Supporting Information for

Catalytic Hydrogenation of Thioesters, Thiocarbamates, and Thioamides

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1. General considerations

All experiments with metal complexes and phosphine ligands were carried out under an atmosphere of purified nitrogen in a Vacuum Atmosphere glovebox equipped with a MO 40-2 inert gas purifier or using standard Schlenk techniques. All solvents were reagent grade or better. All non-deuterated solvents were refluxed over sodium/benzophenoneketyl and distilled under argon atmosphere. Deuterated solvents were used as received. All solvents were degassed with argon and kept in the glove box over 4Å molecular sieves. All ^{1}H NMR, ^{13}C NMR or ^{31}P NMR spectra were recorded on a Bruker AVANCE III 300MHz, 400MHz and AVANCE III HD 500MHz NMR spectrometer and reported in ppm (δ). Chemical shifts were referenced to the residual solvent peaks ($CHCl_3$, ^{1}H NMR at 7.26 ppm, ^{13}C NMR at 77.16 ppm; dioxane, ^{1}H NMR at 3.71 ppm; TMS, ^{1}H NMR at 0.00 ppm;) or an external standard of phosphoric acid (85% solution in D_2O) at 0.0 ppm (^{31}P NMR). NMR spectroscopy abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. GC analysis was performed on HP 6890 series GC system with Hp-5 column and SUPELCO 1-2382 column, flame ionization detector, and N_2 as carrier gas (Column: HP-5, 30 m, 320 μm, Inlets: 280 ^{o}C; Detector: FID 280 ^{o}C; Flow: 1 mL/min; Oven:50 ^{o}C, hold 8 min; 15 ^{o}C/min to 280 ^{o}C, hold 2 min.) GC-MS was carried out on HP 6890 / HP 5973 (MS detector) instruments equipped with a 30 m column (Restek 5MS, 0.32 mm internal diameter) with a 5% phenylmethylsilicone coating (0.25 mm) and helium as carrier gas. IR spectra were recorded on Thermo Nicolet 6700 FT-IR.

Analytical TLC was performed on Merck silica gel 60 F254 plates. The TLC plates were visualized by treatment with a potassium permanganate ($KMnO_4$) stain followed by gentle heating. Complexes **Ru-1**[1], **Ru-3**[2], **Ru-4**[1], **Ru-5**[3], **Ru-6**[4], **Ru-7**[5] were prepared according to literature procedures. Known thioesters were prepared according to dehydrogenative coupling of thiols and alcohols (**1a-1e**),[2] direct acylation of thiols (**1h-1j**, **1l-1o**),[6] or thioesterification of carboxylic acids using DCC as dehydrating reagent (**1k**).[7] Known thiocarbamate **4a-4c** were prepared by the reaction of isocyanate with thiols.[8] Known thioamides **5a-5c** were prepared according

to the reported procedures.[9,10] **1f**,[7] **1g**[7] and **1p**[6] are unreported compounds, which were synthesized according to the reported procedure.

2. Proposed hydrogenation pathways

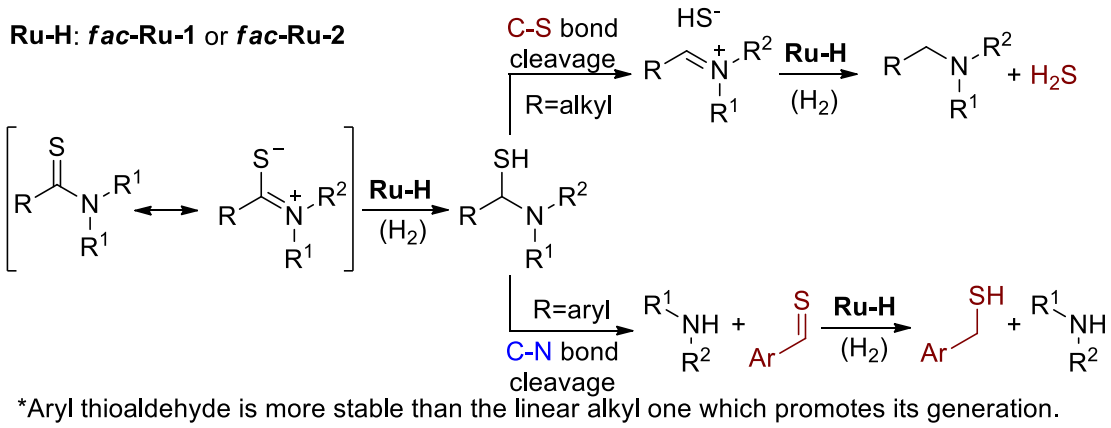


Figure S1. Proposed hydrogenation pathway of thioamides.

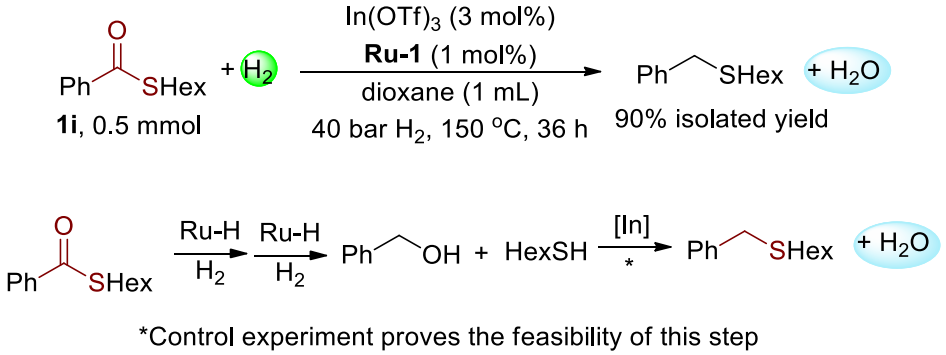


Figure S2. Proposed hydrogenative deoxygenation pathways of thioester **1i**.

3. Ester hydrogenation tests

As tested in dioxane, **Ru-1** does not catalyze hydrogenation of common esters such as hexyl and benzyl benzoate. However, **Ru-1** catalyzes the hydrogenation of glycol-derived esters such as its oligoesters and ethylene diacetate, as published (Fig S3).

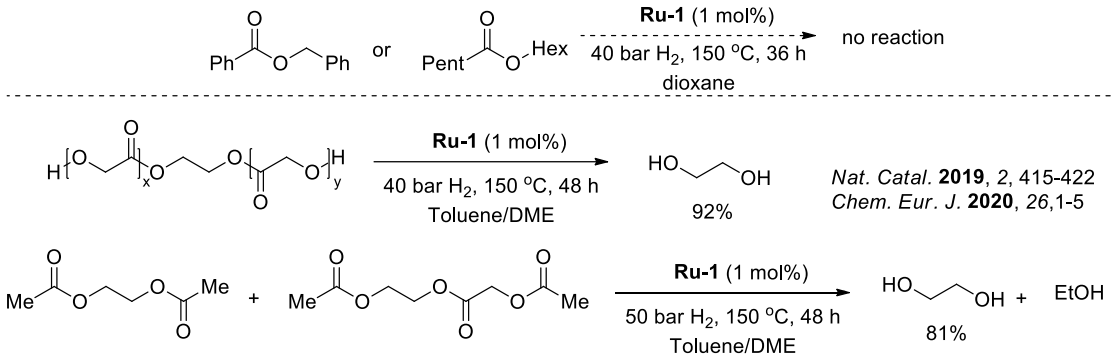


Figure S3. Hydrogenation of general esters.

We selected ethylene diacetate as example to test its hydrogenation in the current system. The results show that in the absence of thiol and thioester, **Ru-1** catalyzes its hydrogenation, although in a low yield (12% yield of EtOH in 16 h). However, under the conditions of hydrogenation of a thioester, no reaction was observed with ethylene diacetate while full conversion of thioester **1a** was still achieved (Fig S4). The result indicates that that the presence of thiol in the system inhibits ester hydrogenation, possibly by retarding coordination of the ester to the ruthenium center.

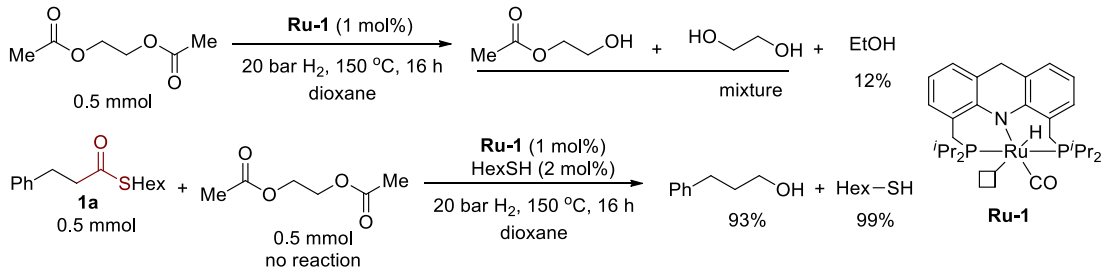
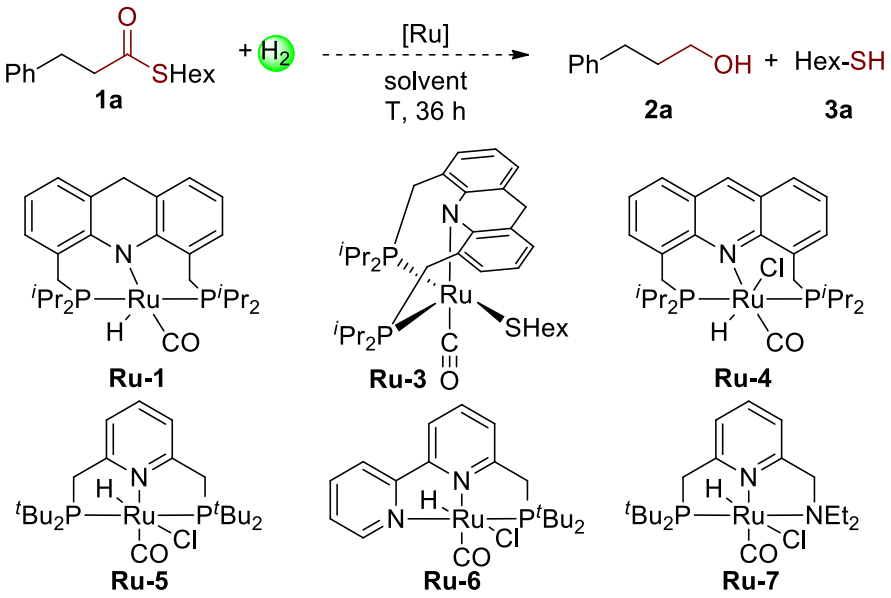


Figure S4. Ethylene diacetate hydrogenation experiments in the absence and presence of thioester.

The current conditions are suitable for all of ester-thioester substrates although we didn't observe any hydrogenation of the ester group in **1d** and **1p** even in the absence of catalytic amount of thiol.

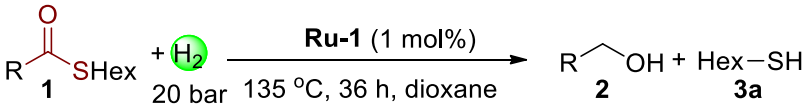
4. Condition Optimization



entry	catalyst	T (^{o}C)	H_2 pressure (bar)	conversion **1a** (%)[a]	yields **2a**/**3a** (%)[a]
1	**Ru-1**	150	40	>99	92/85
2	**Ru-3**	150	40	96	88/91
3	**Ru-4**	150	40	19	14/15
4[b]	**Ru-5**	150	40	34	24[c]/25
5[b]	**Ru-6**	150	40	20	6[c]/14
6[b]	**Ru-7**	150	40	21	18[c]/20
7	**Ru-1**	150	30	64	58/56
8	**Ru-1**	135	40	80	70/67
9[d]	**Ru-1**	150	30	>99	93/90
10[d]	**Ru-1**	150	20	>99	94/86
11[d]	**Ru-1**	150	10	92	86/89
12[d]	**Ru-1**	135	30	>99	88/87
13[d]	**Ru-1**	135	20	>99	90/92
14[d]	**Ru-1**	120	20	78	67/65

Conditions: **1a** (0.33 mmol), catalyst (1.5 mol%), toluene (1 mL), 36 h. [a]Conversions/yields were determined by GC using benzyl benzoate as internal standard. [b]3 mol% ^{t}BuOK was added. [c]Little ester was formed. [d]Dioxane (1 mL) as solvent.

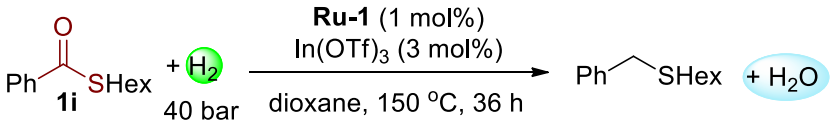
5. General experimental procedures



Representative procedure A:

In a N_2 glove box, **Ru-1** (0.003 g, 0.005 mmol), thioester (0.5 mmol), and dioxane (1 mL) were added to a 30 mL steel autoclave fitted with a Teflon sleeve. The autoclave was taken out of the glove box and pressurized with 20 bar H_2 and heated at 135 ^{o}C for 36 h with stirring, after which the steel autoclave was cooled in cold water bath for 30 min and the H_2 was vented off carefully in a hood. To the solution were added 0.5 mmol internal standard (benzyl benzoate or 1,3,5-trimethoxybenzene) and it was filtered through Celite, which was then rinsed with dioxane (2 mL). The resulting solution was analyzed by GC-MS to determine the generated products. Then 0.1 mL of the solution was dissolved in $CDCl_3$ for determination of the yields of products.

5 mmol scale hydrogenation of **1a**: In a N_2 glove box, **Ru-1** (0.006 g, 0.01 mmol), thioester **1a** (1.25 g, 5 mmol) and dioxane (3 mL) were added to a 30 mL steel autoclave fitted with a Teflon sleeve. The autoclave was taken out of the glove box and pressurized with 30 bar H_2 and heated at 150 ^{o}C for 2 h with stirring, after which the steel autoclave was cooled in a cold water bath for 30 min and the H_2 was vented off carefully in a hood. To the solution were added 5 mmol of benzyl benzoate and it was filtered through Celite, which was then rinsed twice with dioxane (2 ×2 mL). The resulting solution was analyzed by GC-MS indicating the complete conversion of the thioester. Then 0.1 mL of the solution was dissolved in $CDCl_3$ to determine the yields of **2a** (95%) and **3a** (99%) by NMR.



Representative procedure B:

In a N_2 glove box, **Ru-1** (0.003 g, 0.005 mmol), $In(OTf)_3$ (0.008 g, 0.015 mmol), thioester **1i** (0.111 g, 0.5 mmol), and dioxane (1 mL) were added to a 30 mL steel autoclave fitted with a Teflon sleeve. The autoclave was taken out of the glove box and pressurized with 40 bar H_2 and heated at 150 ^{o}C for 36 h with stirring, after which the steel autoclave was cooled in a cold water bath for 30 min and the H_2 was vented off carefully. To the solution were added 0.5 mmol internal standard (1,3,5-trimethoxybenzene) and it was filtered through Celite, which was then rinsed with dioxane (2 mL). The resulting solution was analyzed by GC-MS to determine the generated product. Then 0.1 mL of the solution was dissolved in $CDCl_3$ for determination of the yield of product.

Note:

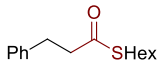
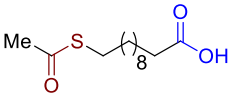
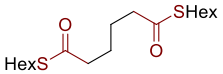
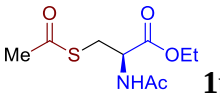
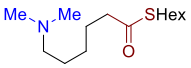
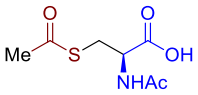
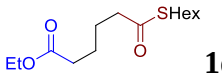
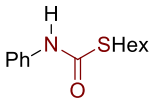
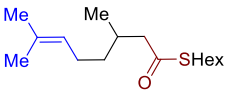
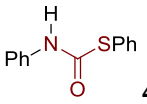
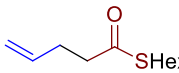
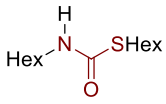
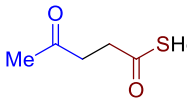
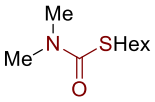
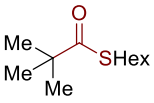
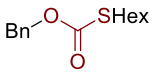
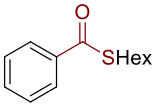
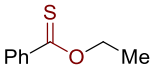
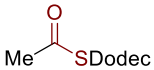
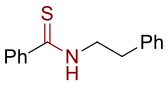
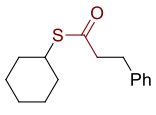
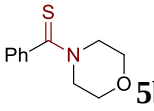
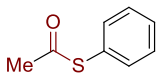
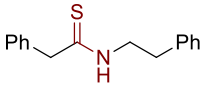
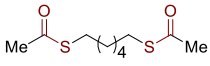
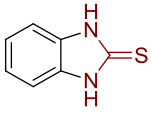
*The generated thiol can be oxidized to disulfide upon exposure to air. Determination of the yields of thiols should be done as soon as possible after the reaction, or the generated disulfide should be taken into consideration. Control experiments show that the disulfide can be hydrogenated to the corresponding thiol under the reaction conditions.

