Note

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Single Electron Transfer from Dimsyl Anion in the Alkylation of Phenols

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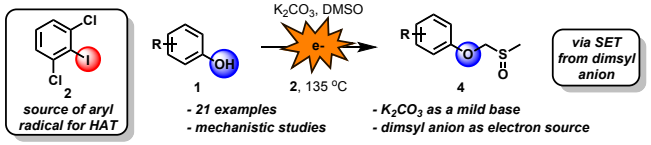
Supporting Information Placeholder



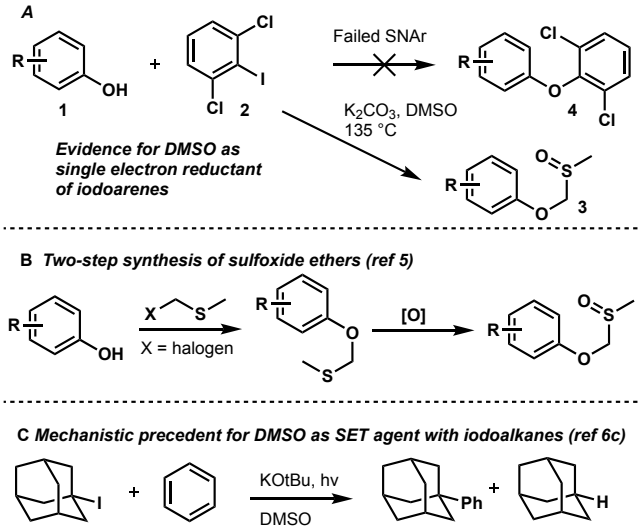
ABSTRACT: While attempting to synthesize biaryl ethers we discovered the inadvertent formation of a methylsulfoxylmethyl ether byproduct. Formation of this unexpected byproduct presented an opportunity to streamline the synthesis of methylsulfoxylmethyl ethers. Mechanistic studies suggest a radical pathway with dimsyl potassium as reducing agent.

Aryl ethers are an important class of organic molecules. In particular, biaryl ether motifs which are found in many biologically active molecules including natural products, pharmaceutical and agrochemical products.[1] Most synthetic methods for the preparation of biaryl ethers are based on the formation of C-O bond through a classic Ullman type coupling reaction using copper (I) or palladium (II) complexes.[2] Alternatively, nucleophilic S_NAr reactions represent an attractive and complementary method for the direct coupling of phenols and aryl halides.[3] As such, we attempted the formation of biaryl **4** using phenol **1** and 2,6-dichloroiodobenzene **2** in DMSO (Scheme 1 A). Surprisingly, the desired biaryl **4** was not isolated but a single byproduct **3** was consistently formed. The identification of this byproduct revealed the addition of DMSO to the phenolic-OH moiety as opposed to the expected arene. Though this result did not advance our immediate goals, we realized this S_NAr "failure" could represent an interesting method to install methylsulfinylmethyl ether units in a one-step process via a unique mechanism.

A cursory survey of the literature reveals that aryl methylsulfinylmethyl ethers are present in many bioactive compounds and also serve as synthetic handles for the installation of various other functional groups.[4] In these examples, the addition of methylsulfoxylmethyl ethers to phenols is mainly conducted via a two-step process which involves the formation of a methylthiomethyl ether (MTM) followed by oxidation into the corresponding sulfoxide (Scheme 1B).[5] Although the first step is generally reliable, the second step could be susceptible to overoxidation of the sulfide and will restrict functional group tolerance in the scope.

Preliminary discussions of the alkylation mechanism raised further interest in this transformation. It was found that ample mechanistic precedent exists for the involvement of DMSO in radical reactions, sometimes as a redox agent,[6] and other times as a source of C1 and other alkyl groups in synthesis.[7] Moreover, there is evidence that dimsyl anion can act as a single electron reducing agent (Scheme 1C).[6c]

Scheme 1. Unexpected alkylation of DMSO

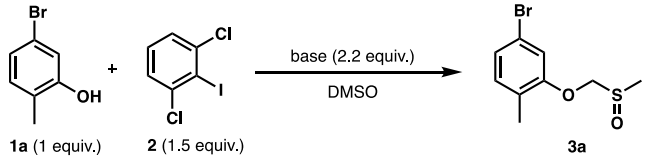


RESULTS AND DISCUSSION

Optimization of the reaction conditions began by first determining the role of the base counterion (entries 1-3). Changing from potassium to sodium proved to counterproductive as only starting materials were recovered (entries 1 and 2). Use of cesium as a counterion, however, led to moderate success (entry 3). Although this trend does not follow the solubility of these carbonate bases in DMSO, one can suggest that the counterion might influence the outcome of electron transfer radical reactions.[8] Lowering base loading resulted in decreased yields (entry 4).

Secondly, the reaction was attempted at temperatures lower than 135 °C with no success (entry 5). When lowering equivalents of iodoarene **2** or reduced to zero, the reaction suffered from reduced yields or failure (entries 6 and 7). Furthermore, performing the reaction at higher concentration in DMSO (entries 8 and 9) proved to be detrimental. Attempts to run reactions in DMSO with various cosolvents resulted in a halting of the reaction or prohibitively low yields (<15%) (see Supporting Information for complete optimization tables).

Table 1. Optimization of DMSO alkylation reaction.



