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# Optically Pure α-(Trimethylsilyl)benzyl Alcohol: A Practical Chiral Auxiliary for Oxocarbenium Ion Reactions

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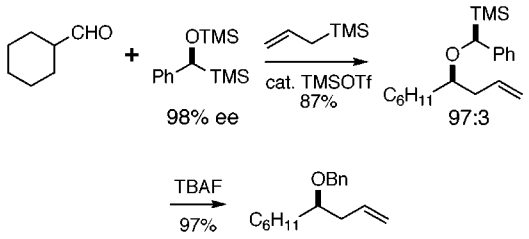
## ABSTRACT




**Enantiopure (*S*)-α-(trimethylsilyl)benzyl alcohol (98% ee) was prepared by Noyori's transfer hydrogenation of benzoyltrimethylsilane. The corresponding trimethylsilyl ether was subjected to Marko's silyl modified Sakurai conditions with a variety of aldehydes to afford homoallylic ethers in high diastereoselectivity. The practicality of the α-trimethylsilyl benzyl group as an oxocarbenium ion auxiliary was further demonstrated by its efficient deprotection or conversion to a benzyl protecting group.**

The synthetic utility of reactions involving oxocarbenium ion intermediates has prompted several groups to develop chiral auxiliaries that exert high diastereofacial selectivity. Various approaches include additions of nucleophiles to chiral acetals,[1] norpseudoephedrine substituted intermediates,[2] and in situ generated oxocarbenium ions.[3,1e] A number of these methods require multistep or harsh deprotection conditions.[1,3] We set out to develop a practical and general chiral auxiliary for oxocarbenium ion reactions. An ideal chiral auxiliary would fulfill several requirements: both enantiomers would be readily accessible, it would be easily incorporated into oxocarbenium ion intermediates, and it would promote the addition of various nucleophiles to one diastereotopic face of the oxocarbenium ion. Additionally, the auxiliary should be easily removed from the ether products to afford alcohols of high enantiopurity. We now report an efficient synthesis of an optically pure α-silyl alcohol and demonstrate its utility as an oxocarbenium ion auxiliary.

Development of this chiral auxiliary finds precedent in Linderman's work with α-silyl and α-stannyl mixed acetals.[4] Linderman demonstrated that additions of nucleophiles to mixed acetals such as **1** proceeded with high diastereoselectivity (Scheme 1). The selectivity was rationalized by

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(2) (a) Tietze, L. F.; Dolle, A.; Schiemann, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1372−1373. (b) Tietze, L. F.; Schiemann, K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851−5852. (c) Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1996**, *2*, 1164−1172. (d) Tietze, L. F.; Volkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schafer, M. *Chem. Eur. J.* **2001**, 7, 1304.

(3) (a) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765−766. (b) Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* **1987**, 1121−1124. (c) Mekhalfia, A.; Marko, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779−4782. (d) Molander, G. A.; Haar, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40−49.

(4) (a) Linderman, R. J.; Anklekar, T. V. *J. Org. Chem.* **1992**, *57*, 5078−5080. (b) Linderman, R. J.; Chen, K. *J. Org. Chem.* **1996**, *61*, 2441−2453. (c) Linderman, R. J.; Chen, S. *Tetrahedron Lett.* **1995**, *43*, 7799−7802. (d) Linderman, R. J.; Chen, S. *Tetrahedron Lett.* **1996**, *37*, 3819−3822.