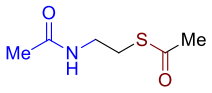
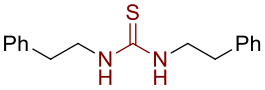
*The integrals of NMR were corrected by auto linear correction in Mestnova (measuring parameters: d1=10s, NS$\geqslant$12) and the peak of dioxane (3.71 ppm) is not fully displayed.

*In some cases, the yields of products were determined by GC. The relative response factors of each compound were determined by the average of three standard samples following the reported procedure.[11]

*The dryness of the system has a great influence on the hydrogenation of **1i** and thioamides. The catalytic amount of base (2% ^{t}BuOK) helps eliminate the harmful effect of moisture.

6. Table of reaction conditions of each substrate and failed examples

substrates	conditions	substrates	conditions
 **1a**	135 °C 20 bar H_2	 **1o**	150 °C 40 bar H_2
 **1b**	135 °C 20 bar H_2	 **1p**	150 °C 20 bar H_2 2% HexSH
 **1c**	135 °C 20 bar H_2		150 °C 40 bar H_2 decomposition
 **1d**	150 °C 20 bar H_2 2% HexSH	 **4a**	135 °C 20 bar H_2
 **1e**	150 °C 20 bar H_2 2% HexSH	 **4b**	135 °C 20 bar H_2
 **1f**	135 °C 20 bar H_2	 **4c**	150 °C 40 bar H_2 >80% conversion
 **1g**	135 °C 20 bar H_2 1 equiv HexSH		135 °C 20 bar H_2 No reaction
 **1h**	150 °C 40 bar H_2 66% conversion		135 °C 20 bar H_2 No reaction
 **1i**	150 °C 40 bar H_2		150 °C 40 bar H_2 <10% products
 **1j**	135 °C 20 bar H_2	 **5a**	150 °C 40 bar H_2 **Ru-1** (1.5 mol%)
 **1k**	135 °C 20 bar H_2	 **5b**	150 °C 40 bar H_2 **Ru-1** (1.5 mol%)
 **1l**	135 °C 40 bar H_2 >90% conversion	 **5c**	150 °C 40 bar H_2
 **1m**	135 °C 20 bar H_2		150 °C 40 bar H_2 trace product

 **1n**	150 °C 20 bar H_2		150 °C 40 bar H_2 trace products

7. Selected ^{1}H NMR spectra of crude mixtures

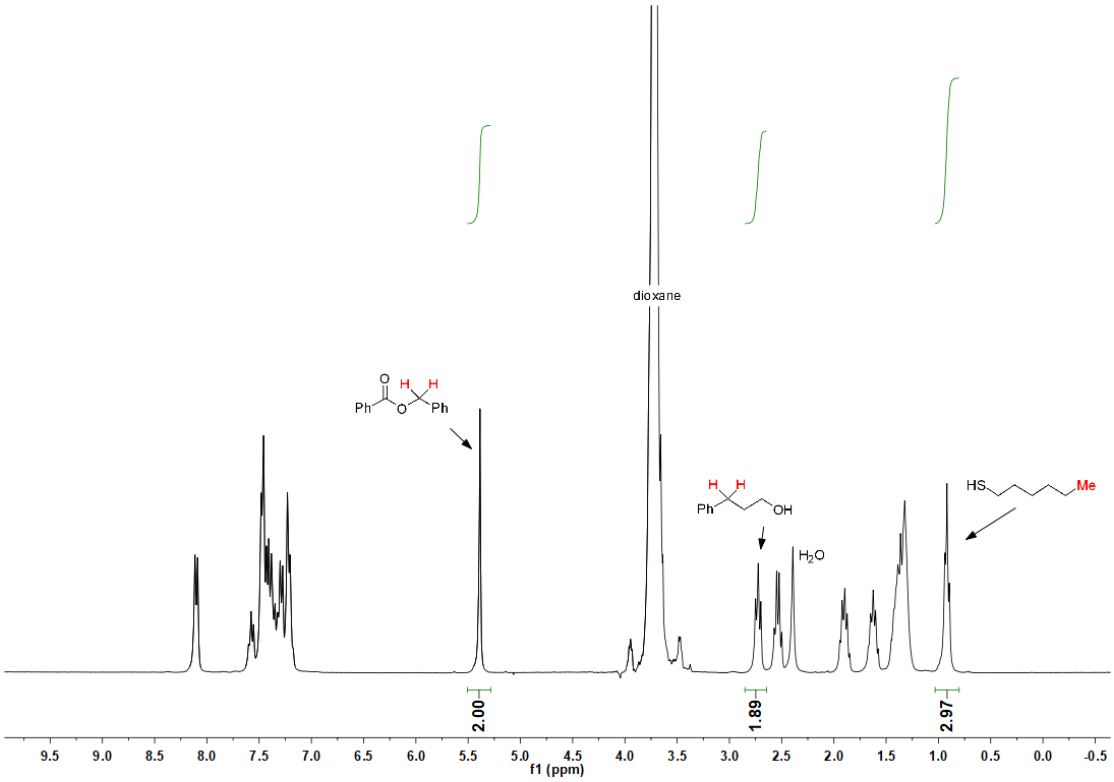


Figure S5. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1a** in 5 mmol scale.

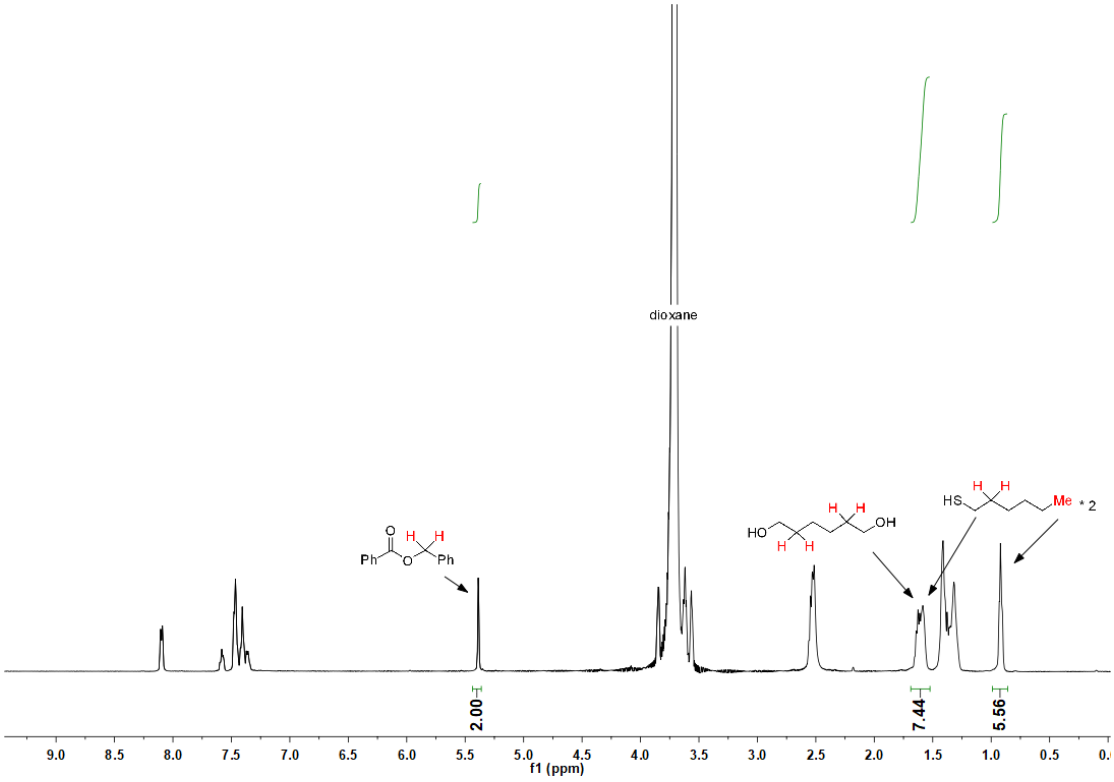


Figure S6. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of the crude reaction mixture of hydrogenation of **1b**.

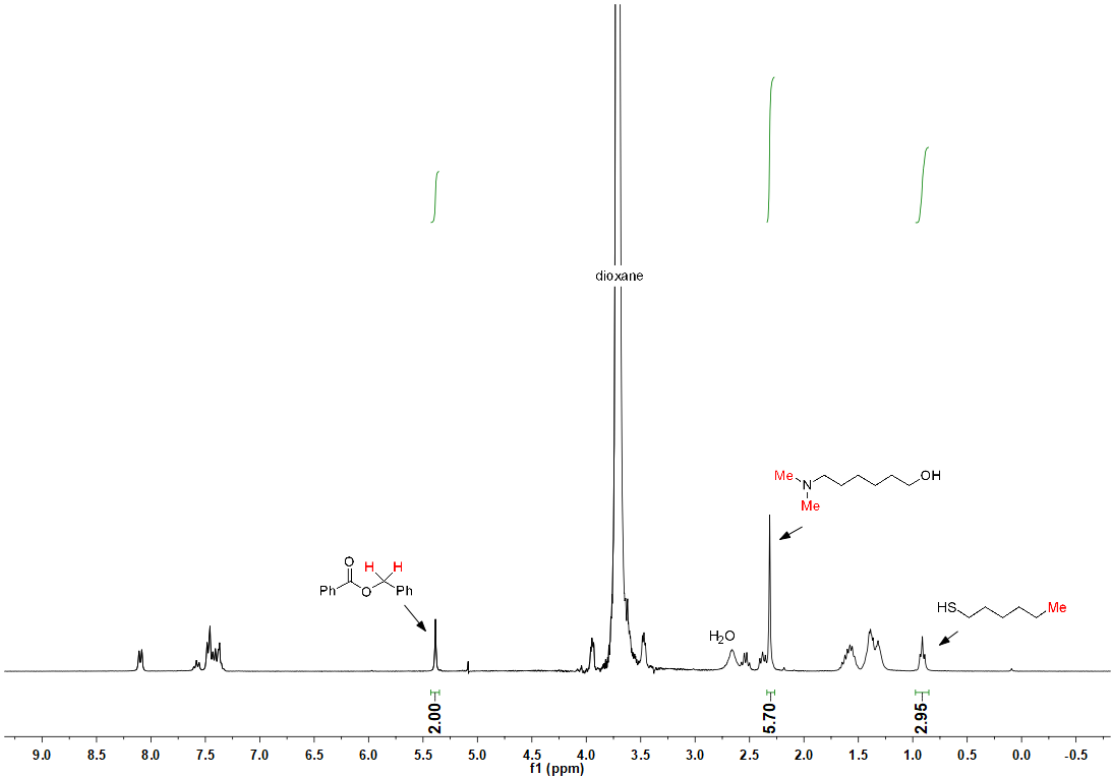


Figure S7. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1c**.

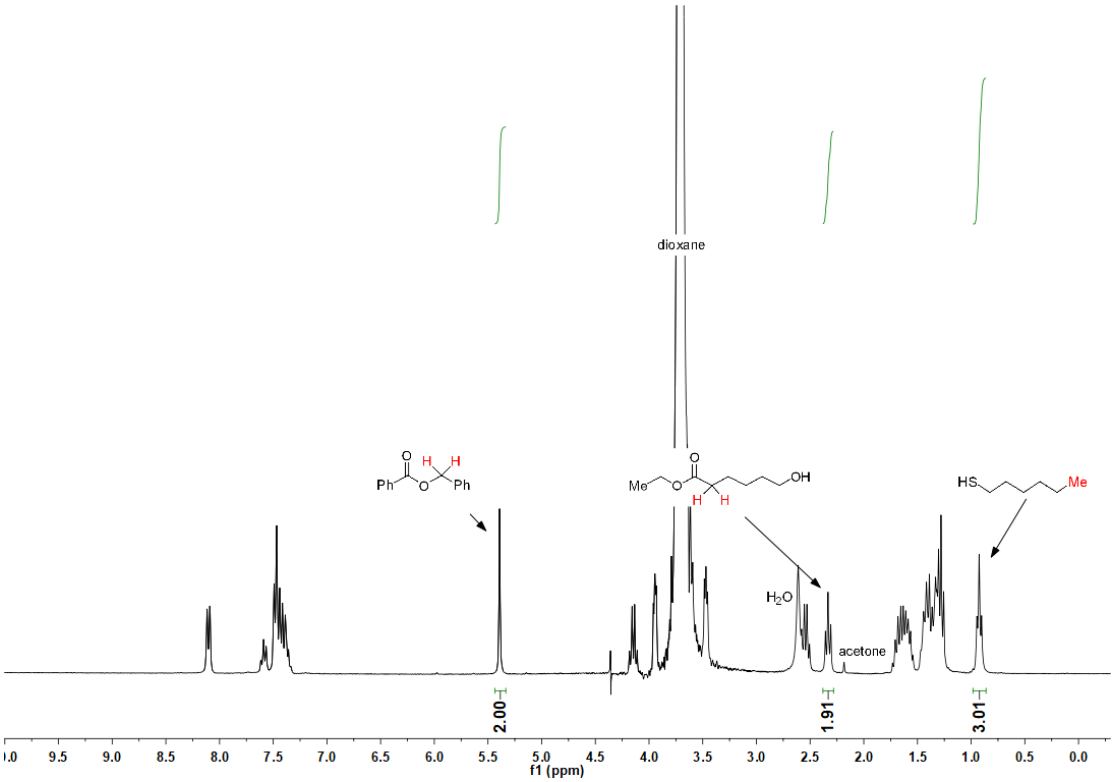


Figure S8. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1d** in the presence of 2% hexanethiol.

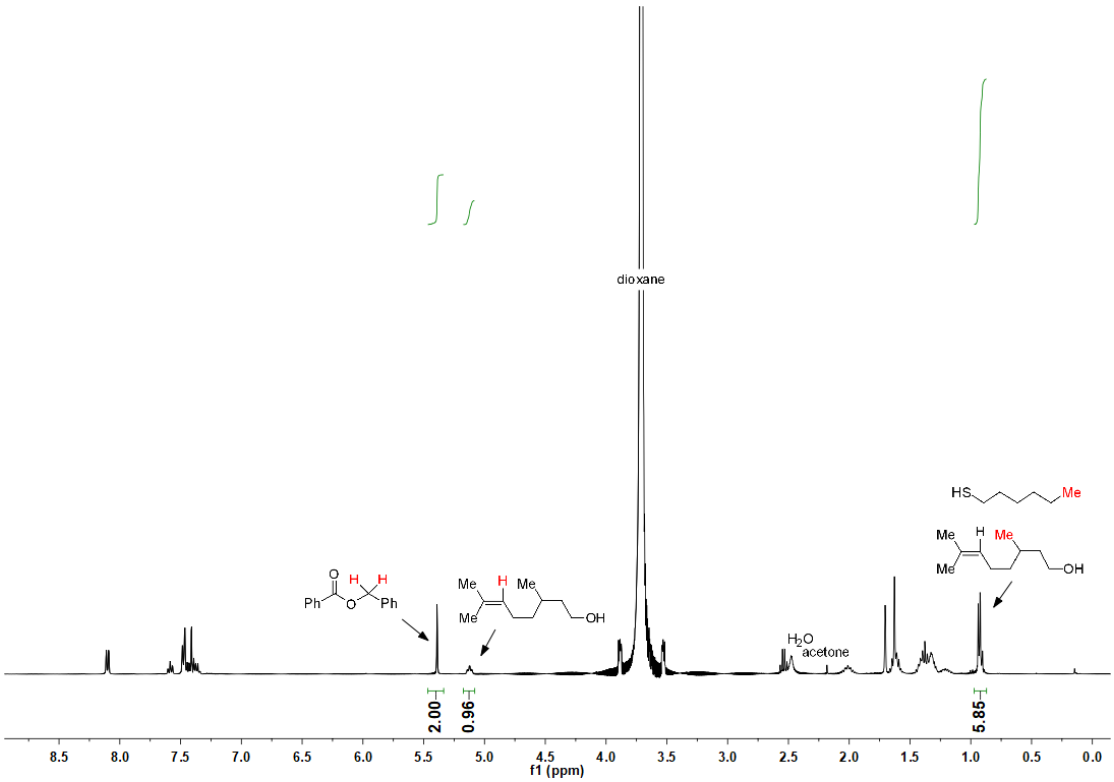


Figure S9. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1e** in the presence of 2% hexanethiol.

