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Stereoselective and enantioselective synthesis of five-membered rings via conjugate additions of allylsulfone carbanions*

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Abstract: This lecture describes some of our studies of lithio derivatives of allyl sulfone carbanions which add α-regioselectively as well as anti diastereoselectively to Michael acceptor olefins. This can be ascribed to chelation in the Michael addition step. When the reaction leads to subsequent ring closure by using a bromoallyl sulfone, the latter acts as a methylenemethane synthon in a (3+2) Michael-initiated ring closure, affording highly functionalized cyclopentane derivatives Such additions proceed with high stereoselectivity and with asymmetric induction leading to nonracemic substituted cyclopentanones. Additions of allyl sulfone carbanions also proceed stereoselectively to C=N systems containing a chiral auxiliary on N. These can be used in the synthesis of optically active five- and six-membered ring N-heterocycles. Furthermore, chiral groups on the allyl sulfone moiety can induce significant remote asymmetric induction, made possible by the presence of an aromatic π-system which promotes intramolecular chelation to the Li cation.

INTRODUCTION

In recent years, there has been a great deal of interest in the stereoselective synthesis of substituted cyclopentanes, because of the considerable importance of cyclopentanoid natural products [1]. Such compounds include prostaglandins, prostacyclines, di and tri-cyclopentanoids (e.g., hirsutic acid), that display a wide range of biological properties. Furthermore, a number of five- and six-membered ring N-heterocycles containing hydroxy functions have been of interest as azasugar analogs [2].

While most cyclopentanation methods have involved sequential one-bond formation, (3+2) annulations employing two moieties offer a clear advantage. Such methodology depends on the availability of the two fragments and the range of substituents. Among the most interesting (3+2) cyclizations is the method by Trost et al. [3], using acetoxymethylallylsilanes as trimethylenemethane equivalents with the aid of palladium catalysts. We envisioned 2-bromomethyl-3-phenylsulfonyl-1-propene **1**, as a trimethylene-methane equivalent.

SYNTHESIS OF CARBALKOXY METHYLENECYCLOPENTANES

Bromoallyl sulfone **1** would take advantage of the carbanion stabilizing ability of sulfones, as well as possess an allyl halide function, thus combining the feature of a nucleophile with that of an electrophile. Such a synthon represents a potential trimethylenemethane species without the need of further transition-metal catalysis. The sulfone group in **1** is an attractive feature, since it can be easily removed or manipulated into other functional groups. We decided to examine bromoallyl sulfone **1**, which in a tandem Michael addition–alkylation sequence with unsaturated esters could lead to substituted methyl-

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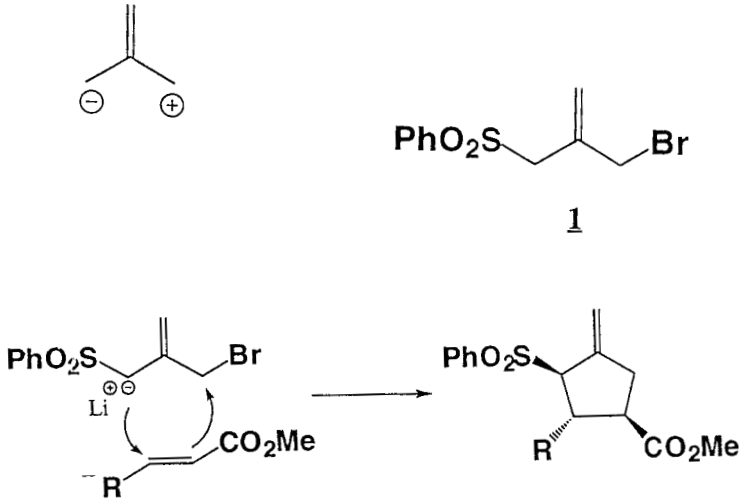
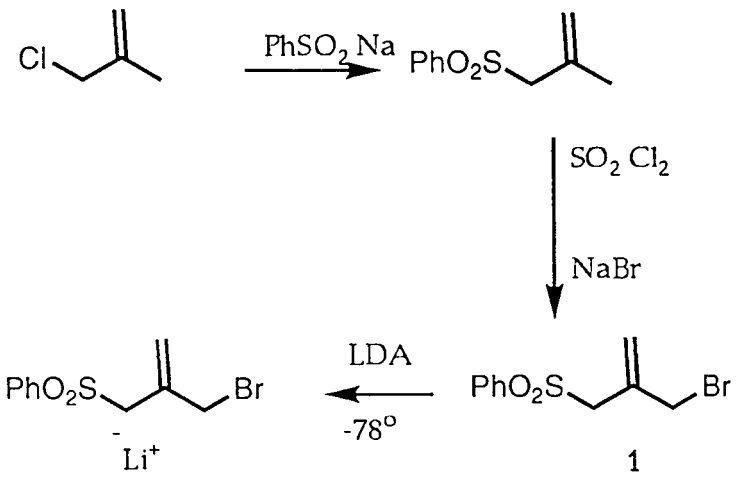
enecyclopentanes containing three additional functional groups, hopefully with well-defined stereochemistry (Scheme 1). Since many cyclopentanoids contain a methylene cyclopentane or a cyclopentanone unit, this method can afford a considerable synthetic advantage.



Scheme 1 Trimethylenemethane synthon.

