

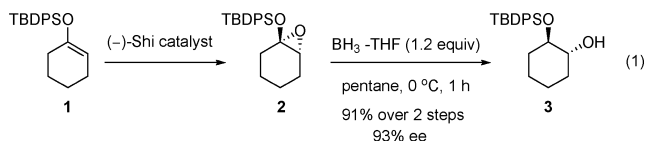
A Method for the Preparation of Differentiated *trans*-1,2-Diol Derivatives with Enantio- and Diastereocontrol

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We describe a synthetic sequence that allows for the preparation of optically active *trans*-1,2-diol monosilyl ether derivatives from ketones, providing a new means for retrosynthetic simplification of differentiated diol and polyol targets. The sequence is exemplified in eq 1 and proceeds by silyl enol ether formation, Shi asymmetric epoxidation,¹ and then regio- and stereospecific addition of hydride, methide, or higher alkylide. The tactical combination presented has not been integrated in synthetic problem solving, so far as we are aware, but has promise for broad application, we believe.



It has been shown that α -hydroxy ketones can be prepared enantioselectively by application of the Shi asymmetric epoxidation protocol to *tert*-butyldimethylsilyl and trimethylsilyl enol ether substrates followed by hydrolysis.² Shi and co-workers noted that certain substrates were problematic in the transformation, especially silyl enol ethers derived from cyclic ketones (racemization and dimerization were specifically mentioned as complicating factors). This led them to direct their studies toward enol ester substrates, where the primary epoxidation products were sufficiently stable to be isolated and manipulated, providing an essential enablement of their general method for the enantiocontrolled synthesis of α -acyloxy ketones.³

While prior research has shown that trimethylsilyloxy and *tert*-butyldimethylsilyloxy epoxides can be prepared as discrete intermediates, especially by epoxidation with nonacidic oxygen atom transfer agents such as arylsulfonyloxaziridines⁴ and dimethyldioxirane,⁵ it is also evident from this prior work that the reactivities of the products complicate their isolation and handling, absent special stabilizing structural features. With these precedents in mind and an awareness of the particular stability of *tert*-butyldiphenylsilyl ethers toward acid-catalyzed hydrolysis,⁶ we undertook to reinvestigate the Shi asymmetric epoxidation of silyl enol ether derivatives with a focus on variation of the trialkylsilyl group. Here we show that *tert*-butyldiphenylsilyl enol ether derivatives of both cyclic and acyclic ketones undergo enantioselective epoxidation according to the Shi paradigm,¹ that the *tert*-butyldiphenylsilyloxy epoxide products can be isolated by simple extraction and, most significantly, that these products undergo highly regio- and stereospecific addition reactions with certain hydride and alkylide donors (vide infra).

tert-Butyl(cyclohexenyloxy)diphenylsilyl ether (1), prepared from cyclohexanone in >95% yield under soft enolization conditions (*tert*-butyldiphenylsilyl triflate,⁷ triethylamine, dichloromethane, 0 °C, 1 h)⁸ or by deprotonation with potassium

hexamethyldisilazide followed by trapping with the silyl chloride, is, as expected, substantially more stable than the corresponding triisopropylsilyl and *tert*-butyldimethylsilyl enol ethers^{6,9} (in that order) under conditions such as exposure to silica gel (see Supporting Information). All three substrates were transformed into the corresponding silyloxy epoxides under typical Shi epoxidation conditions (0.30 equiv of Shi catalyst,¹⁰ borate buffer, slow addition of Oxone and potassium carbonate solutions over 90 min at 0 °C) with similar, high enantioselectivities (91–93% ee, vide infra).² The products were efficiently extracted into pentane without decomposition.⁴ Two-dimensional thin-layer chromatographic analysis of the product solutions revealed the following stability order: *tert*-butyldiphenylsilyl (compound 2) \gg triisopropylsilyl > *tert*-butyldimethylsilyl (see Supporting Information). Solutions of the epoxide 2 could be concentrated, and the crude product stored neat for several weeks at –20 °C without evident decomposition. ¹H NMR spectral data were consistent with expectations for the proposed structure (2) and revealed that the product had been formed cleanly, with the only significant contaminant being a small amount of Shi catalyst that had partitioned into the pentane layer during the extraction. While future applications may benefit from or require using purified silyloxy epoxides, all of the transformations described herein were conducted using the pentane extracts of the Shi epoxidation reaction mixtures directly, without purification, or even concentration in many cases.

