

N-Heterocyclic Carbene-Promoted Rauhut–Currier Reactions between Vinyl Sulfones and α,β -Unsaturated Aldehydes

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N-heterocyclic carbenes (NHCs) promote the addition of 1,1-bis(phenylsulfonyl)ethylene to the α -position of α,β -unsaturated aldehydes. The proposed reaction pathway for this Rauhut–Currier-type reaction includes an unusual conjugate addition of an NHC to a bis-vinyl sulfone.

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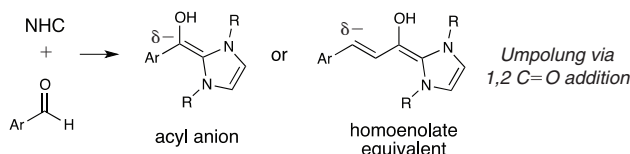
Introduction

Metal-free catalysis is an attractive field of methodology development because of its biomimetic and green nature. Intense efforts over the last decade to investigate organocatalysis have resulted in an eruption of selective and efficient strategies for the synthesis of organic molecules.^[1] Specifically in the field of Lewis base catalysis,^[2] N-heterocyclic carbenes (NHCs) facilitate a wide number of powerful bond-forming reactions.^[3] Inspired by the biological conversion of pyruvate into acetyl Co-A by a thiamin cofactor, NHC catalysis utilizes the electron lone pair of nitrogen-containing heterocycles (i.e., thiazolium, imidazolium, and triazolium-derived carbenes) to promote a variety of reactions including acyl anion chemistry,^[4] homoenolate^[5] and enolate^[6] equivalents, reductions,^[3c] and oxidations.^[7] Carbene catalysis is well known for the 1,2-addition of the carbene to a carbonyl group of a substrate, affording an acyl anion or homoenolate equivalent (Scheme 1). A less developed reactivity mode for these Lewis base catalysts is the conjugate addition of an α,β -unsaturated carbonyl-containing compound to generate a reactive enolate intermediate. Both Fu and Ye have independently reported NHC-catalyzed β -Umpolung-type and Morita–Baylis–Hillman (MBH) reactions^[8] of α,β -unsaturated carbonyl substrates.^[9] The Rauhut–Currier (RC) reaction^[10] involves the nucleophile catalyzed coupling of a reactive intermediate (enolate) generated from an activated alkene to a secondary Michael acceptor, thereby forging a new C–C bond between the α -position of the alkene and the β -position of the secondary electrophile. To the best of our knowledge, there has been no report of a NHC-catalyzed RC reaction. This conjugate addition mode is an under-explored area for carbene catalysis and offers opportunities for reaction design and development beyond the established manifold resulting from 1,2-addition of the NHC to a carbonyl group (e.g., acyl anion and homoenolate equivalent reactions). In this work, we report that NHCs are compatible

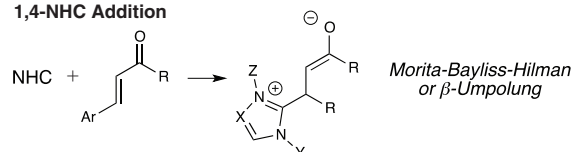
with an atypical NHC electrophile (non-carbonyl containing), resulting in the RC product of α,β -unsaturated aldehydes.

Vinyl sulfones are versatile electrophiles in organic synthesis because of their high reactivity in organometallic and organocatalysis.^[11] Our group has recently reported the use of vinyl sulfones as substrates in a carbene-catalyzed reaction with 1,3-dipolar electrophiles to form cycloaddition products with an unusual sulfonyl transposition.^[12] In our initial investigations exploring homoenolate equivalent cycloadditions with vinyl sulfones, we discovered that NHCs promoted an unexpected process to deliver the apparent RC product (Scheme 1).

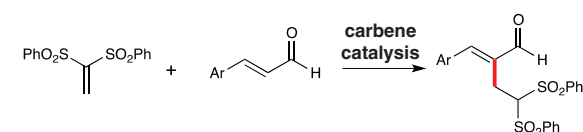
1,2-NHC Addition



1,4-NHC Addition



This work



Scheme 1. 1,2 and 1,4-addition modes of N-heterocyclic carbene (NHC) catalysis.

