Asymmetric *O*- and *N*- Nitroso Aldol Reaction-
an efficient access to α-oxy and α-amino carbonyl compound

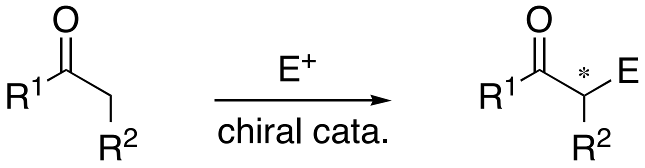
1. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 5360.
2. Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247.
3. Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1109.
4. Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 1112.

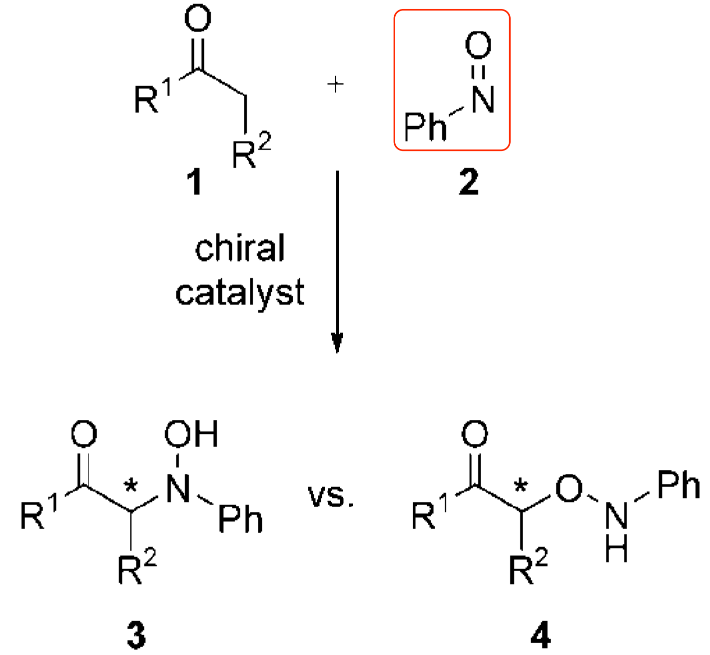
Group Presentation

Zhenjie Lu

May 27, 2003

Introduction





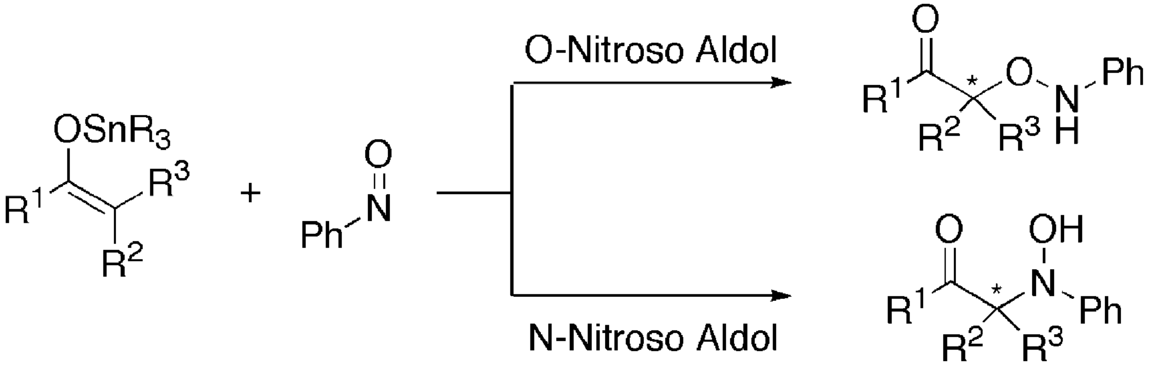
α-oxyamination adduct

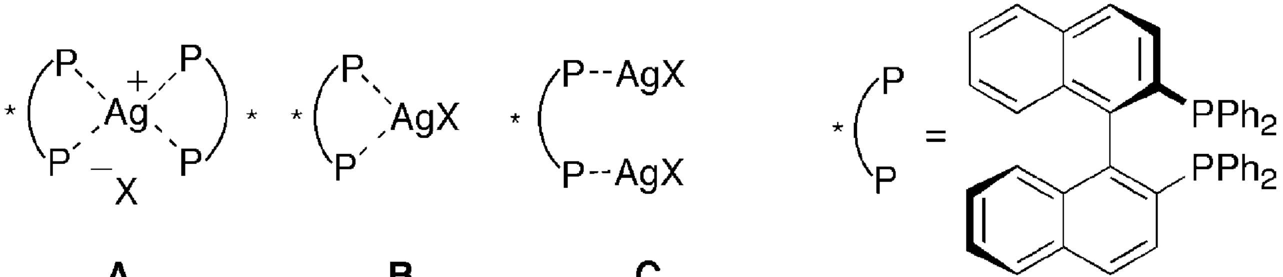
α-aminoxylation adduct

A. Enolate with
transition metal catalyst.

B. Enamine with
metal-free catalyst.

Metal Enolates as the Nucleophile





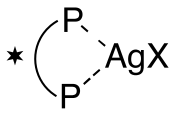
	A	B	C
ligand: AgX	2:1	1:1	1:2

