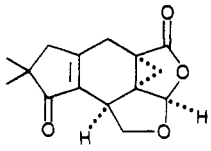
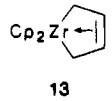
has been applied to the synthesis of (±)-sterepolide (12).[99b] In these reactions, metallabicyclic intermediates presumably undergo dehydrometalation–reductive elimination to give monocyclic products. It now appears that most or essentially all d-block transition metals can participate in bicyclization of enynes, dienes, and diynes, and they will collectively provide a powerful new tool for the synthesis of mono-, bi-, and polycyclic structures.

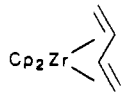
The product of the reaction of butadiene with "$ZrCp_2$" was originally prepared by Nakamura[100a] by the reaction of Cl_2ZrCp_2 with 2-buten-1,4-diylmagnesium and by Erker by photolysis of Cp_2ZrPh_2 in the presence of butadiene.[101a] Interestingly, the product obtained by the former is (*s-cis*-η^4-butadiene)zirconocene (13), whereas the latter product contains its s-trans isomer (14). These compounds not only react readily with



12

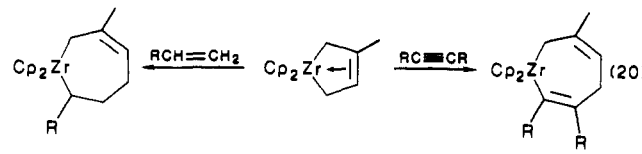


13



14

ketones and nitriles but also undergo carbometalation with alkenes and alkynes.[100,101] Significantly, the carbometalation reactions of (*s-cis*-isoprene)zirconocene are often highly regioselective and form carbon–carbon bonds away from the methyl group of isoprene[100c] (eq 20).



(20)

Concluding Remarks

Until recently, carbometalation reactions had been used nearly exclusively to synthesize polymers and symmetrically structured oligomers of alkenes and alkynes. It now appears that controlled carbometalation provides a new powerful tool for construction of unsymmetrical and complex organic structures as well. The crucially important aspects of controlled carbometalation include (i) controlling the degree of polymerization or oligomerization, (ii) attaining a high regio-, stereo-, and/or chemoselectivity, and (iii) attaining a high cross–homo selectivity. The fact that carbometalation leads to the simultaneous formation of a carbon–carbon bond and a new carbon–metal bond can be exploited in the preparation of various ring structures. The cyclization methods discussed here include (i) cyclialkylation, (ii) cycliacylation, (iii) Zr-catalyzed cyclic carboalumination, (iv) acylpalladation, (v) Zr-promoted bicyclization of enynes, dienes, and diynes. Collectively, these reactions promise to provide attractive routes to cyclic structures. Many additional cyclization procedures involving carbometalation are expected to be developed in the near future. Highly needed in this connection are further explorations of carbometalation reactions involving functionalized alkynes and alkenes as well as functionalized organometals.

I am deeply indebted to my co-workers, whose names appear in our papers cited in this Account. My current co-workers active in this are K. Akiyoshi, S. W. Arnold, V. Bagheri, F. E. Cederbaum, S. R. Miller, K. J. Mouis, D. R. Swanson, T. Takahashi, E. J. Vawter, and Y. Zhang. Our research has been mainly supported by the National Science Foundation, the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. I also thank the Guggenheim Memorial Foundation for a Fellowship.

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Asymmetric Synthesis of Carbon–Carbon Bonds Using Sulfinyl Cycloalkenones, Alkenolides, and Pyrones

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Prior to 1975, asymmetric syntheses proceeding with >90% enantiomeric excess (ee, percent of one enantiomer minus percent of its antipode) were the rare exception. In recent years, however, many research groups have reported ee's of >90%, and the research activity generated by this scientific revolution is leading to a publication explosion in this area. This scientific revolution has stimulated development not only of new synthetic methods but also of new chromatographic methods for analytical and preparative scale separation of enantiomers, development of new NMR techniques for evaluating enantiomeric purity easily and accurately, and development of new and practical industrial processes for asymmetric synthesis of valuable organic in-

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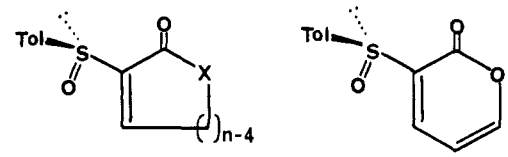
termediates (e.g., amino acids).[1] Recent publication of Morrison's multivolume overview of *Asymmetric Synthesis* and repeated recognition in recent years in the form of the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry provide convincing evidence of the phenomenal progress in this area. This revolution also has inspired its followers to explore ways of designing and using effective chiral catalysts rather than using just chiral auxiliaries which are in some cases recoverable and in some not.

