to the stabilization of the organolithium reagent via the intramolecular chelation of lithium by the enolate oxygen to form a five-membered cyclic structure (6).13

Phosphonate 4 is a stable compound14 and was easily prepared in 75% yield by the reaction of disisopropyl lithiomethylphosphonate15 with methyl 3-(tri-n-butylstannyl)propionate.16 The generation of 6 can be followed either by the disappearance of the starting phosphate (4) or by the appearance of tetra- butytin after acid workup of the reaction aliquots. The transmethylation reaction is essentially complete within 5 min at -78 °C. Lithio compound 6 reacts with various electrophiles (Table I) exclusively at the δ carbon, giving rise to terminally substituted phosphonate esters 7.17

The following experimental procedure is representative of the conversion. A dry 35-mL flask (equipped with a septum and a magnetic stirrer) containing 120 mg (2.5 mmol) of sodium hydride (50%, washed with hexanes to remove mineral oil) was flushed with argon and maintained under a positive pressure of argon. About 10 mL of freshly distilled dry THF was added, and then 1.05 g (2.0 mmol) of 4 was added dropwise. The reaction mixture was stirred at room temperature for 3 h to allow the formation of 3. The reaction mixture was cooled to -78 °C, and 2.2 mmol (1.0 mL of a 2.2 M hexane solution) of n-butyllithium was added. The reaction mixture was stirred at -78 °C for 10 min. The electrophile (2.2 mmol)18 was added, and the reaction mixture was stirred at -78 °C for 15 min and at room temperature for 15 min. The reaction was quenched with 10% HCl (with dimethylacetamide as the electrophile, aqueous NH4Cl was used), and the mixture was extracted with ethyl acetate. The crude product19 was purified by either modified flash chromatography20 or preparative thin-layer chromatography.

When the solution containing 6 (1,4-dianion) was stirred at 0 °C for 20 min, the solution turned red and on reaction with allyl bromide produced the γ-allyl compound (8) as the major product.

Table I

<table>
<thead>
<tr>
<th>electrophile</th>
<th>product</th>
<th>yield, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃OD</td>
<td>7a</td>
<td>E = D</td>
</tr>
<tr>
<td>CH₃=CHCH=Br</td>
<td>7b</td>
<td>E = CH₃=CH₂</td>
</tr>
<tr>
<td>CH₃CH₂CH₂</td>
<td>7c</td>
<td>E = CH₂CH₂</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>7d</td>
<td>E = Me₃Si</td>
</tr>
<tr>
<td>PhCO</td>
<td>7e</td>
<td>E = Ph(COH)</td>
</tr>
<tr>
<td>CH₃CONMe₂</td>
<td>7f</td>
<td>E = CH₃CO</td>
</tr>
</tbody>
</table>

a Yields refer to pure product after purification on silica gel.

There was no evidence of 7b being present in the product. This indicates that 6 is thermodynamically less stable and under conditions conducive to proton transfer gives rise to the more stable 1,3-dianion (9).

The generation of 6 shows for the first time that it is possible to generate a homoenolate anion equivalent by tin/lithium exchange when the carbonyl group is protected electronically from nucleophilic attack by butyllithium. The successful transformations reported here, in conjunction with the known reactions of β-ketophosphonates, allow the use of stannane 4 as a synthon for β-substituted α,β-enes (10). The use of 6 to synthesize biologically useful organic molecules and the generation of similar β-lithio derivatives of other functionalized systems22 are being investigated.

Acknowledgment. I thank Dr. T. H. Whitesides for helpful discussions.

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The First Practical Method for Asymmetric Epoxidation

Sirs:

As revealed in Scheme I, we have discovered a new metal-catalyzed asymmetric epoxidation process which is far more selective than any of the previously described methods1 for this type of asymmetric transformation. The simplicity of this new method is one of its more attractive aspects; the necessary components ([+] or [−]-dialkyl tartrate,2 titanium tetrachloropropoxide, and

Table I

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<td>7f</td>
<td>E = CH₃CO</td>
</tr>
</tbody>
</table>

a Yields refer to pure product after purification on silica gel.

The crude residue is partly purified by partitioning between acetonitrile and hexanes; see: Berge, J. M.; Roberts, S. M. Synthesis 1979, 471.


(1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, NJ, 1971, pp 258-62; (b) S. Yamada, T. Mashiko, and S. Terashima, J. Am. Chem. Soc. 1977, 99, 1888 (1977); (c) R. C. Michaelson, R. E. Palermo, and K. B. Sharpless, J. Org. Chem. 485 (1979) [records the highest (8) asymmetric inductions were noted, but they were not deemed worth publication: R. C. Michaelson and K. B. Sharpless, unpublished results, Massachusetts Institute of Technology, 1974. Otsuka and co-workers have recently described I low (<1% ee) asymmetric inductions in the epoxidation of hydrocarbon olefins with TBHP in the presence of dialkyl tartrate esters and a molybdenum(VI) catalyst.

