Direct nucleophilic substitution of alcohols using an immobilized oxovanadium catalyst

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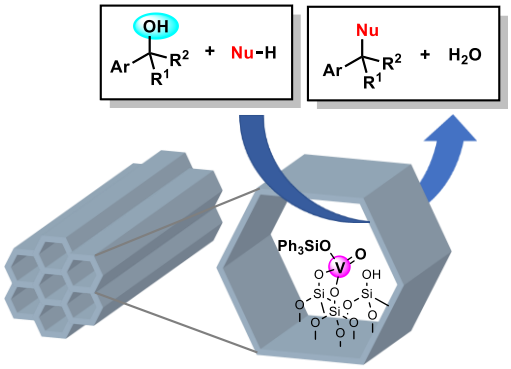


Abstract

Direct nucleophilic substitution of alcohols with thiols or carbon nucleophiles was achieved using a mesoporous silica-supported oxovanadium catalyst (VMPS4). Benzyl and allyl alcohols were compatible in this reaction under mild conditions, affording the products in high yields. The VMPS4 catalyst showed excellent chemoselectivity toward alcohols in the presence of acid-labile functional groups, which is in contrast to that observed for the commonly used Lewis acid catalysts, which exhibit poor selectivity. The VMPS4 catalyst could be recycled by simple centrifugation, and the catalytic activity was maintained over seven cycles.

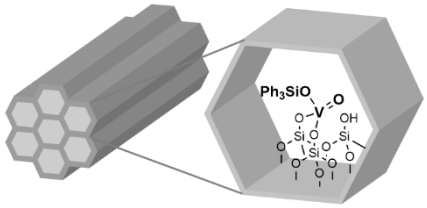
Introduction

Direct substitution of alcohols is considered as one of the most important challenges for the development of green engineering in pharmaceutical and chemical industries[2] and has been mainly studied using Brønsted acids, Lewis acids, and transition metal catalysts.[3–5] However, the strong Lewis acidity of these catalysts often results in poor functional group tolerance. While direct catalytic substitution of π-activated alcohols such as allyl alcohols has been widely accomplished via transition metal π-allyl intermediates, the use of benzylic alcohols in these transformations is relatively rare and requires harsh reaction conditions.[6–10] Additionally, despite the remarkable advantages of heterogenous catalysts with regard to their handling and reuse, only a few direct substitution reactions of alcohols have been reported using such catalysts.[11–13]

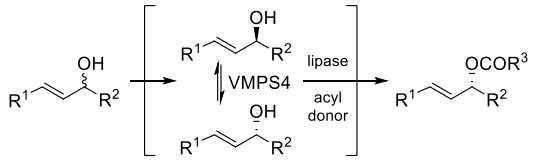
Recently, oxovanadium species have been employed as racemization catalysts for alcohols. For example, oxovanadium compounds such as $VOSO_4 \cdot nH_2O$[14–16] and $VO(OSiPh_3)_3$[17] and a polymer-bound vanadyl phosphate[18] were found to be active in the racemization of allyl and benzyl alcohols. Racemization of alcohols has often been combined with lipase-catalyzed kinetic resolution for realizing chemoenzymatic dynamic kinetic resolution (DKR).[19,20] We recently reported a mesoporous silica-supported oxovanadium catalyst (VMPS4) in which oxovanadium was covalently bound on the surface of the a mesoporous silica pore of 4-nm inner diameter (Figure 1a).[21] VMPS4 was highly compatible with lipase and also exhibited excellent activity in the DKR of allyl, propargyl, and benzyl alcohols (Figure 1b).[22–29] We speculated that the racemization by VMPS4 in these reactions proceeded via a cationic intermediate generated due to C–O bond cleavage in the substrate alcohols.[22] Considering this, we envisioned that VMPS4 could also catalyze the direct substitution of alcohols in the presence of an appropriate nucleophile in the reaction medium.

Herein, we report the VMPS4-catalyzed substitution reactions of benzyl alcohols (Figure 1c). Sulfur nucleophiles were mainly used in this study, because resultant benzylic sulfides are widely found in bioactive compounds and pharmaceutical agents.[30,31] Some carbon nucleophiles were also successfully employed to demonstrate the versatility of the present methodology.

(a)



(b)



(c) This work

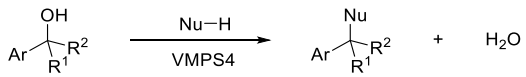
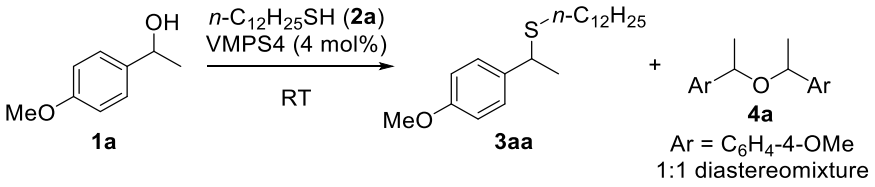


Figure 1. Mesoporous silica-supported oxovanadium (VMPS4) and its application in direct C–O bond activation of alcohols. (a) The structure of VMPS4; (b) Dynamic kinetic resolution of allyl alcohols by VMPS4-catalyzed racemization and following lipase-catalyzed enantioselective acylation; (c) VMPS4-catalyzed direct nucleophilic substitution of alcohols.

Results and Discussion

Initially, the reaction conditions were screened using benzyl alcohol **1a**, bearing a 4-methoxy group, as the substrate and dodecane-1-thiol **2a** as the nucleophile (Table 1) in the presence of VMPS4. When the reaction was conducted using **1a** (0.2 M), **2a** (3.0 equiv.), and VMPS4 (4 mol%) in toluene at room temperature (RT), the desired thioether **3aa** was obtained in 26% NMR yield, along with a significant amount of self-condensation side-product **4a** (28%, Entry 1, Figure S1a). A higher yield and an improved chemoselectivity were obtained in MeCN (Entry 2). The yield, chemoselectivity, and reaction rate improved drastically in CH_2Cl_2 (Entry 3). Although the reaction was conducted in other halogenated solvents such as $CHCl_3$, $ClCH_2CH_2Cl$, and $PhCF_3$ (Entries 4–6), the highest yield was obtained in CH_2Cl_2, which also gave the best results in previously reported other type of VMPS4-catalyzed reactions, such as racemization of allyl and propargyl alcohols.[24,29] Reducing the amount of **2a** to 1.2 equiv. did not reduce the product yield (Entry 7). Interestingly, the formation of undesired **4a** was almost suppressed by reducing the concentration of **1a** to 0.1 M, and **3aa** was obtained in a quantitative yield (Entry 8, Figure S1b).

Table 1. Optimization of reaction conditions of VMPS4-catalyzed thioetherification of benzyl alcohol **1a**[a]



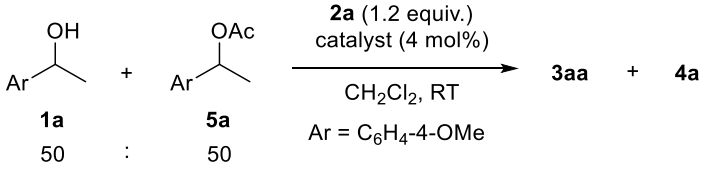
Entry	Solvent	Equiv. (**2a**)	Time (h)	% Yield of **3aa**[b]	% Yield of **4a**[b,c]
1	Toluene	3.0	4	26	28
2	MeCN	3.0	4	42	6
3	CH_2Cl_2	3.0	1	91	7
4	$CHCl_3$	3.0	4	69	13
5	$ClCH_2CH_2Cl$	3.0	4	50	24
6	$PhCF_3$	3.0	4	27	27
7	CH_2Cl_2	1.2	1	91	7
8[d]	CH_2Cl_2	1.2	1	99	trace

[a] Unless otherwise noted, the reaction was conducted with **1a** (0.10 mmol), **2a**, and VMPS4 (4 mol%) in the indicated solvent (0.2 M) at room temperature (RT). [b] Yield was determined by ^{1}H NMR of the crude reaction mixture with 1,1,2-trichloroethene as an internal standard. [c] Yield of **4a** is represented based on the monomeric alcohol unit. [d] Reaction was conducted with 0.1 M of **1a**.

Under the optimal conditions for achieving high yield and selectivity, the chemoselectivity of VMPS4 was compared to those of the previously reported Lewis acid catalysts. Thus, a 1:1 mixture of

benzyl alcohol **1a** and its acetate **5a** was treated with various catalysts in the presence of **2a** (1.2 equiv. to the sum of the equivalents of **1a** and **5a**), and the chemoselectivity was evaluated by determining the molar ratios of residual **1a** and **5a** as well as products **3aa** and **4a** in the resultant mixture by ^{1}H NMR spectroscopy (Table 2). VMPS4 exhibited highly chemoselective activation of alcohol **1a** against acetate **5a**; almost complete conversion of **1a** to thioether **3aa** was achieved, while **5a** remained intact (Entry 1). When commercially available $VOSO_4 \cdot nH_2O$[14–16] was used, the conversion was reasonably low even after 24 h, and a significant amount of **4a** was produced despite the high chemoselectivity for **1a** over **5a** (Entry 2). $VO(OSiPh_3)_3$ was not effective as a catalyst, although it was successfully employed in the direct amination of allyl alcohols (Entry 3).[32] It is noteworthy that the immobilization of oxovanadium species onto a mesoporous silica (MPS) surface drastically improved the catalytic activity (Entry 1 vs 2–3). Although the precise role of MPS is still elusive, the polar environment in the MPS pore might be considered responsible for accelerating the reaction.[23] Some other commonly used Lewis acid catalysts, namely $B(C_6F_5)_3$,[10] $InCl_3$,[33] $Na[AuCl_4]$,[34,35] and $BiBr_3$,[8] consumed both alcohol **1a** and acetate **5a**, resulting in poor chemoselectivity (Entries 4–7). This clearly demonstrates the high activity and superior chemoselectivity of VMPS4 in the direct C–O bond cleavage of alcohols. The specific selectivity of VMPS4 for alcohol over acetate could be rationalized by the favorable covalent V–O bond formation between alcohol substrates and oxovanadium species of VMPS involved in the catalytic cycle.[21,36–38]

Table 2. Chemoselectivity of VMPS4 and other Lewis acid catalysts[a]

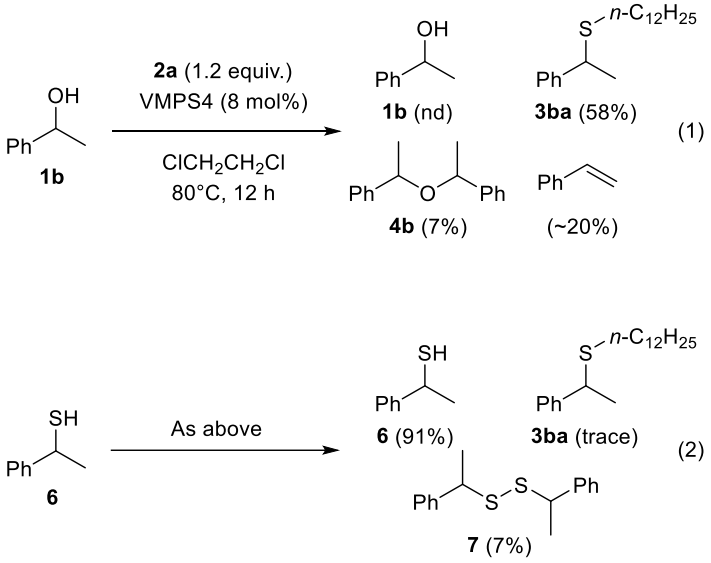


Entry	Catalyst	Time	Molar ratio (**1a**:**5a**:**3aa**:**4a**)[b]
1	VMPS4	15 min	3:48:48:trace
2	$VOSO_4 \cdot nH_2O$	24 h	28:50:8:13
3[c]	$VO(OSiPh_3)_3$	3 h	47:42:nd:nd
4	$B(C_6F_5)_3$	15 min	19:28:43:5
5[d]	$InCl_3$	1 h	3:27:56:trace
6	$Na[AuCl_4]$	18 h	18:25:51:nd
7[d]	$BiBr_3$	5 min	nd:3:96:trace

[a] Unless otherwise noted, the reaction was conducted with **1a** (0.14 mmol), **5a** (0.14 mmol), **2a** (1.2 equiv. to the sum of the equivalents of **1a** and **5a**, 0.34 mmol), and the indicated catalyst (4 mol%, 0.011 mmol) in CH_2Cl_2 (0.05 M each, 2.8 mL) at room temperature. [b] Determined by ^{1}H NMR of the crude reaction mixture with 1,1,2-trichloroethene as an internal standard. Yield of **4a** is represented based on the monomeric alcohol unit. nd: not detected. [c] Molecular sieve 3A (0.20 g) was added.[32] [d] Catalyst loading was 1 mol%.

Chemoselectivity of the VMPS4-catalyzed substitution was further investigated using benzyl alcohol **1b** or thiol **6** (scheme 1) as a substrate. Although the reaction required a higher temperature such as 80 ℃ to proceed, it afforded thioether **3ba** in a moderate yield, along with a considerable amount of styrene and a trace amount of self-condensation product **4b** (eq. 1). The same reaction at room temperature did not afford any products. In contrast, the reaction of **6** afforded only a trace amount of **3ba**, and most of **6** was recovered unreacted (eq. 2). Thus, VMPS4 selectively activated alcohols in the presence of thiols.

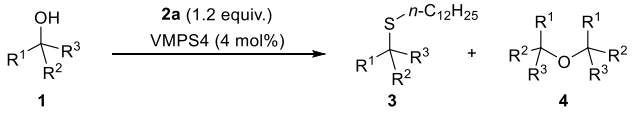
Scheme 1. Reactivity comparison between alcohol and thiol[a]

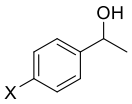
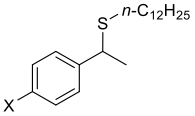
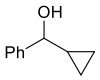
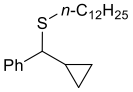
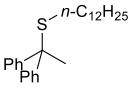
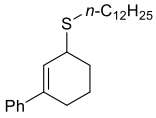
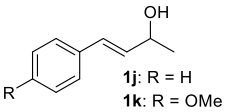
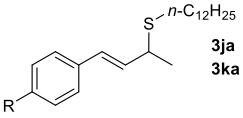
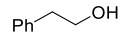
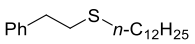
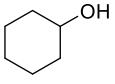
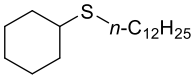


[a] Reaction was conducted with **1b**/**6** (0.20 mmol), **2a** (0.24 mmol), and VMPS4 (8 mol%) in 1,2-dichloroethane (0.1 M) at 80 ºC. Yields were determined by ^{1}H NMR of the crude reaction mixture with 1,1,2-trichloroethene as an internal standard. Yields of **4a** and **7** are represented based on the monomeric alcohol and thiol units, respectively. nd: not determined.