This Account is but a snapshot of one scene in this scientific revolution. The picture takes form in 1900 with the isolation of some optically active organosulfur compounds[2] and in 1925 with the resolution of (*S*)-(−)-menthyl *p*-toluenesulfinate[3] which, along with the (*R*)-(+) antipode, is still the most common source of chiral organosulfur compounds and is now commercially available.[4] Fine details begin to emerge as the stereochemical course of various reactions at, and adjacent to, chiral sulfur centers are studied in depth,[5] leading in the early 1970s to a sharply focused study of chiral vinylic sulfoxides in asymmetric synthesis. Independently, Stirling[6] in England and Tsuchihashi[7] in Japan viewed the sulfur atom in chiral vinylic sulfoxides as a stereogenic center from which chirality might be transferred to a nearby carbon atom: 1,3 asymmetric induction from sulfur to the β-carbon atom during nucleophilic β-addition to some chiral vinylic sulfoxides was found to proceed with 60–74% stereoselectivity.[6,7] In 1977, Cinquini and Cozzi in Italy showed a similar 1,3 asymmetric S → C induction during hydride conjugate reduction of some chiral *N*-alkylidene sulfinamides (57–92% ee).[8]

Starting in the late 1970s with these images in mind, we envisioned adding carbon nucleophiles to the distal, sp^2 carbon atoms of chiral vinylic sulfoxides, focusing on the stereochemistry of carbon–carbon bond formation. Although organometallic (e.g., organocopper) reagents add to the β-carbon atom of α,β-ethylenic carbonyl compounds,[9] most vinylic sulfoxides react very sluggishly via such a nucleophilic addition path but rapidly via an acid–base process in which an α-metallo-α,β-ethylenic sulfoxide is formed.[10] When the α-position is blocked by a carbonyl group, thus preventing α-deprotonation and thus activating the system toward nucleophilic β-addition, then asymmetric β-addition does occur with 59–65% stereoselectivity.[11] Much better stereochemical results, however, are obtained with some more rigid cyclic systems. Our attention, therefore, has centered on nucleophilic conjugate addition of alkyl and aryl groups and of enolate ions to 2-sulfinyl 2-cycloalkenones (**1**) and to 2-sulfinyl 2-alkenolides (**2**) and on Diels–Alder (2 + 4) cycloadditions of enol ethers and thioethers to 3-sulfinyl 2-pyrones (**3**). The results of these studies have helped to form a well-developed picture of sulfoxide-directed asymmetric C–C bond formation.

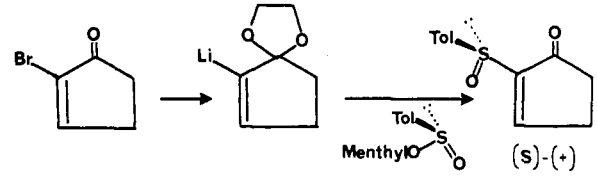


1, X = CH_2
2, X = O
n = 5, 6

3

Preparation of Sulfinyl Cycloalkenones, Alkenolides, and Pyrones

As outlined in eq 1 for preparation of the cyclopentenone sulfoxide, the corresponding cycloalkenone is dibrominated, dehydrobrominated, ketalized, and then subjected to Br → Li exchange.[12] Nucleophilic



(1)[12]

displacement by this vinylic lithium species at the sulfur atom of (*S*)-(−)-menthyl *p*-toluenesulfinate proceeds with complete inversion at sulfur[13] and at the same time liberates enantiomerically pure (−)-menthol, which is the original source of chirality for all of the asymmetric conjugate additions. Deketalization affords multigram quantities of the highly crystalline cycloalkenone sulfoxides which are stable at 0 °C for many months; several different sulfinyl cycloalkenones have been prepared in this way.[12]

The enantiomeric purities (>98%) of these cycloalkenone sulfoxides are easily assayed at the ketal sulfoxide stage by using a chiral, nonracemic europium NMR shift reagent.[14]

The alkenolide sulfoxides are prepared as illustrated for the butenolide sulfoxide in eq 2 by I → Li exchange

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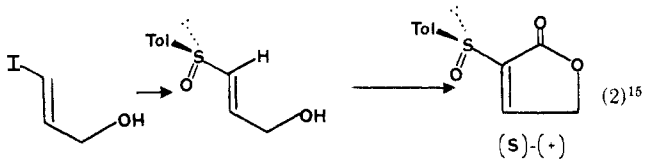
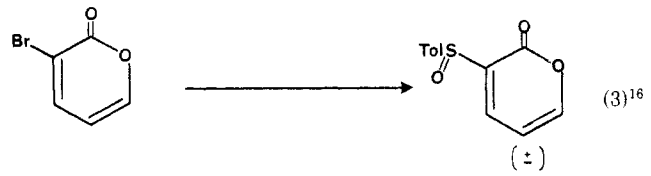


(2)[15]

of an alcohol-protected vinyl iodide, reaction with enantiomerically pure (*S*)-(−)-menthyl *p*-toluenesulfinate, α-metalation, carboxylation, and cyclization. These five- and six-membered ring alkenolide sulfoxides are stable at 0 °C for many months.[15]

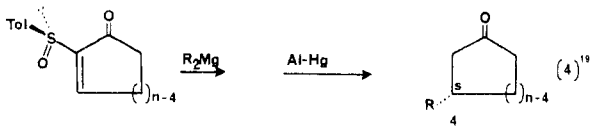
Pyrone sulfoxide (**3**) is prepared in racemic form by bromine → metal exchange of 3-bromo-2-pyrone with (dimethylcopper)lithium and then reaction with *p*-tolyl *p*-toluenethiosulfonate (no reaction occurs with menthyl *p*-toluenesulfinate) and sulfide → sulfoxide oxidation (eq 3). This pyrone sulfoxide is stable indefinitely.[16]



