Literature Report 16

The Asymmetric Synthesis of *N*-Stereogenic Molecules

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Checker: Jian Chen
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Wu, S.; Chen, P.; Houk, K. N.; Tan, B. *et al. Nature* **2025**, *647*, 897-905.
Zhu, C.; Das, S.; Sterling, M. S.; List, B. *et al. Nature* **2025**, *ASAP*

CV of Dr. Tan Bin（谭斌）

Background:

- **2001-2005** M.S., Xiamen University
- **2005-2010** Ph.D., Nanyang Technological University
- **2010-2012** Postdoc., The Scripps Research Institute
- **2012-2018** Tenure-Track, Department of Chemistry, SUSTech
- **2018-present** Full Prof., Department of Chemistry, SUSTech

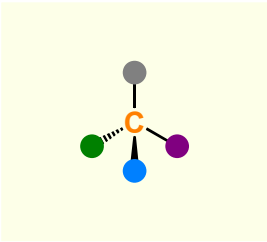
Research:

- ✓ **Construction and Applications of Axially Chiral Molecules**
- ✓ **Development of Catalytic Asymmetric Multicomponent Reactions**
- ✓ **Catalytic Asymmetric Synthesis of Pharmaceuticals and Bioactive Molecules**

Contents

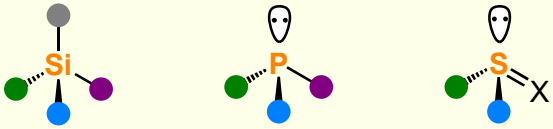
Introduction

Carbon centre

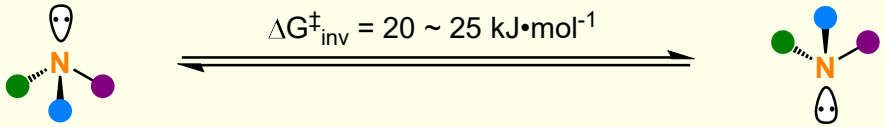


extensively explored

Heteroatom involving stereogenic centre

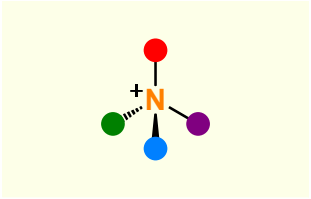


mainly investigated, stable configuration

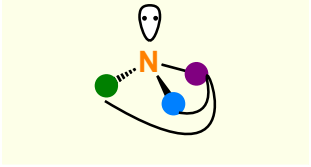


under-explored, low pyramidal inversion barrier

Non-interconvertible
N stereocentre

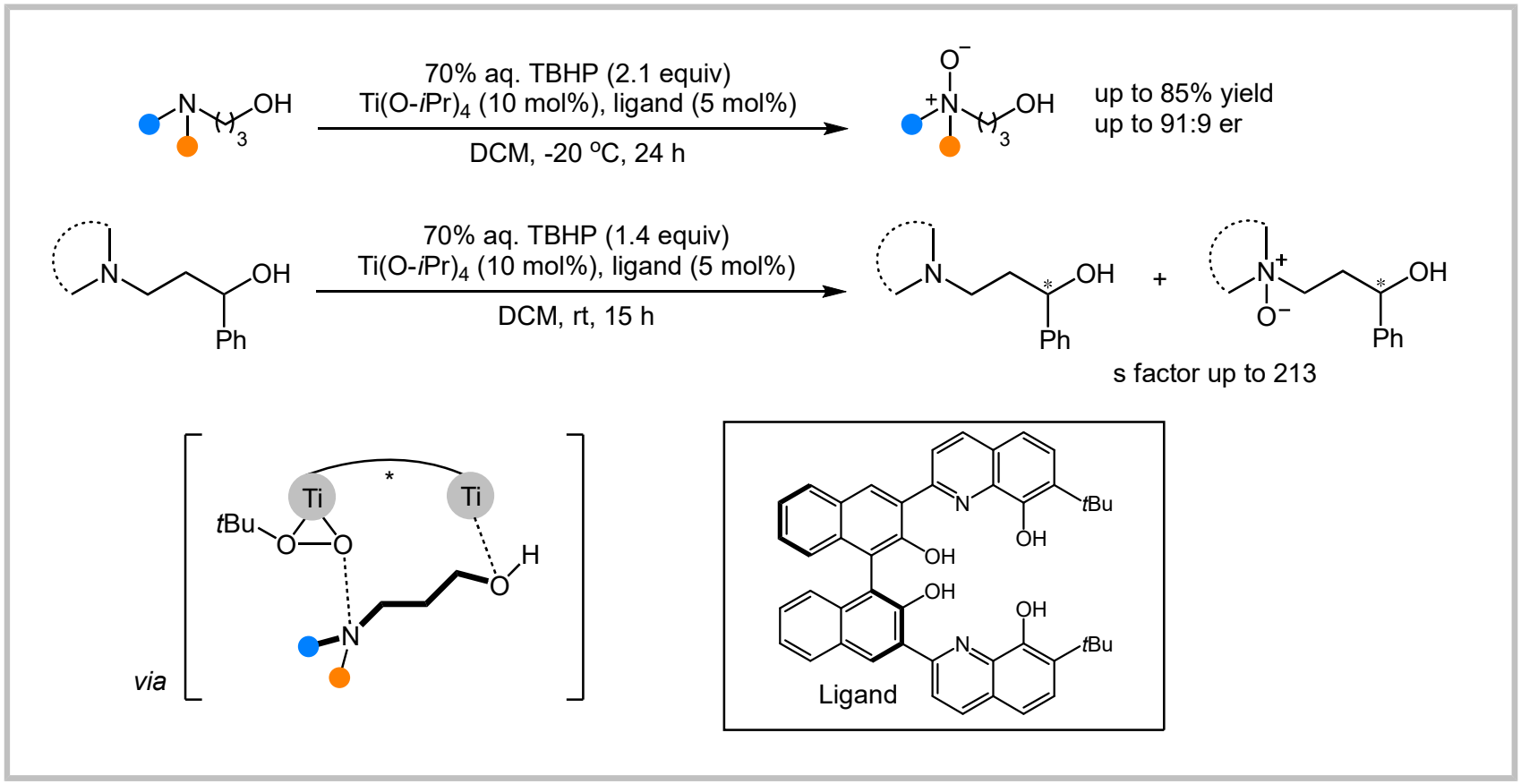


tetrahedral ammonium
or N-oxide



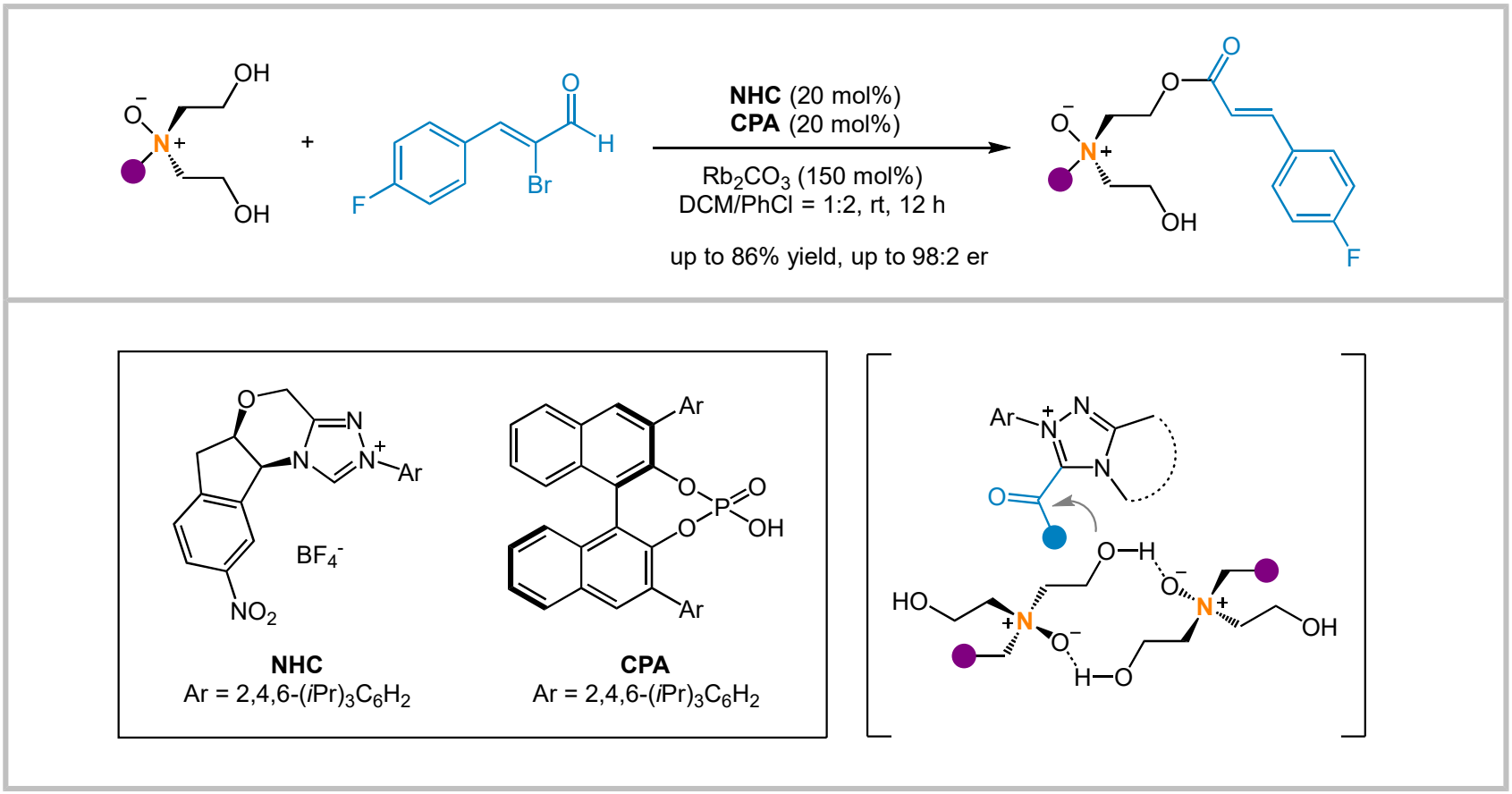
N atom at
bridgehead

Chiral N-Oxide



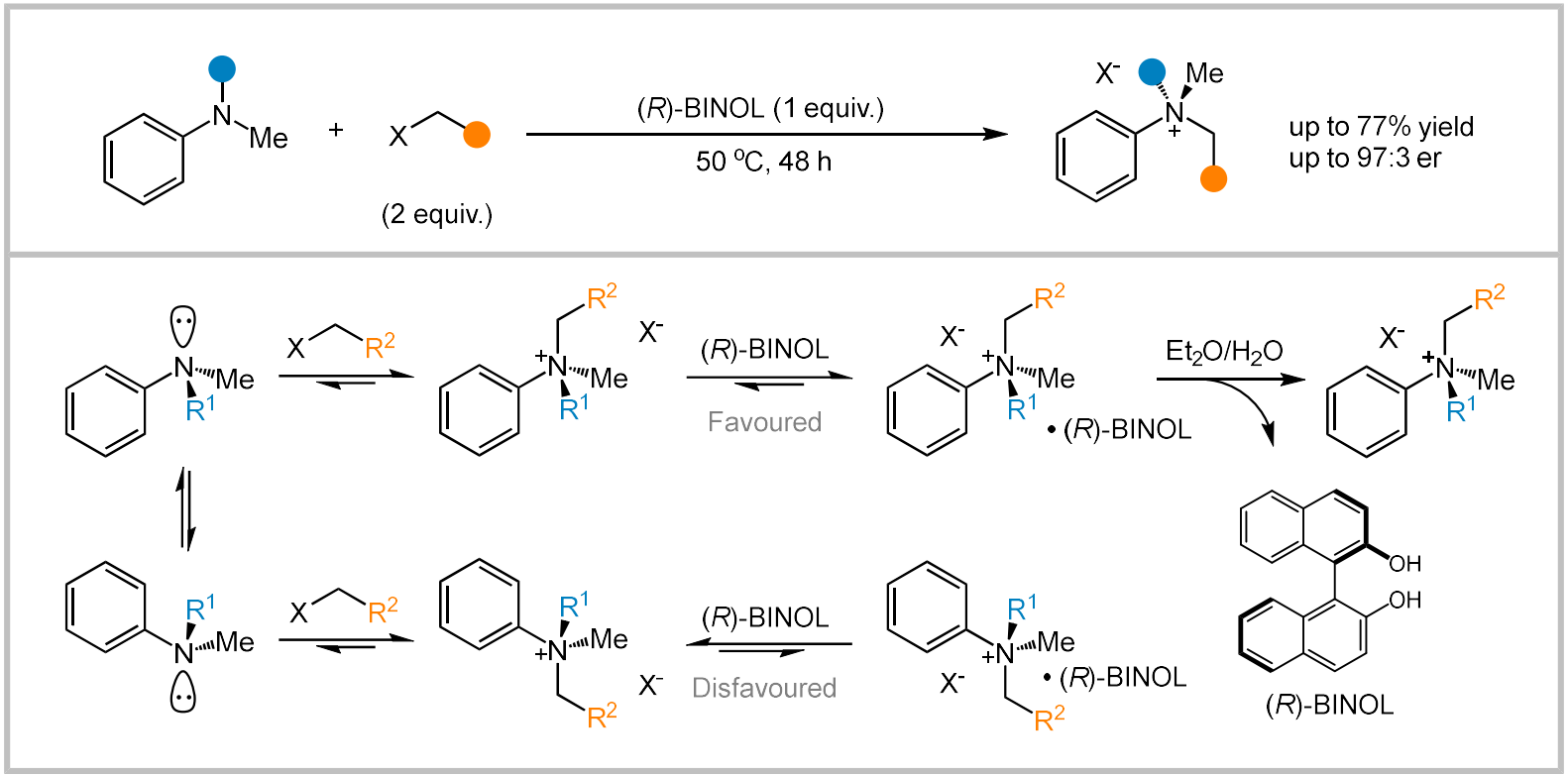
Bhadra, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 13043-13046

Chiral N-Oxide



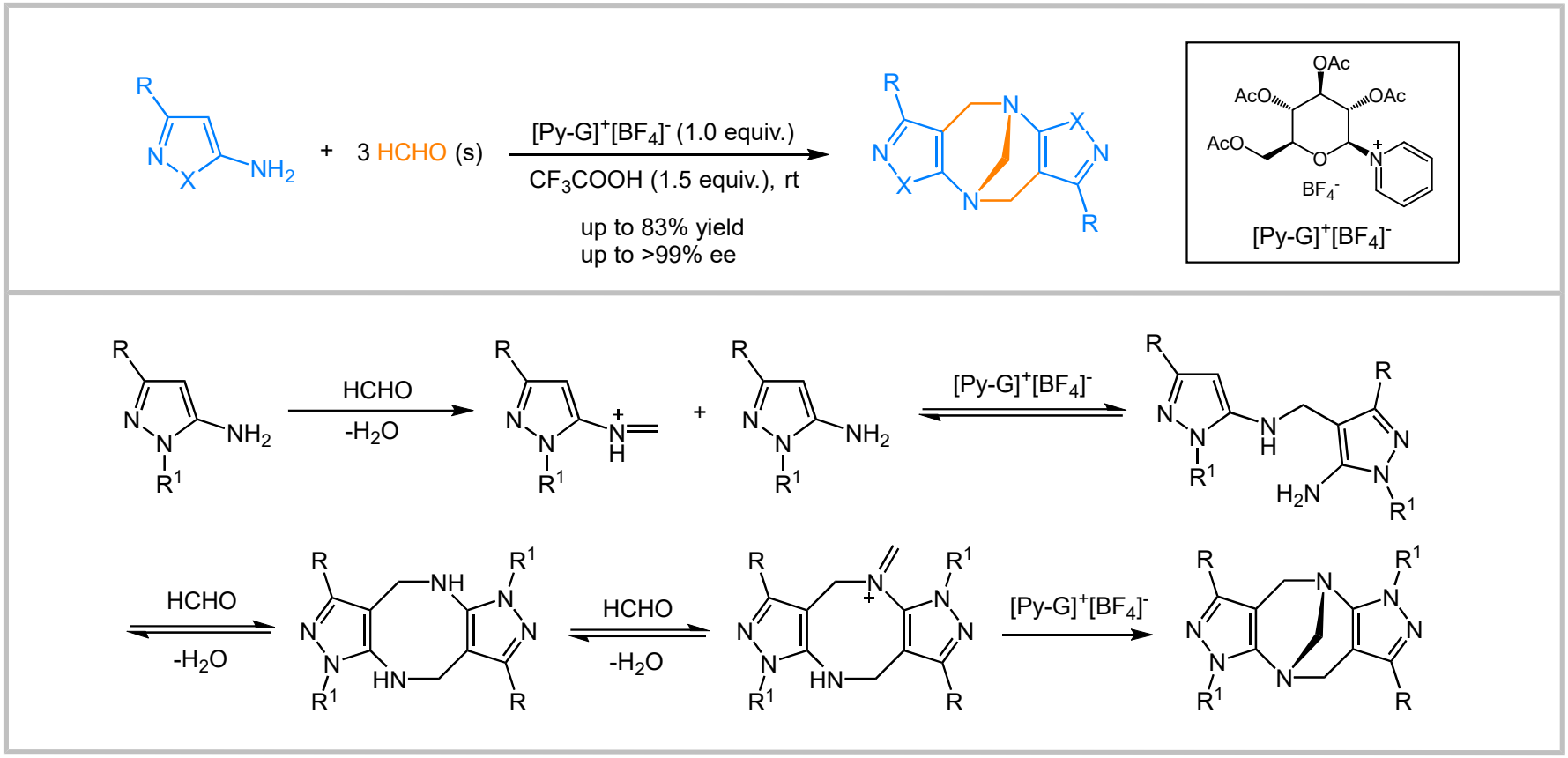
Luo, Z.; Liao, M.; Zhang, X.; Wu, X. *et al. Angew. Chem. Int. Ed.* **2024**, *63*, e202404979

