Synthesis and Diels-Alder reactivity of sulfinyl homo- and hetero- dienes obtained *via* enantio-pure sulfenic acids

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Dedicated to Professor Domenico Spinelli on his 70th birthday
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Abstract
This account is intended to provide a brief survey on our contribution in the field of enantiopure sulfinyl homo and hetero dienes which we are able to obtain *via* enantiopure sulfenic acids. The chemistry of these sulfinyl-dienes was mainly developed taking into account the practical importance of stereoselective homo and hetero Diels-Alder cycloadditions, able to supply useful intermediates in the synthesis of target molecules.

Keywords: Sulfenic acids, sulfinyl-dienes, cycloadditions, regioselectivity, stereoselectivity, chiral auxiliary removal

Introduction

Since the pioneering work in 1983,[1] enantiopure vinyl sulfoxides have been commonly employed as dienophiles in Diels-Alder (DA) reactions. Their use often results in high levels of regio- and stereo-selectivity.[2] Recent years have witnessed an almost explosive development in the syntheses of conjugated diene sulfoxides and a growing interest in their use in stereoselective DA reactions.[3] The results obtained have emphasized the sulfinyl group's efficiency in controlling π-facial diastereoselectivity and the synthetic potential of conjugated sulfinyl dienes in the field of natural product chemistry.[4]

This report is mainly devoted to a survey of our contributions to the synthesis of enantiopure sulfinyl homo- and hetero- dienes, and investigations of their reactivity in DA cycloadditions. The first part of the review deals with a description of the general methodology for the preparation of enantiopure diene sulfoxides, based on the site-selective addition of sulfenic acids to suitable acceptors. The second part illustrates the high degree of stereocontrol observed in cycloadditions of cyclic-, acyclic-, homo-, and hetero- dienophiles with sulfinyl homo- and

hetero- dienes. The final part will be concerned with the transformation of the obtained enantiopure cycloadducts into functionalized cyclohexene derivatives which possess convenient features for their use as versatile intermediates in the synthesis of naturally occurring products.

Synthesis of enantiopure alkyl sulfinyl homo- and hetero dienes

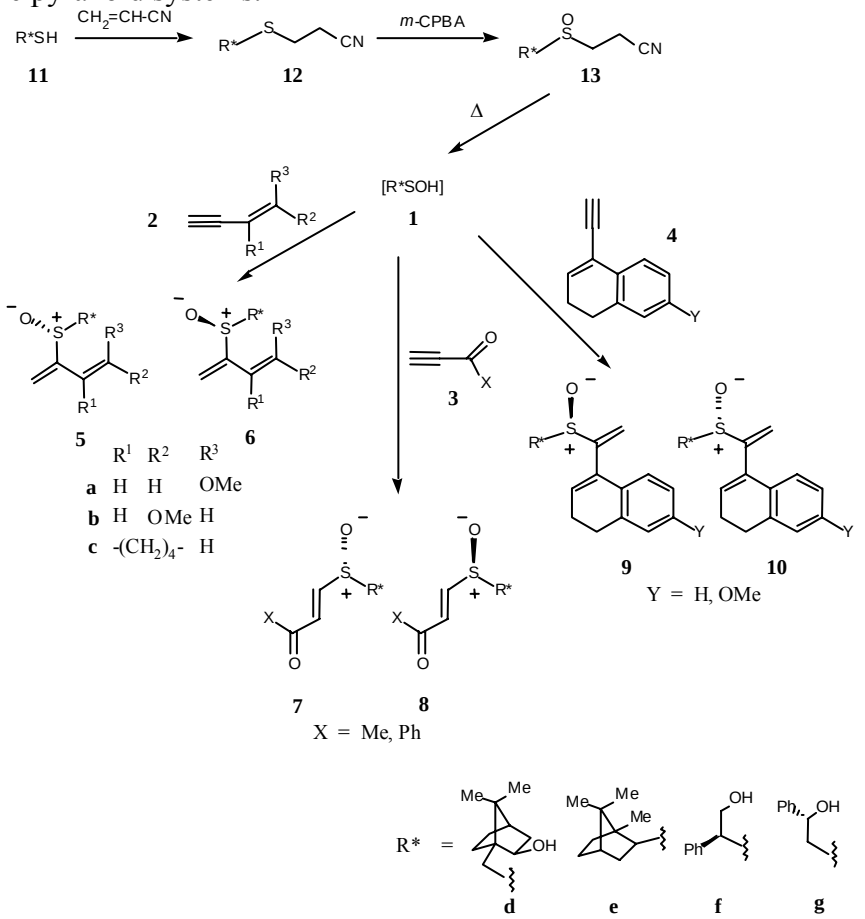
A seemingly general synthetic strategy was set up on the basis of the observation that the addition of sulfenic acids to unsaturated bonds allows easy introduction of a sulfinyl group into a suitably unsaturated substrate. The addition of sulfenic acids to alkenes or alkynes is a concerted reaction in which the nature of the unsaturated bond, on the one hand, and the structural features of the sulfenic acid, on the other, play a role, the former on the regioselectivity and the latter on the total yield of the addition, since stabilizing effects of the sulfenic acid structure, such as high steric demands and/or intramolecular hydrogen bonding, can prevent its self-condensation to give thiosulfinate.

The chiral sulfenic acids, **1**, conveniently generated by thermolysis of readily available sulfoxide precursors, add in a site-, regio-, and stereo-selective manner, and in good yields, to the conjugated enynes **2**, the 2-acylethynes **3,** and 1,2-dihydro-4-ethynylnaphthalenes **4** (Scheme 1),[3a,o,q,5] so providing a general and efficient access to enantiopure sulfoxides **5–10** which can act as homo or hetero dienes in stereoselective DA cycloaddition. The syntheses of alkylsulfinyl-dienes proceeded in four steps, beginning with the base-catalyzed addition of thiols **11** to acrylonitrile, followed by oxidation of the sulfides **12** with 3-chloroperoxybenzoic acid (*m*-CPBA) to give sulfoxides **13**. These were thermolyzed in the presence of an appropriate triple bond conjugated with a homo- or hetero- double bond, to generate transient sulfenic acids **1** which were trapped by the conjugated unsaturation to provide sulfinyl dienes **5–10**.

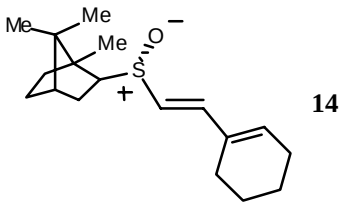
When the sulfenic acid **1e** was generated in the presence of enynes **2a,b**, the sulfinyl-1,3-dienes **5** and **6** were obtained with very high regioselectivity, whereas in the presence of 1-ethynylcyclohexene (**2c**) at 150°C, the formation of epimers **6ce** and **5ce** was observed, together with (S_S,*E*)-1-{2-[(1*S*-*exo*)-2-bornylsulfinyl]vinyl}cyclohexene (**14**), in the ratio 67.8:15.5:16.7, and 90% total yield. This decreased regioselectivity in the addition of sulfenic acid to enyne was regarded as a consequence of the steric characteristics of R*.[6] The strongly electron-donating and directing effects of the methoxy substituent have a notable influence on the reactivity of sulfinyl dienes **5a,b** and **6a,b** (Scheme 1), allowing the occurrence of their DA reactions in mild conditions, with complete regioselectivity, to afford enantiopure cycloadducts in high yields. When one diene double bond participates in a six-membered ring, as in sulfoxides **5c**, **6c,** the cycloadducts obtained with suitable dienophiles can be regarded as useful precursors of molecules having sterically demanding skeletons.