(3)[16]

Alkyl and Aryl Nucleophiles

X-ray analyses of several β-carbonyl sulfoxides such as **1** and **2** reveal that the ground-state conformation has the sulfinyl sulfur–oxygen bond dipole oriented away from (anti to) the carbonyl carbon–oxygen bond dipole,[15] as is expected for minimization of electrostatic interaction and as is indicated by studies on the direction of thermolytic syn elimination of some sulfoxides.[17] From such an anti conformation, the chirality at the sulfinyl sulfur atom might influence the approach of an organometallic reagent to the *si* or the *re* face of the prochiral β-carbon atom of the cyclic α,β-ethylenic carbonyl system. Calculations of the preferred ground-state conformations and of the stereochemistry of nucleophilic β-additions to vinylic sulfoxides are now being done by the Hehre and Houk research groups.[18] As a result of a serendipitous observation by Dr. John Mallamo at Hopkins in 1980, we discovered that in tetrahydrofuran as solvent diorganomagnesium reagents (R_2Mg), free of magnesium salts, add stereoselectively to the β-carbon atom of enantiomerically pure sulfinyl cycloalkenones (**1**) in their nonchelate anti conformations to produce, after reductive removal of the sulfinyl group, several 3-substituted cycloalkanones in excellent enantiomeric purity (eq 4).[19] Our working hypothesis



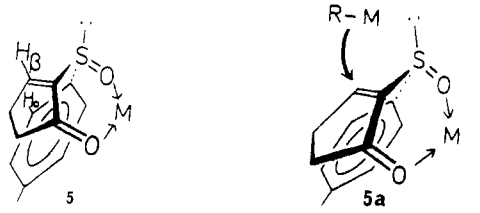
(4)[19]

is that the bulky tolyl group shields one diastereotopic face of the enone system, thus directing the absolute stereochemistry of the newly formed carbon–carbon bond. In this way (*S*)-sulfinyl cycloalkenones reacted with R_2Mg in DME solvent (in some cases also with 18-crown-6 added) to form (*S*)-3-substituted cycloalkanones with very high absolute stereochemical control.[19] Because optical rotation is not reliable as a method for determining *exact* enantiomeric purities,[20] NMR techniques were used on the (−)-2,3-butanediol ketal derivatives of 3-substituted cycloalkanones ((*S*)-**4**) to establish their enantiomeric purity more precisely. For example, (*S*)-3-methylcyclopentanone and (*S*)-3-phenylcyclopentanone were each formed in 97% enantiomeric purity, which corresponds to a 98.5:1.5 ratio of (*S*):(*R*) antipodes.[19]

Table I

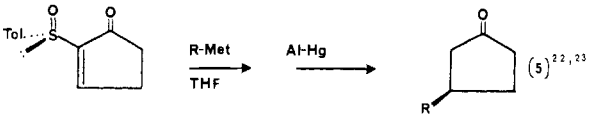
n	R	yield, %	ee, %
5	Me	60	97
	Et	81	81
	Ph	72	97
6	Me	50	79

A control experiment revealed the importance of chelating metals in controlling which conformation of the reactant β-keto sulfoxides predominates. For example, when cycloalkenone sulfoxides (**1**) were exposed to zinc dibromide and *then* to R_2Mg, only the antipodal (*R*)-3-substituted cycloalkanones ((*R*)-**4**) resulted.[21] We have interpreted these results in terms of a zinc-chelated conformer, **5** (M = Zn), which locks the β-keto sulfoxides into a syn conformation and which directs the stereochemistry of approach of the organometallic reagent (for example, see **5a**). Both ^1H and ^{13}C NMR



show clearly that the presence of divalent zinc causes a substantial downfield chemical shift of H_β and of C_β in chelate **5**. Moreover, a substantial nuclear Overhauser effect is observed between H_β and H_0 only in the presence of divalent zinc.[14]

Our best asymmetric induction results for chelate-mode conjugate addition of alkyl and aryl nucleophiles are shown in eq 5. In some cases zinc dibromide is used



(5)[22,23]

to preform a zinc chelate, followed then by conjugate addition of a Grignard reagent. Among the most impressive results obtained by using this procedure is the preparation of (*R*)-3-vinylcyclopentanone in 98.7% ee (>150:1 R:S) as assayed by chiral capillary gas chromatography.[22] 3-Vinylcyclopentanone derivatives are

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Table II

	R	yield, %	ee, %
MeMgCl	Me	91	>98
$ZnBr_2$/EtMgCl	Et	84	80
$EtTi(OPr\text{-}i)_3$	Et	67	>98
$ZnBr_2$/*t*-BuMgCl	*t*-Bu	98	86
$ZnBr_2/CH_2{=}CHMgBr$	$CH_2{=}CH$	75	98.7
$ZnBr_2$/PhMgCl	Ph	70	92
6-MeONaphMgR	6-MeONaph	90	>98

