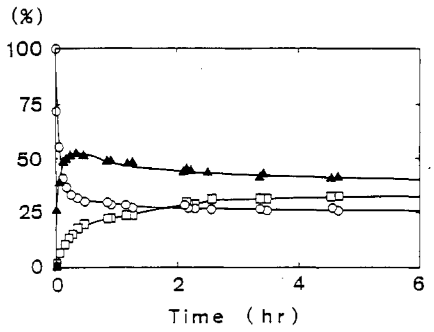

Figure 1. Time dependence of concentrations of R_1^- (○), $R_1^\bullet$ (□), and R_4–R_1 (▲) in the reaction of R_1^- (1×10^{-4} M) with R_4^+ (1×10^{-4} M) in THF at ~20 °C under vacuum.

by UV–vis spectroscopy, and also regenerated the salt $R_4^+R_1^-$ upon reprecipitation in pentane or simply by evaporation under vacuum just as had already been observed in the case of R_3–R_1.[4] However, when the chloroform solution of R_4–R_1 was let stand for longer than 1 min under vacuum, generation of the radical $R_1^\bullet$ (λ_{max} 546 nm)[3] became evident, reaching 93% after 6 h at ~20 °C. This suggests the occurrence of homolytic dissociation of R_4–R_1 (path b).

In contrast, in a solvent with intermediate polarity such as THF (ϵ, 7.58), the coordinative (path a) and SET pathways (path c) are now shown to be occurring concurrently. Thus, either when $R_4^+R_1^-$ was redissolved in THF or when $R_4^+BF_4^-$ was mixed with $K^+R_1^-$ in THF under vacuum, the visible spectrum indicated rapid decrease in R_1^- (λ_{max} 690 nm; $t_{1/2}$ ~3 min) with concomitant increase in $R_1^\bullet$ reaching an apparent equilibrium as shown in Figure 1. After 48 h, the usual workup of the reaction mixture afforded the dimer of 1,3,5-tricyclopropylcycloheptatrienyl radical, R_4–R_4[8] in 20% yield. The difference between the amounts of consumed anion R_1^- and of produced radical $R_1^\bullet$ was shown to be due to the covalent compound R_4–R_1, since the corresponding amount of R_1^- was regenerated by 10-fold dilution with Me_2SO.

The occurrence of SET process in the present cation–anion system seems to be attributed to the presence of three cyclopropyl substituents on the tropylium ring, which bring about steric congestion in the covalent hydrocarbon and also stabilization of the radical species due to possible σ-conjugation between the cyclopropyl group and the π-system.[9]

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[8] The same dimer was obtained by one-electron reduction of R_4^+ with zinc powder in MeCN. For the example of similar equilibria of cycloheptatrienyl and triphenylmethyl radicals with their homo- and cross-coupled covalent compounds, see: Okamoto, K.; Komatsu, K.; Kinoshita, T.; Shingu, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1901.

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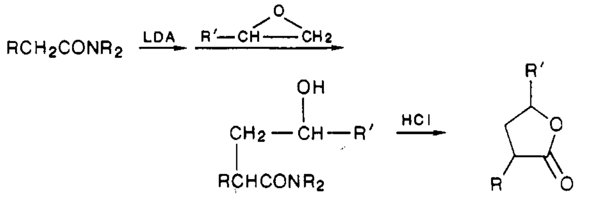
Diastereoselective Reactions of Ester Enolates with Epoxides

Summary: Although epoxides do not undergo facile reactions with lithium enolates of esters, they do undergo highly diastereoselective reactions with aluminum enolates.

Sir: Diastereoselective aldol reactions have been found to be a significant value in organic synthesis.[1] The development of similar, selective enolate/epoxide chemistry has not been demonstrated despite the availability of a virtually unlimited number of optically active epoxides through the Sharpless epoxidation.[2] Development of this chemistry would provide a valuable method of carbon–carbon formation and a general method for the relatively rare 1,3-asymmetric induction.[3a]

Nitrogen-containing enolates (e.g. of amides,[3] enamines,[4] and ketimines[5]) do open epoxides. However, we have found that enolates of ketones and esters do not react with epoxides under conditions which favor selectivity.[6] To get around the latter problem, epoxides have been combined with amide enolates, and the resulting hydroxy amide products have been hydrolyzed and cyclized to lactones (eq 1).[3a] This type of chemistry has recently been utilized in the synthesis of a segment of the immunosuppressant FK-506.[7]



(1)

The diastereoselectivity of the reaction of amide enolates with epoxides has been studied.[3a] The trouble with this approach is that highly hindered amide enolates (e.g. of *N*,*N*-diisopropylamides) are required to achieve high diastereoselectivity. Furthermore, the sterically hindered hydroxy amide products of such reactions are difficult to hydrolyze.[8]

If the enolates of *tert*-butyl esters could be used to open epoxides, hydrolysis of the products (eq 2) could be achieved under mild acidic conditions.[9] Accordingly, we set out to develop this type of chemistry.

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[4] Britten, A. Z.; Owen, W. S.; Went, C. W. *Tetrahedron* **1969**, *25*, 3157.

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[6] Two equivalents of the lithium enolate of *tert*-butyl propionate or 3-pentanone in THF failed to give detectable amounts of reaction product with propylene oxide after 6 h at room temperature.

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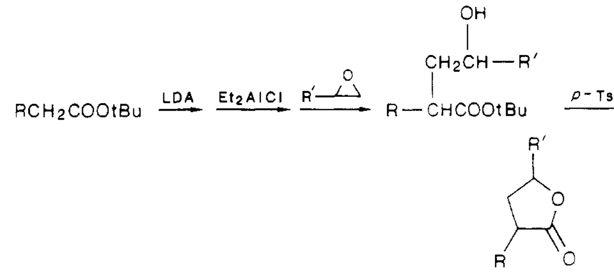
[8] See ref 3a. Also, a private communication with T. B. Grindley confirmed this.



