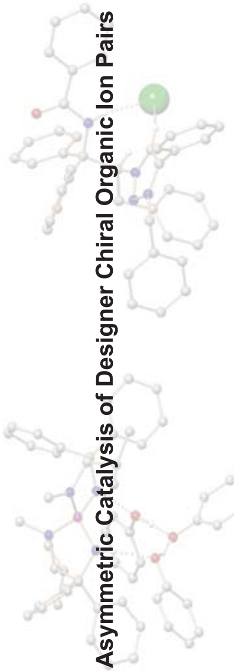
Ischia Advanced School of Organic Chemistry 2014



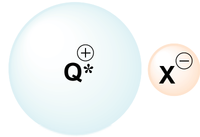
Asymmetric Catalysis of Designer Chiral Organic Ion Pairs

Takashi Ooi

Institute of Transformative Bio-Molecules (WPI-ITbM)
and Department of Applied Chemistry
Graduate School of Engineering
Nagoya University

September 23, 2014, Ischia

Our Approach toward the Chemistry of Chiral Organic Ion Pairs



Control of the Reactivity & Selectivity of Anions

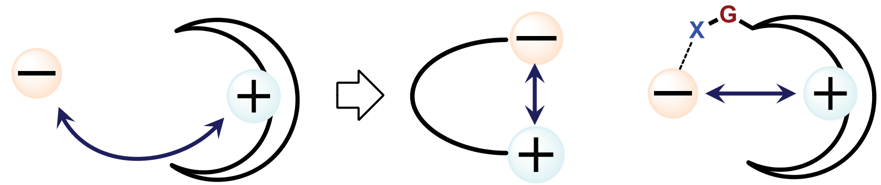
[**Q*** = chiral quaternary onium]

Advantages

- Stability of the Catalysts
- Recycle and Immobilization
- Operational Simplicity

Problems

- Limited Utilities
- Difficulty of Molecular Design
- Electrostatic Interaction



Ion Pair
Ambiguous Distance & Direction

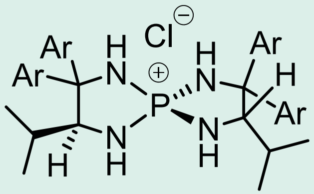
Intramolecular Ion-pairing

Hydrogen-bonding Organic Anions

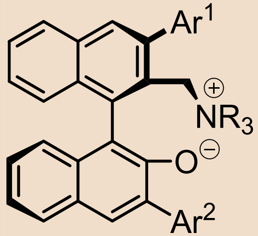
Control of Ion-pair Structure

J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073.
K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, 52, 534
M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, 52, 518.

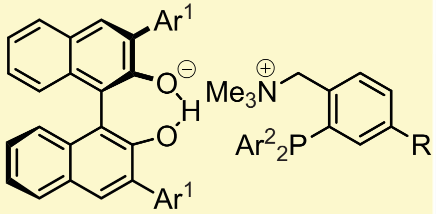
Chiral Quaternary Onium Salts as Molecular Catalysts



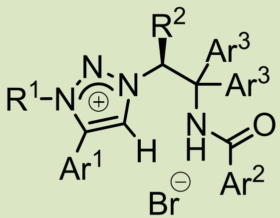
Aminophosphonium



Ammonium betaines

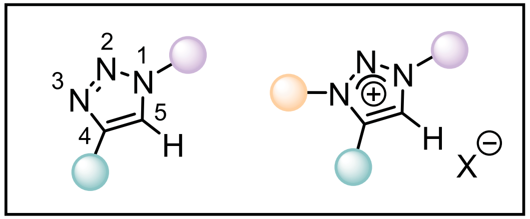


Ion-paired chiral ligands

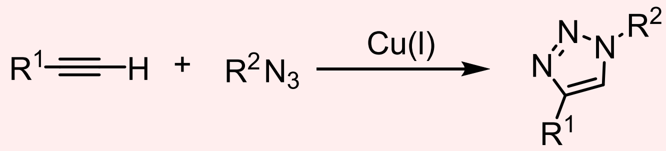


1,2,3-Triazoliums

1,2,3-Triazoles and Triazoliums



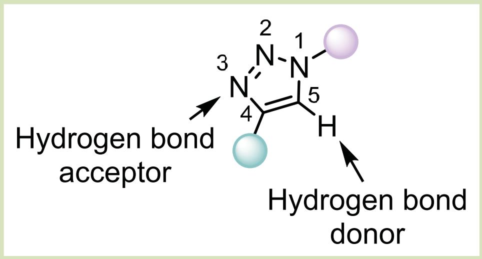
- Ready accessibility

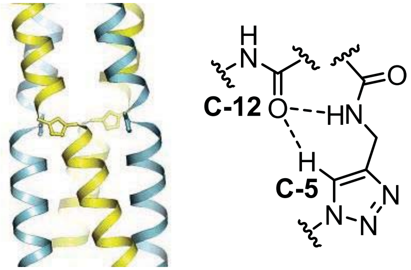


Huisgen cycloaddition

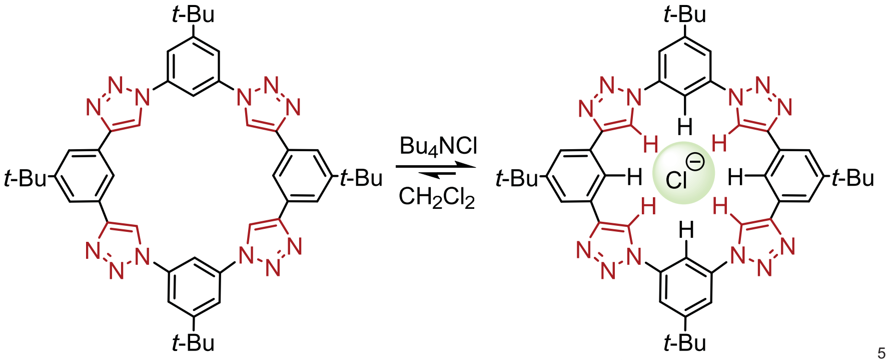
High efficiency
High regioselectivity
Functional group compatibility

Unique Properties of 1,2,3-Triazoles



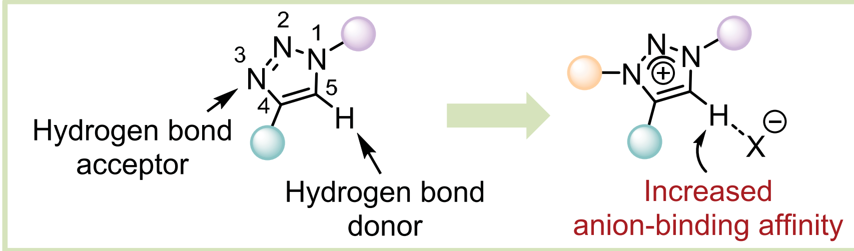


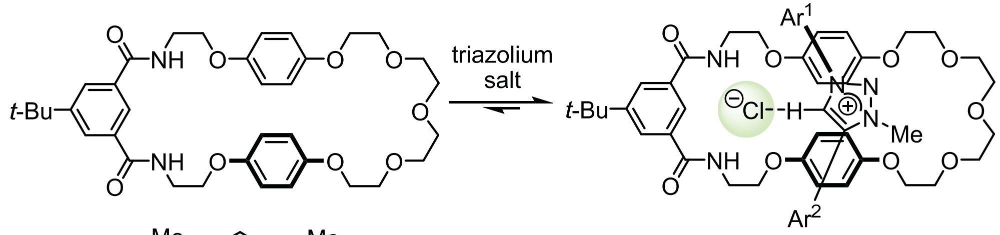
M. R. Ghadiri, *et al. J. Am. Chem. Soc.* **2004**, *126*, 15366.

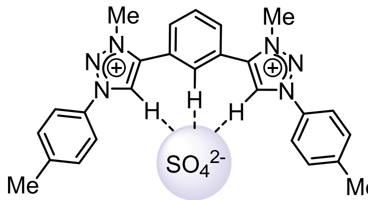


A. H. Flood, *et al. J. Am. Chem. Soc.* **2008**, *130*, 12111.

Anion-Binding Affinity of 1,2,3-Triazoliums





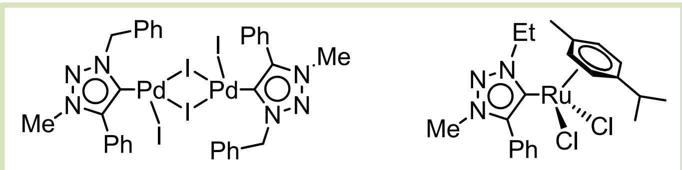


P. D. Beer, *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 4781.

U. S. Schubert, *et al. Org. Lett.* **2010**, *12*, 2710.

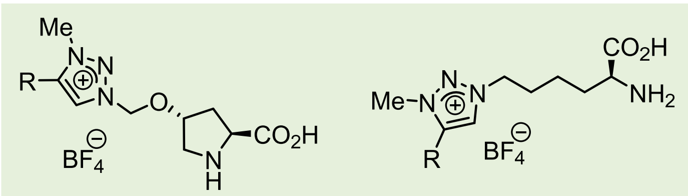
Application of 1,2,3-Triazoles and Triazoliums

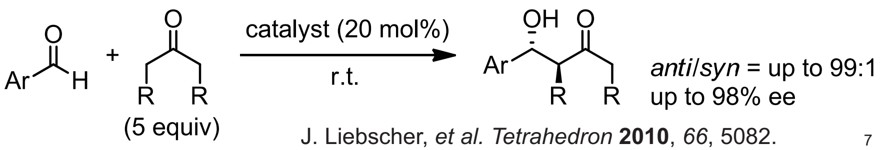
- Abnormal Carbene Ligands for Late Transition Metals



M. Albrecht, *et al. J. Am. Chem. Soc.* **2008**, *130*, 13534.

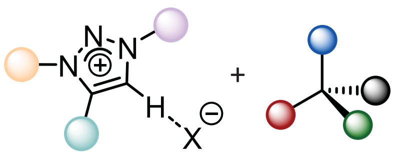
- Chiral Amino Acid-Based Organocatalysts for Aldol Reactions





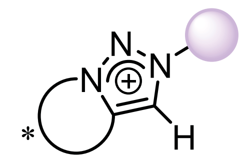
J. Liebscher, *et al. Tetrahedron* **2010**, *66*, 5082.

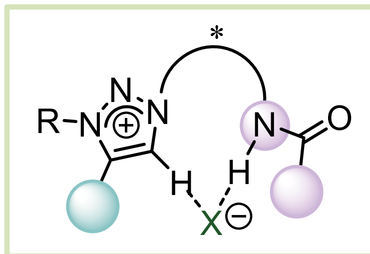
Design of Chiral 1,2,3-Triazoliums



How we can combine 1,2,3-triazolium with chiral structure ?