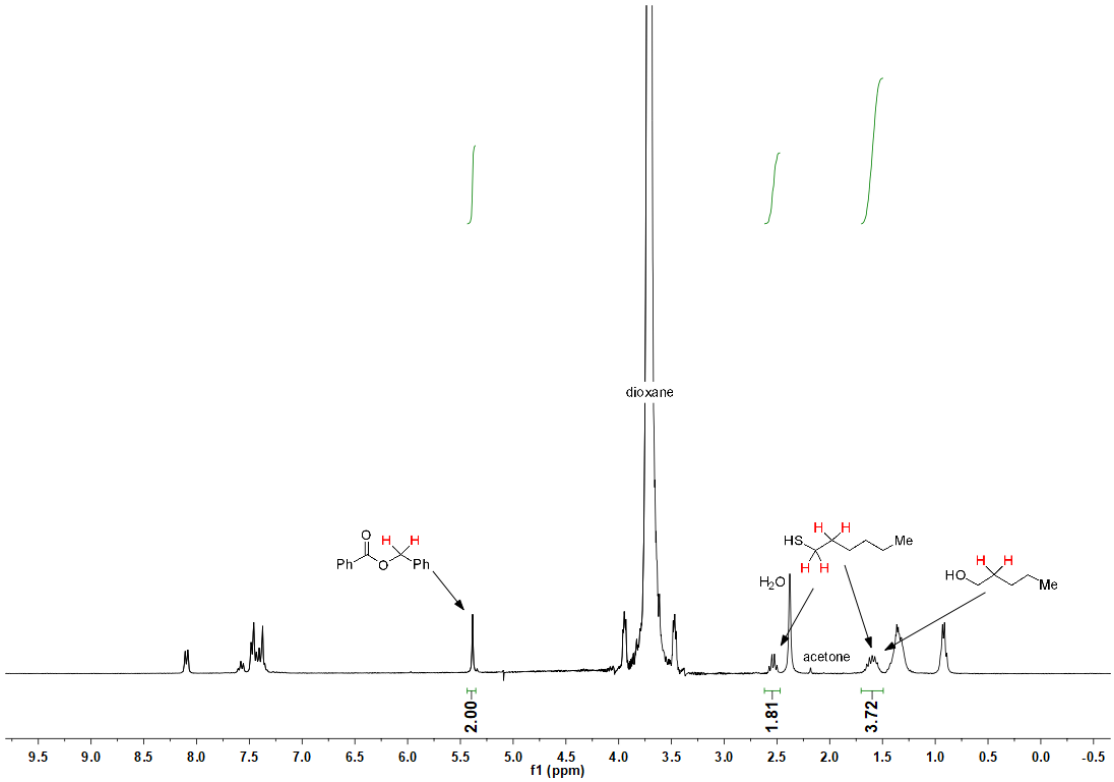


Figure S10. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude reaction mixture of hydrogenation of **1f**.

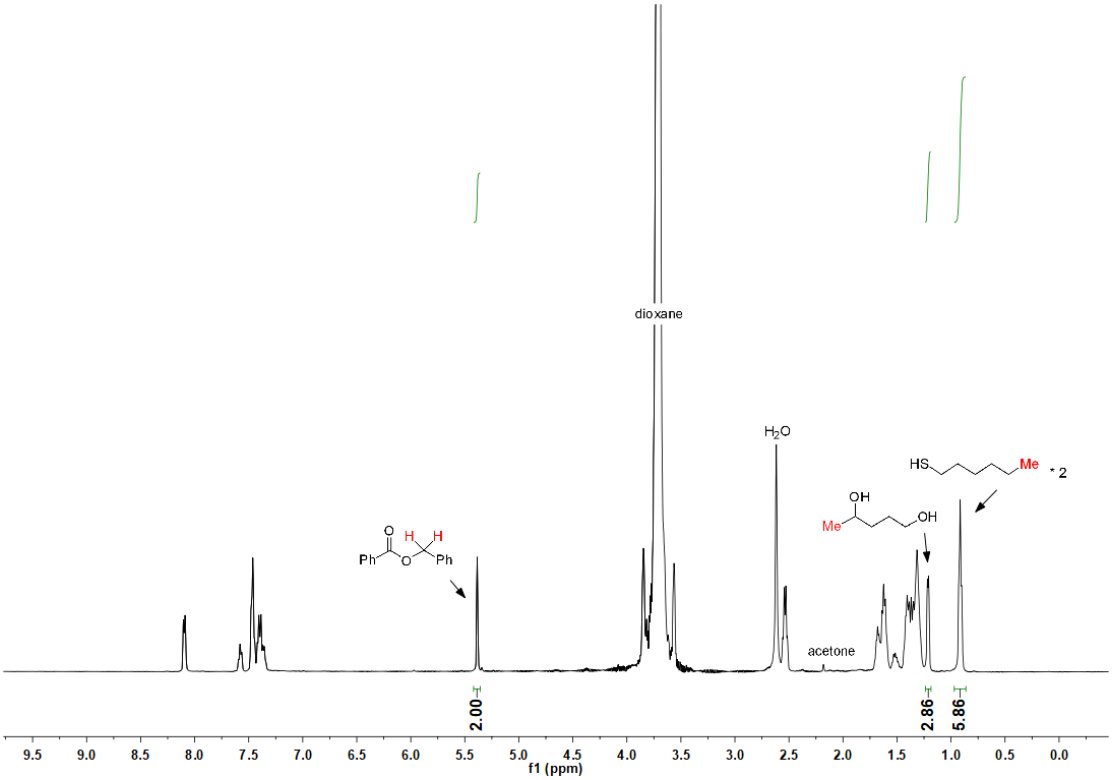


Figure S11. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of the crude reaction mixture of hydrogenation of **1g** in the presence of one equivalent hexanethiol.

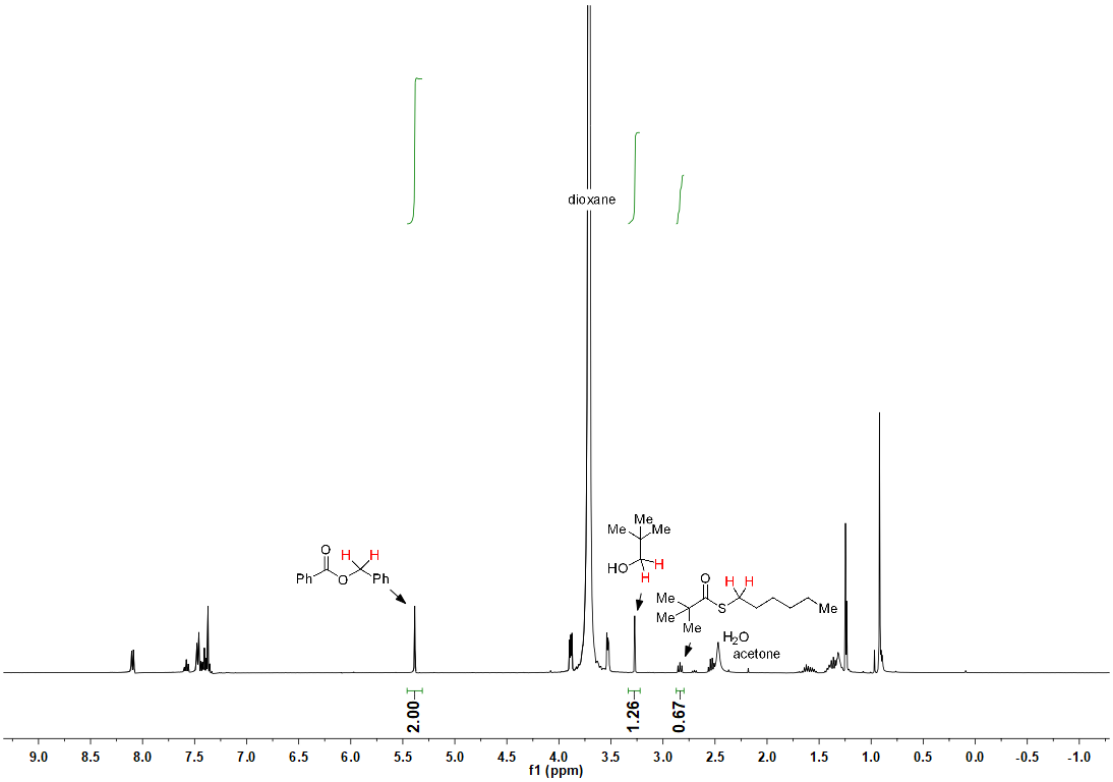


Figure S12. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude reaction mixture of hydrogenation of **1h** with the generation of little disulfide after exposure to air for two days; the yield of hexanethiol was determined by GC immediately after the reaction.

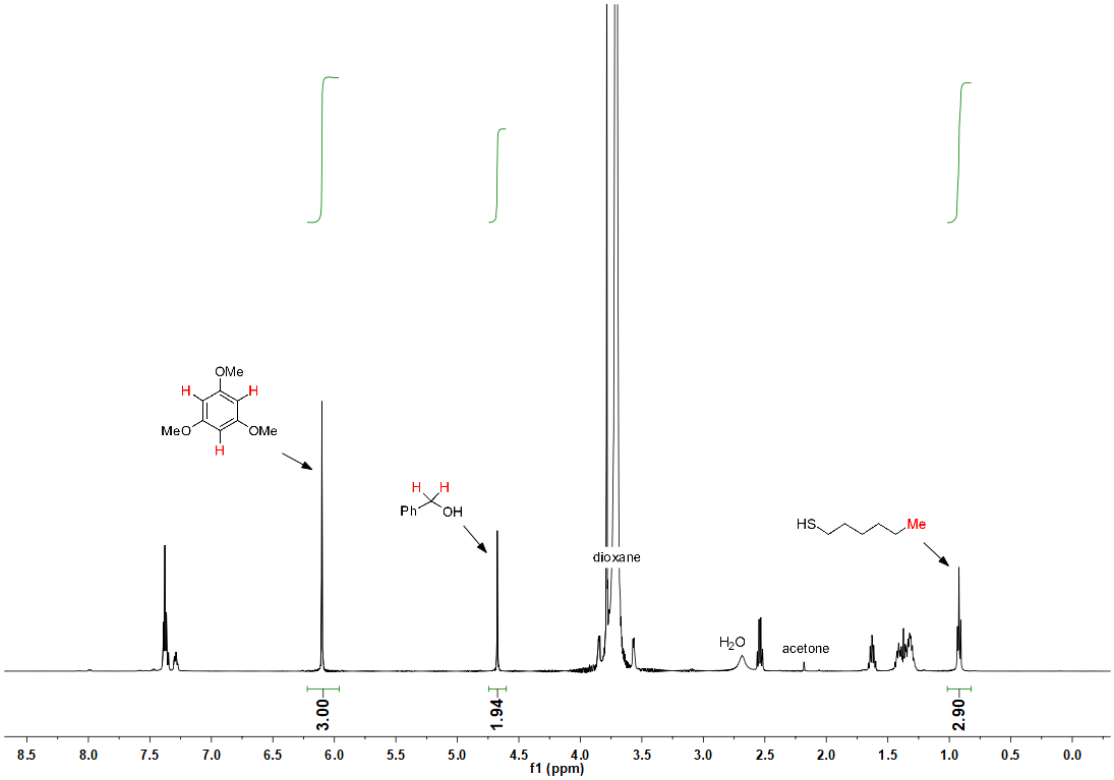


Figure S13. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of the crude reaction mixture of hydrogenation of **1i**.

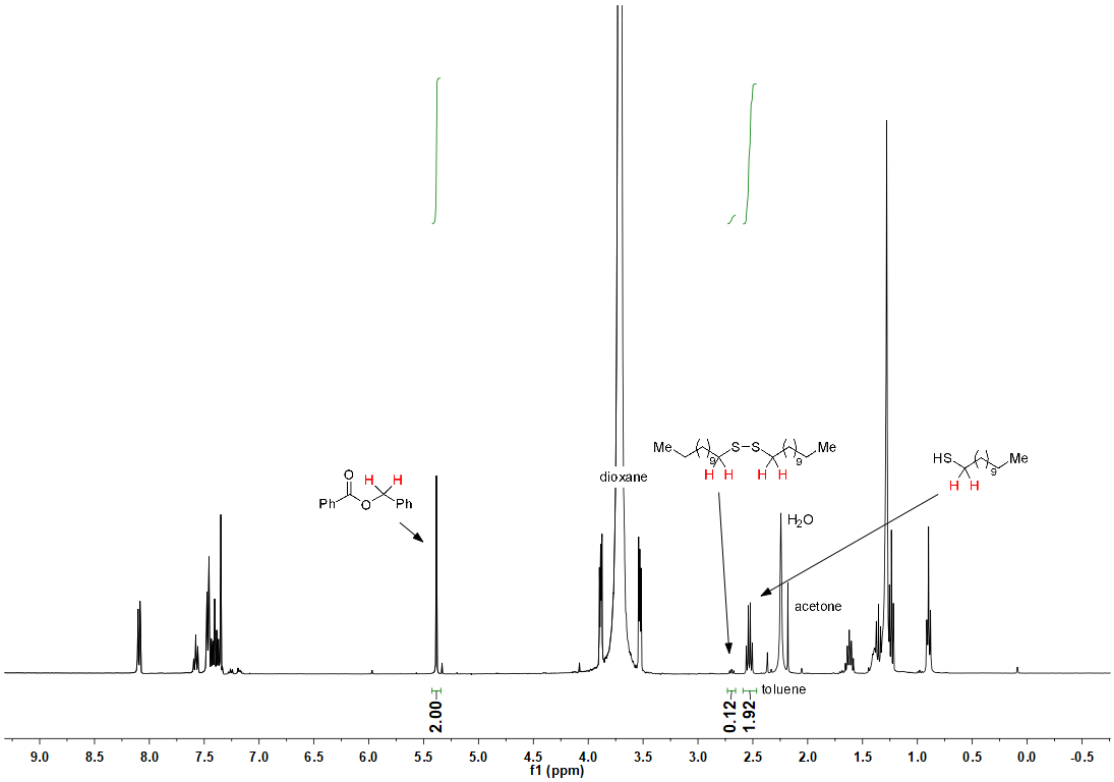


Figure S14. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude reaction mixture of hydrogenation of **1j** with the generation of a little disulfide after exposure to air for three days; the yield of ethanol was determined by GC.

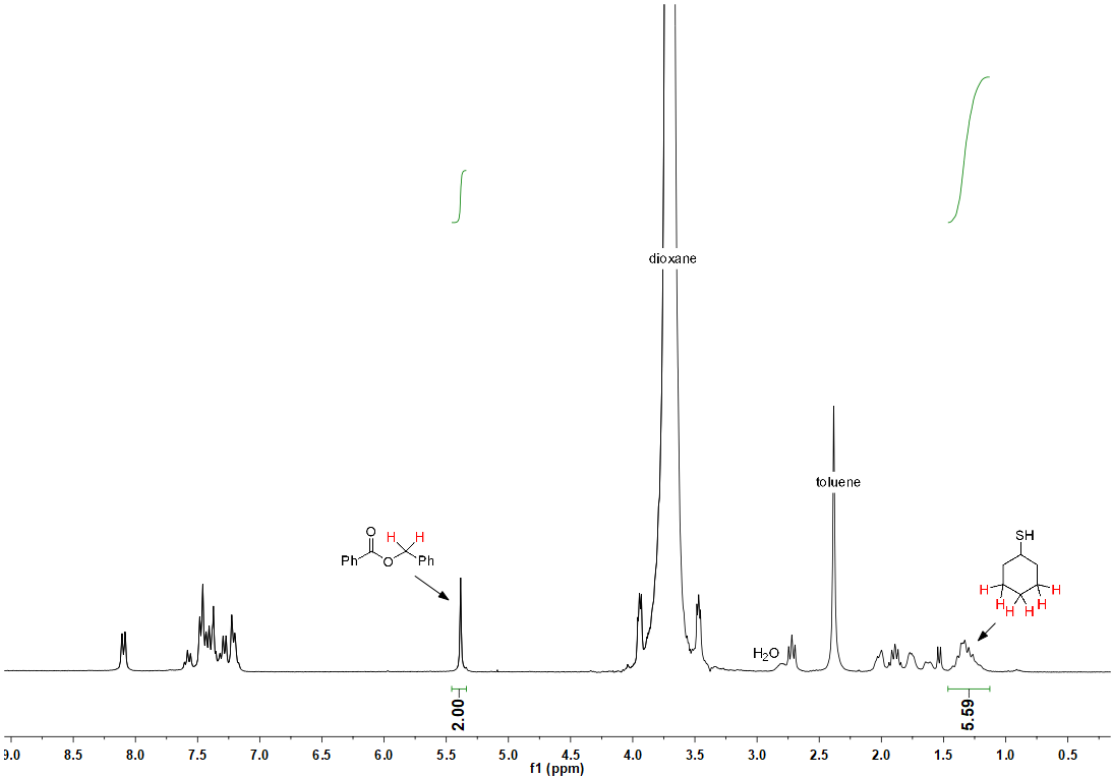


Figure S15. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1k**, the yield of phenylpropanol was determined by GC.

