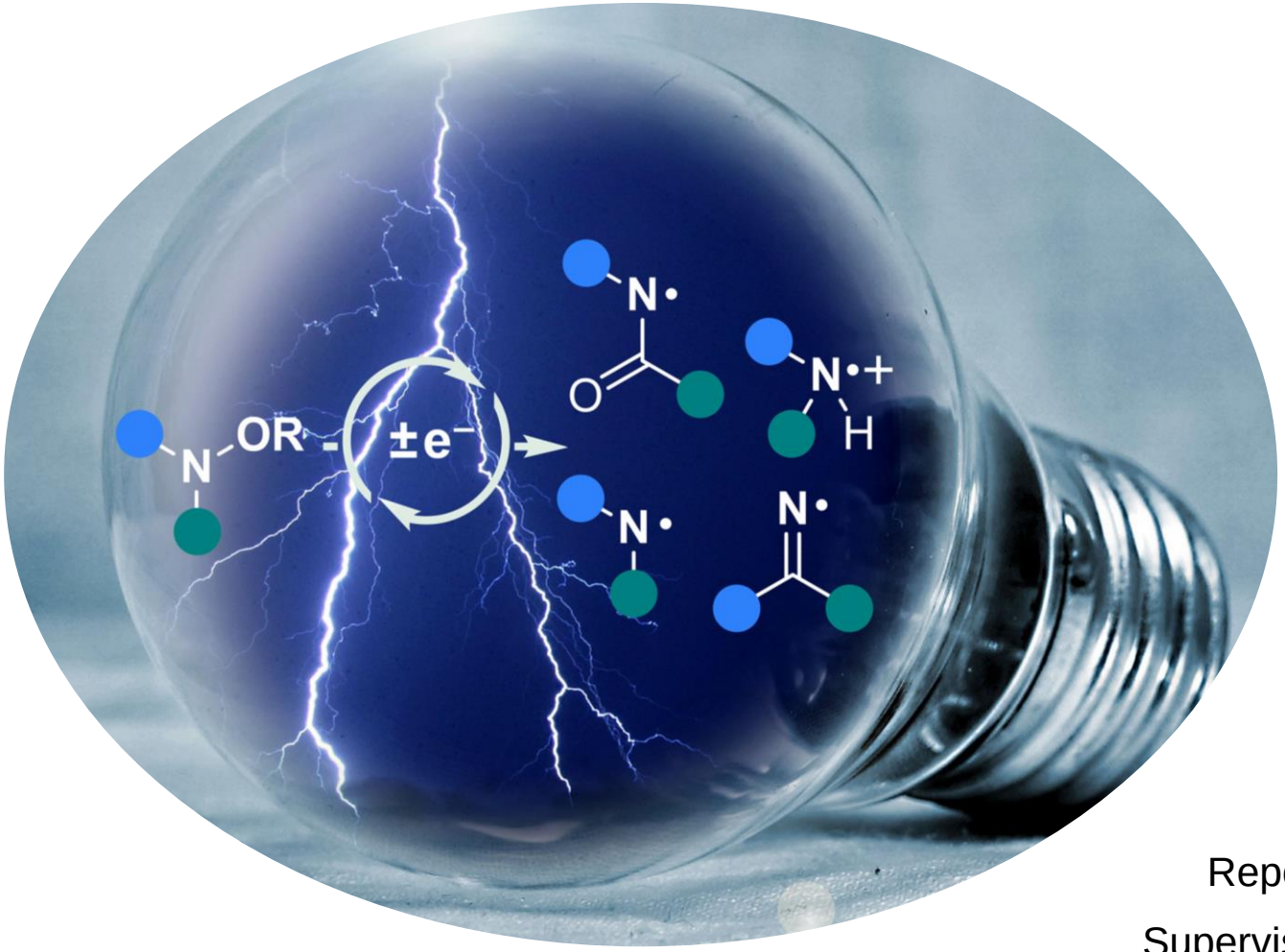
Hydroxylamine Derivatives as Nitrogen-Radical Precursors in Visible-Light Photochemistry



Reporter: Linrui Zhang

Supervisor: *Prof.* Yong Huang

Date: 2019-5-13

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- Introduction
- Nitrogen Radicals: Classification and General Reactivity
- Hydroxylamines as Nitrogen-Radical Precursors
- Four main classes of Hydroxylamines Nitrogen-radicals reactions
- Summary
- Acknowledgement

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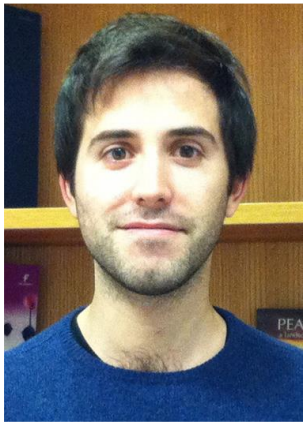
The Author



Daniele Leonori

Career

2018-Now	Reader in Organic Chemistry, **University of Manchester**
2017-Now	EPSRC Early Career Fellow, **University of Manchester**
2014-2018	Lecturer of Organic Chemistry, **University of Manchester**
2012-2014	Research Officer, **University of Bristol** Under the supervision of Prof. Varinder K. Aggarwal FRS
2011-2012	Postdoctoral Research Associate, **Max Planck Institute for Colloids and Interfaces** Under the supervision of Prof. Peter H. Seeberger
2010-2011	Postdoctoral Research Associate, **RWTH-Aachen University** Under the supervision of Prof. Magnus Rueping
2007-2010	PhD, **University of Sheffield** Under the supervision of Prof. Iain Coldham

Awards

Harrison-Meldola Memorial Prize (*2018*), ERC Starting Grant (*2018-2023*), Thieme Chemistry Journal Award (*2017*), EPSRC Early Career Fellowship (*2017-2022*), Silver Medal - 2016 European Young Chemist Award (*2016*), IUPAC/UNESCO/PhosAgro Green Chemistry Award (*2015*), Marie Curie Career Integration Grant (*2014-2019*), Pfizer Poster Symposium Runner-Up Prize (*2009*), Eli Lilly Postgraduate Prize (*2009*)

Research

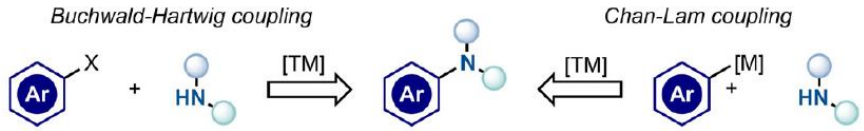
Investigates methods for the formation of C-N bonds and for selective functionalization of bioactive molecules

https://leonoriresearchgroup.weebly.com/daniele.html

Introduction

- The preparation of **Nitrogen-containing** molecules: ubiquitous structural units in drugs, agrochemicals and organic materials

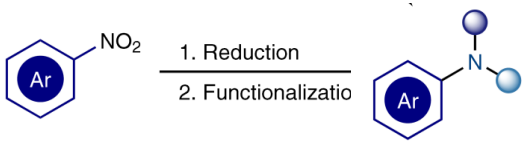
Transition-metal-based protocols
Buchwald, Hartwig, Ullmann, Chan-Lam



Photoredox catalysis SET
to access nitrogen-centered radical
MacMillan, Yoon, Nicewicz et al.

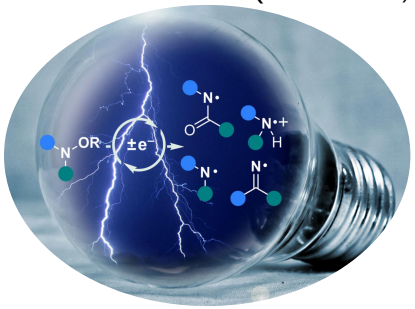
Early stage **2008** **2008** **2013** **2015**

Ionic pathways
Traditional approach



Nitrogen-centered radical
Minisci, Forrester, **Zard**, Newcomb et al.

Hydroxylamines derivatives
as nitrogen-radical precursors
Daniele Leonori (This work)



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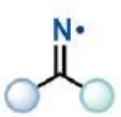
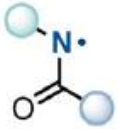
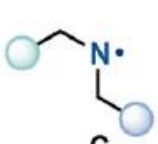
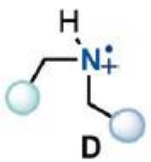
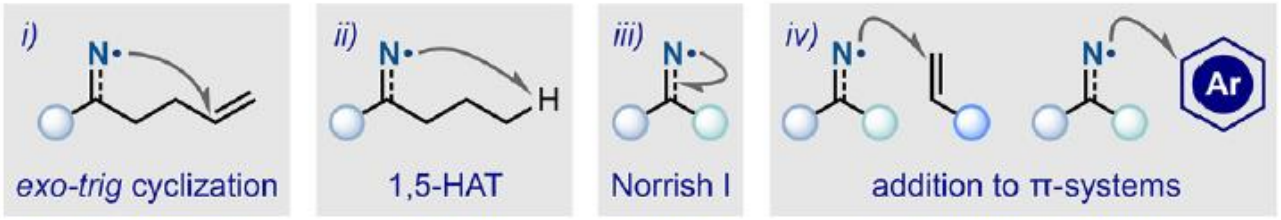
Nitrogen Radicals: Classification and General Reactivity

- Classification of Nitrogen Radicals (based on N-hybridization and substituents)

Structure	 A	 B	 C	 D
Name	iminyl	amidyl	aminyl	aminium
Configuration	σ	π	π	π
Philicity	ambiphilic	electrophilic	nucleophilic	electrophilic

- General Reactivity of Nitrogen Radicals



- These reaction modes are not shared by all classes of nitrogen-radicals as their philicity is responsible for the stabilization of the respected transition states.

J. C. Walton, *Acc. Chem. Res.* **2014**, *47*, 1406.
J. Lessard, *J. Am. Chem. Soc.* **1980**, *102*, 3262.
Y. L. Chow, *Chem. Rev.* **1978**, *78*, 243.

