



華中師範大學

明德、厚學、求實、篤行
The Xiao Group

Transformation of Sulfur Dioxide



Xiang-Kui He
August 10, 2023

The Xiao Group Meeting
Key Laboratory of Pesticide & Chemical Biology



Outline

- **Discovery of Sulfur Dioxide**
- **Non-radical transformation of sulfur dioxide**
- **Radical transformation of sulfur dioxide**
- **Asymmetric reactions involving SO₂ insertion**



Outline

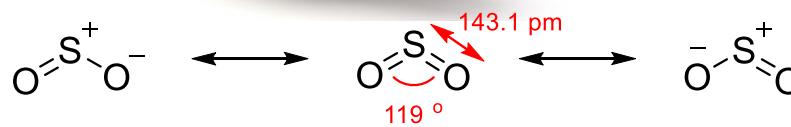
- **Discovery of Sulfur Dioxide**
- Non-radical transformation of sulfur dioxide
- Radical transformation of sulfur dioxide
- Asymmetric reactions involving SO₂ insertion

Discovery of Sulfur Dioxide

■ Introduction to SO₂



共轭结构



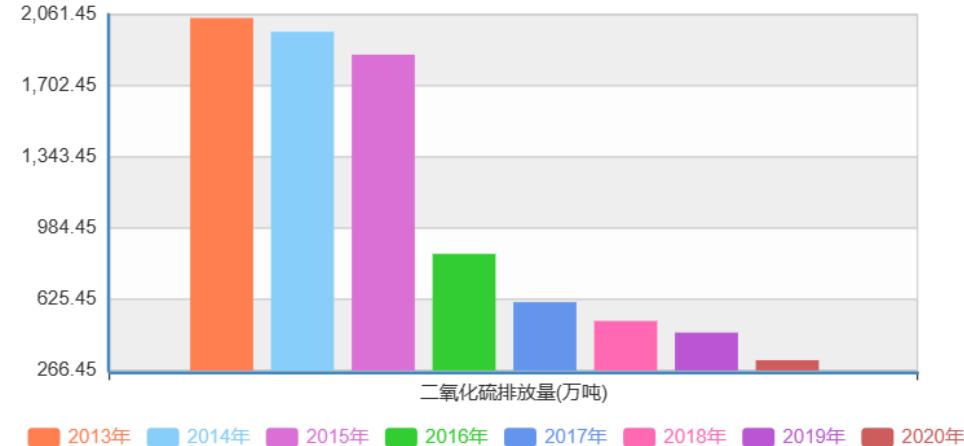
物理性质：无色刺激性气体，有毒，易溶于水，pH = 2-3，沸点：-10 °C

化学性质：呈现还原性和氧化性

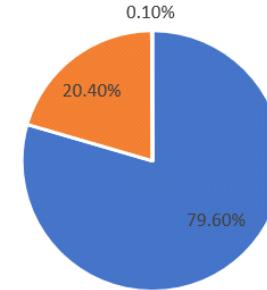
来源：火山喷发，金属冶炼，煤炭燃烧等

应用：漂白剂，防腐剂，化肥以及硫酸制备

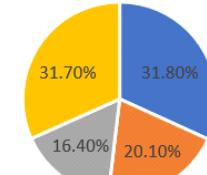
■ Emission of SO₂ in China



2020年全国二氧化碳排放量占比

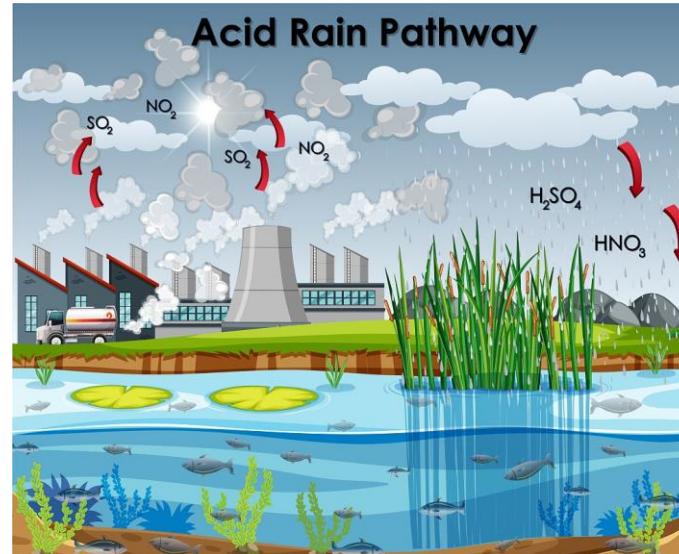


2020年全国各工业行业二氧化硫排放量占比



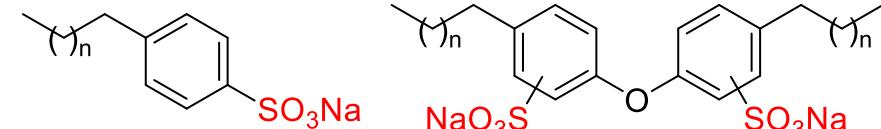
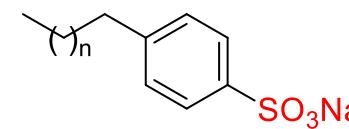
Discovery of Sulfur Dioxide

■ Hazards of SO₂

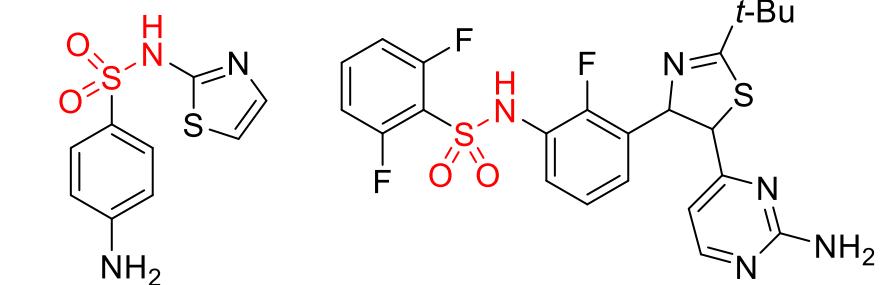
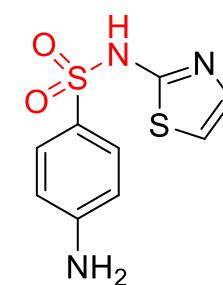


■ Utilization of SO₂

表面活性剂举例

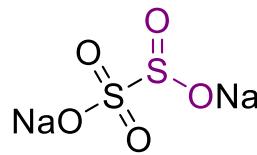


药物分子举例

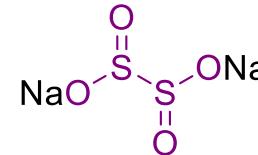


Discovery of Sulfur Dioxide

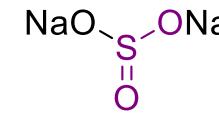
■ Sources of SO₂ in organic synthesis



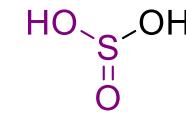
焦亚硫酸钠
340元/10kg



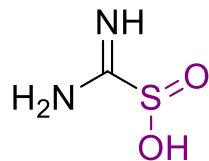
连二亚硫酸钠
560元/10kg



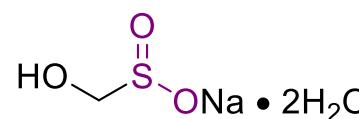
亚硫酸钠
480元/25kg



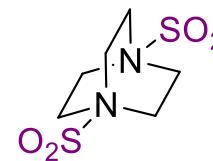
亚硫酸
569元/10L



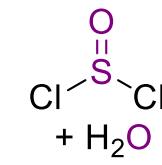
二氧化硫脲
935元/10kg



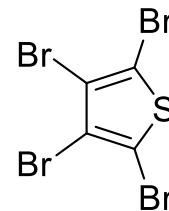
甲醛次硫酸钠
1590元/10kg



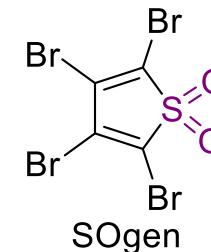
DABSO
4920元/500g



SOCl_2
799元/10kg



$m\text{-CPBA}$





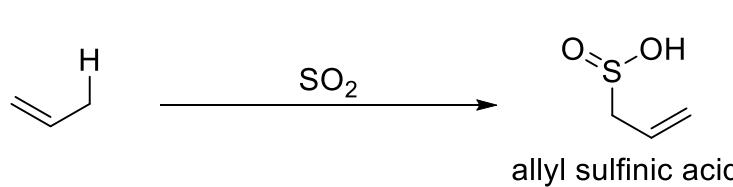
Outline

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- Radical transformation of sulfur dioxide
- Asymmetric reactions involving SO_2 insertion

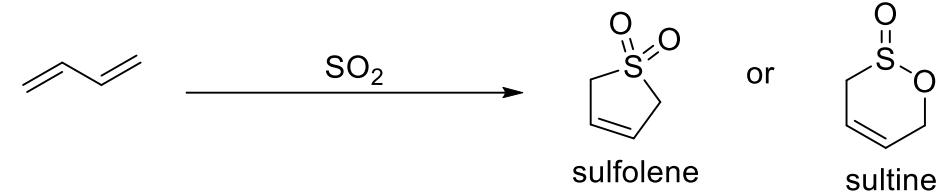
Non-radical transformation of sulfur dioxide

■ Early studies with SO₂ gas

- Alder-ene reaction



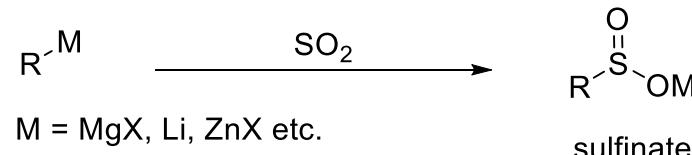
- Pericyclic



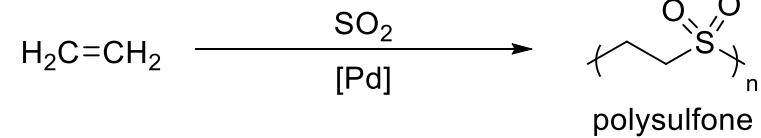
M. M. Rogić, et. al. *J. Am. Chem. Soc.* **1977**, 99, 5219

J. A. Sordo, et. al. *Acc. Chem. Res.* **2007**, 40, 931

- Nucleophile addition



- Polymerization

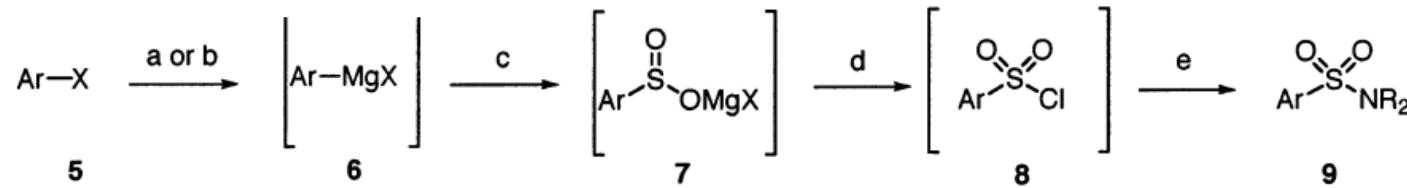


R. Goddard, et. al. *Russ. Chem. Bull.* **1998**, 47, 904

A. Sen, et. al. *Inorg. Chim. Acta* **1998**, 270, 8

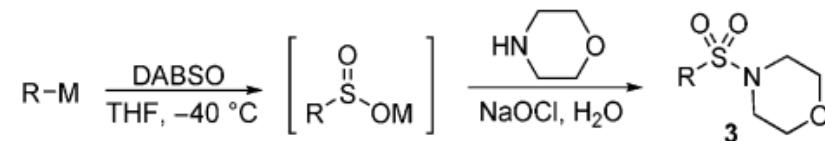
Non-radical transformation of sulfur dioxide

■ A one-pot preparation of sulfonamides involving organometallic reagents



Reagents and conditions: a) Mg, Et₂O; b) ¹PrMgCl; c) SO₂; d) SO₂Cl₂; e) NHR₂

A. G. M. Barrett, et. al. *J. Org. Chem.* **2003**, 68, 8274

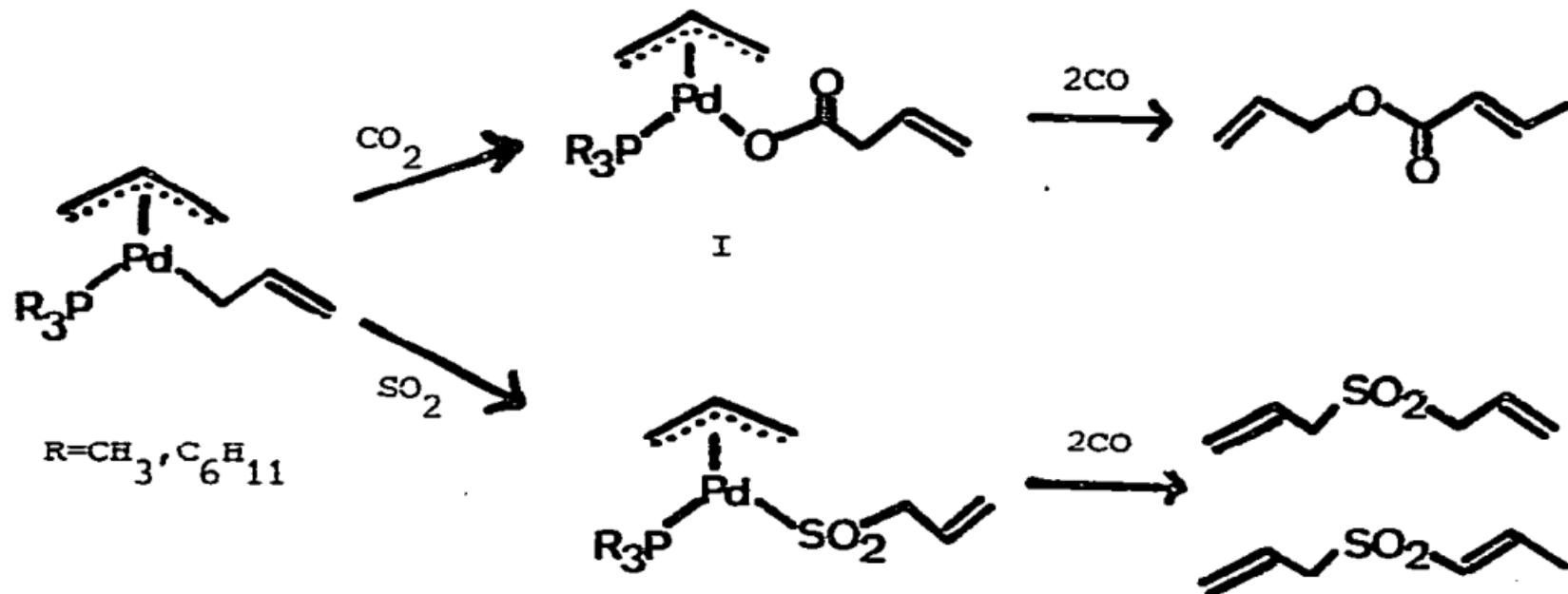


Entry	R-M	Yield [%]	Entry	R-M	Yield [%]
1	Me- <u>CH₂</u> ₃ MgBr	82	9 ^[b]	MeO-C(=O)-Ph-MgI	51
2	Me- <u>CH₂</u> ₃ Li	52	10 ^[c]	Me ₃ Si-Ph-Li	72
3	Me- <u>CH₂</u> ₃ ZnBr	65	11 ^[c]	Me-O-C(=O)-Ph-Li	62

M. C. Willis, et. al. *Angew. Chem. Int. Ed.* **2015**, 54, 1168

Non-radical transformation of sulfur dioxide

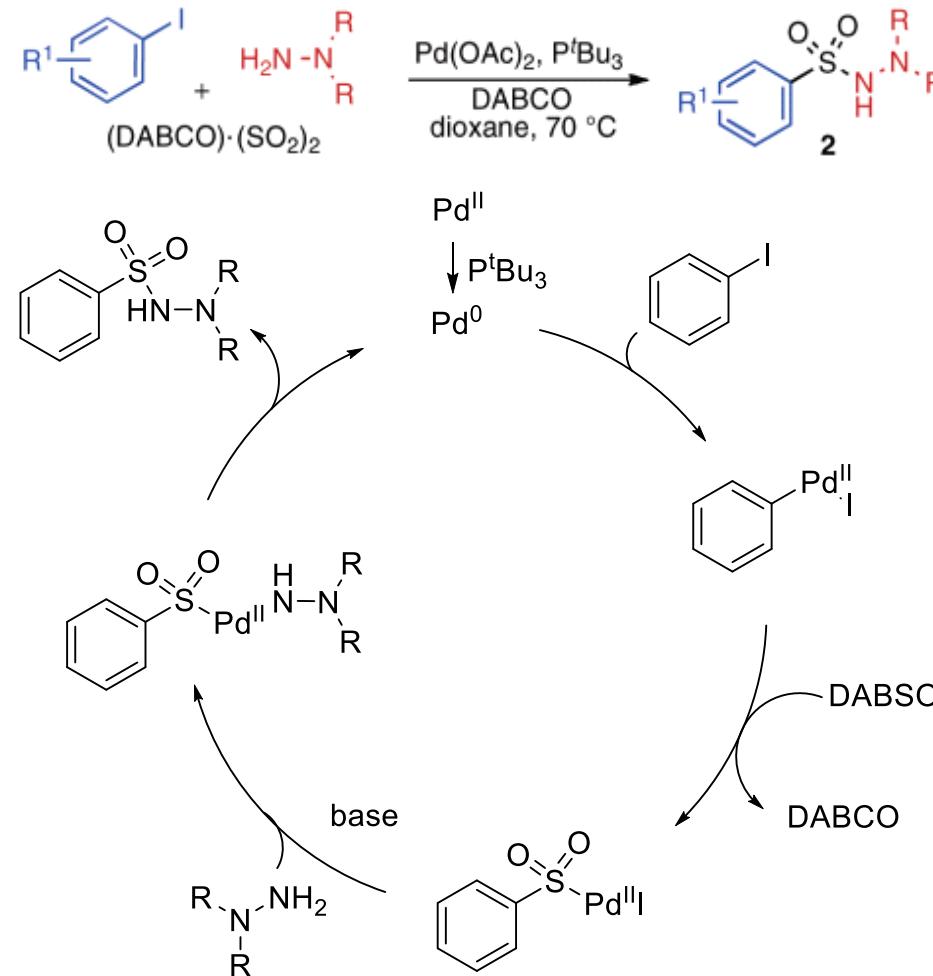
■ Early studies with SO₂ gas



P. W. Jolly, et. al. *Journal~Organometallic Chemistry*, **1980**, 190, C5

Non-radical transformation of sulfur dioxide

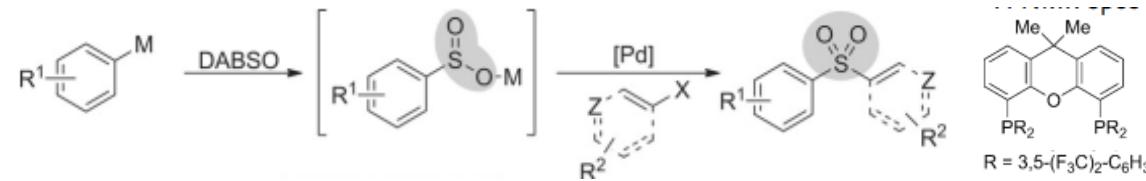
■ Palladium-catalyzed aminosulfonylation of aryl halides



M. C. Willis, et. al. *J. Am. Chem. Soc.* 2010, 132, 16372

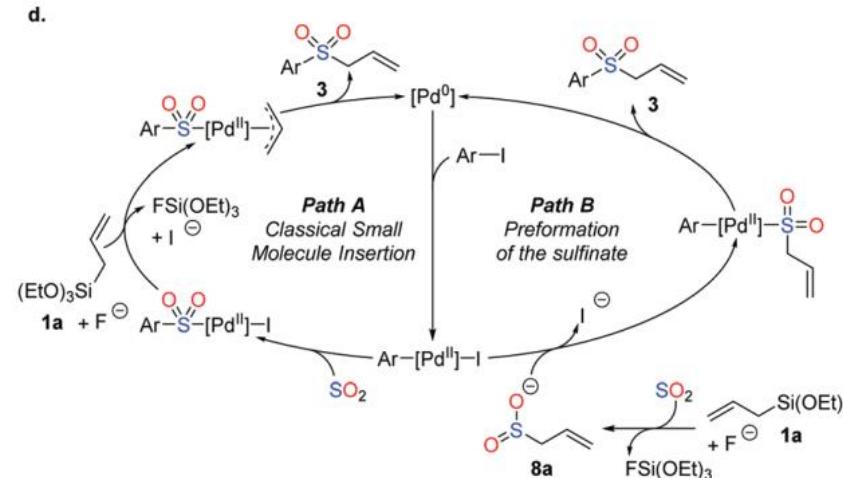
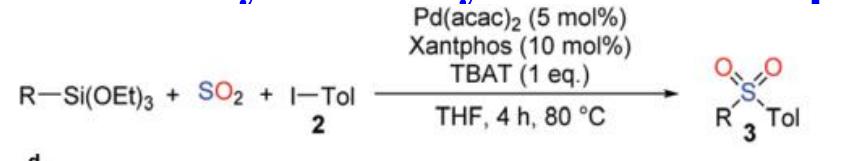
Non-radical transformation of sulfur dioxide

■ Palladium-catalyzed three-component diaryl sulfone synthesis



M. C. Willis, et. al. *Angew. Chem. Int. Ed.* **2013**, 52, 12679

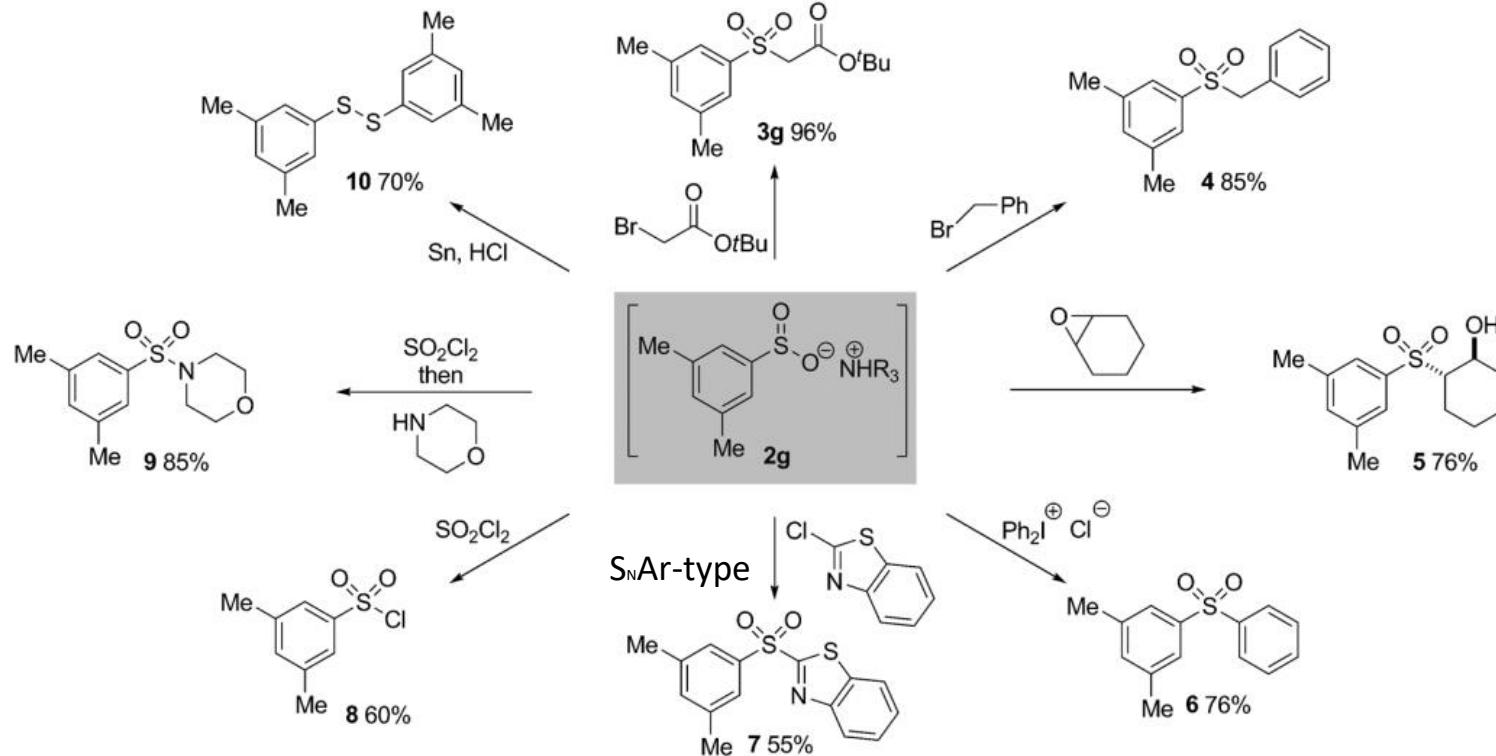
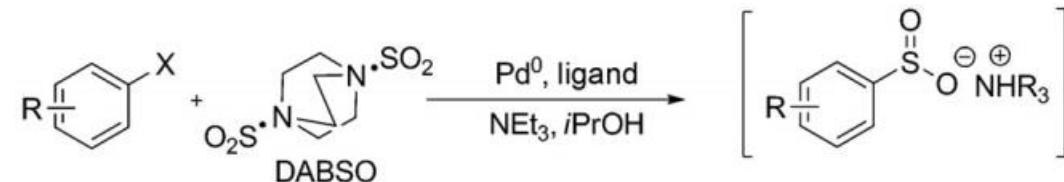
■ Palladium-catalyzed sulfonylative Hiyama cross-coupling