Chiral Tetrahedral Ammonium



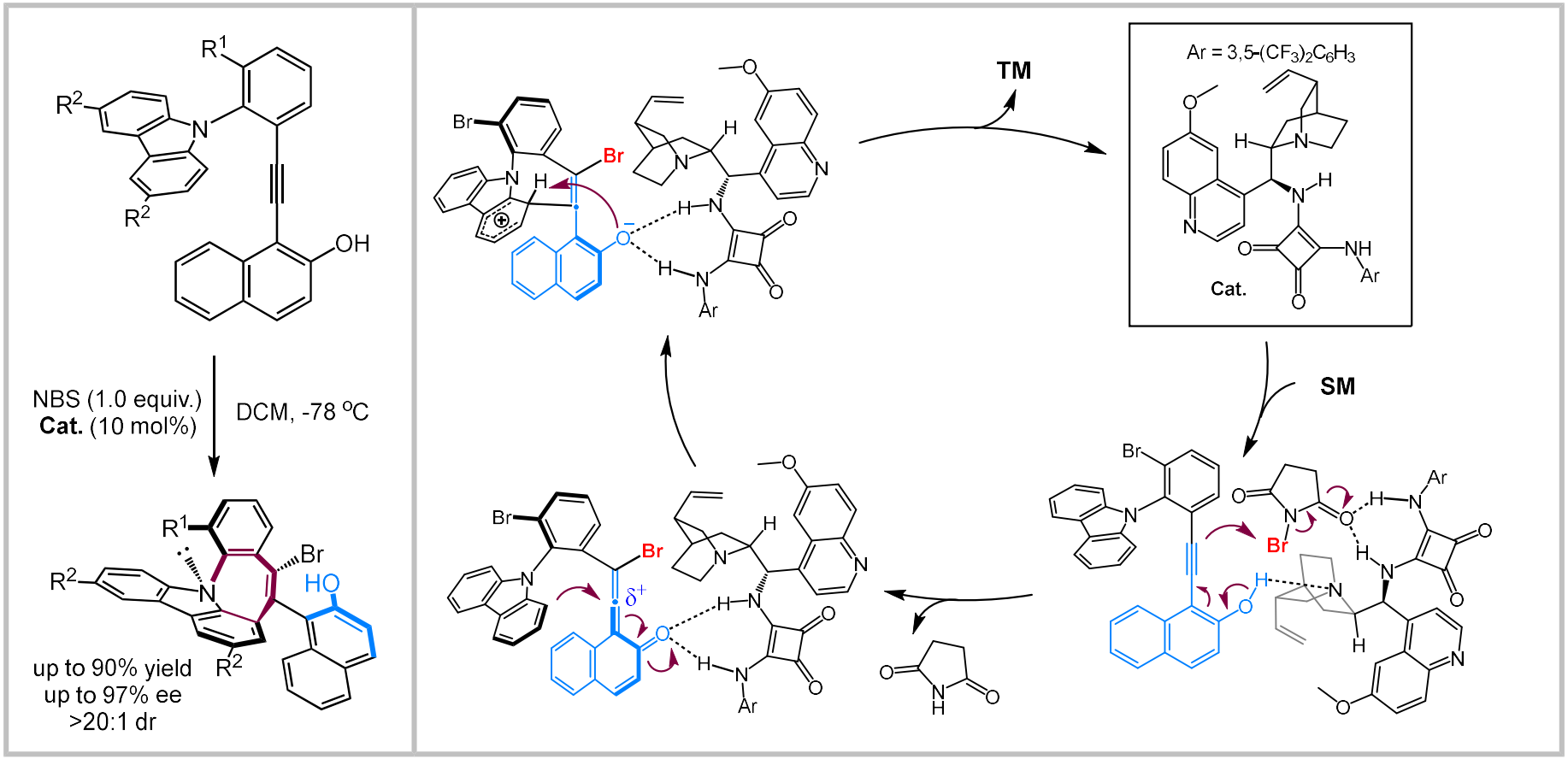
Walsh, M. P.; Phelps, J. M.; Lennon, M. E.; Yufit, D. S.; Kitching, M. O. *Nature* **2021**, *597*, 70-76

N Atom at Bridgehead



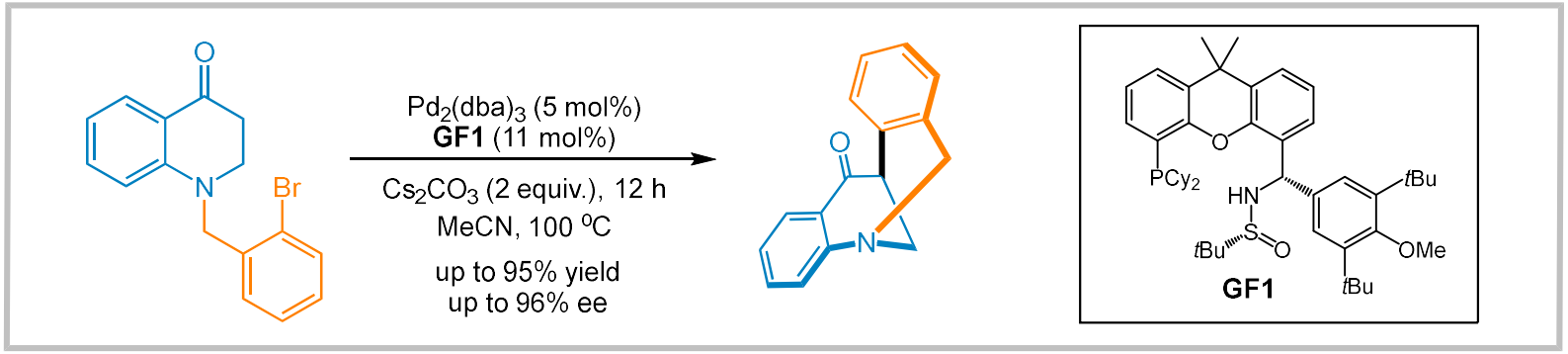
Yuan, R.; Wang, Y.-J.; Li, M.-Q.; Xu, J.-B.; Wan, Y.; Liu, Y.; Wu, H. *et al. Chem. Eng. J.* **2017**, *316*, 1026-1034

