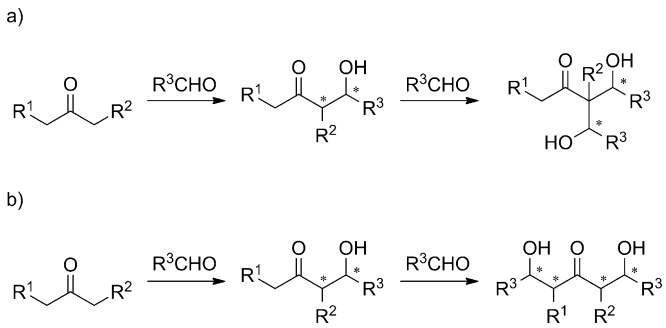
Asymmetric Catalysis

DOI: 10.1002/anie.201209848

Stereoselective Synthesis of Multiple Stereocenters by Using a Double Aldol Reaction**

Yasushi Shimoda, Tatsunori Kubo, Masaharu Sugiura, Shunsuke Kotani, and Makoto Nakajima**

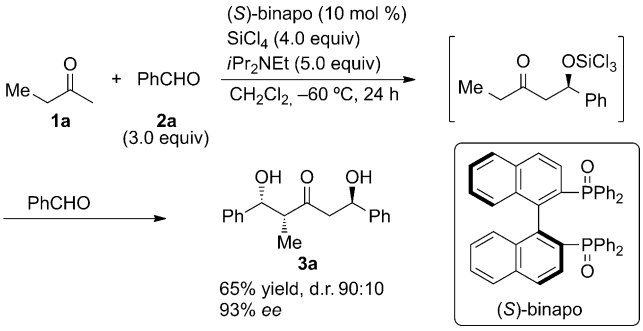
Asymmetric multicomponent reactions have attracted much attention in organic synthesis because they both simplify synthetic processes and permit the construction of multiple chiral centers in a single operation.[1] Although several asymmetric aldol reactions have been developed,[2] relatively few examples of sequential aldol reactions which lead to the formation of multiple carbon–carbon bonds with chiral centers are available. Among the various sequential aldol reactions, double aldol reactions involving one aldol donor and two aldol acceptors have two types of reaction modes (Scheme 1): a) two aldol reactions may occur at a single α-position on an aldol donor to give a branched double aldol adduct with three contiguous stereogenic centers; or, b) a reaction at both α-positions of a carbonyl group in an aldol donor provides a linear double aldol adduct having a 1,5-dihydroxy group with at most four chiral centers in a single operation.



Scheme 1. Classification of the double aldol reactions. a) Branched-type double aldol reaction (previous work). b) Linear-type double aldol reaction (this work).

In 2000, the first asymmetric double aldol reaction was reported by Masamune, Abiko, and co-workers, who used boron triflate in the reaction of a chiral ester and an aldehyde to afford a double aldol adduct diastereoselectively.[3] We recently developed the first enantioselective double aldol reaction[4] using a chiral phosphine oxide[5] as a Lewis base catalyst,[6] thus producing double aldol adducts with high stereoselectivities. In both cases, enol ether intermediates were generated at a single α-position of the aldol donor to give the branched aldol adducts. Linear enantioselective double aldol reactions have not yet been achieved. The stepwise stereoselective synthesis of chiral 1,5-dihydroxy-3-pentanone derivatives from aldolates was reported by Denmark et al.,[7] Dias et al.,[8] and Yamaoka and Yamamoto.[9] The development of an enantioselective sequential method could potentially provide an important alternative synthetic route. Herein, we demonstrate the first enantioselective linear double aldol reaction using silicon tetrachloride and a chiral phosphine oxide as an organocatalyst.

First, we started our studies with the reaction of 2-butanone (**1a**) and benzaldehyde (**2a**) in the presence of 10 mol% (*S*)-binap dioxide (binapo) in dichloromethane at −60 °C, based on our previous report[4] (Scheme 2). Surprisingly, a branched-type adduct did not form. Instead, the linear-type adduct **3a** was obtained in a 65% yield with a high diastereoselectivity (d.r. = 90:10)[10] and a high enantioselectivity (93% *ee*) for the major isomer. This observation prompted further investigations, as described below.



