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Anti-Selective Epoxidation of Methyl α-Methylene-β-*tert*-butyldimethylsilyloxycarboxylate Esters. Evidence for Stereospecific Oxygen Atom Transfer in a Nucleophilic Epoxidation Process

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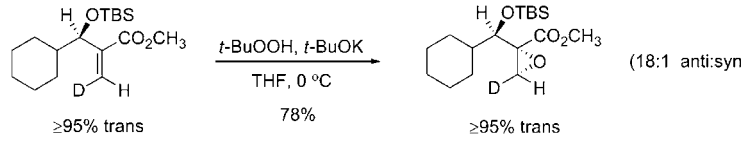
ABSTRACT



Methyl α-methylene-β-*tert*-butyldimethylsilyloxycarboxylate esters are found to undergo diastereoselective epoxidation in the presence of potassium *tert*-butoxide−*tert*-butyl hydroperoxide to form anti products. In an effort to better understand mechanistic details of the transformation and the basis of diastereoselectivities observed, we studied the epoxidation of substrates with α-methylene groups containing (trans) deuterium labels and discovered that oxygen-atom transfer proceeds with ≥95% stereospecificity in all cases examined. These and other experiments suggest that the mechanism of epoxidation is not distinguishable from a concerted process.

In the context of a problem in target-directed, complex synthesis, we were led to explore the epoxidation of methyl α-methylene-β-hydroxycarboxylate esters and their hydroxyl-protected derivatives and report here that the corresponding *tert*-butyldimethylsilyl ethers undergo efficient, anti-selective epoxidation with potassium *tert*-butylperoxide in tetrahydrofuran (THF). While syn-selective epoxidations of α-methylene-β-hydroxycarboxylate esters have been reported,[1] a method for anti-selective epoxidation of this substrate class had not been described previously.

Summarized in Figure 1 are results of epoxidations of nine methyl α-methylene-β-*tert*-butyldimethylsilyloxycarboxylate esters bearing different β-alkyl substituents. All transformations employed stoichiometric amounts of *tert*-butyl hydroperoxide and catalytic quantities of potassium *tert*-butoxide (0.1−0.3 equiv) in THF at 0 °C.[2] Substrates with dimethoxymethyl, benzyloxymethyl, or unsaturated β-substituents reacted relatively rapidly, while those with cyclohexyl, ethyl, or 2-benzyloxyethyl β-substituents reacted more slowly and required distributed addition of as much as 0.3 equiv of potassium *tert*-butoxide to achieve complete conversion. All reactions were complete within 12 h at 0 °C, provided that care was taken to thoroughly dry all substrates, reagents, and solvents (see the Supporting Information). As summarized in Figure 1, anti products were formed selectively in all cases. Substrates with unsaturated β-substituents were

(1) (a) Bailey, M.; Markó, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron Lett.* **1990**, *31*, 4509–4512. (b) Bailey, M.; Staton, I.; Ashton, P. R.; Markó, I. E.; Ollis, W. D. *Tetrahedron: Asymmetry* **1991**, *2*, 495–509.

(2) To the best of our knowledge, these conditions were first reported in the following works: (a) Warrener, R. N.; Butler, D. N.; Margetic, D.; Pfeffer, F. M.; Russell, R. A. *Tetrahedron Lett.* **2000**, *41*, 4671–4675. (b) Pfeffer, F. M.; Russell, R. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2680–2685. Although we have successfully used anhydrous solid potassium *tert*-butoxide in several experiments, for convenience we typically employ a 1.0 M stock solution of base in THF, prepared from the anhydrous solid (see the Supporting Information).

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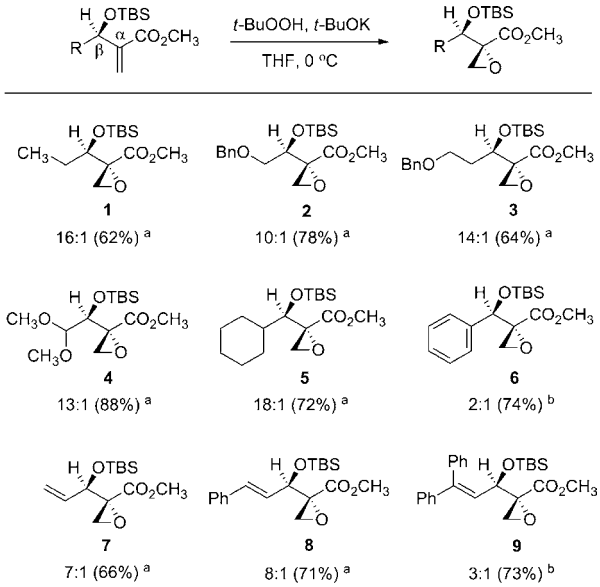
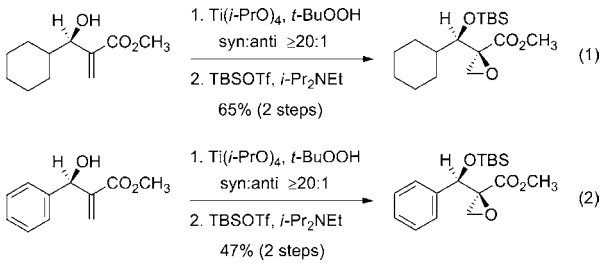