The scope and limitation of the present VMPS4-catalyzed reaction were investigated next (Table 3). A series of benzyl alcohols were first examined. Introduction of halogen at the *para*-position of benzyl alcohol improved the yield relative to that obtained with unsubstituted benzyl alcohol **1b** (Entries 1–3 vs Scheme 1). The highest yield was obtained with fluorine as the substituent, probably because of the resonance effect of the halogen atom. On the other hand, nitro-substituted benzyl alcohol **1f** did not afford any product (Entry 4). Benzyl alcohol **1g** bearing a cyclopropyl group at the α-position reacted smoothly to give the corresponding thioether **3ga** (Entry 5). This is in sharp contrast to the reactions using a π-coordinating Lewis acid catalyst, which promotes ring expansion to furnish pyrrolidines.[39] Tertiary alcohol **1h** also reacted to afford **3ha** in a moderate yield (Entry 6). In the case of tertiary cyclic alcohol **1i**, a more thermodynamically stable conjugated thioether **3ia** was obtained, probably via an allyl cation intermediate generated from **1i** (Entry 7).[24] Allyl alcohols **1j** and **1k** were also compatible in the present reaction, affording products **3ja** and **3ka** (Entries 8 and 9). On the other hand, simple aliphatic alcohols such as **1l** and **1m** did not afford any products at 80 ºC for 12 h (Entries 10 and 11).

Table 3. Scope and limitation of VMPS4-catalyzed thioetherification[a]

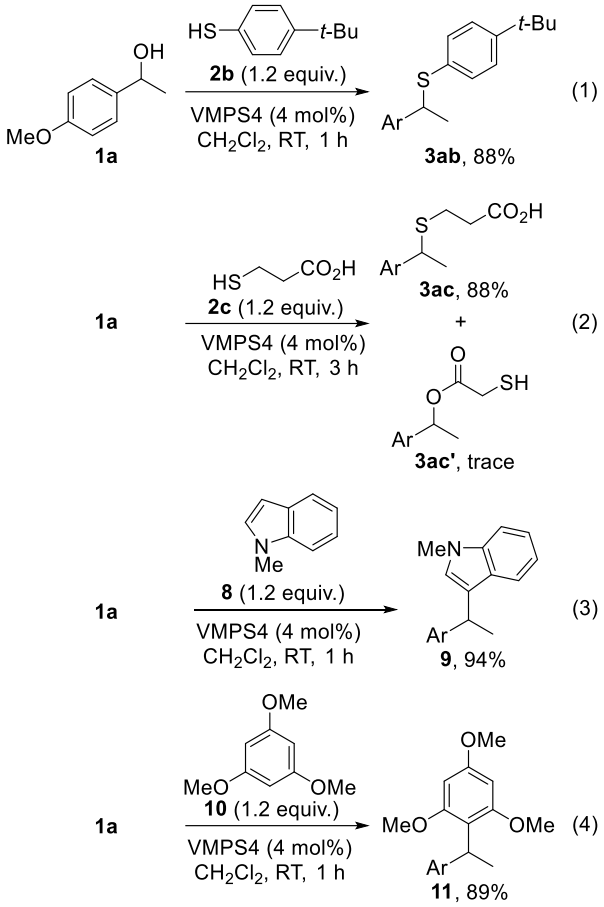


Entry	**1**		Conditions	**3**		Yield (%)[b]
			$ClCH_2CH_2Cl$, 80°C, 12 h			
1[c]		**1c**: X = F	$ClCH_2CH_2Cl$, 80°C, 24 h		**3ca**	78 (**4c**: nd)
2[c]		**1d**: X = Cl			**3da**	62 (**4d**: 9)
3[c]		**1e**: X = Br	$ClCH_2CH_2Cl$, 80°C, 24 h		**3ea**	60 (**4e**: 20)
4[c]		**1f**: X = NO_2			**3fa**	nr (**4f**: -)
			$Cl_2CHCHCl_2$, 130°C, 24 h			
5		**1g**	CH_2Cl_2, RT, 24 h		**3ga**	79
6		**1h**	CH_2Cl_2, RT, 24 h		**3ha**	65
7		**1i**	CH_2Cl_2, RT, 24 h		**3ia**	75
8		**1j**: R = H	CH_2Cl_2, RT, 3 h		**3ja**	85
9		**1k**: R = OMe	CH_2Cl_2, RT, 1 h		**3ka**	69
10[c]		**1l**	$ClCH_2CH_2Cl$, 80°C, 12 h		**3la**	nr
11[c]		**1m**	$ClCH_2CH_2Cl$, 80°C, 12 h		**3ma**	nr

[a] Unless otherwise noted, the reaction was conducted with **1a** (0.20 mmol), **2a** (0.24 mmol), and VMPS4 (4 mol%) in the indicated solvent (0.2 M). [b] Isolated yield. Yields of **4** are indicated in the parentheses. nr: no reaction. [c] Reaction was conducted using 8 mol% of VMPS4.

Next, the reaction scope of the nucleophiles was examined (Scheme 2). The reaction with arylthiol **2b** afforded product **3ab** in 88% yield (eq. 1). 3-Mercaptopropanoic acid **2c** was also used for this reaction to understand the competition between thiol and carboxylic acid as a nucleophile. Indeed, thioether **3ac** was predominantly formed, along with a trace amount of ester **3ac'** (eq. 2). Furthermore, carbon nucleophiles such as *N*-Me indole **8** and 1,3,5-trimethoxybenzene **10** were employed, and the corresponding products **9** and **11** were obtained in high yields (eqs. 3 and 4).

Scheme 2. Further reaction scope with various nucleophiles[a]



[a] Unless otherwise noted, the reaction was conducted with **1a** (0.20 mmol), the indicated nucleophile (0.24 mmol), and VMPS4 (4 mol%) in CH_2Cl_2 (0.1 M). Yields were determined after isolation. Ar = C_6H_4-4-OMe.

Although a precise reaction mechanism has not yet been elucidated, we assume that the reaction proceeds through a benzyl cation intermediate, which is generated by the reaction of **1** with VMPS4.[22,23] The formation of a cationic intermediate was suggested by the reaction of optically active alcohol (*S*)-**1a** with VMPS4, which afforded the product **3aa** in a racemic form (Schemes S2 and S3a). In addition, the prominent substituent effects on the Ph group (Table 3, Entries 1–4) and high reactivity of tertiary alcohol **1h** (Table 3, Entry 6) also indicate the generation of benzyl cations in the reaction pathway. However, we currently do not exclude the possibility of an S_N2-type mechanism and racemization preequilibrium of the alcohol, because **1a** smoothly racemized during the reaction (Scheme S3b).

Finally, the recyclability of the VMPS4 catalyst was investigated (Figure 2). After complete conversion of the substrate **1a**, the reaction mixture was centrifuged, and the supernatant containing the product was collected by decantation and concentrated in vacuo. The residue was purified by chromatography to give **3aa**. The precipitated VMPS4 was washed with EtOAc, centrifuged, and dried in vacuo. The recovered VMPS4 was used for the next reaction under identical conditions. Although the color of VMPS4 changed from ash white to dark red during the first reaction, a high catalytic activity was maintained even after seven recycles.

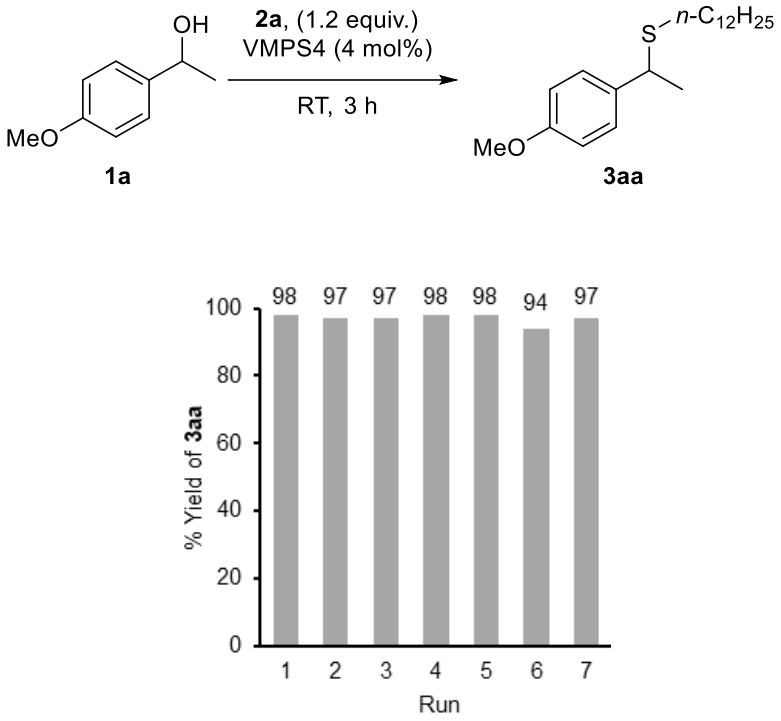


Figure 2. Recycling test of VMPS4 catalyst. Every reaction was conducted with **1a** (0.33 mmol), **2a** (0.50 mmol), and VMPS4 (4 mol%) in CH_2Cl_2 (0.1 M).

Conclusion

In conclusion, we developed the direct nucleophilic substitution of benzyl alcohols using a mesoporous silica-supported oxovanadium (VMPS4) catalyst. The catalyst exhibited high chemoselectivity for alcohols over acetates, which is in contrast to that observed with other commonly used Lewis acid catalysts, which exhibit poor chemoselectivity. VMPS4 could also selectively activate alcohols over thiols. This reaction has a broad substrate scope, and some carbon nucleophiles were also compatible in this reaction. Importantly, the high catalytic activity of VMPS4 was maintained for more than seven recycles. Further investigations to develop new applications of VMPS4 in catalytic transformations are currently in progress in our laboratory.

Experimental Section

General procedure: [Table 1, Entry 8] Under argon atmosphere, VMPS4 (40 mg, 8.6 μmol of vanadium) was added to a CH_2Cl_2 solution (2.0 mL, 0.1 M) of alcohol **1a** (31 mg, 0.20 mmol) and thiol **2a** (58 μL, 0.24 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. After that, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane to hexane/EtOAc=97:3) giving **3aa** as a colorless oil (64 mg, 95%).

Dodecyl(1-(4-methoxyphenyl)ethyl)sulfane (3aa): IR (NaCl): 2924, 2854, 1248, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.92 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 2.32-2.23 (m, 2H), 1.58-1.40 (m, 2H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.30-1.23 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 136.4, 128.4, 113.9, 55.4, 43.5, 32.1, 31.4, 29.8_0, 29.7_8, 29.7_6, 29.6, 29.5_3, 29.5_1, 29.4, 29.1, 22.9, 22.8, 14.3; HRMS(EI) m/z calcd. for $C_{21}H_{36}OS$ [M^+]: 336.2487, found: 336.2482.

Dodecyl(1-phenylethyl)sulfane (3ba): Purified by column chromato-graphy using hexane to hexane/toluene=19:1 as an eluant; 58% yield (25 mg); a colorless oil; IR (NaCl): 2924, 2854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.21 (m, 5H), 3.94 (q, *J* = 7.0 Hz, 1H), 2.33-2.27 (m, 2H), 2.17 (s, 3H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.52-1.43 (m, 2H), 1.33-1.19 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.4, 128.6, 127.4, 127.1, 44.2, 32.1, 31.4, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 22.8_4, 22.7_6, 14.3; HRMS(EI) m/z calcd. for $C_{20}H_{34}S$ [M^+]: 306.2381, found: 306.2380.

Dodecyl(1-(4-fluorophenyl)ethyl)sulfane (3ca): Purified by column chromatography using hexane to hexane/EtOAc=49:1 as an eluant; 78% yield (90 mg); a colorless oil; IR (NaCl): 2963, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.28 (m, 2H), 7.02-6.97 (m, 2H), 3.93 (q, *J* = 7.0 Hz, 1H), 2.33-2.22 (m, 2H), 1.57-1.43 (m, 2H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.24-1.22 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.8 (d, *J* = 244.5 Hz), 140.1, 128.8 (d, *J* = 8.0 Hz), 115.3 (d, *J* = 22.0 Hz), 43.5, 32.1, 31.4, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 22.9, 22.8, 14.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ = -115.7; HRMS(EI) m/z calcd. for $C_{20}H_{33}FS$ [M^+]: 324.2287, found: 324.2286.

(1-(4-Chlorophenyl)ethyl)(dodecyl)sulfane (3da): Purified by column chromatography using hexane to hexane/toluene=19:1 as an eluant; 62% yield (51 mg); a colorless oil; IR (NaCl): 2924, 2854, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.27 (s, 4H), 3.91 (q, *J* = 7.0 Hz, 1H), 2.31-2.24 (m, 2H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.49-1.43 (m, 2H), 1.30-1.22 (m, 18H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.0, 132.6, 128.7_3, 128.6_9, 43.5, 32.1, 31.4, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.0, 22.8_4, 22.8_6, 14.3; HRMS(EI) m/z calcd. for $C_{20}H_{33}{}^{35}ClS$ [M^+]: 340.1992, found: 340.1991.

(1-(4-Bromophenyl)ethyl)(dodecyl)sulfane (3ea): Purified by column chromatography using hexane to hexane/toluene=19:1 as an eluant; 60% yield (60 mg); a colorless oil; IR (NaCl): 2924, 2853, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 3.88 (q, *J* = 7.0

Hz, 1H), 2.33-2.20 (m, 2H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.48-1.42 (m, 2H), 1.30-1.21 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.5, 131.6, 129.1, 120.7, 43.6, 32.1, 31.4, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.0, 22.8, 22.7, 14.3; HRMS(EI) m/z calcd. for $C_{20}H_{33}{}^{79}BrS$ [M^+]: 384.1486, found: 384.1479.

(Cyclopropyl(phenyl)methyl)(dodecyl)sulfane (3ga): Purified by column chromatography using hexane/toluene=19:1 as an eluant; 79% yield (53 mg); a colorless oil; IR (NaCl): 2924, 2854 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.31 (m, 4H), 7.26-7.23 (m, 1H), 3.13 (d, *J* = 10.0 Hz, 1H), 2.36-2.27 (m, 2H), 1.49-1.43 (m, 2H), 1.31-1.22 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.75-0.73 (m, 1H), 0.52-0.47 (m, 1H), 0.45-0.40 (m, 1H), 0.25-0.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.9, 128.5, 128.0, 127.1, 55.0, 32.1, 31.2, 29.8, 29.7, 29.6_2, 29.5_5, 29.5_0, 29.3, 29.1, 22.8, 17.4, 14.3, 6.5, 4.9; HRMS(EI) m/z calcd. for $C_{22}H_{36}S$ [M^+]: 332.2538, found: 332.2544.

(1,1-Diphenylethyl)(dodecyl)sulfane (3ha): Purified by column chromatography using hexane/toluene=19:1 as an eluant; 65% yield (50 mg); a colorless oil; IR (NaCl): 2925, 2854 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.07 (s, 3H), 1.42 (quint, *J* = 7.5 Hz, 2H), 1.31-1.19 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.6, 128.1, 128.0, 126.6, 56.1, 32.1, 30.7, 30.3, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 22.8, 14.3; HRMS(EI) m/z calcd. for $C_{26}H_{38}S$ [M^+]: 382.2694, found: 382.2693.

Dodecyl(3-phenylcyclohex-2-enyl)sulfane (3ia): Purified by column chromatography using hexane/toluene=19:1 as an eluant; 75% yield (57 mg); a colorless oil; IR (NaCl): 2924, 2854 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40-7.38 (m, 2H), 7.33-7.29 (m, 2H), 7.26-7.22 (m, 1H), 6.12-6.11 (m, 1H), 3.58-3.54 (m, 1H), 2.64-2.55 (m, 2H), 2.44-2.41 (m, 2H), 2.05-1.98 (m, 2H), 1.85-1.73 (m, 2H), 1.64-1.58 (m, 2H), 1.41-1.36 (m, 2H), 1.28-1.26 (m, 16H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.9, 139.0, 128.4, 127.3, 125.4, 125.3, 41.7, 32.1, 31.3, 30.2, 29.8_2, 29.7_9, 29.7_6, 29.6_9, 29.5, 29.4, 29.2_9, 29.2_5, 27.5, 22.9, 20.5, 14.3; HRMS(EI) m/z calcd. for $C_{24}H_{38}S$ [M^+]: 358.2694, found: 358.2689.

