Literature Report 9

A Bifunctional Chiral Disulfide Catalyst for Highly Enantioselective Anti-Markovnikov Hydrophosphinylation

Reporter: Bao-Qian Zhao
Checker: Yan-Jiang Yu
Date: 2025-09-29

Tang, L.; Hao, S.; Shen, S.; Dong, K. *J. Am. Chem. Soc.* **2025**, *147*, 34231

CV of Prof. Dong Kaiwu (董开武)

Research:

Continuous Microchannel Reaction & Conversion of Unsaturated C1 and C4 Compounds

Background:

- **2004-2008** B.S., East China Normal University
- **2008-2013** Ph.D., Shanghai Institute of Organic Chemistry
- **2013-2018** Postdoc., Leibniz-Institut für Katalyse
- **2018-now** Professor, East China Normal University

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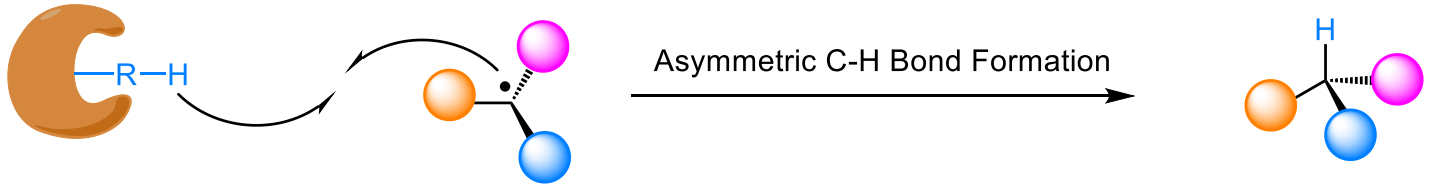
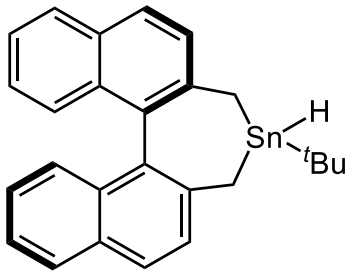
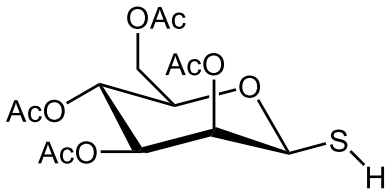
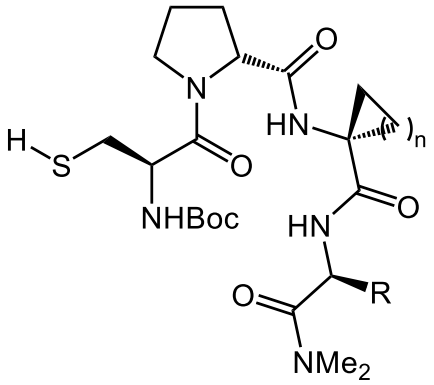




