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Observations on the alkylation of β-acetalic carbanions: monoalkylation versus dialkylation and elimination

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Abstract—The reaction with methyl iodide and a base (*t*-BuOK) of 1,3-dioxolanes and 1,3-dithiolanes substituted at the β-position with an electron-withdrawing substituent (EWG=—CO_2Me, —SO_2Ph, —SO_2Ph-*p*-NO_2, —SO_2Ph-*o*-NO_2) leads to mono- or dialkylated or ring-opened products in good yield.

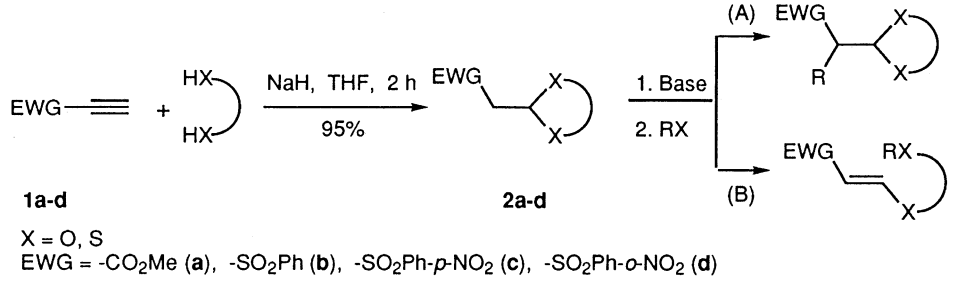
1. Introduction

Cyclic acetals are useful synthons in organic synthesis.[1] They are extensively used as protective groups in carbohydrate chemistry and in the preparation of other polyols.[2] Chiral versions of cyclic acetals and thioacetals are of particular interest owing to their applications in the asymmetric synthesis of natural products and of biologically active molecules.[3,4]

Although the classical method of preparation of cyclic acetals and thioacetals involves acidic catalysis,[5] they can also be obtained by Michael addition of diols or dithiols to electron-poor acetylenes (Scheme 1).[6] The resulting acetals contain an electron-withdrawing group at the β-position and represent interesting substrates for subsequent transformations.[7] For example, considering the formation of a carbanionic species by an appropriate base, two competitive pathways can be envisaged (Scheme 1): alkylation (path A) and elimination (path B), the former leading to substituted compounds, the latter to olefins. Because of the interest in the nucleophilic ring opening of cyclic acetals in stereoselective processes,[1,6b,7,8] we have studied the role of the electron-withdrawing group, with the aim to establish the best reaction conditions to accomplish either one of the transformations in a selective fashion.

2. Results

In order to investigate the role of the electron-withdrawing group and of the acetalic heterocycles, we prepared acetals or thioacetals **2a–d** (Fig. 1) by reaction of either methyl propiolate (**1a**), phenylsulfonyl acetylene (**1b**), *p*-nitrophenylsulfonyl acetylene (**1c**) or *o*-nitrophenylsulfonyl acetylene (**1d**) with diols or thiols as shown in Scheme 1.[6] In the present study the acetals derived from 1,2-ethanediol (**2aA**, **2bA**, **2cA**), 1,2-benzenedithiol (**2bB**), hydrobenzoin (**2aC**, **2bC**, **2dC**), and 2,2′-binaphthol (**2bD**) were considered.



Scheme 1.