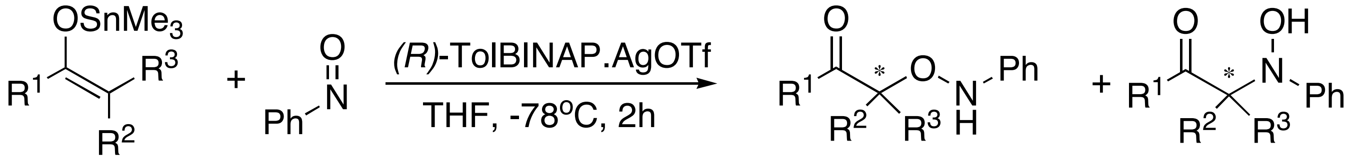
X= OTf, OAc, $OCOCF_3$

Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 5360.

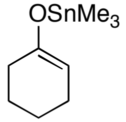
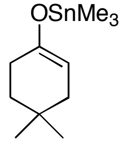
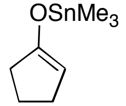
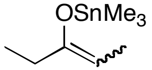
Asymmetric *O*-Nitroso Aldol Reaction Using Metal Enolate

Catalyst B 1:1





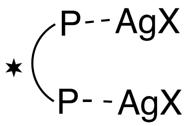
2 **1** **3** **4**

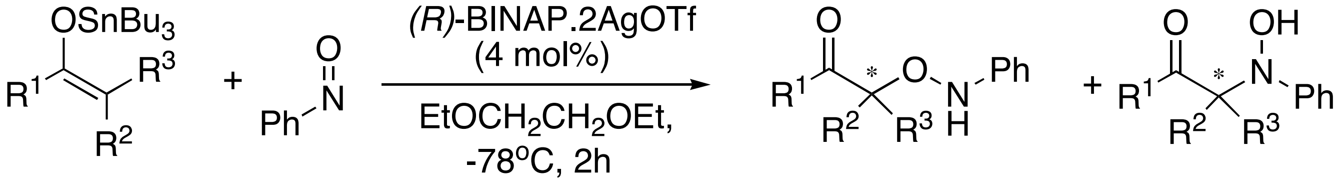
entry	enolate	cat.(mol%)	yield(%)	**3** / **4**	ee of **3**(%)
1		10	95	>99:1	97
2		2	78	>99:1	96
3		10	92	>99:1	90
4		10	93	>99:1	92
5		10	92	81/19	94

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

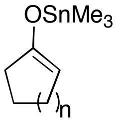
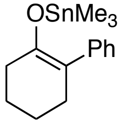
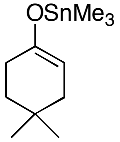
Asymmetric *N*-Nitroso Aldol Reaction Using Metal Enolate

