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Phosphine Oxide-Catalyzed Enantioselective Intramolecular Aldol Reaction via Regioselective Enolization of Unsymmetrical Diketones with Tetrachlorosilane

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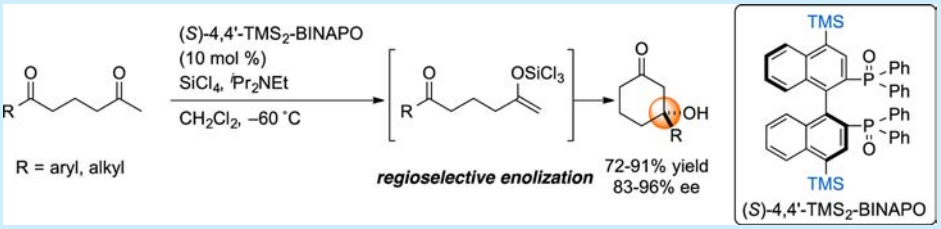
Supporting Information

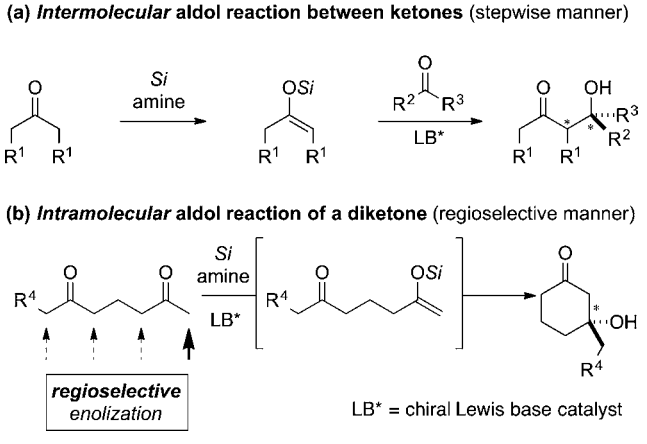


ABSTRACT: The phosphine oxide-catalyzed asymmetric intramolecular aldol reactions of diketones were investigated. The combination of tetrachlorosilane and a chiral phosphine oxide catalyst promoted the acetyl-selective enolization of diketones, and the subsequent intramolecular aldol reaction occurred in an enantioselective manner. The introduction of two trimethylsilyl groups at the 4- and 4′-positions in BINAP dioxide catalyst improved the enantioselectivity. This reaction provides an effective synthetic method to access β-tertiary-hydroxy cyclohexanones in high yields and with high enantioselectivity.

β-Tertiary-hydroxy cyclohexanones (3-hydrocarbyl-3-hydroxy cyclohexanones) are common motifs in several natural products.[1] However, their synthetic methods are not well established because these compounds are reactive and susceptible to dehydration, generating the corresponding enones. Therefore, the efficient asymmetric synthesis of β-tertiary-hydroxy cyclohexanones is still a challenge in organic synthesis.[2] The intramolecular aldol reaction of 1,5-diketones is the most straightforward strategy to afford β-tertiary-hydroxy cyclohexanones. However, there are several problems as follows: (1) the preformed hydroxy compounds may be converted to the more stable 3-substituted-2-cyclohexen-1-ones, (2) the product readily decomposes to the substrate via a retro-aldol reaction, and (3) the direction control of 1,5-diketones in the enolization step is required for producing the desired aldolate alone. A few examples have been reported using a tandem aldol process, thus eliminating the problem of direction control and affording β-tertiary-hydroxy cyclohexanones. Jørgensen developed an asymmetric domino Michael−aldol reaction to access functionalized β-tertiary-hydroxy cyclohexanone derivatives with high stereoselectivity.[3] Thus, despite the simple structures, efficient synthetic routes to β-tertiary-hydroxy cyclohexanones have been scarcely studied.[4]

