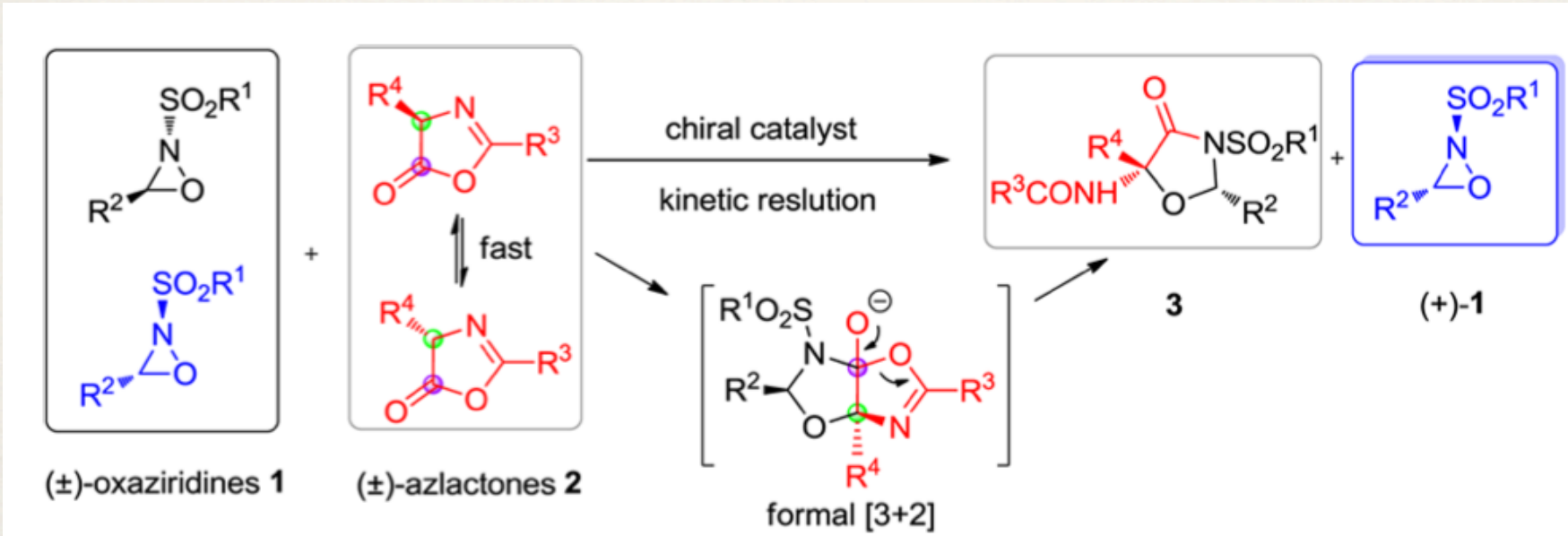


Organocatalytic Oxyamination of Azlactones: Kinetic Resolution of Oxaziridines and Asymmetric Synthesis of Oxazolin-4-ones

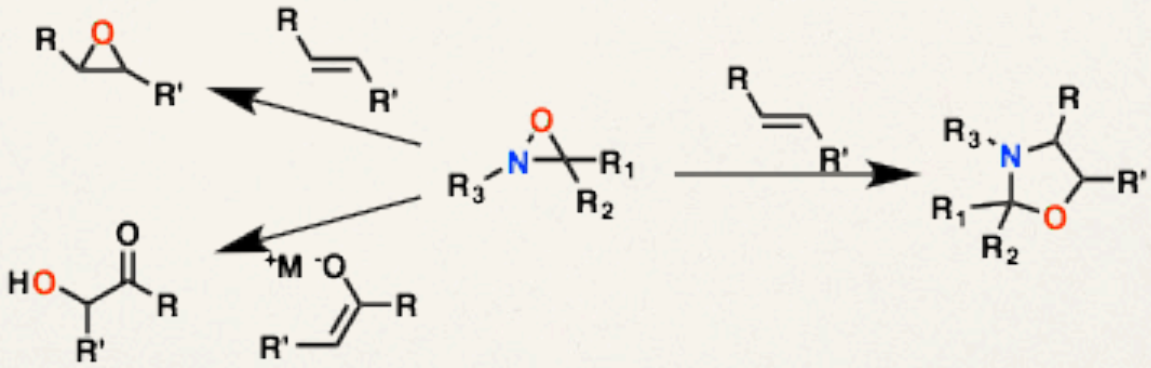
Shunxi Dong, Xiaohua Liu,* Yin Zhu, Peng He, Lili Lin, and Xiaoming Feng*

