[11] Similar strategies have been employed in the total synthesis of natural acetogenins. For example, see: a) J. Marshall, H.-J. Jiang, *J. Org. Chem.* **1998**, *63*, 7066; b) S. Hanessian, T. A. Grillo, *J. Org. Chem.* **1998**, *63*, 1049.

[12] For example, see: Q. Yu, Y.-K. Wu, Y.-L. Wu, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1183, and references therein.

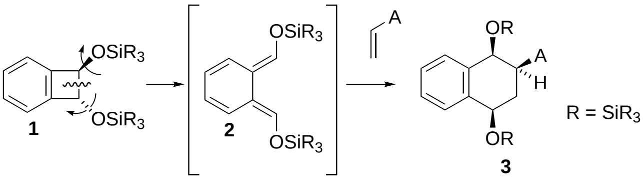
[13] ^{1}H NMR data (CDCl$_3$, 600 MHz) and optical rotations for **2a–d**. Compound **2a**: $\delta = 6.98$ (d, $J = 1.2$ Hz, 1H), 4.99 (dq, $J = 7.2$, 1.2 Hz, 1H), 3.83–3.74 (m, 2H), 3.72–3.60 (m, 4H), 3.53 (dd, $J = 9.6$, 10.2 Hz, 2H), 3.32 (dd, $J = 9.6$, 8.4 Hz, 2H), 2.26 (br. t, $J = 7.8$ Hz, 2H), 1.55 (quint, $J = 6.6$ Hz, 2H), 1.40 (d, $J = 7.2$ Hz, 3H), 1.50–1.20 (m, 40H), 0.88 (t, $J = 6.9$ Hz, 3H); $[\alpha]_D = +3.4$ ($c = 2.31$ in CHCl$_3$). Compound **2b**: $\delta = 6.98$ (br. s, 1H), 4.99 (br. q, $J = 6.6$ Hz, 1H), 3.82–3.74 (br. m, 2H), 3.72–3.60 (br. m, 4H), 3.54 (br. d, $J = 9.6$ Hz, 2H), 3.32 (br. t, $J = 9.0$ Hz, 2H), 2.26 (br. t, $J = 7.5$ Hz, 2H), 1.54 (quint, $J = 7.2$ Hz, 2H), 1.40 (d, $J = 6.6$ Hz, 3H), 1.48–1.16 (br. m, 40H), 0.88 (t, $J = 7.2$ Hz, 3H); $[\alpha]_D = -6.9$ ($c = 0.4$ in CHCl$_3$). Compound **2c**: $\delta = 6.97$ (d, $J = 1.2$ Hz, 1H), 4.98 (dq, $J = 7.2$, 1.2 Hz, 1H), 3.81–3.75 (m, 2H), 3.71–3.61 (m, 4H), 3.52 (dd, $J = 9.6$, 10.2 Hz, 2H), 3.31 (dd, $J = 9.6$, 8.4 Hz, 2H), 2.50 (br. s, 2H, OH), 2.26 (t, $J = 7.8$ Hz, 2H), 1.53 (quint, $J = 7.8$ Hz, 2H), 1.40 (d, $J = 6.6$ Hz, 3H), 1.48–1.20 (m, 40H), 0.87 (t, $J = 7.2$ Hz, 3H); $[\alpha]_D = 16.3$ ($c = 2.17$ in CHCl$_3$). Compound **2d**: $\delta = 6.98$ (d, $J = 1.2$ Hz, 1H), 4.99 (dq, $J = 1.2$, 6.6 Hz, 1H), 3.78 (m, 2H), 3.72–3.62 (m, 4H), 3.53 (dd, $J = 2.4$, 9.6 Hz, 2H), 3.32 (dd, $J = 9.6$, 8.4 Hz, 2H), 2.26 (br. t, $J = 7.8$ Hz, 2H), 2.15 (br. s, 2H, OH), 1.55 (quint, $J = 7.2$ Hz, 2H), 1.40 (d, $J = 6.6$ Hz, 3H), 1.48–1.20 (m, 40H), 0.88 (t, $J = 6.9$ Hz, 3H); $[\alpha]_D = -87.4$ ($c = 0.35$ in CHCl$_3$).

