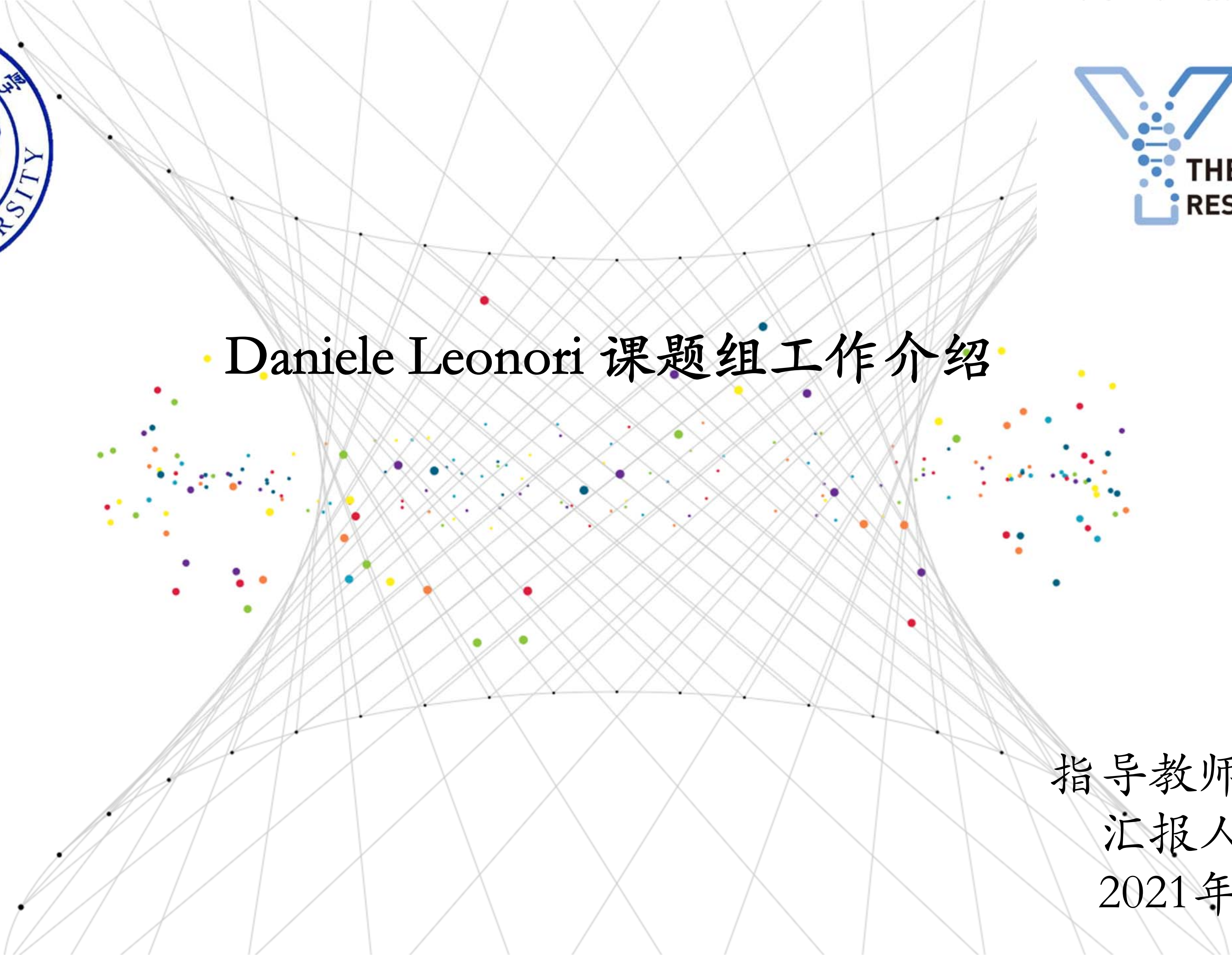
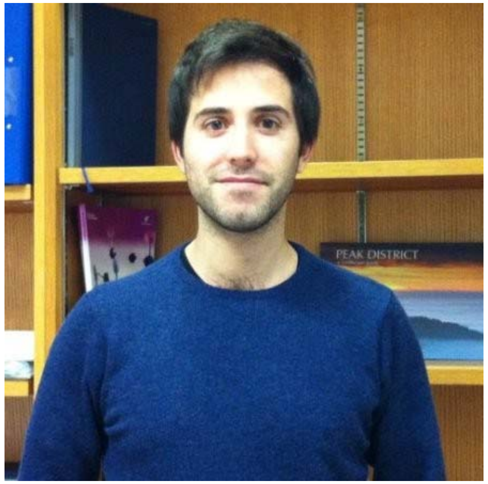
TONGJI UNIVERSITY

THE YANG
RESEARCH GROUP



Daniele Leonori 课题组工作介绍

指导教师：杨泽鹏
汇报人：林垂毅
2021年11月25日

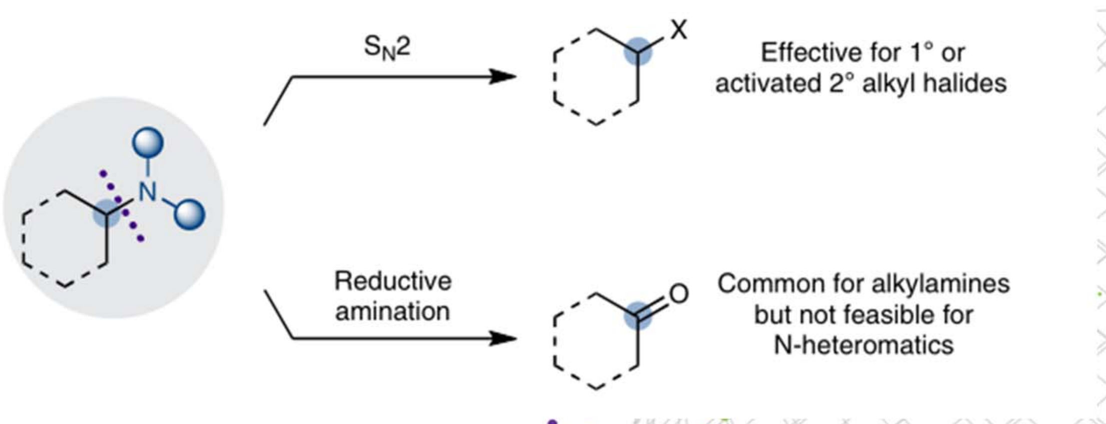


Daniele Leonori

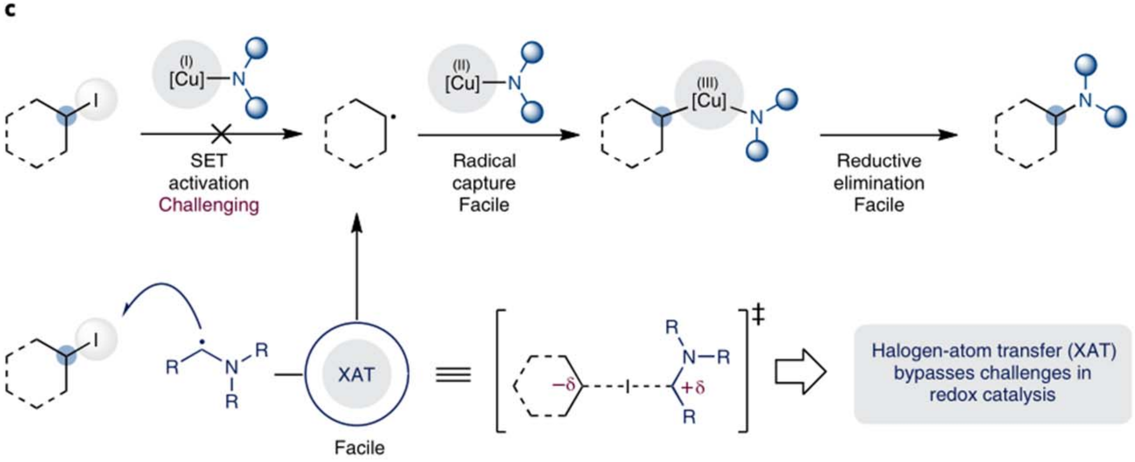
2007-2010: PhD in University of Sheffield Prof. Iain Coldham
2010-2011: Post-Doctoral Research Associate in RWTH Aachen University Prof. Magnus Rueping
2011-2012: Post-Doctoral Research Associate in Max-Planck Institute for Colloids Prof. Peter H. Seeberger
2012-2014: Research Officer in University of Bristol
2014-2020: Lecturer in University of Manchester
2020-today: Professor in University of Manchester

Copper-catalysed amination of alkyl iodides enabled by halogen-atom transfer

Bartosz Górski[1,3], Anne-Laure Barthelemy[1,3], James J. Douglas[2], Fabio Juliá[1] and Daniele Leonori[1]



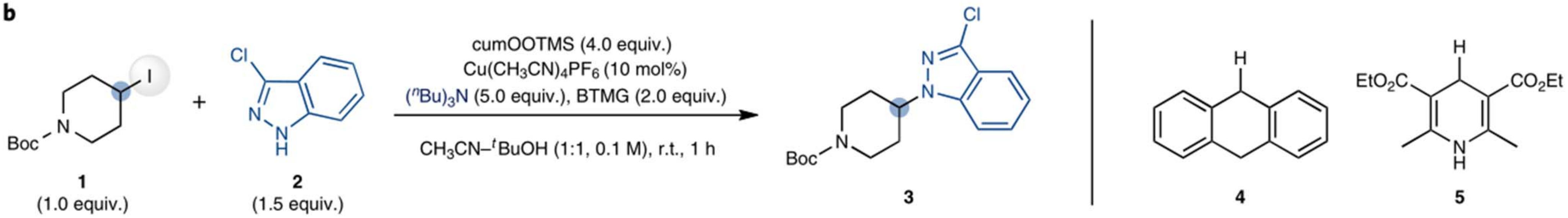
The success of these transformations generally relies on the ability of Cu(II) complexes to trap carbon radicals at near diffusion-controlled rates，and then undergo facile reductive elimination from the resulting high-valent Cu(III) species



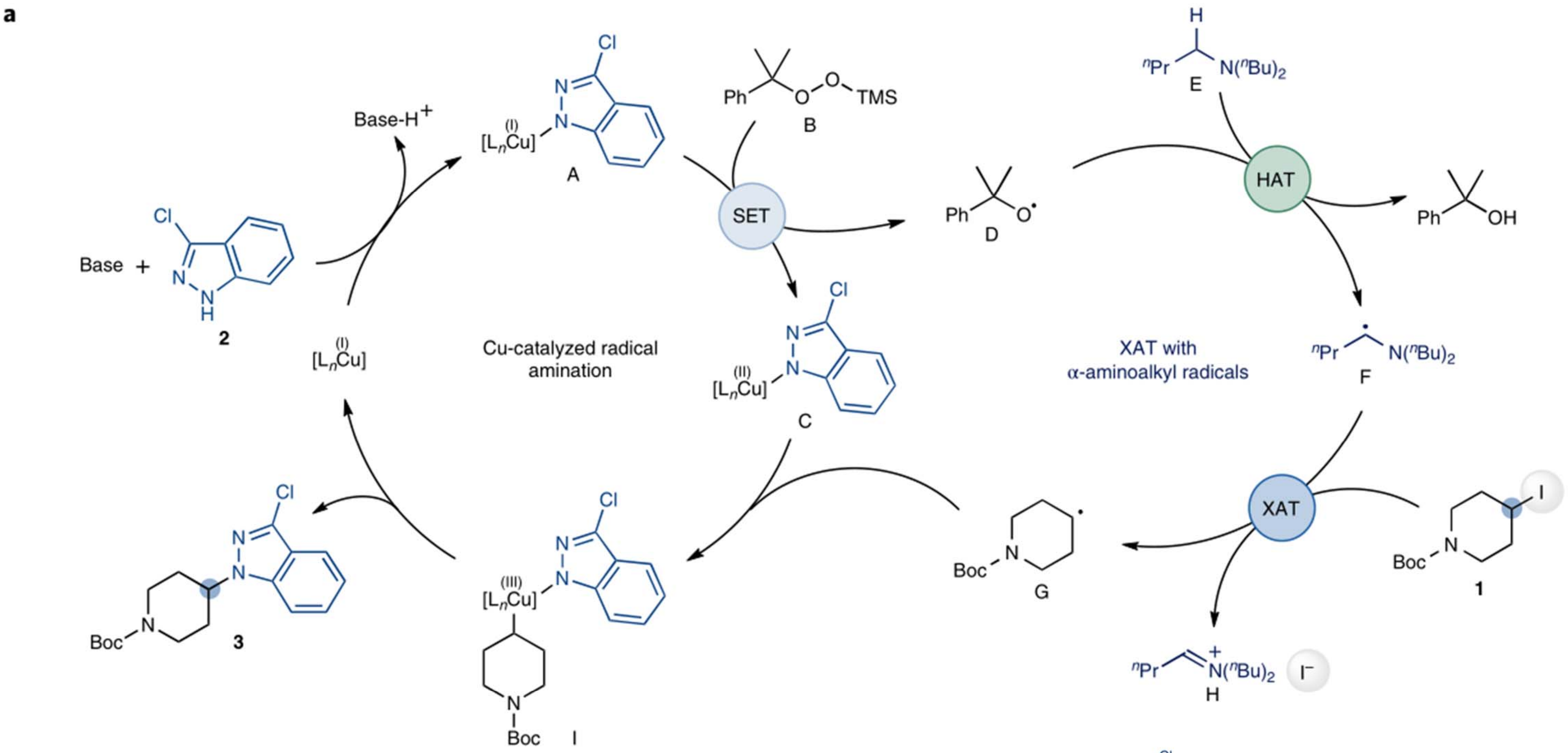
$E_{\text{red}} < -2\text{V}$ for unactivated alkyl halide

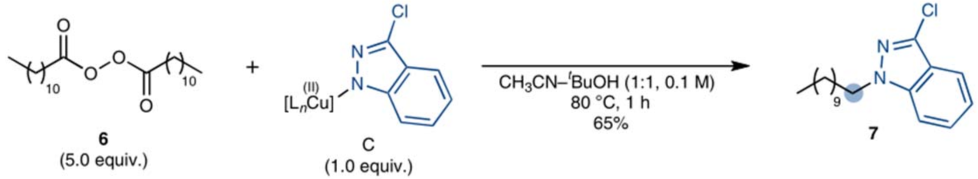
Alkyl radicals can be accessed from the corresponding halides by exploiting the ability of α-aminoalkyl radicals to trigger halogen-atom-transfer (XAT) reactions.

b



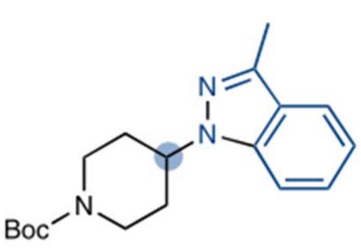
Entry	Variations	Yield (%)	Entry	Variations	Yield (%)	Entry	Variations	Yield (%)
1	None	74	5	No BTMG	–	9	$(Me_3Si)_3SiH$ instead of $(^nBu)_3N$	20
2	No $[Cu(MeCN)_4]PF_6$	–	6	Et_3N instead of $(^nBu)_3N$	68	10	Reaction on 20 mmol	59
3	No cumOOTMS	–	7	DABCO instead of $(^nBu)_3N$	–	11	Additive = **4** (5.0 equiv.)	–
4	No $(^nBu)_3N$	–	8	$T = 0$ °C instead of r.t.	70	12	Additive = **5** (5.0 equiv.)	–





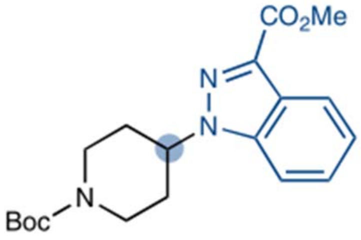
α-aminoalkyl radicals are electron-rich species

by outperforming the amine in the reaction with D



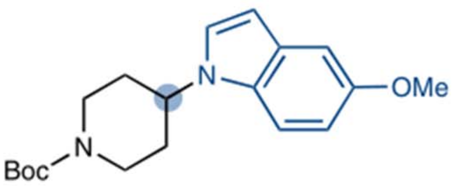
9

50%[a]



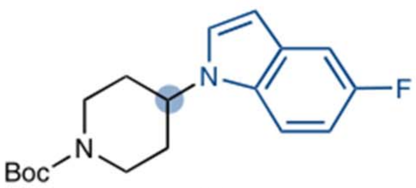
11

80%[b,c]



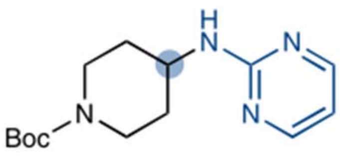
14

84%[b]



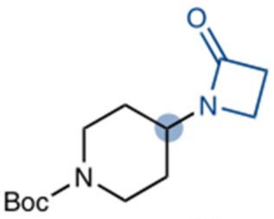
15

73%[b]



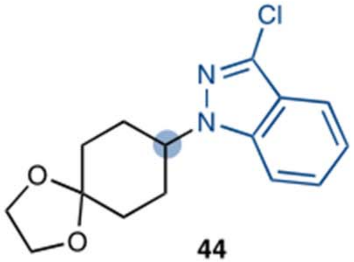
30

77%



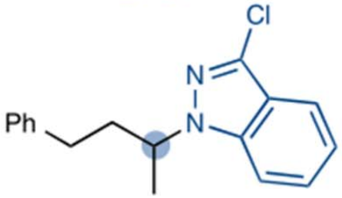
38

98%[b]



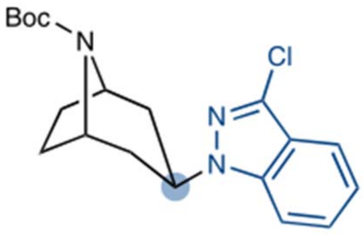
44

96%[b,c]



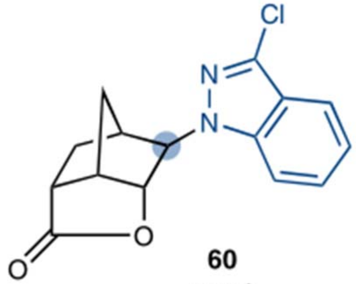
45

37%[a]



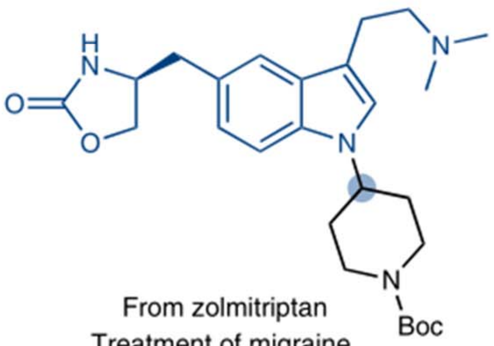
56

74%



60

61%[a]

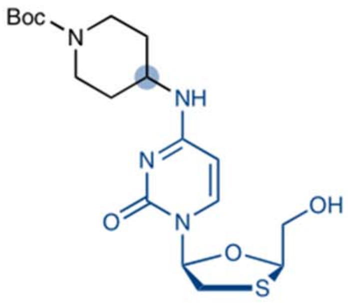


From zolmitriptan

Treatment of migraine

64

57%[b]



From lamivudine

Antiretroviral

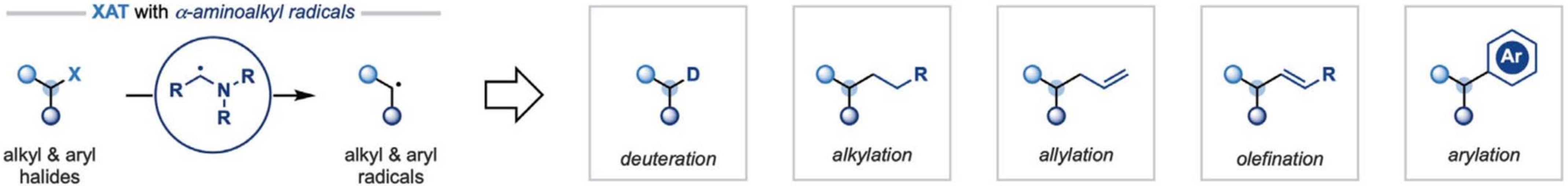
67

52%

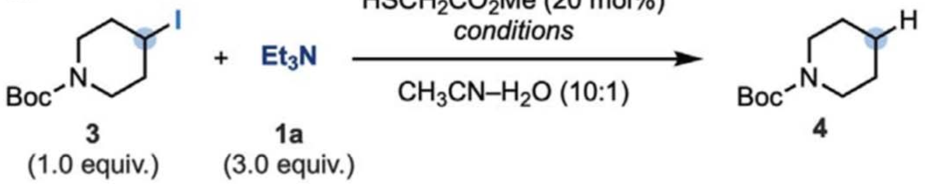
Aminoalkyl radicals as halogen-atom transfer agents for activation of alkyl and aryl halides