(*E*)-Dodecyl(4-phenylbut-3-en-2-yl)sulfane (3ja): Purified by column chromatography using hexane/toluene=19:1 as an eluant; 85% yield (57 mg); a colorless oil; IR (NaCl): 2924, 2854, 1448, 962 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.37 (m, 2H), 7.33-7.30 (m, 2H), 7.25-7.21 (m, 1H), 6.35 (d, *J* = 15.5 Hz, 1H), 6.06 (dd, *J* = 15.5, 9.0 Hz, 1H), 3.50 (dq, *J* = 9.0, 7.0 Hz, 1H), 2.53-2.38 (m, 2H), 1.60-1.51 (m, 2H), 1.45-1.17 (m, 18H), 1.41 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.9, 132.8, 129.3, 128.7, 127.6, 126.4, 42.7, 32.1, 31.0, 29.8_4, 29.7_9, 29.7_5, 29.6_7, 29.5, 29.4, 29.2, 22.8, 20.8, 14.3; HRMS(EI) m/z calcd. for $C_{22}H_{36}S$ [M^+]: 332.2538, found: 332.2538.

(*E*)-Dodecyl(4-(4-methoxyphenyl)but-3-en-2-yl)sulfane (3ka): Purified by column chromatography using hexane/EtOAc=50:1 as an eluant; 69% yield (71 mg); a colorless oil; IR (NaCl): 2955, 2854, 1608,

1250, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.29 (d, *J* = 15.5 Hz 1H), 5.91 (dd, *J* = 15.5, 9.0 Hz, 1H), 3.81 (s, 3H), 3.48 (dq, *J* = 9.0, 7.0 Hz, 1H), 2.51-2.38 (m, 2H), 1.62-1.49 (m, 2H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.37-1.23 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 130.6, 129.6, 128.8, 127.5, 114.1, 55.4, 42.8, 32.0, 30.9, 29.8, 29.7_4, 29.7_0, 29.6, 29.4_4, 29.3_7, 29.1, 22.8, 20.9, 14.2; HRMS(EI) m/z calcd. for $C_{23}H_{38}OS$ [M^+]: 362.2643, found: 362.2646.

(4-(*tert*-Butyl)phenyl)(1-(4-methoxyphenyl)ethyl)sulfane (3ab): Purified by column chromatography using hexane/EtOAc=49:1 as an eluant; 88% yield (87 mg); a colorless oil; IR (NaCl): 2963, 1248, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.29-7.24 (m, 6H), 6.84 (d, *J* = 9.0 Hz, 2H), 4.30 (q, *J* = 7.0 Hz 1H), 3.80 (s, 3H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.7, 150.5, 135.5, 132.6, 131.9, 128.5, 125.9, 113.8, 55.4, 47.6, 34.6, 31.4, 22.6; HRMS(EI) m/z: calcd. for $C_{19}H_{24}OS$ [M^+]: 300.1548, found: 300.1544.

3-((1-(4-Methoxyphenyl)ethyl)thio)propanoic acid (3ac): Purified by column chromatography using hexane/EtOAc/AcOH=80:19:1 as an eluant; 88% yield (50 mg); a colorless oil; IR (NaCl): 1710, 1248, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 11.27 (bs, 1H), 7.26 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.96 (q, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 2.57-2.48 (m, 4H), 1.54 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.2, 158.8, 135.6, 128.4, 114.0, 55.4, 43.8, 34.5, 25.9, 22.7; HRMS(EI) m/z calcd. for $C_{12}H_{16}O_3S$ [M^+]: 240.0820, found: 240.0817.

3-(1-(4-Methoxyphenyl)ethyl)-1-methyl-1*H*-indole (9): Purified by column chromatography using hexane/EtOAc=19:1 as an eluant; 94% yield (49 mg); colorless oil; IR (NaCl): 1510 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ = 7.30 (t, *J* = 7.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.11-7.07 (m, 2H), 6.89 (t, *J* = 7.0 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.30 (q, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 1.63 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ = 158.8, 140.2, 138.4, 129.0, 128.2, 126.7, 122.0, 120.7, 120.3, 119.1, 114.3, 110.0, 55.4, 36.8, 32.7, 23.1; HRMS(EI) m/z calcd. for $C_{18}H_{19}NO$ [M^+]: 265.1467, found: 265. 1465.

1,3,5-Trimethoxy-2-(1-(4-methoxyphenyl)ethyl)benzene (11): Purified by column chromatography using hexane/EtOAc=19:1 as an eluant; 89% yield (53 mg); a colorless oil; IR (NaCl): 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.12 (s, 2H), 4.69 (q, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.70 (s, 6H), 1.62 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.4, 159.1, 157.1, 138.9, 128.3, 116.1, 113.0, 91.5, 55.9, 55.4, 55.3, 32.4, 18.2; HRMS(EI) m/z calcd. for $C_{18}H_{22}O_4$ [M^+]: 302.1518, found: 302.1512.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the JSPS KAKENHI (18H02556 and 20K22542) and Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number 21am0101084. We thank Taiyo Kagaku Co. Ltd., for kindly providing mesoporous silica. High-resolution mass spectrometry analysis was supported by the Analytical Instrumentation Facility, Graduate School of Engineering, Osaka University.

Keywords: oxovanadium • heterogeneous catalysis • mesoporous silica • nucleophilic substitution • thioethers

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Supporting information

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1. General information

Infrared (IR) absorption spectra were recorded on a SHIMADZU IRAffinity-1S spectrophotometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on a JEOL JNM-ECA500 (^{1}H: 500 MHz, ^{13}C: 125 MHz, ^{19}F: 470 MHz) and a JEOL JMN-ECS400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) instruments. Chemical shifts were reported in δ (ppm) relative to the deuterated solvents. The high-resolution mass spectra (HRMS) were measured on a JEOL JMS-700EI instrument at the Analytical Instrumentation Facility, Graduate School of Engineering, Osaka University. Reagents were purchased from Tokyo Chemical Industry Co., Ltd., Sigma-Aldrich Co., LLC, and FUJIFILM Wako Chemical Co., Ltd. Flash chromatography was performed on silica gel 60N (particle size 40–50 μm) purchased from Kanto Chemical Co., Inc. Unless otherwise noted, the reactions were carried out in anhydrous solvents under argon atmosphere. Mesoporous silica (TMPS-4R) was kindly supplied by Taiyo Kagaku Co., Ltd. (Tokyo, Japan).

2. Preparation of VMPS4

2.1 Preparation of $VO(OSiPh_3)_3$

$VO(OSiPh_3)_3$ was prepared according to the literature method.[1] In brief, Ph_3SiOH (1.82 g, 123 mmol) was weighted in a two-neck flask (1 L) and the atmosphere was replaced with argon. Dry toluene (200 mL) was added to the flask, followed by $VO(O^iPr)_3$ (5.1 mL, 41 mmol), and the resultant mixture was refluxed for 4 h using a Dean Stark apparatus. After that, toluene was removed under reduced pressure. The residue was further dried in vacuo to afford $VO(OSiPh_3)_3$ (19.7 g, 54%), which was used in the next reaction without any purification.

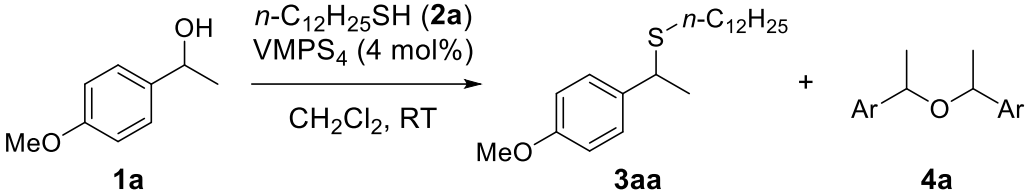
2.2 Preparation of VMPS4

VMPS4 was prepared according to the literature method with a small modification.[1] In brief, mesoporous silica (10.0 g, TMPS-4R supplied by Taiyo Kagaku Co., Ltd., Tokyo, Japan) was placed in a two-neck flask (1 L) and dried overnight at 150°C in vacuo. The flask was then allowed to cool to room temperature under argon atmosphere. To the flask, $VO(OSiPh_3)_3$ (10.7 g, 12.0 mmol) was added, followed by anhydrous benzene (800 mL, 0.015 M). The resultant mixture was refluxed at 100 °C for 8 h. After that, benzene was removed under reduced pressure. The residue was divided into 5-g batches in 50-mL glass centrifuging tubes equipped with a rubber septum. Each batch was suspended in hexane/CH_2Cl_2 (2:3 ratio, 30 mL) and centrifuged (3000*g*, 5 min). After removing the supernatant by cannulation, the suspending/centrifuging process was repeated four more times. After that, each precipitate was dried overnight in vacuo at room temperature to afford VMPS4. The vanadium content of the as-prepared VMPS4 was 0.22 mmol/g, which was determined by inductively coupled plasma-atomic emission spectrometry (ICP-AES). A detailed characterization of VMPS4 was reported previously.[1]

Although benzene was used for the reaction of $VO(OSiPh_3)_3$ with mesoporous silica according

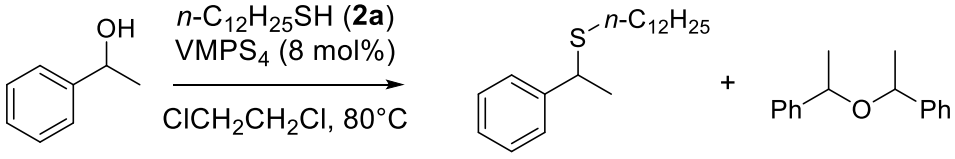
to the previous reports,[1] the same step can be conducted using toluene as an alternative solvent at 80 °C for 8 h. The VMPS4 prepared in toluene showed compatible catalytic activities in the nucleophilic substitution reactions (Scheme S1).

Scheme S1. VMPS4-catalyzed thioetherification of benzyl alcohols



1a **3aa** **4a**

VMPS4 prepared in toluene	97%	3%
Table 1, Entry 8	99%	trace



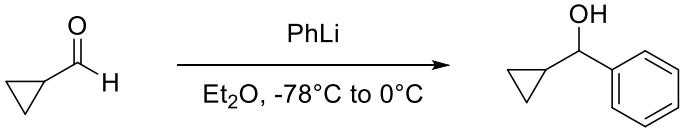
1b **3ba** **4b**

VMPS4 prepared in toluene	64%	nd
Scheme 1	58%	7%

3. Substrate syntheses

Alcohols **1i**[2], **1j**[3], and **1k**[4] were synthesized according to the literature methods. The known alcohols **1g** and **1h** were synthesized as follows.

Cyclopropyl(phenyl)methanol (1g)

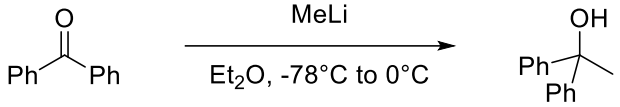


1g

Under argon atmosphere, PhLi (2.1 M in $^{n}Bu_2O$, 2.3 mL, 4.8 mmol) was added dropwise to a solution of cyclopropanecarbaldehyde (0.30 mL, 4.0 mmol) in Et_2O (10.0 mL, 0.4 M) at -78 °C. The resultant mixture was stirred at 0 °C for 1 h. After complete consumption of the starting material, the reaction was quenched with aq. NH_4Cl, and the product was extracted with EtOAc (x3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc=3:1) giving **1g** as a colorless oil (0.29 g, 49% yield). The ^1H NMR spectra were consistent with those in the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44-7.43 (m, 2H), 7.38-7.34 (m, 2H), 7.31-7.27 (m, 1H), 4.02 (d, *J* = 8.0 Hz, 1H), 1.95 (s, 1H), 1.27-1.20 (m, 1H), 0.68-0.62 (m, 1H), 0.59-0.53 (m, 1H), 0.51-0.46 (m, 1H), 0.41-0.36 (m, 1H).

1,1-Diphenylethan-1-ol (1h)



1h

Under argon atmosphere, MeLi (1.1 M in Et_2O, 5.5 mL, 6.0 mmol) was added dropwise to a solution of benzophenone (0.91 g, 5.0 mmol) in Et_2O (12.5 mL, 0.4 M) at -78 °C. The reaction mixture was stirred at 0 °C for 0.5 h. After complete consumption of the starting material, the reaction was quenched with aq. NH_4Cl, and the product was extracted with EtOAc (x3). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc=9:1) giving **1h** as a colorless crystal (0.98 g, 98% yield). The ^{1}H NMR spectra were consistent with those in the literature.[6]
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.24 (t, *J* = 7.5 Hz, 2H), 2.17 (s, 1H), 1.96 (s, 3H).

4. ^{1}H NMR spectra of crude products for entries 1 and 8 in Table 1.

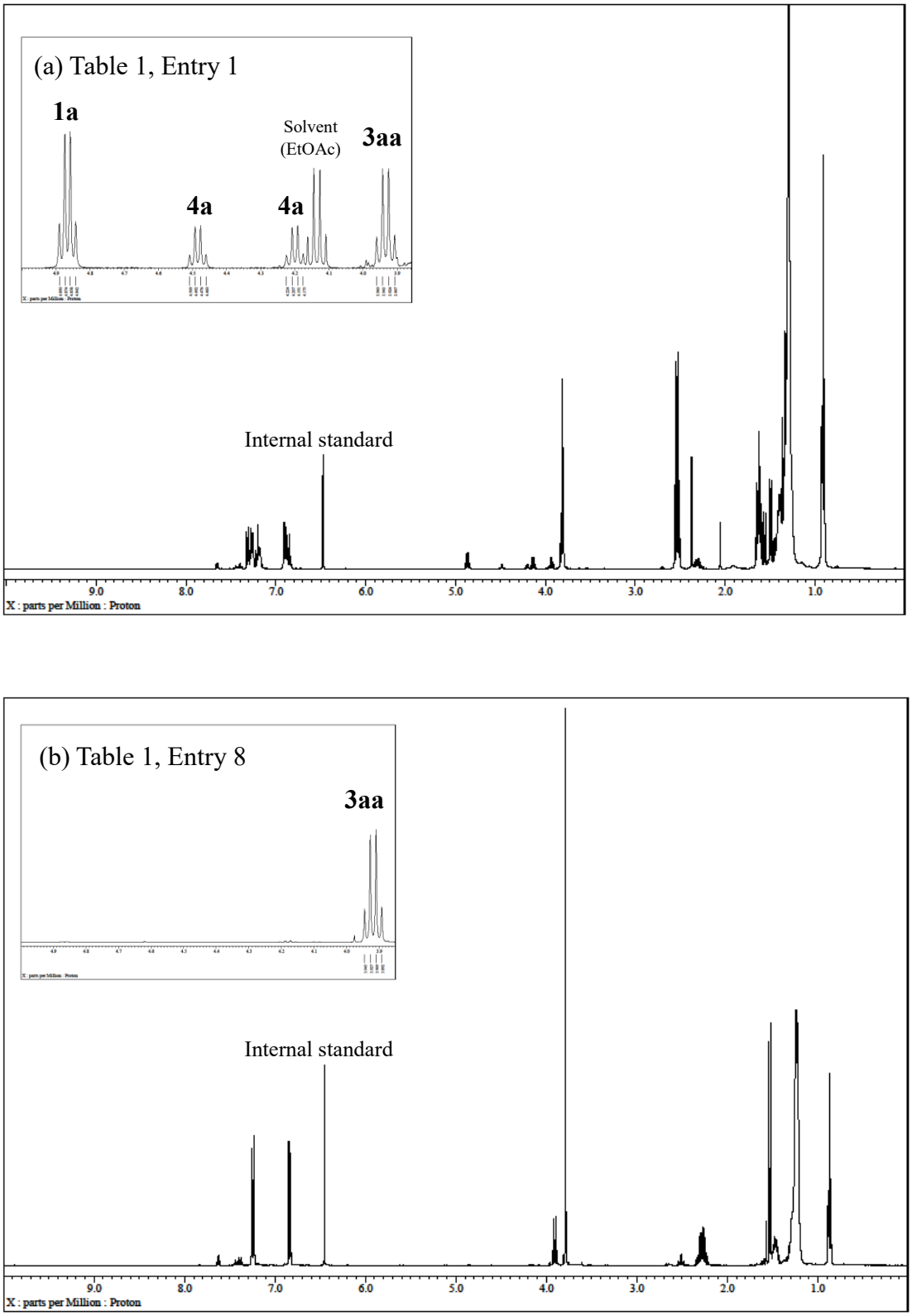


Figure S1. ^{1}H NMR spectra of crude products of VMPS4-catalyzed nucleophilic substitution of **1a** with **2a** (Table 1, Entries 1 and 8) with the internal standard: 1,1,2-trichloroethene.

