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Catalytic Enantioselective *N*-Nitroso Aldol Reaction of γ,δ-Unsaturated δ-Lactones

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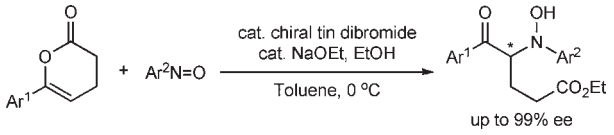
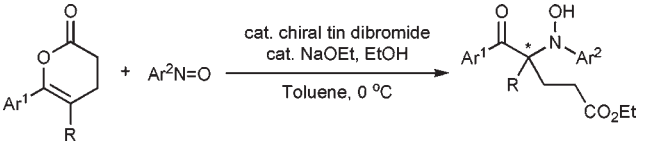
ABSTRACT



A catalytic asymmetric *N*-nitroso aldol reaction of γ,δ-didehydro-δ-lactones with nitrosoarenes was achieved using chiral tin dibromide as the chiral precatalyst and sodium ethoxide as the base precatalyst in the presence of ethanol. Optically active α-hydroxyamino ketones with up to 99% ee were regioselectively obtained in moderate to high yields from various δ-aryl-substituted γ,δ-didehydro-δ-valerolactones and *o*-substituted nitrosoarenes.

The asymmetric nitroso aldol reaction is a useful tool for obtaining optically active α-aminooxy carbonyl compounds and/or α-hydroxyamino carbonyl compounds.[1−5] A key problem in the utilization of the nitroso aldol synthesis is the control of O versus N regioselectivity. In general, simple organocatalysts, such as proline, favorably promote the enantioselective aminoxylation (*O*-nitroso aldol reaction) of aldehydes and ketones.[3] In contrast, the enantioselective hydroxyamination with opposite regioselectivity (*N*-nitroso aldol reaction) is still not an easy task to achieve.[2,4] We have previously reported that dibutyltin dimethoxide behaves as a catalyst in the *N*-nitroso aldol reaction of alkenyl trichloroacetates with nitrosobenzene in methanol.[6] The reaction takes place through a tin enolate, and the tin methoxide is regenerated in the presence of MeOH. We envisioned that if an appropriate chiral tin alkoxide could generate a chiral tin enolate that would efficiently activate a nitrosoarene, the asymmetric version of the nitroso aldol reaction would be realized. Although a variety of organocatalysts[2,3] and chiral Lewis acid catalysts[4,5] have been developed for the asymmetric transformation, to the best of our knowledge, there are no examples of the catalytic process that proceeds via a chiral metal enolate. We report here a novel example of the enantioselective *N*-nitroso aldol reaction of γ,δ-unsaturated δ-lactones using chiral tin dibromide as the asymmetric precatalyst (Scheme 1).

Scheme 1. Chiral Tin-Catalyzed Asymmetric *N*-Nitroso Aldol Reaction of γ,δ-Unsaturated δ-Lactones



We have recently reported a chiral tin alkoxide catalyzed tandem asymmetric aldol reaction/cyclization of β,γ-didehydro-γ-butyrolactones with aldehydes. The sequential reactions provide the corresponding optically active *trans*-β,γ-disubstituted γ-butyrolactones with high enantiomeric excess (ee).[7] In addition, the method employing β,γ-unsaturated γ-lactones as enolate precursors offers the advantage that unnecessary methyl or ethyl trichloroacetate

(1) Reviews: (a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995. (b) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292. (c) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514. (d) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595.

(2) For recent notable examples of *N*-nitroso aldol reactions promoted by organocatalysts, see: (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (b) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046. (c) Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8054. (d) Zhang, T.; Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Tetrahedron: Asymmetry* **2010**, *21*, 2800.