Keywords: acetals; alkylation; elimination.
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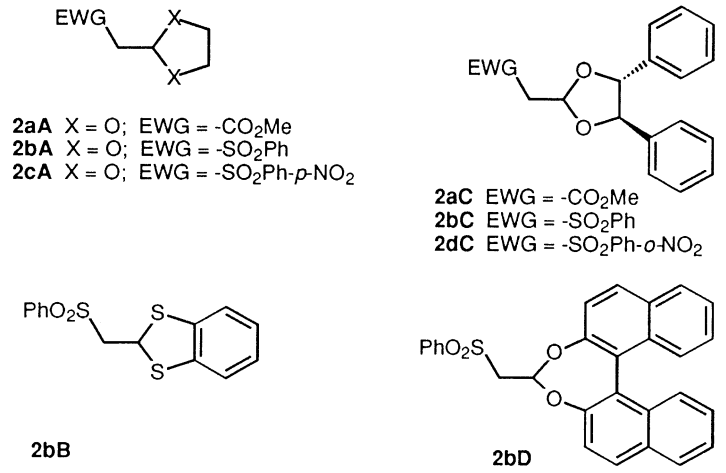
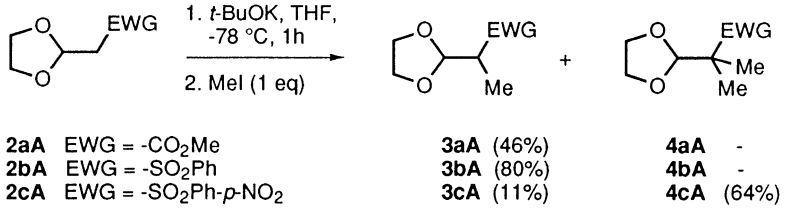


Figure 1.



Scheme 2.

The reactions were carried out by treating THF solutions of acetals **2A–D** with a stoichiometric amount of *t*-BuOK at the indicated temperature and by quenching the resulting species with methyl iodide. The reaction products were purified in all cases by chromatography and characterized by NMR. The results obtained are summarised in Table 1.

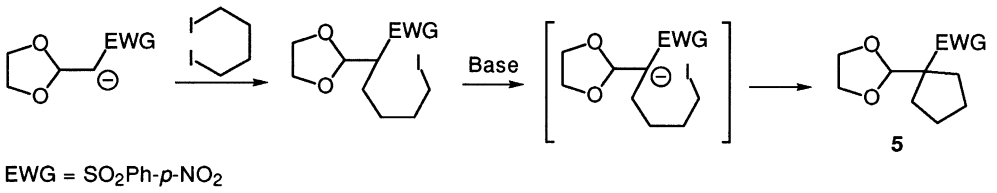
The effect of the nature of the electron-withdrawing group was comparatively tested on **2aA** (EWG=—CO_2Me), **2bA** (EWG=—SO_2Ph) and **2cA** (EWG=—SO_2Ph-*p*-NO_2). The reaction (Scheme 2) carried out on the methylester **2aA** (row 1, Table 1) afforded only the monomethylated derivative **3aA** (46% yield); while acetal **2bA**, containing the phenylsulfonyl group (row 2, Table 1), furnished the monomethyl derivative **3bA** in higher yield (80% yield) as the sole product.

Under the same reaction conditions, the *p*-nitrophenylsulfonyl-substituted acetal **2cA** (row 3, Table 1) led to a mixture of mono- (**3cA**) and dimethylated (**4cA**) compounds in 11% and 64% yields, respectively. In this case, the nitro group appears to exert an additional effect in stabilizing the anion derived from the monomethylated product in apparent contrast to the standard stability of carbanions, but in agreement with what is reported in the literature.[9]

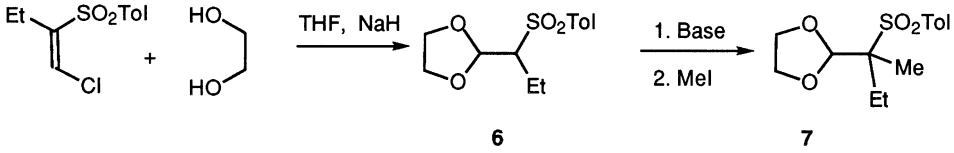
The product distribution is influenced by the concentration of MeI and by the sequence of addition of the reagents. These aspects were studied in the methylation of **2cA** in experiments carried out at 0°C. By treating a solution of **2cA** anion with a fourfold excess of methyl iodide (row 5, Table 1), the dimethylated compound **4cA** (94% yield) was formed predominantly with respect to the monomethylated

Table 1. Reaction conditions and product distribution (yields) in the reaction of **2aA–D**, **6** with base and MeI

