Asymmetric Hydroxylation of Enolates with *N*-Sulfonyloxaziridines

Franklin A. Davis* and Bang-Chi Chen

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

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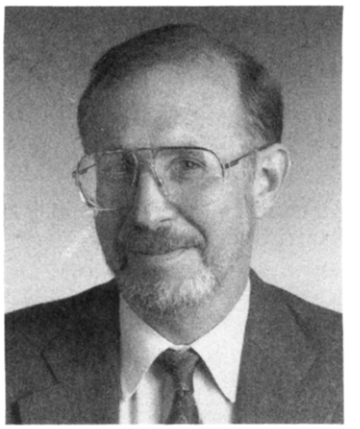
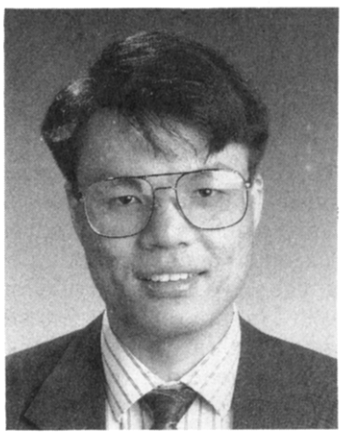
Contents



Franklin A. Davis was born in Des Moines, Iowa. He received his B.S. degree in 1962 from the University of Wisconsin and was granted a Ph.D. degree in 1966 from Syracuse University working under Donald C. Dittmer. After two years with Michael J. S. Dewar as a Welch Postdoctoral Fellow at the University of Texas he joined the faculty at Drexel University in 1968 where he is currently the George S. Sasin Professor of Organic Chemistry. In 1980 he received Drexel University's Research Achievement Award and in 1982 the Philadelphia ACS Section Award. Dr. Davis' research interests lie in the area of asymmetric synthesis, molecular recognition, and new synthetic methods particularly related to enantioselective oxidations. The development of new methods for the regio- and stereoselective fluorination of organic molecules is a recent focus.



Bang-Chi Chen was born in the remote countryside of Zhejiang Province, PRC in 1964. He received his B.Sc. degree in chemistry in 1984 from Hangzhou University where he was an instructor, teaching undergraduate organic chemistry following graduation. During this time period he conducted research with Xian Huang. In 1987 he began graduate study at Drexel University and, in the following year, thesis research under the guidance of Franklin A. Davis. He obtained the M.Sc. degree in 1989 and the Ph.D. in 1991 and, in the same year, joined the Bristol-Meyers Squibb Company in Syracuse New York. He has authored and/or co-authored 26 research and review articles.

I. Introduction

The availability of efficient methods for the construction of enantiopure α-hydroxy carbonyl compounds [RR′C(OH)C(O)Z] is of considerable current interest because this structural array is featured in many biologically relevant molecules. Compounds containing this moiety are also useful auxiliaries[1] and synthons[2] for the asymmetric synthesis of natural products including antitumor agents, antibiotics, pheromones, and sugars. Of particular concern in these structures is the stereochemistry of the hydroxy group attached to the stereogenic carbon because biological activity is often critically dependent upon its orientation. The significance of the α-hydroxy carbonyl unit in bioac-

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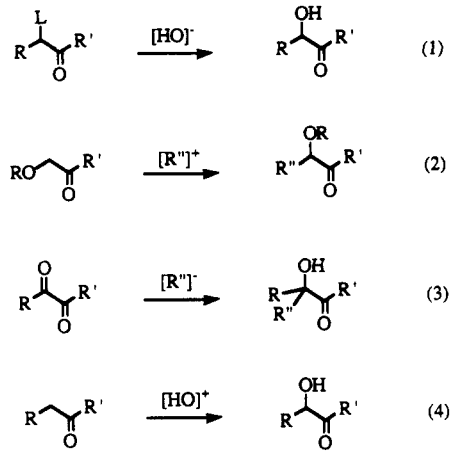
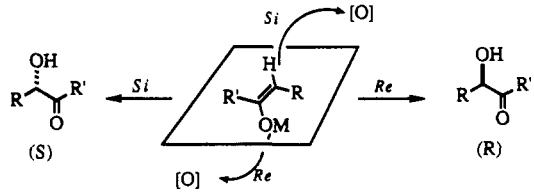
Scheme I. Strategies for the Preparation of α-Hydroxy Carbonyl Compounds



Scheme II. Asymmetric Oxidation of Enolates with *N*-Sulfonyloxaziridines

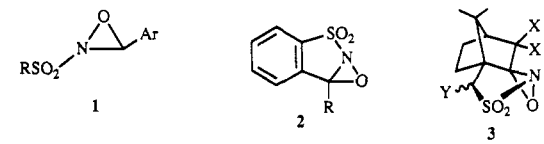


tive compounds and its remarkable versatility as a chiral synthon and auxiliary has stimulated the development of many methods for its synthesis. These methods differ mainly in the substrates used (i.e. the oxidation state of the carbon atom adjacent to the carbonyl group) and can be categorized as nonoxidative (eqs 1–3) and oxidative (eq 4) procedures (Scheme I).

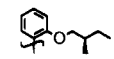
The classical method for the preparation of optically active α-hydroxy carbonyl compounds involves a substitution reaction using optically active α-amino acids (L = NH_2)[3] and α-halo amides (L = Cl, Br)[4] as starting materials (eq 1). Homologation is another approach in which chiral auxiliaries and stereodirecting groups, incorporated into the substrate, are used to induce diastereoselectivity (eq 2).[5] Addition of hydride or a carbanion to α-dicarbonyl compounds (or their monoketal derivatives) has also been used to prepare chiral α-hydroxy carbonyl compounds (eq 3). Either chiral reducing reagents,[6] chiral reducing catalysts,[7] chiral organometallic reagents,[8] or chiral auxiliaries[9] have been employed to induce stereoselectivity. Chiral additives have also been used in some of these transformations.[10] Generally these nonoxidative procedures are limited to the synthesis of acyclic derivatives.

Two oxidative methods have been developed for the synthesis of α-hydroxy carbonyl compounds. One, known as the Rubottom reaction, requires the preformation of a silyl enol ether from the carbonyl compound. The silyl enol ether is then oxidized with reagents such as *m*-chloroperbenzoic acid (*m*-CPBA)[11] or *N*-sulfonyloxaziridines.[12] The past several years have seen the emergence of the second method, the direct oxidation of enolates, as the most widely used method for the stereoselective synthesis of the α-hydroxy carbonyl array (Scheme II). This protocol affords the target functionality directly and is effective for both acyclic and cyclic substrates. The great diversity of metal enolate types makes their oxidation potentially the most versatile method for the preparation of this structural array. Furthermore both enantiomeric forms of α-hydroxy carbonyl compounds are available by use of the antipodal oxidizing reagents. By using aprotic oxidants such as dioxygen,[13] dibenzyl peroxydicarbonate,[14] MoOPH,[15,16] or MoOPD[17] to effect the oxidation product, diastereoselectivity is induced by stereodirecting groups or chiral auxiliaries in the enolate.

In 1984, Davis and co-workers[18] introduced racemic *trans*-(±)-2-(phenylsulfonyl)-3-phenyloxaziridine (**1a**)[19] for the direct hydroxylation of enolates. The availability of enantiopure *N*-sulfonyloxaziridines such as **1d**,[20] **1e**,[20] **2c**,[21] **2d**,[21] and **3**[22–26] for the asymmetric hydroxylation of enolates makes possible control of stereoselectivity by the reagent. This article is intended to summarize progress in the asymmetric hydroxylation of enolates using *N*-sulfonyloxaziridines, with particular emphasis on their applications in natural product synthesis. Both diastereoselective and enantioselective hydroxylations of enolates by these reagents will be covered. Some aspects of this topic have been reviewed elsewhere.[27–33]



[O]	R	Ar
1a	Ph	Ph
1b	*p*-MePh	Ph
1c	*p*-MePh	*o*-MePh
1d		2-Cl-5-O_2NPh
1e		2-Cl-5-O_2NPh

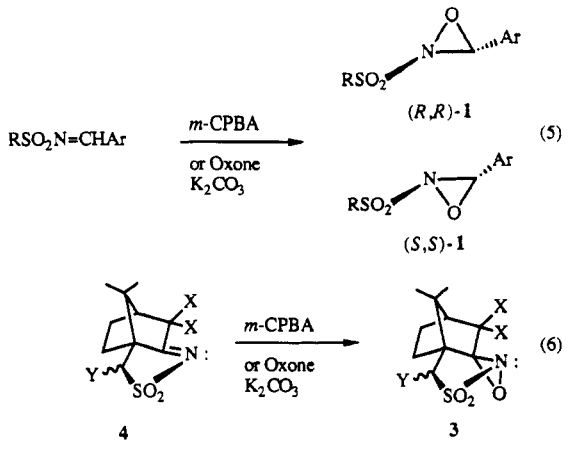
[O]	R
2a	Me
2b	Ph
2c	
2d	

[O]	X	Y
3a	H	H
3b	Cl	H
3c	MeO	H
3d	H	Bn
3e	H	*p*-MeOBn
3f	H	*p*-CF_3Bn

II. Reagents

N-Sulfonyloxaziridines are prepared by the biphasic basic oxidation of the corresponding sulfonimine with *m*-CPBA or Oxone.[19] Oxidation of acyclic chiral sulfonimines affords mixtures of oxaziridine diastereoisomers **1**, requiring separation by crystallization (eq 5).[20] Similar results are observed on oxidation of the sulfonimines corresponding to **2** which limits their production on a large scale.[21] In contrast the (camphorsulfonyl)oxaziridine derivatives **3** [tetrahydro-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide] are readily available on multigram and kilogram scales because the endo face of the C–N double bond in **4** is blocked, affording on oxidation a single oxaziridine isomer (eq 6).[22] (Camphorylsulfonyl)oxaziridine (**3a**) and (8,8-dichlorocamphorsulfonyl)oxaziridine (**3b**) [8,8-dichlorotetrahydro-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide] are commercially available from Aldrich Chemical Co. and Fluka, respectively.

