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Reactions of Epoxides with Ester, Ketone and Amide Enolates

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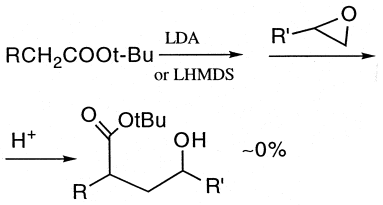
Contents

1. Introduction

Metal enolates are extremely valuable nucleophiles.[1] They are often considered one of the backbones of organic synthesis[2] and are widely used in carbon–carbon bond formation and the elaboration of organic molecules.[2] Lithium enolates are often used because of their versatility, ease of formation and reliability.[2–4]

Lithium ester enolates could conceivably react with epoxides to provide a valuable source of γ-hydroxyesters, which in turn could produce γ-butyrolactones upon treatment with a catalytic quantity of acid.[5,6] (Eq. (1)). This two step approach, in light of the many excellent new methods of making chiral epoxides,[7–18] would be a valuable, general source of important chiral lactones.[19–22]



(1)

Similarly, ketone enolate–epoxide reactions would be a convenient source of γ-hydroxyketones. However, typical lithium enolates of esters and ketones **do not** react directly with epoxides.[23–25] It is probable that not much has been published in these two areas because the traditional enolate methods do not work with epoxides. This review will cover reactions which accomplish the same synthetic objectives as these types of enolate–epoxide reactions, but it will emphasize ester enolate reactions since more progress has been made in this area. Traditional lithium amide enolate–epoxide reactions do work, and they will be covered at the end of the report.

2. Reactions of Aluminum Ester Enolates with Epoxides

Though the lithium enolates of esters do not react with an epoxide,[23–25] Danishefsky and coworkers[26] treated the lithium enolate of *tert*-butylacetate with diethylaluminum chloride, and the resulting aluminum enolate reacted with cyclohexene oxide (**1**) in toluene to give a 68% yield of **3** (Eq. (2)). The resulting hydroxy ester was treated with *p*-toluenesulfonic acid in toluene to yield 85% of the desired lactone.

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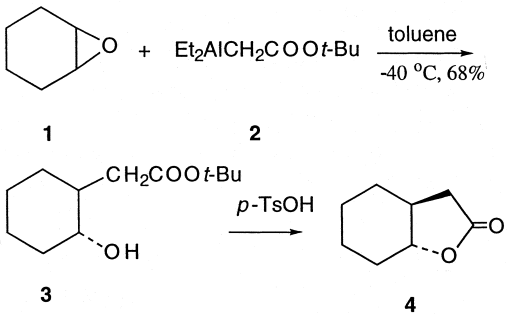
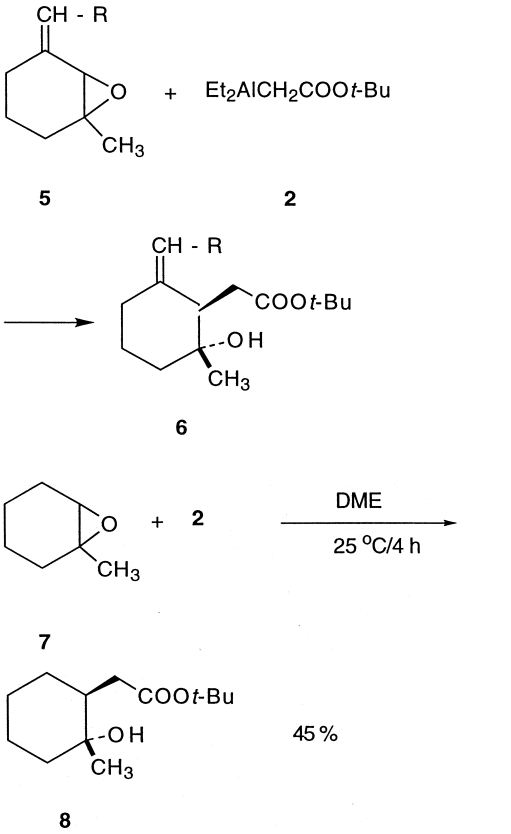
Table 1.

R	Product #	Conditions: solvent/temp/time	Yield (%)
–H	**6a**	THF/−55°C/0.5 h	94
$-CH_2OH$	**6b**	THF/−40°C/1 h	72
$-CH_2OCH_2SCH_3$	**6c**	THF/−55°C/1 h	87
$-CH_2OSi(CH_3)_2t$-Bu	**6d**	THF/−50°C/1 h	82
$-CH_2OCH_2OCH_2CH_2OCH_3$	**6e**	DME/−45°C/1 h	83



1 2 3 4 (2)

Other workers[27] treated substituted analogs of the same epoxide (Eqs. (3) and (4)) with the same enolate. The reaction of the substituted epoxides demonstrated that the method can tolerate several functional groups (Table 1). As shown in Table 1, these reactions can be done in THF or DME with excellent results (72–94% yield).

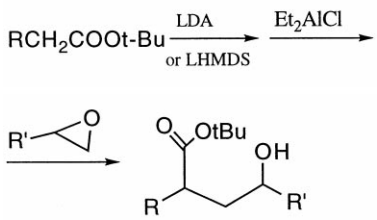


5 2 6 7 8 (3) (4)

Again, no product was obtained with the lithium enolate. Acidic workup (with ~1 M HCl) is necessary to hydrolyze the aluminum salts.

The yields of such aluminum enolate reactions with epoxides are not always high, but it is important to note that alternative methods to obtain the same result usually add steps to the synthetic sequence (see section on Alternate Routes). The efficiency and directness of the method thus attracted our attention. Also, as described below, side products were minimal or completely absent upon workup.

We felt that epoxides derived from acyclic olefins could be combined with enolate **2**. Several epoxides were combined with the enolate[5,28] to give yields similar to those obtained by Danishefsky's group. Most yields were determined after short-path distillation (which gave analytically pure products), and GC yields were generally a few percent higher (Table 2). If the temperature was held below −40°C, Claisen condensation products, generally the only side products, were avoided.[5,28] The *syn* and *anti* isomers resulting from the reactions of the enolate of *tert*-butyl propionate are discussed in the section on Diastereoselectivity.



(5)

Table 2.

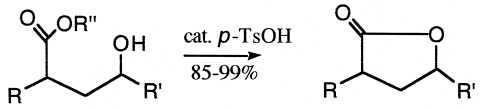
	R	Base	R′	Product #	Yield[a]	*syn:anti*
1	H	LDA	Me	**9**	46	–
2	H	LDA	Et	**10**	52	–
3	H	LDA	*t*-Bu	**11**	49	
4	Me	LDA	Me	**12**	56 (70[b])	84:16
5	Me	LDA	Et	**13**	43	84:16
6	Me	LDA	*i*-Pr	**14**	56	88:12
7	Me	LDA	*t*-Bu	**15**	38	95:5
8	H	LHMDS	Me	**9**	58 (66[b])	–
9	H	LHMDS	Et	**10**	71	–
10	H	LHMDS	*t*-Bu	**11**	54	–
11	Me	LHMDS	Me	**12**	12	56:44
12	Me	LHMDS	Et	**13**	28	62:38

[a] Distilled yields.
[b] GC yields.