Figure 1. Anti-selective epoxidation of methyl α-methylene-*β*-*tert*-butyldimethylsilyloxycarboxylate esters with potassium *tert*-butoxide−*tert*-butyl hydroperoxide in THF at 0 °C. Key: (a) isolated yield of the pure anti diastereomer; (b) isolated yield of the anti and syn diastereomers combined.

epoxidized with somewhat lower selectivities, which evidence suggests may be due in part to a stereoelectronic effect (vide infra).

In an important early finding, Tanaka et al. showed that 1,2-disubstituted allylic alcohols undergo syn-selective epoxidation in the presence of vanadium acetylacetonate and *tert*-butyl hydroperoxide.[3] Later, Baylis−Hillman products were shown to undergo syn-selective epoxidation with both vanadium- and titanium-based reagents.[1] We used the latter method to obtain authentic samples of the syn diastereomers for two of the examples of Figure 1, with the results shown in eqs 1 and 2 below.

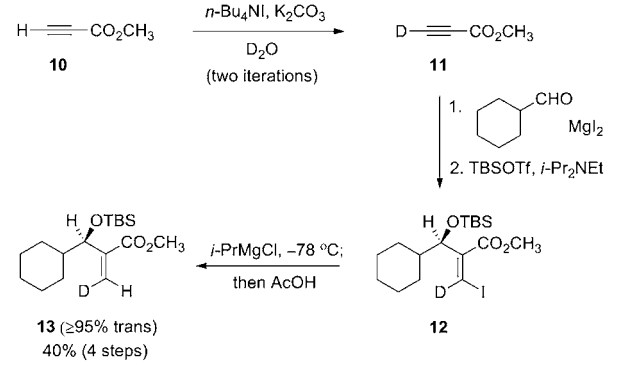


Interestingly, but not unexpectedly, the rates of epoxidations mediated by potassium *tert*-butoxide and titanium tetraisopropoxide varied inversely with substrates bearing electron-donating and electron-withdrawing *β*-substituents. Substrates in Figure 1 with more electron-withdrawing *β*-substituents reacted more rapidly in the base-catalyzed epoxidations.

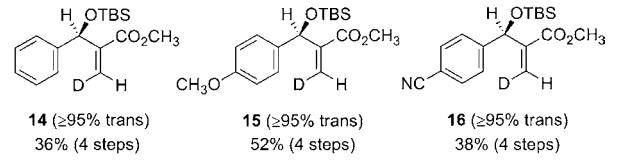
In attempting to rationalize the stereochemical outcomes of the epoxidations of Figure 1, we began by considering the classical extremes of mechanism previously discussed for epoxidations in the literature. Alkene epoxidations with electrophilic reagents such as *m*-chloroperoxybenzoic acid (*m*-CPBA) or dimethyldioxirane are prototypically stereospecific, largely concerted processes.[4] In contrast, epoxidations of electrophilic alkenes with alkaline hydrogen peroxide are established to be non-stereospecific in many instances. For example, in a careful analysis of the epoxidations of (*E*)- and (*Z*)-3-methylpent-3-en-2-one with alkaline hydrogen peroxide in methanol, House and Ro showed that both substrates afforded the same (trans) epoxide.[5] They argued that rotation about the $C_\alpha-C_\beta$ σ bond of a *β*-hydroperoxy enolate intermediate (and stereochemical scrambling) was rapid relative to cleavage of the peroxyl O−O bond to form the oxirane ring. This analysis was consistent with a number of earlier observations by others concerning related processes,[6] and has since been reinforced by studies of the peroxidation of different α,*β*-unsaturated carbonyl compounds with alkaline hydrogen peroxide in both protic and aprotic media.[7] Clearly, a rationalization of the stereochemical outcomes of the transformations of Figure 1 could be framed quite differently for stepwise and concerted processes.