Number	Substrate	Method	Monoalkylated product (% yield)	Dialkylated product (% yield)	Ring-opened product (% yield)
1	**2aA**	−78°C, THF, *t*-BuOK, CH_3I (1 equiv.)	**3aA** (46)	–	–
2	**2bA**	−78°C, THF, *t*-BuOK, CH_3I (1 equiv.)	**3bA** (80)	–	–
3	**2cA**	−78°C, THF, *t*-BuOK, CH_3I (1 equiv.)	**3cA** (11)	**4cA** (64)	–
4	**2cA**	−78°C, THF, *t*-BuOK, CH_3I (2 equiv.)	**3bA** (11)	**4bA** (54)	–
5	**2cA**	0°C, THF, *t*-BuOK, CH_3I (4 equiv.)	–	**4cA** (94)	–
6	**2cA**	0°C, THF, *t*-BuOK, CH_3I (4 equiv. inv. add.)	**3bA** (20)	**4cA** (65)	–
7	**2cA**	0°C, THF, *t*-BuOK, I—$(CH_2)_4$—I	–	**5** (20)	–
8	**6**	−78°C, THF, *t*-BuOK, CH_3I (1 equiv.)	–	**7** (60)	–
9	**2aC**	−78°C, THF, *t*-BuOK, CH_3I (2 equiv.)	**3aC** (quant.)	–	–
10	**2bC**	−78°C, THF, *t*-BuOK, CH_3I (2 equiv.)	**3bC** (50)	**4bC** (50)	–
11	**2dC**	−78°C, THF, *t*-BuOK, CH_3I (1 equiv.)	**3dC** (quant.)	–	–
12	**2bB**	−78°C, THF, *t*-BuOK, CH_3I (1 equiv.)	–	–	**8** (quant.)
13	**2bD**	−78°C, THF, *t*-BuOK, CH_3I (1 equiv.)	–	–	**9** (quant.)



Scheme 3.



Scheme 4.

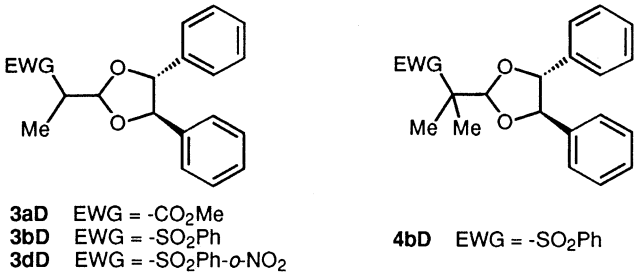


Figure 2.

one, showing that the formation of the dimethylated product is favoured at higher concentration of methyl iodide. By using 2 equiv. of methyl iodide (row 4, Table 1), the monomethylated **3cA** and dimethylated **4cA** derivatives were formed in about 1:5 ratio. Differently, the formation of the dimethylated derivative was slightly disfavoured by the inverse addition of the reagents. In fact, by using the same fourfold excess of methyl iodide (row 6, Table 1), the mono- (**3cA**) and dimethylated (**4cA**) derivatives, were obtained in 1:3 ratio, respectively.

While alkylating agents different from methyl iodide, such as ethyl bromide, butyl bromide, benzyl bromide, benzoyl choride or benzaldehyde were totally unreactive with **2bA** and **2cA** under the same reaction conditions, the quenching of **2cA** with 1,4-diiodobutane (row 7, Table 1) afforded the cyclic derivative **5** (20% yield) through an intramolecular second nucleophilic substitution (Scheme 3).

On the basis of these results, it is not possible to introduce two different electrophiles; therefore we checked the possibility of alkylating the ethyl derivative **6** obtained by reaction of 1-ethyl-1-*p*-toluensulfonyl-2-chloroethylene with ethylene glycol, under standard conditions (Scheme 4). This compound, treated with *t*-BuOK at −78°C and methyl iodide, afforded **7** (row 8, Table 1). Also in this case, the reactions of the anion derived from **6** with electrophiles other then methyl iodide were unsuccessful.