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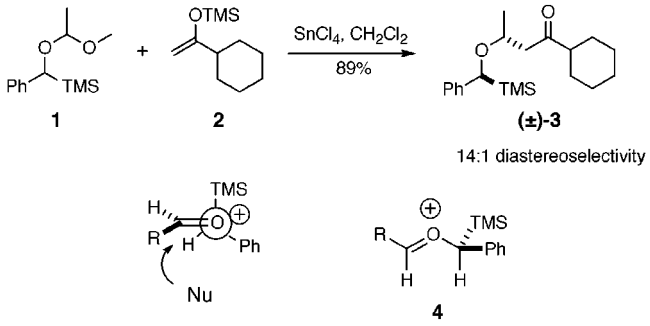
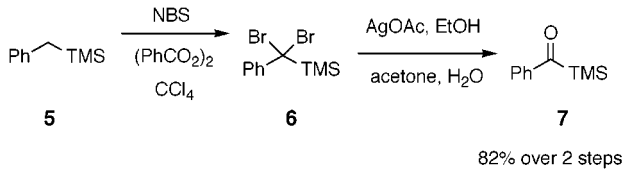
**Scheme 1.** Diastereoselectivity in Linderman's Addition of Nucleophiles to α-Silyl Mixed Acetals




invoking an (*E*)-oxocarbenium ion intermediate **4,** which adopts a well-defined conformation as the result of a stereoelectronic preference analogous to the $\beta$-silyl effect.[5] Linderman proposed that the α-silyl oxocarbenium ion adopts a conformation that provides maximum overlap of $\sigma$ C−Si and $\pi^*$ C═O of the oxocarbenium ion.[4] The nucleophile then adds to the face opposite to the bulky silyl group, resulting in the observed diastereoselectivity. Linderman's mixed acetals were prepared by alkylation of the racemic α-silyl alcohols with α-chloro ethers, providing a narrow range of ether products. Optically pure substrates were not investigated. Linderman's diastereoselective oxocarbenium ion additions laid the groundwork for our investigation.

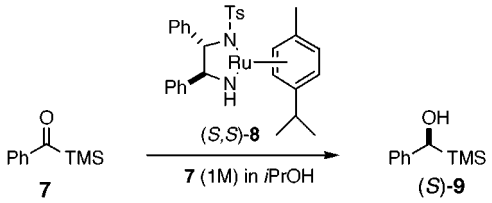
We hoped to access the optically active α-trimethylsilyl benzyl alcohol[6] by an enantioselective reduction of the corresponding acyl silane. Following Olah's procedure, free radical bromination of commercially available benzyltrimethylsilane **5**, followed by treatment of the unpurified dibromide **6** with silver acetate afforded the desired benzoyltrimethylsilane **7** in multigram quantities (Scheme 2).[7]

**Scheme 2.** Synthesis of Benzoyltrimethylsilane **7**




With the requisite acyl silane in hand, several enantioselective reductions were screened. While DIP-Cl was reported to reduce a number of acylsilanes with high enantioselectivity,[8] reduction of **7** with (+)-DIP-Cl afforded the corresponding alcohol in only 23% ee. Reduction with CBS catalyst provided the alcohol of only 9% ee, but stoichiometric CBS reduction was much more selective and gave **9** with 80% ee.[9] As shown in Table 1, a practical enantioselective reduction of **7** was achieved using Noyori's asymmetric transfer hydrogenation conditions with chiral Ru catalyst **8**.[10]

**Table 1.** Noyori's Transfer Hydrogenation of Benzoyltrimethylsilane **7**




| entry | mol % **8** | reaction time (h) | yield (%) | ee[a] (%) |
|---|---|---|---|---|
| 1 | 4 | 0.75 | 94 | 95 |
| 2 | 2 | 1.3 | 80 | 96.5 |
| 3 | 1 | 2.4 | 76 | 96 |
| 4 | 0.5 | 4.3 | 82 | 95 |
| **5** | **0.5** | **3.4** | **91** | **98** |
| 6 | 0.2 | 22 | 45[b] | 95.6 |

[a] The ee's were determined by HPLC analysis on a Chiracel OD-H column. [b] The starting ketone **7** was recovered in 29% yield.

