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π-Face-selective hetero Diels–Alder reactions of 3,4-di-*tert*-butylthiophene 1-oxide. An excellent trapping reagent for thioaldehydes and thioketones

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Abstract—Hetero Diels–Alder reactions of 3,4-di-*tert*-butylthiophene 1-oxide (**1**) with thioaldehydes and thioketones take place exclusively, except the reaction with thiobenzophenone, at the *syn*-π-face of **1** with respect to the S=O bond. The π-face selectivity was explained in terms of the extent of conformational changes of **1** that are brought about in the process to the transition states.

Recently, considerable interest has been paid to the chemistry of thiophene 1-oxides from a number of viewpoints such as syntheses, structures, reactivities, applications to organic synthesis, and intermediates in the metabolism of thiophenes.[1] Thiophene 1-oxides, which have the general structure shown in Figure 1,[2] possess two π-faces for Diels–Alder reactions, i.e. *syn*- and *anti*-π-faces with respect to the S=O bond. Recent studies uncovered that the Diels–Alder reactions of thiophene 1-oxides take place exclusively or predominantly at the *syn*-π-face to the S=O bond in an *endo*-mode (Scheme 1).[2d,3] Although thiocarbonyl compounds serve as a heterodienophile,[4] their Diels–Alder reactions with thiophene 1-oxides have not hitherto been reported. Here we report that 3,4-di-*tert*-butylthiophene 1-oxide (**1**)[2c] undergoes efficient, *syn*-π-face-selective Diels–Alder reactions with thiocarbonyl compounds.

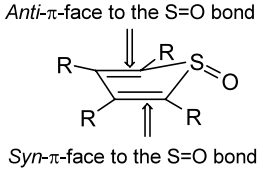
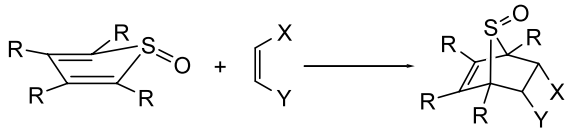


Figure 1. General structure and two π-faces of thiophene 1-oxides.



Scheme 1. π-Face-selective Diels–Alder reactions (*syn* to the S=O bond).

Thiobenzaldehyde and thioacetaldehyde are unstable, transient intermediates. They are generated, for example, by thermolyses of thiosulfinates **2a** and **2b**, respectively.[5,6] Thus, **1** was heated with an equimolar amount of **2a** in refluxing toluene for 1.5 h with the intention of examining the Diels–Alder reaction of **1** with thiobenzaldehyde.[7] The reaction produced the single Diels–Alder adduct **3a**[8] in 79% yield, thus revealing that the reaction took place exclusively at the *syn*-π-face to the S=O bond in an *endo*-mode (Scheme 2).[9] The *endo*-mode stereochemistry of **3a** was determined based on the coupling constant value of 3.4 Hz between H_a and H_b; a much smaller value (nearly zero) would be expected for the *exo*-mode adduct.[10] Furthermore, the structure of **3a** was established by X-ray crystallographic analysis (Fig. 2).[11] Similarly, the reaction with thioacetaldehyde, generated in the same manner, produced **3b**[8] in 87% yield. Even thioformaldehyde,[6] the simplest thioaldehyde, generated from **2c**, could be satisfactorily trapped to furnish **3c**[8] in a surprisingly high yield. These results indicate that **1** serves as an extremely excellent trapping agent for unstable, transient dienophiles such as thioaldehydes.[12]

Keywords: π-face selectivity; Diels–Alder reaction; thiophene 1-oxide; thioaldehydes and thioketones.
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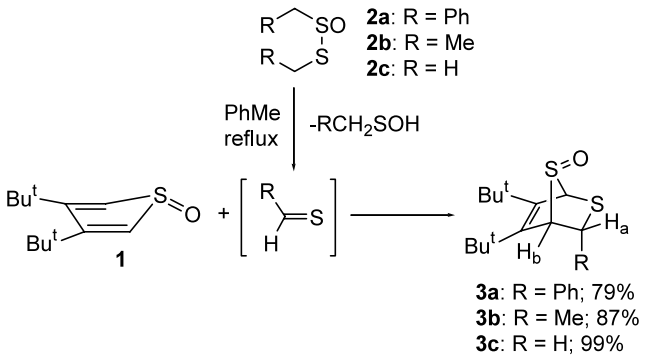


Scheme 2. π-Face-selective Diels–Alder reaction of **1** with thioaldehydes.