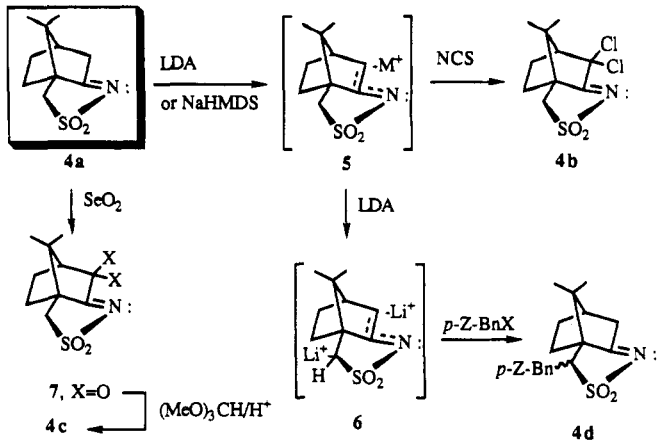
Sulfonimines relating to oxaziridines **1** and **2** are prepared by condensing sulfonamides with aromatic aldehydes[19] and by reacting lithium reagents with saccharin, respectively.[21] The (–)-(camphorsulfonyl)-



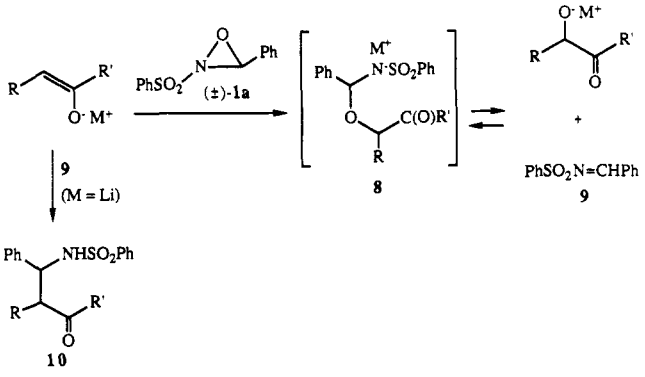
a) X=Y=H, b) X=Cl, Y=H, c) X=OMe, Y=H d) X=H, Y=*p*-Z-Bn

imine **4a** is the common intermediate for the preparation of the (camphorsulfonyl)imine derivatives **4** (Scheme III) and is prepared in 90% overall yield from (1*S*)-(+)-10-camphorsulfonic acid.[22] The (7,7-dichlorocamphorsulfonyl)imine **4b** arises via halogenation of azaenolate **5**.[23] Carbon electrophiles generally react with **5** at the azaenolate nitrogen atom to give enamines which are hydrolytically unstable.[25] However, dianion **6** undergoes smooth monoalkylation α to the sulfonyl moiety to give 1:1 mixtures of *exo*- and *endo*-sulfonimines **4d**.[25,26] With selenium dioxide **4a** gives the (−)-(3-oxocamphorsulfonyl)imine **7** which is transformed to the (7,7-dimethoxycamphorsulfonyl)imine **4c** in 70% overall yield.[24] The antipodal reagents are available starting from (1*R*)-(−)-10-camphorsulfonic acid.

Scheme III. Synthesis of the (Camphorsulfonyl)-imine Derivatives



Scheme IV. General Mechanism for Enolate Oxidation with *N*-Sulfonyloxaziridine



III. Mechanism of Oxygen Transfer

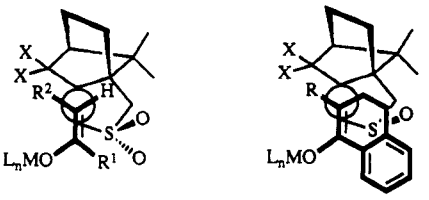
Theoretical[34,35] and experimental[36] studies have suggested an S_N2 type mechanism for the transfer of oxygen from *N*-sulfonyloxaziridines to nucleophiles. Although the early part of the reaction coordinate is dominated by the four-electron repulsion of the nucleophile and the lone pair on oxygen, the "electrophilic" nature of oxaziridines has been attributed to the presence of a low-lying empty Walsh orbitals (LUMO) that rapidly decreases in energy during the C–O and N–O bond elongation induced by the attacking nucleophile.[34,35] Theoretical studies by Bach and co-workers failed to detect any stereoelectronic influences that might favor a planar or spiro transition-state orientation for the oxidation of sulfides to sulfoxides[35] or for the epoxidation of alkenes[34] by oxaziridines. It was concluded that the molecular recognition is steric in origin, dictated by the substituents on the oxaziridine nitrogen and carbon atoms. Support for this hypothesis has been found experimentally.[20,37]

For the hydroxylation of enolates by an oxaziridine, the HOMO of an enolate anion is considerably higher than that of the neutral reactants such as sulfides.[38] Consequently, the mixing of this orbital with both filled and empty orbitals of the oxygen will be facilitated, resulting in a lower activation barrier as evidenced by the fact that enolate oxidations are much faster than sulfide oxidations with oxaziridines; i.e. the former generally takes place at −78 to −40 °C.

An S_N2 type mechanism has been proposed by Davis et al. for the hydroxylation of enolate anions by oxaziridines (Scheme IV).[38] The enolate anion attacks at the oxaziridine oxygen atom to give hemiaminal intermediate **8** which fragments to the sulfonimine **9** and alkoxide. Although there is no direct evidence implicating **8** in the oxidation of enolates by oxaziridines such as **3a**, such evidence exists for the oxidation of enolates (as well as carbanions, RM) by 2-(phenylsulfonyl)-3-phenyloxaziridine (**1a**).[38,39] Oxidation of lithium enolates by **1a** gives, in addition to the α-hydroxy carbonyl compound, the imino–aldol product **10** resulting from addition of the enolate to the sulfonimine **9**.[38-41] Sodium enolates do not give **10**, implying that **8** has a relatively long lifetime. On the other hand, when the counterion is lithium, **8** is short-lived and rapidly collapses to **9** which then gives **10**. Recent theoretical studies[42] suggest, however, that hemiaminal formation occurs in an equilibrium step after the transition state and finds support in the fact that imino–aldol products are not detected for enolate oxidations using the (camphorsulfonyl)oxaziridine derivatives **3**.[38]

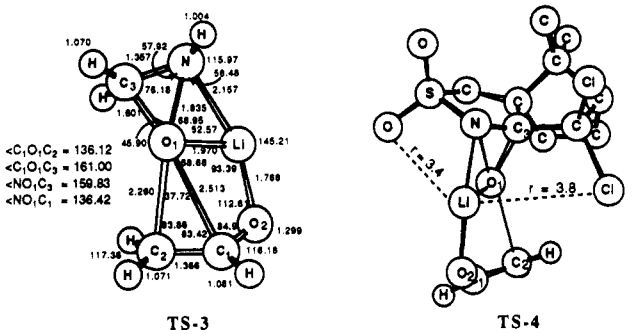
IV. Transition-State Structures

Molecular recognition for the asymmetric hydroxylation of acyclic ketone (propiophenone, deoxybenzoin) and cyclic enolates (tetralones, chromones) by (camphorsulfonyl)oxaziridine derivatives **3** has been interpreted in terms of "open" or "nonchelated" transition-state structures TS-1 and TS-2, respectively (Figure 1).[38] On the basis of the structure–reactivity trends it was argued that the primary transition-state control element is steric in origin, as observed for other enan-



TS-1 TS-2

Figure 1. Proposed transition-state models for the enantioselective hydroxylation of prochiral enolates with (camphorsulfonyl)oxaziridines **3**.



TS-3 TS-4

Figure 2. Geometries for the oxygen transfer from an oxaziridine to the lithium enolate of acetaldehyde.

tioselective oxidations by these reagents. It was assumed that regardless of the actual solution structure of the enolate the enolate–oxygen metal aggregate was the sterically most demanding region in the vicinity of the enolate C–C bond. While these "working models" proved useful in rationalizing the molecular recognition in a number of examples (vide infra) the influence of the reaction parameters (counterion, solvent, cosolvents) on the stereoselectivities was often unpredictable.[38] On the other hand recent studies using oxaziridines **3b** and **3c**, bearing Cl and OMe groups near the reactive side, suggest the possibility of transition-state stabilization via chelation of the metal enolate with these substituents; i.e. a "closed transition state".[23,24]

Molecular orbital calculations, by Bach and coworkers, at the HF/6-31+G*//HF/4-31+G level revealed that oxidation of the monomeric lithium enolate of acetaldehyde proceeds by S_N2 attack of the β-carbon on the enolate along the O–N bond of the parent oxaziridine.[42] In this transition state, TS-3 (Figure 2), the lithium cation is coordinated not only to the enolate oxygen atom, but to the oxaziridine oxygen and nitrogen atoms as well. A more realistic view of the actual bonding interactions was estimated by appending the ab initio geometry of TS-3 to the X-ray geometry of **3b**, giving TS-4. In this idealized geometry the Li–X and Li–sulfonyl oxygen bond distances are too long to provide effective transition-state stabilization via chelation. It was argued however, that twisting about the O_1–C_2 in TS-4 could bring the lithium cation sufficiently close to the sulfonyl oxygen or the Cl substituent to result in significant transition-state stabilization.

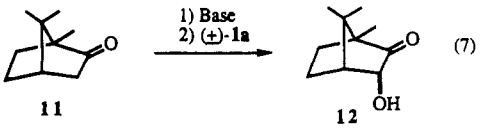
V. Asymmetric Hydroxylation of Enolates

A. Substrate-Induced Hydroxylations

For substrate-induced hydroxylations diastereoselectivity is controlled by the presence of a covalently bound chiral subunit that is retained in the target molecule.

1. Ketones

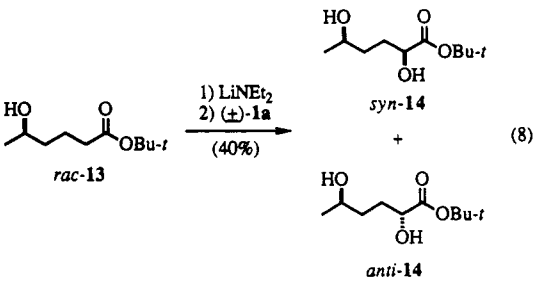
Oxidation of the potassium enolate of camphor (11) with (±)-2-(phenylsulfonyl)-3-phenyloxaziridine (**1a**) afforded the α-hydroxy ketone **12** in 85% yield (eq 7).[18] Lower yields were observed with the lithium enolate due to the imino–aldol-type side reaction. The exclusive formation of the endo product resulted from attack of the *N*-sulfonyloxaziridine at the sterically least hindered face of the enolate and is a general phenomena for these reagents.[27,29]



(7)

2. Esters

Diastereoselective 1,4-chiral induction was explored by Narasaka and co-workers in the hydroxylation of enolates derived from racemic *tert*-butyl δ-hydroxy carboxylates with oxaziridine types 1 and 2.[43] Hydroxylation of the lithium enolate of **13** with (±)-**1a** was immediate at −78 °C giving syn/anti mixtures of **14** in 40% yield and in a ratio of 92/8 (eq 8). Approach of

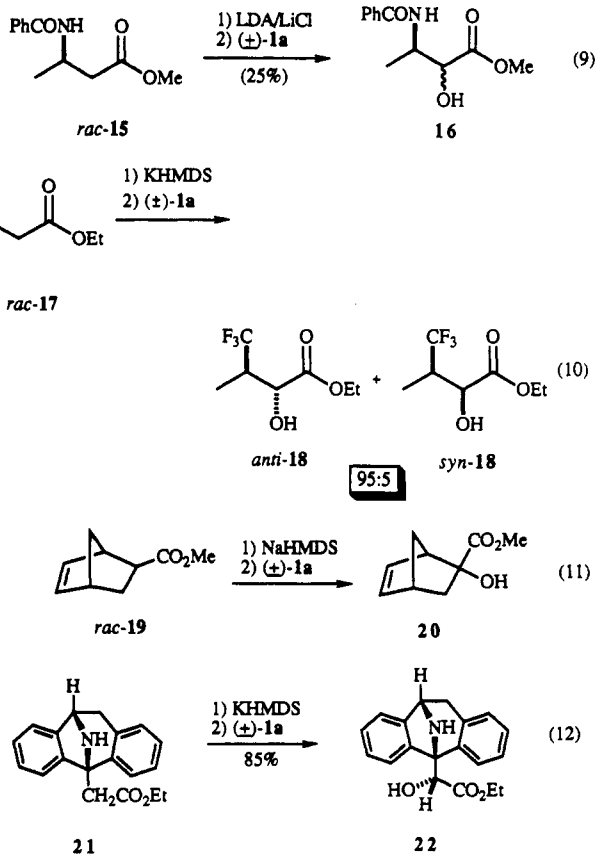


(8)

the oxidant from the sterically least encumbered face of the intramolecularly chelated enolate affords the *syn*-diol **-14** as the major product. Use of the bulkier benzisothiazole oxaziridine **2b** improved the yield to 70% presumably by inhibiting the imino–aldol side reaction product **10**. Moreover, enolate formation at −100 °C in the presence of lithium trifluoromethanesulfonate resulted in better yields and higher diastereoselectivity (Table I).