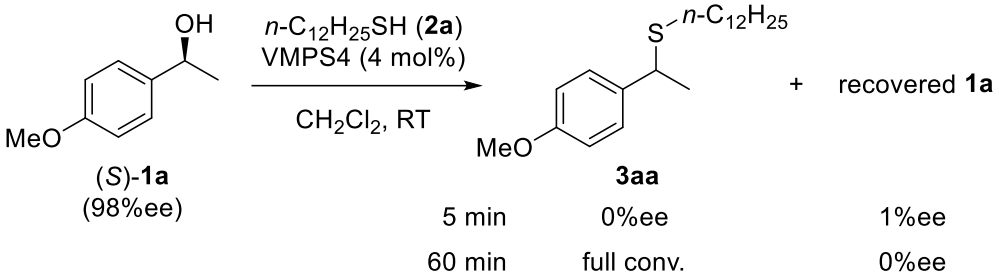
4,4'-(Oxybis(ethane-1,1-diyl))bis(methoxybenzene) (4a)[7]: ^{1}H NMR (500 MHz, $CDCl_3$) (1:1 mixture of diastereomer)

δ = 7.20 (d, *J* = 8.5 Hz, 4H), 6.90 (d, *J* = 8.5 Hz, 4H), 4.18 (q, *J* = 6.5 Hz, 2H), 3.82 (s, 6H), 1.35 (d, *J* = 6.5 Hz, 6H).

δ = 7.20 (d, *J* = 8.5 Hz, 4H), 6.83 (d, *J* = 8.5 Hz, 4H), 4.47 (q, *J* = 6.5 Hz, 2H), 3.79 (s, 6H), 1.43 (d, *J* = 6.5 Hz, 6H).

5. Plausible reaction mechanism

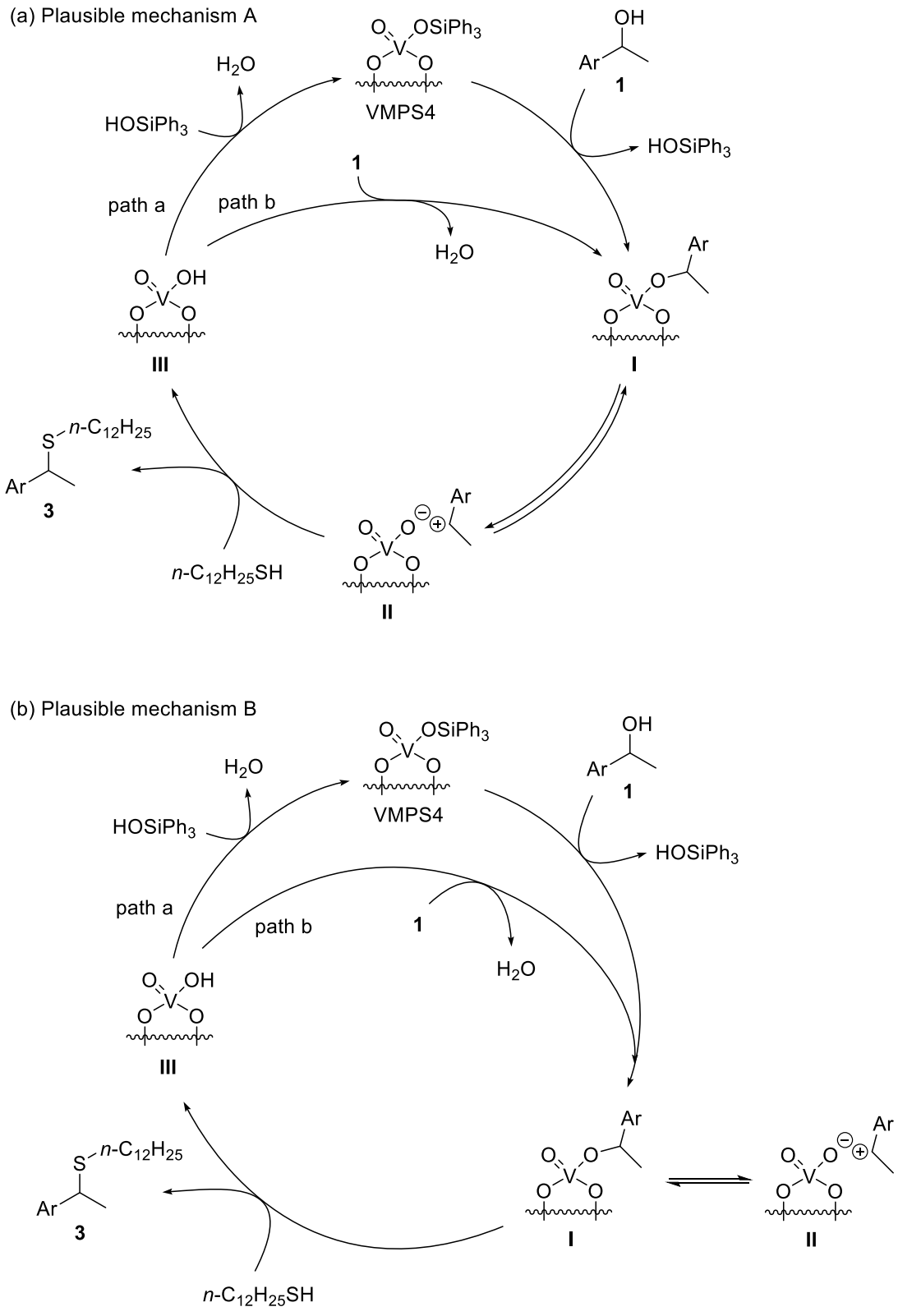
Scheme S2. VMPS4-catalyzed thioetherification of optically active (*S*)-**1a**[a]



[a] The optical purity was determined by chiral HPLC analysis.

Plausible mechanisms are shown in Scheme S3-(a). Thus, Alcohol **1** would react with VMPS4 to form **I** via a V–O bond formation, with concomitant release of Ph_3SiOH. C–O bond cleavage then generates benzyl cation intermediate **II**, followed by nucleophilic attack by thiol **2a** to afford **3**. The resultant intermediate **III** would then react with Ph_3SiOH to regenerate the catalyst (path a), or react with **1** to directly form intermediate **I** (path b). This reaction mechanism is supported by the fact that racemic product **3aa** was obtained from optically active (*S*)-**1a** (Scheme S2). In addition, the prominent substituent effects on the Ph group (Table 3, Entries 1–4) and high reactivity of tertiary alcohol **1h** (Table 3, Entry 6) also indicate the generation of benzyl cation in the reaction pathway. However, we currently do not excrude the possibility of an S_N-2 type mechanism in the reaction of **I** with **2a** (Scheme S3b), in which benzyl cation **II** is involved as an off-cycle intermediate in the racemization equilibrium.

Scheme S3. Plausible reaction mechanism (a) involving a benzyl cation in the catalytic cycle and (b) catalytic cycle involving the benzyl cation as an off-cycle intermediate.



6. Catalyst recycle experiment

To a 15-mL centrifuging tube, VMPS4 (66 mg, 4 mol%), CH_2Cl_2 (3.3 mL, 0.1 M), thiol **2a** (0.40 mmol) and alcohol **1a** (50 mg, 0.33 mmol) were added in this order. The reaction mixture was stirred at room temperature under argon atmosphere for 3 h. After that, the reaction mixture was centrifuged (3,000 rpm, 1 min) and the supernatant containing the product was collected by decantation. The precipitate was resuspended in EtOAc (2 mL), centrifuged, and the supernatant was removed by decantation. After this process was repeated twice, the precipitate was dried in vacuo for 30 min. The resultant precipitate was used for the next reaction cycle by adding CH_2Cl_2, **2a**, and **1a**. The combined supernatant was concentrated in vacuo to give the sulfide **3aa**, which was purified by column chromatography to obtain pure **3aa**.

Refarence

[1] (a) K. Sugiyama, Y. Oki, S. Kawanishi, K. Kato, T. Ikawa, M. Egi, S.Akai, *Catal. Sci. Technol.* **2016**, *6*, 5023–5030.

[2] S. Kawanishi, K. Sugiyama, Y. Oki, T. Ikawa, S. Akai, *Green Chem*. **2017**, *19*, 411–417.

[3] S. Gandomkar, E. Jost, D. Loidolt, A. Swoboda, M. Pickl, W. Elaily, B. Daniel, M. W. Fraaije, P. Macheroux, W. Kroutil, *Adv. Synth. Catal*. **2019**, *361*, 5264–5271.

[4] S. Akai, R. Hanada, N. Fujiwara, Y. Kita, M. Egi, *Org. Lett.* **2010**, *12,* 4900–4903.

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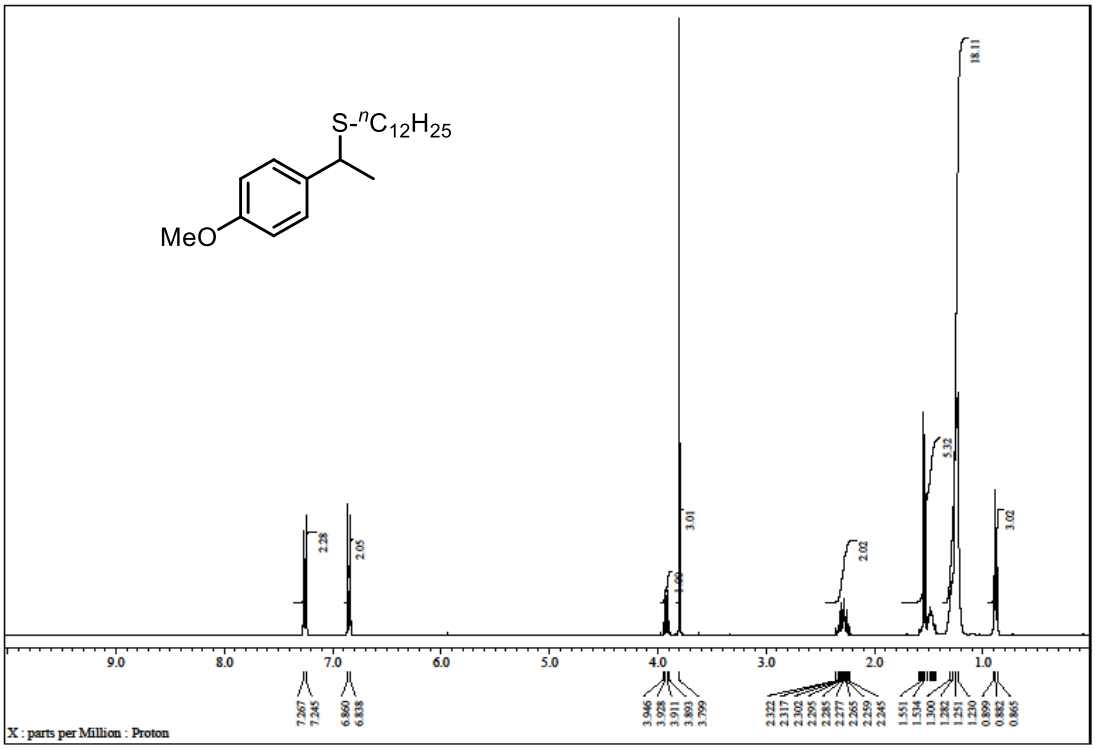
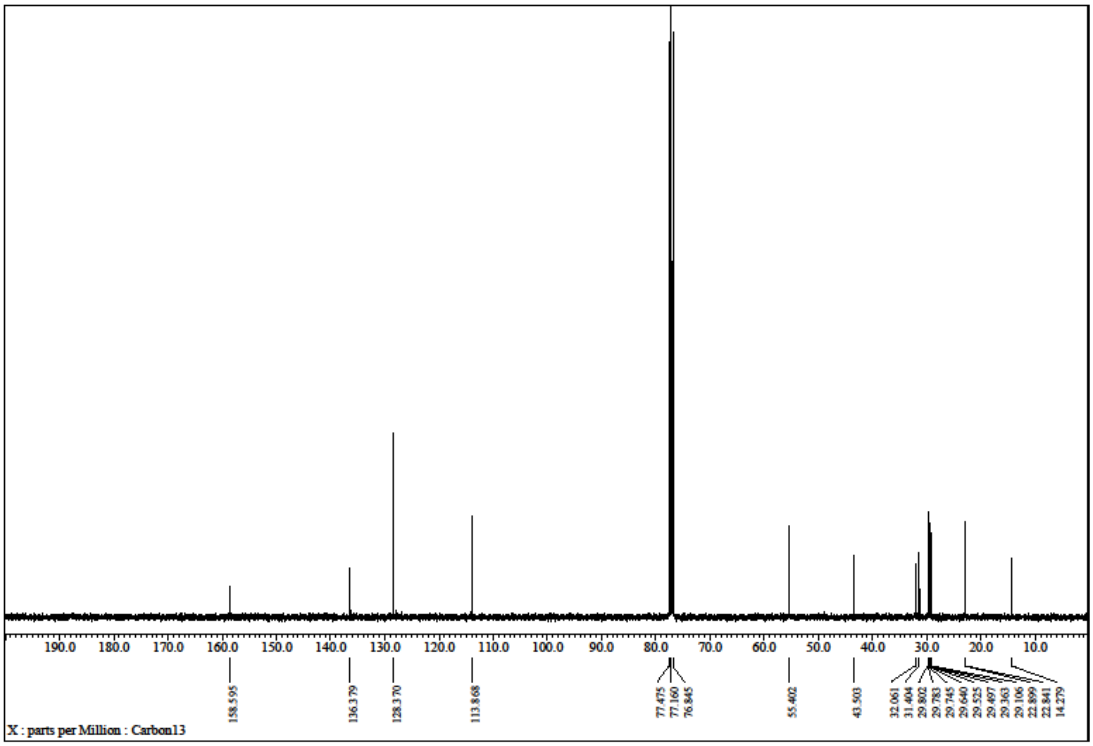
[7] M. Noji, Y. Konno, K. Ishii, *J. Org. Chem.* **2007**, *72*, 5161–5167.

