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Tandem Diels–Alder and Retro-Ene Reactions of 1-Sulfenyl- and 1-Sulfonyl-1,3-dienes as a Traceless Route to Cyclohexenes

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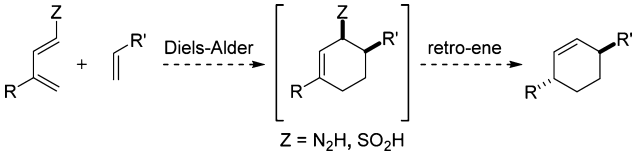
Supporting Information

ABSTRACT: A pericyclic approach for the synthesis of six-membered ring structures is described. The method employs 1,3-dienes with a 1-sulfur substituent in a tandem sequence of Diels–Alder and retro-ene reactions. In this pairing of [4 + 2] cycloaddition and 1,5-sigmatropic rearrangement, 1-sulfenyl-1,3-dienes engage in Diels–Alder reactions with electron-deficient dienophiles. Subsequently, the sulfenyl group of the cycloadducts is oxidized and unmasked to form allylic sulfinic acids, which undergo sterospecific reductive transposition via sulfur dioxide extrusion. The sequence can also include an inverse electron demand Diels–Alder reaction by using a 1-sulfonyl-1,3-diene. This combination of two pericyclic events offers novel stereocontrolled access to cyclohexenes that are inaccessible via a direct [4 + 2] cycloaddition route.

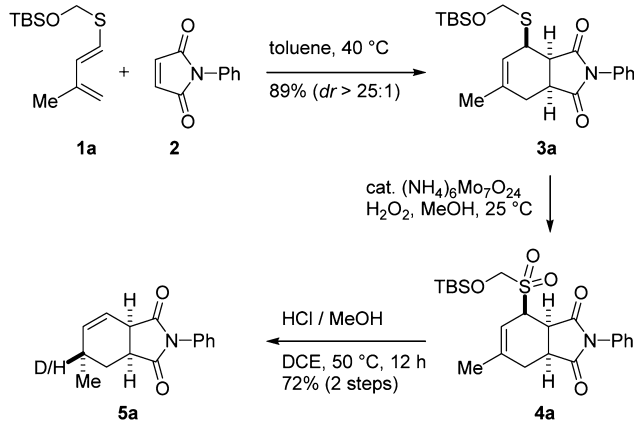
The Diels–Alder reaction is a powerful method for the construction of six-membered ring structures that has impacted profoundly on complex chemical synthesis.[1] Among the most notable developments in this reaction is the employment of functionalized dienes for enhanced reactivity and selectivity.[2] In addition to facilitating the cycloaddition, engineered dienes may also enable structural reorganization subsequent to a Diels–Alder event giving rise to cyclohexenes that are inaccessible via the direct [4 + 2] route.[3] In this context, one of us has reported 1-hydrazino-1,3-dienes for use in a tandem sequence of Diels–Alder and retro-ene reactions.[4] Through this pairing of two pericyclic processes, the initial cycloadduct undergoes a reductive alkene transposition with a 1,3-transfer of stereochemistry while the hydrazino group is removed via an allylic diazene rearrangement accompanying loss of molecular nitrogen (Scheme 1, Z = N_2H). In light of the efficiency of channeling [4 + 2] cycloaddition with 1,5-sigmatropic rearrangement for the synthesis of unusual cyclohexene systems, we envisioned that the concept could be brought further to bear on the formulation of a unique annulation strategy of broad utility. In particular, we were intrigued by the prospect of exploiting a sulfur substituent as an enabling functional handle, which could facilitate the cycloaddition and in turn render an allylic sulfinic acid poised for the postcycloaddition retro-ene reaction (Scheme 1, Z = SO_2H).[5] It was anticipated that our design plan to utilize two aspects of sulfur chemistry in interwoven contexts could offer a traceless route to cyclohexenes defying a usual Diels–Alder retrosynthetic analysis.[6] Along with the suprafacial nature of the sulfur extrusion process that would allow for the alkene transposition to occur in a stereospecific manner,[7] this approach was deemed to be potentially more versatile, since various oxidation states of sulfur (e.g., sulfenyl, sufinyl and sulfonyl) could be tapped into varying settings of the Diels–Alder reaction with stereo- and electronic control.[8]

Scheme 1. Cyclohexene Synthesis via Tandem [4 + 2] Cycloaddition and 1,5-Sigmatropic Rearrangement



