Catalytic Enantioselective α - Hydroxylation of Ketones Using Nitrosobenzene

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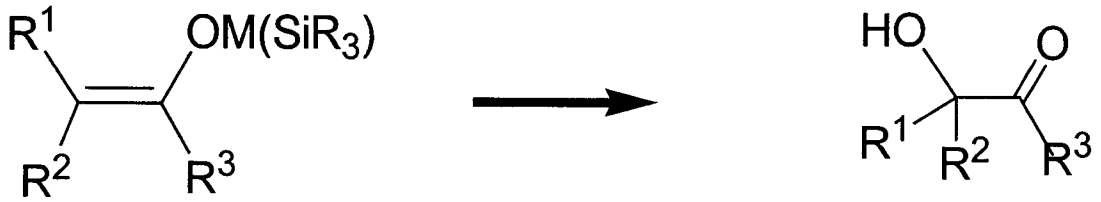
April 20, 2004

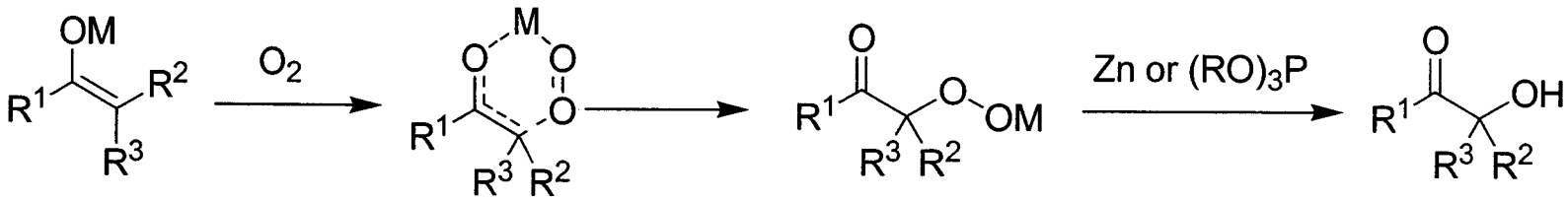
Stoichiometric oxidation of enolates: general synthesis of α -hydroxy carbonyl compound



Oxidants:

- O2
- Peroxy Reagents
- Metal Oxides
- N-Sulfonyloxaziridines

Oxygen

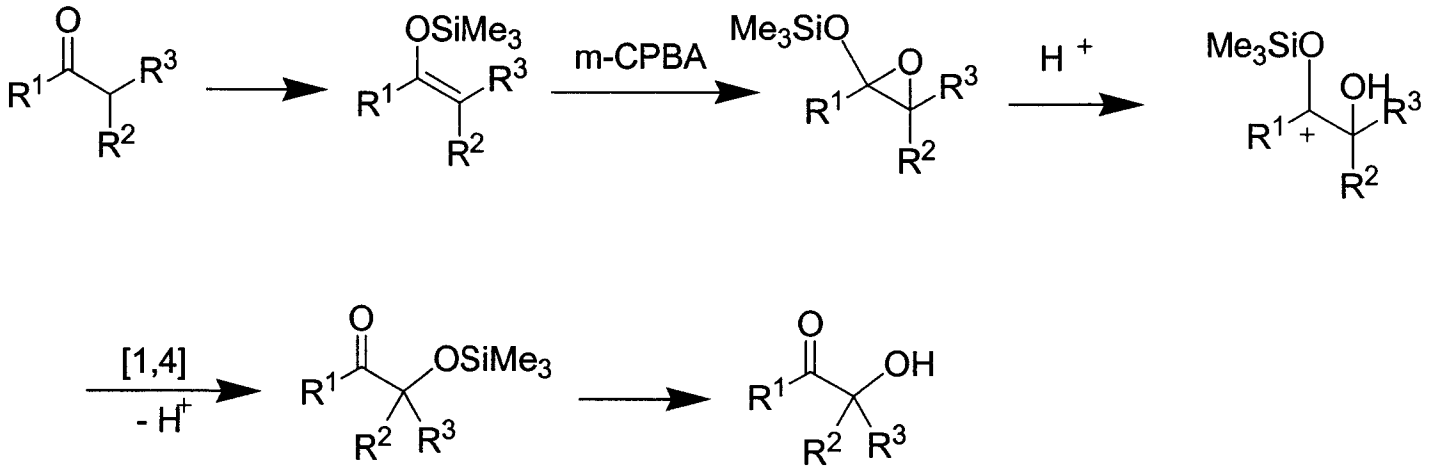


Alternative mechanism: radical chain mechanism.

