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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:

Nitrogen Centered Radicals (NCR) are known in literature since the first years of 1900, but only with the spread of photoredox catalysis, and in particular visible light-mediated radical processes, nitrogen radical chemistry became more accessible generating these kinds of radicals in situ employing mild conditions. In fact, unlike their carbon counterpart, nitrogen radicals have not historically spread in academia or industry due to a lack of an efficient strategy to produce them. Nowadays, NCR are more established, and this graphical review illustrates the key publications from the literature categorized them by both the type of NCR and the type of reaction. In fact, nitrogen radicals can be divided in four different categories according to their electronical configuration, orbital structure and chemical behaviour. The reactivity of all these radicals can be summarized into four main classes: they are mostly exploited into intramolecular cyclization; intramolecular hydrogen atom abstraction; Norrish type-I fragmentation and intermolecular addition to π systems.

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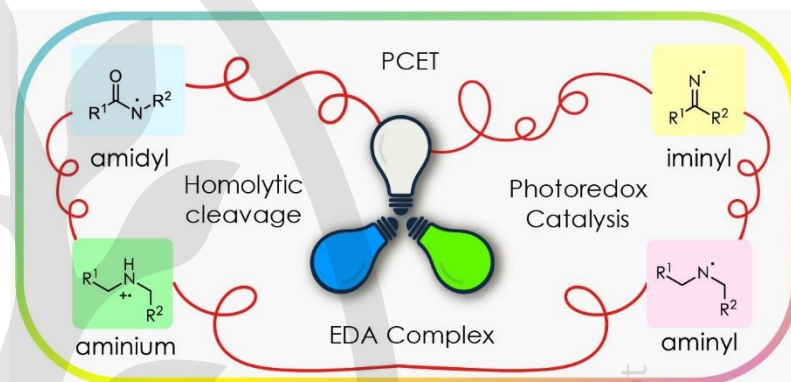
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Nitrogen Centered Radicals in Visible-Light Promoted Reactions

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Abstract Nitrogen Centered Radicals (NCR) are known in literature since the first years of 1900, but only with the spread of photoredox catalysis, and in particular visible light-mediated radical processes, nitrogen radical chemistry became more accessible generating these kinds of radicals *in situ* employing mild conditions. In fact, unlike their carbon counterpart, nitrogen radicals have not historically spread in academia or industry due to a lack of an efficient strategy to produce them. Nowadays, NCR are more established, and this graphical review illustrates the key publications from the literature categorized them by both the type of NCR and the type of reaction. In fact, nitrogen radicals can be divided in four different categories according to their electronical configuration, orbital structure and chemical behaviour. The reactivity of all these radicals can be summarized into four main classes: they are mostly exploited into intramolecular cyclization; intramolecular hydrogen atom abstraction; Norrish type-I fragmentation and intermolecular addition to π systems.

Key words Nitrogen Radicals, Photoredox Catalysis, visible-light-driven reactions, Amidyl Radicals, Cyclizations, Addition to π systems, Hydrogen Atom Transfer

Organic compounds bearing nitrogen atoms are widely spread into pharmaceutical and agrochemical products, in fact the use of C–N cross-coupling methods in medicinal chemistry accounts for approximately 23 % of reported reactions in recent publications, demonstrating the omnipresent nature of the transformation. Furthermore, functionalized amine and amide products are important building blocks in active pharmaceutical ingredients (APIs). For this reason, new and green synthetic strategies to build up new C–N bonds under mild conditions are a central goal for chemists. In traditional chemistry, sp^2 C–N bonds are typically formed by Pd-catalyzed Buchwald-Hartwig reactions or Cu-catalyzed Ullman-Goldberg reactions, while sp^3 C–N bonds are usually built up through reductive amination and

alkylation, Gabriel synthesis and Hoffman degradation. However, both these approaches have the same drawbacks: the requirement of pre-functionalization for the substrates and the use of high temperatures. In the last decades, with the spread of photocatalysis, and in particular visible light-mediated radical processes, nitrogen radical chemistry became more accessible: this revolutionary synthesis technique made possible to develop novel and previously unattainable synthetic approaches. Photocatalysis describes transformations that require light as an energy input to proceed and they typically use catalytic amounts of light-absorbing photocatalysts, such as metal complexes or organic dyes. Moreover, photocatalysis is characterized by the use of low-energy photons as reagent opening the door to environmentally safe, more sustainable, and non-hazardous visible light-based chemical synthesis. The nitrogen radicals can be divided in four different categories according to their electronical configuration, orbital structure and chemical behavior. Iminyl radicals have the nitrogen atom sp^2 -hybridized, a planar structure and a σ configuration with an amphiphilic behavior. Amidyl radicals have the single electron into a p orbital perpendicular to the nitrogen substituents, so they assume a π configuration with an electrophilic chemical behavior. Aminyl and Aminium radicals have both a π configuration, but opposite reactivity: in fact, aminyl radicals are weakly nucleophiles and commonly utilized for their preference for H-atom abstraction, while aminium radicals are strongly electrophiles. Although there are other types of nitrogen radicals, these four main classes can be used to illustrate their reactivity (e.g., carbamyl radicals and *N*-Ts radicals are consistent with the behavior of amidyl radicals). The philicity of radicals has been effectively defined by computational and experimental studies, which is a crucial parameter to develop new radical reactions.

The best way to generate nitrogen radicals is a cleavage promoted by light under mild conditions, in particular the most suitable bonds to be broken are N–H, N–halogens, N–N and N–O, N–S. There are four

main strategies to break these bonds: homolytic cleavage; reductive and oxidative conditions; oxidative proton-coupled electron transfer (PCET).

Homolytic cleavage can occur when a N-Halogen, N-N, N-O and N-S bond is irradiated by UV light, and it generates two radical species which can lead to the desired transformation. The second and third methods involve a photoredox quenching cycle, which can be oxidative or reductive depending on the reaction counterparts. In detail, in the reductive quenching cycle a SET occurs generating the nitrogen radical cation in two different ways: the electron can be abstracted either directly from the HOMO of the precursor or from an oxidizable group external to the key NCR moiety which can undergo a fragmentation (e.g. decarboxylative cascade mechanism). Also, in the oxidative quenching cycle the SET can occur with two different pathways: the electron can be donated either directly to the σ^* -orbital of the nitrogen radical or to a π^* -orbital of a suitable precursor (e.g. the hydroxyamines and the pyridinium ions). In the oxidative Proton-coupled electron transfer (PCET), the nitrogen radical precursor undergoes a concerted homolytic activation through the formation of a hydrogen bond complex between the N-H of the amide and a suitable base.




The reactivity of all these radicals can be summarized into four main classes: they are mostly exploited into intramolecular cyclization onto alkenes or alkynes like a classic *exo-trig* process; intramolecular hydrogen atom abstraction (e.g. 1,5-HAT); Norrish type-I fragmentation (with limited examples) and intermolecular addition to π systems like olefins, alkynes and aromatic compounds. It is significant to highlight that not all the classes of nitrogen radicals share these reaction modes, since their philicity is what stabilizes (or destabilizes) the corresponding transition states.

In this review, we have chosen to summarize the most well-known published examples of nitrogen radical reactions grouping them by their reactivity and the type of the generated radical. Although there are numerous examples of reactions involving nitrogen centered radicals in the literature, we will limit our report to reactions involving visible light.

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Accepted Manuscript

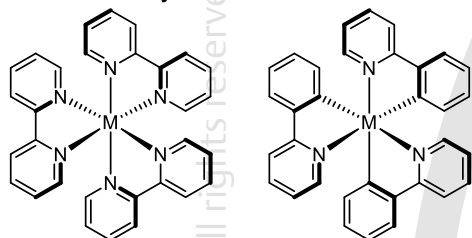
Biosketches

	<p>Monica Fiorenza Boselli earned her master's degree in chemical science in 2019 at the University of Milan, Italy. She worked as an Erasmus + fellow for five months with Prof. M. Kalesse's group at the University of Hannover, Germany, as part of the yearly Master Internship program focused on total synthesis. Following graduation, she worked as a fellowship student in the group of Prof. M. Benaglia at the University of Milan, where she developed continuous-flow processes. In June 2024, she completed her PhD in Chemistry under the guidance of Prof. Alessandra Puglisi, with a thesis on amidyl radicals in light-promoted reactions. During her PhD, she worked for six months in Professor B. Koenig's group at the University of Regensburg, Germany. Currently she is employed with a post-Doc fellowship in the fields of stereoselective photocatalysis and organocatalysis under the direction of Professors Sergio Rossi and Maurizio Benaglia at the University of Milan.</p>
	<p>Fabrizio Medici earned his master's degree in chemical science in 2014 in organometallic chemistry under the supervision of Pr. Angelo Maspero at University of Insubria, Como, Italy. After, he moved to Paris at UPMC, Sorbonne University, where he took his PhD, 2017, in molecular science under the supervision of Pr. Louis Fensterbank and Dr Gilles Lemiere with a thesis entitled: Interactions Between the Martin's Spirosilane and Lewis Bases: Coordination, Frustration and New Anionic Ligands. Then he moved to the ICSN-CNRS gif-sur-Yvette, Fr, in the group of Dr. Angela Marinetti and Dr. Arnaud Voituriez for his first PostDoc focused on Au(I) catalysis. He then returned to Italy in 2020, starting his next postdocs at the University of Milan under the supervision of Pr. Alessandra Puglisi and then Pr. Maurizio Benaglia, spacing from organic photochemistry, organic electrochemistry and flow synthesis. From May 2023, he will be an RTDA (Tenure track Professor) at the University of Milan as part of the MUSA project under the PNRR plan.</p>
	<p>Francesca Franco earned her master's degree in chemical science in 2018 in organometallic chemistry under the supervision of Pr. Mina Mazzeo and Chiara Costabile at the University of Salerno, Italy. Next, she switched to organic chemistry, and she completed her PhD in Chemistry in 2022 under the guidance of Pr. Alessandra Lattanzi, with a thesis entitled: Exploring batch and flow catalytic reactions as valuable tools for safer and greener synthesis of APIs and their fluorine intermediates. During her PhD she spent three months in the company Laboratori Alchemia and six months at University of Milan. After her PhD, she moved to University of Pavia to work as Post-Doc in Zanoni's research group focusing on the application of biomimetic reactions in the synthesis of natural compounds. Currently she is employed with a post-Doc fellowship in the fields of electrochemistry and stereoselective organocatalysis under the direction of Maurizio Benaglia at the University of Milan.</p>

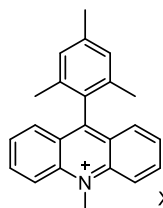
Notable features

- Agrochemical and Pharmaceuticals compounds bearing nitrogen are widely spread
- Tunability of the nitrogen reactivity depending on the substituents
- Low energy bonds can be easily cleaved

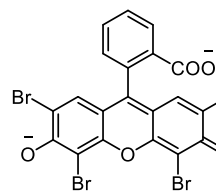
Common Photocatalysts



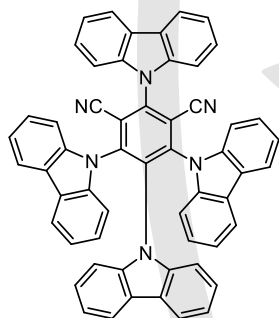
Polypyridyl and Polyphenylpyridyl Metal Complexes



Acridinium Dyes



Flavonoids



Cianoarenes

Further reading

- 1a) Jordan, *J. Med. Chem.* **2011**, *54*, 3451.
 1b) Leonori, *Chem. Eur J.* **2018**, *24*, 12154.
 1c) Murphy, *Chem. Rev.* **2022**, *122*, 8181.
 1d) Karkas, *ACS Catal.* **2017**, *7*, 4999.

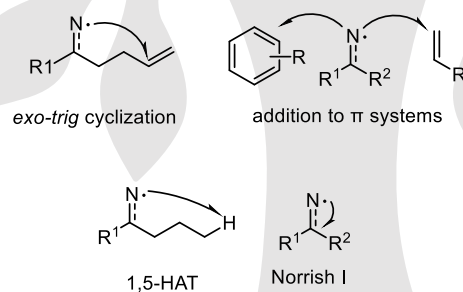
Nitrogen Radical Properties

Nitrogen Radical Classification

Name	iminyl	amidyl	aminyl	aminium
Configuration	σ	π	π	π
Philicity	ambiphilic	electrophilic	nucleophilic	electrophilic

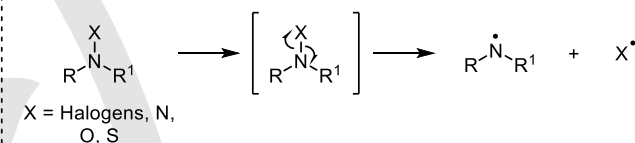
1b) Leonori, *Chem. Eur J.* **2018**, *24*, 12154.

Nitrogen Radical General Reactivity

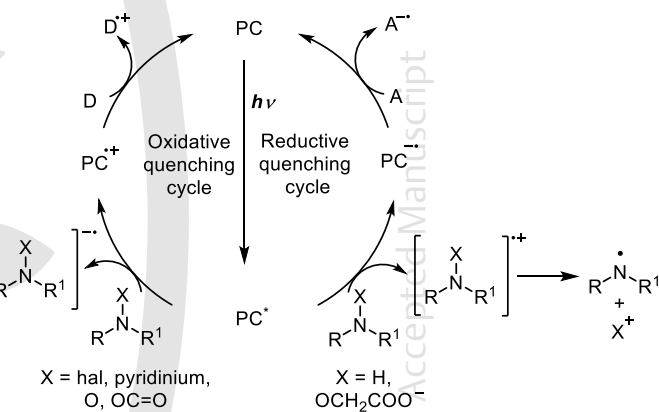
1b) Leonori, *Chem. Eur J.* **2018**, *24*, 12154.