T. Cantat, et. al. *Chem. Commun.*, **2019**, 55, 12924

Non-radical transformation of sulfur dioxide

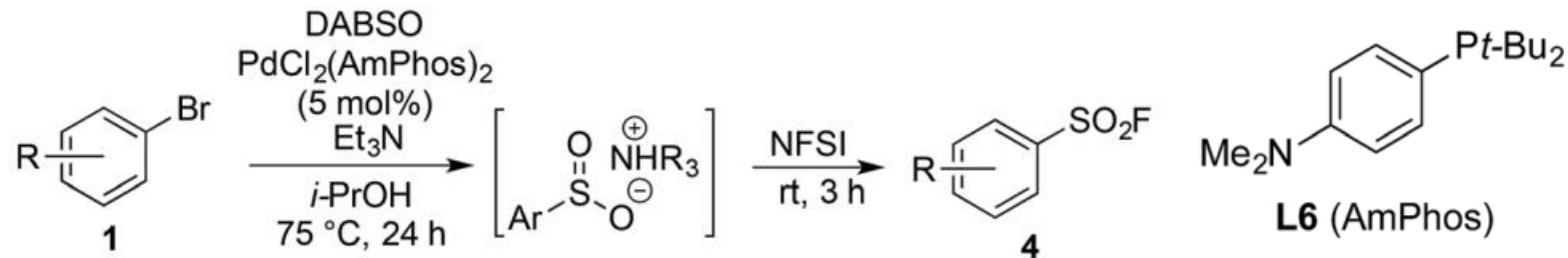
■ Pd-catalyzed synthesis of ammonium sulfinate



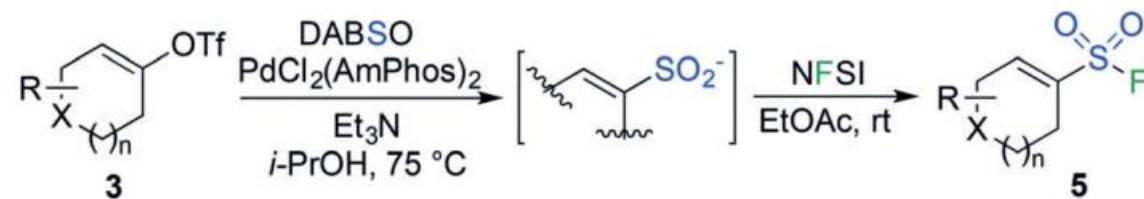
M. C. Willis, et. al. *Angew. Chem. Int. Ed.* **2014**, *53*, 10204

Non-radical transformation of sulfur dioxide

■ Palladium-catalyzed synthesis of sulfonyl fluorides



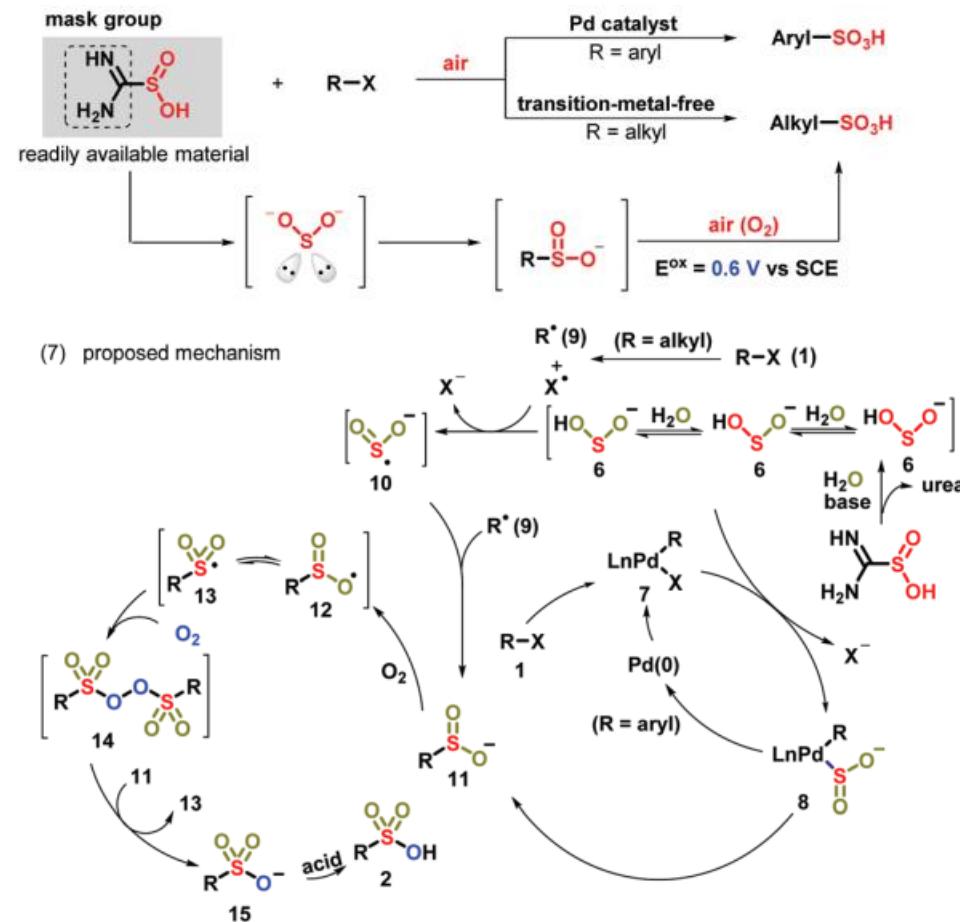
S. W. Bagley and M. C. Willis, et. al. *Chem. Sci.*, 2017, 8, 1233



M. C. Willis, et. al. *Angew. Chem. Int. Ed.* 2019, 58, 18859

Non-radical transformation of sulfur dioxide

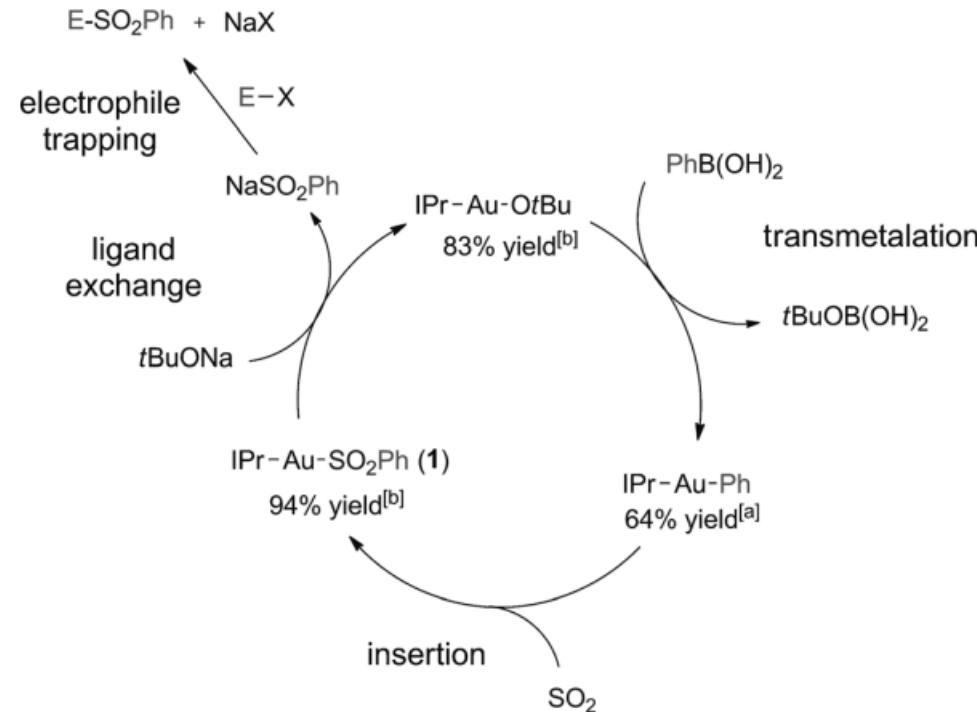
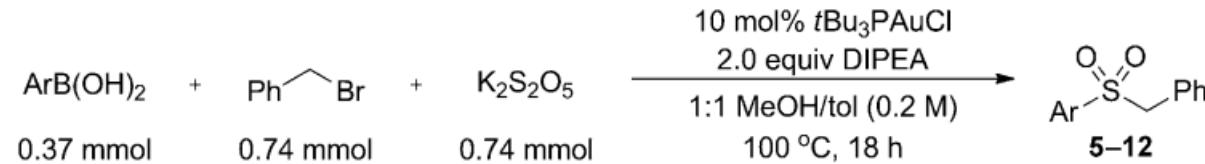
■ General synthesis of sulfonic acids



M. Wang and X. Jiang, et. al. *Green Chem.*, 2020, 22, 8238

Non-radical transformation of sulfur dioxide

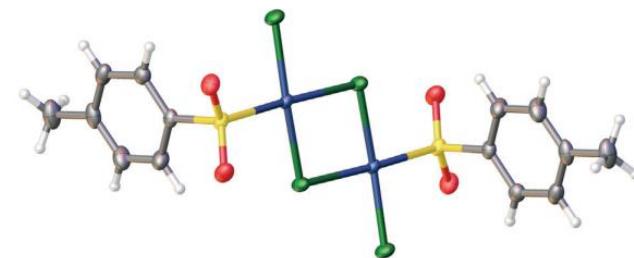
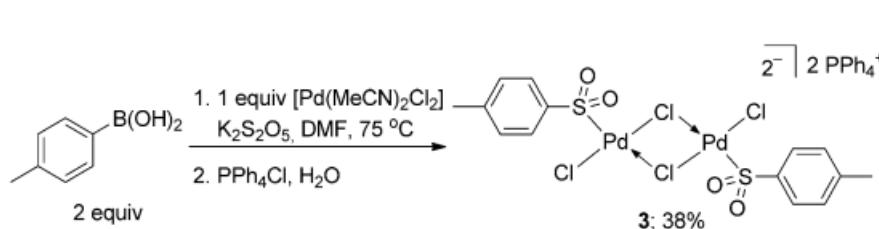
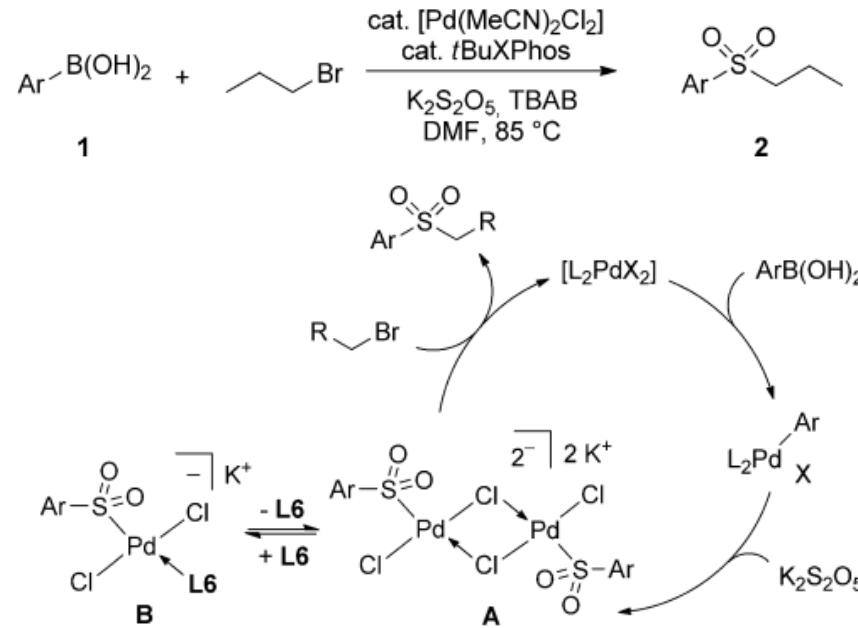
Gold-catalyzed synthesis of sulfinate derivatives



V. Mascitti and F. D. Toste, et. al. *Angew. Chem. Int. Ed.* **2014**, *53*, 4404

Non-radical transformation of sulfur dioxide

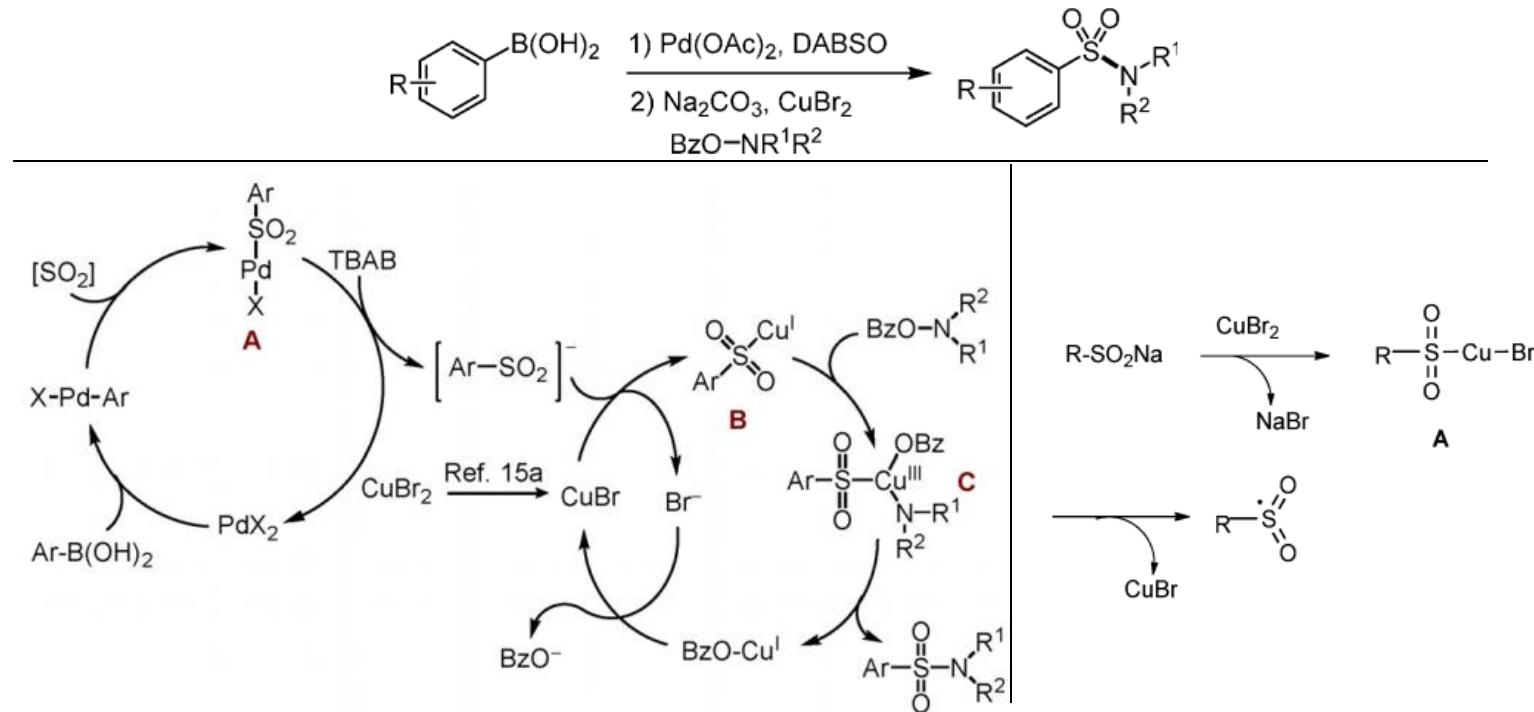
■ Palladium-catalyzed synthesis of (hetero)aryl alkyl sulfones



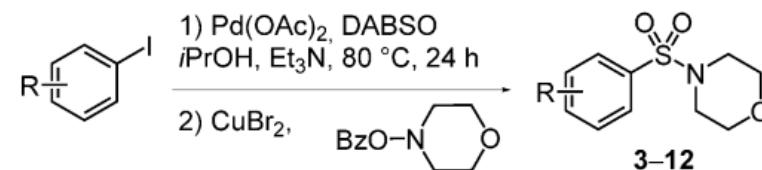
A. Shavnya, et. al. *Angew. Chem. Int. Ed.* **2015**, *54*, 13571

Non-radical transformation of sulfur dioxide

■ Bimetallic Pd/Cu-catalyzed synthesis of sulfonamides



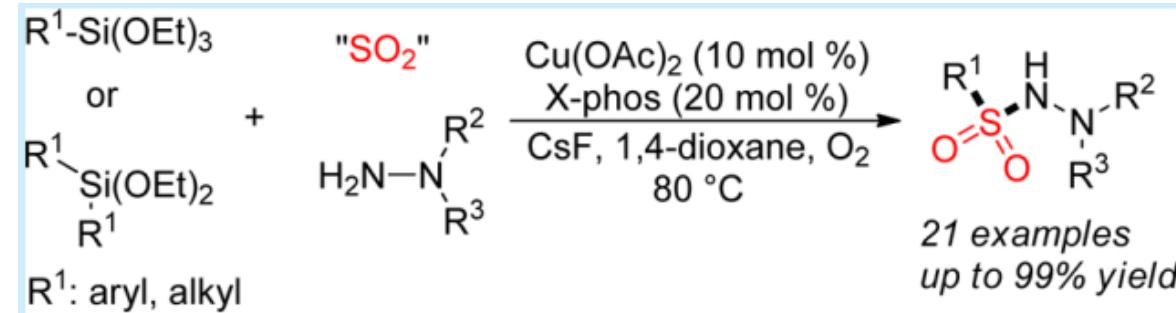
T. Tu, et. al. *Chem. Asian J.* **2017**, *12*, 706



T. Tu, et. al. *Asian J. Org. Chem.* **2017**, *6*, 1542

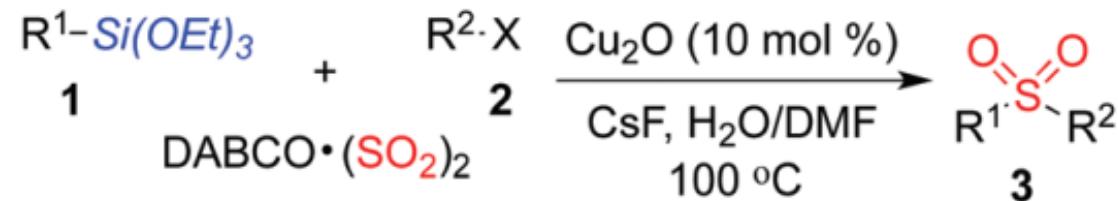
Non-radical transformation of sulfur dioxide

■ Copper-catalyzed aminosulfonylation of arylsilanes



Z. Wang et. al. *Org. Lett.* **2014**, *16*, 4056

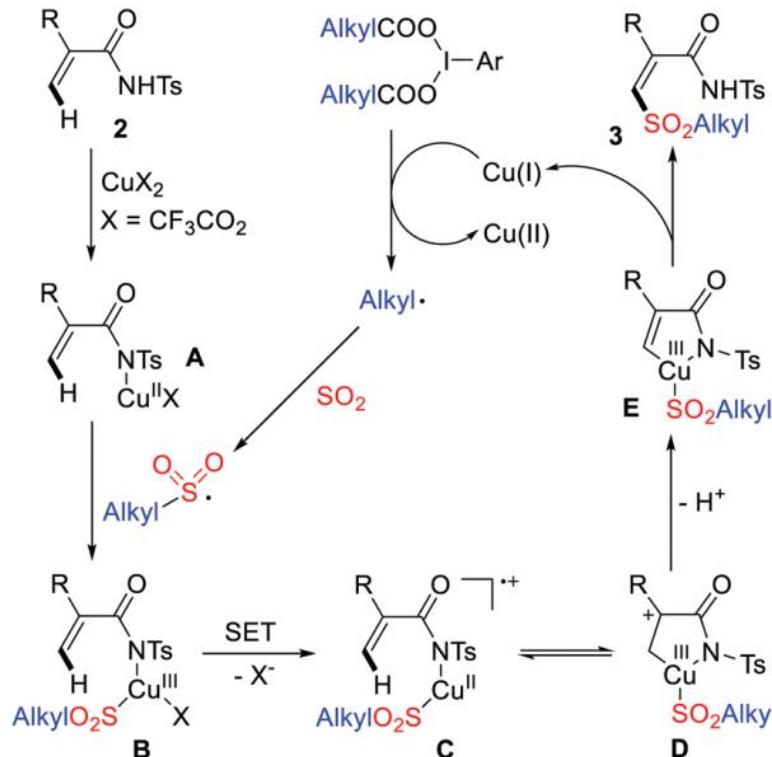
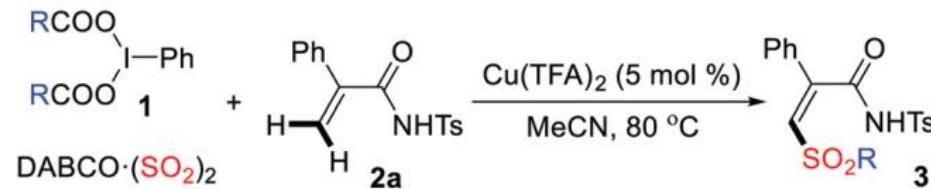
■ Copper-catalyzed synthesis of sulfones