Table III

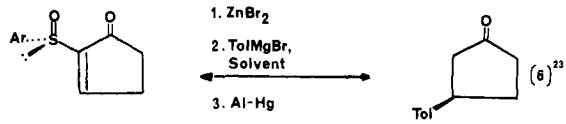
Ar	solvent	ee, %	R:S
p-Tol	THF	58	4:1
p-An	THF	69	6:1
p-Tol	DMTHF	86	13:1

Table IV

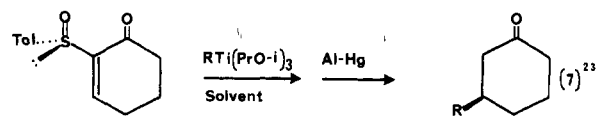
R	solvent	ee, %	R:S
Me	THF	87	13:1
Me	DMTHF	96	49:1
Ph	THF	43	2:1
Ph	DMTHF	93	28:1

valuable synthons in many elegant Diels–Alder *o*-quinodimethane syntheses of estrone steroids; (*R*)-3-vinylcyclopentanone derivatives therefore are valuable enantiomerically pure components for asymmetric steroid syntheses. A survey of metal dibromides (M = Ni, Co, Pd, Mg) showed $ZnBr_2$ to be the most effective in promoting high stereochemical control in the conjugate addition step.[21] Because the metal-chelated cyclopentenone sulfoxide is so electrophilic, even ethyltitanium triisopropoxide, which normally adds directly to the carbonyl group of an enone, adds in a conjugate and highly (>98%) diastereoselective fashion.[23]

If indeed chelation is required before diastereoselective conjugate addition, then making the aryl group in the arylsulfinyl function more electron releasing and making the solvent less coordinating should increase the stability of the chelate and thereby increase the diastereofacial bias. As shown in eq 6, replacing a *p*-tolyl



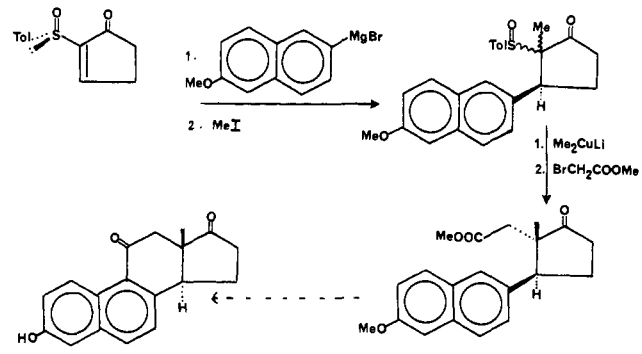
by a *p*-anisyl group in the arylsulfinyl functionality causes a noticeable increase (58 → 69) in diastereoselectivity.[23a,b] Replacing THF by the less coordinating (±)-2,5-dimethyltetrahydrofuran (DMTHF, mixture of cis and trans isomers), however, causes a much more dramatic increase in diastereoselectivity as observed for conjugate methyl (87 → 96) and conjugate phenyl (43 → 93) addition (eq 7).[23c] In the cases studied, the



p-anisyl sulfoxides are not soluble in DMTHF (or in ether); therefore, a combined benefit of the anisyl group *and* the less polar solvent could not be realized. Using

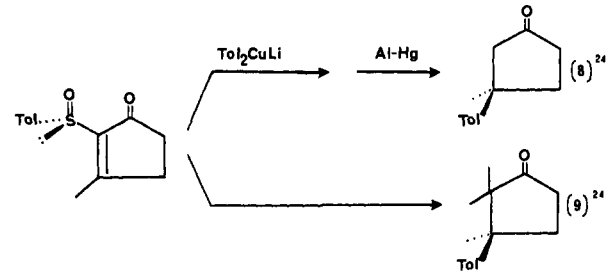
(23) (a) Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401. (b) We are now using this effect in an asymmetric synthesis of (−)-β-vetivone: unpublished results of G. H. Posner and T. G. Hamill. (c) Posner, G. H.; Frye, L. L. *Isr. J. Chem.* **1984**, *24*, 88.

Scheme I[21]



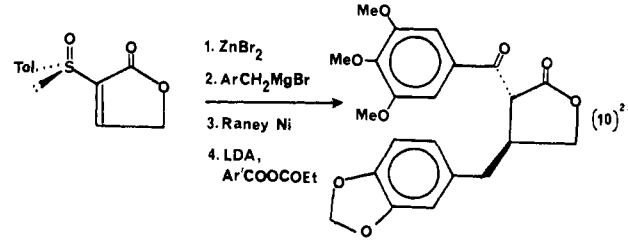
an aryl group bulkier than *p*-tolyl in the arylsulfinyl functionality has not led to increased asymmetric induction.[21]

All of the examples given thus far have involved asymmetric synthesis of *tertiary* carbon centers. Stereocontrolled formation of *quaternary* carbon centers is an even more challenging goal. As shown in eq 8, the same strategy works well for diastereoselective organometallic conjugate addition to some 3-substituted 2-arylsulfinyl 2-cyclopentenones leading, after reductive cleavage of the sulfinyl group, to 3,3-disubstituted cyclopentanones of good to excellent enantiomeric purity. In this way (eq 9), sesquiterpene (+)-α-cuparenone was prepared in good enantiomeric purity.[24]