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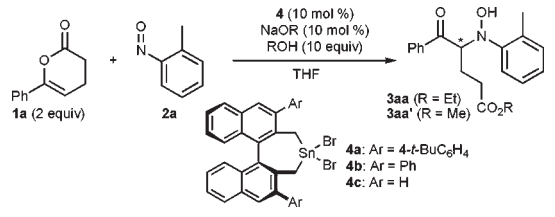
is not generated, as in the case of the reactions of alkenyl trichloroacetates.[8] Thus, we tried to react δ-substituted γ,δ-didehydro-δ-valerolactone with nitrosoarene utilizing chiral tin dibromide **4** and sodium alkoxide as catalysts, and consequently, the expected *N*-nitroso aldol product was obtained with notable asymmetric induction. For instance, when a mixture of 3,4-dihydro-6-phenylpyran-2-one (**1a**, 2 equiv) and 1-methyl-2-nitrosobenzene (**2a**, 1 equiv) was treated with chiral tin dibromide **4a**[8a] (10 mol %) and NaOMe (10 mol %) in THF at room temperature for 15 min, methyl 4-(*N*-hydroxy-*N*-*o*-tolylamino)-5-oxo-5-phenylpentanoate (**3aa′**) was obtained exclusively in 81% yield (Table 1, entry 1). The product had 45% ee, and the corresponding *O*-adduct was not observed at all. We then examined the utility of sodium ethoxide in place of sodium methoxide and as a result found that the former was better than the latter from the viewpoint of enantioselectivity (entry 2 vs entry 1). In order to gain superior results, we further attempted to optimize the reaction conditions. Lowering the reaction temperature to 0 °C improved the enantioselectivity but slowed the reaction (entry 3). The addition of 30 equiv of EtOH overcame the low reactivity at 0 °C without reducing the enantiomeric excess of product **3aa** (entry 4). Changing the solvent to toluene also contributed to the higher yield and ee (entry 6 vs entry 2). Although we investigated the catalytic activity of chiral tin dibromides **4b** and **4c** under the standard reaction conditions shown in entry 2, **4a** was found to be the catalyst of choice with regard to chemical yield and enantioselectivity (entry 2 vs entries 7 and 8).

Table 1. Optimization of Catalytic Asymmetric Nitroso Aldol Reaction of γ,δ-Unsaturated δ-Lactone **1a** with Nitrosoarene **2a**[a]



entry	4	R	temp (°C)	time, h	product	yield[b] (%)	ee[c] (%)
1	**4a**	Me	rt	0.25	**3aa′**	81	45
2	**4a**	Et	rt	0.5	**3aa**	79	75
3	**4a**	Et	0	6	**3aa**	30	79
4[d]	**4a**	Et	0	12	**3aa**	99	82
5[e]	**4a**	Et	rt	0.5	**3aa**	86	59
6[f]	**4a**	Et	rt	0.5	**3aa**	87	83
7	**4b**	Et	rt	24	**3aa**	95	40
8	**4c**	Et	rt	24	**3aa**	72	9

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **4a**–**c** (10 mol %), sodium ethoxide or sodium methoxide (10 mol %), γ,δ-unsaturated δ-lactone **1a** (2 equiv), nitrosoarene **2a** (1 equiv), and ethanol or methanol (10 equiv) in THF. [b] Isolated yield of **3aa** or **3aa′**. [c] Determined by HPLC analysis. [d] Ethanol (30 equiv) was used. [e] NaI (20 mol %) was used as an additive. [f] Toluene was used as a solvent.

With the optimal reaction conditions (entry 4 in Table 1) in hand, we performed the catalytic asymmetric *N*-nitroso aldol synthesis using various nitrosoarenes (Table 2). A definite decrease in the yield and the ee of the product was observed for nitrosobenzene (**2b**, entry 1). In contrast, the introduction of a bulky substituent at the ortho position of the nitrosoarene brought about high enantioselectivity, with the exception of butylated and phenylated derivatives (entries 3–9). Indeed, employment of 1-isopropyl-2-nitrosobenzene (**2d**) resulted in the formation of desired product **3ad** with 88% ee, although the chemical yield was reduced to 66% (entry 4). Switching the solvent to toluene favorably affected both yield and stereoselectivity: product **3ad** had 82% yield and 90% ee (entry 5). In the case of *o*-*tert*-butyl group substituted nitrosobenzene **2e**, extremely high asymmetric induction was realized but with significant loss of reactivity, probably due to its steric bulkiness (entries 7 and 8). A substituent at the meta or para position of nitrosobenzene tended to influence the chemical yield and the ee of the product (entry 1 vs entries 13–15).

