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Methanesulfinylation of benzyl halides with dimethyl sulfoxide

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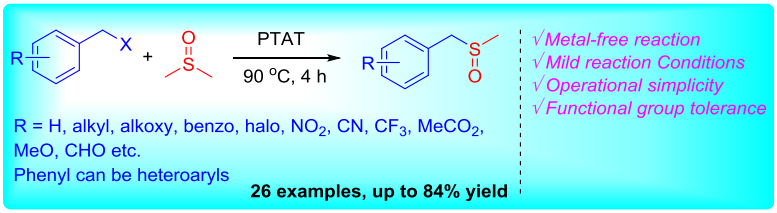


ABSTRACT: A phenyltrimethylammonium tribromide-mediated nucleophilic substitution/oxygen transformation reaction of benzyl halides with DMSO has been developed. In this transition-metal-free reaction, DMSO acts as not only a solvent, but also a "S(O)Me" source, thus providing a convenient method for the efficient and direct synthesis of various benzyl methyl sulfoxides.

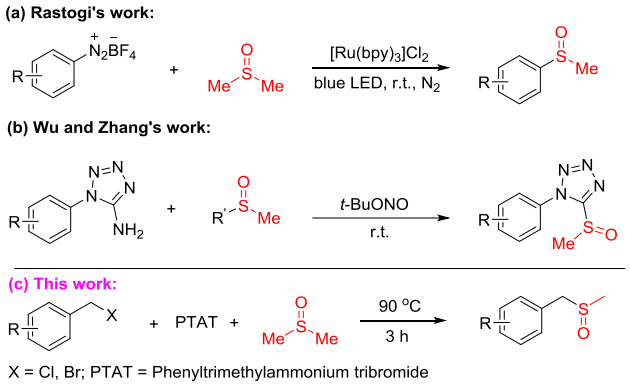
Sulfoxides represent an important class of compounds that have been widely employed as building blocks, chiral ligands, and auxiliaries in transition-metal catalysis.[1] Furthermore, the sulfur functional group is pharmaceutically important cores or moieties of some biological molecules and drugs, such as neurokinin receptor antagonist YM-38336, anti-inflammatory drug sulindac, proton pump inhibitor Omeprazole.[2] Sulfoxides have also been widely used as important intermediates in organic synthesis for the preparation of sulfur-containing compounds.[3]

Due to the importance of sulfoxides, significant effort has been devoted to their preparation. The most popular methods for the synthesis of sulfoxides include (1) oxidation of sulfides with peroxyacids and common organic or inorganic oxidants, organometallic catalytic complexes;[2b,4] (2) metal-catalyzed arylation of sulfenate anions[5] and metal-free alkylation of nucleophilic sulfenate sources;[6] (3) organometallic addition to displacement of electrophilic sulfoxides derivatives.[7] Despite the utility of these approaches, some deficiencies have always existed, such as overoxidation to sulfones, the production of large amount of toxic wastes, the use of expensive catalysts. These methods also suffer from limited functional group tolerance because either strong oxidizing agents or reactive lithium- or magnesium-based reagents are employed. During these approaches, pre-existing sulfur functional groups in the molecules are required. Among these sulfur-containing reagents, DMSO as a cheap, safe, and low-toxic reagent has been widely utilized as a one carbon source,[8] and a sulfur source such as S(O)Me,[2a,9] $S(O)Me_2$,[10] $S(O)_2Me$,[11] and SMe[12] for the incorporation of functional groups into target molecules.

However, to the best of our knowledge, only two examples of methylsulfoxidation utilizing DMSO as S(O)Me source have been reported (Scheme 1). In 2016, Rastogi's group reported the synthesis of (hetero)aryl methyl sulfoxides from DMSO and (hetero)aryl diazonium salts *via* mild photoredox catalysis with ruthenium complexes. [2a] Wu and Zhang's group obtained the antifungal active methylsulfinyl-1*H*-tetrazole derivatives through methylsulfoxidation of tetrazole-amines in neat DMSO under the mediation of *tert*-butyl nitrite.[9c] Both of two strategies undergo the generation of hetero-aryl or aryl radical intermediates which are trapped by DMSO to produce sulfinyl radicals. The generated sulfinyl radicals are oxidized into sulfoxide cations and attacked by the weakly nucleophilic DMSO to produce the final products. However, only (hetero)aryl methly sulfoxides can be obtained with the two reported methods. It is worthwhile to realize the synthesis of alkyl methyl sulfoxides with DMSO as S(O)Me source.