Thermolysis of sulfoxides **13** in the presence of 1-phenyl-2-propyn-1-one or 3-butyn-2-one led to the synthesis of β-sulfinyl enones **7** and **8** in good yield and with complete regioselectivity.[5e] A considerable amount of work has been reported on the use of β-sulfinyl-α,β-unsaturated ketones as dienophiles.[7] However, they can in principle act as hetero dienes in

inverse- electron-demanding DA reactions, so giving a straightforward access to functionalized and enantio-pure pyranoid systems.[8]



Scheme 1



The addition of **1** to the triple bond of dihydroethynylnaphthalenes **4** gave two dihydrovinylnaphthalenes **9** and **10**, epimeric at sulfur, in good total yield and in different amounts. The DA reactions of such dienes with the appropriate dienophiles give a straightforward approach to estrone-like compounds.

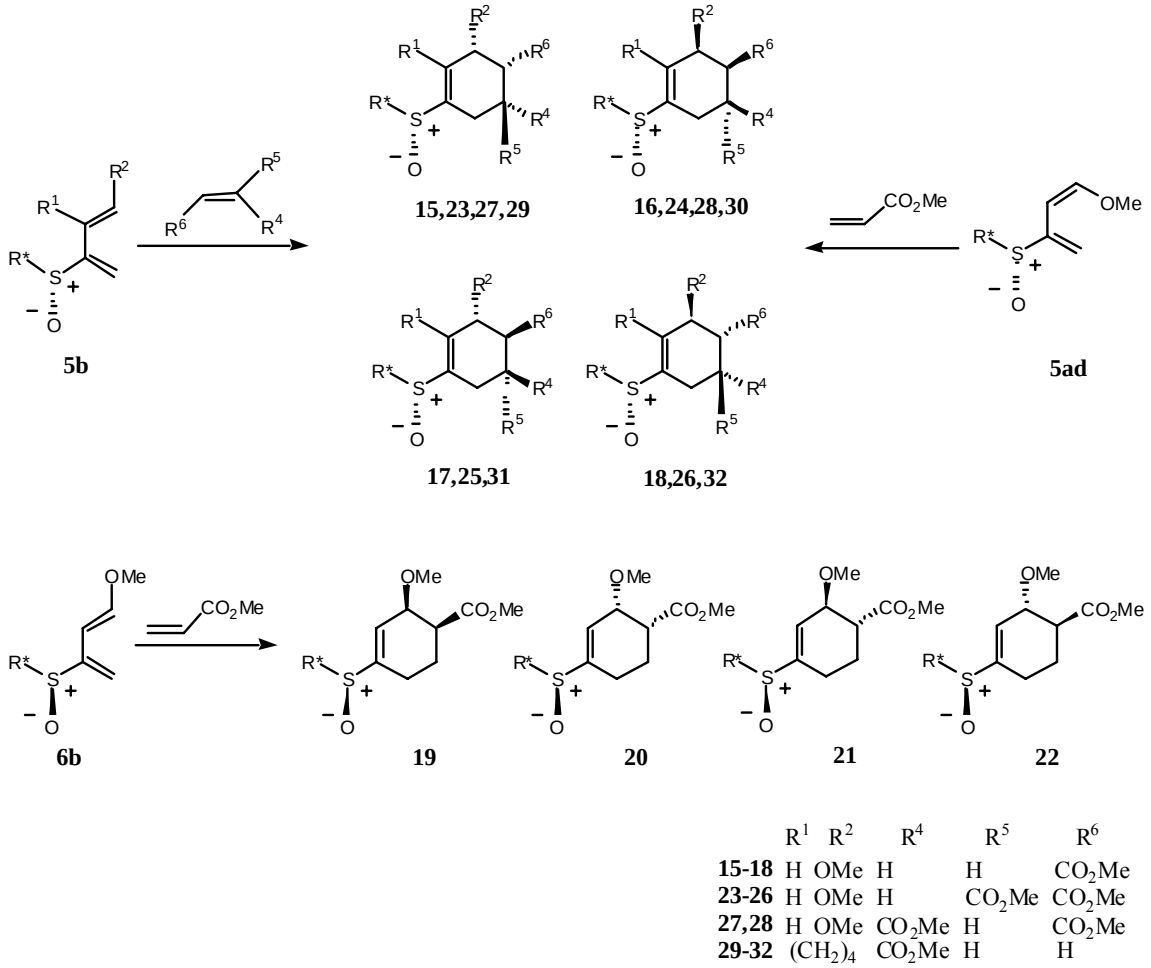
Camphorsulfonic- and mandelic acids, which are readily available members of the chiral pool, provided the precursors for the hydroxythiols **11d,f,g** which were chosen because the contiguity and consequent intramolecular hydrogen bonding between hydroxy and sulfoxide functions in their derivatives **1, 5–10, 13** facilitate the chromatographic separation of diastereoisomers and enhance the stereoselection in concerted processes. 2-Hydroxy-1-

phenylethanethiol, **11f,** and 2-hydroxy-2-phenylethanethiol, **11g,** were exploited as chiral control elements since the chiral auxiliaries derived from these vicinal hydroxythiols may be removed by phenyloxiran formation.[9] Moreover, we decided to compare the behavior of the structural isomers **11f** and **11g**, in order to evaluate whether the position of the asymmetric carbon with respect to the sulfur atom could have any effect on the asymmetric induction during the thermolysis of sulfoxides **13** (Scheme 1). The commercially available [(1*S*)-*endo*]-(-)-borneol was easily transformed into the corresponding thiol **11e** which represented a suitable precursor of sulfinyl-dienes **5–10e** possessing the remarkable characteristics of the camphor skeleton but having no possibilities of intramolecular hydrogen bonding. As a matter of fact, an intramolecular hydrogen bonding requires the presence of a hydroxy group in a suitable position with respect to the sulfoxide oxygen atom. This can be a limitation both in the choice of starting products from the chiral pool and the chemical behavior of the synthesized diene systems, *i.e.*, some unexpected and undesired reactions of the hydroxy function[10] may occur during subsequent chemical transformations. Our final purpose was the assessment of the structural characteristics required by chiral precursors to be effective in our synthesis of enantiopure sulfinyl dienes, in order to provide a larger number of terpene derivatives in the pool of suitable starting products. The obtention of the epimeric dienes **5**, **6**, **9**, **10** and ketones **7**, **8** in good yields, and their almost general easy separation by chromatography, represent favorable features for synthetic application.

Diels-Alder reactions of enantiopure alkyl sulfinyl homo- and hetero- dienes. The Effects of Lewis acids

Most of our investigations have involved the readily accessible dienes **5b,c** and **6b,c** which proved to be reactive DA participants with both cyclic and acyclic electron-deficient carbodienophiles. They undergo cycloadditions at room temperature or below, whereas the diene **5ad** reacted much more sluggishly with methyl acrylate or N-phenylmaleimide (NPM)— an expected consequence of its (*Z*)-configuration.[11]

Some relevant data regarding the DA reactions of dienes **5** and **6** with common acyclic dienophiles such as methyl acrylate, dimethyl maleate and fumarate (Scheme 2) are given in Table 1. In almost all the cases cycloadditions occurred with complete regioselectivity but the uncatalyzed DA reactions were not particularly stereoselective, showing in some experiments low *endo/exo* and facial diastereoselectivities.