Over-oxidation is possible when α -C is monosubstituted.

Chen, B.; Zhou, P.; Davis, F. A.;Ciganek, E. Organic Reactions. Vol.62.

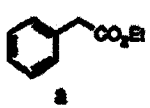
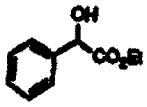
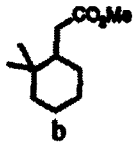
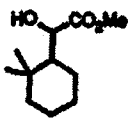
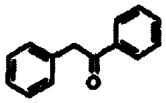
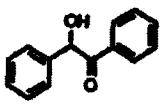
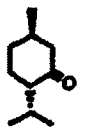
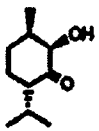
Peroxy Reagents



Chen, B.; Zhou, P.; Davis, F. A.;Ciganek, E. Organic Reactions. Vol.62.

Metal Oxides

Table. Comparison of MoOPH and MoOPD Oxidations of Carbonyl Compounds[a]

carbonyl	α-hydroxy carbonyl	Yield % (S.M.) MoOPH	MoOPD
 a		75 (9)	71 (11)
 b		63 (7)	72 (9)
 c		50 (14) +11% benzil	47 (25) +8% benzil
 f		85 (5) endo:exo 5:1	86 (7) endo:exo 2.4:1
 g		74 (8)	43 (20)

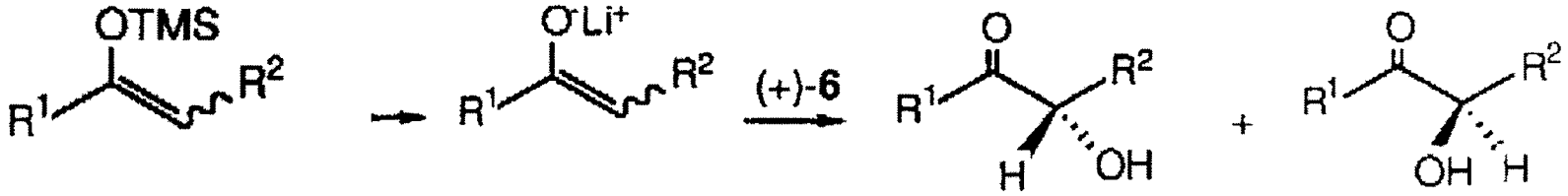
$MoO_5 \cdot Py \cdot HMPA$: MoOPH

$MoO_5 \cdot DMPU \cdot H_2O$: MoOPD

Anderson, J. C.; Smith, S. C.*Synlett* **1990**, 107

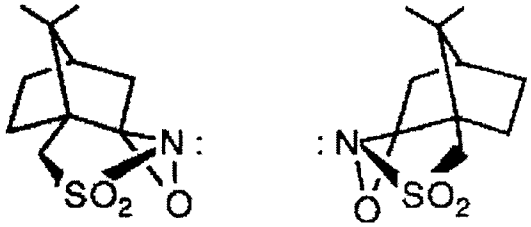
Diastereoselectivity can be induced by stereo-directing groups or chiral auxiliaries in the enolates.

N-Sulfonyloxaziridines



3 (S)-**4** (R)-**4**

50-96% ee



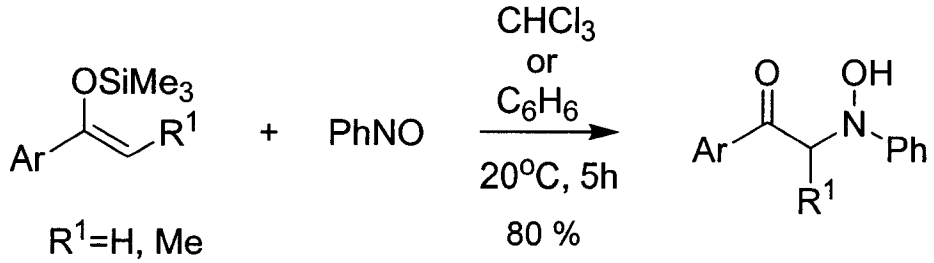
(+)-**6** (-)-**6**

(+) and (-)-(camphorylsulfonyl)oxaziridines 6

Davis, F. A.; Sheppard, A.C., B. C. ; Lai, G. S. *Tetrahedron Lett.*,**1989**,*30, 779*

Limitation:
Stoichiometric enantiopure oxigent transfer reagent.
Enantioselectivity depends on structures of oxaziridines and enolates and reaction conditions.

