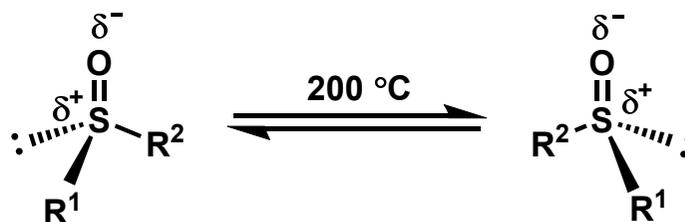




Science and relative work of Maulide's Group



Reporter: Linrui Zhang

Supervisor: Prof. Yong Huang

Date: 2018-9-3



Content

- Introduction
- Brønsted Acid Catalyzed Redox Arylation
- Asymmetric Redox Arylation
- Stereodivergent Synthesis of 1,4-dicarbonyls
- Summary



Content

- **Introduction**
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Introduction of Maulide Professor



Maulide, Nuno

Educations

- 2013—: Full Professor of Organic Synthesis at the University of Vienna (AT)
- 2013: Habilitation at the Ruhr-Universität Bochum (DE)
- 2009-2013: Max-Planck-Research Group Leader at the Max-Planck Institut für Kohlenforschung (DE)
- 2007-2008: Postdoc at Stanford University (USA) (Prof. Barry M. Trost)
- 2007: Ph.D. at the Université catholique de Louvain (BE) (Prof. István E. Markó)
- 2004: Master's Degree at the Ecole Polytechnique (FR) and Université catholique de Louvain (BE)
- 2003: Chemistry Degree at Instituto Superior Técnico (PT)

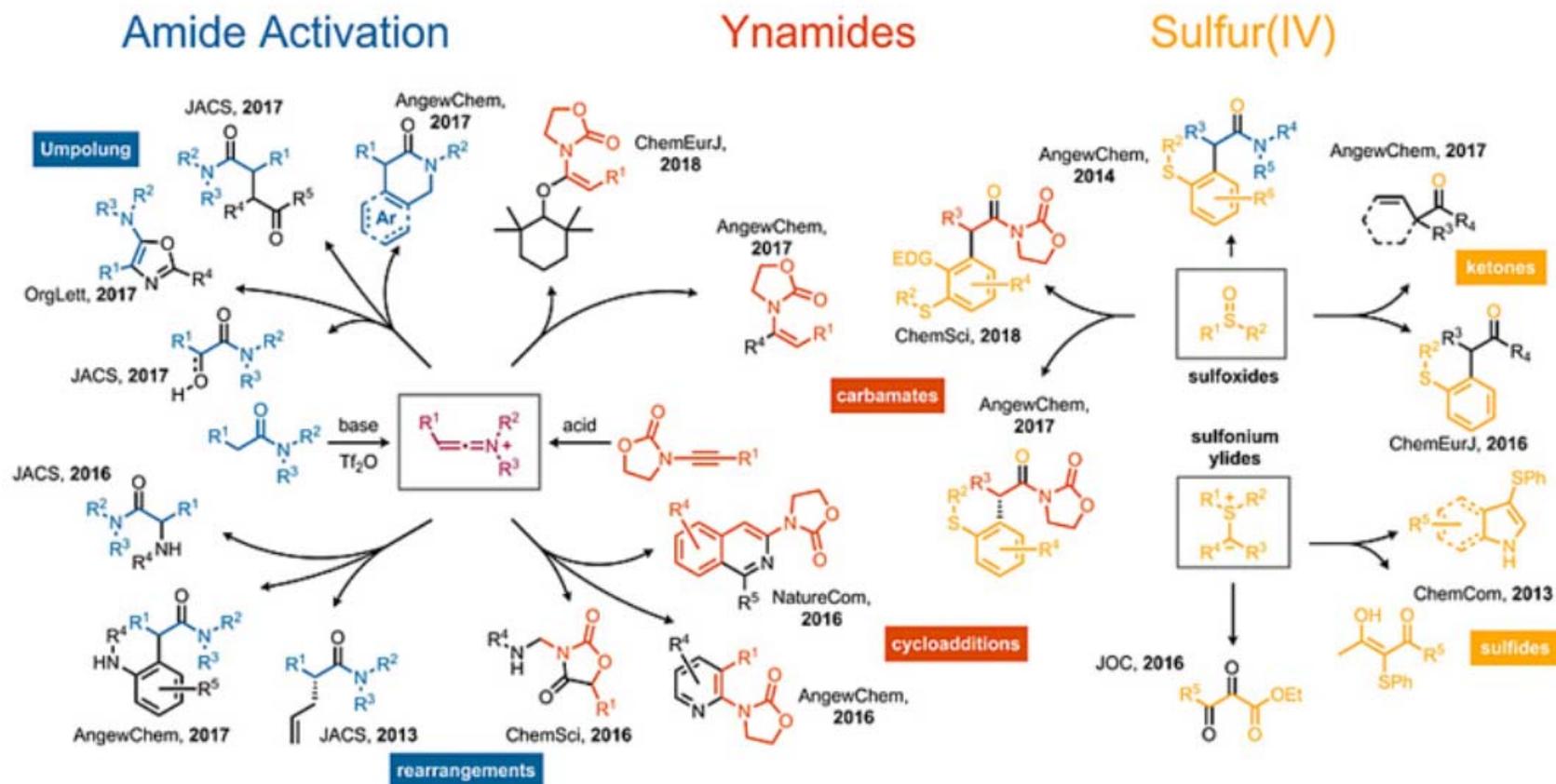
Research Areas

- Unusual or "unconventional" reactivity profiles of organic compounds
- High-energy reactive intermediates that can be generated under mild conditions and subsequently lead to rearrangements, domino reaction sequences or catalytic asymmetric transformations.

<http://www.x-mol.com/university/faculty/44783>



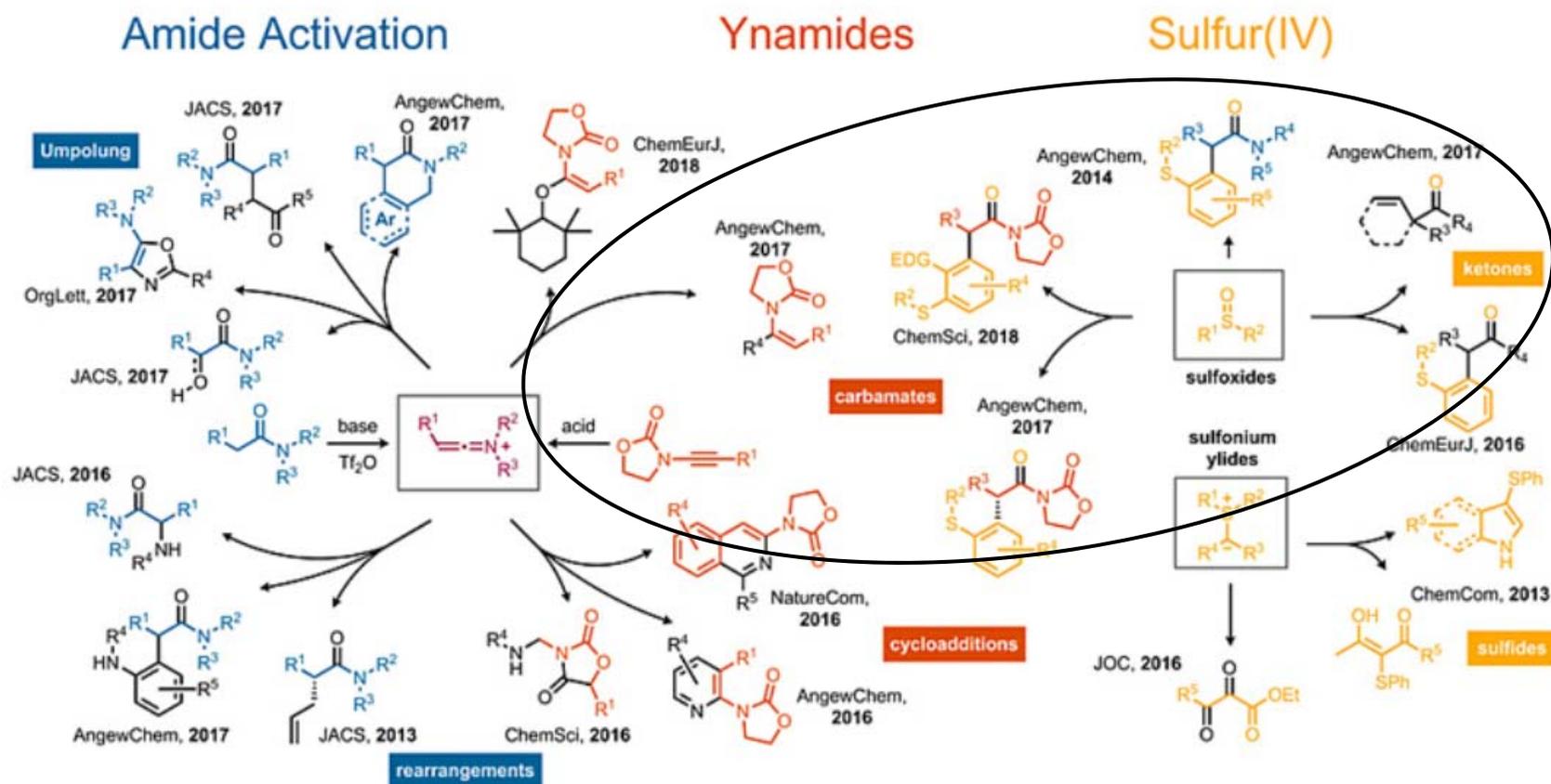
Recent Research of Maulide's group



<https://organicsynthesis.univie.ac.at/research/research-interests/>



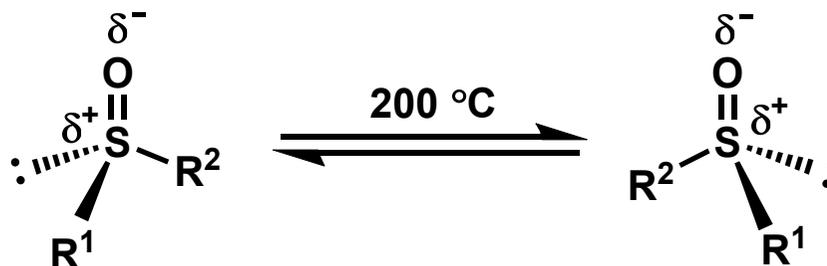
Ynamides and Sulfur (IV)



<https://organicsynthesis.univie.ac.at/research/research-interests/>



Characterization of Sulfoxide



- ◆ pyramidal structure
- ◆ R^1 , R^2 = alkyl, alkenyl or aryl groups
- ◆ three ligand - lone pair electrons
- ◆ with remarkable optical stability
- ◆ useful chiral auxiliary reagent
- ◆ O atoms have a certain nucleophilicity

Paul S. Engel, *et al.*, *J. Am. Chem. Soc.*, **1981**, *103*, 7689-7690.
<http://www.x-mol.com/news/13948>

