Mechanistic investigations in light-driven synthetic chemistry.

From direct photochemistry to organophotoredox catalysis

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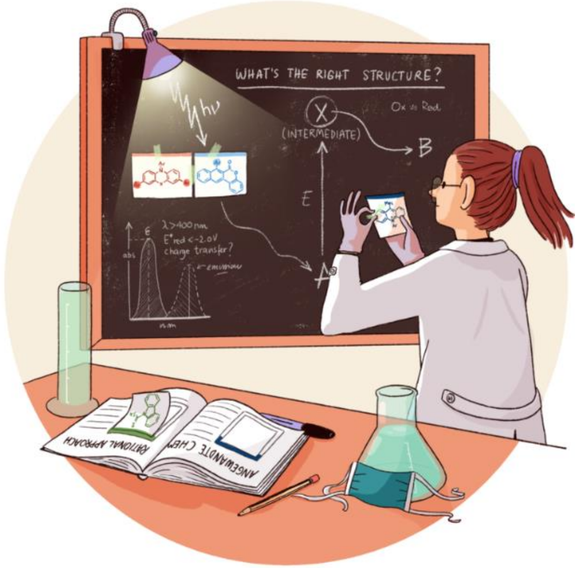
Main scientific interests of the group

- ❑ ***Development of novel synthetic methods and mechanistic investigations***

- *Angew. Chem. Int. Ed.* **2023**, *135*, e2023035
- *Angew. Chem. Int. Ed.* **2023**, *62*, e2023035
- *Nat. Synth.* **2023**, *2*, 26–36
- *Chem. Sci.* **2020**, *11*, 6532–6538
- *ACS Catal.* **2019**, *9*, 6058–6072

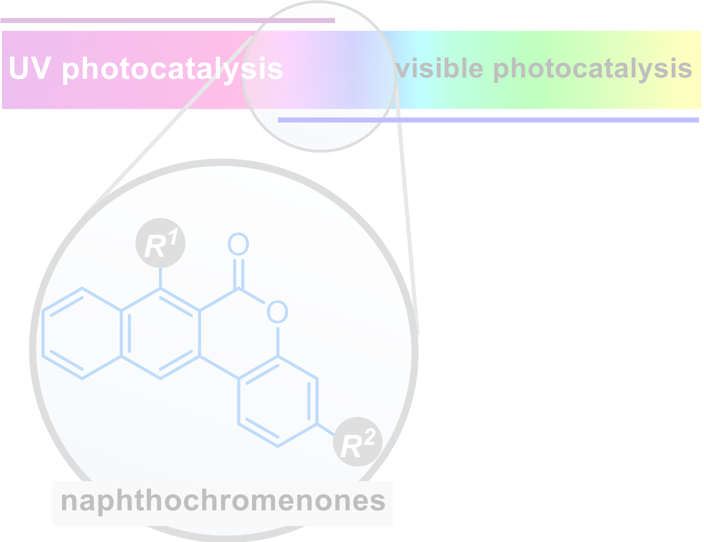
- ❑ ***Photorganocatalysts design, characterisation and application***



- *Nat. Catal.* **2024**, 10.1038/s41929-024-01206-4
- *J. Am. Chem. Soc.* **2023**, *145*, 1835–1846
- *ACS Catal.* **2022**, *12*, 4290–4295
- *Angew. Chem. Int. Ed.* **2021**, *133*, 1096–1111
- *Angew. Chem. Int. Ed.* **2020**, *59*, 1302–1312

The design of novel PCs in the group

by "accident"



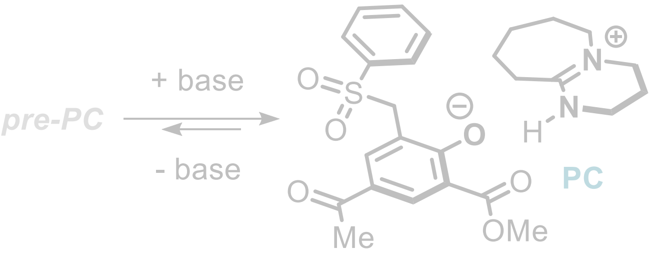
- wide redox window, $E_{0,0}$ = 3.22 eV
- bimodal photoredox activity
- strong oxidant, $PC^*/PC^{\bullet -}$ = 1.65 V
- strong reductant, $PC^{\bullet +}/PC^*$ = -1.77 V
- general, affordable & reusable

Angew. Chem. Int. Ed. **2020**, *59*, 1302-1312

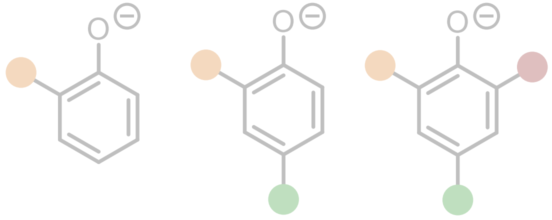
Angew. Chem. Int. Ed. **2021**, *133*, 1096–1111

by "investigation"

in-situ generated photocatalytic system (PC)



phenolate PC screening



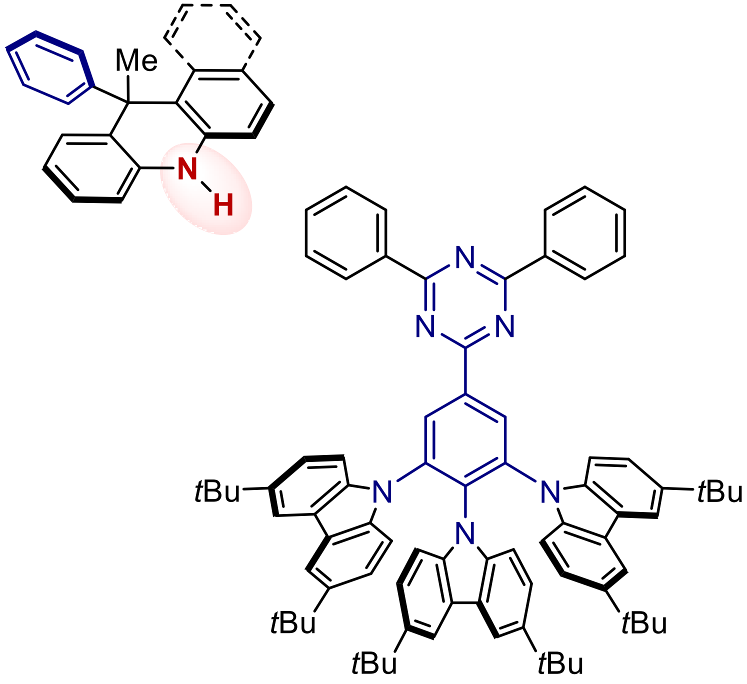
$\lambda_{0,0}$	312 nm	372 nm	***378 nm***
$E_{0,0}$	3.97 V	3.33 V	***3.28 V***
E_{ox}	+ 0.50 V	+ 0.65 V	***+ 0.74 V***
E^*_{ox}	- 3.47 V	- 2.68 V	***- 2.54 V***

ACS Catal. **2022**, *12*, 4290–4295

Org. Lett. **2022**, *24*, 2961–2966

by design

for both ET and EnT processes

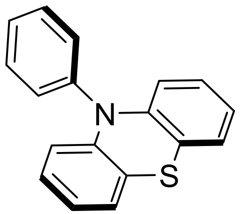


J. Am. Chem. Soc. **2023**, *145*, 1835–1846

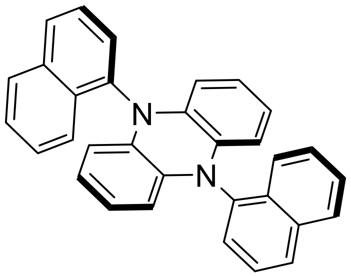
Nat. Catal. **2024**, 10.1038/s41929-024-01206-4

Highly reducing organic PCs

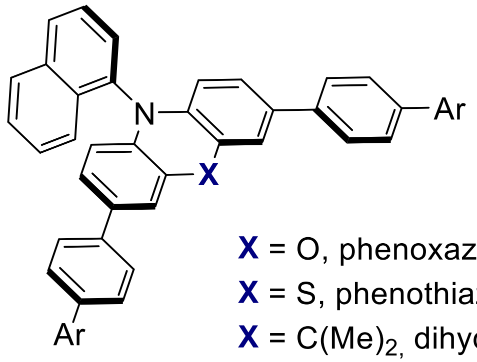
- *Main structural evolution*



phenothiazine



N-aryl dihydrophenazine

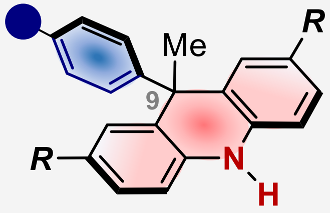


X = O, phenoxazine
X = S, phenothiazine
X = $C(Me)_2$, dihydroacridine

For a review: Wu, C.; Corrigan, N.; Lim, C.-H.; Liu, W.; Miyake, G.; Boyer, C. *Chem. Rev.* **2022**, *122*, 5476–5518.

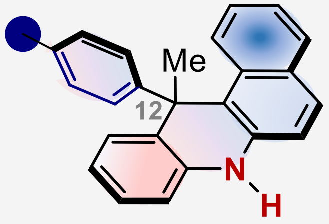
- *A new design…with a free NH group*

two new classes of organic PCs



9ADA

9-aryl dihydroacridine



12ADBA

12-aryl dihydrobenzoacridine

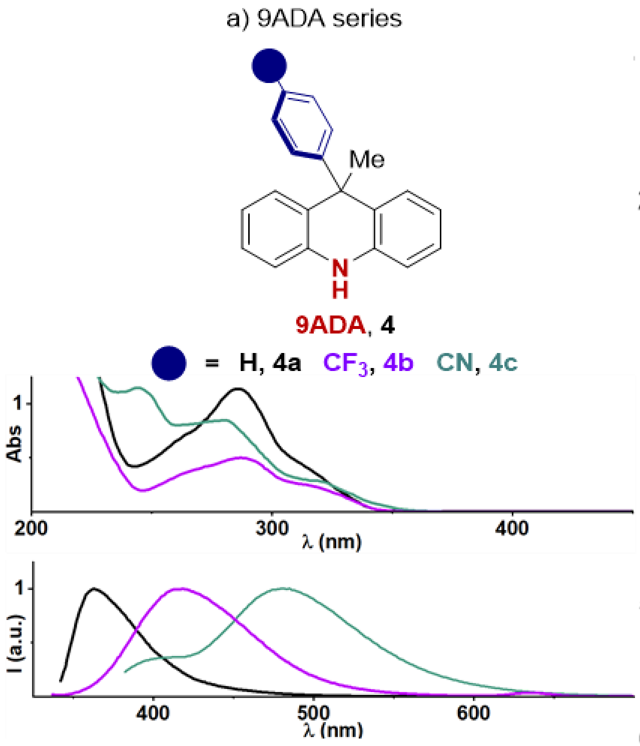
main features

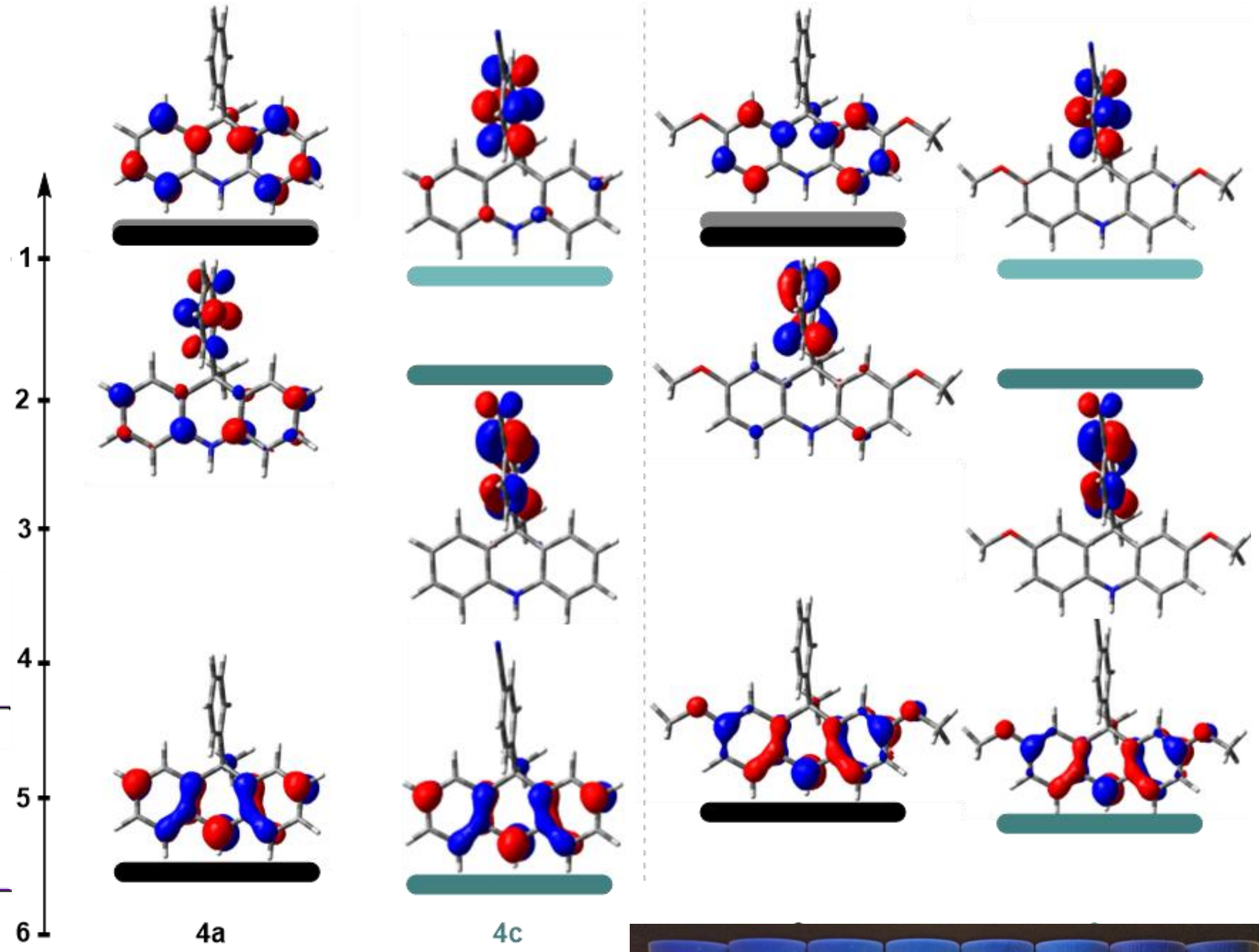
- structure-property relationships
- tunable **LUMO** distribution
- tunable photoredox properties
- free **NH** allows PCET processes
- readily available