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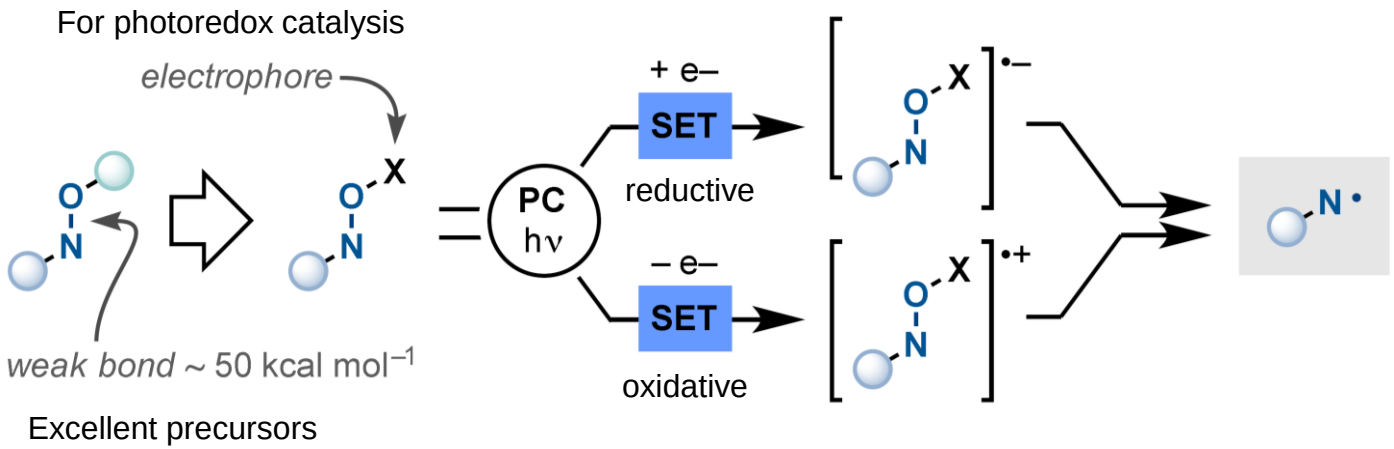
Hydroxylamines as Nitrogen-Radical Precursors

- Formation of nitrogen radicals using hydroxylamines

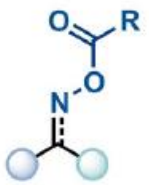
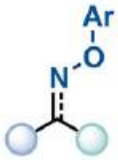
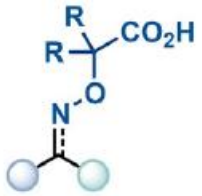
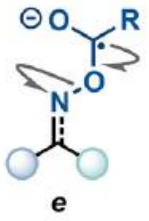
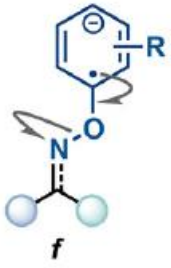
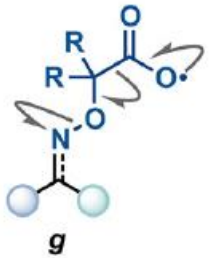


- Advantages: the electrophore redox properties can be tailored by simple structural modification and are typically independent of the substituents on the N atom.

Y.-R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds* **2003**, CRC Press.

Hydroxylamines as Nitrogen-Radical Precursors

- Most common types of electrophores

	E	F	G
Structure			
	O-acyl	O-aryl	α-N-oxyacids
SET	reduction	reduction	oxidation
Electrophore	π* + σ*	π* + σ*	n + σ + σ
Mode of Fragmentation			
	e	*f*	*g*
	homolysis	homolysis	two β-scissions

- The identification of these simple classes of electrophores has provided a strong foundation for the development of many photochemical protocols based on different redox requirements.

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d) Addition to Olefins and Aromatics

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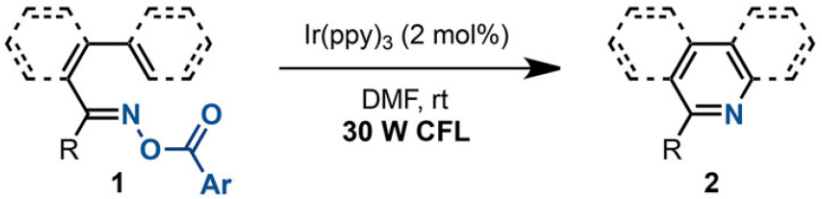
Intramolecular Cyclizations

➢ Reductive SET of Hydoxylamine Precursors (iminyl radicals)

- *6-endo* cyclization

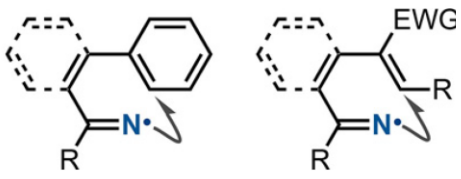


O-benzoyl oximes

$E1^{red}$ = – 0.79 V

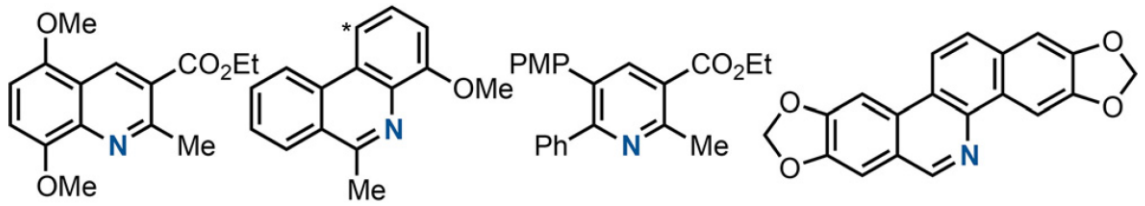
E[*Ir(III)/Ir(IV)] = –1.73 V

Succesful modes of cyclization



iminyl radicals

Selected examples



2a, 88% **2b**, 90% (3:1) **2c**, 90% **2d**, 93%

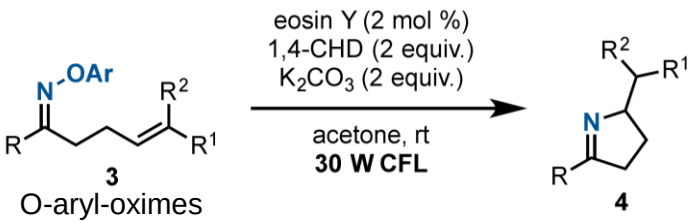
◆ In general, the *6-endo* cyclization to give pyridines necessitated the presence of an ester group at C-3, indicating the polarization required for efficient reactivity.

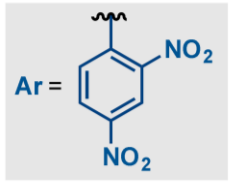
Y. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4055.
S. Yu, *Org. Lett.* **2015**, *17*, 2692.

Intramolecular Cyclizations

➢ Reductive SET of Hydoxylamine Precursors (iminyl radicals)

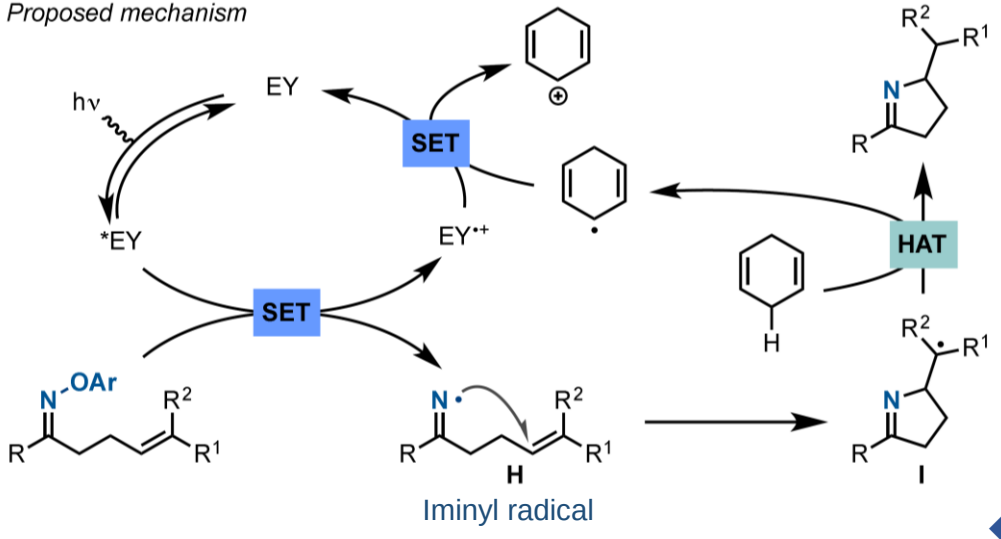
- *5-exo-trig* hydroiminations





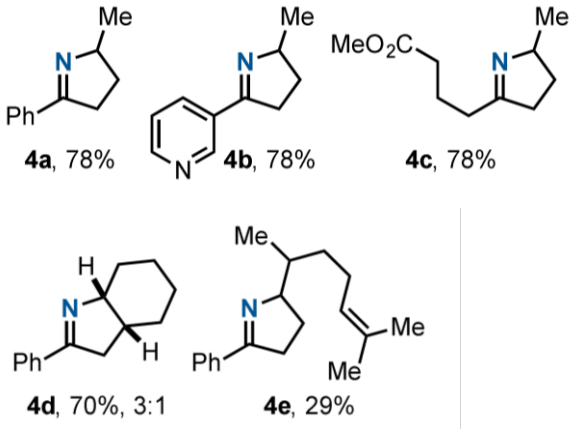
$E\mathbf{3}^{red}$ = –0.9 V
E(EY•+/*EY) = –1.08 V

Proposed mechanism



Iminyl radical

Selected examples

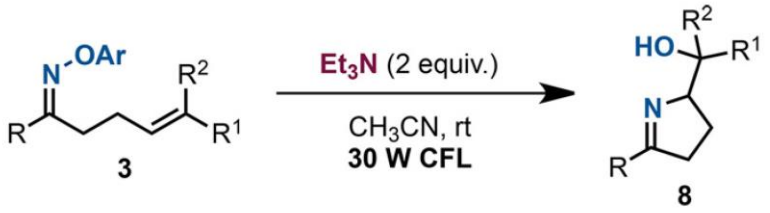


- ◆ 1,4-CHD serves a double role as both H-atom donor and reductant for the oxidised EY•+.
- ◆ Tri-substituted olefins was challenging the increased stability of the tertiary carbon led to slower H abstraction.