Timothée Constantin[1], Margherita Zanini[1], Alessio Regni[1], Nadeem S. Sheikh[2],
Fabio Juliá[1*], Daniele Leonori[1*]

C



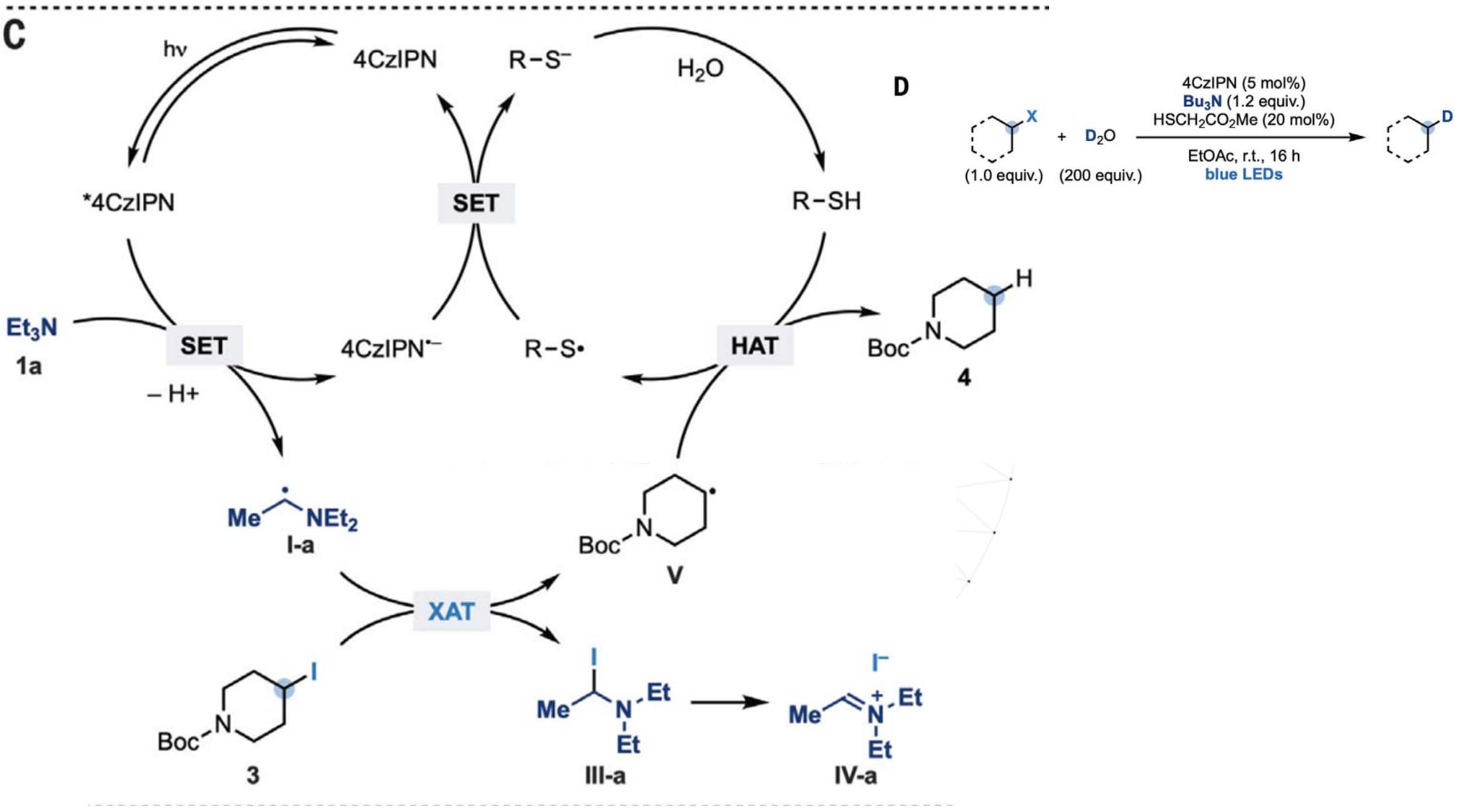
B

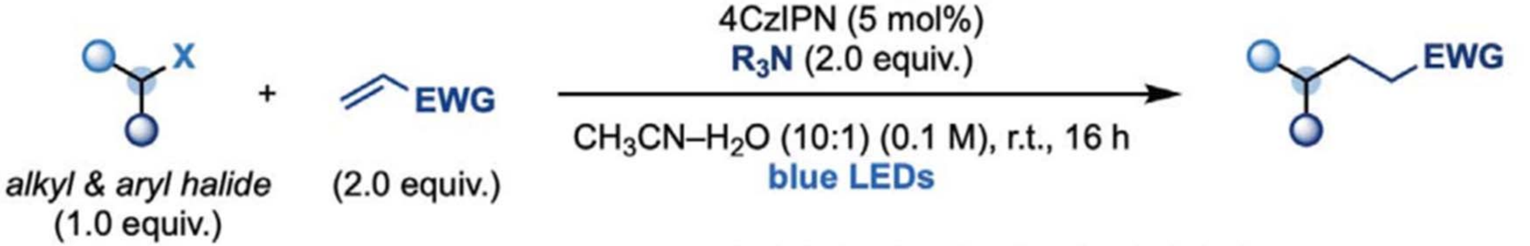


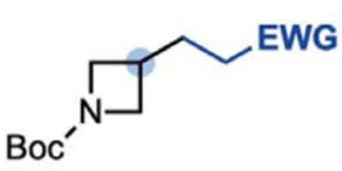
3 (1.0 equiv.) **1a** (3.0 equiv.) **4**

conditions for α-aminoalkyl radical generation

photoredox catalysis	*triplet benzophenone*	$SO_4^{\bullet -}$	*t-BuO•*
4CzIPN (5 mol%)	$Ph_2C{=}O$ (1.0 equiv.)	$K_2S_2O_8$ (2.0 equiv.)	(*t*-BuO)$_2$ (16 equiv.)
blue LEDs, r.t., 4 h	**UV-A LEDs**, r.t., 2 h	70 °C, 2 h	**UV-A LEDs**, r.t., 16 h
98%	70%	40%	67%


C
hν
4CzIPN
R–S⁻
H₂O
*4CzIPN
SET
R–SH
Et₃N
1a
SET
– H+
4CzIPN•⁻
R–S•
HAT
H
Boc
N
4
Me
NEt₂
I-a
Boc
N
V
XAT
I
Boc
N
3
I
Me
N
Et
Et
III-a
I⁻
Me
N
+
Et
Et
IV-a
D
X
+
D₂O
(1.0 equiv.)
(200 equiv.)
4CzIPN (5 mol%)
Bu₃N (1.2 equiv.)
HSCH₂CO₂Me (20 mol%)
EtOAc, r.t., 16 h
blue LEDs
D



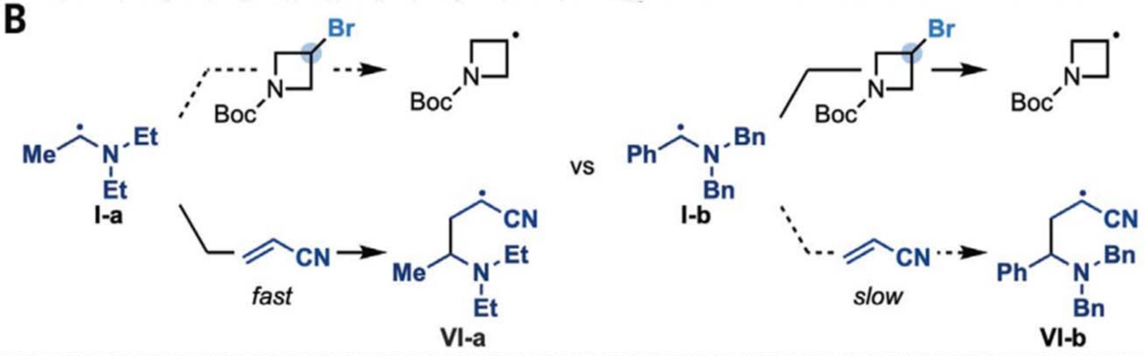


	EWG	X = I*	X = Br†
13:	CN	93%	70%
14:	CO_2Me	90%	56%
15:	CO_2H	63%	40%
16:	$C(O)NH_2$	80%	61%
17:	C(O)Me	73%	50%
18:	$P(O)(OEt)_2$	88%	53%

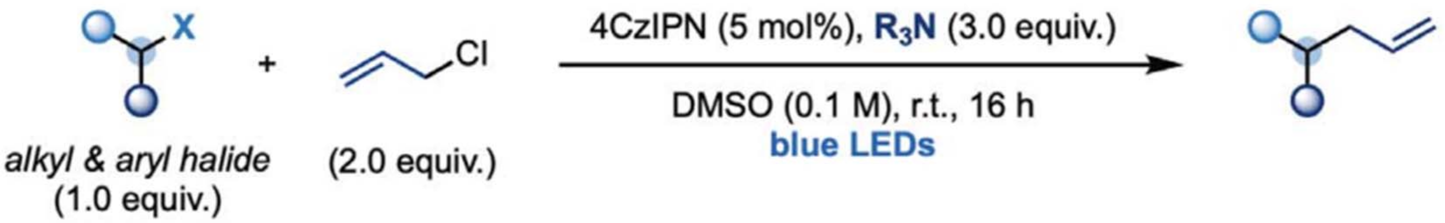
1a **1b**

alkyl iodides *alkyl bromides*

B

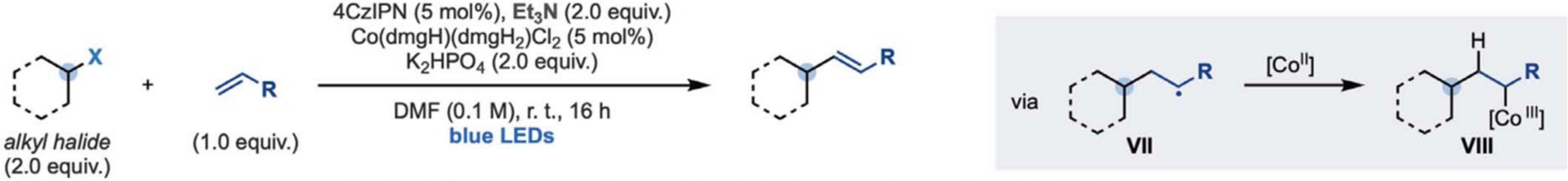


C

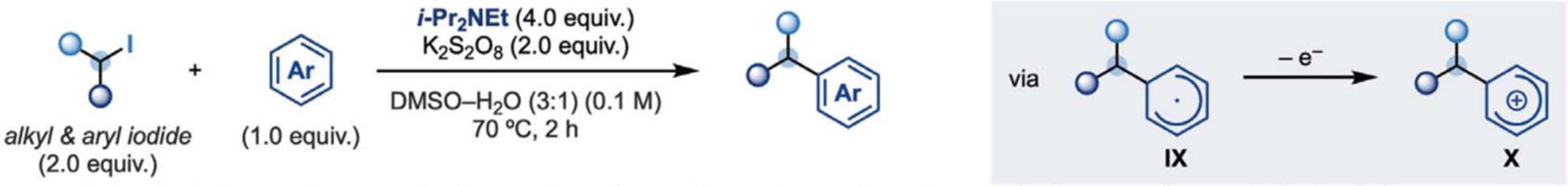


X via β-cleavage

A

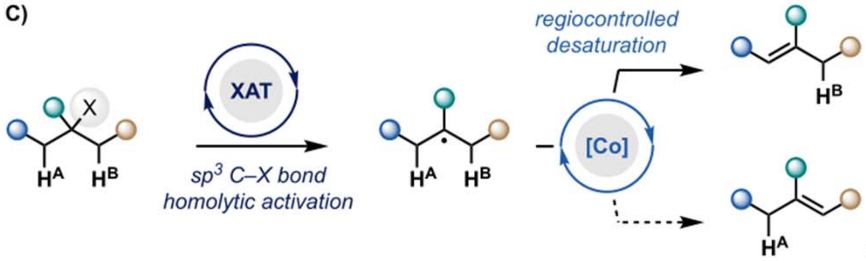


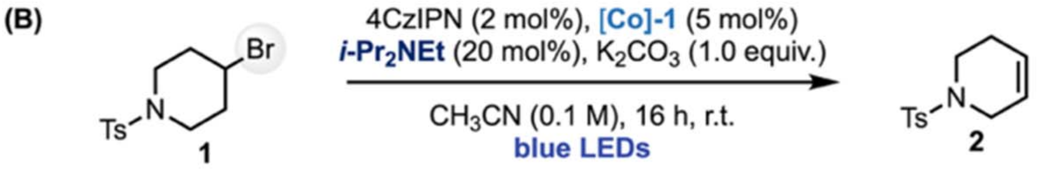
B



Merging Halogen-Atom Transfer (XAT) and Cobalt Catalysis to Override E2-Selectivity in the Elimination of Alkyl Halides: A Mild Route toward *contra*-Thermodynamic Olefins

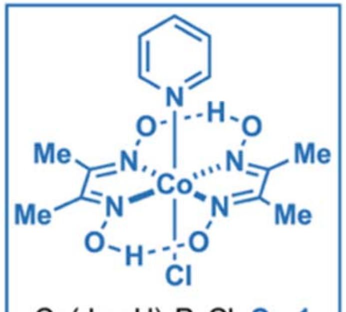
Huaibo Zhao,[†] Alastair J. McMillan,[†] Timothée Constantin, Rory C. Mykura, Fabio Juliá,
and Daniele Leonori*



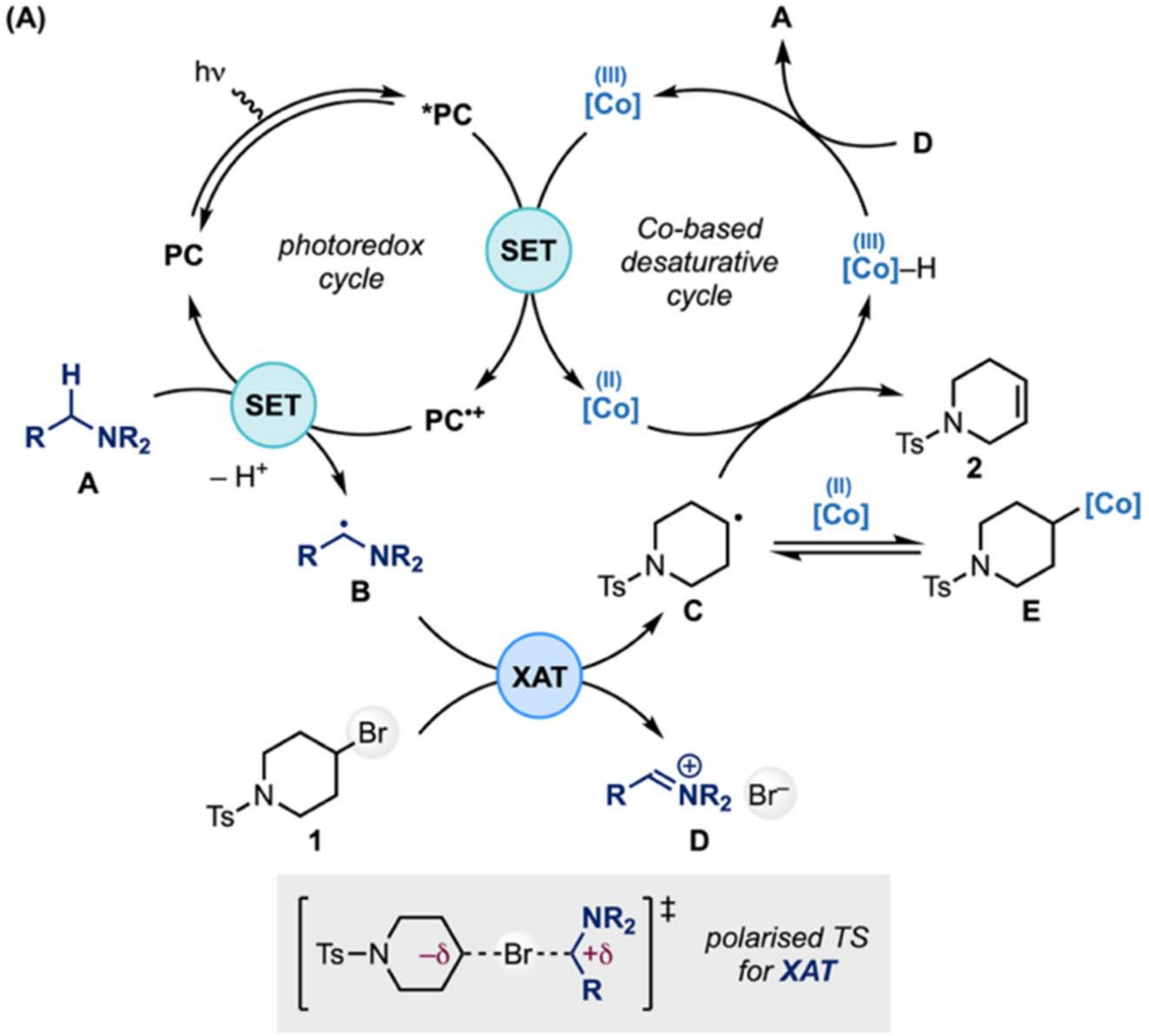


entry	deviation from the standard conditions	yield (%)
1	none	quant.
2	no ***i*-Pr$_2$NEt** or **Co-1** or 4CzIPN	–
3	no **blue LEDs**	–
4	no K$_2$CO$_3$	12
5	2.0 equiv. ***i*-Pr$_2$NEt**, no K$_2$CO$_3$	quant.
6	**DABCO** instead of ***i*-Pr$_2$NEt**	3

Base is needed

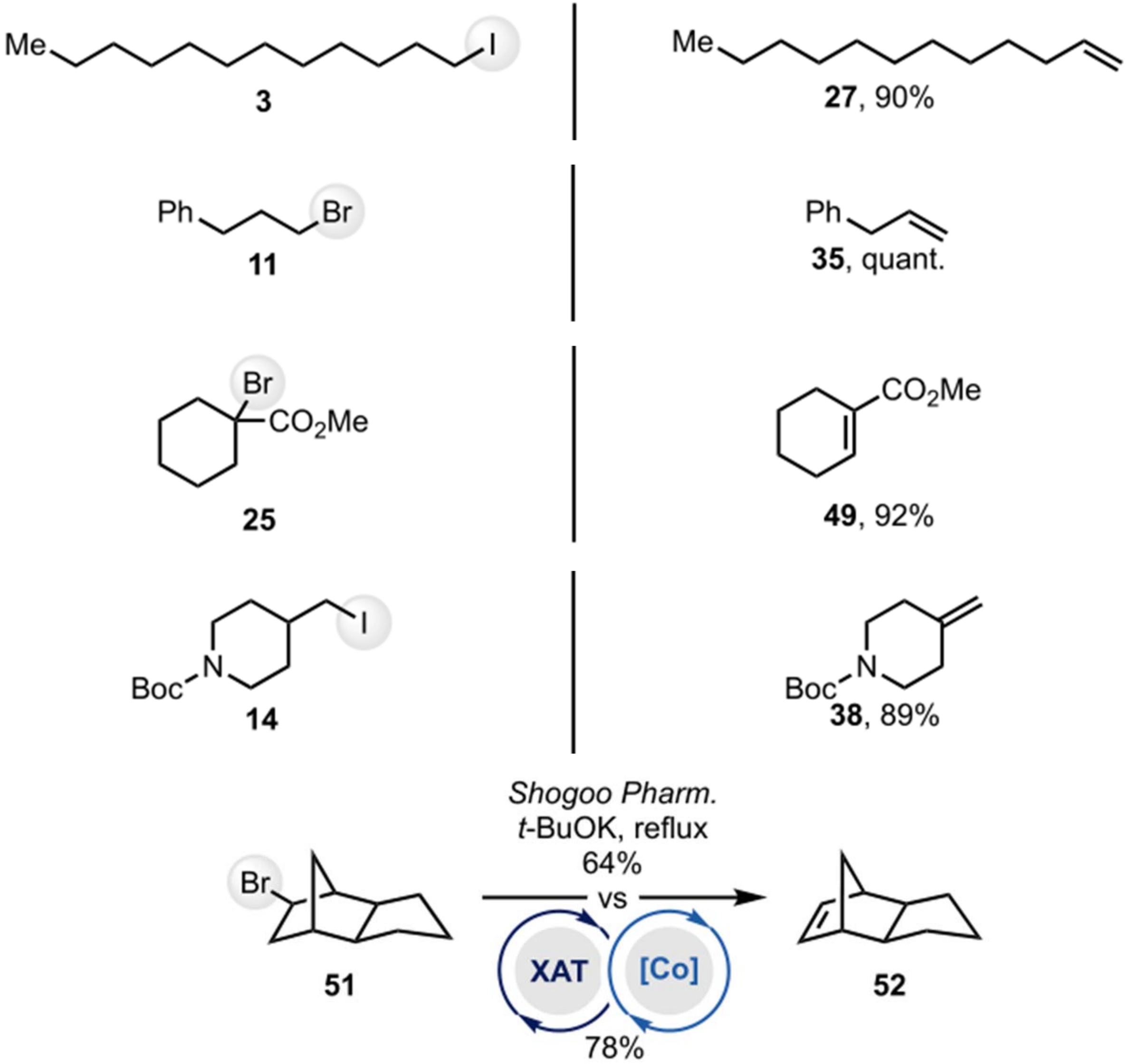


Co(dmgH)$_2$PyCl, **Co-1**



Direct HAT

R_3N is cycled



3

27, 90%

11

35, quant.