The chiral substrates **2aC**, **2bC** and **2dC** in Fig. 1, obtained employing (*R*,*R*)-hydrobenzoin as chiral diol, were prepared in order to evaluate the degree of the stereoselectivity in the alkylation step. Relatively to the nature of electron-withdrawing substituents, the behaviour of **2a–dC** was quite different: while **2aC** (EWG=—CO_2Me) (row 9, Table 1) and **2dC** (EWG=—SO_2Ph-*o*-NO_2) (row 11, Table 1) selectively lead to the monomethylated product **3aC** and **3dC** (Fig. 2), **2bC** (EWG=—SO_2Ph) gave a 1:1 mixture of monomethyl (**3bC**), and dimethyl (**4bC**) derivatives (row 10, Table 1). In all cases diastereoselectivity was poor (6:4 diastereoselective ratio for **3aC**, 7:3 for **3bC** and 1:1 for **3dC**).

Acetals **2bB** and **2bD** (rows 12 and 13, Table 1) exclusively afforded *O*- and *S*-methylated products **8** and **9** (Fig. 3) through a β-elimination pathway (path B in Scheme 1) in almost quantitative yields.[7c] The stereochemistry of the double bond in **8** and **9** was assigned *E*, as suggested by the coupling constants of the vinylic protons (**8**: J=14.6 Hz; **9**: J=12.0 Hz).

In conclusion, in the present study we have observed that the reaction of anions derived from β-electron-withdrawing substituted acetals may occur through different competitive reaction routes, involving either mono-, dialkylation and

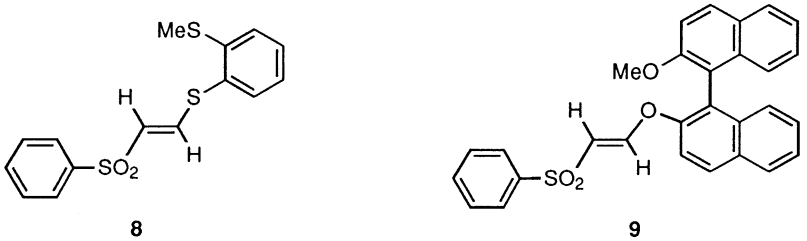


Figure 3.

β-elimination processes. These reactions can be moderatly shifted to a predominant species under appropriate conditions.

3. Experimental

3.1. General methods

Melting points were determined on a Büchi 535 apparatus and are uncorrected. Known compounds used in this research were either purchased from standard chemical suppliers or prepared according to literature procedures. The ^{1}H and ^{13}C NMR were performed with a Bruker AC 200 at 200 MHz (^{1}H) and 50 MHz (^{13}C), respectively, in deuterochloroform solution. IR spectra were recorded on a Biorad FTS 40 spectrophotometer. Known compounds, including optically active compounds, were prepared according to literature procedures or purchased from standard chemical suppliers and purified to match the reported physical and spectral data. NaH was purchased as a dispersion in mineral oil and washed with pentane prior to use. Microanalyses were performed on a Perkin–Elmer 2400 CHN elemental analyzer.

3.2. Reaction of 1a–c with RXH (X=O, S). General procedure for the preparation of 2a–d (A–D)

A stirred solution of the appropriate diol (or thiol) (5 mmol) in anhydrous THF (20 mL) was treated at 0°C, with NaH (0.1 equiv. or stoichiometric amount for ethylenes) under argon. After 15 min, a solution of **1** (5 mmol) in THF (20 mL) was slowly added by syringe at 0°C and the reaction was monitored by TLC. The crude reaction mixture was treated with brine (15 mL) and extracted with Et_2O (3×60 mL), dried, filtered and concentrated at reduced pressure. Flash chromatography (eluant dichloromethane, silica gel 60 mesh) was performed in order to obtain analytically pure samples.

3.2.1. 2-Methoxycarbonylmethyl-1,3-dioxolane (2aA). Yield, 84%. Colourless oil: [Found: C, 44.99; H, 7.70. $C_5H_{10}O_4$ requires C, 44.77; H, 7.51%]; ν_{max} (neat, NaCl) 2956, 2893, 1738, 1439, 1136, 845, 745, 694 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.25 (1H, t, J=5.2 Hz), 4.04–3.78 (4H, m), 3.68 (3H, s), 2.65 (2H, d, J=5.2 Hz). δ_C (50 MHz, $CDCl_3$) 169.7, 100.8, 64.9, 51.7, 39.6.