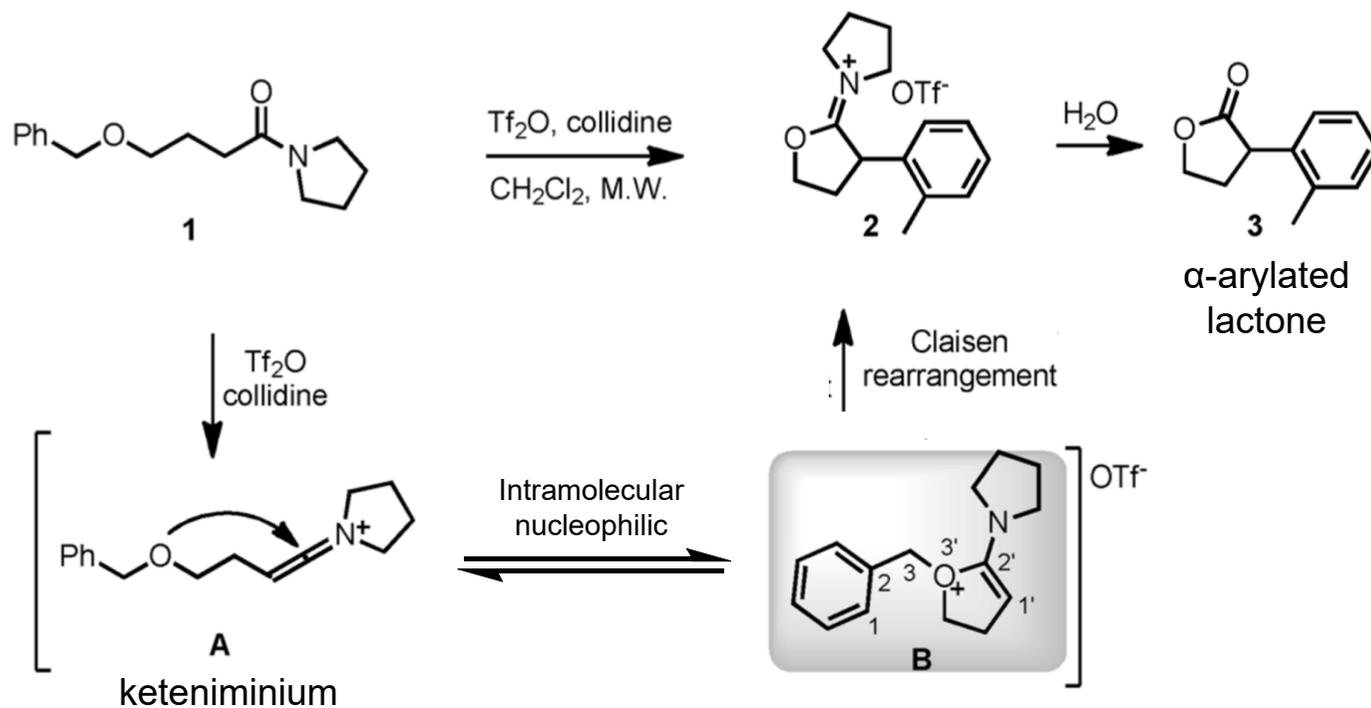


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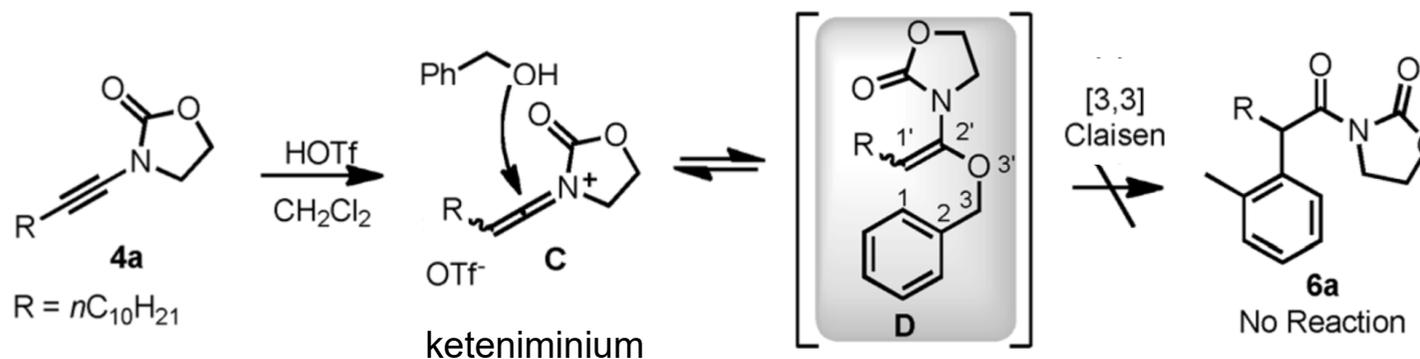
Intramolecular α -arylation by an Claisen Rearrangement



- ◆ Modest to good yields but a relatively narrow scope
- ◆ High energy penalty: the inevitable transient loss of aromaticity during [3,3]-rearrangement



Attempts of Intermolecular Redox Arylation



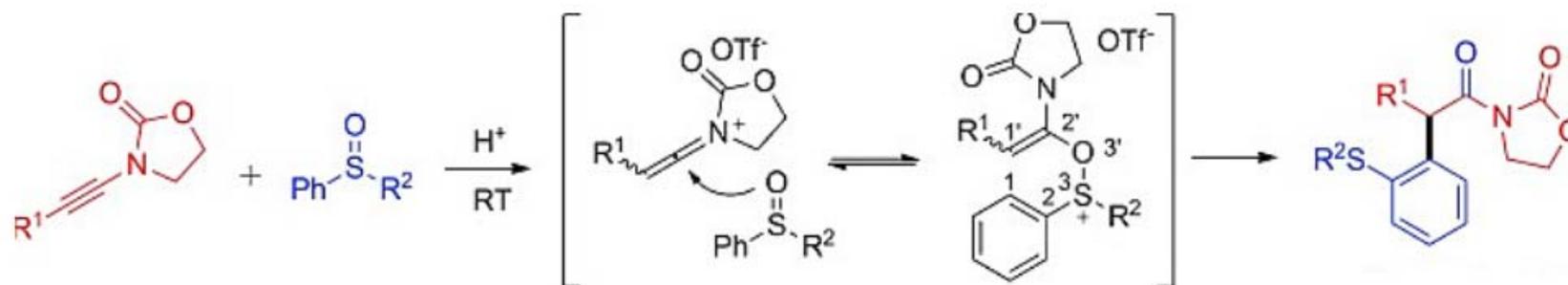
- ◆ This **failure** of benzyl alcohol to serve as the aryl donor might again be attributed to the **challenging transient loss of aromaticity** upon [3,3]-sigmatropic rearrangement.

Y. Minko, *et al.*, *Nature* **2012**, 490, 522 – 526.

K. C. M. Kurtz, *et al.*, *Tetrahedron* **2006**, 62, 3928 – 3938.



Brønsted Acid Catalyzed Redox Arylation



R¹ = Alkyl, aryl, nitrile, ether, ester moiety

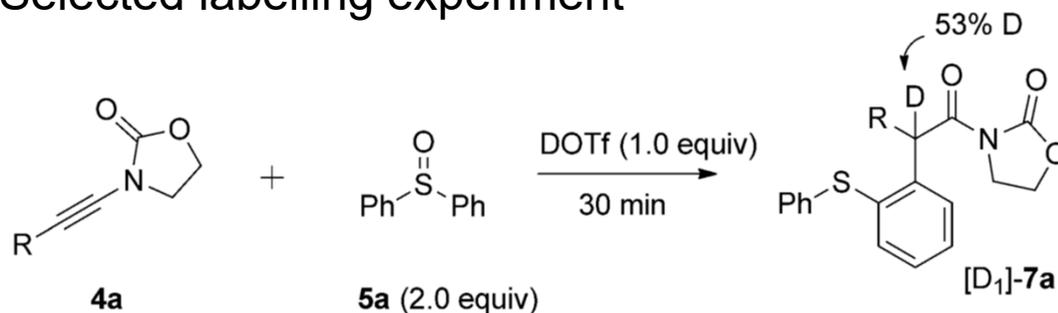
R² = Alkyl, aryl

- ◆ Brønsted acid catalyzed
- ◆ metal-free transformation
- ◆ efficiently
- ◆ under mild condition
- ◆ broad functional groups
- ◆ redox-neutral
- ◆ atom-economic
- ◆ good to excellent yields



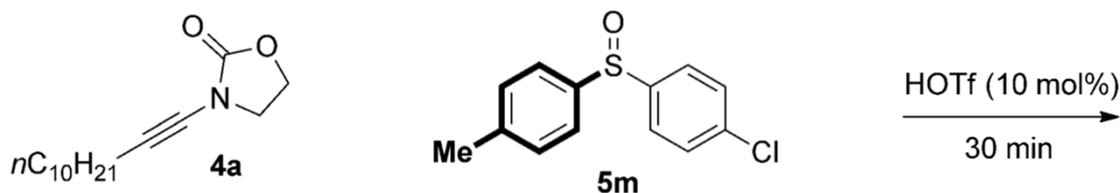
Mechanism Study

➤ Selected labelling experiment

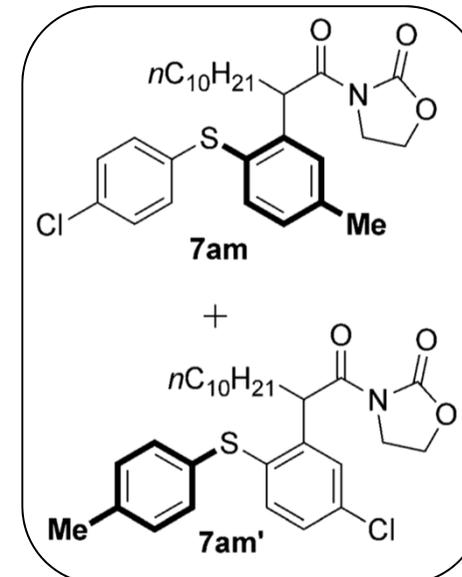


Supports that **protonation of the ynamide** triggers nucleophilic attack to the keteniminium intermediate

➤ Control experiment



Preference for the more electron-rich aryl moiety **rules out an S_N-type** mechanism

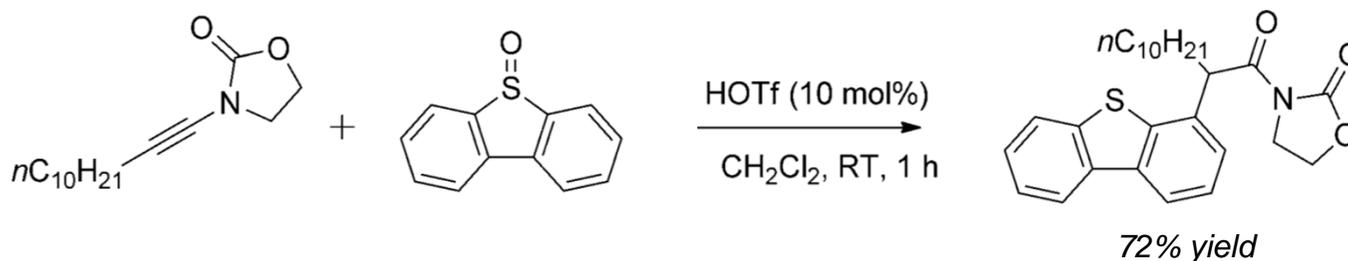


7am/7am' = 66:34
(97% yield)