Z. Li and J. Wu et. al. *Org. Chem. Front.*, **2016**, *3*, 359

Non-radical transformation of sulfur dioxide

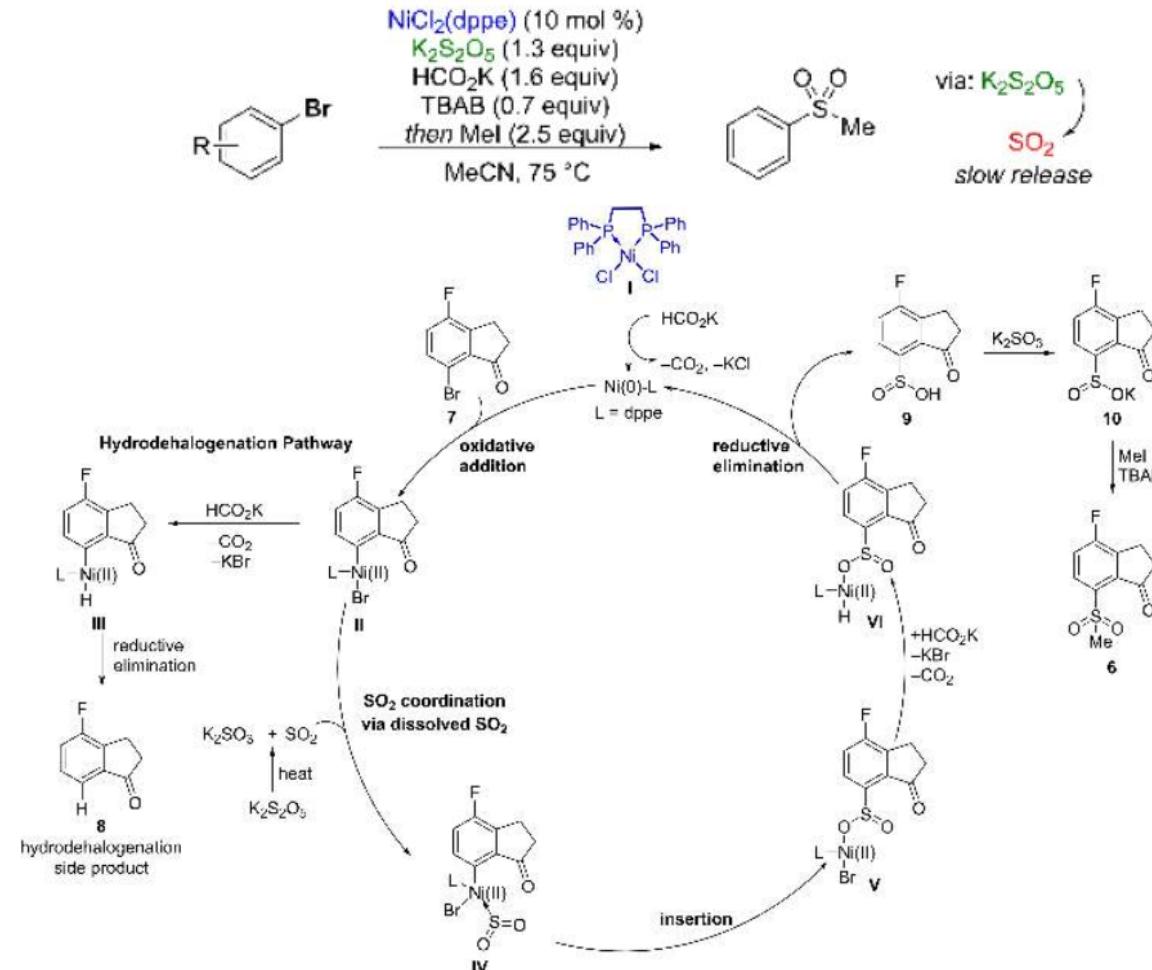
■ Copper-catalyzed decarboxylative alkylsulfonylation



J. Wu et. al. *Org. Chem. Front.*, 2020, 7, 4050

Non-radical transformation of sulfur dioxide

■ Nickel-catalyzed sulfonylation of aryl Bromides



J. C. Hethcox, et. al. *Angew. Chem. Int. Ed.* 2023, e202217623

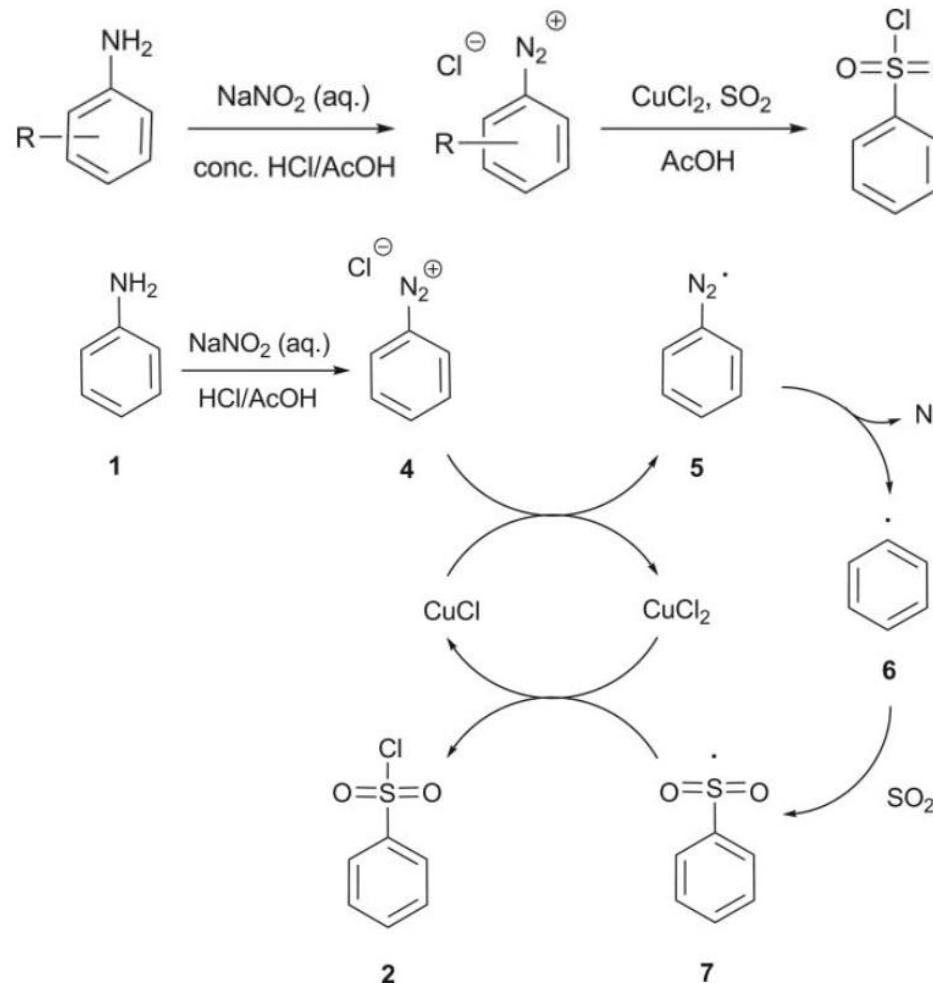


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- **Radical transformation of sulfur dioxide**
- Asymmetric reactions involving SO_2 insertion

Radical transformation of sulfur dioxide

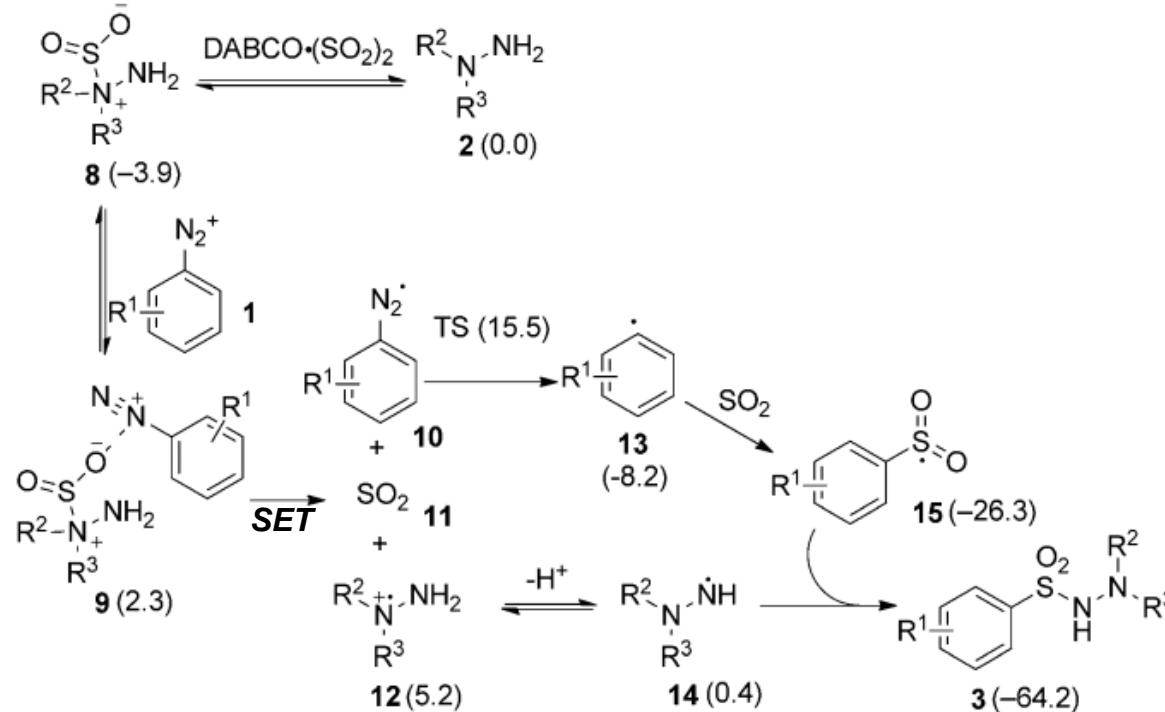
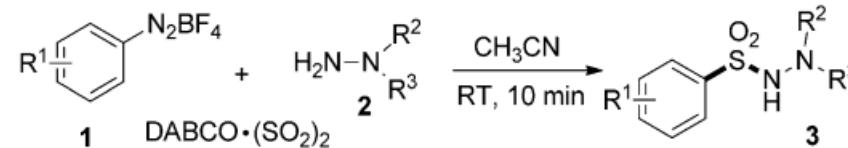
■ The Meerwein reaction —modified Sandmeyer reaction



H. Meerwein, et al *Chem. Ber.*, **1957**, 50, 841

Radical transformation of sulfur dioxide

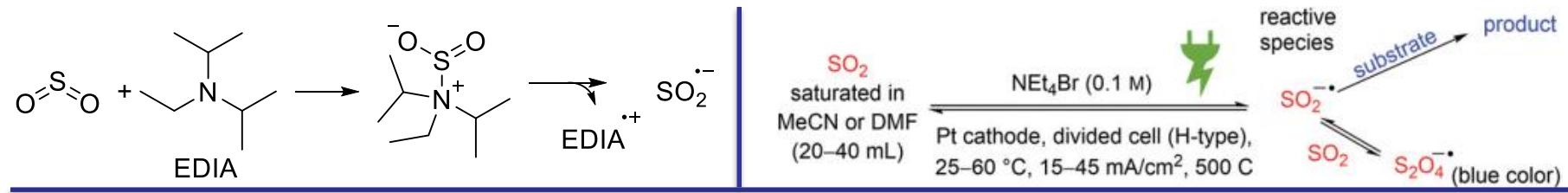
■ Metal-free aminosulfonylation of aryl diazonium tetrafluoroborates



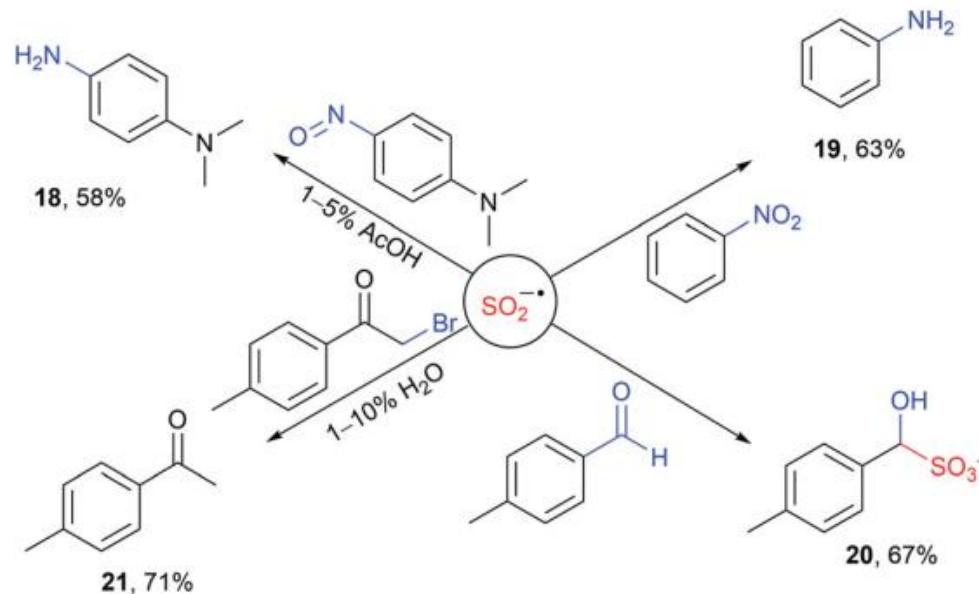
Z. Liu and J. Wu, *et al* Angew. Chem. Int. Ed. 2014, 53, 2451

Radical transformation of sulfur dioxide

■ Early studies with $\text{SO}_2^{\cdot-}$



B Scope

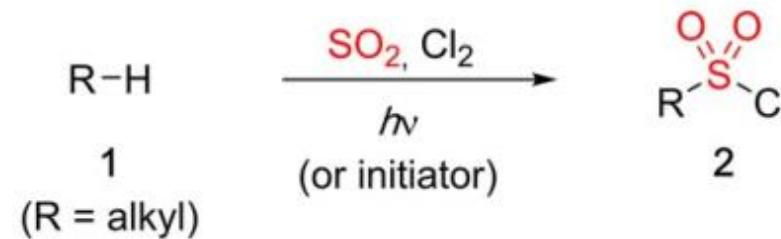


D. Knittel, et. al. *Monatsh. Chem.*, **1986**, 117, 359



Radical transformation of sulfur dioxide

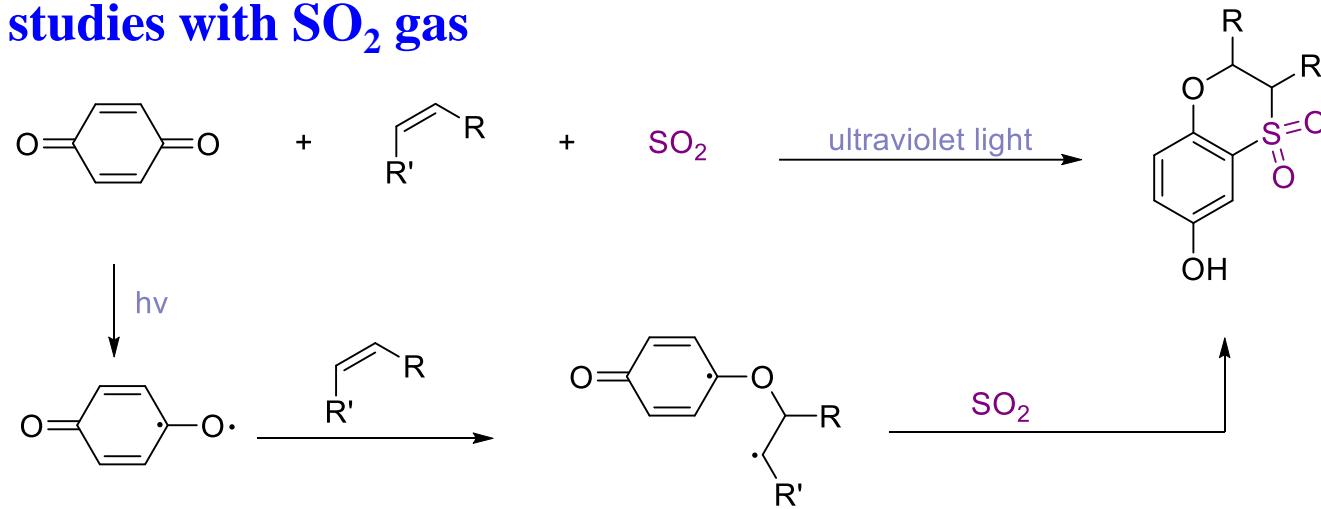
■ The Reed reaction



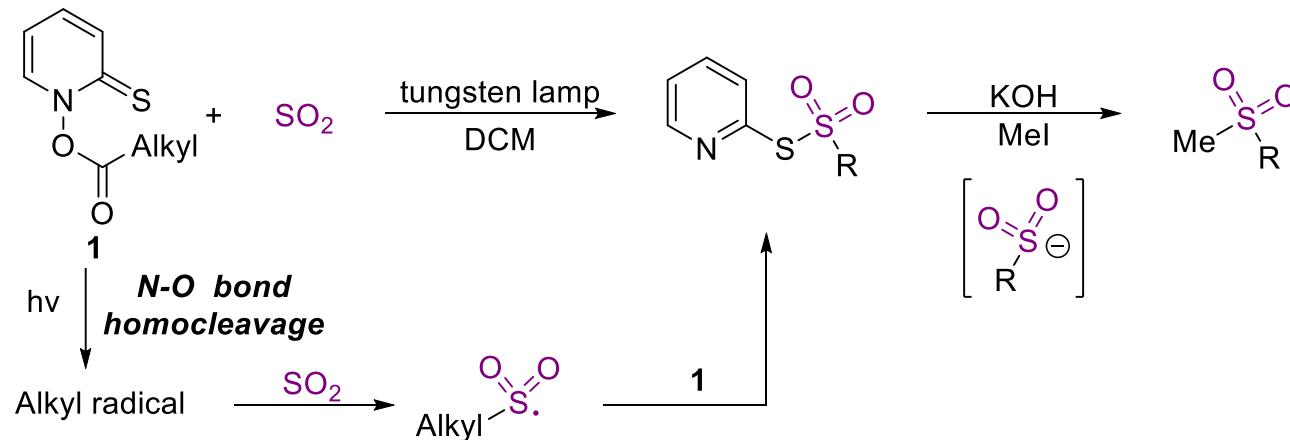
M. P. Sibi, et al *Radicals in Organic Synthesis*; Wiley-VCH, Weinheim, 2001

Radical transformation of sulfur dioxide

■ Early studies with SO₂ gas



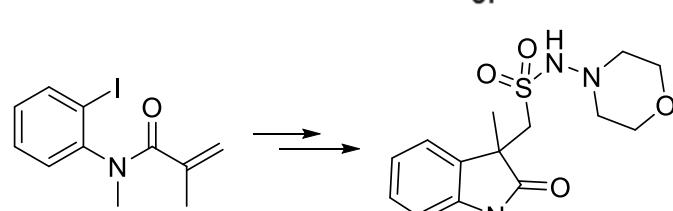
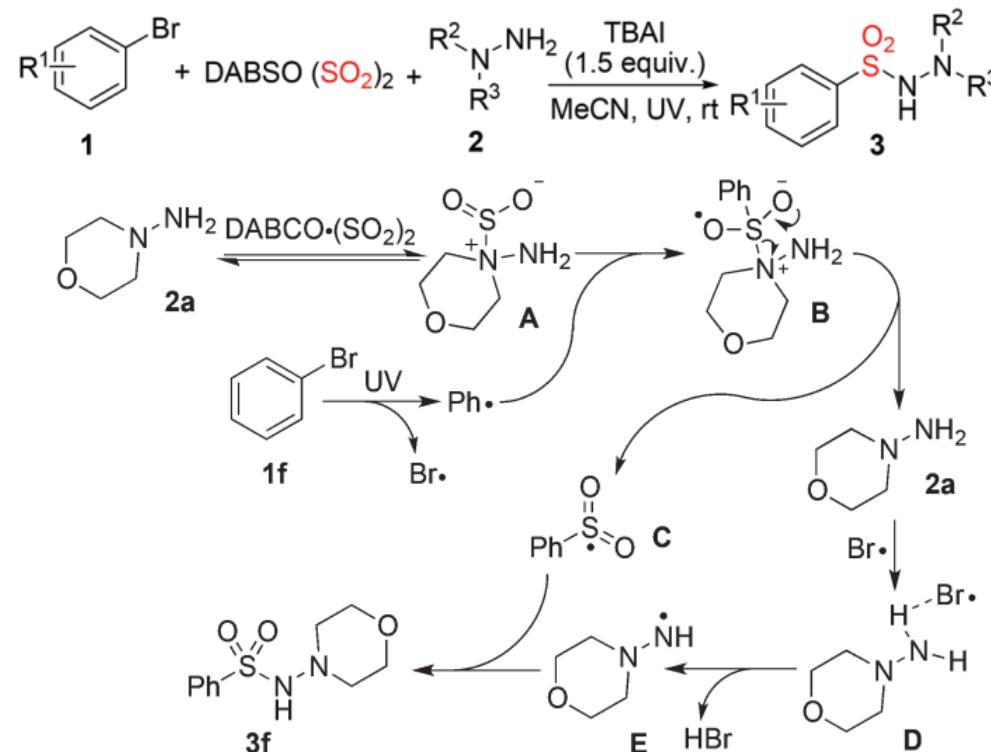
R. M. Wilson, et. al. *J. Am. Chem. Soc.* **1974**, *96*, 7350–7351



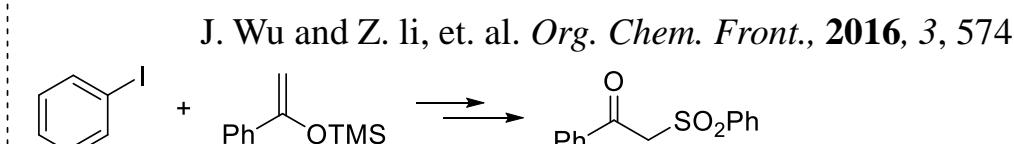
S. Z. Zard, et. al. *Tetrahedron* **1988**, *44*, 1153-1158

