Nitrogen-Centered Radicals in Visible-Light-Promoted Reactions

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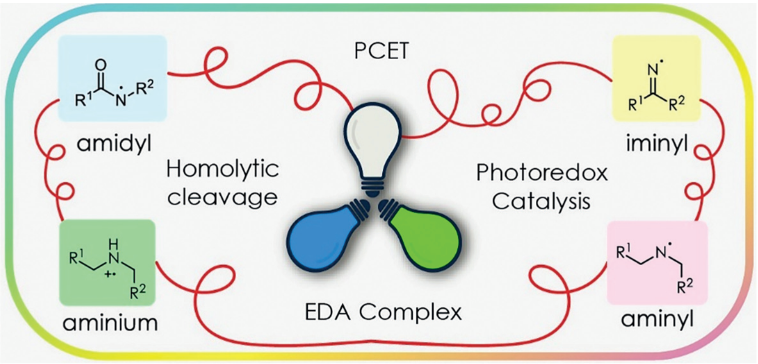

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Abstract Nitrogen-centered radicals (NCRs) have been known in the literature since the beginning of the 1900s, but only with the spread of photoredox catalysis, and in particular visible-light-mediated radical processes, has nitrogen-radical chemistry become more accessible via the in situ generation of such radicals under mild conditions. Historically, unlike their carbon counterparts, nitrogen radicals were not utilized widely in academia or industry due to a lack of efficient strategies for their production. Nowadays, NCRs are more established, and this graphical review highlights key publications from the literature, categorizing them by both the type of NCR and the type of reaction. Such nitrogen radicals can be divided into four different categories according to their electronic configuration, orbital structure and chemical behavior. Additionally, the reactivity of these radicals is mostly exploited via four main types of process: (i) intramolecular cyclization, (ii) intramolecular hydrogen atom abstraction, (iii) Norrish type I fragmentation, and (iv) 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 found in 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, highlighting the ubiquitous nature of this 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 construct 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 installed through reductive amination and alkylation, Gabriel synthesis and Hoffman degradation. However, these approaches have the same drawbacks: the requirement for prefunctionalization of the substrates and the use of high temperatures.

In recent decades, with the increased use of photocatalysis and, in particular, visible-light-mediated radical processes, nitrogen-radical chemistry has become more accessible. This revolutionary technique has made it 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 reagents, opening the door to environmentally safe, more sustainable, and non-hazardous visible-light-based chemical synthesis.

Nitrogen radicals can be divided into four different types according to their electronic configuration, orbital structure and chemical behavior. Iminyl radicals possess an sp^2-hybridized nitrogen atom, a planar structure and a σ-configuration with amphiphilic behavior. Amidyl radicals have single electrons in a p orbital perpendicular to the nitrogen substituents, so they assume a π-configuration with electrophilic chemical behavior. Meanwhile, aminyl and aminium radicals both have a π-configuration but opposite reactivity. In fact, aminyl radicals are weak nucleophiles and are commonly utilized for their preference for H-atom abstraction, while aminium radicals are strong 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, and is a crucial parameter for developing new radical reactions.

The best way to generate nitrogen radicals is via cleavage promoted by light under mild conditions. In particular, the most suitable bonds to be broken are N–H, N–halogen, N–N, N–O and N–S. There are four main strategies to break these types of bond: homolytic cleavage, reduction, oxidation and oxidative proton-coupled electron transfer (PCET).

Homolytic cleavage can occur when an N–halogen, N–N, N–O or N–S bond is irradiated with UV light, generating two radical species that 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, single-electron transfer (SET) occurs to generate a 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., a decarboxylative cascade mechanism). Also, in the oxidative quenching cycle, the SET can occur via 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., hydroxylamine and pyridinium ions). In oxidative PCET, the nitrogen-radical precursor undergoes 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 classified into four main types: (i) intramolecular cyclization onto alkenes or alkynes via a classic *exo*-trig process, (ii) intramolecular hydrogen atom abstraction (e.g., 1,5-HAT), (iii) Norrish type I fragmentation (with limited examples), and (iv) intermolecular addition to π-systems such as olefins, alkynes and aromatic compounds. It is significant to highlight the fact that not all the classes of nitrogen radicals share these reaction modes, since it is their philicity that stabilizes (or destabilizes) the corresponding transition states.

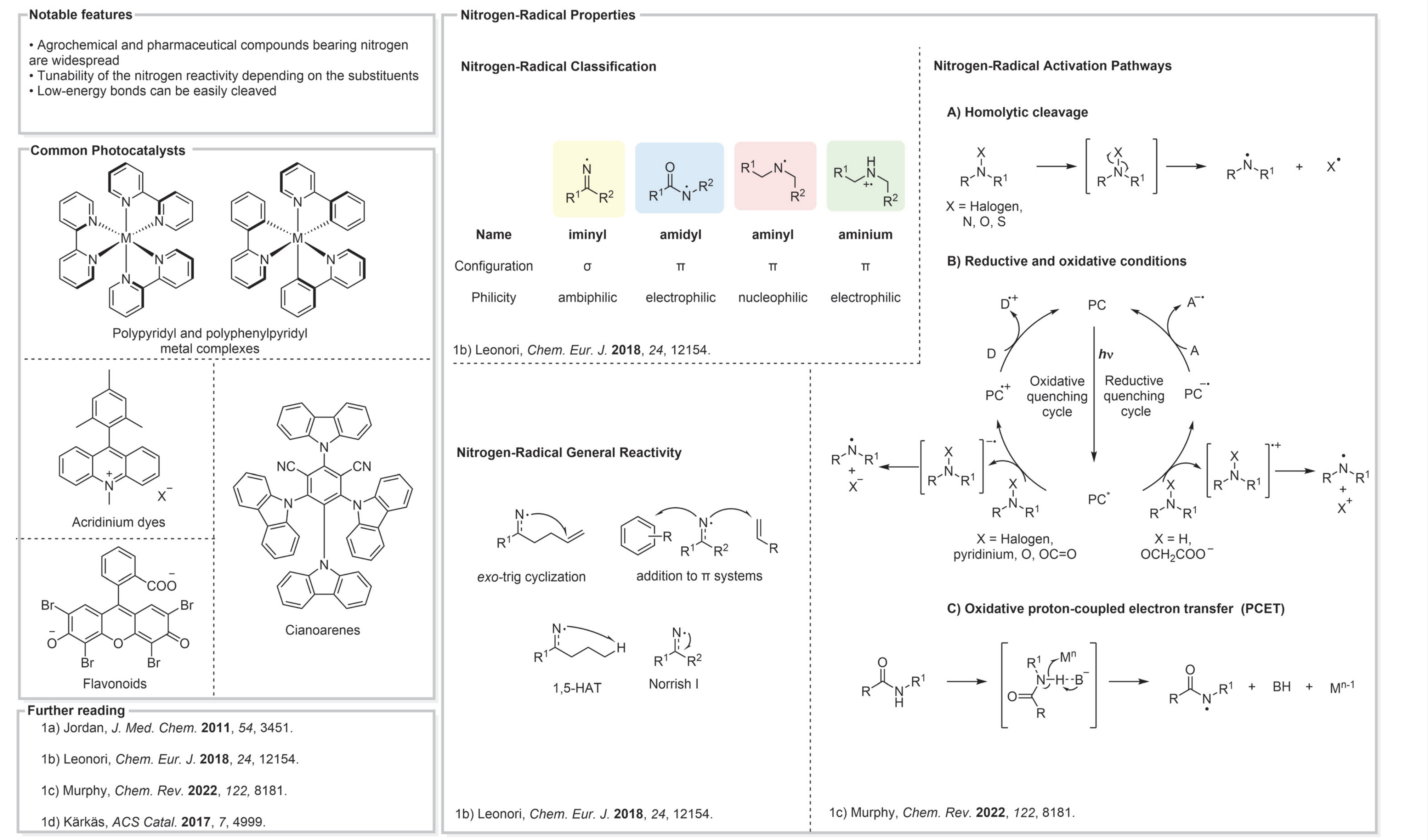
In this graphical review, we have summarized the most well-known published examples of nitrogen-radical reactions, grouping them by their reactivity and the type of radical generated. Although there are numerous examples of reactions involving nitrogen-centered radicals in the literature, we will limit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

Biosketches

Monica F. Boselli earned her master's degree in chemical science in 2019 at the University of Milan, Italy. She then worked as an Erasmus+ fellow for five months in Prof. Markus 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. Maurizio Benaglia at the University of Milan, where she developed continuous-flow processes. In June 2024, she completed her Ph.D. in chemistry under the guidance of Prof. Alessandra Puglisi, with a thesis on amidyl radicals in light-promoted reactions. During her Ph.D., she worked for six months in Prof. Burkhard Koenig's group at the University of Regensburg, Germany. Currently she is a postdoctoral fellow researching the fields of stereoselective photocatalysis and organocatalysis under the direction of Prof. Sergio Rossi and Prof. Maurizio Benaglia at the University of Milan.

Fabrizio Medici earned his master's degree in chemical science (organometallic chemistry) in 2014 under the supervision of Prof. Angelo Maspero at the University of Insubria, Como, Italy. He subsequently moved to UPMC, Sorbonne University, Paris, where he received his Ph.D. in 2017 in molecular science under the supervision of Prof. 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*. He then joined the group of Dr. Angela Marinetti and Dr. Arnaud Voituriez at the ICSN-CNRS, Gif-sur-Yvette, France, to undertake postdoctoral studies focused on Au(I) catalysis. He returned to Italy in 2020 to commence postdoctoral studies at the University of Milan under the supervision of Prof. Alessandra Puglisi and then Prof. Maurizio Benaglia, studying organic photochemistry, organic electrochemistry and flow synthesis. Currently, he is an RTDA (Tenure Track Professor) at the University of Milan as part of the MUSA project under the PNRR plan.

Francesca Franco earned her master's degree in chemical science in 2018 in organometallic chemistry under the supervision of Prof. Mina Mazzeo and Prof. Chiara Costabile at the University of Salerno, Italy. She subsequently switched to organic chemistry and completed her Ph.D. in 2022 under the guidance of Prof. 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 Ph.D. studies she spent three months at Laboratori Alchemia and six months at the University of Milan. After completing her Ph.D., she moved to the University of Pavia to work as a postdoctoral researcher in Prof. Giuseppe Zanoni's group, focusing on the application of biomimetic reactions in the synthesis of natural compounds. Currently, she is employed on a postdoctoral fellowship studying the fields of electrochemistry and stereoselective organocatalysis under the direction of Prof. Maurizio Benaglia at the University of Milan.



Notable features

- Agrochemical and pharmaceutical compounds bearing nitrogen are widespread
- 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

Cianoarenes

Flavonoids

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) Kärkäs, *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

exo-trig cyclization

addition to π systems

1,5-HAT

Norrish I

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

Nitrogen-Radical Activation Pathways

A) Homolytic cleavage

X = Halogen, N, O, S

B) Reductive and oxidative conditions

Oxidative quenching cycle

Reductive quenching cycle

X = Halogen, pyridinium, O, OC=O

X = H, OCH_2COO^-

C) Oxidative proton-coupled electron transfer (PCET)

1c) Murphy, *Chem. Rev.* **2022**, *122*, 8181.

Figure 1 Overview of nitrogen-centered radicals[1a–d]

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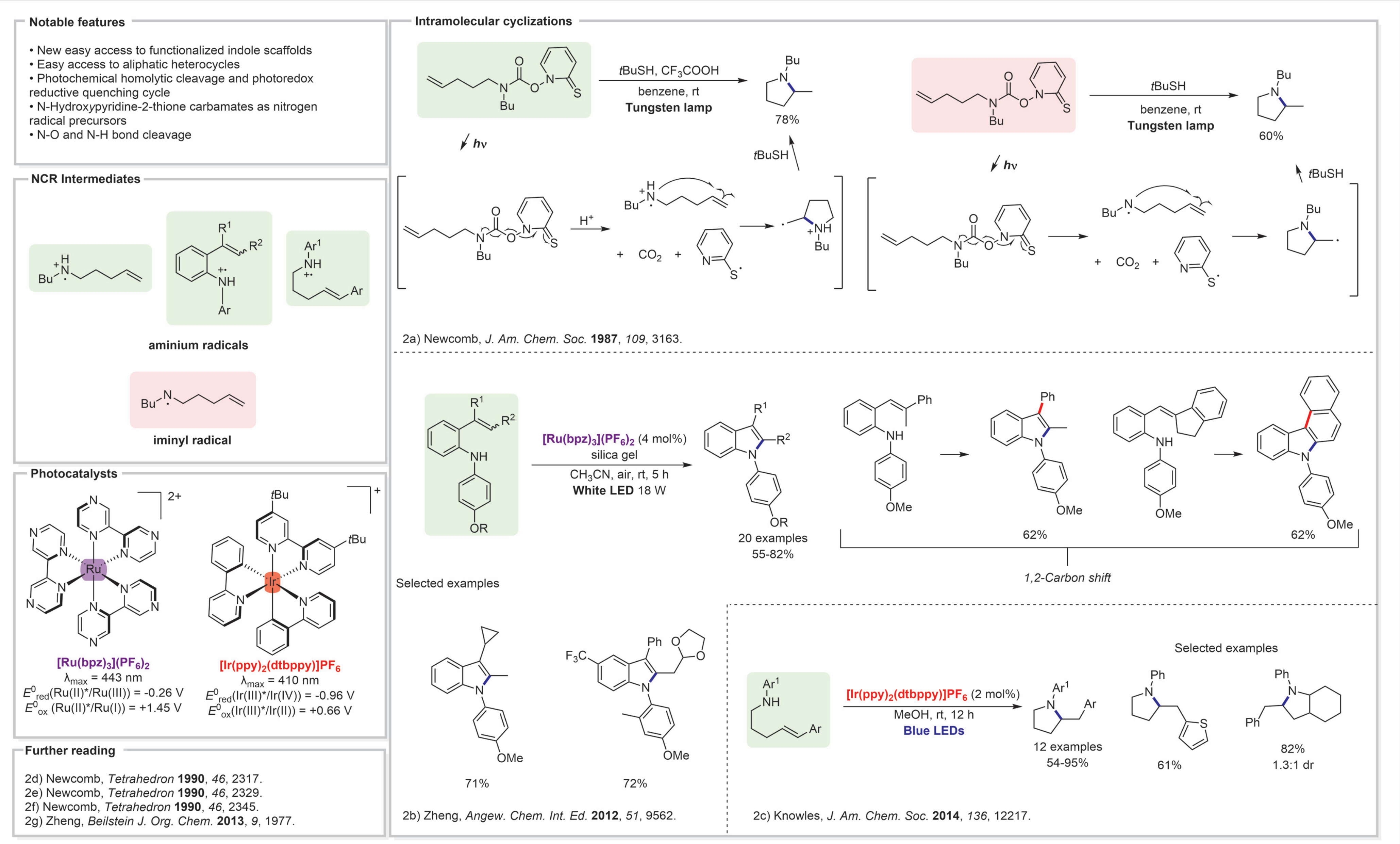


Notable features

- New easy access to functionalized indole scaffolds
- Easy access to aliphatic heterocycles
- Photochemical homolytic cleavage and photoredox reductive quenching cycle
- N-Hydroxypyridine-2-thione carbamates as nitrogen radical precursors
- N-O and N-H bond cleavage

Further reading

2d) Newcomb, *Tetrahedron* **1990**, *46*, 2317.
2e) Newcomb, *Tetrahedron* **1990**, *46*, 2329.
2f) Newcomb, *Tetrahedron* **1990**, *46*, 2345.
2g) Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 1977.