3. Formation of Lactones

The closure of the γ-hydroxyester to a lactone by treatment with a catalytic quantity of *p*-toluenesulfonic acid (*p*-TsOH) is a high yield procedure (Eq. (6)). Below, we describe how the procedure occurs in yields as high as 99% yield without

rearrangement or loss of optical purity. This procedure occurs with incredible ease and efficiency, and it can be performed on the unpurified product of the first step (see Table 2, entry 4). The use of benzene, toluene,[26] or chloroform,[5,6,28] as solvent gives excellent yields, but we have favored the use of chloroform.[5,28,29] A solution of the hydroxy-ester with 3–4% *p*-TsOH can be stirred overnight at room temperature, or refluxed for 30 min to 2 h, giving the lactones in excellent yield.



16 (6)

The original methods, though they yielded important bicyclic lactones, did not address diastereoselectivity.[5,26] Novel 1,3 asymmetric induction[30] would result if these reactions could be developed.

4. Diastereoselectivity

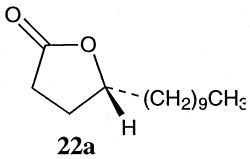
When the enolate of *tert*-butyl propionate (*E:Z* 95:5[31]) was combined with Et_2AlCl, the resulting enolate reacted with four different epoxides to give *syn*:*anti* ratios of 84:16 to 95:5 (entries 4–7, Table 2). The diastereomer predominating was proven by cyclization of **12** to *trans*-2,4-dimethyl-γ-butyrolactone.[28] This was the first demonstration of the diastereoselectivity of the reaction.[32] See the section on Mechanism.

HMPA is known to induce formation of the *Z* enolate,[31] which could react to give the *anti* hydroxy ester. However, we obtained no enolate/epoxide reaction product when this solvent was used.

To illustrate the efficiency of the methodology, the first synthesis of (±)-rubrynolide[33–35] (Scheme 1) was achieved.[36] The *t*-butyl ester of 4-pentenoic acid and the epoxide of 1-dodecen-11-yne were prepared. The aluminum enolate of the pentenoic ester was then made and combined with the epoxide giving a 56% yield of hydroxy ester **19**. The hydroxy ester was then combined with *p*-toluenesulfonic acid and an 85:15 mixture of *trans* and *cis* lactones (95%) resulted. The mixture of isomers was then osmylated to form the reported natural product. The minor isomeric product had the same NMR data as the natural product, and after careful NMR interpretation,[33,36] the natural product was reassigned as the *cis* isomer (**22** rather than **21**).[36]

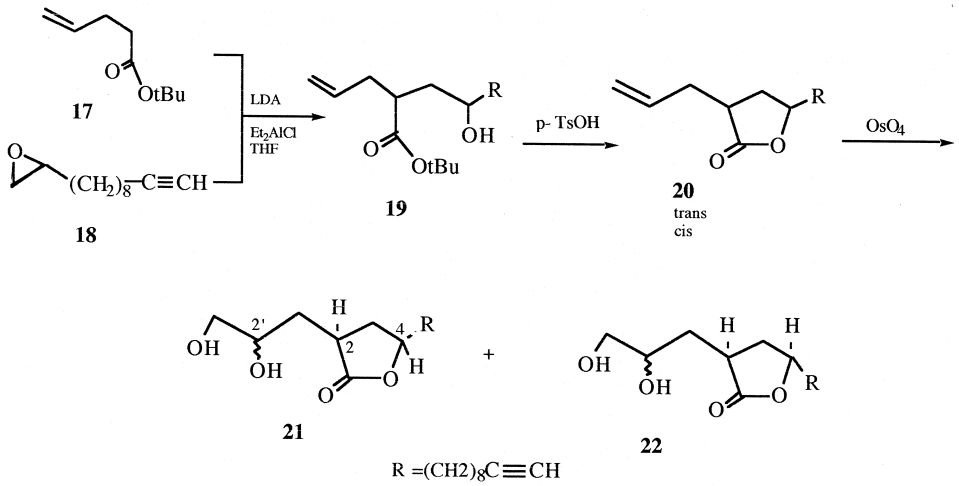
This correction has been corroborated by the subsequent synthesis of the double bond analog, (+)-rubrenolide.[37] The synthesis of this enantiomeric compound by conventional techniques required approximately 23 steps. We did not make the optically active lactone since the method yielded mainly the incorrectly reported *trans* lactone. If (+)-rubrynoloide was the reported *trans* compound, it could have been made using an optically active epoxide[15,16,18] and asymmetric osmylation.[12] These techniques would have given the correct absolute stereochemistry at the 2′ and 4 chiral centers if the relative stereochemistry would have been as assigned initially. (+)-Rubrenolide could have then been made by simple hydrogenation methods.

It is noteworthy that the conventional procedure[37] required lactone **22a**, made in 10 steps.[38] This same compound could easily be made in two steps via the reactions in Eqs. (4) and (5) by using the aluminum enolate of *tert*-butyl acetate and the commercially available (*R*)-1,2-epoxydodecane. These workers did make several important lactones by their methods,[38] and we made three of the same 4-substituted lactones (**22b**–**e**) by our two-step method (see section on Optically Active Products).



22a

It has been mentioned that lactones can be made with these procedures. In an important breakthrough, Smith and



Scheme 1.

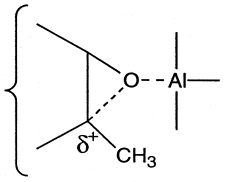
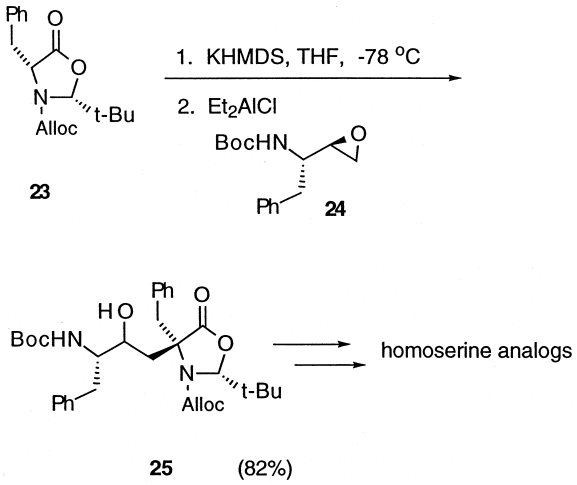


Figure 1.

Hirschmann's group[39] found that oxazolidinones can be made into aluminum enolates (with Et_2AlCl) which react in moderate to good yields with several epoxides (82% in Eq. (7)) in very high diastereoselectivities (≥95% de). These workers found that merely adding other Lewis acids (e.g. $TiCl_4$, BF_3OEt_2, Me_3Al, etc.) to the reaction medium did not give good yields of alkylation products. We observed similar results.[5,28]



(7)

Since the oxazolidinone could behave like a lactone, it is likely that this chemistry could be used to functionalize and elaborate lactones. That is, a lactone should be made into an enolate, treated with Et_2AlCl and then an epoxide in an attempt to alkylate the lactone.