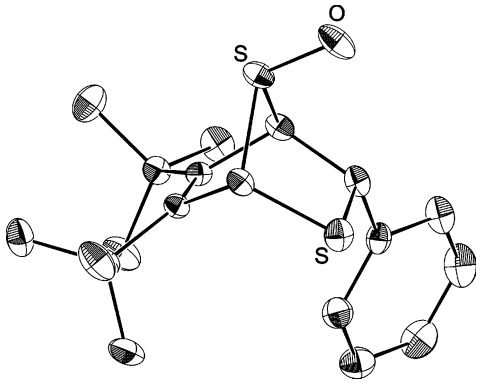
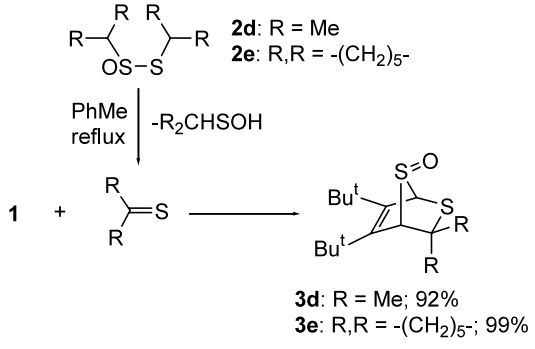


Figure 2. ORTEP drawing of **3a**.

Thioacetone and thiocyclohexanone,[6] generated by thermolysis of **2d** and **2e** in refluxing toluene, reacted with **1** to give the corresponding single Diels–Alder adduct **3d**[8] and **3e**[8] in 92 and 99% yields, respectively (Scheme 3). The *syn*-addition stereochemistry of these compounds was determined by ^{1}H NMR analysis. The shielding and deshielding zones of the S=O group are well documented.[13] The two methyl groups of **3d** show a large difference in chemical shift values (δ 1.38 and 1.79) due to the diamagnetic anisotropy of the S=O group. Thus the singlet at δ 1.79 is assigned to the methyl group which is placed in the S=O side, that is, in the deshielding zone of the S=O group, while the singlet at δ 1.38 is assigned to the *endo*-methyl group. The

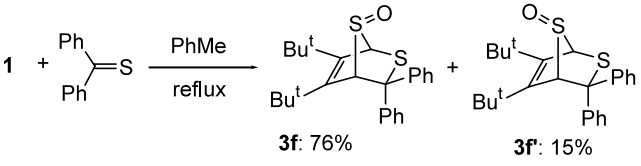


Scheme 3. π-Face-selective Diels–Alder reaction of **1** with thioacetone and thiocyclohexanone.

stereochemistry of the S=O group of **3e** was also determined by the same analysis.

Interestingly, only the Diels–Alder reaction of **1** with thiobenzophenone, which required heating in refluxing toluene to take place, gave the two diastereomers **3f**[8] and **3f′**[8] (Scheme 4). The structure of the minor diastereomer **3f′**, isolated in 15% yield, was established by X-ray diffraction analysis (Fig. 3).[11] Thus, the major diastereomer, isolated in 76% yield, was assigned **3f**, revealing that the reaction took place predominantly at the *syn*-π-face to the S=O bond, though not exclusively. The diastereomer ratio is kinetically controlled; thermal isomerization between **3f** and **3f′** either by retro-Diels–Alder reaction or by inversion at the sulfinyl sulfur atom did not occur for prolonged heating in boiling toluene. This is the first instance that 100% *syn*-π-face selectivity of the Diels–Alder reactions of **1** and the related compounds was violated.[3e]

The reaction of **1** with thiophosgene proceeded at room temperature to give the single diastereomer **3g**[8] in 94% yield (Scheme 5). The reaction of **1** with adamantanethione, a sterically hindered thioketone, in refluxing toluene produced the expected adduct **3h**[8] only in 25% yield. The oxidation of adamantanethione by **1** took place competitively to result in the formation of 3,4-di-*tert*-butylthiophene and adamantanone (Scheme 6).