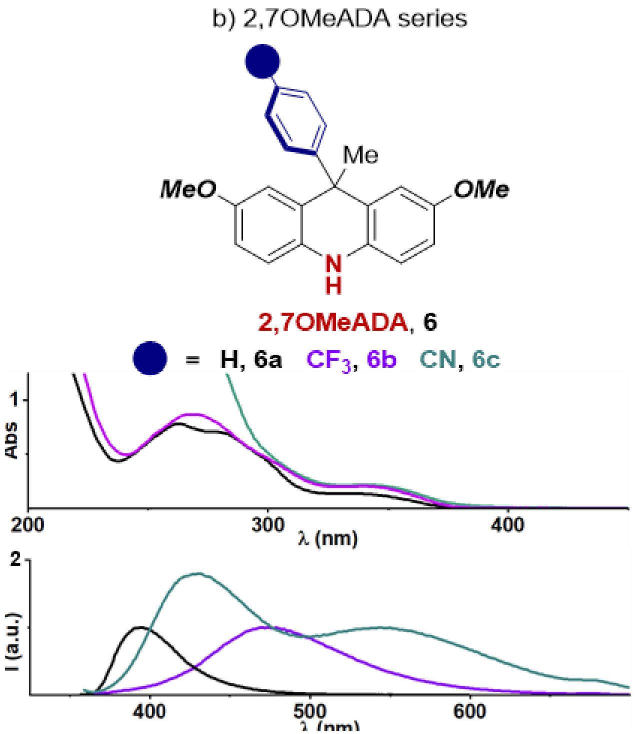
In collaboration with Prof. David . Lebœuf – Strasburg, France

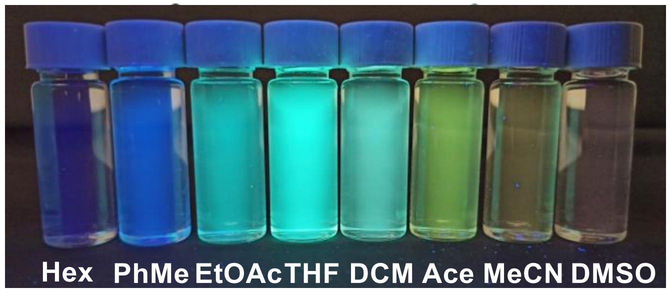
The design of a new PC

- Computational studies





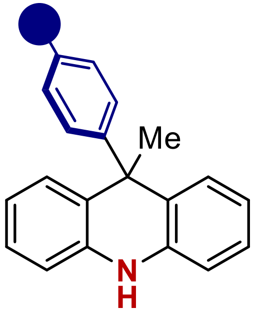




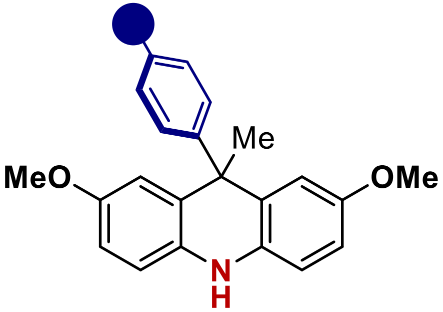
In collaboration with Prof. David . Lebœuf – Strasburg, France

Phothochemical and redox properties

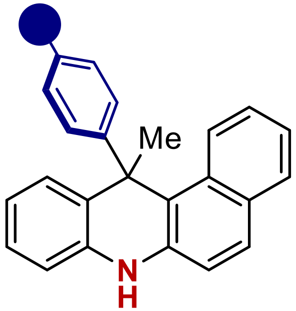
- *The Charge Transfer (CT) excited state*



9ADA



2,7-OMeADA



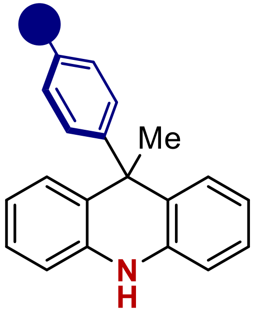
12ADBA

●, PC	H, 4a	CF_3, 4b	CN, 4c	H, 6a	CF_3, 6b	CN, 6c	H, 5a	OMe, 5b	CF_3, 5c	CN, 5d
E_{ox} (V)	0.79	0.84	0.86	0.44	0.49	0.49	0.76	0.74	0.80	0.80
E^*_{ox} (V)	- 2.88	- 2.68	- 2.54	- 2.91	- 2.76	- 2.69	- 2.37	- 2.39	- 2.34	- 2.31
λ_{abs} (nm)	285	285	280	338	340	342	364	363	364	362
λ_{em} (nm)	362	418	484	362	394	543	420	421	420	443
$E_{0,0}$ (eV)	3.67	3.52	3.40	3.35	3.25	3.18	3.13	3.13	3.14	3.11
Stokes shift (nm)	77	133	204	24	54	201	56	58	56	81
QY (%)	11	4	3	8	1.3	0.7	30	26	29	6
τ (ns)	4.2	4.1	14.3	3.3	3.2	4.8	9.0	9.0	8.8	9.4
CT character										

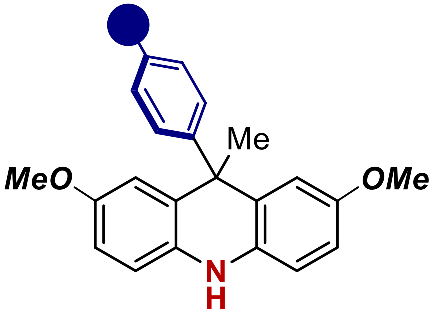
with T. Bortolato, G. Simionato, M. Vayer, C. Rosso, L. Paoloni, E. M. Benetti, A. Sartorel, D. Lebœuf, *J. Am. Chem. Soc.* **2023**, *145*, 1835–1846

Preliminary applications in ET

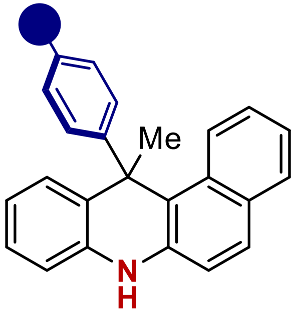
- *Photoreduction processes*



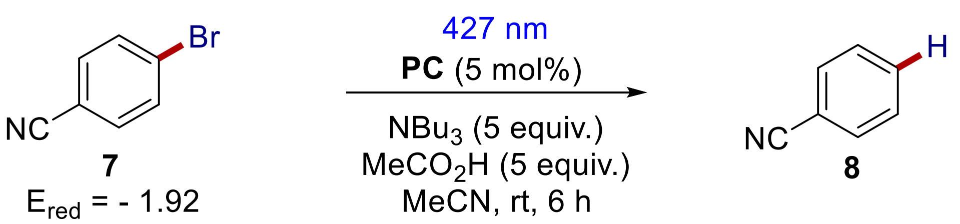
9ADA, **4**

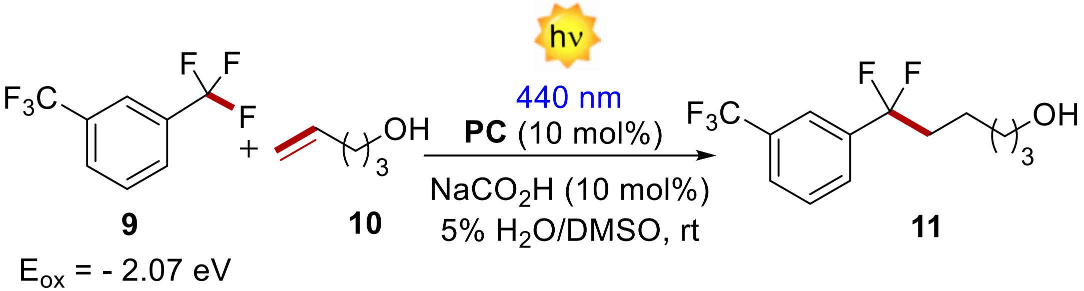


2,7OMeADA, **6**



12ADBA, **5**





●	PC, yield (%)		
H	4a, <5	**6a**, 35	**5a, 84**
OMe	-	-	**5b**, 78
CF_3	**4b**, <5	**6b**, 31	**5c**, 83
CN	**4c**, 13	**6c**, 20	**5d**, 41

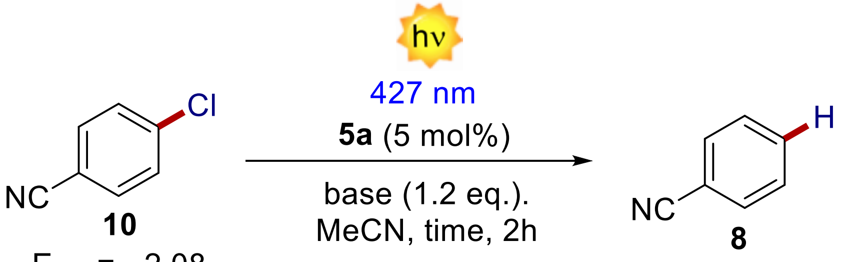
●	PC, yield (%)		
H	4a, nd	**6a**, < 5	**5a, 85**
OMe	-	-	**5b**, 76
CF_3	**4b**, nd	**6b**, 5	**5c**, 53
CN	**4c**, < 5	**6c**, 7	**5d**, <5

with T. Bortolato, G. Simionato, M. Vayer, C. Rosso, L. Paoloni, E. M. Benetti, A. Sartorel, D. Lebœuf, J. Am. Chem. Soc. **2023**, *145*, 1835–1846

From ET to proton-coupled electron transfer

- *Reductive dehalogenation*

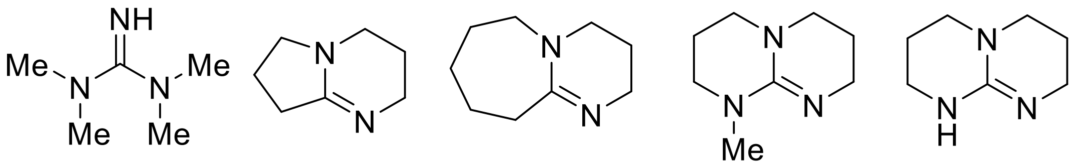
effect of the base on the PCET



E_{red} = - 2.08

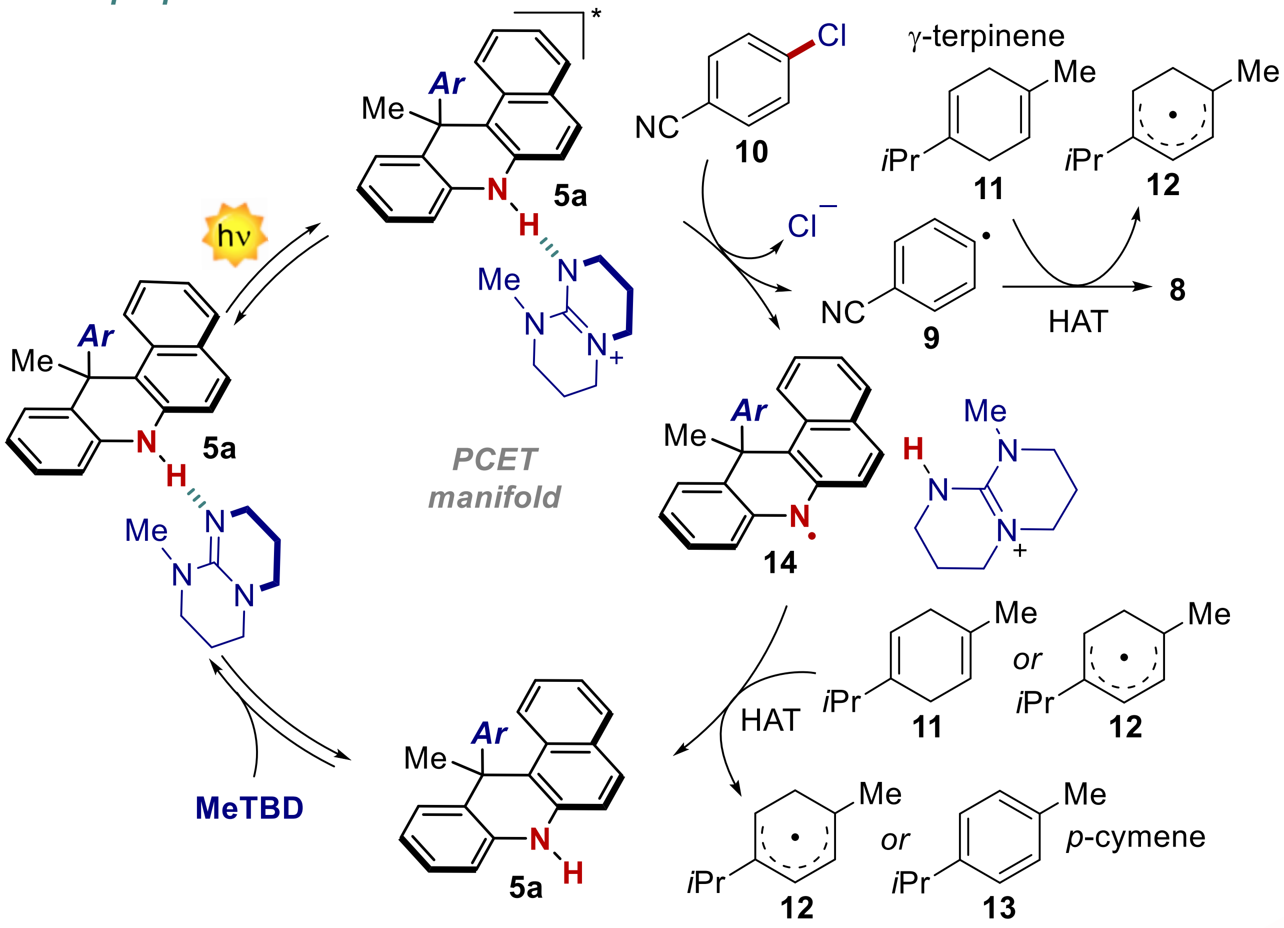
no reaction without base

base screening



	TMG	DBN	DBU	MeTBD	TBD*
pKa	23.4	23.4	23.9	***25.4***	26.0
yield (%)	16	18	16	***27***	21
yield (%) *with **11***	23	25	28	***40***	30

