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Asymmetric synthesis and applications of chiral 3-phenylsulfinyl-3-sulfolenes

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Abstract—The chiral 3-phenylsulfinyl-3-sulfolene **2** (*S*-form) was efficiently prepared in 92% ee by oxidation of sulfide **1** with Ti(O-*i*-Pr)$_4$/(−)-DET/*t*-BuOOH (1:4:1) in toluene. Thermal desulfonylation of **2** gave chiral diene **3**. Deprotonation of **2** by BuLi followed by the reaction with alkyl halides gave regiospecifically the C-2 alkylated 3-sulfolenes **4**–**8**. Intramolecular Diels–Alder reactions of compounds **7** and **8** gave the bicyclic products **9**–**11**. Thermal desulfonylation of **4** generated chiral dienyl sulfoxide **15**, which underwent thermal and Lewis acid-catalyzed Diels–Alder reactions with good regio-, stereo- and enantioselectivity.

Chiral sulfoxides are valuable tools in organic synthesis.[1] The Diels–Alder reaction is also one of the most useful methods in building various ring structures.[2] Although chiral vinyl sulfoxides are versatile dienophiles,[3] chiral dienyl sulfoxides are less commonly used in the Diels–Alder reaction,[4] partly because of their sensitivity to heat, light and acids.[5] It is now well established that 3-sulfolenes are useful precursors to 1,3-dienes.[6] We have previously shown that 3-phenylsulfinyl-3-sulfolene is a good precursor to the dienyl sulfoxide, which can undergo many useful Diels–Alder reactions.[7] Herein we report an efficient synthesis of chiral 3-phenylsulfinyl-3-sulfolenes and their synthetic applications in inter- and intramolecular Diels–Alder reactions.

Asymmetric oxidation of 3-phenylthio-3-sulfolene **1** could be carried out with chemical and enzymatic methods (Table 1). The ee values of product **2** were determined by HPLC using a chiral OD column with an eluent mixture of Hex/EA/IPA = 6:2:0.3. Preliminary experiments showed that Sharpless oxidation[8] was quite efficient. With a fixed ratio of Ti(O-*i*-Pr)$_4$/(−)-diethyl tartrate (DET)/*t*-BuOOH = 1:4:1, the best solvent was found to be toluene (compare entries 1–5). Changing this ratio to 1:2:1 (entry 6), or adding 1 equiv. of

Table 1. Chiral oxidation of 3-phenylthio-3-sulfolene **2**

Entry	Reagents[a]	Solvent	Temp/time	Yield (%)	Ee (%)
1	A	THF	−20 to 0°C/12 h	73	40
2	A	Dioxane	−20 to 0°C/12 h	70	50
3	A	CH_2Cl_2	−20 to 0°C/12 h	82	50
4	A	Xylene	−20 to 0°C/12 h	70	66
5	A	Toluene	−20 to 0°C/12 h	80	92
6	B	Toluene	−20 to 0°C/12 h	78	82
7	C	Toluene	−20 to 0°C/24 h	70	50
8	D	Toluene	−20 to 0°C/12 h	70	80
9	E	EtOH	(1) 5°C/12 h (2) 20°C/12 h	50	32

[a] (A) Ti(O-*i*-Pr)$_4$/(−)-DET/*t*-BuOOH = 1:4:1; (B) Ti(O-*i*-Pr)$_4$/(−)-DET/*t*-BuOOH = 1:2:1; (C) Ti(O-*i*-Pr)$_4$/(−)-DET/*t*-BuOOH/H_2O = 1:4:1:1; (D) Ti(O-*i*-Pr)$_4$/(*R*,*R*)-diphenylethane-1,2-diol/*t*-BuOOH = 1:4:1; (E) (1) pH 5.1 sodium acetate/O_2/glucose oxidase from *Aspergillus*; (2) H_2O_2.