To differentiate these mechanistic possibilities, we prepared methyl α-methylene-*β*-*tert*-butyldimethylsilyloxycarboxylate ester substrates with trans deuterium labels by the sequence shown in Scheme 1. In order to maximize the

Scheme 1. Preparation of Substrates with Trans Deuterium Labels



Other labeled substrates prepared by the sequence above:



(3) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254–5255.

(4) *m*-CPBA: Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385–3386, and references therein. Dimethyldioxirane: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205–211. (b) Schneebeli, S. T.; Hall, M. L.; Breslow, R.; Friesner, R. *J. Am. Chem. Soc.* **2009**, *131*, 3965–3973, and references therein.

(5) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428–2433.

deuterium content of the final product, the isotopic label was introduced in the first step of the sequence by base-catalyzed H/D exchange of the alkynyl hydrogen of methyl propiolate (two iterations).[8] Then, by employing the Paré modification of the Kishi iodoallenolate aldol reaction,[9] the labeled precursor was coupled with cyclohexanecarboxaldehyde and, separately, with benzaldehyde, 4-methoxybenzaldehyde, and 4-cyanobenzaldehyde (Scheme 1). *tert*-Butyldimethylsilylation of the aldol products, followed by sequential stereospecific metal−halogen exchange and stereospecific protonation with acetic acid, then provided the deuterium-labeled substrates for epoxidation. In practice, metal−halogen exchange was best accomplished with isopropylmagnesium chloride[10] (THF, −78 °C, 10 min); exchange with *n*-butyllithium (THF, −100 °C, 2 min) was less efficient.[11] ^{1}H NMR analysis of the products of this reaction sequence (**13**−**16**) showed that the deuterium content at the labeled position was ≥90% and that the labeled compounds were ≥95% trans.[12]

We first studied the epoxidation of the deuterium-labeled β-cyclohexyl substrate (**13**), under the conditions detailed above, and found that a ≥18:1 mixture of anti and syn epoxides was formed, as had been observed with the unlabeled substrate (Figure 1). The pure (deuterium-labeled) anti epoxide (**17**, Figure 2) was obtained in 78% isolated yield after column chromatography. ^{1}H NMR analysis of this product revealed that epoxidation had proceeded with ≥95% stereospecificity, with retention of trans stereochemistry (Figure 2). Aliquots from a separate but identical experiment removed at points of 50, 60, and 70% conversion and analyzed by ^{1}H NMR showed that unreacted substrate retained ≥95% stereochemical purity. The lack of stereochemical scrambling makes clear that, in contrast to the findings of House and Ro, the mechanism of epoxidation in the present case (involving different substrates and different reagents) cannot involve a freely rotating β-*tert*-butylperoxy enolate intermediate.[13] If such an intermediate is formed, then the rate of peroxyl O−O bond cleavage must be quite rapid relative to rotation about the $C_\alpha-C_\beta$ σ bond. The data are also consistent with concerted mechanisms of oxygen-atom transfer. To learn if similar conclusions extended to the least anti-selective transformation of Figure 1 (the β-phenyl-substituted substrate, which had afforded a 2:1 mixture of diastereomers favoring the anti isomer **6**) we examined the epoxidation of the trans deuterium-labeled substrate **14**, with the results summarized in eq 3 of Figure 2. Also presented in Figure 2, in descending order of anti selectivity, are results of epoxidations of the β-4-methoxyphenyl- and β-4-cyanophenyl-substituted, deuterium-labeled substrates **15** and **16** (depicted at the bottom of Scheme 1). All three deuterium-labeled β-aryl substrates were found to undergo epoxidation with ≥95% stereospecificity in both anti and syn manifolds. The variation of anti-syn ratios among the three β-aryl substrates reveals an interesting stereoelectronic effect. The rates of epoxidations with the three β-aryl substrates also varied, with 4-cyanophenyl > phenyl > 4-methoxyphenyl (see the Supporting Information).

