CHEMISTRY
A EUROPEAN JOURNAL

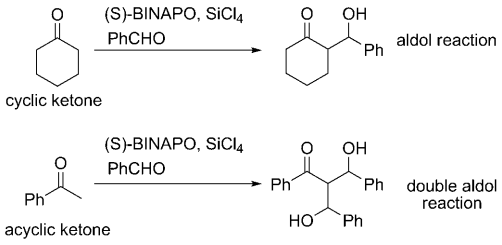
DOI: 10.1002/chem.201100917

Enantioselective Double Aldol Reaction Catalyzed by Chiral Phosphine Oxide

Yasushi Shimoda,[a] Shunsuke Kotani,*[b] Masaharu Sugiura,[a] and Makoto Nakajima*[a]

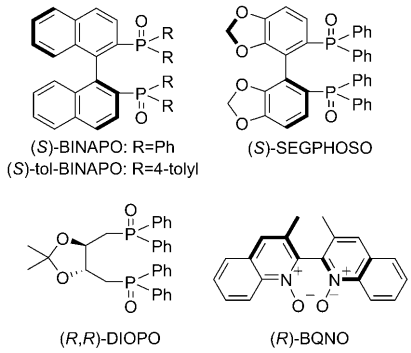
Sequential reactions have gained importance in recent years because they provide attractive approaches to the synthesis of molecules with complex architectures in a single operational step.[1] One of the current challenges in organic chemistry is to develop tandem reactions (domino or cascade reactions) that provide complex molecules from readily available starting compounds. Among the tandem reactions identified, a few sequential aldol reaction strategies have been demonstrated using boron,[2] silicon,[3] or metal reagents.[4] Over the past decade, direct aldol reactions have attracted attention with the goal of improving the atom economy.[5,6] The development of sequential enantioselective direct aldol reactions would improve the preparation of complex structures in the field of organic synthesis. However, no reports have described the use of sequential enantioselective aldol reactions.

We recently found that the combination of silicon tetrachloride and a phosphine oxide enables an aldol transformation through an enolization–aldol reaction process in situ and developed an enantioselective direct aldol reaction of cyclic ketones, catalyzed by a chiral phosphine oxide (Scheme 1).[7,8] The acyclic ketone acetophenone was applied to this system, providing a unique double aldol adduct in good yield with good diastereo- and enantioselectivity. This approach constitutes the first enantioselective double aldol reaction using silicon tetrachloride and a chiral phosphine oxide as a Lewis base organocatalyst.[9]



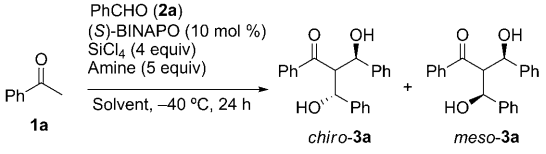
Scheme 1. Direct aldol and double aldol reactions using silicon tetrachloride and phosphine oxide.

Our synthetic study began with the asymmetric double aldol reaction of acetophenone (**1a**) and benzaldehyde (**2a**) using chiral phosphine oxide, (*S*)-BINAPO (Scheme 2), at −40 °C in dichloromethane (Table 1, entry 1). The reaction was complete within 24 h and gave the corresponding product **3a** in 90% yield as a diastereomeric mixture (*chiro*/



Scheme 2. Chiral Lewis base catalysts used in this study.

Table 1. Optimization for the double aldol reaction of **1a** and **2a**.[a]



Entry	Solvent[b]	Amine	Yield [%][c]	d.r[d]	*ee* [%] (*chiro*)[e]
1[f]	CH_2Cl_2	iPr_2NEt	90	81:19	60
2	EtCN	iPr_2NEt	12	73:27	70
3	$EtCN/CH_2Cl_2$	iPr_2NEt	82	77:23	62
4	$EtCN/CH_2Cl_2$	pempidine	72	77:23	64
5	$EtCN/CH_2Cl_2$	$cHex_2NMe$	95	79:21	61
6[g]	$EtCN/CH_2Cl_2$	$cHex_2NMe$	86	78:22	70

[a] Unless otherwise noted, reactions were carried out by addition of silicon tetrachloride (1.0 mmol) to a solution of ketone **1a** (0.25 mmol), aldehyde **2a** (0.55 mmol), an amine (1.25 mmol), and (*S*)-BINAPO (10 mol%) in solvent (2.5 mL) at −40 °C. [b] $EtCN/CH_2Cl_2$ = 1:1. [c] Yield of the diastereomers. [d] Determined by ^1H NMR spectroscopy (*chiro*/*meso*). [e] Determined by HPLC analysis. [f] For 8 h. [g] At −60 °C.