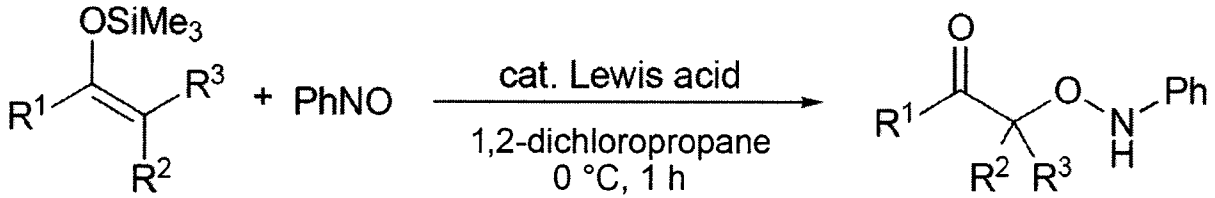
O- vs. N-Nitroso Aldol Reaction



R^1=H, Me

N-adduct

Sasaki, T.; Mori, K.; Ohno, M. *Synthesis* **1985**, 279.



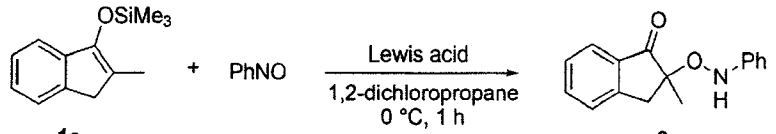
O-adduct

Momiyama, N.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2986,3313.

High O-selectivity was obtained w/ LA catalysts and N-selectivity w/o LA.

LA catalyzed O-Nitroso Aldol Reaction

Table 1. O-Alkylation of **1a** catalyzed by various Lewis acids.

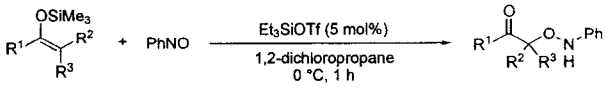


1a **2a**

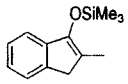
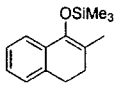
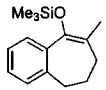
Entry	Lewis acid	Equiv [mol%]	Yield [%][a]
1	none		<1
2	Me_3SiOTf	5	86
3	Et_3SiOTf	10	94
4	Et_3SiOTf	5	88
5	Et_3SiOTf	1	74
6	tBuMe$_2$SiOTf	5	83
7	$TiCl_4$	5	71
8	$FeCl_3$	5	60
9	Me_3SiNTf_2	5	54
10	[AgOTf]	5	52
11	[Cu(OTf)$_2$]	5	58
12	[Sn(OTf)$_2$]	5	50

Momiyama, N.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2986,3313.

Table 2. O-Alkylation of various silyl enol ethers.