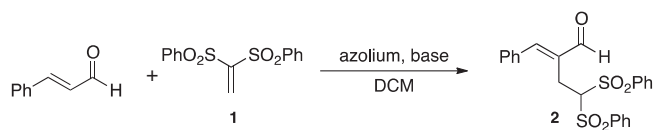
Results and Discussion

We initially explored the compatibility of NHC-homoenolate equivalents with vinyl sulfones to access cyclopentanones by a formal [3+2] annulation. However, the product isolated was confirmed as the intermolecular RC product (the X-ray crystallography data has been submitted to the Cambridge Crystallographic Data Centre) not the desired homoenolate equivalent addition product. This RC process represents a new mode of NHC reactivity and a different type of carbene catalysis compared with the benzoin/Umpolung modality. While intramolecular RC reactions have been reported by the groups of Krische,^[10b] Roush,^[10c,d] Miller,^[10e] and others,^[10h] we have been interested in Lewis base catalysis in general^[13] and developing new intermolecular versions of this reaction for some time.^[10g] After screening potential azolium salts as pre-catalysts, we found that triazolium D was the only catalyst that led to the formation of the RC products such as **2** (Table 1). The product structure was confirmed by single crystal X-ray diffraction. During reaction optimization, we focused on using non-nucleophilic bases to avoid possible complications of competitive base conjugate addition. Our best results were obtained with sodium *tert*-butoxide as the base and dichloromethane as the solvent. The choice of solvent and amount of base was important to avoid an unusual side product, (phenylperoxy)(1,3,3-tris(phenylsulfonyl)propyl)sulfane, which we observed in solvents such as THF and acetonitrile. This compound has been reported previously in studies of 1,1-bis(phenylsulfonyl)ethylene with enamine catalysis.^[11d,i] The use of two equivalents of the enal partner was determined to be the ideal stoichiometry for this process. We found it odd that even though excess of the aldehyde was used, there was no evidence for the typical NHC-homoenolate chemistry present in the reaction mixture (the excess aldehyde was recovered during purification).

With optimized reaction conditions that provided the intermolecular RC product between the vinyl sulfone and α,β -unsaturated aldehyde, we examined the scope of the reaction with respect to the enal component (Table 2). Having an electron withdrawing substituent on the aryl ring resulted in the products in good to moderate yields, potentially because of the increased electrophilicity of the β -position of the α,β -unsaturated aldehyde. Reactions with enals with non-electron withdrawing groups or groups that would block the β -position provided lower yields. The other product generated was *trans*-1,2-bis(phenylsulfonyl)ethylene and accounted for the mass balance. Unfortunately, the substrate scope of this process is currently limited and mixed sulfone/carbonyl group compounds are not suitable substrates.

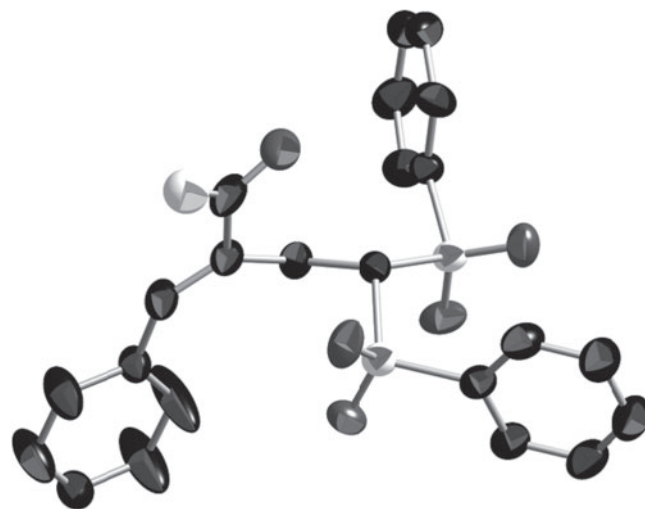
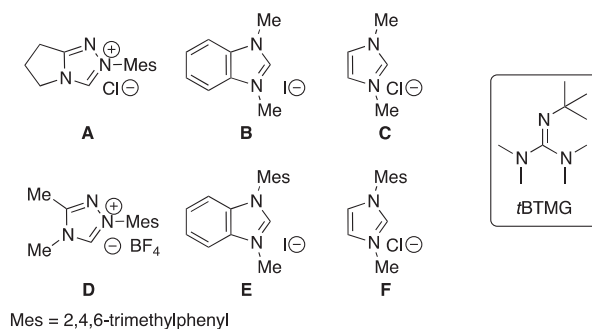
There are two main possible reaction pathways for the generation of the RC product (Scheme 2). In pathway A (NHC catalyzed), the NHC undergoes an initial conjugate addition to the vinyl sulfone, forming intermediate anion **I** that adds to cinnamaldehyde in a conjugate fashion. The resulting enolate **II** then undergoes a 4-*exo*-tet cyclization to produce a heavily substituted cyclobutane intermediate with concomitant regeneration of the carbene catalyst. Subsequent deprotonation of the α -position of the exocyclic aldehyde and elimination provides RC product **2**. The alternative route involves a more complicated process (pathway B, NHC initiated). The NHC performs a conjugate addition to the vinyl sulfone to produce a sulfinate ion in situ. In previous reported studies, we have observed a smooth rearrangement of 1,1-bis vinyl sulfones to