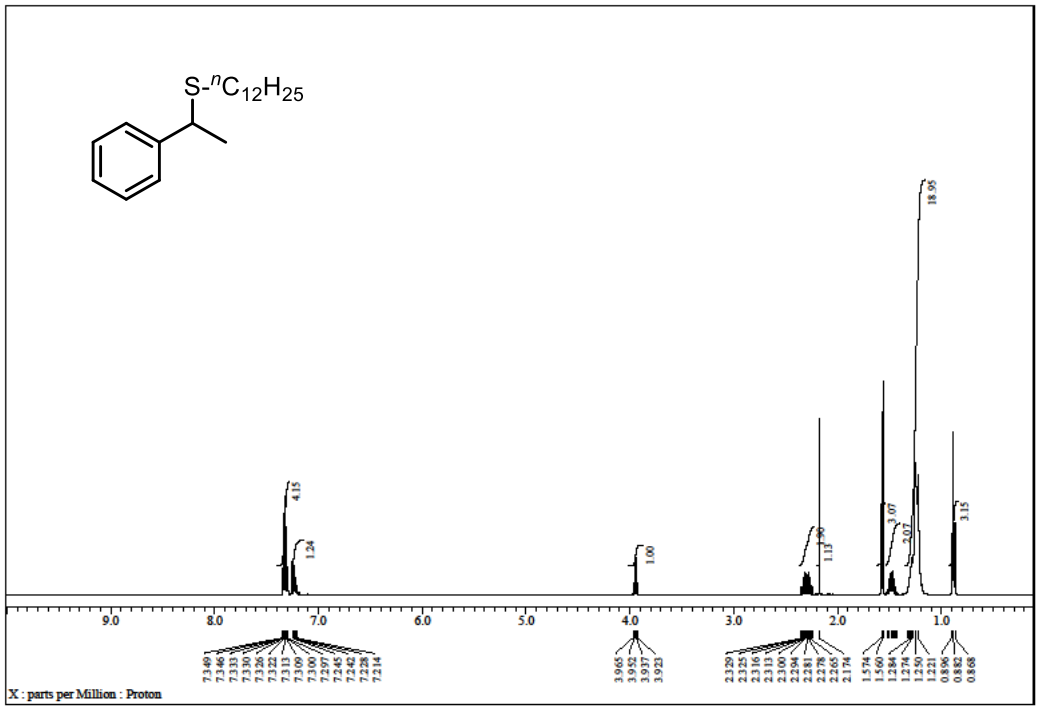
7. Spectra data

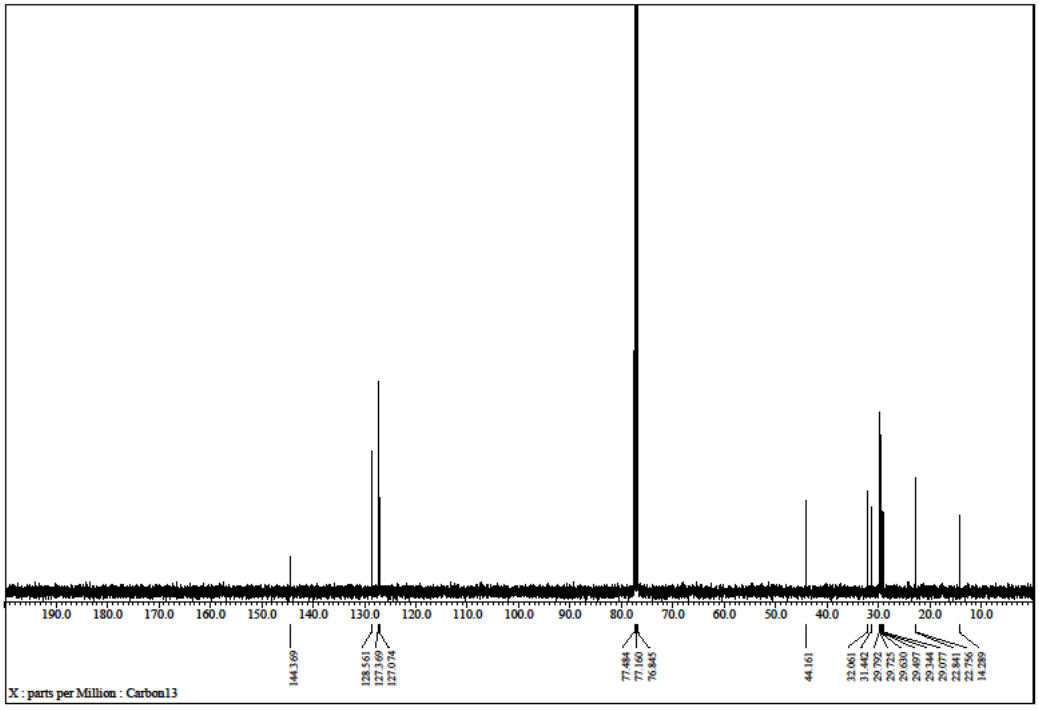
Dodecyl(1-(4-methoxyphenyl)ethyl)sulfane (3aa)



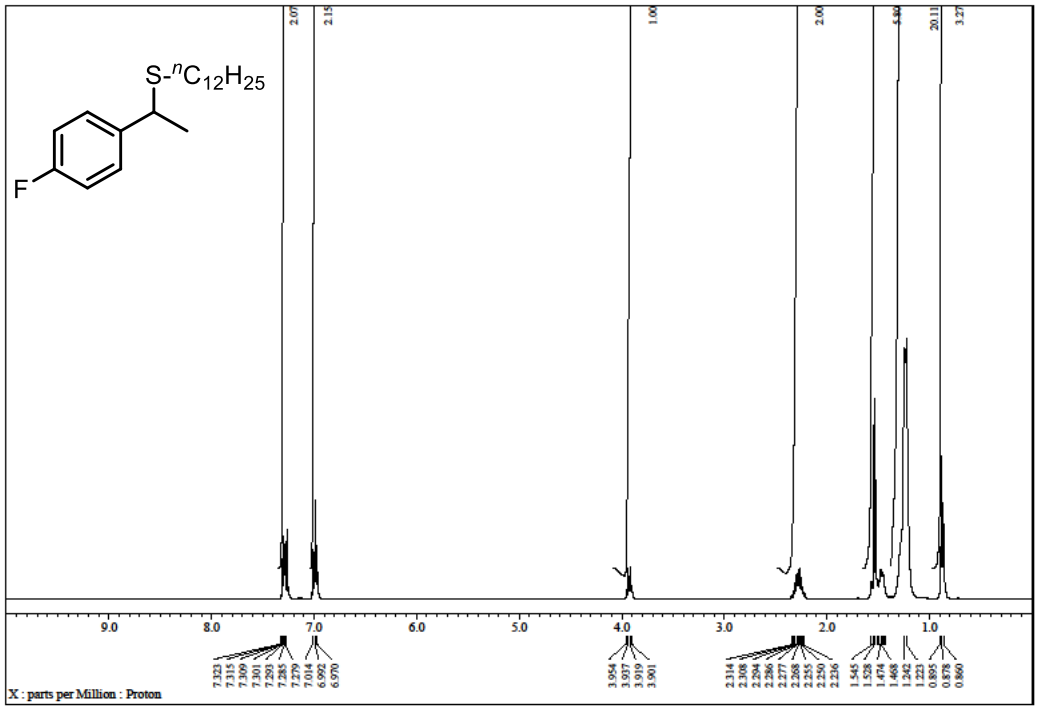


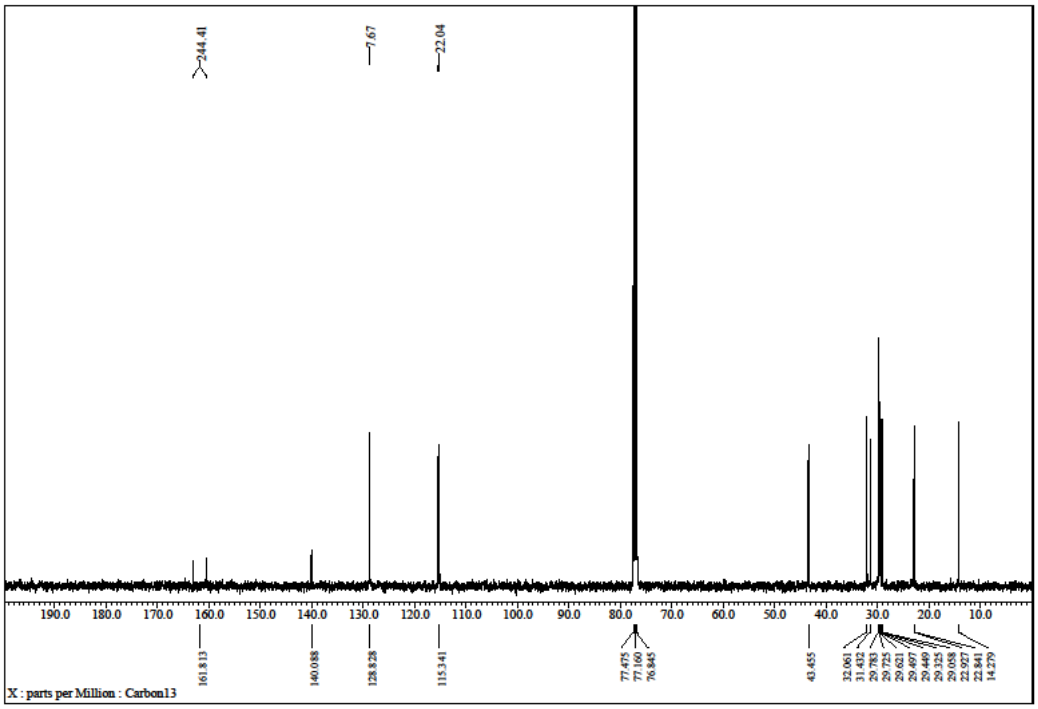
Dodecyl(1-phenylethyl)sulfane (3ba)



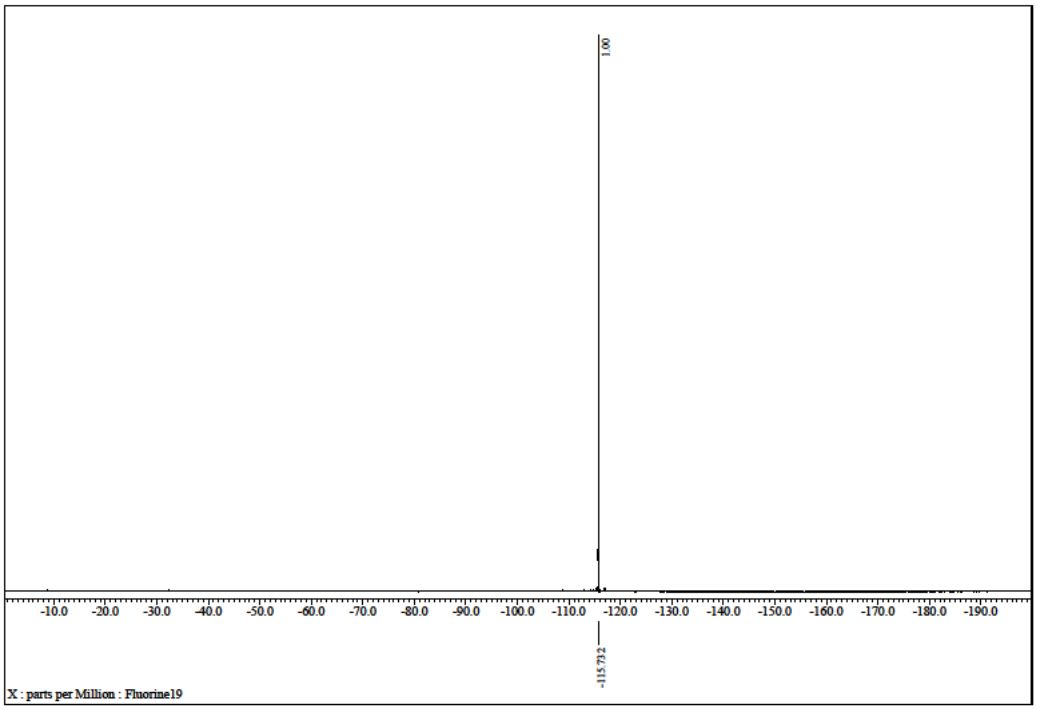


Dodecyl(1-(4-fluorophenyl)ethyl)sulfane (3ca)