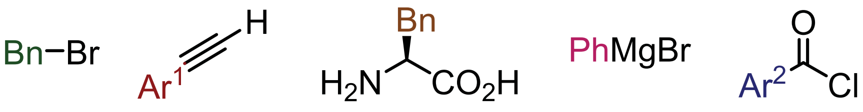
Cyclic structure	Acyclic structure
Rigid	Flexible
Multistep synthesis	Ease of synthesis



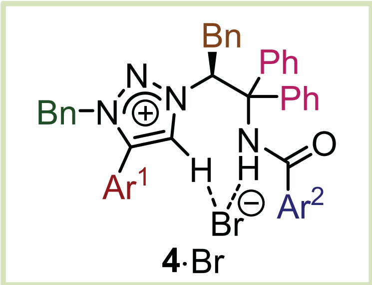


Pseudo Cyclic Structure

Design and Advantages of Chiral 1,2,3-Triazoliums

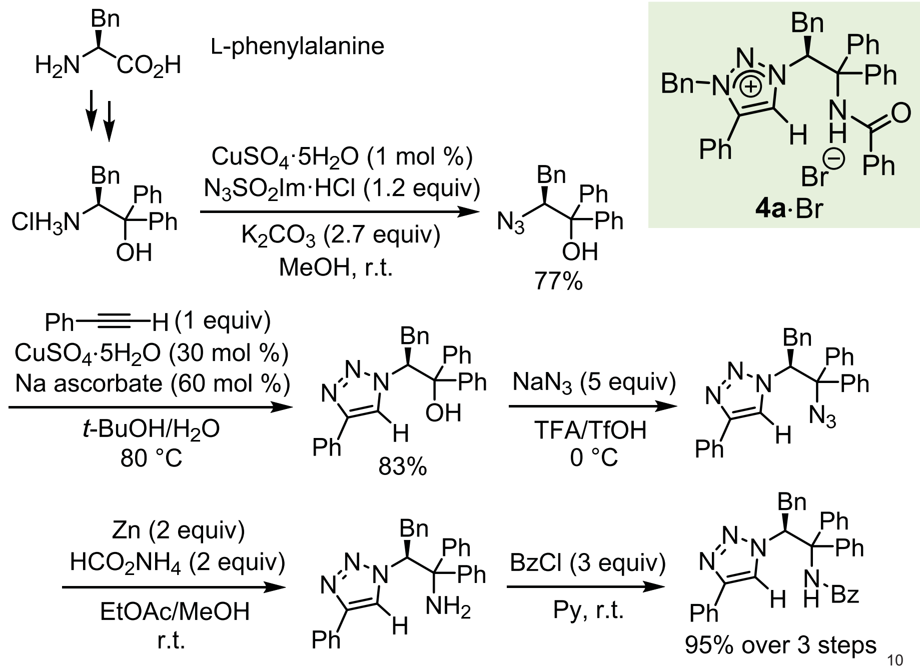


- Ready accessibility
- Numerous possibilities of structural modification

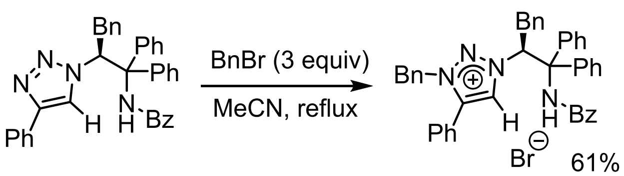


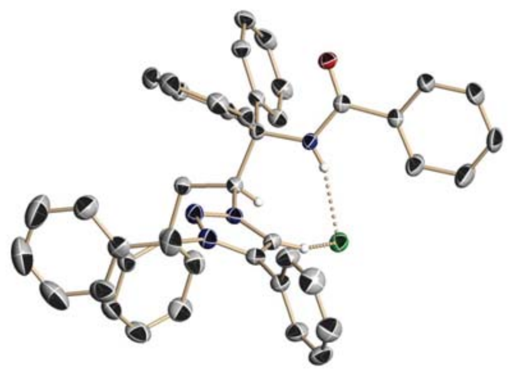
- Anion recognition through the *electrostatic interaction* and *two hydrogen bonds*

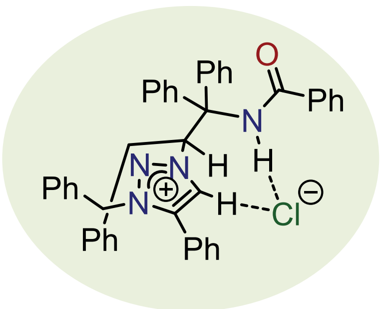
Synthesis of Chiral 1,2,3-Triazolium Salt 4a·Br



Final Step and X-ray Crystal Structure

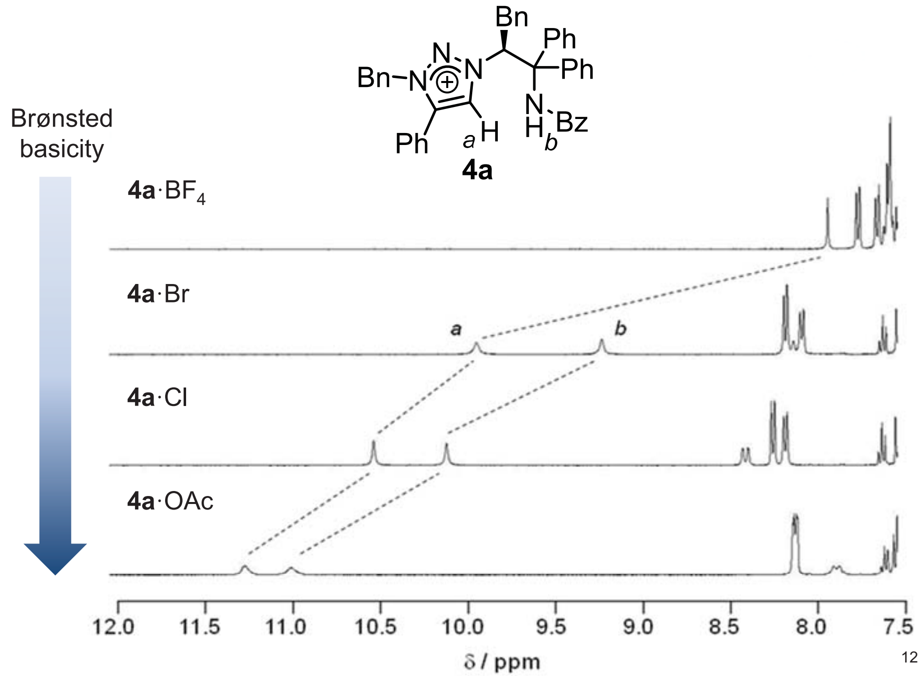




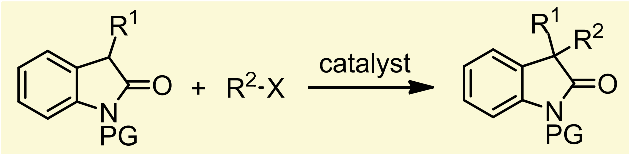


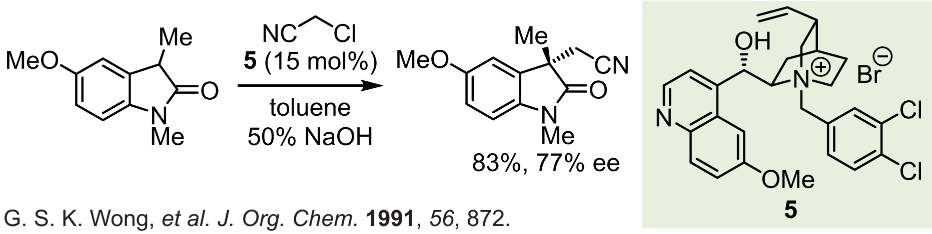
ORTEP diagram of **4a**·Cl

^{1}H NMR Spectra in CD_2Cl_2 (0.01 M) at 293K

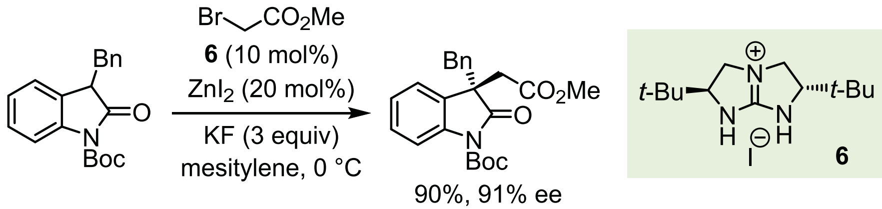


Asymmetric Alkylation of Oxindoles: Previous Examples



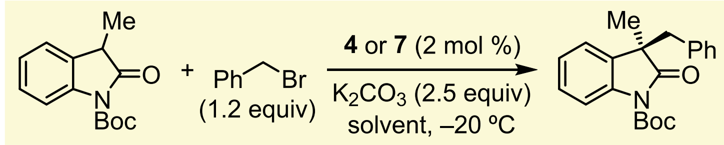


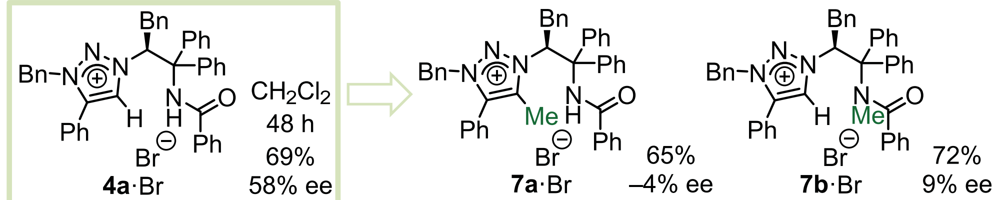
G. S. K. Wong, *et al. J. Org. Chem.* **1991**, *56*, 872.

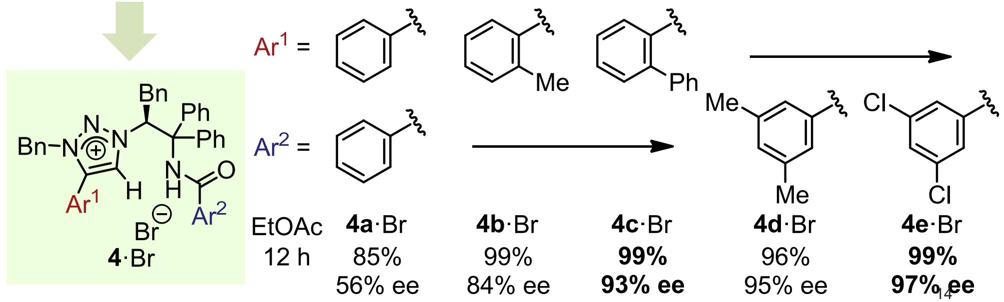


C.-H. Tan, Z. Jiang, *et al. Chem. Commun.* **2013**, *49*, 9854.