[a] Y. Shimoda, Prof. Dr. M. Sugiura, Prof. Dr. M. Nakajima
Graduate School of Pharmaceutical Sciences
Kumamoto University, 5–1 Oe-honmachi
Kumamoto 862-0973 (Japan)
Fax: (+81) 96-362-7692
E-mail: nakajima@gpo.kumamoto-u.ac.jp

[b] Prof. Dr. S. Kotani
Priority Organization for Innovation and Excellence
Kumamoto University, 5–1 Oe-honmachi
Kumamoto 862-0973 (Japan)
Fax: (+81) 96-371-4394
E-mail: skotani@gpo.kumamoto-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201100917.

meso = 81:19).[10] The *chiro* product (*chiro*-**3a**) was obtained with 60% *ee*.[11] A variety of solvents was tested to improve the catalytic activity and selectivity. Relatively high enantioselectivity was observed in propionitrile, although the reactivity was even higher in dichloromethane.[12] The use of EtCN/CH_2Cl_2 (1:1) as a mixed solvent slightly increased the enantioselectivity without loss of the reactivity (Table 1, entry 3).

We next studied the effect of amines on the reaction of **1a** with **2a**, catalyzed by (*S*)-BINAPO in EtCN/CH_2Cl_2 (1:1). Sterically congested aliphatic amines gave good results (Table 1, entries 4 and 5).[13] In particular, dicyclohexylmethylamine allowed the reaction to proceed smoothly, affording the product in good yield and selectivity (Table 1, entry 5). Moreover, lowering the reaction temperature to −60 °C improved the enantioselectivity, yielding the product **3a** with 70% *ee* (Table 1, entry 6).

Next, we tested various chiral Lewis bases in the double aldol reaction of **1a** and **2a** at −60 °C (Scheme 2). (*S*)-tol-BINAPO gave a chemical yield and selectivity similar to those obtained with (*S*)-BINAPO (Table 2, entries 1 and 2).

Table 2. Screening of Lewis base catalysts.[a]

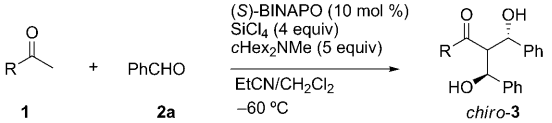
Entry	Lewis base	Yield [%][b]	d.r.[c]	*ee* [%] (*chiro*)[d]
1	(*S*)-BINAPO	86	78:22	70
2	(*S*)-tol-BINAPO	88	76:24	70
3	(*S*)-SEGPHOSO	93	79:21	63
4	(*R*,*R*)-DIOPO	68	68:32	36
5	(*R*)-BQNO	21	69:31	−29

[a]All the reactions were carried out by addition of silicon tetrachloride (1.0 mmol) to a solution of ketone **1a** (0.25 mmol), aldehyde **2a** (0.55 mmol), *c*Hex_2NMe (1.25 mmol), and a Lewis base catalyst (10 mol%) in EtCN/CH_2Cl_2 (1:1, 2.5 mL) at −60 °C. [b] Yield of the diastereomers. [c] Determined by ^{1}H NMR spectroscopy (*chiro*/*meso*). [d] Determined by HPLC analysis.

(*S*)-SEGPHOS dioxide (SEGPHOSO) showed good reactivity but the selectivity decreased slightly (Table 2, entry 3). Lewis bases with electron-donating groups tended to increase the rate of the catalytic cycle. (*R*,*R*)-DIOP dioxide (DIOPO) decreased both the chemical and optical yields (Table 2, entry 4). The efficiency of another Lewis base catalyst, bipyridine *N*,*N*′-dioxide,[14] was tested in the context of the reaction. However, the catalytic activity was quite low in comparison with the activities of the phosphine oxides (Table 2, entry 5).