2a) Newcomb, *J. Am. Chem. Soc.* **1987**, *109*, 3163.

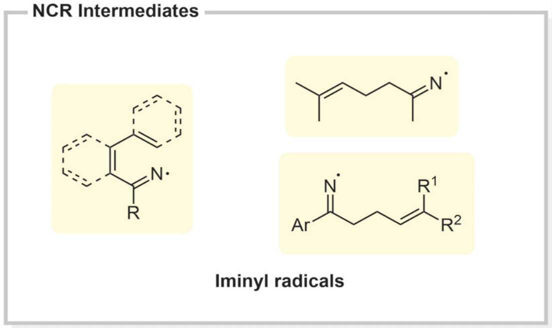
2b) Zheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 9562.

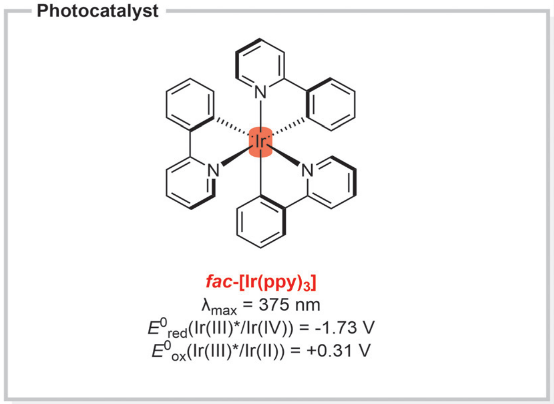
2c) Knowles, *J. Am. Chem. Soc.* **2014**, *136*, 12217.

Figure 2 Intramolecular cyclizations for the synthesis of cyclic amines and substitutes indoles[2a–g]

Notable features

- Access to functionalized pyrrolines starting from deactivated alkenes
- Photoredox oxidative quenching cycle and photochemical homolytic cleavage
- 5-exo-t*rig* cyclization
- Acyl oximes as excellent nitrogen radical precursors
- N-O bond cleavage





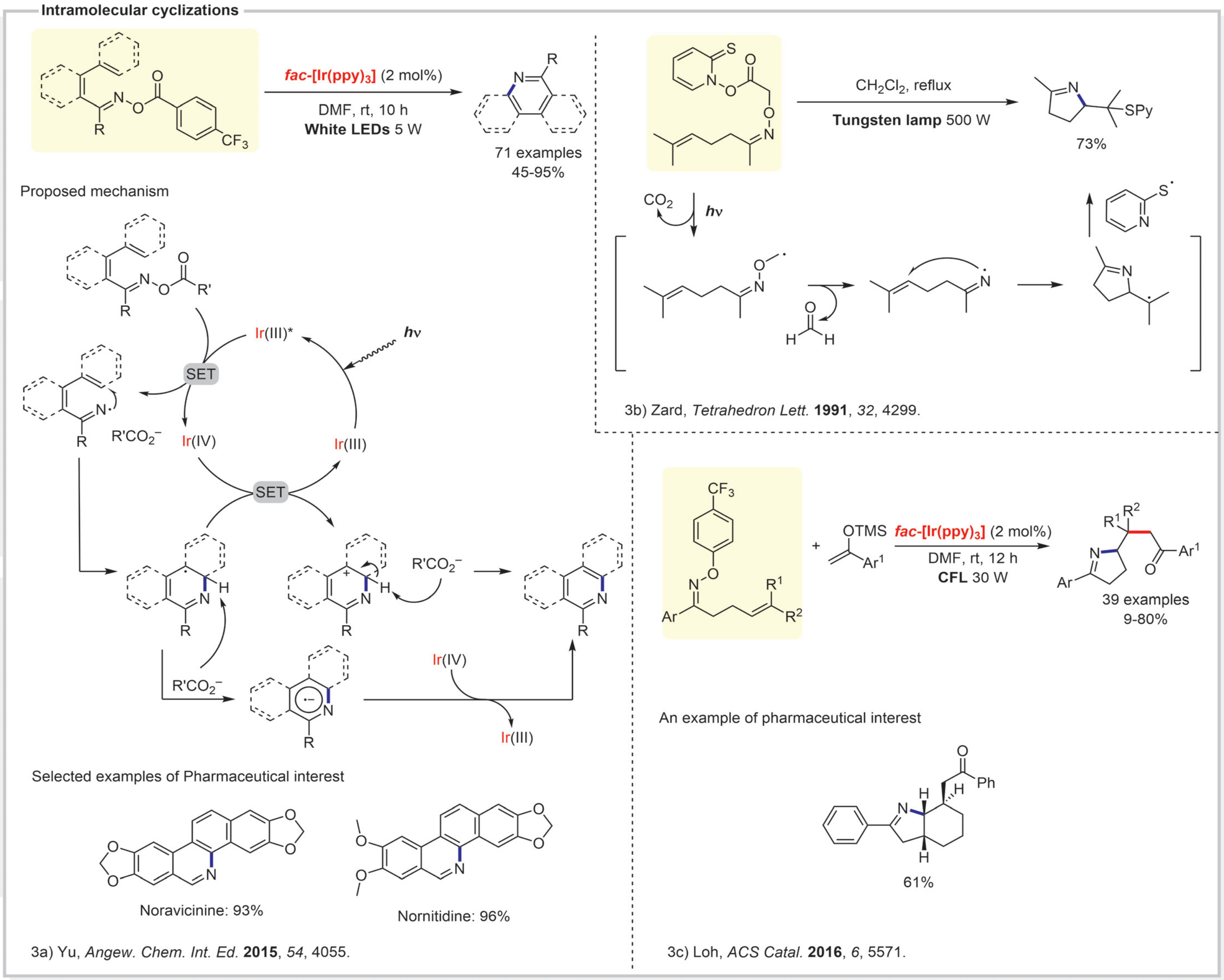


Figure 3 Iminyl radical intramolecular cyclization for the synthesis of heteroarenes and functionalized pyrrolidines[3a–c]

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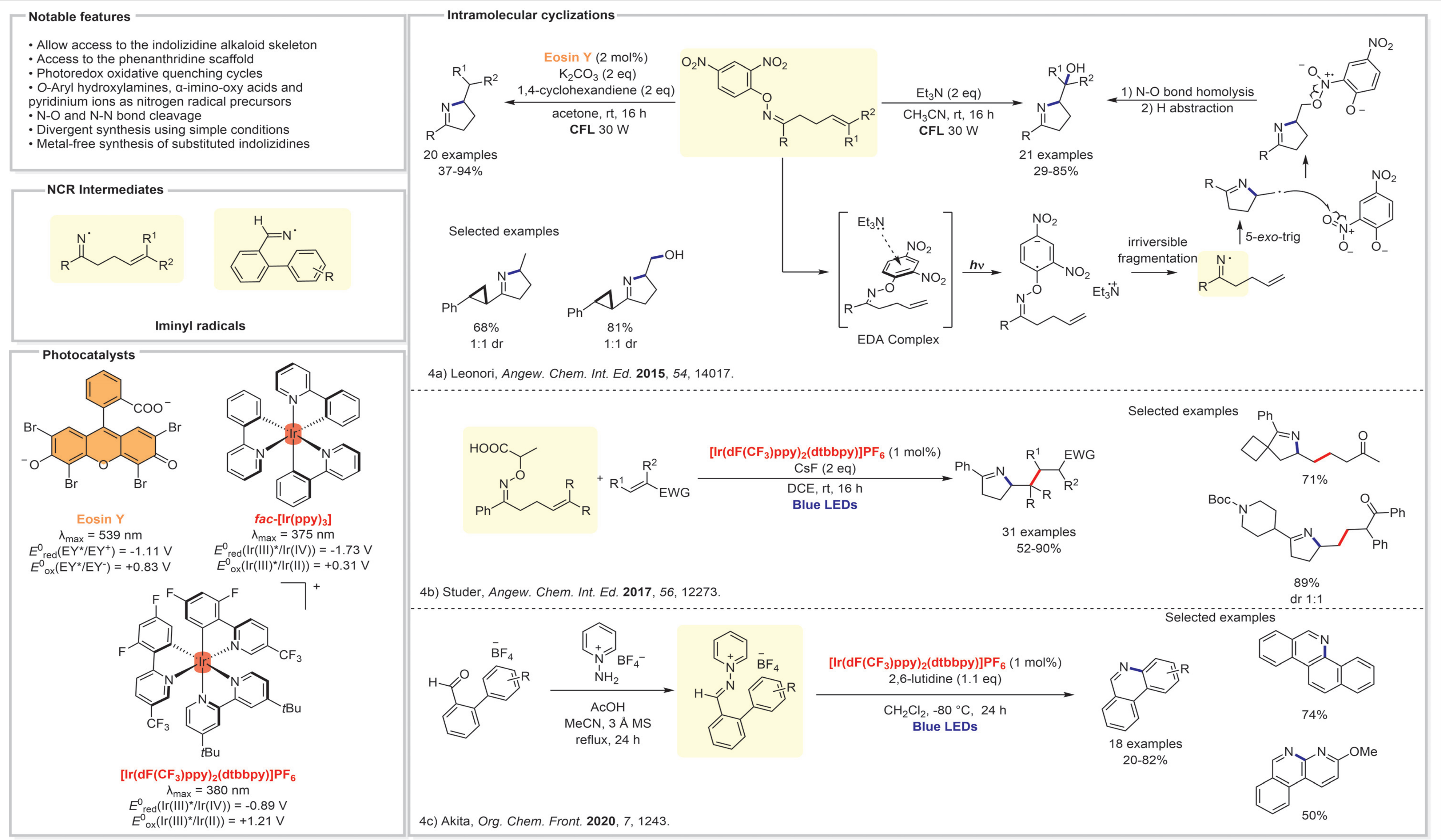
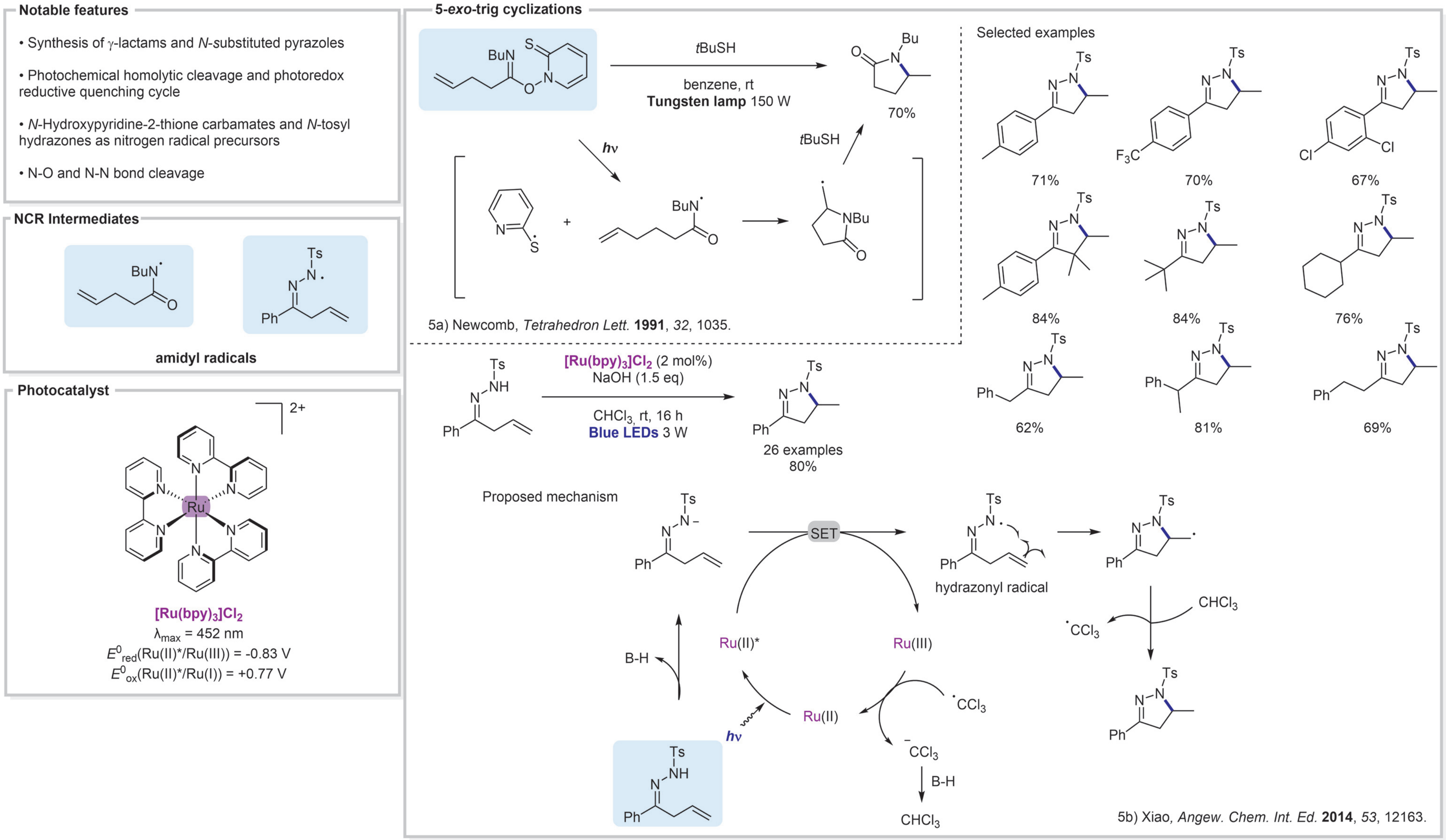

Notable features

- Allow access to the indolizidine alkaloid skeleton
- Access to the phenanthridine scaffold
- Photoredox oxidative quenching cycles
- *O*-Aryl hydroxylamines, α-imino-oxy acids and pyridinium ions as nitrogen radical precursors
- N-O and N-N bond cleavage
- Divergent synthesis using simple conditions
- Metal-free synthesis of substituted indolizidines

Figure 4 Iminyl radical intramolecular cyclization for the synthesis of heteroarenes and functionalized pyrrolidines[4a–c]