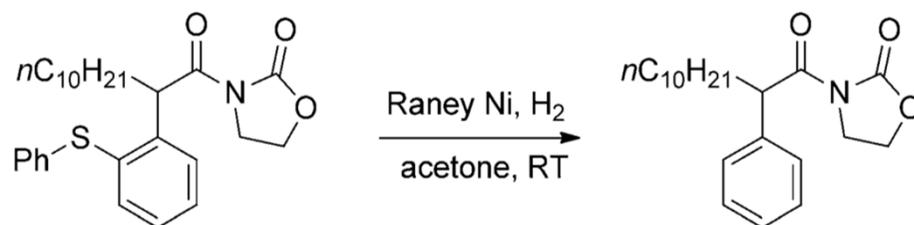


Applications and Asymmetric Experiments

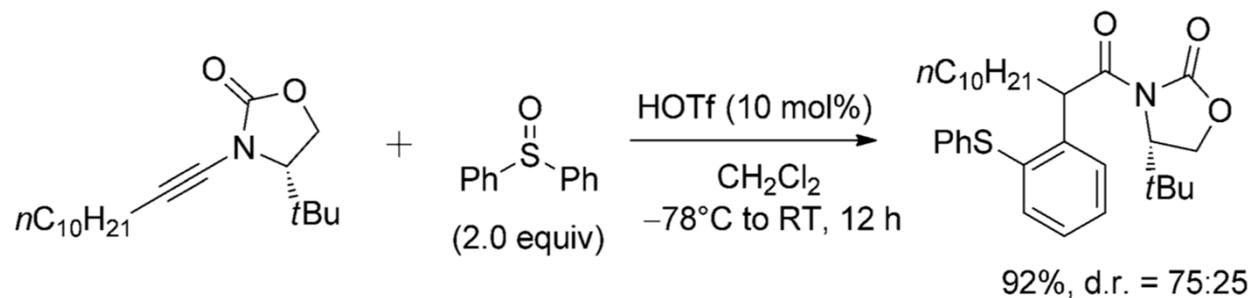
- Synthesis of a dibenzothiophene



- Product elaboration



- Asymmetric experiments (screen of chiral auxiliaries)



- ◆ Demonstrated the feasibility for the asymmetric arylation



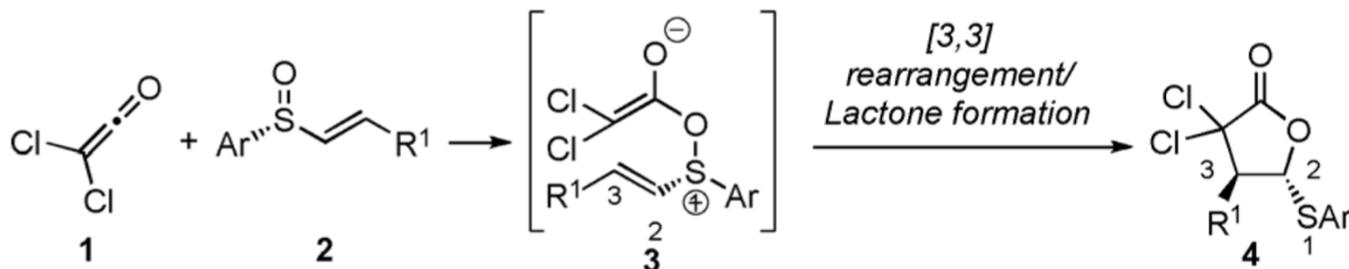
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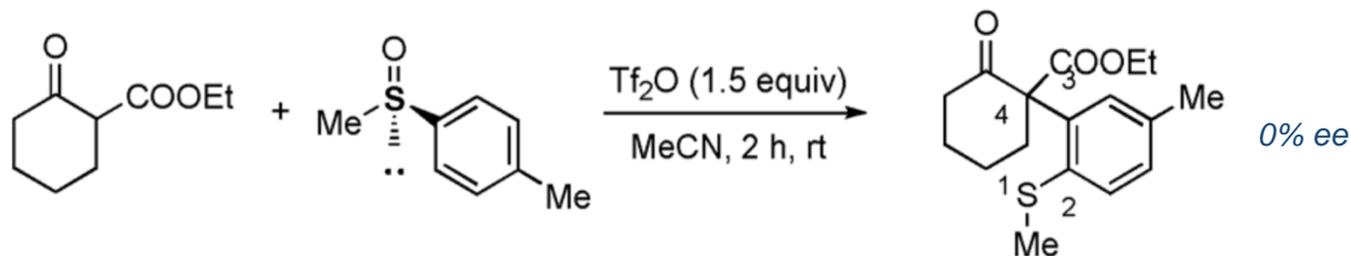
Asymmetric Explore

- Example of 1,3-chirality transfer from sulfur to carbon



This method is **limited** to the use of highly reactive dichloroketene and vinyl sulfoxides

- Unsuccessful attempts of 1,4-chirality transfer



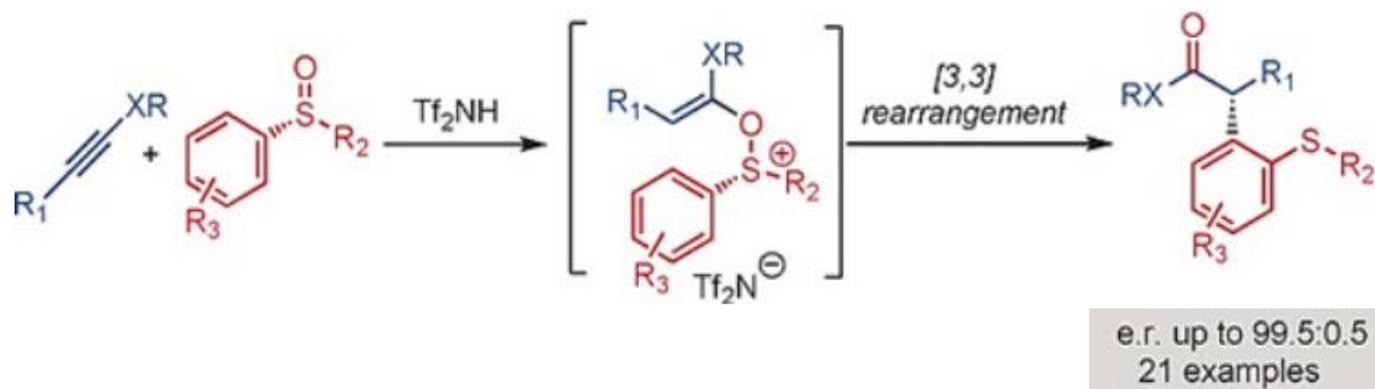
This disappointing result is due to the **instability of the sulfur center** during the reaction

J. P. Marino, *et al.*, *J. Am. Chem. Soc.* **1984**, *106*, 7643–7644.

D. Kaldre, *et al.*, *Angew. Chem. Int. Ed.* **2017**, *56*, 1–5.



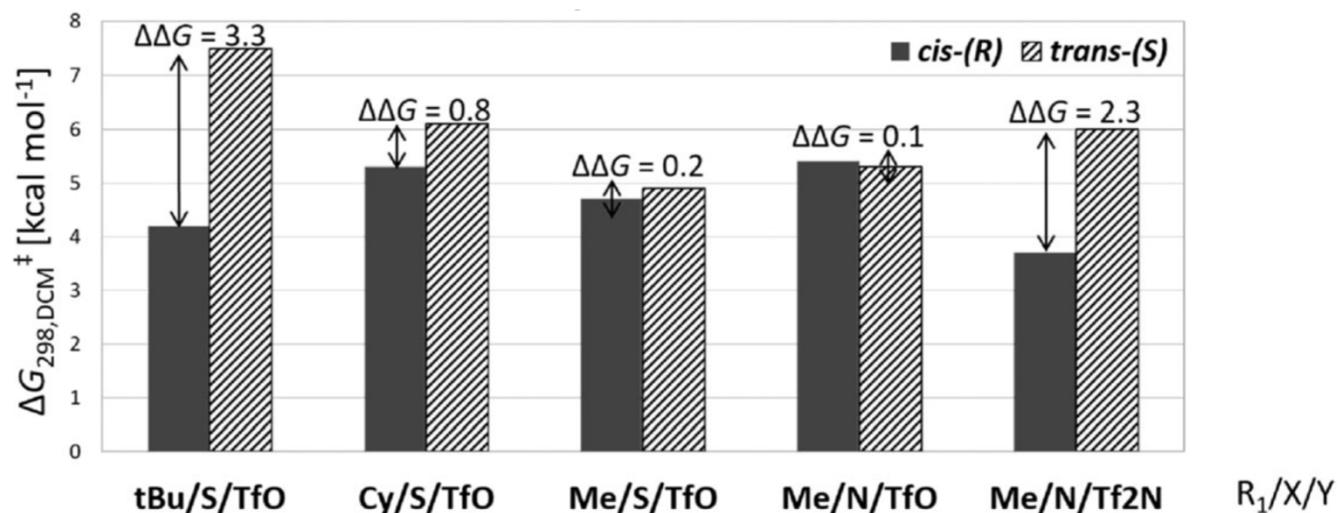
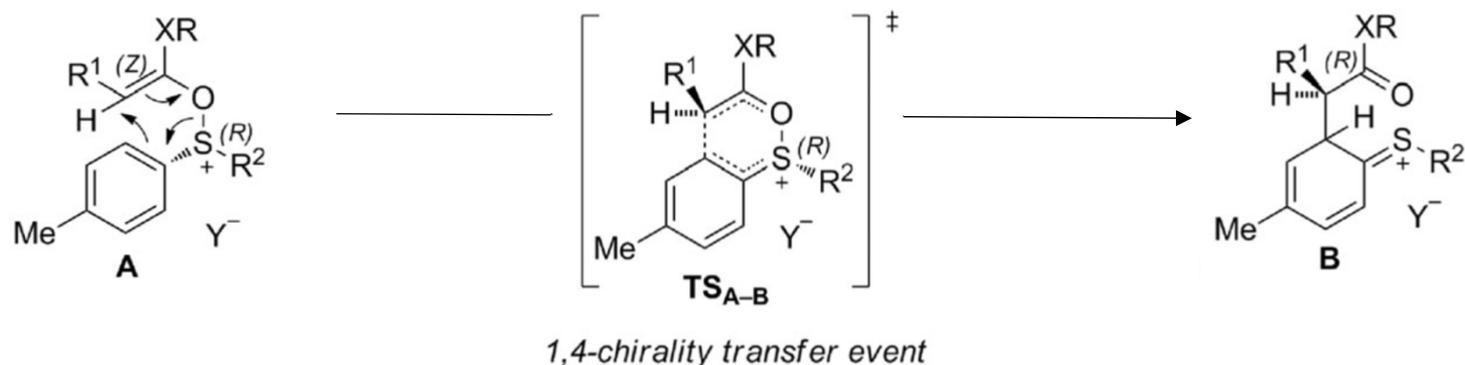
Asymmetric Redox Arylation



- ◆ The first example of a general 1,4-chirality transfer from sulfur to a carbon
- ◆ Under mild conditions in an atom-economical manner
- ◆ Computational studies explain the experimentally observed correlation of the enantioselectivity with both the catalyst and the substrate



