Literature Report 5

Catalytic Enantioselective Sulfur Alkylation of Sulfenamides for the Asymmetric Synthesis of Sulfoximines

Reporter: Tong Niu

Checker: Li-Xia Liu

Greenwood, N. S.; Champlin, A. T.; Ellman, J. A. *J. Am. Chem. Soc.* 2022, *144*, 17808

2022.11.30

CV of Prof. Jonathan A. Ellman

Research:

Asymmetric Synthesis of Amines *&* C-H Functionalization *&* Chemical Biology

Education & Professional Experience:

- **1980-1984** B.S., Chemistry, MIT
- **1984-1989** Ph.D., Organic Chemistry, Harvard University
  (Advisor: Prof. David A. Evans)
- **1989-1992** Postdoc., UC Berkeley
  (Research mentor: Prof. Peter G. Schultz)
- **1992-1997** Assistant Professor, UC Berkeley
- **1997-1998** Associate Professor, UC Berkeley
- **1999-2010** Professor, UC Berkeley
- **2010-Present** Professor, Yale University

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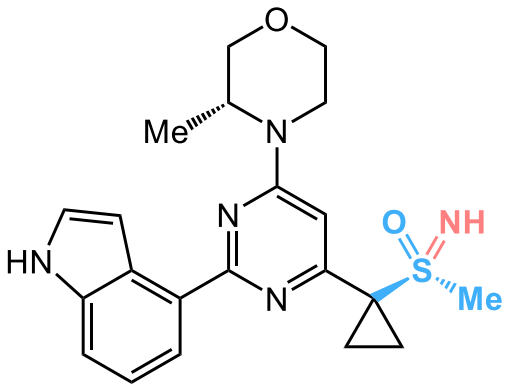
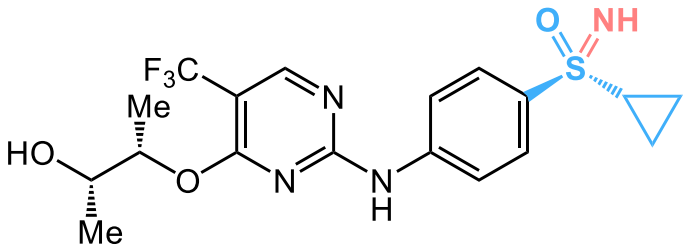
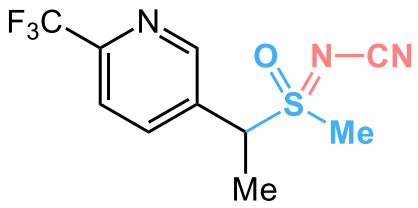
Examples of Bioactive Sulfoximines



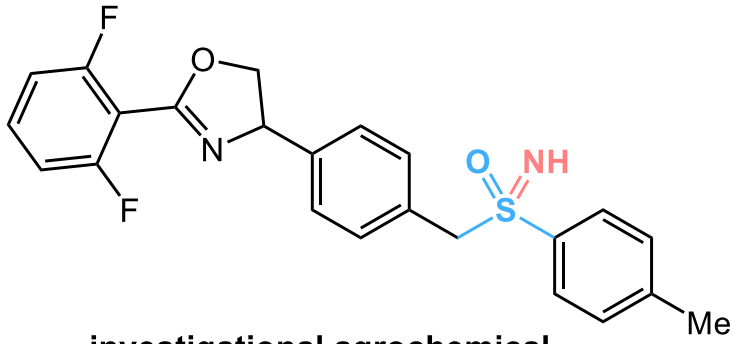
Ceralasertib
(ATR inhibitor)



Roniciclib
(pan-CDK inhibitor)

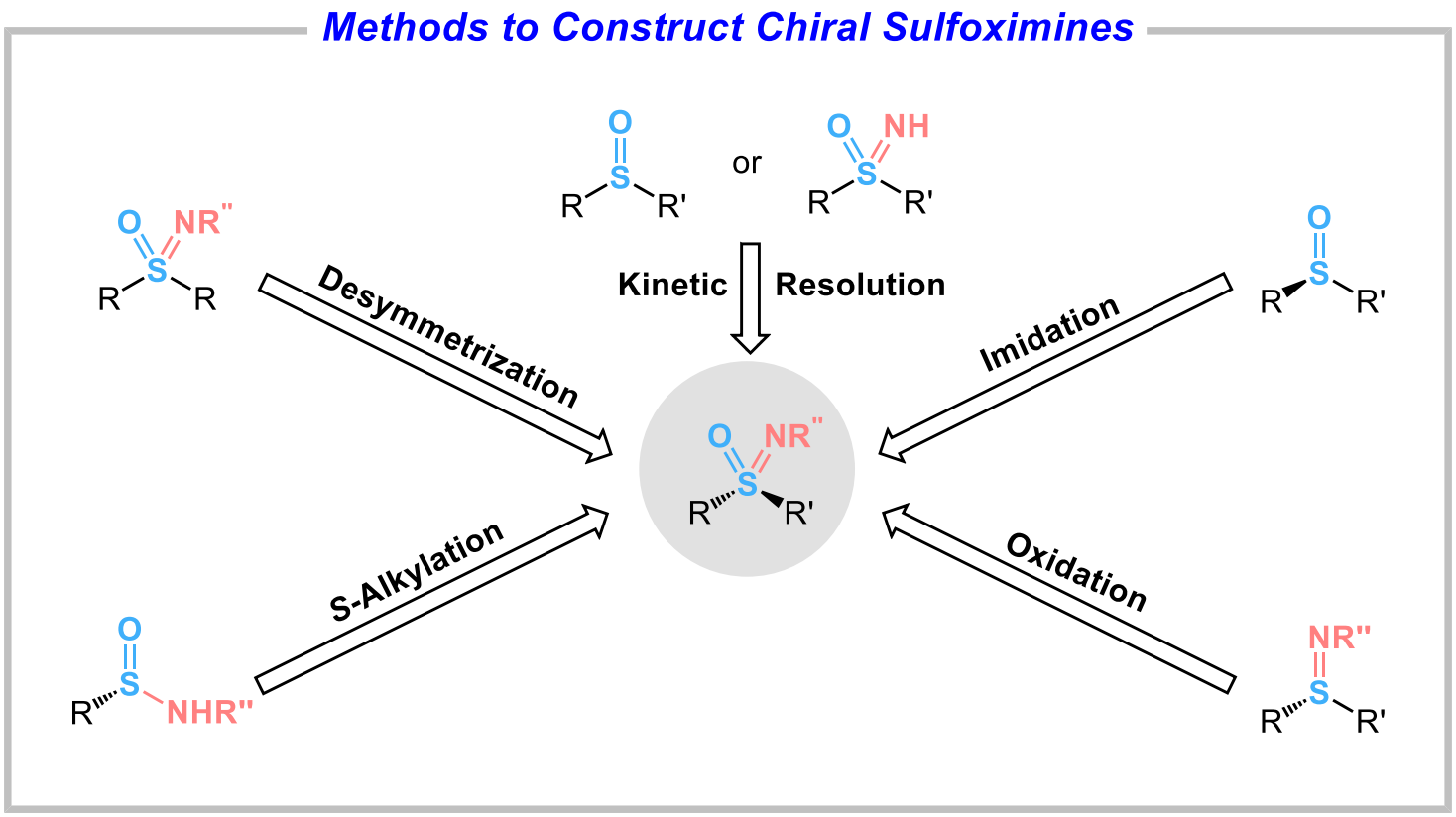


Sulfoxaflor
(nAChRs agonist)



investigational agrochemical

Introduction



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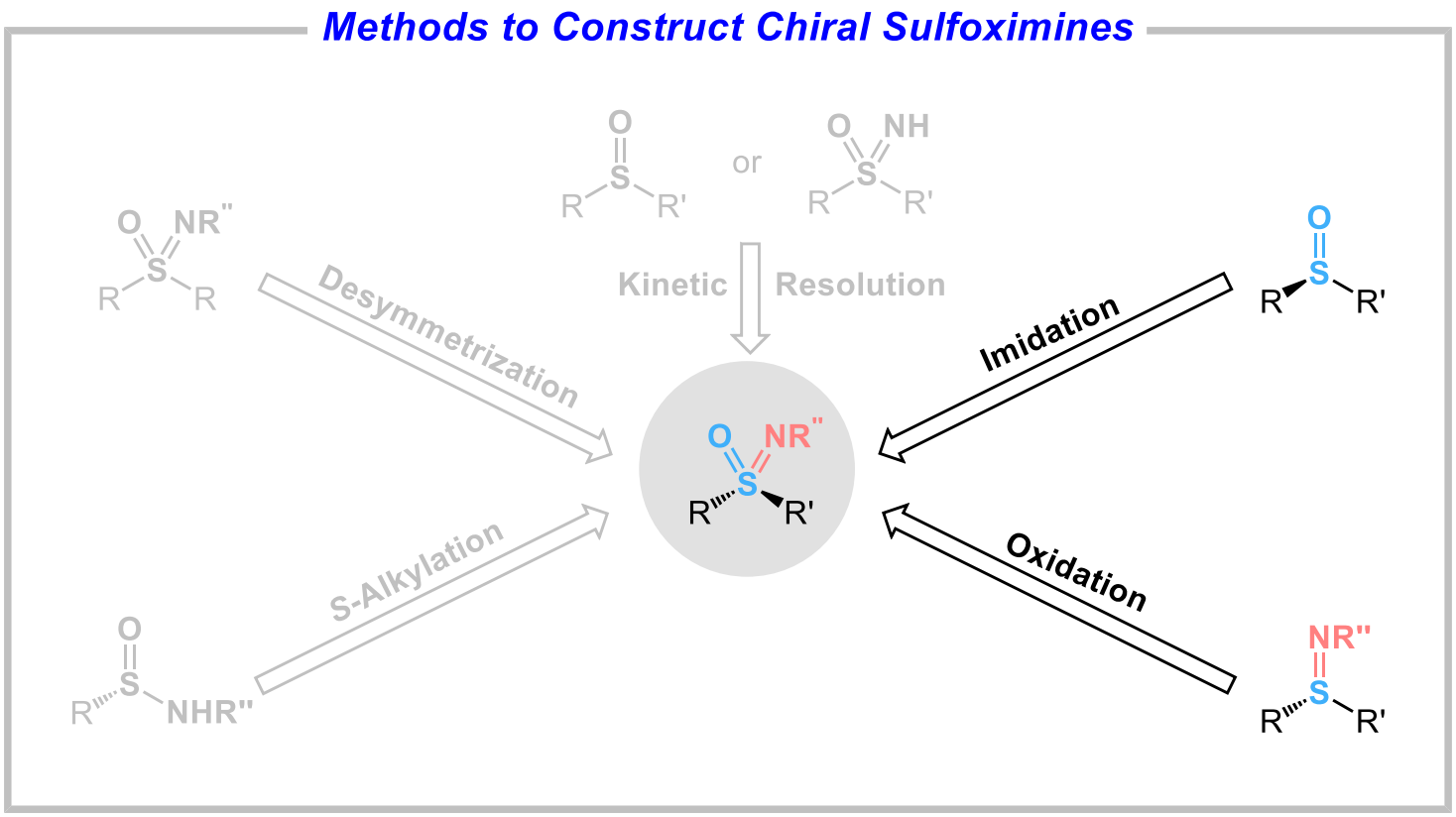
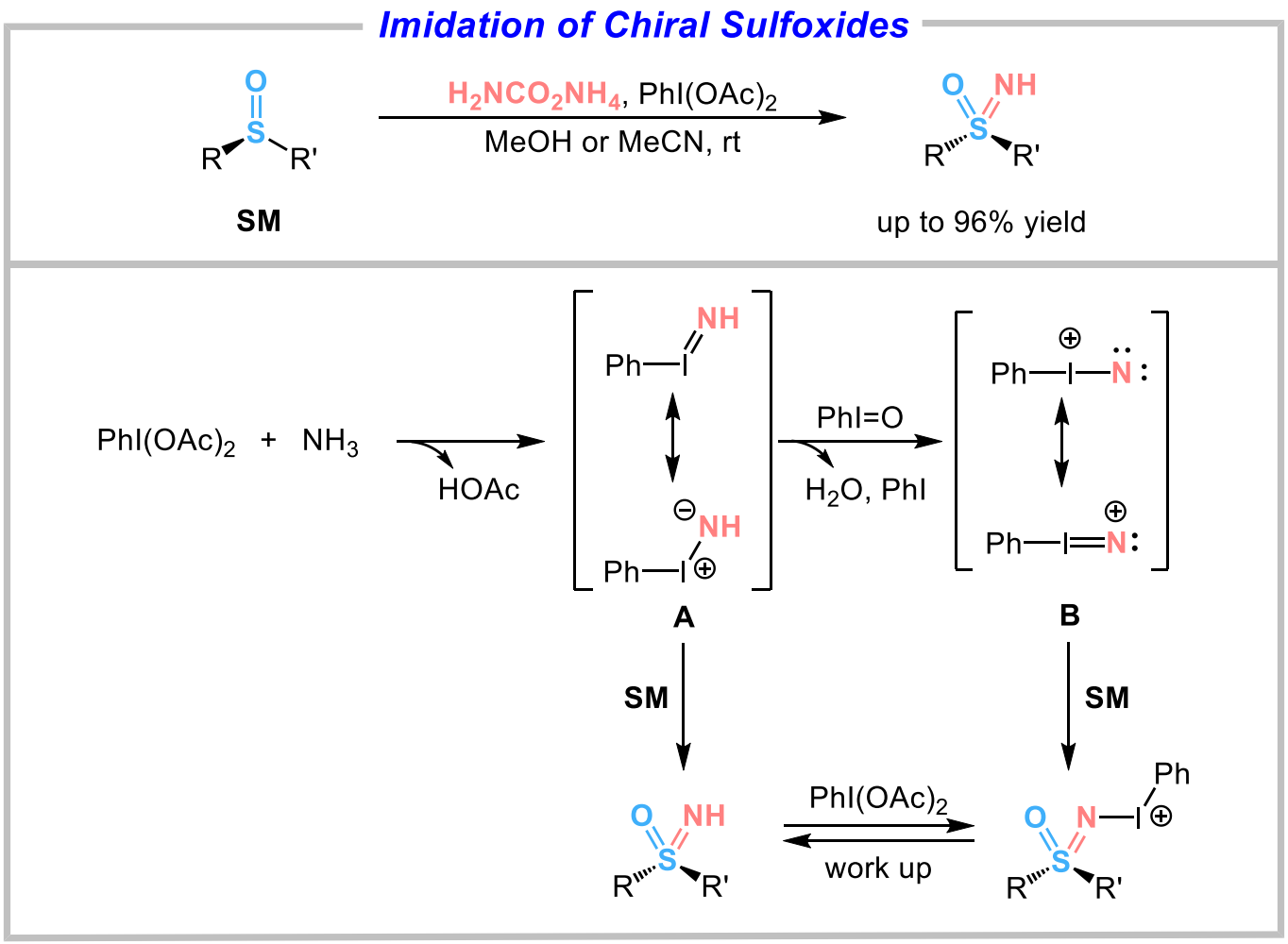