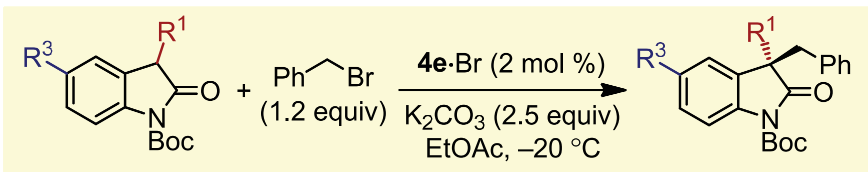
Effect of Substituents of Triazolium Cation

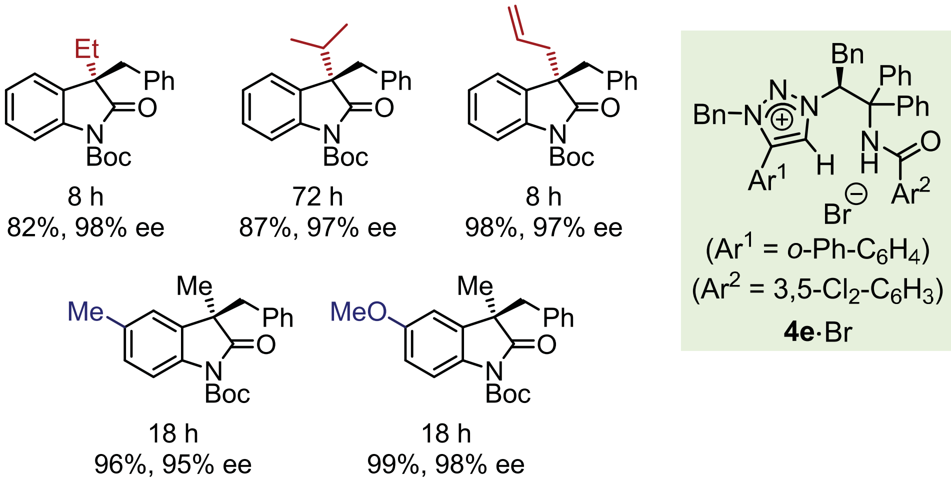






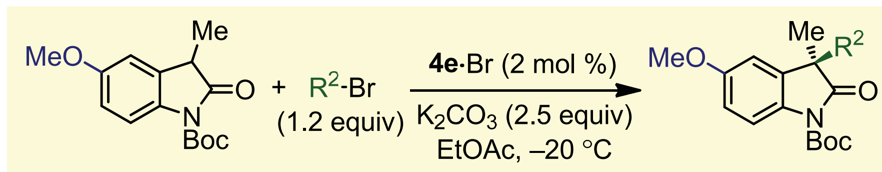
Substrate Scope

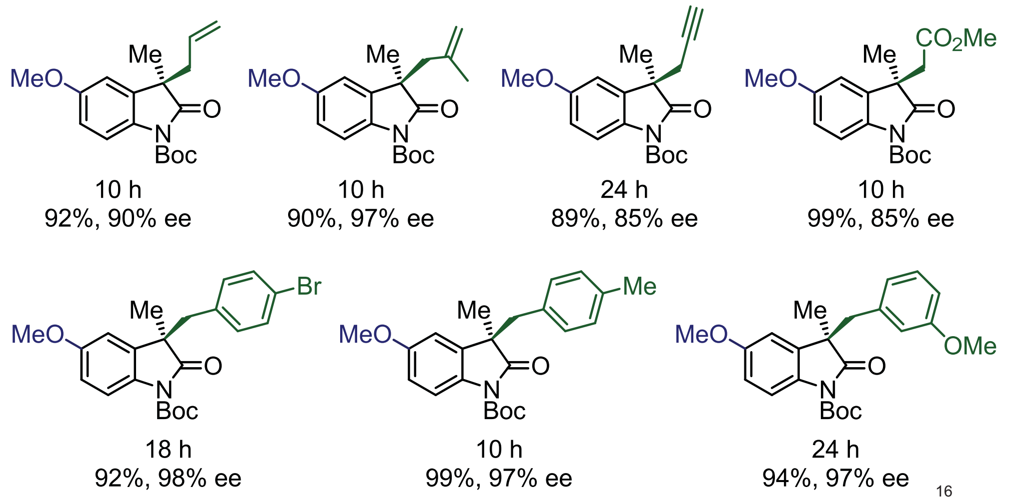




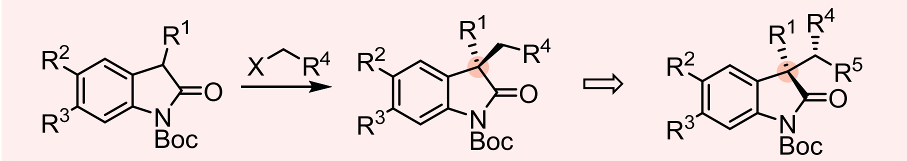
K. Ohmatsu, M. Kiyokawa, T. Ooi, *J. Am. Chem. Soc.* **2011**, *133*, 1307.

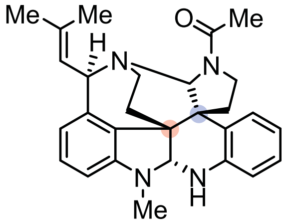
Substrate Scope



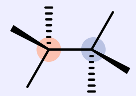


Construction of Contiguous Chiral Quaternary Carbons

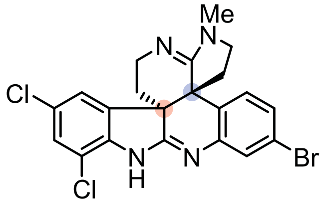




(–)-Communesin F

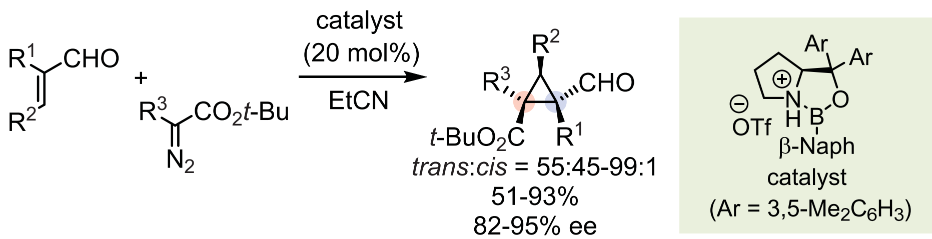


Contiguous All-Carbon Quaternary Stereocenters

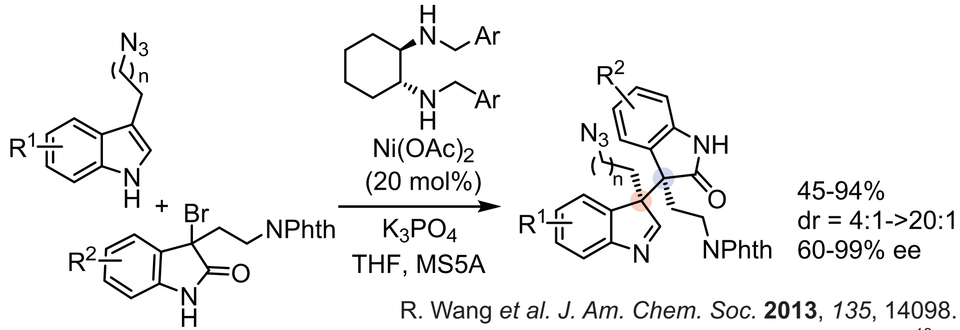


(+)-Perophoramidine

Examples of Catalytic Asymmetric Construction of Contiguous All-Carbon Quaternary Stereocenters

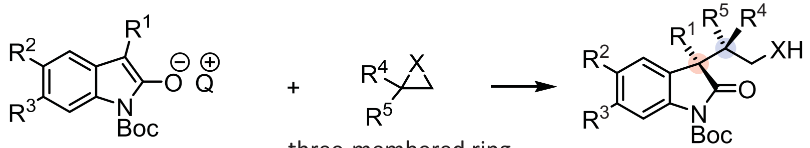


D. H. Ryu *et al.* *J. Am. Chem. Soc.* **2011**, *133*, 20708.



R. Wang *et al.* *J. Am. Chem. Soc.* **2013**, *135*, 14098.

Use of Highly Strained Electrophiles



[Q = 1,2,3-Triazolium]

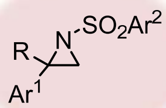
2,2-disubstituted aziridines

Good reactivity

electron-withdrawing group on nitrogen

Easily accessible

preparable from styrene derivatives in 2 steps



Aromatic substituents

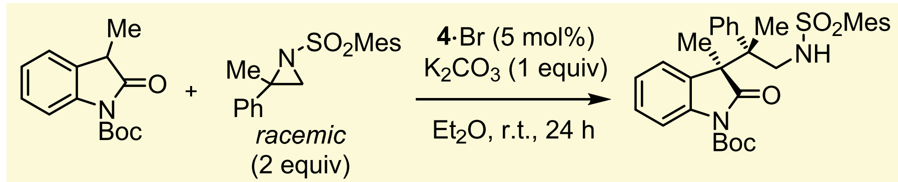
beneficial effect on regioselective ring-opening

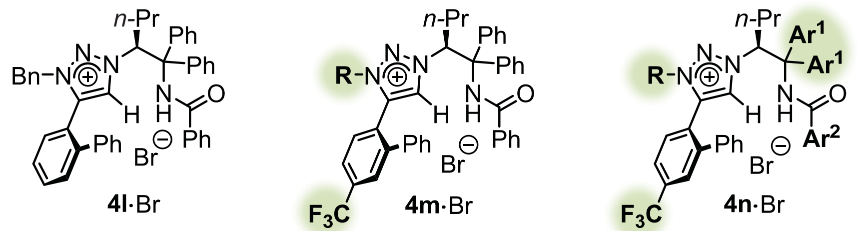
Versatile intermediate

useful for the synthesis of biologically active compounds

For asymmetric reactions of aziridines: Schneider, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2082.