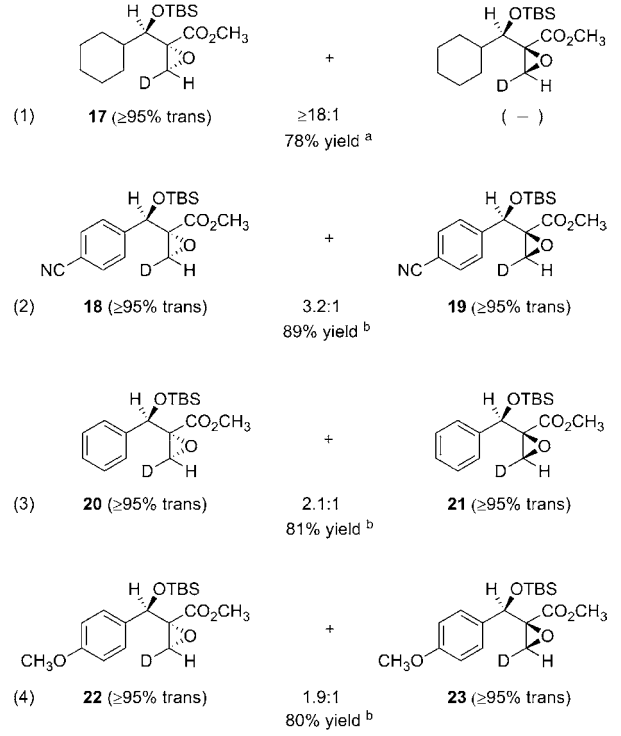


Figure 2. Stereospecific epoxidations of trans deuterium-labeled substrates. Key: (a) isolated yield of the pure anti diastereomer; (b) isolated yield of the anti and syn diastereomers combined.

To further explore the mechanism of epoxidation, we conducted a competition experiment wherein a ∼1:1 mixture of the deuteriated substrate **13** and its nonlabeled counterpart was subjected to standard conditions of epoxidation, with quenching of the reaction at ∼80% conversion. By integration of the α-methylene resonances in ^{1}H NMR spectra of

(6) (a) Bunton, C. A.; Minkoff, G. J. *J. Chem. Soc.* **1949**, 665–670. (b) Wasserman, H. H.; Aubrey, N. E.; Zimmerman, H. E. *J. Am. Chem. Soc.* **1953**, *75*, 96–98. (c) Black, W. B.; Lutz, R. E. *J. Am. Chem. Soc.* **1953**, *75*, 5990–5997.

(7) (a) Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108–116, and references therein. (b) Kelly, D. R.; Caroff, E.; Flood, R. W.; Heal, W.; Roberts, S. M. *Chem. Commun.* **2004**, 2016–2017.

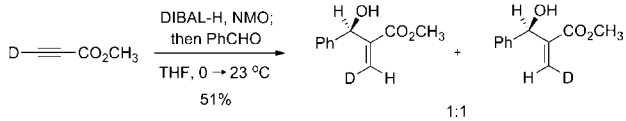
(8) (a) Labuschange, A. J. H.; Schneider, D. F. *Tetrahedron Lett.* **1983**, *24*, 743–744. (b) Schwier, T.; Gevorgyan, V. *Org. Lett.* **2005**, *7*, 5191–5194.

(9) (a) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767–4770. (b) Wei, H. X.; Hu, J.; Jasoni, R. L.; Li, G.; Paré, P. W. *Helv. Chim. Acta* **2004**, *87*, 2359–2363.

(10) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080–1081.

(11) Metal−halogen exchange using *i*-PrMgCl and *n*-BuLi provided the following isolated yields of labeled substrates (respectively): **13** (88% and 85%), **14** (77% and 52%), **15** (87% and 45%), and **16** (91% and 18%).

(12) In the course of developing a synthetic route to the deuterium-labeled substrates, we made the following observation: treatment of 3-deuteriopropiolate with diisobutylaluminum hydride−*N*-methylmorpholine-*N*-oxide complex (Ramachandran, P. V.; Reddy, M. V.; Rudd, M. T. *Chem. Commun.* **1999**, 1979−1980) followed by addition of benzaldehyde afforded a 1:1 mixture of stereoisomeric (*E*)- and (*Z*)-alkenes. This stereochemical outcome is consistent with the intermediacy of an aluminum allenolate, as previously discussed by Tsuda et al. (Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037–1040).



the recovered, unreacted starting materials we determined that there was a significant inverse secondary deuterium isotope effect ($k_H/k_D = 0.95$) upon substitution of the exo-carbon atom of the α-methylene group (Figure 3), suggesting that this carbon is rehybridized in the transition state.