5. Regioselectivity

Eqs. (3)–(5) suggest that the aluminum enolate/epoxide reactions are sterically controlled, despite the presence of the Lewis-acidic aluminum. The Lewis acid could promote electronic control,[40] by activating the carbon that could best support positive charge (the most hindered position, see Fig. 1). No products that resulted from attack at the most hindered position were detected.[5,26,28] Also apparent is the lack of rearrangement products so readily formed in epoxide reactions.[3,40]

The lack of rearrangement and steric control suggested we might be able to make spirolactones by aluminum enolate–spiroepoxide reactions. Spiro γ-lactones have been shown to be an important class of molecules owing to their interesting structures and biological activity. Some natural products that possess this structural element include the antitumor-antibiotic plumericin[41,42] (**26**), the antitumor agent allamandin[43] (**27**), the norsesquiterpenoids napalilactone (**28a**, X=Cl)[44] and pathylactone A (**28b**, X=OH),[45] and the zedoary extract curcumanolide A (**29**)[46–49] and its derivatives. Spiro γ-lactones like **30** and **31** have also been employed as templates for the construction of conformationally constrained diacylglycerol mimics for binding protein kinase C (PKC) (Fig. 2).[50,51]

The results of our spirolactone syntheses[29] are shown in Table 3.

6. Mechanism

Though other enolate reaction mechanisms often involve a cyclic transition state,[31] that is probably not the case for Eqs. (5),[26,28] (7)[39] and similar aluminum enolate reactions. The reaction in Eq. (7) requires 2 equiv. of diethylaluminum chloride per equivalent of epoxide,[39] suggesting that 1 equiv. is required for generation of the enolate, and one aids by complexation with the epoxide oxygen (through the aluminum). In the standard ester enolate method, 2 equiv. of aluminum ester enolate per equivalent of epoxide give the highest yields of reaction product.[26,28] The probable

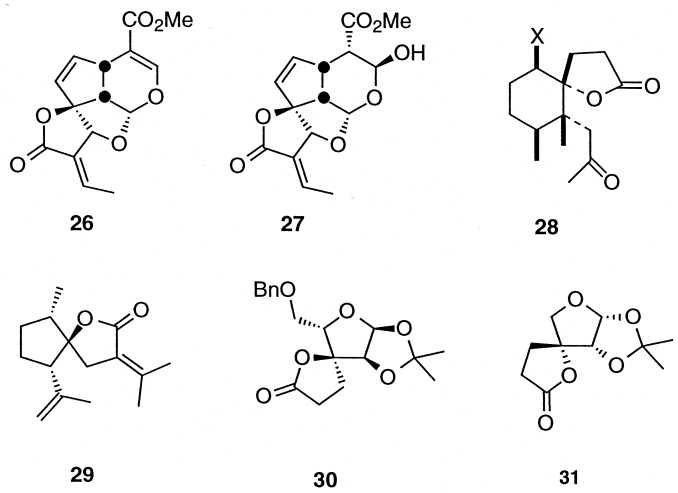
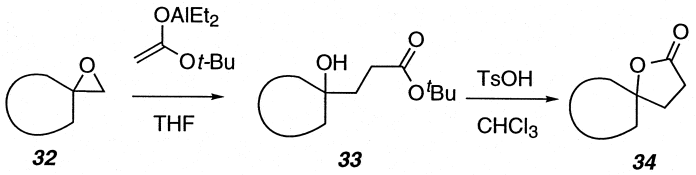


Figure 2.

Table 3.



entry	epoxide	hydroxyester	ester yield (%)	lactone	lactone yield,(%)
1	32a	33a	64	34a	91
2	32b	33b	76	34b	81
3	32c	33c	62	34c	86
4	32d	33d	68[a]	34d	99[b]
5	32e	33e	61[c]	34e	99
6	32f	33f	45[d]	34f	99

[a]The lactone was obtained in 68% yield by direct treatment of the crude ester with *p*-TsOH. Hence the yield of the ester had to be at least 68%. [b]The yield was determined on a small scale reaction. [c]The other diastereomer was obtained in 14% yield. [d]Not optimized.

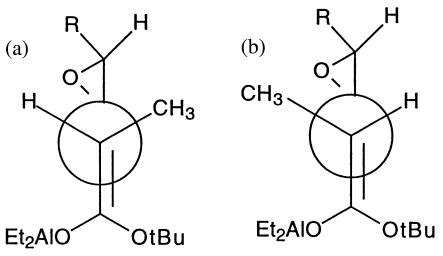


Figure 3.

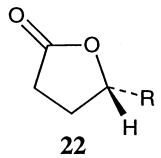
pre-transition state for the S_N2-type reaction leading to the major *syn* diastereomer is depicted in Fig. 3a. The transition state leading to the *anti* isomer (Fig. 3b) would lead to worse steric interactions (e.g. between the R and the methyl group).

7. Optically Active Products

The ready availability of optically active epoxides makes this chemistry highly useful for the synthesis of optically active compounds. We have made three pheromones[28,44]

from commercially available (*R*)-epoxides (available this year for the first time) in high optical purity, and a fourth lactone (**22b**) was made in 98% ee that is used in the synthesis of geodiamolide A[52] and (−)-botryococcene.[53,54] The same chiral lactone was made by an indirect route (see Eq. (15)) that added a desulfurization step[54] to the synthetic pathway.

The pheromone syntheses utilize the chemistry in Eqs. (4) and (5), where R=H and R′=methyl, ethyl, butyl, and octyl groups.[28,55] Compounds **22c**, **22d**, and **22e** are the *Trogoderma* beetle,[28,56] parasitic wasp,[57] and rove beetle pheromones,[58] respectively. The ee% of the lactone product was the same as that of the starting epoxide,[55] indicating no loss in enantiomeric purity from the enolate or *p*-TsOH lactonization reactions.



22

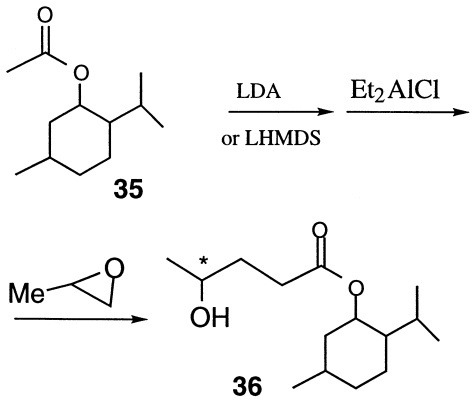
22b, R= -CH_3

22c, R= -CH_2CH_3

22d, R= -$(CH_2)_3CH_3$

22e, R= -$(CH_2)_7CH_3$

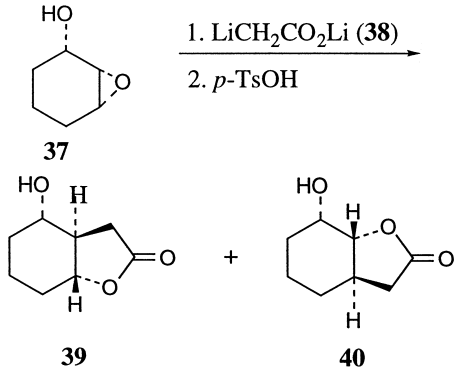
In limited studies, we explored asymmetric induction in reactions using (+)- and (−)-menthol esters (Eq. (8)). The enolate/epoxide reaction stopped at 20% conversion and the ratio of *R*:*S* stereocenters (indicating the kinetic enantioselection) at the newly formed chiral centers was only 43:57 and 57:43, respectively,[28] when the (−)- and (+)-menthol acetates were used. Since the yield was low and the enantioselectivity poor, we did not pursue the reaction further.