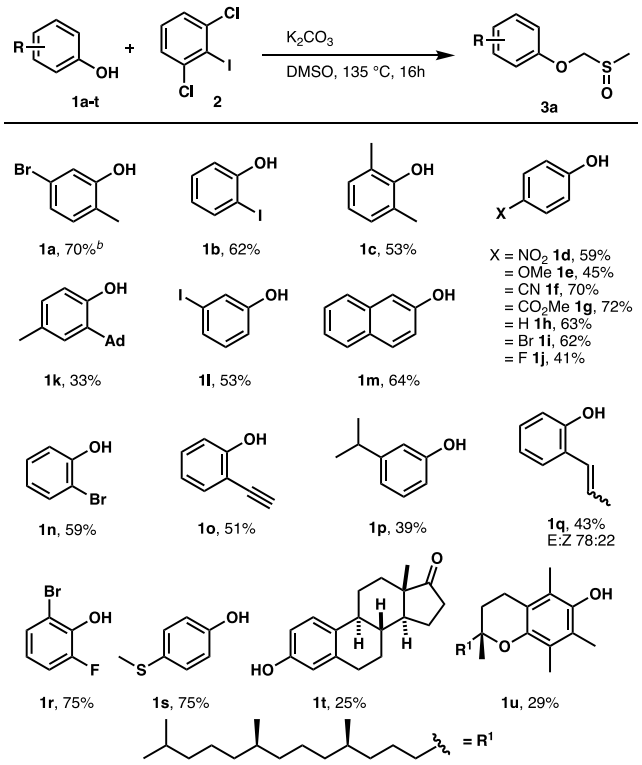
Entry	Base	Conc (M)	Temp (°C)	Time (h)	Yield (%)[a]
1	K_2CO_3	0.1	135	16	**96** (70)[b]
2	Na_2CO_3	0.1	135	16	0
3	Cs_2CO_3	0.1	135	16	54
4[c]	K_2CO_3	0.1	135	16	79
5	K_2CO_3	0.1	22	16	0
6[d]	K_2CO_3	0.1	135	16	67
7[e]	K_2CO_3	0.1	135	16	0
8	K_2CO_3	0.5	135	16	26
9	K_2CO_3	0.05	135	16	84

[a]Yields determined by NMR internal standard using trimethyl(phenyl)silane. [b]Isolated yield in brackets. [c]1.1 equivalents of base. [d]1.1 equivalents of **2**. [e]Reaction performed without **2**.

Following determination of optimal conditions, the scope of the reaction was examined (Scheme 2). Overall, yields varied widely from poor to good (25-75%). The reaction was not contingent to phenol electronics, good yields were obtained with electronically opposite substrates **1d** and **1e** (59% and 45% yields respectively). Interestingly, the reaction was amenable to steric hindrance, such as the hindrance exhibited in *ortho*-substituted phenols **1a**, **1b**, and **1r** (70%, 62% and 75% yields), though the presence of bulky groups such as the 2-adamantyl-4-methylphenol **1k** led to reductions in yield (33%).

All reactions went to completion except when phenol **1f** was used, which resulted in isolation of 5% of the phenol starting material. No major byproduct was observed and haloarene **2** was completely consumed in every case**,** though occasionally traces of S_NAr product **4** were detected via GC-MS. Notably, iodophenols **1b** and **1l** were converted to the desired products in 62% and 53% yields, respectively. These results showed that aryl-halogen bonds are resilient towards the reaction conditions aside from the required haloarene **2**. The conditions were also tolerant of functionally important substrates 2-propenylphenol **1q** (43%), which exhibited minimal thermal *cis-trans* isomerization (starting material 72:28 *E:Z*, see SI), and 2-hydroxyphenylacetylene **1o** (51%), where the alkyne remained untouched throughout the transformation. The substrate **1s** (75%) demonstrates the utility of this transformation, as the thioether remained intact under the reaction conditions. The existing methods to alkylate phenols with sulfoxides would likely oxidize any other thioethers, thiols, or sulfoxides present.[5] Finally, the reaction was amenable to large molecules of biological relevance such as estrone **1t** (25%) and α-tocopherol **1u** (29%).

Scheme 2. Substrate scope[a]

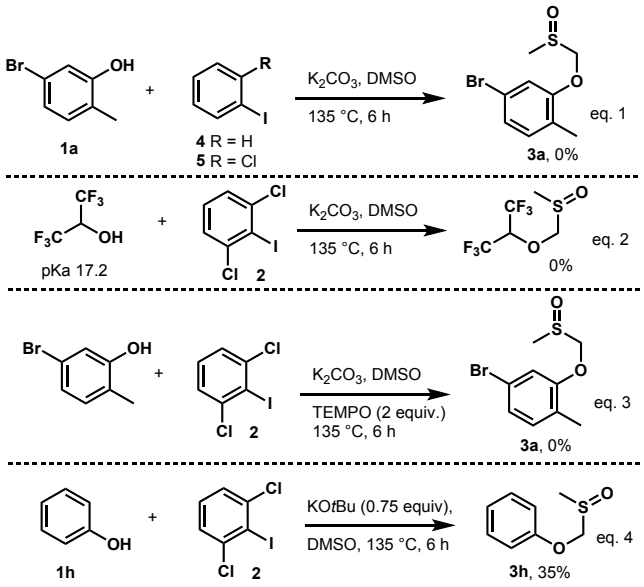


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), K_2CO_3 (0.66 mmol), DMSO (3 mL), 135 °C, 16h. [b]Reaction run on 1g scale, yield = 60%.

A few sulfoxides other than DMSO were examined as solvents to expand the sulfoxide scope (see SI). Though product was observed by NMR and GC-MS, this product was inseparable from the parent sulfoxide. Unusual results were observed when diethyl sulfoxide (DESO) was employed as the solvent, forming complex mixtures of products in which tarry black polymer dominated. This may be due to slower single electron reduction from highly aliphatic sulfoxides such as DESO.[9]

We then delved into mechanistic elucidation by considering many possibilities. Firstly, the role of the iodoarene was probed (Scheme 3). The 2,6-dichloroiodobenzene **2** proved essential to the transformation, as attempts to substitute it with 2-chloroiodobenzene and iodobenzene did not produce any desired products and simply resulted in decomposition of the phenol (eq. 1). We then considered that the iodine on **2** may be oxidizing DMSO and attempted other sources of iodine in the reaction. Use of N-iodosuccinimide (NIS) and molecular iodine, in place of the iodoarene, also resulted in decomposition of the phenol or inseparable mixtures of products respectively.