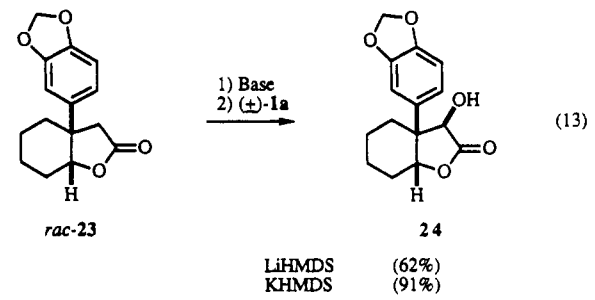
A mixture of diastereomers **16** was obtained when the lithium enolate of **15** was allowed to react with oxaziridine (±)-**1a** in the presence of LiCl (eq 9).[44] A 95:5 diastereomeric mixture of α-hydroxy esters *anti*/*syn*-**18** was produced on oxidation of the potassium enolate of ethyl (±)-3-methyl-4,4,4-trifluorobutyrate (**17**) with (±)-**1a** (eq 10).[45] On the other hand, Roush et al. reported that α-hydroxylation of the sodium enolate of methyl norbornene-4-carboxylate (**19**) with (±)-**1a** afforded the endo diastereomer **20** exclusively (eq 11).[46]

A single diastereomeric hydroxy ester, **22**, was obtained on oxidation of the potassium enolate derived from ester **21** with (±)-**1a** (eq 12).[47]



3. Lactones

The lithium enolate of lactone **23** on oxidation with oxaziridine (±)-**1a** affords α-hydroxy lactone **24** in 62% yield as the only product (eq 13). When KHMDS is used to generate the enolate the isolated yield of **24** improves to 91% (eq 13). This lactone is presumed to have the cis stereochemistry on the basis of the fact that *N*-sulfonyloxaziridines approach the enolate from the sterically least hindered direction.[18] Hydroxylation of **23** with MoOPH gives **24** in much lower yield (ca. 15%) and as a mixture of diastereoisomers.



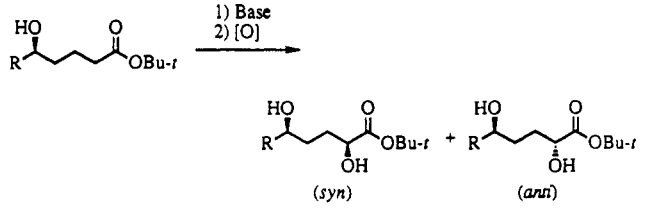
B. Auxiliary-Induced Hydroxylations

Diastereoselectivity for auxiliary-induced hydroxylations is under the control of a covalently bonded chiral auxiliary that is removed after the stereoinduction step.

1. Ketones

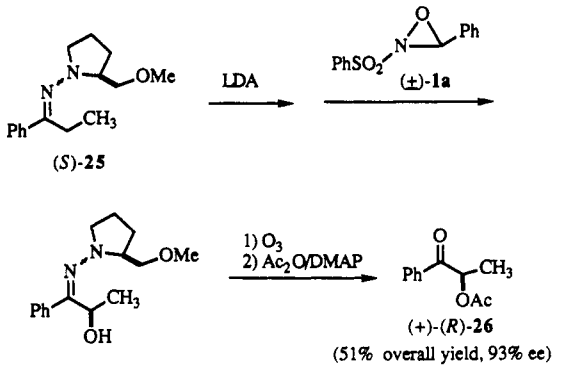
Enders and Bhushan described the preparation of α-acetoxy ketones of high enantiomeric purity and in good overall yield by hydroxylation of the azaenolates, derived from chiral SAMP hydrazones ((*S*)-(−)-amino-2-(methoxymethyl)pyrrolidine hydrazone) with (±)-**1a**

Table I. Diastereoselective Hydroxylation of the Lithium Enolates of δ-Hydroxy Esters with *N*-Sulfonyloxaziridines (±)-1 and (±)-2[43]



R	base	T (°C)	oxaziridine	syn/anti	% yield
Me	$LiNEt_2$	−100 to −78	(±)-**1a**	92:8	40
	LDA	−78	(±)-**1c**	89:11	48
	$LiNEt_2$	−78	(±)-**2a**	88:12	34
	$LiNEt_2$	−100 to −78	(±)-**2b**	90:10	70
	$LiNEt_2$/LiOTf	−100	(±)-**2b**	92:8	83
n-Bu	$LiNEt_2$/LiOTf	−100	(±)-**2b**	92:8	82

Scheme V. Diastereoselective Hydroxylation of Chiral Propiophenone Hydrazone Azaenolates with 2-(Phenylsulfonyl)-3-phenyloxaziridine



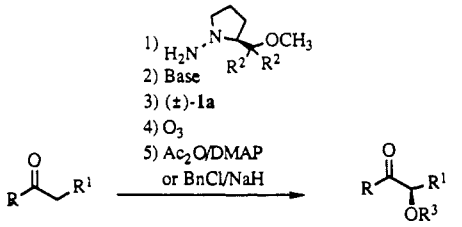
as the key step.[48] The chiral auxiliary can be removed, without racemization, by ozonolysis of the α-hydroxy hydrazone at −78 °C affording the α-hydroxy ketone which was isolated as the acetate. This protocol was used to prepare (+)-(*R*)-2-acetoxypropiophenone (**26**) in 51% overall yield and in 93% ee from (*S*)-**25** (Scheme V).

Additional examples of the enantioselectivity synthesis of acetoxy ketones are given in Table II. In general, the base LDA was superior to *t*-BuLi giving better overall chemical yields. As might be anticipated the hydrazine auxiliary has a large effect on the hydroxylation stereoselectivity. For example, with the propiophenone and deoxybenzoin systems higher stereoselectivities were observed with the SAMP (R^2 = H) chiral auxiliary. Whereas with 1,3-diphenylacetone a bulkier chiral auxiliary (R^2 = Ph) gave better results (Table II).

2. Aldehydes

The direct hydroxylation of enolates obtained from aldehydes has apparently not been reported, due perhaps to facile aldol reactions that can occur during formation of the enolate. However, protected α-hydroxy aldehydes in high enantiomeric purity can be prepared in a manner similar to the synthesis of α-hydroxy ketones (Scheme V). Thus hydroxylation of metalated aldehyde chiral hydrazones with (±)-**1a** followed by trapping with benzyl chloride gives α-benzyloxy aldehydes in ≥96% ee following removal of the

Table II. Diastereoselective Hydroxylation of Chiral Lithium Azaenolates of Ketone and Aldehyde Hydrazones Using (±)-2-(Phenylsulfonyl)-3-phenyloxaziridine (1a)[48]



R	R^1	R^2	R^3	base	% yield[a]	% ee	config
Ph	Me	H	Ac	LDA	51 (60)	93	(*R*)
Ph	Me	Me	Ac	*t*-BuLi	51 (62)	85	(*R*)
Ph	Me	Me	Ac	LDA	73 (86)	88	(*R*)
Ph	Ph	H	Ac	*t*-BuLi	54 (62)	≥96	(*R*)
Ph	Ph	H	Ac	LDA	74 (82)	≥96	(*S*)[b]
Bn	Ph	H	Ac	*t*-BuLi	48 (52)	36	(*R*)
Bn	Ph	Ph	Ac	LDA	62 (75)	89	(*R*)
H	n-C_6H_{13}	H	Bn	LDA	63 (82)	56	(*R*)
H	n-C_6H_{13}	Me	Bn	LDA	44 (85)	≥96	(*S*)
H	n-C_6H_{13}	Et	Bn	LDA	55 (80)	≥96	(*S*)
H	Bn	Et	Bn	LDA	66 (83)	≥96	(*S*)
H	n-C_4H_9	Et	Bn	LDA	53 (70)	≥96	(*S*)

[a] Overall yield of the process; in parentheses, yield of hydroxylation step. [b] RAMP was used as chiral auxiliary.

chiral auxiliary (Table II).[48] The absolute configuration of the final products are in agreement with a metallo retentive mechanism, postulated for the electrophilic substitutions of the SAMP/RAMP hydrazones.[49] However, unpredictable results were noted in the aldehyde hydroxylations when SAMP (R^2 = H) was changed to a more hindered auxiliary (R^2 = Me, Et) (Table II).

3. Esters

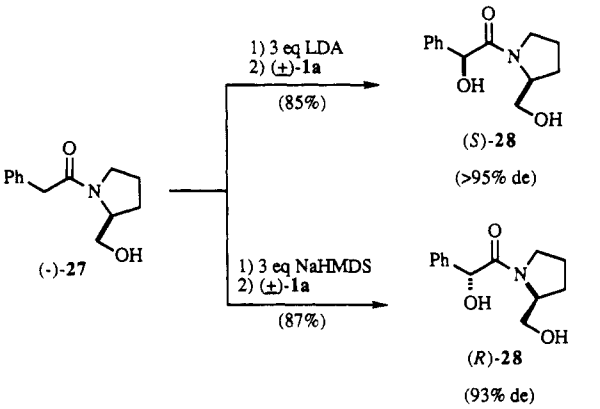
The only report of an auxiliary-induced diastereoselective hydroxylation of ester enolates with (±)-1a was by Gamboni and Tamm.[50] Hydroxylation of the nonracemic enolate of 3-phenylpropionate using the alcohol derived from (+)-camphor as the chiral auxiliary and lithium isopropylcyclohexylamide (LICA) as base afforded the corresponding α-hydroxy ester in a (*R*)/(*S*) ratio of approximately 89:11. A side reaction, which could be the imino–aldol type reaction of the sulfonimine with the ester enolate, prevented isolation of the product. Use of other bases such as KHMDS avoided the side reaction, but no diastereoselection was observed at −78 °C (*R*)/(*S*) ratio (45:55).