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tert-butyl hydroperoxide) are all\(^3\) commercially available at low to moderate cost.\(^4\)

This new chiral epoxidation system possesses two especially striking features. First, it gives uniformly high asymmetric inductions throughout a range of substitution patterns\(^5\)\(^6\)\(^7\) in the allylic alcohol substrate (Table I). Second, upon use of a given tartrate enantiomer, the system seems obliged to deliver the epoxide oxygen from the same enantiomer of the olefin regardless of the substitution pattern. This latter characteristic is highlighted in Scheme I: when the olefinic unit is in the plane of the drawing with the hydroxymethyl substituent at the lower right as shown, the use of (+)-diethyl tartrate leads to addition of the epoxide oxygen from the bottom of the olefin. Of course, when (-)-diethyl tartrate is employed, the epoxide oxygen comes from the top.

A 500-mL 1-neck round-bottom flask equipped with a Teflon-coated magnetic stir bar was oven dried and then fitted with a serum cap and flushed with nitrogen. The flask was charged with 200 mL of dry (distilled from CaH\(_2\)) reagent-grade dichloromethane and cooled by stirring in a -23 °C bath (dry ice/C\(_2\)Cl\(_2\)).\(^6\) Then the following liquids were added sequentially via syringe while stirring in the cooling bath: 5.94 mL (5.68 g, 20 mmol) of titanium tetraisopropoxide (Aldrich); 3.43 mL (4.12 g, 20 mmol) of 1,1-diethyl tartrate (used as received from Aldrich), stirred 5 min before next addition; 3.47 mL (3.08 g, 20 mmol) of geraniol (Aldrich Gold Label); and, finally, ca. 11 mL of a dichloromethane solution (3.67 M in TBHP) containing ca. 40 mmol (2 equiv) of anhydrous tert-butyl hydroperoxide (TBHP). (One can just as well use dichloroethane or carbon tetrachloride solutions of anhydrous TBHP. Complete experimental details for preparing these anhydrous TBHP solutions are given elsewhere.\(^*\)) The resulting homogeneous solution was then stored overnight (ca. 18 h) in the freezer at ca. -20 °C in the sealed (serum cap) reaction vessel (the progress of the epoxidation can be monitored by TLC). Then the flask was placed in a -23 °C bath (dry ice/C\(_2\)Cl\(_2\)).\(^6\)

(3) The diethyl ester of unnatural (-)-tartric acid has recently become available from Aldrich.

(4) Unnatural L(-)-tartric acid costs about 34 times more than natural L(+)-tartric acid when both are purchased in 100-kg quantities; see note 5: E. Hungerbücher, D. Seebach, and D. Wasmund, Angew. Chem., Int. Ed. Engl., 18, 958 (1979). This makes it by far the most expensive component since the other three are all available for a few dollars a pound, even in research quantities.

(5) Five of the eight possible basic substitution patterns for a primary allylic alcohol are represented in Table I. We plan to examine the three remaining types, but based on the existing cases no surprises (low ee and/or change in enantioselection pattern) are expected.

(6) Cooling serves two purposes, the obvious one of enhancing enantioselectivity, and the less obvious one of minimizing transesterification processes. Titanium alkoxides are excellent transesterification catalysts, and there is an extensive patent literature on this subject. We have found that the rate of transesterification is substantially accelerated by an \(\alpha\)-hydroxy substituent. Thus, in the presence of Ti(O-\(\alpha\)-Pr)_4, \(\alpha\)-methyl mandelate transesterifies much faster than methyl phenylacetate (P. H. J. Carlsen and K. B. Sharpless, unpublished results). As \(\alpha\)-hydroxy esters, the tartrates also undergo rather facile transesterification in our reaction system at room temperature. This produces tartrate esters which incorporate 2-propanol and also the allylic alcohol substrate, and gives rise to a multitude of problems at the product isolation stage. Fortunately, transesterification is slow at -20 °C, and running the reactions near that temperature has so far proved a viable solution to the isolation stage. This epoxidation was run for 40 h at -20 °C, and a trace of 7a still remained. 7b was correlated with (R)-(-)-\(\alpha\)-cy- clohexyl-2-butanol [D. J. Cran and J. Tadanori, J. Am. Chem. Soc., 81, 2737 (1959)] through the following steps: LiAlH\(_4\), Et\(_2\)O, TscI/pyridine; LiCuMe\(_2\), Et\(_2\)O.