Notable features

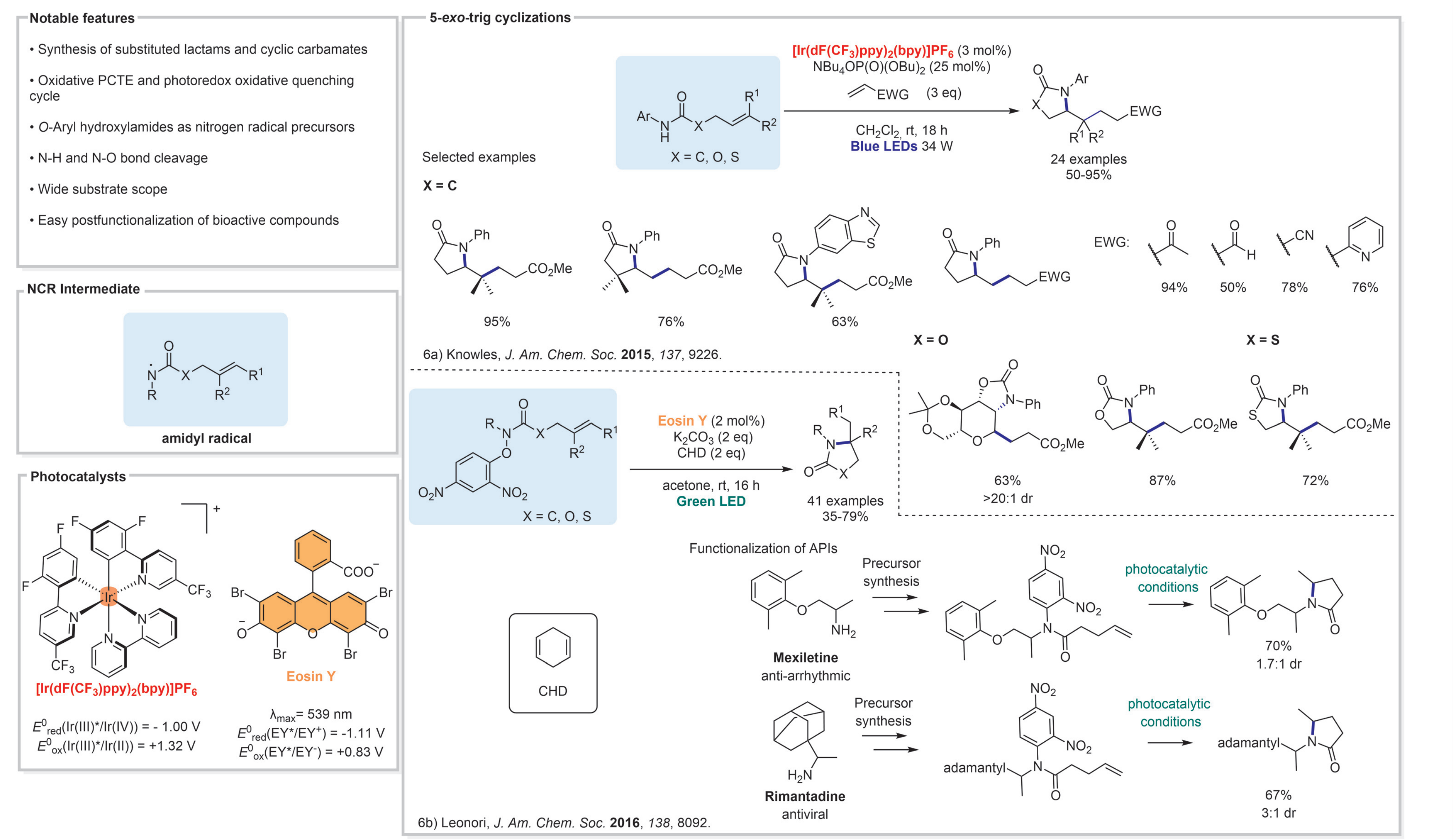
- Synthesis of γ-lactams and *N*-substituted pyrazoles
- Photochemical homolytic cleavage and photoredox reductive quenching cycle
- *N*-Hydroxypyridine-2-thione carbamates and *N*-tosyl hydrazones as nitrogen radical precursors
- N-O and N-N bond cleavage

λ_{max} = 452 nm
E^0_{red}(Ru(II)*/Ru(III)) = -0.83 V
E^0_{ox}(Ru(II)*/Ru(I)) = +0.77 V

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

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

Figure 5 Synthesis of γ-lactams and substituted pyrazoles via 5-*exo*-trig cyclization[5a,b]



Notable features

- Synthesis of substituted lactams and cyclic carbamates
- Oxidative PCTE and photoredox oxidative quenching cycle
- *O*-Aryl hydroxylamides as nitrogen radical precursors
- N-H and N-O bond cleavage
- Wide substrate scope
- Easy postfunctionalization of bioactive compounds

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

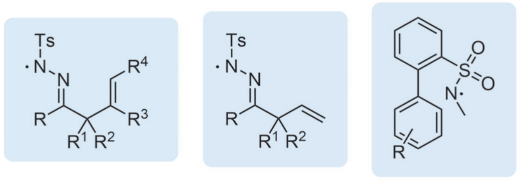
6b) Leonori, *J. Am. Chem. Soc.* **2016**, *138*, 8092.

Figure 6 Bioactive heterocycle formation[6a,b]

Notable features

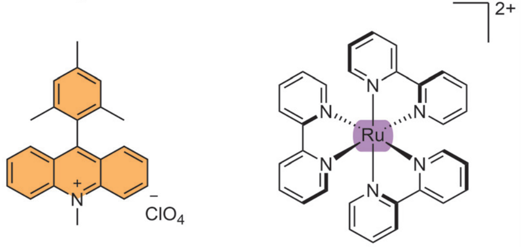
- Easy access to dihydropyrazoles and tetrahydropyridazines
- Photoredox reductive quenching cycle
- *N*-Tosyl hydrazines as nitrogen-radical precursors
- N–H bond cleavage
- New methodology for the synthesis of sulfonamides, a very important class of APIs

NCR Intermediates



amidyl radicals

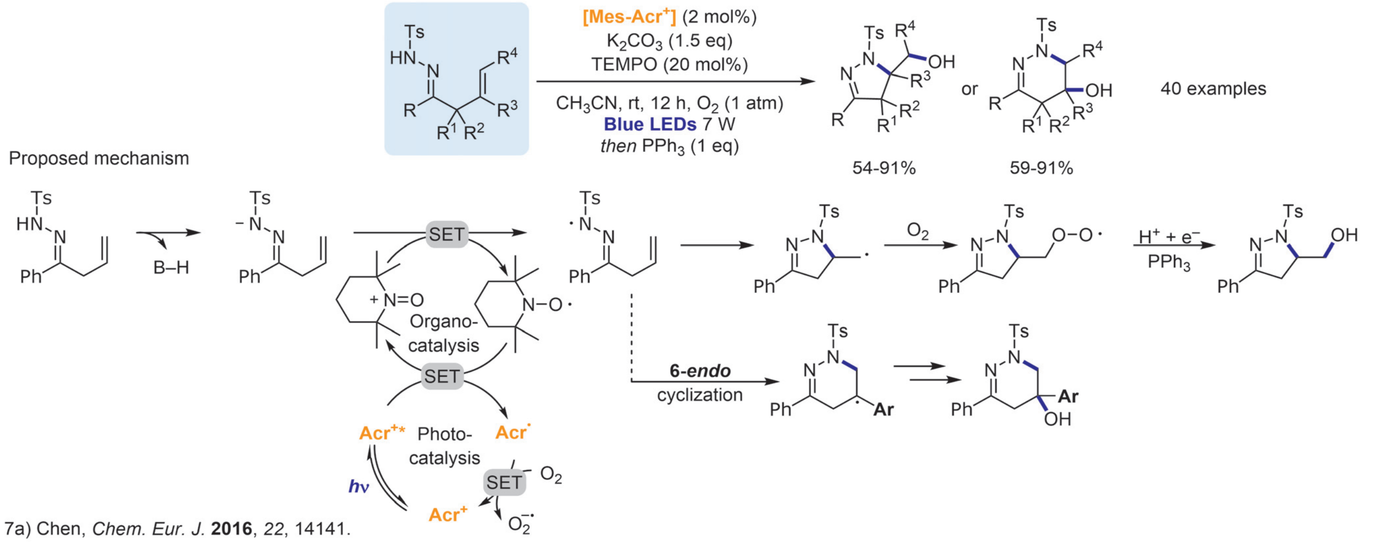
Photocatalysts



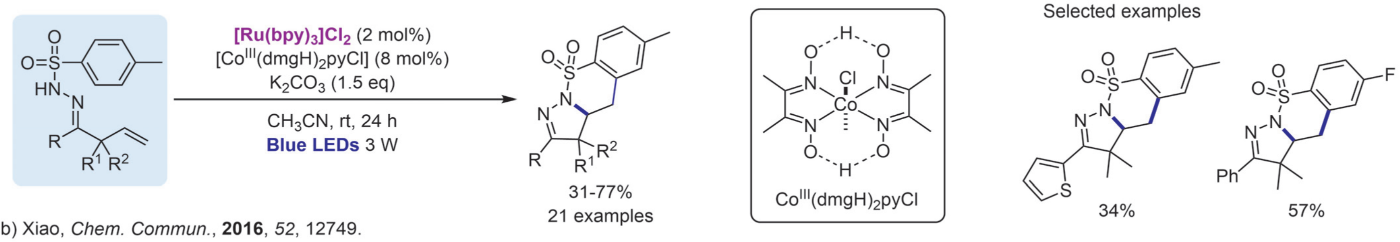
Acridinium dye
λ_{max} = 455 nm
$E^0_{ox}(Acr^{+*}/Acr)$ ~ +1.88 V (T), +2.28 V (S)

[Ru(bpy)$_3$]Cl$_2$
λ_{max} = 452 nm
$E^0_{red}(Ru(II)^*/Ru(III))$ ~ -0.83 V
$E^0_{ox}(Ru(II)^*/Ru(I))$ ~ +0.77 V

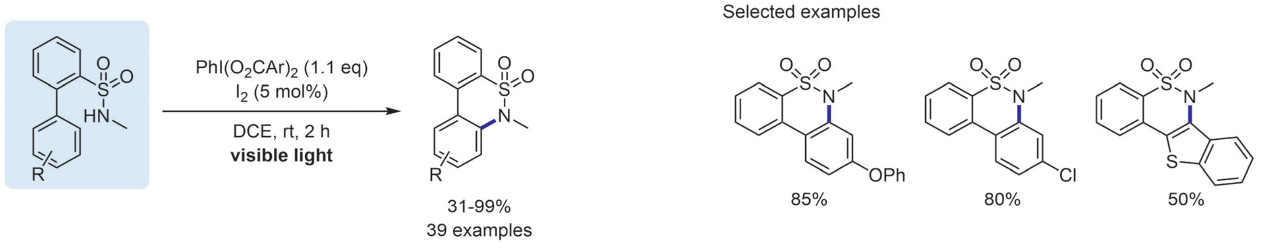
Intramolecular cyclizations



7a) Chen, *Chem. Eur. J.* **2016**, *22*, 14141.



7b) Xiao, *Chem. Commun.*, **2016**, *52*, 12749.



7c) Muniz, *Chem. Eur. J.*, **2016**, *22*, 9929.

Figure 7 Heterocycle and sulfonamide formation[7a–c]

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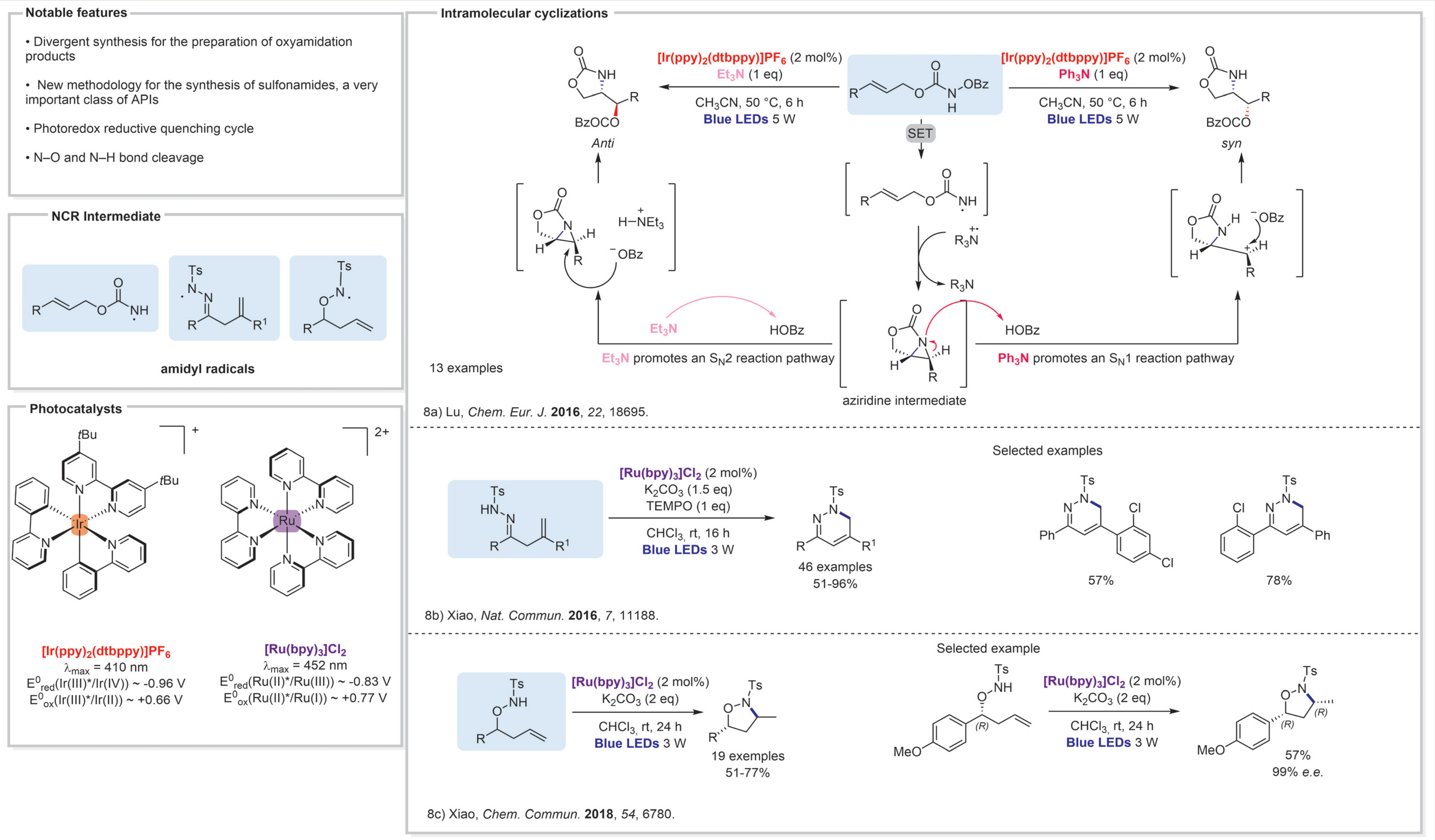


Notable features

- Divergent synthesis for the preparation of oxyamidation products
- New methodology for the synthesis of sulfonamides, a very important class of APIs
- Photoredox reductive quenching cycle
- N–O and N–H bond cleavage

8a) Lu, *Chem. Eur. J.* **2016**, *22*, 18695.

8b) Xiao, *Nat. Commun.* **2016**, *7*, 11188.

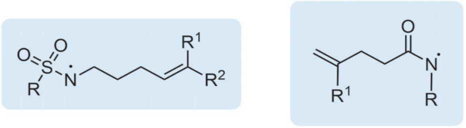
8c) Xiao, *Chem. Commun.* **2018**, *54*, 6780.