4. Amides

In 1985, Davis and Vishwakarma reported the diastereoselective hydroxylation of chiral amide enolate (−)-27 with *N*-sulfonyloxaziridine (±)-1a (Table III).[51] High yields (93–96%) and excellent diastereoselectivities (93–95% de) for the α-hydroxy amides were observed when (+)-(*S*)-2-pyrrolidinemethanol was used as the chiral auxiliary. The pyrrolidinemethanol auxiliary was readily removed by heating with 2 M H_2SO_4 to give mandelic acid without racemization. The stereoselectivity proved to be counterion dependent with the lithium enolate affording (*S*)-28 (>95% de), while the sodium enolate gave (*R*)-28 (93% de) (Scheme VI).[51]

Use of (+)-(*S*)-2-(methoxymethyl)pyrrolidine as the

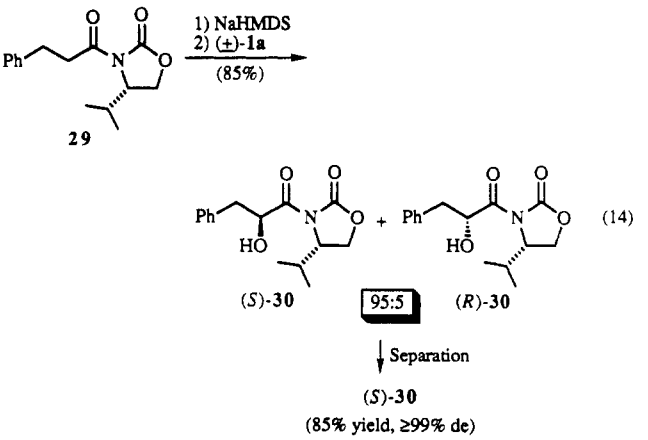
Scheme VI. Diastereoselective Hydroxylation of Chiral Amide Enolates with 2-(Phenylsulfonyl)-3-phenyloxaziridine



auxiliary **27** (OH=OMe) gives quite different results. Not only are the de's lower, but the configuration of the α-hydroxy amide product is now solvent dependent. In the absence of HMPA or at low HMPA concentrations the (*R*) product is preferentially formed, whereas high levels of HMPA favor the (*S*) product (Table III).[51] These results were thought to be due to the disruption of the intramolecular chelation in the enolate system caused by the polar HMPA solvent.

5. Carboximides

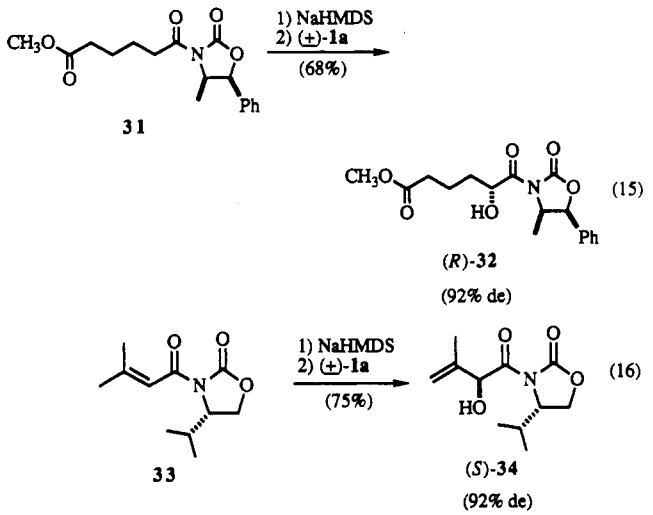
α-Hydroxy acids of high enantiomeric purity are available using (±)-1a and carboximides as chiral auxiliaries.[41] For example, Evans and co-workers reported that hydroxylation of the sodium enolate of **29** with a slight excess of the oxaziridine gives (*S*)-**30** and (*R*)-**30** in a ratio of 95:5. The major (*S*) product **30** was readily obtained, diastereomerically pure, by flash chromatography (eq 14). The carboximide auxiliary was removed without concurrent racemization by transesterification with magnesium methoxide in methanol.



It is evident from the data summarized in Table III that the diastereoselectivities in these enolate hydroxylation experiments are generally high. Comparable levels of diastereoselection were noted for three different oxazolidinone chiral auxiliaries. On the other hand, increased steric requirements in the R group vicinal to the prochiral enolate center appear to amplify the diastereofacial bias for a given chiral auxiliary.

In addition to the examples summarized in Table III, two less-conventional substrates were also exam-

ined.[41] Selective enolization of the half-ester imide of glutaric acid **31** with NaHMDS and subsequent hydroxylation afforded a 96:4 ratio of α-hydroxy imides from which the (*R*) isomer **32** was isolated in 68% yield demonstrating that it is possible to selectively hydroxylate the carbon atom α to the imidic carbonyl in the presence of an ester group (eq 15). The regioselective hydroxylation of dienolates is also feasible. Enolization and subsequent hydroxylation of **33** afforded a 96:4 ratio of diastereomers from which the (*S*) isomer **34** was isolated in 75% yield (eq 16).[41]



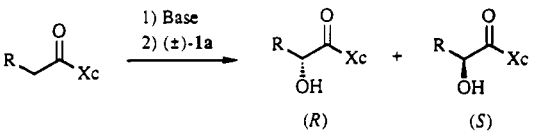
C. Reagent-Induced Hydroxylations

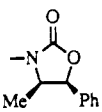
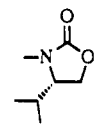
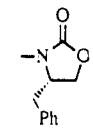
Although the chiral auxiliary induced asymmetric hydroxylation of enolates often provides high levels of stereoinduction, an inherent disadvantage of any chiral auxiliary based asymmetric synthesis is the necessity for preparing and eventually removing the auxiliary. This problem can be avoided by using the so called reagent-induced stereoselectivity approach. Here product stereoselectivity is generated under the influence of a noncovalently bonded chiral reagent. This method requires an enantiopure aprotic oxidant of which the nonracemic *N*-sulfonyloxaziridines **1–3** are the only examples. Of these reagents the (camphorsulfonyl)-oxaziridine derivatives **3** have proven to be the most effective not only giving higher enantioselectivities, but also being easier to prepare. Both enantiomers of the α-hydroxyl carbonyl compound are readily available by selecting (+)-**3** or (−)-**3**, because the configuration of the oxaziridine controls the absolute stereochemistry of the product.[27,28]

1. Ketones

By choice of the appropriate reaction conditions and (camphorsulfonyl)oxaziridine derivative **3** acyclic α-hydroxy ketones of high enantiomeric purity have been prepared using the asymmetric enolate oxidation protocol. For example, treatment of deoxybenzoin (**35a**) with NaHMDS followed by addition of (+)-(camphorsulfonyl)oxaziridine (**3a**) at −78 °C affords (+)-(*S*)-benzoin (**36**) in 95% ee and 88% isolated yield (Scheme VII).[38,52,53] Similarly, (−)-(*S*)-2-hydroxy-1-phenyl-1-propanone (**37**) is produced in 95% ee by the oxidation of the sodium enolate of propiophenone (**35b**) using, this time, (+)-(8,8-dichlorocamphorsulfonyl)oxaziridine (**3b**) (Scheme VII).[23] Additional examples are given in Table IV.

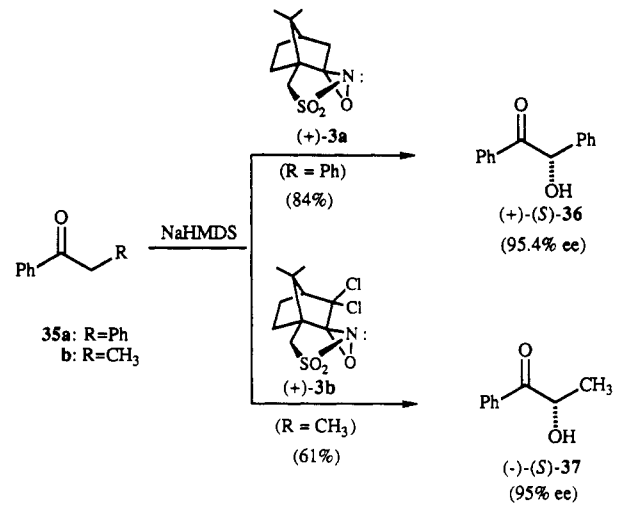
Table III. Diastereoselective Hydroxylation of Chiral Amide and Carboximide Enolates with (±)-2-(Phenylsulfonyl)-3-phenyloxaziridine (1a) at −78 °C



X_c	R	base	% de (config)	% yield	ref
	Ph	LDA	>95 (*S*)	85	51
		NaHMDS	93 (*R*)	94	51
	Ph	LDA	46 (*R*)	70	51
		LDA/HMPA[a]	33 (*R*)	55	51
		LDA/HMPA[b]	18 (*S*)	60	51
		NaHMDS	18 (*R*)	80	51
	Ph	NaHMDS	80 (*R*)	77	41
	Bn	NaHMDS	88 (*R*)	86	41
	Et	NaHMDS	88 (*R*)	86	41
	t-Bu	NaHMDS	98 (*R*)	94	41
	CH_2=$CHCH_2$	NaHMDS	90 (*R*)	91	41
	$CH_3O_2C(CH_2)_3$	NaHMDS	92 (*R*)	68	41
	Bn	NaHMDS	90 (*S*)	85	41
	i-Pr	NaHMDS	98 (*S*)	86	41
	Bn	NaHMDS	90 (*S*)	83	41

[a] 3% HMPA used. [b] 30% HMPA used.

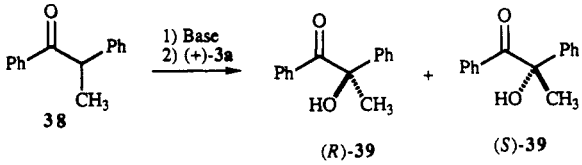
Scheme VII. Enantioselective Hydroxylation of Prochiral Acyclic Ketone Enolates with (Camphorsulfonyl)oxaziridine Derivatives



Not surprisingly the results summarized in Table IV indicate that generation of a single enolate regioisomer is a precondition for high enantioselectivity. However, this does not necessarily translate into high ee's. In addition to enolate geometry, molecular recognition depends on the structures of the oxidant and enolate as well as the reaction conditions.[23,24,38] In general oxidation of the Li, K, or Zn enolates of acyclic ketones with **3** resulted in lower ee's as did the addition of

HMPA. Exceptions were noted.[38] Generally the stereoselectivity trends summarized in Table IV have been interpreted in terms of transition-state structure TS-1 (Figure 1).[38]

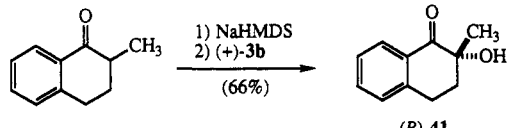
Hydroxylation of tertiary substituted acyclic ketone enolates usually gives lower stereoselectivities. Oxidation of enolate **38** with oxaziridine (+)-**3a** gave, for example α-hydroxy product **39** in 9–21% ee and 57–71% yield (eq 17).[38] The main reason for the poor asymmetric induction is the formation of *E*/*Z* enolate mixtures.