Table 1. Optimization table and ORTEP of **2** (displayed at 50 % probability).



Entry	Azolium	mol %	Base	Solvent ^a	Yield 2 (%) ^{b, c}
1	A	20	<i>t</i> BTMG	CH ₂ Cl ₂	10
2	B	20	<i>t</i> BTMG	CH ₂ Cl ₂	0
3	C	20	<i>t</i> BTMG	CH ₂ Cl ₂	0
4	D	20	<i>t</i> BTMG	CH ₂ Cl ₂	15
5	E	20	<i>t</i> BTMG	CH ₂ Cl ₂	0
6	F	20	<i>t</i> BTMG	CH ₂ Cl ₂	0
7	D	20	NaOtBu	CH ₂ Cl ₂	39
8	D	20	DBU	CH ₂ Cl ₂	trace
9	D	20	Et ₃ N	CH ₂ Cl ₂	0
10	D	20	K ₂ CO ₃	CH ₂ Cl ₂	0

^a—0.25 M. ^bisolated yields. ^c—20 mol % azolium, 20 mol % base at 25°C for 25 h



1,2-bis sulfones by a sulfinate ejection/re-addition process.^[12] The in situ sulfinate anion generated by NHC addition to the vinyl sulfone acts as the nucleophilic catalyst which then undergoes 1,4-addition to the enal, thereby forming enolate **VI**. At this point, anion **VI** would add to the vinyl sulfone and deprotonation results in the RC product **2**. In support of pathway B, we have added sodium sulfinate (1 equiv.) to a solution of cinnamaldehyde and vinyl sulfone and observed the RC product

Table 2. Enal substrate scope.

Reaction scheme: Enal + 1 $\xrightarrow[\text{DCM, 24 h}]{\text{D, NaOtBu}}$ Product

Entry	Product ^a	Yield (%) ^b
1		39
2		55
3		61
4		56
5		49
6		64
7		58
8		98
9		41
10		49

a – 20 mol % **D**, 20 mol % base, 3 Å MS, and 0.25 M at 40°C. b – isolated yield



All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. Dichloromethane was purified by passage through a bed of activated alumina.^[14] Reagents were purified before use unless otherwise stated following the guidelines of Perrin and Armarego.^[15] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization of TLC plates was accomplished with UV light. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H NMR spectra were recorded on a Bruker A500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C NMR spectra were recorded on a

Bruker A500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl_3 at 77.0 ppm). Mass spectrometric data for the products were acquired on an Agilent 6210 LC-Tof High Resolution Mass Spectrometer, using an Electro Spray Ionization source. Samples were introduced using 1 μL direct injection. The solvent used was 90 % $\text{MeOH}/10\%$ water/ 0.1% formic acid flowing at 0.5 mL min^{-1} .

General Procedure for Formation of RC Product

To a reaction vial containing a magnetic stirring bar was added the corresponding 1,1-bis(phenylsulfonyl)ethylene (50 mg, 0.16 mmol), enal (2 equiv.), flame-dried 3 Å molecular sieves, and dichloromethane (0.4 mL). A dichloromethane solution (0.2 mL) containing the azolium salt (0.03 mmol) and base (0.03 mmol) was then added, bringing the reaction solution to 0.25 M. The reaction was then heated to 40°C for 24 h. The unpurified reaction was filtered through a pad of silica, washing with EtOAc and concentrated under vacuum. The material was purified by column chromatography (silica, 25 % EtOAc/hexanes), and after concentration of the appropriate fractions afforded the product.