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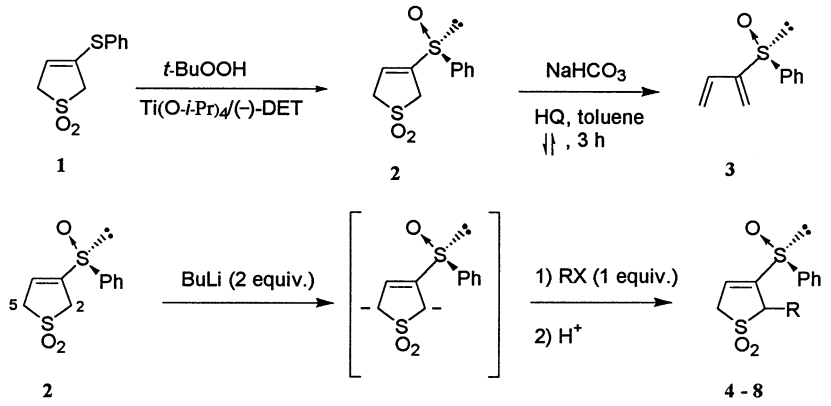


water[9] (entry 7) to the system lowered the enantioselectivity. Using a chiral diol (entry 8) to replace (–)-DET also decreased the ee. The enzymatic oxidation[10] (entry 9) was less efficient. The highest ee value we obtained for **2** was 92% (entry 5). After a single recrystallization the pure *S*-form of chiral 3-phenylsulfinyl-3-sulfolene **2** was obtained, $[\alpha]_D^{24}$ +142.5 (*c* 1.0, CH_2Cl_2). The structure of **2** was proven by X-ray crystallography (Fig. 1).† The vinyl proton of **2** appeared at δ 6.8 ppm, significantly more downfield than that of the sulfide **1** (δ 5.8 ppm). Compound **2** was desulfonylated to the diene **3** (*R*-form), $[\alpha]_D^{24}$ +96.0 (*c* 1.0, CH_2Cl_2), in 82% yield by refluxing in toluene for 3 h. In this reaction it is essential to use sodium bicarbonate to quench the acid generated, and to add some hydroquinone (HQ) to prevent the free-radical initiated polymerization of diene **3**.

Treatment of a mixture of 3-sulfolene **2** and hexamethylphosphoric amide (HMPA, 4 equiv.) in THF with BuLi/hexane (2.2 equiv.) at −105°C followed by the addition of an alkyl halide (1 equiv.) gave regiospecifi-

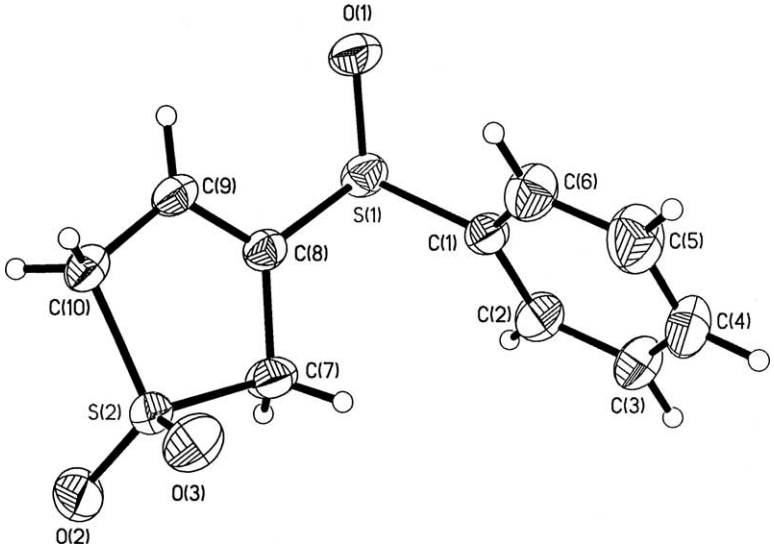


Figure 1. X-Ray crystal structure of compound **2**.

Table 2. Deprotonation of 3-sulfolene **2** and subsequent reaction with electrophiles

Entry	Alkyl halide	R	Product (*S*,*S*)/(*S*,*R*)[a]	Yield (%)
1	CH_3I	CH_3	**4** (6:1)	88
2	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	**5** (100:0)	84
3	$PhCH_2Br$	$PhCH_2$	**6** (5:1)	75
4	CH_2=$CH(CH_2)_3I$	CH_2=$CH(CH_2)_3$	**7** (4:1)	80
5	CH_2=$CH(CH_2)_4I$	CH_2=$CH(CH_2)_4$	**8** (4:1)	82