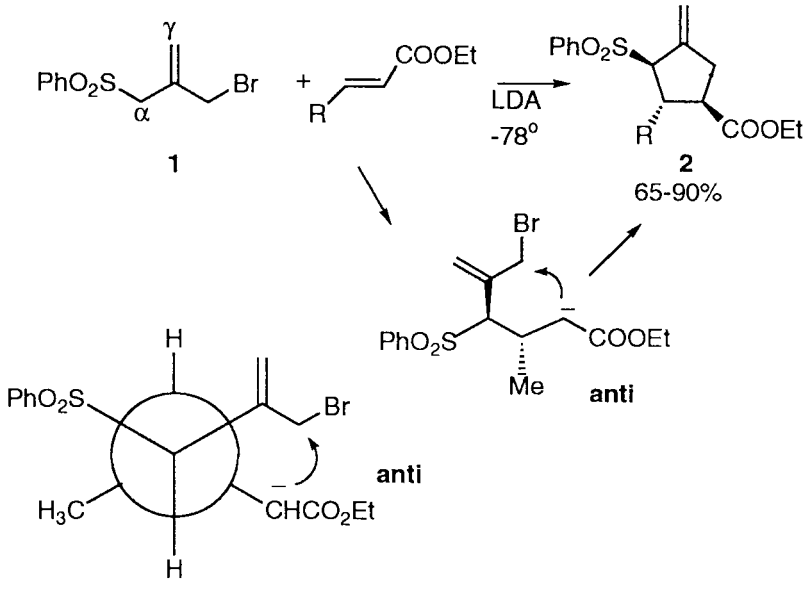
However, an examination of sulfone **1** indicates the danger of many possible pitfalls. First, allyl carbanions are known to be fickle, as they are capable of undergoing reaction via the α- or the γ–terminus [4]. In fact, several years ago Seebach [5] stated that the regiochemical control of reactions of unsymmetrical allyl carbanions with electrophiles is still more an art than a science. If the Michael addition of **1** would take place via the γ-terminus, cyclopentene rather than methylenecyclopentanes would result and with fewer interesting stereochemical features. Second, bromoallyl sulfone **1** in the presence of base could undergo intramolecular ring closure to a cyclopropane instead of undergoing Michael addition.

Nevertheless, we decided to examine the reactions of allylsulfone **1** with Michael acceptor substrates and we synthesized **1** from simple methallyl chloride by sulfinate displacement followed by chlorination and bromide exchange (Scheme 2). The intermediate chloroallyl sulfone can also be employed in the Michael additions but often with poorer results.



Scheme 2

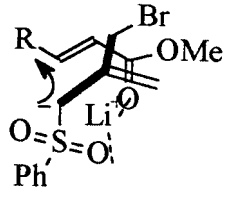
When bromoallyl sulfone **1** was converted into its lithio derivative by treatment with lithium diisopropylamide (LDA) at –78 °C, it was found to undergo facile Michael-initiated ring closure (MIRC) with ethyl crotonate and related α,β-unsaturated esters, to provide trisubstituted methylenecyclopentanes. All additions occurred in a regioselective manner via the α-phenylsulfonyl terminus of the allylic carbanion and were characterized by complete stereoselectivity at the three stereogenic centers of the resulting methylenecyclopentanes [6]. The stereochemical assignments were based on consistent nuclear Overhauser effect (NOE) data (Scheme 3).



Scheme 3 Tandem Michael addition substitution.

STEREO- AND REGIOSELECTIVE MIRC

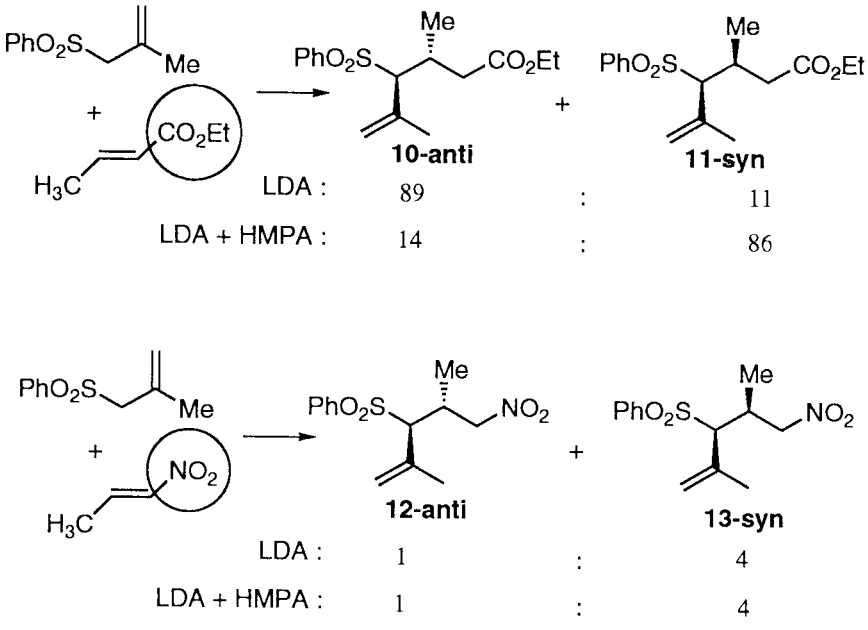
The formation of the trans-trans products presupposes that the Michael addition step leads to the anti diastereomer, which undergoes subsequent ring closure. The subsequent ring closure step is most likely thermodynamically determined giving rise to the more stable trans 3,4-disubstituted methylenecyclopentanes. We surmised that the high diastereoselectivity during the Michael addition may be due to coordination of the lithium ion with the oxygens of the sulfone as well as of the ester carbonyl group, providing a rather rigid transition state (Scheme 4) [7].