With the optimal conditions and an organocatalyst in hand, we explored the scope of the double aldol reaction of various types of ketones **1** with benzaldehyde (**2a**) (Table 3). *p*-Bromoacetophenone (**1b**), a ketone with an electron-withdrawing group, was less reactive and gave the corresponding adduct in 78% yield after 48 h (Table 3, entry 2).[15] On the other hand, *p*- or *o*-methoxyacetophenone (**1c** and **1d**, respectively), which contained an electron-donating group, yielded the corresponding adducts in good chemical yields,

Table 3. Enantioselective double aldol reaction of various ketones **1** with **2a**.[a]



1 **2a** *chiro*-**3**

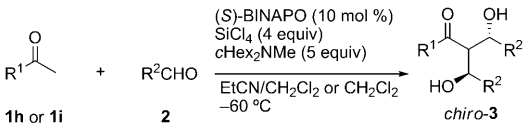
Entry	Ketone **1**	R	Product **3**	Yield [%][b]	d.r.[c]	*ee* [%] (*chiro*)[d]
1	**1a**	Ph	**3a**	86	78:22	70
2[e]	**1b**	4-BrC_6H_4	**3b**	78	77:23	75
3	**1c**	4-$MeOC_6H_4$	**3c**	88	85:15	70
4	**1d**	2-$MeOC_6H_4$	**3d**	82	90:10	56
5	**1e**	2-Naphthyl	**3e**	88	78:22	72
6[f]	**1f**	PhCH=CH	**3f**	87	83:17	74
7	**1g**	2-Thienyl	**3g**	95	91:9	84
8	**1h**	2-Furyl	**3h**	88	86:14	91
9[f]	**1i**	Cyclopropyl	**3i**	77	98:2	93

[a] Unless otherwise noted, reactions were carried out by addition of silicon tetrachloride (1.0 mmol) to a solution of ketone **1** (0.25 mmol), aldehyde **2a** (0.55 mmol), *c*Hex_2NMe (1.25 mmol), and (*S*)-BINAPO (10 mol%) in EtCN/CH_2Cl_2 (1:1, 5 mL) at −60 °C. [b] Yield of the diastereomers. [c] Determined by ^{1}H NMR spectroscopy (*chiro*/*meso*). [d] Determined by HPLC analysis. [e] For 48 h. [f] In CH_2Cl_2 instead of EtCN/CH_2Cl_2.

but the enantioselectivities decreased slightly (Table 3, entries 3 and 4). The steric effects of the *ortho* substituent on the benzene ring on **1d** particularly affected the enantioselectivity. Ketone **1e** afforded a product with a similar reactivity and selectivity to those observed in acetophenone (**1a**) (Table 3, entry 5). Although benzalacetone (**1f**), a conjugate ketone, was less reactive compared to aromatic ketones, the use of dichloromethane improved the reactivity and gave the corresponding product in 87% yield (Table 3, entry 6). Ketones **1g** and **1h**, which contained heteroaromatic rings, showed good diastereo- and enantioselectivities (Table 3, entries 7 and 8). The reaction of 2-acetylfuran (**1h**), in particular, yielded a high enantioselectivity (91% *ee*, entry 8). Cyclopropyl ketone **1i** was less reactive but afforded high diastereo- and enantioselectivities using CH_2Cl_2 as the solvent (Table 3, entry 9).

The double aldol reactions of various aldehydes **2** with ketones **1h** and **1i** were investigated (Table 4). The reaction of the *para*-substituted aldehydes **2b** and **2c** with ketone **1h** produced similar yields and selectivities to those with **2a**, although the substituents affected the reactivity of the aldehyde (Table 4, entries 2 and 3). Other aromatic aldehydes also gave the corresponding products in high yields and selectivities (Table 4, entries 4 and 5). Aldehyde **2e**, in particular, provided excellent enantioselectivity (97% *ee*, Table 4, entry 5). Cyclopropyl ketone **1i** provided the double aldol product in high yield with high diastereo- and enantioselectivities (Table 4, entries 6–12). The reaction of cinnamaldehyde (**2f**) gave a lower yield than the reactions of the aromatic aldehydes, although good stereoselectivity was observed (Table 4, entry 7). Aromatic aldehydes gave the corresponding double aldol adducts in good yields with high diastereo- and enantioselectivities (Table 4, entries 8–12).