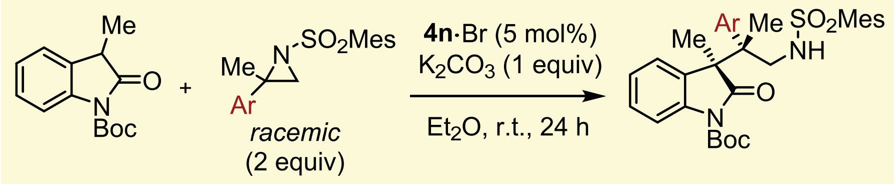
Ring-Opening Alkylation of Aziridines

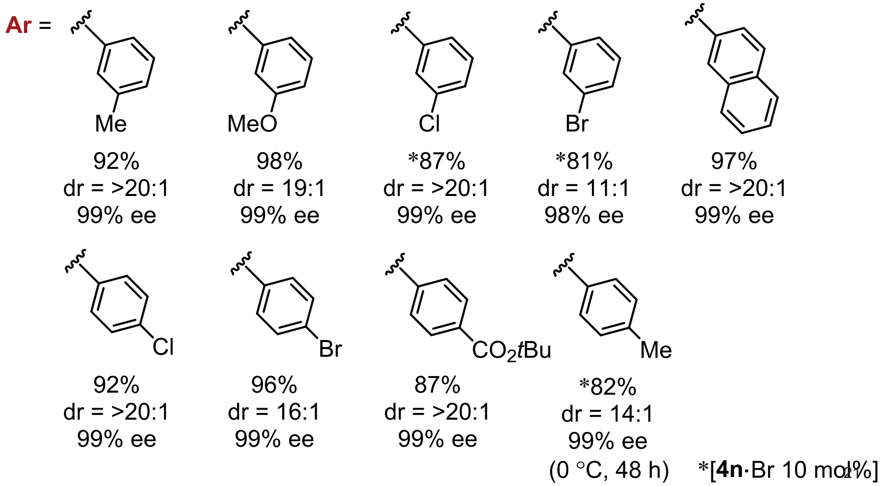




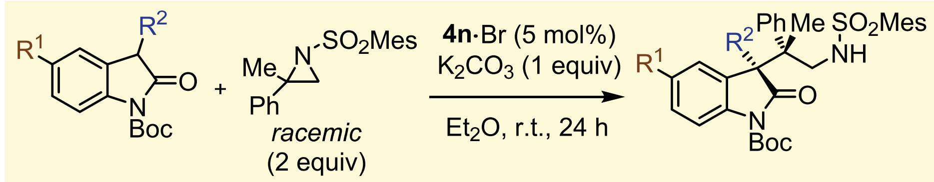
4l·Br	**4m**·Br	**4n**·Br
56%	95%	99%
dr* = *4.4:1	***dr* = *16:1***	***dr* = *>20:1***
93% ee	99% ee	99% ee
	[**R** = $CH_2(4\text{-}CF_3)C_6H_4$]	[**R** = $CH_2(4\text{-}CF_3)C_6H_4$; **Ar^1** = 4-Cl-$C_6H_4$; **Ar^2** = 4-Me-$C_6H_4$]