Scheme 4 Does Li^+ chelation between sulfone carbanion and C=O of ester account for high diastereoselectivity?

LITHIUM ION CHELATION

This hypothesis can be tested by addition of lithium ion solvating agents, known to disrupt chelation, but the bromoallyl sulfone **1** was unstable in the presence of hexamethylphosphoric triamide (HMPA). We tried in vain to isolate open-chain intermediates leading to the cyclized products; even when the reaction was slowed down or when fast quenching at low temperature was employed, only cyclized product and unreacted starting material were isolated. Apparently, the ring closure in this system occurs faster than the rate determining Michael addition. Hence, we resolved to study the Michael addition of methallyl sulfone with ethyl crotonate and cinnamate, leading to open-chain products that cannot cyclize. Indeed, the major product in this Michael addition was the anti diastereomer, as determined by 2D-NMR. However, if the reaction was carried out in the presence of HMPA the ratio was completely reversed, shifting in favor of the syn isomer; (e. g., with ethyl cinnamate from 100% anti to 20% anti:80% syn) [7]. By comparison the Michael addition of methallyl sulfone to nitro olefins such as nitrostyrene, which led to a mixture of syn and anti adducts (syn predominating), was unaffected by HMPA, apparently the Michael addition to nitro olefins is so fast there is little difference in activation energy for anti and syn products (Scheme 5) [7].



Scheme 5 Influence of HMPA chelation on anti/syn.

An examination of the four Li chelated transition states (**A–D**) for formation of the methylenecyclopentanes, suggests at first glance, that what might appear to be a favorable TS, namely (C), is expected to lead preferentially to the syn diastereomer; this was not observed. Therefore, in addition to Li ion chelation, the preferred formation of anti adduct (and ultimately of the trans-trans trisubstituted methylenecyclopentane) can be rationalized by considering a secondary pi orbital interaction (a HOMO-LUMO complex) between the enoate moiety and the parallel oriented double bond of the allylic anion. Such a stabilizing interaction is most favorable in (A) (Fig. 1) [7].

The coordination of the lithiated sulfone with the ester group of the acceptor has a negative effect on the addition to Z-unsaturated alkenes, involving apparently hindered conjugate attack on the Z-olefin and leading mainly to polymerization. However, reaction of **1** with the Z-unsaturated ester, diethyl

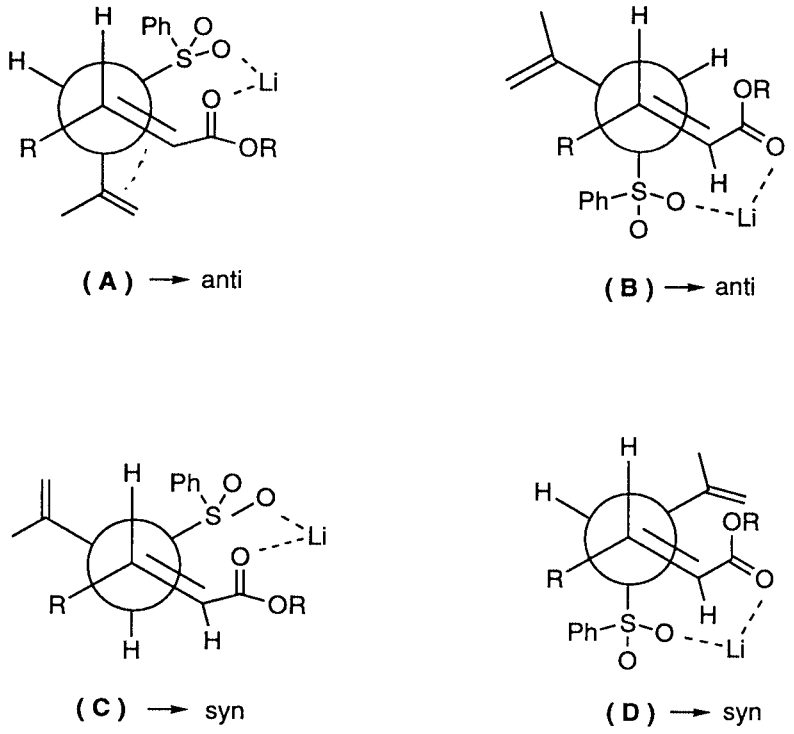
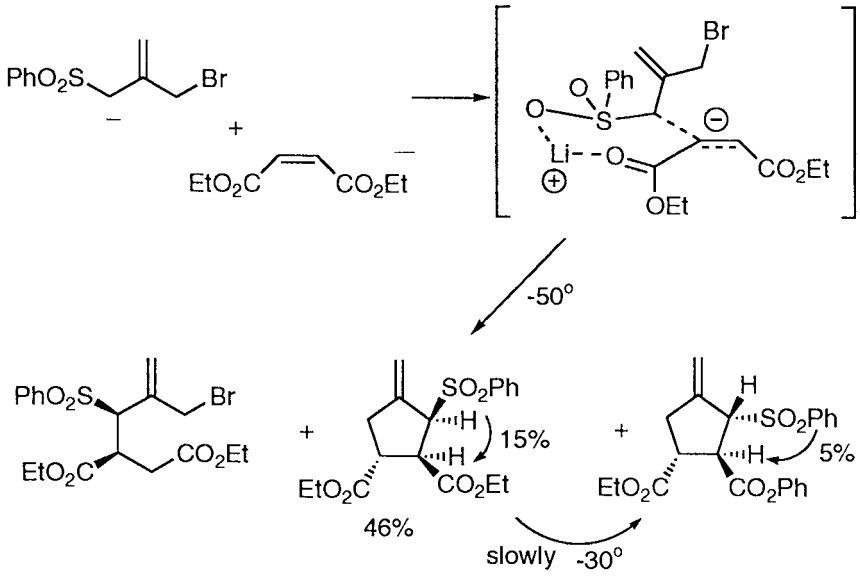