proposed reaction manifold



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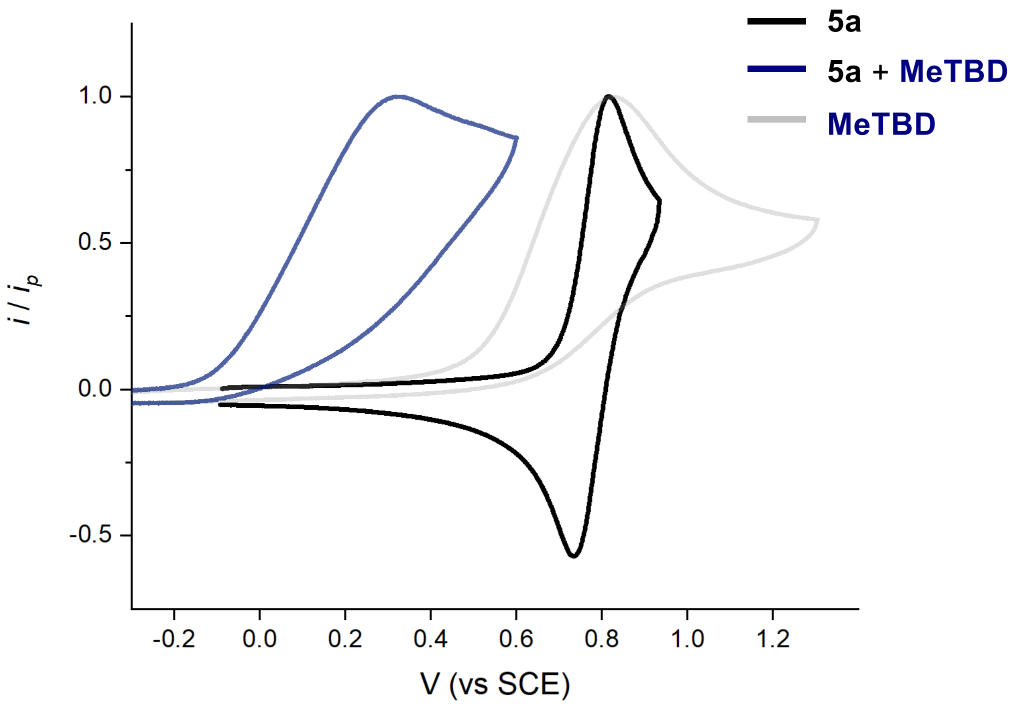
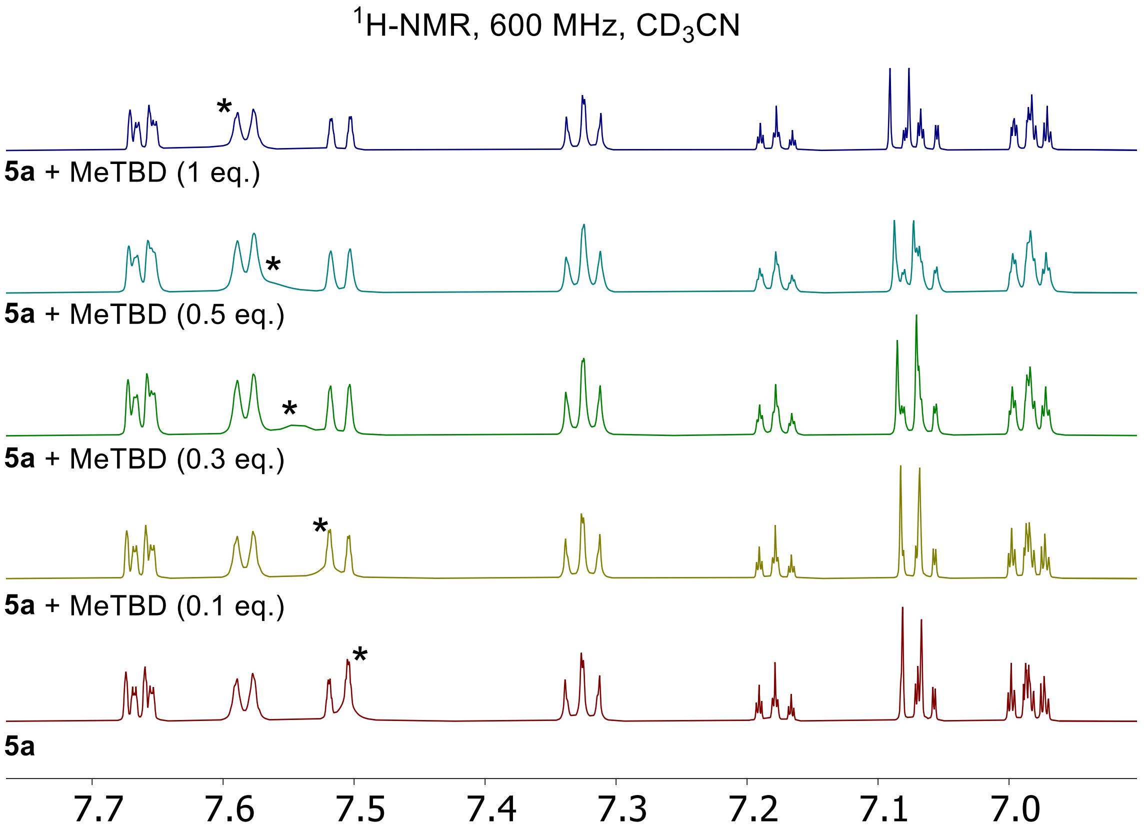
From ET to proton-coupled electron transfer

- Mechanistic investigation

cyclic voltammetry with and without base



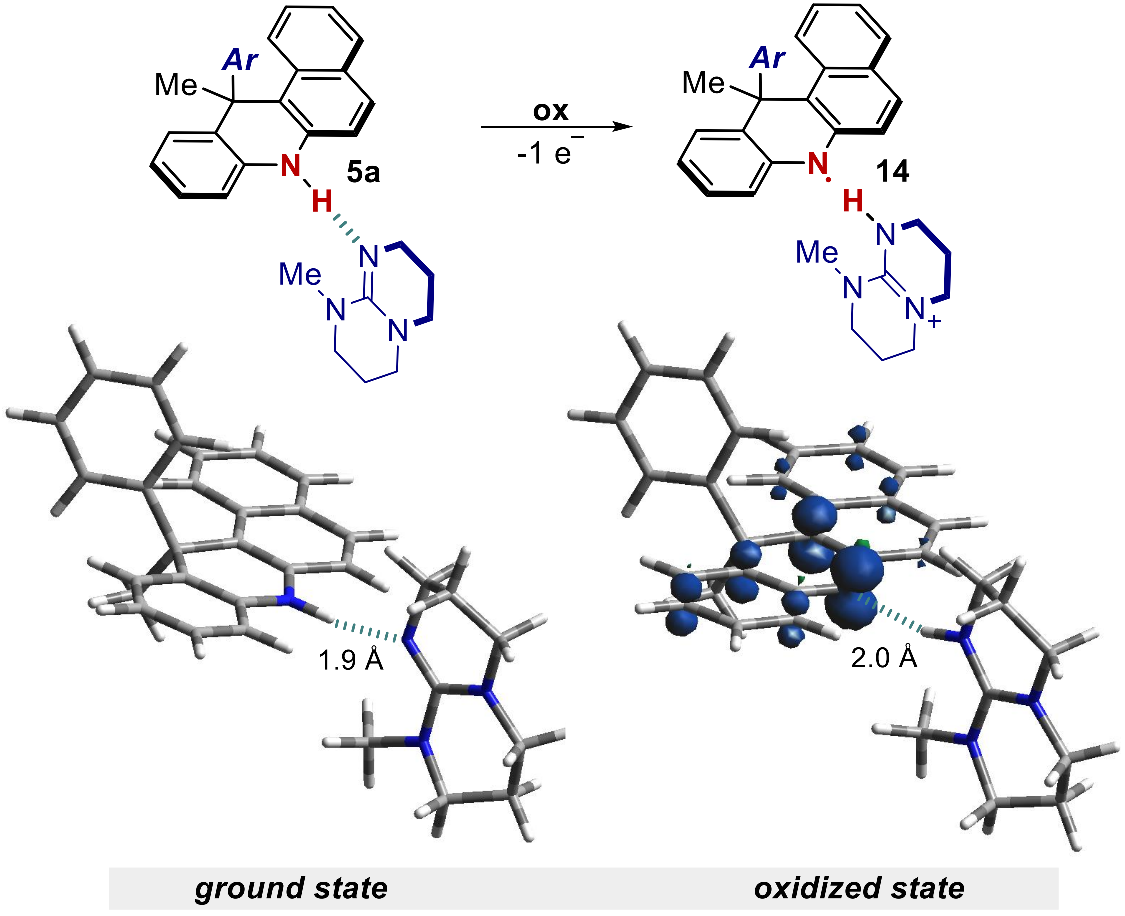
[1]H-NMR titration experiments

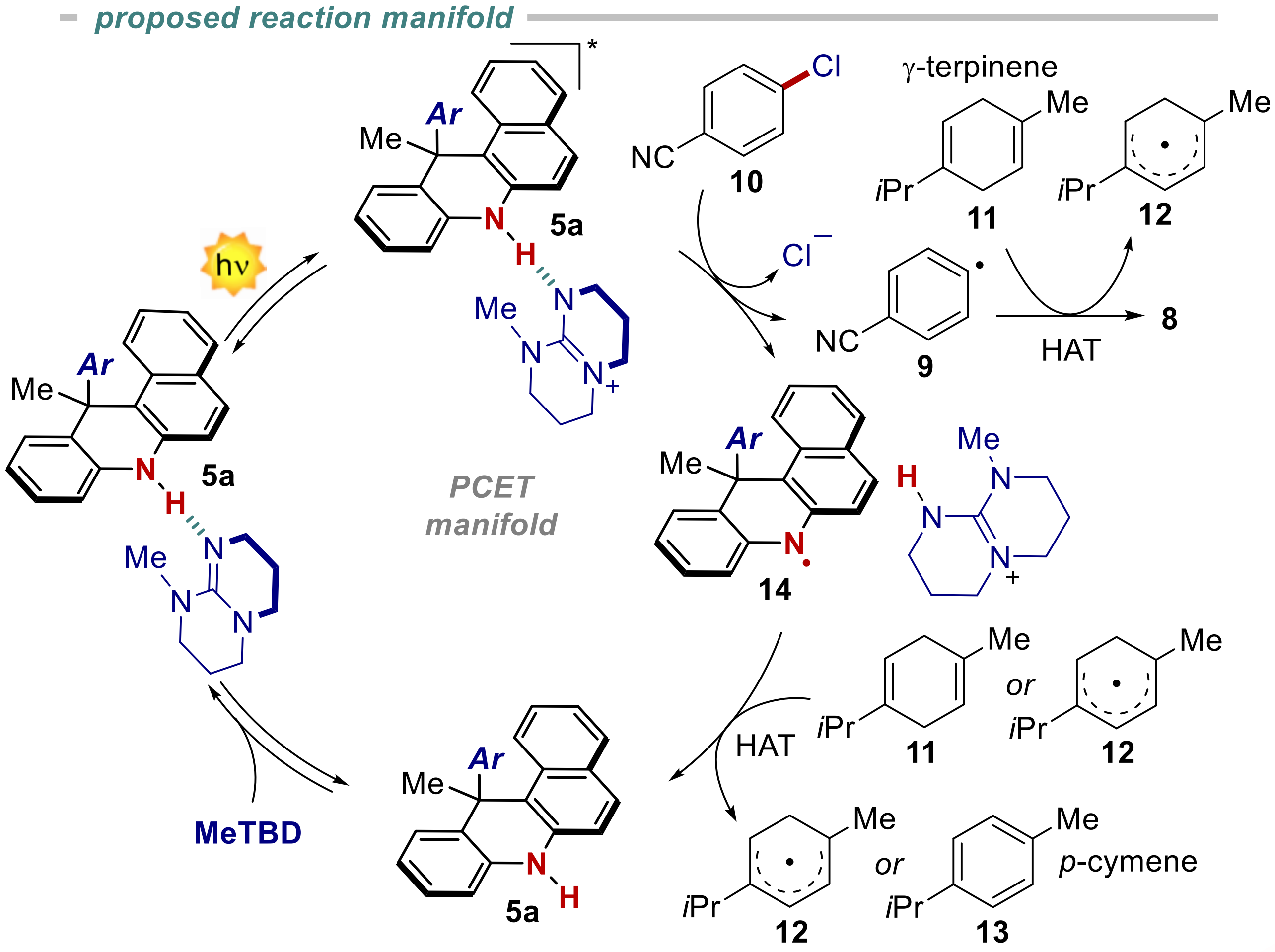


with T. Bortolato, G. Simionato, M. Vayer, C. Rosso, L. Paoloni, E. M. Benetti, A. Sartorel, D. Lebœuf, *J. Am. Chem. Soc.* **2023**, *145*, 1835–1846