Yongzhao Yan
7-9-2013

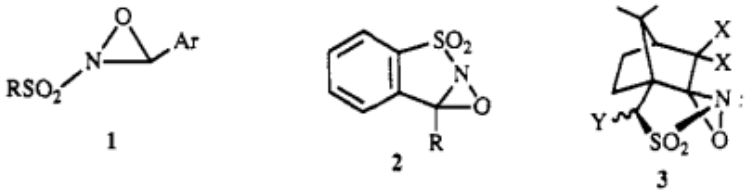
Wipf group Current Literature

Oxaziridines

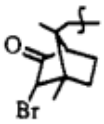
- Three-member hetercycle containing oxygen, nitrogen, and carbon.
- Useful reagent for epoxidation and alpha-hydroxylation of enolate.
- Synthetically, useful intermediate for formal [3+2] cycloaddition.

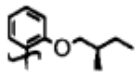


N-Sulfonyloxaziridines



1 2 3

[O]	R	Ar
1a	Ph	Ph
1b	*p*-MePh	Ph
1c	*p*-MePh	*o*-MePh
1d		2-Cl-5-O_2NPh
1e		2-Cl-5-O_2NPh

[O]	R
2a	Me
2b	Ph
2c	
2d	

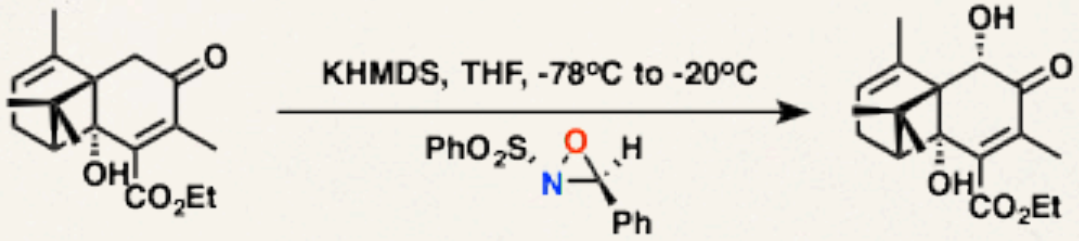
[O]	X	Y
3a	H	H
3b	Cl	H
3c	MeO	H
3d	H	Bn
3e	H	*p*-MeOBn
3f	H	*p*-CF_3Bn

- Most predominantly used aziridines today since the discovery in early 1980s.
- Aprotic and neutral oxidant, useful in late-stage transformation.
- Chiral N-sulfonyloxaziridines allows reagent stereoselectivity control.

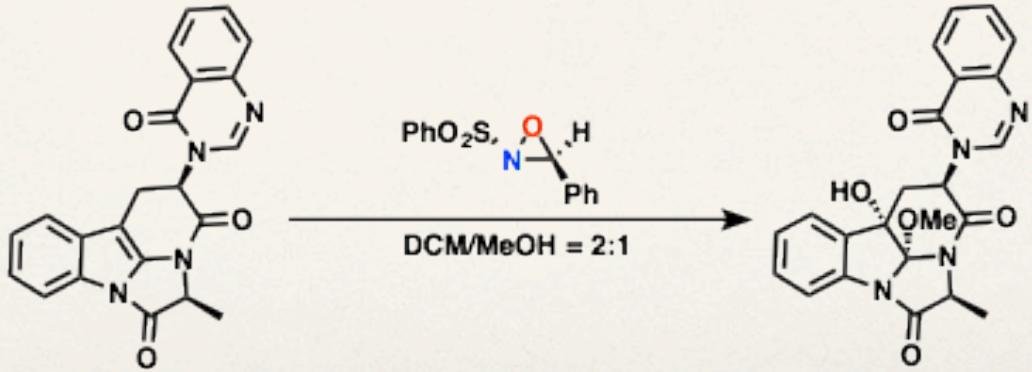
Davis, F. A.; Sheppard, A. C. *Tetrahedron.*, 1982, **45**, 5703.
Davis, F. A.; Stringer, O. D. *J. Org. Chem.,* 1982, **47**, 1774.
Davis, F. A.; Chen, B. C. *Chem. Rev.,* 1992. **92**, 919.