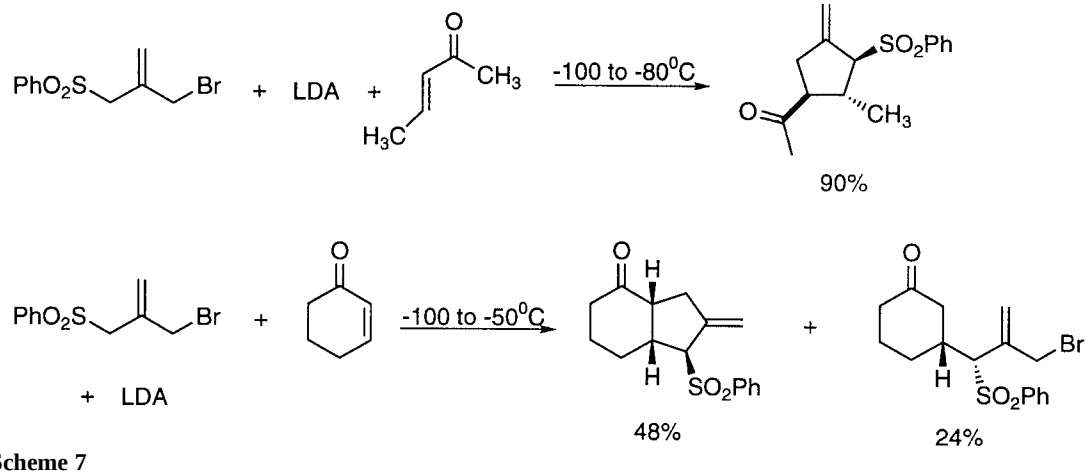
Fig. 1

maleate, provided surprisingly not only a cis-trans substituted methylenecyclopentane but also the syn open-chain adduct (all structures ascertained by NOE). Chelation between the lithiated sulfone and the second ester carbonyl explains the ready formation of syn, and hence of cis adducts (Scheme 6).



Scheme 6 Reaction with diethyl maleate.

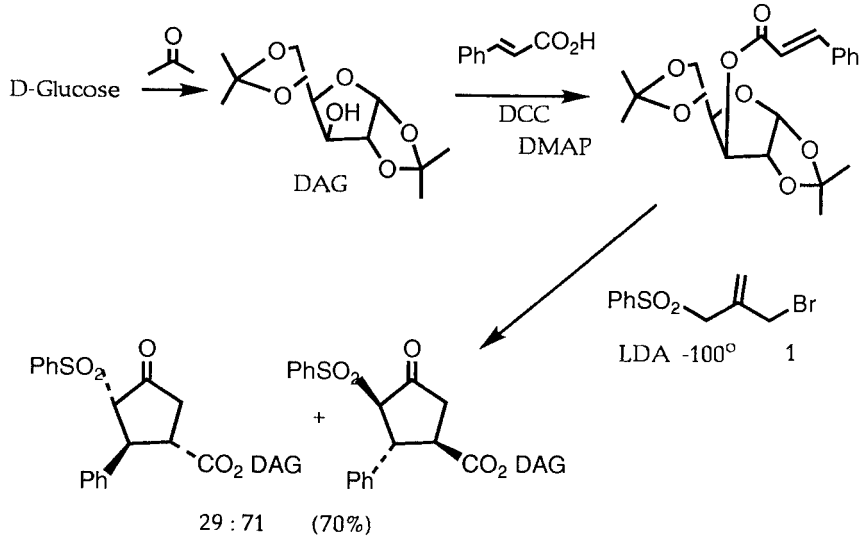
Bromoallyl sulfone as its lithio derivative also added to acyclic unsaturated ketones in high yield and excellent stereoselectivity. Cyclohexenone and unsaturated lactones, representing Z-unsaturated carbonyls, react less efficiently and produce bicyclic methylenecyclopentanes as well as open-chain products (Scheme 7) [7].



