Cleavage of disulfide bonds using visible light

Literature seminar

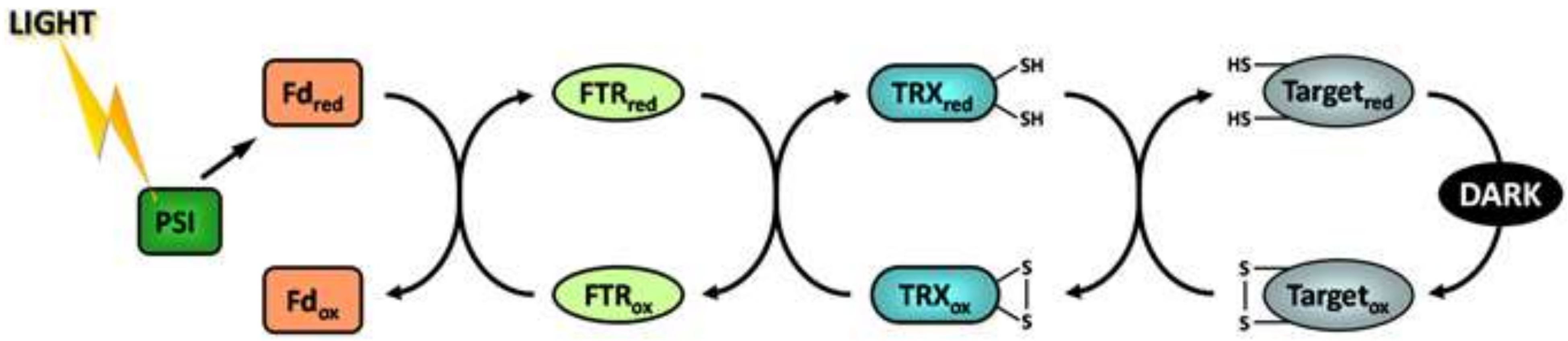
M1 Yuto Azumaya

index

1. Introduction
2. Formation of CTC
3. Triplet–triplet energy transfer
4. Photoreduction
5. Summary

Introduction : Disulfide cleavage

Ex. Regulation of the activity of enzymes related to photosynthesis

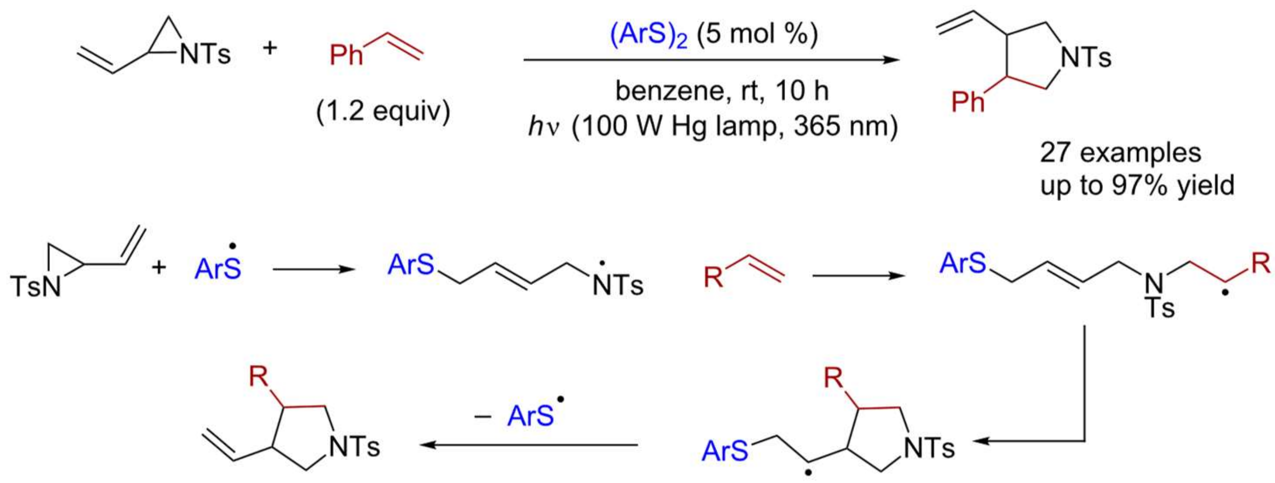


Michelet L, Zaffagnini M, et. al,., (2013) *Front. Plant Sci*. **4**:470.

Introduction : Disulfide cleavage ②

Disulfide cleaves with UV.

ex.) T. Hashimoto, K. Takino, K. Hato, K. Maruoka, *Angew. Chem. Int. Ed.* **2016**, *55*, 8081.



- Visible light: more desirable (for use with biomolecules)

→How to break disulfide bonds using visible light?

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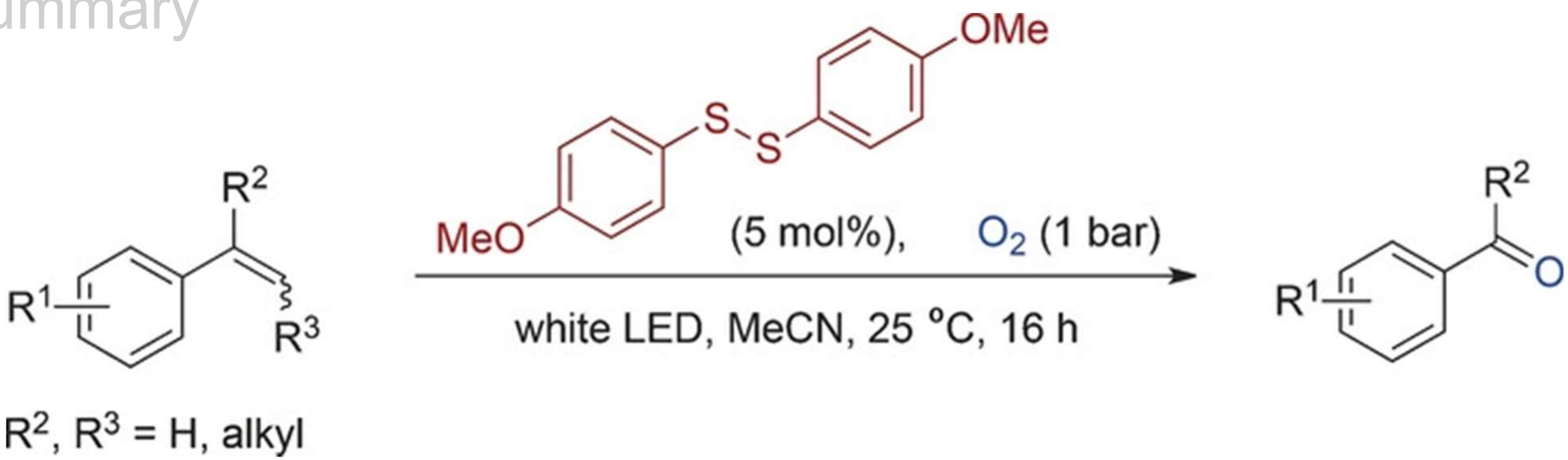


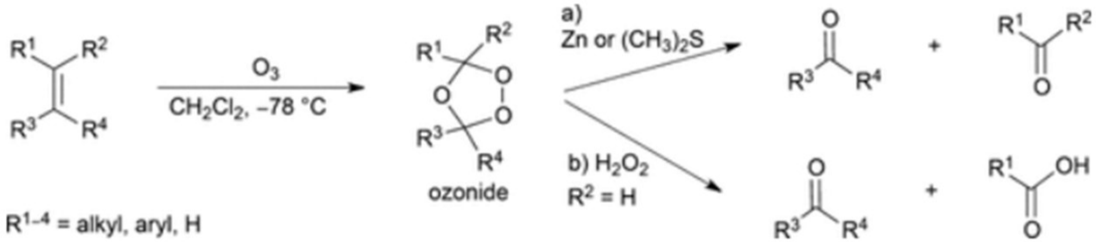
Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

Oxidative cleavage of olefins

Oxidative cleavage of olefins → useful method for obtaining ketones and aldehydes from olefins

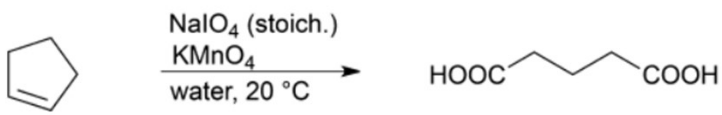
Typical Methods

ozonolysis



Oxidative cleavage with metal oxidizers: sometimes too strong

B)

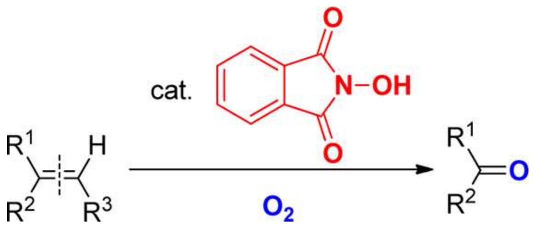


Both have safety issues.

Oxidative cleavage of olefins using molecular oxygen

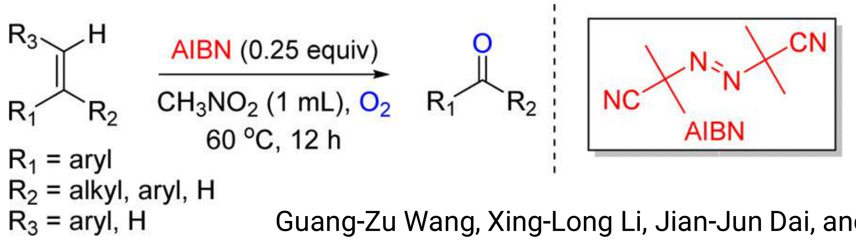
Molecular oxygen + radical initiator or transition metal catalyst
Cleaner method

NHPI



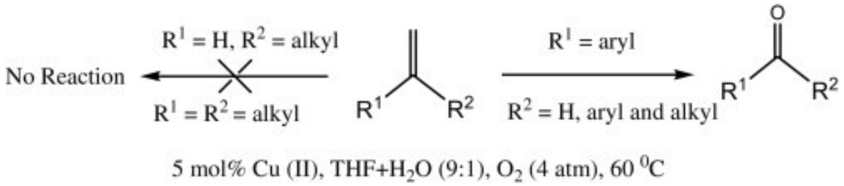
Riyuan Lin, Feng Chen, and Ning Jiao
Organic Letters **2012** *14* (16), 4158-4161

AIBN



Guang-Zu Wang, Xing-Long Li, Jian-Jun Dai, and Hua-Jian Xu
The Journal of Organic Chemistry **2014** *79* (15), 7220-7225

Cu



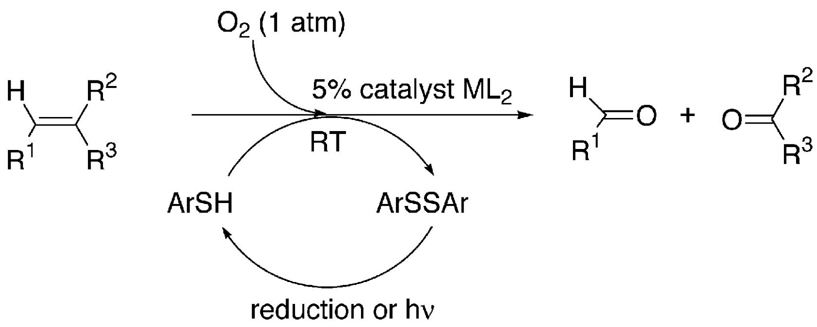
Md. Munkir Hossain, Shin-Guang Shyu,
Tetrahedron,70, 2,2014,251-255,0040-4020,

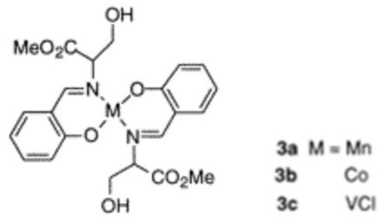
→ Both require heat

There is still no method of cleavage under mild and safe conditions.

Oxidative cleavage of olefins using light

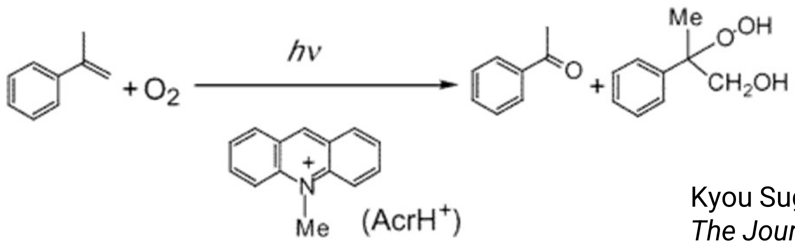
Metal or toxic non-metal catalysts





Xavier Baucherel, Jacques Uziel, and Sylvain Jugé
The Journal of Organic Chemistry **2001** *66* (13), 4504-4510

Photo-oxidation using Photoredox catalyst
→cost



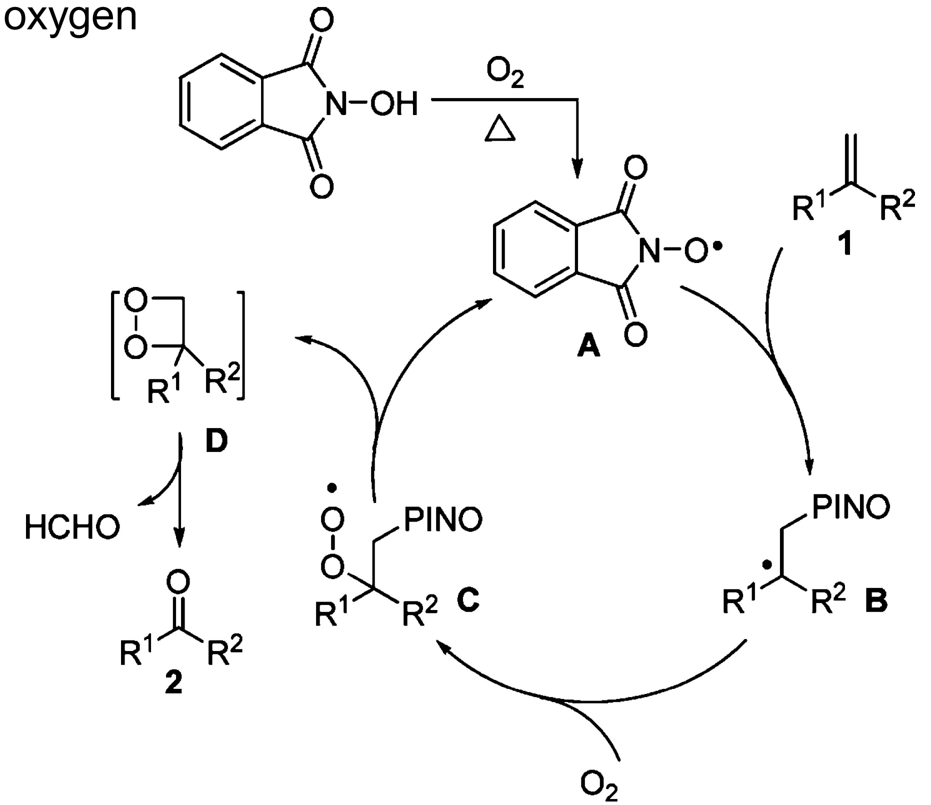
Kyou Suga, Kei Ohkubo, and Shunichi Fukuzumi
The Journal of Physical Chemistry A **2003** *107* (22), 4339-4346

Metal-free, low-cost catalysts are required.

Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

strategy

ex. Oxidative cleavage using NHPI and molecular oxygen

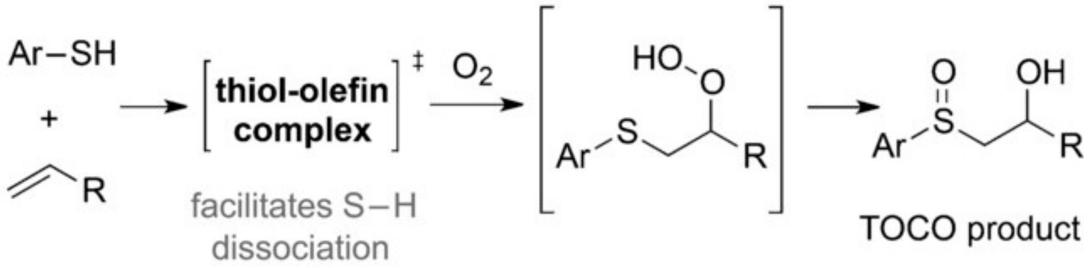


- In systems using molecular oxygen and radical initiators, dioxetane is the intermediate structure.
- They wondered if the thiyl radical could be used to catalyze the addition of oxygen and the formation of dioxetanes.
- But UV was needed.