N-Sulfonyloxaziridines in Total Synthesis

- Wender Taxol Total Synthesis:



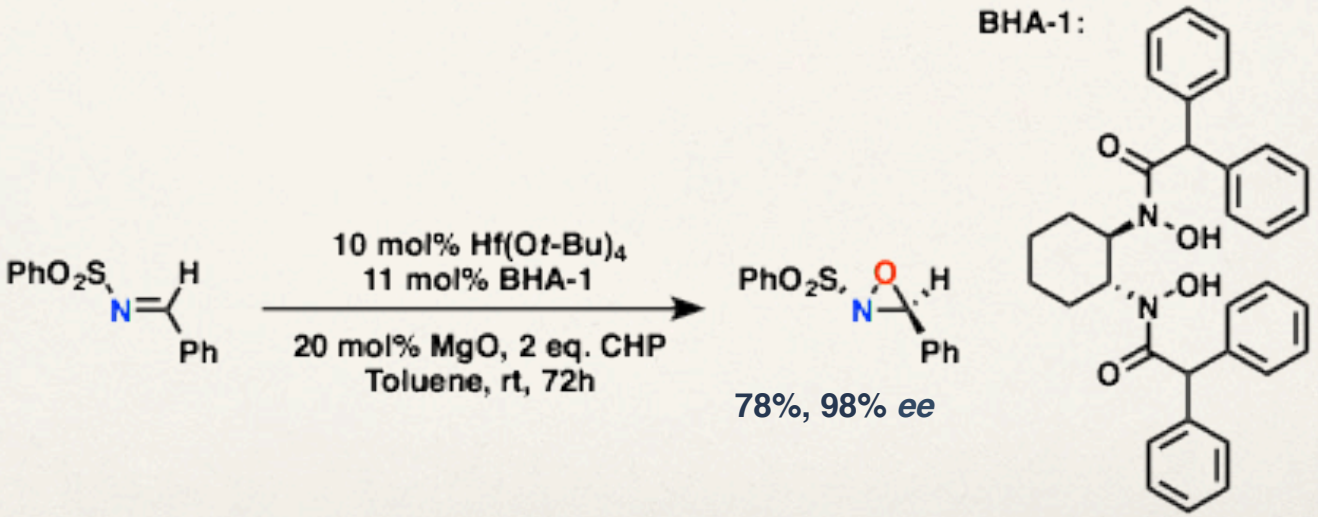
- Total Synthesis of (-)-Chaetominine:



Malgesini, Beatrice; Forte, Barbara; Borghi, Daniela; Quartieri, Francesca; Gennari, Cesare; Papeo, Gianluca, *Chem. Eur. J.* 2009, **15**, 7922
Paul A. Wender et al. *J. Am. Chem. Soc.,* 1997, **119**, 2755

Enantiopure N-Sulfonyloxaziridines

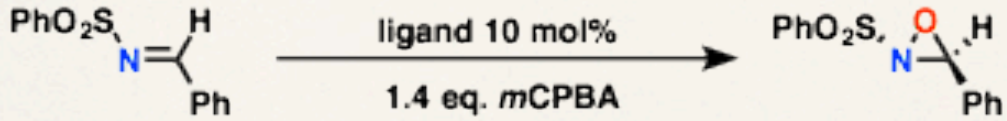
- The optically active oxaziridines have been used in a variety of oxidation reactions.
- But the catalytic enantioselective synthesis was first developed recently in 2011.
- Yamamoto:



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

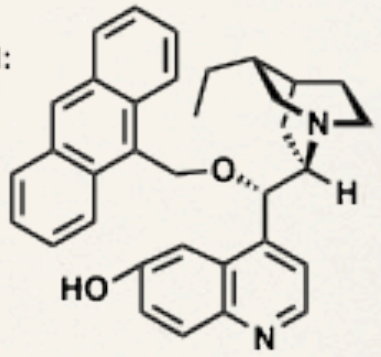
Enantiopure N-Sulfonyloxaziridines

- Jorgensen:

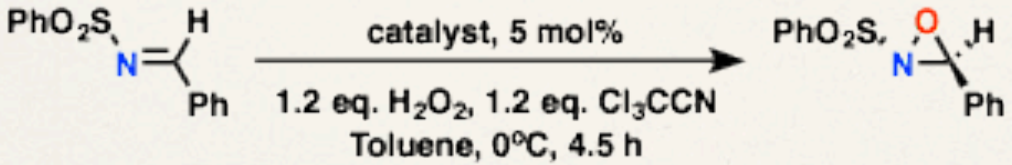


89%, 92% *ee*

ligand:

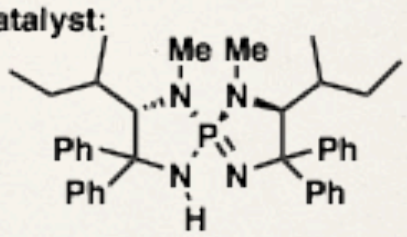


- Ooi:



