Light Synthesis of Azetidines

nature catalysis

Article https://doi.org/10.1038/s41929-024-01206-4

Radical strain-release photocatalysis for the synthesis of azetidines

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

ORGANIC CHEMISTRY

Visible light–mediated aza Paternò–Büchi reaction of acyclic oximes and alkenes to azetidines

Emily R. Wearing[1], Yu-Cheng Yeh[1], Gianmarco G. Terrones[2]†, Seren G. Parikh[1]†, Ilia Kevlishvili[2], Heather J. Kulik[2,3]*, Corinna S. Schindler[1,4,5,6]*

The aza Paternò–Büchi reaction is a [2+2]-cycloaddition reaction between imines and alkenes that produces azetidines, four-membered nitrogen-containing heterocycles. Currently, successful examples rely primarily on either intramolecular variants or cyclic imine equivalents. To unlock the full synthetic potential of aza Paternò–Büchi reactions, it is essential to extend the reaction to acyclic imine equivalents. Here, we report that matching of the frontier molecular orbital energies of alkenes with those of acyclic oximes enables visible light–mediated aza Paternò–Büchi reactions through triplet energy transfer catalysis. The utility of this reaction is further showcased in the synthesis of *epi*-penaresidin B. Density functional theory computations reveal that a competition between the desired [2+2]-cycloaddition and alkene dimerization determines the success of the reaction. Frontier orbital energy matching between the reactive components lowers transition-state energy ($\Delta G^{\ddagger}$) values and ultimately promotes reactivity.

Science **2024**, 1468

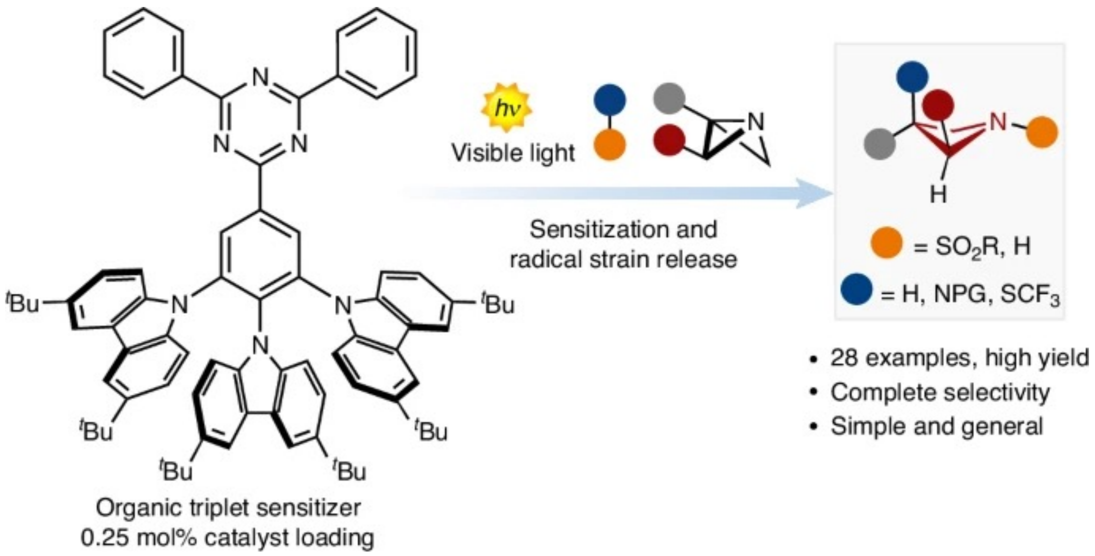
Scripps Research

Shenvi Laboratory

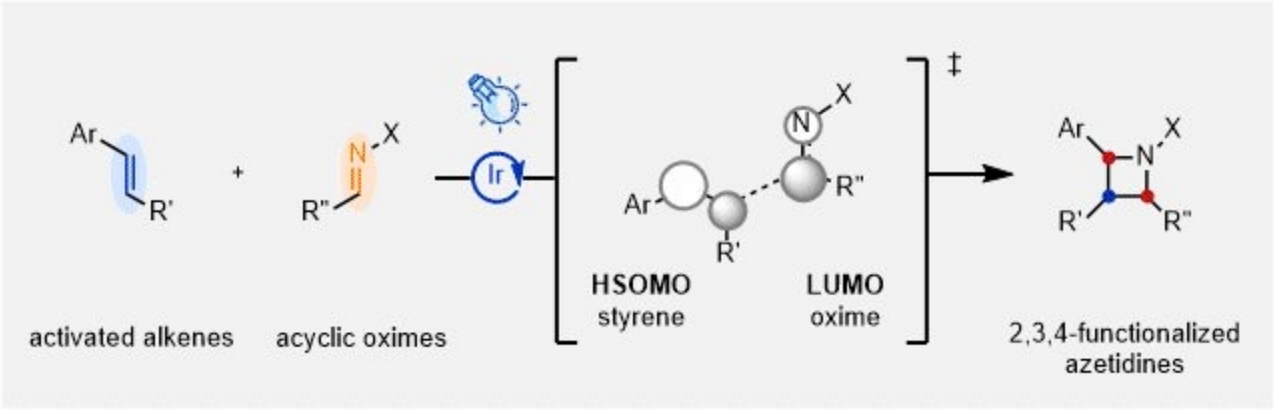
Juan Rojas

GM 19th Oct 2024

The Papers



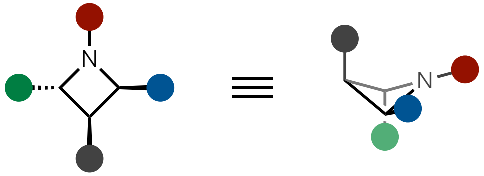
Nat. Catal. 2024, 10.1038/s41929-024-01206-4



Science 2024, 1468

Why bother about azetidines?

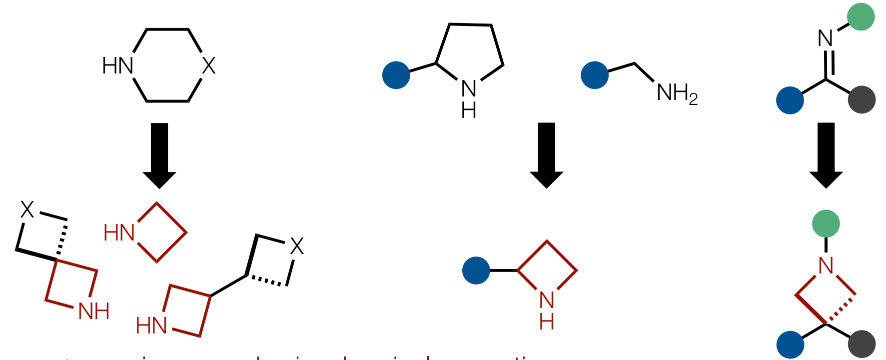
New motifs for drug discovery



- polar, low MW
- 3-dimensional
- defined vectors
- stable

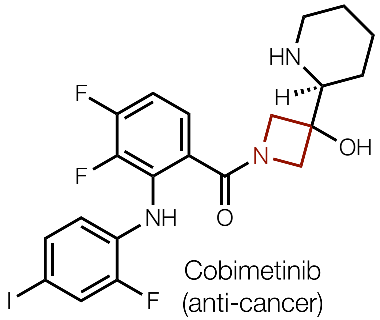
➡ can improve physicochemical properties

Potential as bioisosteres

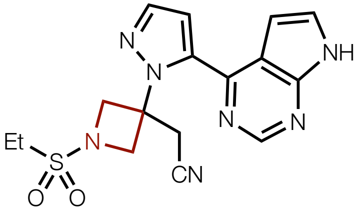


➡ can improve physicochemical properties

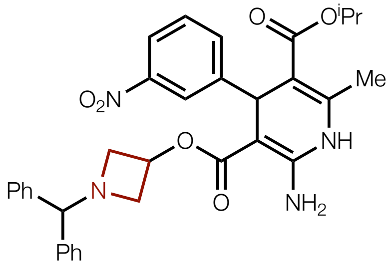
Only nine azetidine-containing approved drugs



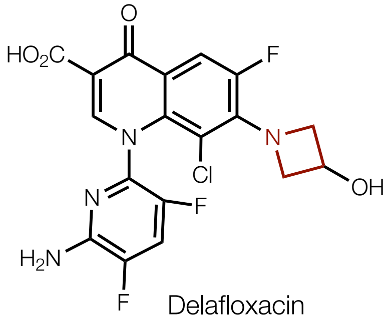
Cobimetinib
(anti-cancer)



Baricitinib
(rheumatoid arthritis)

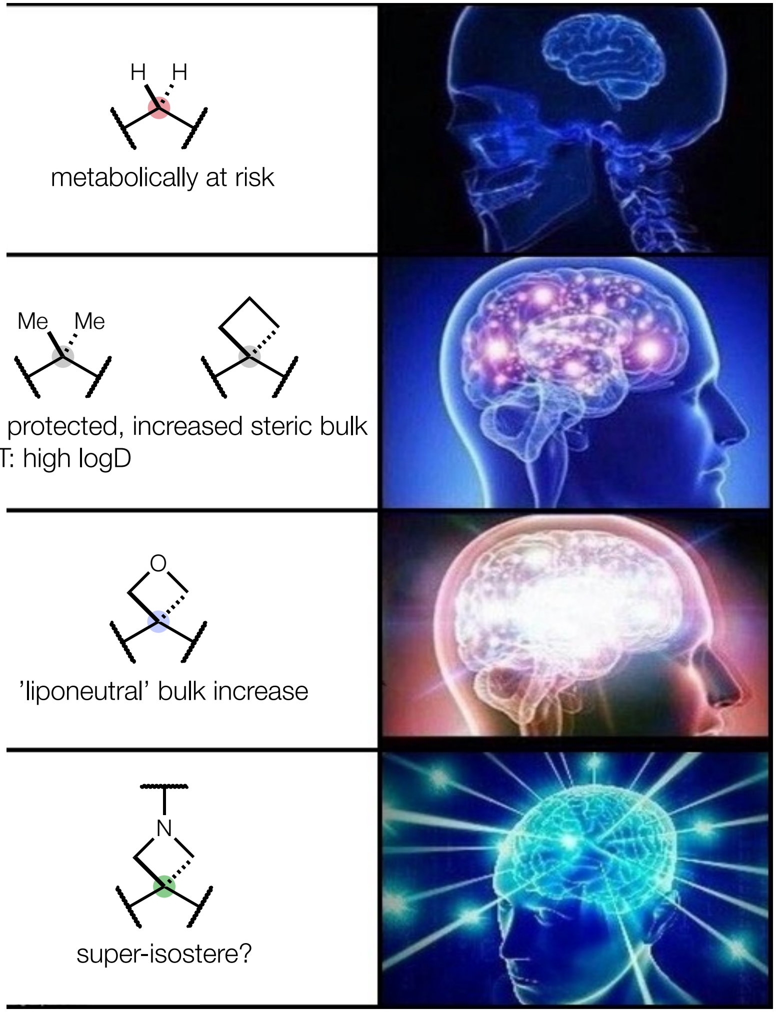


Azelnidipine
(calcium channel blocker)



Delafloxacin
(fluoroquinolone antibiotic)

➡ Opportunities for medicinal chemistry AND synthesis

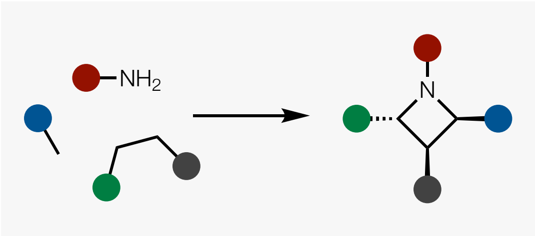


Some useful references: *RSC Med. Chem.* **2021**, 448; *Chem. Rev.* **2014**, 8257; *Arc. Pharm.* **2021**, e2100062; *ACIE* **2010**, 3524; *JOC* **2019**, 1363; *Bioorg. Med. Chem. Lett.* **2012**, 6469; *J. Med. Chem.* **2019**, 4936; *ACS Med. Chem. Lett.* **2020**, 303; *J. Med. Chem.* **2020**, 88.

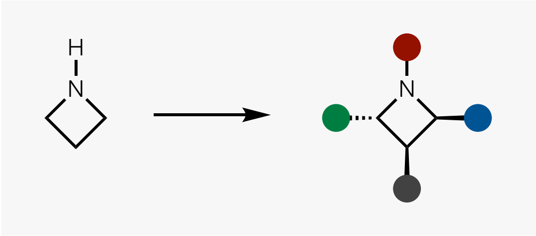
How to access azetidines

vs.

Building the ring

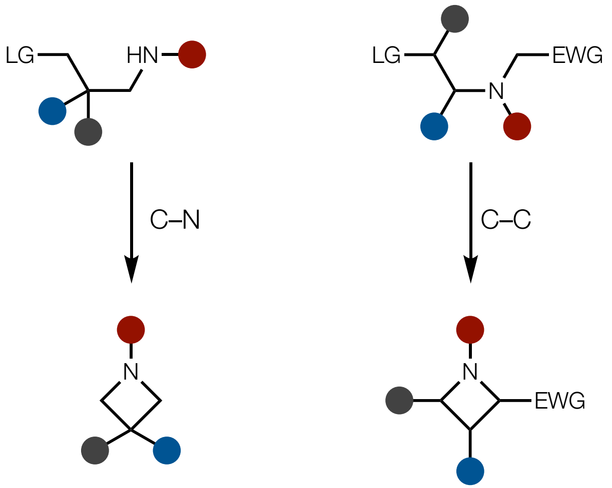


Functionalizing the ring



Popular ways of building azetidines

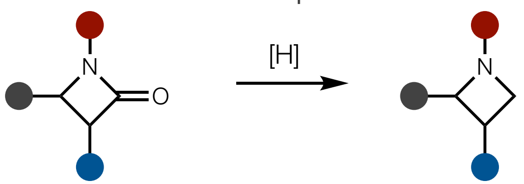
Intramolecular cyclization



- Highly substituted azetidines obtainable
- Not modular

Examples: *JOC* **1994**, 6098; *Tet. Asymm.* **2002**, 297.

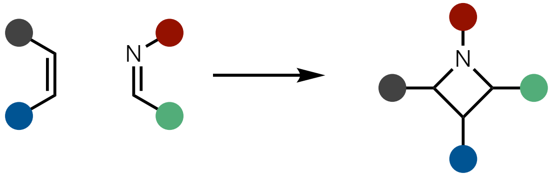
Reduction of β-lactams



- Well-studied synthesis of precursors
- Harsh reduction conditions, no C2 substituents

Examples: *JOC* **1994**, 7994; *Tet. Lett.* **1998**, 467.

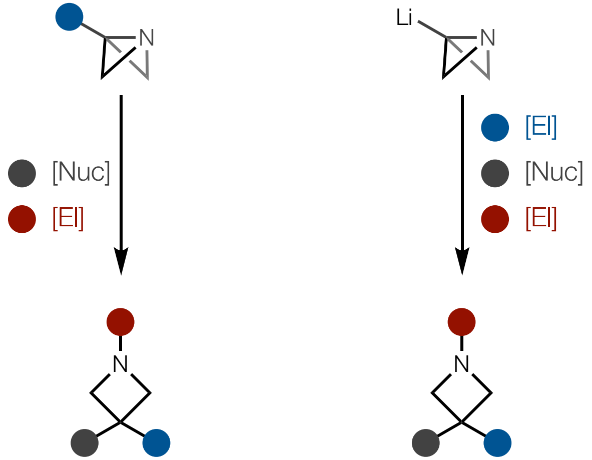
aza Paternò-Büchi



- In principle very modular
- In reality, (very) restricted substitution patters

Examples: *JOC* **1984**, 827; *Chem. Lett.* **1980**, 655.

(Aza)bicyclo[1.1.0]butanes



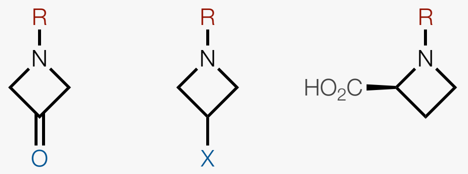
- Modular and predictable multi-functionalization
- Multi-step synthesis of strained precursor

Examples: *Science* **2016**, 241; *JACS* **2019**, 4573.

Reviews: *OBC* 2021, 3274; *Chem. Rev.* 2008, 3988. *Chem. Sci.* 2020, 7553; *Chem. Eur. J.* 2023, e202300008.