Radical transformation of sulfur dioxide

■ Photoinduced C-X bond cleavage



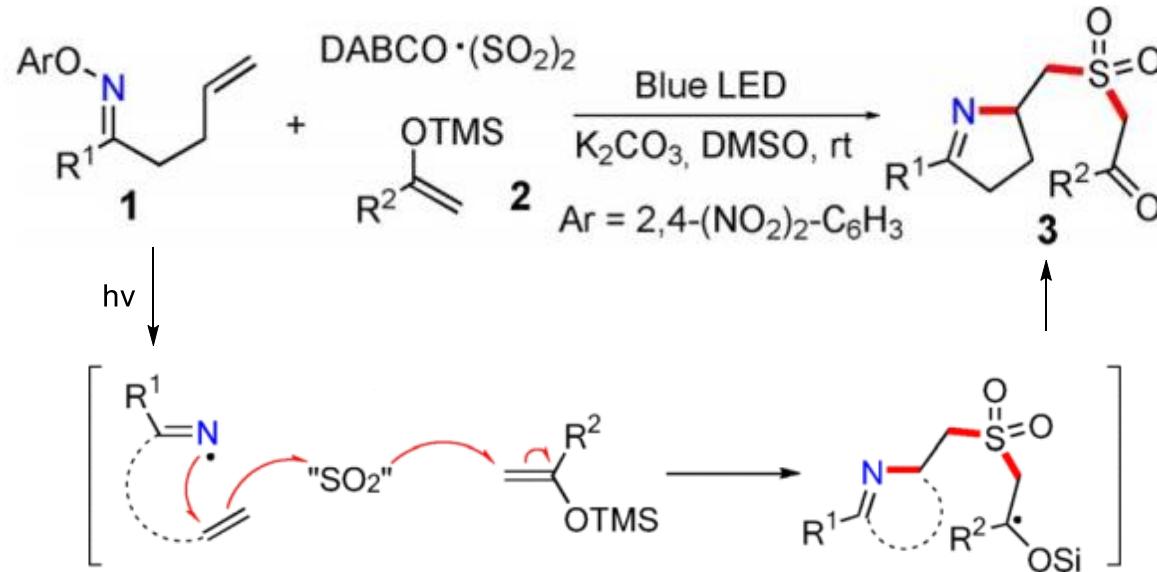
Org. Chem. Front., 2016, 3, 865



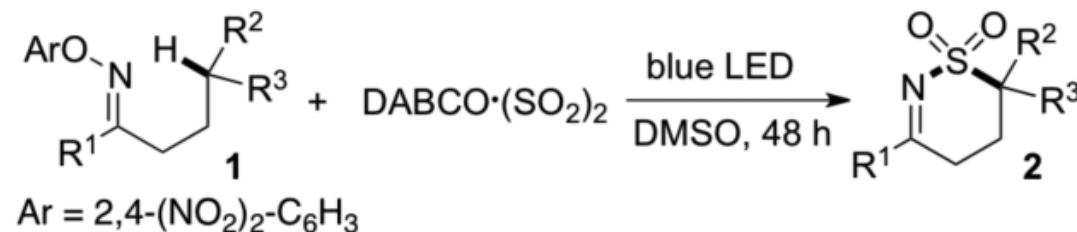
Adv. Synth. Catal., 2017, 359, 2999

Radical transformation of sulfur dioxide

■ Photoinduced N-O bond cleavage



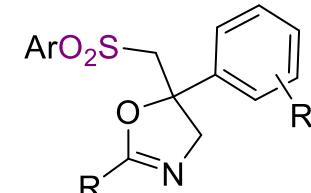
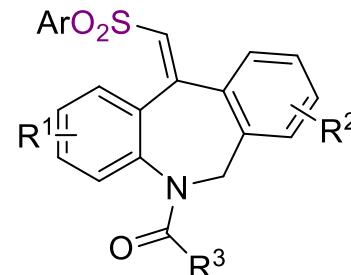
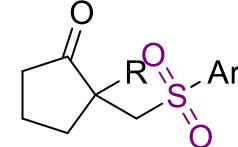
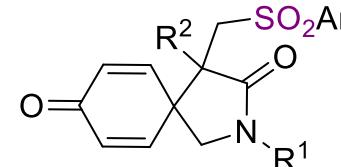
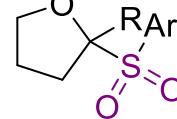
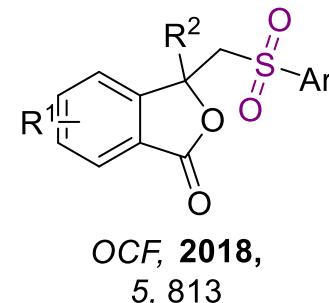
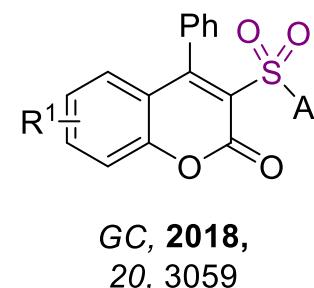
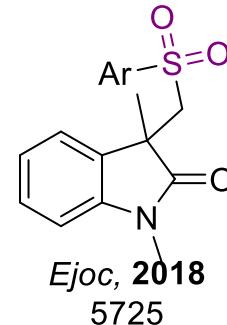
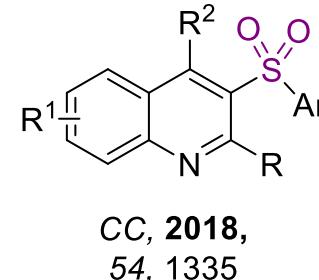
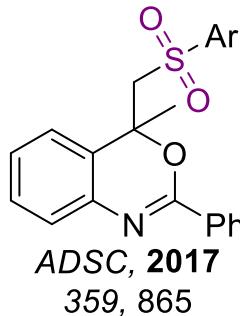
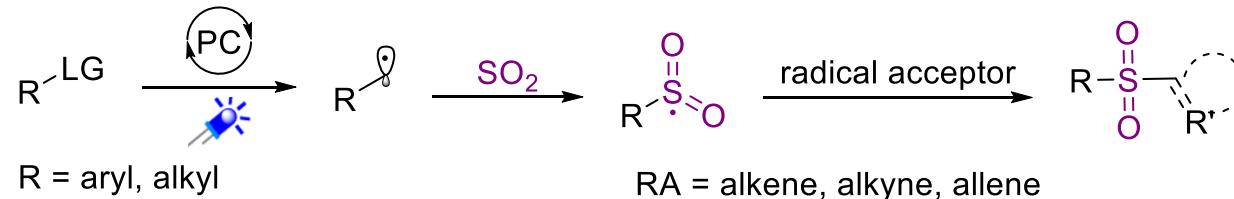
J. Wu, et. al. *Chem. Eur. J.* **2017**, 23, 8176



J. Wu, et. al. *Org. Lett.* **2017**, 19, 4472

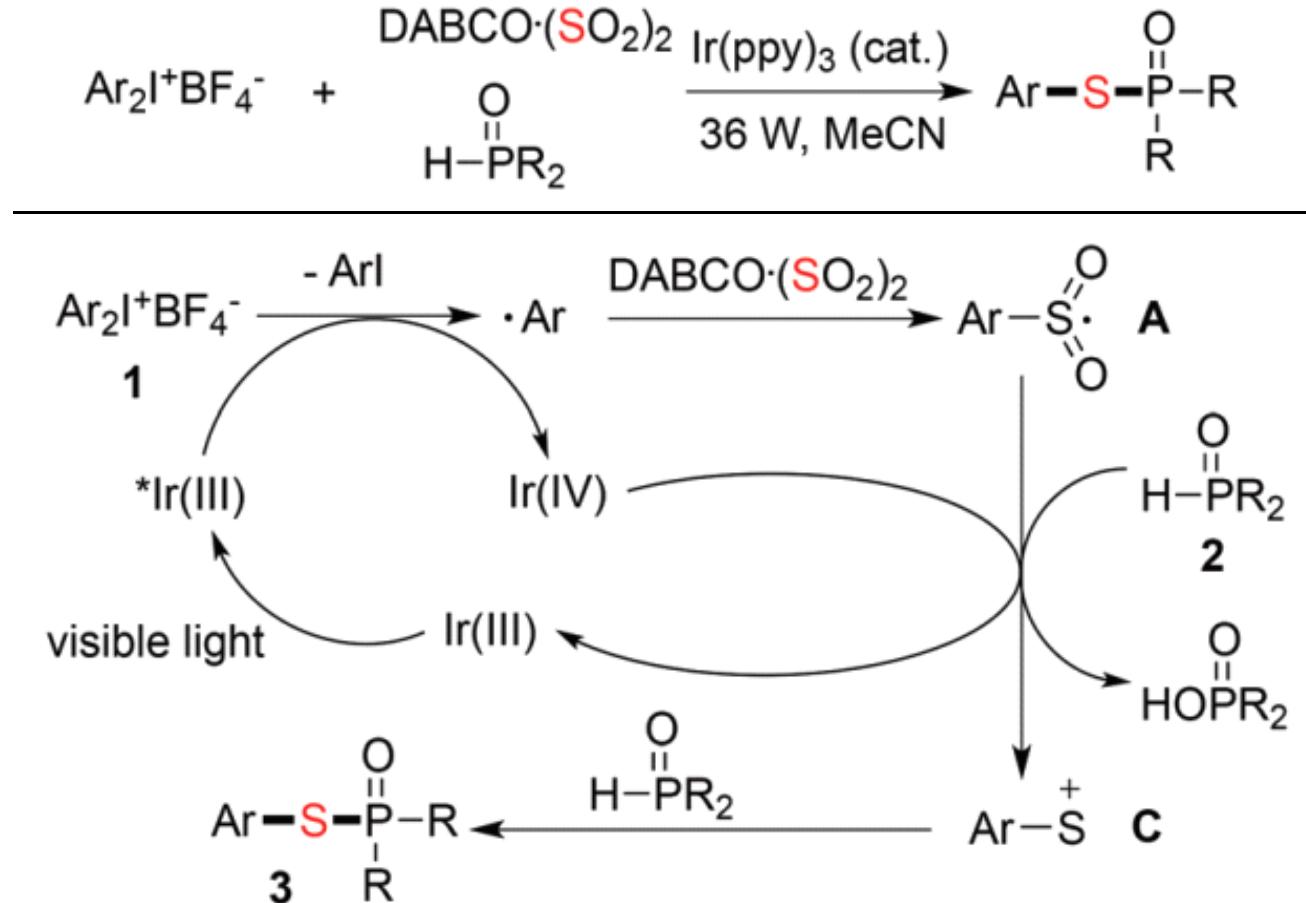
Radical transformation of sulfur dioxide

■ Photoredox catalyzed radical cyclization reactions



Radical transformation of sulfur dioxide

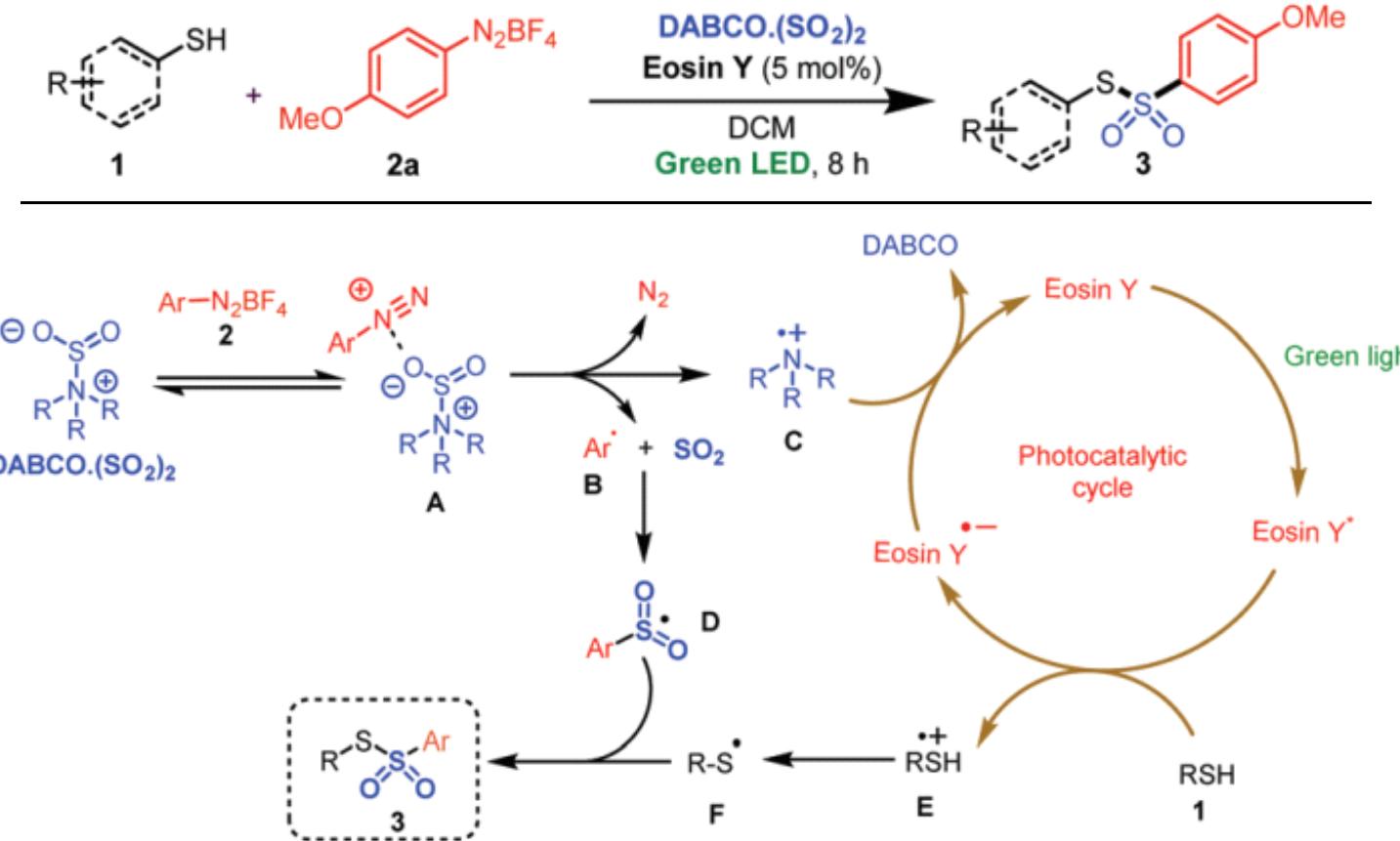
■ Photoredox catalyzed S-P bond construction



J. Liu and J. Wu, et. al. *Org. Chem. Front.*, 2017, 4, 2221

Radical transformation of sulfur dioxide

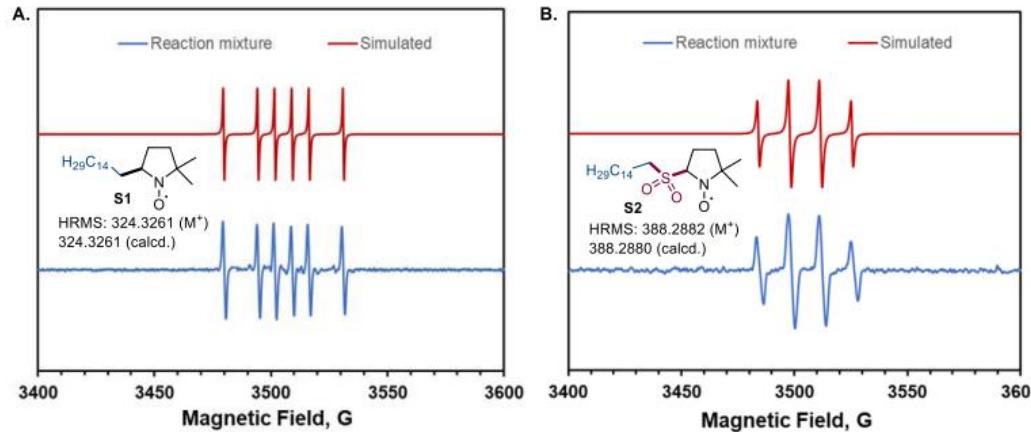
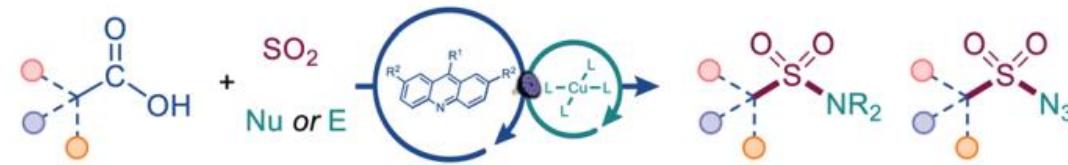
■ Photoredox catalyzed S-S bond construction



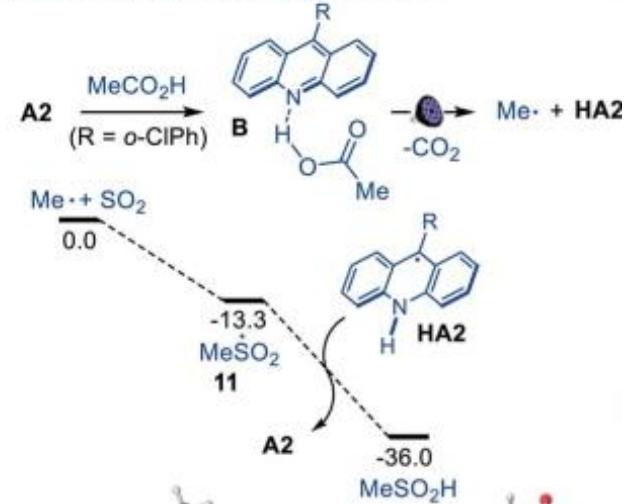
C. M. R. Volla, et. al. *Org. Biomol. Chem.*, 2019, 17, 5897

Radical transformation of sulfur dioxide

■ Photoredox catalyzed N-S bond construction



A. Acridine catalyst turnover



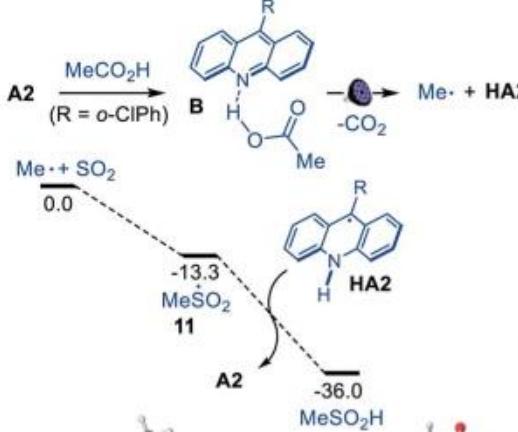
O. V. Larionov, et al. *Chem. Sci.*, 2021, 12, 6429

Radical transformation of sulfur dioxide

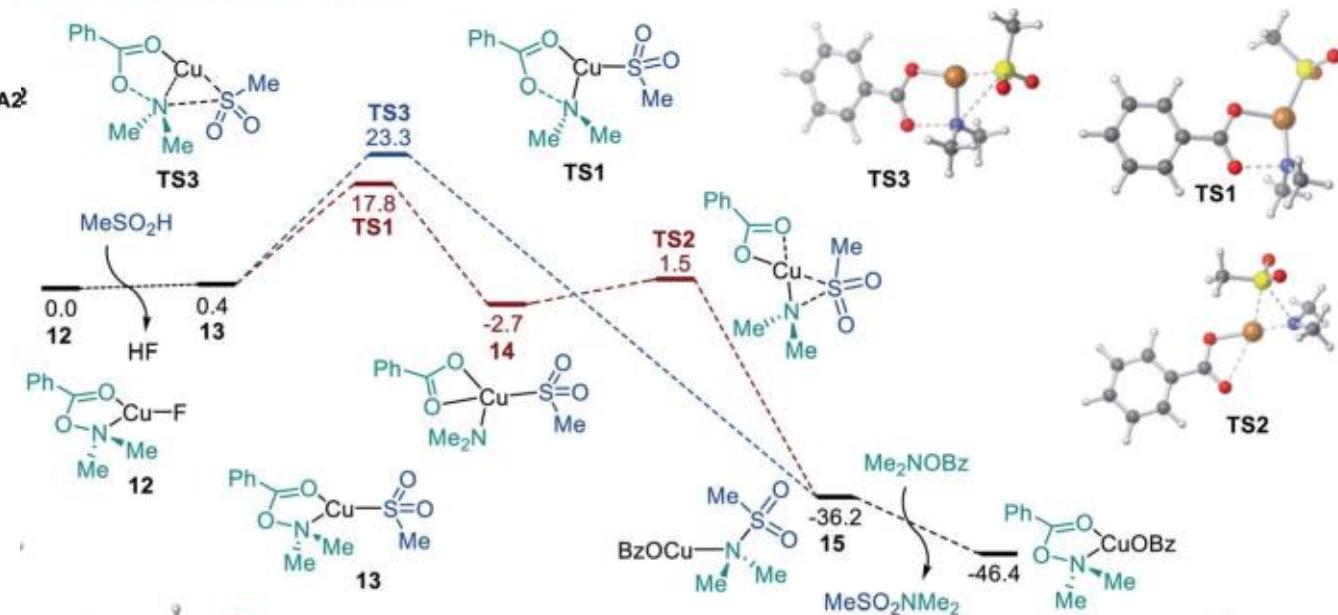
■ Photoredox catalyzed N-S bond construction



A. Acridine catalyst turnover



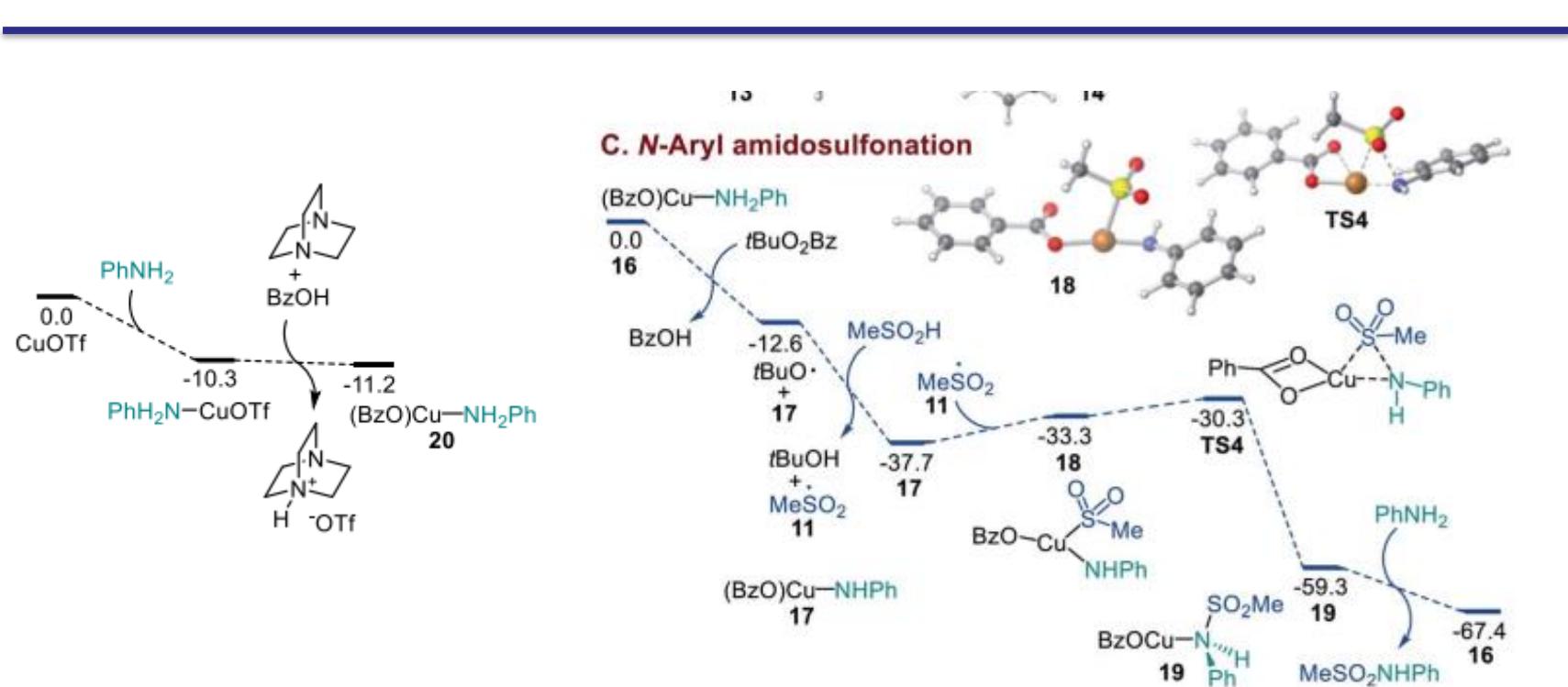
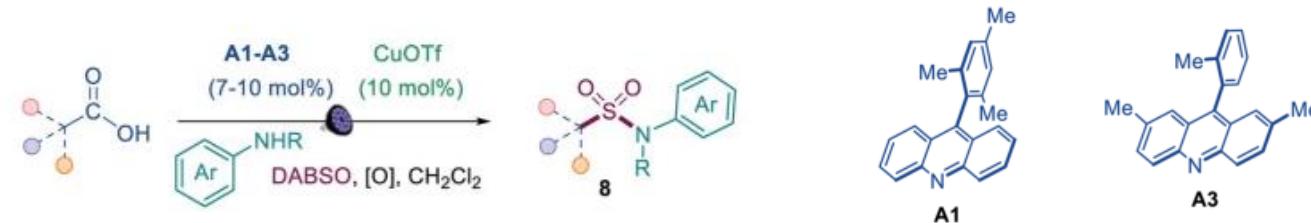
B. N-Alkyl amidosulfonation



