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Enantioselective Cycloaddition via a Chiral Keto-Ester Ketene Equivalent

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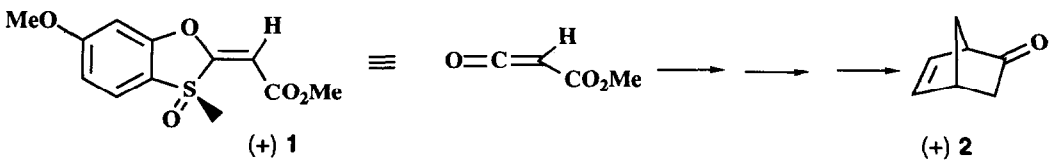
Abstract: The synthesis and cycloaddition of (+)-6-methoxy-1,3-benzoxathiolan-(Z)-2-carbomethoxypropenyl-3-oxide (**1**) with cyclopentadiene is described. This procedure allows the direct synthesis of useful enantiopure building blocks such as (+)-(1R,4R)-bicyclo[2.2.1]hept-5-en-2-one (**2**) and the precursor ketoester **11**. Cycloaddition, at -78 °C in the presence of BCl_3, proceeded with complete π–facial preference syn to the sulfoxide lone pair of the dienophile **1**.

Enantioselective cycloadditions and the use of chiral ligands in asymmetric synthesis are areas of active investigation.[1] Ketenes react preferentially with dienes in a [2+2] manner rather than by [4+2] cycloaddition to give the Diels-Alder adducts. Consequently several synthetically useful ketene equivalents have been developed to overcome this difficulty.[2] Some of these have embodied vinyl sulfoxides[3] since they are reasonable dienophiles, particularly if substituted with an additional electron withdrawing group. In addition, they are potentially capable of significant asymmetric induction provided the enantiopure sulfoxide can be prepared in a straightforward manner.[4,5] In several cases their utility as a latent chiral ketene equivalent is limited due to the low level of enantiofacial selectivity and modest reactivity. Stimulated by our interest in understanding and controlling the π-facial selectivity of various cycloadditions[6] coupled with the use of 1,3-oxathiolanes as versatile building blocks for organic synthesis[7] we wish to report the preparation of (+)-6-methoxy-1,3-benzoxathiolan-(Z)-2-carbomethoxypropenyl-3-oxide (**1**). This ketene acetal sulfoxide is a versatile keto-ester ketene equivalent that underwent a facile, enantiocontrolled Diels-Alder reaction with cyclopentadiene at -78 °C in the presence of BCl_3. Subsequent reduction and hydrolysis generated keto-ester **11** and decarboxylation afforded (+)-(1R,4R)-5-norbornen-2-one (**2**). This protocol will allow the direct asymmetric synthesis of various highly functionalized, enantiopure bicyclo[2.2.1]hepane systems for natural product synthesis, an area of considerable current interest and research.[8] Previous examples of alkoxycarbonylketene equivalents include methylthiomaleic anhydride,[9] 1,3-diethoxycarbonylallene,[10] and methyl 3-bromopropiolate.[11] These dienophiles were used as racemates.



(+) **1** (+) **2**

6-Hydroxy-1,3-benzoxathiol-2-one was converted to its methyl ether **3** (NaH, MeI, 81%) and condensed with methyl (triphenylphosphoranylidene)acetate to provide the ketene-acetal-ester **4** (73%). The dominance of

this isomer is a consequence of the rapid collapse of the oxaphosphetane intermediate to generate the Z-olefin preferentially as observed for related anhydrides.[12] Oxidation with *meta*-chloroperbenzoic acid generated the racemic sulfoxide **1**. Enantiopure material was obtained by oxidation under Kagan-Sharpless conditions[13] to give (+)-**1** as a single enantiomer (74%, $[\alpha]_D^{22}$ = +497.0°, c = 2.8, $CHCl_3$) after recrystallization from methanol.[14]

Thermally induced cycloaddition with cyclopentadiene proceeded in good yield (98%) in refluxing *o*-xylene (139 °C, no reaction at 80 °C) but with a disappointing level of selectivity to give all four possible adducts **5-8** in a 7:4:4:1 ratio. The oxathiolane **4** did not react with cyclopentadiene due to its donor-acceptor electronic nature[15] but the corresponding sulfone, obtained by oxone oxidation, cyclized readily (82%, 139 °C) but also with poor endo:exo preference (1.4:1 ratio).