(8)

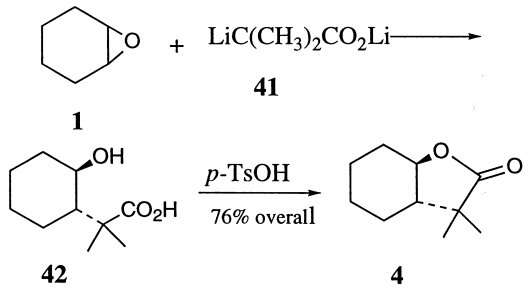
8. Alternate Routes

The reactions of the dianions of carboxylic acids with epoxides represent an alternative to the aluminum enolate chemistry discussed, and this chemistry has been reviewed.[59] The general applicability of the reactions has been questioned,[59] but selected examples of the reactions suggest (Eqs. (9) and (10)) they can be of significant use. The use of large amounts of base and low dianion solubilities seem to be deterrents to the use of the reaction where mild conditions are necessary. For example, 20 equiv. of LDA were added to 10 equiv. of dry acetic acid to generate the dianion **38**. One equivalent of epoxide **37** was then added to this solution to produce a 3:1 mixture of **39** and **40** (66% yield).[60]



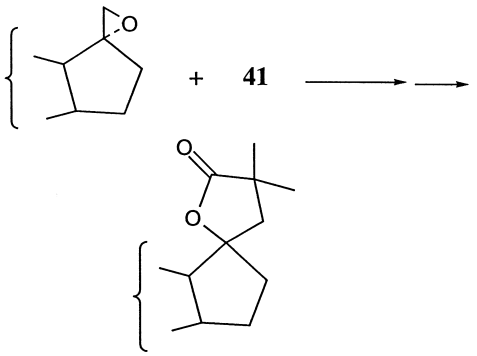
(9)

Creger[61,62] has opened cyclohexene oxide with a dianion (Eq. (10)) and then cyclized the resulting hydroxy acid to a lactone (76% overall yield). He also made several steroidal γ-spirolactones from this chemistry (Eq. (11)).[61]



(10)

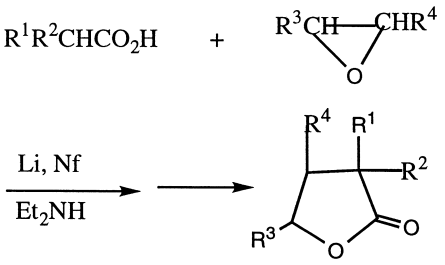
The large number of equivalents of base necessary for this chemistry is probably due to the low solubility of the dianion, particularly in the case of the dianion of acetic acid (Eq. (9)).[60,62] The heterogeneous suspension involved in the reaction can be stirred for a long period of time to maximize yields. Acetic acid is cheap and readily available, so the excess required is not a matter of availability or economic concern. Also advantageous is that, unlike the ester enolate chemistry, the dianion of acetic acid is very stable, even to the boiling point of THF.



(11)

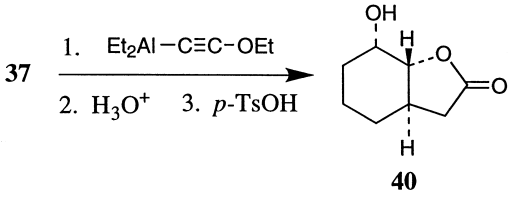
Many hydroxy acids were been made in modest yields

(approximately 25–68%) using Et_2NH and lithium naphthylide. The γ-hydroxyacid products, as they typically do, tended to form lactones upon standing (see Eq. (12)).[63]



(12)

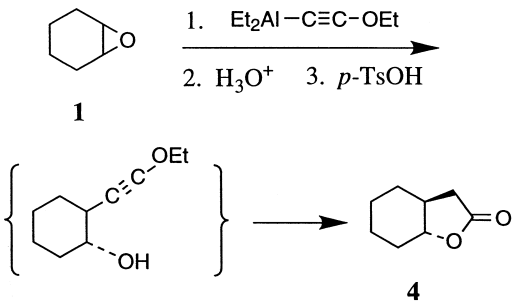
Danishefsky has used the diethylethoxyalkynylalanes[26,60] to open epoxides (lithium acetylides do not work). The products can then be treated with acid and *p*-TsOH to yield the equivalent of the ester enolate/lactonization procedures in 50–60% yield (Eq. (13)). In the case shown, the regioselectivity is opposite to that of the dianion reaction (Eq. (9)).



40

(13)

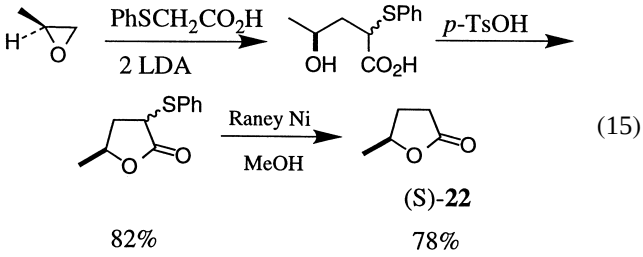
The same alane reagent was used to open cyclohexene oxide,[26] and the overall yield of the lactone was 84%. Eq. (14) shows the intermediate the reaction goes through. Though the synthesis is indirect, it seems like a useful alternative to the ester enolate chemistry discussed.



4

(14)

The lack of lithium enolate/epoxide reactivity led White and coworkers[52–54] to synthesize a lactone by an indirect route. Their work illustrates the use of dianions and of sulfur-containing enolates to effect the epoxide alkylation reaction. They prepared the dianion of (phenylthio)acetic acid and combined it with (*R*)- and (*S*)-propylene oxide. The sulfur-containing enolate did react with the epoxide. The resulting hydroxy-acid was treated with a catalytic quantity of *p*-TsOH and the sulfur was removed by treatment with Raney nickel.



(15)

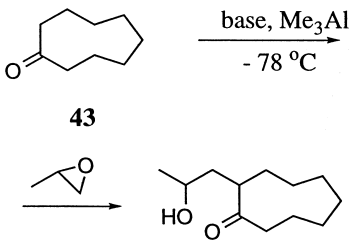
This is an excellent example of how sulfur containing enolates can circumvent the lack of reactivity of lithium enolates with epoxides. The products were essentially enantiomerically pure, so the lactonization and other steps occurred with no loss in enantiomeric purity.[52–54]

9. Ketone Enolate–Epoxide Reactions

Lithium enolates of ketones also do not react directly with epoxides.[23–25] The development of protocols that do result in the reactions of ketone enolates with epoxides began later and are less developed than those of the ester enolate chemistry described above. Most of the developments in this area have come through the efforts of Crotti's group since approximately 1991.[64] His work will be featured below since little or no similar chemistry has been reported.[65]

Upon treatment of the enolates of acetophenone, 3-pentanone, and cyclohexanone with epoxides, we observed no reaction product (e.g. upon treatment of the enolate of 3-pentanone with propylene oxide for several hours at room temperature).[5,28] Attempts at the use of the aluminum enolates (by treatment of lithium enolates of ketones with Et_2AlCl) also did not result in a significant yield of γ-hydroxy ketone.