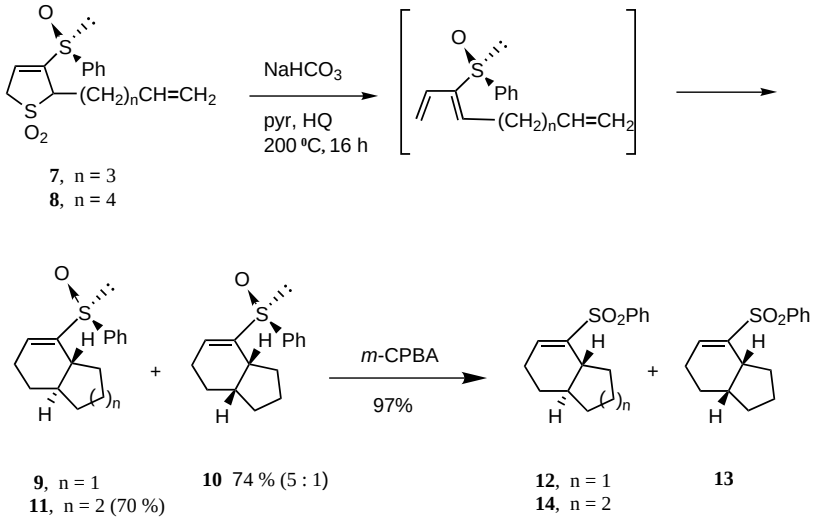
[a] The diastereomeric ratios were determined by ^1H NMR.

† Crystallographic data (excluding structure factors) for structures **2**, **16**, **17** and **20** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 181299, 181300, 181301 and 181454, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk; or www: http://www.ccdc.cam.ac.uk].

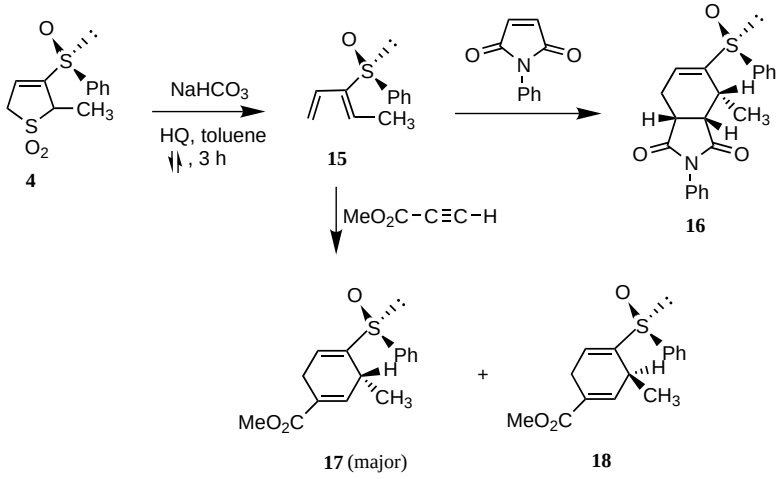
cally the C-2 alkylated products **4–8** in good yields (Table 2). The regiospecific alkylation can be explained by first deprotonation at the most acidic C-5 position followed by second deprotonation at C-2, as similar to that observed for 3-phenylsulfonyl-3-sulfolene.[11] The reaction with allyl bromide (entry 2) yielded only one enantiomer, whereas the reactions with other electrophiles all gave a mixture of two diastereomers. The stereoselective formation of the (*S*,*S*)-diastereomer for compounds **4–8** seems to derive from a preferential deprotonation of the pro-*S* hydrogen due to the steric hindrance of the phenyl group. Although these diastereomers could not be separated by column chromatography, both of these isomers could be converted to the same diene by thermal desulfonylation.

Compounds **7** and **8** could be converted to the bicyclic products **9–11** by heating in toluene at 200°C for 16 h (Scheme 1). Presumably, the triene intermediates were generated in situ, which then underwent intramolecular Diels–Alder reactions to give the cyclized products. Compound **7** yielded an inseparable mixture of *trans*/*cis* products **9** and **10** (5:1). However, their structures could be assigned on the basis of the ^{13}C NMR spectra. The *trans* isomer has more downfield chemical shifts for the aliphatic carbons at the ring junction than those of the *cis* isomer.[12] In contrast, the cyclization of **8** gave only the *trans* stereoisomer **11**, $[\alpha]_D^{24}$ +36.5 (*c* 1.0, CH_2Cl_2). The ring junction stereochemistry of compounds **9–11** was confirmed by *m*-CPBA oxidation to the corresponding sulfones **12–14**, which were identical with the literature data.[11] The stereoselectivity of these IMDA reactions was similar to that observed for the sulfone-substituted dienes.[11]