In 1957, Kornblum and co-workers reported that activated primary benzyl bromides were efficiently oxidized to the corresponding aldehydes by simply dissolving the substrates in DMSO.[13] Subsequent studies showed that DMSO can be used as an oxygen source and solvent in these reactions. Therefore, expanding the application range of DMSO in Kornblum oxidation reaction is meaningful. Considering the development of DMSO in organic transformation during the recent years[14] and the importance to synthesize sulfoxide compounds, we report a novel and efficient method to synthesize benzyl methyl sulfoxides from the corresponding benzyl halides and dimethyl sulfoxide with the mediation of phenyltrimethylammonium tribromide (PTAT) in one step. The significance of the present protocol includes that (1) DMSO is not only introduced as a common solvent, but also as the source of the methylsulfinyl group. (2) The chemistry provides a direct and experimentally simple approach to synthesize methyl sulfoxides without the generation of over oxidized product sulfones which inevitably occurs with conventional oxidizing agents. (3) The role of DMSO in the Kornblum reaction is changed from the oxygen source to the S(O)Me source.

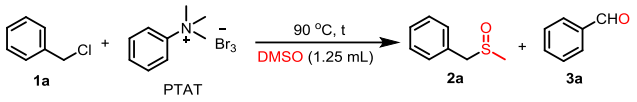
Scheme 1. DMSO as "S(O)Me" source to synthesize sulfoxides



At the outset of this study, benzyl chloride (**1a**) and PTAT were employed as the model substrates to optimize reaction conditions in DMSO (Table 1). We first optimized the reactant ratio (Table 1, entries 1–6). When the ratio of **1a**:PTAT was increased from 1:0.10 to 1:0.25 to 1:0.50 (Table 1, entries 1–3), the yield of **2a** increased from 25% to 59% to 77%. Further increasing the ratio of **1a**:PTAT to 1:1.00, product **2a** was obtained in 81% and by-product benzaldehyde (**3a**) was observed in 10% yield (Table 1, entry 4). However, the yield decreased to 59% when the ratio of **1a**:PTAT was increased from 1:1.00 to 1:1.25 (Table 1, entry 5). No product **2a** was observed and only benzaldehyde **3a** was received in 45% yield when the ratio of **1a**:PTAT was increased to 1:1.50 (Table 1, entry 6). The other choices of brominium (Br^+) precursors, such as NBS and DBDMH (1,3-dibromo-5,5-dimethylhydantoin), were also attempted and the product **2a** was obtained in 64% and 76% yields, respectively (Table 1, entries 7 and 8). It was noteworthy mentioned that only 4% yield of product **2a** was generated when NCS (*N*-chlorosuccinimide) was used as a halogenium (X^+) precursor instead of PTAT (Table 1, entry 9). We further optimized the reaction time (Table 1, entries 10–12). When the reaction time was shortened to 4 h, 83% yield of product **2a** was obtained (Table 1, entries 10). Next, the reaction time was shortened to 2 h, product **2a** was only obtained in 57% yield (Table 1, entry 11). Further prolonging the reaction time to 8 h resulted in the yield of **2a** to decrease to 48%, but **3a** was obtained 24% yield (Table 1, entry 12). Then we carried out further optimizations for 4 h at different reaction temperatures and found that when the temperature was decreased to 80 °C, the yield dropped sharply to 3% (Table 1, entry 13). When the temperature

was increased to 100 °C, the yield of **2a** was 78% (Table 1, entry 14). The results indicated that the temperature had an important impact on the reaction yield. And then, the yield of **2a** was only detected in 35% when the solvent DMSO was used without waterless treatment (Table 1, entry 15). At last, the product **2a** was obtained in 78% yield when the reaction was conducted at 90 °C for 30 min. under microwave irradiation (Table 1, entry 16).

Table 1. Optimization of the reaction conditions[a)]



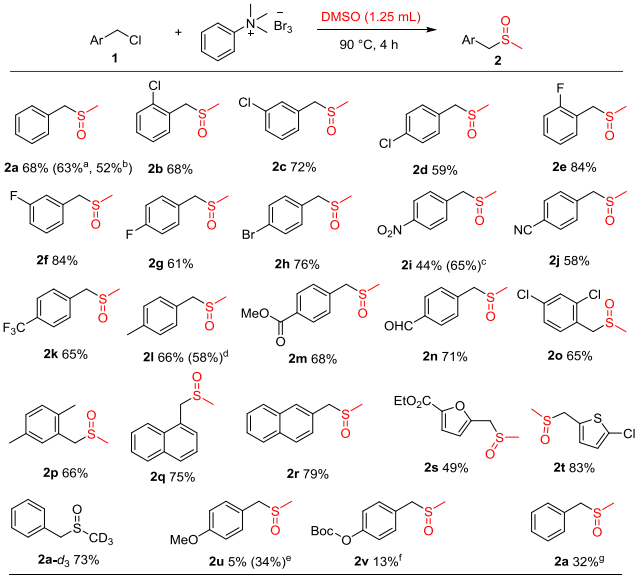
Entry	PTAT (equiv)	t (h)	Yield (%)	
			2a[i]	**3a**[i]
1	0.10	6	25	1
2	0.25	6	59	3
3	0.50	6	77	5
4	1.00	6	81	10
5	1.25	6	59	16
6	1.50	6	0	45
7	1.00[b]	6	64	2
8	1.00[c]	6	76	3
9	1.00[d]	6	4	trace
10	1.00	4	83(68)	6
11	1.00	2	57	trace
12	1.00	8	48	24
13[e]	1.00	4	3	1
14[f]	1.00	4	78	5
15[g]	1.00	4	35	7
16[h]	1.00	0.5	78	10