Scheme 3. Additional mechanistic studies



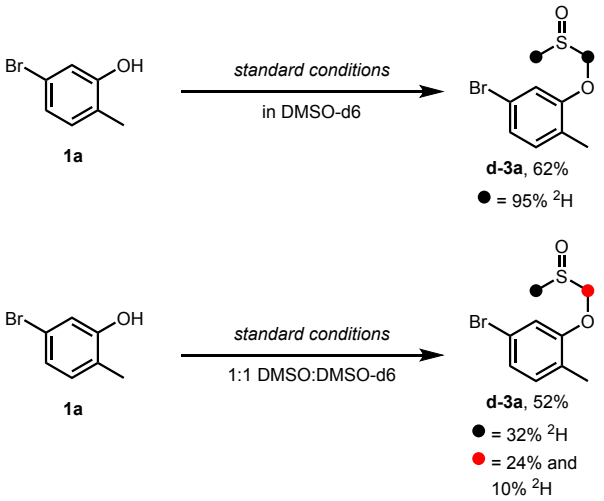
An ionic mechanism was then considered. Intermediacy of an alkoxide was probed by using aliphatic alcohol HFIP in place of phenol, as the pKa's in DMSO are similar (pka_{phenol} = 18, pKa_{HFIP} = 17.2) (eq. 2).[10] However, no product was observed. The use of nucleophiles such as anilines, thiophenols, and cyclopentanol afforded only decomposition or recovery of starting material, indicating that the mechanism is not simply bimolecular substitution on iodomethyl methyl sulfoxide. A putative benzyne intermediate, generated via an ionic pathway, was then probed using trapping experiments. Trihalogenated arenes such as **2** can form benzyne relatively slowly,[11] however, studies of similar substrates indicate that the aryl radical can be formed more rapidly.[6a,12] Our attempts to trap a benzyne intermediate with furan or 1,3-cyclohexadiene resulted in complex mixtures containing no Diels-Alder adduct. However, these experiments do not completely rule out involvement of phenoxide or diradical benzyne intermediates.

A radical mechanism was then considered. Addition of 2 equivalents of TEMPO or BHT to the standard conditions resulted in exclusive formation of insoluble polymer containing only traces of product, which indicates mechanistic involvement of radicals (eq. 3). Peñéñory and co-workers suggested that dimsyl anion can function as a single electron reductant in the presence of KO*t*Bu and can form complexes that facilitate charge transfer to iodoalkanes, with electron transfer occurring from dimsyl anion rather than potassium *tert*-butoxide.[8c, 12] One can suppose that dimsyl potassium generated in the presence of K_2CO_3 may function similarly. Attempts to reproduce these results in our system by replacing the carbonate base with 0.75 equivalents of KO*t*Bu resulted in 35% yield of desired product (eq. 4). However, it is important to note that using 2 equivalents of KOtBu or KH led to the recovery of the starting material. These results suggest that the presence of the phenol O-H bond is essential for the reaction to proceed.

Involvement of an aryl radical offers rationale for the requirement of **2** as additive. Iodoarenes, especially those vicinally *bis*-substituted with other halogens such as chlorine, can undergo dissociative electron transfer, forming iodide and a corresponding high-energy aryl radical. [13] Indeed, 2,2',6,6'-tetrachloro-1,1'-biphenyl, the dimer of this aryl radical, was detected in low yields in all scope reactions (see Supporting Information). Attempts to quantitatively trap aryl radical intermediates have thus far met with failure.[14]

Consideration of a radical mechanism imparts an explanation for some unusual scope results. As steric hindrance tends to decrease nucleophilicity of a compound, yet several sterically encumbered examples in the scope provide excellent yields (**1c**, 53% yield and **1r**, 75% yield), nucleophilic substitution is not indicated as a major mechanistic factor. However, *bis-ortho* substitution of phenols can stabilize the associated O-centered radical, increasing its longevity to the point where it may react with a nucleophilic species.[15] Our attempts to trap such a phenoxyl radical with 2-allylphenol have unfortunately met with failure due to the substrate's slow cyclization rate.[16]

Scheme 4. Deuterium studies[a]

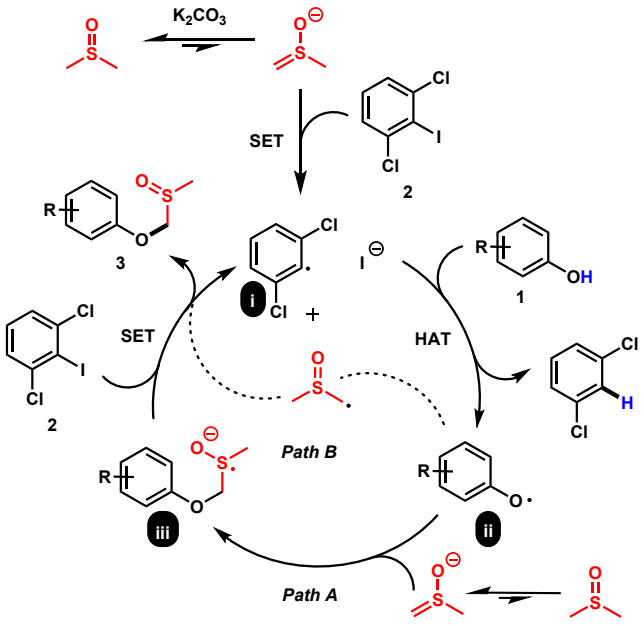


[a] Ratios of H:D determined by comparison of ^{1}H NMR integrals between aromatic or aliphatic C-H bonds and alpha-sulfoxide C-H bonds. See Supporting Information for details.