Functionalization of azetidinone derivatives

Popular building blocks

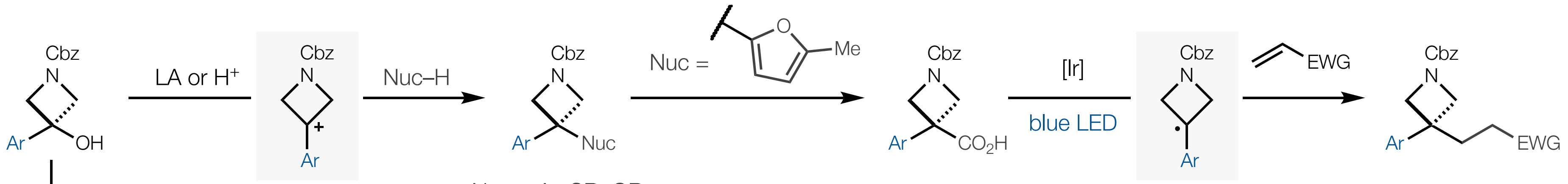


~ \$1–10/g

R = H, Boc, Cbz, $CHPh_2$

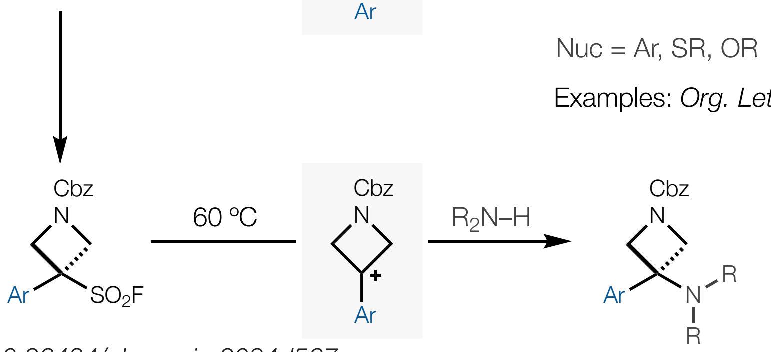
X = OH, NH_2, I, Br, CH_2OH, CO_2H, CN

1. From azetidinols *via* reactive intermediates



Nuc = Ar, SR, OR

Examples: *Org. Lett.* **2019**, 300; *JOC* **2019**, 5943; *OBC* **2023**, 5553; *Org. Lett.* **2020**, 5279; *JOC* **2023**, 6476.



10.26434/chemrxiv-2024-l567g

Organic Letters
pubs.acs.org/OrgLett
Letter

Short Synthesis of Oxetane and Azetidine 3-Aryl-3-carboxylic Acid Derivatives by Selective Furan Oxidative Cleavage

Maryne A. J. Dubois, Milo A. Smith, Andrew J. P. White, Alvin Lee Wei Jie, James J. Mousseau, Chulho Choi, and James A. Bull*

The Journal of Organic Chemistry
pubs.acs.org/joc
Article

Visible Light Photoredox-Catalyzed Decarboxylative Alkylation of 3-Aryl-Oxetanes and Azetidines via Benzylic Tertiary Radicals and Implications of Benzylic Radical Stability

Maryne A. J. Dubois,‖ Juan J. Rojas,‖ Alistair J. Sterling,‖ Hannah C. Broderick, Milo A. Smith, Andrew J. P. White, Philip W. Miller, Chulho Choi, James J. Mousseau, Fernanda Duarte,* and James A. Bull*

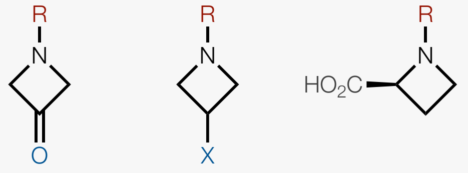
Organic & Biomolecular Chemistry
ROYAL SOCIETY OF CHEMISTRY
PAPER
View Article Online
View Journal | View Issue
Check for updates
Cite this: *Org. Biomol. Chem.*, 2023, **21**, 5553

Synthesis of oxetane and azetidine ethers as ester isosteres by Brønsted acid catalysed alkylation of alcohols with 3-aryl-oxetanols and 3-aryl-azetidinols†

Peerawat Saejong, [a] Juan J. Rojas, [a] Camille Denis,[a,b] Andrew J. P. White, [a] Anne Sophie Voisin-Chiret, [b] Chulho Choi [c] and James A. Bull *[a]

Functionalization of azetidinone derivatives

Popular building blocks



~ $1–10/g

R = H, Boc, Cbz, $CHPh_2$

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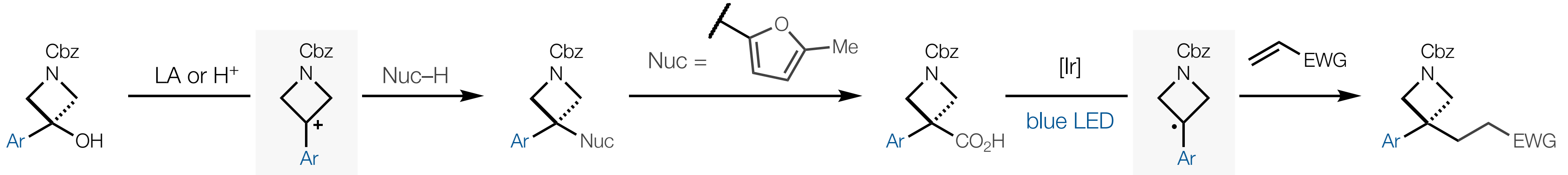
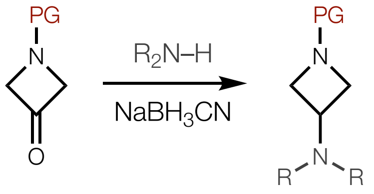


Nuc = Ar, SR, OR

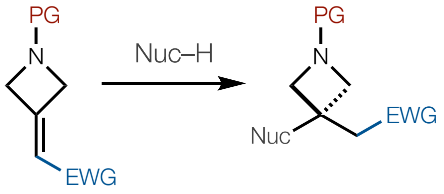
Examples: *Org. Lett.* **2019**, 300; *JOC* **2019**, 5943; *OBC* **2023**, 5553; *Org. Lett.* **2020**, 5279; *JOC* **2023**, 6476.

2. Reductive amination



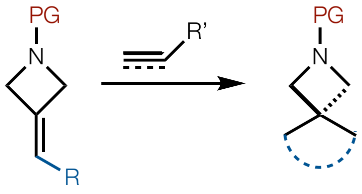
Examples: *J. Med. Chem.* **2024**, 2712; *Eur. J. Med. Chem.* **2024**, 116011; *J. Med. Chem.* **2024**, 2321.

3. Conjugate addition



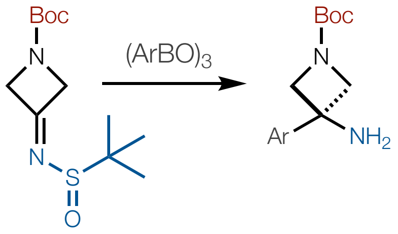
Examples: *Molecules* **2023**, 1091; *Chem. Eur. J.* **2024**, e202400308; *Chin. J. Chem.* **2024**, 1341.

4. Cycloadditions



Examples: *Org. Lett.* **2024**, 2888; *Nat. Catal.* **2024**, 307.

5. Addition into sulfinimines



Org. Lett. **2011**, 3912.

Paper 1: radical addition into ABBs

nature catalysis

Article

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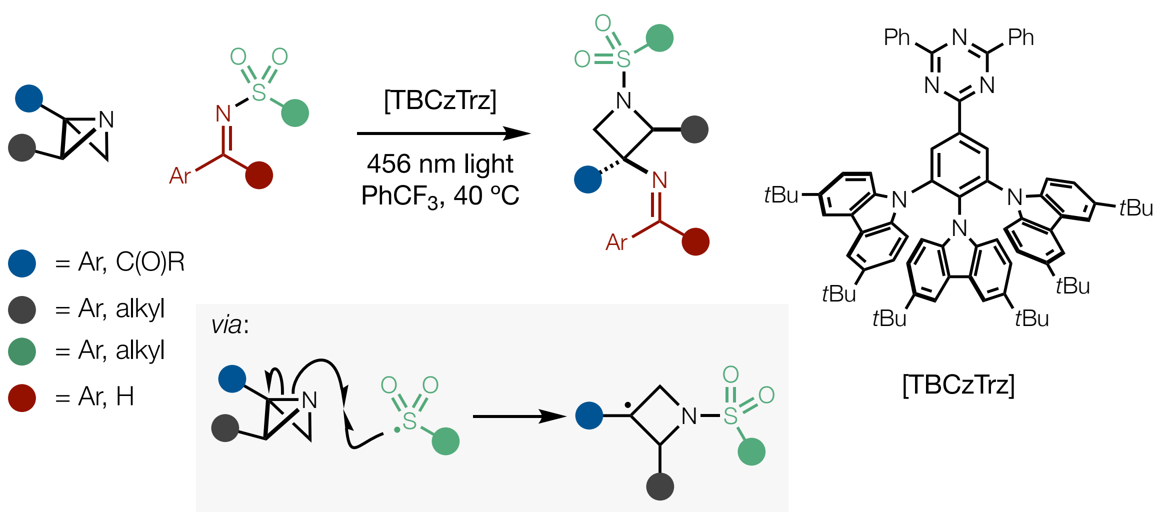
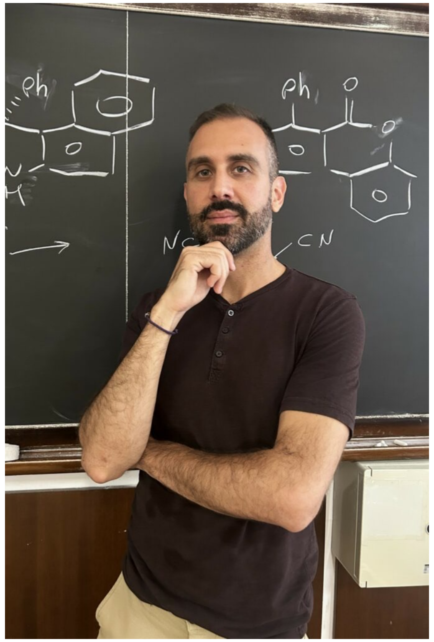
The paper in short: first radical addition into ABBs



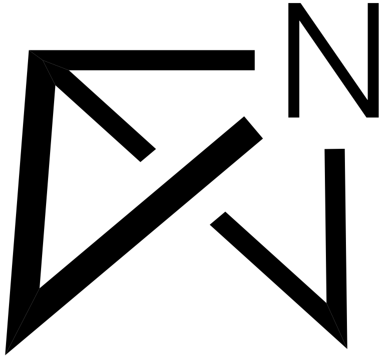


- Born in Carrara, Italy.
- 2010: MSc in MedChem Parma U.
- 2010–2014: PhD, Parma U. with Prof. Franca Zanardi.
- 2014–2016: PostDoc ICIQ with Prof. Paolo Melchiorre.
- 2016–now: independent career University of Padova.

Asymmetric organocatalysis
Mechanistic investigations
Photocatalysis

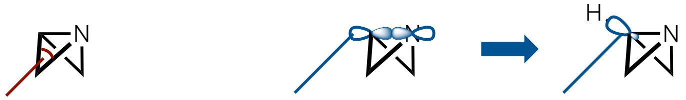
(Aza)bicyclo[1.1.0]butanes (ABBs)

Not to be confused with:



Key properties

First report:
Hortmann and Robertson
JACS **1967**, 5974



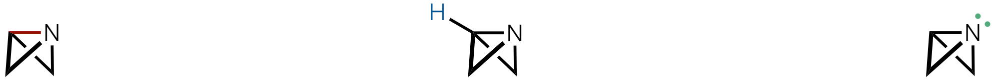
internal bond angles ~60° (*JCSCC* **1993**, 148)

increased p character *Synlett* **1997**, 1029

increased s character

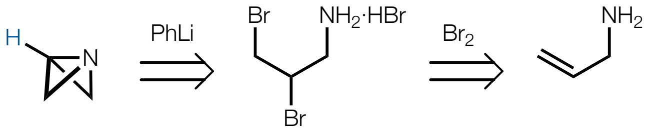
acidic C–H! (~acetylene)

Reactivity dominated by:

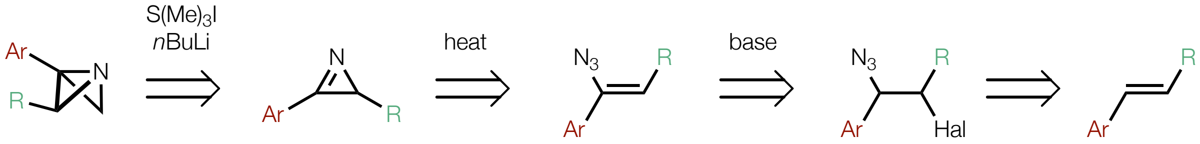


ring strain | C3–H acidity | N nucleophilicity

Typical synthetic strategies

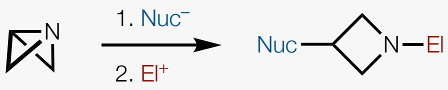


see: *JACS* **2017**, 3209.

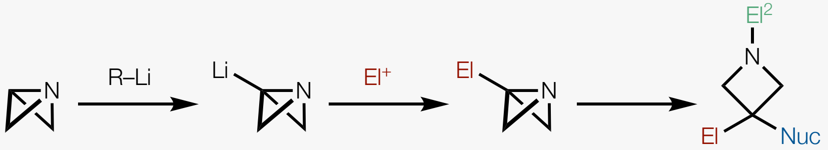


see: *Nat. Catal.* **2024**, 10.1038/s41929-024-01206-4.

Typical reactivity



Nuc = SH, Cl	Nuc = NR_2	Nuc = alkyl	Nuc = Ar
El = Ac, Ts	El = Boc	El = Ts	El = Ar’
Tet. Lett. **1999**, 3761.	*Science* **2016**, 241.	*Org. Lett.* **2019**, 2060.	*Chem. Commun* **2022**, 2564.

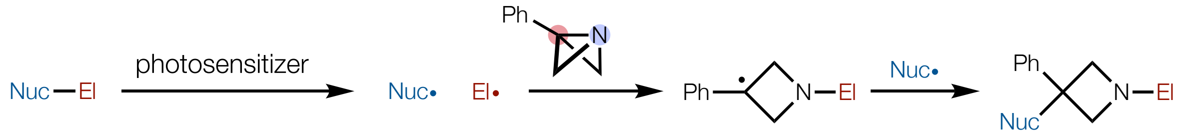


JACS **2019**, 4573
ACIE **2021**, 7360
ACIE **2022**, e202214049
JACS **2023**, 19049

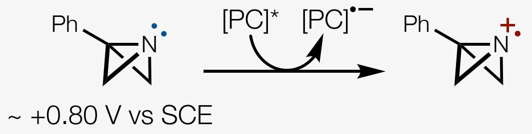
Reviews: *OBC* 2020, 5798; *Chem. Eur. J.* 2023, e202300008.