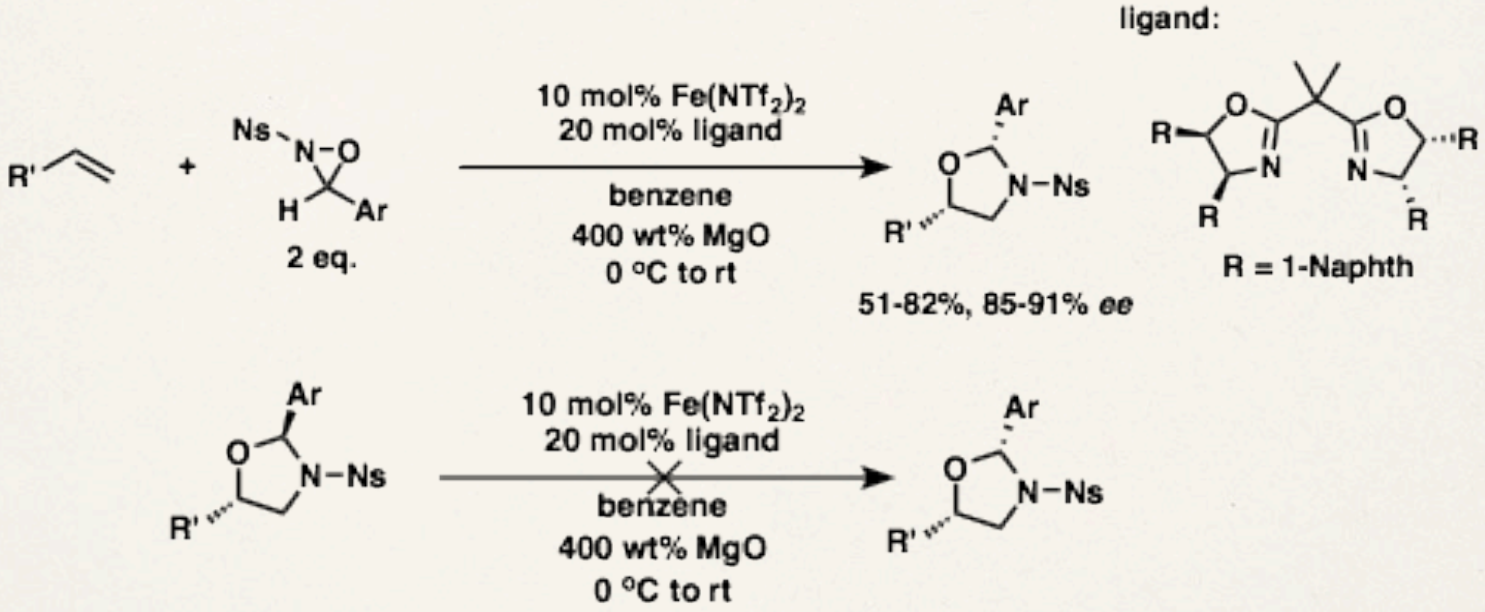
90%, 95% *ee*

catalyst:



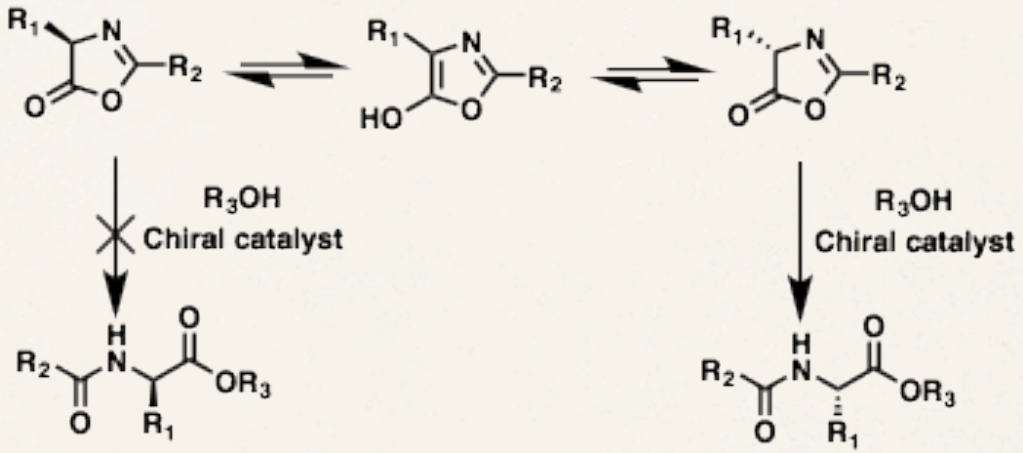
Lykke, L.; Rodríguez-Escrich, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* 2011, **133**, 14932.
Uraguchi, D.; Tsutsumi, R.; Ooi, T. *J. Am. Chem. Soc.* 2013, **135**, 8161.