Catalyst C 1:2





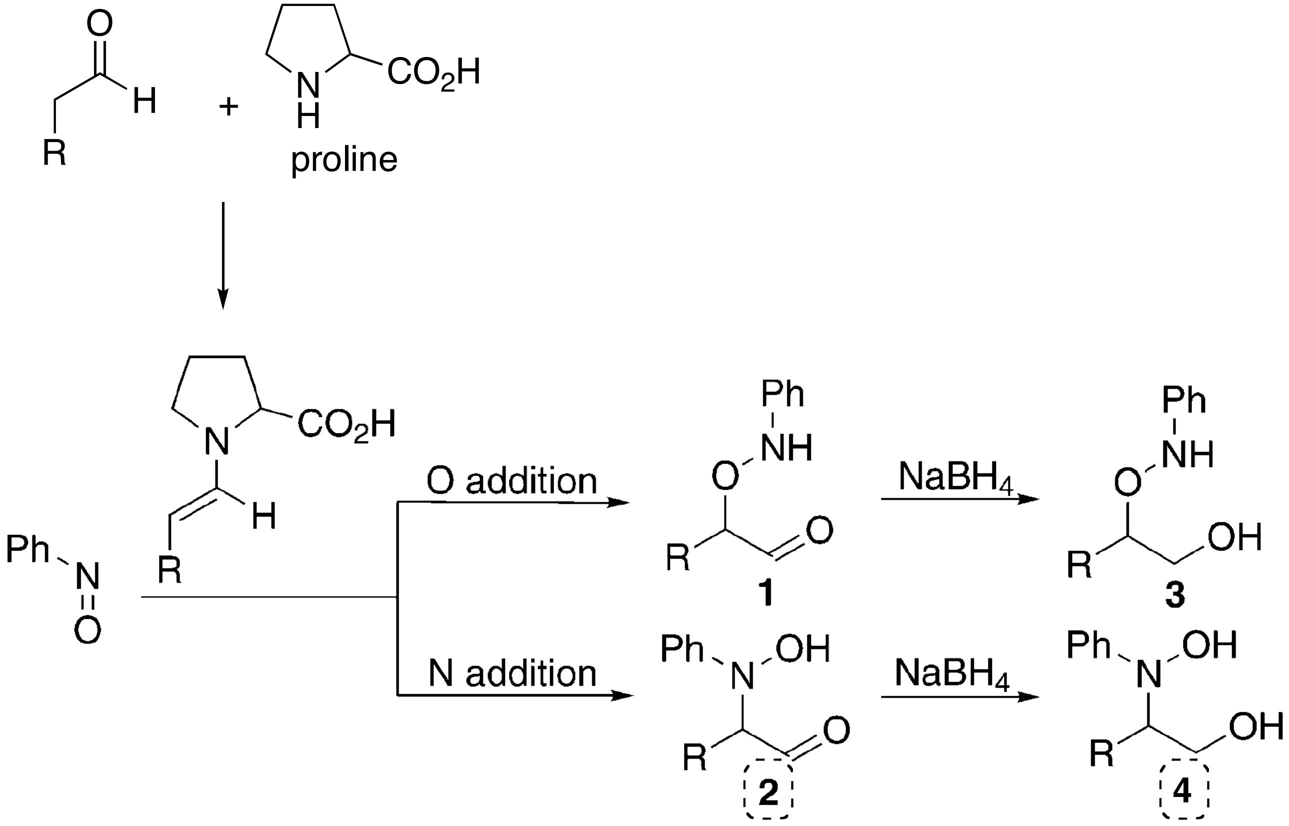
3 **4**

entry	enolate		yield(%)	**4** / **3**	ee of **4** (%)
1		n= 1	90	97/3	86
2		n= 2	95	96/4	>99
3		n= 3	96	>99:1	97
4			94	>99:1	77
5			97	>99:1	98

Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 5360.

Metal-free Proline Catalyzed α-Aminoxylation of Carbonyl Compound

➢ Possible nucleophilic addition of the enamine intermediate on the nitroso double bond.

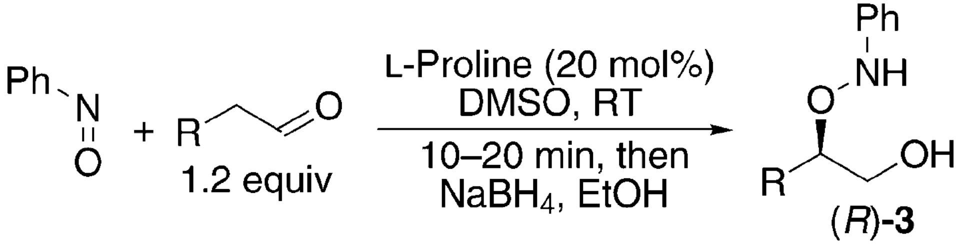


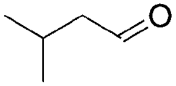
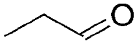
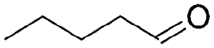
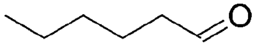
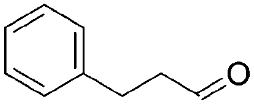
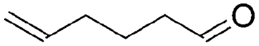
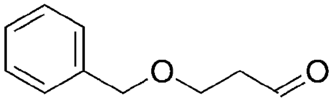
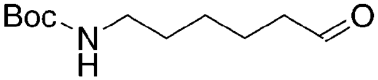
✶ Only the *O*-regioselective product **1** was observed after the addition.