Reaction discovery

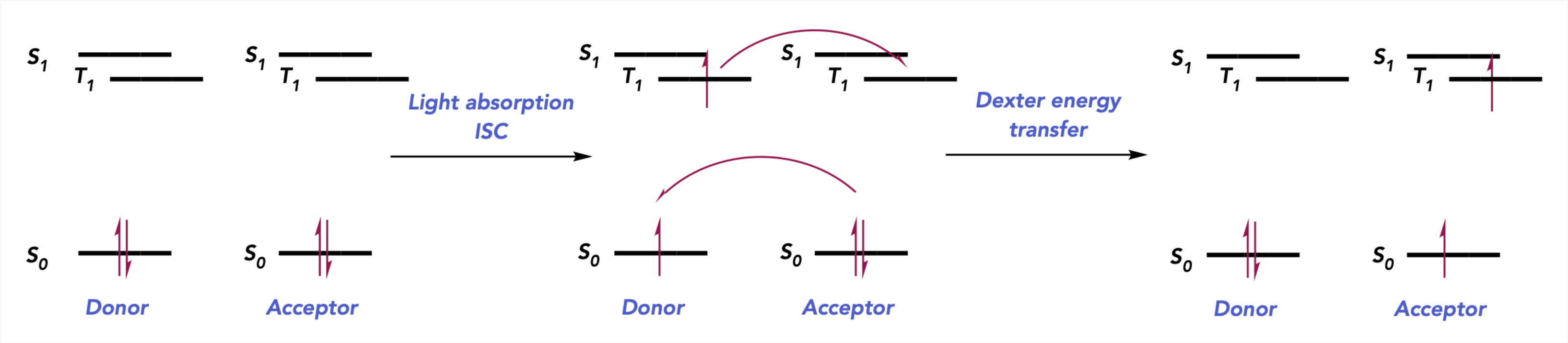
Idea:

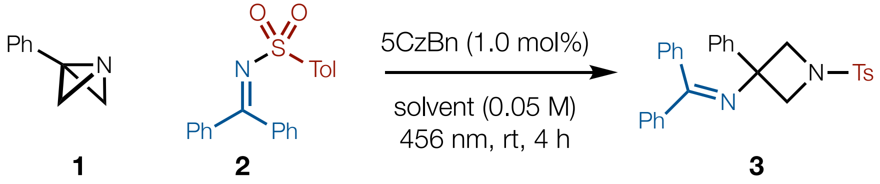


Avoid:

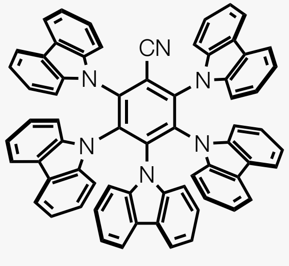


Energy transfer mechanism (Dexter)





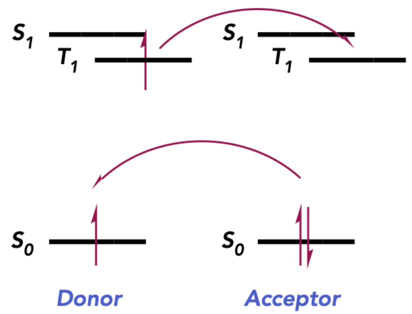
Entry	Solvent	Yield (%)	Entry	Solvent	Yield (%)
1	AcOEt	28	6	Dimethylcarbonate	22
2	MeCN	24	7	Acetone	11
3	DMSO	0	8	$PhCF_3$	30
4	1,2 Dichloroethane	21	9	Toluene	28
5	DCM	15	10	THF	0

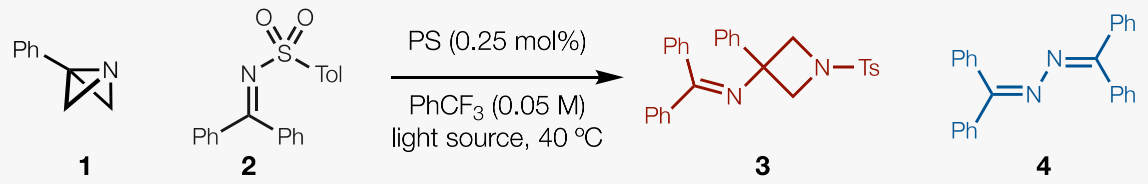


[5CzBn]

Diagram from: https://knowleslab.princeton.edu/wp-content/uploads/2022/03/Energy-Transfer-Catalysis-Phil-Murray.pdf

Reaction development





Requirements for the PS:

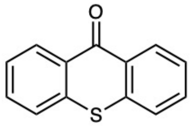
- Sufficiently high T_1 $E_{0,0}$ (>2.55 eV)
- Very low ΔST

➔ rapid $S_1 \rightarrow T_1$ (ISC) and $T_1 \rightarrow S_1$ (RISC)

➔ lower [PS T_1]

➔ lower [imine radical]

➔ slower rate of dimerization (4)

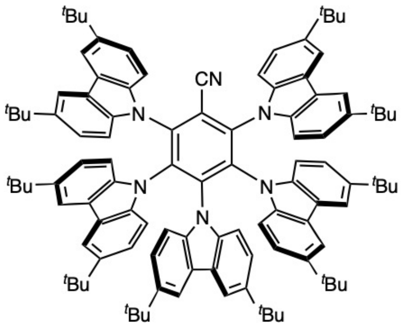


PS loading = 5 mol%
in AcOEt (not soluble in $PhCF_3$)

TXO, **6**
S_1 = 3.38 eV
T_1 = 2.88 eV
ΔST = 0.50 eV

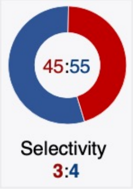
@ 427 nm
3 (10%)

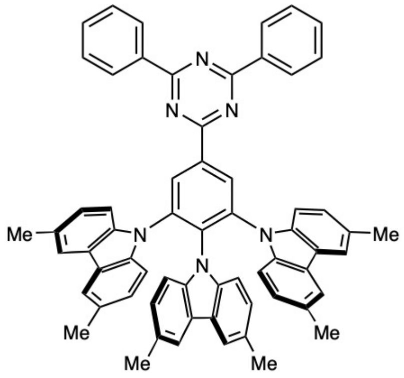
@ 456 nm
No reaction



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

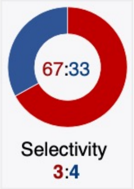
@ 456 nm
3 (51%)

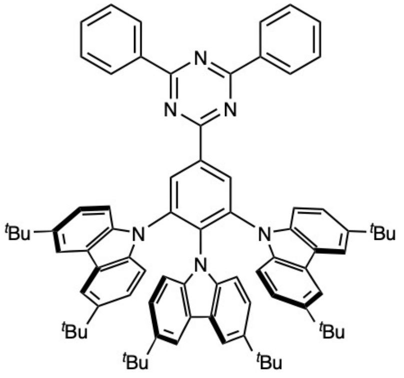




MeCzTrz, **8**
S_1 = 2.86 eV
T_1 = 2.79 eV
ΔST = 0.07 eV

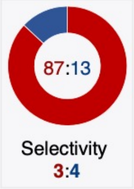
@ 456 nm
3 (50%)



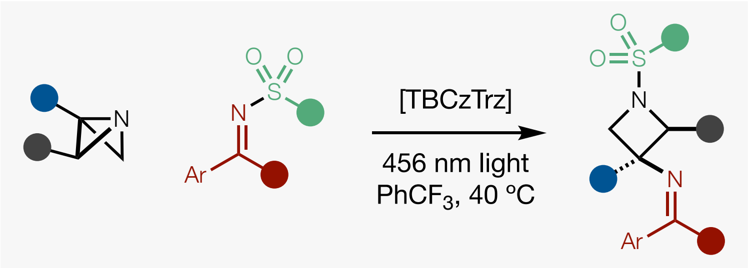


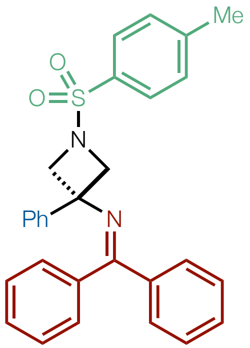
TBCzTrz, **9**
S_1 = 2.79 eV
T_1 = 2.74 eV
ΔST = 0.05 eV

@ 456 nm
3, yield = 79%



Selected scope

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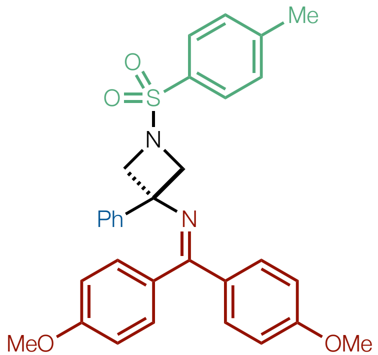
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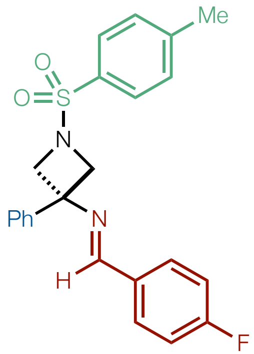
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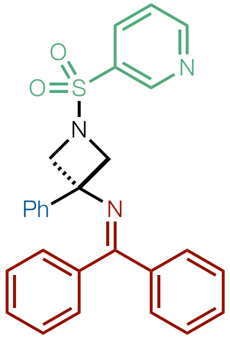
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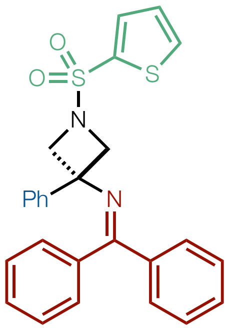
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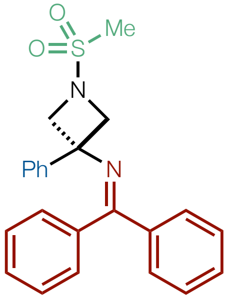
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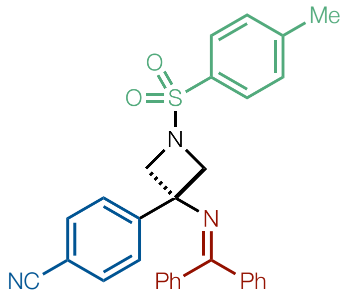
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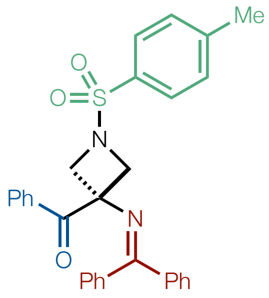
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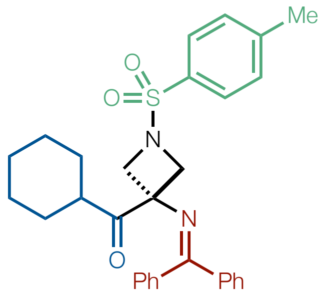
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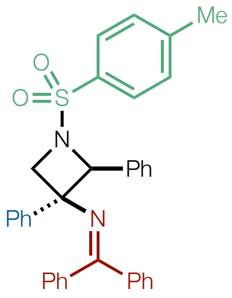
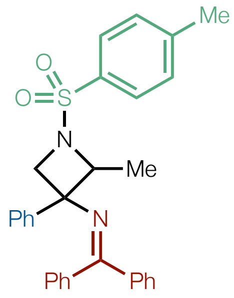

61%
(7:3 dr)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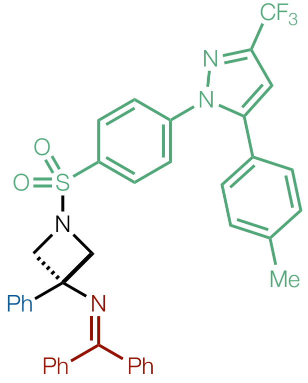
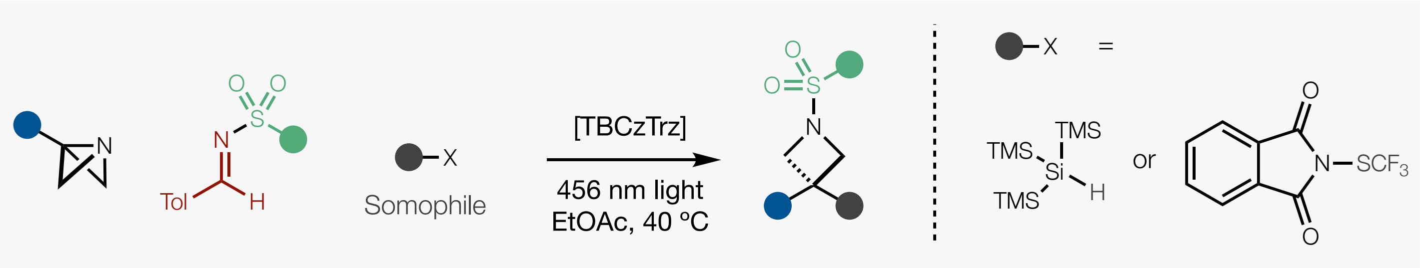
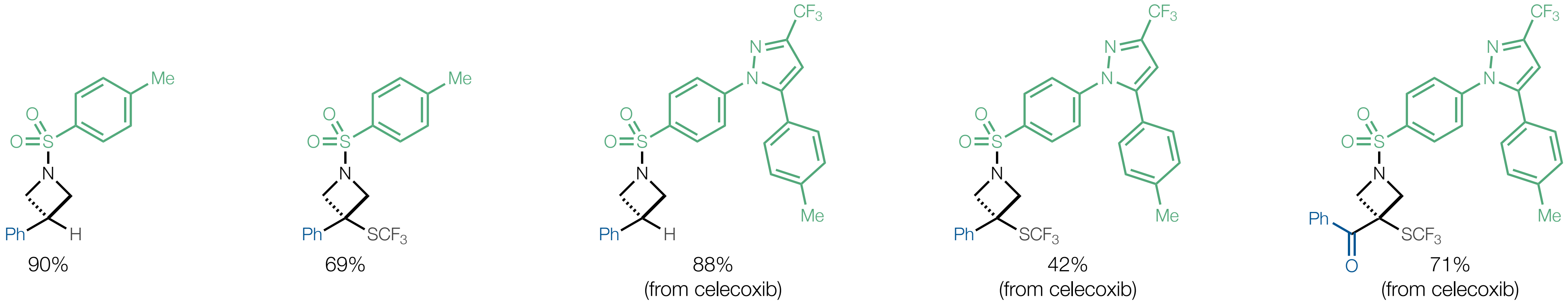
(1:1 dr)

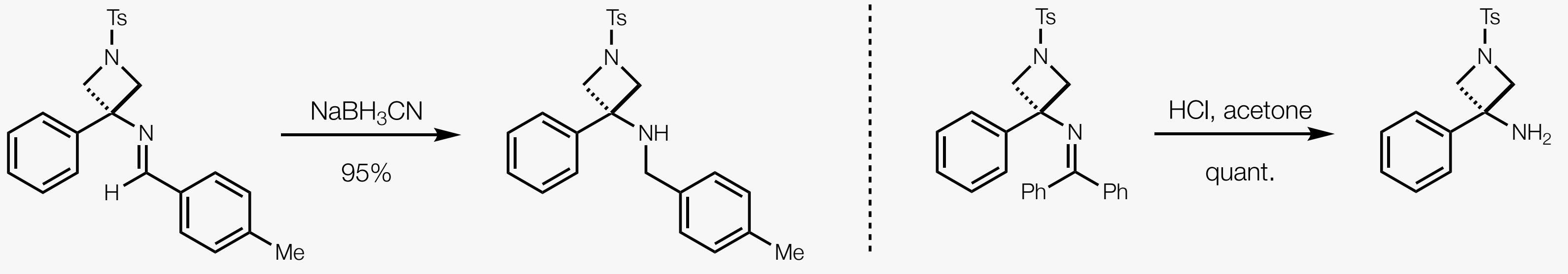

71%
(from celecoxib)