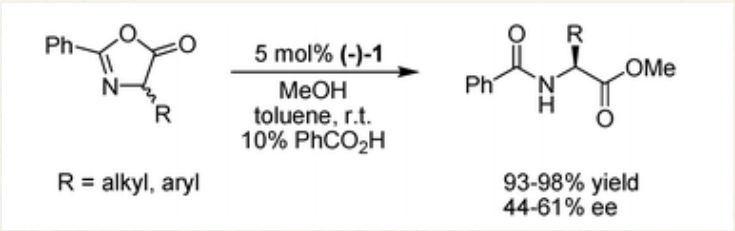
Yoon's Asymmetric Oxyamination

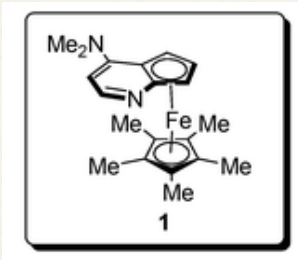


Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2012**, 134, 12370

Dynamic Kinetic Resolution of Azlactone

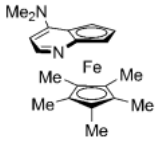
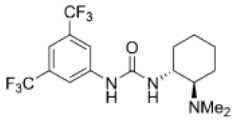
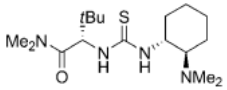
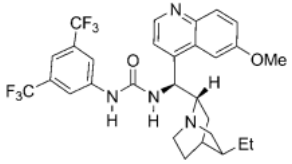
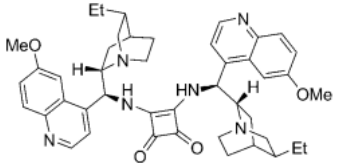
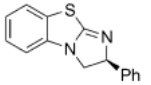






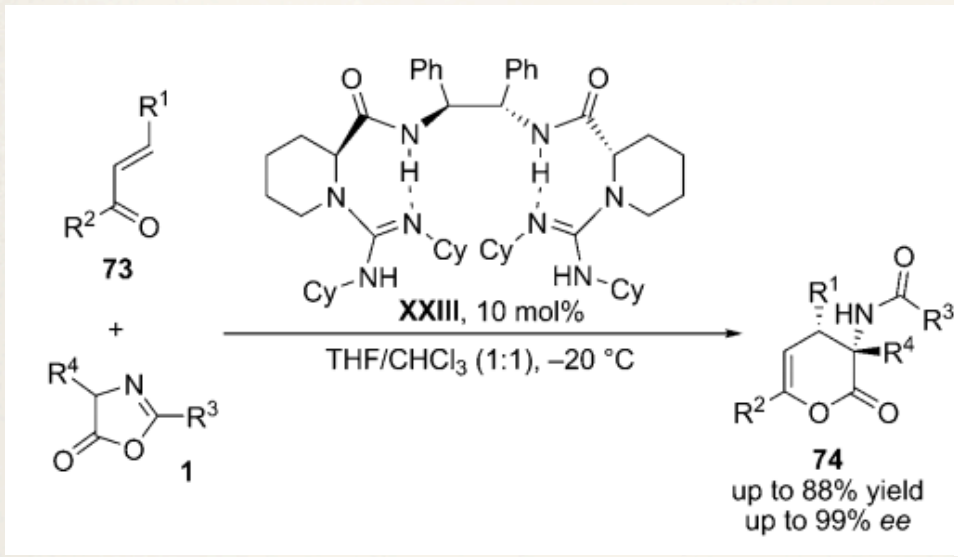
Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, 36,1432
J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154