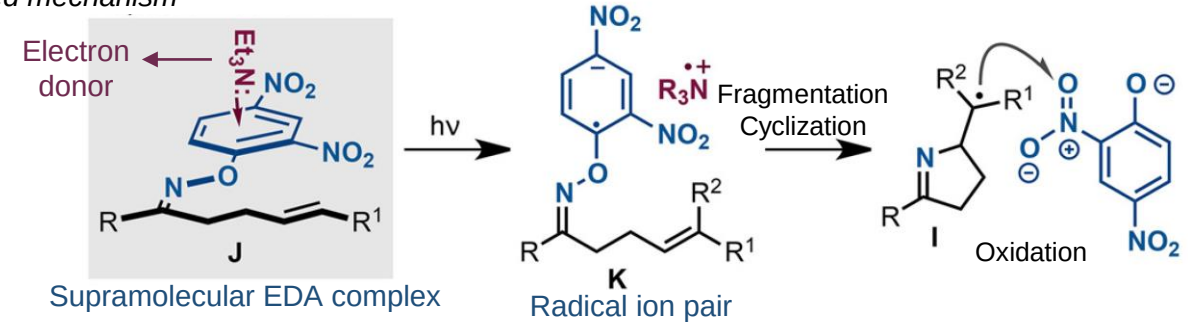
D. Leonori, *Angew. Chem. Int. Ed.* **2015**, *54*, 14017.
B. König, *Chem. Commun.* **2014**, *50*, 6688.

Intramolecular Cyclizations

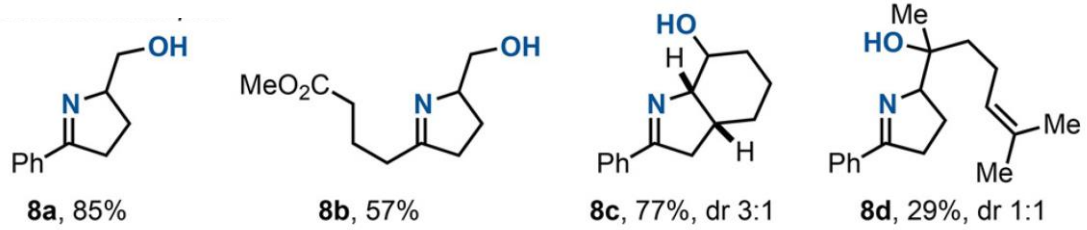
- Reductive SET of Hydoxylamine Precursors (iminyl radicals)
  - Direct photochemical activation of oximes in the absence of *EY*



Proposed mechanism



Selected examples



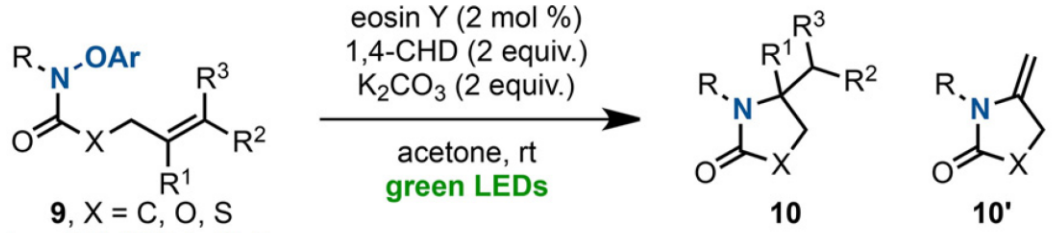
- Control experiments suggested a mechanism via a rebound reaction, with the NO_2 group serving as the oxidant via concurrent reduction to the nitroso.

M. W. Paixão, *ACS Catal.* **2016**, *6*, 1389.

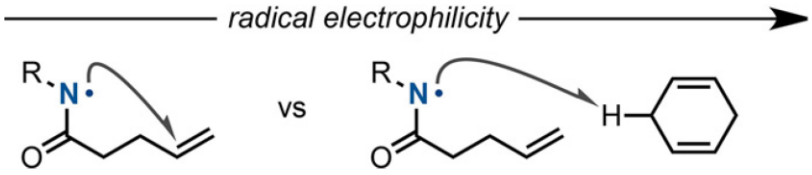
Intramolecular Cyclizations

➢ Reductive SET of Hydoxylamine Precursors (amidyl radicals)

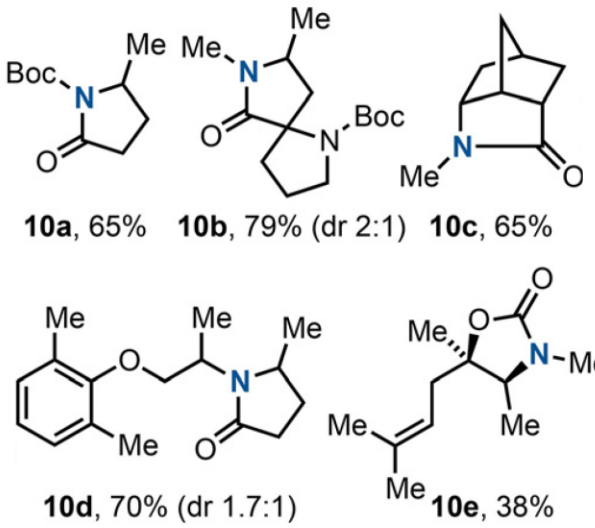
- *5-exo-trig and 5-exo-dig* cyclizations



Cyclization vs direct H-abstraction



Selected examples



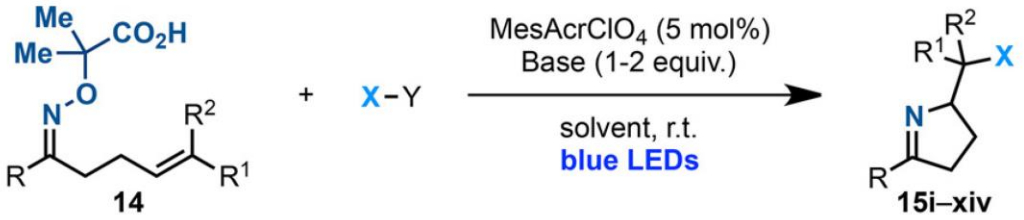
◆ A broad range of substrates including spirocyclic, tricyclic derivatives and modification of drugs and terpenes.

D. Leonori, *J. Am. Chem. Soc.* **2016**, *138*, 8092.
D. Leonori, *Eur. J. Org. Chem.* **2017**, 2108.

Intramolecular Cyclizations

➢ Oxidative SET of Hydoxylamine Precursors (only iminyl radicals)

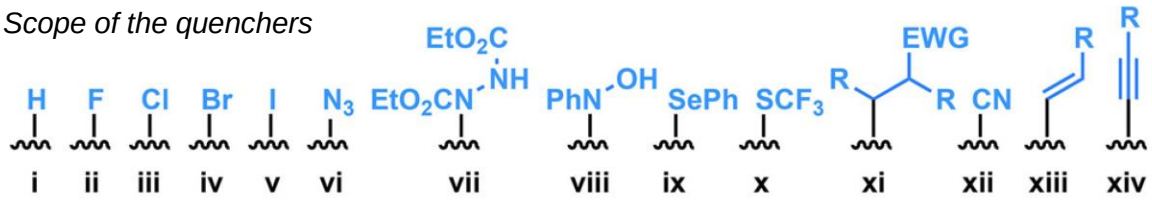
- Imino-functionalization reaction transition metal-free



α-imino-oxy acids

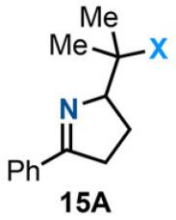
E**14**^{ox} ≈ +1.6V
Fukuzumi's catalyst, *E^{ox} = +2.1 V

Scope of the quenchers

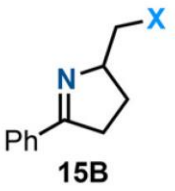


- **Studer:** Michael acceptors (**xi**)
- **Leonori:** divergent strategy encompassing 14 different functionalizations (**i-x, xii-xiv**)

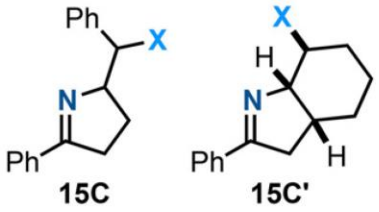
Accessible pyrrolines and modification of thevinone