\(\alpha\) The enantiomer of 1b has been correlated with (R)-(-)-\(\alpha\)-linalool.\(^1\) The enantiomer of 2b has been correlated with (S)(-)-\(\alpha\)-linalool.\(^1\) The alkaline hydrolysis step was omitted in this case; the diethyl tartrate was removed by chromatography. 6(S),7(S)-3b was correlated with (S)(-)-6,7-epoxygeraniol [S. Yamada, N. Oh-hashi, and K. Achiwa, Tetrahedron Lett., 2557 (1976)]. The 9-hydroxy group of 3b was replaced by hydrogen via the following reaction sequence: TscI/pyridine; NaI/acetonitrile; NaH, BnCl/HMPA; LiOH/CH\(_2\)OH, H\(_2\)O. Epoxidation was performed at 0 °C and was complete in less than 30 min. Co-worker Victor S. Martin (unpublished results) has correlated 4b with methyl (S)(+)-2,3-diphenyl-2-hydroxypropanoate (ii) [H. R. Sullivan, J. R. Beck, and A. Pohland, J. Org. Chem., 28, 2381 (1963); see also: E. Bye, Acta Chem. Scand., 27, 3403 (1973)]. Epoxy alcohol 4b was transformed to ii by the following steps: RuO\(_4\)/CCl\(_4\), CH\(_2\)CN, H\(_2\)O; CH\(_2\)N\(_2\)/Et\(_2\)O; W-2 Raney nickel, H\(_2\) (in ethanol). 5b was correlated with (R)(-)-tridecan-3-ol (K. Sullivan, Grundlagen und Probleme, Franz Deuticke, Ed., Leipzig und Wien, p 696) by the following sequence: TsCl/pyridine; NaI/acetone; NaH, BnCl/HMPA; LiOH/CH\(_2\)OH, H\(_2\)O. Epoxidation was performed at 0 °C and was complete in less than 30 min.

(7) It is important to have at least 1 mol of tartrate per mol of Ti(OR)\(_4\). This article also contains the best previous result (80% ee) for asymmetric epoxidation of an allylic alcohol (see eq 26, p 67).
ice/CCl₄) and 50 mL of 10% aqueous tartaric acid solution was added while stirring; the aqueous layer solidified. After 30 min, the cooling bath was removed and stirring was continued at room temperature for 1 h or until the aqueous layer became clear. After separation of the aqueous layer, the organic layer was washed once with water, dried (Na₂SO₄), and concentrated to afford a colorless oil with an odor revealing contamination by TBHP.

This oil was diluted with 150 mL of ether, and the resulting solution was cooled in an ice bath, and then 60 mL of 1 N sodium hydroxide solution was added. This produced a two-phase mixture which was stirred at 0 °C for 1/2 h. The ether phase was washed with brine, dried (Na₂SO₄), and concentrated to give 4.24 g of a clear oil. Chromatography on silica gel afforded 2.6 g (77%) of 2(S),3(S)-epoxygeraniol. [α]D = -6.36° (c 1.5, CHCl₃). Analysis of this material as the MTPA ester gave an enantiomeric excess of >95% whereas analysis of the derived epoxy acetate by using Eu(hfc)₃ chiral shift reagent gave 94% ee.

The "typical procedure" given for geraniol has a limitation which is important to emphasize. Very poor yields are realized if the epoxy alcohol produced is fairly water soluble. For example, although allyl alcohol and crotyl alcohol are epoxidized by this system, it is difficult to extract (even with "salting-out" techniques) more than 10-30% of the intact epoxy alcohol product. We are working on solutions to the isolation problems presented by these and related cases.

The procedure described above for epoxidation of geraniol calls for 1 equiv of both titanium isopropoxide and diethyl tartrate. This is the reason necessary in all cases. With reactive allylic alcohols (1a, 2a, 3a, and 4a in Table I), a catalytic amount (e.g., 0.1 equiv) of both Ti(O-i-Pr)₄ and diethyl tartrate suffices under otherwise identical reaction conditions. However, for the less-reactive substrates in Table I (5a, 6a, and 7a), the "1-equiv" conditions described above were necessary to achieve reasonable reaction rates. Even under the "1-equiv" conditions, allylic alcohol 7a required almost 2 days to approach completion. For this first report, the most general method (stoichiometric amount of the chiral catalyst system) was chosen for presentation. The catalytic system (which has some important advantages in addition to the obvious ones) is under further study.