Scheme 2. Preliminary result of the linear-type double aldol reaction.

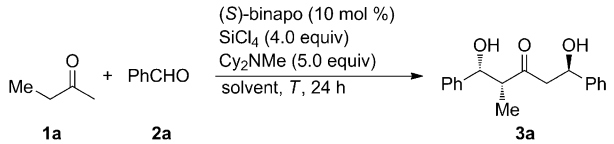
To improve both the yield and selectivity, we conducted the double aldol reaction under various reaction conditions using (*S*)-binapo[11] as a Lewis base catalyst (Table 1). Several amines were screened,[12] and dicyclohexylmethylamine gave the corresponding product in a better yield than diisopropyl-

[*] Y. Shimoda, T. Kubo, Prof. Dr. M. Sugiura, Prof. Dr. M. Nakajima
Graduate School of Pharmaceutical Sciences, Kumamoto University
5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973 (Japan)
E-mail: nakajima@gpo.kumamoto-u.ac.jp
Prof. Dr. S. Kotani
Priority Organization for Innovation and Excellence
Kumamoto University
5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973 (Japan)
E-mail: skotani@gpo.kumamoto-u.ac.jp

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

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209848.

Table 1: Double aldol reaction of 2-butanone (**1a**) and benzaldehyde (**2a**) catalyzed by (*S*)-binapo.[a]

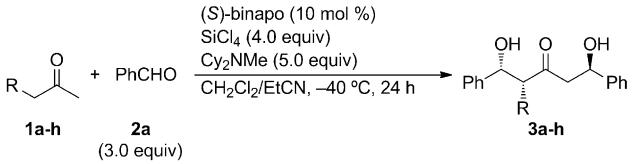


1a **2a** (3.0 equiv) **3a**

Entry	Solvent	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	CH_2Cl_2	−60	65	90:10	93
2	CH_2Cl_2	−60	71	91:9	95
3[f]	CH_2Cl_2	−60	73	91:9	94
4	CH_2Cl_2	−40	80	90:10	86
5	EtCN	−40	28	89:11	97
6	CH_2Cl_2/EtCN (1:1)	−40	86	90:10	91

[a] Unless otherwise noted, reactions were carried out by adding of $SiCl_4$ (2.0 mmol) to a solution of **1a** (0.5 mmol), **2a** (1.5 mmol), Cy_2NMe (2.5 mmol), and (*S*)-binapo (10 mol%) in solvent (5 mL). [b] Yield of isolated product. [c] The ratio of the major isomer to the minor isomer was determined by ^{1}H NMR analysis. [d] The *ee* value (major isomer) was determined by HPLC analysis. [e] iPr_2NEt was used in place of Cy_2NMe. [f] For 48 h.

Table 2: Double aldol reaction of various ketones (**1a–h**) and benzaldehyde (**2a**) catalyzed by (*S*)-binapo.[a]



1a-h **2a** (3.0 equiv) **3a-h**

Entry	R (**1**)	**3**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me (**1a**)	**3a**	86	90:10	91
2[e]	H (**1b**)	**3b**	84	–	91
3	Et (**1c**)	**3c**	87	90:10	95
4	*n*Pr (**1d**)	**3d**	86	89:11	94
5	Bn (**1e**)	**3e**	69	89:11	79
6	$-CH_2CH{=}C(CH_3)_2$ (**1f**)	**3f**	84	89:11	92
7[f]	$-(CH_2)_2CO_2Et$ (**1g**)	**3g**	65 (15)[g]	89:11	94
8[f]	$-(CH_2)_3C(O)Ph$ (**1h**)	**3h**	67	90:10	81