25

49, 92%

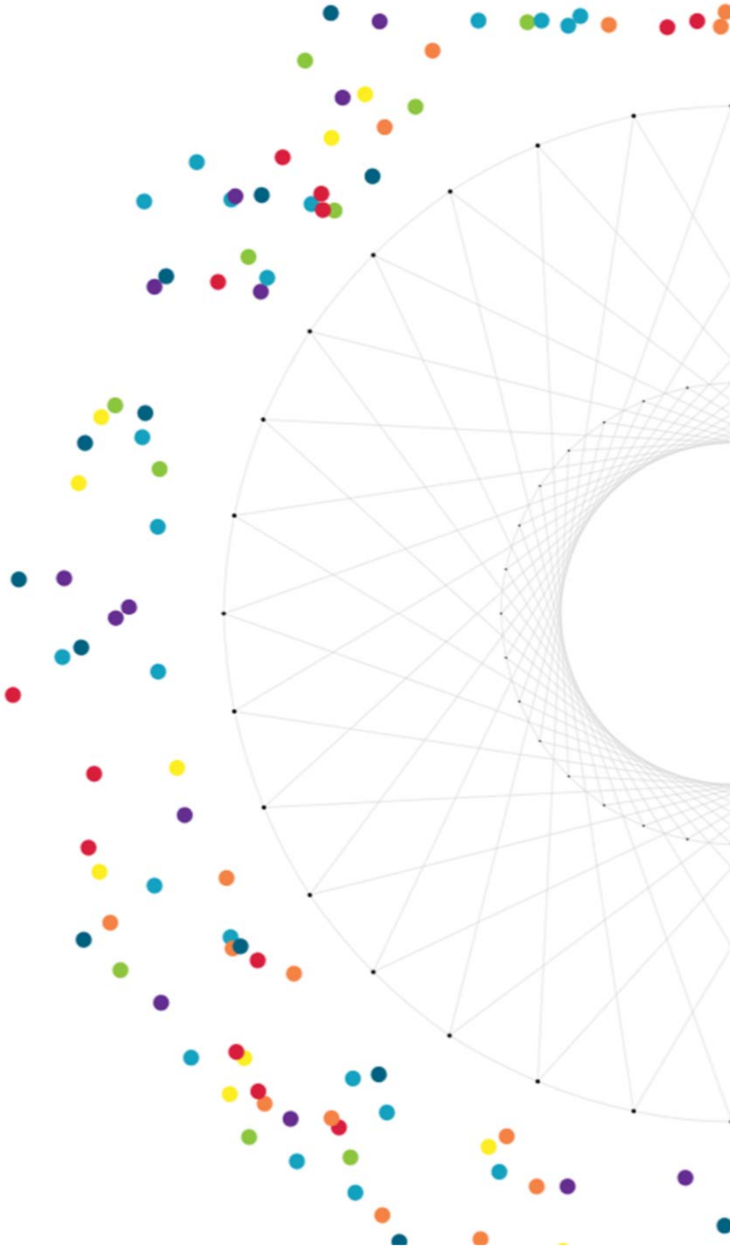
14

38, 89%

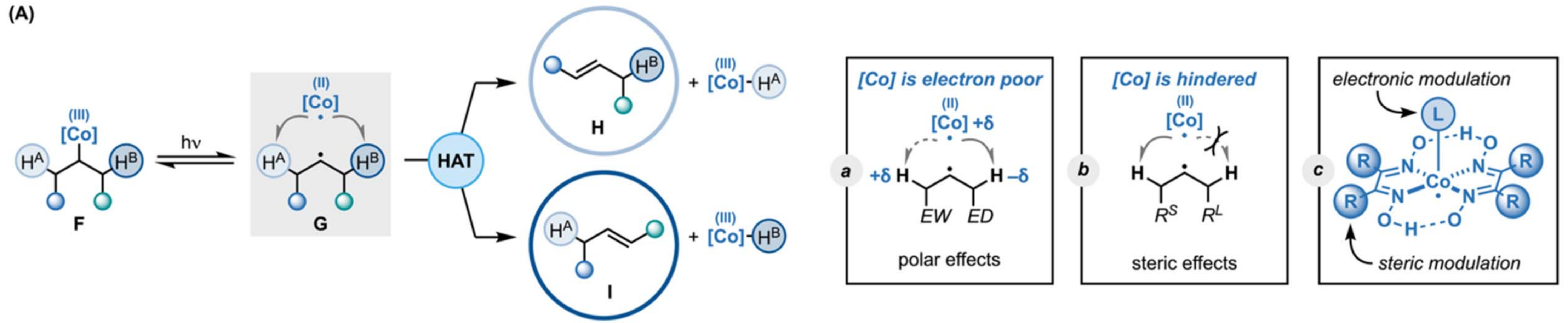
Shogoo Pharm.
t-BuOK, reflux
64%
vs
78%

51

52



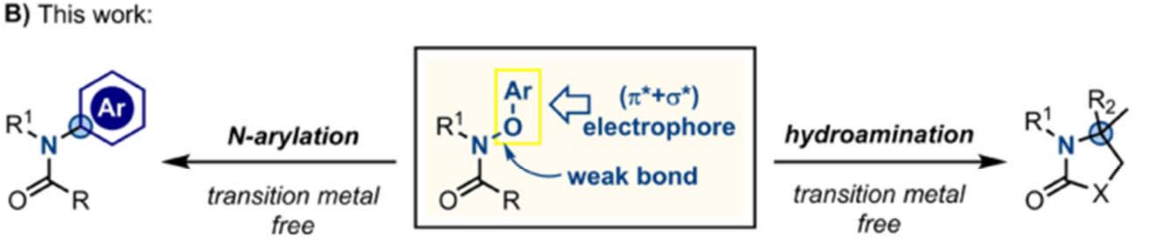
Scheme 4. (A) Proposed HAT-Based Approach to Control the Desaturation Selectivity by Exploiting Polar and Steric Effects and (B) Substrate Scope and Selectivity Using Unsymmetrical Alkyl Halides and Different Cobaloximes



[Co(III)]−alkyl species (F) have weak sp^3 C−Co bonds (BDE < 30 kcal/mol)that, upon blue light irradiation, readily homolyze to a [Co(II)]/alkyl radical cage

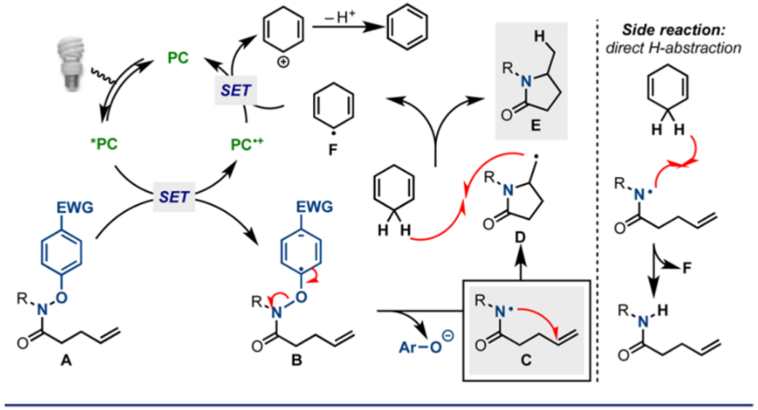
Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and N-Arylation Reactions

Jacob Davies,[†,§] Thomas D. Svejstrup,[†,§] Daniel Fernandez Reina,[†] Nadeem S. Sheikh,[‡] and Daniele Leonori*,[†]

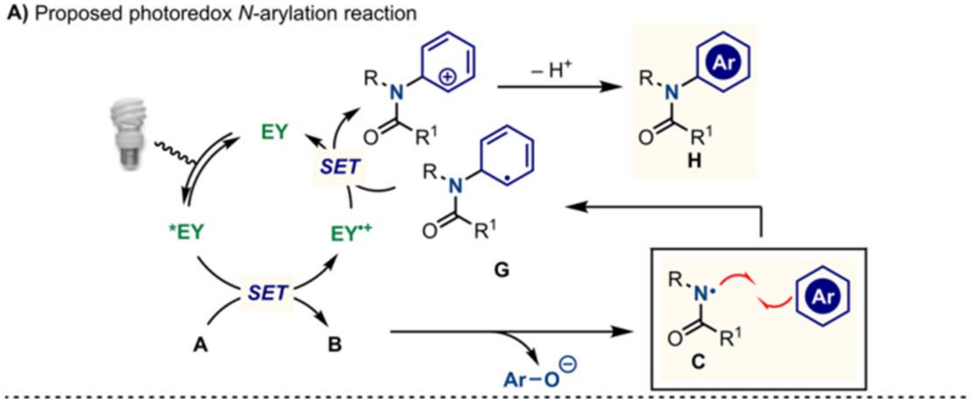


Amidyl radical is electrophile

Scheme 2. Proposed Photoredox Cycle for the Hydroamination−Cyclization Reaction

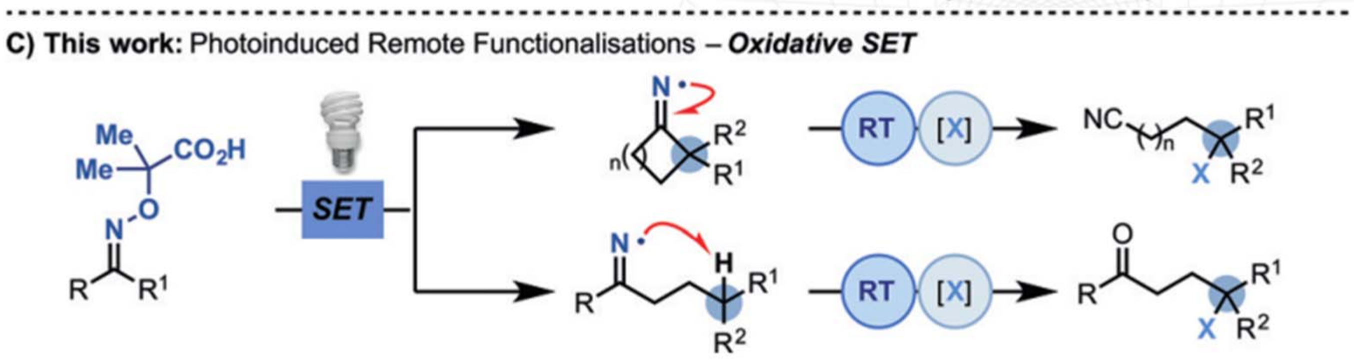


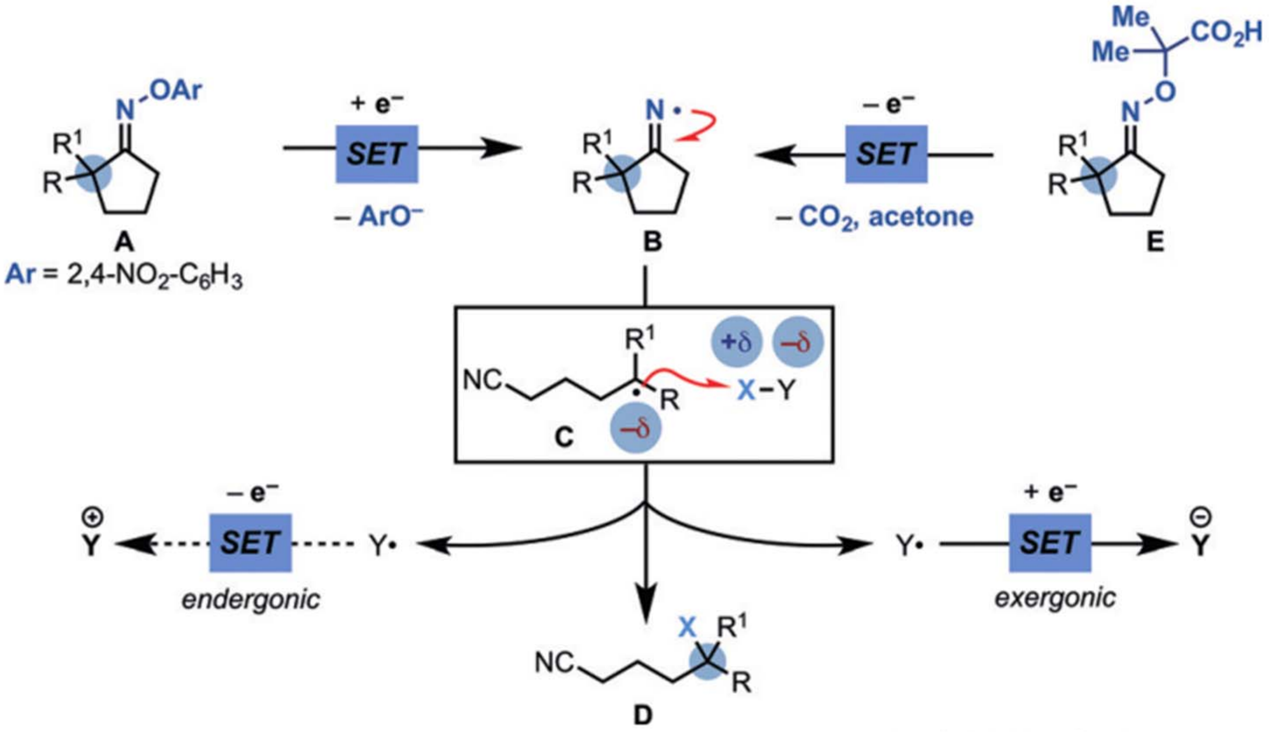
Scheme 5. Photoredox N-Arylation Reaction



Photoinduced Remote Functionalisations by Iminyl Radical Promoted C−C and C−H Bond Cleavage Cascades

Elizabeth M. Dauncey[+], *Sara P. Morcillo*[+], *James J. Douglas, Nadeem S. Sheikh, and Daniele Leonori**

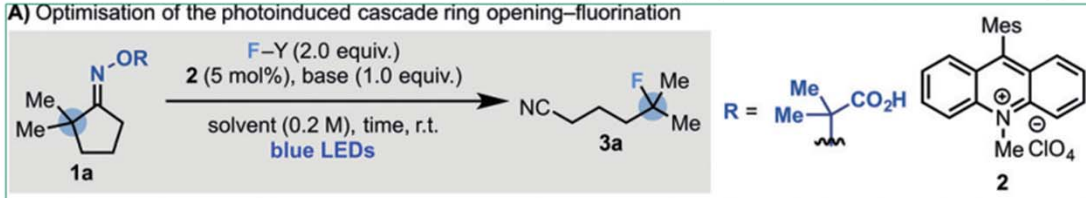




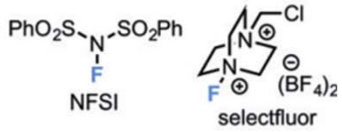
upon SET reduction and fragmentation of precursor A, the iminyl radical B should undergo a fast β-fission generating the δ-CN radical C(nucleophilic)

Owing to its electrophilic nature, a final SET oxidation will be highly endergonic, thus thwarting the development of a redox-neutral process

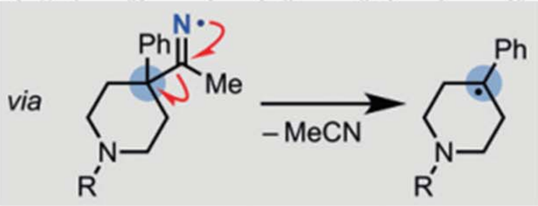
A) Optimisation of the photoinduced cascade ring opening–fluorination

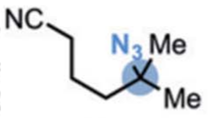


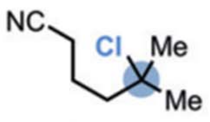
Entry	F–Y	Base	Solvent	Time	Yield (%)
1	NFSI	Cs_2CO_3	CH_3CN	1h	–
2	selectfluor	Cs_2CO_3	CH_3CN	1h	13
3	selectfluor	Cs_2CO_3	$CH_3CN–H_2O$ (1:1)	1h	67
4	**selectfluor**	**K_2CO_3**	**$CH_3CN–H_2O$ (1:1)**	**15 min**	**84**

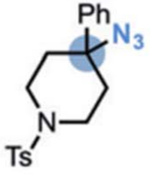



3o, 64%

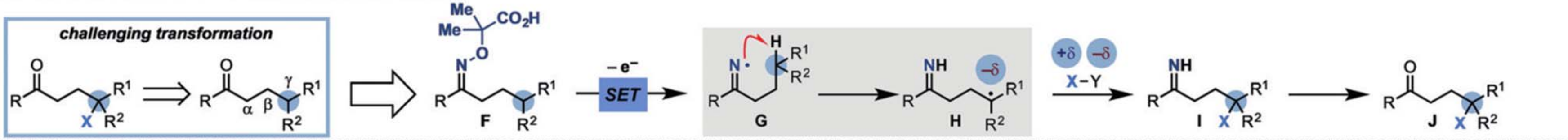



5a, 64%

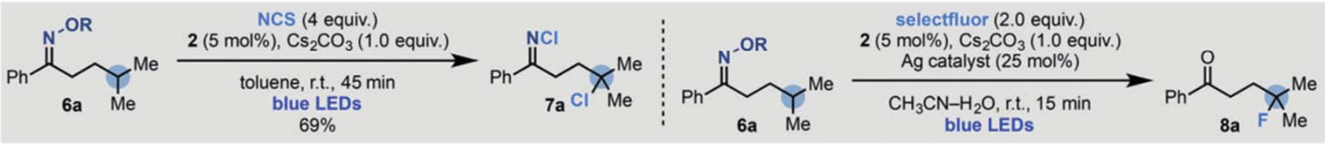

4a, 94%


5d, 64%

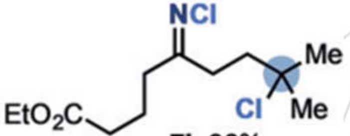
A) γ-Functionalisations of ketones via cascade reaction of iminyl radicals

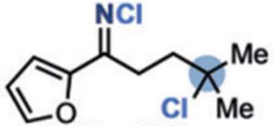


B) Development of γ-chlorination and γ-fluorination and scope of the two processes