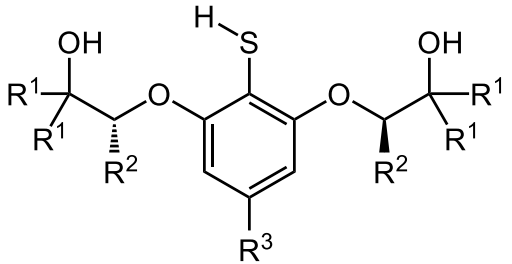
1997, Metzger



2002, Roberts
2022, Ye

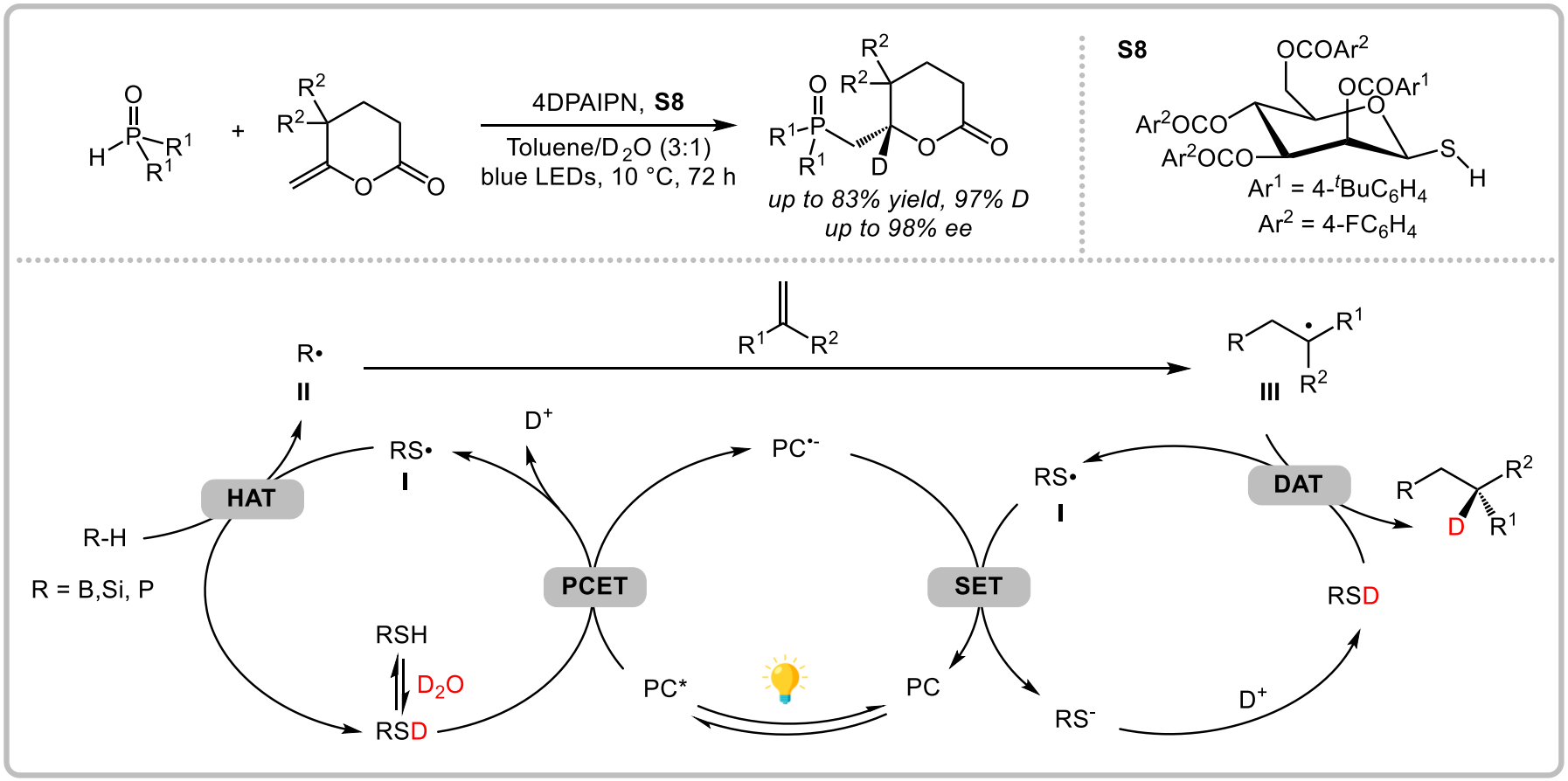


2019, Knowles & Miller
2022, Ye



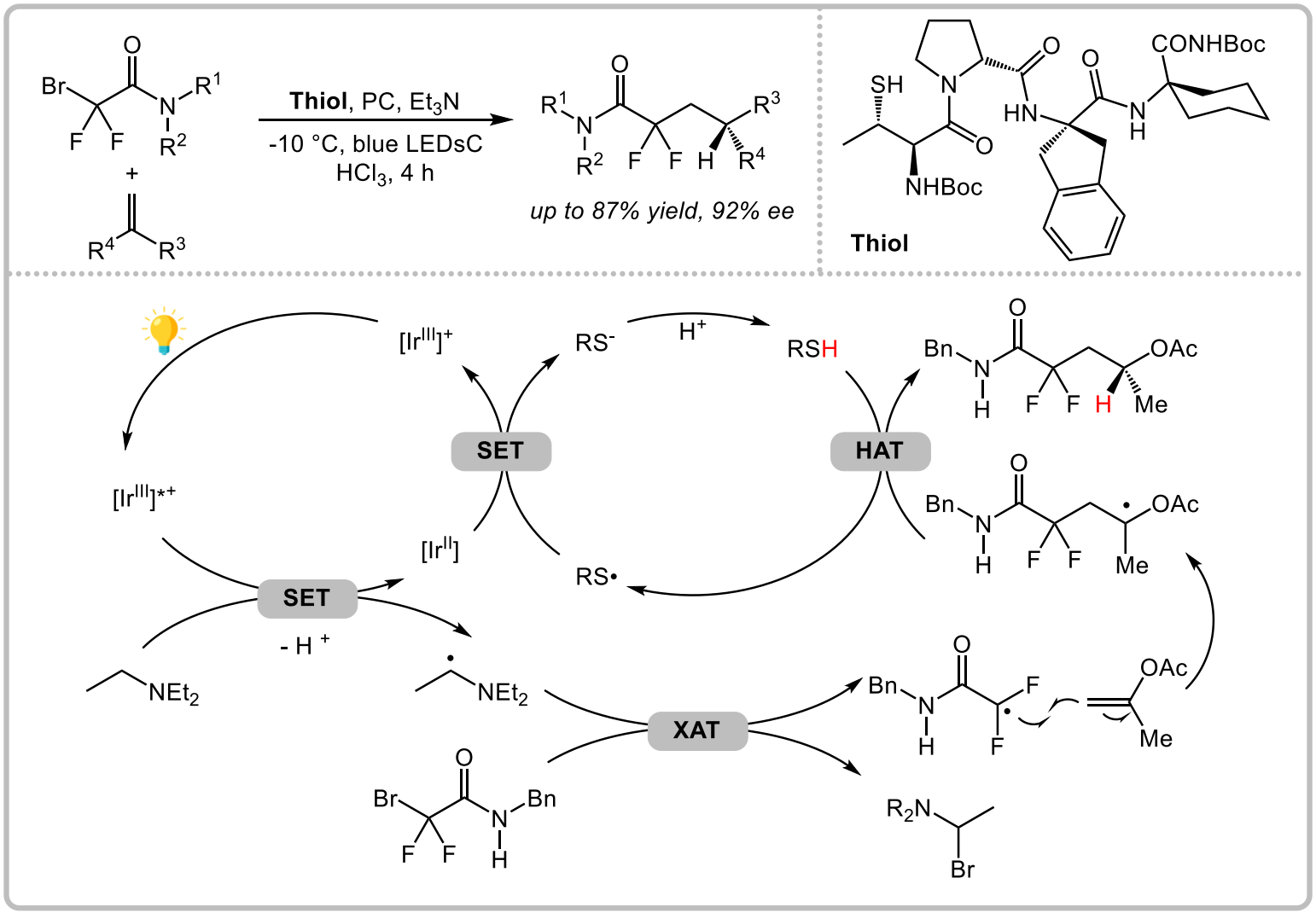
2024, Dong

Introduction



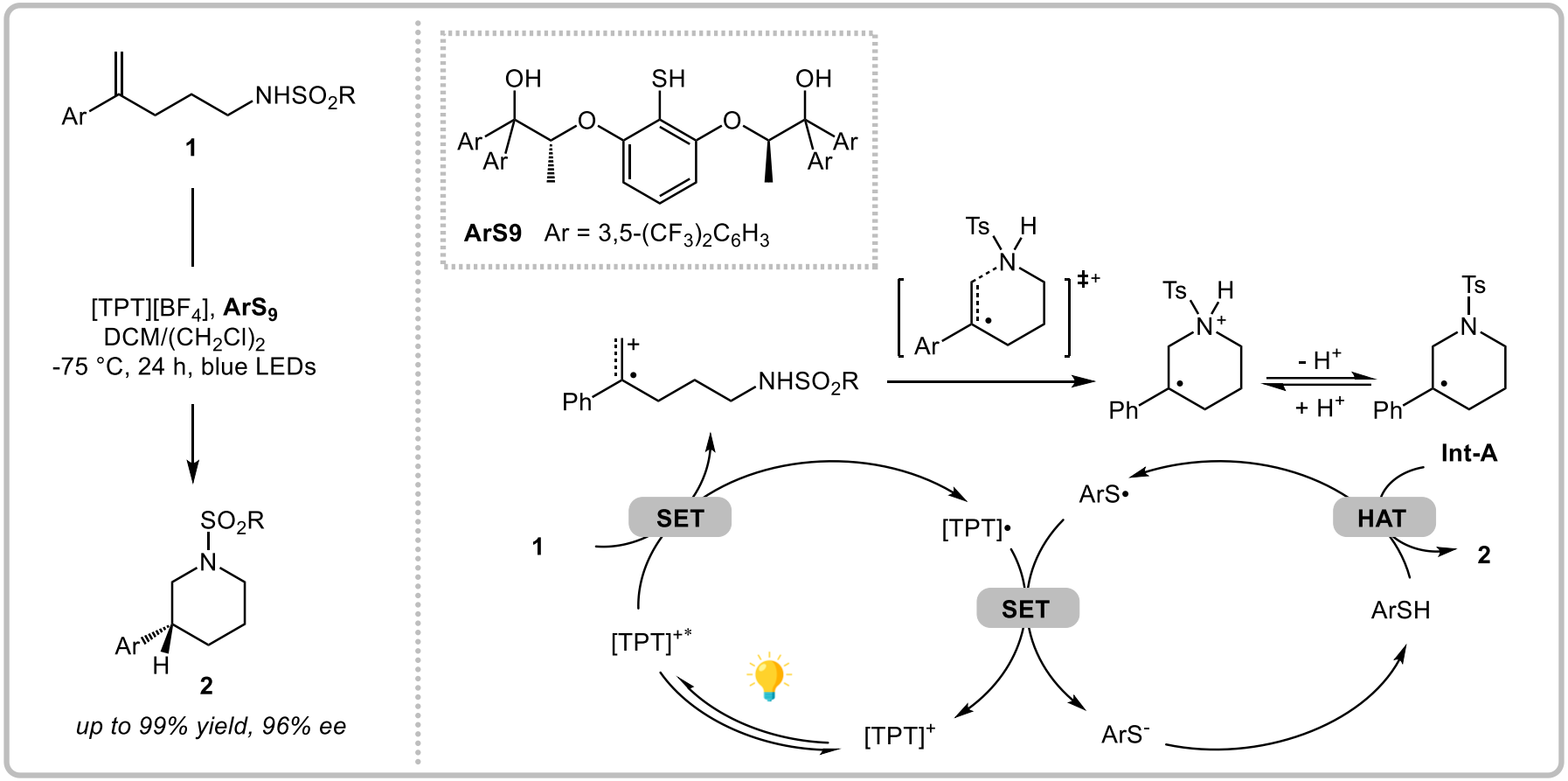
Shi, Q.; Xu, M.; Chang, R.; Ramanathan, D.; Peñin, B.; Ye, J. *Nat. Commun.* **2022**, *13*, 4453