Figure 8 Heterocycle formation[8a–c]

Notable features

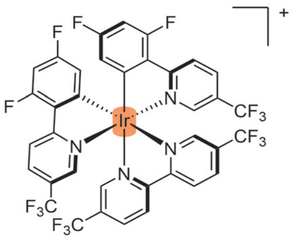
- Stereocontrolled synthesis
- New methodology for the synthesis of API derivatives
- Easy access to boron derivatives
- EDA complex formation
- Chiral phosphonate as a chiral base in oxidative PCET
- N–H and N–O bond cleavage

NCR Intermediate



amidyl radicals

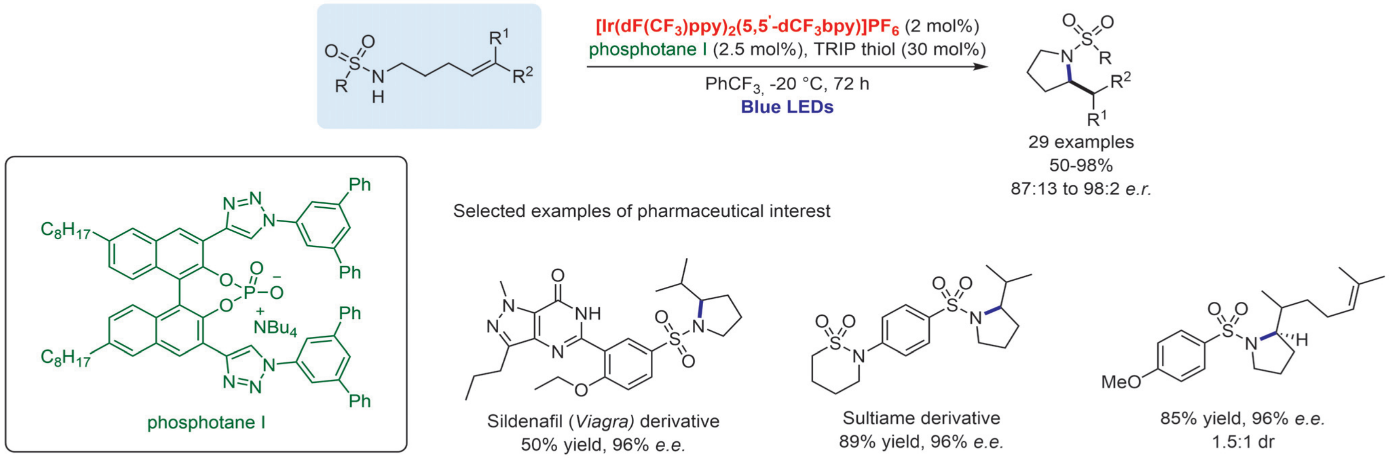
Photocatalyst



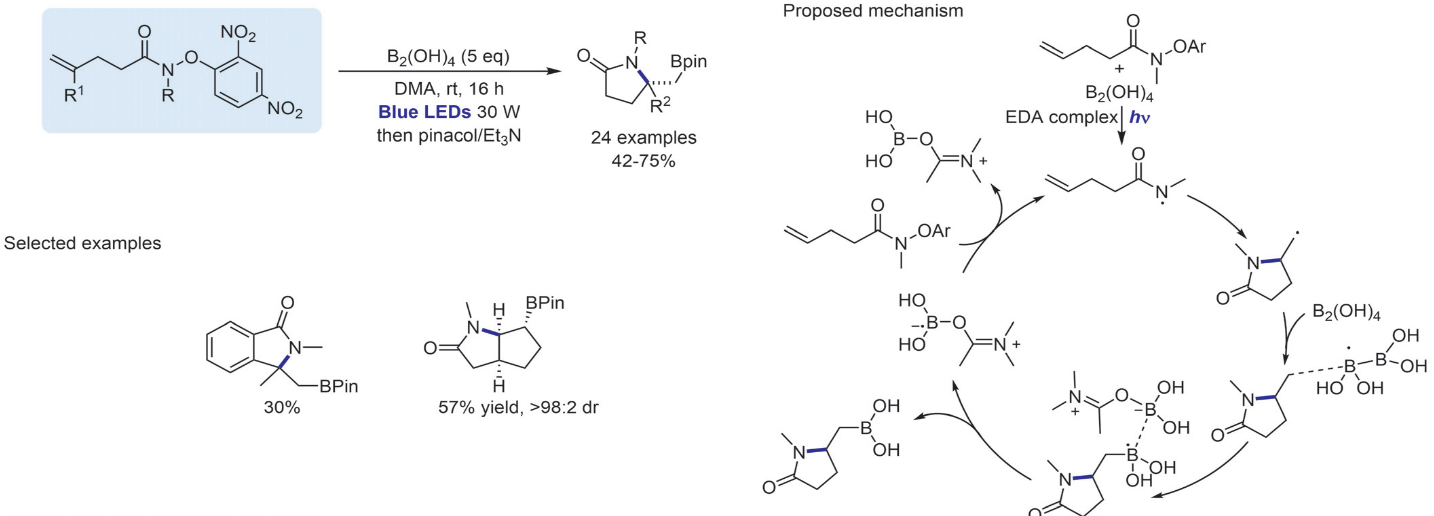
[Ir(dF(CF$_3$)ppy)$_2$(5,5'-dCF$_3$bpy)]PF$_6$

E^0_{red}(Ir(III)*/Ir(IV)) ~ -0.9 V
E^0_{ox}(Ir(III)*/Ir(II)) ~ +1.68 V

5-*exo*-trig cyclizations



9a) Knowles, *J. Am. Chem. Soc.* **2020**, *142*, 5974.



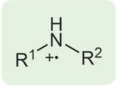
9b) Studer, *Org. Lett.* **2021**, *23*, 7688.

Figure 9 Heterocycle formation via 5-*exo*-trig cyclization[9a,b]

Notable features

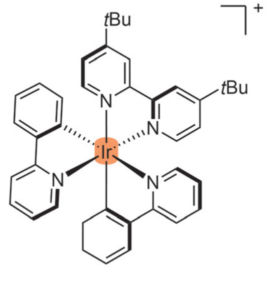
- New easy access to functionalized aliphatic amines
- Easy access to aminated benzoxazoles
- Photochemical homolytic cleavage and photoredox reductive quenching cycle
- *N*-Hydroxypyridine-2-thione carbamates and *N*-chloroamines as nitrogen-radical precursors
- N–O and N–Cl bond cleavage

NCR Intermediate



aminium radical

Photocatalyst



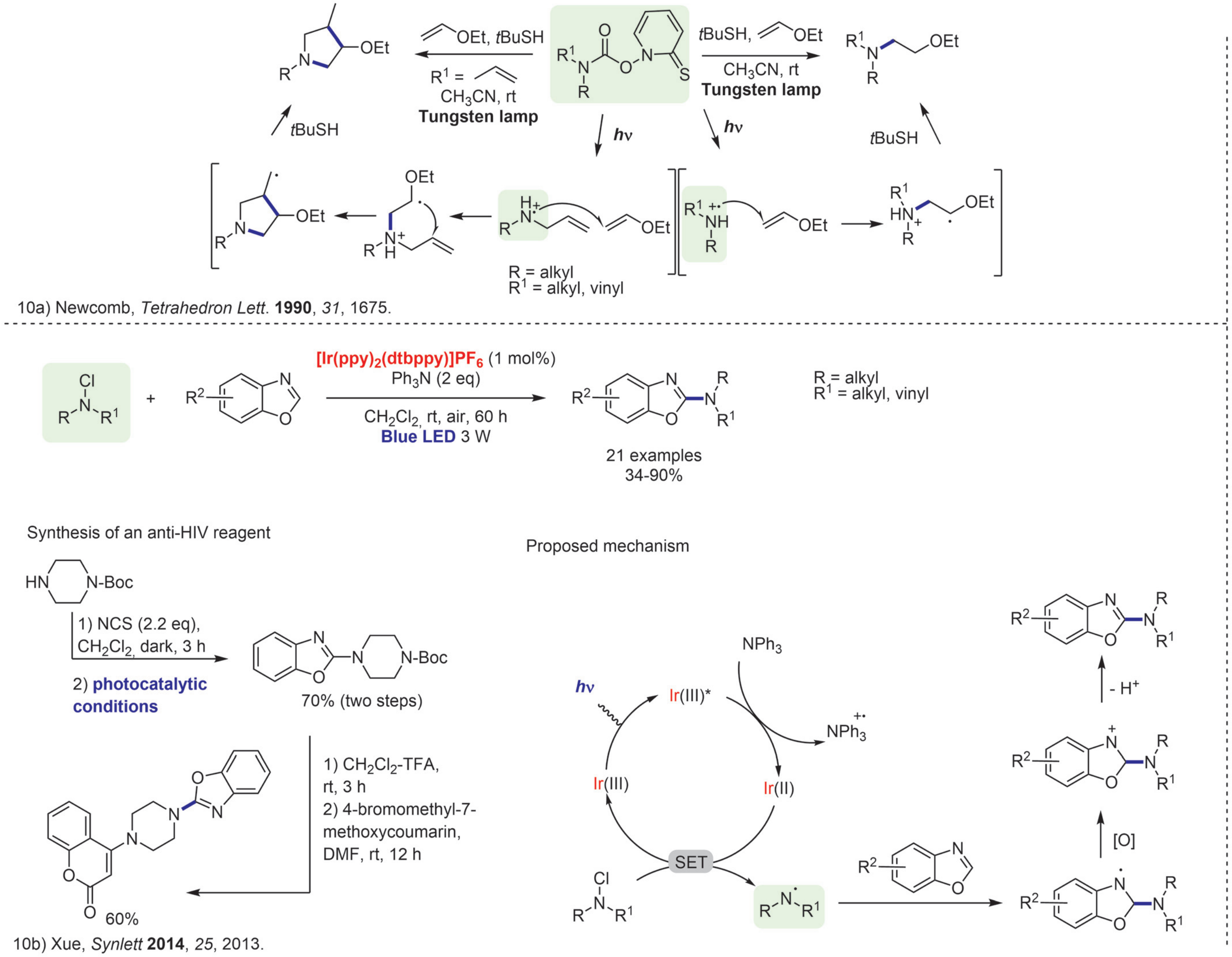
[Ir(ppy)$_2$(dtbppy)]PF$_6$

λ_{max} = 410 nm

E^0_{red}(Ir(III)*/Ir(IV)) ~ -0.96 V

E^0_{ox}(Ir(III)*/Ir(II)) ~ +0.66 V

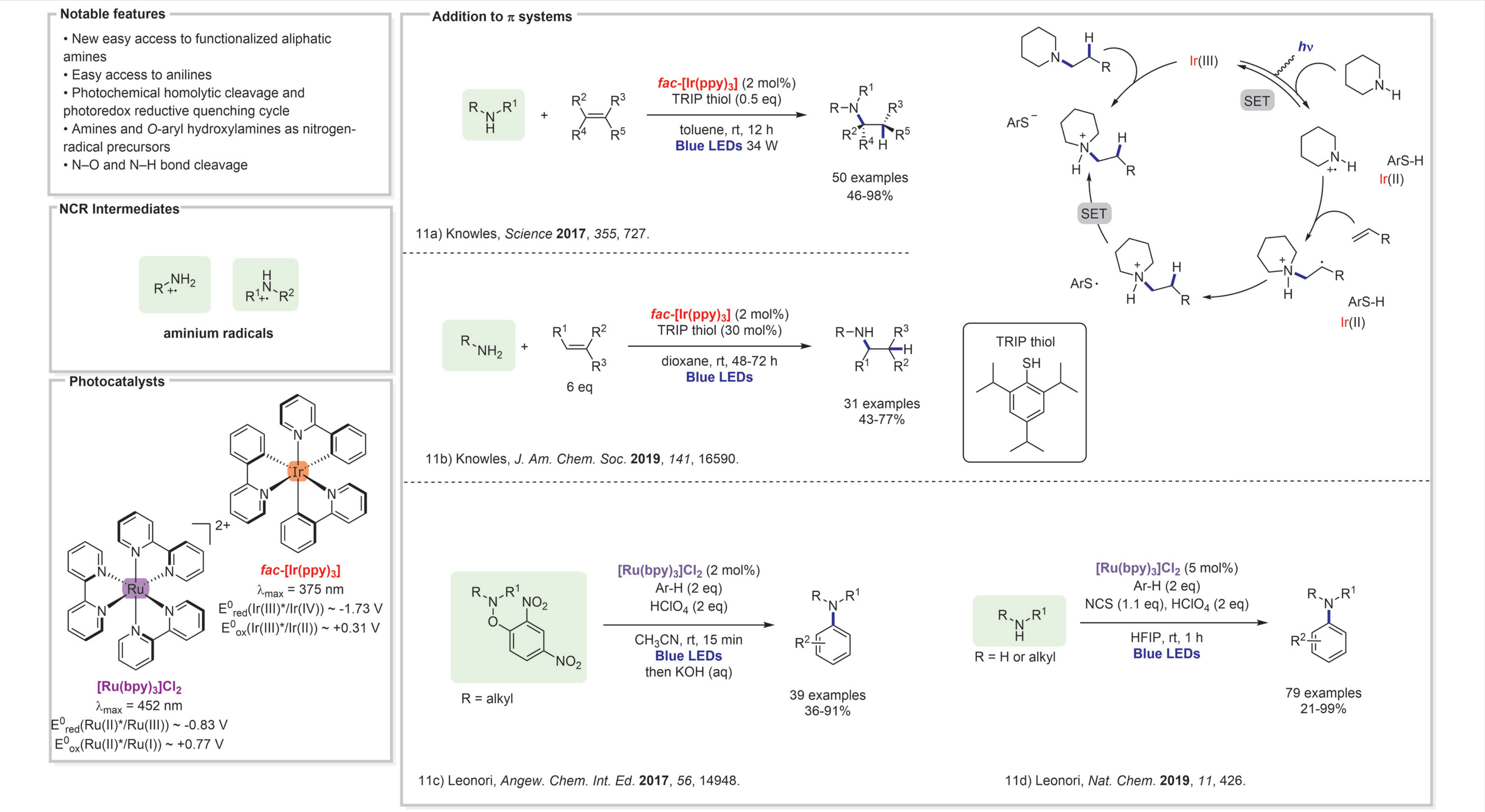
Addition to π systems



10a) Newcomb, *Tetrahedron Lett.* **1990**, *31*, 1675.

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

Figure 10 Addition of aminium radicals to ethyl vinyl ether and benzoxazoles[10a,b]



Notable features

- New easy access to functionalized 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

11a) Knowles, *Science* **2017**, *355*, 727.

11b) Knowles, *J. Am. Chem. Soc.* **2019**, *141*, 16590.

11c) Leonori, *Angew. Chem. Int. Ed.* **2017**, *56*, 14948.

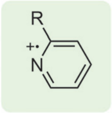
11d) Leonori, *Nat. Chem.* **2019**, *11*, 426.