[a)]Reactions were conducted on a 0.125 mmol scale of **1a** (0.125 mmol) in 1.25 mL of anhydrous DMSO. [b)]NBS instead of PTAT. [c)]DBDMH (1,3-dibromo-5,5-dimethylhydantoin). [d)]NCS instead of PTAT. [e)]At 80 °C. [f)]At 100 °C. [g)]Reaction was conducted in commercial DMSO (without waterless treatment). [h)]Reaction was carried out under microwave irradiation at 90 °C for 30 min. [i)]NMR yield of the crude products **2a** and **3a** using 1,3,5-trimethoxybenzene as an internal standard except for the yield in brackets in entry 10.

With the optimized reaction conditions in hand (Table 1, entry 10), we subsequently investigated the substrate scope of this transformation (Scheme 2). Benzyl chloride bearing neutral, electron-donating, and electron-withdrawing substituents at the *o*, *m*, *p*-positions of the aromatic ring reacted smoothly under the optimized reaction conditions, affording the corresponding products **2** in high yields in most of the cases (Scheme 2). Besides benzyl chlorides, other benzyl bromide derivatives like benzyl bromide (**4a**), 4-nitrobenzyl bromide (**4i**), and 4-methylbenzyl bromide (**4l**) can also generate the corresponding products **2** in moderate yields from 58–65%. Moreover, the reaction also tolerated several functional groups, such as nitrile for **2j**, ester for **2m**, aldehyde for **2n** on aryl. After replacing the phenyl group with naphthyl, the corresponding products **2q** and **2r** were obtained in 75% and 79% yields, respectively. To our delight, the heteroarylmethyl halides **1s** and **1t** can also produce the corresponding sulfoxides **2s** and **2t** in 49% and 83% yields, respectively. The reaction also worked well with deuterated DMSO since methylsulfoxidation of substrate **1a** using deuterated DMSO was carried out smoothly, yielding deuterated methylsulfoxide **2a**-d_3 in 73% yield. Because 4-(chloromethyl)phenol and 4-(chloromethyl)aniline are too active and can react themselves intermolecularly, 4-methoxybenzyl chloride (**1u**) and *tert*-butyl (4-(chloromethyl)phenyl) carbonate (**1v**) were attempted, affording the corresponding products in low yields (**2u** in 34% and **2v** in 13%), respectively. The reaction of benzyl chloride with 4-methylphenol (1 eq.) as an additive was also performed, affording benzyl methyl sulfoxide (**2a**) in 32% yield, revealing that the phenolic hydroxy group is tolerance in the reaction system, but inhibited the reaction. However, neither of reactions of *tert*-butyl (4-(chloromethyl)phenyl)carbamate (**1w**) and benzyl chloride with 4-methylaniline (1 eq.) as an additive worked. Two C=C double bond containing substrates (1-allyloxy-4-chloromethylbenzene (**1x**) and 1-chloromethyl-4-vinylbenzene (**1y**)) were tested as well. However, no desired products were observed.

More practically, this reaction can be performed at a 7.90 mmol scale, which clearly showing the potential application in a large scale preparation (Scheme 3). For example, 7.90 mmol (1.00 g) of benzyl chloride and 7.90 mmol (2.97 g) of PTAT were heated in 60 mL of DMSO at 90 °C for 2 h to afford **2a** in 53 % yield (640 mg) by flash column chromatograph on silica gel.

Scheme 2. Scope of benzyl halides and sulfonates



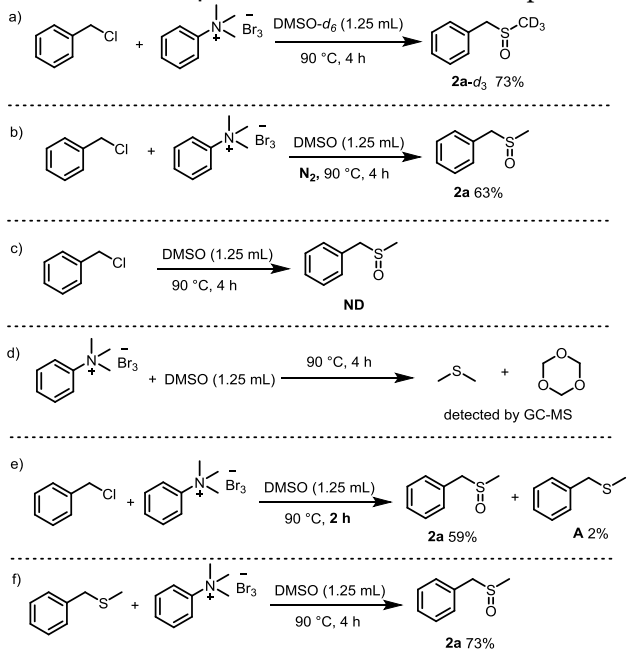
[a)]Benzyl bromide (**4a**) was used instead of benzyl chloride (**1a**). [a)]Benzyl tosylate was used instead of benzyl chloride (**1a**). [c)]4-Nitrobenzyl bromide (**4i**) was used instead of 4-nitrobenzyl chloride (**1i**). [d)]4-Methylbenzyl bromide **(4l)** was used instead of 4-methylbenzyl chloride (**1l**). [e)]Reaction time is 100 min. [f)]Product **2v** was verified by GC-MS and ^{1}H NMR, but cannot be purified due to impurity with very close polarity. [g)]4-Methylphenol (1 eq.)

was added as an additive.