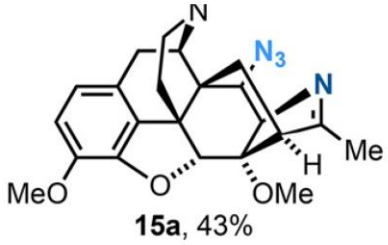
15A
quaternary centres



15B
primary



15C **15C'**
secondary

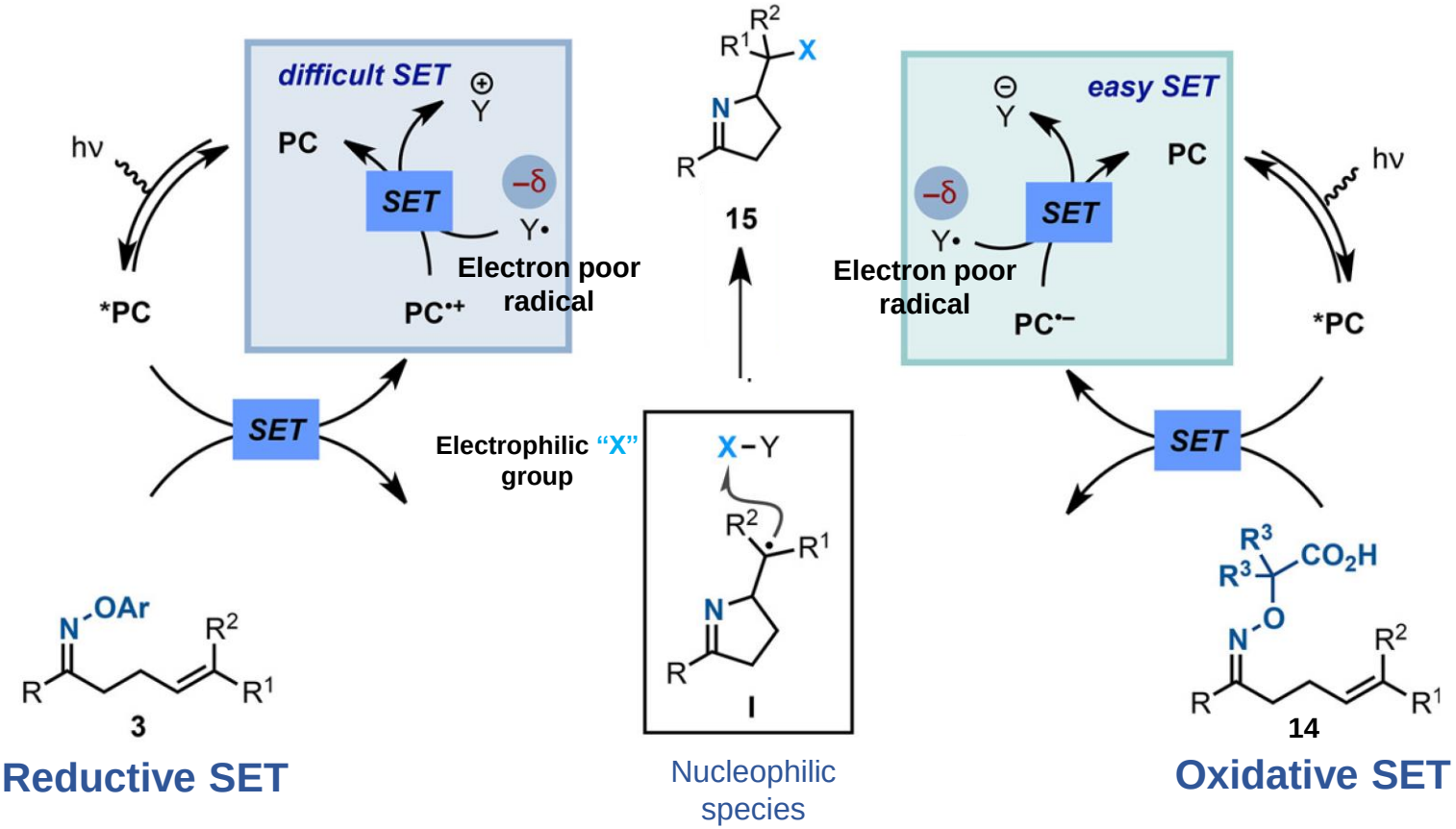


15a, 43%
late-stage modification of thevinone

A. Studer, *Angew. Chem. Int. Ed.* **2017**, *56*, 12273.
D. Leonori, *Angew. Chem. Int. Ed.* **2017**, *56*, 13361.
S. Fukuzumi, *Org. Biomol. Chem.* **2014**, *12*, 6059.

Intramolecular Cyclizations

- Mechanistic analysis for redox neutral iminofunctionalizations



- The effectiveness of the oxidative with respect to the reductive one can be rationalized by the electronic requirements necessary to render the overall process redox neutral.

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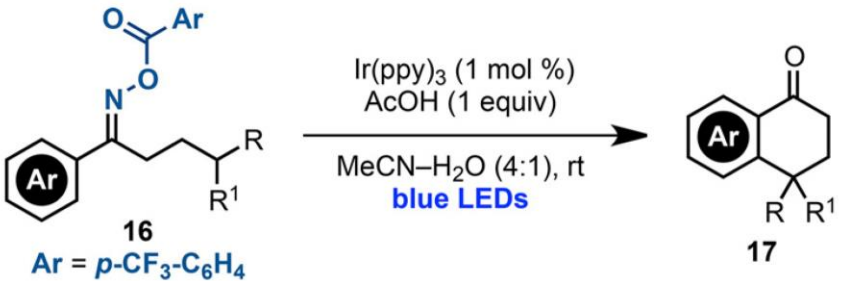
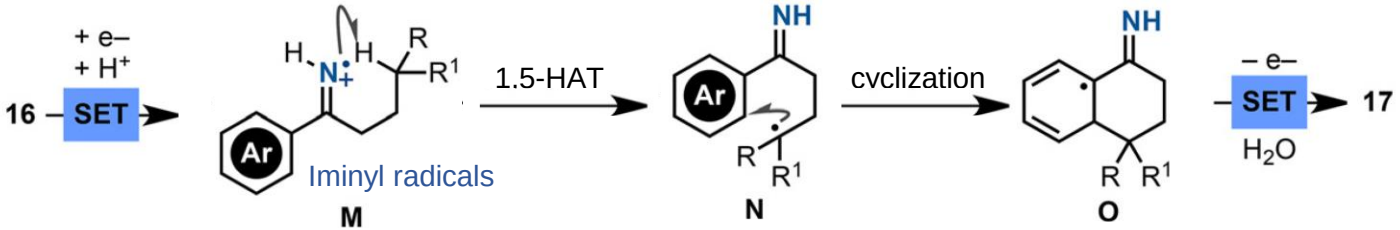
Intramolecular H-Abstractions: 1,5-HAT

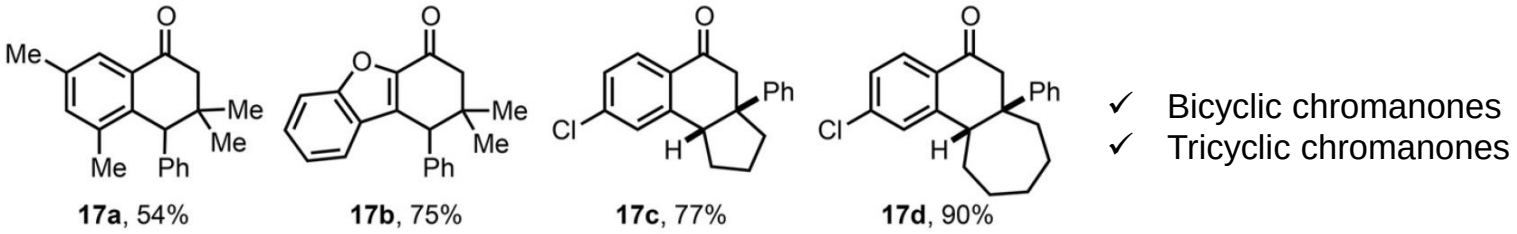
- Reductive SET of Hydoxylamine Precursors (iminyl radicals)



Individual steps



Selected examples



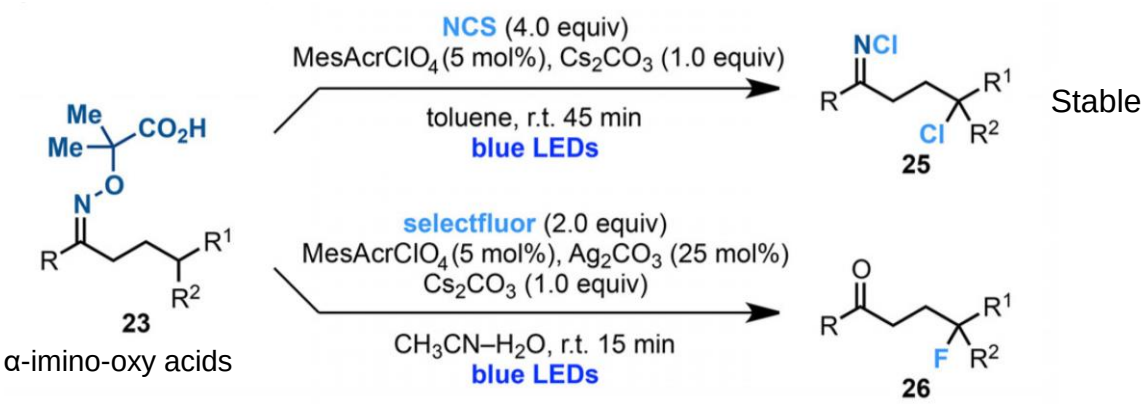
- ✓ Bicyclic chromanones
- ✓ Tricyclic chromanones

- Be facilitated by a Brönsted acid via protonation of the iminyl radical (M), enhancing its electrophilicity and lowering the enthalpic requirements for the HAT.

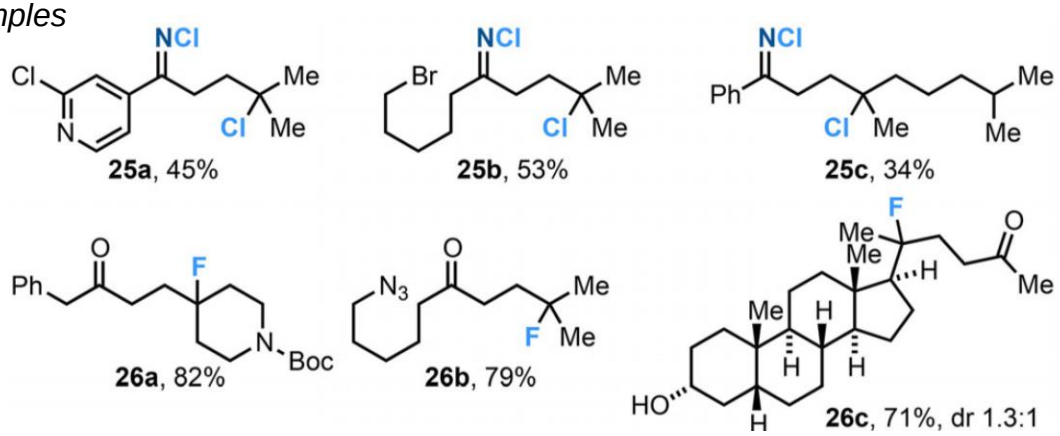
C. Nevado, *Angew. Chem. Int. Ed.* **2017**, *56*, 1881.
A. R. Forrester, *J. Chem. Soc., Perkin Trans. 1* **1979**, 632.

Intramolecular H-Abstractions: 1,5-HAT

- Oxidative SET of Hydoxylamine Precursors (iminyl radicals)
  - γ-Chlorination and fluorination



Selected examples



✓ High functional group compatibility

✓ Modification of a lithocholic derivative

D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 744.