Scheme 7

OPTICALLY ACTIVE CYCLOPENTANONES

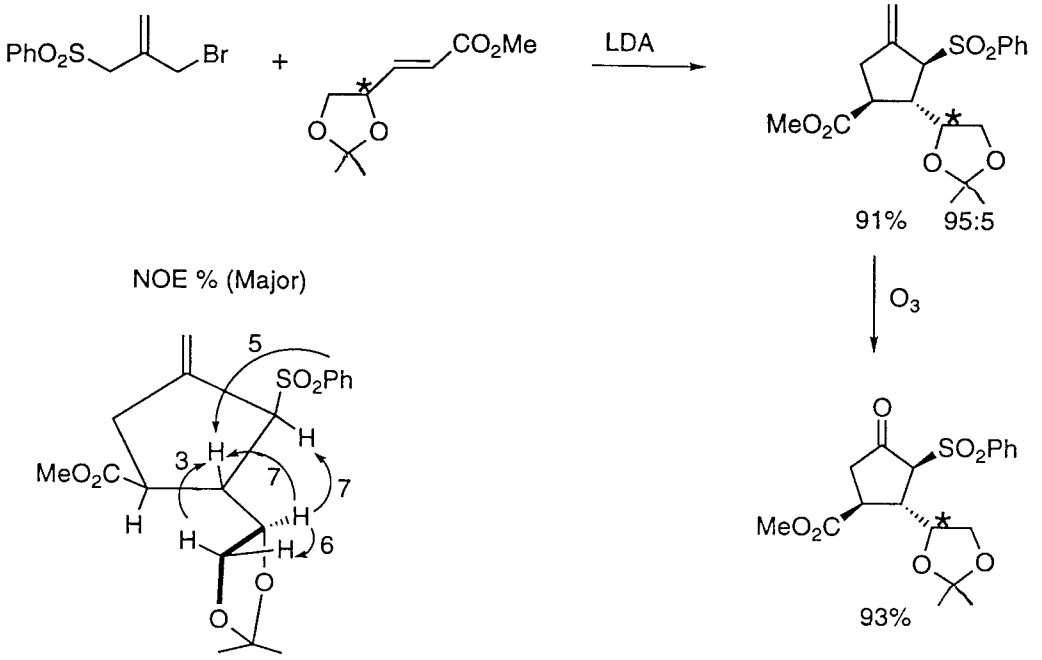
In order to obtain optically active cyclopentane derivatives, we first investigated stereofacial control by introducing 1,2:5,6-diisopropylidene-D-glucofuranose and diisopropylidine-D-galactose as the chiral moiety in the unsaturated ester substrates. While the cyclopentanation proceeded with complete stereoselectivity in the cyclopentane stereocenters, an inseparable mixture of diastereomers was obtained (Scheme 8).



Scheme 8

Hence, we explored the introduction of the chiral center at the gamma position of the α,β-unsaturated esters. First, γ-alkoxy–α,β-unsaturated E-enoates were examined as acceptors, and they were found to still provide a high degree of stereocontrol, in spite of confusing literature reports referring to addition of organometallics to such systems.

By using a nonracemic unsaturated ester derived from acetonyl protected glyceraldehyde and our bromosulfone **1**, we were able to achieve asymmetric cyclopentanation, ultimately leading in high yield to optically active trans-trans trisubstituted cyclopentanones (Scheme 9) [8].

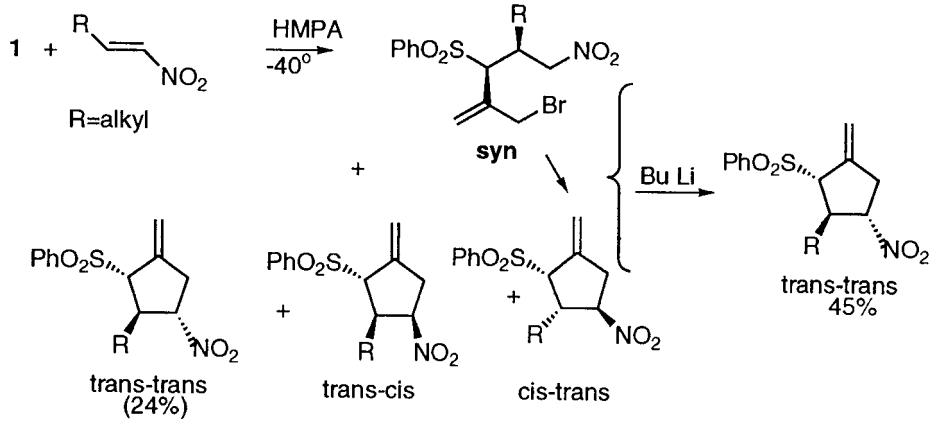


Scheme 9 Enantioselective synthesis of cyclopentanones.