Introduction



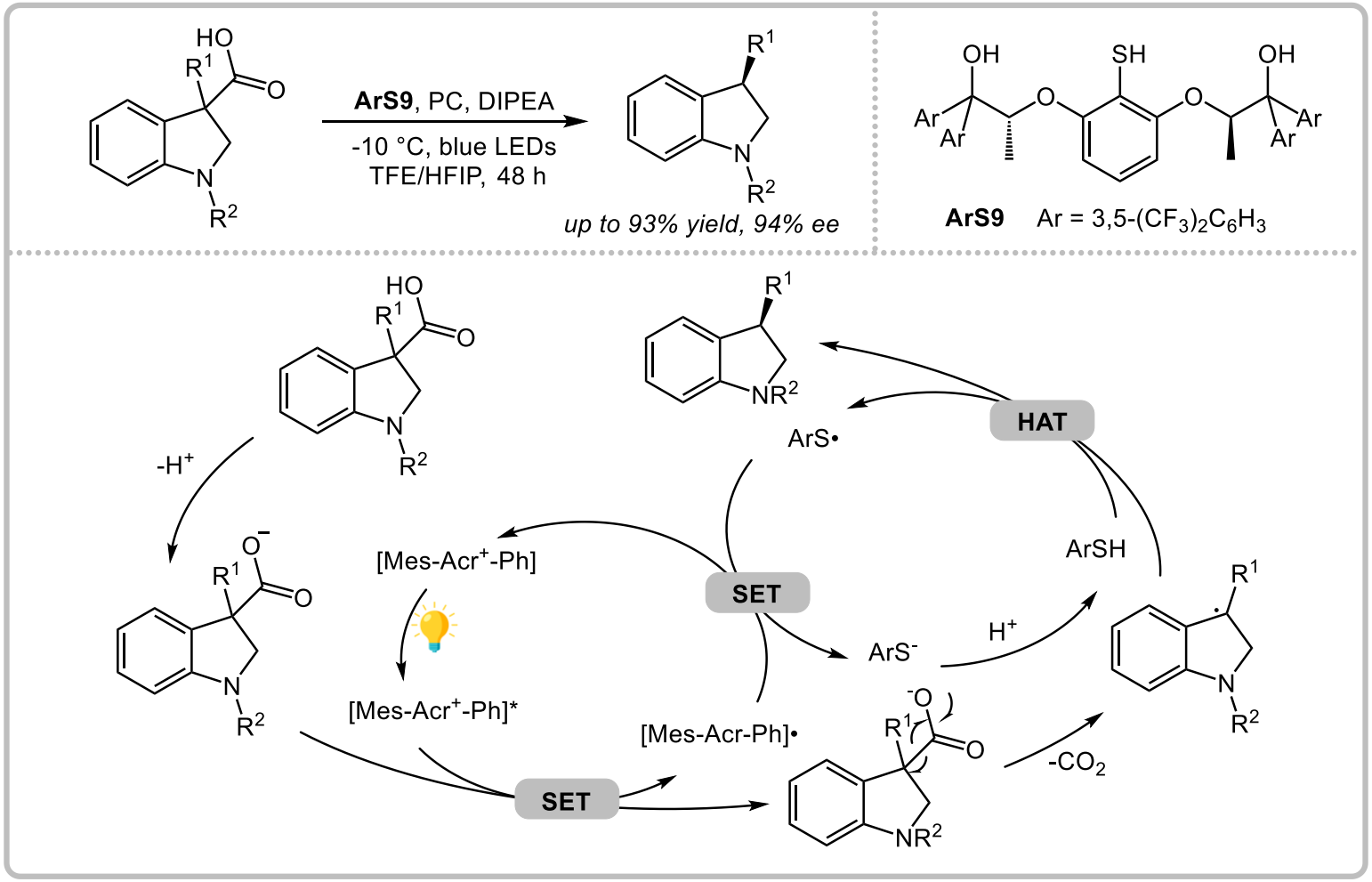
Mayer, J. M.; Houk, K. N.; Knowles, R. R.; Miller, S. J. *J. Am. Chem. Soc.* **2025**, *147*, 11412