We recently developed an asymmetric intermolecular cross-aldol reaction between two simple ketones using a combination of trichlorosilyl triflate as the activator and a chiral phosphine oxide[5−7] as the Lewis base catalyst.[8,9] In the reaction, the undesired homoaldol products could be effectively eliminated by the stepwise addition of the two ketone components; i.e., trichlorosilyl triflate first converts one of the two ketones to the corresponding trichlorosilyl enol ether, and then the addition to the second ketone affords the cross-aldol product predominantly in a highly enantioselective manner (Scheme 1a). We thus envisaged that the phosphine oxide-catalyzed intramolecular aldol reaction of 1,5-diketones would provide the corresponding β-tertiary-hydroxy cyclohexanones selectively, if the regioselec-

Scheme 1. Intermolecular (a) and Intramolecular (b) Aldol Reactions of Ketones



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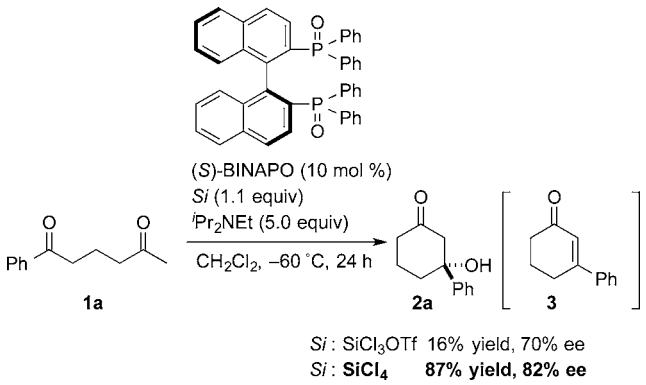
tive enolization of the diketones is possible (Scheme 1b). Herein, we report that a combination of tetrachlorosilane[10] and the newly modified BINAPO catalyst promotes the enolization of diketone substrates at the terminal acetyl group selectively, thus achieving the intramolecular aldol reaction of unsymmetrical 1,5-diketones to afford the corresponding β-tertiary-hydroxy cyclohexanones exclusively in high yields and with high enantioselectivity.

Treatment of diketone **1a** with 1.1 equiv of trichlorosilyl triflate and 5.0 equiv of *N*,*N*-diisopropylethylamine in the presence of 10 mol % of (*S*)-BINAP dioxide (BINAPO) in dichloromethane at −60 °C afforded the desired β-phenyl-β-hydroxy cyclohexanone (**2a**) in only 16% yield, albeit with promising enantioselectivity (Scheme 2). After studying various

Scheme 2. Asymmetric Intramolecular Aldol Reaction of 1a Catalyzed by (*S*)-BINAPO

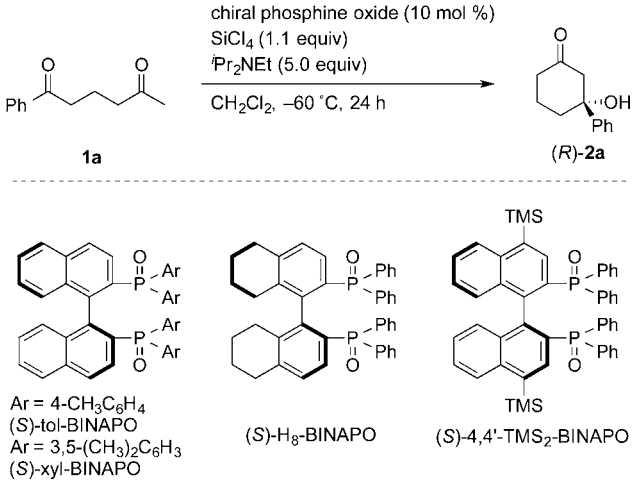


conditions, it was found that the use of tetrachlorosilane instead of trichlorosilyl triflate dramatically improved both the chemical yield and enantioselectivity of **2a** without the dehydration of **2a** to produce **3**.