(2)

Again, lithium enolates would not open epoxides. However, in an isolated report, Danishefsky[10] and coworkers have reported the reaction of an aluminum enolate with an epoxide. The epoxide used was symmetrical (cyclohexene oxide), and the enolate used was made from *tert*-butyl acetate, which is not a prochiral ester. Hence, the diastereoselectivity envisioned herein was not demonstrated.

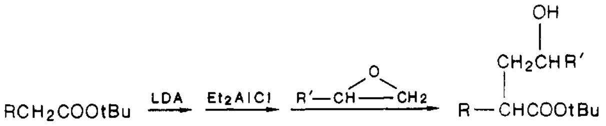
We have now found that the *E* aluminum enolate of *tert*-butyl propionate can be generated by similar techniques and that it reacts in a highly diastereoselective manner with unsymmetrical epoxides. The products can be easily cyclized to lactones by reported methods. In contrast to the aldol condensation,[1] these reactions are highly exothermic due to the relief of angle strain upon epoxide ring opening.

The *E* lithium enolate of *tert*-butyl propionate, formed by established methods (*E*:*Z* 95:5),[1a] was converted into the diethylaluminum enolate by reaction with Et_2AlCl.[10] The resulting enolate reacts with a series of epoxides (entries 4–7, Table I). The results indicate that the stereochemistry of the lithium enolate is preserved during the Li to Al exchange (the most diastereoselective reaction gives a syn:anti ratio of 95:5). The diethylaluminum enolate of *tert*-butyl acetate was also combined with epoxides (entries 1–3, Table I).

In a typical reaction, 34.4 mmol of freshly distilled diisopropylamine was added dropwise to a mixture of 60 mL of dry THF and 34.4 mmol of *n*-BuLi (13.8 mL, 2.5 M in hexane) that was cooled to −78 °C under N_2. After the solution was stirred for 30 min, 34 mmol of *tert*-butyl propionate was added dropwise, and then, after 30 min of stirring and warming the solution to −35 to −45 °C, 34.4 mmol of Et_2AlCl (1 M solution in hexane) was added over 5 min. After 15 min, 17.2 mmol of epoxide was added dropwise. After 5 h at −45 to −35 °C, 20 mL of saturated NH_4Cl was added, and the mixture was added to 50 g of ice in 50 mL of 6 M HCl. The mixture was extracted twice with ether, and the organic layers were washed twice with 5% $NaHCO_3$ and once with saturated aqueous NaCl. The organic extract was dried ($MgSO_4$), concentrated with a rotary evaporator, and distilled with a 5-cm Vigreux column (**4**, bp 72–73 °C at 1.2 mm, 56% distilled yield). The lowest diastereoselectivity observed was 84:16 for propylene oxide and the highest observed was 95:5 for 3,3-dimethyl-1,2-epoxybutane.

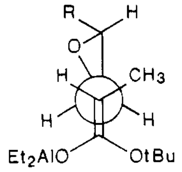
From an examination of Dreiding models, it appears that the syn diastereomer should predominate. To confirm this, hydroxy ester **4** was cyclized to a lactone of known stereochemistry. A solution of 66 mg of *p*-toluenesulfonic acid, 1.20 g of *tert*-butyl-2-methyl-4-hydroxyhexanoate, and 65 mL $CHCl_3$ was refluxed 30 min and then washed with 5% $NaHCO_3$ and 16% NaCl and dried ($MgSO_4$).[9] The distilled lactone, bp 99–100 °C (25 mm), 0.47 g (60%), was identical in all respects with the known *trans*-2,4-dimethyl-γ-butyrolactone,[11] which would result from cyclization of the syn isomer.[3]

Table I. Ester Enolate–Epoxide Reaction Products



entry	R	R′	product no.	yield,[a] %	syn:anti
1	H	Me	**1**	46	
2	H	Et	**2**	52	
3	H	tBu	**3**	49 (GC)	
4	Me	Me	**4**	56 (70 GC)	84:16
5	Me	Et	**5**	43	84:16
6	Me	iPr	**6**	56	88:12
7	Me	tBu	**7**	38	95:5

[a] Distilled yield.



The products of the reactions of the aluminum enolate of *tert*-butyl acetate and (*R*)- and (*S*)-propylene oxide gave enantiomeric ratios 92:8 and 6:94, $[\alpha]^{22}_D = -7.7°$ (*c* 2.5, $CHCl_3$) and $[\alpha]^{22}_D = +6.1°$ (*c* 2.4, $CHCl_3$), respectively, as determined by Pirkle column techniques.[12] The propionate enolate–propylene oxide reactions gave ee's of 98 and 96 (see below) for the major diastereomer of the *R* and *S* epoxide reactions (assuming the commercial epoxides are optically pure).

The high selectivity of these reactions suggests that they should be very useful in the preparation of compounds that are nearly optically pure. For example, the propionate enolate–(*S*)-propylene oxide reaction product gave a stereoisomeric ratio of *SS*:*RR*:*SR*:*RS* (assuming an inversion reaction) of 83:1:16:<1. Removal of the *SR* diastereomer by chromatographic techniques (we were able to separate the diastereomers of a racemic material by silica gel HPLC) would leave almost exclusively one enantiomer.

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Supplementary Material Available: Spectral data of compounds **1**–**7** and HPLC, IR, and NMR spectra of **4** (8 pages). Ordering information is given on any current masthead page.

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