	R^1	R^2	R^4	R^5	R^6
15-18	H	OMe	H	H	CO_2Me
23-26	H	OMe	H	CO_2Me	CO_2Me
27,28	H	OMe	CO_2Me	H	CO_2Me
29-32	$(CH_2)_4$		CO_2Me	H	H

Scheme 2

The effect of Lewis acid catalysis was investigated in some detail with diene **5bd** (entries 3–13 in Table 1). All the catalysts investigated, except $BF_3.Et_2O$, served markedly to increase the *endo/exo* ratio, and the use of $LiClO_4$ or $ZnCl_2$ in CH_2Cl_2 led also to high diastereofacial selectivity, apart from the special case of dimethyl fumarate. The best catalyst was $LiClO_4$, whose use as a suspension in CH_2Cl_2 gave only the *endo* isomers **15**, **16**, **23**, **24**, **27**, **28** in high yield and very high facial diastereoselectivity. This was the first illustration that $LiClO_4$ suspended in CH_2Cl_2 catalyzed DA reactions,[12] and that it did so highly stereoselectively. Reetz and Fox[13] have shown that Mukaiyama aldol reactions and conjugate additions were more efficiently catalyzed in this way than by 5 *M* $LiClO_4$ in Et_2O, conditions which were previously advocated for the dramatic acceleration of DA reactions.[14]

A rationalization of the stereochemical features observed in these cycloadditions has been proposed, and is discussed here for the DA reaction of diene **5bd** with methyl acrylate (Scheme 2).

The predominance of **15** among the products of the uncatalyzed cycloaddition of **5bd** may be interpreted on the basis of *Re* face approach of methyl acrylate to the diene in its (**h**) conformation, taking into account

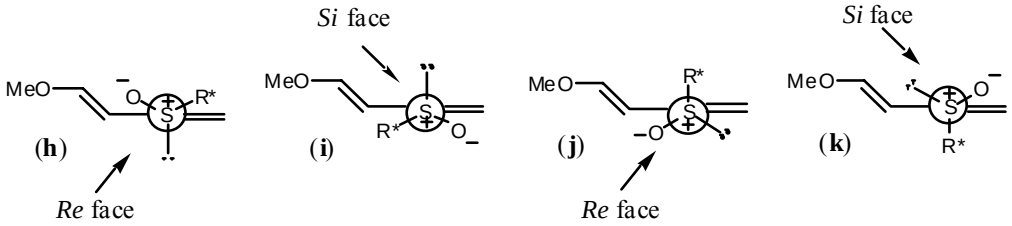
Table 1. Cycloadditions of sulfinyl dienes **5** and **6** with acyclic homo dienophiles[a]

					Adducts		
Entry	Diene	Dienophile	Catalyst	Ref.	*Endo*	*exo*	(ratio)
1	**5ad**	Acrylate	$LiClO_4$	3o	**17** : **18**	**15** : **16**	(17:80:3[b])
2	**5ad**	Acrylate	None	3o	**17** : **18**	**15** : **16**	(27:47:11:15)
3	**5bd**	Acrylate	$BF_3.Et_2O$	28	**15** : **16**	**17** : **18**	(54:29:12:5)
4	**5bd**	Acrylate	$EtAlCl_2$	28	**15** : **16**		(73:27)
5	**5bd**	Acrylate	Et_2AlCl	28	**15** : **16**	**17** : **18**	(65:28:4:3)
6	**5bd**	Acrylate	$LiClO_4$	28	**15** : **16**		(96:4)
7	**5bd**	Acrylate	$MgBr_2$	28	**15** : **16**		(75:25)
8	**5bd**	Acrylate	None	28	**15** : **16**	**17** : **18**	(54:31:8:7)
9	**5bd**	Acrylate	$ZnCl_2$	28	**15** : **16**		(94:6)
10	**5bd**	Fumarate	$LiClO_4$	3u	**23** : **24**	**25** : **26**[c]	(78:6:10:6)
11	**5bd**	Fumarate	None	3u	**23** : **24**	**25** : **26**	(51:13:20:16)
12	**5bd**	Maleate	$LiClO_4$	3u	**27**		(100)
13	**5bd**	Maleate	None	3u	**27** : **28**		(74:26)
14	**5be**	Acrylate	None	5c	**15** : **16**	**17** : **18**	(44:34:13:9)
15	**5cd**	Acrylate	$LiClO_4$	22	**29** : **30**	**31** : **32**	(59:31:6:4)
16	**5cd**	Acrylate	None	22	**29** : **30**	**31** : **32**	(54:27:12:7)
17	**6bd**	Acrylate	$ZnCl_2$	3o	**19** : **20**	**21** : **22**	(89:0:11[b])
18	**6be**	Acrylate	$LiClO_4$	5c	**19** : **20**		(93:7)
19	**6be**	Acrylate	None	5c	**19** : **20**	**21** : **22**	(38:26:25:11)
20	**6bf**	Acrylate	$LiClO_4$	5b	**19** : **20**		(90:6)
21	**6bf**	Acrylate	None	5b	**19** : **20**	**21** : **22**	(56:22:16:6)
22	**6bf**	Acrylate	$ZnCl_2$	5b	**19** : **20**		(81:13)
23	**6bg**	Acrylate	$LiClO_4$	5b	**19** : **20**		(93:2)
24	**6bg**	Acrylate	None	5b	**19** : **20**	**21** : **22**	(44:26:19:11)
25	**6bg**	Acrylate	$ZnCl_2$	5b	**19** : **20**		(92:2)

[a] Identification by numbers of cycloadducts in Scheme 2 and Table 1 is independent from R* features.

[b] Figure referring to both *exo*- adducts as a whole.

[c] *endo-/exo*- Selectivity refers to substituents at C-3 and C-4.



the relative stabilities of the transition states originating from the *endo* approach of the dienophile to different conformations of the diene around the S--C-3 bond. The isolation from the same reaction mixture of a certain percentage of the diastereomer **16** may be explained by considering the *Si*- face approach of the dienophile to the diene in the less favored (**i**) conformation. The great improvement of diastereoselectivity and increased reaction rate observed in the $LiClO_4$ catalyzed DA reaction of **5bd** suggest the approach of methyl acrylate to the *Re* face of the diene in its (**j**) conformation, with the catalyst coordinating the sulfinyl oxygen of the diene and the carbonyl oxygen of the dienophile, as depicted in Figure 1.

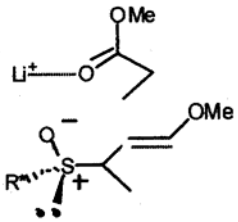


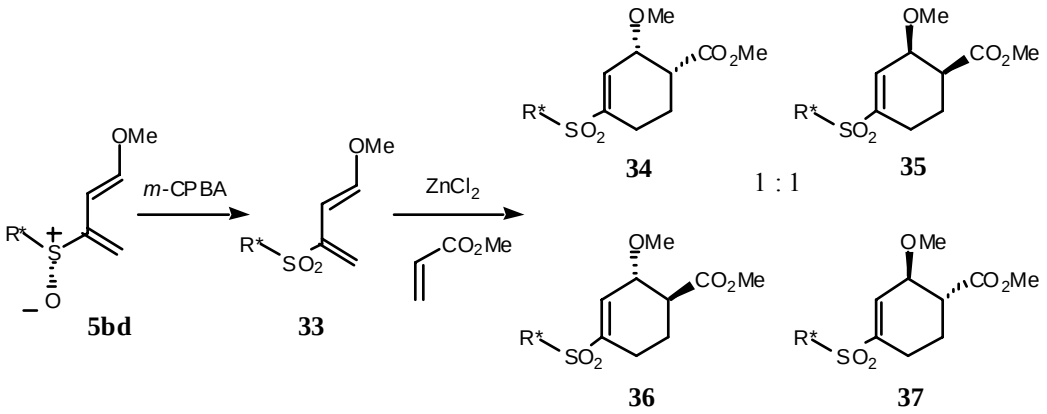
Figure 1

The failed increase of facial diastereoselectivity in the $LiClO_4$ catalyzed cycloaddition of (R_S)-1-{1-[(1*S*)-isoborneol-10-sulfinyl]vinyl}cyclohexene (**5cd**) with methyl acrylate (Table 1, entry 15) was unexpected on the basis of the results obtained in the reaction of diene **5bd** with the same dienophile and in the presence of the same catalyst. However, the observed coordination *via* Li^+ of both the diene and dienophile requires a suitable diene conformation in the transition state where the sulfinyl oxygen is directed towards the dienophile; this situation could be too sterically demanding and thus unfavored when **5cd** and methyl acrylate are involved in a DA reaction.