3-Component reactions

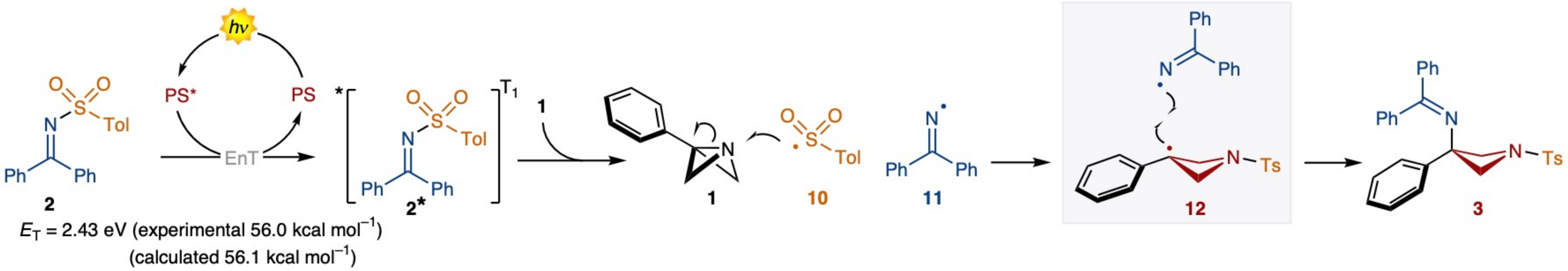


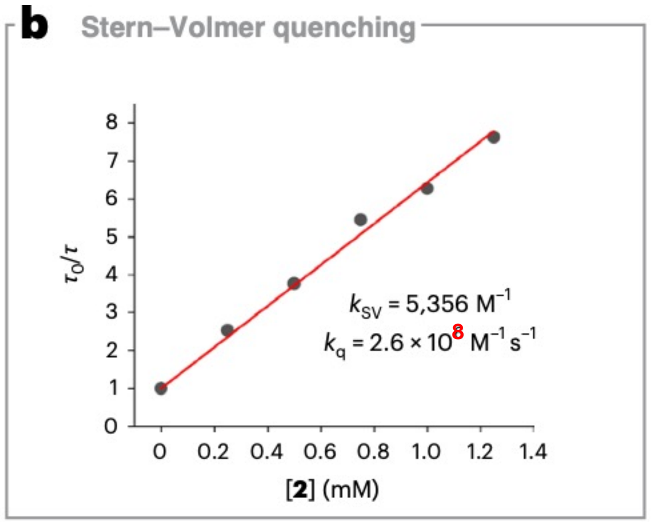


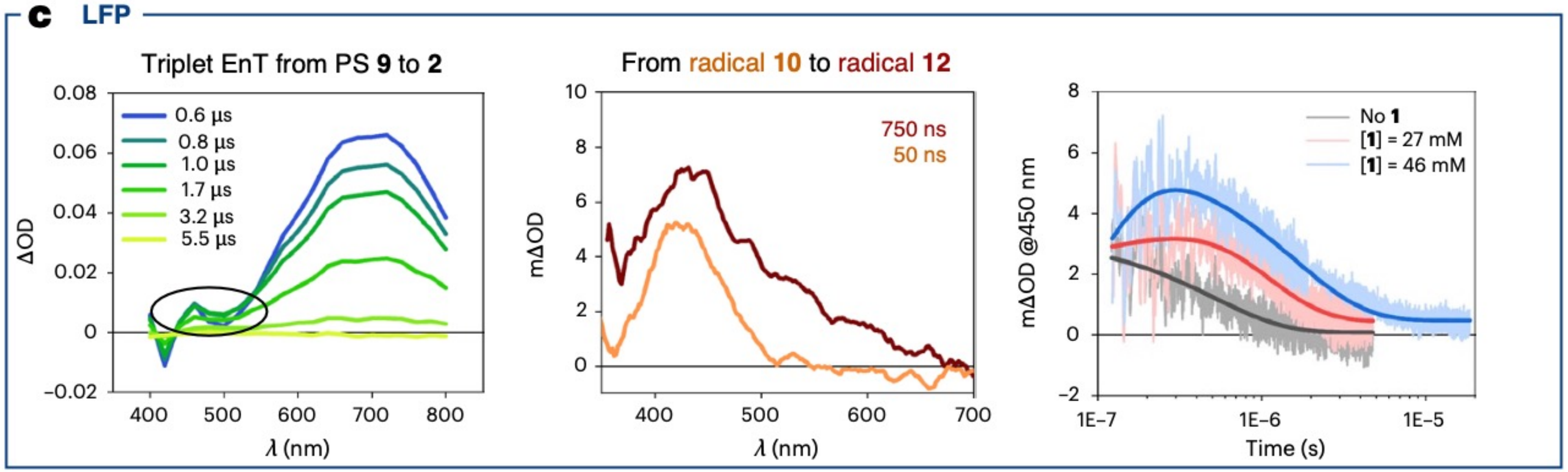
Product derivatizations



Mechanistic experiments



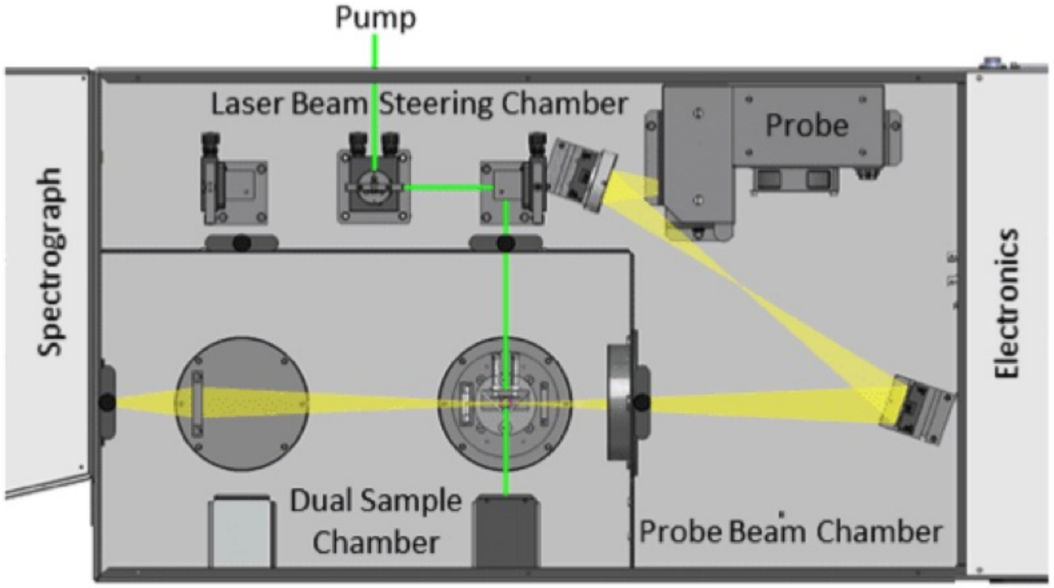




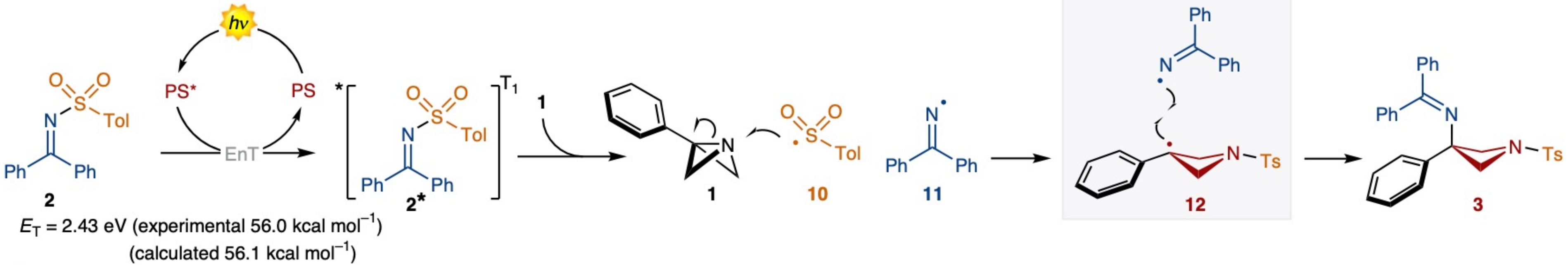
- PS* is quenched by sulfonyl imine.
- Quench by ABB slower (3.8×10^6 M^{-1} s^{-1}).

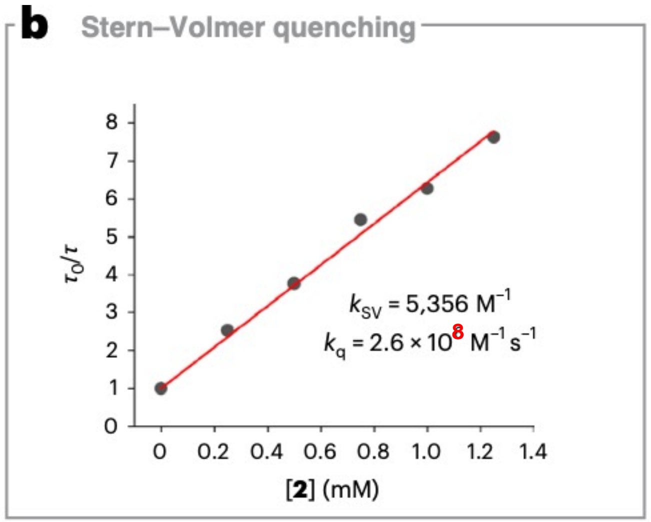
- Left: reaction of PS* with 2 leads to new species (presumably 10 + 11), but decay faster than formation.
- Middle: ABB added. At 50 ns, radical 10 (410 nm); at 750 ns, new species (presumably 12 (435 nm)).
- Right: increased intensity with higher [ABB], decay attributed to reaction of 12 with 11.

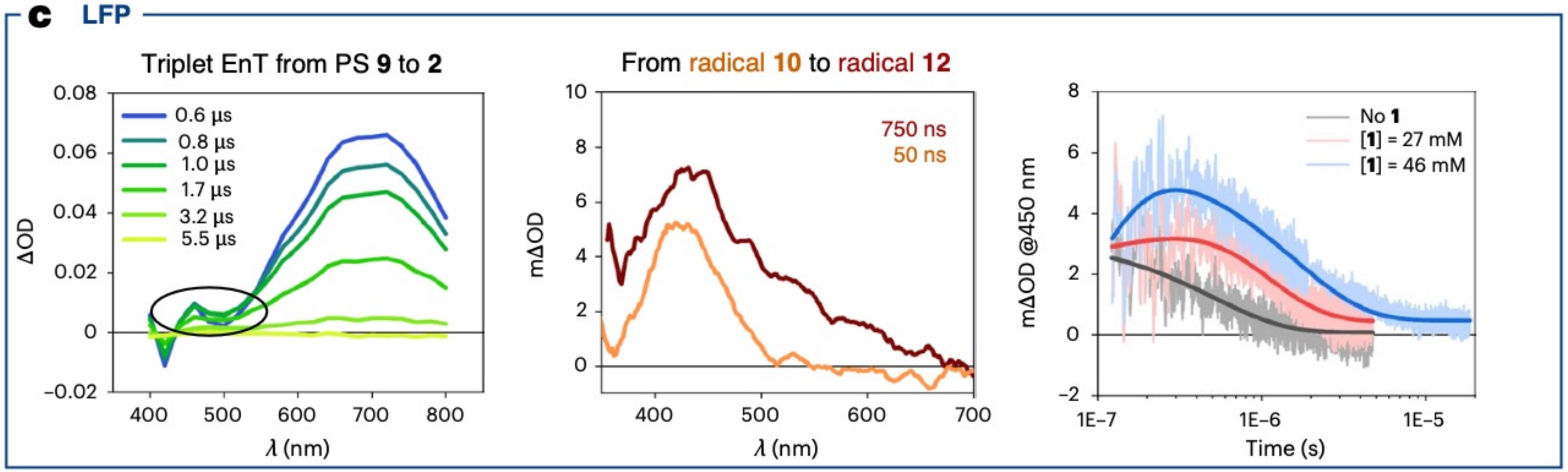
Laser Flash Photolysis



Mechanistic experiments







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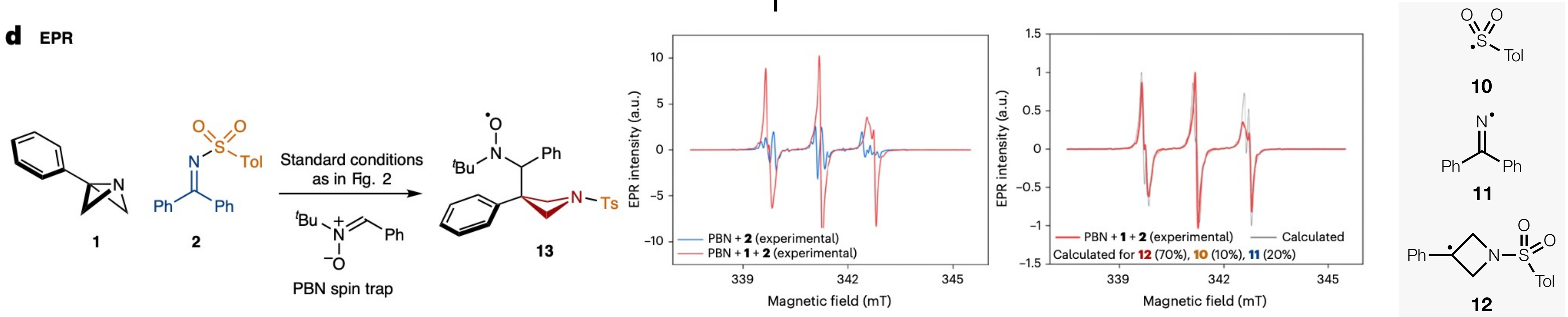
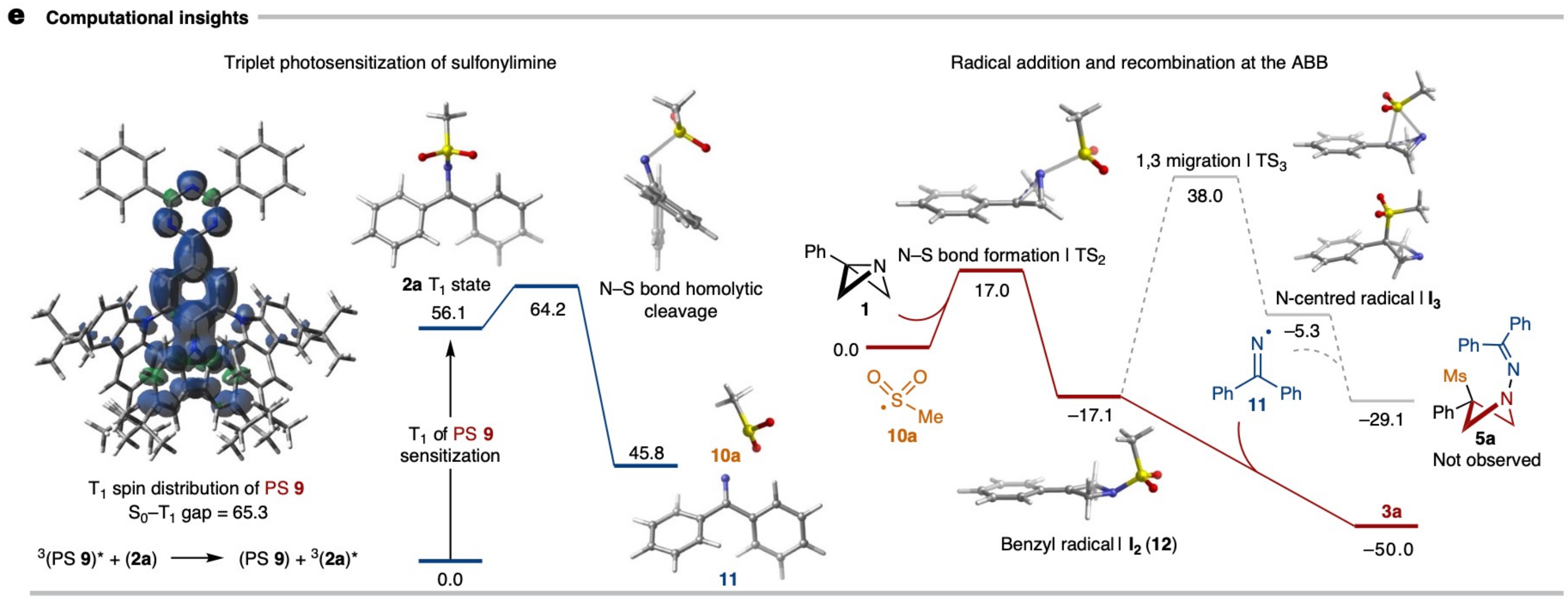
- Right: increased intensity with higher [ABB], decay attributed to reaction of 12 with 11.

Mechanistic experiments



- In the absence of ABB (1), EPR shows sulfonyl (10) and iminyl radicals (11) – blue signal, left graph.
- With ABB (1), EPR consistent with 70% azetidine radical (12), 10% sulfonyl (10) and 20% iminyl radical (11) – red signal, both graphs.



Summary

- First radical strain-release reaction of ABBs.
- Nice rationale (ΔST) to develop reaction, including a new photosensitizer.
- Thorough spectroscopic studies (SV, EPR, LFP).
- Promising development of 3-component reaction.

➜ Important fundamental blueprint for the radical reactivity of ABBs.

Future directions?

- Other radical precursors apart from sulfonyl imines?
- Other radical traps for the azetidine radical? For example, ArNi(II), Michael acceptors, etc.

Paper 2: aza-PB with acyclic oximes and alkenes

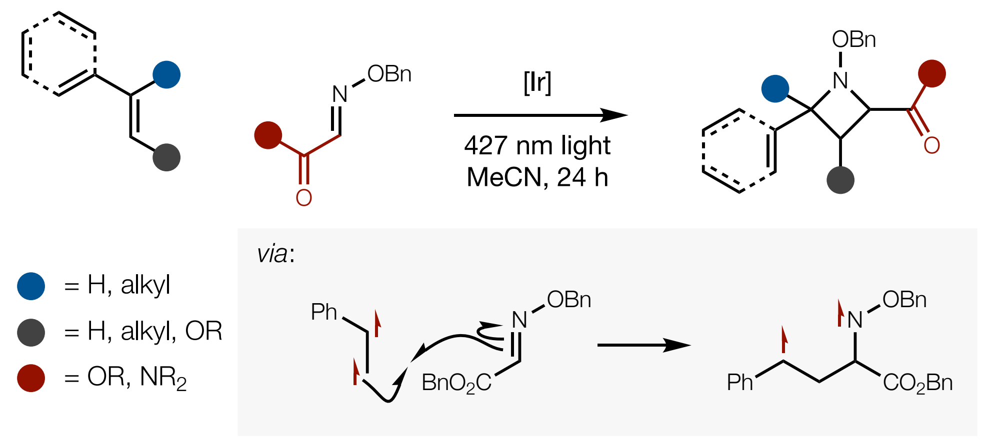
ORGANIC CHEMISTRY

Visible light–mediated aza Paternò–Büchi reaction of acyclic oximes and alkenes to azetidines

Emily R. Wearing[1], Yu-Cheng Yeh[1], Gianmarco G. Terrones[2]†, Seren G. Parikh[1]†, Ilia Kevlishvili[2], Heather J. Kulik[2,3]*, Corinna S. Schindler[1,4,5,6]*

The aza Paternò–Büchi reaction is a [2+2]-cycloaddition reaction between imines and alkenes that produces azetidines, four-membered nitrogen-containing heterocycles. Currently, successful examples rely primarily on either intramolecular variants or cyclic imine equivalents. To unlock the full synthetic potential of aza Paternò–Büchi reactions, it is essential to extend the reaction to acyclic imine equivalents. Here, we report that matching of the frontier molecular orbital energies of alkenes with those of acyclic oximes enables visible light–mediated aza Paternò–Büchi reactions through triplet energy transfer catalysis. The utility of this reaction is further showcased in the synthesis of *epi*-penaresidin B. Density functional theory computations reveal that a competition between the desired [2+2]-cycloaddition and alkene dimerization determines the success of the reaction. Frontier orbital energy matching between the reactive components lowers transition-state energy ($\Delta G^\ddagger$) values and ultimately promotes reactivity.