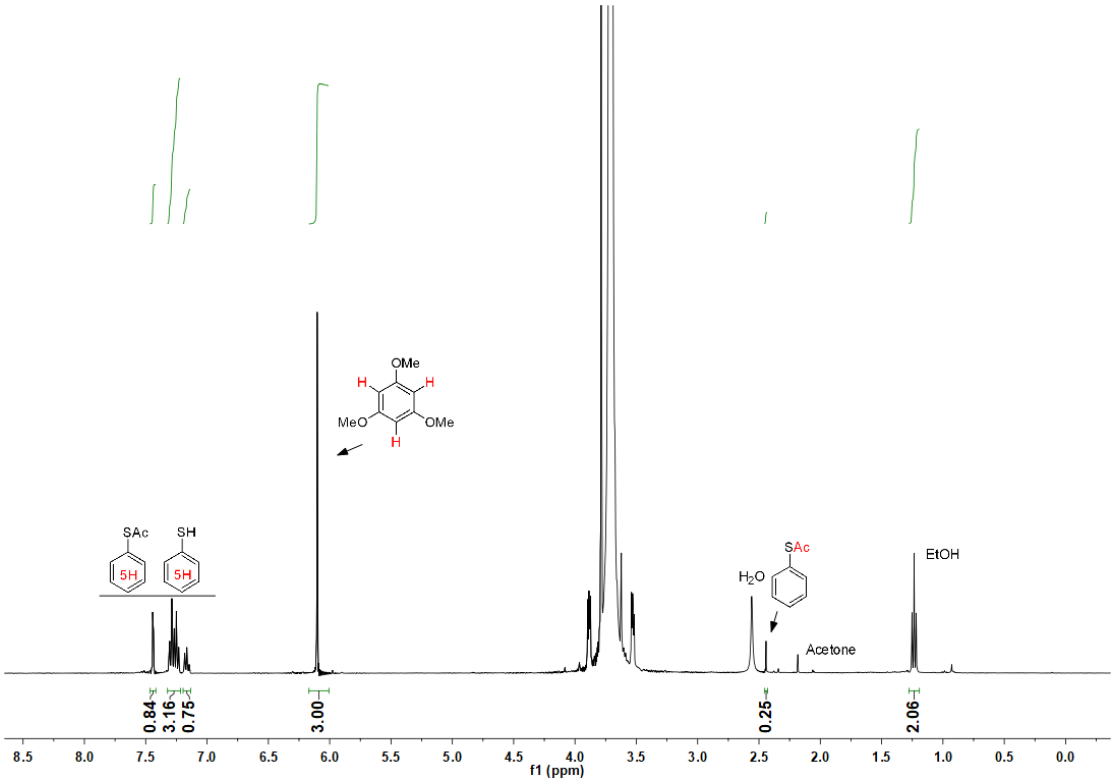


Figure S16. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude reaction mixture of hydrogenation of **1l**, the yield of thiophenol was further confirmed by GC (86%).

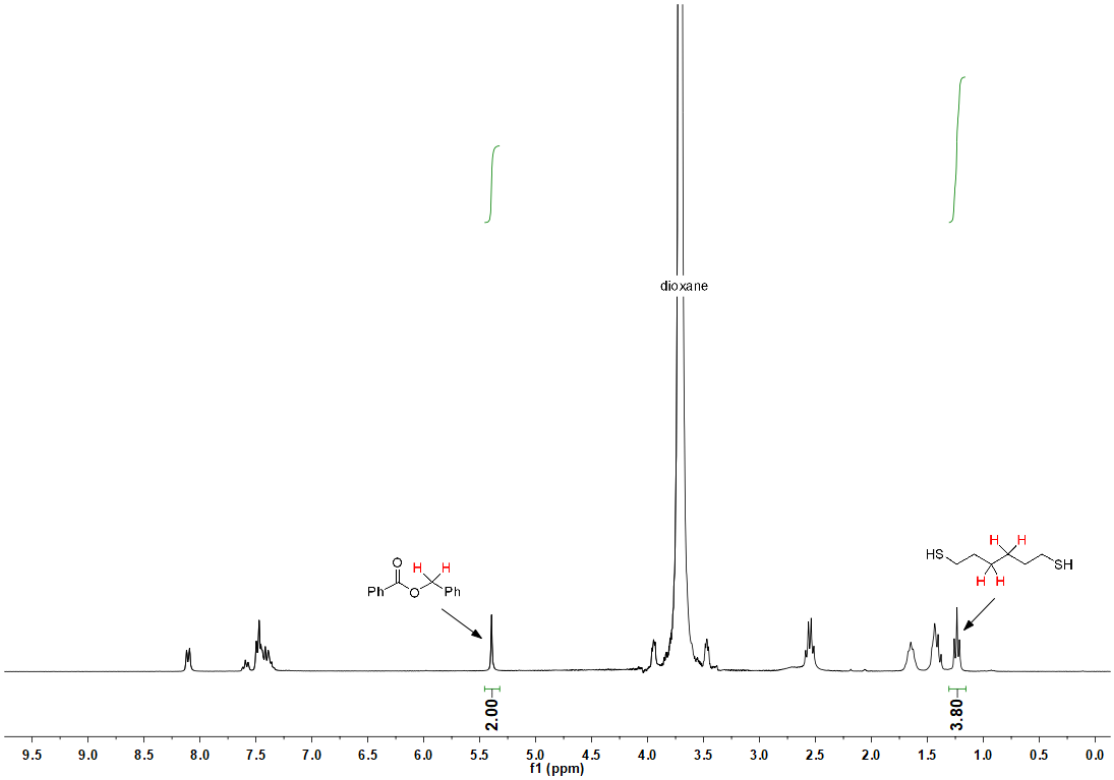


Figure S17. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1m**, the yield of ethanol was determined by GC.

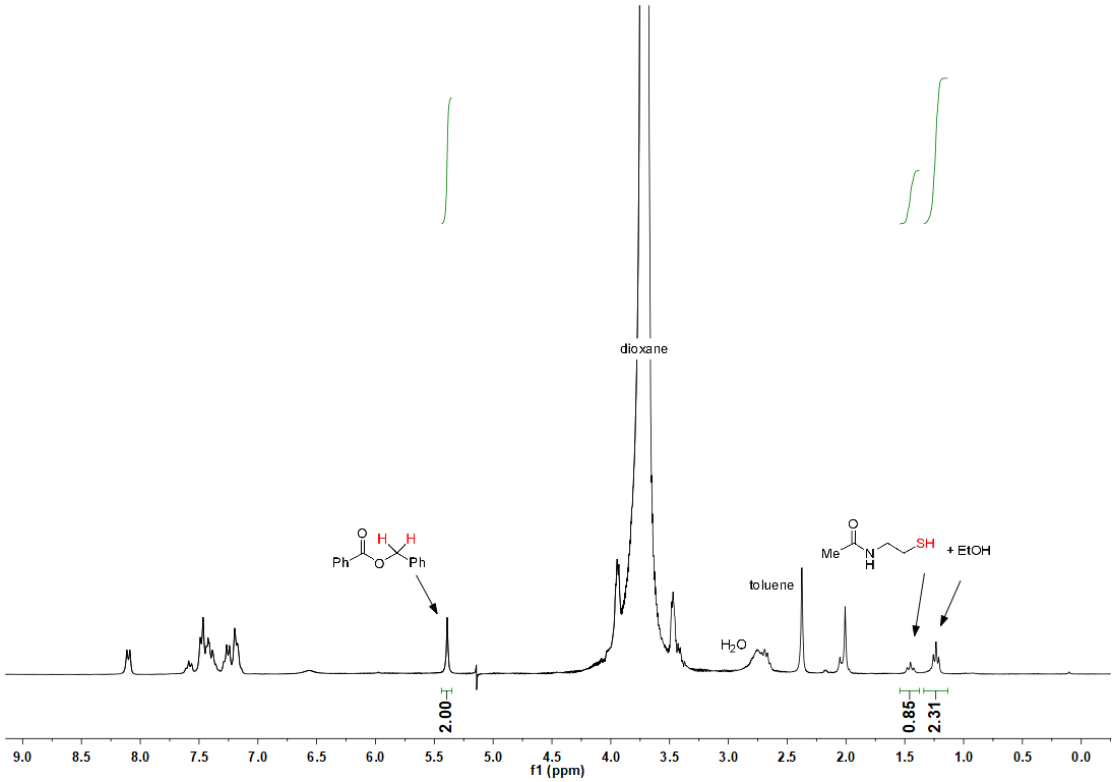


Figure S18. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1n**, the yield of *N*-acetyl cysteamine was determined after removal of solvent (See Figure S19).

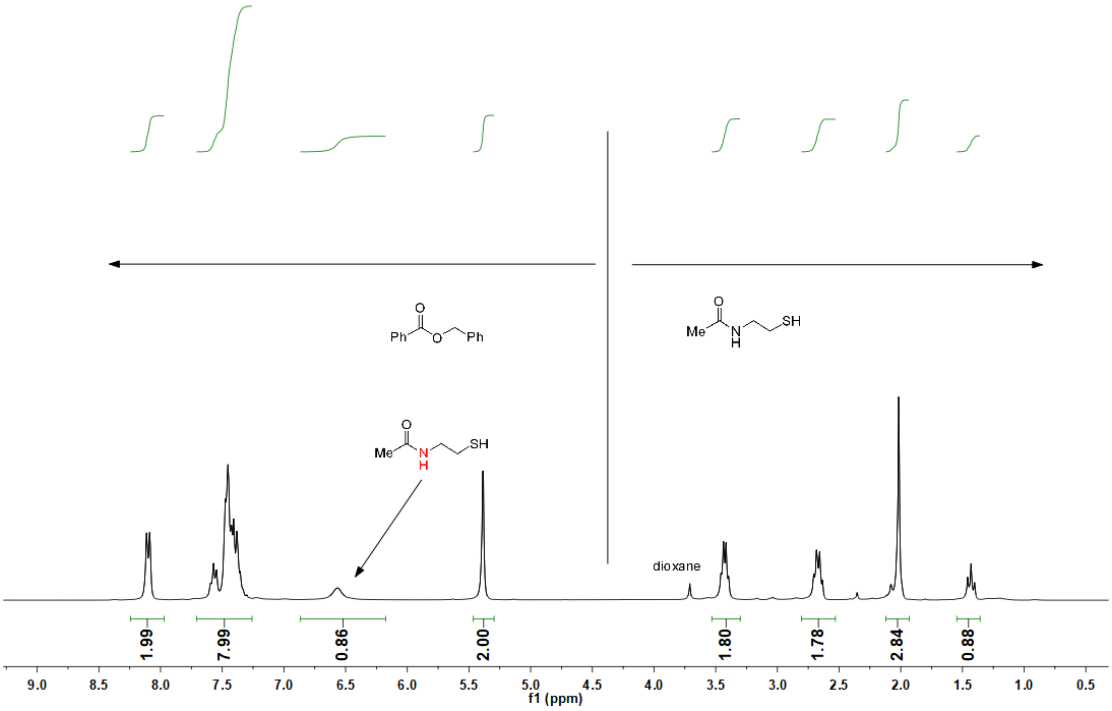


Figure S19. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1n** after removal of solvent and ethanol.

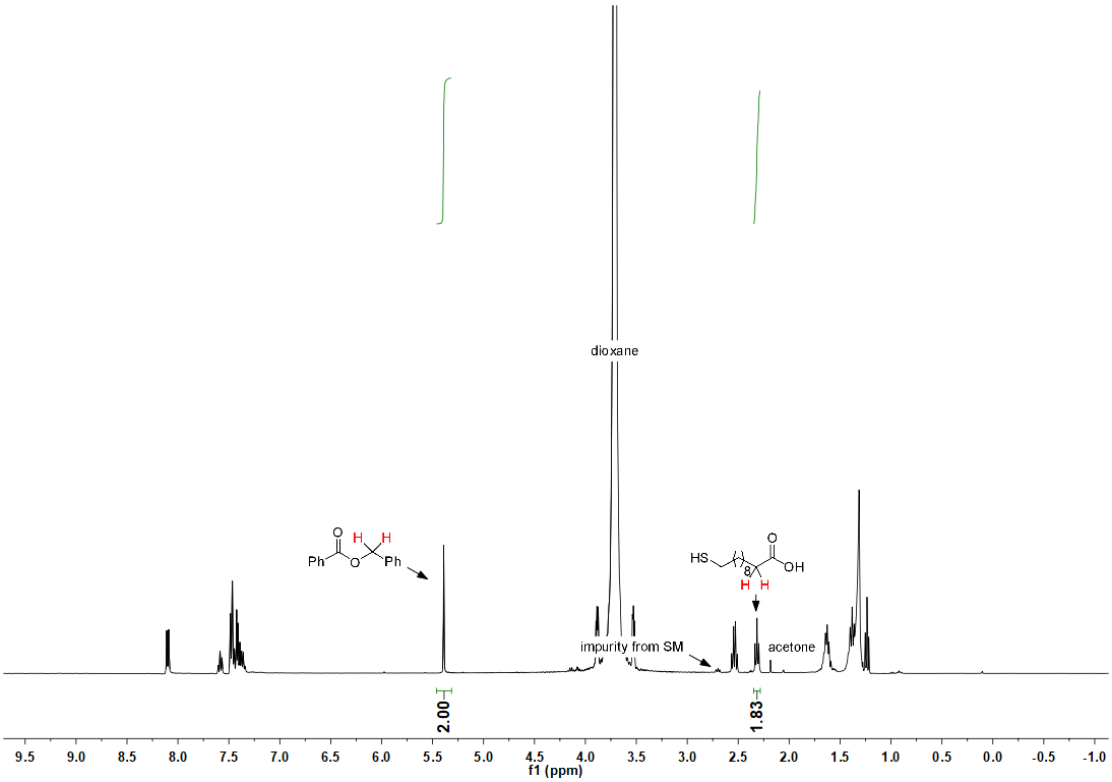


Figure S20. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude reaction mixture of hydrogenation of **1o**, the yield of ethanol was determined by GC.

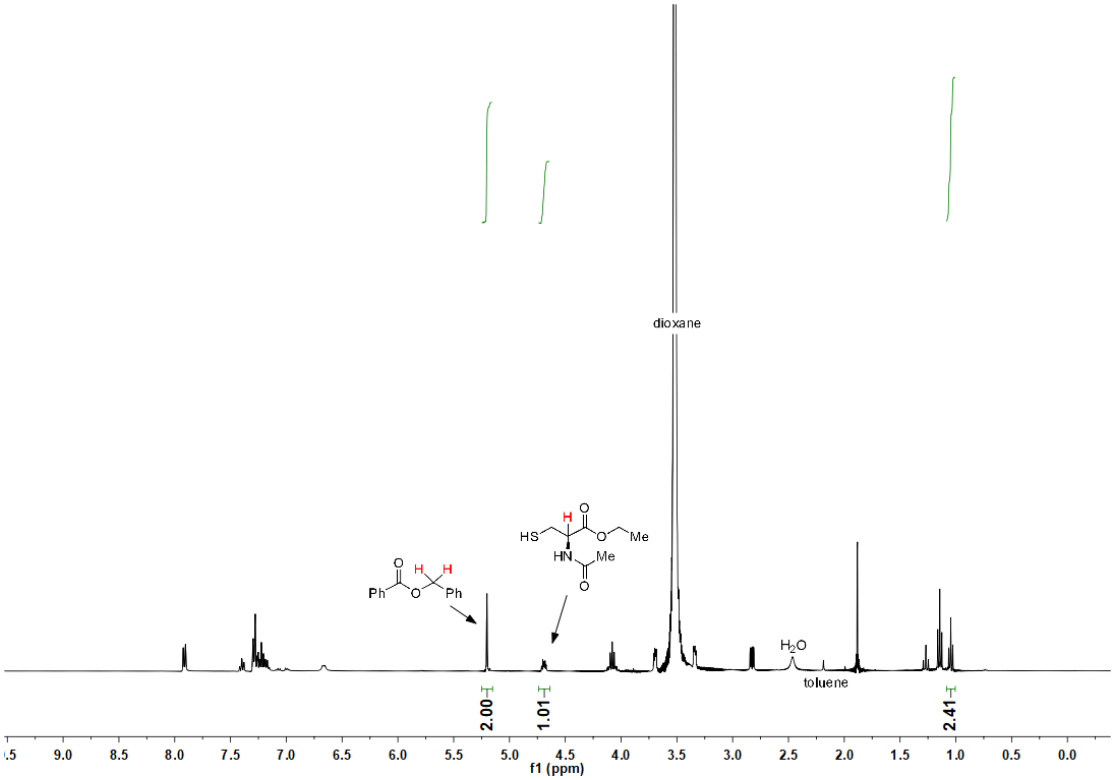


Figure S21. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude reaction mixture of hydrogenation of **1p**.