Figure 11 Addition of aminium radicals to olefins and arenes[11a–d]

Notable features

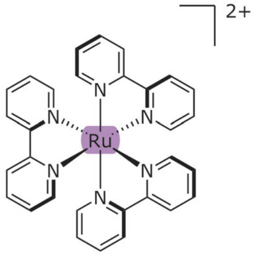
- New easy access to functionalized anilines
- Photoredox oxidative quenching cycle
- Activated pyridine *N*-oxides as nitrogen-radical precursors
- N–O bond cleavage
- Pyridyl radical cations: a highly reactive class of nitrogen-centered radicals due to an unpaired electron located in an sp^2-hybridized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

NCR Intermediate



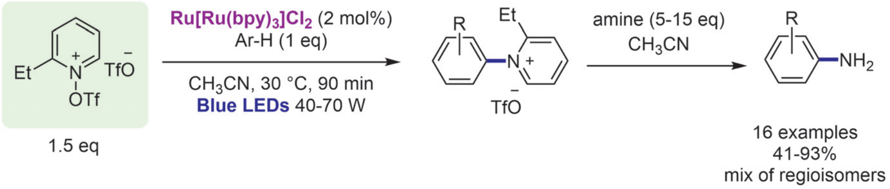
pyridyl radical

Photocatalyst

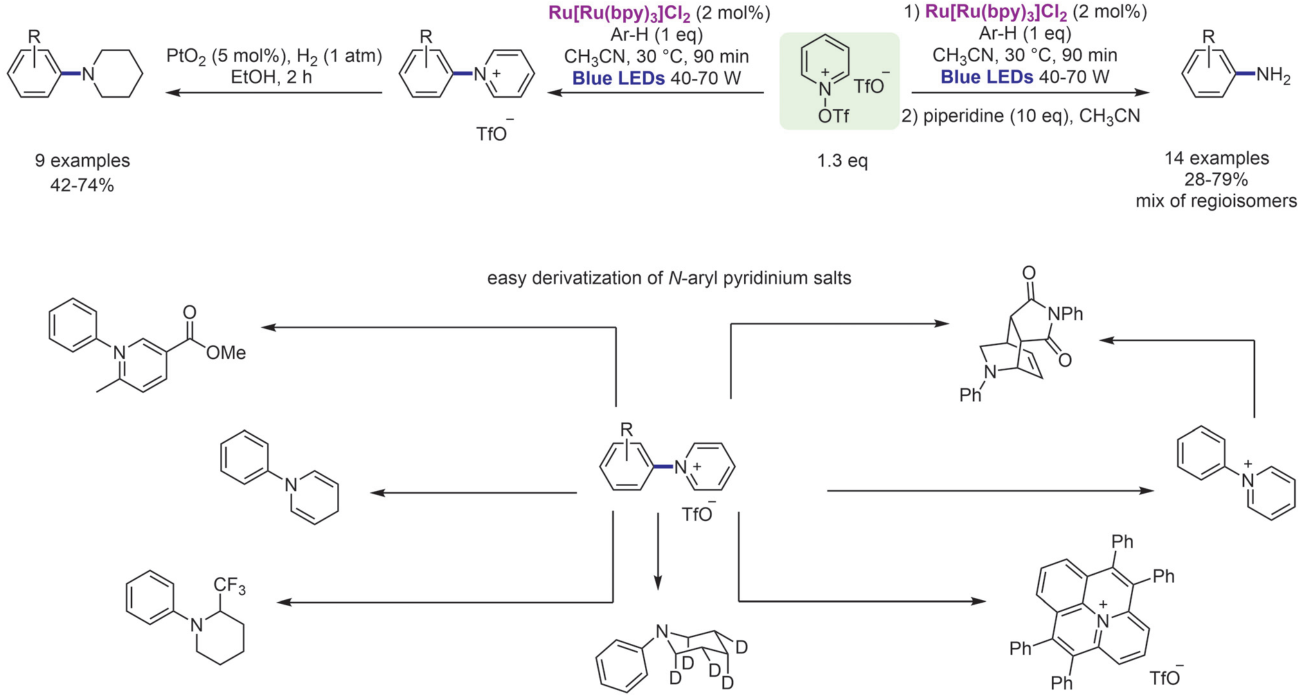


$[Ru(bpy)_3]Cl_2$
λ_{max} = 452 nm
$E^0_{red}(Ru(II)^*/Ru(III)) \sim -0.83$ V
$E^0_{ox}(Ru(II)^*/Ru(I)) \sim +0.77$ V

Addition to π systems



12a) Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 532.



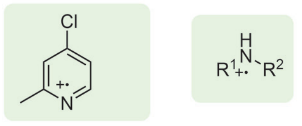
12b) Carreira, *Angew. Chem. Int. Ed.* **2019**, *58*, 526.

Figure 12 Addition of pyridyl radicals to arenes for the synthesis of highly tunable pyridinium salts[12a,b]

Notable features

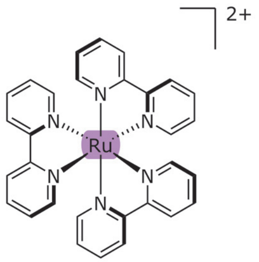
- New easy access to functionalized anilines and diamines
- Photoredox reductive quenching cycle
- Activated pyridine *N*-oxides and chloroamines as nitrogen-radical precursors
- N–O and N–Cl bond cleavage

NCR Intermediate



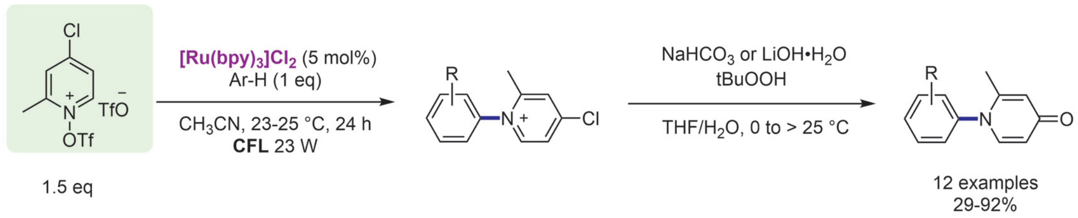
aminium radicals

Photocatalyst

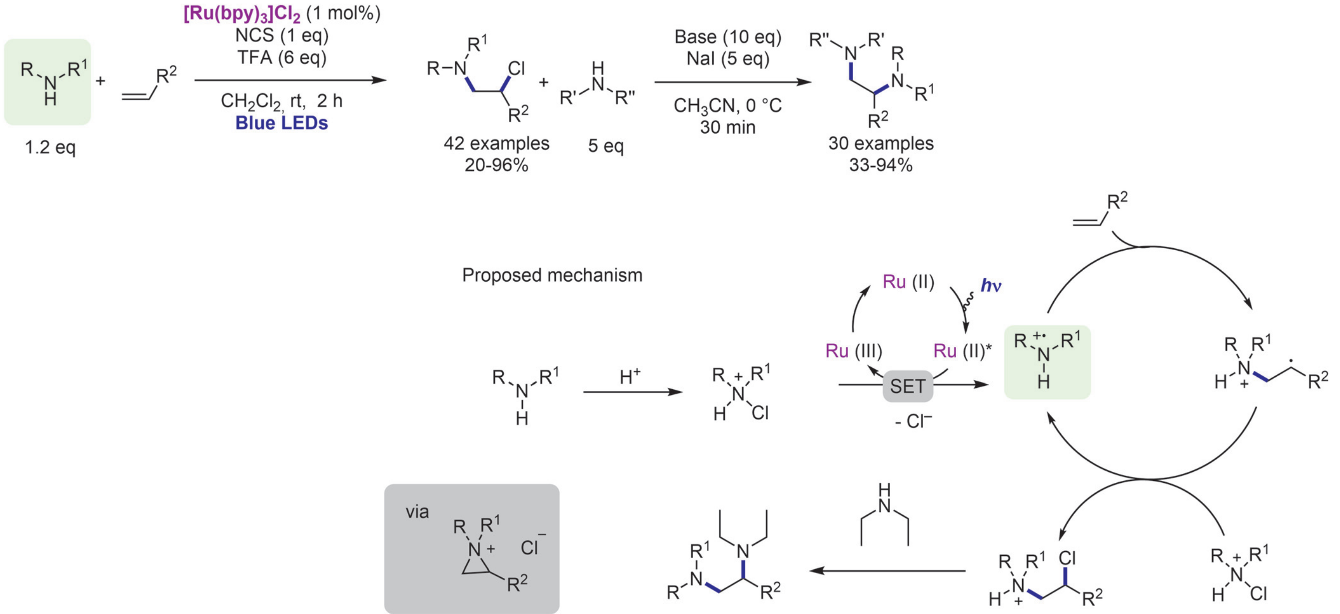


[Ru(bpy)$_3$]Cl$_2$
λ_{max} = 452 nm
E^0_{red}(Ru(II)*/Ru(III)) ~ -0.83 V
E^0_{ox}(Ru(II)*/Ru(I)) ~ +0.77 V

Addition to π systems



13a) Ritter, *Org. Lett.* **2019**, *21*, 5363.



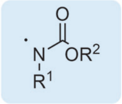
13b) Leonori, *Angew. Chem. Int. Ed.* **2020**, *59*, 15021.

Figure 13 Addition of aminium radicals to arenes and olefins to synthesize pyridinium salts and diamines[13a,b]

Notable features

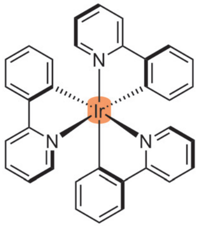
- Enantioselective α-amination of aldehydes
- In-flow synthesis of an enantioenriched α-aminated aldehyde
- Carbamates as nitrogen-radical precursors
- N–O bond cleavage

NCR Intermediate



amidyl radical

Photocatalyst



***fac*-[Ir(ppy)$_3$]**

λ_{max} = 375 nm

E^0_{red}(Ir(III)*/Ir(IV)) ~ -1.73 V

E^0_{ox}(Ir(III)*/Ir(II)) ~ +0.31 V

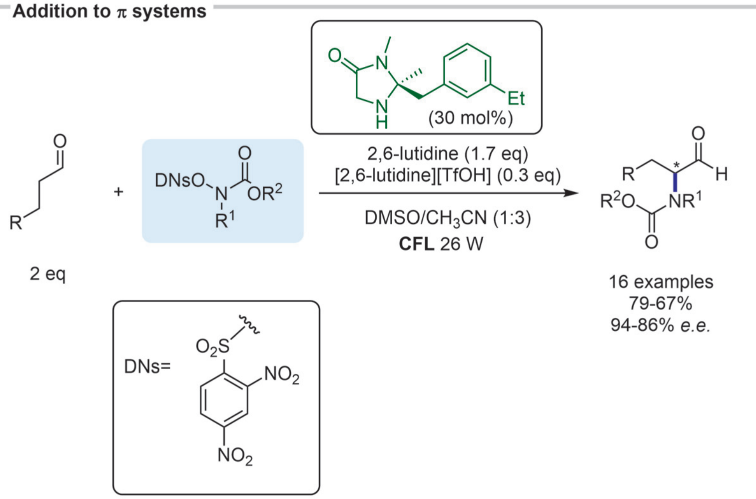
Further reading

14c) MacMillan, *Science* **2008**, *322*, 77.

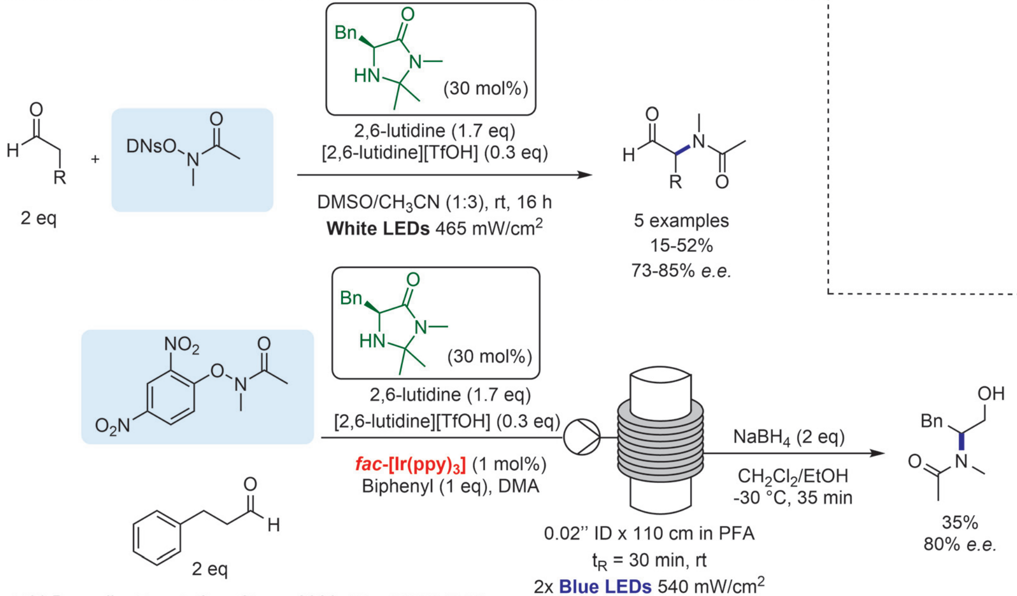
14d) Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

14e) Noël, *Trends Chem.* **2020**, *2*, 92.

Addition to π systems



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



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

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

Common mechanism

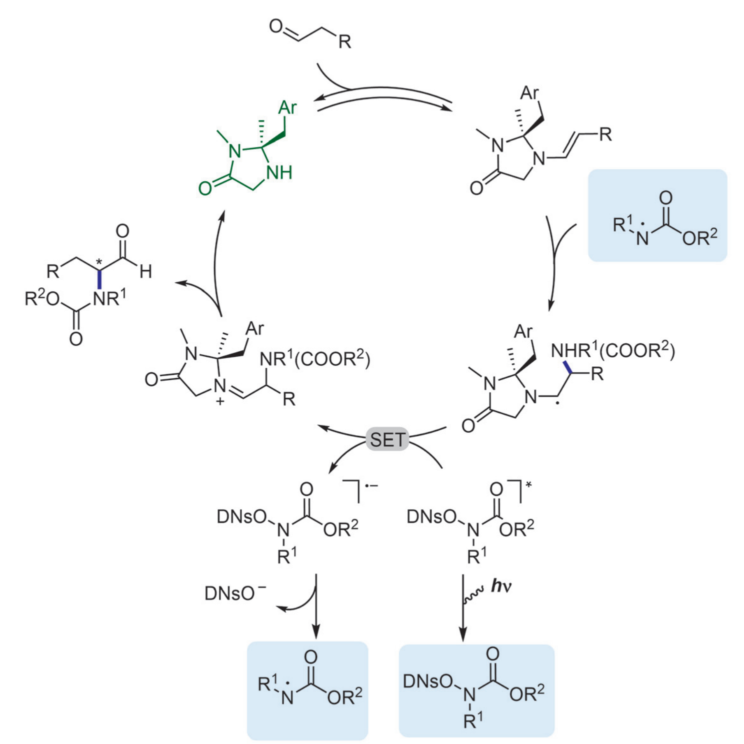
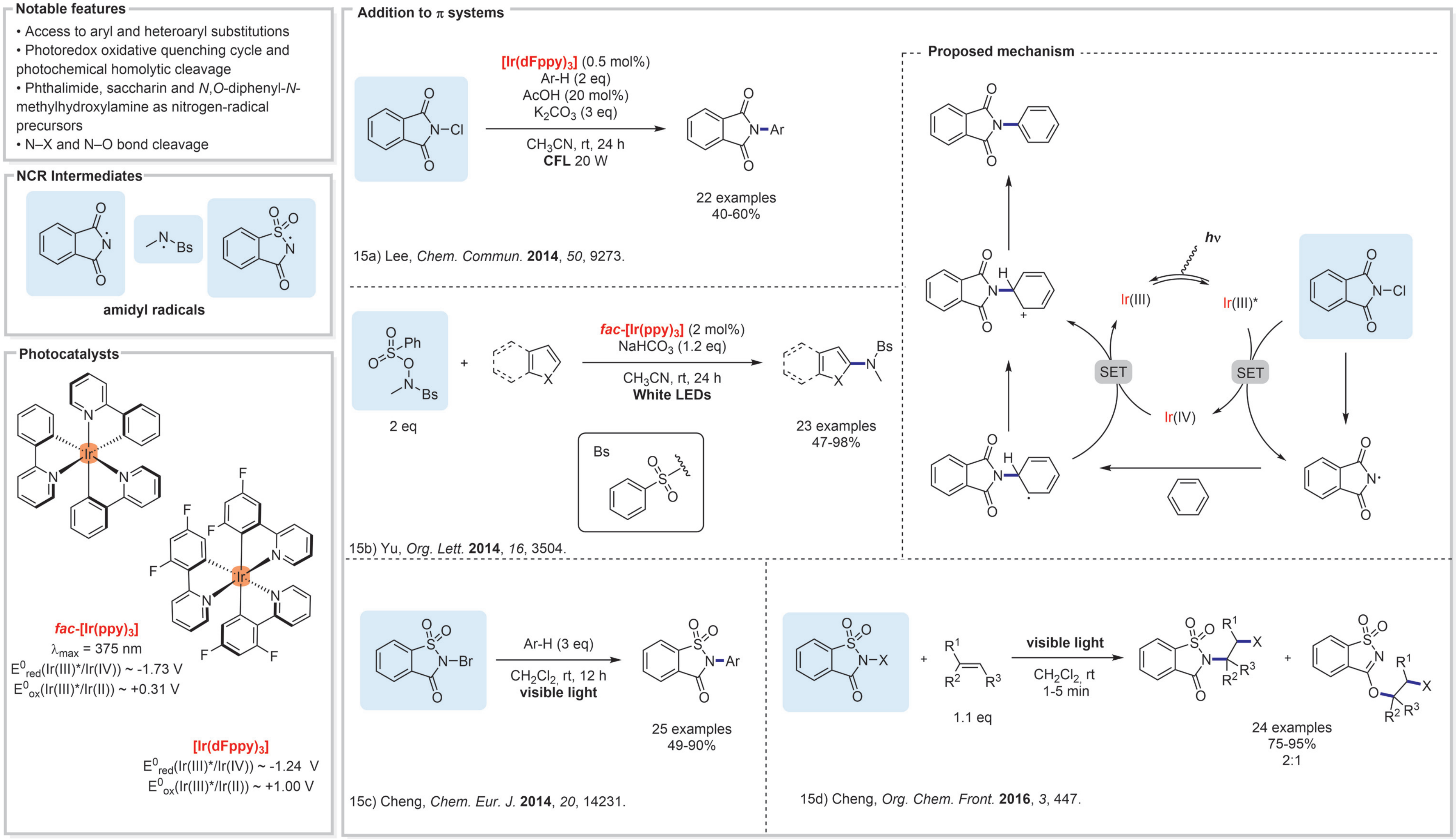