(E)-2-Benzylidene-4,4-bis(phenylsulfonyl)butanal (2)

Prepared according to the general procedure with dichloromethane, yielding 28 mg (39 %) as a white solid (25 % EtOAc/hexanes, $R_F = 0.18$). ν_{max} (film)/ cm^{-1} 3065, 2957, 2849, 1665, 1625, 1447, 1313, 1146, 1079. δ_{H} (500 MHz, CDCl_3) 9.22 (s, 1H), 7.58–7.57 (m, 4H), 7.42 (m, 2H), 7.26–7.04 (m, 10H), 5.36 (t, J 6.9, 1H), 3.25 (d, J 6.9, 2H). δ_{C} (125 MHz, CDCl_3) 195.0, 152.3, 137.6, 135.9, 134.6, 133.8, 130.2, 129.6, 129.19, 129.01, 78.9, 22.1. m/z HRMS (ESI) Calc. for $\text{C}_{23}\text{H}_{21}\text{O}_5\text{S}_2^+ [\text{M} + \text{H}]^+$ 441.0825. Found 441.0825.

A colourless tabular crystal of $\text{C}_{23}\text{H}_{20}\text{O}_5\text{S}_2$ having approximate dimensions of $0.52 \times 0.29 \times 0.12\text{ mm}^3$ was mounted using oil (Infinite V8512) on a glass fiber. All measurements were made on a Bruker APEX-II CCD Diffractometer with a $\text{Cu K}\alpha$ I S source at a temperature of $250(2)\text{ K}$ with a theta range for data collection of 1.84° to 30.47° . Cell constants and an orientation matrix for data collection corresponded to a triclinic, space group $P-1$, with a 9.3104(5), b 10.4613(6), and c 11.7985(6) Å, α 89.825(3)°, β 70.317(2)° and γ 72.560(2)°. For $Z = 2$ and $\text{FW} = 440.51$, the calculated density is 1.426 g cm^{-3} . The linear absorption coefficient, μ , for $\text{Mo K}\alpha$ radiation is 0.293 mm^{-1} . The maximum and minimum transmission factors were: 0.9662 and 0.8625, respectively. Of the 27 149 reflections collected, 6158 were unique ($R_{\text{int}} 0.0668$). The final cycle of full-matrix least-squares refinement on F_2 was based on 6158 reflections and 271 variable parameters and converged with agreement factors of R_1 0.0496 and wR_2 0.1468 and goodness-of-fit on $F^2 = 0.990$. Further information is contained in the CIF file, available from the Cambridge Crystallographic Data Centre, CCDC 833171.

(E)-2-(4-Chlorobenzylidene)-4,4-bis(phenylsulfonyl)butanal (3)

Prepared according to the general procedure with dichloromethane, yielding 42 mg (55 %) as a white solid (25 % EtOAc/hexanes, $R_F = 0.18$). ν_{max} (film)/ cm^{-1} 3067, 2924, 2853, 1677, 1628, 1448, 1330, 1150, 1090, 1080. δ_{H} (500 MHz, CDCl_3) 9.44 (s, 1H), 7.81–7.79 (m, 4H), 7.66 (ap t, 2H), 7.51–7.36 (m, 9H), 5.54 (t, J 6.9, 1H), 3.42 (d, J 6.9, 2H). δ_{C} (125 MHz, CDCl_3) 194.8, 150.8, 137.6, 136.4, 134.7, 132.2, 130.8, 129.52, 129.46,

129.1, 78.8, 22.2. m/z HRMS (ESI) Calc. for $\text{C}_{23}\text{H}_{20}\text{ClO}_5\text{S}_2^+ [\text{M} + \text{H}]^+$ 475.0435. Found 475.0438.

(E)-2-(Naphthalen-2-ylmethylene)-4,4-bis(phenylsulfonyl)butanal (4)

Prepared according to the general procedure with dichloromethane, yielding 48 mg (61 %) as a pale yellow solid (25 % EtOAc/hexanes, $R_F = 0.17$). ν_{max} (film)/ cm^{-1} 3062, 2924, 2853, 1676, 1620, 1448, 1331, 1149, 1079. δ_{H} (500 MHz, CDCl_3) 9.53 (s, 1H), 8.07 (s, 1H), 7.96 (dd, J 13.1, 5.9, 3H), 7.79 (d, J 8.4, 4H), 7.67–7.58 (m, 6H), 7.41–7.38 (m, 4H), 5.55 (t, J 6.8, 1H), 3.62 (d, J 6.8, 2H). δ_{C} (125 MHz, CDCl_3) 194.9, 152.3, 137.5, 136.1, 134.5, 133.7, 133.1, 131.2, 130.0, 129.6, 128.94, 128.94, 127.92, 127.79, 127.1, 126.3, 79.1, 21.9. m/z HRMS (ESI) Calc. for $\text{C}_{27}\text{H}_{23}\text{O}_5\text{S}_2^+ [\text{M} + \text{H}]^+$ 491.0981. Found 491.0983.