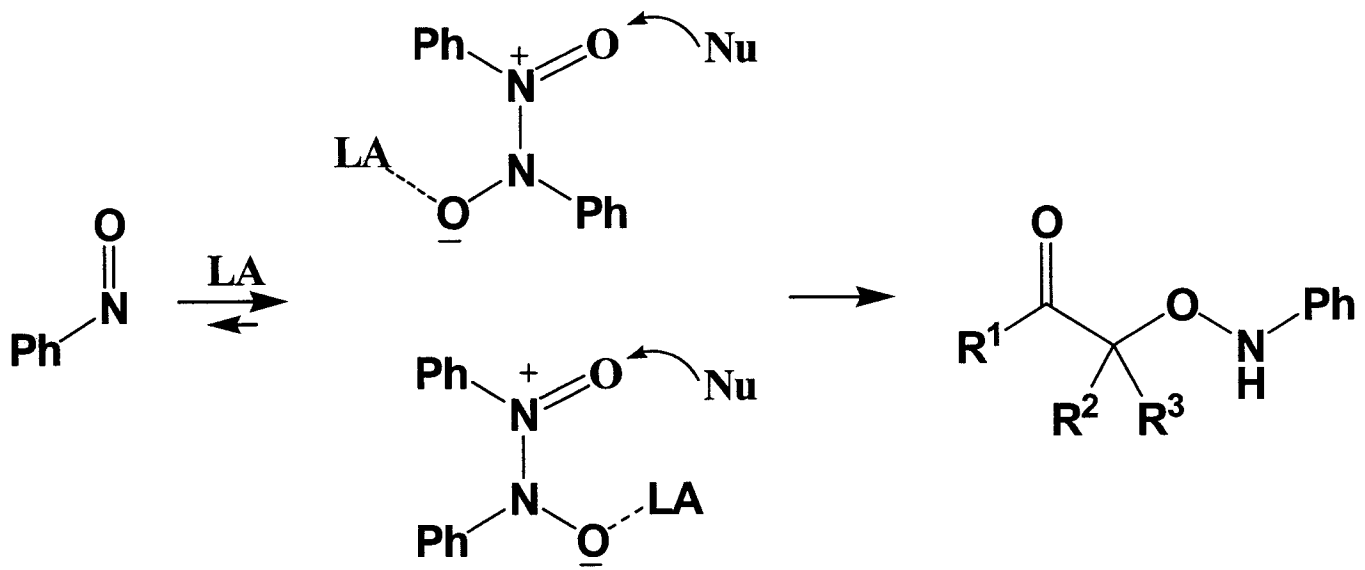
1 **2**

Entry	**1**		Yield [%][a]
1		**1a**	94
2		**1b**	51
3		**1c**	62
4		**1d**	44
5		**1e**	54
6		**1f**	62

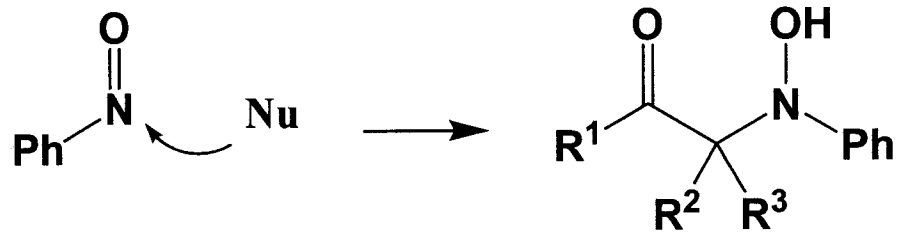
O-selectivity remained through significant structural variation.

Roles of LA in Regioselectivity

Pathway with LA Cat. : dimer



Pathway without LA Cat. : monomer



Momiyama, N.; Yamamoto, H. *Org .Lett.* **2002**, *4*, 3579.

Roles of LA in Regioselectivity

Promotion of the dimerization of PhNO:

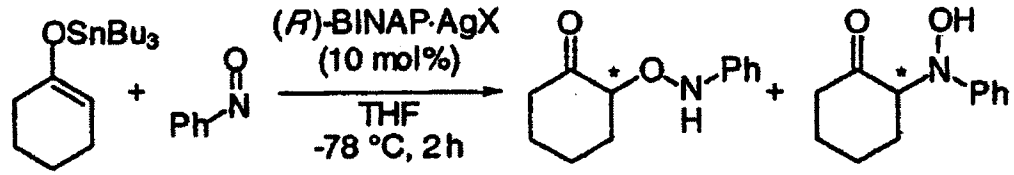
- In situ IR spectra were recorded on a ReactIR 1000 instrument from ASI Applied Systems. Me_3SiOTf (1 equiv) was added to a solution of PhNO (1 equiv) in 1,2-dichloropropane; as Me_3SiOTf was added, the absorption at 1505 cm^{-1} (PhNO N=O stretch) decreased in intensity while the absorption at 1264 cm^{-1} (trans azoxybenzene N-O stretch) simultaneously increased in intensity.

- ESI mass spectra of the triethylsilyl triflate-nitrosobenzene complex showed peaks at m/z 214 ($Ph_2N_2O_2$+) and m/z 329 [$Et_3Si(PhNO)_2$+], thus confirming the presence of the dimer.

Momiyama, N.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2986,3313.

Enantioselective O-Nitroso Aldol Reaction : BINAP·AgX Catalysts

Table 1. (*R*)-BINAP–Silver Complex-Catalyzed Nitroso Aldol Reaction of Tin Enolate **2a** with Nitrosobenzene[a]