From ET to proton-coupled electron transfer

- Mechanistic investigation

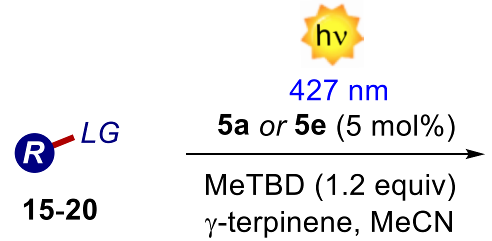


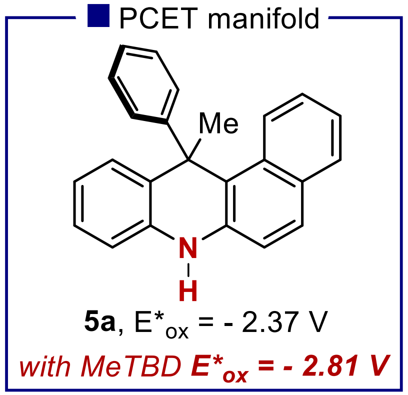


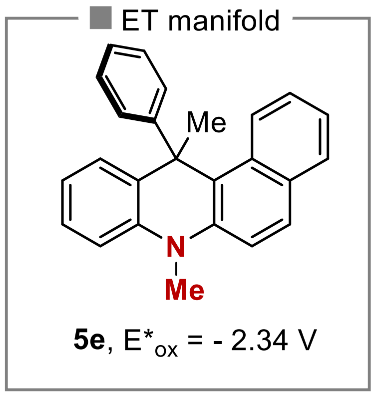
with T. Bortolato, G. Simionato, M. Vayer, C. Rosso, L. Paoloni, E. M. Benetti, A. Sartorel, D. Lebœuf, *J. Am. Chem. Soc.* **2023**, *145*, 1835–1846

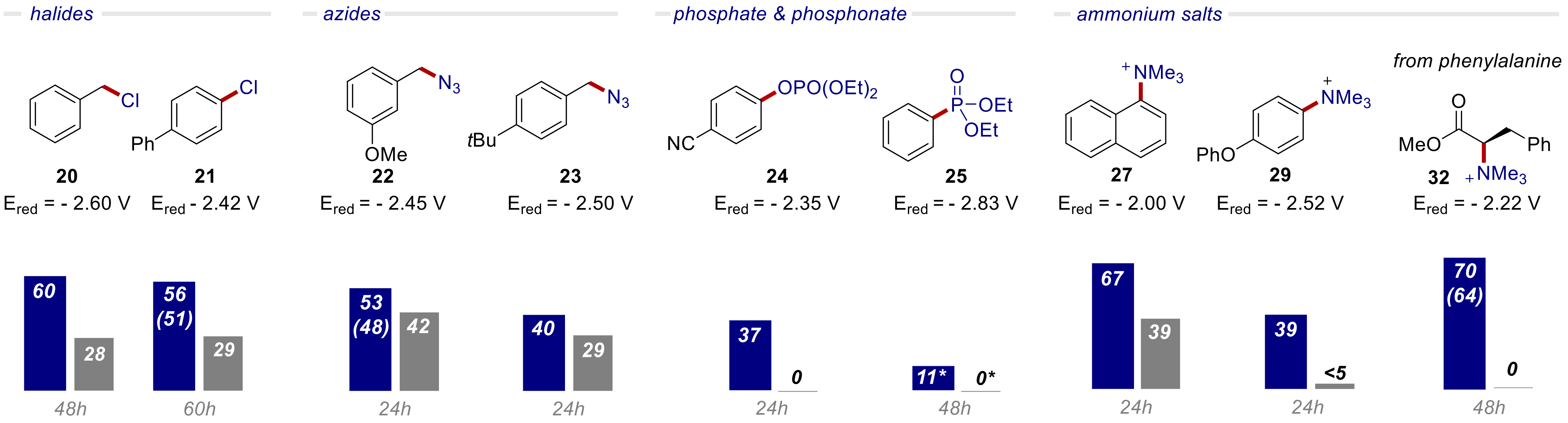
Why a proton-coupled electron transfer ?

- *Applications*







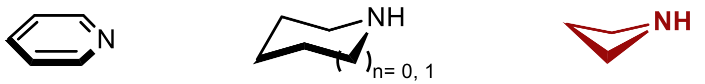


with T. Bortolato, G. Simionato, M. Vayer, C. Rosso, L. Paoloni, E. M. Benetti, A. Sartorel, D. Lebœuf, *J. Am. Chem. Soc.* **2023**, *145*, 1835–1846

How we can build azetidines

Examples of nitrogen-contating heterocycles

improved physicochemical properties →



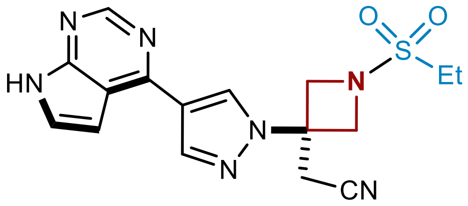
2D-shape
achiral

3D-shape
potentially chiral

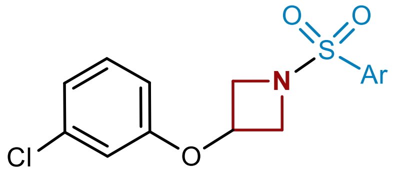
3D-shape
potentially chiral
ring strain

← current prevalence in approved drugs

Selected examples of drugs featuring the azetidine scaffold

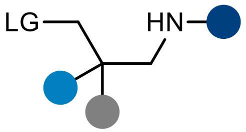


Baricitinib
JAK inhibitor

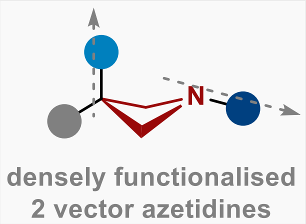


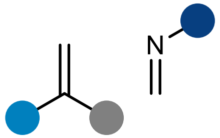
5-HT_{2c} agonist
piperidine analogue

Current methods for constructing the the azetidine scaffold

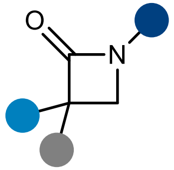


intramolecular
displacement

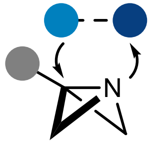




aza Paternò-Büchi

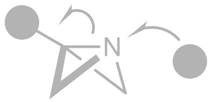


β-lactam reduction



polar
strain-release

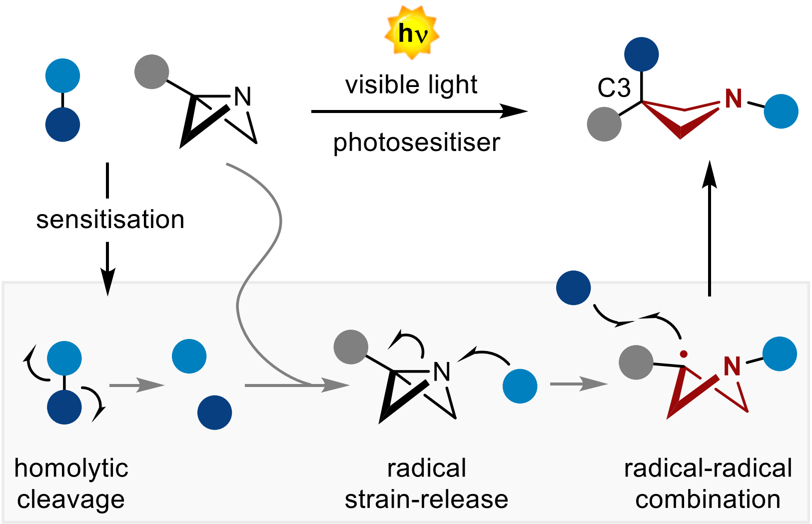
unknown



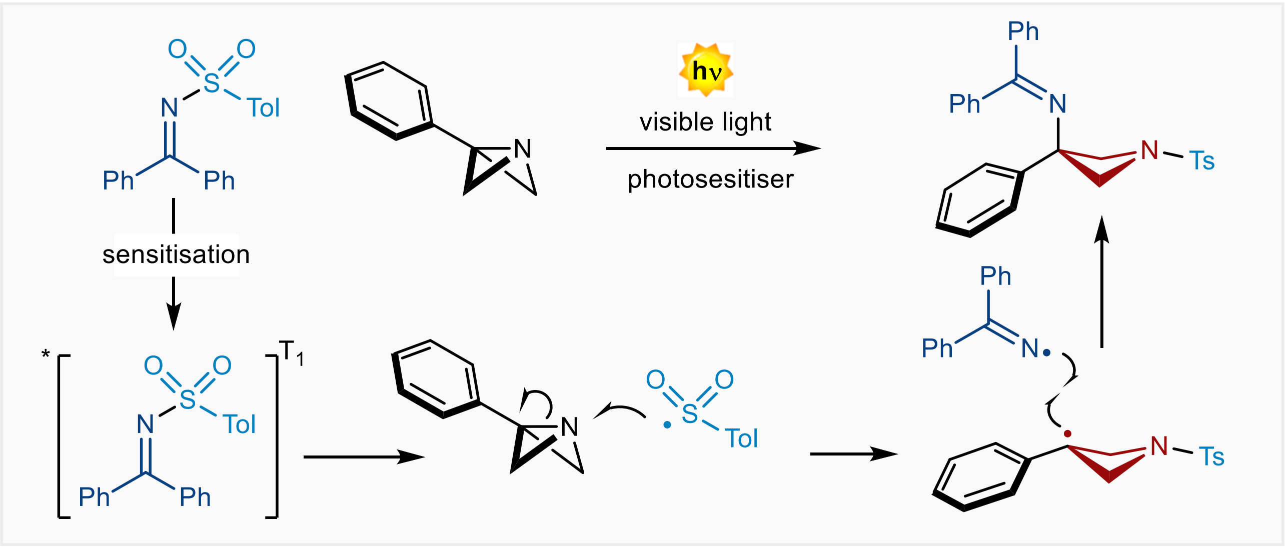
radical
strain-release

How we can build azetidines

- From the idea…to the reaction



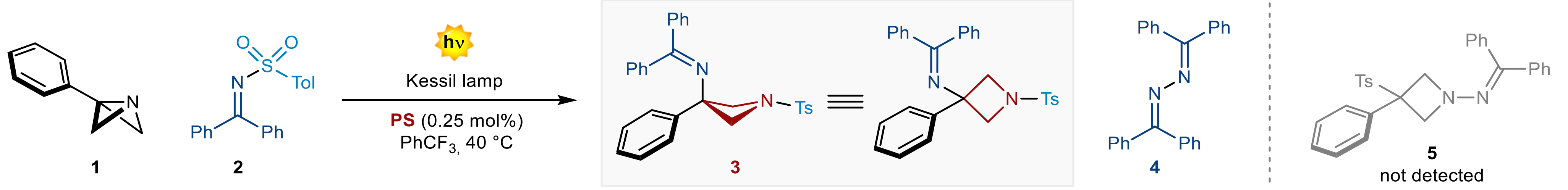
A radical strain release (RSR) approach mediated by visible light



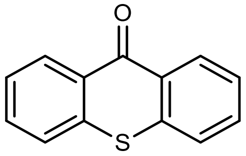
with R. I. Rodríguez, V. Corti, L. Rizzo, S. Visentini, M. Bortolus, A. Amati, M. Natali, G. Pelosi, P. Costa

Nat. Cat., **2024**, 10.1038/s41929-024-01206-4

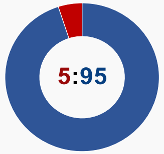
Optimisation process and design of the PC



Optimisation - selected results

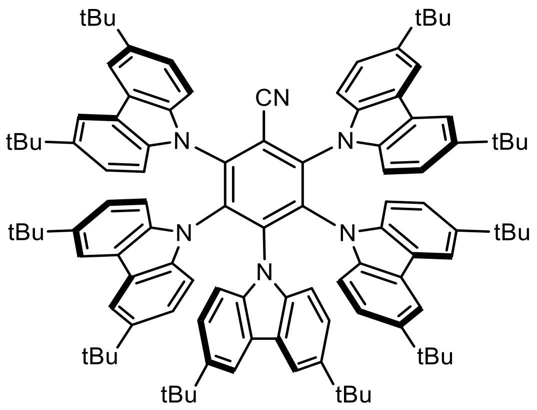


TXO, **6**
S_1 = 3.38 eV
T_1 = 2.88
ΔST = 0.5 eV

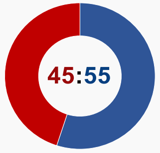


@ 427 nm
3, yield = 10%

selectivity
3 : 4

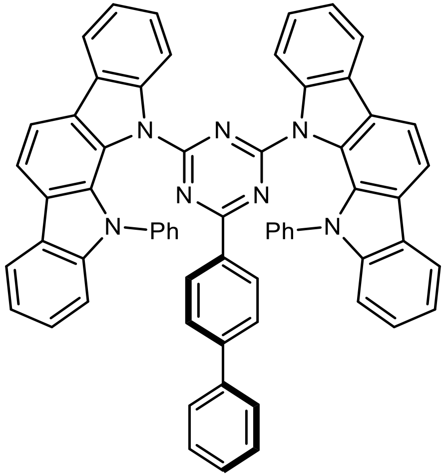


5TCzBN, **7**
S_1 = 2.77 eV
T_1 = 2.60 eV
ΔST = 0.17 eV

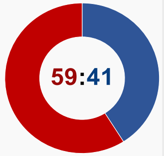


@ 456 nm
3, yield = 51%

selectivity
3 : 4

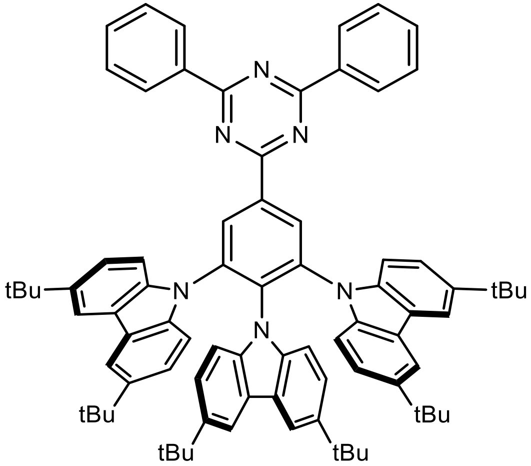


PIC-TRZ, **8**
S_1 = 2.66 eV
T_1 = 2.55 eV
ΔST = 0.11 eV

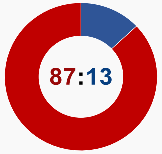


@ 427 nm
3, yield = 32%

selectivity
3 : 4



TBCzTrz, **9**
S_1 = 2.79 eV
T_1 = 2.74 eV
ΔST = 0.05 eV



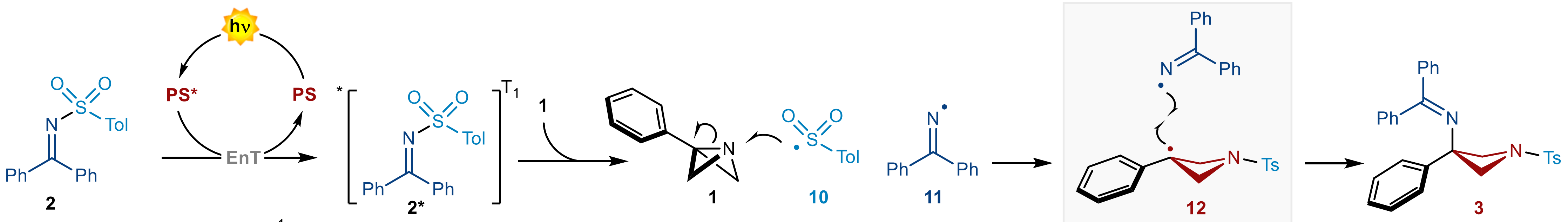
@ 456 nm
3, yield = 79%

selectivity
3 : 4

with R. I. Rodríguez, V. Corti, L. Rizzo, S. Visentini, M. Bortolus, A. Amati, M. Natali, G. Pelosi, P. Costa
Nat. Cat., **2024**, 10.1038/s41929-024-01206-4