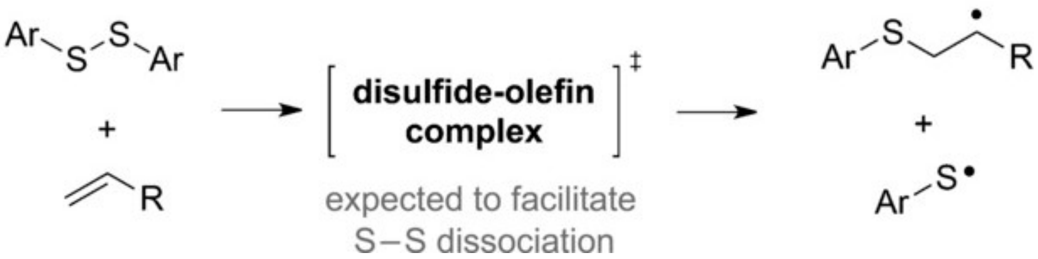
Riyuan Lin, Feng Chen, and Ning Jiao *Organic Letters* **2012** *14* (16), 4158-4161

strategy

TOCO： Olefins and thiols form CTCs and promote the entire oxidation process

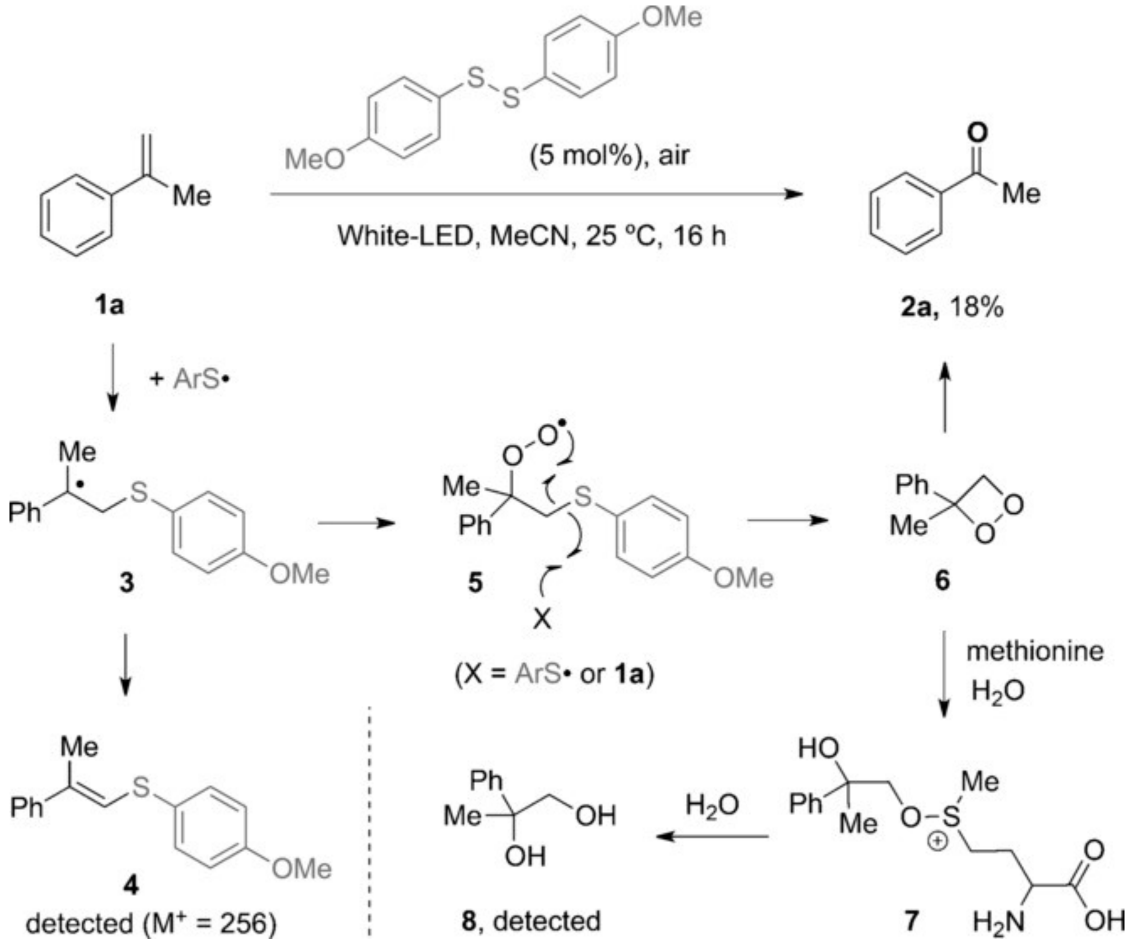


→ Can disulfide achieve the same effect?



Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

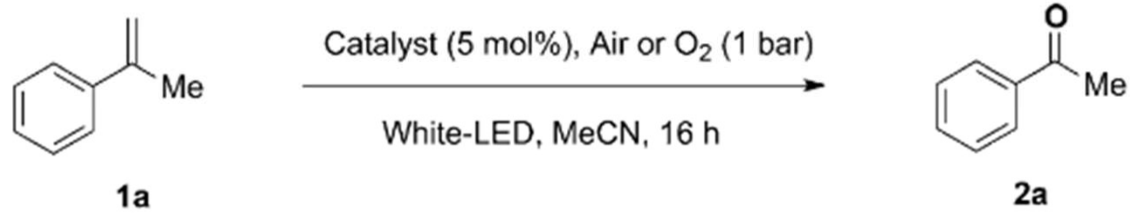
Initial conditions



Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

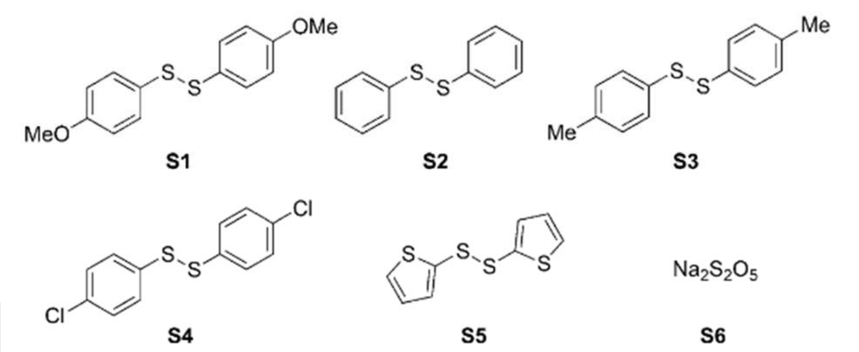
optimization

Table 1: Exploring reaction conditions.



Entry	Catalyst	Oxidant	Light	*T* [°C]	Yield [%][a]
1	none	air	white LED	25	0
2	**S1**	air	dark	25	0
3	**S1**	air	dark	45	0
4	**S1**	O_2	white LED	25	83
5	**S2**	O_2	white LED	25	53
6	**S3**	O_2	white LED	25	72
7	**S4**	O_2	white LED	25	70
8	**S5**	O_2	white LED	25	29
9	**S6**	O_2	white LED	25	0

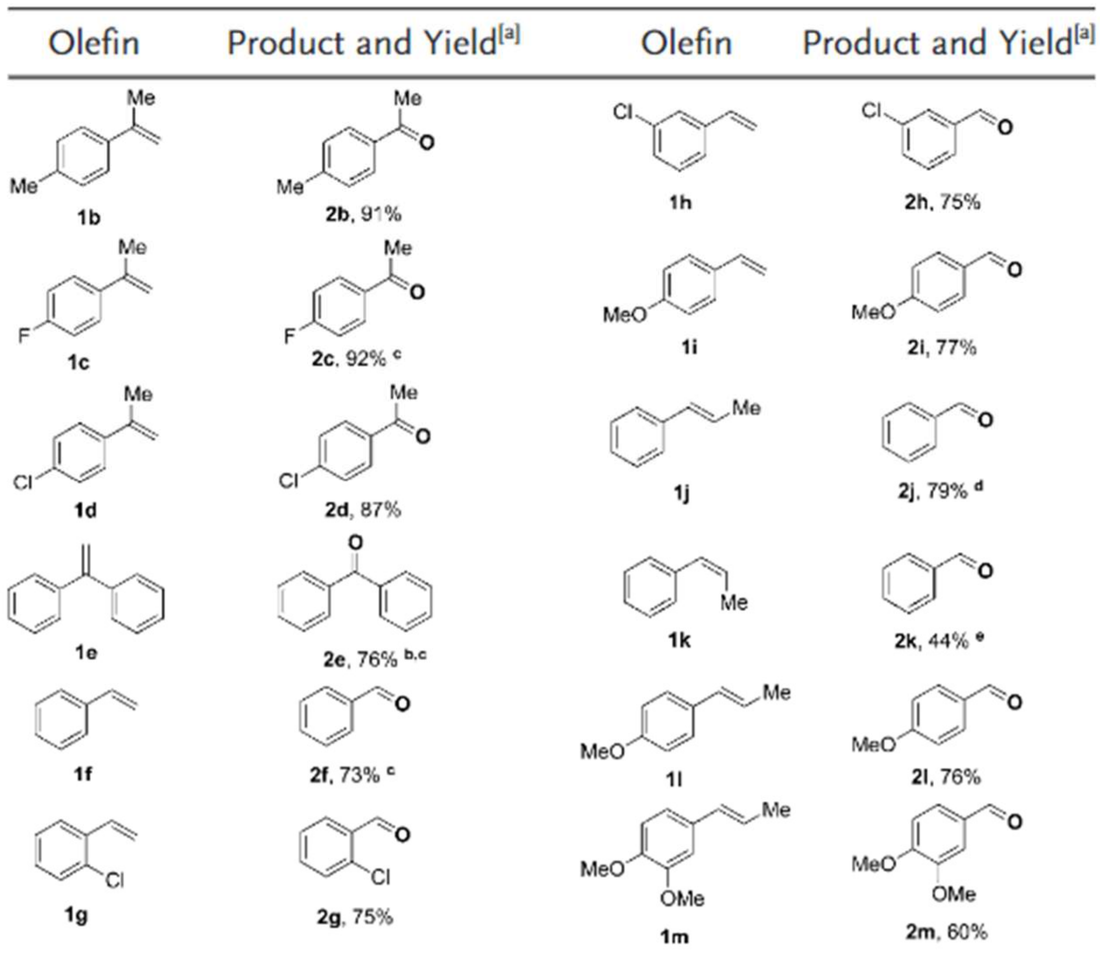
[a] Based on yields of isolated product.



Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

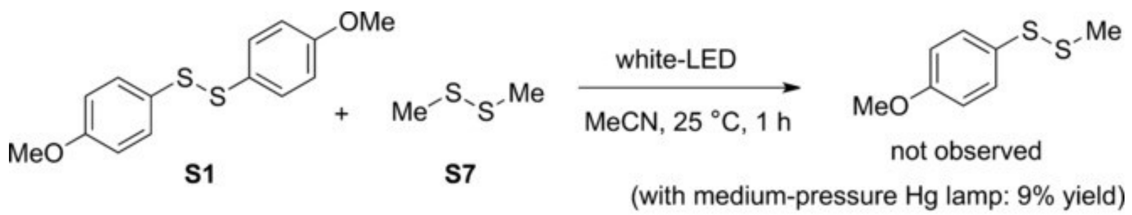
substrate scope

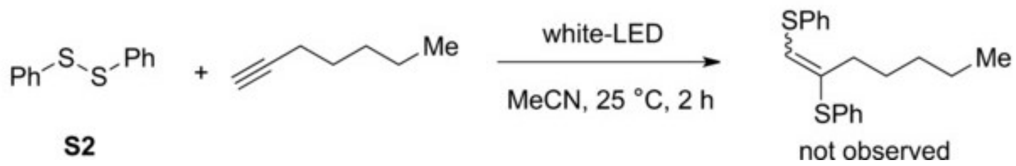
Olefin —[S1 (5 mol%), O_2 (1 bar); white-LED, MeCN, 25 °C, 16 h]→ Ketone / Aldehyde



Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

Mechanistic investigations

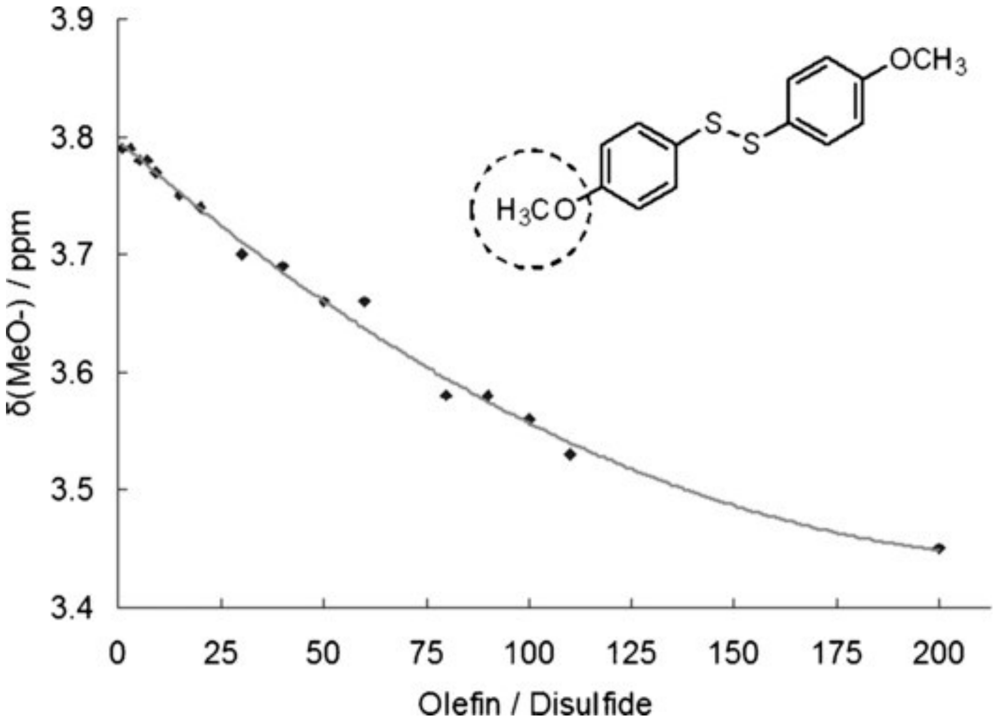




※Medium pressure HgLamp
→ Reaction progress (known)

Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

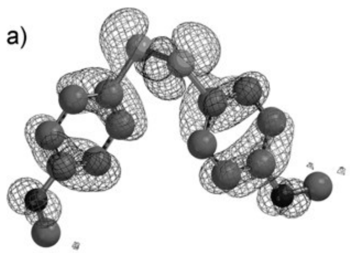
Mechanistic investigations



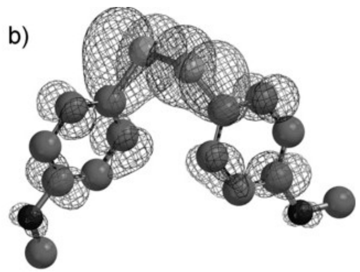
Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