N Atom at Bridgehead

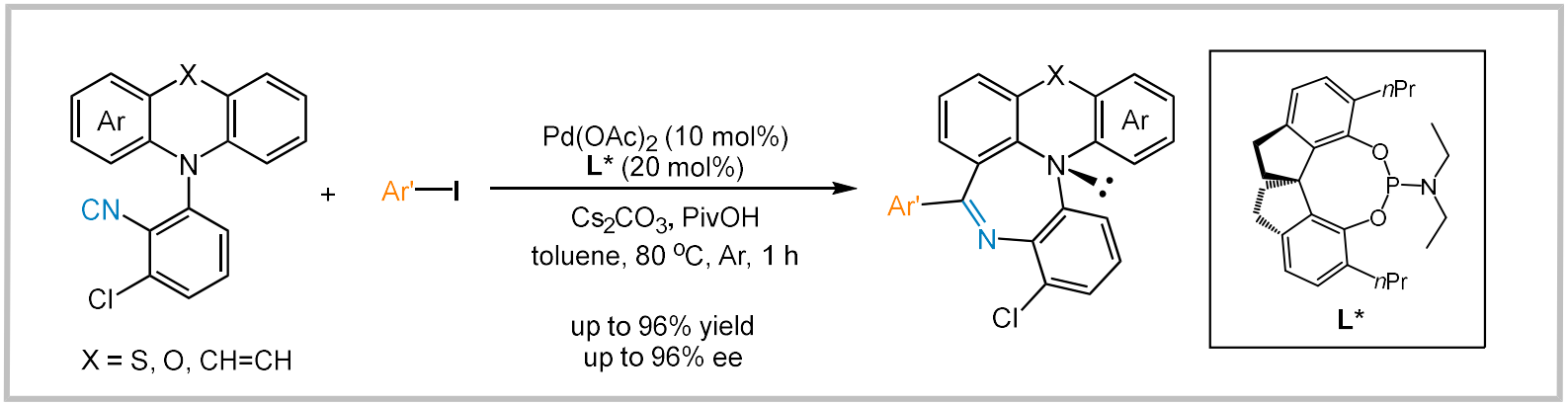


Huang, S.; Wen, H.; Tian, Y.; Wang, P.; Qin, W.; Yan, H. *Angew. Chem. Int. Ed.* **2021**, *60*, 21486-21493

N Atom at Bridgehead

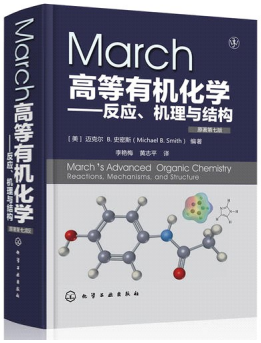


Ma, C.; Sun, Y.; Yang, J.; Guo, H.; Zhang, J. *ACS Cent. Sci.* **2023**, *9*, 64-71



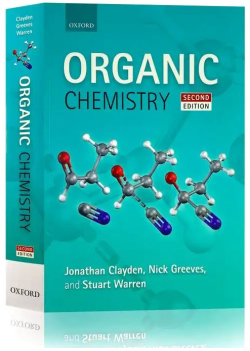
Yu, T.; Cheng, S.; Luo, Y.; Li, J.; Liang, Y.; Luo, S.; Zhu, Q. *ACS Catal.* **2023**, *13*, 9688-9694

Prospect



"The inversion barrier of trivalent nitrogen is typically 5-7 kcal/mol (~20-30 kJ/mol) but it increases when electronegative substituents (e.g., O, F, Cl) are attached to nitrogen."

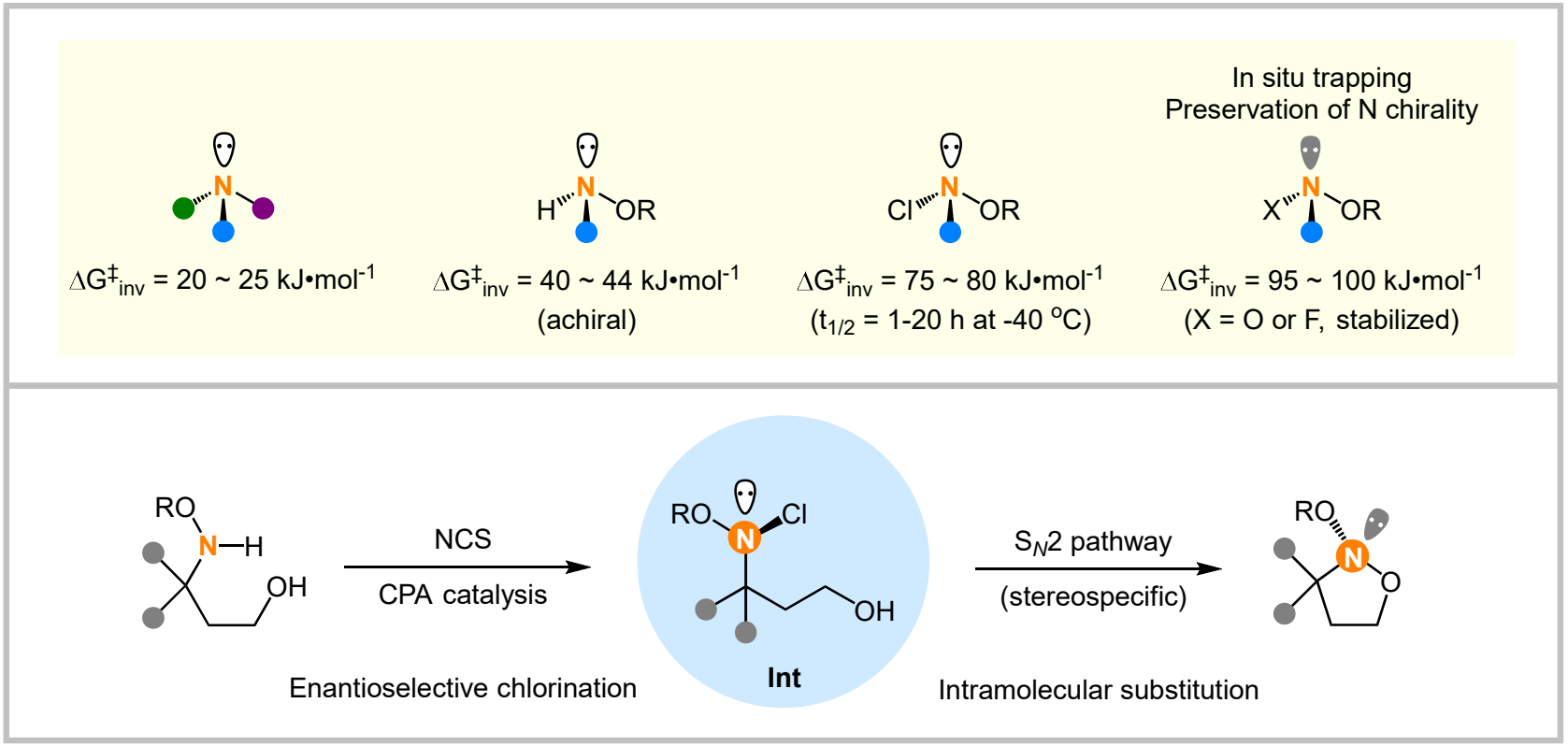
三价氮的翻转能垒通常为5-7 kcal/mol，但当连有电负性取代基如O、F、Cl时会升高。



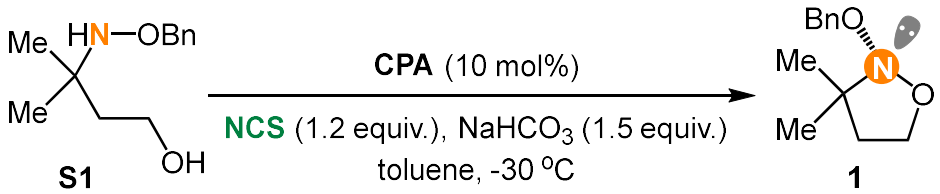
"Electron-withdrawing groups on nitrogen raise the inversion barrier by stabilizing the ground-state pyramidal geometry relative to the planar transition state."

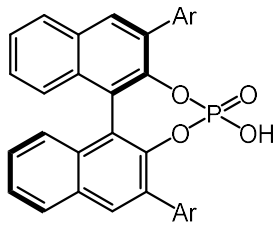
氮原子上的吸电子基团通过稳定其基态的锥形构型，从而提高构型翻转能垒。

Tan's Work

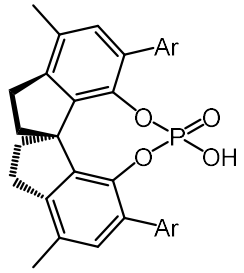

In situ trapping
Preservation of N chirality
ΔG‡inv = 20 ~ 25 kJ•mol-1
ΔG‡inv = 40 ~ 44 kJ•mol-1
(achiral)
ΔG‡inv = 75 ~ 80 kJ•mol-1
(t1/2 = 1-20 h at -40 °C)
ΔG‡inv = 95 ~ 100 kJ•mol-1
(X = O or F, stabilized)
RO
N—H
OH
NCS
CPA catalysis
RO
Cl
OH
Int
SN2 pathway
(stereospecific)
RO
O
Enantioselective chlorination
Intramolecular substitution

Optimization of the Reaction Conditions





(*R*)-**C1**: Ar = 1-naphthyl
(*R*)-**C2**: Ar = 9-anthracenyl
(*R*)-**C3**: Ar = 1-pyrenyl
(*R*)-**C4**: Ar = 2,4,6-*i*Pr$_3$-C$_6$H$_2$
(*R*)-**C5**: Ar = 2,4,6-Cy$_3$-C$_6$H$_2$