Nitrogen Radical Activation Pathways

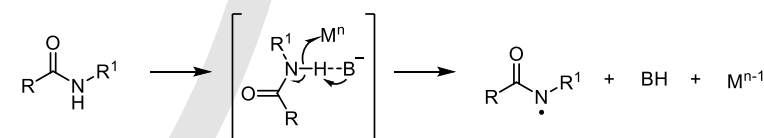
A) Homolytic cleavage



B) Reductive and oxidative conditions



C) Oxidative proton-coupled electrontransfer (PCET)

1c) Murphy, *Chem. Rev.* **2022**, *122*, 8181.Figure 1 Nitrogen Centered Dyes Radical Overview^{1a-d}

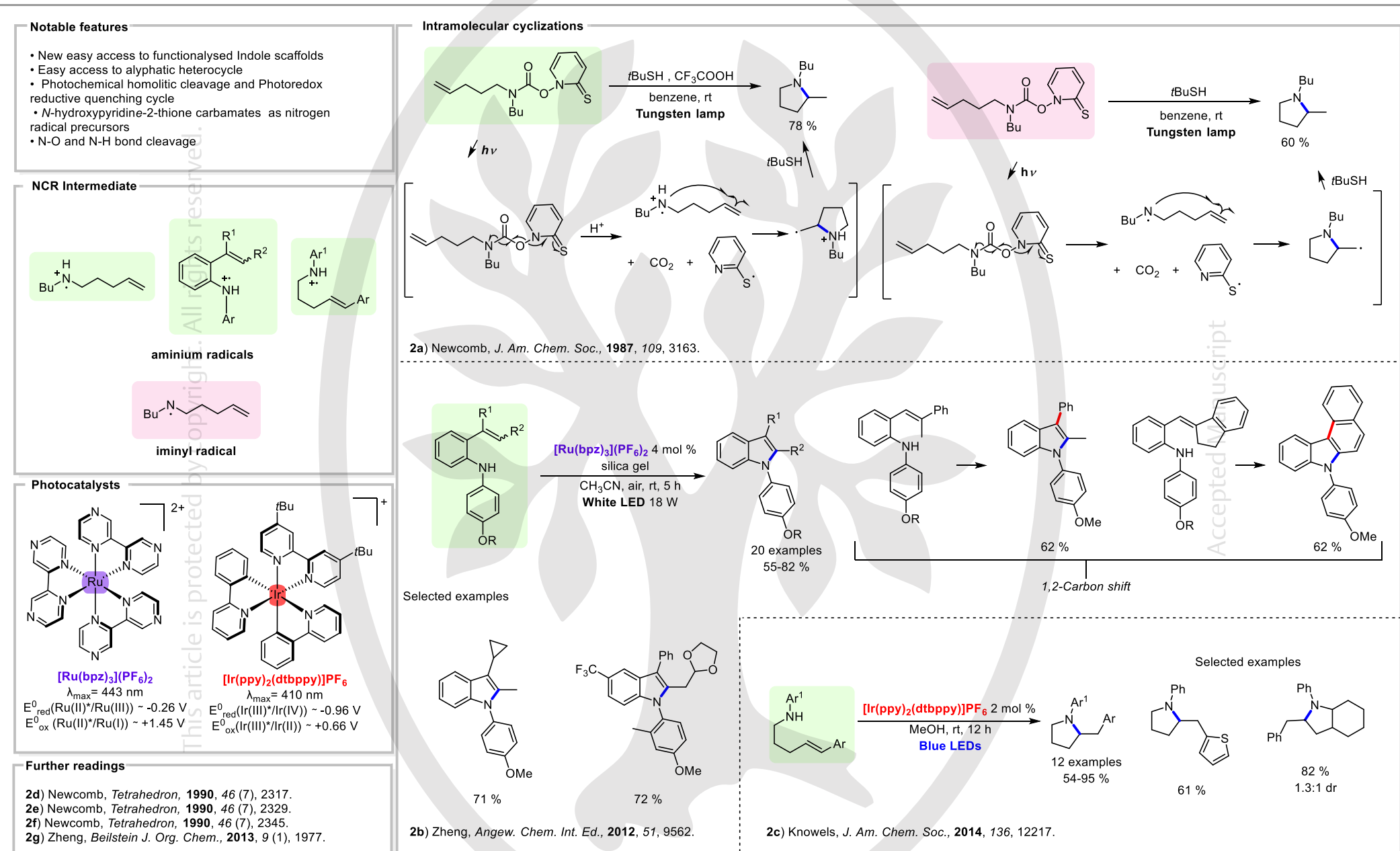


Figure 2 Intramolecular cyclizations for the synthesis of cyclic amines and substituted indoles^{2a-g}

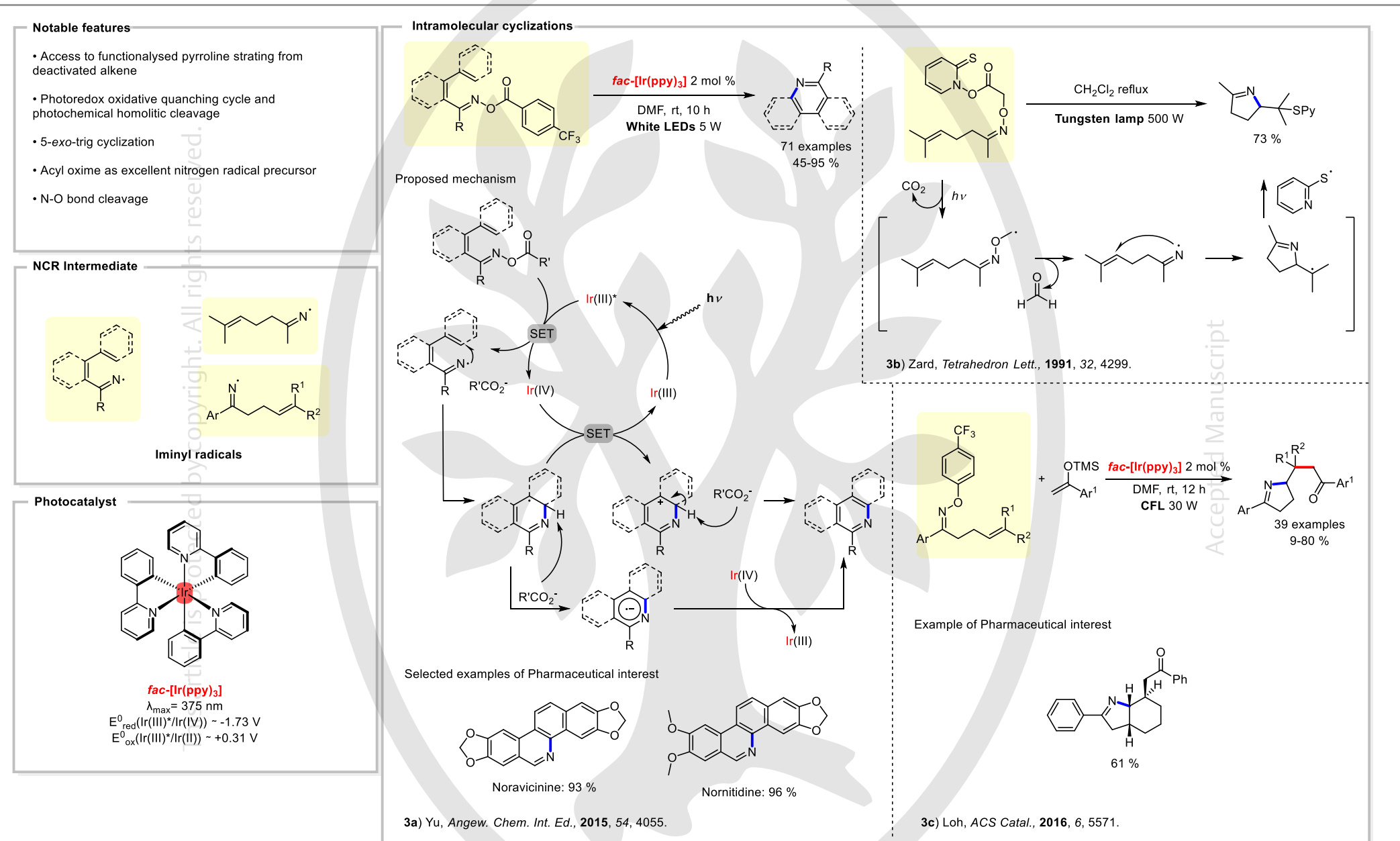
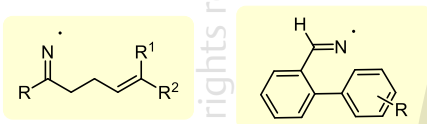


Figure 3 Iminyl radical intramolecular cyclization for the synthesis of heteroarenes and functionalized pyrrolidines^{3a-c}

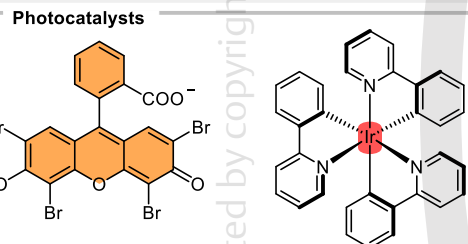
Notable features

- Allow access to indolizidine alkaloid skeleton
- Access to phenanthridine scaffold
- Photoredox oxidative quenching cycles
- O-aryl hydroxylamines, α -imino-oxy acid and pyridinium ion as nitrogen radical precursors
- N-O and N-N bond cleavage
- Divergent synthesis with easy condition
- Metal-free synthesis of substituted indolizidine

NCR Intermediate

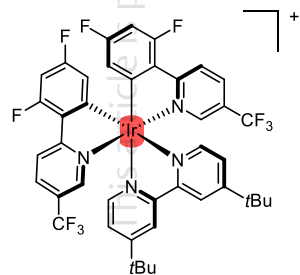


Iminyl radicals



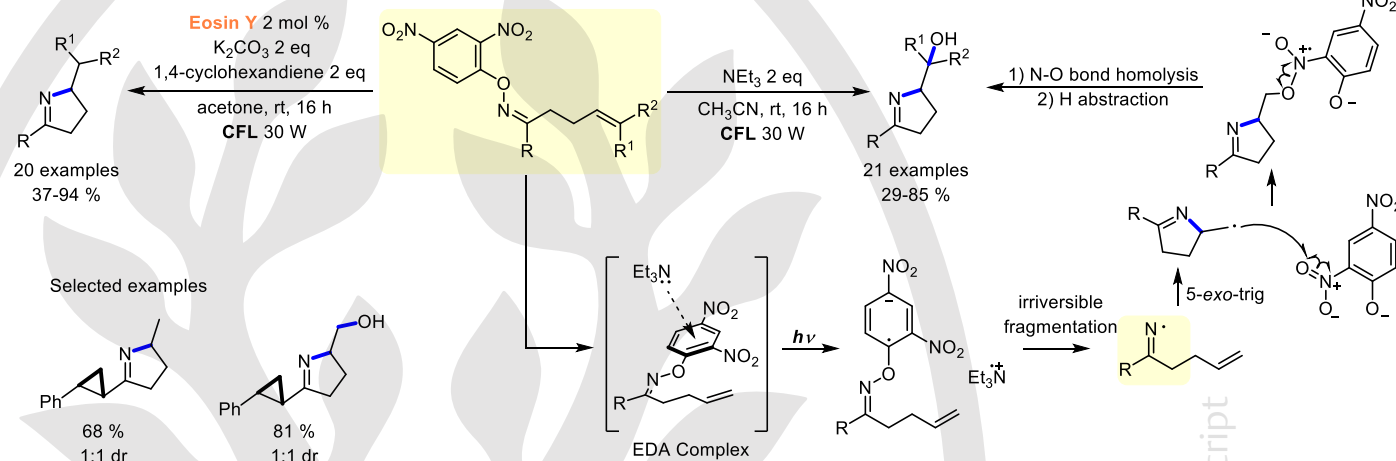
Eosin Y
 $\lambda_{\max} = 539 \text{ nm}$
 $E_{\text{red}}^0(\text{EY}^*/\text{EY}^{\cdot-}) \sim -1.11 \text{ V}$
 $E_{\text{ox}}^0(\text{EY}^*/\text{EY}^{\cdot-}) \sim +0.83 \text{ V}$

fac-[Ir(ppy)₃]
 $\lambda_{\max} = 375 \text{ nm}$
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -1.73 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.31 \text{ V}$

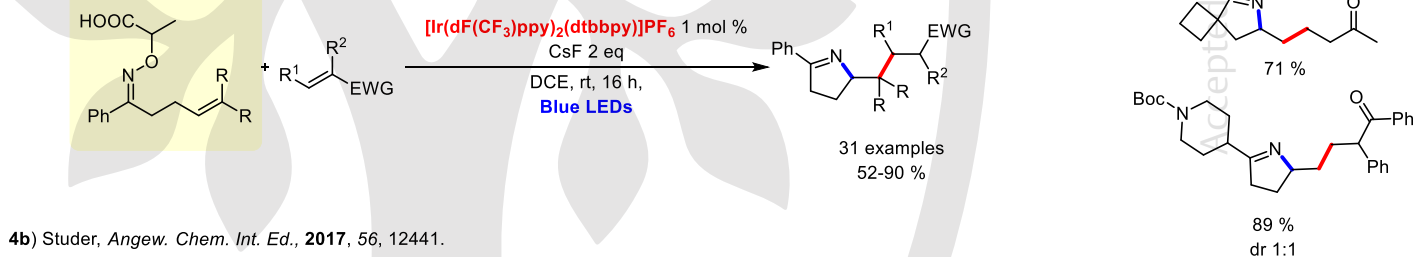


[Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆
 $\lambda_{\max} = 380 \text{ nm}$
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.89 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +1.21 \text{ V}$

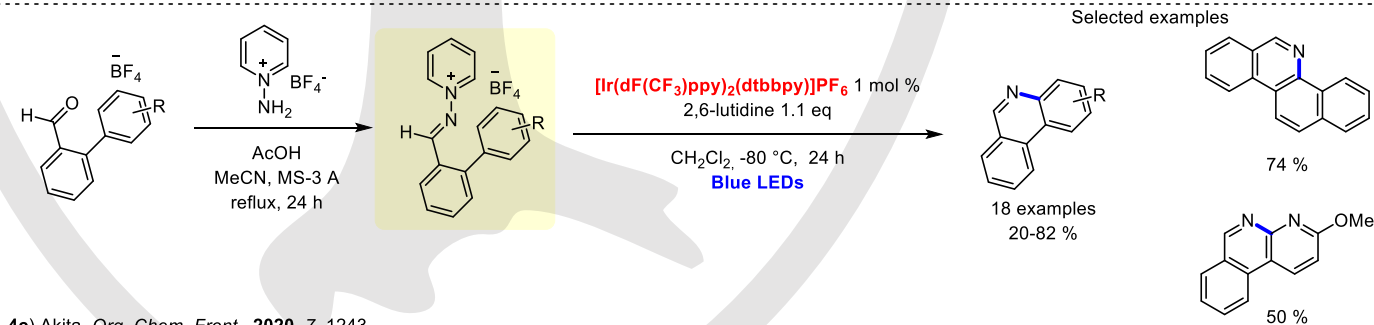
Intramolecular cyclizations



4a) Leonori, *Angew. Chem. Int. Ed.*, **2015**, *54*, 14017.



4b) Studer, *Angew. Chem. Int. Ed.*, **2017**, *56*, 12441.



4c) Akita, *Org. Chem. Front.*, **2020**, *7*, 1243.

Figure 4 Iminyl radical intramolecular cyclization for the synthesis of heteroarenes and functionalized pyrrolidines^{4a-c}

Notable features

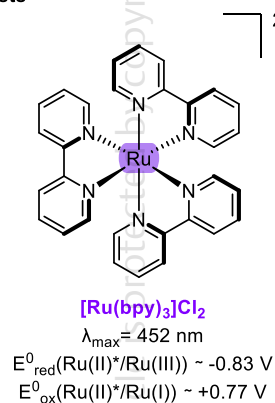
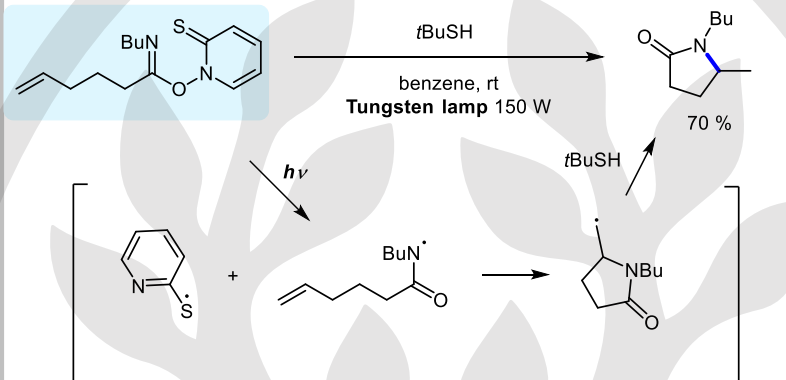
- Synthesis of γ -lactams and *N*-substituted pyrazoles
- Photochemical homolytic cleavage and Photoredox reductive quenching cycle
- *N*-hydroxypyridine-2-thione carbamates and *N*-tosyl hydrazones as nitrogen radical precursors
- N-O and N-N bond cleavage

NCR Intermediate



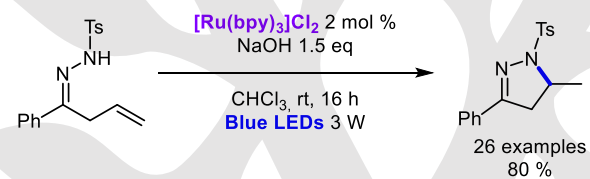
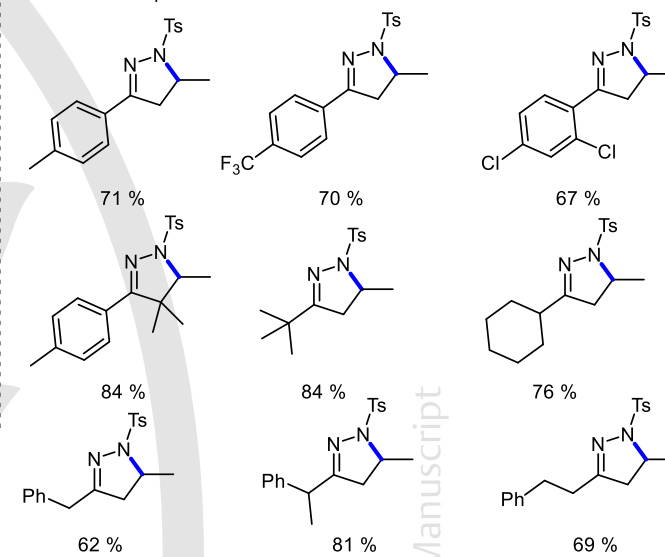
amidyl radicals

Photocatalysts

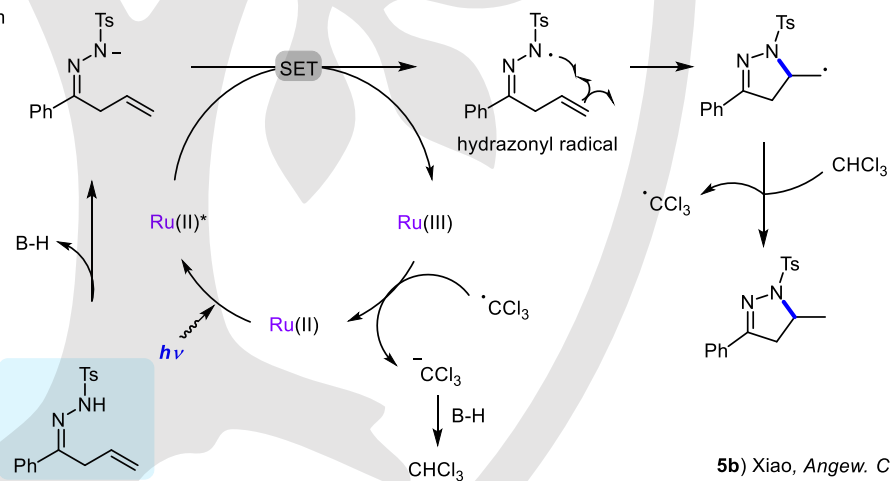
5-*exo*-trig cyclizations

5a) Newcomb, *Tetrahedron Letters*, 1991, 32, 1035.

