylamine





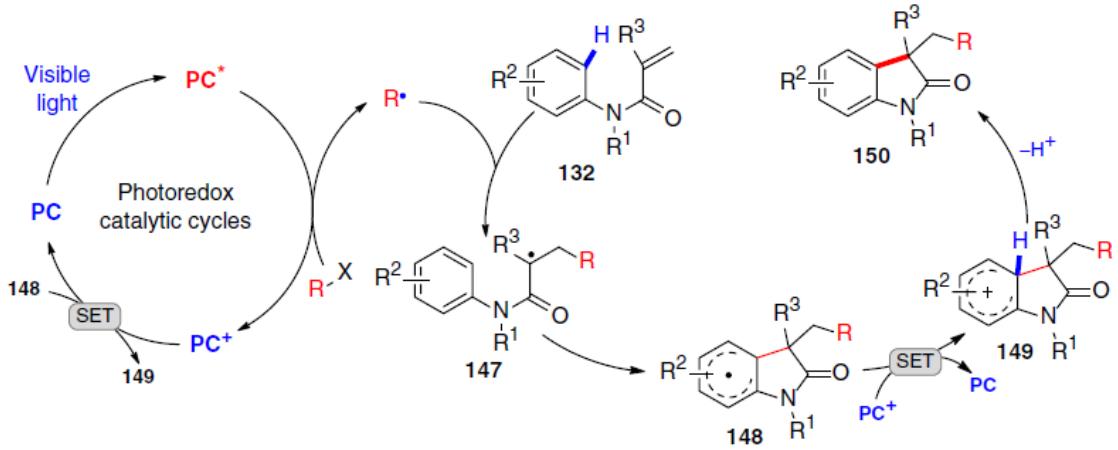
Photocatalytic sp^2 C–H Functionalization

Synthesis of 3,3-disubstituted oxindoles from *N*-arylacrylamides



Photocatalytic sp^2 C–H Functionalization

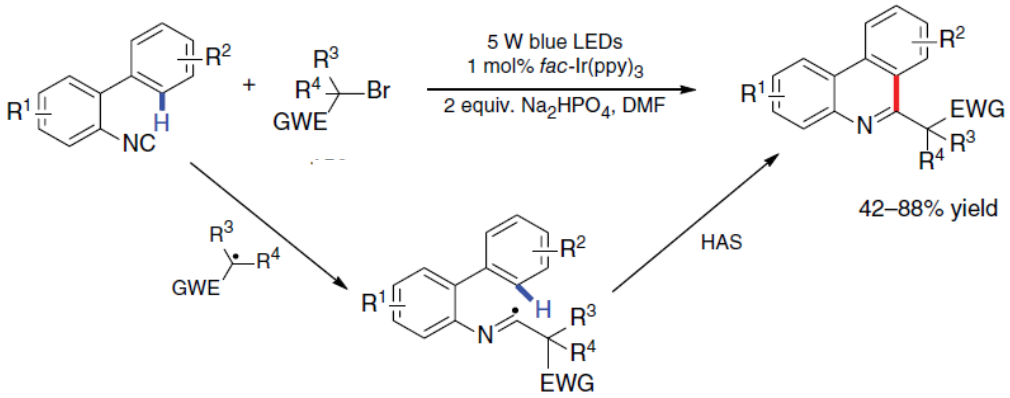
Synthesis of 3,3-disubstituted oxindoles



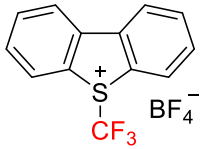
Xie, J.; Xu, P.; Li, H.; Xue, Q.; Jin, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 5672–5674.
Xu, P.; Xie, J.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem. Eur. J.* **2013**, *19*, 14039–14042.
Fu, W.; Xu, F.; Fu, Y.; Zhu, M.; Yu, J.; Xu, C.; Zou, D. *J. Org. Chem.* **2013**, *78*, 12202–12206.
Tang, X. J.; Thomoson, C. S.; Dolbier, W. R. Jr. *Org. Lett.* **2014**, *16*, 4594–4597.
Li, J.-H.; Jiang, G.-F.; Zhang, J.-L.; Liu, Y.; Song, R.-J. *Synlett* **2014**, *25*, 1031–1035.
Liu, Y.; Zhang, J.-L.; Song, R.-J.; Li, J.-H. *Org. Chem. Front.* **2014**, *1*, 1289–1294.

Photocatalytic sp^2 C–H Functionalization

Synthesis of 6-substituted phenanthridines from biphenyl isocyanides



Other reagents: **$RNHNH_2$**, **$ArSO_2Cl$**, **Ar_2IBF_4**,

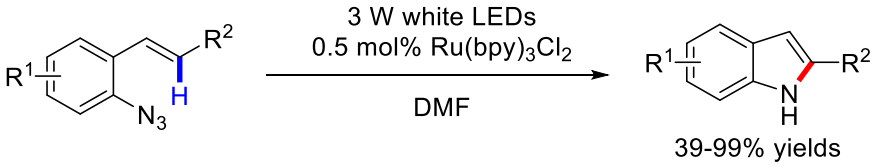


Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem. Int. Ed*. **2013**, *52*, 13289–13292.
Xiao, T.; Li, L.; Lin, G.; Wang, Q.; Zhang, P.; Mao, Z.-W.; Zhou, L. Green Chem. **2014**, *16*, 2418–2421.
Gu, L.; Jin, C.; Liu, J.; Ding, H.; Fan, B. Chem. Commun. **2014**, *50*, 4643–4645.
He, Z.; Bae, M.; Wu, J.; Jamison, T. F. Angew. Chem. Int. Ed. **2014**, *53*, 14451–14455.