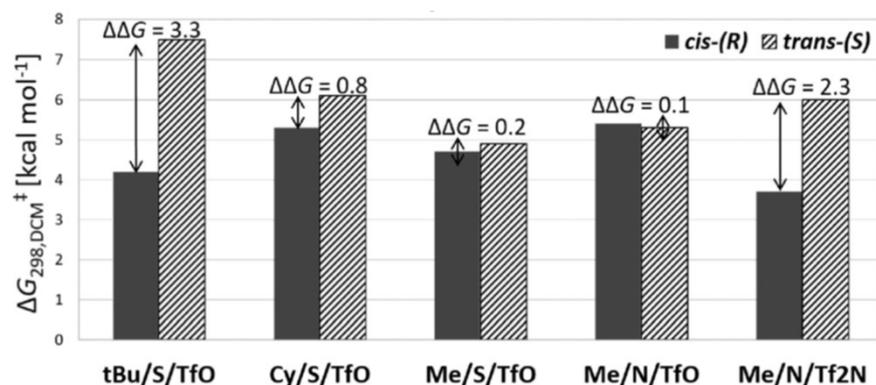
Mechanism of Chirality Transfer



- ◆ Cis-(R) pathway has the smallest barrier is thus the most favored. The most probable (S) pathway is generally the trans-(S)

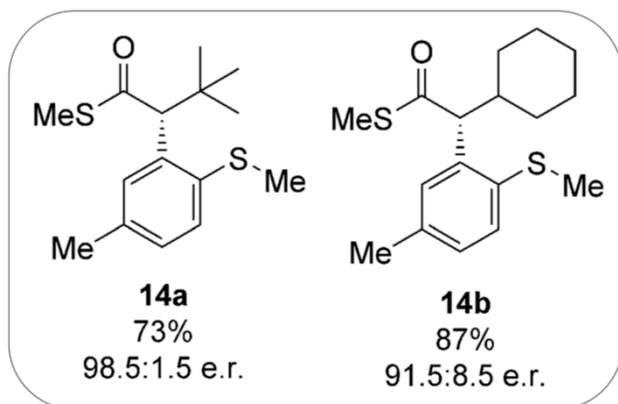


Experiment Evidence



- Gap between cis-(R) and trans-(S) is largest for the ^tBu and smallest for the Me group
- (R) and (S) barriers are similar for TfOH and very different for the Tf₂NH catalyst

a) Enantioselectivity of two substituents

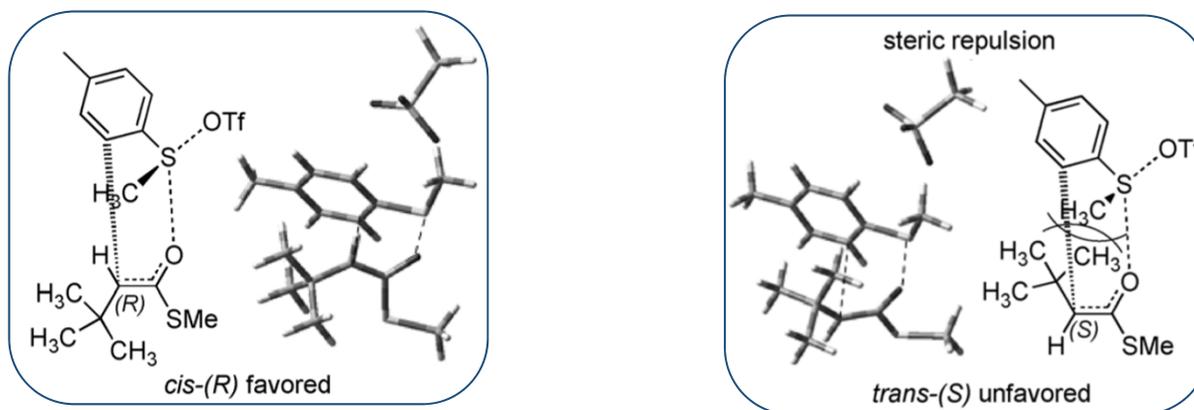


b) Enantioselectivity of two catalysts

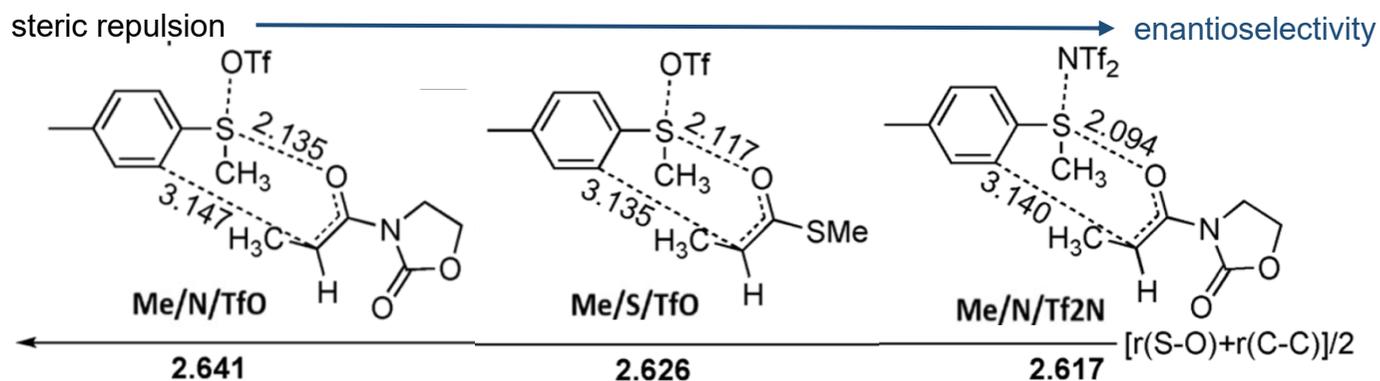
| Entry ^[a] | Catalyst (50 mol %) | Solvent | Yield [%] | e.r. ^[a] |
|----------------------|---------------------|---------|-----------|---------------------|
| 1 | TfOH | DCM | 71 | 73:27 |
| 2 | Tf ₂ NH | DCM | 70 | 90.5:9.5 |

Structures of Transition States TS_{A-B}

- Conformations of TS_{A-B} from *cis*-(R) and *trans*-(S)



- Comparison of the S-O and the newly formed C-C bond lengths in *trans*-(S)



- ◆ Dependence of the enantio-selectivity on the catalyst for the ynamide substrate



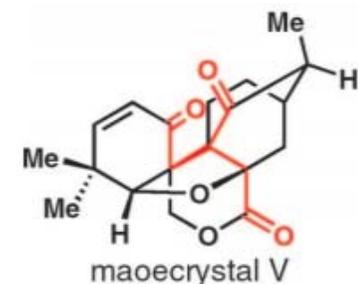
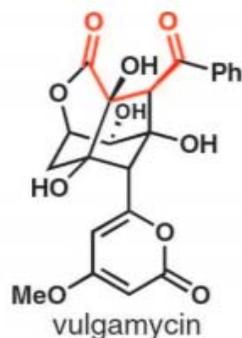
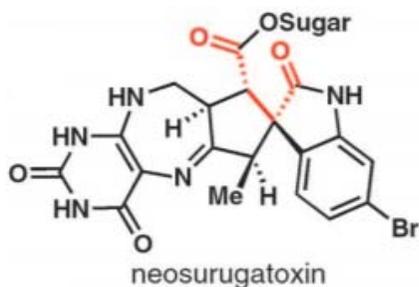
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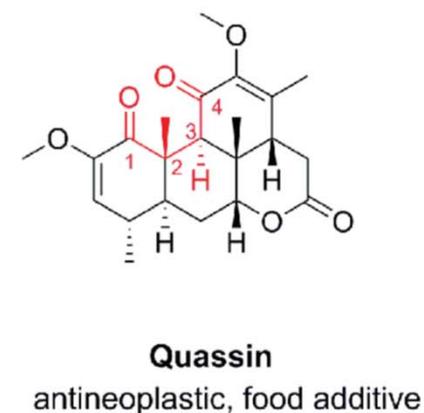
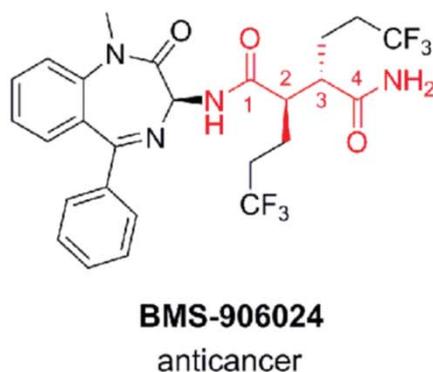
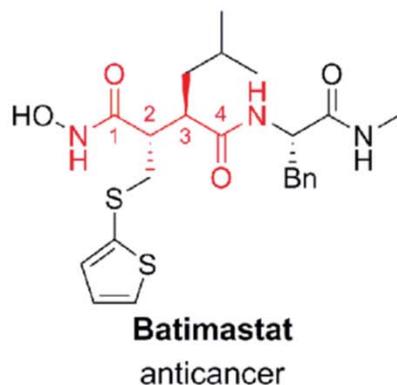


Importance of 1,4-Dicarbonyl Motifs

➤ Natural products



➤ Drug scaffolds



M. P. DeMartino, *et al.*, *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560.

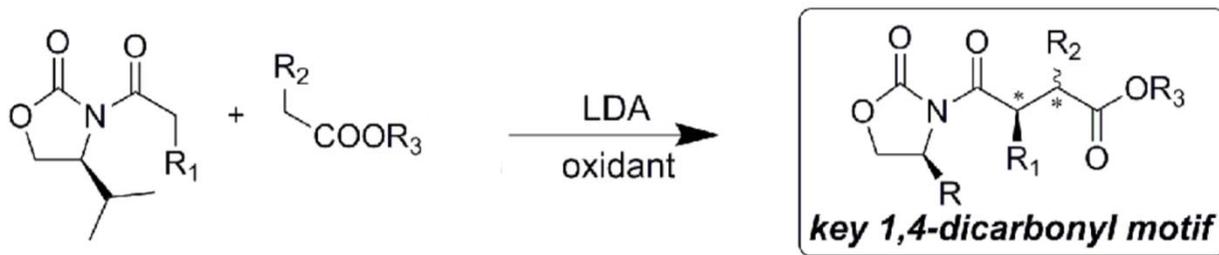
M. Whittaker, *et al.*, *Chem. Rev.* **1999**, *99*, 2735–2776.