(E)-2-(4-Bromobenzylidene)-4,4-bis(phenylsulfonyl)butanal (5)

Prepared according to the general procedure with dichloromethane, yielding 47 mg (56 %) as a yellow solid (25 % EtOAc/hexanes, $R_F = 0.14$). ν_{max} (film)/ cm^{-1} 3067, 2923, 2852, 1677, 1628, 1448, 1330, 1149, 1079, 1009. δ_{H} (500 MHz, CDCl_3) 9.43 (s, 1H), 7.80–7.78 (m, 4H), 7.68–7.60 (m, 5H), 7.49 (t, J 7.8, 4H), 7.38–7.34 (m, 2H), 5.52 (t, J 6.9, 1H), 3.41 (d, J 6.9, 2H). δ_{C} (125 MHz, CDCl_3) 194.8, 150.8, 137.5, 136.5, 134.7, 132.7, 132.4, 131.0, 129.5, 129.1, 124.7, 78.9, 22.1. m/z HRMS (ESI) Calc. for $\text{C}_{23}\text{H}_{20}\text{BrO}_5\text{S}_2^+ [\text{M} + \text{H}]^+$ 518.9930. Found 518.9942.

(E)-2-(3-Chlorobenzylidene)-4,4-bis(phenylsulfonyl)butanal (6)

Prepared according to the general procedure with dichloromethane, yielding 38 mg (49 %) as a yellow solid (25 % EtOAc/hexanes, $R_F = 0.17$). ν_{max} (film)/ cm^{-1} 3068, 2925, 2855, 1679, 1629, 1448, 1331, 1150, 1079. δ_{H} (500 MHz, CDCl_3) 9.47 (s, 1H), 7.84–7.82 (m, 5H), 7.69–7.66 (m, 2H), 7.52–7.36 (m, 8H), 5.59 (t, J 7.0, 1H), 3.43 (d, J 6.9, 2H). δ_{C} (125 MHz, CDCl_3) 194.7, 150.4, 137.5, 137.0, 135.5, 135.1, 134.7, 130.5, 130.1, 129.54, 129.36, 129.1, 127.4, 78.9, 22.3. m/z HRMS (ESI) Calc. for $\text{C}_{23}\text{H}_{20}\text{ClO}_5\text{S}_2^+ [\text{M} + \text{H}]^+$ 475.0435. Found 475.0440.

(E)-4-(2-Formyl-4,4-bis(phenylsulfonyl)but-1-en-1-yl)benzonitrile (7)

Prepared according to the general procedure with dichloromethane, yielding 49 mg (64 %) as a yellow solid (25 % EtOAc/hexanes, $R_F = 0.14$). ν_{max} (film)/ cm^{-1} 3067, 2929, 2229, 1681, 1448, 1331, 1313, 1148, 1079. δ_{H} (500 MHz, CDCl_3) 9.48 (s, 1H), 7.75 (t, J 8.8, 6H), 7.66–7.60 (m, 4H), 7.49–7.41 (m, 5H), 5.53 (t, J 7.1, 1H), 3.37 (d, J 7.1, 2H). δ_{C} (125 MHz, CDCl_3) 194.6, 149.4, 138.24, 138.20, 137.5, 134.8, 132.7, 129.9, 129.4, 129.1, 118.2, 113.4, 78.6, 22.5. m/z HRMS (ESI) Calc. for $\text{C}_{24}\text{H}_{20}\text{NO}_5\text{S}_2^+ [\text{M} + \text{H}]^+$ 466.0777. Found 466.0736.