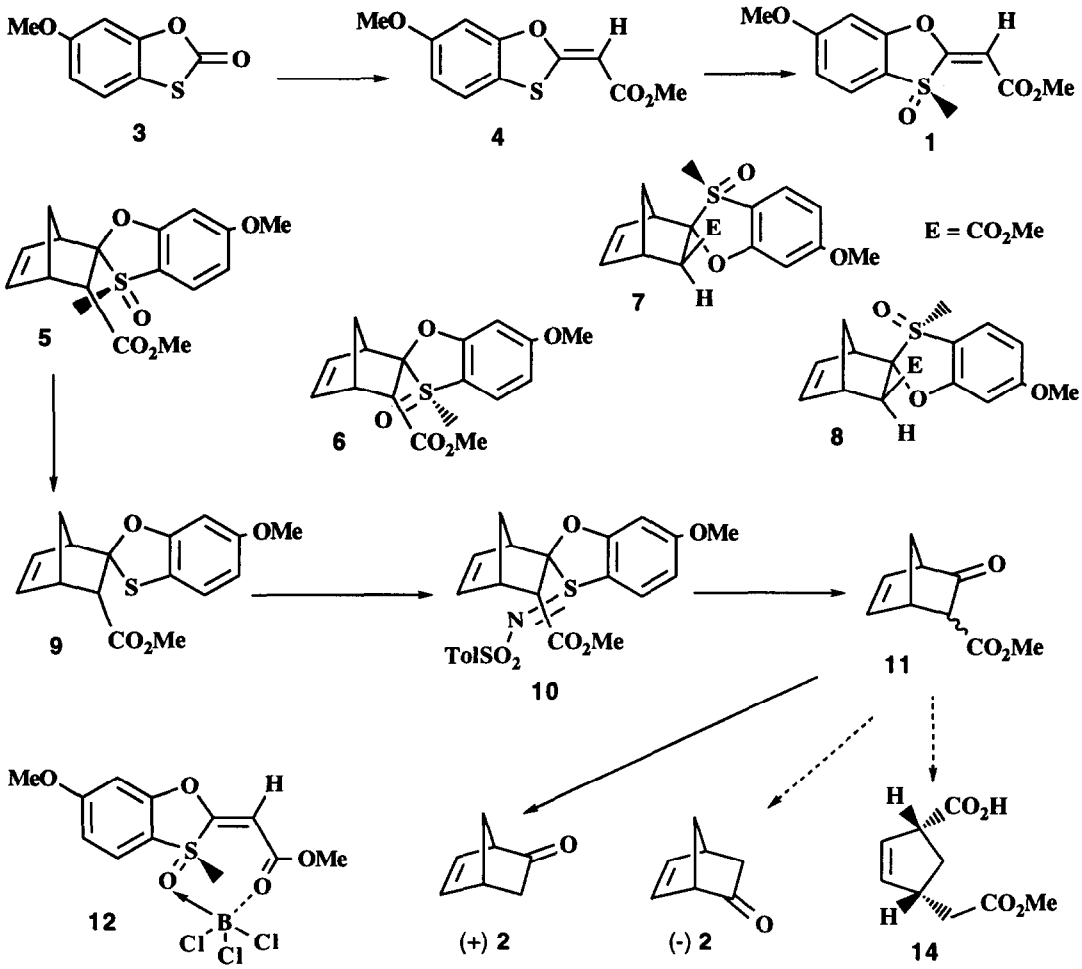
The cis disposition of the sulfoxide oxygen and the ester carbonyl implied that Lewis acid catalysts should complex preferentially with these oxygens and improve the reactivity of the dienophile. The results summarized in the Table indicate this was the case. Reactivity and selectivity were increased with $SnCl_2$, Et_2AlCl-$TiCl_4$ (20:1), and $ZnCl_2$, although in these examples the dominant endo adduct **5**[16] was accompanied by varying amounts of the exo isomer **7**. Nevertheless, adduct **5** was isolated in 74% yield from the reaction conducted at 0 °C in dichloromethane with zinc chloride. These catalysts were not effective at -78 °C, but boron trichloride resulted in a dramatic improvement to generate the single diastereomer **5** in 88% isolated yield.