The paper in short: first intermolecular aza Paternò-Büchi with acyclic oximes



- Born in Schwäbisch Hall, Germany.
- 2004: MSc in Chem., TU München
- 2005–2010: PhD, ETHZ with Prof. Erick Carreira.
- 2010–2013: PostDoc at Harvard with Prof. Eric Jacobsen.
- 2013–2024: Professor at University of Michigan.
- 2024–now: Professor at UBC, Vancouver.

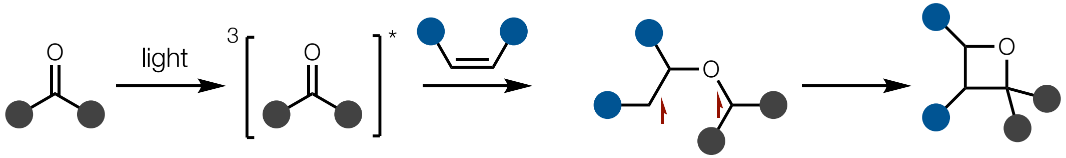
Catalytic methods
Total synthesis
Biological applications

- 2004: BE in Chem. Eng., Cooper Union.
- 2009: PhD, MIT with Prof. Nicola Marzari.
- 2010: PostDoc at Lawrence Livermore with Prof. Felice Lightstone.
- 2013: PostDoc at Stanford with Prof. Todd Martínez.
- 2013–now: Professor at MIT.

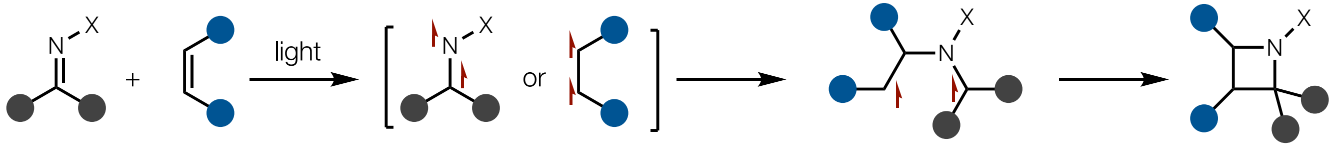
Computational chemistry
Chemical engineering
Materials science

Paternò-Büchi and aza Paternò-Büchi

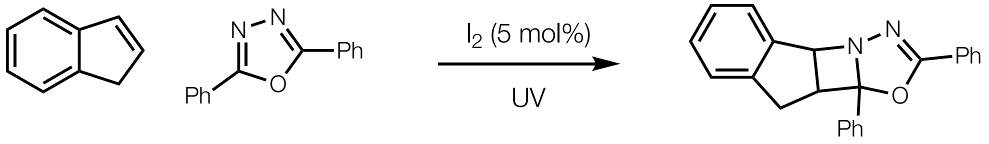
Paternò-Büchi Reaction



aza Paternò-Büchi Reaction



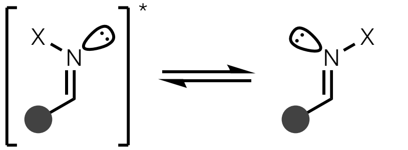
First example: Tsuge 1968



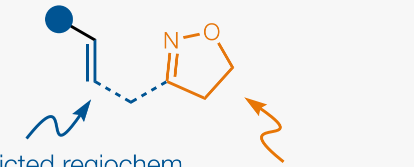
Tetrahedron Lett. **1968**, 3971. Also see: *Tetrahedron* **1973**, 41; *JOC* **1977**, 1496

Main challenges

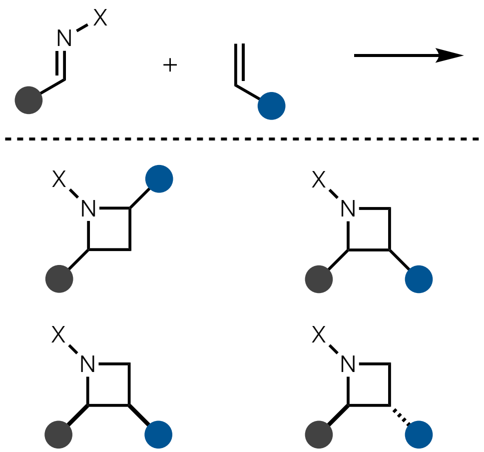
1. Radiationless imine isomerization



Typical solution: biased substrates

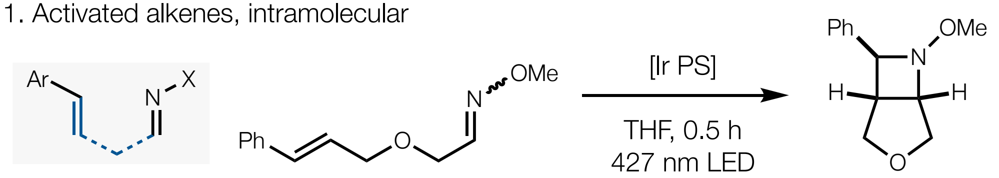


2. Regio- and stereoselectivity



Recent examples of different combinations

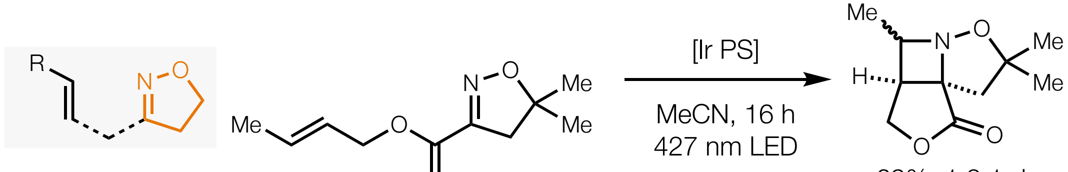
1. Activated alkenes, intramolecular



Nat. Commun. **2019**, 5095

Also see:
ACS Catal. **2020**, 12618;
ACIE **2017**, 7056.

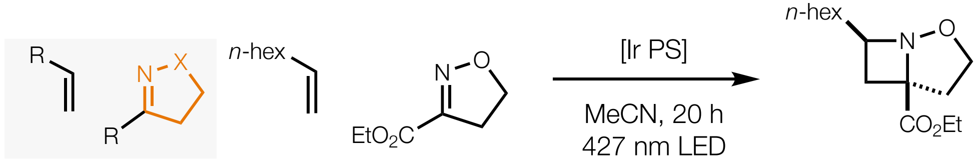
2. Activated cyclic imine equivalents, intramolecular



Org. Lett. **2022**, 3053

Also see:
JACS **2022**, 19089.

3. Activated cyclic imine equivalents, intermolecular



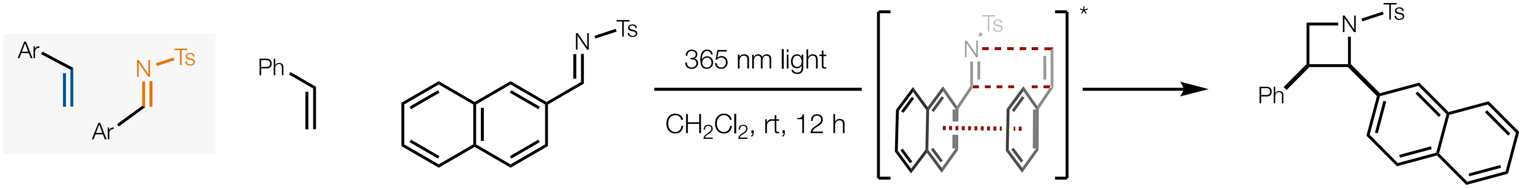
Nat. Chem. **2020**, 898

Also see:
JACS **2022**, 19089;
ACIE **2023**, e202305622.

Reviews: *ACIE* **2023**, e202217210; *Photochem. Photobiol. Sci.* **2019**, 2297; *Chem. Sci.* **2020**, 7553; *Chem. Soc. Rev.* **2021**, 1617.

Aza Paternò-Büchi *via* alt. mechanisms

[2+2] Photocycloaddition *via* a singlet exciplex intermediate (proposed)

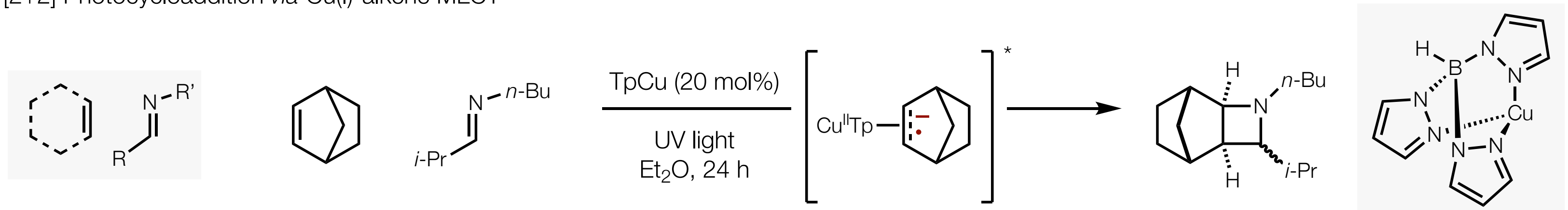


Maruoka, *Org. Lett.* **2016**, 6252

singlet exciplex

61%, >20:1 dr, >20:1 rr

[2+2] Photocycloaddition *via* Cu(I)-alkene MLCT

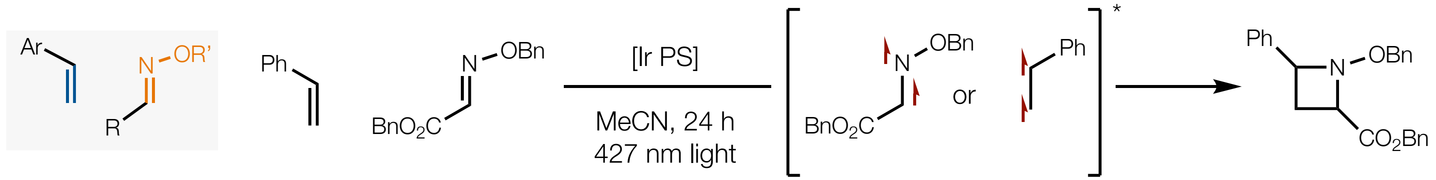


Schmidt, *Nat. Commun.* **2022**, 2764

79%, >20:1 dr

TpCu

This paper: activated alkenes and activated acyclic oximes, intermolecular

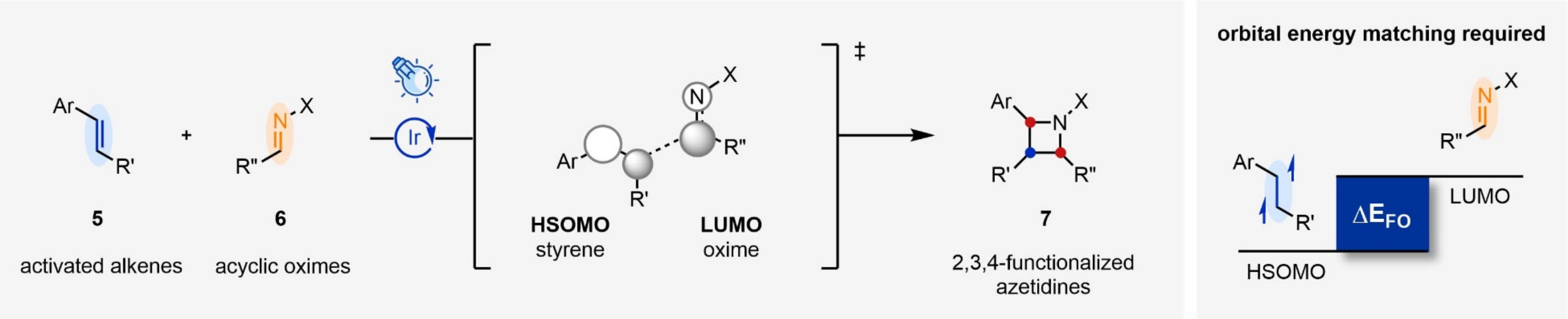


Science **2024**, 1468.

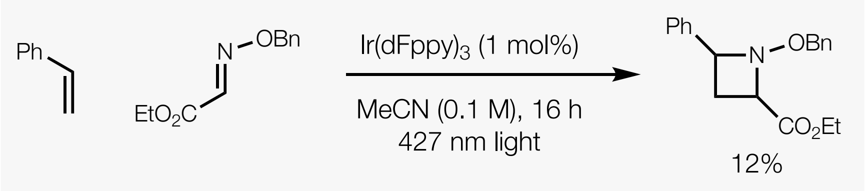
67%, >1.2:1 dr

Reaction design

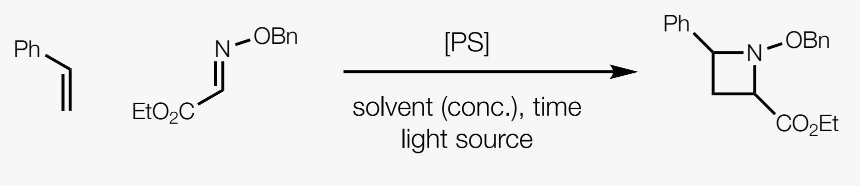
Idea: use both activated alkenes and activated acyclic oximes to match the energy of frontier orbitals and favor the aza PB pathway:



Initial hit:



Reaction optimization



159 reactions!

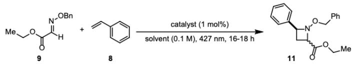


Table S1: Screen for optimal solvent and photocatalyst combinations.

Entry Number	Solvent	Catalyst	Yield
1	Toluene	2CzPN	5%
2	Toluene	4DPAIPN	0%
3	Toluene	2,2'-MeOTx	12%
4	Toluene	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	3%
5	Toluene	*fac*-$Ir(dFppy)_3$	8%
6	Toluene	$[Ir(dFppy)_2(dtbbpy)]PF_6$	5%
7	Toluene	*fac*-$Ir(Fppy)_3$	13%
8	Toluene	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	6%
9	Acetonitrile	2CzPN	3%
10	Acetonitrile	4DPAIPN	0%
11	Acetonitrile	2,2'-MeOTx	15%
12	Acetonitrile	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	12%
13	Acetonitrile	*fac*-$Ir(dFppy)_3$	5%
14	Acetonitrile	$[Ir(dFppy)_2(dtbbpy)]PF_6$	4%
15	Acetonitrile	*fac*-$Ir(Fppy)_3$	11%
16	Acetonitrile	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	7%
17	Dichloromethane	2CzPN	5%
18	Dichloromethane	4DPAIPN	0%
19	Dichloromethane	2,2'-MeOTx	12%
20	Dichloromethane	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	11%
21	Dichloromethane	*fac*-$Ir(dFppy)_3$	11%
22	Dichloromethane	$[Ir(dFppy)_2(dtbbpy)]PF_6$	12%
23	Dichloromethane	*fac*-$Ir(Fppy)_3$	18%
24	Dichloromethane	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	5%
25	1:1 Acetonitrile/water	2CzPN	4%
26	1:1 Acetonitrile/water	4DPAIPN	0%
27	1:1 Acetonitrile/water	2,2'-MeOTx	29%
28	1:1 Acetonitrile/water	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	34%
29	1:1 Acetonitrile/water	*fac*-$Ir(dFppy)_3$	27%
30	1:1 Acetonitrile/water	$[Ir(dFppy)_2(dtbbpy)]PF_6$	25%
31	1:1 Acetonitrile/water	*fac*-$Ir(Fppy)_3$	21%
32	1:1 Acetonitrile/water	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	42%
33	1:1 Acetonitrile/water	Thioxanthone	34%
34	1:1 Acetonitrile/water	2-F,2'MeOTX	15%
35	Methanol	2,2'MeOTx	4%
36	Methanol	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	17%
37	Methanol	*fac*-$Ir(Fppy)_3$	0%
38	Methanol	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	3%
39	1:1 Acetone/water	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	45%
40	1:1 THF/water	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	37%
41	1:1 Acetonitrile/water	$[Ru(bpz)_3](PF_6)_2$	0%
42	1:1 Acetonitrile/water	$[Ru(bpy)_3]Cl_2\text{-}6H_2O$	0%
43	1:1 Acetonitrile/water	$[Ru(phen)_3](PF_6)_2$	0%
44	1:1 Acetonitrile/water	$[Ru(bpy)_3](PF_6)_2$	0%
45	1:1 Acetonitrile/water	$[Ru(bpm)_3]Cl_2$	0%

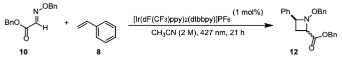


Table S11: Impact of styrene treatment on yield.