Figure 14 Amidyl radicals in enantioselective photoredox α-aminations of aldehydes[14a–e]


Notable features

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

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

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

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

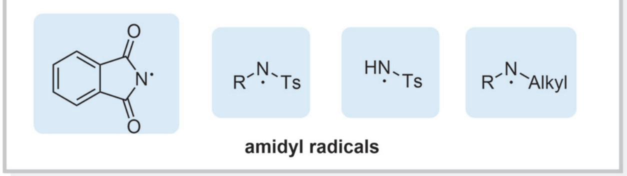
15d) Cheng, *Org. Chem. Front.* **2016**, *3*, 447.

Figure 15 Amidyl radicals in imidations and amidations of arenes and heteroarenes and the halo-functionalization of alkenes[15a–d]

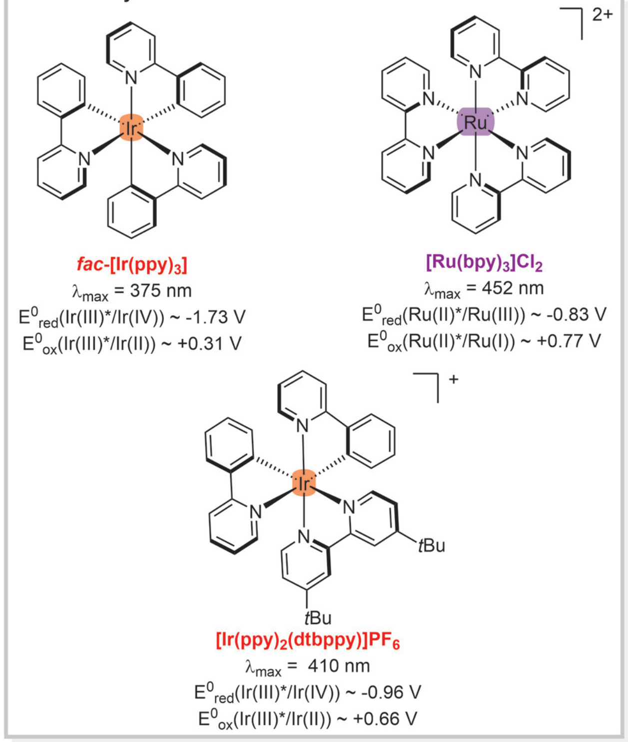
Notable features

- Aryl functionalization and double addition to alkenes
- Photoredox oxidative quenching cycle
- *N*-Acyloxyphthalimides and pyridinium salts as nitrogen-radical precursors
- Amines and *N*-chloroamines as nitrogen-radical precursors
- N–O, N–N, N–Cl and N–H bond cleavage

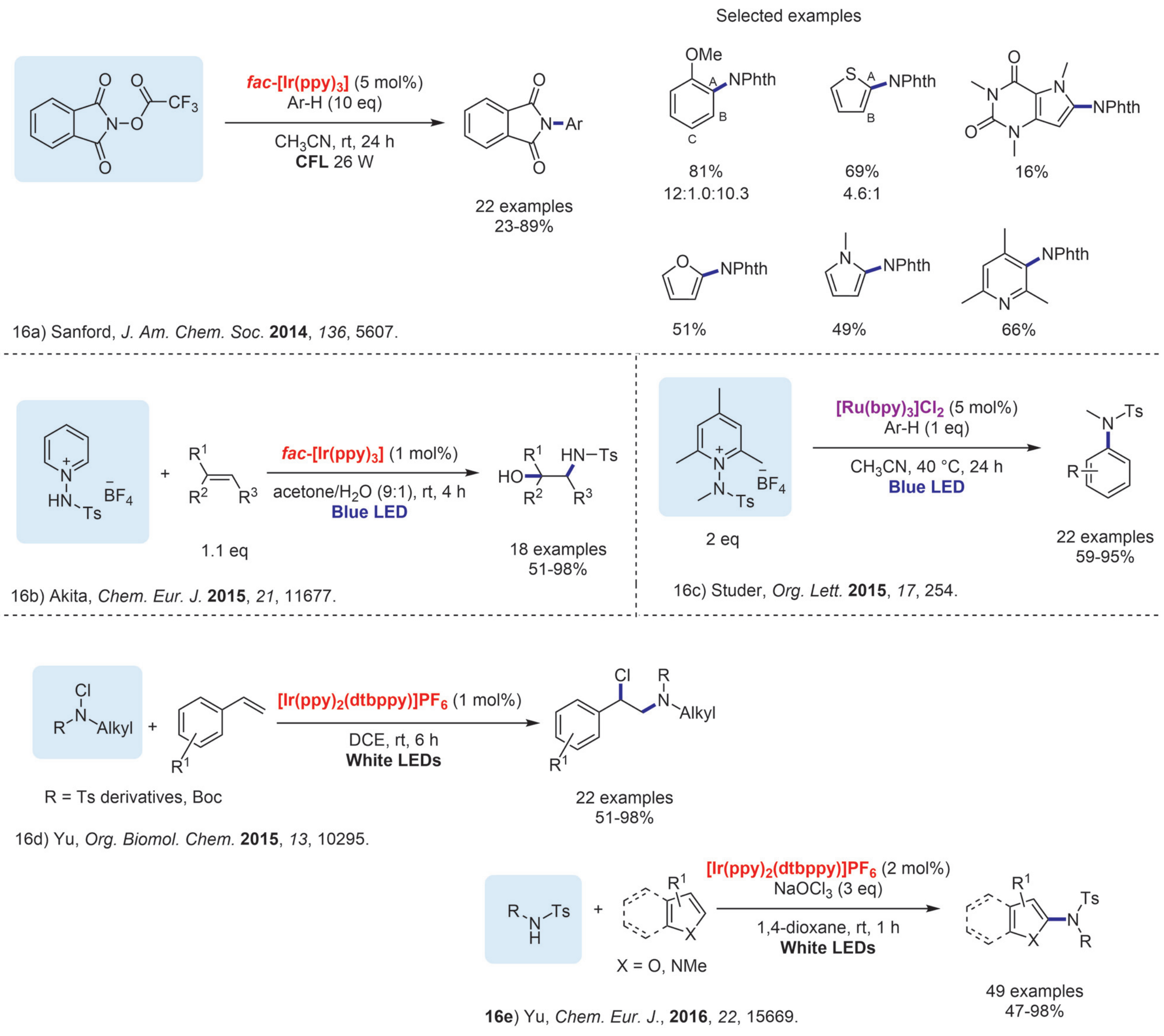
NCR Intermediates



Photocatalysts



Addition to π systems



16a) Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607.

16b) Akita, *Chem. Eur. J.* **2015**, *21*, 11677.

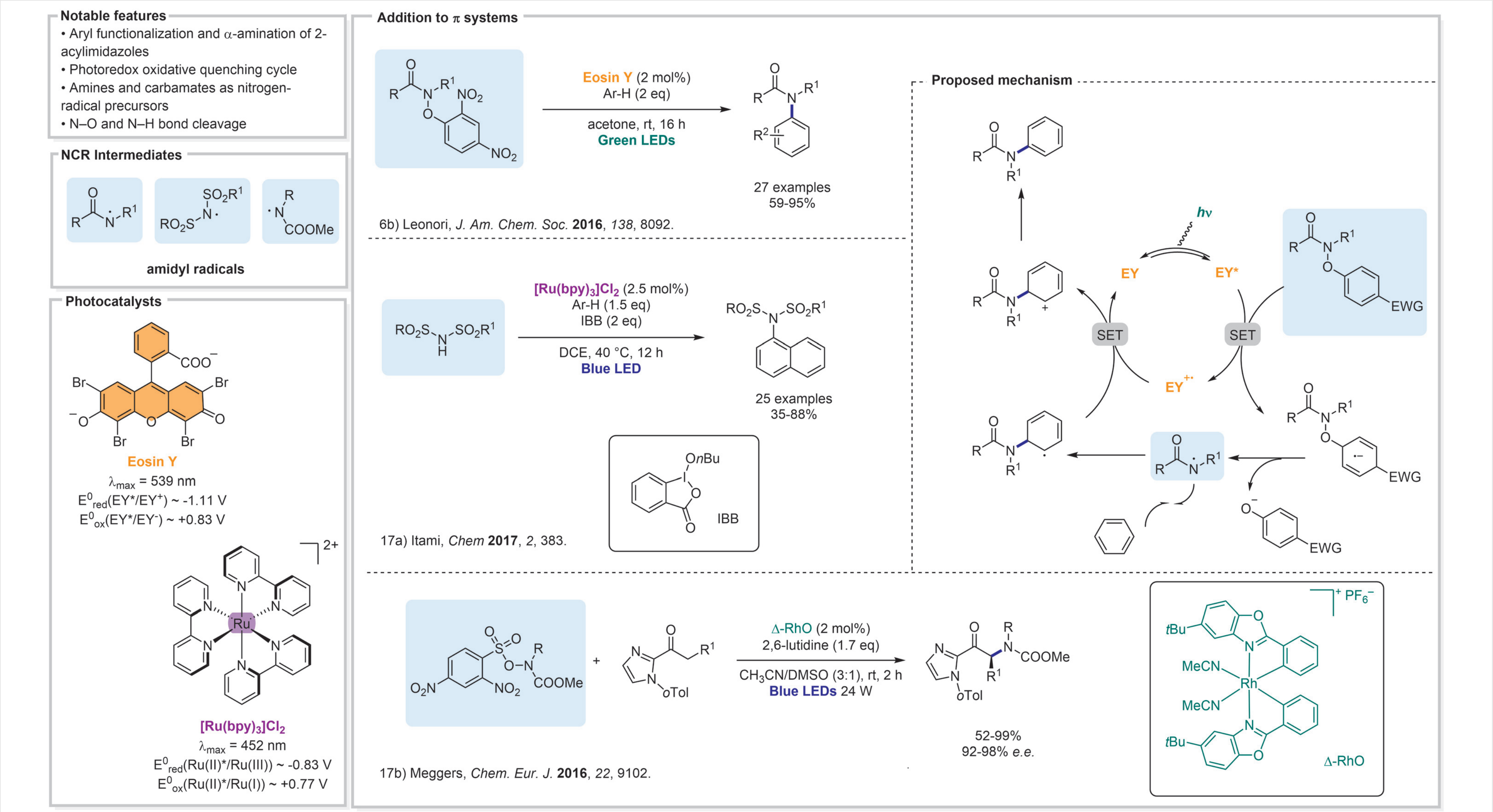
16c) Studer, *Org. Lett.* **2015**, *17*, 254.

16d) Yu, *Org. Biomol. Chem.* **2015**, *13*, 10295.

16e) Yu, *Chem. Eur. J.*, **2016**, *22*, 15669.

Figure 16 Amidyl radicals in imidations and amidations of arenes and heteroarenes and double addition to alkenes[16a–e]

Georg Thieme Verlag KG, Oswald-Hesse-Str. 50, 70469 Stuttgart, Germany



Notable features

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

NCR Intermediates

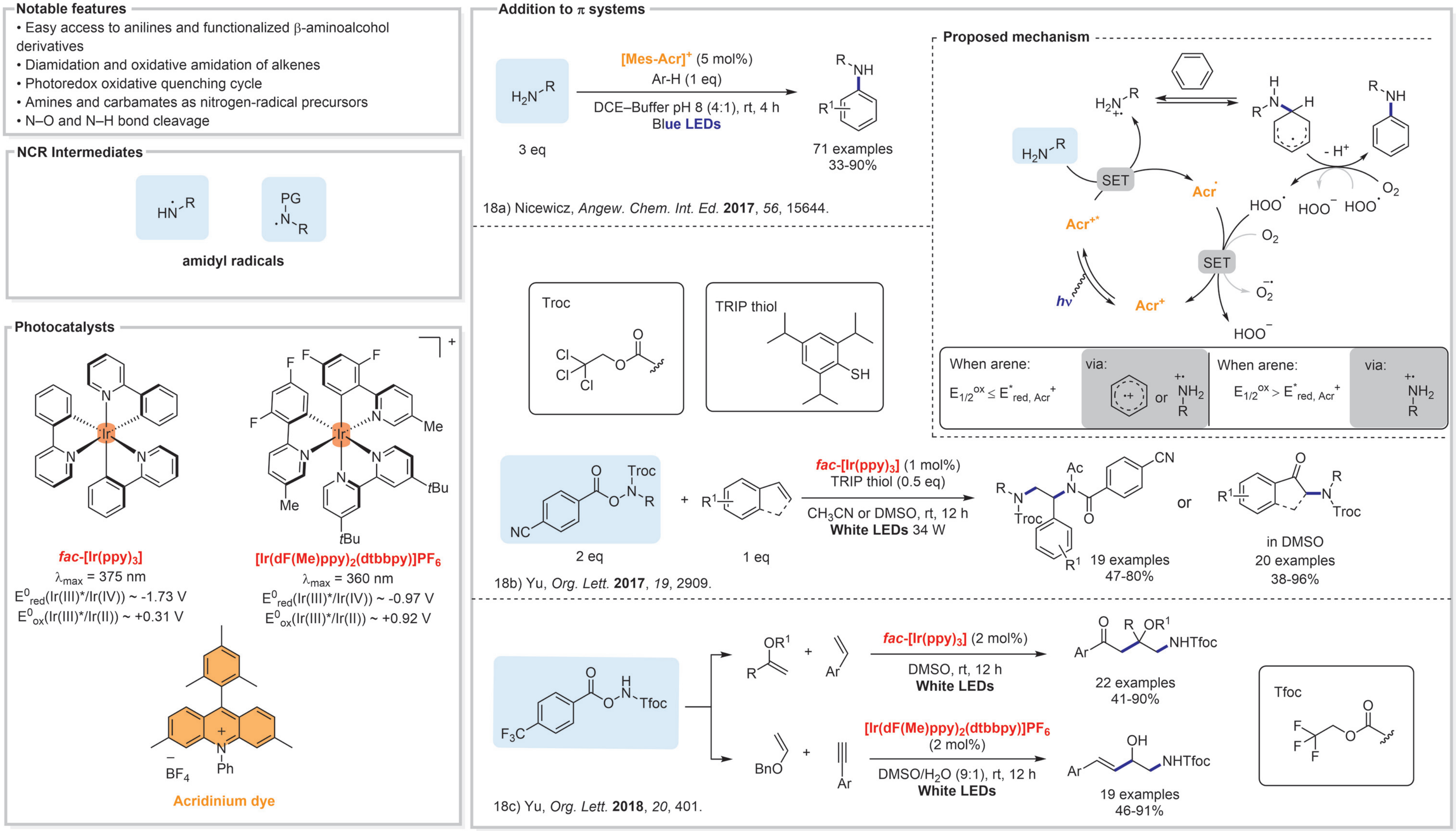
6b) Leonori, *J. Am. Chem. Soc.* **2016**, *138*, 8092.