Introduction



Tang, L.; Shen, C.; Hao, S.; Dong, K. *J. Am. Chem. Soc.* **2024**, *146*, 16248

Introduction



Xu, Y.; Shen, C.; Dong, K. *J. Am. Chem. Soc.* **2025**, *147*, 6259

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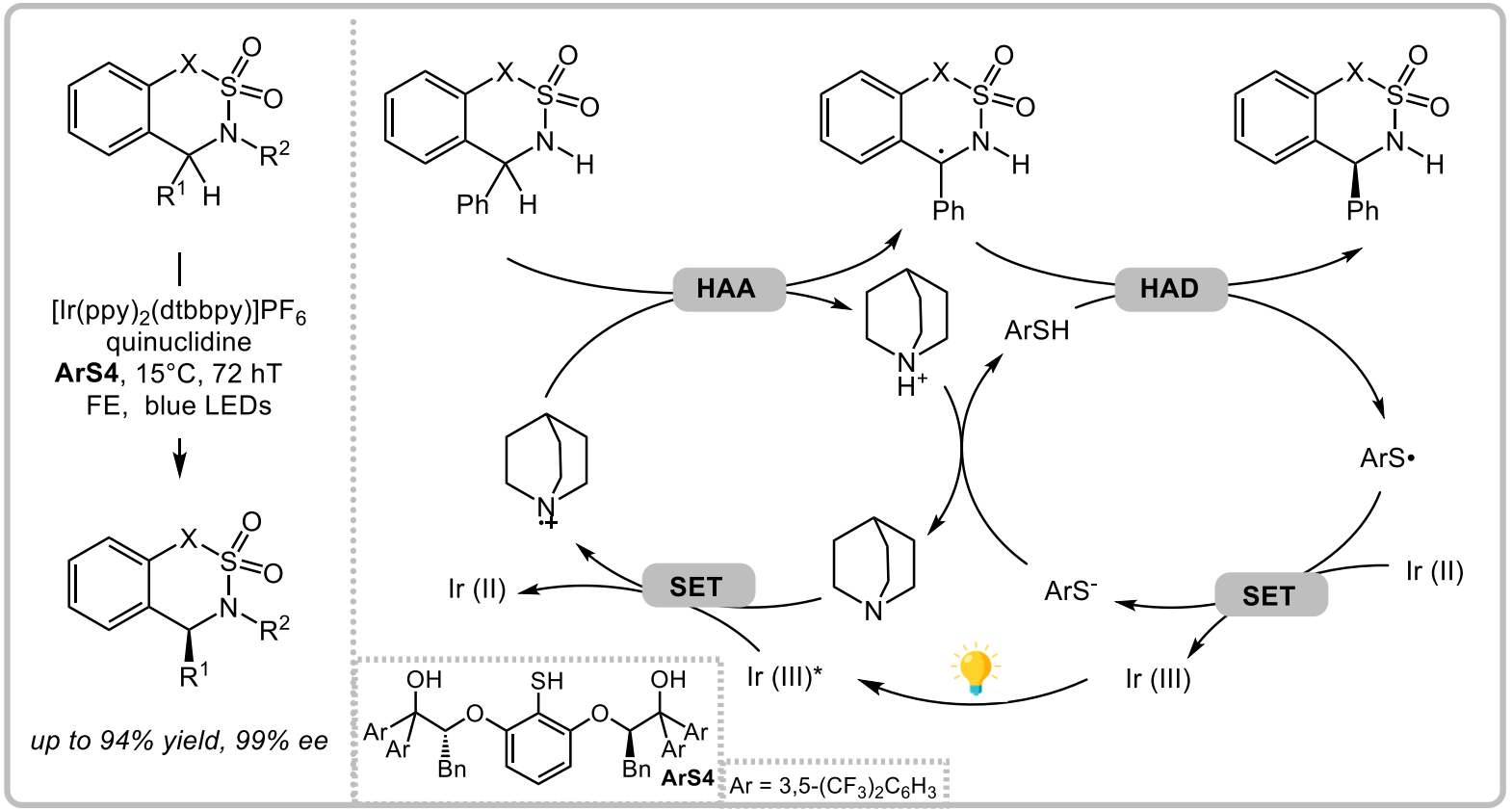
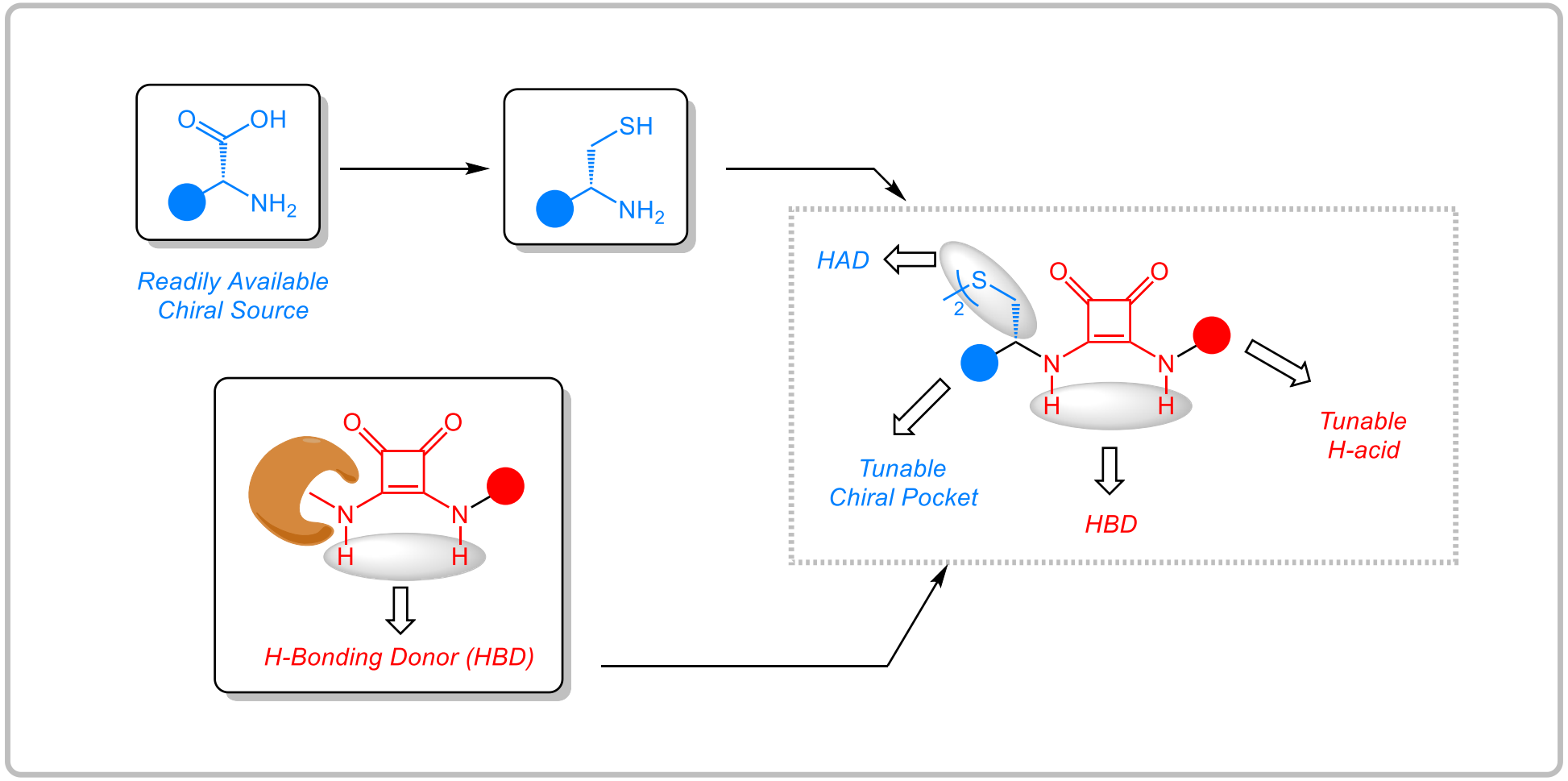


Dai, L.; Wang, J.; Shen, C.; Li, Y. Z.; Dong, K. *Angew. Chem., Int. Ed*. **2025**, *64*, e202505719

Introduction



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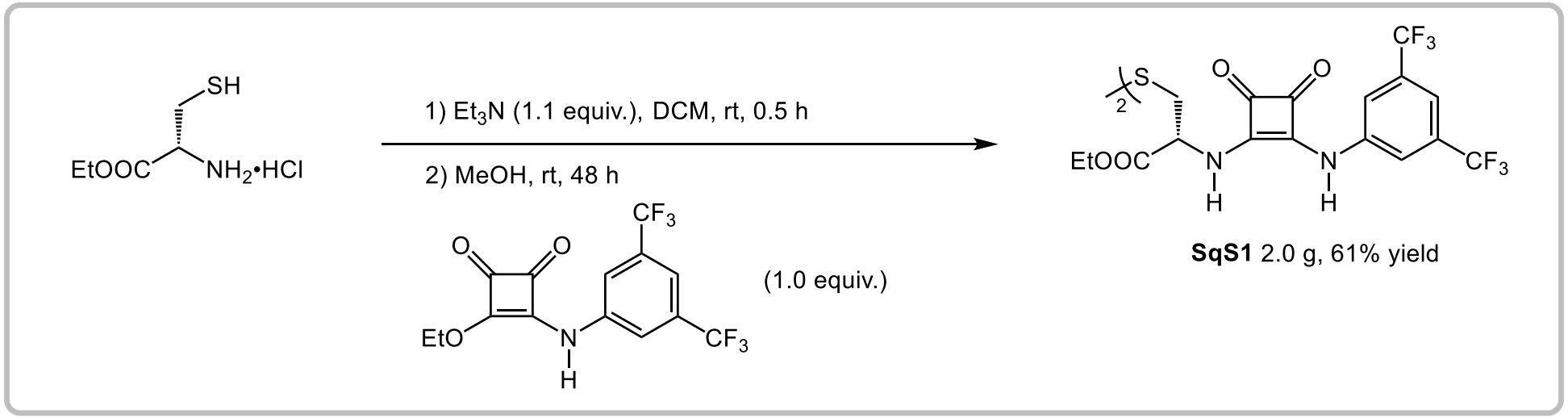
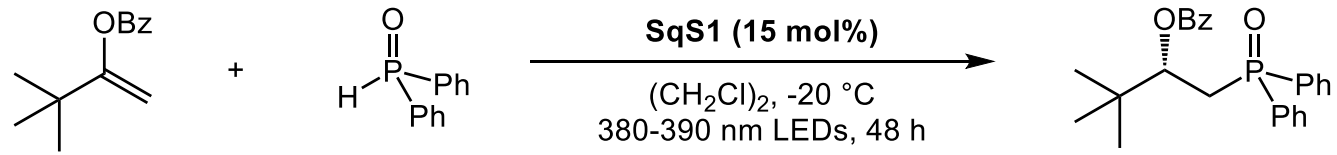
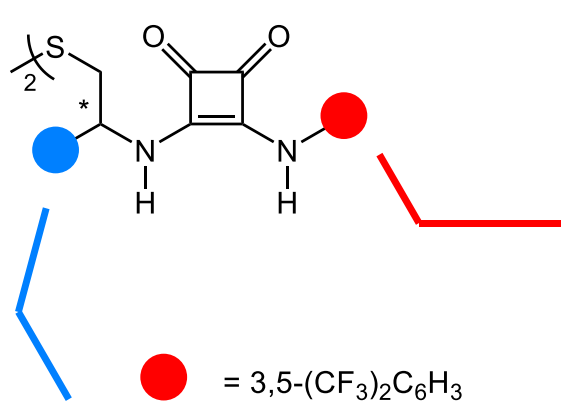