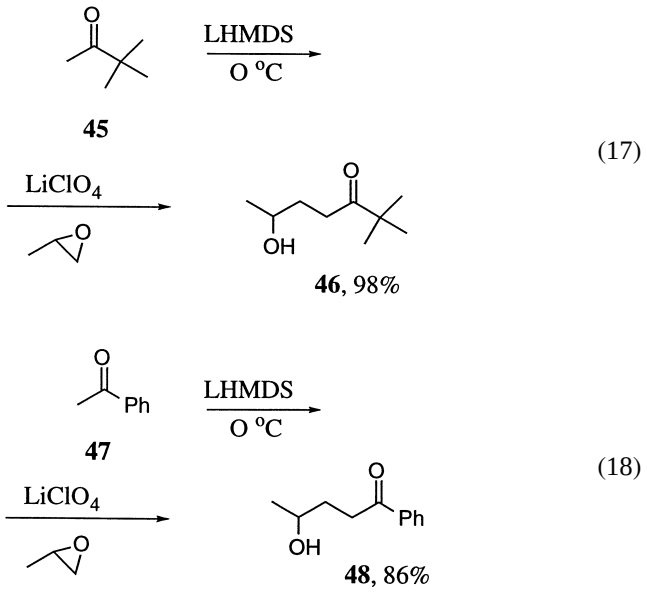
In an isolated report,[66] Schreiber found that a single ketone, cyclononanone, reacted with propylene oxide in the presence of 2.4 equiv. of Me_3Al (Eq. (16)). No further reports came out of this work.



44

(16)

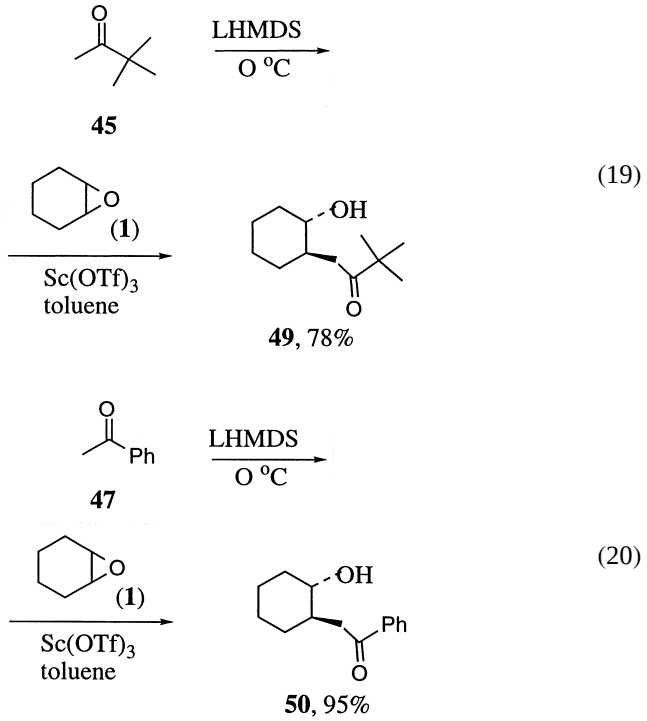
However, the use of $LiClO_4$ in a 1:2.5:1.5 epoxide/enolate/$LiClO_4$ molar ratio gave very good to excellent yields of γ-hydroxy ketones (Eqs. (17) and (18)).[64] Propylene oxide gave 80 and 95% yields of γ-hydroxyketones with the enolates of **45** and **47** after 72 h at 25°C (or 50°C for 24 h). Styrene oxide gave a 95% yield with the enolate of **45**, but 9% of the product mixture resulted from attack at the benzylic position.[64]



(17)

(18)

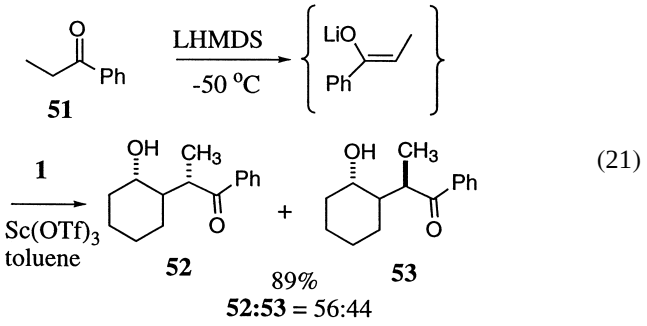
Crotti's group then turned to the use of catalytic quantities of lanthanum triflates to promote the ketone enolate/epoxide reactions.[67] Initially, yttrium triflate[67] was shown to be quite effective, but later, scandium triflate, $Sc(OTf)_3$ at 10 mol%, was shown to be the most efficient catalyst (of the many tested) for this chemistry[68] (Eqs. (19) and (20)). It should be noted that the products can exist as an equilibrium mixture of hydroxyketone and lactol (e.g. an 8:2 mixture; see Eq. (24) for an example).



(19)

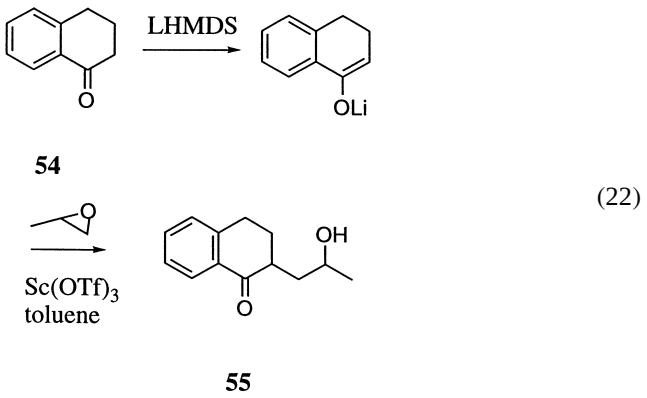
(20)

In addition to testing for reaction efficiencies, Crotti's group tested[68] for diastereoselectivity (Eqs. (21) and (22)). Unfortunately, the diastereoselectivity was not high (Eq. (21), 56:44 or comparable), and the products (particularly the *syn* isomer) tend to equilibrate during the long reaction times that are necessary for high yields.