Finally, deuterium studies were conducted to probe DMSO's involvement in the reaction (Scheme 4). As all positions alpha to the sulfoxide are enolizable and will therefore exchange with any water present, it was not feasible to determine accurate KIEs.[17] However, when the reaction was run in DMSO-d6, the product contained 95% deuterium incorporation at both alpha-sulfoxide positions. The yield (**d-3a**, 62%) is comparable to the same reaction run in proteated DMSO (**3a**, 70%), indicating that the presence of deuterium scarcely impacted reaction kinetics. Likewise, when the reaction was run in a 1:1 mixture of DMSO:DMSO-d6, the alpha-sulfoxide CH_3 was 32% deuterated and the alpha-oxo CH's were 10% and 24% deuterated. A small reduction in yield (52% compared to 70% in DMSO) was observed, though no additional byproducts were identified, and all starting materials were consumed. Due to the elevated concentration of protons in the mixed solvent, it seems that H-D exchange is so prevalent as to obfuscate meaningful results in the second trial.

Based on precedent and the above mechanistic studies, the following mechanism is proposed (Scheme 5). The mixture of K_2CO_3 and DMSO produces a low concentration of dimsyl potassium. We propose that this dimsyl anion can inject a single electron into the weak carbon-iodine bond of **2** under these conditions [BDE(iodobenzene) = 64], generating a stabilized dichloroaryl radical **i**, a DMSO radical, and iodide.[18] The aryl radical (BDE ≈ 103 kcal/mol) is then able to perform H-atom transfer (HAT) on the phenol (BDE ≈ 86),[19,20] generating a more stable radical species **ii** and 1,3-dichlorobenzene.[21] The resulting oxygen-centered radical **ii** reacts with dimsyl anion via **Path A**, creating a powerfully reducing radical ion **iii** that becomes oxidized by molecular oxygen or can propagate a chain cycle by SET to iodoarene **2**.[22] Alternatively, the phenol radical **ii** could recombine with the DMSO radical anion generated during an initiating SET event as seen in **Path B**. As the dimsyl anion is likely present in higher concentrations than the DMSO radical, **Path A** is proposed to be the dominant pathway. This mechanistic proposal involves reactions of species present in relatively low concentrations, which contextualizes the long reaction time and non-quantitative yields. These results do not completely eliminate the possibility that the iodoarene **2** may be oxidizing DMSO, making iodomethyl methyl sulfoxide which then undergoes nucleophilic substitution with a phenolate. If this pathway is present, we suspect that it is minor based on available evidence.

Scheme 5. Proposed mechanism



CONCLUSIONS

In summary, the examination of a curious byproduct of S_NAr has led to a serendipitous streamlining of methylsulfoxylmethyl ether synthesis. Submitting this unusual transformation to mechanistic studies suggests the role of DMSO as not only solvent but also possibly single electron reducing agent in the presence of base. Investigations into the capacity of DMSO as a radical reducing agent are currently under investigation by our group.

EXPERIMENTAL SECTION

General Information. All reactions were performed in Pyrex glassware equipped with a magnetic stir bar, capped with a septum, unless otherwise indicated. All commercial reagents including HPLC-grade DMSO were obtained from Sigma Aldrich, Alfa Aesar or Combi Blocks and used without further purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with potassium permanganate or p-anisaldehyde staining solution. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 400 MHz, Bruker Avance 500, or a Bruker Avance III HD 600 MHz instrument. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments (101, 126, and 151 MHz respectively). Carbon peak assignments (CH_3, CH_2, CH, and C) were completed using DEPT-135 and DEPT-90 NMR on the same Bruker instruments (101, 126, and 151 MHz respectively). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker Avance 377 MHz instrument. NMR samples were dissolved in chloroform-d (unless specified otherwise) and chemical shifts are reported in ppm referenced to residual non-deuterated solvent. IR spectra were recorded with an Agilent Technologies Cary 630 FTIR Spectrometer equipped with a diamond ATR module. GC-MS (EI) were obtained on an Agilent 5975 series MSD instrument (University of Ottawa Centre for Catalysis Research and Innovation High-Throughput Experimentation Core Facility). HRMS were obtained on a Kratos Analytical Concept instrument (EI) and a Micromass Q-TOF I instrument (ESI) at the University of Ottawa Mass Spectrum Centre.

General Procedure: methylsulfoxyl methyl etherification of phenols (Table 1, Scheme 2). To an open-air round-bottom flask equipped with a stir bar was added K_2CO_3 (0.66 mmol, 2.2 eq.), 2,6-dichloroiodobenzene (0.45 mmol, 1.5 eq.), and phenol substrate (0.3 mmol, 1 eq.). DMSO (0.1M, 3mL) was added and the flask was fitted with a Vigreux column OR a reflux condenser open at the top to ambient atmosphere. The reaction was stirred at 135 °C in a bath of aluminum granules on a hot plate with temperature probe for 16 hours. Upon completion, the reaction was cooled to room temperature and diluted with water (20 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous phase was extracted a further 2x with 10 mL ethyl acetate. The organic layers were combined and washed successively with water (10 mL) and brine (10 mL). The organic layer was dried, filtered, and concentrated under reduced pressure to afford the crude brown oil product. The crude residue was purified *via* silica gel chromatography to afford the final product (solvent system: gradient of 5 – 80% ethyl acetate in hexanes).