Selected examples



Proposed mechanism



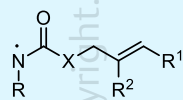
5b) Xiao, *Angew. Chem. Int. Ed.*, 2014, 53, 12163.

Figure 5 5-*exo*-trig cyclization for the synthesis of γ -lactams and substituted pyrazoles^{5a-b}

Notable features

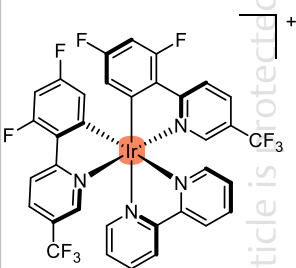
- Synthesis of substituted lactams and cyclic carbamates
- Oxidative PCTE and Photoredox oxidative quenching cycle
- O-aryl hydroxylamides as nitrogen radical precursor
- N-H and N-O bond cleavage
- Wide substrate scope
- Easy postfunctionalisation of bio active compounds

NCR Intermediate



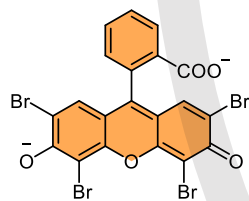
amidyl radical

Photocatalysts

 $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})]\text{PF}_6$

$$E_{\text{red}}^0(\text{Ir}(\text{III})^*/\text{Ir}(\text{IV})) \sim -1.00 \text{ V}$$

$$E_{\text{ox}}^0(\text{Ir}(\text{III})^*/\text{Ir}(\text{II})) \sim +1.32 \text{ V}$$



Eosin Y

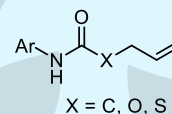
$$\lambda_{\text{max}} = 539 \text{ nm}$$

$$E_{\text{red}}^0(\text{EY}^*/\text{EY}^+) \sim -1.11 \text{ V}$$

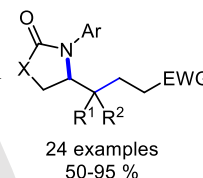
$$E_{\text{ox}}^0(\text{EY}^*/\text{EY}^+) \sim +0.83 \text{ V}$$

5-exo-trig cyclizations

$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})]\text{PF}_6$ 3 mol %
 NBu₄OP(O)(OBu)₂ 25 mol %

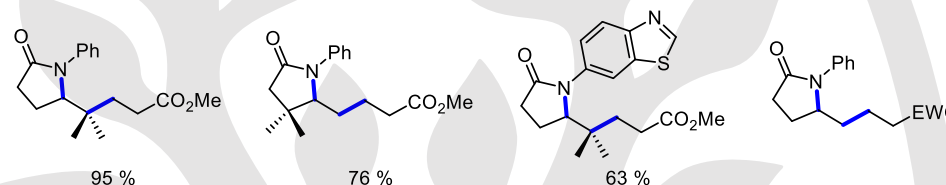


CH₂Cl₂, rt, 18 h
 Blue LEDs 34 W

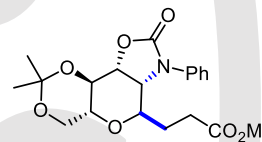


Selected examples

X = C

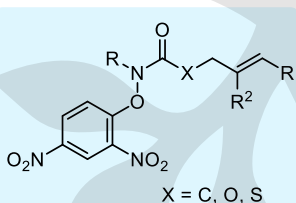
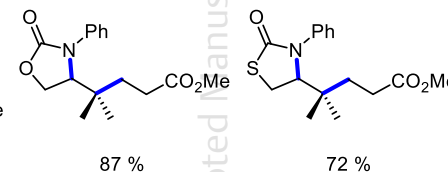
6a) Knowles, *J. Am. Chem. Soc.*, 2015, 137, 9226.

X = O



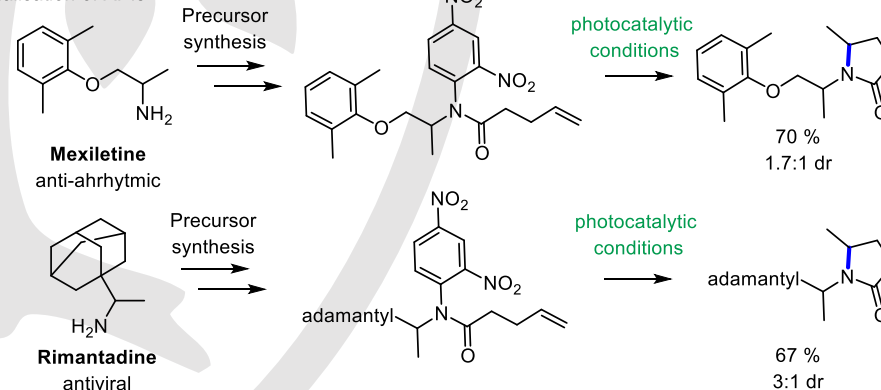
41 examples
35-79 %

X = S



Eosin Y 2 mol %
 K₂CO₃ 2 eq
 CHD 2 eq
 acetone, rt, 16 h
 Green LED

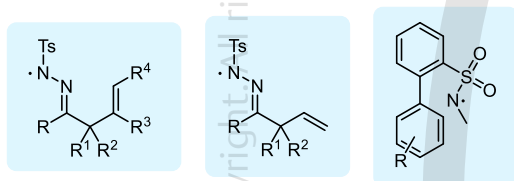
Functionalisation of APIs

6b) Leonori, *J. Am. Chem. Soc.*, 2016, 138, 8092.Figure 6 Bioactive heterocycle formation ^{6a-b}

Notable features

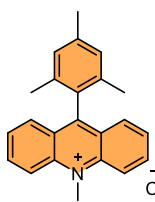
- Easy access to dihydropyrazole and tetrahydropyridazine
- Photoredox reductive quenching cycle
- *N*-tosyl hydrazines as nitrogen radical precursors
- N-H bond cleavage
- New methodology for the synthesis of sulfonamides, a really important class of API

NCR Intermediate

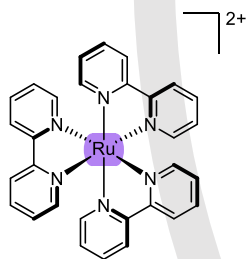


amidyl radicals

Photocatalysts

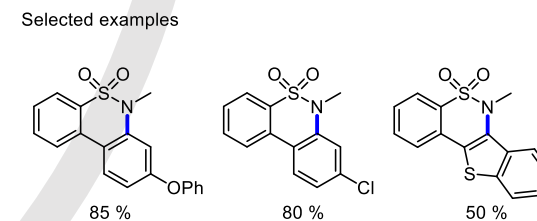
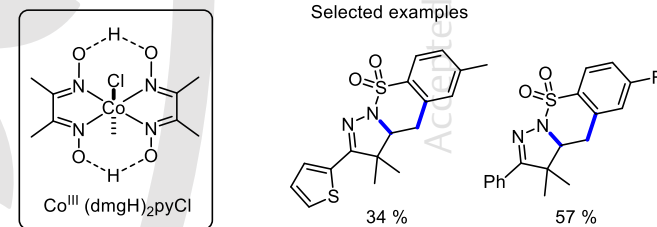
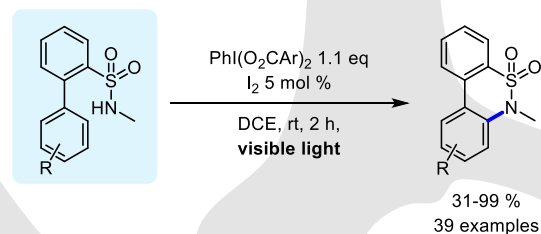
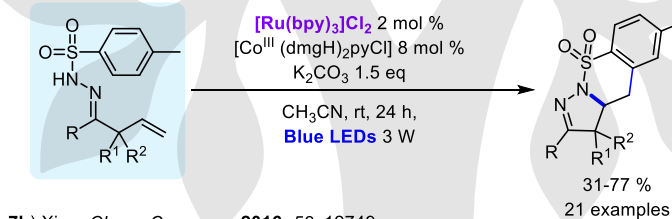
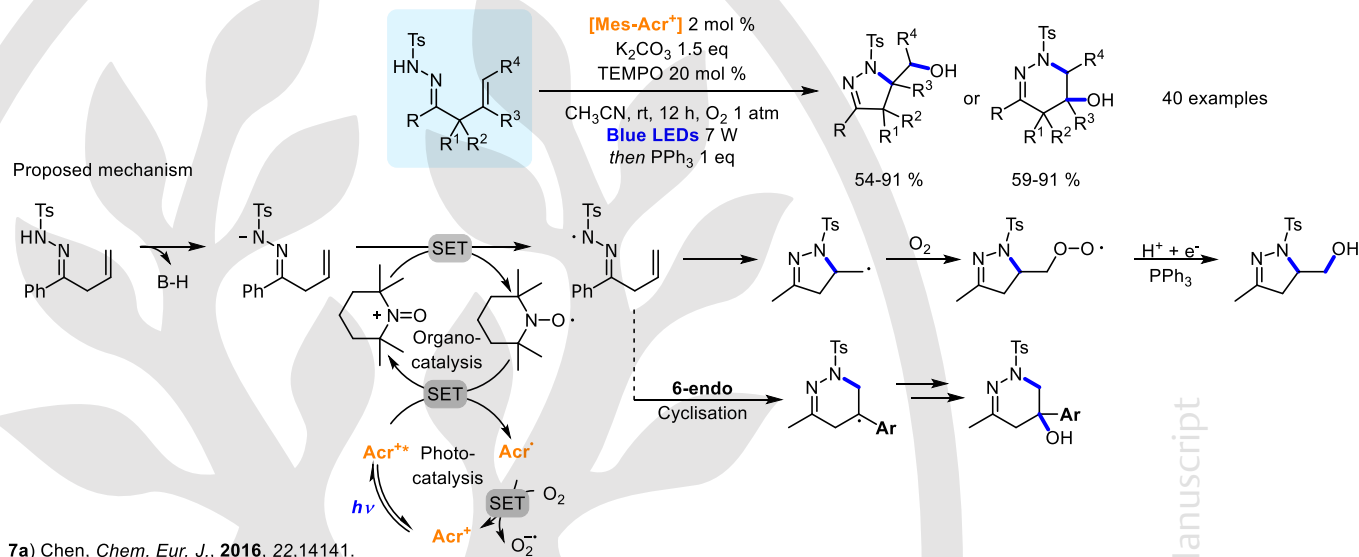


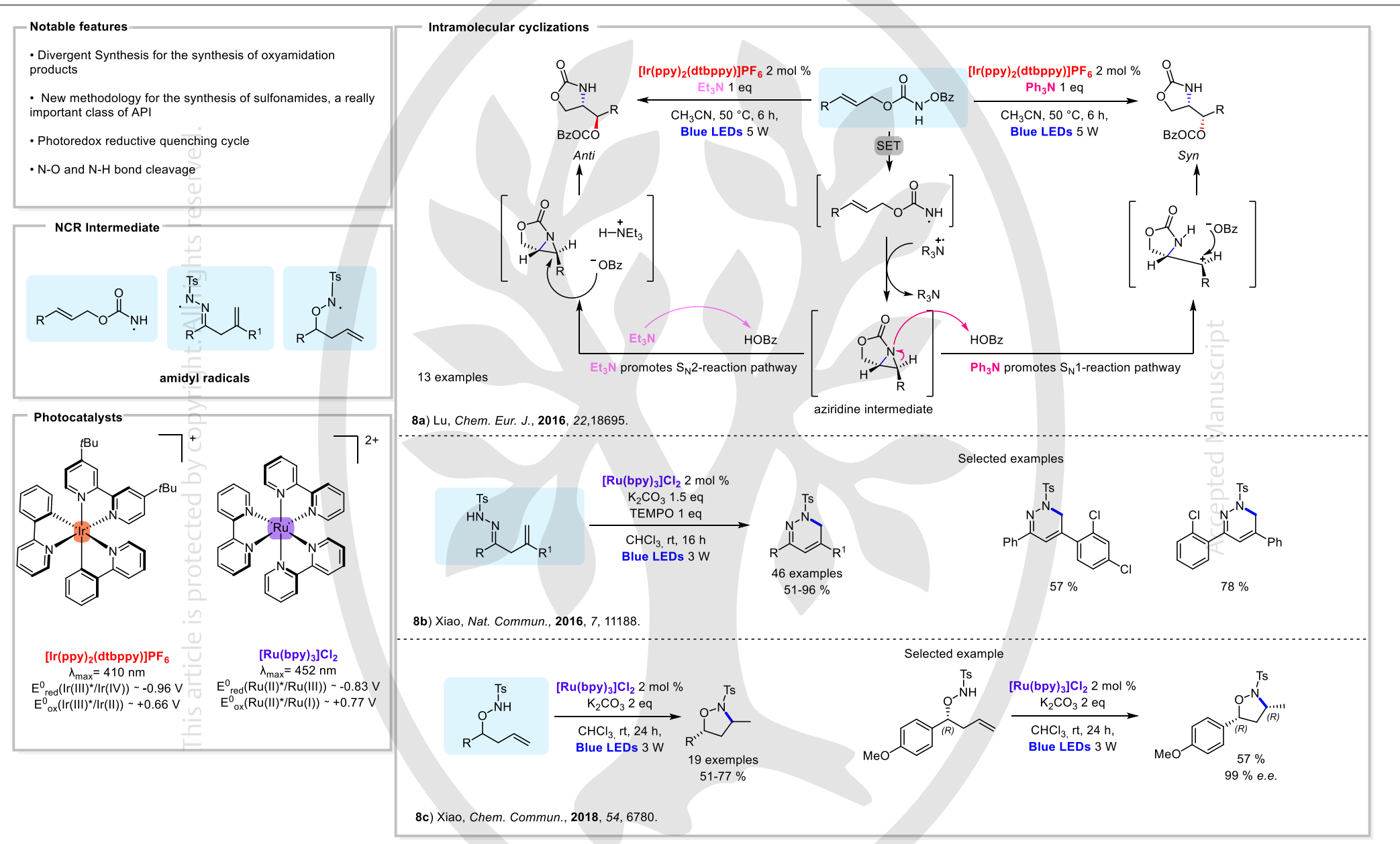
Acridinium dye
 $\lambda_{\max} = 455 \text{ nm}$
 $E_{\text{ox}}^0(\text{Acr}^{+}/\text{Acr}) \sim +1.88 \text{ V (T)}$,
 $+2.28 \text{ V (S)}$