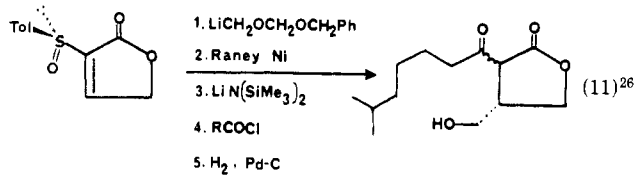
In the examples given so far, the initial conjugate adducts have been reductively cleaved to remove the sulfinyl group. In an asymmetric synthesis of the steroid equilenin (see Scheme I) we show that the sulfinyl group can be used not only as an effective, temporary, stereogenic auxiliary but also as an excellent means of controlling the regiochemistry of enolate ion formation. Thus, a 9,11-seco steroid and ultimately a tetracyclic steroid can be formed in excellent chemical yield and enantiomeric purity.[21]

Zinc-promoted chelate-mode conjugate addition of a functionalized benzylic Grignard reagent to lactone sulfoxide (**2**, *n* = 5) leads ultimately to (−)-podorhizon, a member of the anticancer podophyllotoxin family, in 95% enantiomeric purity (eq 10).[25]



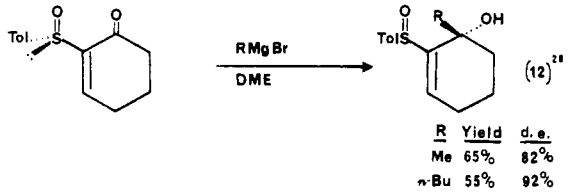
(24) Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, 25, 383. Cf. Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196. Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541.

Asymmetric conjugate addition of a $^{-}CH_2OH$ synthetic equivalent in the form of apparently intramolecular coordinated $LiCH_2OCH_2OCH_2Ph$ (derived from n-$Bu_3SnCH_2OCH_2OCH_2Ph$)[26a,b] to lactone sulfoxide (**2**, n = 5) leads to the (+)-*A* factor,[27] a potent autoregulating factor essential for streptomycin production (eq 11),[26a,c] presumably via the *non*chelated ground-state conformation of keto sulfoxide (**2**).



(11)[26]

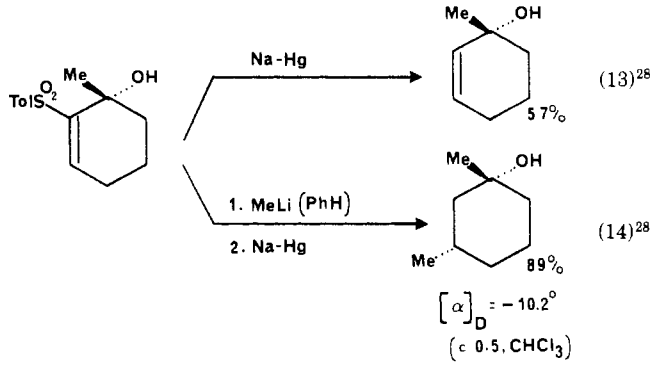
Finally, cycloalkenone sulfoxides (**1**) are electrophilic not only at the β-carbon atom but also at the carbonyl carbon atom and at the sulfinyl sulfur atom. Under special conditions (e.g., DME solvent), 1,2 carbonyl additions with some (i.e., only methyl and n-butyl) Grignard reagents occur (eq 12).[28] Although this



(12)[28]

R	Yield	d.e.
Me	65%	82%
n-Bu	55%	92%

asymmetric carbonyl addition process is very limited in scope (vinyl, phenyl, and allyl Grignards give mainly 1,4-adducts) in the methyl and n-butyl cases, substantial (i.e., 82–92%) diastereoselectivity is observed with carbonyl addition occurring apparently via the chelated form of the β-keto sulfoxide. These results resemble those obtained in asymmetric reduction of the carbonyl group of some enantiomerically pure β-keto sulfoxides.[29] Easy chromatographic separation of diastereomers, sulfoxide → sulfone oxidation, and subsequent chemical manipulation of these 1,2-adducts lead to some stereospecifically functionalized compounds in virtually complete enantiomeric purity (eq 13 and 14).[28,30]



(13)[28]

(14)[28]

(25) Posner, G. H.; Kogan, T. P.; Haines, S. R.; Frye, L. L. *Tetrahedron Lett.* **1984**, *25*, 2627.

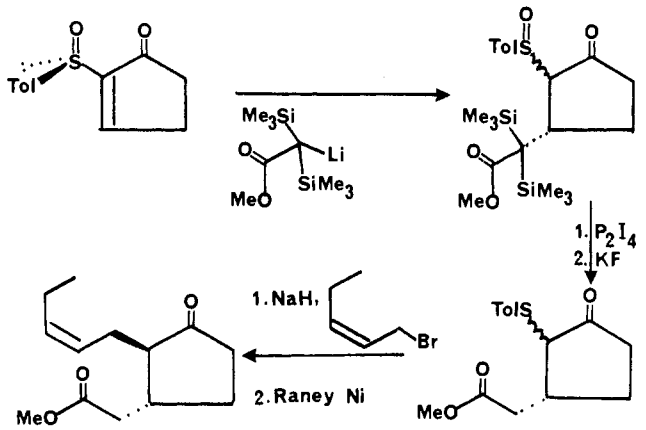
(26) (a) Posner, G. H.; Weitzberg, M., unpublished results. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (c) Biological evaluation of our synthetic *A* factor confirmed its activity; we thank Dr. Richard Monaghan and his group at Merck for doing these tests.