Content

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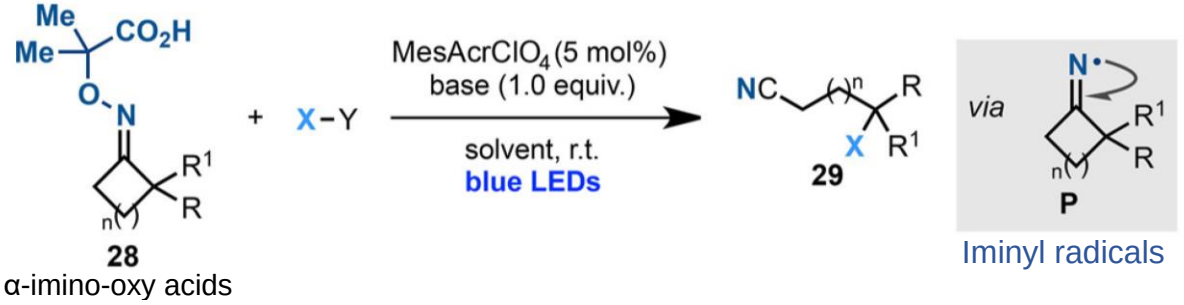
- Nitrogen Radicals: Classification and General Reactivity
- Hydroxylamines as Nitrogen-Radical Precursors
- Four main classes of Hydroxylamines Nitrogen-radicals reactions

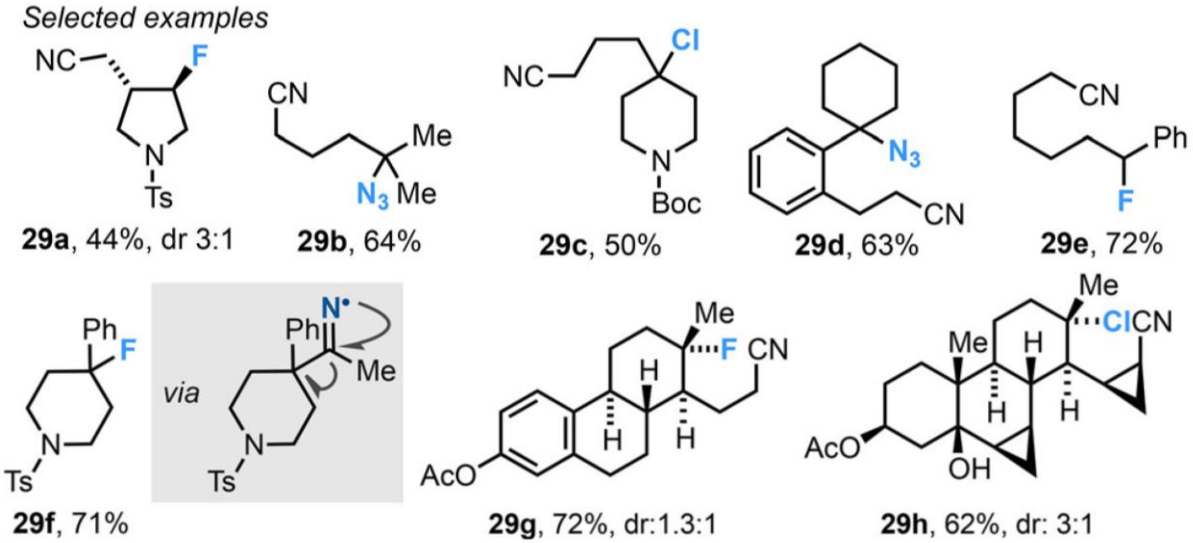
a) Intramolecular Cyclizations
b) Intramolecular H-Abstractions: 1,5-HAT
c) Fragmentations
d) Addition to Olefins and Aromatics

- Summary
- Acknowledgement

Fragmentations

- Oxidative fragmentation to access distally functionalized nitriles





C-4 functionalization

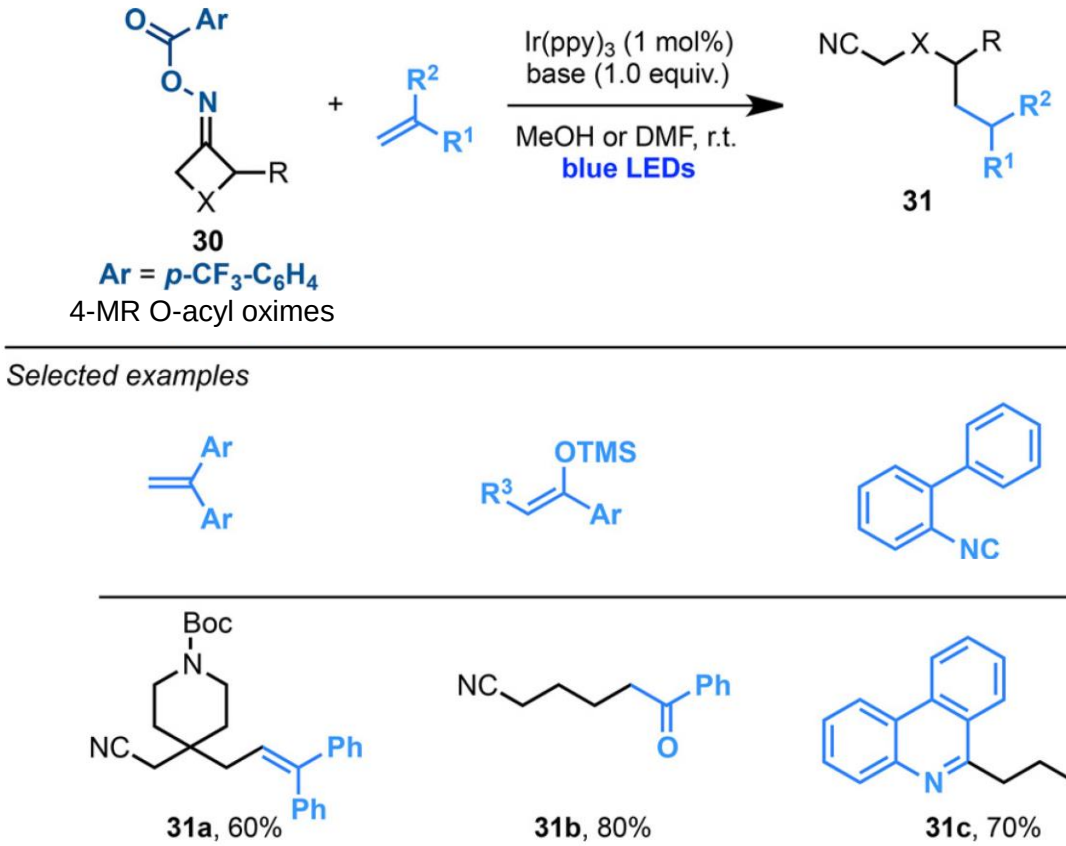
Selective deconstruction and functionalization

- Limitation: This process only been applied to the ring opening of cyclic oximes, 6- and 7-MRs was possible only on α-aryl substrates.

D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 744

Fragmentations

- Reductive approaches for the generation of iminyl radicals



- Demonstrated the ring opening using various π-acceptors to trap of the γ-nitrile radicals.

L. Zhou, *Chem. Commun.* **2017**, *53*, 11544.
W.-J. Xiao, *Angew. Chem. Int. Ed.* **2018**, *57*, 738.

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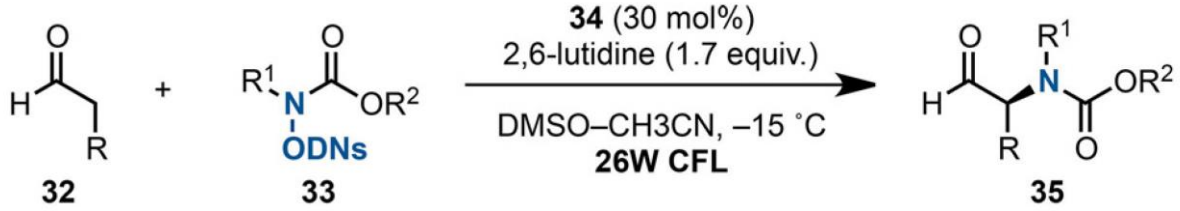
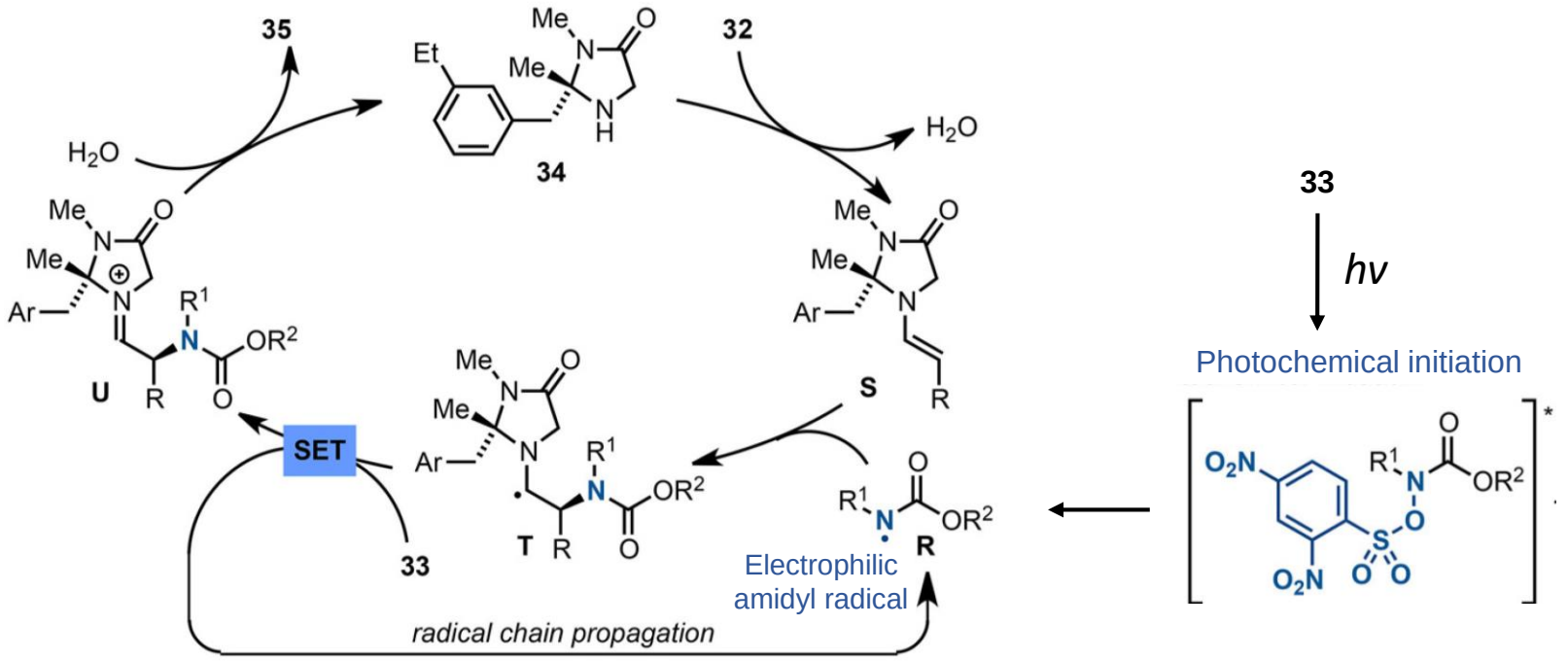
Addition to Olefins