Among the new and useful reactions of silyloxy epoxides we have investigated is a simple regio- and stereoselective reduction with borane–THF, which gives rise to *trans*-diol monosilyl ethers.¹¹ In a specific illustration (eq 1 and entry 1, Table 1), addition of a 1.0 M solution of borane–THF (1.2 equiv) to an ice-cold solution of the pentane extracts containing the Shi epoxidation product 2, stirring at 0 °C for 1 h, then careful quenching with an aqueous solution of tris(hydroxy-methyl)aminomethane, extractive isolation, and chromatographic purification afforded pure (1*R*,2*R*)-2-(*tert*-butyldiphenylsilyloxy)cyclohexanol 3 in 91% yield for the two-step (epoxidation–reduction) sequence. The product was shown to be of 93% ee by ¹H NMR analysis of the corresponding Mosher ester.¹² Similarly, the triisopropylsilyl and *tert*-butyldimethylsilyl enol ethers (entries 2 and 3, respectively, Table 1) were transformed directly into the corresponding *trans*-1,2-diol monosilyl ethers, in yields that reflected the stabilities of the silyloxy epoxide intermediates.

As the examples of Table 1 reveal, the two-step Shi epoxidation–reduction sequence appears to hold promise as a general method for the enantio- and diastereocontrolled synthesis of differentiated cyclic *trans*-1,2-diols and, as entry 9 suggests, may also allow for simplification of certain polyol targets by simultaneous multiple application.^{13,14} Because epimerization is unlikely to have occurred at any point during the transformations summarized in Table 1, we believe the ee values presented

Table 1. Cyclic *trans*-1,2-Diol Monosilyl Ether Derivatives Formed by Shi Asymmetric Epoxidation^a of Silyl Enol Ethers Followed by Stereospecific Reduction with Borane–THF

Entry	Substrate	Product	Yield ^b	ee ^c
1			91	93
2			82	91
3			68	91
4			92	89
5			82	88
6			95	90
7			81	90
8 ^d			81	91
9 ^d			69	90

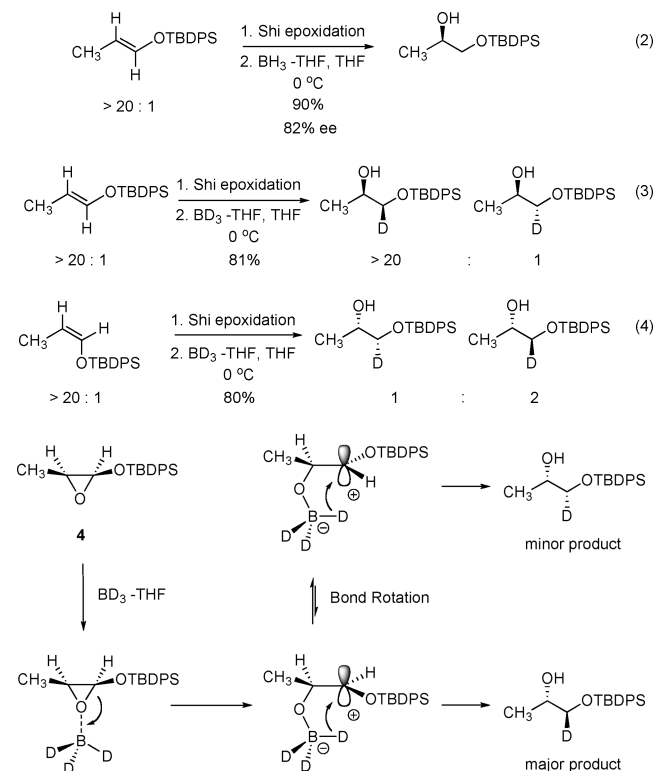
^a Shi epoxidation conditions: 0.3 equiv of Shi catalyst, 1.38 equiv of Oxone, 5.8 equiv of K₂CO₃, CH₃CN–CH₃OCH₂OCH₃–borate buffer, 0 °C, 2 h. ^b Isolated yields over two steps. ¹H NMR analysis revealed that in all cases diastereoselectivities were >20:1, favoring the *trans*-1,2-diol derivatives. ^c Enantiomeric excesses were determined by ¹H NMR analysis of the corresponding Mosher esters, except for entries 7 and 8, where ee's were determined by HPLC using a chiral column (see Supporting Information for details). ^d These entries involved slight procedural modifications; see Supporting Information for details.

there provide an accurate assessment of the enantioselectivities of the epoxidation step, which are typically above 90%, in keeping with Shi's prior observations.¹

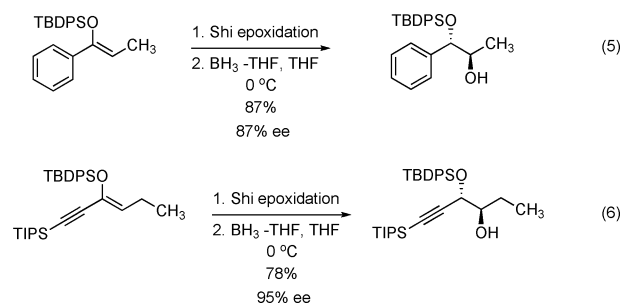
The stereochemistry of hydride addition supports a mechanism involving prior coordination of borane to the epoxide oxygen followed by epoxide opening and internal hydride transfer, as has been proposed for reductions of glycal epoxide-like substrates with borane–THF,¹⁵ although the trajectories for hydride addition are presumably quite different.¹⁶