(27) Mori, K. *Tetrahedron* **1983**, *39*, 3107.

(28) Posner, G. H.; Switzer, C., unpublished results. We thank Prof. Amos Smith for a comment stimulating our examination of the stereochemistry of this carbonyl addition pathway.

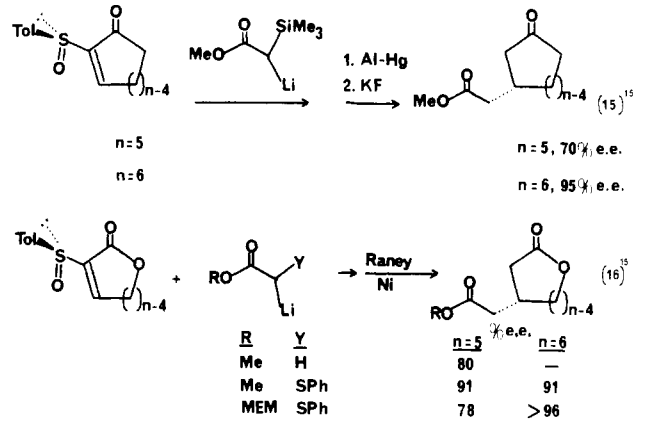
(29) (a) Kosugi, H.; Konta, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 211 and references therein. (b) Solladié, G.; Fréchou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912.

Scheme II[32]



Enolate Nucleophiles

Asymmetric Michael additions of enolate ions is a subject of considerable worldwide interest.[31] Cycloalkenone sulfoxides (**1**) and alkenolide sulfoxides (**2**) undergo asymmetric Michael additions with ester enolate ions, as shown in eq 15 and 16.[15] Equation 16

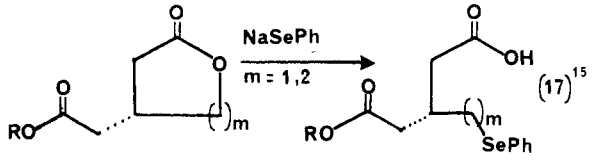


(15)[15]

(16)[15]

R	Y	n=5	n=6
Me	H	80	—
Me	SPh	91	91
MEM	SPh	78	>96

represents an entry, after alkyl–oxygen bond cleavage of the derivatized lactone products, into the class of variously 3-substituted glutarate half-esters of high enantiomeric purity (e.g., eq 17); such small molecules



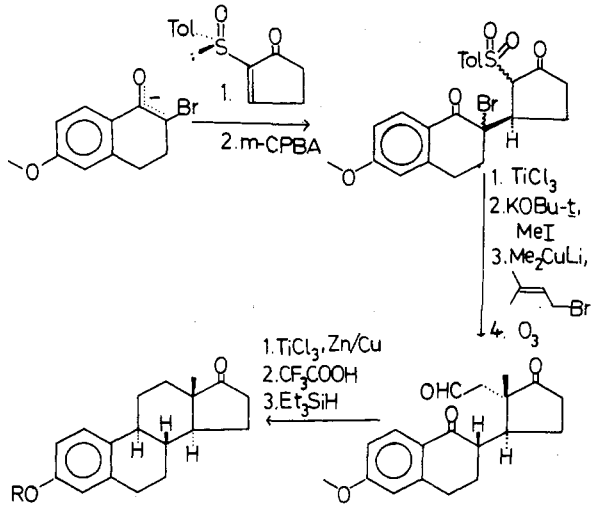
(17)[15]

carrying three different functional groups are flexible homochiral compounds of very considerable synthetic potential. In all of the cases studied, the absolute sense of asymmetric induction is consistent with Michael addition of these α-*mono*substituted lithium acetate

(30) (*R*)-(+)-1-Methyl-2-cyclohexen-1-ol: Matsubara, S.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 3741 and references therein.

(31) (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057. (b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2738. (c) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (d) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673. (e) Hodge, P.; Khosdel, E.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2205. (f) Oppolzer, W.; Pitteloud, R.; Bernardinelli, G.; Baettig, K. *Tetrahedron Lett.* **1983**, *24*, 2475. (g) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312. (h) Pfau, M.; Revial, G.; Guingant, A.; D'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. (i) Nebout, B.; de Jeso, B.; Pommier, J.-C. *J. Chem. Soc., Chem. Commun.* **1985**, 504. (j) Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235. (k) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710.

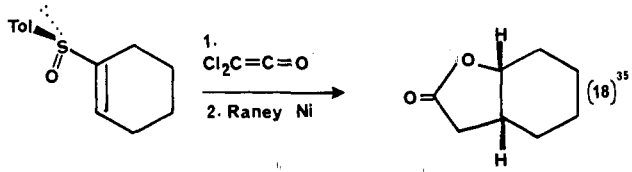
Scheme III[33]



esters to the nonchelated conformer of the β-carbonyl sulfoxides.