Scheme 4. Diels–Alder reaction of **1** with thiobenzophenone; violation of 100% π-face-selectivity.

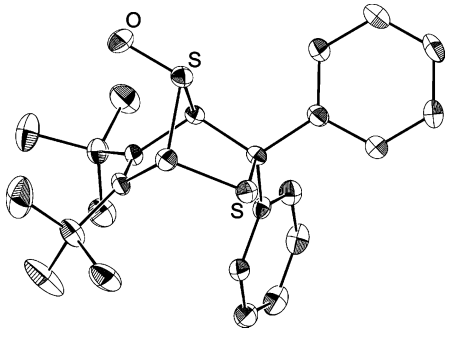
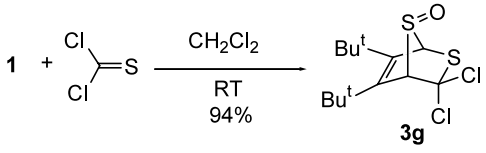
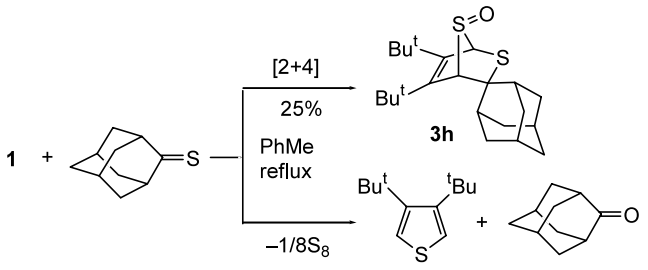


Figure 3. ORTEP drawing of **3f′**.



Scheme 5. π-Face-selective Diels–Alder reaction of **1** with thiophosgene.



Scheme 6. Reaction of **1** with adamantanethione.

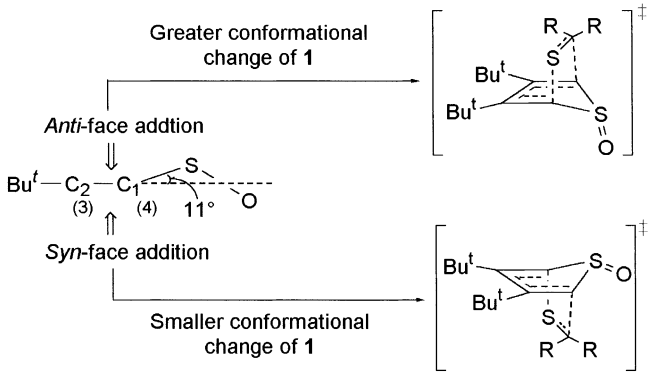


Figure 4. Conformational changes required for transition states.

The observed *syn*-π-face selectivity would be explained as follows, although other explanations were proposed previously.[14] The 1-oxide **1** has a bent structure at C_2 and C_4 with a tilt angle of 11° (Fig. 4). Thus, for the *syn*-π-face addition, the transition state can be easily reached with a small conformational change of **1**, whereas, for the *anti*-face addition, a large conformational change would be required; the inversions at C_1 and C_4 are required. Accordingly, the activation energy would become much smaller for the *syn*-π-face addition, and hence it takes place exclusively in most cases.

