



# Novel enantioselective direct aldol-type reaction promoted by a chiral phosphine oxide as an organocatalyst

Shunsuke Kotani<sup>a</sup>, Yasushi Shimoda<sup>b</sup>, Masaharu Sugiura<sup>b</sup>, Makoto Nakajima<sup>b,\*</sup>

<sup>a</sup> Priority Organization for Innovation and Excellence, Kumamoto University, Kumamoto 862-0973, Japan

<sup>b</sup> Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto 862-0973, Japan

## ARTICLE INFO

### Article history:

Received 25 April 2009

Revised 18 May 2009

Accepted 21 May 2009

Available online 25 May 2009

## ABSTRACT

Chiral phosphine oxide successfully catalyzed the direct aldol-type reactions of cyclohexanone derivatives and benzaldehyde derivatives in high stereoselectivities. The reaction mechanism involves the in situ formation of trichlorosilyl enol ethers. The present reaction could be extended to the cross-aldol reactions between two aldehydes.

© 2009 Elsevier Ltd. All rights reserved.

The enantioselective aldol reaction is a powerful method for constructing one or two successive chiral carbon centers.<sup>1</sup> Progress in catalytic, enantioselective aldol reaction has been made by chiral Lewis acid-catalyzed reactions of trimethylsilyl enol ethers, which act as aldol donors and are prepared from parent carbonyl compounds. In the last decades, catalytic enantioselective *direct* aldol reactions, which do not require masked enol ethers to be prepared beforehand from ketones or esters (aldol donors), have attracted much attention due to their simple manipulation and high atom economy.<sup>2</sup> Two types of direct aldol reactions have been reported: the reactions catalyzed by chiral metal alkoxide complexes, which were initially reported by Shibasaki,<sup>3,4</sup> and the reactions involving enamine process, which were pioneered by List and Barbas.<sup>5,6</sup> Both strategies have been extensively investigated, and are commonplace in the development of asymmetric reactions.<sup>7</sup> Herein, we report a novel type of enantioselective direct aldol-type reaction, which employs a new concept involving a silicate intermediate promoted by a chiral phosphine oxide<sup>8</sup> as an organocatalyst.<sup>9</sup>

The aldol reaction of trichlorosilyl enol ethers developed by Denmark, which likely proceeds via a six-membered transition state involving hypervalent silicate, provides a high *syn/anti* selectivity (diastereoselectivity) as reflected by the *E/Z* ratio of the enol ether.<sup>10</sup> We have demonstrated that chiral *N*-oxides or phosphine oxides catalyze the aldol reaction of trichlorosilyl enol ethers to afford the  $\beta$ -hydroxy carbonyl compounds in the high diastereo- and enantioselectivities.<sup>11</sup> To improve the efficiency, we envisaged an in situ preparation of the enol ethers from the mother carbonyl compounds. If trichlorosilyl enol ether is prepared from the corresponding ketone and tetrachlorosilane in the presence of phosphine oxides, and the resulting enol ether is simultaneously activated by phosphine oxide to react with aldehydes, then a direct aldol-type reaction of two carbonyl compounds will be realized.

We initially examined the aldol reaction of cyclohexanone and benzaldehyde with tetrachlorosilane and diisopropylethylamine in dichloromethane at rt using BINAPO (BINAP dioxide) as a catalyst (Eq. 1). Benzaldehyde was slowly added to the mixture containing all the other components at rt,<sup>12</sup> which afforded the aldol adduct with good *anti*-selectivity, but in low chemical and optical yields (rt, 4 h, 30% yield, *syn/anti* = 1/5, 16% ee (*anti*)). Among the various conditions surveyed, propionitrile was the solvent of choice, and this gave the adduct in high yield with a good selectivity (rt, 1 h, 85% yield, *syn/anti* = 1/6, 51% ee (*anti*)). Decreasing the reaction temperature gave a slightly better stereoselectivity (0 °C 2 h, 81% yield, *syn/anti* = 1/6, 54% ee (*anti*)).