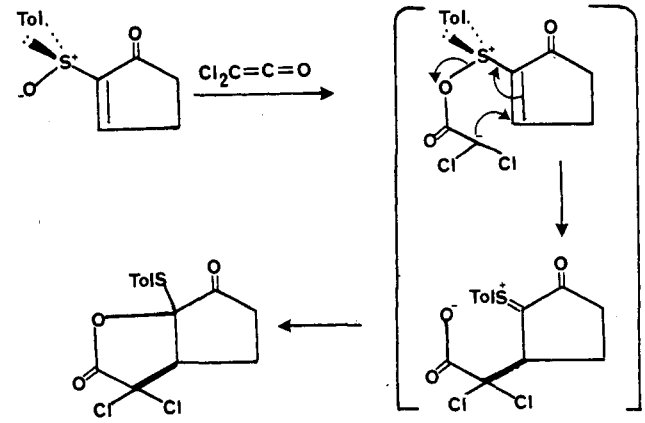
In sharp contrast, however, Michael additions of α,α-*di*substituted lithium enolates proceed apparently via the chelated form of the β-keto sulfoxides with almost complete π-facial diastereoselectivity;[15] such asymmetric Michael additions are the key steps in our preparation of natural (−)-methyl jasmonate (Scheme II)[32] and of natural (−)-estrone (Scheme III)[33] in extremely high enantiomeric purities. A reasonable but speculative interpretation of these results is that the chelated and nonchleated forms of the β-keto sulfoxides are both present in the reaction medium, with the nonchelated form predominating but being less electrophilic (i.e., less reactive) than the chelated form. A relatively unencumbered α-*mono*substituted enolate would then react with the more abundant nonchelated β-keto sulfoxide, whereas an α,α-*di*substituted enolate having a sterically congested nucleophilic center would react selectively with the more reactive chelated form of the β-keto sulfoxide.[33]

An intramolecular version of enolate Michael addition to enantiomerically pure vinylic sulfoxides is represented by reaction of cyclopentenone sulfoxide (1) with dichloroketene (Scheme IV);[34] this type of additive Pummerer rearrangement has been developed by Marino into a highly effective way of constructing variously substituted lactones in very high enantiomeric purity (eq 18).[35]

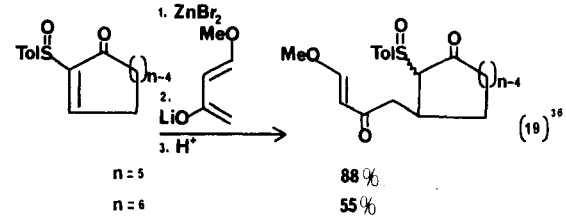


Successful Michael additions of enolate ions to cycloalkenone sulfoxides (1) prompted a study of *di*enolate ion additions; it was hoped that a one-pot overall (2 + 4) cycloaddition might occur via two sequential

Scheme IV[34]



Michael reactions. Although the first Michael addition proceeds well (eq 19, no reaction occurred between en-

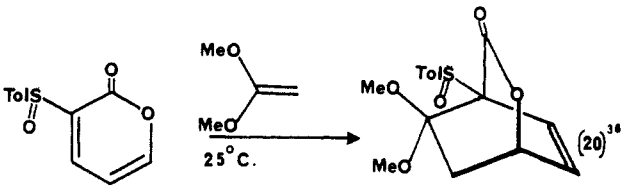


one sulfoxide (1) and dienol silyl ethers), the resultant, highly stabilized β-keto sulfoxide anion did not react further, presumably because it is too stable to undergo intramolecular cyclization to consummate a cycloaddition process.[36] Using sodium hydride to form the corresponding, presumably more reactive, β-keto sulfoxide *sodio* enolate also failed to produce a bicyclic product. *m*-Chloroperbenzoic acid oxidation of the sulfoxide produced the corresponding sulfone in 94% yield; sodium hydride deprotonation and treatment with excess methyl iodide gave an α-methylated β-keto sulfone in 91% yield without any detectable intramolecular cyclization. In contrast, several research groups have used ArS*(O)CH=CHCOOR species very successfully in highly asymmetric Diels–Alder cycloadditions,[37] and quinone sulfoxides also undergo effective (2 + 4) cycloadditions.[38]

Enol Ether and Enol Thioether Nucleophiles

Pyrone sulfoxide (3) is a strongly electrophilic sulfinylidiene which undergoes a mild (25 °C) inverse electron demand Diels–Alder cycloaddition with 1,1-dimethoxyethylene to give a bridged bicyclic adduct in nearly quantitative fashion (eq 20).[36] Extrusion of carbon dioxide does *not* occur under the reaction conditions. The stereogenic sulfinyl group in racemic pyrone sulfoxide (3) influences the stereochemical course of this cycloaddition so that the adduct is formed as a mixture of two diastereomers. The diastereomeric ratio is determined conveniently by 400-MHz ^1H NMR. The