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

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

Figure 17 Amidyl radicals in amidations of arenes and α-aminations of 2-acylimidazoles[6b,17a,b]

Georg Thieme Verlag KG, Oswald-Hesse-Str. 50, 70469 Stuttgart, Germany



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

18a) Nicewicz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15644.

18b) Yu, *Org. Lett.* **2017**, *19*, 2909.

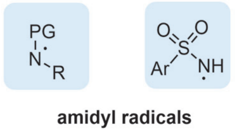
18c) Yu, *Org. Lett.* **2018**, *20*, 401.

Figure 18 Amidyl radicals in arene functionalization and double addition of olefins[18a–c]

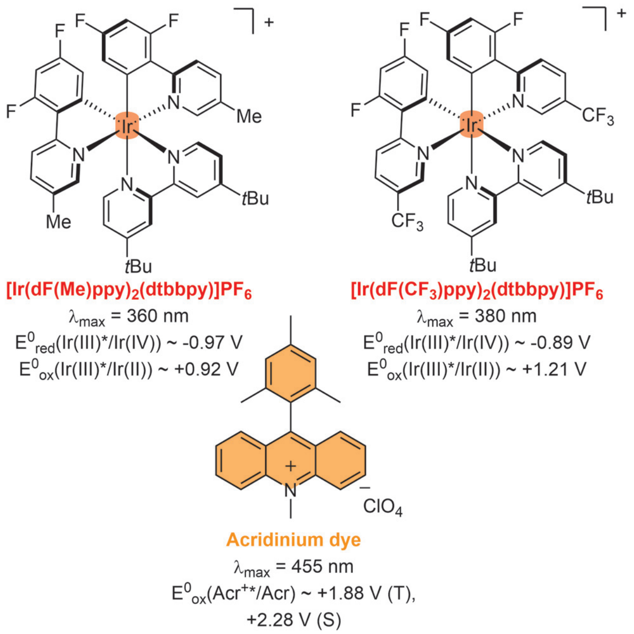
Notable features

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

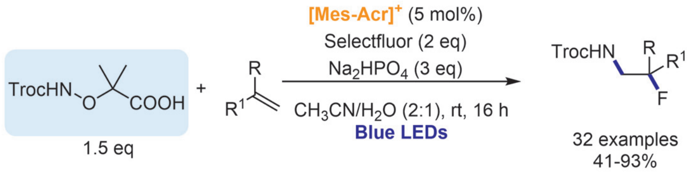
NCR Intermediates



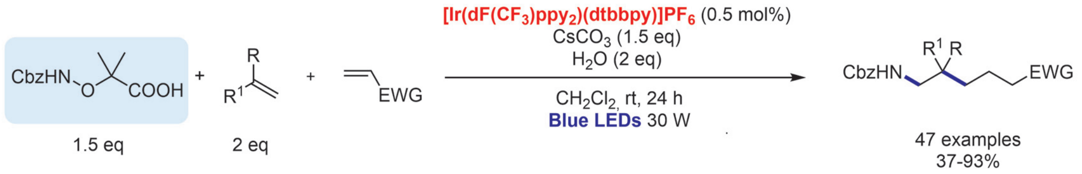
Photocatalysts



Addition to π systems

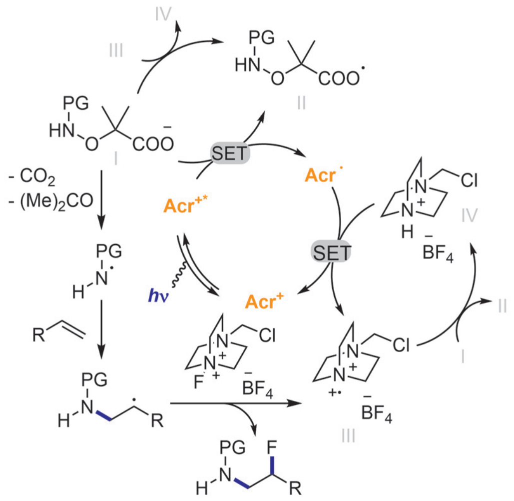


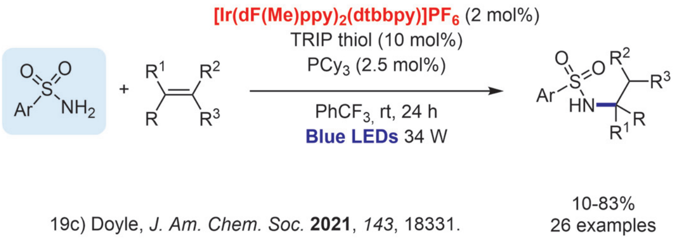
19a) Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 10707.



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

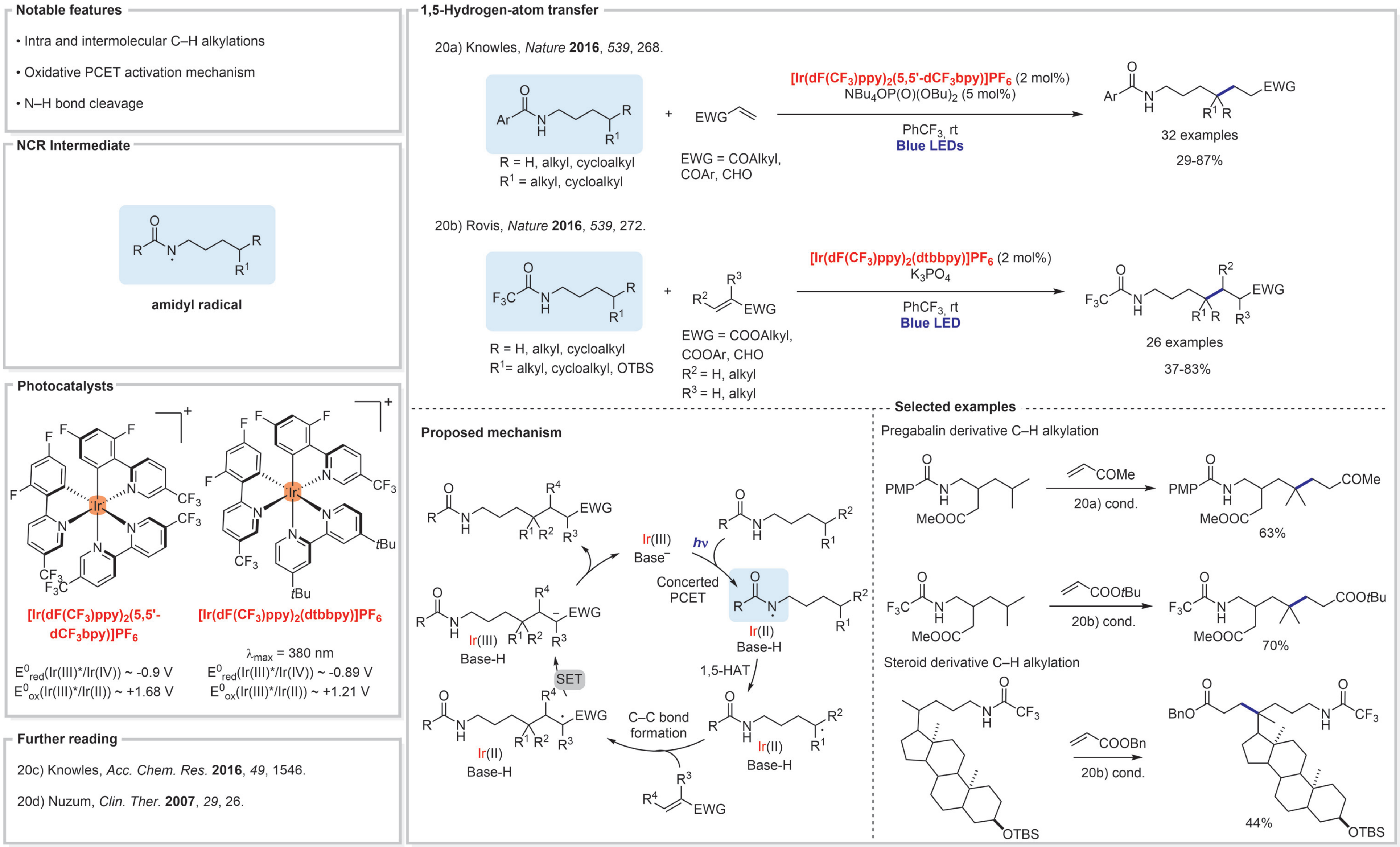
Common mechanism





19c) Doyle, *J. Am. Chem. Soc.* **2021**, *143*, 18331.

Figure 19 Amidyl radicals in three-component reactions to aliphatic amines and the synthesis of sulfonamines[19a–c]



Notable features

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

NCR Intermediate

1,5-Hydrogen-atom transfer

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

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

Photocatalysts

Proposed mechanism

Selected examples

Pregabalin derivative C–H alkylation

Steroid derivative C–H alkylation

Further reading

20c) Knowles, *Acc. Chem. Res.* **2016**, *49*, 1546.

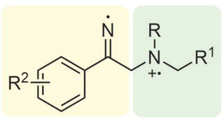
20d) Nuzum, *Clin. Ther.* **2007**, *29*, 26.

Figure 20 Remote C–H alkylation promoted by PCET[20a–d]

Notable features

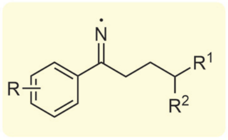
- Synthesis of functionalized imidazoles and 1,2-thiazine-1,1-dioxide
- Intramolecular and intermolecular EDA complex activation
- β-*O*-Aryl oximes as nitrogen-radical precursors
- N–O bond cleavage

NCR Intermediate



iminyl + aminium radicals

NCR Intermediate

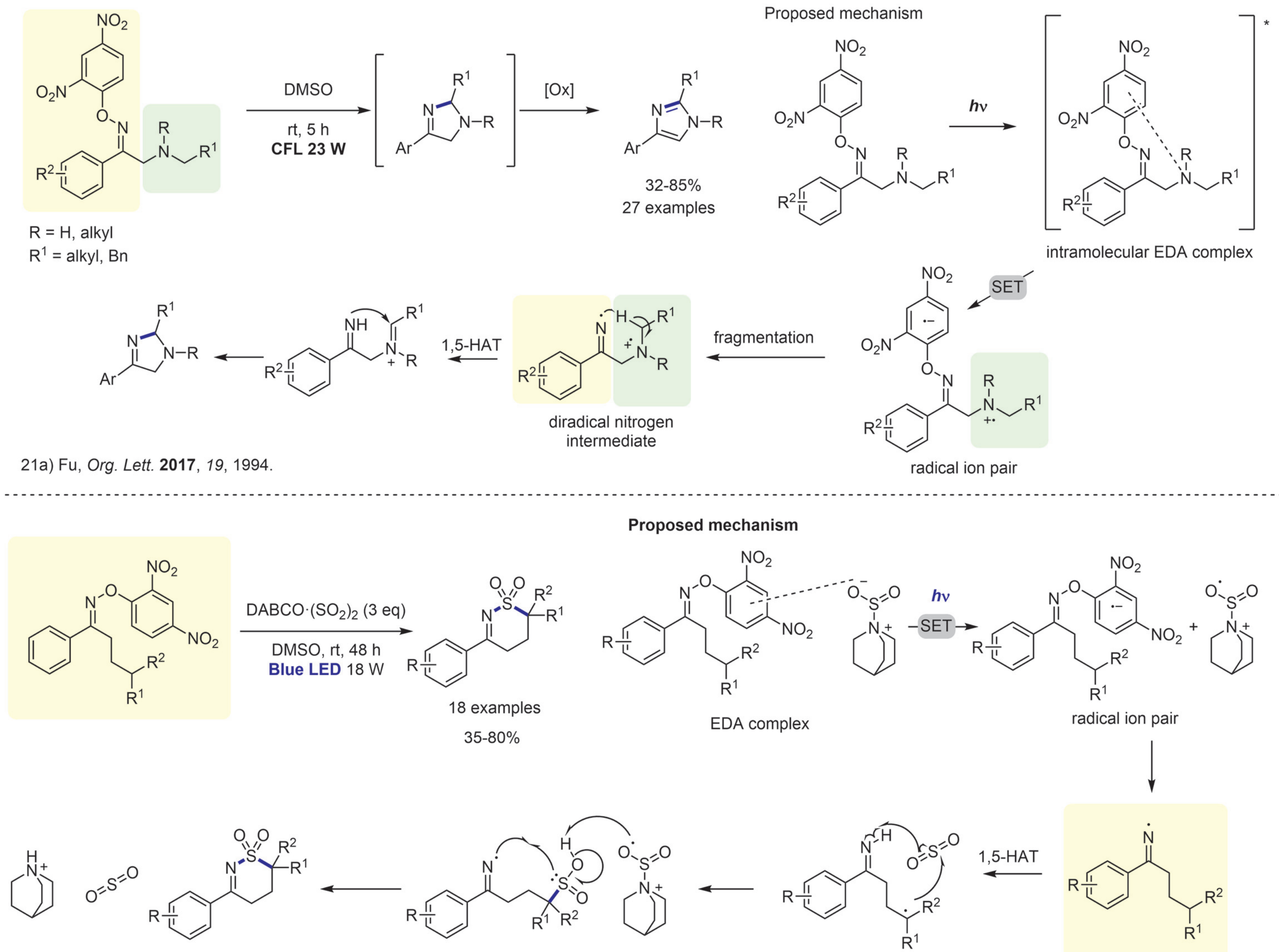


iminyl radical

Further reading

21c) Melchiorre, *J. Am. Chem. Soc.* **2021**, *143*, 12304.