Thermal desulfonylation of **4** gave the diene **15**, $[\alpha]_D^{24}$ +280.2 (*c* 1.0, CH_2Cl_2), in 90% yield. Diene **15** was found by NOE technique to have the *Z* configuration. Although quite a few chiral 2-sulfinyl-1,3-butadienes have been used to study the Diels–Alder reactions,[13–17] chiral diene **15** has never been synthesized.[18] Thus we were interested in studying the Diels–Alder reactions of diene **15** with some dienophiles in order to determine the regio-, stereo- and enantioselectivity of these reactions (Scheme 2), which were found to vary with the reaction conditions (Table 3). Heating a solution of **15**



Scheme 1.

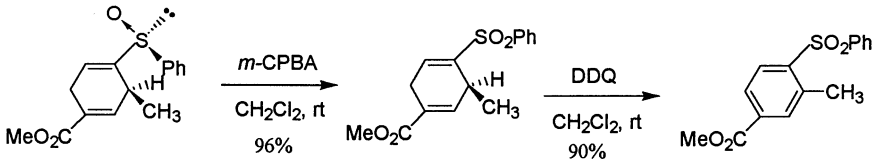


Scheme 2.

Table 3. Diels–Alder reactions of diene **15** with dienophiles

Entry	Dienophile[a]	Reaction condition[b]	Product	Yield (%)
1	*N*-Phenylmaleimide	Toluene, reflux, 24 h	**16**	80
2	*N*-Phenylmaleimide	CH_2Cl_2, rt, 36 h	**16**	84
3	*N*-Phenylmaleimide	$ZnCl_2$, CH_2Cl_2, rt, 24 h	**16**	90
4	H–C≡C–CO_2Me	Toluene, reflux, 24 h	**17**+**18** (4:1)	60
5	H–C≡C–CO_2Me	Toluene, 90°C, 24 h	**17**+**18** (7:1)	70
6	H–C≡C–CO_2Me	$ZnCl_2$, toluene, 75°C, 36 h	**17**	75

[a] The dienophile was used in 4 equiv.
[b] Small amount of hydroquinone (HQ) was present.



18 **19** **20**

and *N*-phenylmaleimide (4 equiv.) in toluene at reflux gave the cycloaddition product **16**, $[\alpha]_D^{24}$ +90.3 (*c* 1.0, CH_2Cl_2), in 80% yield (entry 1). This reaction could also be carried out in CH_2Cl_2 at room temperature (entry 2) or in the presence of $ZnCl_2$ (entry 3) to give higher yields of **16**. The reaction of diene **15** with methyl propiolate (4 equiv.) in refluxing toluene (entry 4) gave a separable mixture of stereoisomers **17** and **18** (4:1). The ratio of the mixture changed to 7:1 if the reaction was carried out at 90°C (entry 5). Furthermore, only product **17**, $[\alpha]_D^{24}$ +150.2 (*c* 1.0, CH_2Cl_2), was obtained when $ZnCl_2$ was used as the catalyst (entry 6). The structures of **16** and **17** were proven by X-ray crystallography (Figs. 2 and 3).† The structure of **18**, $[\alpha]_D^{24}$ +86.0 (*c* 1.0, CH_2Cl_2), was proven by first *m*-CPBA oxidation to the sulfone **19**, $[\alpha]_D^{24}$ −72.0 (*c* 1.0, CH_2Cl_2), which upon treatment with DDQ in CH_2Cl_2 gave the aromatized product **20** whose structure was proven by X-ray crystallography (Fig. 4).†

The stereospecific formation of cycloaddition product **16** from diene **15** and *N*-phenylmaleimide can be rationalized as shown in Fig. 5. The chiral dienyl sulfoxide **15** prefers to adopt a conformation in which the S–O bond is parallel to the C=C bond,[13] and *endo* addition of *N*-phenylmaleimide from the less hindered side of the diene (below the plane) would give the observed product **16**. Since the Lewis acid-catalyzed reaction gave the same product **16**, it is assumed that similar steric arrangements are involved. The formation of products **17** and **18** from the thermal reaction of diene **15** with methyl propiolate indicates that the regioselectivity of the cycloaddition is dominated by the phenylsulfinyl group at C-2 over the methyl group at C-1. Preferential approach of methyl propiolate from the bottom face of the diene would give the major product **17** (Fig. 6). It is important to note that in the presence of Lewis acid this reaction leads to only one stereoisomer **17**, presumably by lowering the energy difference of HOMO (diene)–LUMO (dienophile) and thus making this reaction more stereoselective.