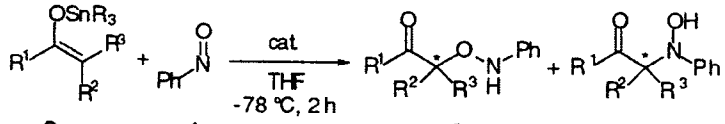
2a **1** **3a** **4a**

entry	AgX	yield, %[b]	**3a**/**4a**	ee, %[c]	
1	$AgOTf$	88	>99/1	**3a**: 91	**4a**: n.d.[d]
2	$AgClO_4$	95	>99/1	**3a**: 95	**4a**: n.d.
3	$AgBF_4$	64	>99/1	**3a**: 54	**4a**: n.d.
4	$AgNTf_2$	78	88/12	**3a**: 63	**4a**: 3
5	$AgSbF_6$	85	81/19	**3a**: 87	**4a**: <1
6	$AgPF_6$	86	80/20	**3a**: 76	**4a**: <1
7	AgOAc	82	72/28	**3a**: 87	**4a**: 23

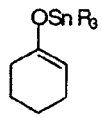
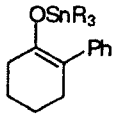
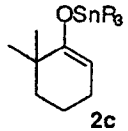
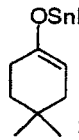
BINAP·AgOTf & BINAP·$AgClO_4$ provide best diastereo- and enantioselectivities.

Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.

Enantioselective O-Nitroso Aldol Reaction : Tin enolate



2 1 3 4

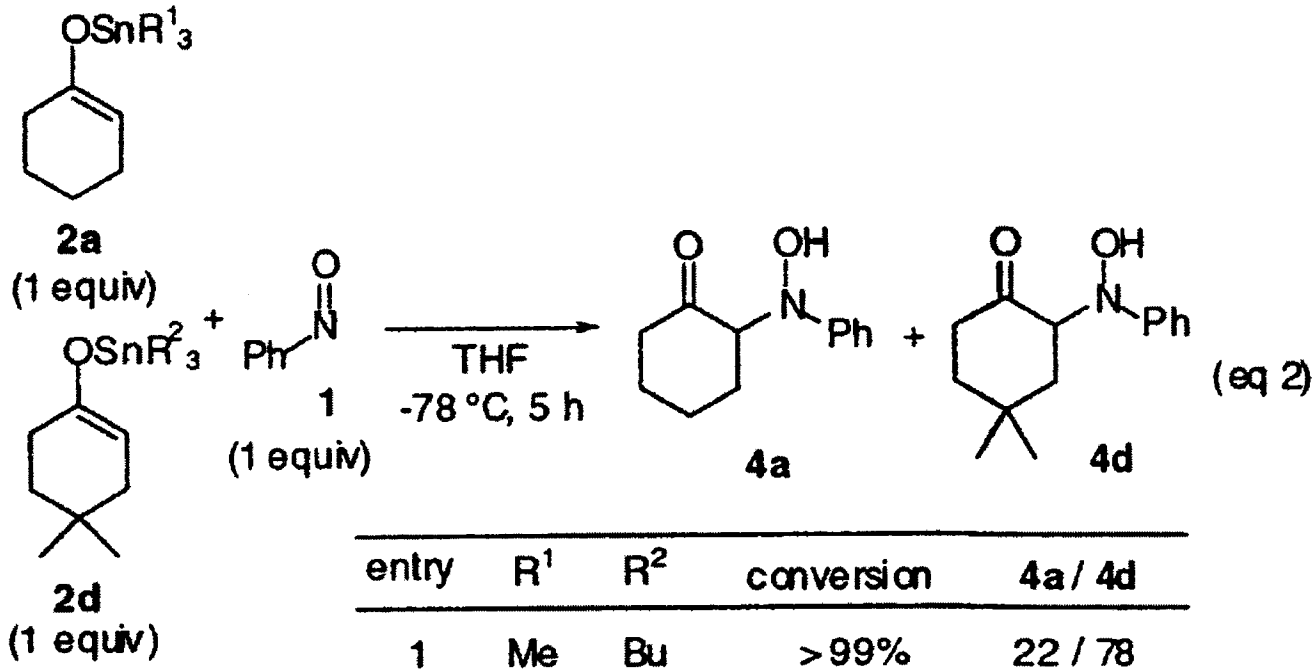
entry	enolate	cat. (mol%) [i]	R	yield,% [j]	3 / 4	ee,% of 3 [k]
1 [h, g]		A (10)	Bu	95	>99 / 1	95
2 [b, g]		B (10)	Bu	92	>99 / 1	91
3 [h, g]		C (10)	Bu	93	>99 / 1	92
4 [b, h]		B (10)	Me	95	>99 / 1	97
5 [b, h]	**2a**	C (10)	Me	94	>99 / 1	94
6 [h, h]		B (2)	Me	78	>99 / 1	96
7 [b, g]		A (10)	Bu	97	85 / 15	91
8 [b, g]		C (10)	Bu	97	83 / 17	95
9 [b, h]		B (10)	Bu	96	>99 / 1	95
10 [b, h]	**2b**	C (10)	Me	97	>99 / 1	88
11 [h, h]		B (10)	Me	94	>99 / 1	87
12 [b, g]	**2c**	C (10)	Bu	90	66 / 34	85
13 [b, h]	 **2d**	B (10)	Me	92	>99 / 1	90