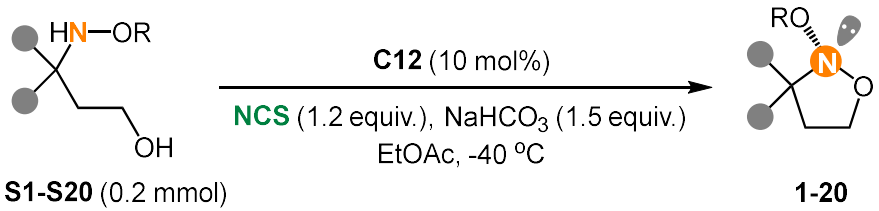
(*R*)-**C6**: Ar = 1-naphthyl
(*R*)-**C7**: Ar = 9-anthracenyl
(*R*)-**C8**: Ar = 1-pyrenyl
(*R*)-**C9**: Ar = 2,4,6-Me$_3$-C$_6$H$_2$
(*R*)-**C10**: Ar = 2,4,6-*i*Pr$_3$-C$_6$H$_2$
(*R*)-**C11**: Ar = 2,4,6-Cp$_3$-C$_6$H$_2$
(*R*)-**C12**: Ar = 2,4,6-Cy$_3$-C$_6$H$_2$

Entry	CPA	Yield (%)	Ee (%)
1	(*R*)-**C1**	70	-27
2	(*R*)-**C2**	79	-24
3	(*R*)-**C3**	81	-12
4	(*R*)-**C4**	64	-3
5	(*R*)-**C5**	69	-7
6	(*R*)-**C6**	73	23
7	(*R*)-**C7**	75	23
8	(*R*)-**C8**	82	25
9	(*R*)-**C9**	80	28
10	(*R*)-**C10**	88	63
11	(*R*)-**C11**	81	75
12	(*R*)-**C12**	88	78

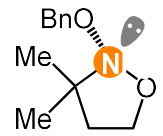
Optimization of the Reaction Conditions

Entry[a]	Base	Solvent	Temp.	Yield (%)	Ee (%)
1	$NaHCO_3$	Toluene	-30	88	78
2	$NaHCO_3$	DCM	-30	76	50
3	$NaHCO_3$	THF	-30	81	54
4	$NaHCO_3$	EtOAc	-30	85	90
5	$NaHCO_3$	Et_2O	-30	90	80
6	$NaHCO_3$	*n*-Hexane	-30	88	54
7	Et_3N	EtOAc	-30	58	15
8	DBU	EtOAc	-30	68	4
9	DABCO	EtOAc	-30	82	10
10	Na_2CO_3	EtOAc	-30	80	55
11	K_2CO_3	EtOAc	-30	85	31
12	Cs_2CO_3	EtOAc	-30	81	60
13	$NaHCO_3$	EtOAc	-40	85	92