SqS1 2.0 g, 61% yield

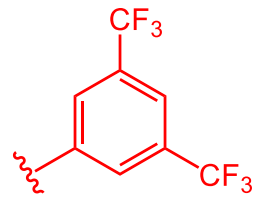
Conditions Optimization



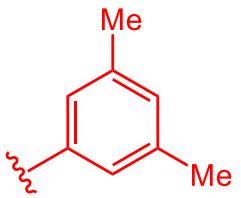


= COOEt

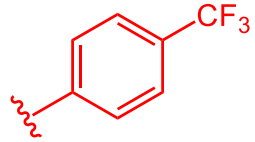
= 3,5-$(CF_3)_2C_6H_3$



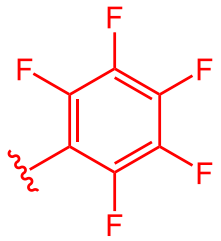
SqS1 86%, 94% ee



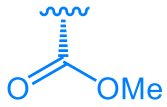
SqS2 63%, 90% ee



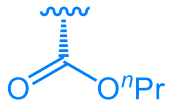
SqS3 54%, 88% ee



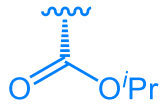
SqS4 50%, 77% ee



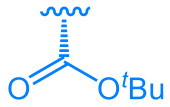
SqS5 70%, 92% ee



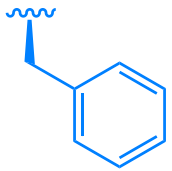
SqS6 64%, 92% ee



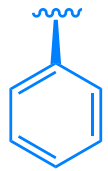
SqS7 68%, 91% ee



SqS8 60%, 90% ee

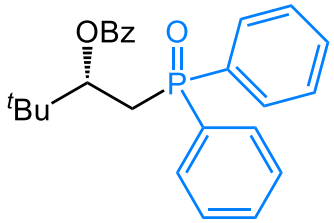


SqS9 62%, -70% ee

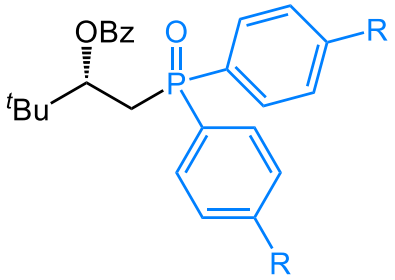


SqS10 30%, -49% ee

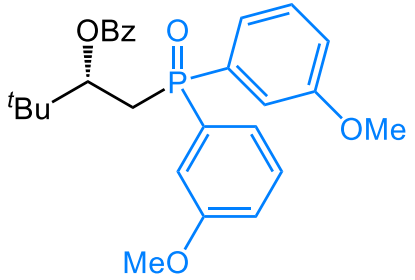
Phosphine Oxide Scope



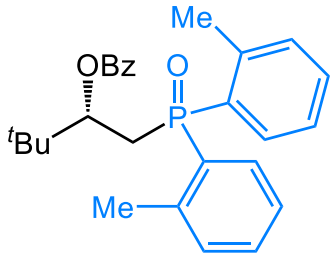
3a 78%, 94% ee



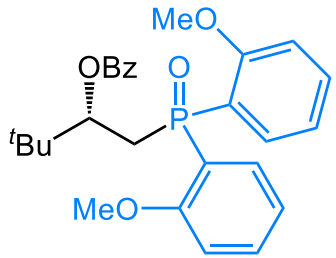
3b R = F, 50%, 94% ee
3c R = Cl, 51%, 88% ee
3d R = Br, 63%, 81% ee
3e R = Ph, 45%, 82% ee
3f R = Me, 31%, 90% ee
3g R = *t*-Bu, 86%, 87% ee
3h R = OMe, 69%, 92% ee



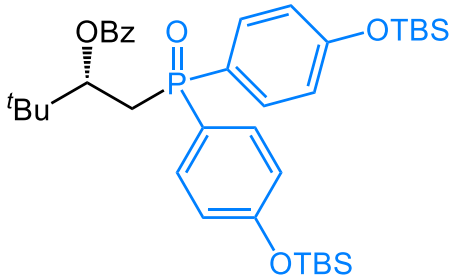
3i 30%, 90% ee



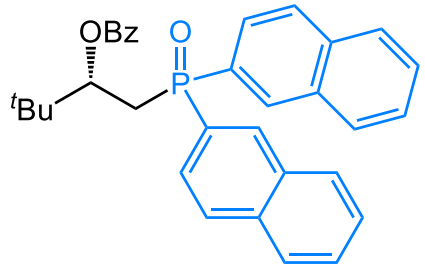
3j 51%, 97% ee



3k 94%, 63% ee

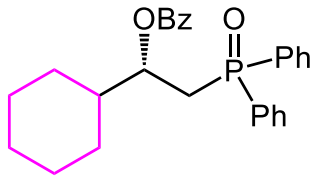


3l 60%, 96% ee

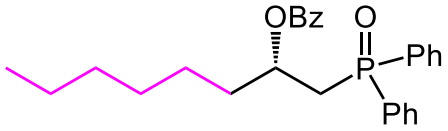


3m 57%, 93% ee

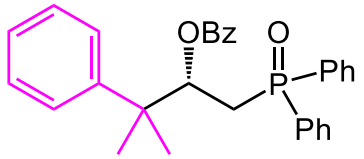
Alkene Scope



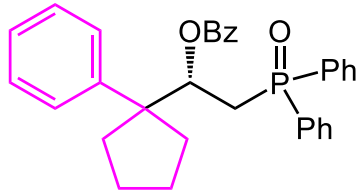
3r 45%, 80% ee



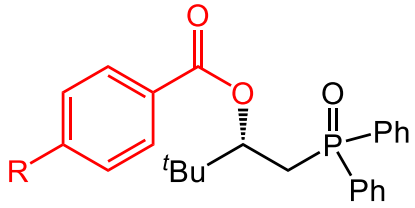
3s 25%, 54% ee



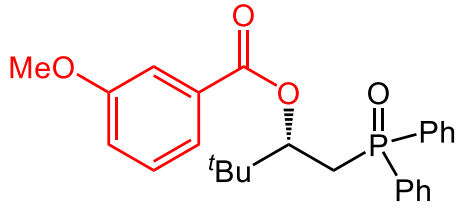
3u 22%, 91% ee



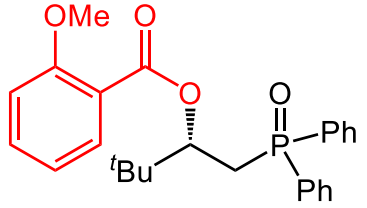
3v 22%, 92 % ee



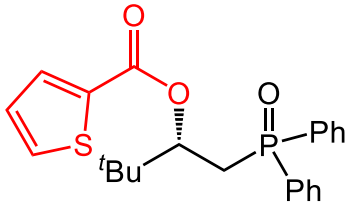
3w R = Br, 89%, 90% ee
3x R = CN, 98%, 85% ee
3y R = Me, 61%, 94% ee
3z R = *t*-Bu, 76%, 92% ee
3aa R = OMe, 74%, 92% ee