- The first asymmetric reaction of nitrogen-radicals using organocatalysis



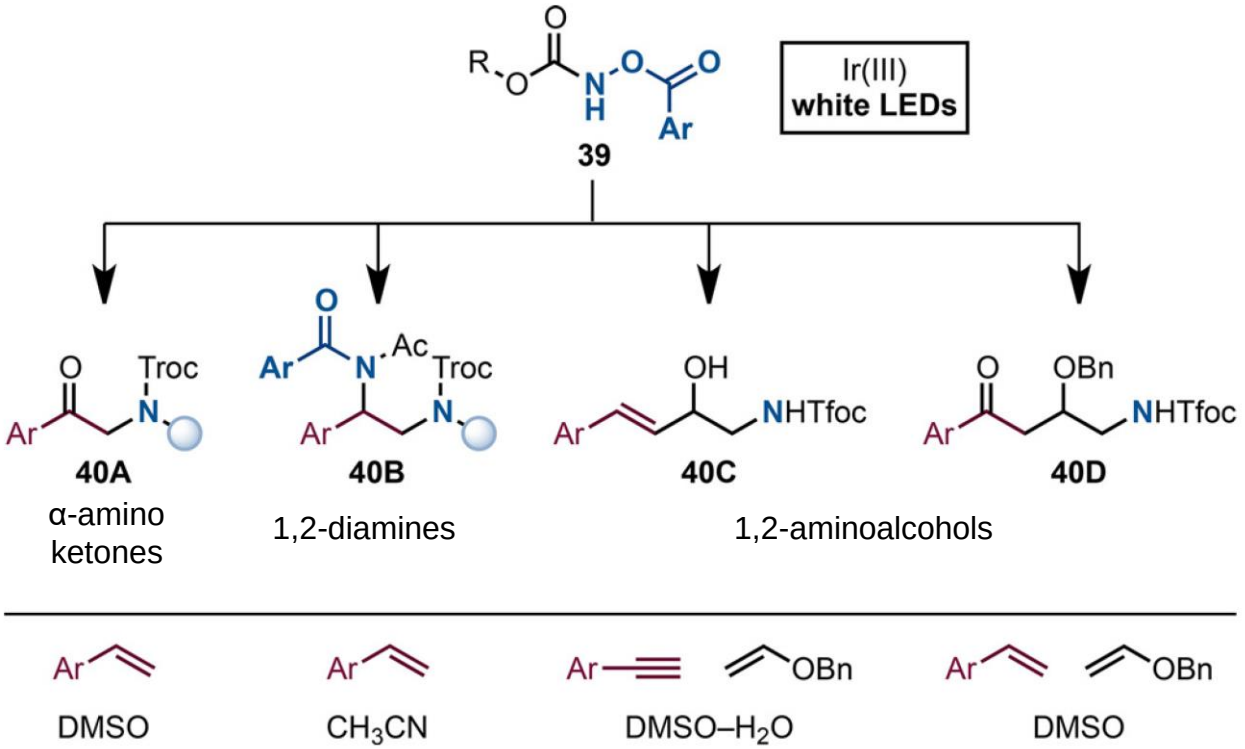
Proposed mechanism



D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 11521.

Addition to Olefins

- Demonstrated in the divergent assembly of polyfunctionalised carbamates

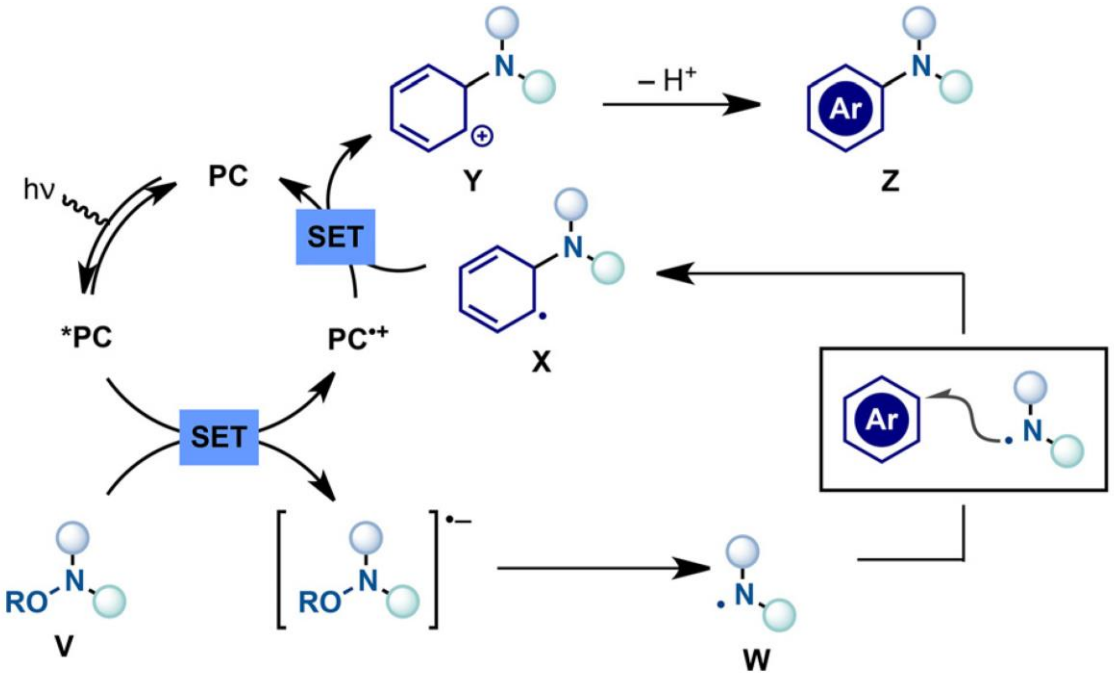


- Critical for the success of this strategy was the choice of solvent, with DMSO utilized to achieve Kornblum oxidations leading to 40A and 40D.

S. Yu, *Org. Lett.* **2017**, *19*, 2909.
S. Yu, *Org. Lett.* **2018**, *20*, 401.

Addition to Aromatics

- General mechanism for amination of aromatics using nitrogen radicals

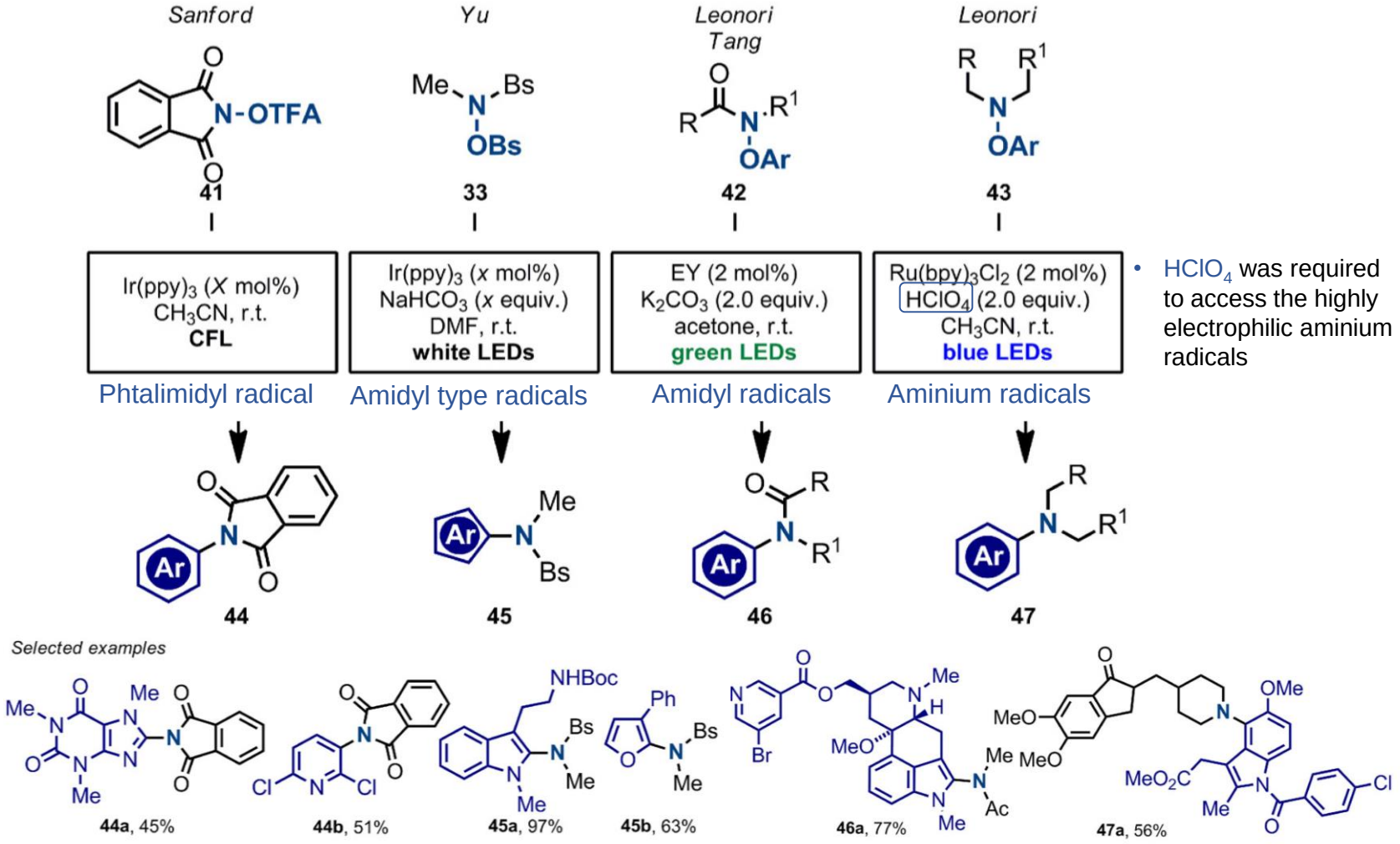


- This reactivity is restricted to amidyl and aminium radicals, with a limited iminyls and no current reports of aminyls;
- The key radical addition is influenced by polar effects, so the best combination between electron rich aromatics and electrophilic nitrogen radicals.