The enantioselective reductions were carried out with 1 M solutions of benzoyltrimethylsilane in 2-propanol, and the details are recorded in Table 1. Variation of the catalyst loading provided the alcohol in good yields and high optical purity (95−98% ee, entries 1−5). Optimal conditions utilized 0.5 mol % of the catalyst and provided the alcohol in 91% yield and 98% ee (entry 5).[11] A lower catalyst loading and longer reaction time afforded the alcohol in good enantioselectivity but poor yield, with significant recovery of the starting ketone (entry 6). The absolute configuration was

(5) For a review of the $\beta$-silyl effect, see: Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677−2689.

(6) (a) Mosher, H. S.; Biernbaum, M. S. *J. Org. Chem.* **1971**, *36*, 3168−3177. (b) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236−241. (c) Linderman, R. J.; Ghannam, A.; Badejo, I. *J. Org. Chem.* **1991**, *56*, 5213−5216. (d) Yamazaki, Y.; Kobayashi, H. *Chem. Express* **1993**, *8*, 97−100. (e) Takeda, K.; Ohnishi, Y.; Koizumi, T. *Org. Lett.* **1999**, *1*, 237−239. (f) Patrocinio, A. F.; Correa, I. R., Jr.; Moran, P. J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3133−3137. (g) Zani, P. *J. Mol. Catal. B: Enzym.* **2001**, *11*, 279−285.

(7) Olah, G. A.; Berrier, A. L.; Field, L. D.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1982**, *104*, 1349−1355.

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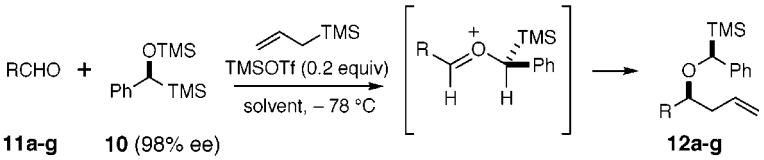
(11) **Alcohol 9.** To a 21 °C solution of benzoyltrimethylsilane (8.84 g, 49.6 mmol, 1.0 equiv) in 49.6 mL 2-propanol was added catalyst (*S*,*S*)-**8** (149 mg, 0.25 mmol, 0.005 equiv). After stirring for 3.4 h at 21 °C, the reaction mixture was filtered through a short plug of silica gel, which was washed with $Et_2O$ (80 mL). Concentration in vacuo provided a crude oil that was purified by flash column chromatography (2−5−10% diethyl ether/hexanes) to afford the title alcohol (8.12 g, 91%) as a white solid: $[\alpha]^{23}_D$ −109.2 (*c* 1.00, $CHCl_3$); mp 28−30 °C; IR (KBr) 3423, 2957, 1248, 998, 841 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.32−7.29 (m, 2 H), 7.20−7.17 (m, 3 H), 4.53 (s, 1 H), 1.67 (d, $J$ = 2.4 Hz, 1 H), 0.01 (s, 9 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 144.2, 128.1, 125.8, 124.9, 70.6, −4.1; HRMS (EI) *m*/*z* calcd for $C_{10}H_{15}OSi$ $(M - H)^+$ 179.0892, found 179.0888. Anal. Calcd for $C_{10}H_{16}OSi$: C, 66.61; H, 8.94. Found: C, 66.89; H, 8.93.