Thermal Intermolecular Hetero Diels–Alder Cycloadditions of Aldehydes and Imines via *o*-Quinone Dimethides**

Martin F. Hentemann, John G. Allen, and
Samuel J. Danishefsky*

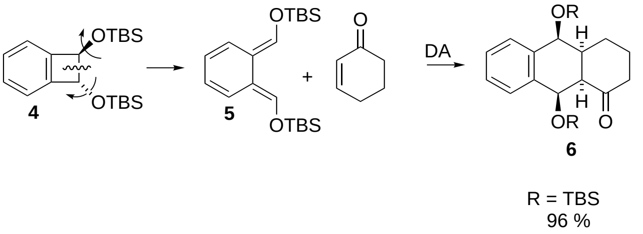
In memory of Wolfgang Oppolzer

The value of the Diels–Alder (DA) reaction in chemical synthesis can scarcely be overstated.[1] Our research group has been continuing to pursue its long-term interest in such cycloadditions, especially using suitable benzocyclobutenes.[2] In particular, we have focused on 1,2-*trans*-disubstituted disilyloxy compounds of the type **1** and have found that such systems partake in intermolecular DA cycloadditions with suitable dienophiles under remarkably mild conditions.[3] These results strongly suggest that **1** undergoes facile bond reorganization to produce *o*-quinone dimethides (5,6-dimethylenecyclohexa-1,3-diene derivatives, such as **2**), which function as dienes in DA reactions to produce products of type **3** (Scheme 1).



Scheme 1. A = activator.

While this kind of cycloaddition is well known, its primary applications have been at the intramolecular level. Thus, many of the elegant sequences that have traditionally been used to generate *o*-quinone dimethides as a prelude to cycloaddition work well only when the putative dienophile is tethered to the diene.[4] A particularly impressive illustration of our recently discovered "*trans*-1,2-bissiloxy effect" was seen in the uncatalyzed, near-quantitative formation of **6** from the cycloaddition of **4** with 2-cyclohexen-1-one (a notoriously sluggish dienophile) at 40 °C! (Scheme 2).[5] It was subsequently discovered that **4** will also effect cycloaddition with 2-cyclohexen-1-one even at ambient temperatures, presumably via **5**.



Scheme 2. TBS = *tert*-butyldimethylsilyl.

We subsequently noted that benzocyclobutene **4** exhibits thermochromic behavior, a characteristic that simplifies the monitoring of these types of reactions. Compound **4** exists as a colorless oil, either neat, or in benzene solution at temperatures below 0 °C. However, it becomes yellow upon being warmed to room temperature. This color is discharged upon recooling. The color also disappears following exposure to a dienophile. Accordingly, it seems reasonable[6] to interpret our findings in terms of a low equilibrium concentration of **5**, although in insufficient amount for detection by NMR analyses.

The initial successes with carbon dienophiles prompted us to expand the scope of our inquiry by focusing on heterodienophiles. In an extensive series of investigations in the 1980s our research group discovered and developed the first examples of diene–aldehyde and diene–imine condensations in cases where the formal heterodienophile was not especially activated.[7] However, in those studies it was necessary to take recourse to Lewis acid catalysis to accomplish such reactions with general, as opposed to specially activated, heterodieno-

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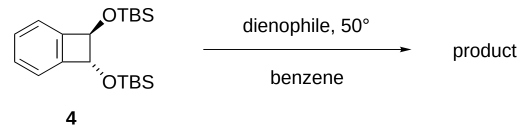
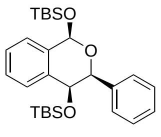
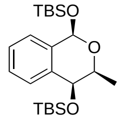
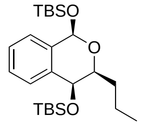
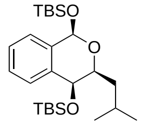
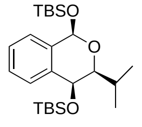
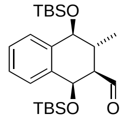
[**] This work was supported by the National Institutes of Health (AI 16943/CA 28824). Postdoctoral Fellowship support is gratefully acknowledged by M.F.H. (5T32 CA62948-05) and J.G.A (NIH, CA-80356). We are grateful to Dr. George Sukenick (NMR Core Facility, Sloan-Kettering Institute) for NMR and mass spectral analyses.