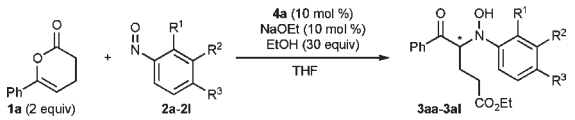
The aforementioned results encouraged us to apply a variety of δ-substituted γ,δ-didehydro-δ-valerolactones to the catalytic asymmetric *N*-nitroso aldol reaction of nitrosoarenes **2d** and **2e**. The results are shown in Table 3. Not only electron-deficient aromatic groups but also electron-rich aromatic groups could be employed as the δ-substituent of the lactones, and enantioselectivities exceeded 90% ee without a reduction of the isolated yields (entries 2–7). γ,δ-Disubstituted γ,δ-didehydro-δ-valerolactone **1g** was also a suitable substrate for the transformation (entry 8). Use of *tert*-butyl-substituted nitrosobenzene **2e** as the electrophile was effective in raising the level of asymmetric induction, although the reactivity was decreased (entries 9–12). As regards γ,δ-disubstituted substrate **1g**, almost perfect enantioselectivity (99% ee) was observed (entry 12). In the case of **1g**, even less bulky nitrosoarene **2a** reacted with it to yield a product with remarkable ee (entry 13). The absolute configuration of product **3ee** was determined to be *S* by X-ray single-crystal structure analysis (Figure 1).

We further attempted to perform the catalytic asymmetric *N*-nitroso aldol reaction of γ-phenyl-β,γ-didehydro-γ-butyrolactone (**1h**) using chiral tin dibromide **4b** under the optimized reaction conditions. However, desired *N*-adduct **3hd** was obtained in only 36% yield with 75% ee (Scheme 2).

(3) For recent notable examples of O-nitroso aldol reactions promoted by organocatalysts, see: (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (c) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. (d) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. (e) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187. (f) Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562. (g) Kano, T.; Yamamoto, A.; Shirozu, F.; Maruoka, K. *Synlett* **2009**, 1557. (h) Jiao, P.; Kawasaki, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3333. (i) Jiao, P.; Yamamoto, H. *Synlett* **2009**, 2685. (j) Bui, T.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2010**, *132*, 5574. (k) Mielgo, A.; Velilla, I.; Gómez-Bengoa, E.; Palomo, C. *Chem.—Eur. J.* **2010**, *16*, 7496. (l) Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8588. (m) Rios, R.; Schyman, P.; Sundén, H.; Zhao, G.-L.; Ullah, F.; Chen, L.-J.; Laaksonen, A.; Córdova, A. *Chem.—Eur. J.* **2010**, *16*, 13935. Also see ref 2a.

(4) For examples of *N*-nitroso aldol reactions catalyzed by chiral Lewis acids (Ag and Sc), see: (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360. (b) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (c) Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 4684.

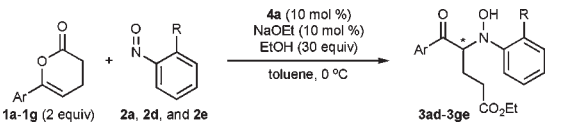
Table 2. Catalytic Asymmetric *N*-Nitroso Aldol Reaction of Diverse Nitrosoarenes[a]