Mechanistic investigations

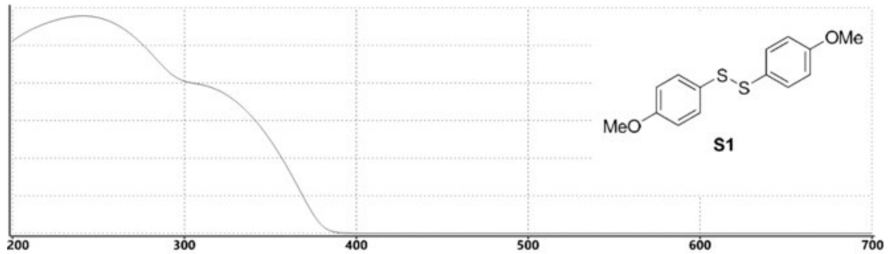
DFT calculation

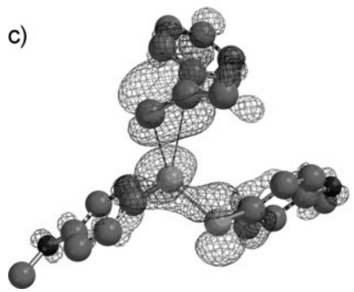


a) HOMO (**S1**)=−7.83 eV

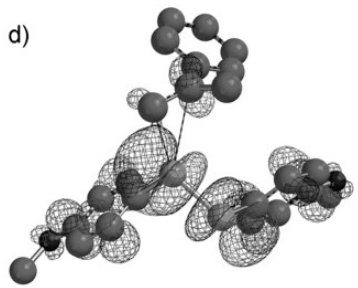


b) LUMO (**S1**)=+0.59 eV

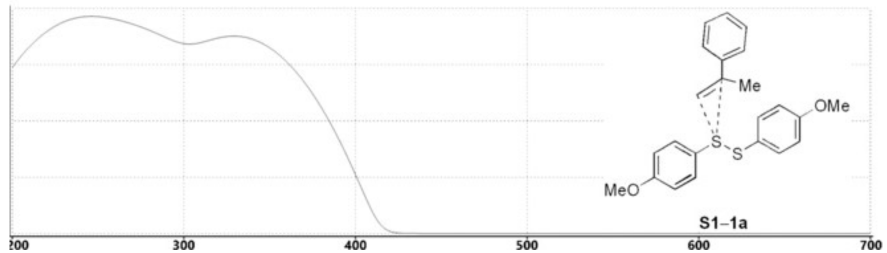




c) HOMO (**S1-1 a**)=−6.89 eV



d) LUMO (**S1-1 a**)=+0.42 eV

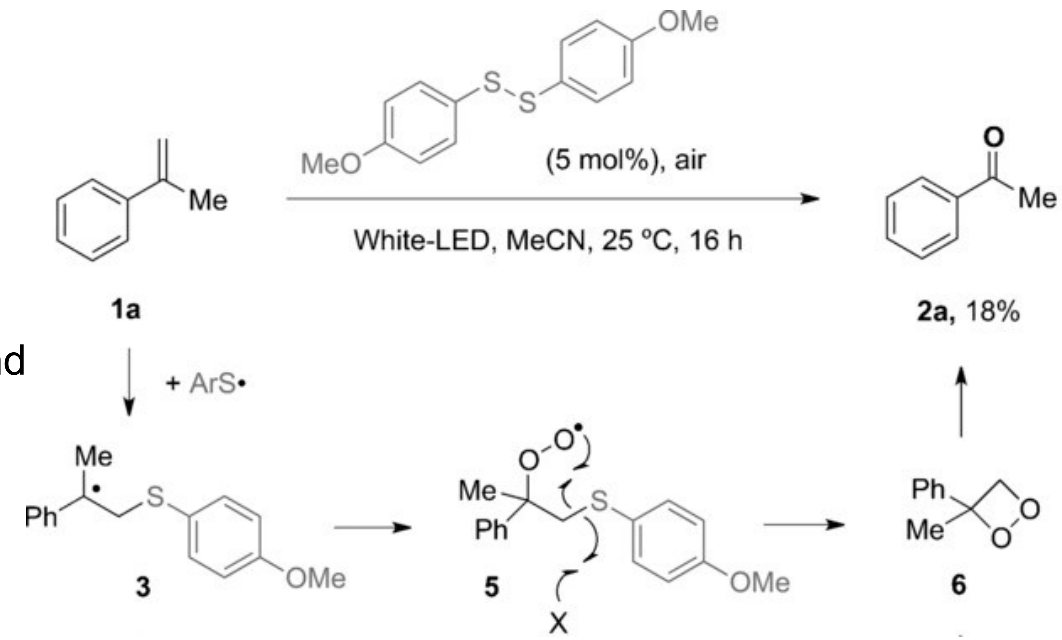


Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

short summary

Oxidative cleavage of olefins

Formation of CTC
→cleavage of disulfide bond
by visible light

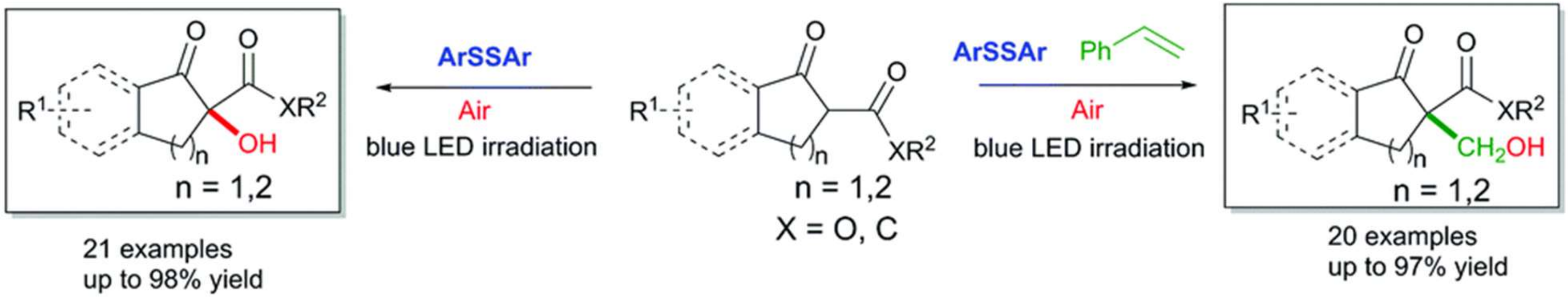


Addition of oxygen
→Formation of dioxetanes

Y. Deng, X.-J. Wei, H. Wang, Y. Sun, T. Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832.

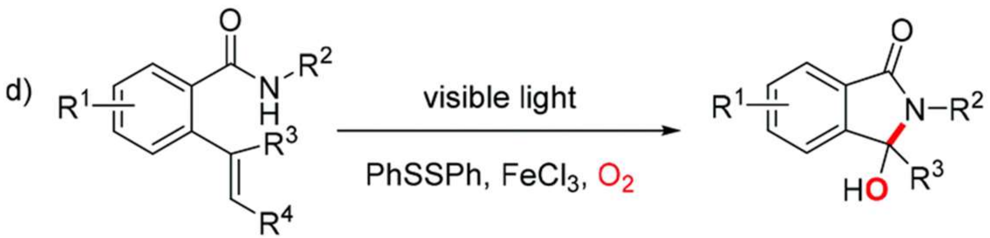
application

α-position hydroxylation of β-diketones



Jingnan Zhao, Fan Yang, et. al. Chem. Commun., 2019,**55**, 13008-13011

Synthesis of isoindolinone



Tao Ma, Jiawei Hua, et. al., Org. Chem. Front., 2022,**9**,25-31

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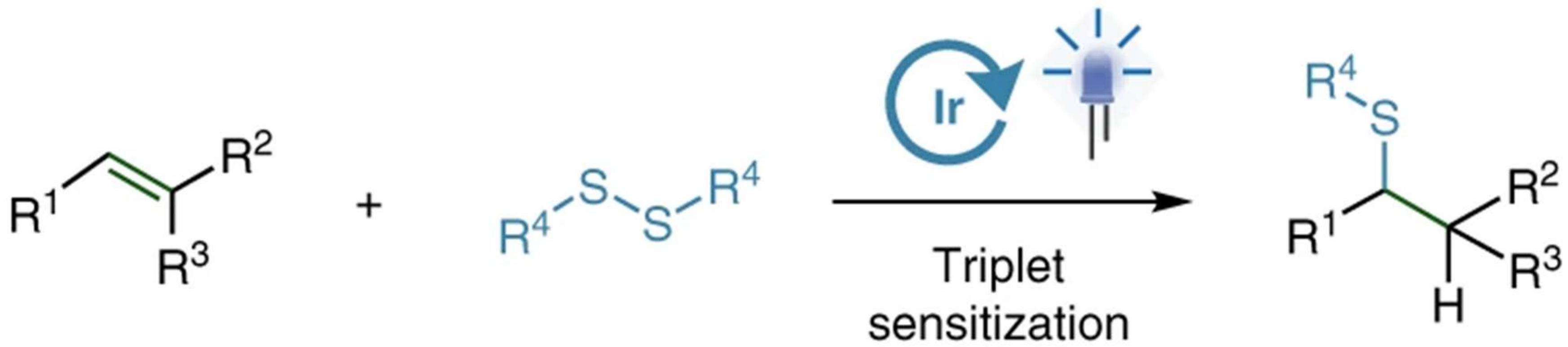
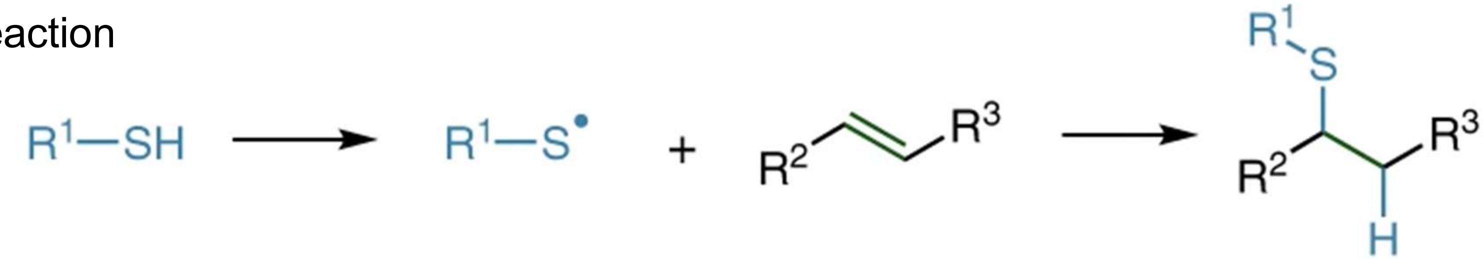


Teders, M., Henkel, C., Anhäuser, L. et al. Nature Chem 10, 981–988 (2018).

thiol-ene reaction

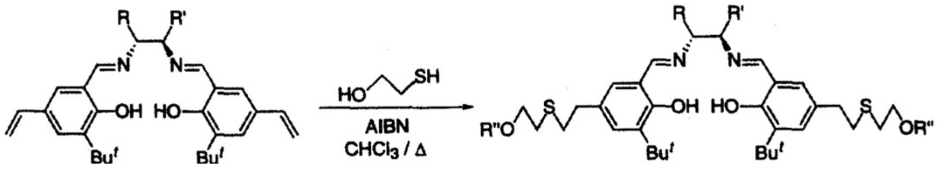
Thiol-ene reaction



Highly orthogonal → It has been applied to biomolecules

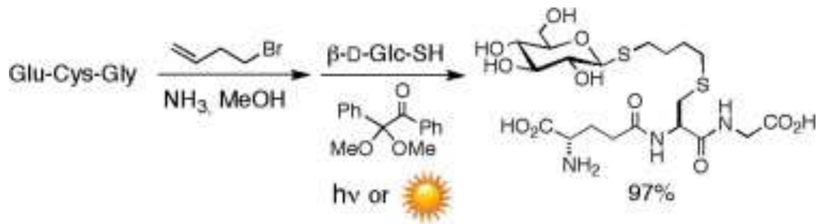
thiol-ene reaction without visible light

Radical initiator + heat



Filippo Minutolo, Dario Pini, et.al.
Tetrahedron:Asymmetry,7,8,1996,2293-2302,0957-4166,

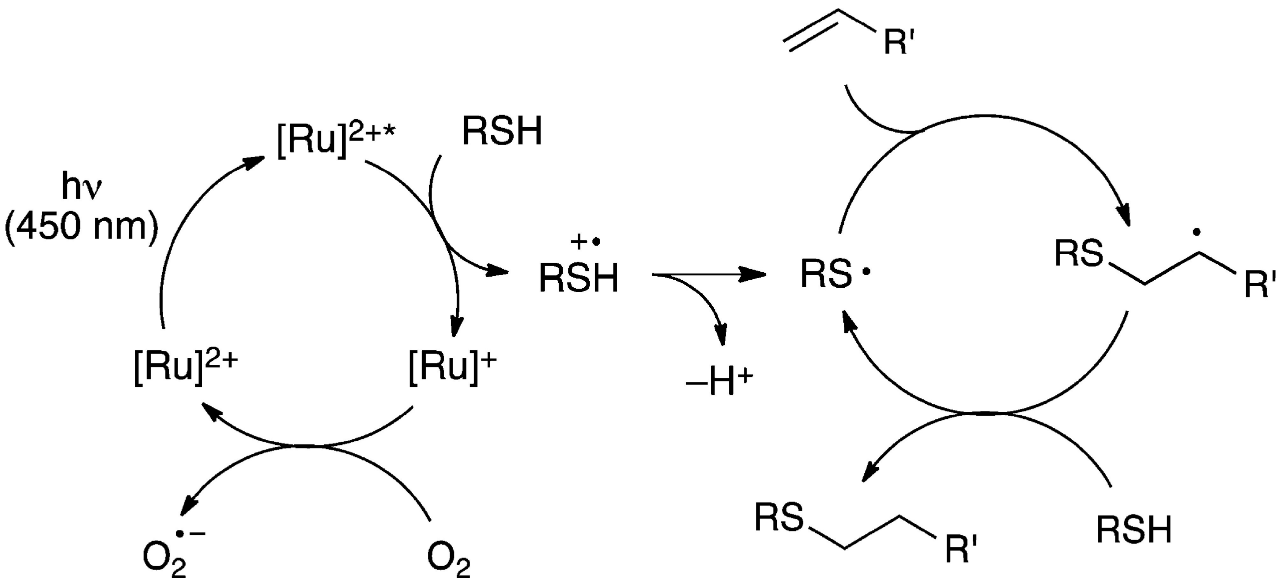
＋UV



Michele Fiore, Mauro Lo Conte,et.al.,
Tetrahedron Letters,52, 3,2011,444-447,0040-4039,

- Both are difficult to apply to biomolecules
- Cannot take advantage of high bio-orthogonality

thiol-ene reaction using visible light and thiol

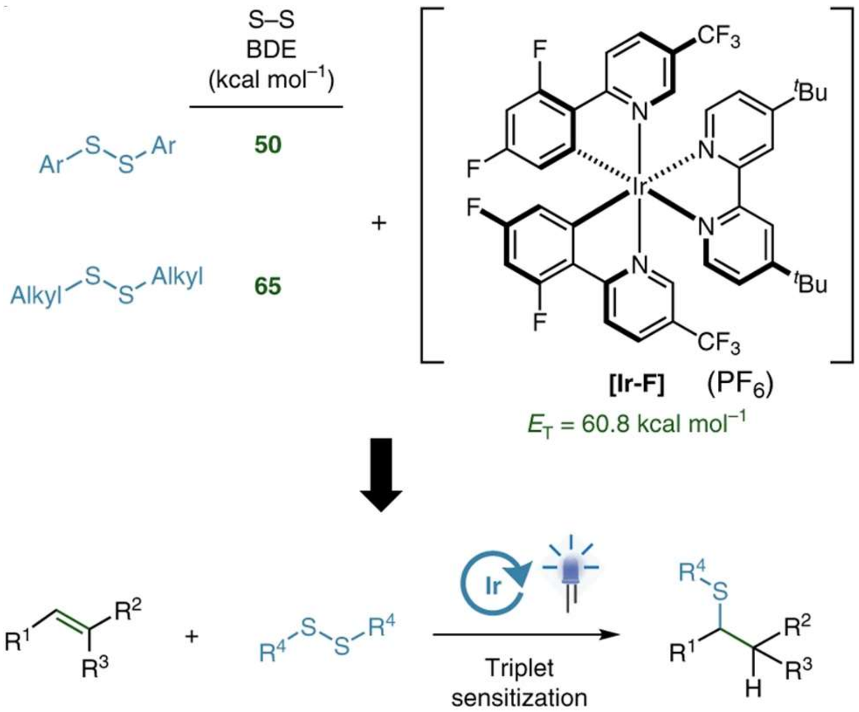


Elizabeth L. Tyson, Michael S. Ament, and Tehshik P. Yoon, J. Org. Chem. 2013, 78, 5, 2046–2050

- Mild reaction conditions
- Nucleophilicity of thiols
- Thiols that are gas at room temperature are difficult to handle
- Selectivity in the presence of other thiols

Teders, M., Henkel, C., Anhäuser, L. et al. Nature Chem 10, 981–988 (2018).

This time : thiol-ene reaction using visible light and disulfide



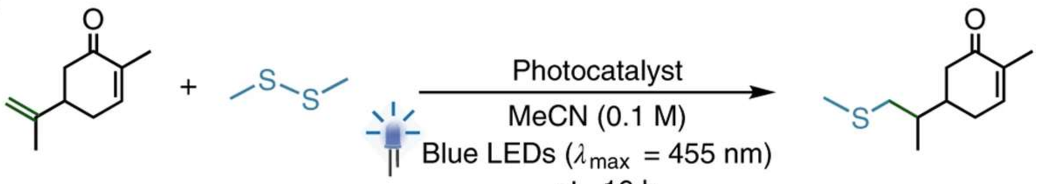
- S–S bond dissociation energies of aliphatic disulfides : ~65 kcal mol^{-1}
- direct sensitization of aryl disulfides using UV light

→alkylthiyl radicals would be accessible by using suitable photocatalysts for the energy transfer activation.