3.2.2. 2-(4-Nitrophenylsulfonylmethyl)-1,3-dioxolane (2cA). Pale yellow oil: [Found: C, 44.12; H, 4.15; N, 5.25. $C_{10}H_{11}NO_6S$ requires C, 43.95; H, 4.06; N, 5.13%]; ν_{max} (neat, NaCl) 2990, 2995, 1520, 1351, 1306, 1130, 767, 740, 705 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.47–8.38, 8.20–8.11 (4H, series of m, AA′BB′ system, Ar), 5.33 (1H, t, J=4.7 Hz), 3.87 (4H, bs), 3.53 (2H, d, J=4.7 Hz); δ_C (50 MHz, $CDCl_3$) 145.9, 129.8, 125.8, 124.1, 98.5, 65.0, 59.6.

3.2.3. (4*R*,5*R*)-4,4-Diphenyl-2-methoxycarbonylmethyl-1,3-dioxolane (2aC). Yield, 93%. White solid, mp 82–83°C (Et_2O–petrol. ether): [Found: C, 72.76; H, 6.31. $C_{18}H_{18}O_4$ requires C, 72.47; H, 6.08%]; ν_{max} (KBr disk) 3085, 3033, 2953, 2880, 1740, 1455, 1430, 1253, 1132, 762, 758, 702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.45–7.10 (10H, series of m, Ar), 5.93 (1H, t, J=5.2 Hz), 4.81 (2H, s), 3.78 (3H, s), 2.98 (1H, d, J=5.2 Hz); δ_C (50 MHz, $CDCl_3$) 169.7, 137.6, 136.3, 128.6, 128.3, 128.11, 126.9, 126.8, 126.4, 102.0, 86.9, 85.0, 51.9, 40.4.

3.2.4. (4*R*,5*R*)-4,4-Diphenyl-2-(2-nitrophenylsulfonylmethyl)-1,3-dioxolane (2dC). Yield, 93%. Pale yellow oil: [Found: C, 62.27; H, 4.65; N, 3.43. $C_{22}H_{19}NO_6S$ requires C, 62.11; H, 4.50; N, 2.29%]; ν_{max} (neat, NaCl) 3093, 3053, 2916, 1539, 1451, 1322, 1147, 1104, 762, 702, 645 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.30–8.20, 7.95–7.62, 7.55–7.00 (14H, series of m, Ar), 6.02 (1H, t, J=4.9 Hz), 4.75 (1H, d, 1/2 AB system, J=8.3 Hz), 4.69 (1H, d, 1/2 AB system, J=8.3 Hz), 4.29 (1H, dd, 1/2 AB system, J=14.6, 5.3 Hz), 4.18 (1H, dd, 1/2 AB system, J=14.6, 5.3 Hz); δ_C (50 MHz, $CDCl_3$) 139.9, 136.4, 135.3, 1134.8, 133.9, 132.9, 132.5, 128.7, 128.6, 128.6, 126.9, 126.5, 126.3, 124.7, 99.7, 86.7, 84.7, 60.8.

3.3. Alkylation of acetals. General procedure

A solution of acetal **2b** (1.5 mmol) in freshly dried THF, stirred under argon at the appropriate temperature, was treated with *t*-BuOK (1.5 mmol) and the resulting solution was stirred at the same temperature for 1 h. The methyl iodide (1 equiv.) was added to the carbanion solution and the mixture was stirred until the reaction reached room temperature.The resulting mixture was treated with water (5 mL), extracted with diethyl ether (3×25 mL), dried (Na_2SO_4) and concentrated at reduced pressure. The residue was purified by flash chromatography (eluting with a gradient of *n*-hexane–ethyl acetate starting from *n*-hexane).