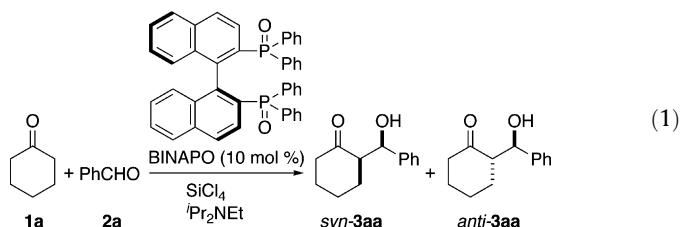


Table 1 summarizes the results obtained for the reaction of various ketones and benzaldehyde under the optimal conditions. The reaction of cyclopentanone gave a similar selectivity, but with a low yield due to dehydration (entry 2). 4,4-Disubstituted cyclohexanones (entries 3 and 4) gave better stereoselectivities, especially the 4,4-ethylenedioxy group, which dramatically increased the enantioselectivity (entry 4). Heterocyclic ketones also yielded the adducts with good yields and selectivities without loss of reactivities (entries 5–7). Pinacolone, an acyclic ketone, did not give the corresponding adduct (entry 8).

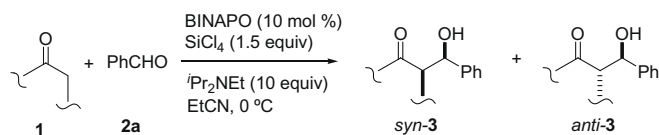
Direct aldol-type reactions were examined using 4,4-(ethylenedioxy)cyclohexanone as an aldol donor and several other aldehydes

\* Corresponding author. Tel.: +81 96 371 4680; fax: +81 96 362 7692.

E-mail address: [nakajima@gpo.kumamoto-u.ac.jp](mailto:nakajima@gpo.kumamoto-u.ac.jp) (M. Nakajima).

**Table 1**

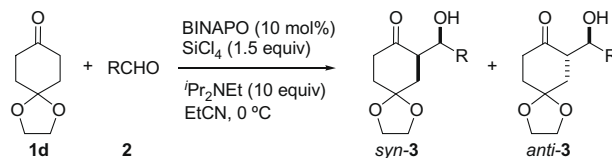
Enantioselective direct aldol-type reactions between various ketones and benzaldehyde catalyzed by BINAPO



Entry	Ketone	Time (h)	<b>3</b>	Yield <sup>a</sup> (%)	syn/anti <sup>b</sup>	% ee <sup>c</sup> ( <i>anti</i> )
1	Cyclohexanone ( <b>1a</b> )	2	<b>3aa</b>	81	1/6	54
2	Cyclopentanone ( <b>1b</b> )	2	<b>3ba</b>	58	1/5	53
3	( <b>1c</b> )	4	<b>3ca</b>	84	1/24	53
4	( <b>1d</b> )	6	<b>3da</b>	79	1/31	73
5	( <b>1e</b> )	6	<b>3ea</b>	82	1/11	45
6	( <b>1f</b> )	6	<b>3fa</b>	75	1/16	62
7	( <b>1g</b> )	6	<b>3ga</b>	79	1/11	55
8	Pinacolone ( <b>1h</b> )	12	<b>3ha</b>	Trace	—	—

<sup>a</sup> Isolated yields.<sup>b</sup> Determined by <sup>1</sup>H-NMR and HPLC analyses.<sup>c</sup> Determined by HPLC analysis.**Table 2**

Enantioselective direct aldol-type reactions between a ketone and various aldehydes catalyzed by BINAPO



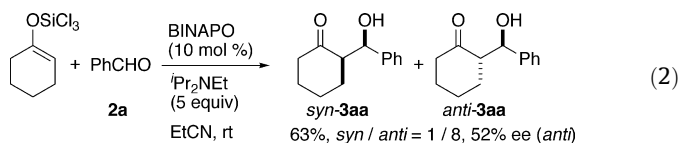
Entry	R	Time (h)	<b>3</b>	Yield <sup>a</sup> (%)	syn/anti <sup>b</sup>	% ee <sup>c</sup> ( <i>anti</i> )
1	Ph ( <b>2a</b> )	6	<b>3da</b>	79	1/31	73
2	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	6	<b>3db</b>	69	1/38	71
3	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	6	<b>3dc</b>	74	1/19	64
4	1-Naphthyl ( <b>2d</b> )	6	<b>3dd</b>	62	1/45	61
5	2-Naphthyl ( <b>2e</b> )	6	<b>3de</b>	54	1/46	65
6	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>2f</b> )	6	<b>3df</b>	93	1/38	63
7	PhCH=CH ( <b>2g</b> )	6	<b>3dg</b>	53	1/6	51
8	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>2h</b> )	12	<b>3dh</b>	Trace	—	—

<sup>a</sup> Isolated yields.<sup>b</sup> Determined by <sup>1</sup>H NMR and HPLC analyses.<sup>c</sup> Determined by HPLC analysis.