Catalyst A: (*R*)-BINAP· $AgClO_4$
Catalyst B: (*R*)-TolBINAP· AgOTf
Catalyst C: (*R*)-TolBINAP· $AgClO_4$

Bu_3Sn enolates have slightly increased N-selectivity.

Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.

Bu_3Sn vs. Me_3Sn Enolates

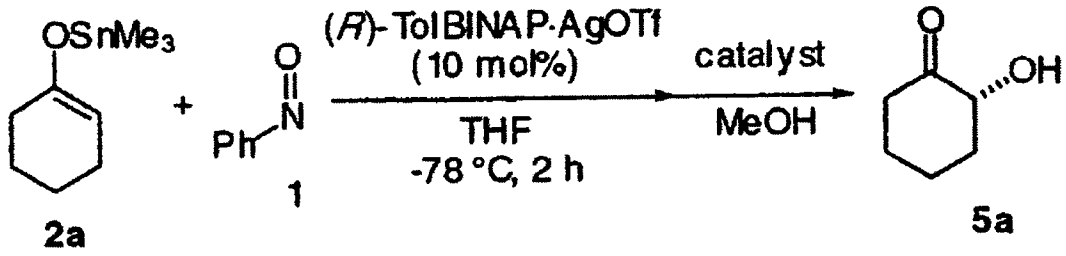


entry	R^1	R^2	conversion	4a / 4d
1	Me	Bu	>99%	22 / 78
2	Bu	Me	>99%	79 / 21

Higher reactivity of Bu_3Sn enolates resulted in more significant uncatalyzed process.

Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.

Synthesis of Enantioenriched α -Hydroxy ketones



(eq 3)

catalyst	conditions	yield,%	ee, %
$CuSO_4$ (0.3 eq)	0 °C, 12 h	93	97

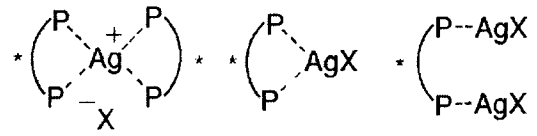
Transformation to α -hydroxy ketone is smooth and facile.

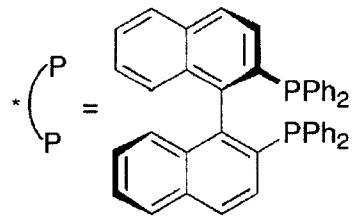
Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.

Role of LA in Enantioselectivity: Structure of BINAP·AgX Complexes

BINAP·AgX Catalysts:

1:2 (AgOTf·(*R*)-BINAP) complex (A)
1:1 (AgOTf·(*R*)-BINAP) complex (B)
2:1 (AgOTf·(*R*)-BINAP) complex (C)



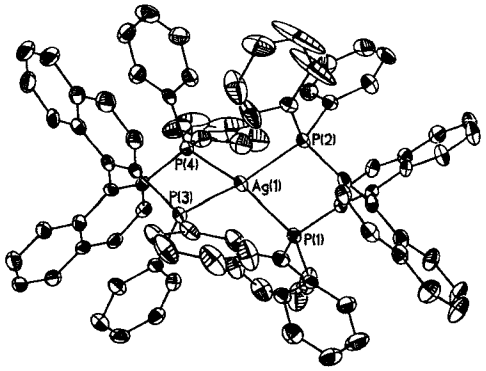


		A / B / C, mol.ratio
entry	Silver salt (eq)	
1	AgOTf (0.4)	<1 / <1 / >99
2	AgOTf (0.5)	<1 / 19 / 81
3	AgOTf (0.6)	3 / 53 / 44
4	AgOTf (0.8)	17 / 65 / 18
5	AgOTf (1.0)	21 / 63 / 16
6	AgOTf (1.5)	69 / 31 / <1
7	AgOTf (2.0)	>99 / <1 / <1
8	AgOAc (1.0)	<1 / 93 / 7
9	$AgOCOCF_3$ (1.0)	29 / 71 / <1

3 complexes can be exclusively formed and separated.

Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc. ASAP Article*

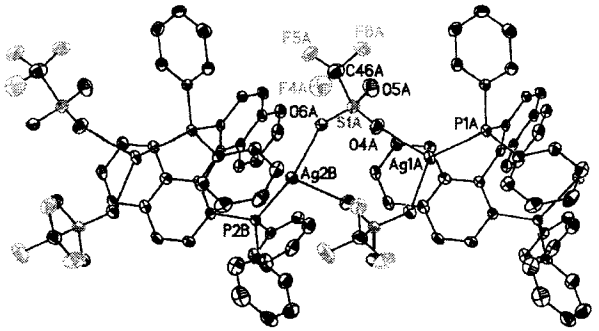
Structure of BINAP·AgX



1. 1:2 (AgOTf-(*R*)-BINAP) complex

Catalyst A

Figure 2. 1:1 ($AgOCOCF_3$-BINAP) complex



Catalyst B

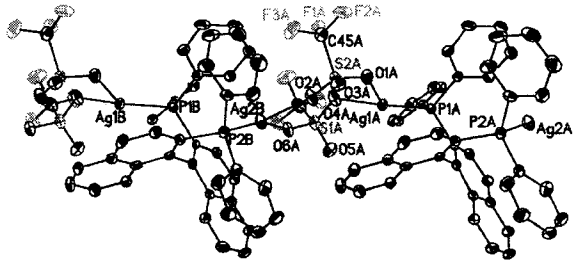
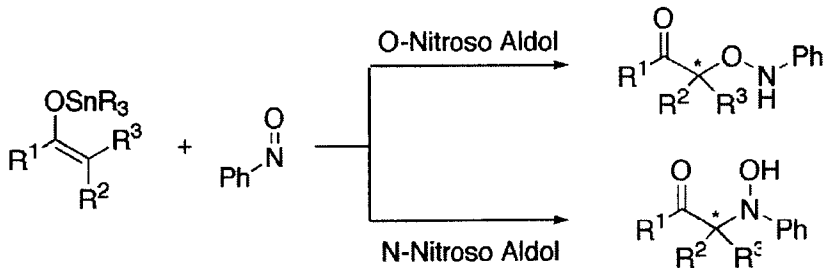


Figure 3. 2:1 (AgOTf-(*R*)-BINAP) complex

Catalyst C

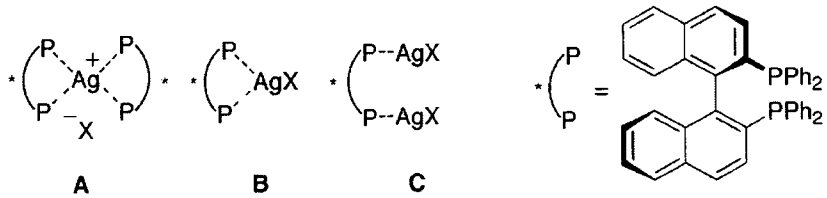
Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc. ASAP Article*

Role of LA in Enantioselectivity



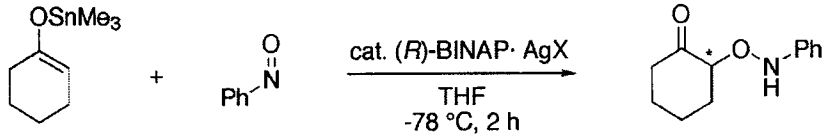
Complex A: >99% N-selective, <1% ee

Complex C: O- / N- = 95 : 5, 9% ee



Complex B:

Table 1. 1:1 (AgX·(*R*)-BINAP) Complexes in *O*-Nitroso Aldol Synthesis[a]



entry	mol %	AgX	yield, %[b]	ee, %[c]
1[d]	10	AgOTf	88	99
2	2	AgOAc	93	97
3	2	$AgOCOCF_3$	94	95

1:1 complex **B** is the responsible catalyst for catalyzed *O*-nitroso aldol process.

Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc. ASAP Article*

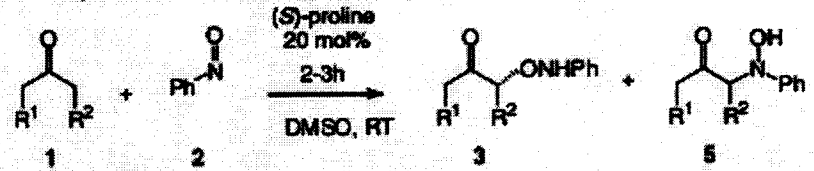
Drawback

- Stoichiometric use of toxic trialkyltin compounds.