T. Fujisawa, *et al.*, *Bioorg. Med. Chem.* **2002**, *10*, 2569–2581.

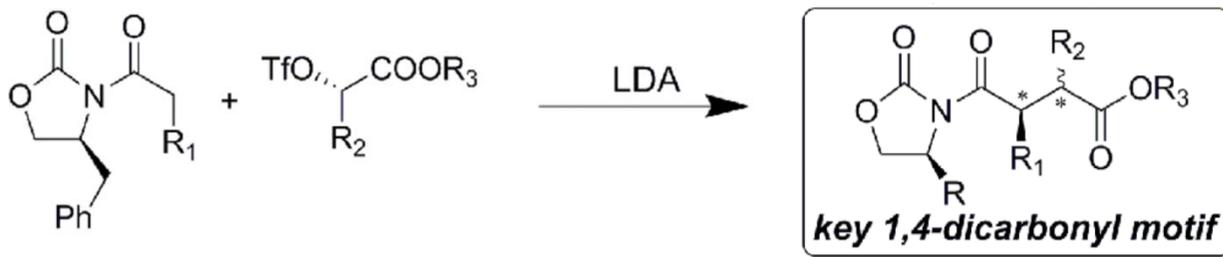


Current Strategies and Common Limitations

- Oxidative enolate coupling (Baran and Thomson)



- Umpolung / enolate alkylation (Decicco)



- ◆ poor to moderate stereoselectivity
- ◆ quaternary centers unresolved
- ◆ strongly basic conditions
- ◆ low functional group tolerance
- ◆ two chiral prefunctionalized starting materials
- ◆ troublesome matched/mismatched pairings

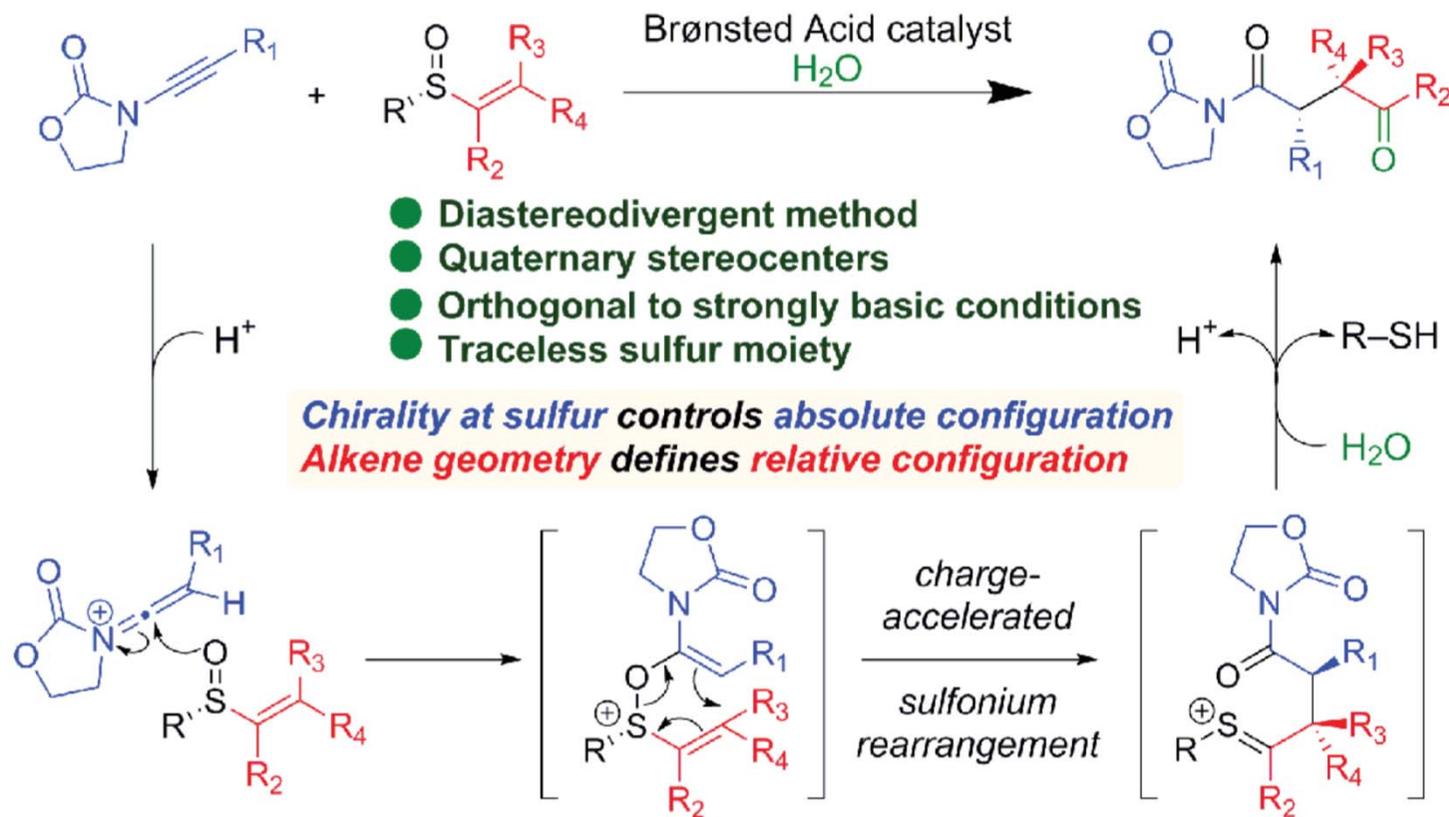
M. P. DeMartino, *et al.*, *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560.

E. E. Robinson, *et al.*, *J. Am. Chem. Soc.* **2008**, *140*, 1956–1965.

C. P. Decicco, *et al.*, *J. Org. Chem.* **1996**, *60*, 4782–4785.



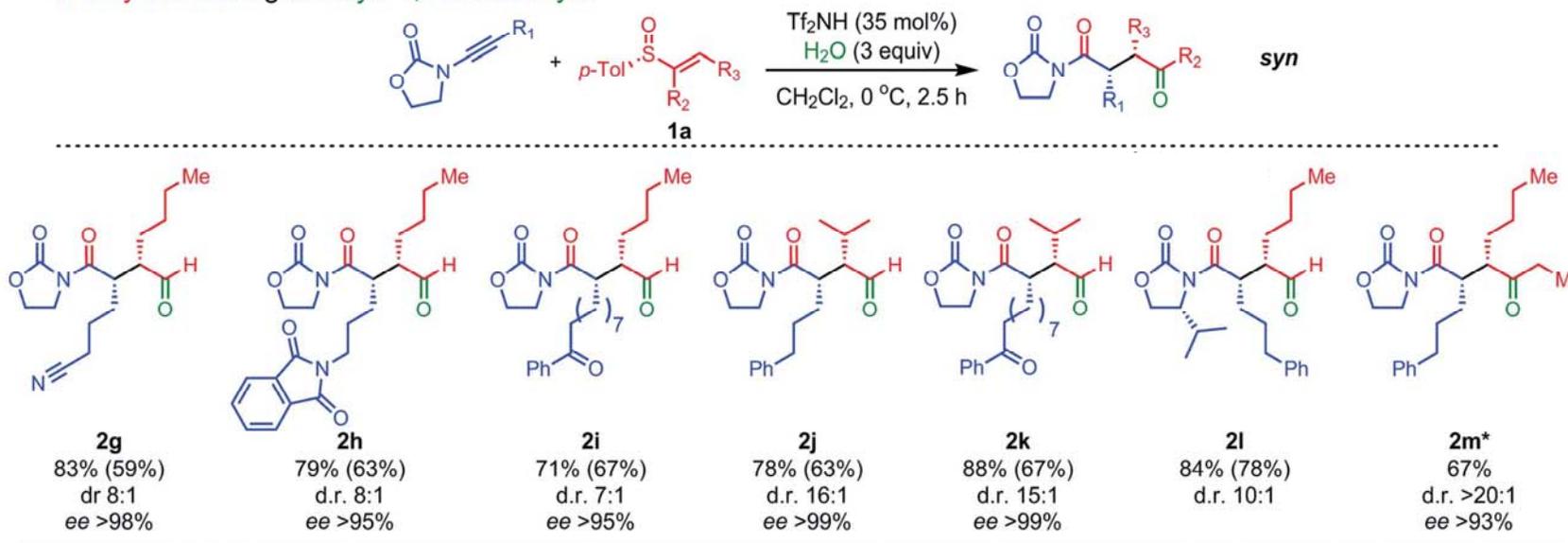
Maulide's Approach for the Synthesis of 1,4-Dicarbonyls