Entry	Styrene Source	Yield
1	bottle- added before sparge	66%
2	bottle- added after sparge	73%
3	degassed (Stored in freezer for ~ 1 month)	72%
4	freshly degassed with FPT	65%
5	washed to remove stabilizer	73%
6	styrene double addition (bottle) 2.5 equiv. at t = 0 h and t = 2 h	69%
7	styrene double addition (bottle) 2.5 equiv. at t = 0 h and t = 4 h	77%
8	styrene double addition (bottle) 2.5 equiv. at t = 0 h and t = 6 h	83%
9	styrene double addition (bottle) 2.5 equiv. at t = 0 h and t = 8 h	77%

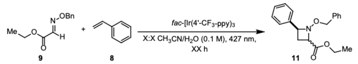
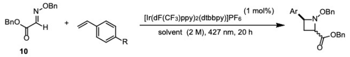


Table S2: Further optimization experiments for the reaction conditions utilizing a water/acetonitrile solvent mixture and *fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$.

Entry Number	Change from Initial condition	Yield
1	none	42%
2	0.5 h	13%
3	1 h	20%
4	2 h	40%
5	3 h	38%
6	4 h	42%
7	6 h	35%
8	60 h	14%
9	10% water in acetonitrile	12%
10	25% water in acetonitrile	0%
11	75% water in acetonitrile	50%
12	100% water	19%
13	3.0 equiv. styrene	48%
14	additional 1.5 equiv. styrene added after 2 h	29%
15	slow addition of organics to water over 4 h	46%
16	neat reaction, no solvent	51%
17	1.0 M acetonitrile, no water	42%
18	2.0 M acetonitrile, no water	46%
19	5.0 M acetonitrile, no water	53%



Conditions: solvent (sparged) (1.0 M), styrene (2.0 equiv.), 427 nm wavelength irradiation, 20-24 h reaction time.

Table S6: Evaluation of HFIP Optimal Condition with electron-poor and electron-rich substrates.

Entry Number	R	Solvent	Yield
1*	-H	HFIP	84%
2	-OMe	HFIP	0% by NMR‡
3	-OMe	CH_3CN	78%
4	-F	HFIP	81%
5	-F	CH_3CN	75%

*465 nm, ‡isolated yield ~15%

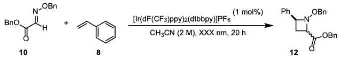


Table S9: Catalyst and wavelength optimization for acetonitrile conditions.

Entry	Catalyst Loading	Wavelength	Yield
1	2 mol%	427 nm	76%
2	1 mol%	427 nm	74%
3	0.5 mol%	427 nm	66%
4	0.25 mol%	427 nm	69%
5	2 mol%	465 nm	79%
6	1 mol%	465 nm	70%
7	0.5 mol%	465 nm	57%

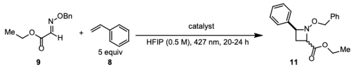


Table S3: Optimization of photocatalysts with HFIP as solvent.

Entry	Catalyst	Yield
1	2,2'MeOTx	0%
2	*fac*-$Ir(4'\text{-}CF_3\text{-}ppy)_3$	20%
3	$[Ir(dF(CF_3)ppy)2(dtbbpy)]PF_6$	59%
4	2'MeOTx	0%
5	thioxanthone*	32%
6	$[Ir(Fppy)_2(dtbbpy)]PF_6$	54%
7	$[Ir(dFppy)_2(dtbbpy)]PF_6$	52%
8	$[Ru(bpz)_3](PF_6)_2$‡	0%

*390 nm lights, ‡456 nm lights

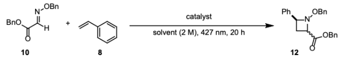


Table S7: Photocatalyst combinations with acetonitrile and THF.

Entry Number	Catalyst	Solvent	Yield
1	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	acetonitrile	65%
2*	$[Ir(Fppy)_2(dtbbpy)]PF_6$	acetonitrile	59%
3	$[Ir(dFppy)_2(dtbbpy)]PF_6$	acetonitrile	62%
4	*fac*-$Ir(dFppy)_3$	acetonitrile	55%
5	*fac*-$Ir(Fppy)_3$	acetonitrile	47%
6	*fac*-$Ir(ppy)_3$	acetonitrile	0%
7	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	THF	63%
8	$[Ir(Fppy)_2(dtbbpy)]PF_6$	THF	17%
9	$[Ir(dFppy)_2(dtbbpy)]PF_6$	THF	43%
10	*fac*-$Ir(dFppy)_3$	THF	39%
11	*fac*-$Ir(Fppy)_3$	THF	57%
12	*fac*-$Ir(ppy)_3$	THF	7%

*Run on a 0.050 mmol scale

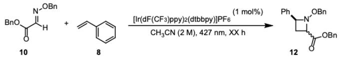


Table S10: Optimization of reaction time.

Entry	Time	Yield
1	1 h	11%
2	2 h	22%
3	6 h	42%
4	8 h	58%
5	16 h	72%
6	18 h	76%
7	24 h	72%
8	48 h	68%

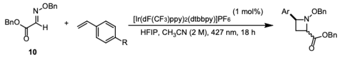
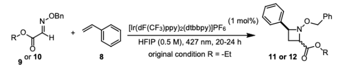


Table S12: Probing HFIP as a potential additive.

Entry	R Group	HFIP Loading	Yield
1	-H	0 equiv.	76%
2	-H	1.0 equiv.	78%
3	-H	5.0 equiv.	80%
4	-OMe	0 equiv.	69%
5	-OMe	1.0 equiv.	65%
6	-OMe	5.0 equiv.	22%



Original condition: HFIP (0.5 M), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%), styrene (5.0 equiv.), R = -Et, 427 nm irradiation, 20-24 h.

Table S4: Further optimization of HFIP conditions.

Entry	Change from Original Condition	Yield
1	none	59%
2	Neat reaction – no solvent	56%
3	2.0 equiv. styrene	45%
4	*i*PrOH as solvent (no HFIP)	49%
5	2.0 equiv. HFIP additive with THF solvent	16%
6	2.0 equiv. HFIP additive with CH_3CN as solvent	34%
7	2.0 equiv. HFIP additive with DCM as solvent	44%
8	2.0 equiv. HFIP additive with MeOH as solvent	29%
9	2.0 equiv. HFIP additive with toluene as solvent	24%
10	2.0 equiv. HFIP additive with DCE as solvent	16%
11	2.0 equiv. HFIP additive with acetone as solvent	16%
12	456 nm*	68%
13	R = -Bn	79%
14	R = -Bn, 465 nm (SynLED reactor)	61%

*run for 16 hours

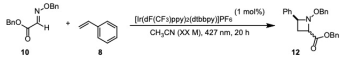
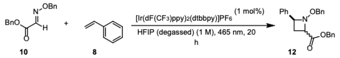


Table S8: Concentration and styrene loading screen in acetonitrile.

Entry	Styrene Loading	Concentration	Yield
1	5.0 equiv.	1 M	70%
2	5.0 equiv.	2 M	78%
3	2.0 equiv.	1 M	64%
4	2.0 equiv.	2 M	61%
5	2.0 equiv.	2 M	58%
6	2.5 equiv.	2 M	64%
7	3.0 equiv.	2 M	64%
8	4.0 equiv.	2 M	71%
9	5.0 equiv.	2 M	72%



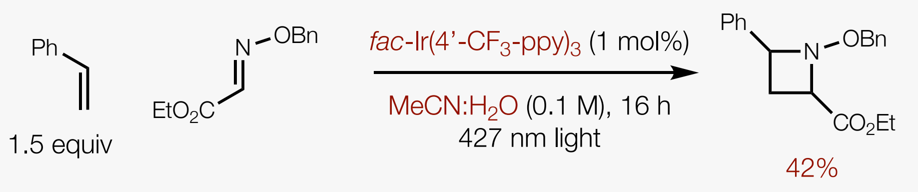
Original Conditions: HFIP (degassed by freeze-pump-thaw) (1.0 M), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol %), styrene (2.0 equiv.), 465 nm irradiation, 20 h.

Table S5: Final optimization of conditions in HFIP.

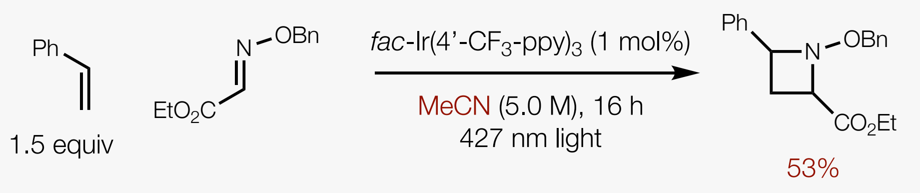
Entry	Change from Original Condition	Yield
1	none	84%
2	10.0 equiv. styrene	69%
3	5.0 equiv. styrene	79%
4	2.5 equiv. styrene	86%
5	1.0 equiv. styrene	60%
6	0.25 M	73%
7	0.5 M	78%
8	2.0 M	83%
9	1 h	15%
10	2 h	29%
11	4 h	47%
12	6 h	63%
13	16 h	73%
14	20 h	75%
15	24 h	76%
16	48 h	55%
17	456 nm Kessil lamp	56%
18	sparging HFIP rather than freeze pump thaw HFIP	84%
19	456 nm low intensity	70%
20	acetonitrile as solvent	62%

Reaction optimization

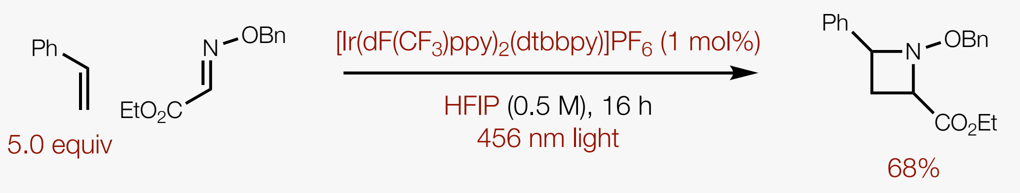
Round 1: solvents and photosensitizers



Round 2: water is just generating concentrated MeCN droplets

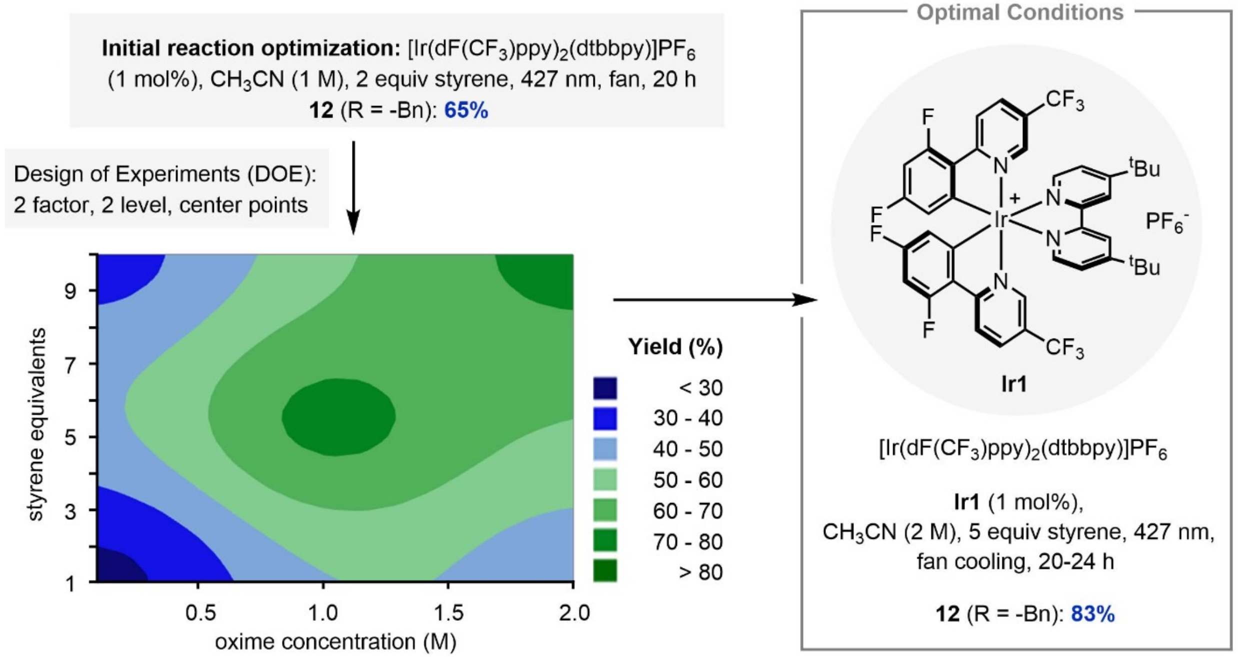


Round 3: more combinations of equivs, solvents, PSs and lights

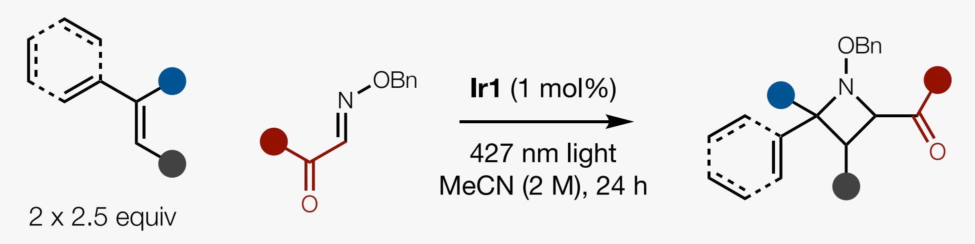


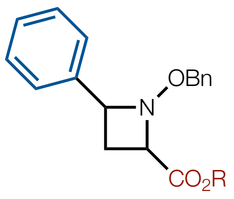
Round 4 and beyond

1. Switched to CO_2Bn oxime because higher yielding.
2. DoE with HFIP as solvent.
3. HFIP incompatible with electron-rich styrenes ➜ change to MeCN.
4. DoE with MeCN and final optimization.