4-Bromo-1-methyl-2-(((methyl-d3)sulfinyl)methoxy-d2)benzene (d-3a). From 5-bromo-2-methylphenol (**1a**, 56 mg, 0.3 mmol) and DMSO-d6 as solvent (3 mL, 0.1M), **d-3a** was obtained as an amorphous off-white solid (in DMSO-d6: 49 mg, 0.19 mmol, 62% yield; in 1:1 DMSO:DMSO-d6: 42 mg, 0.16 mmol, 52% yield). IR (neat, cm^{-1}): 3060, 2964, 2919, 2916, 2844, 2280, 1582; ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.12 – 7.06 (m, 2H), 7.03 – 7.00 (m, 1H), 4.96 (s, 1H), 4.85 (s, 1H), 2.66 (t, *J* = 1.9 Hz, 3H), 2.19 (d, *J* = 0.7 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ = 156.2 (C), 132.3 (CH), 126.4 (C), 125.7 (CH), 119.6 (C), 116.3 (CH), 83.9 (CD_2), 34.9 (CD_3), 15.9

(CH_3); HRMS (ESI): m/z [M + Na, ^{79}Br]$^+$ calc'd for $C_9H_6D_5BrO_2SNa$, 289.9875; found, 289.9887.

4-Bromo-1-methyl-2-((methylsulfinyl)methoxy)benzene (3a). From 5-bromo-2-methylphenol (**1a**, 56 mg, 0.3 mmol; or 0.5g, 2.67 mmol; or 1g, 5.35 mmol), **3a** was obtained as an amorphous pale red solid (56 mg scale: 49 mg, 0.19 mmol, 70% yield; 0.5 g scale: 0.55 g, 2.1 mmol, 79% yield; 1 g scale: 0.84 g, 3.2 mmol, 60% yield). IR (neat, cm^{-1}): 3062, 2922, 2914, 2089, 1582; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 – 7.07 (m, 2H), 7.01 (dt, *J* = 7.8, 0.7 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 4.86 (d, *J* = 10.0 Hz, 1H), 2.69 (s, 3H), 2.19 (d, *J* = 0.7 Hz, 3H); $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$) δ = 156.2 (C), 132.3 (CH), 126.4 (C), 125.8 (CH), 119.6 (C), 116.3 (CH), 84.4 (CH_2), 35.8 (CH_3), 15.9 (CH_3); HRMS (ESI): m/z [M + Na, ^{81}Br]$^+$ calc'd for $C_9H_{11}BrO_2SNa$, 286.9540; found, 286.9556.

1-Iodo-2-((methylsulfinyl)methoxy)benzene (3b). From 2-iodophenol (**1b**, 89 mg, 0.3 mmol) **3b** was obtained as an amorphous pale yellow solid (55 mg, 0.19 mmol, 62% yield). IR (neat, cm^{-1}): 3055, 2995, 2915, 2909, 1582, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.06 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.82 (ddd, *J* = 7.8, 7.4, 1.3 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 4.89 (d, *J* = 10.0 Hz, 1H), 2.78 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 156.3 (C), 139.9 (CH), 129.9 (CH), 124.9 (CH), 114.4 (CH), 86.6 (C), 84.5 (CH_2), 36.3 (CH_3); HRMS (ESI): m/z [M + Na]$^+$ calc'd for $C_8H_9IO_2SNa$, 318.9260; found, 318.9264.

1,3-Dimethyl-2-((methylsulfinyl)methoxy)benzene (3c). From 2,6-dimethylphenol (**1c**, 37 mg, 0.3 mmol) **3c** was obtained as an amorphous colorless solid (32 mg, 0.16 mmol, 53% yield). IR (neat, cm^{-1}): 3040, 2998, 2919, 2852, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.04 – 6.99 (m, 2H), 6.99 – 6.94 (m, 1H), 4.76 (d, *J* = 9.5 Hz, 1H), 4.71 (d, *J* = 9.5 Hz, 1H), 2.71 (s, 3H), 2.29 (d, *J* = 0.7 Hz, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.1 (C), 130.1 (2 X C), 129.3 (2 X CH), 125.1 (CH), 88.3 (CH_2), 35.9 (CH_3), 16.7 (2 X CH_3); HRMS (ESI): m/z [M + Na]$^+$ calc'd for $C_{10}H_{14}O_2SNa$, 221.0612; found, 221.0604.

1-((Methylsulfinyl)methoxy)-4-nitrobenzene (3d). From 4-nitrophenol (**1d**, 42 mg, 0.3 mmol) **3d** was obtained as an amorphous deep yellow solid (38 mg, 0.18 mmol, 59% yield). Characterized by NMR comparison.[5c] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 – 8.13 (m, 2H), 7.18 – 7.10 (m, 2H), 5.04 (d, *J* = 2.0 Hz, 2H), 2.71 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 162.2 (C), 143.1 (C), 126.0 (2 X CH), 115.7 (2 X CH), 83.7 (CH_2), 35.5 (CH_3).

1-Methoxy-4-((methylsulfinyl)methoxy)benzene (3e). From 4-methoxyphenol (**1e**, 37 mg, 0.3 mmol) **3e** was obtained as an amorphous pale yellow solid (27 mg, 0.14 mmol, 45% yield). Characterized by NMR comparison.[5c] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.06 – 6.90 (m, 2H), 6.90 – 6.73 (m, 2H), 4.96 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.86 – 4.75 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.84 – 3.67 (m, 3H), 2.66 (d, *J* = 3.0 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.5 (C), 151.6 (C), 117.0 (2 X CH), 114.9 (2 X CH), 85.5 (CH_2), 55.7 (CH_3), 35.6 (CH_3).

4-((Methylsulfinyl)methoxy)benzonitrile (3f). From 4-cyanophenol (**1f**, 36 mg, 0.3 mmol) **3f** was obtained as an amorphous colorless solid (41 mg, 0.21 mmol, 70% yield). IR (neat, cm^{-1}): 3068, 3009, 3003, 2918, 2852, 2221, 1594; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 – 7.59 (m, 2H), 7.18 – 7.10 (m, 2H), 4.99 (d, *J* = 0.9 Hz, 2H), 2.70 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 160.6 (C), 134.2 (2 X CH), 118.5 (C), 116.3 (2 X CH), 106.5 (C), 83.6 (CH_2), 35.4 (CH_3); HRMS (ESI): m/z [M + Na]$^+$ calc'd for $C_9H_9NO_2SNa$, 218.0268; found, 218.0252.