SULFONE ADDITIONS TO NITROALKENES

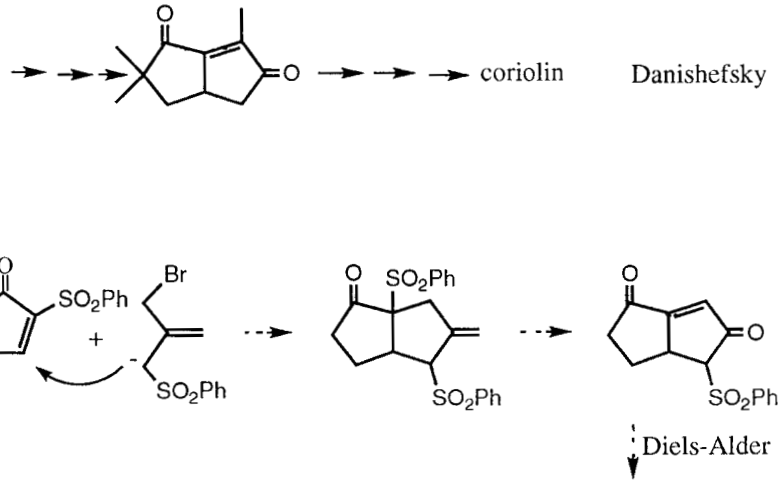
We also examined the possibility of achieving cyclopentanation with **1** and α,β-unsaturated nitro compounds. Since nitro groups can readily be removed or transformed into a keto function, this would represent a useful entry into various substituted cyclopentanes. Such a sequence would require that the Michael addition of the sulfone carbanion be followed in tandem by a C-alkylation of the resulting nitronate ion. However, it has been shown that nitronate anions do not undergo C-alkylation, even with allyl halides; at best they undergo O-alkylation.

When we carried out the reaction of the lithio derivative of **1** with several conjugated nitro olefins at –100 °C, we found that syn and anti open-chain addition products had formed with little stereoselectivity. However, in the presence of HMPA, already at –78 °C and more readily at –40 °C, cyclization via C-alkylation of the nitronate was achieved, and the nitro substituted methylenecyclopentanes could be obtained in up to 50% yield [9]. This represents the first examples of C-alkylation of nitronate anions (Scheme 10). In this manner 1-nitrocyclohexene can be converted into a bicyclic methylenecyclopentane.



Scheme 10 Reaction leading to ring closure of anti and syn adducts.

Bromoallyl sulfone **1** also underwent Michael addition to unsaturated sulfones. With 2-sulfonyl-2-cyclopentenone and 2-sulfonyl-2-cyclohexenone as substrates bicyclic cyclopentanones were obtained [10]. One of these was an enedione useful in the synthesis of naturally occurring cyclopentanoids. We also showed by NOE as well as by molecular orbital (MO) calculations that a phenylsulfonyl group alpha to a cyclohexanone greatly prefers the axial orientation. (Scheme 11)



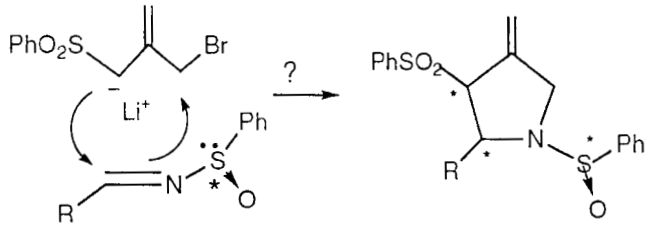
Scheme 11

SYNTHESIS OF CHIRAL PYRROLINES

Many hydroxylated pyrrolidine and piperidine derivatives are known to possess antiviral or glycosidase-inhibiting properties [2]. In an attempt to extend our (3+2) cycloaddition to N-analogs, specifically to optically active pyrrolidine derivatives, we examined the lithio derivative of **1** in reaction with an optically active imine (Scheme 12).

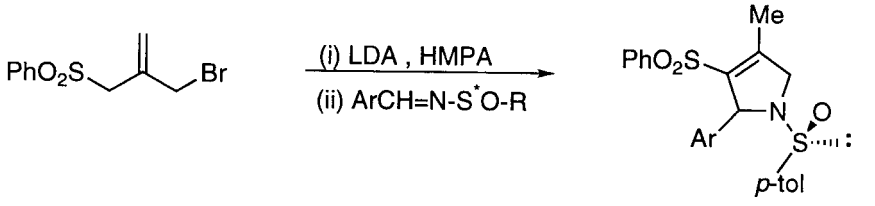
known glycosidase inhibitorsor antiviral agents

Synthesis of optically active functionalized pyrrolidines
via allyl sulfone addition to chiral imines?

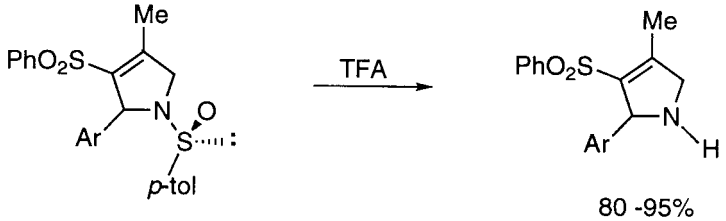


Scheme 12

The chiral sulfinimines were prepared by the method of Davis [11]. At –100 °C in the presence of HMPA, stereoselective (3+2) MIRC took place with double bond migration to the endo position to afford N-sulfinylpyrrolines in up to 88:12 diastereomeric ratio. Chromatographic separation and removal of the sufinyl group led to optically pure 2-arylpyrroline derivatives or to substituted pyrroles (Scheme 13) [12]. Efforts to hydroxylate such compounds are in progress.