philes. Herein we demonstrate formal cycloadditions between benzocyclobutenes and general aldehydes, as well as selected imines, under strictly thermal conditions.

Reactions of **4** were carried out with various potential heterodienophiles in benzene or toluene and monitored by NMR spectroscopy. Uncatalyzed cycloadditions occurred under remarkably mild conditions in 2–8 h with complete stereospecificity. Particularly striking was the observation that the cycloaddition reactions proceed smoothly, albeit more slowly, even at room temperature. Reactions occurred well even with aliphatic aldehydes sterically encumbered by α and β branching (Table 1, entries 5 and 4, respectively). With the severely hindered heterodienophile pivalaldehyde, however, no reaction occurred even upon application of higher temperatures. To the best of our knowledge these reactions constitute the first examples of completely stereodefined [4+2] intermolecular cycloadditions of dienes with unactivated aldehydes in the absence of catalysis.[8] We note that cycloaddition with crotonaldehyde (entry 6) affords exclusively the product resulting from cycloaddition at the olefin group.

Table 1.

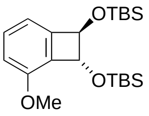


Entry	Dienophile	Time [h]	Product	Yield [%]
1	benzaldehyde	2	 **7**	92
2	acetaldehyde	2	 **8**	90
3	butyraldehyde	8	 **9**	88
4	isovaleraldehyde	8	 **10**	90
5	isobutyraldehyde	13	 **11**	89
6	crotonaldehyde	1.5	 **12**	82

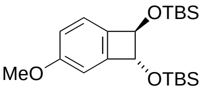
The stereochemistry of the adducts formed with aldehyde dienophiles was determined by NOE experiments. The complete *endo* specificity is intriguing, as it is exhibited even in the DA reactions of aliphatic aldehydes that have no obvious potential for stabilizing secondary orbital interactions during the course of the cycloaddition (Table 1, entries 2–5). This phenomenon, which awaits full explanation, is in contrast to previous stereochemical observations made in Lewis acid catalyzed hetero DA reactions.[9]

We reported[3] that incorporation of an *ortho* methoxy group in the benzocyclobutene **13** resulted in substantially decreased, but still exploitable, cycloaddition chemistry in the "all carbon" DA reaction. This attenuation of reactivity can be attributed to the electrocyclic ring-opening step, or to the cycloaddition reaction itself being hindered by steric constraints. Apropos of the first argument, we note that **13** is colorless at room temperature.

This weakened activity of **13** is even more obvious in the heterodienophilic cases. Thus, **13** does not undergo cycloaddition with any of the simple aldehydic DA dienophiles described above. However, placement of the methoxy group at the *meta* position, (see substrate **14**[10] and Table 2) restores the reactivity towards cycloaddition. Qualitatively, the rates of cycloaddition of **14** are even greater than those of **3**.[11]



13



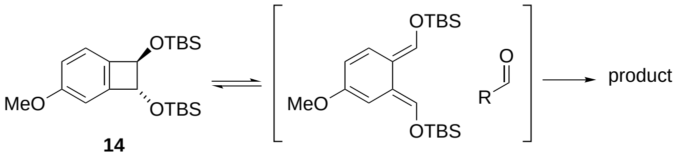
14

In addition to complete stereospecificity, the DA reactions of **14** with aldehydes occur with complete regiospecificity (Table 2). This observation is in striking contrast to the behavior of compounds **13** and **14** towards "all carbon" dienophiles, where mixtures of regioisomers may be produced.[12] It is worthy of note that the more electron-rich **14** reacts more readily with isobutryaldehyde (Table 2, entry 5) than does the demethoxy derivative **4** (Table 1, entry 5). This effect may be the result of an accelerating effect of the methoxy group in **14** on the conrotary electrocyclic reorganization step, or on the cycloaddition itself.