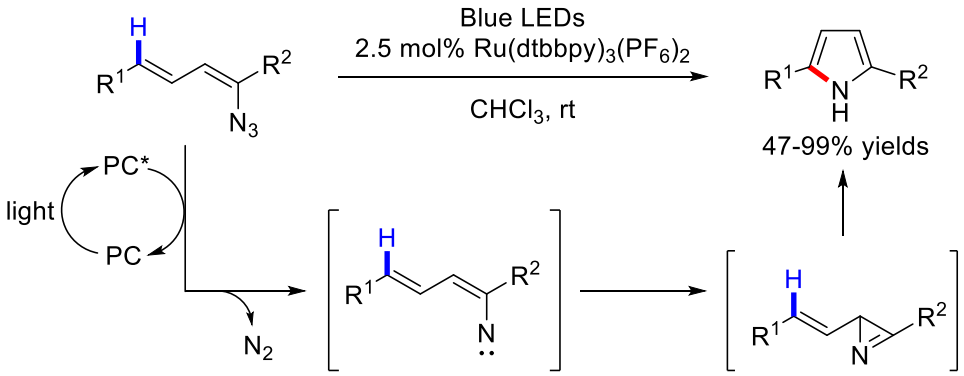
Photocatalytic sp^2 C–H Functionalization

Energy transfer process

Xiao's work (2014)



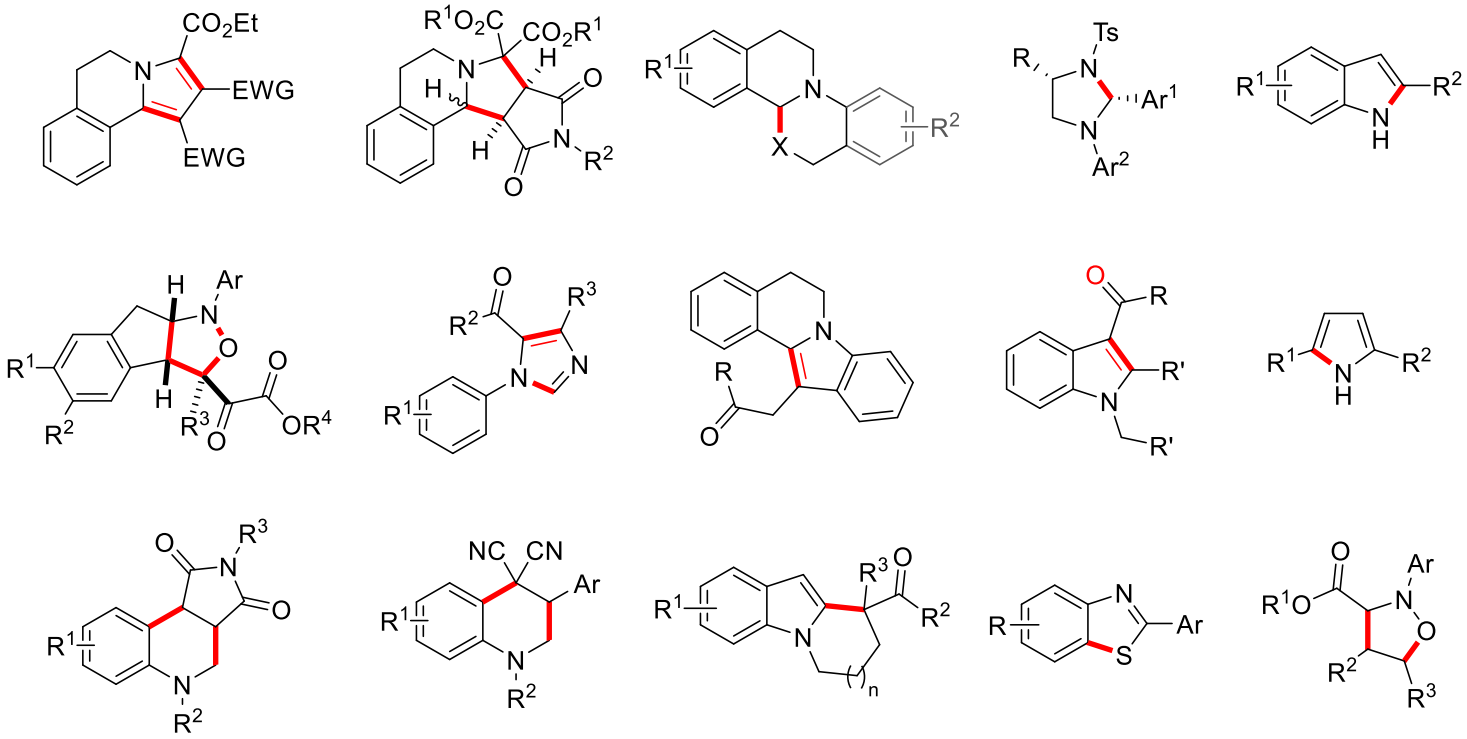
Yoon's work (2014)



Xia, X.-D.; Xuan, J.; Wang, Q.; Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Adv. Synth. Catal*. **2014**, *356*, 2807–2812.
Farney, E. P.; Yoon, T. P. *Angew. Chem. Int. Ed*. **2014**, *53*, 793–797.

Conclusion

- Various types of heterocycles were synthesized via the visible-light-induced photocatalytic C–H Functionalization.



- Photoredox catalysis avoids harsh conditions: high temperatures, catalyst loadings.

Reviews:

- Ding, W.; Guo, W.; Zeng, T.-T.; Lu, L.-Q.; Xiao, W.-J. *Transition Metal-Catalyzed Heterocycle Synthesis via C–H Activation*, 1st ed.; Wiley-VCH Verlag GmbH & Co. KGaA., 2016.
- Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Acc. Chem. Res*. **2016**, *49*, 1911−1923.


THANK
YOU!