(21)

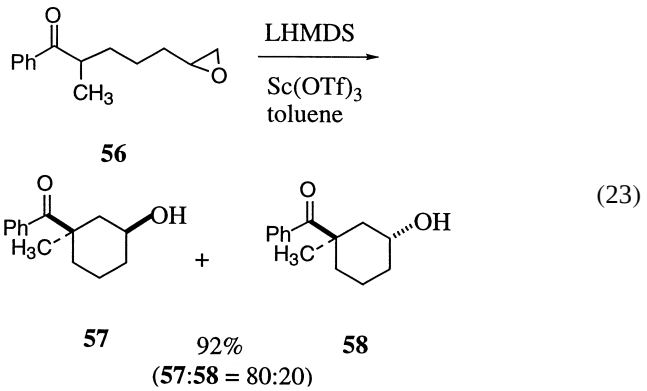
Similar results were obtained with another enolate (Eq. (22)). Though a 90% yield was obtained, a 55:45 ratio of diastereomers was observed.



(22)

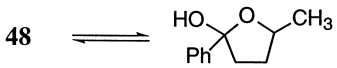
Although the reaction is not diastereoselective, an optically active epoxide has been used successfully in this chemistry. The enolate of acetophenone reacts with (*R*)- and (*S*)-propylene oxide in the presence of $Sc(OTf)_3$ to give a 4:1 mixture of diastereomeric γ-hydroxyketones (98 and 96% ee).[69] The chemistry can thus be used to synthesize optically active compounds. Crotti and coworkers[69] have also developed an enzymatic resolution of these types of compounds.

In more recent work, the same group has reported intramolecular reactions using this chemistry. This example is representative of the study, which included cyclizations observed to form 3-, 5- and 7-membered rings.[70]



(23)

The lactols present in equilibrium with the hydroxyketone products present a promising structural feature. They have the basic structure shown in Eq. (24), and this chemistry has been suggested as a possible way to make polysubstituted tetrahydrofurans,[68] an area of current synthetic interest.[71]

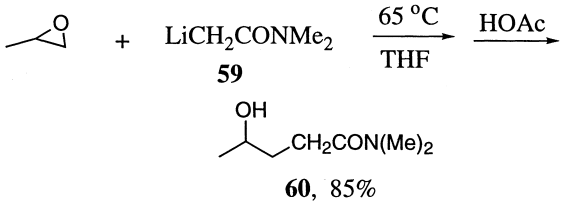


(24)

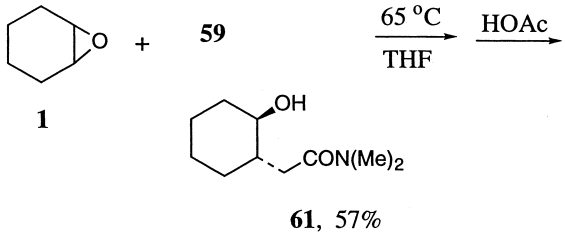
10. Amide Enolate–Epoxide Reactions

One purpose of this review has been to alert the chemical community on how to successfully carry out ester and ketone enolate reactions with epoxides. Unlike the chemistry discussed above, tertiary amides do form lithium enolates that directly react with epoxides,[23,30,72] presumably because of their greater stability (relative to ester enolates) and nucleophilicity.[23] Here, enough comments are made on this straightforward chemistry to allow a chemist to know what can be done with it.[73]

Woodbury and Rathke[74] treated propylene oxide with the lithium enolate of *N*,*N*-dimethylacetamide, and got an 85% yield of the expected hydroxyamide **60** (Eq. (25)). The enolate was generated in THF using LDA and standard methods. The reaction mixture had to be refluxed 2 h to obtain this good yield, and mild workup with 1 M acetic acid in ether was used. Cyclohexene oxide reacted similarly in 57% yield (Eq. (26)). These reactions allow a direct comparison with similar ester enolate reactions.

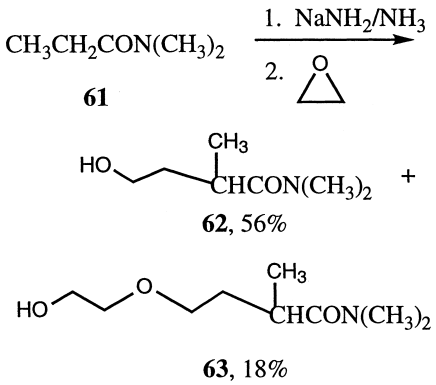


(25)

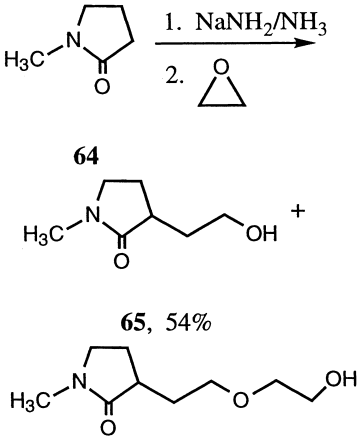


(26)

Even before Woodbury and Rathke's work, other researchers[75] generated tertiary amide enolates in ammonia using $NaNH_2$ and demonstrated eleven examples of enolate–epoxide reactions. The reactions using this protocol were quite general (NH_4Cl workup and extraction with CH_2Cl_2), but the yields were not very high. The examples that show yields of >50% are shown in Eqs. (27) and (28).

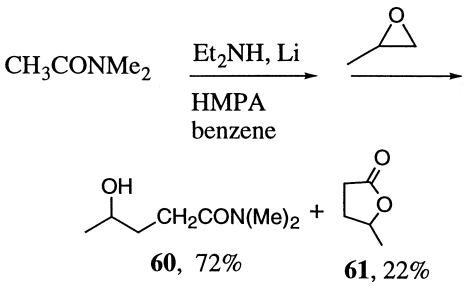


(27)

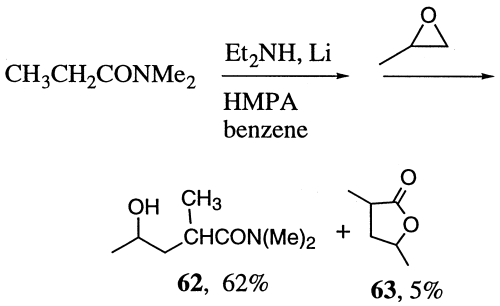


(28)

Normant's group[76] prepared 'activated' lithium dialkylamides using Li, Et_2NH and HMPA in benzene. These amide enolates reacted with epoxides in 20–72% yields. Representative reactions are shown in Eqs. (29) and (30). This group also used standard generation of the enolate by treating the *N*,*N*-dialkylamide with lithium diethylamide, but the yields were slightly lower. Note that when the workup was done under neutral conditions,[77] some lactone product always formed. However, crude hydroxyamide product mixtures (or pure products) could form lactones (easlily isolated in pure form) after a 24 h treatment with 4 M HCl at ambient temperature (typical lactonization yields of 80–90%). This method was described as a good general synthesis of lactones.[76] When other workers used 1 M acetic acid in ether for hydrolysis,[30,74] no lactones were reported in the product mixtures. If pure hydroxyamides are desired, this workup may be preferable.