[Ru(bpy)₃]Cl₂
 $\lambda_{\max} = 452 \text{ nm}$
 $E_{\text{red}}^0(\text{Ru(II)}^*/\text{Ru(III)}) \sim -0.83 \text{ V}$
 $E_{\text{ox}}^0(\text{Ru(II)}^*/\text{Ru(I)}) \sim +0.77 \text{ V}$

Intramolecular Cyclizations

Figure 7 Heterocycle and sulfonamide formation^{7a-c}

Figure 8 Heterocycle formation ^{8a-c}

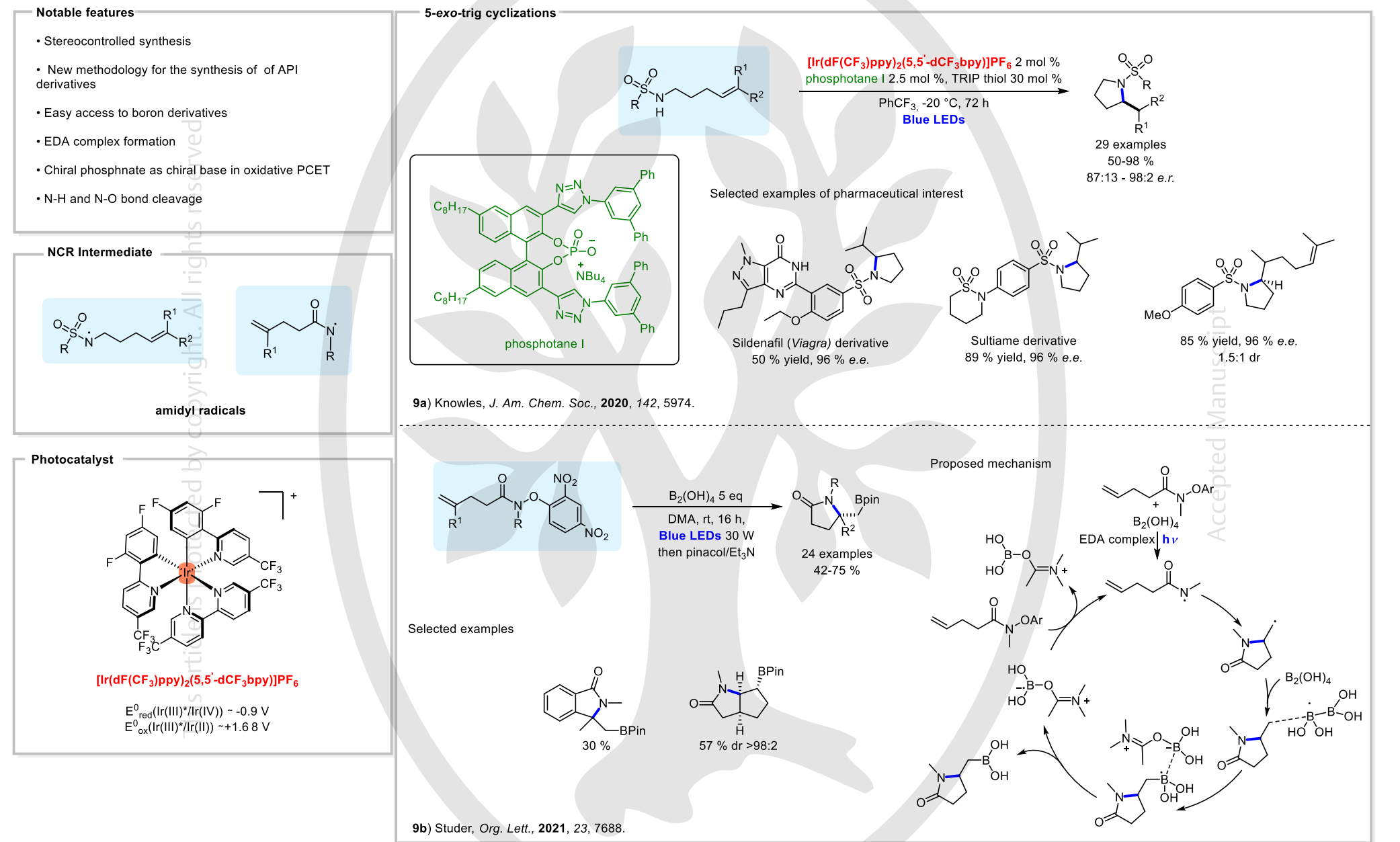
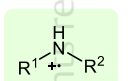


Figure 9 5-exo-trig applied to heterocycle formation 9a-b

Notable features

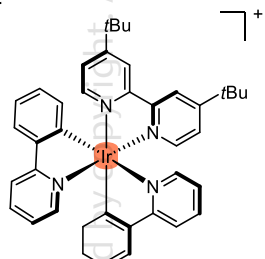
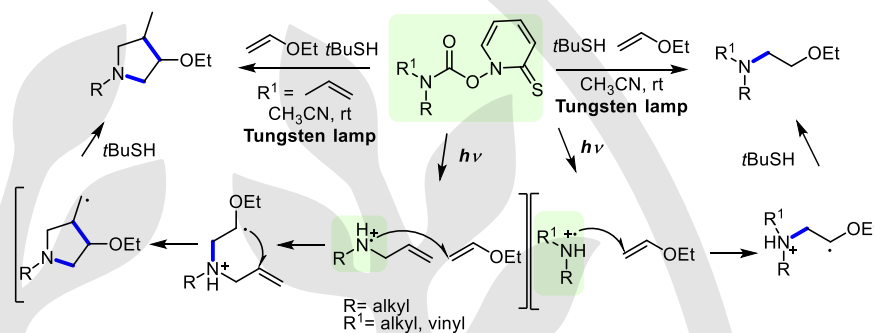
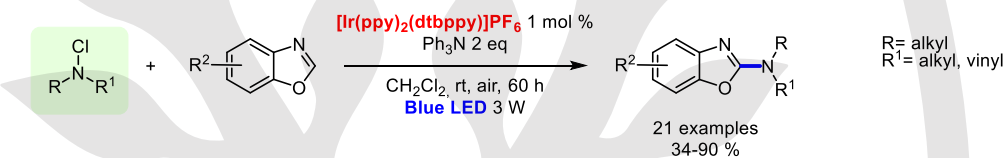
- New easy access to functionalised aliphatic amines
- Easy access to aminated benzoxazole
- Photochemical homolytic cleavage and Photoredox reductive quenching cycle
- *N*-hydroxypyridine-2-thione carbamates and *N*-chloro amines as nitrogen radical precursors
- N-O and N-Cl bond cleavage

NCR Intermediate

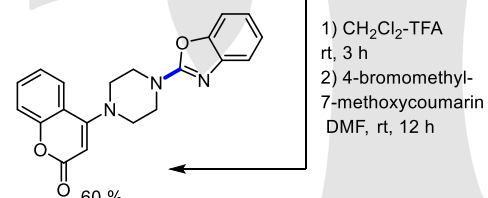
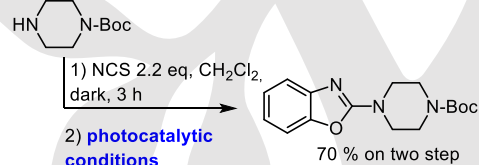


aminium radical

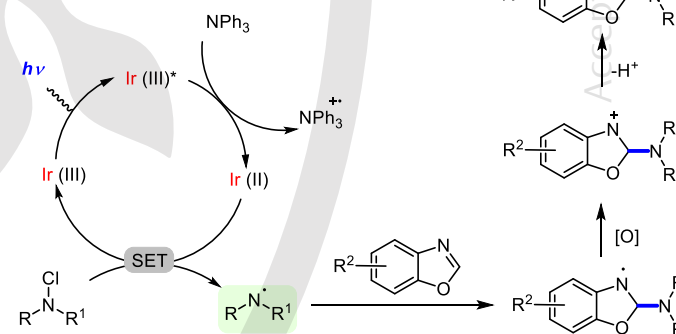
Photocatalyst

**[Ir(ppy)₂(dtbbpy)]PF₆** $\lambda_{\max} = 410 \text{ nm}$ $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.96 \text{ V}$ $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.66 \text{ V}$ Addition to Π systems**10a)** Newcomb, *Tetrahedron Lett.*, **1990**, 31, 1675.

Synthesis of anti- HIV reagent

**10b)** Xue, *Synlett*, **2014**, 25, 2013.

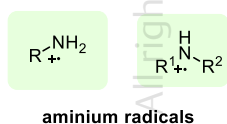
Proposed mechanism

**Figure 10** Addition of aminium radicals to Ethyl vinyl ether and benzoxazoles^{10a-b}

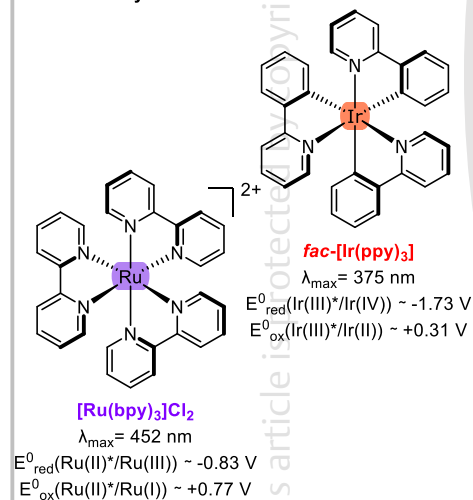
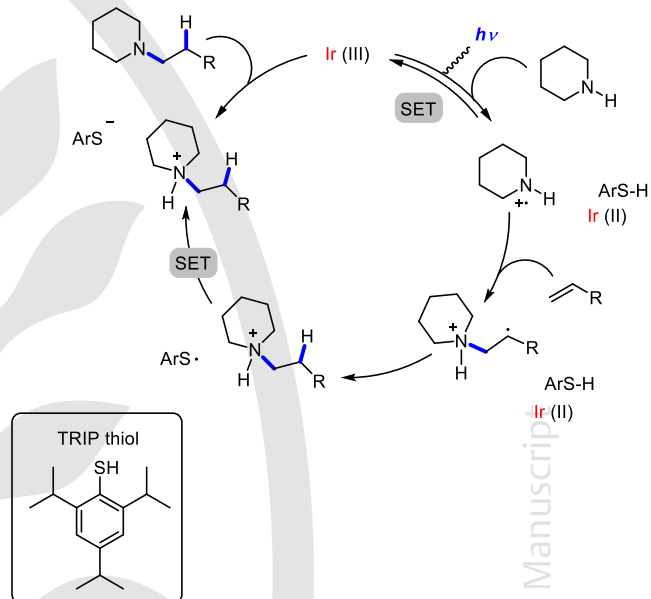
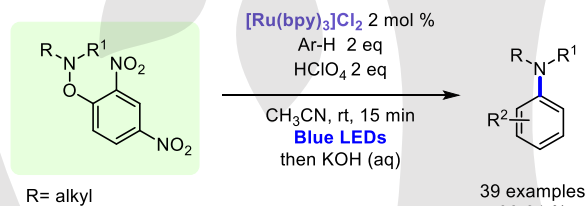
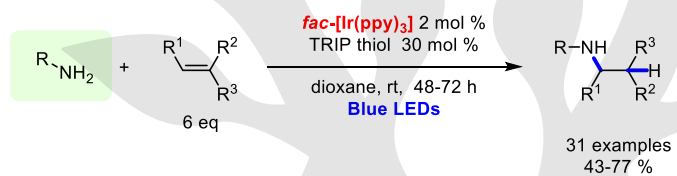
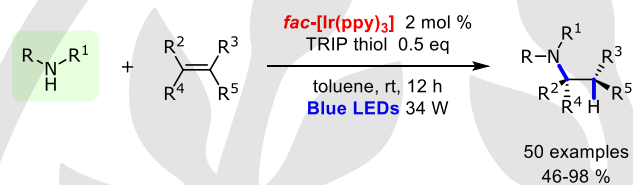
Notable features

- New easy access to functionalised aliphatic amines
- Easy access to anilines
- Photochemical homolytic cleavage and photoredox reductive quenching cycle
- Amines and O-aryl hydroxylamines as nitrogen radical precursors
- N-O and N-H bond cleavage

NCR Intermediate



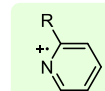
Photocatalysts

Addition to Π systemsFigure 11 Addition of aminium radicals to olefins and arenes^{11a-d}

Notable features

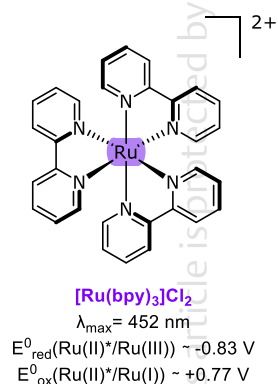
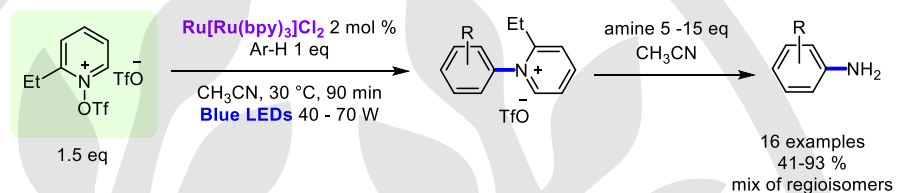
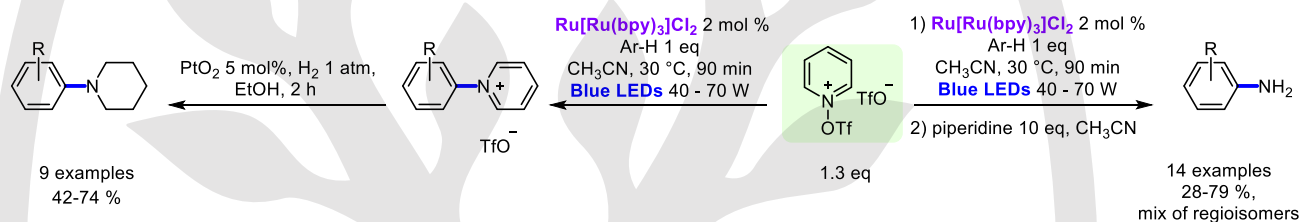
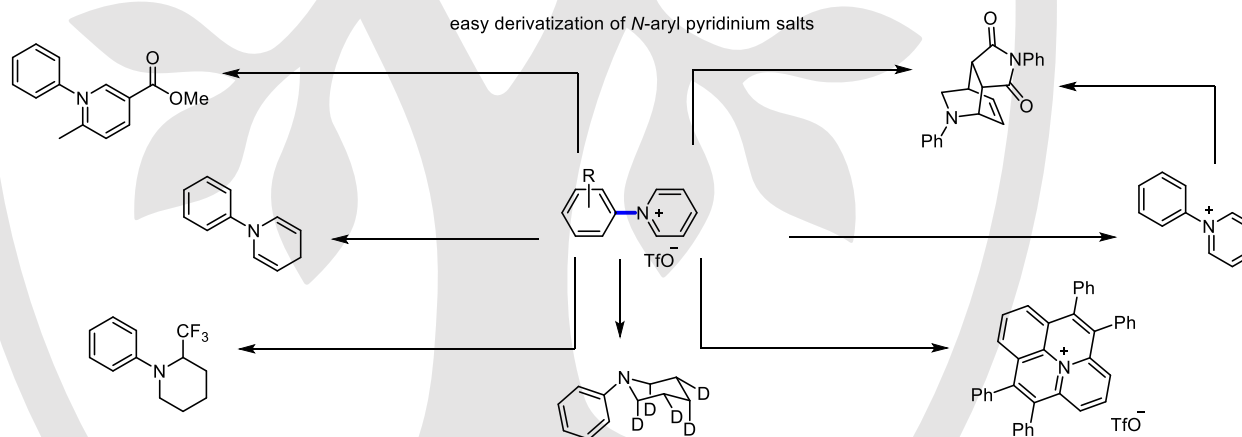
- New easy access to functionalised anilines
- Photoredox oxidative quenching cycle
- Activated pyridine *N*-oxide as nitrogen radical precursors
- N-O bond cleavage
- Pyridyl radical cations: a highly reactive class of nitrogen centered radicals due to an unpaired electron located in an sp^2 -hybridized orbital.