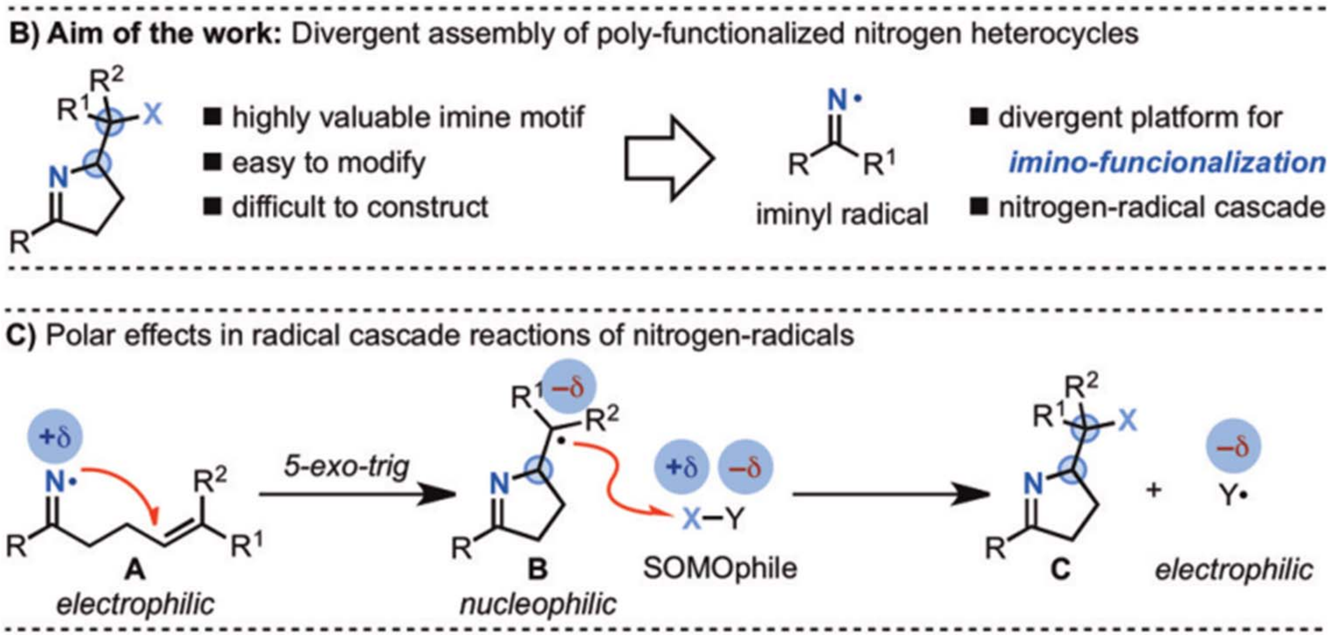
Entry	Ag Catalyst	Yield (%)
1	–	17
2	$AgNO_3$	60
3	Ag_2CO_3	81
4	AgO	19


7i, 36%


7e, 66%

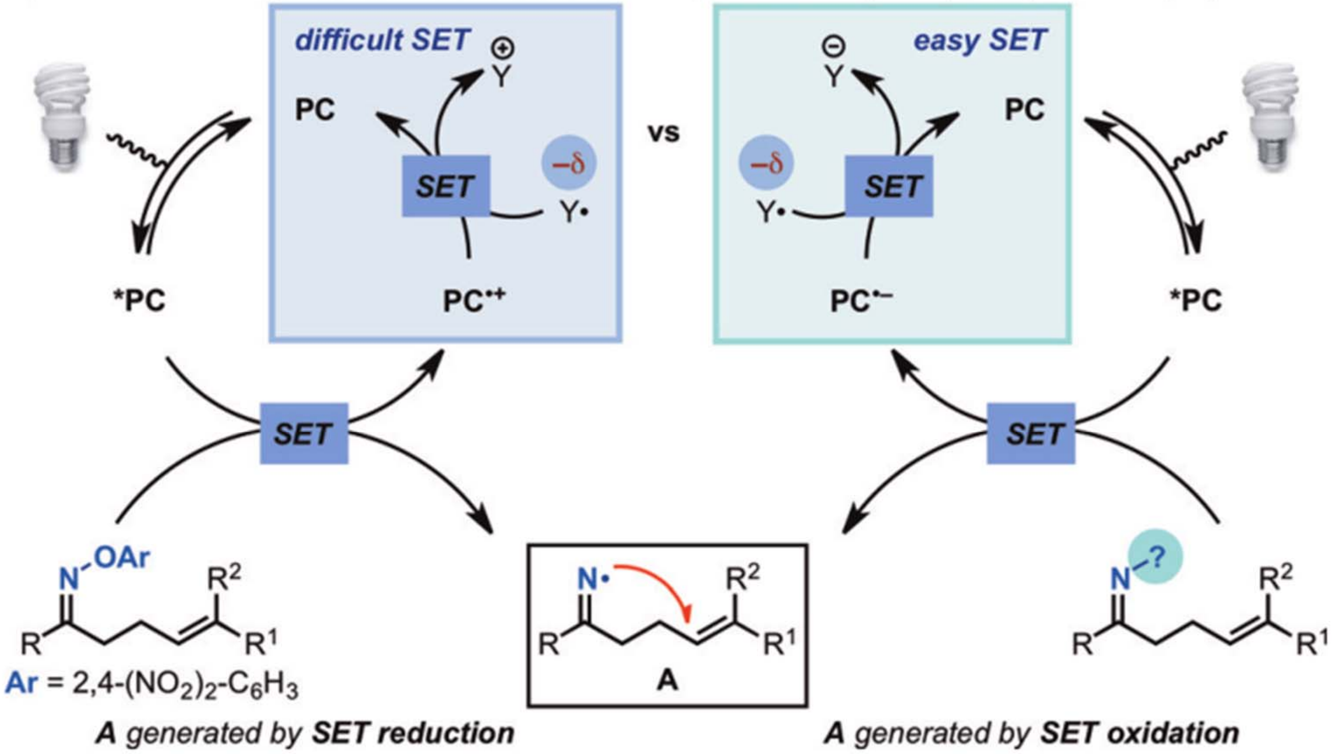
Photoredox Imino Functionalizations of Olefins

*Jacob Davies, Nadeem S. Sheikh, and Daniele Leonori**



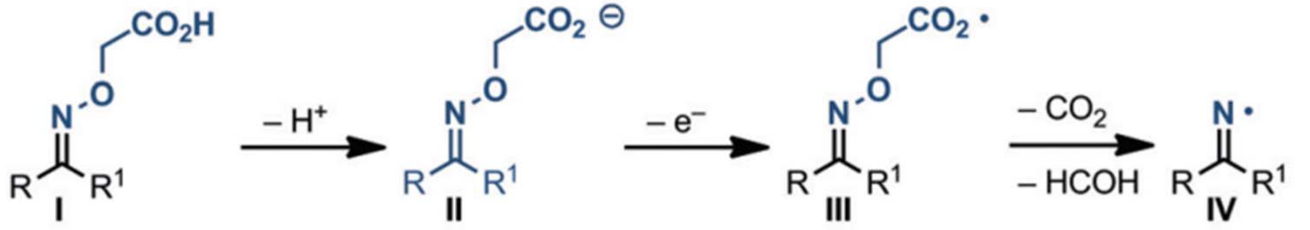
This divergent strategy features the oxidative generation of iminyl radicals and subsequent cyclization/radical trapping

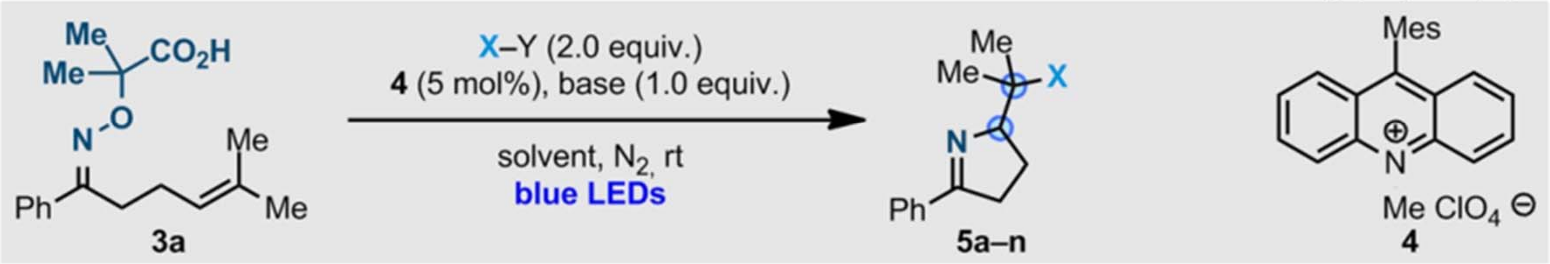
D) Mechanistic analysis for reductive and oxidative photoredox cycles (PC = photocatalyst)



Y radical is electrophile

A) Substrate design for oxidative generation of iminyl radiclas

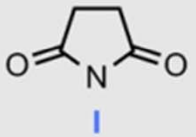




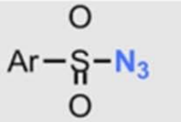
3a

5a–n

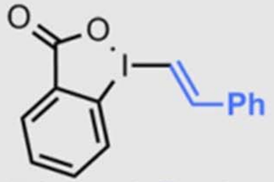
4



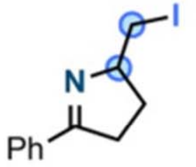
■ iminoiodination



■ iminoazidation

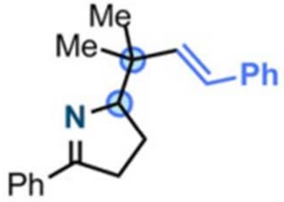


■ iminoolefination

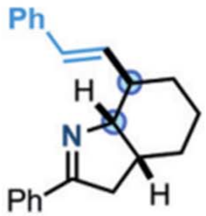


5d, 67%^{c,h}

5f, 95%^{c,e}



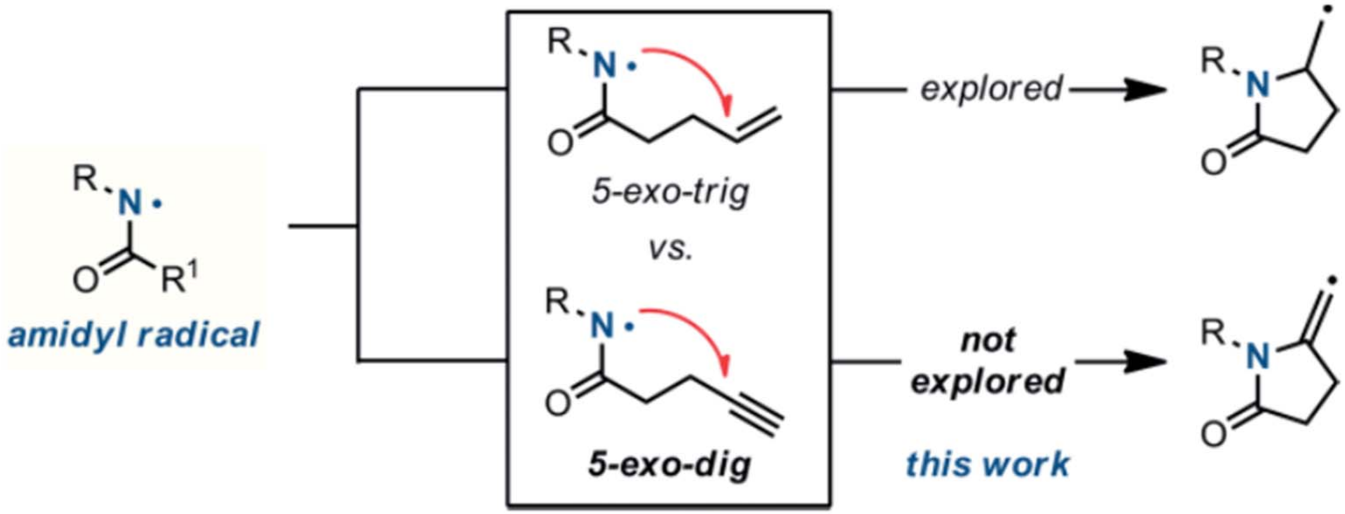
5m, 83%^{c,e}



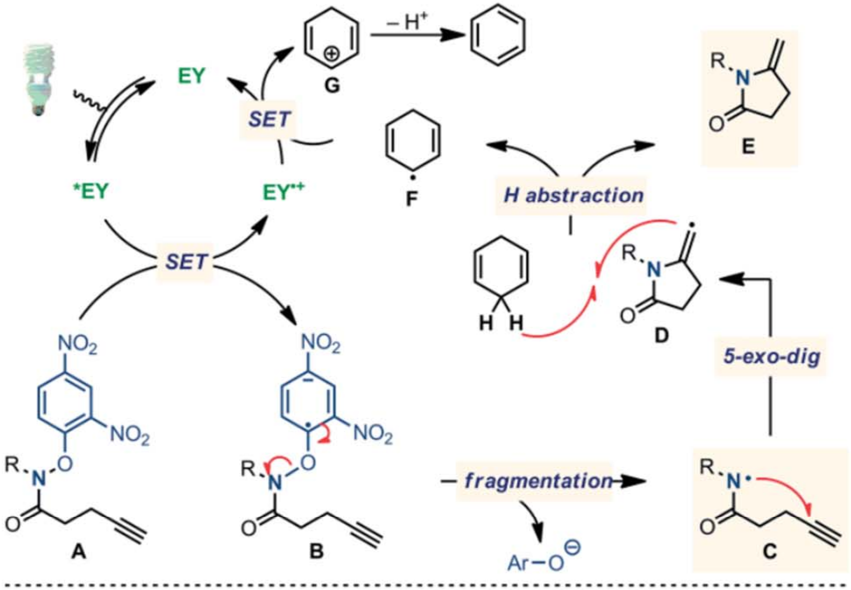
7q, 61%, dr 2:1

Visible-Light-Mediated 5-*exo*-*dig* Cyclizations of Amidyl Radicals

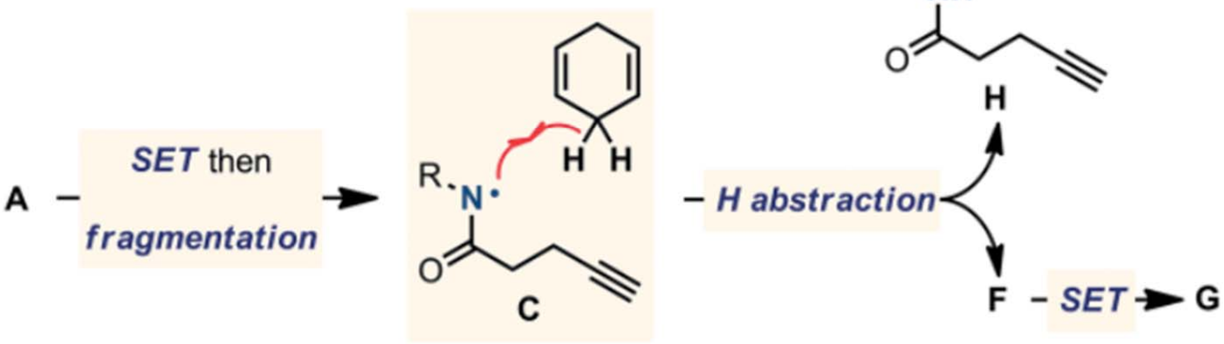
Daniel Fernandez Reina,[a] Elizabeth M. Dauncey,[a] Sara P. Morcillo,[a]
Thomas D. Svejstrup,[a] Mihai V. Popescu,[a] James J. Douglas,[b] Nadeem S. Sheikh,*[c] and
Daniele Leonori*[a]



A) Proposed photoredox mechanism

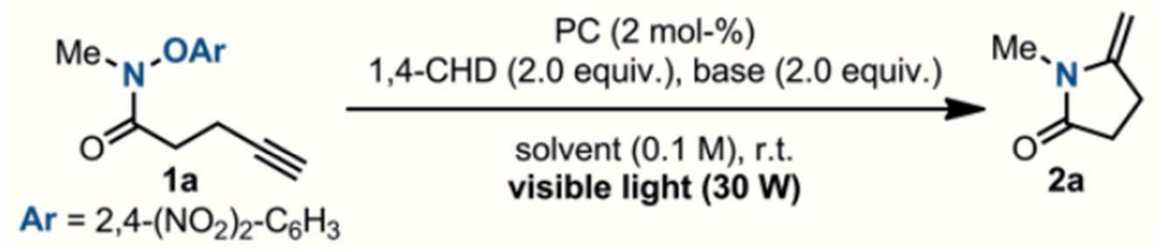


B) Potential side reaction: direct H abstraction



This is particularly evident when alkyl and acyl substituents are present at the N atom, as they increase the electrophilic character of the NCR. Furthermore, as radical 5-exo-dig cyclizations are slower than 5-exo-trig cyclizations, this could result in significant quantity of unproductive H-atom abstraction.

A) Screening of reaction conditions



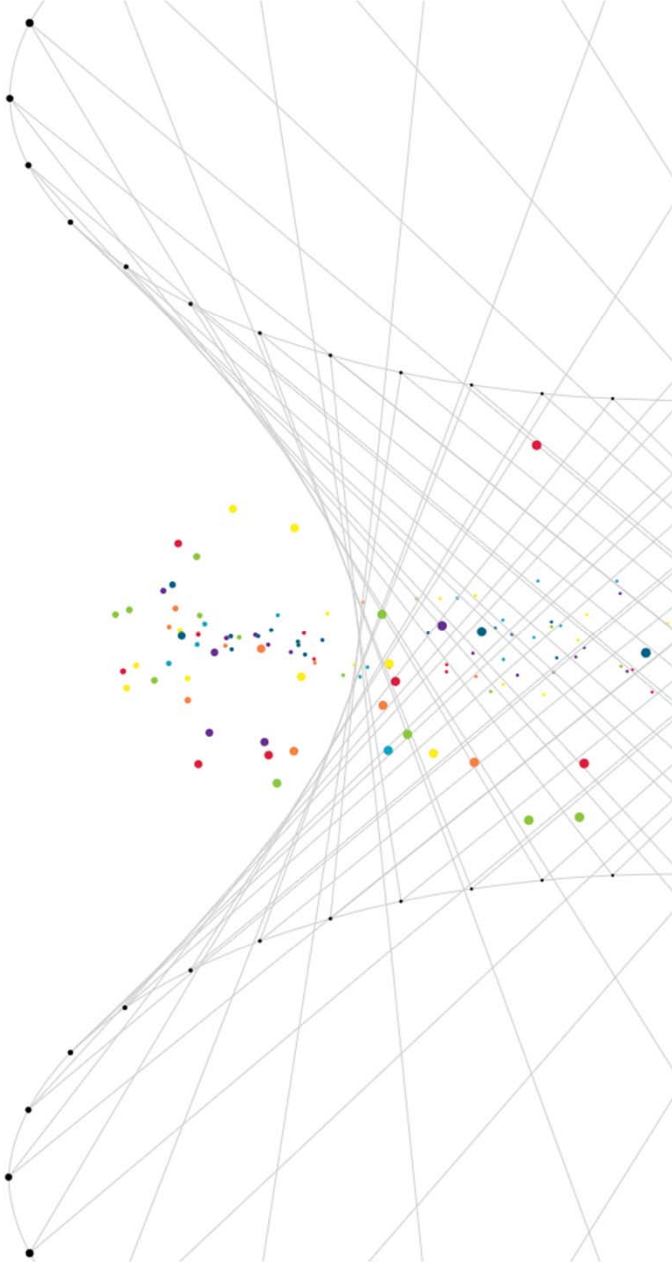
1a

Ar = 2,4-$(NO_2)_2$-C_6H_3

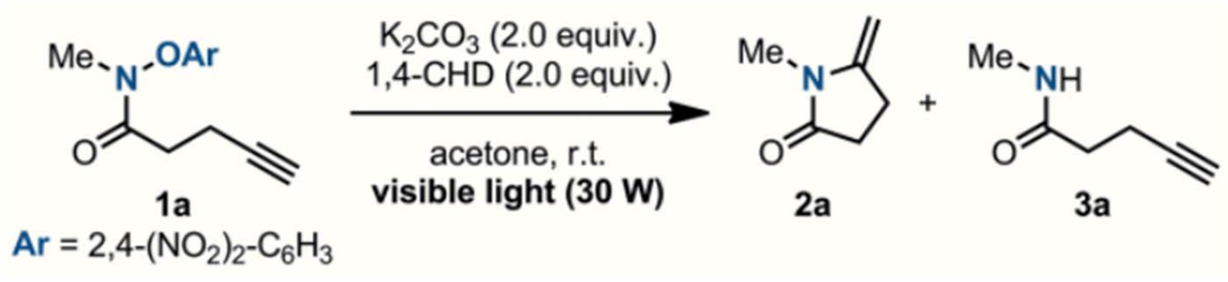
2a

Entry	PC	Base	Solvent (M)	Yield (%)
1	EY	K_2CO_3	acetone (0.1)	43%
2[a]	EY	K_2CO_3	acetone (0.1)	traces
3	–	K_2CO_3	acetone (0.1)	41%
4	**–**	**K_2CO_3**	**acetone (0.05)**	**63%**
5	–	Cs_2CO_3	acetone (0.1)	52%
6	–	Et_3N	acetone (0.1)	25%
7	–	K_2CO_3	CH_3CN (0.1)	44%
8	–	K_2CO_3	DMSO (0.1)	56%
9	–	K_2CO_3	toluene (0.1)	56%
10	–	K_2CO_3	$CHCl_3$ (0.1)	8%

[a] The reaction was run in the dark.