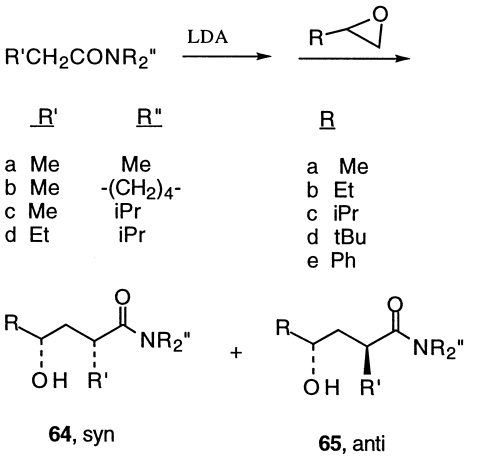


(29)



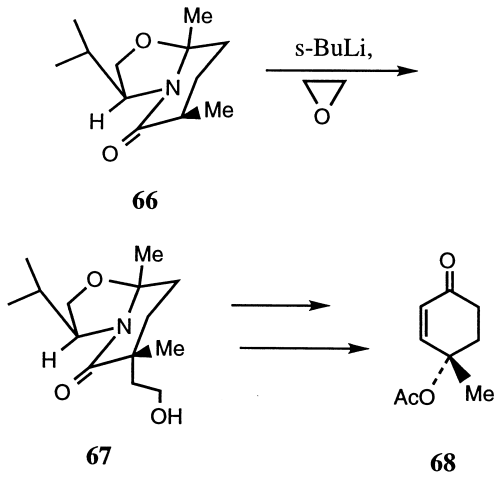
(30)

Sauriol-Lord and Grindley[30] were the first to address the issue of diastereoselectivity in the reactions of epoxides with lithium enolates of *N*,*N*-dialkylamides. They generated the enolates at 0°C using ether or THF as solvent and LDA as the base. Also, the neutralization of the reaction mixture was done using 1 M acetic acid in ether. Most of their table is shown below. Their reactions were more selective in ether than in THF. However, the diastereoselectivity was only high in reactions involving bulky amide and epoxide groups (e.g. entries 9 and 10, Table 4). See Fig. 2 to infer steric reasons for the *syn* selectivity.



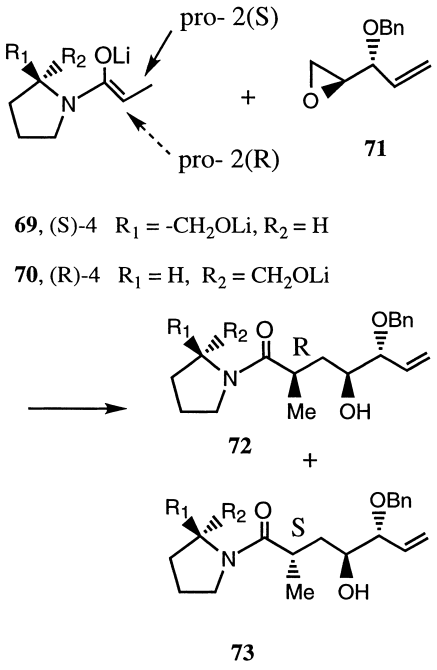
(31)

Though the diastereoselectivity is low, this type of chemistry has been used in asymmetric synthesis. Meyers' group alkylated a bicyclic lactam with ethylene oxide[78] (Eq. (32)), and showed how the products are turned into 4-substituted cyclopentenes and cyclohexenes in high enantiomeric purity. The products of this amide enolate chemistry could be used to make compounds such as (+)-mesembrine.



(32)

Other workers alkylated chiral propionamide enolates with epoxides.[79,80] The facial selectivity of the reactions was of significant interest, and is illustrated in Eq. (33)



(33)

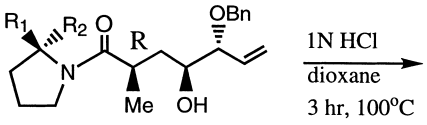
Table 4.

	Amide	Epoxide	Solvent	Temperature (°C)[a]	% Conversion	*syn:anti*
1	a	a	Ether	35[b]	82	51:49
2	b	a	Ether	35[b]	100	55:45
3	c	a	Ether	35	93	65:35
4	c	a	Ether	0	81	74:26
5	c	a	Ether	−23.5[c]	66	77:23
6	c	a	Ether	−78	1–2	>95:5
7	c	a	THF	0	75	63:37
8	c	b	Ether	0	58	79:21
9	c	d	Ether	0	48	90:10
10	c	e	Ether	0	78	90:10
11	d	a	Ether	0	84	78:22

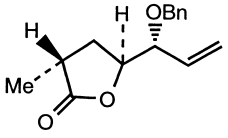
[a] Reaction times 5–6 h.
[b] 2 h.
[c] 24 h reaction time.

The prolinol amide enolates **69** and **70** were prepared by treating the corresponding prolinol amides with LDA.[79] Five equivalents of the enolate with one mole of epoxide **71** gave products as follows. Based on steric effects alone, one would expect pro-2(*R*) attack of **69** on the epoxide to give, after hydrolysis, predominantly **72**. However, the **72:73** ratio was 13:87. When **70** was combined similarly with **71** it reacted more selectively to give almost exclusively **72**. The reason for this selectively is not clearly established, but a possible explanation for this lack of steric control is that of intermolecular chelation control. That is, the epoxide oxygen could complex with the lithioalkoxy group, and that could direct alkylation from the more hindered face of the enolate.

Compounds **72** and **73** can be treated with 1N HCl in dioxane at 100°C for 3 h to give the optically active lactones **74** and **75** (Eqs. (34) and (35)).[79] This work was pursued in connection with the synthesis of the immunosuppressant FK-506.

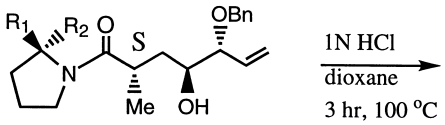


72

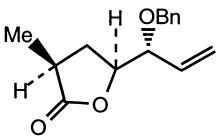


74

(34)



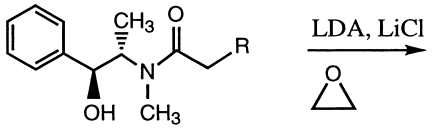
73



75

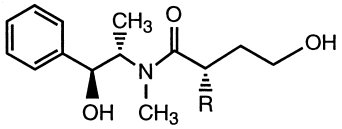
(35)

In extensive studies, Myers and McKinstry[23] investigated the use of pseudoephedrine amide enolates to determine the stereochemistry of their reactions with epoxides. As in the above chemistry, a chiral auxiliary proved very useful in chiral induction. Here the workers generated the enolate of (*S*,*S*)-pseudoephedrine or pseudoephedrine hydrocinnamide (R=CH_3 and CH_2Ph, respectively) with 2.1 equiv. of LDA (at −78°C for 1 h, 0°C for 15 min, and 23°C 5 min) and treated it with 5 equiv. of epoxide in the presence of 6 equiv. of LiCl. Alkylation proceeded in high yields. Eq. (36) shows reactions that give high yields but with low diastereoselectivity.