For the evaluation of our proposition, 1-sulfenyldiene **1a** was prepared from methacrolein[9] and probed for its potential in the Diels–Alder reaction with *N*-phenylmaleimide (**2**) (Scheme 2). The sulfenyl ($TBSOCH_2S$) group was expected to accelerate the cycloaddition due to its donor capacity and could, in turn, be converted to the requisite sulfinic acid through a simple oxidation–deprotection sequence under mild conditions.[10] In the event, heating a 1:1 mixture of **1a** and **2** at 40 °C for 2 h

Scheme 2. Diels–Alder and Retro-Ene Sequence for Cyclohexene Synthesis Using 1-Sulfenyl-1,3-diene



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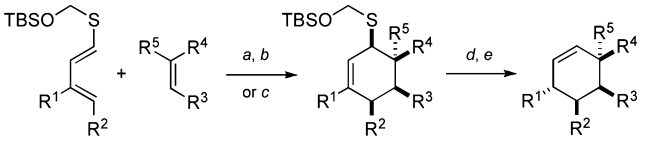
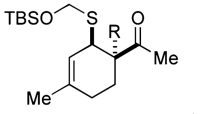
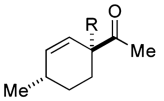
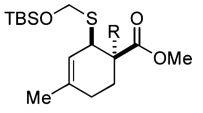
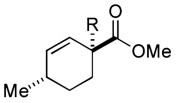
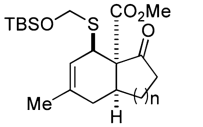
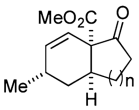
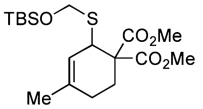
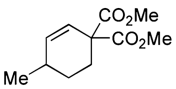
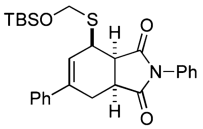
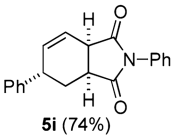
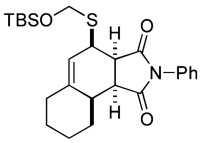
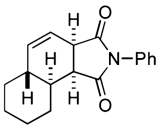
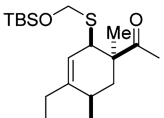
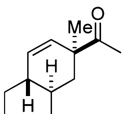
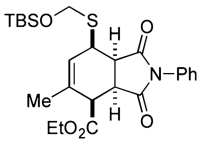
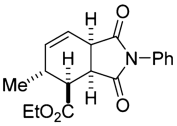
gave rise to cycloadduct **3a** as a single diastereomer in 89% yield. This finding attested to the markedly enhanced reactivity of the diene imparted by the sulfenyl group, forming a contrast to the cases of hydrazinodienes in which the cycloaddition did not occur under simple thermal conditions.[4] To set the stage for the second pericyclic event, the allylic sulfinic acid rearrangement, sulfide **3a** was subjected to an unmasking sequence. It was found that the oxidation of sulfide **3a** to sulfone **4a** could be most efficiently achieved using hydrogen peroxide under paramolybdate catalysis.[11] Subsequently, treatment of sulfone **4a** with methanolic HCl at 50 °C for 12 h led to smooth removal of the $TBSOCH_2SO_2$ group to generate cyclohexene **5a** as a single isomer in 72% yield (2 steps). When $DCl–CD_3OD$ was instead employed for this reaction, deuterio-**5a** was produced in 66% yield (D incorporation >95%) again as a single diastereomer, indicating the reductive alkene transposition to be the consequence of the stereospecific 1,5-sigmatropic rearrangement of a putative allylic sulfinic acid intermediate.[12]

Having established conditions for the cyclohexene synthesis, we examined the scope of the protocol with an assortment of substrates (Table 1). The one-pot pericyclic sequence of [4 + 2] cycloaddition and 1,5-sigmatropic rearrangement proved to be viable with a broad range of sulfenyldiene and dienophile pairs, affording the corresponding cyclohexene products. In addition to the methyl-substituted diene **1a** (entries 1–4), sulfenyldienes possessing a phenyl group (entry 5), a ring fusion (entries 6–7), and 3,4-disubstitution (entry 8) all participated well in the process to furnish deconjugated cyclohexene **5i**, *trans*-decalins **5j** and **5k**, and highly substituted cyclohexene **5l**, respectively. The dienophiles could also be varied to include both acyclic and cyclic enones as well as enoates. In general, simple thermal conditions (40–110 °C in toluene) were sufficient for the Diels–Alder reaction to yield endoadducts as the major products. In the presence of a Lewis acid, the reaction temperatures and times could be significantly decreased (entries 3 and 7), while preference for the formation of an endo product increased (e.g., entry 1, **3b**, 3:1 to 20:1). The standard oxidation–deprotection conditions were found to be uniformly effective for facile reductive alkene transposition of the cycloadducts, with the exception of tricyclic **3j** which gave a low yield of **5j** presumably due to the rigid ring system that might render the conformation required for an allylic sulfinic acid rearrangement less accessible.[3h,i] In all cases, the retro-ene reaction took place with complete 1,3-chirality transfer, manifesting high stereospecificity of the 1,5-sigmatropic rearrangement. It is noteworthy that the cyclohexenyl ring structures contained within products **5** would not be easily constructed with comparable efficiency by means of other annulation methods.