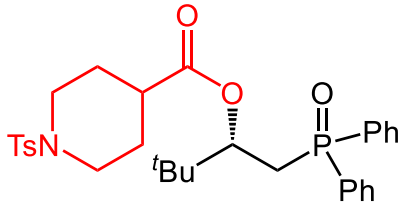
3ab 72%, 94% ee



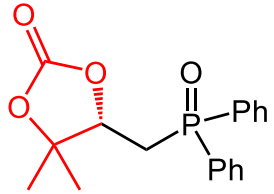
3ac 62%, 94% ee



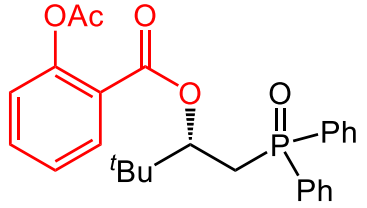
3af 42%, 99% ee



3ag 46%, 72% ee



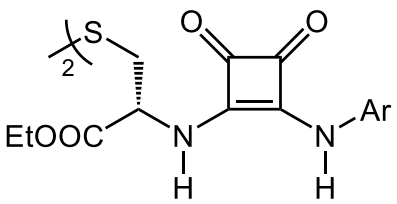
3ah 32%, 66% ee



3al 44%, 95% ee

Radical Trapping

Thiyl Radical Trapping



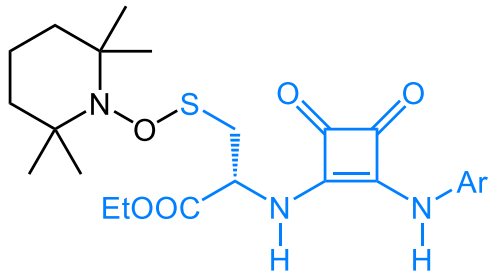
Ar = 3,5-$(CF_3)_2C_6H_3$

SqS1 (1 equiv.)

TEMPO (8 equiv.)

$(CH_2Cl)_2$, -20 °C

380-390 nm LEDs, 48 h

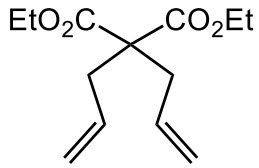


TEMPO-SqS1

detected by HRMS, $[M+Na]^+$

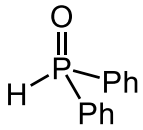
Cal. 634.1781, Found: 634.1790

Phosphine Radical Trapping



4 (3 equiv.)

+

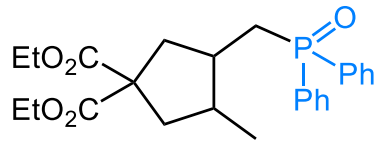


2a

SqS1 (15 mol%)

$(CH_2Cl)_2$, -20 °C

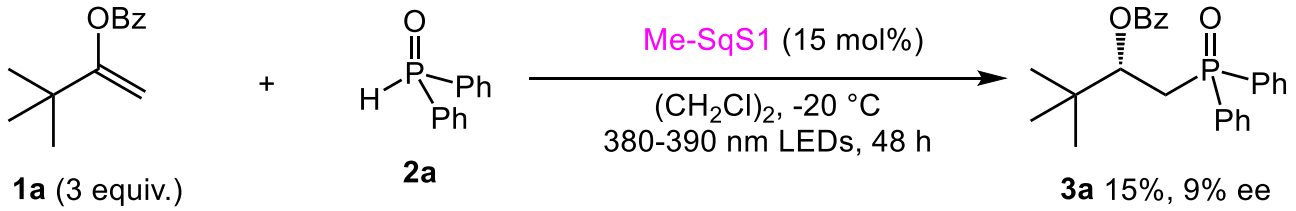
380-390 nm LEDs, 48 h



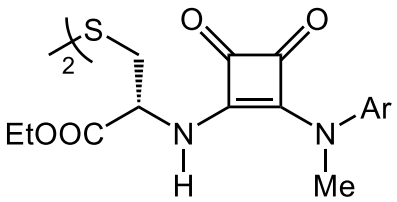
5, 18%, 14:1 dr

Study of Squaramide Scaffold

Investigation of Hydrogen Bonding Donor



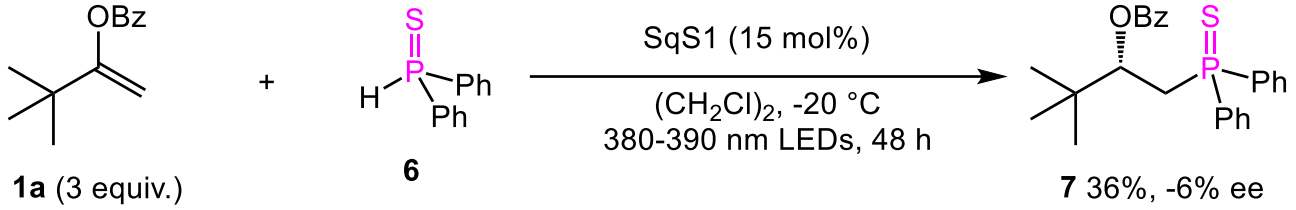
1a (3 equiv.) + **2a** → **3a** 15%, 9% ee



Ar = 3,5-$(CF_3)_2C_6H_3$

Me-SqS1

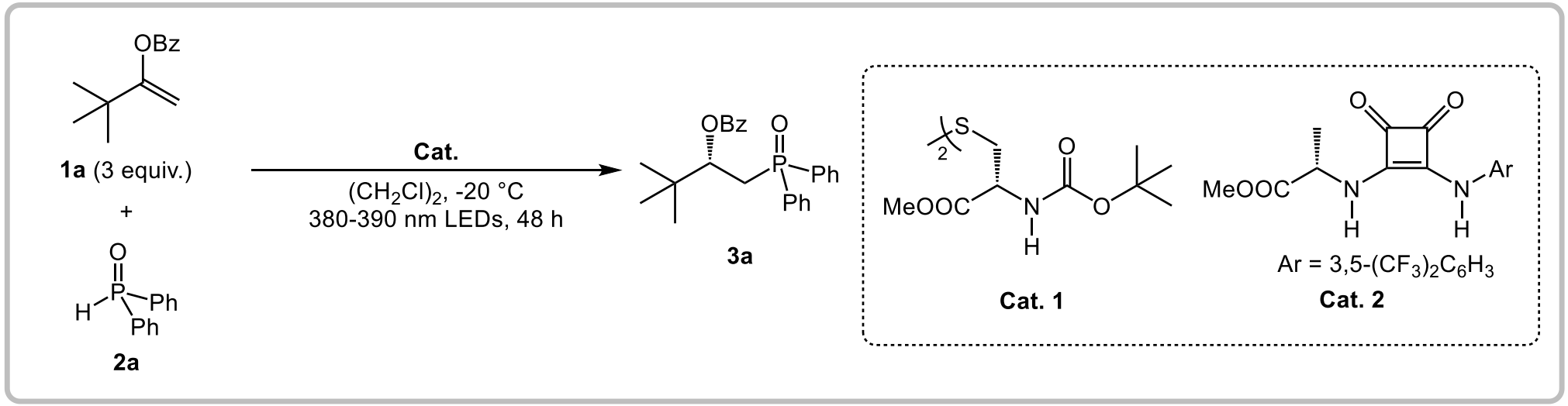
Investigation of Hydrogen Bonding Acceptor