Table 4. Scope of aldehyde **2** in the double aldol reaction.[a]



1h or **1i**

1h: R^1=2-furyl
1i: R^1=cyclopropyl

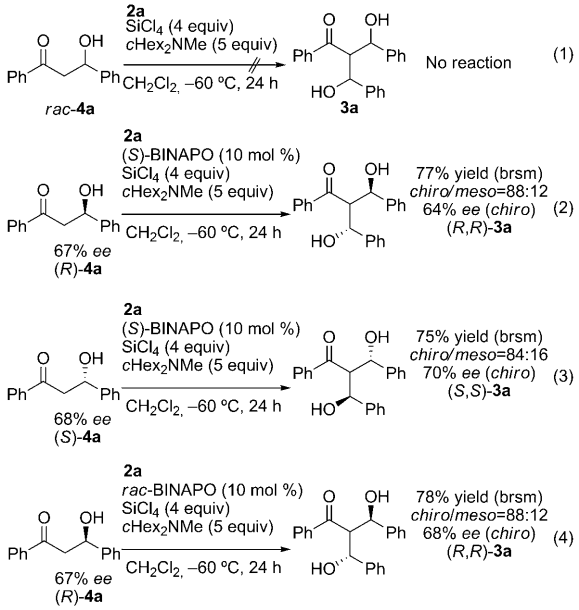
2

2a: R^2=Ph
2b: R^2=4-Me-C_6H_4
2c: R^2=4-Br-C_6H_4
2d: R^2=2-naphthyl
2e: R^2=2-furyl
2f: R^2=PhCH=CH
2g: R^2=4-MeO-C_6H_4

Entry	Ketone **1**[b]	Aldehyde **2**	Product **3**	Yield [%][c]	d.r.[d]	*ee* [%] (*chiro*)[e]
1	**1h**	**2a**	**3h**	88	86:14	91
2	**1h**	**2b**	**3j**	90	86:14	90
3	**1h**	**2c**	**3k**	75	83:17	88
4	**1h**	**2d**	**3l**	84	87:13	85
5	**1h**	**2e**	**3m**	80	92:8	97
6	**1i**	**2a**	**3i**	77	98:2	93
7	**1i**	**2f**	**3n**	61	80:20	85
8	**1i**	**2g**	**3o**	76	88:12	88
9	**1i**	**2b**	**3p**	90	97:3	91
10	**1i**	**2c**	**3q**	93	97:3	90
11	**1i**	**2d**	**3r**	96	96:4	87
12	**1i**	**2e**	**3s**	77	95:5	88

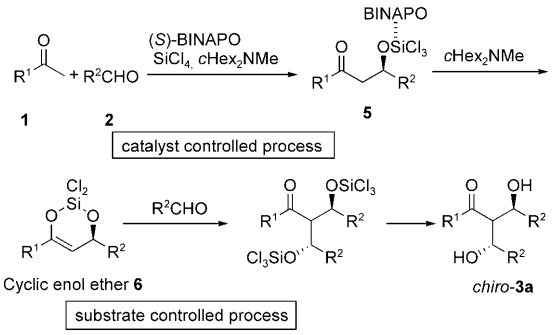
[a] All the reactions were carried out by addition of silicon tetrachloride (1.0 mmol) to a solution of ketone **1** (0.25 mmol), an aldehyde **2** (0.55 mmol), *c*Hex_2NMe (1.25 mmol), and (*S*)-BINAPO (10 mol %) at −60 °C. [b] The reaction of **1h** was conducted in EtCN/CH_2Cl_2 (1:1, 5 mL), whereas the reaction of **1i** was conducted in CH_2Cl_2 (5 mL). [c] Yield of the combined isolated diastereomers. [d] Determined by ^{1}H NMR spectroscopy (*chiro*/*meso*). [e] Determined by HPLC analysis.

As we have reported previously,[7] the use of a phosphine oxide is essential to promoting the enantioselective aldol reaction. In this process, a phosphine oxide catalyzed both the generation of the trichlorosilyl enol ether and the subsequent enantioselective aldol reaction. Further aldolization of the silylated aldol adduct would have provided the double aldol product, however, the effect of the phosphine oxide in the second aldol reaction was unclear. To confirm this point, the following control experiments were performed (Scheme 3, reactions (1)–(4)). First, the aldol reaction of the racemic aldol adduct **4a** in the absence of BINAPO yielded no products, only the starting material **4a** was recovered (Scheme 3, reaction (1)). This result suggested that a phosphine oxide was also necessary for the second aldol transformation. Second, the aldol reaction of the (*R*)- or (*S*)-aldol adduct **4a**[16] in the presence of (*S*)-BINAPO afforded the double aldol product **3a** in good yield (Scheme 3, reactions (2) and (3)). Interestingly, despite the use of (*S*)-BINAPO in both cases, the absolute configuration of the starting material **4a** was reflected in the configuration of the product **3a**. These results suggested that the enantioselectivity of the double aldol reaction was determined in the first aldol process, and that the second aldol process was controlled diastereoselectively by the chirality of the first aldol product, although small matched/mismatched effects were observed. Third, the reaction of (*R*)-**4a** with racemic BINAPO produced (*R*,*R*)-**3a** with the same enantioselectivity as was produced in the presence of (*S*)-BINAPO (Scheme 3, reaction (4)). Therefore phosphine oxide was required for the second aldol reaction but the chirality of the catalyst did not influence the stereoselectivity of the second aldol reaction.