Methyl 4-((methylsulfinyl)methoxy)benzoate (3g). From methyl 4-hydroxybenzoate (**1g**, 47 mg, 0.3 mmol) **3g** was obtained as an amorphous pale yellow solid (49 mg, 0.22 mmol, 72% yield). Characterized by NMR comparison.[5c] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 – 7.95 (m, 2H), 7.14 – 6.96 (m, 2H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 3.88 (s, 3H), 2.70 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 166.3 (C), 160.9 (C), 131.8 (2 X CH), 124.9 (C), 115.0 (2 X CH), 83.6 (CH_2), 52.1 (CH_3), 35.7 (CH_3).

((Methylsulfinyl)methoxy)benzene (3h). From phenol (**1h**, 28 mg, 0.3 mmol) **3h** was obtained as a yellow oil (32 mg, 0.19 mmol, 63% yield). Characterized by NMR comparison.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.26 (m, 2H), 7.07 – 6.98 (m, 3H), 5.00 (d, *J* = 10.1 Hz, 1H), 4.84 (d, *J* = 10.1 Hz, 1H), 2.65 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 157.4 (C), 129.8 (2 X CH_2), 123.0 (CH), 115.6 (2 X CH), 84.4 (CH_2), 35.8 (CH_3).

1-Bromo-4-((methylsulfinyl)methoxy)benzene (3i). From 4-bromophenol (**1i**, 52 mg, 0.3 mmol) **3i** was obtained as an amorphous pale yellow solid (46 mg, 0.19 mmol, 62% yield). Characterized by NMR comparison.[5c] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.35 (m, 2H), 7.00 – 6.86 (m, 2H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.85 (d, *J* = 10.3 Hz, 1H), 2.65 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 156.7 (C), 132.7 (2 X CH), 117.5 (2 X CH), 115.5 (C), 84.4 (CH_2), 35.6 (CH_3).

1-Fluoro-4-((methylsulfinyl)methoxy)benzene (3j). From 4-fluorophenol (**1j**, 34 mg, 0.3 mmol) **3j** was obtained as an amorphous off-white solid (23 mg, 0.12 mmol, 41% yield). **IR** (neat, cm^{-1}): 3051, 2960, 2932, 2910, 2835, 1503; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.03 – 6.93 (m, 4H), 4.93 (d, *J* = 10.3 Hz, 1H), 4.84 (d, *J* = 10.4 Hz, 1H), 2.65 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 158.5 (d, *J* = 242.4 Hz, C), 153.7 (C), 117.2 (d, *J* = 8.1 Hz, CH), 116.2 (d, *J* = 23.2 Hz), 85.1 (CH_2), 35.4 (CH_3); $^{19}F\{1H\}$ NMR (377 MHz, $CDCl_3$) δ = -120.5 ppm; HRMS (ESI): m/z [M + Na]$^+$ calc'd for $C_8H_9FO_2SNa$, 211.0205; found, 211.0215.

1-(5-Methyl-2-((methylsulfinyl)methoxy)phenyl)adamantane (3k). From 2-(adamantan-1-yl)-4-methylphenol (**1k**, 73 mg, 0.3 mmol) **3k** was obtained as an amorphous yellow solid (32 mg, 0.10 mmol, 33% yield). IR (neat, cm^{-1}): 3058, 2994, 2903, 2846, 1583, 1045; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.07 – 7.01 (m, 1H), 6.98 (ddd, *J* = 8.3, 2.2, 0.8 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.01 (d, *J* = 9.8 Hz, 1H), 4.86 (d, *J* = 9.8 Hz, 1H), 2.72 (s, 3H), 2.28 (s, 3H), 2.10 – 2.01 (m, 9H), 1.80 – 1.68 (m, 6H); $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ = 154.7 (C), 138.7 (C), 132.1 (C), 127.9 (CH), 127.3 (CH), 114.2 (CH), 85.1 (CH_2), 40.9 (3 X CH_2), 37.0 (3 X CH_2), 36.9 (C), 36.0 (CH_3), 29.0 (3 X CH), 20.9 (CH_3); HRMS (ESI): m/z [M + Na]$^+$ calc'd for $C_{19}H_{26}O_2SNa$, 341.1551; found, 341.1542.

1-Iodo-3-((methylsulfinyl)methoxy)benzene (3l). From 3-iodophenol (**1l**, 66 mg, 0.3 mmol) **3l** was obtained as an amorphous off-white solid (31 mg, 0.16 mmol, 53% yield). **IR** (neat, cm^{-1}): 3055, 2992, 2915, 2909, 1582, 1034; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.44 – 7.35 (m, 2H), 7.07 – 6.97 (m, 2H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.85 (d, *J* = 10.2 Hz, 1H), 2.68 (s, 3H); $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ = 157.9 (C), 132.3 (CH), 131.1 (CH), 125.0 (CH), 115.0 (CH), 94.3 (C), 84.0 (CH_2), 35.7 (CH_3); HRMS (ESI): m/z $[M + Na]^+$ calc'd for $C_8H_9IO_2SNa$, 318.9266; found, 318.9261.

2-((Methylsulfinyl)methoxy)naphthalene (3m). From naphthalen-1-ol (**1m**, 43 mg, 0.3 mmol) **3m** was obtained as an amorphous yellow solid (42 mg, 0.19 mmol, 64% yield). Characterized by NMR comparison.[5c] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.76 (dd, *J* = 12.3, 8.4 Hz, 3H), 7.47 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.39 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.34 (d, *J* = 2.6 Hz, 1H), 7.21 (dd, *J* = 9.0, 2.6 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 2.72 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.2 (C), 134.1 (C), 130.1 (CH), 129.9 (C), 127.7 (CH), 127.1 (CH), 126.9 (CH), 124.8 (CH), 118.1 (CH), 109.0 (CH), 84.1 (CH_2), 35.9 (CH).