To gain insight into the reaction mechanism, a number of control experiments were conducted as shown in Scheme 4. First, when DMSO-d_6 was used to replace DMSO, the deuterated product **2a**-d_3 was formed in 73% yield under our optimized conditions (eq. a). ^{1}H and ^{13}C{1H} NMR analyses confirm the complete deuterated incorporation at the "CH_3" moiety, which reveals that DMSO is not only as the solvent, but also as the "SMe" source. To further investigate the reaction mechanism, other designed experiments were performed. When the reaction of substrate **1a** was performed under standard conditions and N_2 atmosphere, product **2a** was received in 63% yield, confirming that the oxygen of **2a** comes from DMSO rather than oxygen in air (eq. b). No product **2a** was detected when PTAT was not used (eq. c). Moreover, the formation of dimethyl sulfide and 1,3,5-trioxane was observed in gas chromatography-mass spectrometric (GC-MS) analysis, under the standard conditions without the addition of benzyl chloride (**1a)** (eq. d). When we carried out this reaction under standard conditions for 2 h (eq. e), side product benzyl(methyl)sulfane (**A**) was obtained in 2% yield. In our reaction system, benzyl(methyl)sulfane (**A**) potentially generated from benzyl chloride. When we employed **A** as the substrate, product **2a** was obtained in 73% yield under our optimized reaction conditions (eq. f), which implied that **A** generated from benzyl chloride under standard conditions.

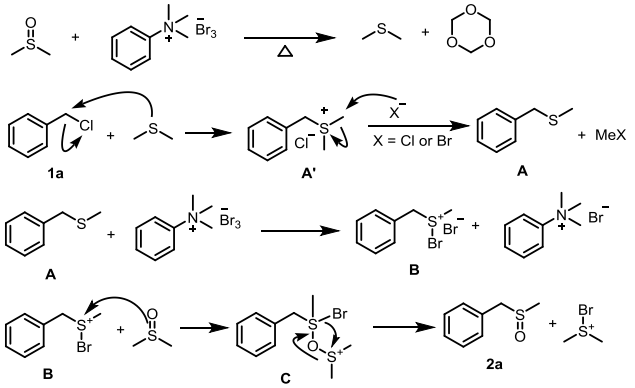
Scheme 3. Gram-scale synthesis of product **2a**

Scheme 4. Control experiments



Based on the preceding literature reports[15] and the above-mentioned control experiments, we proposed the reaction mechanism as depicted in Scheme 5. Initially, dimethyl sulfide is generated through the decomposition of dimethyl sulfoxide with the aid of PTAT under heating. Subsequently, benzyl chloride (**1a**) is attacked by dimethyl sulfide to furnish benzylchlorodimethyl-λ^4-sulfane (**A'**).[16] Subsequently, the generated intermediate **A'** is nucleophilically attacked by a halide (Cl^- or Br^-) in the reaction system to produce phenyl(methyl)sulfane (**A**). Phenyl(methyl)sulfane (**A**) further serves as a nucleophile to attack PTAT to afford benzylbromo(methyl)sulfonium (**B**). Finally, dimethyl sulfoxide as the oxygen source attacks benzyl (methyl)sulfonium bromide (**B**) to form intermediate **C**, which undergoes an elimination to get the product benzyl methyl sulfoxide (**2a**) and dimethylsulfonium bromide.

Scheme 5. Proposed mechanism



To further extend application of the synthetic method, we tested other sulfoxides, including methyl phenyl sulfoxide (in DMF or HMPT as solvent), dodecyl methyl sulfoxide, and tetrahydrothiophene 1-oxide, in the reaction with benzyl chloride under the optimal reaction conditions. However, unfortunately, no corresponding desired products sulfoxides were obtained. Thioanisole was observed in the reaction of methyl methyl sulfoxide by GC-MS analysis. No reactions occurred for other two sulfoxides.

In conclusion, we have developed an efficient and convenient approach to synthesize benzyl methyl sulfoxides under Kornblum-like conditions from benzyl halides and DMSO. DMSO plays a vital role in this transformation, not only as a solvent, but also as a "S(O)Me" source.