1a (3 equiv.) + **6** → **7** 36%, -6% ee

Investigation of Module Combination

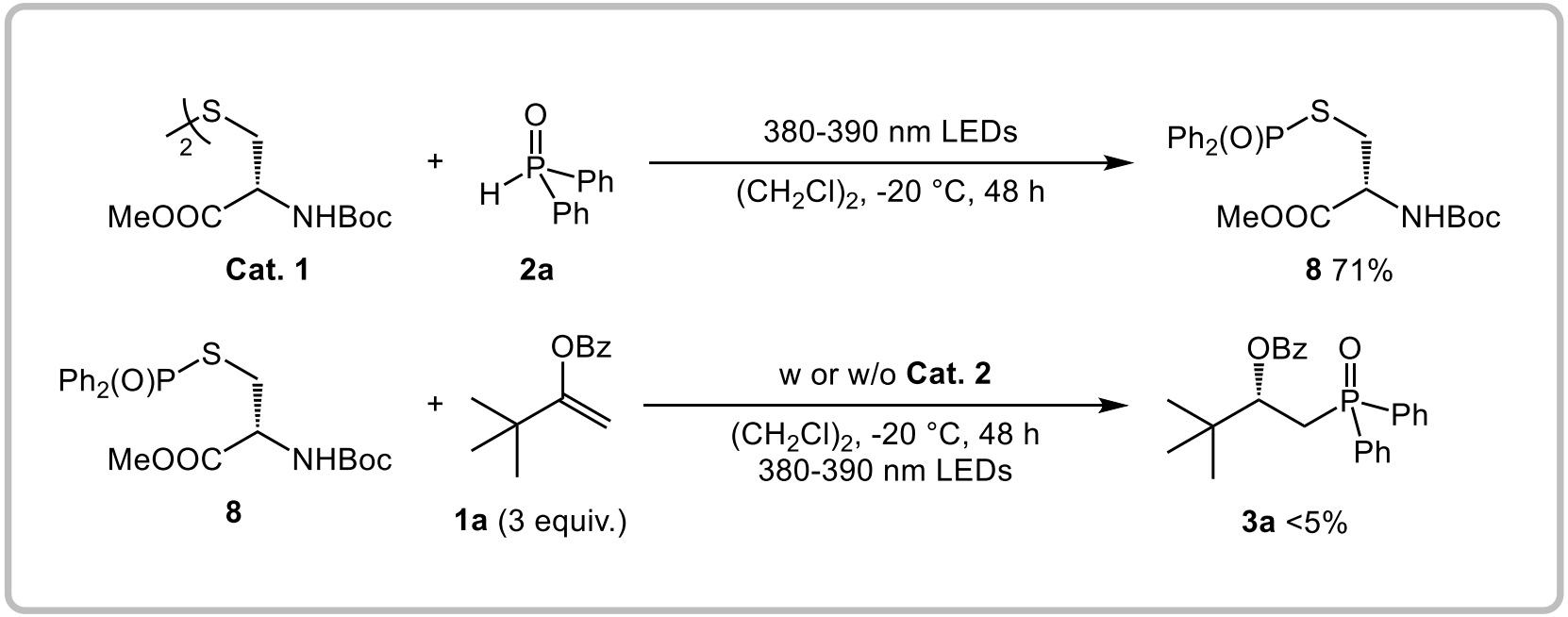
✓ **Experiment for Necessity of Module Combination**



Entry	Cat.	3a (%)	Ee (%)
1	**SqS1 (15 mol%)**	86	94
2	**Cat. 1 (15 mol%)**	-	-
3	**Cat. 2 (30 mol%)**	9	18
4	**Cat.1 (15 mol%) + Cat. 2 (30 mol%)**	15	12