Scheme 3. Control experiments (reactions (1)–(4)). brsm = based on recovered starting material.

On the basis of these results, we propose a mechanism for the double aldol reaction, as shown in Scheme 4. Initially, the first enantioselective aldol reaction was controlled by the chiral phosphine oxide to give the optically active trichlorosilyl ether **5**. Subsequently, intramolecular enolization of **5** occurred under activation by the phosphine oxide to provide the chiral cyclic enol ether **6**. The enol ether **6** reacted diastereoselectively with another aldehyde to give the *chiro* product **3** with an enantiomeric excess that reflected that of the mono-aldol adduct **5**.



Scheme 4. Proposed reaction mechanism for the double aldol reaction.

In conclusion, we have demonstrated, for the first time, an enantioselective double aldol reaction using silicon tetrachloride with a phosphine oxide as an organocatalyst. The

cyclic enolization of the first aldol product enabled the subsequent aldol reaction to proceed with good yields and stereoselectivities. Several control experiments suggested that the enantio-determining step may have been the first aldol reaction and that the second step proceeded by the diastereoselective enolization of the mono-aldol adduct. Further investigations to improve the diastereo- and enantioselectivities and to evaluate the detailed mechanism are currently in progress.

Experimental Section

Representative procedure: Silicon tetrachloride (0.11 mL, 1.0 mmol, 4.0 equiv) was added to a solution of aldehyde **2a** (0.056 mL, 0.55 mmol, 2.2 equiv), ketone **1a** (0.027 mL, 0.25 mmol, 1.0 equiv), dicyclohexylmethylamine (0.27 mL, 1.25 mmol, 5.0 equiv), and (*S*)-BINAPO (16.4 mg, 0.025 mmol, 10 mol%) in CH_2Cl_2 (1.25 mL) and propionitrile (1.25 mL) at −60°C. After being stirred for 24 h, the reaction was quenched with sat. $NaHCO_3$ (3 mL) and then the slurry was stirred for 0.5 h. The two-layer mixture was filtered through a celite pad and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with 10% HCl (20 mL), sat. $NaHCO_3$ (20 mL), and brine (20 mL) then dried over Na_2SO_4. After filtration and concentration, the obtained crude product was purified by column chromatography (hexane/EtOAc = 4:1, SiO_2 10 g) to give *meso*-**3a** (15.7 mg) and *chiro*-**3a** (55.8 mg) (total yield: 86%, d.r. = 78:22). The enantiomeric excess was determined to be 70% *ee* (*chiro*) by HPLC analysis with Daicel Chiralpak AD-H column (eluent: 9:1 hex/IPA; flow rate: 1.0 mL min^{-1}; detection: 254 nm; R_t: 17.0 min for (*S*,*S*)-isomer, 22.3 for (*R*,*R*)-isomer).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Keywords: aldol reaction · asymmetric catalysis · domino reactions · intramolecular enolization · Lewis base

[1] For reviews of sequential reactions, see: a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.

[2] For borane-mediated double aldol reactions, see: a) A. Abiko, J.-F. Liu, D. C. Buske, S. Moriyama, S. Masamune, *J. Am. Chem. Soc.* **1999**, *121*, 7168–7169; b) A. Abiko, T. Inoue, S. Masamune, *J. Am. Chem. Soc.* **2002**, *124*, 10759–10764; c) H. Furuno, T. Inoue, A. Abiko, *Tetrahedron Lett.* **2002**, *43*, 8297–8299; d) A. Abiko, *Acc. Chem. Res.* **2004**, *37*, 387–395.

[3] For a triple aldol cascade reaction, see: B. J. Albert, H. Yamamoto, *Angew. Chem.* **2010**, *122*, 2807–2809; *Angew. Chem. Int. Ed.* **2010**, *49*, 2747–2749.