NCR Intermediate



pyridyl radical

Photocatalyst

Addition to Π systems12a) Ritter, *Angew. Chem. Int. Ed.*, 2019, 58, 532.12b) Carreira, *Angew. Chem. Int. Ed.*, 2019, 58, 526.easy derivatization of *N*-aryl pyridinium saltsFigure 12 Pyridyl radicals addition to arenes for the synthesis of high tunable pyridinium salts^{12a-c}

Notable features

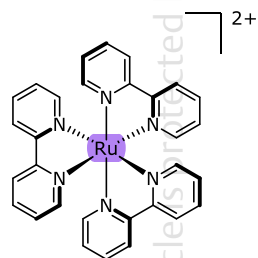
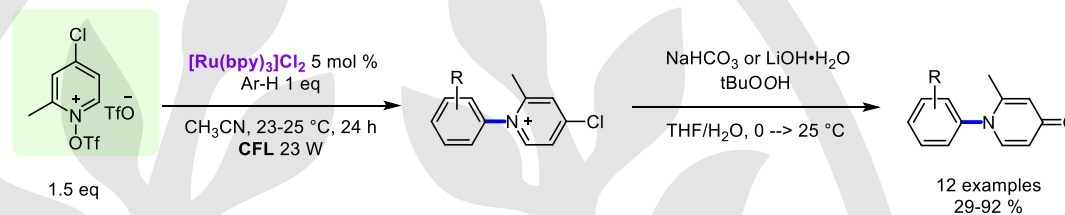
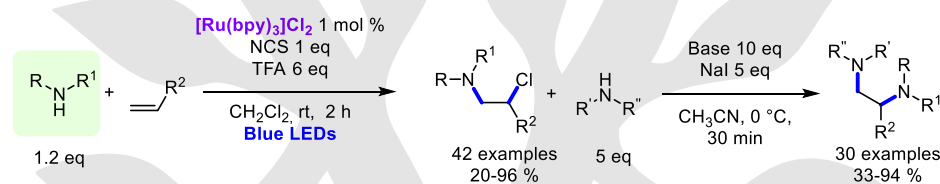
- New easy access to functionalised anilines and diamones
- Photoredox reductive quenching cycle
- Activated pyridine *N*-oxide and chloroamines as nitrogen radical precursors
- N-O and N-Cl bond cleavage

NCR Intermediate

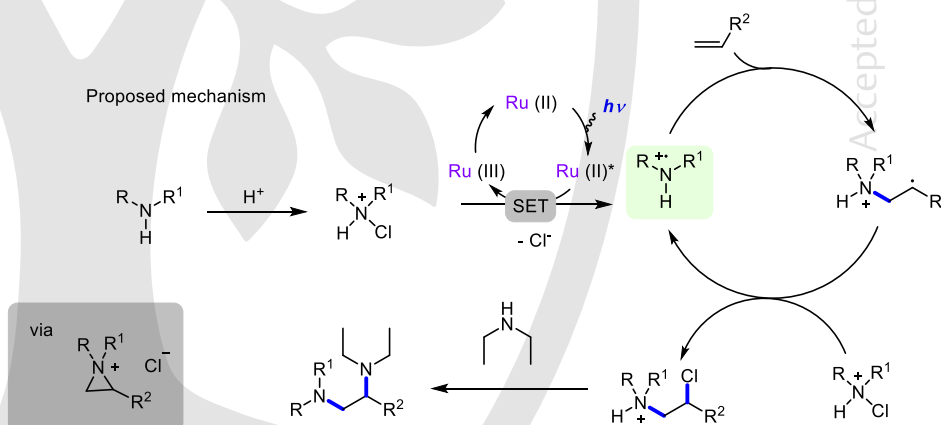


aminium radicals

Photocatalyst

**[Ru(bpy)₃]Cl₂** $\lambda_{\text{max}} = 452 \text{ nm}$ $E_{\text{red}}^0(\text{Ru(II)}^*/\text{Ru(III)}) \sim -0.83 \text{ V}$ $E_{\text{ox}}^0(\text{Ru(II)}^*/\text{Ru(I)}) \sim +0.77 \text{ V}$ Addition to Π systems13a) Ritter, *Org. Lett.*, 2019, 21, 5363.

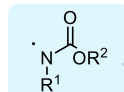
Proposed mechanism

13b) Leonori, *Angew. Chem. Int. Ed.*, 2020, 59, 15021.Figure 13 Aminium Radical addition to arenes and olefins to synthesize pyridinium salts and diamines^{13a-b}

Notable features

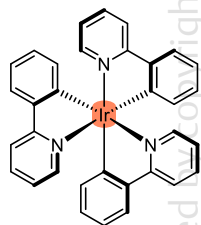
- Enantioselective α -amination of aldehydes
- In flow synthesis of enantioenriched α -aminated aldehyde
- Carbamate as nitrogen radical precursors
- N-O bond cleavage

NCR Intermediate



amidyl radical

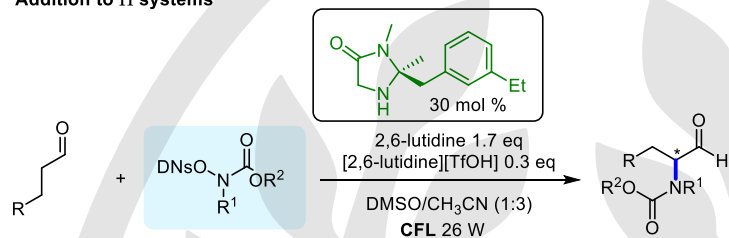
Photocatalyst

**fac-Ir(ppy)₃** $\lambda_{\text{max}} = 375 \text{ nm}$ $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -1.73 \text{ V}$ $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.31 \text{ V}$

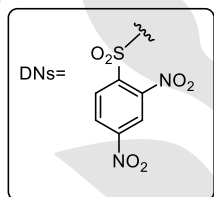
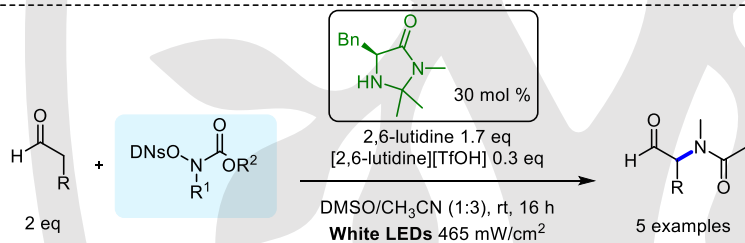
Further reading

- 14c)** MacMillan, *Science*, **2008**, 322, 77.
- 14d)** Seeberger, *Chem. Rev.*, **2017**, 117, 11796.
- 14e)** Noël, *Trends in Chemistry*, **2020**, 2, 92.

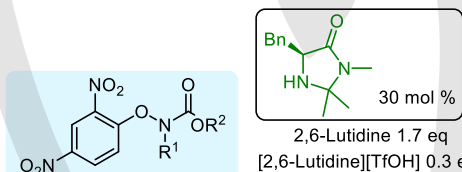
Addition to II systems



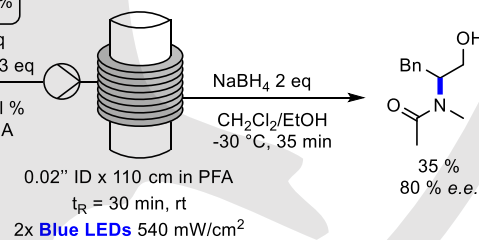
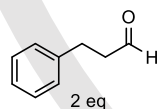
16 examples
79-67 %
94-86 % e.e.

**14a)** MacMillan, *J. Am. Chem. Soc.*, **2013**, 135, 11521.

5 examples
15-52 %
73-85 % e.e.

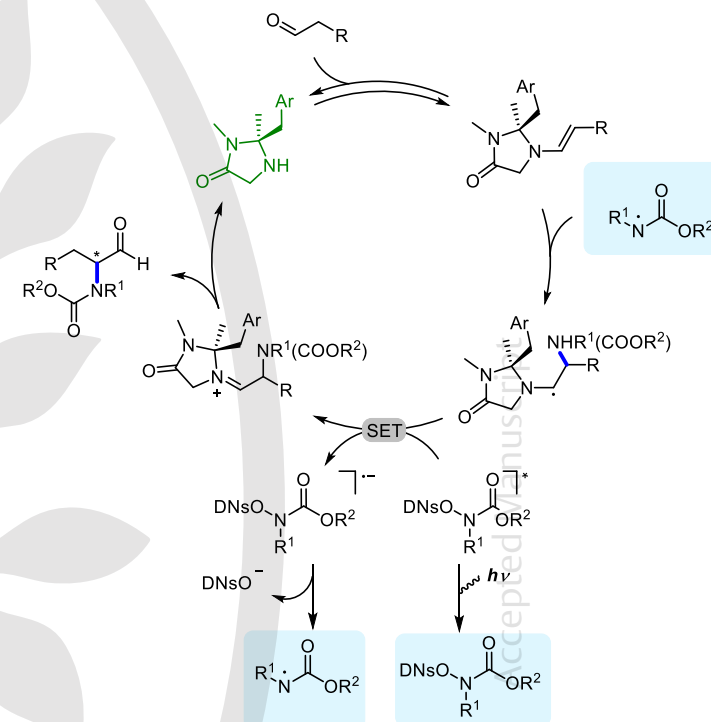


14b) Benaglia, *Eur. J. Org. Chem.*, **2023**, 26, e202201309.



35 %
80 % e.e.

Common mechanism



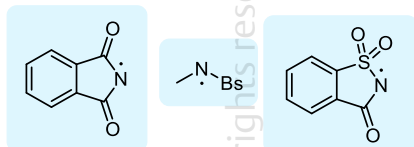
Method	Productivity(mmol/h)	Rel. factor
batch	0.004687	1
coil 223 μL	0.48176	103
coil 995 μL	0.97714	208

Figure 14 Amidyl radical in the enantioselective photoredox α -amination of aldehyde^{14a-e}

Notable features

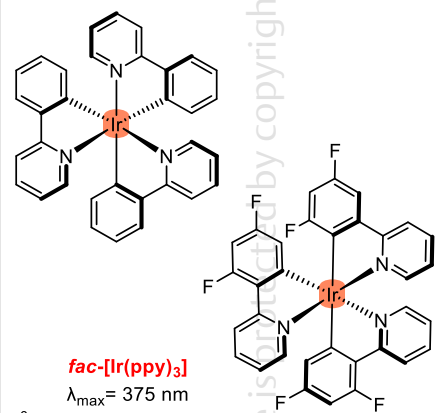
- Access to aryl and heteroaryl substitutions
- Photoredox oxidative quenching cycle and photochemical homolytic cleavage
- Phthalimide, saccarin and *N,O*-diphenyl-*N*-methylhydroxylamine as nitrogen radical precursors
- N-X and N-O bond cleavage

NCR Intermediate



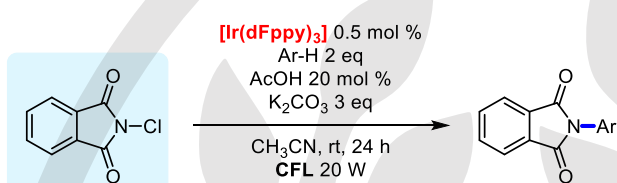
amidyl radicals

Photocatalysts



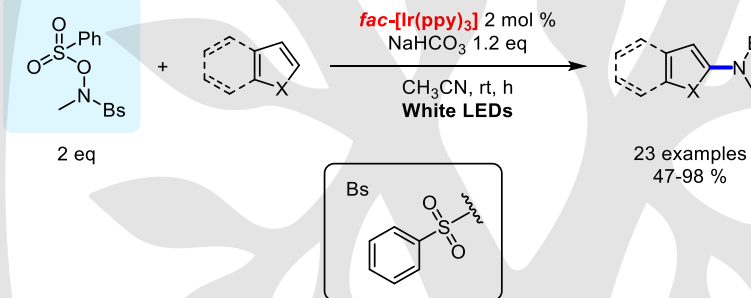
fac-[Ir(ppy)₃]
 $\lambda_{\max} = 375 \text{ nm}$
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -1.73 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.31 \text{ V}$

[Ir(dFppy)₃]
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -1.24 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +1.00 \text{ V}$

Addition to Π systems

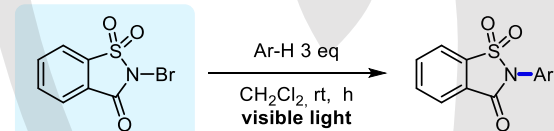
22 examples
40-60 %

15a) Lee, *Chem. Commun.*, 2014, 50, 9273.



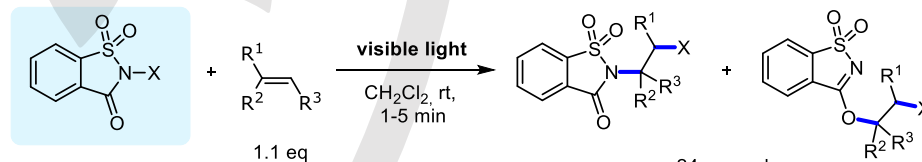
23 examples
47-98 %

15b) Yu, *Org. Lett.*, 2014, 16, 3504.



25 examples
49-90 %

15c) Cheng, *Chem. Eur. J.*, 2014, 20, 14231.



24 examples
75-95 %
2 : 1

15d) Cheng, *Org. Chem. Front.*, 2016, 3, 447.

Proposed mechanism

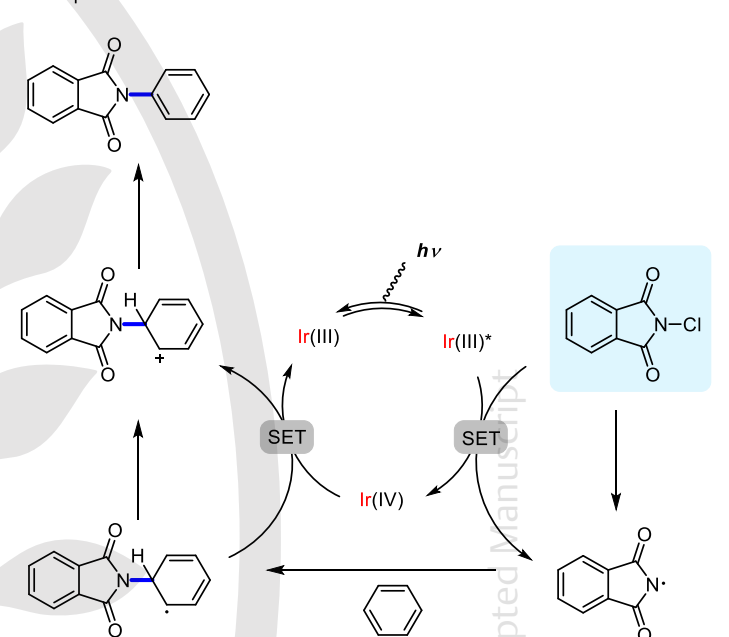
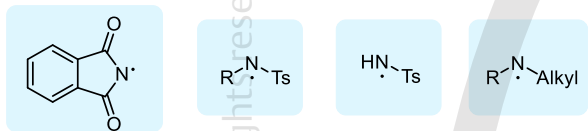


Figure 15 Amidyl radicals in imidation and amidation of arenes and heteroarenes and halo functionalization of alkenes^{15a-d}