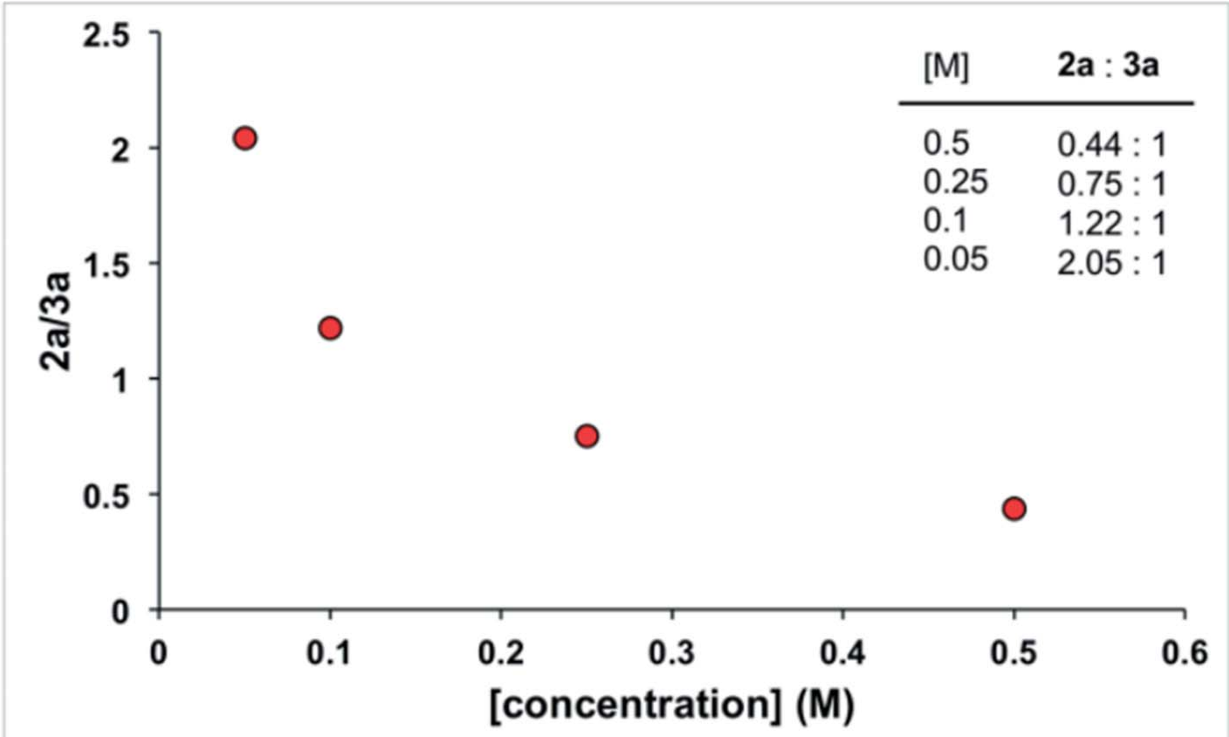


B) Concentration studies

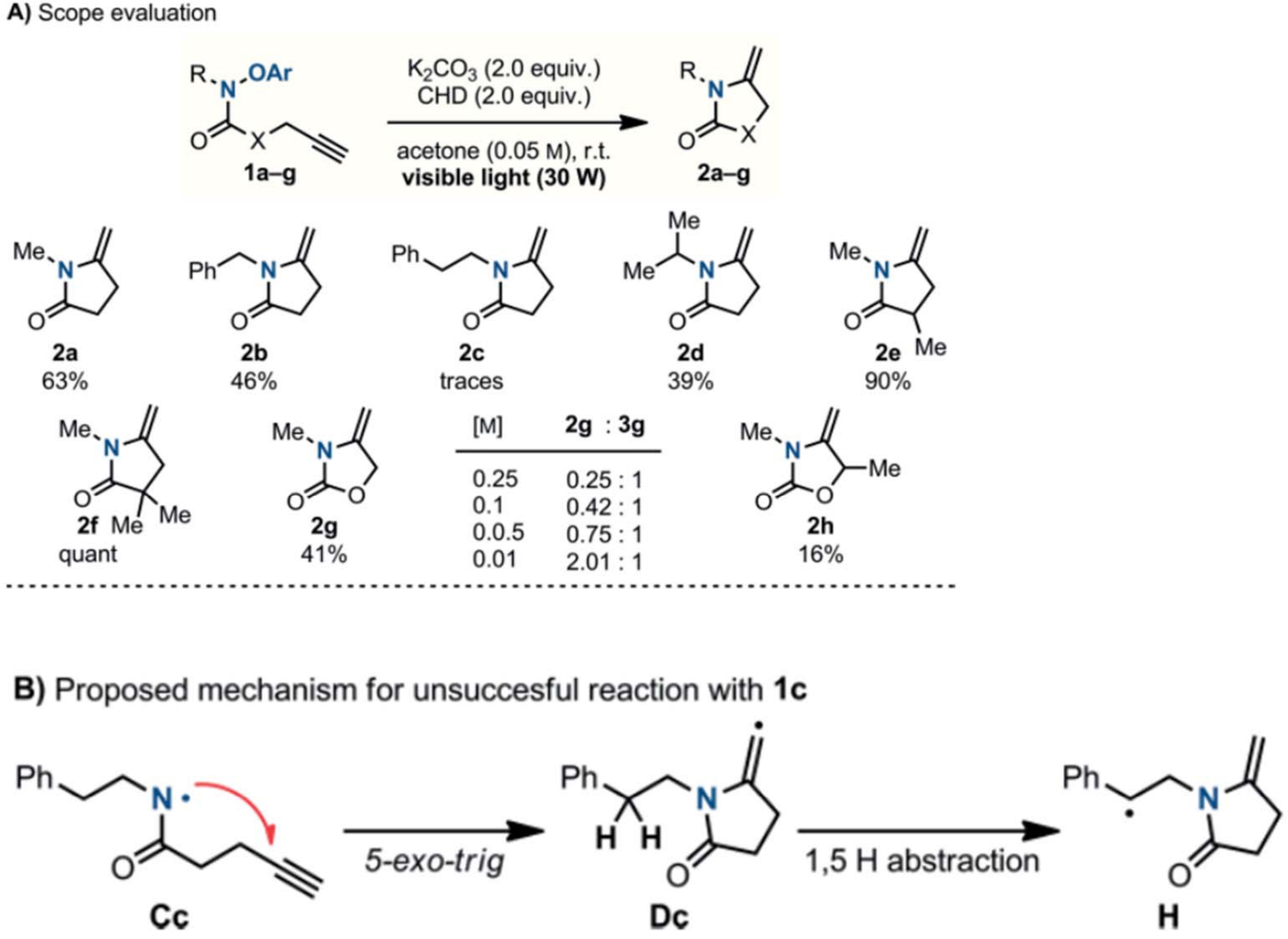

K_2CO_3 (2.0 equiv.)
1,4-CHD (2.0 equiv.)
acetone, r.t.
visible light (30 W)

1a **2a** + **3a**

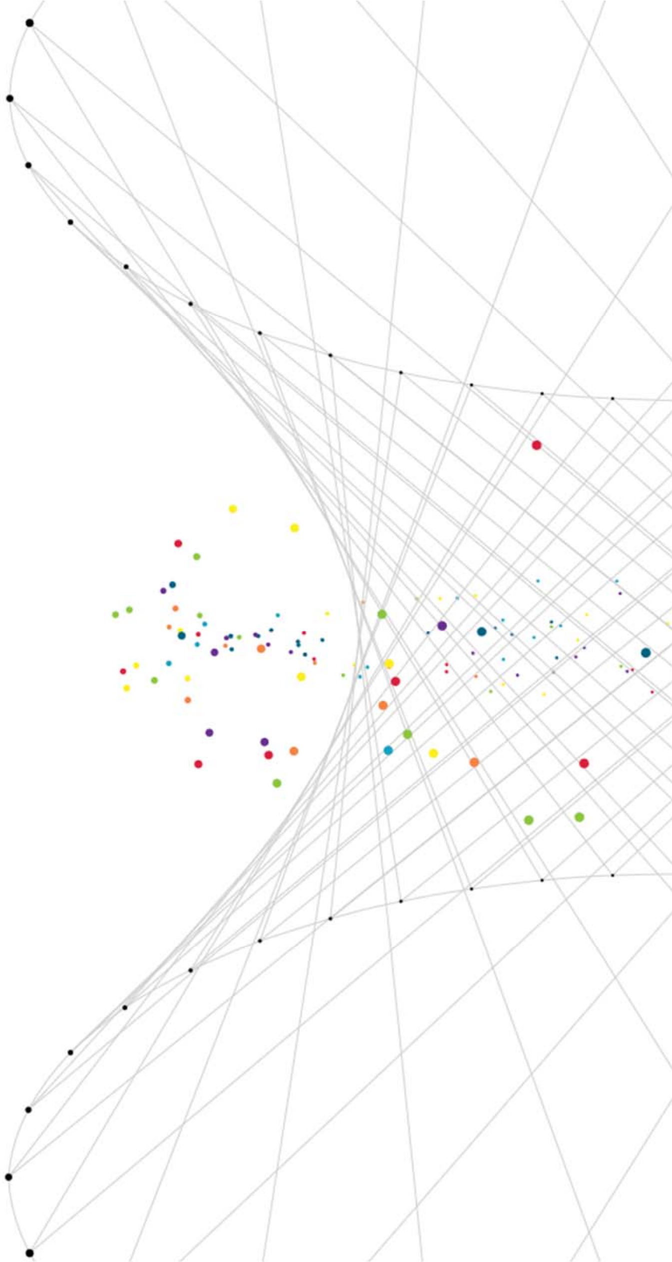
Ar = 2,4-$(NO_2)_2$-C_6H_3



[M]	**2a** : **3a**
0.5	0.44 : 1
0.25	0.75 : 1
0.1	1.22 : 1
0.05	2.05 : 1

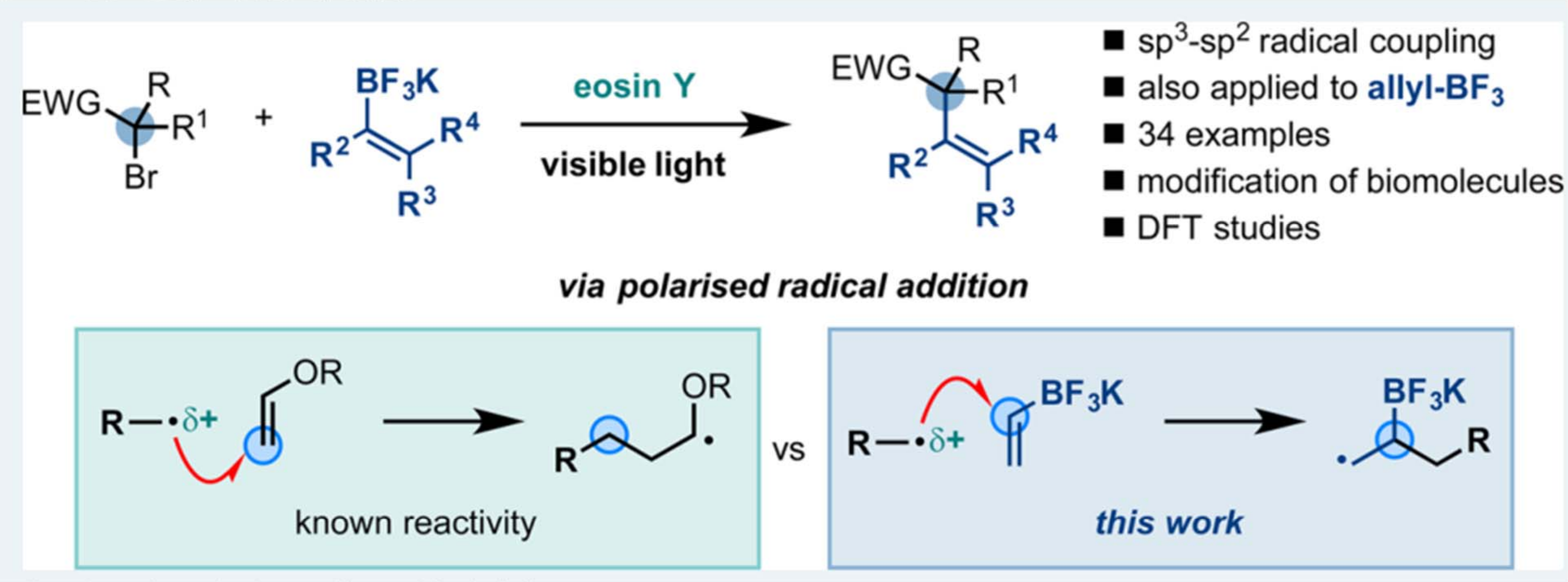


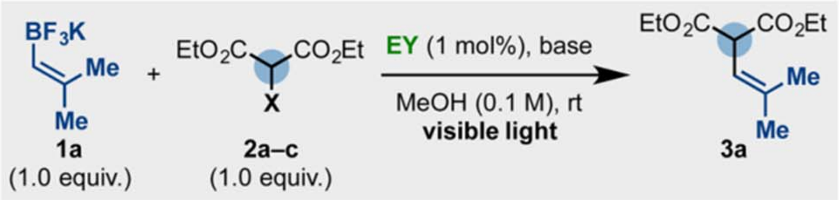
Scheme 4. Scope of the 5-*exo-dig* hydroamination via amidyl radicals.



Visible-Light-Mediated Reactions of Electrophilic Radicals with Vinyl and Allyl Trifluoroborates

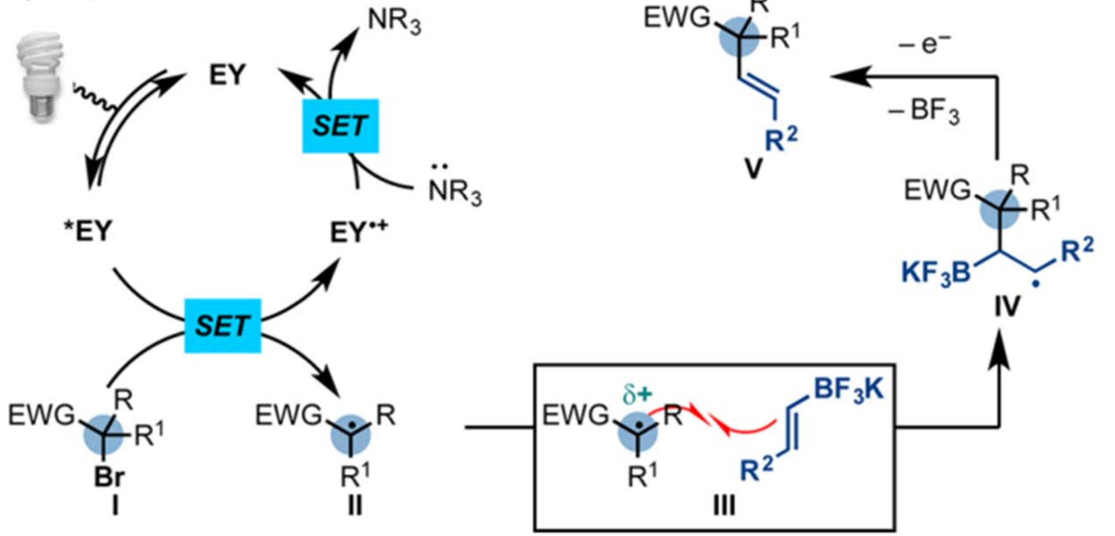
Daniel Fernandez Reina,[†,¶] Alessandro Ruffoni,[†,¶] Yasair S. S. Al-Faiyz,[‡] James J. Douglas,[§]
Nadeem S. Sheikh,[*,‡] and Daniele Leonori[*,†]





Entry	X	Base (equiv.)	Light Source	Yield (%)
1	**Br**	**EtN(*i*-Pr)$_2$ (1.0)**	**green LEDs**	**81**
2	Br	–	green LEDs	traces
3	Br	EtN(*i*-Pr)$_2$ (1.0)	green LEDs	–
4	Br	EtN(*i*-Pr)$_2$ (1.0)	–	–
5	Br	EtN(*i*-Pr)$_2$ (0.2)	green LEDs	24
6	Br	K$_2$CO$_3$ (1.0)	green LEDs	37
7	I	EtN(*i*-Pr)$_2$ (1.0)	green LEDs	67
8	Cl	EtN(*i*-Pr)$_2$ (1.0)	green LEDs	6

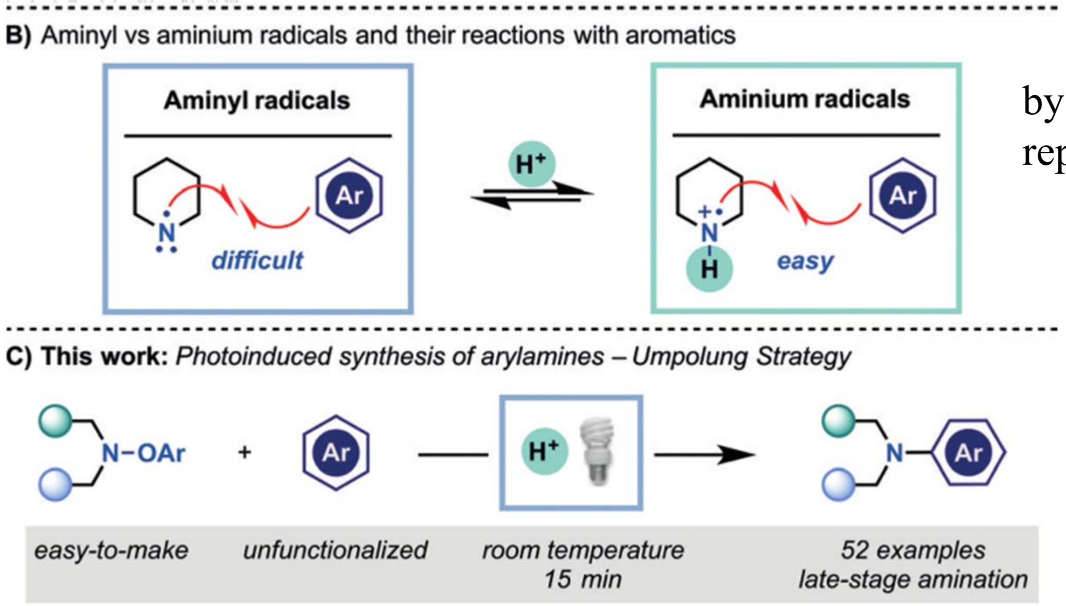
B) Proposed mechanism



Synthesis of Arylamines via Aminium Radicals

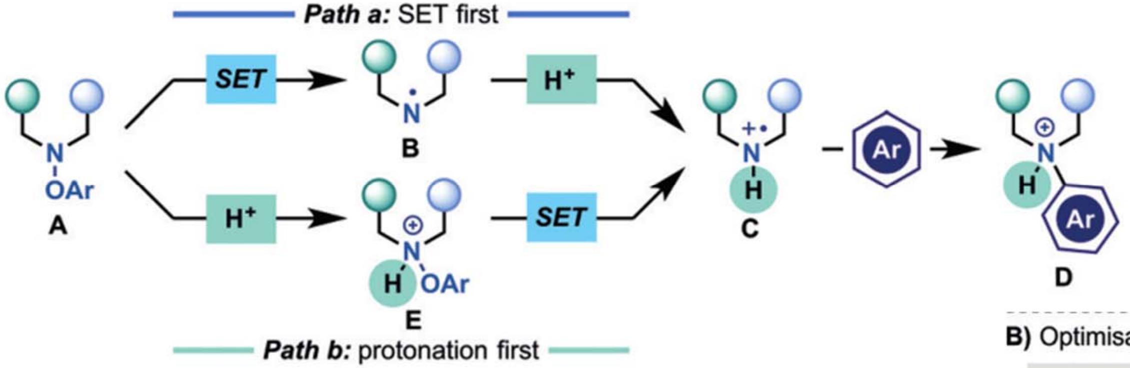
*Thomas D. Svejstrup, Alessandro Ruffoni, Fabio Juliá, Valentin M. Aubert, and Daniele Leonori**

protonated electron-poor O-aryl hydroxylamines give aminium radicals in the presence of $Ru(bpy)_3Cl_2$. These highly electrophilic species undergo polarized radical addition to aromatic compounds in high yield and selectivity.