Literature data on the cycloaddition of dimethyl maleate with (*E*)-1-methoxybuta-1,3-diene report the formation of *endo/exo* products in an approximately 70:30 ratio.[15] Our observation of complete *endo* diastereoselectivity in the reaction between **5bd** and maleate (entry 13 in Table 1) indicates the remarkable control exerted by a sulfinyl group on the *endo* selectivity when the dienophile is suitably substituted.

$ZnCl_2$-catalyzed cycloaddition of methyl acrylate with the sulfonyl-diene **33**, readily obtained by oxidation of **5bd** with *m*-CPBA, provided a 10:1 mixture of *endo*- (**34+35**) and *exo*- (**36+37**) adducts (Scheme 3). The ratio **34/35** was 1:1, which showed that the isoborneol group

did not significantly influence the stereoselectivity of cycloaddition, and so confirmed the fundamental role that sulfoxide chirality plays in determining the diastereoselectivity of cycloadditions of sulfinyl dienes.



Scheme 3

An additional confirmation of the observation that the asymmetric induction in these DA reactions of sulfinyl dienes is overwhelmingly influenced by the sulfur configuration can be inferred from a careful inspection of Table 1, where the results of DA reactions of dienes **5bd**, and **6be–g** (entries 6, 18, 20, 23) with methyl acrylate in the presence of $LiClO_4$ are reported. While the structural features of the alkyl residues directly linked to the sulfur function in enantiopure alkyl sulfinyl dienes play a relevant role in their synthesis based on sulfenic acid / enyne addition, the stereogenic nature of these alkyl skeletons has no significant effect on the stereocontrol observed in the DA reaction of such sulfinyl dienes.

Electron-deficient cyclic dienophiles, such as maleimides and maleic anhydride, have been used widely in cycloadditions with enantiomerically pure 1- and 2-sulfinyl-dienes, and complete *endo*-, and very high facial-diastereoselectivities were generally observed. Dienes **5** and **6** were reacted with maleimide and NPM, and the results of these uncatalyzed and catalyzed cycloadditions are summarized in Table 2. The nearly exclusive formation of **38**, **42**, and **50** (Scheme 4, entries 3, 8, 11 in Table 2) indicate the great control exerted by a sulfinyl group on the π-facial selectivity: the cyclic dienophiles approach dienes on their *Re* faces, which are the more nucleophilic sides, opposite to the sulfinyl oxygen, with the dienes adopting the less sterically hindered conformation along the C-S bond.

Although the results on both the reactivity and stereoselection of dienes **5** and **6** with cyclic electron-deficient dienophiles are impressive, we found of interest the progression of our investigation into the effect of Lewis acid catalysis. The cycloadditions of our dienes with maleimides occurred with reduced reaction times, and sometimes complete *endo/exo* diastereoselectivity in favor of the *endo*- isomer (compare entry 10 with 11, and 14 with 15 in Table 2) if performed in the presence of $LiClO_4$, which was chosen for its good ability in enhancing facial diastereoselectivity. The reported lack of influence, or decrease in facial

diastereoselectivity (compare entry 2 with 3, 6 with 8, and 10 with 11 in Table 2) induced us to investigate the cycloadditions of diene **5bd** with NPM in the presence of different Lewis acids: all of these led to a diminished facial selectivity, which turned over to favor the diastereoisomer **51** when $Eu(fod)_3$ was the catalyst (entry 5 in Table 2).

Table 2. Cycloadditions of sulfinyl dienes **5**, **6**, **9**, **10** with cyclic homo dienophiles[a]

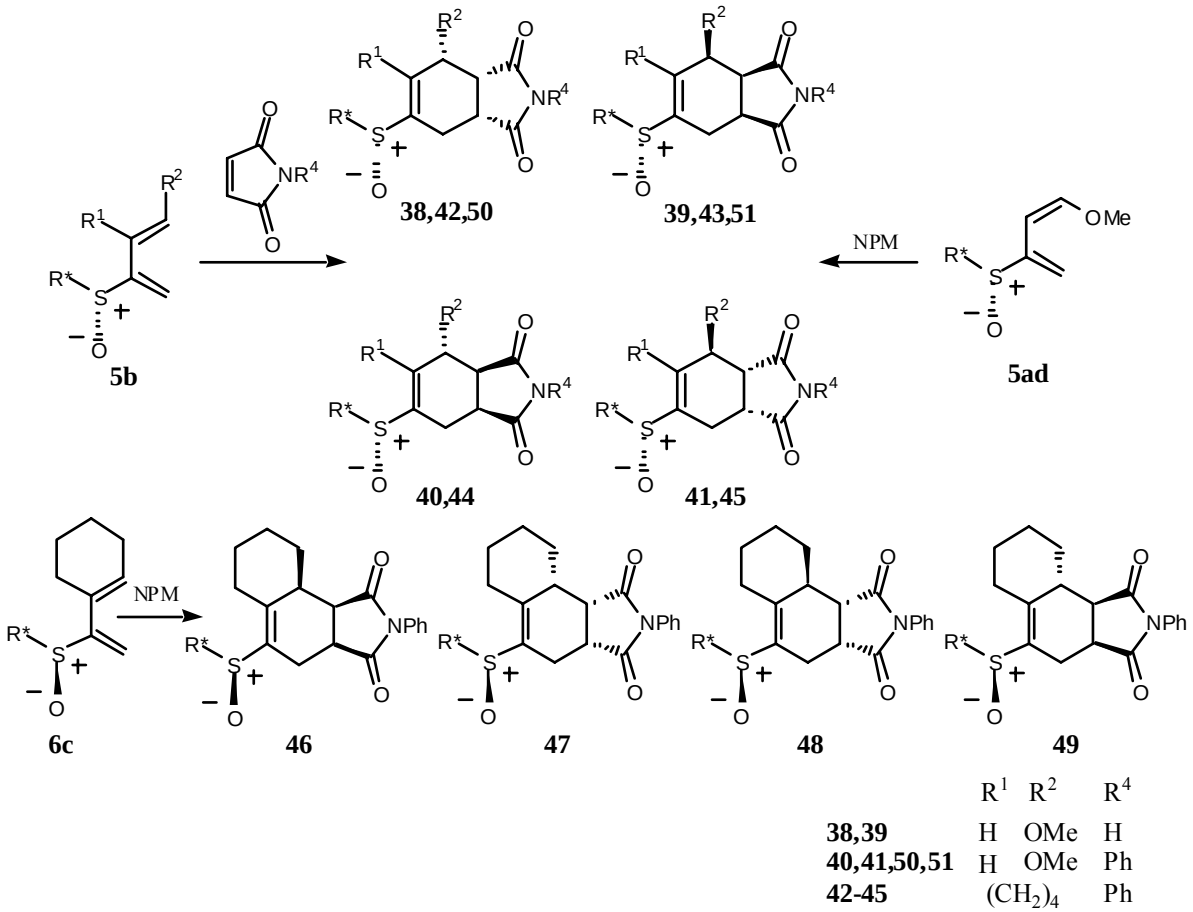
Entry	Diene	Dienophile	Catalyst	Reference	Adducts		
					endo	*Exo*	(ratio)
1	**5ad**	NPM	none	3u	**40** : **41**		(12:88)
2	**5bd**	maleimide	$LiClO_4$	3u	**38** : **39**		(88:12)
3	**5bd**	maleimide	none	3u	**38** : **39**		(97:3)
4	**5bd**	NPM	$BF_3.Et_2O$	3u	**50** : **51**		(75:25)
5	**5bd**	NPM	$Eu(fod)_3$	3u	**50** : **51**		(36:64)
6	**5bd**	NPM	$LiClO_4$	3u	**50** : **51**		(60:40)
7	**5bd**	NPM	$MgBr_2$	3u	**50** : **51**		(80:20)
8	**5bd**	NPM	none	3u	**50** : **51**		(87:13)
9	**5bd**	NPM	$ZnCl_2$	3u	**50** : **51**		(73:27)
10	**5cd**	NPM	$LiClO_4$	6	**42** : **43**		(89:11)
11	**5cd**	NPM	none	6	**42** : **43**	**44**	(90:9:1)
12	**5ce**	NPM	none	6	**42**	**44** : **45**	(77:12:11)[b]
13	**6cd**	NPM	none	6	**46** : **47**	**48**	(75:15:10)
14	**6ce**	NPM	$LiClO_4$	6	**46** : **47**		(67:33)
15	**6ce**	NPM	none	6	**46** : **47**	**48** : **49**	(63:9:16:12)
16	**9d** (Y=H)	NPM	none	5d	**52**	**56** + **57**	(42:58)
17	**9d** (Y=OMe)	NPM	none	5d	**53** : **54**	**58** + **59**	(52:5:43)
18	**10e** (Y=OMe)	NPM	none	5d	**55**	**60** + **61**	(67:33)