O. V. Larionov, et al. *Chem. Sci.*, 2021, 12, 6429

Radical transformation of sulfur dioxide

■ Photoredox catalyzed N-S bond construction



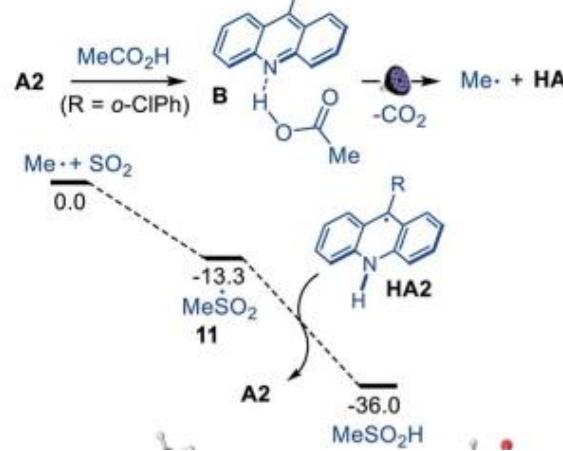
O. V. Larionov, et al. *Chem. Sci.*, 2021, 12, 6429

Radical transformation of sulfur dioxide

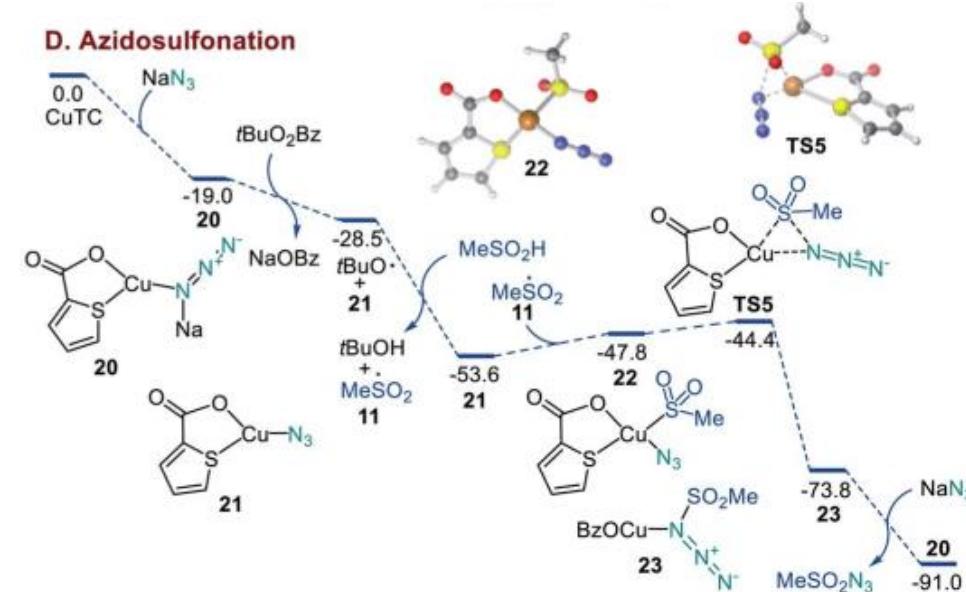
■ Photoredox catalyzed N-S bond construction



A. Acridine catalyst turnover

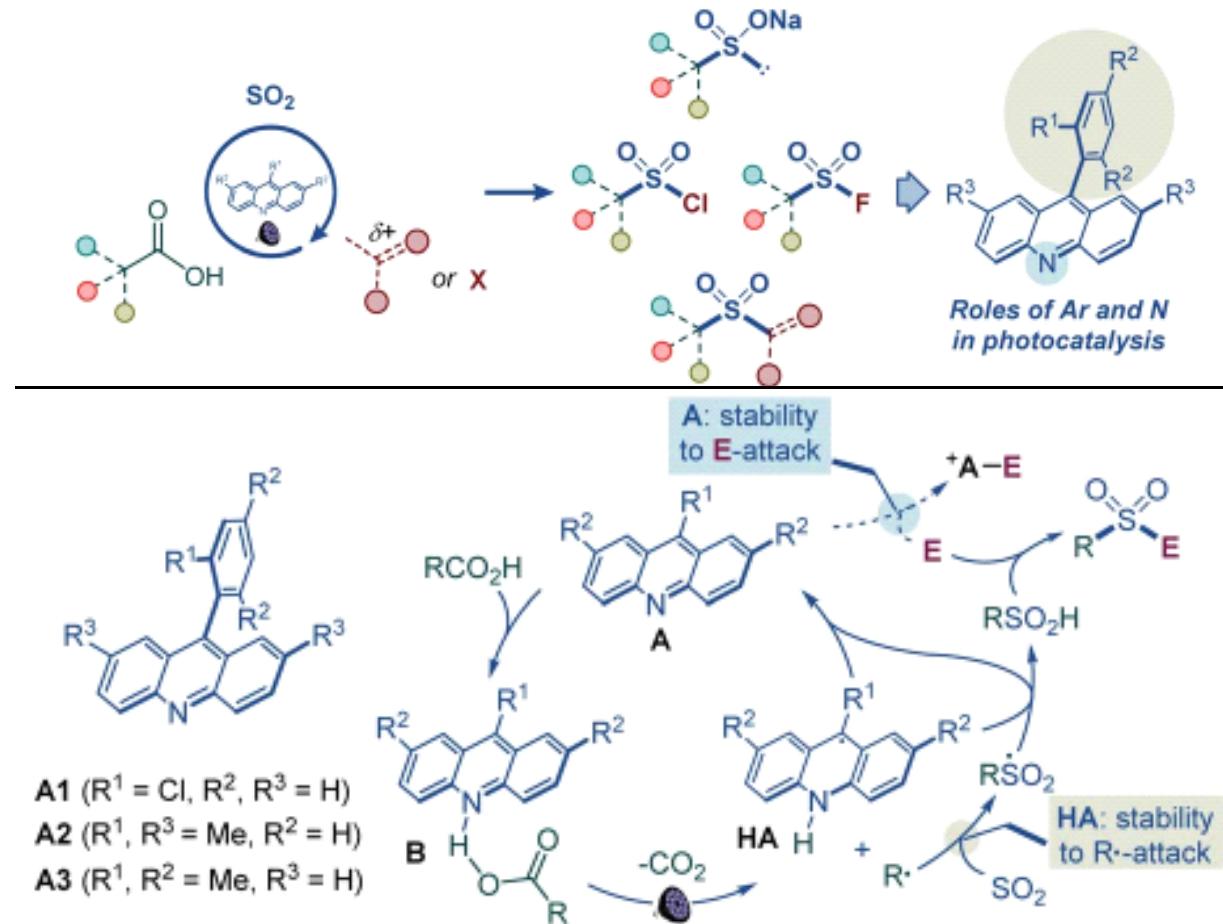


D. Azidosulfonation



Radical transformation of sulfur dioxide

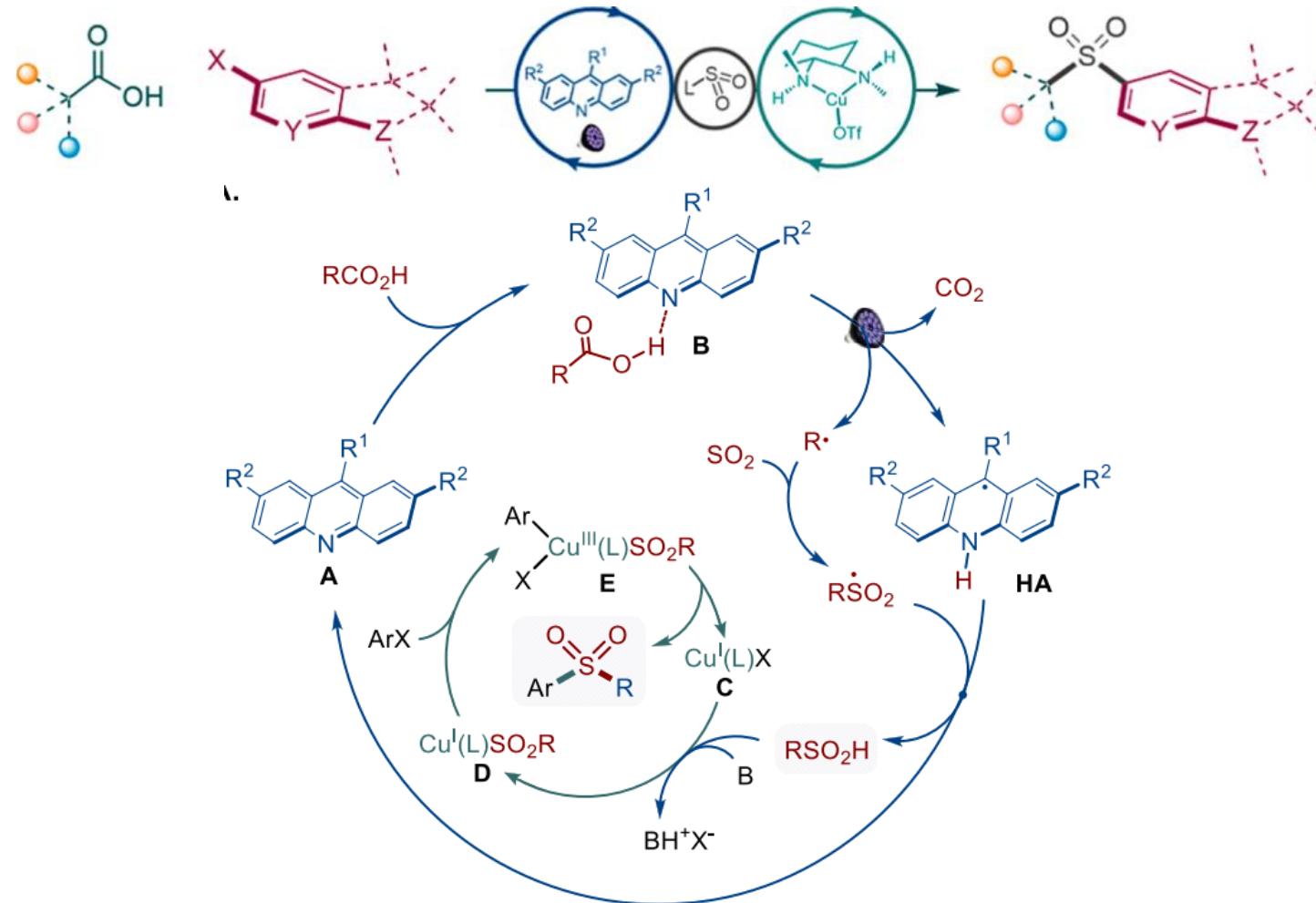
■ Photoredox catalyzed X-S bond construction



O. V. Larionov, et. al. *Chem. Sci.*, 2022, 13, 4170

Radical transformation of sulfur dioxide

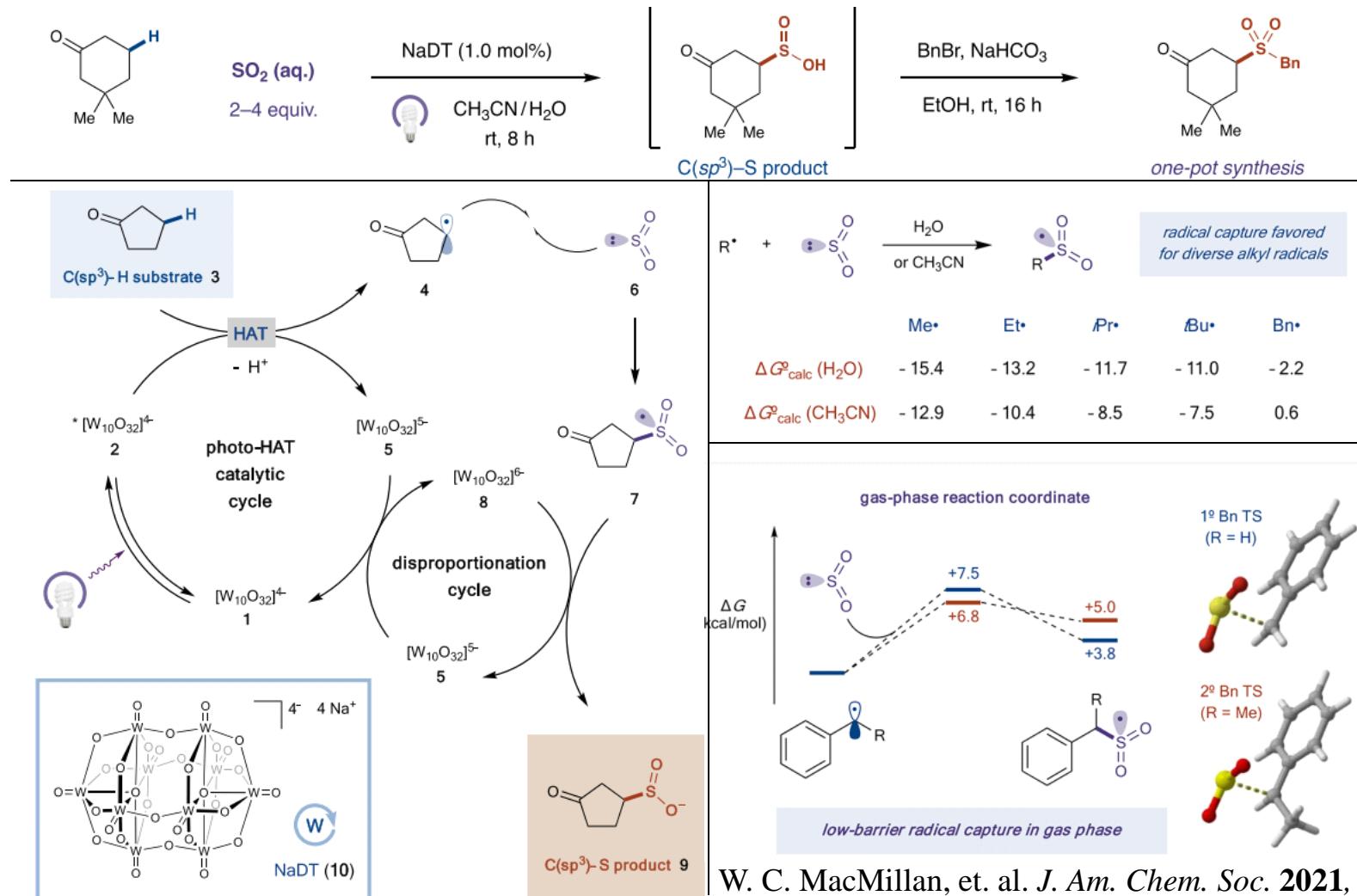
■ Photoredox catalyzed C-S bond construction



O. V. Larionov, et. al. ACS Catal. 2022, 12, 8729

Radical transformation of sulfur dioxide

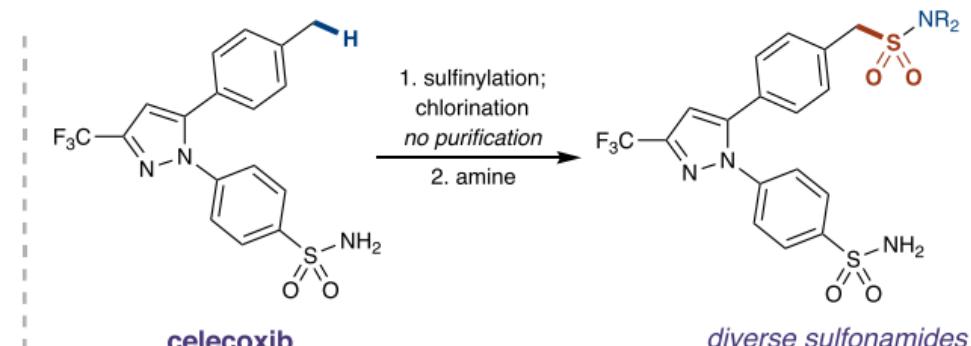
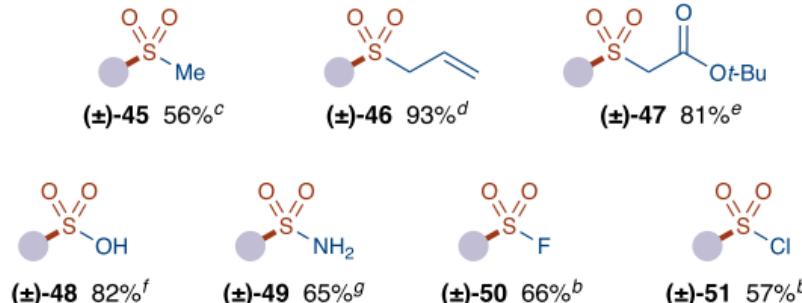
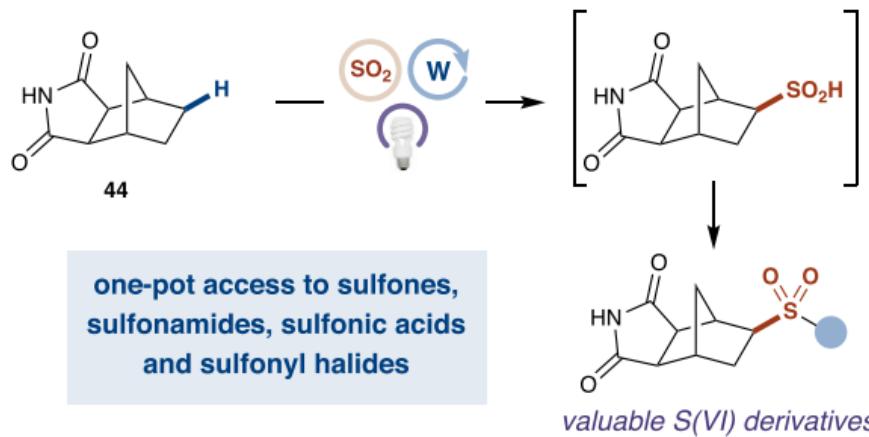
Decatungstate-catalyzed C(sp³)–H sulfinylation



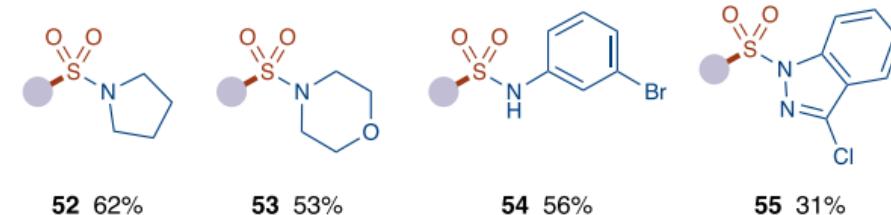
W. C. MacMillan, et. al. *J. Am. Chem. Soc.* **2021**, *143*, 9737

Radical transformation of sulfur dioxide

■ Decatungstate-catalyzed C(sp³)–H sulfinylation



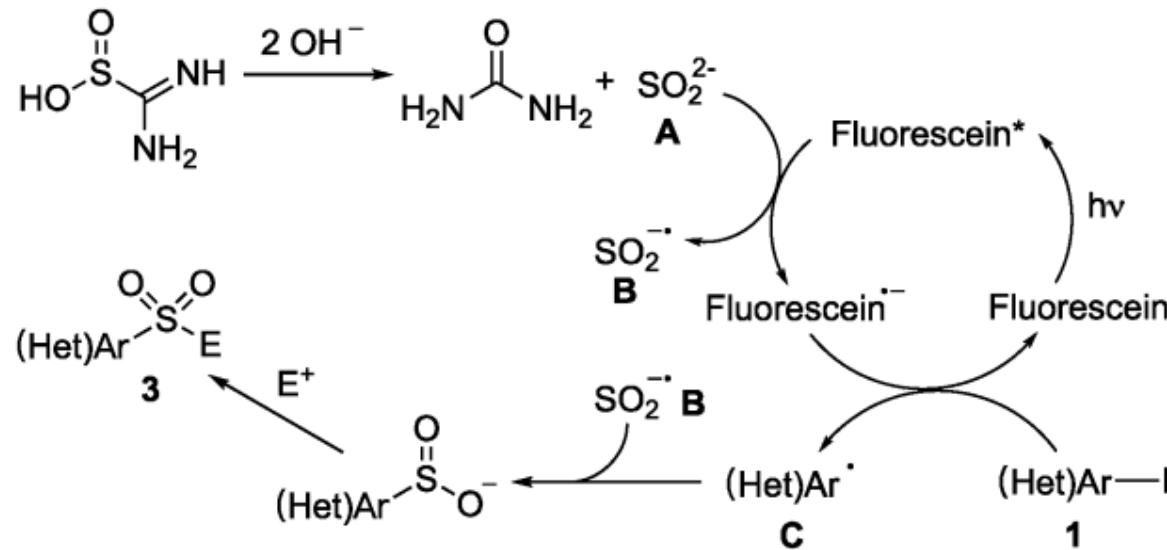
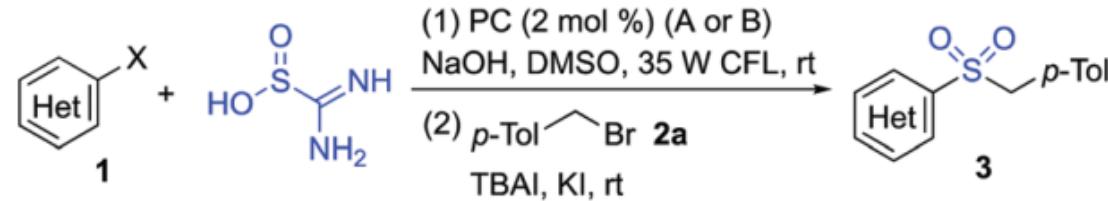
two-step sulfonamide synthesis via sulfonyl chloride



D. W. C. MacMillan, et. al. *J. Am. Chem. Soc.* **2021**, *143*, 9737

Radical transformation of sulfur dioxide

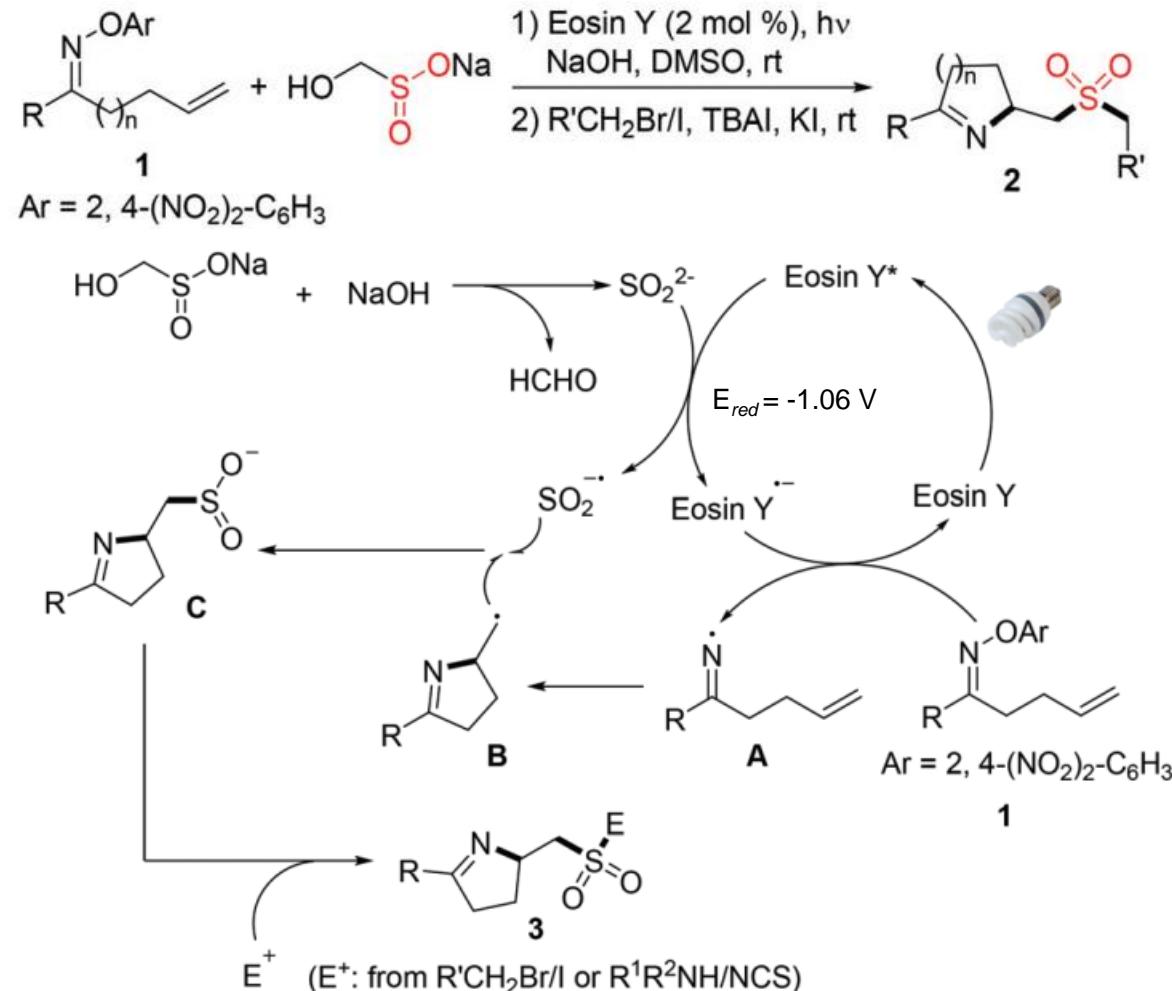
■ Photoredox catalyzed SO_2 insertion —— $\text{SO}_2^{\cdot-}$ intermediate