This new chemistry was extended to selected imines. Thus, reaction with *p*-toluenesulfonyl cyanide and *N*-benzylidenebenzenesulfonamide also proceeded smoothly with **4** and **14**, to provide adducts **20**–**23**. The slightly diminished yields reflected partial hydrolysis of the silyl ethers during purification, particularly for the 4-OMe derivatives (Table 3). The DA reaction of **4** and **14** with azadienophiles provides an excellent entry into the area of functionalized isoquinolines.

The Diels–Alder adducts can undergo post-cycloaddition processing to afford differentially oxidized products. For instance, cycloaddition of acetaldehyde and the bis(TMS-protected) benzocyclobutene derivative **23** gives adduct **24**, which was not isolated but rather treated with excess DDQ in

Table 2.



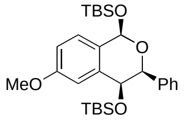
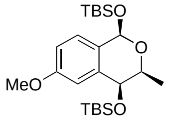
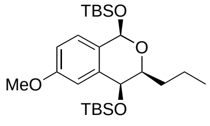
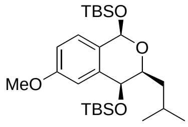
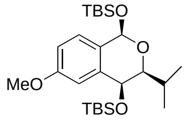
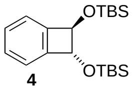
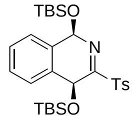
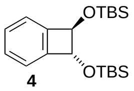
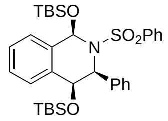
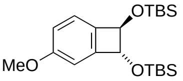
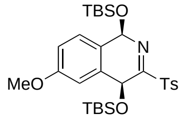
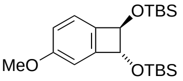
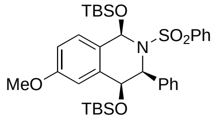
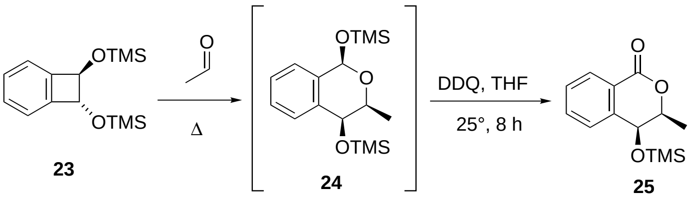
Entry	Dienophile	Time [h]	Product	Yield [%]
1	benzaldehyde	2	 **15**	90
2	acetaldehyde	2	 **16**	82
3	butyraldehyde	8	 **17**	73
4	isovaleraldehyde	3	 **18**	90
5	isobutyraldehyde	3	 **19**	83

Table 3.

Benzocyclobutene	Dienophile	Time [h]	Product	Yield [%]
 **4**	toluenesulfonyl cyanide	1	 **20**	73
 **4**	*N*-benzylidene-phenylsulfonamide	4	 **21**	68
 **14**	toluenesulfonyl cyanide	1	 **22**	63
 **14**	*N*-benzylidene-phenylsulfonamide	3	 **23**	57

Ts = toluene-4-sulfonyl.

THF[13] at 25 °C to give mono-oxidized product **25** in 82 % yield (Scheme 3). This structural motif is present in nature[14] and the chemistry described above would provide a mild and concise route to other targets of this type.



Scheme 3. TMS = trimethylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In summary, stereocontrolled cycloadditions have been developed that proceed in the absence of catalyst. These interesting results, while establishing the power of the bis(siloxy) effect in providing synthetically valuable access to highly reactive, yet well behaved 1,2-quinone dimethides for cycloaddition reactions, raise interesting issues of mechanism, scope, and possibilities for catalysis. It seems likely that these advances will spur applications to heterocyclic synthesis, including target structures that are of biological interest.