1-Bromo-2-((methylsulfinyl)methoxy)benzene (3n). From 2-bromophenol (**1n**, 52 mg, 0.3 mmol) **3n** was obtained as an amorphous colorless solid (44 mg, 0.18 mmol, 59% yield). Characterized by NMR comparison.[5c] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.54 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.15 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.95 (ddd, *J* = 7.9, 7.4, 1.4 Hz, 1H), 5.07 (d, *J* = 10.1 Hz, 1H), 4.90 (d, *J* = 10.1 Hz, 1H), 2.76 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.1 (C), 133.8 (CH), 128.9 (CH), 124.5 (CH), 115.9 (CH), 112.9 (C), 84.7 (CH_2), 36.0 (CH_3).

1-Ethynyl-2-((methylsulfinyl)methoxy)benzene (3o). From 2-ethynylphenol (**1o**, 35 mg, 0.3 mmol) **3o** was obtained as an amorphous pale yellow solid (30 mg, 0.15 mmol, 51% yield). IR (neat, cm^{-1}): 3286, 3061, 2993, 2916, 2850, 2100, 1584, 1574; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24 (t, *J* = 7.9 Hz, 1H), 7.16 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.12 (dd, *J* = 2.7, 1.4 Hz, 1H), 7.02 (ddd, *J* = 8.3, 2.7, 1.1 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.85 (d, *J* = 10.2 Hz, 1H), 3.07 (s, 1H), 2.65 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 157.2 (C), 129.8 (CH), 126.9 (CH), 123.7 (C), 118.9 (CH), 116.5 (CH), 84.1 (CH_2), 82.8 (C), 78.0 (CH), 35.7 (CH_3); HRMS (ESI): m/z $[M + Na]^+$ calc'd for $C_{10}H_{10}O_2SNa$, 217.0294; found, 217.0299.

1-Isopropyl-3-((methylsulfinyl)methoxy)benzene (3p). From 3-isopropylphenol (**1p**, 41 mg, 0.3 mmol) **3p** was obtained as a yellow oil (25 mg, 0.12 mmol, 39% yield). IR (neat, cm^{-1}): 3031, 2957, 2924, 1589, 1585; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.21 (t, *J* = 7.9 Hz, 1H), 6.91 (ddt, *J* = 7.7, 1.5, 0.7 Hz, 1H), 6.88 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.82 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 5.02 (d, *J* = 10.0 Hz, 1H), 4.82 (d, *J* = 10.0 Hz, 1H), 2.86 (hept, *J* = 6.9 Hz, 1H), 2.66 (s, 3H), 1.21 (d, *J* = 7.0 Hz, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 157.5 (C), 151.2 (C), 129.6 (CH), 121.2 (CH), 113.9 (CH), 112.4 (CH), 84.2 (CH_2), 35.8 (CH_3), 34.1 (CH), 23.9 (2 X CH_3); HRMS (ESI): m/z $[M + Na]^+$ calc'd for $C_{11}H_{16}O_2SNa$, 235.0764; found, 235.0769.

1-((Methylsulfinyl)methoxy)-2-(prop-1-en-1-yl)benzene (3q). From 3-(prop-1-en-1-yl)phenol (**1q**, 40 mg, 0.3 mmol, 72:28 *E*:*Z*) **3q** was obtained as an amorphous pale yellow solid (27 mg, 0.13 mmol, 43% yield, 78:22 *E*:*Z*). IR (neat, cm^{-1}): 3030, 2941, 2923, 2853, 1972, 1685, 1599, 1048; ^1H NMR (trans isomer) (400 MHz, $CDCl_3$) δ = 7.41 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.32 – 7.09 (m, 1H), 7.10 – 6.95 (m, 2H), 6.64 (dq, *J* = 15.8, 1.8 Hz, 1H), 6.21 (dq, *J* = 15.9, 6.6 Hz, 1H), 5.03 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.83 (dd, *J* = 11.9, 10.0 Hz, 1H), 2.59 (s, 3H), 1.89 (dd, *J* = 6.6, 1.8 Hz, 3H); $^{13}C\{1H\}$ NMR (trans isomer) (101 MHz, $CDCl_3$) δ = 154.0 (C), 130.7 (C), 128.0 (CH), 127.8 (CH), 126.8 (CH), 124.7 (CH), 123.3 (CH), 114.1 (CH), 85.1 (CH_2), 41.0 (CH_3), 18.9 (CH_3); ^1H NMR (cis isomer) (400 MHz, $CDCl_3$) δ = 7.32 – 7.09 (m, 2H), 7.10 – 6.95 (m, 2H), 6.47 (dd, *J* = 11.5, 2.0 Hz, 1H), 5.85 (dq, *J* = 11.6, 7.1 Hz, 1H), 5.03 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.83 (dd, *J* = 11.9, 10.0 Hz, 1H), 2.68 (s, 3H), 1.79 (dd, *J* = 7.1, 1.8 Hz, 3H); $^{13}C\{1H\}$ NMR (cis isomer) (101 MHz, $CDCl_3$) δ = 154.0 (C), 130.7 (C), 128.2 (CH), 128.1 (CH), 128.1 (CH), 124.5 (CH), 122.7 (CH), 114.2 (CH), 85.0 (CH_2), 35.9 (CH_3), 14.6 (CH_3); HRMS (ESI): m/z $[M + Na]^+$ calc'd for $C_{11}H_{14}O_2SNa$, 233.0607; found, 233.0612.