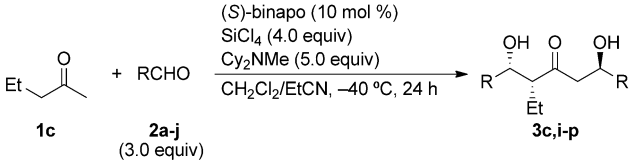
[a] Unless otherwise noted, reactions were carried out in the presence of **1a–h** (0.5 mmol), **2a** (1.5 mmol), $SiCl_4$ (2.0 mmol), Cy_2NMe (2.5 mmol), and (*S*)-binapo (10 mol%) in EtCN (2.5 mL) and CH_2Cl_2 (2.5 mL) at −40°C. [b] Yield of isolated product. [c] The ratio of the major isomer to the minor isomer was determined by ^{1}H NMR analysis. [d] The *ee* value (major isomer) was determined by HPLC analysis. [e] The reaction was conducted with iPr_2NEt in place of Cy_2NMe in CH_2Cl_2 at −60°C. [f] For 48 h. [g] The yield of lactonized product is given within the parentheses.

ethylamine (Table 1, entry 2).[13] To improve the chemical yield, we extended the reaction time to 48 hours, but almost the same chemical yield was obtained (Table 1, entry 3). Increasing the reaction temperature to −40°C improved the chemical yield, although the selectivity decreased slightly (Table 1, entry 4). Among the solvents tested, propionitrile provided a high enantioselectivity but the reactivity was reduced (Table 1, entry 5). The mixture of dichloromethane and propionitrile (1:1) efficiently promoted the transformation without incurring a significant loss in either the reactivity or the selectivity (Table 1, entry 6).

With the optimal reaction conditions in hand (Table 1, entry 6), we next conducted the double aldol reaction of various ketones (**1a–h**) in benzaldehyde (**2a**; Table 2). Acetone (**1b**) gave the C_2-symmetrical 1,5-diol **3b** as a single diastereomer with a high enantioselectivity (Table 2, entry 2). Various alkyl methyl ketones (**1c–f**) reacted with **2a** to afford the corresponding double aldol adducts in good yields with high stereoselectivities (Table 2, entries 3–6). In the reaction of the ketone **1g** and **2a**, the obtained aldol adduct **3g** was partially cyclized to give the lactonized adduct (Table 2, entry 7). The ketone **1h**, containing a benzoyl moiety, reacted specifically at the acetyl group to afford the corresponding aldol adduct (Table 2, entry 8).

Using 2-pentanone (**1c**) as an aldol donor, we investigated the double aldol reaction with various aldehydes (**2a–i**; Table 3). *p*-Bromobenzaldehyde (**2b**) bearing an electron-withdrawing group gave the product **3i** in good yield with a high enantioselectivity (Table 3, entry 2). Although *p*-anisaldehyde (**2c**) was less reactive than **2a** or **2b** and required a long reaction time, the observed enantioselectivity of **3j** was excellent (Table 3, entry 3). Other aromatic aldehydes **2d–i** also gave the corresponding double aldol adducts in good yields with high diastereo- and enantioselectivities (Table 3, entries 4–9).

Table 3: Double aldol reaction of 2-pentanone (**1c**) and various aldehydes (**2a–i**) catalyzed by (*S*)-binapo.[a]



1c **2a-j** (3.0 equiv) **3c,i-p**

Entry	R (**2**)	**3**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph (**2a**)	**3c**	87	90:10	95
2	4-BrC_6H_4 (**2b**)	**3i**	89	90:10	92
3[e]	4-$MeOC_6H_4$ (**2c**)	**3j**	66	92:8	98
4	4-MeC_6H_4 (**2d**)	**3k**	76	91:9	97
5[e]	3,5-$Me_2C_6H_3$ (**2e**)	**3l**	72	92:8	91
6	2-naphthyl (**2f**)	**3m**	78	90:10	93
7	1-naphthyl (**2g**)	**3n**	58	89:11	93
8	2-furyl (**2h**)	**3o**	65	90:10	88
9	2-thienyl (**2i**)	**3p**	71	92:8	95

[a] All reactions were carried out in the presence of **1c** (0.5 mmol), **2a–i** (1.5 mmol), $SiCl_4$ (2.0 mmol), Cy_2NMe (2.5 mmol), and (*S*)-binapo (10 mol%) in CH_2Cl_2 (2.5 mL) and EtCN (2.5 mL) at −40°C. [b] Yield of isolated product. [c] The ratio of the major isomer to the minor isomer was determined by ^{1}H NMR analysis. [d] The *ee* value (major isomer) was determined by HPLC analysis. [e] For 48 h.