(32) Posner, G. H.; Asirvatham, E. *J. Org. Chem.* **1985**, *50*, 2589.
(33) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239.
(34) Posner, G. H.; Asirvatham, E.; Ali, S. *J. Chem. Soc., Chem. Commun.* **1985**, 542.
(35) (a) Marino, J. P.; de la Pradella, R. F. *Tetrahedron Lett.* **1985**, *26*, 5381. (b) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643.
(36) Posner, G. H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1786.
(37) (a) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457. (b) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, *25*, 1727. (c) Koizumi, T.; Hakamada, I.; Yoshii, E. *Ibid.* **1984**, *25*, 87. (d) Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4005. (e) Glass, R. S.; Reineke, K.; Shanklin, M. *Ibid.* **1984**, *49*, 1527. (f) Brimble, M. A.; Davis, B. R. *Tetrahedron* **1985**, *41*, 4965. (g) Arai, Y.; Yamamoto, M.; Koizumi, T. *Chem. Lett.* **1986**, 1225. (h) Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1986**, *27*, 5509.
(38) Kraus, G.; Woo, S. H. *J. Org. Chem.* **1986**, *51*, 114.



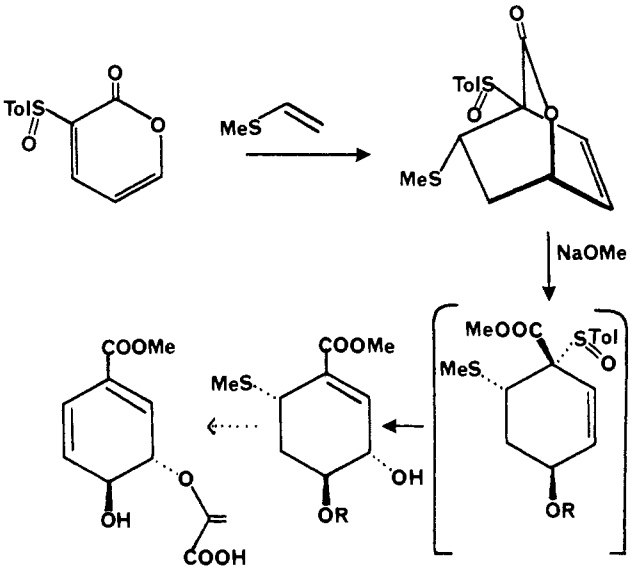
best diastereoselectivity of 76% (i.e., 88:12 ratio of diastereomers) is achieved with toluene or hexanes as solvent with 40–50 equiv of 1,1-dimethoxyethylene per equivalent of sulfinyldiene in a 0.1–0.2 M solution with a reaction time of 48 h at 25 °C. This is the first example of an asymmetric Diels–Alder cycloaddition with a sulfinyldiene as an enophile.[36]

Pyrone sulfoxide (3) reacts smoothly via a (2 + 4) cycloaddition path also with ethyl vinyl ether;[39a] reaction with methyl vinyl sulfide (an enol thioether) produces the corresponding Diels–Alder cycloadduct (Scheme V) with a diastereoselectivity at least comparable to that observed in eq 20.[39b] Methanolysis of this cycloadduct gives an allylic sulfoxide which spontaneously undergoes a [2,3] sigmatropic rearrangement to form a polyfunctionalized cyclohexene rapidly, efficiently, and in a highly stereocontrolled manner. Such richly substituted cyclohexenes are versatile and advanced intermediate for construction of various complex organic target compounds. Work is in progess on preparing enantiomerically pure sulfoxide (3) and on converting the cyclohexenes in Scheme V into chorismic acid, an important member of the shikimate biosynthetic pathway in plants and microorganisms linking carbohydrate to aromatic natural products.[40,41]

Conclusion

A combination of several characteristics makes the sulfoxide functionality especially useful in asymmetric synthesis: availability of enantiomerically pure (*S*) and (*R*) antipodes, ease of introduction into a variety of chemical environments, configurational stability under many different reaction conditions, convertibility into

Scheme V[39b]



different functional groups, and clean removal under mild conditions. In this Account, only one of many uses of chiral sulfoxides in asymmetric synthesis has been reviewed,[42] with special focus on the development of new synthetic methods for conversion of sp^2 carbon centers into homochiral sp^3 centers via C–C bond formation. Although all of the structurally diverse natural products discussed in this Account lack a sulfur atom, each one was prepared by using a sulfoxide functional group as a critical stereogenic center. The excellent success and rapid rate of progress in using sulfoxide functionalities as temporarily attached, stereogenic auxiliaries for asymmetric C–C bond formation certainly will continue; this area promises substantial additional rewards for adventurers choosing to explore further this particular frontier of asymmetric organic synthesis.

Financial support from the NSF (CHE 83-12161) and from the NIH (GM-30052) is very gratefully acknowledged. Special appreciation goes to the many dedicated and talented co-workers who have produced the results discussed here and whose names are indicated in the references.

(39) (a) Posner, G. H.; Harrison, W., unpublished results. (b) Posner, G. H.; Haces, A., unpublished results.

(40) Haslam, E. *The Shikimate Pathway*; Wiley: New York, 1974.

(41) For use of a pyrone sulfone and a chiral vinyl ether for preparation of (−)-methyl triacetyl-4-epishikimate, see: Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373. Cf. Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667.

(42) Posner, G. H. In *The Chemistry of the Functional Groups*, in press.