(Table 2). The aldol reactions of aromatic aldehydes gave similar results to those in benzaldehyde (entries 3–6). Sterically hindered aldehydes tended to give higher diastereoselectivities, but slightly lower enantioselectivities (entries 4–6). Although the reaction of cinnamaldehyde, a conjugated aldehyde, afforded the product in modest chemical yield and selectivities, dihydrocinnamaldehyde did not afford the aldol adduct under these conditions, which may be due to the formation of the corresponding chlorohydrin.<sup>13</sup>

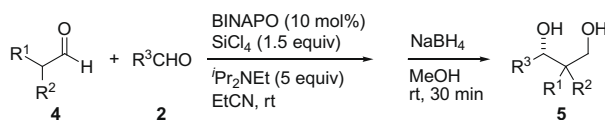
To elucidate the reaction mechanism, BINAPO-catalyzed aldol reactions of the isolated trichlorosilyl enol ethers of cyclohexanone with benzaldehyde were conducted (Eq. 2). The indirect and direct methods gave comparable results (indirect method: 63%, *syn/anti* = 1/8, 52% ee (*anti*); direct method: 85%, *syn/anti* = 1/6, 54% ee (*anti*)). Moreover, in situ formation of the trichlorosilyl enol

ether was confirmed by <sup>1</sup>H NMR analysis for the reaction of cyclohexanone with tetrachlorosilane, diisopropylethylamine, and BINAPO in CD<sub>3</sub>CN.<sup>14</sup> Interestingly, the intermediate was not generated in the absence of BINAPO, indicating that the Lewis base catalyst plays an important role not only in the aldol process, but also for enolate generation. It is hypothesized that trichlorosilyl enol ethers generated in situ with the assistance of BINAPO subsequently react with the coexisting aldehyde via a six-membered chair-like transition state to give the corresponding aldol adducts.



**Table 3**

Enantioselective direct aldol-type reactions between various aldehydes



Entry	Aldol donor (R <sup>1</sup> , R <sup>2</sup> )	Aldol acceptor (R <sup>3</sup> )	Time (h)	5	Yield <sup>a</sup> (%)	% ee <sup>b</sup> (anti)
1	Me, Me ( <b>4a</b> )	Ph ( <b>2a</b> )	0.5	<b>5aa</b>	87	55
2	–(CH <sub>2</sub> ) <sub>3</sub> – ( <b>4b</b> )	Ph ( <b>2a</b> )	0.5	<b>5ba</b>	80	49
3	Me, Me ( <b>4a</b> )	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	0.5	<b>5ab</b>	99	58
4	Me, Me ( <b>4a</b> )	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	0.5	<b>5ac</b>	86	58
5	Me, Me ( <b>4a</b> )	1-Naphthyl ( <b>2d</b> )	2	<b>5ad</b>	71	51
6	Me, Me ( <b>4a</b> )	2-Naphthyl ( <b>2e</b> )	2	<b>5ae</b>	94	53
7	Me, Me ( <b>4a</b> )	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>2h</b> )	24	<b>5ah</b>	16	63
8	Me, nPr ( <b>4c</b> )	Ph ( <b>2a</b> )	4	<b>5ca</b>	80 <sup>c</sup>	49 <sup>d</sup> , 45 <sup>e</sup>

<sup>a</sup> Isolated yields.<sup>b</sup> Determined by HPLC analysis.<sup>c</sup> dr = 2:1.<sup>d</sup> The ee of the major diastereomer.<sup>e</sup> The ee of the minor diastereomer.

As mentioned above, aliphatic aldehydes showed little reactivity as electrophiles. Therefore, we next envisioned that aliphatic aldehydes might act as good aldol donors via enolization by tetrachlorosilane with an amine base.<sup>15</sup> Direct aldol-type reactions between two different aldehydes are classical C–C bond-forming reactions in organic synthesis. However, few examples of enantioselective direct aldol reactions have been reported between aldehydes due to crucial side reactions, including self-aldol reactions, dehydration, and multiple aldol reactions.<sup>16</sup>

Thus, we investigated the reaction between benzaldehyde and isobutyraldehyde in the presence of BINAPO as an organocatalyst.<sup>17</sup> The reaction was conducted similar to the case using ketones and the aldol products were transformed to the corresponding diols by NaBH<sub>4</sub> reduction to facilitate isolation. Table 3 shows the results for the reactions between various aldehydes. Although stereoselectivities were modest, the reactions proceeded smoothly to afford the corresponding adduct without any self-condensation in every case. Finally, the diastereo- and enantioselective reaction of 2-methylpentanal with benzaldehyde afforded the desired aldol adduct, which possessed an α-quaternary stereogenic center with moderate stereoselectivity (entry 8).<sup>18</sup>

In summary, we have demonstrated a new concept for the asymmetric direct aldol-type reactions between ketones and aldehydes or between two aldehydes by using a chiral phosphine oxide, BINAPO as an organocatalyst. Further investigations, including improving the enantioselectivity, extending the scope of the reaction, and applying to natural product synthesis, are currently underway.