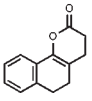


entry	nitrosoarene	R^1	R^2	R^3	temp (°C)	time (h)	solvent	product	yield[b] (%)	ee[c] (%)
1	**2b**	H	H	H	0	12	toluene	**3ab**	27	49
2	**2a**	Me	H	H	0	12	THF	**3aa**	99	82
3	**2c**	n-C_4H_9	H	H	0	12	THF	**3ac**	66	82
4	**2d**	i-C_3H_7	H	H	0	12	THF	**3ad**	66	88
5	**2d**	i-C_3H_7	H	H	0	12	toluene	**3ad**	82	90
6	**2d**	i-C_3H_7	H	H	−20	48	toluene	**3ad**	58	91
7	**2e**	t-C_4H_9	H	H	0	12	THF	**3ae**	23	95
8	**2e**	t-C_4H_9	H	H	0	12	toluene	**3ae**	37	99
9	**2f**	Ph	H	H	0	12	THF	**3af**	44	52
10	**2g**	F	H	H	0	12	toluene	**3ag**	87	57
11	**2h**	Br	H	H	0	12	toluene	**3ah**	73	38
12	**2i**	CF_3	H	H	0	12	toluene	**3ai**	93	43
13	**2j**	H	OMe	H	0	12	toluene	**3aj**	82	46
14	**2k**	H	H	Me	0	12	toluene	**3ak**	81	38
15	**2l**	H	H	Br	0	12	toluene	**3al**	46	69

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **4a** (10 mol %), sodium ethoxide (10 mol %), γ,δ-unsaturated δ-lactone **1a** (2 equiv), nitrosoarene **2a**−**l** (1 equiv), and ethanol (30 equiv) in the specified solvent. [b] Isolated yield of **3aa**−**al**. [c] Determined by HPLC analysis.

Table 3. Catalytic Asymmetric *N*-Nitroso Aldol Reaction of Various γ,δ-Unsaturated δ-Lactones[a]



entry	lactone	Ar	nitrosoarene	R	time, h	product	yield, %[b]	ee, %[c]
1	**1a**	Ph	**2d**	i-C_3H_7	12	**3ad**	82	90
2	**1b**	4-MeC_6H_4	**2d**	i-C_3H_7	12	**3bd**	94	95
3	**1c**	4-$MeOC_6H_4$	**2d**	i-C_3H_7	12	**3cd**	97	92
4	**1d**	2-FC_6H_4	**2d**	i-C_3H_7	18	**3dd**	75	>99
5	**1e**	4-BrC_6H_4	**2d**	i-C_3H_7	12	**3ed**	92	95
6[d]	**1e**	4-BrC_6H_4	**2d**	i-C_3H_7	12	**3ed**	>99	94
7	**1f**	2-naphthyl	**2d**	i-C_3H_7	16	**3fd**	>99	98
8	**1g**		**2d**	i-C_3H_7	16	**3gd**	>99	90
9	**1a**	Ph	**2e**	t-C_4H_9	12	**3ae**	37	99
10	**1b**	4-MeC_6H_4	**2e**	t-C_4H_9	12	**3be**	30	97
11	**1e**	4-BrC_6H_4	**2e**	t-C_4H_9	12	**3ee**	73	96
12	**1g**		**2e**	t-C_4H_9	17	**3ge**	52	>99
13	**1g**		**2a**	Me	15	**3ga**	75	92

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **4a** (10 mol %), sodium ethoxide (10 mol %), γ,δ-unsaturated δ-lactone **1a**−**g** (2 equiv), nitrosoarene **2a**, **2d**, or **2e** (1 equiv), and ethanol (30 equiv) at 0 °C in toluene. [b] Isolated yield of **3ad**−**ge**. [c] Determined by HPLC analysis. [d] Chiral tin dibromide **4a** (5 mol %) was used.

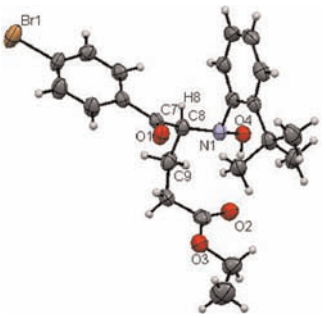
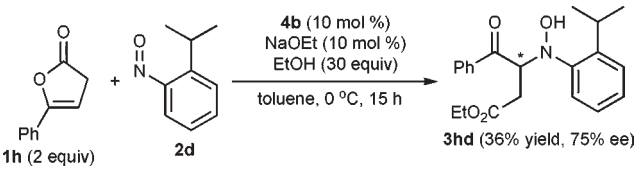


Figure 1. Crystal structure of **3ee**.