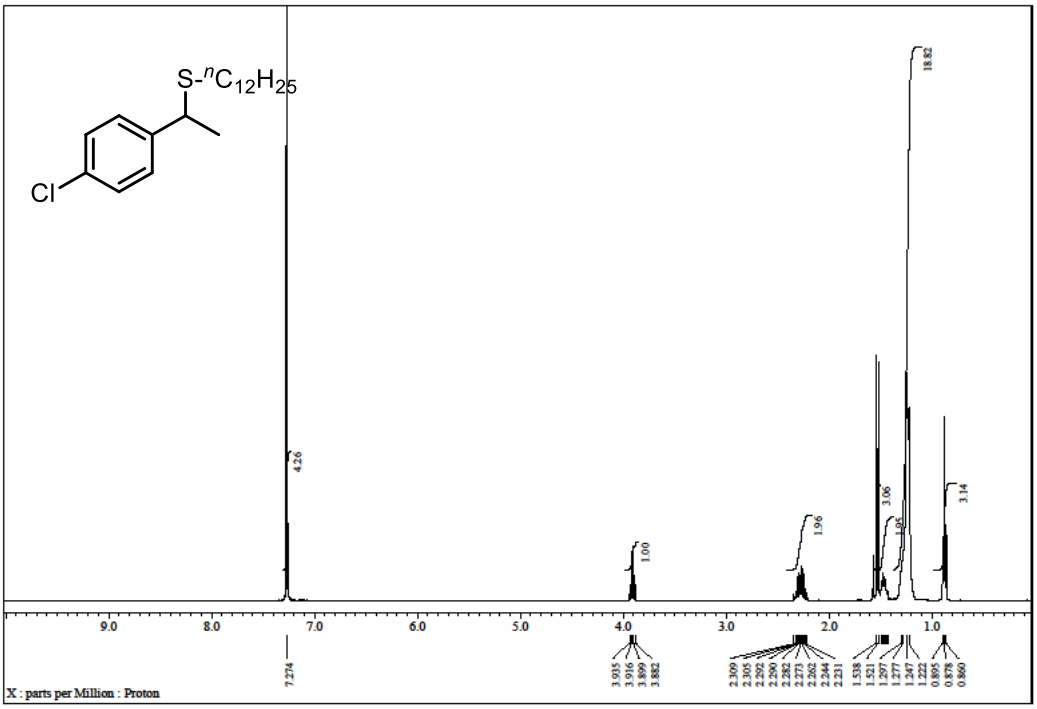


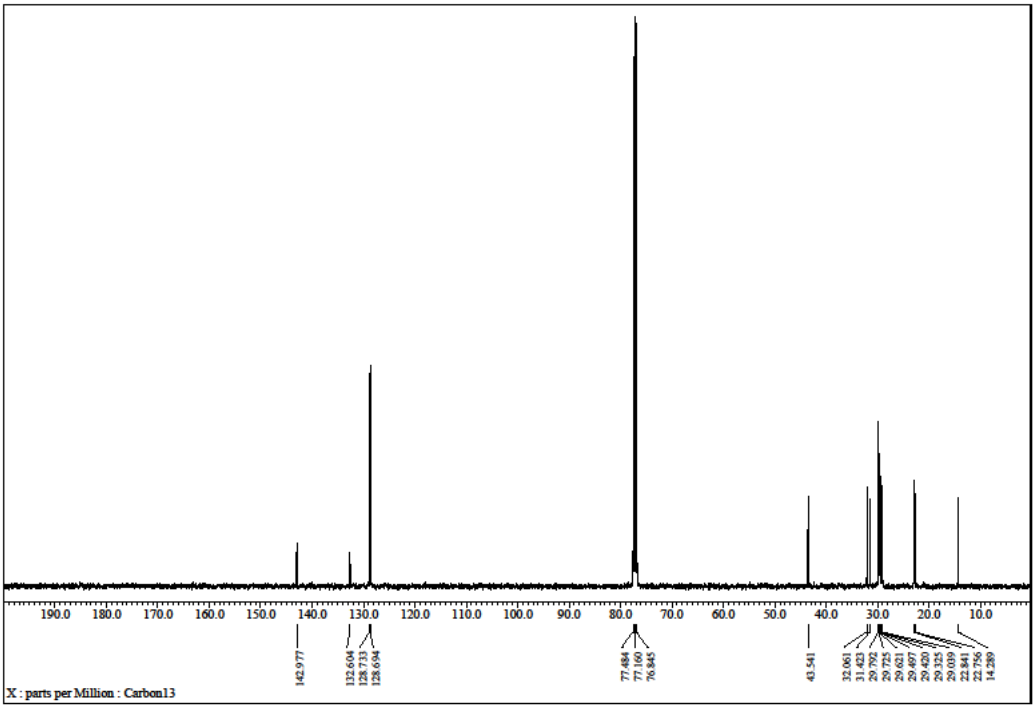


^{19}F NMR

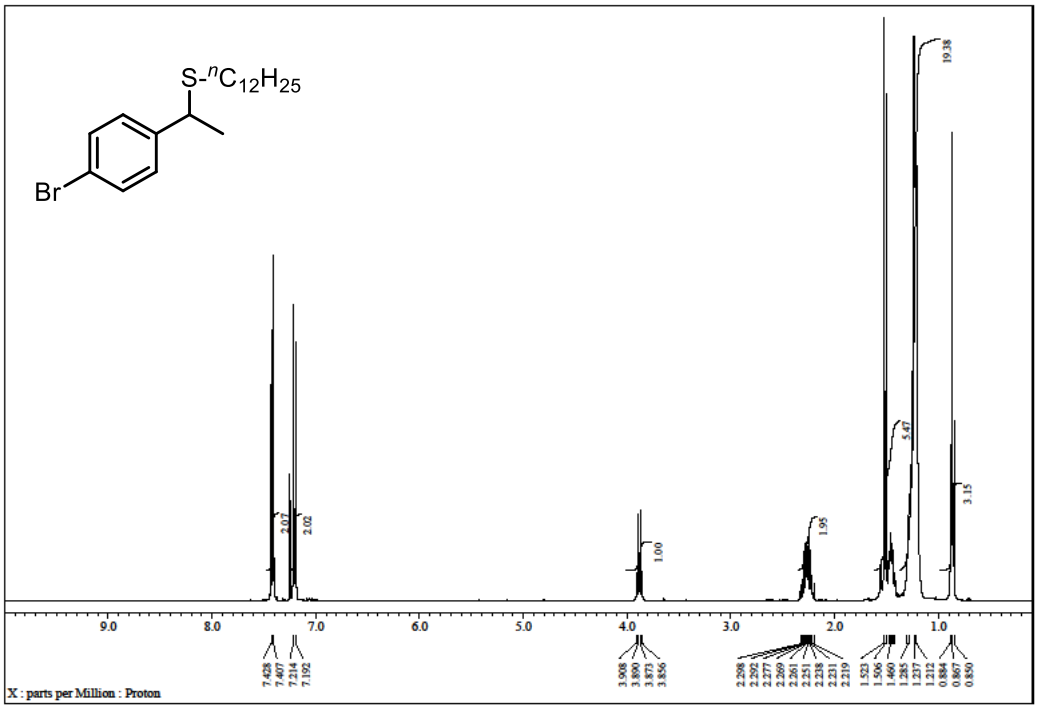

1.00
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-180.0
-190.0
-115.752
X : parts per Million : Fluorine19

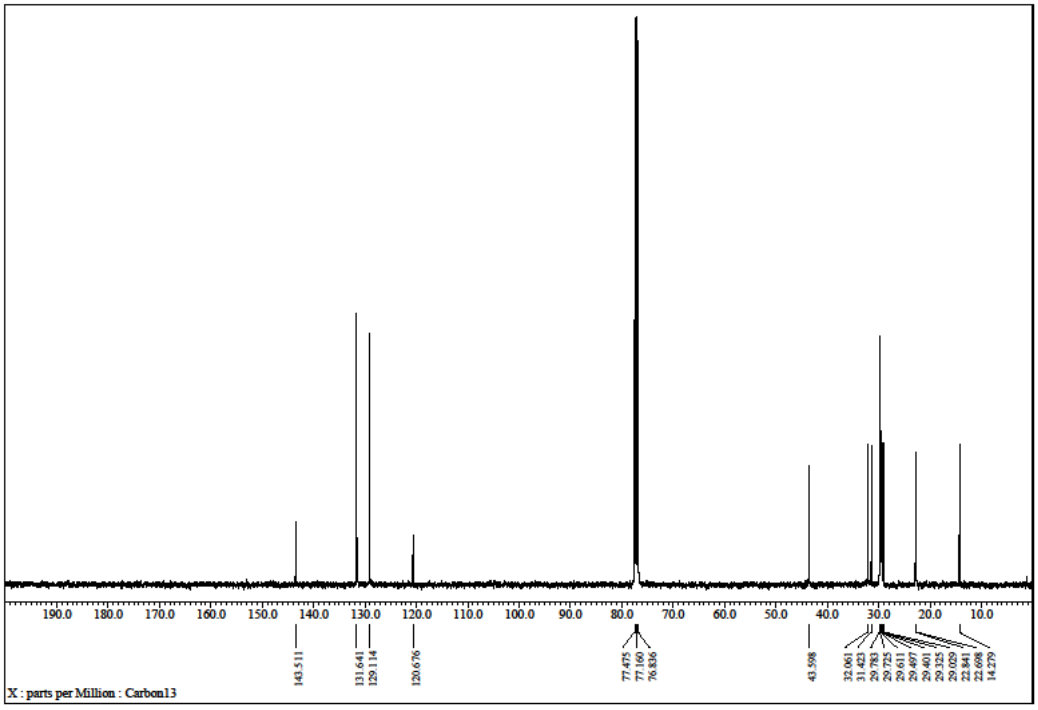
(1-(4-Chlorophenyl)ethyl)(dodecyl)sulfane (3da)



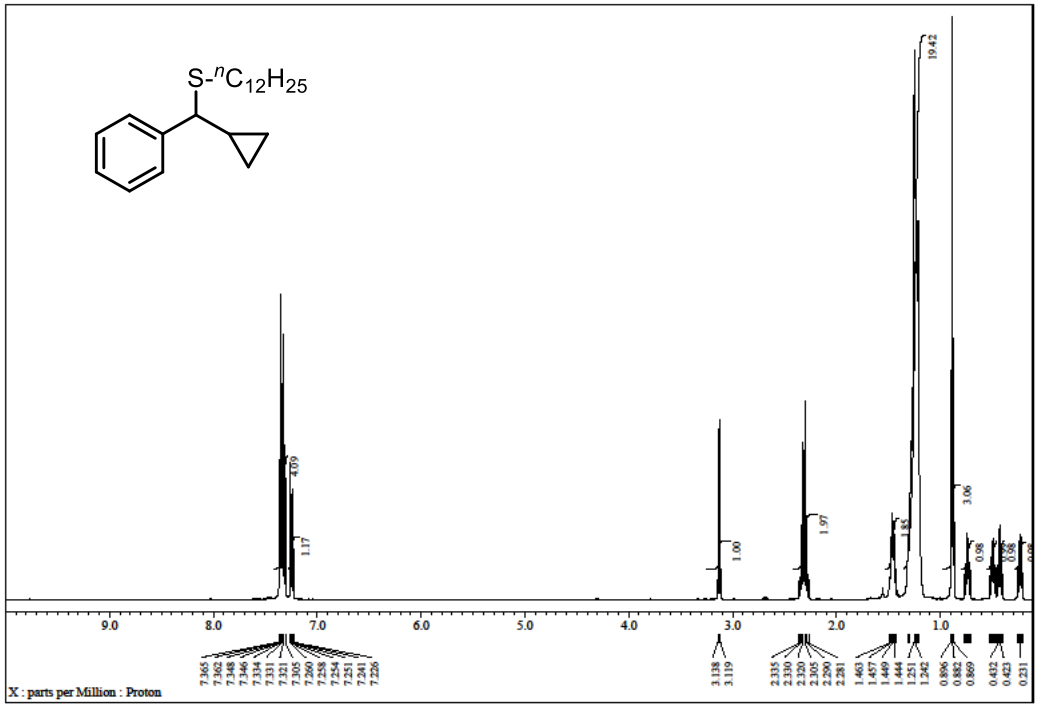


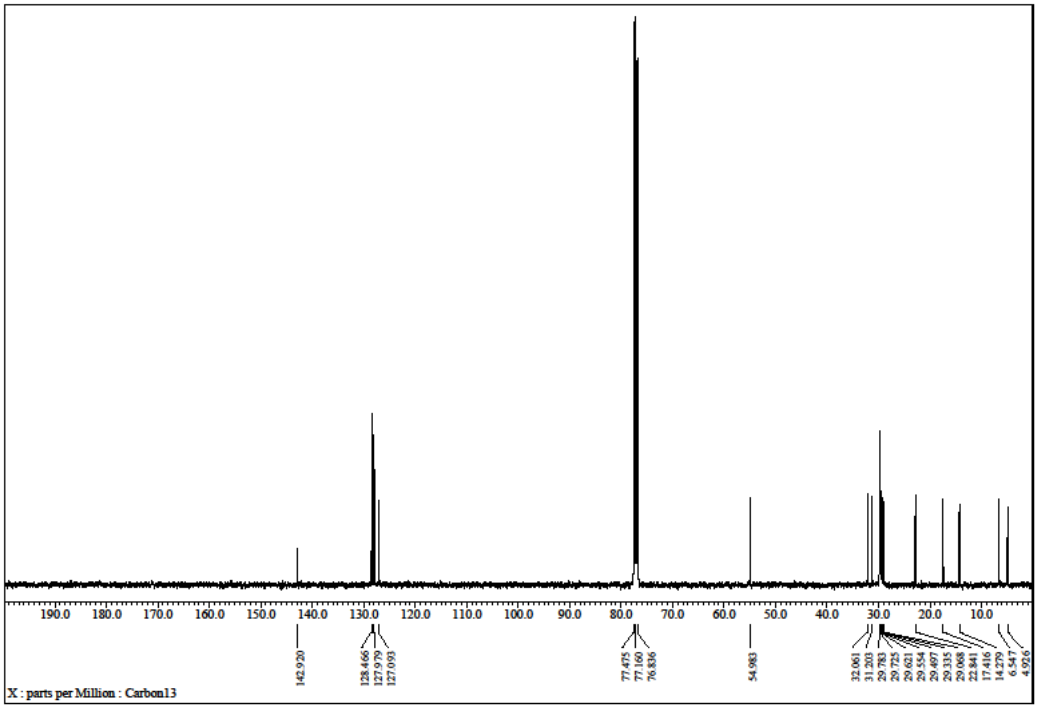
(1-(4-Bromophenyl)ethyl)(dodecyl)sulfane (3ea)



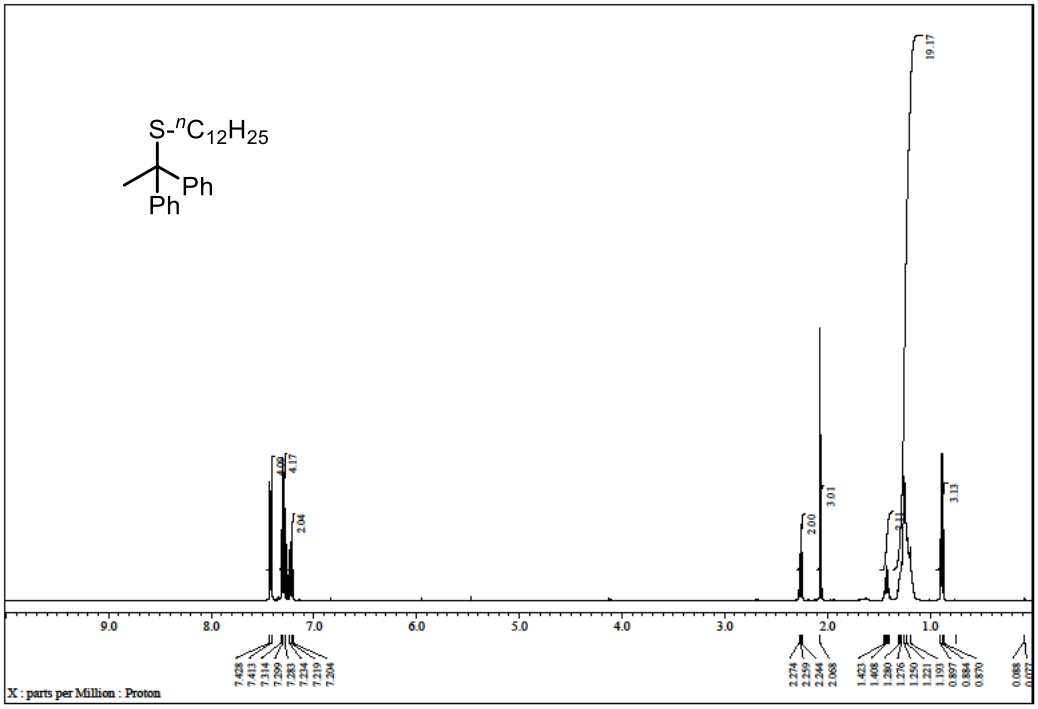


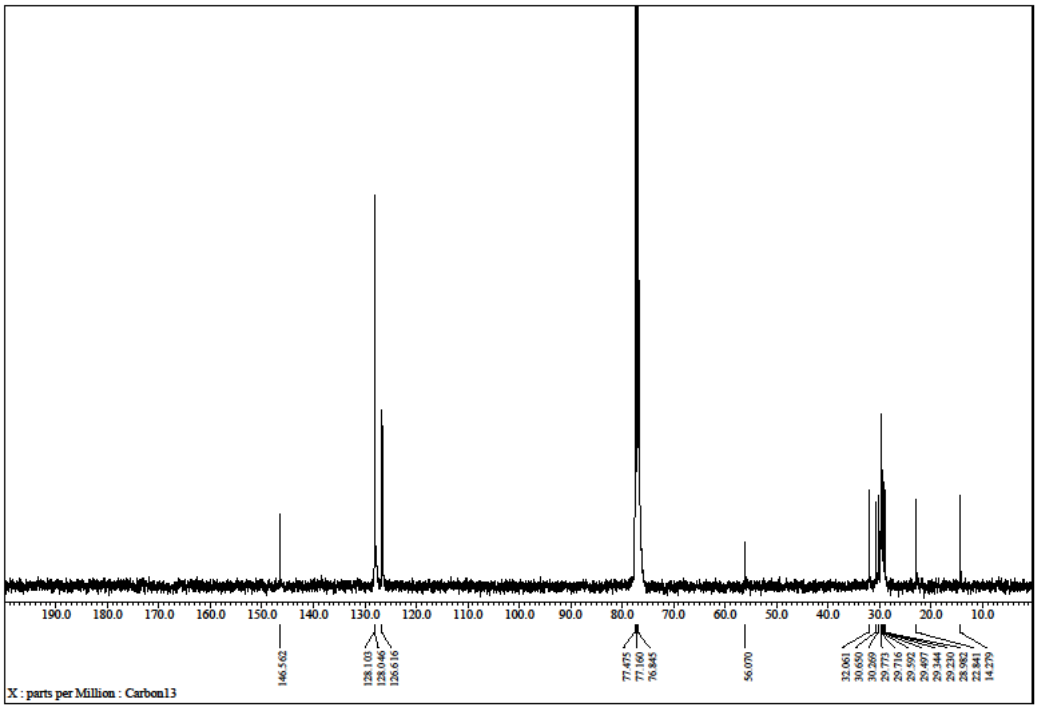
(Cyclopropyl(phenyl)methyl)(dodecyl)sulfane (3ga)