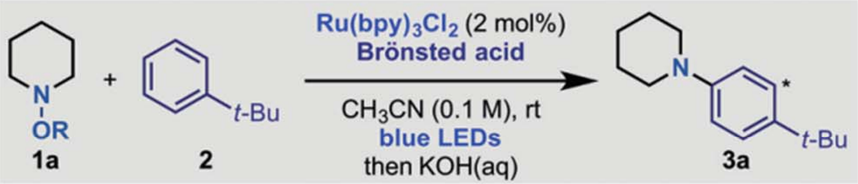


by the intrinsic nucleophilic nature of aminyls, which causes repulsive interactions between their lone pair and the aromatic ring

A) Possible strategies for aminium radical generation and N-arylation

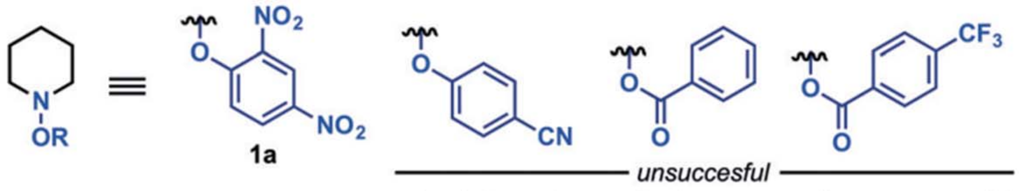


B) Optimisation of the process using **1a**

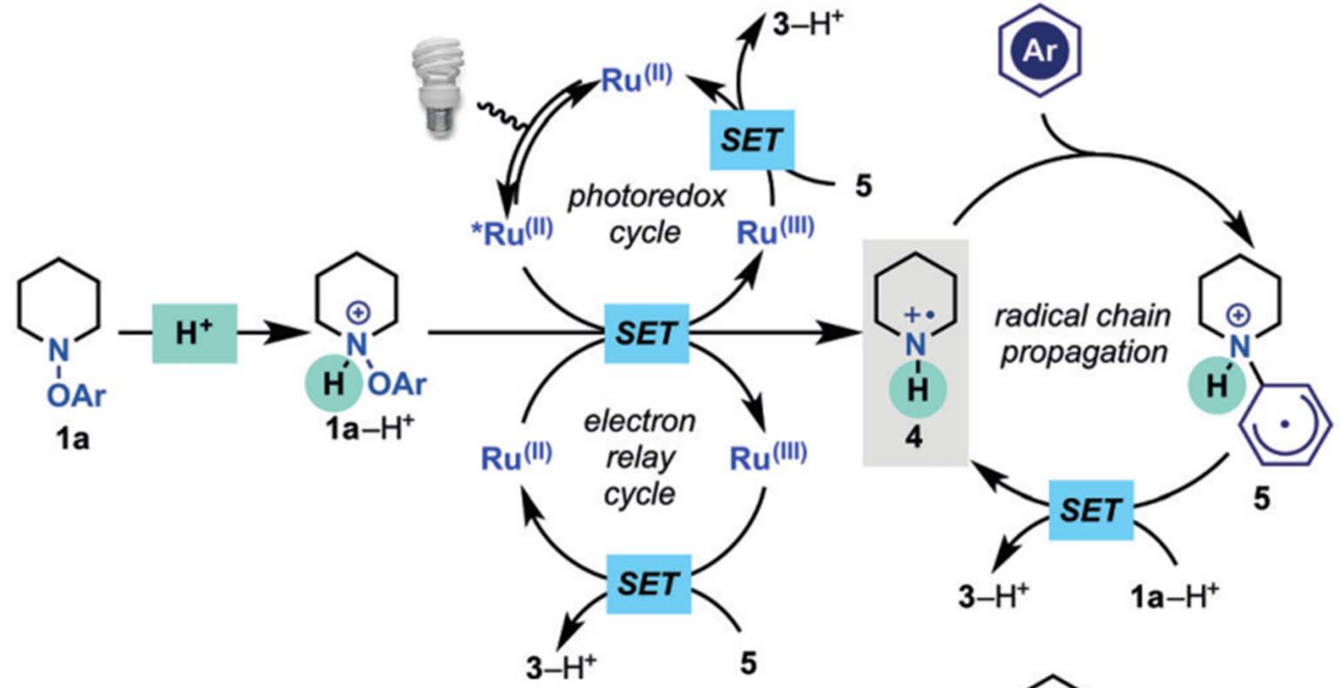


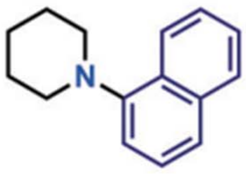
Entry	Brönsted acid	equiv.	p*K*a (H_2O)	time	Yield (%)
1	–	–	–	24 h	–
2	AcOH	2.0	4.7	24 h	–
3	TFA	2.0	0.2	24 h	–
4	*p*TsOH	2.0	–2.8	24 h	19
5	**$HClO_4$**	**2.0**	**–10**	**15 min**	**61**
6	$HClO_4$	0.2	–10	15 min	9
7[a]	$HClO_4$	2.0	–10	1 h	51

[a] the reaction was run in the dark

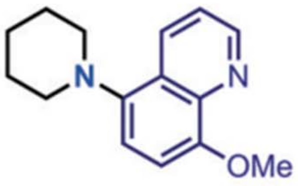


C) Proposed productive pathways leading to the formation of products

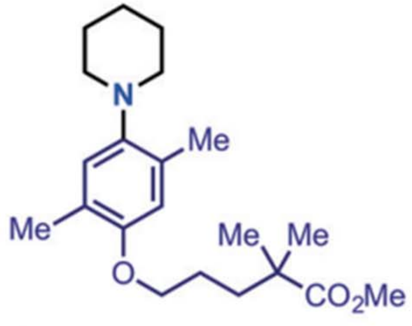




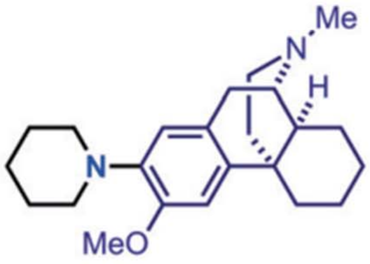
3o, 90%



3z, 50%



from gemfibrozil methyl ester
lipid lowering drug
3as, 43%

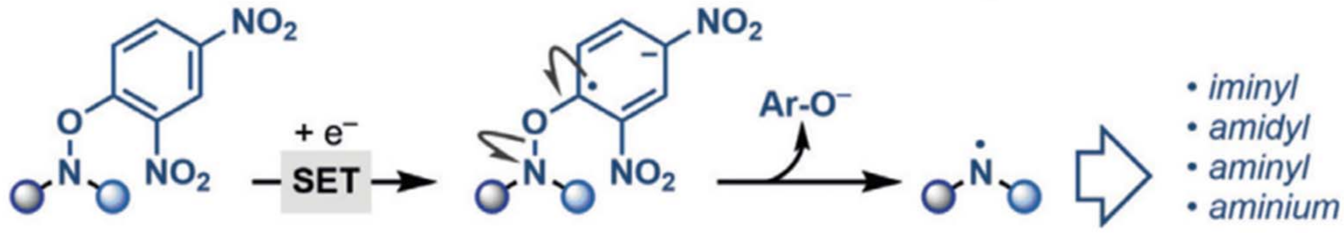


from dextromethorphan
sedative and anti-cough
3at, 44%

Reaction of Nitrogen-Radicals with Organometallics Under Ni-Catalysis: N-Arylations and Amino-Functionalization Cascades

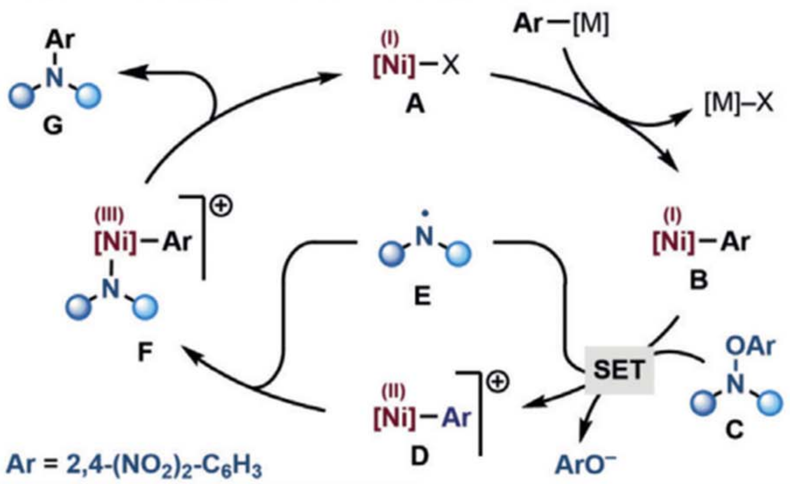
*Lucrezia Angelini[+], Jacob Davies[+], Marco Simonetti, Laia Malet Sanz, Nadeem S. Sheikh, and Daniele Leonori**

a strategy for the generation of nitrogen-radicals by ground-state single electron transfer with organyl–Ni(I)species



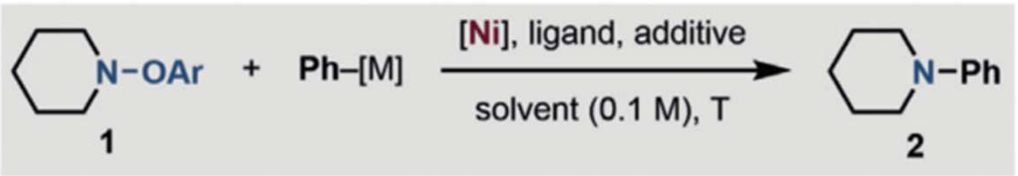
C) Generation of N-radicals via SET reduction of N–OAr electrophores

A) Proposed Ni-catalysed amination of organometallics



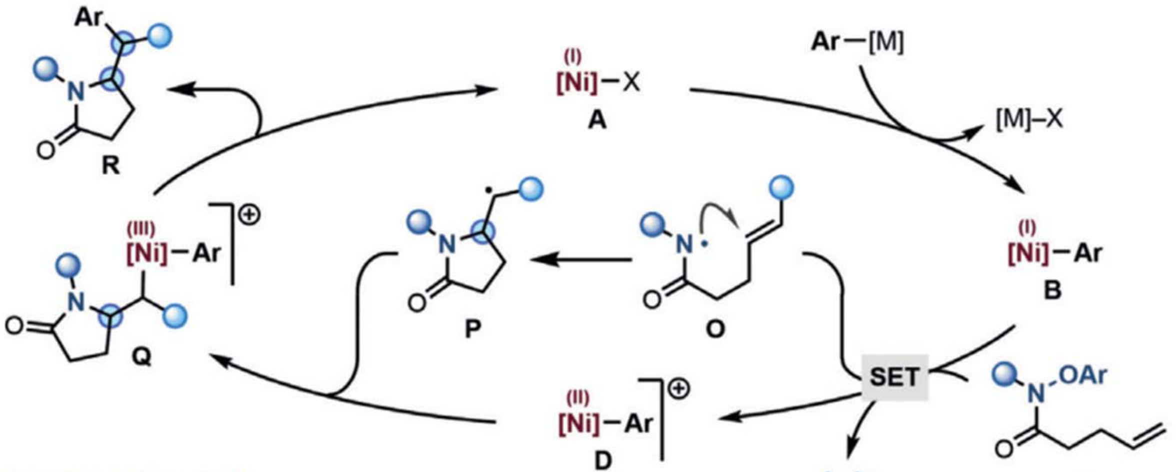
Cs_2CO_3 was critical, likely by easing the transmetalation of the boronic acid at the Ni(I)center

B) Optimization of the amination of organometallics via aminyl radicals



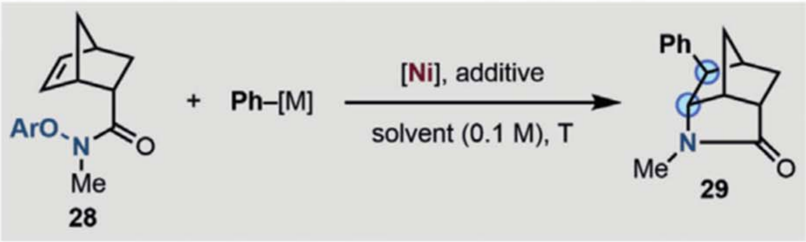
Entry	[M]	[Ni] (mol%)	Ligand (mol%)	Additive	Solvent	T (ºC)	Yield (%)
1	ZnPh	$NiCl_2•6H_2O$ (5)	–	–	THF	rt	–
2	ZnPh	$NiCl_2•6H_2O$ (5)	dtbpy (5)	–	THF–DMF	rt	99
3	$B(OH_2)$	$NiCl_2•6H_2O$ (5)	dtbpy (5)	–	THF–DMF	75	–
4	$B(OH_2)$	$NiCl_2$•glyme (5)	dtbpy (5)	Cs_2CO_3	MTBE	75	90
5	$Si(OEt)_3$	$NiCl_2$•glyme (5)	dtbpy (5)	–	DMSO	50	–
6	$Si(OEt)_3$	$NiCl_2$•glyme (5)	dtbpy (5)	TBAT	DMSO	50	86

A) Proposed mechanism for cyclization-arylation cascades with amidyl radicals

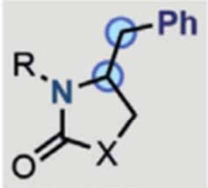


Ar = 2,4-$(NO_2)_2$-C_6H_3

B) Screaning of phenyl-organometallics



Entry	[M]	[Ni] (mol%)	Additive	Solvent	T (ºC)	Yield (%)
1	ZnPh	$NiBr_2$•dtbpy (20)	–	THF–DMF	rt	76
2	$B(OH)_2$	$NiCl_2$•dtbpy (20)	Cs_2CO_3	MTBE	75	83
3	$Si(OEt)_3$	$NiCl_2$•dtbpy (20)	TBAT	DMSO	50	45

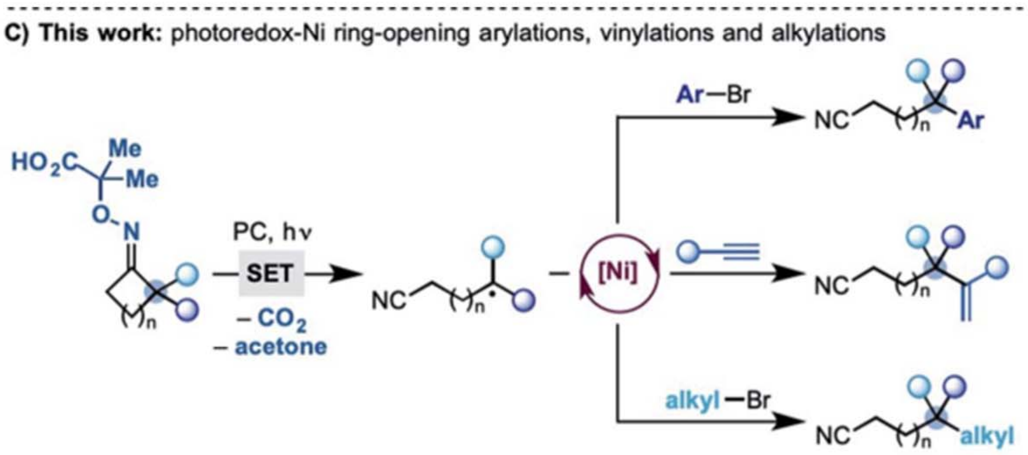


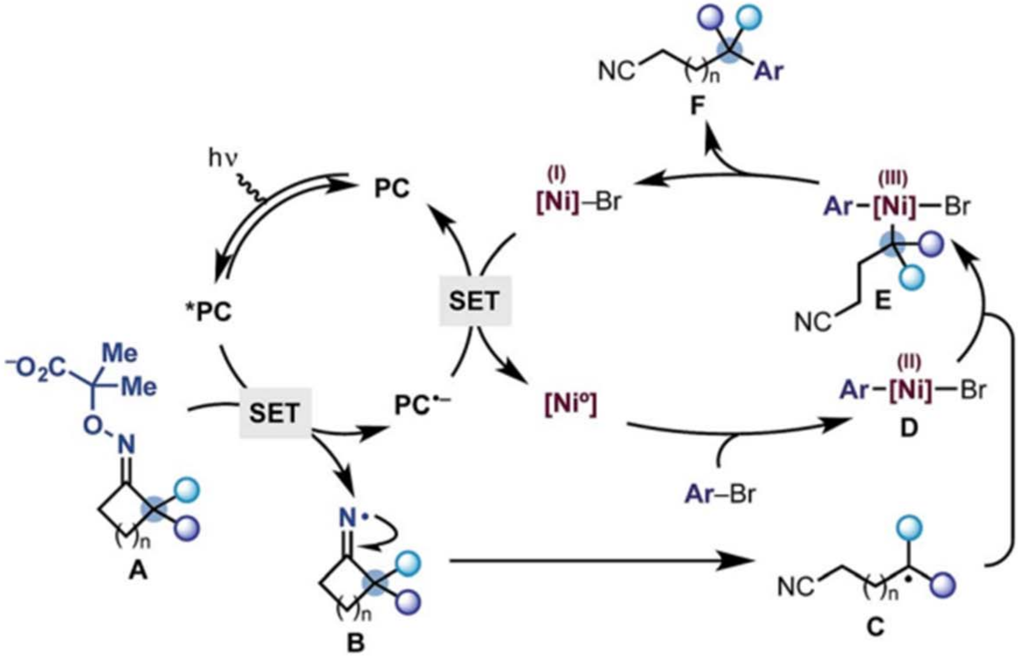
	X	R	yield (%)
46:	CH_2	Me	73
47:	CH_2	CH_2CH_2Ph	76
50:	O	Cy	50
51:	S	Me	48

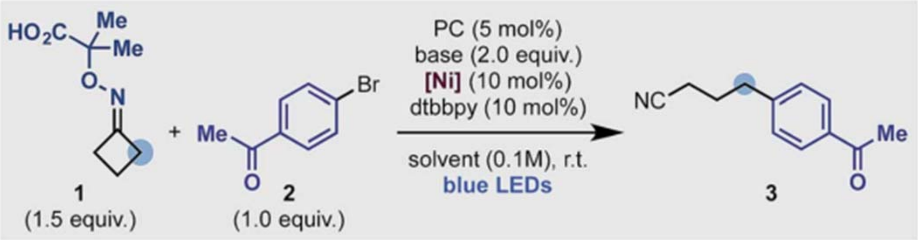
	R	yield (%)
53:	H	73
54:	OMe	61
55:	Cl	75
56:	CN	73

A dual photoredox-nickel strategy for remote functionalization *via* iminyl radicals: radical ring-opening-arylation, -vinylation and -alkylation cascades†

Elizabeth M. Dauncey,[‡a] Shashikant U. Dighe,[‡a] James J. Douglas[b]
and Daniele Leonori[*a]


C) **This work:** photoredox-Ni ring-opening arylations, vinylations and alkylations