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[1] For many recent examples, see K. C. Nicolaou, E. J. Sorenson, *Classics in Total Synthesis*, VCH, Weinheim, **1996**, and references therein.

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[5] a) F. Fringuelli, A. Taticchi, E. Wenkert, *Org. Prep. Proced. Int.* **1990**, *22*, 131; b) P. D. Barlett, G. F. Woods, *J. Am. Chem. Soc.* **1940**, *62*, 2933; c) F. Friguelli, F. Pizzo, A. Taticchi, T. D. J. Halls, E. Wenkert, *J. Org. Chem.* **1982**, *47*, 5057.

[6] W. Choy, H. Yang, *J. Org. Chem.* **1988**, *53*, 5796.

[7] a) J. F. Kerwin, S. J. Danishefsky, *Tetrahedron Lett.* **1982**, *23*, 3739; b) S. J. Danishefsky, *Chemtracts* **1989**, *2*, 273; c) S. J. Danishefsky, M. T. Bilodeau, P. H. Seeberger, *Aldrichimica Acta* **1997**, *30*, 75.

[8] While there are examples of highly activated dienophiles reacting under strictly thermal conditions: a) P. A. Wender, R. M. Keenan, H. Y. Lee, *J. Am. Chem. Soc.* **1987**, *109*, 4390; b) A. Hosomi, Y. Sakata, H. Sakurai, H. *Tetrahedron Lett.* **1985**, *26*, 5175, simple aliphatic aldehydes typically require high pressure for noncatalyzed reactions: c) M. Chmielewsky, J. Jurczak, *J. Carbohydr. Chem.* **1987**, *6*, 1; d) J. Jurczak, A. Golebiowski, *Chem. Rev.* **1989**, *89*, 149, and references therein.

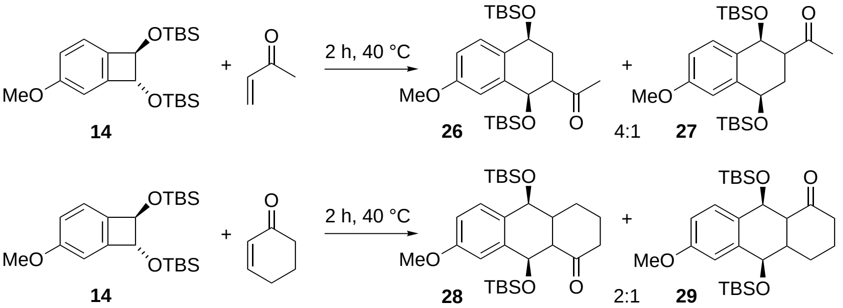
[9] a) G. R. Krow, R. Rodebaugh, R. Cramosin, W. Figures, H. Pannella, G. DeVicaris, M. Grippi, *J. Am. Chem. Soc.* **1973**, *95*, 5273; b) G. R. Krow, C. Pyun, C. Leitz, J. Marakowski, *J. Org. Chem.* **1974**, *39*, 2449;

c) G. R. Krow, K. J. Henz, S. W. Szczepanski, *J. Org. Chem.* **1985**, *50*, 1888.

[10] L. S. Liebeskind, L. J. Lescosky, C. M. McSwain Jr., *J. Org. Chem.* **1989**, *54*, 1435; b) H. Dürr, H. Nickels, *J. Org. Chem.* **1980**, *45*, 973; c) O. Abou-Teim, M. C. Goodland, M. F. W. McOmie, *J. Chem. Soc. Perkin Trans. 1* **1983**, 2659; d) L. S. Liebeskind, M. S. South, *J. Org. Chem.* **1982**, *47*, 3815.

[11] In a competition experiment between compounds **4** and **14**, 2-cyclohexen-1-one reacted preferentially with **14**.