**Table 2.** Diastereoselective Additions of Allyltrimethylsilane to Oxocarbenium Ions Generated in Situ




**11a-g** **10** (98% ee) **12a-g**

| entry | R | | solvent | yield[a] (%) | diastereo ratio | abs config[b] |
|---|---|---|---|---|---|---|
| 1 | $C_6H_{11}$ | **(a)** | $PhCH_3$ | 87 | 97:3[c] | *S*[e] |
| 2 | $(CH_2)_2$-$C_6H_5$ | **(b)** | $PhCH_3$ | 75 | 95:5[d] | *R*[e] |
| 3 | $(CH_2)_4CH_3$ | **(c)** | $PhCH_3$ | 86 | 97:3[c] | *R*[e] |
| 4 | $CH(CH_3)_2$ | **(d)** | $PhCH_3$ | 83 | 97:3[c] | |
| 5 | $(CH_2)_2OTBDPS$ | **(e)** | $PhCH_3$ | 69 | 95:5[d] | |
| 6 | $(CH_2)_2OTBDPS$ | **(e)** | $CH_2Cl_2$ | 72 | 95:5[d] | |
| 7 | $C_6H_5$ | **(f)** | $PhCH_3$ | 96 | 91:9[c] | *S*[f] |
| 8 | $CH{=}CH$-$C_6H_5$ | **(g)** | $PhCH_3$ | 69 | 86:14[c] | |
| 9 | $CH{=}CH$-$C_6H_5$ | **(g)** | $CH_2Cl_2$ | 75 | 86:14[c] | |

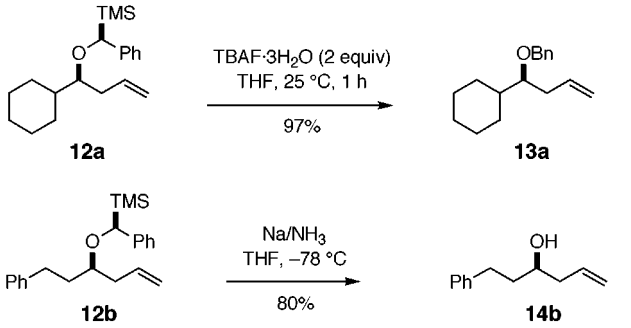
[a] Yield of purified product. [b] Absolute configuration of newly formed stereocenter. [c] Based on GC analysis of unpurified product. [d] Based on $^1H$ NMR analysis of purified product. [e] Determined by deprotection ($Na/NH_3$) and comparison to literature rotation of the known alcohol (details in Supporting Information.) [f] Determined by comparison of the rotation of the corresponding benzyl ether to an authentic sample (details in Supporting Information.)

determined to be *S* on the basis of advanced Mosher's ester analysis[12] and by comparison of the sign of the rotation to literature values.[6] The *R* enantiomer would be available using the enantiomeric catalyst. Thus, gram quantities of crystalline,[13] enantiopure alcohol **9** were accessed by an efficient synthesis in three steps from commercially available material.

Marko's in situ allylation reaction was used to evaluate the utility of the chiral auxiliary.[3c] Silyl ether **10** was prepared in 81−91% yield by treatment of alcohol **9** (98% ee) with catalytic saccharin and HMDS.[14] Marko's conditions involved the treatment of a silyl ether, in our case compound **10**, with an aldehyde and catalytic TMSOTf to generate an oxocarbenium ion intermediate in situ. The allylsilane adds to the oxocarbenium ion to afford homoallylic ether **12** (Table 2). Homoallylic ethers **12a**−**e**, derived from aliphatic aldehydes, were obtained in good yields with diastereoselectivities ranging from 95:5 to 97:3 (entries 1−6). Ether **12f**, derived from benzaldehyde, was accessed in excellent yield but slightly lower diastereoselectivity (entry 7). The lowest diastereoselectivity was observed from allylation of the oxocarbenium ion derived from *trans*-cinnamaldehyde (entries 8 and 9). In both toluene and dichloromethane, ether **12g** was obtained in good yield but only 6:1 diastereoselectivity. In four cases, the configurations of the newly formed stereogenic centers were assigned by deprotection and comparison of the optical rotations with known compounds.[15] In each case the configuration of the product was that predicted by Linderman's model.[4] These results demonstrate that the α-(trimethylsilyl)benzyl alcohol auxiliary leads to high levels of diastereoselectivity, particularly when used with alkyl oxocarbenium ions.

With an efficient synthesis and the demonstration of the auxiliary's utility in a sample reaction, we turned to the investigation of deprotection strategies. Conversion of the auxiliary to the widely used benzyl protecting group was achieved by treatment of ethers **12** with TBAF at room temperature. For example, ether **12a** was converted to the corresponding benzyl ether **13a** in 97% yield (Scheme 3).