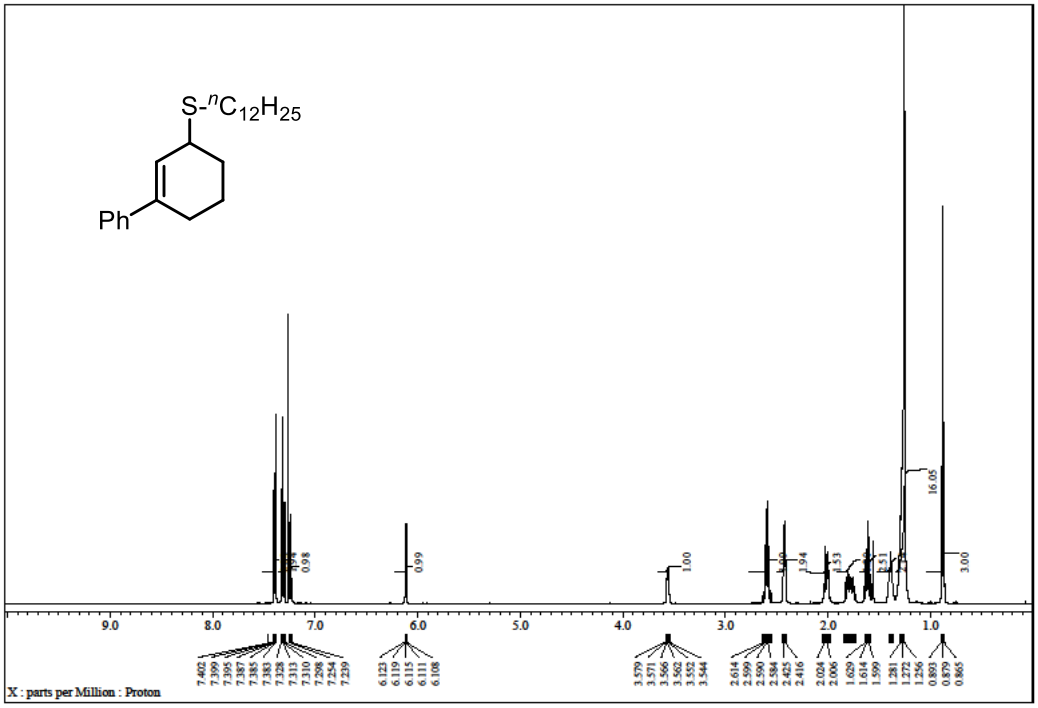


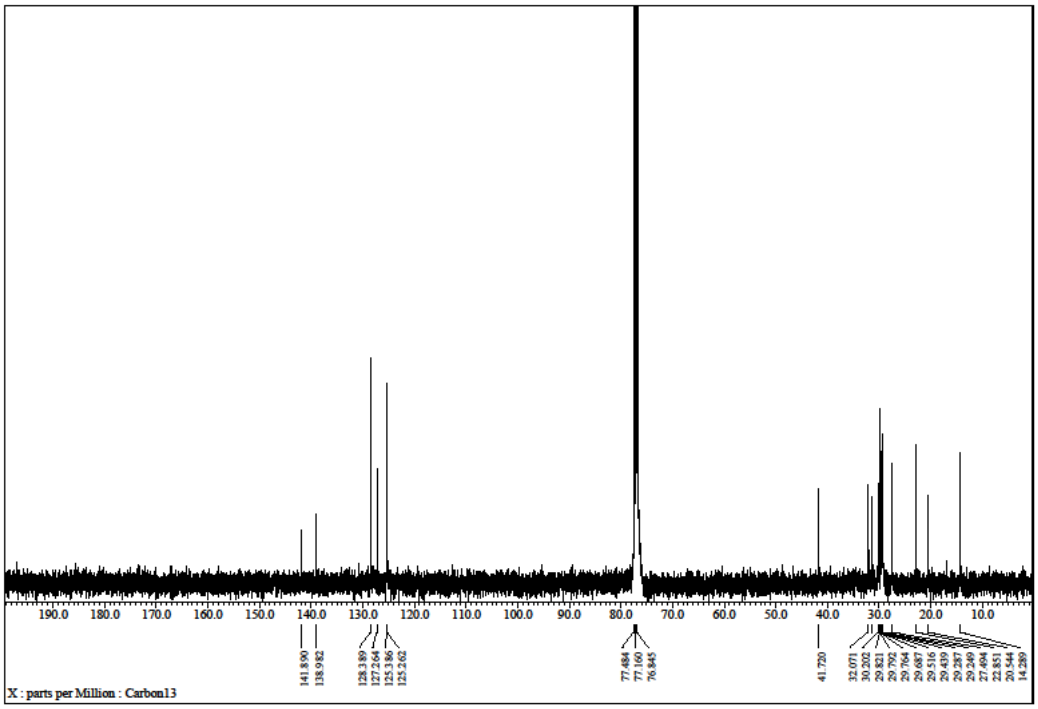
(1,1-Diphenylethyl)(dodecyl)sulfane (3ha)



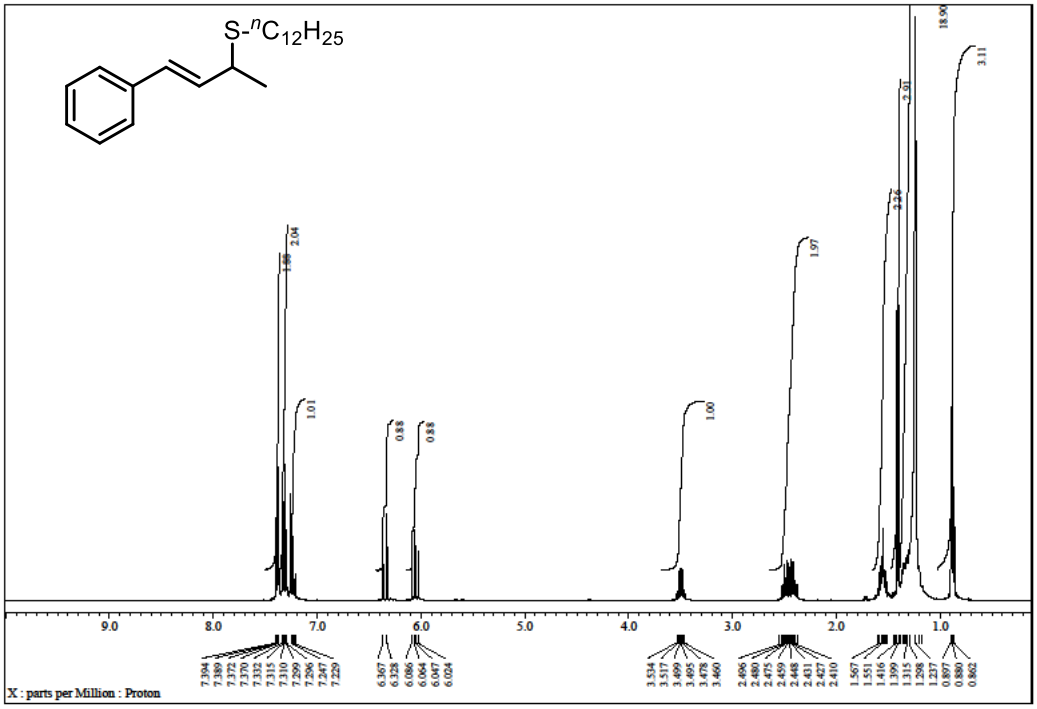


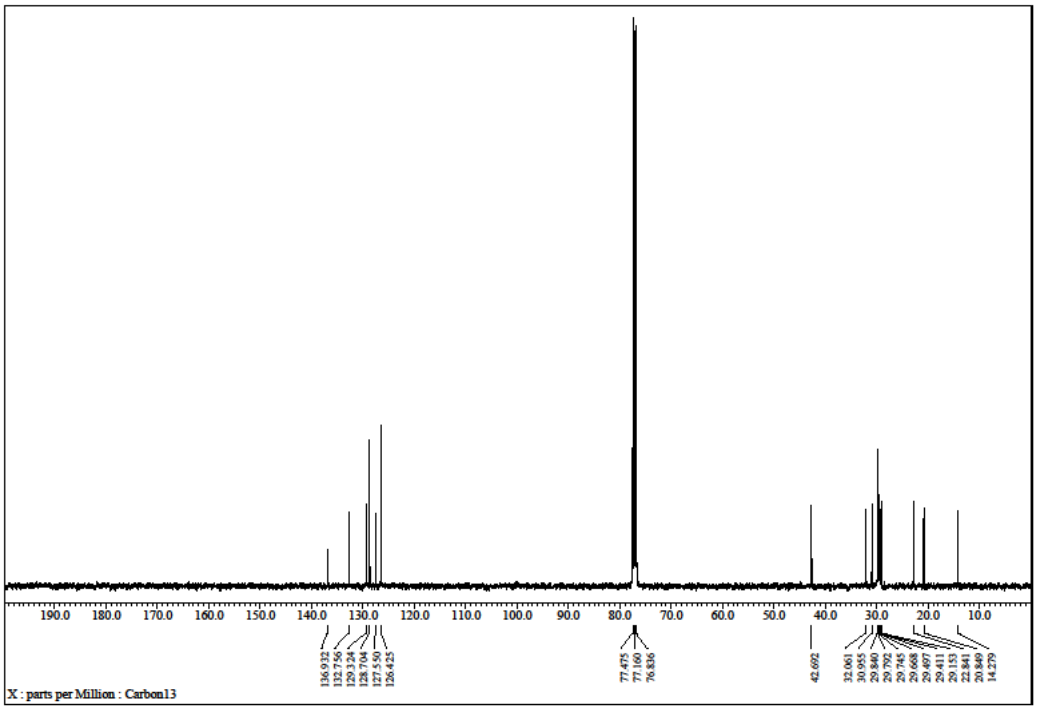
Dodecyl(3-phenylcyclohex-2-enyl)sulfane (3ia)



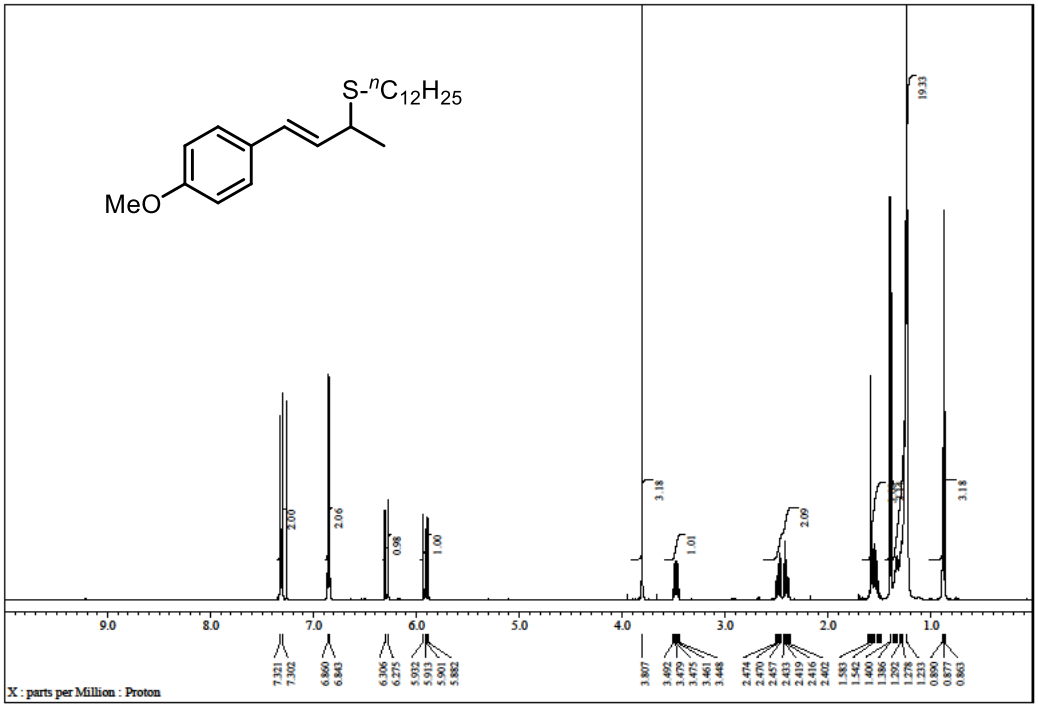


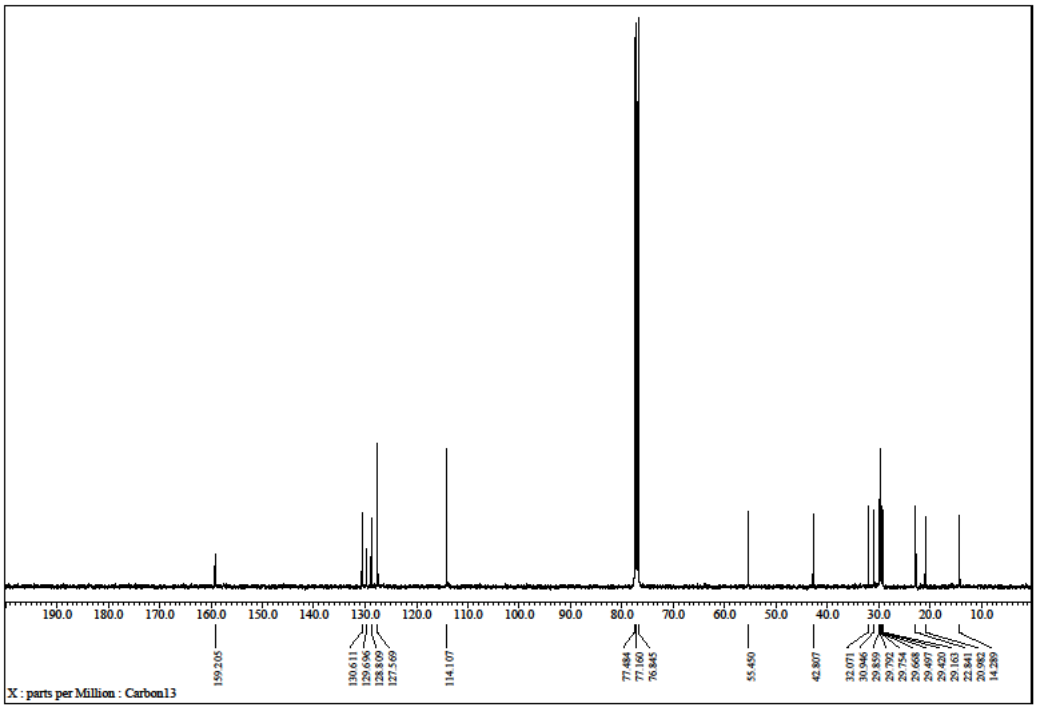
(*E*)-Dodecyl(4-phenylbut-3-en-2-yl)sulfane (3ja)