(17)

NaHMDS	(62%)	21% ee (S)
NaHMDS/HMPA	(59%)	12% ee (S)
LDA	(71%)	9% ee (S)
LDA/HMPA	(57%)	20% ee (R)

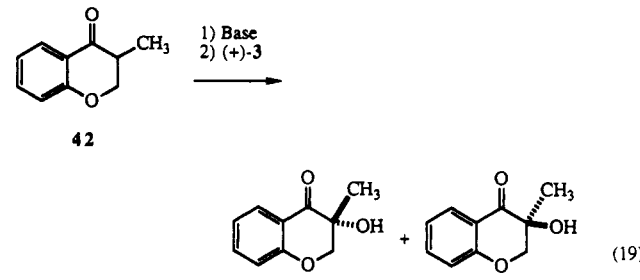
(+)-(*R*)-2-Hydroxy-2-methyl-1-tetralone (**41**), a model for many natural products, is obtained in ≥95% ee via hydroxylation of the sodium enolate of 2-methyl-1-tetralone (**40**) with (+)-(8,8-dichlorocamphorsulfonyl)-oxaziridine (**3b**) (eq 18).[23] Reduced enantioselectivities were observed with other oxaziridine derivatives (Table V). In part the stereoselectivities for these hydroxylations were evaluated using transition-state structure TS-2 (Figure 1).



(18)

The tetralone's substitution pattern, which alters the solution structure of the enolate, influences the hydroxylation stereoselectivities (Table V). As long as the oxidant is chloro oxaziridine **3b** high ee's (>90%) are observed for 2-substituted 1-tetralones having a variety of groups at C-2 (Me, Et, $PhCH_2$). However substitution of a methoxy group into the 8-position lowers the stereoselectivity to 83%.[24] For the 8-methoxy tetralones (+)-8,8-dimethoxycamphorsulfonyl)oxaziridine (**3c**) becomes the reagent of choice improving the ee's to better than 94% (Table V). Apparently the presence of an 8-methoxy group in this ring system is necessary for high ee's with (+)-**3c**, because this reagent gives significantly lower ee's (2–36%) when this group is absent (Table V).

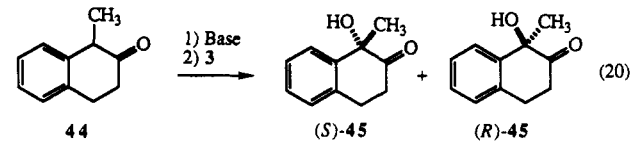
The 3-hydroxy-4-chromanone ring skeleton is found in a number of natural products and can be conveniently prepared using the asymmetric enolate oxidation protocol.[23,55] For example, oxidation of the sodium enolate of 3-methyl-4-chromanone (**42**) with (+)-(8,8-dichlorocamphorsulfonyl)oxaziridine (**3b**) afforded (*R*)-**43** in 96% ee and 64% yield (eq 19).[23] Interestingly the absolute stereochemistry of **43** depends on the counterion; i.e. the sodium enolate gives the *R* product while the lithium enolate gives the (*S*) enantiomer. A similar counterion dependency was not observed for the tetralones and appears to be unique to the chromanone system (Table V).



(19)

NaHMDS/(+)-3a	(80%)	71% ee (*R*)
LDA(+)-3a	(56%)	30% ee (*S*)
NaHMDS/(+)-3b	(77%)	96% ee (*R*)
LDA/(+)-3b	(70%)	64% ee (*S*)

Hydroxylation of the enolate of 1-methyl-2-tetralone (**44**) to **45** gives, under a variety of conditions, poor to moderate stereoselectivities (eq 20).[23] Optimum results, 76% ee, were obtained using the sodium enolate and oxaziridine (+)-**3a**.[23]

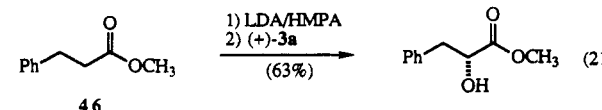


(20)

NaHMDS/ (+)-3a	(60%)	76% ee (*S*)
NaHMDS/HMPA/(+)-3a	(70%)	65% ee (*S*)
LDA/(+)-3a	(58%)	10% ee (*S*)
NaHMDS/(+)-3b	(55%)	16% ee (*S*)
LDA/(+)-3b	(56%)	54% ee (*S*)

2. Esters

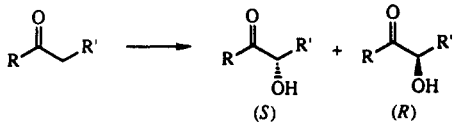
Only limited studies are available on the asymmetric hydroxylation of ester enolates with *N*-sulfonyloxaziridines.[25,56] Stereoselectivities are generally modest (Table VI)and less is known about the influence of the reaction parameters on the molecular recognition. For example, (*R*)-methyl 2-hydroxy-3-phenylpropionate (**47**) can be prepared in 85.5% enantiomeric excess by oxidizing the lithium enolate of methyl 3-phenylpropionate (**46**) with (+)-**3a** in the presence of HMPA (eq 21).[56] In the absence of HMPA (*R*)-**47** was obtained in 58% ee.



(21)

Additional examples of the enantioselective hydroxylation of prochiral ester enolates are found in Table VI. From the summarized data, α-hydroxy esters are isolated in good yield, but with low to moderate ee's. The difficulty in forming a specific enolate geometric isomer is likely to contribute to the modest stereoselectivities. It is worth mentioning that for the hydroxylation of methyl 2-phenylpropionate (Table VI, R^1 = Ph, R^2 = Me) the *exo*-(4-benzylcamphorsulfonyl)oxaziridines (*exo*-**3d**) gave higher ee's (64% ee) than did the *endo*-**3d** analogue (48% ee) despite the fact that in the former the benzyl group appears to be too remote from the active site to influence transition-state geometries.[25]

Table IV. Enantioselective Hydroxylation of Prochiral Acyclic Ketone Enolates

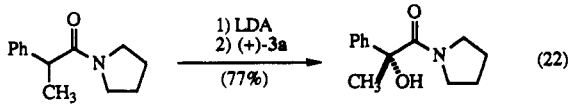


R	R'	base	% Z/E^b	oxaziridine	% yield	% ee	config	ref(s)
Ph	Ph	NaHMDS	100/0	(+)-**3a**	84	95	(*S*)	38,52,53
		LDA	87/13	(+)-**3a**	65	68	(*S*)	38,52
		KHMDS	*c*	(+)-**3a**	73	93	(*S*)	38,52
		NaHMDS		(−)-**3a**	88	95	(*R*)	38,52
Ph	Me	NaHMDS	100/0	(+)-**3a**	73	62	(*S*)	38,52
		LDA	100/0	(+)-**3a**	45	40	(*S*)	38,52
		KHMDS	*c*	(+)-**3a**	85	47	(*S*)	38,52
		NaHMDS		(+)-**3b**	61	95	(*S*)	23
		NaHMDS		(+)-**3c**	73	79	(*S*)	24
		LDA		(+)-**3c**	70	75	(*S*)	24
		NaHMDS	100/0	(2*R*,3*S*)-**2c**	40	11	(*R*)	21
		LDA	100/0	(2*R*,3*S*)-**2c**	40	60	(*R*)	21
		NaHMDS		(2*R*,3*S*)-**2d**	55	68	(*R*)	21
		LDA		(2*R*,3*S*)-**2d**	45	81	(*R*)	21
t-Bu	Me	NaHMDS	100/0	(+)-**3a**	71	89	(*R*)	38
		LDA	100/0	(+)-**3a**	55	32	(*R*)	38
Me	Ph	NaHMDS	60/40	(+)-**3a**	70	40	(*S*)	38
		LDA	11/89	(+)-**3a**	41	3	(*S*)	38
n-C_5H_{11}	Me	MeLi[a]	*c*	(+)-**3a**	57	12	(*S*)	54

[a] Silyl enol ether is used as substrate instead of ketone. [b] Referred to the geometry of enolate formed. [c] Not determined.

3. Amides

Like esters, the hydroxylation of prochiral amide enolates with *N*-sulfonyloxaziridines affords the corresponding optically active α-hydroxy amides. Thus treatment of amide **48** with LDA at −78 °C followed by addition of (+)-(camphorsulfonyl)oxaziridine (**3a**) produces α-hydroxy amide **49** in 77% isolated yield and 60% ee (eq 22).[56] From the limited results available α-hydroxy amide products are isolated in good yield, but with poor to moderate stereoselectivities (Table VII).

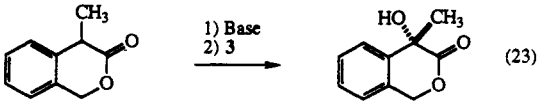


(22)

48 (*R*)-**49** (60% ee)

4. Lactones

Hydroxylation of the sodium enolate of lactone **50** with (+)-(camphorsulfonyl)oxaziridine (**3a**) gives a 40% yield of α-hydroxy lactone **51** in 77% ee.[23] Oxidation of the lithium enolate with oxaziridine (+)-**3b** reduces the stereoselectivity to 23% (eq 23). In all cases the product is proposed to have (*S*) configuration.