- mild reaction conditions
- No reaction with Michael acceptor
- Dimethyldisulfide is liquid→No need to handle gases
- Reduced odor and toxicity
- No other thiols in the system are involved

Initial screening

a

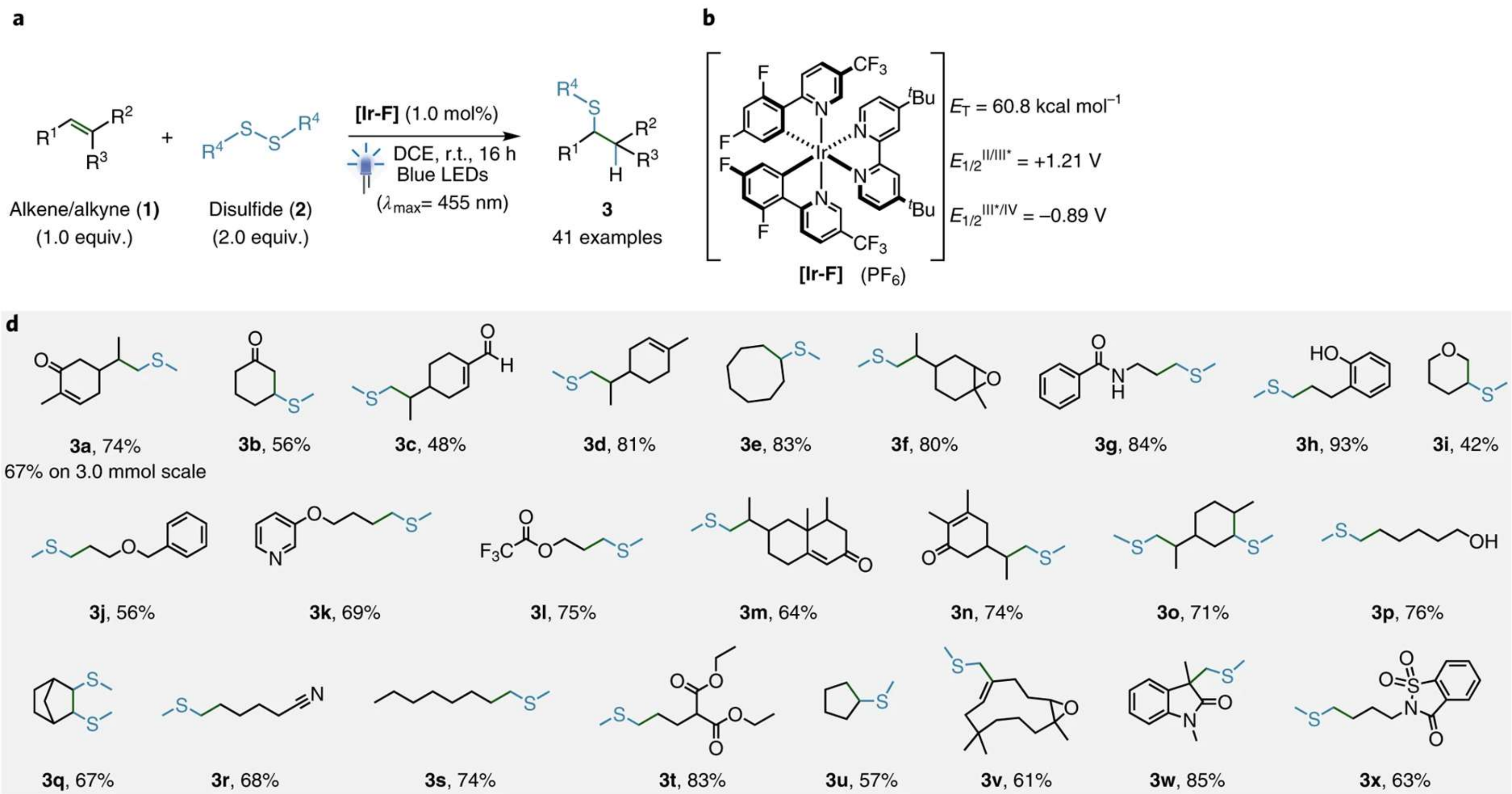


1a (1.0 equiv.) **2** (2.0 equiv.) **3a**

Photocatalyst	E_T (kcal mol^{-1})	$E_{1/2}^{II/III*}$ (V)	$E_{1/2}^{III*/IV}$ (V)	Quenching fraction F	Yield **3a** (%)
[Ir-F]	60.8	+1.21	–0.89	42	58
fac-[Ir(dF(ppy))$_3$]	59.1	+0.34	–1.44	24	53
[Ir(ppy)$_2$(NHC-F$_2$)]	57.8	+0.38	–1.49	31	47
fac-[Ir(ppy)$_3$]	57.8	+0.31	–1.73	19	46
[Ir(ppy)$_2$(dtbbpy)](PF$_6$)	49.2	+0.66	–0.96	<5	0
[Ru(bpz)$_3$](PF$_6$)$_2$	48.4	+1.45	–0.26	<5	0
[Ru(phen)$_3$](PF$_6$)$_2$	46.8	+0.82	–0.87	<5	0
[Ru(bpy)$_3$](PF$_6$)$_2$	46.5	+0.77	–0.81	<5	0

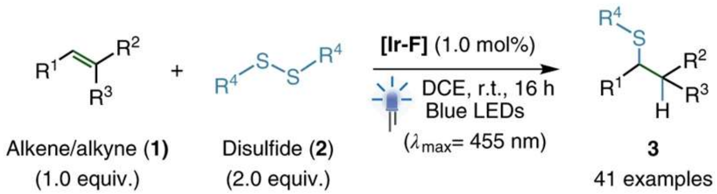
Increasing triplet excited-state energy

substrate scope (olefin)

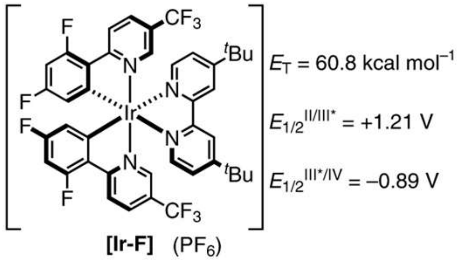


Substrate scope (disulfide)

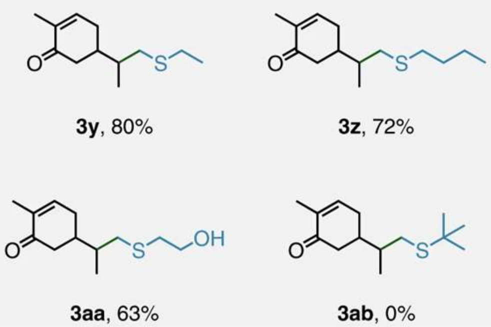
a



b



e



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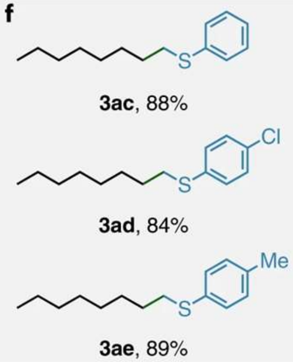
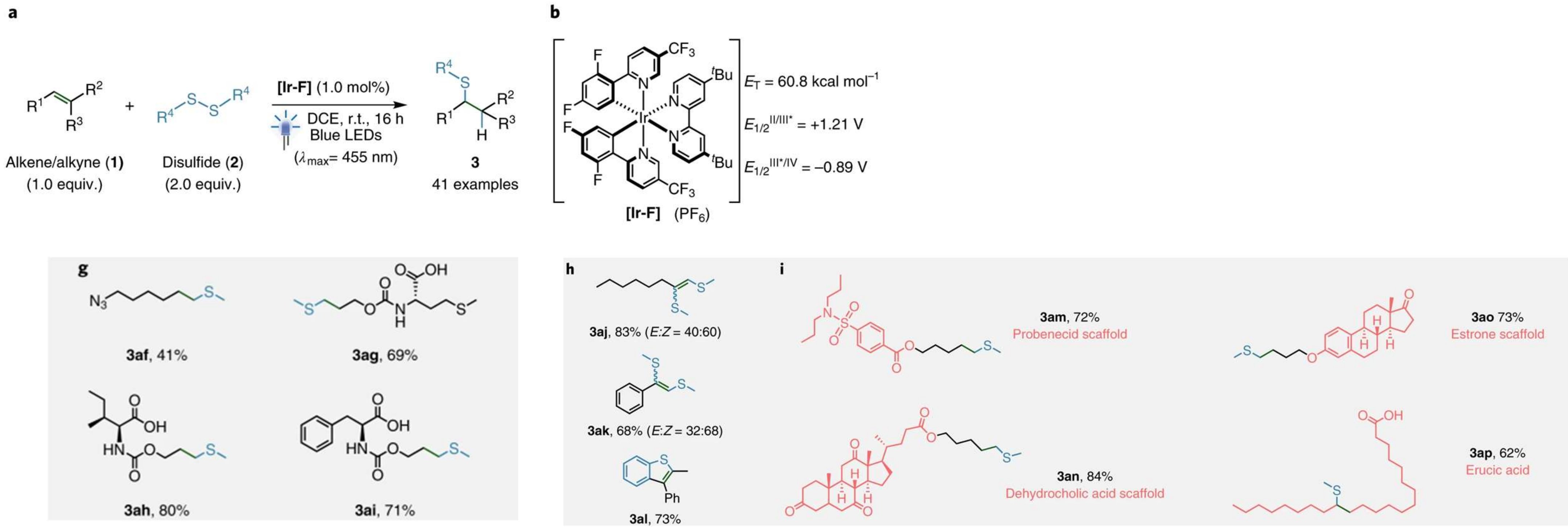
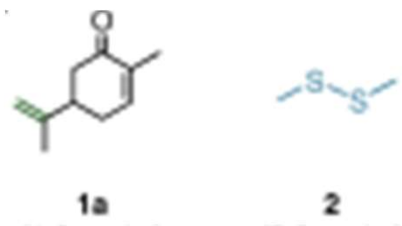


Mark W.H. Hoorens, Wiktor Szymanski,Volume 43, Issue 8,2018, 567-575,0968-0004,

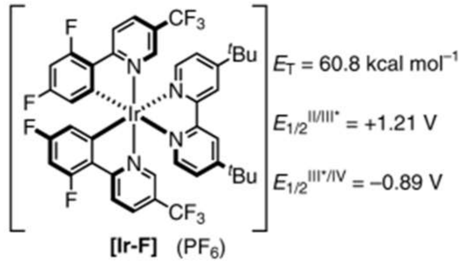
Substrate scope (olefin)