In further evaluating the scope of the epoxidation–reduction sequence we explored acyclic *tert*-butyldiphenylsilyl enol ethers as substrates and, in this context, gained mechanistic insight into

the reduction process. Asymmetric epoxidation–reduction of *trans*-1-*tert*-butyldiphenylsilyloxypropene¹⁷ afforded (*R*)-1-(*tert*-butyldimethylsilyloxy)propan-2-ol in 90% yield and 82% ee (eq 2). Employing BD₃–THF in lieu of BH₃–THF, we found that the reduction proceeded with >95% stereospecificity (eq 3),¹⁸ as observed in the cyclic substrate series (Table 1). Epoxidation–reduction (also with BD₃–THF) of *cis*-1-*tert*-butyldiphenylsilyloxypropene,¹⁹ however, proceeded with substantially diminished stereospecificity (~33%, eq 4), which we rationalize in Figure 1.²⁰

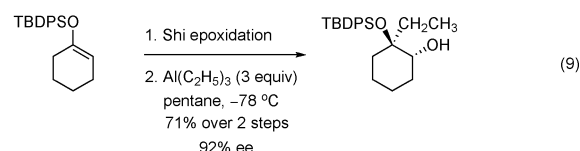
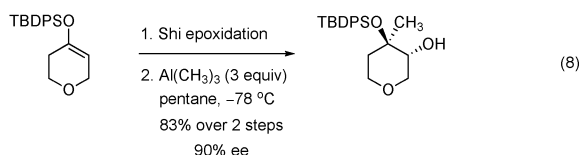
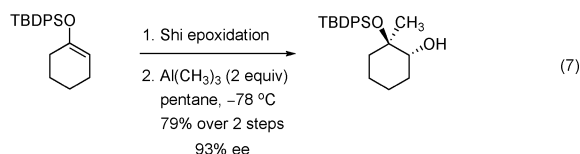
**Figure 1.** Reduction of the *cis*-*tert*-butyldiphenylsilyloxy epoxide **4** with BD₃–THF provides evidence for a short-lived carbocationic intermediate. The data suggest that the rate of deuteride transfer is slightly more rapid than rotation about the internal C–C bond.

Two additional examples in the acyclic series, employing trisubstituted *Z*-*tert*-butyldiphenylsilyl enol ethers as substrates (each ≥ 14:1, *Z/E*, prepared by enolate formation with potassium hexamethyldisilazide followed by trapping with *tert*-butyldiphenylsilyl chloride), suggest that the present method may have general value for the preparation of differentiated *anti*-1,2-diols (eqs 5 and 6).



Lastly, we have observed that *tert*-butyldiphenylsilyloxy epoxides react stereospecifically with trimethyl- and triethyla-

luminum to form differentiated *trans*-1,2-diol products (eqs 7–9). It is noteworthy that the tertiary hydroxyl groups of the product diols emerge bearing the *tert*-butyldiphenylsilyl protecting group. Thus far, we have not seen evidence of silyl group transfer. Here, too, substantial literature precedent exists for stereospecific additions of trialkylaluminum reagents to glycol epoxides²¹ although, as discussed above in the context of hydride addition,¹⁶ the stereoelectronic features of the present transformations are presumably very different and seemingly less favorable.



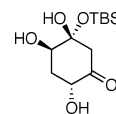
We imagine that the asymmetric epoxidation–reduction and epoxidation–alkylide addition sequences presented herein will be useful for the preparation of a number of complex diol and polyol targets.

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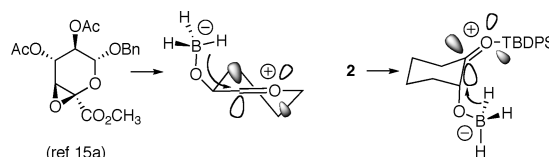
Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (13) The absolute stereochemistry of the product (entry 9, Table 1) was established by X-ray crystallographic analysis of the corresponding bis-*p*-bromophenyl ester derivative (see Supporting Information). Interestingly, we observed that when a pentane–ethyl acetate solution of the bis-epoxide intermediate of entry 9 was shaken briefly with a 1 N aqueous hydrochloric acid solution, the hemiketal monosilyl ether depicted was obtained as a stable substance. The structure was verified by X-ray crystallography (see Supporting Information).



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