The relative configuration of the major diastereomer was determined to be 1,2-*syn*-1,5-*anti* by the X-ray crystallographic analysis of **3f** (Figure 1). The relative configurations of the other compounds were analogously assigned by comparison with the ^{1}H NMR spectra.

Two routes to the double aldol product **3** were possible from the alkyl methyl ketone **1**, as shown in Scheme 3. The first aldol reaction could have occurred at either the methyl or

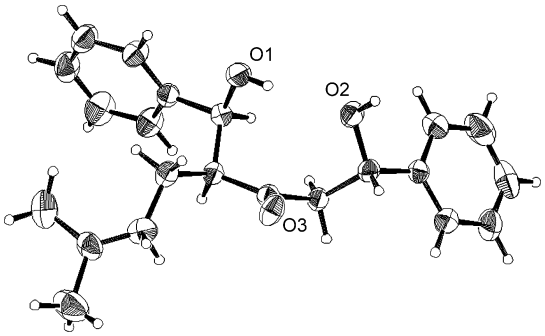
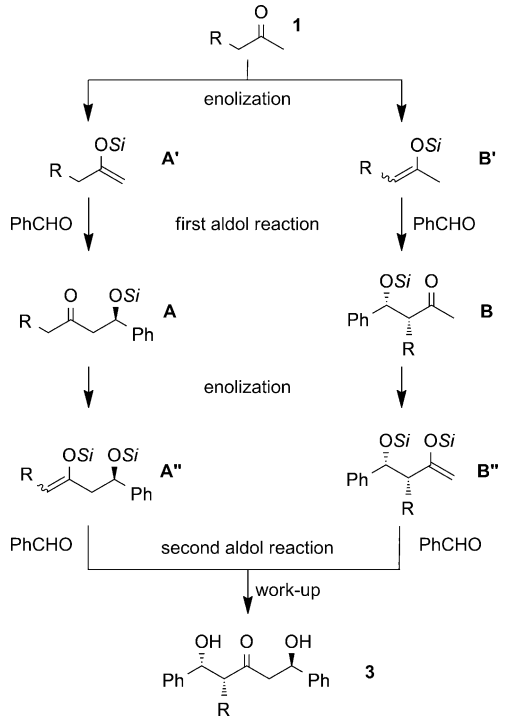


Figure 1. X-ray crystallographic structure of the double aldol adduct **3 f**. Thermal ellipsoids are shown at 30% probability.[14]

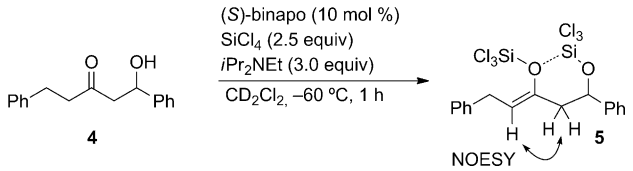


Scheme 3. Possible reaction routes of the double aldol reaction. *Si* = $SiCl_3$.

alkyl group to give the silylated aldol adducts **A** or **B**, respectively, both of which would then convert into the same double aldol adduct **3** after the second aldol transformation.

To investigate the first aldolization process, we performed the reaction of 3-pentanone with benzaldehyde under the same reaction conditions. No aldol adducts were obtained. This result indicated a low reactivity for any alkyl ketones other than methyl ketones, thus substantiating that the silyl enol ether **A'** was selectively generated to give the aldolate **A** for the first aldol reaction.