Experimental Section

General Information. Unless otherwise noted, all starting materials were purchased from commercial suppliers. Anhydrous DMSO, DMF, and HMPT were purchased from J & K chemical company. Acetonitrile was refluxed over CaH_2 and freshly distilled prior to use. Chloroform was dried over anhydrous $MgSO_4$ and freshly distilled prior to use. Column chromatography was performed using silica gel (normal phase, 200–300 mesh) from Branch of Qingdao Haiyang Chemical, with dichloromethane and methanol as eluent. Reactions were monitored by thin-layer chromatography on GF254 silica gel

plates (0.2 mm) from Institute of Yantai Chemical Industry. The plates were visualized under UV light, as well as other TLC stains (10% phosphomolybdic acid in ethanol; 1% potassium permanganate in water; 10 g of iodine absorbed on 30 g of silica gel). ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 400 MHz spectrometer, usually in $CDCl_3$ as an internal standard, and the chemical shifts (δ) are reported in parts per million (ppm). And multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). HRMS measurements were carried out on an Agilent LC/MSD TOF mass spectrometer. Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected.

General procedure for the Synthesis of Benzyl Methyl Sulfoxides 2. To a stirred suspension of PTAT (phenyltrimethylammonium tribromide) (0.125 mmol, 47 mg) in anhydrous DMSO (1.25 mL) was added benzyl halides 1 or 3 (0.125 mmol). The reaction mixture was further stirred at 90 °C in an oil-bath for 4 hours. After cooling and addition of water, the mixture was extracted with DCM, and combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with DCM and methanol (150/1 to 10/1, *v/v)* as eluent to afford benzyl methyl sulfoxides 2.

((Methylsulfinyl)methyl)benzene (2a).[17] Orange oil, yield: 13 mg, 68%; R_f = 0.48 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2915, 1604, 1496, 1455, 1028, 767, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 3H), 7.29–7.27 (m, 2H), 4.05 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 130.0, 129.6, 128.9, 128.4, 60.3, 37.3. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{11}OS^+$: 155.0525, found: 155.0526.

1-Chloro-2-((methylsulfinyl)methyl)benzene (2b). Yellow oil, yield: 16 mg, 68%; R_f = 0.49 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2919, 1444, 1053, 763 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 1H), 7.40–7.37 (m, 1H), 7.30–7.28 (m, 2H), 4.17 (s, 2H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.5, 132.3, 129.9, 128.1, 127.3, 57.4, 37.6. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}ClOS^+$: 189.0135, found: 189.0131.

1-Chloro-3-((methylsulfinyl)methyl)benzene (2c). Orange oil, yield: 17 mg, 72%; R_f = 0.47 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2917, 1598, 1573, 1430, 1043, 791, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 3H), 7.20–7.17 (m, 1H), 3.96 (d, *J* = 13.2 Hz, 1H), 3.90 (d, *J* = 12.8 Hz, 1H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.8, 131.7, 130.2, 130.0, 128.6, 128.2, 59.4, 37.5. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}ClOS^+$: 189.0135, found: 189.0131.

1-Chloro-4-((methylsulfinyl)methyl)benzene (2d).[17] Yellow oil, yield: 14 mg, 59%; R_f = 0.40 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2921, 1595, 1492, 1045, 836 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.25–7.21 (m, 2H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.91 (d, *J* = 12.8 Hz, 1H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.6, 131.3, 129.1, 128.1, 59.2, 37.3. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}ClOS^+$: 189.0135, found: 189.0130.

1-Fluoro-2-((methylsulfinyl)methyl)benzene (2e). Orange oil, yield: 14 mg, 84%; R_f = 0.48 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2926, 1618, 1586, 1492, 1455, 1049, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 2H), 7.19–7.09(m, 2H), 4.06 (d, *J* = 14.0 Hz, 1H), 4.02 (d, *J* = 13.6 Hz, 1H), 2.48 (d, *J* = 0.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.0 (d, J_{F-C} = 248.5 Hz), 132.4 (d, J_{F-C} = 3.1 Hz, 1H), 130.4 (d, J_{F-C} = 8.2 Hz), 124.6 (d, J_{F-C} = 3.5 Hz), 117.0 (d, J_{F-C} = 15.1 Hz), 115.6 (d, J_{F-C} = 21.6 Hz), 52.7, 37.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.8. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}FOS^+$: 173.0431, found: 173.0427.

1-Fluoro-3-((methylsulfinyl)methyl)benzene (2f).Yellow oil, yield: 18 mg, 84%; R_f = 0.46 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2917, 1617, 1589, 1488, 1448, 1033, 791, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 1H), 7.08–7.01 (m, 3H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8 (d, J_{F-C} = 248.4Hz), 132.0 (d, J_{F-C} = 7.7 Hz, 1H), 130.4 (d, J_{F-C} = 8.4 Hz), 125.8 (d, J_{F-C} = 2.6 Hz), 117.0 (d, J_{F-C} = 22.0 Hz), 115.5 (d, J_{F-C} = 21.0 Hz), 59.6, 37.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.9**.** HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}FOS^+$: 173.0431, found: 173.0437.