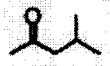
- Aldehydes are not reported as substrates.

Proline-Catalyzed Asymmetric α -Aminooxylation of Ketones

Table 1: Proline-catalyzed direct α-aminoxylation of different ketones.[a]



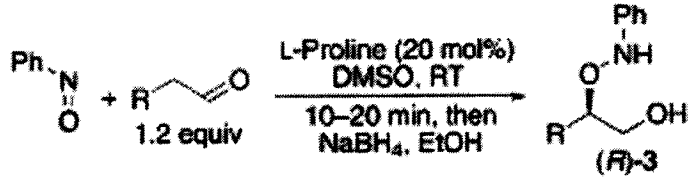
1 2 3 5

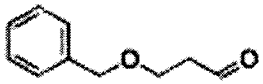
Entry	Ketone	R^1	R^2	Yield [%][b]	3:5	*ee* [%] of 3[c]	*ee* [%] of 5[c]
1	 1a		$-(CH_2)_3-$	70	>100/1	>99	–
				(91)[d]	(>100/1)[d]	(>99)[d]	–
2	 1b	H	Me	93	81:19	>99	11
3	 1c	Et	Me	66	98:2	99	7
4	 1d	H	$CH_2CH{=}CH_2$	87	8:22	>99	n.d.[e]
5	 1e	H	*i*Pr	64	90:10	>99	n.d.[e]

A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem. Int. Ed.* **2004**, *43*, 1109

Proline-Catalyzed Asymmetric α -Aminooxylation of Aldehydes

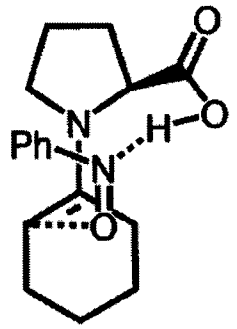
Table 1: Direct catalytic enantioselective α-aminoxylation of aldehydes.



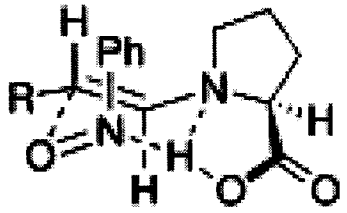
Aldehyde	Product	Yield[a] [%]	ee[b] [%]
	3a	82	99
	3b	60	97
	3c	71	99
	3d	75	99
	3e	86	99
	3f	73	99
	3g	54	99
	3h	61	94

G. Zhong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4247.

Possible TS in Proline-Catalyzed Asymmetric α -Aminooxylation

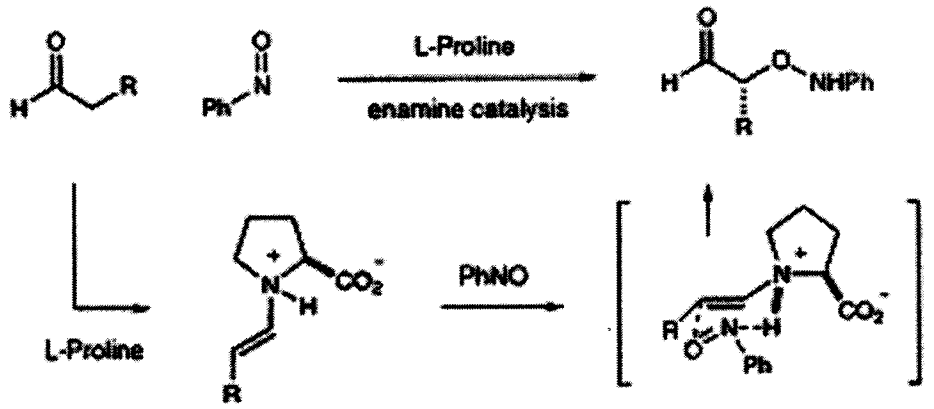


Y. Hayashi, J.Yamaguchi, K.Hibino, M.Shoji,
Tetrahedron Lett. **2003**,*44*, 8293



G. Zhong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4247.

Organocatalyzed Direct α-Oxyamination



Brown, S.P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C.
J. Am. Chem. Soc. **2003**, *125*, 19808.

Si face of E-enamine is attacked by PhNO.

Conclusion

- Synthesis of α -hydroxy ketones using nitrosobenzene has been demonstrated.

- Catalytic systems with high regio- and enantioselectivity have been proved promising.