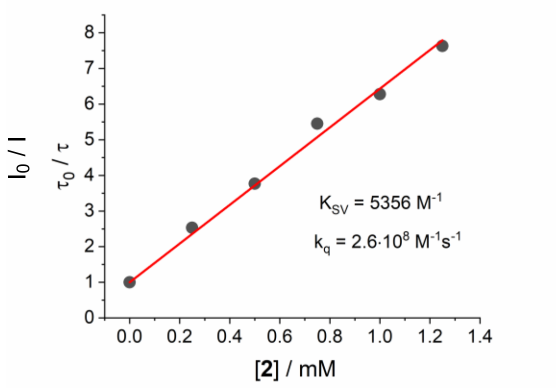
The mechanism

- Insights from the laser flash photolysis

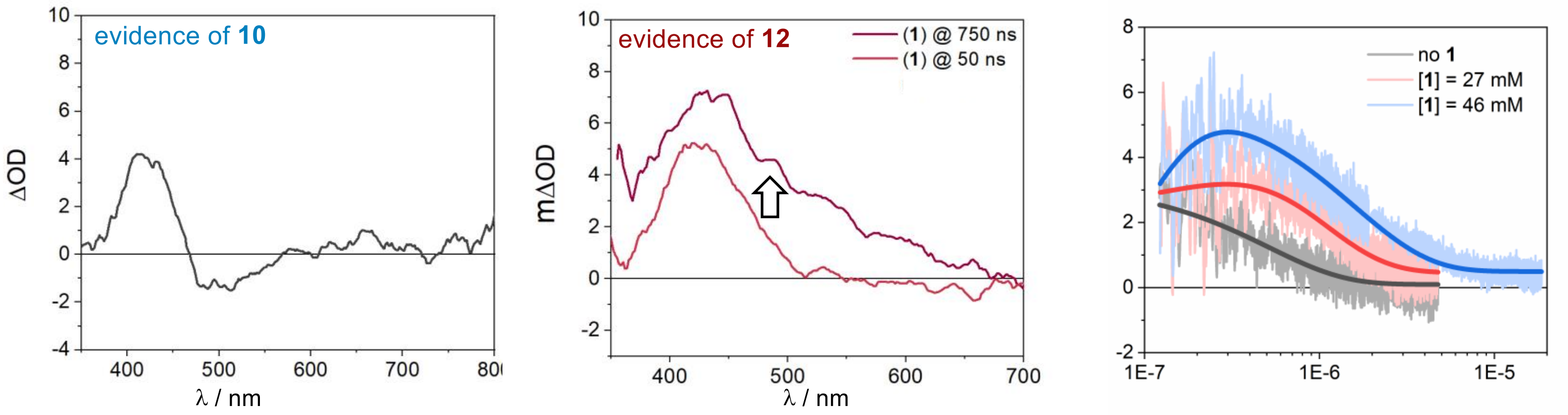


E_T = 2.43 eV (exp. 56.0 kcal mol^{-1})
(calc. 56.1 kcal mol^{-1})

b) Stern-Volmer quenching



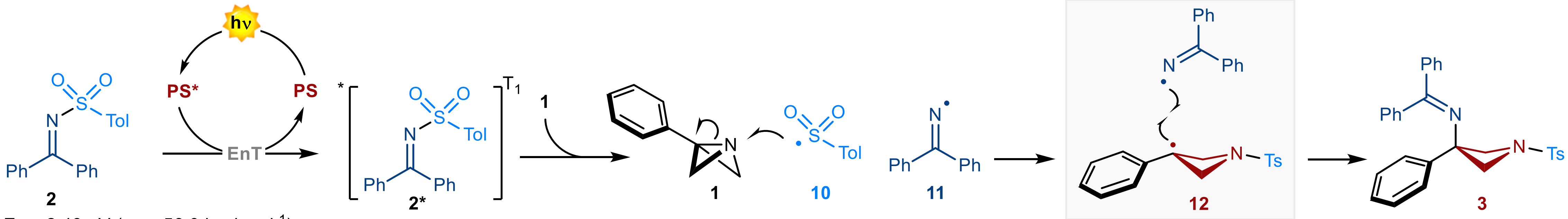
c) Laser flash photolysis (LFP)



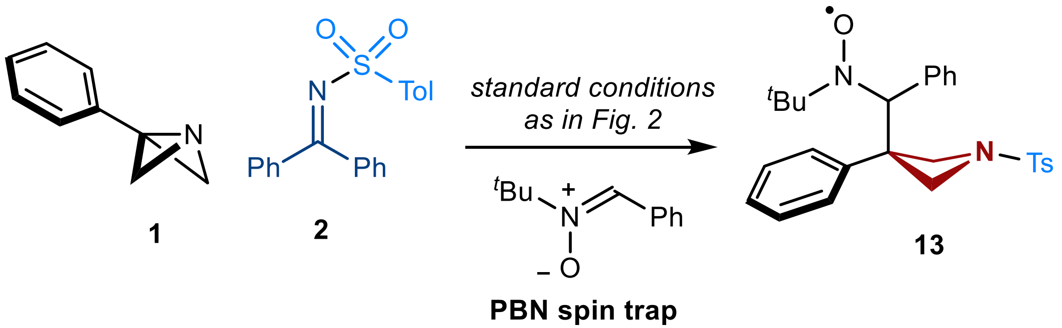
with R. I. Rodríguez, V. Corti, L. Rizzo, S. Visentini, M. Bortolus, A. Amati, M. Natali, G. Pelosi, P. Costa
Nat. Cat., **2024**, 10.1038/s41929-024-01206-4

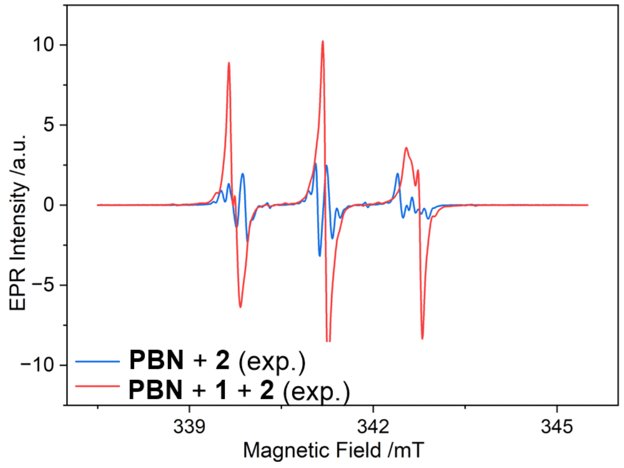
The mechanism

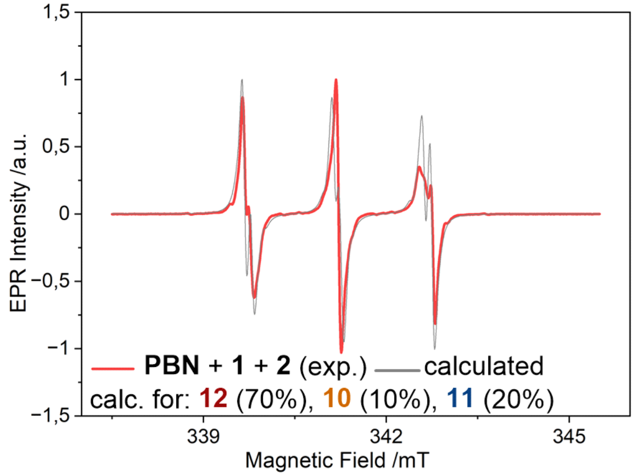
- *Insights from the EPR experiments*



E_T = 2.43 eV (exp. 56.0 kcal mol^{-1})
(calc. 56.1 kcal mol^{-1})





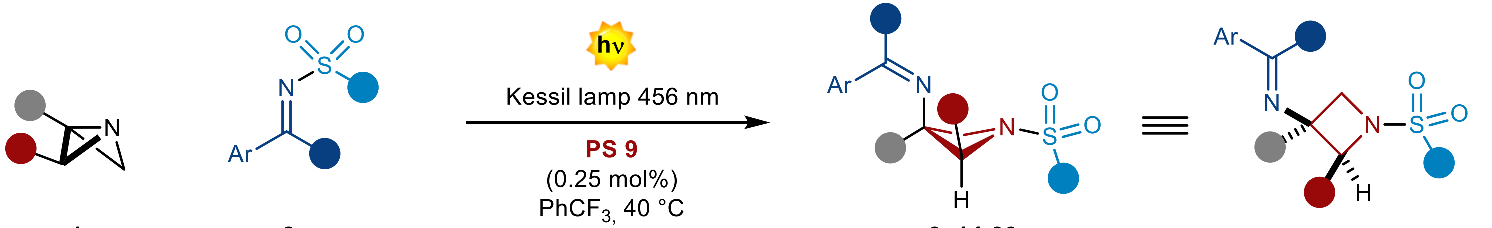


with R. I. Rodríguez, V. Corti, L. Rizzo, S. Visentini, M. Bortolus, A. Amati, M. Natali, G. Pelosi, P. Costa

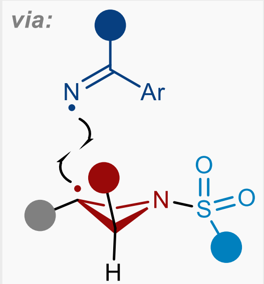
Nat. Cat., **2024**, 10.1038/s41929-024-01206-4