The cycloaddition–sigmatropic rearrangement sequence could also be practiced with an enal dienophile (Scheme 3). When methacrolein (**6**) was exposed to diene **1a** in DCM at −78 °C in the presence of catalytic $Sc(OTf)_3$, a rapid Diels–Alder reaction occurred to generate only the endo adduct, which upon oxidation furnished allylic sulfone **7a** in 80% yield (2 steps). The unmasking of the allylic sulfinic acid under the methanolic HCl conditions, however, did not induce the removal of SO_2, but instead resulted in the formation of acetal **8a** as a 1:1 mixture of diastereomers. Hence, the cyclic mixed acetal **8a** was further treated with ethylene glycol to bring about transacetalization. Indeed, the acetal exchange process led to the formation of the desired alkene product **10a** as a single

Table 1. Tandem Diels–Alder and Retro-Ene Reaction



entry	Diels-Alder adduct (yield, *dr*)[f,g]	retro-ene product (yield, 2 steps)
1	 **3b** R = Me (80%, 3:1)[b] **3c** R = allyl (82%, 9:1)[b]	 **5b** R = Me (66%) **5c** R = allyl (73%)[f]
2	 **3d** R = H (84%, 2:1)[a] **3e** R = Me (66%, 9:1)[a]	 **5d** R = H (50%) **5e** R = Me (49%)
3	 **3f** n=1 (83%, 1.5:1)[b] **3g** n=2 (84%, 10:1)[b]	 **5f** n=1 (58%) **5g** n=2 (73%)
4	 **3h** (93%, NA)[a]	 **5h** (66%)
5	 **3i** (79%, >25:1)[a]	 **5i** (74%)
6	 **3j** (87%, >25:1)[a]	 **5j** (25%)
7	 **3k** (64%, 5:1)[c]	 **5k** (45%)[f]
8	 **3l** (88%, 15:1)[a]	 **5l** (62%)

[a]Standard reaction conditions. diene (0.4 mmol), dienophile (1.2 mmol), toluene, 40–110 °C. [b]$Sc(OTf)_3$ (10 mol %), 3 Å MS, CH_2Cl_2, −78 to 0 °C. [c]Dienophile (0.5 mmol), Et_2AlCl (100 mol %), CH_2Cl_2, −78 °C. [d]H_2O_2 (5 equiv), $(NH_4)_6Mo_7O_{24}$ (10 mol %), MeOH, 25 °C. [e]HCl (1 N in MeOH, 2 equiv), DCE, 50 °C. [f]Isolated yield of both diastereomers. [g]The diasteromeric ratio was determined by ^1H NMR.

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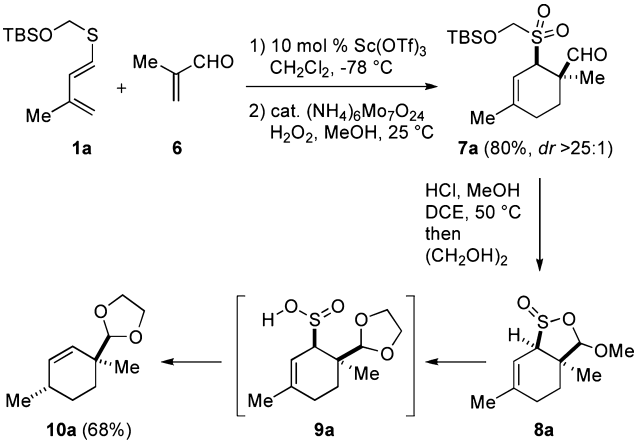
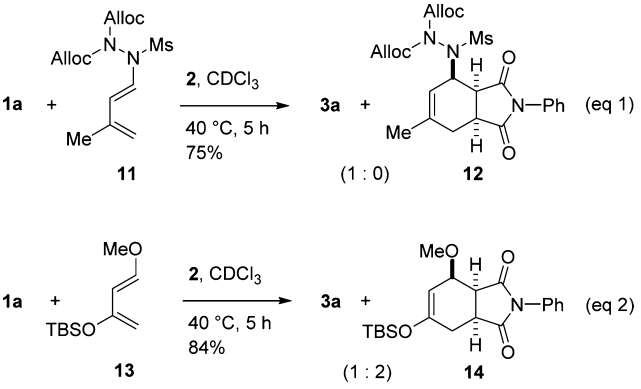
Scheme 3. Diels–Alder Reaction with Methacrolein and Subsequent Allylic Sulfinic Acid Rearrangement