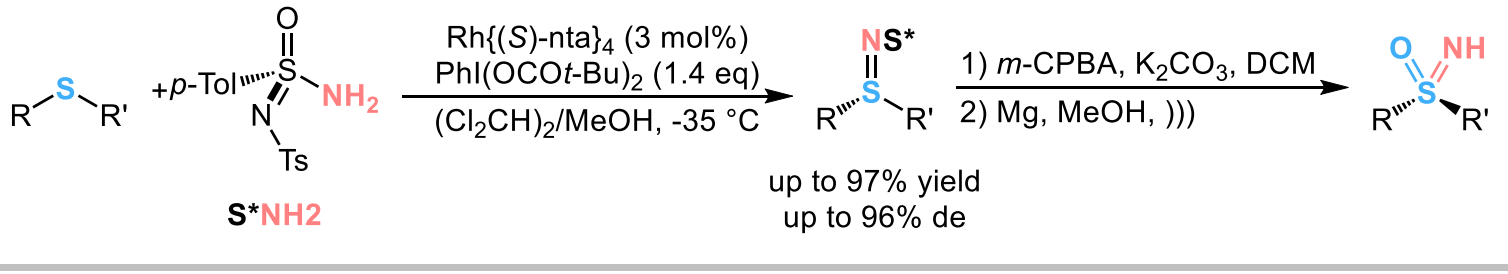
Methods to Construct Chiral Sulfoximines

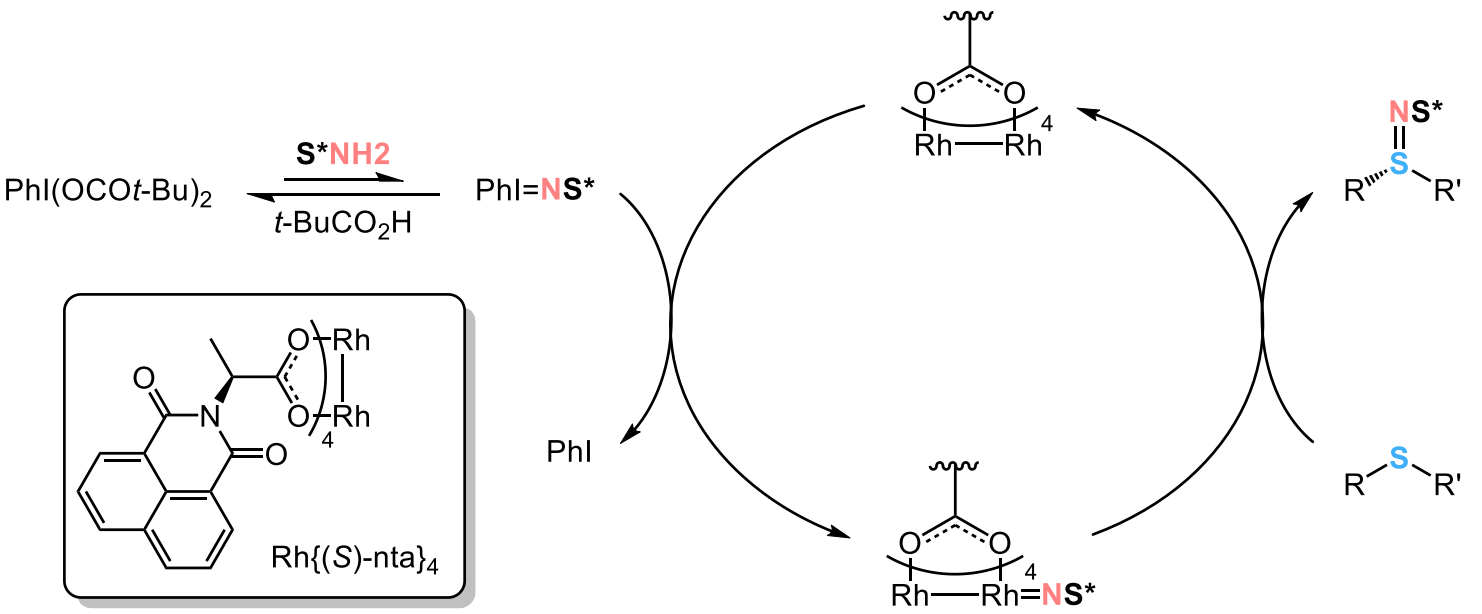


Zenzola, M.; Doran, R.; Degennaro, L.; Luisi, R.; Bull, J. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 7203