Table Cycloadditions with Cyclopentadiene and (±) **1**.

Entry	Catalyst	Conditions	Yield	Adducts **5** : **7**
1	None	139 °C, 15 h	98%	7 : 4
2	$SnCl_2$	21 °C, CH_2Cl_2, 12 h	90%	2.2 : 1
3	Et_2Al-$TiCl_4$ (20:1)	-78-21 °C, CH_2Cl_2, 5 h	87%	2.5 : 1
4	"	-78 °C, CH_2Cl_2, 24 h	No reaction	
5	$ZnCl_2$	21 °C, C_6H_6, 18 h	98%	2.6 : 1
6	"	0 °C, CH_2Cl_2, 38 h	97%	3.1 : 1
7	"	-78-21 °C, CH_2Cl_2, 14 h	94%	3.1 : 1
8	"	-78 °C, CH_2Cl_2, 25 h	No reaction	
9	BCl_3	-78 °C, CH_2Cl_2, 5 h	88%	10 : 0

A parallel series of reactions with (+)-**1** afforded the enantiopure isomer **5** ($[\alpha]_D^{22}$ = +104.2°, c = 1.7, $CHCl_3$) in 77% yield after a single recrystallization from ether. ^1H NMR analysis of the total reaction mixture revealed an initial endo:exo ratio of 96:4 and indicated that the cycloaddition had proceeded with complete π-facial control syn to the sulfoxide lone pair. As illustrated in **12**, it seems likely that the boron is coordinated preferentially to the sulfoxide oxygen and associated with the carbonyl group. This leaves the opposite face exposed and contributes to the selectivity observed.

Frequently hydrolysis of bicyclic acetals is troublesome.[11] However the following protocol proved effective. Treatment with phenyl phosphorodichloridate or triphenylphosphine/iodine afforded **9** (96%) and sequential reactions with TsNClNa-$3H_2O$ (Chloramine T) to generate the sulfinylimine **10** (which may be isolated if desired)[17] followed by aqueous acid (HOAc or trifluoroacetic acid/THF/H_2O) provided the keto-ester **11** (95%).[18] This keto-ester is known to epimerize readily[18] and it was not possible to entirely avoid this even with acetic acid. For many applications this will not be a limitation due to the preferential alkylation of these systems from the exo face. Unlike acyclic keto-esters, hydrolysis and decarboxylation of **11** was difficult and required the use of trimethylsilyl iodide followed by heating (100 °C) to afford (+)-(1R,4R)-norbornenone (**2**) (60%).[8a,19]



The bicyclo[2.2.1]heptane nucleus is widely distributed in nature and consequently there is considerable interest in the preparation of optically pure building blocks containing this ring system.[8] The ketene-acetal (+)-**1** adds to this arsenal and functions as an ester substituted ketene equivalent. It should allow a variety of transformations to enantiopure compounds that were not readily available previously. For example, base

catalyzed cleavage of the keto-ester **11** generates the cyclopentene carboxylic acid **14**.[18] In addition, removal of the ketone from **11** and oxygenation of the methyl ester site[20] would provide (-)-(1S,4S)-norbornenone (**2**). Thus entry to either enantiomeric series can be achieved from a common intermediate. Further modification of the substituents in **1** will permit the directing influence of related optically active sulfoxides to be examined and provide additional methods for enantioselective synthesis.

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