1,5-Hydrogen-atom transfer



R = H, alkyl
R¹ = alkyl, Bn

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

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

Figure 21 Intramolecular C(sp^3)–H imination for the synthesis of functionalized imidazoles[21a–c]

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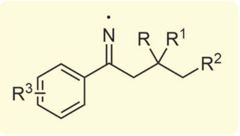
Notable features

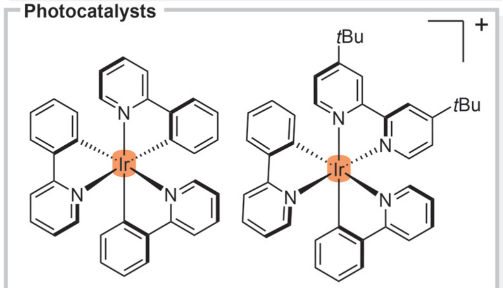
- Synthesis of fused cyclohexanones
- Photoredox reductive quenching cycle
- Acyl oxime as a nitrogen-radical precursor
- N–O bond cleavage

NCR Intermediate



iminyl radical

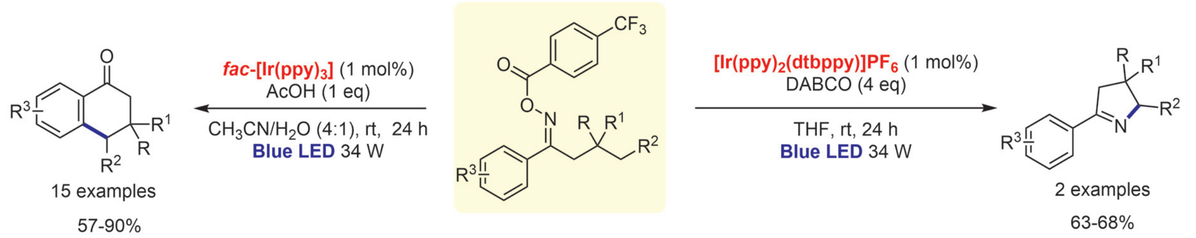
Photocatalysts



fac-[Ir(ppy)$_3$]
λ_{max} = 375 nm
E^0_{red}(Ir(III)*/Ir(IV)) ~ -1.73 V
E^0_{ox}(Ir(III)*/Ir(II)) ~ +0.31 V

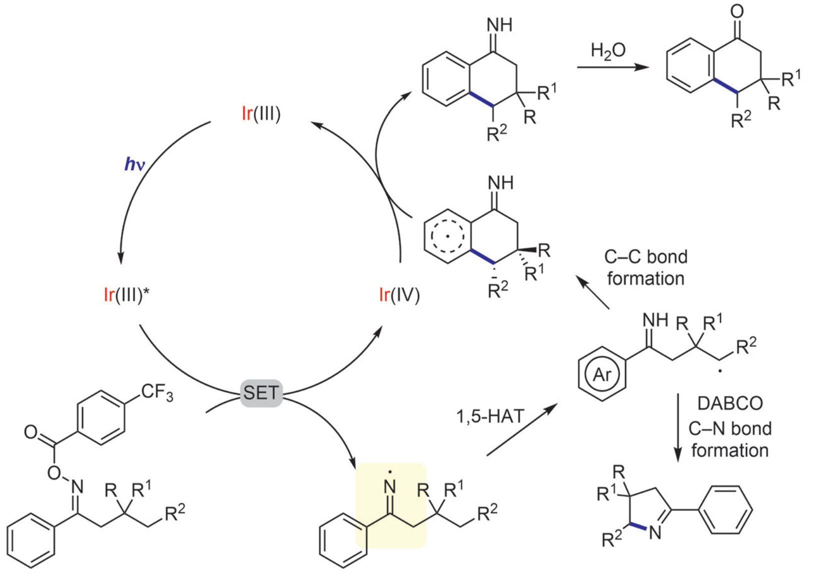
[Ir(ppy)$_2$(dtbppy)]PF$_6$
λ_{max} = 410 nm
E^0_{red}(Ir(III)*/Ir(IV)) ~ -0.96 V
E^0_{ox}(Ir(III)*/Ir(II)) ~ +0.66 V

1,5-Hydrogen-atom transfer



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

Proposed mechanism



Selected examples

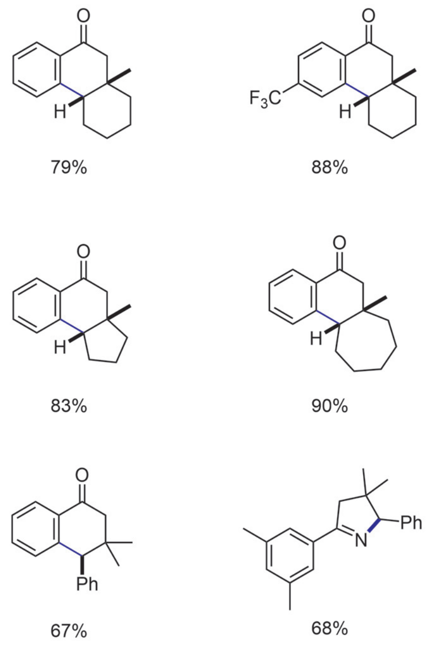
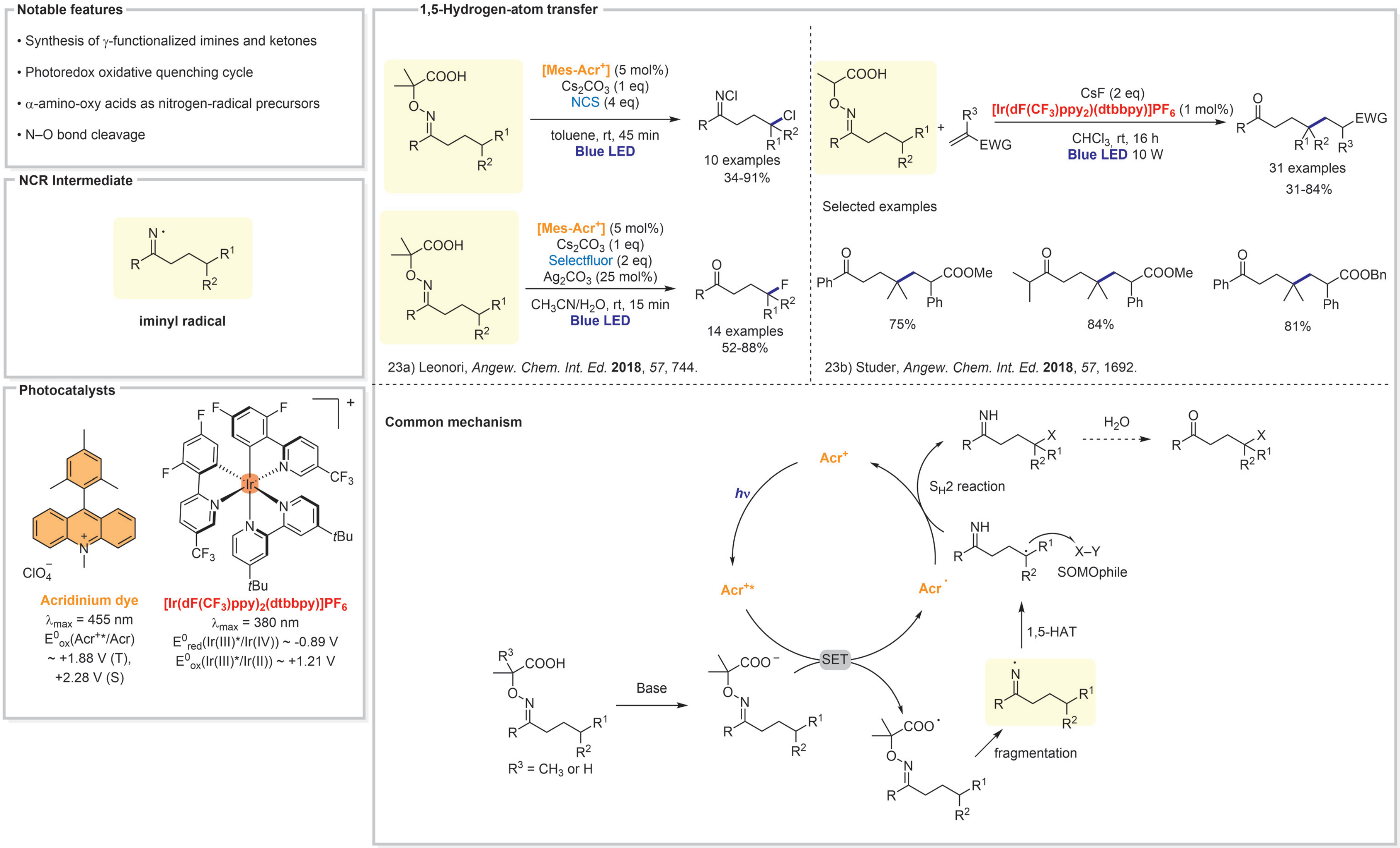


Figure 22 Aliphatic C–H functionalization through a 1,5-HAT cascade[22]



Notable features

- Synthesis of γ-functionalized imines and ketones
- Photoredox oxidative quenching cycle
- α-amino-oxy acids as nitrogen-radical precursors
- N–O bond cleavage

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

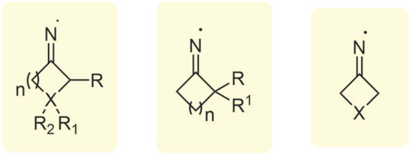
23b) Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 1692.

Figure 23 γ-C(sp^3)–H functionalization of ketones[23a,b]

Notable features

- Easy access to cyanoalkyl scaffold as future building blocks

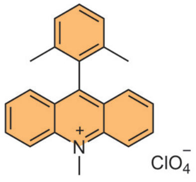
NCR Intermediate



iminyl radicals

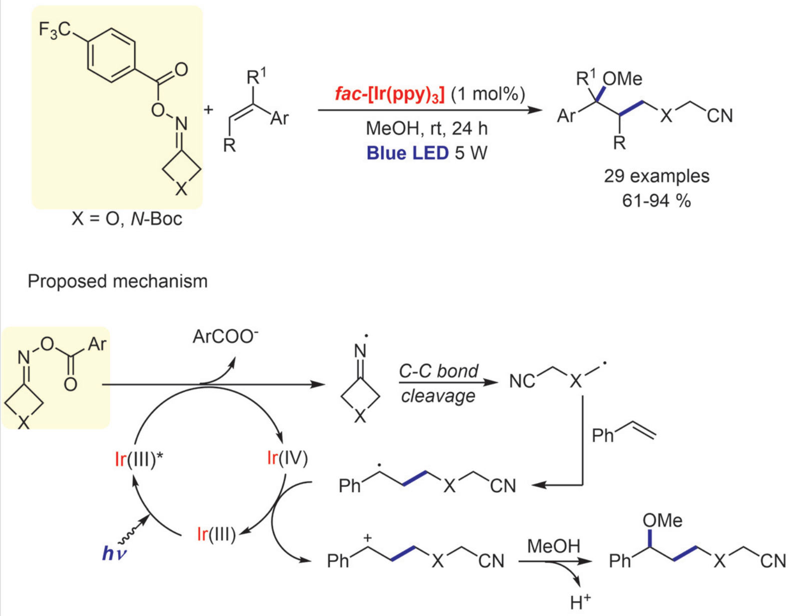
Photocatalysts

fac-[Ir(ppy)$_3$]
λ_{max}= 375 nm
E^0_{red}(Ir(III)*/Ir(IV)) ~-1.73 V
E^0_{ox}(Ir(III)*/Ir(II)) ~+0.31 V

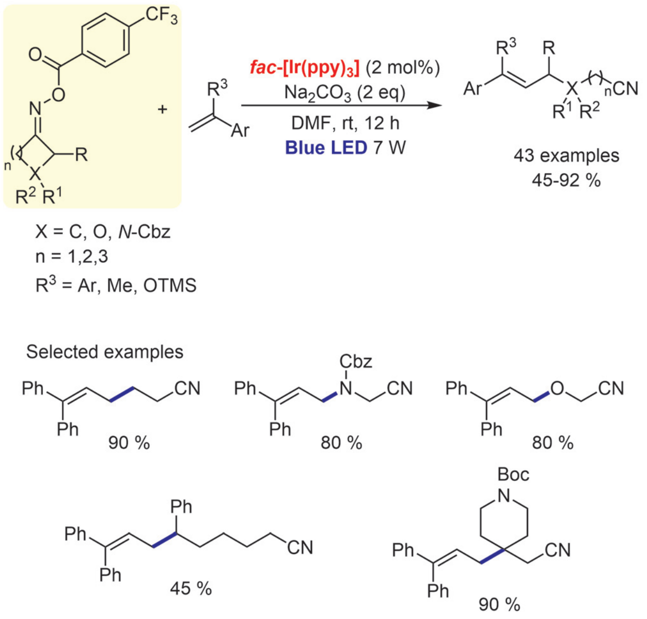


Acridinium dye
λ_{max}= 455 nm
E^0_{ox}(Acr^{+*}/Acr) ~+1.88 V (T), +2.28 V (S)

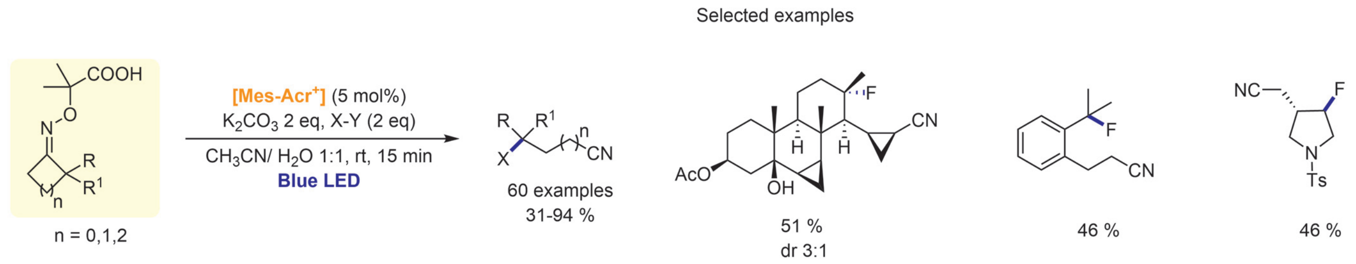
Norrish Fragmentation



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



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



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

Figure 24 Norrish fragmentations[23a,24a,b]

Conflict of Interest

The authors declare no conflict of interest.

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(3) (a) Jiang, H.; An, X.; Tong, 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**, *56*, 12273. (c) Matsushita, Y.; Ochi, R.; Tanaka, Y.; Koike, T.; Akita, M. *Org. Chem. Front.* **2020**, *7*, 1243.

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(7) (a) Hu, X.-Q.; Chen, J.; Chen, J.-R.; Yan, D.-M.; Xiao, W.-J. *Chem. Eur. J.* **2016**, *22*, 14141. (b) Zhao, Q.-Q.; Hu, X.-Q.; Yang, M.-N.; Chen, J.-R.; Xiao, W.-J. *Chem. Commun.* **2016**, *52*, 12749. (c) Martínez, C.; Bosnidou, A. E.; Allmendinger, S.; Muñiz, K. *Chem. Eur. J.* **2016**, *22*, 9929.

(8) (a) Ren, X.; Guo, Q.; Chen, J.; Xie, H.; Xu, Q.; Lu, Z. *Chem. Eur. J.* **2016**, *22*, 18695. (b) Hu, X.-Q.; Qi, X.; Chen, J.-R.; Zhao, Q.-Q.; Wei, Q.; Lan, Y.; Xiao, W.-J. *Nat. Commun.* **2016**, *7*, 11188. (c) Chen, J.; Guo, H.-M.; Zhao, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Chem. Commun.* **2018**, *54*, 6780.

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