Methods to Construct Chiral Sulfoximines

Oxidation of Chiral Sulfilimines





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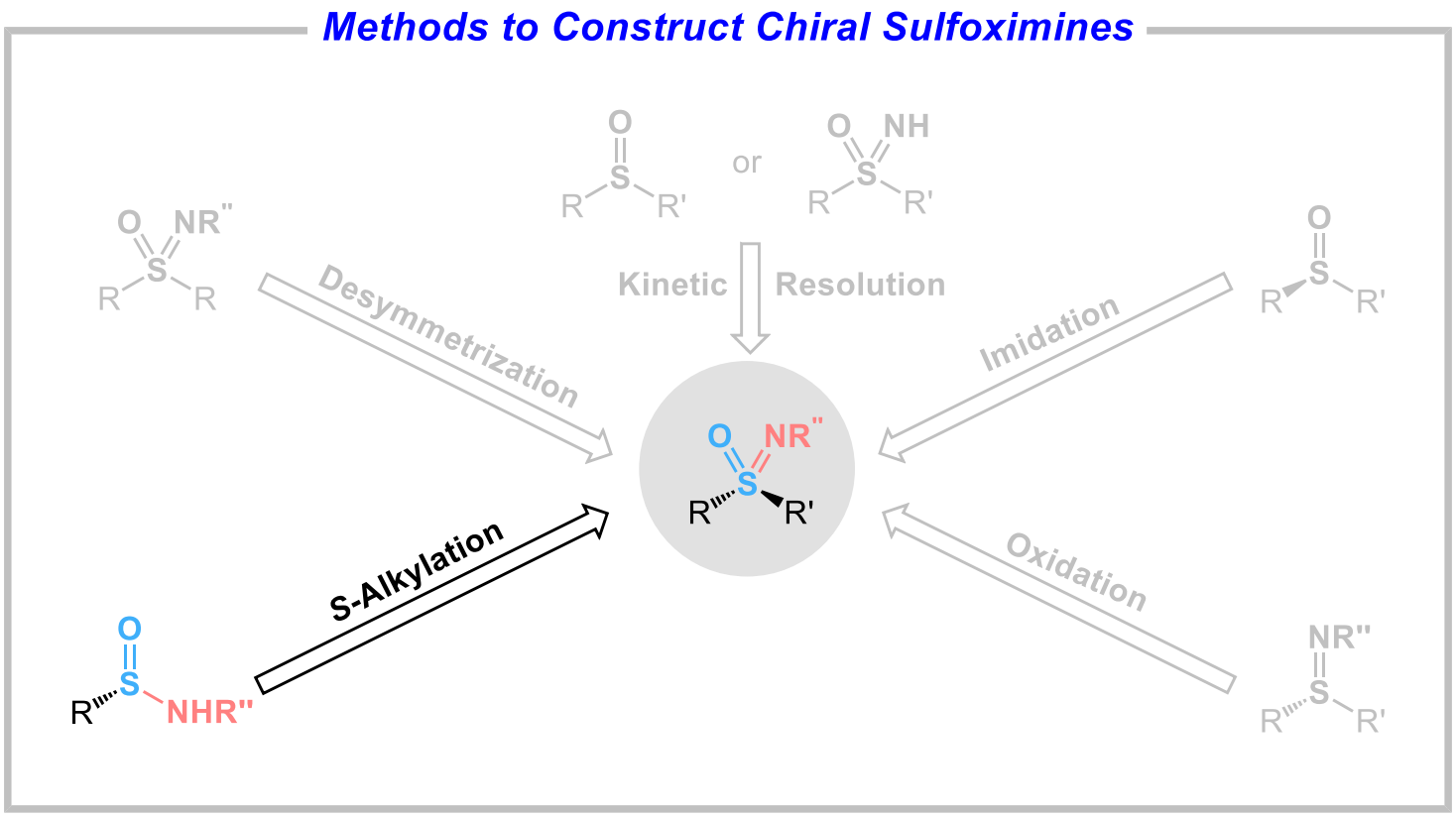
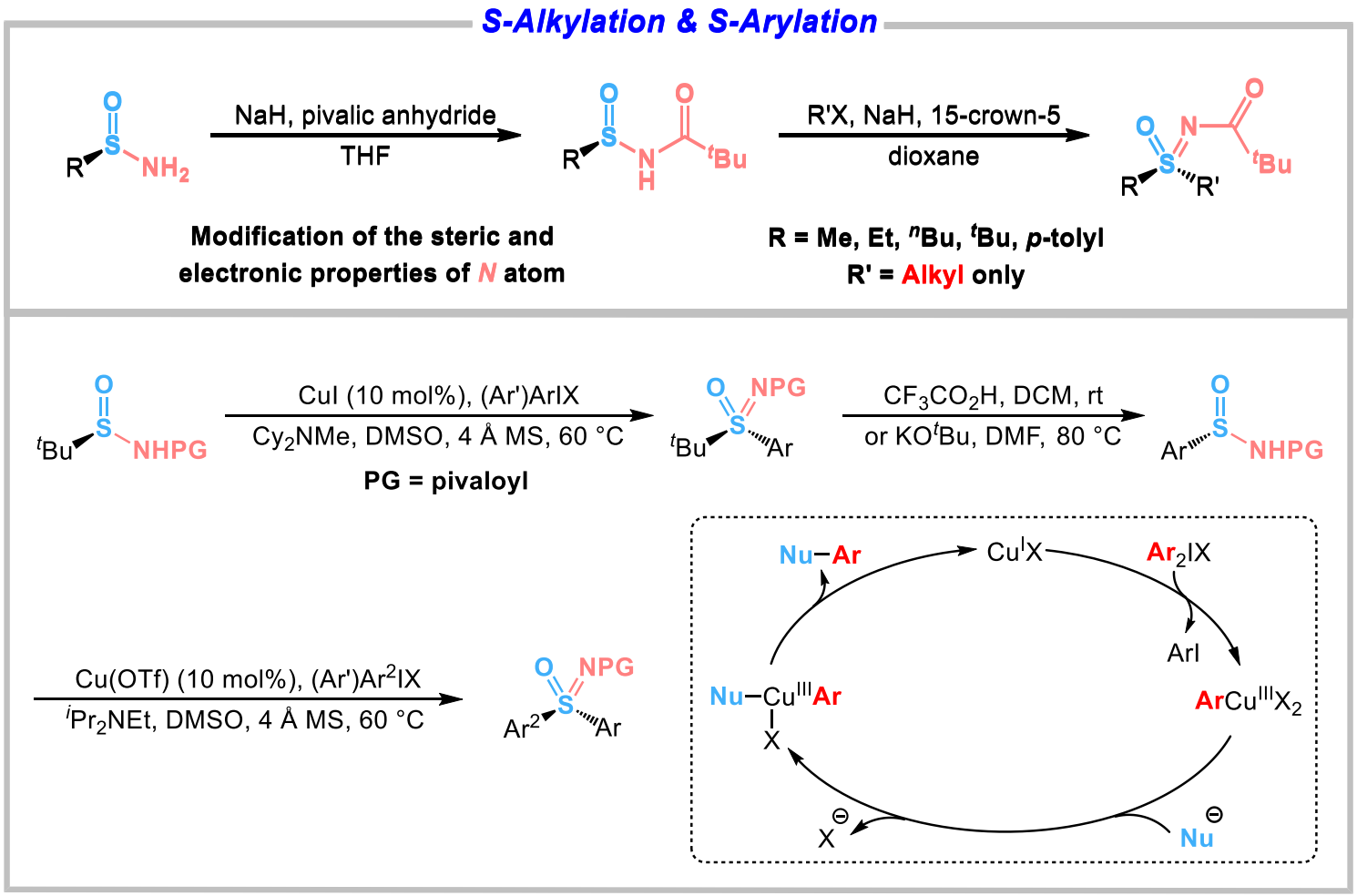
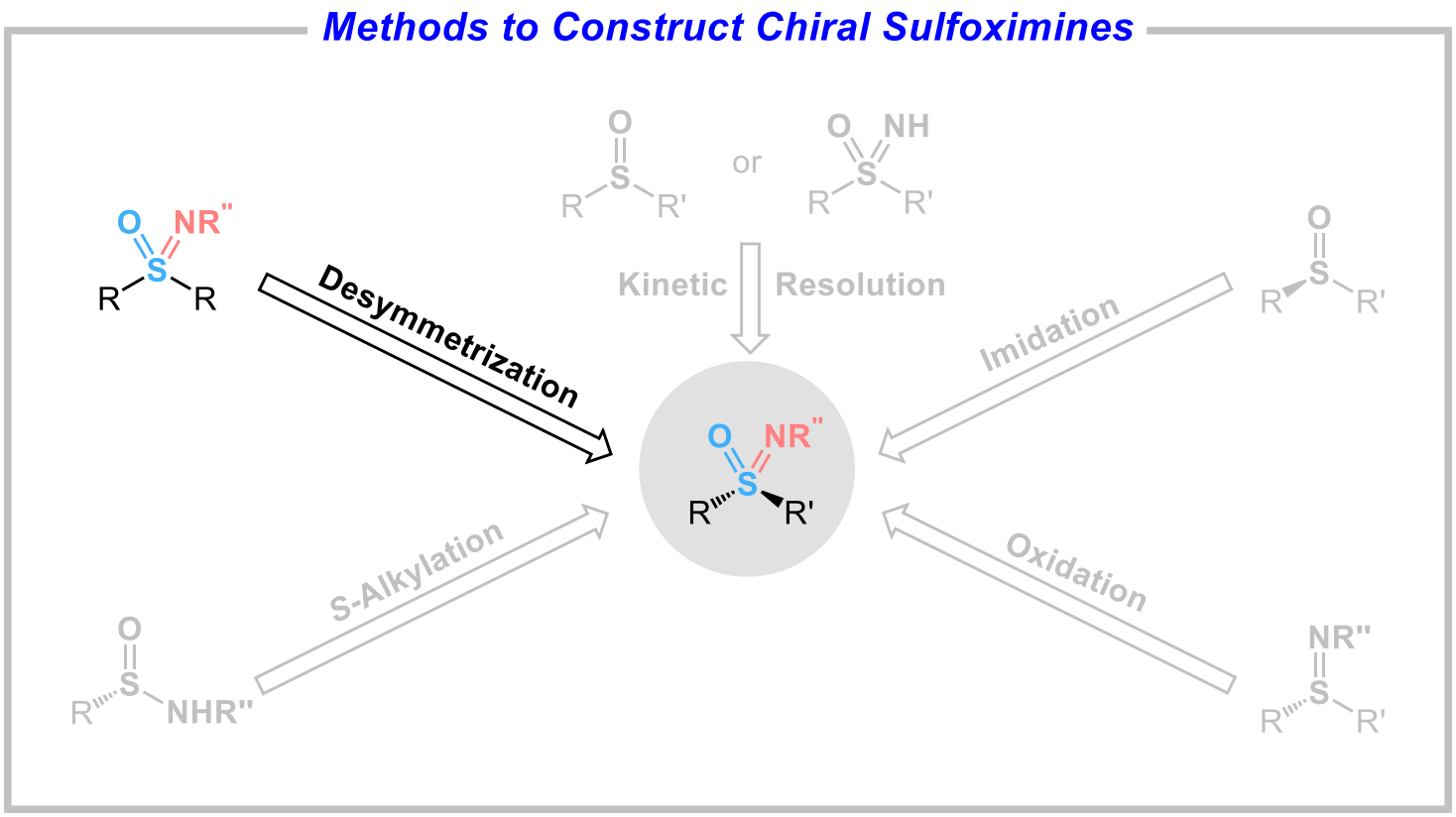


Methods to Construct Chiral Sulfoximines



Aota, Y.; Kano, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 17661
Aota, Y.; Kano, T.; Maruoka, K. *J. Am. Chem. Soc.* **2019**, *141*, 19263

Introduction



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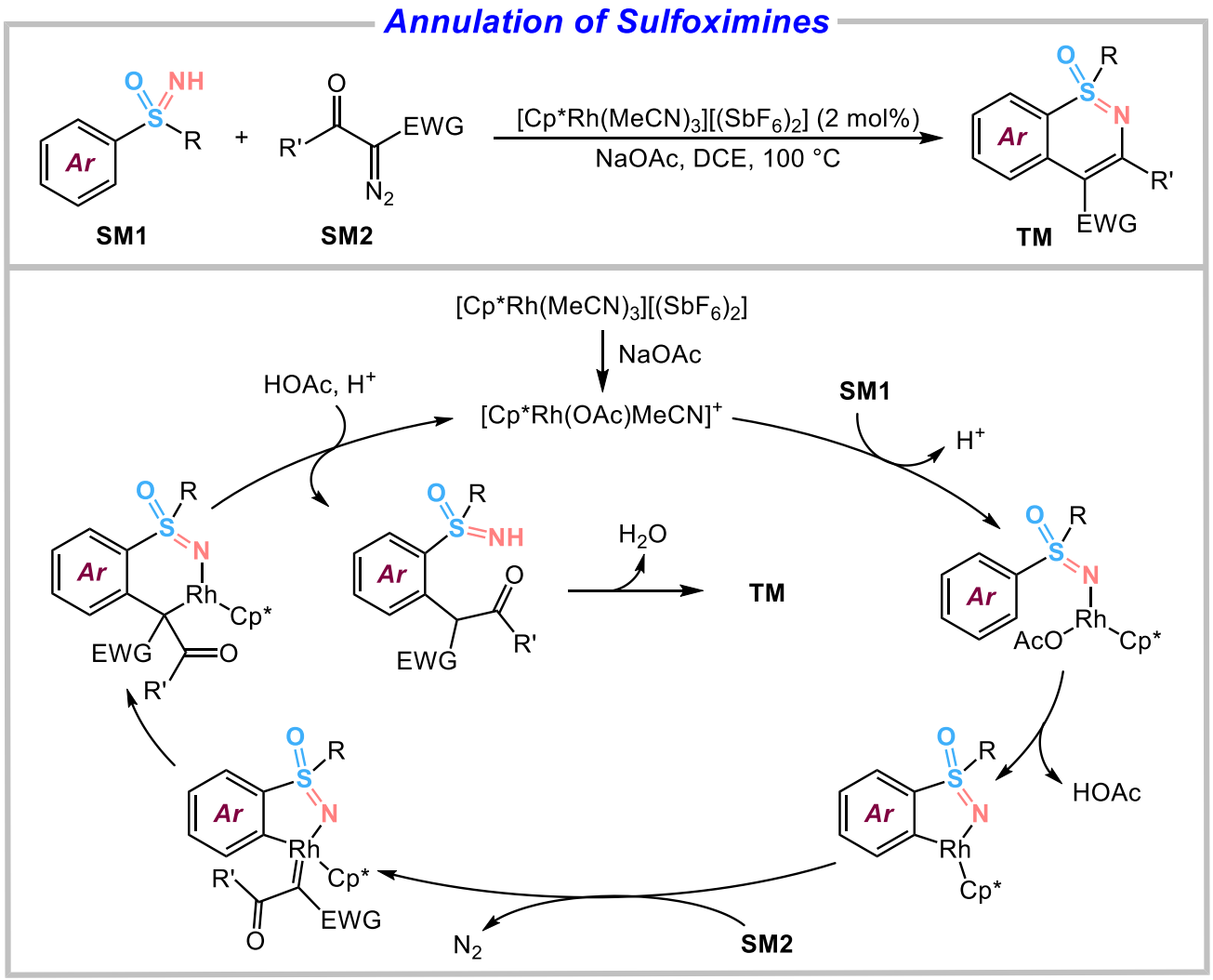
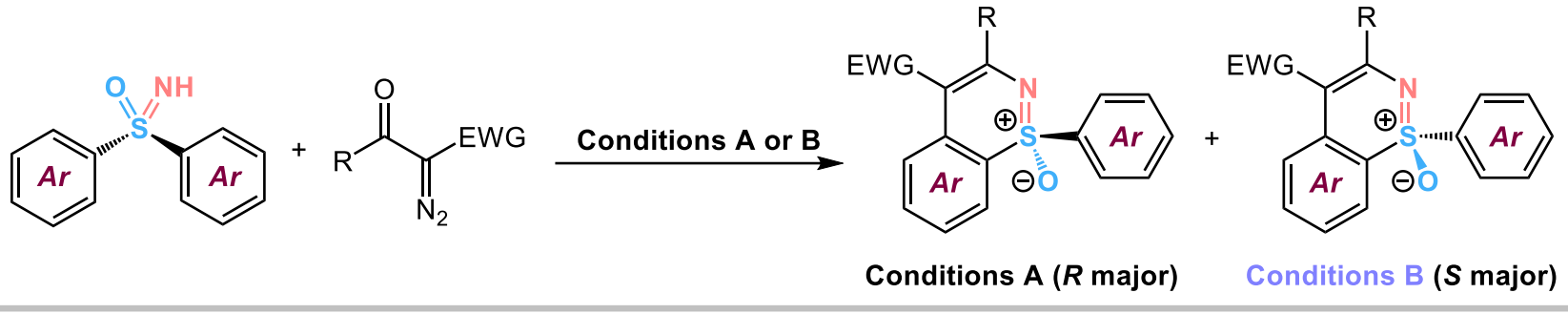


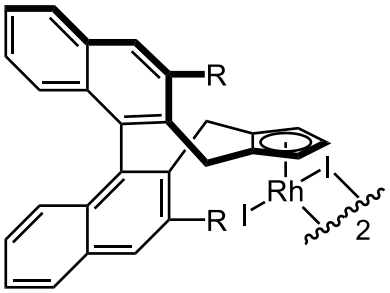
Cheng, Y.; Bolm, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 12349