We next screened chiral phosphine oxide catalysts to further improve the enantioselectivity of the reaction (Table 1). The catalysts bearing bulkier PAr_2 groups such as tol-BINAPO and xyl-BINAPO showed lower enantioselectivity than the parent BINAPO (entries 2 and 3). H_8-BINAPO bearing a partially hydrogenated binaphthyl skeleton was also ineffective (entry 4). Gratifyingly, the introduction of bulky trimethylsilyl groups at the 4- and 4′-positions of BINAPO improved the enantioselectivity of **2a** to 91% ee (entry 5).[11] The trimethylsilyl groups in 4,4′-TMS_2-BINAPO may regulate the orientation of the phenyl groups in the PPh_2 moieties, thus achieving high enantiodifferentiation in the aldol reaction of **1a**.[12] After a slight modification of the reaction conditions, **2a** was obtained in 91% yield and with 92% ee (Table 1, entry 6). The absolute configuration of **2a** was determined to be *R* by comparison of the $[\alpha]_D$ data and HPLC retention time.[2a]

With the optimized reaction conditions in hand, we performed the asymmetric intramolecular aldol reaction of various diketones **1** (Scheme 3). The reactions of substrates **1b−g**, 1-arylhexa-1,5-diones, afforded the corresponding β-tertiary-hydroxy cyclohexanones **2b−g** in high yields and with high enantioselectivity. Diketones **1b** and **1c** bearing electron-donating groups gave similar results to **1a** regardless of their positions, whereas **1d−f** bearing electron-withdrawing groups afforded the corresponding intramolecular aldol products **2d−f** with excellent enantioselectivity. In the reaction of 2-naphthyl ketone **1g**, high selectivity remained. Notably, the reactions of **1h−j**, bearing enolizable alkyl groups as the R substituent,

Table 1. Screening of Chiral Phosphine Oxides[a]



entry	catalyst	yield (%)[b]	ee (%)[c]
1	(*S*)-BINAPO	87	82
2	(*S*)-tol-BINAPO	78	79
3	(*S*)-xyl-BINAPO	80	60
4	(*S*)-H_8-BINAPO	76	75
5	(*S*)-4,4′-TMS_2-BINAPO	82	91
6[d]	(*S*)-4,4′-TMS_2-BINAPO	91	92

[a]Unless otherwise noted, the reactions were carried out by adding a silylating reagent (1.1 equiv) to a solution of **1a** (0.5 mmol), $^iPr_2NEt$ (5.0 equiv), and a chiral phosphine oxide (10 mol %) in CH_2Cl_2 (5 mL) at −60 °C. [b]Yield of isolated product. [c]The ee value was determined by HPLC analysis. [d]$SiCl_4$: 1.5 equiv. $^iPr_2NEt$: 3.0 equiv. TMS = trimethylsilyl.

smoothly afforded the corresponding β-tertiary-hydroxy cyclohexanone derivatives **2h−j** exclusively with high enantioselectivity, even though the isomeric cyclohexanones were possible. The results indicated that tetrachlorosilane selectively promoted the enolization at the acetyl group in diketone **1**.[13]

To clarify the difference in the reactivities between the two silylating reagents ($SiCl_3OTf$ and $SiCl_4$), several deuterium-labeling experiments were conducted (Schemes 4 and 5). The D_2O treatment of the reaction mixture of **1a**, $SiCl_3OTf$, and 10 mol % of BINAPO afforded deuterated diketone **1a**-2D in 57% yield (74% D) together with cyclized product **2a** in 16% yield (Scheme 4). This result indicates the concomitant formation of two intermediates **4a** and **5a** in the reaction mixture. The reaction of silyl enol ether **4a** failed due to the difficulty in forming the 4-membered ring; thus, **4a** was subsequently deuterated to afford **1a**-2D. However, **5a** was converted to **2a** smoothly via the intramolecular aldol reaction; thus, **1a**-6D was not detected after the D_2O treatment. In contrast, the high-yield (87%) formation of **2a** in the reaction with $SiCl_4$ (Table 1, entry 1) confirmed that the use of $SiCl_4$ selectively promoted the enolization of **1a** at the acetyl terminal.