3.3.1. 2-(1′-Methoxycarbonylethyl)-1,3-dioxolane (3aA). Colourless oil: [Found: C, 52.12; H, 7.36. $C_7H_{12}O_4$ requires C, 52.49; H, 7.55%]; ν_{max} (neat, NaCl) 2985, 2957, 2885, 1744, 1700,1640, 1438, 1293, 1253, 1189, 1124, 798 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.11 (1H, d, J=5.1 Hz), 4.12–3.85 (4H, m), 3.72 (3H, s, OMe), 2.76 (1H, qd, J=7.1, 5.1 Hz), 1.26 (6H, d, J=7.1 Hz); δ_C (50 MHz, $CDCl_3$) 157.5, 104.3, 73.2, 71.6, 65.2, 51.1, 44.1.

3.3.2. 2-(1′-Phenylsulfonylethyl)-1,3-dioxolane (3bA). Colourless oil: [Found: C, 54.32; H, 6.04. $C_{11}H_{14}SO_4$ requires C, 54.53; H, 5.82%]; ν_{max} (neat, NaCl) 3057, 2948, 2880, 1620, 1446, 1382, 1304, 1205, 1169, 758, 726, 689 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.96–7.85, 7.70–7.50 (5H, series of m, Ar), 5.30 (1H, d, J=3.3 Hz), 3.91–3.79 (4H, m), 3.39 (1H, qd, J=7.1, 3.3 Hz), 1.30 (6H, d, J=7.1 Hz); δ_C (50 MHz, $CDCl_3$) 133.7, 129.2, 128.9, 128.2, 100.7, 68.0, 65.7, 65.0, 26.6.

3.3.3. 2-[1′-(4-Nitrophenylsulfonyl)ethyl]-1,3-dioxolane (3cA). White solid, mp 101–103°C (Et_2O–*n*-hexane): [Found: C, 45.77; H, 4.65; N, 5.15. $C_{11}H_{13}NO_6S$ requires C, 45.99; H, 4.56; N, 4.88%]; ν_{max} (KBr) 3010, 2985, 2896, 1523, 1354, 1297, 1128, 1078, 846, 770, 742, 706, 677 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.41–8.37, 8.13–8.09 (4H, series of m, AA′BB′ system, Ar), 5.29 (1H, d, J=3.6 Hz), 3.88–3.79 (4H, m), 3.43 (1H, qd, J=7.2, 3.6 Hz), 1.37 (6H, d, J=7.2 Hz). δ_C (50 MHz, $CDCl_3$) 144.0, 130.9, 123.9, 100.9, 65.6, 65.2, 63.6, 8.0.

3.3.4. 2-[1′-Methyl-1′-(4-nitrophenylsulfonyl)ethyl]-1,3-dioxolane (4cA). White solid, mp 144–146°C (Et_2O): [Found: C, 48.09; H, 5.17; N, 4.86. $C_{12}H_{15}NO_6S$ requires C, 47.83; H, 5.02; N, 4.65%]; ν_{max} (KBr) 3097, 2896, 2876, 1539, 1362, 1297, 1161, 1104, 738, 689, 608 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.36–8.31, 8.12–8.08 (4H, series of m, AA′BB′ system, Ar), 5.12 (1H, s), 3.86–3.76 (4H, m), 1.36 (6H, s); δ_C (50 MHz, $CDCl_3$) 150.8, 143.3, 132.2, 123.2, 103.4, 66.9, 65.5, 16.5.

3.3.5. 2-[1′-(4-Methyl-phenylsulfonyl)cyclopentyl]-1,3-dioxolane (5). Pale yellow oil: [Found: C, 59.91; H, 5.97; N, 4.88. $C_{14}H_{17}NO_4S$ requires C, 59.63; H, 5.80; N, 4.74%]; ν_{max} (neat, NaCl) 3096, 2880, 1532,1360, 1298, 1105, 737, 690, 610 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.34 (2H, d, 1/2 AB system, J=9.0 Hz, Ar), 8.13 (2H, d, 1/2 AB system, J=9.0 Hz, Ar), 5.18 (1H, s), 3.82 (4H, bs), 2.40–1.75 (8H, series of m); δ_C (50 MHz, $CDCl_3$) 150.6, 141.5, 131.4, 123.1, 96.5, 68.2, 66.7, 27.3, 22.5.