isomer in 68% yield. Although **7a** could not enter into a retro-ene process with the aldehyde group intact, the observation of the formation of **8a** and its conversion to **10a** provided support for the intermediacy of an allylic sulfinic acid (e.g., **9a**).

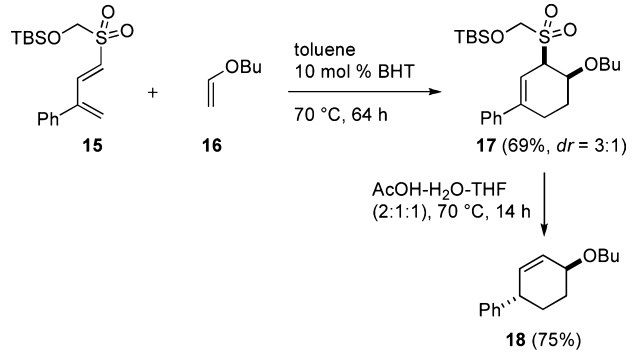
The reactivity of the new sulfenyldiene was assessed by further competition experiments where **1a** was directly compared with hydrazinodiene **11** and Danishefsky's diene **13**, respectively. As expected, the reaction of maleimide **2** with a mixture containing equimolar amounts of two dienes **1a** and **11** at 40 °C gave rise exclusively to **3a** (eq 1). On the other hand,



cycloadducts **3a** and **14** arose in a 1:2 ratio from a similar reaction performed with a 1:1 mixture of **1a** and **13** (eq 2),[2c] suggesting the reactivity of diene **1a** possessing the sulfenyl group to be comparable to that of synergistic diene **13**.[13]

Having verified the high reactivity of the new sulfenyldiene toward various electron-deficient dienophiles, we probed the feasibility of altering the electronic nature of the diene by changing the sulfur oxidation state. Indeed, 1-sulfonyldiene **15** (Scheme 4), an oxidized variant of the phenyl-substituted sulfenyldiene (cf. Table 1, entry 5),[14] proved to be capable of undergoing an inverse electron demand Diels–Alder reaction (IEDDA) with butyl vinyl ether (**16**), giving cyclohexene **17** in 69% yield as a 3:1 mixture of endo and exo isomers.[15] Subsequently, removal of the $TBSOCH_2SO_2$ group was accomplished by heating a solution of the major diastereomer *cis*-**17** (*endo* adduct) in AcOH-H_2O-THF (2:1:1) at 70 °C,[16] which led to clean conversion of the *cis*-3,4-substituted cyclohexene to the deconjugated alkene **18** possessing a *trans*-1,4-stereochemical relationship. This result serves to

Scheme 4. Inverse Electron Demand Diels–Alder Reaction of Sulfonyldiene and Retro-Ene Reaction



illustrate the potential utility of the protocol in the expeditious access to diverse cyclohexene systems.

In summary, a new approach for the stereoselective synthesis of six-membered ring structures has been developed. The method employs 1-sulfenyl-1,3-dienes in the tandem sequence of [4 + 2] cycloaddition and 1,5-sigmatropic rearrangement to produce cyclohexenes that are unavailable directly through a cycloaddition route. The dienes equipped with a $TBSOCH_2S$ group are highly reactive toward electron-deficient dienophiles, readily engaging in Diels–Alder reactions under simple thermal conditions or mild Lewis acid catalysis. The allylic sulfide arising from the initial cycloaddition process is then subjected to a mild oxidation-deprotection sequence to form an allylic sulfinic acid, which undergoes a facile retro-ene reaction effecting stereospecific alkene transposition with removal of SO_2 and transfer of chirality. The protocol can also be practiced via an inverse electron demand Diels–Alder reaction using an electron-rich dienophile and a sulfonyldiene derived from oxidation of a sulfenyldiene. This pairing of two pericyclic events constitutes a unique and efficient means of stereocontrolled cyclohexene synthesis that can be permuted in many ways in the application to complex synthesis. Further efforts to extend the utility of this chemistry are continuing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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