Investigation of Module Combination

✓ **Research on Reactivity Promotion by Affording [S-P] Species**



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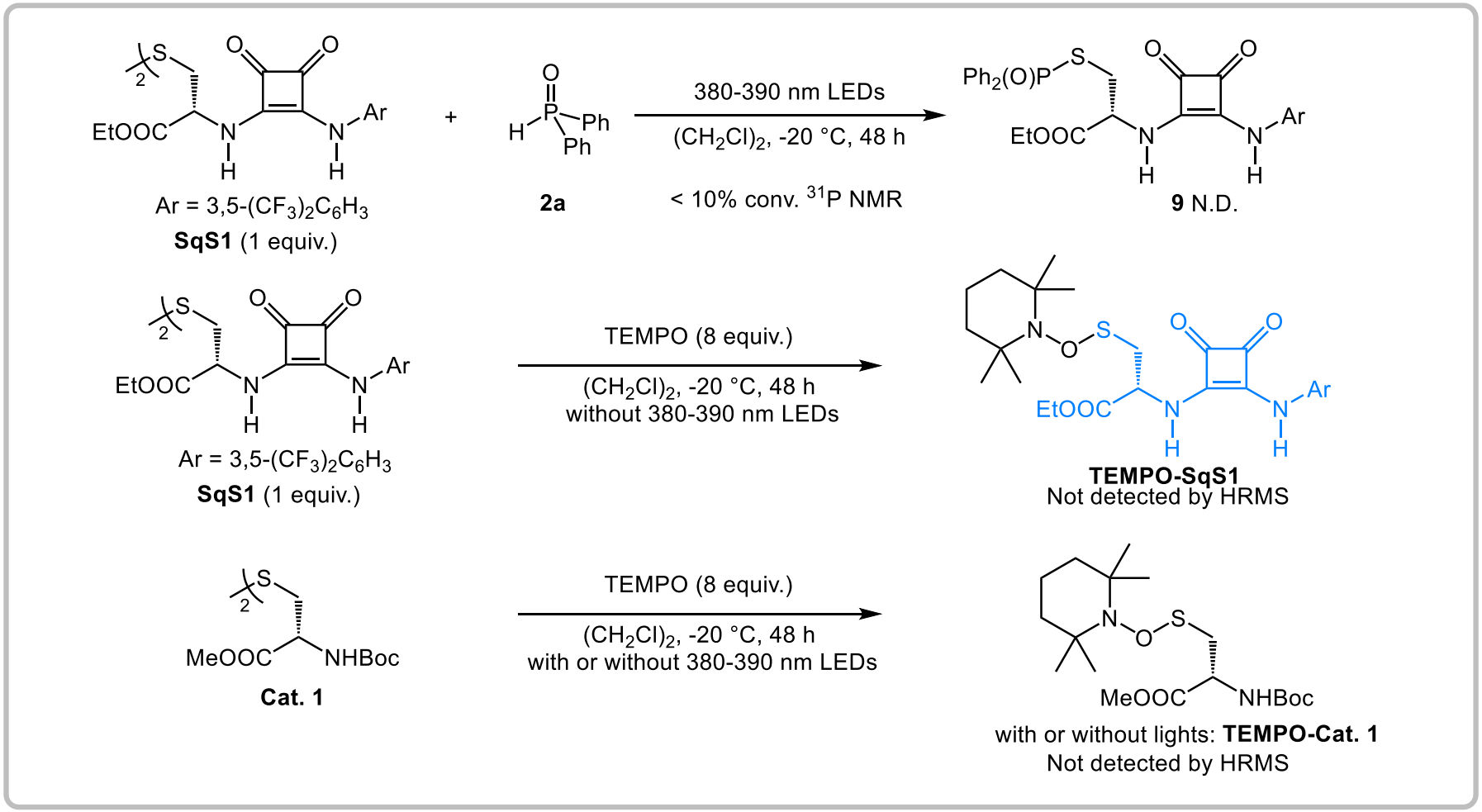
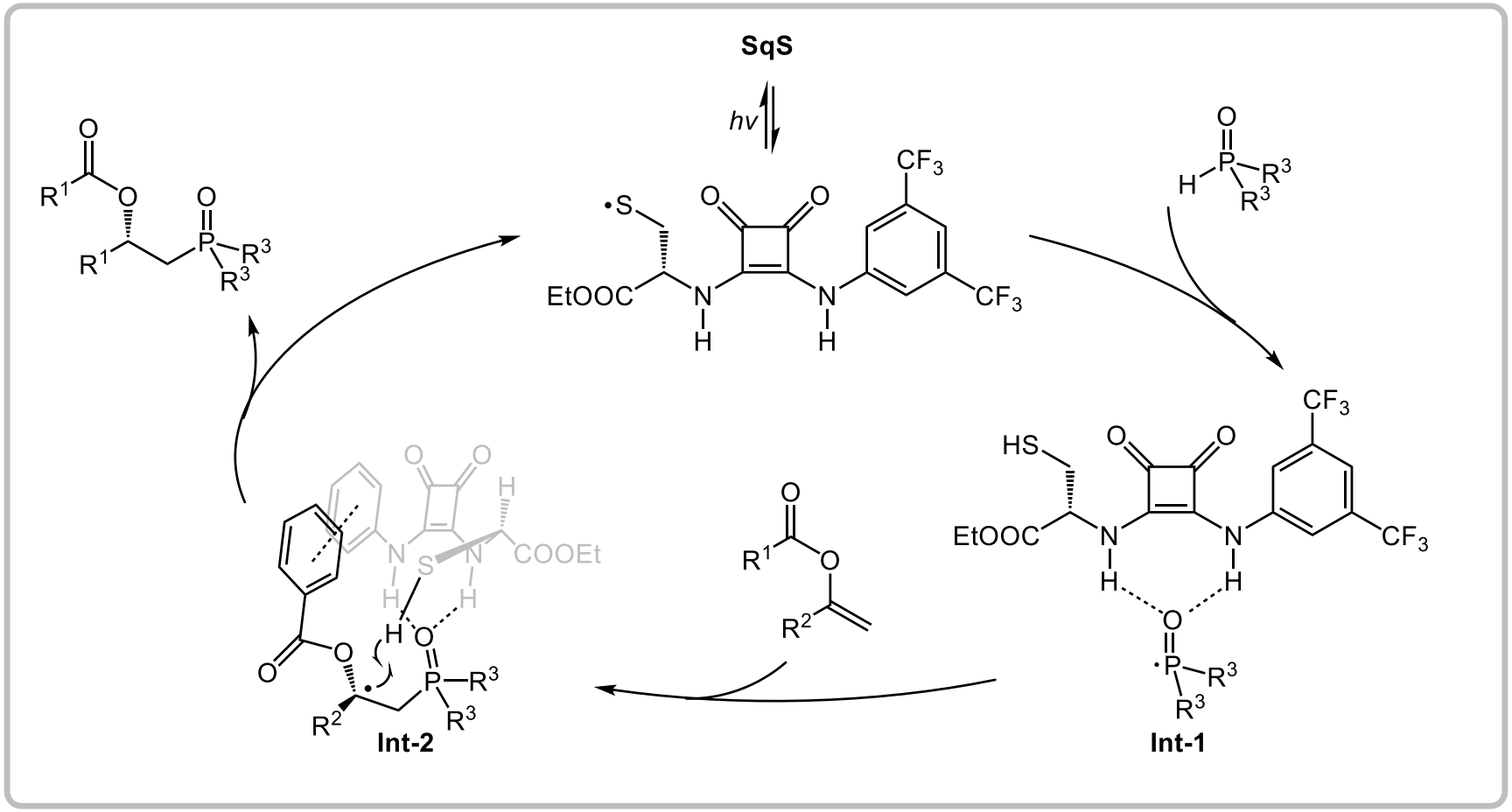
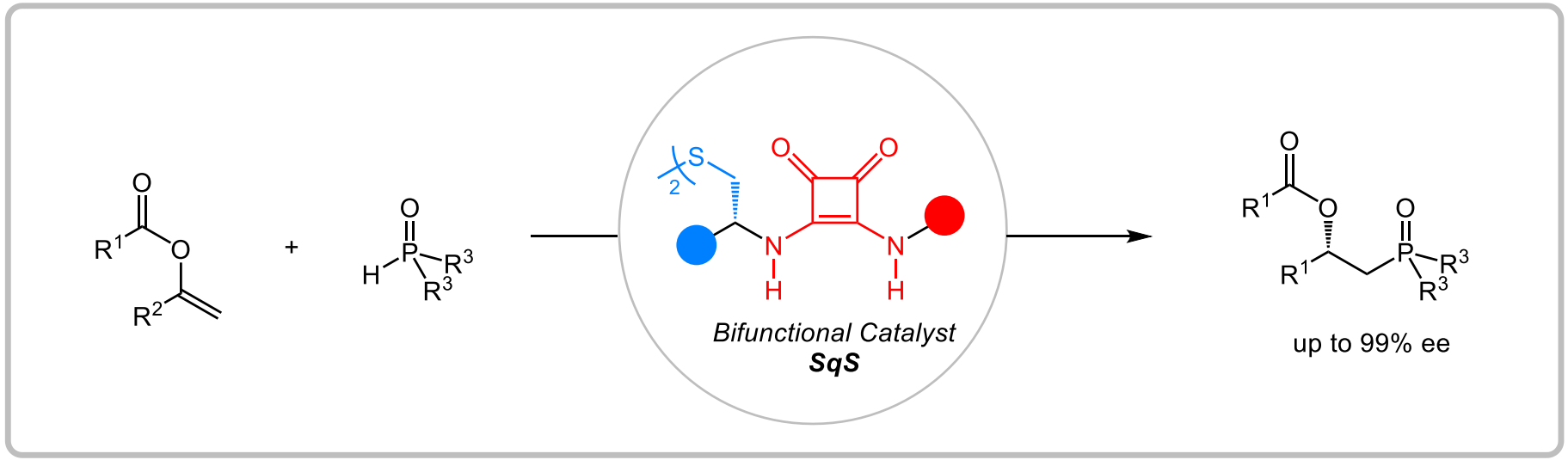


Proposed Mechanism



Summary



- A Type of H-bonding HAT Catalysts were Developed
- A Series of Chiral *β*-Hydroxyphosphine Oxides with Acceptable Yield

Writing Strategies

☐ The First Paragraph

Introduction of HAT

↓

Previous Work

↓

Main Content of This Work

✓ Hydrogen atom transfer (HAT) to carbon-centered radicals constitutes a fundamental elementary step in both chemistry and biological systems. Because of the relatively high reactivity and conformational mobility of free radical intermediates, achieving acceptable enantioselectivity in constructing tertiary stereogenic centers remains a long-standing challenge.

✓ To address this, several elegant small molecules, including an axially chiral organotin hydride and mannose- and peptide-derived alkylthiols, have been developed as hydrogen atom delivery (HAD) catalysts by Metzger, Roberts, and Knowles and Miller during the last decades.

✓ Consequently, developing advanced chiral catalysts capable of effectively inducing stereoselectivity in the HAD step is crucial in contemporary asymmetric organocatalysis.

Writing Strategies

☐ The Last Paragraph

Summary of This Work

Highlights of the Current Method

Outlook of This Work

✓ In conclusion, an unprecedented type of H-bonding HAT catalysts integrating squaramide and amino acid derivative motifs were developed through modular synthesis. These catalysts feature tunable acidity of the H-bond donor and steric hindrance of the chiral pocket. .

✓ Results of the mechanism experiments verify the critical role of the squaramide scaffold in enantioselectivity control and activity enhancement as well as the necessity of integrating the disulfide moiety with the squaramide unit within a single molecule.

✓ We believe that the modular synthesis, flexible tunability, and effective enantioselectivity-controlling capability of these catalysts will stimulate the development of versatile chiral HAT catalysts and related asymmetric reactions.

Representative Examples

- ✓ The critical role of the H-bonding interactions between the squaramide scaffold and radical intermediates in controlling the enantioselectivity and improving the catalytic reactivity was **validated**. (**证实，证明**)

- ✓ **Last but not least**, (**最后但并非不重要的是**) the hydrophosphinylation of N-tosyl piperidinyl and methylenecarbonate substrates proceeded smoothly in synthetically useful yield and enantioselectivity (**3ag** and **3ah**).

- ✓ In contrast, the C6 stereocenter **underwent** (**经历**) the complete epimerization, resulting in the cis-configuration between C6 and C7.

Acknowledgment

Thanks for your attention !