Methods to Construct Chiral Sulfoximines

Desymmetrization of Sulfoximines



Conditions A (*R* major) **Conditions B (*S* major)**



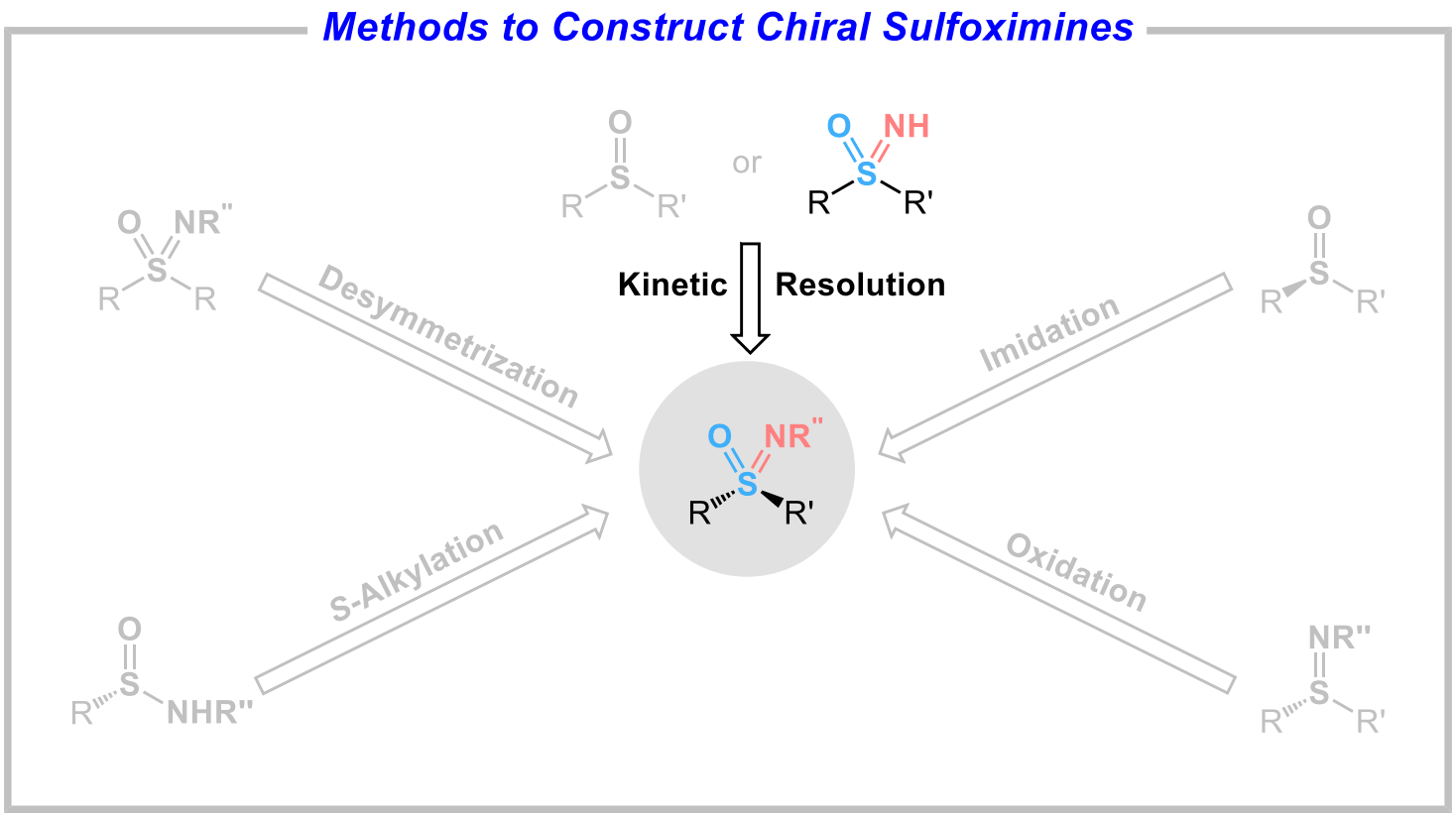
(*R*)-**[Rh]** (R = OMe)

A: **[Rh]** (2.5 mol%), $AgNTf_2$ (20 mol%), 2-methoxybenzoic acid, MeOH

B: **[Rh]** (2.5 mol%), $AgNTf_2$ (20 mol%), 2,6-dimethoxybenzonic acid, TCE

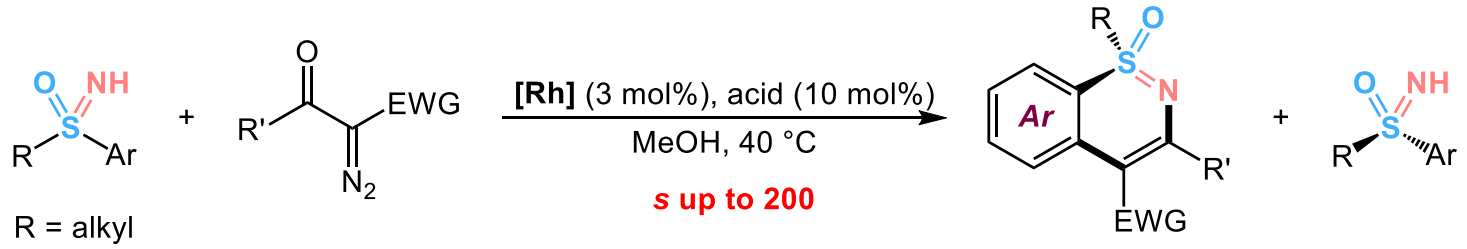
Shen, B.; Wan, B.; Li, X. *Angew. Chem. Int. Ed.* **2018**, *57*, 15534

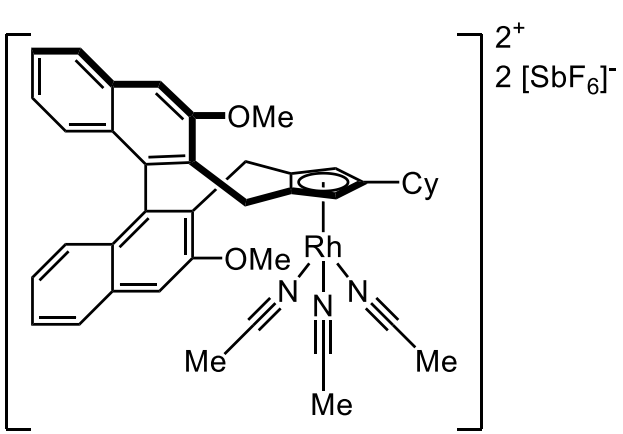
Introduction

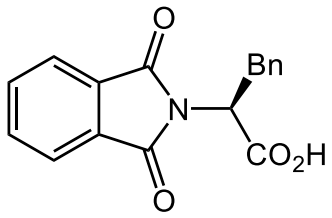


Methods to Construct Chiral Sulfoximines

Kinetic Resolution of Sulfoximines







chiral acid

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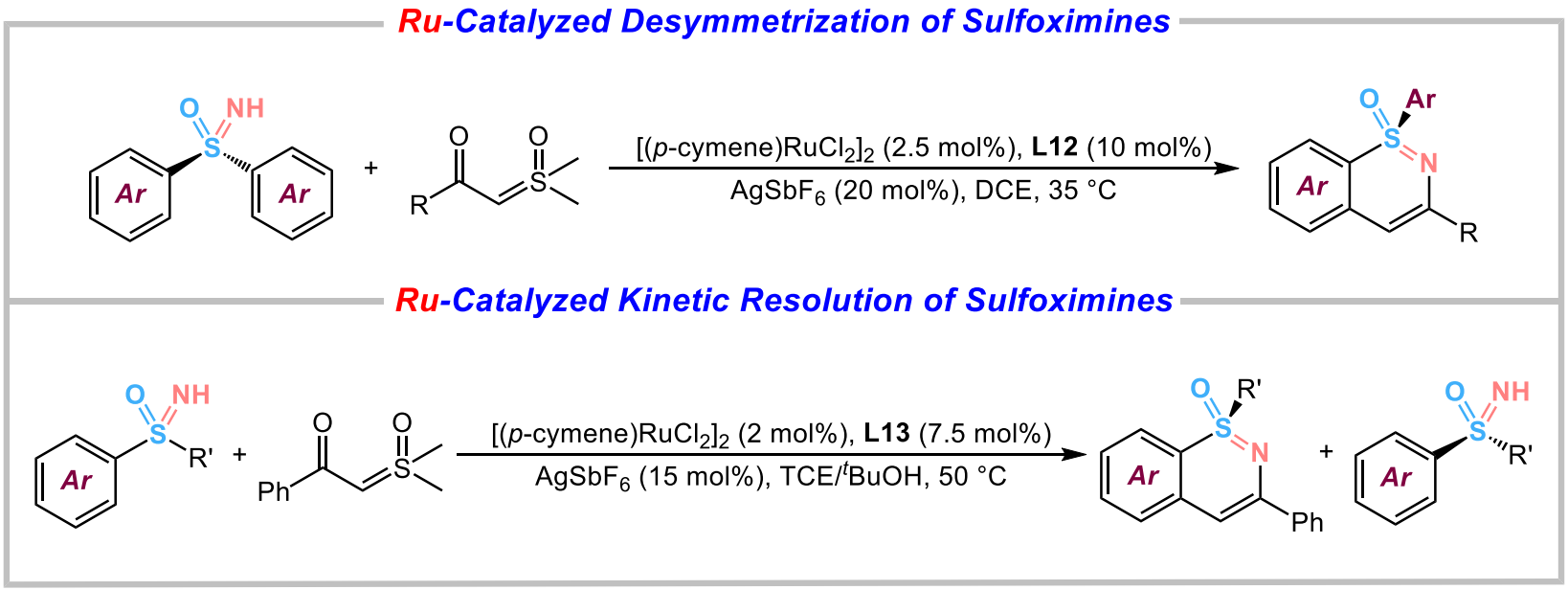
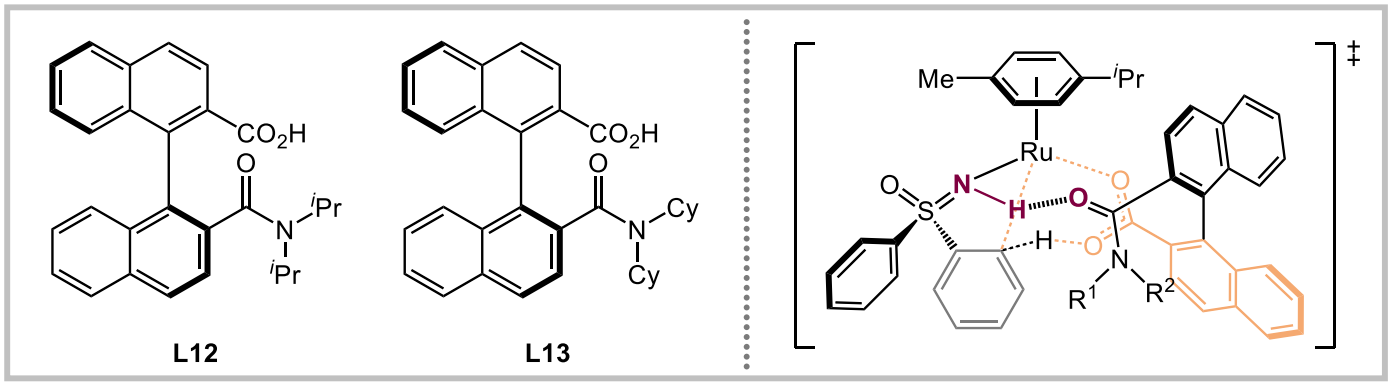
Methods to Construct Chiral Sulfoximines

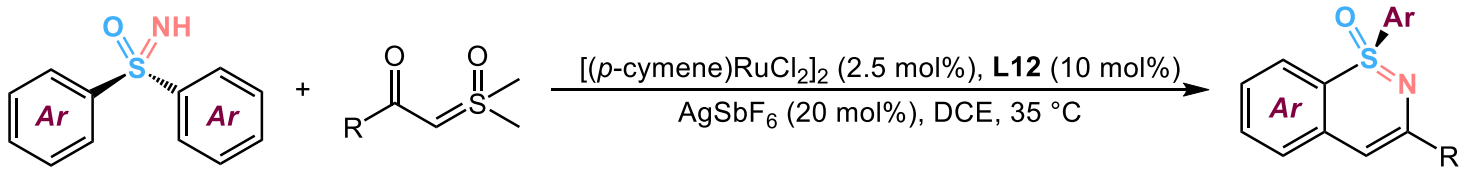


Zhou, T.; Qian, P.-F.; Shi, B.-F. *J. Am. Chem. Soc.* **2021**, *143*, 6810

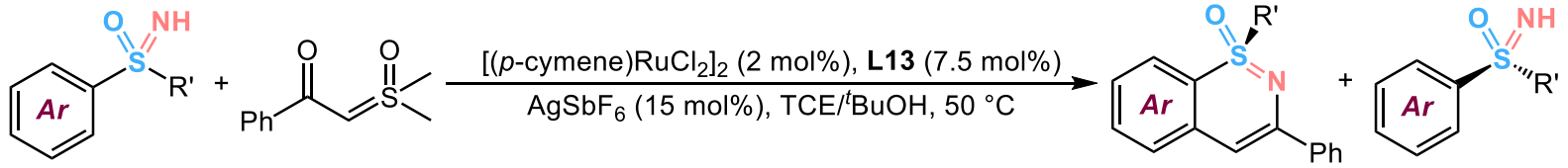
Methods to Construct Chiral Sulfoximines