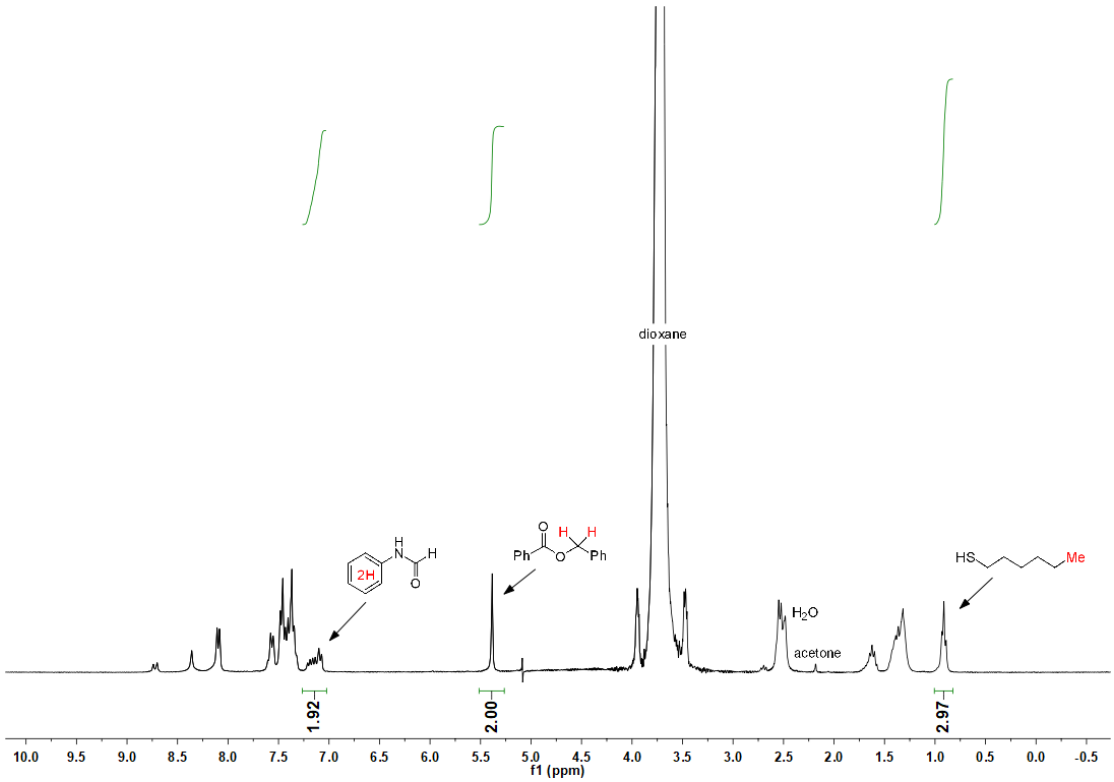


Figure S22. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **4a**.

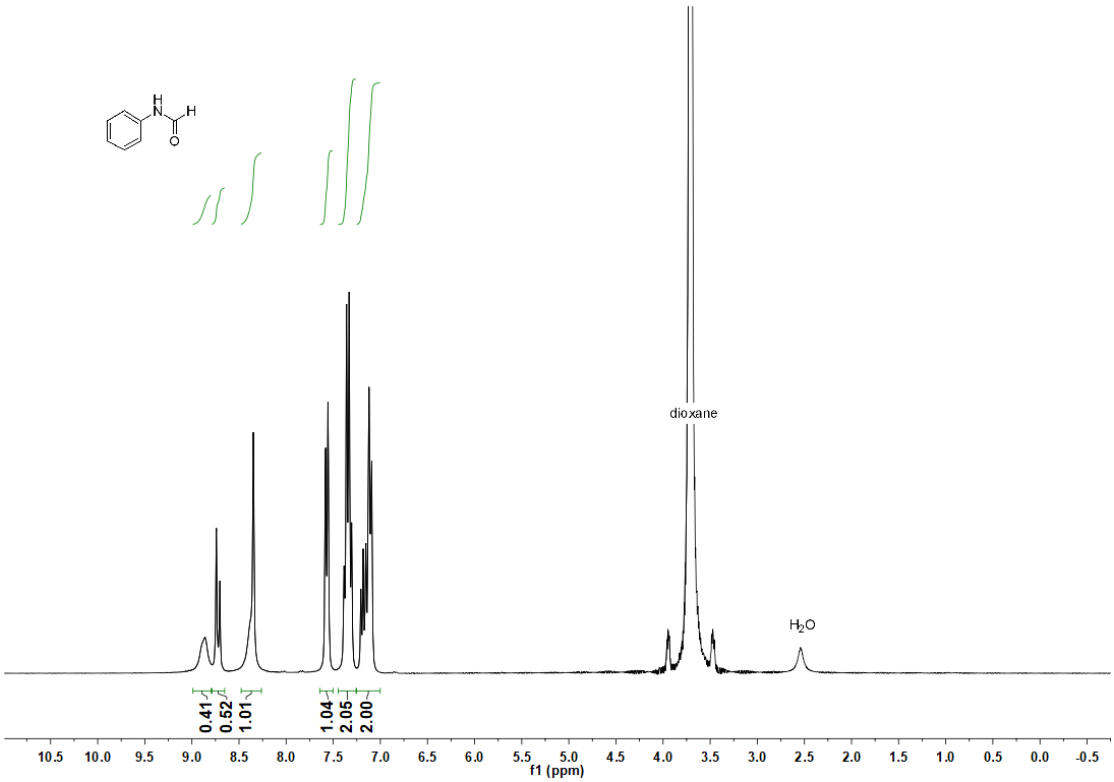


Figure S23. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of formanilide with 0.1 mL dioxane.

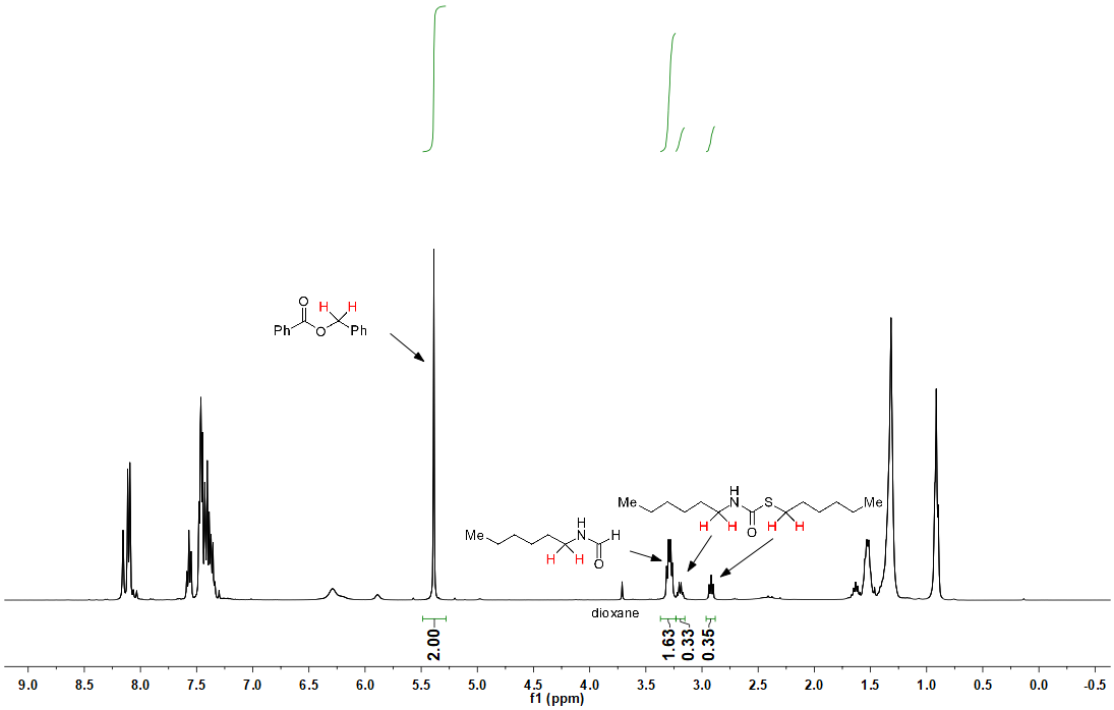


Figure S24. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude reaction mixture of hydrogenation of **4c** after removal of solvent and hexanethiol, the yield of hexanethiol was determined by GC.

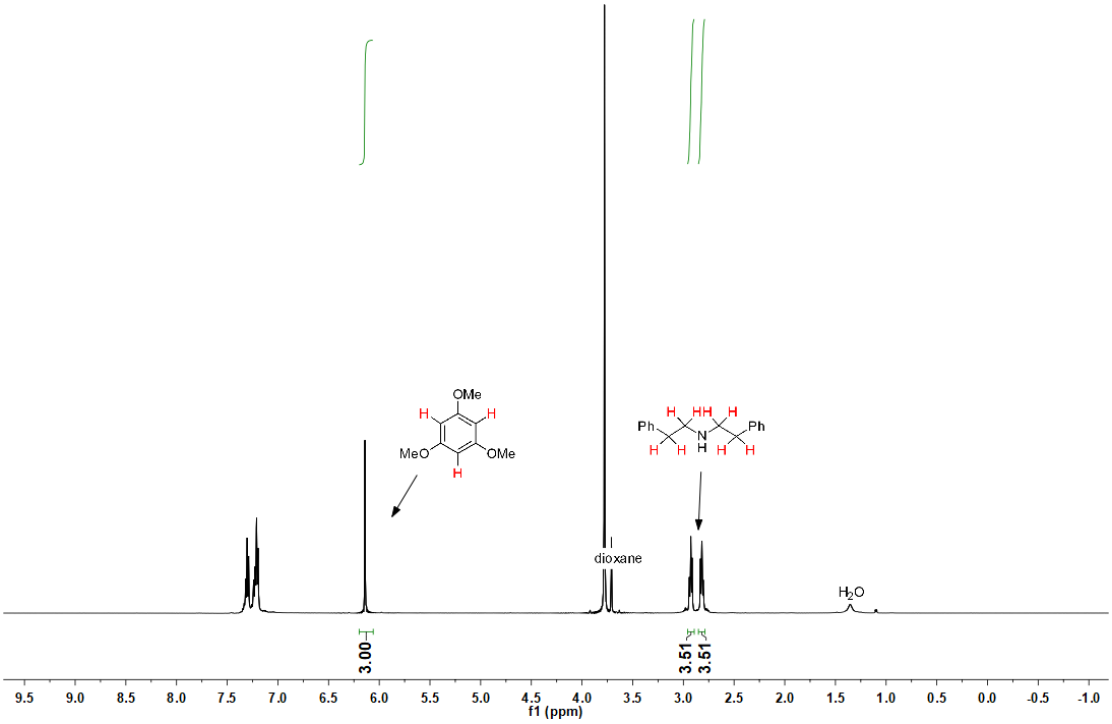


Figure S25. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of the crude reaction mixture of hydrogenation of **5c** after removal of solvent.

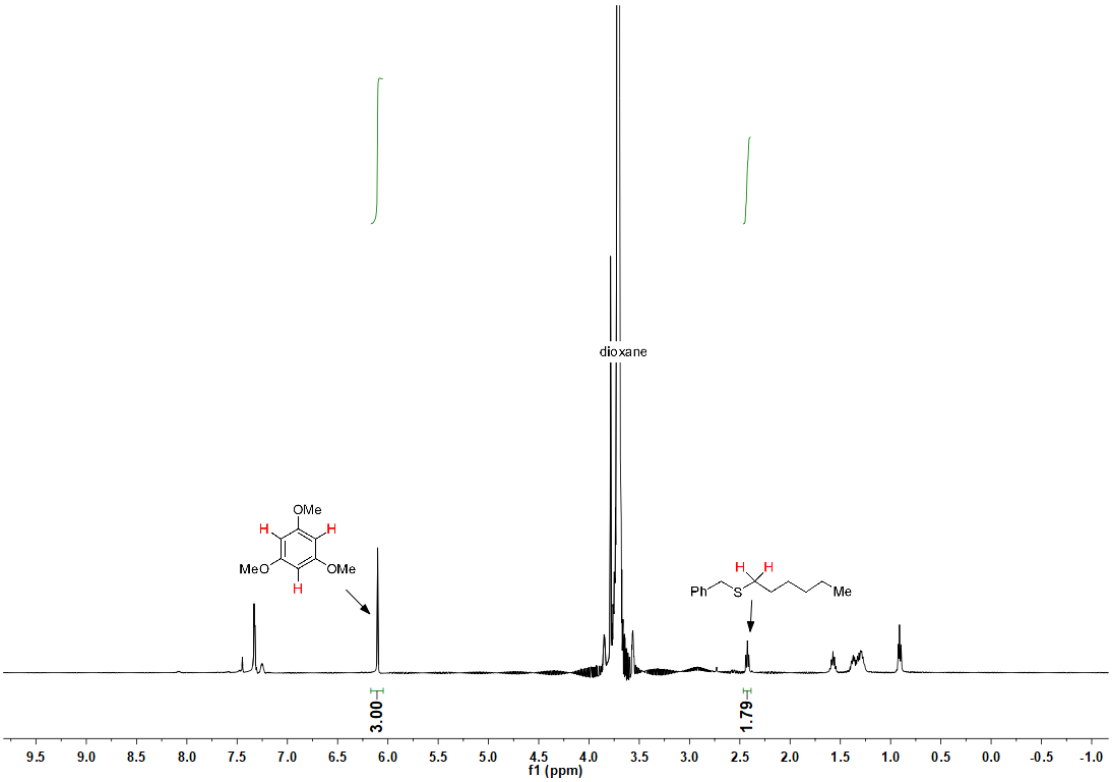


Figure S26. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the crude reaction mixture of hydrogenation of **1i** (condition B).

8. Selected GC-MS and GC traces

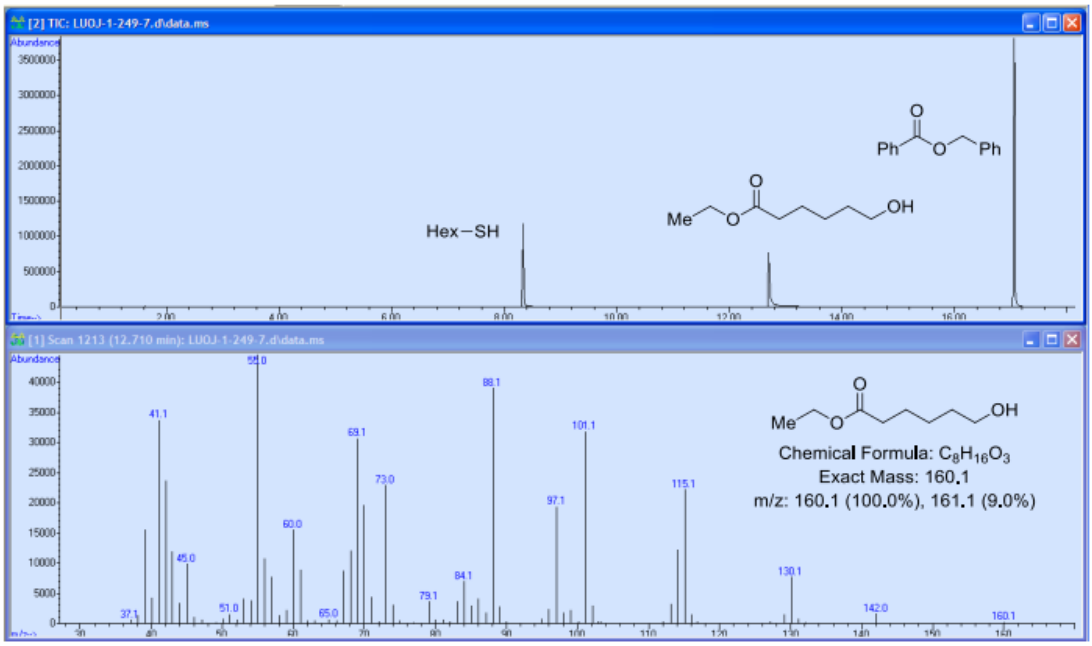


Figure S27. GC-MS chromatogram of crude reaction mixture: Scheme 4, **1d**.

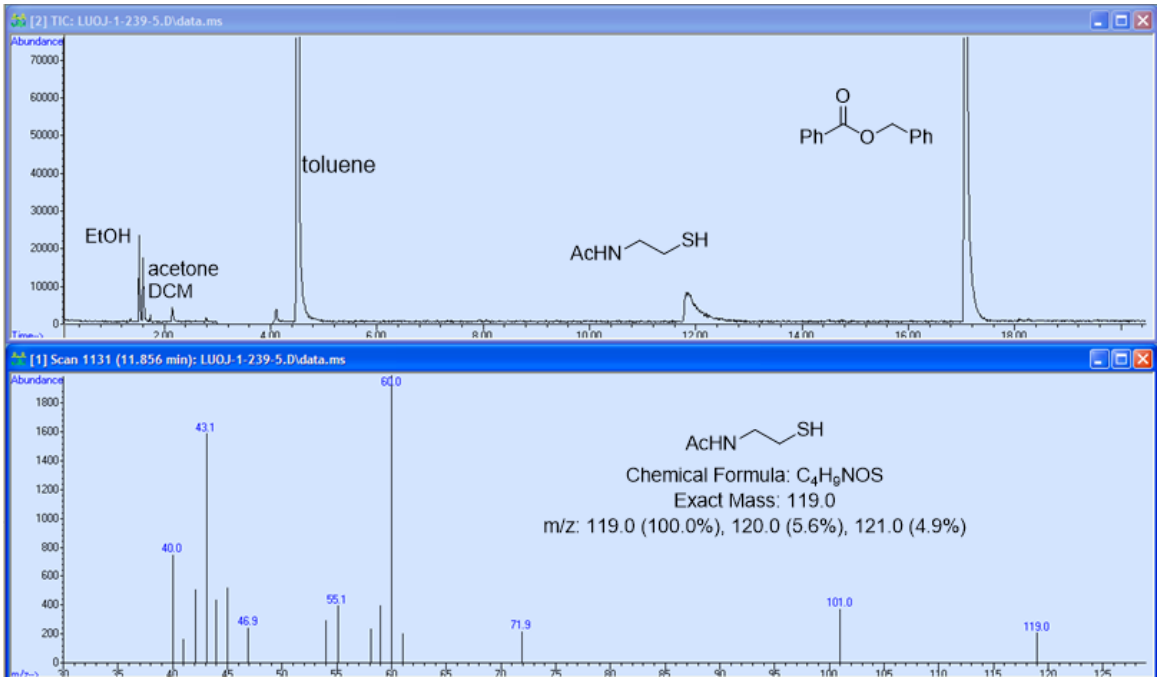


Figure S28. GC-MS chromatogram of crude reaction mixture: Scheme 5, **1n**.