[a] Identification by numbers of cycloadducts in Scheme 4 and Table 2 is independent from R* features.

[b] The minor *endo* adduct was not isolated from the reaction mixture.

The stereochemical outcome of these catalyzed reactions can be interpreted by considering the *endo*- approach of the dienophile once again on the *Re* face of the diene, which adopts the conformation (**j**) where the catalyst is able to co-ordinate both the carbonyl oxygen of the dienophile and the sulfinyl oxygen of the diene. However the dienophile's approach to the *Si* face of the diene in its (**k**) conformation also becomes effective owing to the catalyst participation and steric requirements of a conformationally biased dienophile such as NPM: the (**k**) conformation appears electronically less favored than (**j**), but this adverse characteristic is counterbalanced in part by a reduced steric congestion in the transition state. If this is true, the

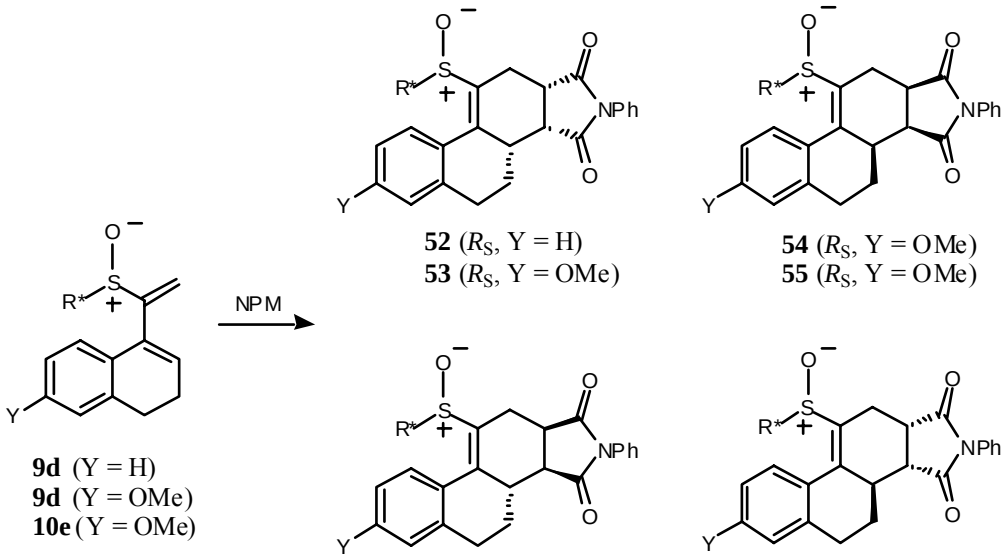
size of the Lewis acid should influence the relative stabilities of the transition states originating from NPM's *endo* approach to conformations (**j**) or (**k**): in fact, the approach to the *Si* face of the diene **5bd** in its conformation (**k**) becomes the favorite one when the bulky $Eu(fod)_3$ catalyzes the cycloaddition (entry 5 in Table 2).



Scheme 4

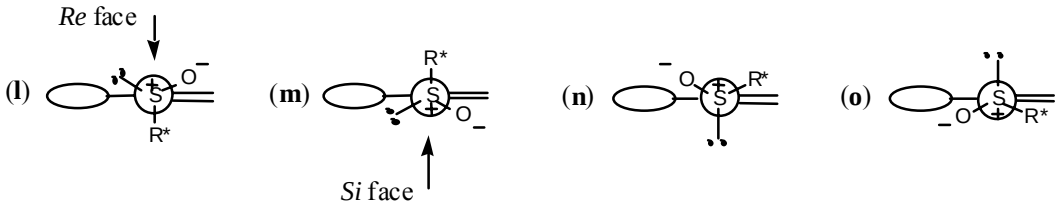
NPM was also chosen as the dienophile in DA cycloaddition with dienes **9** and **10,** since the reaction would lead to enantiopure cycloadducts showing the 16-azasteroid skeleton. On the basis of present knowledge, 16-azasteroids do not exist in nature but they have been synthesized in racemic form and biologically tested.[16] The conditions and results of the DA reactions performed are reported in Table 2. The diastereomeric cycloadducts **52–61** (Scheme 5) were obtained in very good total yields and are easily separable by column chromatography.[5d] The very long reaction times are evidence of the low DA reactivity of sulfinyl dienes **9**, **10**, even though the presence of the methoxy substituent appears to significantly increase the reaction rate. It is evident (Table 2, entries 16–18) that the *endo/exo* diastereoselectivity was low in these cases, and for diene **9d** (Y = H) quite in favor of the usually less-favored *exo* isomers. A very good facial diastereoselectivity was observed for the *end-o* approach while both *exo*- isomers

were obtained in almost equal amounts. A tentative rationalization of these results resides in the high steric requirements of both the diene and dienophile, such that the less sterically congested *exo* approaches occur in high percentage, without significant facial discrimination, while the *endo* approach, which is much more sterically demanding, requires an almost complete facial selection. This last aspect is very useful from the synthetic point of view.



Scheme 5

We suggest that the formation of the only *endo* adduct **55** comes from the NPM approach to the *Si* face of the (S_S)-diene **10e** (Y = OMe) in its (**m**) conformation. Concordantly, the (R_S)-dienes **9d** (Y = H, OMe) cyclo-add in *endo* fashion, mainly from their *Re* face in conformation (**l**).