Generality of the process

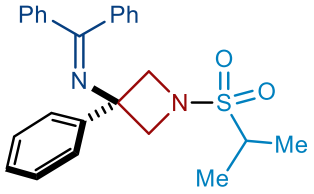
- *Selected examples*



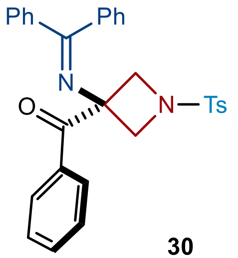
1 2 3, 14-39



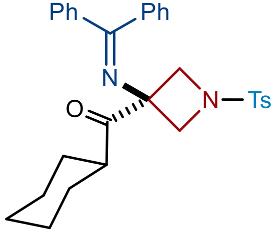
Generality of the process



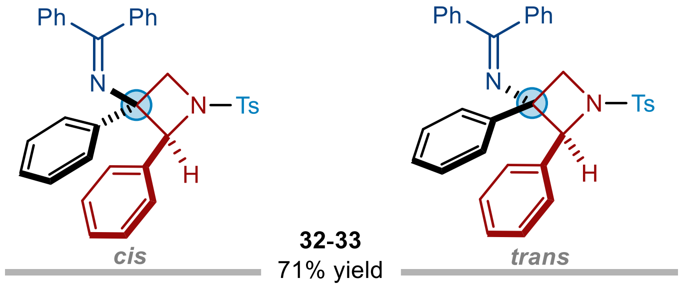
27
67% yield



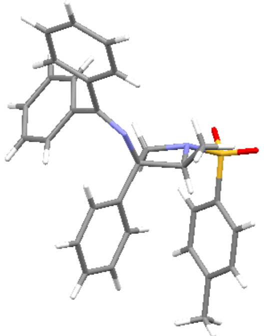
30
72% yield*



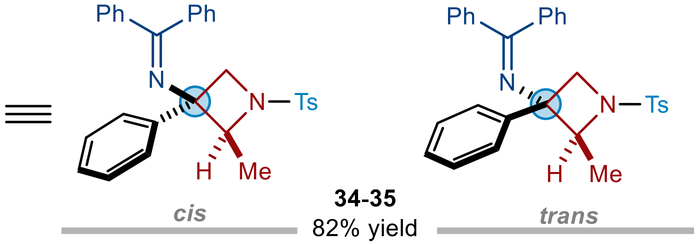
31
61% yield*



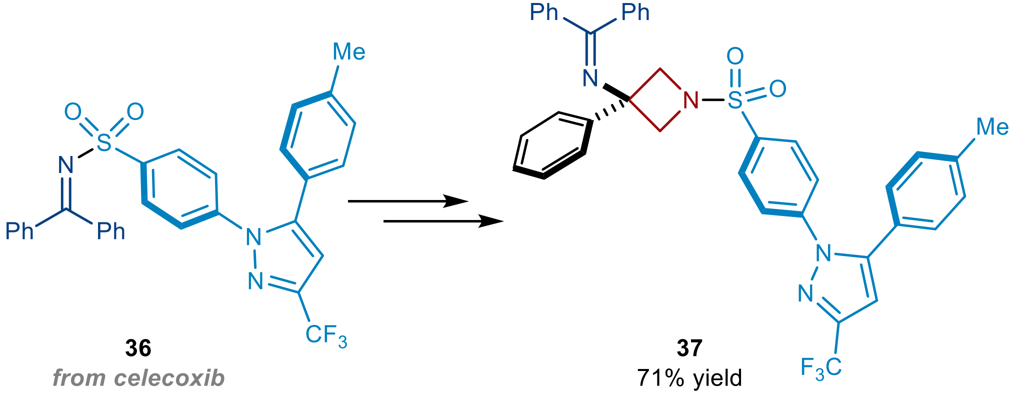
32-33
71% yield
2.3:1 dr



CSD 2305657



34-35
82% yield
1:1 dr

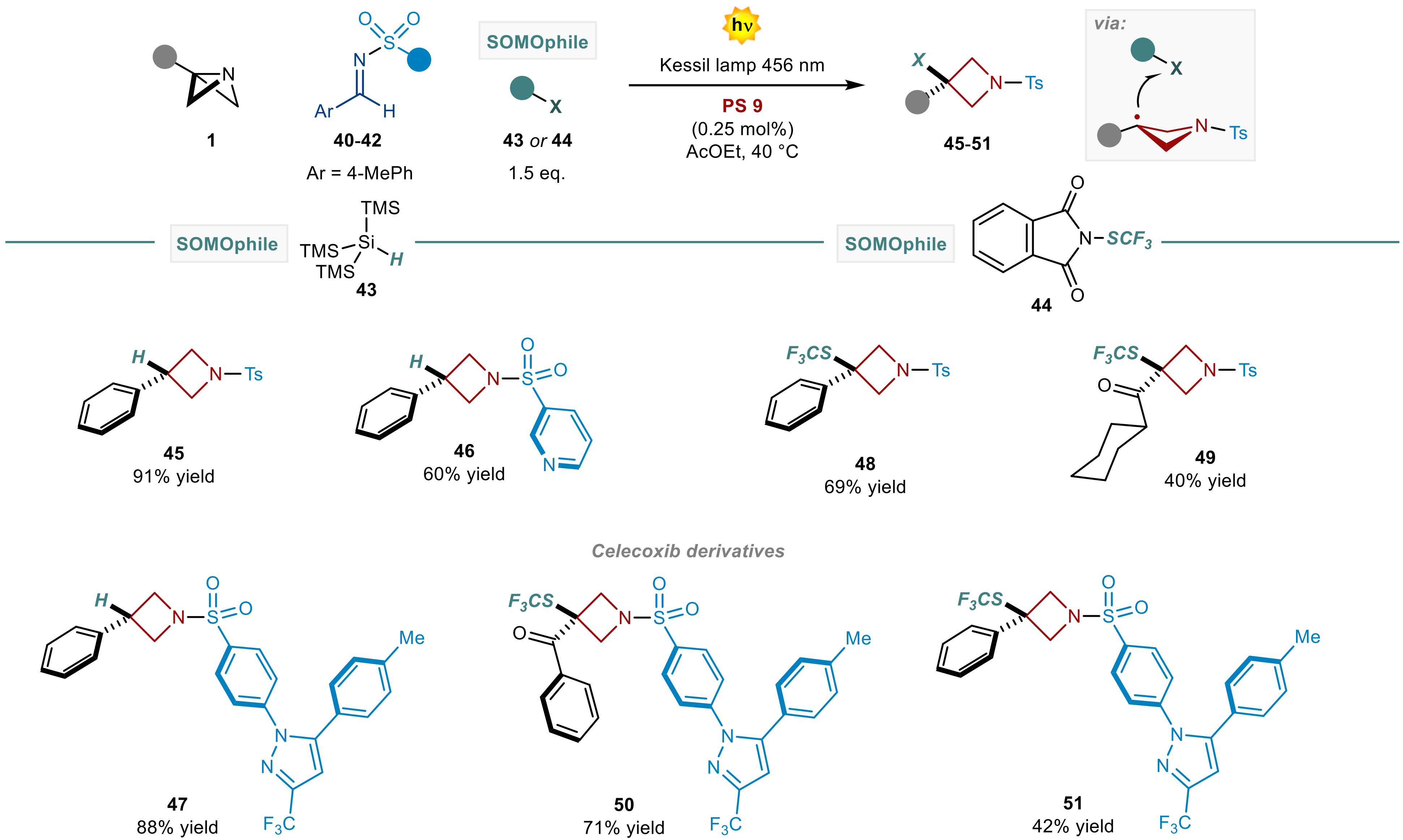


36
from celecoxib

37
71% yield

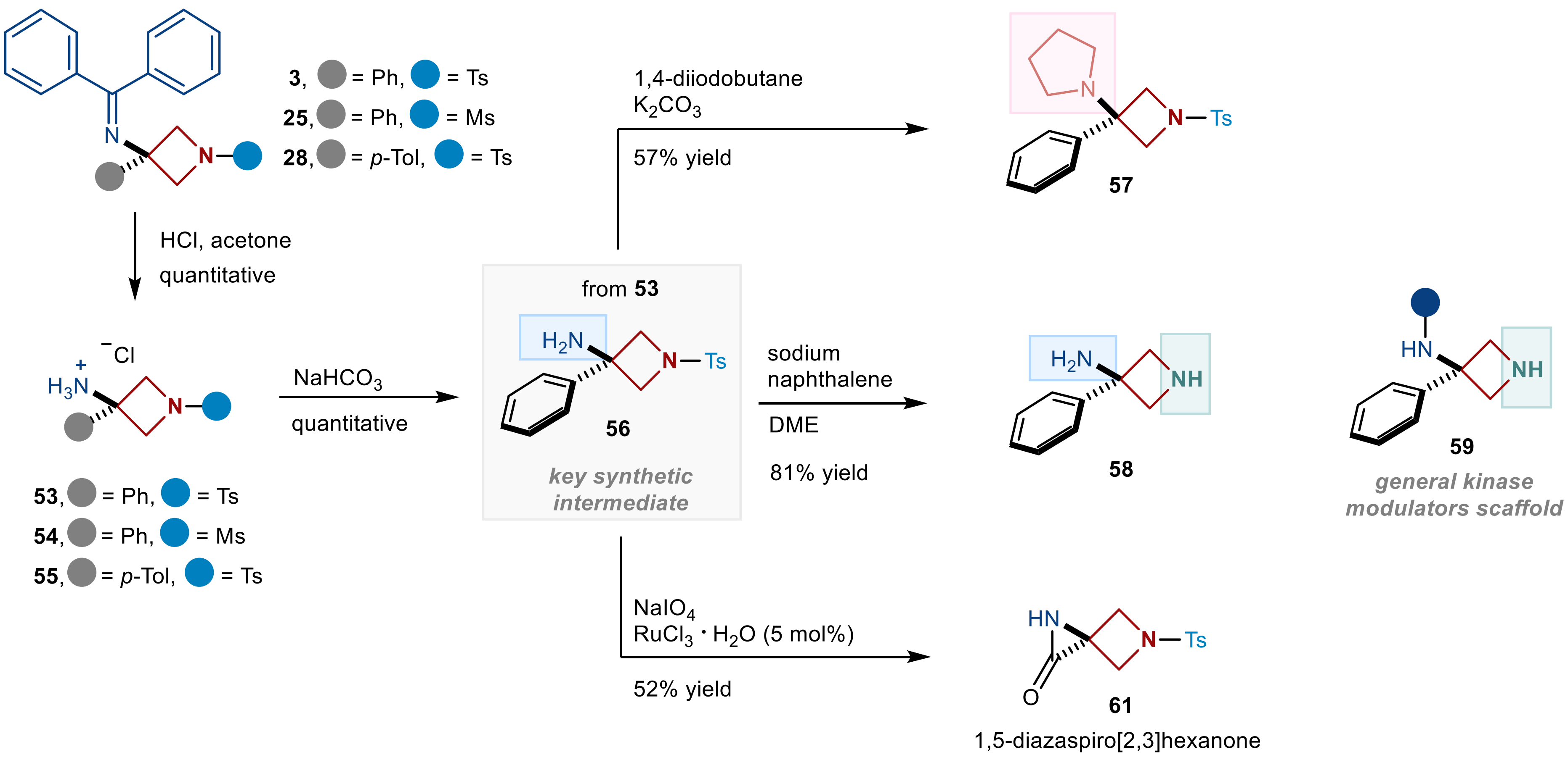
with R. I. Rodríguez, V. Corti, L. Rizzo, S. Visentini, M. Bortolus, A. Amati, M. Natali, G. Pelosi, P. Costa
Nat. Cat., **2024**, 10.1038/s41929-024-01206-4

Extending the reactivity



with R. I. Rodríguez, V. Corti, L. Rizzo, S. Visentini, M. Bortolus, A. Amati, M. Natali, G. Pelosi, P. Costa
ChemRxiv **2024**, 10.26434/chemrxiv-2024-f5g9p

Synthetic usefulness of the products

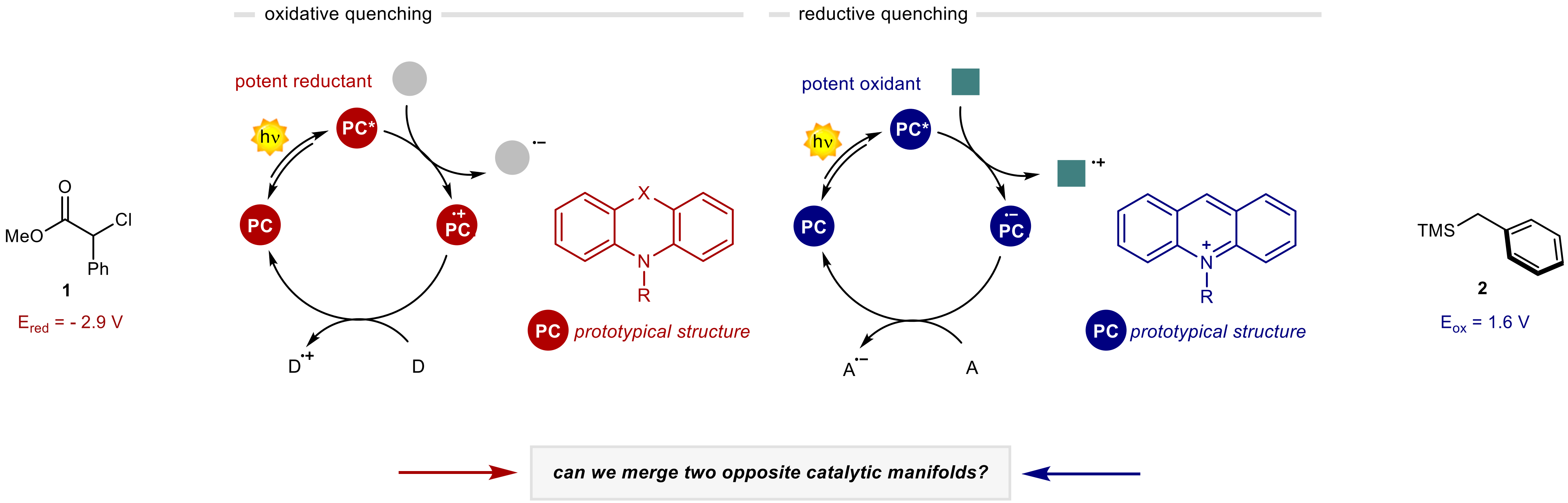


with R. I. Rodríguez, V. Corti, L. Rizzo, S. Visentini, M. Bortolus, A. Amati, M. Natali, G. Pelosi, P. Costa

Nat. Cat., **2024**, 10.1038/s41929-024-01206-4

State of the art in photoredox catalysis

- *How can we activate two opposite redox cycles at once?*



with C. Rosso, G. Barison, N. Michelazzo, A. Sartorel, P. Costa, M. Natali. Submitted

1222 · 2022

800 ANNI

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@ University of Ferrara

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Prof. Andrea Sartorel
computational support