Yield : 80 - 90 %
d.e. 50 - 80 %



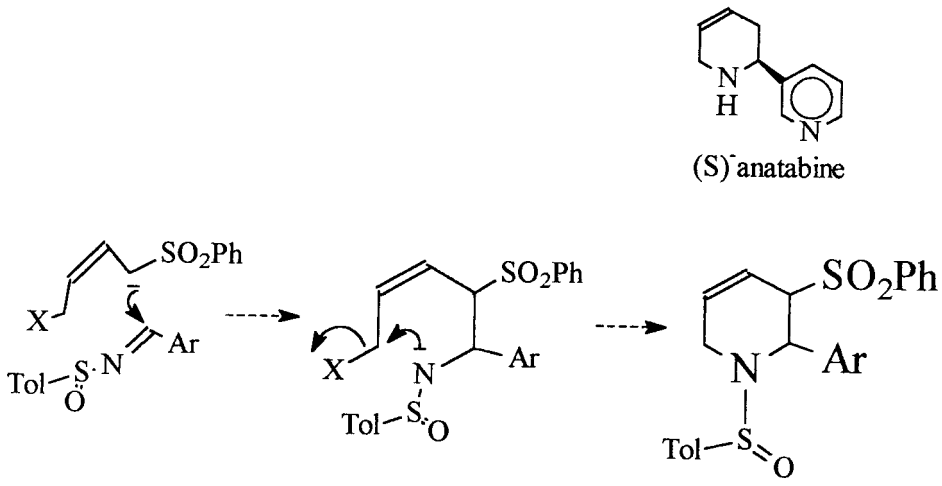
major diastereomer

80 -95%

Scheme 13

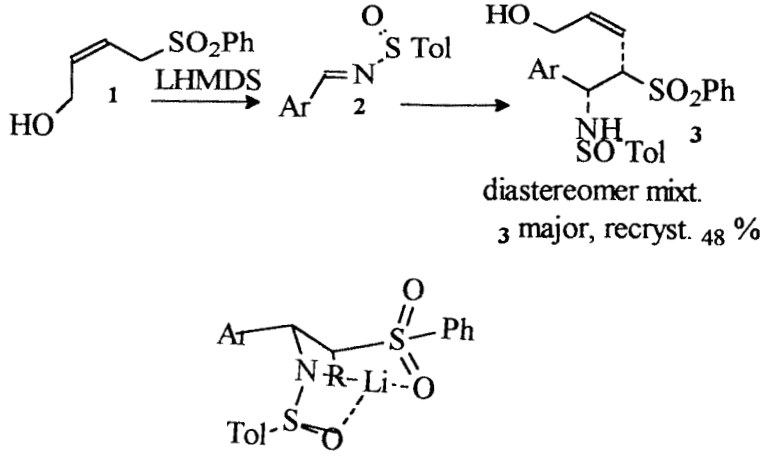
SYNTHESIS OF CHIRAL PIPERIDINES

We then focused our attention on Michael addition of other sulfone carbanions to chiral imines, that could lead to the synthesis of optically active 2-aryl piperidines, specifically to the alkaloid (S)-anatabine (Scheme 14).



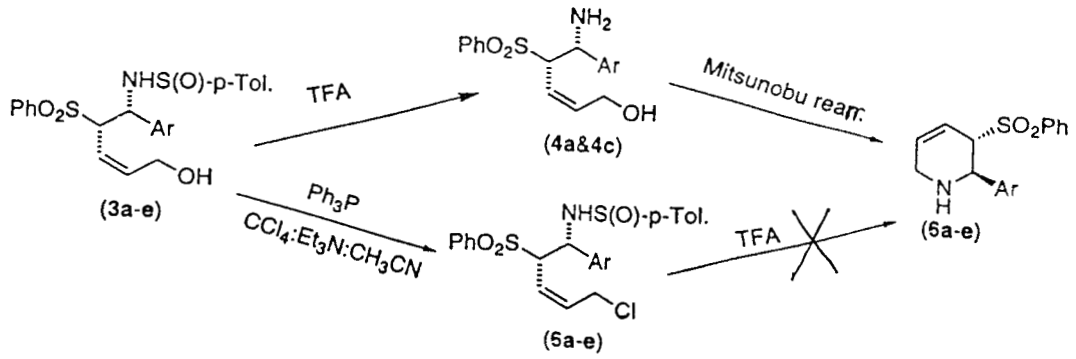
Scheme 14 Synthesis of optically active piperidines.

For this purpose, 4-phenylsulfonyl-cis-2-buten-1-ol was prepared from 2-butene-1,4-diol and converted into its lithio derivative by means of Li-HMDS. Addition to chiral arylsulfinimines at –100 °C afforded with fair diastereoselectivity a major stereoisomer **3** (Scheme 15).