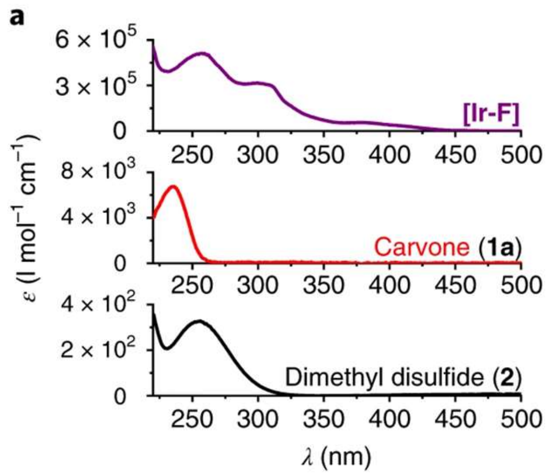


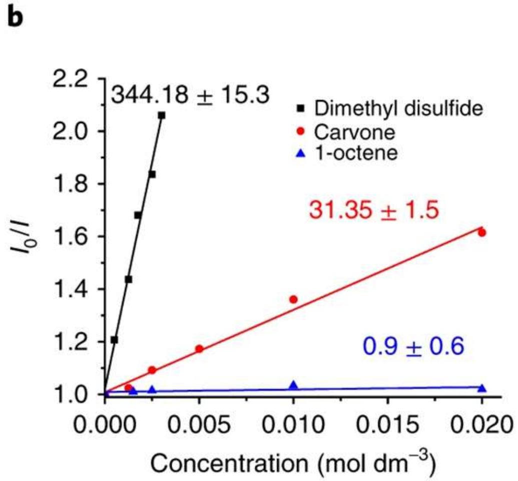
Mechanistic study

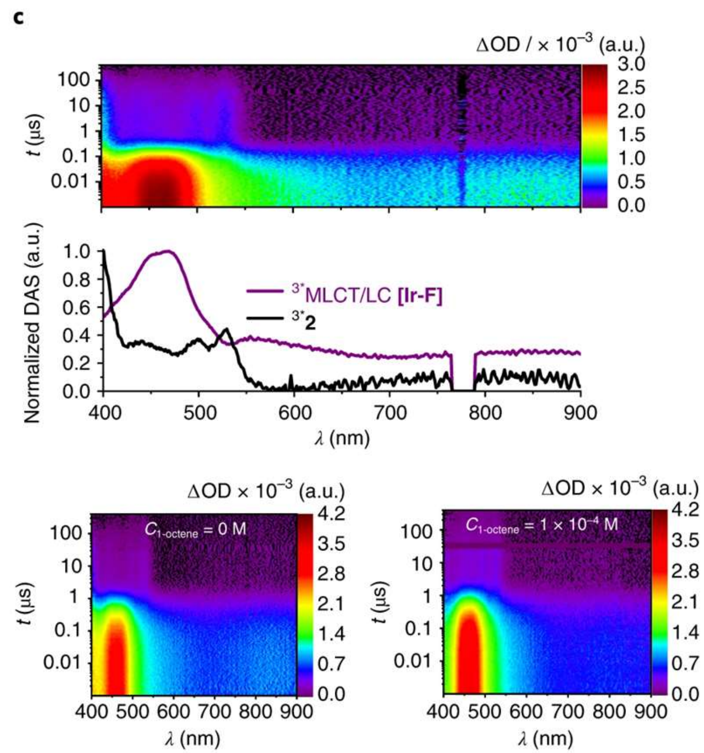


E_T=66.1 ± 2.2 kcal mol^{-1}



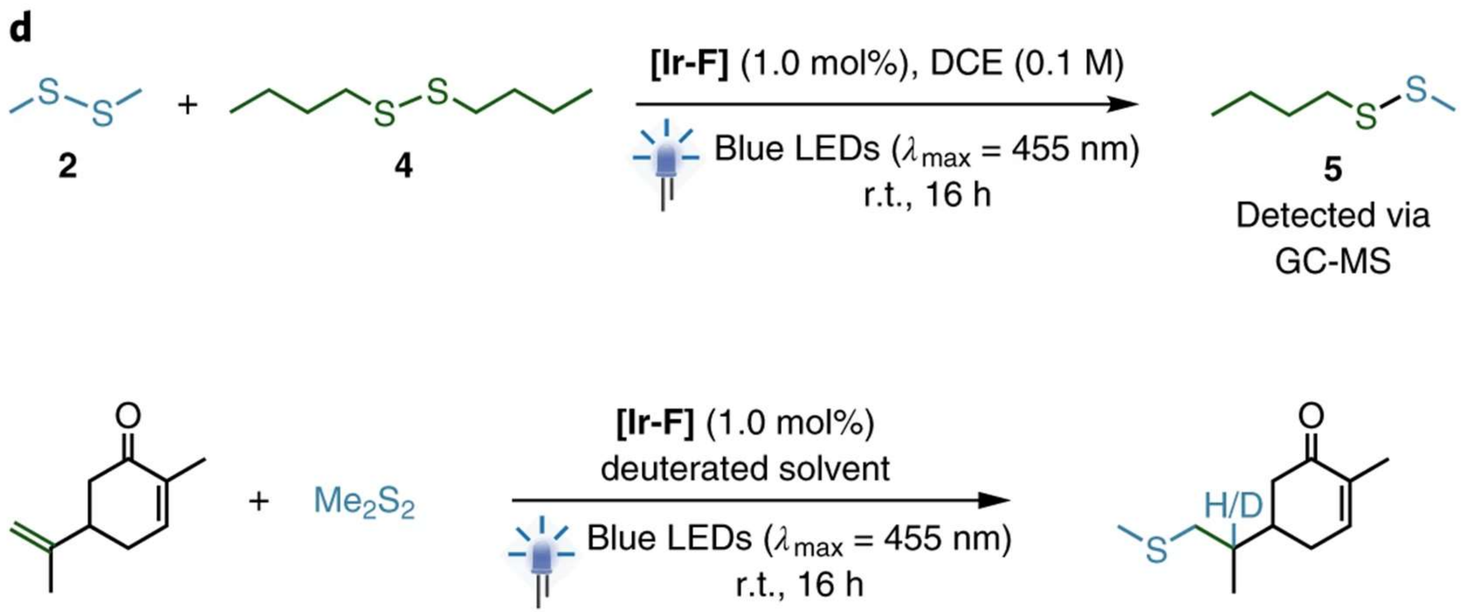






Mark W.H. Hoorens, Wiktor Szymanski,Volume 43, Issue 8,2018, 567-575,0968-0004,

Mechanistic study



Mark W.H. Hoorens, Wiktor Szymanski,Volume 43, Issue 8,2018, 567-575,0968-0004,

Proposed reaction mechanism

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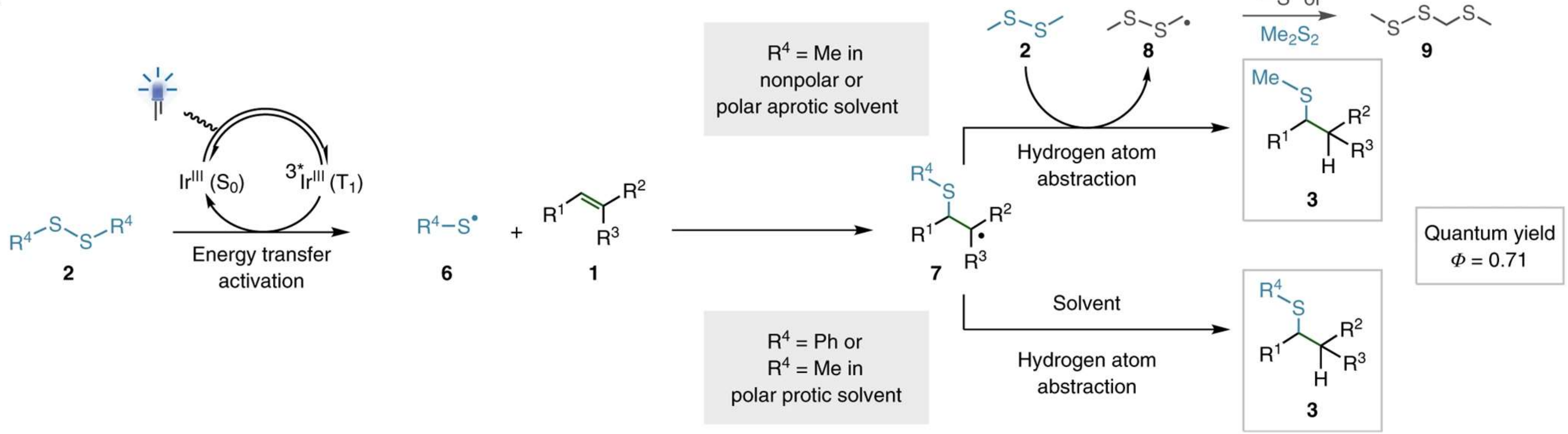
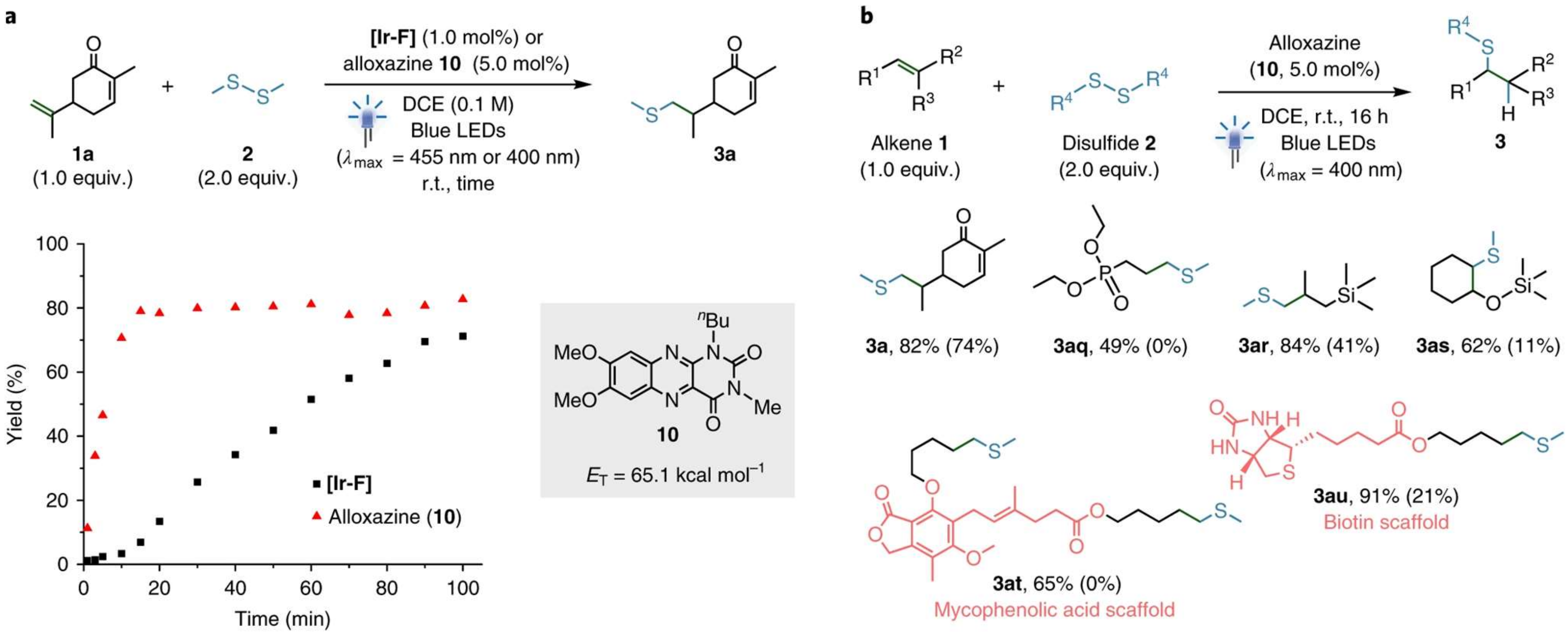
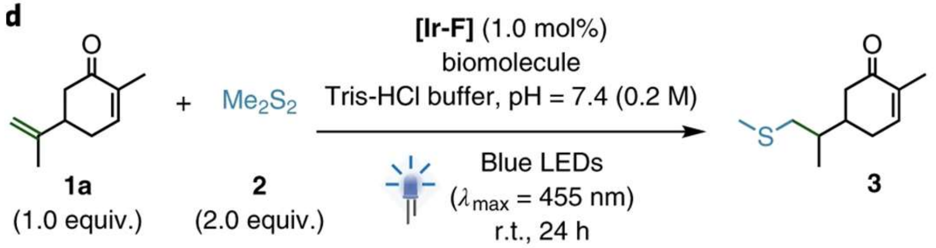


application



application

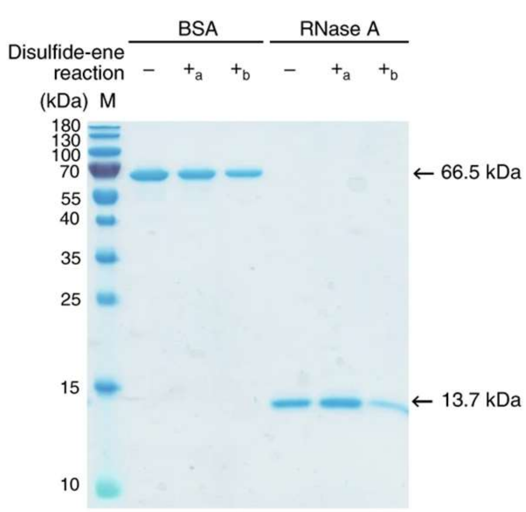
d



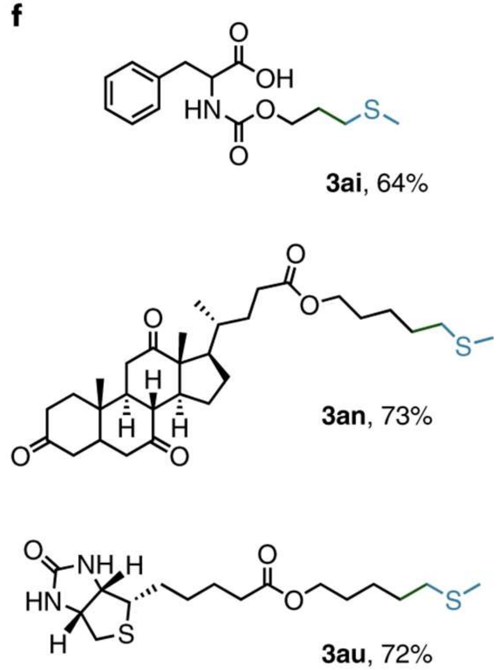
Entry	Bio-additive	Conversion (%)	Yield (%)	Additive recovery
1	None	99	68	-
2	L-glutathione (1.0 equiv.)	98	65	B
3	Bovine serum albumine (100 μM)	98	54	A
4	RNase A (100 μM)	98	63	A
5	ssDNA (5 μM)	98	66	A
6	RNA (2.5 μM)	98	68	C
7	Total RNA (5.5 μg ml^{-1})	98	64	C
8	Cell lysate (1:10 vol/vol)	98	62	ND

- 20 biomolecule additives investigated
- No significant influence on yield
- Overall good biomolecule preservation

e

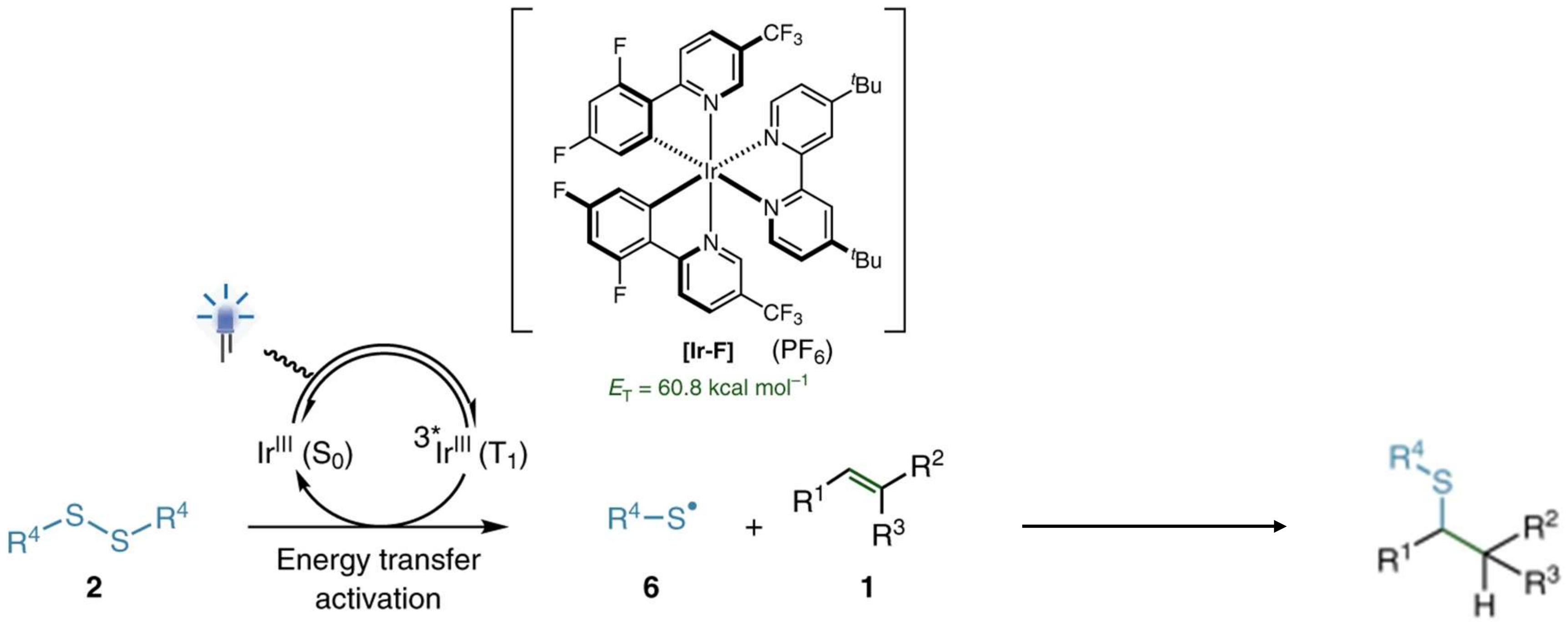


f



Mark W.H. Hoorens, Wiktor Szymanski,Volume 43, Issue 8,2018, 567-575,0968-0004,

Short summary



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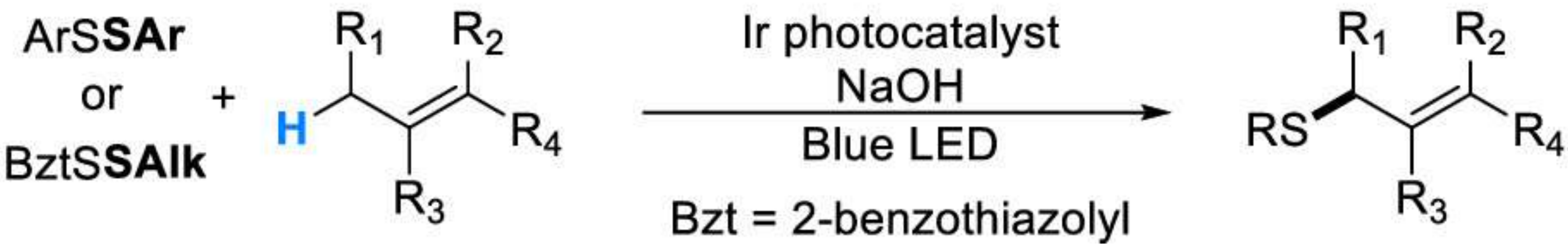
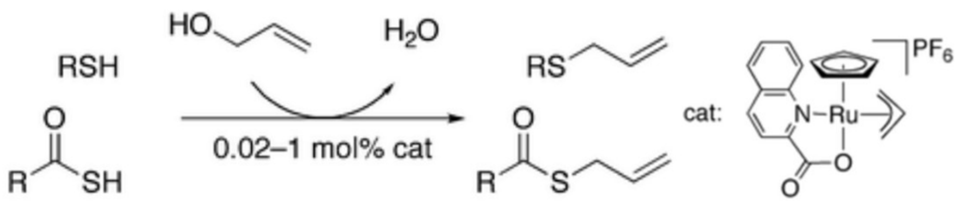
2. Formation of CTC
3. Triplet–triplet energy transfer
4. Electron-transfer
5. Summary



Jungwon Kim, Byungjoon Kang, et.al., CS Catal. 2020, 10, 11, 6013–6022

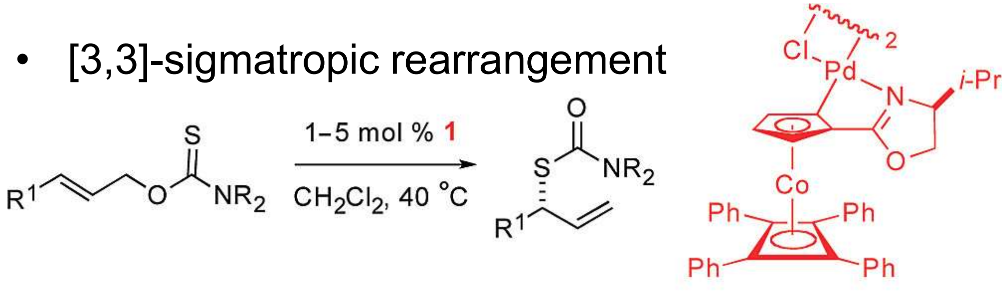
synthesis of allyl thioethers

- allyl (pseudo)halide



Shinji Tanaka, Prasun Kanti Pradhan, et.al.,
Chem. Commun., 2010,**46**, 3996-3998

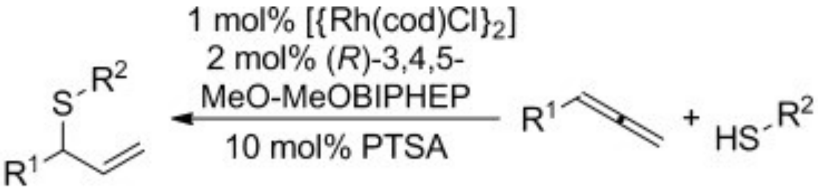
- [3,3]-sigmatropic rearrangement



[(*Rp*,*S*)-COP-Cl]$_2$ (**1**)

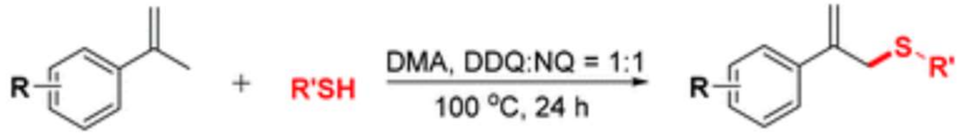
Larry E. Overman, Scott W. Roberts et.al.
Organic Letters **2008** *10* (7), 1485-1488

- hydrothiolation of allenes or 1,3-dienes



Pritzius, A.B. and Breit, B. (2015)
Angew. Chem. Int. Ed., 54: 3121-3125.

- Direct conversion using DDQ

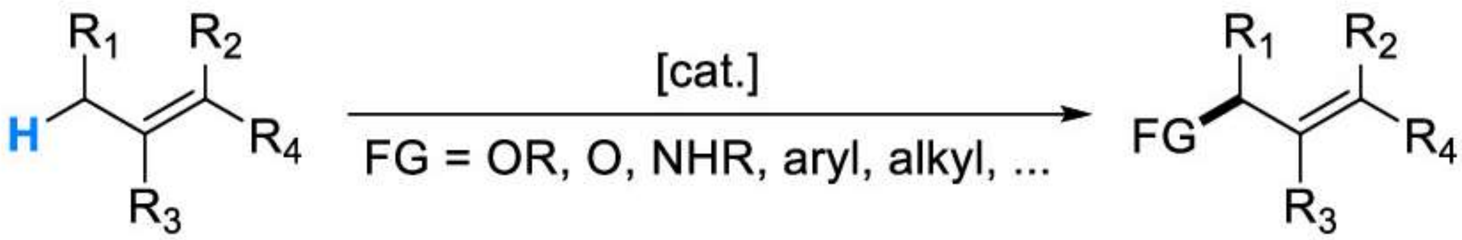


Chunsheng Li, Jianxiao Li, et. al.,
Org. Chem. Front., 2018,5, 3158-3162

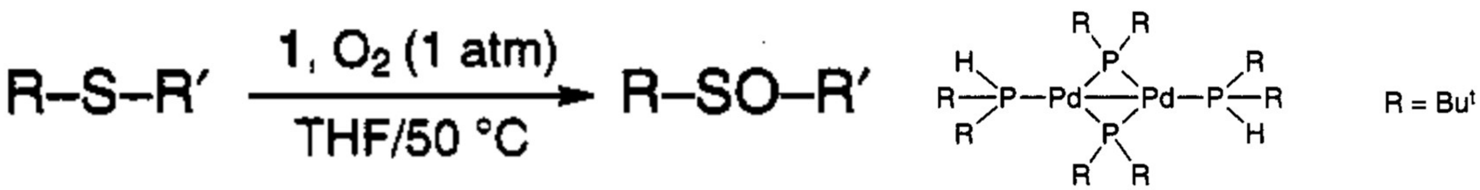
※ Catalytic direct conversion had not yet been achieved.