Many other aspects of this unique epoxidation system are also being investigated in our laboratory. Of foremost interest is a good mechanistic rationale for the remarkable selectivities which are seen. Our approach to the mechanism involves both kinetic studies and structural modifications of the chiral ligand. From a synthetic point of view, there are several interesting further developments, among them: 1) this same epoxidation system is effective for the kinetic resolution of racemic allylic alcohols, 2) predominant inversion of the enantioselectivity pattern shown in Scheme I is observed with certain minor structural modifications of the chiral tartrate ligand. We also are extending our studies to include homo- and bishomocrotylalcohols, and δ-hydroxy sulfides.

(9) Due to the small scale, we have chosen to ignore the excess TBHP. If one wishes to remove it, a number of reductive procedures are available.

(10) Do not expose the reaction mixture to this base treatment for longer than 1/2 h as base-catalyzed rearrangements of the epoxy alcohol may occur: G. B. Payne, J. Org. Chem., 27, 3819 (1962). Diethyl tartrate is fairly soluble in water, and hydrolyzes readily under these conditions. We have found that (Z)-dimethyl tartrate (Aldrich) is as effective (>95% ee) as the ethyl ester for epoxidation of 4a. The methyl ester is much more water soluble and may prove advantageous when the hydrolysis step is unacceptable. The isopropyl ester also works well, but leads to increased trouble at the workup stage.


(12) Under these catalytic conditions, (0.1 equiv of Ti(OR)₃/DET), the yields of 1b, 2b, and 4b were comparable to or somewhat better than those with 1 equiv, and the product isolations were cleaner and easier. The enantiomeric excess was somewhat poorer for 1b (91% ee) and 2b (84% ee) but was still >95% ee for 4b.

(13) The possibilities for product stability problems, transesterification problems, and most other workup and isolation problems are generally diminished.

(14) M. Ikedu, Y. Yamasda, T. Katuki, V. S. Martin, and K. B. Sharpless, unpublished results.

(15) J. Ryan Zilenovski and K. B. Sharpless, unpublished results.

To the best of our knowledge, this new enantioselective, catalytic process is discriminating to a degree barely rivaled by any other nonenzymatic catalytic process. In its promiscuous acceptance of varied allylic alcohol substrates, 16 it also has some desirable features which would be difficult for even an enzymatic catalyst to achieve.

Acknowledgments. We dedicate this work to Professor Harry S. Mosher. Through patient sharing of his unique insights into asymmetric synthesis, he has had a profound influence on us. The National Institutes of Health (GM24551) is thanked for financial support.

(16) Asymmetric catalytic hydrogenations can be extremely enantioselective; for an example of 100% ee, see: M. D. Fryzuk and B. Bannich, J. Am. Chem. Soc. 99, 6282 (1977). However, these asymmetric hydrogenation processes appear more sensitive to permutation of the olefin substitution patterns than does the asymmetric epoxidation process which we have described here.

(17) Note Added in Proof. We now have results for two more of the basic substitution patterns of primary allylic alcohols (see note 5). Allyl alcohol itself affords 2(S)-glycidol, ca. 15% yield, 73% ee (performed at 0 °C by using (+)-disopropyl tartrate and Ti(OiPr)₄). The higher temperature probably contributes to the lower ee observed in this case. (2Z)-2-Methylhept-2-ene gives the 2(S),3(R)-epoxy alcohol, 80% yield, 89% ee (performed at -20 °C, using (+)-diethyl tartrate and Ti(OiPr)₄). Thus, both conform to the rules stated in paragraph two and only the tetrasubstituted type of primary allylic alcohol remains to be tried.

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2,3-Di-n-propyl-1,4-dehydrobenzene

Sir:

Rearrangement and trapping studies1 have implicated an "open" or biradical form (2) of 1,4-dehydrobenzene as an intermediate in the thermal reaction of (Z)-hexa-1,5-diyln-3-ene (1, R = H; Scheme I). Attempts to obtain kinetic evidence for the existence of a true intermediate in this reaction, however, have been frustrated by the low yield of aromatic products obtained in solution pyrolysis of several compounds of type 1. In this paper, we report a detailed study of the thermolysis of (Z)-4,5-diethyl-4-octene (4).2 This reaction gives high yields of products formed by rearrangement and intramolecular and intermolecular trapping of the intermediate 1,4-dehydrobenzene 5. The kinetics of the solution pyrolysis of 4 in the presence and absence of trapping agent establish that the 1,4-dehydrobenzene is a discrete intermediate on the pathway leading to products. By following this reaction in the probe of an NMR spectrometer at high temperature, we have, for the first time, observed CIDNP in a 1,4-dehydrobenzene reaction. This observation, along with kinetic and trapping chemical evidence, indicates the subsequent formation of two additional intermediates on the pathway to products. The observation of CIDNP, coupled with the reactivity exhibited by 5 and the other two intermediates, implicates a biradical description of these molecules.


(2) Details of the synthesis of compound 4 will be presented in a full paper.