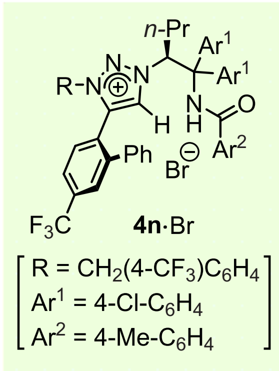
Scope of Aziridines

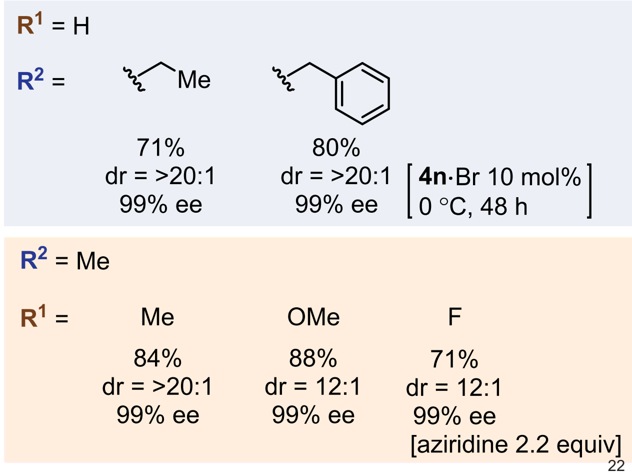




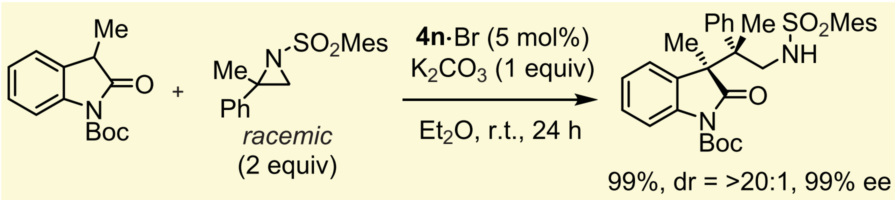
Scope of Oxindoles

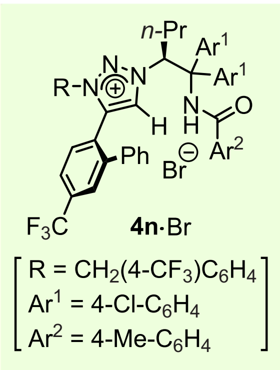


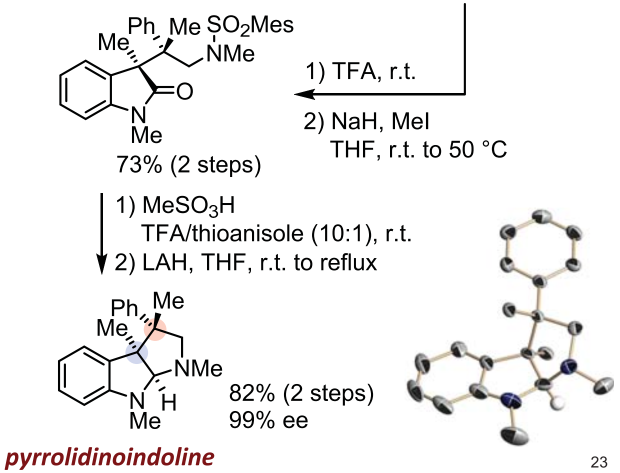




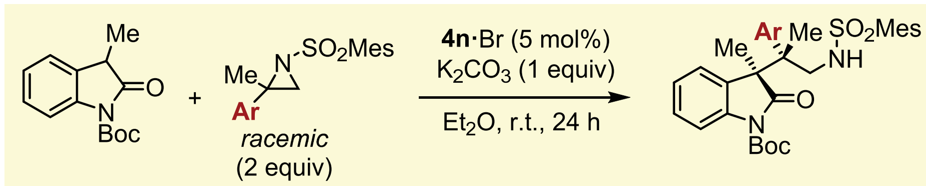
Product Derivatization







Stereochemistry of Recovered Aziridines



Ar = Ph

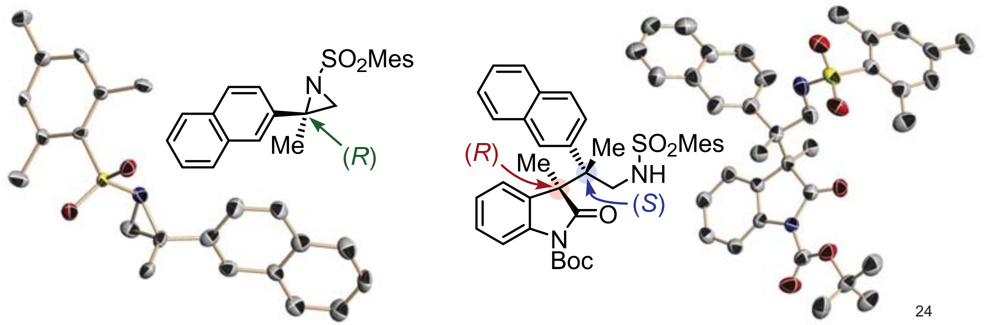
product: 99%, dr = >20:1, 99% ee

aziridine: 99%, 76% ee

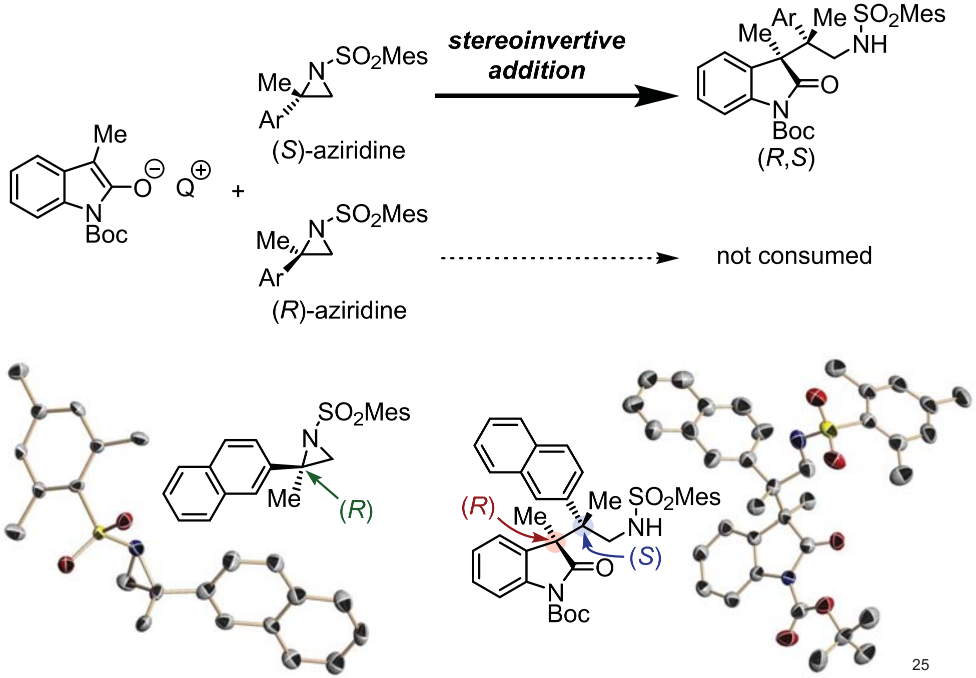
Ar = 2-Naph

product: 97%, dr = >20:1, 99% ee

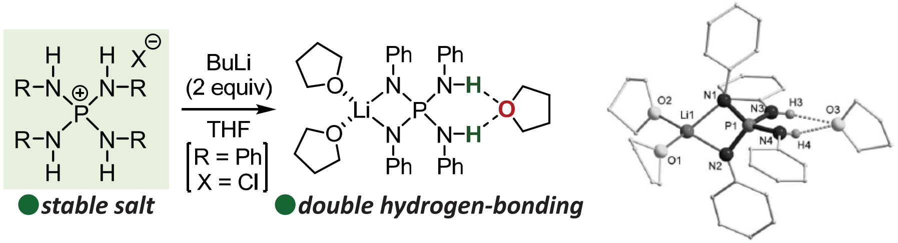
aziridine: 99%, 76% ee



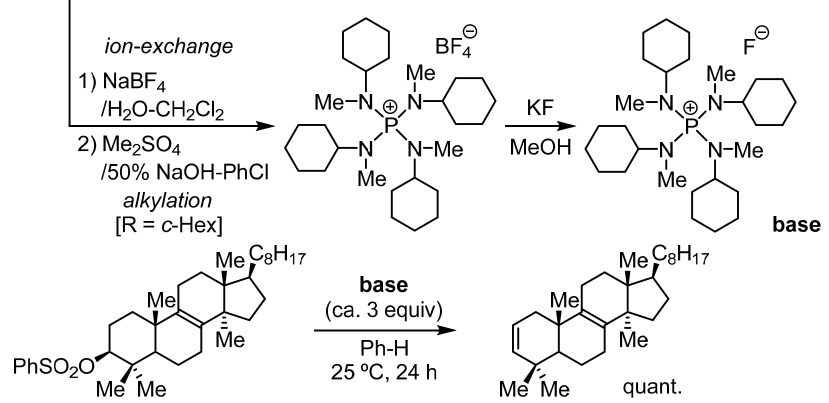
Intervention of Kinetic Resolution



Tetraaminophosphonium Salts

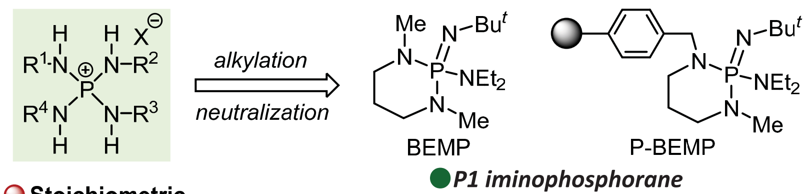


A. Steiner *et al. Dalton Trans.* **2004**, 898.

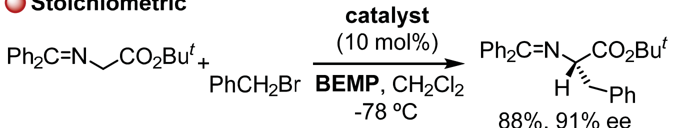


R. Schwesinger, *et al. Chem. Eur. J.* **2006**, *12*, 438.

Tetraaminophosphonium Salts



Stoichiometric



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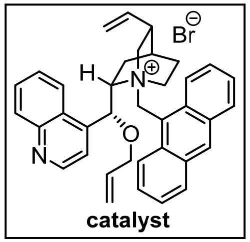
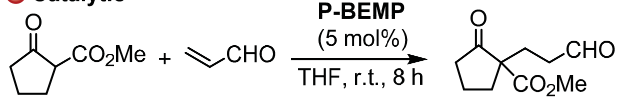
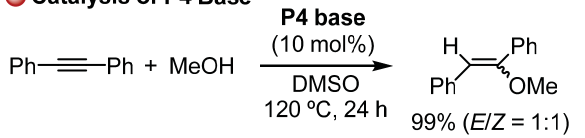


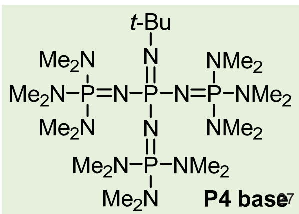
Catalytic



J. Rodriguez, *et al. Synthesis* **2004**, 923.

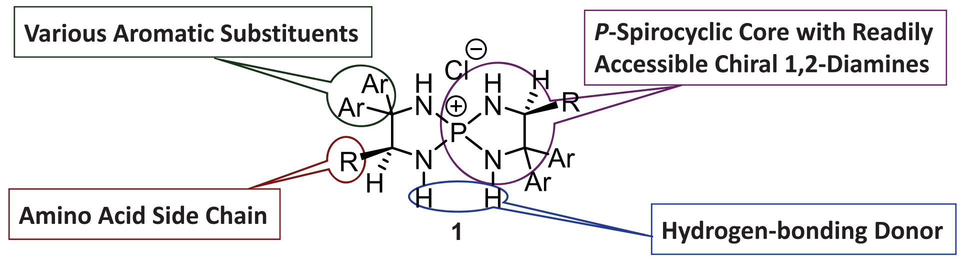
Catalysis of P4 Base

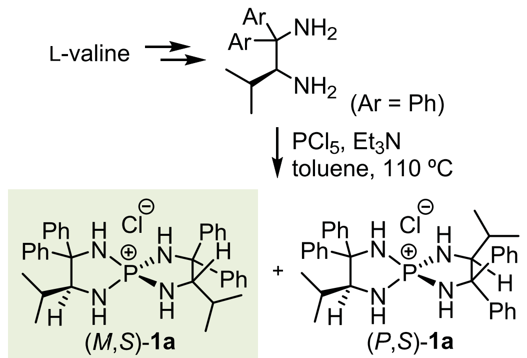




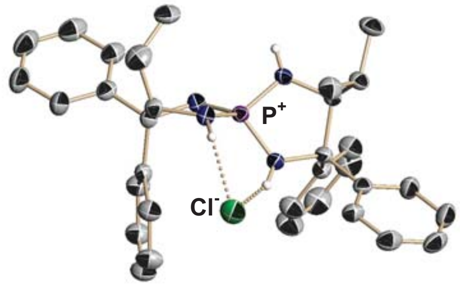
T. Imahori, C. Hori, Y. Kondo, *Adv. Synth. Catal.* **2004**, *346*, 1090.

Design of Chiral *P*-Spiro Tetraaminophosphonium Salts



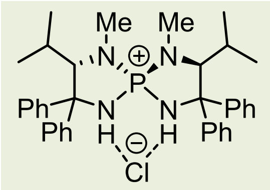


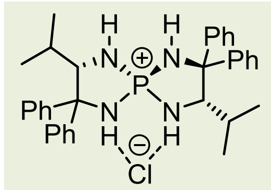
1a: 92% (combined yield; *MS*/*PS* = 6:1)

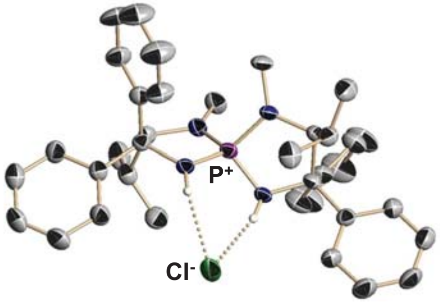


X-ray Crystal Structure of (*M*,*S*)-**1a**

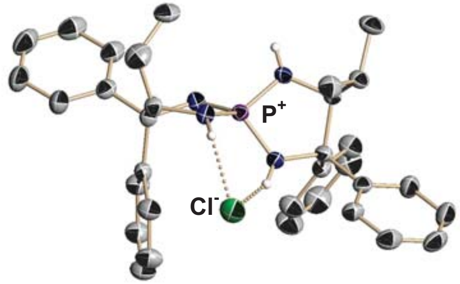
Design of Chiral *P*-Spiro Tetraaminophosphonium Salts





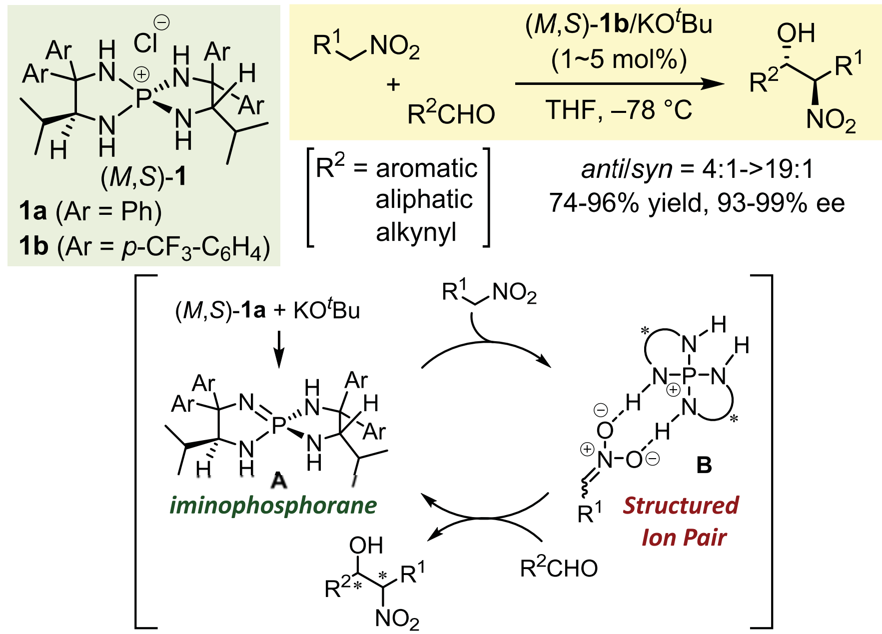


(P,S)-**2a**·HCl



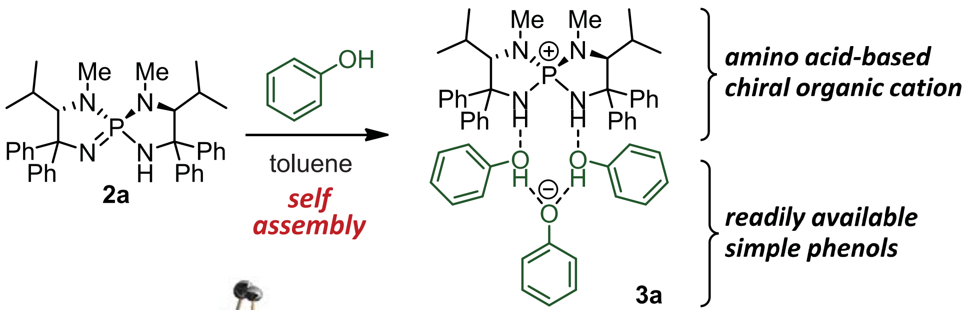
X-ray Crystal Structure of (M,S)-**1a**

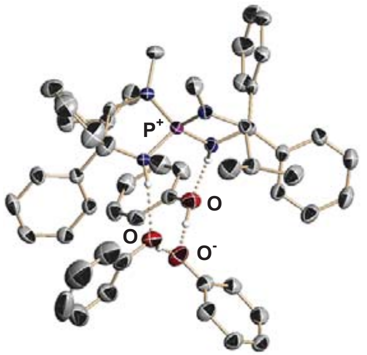
Application of Chiral *P*-Spiro Tetraaminophosphonium Salts



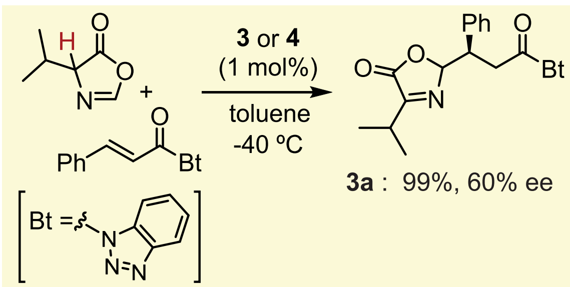
D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392.
D. Uraguchi, S. Nakamura, T. Ooi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7562.

