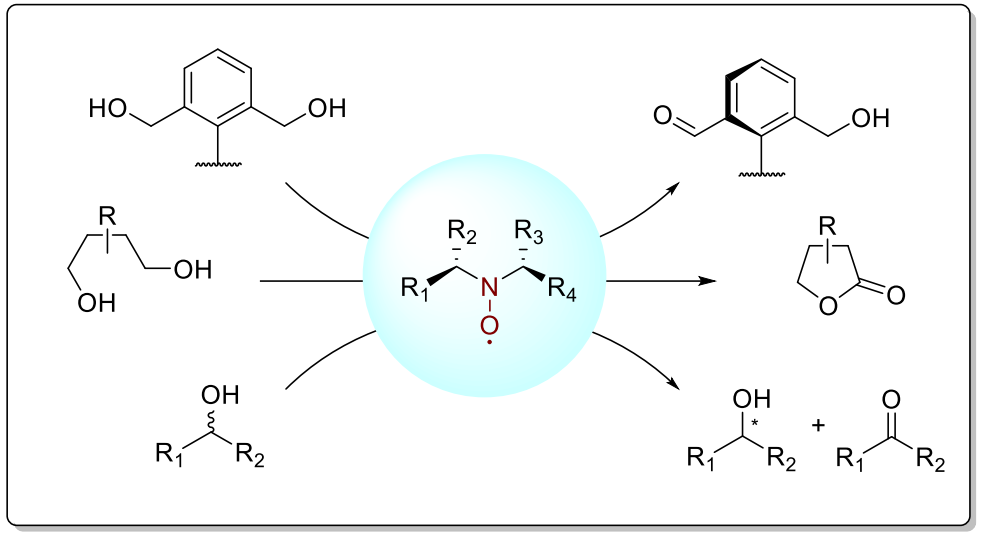

Asymmetric Oxidation of Alcohol Catalyzed by Chiral Nitroxide

Speaker: Jueqi Dong

Supervisor：Prof. Shengming Ma

Prof. Hui Qian

Date：2025.03.28

Outline

- Introduction
- Oxidative Desymmetrization Catalyzed by Chiral Nitroxide
- Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide
- Summary and Outlook

Outline

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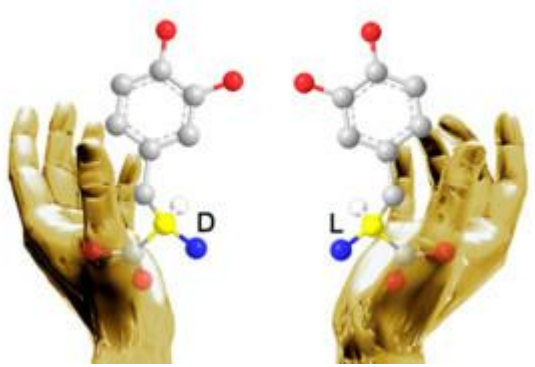
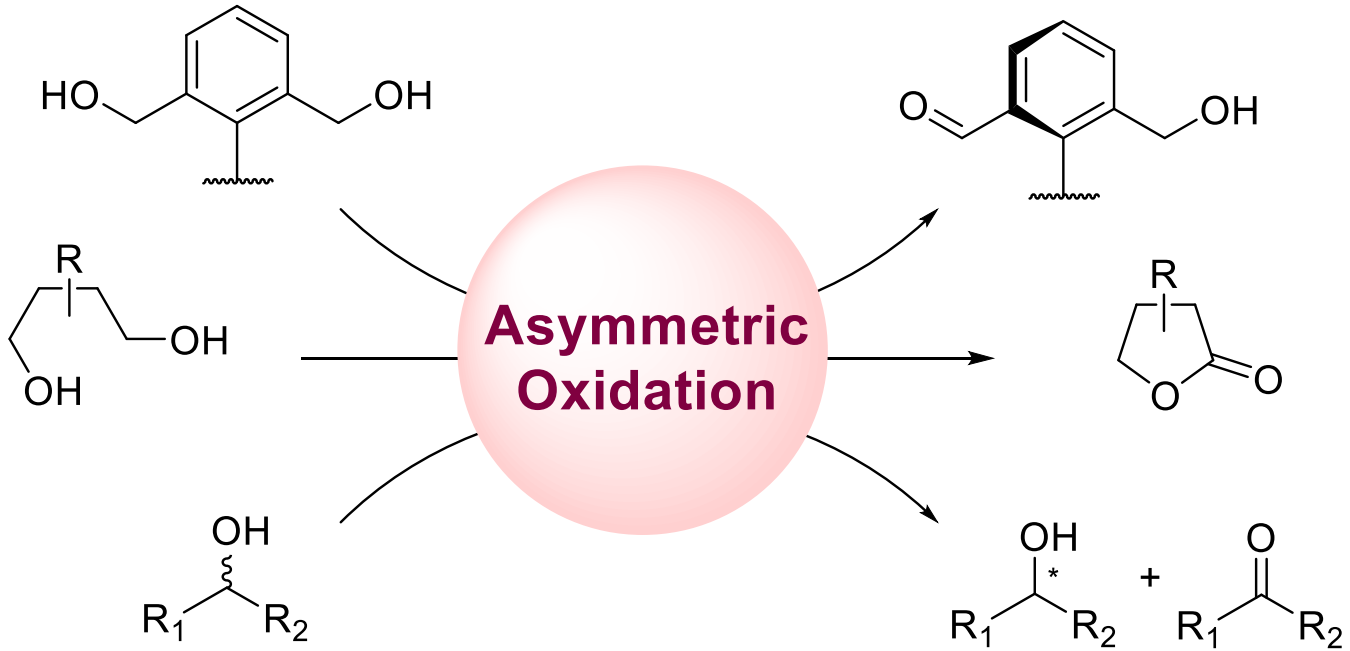
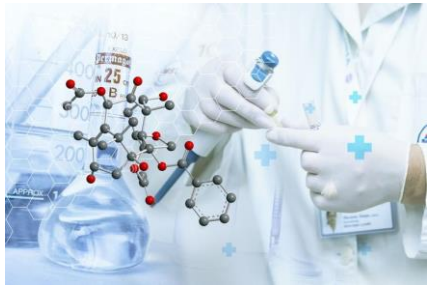
Introduction—Asymmetric Oxidation of Alcohols





Scientific Research

Pesticide



Medicine

Chem. Rev. **2023**, *123*, 10302−10380 *J. Am. Chem. Soc.* **2006**, *128*, 8412-8413

Introduction—Asymmetric Oxidation of Alcohols

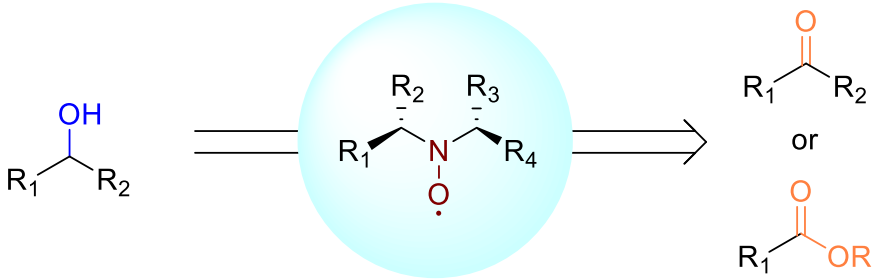
Transition Metal Catalysis

- ✓ Well developed
- ✓ High activity
- ✓ High selectivity
- ● Heavy metals required

Enzymatic Catalysis

- ✓ High efficiency
- ✓ High selectivity
- ✓ Mild condition
- ✓ Environmental-friendly
- ● Poor stability
- ● Poor substrate universality

N-oxyl radicals

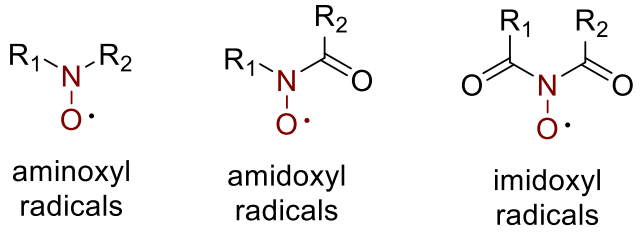


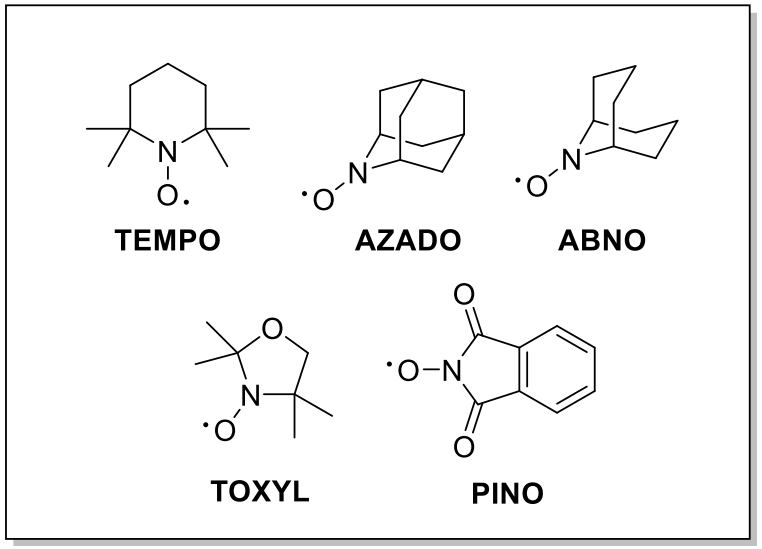
- ✓ Environmental-friendly
- ✓ Mild condition
- ✓ Easy to store
- ✓ High efficiency