***Ru*-Catalyzed Desymmetrization of Sulfoximines**



***Ru*-Catalyzed Kinetic Resolution of Sulfoximines**



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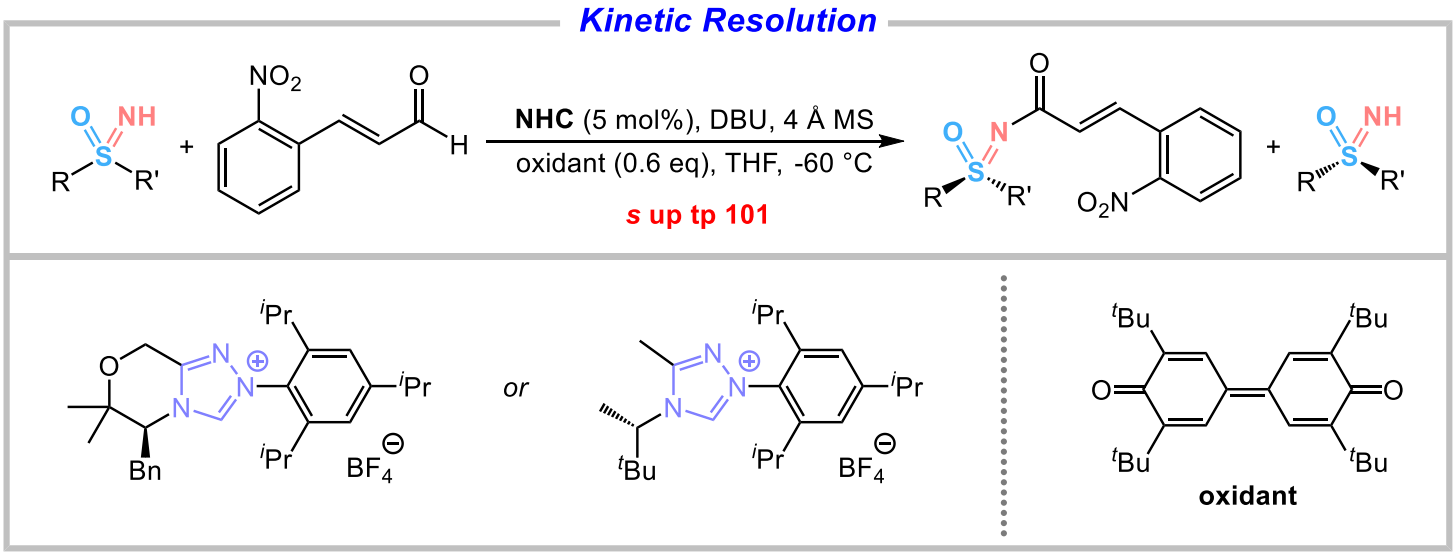
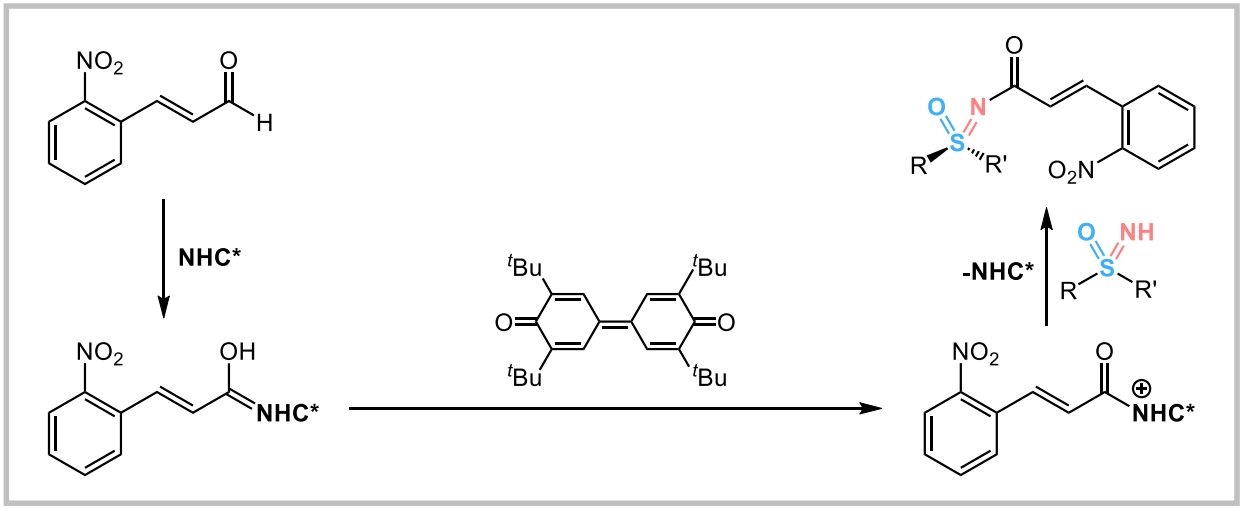
Methods to Construct Chiral Sulfoximines

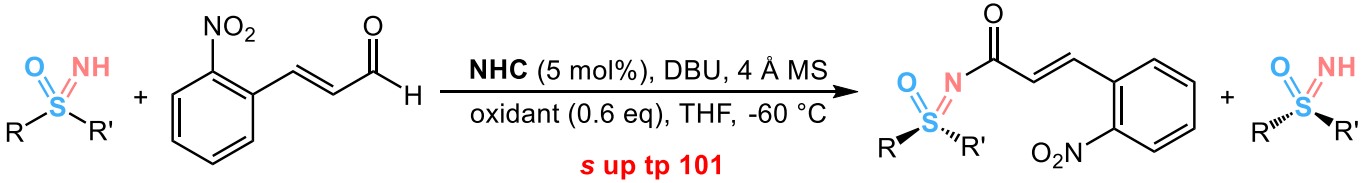


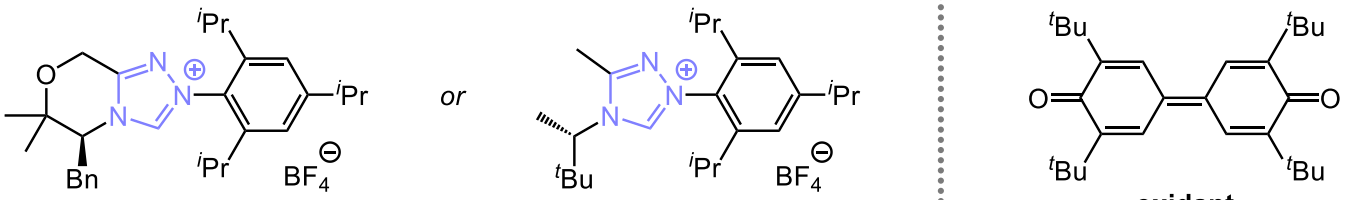
Dong, S.; Frings, M.; Bolm, C. *J. Am. Chem. Soc.* **2016**, *138*, 2166