In summary, we have efficiently synthesized the chiral 3-phenylsulfinyl-3-sulfolene **2**, which can not only be converted to the chiral diene **3**, but also be regiospecifically alkylated to give substituted products **4**–**8**. Compounds **7** and **8** underwent intramolecular Diels–Alder reactions to give bicyclic products **9**–**11**. The intermolecular Diels–Alder reactions of diene **15** with dienophiles gave the cyclized products **16**–**18** with good

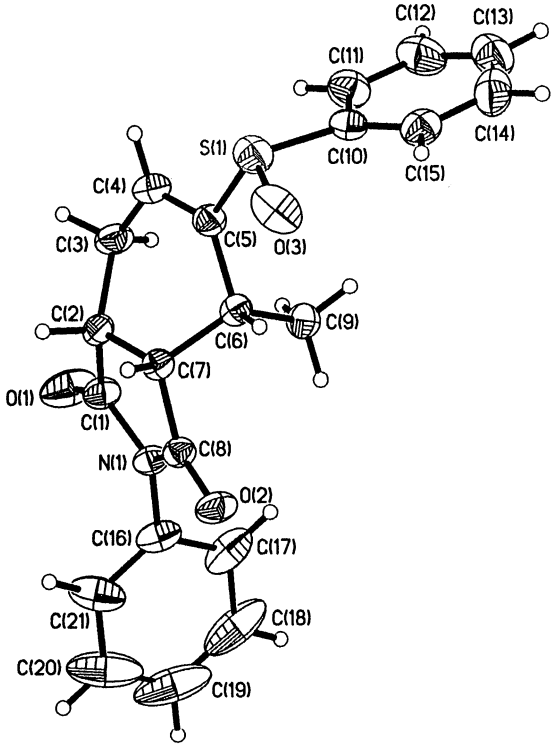


Figure 2. X-Ray crystal structure of compound **16**.

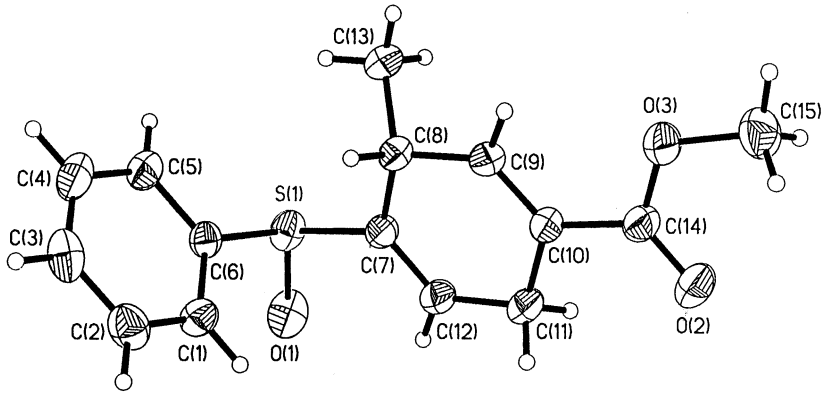


Figure 3. X-Ray crystal structure of compound **17**.

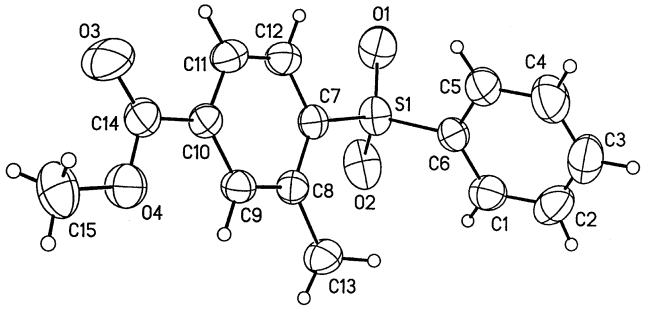


Figure 4. X-Ray crystal structure of compound **20**.