Supramolecularly Assembled Chiral Organic Ion Pairs

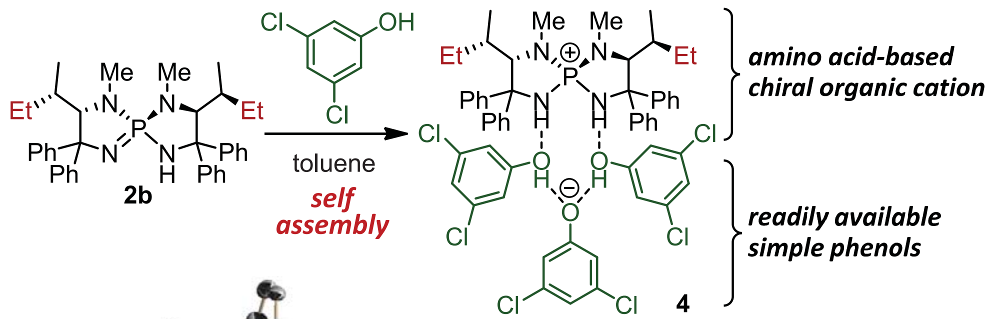


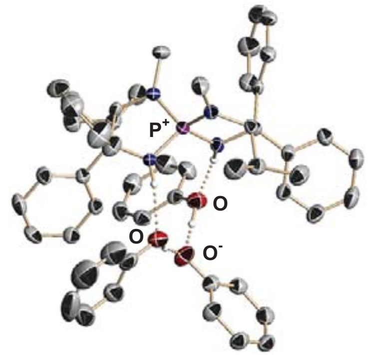


crystal structure of **3a**

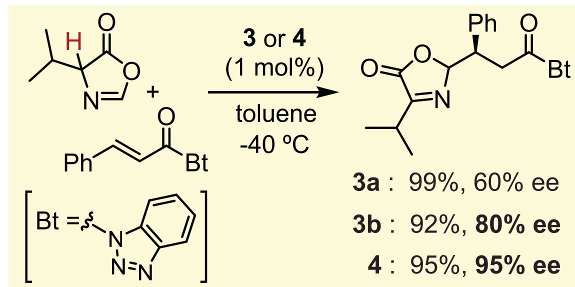


Supramolecularly Assembled Chiral Organic Ion Pairs



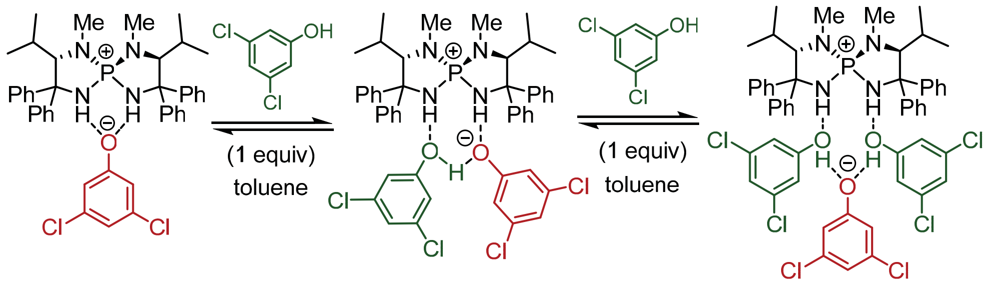


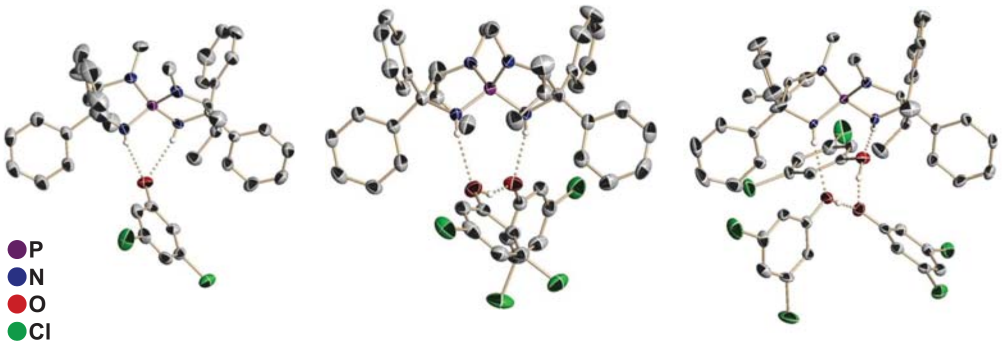
crystal structure of **3a**



D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120.

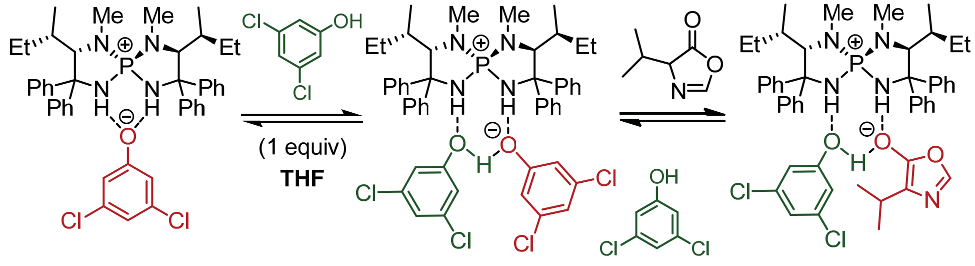
Controlled Self Assembly

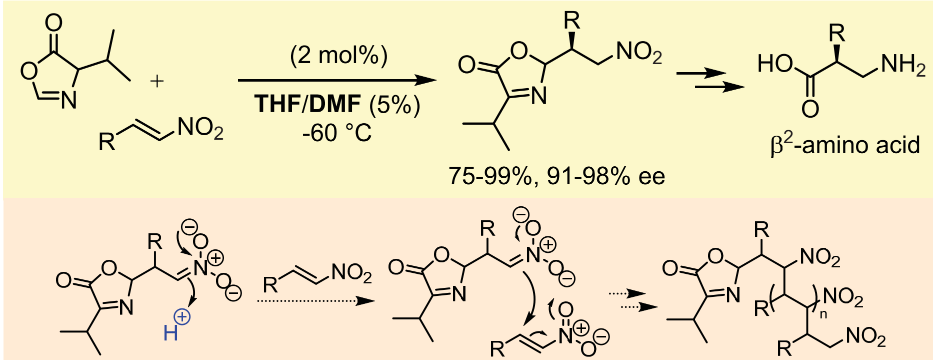




D. Uraguchi, Y. Ueki, T. Ooi, *Angew. Chem. Int. Ed.* **2011**, *50*, 3681.

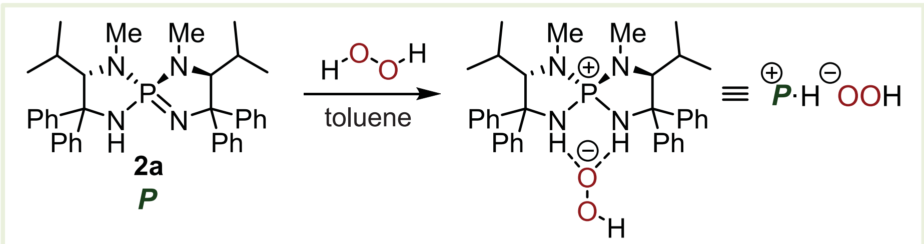
Polarity-Dependent Mode of Assembly



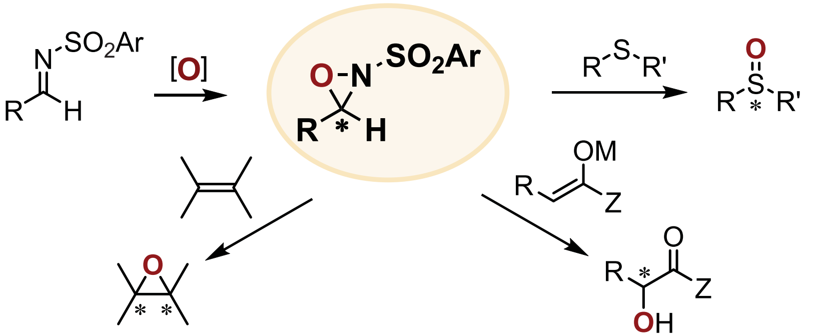


D. Uraguchi, Y. Ueki, T. Ooi, *Chem. Sci.* **2012**, *3*, 842.

Generation of Chiral Aminophosphonium Hydroperoxide

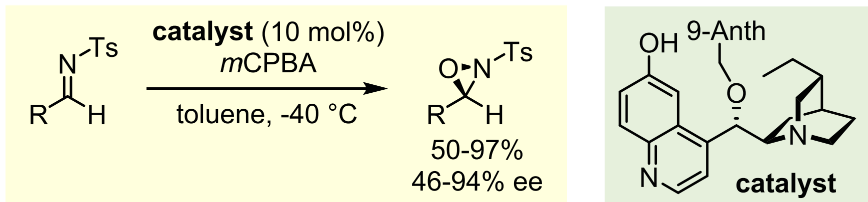


N-Sulfonyloxaziridines (Davis' Oxaziridines)

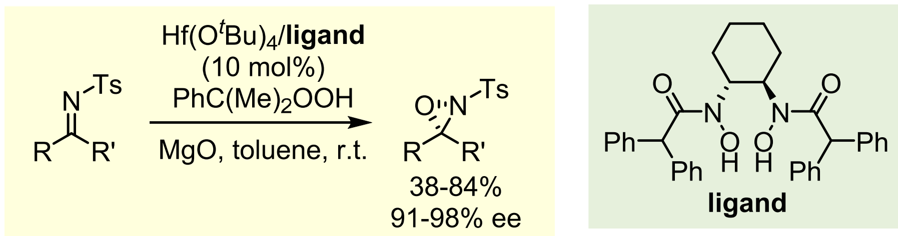


Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *133*, 5703.
Yoon, T. P. *et al. Chem. Rev.* **2014**, *114*, DOI: 10.1021/cr400611n.

Catalytic Asymmetric Synthesis of *N*-Sulfonyloxaziridines

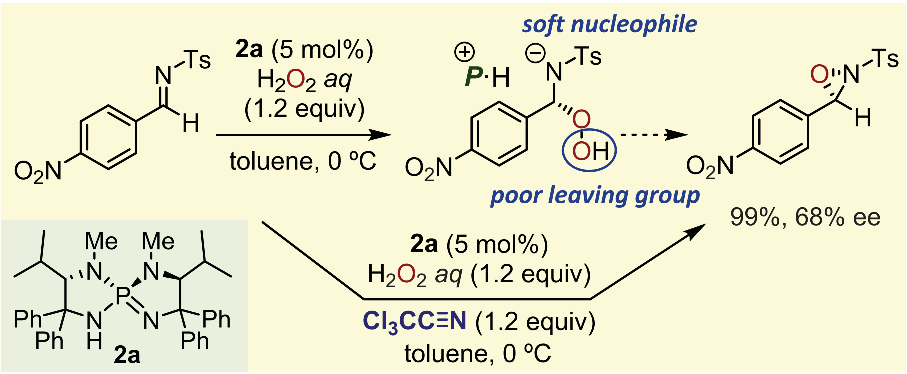


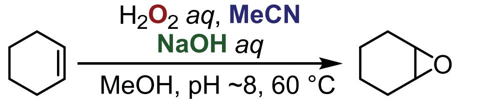
Lykke, L.; Rodríguez-Escrich, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 14932.