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

Enantioselective *(S)*-Proline Catalyzed α-Aminoxylation of Aldehydes

- Direct catalytic enantioselective α-aminoxylation of aldehydes

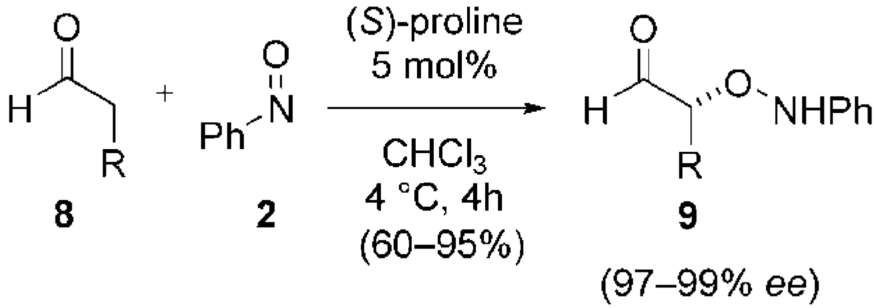


Aldehyde	Product	Yield[a] [%]	*ee*[b] [%]
	**3a**	82	99
	**3b**	60	97
	**3c**	71	99
	**3d**	75	99
	**3e**	86	99
	**3f**	73	99
	**3g**	54	99
	**3h**	61	94

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

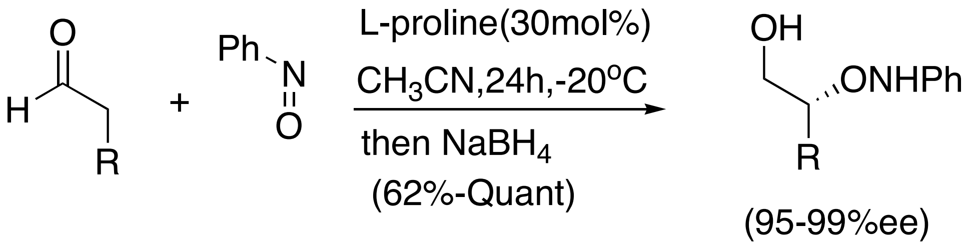
Enantioselective *(S)*-Proline Catalyzed α-Aminoxylation of Aldehydes

- α-Aminoxylation - by Macmillan



R = Me, *n*Bu, *i*Pr, Ph, CH_2-CH=CH_2, CH_2Ph,
(CH_2)$_3$OTIPS, CH_2-(3'-*N*-methylindole)