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6. Generation of thioformaldehyde, thioacetone, and thiocyclohexanone by this thermolysis method was not reported.[5]
7. If $RCH_2S(O)SCH_2R$ could be reproduced repeatedly and quantitatively by the following reaction from RCH_2SOH, generated as the counterpart of RCH=S, the stoichiometric relationship of **1**:$RCH_2S(O)SCH_2R$ = 1.0:0.5 would be valid.

$$2\ RCH_2SOH \longrightarrow RCH_2S(O)SCH_2R + H_2O$$

8. **3a**: mp 158–159°C (dec.); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (s, 9H), 1.41 (s, 9H), 4.31 (dd, 1H, J=3.4, 2.0 Hz), 4.86 (d, 1H, J=2.0 Hz), 5.29 (d, 1H, J=3.4 Hz), 7.15–7.42 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 32.2, 32.3, 33.8, 35.5, 52.6, 73.6, 75.0, 128.0, 128.5, 129.2, 136.6, 139.3, 146.6; IR (KBr) 1084 (S=O) cm^{-1}. Anal. calcd for $C_{19}H_{26}OS_2$: C, 68.21; H, 7.83. Found: C, 68.43; H, 7.92. **3b**: mp 112–114°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.34 (s, 9H), 1.37 (d, 3H, J=6.7 Hz), 4.14–4.20 (m, 2H), 4.67 (d, 1H, J=1.2 Hz); ^{1}H NMR (300 MHz, C_6D_6) δ 0.91 (s, 9H), 0.99 (d, 3H, J=7.0 Hz), 1.03 (s, 9H), 3.69 (dd, 1H, J=3.3, 1.7 Hz), 4.23 (dq, 1H, J=7.0, 3.3 Hz), 4.44 (d, 1H, J=1.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.9, 32.2, 32.8, 33.6, 35.6, 43.4, 73.0, 73.1, 138.7, 147.0; IR (KBr) 1088 (S=O) cm^{-1}. Anal. calcd for $C_{14}H_{24}OS_2$: C, 61.71; H, 8.88. Found: C, 61.85; H, 8.99. **3c**: mp 126–127°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.32 (s, 9H), 2.80 (dd, 1H, J=10.6, 1.2 Hz), 3.53 (dd, 1H, J=10.6, 3.6 Hz), 4.30 (ddd, 1H, J=3.6, 1.7, 1.2 Hz), 4.81 (d, 1H, J=1.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 32.0, 32.5, 32.5, 34.7, 34.8, 68.6, 72.2, 140.2, 145.8; IR (KBr) 1086 (S=O) cm^{-1}. Anal. calcd for $C_{13}H_{22}OS_2$: C, 60.41; H, 8.58. Found: C, 60.14; H, 8.67. **3d**: mp 105–106°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 1.32 (s, 9H), 1.37 (s, 3H), 1.79 (s, 3H), 3.84 (d, 1H, J=2.0 Hz), 4.76 (d, 1H, J=2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.6, 31.7, 31.8, 32.7, 33.7, 35.5, 57.6, 74.3, 77.9, 141.4, 144.5; IR (KBr) 1091 (S=O) cm^{-1}. Anal. calcd for $C_{15}H_{26}OS_2$: C, 62.88; H, 9.15. Found: C, 63.10; H, 9.32. **3e**: mp 172–173°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.21 (m, 1H), 1.25 (s, 9H), 1.30 (s, 9H), 1.34–1.38 (m, 1H), 1.45–1.57 (m, 4H), 1.68–1.78 (m, 2H), 1.82–1.86 (m, 1H), 2.80–2.93 (m, 1H), 3.90 (d, 1H, J=2.1 Hz), 4.71 (d, 1H, J=2.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.0, 25.4, 26.5, 31.7, 32.7, 33.7, 35.6, 37.0, 40.1, 65.9, 72.9, 78.0, 140.2, 144.4; IR (KBr) 1090 (S=O) cm^{-1}. Anal. calcd for $C_{25}H_{30}OS_2$: C, 66.20; H, 9.26. Found: C, 66.26; H, 9.39. **3f**: mp 242–243°C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (s, 9H), 1.35 (s, 9H), 4.91 (d, 1H, J=2.0 Hz), 5.11 (d, 1H, J=2.0 Hz), 7.12–7.36 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.4, 31.6, 34.0, 35.7, 71.7, 75.3, 75.5, 126.5, 127.0, 127.7, 127.7, 127.9, 130.0, 140.6, 143.9, 144.3, 144.7; IR (KBr)

