Facile Synthesis of cis-2-Alkyl-3-trialkylsilyloxy cycloalkanones via the Non-Aldol Aldol Rearrangement of 2,3-Epoxycycloalkanols

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ABSTRACT

Silyl triflate-promoted rearrangement of cis-2,3-epoxycycloalkanols A, prepared by epoxidation of the cyclic allylic alcohol and then silylation, afforded good yields (~70–75%) of the cis-2-alkyl-3-silyloxy cycloalkanones B, presumably via the intermediates C and D, even with quite large α-substituents, e.g., tert-butyl. Finally, it has been shown that the stereochemistry of the epoxy alcohol is crucial as one would expect from the mechanism.

Functionalized carbocyclic rings are important synthons in organic synthesis. In particular, cis-2-alkyl-3-hydroxycycloalkanones are valuable intermediates that can be readily converted into a variety of motifs found in natural products. Unfortunately, no procedures currently exist for their synthesis. In acyclic systems, such β-hydroxy carbonyl compounds are usually made using the aldol condensation and asymmetric variants thereof. But few synthetic methods have been reported for the asymmetric intramolecular aldol to make α-alkyl β-hydroxy cyclic systems.

An alternative method to synthesize asymmetric β-hydroxy carbonyl compounds is the Lewis acid promoted semipinacol rearrangement of optically active epoxy alcohols, obtained using methodology developed by Sharpless.1 The activated epoxide is opened with inversion of stereochemistry via a concerted [1,2] migration, thereby transferring the stereochemistry of the starting material to the product. Much of this work has focused on phenyl, vinyl, or alkyl migration in acyclic systems.2 More recently, a few studies have been reported in cyclic systems in an effort to construct quaternary carbon centers. Several years ago, we reported a semipinacol rearrangement3a involving not phenyl, vinyl, or alkyl migration, but rather hydride migration, and named the process the nonaldol aldol reaction3–5 (Scheme


1). Good yields of 3 were obtained from the epoxide 2 using a silyl triflate in combination with a hindered base as a unique Lewis acid system to promote hydride migration, a process that requires more rigorous conditions than phenyl or vinyl migration. However, these studies were mostly confined to acyclic systems. We report herein the use of the non-aldol aldol reaction in cyclic systems for the preparation of cis-α-alkyl β-silyloxy cycloalkanones from α-alkyl epoxy alcohols.

The α-alkyl epoxy alcohols 6 were prepared in four steps from the corresponding cycloalkanones 4 (Scheme 2).

Bromination with NBS followed by elimination gave the cycloalkanones 5. DIBAL reduction and hydroxyl-directed epoxidation gave the desired cis-epoxy alcohols 6. The results of the treatment of either the free epoxy alcohol or the derived silyl ether of the dimethyl-substituted cyclohexane system are shown in Table 1. Treatment of the triethylsilyl ether, so the TES ether 7a was treated with various Lewis acids, e.g., TiCl₄, SnCl₄, BF₃·OEt₂, and LiBF₄, to induce the rearrangement, but they afforded the β-hydroxy ketone 8b in lower yields (32–65%). Thus, this is the first example of the formation of cis-α-alkyl β-silyloxy cycloalkanones from such epoxy ethers.

The less substituted epoxy ether 10a reacted similarly with the silyl triflate and base to afford the β-silyloxy ketone 11a in 50% yield along with some allylic ether 12 (Scheme 3).

In this case, the reaction went to completion at −40 °C while the rearrangement of 7a required warming to 0 °C. However, treatment of 10b with various Lewis acids—TiCl₄, SnCl₄, BF₃·OEt₂, and LiBF₄—led mainly to decomposition, and only small amounts of 11b were obtained. Thus, the mild silyl triflate/Hünig’s base conditions are superior for less hindered compounds where the products are more prone to side reactions. Overall, the silyl triflate/Hünig’s base protocol gave the highest yields.