Notable features

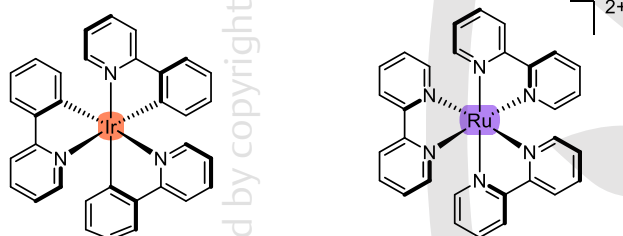
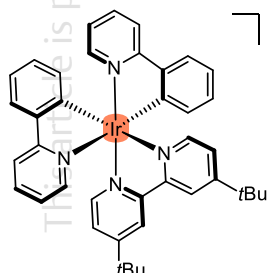
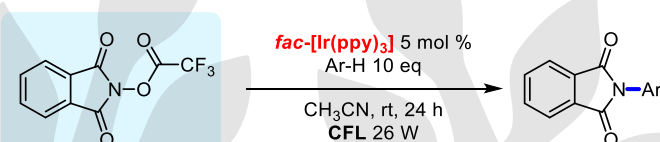
- Aryl functionalisation and double addition to alkenes
- Photoredox oxidative quenching cycle
- *N*-acyloxyphthalimide and pyridinium salt as nitrogen radical precursors
- Amine and *N*-chloro amine as nitrogen radical precursors
- N-O, N-N, N-Cl and N-H bond cleavage

NCR Intermediate

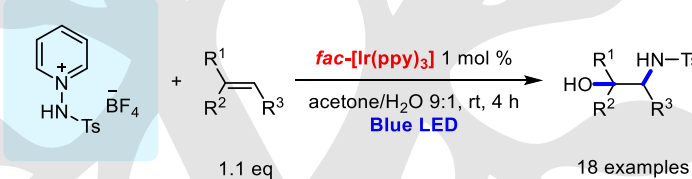
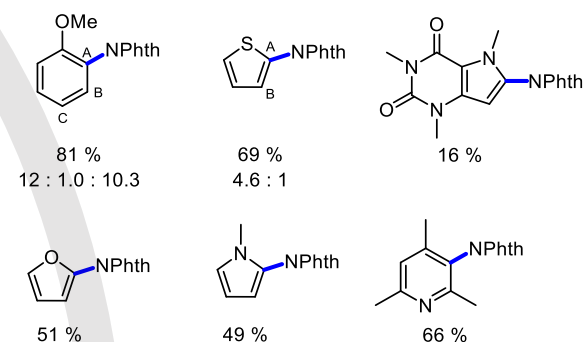
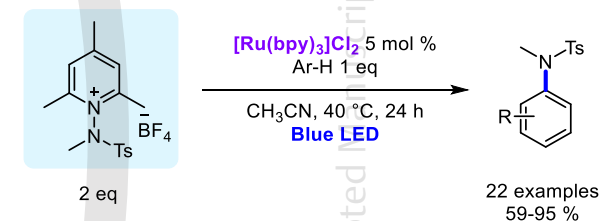
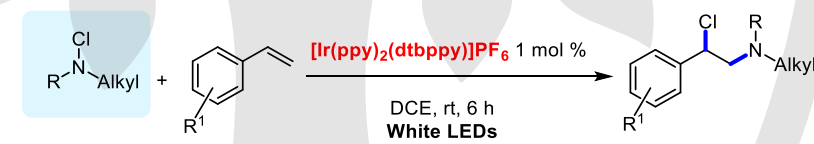


amidyl radicals

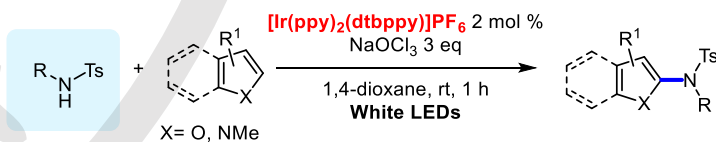
Photocatalysts

**fac-[Ir(ppy)₃]** $\lambda_{\text{max}} = 375 \text{ nm}$ $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -1.73 \text{ V}$ $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.31 \text{ V}$ **[Ru(bpy)₃]Cl₂** $\lambda_{\text{max}} = 452 \text{ nm}$ $E_{\text{red}}^0(\text{Ru(II)}^*/\text{Ru(III)}) \sim -0.83 \text{ V}$ $E_{\text{ox}}^0(\text{Ru(II)}^*/\text{Ru(I)}) \sim +0.77 \text{ V}$ **[Ir(ppy)₂(dtbbpy)]PF₆** $\lambda_{\text{max}} = 410 \text{ nm}$ $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.96 \text{ V}$ $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.66 \text{ V}$ Addition to Π systems22 examples
23-89 %16a) Sanford, *J. Am. Chem. Soc.*, 2014, 136, 5607.

Selected examples

18 examples
51-98 %16b) Akita, *Chem. Eur. J.*, 2015, 21, 11677.22 examples
59-95 %16c) Studer, *Org. Lett.* 2015, 17, 254.

R = Ts derivatives, Boc

22 examples
51-98 %16d) Yu, *Org. Biomol. Chem.*, 2015, 13, 10295.

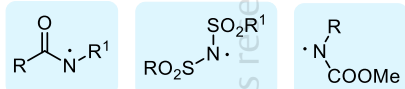
X = O, NMe

49 examples
47-98 %16e) Yu, *Chem. Eur. J.*, 2016, 22, 15669.Figure 16 Amidyl radicals in the imidation and amidation of arenes heteroarenes and double addition to alkenes^{16a-e}

Notable features

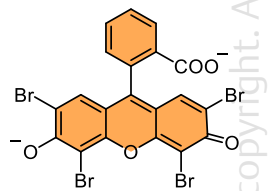
- Aryl functionalization and α -amination of 2-acyl imidazoles
- Photoredox oxidative quenching cycle
- Amines and carbamates as nitrogen radical precursors
- N-O and N-H bond cleavage

NCR Intermediate



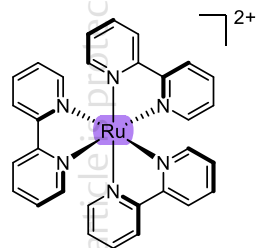
amidyl radicals

Photocatalysts

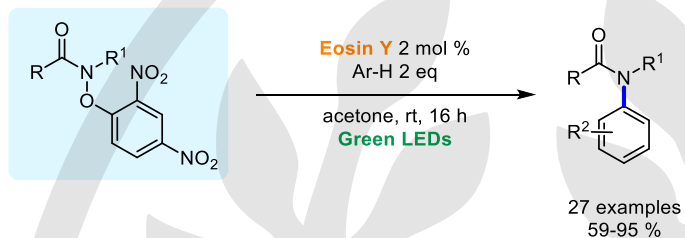


Eosin Y

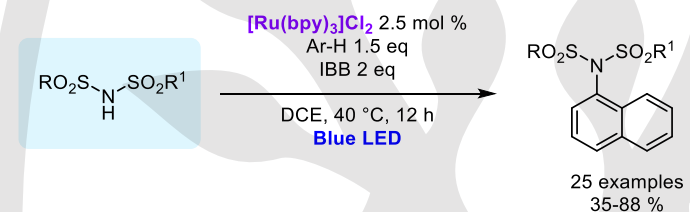
$\lambda_{\max} = 539 \text{ nm}$
 $E_{\text{red}}^0(\text{EY}^*/\text{EY}^+) \sim -1.11 \text{ V}$
 $E_{\text{ox}}^0(\text{EY}^*/\text{EY}^{\cdot-}) \sim +0.83 \text{ V}$

 $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$

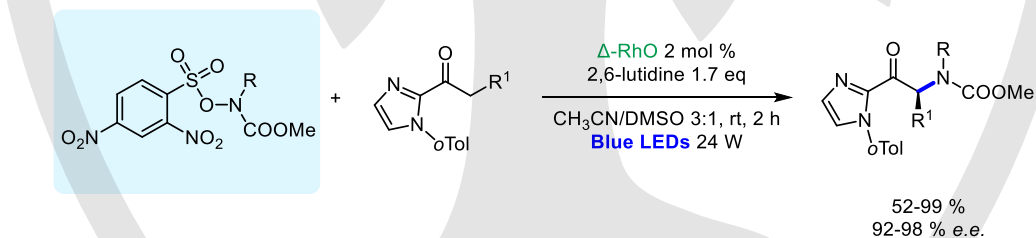
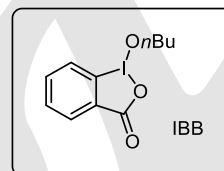
$\lambda_{\max} = 452 \text{ nm}$
 $E_{\text{red}}^0(\text{Ru}(\text{II})^*/\text{Ru}(\text{III})) \sim -0.83 \text{ V}$
 $E_{\text{ox}}^0(\text{Ru}(\text{II})^*/\text{Ru}(\text{I})) \sim +0.77 \text{ V}$

Addition to Π systems

6b) Leonori, *J. Am. Chem. Soc.* **2016**, *138*, 8092.



17a) Itami, *Chem.* **2017**, *2*, 383.



17b) Meggers, *Chem. Eur. J.* **2016**, *22*, 9102.

Proposed mechanism

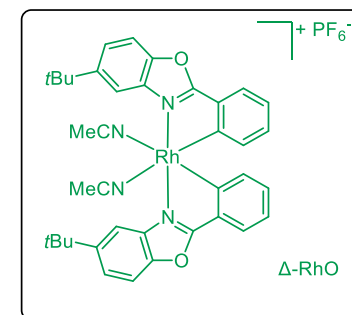
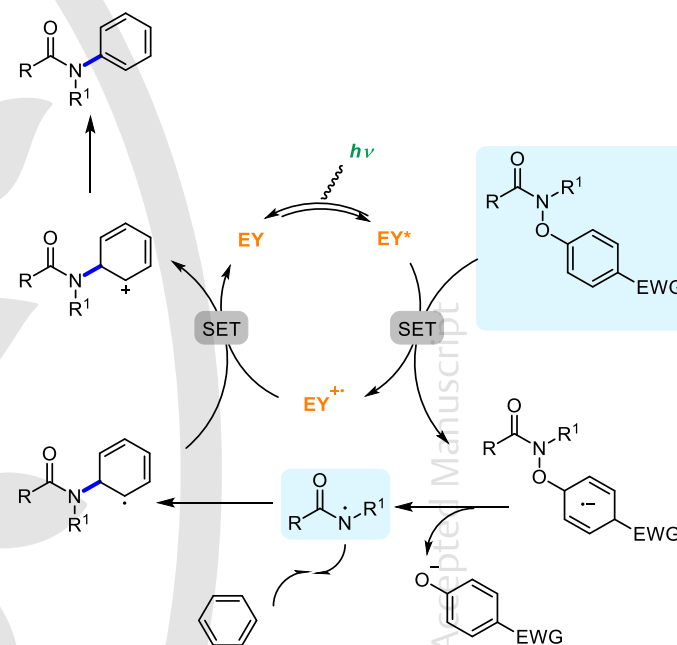


Figure 17 Amidyl radicals in amidation of arenes and α -amination of 2-acyl imidazoles^{6b,17a-b}

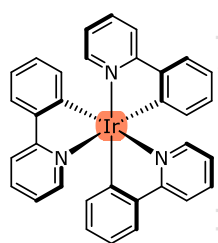
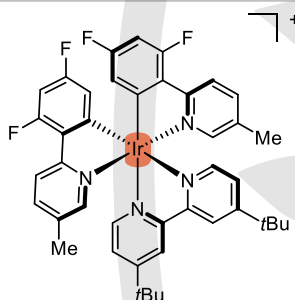
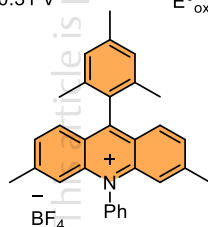
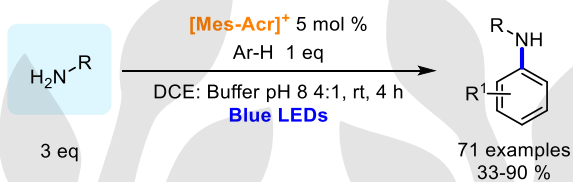
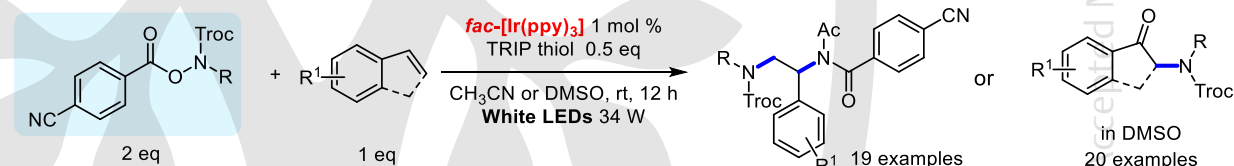
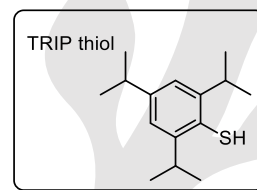
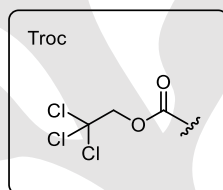
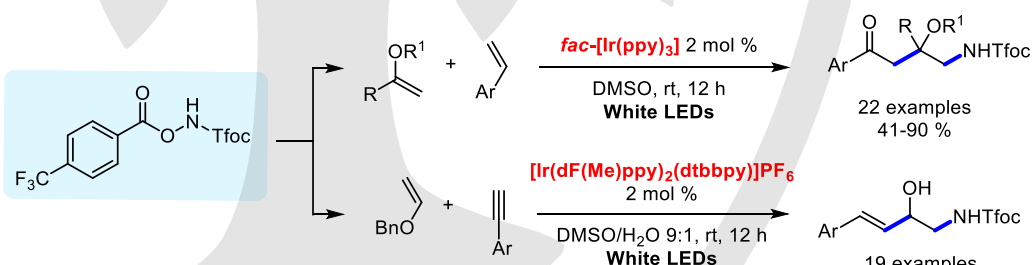
Notable features

- Easy access to anilines and functionalized β -aminoalcohol derivatives
- Diamidation and oxidative amidation of alkenes
- Photoredox oxidative quenching cycle
- Amines and carbamates as nitrogen radical precursors
- N-O and N-H bond cleavage

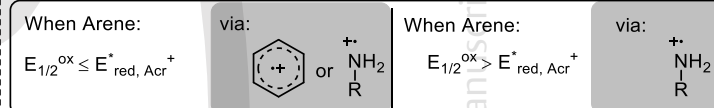
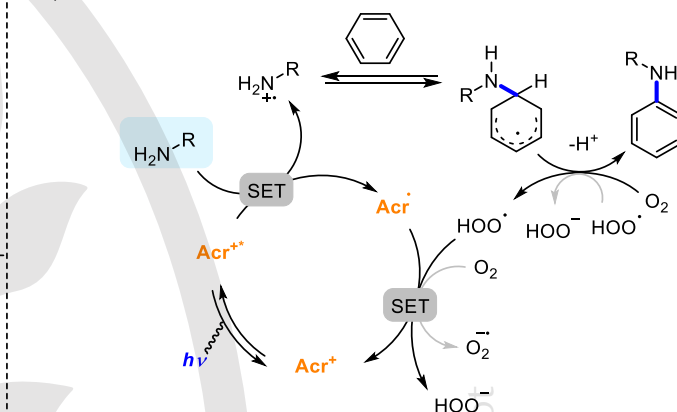
NCR Intermediate



Photocatalysts

**fac-[Ir(ppy)₃]** $\lambda_{\max} = 375 \text{ nm}$ $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -1.73 \text{ V}$ $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.31 \text{ V}$ **[Ir(dF(Me)ppy)₂(dtbbpy)]PF₆** $\lambda_{\max} = 360 \text{ nm}$ $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.97 \text{ V}$ $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.92 \text{ V}$ **Acridinium dye**Addition to Π systems18a) Nicewicz, *Angew. Chem. Int. Ed.*, **2017**, *56*, 15644.18b) Yu, *Org. Lett.*, **2017**, *19*, 2909.18c) Yu, *Org. Lett.*, **2018**, *20*, 401.