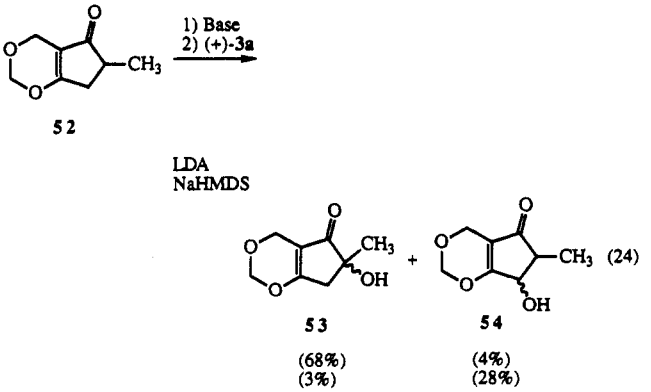
(23)

50 (*S*)-**51**

NaHMDS/(+)-**3a**	(40%)	77% ee
LDA/(+)-**3a**	(45%)	23% ee
NaHMDS/(+)-**3b**	(60%)	45% ee
LDA/(+)-**3b**	(65%)	17% ee

5. Enones

As previously noted hydroxylation of α,β-unsaturated carboximides with (±)-**1a** gave the α-hydroxy imide with concurrent migration of the carbon–carbon double bond to the β,γ-position (see eq 16).[41] Smith et al., in a study of the oxidation of enolates derived from 1,3-dioxin vinylogous ester **52**, observed both α′- and γ-hydroxylation depending on the reaction conditions (eq 24).[40] With (+)-**3a** the lithium enolate of **52** gave primarily the α′-hydroxylation product **53** while the sodium enolate gave γ-hydroxylation. Only low levels of asymmetric induction (ca. 16% ee) were found in these oxidations. With (±)-2-(phenylsulfonyl)-3-phenyloxaziridine (**1a**) the sodium enolate of **52** gave **53**/**54** in 4 and 76% yield, respectively. With (±)-**1a**, but not with (+)-**3a**, the imino–aldol side reaction was observed, an advantage of using the latter reagent in enolate hydroxylations (see section III, Scheme IV). α-Hydroxy ketone **53** is an intermediate in the total synthesis of the antileukemic diterpene macrocycles (+)-hydroxyjatrophone A and (+)-hydroxyjatrophone B.[58]



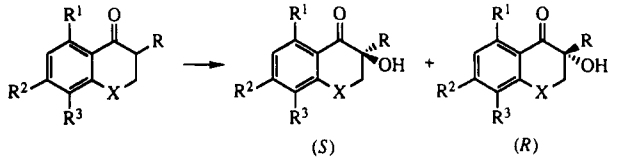
(24)

52 **53** (68%) (3%) **54** (4%) (28%)

D. Double Stereodifferentiation

The ee's for the asymmetric hydroxylation of acyclic enolates derived from α-branched carbonyl compounds with oxaziridines is generally low (see Tables VI and

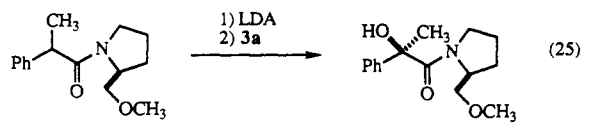
Table V. Enantioselective Hydroxylation of Prochiral Cyclic Ketone Enolates



(S) (R)

R	R^1	R^2	R^3	X	base	oxaziridine	% yield	% ee	config	ref(s)
Me	H	H	H	CH_2	NaHMDS	(+)-**3a**	90	16	(*R*)	23,38
					LDA	(+)-**3a**	90	36	(*R*)	23,38
					NaHMDS	(+)-**3b**	66	≥95	(*R*)	23
					LDA	(+)-**3b**	60	≥95	(*R*)	23
					NaHMDS	(+)-**3c**	66	36	(*R*)	24
					LDA	(+)-**3c**	67	2	(*R*)	24
					NaHMDS	*exo*-**3d**	61	67	(*R*)	25
					LDA	*exo*-**3d**	80	54	(*R*)	25
					LDA	(2*S*,3*R*)-**2c**	21	4	(*S*)	21
					LDA	(2*S*,3*R*)-**2c**	45	39	(*S*)	21
Me	H	H	OMe	CH_2	Na HMDS	(+)-**3a**	68	14	(*R*)	23
					NaHMDS	(+)-**3b**	62	≥95	(*R*)	23
					NaHMDS	(+)-**3c**	62	5	(*R*)	24
					LDA	(+)-**3c**	66	19	(*R*)	24
Et	OMe	H	OMe	CH_2	NaHMDS	(+)-**3a**	72	83	(*R*)	24
					LDA	(+)-**3a**	66	61	(*R*)	24
					NaHMDS	(+)-**3b**	70	68	(*R*)	24
					LDA	(+)-**3b**	55	73	(*R*)	24
					NaHMDS	(+)-**3c**	56	60	(*R*)	24
					LDA	(+)-**3c**	66	94	(*R*)	24
Bn	H	H	H	O	NaHMDS	(+)-**3a**	70	15	(*R*)	23
					NaHMDS	(+)-**3b**	71	91	(*R*)	23
					NaHMDS	(−)-**3b**	67	92	(*S*)	23
p-MeOBn	OMe	OMe	H	O	NaHMDS	(+)-**3a**	77	6	(*R*)	55
					NaHMDS	(+)-**3b**	66	88	(*R*)	55
					LDA	(+)-**3b**	70	71	(*R*)	55
					NaHMDS	(+)-**3c**	75	77	(*R*)	55
					LDA	(+)-**3c**	73	≥96	(*R*)	55
					LDA	(−)-**3c**	72	≥96	(*S*)	55

VII). The poor stereoselectivities are related to the difficulty in generating a specific enolate geometric isomer as well as poor enantiofacial discrimination between the *re* and *si* faces of the enolate. In one example a double stereodifferentiation process, the asymmetric oxidation of a chiral enolate, was successfully employed to circumvent these difficulties.[57] For the matched pair, (−)-**55** and (−)-**3a**, the de was 88–91% whereas with the mismatched pair, (−)-**55** and (+)-**3a**, the de dropped to 48.4% (eq 25). Interestingly the de for the mismatched pair improved to 89% on addition of the cosolvent HMPA. The pyrrolidine methanol chiral auxiliary was removed without racemization by basic hydrolysis affording nonracemic atrolactic acid in 70–89% yield.[57]



(-)-**55** **56** (25)

(+)-**3a**	48.4% (de)
(+)-**3a**/HMPA	88.7% (de)
(-)-**3a**	88.3% (de)
(-)-**3a**/HMPA	90.7% (de)

VI. Synthesis of Natural Products

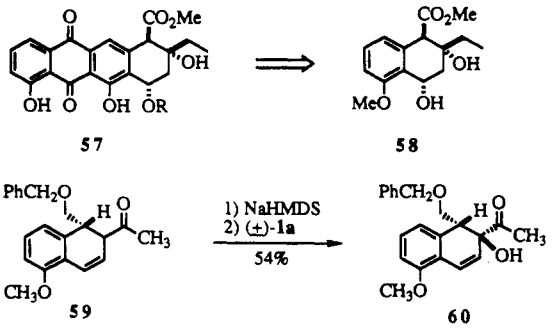
The hydroxylation of enolates using *N*-sulfonyloxaziridines has been widely employed in the synthesis of natural products. This section is organized into natural product syntheses employing diastereo- and enantioselective hydroxylations and further subdivided as to the type of carbonyl enolate precursor.

A. Diastereoselective Hydroxylations

1. Ketones

There are many examples of the diastereoselective hydroxylation of ketone enolates using racemic 2-(phenylsulfonyl)-3-phenyloxaziridine (**1a**). In general, only single diastereoisomers are isolated with the stereochemistry consistent with approach of the oxidant from the least hindered direction.

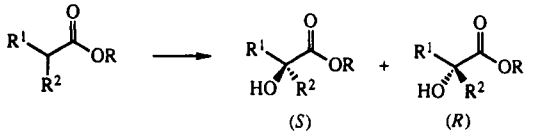
In studies directed toward the asymmetric synthesis of **58**, the AB ring of the antitumor antibiotic aklavinone (**57**), Meyers and Higashiyama isolated **60** as a single diastereomer in 54% yield on oxidation of the sodium enolate of **59** with (±)-**1a**.[59]



57 **58**

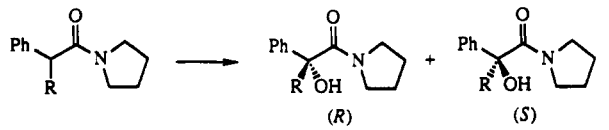
59 **60**

Table VI. Enantioselective Hydroxylation of Prochiral Lithium Ester Enolates



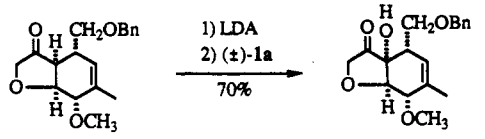
R	R^1	R^2	base	oxaziridine	T (°C)	% yield	% ee	config	ref
Me	Ph	H	LDA	(+)-**3a**	−78	84	54	(*R*)	56
			LDA/HMPA	(+)-**3a**	−78	88	12	(*R*)	56
t-Bu	Ph	H	LDA	(+)-**3a**	−78	82	64	(*R*)	56
			LDA	(+)-**3a**	−90	84	71	(*R*)	56
			LDA	(−)-**3a**	−90	86	66	(*S*)	56
Me	Bn	H	LDA	(+)-**3a**	−90	73	58	(*R*)	56
			LDA/HMPA	(+)-**3a**	−90	63	86	(*R*)	56
Me	Ph	Me	LDA	(+)-**3a**	−78	61	24	(*R*)	57
			LDA	(−)-**3a**	−78	57	28	(*S*)	57
			LDA	(2*S*,3*R*)-**2c**	0	60	15	(*R*)	21
			LDA	(2*S*,3*R*)-**2d**	0	55	10	(*R*)	21
			LDA	*exo*-**3d**	−78	51	64	(*R*)	25
			LDA	*endo*-**3d**	−78	65	48	(*R*)	25

Table VII. Enantioselective Hydroxylation of Prochiral Lithium Amide Enolates[56]



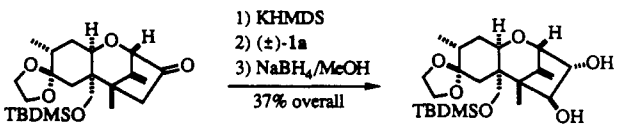
R	base	oxaziridine	T (°C)	% yield	% ee	config
H	LDA	(*S*,*S*)-**1d**	−78	71	41	(*S*)
H	LDA	(+)-**3a**	−78	70	30	(*S*)
H	LDA	(+)-**3a**	−90	85	18	(*S*)
H	LDA/HMPA	(+)-**3a**	−78	74	50	(*R*)
Me	LDA	(*S*,*S*)-**1d**	−78	60	40	(*R*)
Me	LDA	(+)-**3a**	−78	77	60	(*R*)
Me	LDA	(+)-**3a**	−90	70	46	(*R*)
Me	LDA/HMPA	(+)-**3a**	−78	35	20	(*S*)

Treatment of ketone **61** with LDA followed by oxidation with (±)-**1a** gives hexahydrobenzofuran **62**, as the only product.[60] Compound **62** is a subunit of the avermectins and the milbemycins family of macrolide natural products, potent antiparasitics.