To confirm this hypothesis, a mixture of ketones **6** and **7** was treated with the silylating reagent in the presence of BINAPO (10 mol %) and *N*,*N*-diisopropylethylamine (5 equiv), and then the reaction mixture was quenched with D_2O after stirring for 4 h at −60 °C (Scheme 5). The ketones were partially recovered, and the positions and ratios of the deuterium incorporation were determined by ^1H NMR measurements. In the reaction using trichlorosilyl triflate, the enolizable α-carbonyl positions in **6** and **7** were randomly deuterated to afford a mixture of **6**-1D, **6**-3D, and **7**-2D. In contrast, tetrachlorosilane promoted the

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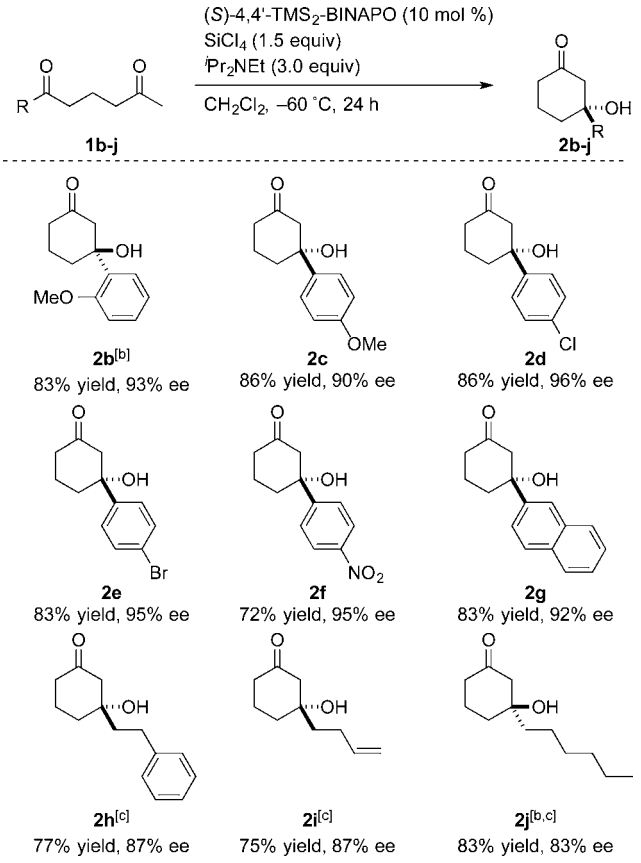
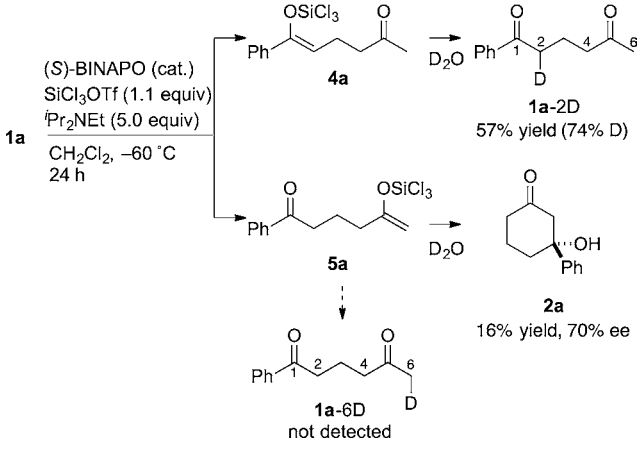
Scheme 3. Substrate Scope[a]