Methods to Construct Chiral Sulfoximines



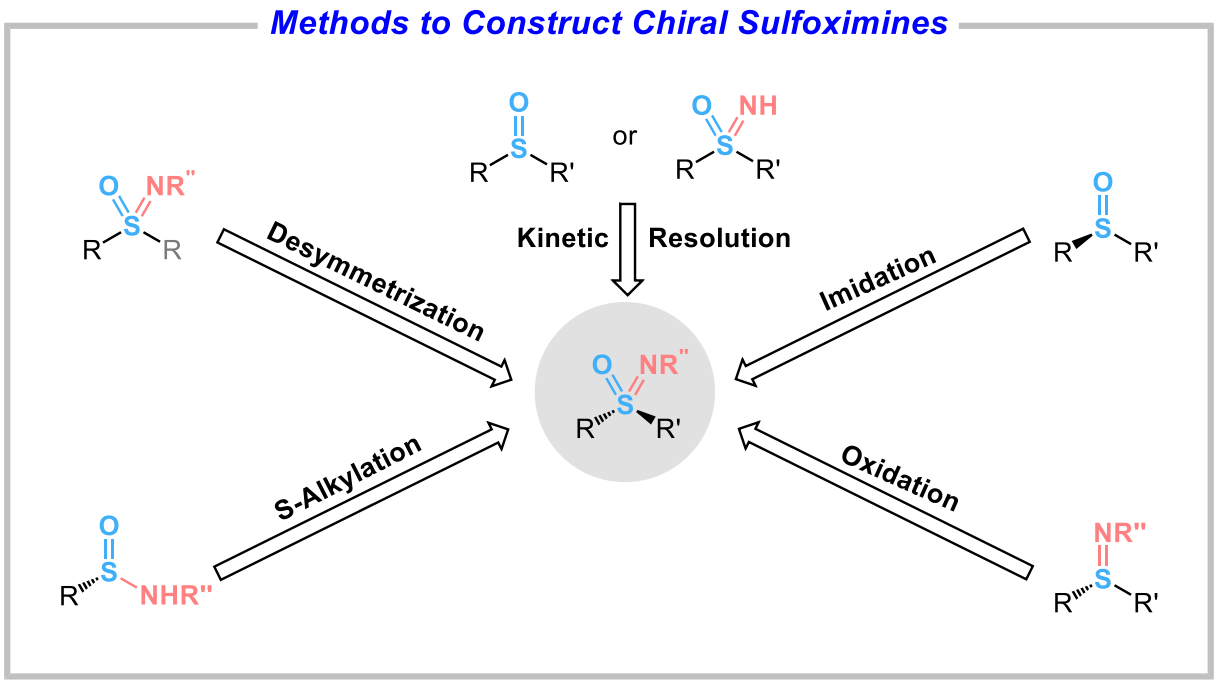
Kinetic Resolution



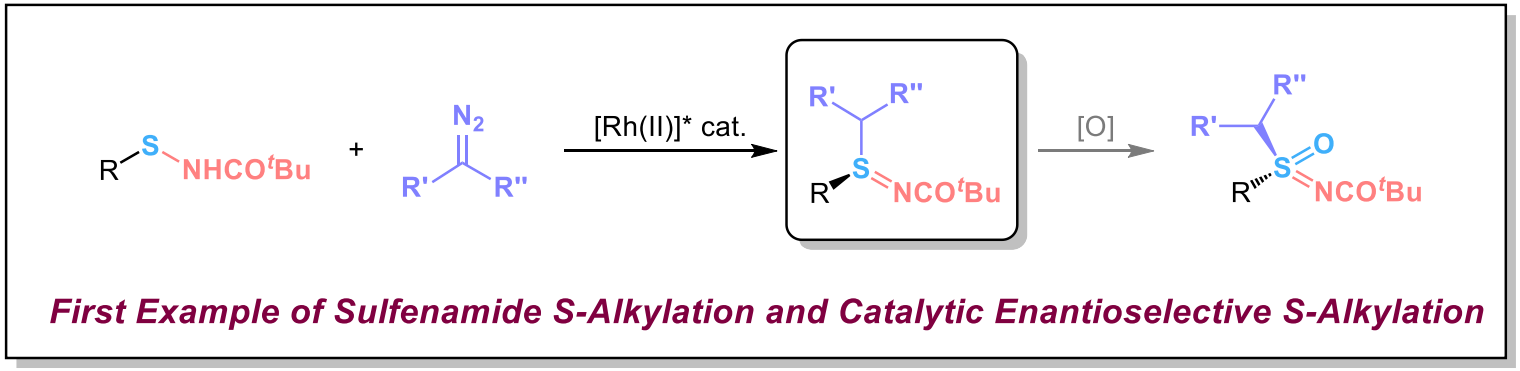


Dong, S.; Frings, M.; Bolm, C. *J. Am. Chem. Soc.* **2016**, *138*, 2166

Methods to Construct Chiral Sulfoximines

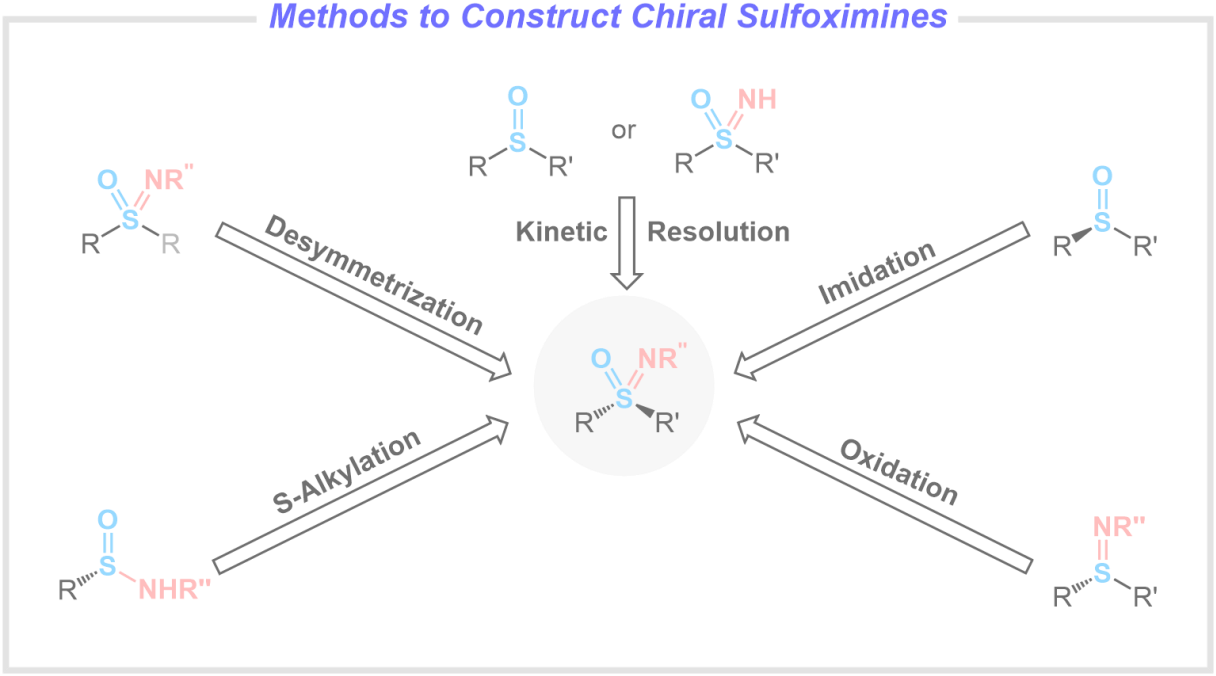


Enantioselective Sulfur Alkylation of Sulfenamides



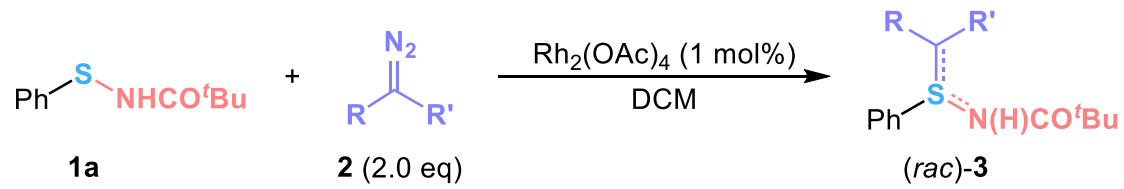
First Example of Sulfenamide S-Alkylation and Catalytic Enantioselective S-Alkylation

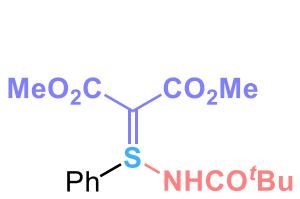
Methods to Construct Chiral Sulfoximines



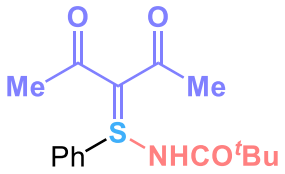
Enantioselective Sulfur Alkylation of Sulfenamides

Racemic S-Alkylation Scope

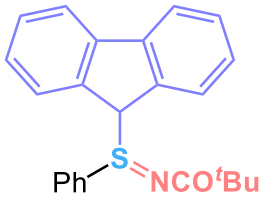




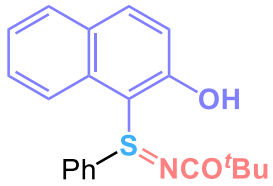
3a, 80%



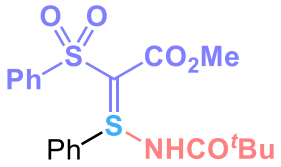
3b, 73%



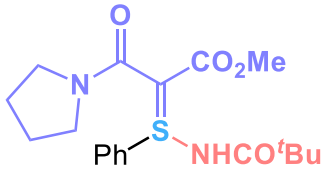
3i, 82%



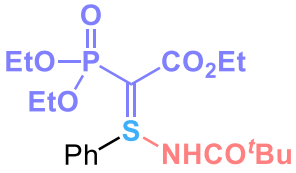
3j, 96%



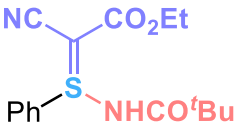
3e, 99%



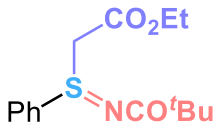
3f, 85%



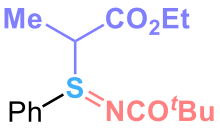
3g, 99%



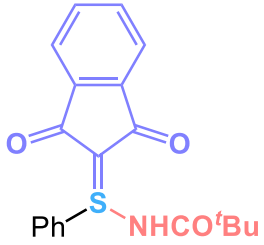
3h, 98%



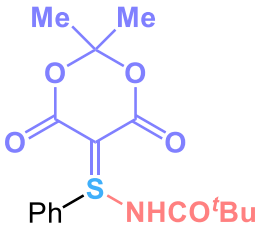
3l, 80%



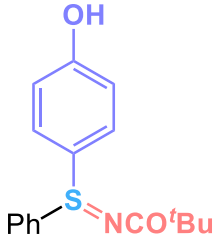
3m, 78%



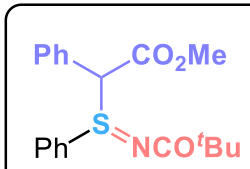
3c, 74%



3d, 78%



3k, 88%

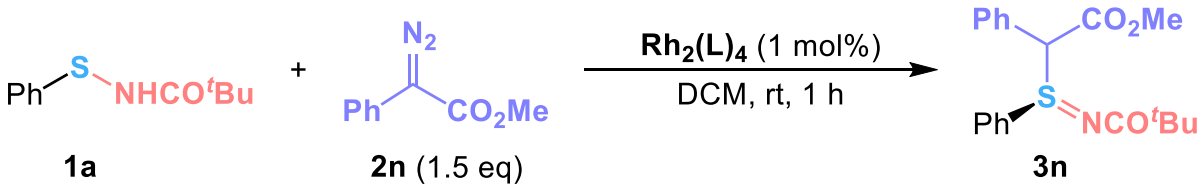


3n, 91%

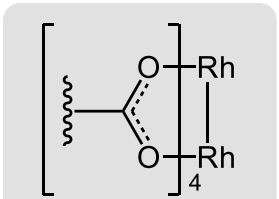
1 g scale
1.1 eq. diazo

Enantioselective Sulfur Alkylation of Sulfenamides

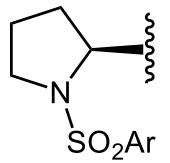
Optimization of Enantioselective Reaction Conditions



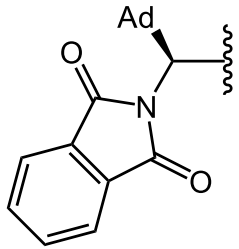
1a **2n** (1.5 eq) **3n**



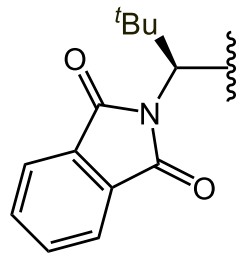
$Rh_2(L)_4$



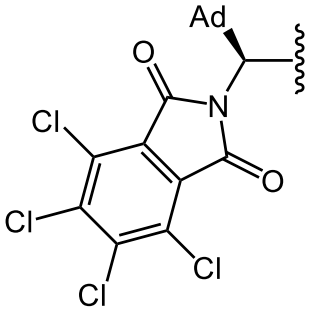
L = *S*-DOSP
Ar = *p*-$C_{12}H_{25}C_6H_4$
97% yield, 46:54 er



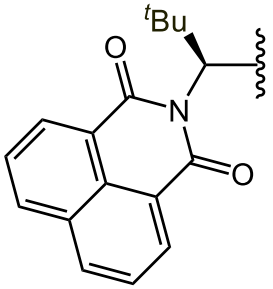
L = *S*-PTAD
99% yield, 87:13 er



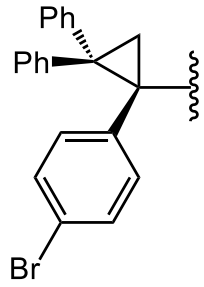
L = *S*-PTTL
99% yield, 88:12 er



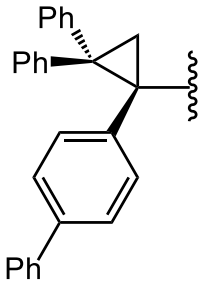
L = *S*-TCPTAD
97% yield, 56:44 er



L = *S*-NTTL
98% yield, 92:8 er



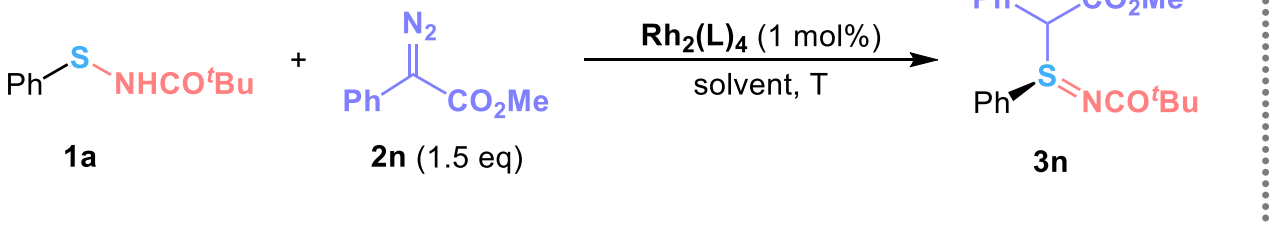
L = *R*-*p*-Br-TPCP
98% yield, 94:6 er

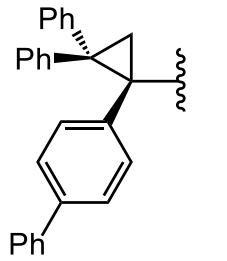


L = *R*-*p*-Ph-TPCP
93% yield, 96:4 er

Enantioselective Sulfur Alkylation of Sulfenamides

Optimization of Enantioselective Reaction Conditions



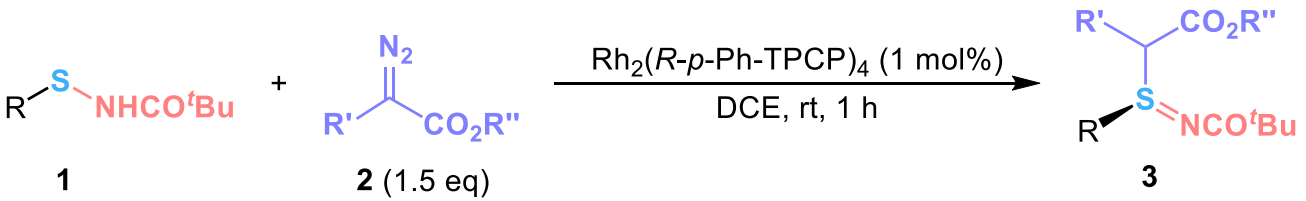


L = *R*-*p*-Ph-TPCP

Entry	Solvent	Conc. (M)	T	Yield (%)	Er (%)
1	DCM	0.2	rt	93	96:4
2	PhCl	0.2	rt	96	88:12
3	$CHCl_3$	0.2	rt	48	89:11
4	**DCE**	**0.2**	**rt**	**99**	**96:4**
5	DCE	0.05	rt	99	96.5:3.5
6	DCE	0.2	0 °C for 5 h	98	96:4
7	DCE	0.2	50 °C for 5 min	91	96:4