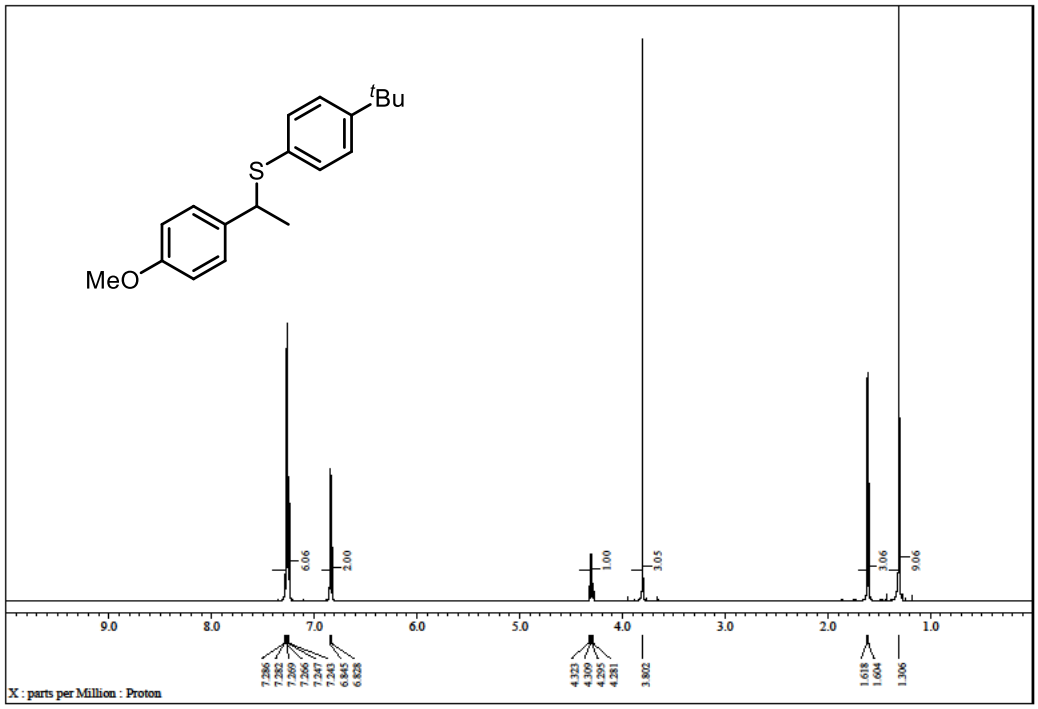


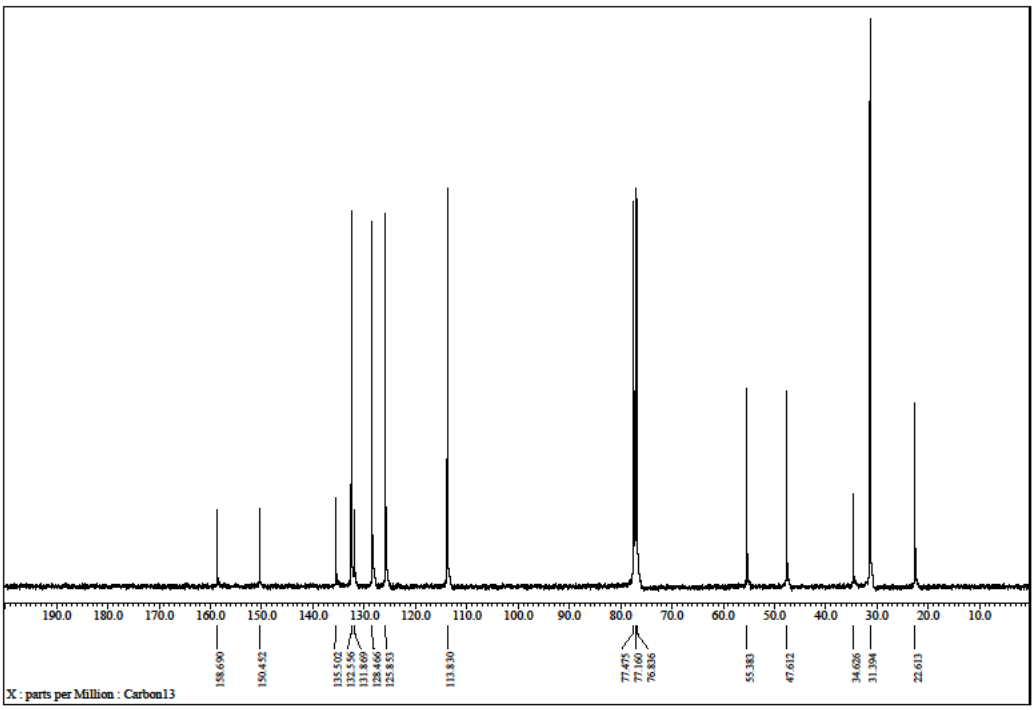
(*E*)-Dodecyl(4-(4-methoxyphenyl)but-3-en-2-yl)sulfane (3ka)



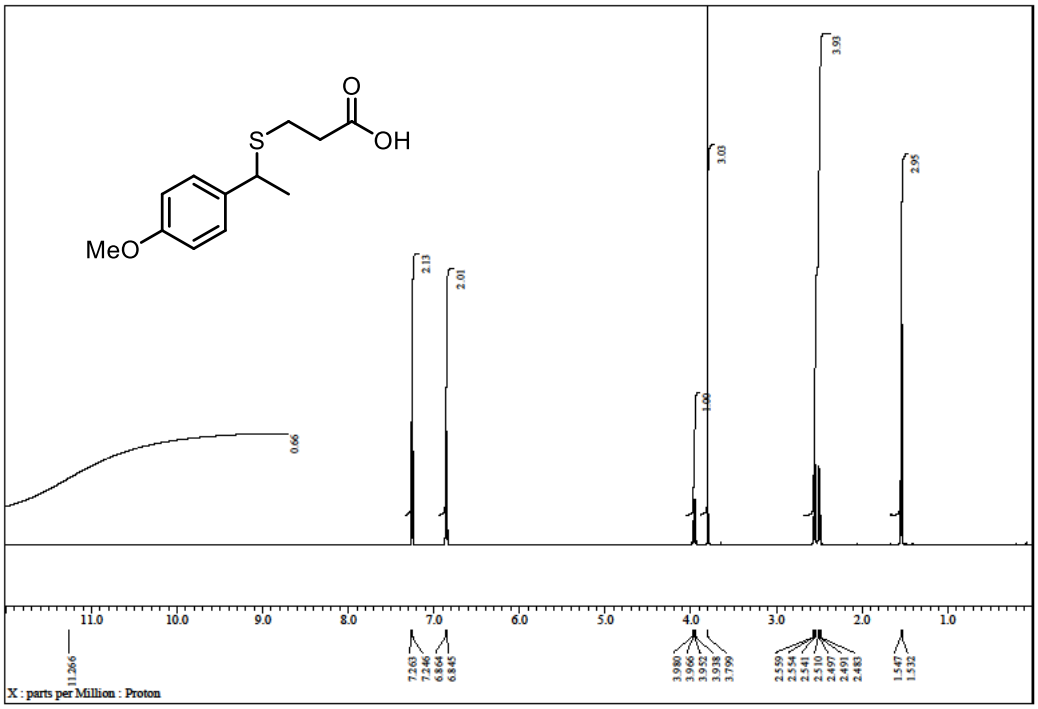


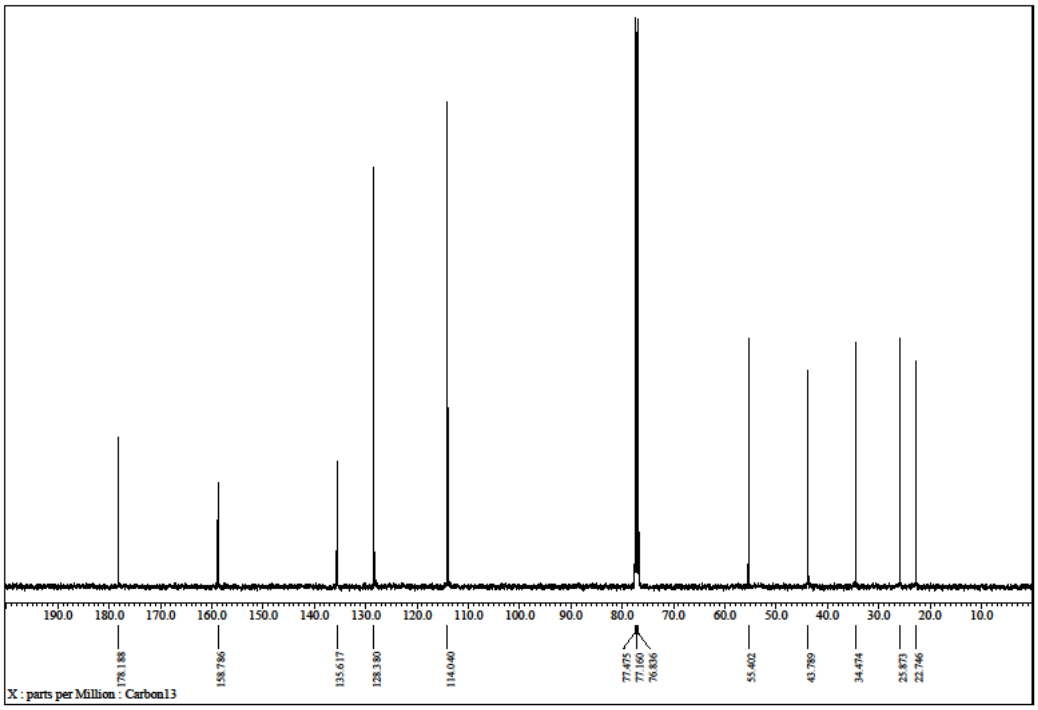
(4-(*tert*-Butyl)phenyl)(1-(4-methoxyphenyl)ethyl)sulfane (3ab)



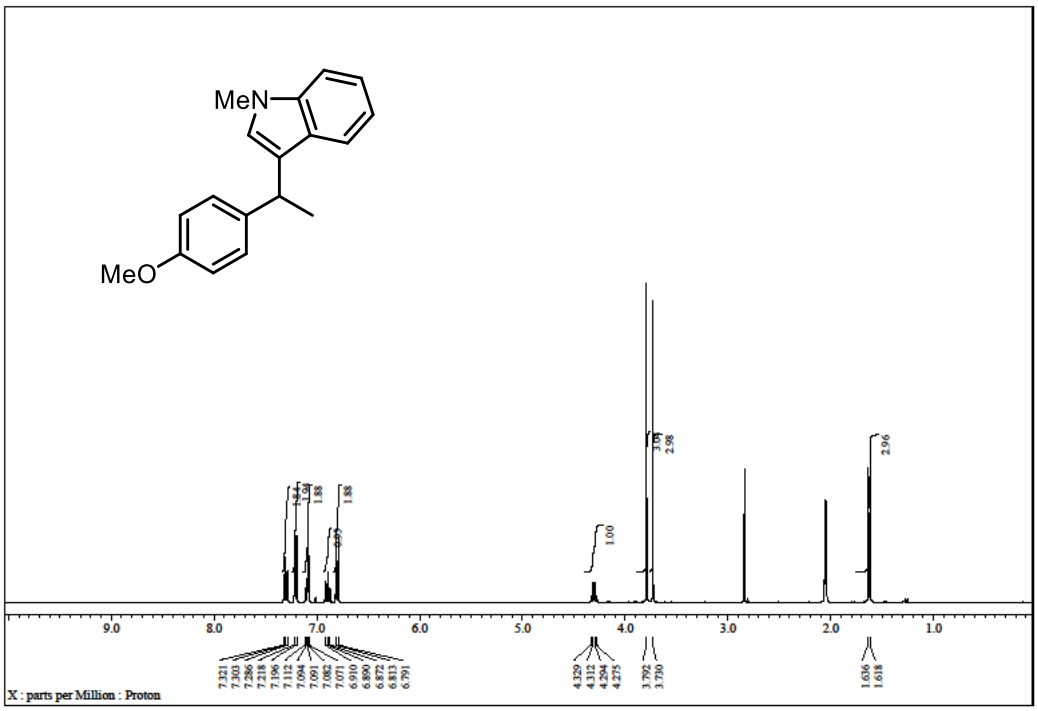


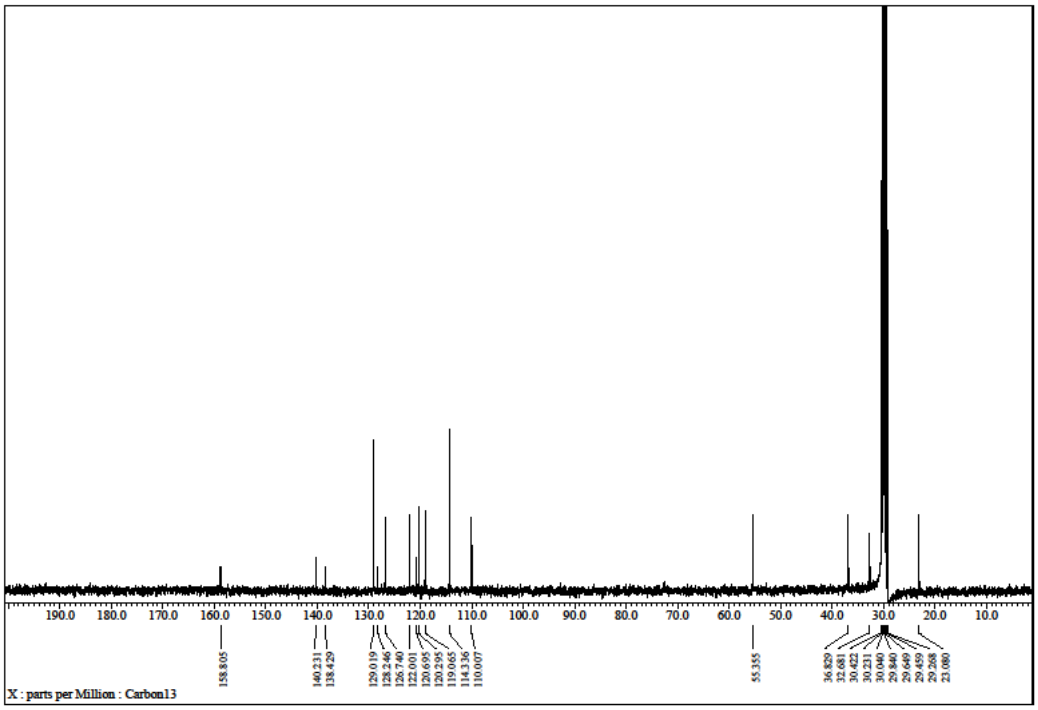
3-((1-(4-Methoxyphenyl)ethyl)thio)propanoic acid (3ac)





3-(1-(4-Methoxyphenyl)ethyl)-1-methyl-1*H*-indole (9)





1,3,5-Trimethoxy-2-(1-(4-methoxyphenyl)ethyl)benzene (11)