Previously we had observed preferential *endo* approach to the opposite face of analogous sulfinyl dienes **5** and **6,** but the conformational preferences proposed in these cases [analogous to (**n**) and (**o**)] can be prevented here by electrostatic repulsion between the sulfinyl oxygen and the π-system of the fused benzene ring. With the hope of gaining experimental support for the arguments given above, we oxidized diene **10e** (Y = OMe) to 4-{1-[(1*S*-*exo*)-2-

bornylsulfonyl]vinyl}-1,2-dihydro-7-methoxynaphthalene following the usual procedure with *m*-CPBA, and submitted this sulfone, without isolation, to DA cycloaddition with NPM. The DA procedure was performed in CH_2Cl_2 at room temperature for eight days, and then the reaction mixture, dissolved in 1,2-dichloroethane, was maintained at reflux for a further eight days, but unreacted diene and dienophile were recovered. The failure of this sulfone cycloaddition can be ascribed to its concurrent steric and electronic requirements which prevent fruitful DA approaches with NPM under the reaction conditions adopted.

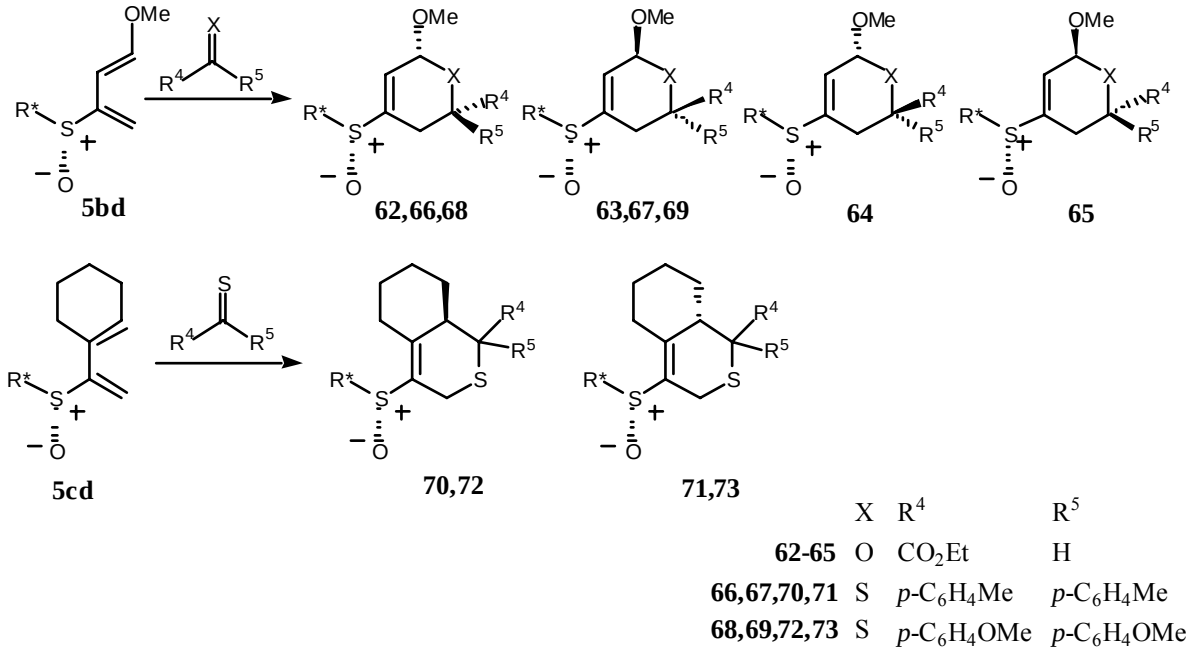
As a part of our investigation on the behavior of enantiomerically pure sulfinyl -1,3-dienes in DA cycloadditions, we compared the reactivity of open-chain 1- and 2-*p*-tolyl sulfinyl dienes possessing a highly DA activating substituent such as the trimethylsilyloxy group,[17] and confirm our remark, made for the 1- and 2-sulfinylvinylcyclohexenes, **14** and **6ce,**[6] regarding the influence exerted by the sulfinyl group's position on the conjugated system; 2-sulfinyl-dienes exhibit a higher reactivity in DA cycloadditions than 1-sulfinyl-dienes.

Hetero- Diels-Alder (HDA) reactions give easy access to heterocycles which constitute the structural skeleton of a large number of widespread natural compounds.[18] The most common HDA cycloadditions have been directed towards the synthesis of pyran derivatives as carbohydrate precursors; in this, we have extended the use of our enantio-pure sulfinyl homo- and hetero- dienes.

HDA reactions of **5bd** with commercially available aromatic aldehydes were attempted under mild conditions and in the presence of Lewis acids. The results obtained,[10] were disappointing in many ways, and prompted us to study an electron-deficient aldehyde, ethyl glyoxalate, which represents a more reactive dienophile, and is more convenient for application of the corresponding pyranoid cycloadducts to the synthesis of enantiopure carbohydrates and carbohydrate-like products (Scheme 6).[8,19] The facial diastereoselection was moderate (63% attack of the dienophile onto the preferred diene face; entry 5 in Table 3) even when performed in the presence of a suspension of $LiClO_4$ in CH_2Cl_2 (entry 4). Further experiments (entries 3,6,7 in Table 3) were performed in the presence of different Lewis acids in CH_2Cl_2 solution. The results obtained deserve some comments. When a very strong Lewis acid such as $TiCl_4$ was used, extensive decomposition of the reactants was observed, even at low temperature.[20]

$ZnCl_2$ or $Eu(fod)_3$ catalysis led to a reversal of the *endo/exo* diastereoselectivity in favor of the *exo* approach (compare entry 5 with entries 3 and 7 in Table 3).

This result can be attributed to catalyst sizes. Because Lewis acid co-ordination forces the dienophile into its *s-cis* conformation, the highly sterically demanding $ZnCl_2$ or $Eu(fod)_3$ can favor the less sterically congested *exo*- transition state. A moderate enhancement of facial diastereoselection was observed in the $Eu(fod)_3$ catalyzed cycloaddition but the yield of the reaction was low.



	X	R^4	R^5
62-65	O	CO_2Et	H
66,67,70,71	S	*p*-C_6H_4Me	*p*-C_6H_4Me
68,69,72,73	S	*p*-C_6H_4OMe	*p*-C_6H_4OMe

Scheme 6

Table 3. Cycloadditions of sulfinyl dienes **5** with hetero- dienophiles[a]

					Adducts		
Entry	Diene	Dienophile	Catalyst	Reference	*endo*	*exo*	(ratio)
1	**5bd**	di-(*p*-anisyl) thioketone	none	22	**68** : **69**		(70:30)
2	**5bd**	di-(*p*-tolyl) thioketone	none	22	**66** : **67**		(70:30)
3	**5bd**	ethyl glyoxalate	$Eu(fod)_3$	8	**62** : **63**	**64** : **65**	(9:5:61:25)
4	**5bd**	ethyl glyoxalate	$LiClO_4$	8	**62** : **63**	**64** : **65**	(59:21:14:6)
5	**5bd**	ethyl glyoxalate	none	8	**62** : **63**	**64** : **65**	(45:28:18:9)
6	**5bd**	ethyl glyoxalate	$TiCl_4$[b]	8			
7	**5bd**	ethyl glyoxalate	$ZnCl_2$	8	**62** : **63**	**64** : **65**	(9:9:39:43)
8	**5cd**	di-(*p*-anisyl) thioketone	none	22	**72** : **73**		(50:50)
9	**5cd**	Di-(*p*-tolyl) thioketone	none	22	**70** : **71**		(50:50)