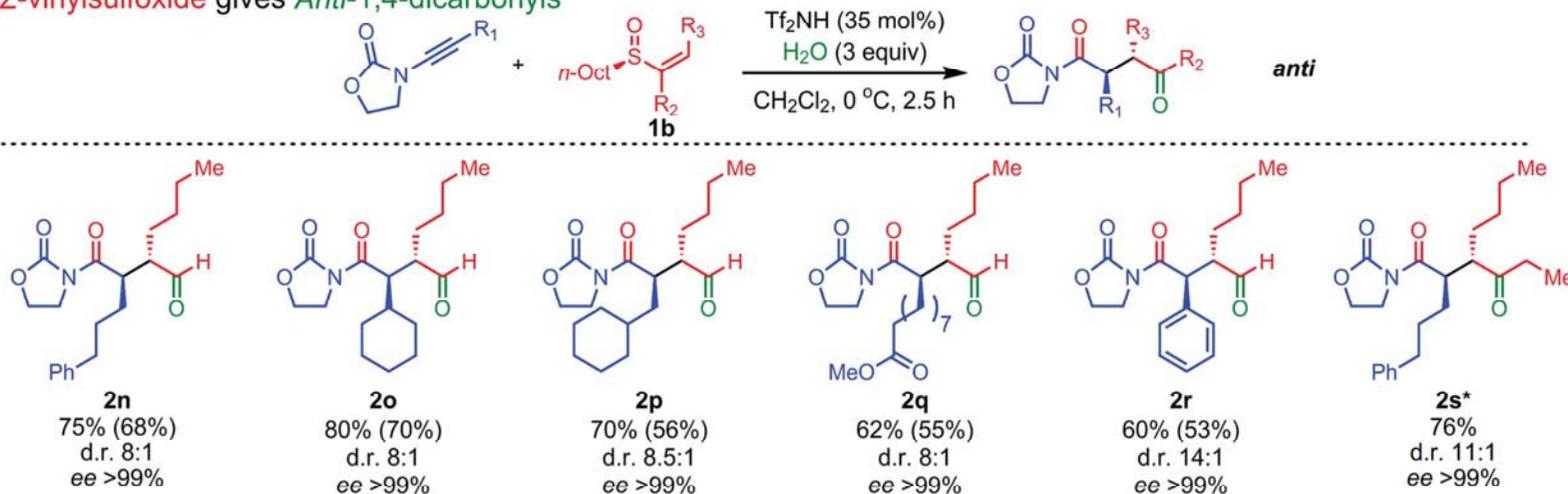


Substrate Scope

E-vinylsulfoxide gives *Syn*-1,4-dicarbonyls

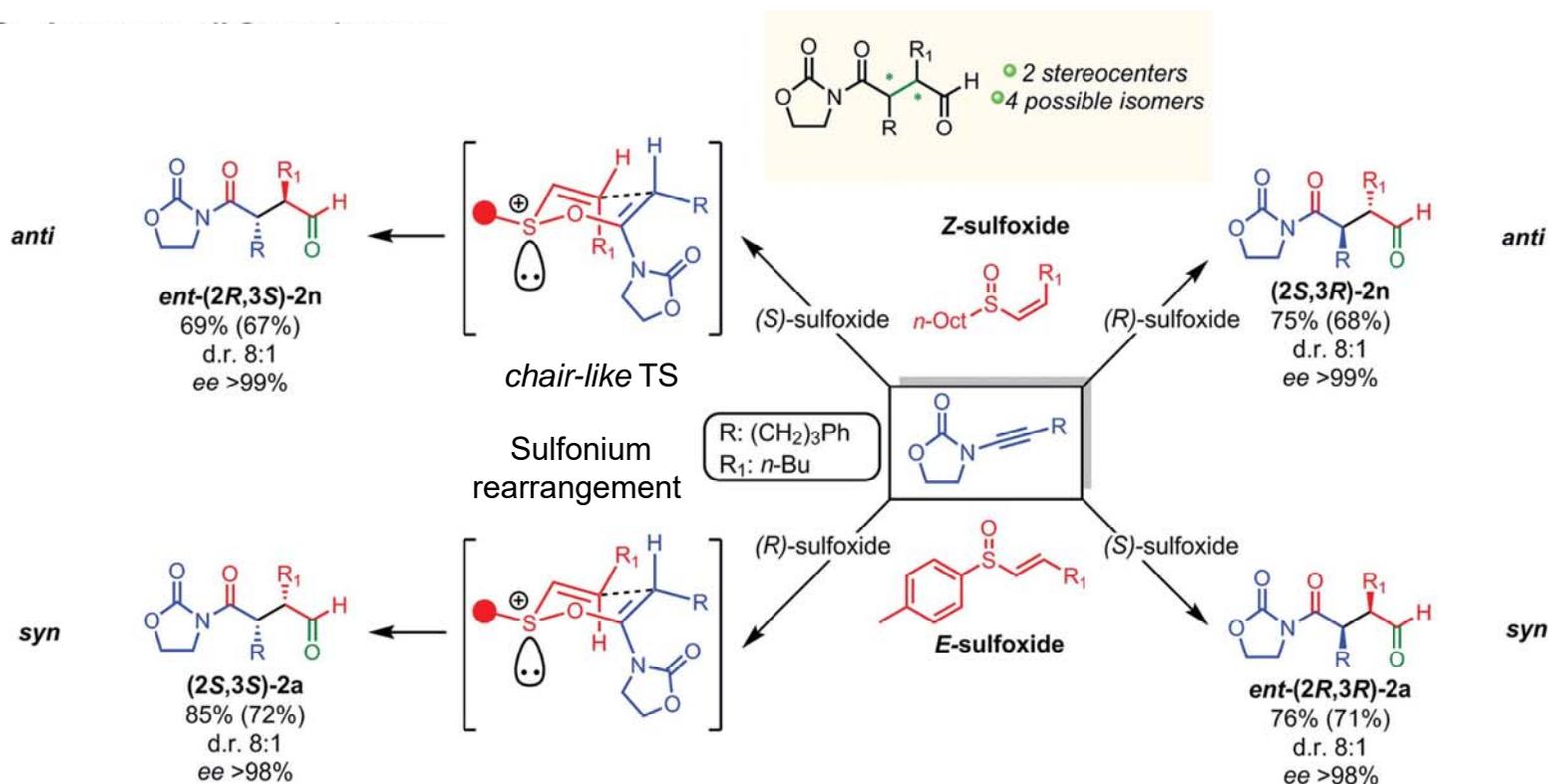


Z-vinylsulfoxide gives *Anti*-1,4-dicarbonyls





Access to All Possible Stereoisomers

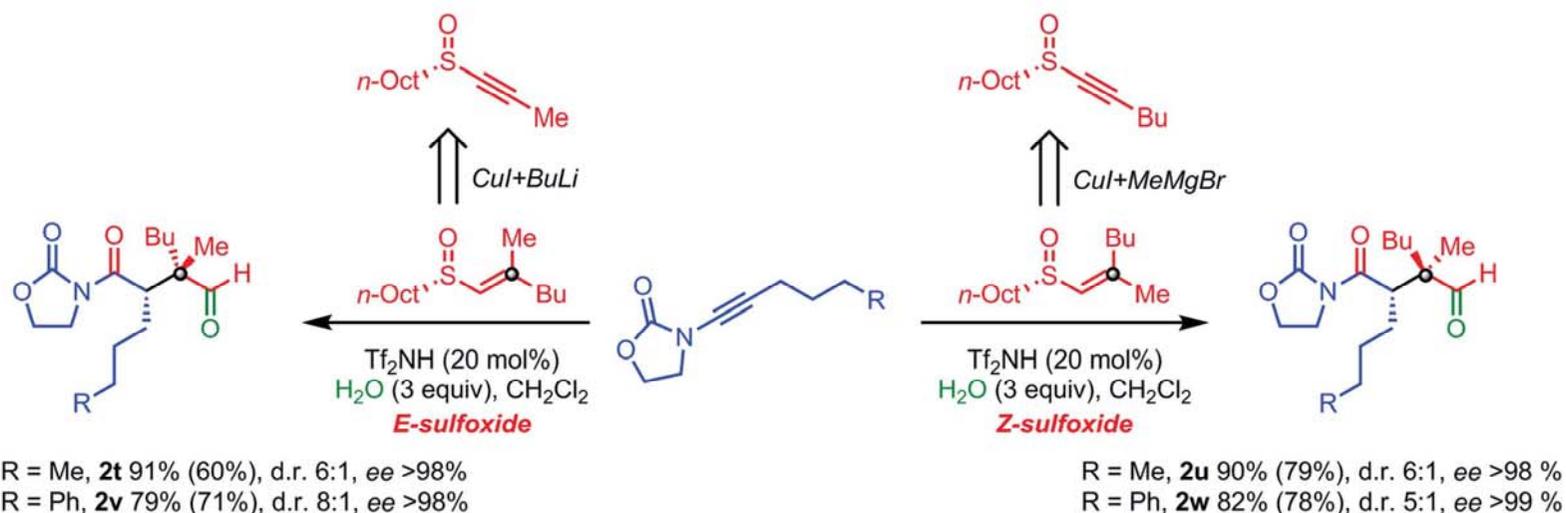


- ◆ The stereochemistry at **sulfur** governs the **absolute** sense of chiral induction, **double bond** geometry dictates the **relative** stereochemistry of the final products.



Synthesis of All-carbon Quaternary Products

- Vinyl sulfoxide geometry controlled the quaternary carbon stereocenter

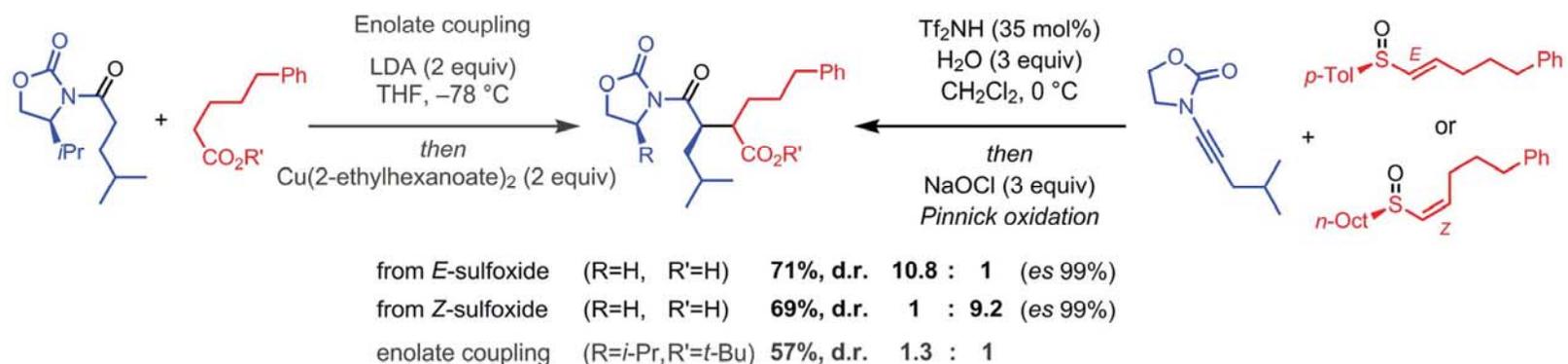


- ◆ β , β -disubstituted alkenylsulfoxides access all-carbon quaternary stereocenters
- ◆ Sulfoxide double bond geometry dictates relative and absolute configuration of quaternary carbon stereocenter



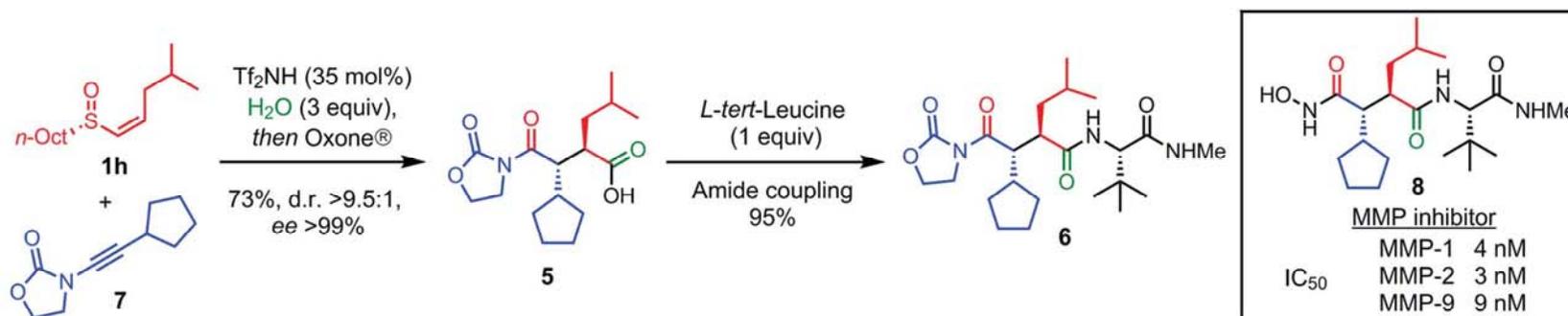
Applications

➤ Comparison of Maulide's method to state-of-the-art enolate coupling



◆ Both stereoisomers available, in high purity, under comparably mild, catalytic conditions

➤ Direct stereoselective access to succinate building blocks



D. Kaldre, *et al.*, *Science* **2018**, 361, 664-667.

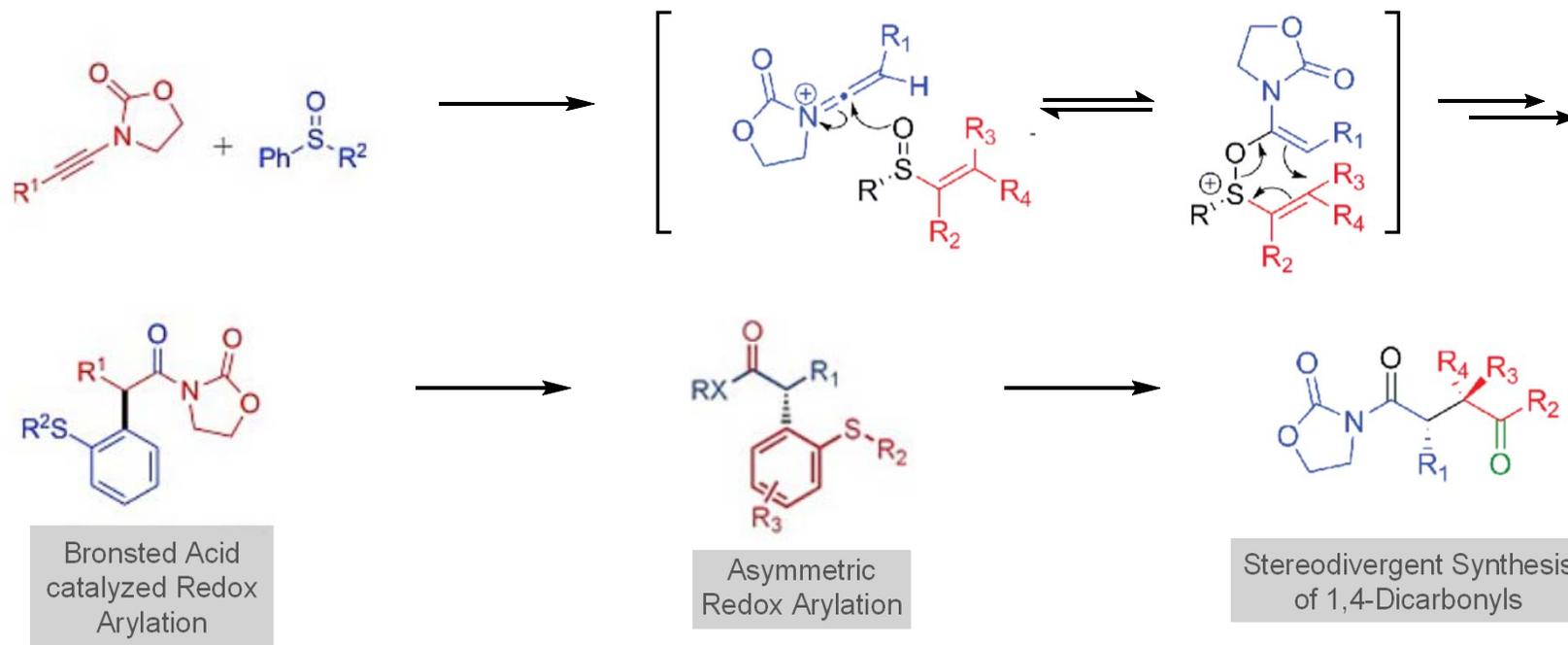


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Summary



- metal-free transformation
- under mild conditions
- atom-economical
- broad functional groups