1-Bromo-3-fluoro-2-((methylsulfinyl)methoxy)benzene (3r). From 2-bromo-6-fluorophenol (**1r**, 57 mg, 0.3 mmol) **3r** was obtained as an amorphous colorless solid (60 mg, 0.23 mmol, 75% yield). IR (neat, cm^{-1}): 3059, 3030, 2939, 2920, 2848, 1603, 1585, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.46 (dd, *J* = 8.8, 6.0 Hz, 1H), 6.92 (dd, *J* = 9.7, 2.7 Hz, 1H), 6.67 (ddd, *J* = 8.8, 7.7, 2.7 Hz, 1H), 4.99 (d, *J* = 10.3 Hz, 1H), 4.92 (d, *J* = 10.3 Hz, 1H), 2.73 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 162.4 (d, *J* = 250.5 Hz, C), 154.8 (d, *J* = 10.1 Hz, C), 134.1 (d, *J* = 9.1 Hz, CH), 111.3 (d, *J* = 22.2 Hz, C), 107.0 (d, *J* = 4.0 Hz, C), 104.2 (d, *J* = 27.3 Hz, CH), 84.5 (CH_2), 35.7 (CH_3); $^{19}F\{1H\}$ NMR (377 MHz, $CDCl_3$) δ = -110.3 ppm; HRMS (ESI): m/z $[M + Na, ^{81}Br]^+$ calc'd for $C_8H_8BrFO_2SNa$, 290.9291; found, 290.9290.

Methyl(4-((methylsulfinyl)methoxy)phenyl)sulfane (3s). From 4-(methylthio)phenol (**1s**, 42 mg, 0.3 mmol) **3s** was obtained as an amorphous colorless solid (49 mg, 0.23 mmol, 75% yield). IR (neat, cm^{-1}): 3057, 3002, 2981, 2919, 1592, 1585; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.17 (m, 2H), 7.04 – 6.91 (m, 2H), 4.98 (d, *J* = 10.2 Hz, 1H), 4.84 (d, *J* = 10.2 Hz, 1H), 2.66 (d, *J* = 1.8 Hz, 3H), 2.44 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.7 (C), 132.2 (C), 129.4 (2 X CH), 116.3 (2 X CH), 84.5 (CH_2), 35.7 (CH_3), 17.3 (CH_3); HRMS (ESI): m/z $[M + Na]^+$ calc'd for $C_9H_{12}O_2S_2Na$, 239.0171; found, 239.0176.

3-((Methylsulfinyl)methoxy)-estrone (3t). From estrone (**1t**, 81 mg, 0.3 mmol) **3t** was obtained as an amorphous colorless solid (26 mg, 0.08 mmol, 25% yield). IR (neat, cm^{-1}): 3030, 2923, 2863, 1734, 1606, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.21 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.76 (dd, *J* = 2.9, 1.2 Hz, 1H), 5.00 (d, *J* = 10.1 Hz, 1H), 4.81 (dd, *J* = 10.1, 1.5 Hz, 1H), 2.88 (dd, *J* = 8.8, 4.1 Hz, 2H), 2.66 (s, 3H), 2.53 – 2.43 (m, 1H), 2.37 (ddt, *J* = 9.0, 3.9, 1.8 Hz, 1H), 2.31 – 2.03 (m, 2H), 2.07 – 1.86 (m, 3H), 1.68 – 1.34 (m, 6H), 0.88 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.4 (C), 138.4 (C), 134.6 (C), 126.7 (CH), 115.6 (CH), 113.0 (CH), 84.3 (CH_2), 50.4 (CH), 48.0 (C), 44.0 (CH), 38.2 (CH), 35.8 (CH_2), 35.8 (CH_3), 31.6 (CH_2), 29.6 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 21.6 (CH_2), 13.8 (CH_3), -18.1 (C); HRMS (ESI): m/z $[M + Na]^+$ calc'd for $C_{20}H_{26}O_3SNa$, 369.1495; found, 369.1500.

(2R)-2,5,7,8-Tetramethyl-6-((methylsulfinyl)methoxy)-2-((4R,8R)-4,8,12-trimethyltridecyl)chromane (3u). From α-tocopherol (**1u**, 130 mg, 0.3 mmol) **3u** was obtained as a viscous dark brown oil (44 mg, 0.09 mmol, 29% yield). IR (neat, cm^{-1}): 2952, 2922, 2895, 2844, 1457; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.67 (d, *J* = 9.4 Hz, 1H), 4.61 (d, *J* = 9.3 Hz, 1H), 2.70 (s, 3H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.16 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 1.78 (dp, *J* = 19.7, 6.9 Hz, 2H), 1.58 – 1.44 (m, 2H), 1.43 – 0.95 (m, 17H), 0.83 (dd, *J* = 9.7, 6.5 Hz, 16H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ = 148.7 (C), 147.7 (C), 127.0 (C), 125.2 (C), 123.5 (C), 117.9 (C), 89.3 (CH_2), 75.1 (C), 40.0 (CH_2), 39.4 (CH_2), 37.6-37.3 (m, 4 X CH_2), 35.9 (CH_3), 32.8 (CH), 32.7 (CH), 31.2 (CH_2), 28.0 (CH), 24.8 (CH_2), 24.4 (CH_2), 23.9 (2 X CH_3), 22.7 (CH_3), 21.0 (CH_2), 20.7 (CH_2), 19.8-19.6 (m, 2 X CH_3), 13.2 (CH_3), 12.3 (CH_3), 11.8 (CH_3); HRMS (ESI): m/z $[M + Na]^+$ calc'd for $C_{31}H_{54}O_3SNa$, 529.3691; found, 529.3688.

ASSOCIATED CONTENT

Supporting Information

The complete optimization tables, additional mechanistic data, and copies of ^1H and ^{13}C NMR spectra (PDF).

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