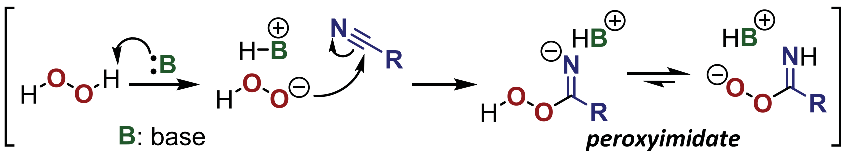
Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 5440.

Initial Trial and Payne-type Oxidation System

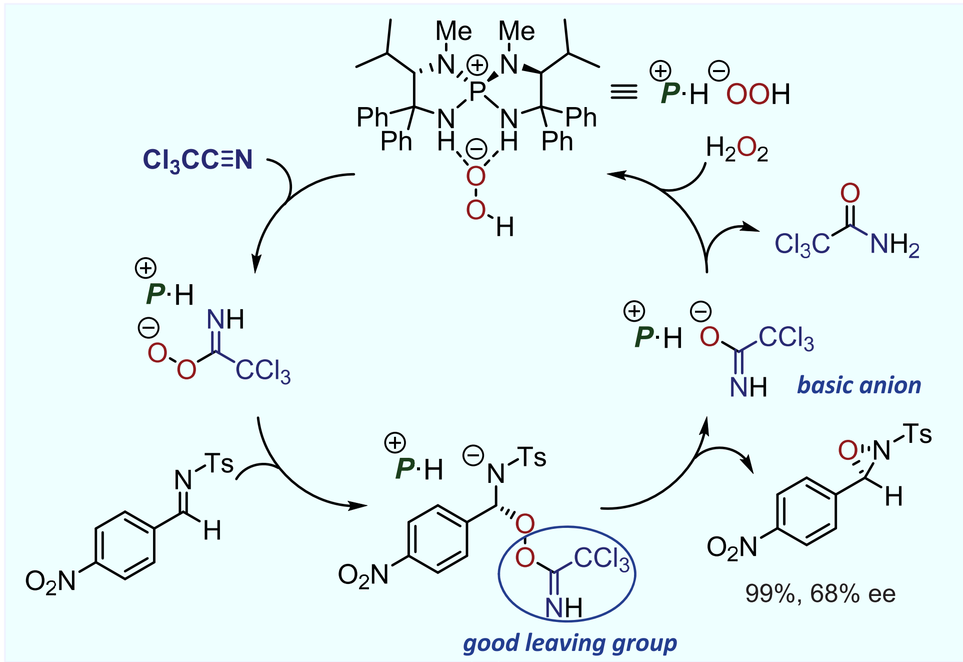




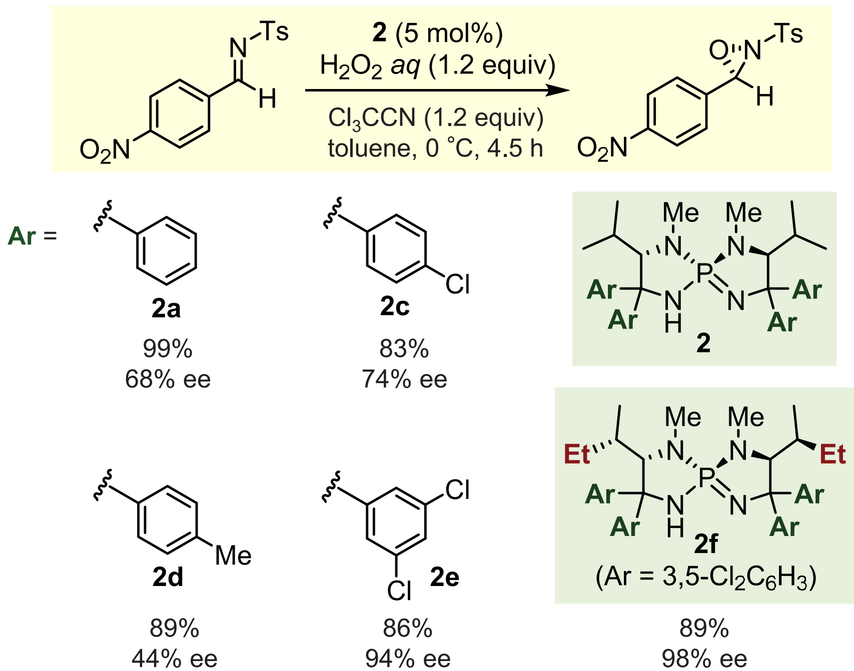
Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1969**, *26*, 659.



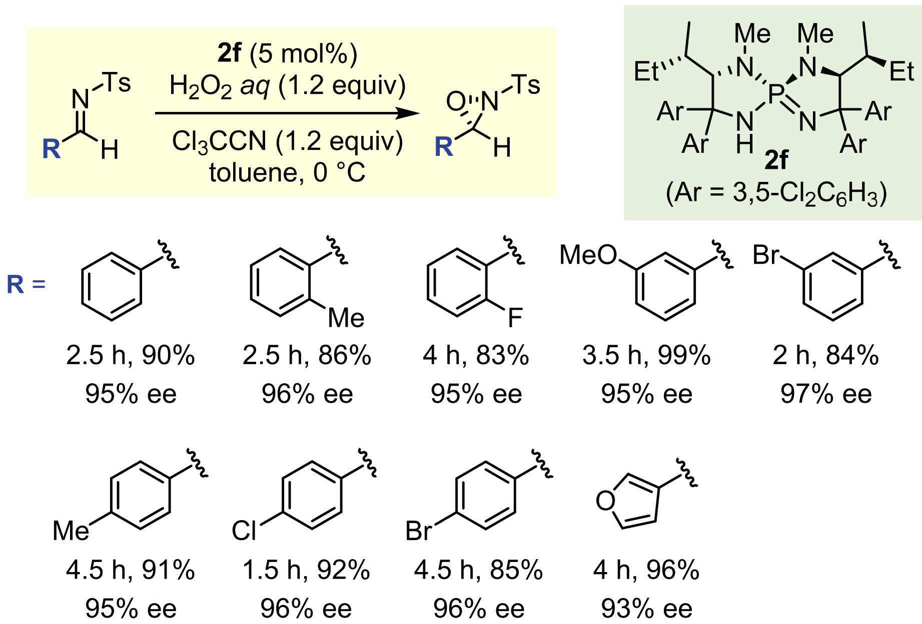
Reaction Mechanism



Optimization of Catalyst Structure



Substrate Scope



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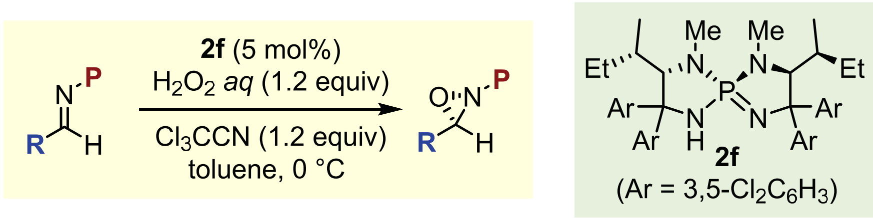
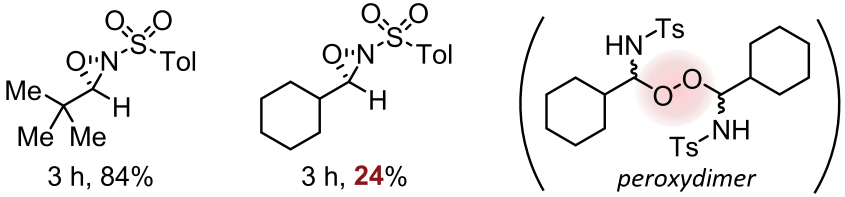
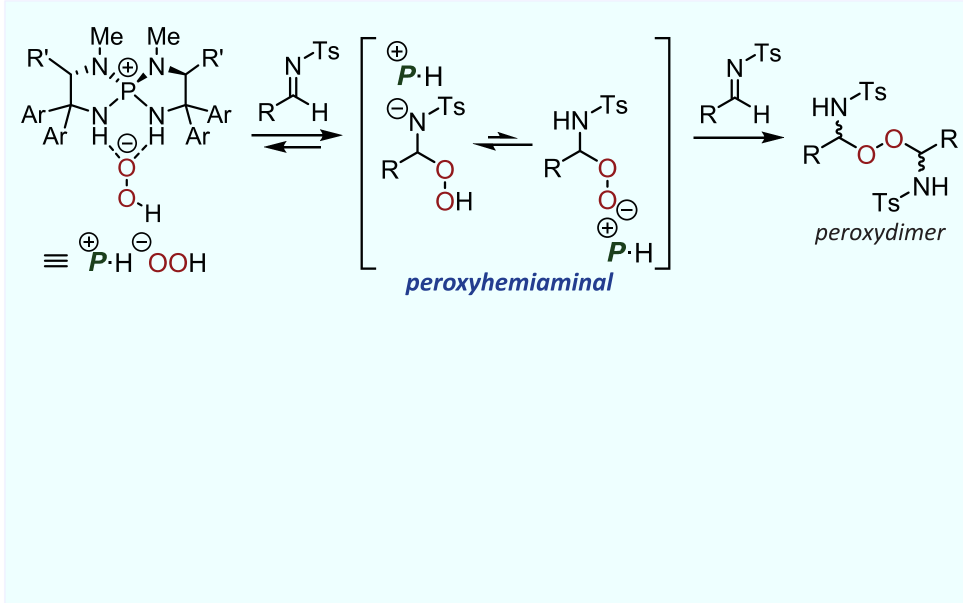