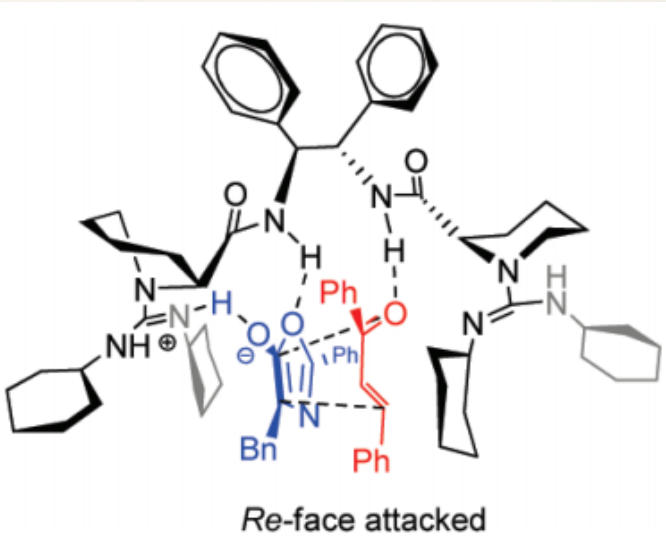
Dynamic Kinetic Resolution of Azlactone

Method (year)	Catalyst		Nucleophile(s)	DKR of 2-phenyl-4-*iso*-propyl azlactone			DKR of 2,4-di-phenyl azlactone		
				t [h]	yield [%]	*ee* [%]	*t* [h]	yield [%]	*ee* [%]
Fu (1998)	**I**		methanol ethanol *iso*-propanol	48	95	55	n.d.[a]	n.d.	n.d.
Berkessel (2004)	**II**		allyl alcohol (**7**)	48	76	85	48	76	75
Berkessel (2004)	**IV**		allyl alcohol (**7**)	48	89	90	n.d.[a]		
Connon (2008)	**VI**		allyl alcohol (**7**) cyclohexane-thiol (**13**)	34	99	85	n.d.		
Song (2009)	**VII**		allyl alcohol (**7**) ethanol propanol	3	95	94	24	81	81
Birman (2010)	**VIII**		(1-Np)$_2$CHOH (**15**)	96	<5	n.d.[a]	48	89	94

J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154

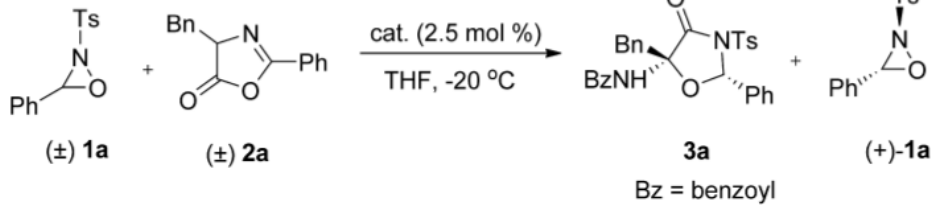
Chiral Bisguanidine Catalyst

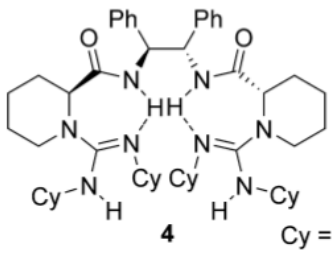




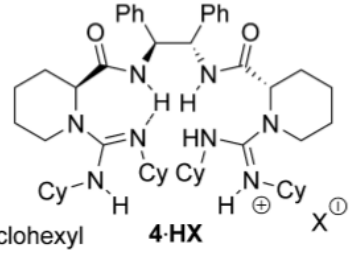
Dong, S. X.; Liu, X. H.; Chen, X. H.; Mei, F.; Zhang, Y. L.; Gao, B.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2010**, 132, 10650
Alba, A.-N. R.; Rios, R. *Chem.—Asian J.* **2011**, 6,720

Optimization of Reaction Conditions





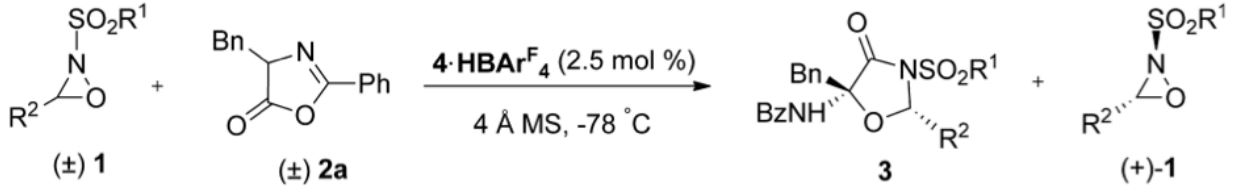
Cy = cyclohexyl



				3a			1a		
entry	cat.	T (°C)	t (h)	yield (%)[b]	cis:trans[c]	ee (%)[c]	yield (%)[b]	ee (%)[c]	S
1	**4**	−20	24	45	64:36	0/0	51	0	–
2	**4·HCl**	−20	24	40	66:34	0/0	54	0	–
3	**4·HBF$_4$**	−20	24	41	75:25	20/11	55	8	2
4[d]	**4·HBAr$^F_4$**	−20	24	48	86:14	55/37	50	40	5
5	**4·HBAr$^F_4$**	−45	48	41	90:10	63/53	49	50	7
6	**4·HBAr$^F_4$**	−78	48	33	94.5:5.5	81	65	40	14
7[e]	**4·HBAr$^F_4$**	−78	48	47	95:5	87	49	76	32
8[e,f]	**4·HBAr$^F_4$**	−78	46	52	95:5	84	43	95	43
9[e,f]	*ent*-**4·HBAr$^F_4$**	−78	46	52	95:5	−84	41	−96	45

[a]Unless otherwise noted, the reaction was carried out with catalyst **4** or **4·HX** (5×10^{-3} mmol, 2.5 mol %), **1a** (0.20 mmol), and **2a** (0.10 mmol) in THF (1.5 mL). [b]Isolated yields according to the amount of **1a**. [c]Determined by chiral HPLC analysis. [d]HBAr$^F_4$ = HB[3,5-$(CF_3)_2C_6H_3]_4$. [e]A 1:2 (v/v) THF/*t*-BuOMe mixed solvent (1.5 mL) and 4 Å MS (10 mg) were used. [f]**2a** (0.125 mmol) was used.