- α-Aminoxylation - by Hayashi



R = Me, Et, *n*-Pr, *i*-Pr, Ph, CH_2Ph

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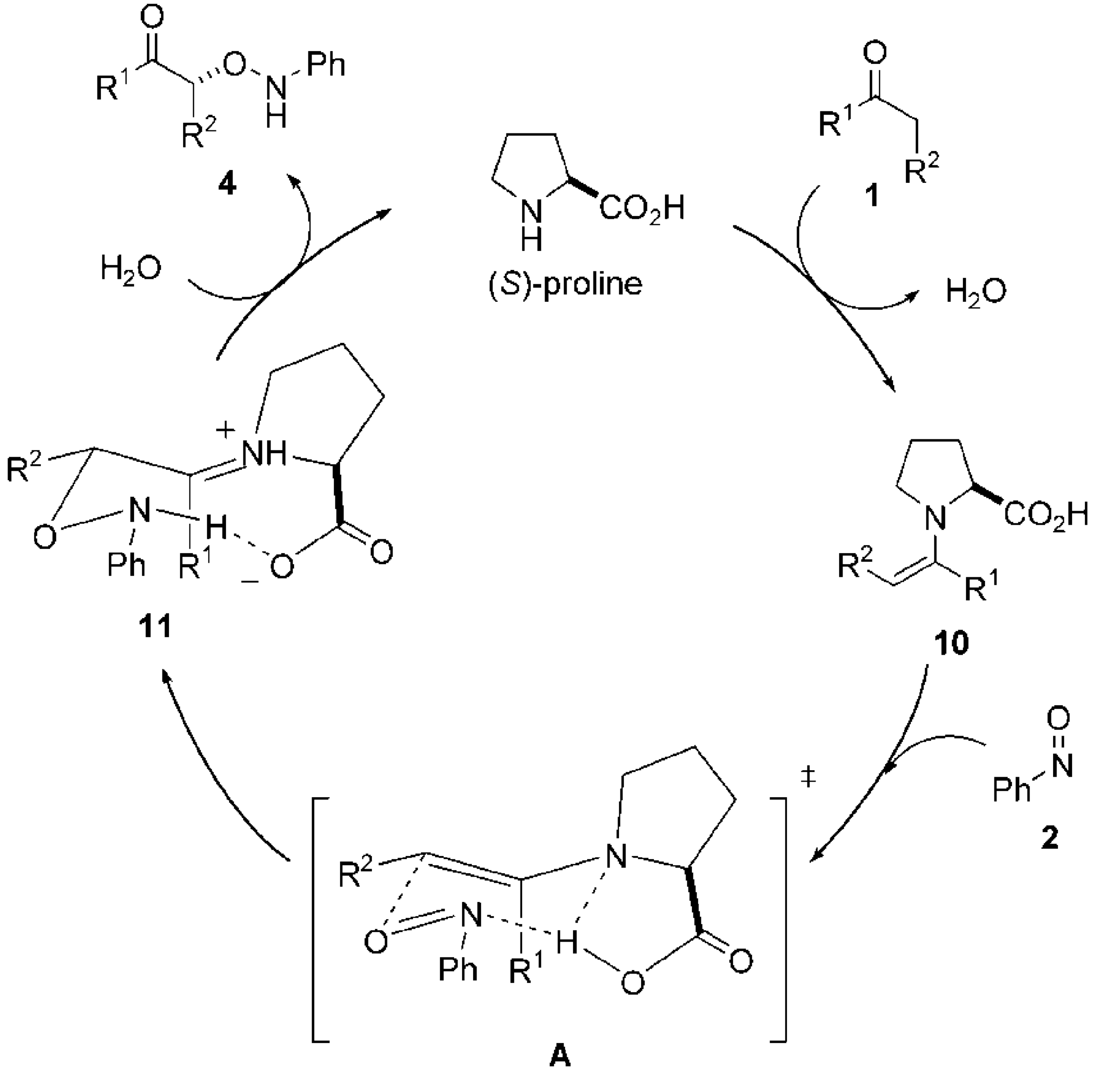
1. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W.C. *J. Am. Chem. Soc*. **2003**, *125*, 10808.
2. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetra. Lett.* **2003**, *44*, 8293.

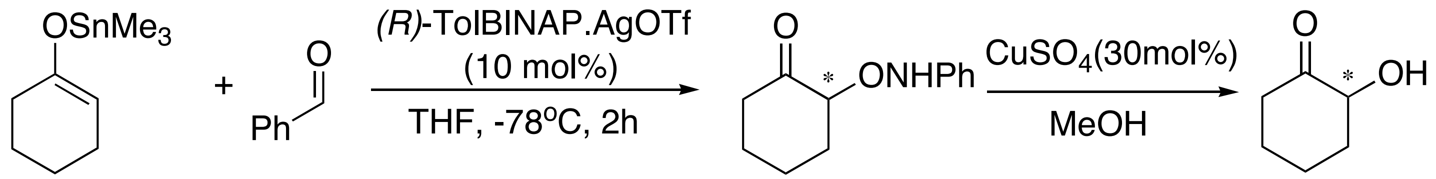
Proposed Catalytic Cycle for the *(S)*-Proline-catalyzed α-Aminoxylation of Carbonyl Compounds