3 h, 84%
98% ee

3 h, **24**%
94% ee

Generation of Peroxyhemiaminal



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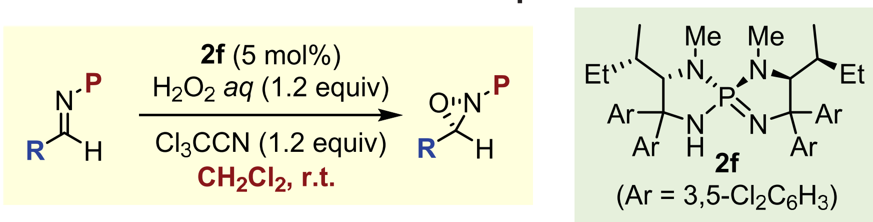
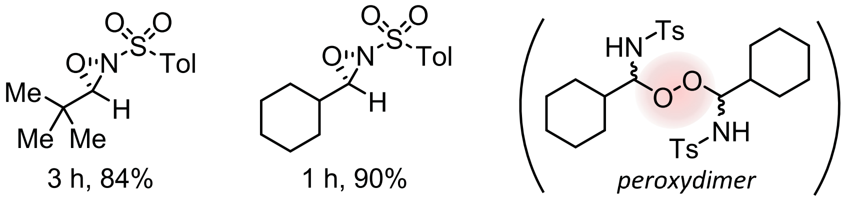
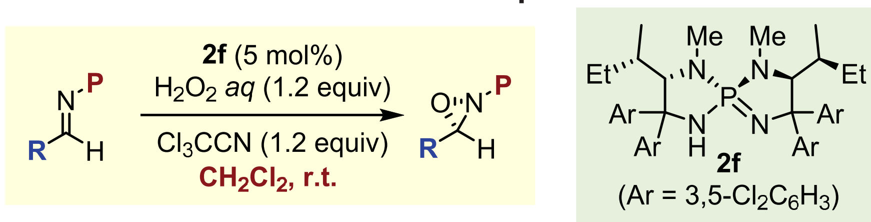


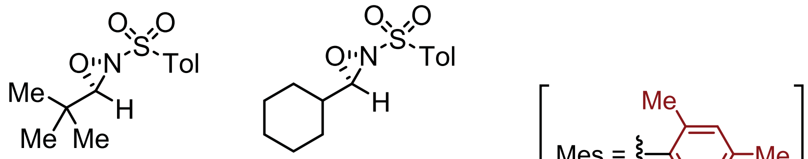


3 h, 84%
98% ee
(toluene, 0 °C)

1 h, 90%
98% ee

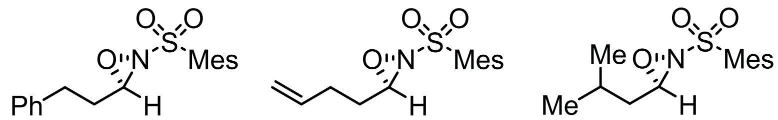
Substrate Scope





3 h, 84%
98% ee
(toluene, 0 °C)

1 h, 90%
98% ee

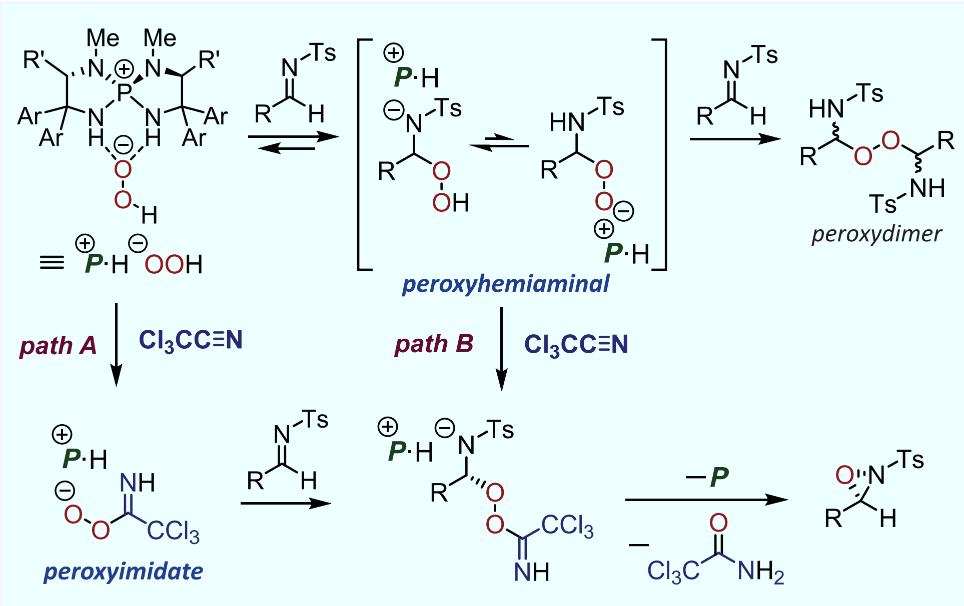


0.5 h, 87%
96% ee

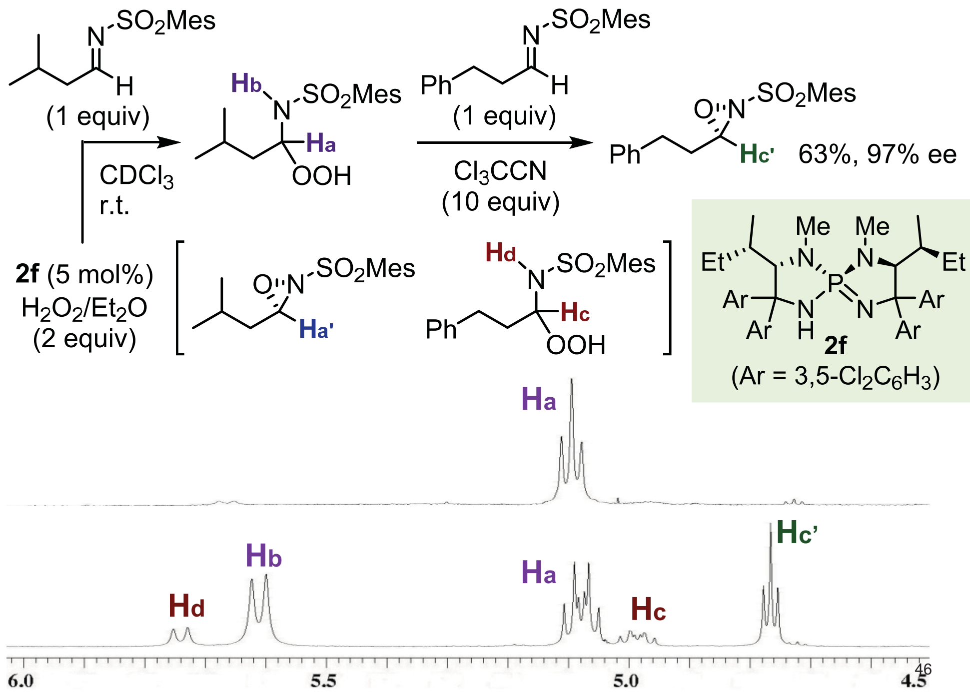
1 h, 84%
96% ee

1 h, 98%
95% ee

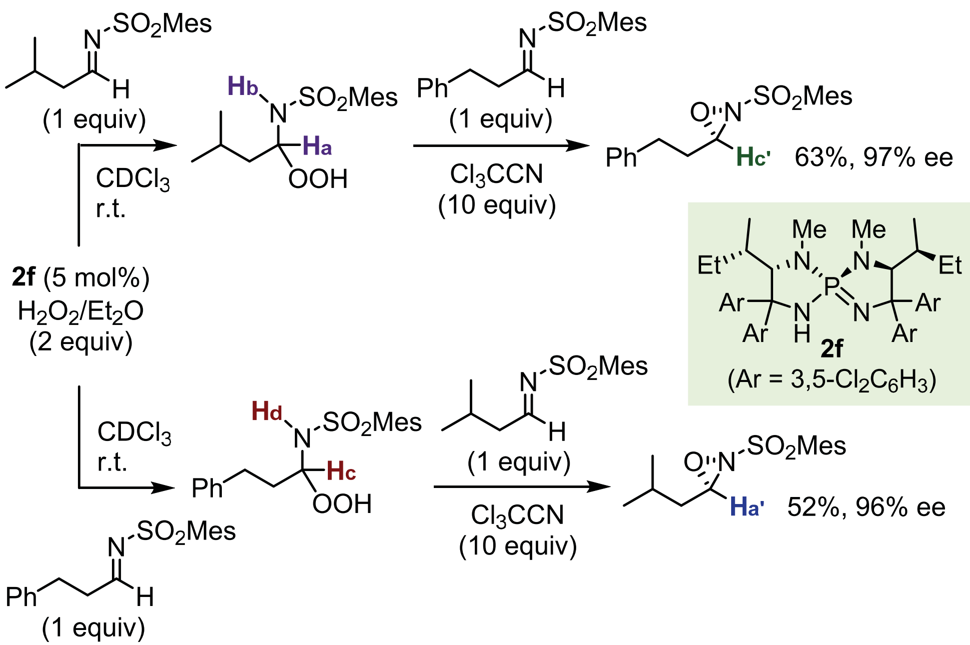
Plausible Alternative Mechanism



Cross-Over Experiments

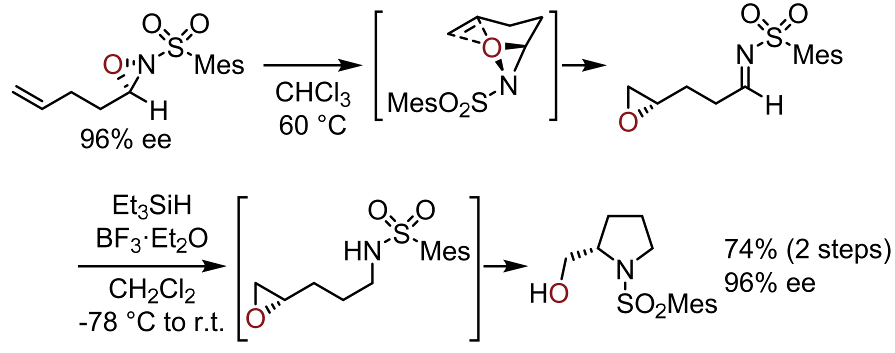


Cross-Over Experiments

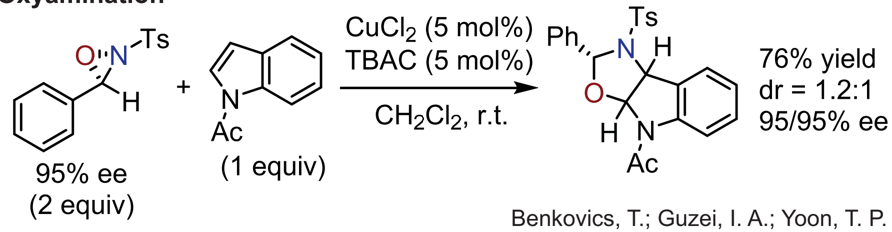


Product Derivatization

- **Intramolecular Oxygen-Transfer Reaction**



- **Oxyamination**



Benkovics, T.; Guzei, I. A.; Yoon, T. P. *Angew. Chem. Int. Ed.* **2010**, *49*, 9153.