1-Fluoro-4-((methylsulfinyl)methyl)benzene (2g).[17] Yellow oil, yield: 13 mg, 61%; R_f = 0.47 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2920, 1604, 1510, 1028, 841 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.27 (m, 2H), 7.10–7.05 (m, 2H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8 (d, J_{F-C} = 248.9 Hz), 131.7 (d, J_{F-C} = 8.3 Hz), 125.5, 116.0 (d, J_{F-C} = 21.8 Hz), 59.1, 37.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.1. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}FOS^+$: 173.0431, found: 173.0426.

1-Bromo-4-((methylsulfinyl)methyl)benzene (2h).[17] White solid, yield: 22 mg, 76%; M.p. 84–86 °C, R_f = 0.51 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2915, 1590, 1487, 1033, 833 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2H), 7.17–7.15 (m, 2H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.90 (d, *J* = 13.6 Hz, 1H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 132.1, 131.6, 128.6, 122.7, 59.2, 37.3. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}BrOS^+$: 232.9630, found: 232.9624.

1-((Methylsulfinyl)methyl)-4-nitrobenzene (2i).[17] White solid, yield: 12 mg, 44%; 16 mg, 65%; M.p. 99–100 °C, R_f = 0.49 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2922, 1604, 1519, 1028, 860 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.24 (m, 2H), 7.50–7.48 (m, 2H), 4.09 (d, *J* = 13.2 Hz, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.0, 137.1, 131.1, 124.0, 59.0, 37.8. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_8H_{10}NO_3S^+$: 200.0376, found: 200.0372.

4-((Methylsulfinyl)methyl)benzonitrile (2j).[17] White solid, yield: 13 mg, 58%; M.p. 74–76 °C, R_f = 0.32 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2919, 2227, 1606, 1504, 1025, 844 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz 2H), 7.42 (d, *J* = 8.2 Hz 2H), 4.03 (d, *J* = 12.8 Hz, 1H), 3.94 (d, *J* = 12.8 Hz, 1H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.1, 132.5, 130.9, 118.3, 112.4, 59.3, 37.7. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_9H_{10}NOS^+$: 180.0478, found: 180.0471.

1-((Methylsulfinyl)methyl)-4-(trifluoromethyl)benzene (2k).[17] White solid, yield: 18 mg, 65%; M.p. 80–82 °C, R_f = 0.37 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2916, 1034, 849 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 4.02 (d, *J* = 12.8 Hz, 1H), 3.99 (d, *J* = 12.8 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.7, 130.7 (q, J_{F-C} = 32.5 Hz), 130.4, 125.8 (q, J_{F-C} = 3.6 Hz), 123.9 (q, J_{F-C} = 272.0 Hz), 59.3,

37.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_{10}F_3OS^+$: 223.0399, found: 223.0394.

1-Methyl-4-((methylsulfinyl)methyl)benzene (2l).[17] Orange oil, yield: 12 mg, 58%; 14 mg, 66%; R_f = 0.31 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2918, 1515, 1030, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.15 (m, 4H), 4.04 (d, *J* = 12.8 Hz, 1H), 3.89 (d, *J* = 12.8 Hz, 1H), 2.44 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.3, 129.9, 129.7, 126.5, 60.1, 37.2, 21.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_{13}OS^+$: 169.0682, found: 169.0678.

Methyl 4-((methylsulfinyl)methyl)benzoate (2m).[17] White solid, yield: 18 mg, 68%; M.p. 74–76 °C, R_f = 0.27 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2920, 1719, 1611, 1575, 1509, 1284, 864 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 4.03 (d, *J* = 12.8 Hz, 1H), 3.99 (d, *J* = 12.8 Hz, 1H), 3.91 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5,134.7, 130.2, 130.19, 130.09, 59.8, 52.2, 37.5. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_{13}O_3S^+$: 213.0580, found: 213.0576.

4-((Methylsulfinyl)methyl)benzaldehyde (2n). Orange oil, yield: 16 mg, 71%; R_f = 0.28 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2920, 1719, 1611, 1436, 1284 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.4 Hz 2H), 4.05 (d, *J* =12.8 Hz, 1H), 4.02 (d, *J* = 12.8 Hz, 1H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.6, 136.4, 136.2, 130.8, 130.1, 59.7, 37.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_{11}O_2S^+$: 183.0474, found: 183.0471.

2,4-Dichloro-1-((methylsulfinyl)methyl)benzene (2o). Orange oil, yield: 14 mg, 65%; R_f = 0.56 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2925, 1626, 1588, 1052, 867, 826 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* =2.0 Hz, 1H), 7.33 (d, *J* =8.0 Hz, 1H), 7.28 (dd, *J* =8.0, 2.0 Hz, 1H), 4.14 (d, *J* = 12.8 Hz, 1H), 4.08 (d, *J* = 12.8 Hz, 1H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.2, 135.1, 133.1, 129.7, 127.6, 126.7, 56.5, 37.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_8H_{19}Cl_2OS^+$: 222.9746, found: 222.9740.