D. Leonori, *Angew. Chem. Int. Ed.* **2017**, *56*, 14948.

Addition to Aromatics

- Strategies for the amination of aromatics using nitrogen radicals

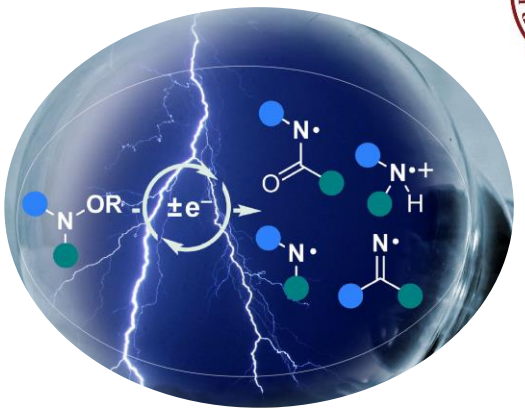


- $HClO_4$ was required to access the highly electrophilic aminium radicals

M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607; S. Yu, *Org. Lett.* **2014**, *16*, 3504.
D. Leonori, *J. Am. Chem. Soc.* **2016**, *138*, 8092; T. Wang, *Org. Lett.* **2017**, *19*, 5669.
D. Leonori, *Angew. Chem. Int. Ed.* **2017**, *56*, 14948.

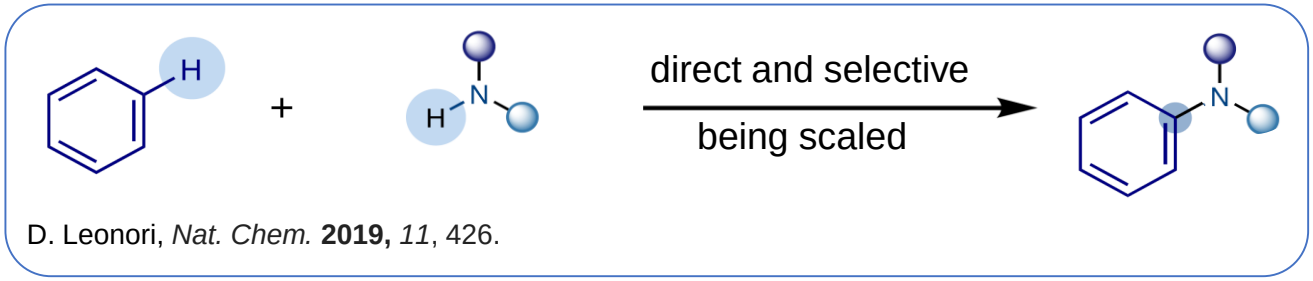
Summary

- Significant progress has been made in the development of methods for the generation of nitrogen radicals from hydroxylamines.



- Challenges:
- Enantioselective variants of these reactions are especially needed;
- Limitation of 1-5 HAT process to the functionalization of tertiary C-H bonds;
- Generation of nitrogen radicals often require multiple steps;

- New, more direct methods to access the active species should be explored;
- Expanding these methods on larger, preparative scale where the in-situ generation of nitrogen radical precursor is particularly attractive.



D. Leonori, *Nat. Chem.* **2019,** *11*, 426.

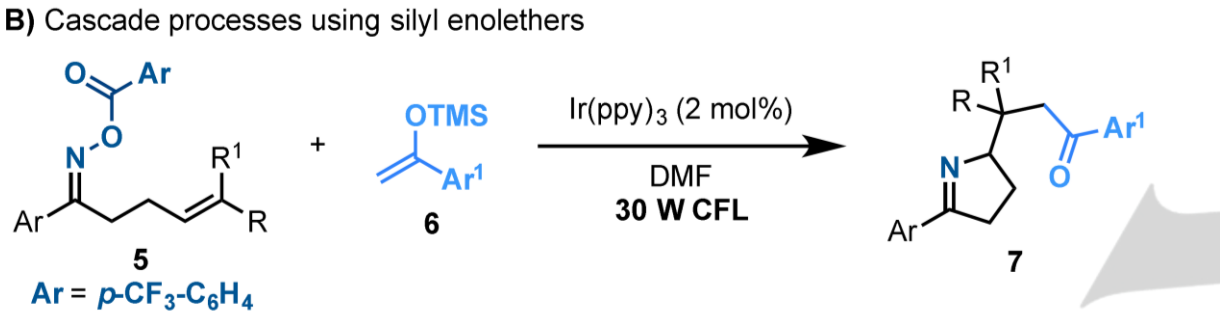
Acknowledgement

- ***Prof.*** **Huang**
- ***Dr.*** **Chen**
- **All group members in E201**

Thanks for your attention !

Intramolecular Cyclizations

- Reductive SET of Hydoxylamine Precursors (iminyl radicals)



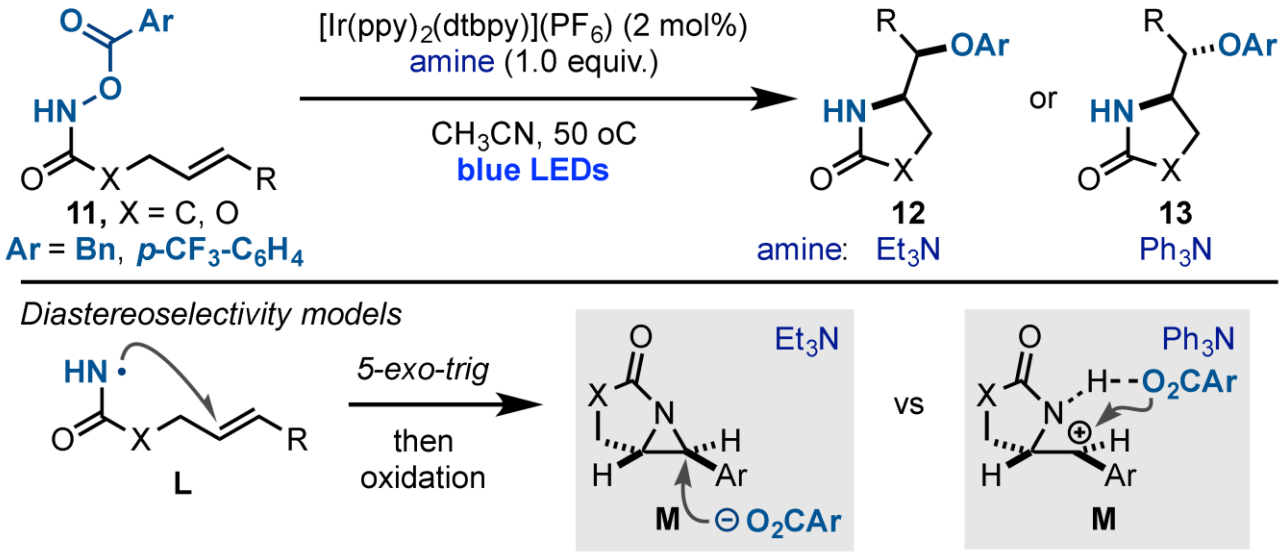
extended this approach for iminyl radical generation and cyclization via the introduction of an additional C–C bond forming step

limited to iminyl radicals with an α-aromatic substituent and terminal aryl silyl enol ethers.

Intramolecular Cyclizations

- Reductive SET of Hydoxylamine Precursors (primary **amidyl** radicals)

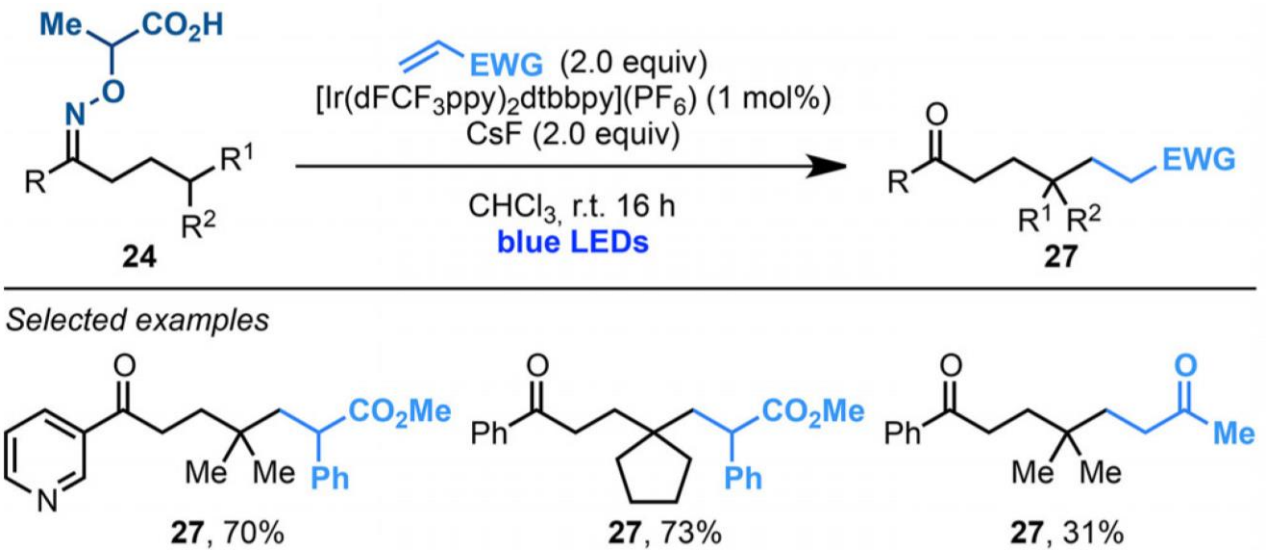
stereodivergent oxy-amination



amine used as the stoichiometric electron donor and base, products of syn (12) or anti (13) addition were selectively obtained upon ring-opening by ArCO2– Depending on the basicity of the it

Intramolecular H-Abstractions: 1,5-HAT

- Oxidative SET of Hydoxylamine Precursors (**iminyl radicals**)
  - γ-Alkylation via radical 1,4-addition by Studer



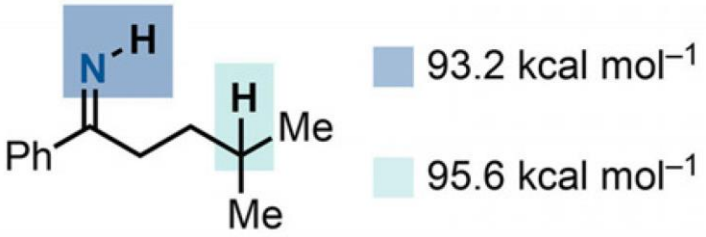
- Cascade process leading to γ-C–C bond formation using Michael acceptors in the presence of an Ir-based photocatalyst to give a broad range of products.