1098 (S=O) cm^{-1}. Anal. calcd for $C_{25}H_{30}OS_2$: C, 73.12; H, 7.36. Found: C, 73.11; H, 7.42. **3f′**: mp 234–235°C (dec.); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (s, 9H), 1.40 (s, 9H), 4.92 (d, 1H, $J=2.2$ Hz), 5.04 (d, 1H, $J=2.2$ Hz), 7.18–7.34 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.2, 31.6, 33.6, 35.4, 62.8, 75.4, 79.3, 126.8, 127.1, 127.3, 127.9, 128.4, 130.3, 141.7, 143.3, 143.6, 147.6; IR (KBr) 1071 (S=O) cm^{-1}. Anal. calcd for $C_{25}H_{30}OS_2$: C, 73.12; H, 7.36. Found: C, 73.03; H, 7.40. **3g**: mp 119–120°C (dec.); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.37 (s, 9H), 4.89 (d, 1H, $J=2.6$ Hz), 5.10 (d, 1H, $J=2.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.4, 32.8, 34.0, 36.0, 76.9, 83.8, 142.7, 146.0; IR (KBr) 1099 (S=O) cm^{-1}. Anal. calcd for $C_{13}H_{20}OS_2$: C, 47.70; H, 6.16. Found: C, 47.79; H, 6.14. **3h**: mp 178–179°C (dec.); ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.31 (s, 9H), 1.46 (m, 1H), 1.71–1.91 (m, 8H), 2.00–2.20 (m, 4H), 2.82 (m, 1H), 4.46 (d, 1H, $J=1.9$ Hz), 4.57 (d, 1H, $J=1.9$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.4, 26.5, 31.3, 32.0, 34.6, 34.9, 35.4, 35.8 (overlapping of two peaks), 37.5, 38.0, 38.3, 39.3, 72.3, 72.8, 73.2, 140.0, 146.6; IR (KBr) 1097 (S=O) cm^{-1}. Anal. calcd for $C_{22}H_{34}OS_2$: C, 69.79, H, 9.05. Found: C, 69.92; H, 9.24.

9. A typical procedure for the Diels–Alder reactions of **1** with thioaldehydes and thioketones. A solution of 66.2 mg (0.25 mmol) of **2a** and 53.7 mg (0.25 mmol) of **1** in 3 mL of toluene was heated at reflux for 1.5 h under argon. The reaction mixture was evaporated under reduced pressure and the resulting residue was chromatographed on a column of silica gel. Elution of the column with ether/hexane (3:1) gave 66.5 mg (79%) of **3a**.
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11. X-Ray crystallographic data of **3a**: $C_{19}H_{26}OS_2$, 334.54 g mol^{-1}, triclinic, *P*-1, $a=8.574(1)$ Å, $b=9.031(1)$ Å, $c=12.258(1)$ Å, $\alpha=100.363(2)°$, $\beta=94.250(2)°$, $\gamma=106.988(3)°$, $V=884.81(9)$ $Å^3$, $D_{calcd}=1.256$ g cm^{-1}, $Z=2$, μ(Mo-$K\alpha$)$=0.30$ mm^{-1}, no. of measured reflections 3367, no. of independent reflections 3367, no. of reflections with $I>2\sigma(I)$ 3028, $R_1=0.0483$, $wR_2=0.1450$, $S=1.172$, $T=153$ K. X-Ray crystallographic data of **3f′**: $C_{25}H_{30}OS_2$, 410.64 g mol^{-1}, monoclinic, C_2/c, $a=23.493(2)$ Å, $b=9.052(1)$ Å, $c=21.970(1)$, $\beta=105.635(2)°$, $V=4492.2(4)$ $Å^3$, $D_{calcd}=1.212$ g cm^{-1}, $Z=8$, μ(Mo-$K\alpha$)$=0.249$ mm^{-1}, no. of reflections measured 5180, no. of independent reflections 4889, no. of reflections with $I>2\sigma(I)$ 3028, $R_1=0.0494$, $wR_2=0.1085$, $S=0.849$, $T=153$ K.
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14. We have explained the π-face selectivity in a different way in our previous paper.[3e] The present explanation would be more reasonable. It was also explained by nonequivalent orbital extension rule[2d] or by Cieplak effect.[3c]