1,4-Dimethyl-2-((methylsulfinyl)methyl)benzene (2p). White solid, yield: 15 mg, 66%; M.p. 84–86 °C, R_f = 0.36 (DCM/MeOH 15:1, v/v). IR (KBr) 2917, 1505, 1382, 1023, 823 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.02 (m, 3H), 4.17 (d, *J* = 12.8 Hz, 1H), 3.90 (d, *J* = 12.4 Hz, 1H), 2.51 (s, 3H), 2.36 (s, 3H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.0, 134.0, 131.5, 130.7, 129.4, 128.3, 59.1, 37.7, 20.8, 19.3. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_{15}OS^+$: 183.0838, found: 183.0835.

1-((Methylsulfinyl)methyl)naphthalene (2q). Light yellow solid, yield: 19 mg, 75%; M.p. 68–70 °C, R_f = 0.38 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2920, 1627, 1595, 1400, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.90–7.84 (m, 2H), 7.59 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 2H), 7.54 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 2H), 4.68 (d, *J* = 13.2 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.9, 131.8, 129.4, 129.0, 128.9, 126.8, 126.34, 126.27, 125.4, 123.5, 58.8, 38.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}OS^+$: 205.0682, found: 205.0678.

2-((Methylsulfinyl)methyl)naphthalene (2r). Colorless solid, yield: 20 mg, 79%; M.p. 104–106 °C, R_f = 0.36 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2910, 1597, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.82 (m, 3H), 7.77 (s, 1H), 7.52–7.49 (m, 2H), 7.39 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 4.08 (d, *J* = 12.8 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.3, 133.0, 129.2, 128.8, 127.8, 127.7, 127.3, 127.1, 126.55, 126.47, 60.6, 37.4. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}OS^+$: 205.0682, found: 205.0678.

Ethyl 5-((methylsulfinyl)methyl)furan-2-carboxylate (2s). Yellow oil, yield: 13 mg, 49%; R_f = 0.29 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2983, 2922, 1717, 1594, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 3.6 Hz, 1H), 6.54 (d, *J* = 3.6 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.10 (d, *J* = 14.0 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 2.56 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.3, 148.1, 145.4, 118.9, 113.3, 61.1, 52.3, 38.2, 14.3. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_{13}O_4S^+$: 217.0529, found: 217.0527.

2-Chloro-5-((methylsulfinyl)methyl)thiophene (2t). Yellow oil, yield: 20 mg, 83%; R_f = 0.42 (DCM/MeOH 15:1, *v/v*). IR (KBr) 2921, 1656, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 4.0 Hz, 1H), 6.82 (d, *J* = 4.0 Hz, 1H), 4.08 (d, *J* = 14.0 Hz, 1H), 4.02 (d, *J* = 14.0 Hz, 1H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 131.1, 128.8, 128.3, 126.5, 54.1, 37.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_6H_8ClOS_2^+$: 194.9700, found: 194.9696.

(((Trideuteromethyl)sulfinyl)methyl)benzene (2a-d_3). Colorless oil, yield: 14 mg, 73%; R_f = 0.35 (DCM /MeOH 20:1, v/v). IR (KBr) 1603, 1496, 1455, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 3H, ArH), 7.32–7.25 (m, 2H, ArH), 4.05 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 129.9, 129.6, 128.9, 128.4, 59.9, 36.4 (hept, $J_{D\text{-}C}$ = 20.9 Hz). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_8H_8D_3OS^+$: 158.0713, found: 158.0713.

1-Methoxy-4-((methylsulfinyl)methyl)benzene (2u).[17] Collorless crystals; M.p. 55–56 °C, yield: 23 mg, 34%; R_f = 0.68 (DCM/MeOH 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.01 (d, *J* = 12.8 Hz, 1H), 3.90 (d, *J* = 12.8 Hz, 1H), 3.81 (s, 3H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7, 131.2, 121.4, 114.4, 59.5, 55.2, 37.0.

Large scale synthesis of benzyl methyl sulfoxide (2a). To a stirring suspension of PTAT (7.90 mmol, 2.97 g) in anhydrous DMSO (60 mL) (Caution: with 480 mL pressure tube) was added benzyl chloride (**1a**) (7.90 mmol, 1 g). The reaction mixture was further stirred at 90 °C for 160 minutes. After cooling and addition of water, the mixture was extracted with DCM, and the combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with DCM and methanol (150:1 to 10/1, *v/v*) as eluent to afford 0.64 g (53%) of benzyl methyl sulfoxide (**2a**) as an orange oil.