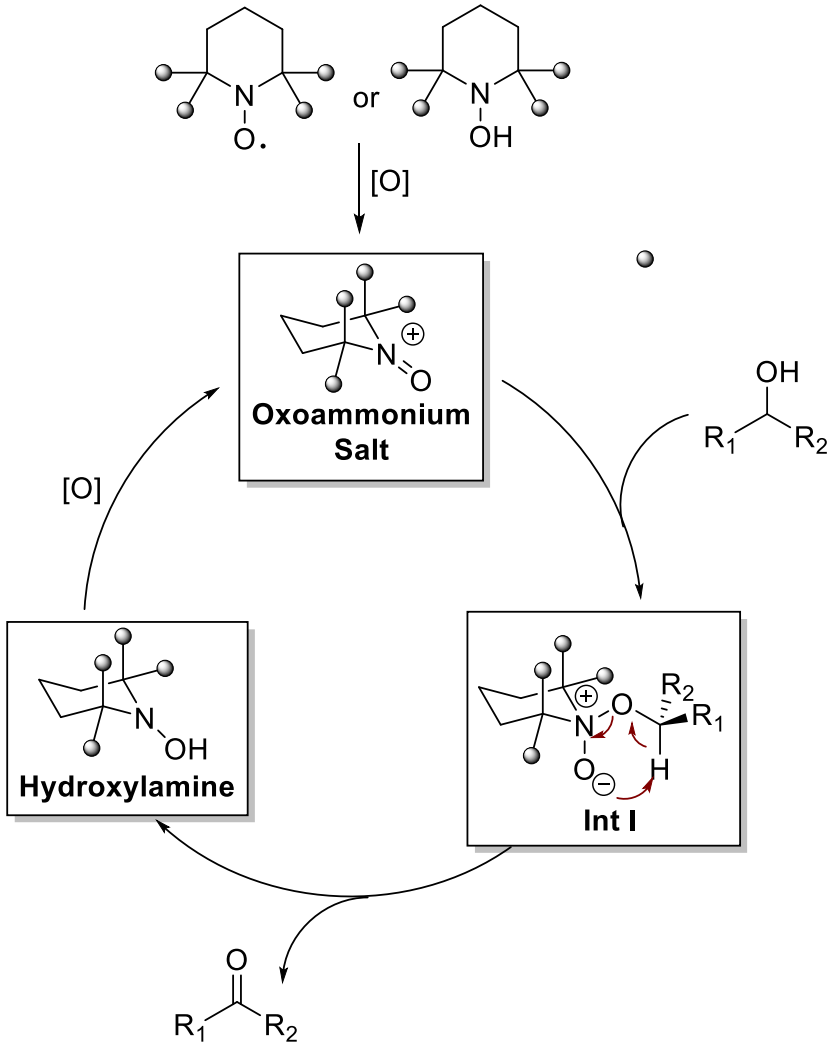
Chem. Rev. **2023**, *123*, 10302−10380 *J. Am. Chem. Soc.* **2006**, *128*, 8412-8413

Introduction—Chiral Nitroxide

N-oxyl radicals







Chem. Rev. **2023**, *123*, 10302−10380

J. Am. Chem. Soc. **2006**, *128*, 8412-8413

Outline

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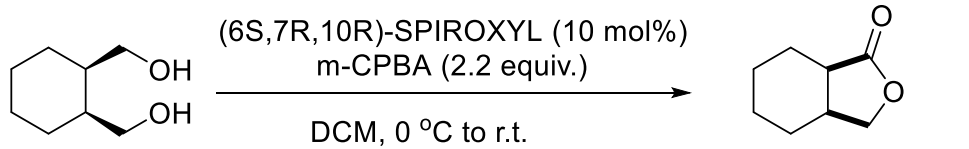
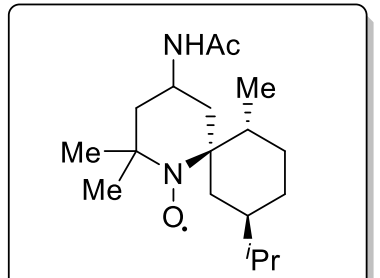
Oxidative Desymmetrization Catalyzed by Chiral Nitroxide

James Bobbitt

J. Bobbitt (1993)

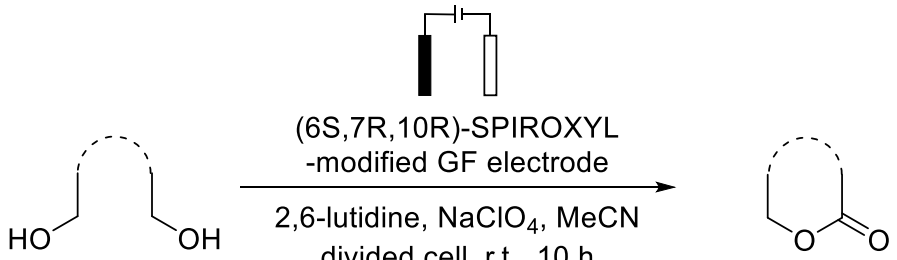


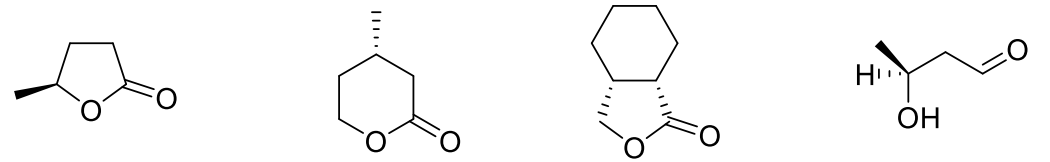
84% yield, 14% *ee*



(6S,7R,10R)-SPIROXYL

J. Bobbitt (2003)



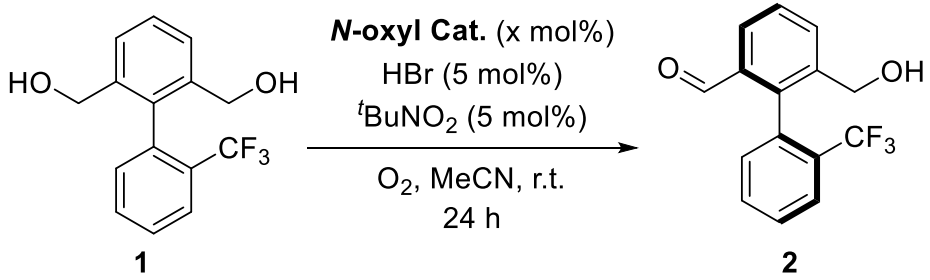


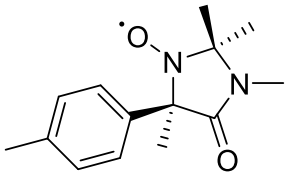
96.4%, 98% ee | 96.4%, 98% ee | 92%, 82% ee | 80.4%, 99% ee

J. Org. Chem. **1993**, *58*, 4837−4843 *Chem. Commun.* **2003**, 114-115

Oxidative Desymmetrization Catalyzed by Chiral Nitroxide

V. Blandin (2014)





Imidazolidinone-based Hydroxylamines

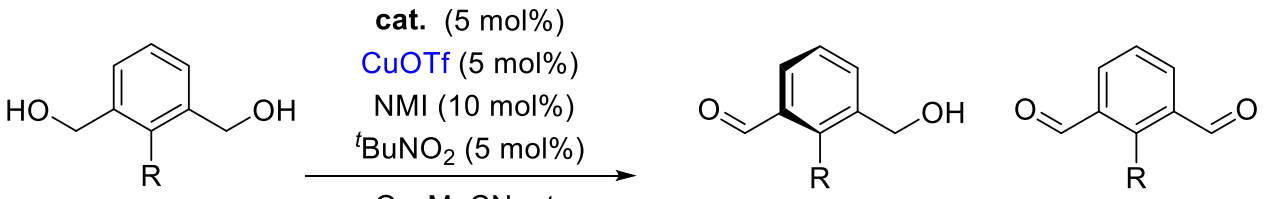
Entry	Amount of **cat.** [x mol%]	Time [h]	Conv. of **2** [%]	*ee* of **2** [%]
1	0	24	2	-
		48	4	-
		96	8	-
2	5	24	12	36
		96	39	24
3	20	24	22	44

Eur. J. Org. Chem. **2014**, 22, 4884–4896

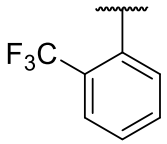
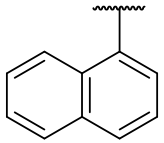
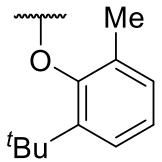
Oxidative Desymmetrization Catalyzed by Chiral Nitroxide

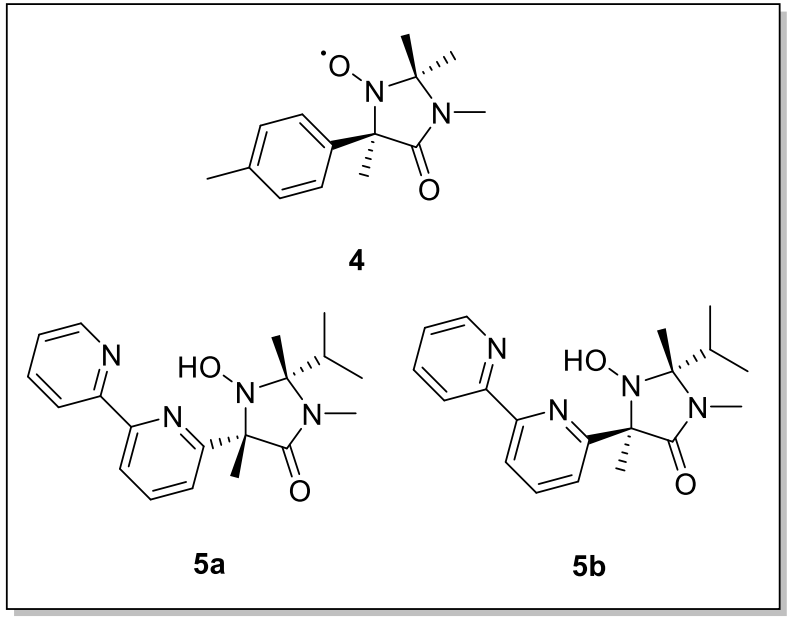
V. Blandin(2017)