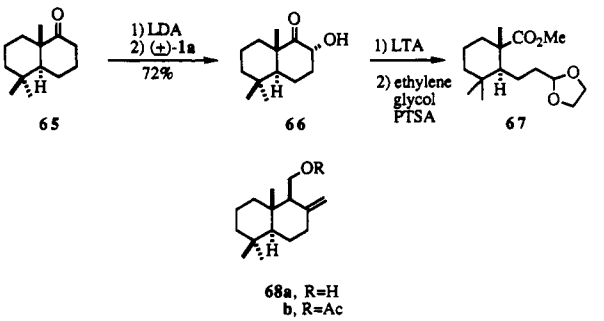
61 **62**

Oxaziridine-mediated α-hydroxylation of the potassium enolate of ketone **63**, followed by hydride reduction gave the 3α,4β-diol **64**. Both reagents attacked at the less hindered exo face of the oxabicyclo[3.2.1]octane subunit. Compound **64** is a precursor of T-2 tetraol, the parent member of a group of trichothecene mycotoxins which include the highly toxic T-2 and HT-2 toxins.[61]



63 **64**

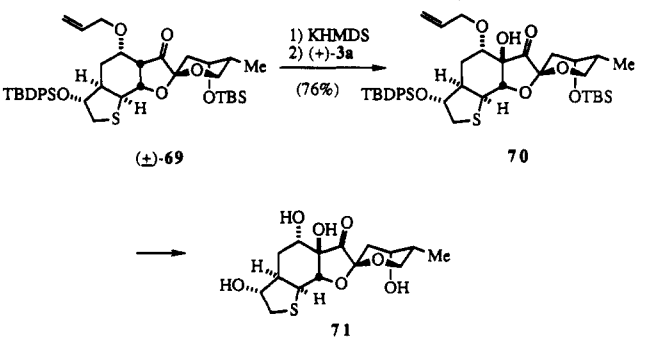
A step in the dipolar enantioselective synthesis of the sesquiterpene (+)-albicanol (**68a**) and albicanyl acetate (**68b**), fish antifeedants, included oxidation of the lithium enolate of ketone **65**.[62,63] Oxidative cleavage of **66** with lead tetraacetate gave **67** which was further elaborated to **68**. A key step in the synthesis of **68** involved a diastereoselective intramolecular cycloaddition of a nitrile oxide derived from **67**.



65 **66** **67**

68a, R=H
b, R=Ac

α-Hydroxy ketone **70**, required for the total synthesis of (±)-breynolide (**71**), a novel sulfur-containing glycoside possessing oral hypocholesterolemic activity, was prepared by hydroxylation of the potassium enolate of**69** with (+)-(camphorsulfonyl)oxaziridine (**3a**).[64] Protecting-group removal gave **71** in 70% overall yield.

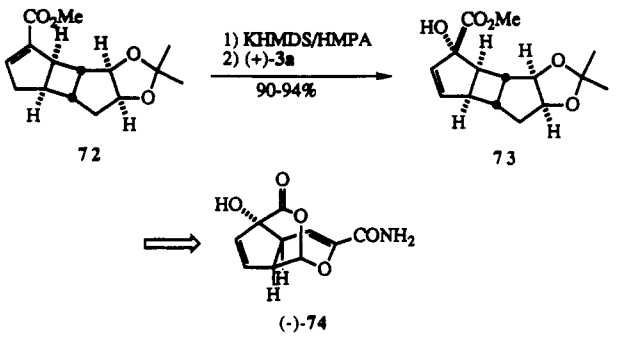


(±)-**69** **70**

71

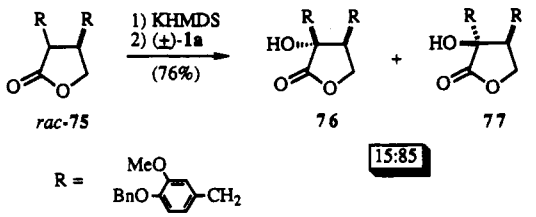
2. α,β-Unsaturated Esters

Smith et al. prepared α-hydroxy ester **73**, a key intermediate in the enantioselective synthesis of the antibiotic echinosporin (**74**), by oxidation of the dienolate of **72** with (+)-**3a**.[65] (−)-Echinosporin (**74**), a new antitumor antibiotic, is produced by *Streptomyces echinosporus* MK-213.

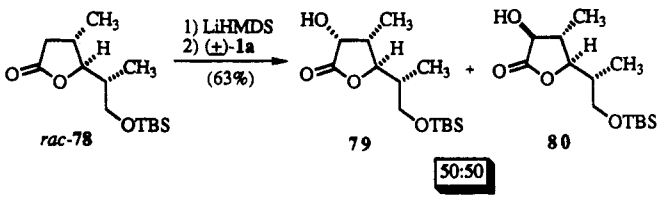


3. Lactones

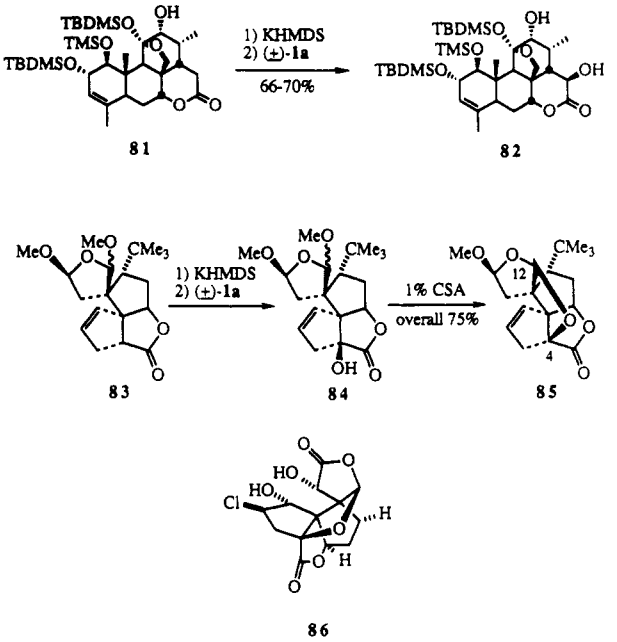
The antineoplastic prototype lignan natural product (±)-wikstromol (77) was prepared by Belletire and Fry by oxidation of the potassium enolate of 75 with (±)-1a affording 76 and 77 in a ratio 15:85.[66] The major product, identified as 77 by X-ray crystallography, appears to result from attack of the oxaziridine at the *more* sterically hindered face of enolate.[67] However, Moritani et al. argues that the bottom face of this enolate is actually shielded by the phenyl group of the α-benzyl group as a consequence of 1,3-allylic strain accounting for the preferential attack of electrophiles at the upper face despite the presence of the β-benzyl group.[68]



Taschner and Aminbhavi, as part of a program aimed at the synthesis of the 3-acetyltetramic acid antibiotics, explored the hydroxylation of lactone 78.[69] Oxidation of the lithium enolate with (±)-1a gave a 50:50 mixture of hydroxy lactones 79 and 80.

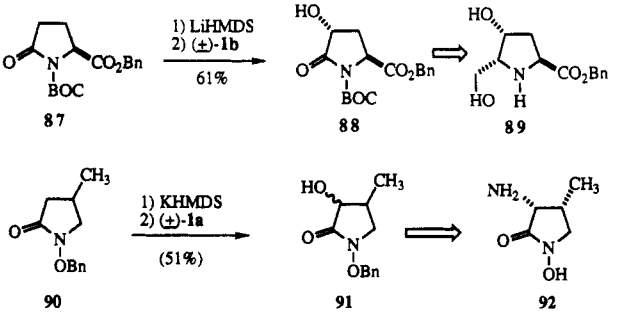


The conversion of readily available chaparrin (81) into the biologically active α-hydroxy lactone of glaucarubone (82) requires introduction of the lactone hydroxy group. A single isomeric hydroxy lactone 82 resulted from oxidation of the potassium enolate of 81 with (±)-1a.[70] In Corey et al.'s total synthesis of (±)-ginkgolide B, the C(4)–C(12) oxygen bridge was incorporated by deprotonation of 83 with LDA followed by oxidation with (±)-1a to give 84.[71] Subsequent treatment with camphorsulfonic acid (CSA) gave 85 in 75% overall yield from 83. Similar oxaziridine-mediated lactone hydroxylations using (±)-1a have recently been employed in the enantioselective synthesis of ginkgolide analogue 86.[72]



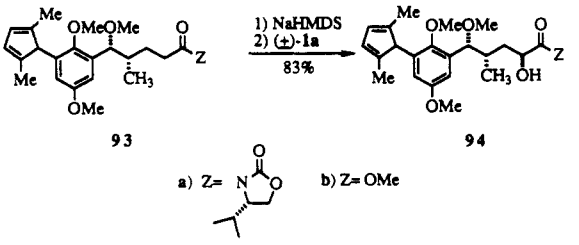
4. Lactams

α-Hydroxy lactam 88 is an intermediate in the synthesis of (−)-bulgecinine (89), a glycopeptide isolated from *Pseudomonas acidophila* and *P. mesoacidophila*. Oxidation of the lithium enolate of *N*-(*tert*-butoxycarbonyl)-L-pyroglutamate (87) proved to be both highly regio- and diastereoselective affording (+)-4-hydroxypyroglutamate (88) in 61% yield.[73] Similarly, hydroxylation of 90 gave 91, which was utilized in the synthesis of 3(*R*)-amino-1-hydroxy-4(*R*)-methylpyrrolidin-2-one, a potent glycine/*N*-methyl-D-aspartate receptor antagonist.[74]



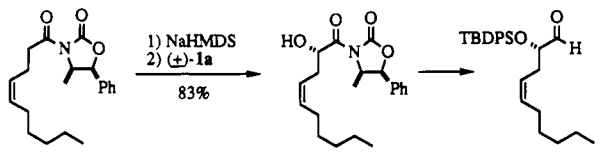
5. Carboximides

Several natural products have been prepared via the oxaziridine-mediated diastereoselective hydroxylation of chiral enolates using oxazolidinones as chiral auxiliaries. Treatment of the sodium enolate of carboximide 93a with (±)-1a afforded a single α-hydroxy product 94a in 83% yield.[75] However, hydroxylation of the lithium enolate of 93b (Z = OMe) with (−)-(cam-



phorsulfonyl)oxaziridine (**3a**) resulted in a 78:22 mixture of the hydroxylated products.[76] Compound **94** is an intermediate in the synthesis of the $C_{1,6}$–$C_{21,16}$ segments of the antitumor antibiotics macbecin I and II.

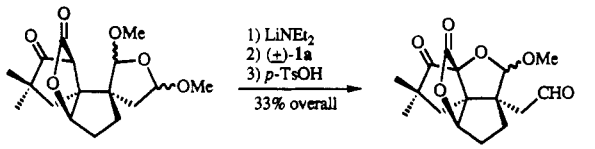
Protected α-hydroxy aldehyde **97** is a key intermediate in the enantioselective synthesis of 12(*R*)-hydroxyeicosaterraenoic acid, shown to possess human neutrophil chemotatic and chemokinetic activity, and in the synthesis of leukotriene B_4.[77] Oxaziridine-mediated hydroxylation of the enolate derived from **95** gave **96** (≥98:2), which was readily elaborated to **97**.