Scheme 2. Catalytic Asymmetric *N*-Nitroso Aldol Reaction of γ-Phenyl-β,γ-didehydro-γ-butyrolactone (**1h**)



The proposed catalytic mechanism is indicated in Figure 2. First, chiral tin dibromide **4** reacts with an equimolar amount of sodium ethoxide to yield the corresponding chiral tin bromide ethoxide, which is the true catalyst in the present asymmetric nitroso aldol synthesis. Next, the thus-formed chiral tin bromide ethoxide is added to γ,

(5) For examples of *O*-nitroso aldol reactions catalyzed by chiral Ag Lewis acids, see: (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 6498 (correction). (c) Kawasaki, M.; Li, P.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3795. (d) Yanagisawa, A.; Takeshita, S.; Izumi, Y.; Yoshida, K. *J. Am. Chem. Soc.* **2010**, *132*, 5328. Also see refs 4a and 4b.

(6) Yanagisawa, A.; Izumi, Y.; Takeshita, S. *Synlett* **2009**, 716.

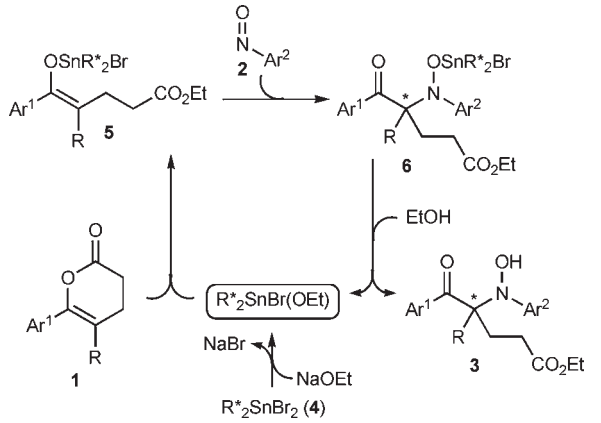


Figure 2. Plausible catalytic cycle for the asymmetric *N*-nitroso aldol reaction.

δ-didehydro-δ-valerolactone **1** to generate chiral tin enolate **5**. Subsequent *N*-nitroso aldol reaction between chiral tin enolate **5** and nitrosoarene **2** affords tin alkoxide of α-hydroxyamino ketone **6**. Finally, protonation of tin alkoxide **6** with EtOH results in the formation of optically active α-hydroxyamino ketone **3** with regeneration of the chiral tin bromide ethoxide. The rapid ethanolysis of tin alkoxide **6** promotes the catalytic cycle efficiently.

In conclusion, we have developed a novel catalytic asymmetric α-hydroxyamination system. The use of in situ generated chiral tin bromide ethoxide as the chiral catalyst promoted the synthesis of various nonracemic α-hydroxyamino ketones with enantioselectivities of up to 99% ee.

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Supporting Information Available. Experimental procedures, spectral data for products in Tables 1−3 and Scheme 2, and X-ray crystal structure file (CIF) for **3ee**. This material is available free of charge via the Internet at http://pubs.acs.org.

(7) Yanagisawa, A.; Kushihara, N.; Yoshida, K. *Org. Lett.* **2011**, *13*, 1576.

(8) (a) Yanagisawa, A.; Satou, T.; Izumiseki, A.; Tanaka, Y.; Miyagi, M.; Arai, T.; Yoshida, K. *Chem.—Eur. J.* **2009**, *15*, 11450. (b) Izumiseki, A.; Yoshida, K.; Yanagisawa, A. *Org. Lett.* **2009**, *11*, 5310.

The authors declare no competing financial interest.