A. Studer, *Angew. Chem. Int. Ed.* **2018**, *130*, 1708.

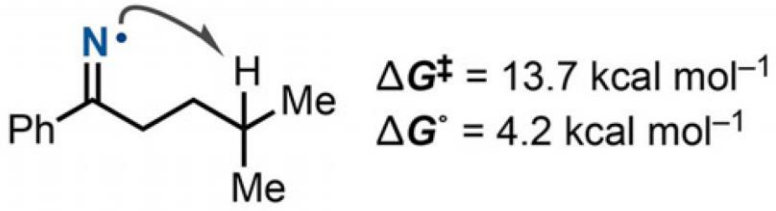
Intramolecular H-Abstractions: 1,5-HAT

- Thermodynamic analysis of the 1,5-HAT process

BDE analysis



Reaction Parameters



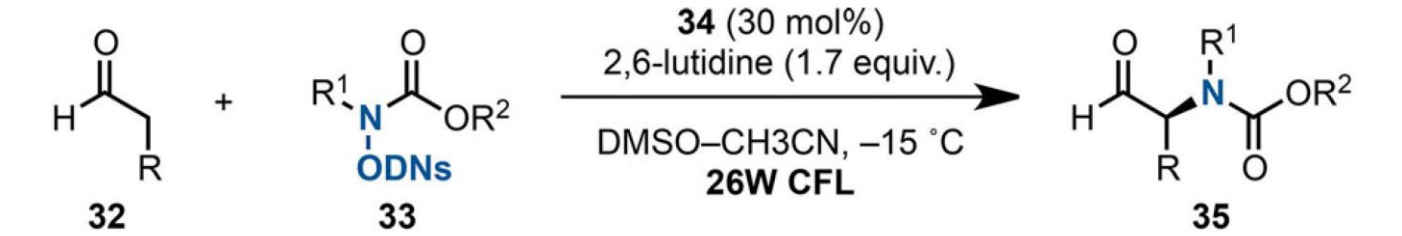
- The similarity in BDEs results in no significant enthalpic gain in the H-abstraction step, which is also slightly endothermic.
- Limitation of the 1,5-HAT methodologies the requirement for tertiary centres to allow efficient functionalization.

D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 744.

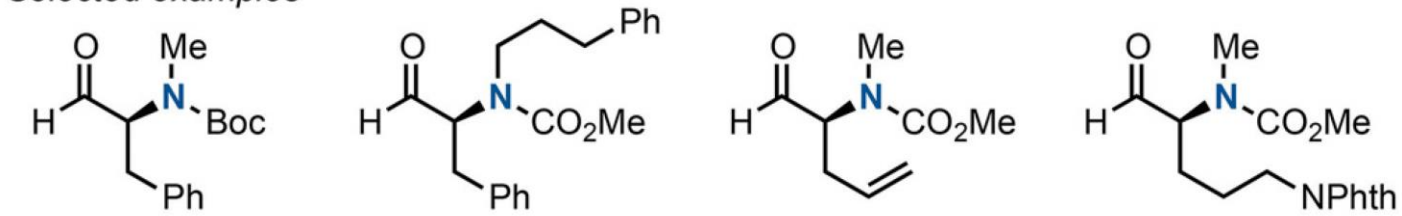
Addition to Olefins

- The first reported enantioselective reaction of nitrogen-radicals

amidyl radicals

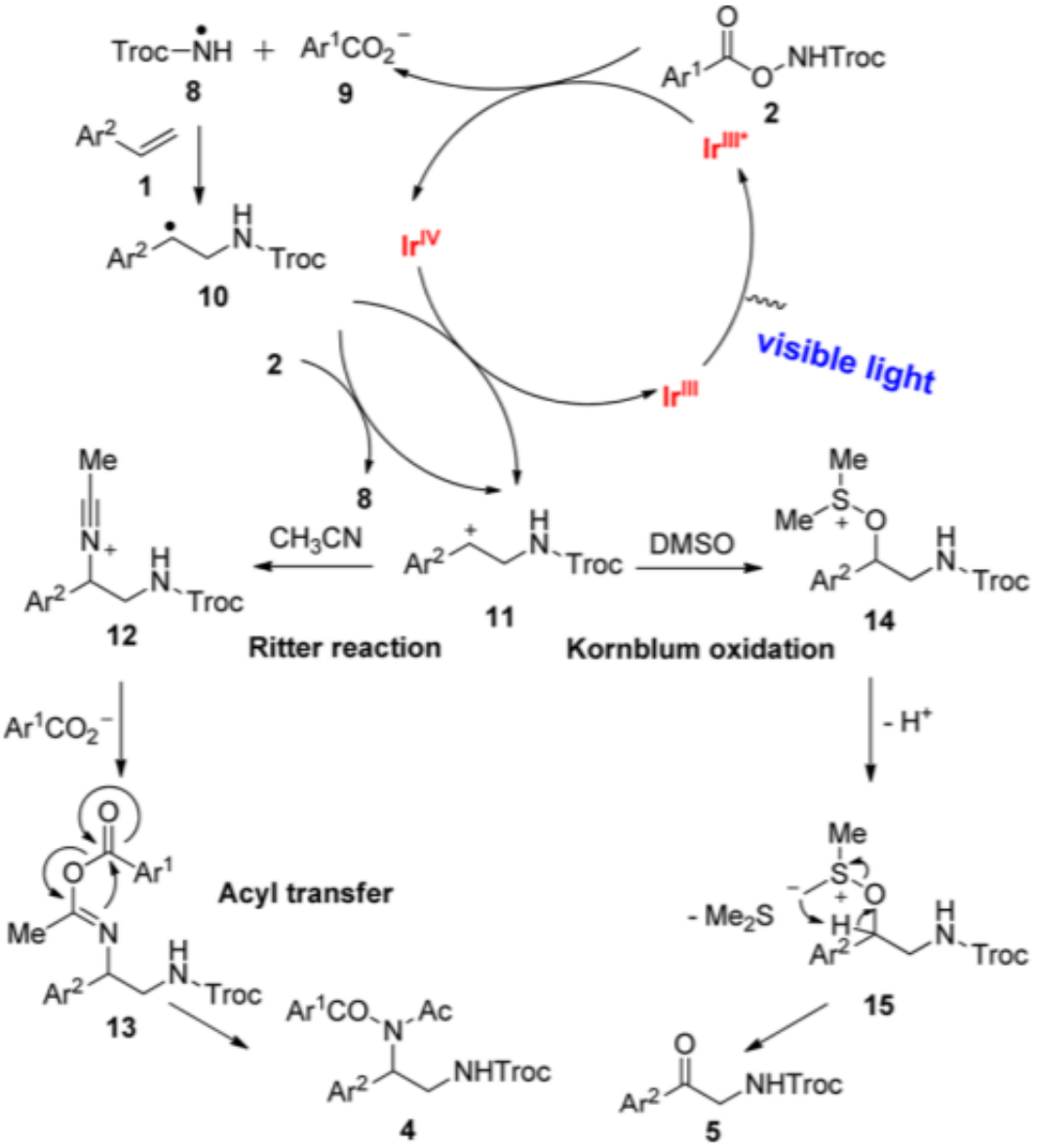


Selected examples



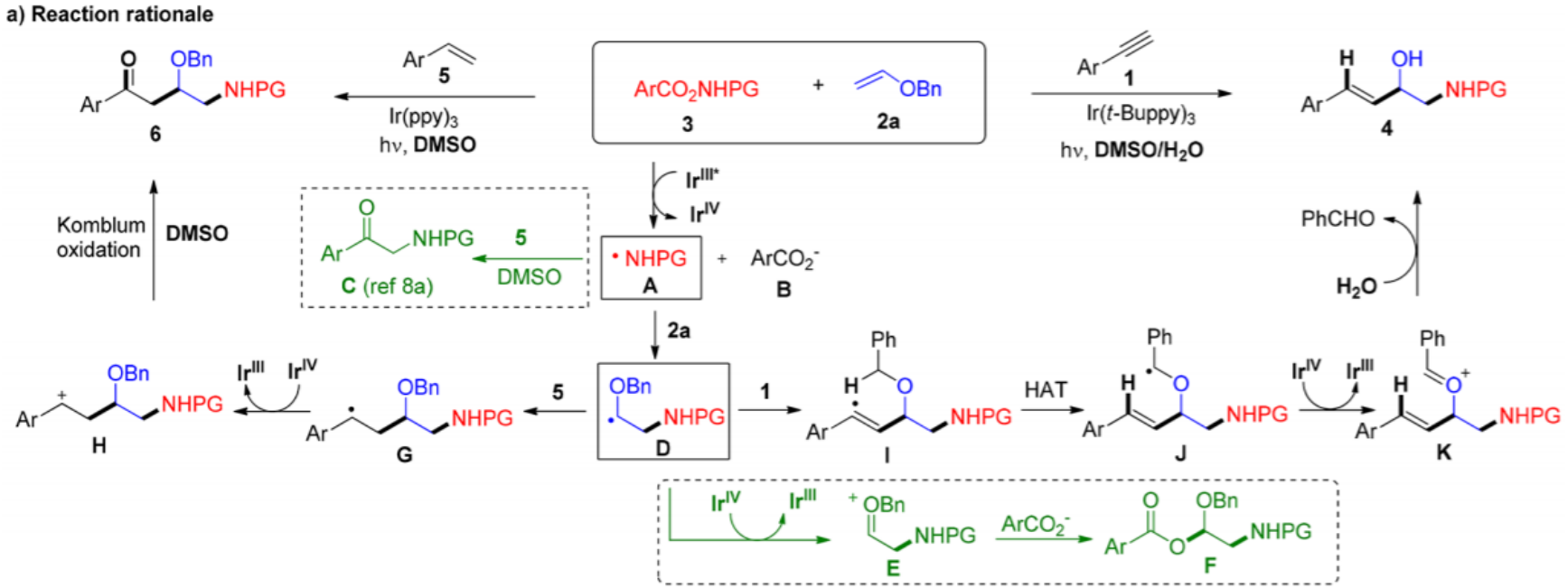
D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 11521.

Addition to Olefins



S. Yu, *Org. Lett.* **2017**, *19*, 2909.

Addition to Olefins



S. Yu, *Org. Lett.* **2018**, *20*, 401.