a) Substrates Scope



1 **2** **3**

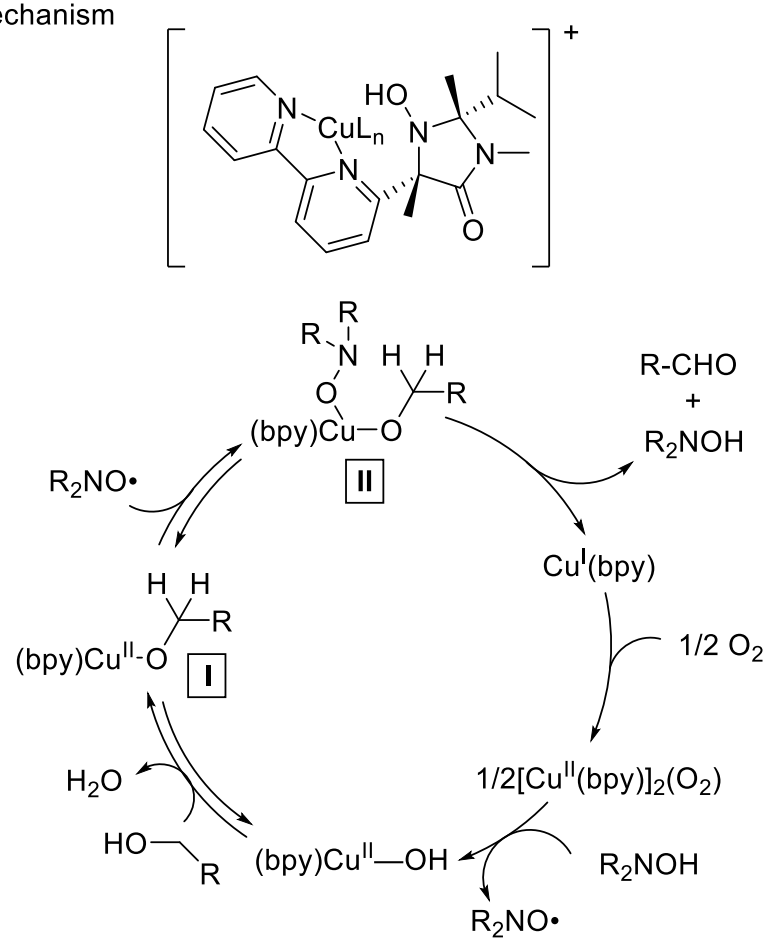
Entry	R-	Cat.	Add.	Time [h]	**2** [%]	*er* of **2** [%]	**5** [%]
1		**4**	bpy	8	60	65:35	20
2		**5a**	-	31	49	51:49	37
3		**5b**	-	23	45	32:68	49
4		**4**	bpy	6	41	66:34	34
5		**5a**	-	25	31	50:50	16
6				32	44	51:49	25
7		**5b**	-	8	33	44:56	13
8				31	25	42:58	42
9		**4**	bpy	30	36	55:45	18
10		**5a**	-	23	40	63:37	22
11		**5b**	-	23	42	17:83	40



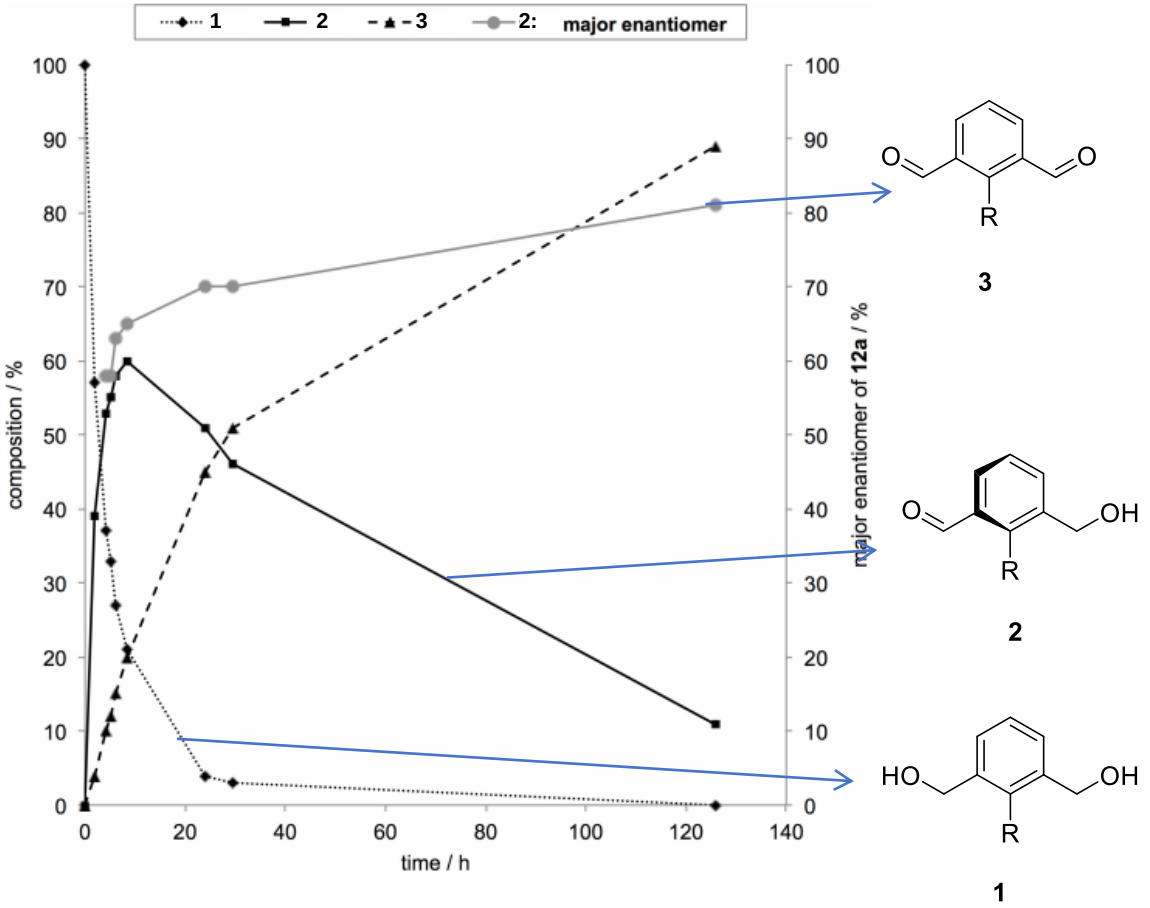
ChemistrySelect **2017**, *2*, 443–450

Oxidative Desymmetrization Catalyzed by Chiral Nitroxide

b) Possible mechanism

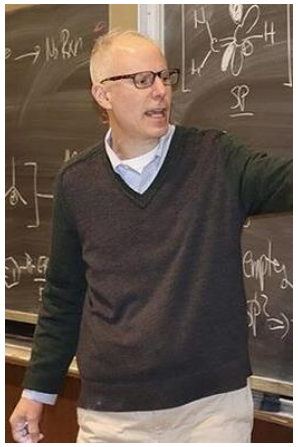


c) Evolution of the composition of the reaction mixture during oxidation of diol

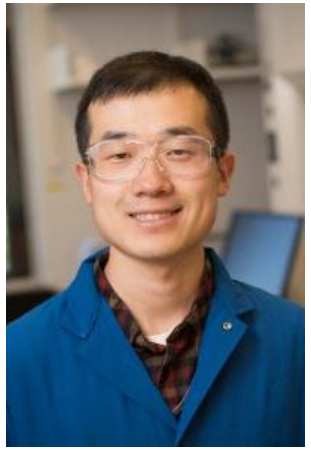


ChemistrySelect **2017**, *2*, 443–450

Oxidative Desymmetrization Catalyzed by Chiral Nitroxide

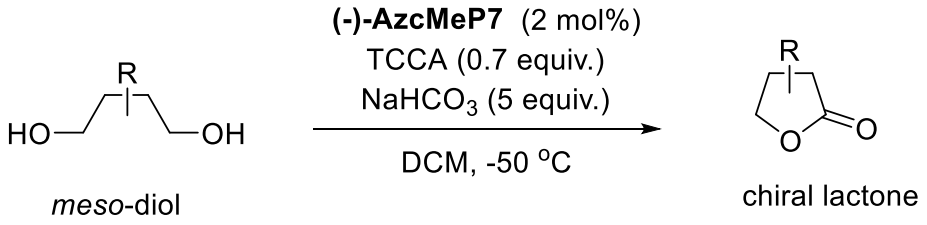


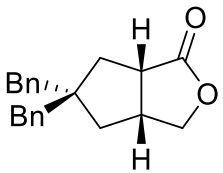
Scott. J. Miller

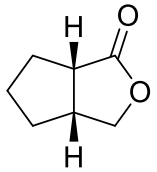


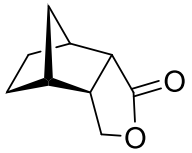
Song Lin

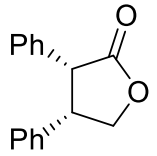
Miller and Lin (2023)