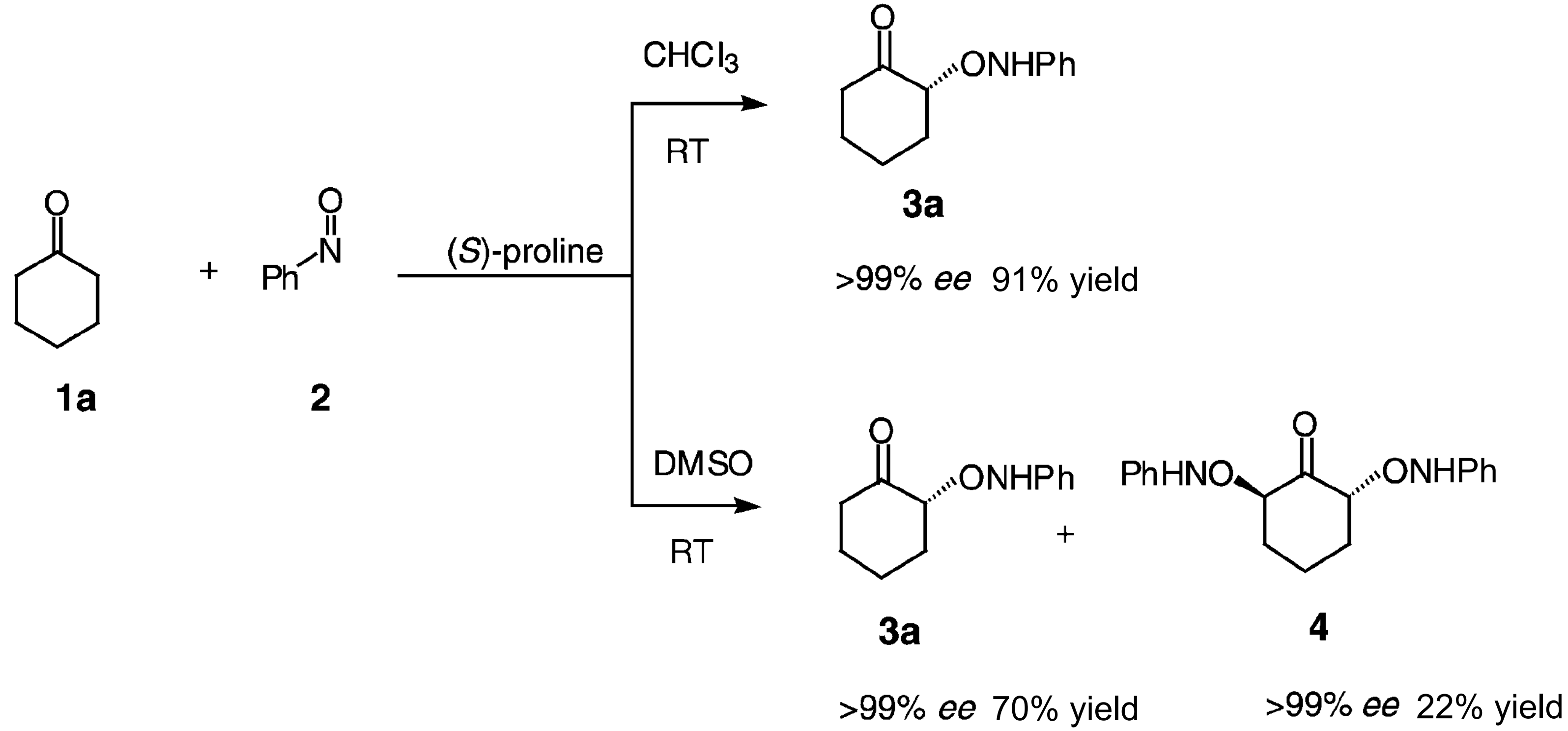
Merino, P.; Tejero, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 2.

Enantioselective α-Aminoxylation of Ketone

- α-Aminoxylation of ketones - using tin-enolate with chiral L.A. (Yamamoto)

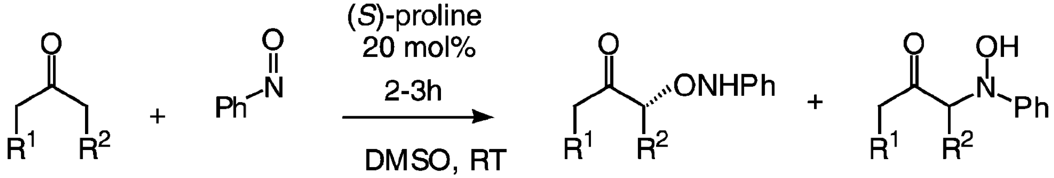


- α-Aminoxylation of ketones - using *(s)*-proline

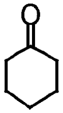
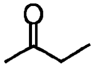
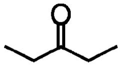
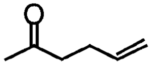
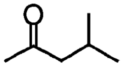


Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1109.