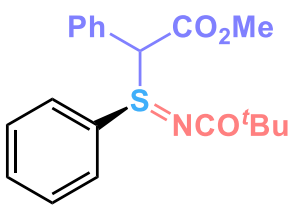
Enantioselective Sulfur Alkylation of Sulfenamides

Enantioselective S-Alkylation Scope

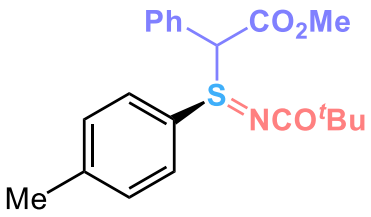


1 **2** (1.5 eq) **3**

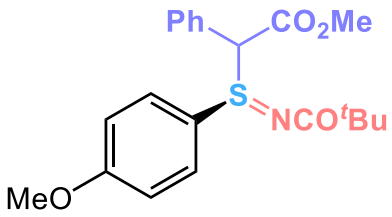
para-Substituents



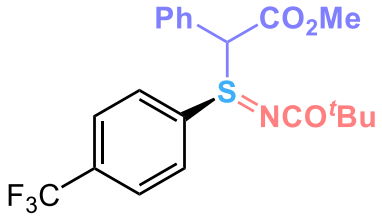
3n, 97%, 97:3 er



3o, 99%, 96.5:3.5 er

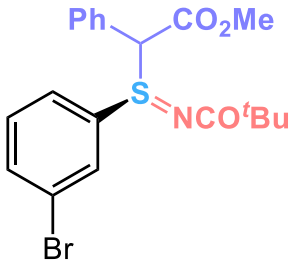


3p, 99%, 97.5:2.5 er

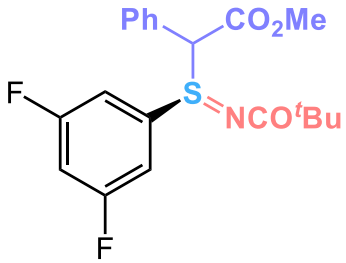


3q, 96%, 96:4 er

meta-Substituents

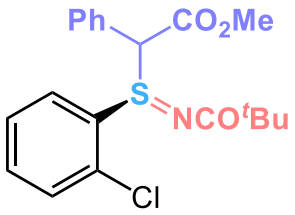


3r, 99%, 97:3 er

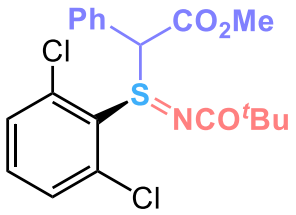


3t, 98%, 98:2 er

ortho-Substituents



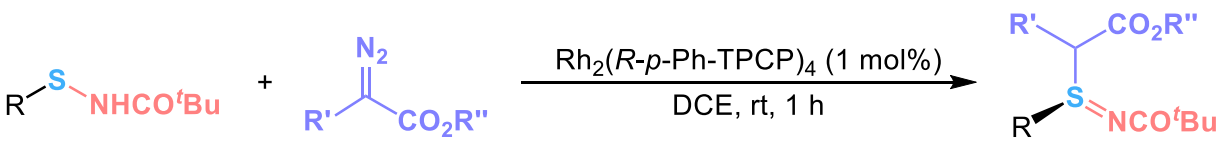
3u, 98%, 94:6 er



3w, 90%, 85:15 er

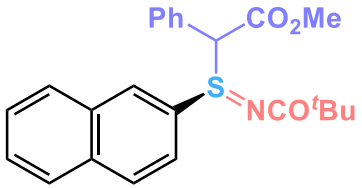
Enantioselective Sulfur Alkylation of Sulfenamides

Enantioselective S-Alkylation Scope

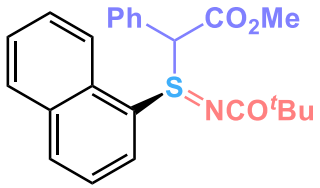


1 **2** (1.5 eq) **3**

Condensed Rings

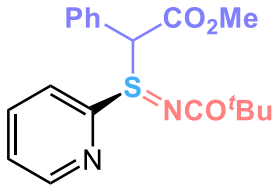


3s, 90%, 97.5:2.5 er

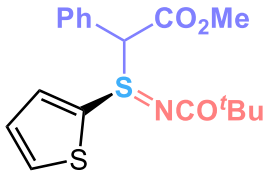


3v, 97%, 92:8 er

Aromatic Heterocycles

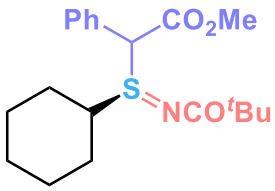


3x, 94%, 94:6 er

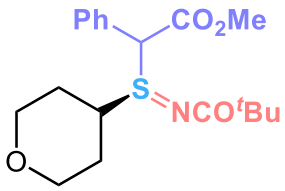


3y, 86%, 96:4 er

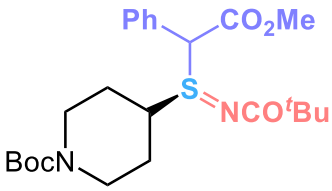
Alkyl Group



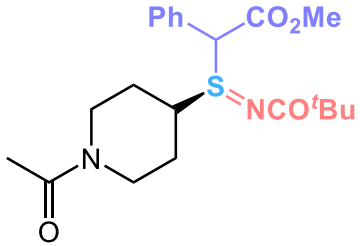
3z, 82%, 92:8 er[a]



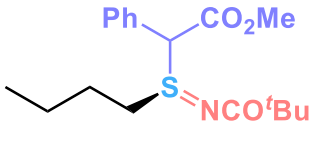
3aa, 66%, 92:8 er[a]



3ab, 91%, 93:7 er[a,b]



3ac, 69%, 90:10 er[a,c]

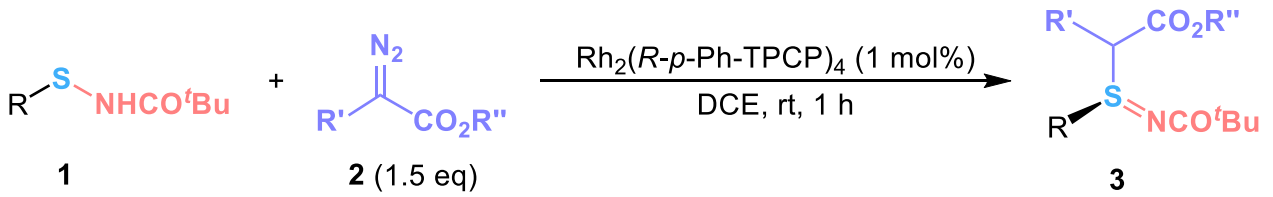


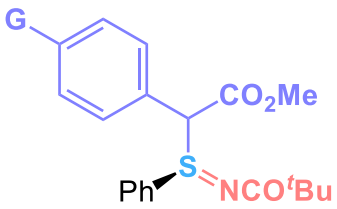
3ad, 71%, 62:38 er[a,b]

[a]40 °C. [b]2 h. [c]2 mol% catalyst

Enantioselective Sulfur Alkylation of Sulfenamides

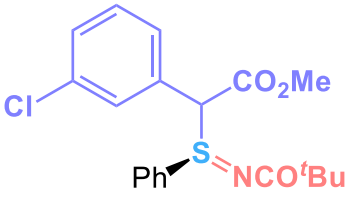
Enantioselective S-Alkylation Scope



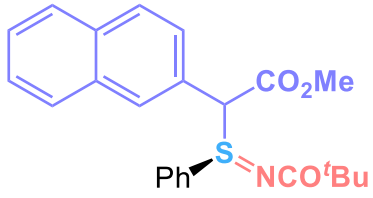


3ae, G = CF_3, 99%, 96:4 er
3af, G = Me, 93%, 95.5:4.5 er
3ag, G = OMe, 94%, 91:9 er
3ah, G = Cl, 94%, 95:5 er
3ai, G = Br, 95%, 96.5:3.5 er

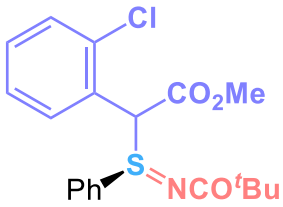
3aj, G = I, 93%, 95:5 er
3an, G = NO_2, 80%, 95:5 er[e]
3ao, G = CN, 94%, 95.5:4.5 er
3ap, G = CO_2Me, 99%, 94:6 er
3aq, G = ^{t}Bu, 93%, 95.5:4.5 er



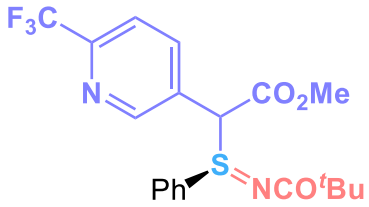
3ak, 99%, 96.5:3.5 er



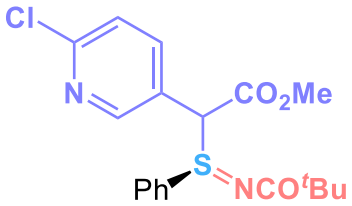
3al, 98%, 97:3 er



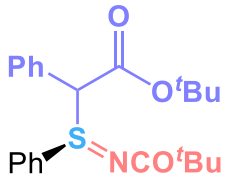
3am, 96%, 86:14 er[d]



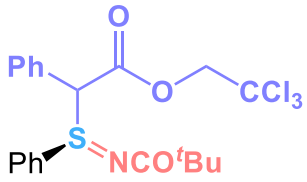
3ar, 99%, 93:7 er[b]



3as, 97%, 89:11 er[b]



3at, 98%, 92:8 er[b]

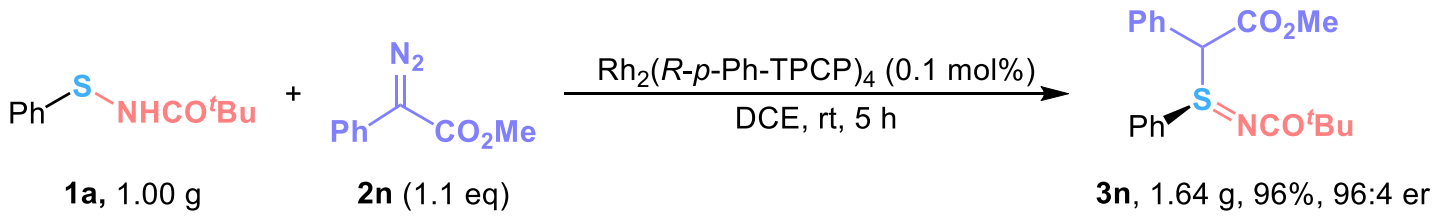


3au, 97%, 93:7 er

[b]2 h. [d]12 h. [e]20 h.