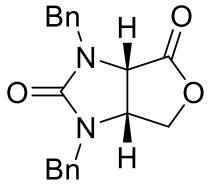


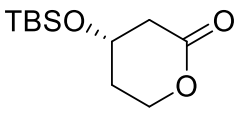

77% yield
96% *ee*

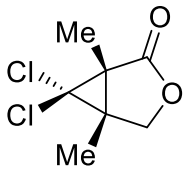

75% yield
96% *ee*

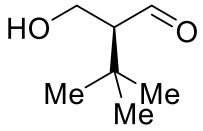

70% yield
97% *ee*

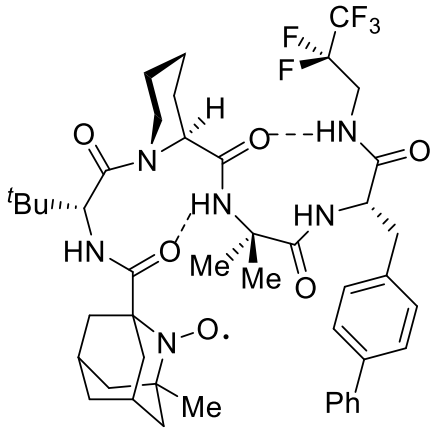

80% yield
91% *ee*

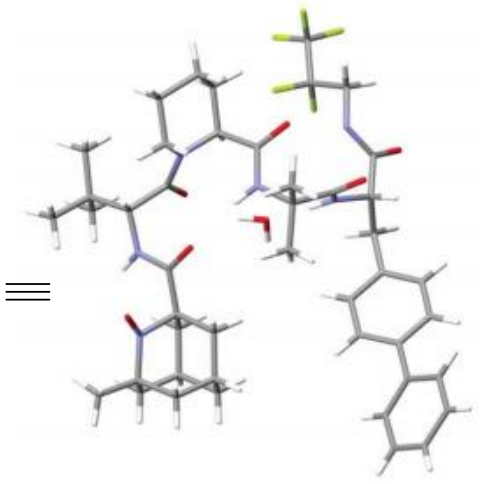

67% yield
60% *ee*

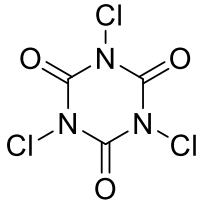

68% yield
37% *ee*


91% yield
33% *ee*


95% yield
91% *ee*

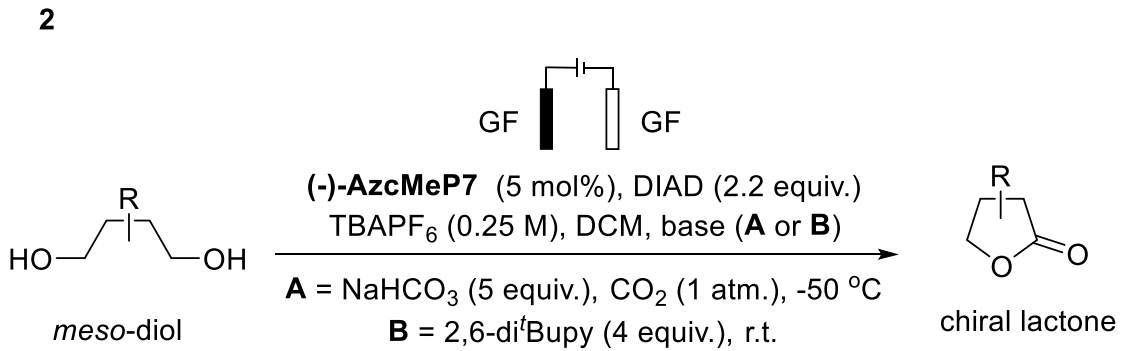

(-)-AzcMeP7

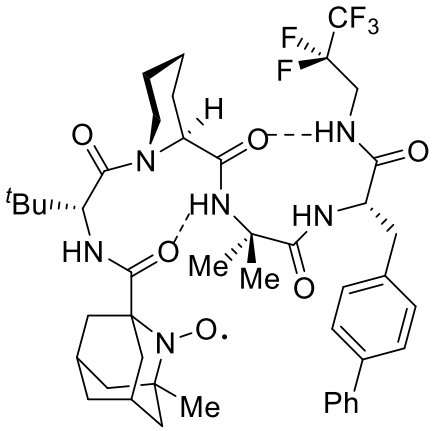



TCCA

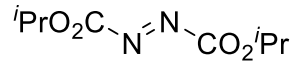
Science **2023**, *380*, 706–712

Oxidative Desymmetrization Catalyzed by Chiral Nitroxide





(-)-AzcMeP7

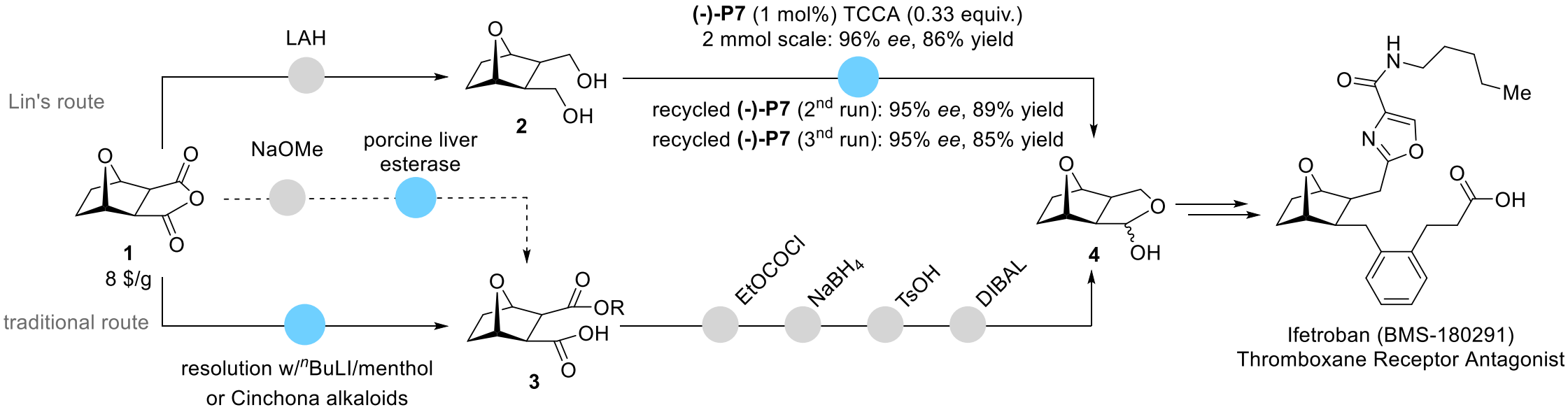


DIAD
mild oxidant

Science **2023**, *380*, 706–712

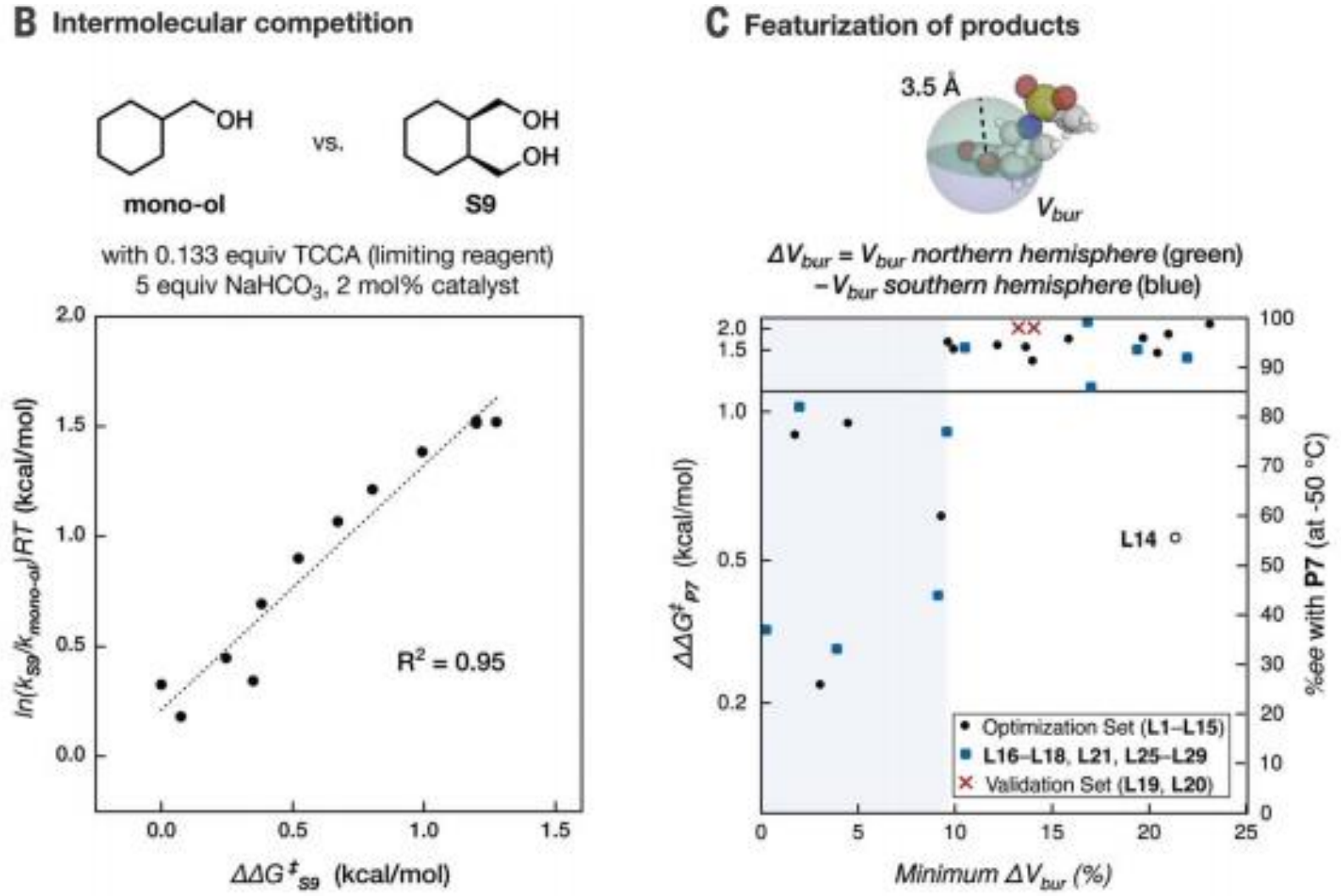
Oxidative Desymmetrization Catalyzed by Chiral Nitroxide