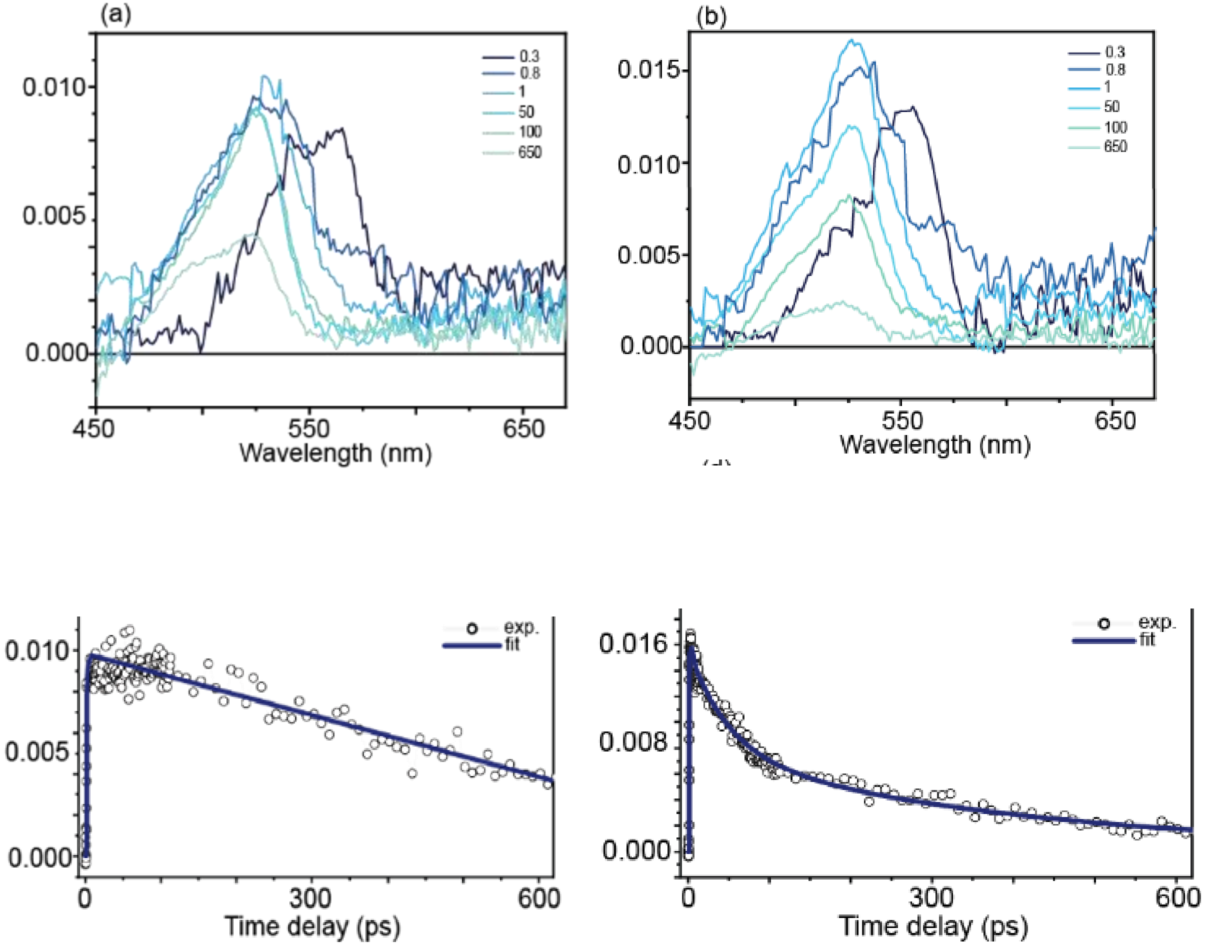
Javier Mateos
Sara Cuadros
Tommaso Bortolato
Cristian Rosso
Gianluca Simionato
Ricardo Rodriguez
Vasco Corti
Giorgia Barison

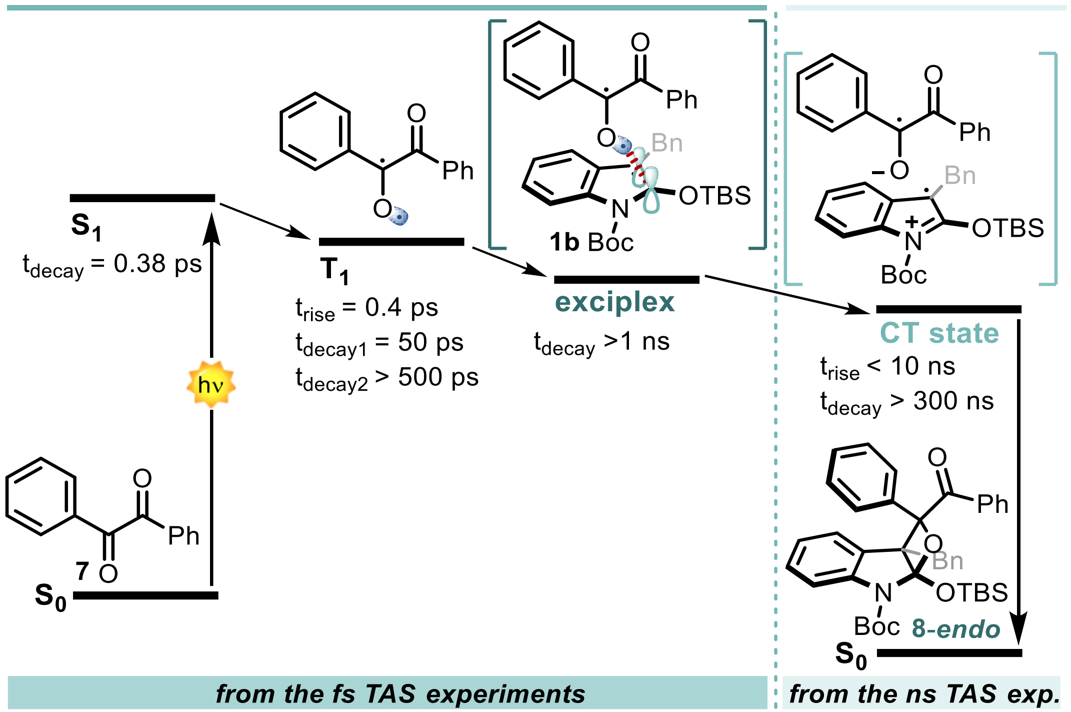
European Research Council
MARIE CURIE ACTIONS
MINISTERO DELL' ISTRUZIONE, DELL'UNIVERSITÀ E DELLA RICERCA
DiSC Department of Chemical Sciences

Thank you for your kind attention!

Identification of the exciplex intermediate

- *TAS at fs analysis*

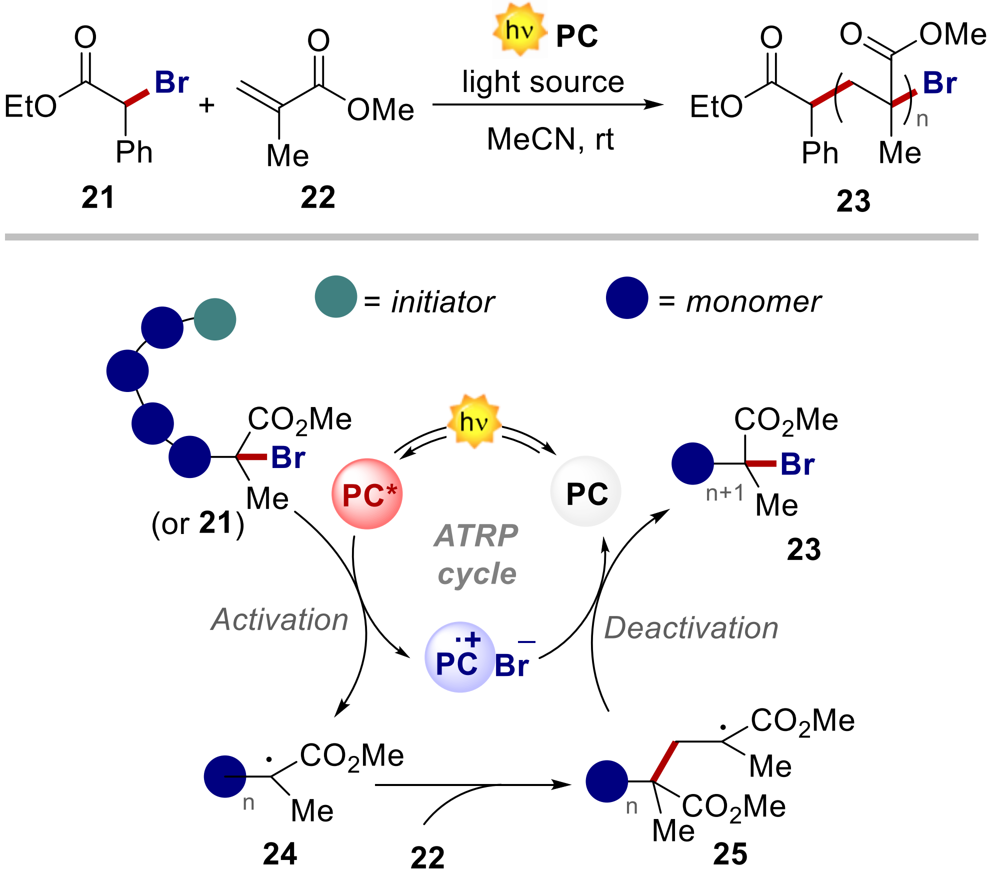




with Mateos, J., Vega-Peñaloza, A., Rigodanza, F., Costa P., Bonchio, M., Sartorel, A., Natali, M.
Nat. Synth. **2023**, *2*, 26–36

From PCET to ATRP with the same PC

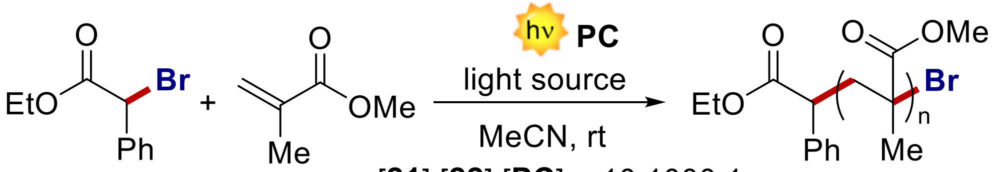
- *Atom transfer radical polymerization*



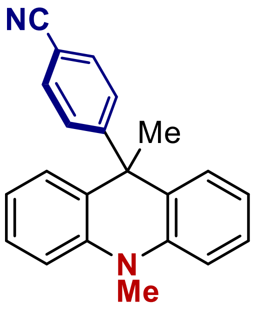
Manuscript under review

From PCET to ATRP with the same PC

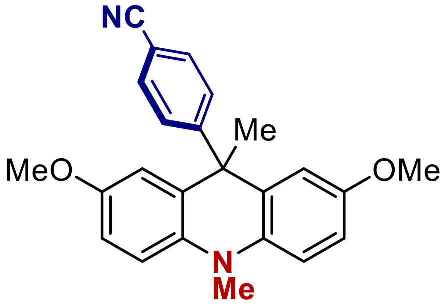
- *Atom transfer radical polymerization*



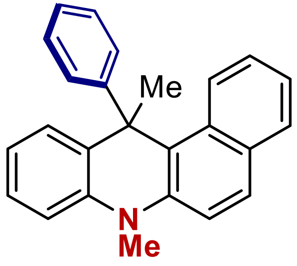
21 22 23



4d



6d

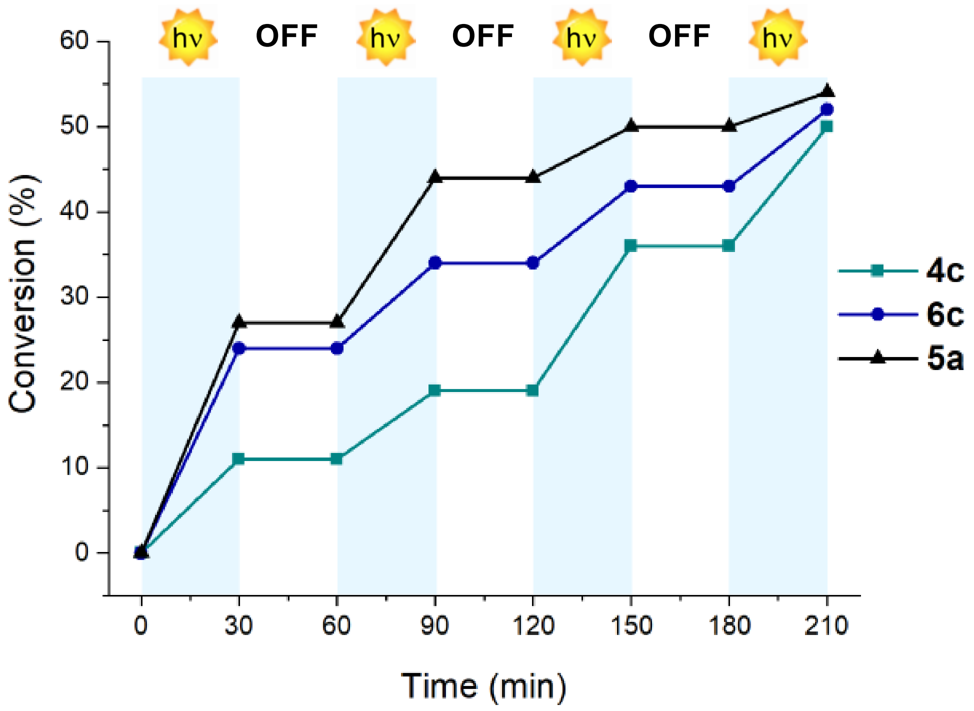


5e

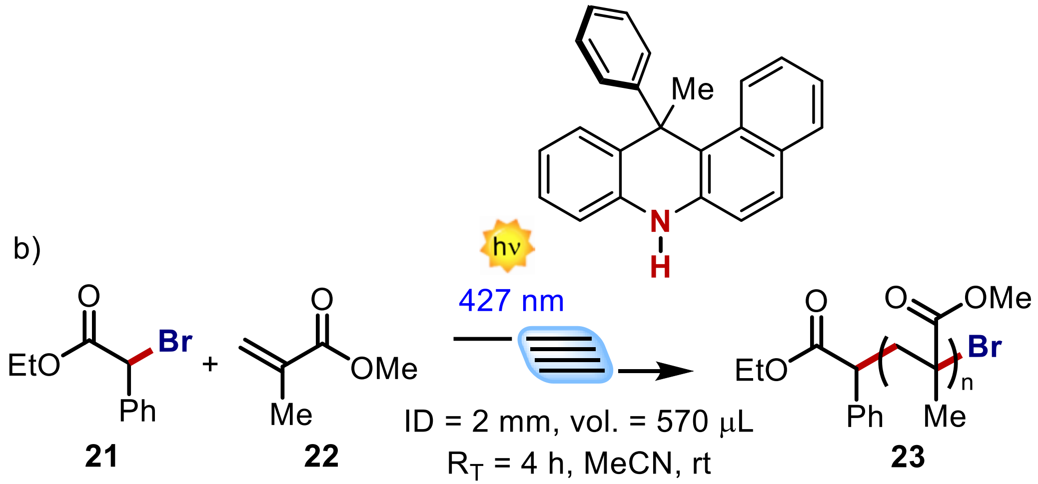
Entry	PC	Wavelength (nm)	Polymerization time (h)	Conversion (%)	M_w (kDa)	M_n (kDa)	Đ (M_w/M_n)	I* (%)
1	4a	390	9	>98	19.8	12.6	1.59	78
2	4b	390	7	85	18.7	13.4	1.40	63
3	4c	390	2	95	13.1	8.4	1.56	113
4	4c	400	4	98	18.5	13.9	**1.33**	70
5	6a	390	2	84	12.1	8.6	1.41	**98**
6	6b	390	2	76	13.8	9.6	1.43	79
7	6c	390	2	86	13.2	9.0	1.46	**96**
8	6c	400	4	81	17.4	12.6	**1.38**	64
9	5a	427	6	86	10.8	6.9	1.52	124
10	5b	427	6	81	25.8	13.2	1.96	61
11	5c	427	6	>98	13.1	8.2	1.57	119
12	5d	427	6	>98	12.4	8.0	1.55	122
13	4d	400	4	76	19.8	13.1	1.51	58
14	6d	400	4	91	16.3	12.2	1.34	74
15	5e	427	6	>98	16.2	12.2	1.44	80