Direct catalytic conversion of allyl C-H→C-S had not been achieved

- There are many examples of direct catalytic conversion of allylic C-H



- Catalytic direct conversion had not yet been achieved.
    - Tends to act as a catalytic poison due to high coordination ability of sulfur atoms
    - Under conditions that oxidize the allyl position, oxidation to sulfur itself also tends to proceed

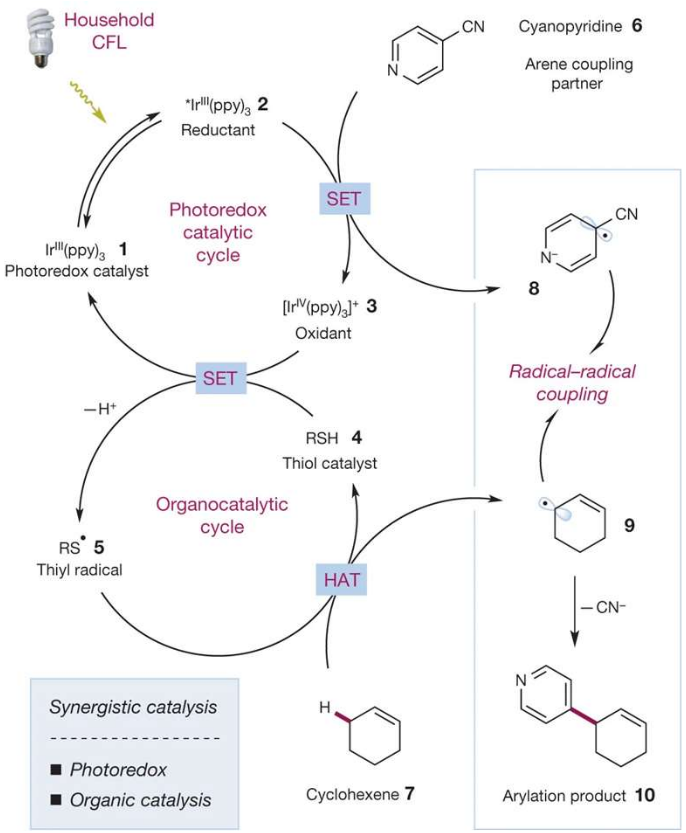


1

Raluca Aldea and Howard Alper, *J. Org. Chem.* 1995, 60, 26, 8365−8366

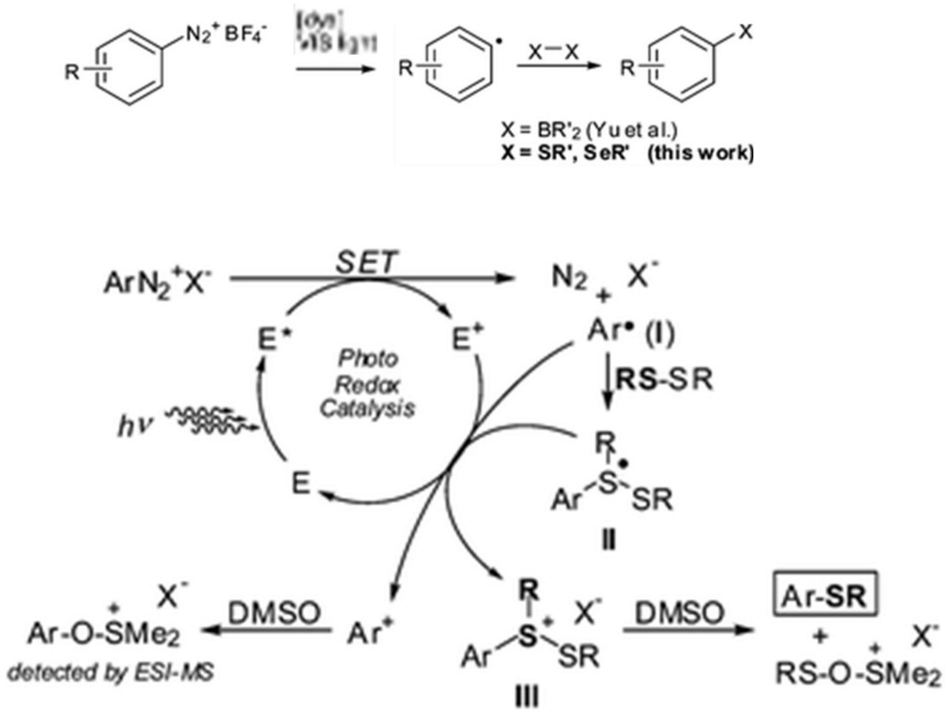
This time : Strategies using photocatalyst

- Photocatalytic conversion of allylic C-H



Cuthbertson, J., MacMillan, D. *Nature* **519,** 74–77 (2015).

- Example of disulfide reacted by photocatalyst

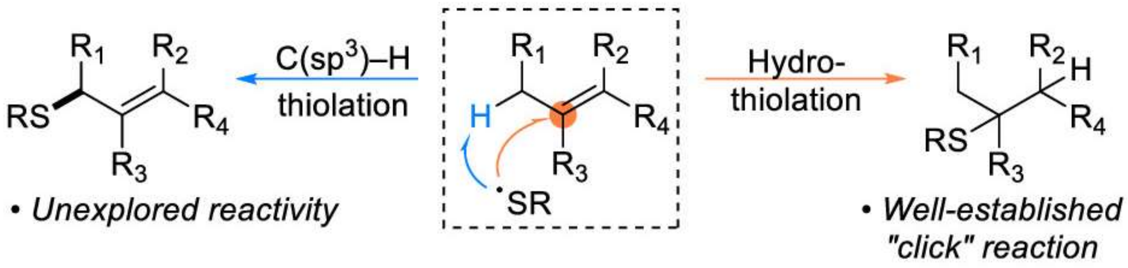


Chem. Commun., 2013,**49**, 5507-5509

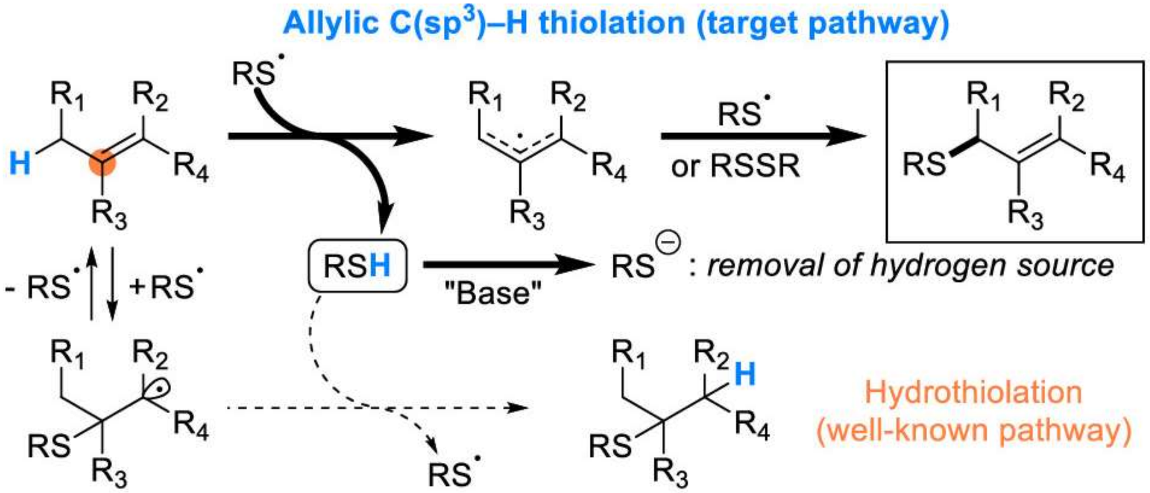
- Couldn't these be combined?

Competition with thiol-ene reaction

- There was concern that this approach would be preceded by additions to alkenes (thiol-ene reactions).



- adding a base→preventing addition?



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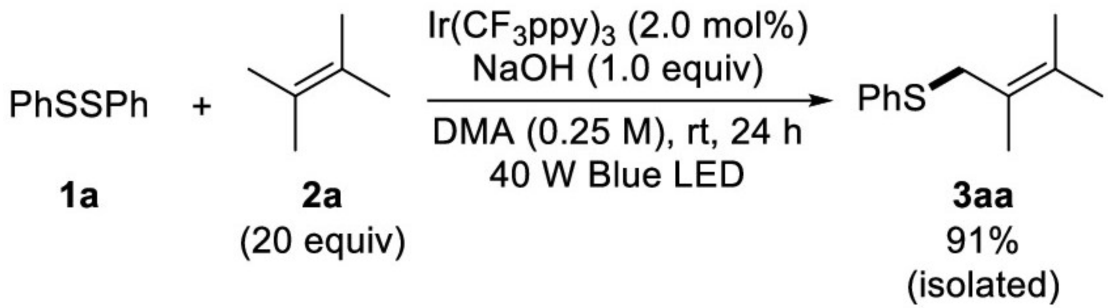
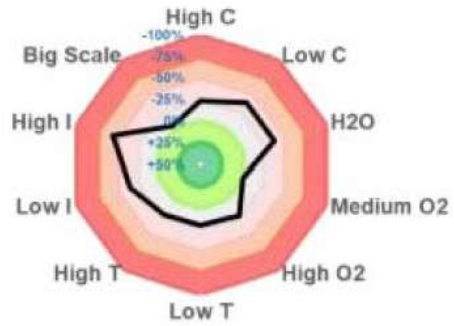
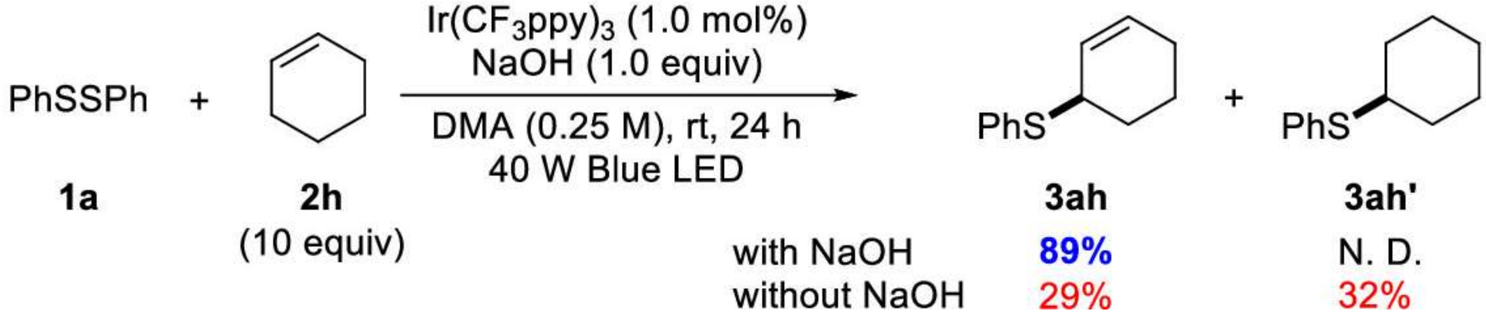
Initial optimization



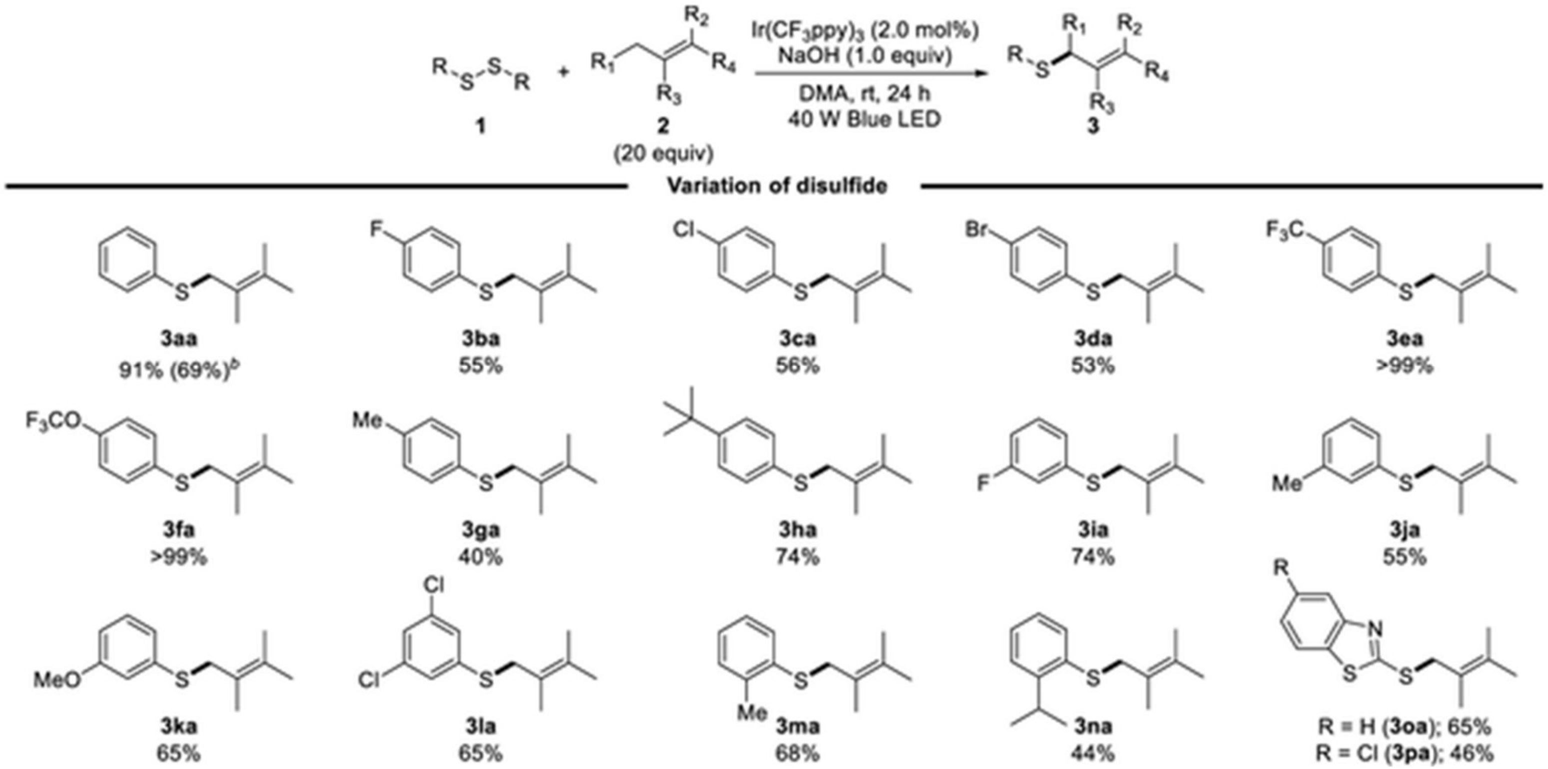


thiol-ene reaction product wasn’t produced.