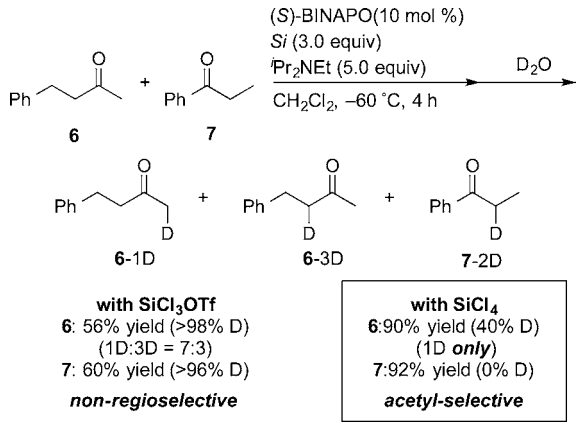
[a]Unless otherwise noted, the reactions were carried out by adding $SiCl_4$ (1.5 equiv) to a solution of diketone **1** (0.5 mmol), $^iPr_2NEt$ (3.0 equiv), and (*S*)-4,4′-TMS_2-BINAPO (10 mol %) in CH_2Cl_2 (5 mL) at −60 °C. [b]With (*R*)-4,4′-TMS_2-BINAPO as the catalyst. [c] $SiCl_4$: 1.1 equiv.

Scheme 4. Analysis of Intramolecular Aldol Reaction with $SiCl_3OTf$



enolization at the acetyl group exclusively to afford **6**-1D. The results clearly show that a combination of tetrachlorosilane and (*S*)-BINAPO afforded the silyl enol ethers only at the acetyl terminal. That is the reason why not trichlorosilyl triflate but tetrachlorosilane efficiently promoted the intramolecular cross-aldol reaction of **1a** via the terminal silyl enolate.

Scheme 5. Regioselectivity in the Enolization of Ketones 6 and 7



A proposed mechanism for the intramolecular aldol reaction of diketones is shown in Figure 1. First, phosphine oxide **A**

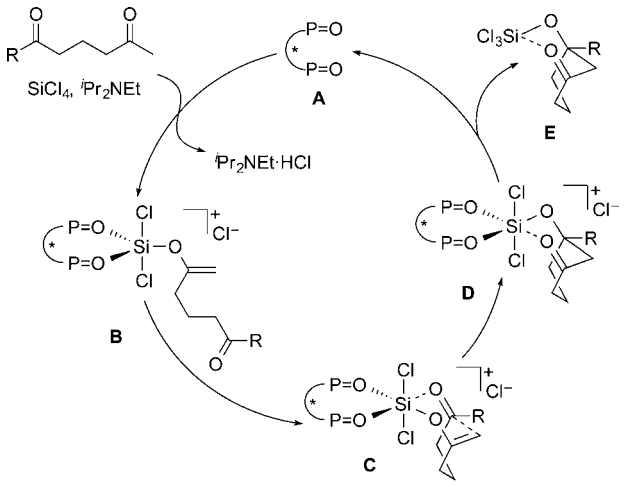


Figure 1. Proposed catalytic cycle of intramolecular aldol reaction.

coordinates to tetrachlorosilane to form a hypervalent silicon complex, which preferably activates the less-hindered acetyl group of diketone followed by the deprotonation by *N*,*N*-diisopropylethylamine to form trichlorosilyl enol ether **B**. Next, silicon complex **B** forms a six-coordinated hypervalent silicon species **C**. The intramolecular aldol reaction then occurs via a cyclic transition state to afford the silylated *β*-tertiary-hydroxy cyclohexanone **D**. Subsequently, phosphine oxide dissociates from the silicon atom. The silyl aldolate obtained may retain a cyclic structure **E**, which appears to be the key intermediate for the prevention of both dehydration and retro-aldol reaction, thus affording the aldol adduct in a good yield.

In conclusion, we demonstrated that the combination of a catalytic amount of chiral phosphine oxide and tetrachlorosilane promoted the enantioselective intramolecular aldol reaction of 1,5-diketones. The trichlorosilyl group effectively prevented the decomposition of the hydroxy product to 2-cyclohexen-1-ones, thus affording the *β*-tertiary-hydroxy cyclohexanones in good yields. This reaction is advantageous in enabling easy access to chiral *β*-tertiary-hydroxy cyclohexanones with high enantioselectivity. As several natural products contain similar *β*-tertiary-hydroxy cyclohexanone substructures, the synthesis of such natural products is currently ongoing in our laboratories.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Piel, J.; Hoang, K.; Moore, B. S. *J. Am. Chem. Soc.* **2000**, *122*, 5415. (b) Xiang, L.; Kalaitzis, J. A.; Nilsen, G.; Chen, L.; Moore, B. S. *Org. Lett.* **2002**, *4*, 957. (c) Xiang, L.; Kalaitzis, J. A.; Moore, B. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 15609.