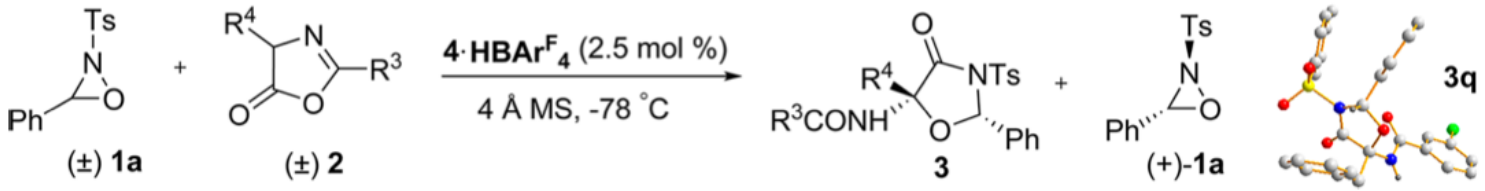
Substrate Scope of Oxaziridines



				3			1		
entry	R^1	R^2	t (h)	yield (%)[b]	cis:trans[c]	ee (%)[c]	yield (%)[b]	ee (%)[c]	S
1	4-MeC_6H_4	C_6H_5	46	52 (**3a**)	95:5	84	43 (**1a**)	95	43
2	C_6H_5	C_6H_5	46	47 (**3b**)	94:6	80	39 (**1b**)	93	31
3	4-ClC_6H_4	C_6H_5	48	54 (**3c**)	94:6	80	41 (**1c**)	90	28
4[d,e]	4-$O_2NC_6H_4$	C_6H_5	80	67 (**3d**)	85:15	43 (99)[f]	29 (**1d**)	98	10
5	4-$iPrC_6H_4$	C_6H_5	48	48 (**3e**)	94:6	81	44 (**1e**)	93	32
6	4-MeC_6H_4	2-MeC_6H_4	48	53 (**3f**)	>95:5	83	46 (**1f**)	87	31
7	4-MeC_6H_4	3-MeC_6H_4	48	51 (**3g**)	97:3	86	45 (**1g**)	91	42
8	4-MeC_6H_4	4-MeC_6H_4	48	54 (**3h**)	97:3	85	41 (**1h**)	91	39
9	4-MeC_6H_4	3-$MeOC_6H_4$	48	58 (**3i**)	97:3	80	30 (**1i**)	97	37
10	4-MeC_6H_4	3-FC_6H_4	48	54 (**3j**)	95:5	80	39 (**1j**)	98	41
11	4-MeC_6H_4	3-furyl	120	43 (**3k**)	95:5	85	36 (**1k**)	85	34
12	4-MeC_6H_4	3-thienyl	96	49 (**3l**)	95:5	83	45 (**1l**)	98	49
13[d]	4-MeC_6H_4	1-naphthyl	96	43 (**3m**)	95:5	82	33 (**1m**)	85	32
14	4-MeC_6H_4	Bn	120	48 (**3n**)	90:10	71	40 (**1n**)	82	15
15	4-MeC_6H_4	Et	120	49 (**3o**)	95:5	88	39 (**1o**)	82	40
16[g]	4-MeC_6H_4	C_6H_5	48	57 (**3a**)	94:6	81	36 (**1a**)	99	49

[a]Unless otherwise noted, the reaction was carried out with **4·HBAr$^F_4$** (2.5 mol %), **1** (0.20 mmol), and **2a** (0.125 mmol) in 1:2 (v/v) THF/*t*-BuOMe (1.5 mL) at −78 °C. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]THF (1.5 mL) was used as the solvent without 4 Å MS. [e]**2a** (0.14 mmol) was used. [f]After recrystallization (21% yield). [g]**1a** (6.0 mmol) and **2a** (3.75 mmol) were used.