[12] The Diels–Alder reaction of **14** with methyl vinyl ketone gave a 4:1 ratio of regioisomers **26**:**27**, while that between 2-cyclohexen-1-one and **14** gave a 2:1 ratio of **28**:**29**. Poor regioselectivity of 4-methoxy-substituted *o*-quinone dimethides in Diels–Alder cycloadditions is precedented in reactions with methyl acrylate: Y. Ito, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.* **1982**, *104*, 7609. For information regarding the regiochemistry of **13**, see reference [3].



[13] a) M. E. Jung, *J. Org. Chem.* **1976**, *41*, 1479; b) M. E. Jung, Y.-G. Pan, *J. Org. Chem.* **1977**, *42*, 3961; c) J. Muzart, *Synthesis* **1993**, 11.

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First Experimental Observation on Different Ionic States of both Methylthio ($CH_3S^\bullet$) and Methoxy ($CH_3O^\bullet$) Radicals[**]

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When combined with ab initio or density-functional theory (DFT) calculations, HeI photoelectron spectroscopy (PES) richly provides information on orbital energies, ionic states, bonding, and vibrational fine structure data that cannot be easily obtained by other experimental techniques. While there have been many PE spectroscopic studies of stable closed-shell molecules over the past 30 years, corresponding studies of open-shell radicals have been fewer.[1–3] Both the methylthio ($CH_3S^\bullet$)[4–14] and methoxy ($CH_3O^\bullet$)[15–18] radicals are important intermediates in combustion, photochemical smog and atmospheric reactions. The competitive effects of the dynamic Jahn–Teller distortion and spin–orbit coupling and their influences on the ground states of both $CH_3S^\bullet$ and $CH_3O^\bullet$ are the subject of numerous experimental and theoretical studies.[19–26]

Studies on these two radicals have been based on ab initio calculations to determine the energetics and geometry of the $CH_3S^\bullet$ radical in its ground and excited electronic states,[27–29] but as yet there is no report on the different ionic states for $CH_3S^\bullet$ or of direct experimental evidence of the ionization energies of different ionic states for $CH_3O^\bullet$. Two separate photoionization mass spectrometry (PIMS) studies gave the first ionization energy of the $CD_3O^\bullet$ isotopomer ((10.726 ± 0.008) eV,[23] (10.74 ± 0.02) eV[30]). Slightly different calculated ionization energies of $CH_3O^\bullet$ have been reported by Curtiss et al.[20] and Dyke et al.[25] (10.78 and (10.72 ± 0.02) eV, respectively). Clearly, experimental measurements of the ionization energies for both radicals are necessary.

In our laboratory, we generate a well characterized source of radicals or atoms by in situ pyrolysis and microwave discharge of precursor molecules.[31–35] In this communication, we would like to report the PES studies on the electronic structures of both methylthio and methoxy radicals. To our knowledge, this is the first experimental observation of different ionic states for both radicals.

The methylthio radical

The thermal, homolytic dissociation of suitable precursors is the most widely used method for generating radicals. Thermal decomposition of disulfides gives alkylthio radicals.[36] Calculations on CH_3SSCH_3 indicate that the S–S bond is the weakest present and therefore pyrolysis of CH_3SSCH_3 offers a simple route to the $CH_3S^\bullet$ radical [Eq. (1)].

$$\mathrm{CH_3SSCH_3} \xrightarrow{(285\pm0.5)\,^{\circ}\mathrm{C}} 2\,\mathrm{CH_3S^\bullet} \tag{1}$$

Figure 1a shows the in situ PE spectrum of the species generated by pyrolysis of the CH_3SSCH_3 molecule at 285 °C and Figure 1b shows the lower ionization energy region ($E <$ 11.00 eV) in greater detail. The three bands at $E = 9.26$, 9.91, and 10.32 eV are very sharp and correspond to the ionization of nonbonding electrons of the generated radical, because, in this case, the vertical ionization energy E_V is equivalent to the adiabatic ionization energy E_A. The first ionization energy of the $CH_3S^\bullet$ radical[36] (9.26 eV) is in good agreement with both

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