Enantioselective Sulfur Alkylation of Sulfenamides

Gram-Scale Reaction at 0.1 mol% Catalyst Loading

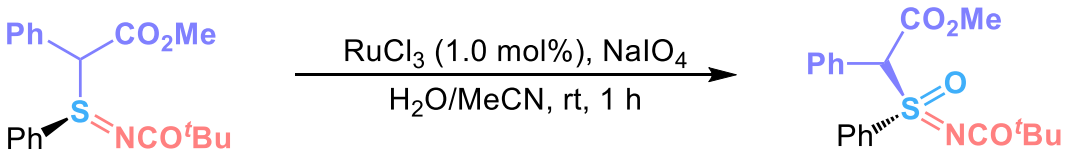


1a, 1.00 g

2n (1.1 eq)

3n, 1.64 g, 96%, 96:4 er

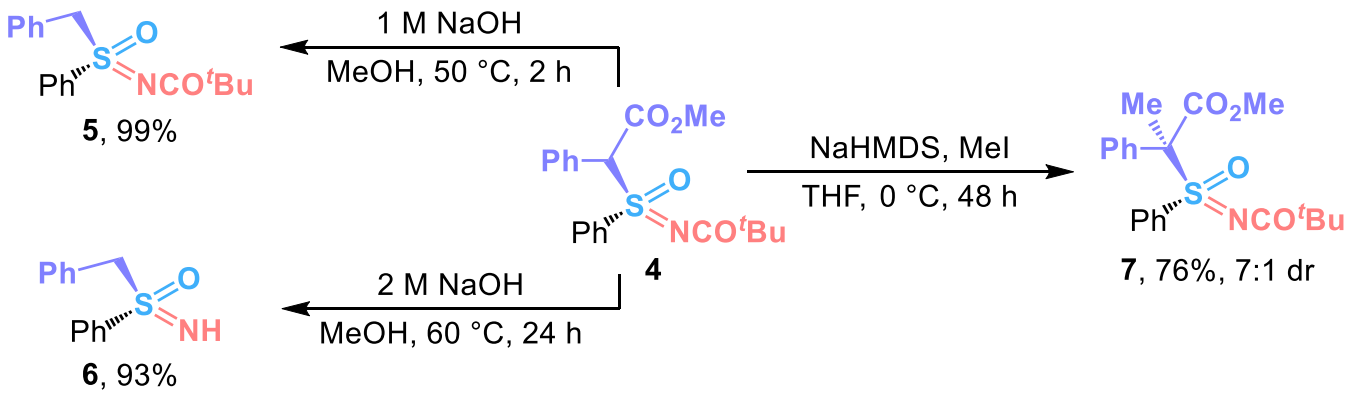
Stereospecific Oxidation to Sulfoximine



3n, 96:4 er

4, 88%, 96:4 er

Derivatizations of Enantioenriched Sulfoximine



5, 99%

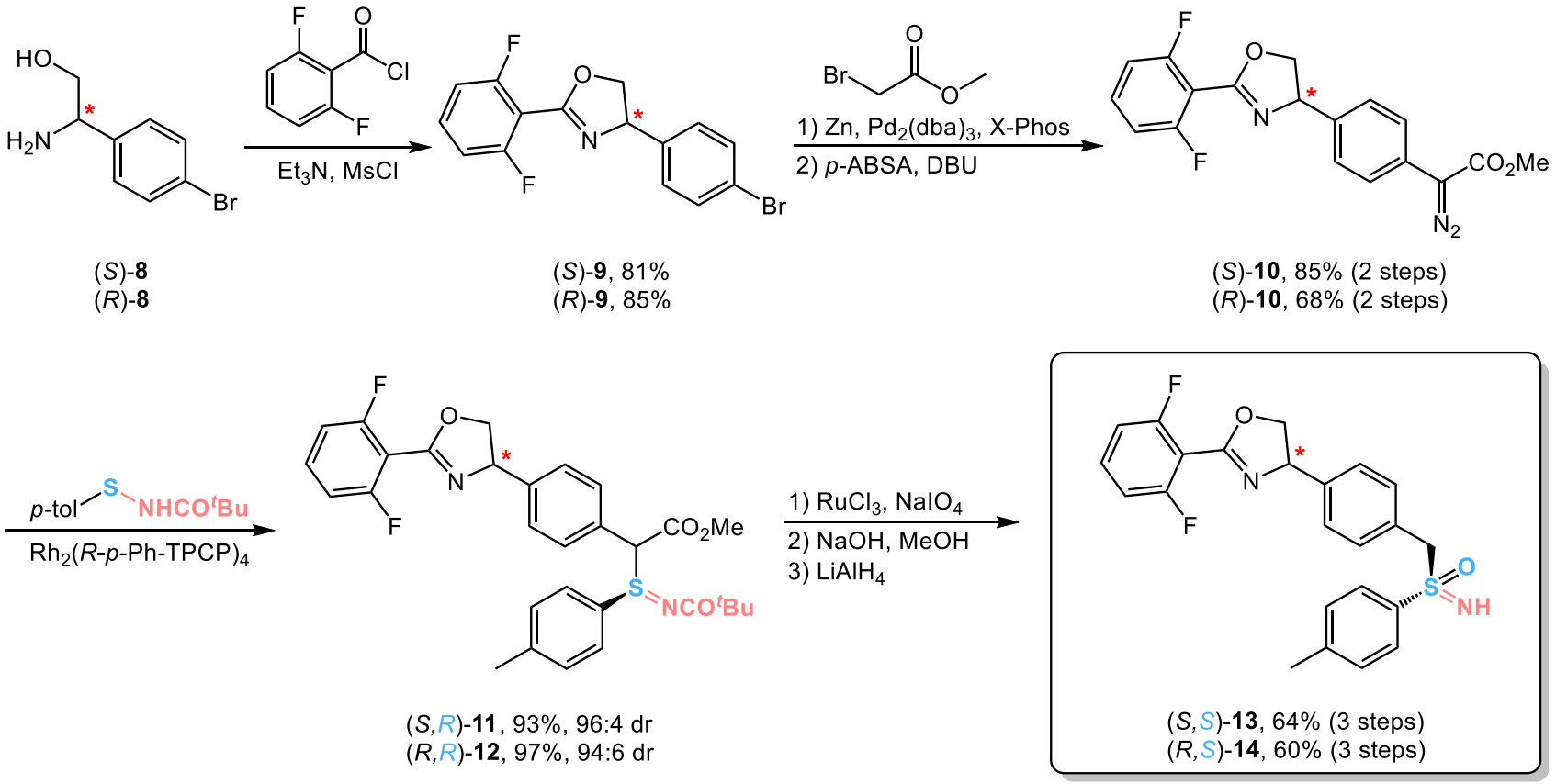
4

7, 76%, 7:1 dr

6, 93%

Enantioselective Sulfur Alkylation of Sulfenamides

Application to Stereoselective Agrochemical Syntheses



(*S*)-**8**
(*R*)-**8**

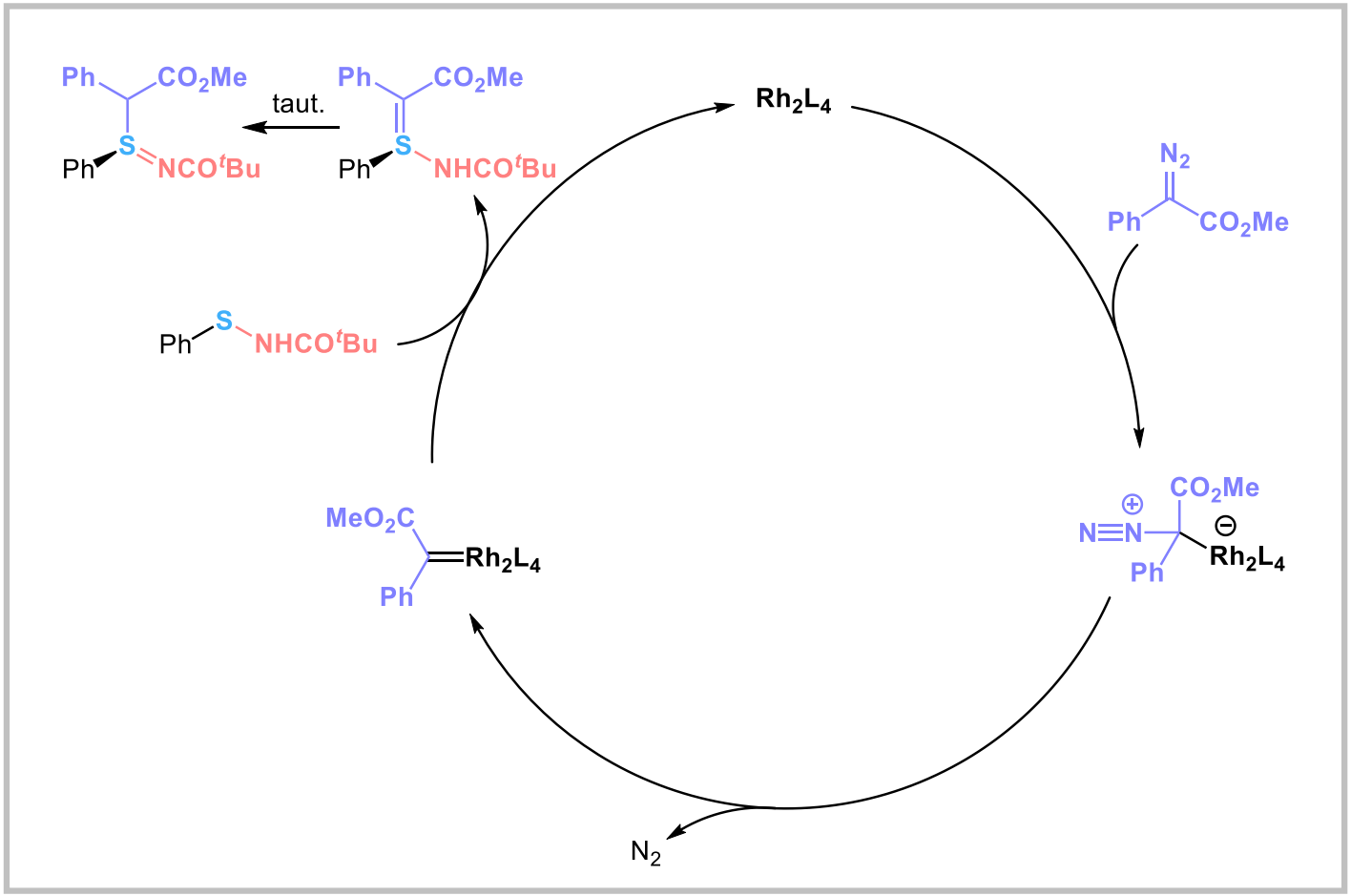
(*S*)-**9**, 81%
(*R*)-**9**, 85%

(*S*)-**10**, 85% (2 steps)
(*R*)-**10**, 68% (2 steps)

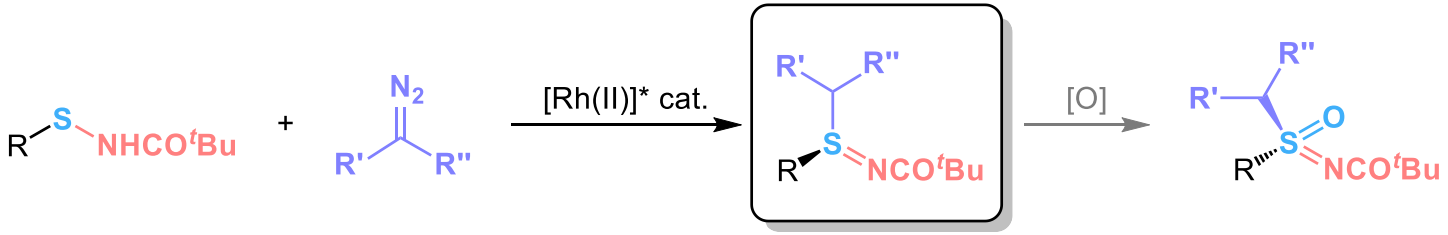
(*S*,*R*)-**11**, 93%, 96:4 dr
(*R*,*R*)-**12**, 97%, 94:6 dr

(*S*,*S*)-**13**, 64% (3 steps)
(*R*,*S*)-**14**, 60% (3 steps)

Enantioselective Sulfur Alkylation of Sulfenamides



Summary



First Example of Sulfenamide S-alkylation and Catalytic Enantioselective S-alkylation

Unprecedented sulfur alkylation

Readily available starting materials

Readily diversified to high-value sulfoximines

Writing Strategies

☐ The First Paragraph

The importance of sulfoximines

↓

Limitation of accessing chiral sulfoximines

↓

The necessity to develop new approach

✓ Sulfoximines, the monoaza analogues of sulfones, have attracted considerable attention as privileged functional groups in medicinal chemistry.

✓ Sulfoximines are now established pharmacophores in medicinal chemistry, but their stereocontrolled synthesis can be challenging and limits wider implementation.

✓ With this challenge in mind, we focused on a new approach for the asymmetric synthesis of sulfoximines by enantioselective sulfur alkylation of readily available sulfenamide inputs followed by sulfilimine oxidation.

Writing Strategies

☐ The Last Paragraph

Summary of the work

✓ In summary, we have reported the catalytic enantioselective synthesis of sulfilimines by an unprecedented sulfur alkylation of readily accessible sulfenamides.

Advantages of the current approach

✓ This transformation is compatible with a range of reaction inputs, and the products are readily diversified to high-value sulfoximines.

Outlook of this work

✓ We anticipate that the reported method will serve as a platform for the further discovery and development of medicinally relevant sulfoximine-containing compounds.

Representative Examples

- ✓ The coupling was **sluggish** (*adj.* **缓慢的，迟钝的，懒洋洋的；性能欠佳的**) in the absence of any acid additive.

- ✓ Although the electronic effect of the acid is also **convoluted** (*adj.* **复杂的；费解的；旋绕的**), there is no direct correlation of this effect with the enantioselectivity of the reaction.

- ✓ **Drawing motivation from** (**从...中汲取灵感**) the elegant studies by Davies et al. and others on the development of donor−acceptor diazocompounds for Rh(II)-catalyzed enantioselective transformations such as C−H functionalization and cyclopropanation.

Acknowledgement

Thanks for your attentions!