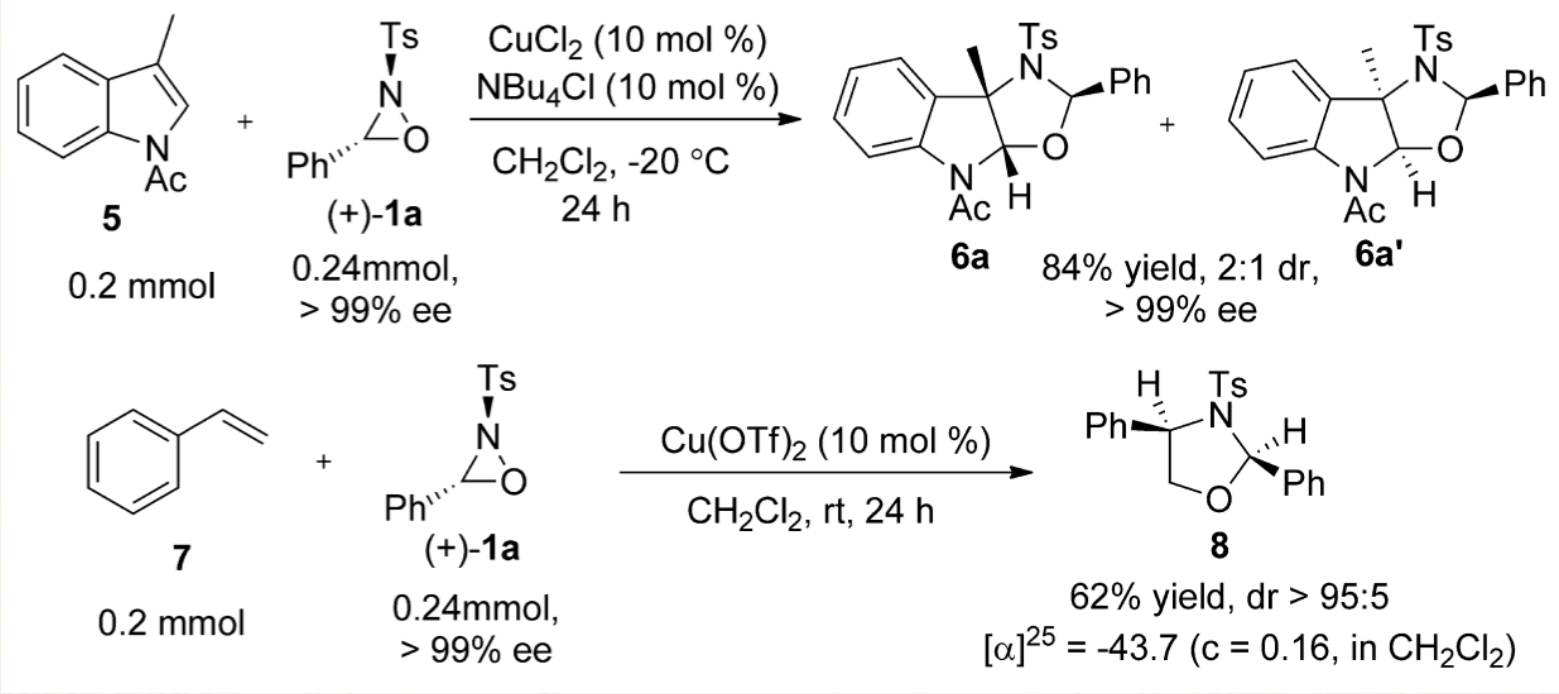
Substrate Scope of Azlactones



				3			1a		
entry	R^3	R^4	t (h)	yield (%)[b]	cis:trans[c]	ee (%)[c]	yield (%)[b]	ee (%)[c]	S
1[d]	2-ClC_6H_4	Bn	48	49 (**3p**)	98:2	81	41	98	43
2[d]	3-ClC_6H_4	Bn	48	55 (**3q**)	97:3	82	41	93	34
3[d]	4-MeC_6H_4	Bn	60	53 (**3r**)	95:5	80	40	90	28
4[d]	3,5-$Me_2C_6H_3$	Bn	60	49 (**3s**)	97:3	88	39	92	52
5[d]	4-$O_2NC_6H_4$	Bn	48	53 (**3t**)	95:5	72	38	99	31
6	C_6H_5	4-$HOC_6H_4CH_2$	96	36 (**3u**)	95:5	92	60	55	42
7	C_6H_5	3-indolylmethyl	118	54 (**3v**)	98:2	88	45	82	40

[a–c]See Table 2, footnotes *a*–*c*. [d]DMAP (0.5 mg, 2 mol %) was added.

Application of Enantiopure Oxaziridine



Conclusion

- Efficient Oxyamination of azlactone.
- Potential biological activity of oxazolin-4-one derivatives.
- Remarkable triple stereo-differentiation.
- Oxazilidines were recovered with good S factors.
- Further application of the catalyst is still under investigation.