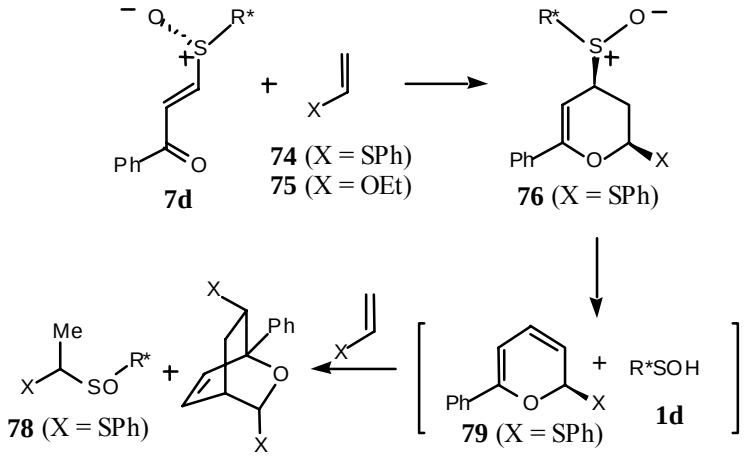
[a] The identification by numbers of the cycloadducts in Scheme 6 and Table 3 is independent of the R* features. [b] Extensive decomposition of reactants was observed.

In Table 3 (entries 1, 2, 8, 9) the results of HDA reactions of dienes **5bd** and **5cd** with thio-dienophiles are also reported. Although the most common HDA cycloadditions have been directed towards the synthesis of pyran derivatives as carbohydrate precursors, conveniently substituted thiopyrans (obtained by using the HDA approach) have received special attention as intermediates in the synthesis of biologically active agents.[21]

The lack of facial diastereoselectivity in the HDA cycloaddition of diene **5cd** to thiobenzophenones (Table 3, entries 8 and 9) can be ascribed to the combined steric characteristics of the cyclohexene moiety of the diene and aryl substituents of the dienophile in the transition states of the cycloadditions.[22] These high steric requirements, which are due in the dienophile to the nearly perpendicular disposition of the aryl groups with respect to the C=S plane, make unimportant the topological differentiation between the diene faces induced by the alkylsulfinyl auxiliary, and poor stereochemical results are observed.

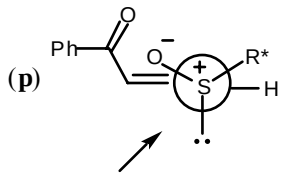
In order to corroborate the interpretation above, we reacted di-(*p*-anisyl) and di-(*p*-tolyl) thioketones with the less sterically demanding (R_S,*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-3-methoxybuta-1,3-diene (**5bd**), and the facial diastereoselectivity value (**66**/**67** and **68**/**69**, 70:30, Entries 1 and 2 in Table 3) was as expected for thermal cycloadditions of diene **5bd**. Although the observed facial diastereoselection in all cases was unsatisfactory or completely absent, the easy separation and high yields of cycloadducts can render this procedure attractive from the synthetic point of view.

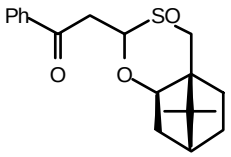
As part of our study on HDA reactions we were also interested in investigating the reactivity of enantiomerically pure β-sulfinyl α,β-unsaturated ketones as hetero dienes in cycloadditions with electron- rich dienophiles such as phenyl vinyl sulfide **74**, and ethyl vinyl ether **75** (Scheme 7).[5e] Reaction of **7d** (X = Ph) with the readily available phenyl vinyl sulfide **74**, performed in refluxing



Scheme 7

1,2-dichloroethane for 43 hrs, led to (4*S*,6*R*,*R*S)-4-[(1*S*)-isoborneol-10-sulfinyl]-5,6-dihydro-2-phenyl-6-phenylthio-4*H*-pyran (**76**, 20 % yield), as the only cycloadduct of the reaction among four possible diastereoisomers, together with (1*R*,3*R*,4*S*,7*S*)-2-oxa-1-phenyl-3,7-diphenylthiobicyclo[2.2.2]oct-5-ene (**77**, 10 % yield) and an almost 1:1 mixture of diastereomeric sulfoxides **78** (15 % total yield). The fused compound **77** is the product of a second DA reaction of phenyl vinyl sulfide (**74**), used in large excess, onto the diene intermediate **79** which was generated from **76** by elimination of (1*S*)-isoborneol-10-sulfenic acid (**1d**) under the reaction conditions. The isolation of sulfoxides **78** confirmed the mechanistic pathway proposed in Scheme 7 since they are products of the trapping of sulfenic acid **1d** by the vinyl sulfide **74**. Taking into account the detection of only one cycloadduct in the reaction mixture, and its partial conversion to **77**, it appears well-grounded that the DA reaction (**7d** + **74**) occurred with complete *endo* and facial diastereoselection, the dienophile **74** approaching the (1*Re*,2*Re*,3*Si*) face of the diene **7d** in its (**p**) conformation.





81

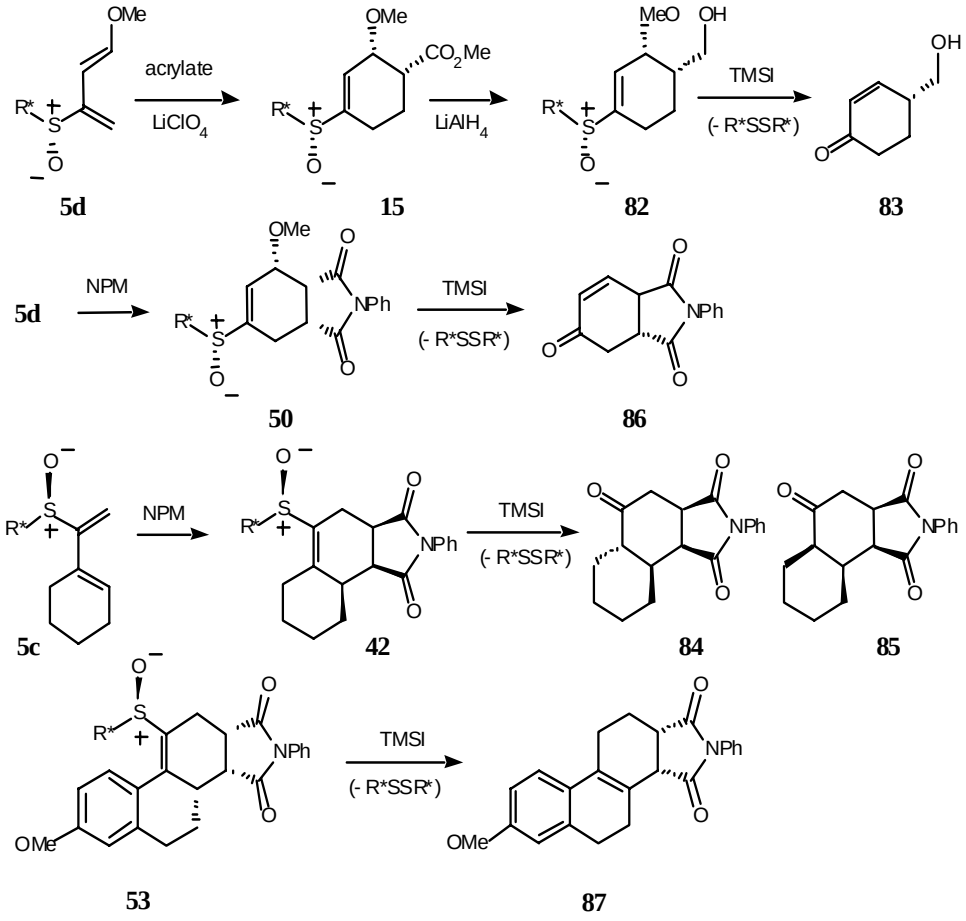
When ethyl vinyl ether (**75**) was reacted with **7d**, only the condensed compound **80** was isolated, in 15 % yield.