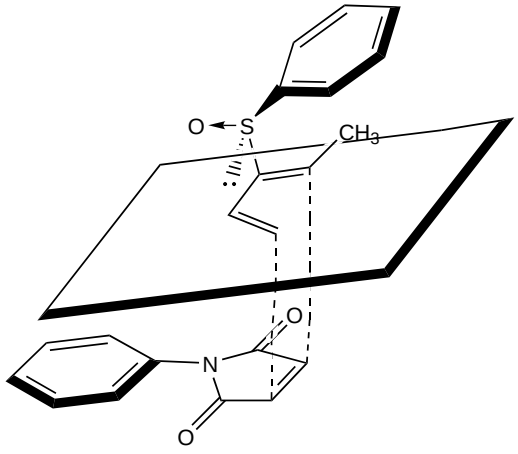


Figure 5. Favorable approach of *N*-phenylmaleimide with chiral dienyl sulfoxide **15**.

regio-, stereo- and enantioselectivity, especially with Lewis acid catalysis. The vinylic sulfoxide group present in the cycloaddition products should be useful for further synthetic transformations.[19]

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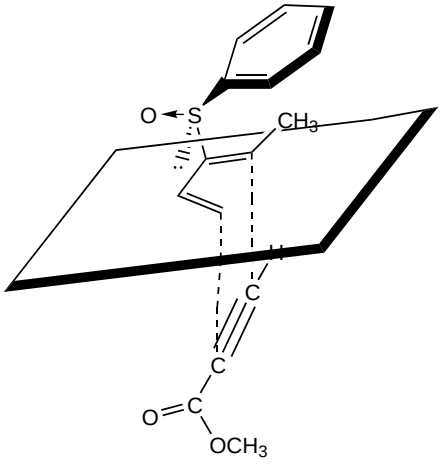

Figure 6. Favorable approach of methyl propiolate with chiral dienyl sulfoxide **15**.

References

1. For a recent review see: Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760.
2. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990.
3. Carretero, J. C.; Garcia Ruano, J. L.; Martin Cabrejas, L. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2215–2225 and references cited therein.
4. For a recent review see: Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1339–1367.
5. Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; Wiley & Sons: New York, 1990.
6. Chou, T. S.; Chou, S. S. P. *J. Chin. Chem. Soc.* **1992**, *39*, 625–633.
7. Chou, S. S. P.; Liang, P. W. *J. Chin. Chem. Soc.* **2000**, *47*, 83–90.

8. Sharpless, K. B.; Katsuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
9. Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
10. Colonna, S.; Gaggero, N.; Pasta, P.; Ottolina, G. *Chem. Commun.* **1996**, 2303–2307.
11. Chou, S. S. P.; Lee, C. S.; Cheng, M. C.; Tai, H. P. *J. Org. Chem.* **1994**, *59*, 2010–2013.
12. Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, 1981; p. C75.
13. Gosselin, P.; Bonfand, E.; Hayes, P.; Retoux, R.; Maignan, C. *Tetrahedron: Asymmetry* **1994**, *5*, 781–784.
14. Yang, T. K.; Chu, H. Y.; Lee, D. S.; Jiang, Y. Z.; Chou, T. S. *Tetrahedron Lett.* **1996**, *37*, 4537–4540.
15. Gosselin, P.; Bonfand, E.; Maignan, C. *J. Org. Chem.* **1996**, *61*, 9049–9052.
16. Fernandez de la Pradilla, R.; Montero, C.; Viso, A. *Chem. Commun.* **1998**, 409–410.
17. Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Nicolo, F.; Rizzo, S. *Tetrahedron: Asymmetry* **1999**, *10*, 3907–3917.
18. An analogue of **15**, chiral (*Z*)-1-butyl-2-(*p*-toluenesulfinyl)-1,3-butadiene, has been synthesized, but no Diels–Alder reactions have been reported: Paley, R. S.; Weers, H. L.; Fernandez, P. *Tetrahedron Lett.* **1995**, *36*, 3605–3608.
19. Mikolajczyk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents*: *Applications in Asymmetric and Stereoselective Synthesis*; CRC Press: Boca Raton, FL, New York, 1997.