Utility in the synthesis of drug molecules



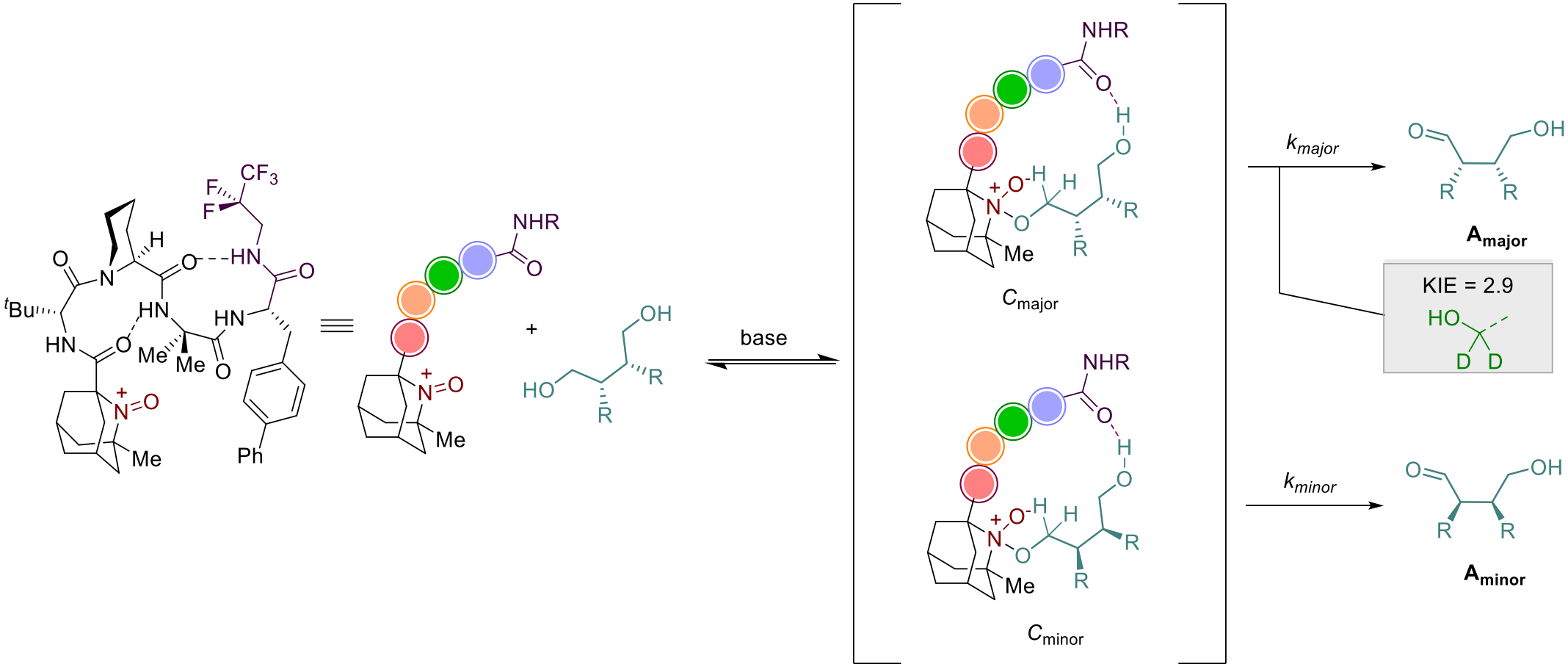
Science **2023**, *380*, 706–712

Oxidative Desymmetrization Catalyzed by Chiral Nitroxide



Science **2023**, *380*, 706–712

Oxidative Desymmetrization Catalyzed by Chiral Nitroxide



Science **2023**, *380*, 706–712

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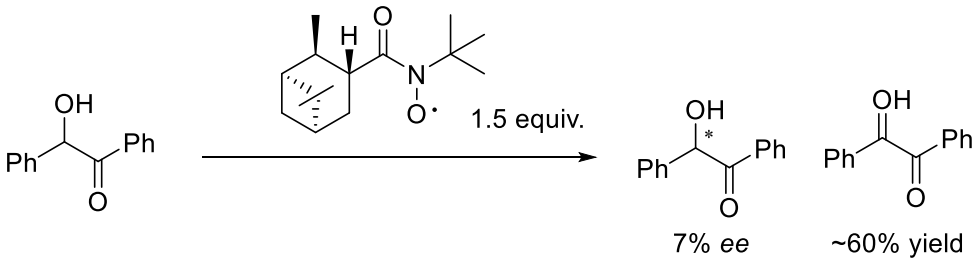
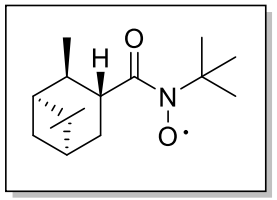
Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

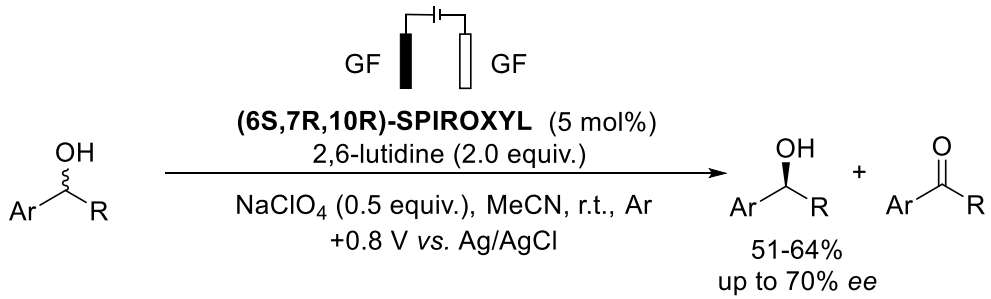
Early works:

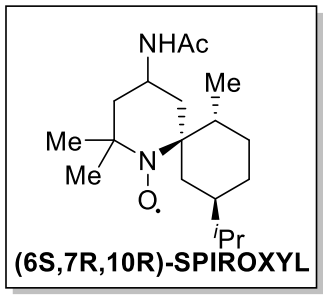
C. Berti & M. J. Perkins(1979)



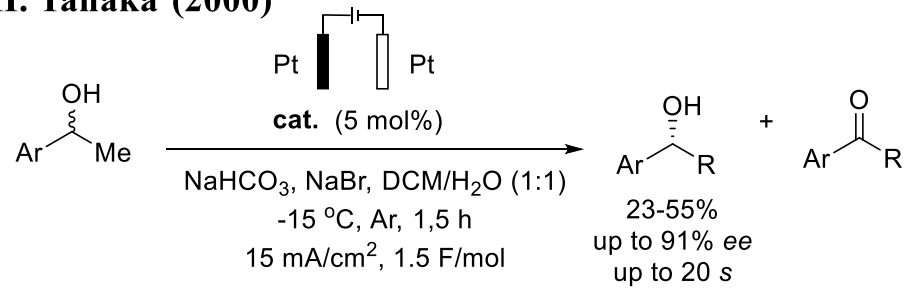


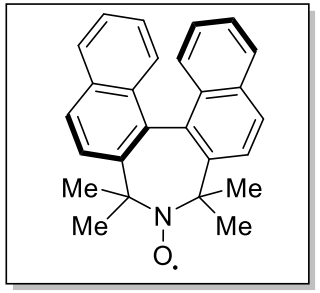
J. Bobbitt (1999)





H. Tanaka (2000)

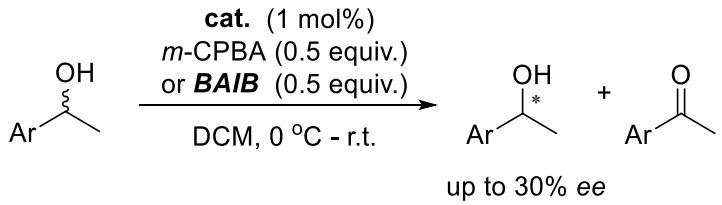


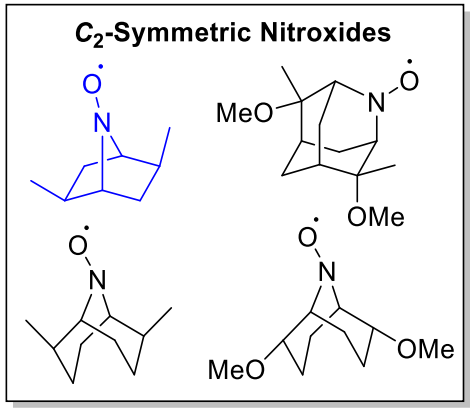


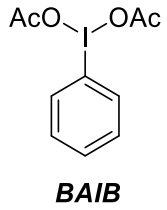
Angew. Chem., Int. Ed. Engl. **1979**, *18*, 864– 865 *Tetrahedron Lett.* **2000**, *41*, 8131–8135. *Tetrahedron Lett.* **1999**, *40*, 6469–6472.

Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

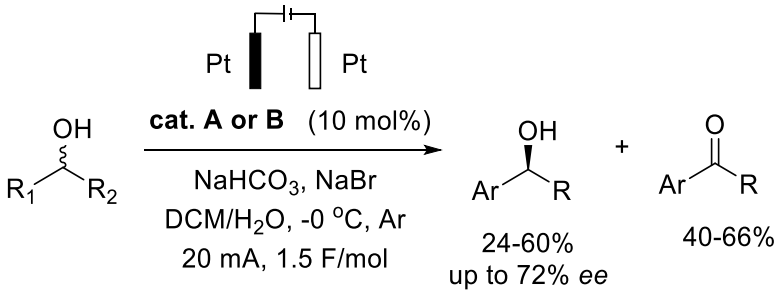
S. Rychnovsky & P. Farmer (2005)

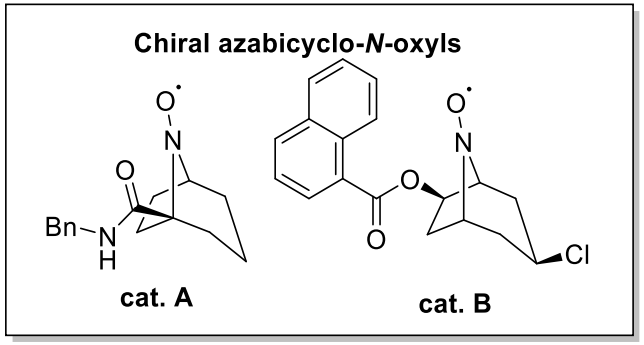






O. Onomura (2008)

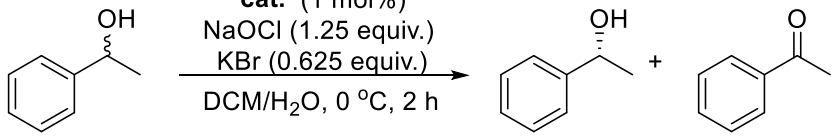


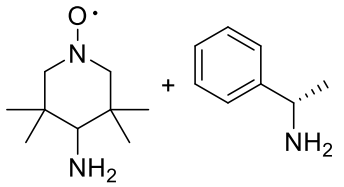
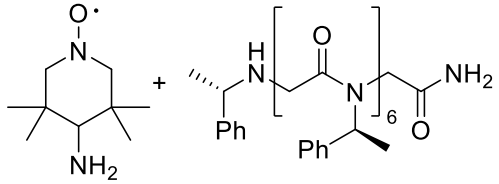


Tetrahedron: Asymmetry **2005**, *16*, 3584–3598. *Tetrahedron Lett.* **2008**, *49*, 5247−5251

Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

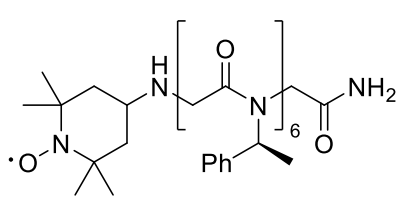
M. Ward & K. Kirshenbaum (2009)



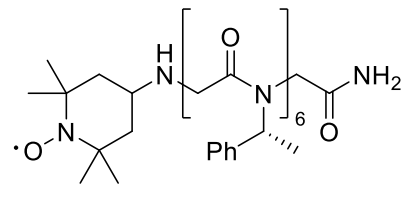
Catalytic system	Conversion (%)	Selectivity[b] (%)	*ee* %	*S*[c]
	22	None	None	1
	86	None	None	1
1S NTEMPO(Nspe)$_6$	84	60 (*S*)	>99 (*R*)	5.6
1R NTEMPO(Nrpe)$_6$	85	59 (*R*)	>99 (*S*)	5.4
2S NspeNTEMPO(Nspe)$_5$	26[a]	None	None	1
3S (Nspe)$_2$NTEMPO(Nspe)$_4$	25[a]	None	None	1
4S (Nspe)$_3$NTEMPO(Nspe)$_3$	56	52 (*R*)	5 (*S*)	1.1

[a] conversion values at 30 min. [b] Selectivity at the quoted conversion value is defined as (% preferred enantiomer / % conversion). [c] S is the selectivity coefficient, as defined by S= ln(1-*C*)(1- ee)/ln[(1- *C*)(1 + ee)], *C* is the Conversion