(2) As alternative methods to access β-tertiary-hydroxy cyclohexanones, see: (a) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. (b) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677.

(3) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272.

(4) We have reported the asymmetric reductive aldol reaction of a 2-ene-1,7-dione with trichlorosilane under Lewis base catalysis, affording a tertiary-hydroxy cyclohexane derivative, see: Sugiura, M.; Sato, N.; Sonoda, Y.; Kotani, S.; Nakajima, M. *Chem.—Asian J.* **2010**, *5*, 478.

(5) Aoki, S.; Kotani, S.; Sugiura, M.; Nakajima, M. *Chem. Commun.* **2012**, *48*, 5524.

(6) For examples of phosphine oxide-catalyzed asymmetric aldol reactions by this laboratory, see: (a) Kotani, S.; Hashimoto, S.; Nakajima, M. *Synlett* **2006**, 1116. (b) Kotani, S.; Hashimoto, S.; Nakajima, M. *Tetrahedron* **2007**, *63*, 3122. (c) Kotani, S.; Shimoda, Y.; Sugiura, M.; Nakajima, M. *Tetrahedron Lett.* **2009**, *50*, 4602. (d) Kotani, S.; Aoki, S.; Sugiura, M.; Nakajima, M. *Tetrahedron Lett.* **2011**, *52*, 2834. (e) Kotani, S.; Sugiura, M.; Nakajima, M. *Chem. Rec.* **2013**, *13*, 362.

(7) For examples of phosphine oxide-catalyzed asymmetric aldol reactions by other laboratories, see: (a) Rossi, S.; Benaglia, M.; Genoni, A.; Benincori, T.; Celentano, G. *Tetrahedron* **2011**, *67*, 158. (b) Rossi, S.; Benaglia, M.; Cozzi, F.; Genoni, A.; Benincori, T. *Adv. Synth. Catal.* **2011**, *353*, 848. (c) Bonsignore, M.; Benaglia, M.; Cozzi, F.; Genoni, A.; Rossi, S.; Raimondi, L. *Tetrahedron* **2012**, *68*, 8251.

(8) For reviews on Lewis base organocatalysis, see: (a) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373. (b) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727. (c) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391. (d) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29. (e) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (f) Benaglia, M.; Guizzetti, S.; Pignataro, L. *Coord. Chem. Rev.* **2008**, *252*, 492. (g) Benaglia, M.; Rossi, S. *Org. Biomol. Chem.* **2010**, *8*, 3824.

(9) For leading papers on Lewis base-catalyzed aldol reactions, see: (a) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (b) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (c) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron* **1998**, *54*, 10389. (d) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 918. (e) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990. (f) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (g) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837. (h) Denmark, S. E.; Pham, S. M.; Stavenger, R. A.; Su, X.; Wong, K.-T.; Nishigaichi, Y. *J. Org. Chem.* **2006**, *71*, 3904.

(10) For reviews on silicon tetrachlorosilane-mediated reactions, see: Rossi, S.; Benaglia, M.; Genoni, A. *Tetrahedron* **2014**, *70*, 2065.

(11) (a) Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2501. (b) Ogasawara, M.; Ngo, H. L.; Sakamoto, T.; Takahashi, T.; Lin, W. *Org. Lett.* **2005**, *7*, 2881.

(12) X-ray crystal structure analysis of TMS_2-BINAPO (CCDC 1022097) confirmed the structural relationship between the trimethylsilyl group and phenyl group; see Supporting Information. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) In the reactions with ketones **2h–j**, the use of excess tetrachlorosilane should be avoided to achieve high yields of the aldol products because the excess tetrachlorosilane may induce additional enolization, resulting in lower yields.