## Acknowledgments

This work was partly supported by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformations of Carbon Resources' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We thank Takasago International Corporation for its generous gift of chiral phosphines.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.065.

## References and notes

- For recent reviews on enantioselective aldol reaction, see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, 9, 357–389; (b) Gröger, H.; Vogl, E. M.; Shibasaki,

- M. Chem. Eur. J. **1998**, 4, 1137–1141; (c) Mahrwald, R. *Chem. Rev.* **1999**, 99, 1095–1120; (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, 39, 1352–1374; (e) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, 33, 65–75.
- For reviews on direct aldol reaction, see: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601; (b) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, 37, 570–579; (c) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, 18, 2249–2293.
- (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, 36, 1871–1873; (b) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, 102, 2187–2210; (c) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, 35, 269–279.
- For related catalyses, see: (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, 122, 12003–12004; (b) Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* **2001**, 42, 4669–4671.
- (a) List, B.; Lerner, R. A.; Barbas, C. F. J. *Am. Chem. Soc.* **2000**, 122, 2395–2396; (b) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, 37, 580–591; (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, 107, 5471–5569.
- For related catalyses, see: (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, 43, 1983–1986; (b) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808–1809; (c) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, 44, 3055–3057.
- Although the substrates are limited to glycine Schiff bases, the aldol reactions promoted by phase transfer catalysts have been reported, see: Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, 41, 4542–4544.
- For chiral phosphine oxide-catalyzed reactions, see: (a) Nakajima, M.; Kotani, S.; Ishizuka, T.; Hashimoto, S. *Tetrahedron Lett.* **2005**, 46, 157–159; (b) Tokuoka, E.; Kotani, S.; Matsunaga, H.; Ishizuka, T.; Hashimoto, S.; Nakajima, M. *Tetrahedron: Asymmetry* **2005**, 16, 2391–2392; (c) Nakanishi, K.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron* **2008**, 64, 6415–6419; (d) Simonini, V.; Benaglia, M.; Benincori, T. *Adv. Syn. Catal.* **2008**, 350, 561–564.
- For recent reviews on related organocatalyses, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, 43, 5138–5175; (b) Pellissier, H. *Tetrahedron* **2007**, 63, 9267–9331; (c) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29–36; (d) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, 47, 1560–1638; (e) MacMillan, D. W. C. *Nature* **2008**, 455, 304–308.
- (a) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, 118, 7404–7405; (b) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, 33, 432–440.
- (a) Nakajima, M.; Yokota, T.; Saito, M.; Hashimoto, S. *Tetrahedron Lett.* **2004**, 45, 61–64; (b) Kotani, S.; Hashimoto, S.; Nakajima, M. *Synlett* **2006**, 1116–1118; (c) Kotani, S.; Hashimoto, S.; Nakajima, M. *Tetrahedron* **2007**, 63, 3122–3132; (d) Sugiura, M.; Sato, N.; Kotani, S.; Nakajima, M. *Chem. Commun.* **2008**, 4309–4311.
- Although adding tetrachlorosilane to the mixture of the other components gave the same results, adding a ketone to the mixture decreased the stereoselectivities.
- For a discussion on the chlorohydrin formation, see: Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, 127, 3774–3789.
- The signal of the olefin proton was observed at 5.28 ppm derived from cyclohexanone. See [Supplementary data](#).
- Denmark reported that HMPA catalyzed the formation of the trichlorosilyl enol ether of isobutyraldehyde with tetrachlorosilane and 2,4,6-trimethylpyridine, see: Denmark, S. E.; Bui, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5439–5444.
- For recent reports on asymmetric cross-aldol reactions of aldehyde enolate equivalents, see: (a) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, 40,

- 4759–4762; (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (c) Mase, N.; Tanaka, F.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423; (d) Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814–3816; (e) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–5529; (f) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738–1740.
17. (*R*)-3,3'-Dimethyl-2,2'-biquinoline *N,N'*-dioxide catalyzed the reaction of benzaldehyde and isobutyraldehyde with a similar stereoselectivity but with lower chemical yield (2 h, 71%, 55% ee).
18. For a review on enantioselective construction of quaternary carbon centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401; (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146; (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396.