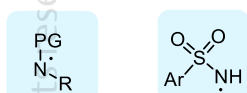
Proposed mechanism

Figure 18 Amidyl radicals in arene functionalization and double addition of olefines^{18a-c}

Notable features

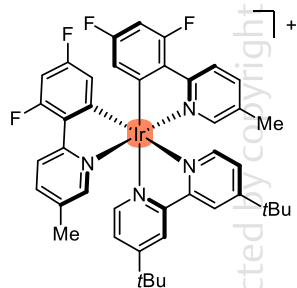
- Double additions to terminal alkenes
- Anti-Markovnikov hydroamination of olefins
- Photoredox oxidative and reductive quenching cycle
- Carbamates and sulfonamide as nitrogen radical precursors
- N-O and N-H bond cleavage

NCR Intermediate

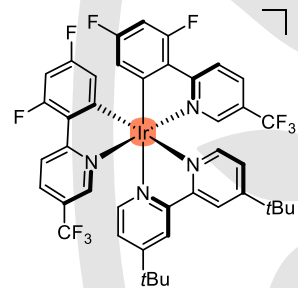


amidyl radicals

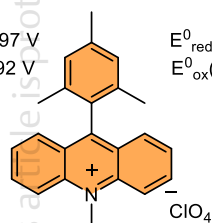
Photocatalysts

**[Ir(dF(Me)ppy)₂(dtbbpy)]PF₆**

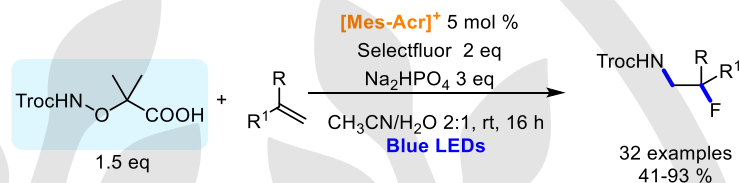
$\lambda_{\text{max}} = 360 \text{ nm}$
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.97 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.92 \text{ V}$

**[Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆**

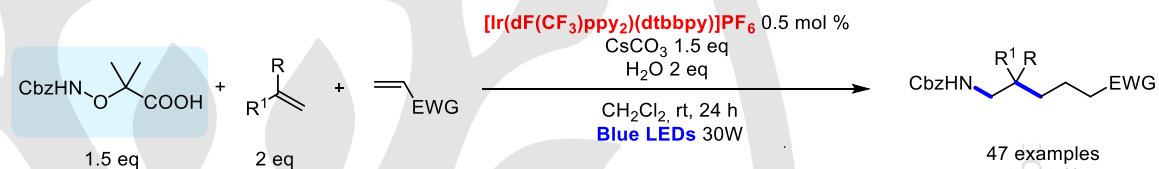
$\lambda_{\text{max}} = 380 \text{ nm}$
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.89 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +1.21 \text{ V}$

**Acridinium dye**

$\lambda_{\text{max}} = 455 \text{ nm}$
 $E_{\text{ox}}^0(\text{Acr}^{+*}/\text{Acr}) \sim +1.88 \text{ V (T)},$
 $+2.28 \text{ V (S)}$

Addition to Π systems

19a) Studer, *Angew. Chem. Int. Ed.*, **2018**, 57, 10707.



19b) Studer, *Angew. Chem. Int. Ed.*, **2019**, 58, 16528.

Common mechanism

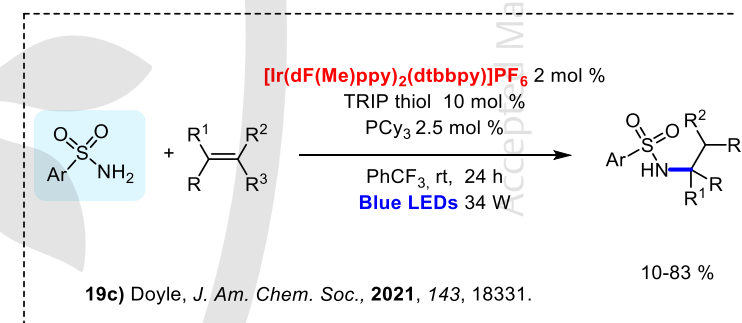
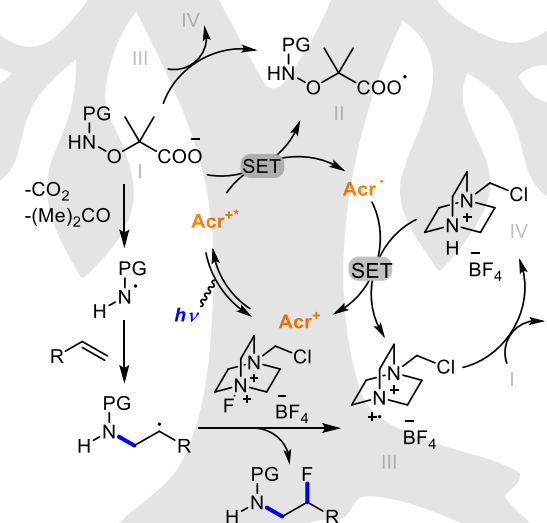
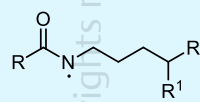


Figure 19 Amidyl radicals in three components reaction to aliphatic amines and synthesis of sulfonamides ^{19a-c}

Notable features

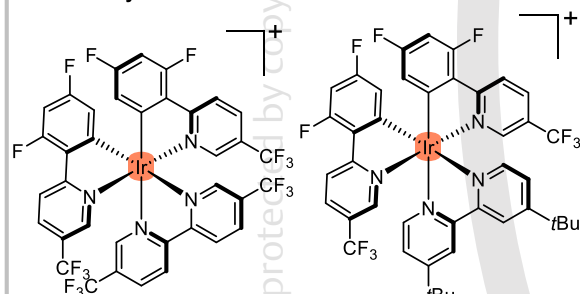
- Intra and intermolecular C-H alkylations
- Oxidative PCET activation mechanism
- N-H bond cleavage

NCR Intermediate



amidyl radical

Photocatalysts



[Ir(dF(CF₃)ppy)₂(5,5'-dCF₃bpy)]PF₆

λ_{\max} = nm
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.9$ V
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +1.68$ V

[Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆

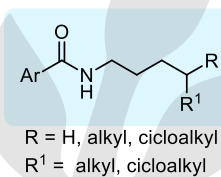
λ_{\max} = 380 nm
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -0.89$ V
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +1.21$ V

Further reading

- 20c) Knoles, *Acc. Chem. Res.* **2016**, *49*, 1546.
 20d) Nuzum, *Clin. Ther.* **2007**, *29*, 26.

1,5- Hydrogen Atom Transfer

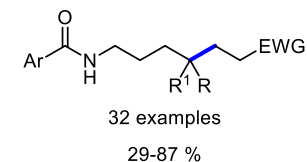
20a) Knowles, *Nature* **2016**, *539*, 268.



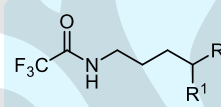
EWG = COAlkyl,
COAr, CHO

[Ir(dF(CF₃)ppy)₂(5,5'-dCF₃bpy)]PF₆ 2 mol %
 NBu₄OP(O)(OBu)₂ 5 mol %

PhCF₃, rt,
Blue LEDs



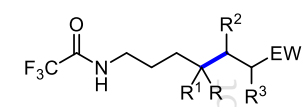
20b) Rovis, *Nature* **2016**, *539*, 272.



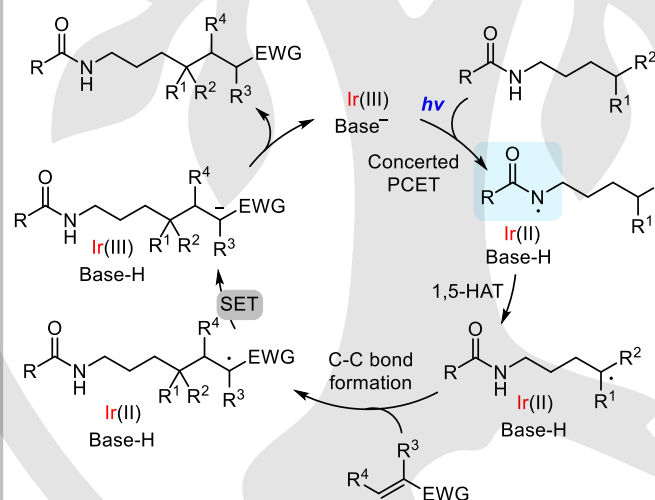
R = H, alkyl, cycloalkyl
 R¹ = alkyl, cycloalkyl, OTBS

[Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ 2 mol %

K₃PO₄
 PhCF₃, rt
 Blue LED

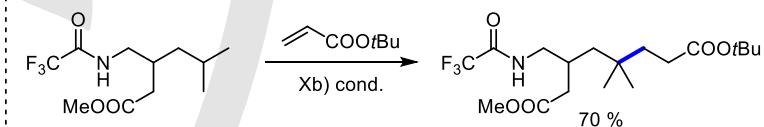
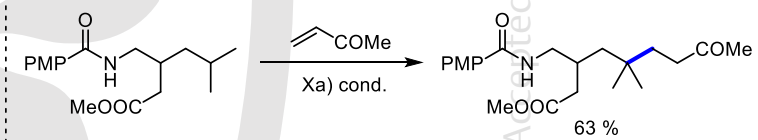


Proposed Mechanism



Selected examples

Pregabalin derivative C-H alkylation



Steroid derivative C-H alkylation

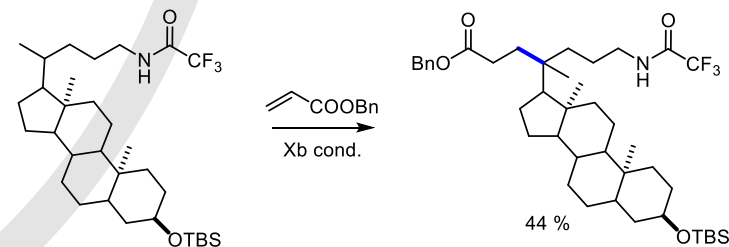
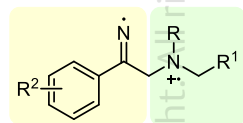


Figure 20 Remote C-H alkylation promoted by PCET^{20a-d}

Notable features

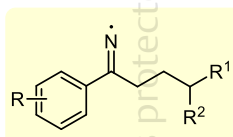
- Synthesis of functionalized imidazoles and 1,2-thiazine-1,1-dioxide
- Intramolecular and Intermolecular EDA complex activation
- β -O-aryl oximes as nitrogen radical precursors
- N-O bond cleavage

NCR Intermediate



iminyl + aminium radicals

NCR Intermediate

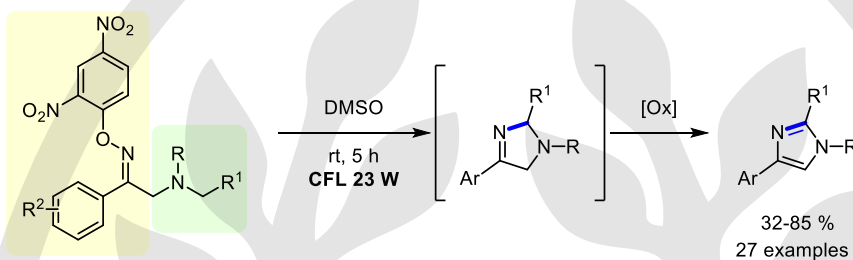


iminyl radical

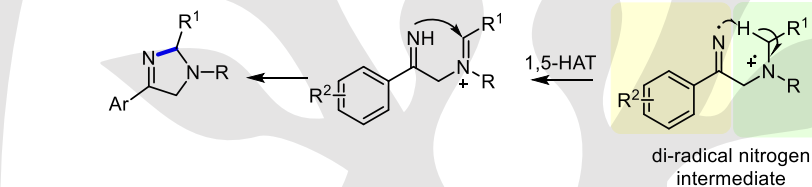
Further reading

21c) Melchiorre, *JACS*, **2021**, *143*, 12304.

1,5- Hydrogen Atom Transfer

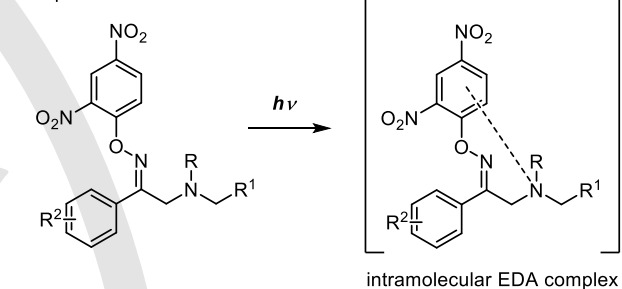


R = H, alkyl
R¹ = alkyl, Bn

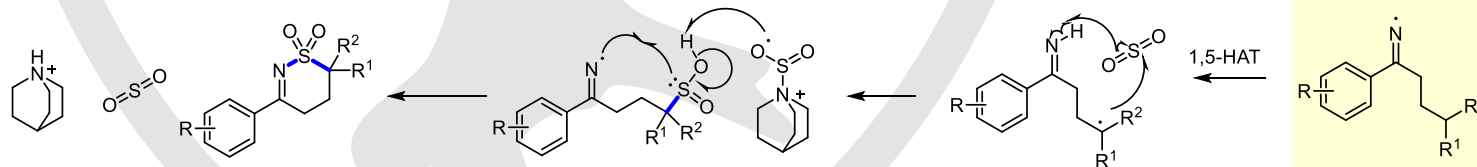
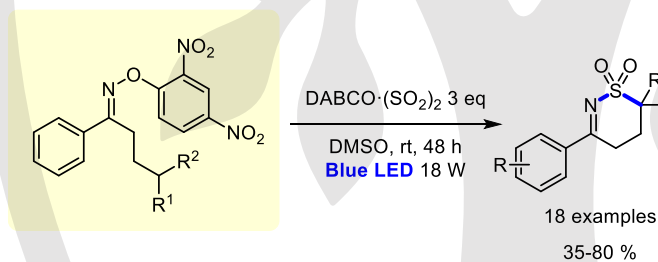
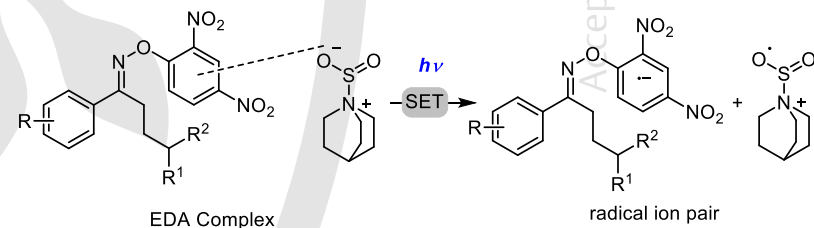


21a) Fu, *Org. Lett.*, **2017**, *19*, 1994.

Proposed mechanism



Proposed mechanism



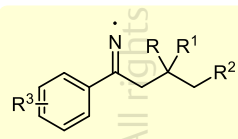
21b) Wu, *Org. Lett.*, **2017**, *19*, 4472.