Proline Catalyzed Direct α-Aminoxylation of Different Ketones-I



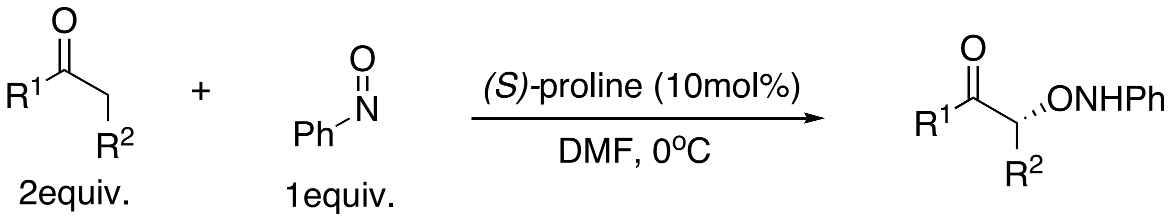
1 **2** **3** **5**

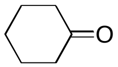
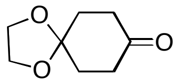
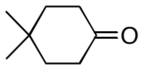
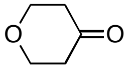
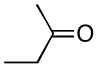
Entry	Ketone	R^1	R^2	Yield [%][b]	**3**:**5**	*ee* [%] of **3**[c]	*ee* [%] of **5**[c]
1	 **1a**		-$(CH_2)_3$-	70	$>$100/1	$>$99	–
				(91)[d]	($>$100/1)[d]	($>$99)[d]	–
2	 **1b**	H	Me	93	81:19	$>$99	11
3	 **1c**	Et	Me	66	98:2	99	7
4	 **1d**	H	$CH_2CH{=}CH_2$	87	8:22	$>$99	n.d.[e]
5	 **1e**	H	*i*Pr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

[a] Experimental conditions: A mixture of **1** (10 mmol, 10 equiv), **2** (1 mmol), and (*S*)-proline was stirred at room temperature for 2–3 h. The crude product obtained after aqueous workup was purified by column chromatography. [b] Combined yield of isolated products after silica gel column chromatography. [c] Determined by chiral-phase HPLC analyses. [d] The reaction was performed in $CHCl_3$. [e] Not determined.

Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1109.

Proline Catalyzed Direct α-Aminoxylation of Different Ketones-II



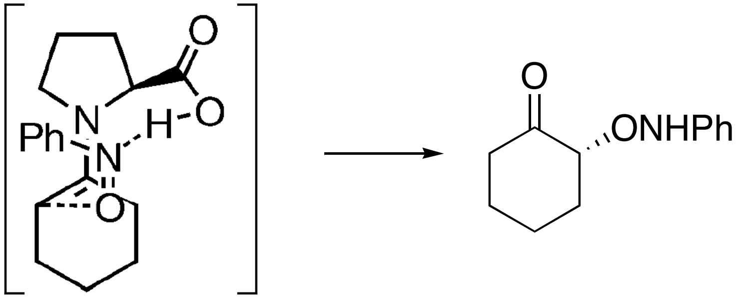
entry	ketone	add.time(h)	yield(%)	ee(%)
1		5.5	77	>99
2		24	93	>99
3		24	84	>99
4		24	53	96
5[a]		2[b]	40 (*O*-), 33 (*N*-)	>99 (*O*-), 4 (*N*-)

a. The reaction was conducted with 1.0 equiv nitrosobenzene, and 10.0 equiv ketone in DMSO at room temperature. b. After addition of mitrosobenzene, the reaction mixture was stirred for a further 4h at room temperature.

Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 1112.

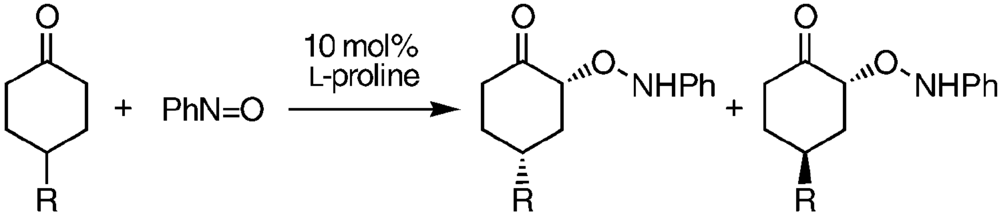
Enantioselective *(S)*-Proline Catalyzed α-Aminoxylation of Ketones

- Transition-state model



- Enamine was attacked by the nitrosobenzene from its *si* face.