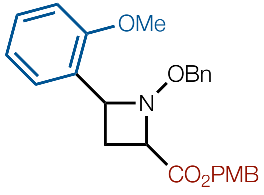
Selected scope



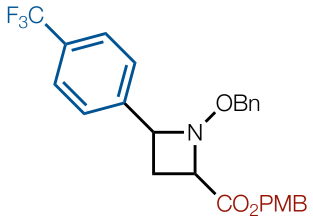


R = Et 43%, 1.2:1 dr

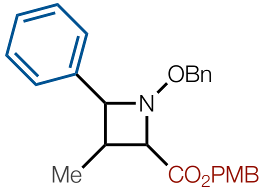
R = Bn 67%, 1.2:1 dr



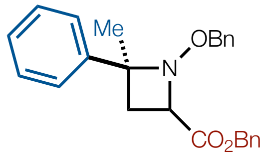
80%, 1:1 dr



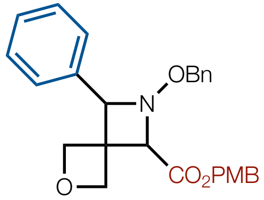
33%, 1.4:1 dr



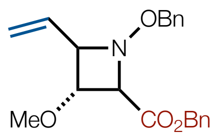
49%, 1:1 dr



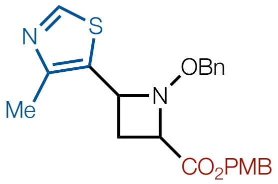
20%, 1.4:1 dr



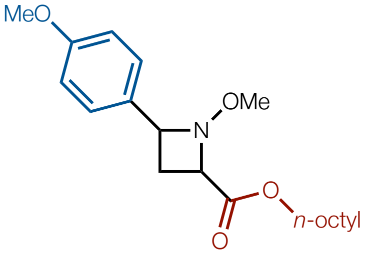
31%, 6.4:1 dr



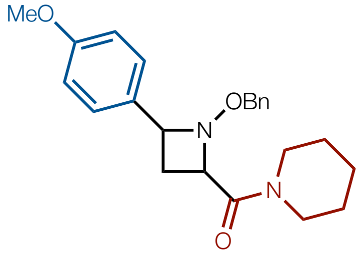
48%, single isomer



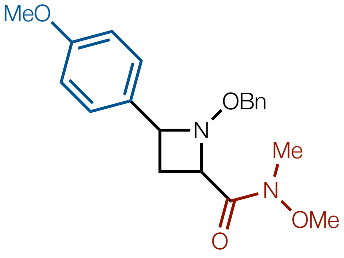
55%, 1.2:1 dr



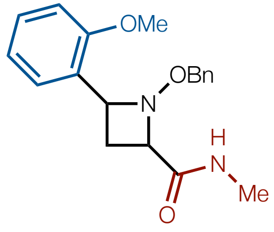
57%, 1:1 dr



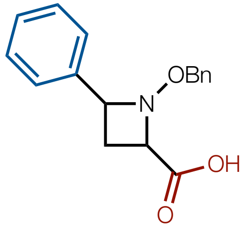
17%, 1.5:1 dr



26%, 2.2:1 dr

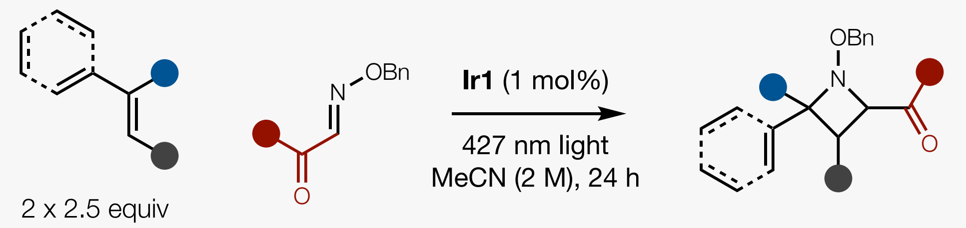


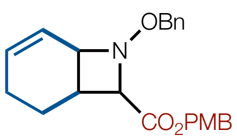
46%, 1:1 dr



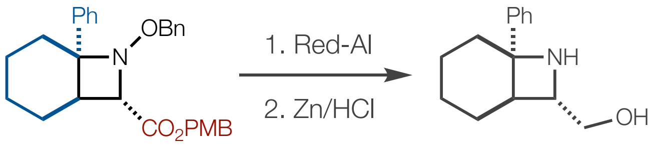
46%, 1.2:1 dr

Selected scope



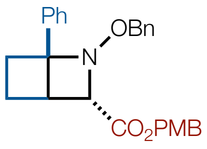


73%, 1.8:1 dr

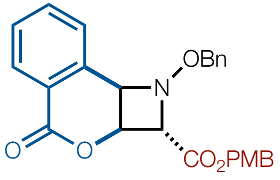


99%, single isomer

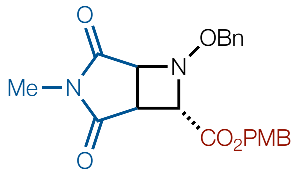
41%



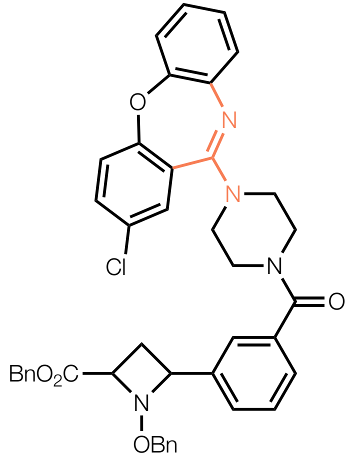
30%, single isomer



34%, single isomer

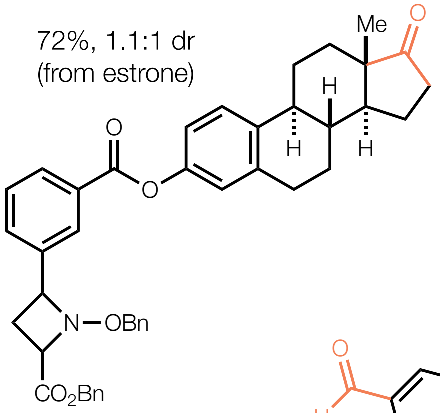


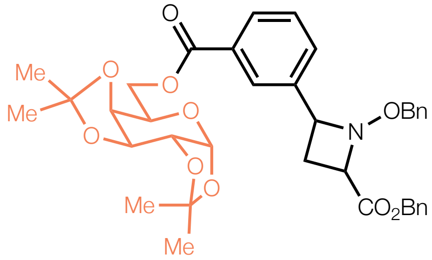
60%, 2:1 dr



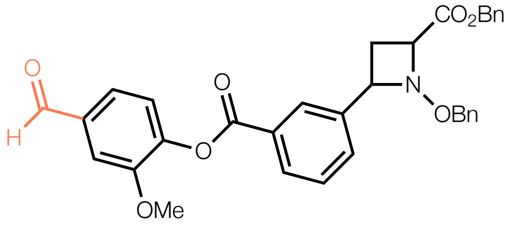
33%, 1.1:1 dr
(from amoxapine)

72%, 1.1:1 dr
(from estrone)

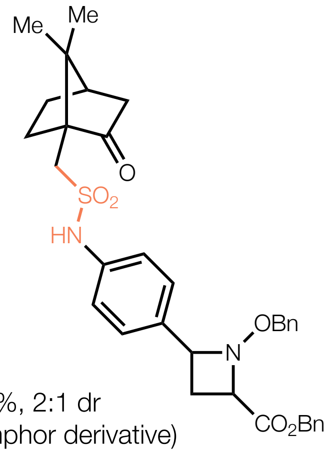




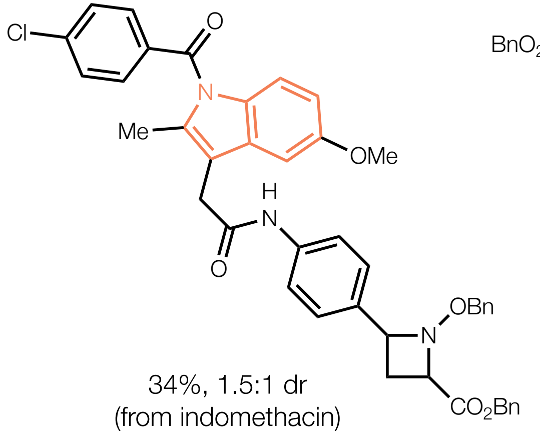
40%, 1.4:1 dr
(from D-galactose diacetal)



31%, 1.1:1 dr
(from vanillin)



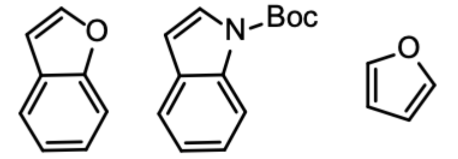
69%, 2:1 dr
(from camphor derivative)



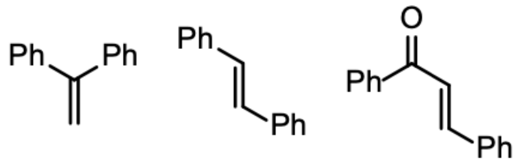
34%, 1.5:1 dr
(from indomethacin)

Unsuccessful substrates

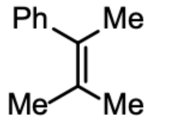
Alkenes



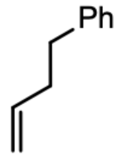
cyclic heteroaromatic compounds



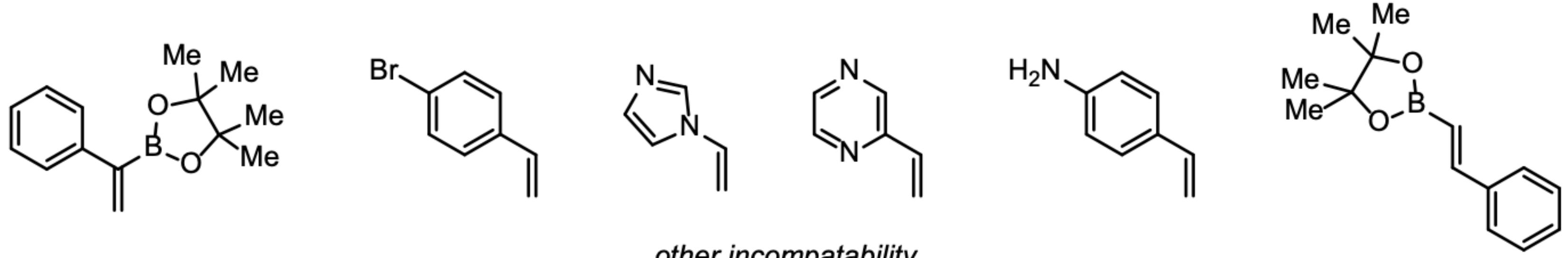
highly conjugated alkenes



steric hindrance

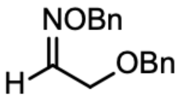


unactivated alkene

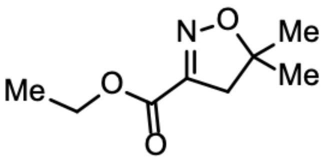


other incompatability

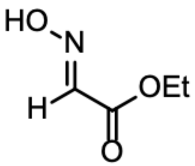
Oximes



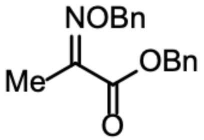
unactivated oxime



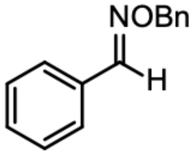
isoxazoline



unprotected oxime



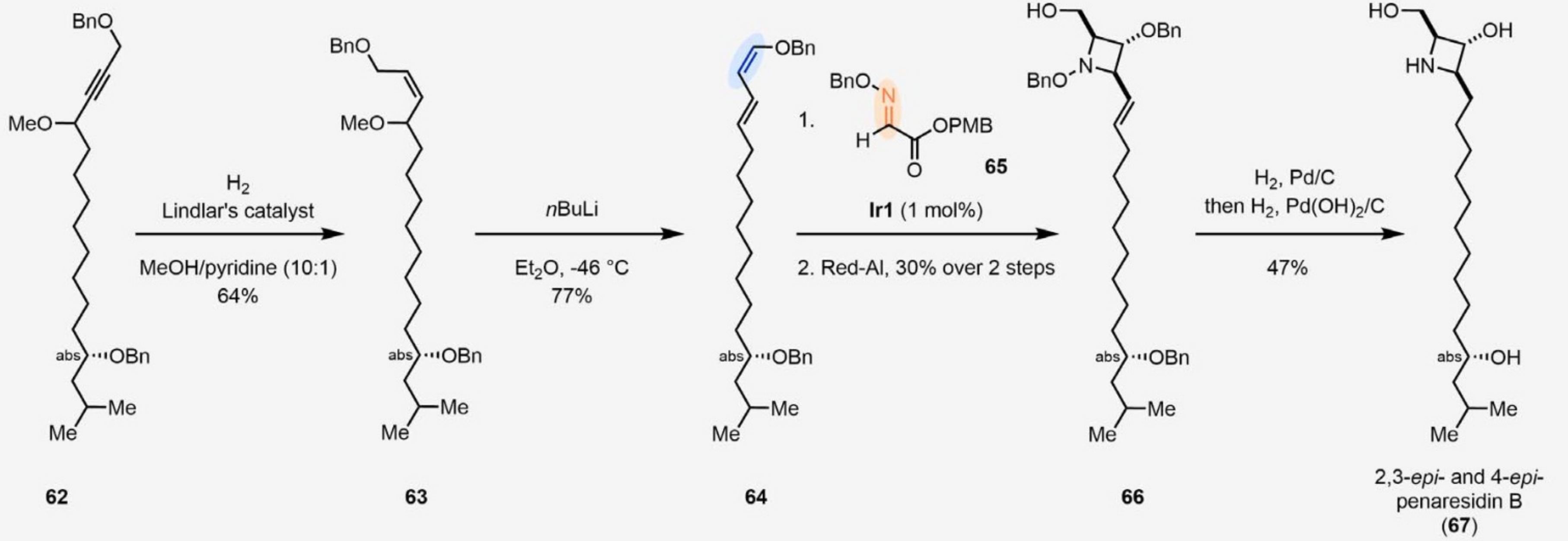
ketone-derived acyclic oximes



aryl oximes

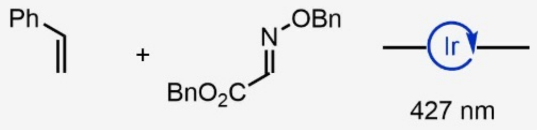
Application

Synthesis of *epi*-penaresidin B via visible-light-mediated aza Paternò-Büchi reaction:



Mechanistic studies

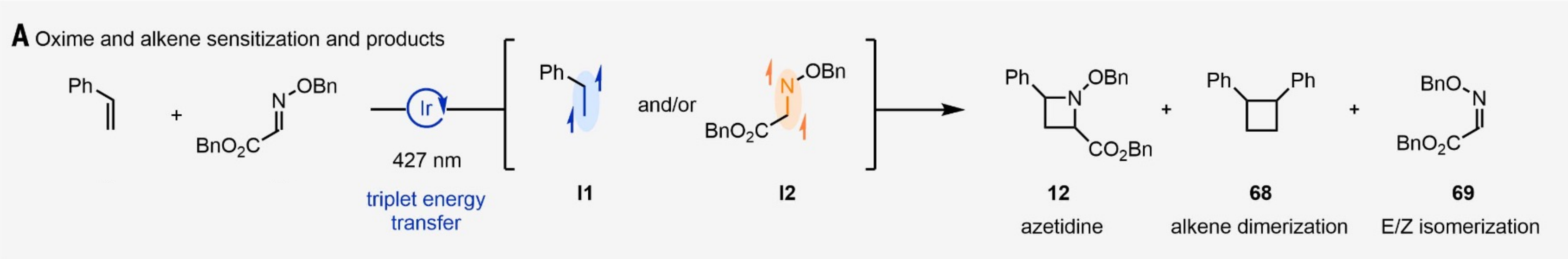
A Oxime and alkene sensitization and products



EnT with photocatalyst more likely than RedOx events

1. CV data
2. Photocatalysts with different RedOx potentials.

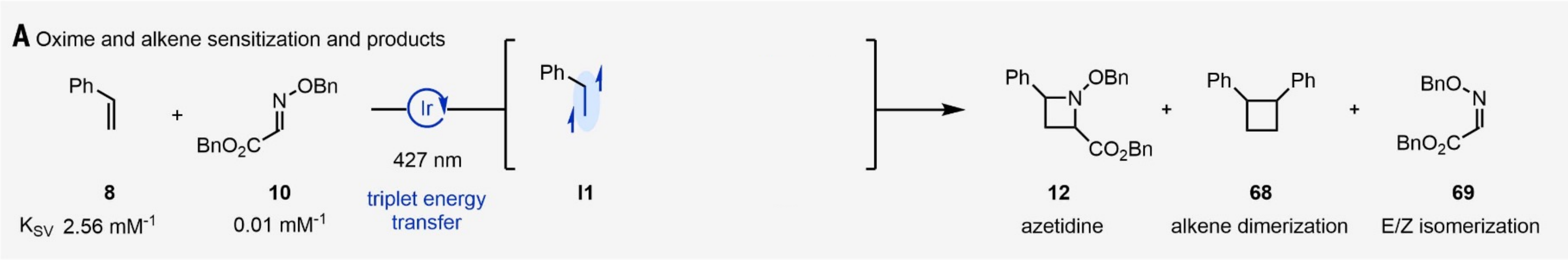
Which substrate is sensitized?



EnT with photocatalyst more likely than RedOx events

1. CV data
2. Photocatalysts with different RedOx potentials.

Which substrate is sensitized?