Finally, we employed the Singleton method[14] to measure the $^{12}C/^{13}C$ isotope effects at C2 and C3 during epoxidation in the specific case of the *β*-cyclohexyl-substituted substrate, with the results summarized in Figure 3. A large isotope effect was observed at C3 (∼1.032) and a smaller but significant isotope effect observed at C2 (∼1.009). A strikingly similar data set was reported by Singleton et al. in their recent study of the mechanism of epoxidation of 2-cyclohexenone with *tert*-butyl hydroperoxide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 1,2-dichloroethane.[15] There, as here, the kinetic isotope effects provide evidence for an asynchronous transition state with substantial rehybridization of the *β*-olefinic carbon atom. Stepwise mechanisms involving rate-limiting oxirane formation within a *β*-peroxy enolate intermediate are not supported, while concerted mechanisms cannot be ruled out.

The experimental results presented herein make evident that the basis of anti selectivity in epoxidations of methyl α-methylene-*β*-*tert*-butyldimethylsilyloxycarboxylate esters arises from a face-selective attack of the *tert*-butylperoxide reagent upon the substrate. We have evidence that stereoelectronic factors play a role in determining the diastereofacial preference, at least within one substrate subset (the *β*-aryl series). Ground-state conformational analyses of the methyl α-methylene-*β*-*tert*-butyldimethylsilyloxycarboxylate ester substrates studied herein reveal a large number of closely spaced, quite different rotameric forms within 3.0 kcal/mol of the global energy minimum and do not suggest

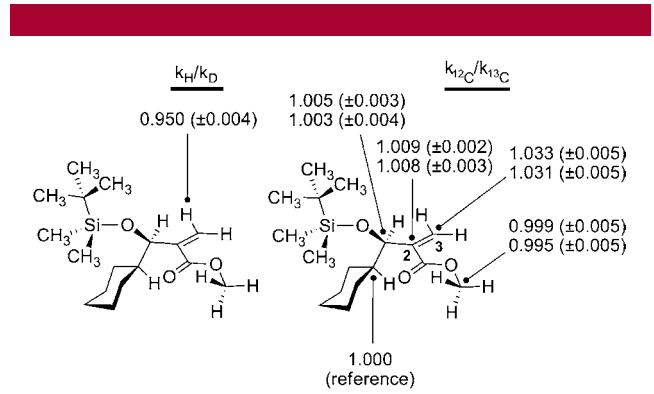


Figure 3. Measured isotope effects for epoxidation of the *β*-cyclohexyl-substituted substrate depicted.

that a clear basis for the facial selectivity of reagent addition can be gained by consideration of the substrate alone.[16] High-level computational modeling of transition-states is clearly necessary, but beyond the scope of the present study. Regardless of its theoretical underpinnings, the anti-selective epoxidation process we describe provides unique access to highly functionalized, stereochemically complex structures and in this regard is likely to be quite useful. Our understanding of the mechanism of this nucleophilic epoxidation process, while incomplete, is informed by the self-consistent series of experiments presented herein, which leads to a view of the reaction that is not distinguishable from a concerted, albeit asynchronous process.

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

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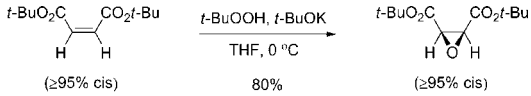
(13) Meth-Cohn et al. have reported examples of both stereospecific and non-stereospecific epoxidations with lithium *tert*-butylperoxide in THF ((a) Clark, C.; Hermans, P.; Meth-Cohn, O.; Moore, C.; Taljaard, H. C.; van Vuuren, G. *J. Chem. Soc., Chem. Commun.* **1986**, 1378–1380. (b) Meth-Cohn, O.; Moore, C.; Taljaard, H. C. *J. Chem. Soc., Perkin Trans. 1*, **1988** 2663−2674).For example, these authors found that epoxidation of phenyl (*Z*)-2-phenylethenylsulfone proceeded with retention of stereochemistry, providing the corresponding cis epoxide in 90% yield, while epoxidation of di-*tert*-butyl maleate (cis) proceeded with inversion of stereochemistry, providing the trans epoxide in 60% yield. We have examined the epoxidation of the latter substrate under the optimized conditions described above and found that the cis epoxide was formed with ≥95% stereospecificity in 80% yield after column chromatography (see the Supporting Information).



(14) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357–9358.

(15) Christian, C. F.; Takeya, T; Szymanski, M. J.; Singleton, D. A. *J. Org. Chem.* **2007**, *72*, 6183–6189.

(16) For discussions of the diastereoselectivities of dihydroxylations of closely related substrates, see: (a) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698–1700. (b) Markó, I. E.; Giles, P. R.; Janousek, Z.; Hindley, N. J.; Declercq, J. P.; Tinant, B.; Feneau-Dupont, J.; Svendsen, J. S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 239–241.