95 96 97

6. β-Dicarbonyl Compounds

Unlike Vedej's MoOPH reagent,[15] *N*-sulfonyloxaziridines are reactive toward stabilized enolates of β-dicarbonyl compounds (see also section VI.B.2). In studies directed toward the synthesis of the pentacyclic analogues of ginkgolides A and B Crimmins and Thomas described the α-hydroxylation of β-keto ester **98**. Of the several methods tested the combination of lithium diethylamide and oxaziridine (±)-**1a** resulted in hydroxylation of the keto ester and isolation of tetracycle **99** after exposure to *p*-toluenesulfonic acid.[78]



98 99

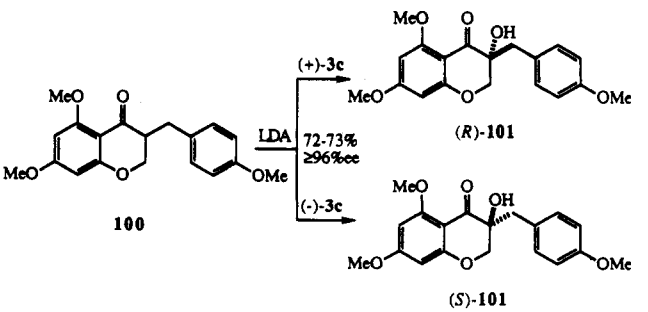
B. Enantioselective Hydroxylations

The application of enantiopure *N*-sulfonyloxaziridines for the asymmetric synthesis of natural products is in its infancy. To date applications of the asymmetric enolate oxidation protocol have been primarily limited to those natural products featuring the tetralin (tetralone) and 4-chromanone ring systems. While high ee's have been achieved using this protocol the stereoselectivities are highly dependent on both the oxidant and the reaction conditions.

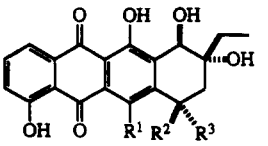
1. Ketones

Davis and Chen recently described the synthesis of both enantiomers of (*R*)- and (*S*)-5,7-dimethyleucomol (**101**), a member of the homoisoflavanone class of natural products.[55] The key step involved the enantioselective α-hydroxylation of the lithium enolate of chromanone **100** in better than 96% ee with (+)- and (−)-(8,8-dimethoxycamphorsulfonyl)oxaziridine (**3c**). Hydroxylation of the sodium enolate of **100** with **3c** (77% ee) or with oxaziridines **3a** and **3b** gave lower ee's (6–88% ee).

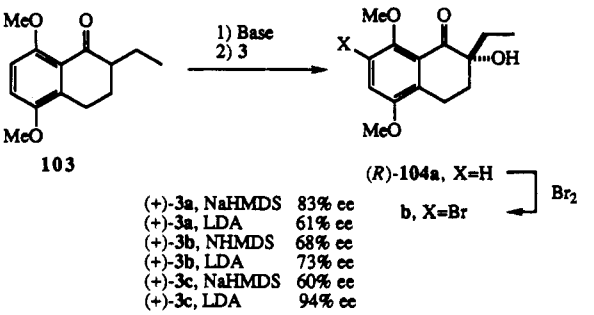
γ-Rhodomycinone (**102a**) and α-citromycinone (**102b**) are the aglycones of the rhodomycins, members of the potent anthracycline class of antitumor antibiotics. Hydroxy tetralone (*R*)-**104a**, the AB-ring segment of **102a**, was prepared in 94% ee by hydroxylation of the lithium



enolate of **103** at 0 °C with (+)-(8,8-dimethoxycamphorsulfonyl)oxaziridine (**3c**).[24] Treatment of **104a** with Br_2 gave **104b**, the AB-ring segment of **102b**, in 80% yield without racemization. As indicated below, lower stereoselectivities were observed with other counterions and oxidants.



102a, R^1=OH, R^2,R^3=H
b, R^1,R^2=H, R^3=OH

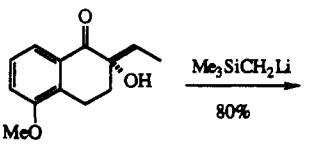


103

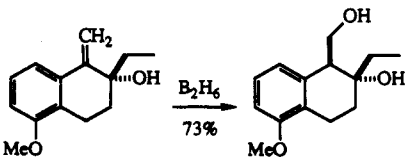
(*R*)-**104a**, X=H
b, X=Br

(+)-3a, NaHMDS	83% ee
(+)-3a, LDA	61% ee
(+)-3b, NHMDS	68% ee
(+)-3b, LDA	73% ee
(+)-3c, NaHMDS	60% ee
(+)-3c, LDA	94% ee

Aklavinone (**57**) differs from the other anthracyclinones in the absence of a C-11 hydroxyl group and the presence of a carbomethoxy group at the C-10 position. A formal synthesis of **58**, the AB ring of **57**, has been described by Davis and Kumar.[79] Hydroxytetralone (*R*)-**105**, prepared in >95% ee and 76% yield by hydroxylation of the corresponding lithium enolate with chloro oxaziridine (+)-**3b**, was converted to the terminal alkene (*R*)-**106** and hydroborated to diol **107**, obtained as a 13:1 mixture of epimers. Diol **107** has previously been transformed to **57** by Meyers et al.[59]



(*R*)-(+)-**105**

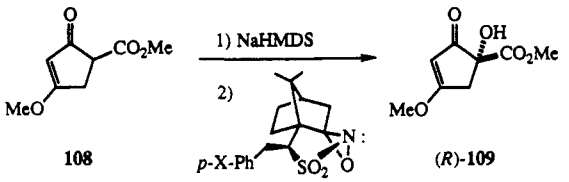


(*R*)-(+)-**106** (1*S*,2*R*)-(-)-**107**

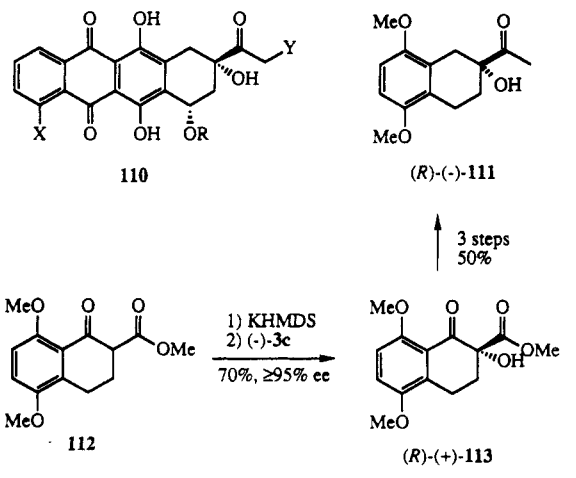
2. β-Keto Esters

Asymmetric oxidation of the sodium enolate of β-keto ester **108** furnishes kjellmanianone (**109**), an

antibacterial agent isolated from marine algae.[26] With diastereopure oxaziridines **1d** and **1e** the yields (33–44%) and ee's (8–37%) were low to modest.[26,80] With (+)-**3a** yields improved to better than 70%, but the ee's were still only modest; ca. 40%. Remarkably, variation of the para substituent in *exo*-benzyl oxaziridines **3d–f** significantly influences the observed ee's even though the benzene ring is separated from the active site by five bonds and is trans orientated on the five-membered ring. An attractive interaction between the metal enolate and the benzene ring in **3d–f** has been proposed to account for this.[26]



(*R*)-(+)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**111**) is a key intermediate in the asymmetric synthesis of anthracycline antitumor agents demethoxyadriamycin (**110**, X = Y = OH) and 4-demethoxydaunomycin (**110**, X = Y = H). The crucial step in a highly efficient asymmetric synthesis of **111** involves the enantioselective hydroxylation (>95% ee) of the potassium enolate of **112** with methoxy oxaziridine (−)-**3c**.[81] Conversion to **111** was accomplished in three steps in 50% overall yield from **113** without racemization.



VII. Summary

Metal enolates derived from ketones, esters (lactones), and amides are hydroxylated to α-hydroxy carbonyl compounds in good to excellent yields by *N*-sulfonyloxaziridines. Stabilized enolates of β-dicarbonyl compounds are also efficiently hydroxylated by these reagents, in contrast to the MoOPH reagent. Very high stereoselectivities are generally observed for the substrate and auxiliary-induced diastereoselective hydroxylation of enolates by oxaziridines **1** and **3**. The product stereochemistry is consistent with approach of the oxidant at the least hindered face of the enolate. An occasional side reaction observed in the hydroxylation of lithium enolates with (±)-2-(phenylsulfonyl)-3-phenyloxaziridine (**1a**) is the imino–aldol addition product. This product can be avoided by using the corresponding sodium or potassium enolates or, preferably, the (camphorsulfonyl)oxaziridines derivatives **3**, which are also commercially available.

While the enantioselective hydroxylation of prochiral enolates with enantiopure *N*-sulfonyloxaziridines has been less studied, the (camphorsulfonyl)oxaziridine derivative **3** appears to be much more efficient than other oxaziridine types in terms of yields and ee's. Since the structure of the oxaziridine determines the absolute configuration of the product, either enantiomer is available by choice of the appropriate reagent. High enantioselectivities (>95%) are observed for the hydroxylation of acyclic and cyclic ketone enolates with **3** with the ee's dependent not only on the structure of the oxaziridine and enolate, but the reaction conditions as well. Future studies are expected to clarify the application of these reagents for the enantioselective hydroxylation of other enolate types.

Note Added in Proof

Since submitting this review several papers have appeared which are particularly relevant to the subject.

An improved multigram synthesis of (8,8-dichlorocamphorsulfonyl)oxaziridine (**3b**) has been described.[82] Details of the enantioselective synthesis of the glycine/NMDA antagonist (3*R*,4*R*)-3-amino-1-hydroxy-4-methyl-2-pyrrolidinone (**92**) using (±)-2-(phenylsulfonyl)-3-phenyloxaziridine (**1a**) has been reported.[83] The oxidation of a chiral oxazolidinone enolate with (±)-**1a** (>99% de) was employed in the asymmetric synthesis of the C_1–C_{25} spiroketal fragment of calyculin A.[84] Addition of diethyl aluminum chloride to an α,β-unsaturated chiral oxazolidinone affords an aluminum enolate that on hydroxylation with (±)-**1a** gives the β-ethyl-α-hydroxy carboxylic acid (85%) with high antiselectivity (>95:5).[85] β-Hydroxy-γ-keto phosphates are obtained in fair to excellent yields on treatment of 2,2,2-triethoxy-1,2λ⁵-oxaphospholene with *N*-sulfonyloxaziridines (±)-**1b** and (+)-**3a** and (+)-**3b**.[86] The best yields (70–95%) and ee's (30–49%) were obtained using (8,8-dichlorocamphorsulfonyl)oxaziridine (**3b**). Asymmetric hydroxylation of the enolate derived from the Birch reduction (Li/NH_3) of methyl 2-methoxybenzoate with (+)-**3a** affords 6-hydroxy-1,4-cyclohexadiene in 50–60% yields and 30% ee.[87] Birch reduction of the related chiral benzamide and hydroxylation with (+)-**3a** (double stereodifferentiation) gives the corresponding 6-hydroxy-1,4-cyclohexadiene in 85% de and 57% yield based on recovered starting material. With (−)-**3a** this material was obtained in 33% de. Details of the asymmetric synthesis of (−)-echinosporin (**74**) have appeared in which the α-hydroxy lactone was constructed by the hydroxylation of a potassium dienolate with (+)-**3a**.[88]

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IX. References

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