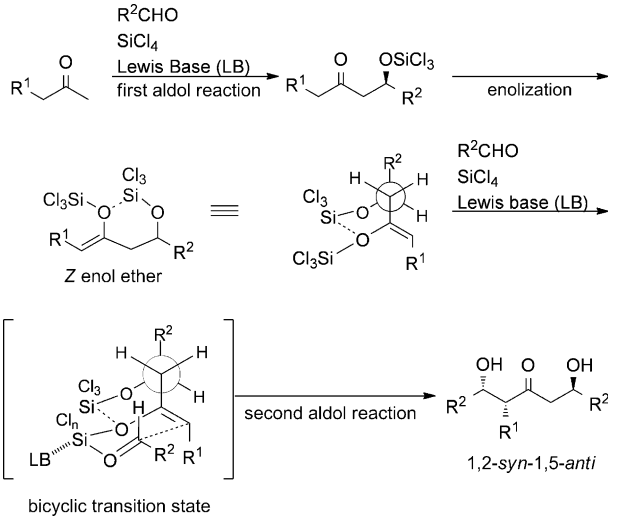
To investigate the second aldolization process, we examined the NMR spectra associated with the enolization of the *mono*-aldol adduct **4** (Scheme 4). The ^{1}H NMR analysis showed the clean generation of the enol ether **5** as almost a single isomer.[15] The NOESY correlation revealed that the geometry of **5** was the *Z* isomer. The (*Z*)-trichlorosilyl enol ethers are known to react with aldehydes via a six-membered



Scheme 4. NMR experiment for the enolization of the aldol adduct **4**.

chairlike transition state involving a hypervalent silicon species, thus affording the 1,2-*syn* adduct stereoselectively.[16]

Based on these results and previous observations,[9,16,17] we propose a reaction mechanism for the double aldol reaction (Scheme 5). The first aldol reaction occurs at the methyl



Scheme 5. Proposed reaction mechanism for the double aldol reaction.

group to give the silylated aldol adduct. The second enolization step at the less congested *exo* position affords a chiral cyclic *Z*-silyl enol ether. The enol ether reacts with another aldehyde via a bicyclic six-membered transition state with the assistance of a Lewis base silicon complex, thus giving the 1,2-*syn*-1,5-*anti* product.

In summary, we demonstrated a novel enantioselective double aldol reaction of an alkyl methyl ketone and two aldehydes using a chiral phosphine oxide as an organocatalyst. The present reaction allows ready access to the 1,2-*syn*-1,5-*anti*-1,5-dihydroxy-3-pentanones with high stereoselectivity in a single operation. Investigations focused on achieving higher reactivity and selectivity for double aldol reaction are in progress.

Received: December 10, 2012
Published online: February 18, 2013

Keywords: aldol reaction · asymmetric catalysis · Lewis bases · silanes · synthetic methods

[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; c) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551 – 564; d) K. C. Nicolaou, D. J. Edmons, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292 – 7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134 – 7186.

[2] For reviews on direct aldol reactions, see: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187 – 2209; b) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570 – 579; c) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580 – 591; d) B. Schetter, R. Mahrwald, *Angew. Chem.* **2006**, *118*, 7668 – 7687; *Angew. Chem. Int. Ed.* **2006**, *45*, 7506 – 7525; e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471 – 5569; f) G. Guillena, C. Najera, D. J. Ramon, *Tetrahedron: Asymmetry* **2007**, *18*, 2249 – 2293; g) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600 – 1632.

[3] 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.

[4] Y. Shimoda, S. Kotani, M. Sugiura, M. Nakajima, *Chem. Eur. J.* **2011**, *17*, 7992 – 7995.