- Suppression of addition by bases

Substrate scope (disulfide)



- Reaction did not proceed with dibenzyl disulfide (only produced thiols)

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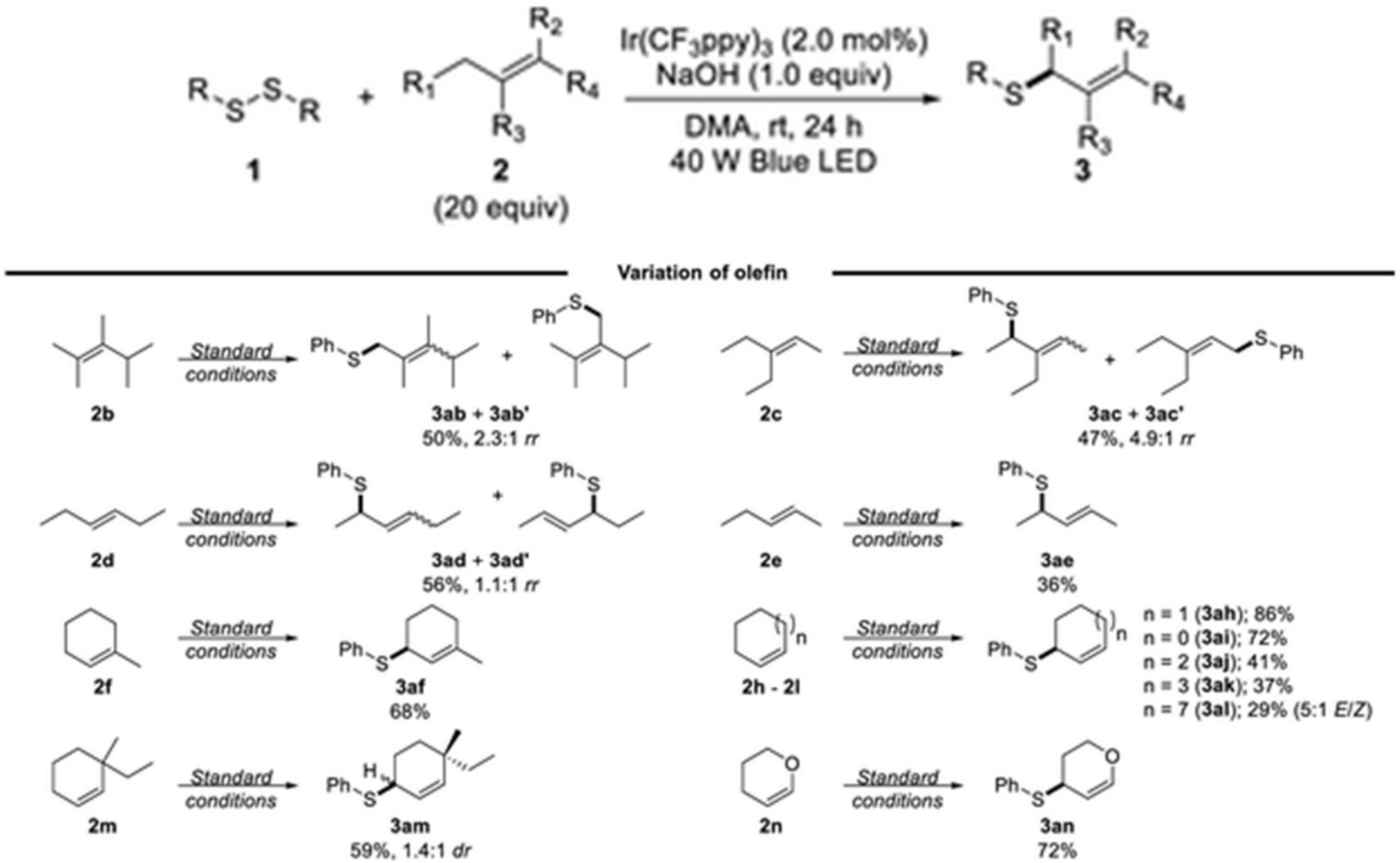
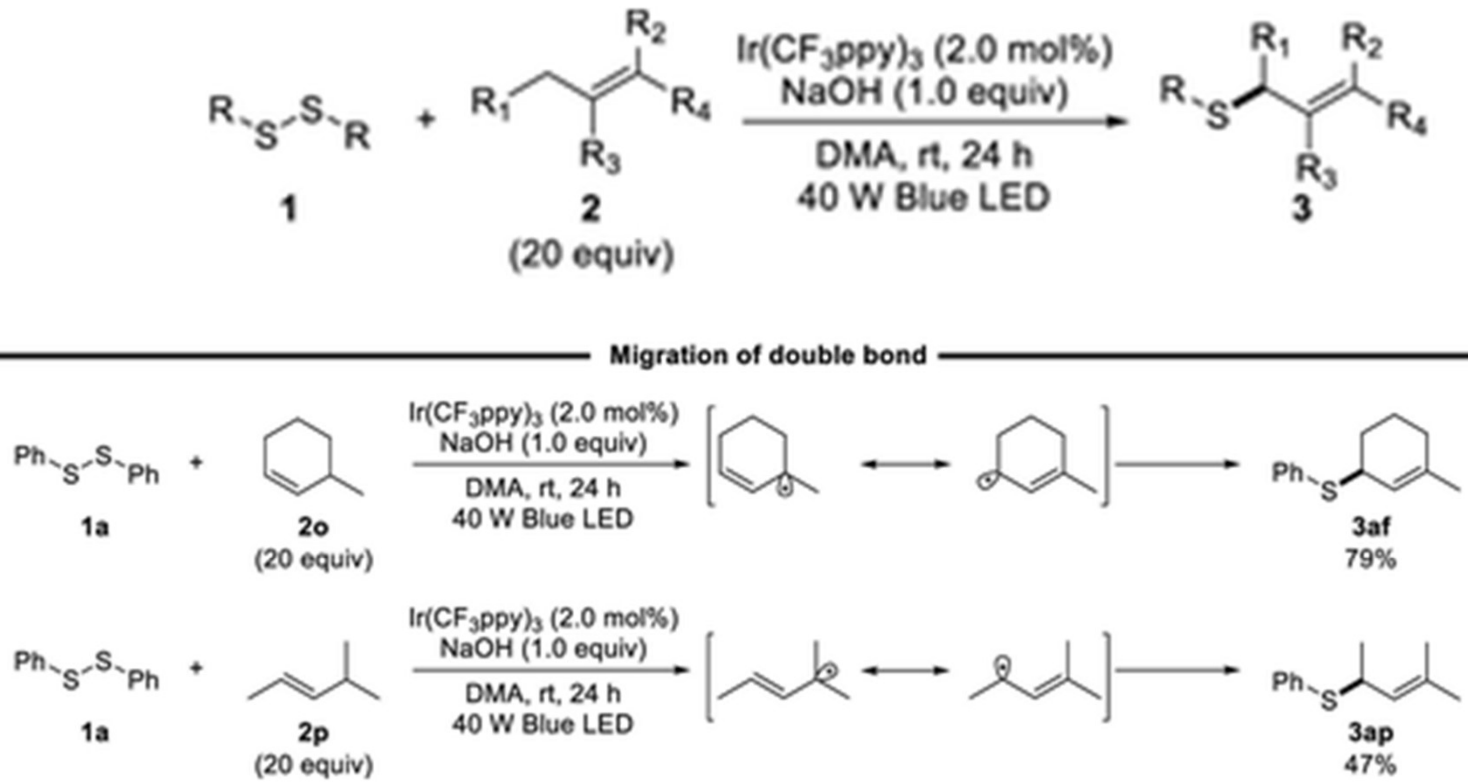
Substrate scope (olefin)



Substrate scope (olefin)



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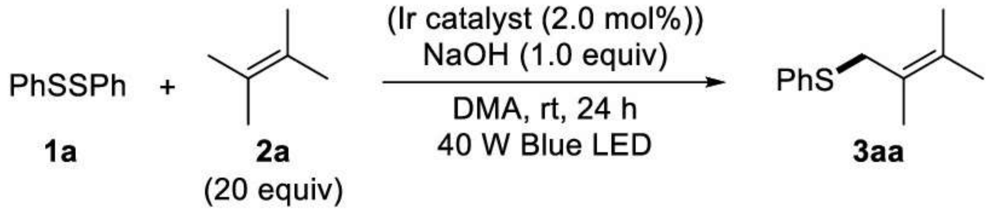
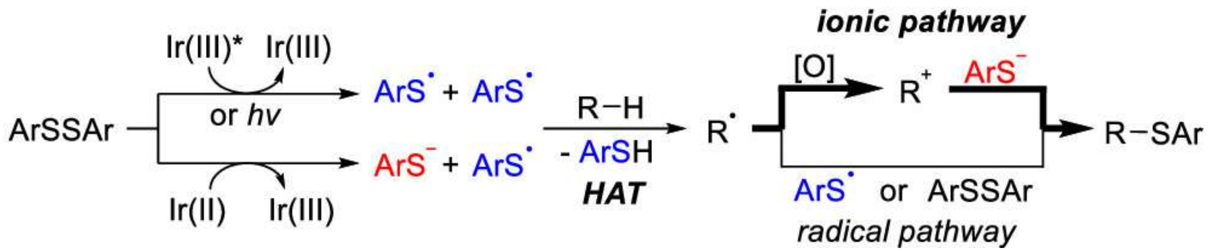
Mechanistic study

- Initially, the reaction was thought to proceed by the addition of allyl radicals to the disulfide...



Entry	Variation	Yield **3aa**
1	with $Ir(CF_3ppy)_3$ (E_T = 56.4 kcal/mol)	91%
2	without Ir catalyst	<2%
3	with $[Ir(dFCF_3ppy)_2(dtbbpy)](PF_6)$ (E_T = 60.4 kcal/mol)	<2%
4	without Ir catalyst, 370 nm LED	<1%

B. Proposed reaction mechanism - possible role of Ir photocatalyst



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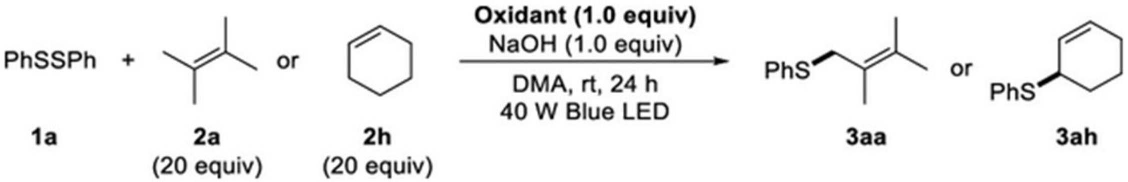
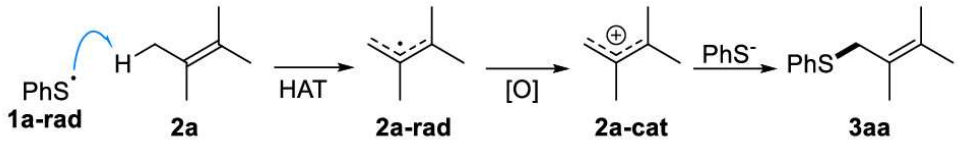
Mechanistic study



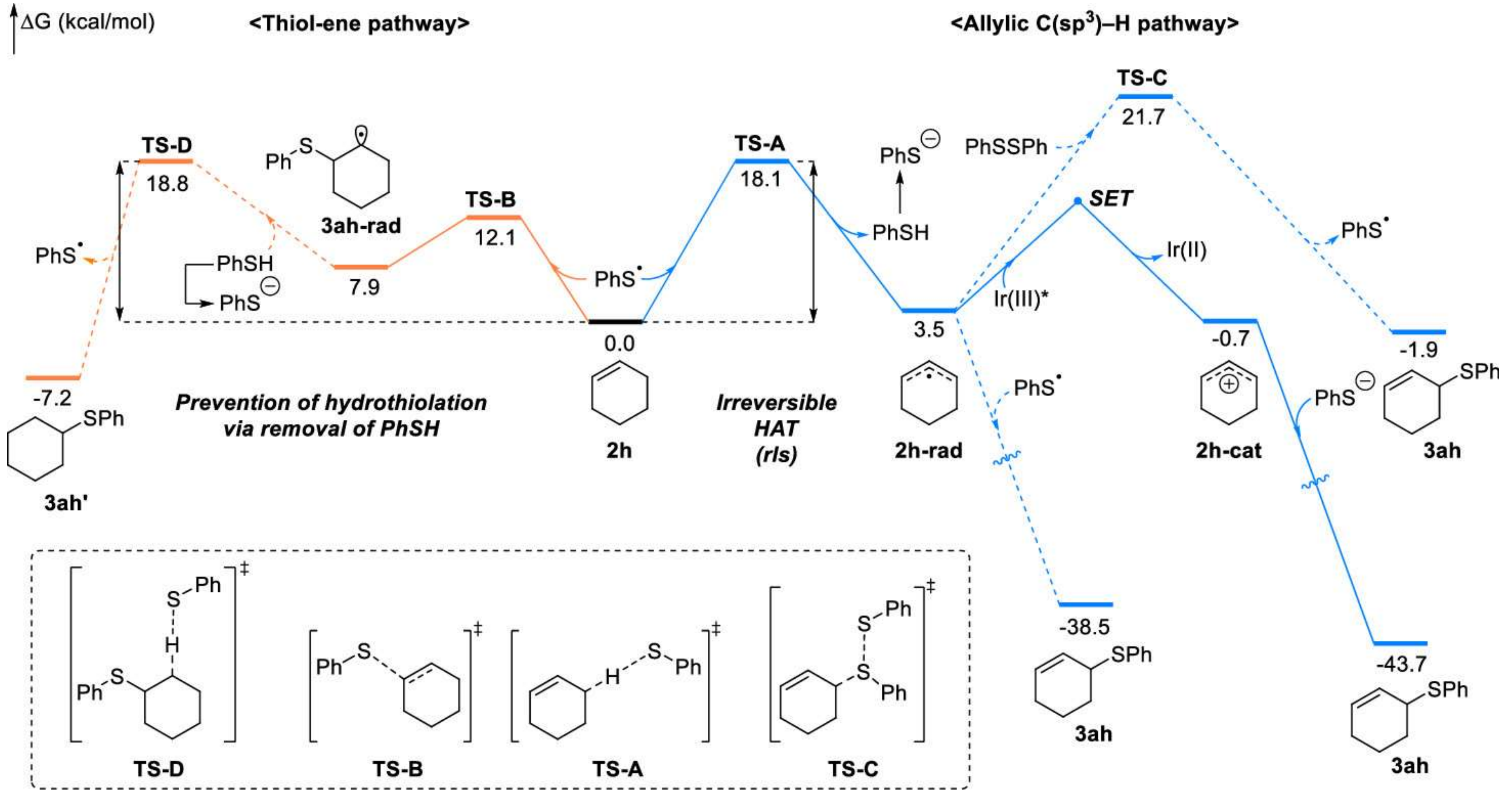
entry	Oxidant	E^o[b]	yield 3aa[c]	yield 3ah[c]
1	None		<2%	N. D.
2	$Ce(NH_4)_2(NO_3)_6$	1.06 V[d]	17%	19%[e]
3	(TBPA)($SbCl_6$)	1.05 V[f]	36%	6%
4	TEMPO	0.65 V[g]	13%	23%
5	DDQ	0.51 V[h]	3%	<1%
6	(Fc)(BF_4)	0.4 V[i]	N. D.	N. D.
7[j]	(TBPA)($SbCl_6$)	1.05 V[f]	N. D.	N. D.

A. Reaction pathway between diphenyl disulfide (1a) and 2,3-dimethyl-2-butene (2a)



E° (calc., **2a-cat** / **2a-rad**) = 0.54 V (vs SCE in MeCN)

Mechanistic study : Allyl substitution vs thiol-ene reaction



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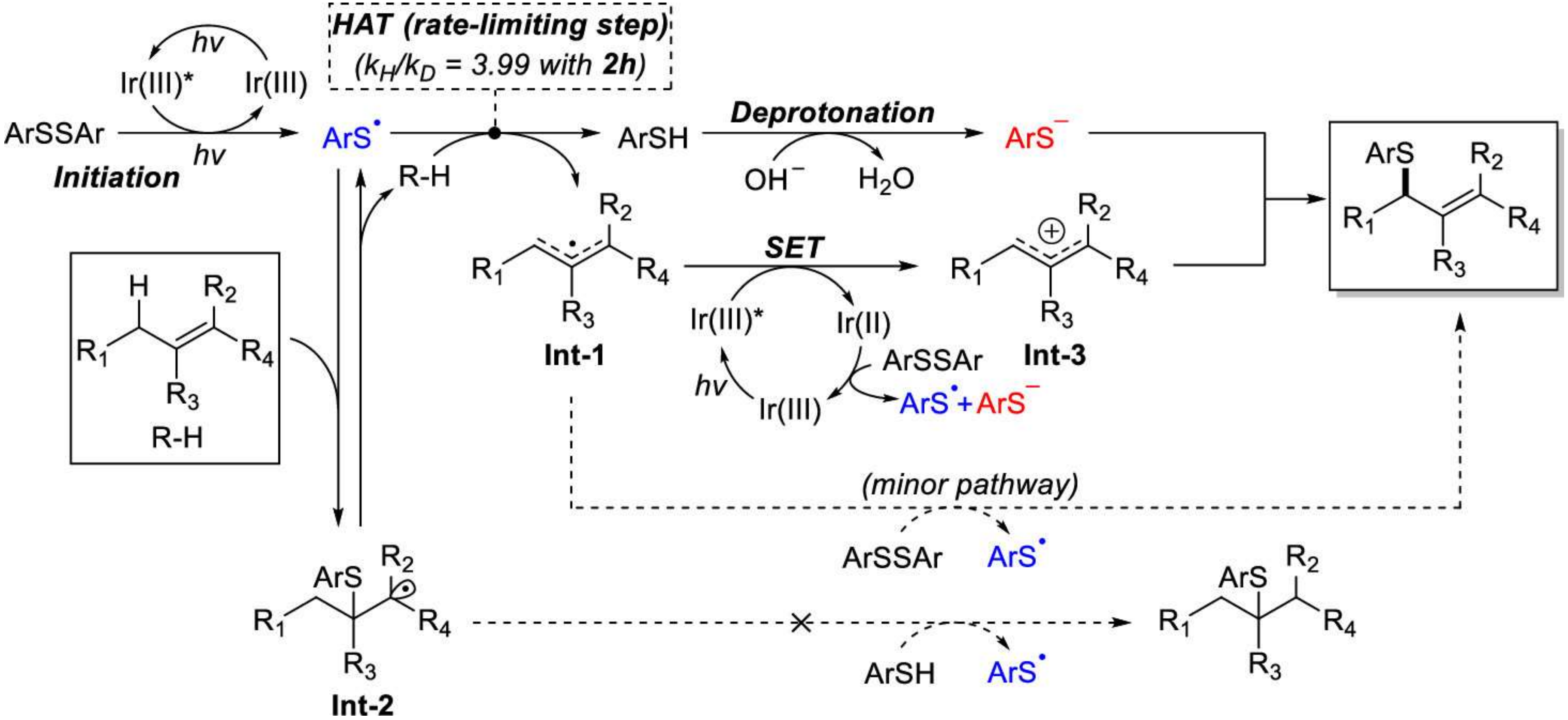
Proposed reaction mechanism