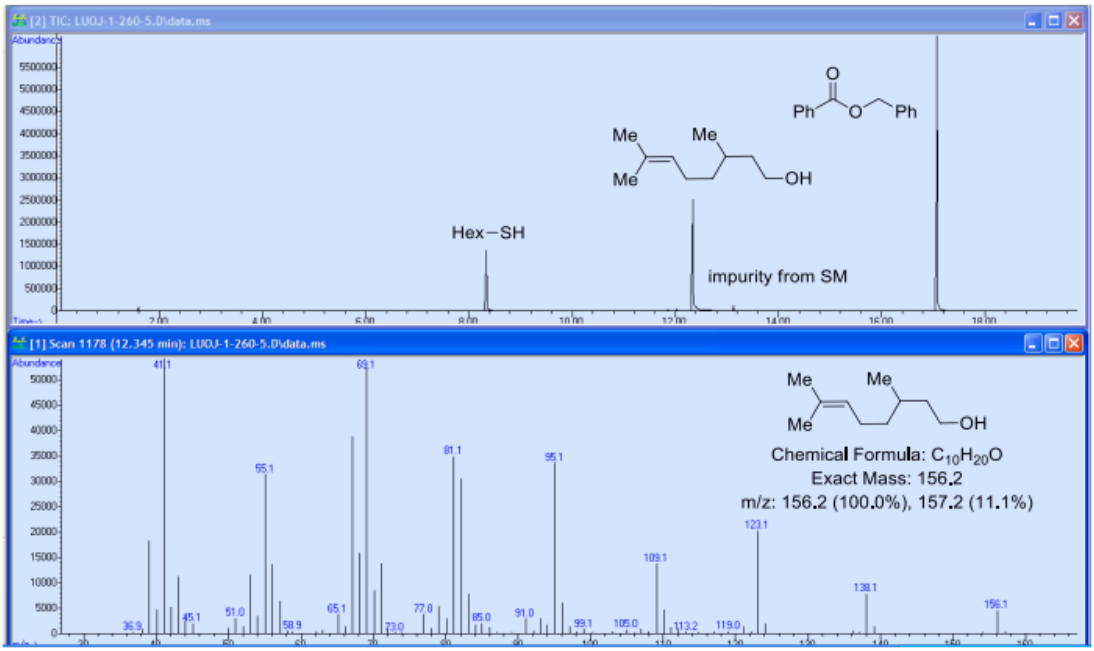


Figure S29. GC-MS chromatogram of crude reaction mixture: Scheme 4, **1e**.

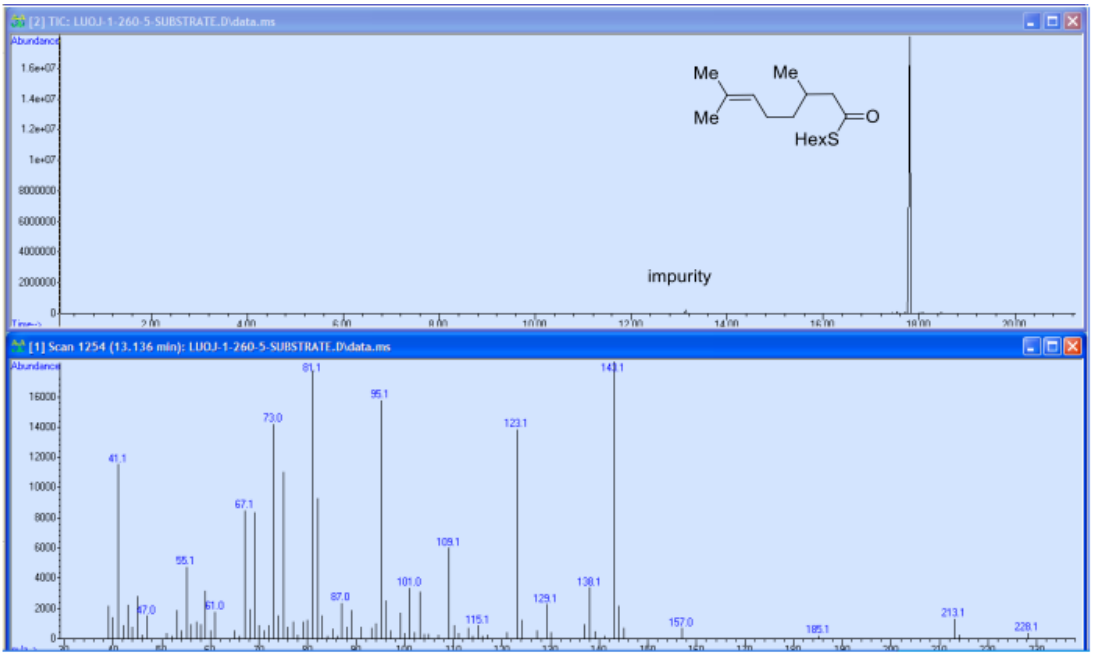


Figure S30. GC-MS chromatogram of substrate **1e**.

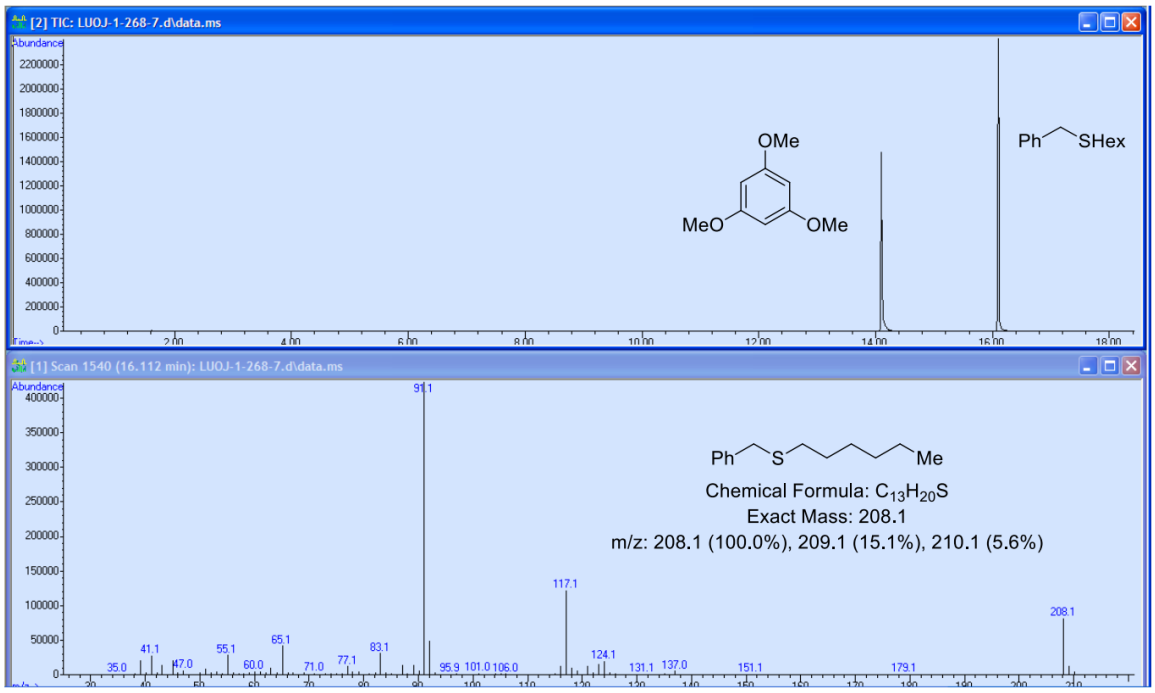


Figure S31. GC-MS chromatogram of crude reaction mixture: **1i** in the presence of 3% $In(OTf)_3$.

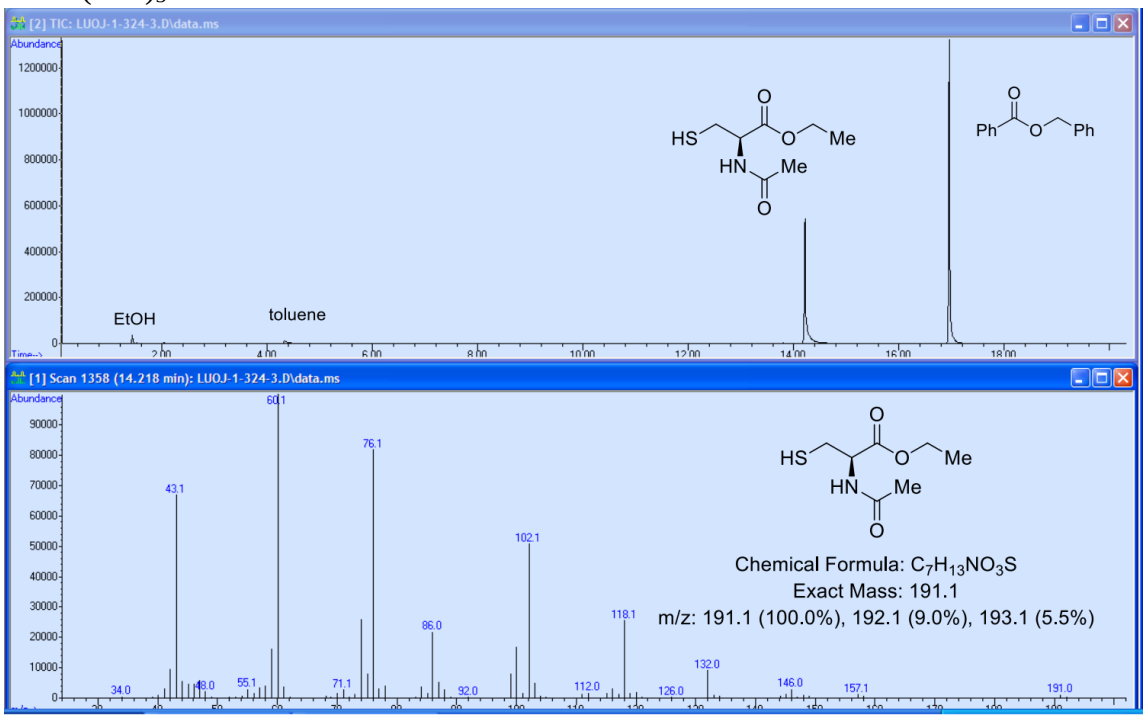


Figure S32. GC-MS chromatogram of crude reaction mixture: Scheme 5, **1p**.

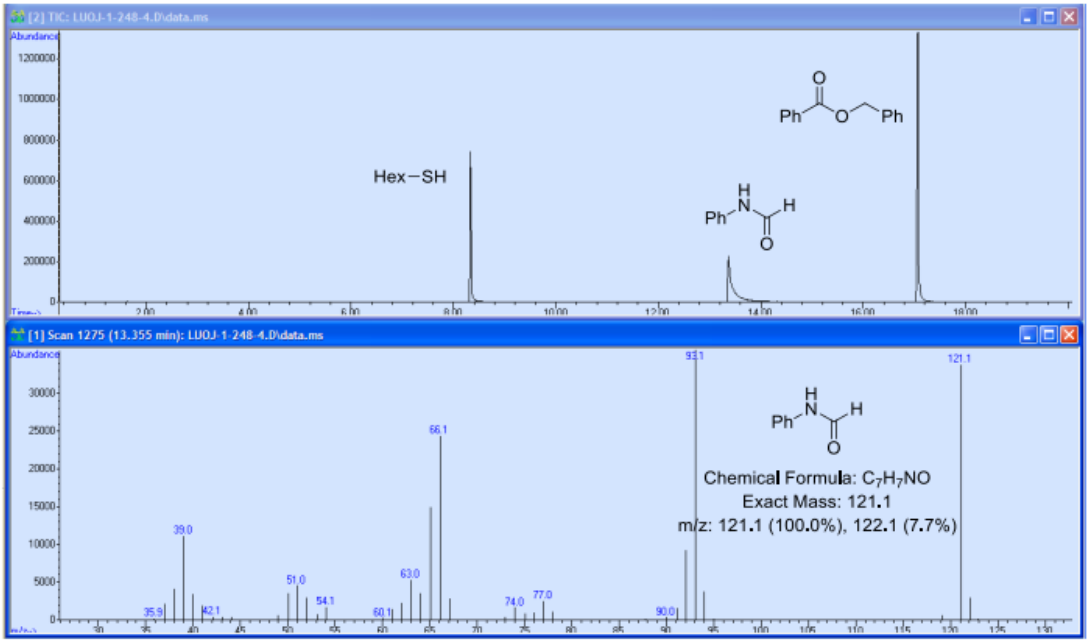


Figure S33. GC-MS chromatogram of crude reaction mixture: Scheme 6, **4a**.

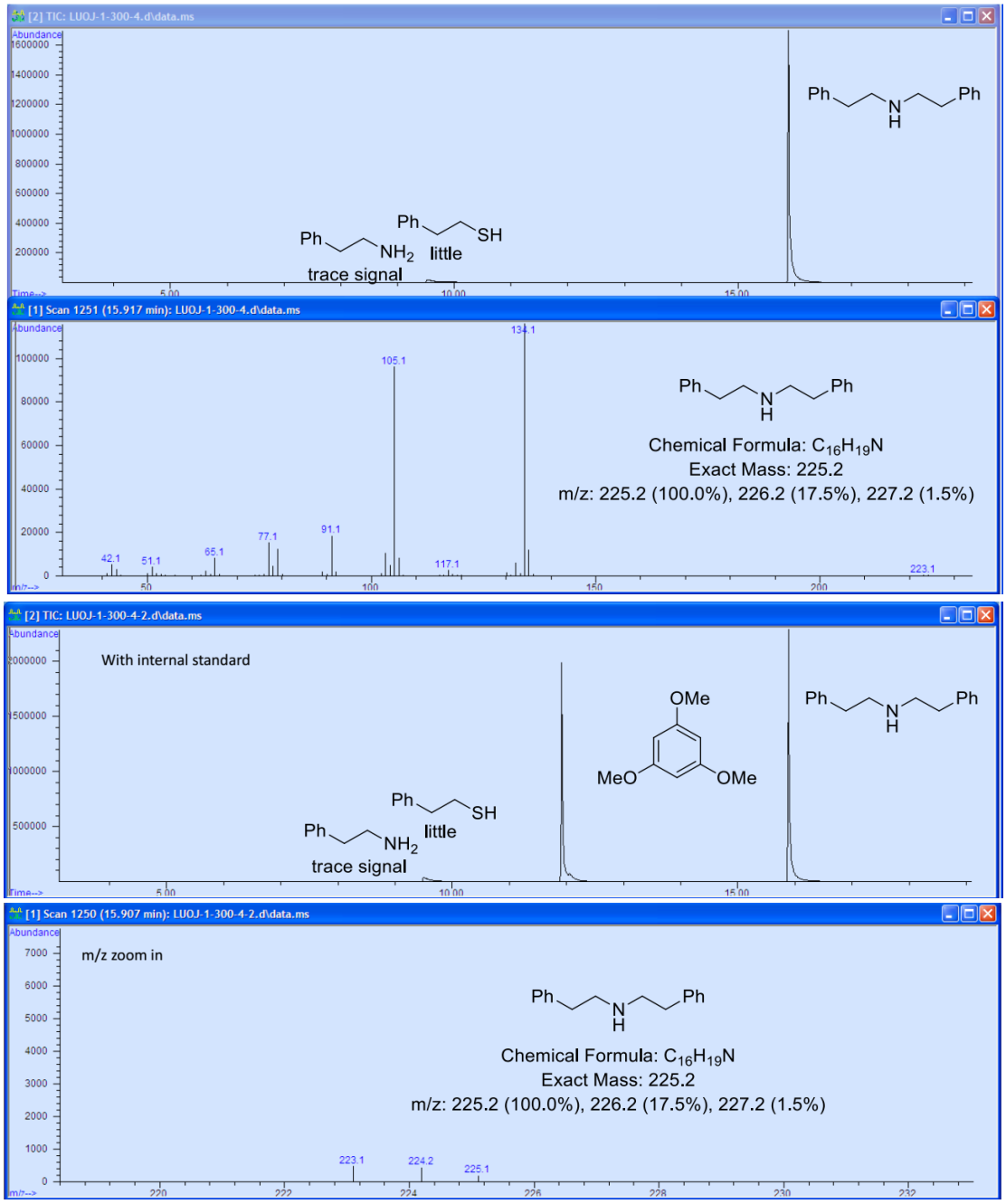


Figure S34. GC-MS chromatogram of crude reaction mixture: Scheme 6, **5c**

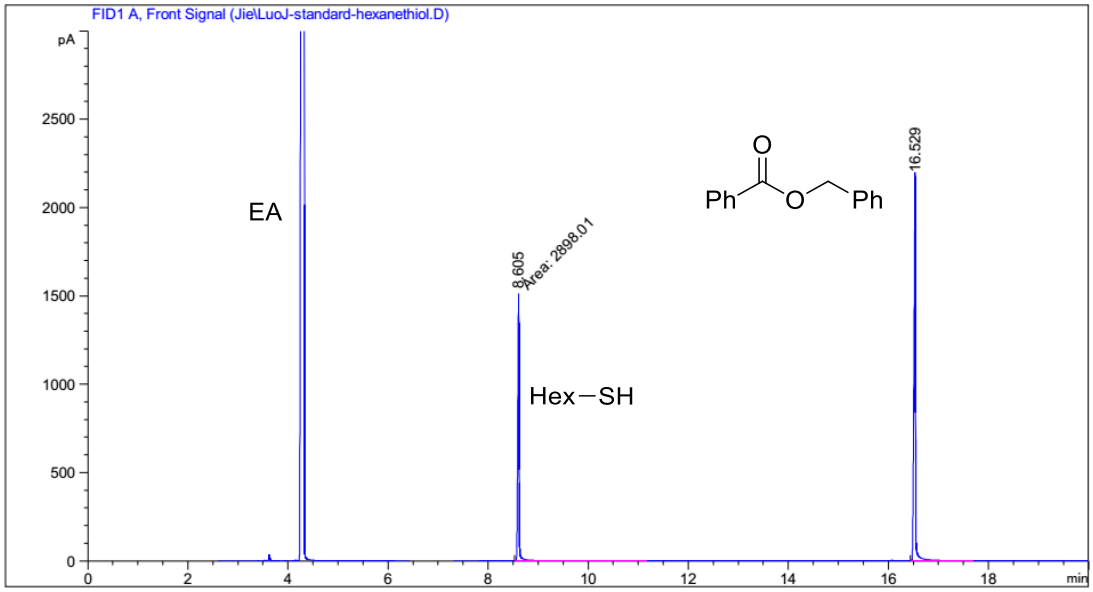


Figure S35. GC chromatogram of authentic sample: hexanethiol and benzyl benzoate, relative response factor = 2.61