The long reaction times and moderate- to low- yields observed in the HDA cycloadditions shown in Scheme 7 directed our efforts towards the use of Lewis acid catalysis in the cycloaddition of (*R*S,*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-phenyl-2-propen-1-one (**7d**) with phenyl vinyl sulfide (**74**). The presence of Lewis acids ($LiClO_4$ suspended in CH_2Cl_2, $TiCl_4$, $ZnCl_2$ or $BF_3.Et_2O$) in all cases favored polymerization of the dienophile **74**, decomposition of the β-sulfinyl-α,β-unsaturated ketone **7d**, and formation of diastereomeric mixtures of 2-oxa-4-thiatricyclo-undecane 4-oxides **81**, arising from intramolecular 1,4–conjugate addition of the isoborneol hydroxy function onto the α,β-unsaturated ketone moiety.[10] The reaction of (*R*S,*E*)-3-[(1*S*-*exo*)-2-bornylsulfinyl]-1-phenyl-2-propen-1-one [**7e** (X = Ph)] with phenyl vinyl sulfide (**74**) resulted in extensive polymerization when performed in the presence of $LiClO_4$.

Conversion of Diels-Alder cycloadducts into enantiopure cyclohexene derivatives

The high control exerted by the sulfoxide chirality on the stereochemistry of the final adducts such as **15** (Scheme 2), and the easy isolation of the cycloaddition products in high yields, prompted us to explore their usefulness in stereoselective syntheses of target molecules. With the aim of obtaining enantiopure polyhydroxylated molecules from (3*R*,4*S*,*R*S)-4-hydroxymethyl-1-[(1*S*)-isoborneol-10-sulfinyl]-3-methoxycyclohexene (**82**) (Scheme 8) we decided to use iodotrimethylsilane (TMSI) to cleave the O-Me bond, following a well-assessed literature

procedure.[23] The reaction afforded (*R*)-4-(hydroxymethyl)cyclohex-2-ene-1-one (**83**) [24] and the more mobile bis-{(1*S*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethyl}disulfide (R*SSR*) [25] as the major products.[26] In contrast to the disappointing result of losing the unmasked hydroxy substituent from the cyclohexene skeleton, the presence of a carbonyl function—which had taken the place of the alkylsulfinyl moiety—appeared to be an unexpected but remarkable outcome of the TMSI-induced reaction. It must be noted that alkyl(vinyl)sulfinyl cycloadducts frequently suffer the problem of ineffective removal of the chiral auxiliary by classical procedures, such as Raney nickel desulfurization.[5c,27]

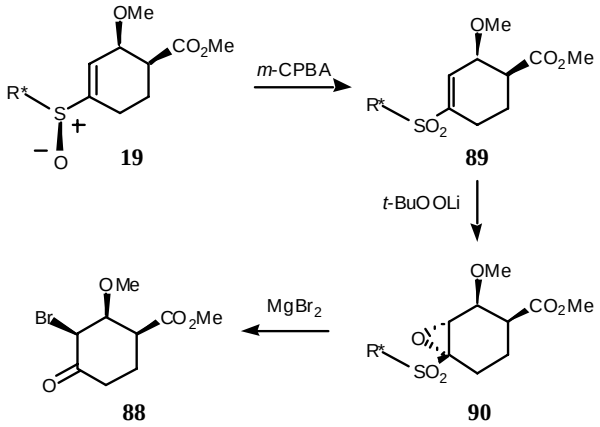


Scheme 8

We have explored the reactivity of TMSI with 1-sulfinylcyclohexene adducts other than **15** and/or its derivative **82**. For instance, compounds **42** and **50** led, respectively, to (**84** + **85**) and **86** in the presence of the halogenated reagent (Scheme 8), while the reaction of TMSI with cycloadduct **53** afforded (3a*S*,11a*S*)-7-methoxy-2,3,3a,4,5,10,11,11a-octahydro-2-phenylnaphthalene-[2,1-*e*]-isoindole-1,3-(1*H*)- dione (**87**), which may be the thermodynamically favored product of the reduction and dehydration of an intermediate carbonyl compound transiently formed by TMSI-promoted conversion of the α,β-unsaturated sulfoxide **53**.[5d]

Moreover we have studied the behavior of simple open-chain vinyl sulfoxides in the presence of TMSI, owing to our interest in testing the generality and efficiency of the procedure, and consistent results were obtained.[26]

The conversion of vinyl sulfoxides into aldehydes or ketones has the advantage of transforming the C-S cleavage of vinyl sulfoxides (which is generally not easy to achieve), in the functionalization of the molecule with a carbonyl group which can be subjected to numerous synthetic transformations. To the best of our knowledge, this conversion is without precedent in the literature. All of these considerations allow us to anticipate many applications which will be developed around this reaction, and further studies in this direction are now in progress.



Scheme 9

The cycloadduct **19** (R* = **e**) was also converted into the polyfunctionalized enantio-pure cyclohexanone **88** by a sequence of highly stereoselective reactions (Scheme 9). The cyclic vinyl sulfone **89** was obtained in high yield from cycloadduct **19** by *m*-CPBA oxidation. The reaction of sulfone **89** with *t*-BuOOLi uniquely afforded the epoxide **90**, showing complete diastereoselectivity. Epoxide **90** was used without further purification in the next and final step of the process. Epoxide ring opening and concomitant loss of the alkylsulfonyl group were achieved by using $MgBr_2.Et_2O$, and the diastereoselection was complete.[5c]

Conclusions

The synthetic strategy based on the addition of sulfenic acids to triple bonds conjugated with double- homo- and hetero- bonds has been applied successfully to the preparation of enantio-pure sulfinyl homo- and hetero- dienes, which are not easily accessible by other synthetic routes. A large number of monoterpene systems, belonging to the chiral pool, can be used as starting products in this methodology. In particular, the good yield in DA cycloadducts, easy separation of diastereomeric mixtures, and crystallinity of the final products demonstrate the utility of the camphor skeleton in the design of chiral auxiliaries based on sulfoxides.

High *endo/exo*- and/or π-facial- diastereoselectivities were observed in most homo- and hetero-DA reactions of sulfinyl dienes with cyclic and acyclic dienophiles. The structural features of the alkyl residue linked directly to the sulfur function play a relevant role in the key step of our synthetic pathway towards enantiopure sulfinyl dienes, but have no significant effect in their DA reactions with regard to the observed asymmetric induction which is overwhelmingly influenced by sulfur configuration. Lewis acid catalysis plays an important role in increasing both the rate and the stereoselection of these reactions when sulfinyl dienes are reacted with acyclic dienophiles. In these cases, Li^+ coordination to both the diene and dienophile has been proposed in order to explain some very good stereochemical results. Removal of the chiral auxiliary from DA cycloadducts represents an important achievement in this research and opens the way to the use of such enantio-pure cyclic derivatives in target-oriented syntheses.

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