J. Wu and Z. Li, et. al. *Chem. Commun.*, 2019, 55, 2489

Radical transformation of sulfur dioxide

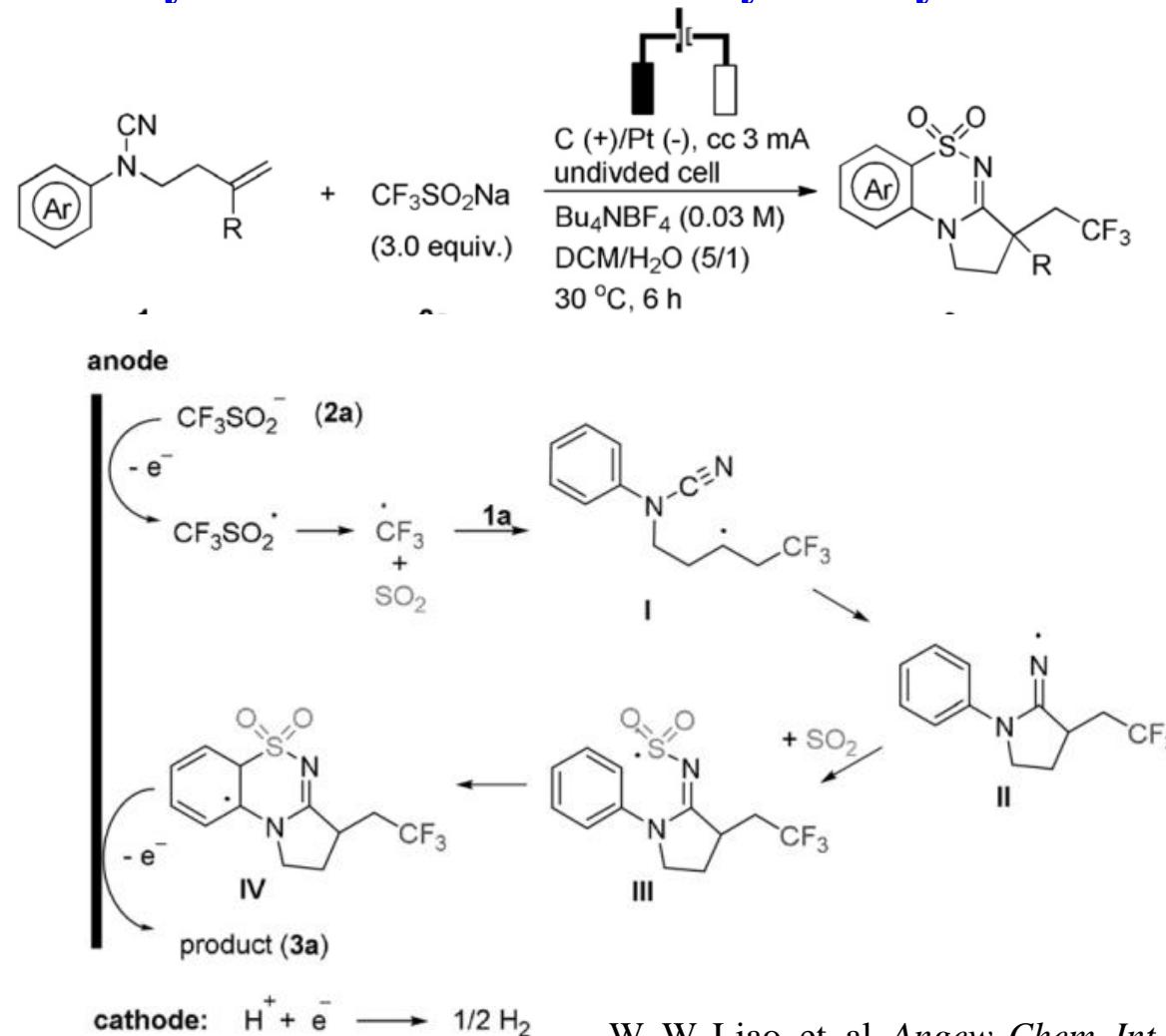
■ Photoredox catalyzed SO_2 insertion — $\text{SO}_2^{\cdot-}$ intermediate



F-S. He and J. Wu, et. al. *Org. Chem. Front.*, 2021, 8, 3746

Electrochemical radical transformation of sulfur dioxide — radical acceptor

■ Electrochemical synthesis of trifluoromethylated cyclic N-sulfonylimines



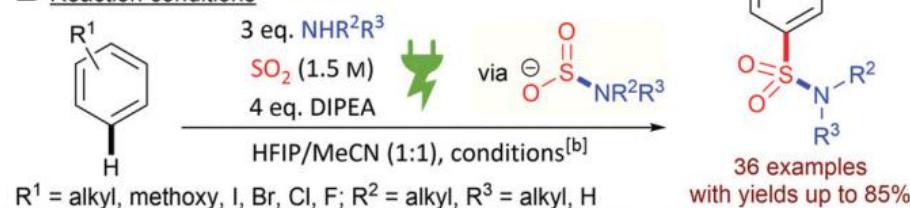
W.-W. Liao, et. al. *Angew. Chem. Int. Ed.* **2020**, 59, 7266

Electrochemical radical transformation of sulfur dioxide — electrophile

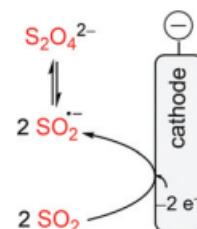
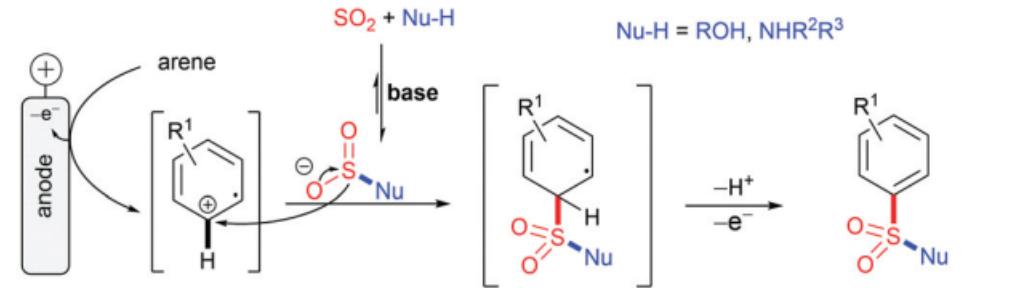
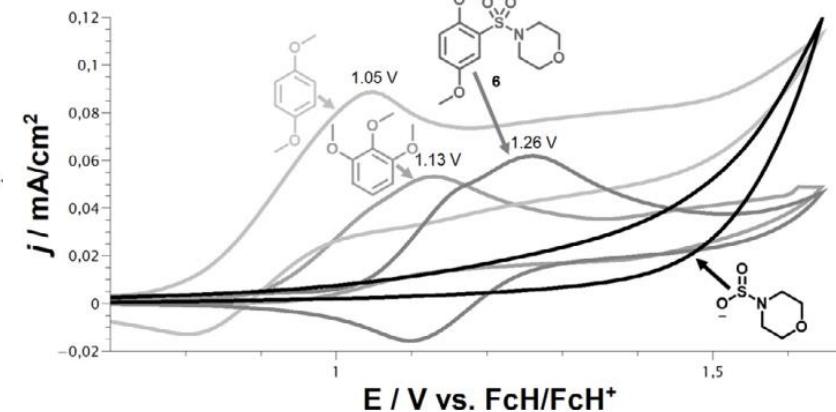
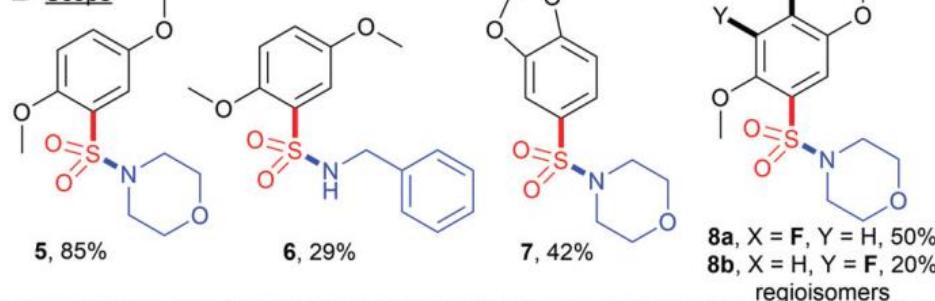
■ Electrochemical synthesis of sulfonamides

Sulfonamides, Waldvogel (2021)

B Reaction conditions



D Scope

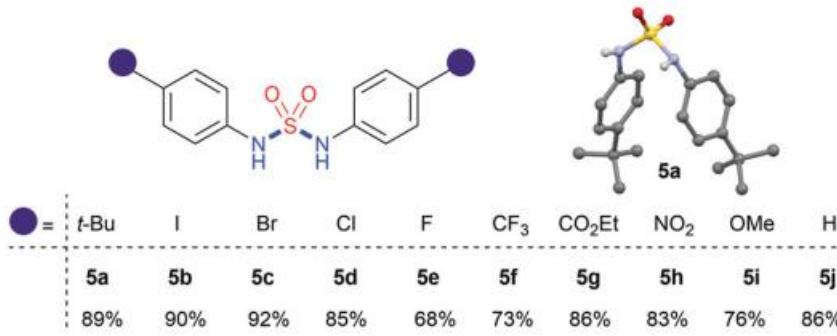
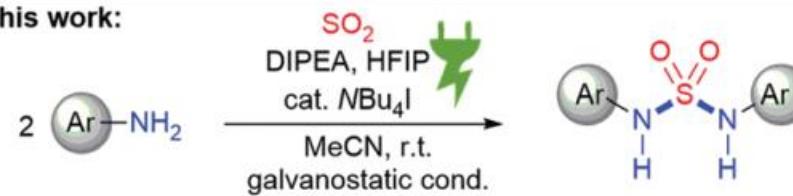


S. R. Waldvogel, et. al. *Angew. Chem. Int. Ed.* **2021**, *60*, 5056; *Chem. Eur. J.* **2020**, *26*, 8358

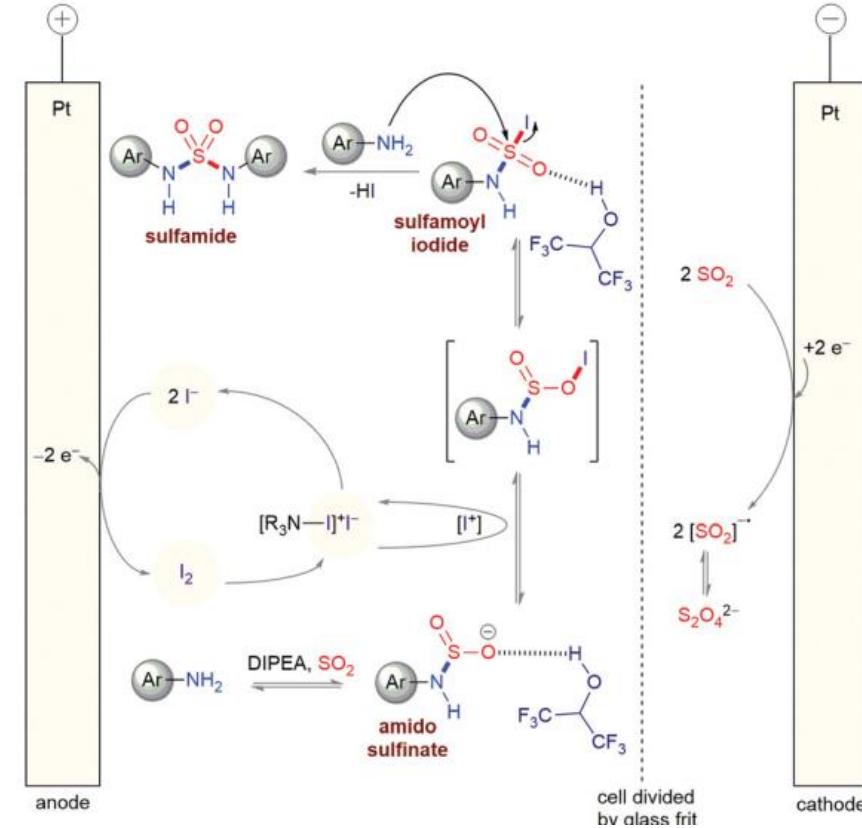
Electrochemical radical transformation of sulfur dioxide — electrophile

■ Electrochemical synthesis of sulfamides

this work:



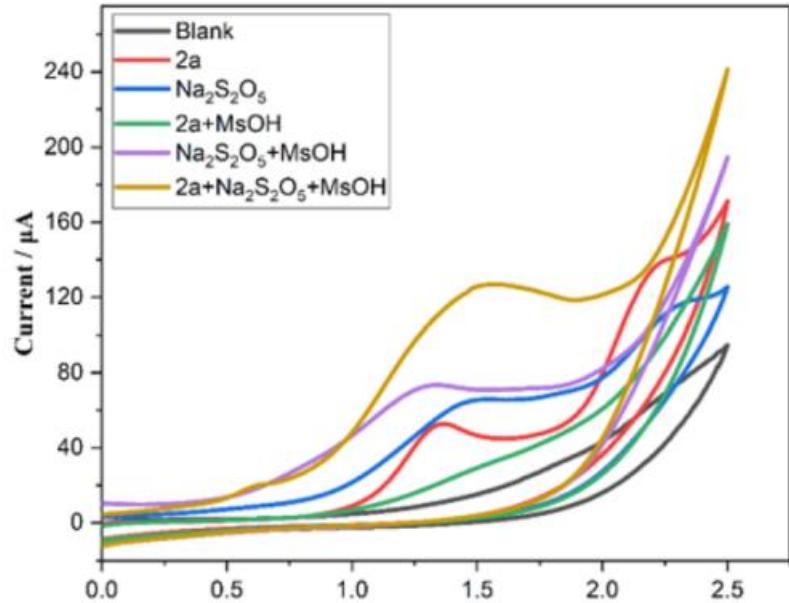
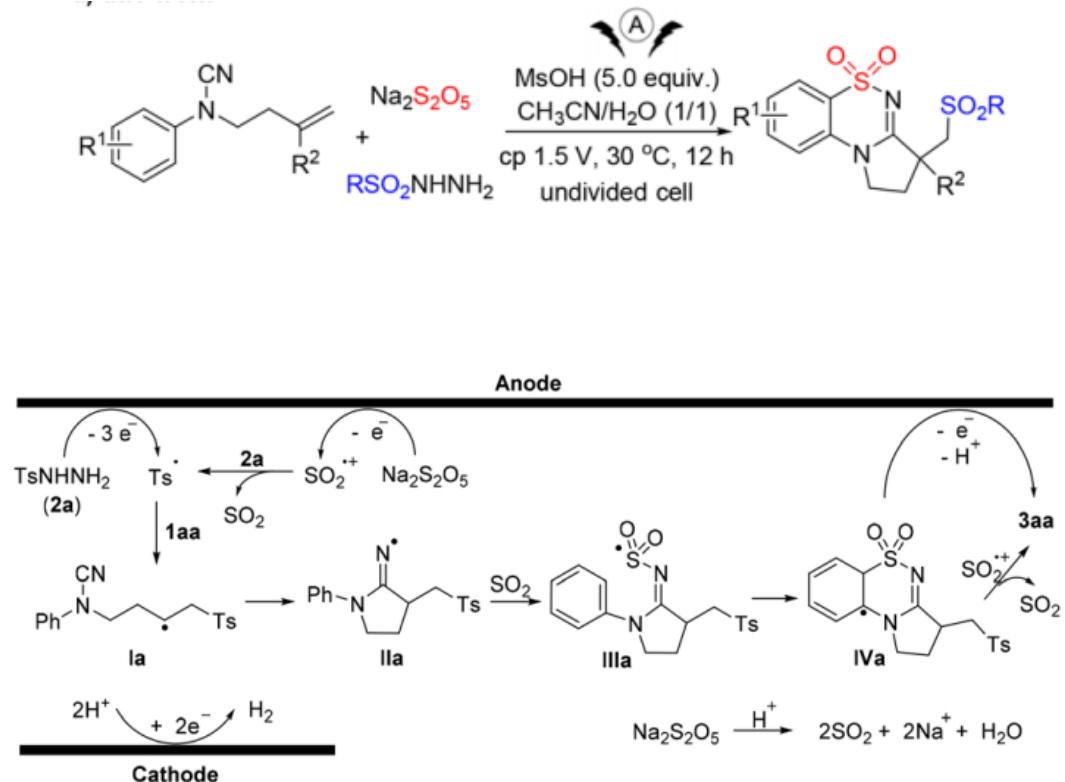
13-fold scale-up
of 5a in H-type
divided glass cell



S. R. Waldvogel, et. al. *Chem. Commun.*, 2021, 57, 4775

Electrochemical radical transformation of sulfur dioxide — radical cation

■ Electrochemical multi-component reaction — sulfonamides

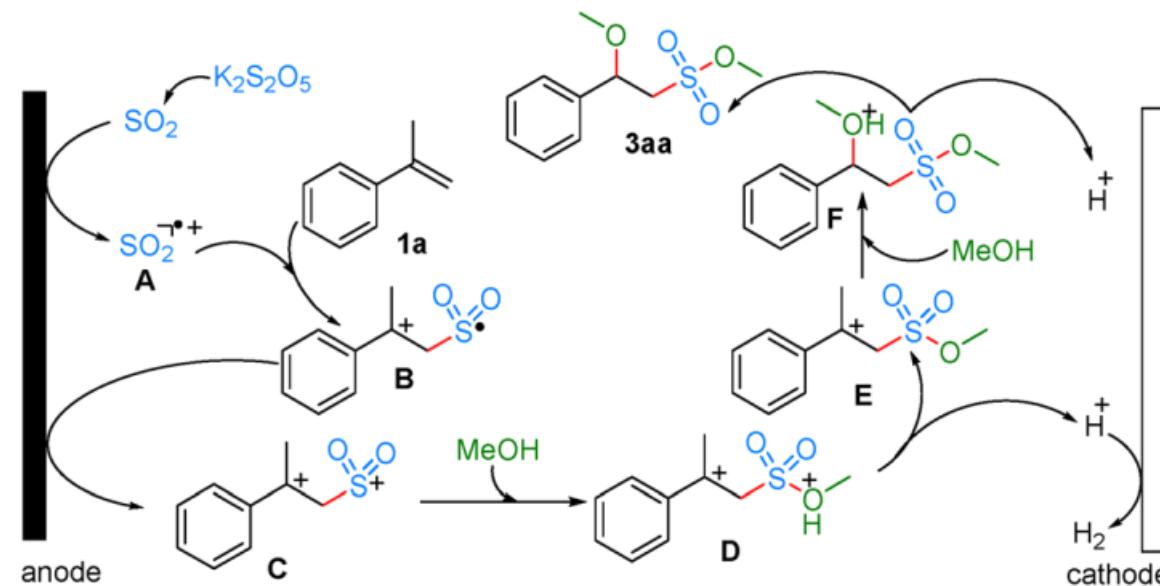
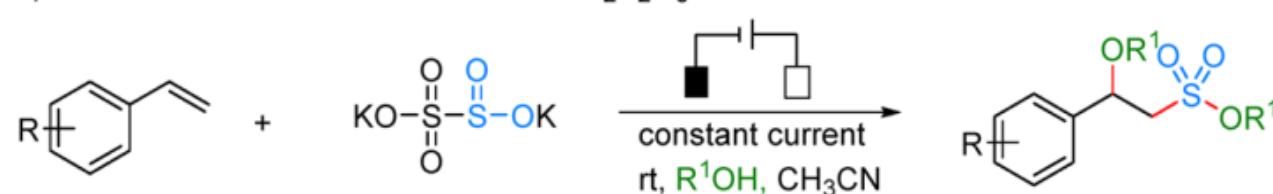


$\text{Na}_2\text{S}_2\text{O}_5$ (blue line): $E_{ox} = 1.46 \text{ V}$;

P. S. Baran, et. al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202208080

Electrochemical radical transformation of sulfur dioxide — radical cation

■ Electrochemical multi-component reaction — sulfonate esters

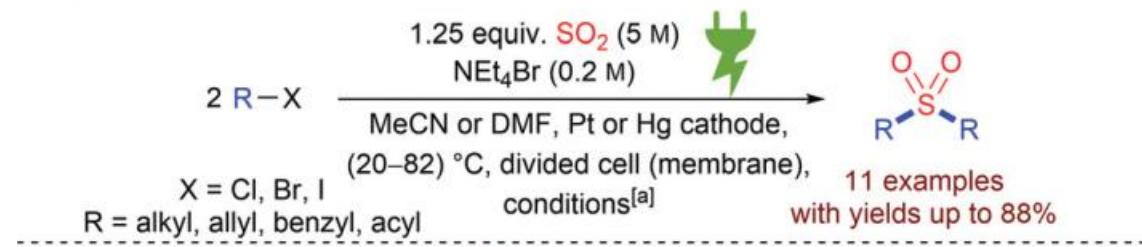


H. Mei and J. Han, et. al. *Green Chem.*, 2022, 24, 6113

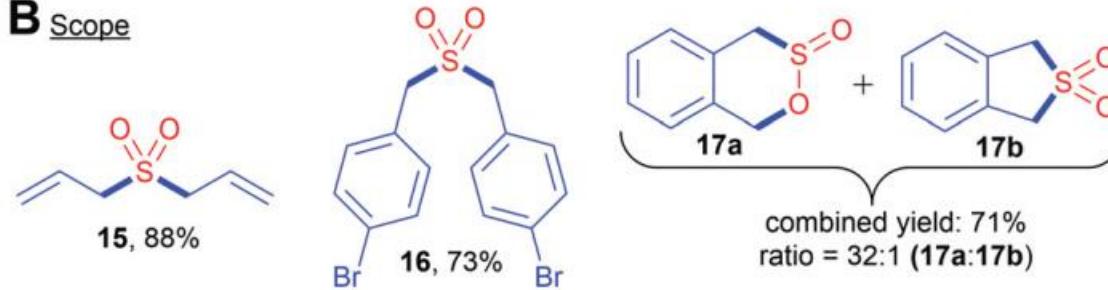
Electrochemical radical transformation of sulfur dioxide — radical anion