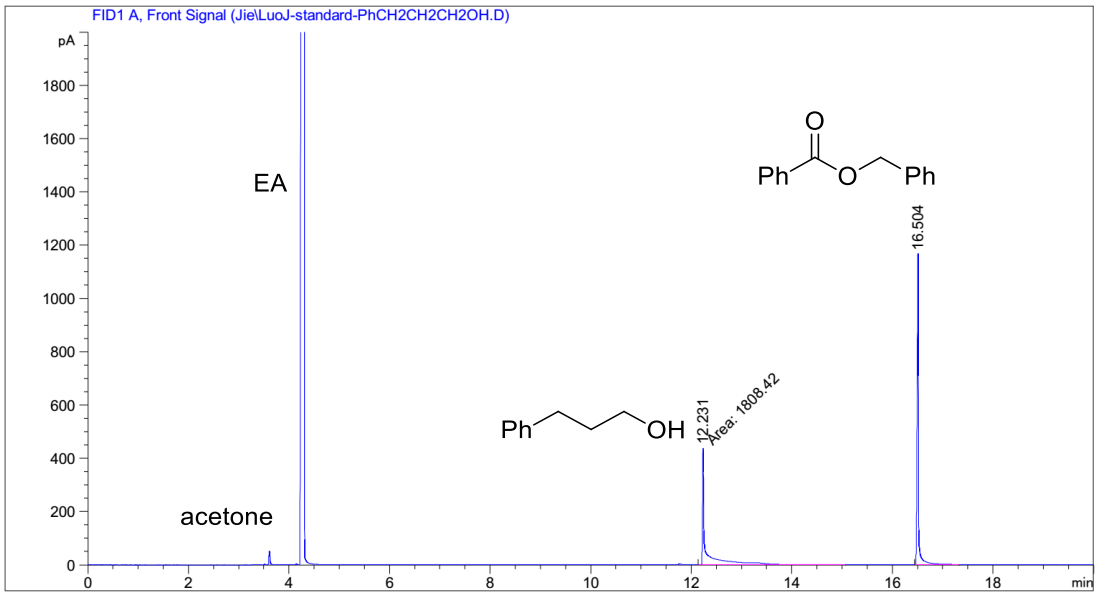


Figure S36. GC chromatogram of authentic sample: 3-phenylpropan-1-ol and benzyl benzoate, relative response factor = 1.49

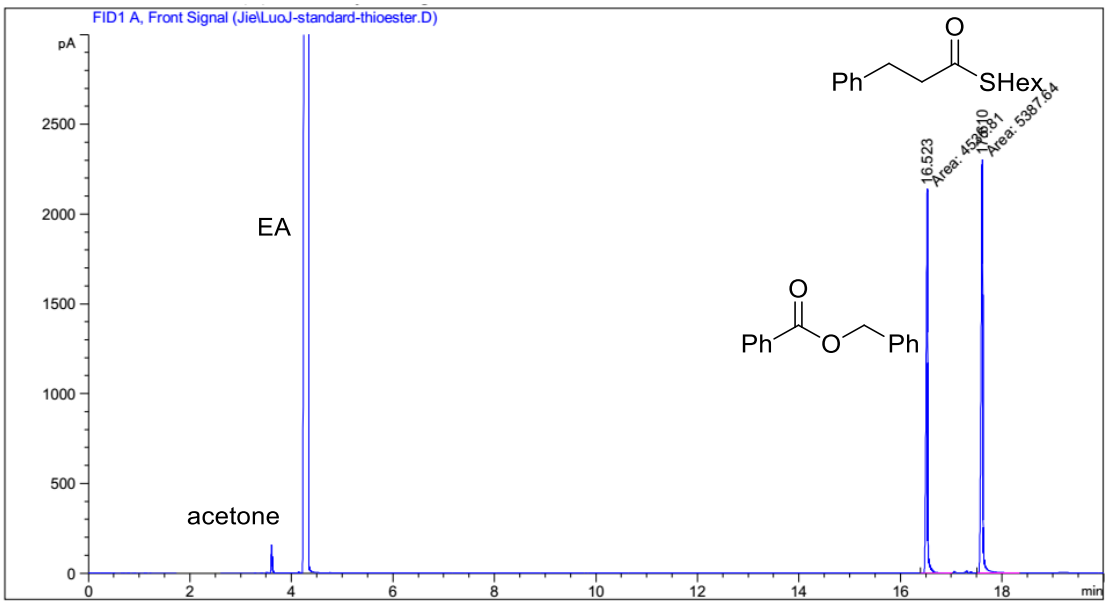
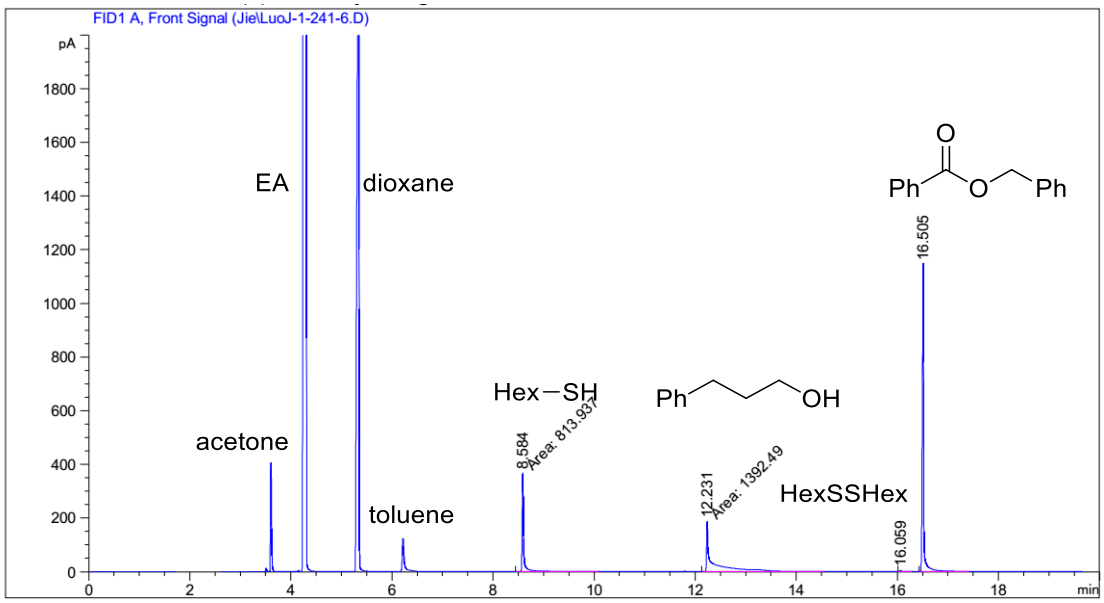


Figure S37. GC chromatogram of authentic sample: S-hexyl 3-phenylpropanethioate and benzyl benzoate, relative response factor = 0.91



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	8.584	MM	0.0369	813.93744	367.85257	18.35811
2	12.231	MM	0.1242	1392.49414	186.90668	31.40727
3	16.059	BB	0.0326	9.24848	4.20666	0.20860
4	16.505	BB	0.0286	2217.98755	1143.19055	50.02602

Figure S38. GC chromatogram of crude reaction mixture: Table 1, entry 7.

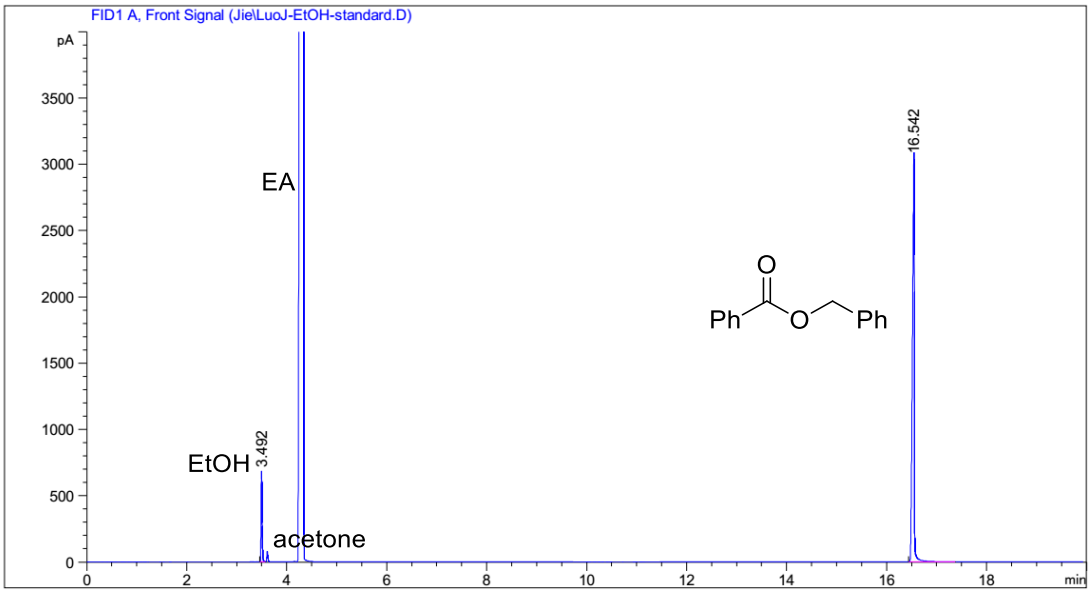
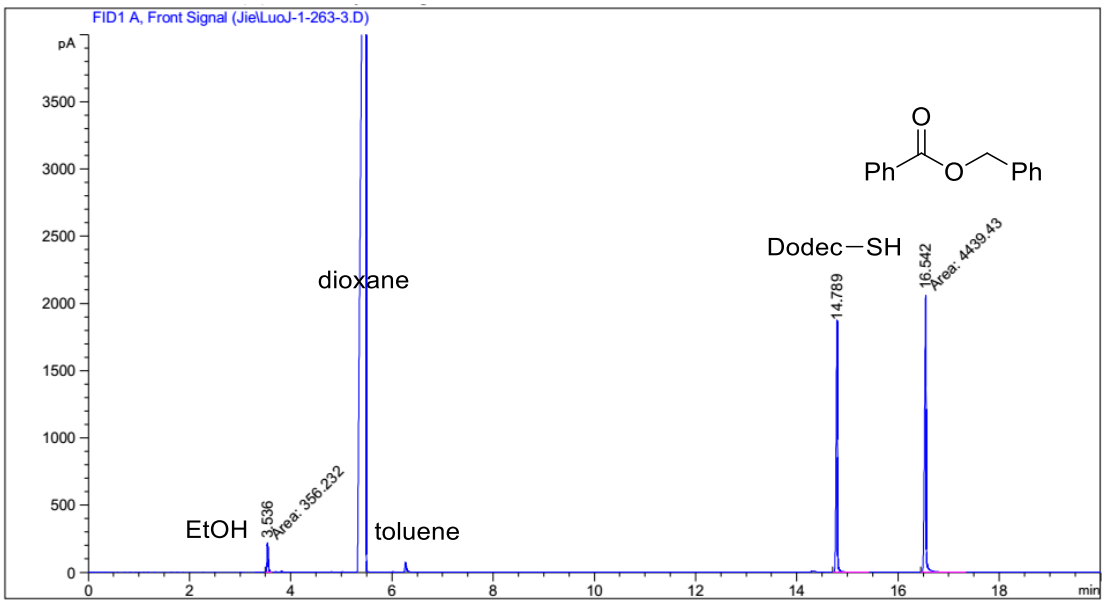


Figure S39. GC chromatogram of authentic sample: ethanol and benzyl benzoate, relative response factor = 11.72



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.536	MM	0.0266	356.23169	223.24672	4.34071
2	14.789	BB	0.0286	3411.10352	1846.16370	41.56454
3	16.542	MM	0.0357	4439.42871	2072.53662	54.09475

Figure S40. GC chromatogram of crude reaction mixture: Scheme 5, **1j**

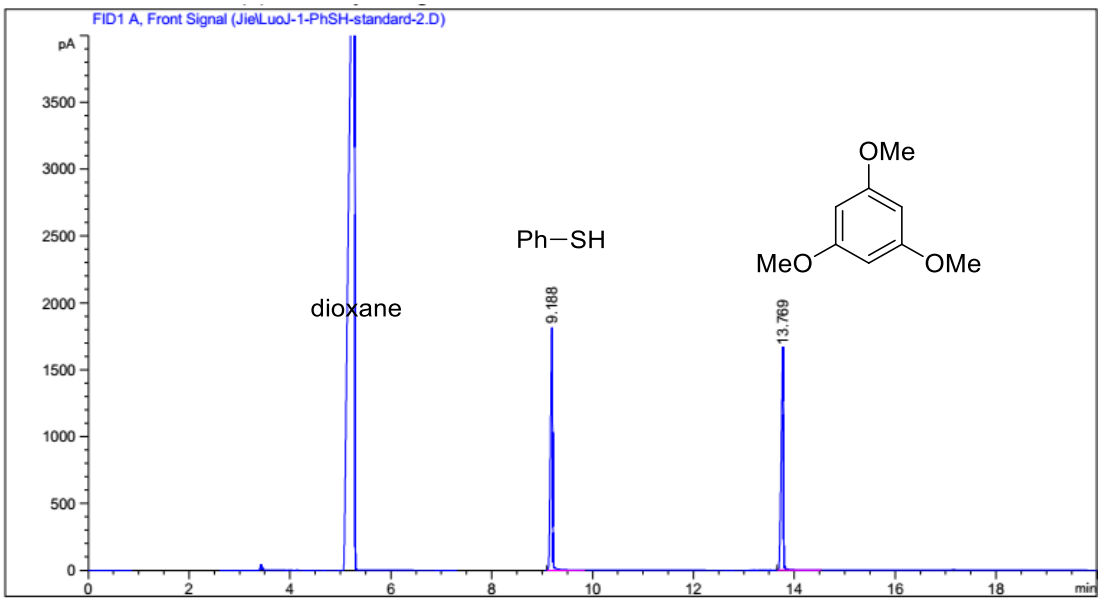
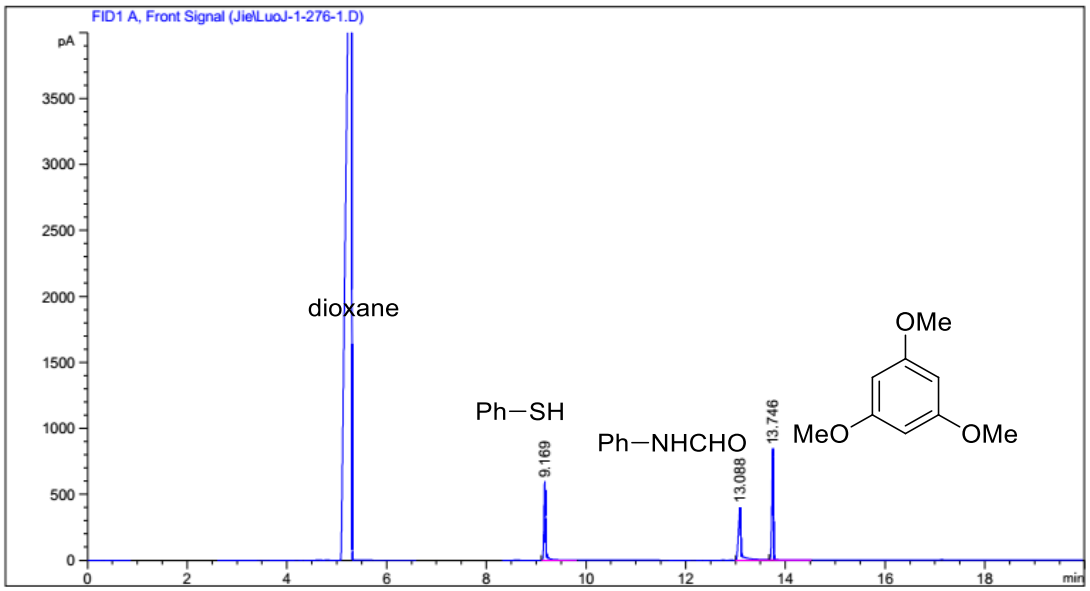