3.3.6. 2-[1′-(4-Methyl-phenylsulfonyl)propyl]-1,3-dioxolane (6). Yield, 90%. White solid, mp 68–69°C (Et_2O–petrol. ether): [Found: C, 57.50; H, 6.87. $C_{13}H_{18}O_4S$ requires C, 57.76; H, 6.71%]; ν_{max} (KBr) 2973, 2944, 2884, 1595, 1451, 1390, 1378, 13340, 1320, 1144, 1076, 822, 718, 681 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85–7.74, 7.40–7.30 (4H, series of m, Ar), 5.27 (1H,d, J=2.3 Hz,), 4.00–3.80 (4H, m), 3.21 (1H, td, J=4.0, 2.3 Hz), 2.43 (3H, s), 1.80 (2H, dq, J=8.1, 4.0 Hz), 1.05 (3H, t, J=8.1 Hz); δ_C (50 MHz, $CDCl_3$) 144.5, 129.5, 129.4, 129.0, 101.1, 68.5, 65.4, 64.6, 21.6, 17.2, 12.6.

3.3.7. 2-[1′-Methyl-1′-(4-methyl-phenylsulfonyl)propyl]-1,3-dioxolane (7). Slurry: [Found: C, 59.32; H, 7.25. $C_{14}H_{20}O_4S$ requires C, 59.13; H, 7.09%]; ν_{max} (NaCl) 2996, 2932, 2884, 1640, 1446, 1398, 1289, 1157, 1124, 734, 657 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85–7.74, 7.40–7.30 (4H, series of m, Ar), 5.12 (1H, s), 3.92–3.75 (4H, m), 2.40 (3H, s), 1.90 (2H, dq, J=7.8, 2.0, Hz), 1.28 (3H, s, CH3), 1.08 (3H, t, J=7.8 Hz); δ_C (50 MHz, $CDCl_3$) 143.3, 130.4, 128.8, 127.4, 103.5, 73.7, 65.2, 64.9, 23.8, 21.3, 17.8, 12.6.

3.3.8. (*E*)-1-Phenylsulfonyl-2-(2′-methylthiophenylthio)-ethylene (8). White solid, mp 105–107°C (Et_2O): [Found: C, 55.35; H, 5.71. $C_{15}H_{18}O_2S_3$ requires C, 55.18; H, 5.56%]; ν_{max} (KBr) 3029, 2920, 2848, 1551, 1430, 1348, 1306, 1144, 1076, 835, 750 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.97–7.78 (2H, m, Ar), 7.72 (1H, d, J=14.6 Hz), 7.65–7.36, 7.29–7.09 (7H, series of m, Ar), 5.91 (1H, d, J=14.6 Hz), 2.39 (3H, s); δ_C (50 MHz, $CDCl_3$) 144.9, 144.2, 141.00, 135.5, 133.0, 130.9, 129.1, 127.3 (2C), 125.5, 125.4, 123.2, 15.4.

3.3.9. 2-[(*E*)-2-Phenylsulfonylethenyl]-2′-methoxy-1,1′-binaphthalene (9). White solid, mp 115–117°C (CH_2Cl_2–Et_2O): [Found: C, 74.90; H, 4.83. $C_{29}H_{22}O_4S$ requires C, 74.66; H, 4.75%]; ν_{max} (KBr) 3061, 2928, 2832, 1620, 1306, 1250, 1150, 1084, 814, 754, 730, 689 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.15–7.83, 7.76–7.12, 7.10–6.93 (18H, series of m, Ar and vinylic), 5.66 (1H, d, J=12.0 Hz, vinylic), 3.68 (3H, s, OMe); δ_C (50 MHz, $CDCl_3$) 159.6, 154.8, 142.1, 132.7, 131.8, 130.44, 130.2, 129.4, 129.3, 129.0, 128.8, 128.2, 128.0, 127.0 (3C), 126.3, 126.1, 125.9, 124.5, 123.7, 119.4, 113.0, 109.7, 56.1.

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