The stereochemistry of the products were assigned by comparison of the coupling constants, especially J₃, to the same J values in analogous literature compounds. Thus, the J₃ value for the trans isomer is 8–9 Hz for similar 3-hydroxy- or 3-alkoxy-2-alkylcyclohexanones, while the J₃ value for the cis isomer is 3 Hz. In compounds 8a, 8b, and 11a, J₃ was 2.4, 3.1, and 2.1 Hz, respectively. In addition, the proton and carbon NMR data of the cis isomer 8b do not match those reported for the known trans compound. Thus, the structures of 8 and 11 were assigned by this coupling constant and literature comparison.

The effect of the epoxy substituent and the ring size on the rearrangement was also tested by treating a number of analogues with TBSOTf and Hünig’s base (Scheme 4). The ethyl analogue 13a afforded the expected product 14a in 77% yield, and the 5-membered methyl analogue 13d also worked.

<table>
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<tr>
<th>compd</th>
<th>R</th>
<th>Lewis acid</th>
<th>additive</th>
<th>T (°C)</th>
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<tr>
<td>7a</td>
<td>TES</td>
<td>TESOTf</td>
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<td>10</td>
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</table>

(7) This byproduct 9 is seen whenever there is a methyl substituent α to the epoxide and the rearrangement is relatively slow.²⁹
very well to give the cyclopentanone 14d in 73% yield.\(^9\) Not unexpectedly, the unsubstituted epoxy ether 13c produced no product, presumably because, as we had shown earlier, an alkyl-stabilizing group is required to direct cleavage of the oxirane ring at C2 (a tertiary carbocation is required). Finally treatment of the 6-membered tert-butyl analogue 13b with TBSOTf, even on heating to 40 °C for more than 12 h, resulted in less than 10% conversion to the desired product 14b. The low conversion for this analogue is probably due to steric hindrance of the coordination of the hindered epoxide to the hindered silyl triflate, although we could not a priori rule out some unusual stereoelectronic effect due to the tert-butyl group, namely that the ring could no longer adopt a conformation such that the hydride could align with the \(\sigma^*\) orbital of the epoxide. We could distinguish between these two effects and carry out the rearrangement by changing the Lewis acid from the bulky TBSOTf to the less bulky TESOTf or TMSOTf (Scheme 5). Treatment of the tert-butyl substrate 13b with the smaller TESOTf afforded the TES ether 14e in 50% yield. The yield could be improved by using the less hindered TMSOTf to give the TMS ether 14f in 73% yield. We showed that the silyl ether present in the substrate had little effect since treatment of the less hindered TES ether analogue 13e with the hindered TBSOTf afforded a low yield (<10%) of the expected product 14b.

We presume that the mechanism of this cyclic nonaldol aldol process is similar to the acyclic version, namely the pathway shown in Scheme 6. Complexation of the basic epoxide oxygen to the silyl triflate Lewis acid would afford the silylated epoxide A, which would undergo concerted 1,2-hydride migration promoted by the lone pair of electrons on the oxygen of the silyl ether to give the oxonium ion B in which inversion of configuration has occurred. Final loss of the silyl group would then furnish the observed ketone products.

Evidence in support of this mechanism was obtained by the attempted rearrangement of the anti epoxy silyl ether 15 (Scheme 7). Treatment of 15 with TESOTf afforded a mixture of the two diastereomeric aldehydes 16 and 17 in 57% and 26% yields, respectively. The structures were assigned based on extensive proton NMR analysis and NOE experiments.\(^{10}\) Since the normally favored anti 1,2-hydride migration is disfavored due to poor orbital overlap, the normally less favored ring contraction via alkyl migration is observed, with pathway a being favored over pathway b in intermediate C.

In summary, we describe the first example of the nonaldol aldol rearrangement of cyclic \(\alpha\)-alkyl epoxy silyl ethers to afford \(\alpha\)-alkyl/\(\beta\)-silyloxy cycloalkanones. The process works for nearly all \(\alpha\)-alkyl substituents as long as the hydrogen is anti to the epoxide oxygen. Further work on this rearrangement and its use in synthesis will be reported in due course.

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**Supporting Information Available:** Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The stereochemistry of these compounds were assigned by analogy to the earlier analogues 8 and 11.

(10) There was a strong NOE between the proton \(\alpha\) to the OTES group and the aldehyde in 17 which was absent from 16.