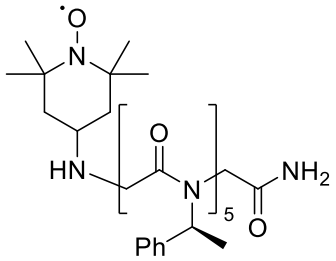
Helical "Peptoid" Oligomers



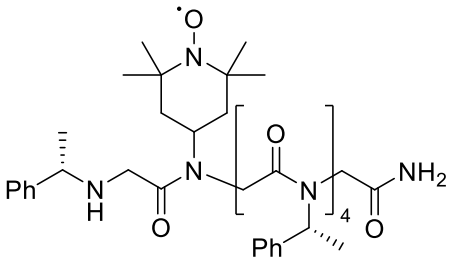
1S NTEMPO(Nspe)$_6$



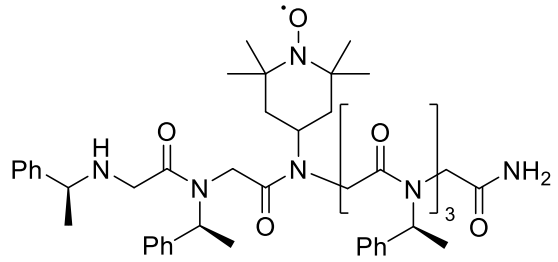
1R NTEMPO(Nrpe)$_6$



2S NspeNTEMPO(Nspe)$_5$



3S (Nspe)$_2$NTEMPO(Nspe)$_4$

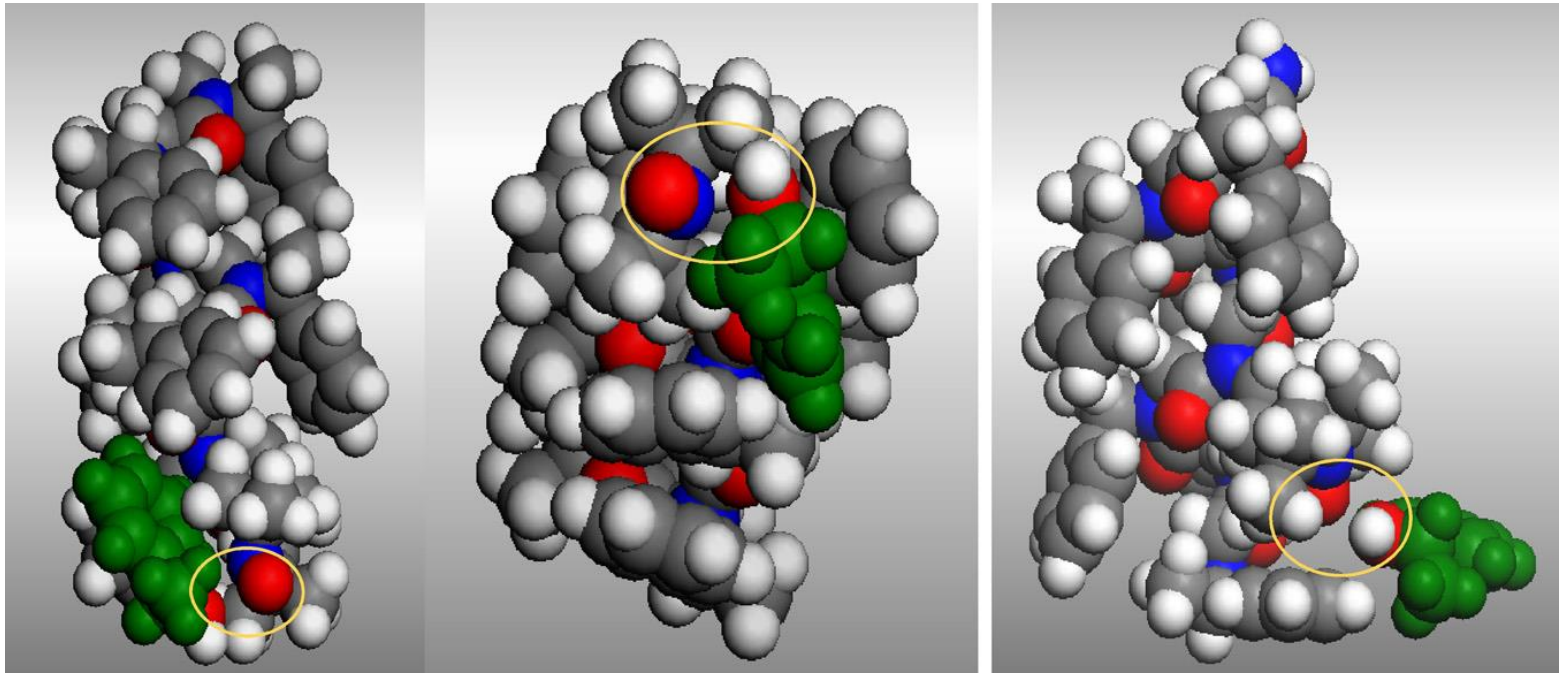


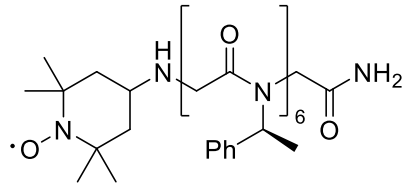
4S (Nspe)$_3$NTEMPO(Nspe)$_3$

Proceedings of the National Academy of Sciences **2009**, *106*, 13679-13684

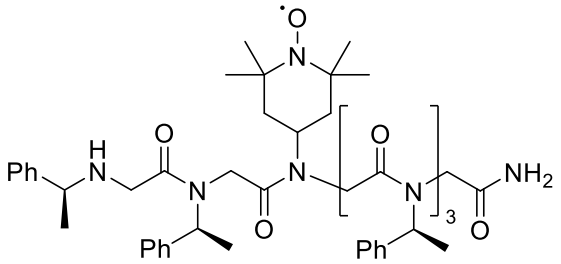
Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

Models of substrate– catalyst interaction





1S NTEMPO(Nspe)$_6$

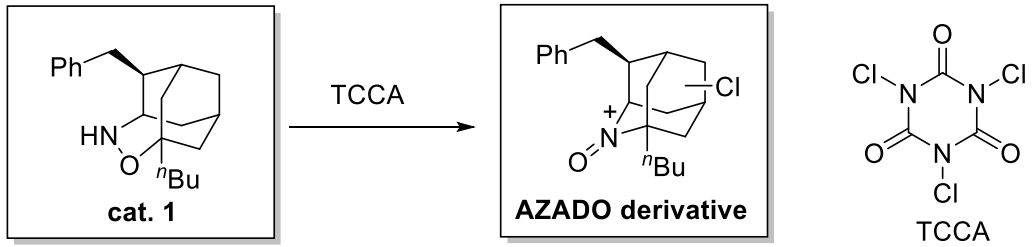


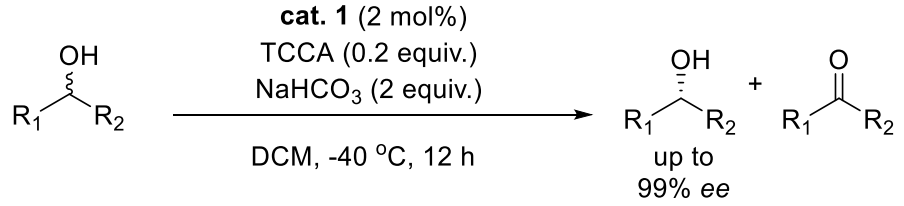
4S (Nspe)$_3$NTEMPO(Nspe)$_3$

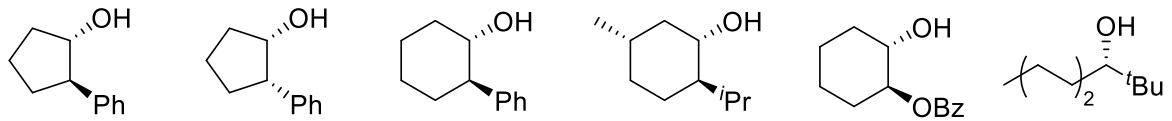
Proceedings of the National Academy of Sciences **2009**, *106*, 13679-13684

Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

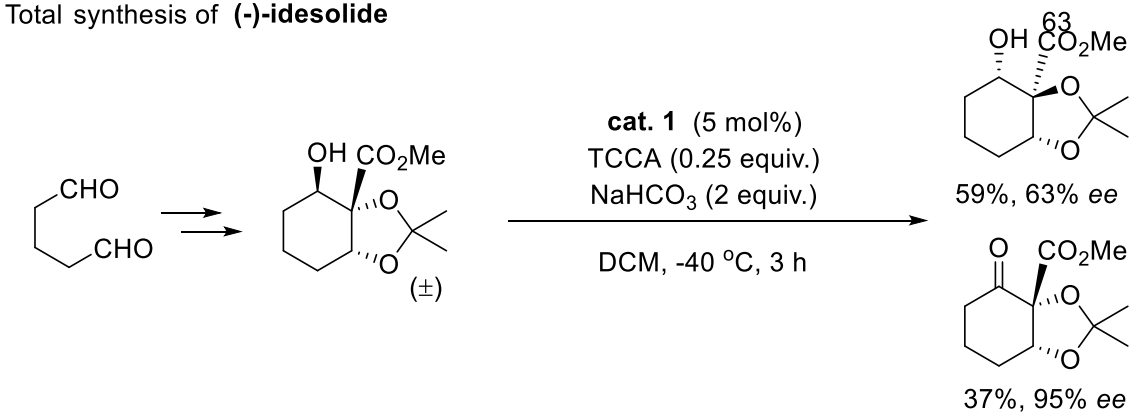
Y. Iwabuchi (2009)





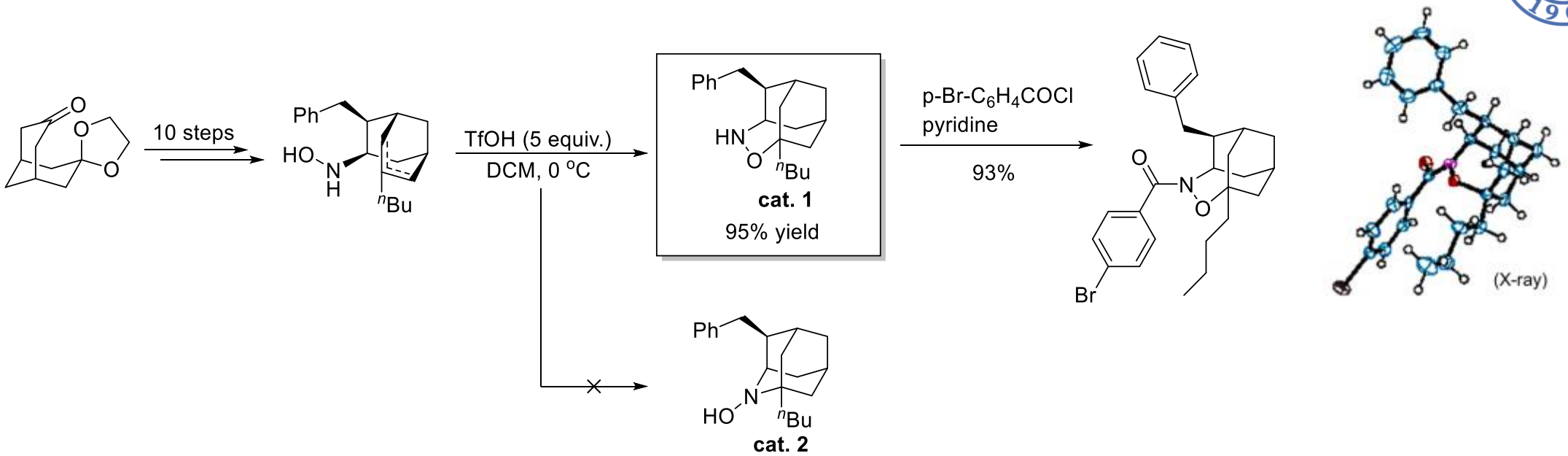


Total synthesis of **(-)-idesolide**



Org. Lett. **2009**, *11*, 1829–1831. *Org. Lett.* **2010**, *12*, 5, 980–983 *J. Am. Chem. Soc.* **2014**, *136*, 17591−17600