From PCET to ATRP with the same PC

- Atom transfer radical polymerization



b)



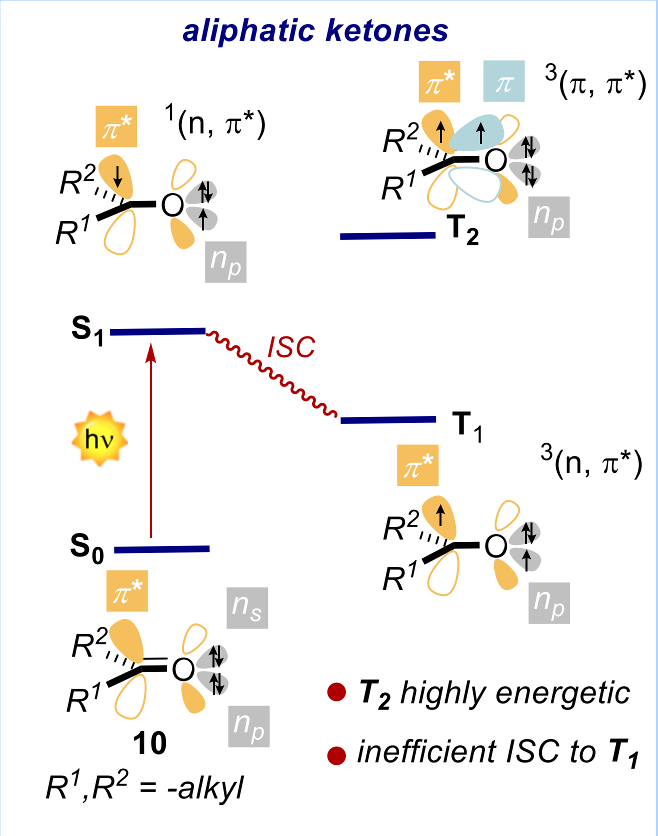
monomer MMA, 28.2 mmol

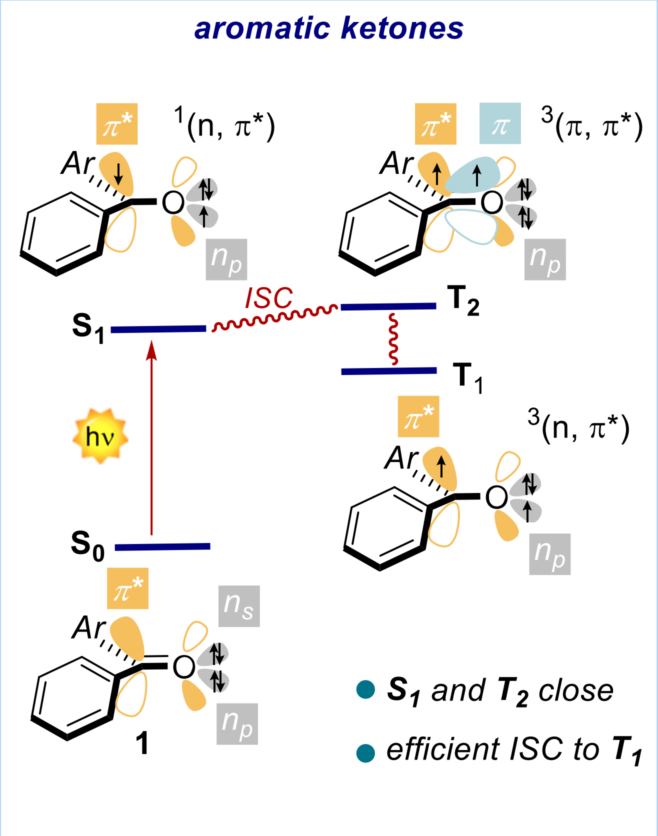
Conv. (%) = 86
M_w = 15.8
M_n = 19.1
$Đ$ = 1.21
I* (%) = 54

Manuscript under review

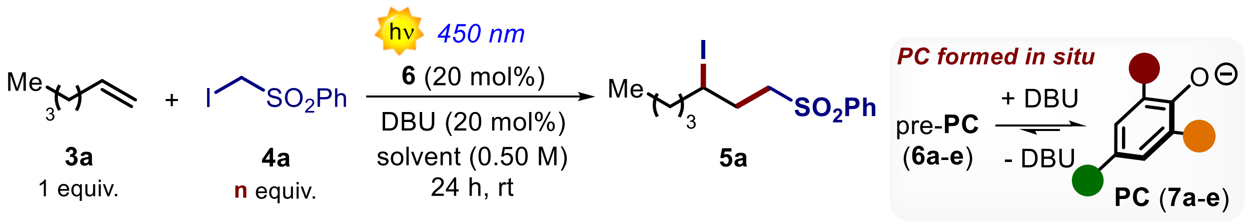
Shining Light on Aryl Ketones

- Why aryl ketones?

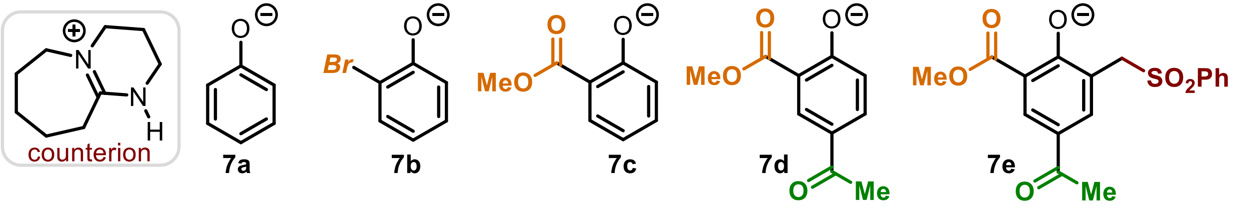




For a pertinent paper see: Mateos, J., Cuadros, S., Vega-Peñaloza, A., Dell'Amico, L. *Synlett* **2021**, doi: 10.1055/a-1403-4613, and *Angew. Chem. Int. Ed.* **2021**, *60*, 1082–1097



(a) phenolate PC screening

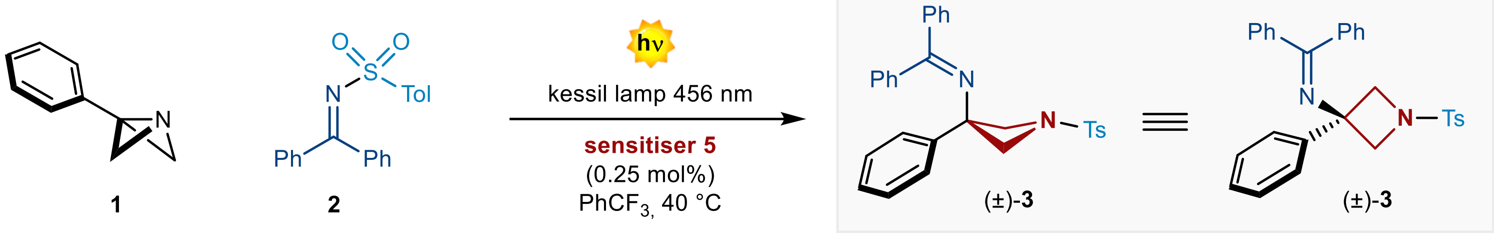


	7a	7b	7c	7d	7e
$\lambda_{0,0}$	277 nm	258 nm	312 nm	372 nm	***378 nm***
$E_{0,0}$	4.48 V	4.81 V	3.97 V	3.33 V	***3.28 V***
E_{ox}	+ 0.30 V	+ 0.34 V	+ 0.50 V	+ 0.65 V	***+ 0.74 V***
E^{*}_{ox}	- 4.18 V	- 4.47 V	- 3.47 V	- 2.68 V	***- 2.54 V***
yield (5a)[b]	47%	56%	52%	53%	***85%***
residual (6)[b]	35%	87%	<5%	85%	***>99%***

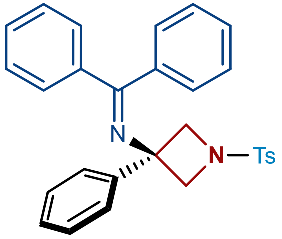
(b) optimization of the reaction conditions

entry[a]	***4a** (equiv.)*	*solvent*	*additives and conditions*	*yield % (5a)*[b]	*residual % (6)*[b]
1	1.0	MeCN	-	85%	>99%
2	1.5	MeCN/H_2O (3:1)	NaAsc (25 mol%)	>99%	>99%
3	1.5	MeCN/H_2O (3:1)	NaAsc (25 mol%) *in the dark*	0%	>99%
4	1.5	MeCN/H_2O (3:1)	NaAsc (25 mol%) *without* **6e** *and* DBU	8%	>99%
5	***1.5***	***MeCN/H_2O (3:1)***	***NaAsc (25 mol%) 8 h***	***>99%***	***>99%***

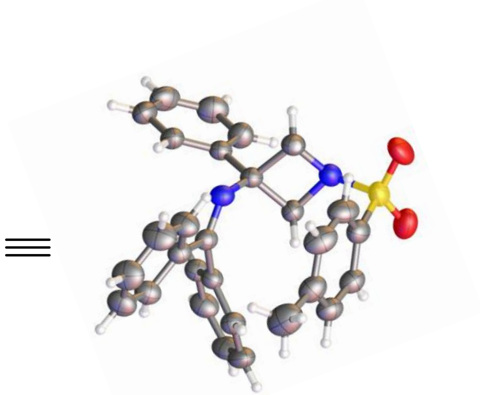
An energy-transfer strategy to aziridine

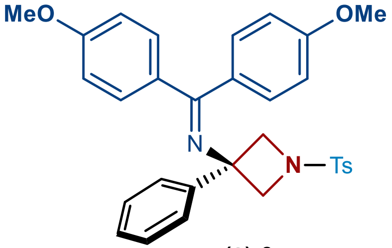


reaction scope - selected results

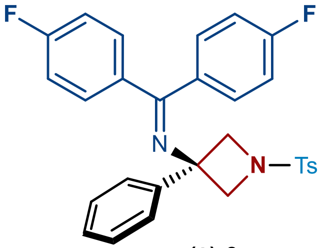


(±)-3
71% yield

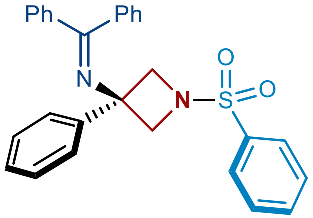




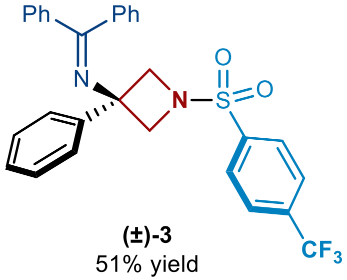
(±)-3
70% yield



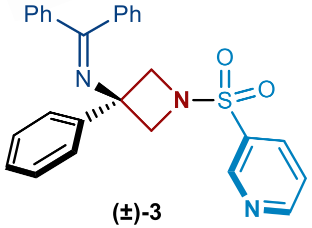
(±)-3
44% yield



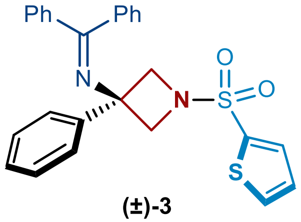
(±)-3
60% yield



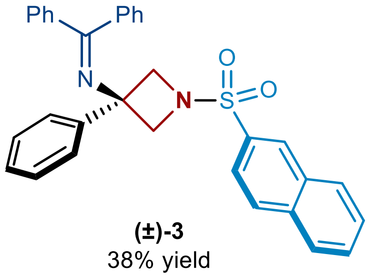
(±)-3
51% yield



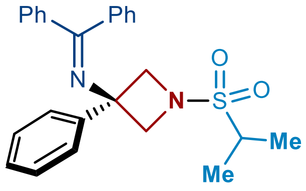
(±)-3
71% yield



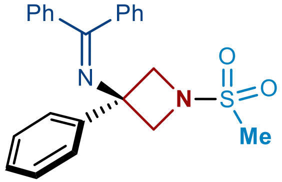
(±)-3
52% yield



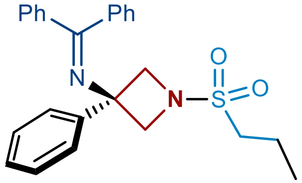
(±)-3
38% yield



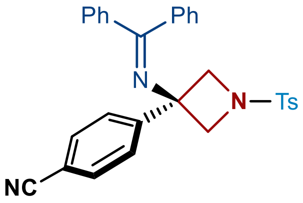
(±)-3
67% yield



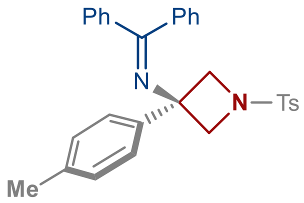
(±)-3
45% yield



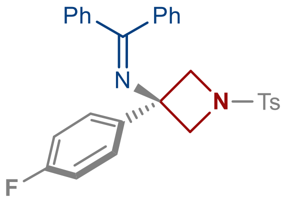
(±)-3
67% yield



(±)-3
71% yield



(±)-3
71% yield



(±)-3
71% yield