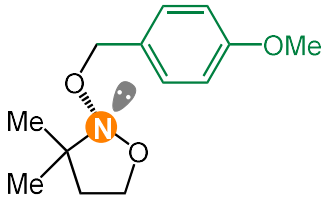
Substrate Generality



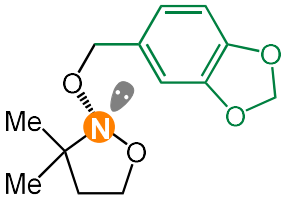
S1-S20 (0.2 mmol) **1-20**



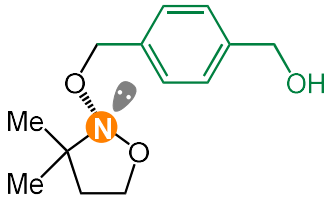
1, 92%, 91% ee



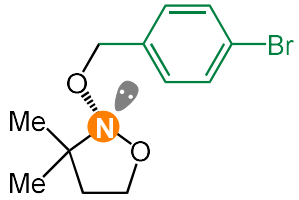
2, 89%, 92% ee



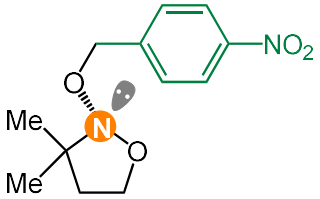
3, 87%, 94% ee



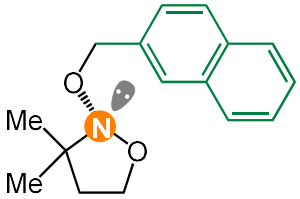
4, 87%, 93% ee



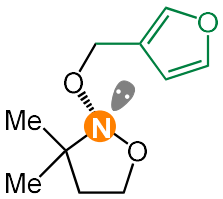
5, 83%, 92% ee



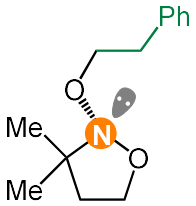
6, 81%, 56% ee



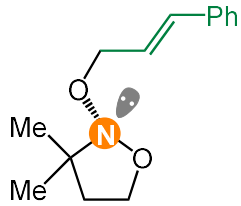
7, 92%, 94% ee



8, 63%, 76% ee

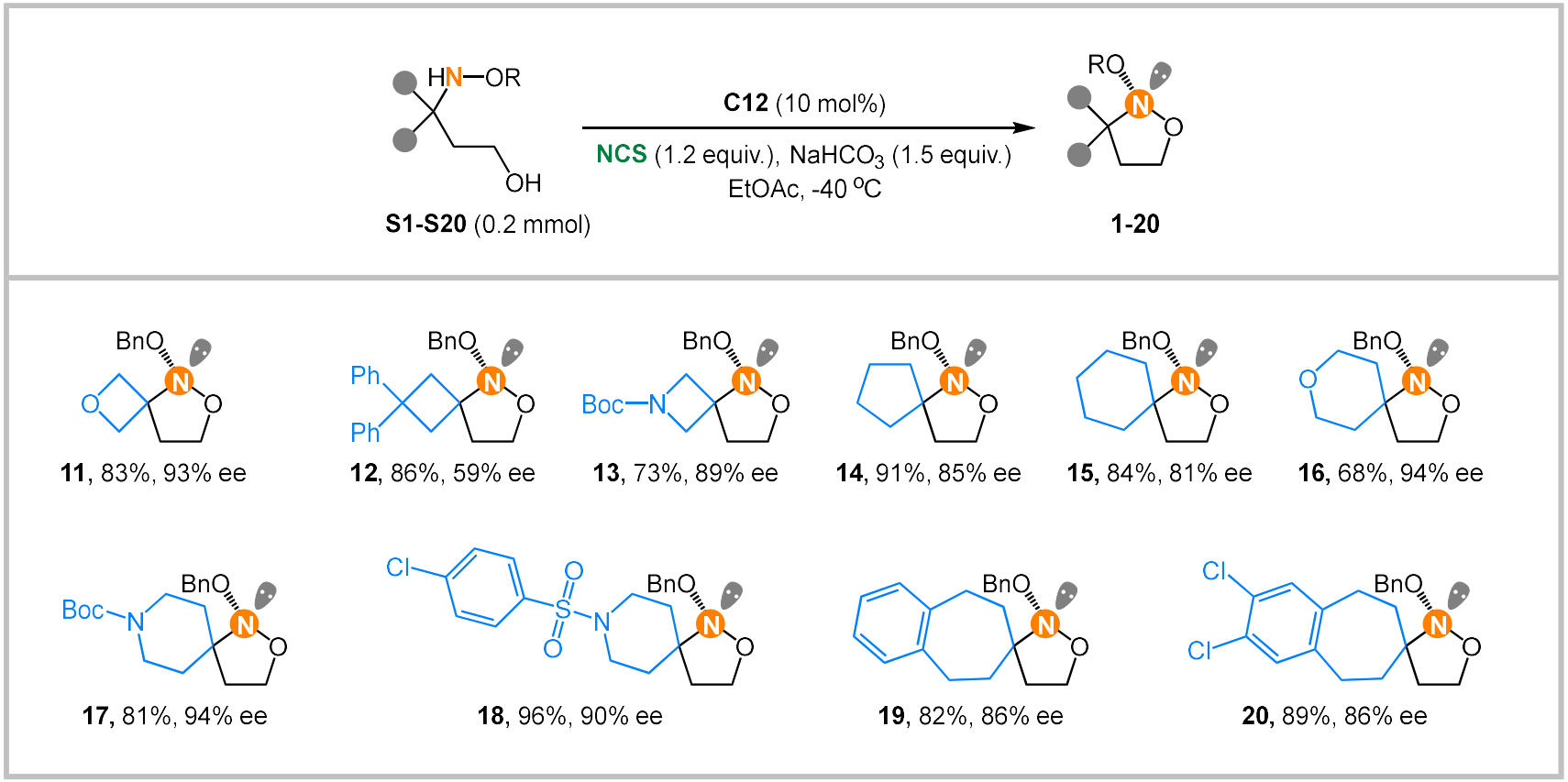


9, 84%, 89% ee

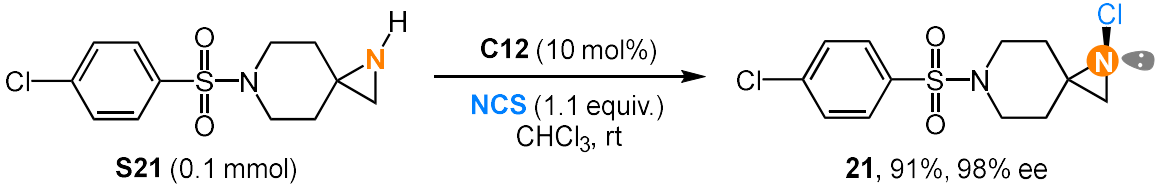


10, 94%, 93% ee

Substrate Generality

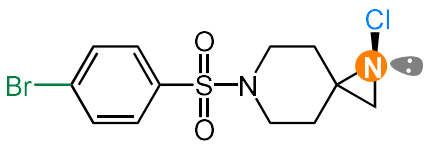


Substrate Generality

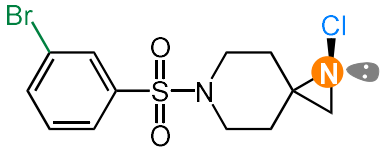


S21 (0.1 mmol)

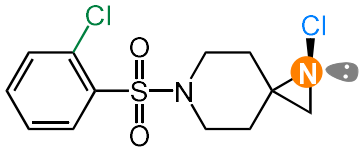
21, 91%, 98% ee



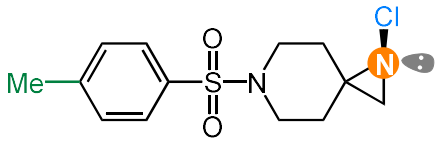
22, 88%, 97% ee



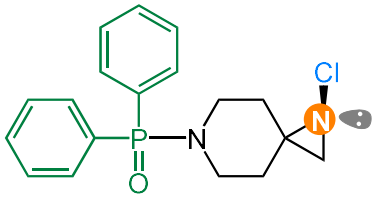
23, 84%, 98% ee



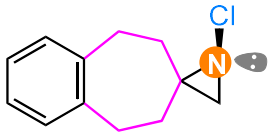
24, 82%, 98% ee



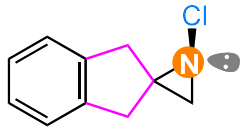
25, 82%, 97% ee



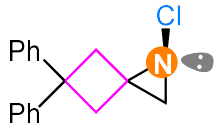
26, 91%, 91% ee



27, 92%, 93% ee



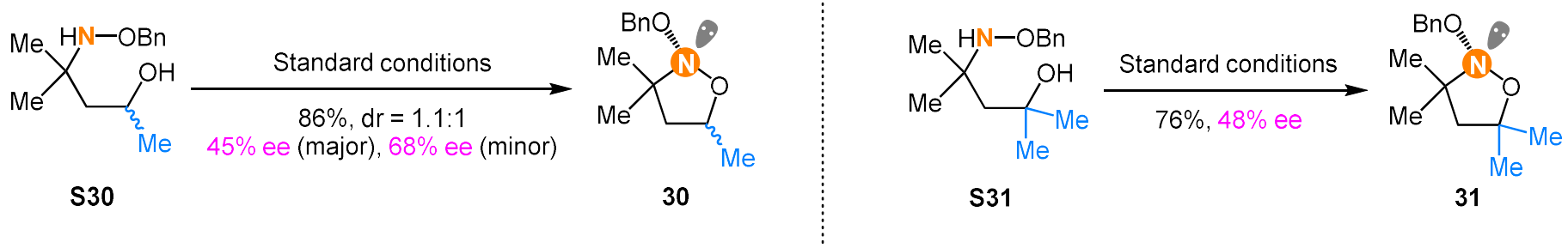
28, 92%, 96% ee



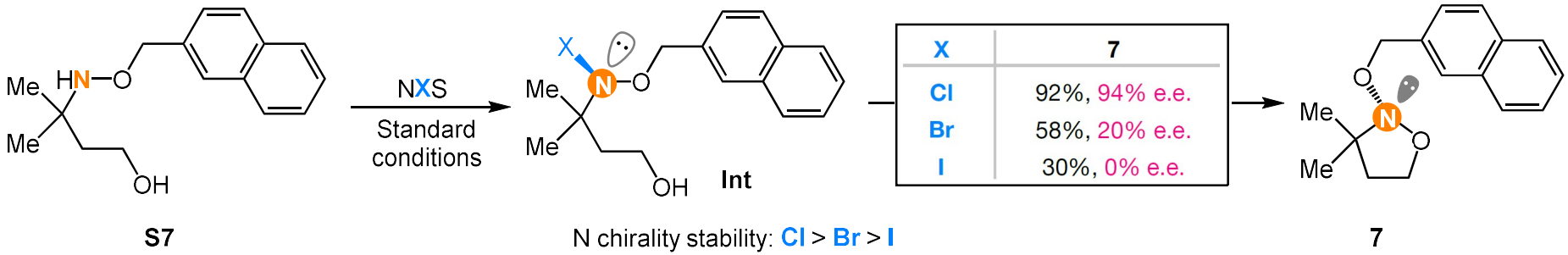
29, 85%, 97% ee

Mechanistic Investigations

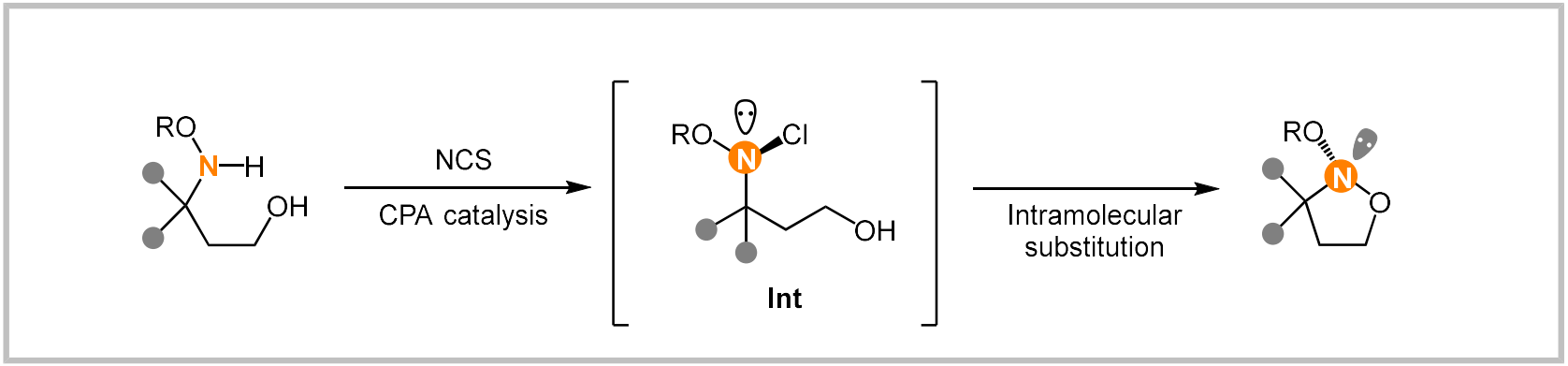
Control experiments with secondary and tertiary alcohols