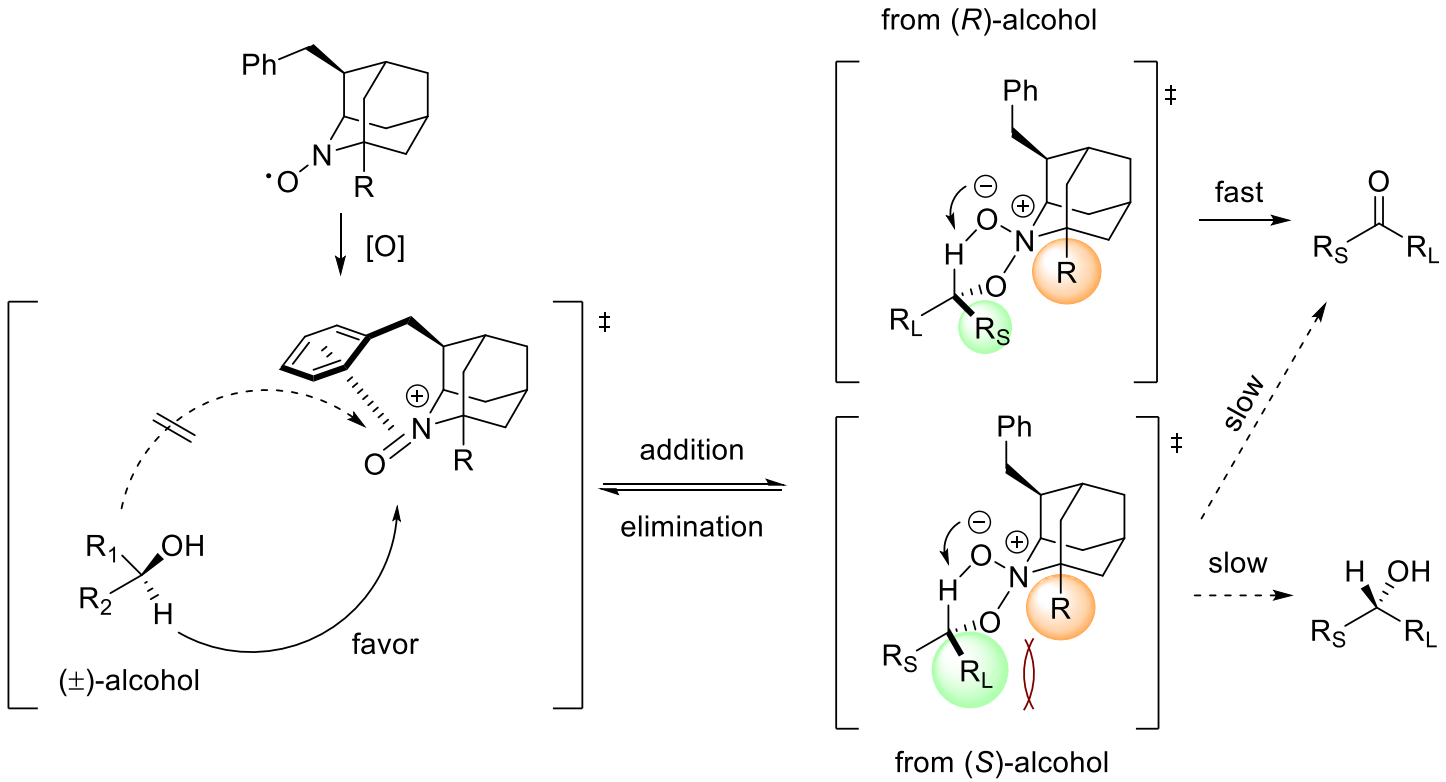
Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide



Org. Lett. **2009**, *11*, 1829–1831. *Org. Lett.* **2010**, *12*, 5, 980–983 *J. Am. Chem. Soc.* **2014**, *136*, 17591−17600

Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

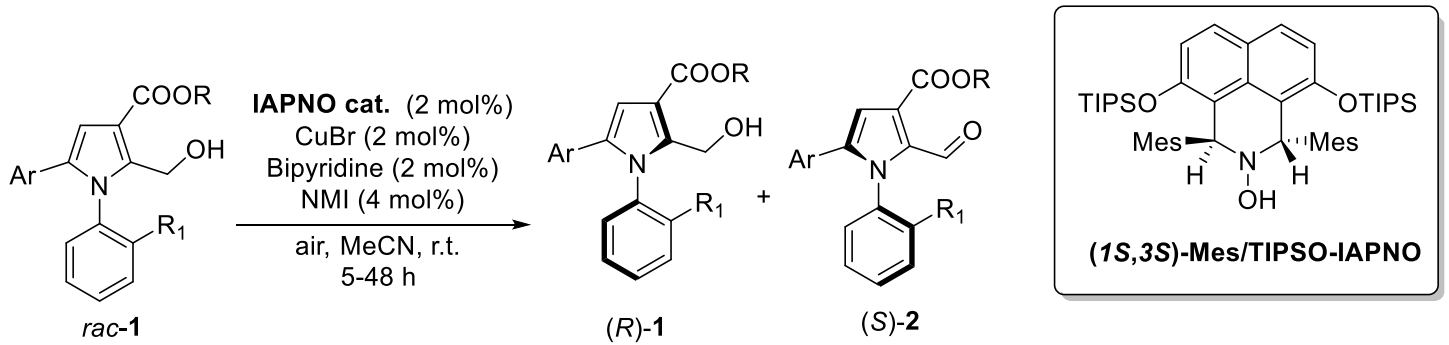
Working hypothesis of OKR catalyzed by chiral AZADO

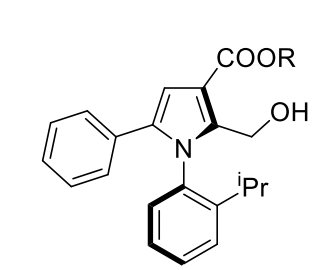


Org. Lett. **2009**, *11*, 1829–1831. *Org. Lett.* **2010**, *12*, 5, 980–983

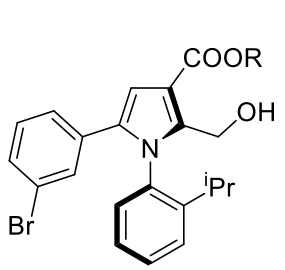
Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

Szpilman (2022)

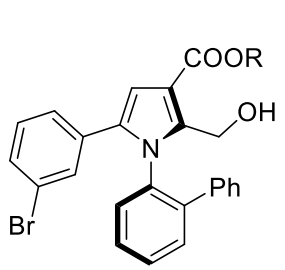




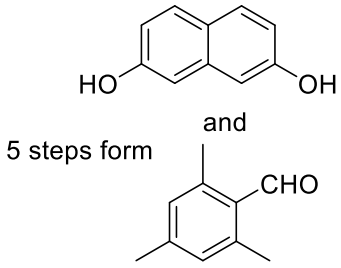
(*R*)-**1a:** 38% *er* = 3.5:96.5
(*S*)-**2a:** 53% *er* = 76.4:23.6

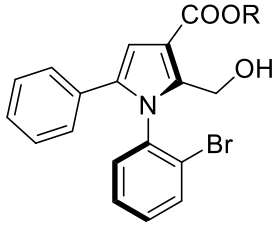


(*R*)-**1b:** 37% *er* = 3.8:96.2
(*S*)-**2b:** 54% *er* = 76.7:23.3

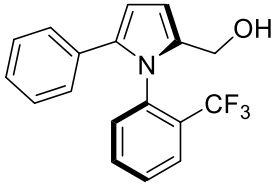


(*R*)-**1c:** 42% *er* = 11:89
(*S*)-**2c**: 46% *er* = 76.2:23.8





(*R*)-**1d**: 42% *er* = 12.2:87.8
(*S*)-**2d**: 45% *er* = 80.4:19.6

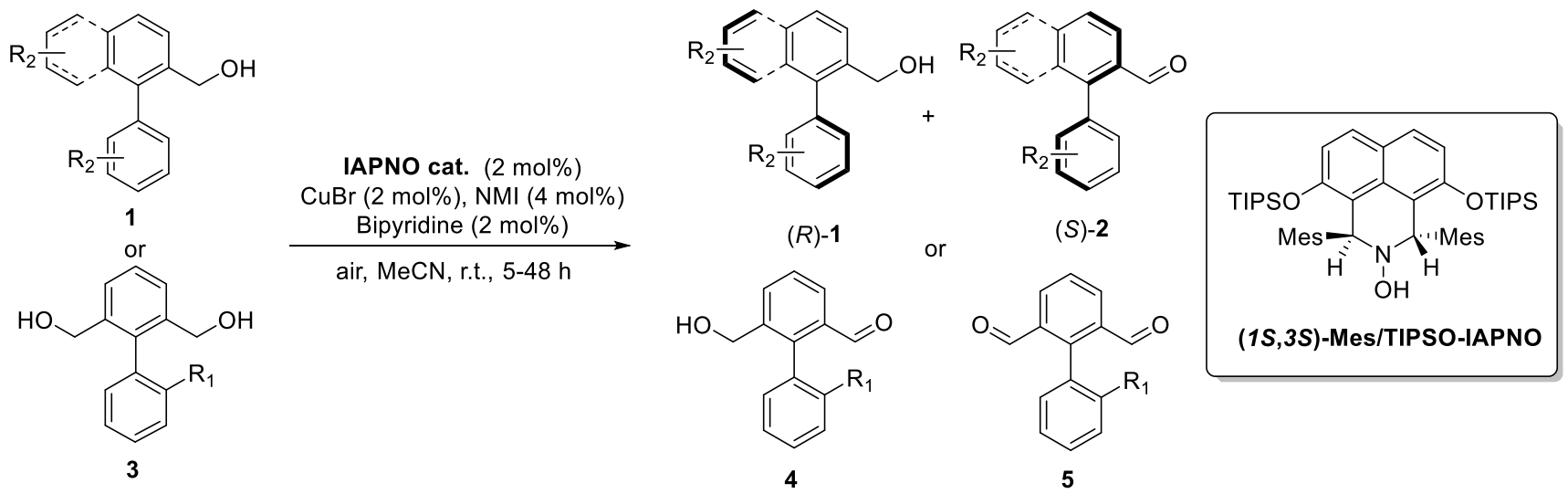


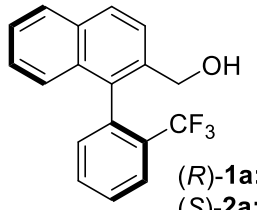
(*R*)-**1d**: 30% *er* = 56.5:43.5
(*S*)-**2d**: 45% *er* = 45.5:54.5