(E)-2-(Naphthalen-1-ylmethylene)-4,4-bis(phenylsulfonyl)butanal (8)

Prepared according to the general procedure with dichloromethane, yielding 46 mg (58 %) as a yellow solid (25 % EtOAc/hexanes, $R_F = 0.21$). ν_{max} (film)/ cm^{-1} 3063, 2925, 1679, 1627, 1448, 1331, 1151, 1079. δ_{H} (500 MHz, CDCl_3) 9.75 (s, 1H), 8.11–7.99 (m, 5H), 7.71–7.48 (m, 8H), 7.33–7.29 (m, 5H), 5.56 (t, J 6.8, 1H), 3.42 (d, J 6.8, 2H). δ_{C} (125 MHz, CDCl_3)

194.7, 150.5, 137.2, 134.5, 131.1, 130.7, 130.4, 129.6, 128.8, 127.4, 127.0, 126.9, 125.5, 124.2, 79.3, 22.3. *m/z* HRMS (ESI) Calc. for $C_{27}H_{23}O_5S_2^+$ $[M + H]^+$: 491.0981. Found 491.0982.

(*E*)-2-(4-Nitrobenzylidene)-4,4-bis(phenylsulfonyl)butanal (**9**)

Prepared according to the general procedure with dichloromethane, yielding 77 mg (98 %) as a pale orange solid (25 % EtOAc/hexanes, R_F = 0.12). $\nu_{\max}$ (film)/ cm^{-1} 3070, 2926, 1682, 1572, 1448, 1341, 1313, 1150, 1079. δ_H (500 MHz, CDCl_3) 9.56 (s, 1H), 8.29 (d, J 8.2, 2H), 7.91 (d, J 7.2, 2H), 7.79–7.48 (m, 11H), 5.57 (t, J 7.0, 1H), 3.20 (d, J 6.9, 2H). δ_C (125 MHz, CDCl_3) 194.7, 149.5, 138.0, 134.6, 134.3, 129.2, 125.5, 78.5, 22.6. *m/z* HRMS (ESI) Calc. for $C_{17}H_{16}NO_5S^+$ $[M + H]^+$: 486.0676. Found 486.0677.

(*E*)-2-(4-Acetylbenzylidene)-4,4-bis(phenylsulfonyl)butanal (**10**)

Prepared according to the general procedure with dichloromethane, yielding 32 mg (41 %) as a pale yellow solid (25 % EtOAc/hexanes, R_F = 0.23). $\nu_{\max}$ (film)/ cm^{-1} 3067, 2620, 2848, 1680, 1604, 1448, 1359, 1330, 1313, 1267, 1148, 1079. δ_H (500 MHz, CDCl_3) 9.46 (s, 1H), 8.02 (d, J 8.3, 1H), 7.77–7.75 (m, 4H), 7.64–7.57 (m, 6H), 7.46–7.41 (m, 4H), 5.52 (t, J 7.0, 1H), 3.42 (d, J 7.0, 2H), 2.64 (s, 3H). δ_C (125 MHz, CDCl_3) 197.3, 194.8, 150.5, 138.2, 137.6, 134.7, 129.62, 129.46, 129.09, 128.95, 78.7, 26.9, 22.4. *m/z* HRMS (ESI) Calc. for $C_{25}H_{23}O_6S_2^+$ $[M + H]^+$: 483.0931. Found 483.0924.

(*E*)-Methyl 4-(2-formyl-4,4-bis(phenylsulfonyl)but-1-en-1-yl)benzoate (**11**)

Prepared according to the general procedure with dichloromethane, yielding 40 mg (49 %) as a white solid (25 % EtOAc/hexanes, R_F = 0.12). $\nu_{\max}$ (film)/ cm^{-1} 3065, 2953, 2847, 1721, 1678, 1448, 1437, 1331, 1313, 1282, 1183, 1149, 1114, 1079. δ_H (500 MHz, CDCl_3) 9.48 (s, 1H), 8.12 (d, J 8.3, 1H), 7.80–7.78 (m, 4H), 7.66–7.63 (m, 3H), 7.55 (d, J 8.0, 2H), 7.49–7.44 (m, 5H), 5.54 (t, J 7.0, 1H), 3.98 (d, J 0.8, 2H), 3.43 (d, J 7.0, 3H). δ_C (125 MHz, CDCl_3) 194.7, 166.3, 150.6, 138.1, 137.52, 137.43, 134.7, 131.2, 130.2, 129.50, 129.37, 129.1, 78.8, 52.5, 22.3. *m/z* HRMS (ESI) Calc. for $C_{25}H_{23}O_7S_2^+$ $[M + H]^+$: 499.0880. Found 499.0878.

Materials

Compound **1** was prepared as described previously and is also commercially available.^[16]

Accessory Publication

Spectroscopic and X-ray crystallography data are available as an accessory publication available on the Journal's website. CCDC 833171 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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