76, R = CH_3

77, R = CH_2Ph

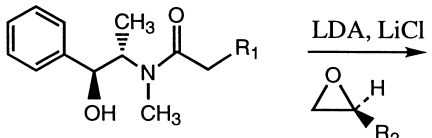


(36)

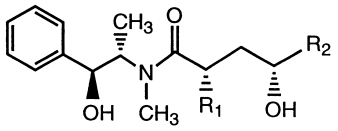
78, R = CH_3 96% (49% de)

79, R = CH_2Ph 96% (59% de)

Other reactions showed both good yields and diastereoselectivities, and also conclusively showed which enantiomeric epoxides were matched and mismatched substrates. Included in this work were optically active epoxides, which showed that the (*S*)-epoxides were the matched ones (see Fig. 4). For reactions involving different (*S*)-epoxides, and several different R groups on the enolate (see **76** and **77**, Eq. (36)), the yields were all over 80%, and the de's were 90 to ≥95%. For the enantiomeric (*R*)-epoxides, the yields (72–86%) and de's (12–73%) leading to the anti isomer were lower. The *syn* isomer is clearly preferred.



80



81

(37)

For complimentary synthetic strategies, it should be noted that alkyl halides (e.g. RI) show the opposite stereochemical preference, and lead to the opposite stereoisomer (see Fig. 4 and references explaining this).[23,81]

The racemic epoxides react with the amide enolates to give complex mixtures of products, and that will not be discussed here. However, isobutylene oxide was alkylated in 84 and 71% yields for R=CH_3 and CH_2Ph (see Eq. (36), enolates of **76** and **77**), and de's were 95 and ≥99%. These reaction products, as well as other products, could be transformed into optically lactones when heated with 0.2 M sulfuric acid

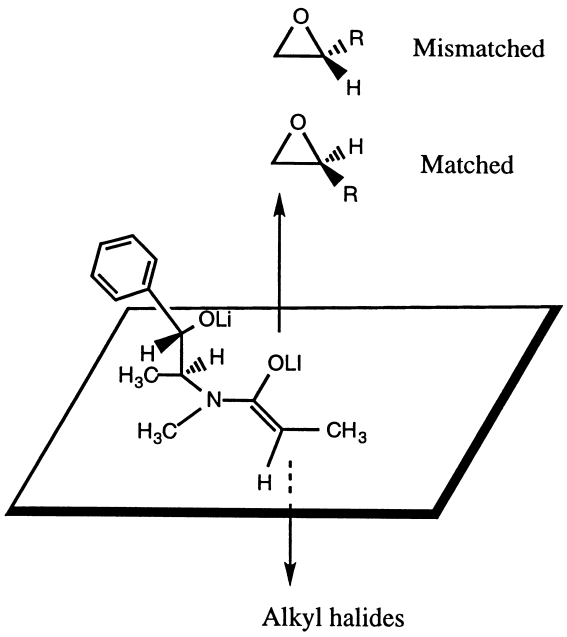
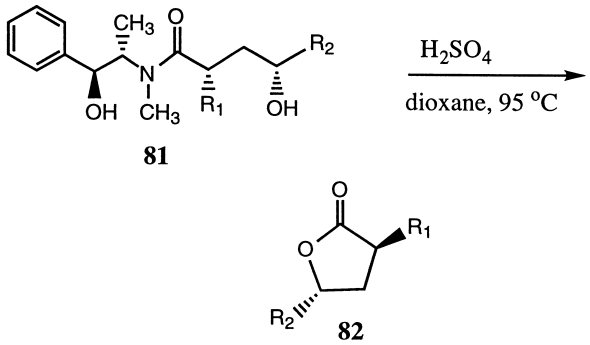


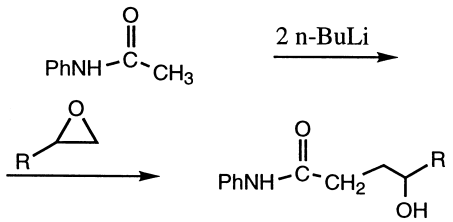
Figure 4.

(Eq. (38)) in dioxane (70–95°C).



81 **82** (38)

The dianions of secondary amides react with epoxides.[82] The dianion of acetanilide can be generated by treatment with 2 equiv. of *n*-BuLi, and when combined with $BF_3{\cdot}OEt_2$, and various epoxides, γ-hydroxyamides are formed (Eq. (39)). The products can be made into lactams by treatment with base in HMPA.



(39)

R = Me (80%)
R = Et (80%)
R = Ph (86%)
R = $(CH_2)CH_3$ (66%)
R = CH_2OCH_3 (81%)

11. Concluding Remarks

The reactions of aluminum ester enolates with epoxides provide a very direct route to γ-hydroxyesters, which can then be cyclized in very high yields (85–99%) into γ-butyrolactones. The importance of such lactones is significant, and it provides adequate justification for development of this chemistry. These reactions occur in a stereoselective enough fashion to be useful in the synthesis of natural products, including single enantiomeric pheromones. The reactions can tolerate a wide variety of functional groups, and generally occur in yields of approximately 65–78%.

The reaction of ketone enolates with epoxides is a surprisingly new area, and high yields have been demonstrated. A promoter such as $LiClO_4$ or $Sc(OTf)_3$ is required to effect the ketone enolate–epoxide reaction. Optically active compounds can be made, but the diastereoselectivity of the reactions needs to be improved. This area shows significant promise, and it may be a route to tetrahydrofurans of significant importance.[68]

Unlike the lithium enolates of simple esters and ketones, the enolates of tertiary amides are nucleophilic enough to react directly with epoxides. The amide enolate–epoxide reactions have been extensively investigated. The yields of such reactions are very high, and they can involve chiral auxiliaries that lead to important optically active compounds.

Note Added in Proof. In work published during the writing of this manuscript, Woerpel and Shaw[83] reported a 92% yield for the reaction in Table 2, entry 6. Their work reflects a higher yield than ours does, and we currently have no explanation as to why that is. The report does not describe an experimental preparation. However, this recent work does add credibility to the synthetic usefulness of the chemistry.

Acknowledgements

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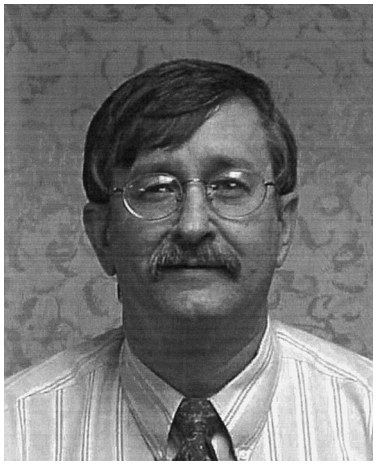
Biographical sketch



Stephen K. Taylor was born in Los Angeles, California. After completing his B.A. in chemistry at Pasadena College (now Point Loma Nazarene University) in 1969, he was attracted to the University of Nevada, Reno, by the presence of R. C. Fuson and a recent R. B. Woodward Ph.D. and postdoc, Charles B. Rose. After completing the requirements for the Ph.D. Degree, he joined Du Pont at the Experimental Station in Wilmington, DE. From 1973 to 1978, he served as a Research Chemist there, and became a Senior Research Chemist in 1978. In 1978, he began teaching and doing research at Olivet Nazarene University, and went to Hope College in 1985, where he is currently Professor of Chemistry. His research interests have been in the areas of epoxide cyclizations, enolate–epoxide alkylations, and more recently biotransformation reactions. This is his 30th publication.