Control experiments with different halogenation reagents



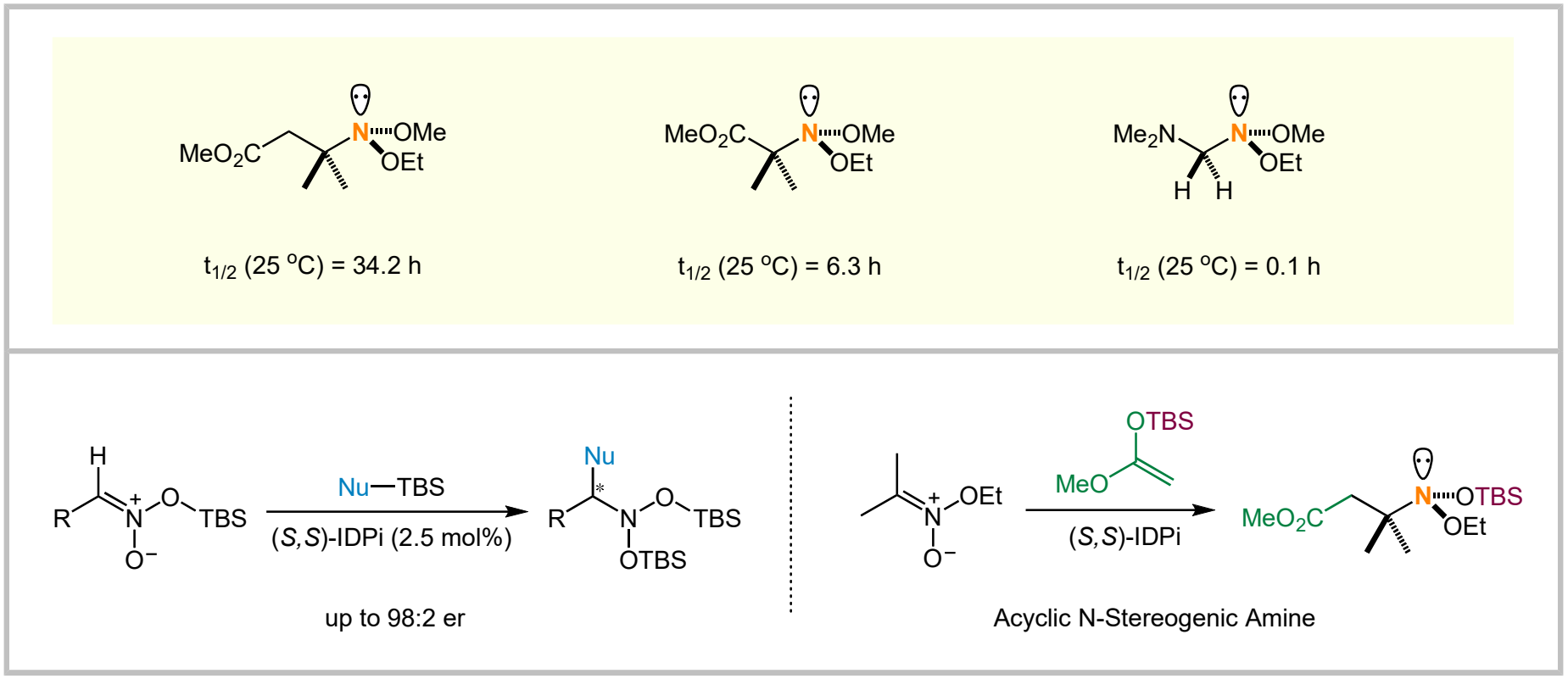
Summary



- Asymmetric control of N chirality through CPA-catalyzed chlorination;
- N stereocentre has been demonstrated through intramolecular trapping;
- Advancing method for the production of N-stereogenic structures.

Wu, S.; Chen, P.; Houk, K. N.; Tan, B. *et al. Nature* **2025**, *647*, 897-905.

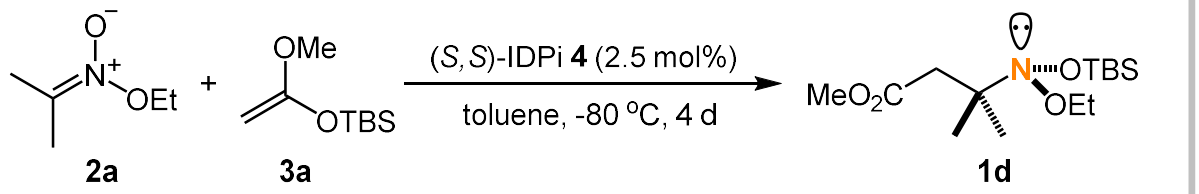
List's Work



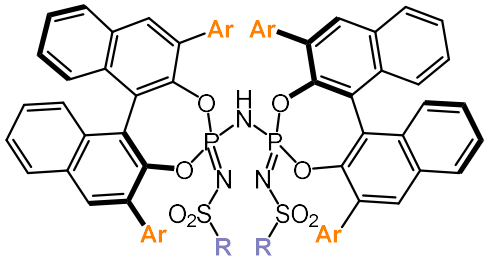
Kostyanovsky, R. G.; Shtamburg, V. G.; Chervin, I. I.; Nasibov, S. S. *et al. Tetrahedron* **1981**, *37*, 4245-4254

Das, S.; Mitschke, B.; Kanta De, C.; Harden, I.; Bistoni, G.; List, B. *Nat. Catal.* **2021**, *4*, 1043-1049

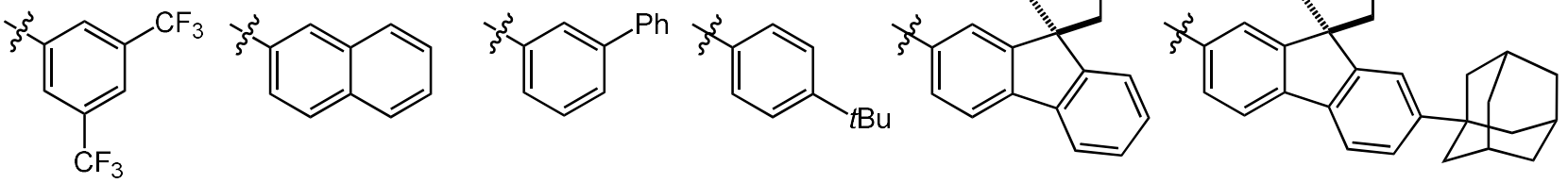
Optimization of the Reaction Conditions



2a **3a** **1d**

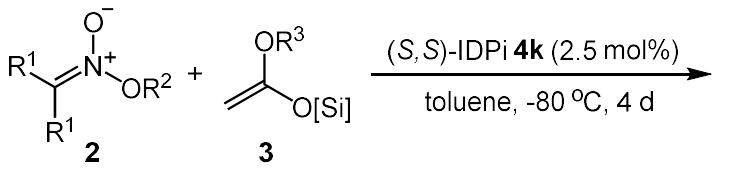


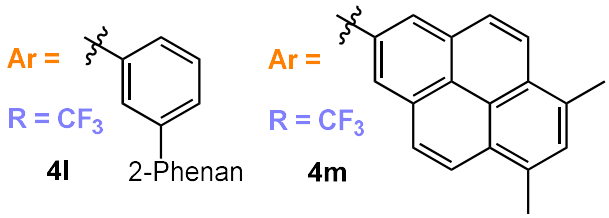
Ar =

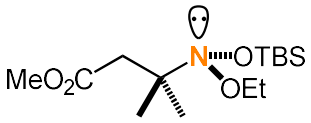


R = CF_3	**4a** 34%, 69:31 er	**4b** 40%, 61:39 er	**4c** 33%, 68:32 er	**4d** 33%, 65.7:34.3 er	**4e** 59%, 75:25 er	
R = C_6F_5	**4f** 86%, 32:68 er	**4g** 86%, 71.6:28.4 er	**4h** 49%,84:16 er	**4i** <5%, N. D. er	**4j** 95%, 89.7:10.3 er	**4k** 95%, 96.6:3.4 er

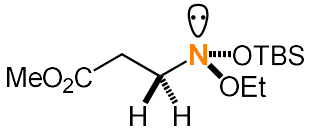
Substrate Generality



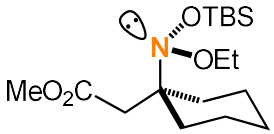




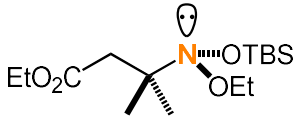
1d
68%, 96.6:3.4 er
$t_{1/2}$ = 44.4 h



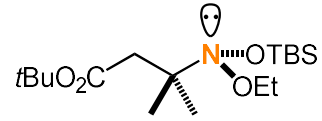
1e
95%, 92.5:7.5 er
$t_{1/2}$ = not possible