Figure 21 Intramolecular C(sp³)-H Imination for the synthesis of functionalized imidazoles^{21a-b}

Notable features

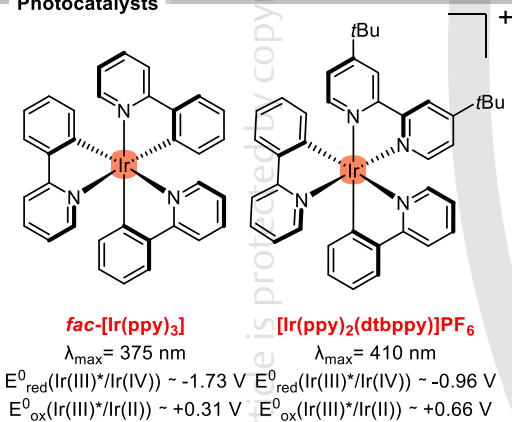
- Synthesis of fused cicloexanones
- Photoredox reductive quenching cycle
- Acyl oxime as nitrogen radical precursor
- N-O bond cleavage

NCR Intermediate

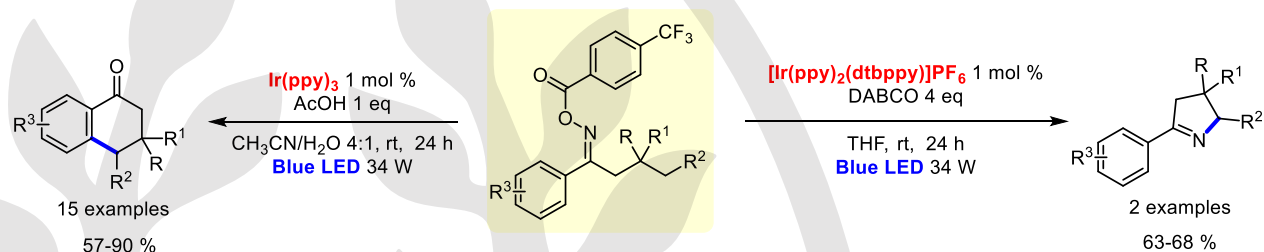


iminyl radical

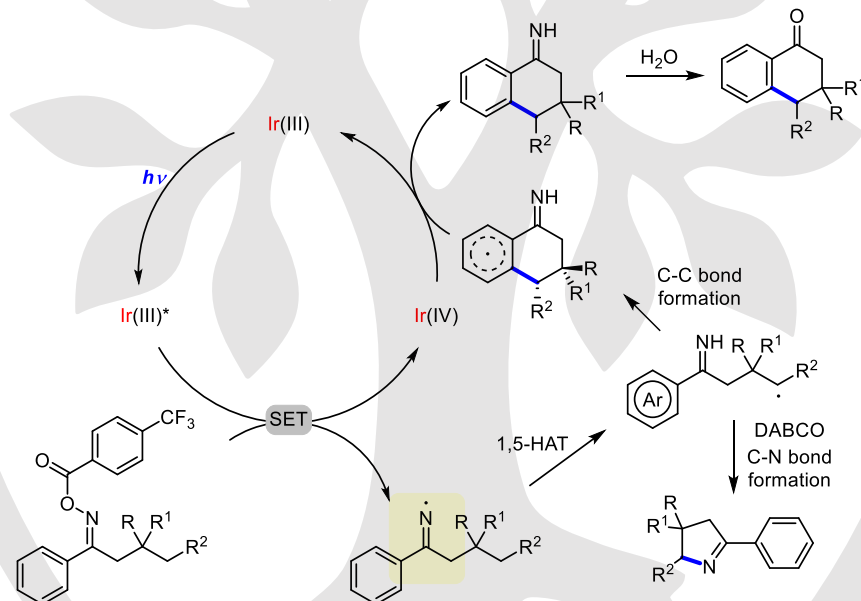
Photocatalysts



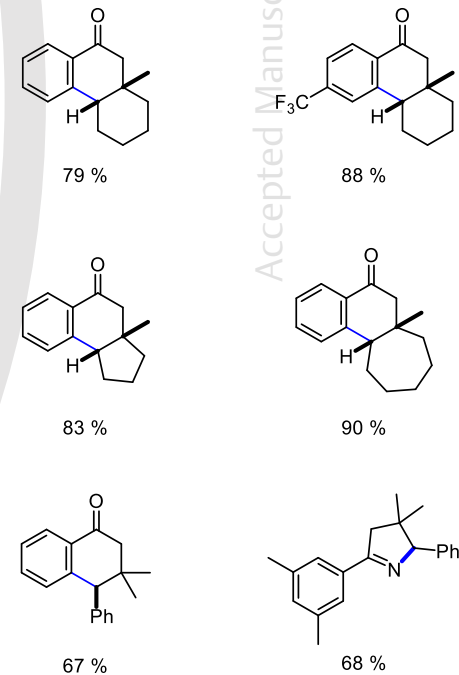
1,5- Hydrogen Atom Transfer

22a) Nevado, *Angew. Chem. Int. Ed.* 2017, 56, 1881

Proposed mechanism



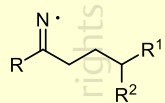
Selected examples

Figure 22 Aliphatic C-H functionalization through a 1,5-HAT cascade ^{22a}

Notable features

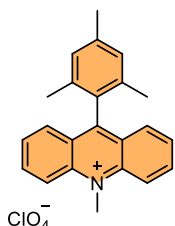
- Synthesis of γ -functionalised imines and ketones
- Photoredox oxidative quenching cycle
- α -amino-oxy acid as nitrogen radical precursor
- N-O bond cleavage

NCR Intermediate



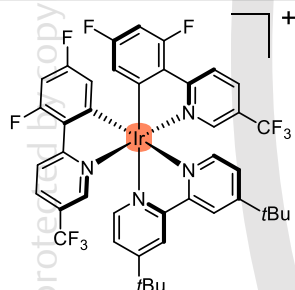
iminyl radical

Photocatalysts



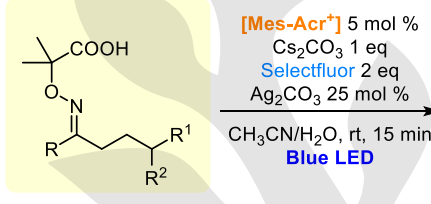
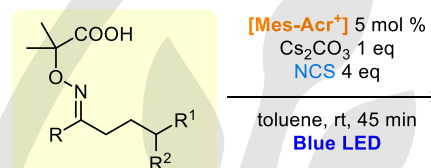
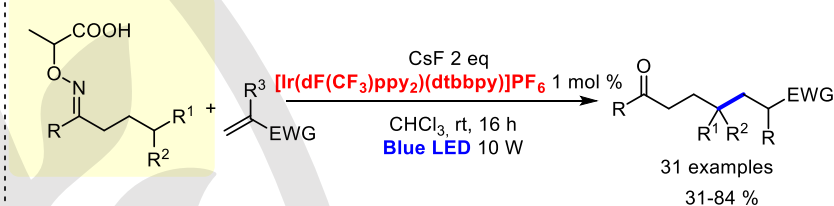
Acridinium dye

$\lambda_{\max} = 455 \text{ nm}$
 $E_{\text{ox}}^0(\text{Acr}^{+}/\text{Acr}) \sim +1.88 \text{ V (T)}$
 $+2.28 \text{ V (S)}$

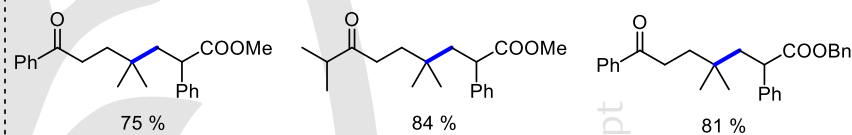
 $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$

$\lambda_{\max} = 380 \text{ nm}$
 $E_{\text{red}}^0(\text{Ir}(\text{III})^*/\text{Ir}(\text{IV})) \sim -0.89 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir}(\text{III})^*/\text{Ir}(\text{II})) \sim +1.21 \text{ V}$

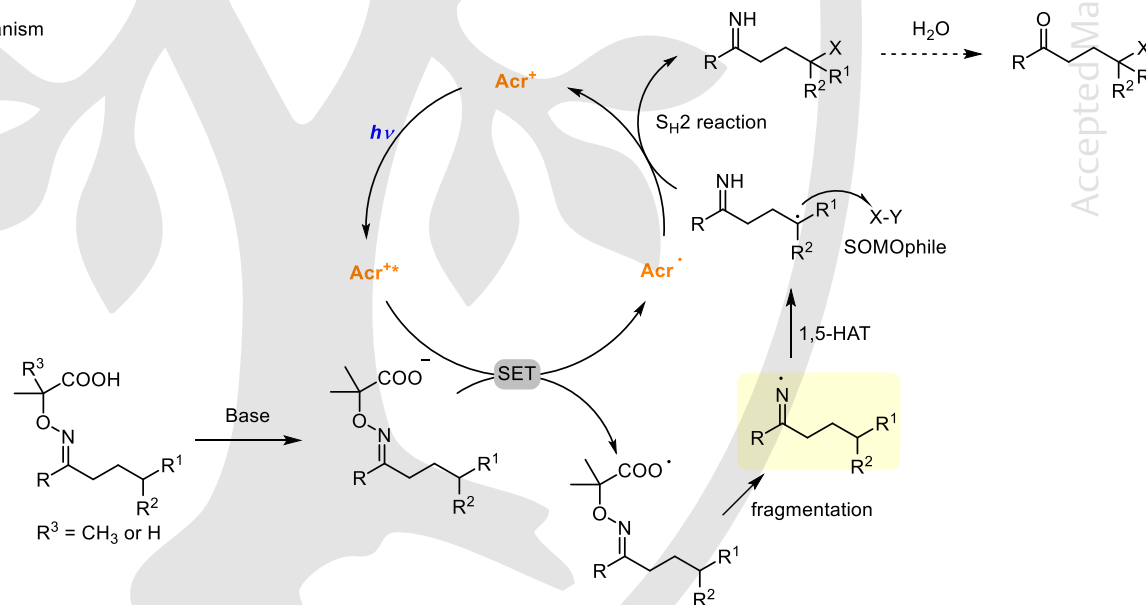
1,5-Hydrogen Atom Transfer

23a) Leonori, *Angew. Chem. Int. Ed.*, 2018, 57, 744.

Selected examples

23b) Studer, *Angew. Chem. Int. Ed.*, 2018, 130, 1708.

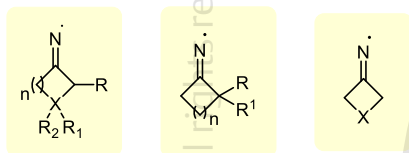
Common mechanism

Figure 23 γ -C(sp³)-H functionalization of ketones^{23a-b}

Notable features

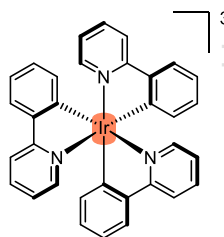
- Easy access to cyanoalkyl scaffold as future building blocks

NCR Intermediate

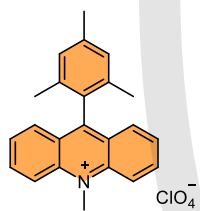


iminyl radicals

Photocatalysts

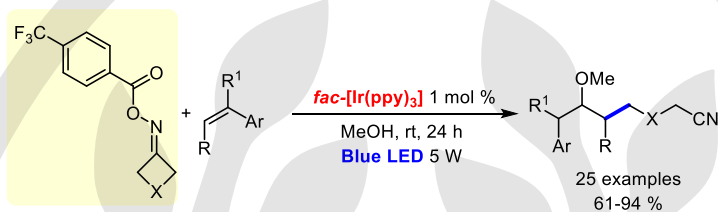
**fac-[Ir(ppy)₃]**

$\lambda_{\text{max}} = 375 \text{ nm}$
 $E_{\text{red}}^0(\text{Ir(III)}^*/\text{Ir(IV)}) \sim -1.73 \text{ V}$
 $E_{\text{ox}}^0(\text{Ir(III)}^*/\text{Ir(II)}) \sim +0.31 \text{ V}$

**Acridinium dye**

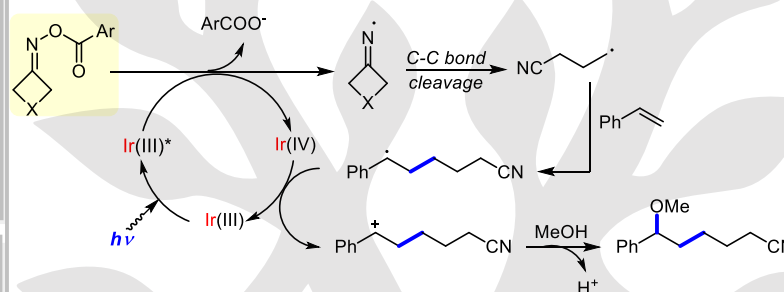
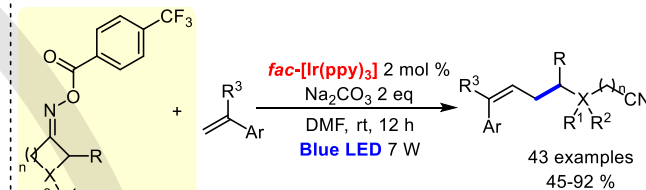
$\lambda_{\text{max}} = 455 \text{ nm}$
 $E_{\text{ox}}^0(\text{Acr}^*/\text{Acr}) \sim +1.88 \text{ V (T)}$
 $+2.28 \text{ V (S)}$

Norrish Fragmentation



X = O, N-Boc

Proposed mechanism

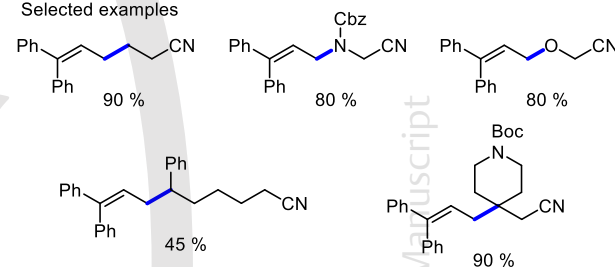
24a) Zhou, *Chem. Commun.*, 2017, 53, 11544.

X = C, O, N-Cbz

n = 1, 2, 3

R³ = Ar, Me, OTMS

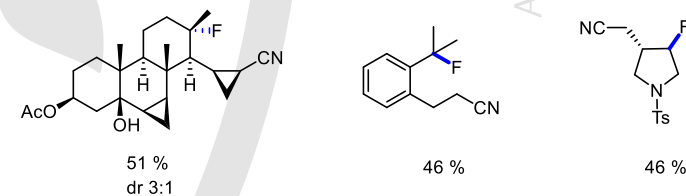
Selected examples

24b) Xiao, *Angew. Chem. Int. Ed.*, 2018, 57, 738.

Selected examples



n = 0, 1, 2

24c) Leonori, *Angew. Chem. Int. Ed.*, 2018, 57, 744.Figure 24 Norrish Fragmentations^{24a-c}

Insert all full-page Figures ahead of this line, and leave this line here – it includes a necessary section break.

Acknowledgment

MFB thanks MUR - Project PRIN2022 "BEST-CAT", financed by EU - NextGeneration EU for a postdoctoral fellowship. FF thanks MITE - Project "innovative recycling critical raw materials - RAEE" for a postdoctoral fellowship. FM thanks MUSA - Multilayered Urban Sustainability Action - project, funded by the European Union - NextGenerationEU, under the National Recovery and Resilience Plan (NRRP) Mission 4 Component 2 Investment Line 1.5: Strengthening of research structures and creation of R&D "innovation ecosystems", set up of "territorial leaders in R&D".

Conflict of Interest

The authors declare no conflict of interest.

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- (1) (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (b) Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. *Chem. Eur. J.* **2018**, *24*, 12154. (c) Pratley, C.; Fenner, S.; Murphy, J. A. *Chem. Rev.* **2022**, *122*, 8181. (d) Kärkäs, M. D. *ACS Catal.* **2017**, *7*, 4999.
- (2) (a) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.*, **1987**, *109*, 3163. (b) Maity, S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9562. (c) Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R. R. *J. Am. Chem. Soc.* **2014**, *136*, 12217. (d) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317. (e) Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2329. (f) Newcomb, M.; Marquardt, D. J.; Kumar, M. U. *Tetrahedron* **1990**, *46*, 2345. (g) Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem.* **2013**, *9*, 1977.
- (3) (a) Jiang, H.; Tong, X. A.; K., Zheng, T.; Zhang, Y.; Yu, S., *Angew. Chem. Int. Ed.* **2015**, *54*, 4055. (b) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 4299. (c) Cai, S.-H.; Xie, J. H.; Song, S.; Ye, L.; Feng, C.; Loh, T.-P. *ACS Catal.* **2016**, *6*, 5571.
- (4) (a) Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D.; *Angew. Chem. Int. Ed.* **2015**, *54*, 14017. (b) Jiang, H.; Studer, A. *Angew. Chem. Int. Ed.* **2017**, *129*, 12441. (c) Matsushita, Y.; Ochi, R.; Tanaka, Y.; Koike, T.; Akita, M. *Org. Chem. Front.* **2020**, *7*, 1243.
- (5) (a) Newcomb, M.; Esker, J. L.; *Tetrahedron Lett.* **1991**, *32*, 1035. (b) Hu, X.-Q.; Chen, J.-R.; Wei, Q.; Liu, F.-L.; Deng, Q.-H.; Beauchemin, A. M.; Xiao, W.-J., *Angew. Chem. Int. Ed.* **2014**, *53*, 12163.
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