[4] For stepwise double aldol reactions, see: a) T. Mukaiyama, H. Arai, I. Shiina, *Chem. Lett.* **2000**, 580–581; b) H. Arai, I. Shiina, T. Mukaiyama, *Chem. Lett.* **2001**, 118–119; c) T. Mukaiyama, K. Pubhom, K. Yamane, H. Arai, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 413–425.

[5] For reviews on direct aldol reactions, see: a) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2002**, 1595–1601; b) M. Shibasaki, N. Yoshkawa, *Chem. Rev.* **2002**, *102*, 2187–2209; c) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579; d) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591; e) G. Guillena, C. Nájera, D. J. Róamn, *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293; f) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.

[6] For leading and recent papers on direct asymmetric aldol reactions, see: a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942–1944; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873; b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; c) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; d) T. Suzuki, N. Yamagiwa, Y. Matsuo, S. Sakamoto, K. Yamaguchi, M. Shibasaki, R. Noyori, *Tetrahedron Lett.* **2001**, *42*, 4669–4671; e) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, C. F. Barbas III, *Org. Lett.* **2008**, *10*, 1621–1624; f) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 2112–2114; *Angew. Chem. Int. Ed.* **2008**, *47*, 2082–2084; g) K. Nakayama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 17666–17667; h) K. Baer, M. Kraußer, E. Burda, W. Hummel, A. Berkessel, H. Gröger, *Angew. Chem.* **2009**, *121*, 9519–9522; *Angew. Chem. Int. Ed.* **2009**, *48*, 9355–9358; i) M. Iwata, R. Yazaki, Y. Suzuki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 18244–18245; j) H. Ube, N. Shimada, M. Terada, *Angew. Chem.* **2010**, *122*, 1902–1905; *Angew. Chem. Int. Ed.* **2010**, *49*, 1858–1861.

[7] a) S. Kotani, Y. Shimoda, M. Sugiura, M. Nakajima, *Tetrahedron Lett.* **2009**, *50*, 4602–4605; b) S. Kotani, S. Aoki, M. Sugiura, M. Nakajima, *Tetrahedron Lett.* **2011**, *52*, 2834–2836.

[8] We have also demonstrated that chiral phosphine oxides catalyze the aldol reaction of trichlorosilyl enol ethers to provide high diastereo- and enantioselectivities: a) S. Kotani, S. Hashimoto, M. Nakajima, *Synlett* **2006**, 1116–1118; b) S. Kotani, S. Hashimoto, M. Nakajima, *Tetrahedron* **2007**, *63*, 3122–3132; for related chiral phosphine oxide-catalyzed reductive aldol reactions, see: c) M. Sugiura, N. Sato, S. Kotani, M. Nakajima, *Chem. Commun.* **2008**, 4309–4311; d) M. Sugiura, N. Sato, Y. Sonoda, S. Kotani, M. Nakajima, *Chem. Asian J.* **2010**, *5*, 478–481.

[9] For reviews on Lewis base organocatalysts, see: a) Y. Orito, M. Nakajima, *Synthesis* **2006**, 1391–1401; b) A. V. Malkov, P. Kočovský, *Eur. J. Org. Chem.* **2007**, 29–36; c) S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584–1663; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638; d) M. Benaglia, S. Rossi, *Org. Biomol. Chem.* **2010**, *8*, 3824–3830.

[10] The diastereomers were represented as *chiro* and *meso* isomers according to the nomenclature of the isomers of inositol.

[11] The *chiro*- and *meso*-**3a** are separable by silica gel chromatography. The enantiomeric excess of *chiro* isomer can be determined by HPLC analysis even as a diastereomeric mixture (see the Supporting Information for details).

[12] Other solvents such as tetrahydrofuran or toluene did not yield the double aldol products.

[13] The high nucleophilicities and/or low basicities of amines such as triethylamine and pyridine might interrupt the production of the double aldol adduct **3a**.

[14] (*R*)-BQNO was prepared according to the literature, see: M. Nakajima, M. Saito, M. Shiro, S. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420.

[15] Small amounts (<5%) of mono-aldol adduct were obtained in most cases.

[16] (*R*)- and (*S*)-**4a** were prepared following the procedure, see: M. Nakajima, Y. Orito, T. Ishizuka, S. Hashimoto, *Org. Lett.* **2004**, *6*, 3763–3765.

Received: March 25, 2011
Published online: May 30, 2011