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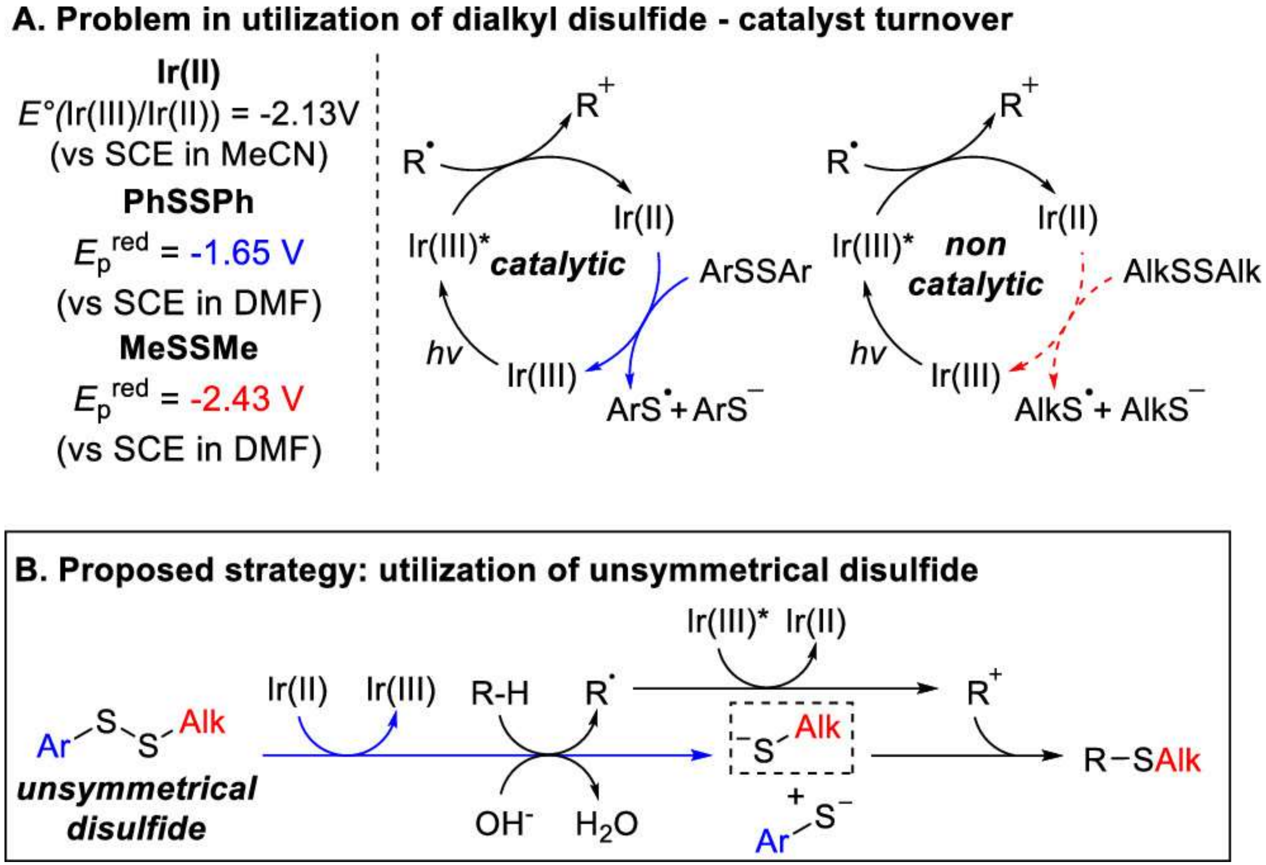
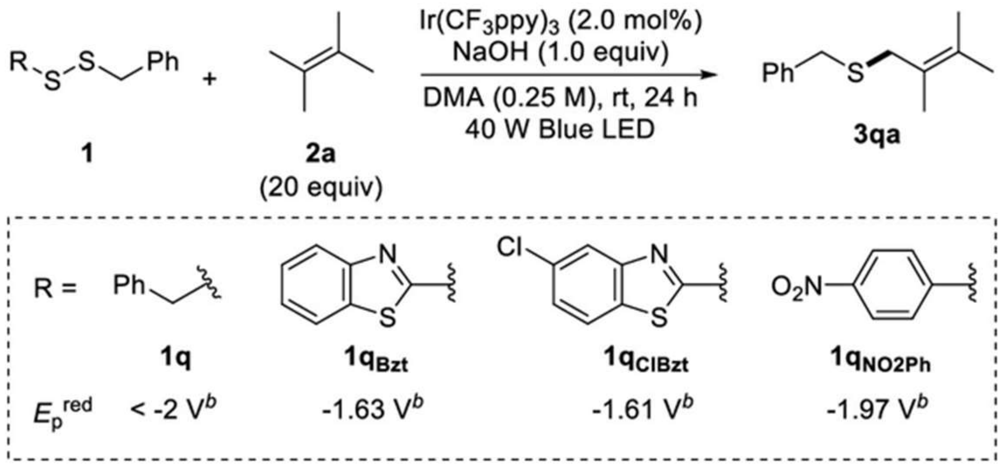
Synthesis of Alkyl Allyl Sulfides Using Asymmetric Disulfides



Synthesis of Alkyl Allyl Sulfides Using Asymmetric Disulfides

Table 3. Survey of Unsymmetrical Disulfides[a]



entry	disulfide	changes in conditions	yield 3qa[c]
1	**1q**	None	N. D.
2	**$1q_{Bzt}$**	None	26%
3	**$1q_{ClBzt}$**	None	23%
4	**$1q_{NO2Ph}$**	None	5%

Jungwon Kim, Byungjoon Kang, et.al., CS Catal. 2020, 10, 11, 6013–6022

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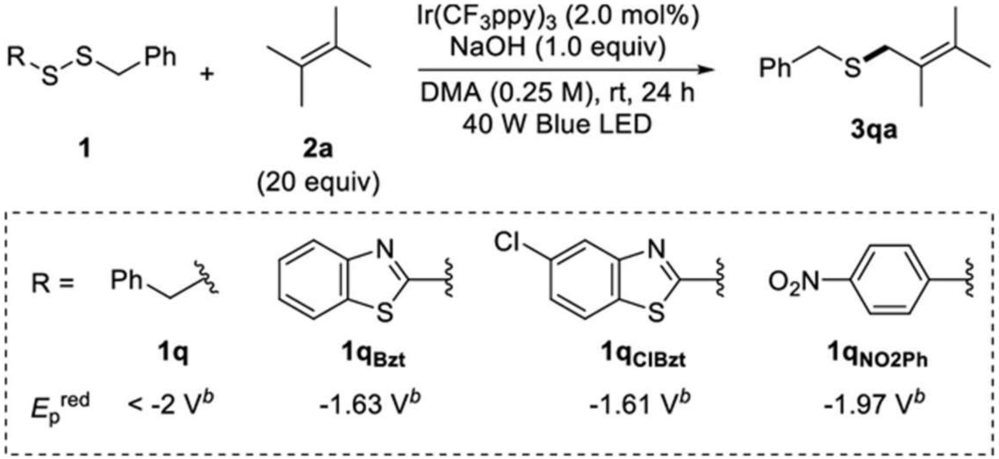
Table 3. Survey of Unsymmetrical Disulfides[a]

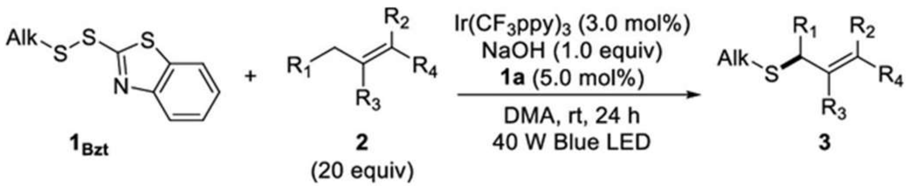


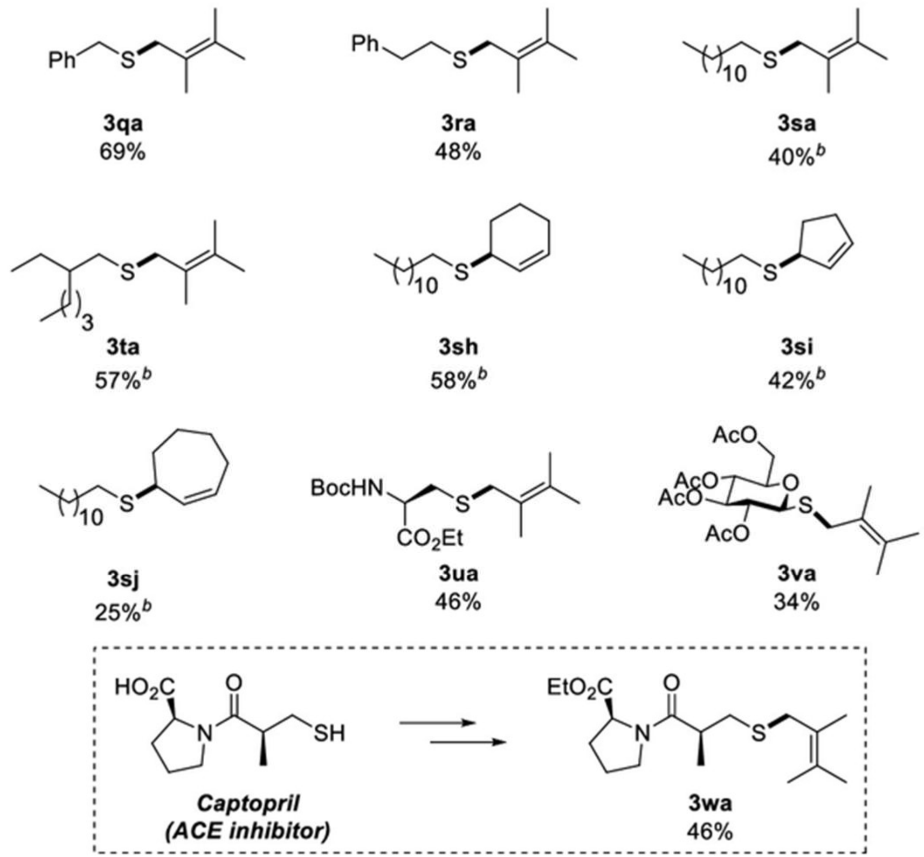
5	**1q**$_{Bzt}$	+5.0 mol % **1a**	48%
6	**1q**$_{Bzt}$	+10.0 mol % **1a**	26%
7	**1q**$_{Bzt}$	+5.0 mol % **1a**, 3.0 mol % Ir(CF_3ppy)$_3$	57%
8	**1q**$_{Bzt}$	+5.0 mol % **1a**, 3.0 mol % Ir(CF_3ppy)$_3$, 0.17 M	70% (69%)[d]

Jungwon Kim, Byungjoon Kang, et.al., CS Catal. 2020, 10, 11, 6013–6022

Synthesis of Alkyl Allyl Sulfides Using Asymmetric Disulfides

Table 4. Synthesis of Alkyl Allyl Sulfides[a]





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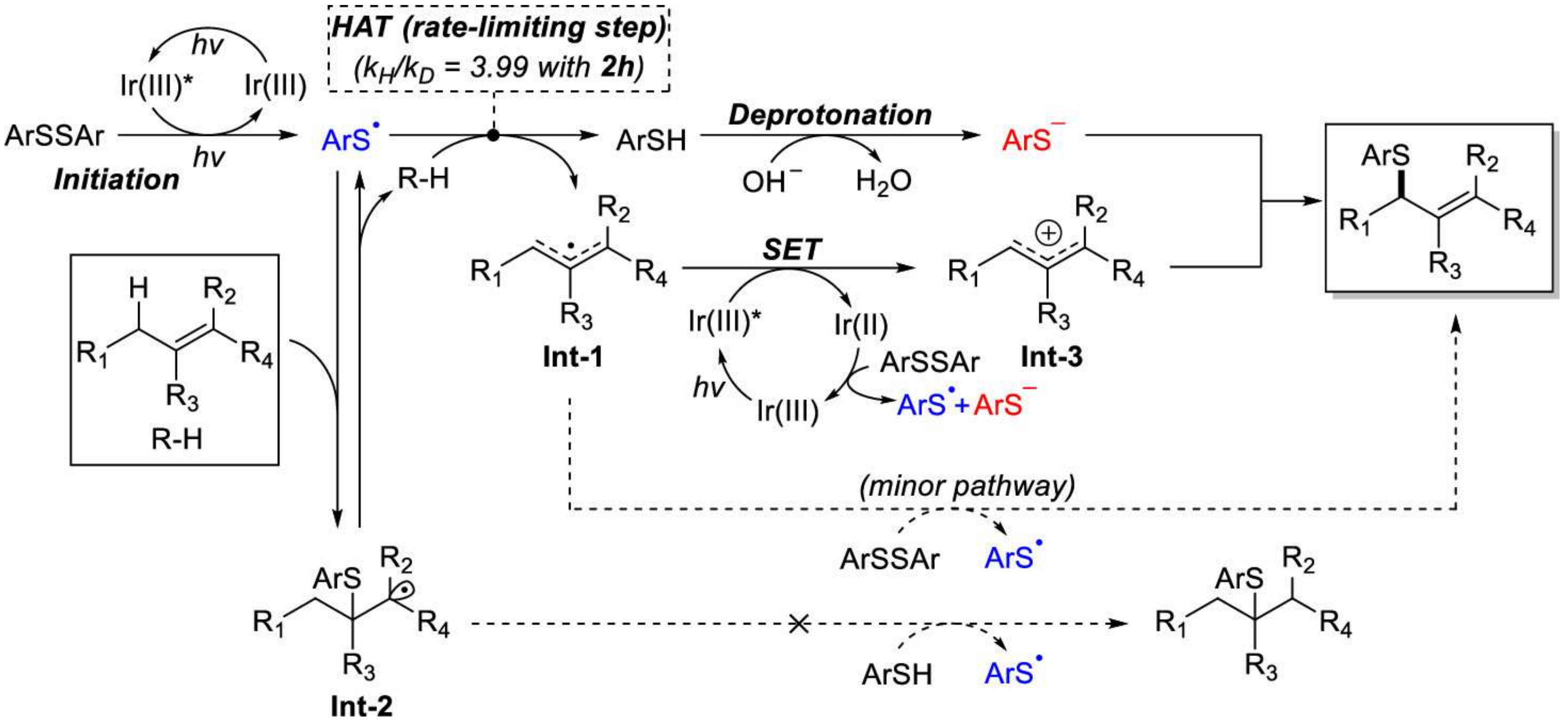
Short summary



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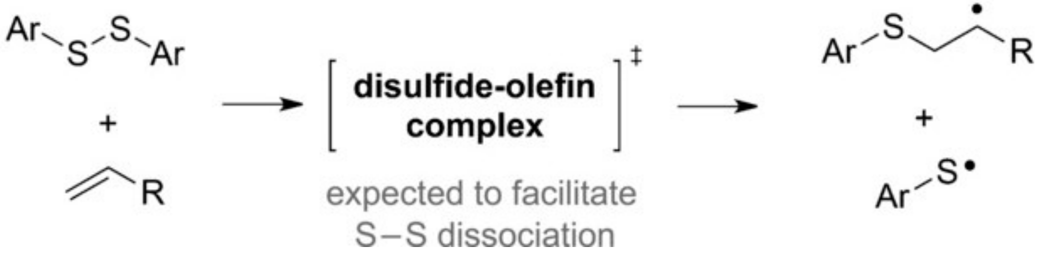
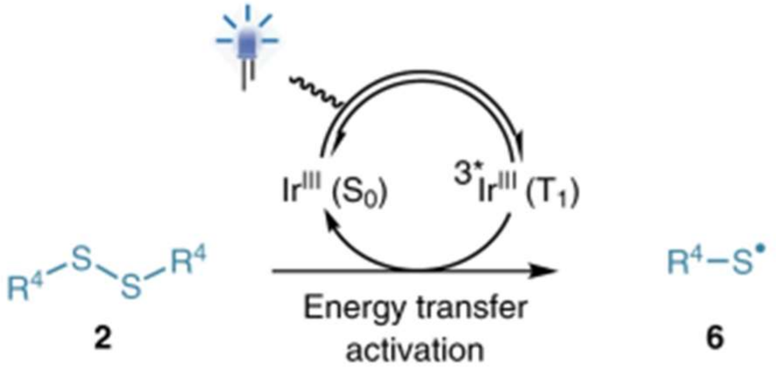
Summary

1.Formation of CTC



2.Triplet–triplet energy transfer



3.Electron-transfer