- 1,4-chirality transfer from sulfur to a carbon
- [3,3]-sulfonium rearrangement
- stereodivergent strategy
- quaternary carbon stereocenter

- ◆ Computational studies correlation of the enantioselectivity with both catalyst and substrate
- ◆ Stereochemistry at sulfur governs the absolute sense of chiral induction, whereas the double bond geometry dictates the relative configuration of the final products

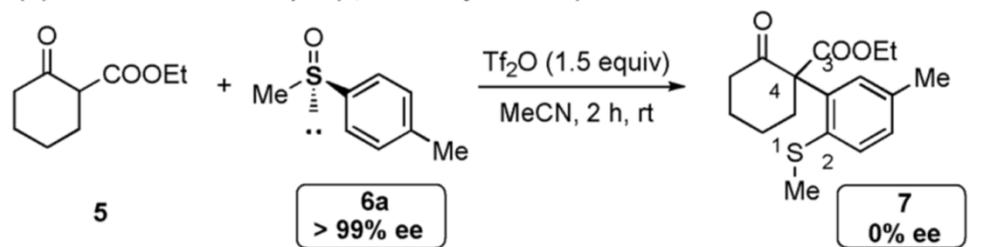


Acknowledgement

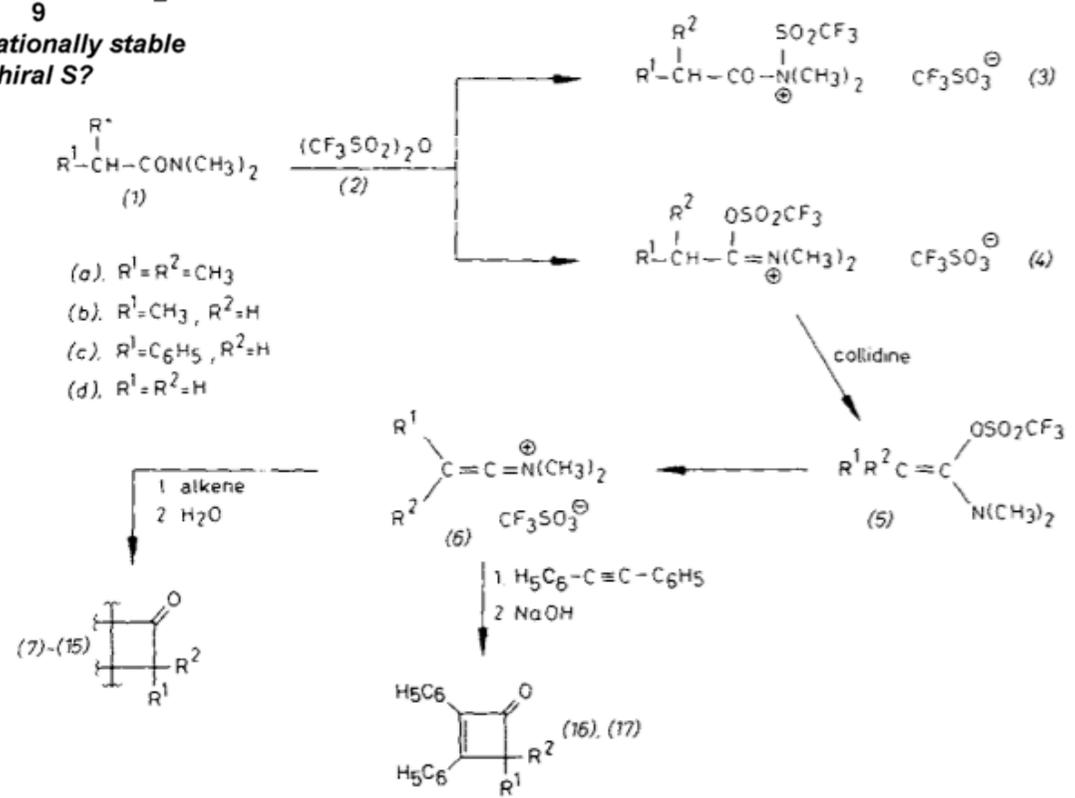
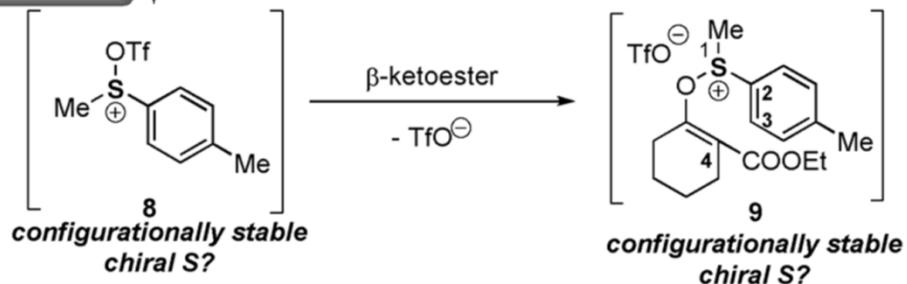
- **Prof. Huang**
- **Dr. Chen**
- **All group members in E201**

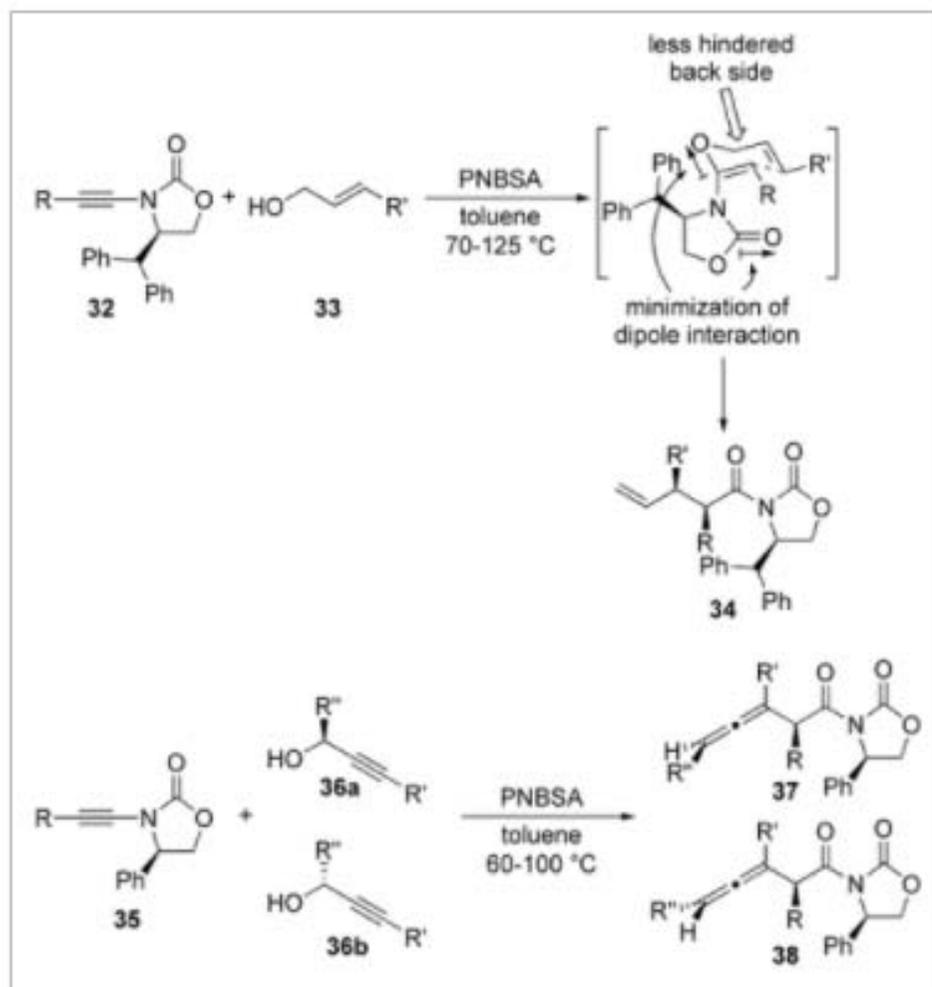
Thanks for your attention !

(B) Unsuccessful attempts (1,4-chirality transfer)



Activation of Sulfoxide





Scheme 12

[Open in figure viewer](#) | [PowerPoint](#)

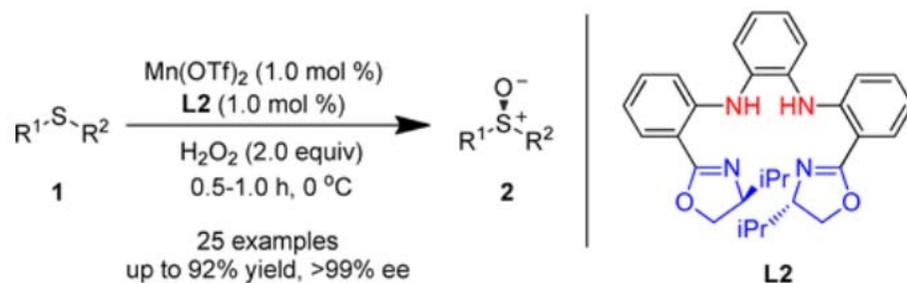
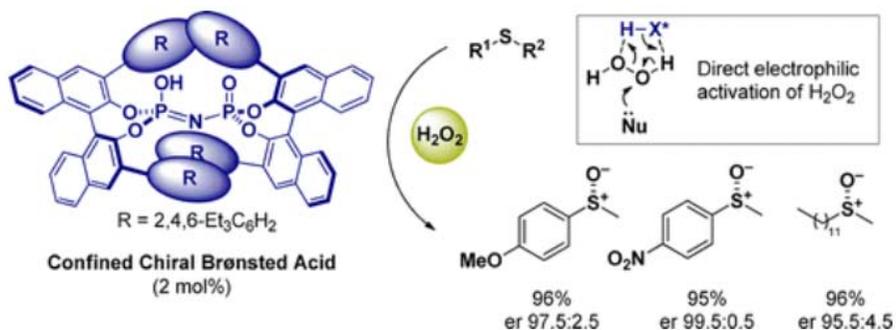
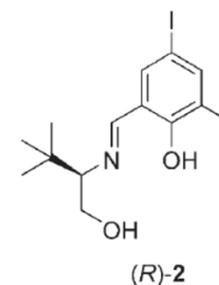
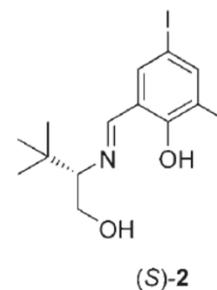
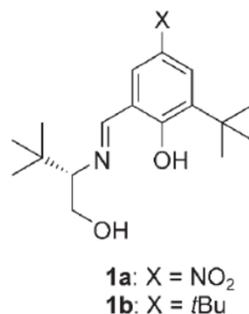
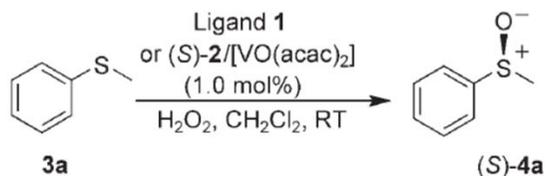
Stereoselective Fici-Claisen and Saucy-Marbet rearrangements with chiral ynamides. PNBSA=*p*-nitrobenzenesulfonic acid.