**Scheme 3.** Deprotection Strategies




The other aliphatic ethers **12b**−**e** were also transformed to the corresponding benzyl ethers in good to excellent yields.[15] However, lower yields were observed for the unsaturated derivatives **12f** and **12g** (vide infra). A one-step deprotection was also realized by treatment of **12b** with sodium in ammonia; the corresponding homoallylic alcohol **14b** was obtained in 80% yield.[16] Both direct deprotection and conversion of the auxiliary-derived ethers **12** to benzyl protected ethers were achieved.

(12) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(13) Optically pure **9** is a low melting, crystalline solid, whereas the racemate is an oil. Alcohol **9** apparently crystallizes as a conglomerate, which will facilitate the preparation of optically pure samples.

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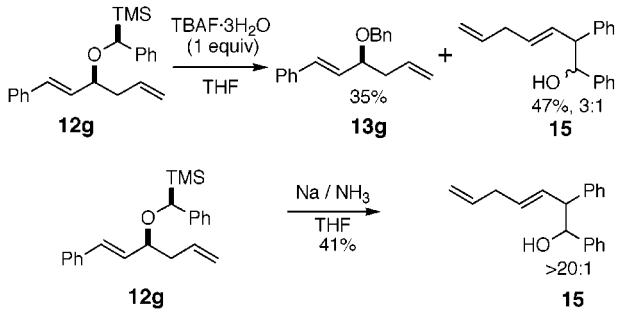
(15) See Supporting Information for details.

(16) The $Na/NH_3$ deprotection was less reliable than the TBAF deprotection, and the yields varied from substrate to substrate.

**Scheme 4.** A 2,3-Wittig Rearrangement Product




The TBAF reaction of the *trans*-cinnamyl product **12g** was anomalous. As shown in Scheme 4, treatment of **12g** with TBAF afforded only 35% of the desired benzyl alcohol **13g**. It was accompanied by alcohol **15**, which was isolated in 47% yield as a 3:1 mixture of diastereomers. Compound **15** presumably arose from a 2,3-Wittig rearrangement that occurs upon generation of the benzylic anion equivalent. Maleczka recently reported a 2,3-Wittig rearrangement product resulting from treatment of an α-trimethylsilyl benzyl ether with cesium fluoride.[17] Rearrangement product **15** was also isolated in 41% yield as a >20:1 mixture of diastereomers when ether **12g** was treated with sodium in ammonia. The difference in diastereoselectivities with TBAF and Na/$NH_3$ conditions might arise from a deprotonation, 2,3-Wittig rearrangement, and Brook rearrangement in the latter case, but we have no direct evidence supporting this hypothesis. The in situ allylation reaction provides a facile route to the 2,3-Wittig rearrangement precursor **12g**.

In summary, optically pure α-trimethylsilyl benzyl alcohol has been developed as a practical chiral auxiliary for oxocarbenium ion reactions. The optically pure auxiliary was prepared in three steps from commercially available benzyltrimethylsilane in 75% overall yield. A key step was Noyori's transfer hydrogenation of benzoyltrimethylsilane **7** using Ru catalyst (*S*,*S*)-**8**. Further investigation to determine the scope of this asymmetric reduction for generating optically active α-silyl alcohols is underway. The auxiliary was effective in directing allyltrimethylsilane to one diastereotopic face of an oxocarbenium ion, generated in situ according to Marko's protocol. The absolute configuration of the newly formed stereocenter was in accordance with the predicted configuration based on Linderman's model. The TBAF-mediated conversion of the auxiliary to the synthetically useful benzyl protecting group was efficient for all alkyl derivatives. Alcohol **9** has many of the features of an ideal oxocarbenium ion chiral auxiliary. The scope and utility of auxiliary **9** in other oxocarbenium ion reactions is under investigation and will be reported in due course.

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**Supporting Information Available:** Preparation and characterization of the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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