Synthesis of benzyl 4-methylbenzenesulfonate.[18] To a stirring solution of benzyl alcohol (270 mg, 2.5 mmol), triethylamine (0.55 ml, 3.75 mmol), and DMAP (75 mg, 0.5 mmol) in anhydrous DCM (10 mL) in a 50 mL round bottom flask in an ice-water bath was added dropwise a solution of 4-methylbenzenesulfonyl chloride (715 mg, 3.75 mmol) in dried DCM (10 mL). After addition, the reaction mixture was further stirred at 0 °C for 2 hours. After addition of water (10 mL), stirring, and separation, the organic phase was washed with saturated aqueous sodium bicarbonate solution (20 mL x 2), saturated brine (20 mL), and dried over anhydrous sodium sulfate. After concentrated *in vacuo*, the resulting residue was purified by silica gel column chromatography with petroleum ether (60 – 90 °C) and ethyl acetate (10:1, *v/v*)

as eluent to afford 190 mg (29%) of benzyl 4-methylbenzenesulfonate as colorless crystals, M.p. 48–50 °C, R_f = 0.18 (PE:EA 10:1, *v/v*). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.32–7.27 (m, 5H), 7.26–7.20 (m, 2H), 5.03 (s, 2H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) *δ* 144.7, 133.14, 133.06, 129.7, 128.9, 128.5, 128.4, 127.8, 71.8, 21.5.

Synthesis of *tert*-butyl (4-(hydroxymethyl)phenyl) carbonate.[19] Boc_2O (879 mg, 4.03 mmol), carbon tetrachloride (134 mg, 0.40 mmol), and 4-hydroxymethylphenol (500 mg, 4.03 mmol) were stirred in an oil bath at 75 °C for 2 hours. After addition of water (10 mL), the mixture was extracted with ethyl acetate (10 mL x 2). The combined organic phase was washed with saturated brine (10 mL), and dried over anhydrous sodium sulfate. After concentrated *in vacuo*, the resulting residue was purified by silica gel column chromatography with petroleum ether (60 – 90 °C) and ethyl acetate (50:1 and then 10:1, *v/v*) as eluent to afford 630 mg (70%) of *tert*-butyl (4-(hydroxymethyl)phenyl) carbonate as colorless oil, R_f = 0.32 (PE:EA 3:1, *v/v*).

Synthesis of *tert*-butyl (4-(hydroxymethyl)phenyl)carbamate.[20] 4-(Aminophenyl)methanol (500 mg, 4.07 mmol) was dissolved in a mixture of 1,4-dioxane (3 mL), water (3 mL), and 1 mol/L NaOH (4 mL) at 0 °C in an ice-water bath. Boc_2O (1.33 g, 6.09 mmol) was added under stirring in an oil bath at 0 °C. After stirred for 10 min., the ice-water bath was removed. The mixture was stirred at room temperature for 12 hours. After addition of water (10 mL), the resulting mixture was extracted with ethyl acetate (10 mL x 2). The combined organic phase was washed with 1 mol/L HCl (20 mL x 2) twice, saturated brine (10 mL), and dried over anhydrous sodium sulfate. After concentrated *in vacuo*, the crude *tert*-butyl (4-(hydroxymethyl)phenyl)carbamate was obtained 895 mg (98.7% yield) as yellow oil, R_f = 0.28 (PE:EA 2:1, *v/v*).

Synthesis of substituted benzyl chlorides via chlorination with thionyl chloride (General procedure).[21] To a solution of thionyl chloride (1.01 g, 8.46 mmol) in chloroform (15 mL) in an ice-water bath was added the above prepared substituted benzyl alcohol (2.82 mmol) with a syringe during 30 min. After addition, the reaction mixture was stirred at 0 °C for 2 hours. The mixture was washed with water (10 mL x 3) and saturated brine (10 mL). The organic phase was dried over anhydrous sodium sulfate. After concentrated *in vacuo*, the resulting residue was purified by silica gel column chromatography with petroleum ether (60 – 90 °C) and ethyl acetate (50:1, *v/v*) as eluent to afford substituted benzyl chloride.

***tert*-Butyl (4-(chloromethyl)phenyl) carbonate (1v).**[22] Colorless oil, yield: 170 mg, 25%; R_f = 0.50 (PE:EA 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.57 (s, 2H), 1.56 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.6, 150.9, 134.9, 129.7, 121.5, 83.7., 45.5, 27.6.

***tert*-Butyl (4-(chloromethyl)phenyl)carbamate (1w).**[23] White solid; yield: 160 mg, 18%; M.p. 95–96 °C, R_f = 0.64 (PE:EA 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.36–7.26 (m, 4H), 6.55 (s, 1H), 4.55 (s, 2H), 1.52 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) *δ* 152.6, 138.5, 131.9, 129.4, 118.5, 80.7, 46.1, 28.3.

1-(Allyloxy)-4-(chloromethyl)benzene (1x).[24] Colorless oil; yield: >98%, R_f = 0.64 (PE:EA 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.29 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.04 (ddt, *J* = 17.2, 10.8, 6.0 Hz 1H), 5.40 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.55 (s, 2H), 4.52 (dt, *J* = 5.6, 1.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) *δ* 158.6, 133.01, 129.98, 129.8, 117.7, 114.9, 46.2.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H and ^{13}C{H} NMR spectra of all products, prepared starting materials, and GC-MS profiles on mechanistic investigations (PDF file)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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