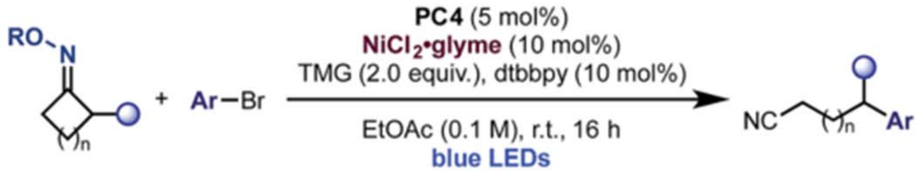


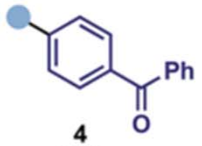


Entry	PC	[Ni]	Base	Solvent	Yield (%)
1	**PC1**	$NiCl_2$•glyme	K_2CO_3	DME	15
2	**PC2**	$NiCl_2$•glyme	K_2CO_3	DME	–
3	**PC3**	$NiCl_2$•glyme	K_2CO_3	DME	24
4	**PC4**	$NiCl_2$•glyme	K_2CO_3	DME	41
5	**PC4**	$NiCl_2$•glyme	Cs_2CO_3	DME	35
6	**PC4**	$NiCl_2$•glyme	K_2HPO_4	DME	–
7	**PC4**	$NiCl_2$•glyme	DBU	DME	38
8	**PC4**	$NiCl_2$•glyme	TMG	DME	55
9	**PC4**	$NiBr_2$•glyme	TMG	DME	39
10	**PC4**	$Ni(acac)_2$	TMG	DME	–
11	**PC4**	$Ni(OAc)_2$•$4H_2O$	TMG	DME	12
12	**PC4**	$NiCl_2$•glyme	TMG	acetone	41
13	**PC4**	$NiCl_2$•glyme	TMG	DMF	23
14	**PC4**	$NiCl_2$•glyme	TMG	EtOAc	61
15	–	$NiCl_2$•glyme	TMG	EtOAc	–
16	**PC4**	–	TMG	EtOAc	–
17	**PC4**	$NiCl_2$•glyme	–	EtOAc	–
18[a]	**PC4**	$NiCl_2$•glyme	TMG	EtOAc	–

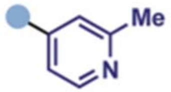
[a] The reaction was run in the dark

PC1: $(Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$
PC2: $MesAcr(ClO_4)$
PC3: 4CzIPN
PC4: $[Ir(dtbbpy)(ppy)_2]PF_6$

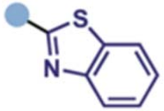




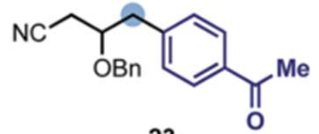
4
73%



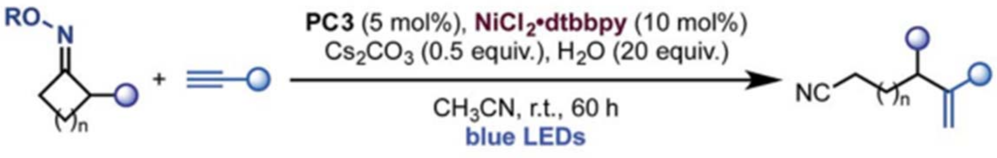
16
47%

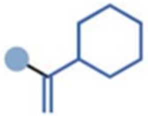


20
75%

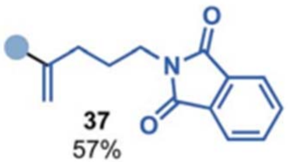


23
20%

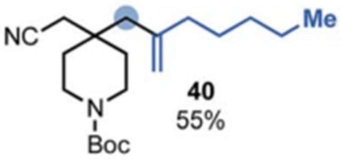




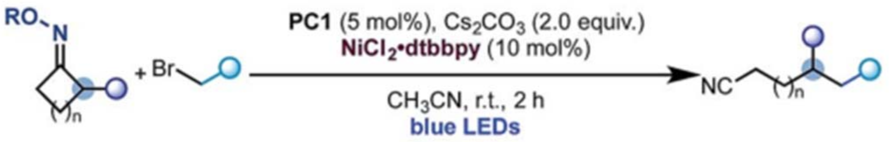
32
49%



37
57%



40
55%



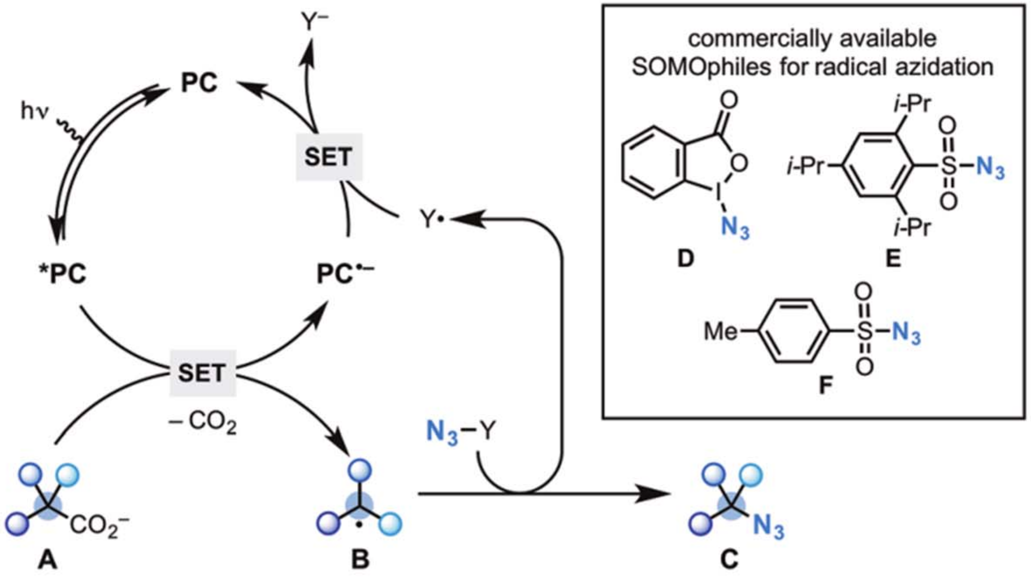
48
66%

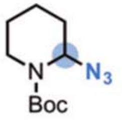
49
55%

50
64%

Photoinduced decarboxylative azidation of cyclic amino acids†

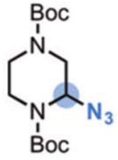
David C. Marcote,[a] Rosie Street-Jeakings,[a] Elizabeth Dauncey,[a]
James J. Douglas,[b] Alessandro Ruffoni *[a] and Daniele Leonori *[a]



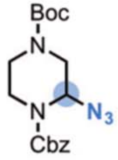


7
86%[a]

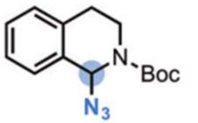
8
76%



9
85%



10
59%



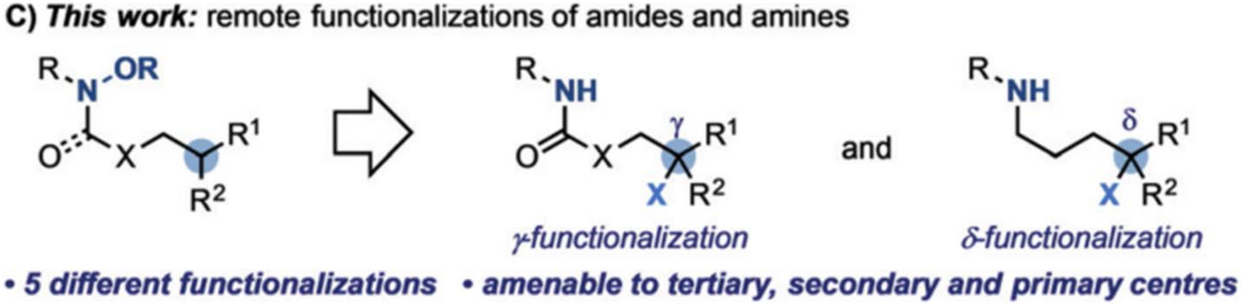
11
70%

Extension of this methodology to non-cyclic amino acids is a current limitation of the protocol and despite extensive re-optimization of the process we did not manage to achieve the decarboxylative azidation of, for example, protected phenylalanine

Photoinduced Remote Functionalization of Amides and Amines Using Electrophilic Nitrogen Radicals

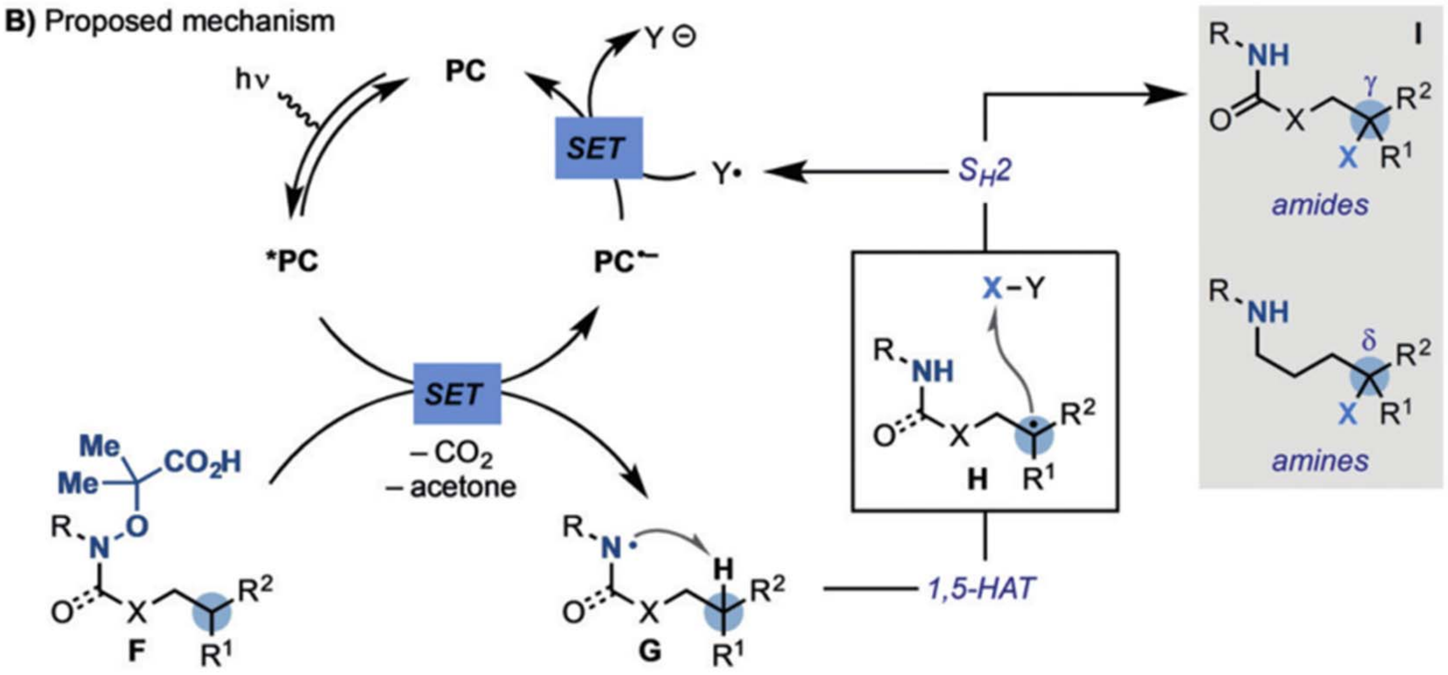
Sara P. Morcillo[+], *Elizabeth M. Dauncey*[+], *Ji Hye Kim, James J. Douglas, Nadeem S. Sheikh, and Daniele Leonori**

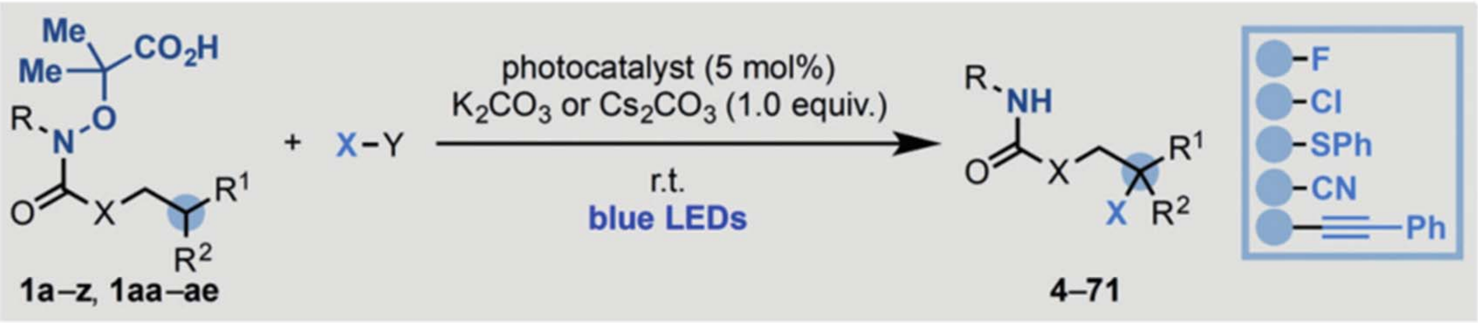
The process is based on the oxidative generation of electrophilic amidyl radicals and their subsequent transposition by 1,5-H-atom transfer, resulting in remote fluorination, chlorination and, for the first time, thioetherification, cyanation, and alkynylation.



C) *This work:* remote functionalizations of amides and amines

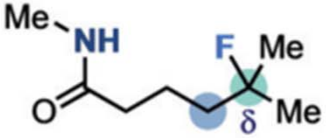
- ***5 different functionalizations***
- ***amenable to tertiary, secondary and primary centres***


B) Proposed mechanism

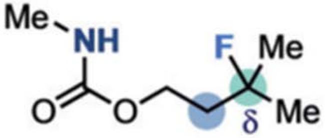


1a–z, 1aa–ae

4–71



22
71%



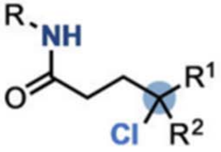
23
59%

16–21

	R	R^1	R^2	Yield (%)
16:	Cbz	Me	Me	72
17:	Boc	Me	Me	68
18:	Ts	Me	Me	61
19:	Boc	Me	H	85
20:	Boc	Ph	H	68
21:	Boc	H	H	30

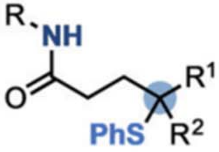
8, 34–37

	R	R^1	R^2	Yield (%)
8:	Me	Me	Me	80
34:	Me	Me	H	65
35:	Me	Ph	H	–
36:	Bn	Me	Me	30
37:	H	Me	Me	28



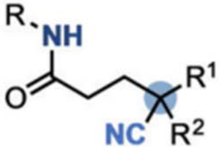
5, 25–28

	R	R^1	R^2	Yield (%)
5:	Me	Me	Me	75
25:	Me	Me	H	42
26:	Me	Ph	H	–
27:	Me	H	H	11
28:	Bn	Me	Me	52



6, 29–31

	R	R^1	R^2	Yield (%)
6:	Me	Me	Me	71
29:	Me	Me	H	55
30:	Me	Ph	H	38
31:	Me	H	H	10

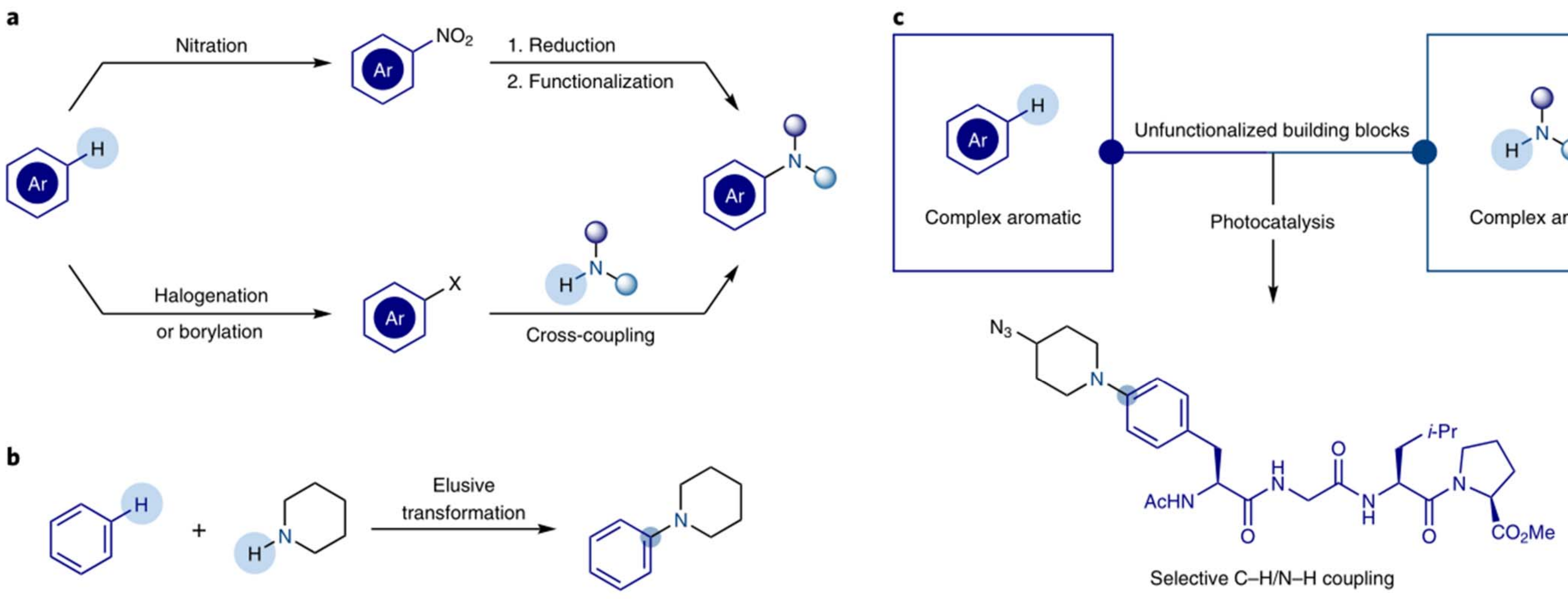


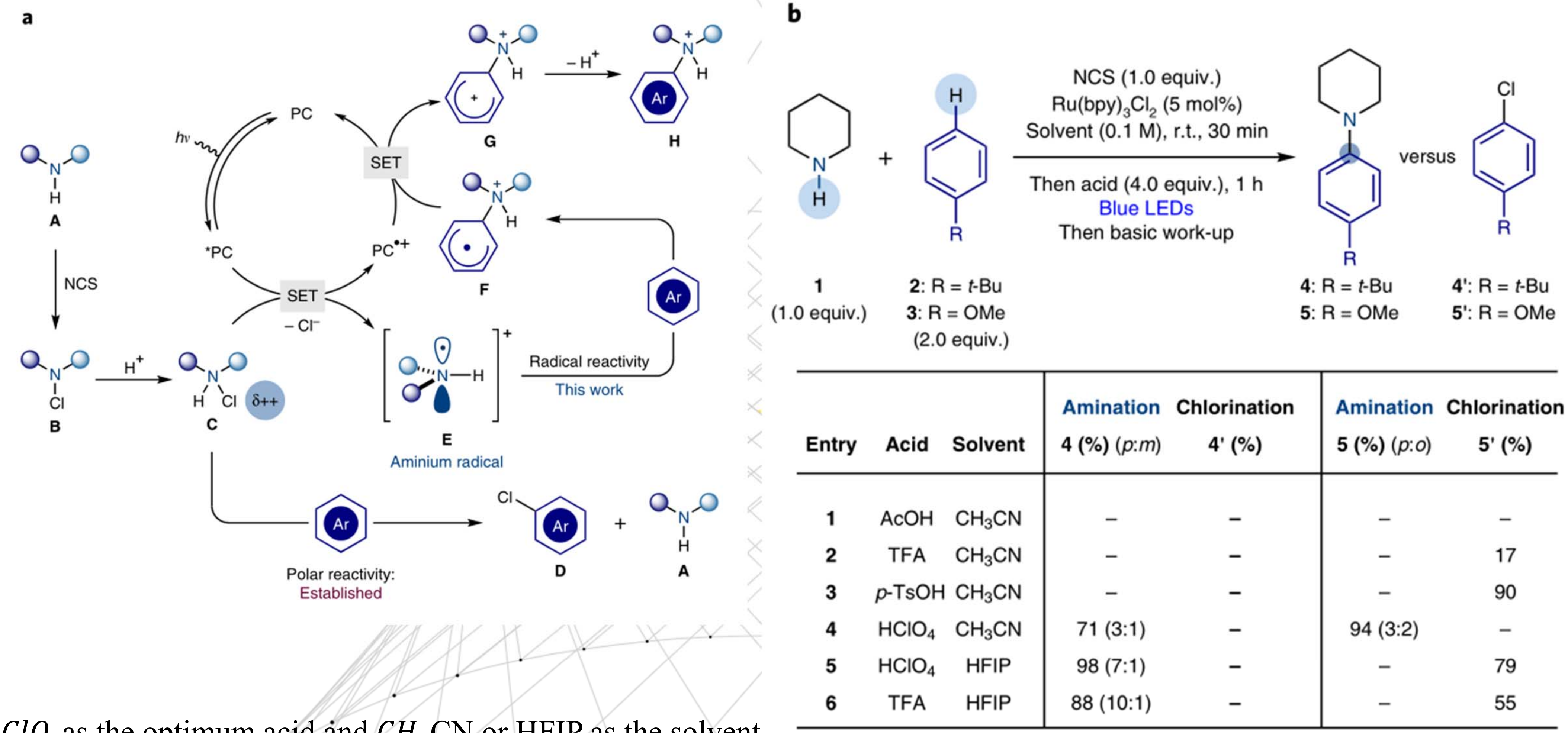
7, 32, 33

	R	R^1	R^2	Yield (%)
7:	Me	Me	Me	97
32:	Me	Me	H	37
33:	Me	Ph	H	–

Practical and regioselective amination of arenes using alkyl amines

Alessandro Ruffoni[1,3], Fabio Juliá[1,3], Thomas D. Svejstrup[1], Alastair J. McMillan[1],
James J. Douglas[2] and Daniele Leonori[1]*