■ Early studies with SO₂ gas

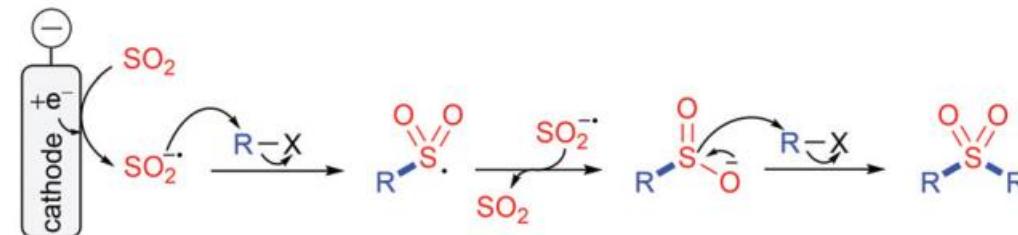
A Reaction conditions



B Scope



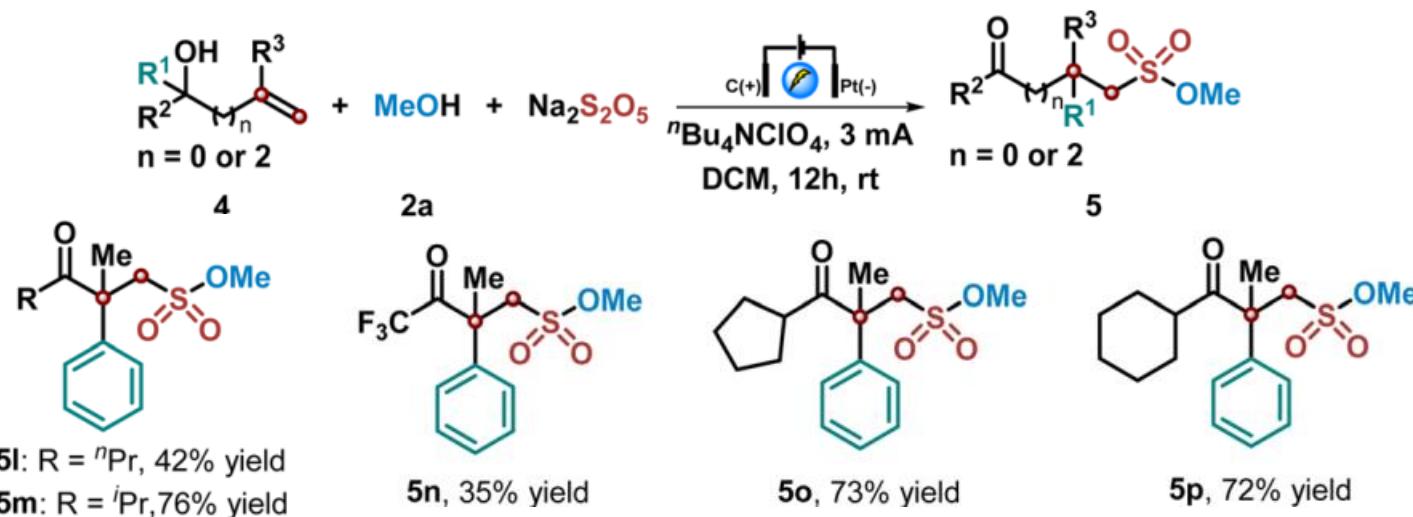
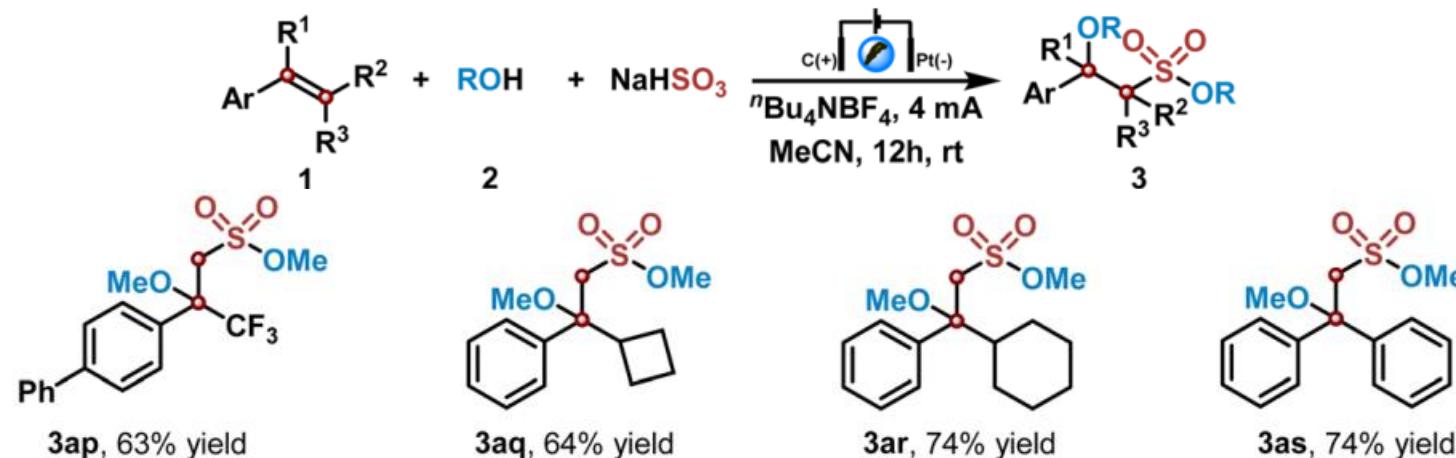
C Mechanism



D. Knittel, et. al. *J. Appl. Electrochem.*, 1973, 3, 291

Electrochemical radical transformation of sulfur dioxide — radical anion

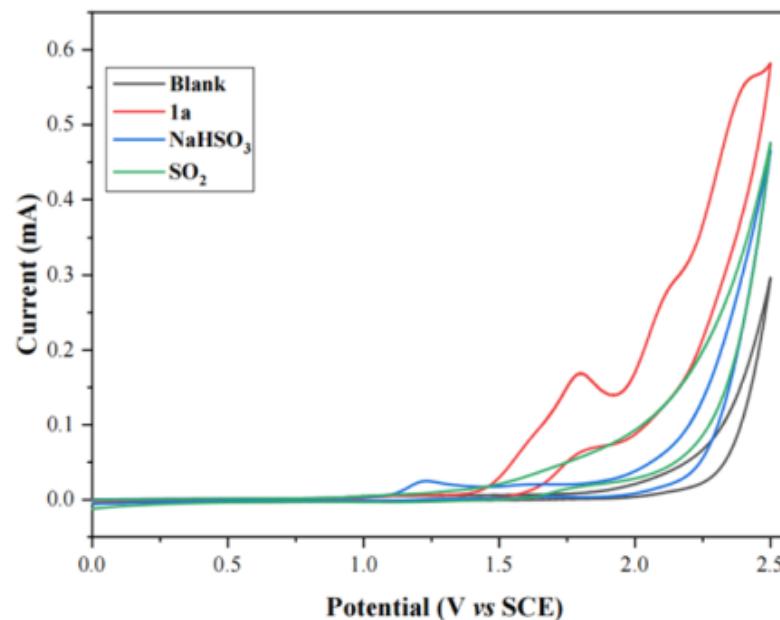
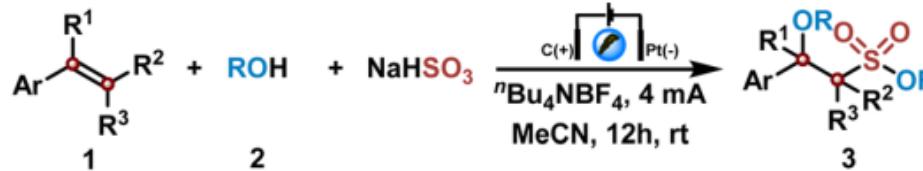
■ Electrochemical alkoxy sulfonyl radical species



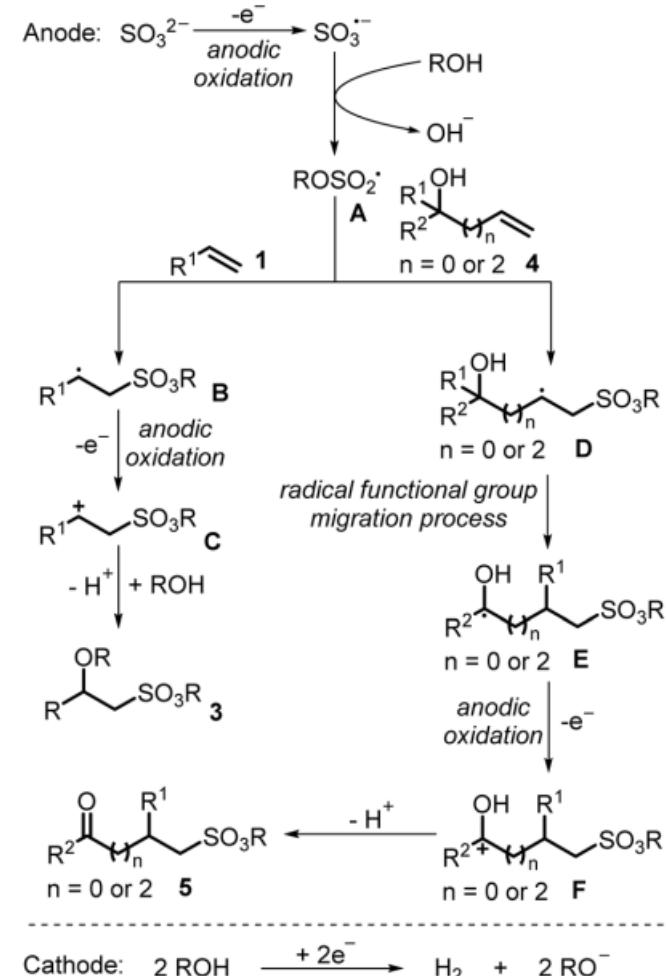
J. Wu and S. Ye, et. al. *Chem. Sci.*, 2022, 13, 11785

Electrochemical radical transformation of sulfur dioxide — radical anion

■ Electrochemical alkoxy sulfonyl radical species



$E_{ox} = 1.23 \text{ V vs. SCE}$ in MeCN/MeOH (V/V ¼ 4/1)

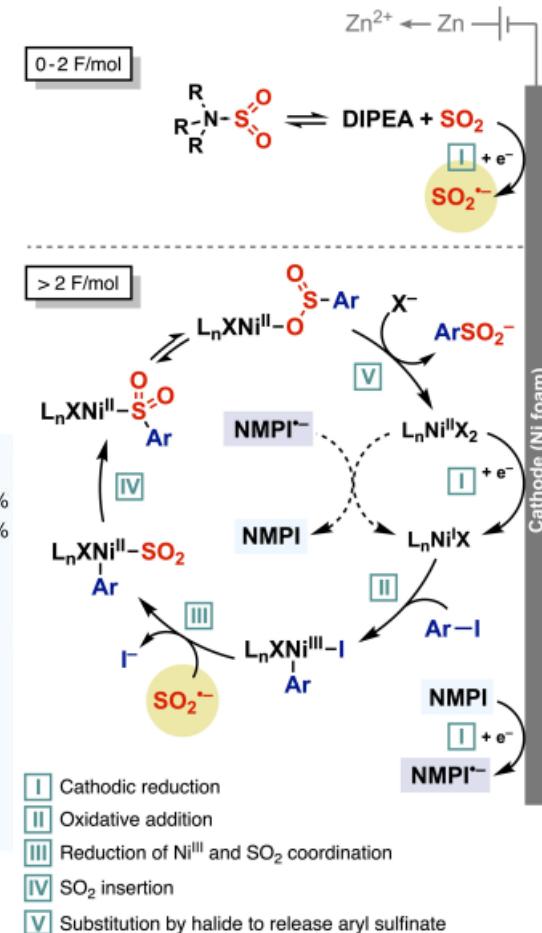
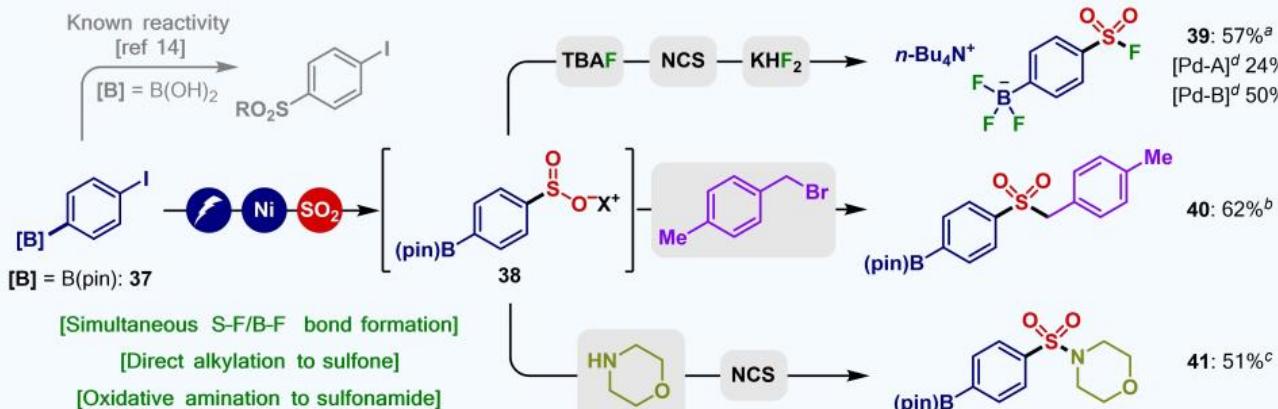
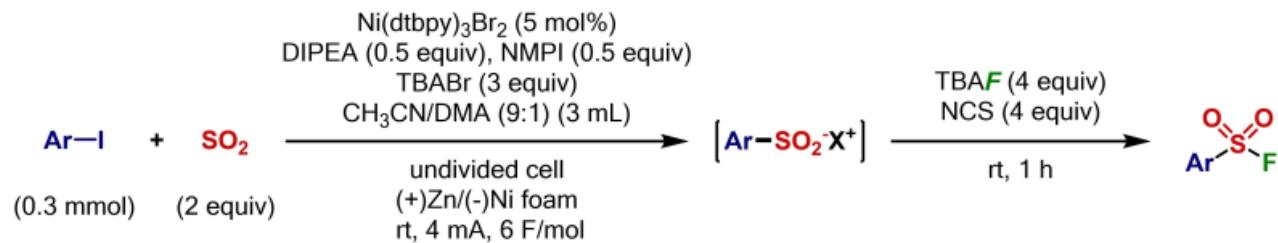


J. Wu and S. Ye, et. al. *Chem. Sci.*, 2022, 13, 11785



Electrochemical radical transformation of sulfur dioxide — radical anion

■ Nickel electrocatalytic sulfinylation of aryl halides with SO_2



P. S. Baran, et. al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202208080

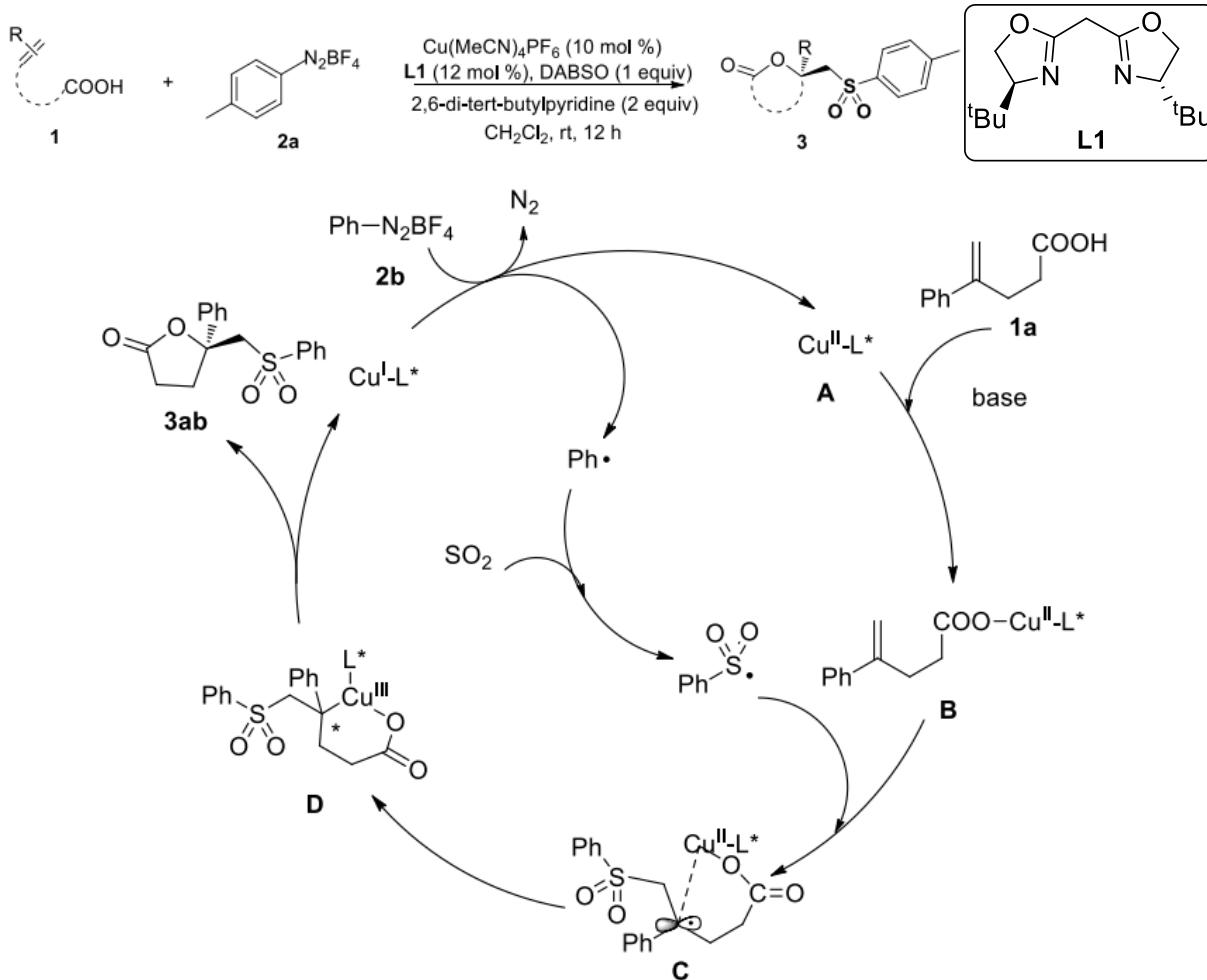


Outline

- Discovery of Sulfur Dioxide
- Non-radical transformation of sulfur dioxide
- Radical transformation of sulfur dioxide
- **Asymmetric reactions involving SO₂ insertion**

Asymmetric reactions involving SO_2 insertion

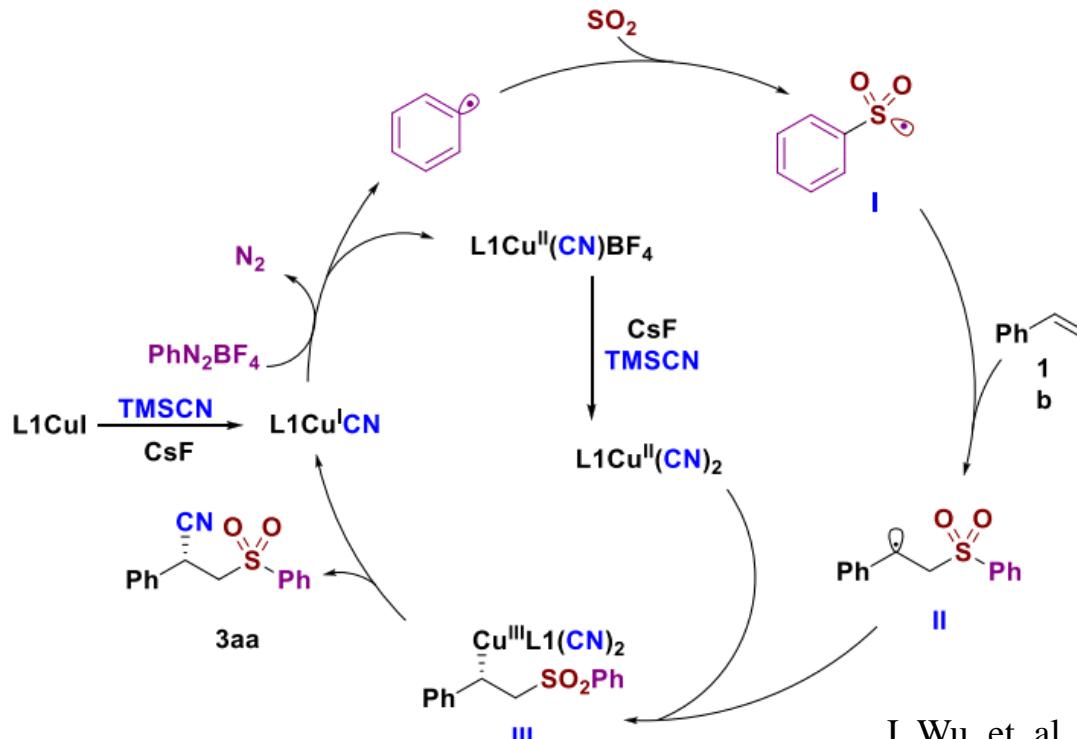
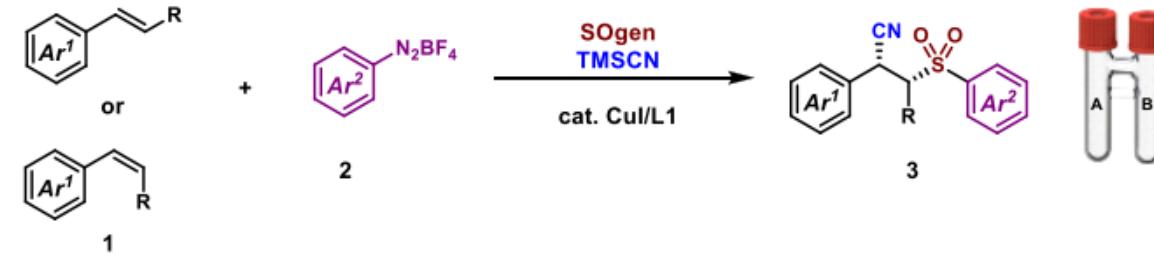
■ Copper-catalyzed asymmetric radical reaction of $\text{DABCO}\cdot(\text{SO}_2)$