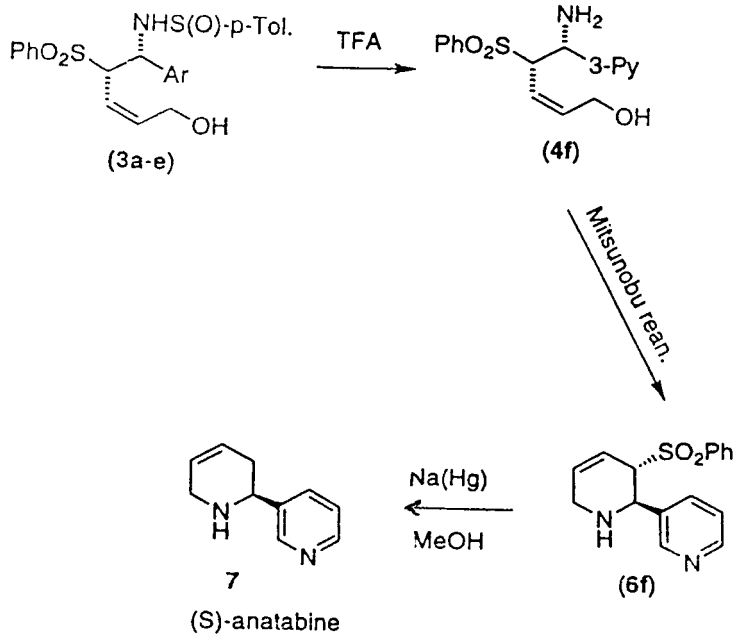
Scheme 15

Unfortunately, neither **3** nor its chloro analog underwent Mitsunobu cyclization. However, after removal of the sulfinyl group from N with trifluoroacetyl (TFA), Mitsunobu reaction afforded 5,6-trans-disubstituted 1,2,5,6-tetrahydropyridines (Scheme 16) [13].



Scheme 16

Removal of the sulfonyl group with Na(Hg), in the case of the 2-pyridinyl substituted tetrahydropyridine, furnished (S)-anatabine (Scheme 17).

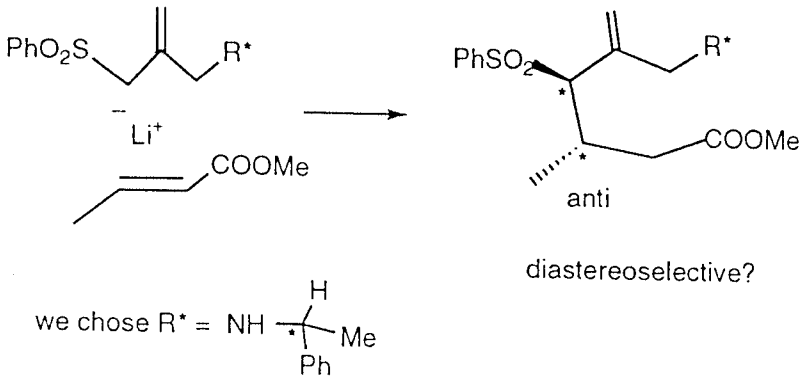


Scheme 17

REMOTE CHIRALITY TRANSFER DURING MICHAEL ADDITIONS

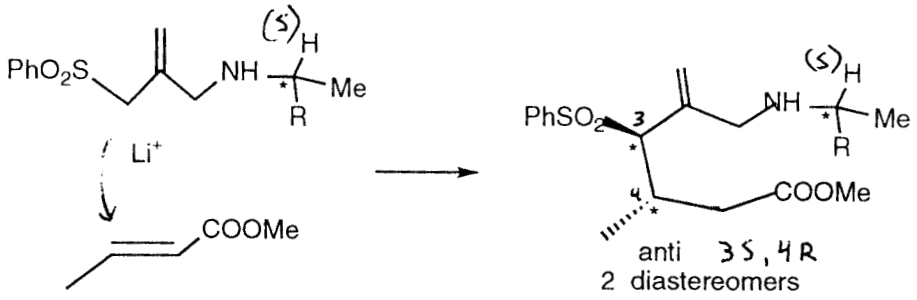
The high diastereoselectivity and α-regioselectivity observed during the Michael addition of the lithio derivative of 1 to unsaturated carbonyl compounds, as described above, led us to examine the possibility of remote asymmetric induction during a chiral auxiliary-controlled Michael addition (Scheme 18).

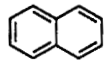
Hence, we prepared the nonracemic aminomethyl allylsulfone and on treatment with LDA at –78 °C followed by ethyl crotonate or cinnamate it led to two out of four diastereomers both possessing the anti arrangement of the newly formed stereogenic centers [14]. The diastereomeric ratio of 82:18 could be improved to a 9:1 remote asymmetric induction by using Li-HMDS at –108 °C (Scheme 19).



Scheme 18 Is remote chirality transfer from R* feasible during Michael addition?

A remarkable finding was the complete loss of diastereoselectivity on replacing the N-phenyl by a N-cyclohexyl group, while the asymmetric induction was improved to 93:7 on replacing of N-phenyl by N-naphthyl (Scheme 19).

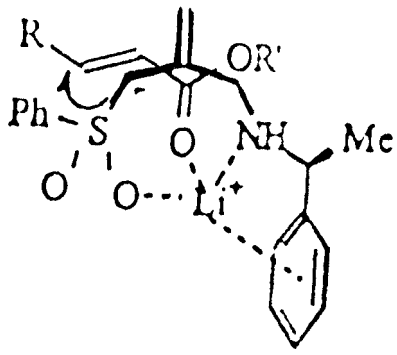


conditions	R	diastereomeric ratio
LHMDS, -108°		89 : 11
" "		50 : 50
" "		93 : 7

Scheme 19 Effect of remote aromatic group on chirality transfer during Michael addition of Li allylsulfone amine derivatives.

ENHANCED LI$^+$ CHELATION BY AN AROMATIC GROUP

The remarkable preference in diastereofacial approach of the lithio sulfonyl carbanion can be rationalized by assuming enhanced Li ion chelation by the pi system of the aromatic ring bound to the chiral center, in addition to chelation by the sulfonyl and carbonyl groups (Scheme 20). Similar effects of a phenyl substituent on Li ions have subsequently been found in other systems.



Scheme 20

ACKNOWLEDGMENT

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