Table S8. Calculated ΔG_{298}^\ddagger activation barriers of the chiral transfer step for different systems

| | | <i>t</i> -butyl | <i>c</i> -hexyl | Me (thioalkyne, TfOH) | Me (ynamide, TfOH) | Me (ynamide, Tf ₂ NH) |
|---------------------------------|----------------|--|---------------------|-----------------------------|--------------------------|--|
| <i>Cis</i> | (<i>R</i>) | 2.6 ^[a] (4.2) ^[b] | 2.8 (5.3) | 1.7 (4.7) | 4.4 (5.4) | 2.4 (3.7) |
| <i>Cis</i> | (<i>S</i>) | 5.2 (7.0) | 4.3 (7.2) | 4.4 (7.7) | 9.6 (12.0) | - ^[c] |
| <i>Trans</i> | (<i>S</i>) | 4.9 (7.5) | 3.7 (6.1) | 2.4 (4.9) | 2.7 (5.3) | 4.0 (6.0) |
| <i>Trans</i> | (<i>R</i>) | 7.7 (10.5) | 7.0 (10.0) | 4.8 (7.7) | 5.8 (9.6) | - ^[c] |
| $\Delta\Delta G_{298}^\ddagger$ | ^[d] | 2.3 (3.3) | 0.9 (0.8) | 0.7 (0.2) | -1.7 (-0.1) | 1.6 (2.3) |

Asymmetric synthesis of sulfoxides

Scheme 1. Vanadium-catalyzed asymmetric oxidation of alkyl aryl sulfides.



- wide substrate scope
- short reaction time

Used as chiral sulfur reagent

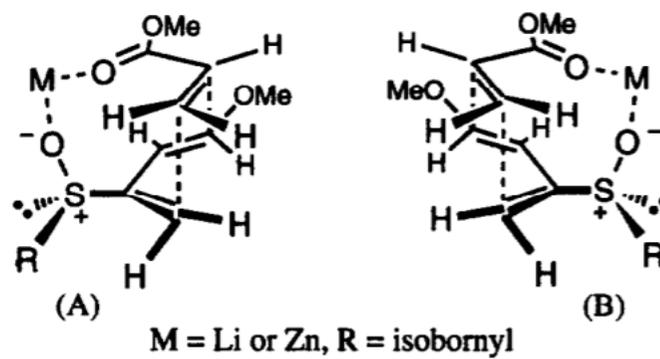
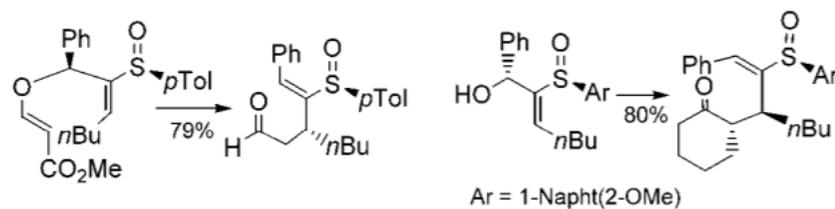
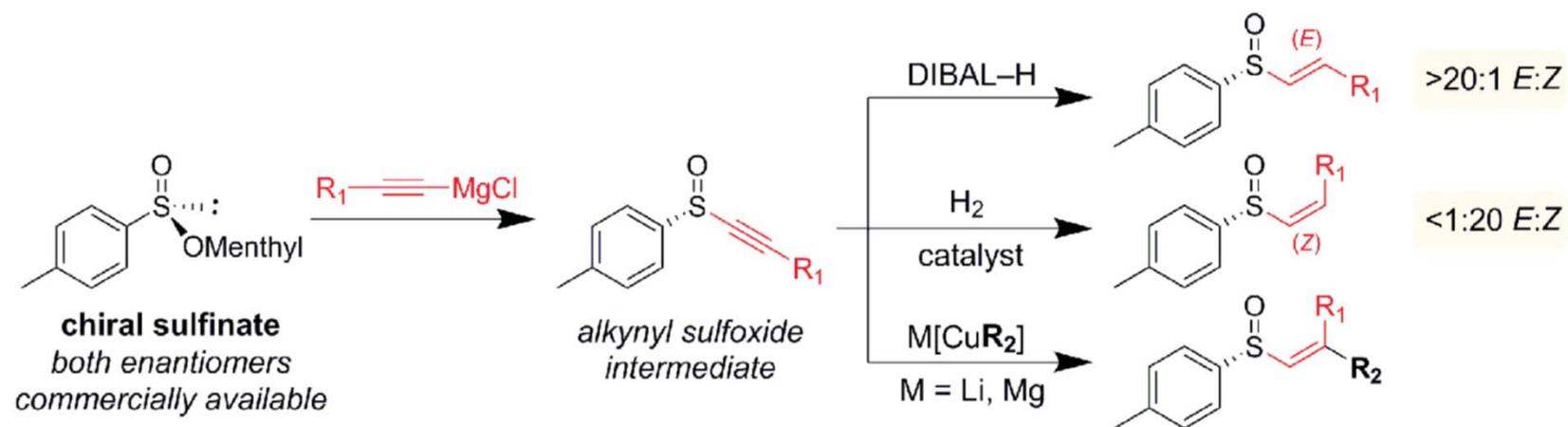


Figure 2



Highly modular and stereoselective synthesis of vinyl sulfoxides



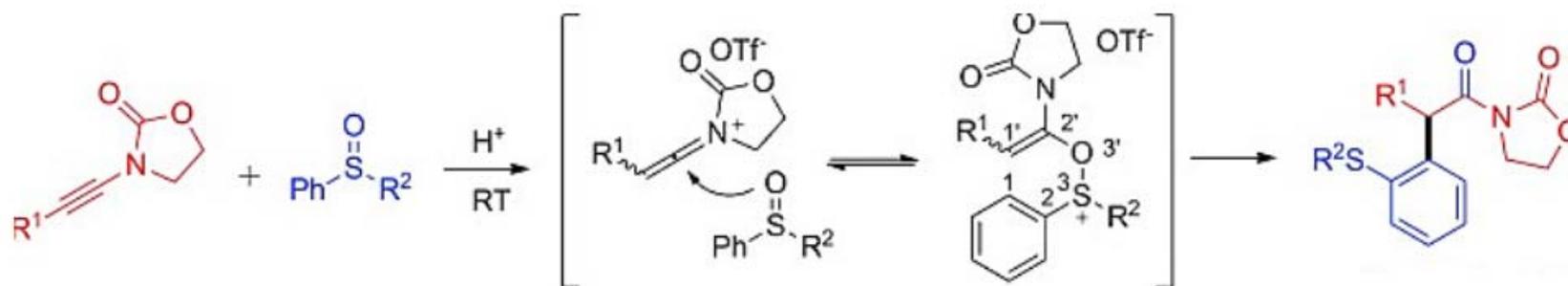
D. Kaldre, *et al.*, *Angew. Chem. Int. Ed.* **2017**, 56, 2212–2215.

J. P. Marino, *et al.*, *J. Am. Chem. Soc.* **1981**, 103, 7687–7689.

H. Kosugi, *et al.*, *J. Org. Chem.* **1987**, 52, 1078–1082.

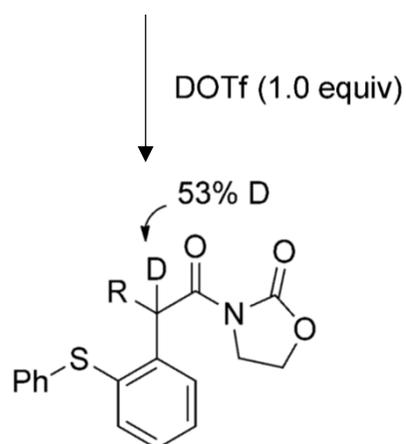


Brønsted Acid Catalyzed Redox Arylation



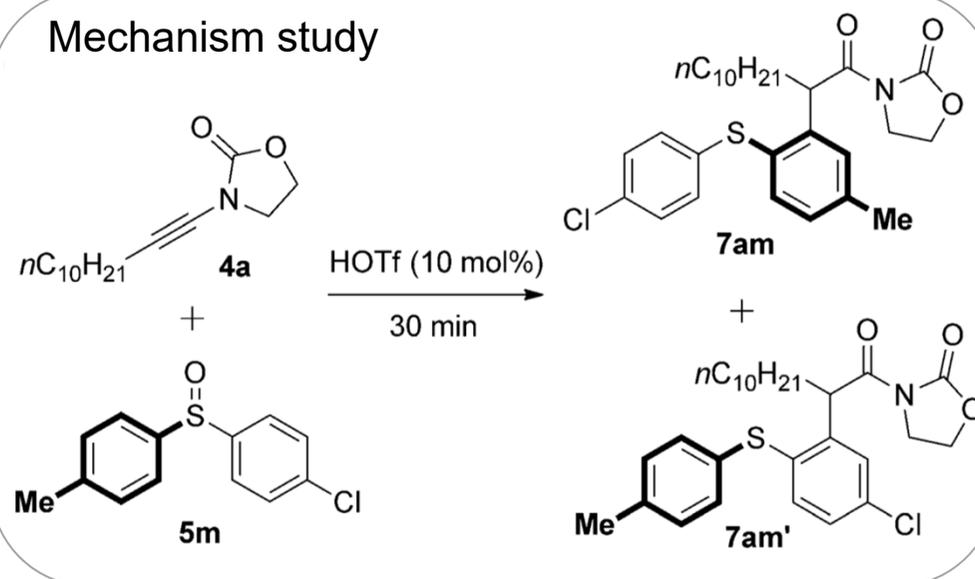
R¹ = Alkyl, aryl, nitrile, ether, ester moiety

R² = Alkyl, aryl



Supports that **protonation of the ynamide** triggers nucleophilic attack to the keteniminium intermediate

Mechanism study



Preference for the more electron-rich aryl moiety rules out an S_N-type mechanism