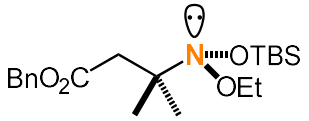
1f
64%, 80.7:19.3 er
$t_{1/2}$ = 13.3 h



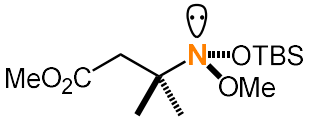
1g
38%, 87.2:12.8 er
$t_{1/2}$ = 46.2 h



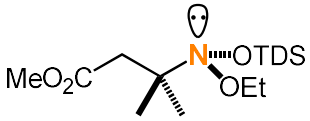
1h
86%, 86.2:13.8 er
$t_{1/2}$ = 48.5 h



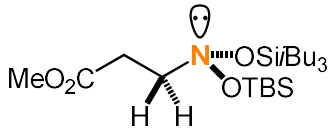
1i (4l)
66%, 95.9:4.1 er
$t_{1/2}$ = 36.9 h



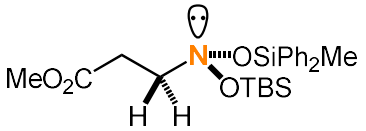
1j (4m)
93%, 92.8:7.2 er
$t_{1/2}$ = 58.3 h



1k
80%, 96.8:3.2 er
$t_{1/2}$ = 41.3 h



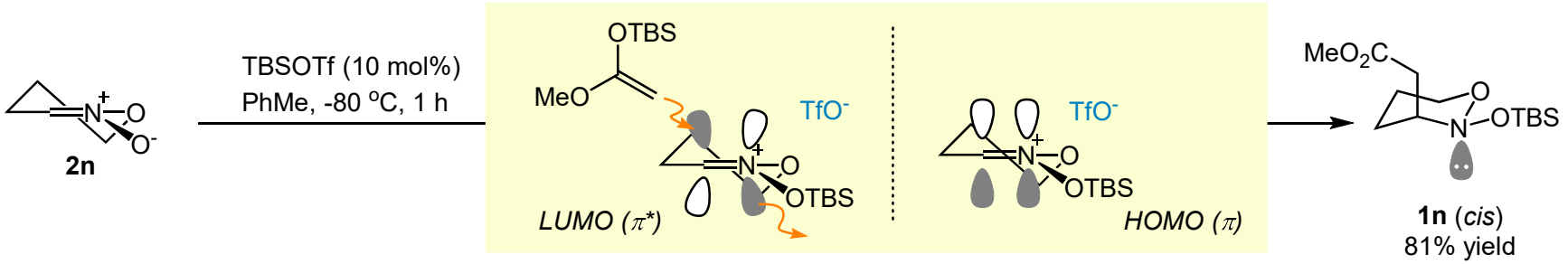
1l
36%, 67.7:32.3 er
$t_{1/2}$ = 256.7 h



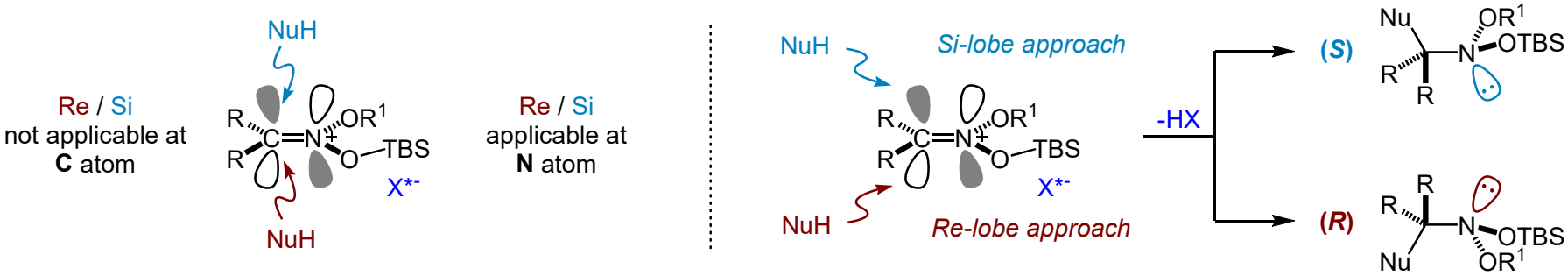
1m
47%, 75:25 er
$t_{1/2}$ = 288.8 h

Mechanistic Investigations

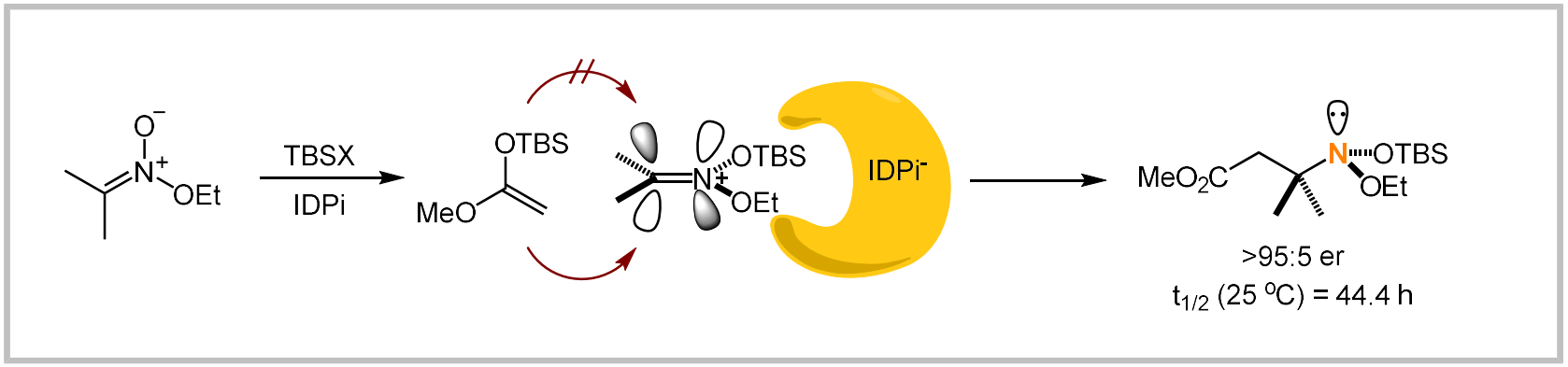
Antiperiplanar mechanism of the reaction



Enantiolobal differentiation



Summary



- Asymmetric synthesis of configurationally stable acyclic amines;
- Enzyme-like IDPi catalysts provide a uniquely defined chiral environment;
- Unique type of enantioselectivity "enantiolobal differentiation".

Zhu, C.; Das, S.; Sterling, M. S.; List, B. *et al. Nature* **2025**, *ASAP*

Writing Strategy

➢The First Paragraph

手性的重要性
硅膦硫手性发展

氮手性中心构建
的挑战和现状

- Although significant achievements have primarily focused on chirality at tetrahedral carbon stereocentres, progress in catalytic enantioselective construction of stereogenic centres involving heteroatoms has predominantly centred around period 3 elements such as silicon, phosphorus and sulfur, which can exhibit a remarkably stable configuration.
- Tri-substituted amines are pyramidal and show chirality when the substituents are different. However, the extremely low inversion barrier of the configuration at the nitrogen centre. As is well known, the labile configuration of the N stereocentre can be locked by quaternization to form the tetrahedral ammonium cation, and embedding the N atom at the bridgehead of bridged bicyclic structures is the most common means to stabilize the configuration of pyramidal N chirality. Recently, catalytic asymmetric construction of N stereogenic centres in bridged bicyclic tri-substituted amines has been sporadically realized through the formation of another cycle containing the stereogenic N centre.

Writing Strategy

➢**The Last Paragraph**

总结工作介绍亮点

方法学的意义

- We have developed the asymmetric control of N chirality through CPA-catalysed enantioselective chlorination. The effective stereoinduction of the transiently configurationally stable N stereocentres has been demonstrated through its stereospecific intramolecular trapping, leading to the formation of enantio-enriched N-alkoxy-1,2-oxazolidines.
- Control experiments and DFT calculations provide evidence for an S_N2 pathway for the intramolecular nucleophilic substitution process. This strategy has been applied to the direct synthesis of chloroaziridines featuring a configurationally stable N-stereogenic centre. This research advances methods for the production of N-stereogenic structures.

Representative Examples

- Chirality is central to life, and controlling the formation of one of a pair of mirror-image molecules (enantiomers) is a central **tenet** of synthetic chemistry. (n. 宗旨)

- Recently, catalytic asymmetric construction of N stereogenic centres in bridged bicyclic tri-substituted amines has been **sporadically realized** through the formation of another cycle containing the stereogenic N centre. (零星实现)

- Although direct isolation and characterization of these chiral species is **impractical**, we envision that their high activity can be **harnessed** to preserve stereochemical information through stereospecific. (impractical adj. 不切实际的; harness vt. 利用)