Org. Lett. **2022**, 24, 5078−5083 *J. Org. Chem.* **2023**, *88*, 8413−8430

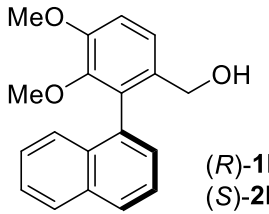
Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide

Szpilman (2023)

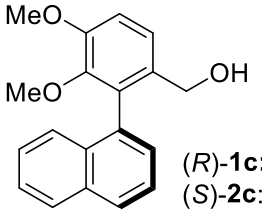




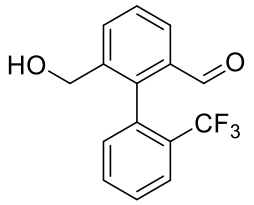
(*R*)-**1a:** 28%, *er* = 5.5:94.5
(*S*)-**2a:** 54%, *er* = 60:40



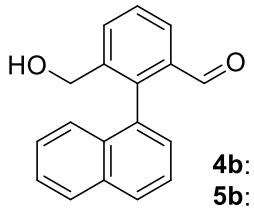
(*R*)-**1b:** 36%, *er* = 22:78
(*S*)-**2b:** 55%, *er* = 62:38



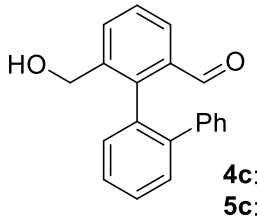
(*R*)-**1c:** 22%, *er* = 6.5:93.5
(*S*)-**2c**: 73%, *er* = 62.5:37.5



4a: 58%, *er* = 8:92
5a: 18%



4b: 68%, *er* = 4.5:95.5
5b: 28%



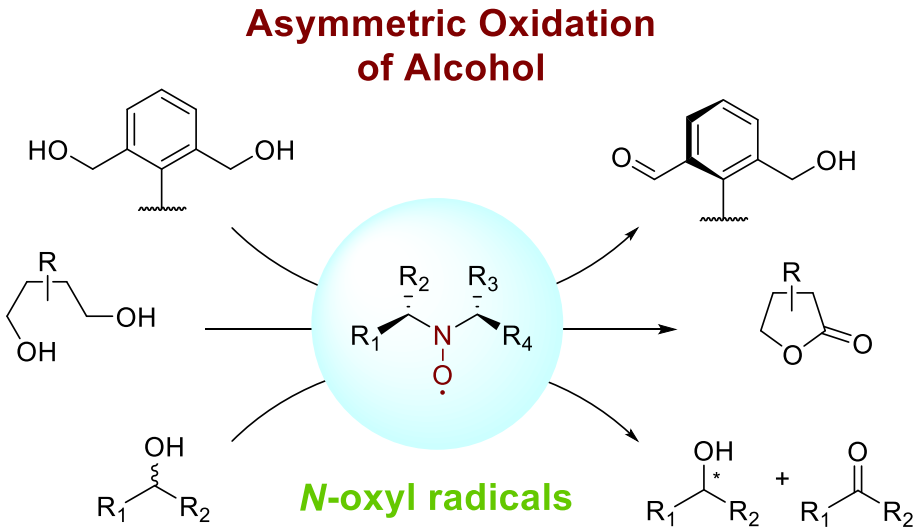
4c: 73%, *er* = 99:1
5c: 22%

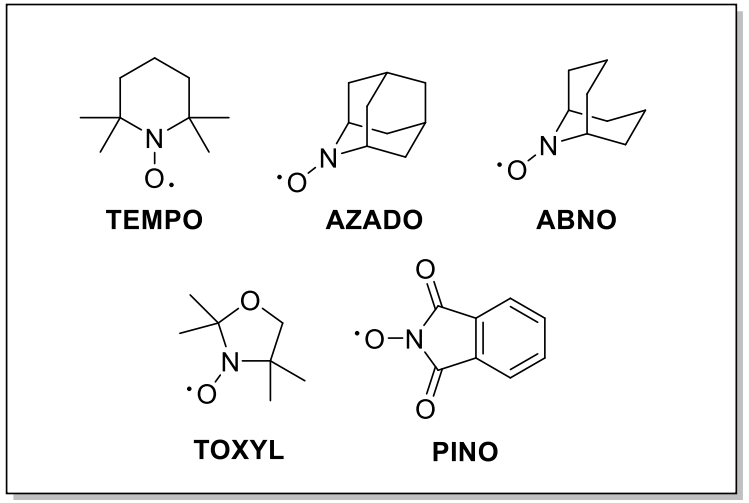
Org. Lett. **2022**, 24, 5078−5083 *J. Org. Chem.* **2023**, *88*, 8413−8430

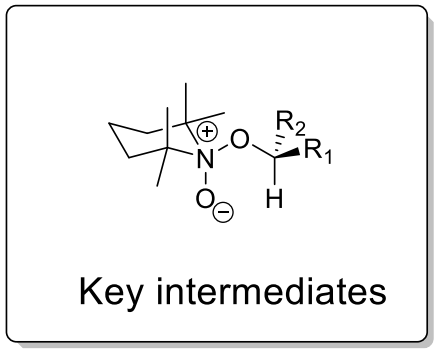
Outline

- Introduction
- Oxidative Desymmetrization Catalyzed by Chiral Nitroxide
- Oxidative Kinetic Resolution Catalyzed by Chiral Nitroxide
- Summary and Outlook

Summary

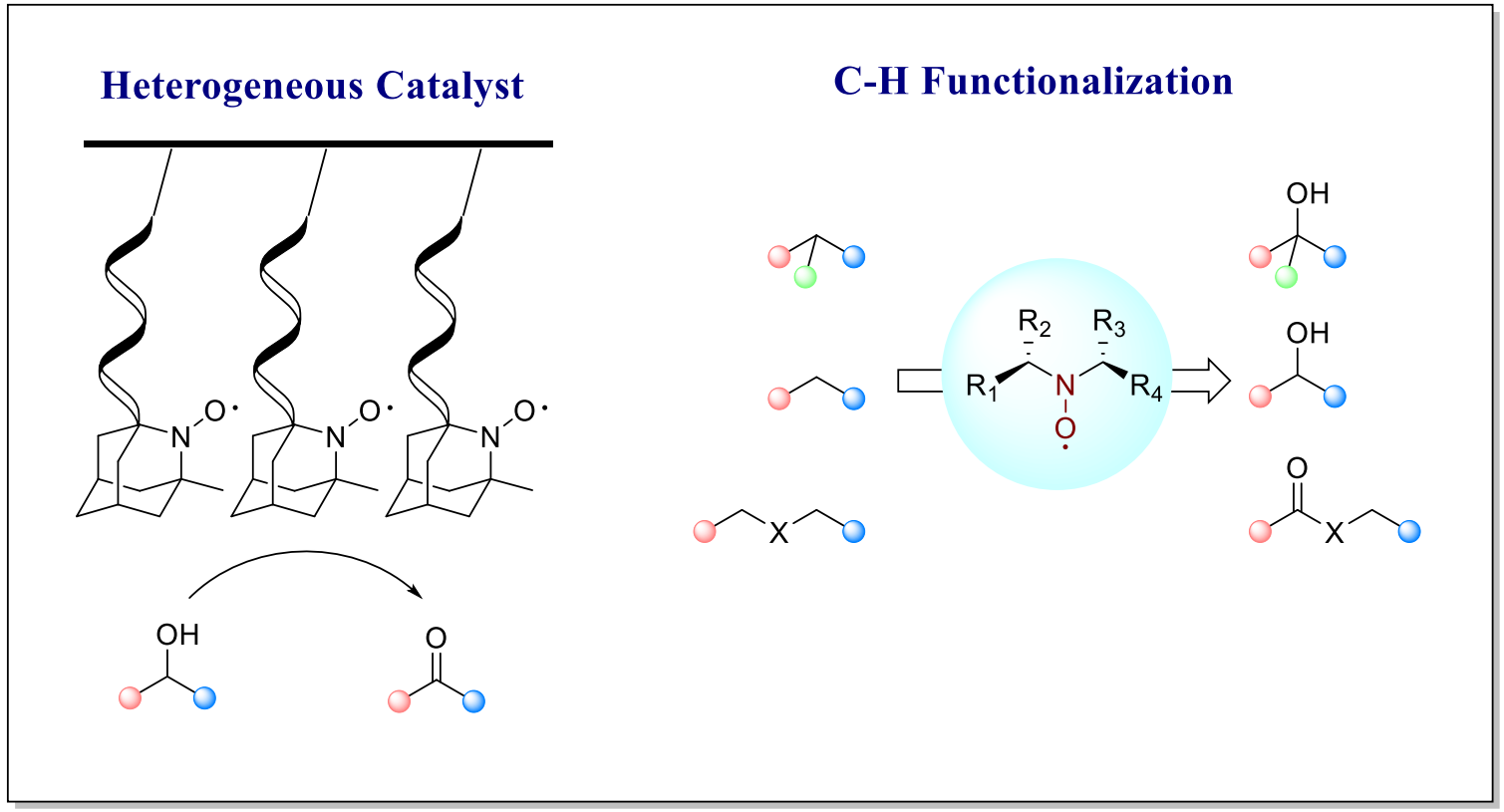






- ✔ Environmental-friendly
- ✔ Mild condition
- ✔ Easy to store
- ✔ High efficiency

Outlook


Heterogeneous Catalyst
C-H Functionalization
N
O
OH
O
X
R1
R2
R3
R4

Thanks for you listening

s (selectivity coefficient) = $\ln [(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$

C: Convension

accounts for the dependence of the measured selectivity on overall conversion