Y. Pan, et. al. *Adv. Synth. Catal.* 2008, 130, 10082.

Asymmetric reactions involving SO_2 insertion

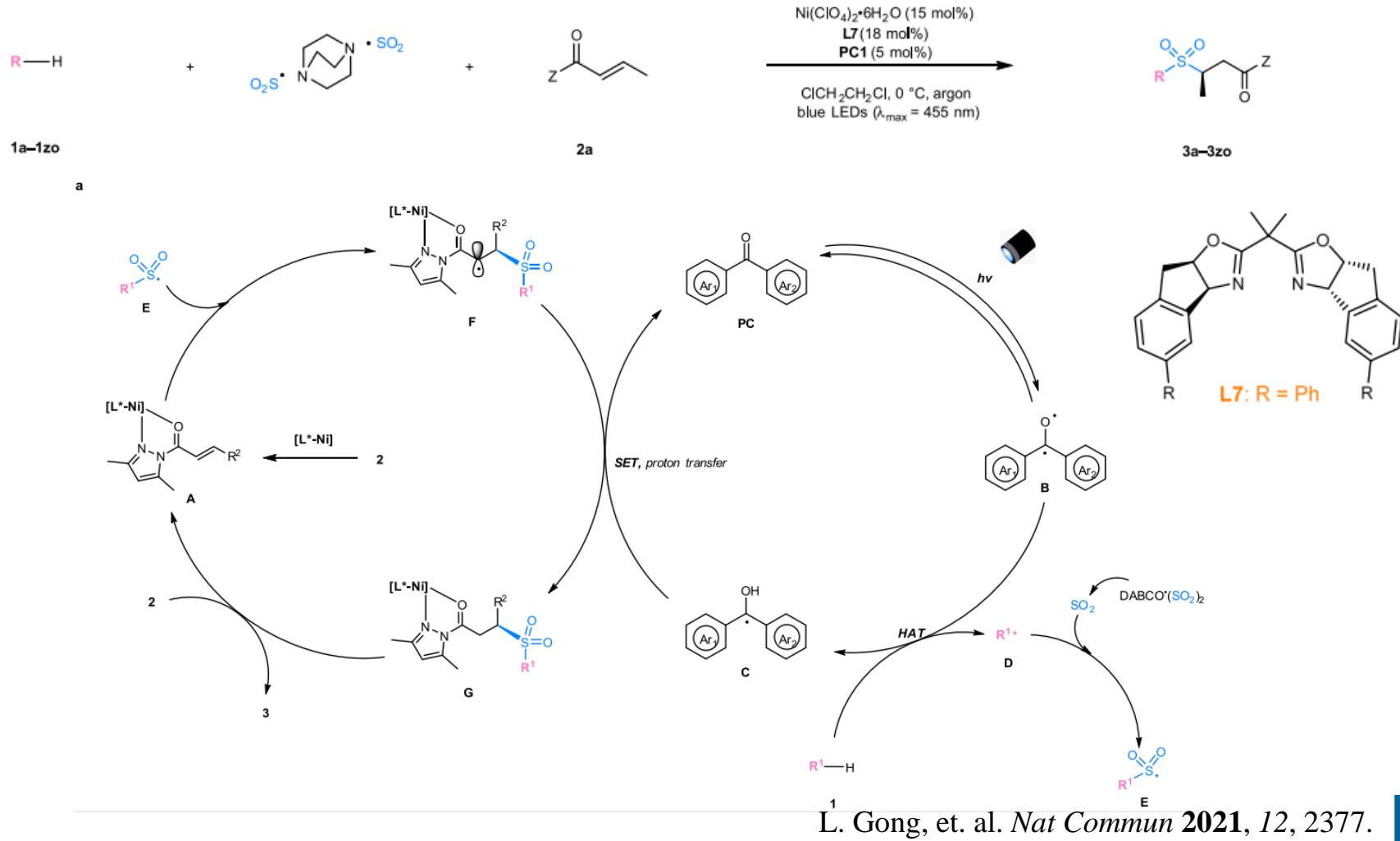
■ Enantioselective four-component arylsulfonylcyanation of vinylarenes



J. Wu, et. al. ACS Catal. 2022, 12, 10764

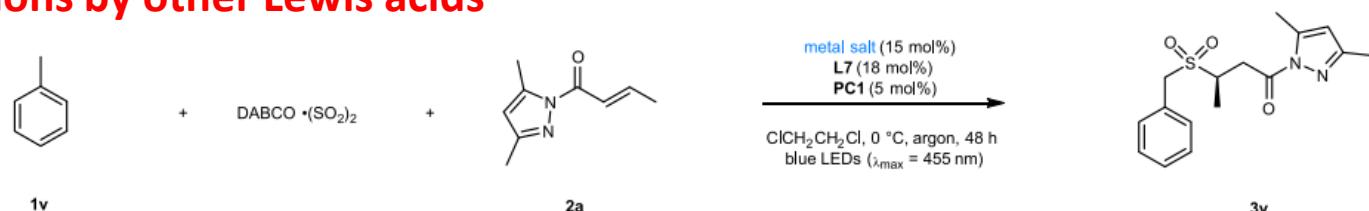
Asymmetric reactions involving SO_2 insertion

■ Photocatalytic three-component asymmetric sulfonylation



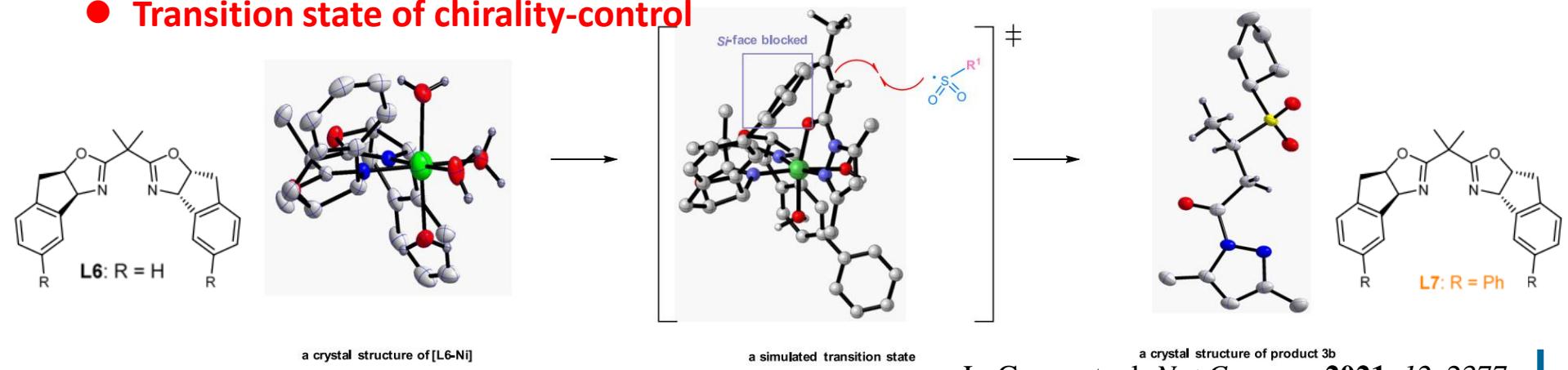
Asymmetric reactions involving SO₂ insertion

- Photocatalytic three-component asymmetric sulfonylation
- Reactions by other Lewis acids



metal salt	conv. (%)	ee (%)	metal salt	conv. (%)	ee (%)
Ni(ClO ₄) ₂ •6H ₂ O	75	92	none	0	n.a.
Cu(ClO ₄) ₂ •6H ₂ O	37	0	Zn(ClO ₄) ₂ •6H ₂ O	22	0
Fe(ClO ₄) ₃ •xH ₂ O	17	13	Co(ClO ₄) ₂ •6H ₂ O	31	80

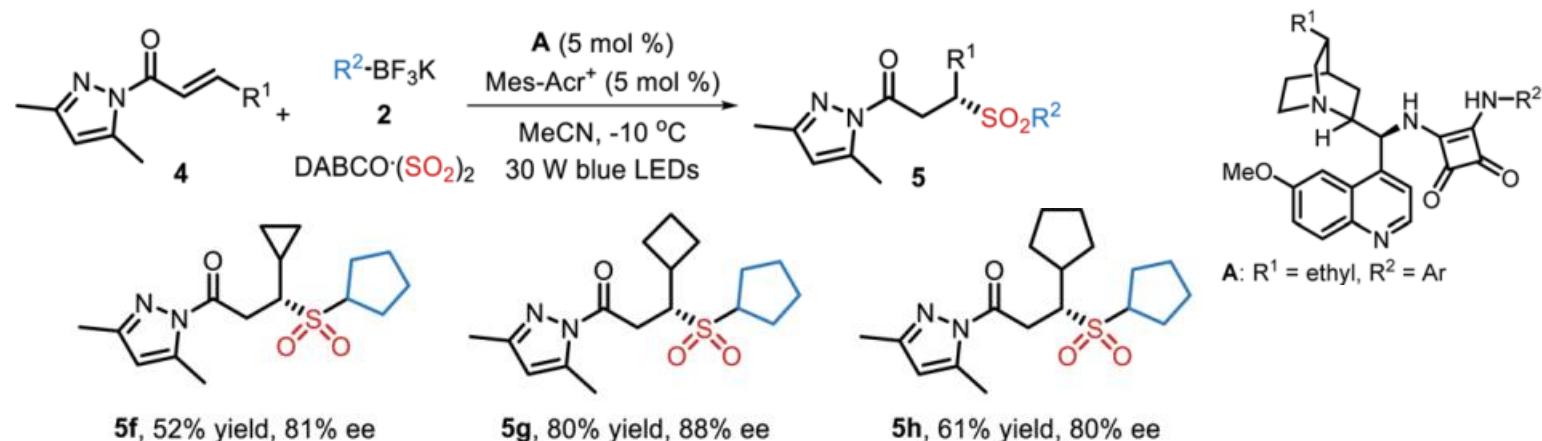
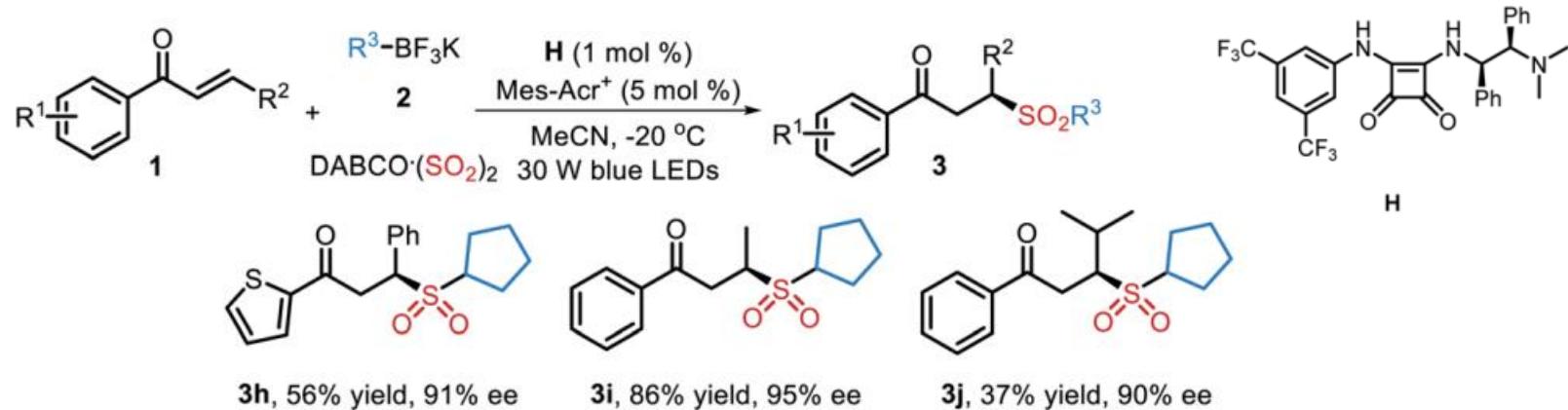
- Transition state of chirality-control



L. Gong, et. al. *Nat Commun* **2021**, *12*, 2377.

Asymmetric reactions involving SO_2 insertion

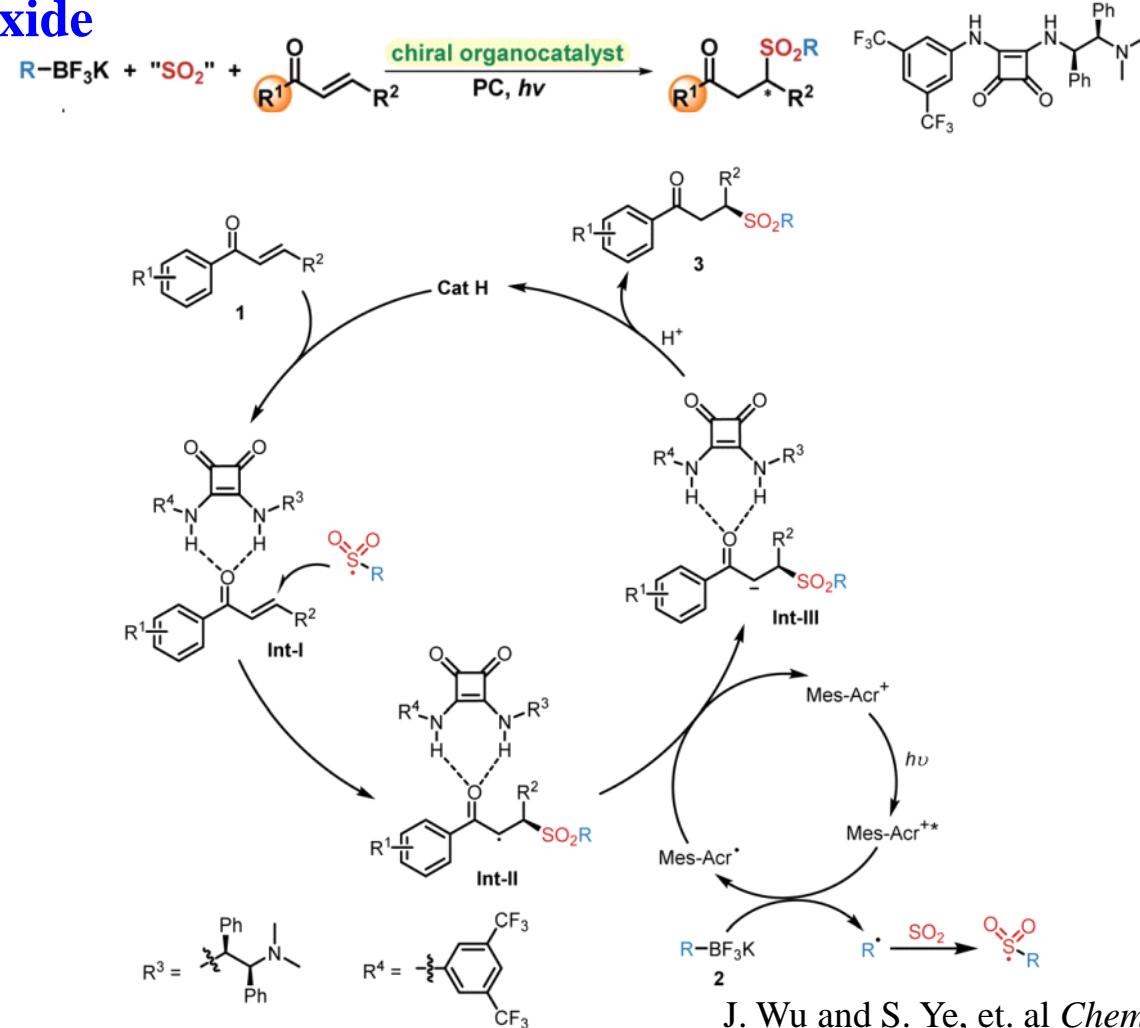
Photoinduced organocatalytic asymmetric radical sulfonylation with sulfur dioxide



J. Wu and S. Ye, et. al *Chem. Sci.*, 2022, 13, 8834.

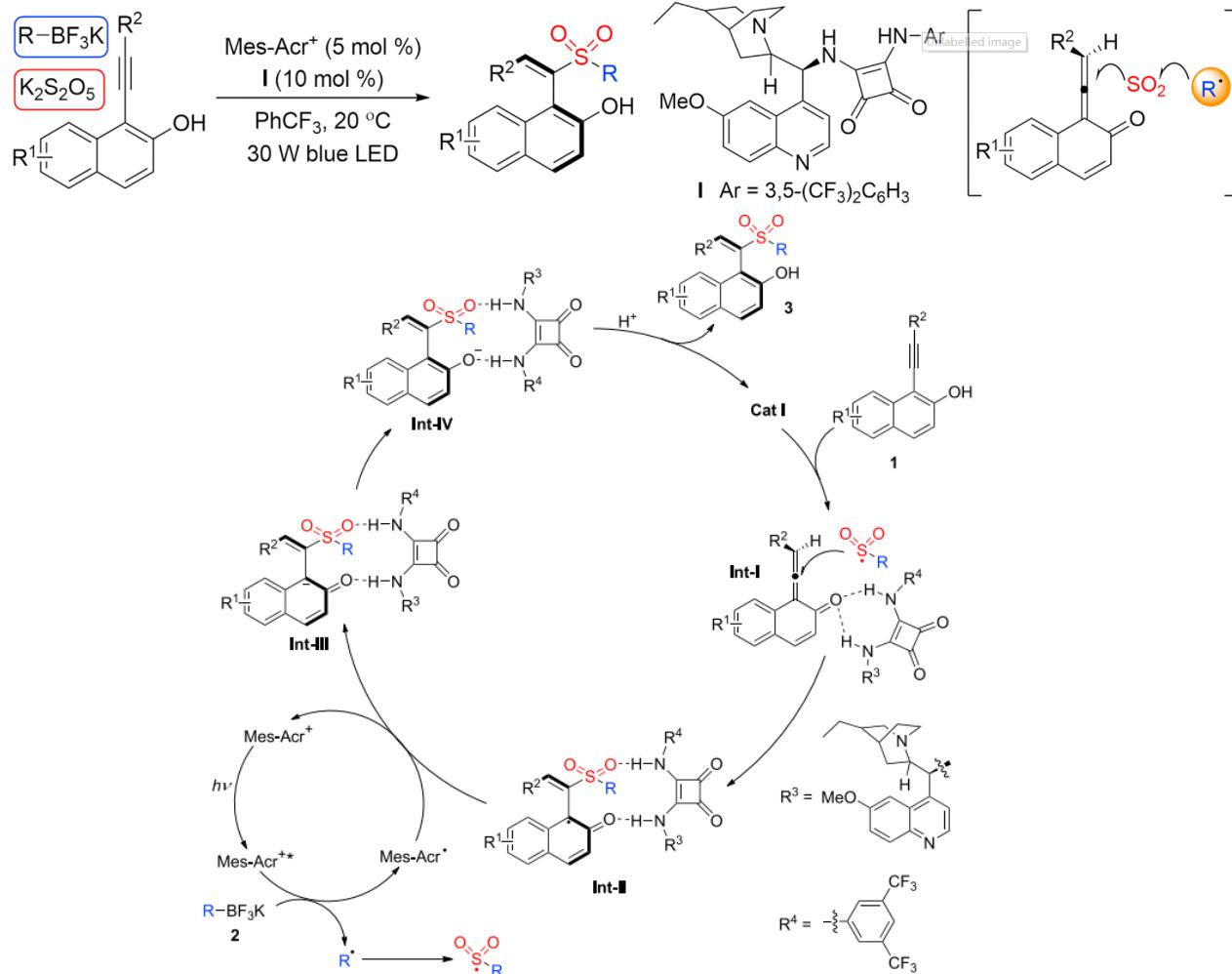
Asymmetric reactions involving SO_2 insertion

Photoinduced organocatalytic asymmetric radical sulfonylation with sulfur dioxide



Asymmetric reactions involving SO_2 insertion

■ Access to axially chiral styrenes involving a sulfur dioxide insertion

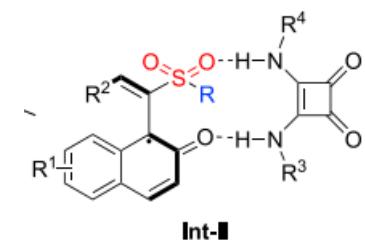
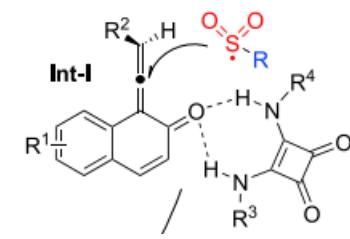
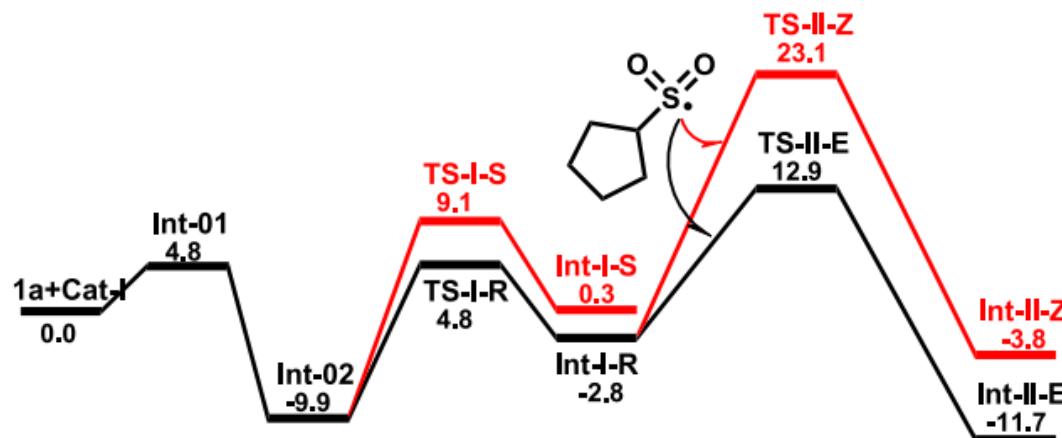


J. Wu, et. al. *Chem Catalysis* 2022, 2, 164.

Asymmetric reactions involving SO_2 insertion

■ Access to axially chiral styrenes involving a sulfur dioxide insertion

A





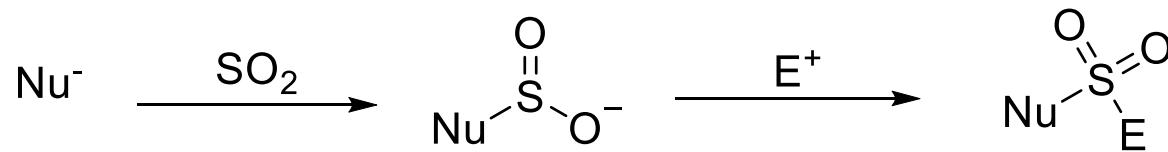
My Comments



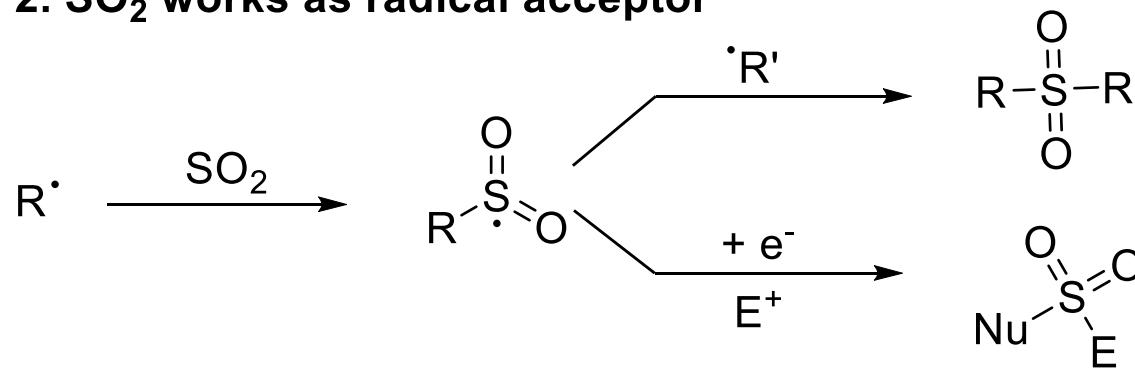
- Transition-metal catalyzed transformation of SO_2 .
- Photo/electrochemical radical cascade reaction involving SO_2 .
- Successfully build a series of S-X bonds (X = C, N, O, S, P, F, Cl etc.).
- More asymmetric methods and reactivity of SO_2 still need to be explored.
- The active intermediates ($\text{SO}_2^{+\cdot}$, $\text{SO}_2^{\cdot-}$) should be employed into novel radical reactions.

■ Roles of SO₂ in organic synthesis

1. SO₂ works as electrophile



2. SO₂ works as radical acceptor



3. SO₂ works as radical source





Seminal reviews

■ Reviews for insertion of SO₂

- **The Development and Application of Sulfur Dioxide Surrogates in Synthetic Organic Chemistry.** M. C. Willis, et. al. *Asian J. Org. Chem.* **2015**, *4*, 602
- **Radicals and Sulfur Dioxide: A Versatile Combination for the Construction of Sulfonyl-Containing Molecules.** G. Manolikakes, et. al. *Chem. Eur. J.* **2018**, *24*, 11852.
- **Photoinduced Sulfonylation Reactions through the Insertion of Sulfur Dioxide .** J. Wu, et. al. *Eur. J. Org. Chem.* **2020**, *2020*, 1274.
- **DABSO as a SO₂ gas surrogate in the synthesis of organic structures.** S. Balalaie, et. al. *Org. Biomol. Chem.*, **2022**, *20*, 2149
- **Multicomponent Reactions Based on SO₂ Surrogates: Recent Advances.** Z. Lian, et. al. *Eur. J. Org. Chem.* **2023**, e202300217.



Thanks for your kind attention !