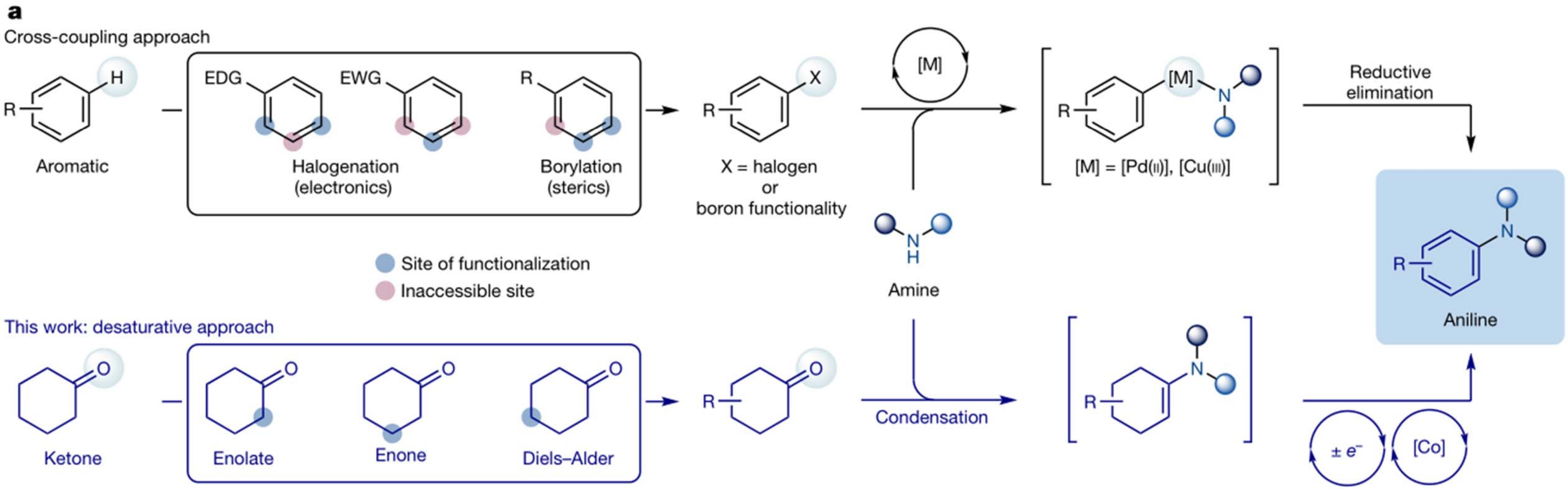


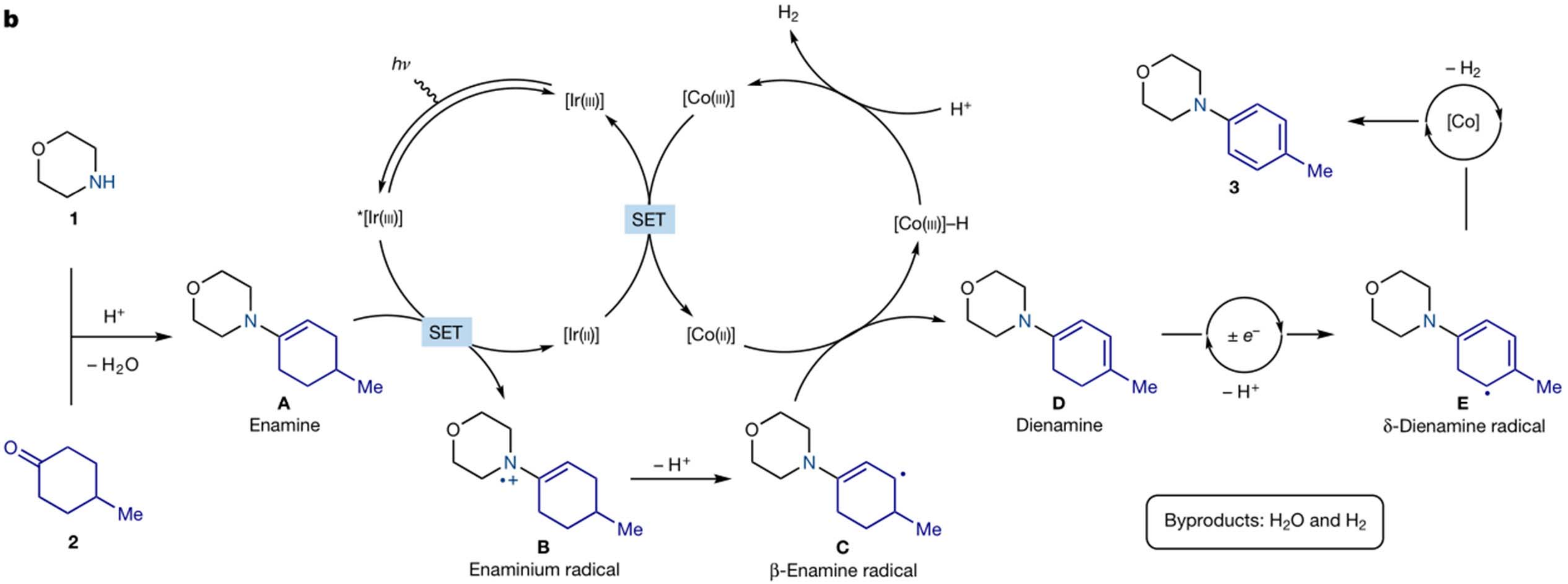
Entry	Acid	Solvent	Amination 4 (%) (*p*:*m*)	Chlorination 4' (%)	Amination 5 (%) (*p*:*o*)	Chlorination 5' (%)
1	AcOH	CH_3CN	–	–	–	–
2	TFA	CH_3CN	–	–	–	17
3	*p*-TsOH	CH_3CN	–	–	–	90
4	$HClO_4$	CH_3CN	71 (3:1)	–	94 (3:2)	–
5	$HClO_4$	HFIP	98 (7:1)	–	–	79
6	TFA	HFIP	88 (10:1)	–	–	55

$HClO_4$ as the optimum acid and CH_3CN or HFIP as the solvent of choice depending on the electron density of the arene partner, CH_3CN for highly electron-rich aromatics and HFIP for weakly electron-rich ones.

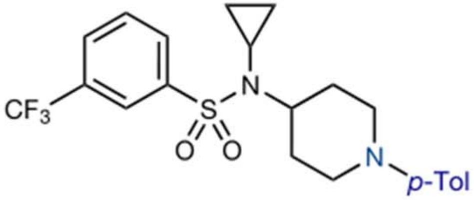
A photochemical dehydrogenative strategy for aniline synthesis

Shashikant U. Dighe[1], Fabio Juliá[1], Alberto Luridiana[1], James J. Douglas[2] & Daniele Leonori[1] ✉

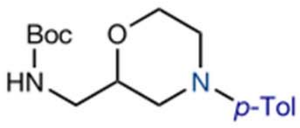




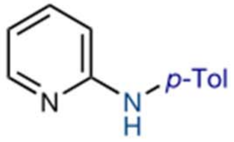
Owing to the enhanced acidity of the β-methylene unit in the enaminium radical B , a deprotonation can take place, leading to the nucleophilic 5πe – β-enamine radical C



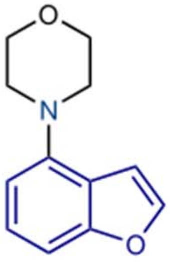
7, 90%



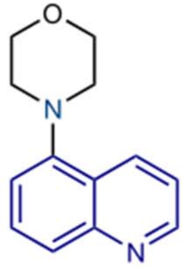
12, 88%



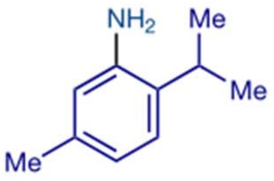
35, 60%



71, 68%

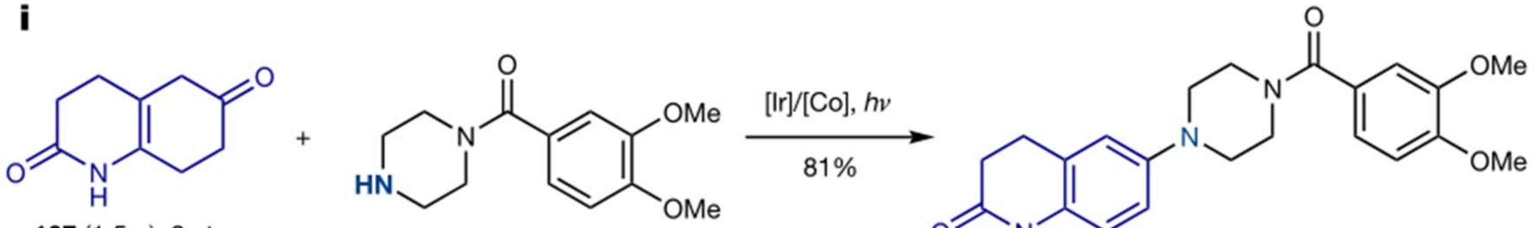


67, 81%



82, 90%

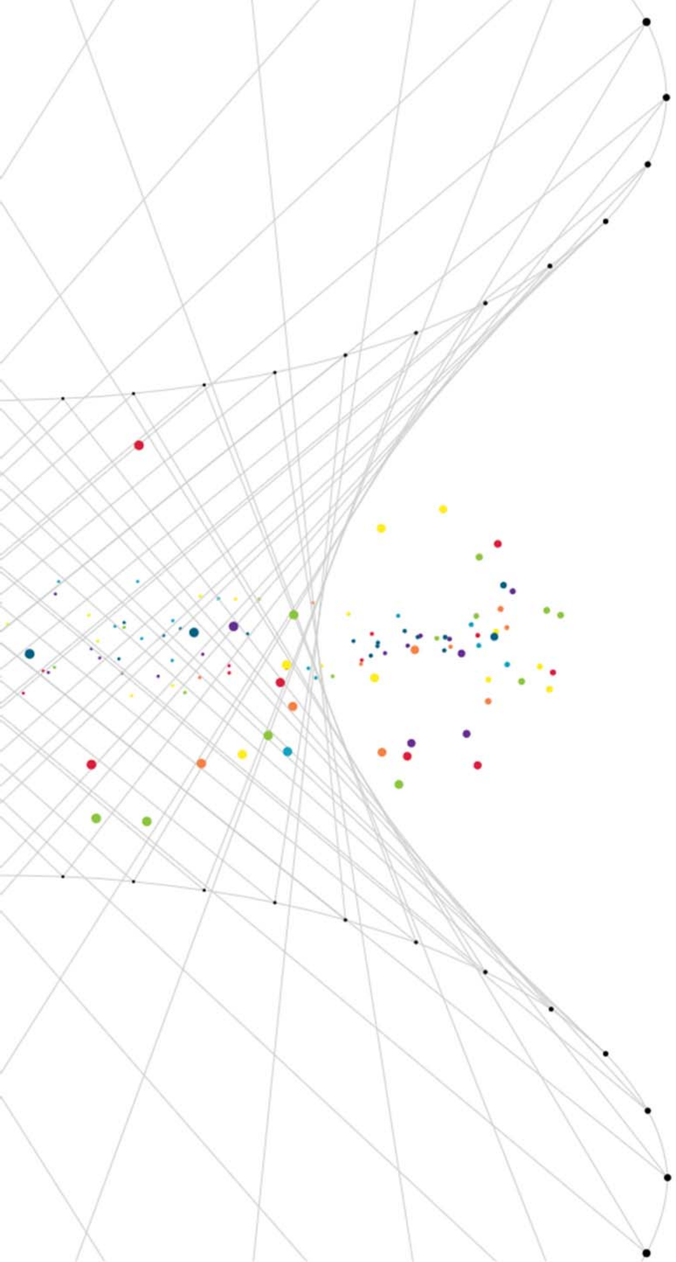
i



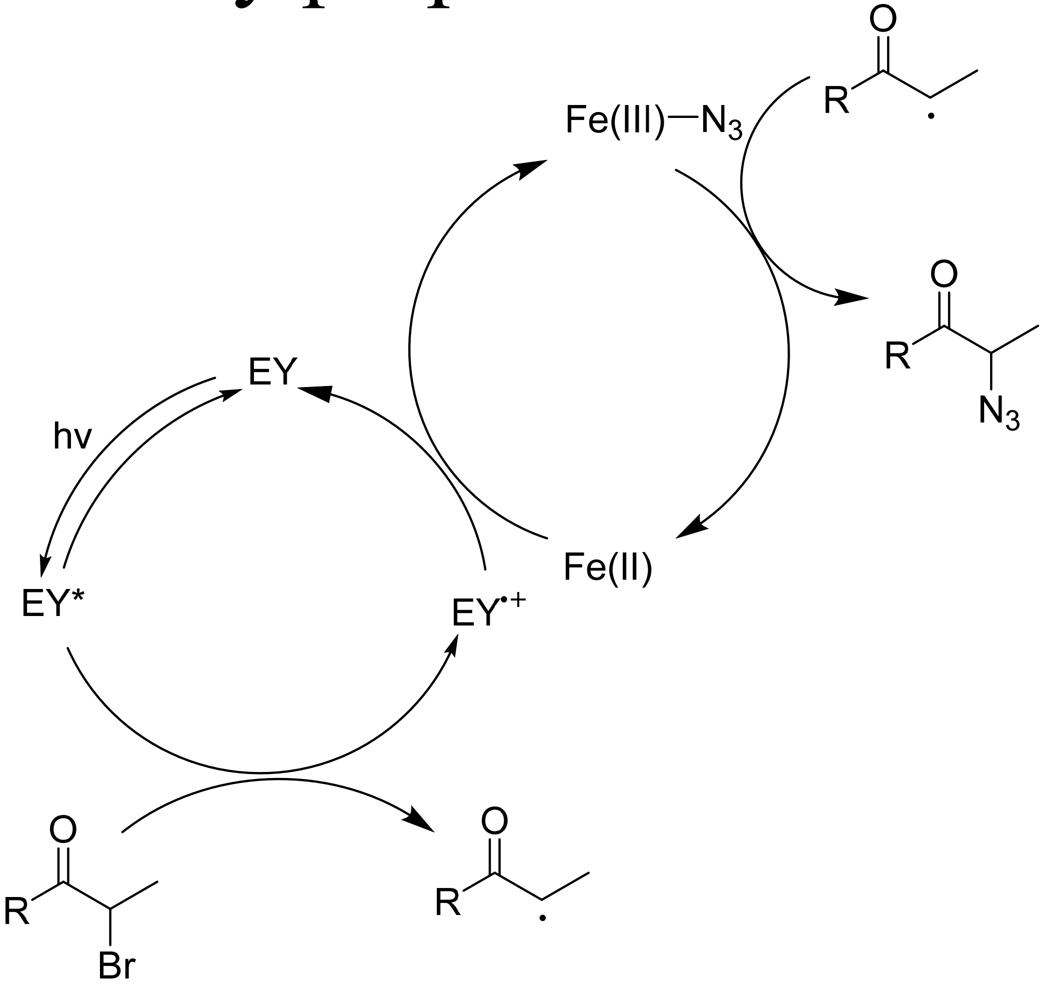
107 (1.5 g), 2 steps

108

109 (2.9 g), Vesnarinone

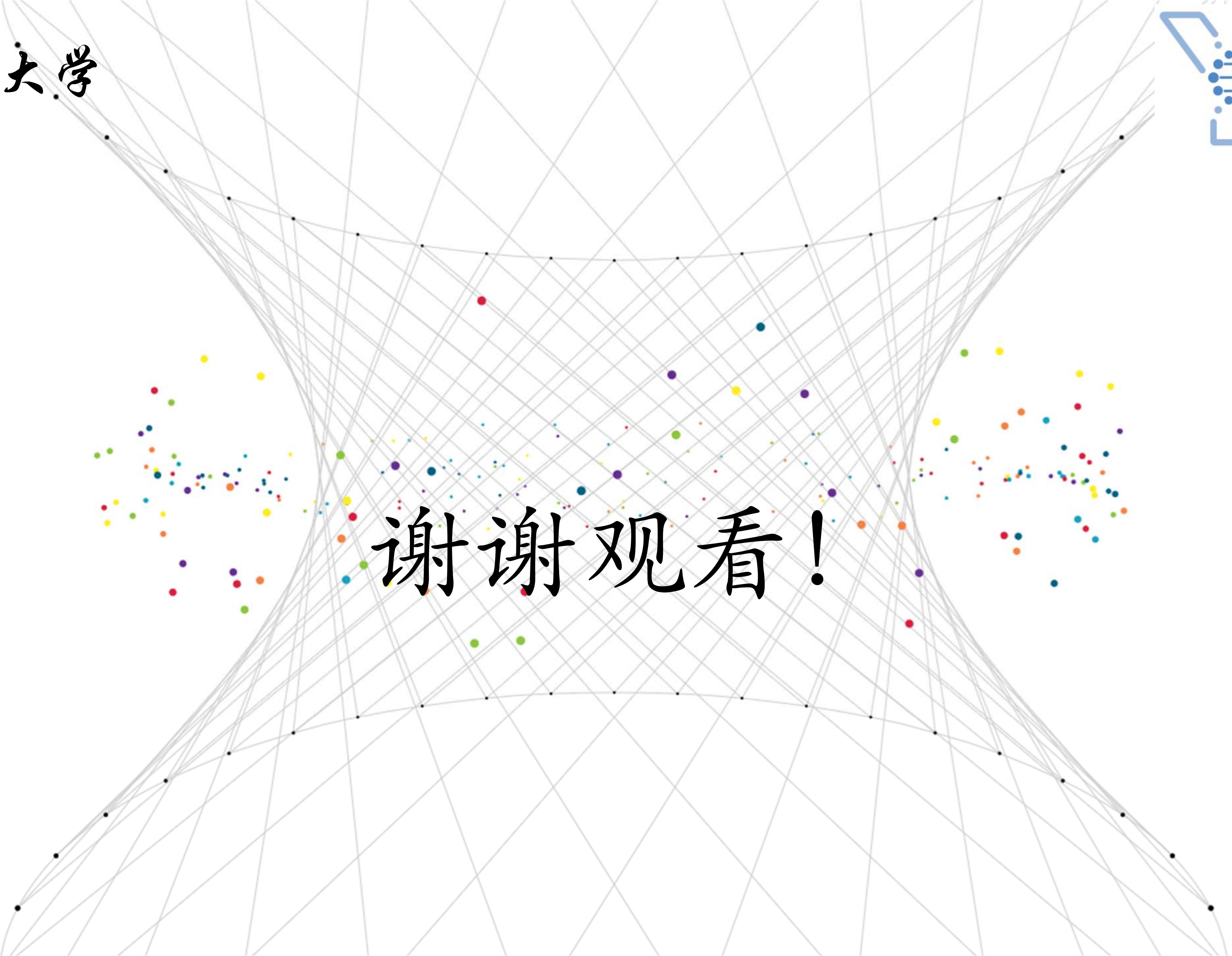


My proposal



同济大学

THE YANG
RESEARCH GROUP



谢谢观看！