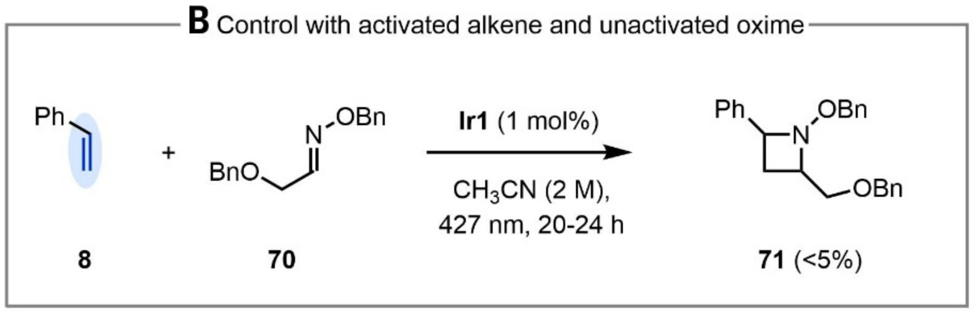


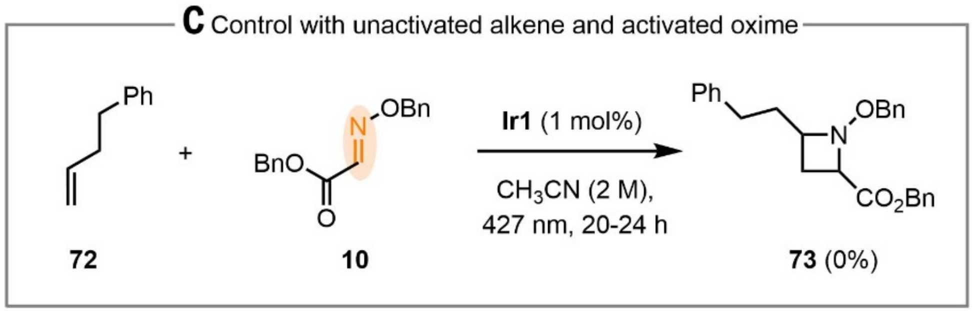
EnT with photocatalyst more likely than RedOx events

1. CV data
2. Photocatalysts with different RedOx potentials.

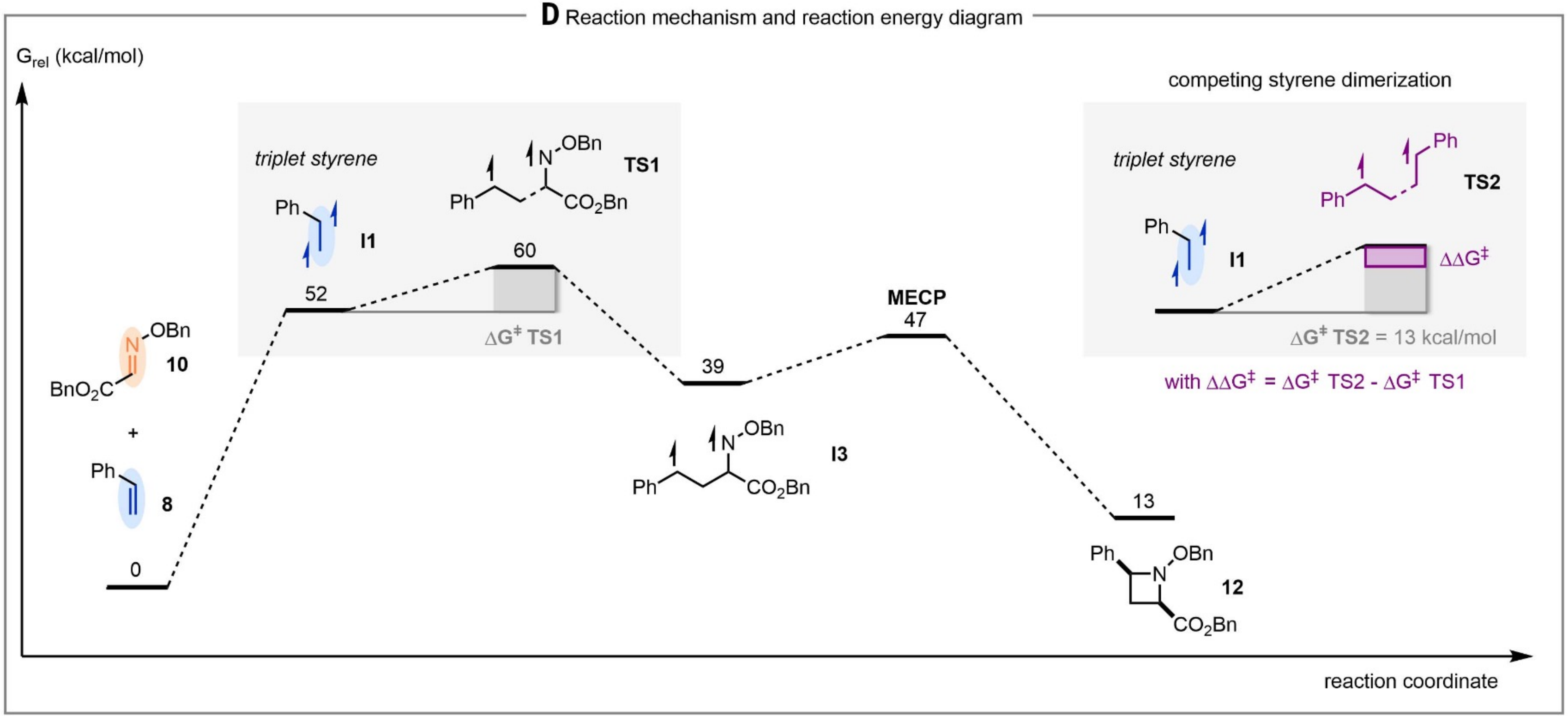
Sensitization of styrene most likely for productive pathway

1. Stern–Volmer analysis
2. 5 equivalents of styrene required.

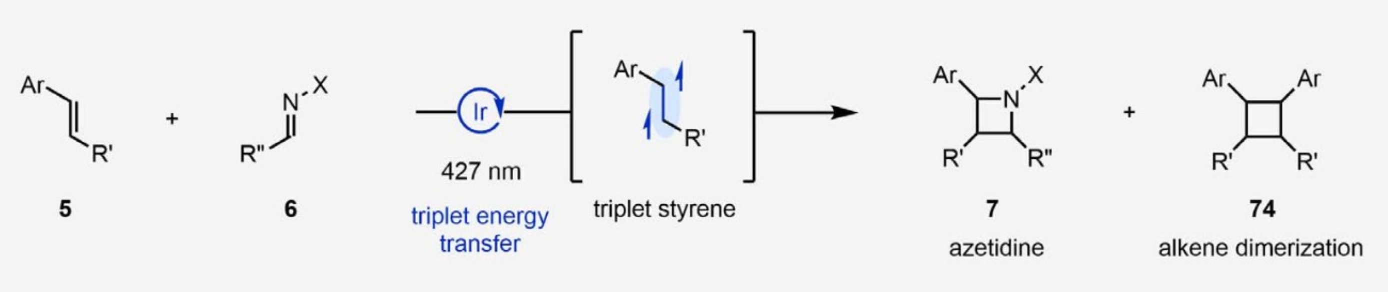


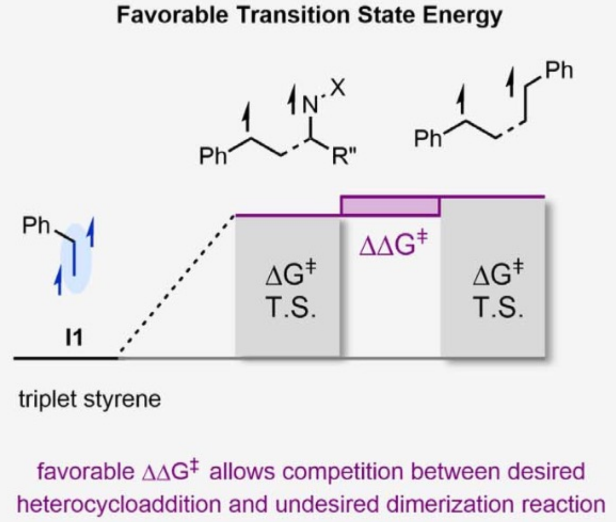


Reaction Energy Diagram

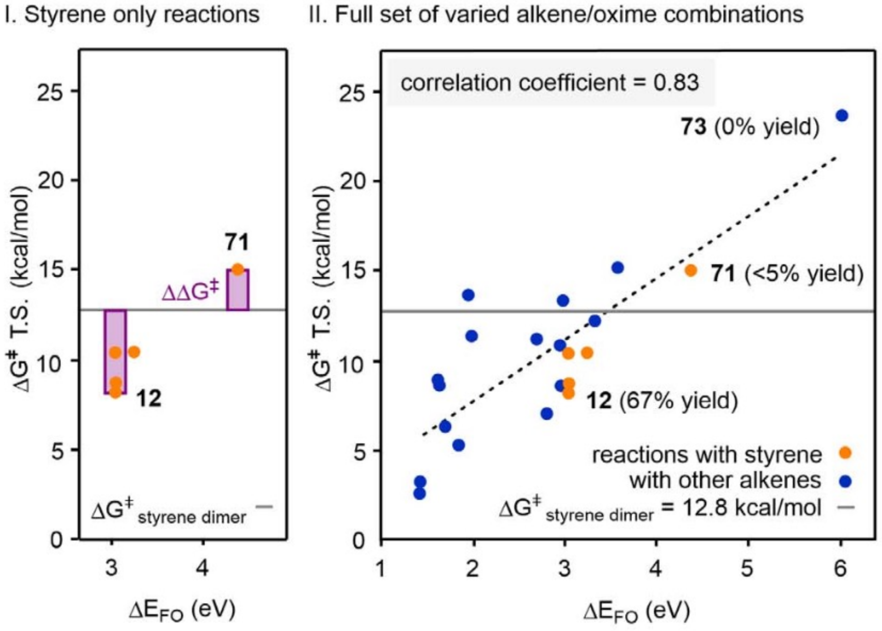


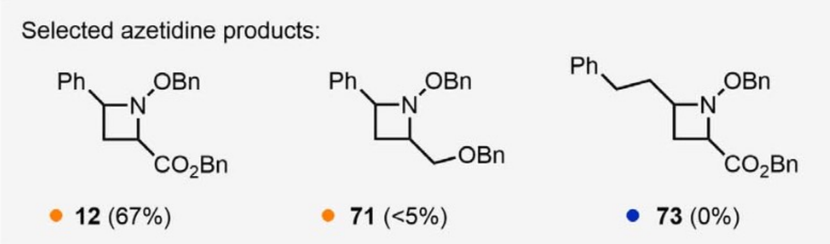
Requirement for desired reactivity



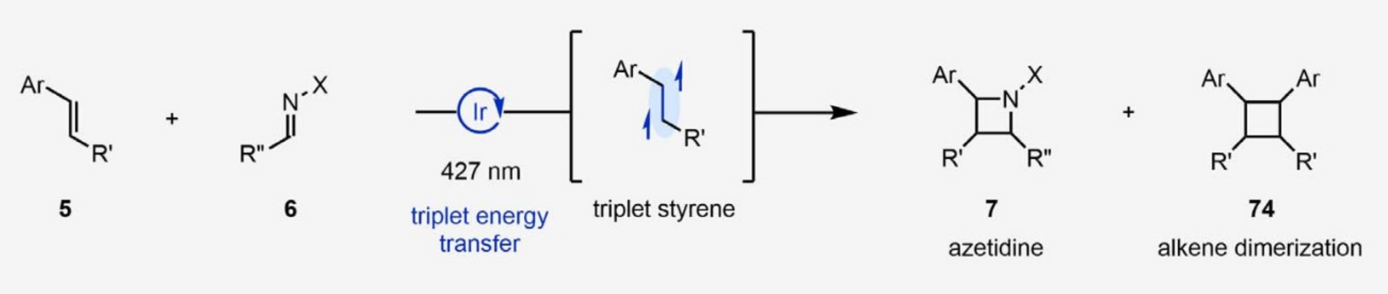


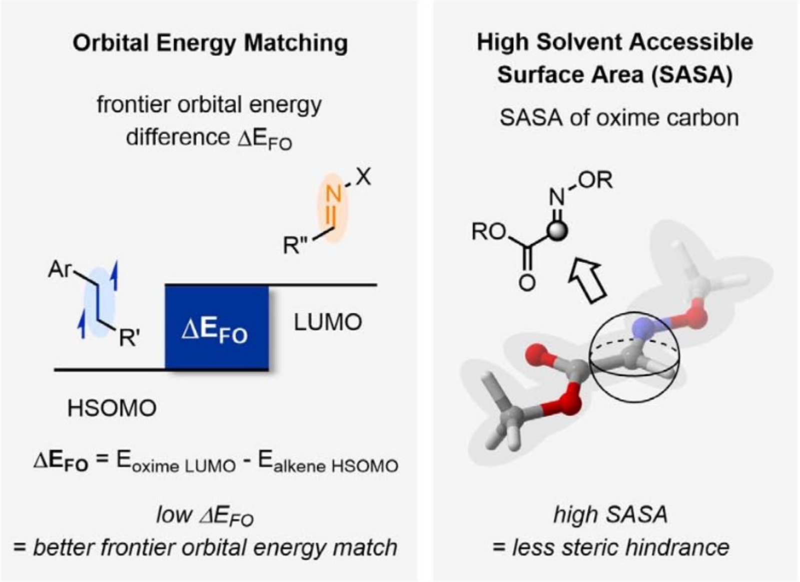
Competitive $\Delta G^{\ddagger}$ required for azetidine formation
Low $\Delta G^{\ddagger}$ enabled by low ΔE_{FO}





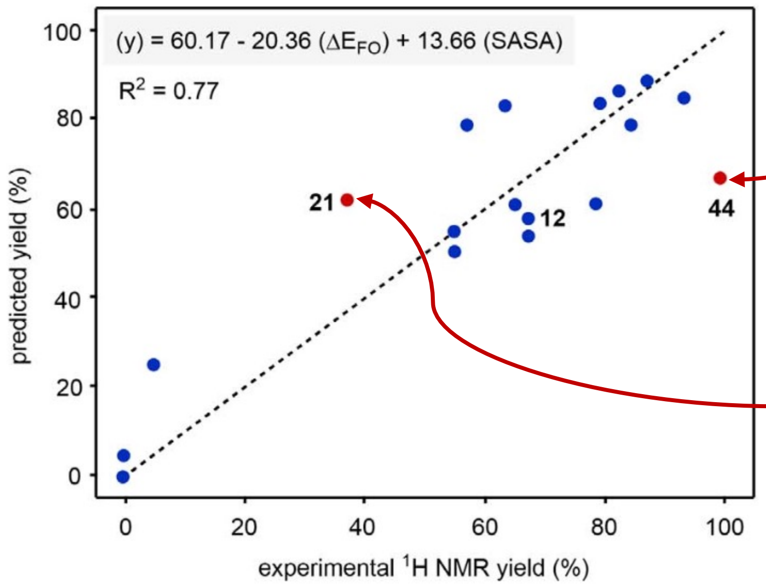
Requirement for high yields





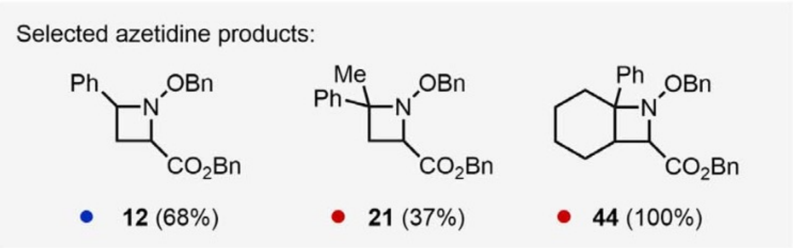
Low ΔE_{FO} and high oxime SASA enable high yield

III. Linear regression model relating yield to ΔE_{FO} and SASA



Increased triplet lifetime of cyclic styrene

Increased steric hindrance of disubstituted alkene



Summary

- Modular synthesis of di, tri and tetra-substituted azetidines.

➜ Seems very useful for library-generation in MedChem.

- First useful strategy for monocyclic aza Paternò-Büchi.
- Thorough documentation (optimization, failed substrates…)
- Thorough mechanistic study gives fundamental insight into the underlying factors that control reactivity.

➜ Actually useful for future practitioners to choose substrates likely to work.

➜ Concepts potentially applicable to [2+2] photoredox-catalyzed reactions in general.

Future directions?

- Find a way to expand scope to non-activated alkenes.
- Other activated imines (non-ester oximes, sulfinimines [Ellman!], sulfonyl imines, hydrazones…)
- Apply mechanistic concept of ΔE_{FO} to other [2+2] cycloadditions (PB, hetero alkene [2+2]).

Light Synthesis of Azetidines

nature catalysis

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Radical strain-release photocatalysis for the synthesis of azetidines

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ORGANIC CHEMISTRY

Visible light–mediated aza Paternò–Büchi reaction of acyclic oximes and alkenes to azetidines

Emily R. Wearing[1], Yu-Cheng Yeh[1], Gianmarco G. Terrones[2]†, Seren G. Parikh[1]†, Ilia Kevlishvili[2], Heather J. Kulik[2,3]*, Corinna S. Schindler[1,4,5,6]*

The aza Paternò–Büchi reaction is a [2+2]-cycloaddition reaction between imines and alkenes that produces azetidines, four-membered nitrogen-containing heterocycles. Currently, successful examples rely primarily on either intramolecular variants or cyclic imine equivalents. To unlock the full synthetic potential of aza Paternò–Büchi reactions, it is essential to extend the reaction to acyclic imine equivalents. Here, we report that matching of the frontier molecular orbital energies of alkenes with those of acyclic oximes enables visible light–mediated aza Paternò–Büchi reactions through triplet energy transfer catalysis. The utility of this reaction is further showcased in the synthesis of *epi*-penaresidin B. Density functional theory computations reveal that a competition between the desired [2+2]-cycloaddition and alkene dimerization determines the success of the reaction. Frontier orbital energy matching between the reactive components lowers transition-state energy ($\Delta G^{\ddagger}$) values and ultimately promotes reactivity.

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