[5] For examples of phosphine oxide-catalyzed asymmetric reactions, see: a) M. Nakajima, S. Kotani, T. Ishizuka, S. Hashimoto, *Tetrahedron Lett.* **2005**, *46*, 157 – 159; b) E. Tokuoka, S. Kotani, H. Matsunaga, T. Ishizuka, S. Hashimoto, M. Nakajima, *Tetrahedron: Asymmetry* **2005**, *16*, 2391 – 2392; c) S. Kotani, S, Hashimoto, M. Nakajima, *Tetrahedron* **2007**, *63*, 3122 – 3132; d) K. Nakanishi, S. Kotani, M. Sugiura, M. Nakajima, *Tetrahedron* **2008**, *64*, 6415 – 6419; e) Y. Shimoda, T. Tando, S. Kotani, M. Sugiura, M. Nakajima, *Tetrahedron: Asymmetry* **2009**, *20*, 1369 – 1370; f) S. Kotani, Y. Shimoda, M. Sugiura, M. Nakajima, *Tetrahedron Lett.* **2009**, *50*, 4602 – 4605; g) M. Sugiura, M. Kumahara, M. Nakajima, *Chem. Commun.* **2009**, 3585 – 3587; h) M. Sugiura, N. Sato, Y. Sonoda, S. Kotani, M. Nakajima, *Chem. Asian J.* **2010**, *8*, 3824 – 3830; i) A. V. Markov, C. MacDonald, P. Kočovský, *Tetrahedron: Asymmetry* **2010**, *21*, 1173 – 1175; j) S. Rossi, M. Benaglia, F. Genoni, T. Benincori, G. Celentano, *Tetrahedron* **2011**, *67*, 531 – 539; k) S. Rossi, M. Benaglia, F. Cozzi, A. Genoni, T. Benincori, *Adv. Synth. Catal.* **2011**, *353*, 848 – 854; l) M. Bonsignore, M. Benaglia, F. Cozzi, A. Genoni, S. Rossi, L. Raimondi, *Tetrahedron* **2012**, *68*, 8251 – 8255; m) S. Aoki, S. Kotani, M. Sugiura, M. Nakajima, *Chem. Commun.* **2012**, *48*, 5524 – 5526; n) Y. Ohmaru, N. Sato, M. Mizutani, S. Kotani, M. Sugiura, M. Nakajima, *Org. Biomol. Chem.* **2012**, *10*, 4562 – 4570.

[6] 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. Guizzetti, L. Pignataro, *Coord. Chem. Rev.* **2008**, *252*, 492 – 512; e) M. Benaglia, S. Rossi, *Org. Biomol. Chem.* **2010**, *8*, 3824 – 3830.

[7] a) S. E. Denmark, S. Fujimori, *Org. Lett.* **2002**, *4*, 3477 – 3480; b) S. E. Denmark, S. Fujimori, S. M. Pham, *J. Org. Chem.* **2005**, *70*, 10823 – 10840.

[8] a) L. C. Dias, A. A. de Marchi, M. A. B. Ferreira, A. M. Aguilar, *Org. Lett.* **2007**, *9*, 4869 – 4872; b) L. C. Dias, A. A. de Marchi, M. A. B. Ferreira, A. M. Aguilar, *J. Org. Chem.* **2008**, *73*, 6299 – 6311; c) L. C. Dias, E. C. de Lucca, M. A. B. Ferreira, D. C. Garcia, C. F. Tormena, *J. Org. Chem.* **2012**, *77*, 1765 – 1788; d) L. C. Dias, E. C. Polo, M. A. B. Ferreira, C. F. Tormena, *J. Org. Chem.* **2012**, *77*, 3766 – 3792.

[9] Y. Yamaoka, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5354 – 5356.

[10] In this reaction, two diastereomers of the four possible diastereomers were obtained.

[11] A screening of the chiral Lewis base catalysts demonstrated that BINAPO gave the best results for the reaction of acetone (**1b**) and benzaldehyde (**2a**), see: supporting information.

[12] Triethylamine, 2,6-lutidine, and DBU did not give the product at all.

[13] Diisopropylethylamine slowly reduced benzaldehyde to benzyl alcohol in the presence of the silyl reagents, leading to a decrease in the product yield. For details and related reactions, see: a) S. Kotani, K. Osakama, M. Sugiura, M. Nakajima, *Org. Lett.* **2011**, *13*, 3968 – 3971; b) K. Osakama, M. Sugiura, M. Nakajima, S. Kotani, *Tetrahedron Lett.* **2012**, *53*, 4199 – 4201.

[14] CCDC 922210 (**3f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[15] For details, see the Supporting Information.

[16] a) S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 12021 – 12022; b) S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432 – 440; c) S. E. Denmark, S. M. Pham, R. A. Stavenger, X. Su, K.-T. Wong, Y. Nishigaichi, *J. Org. Chem.* **2006**, *71*, 3904 – 3922.

[17] In a previous report, we verified that the first aldol reaction was controlled by the chirality of the catalyst, and the second aldol reaction proceeded diastereoselectively. For details, see Ref. [4].