- Asymmetric desymmetrization of 4-substituted cyclohexanones

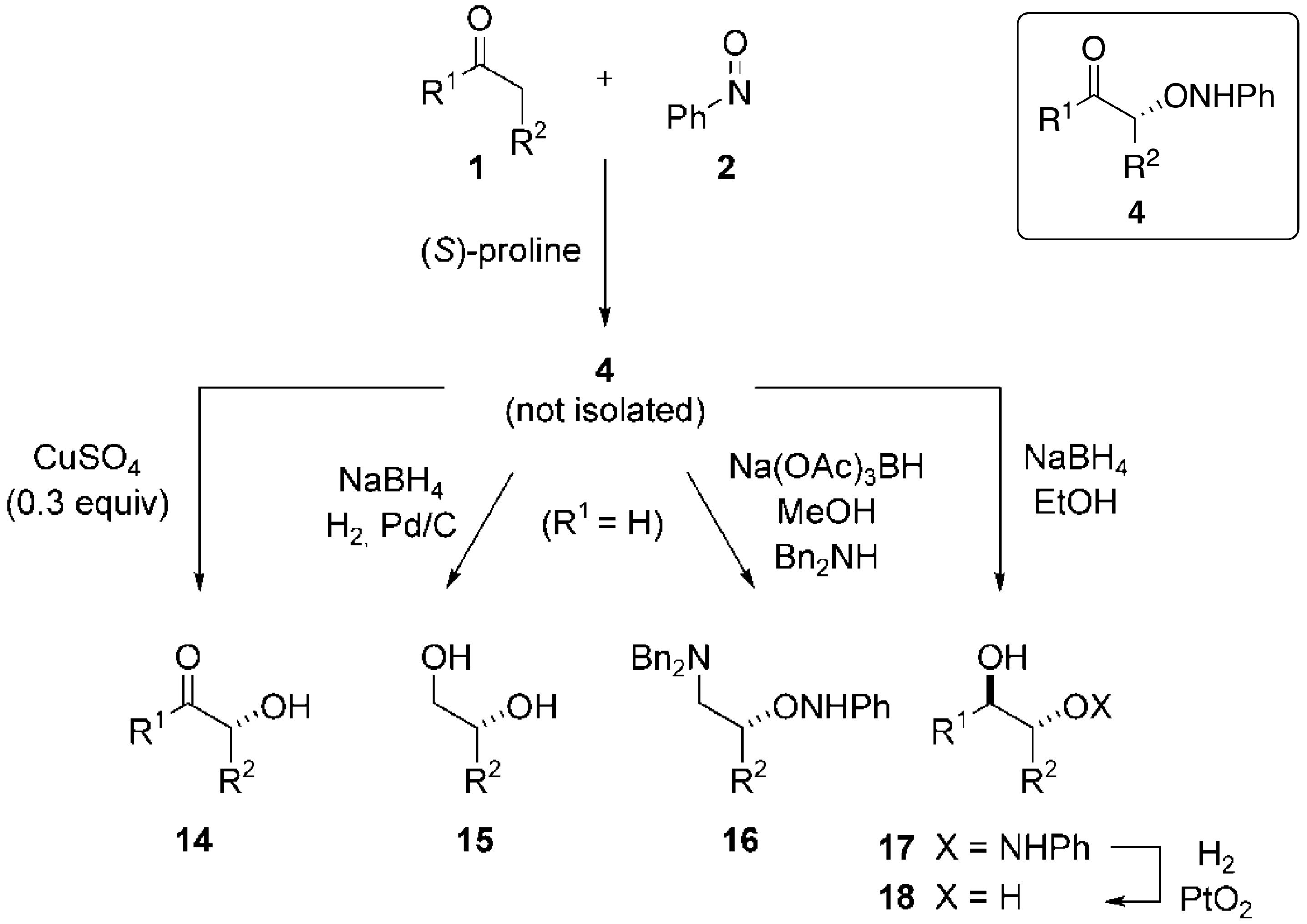


3 **4**

R	Yield [%]		*ee* [%][b]	
	3	**4**	**3**	**4**
*t*Bu	31	31	>99	94
OSi-*t*BuPh$_2$	46	23	>99	96

Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 1112.

Some Applications



Merino, P.; Tejero, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 2.

Summary

Nitroso compound works as electrophile to introduce a heteroatom at the α-position of a carbonyl compound.

- Enantiomerically pure α-oxy or α-amino carbonyl compounds.

- Good to excellent yield, excellent regio and enantioselectivity

- Proline provided a powerful, direct method with great flexibility in selection of aldehydes and ketones.

Merino, P.; Tejero, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 2.