Figure S41. GC chromatogram of authentic sample: thiophenol and 1,3,5-trimethoxy-benzene, relative response factor = 1.21



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	9.169	BB	0.0367	1411.53015	594.09772	28.85256
2	13.088	BV	0.0543	1591.74658	401.12973	32.53630
3	13.746	VB	0.0342	1888.94067	841.10016	38.61114

Figure S42. GC chromatogram of crude reaction mixture: Scheme 6, **4b**

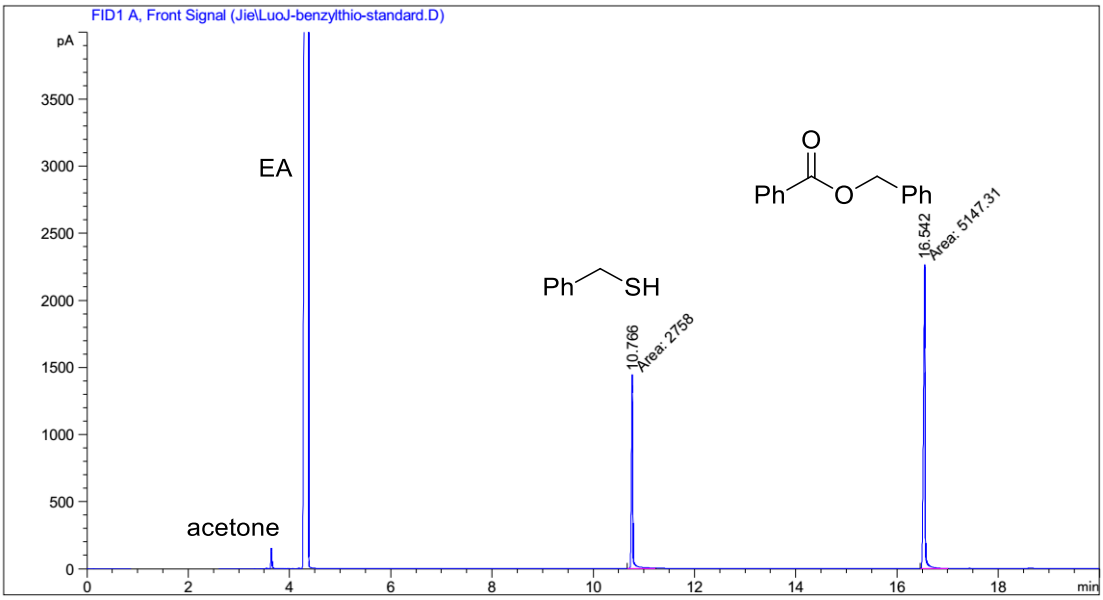


Figure S43. GC chromatogram of authentic sample: benzyl thiol and benzyl benzoate, relative response factor = 2.39

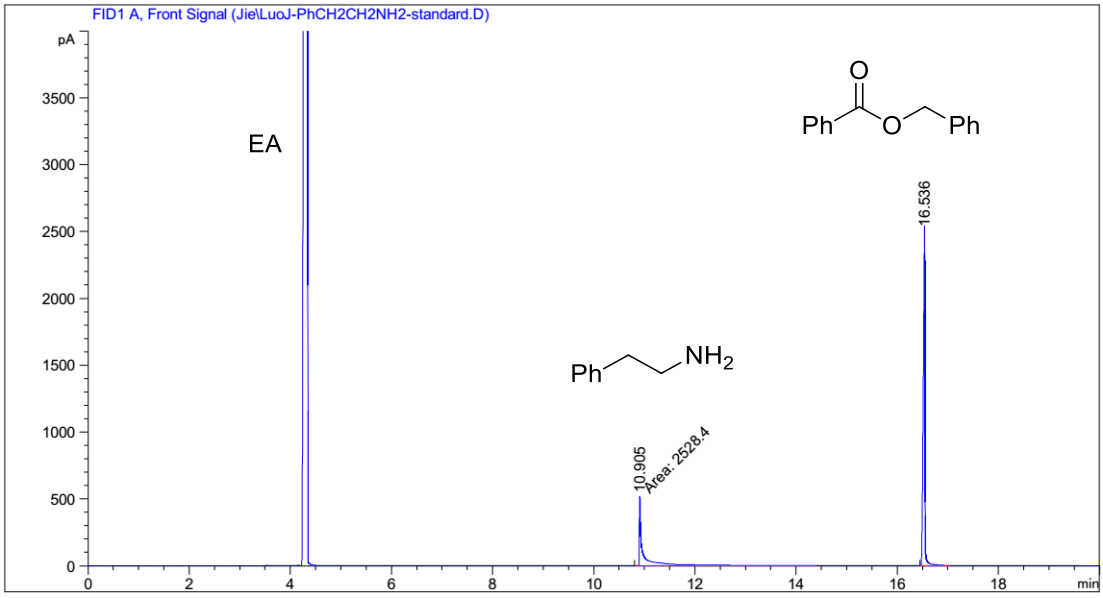
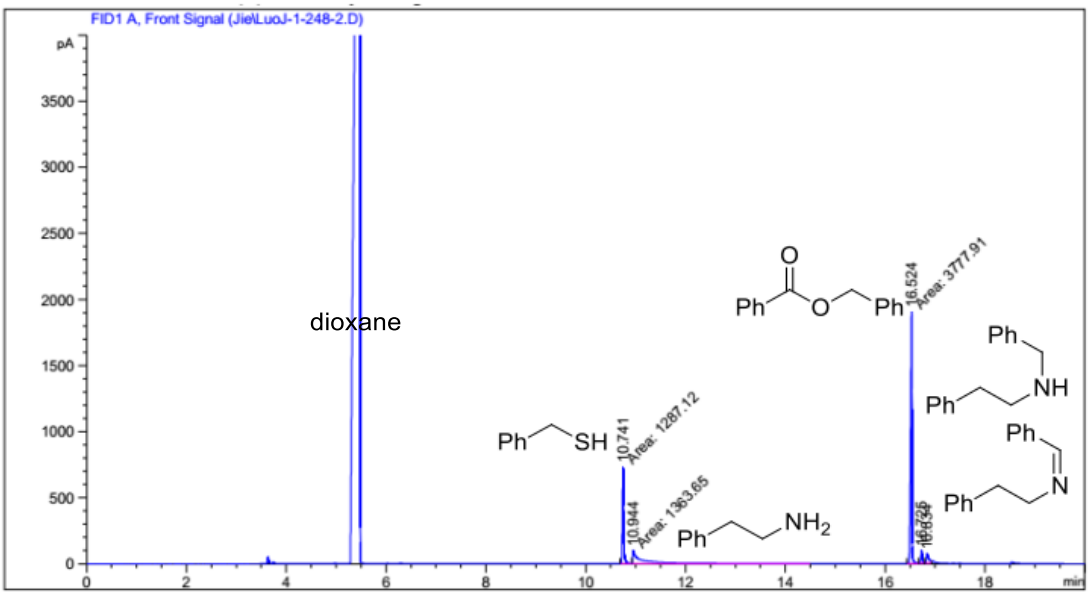


Figure S44. GC chromatogram of authentic sample: 2-phenylethanamine and benzyl benzoate, relative response factor = 2.27



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	10.741	MM	0.0291	1287.11743	736.19598	18.74243
2	10.944	MM	0.2274	1363.64563	99.95888	19.85680
3	16.524	MM	0.0330	3777.90625	1908.92322	55.01219
4	16.725	BV	0.0295	185.58269	96.30071	2.70237
5	16.834	VV	0.0488	253.14659	72.40987	3.68621

Figure S45. GC chromatogram of crude reaction mixture: Scheme 6, **5a**

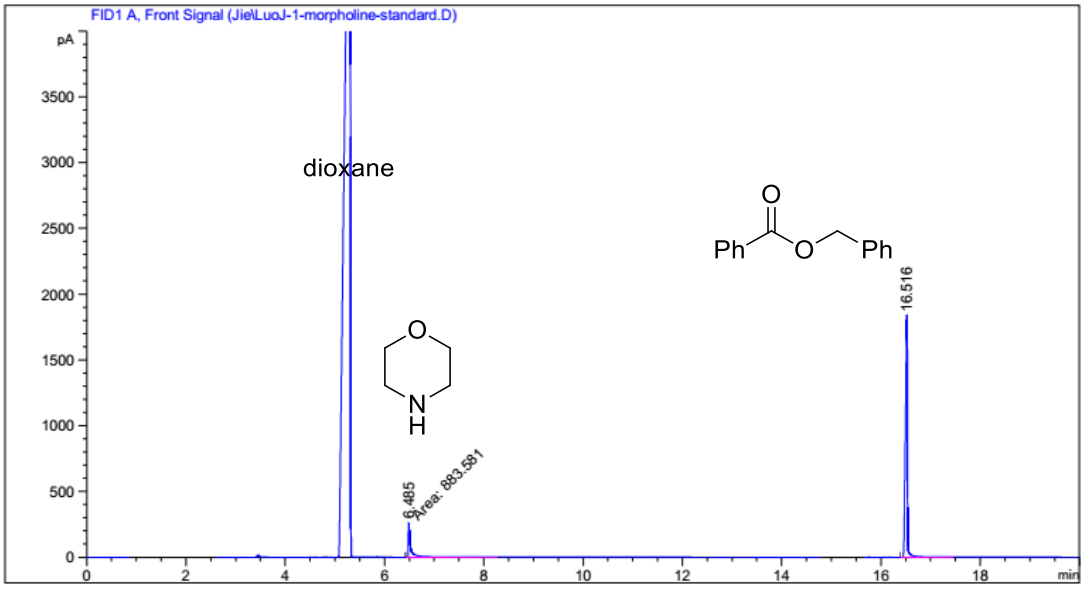
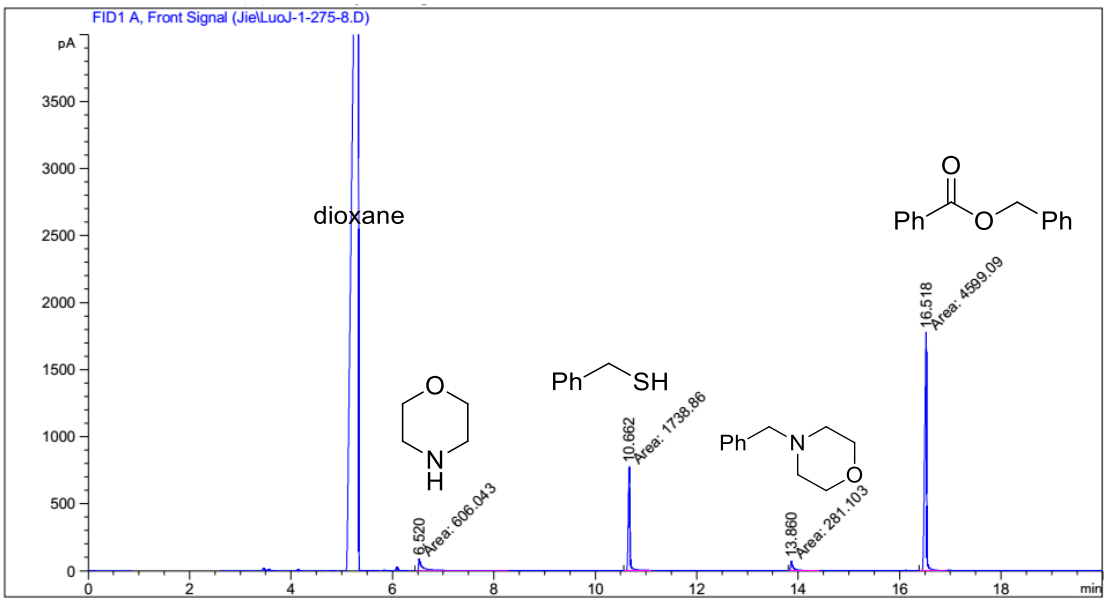


Figure S46. GC chromatogram of authentic sample: morpholine and benzyl benzoate, relative response factor = 6.28

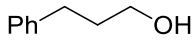


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.520	MM	0.1133	606.04285	89.13263	8.38802
2	10.662	MM	0.0374	1738.86426	773.96118	24.06698
3	13.860	MM	0.0661	281.10266	70.86086	3.89064
4	16.518	MM	0.0431	4599.09424	1777.11584	63.65437

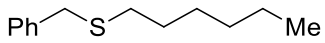
Figure S47. GC chromatogram of crude reaction mixture: Scheme 6, **5b**.

9. Selected isolated compounds

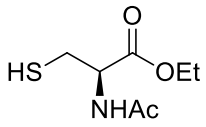
Following the general procedures of hydrogenation, the resulting reaction mixture was directly filtered through Celite without the addition of an internal standard. The Celite was then rinsed with $CHCl_3$ (2×2 mL) and the solution and washings were combined. The solvent and volatiles were removed under vacuum, resulting in quite pure product(s) (see Figure S19 and Figure S49). The isolated yields were obtained after further purification by flash column chromatography



3-Phenylpropan-1-ol: By hydrogenation of **1a** using the general procedure A. Eluent: hexane/EtOAc = 2/1, v/v. 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.01 (m, 5H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.69 – 2.53 (m, 2H), 2.21 (s, 1H), 1.88 – 1.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9, 128.4, 128.4, 125.9, 62.1, 34.2, 32.1.



Benzyl(hexyl)sulfane: By hydrogenation of **1i** using the general procedure B. Eluent: hexane/EtOAc = 30/1. 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 5H), 3.72 (s, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.57 (dt, *J* = 14.9, 7.3 Hz, 2H), 1.42 – 1.23 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 128.8, 128.4, 126.9, 36.3, 31.5, 31.4, 29.2, 28.6, 22.6, 14.1.



***N*-acetyl L-cysteine ethyl ester**: By hydrogenation of **1p** using the general procedure A in the presence of 2% HexSH at 150 ^{o}C. Eluent: hexane/EtOAc = 1/2. 98% yield. $[\alpha]^{25}_D$ = +60.1 (c = 2.6, $CHCl_3$, +60.4 for standard sample). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 6.6 Hz, 1H), 4.83 – 4.69 (m, 1H), 4.20 – 4.04 (m, 2H), 2.89 (dd, *J* = 8.9, 4.3 Hz, 2H), 1.97 (s, 3H), 1.35 (t, *J* = 8.9 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.13, 170.09, 61.8, 53.6, 26.7, 22.8, 14.0.

The circular dichroism (CD) spectrum in $CHCl_3$ was carried out using a nitrogen-purged Chirascan™-Plus spectrometer, (Applied Photophysics, UK). The spectrum was carried out over a scan range of 450 to 180 nm, 2sec time per point, 1nm step size, and a 1nm bandwidth. The CD spectra were scanned using a 0.2 cm path length cuvette and the $CHCl_3$ spectrum subtracted. The standard sample was prepared according to a reported method[12] and measured under the same conditions.

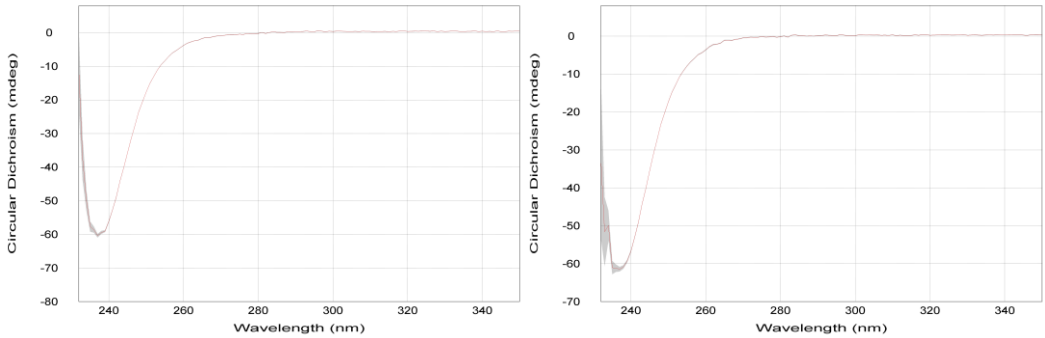
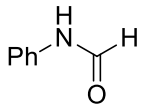
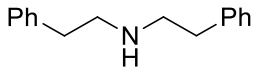


Figure S48. CD spectra (230-350 nm) of product of **1p** (left) and standard sample (right) in $CHCl_3$ (0.027 M) at 25 ℃.

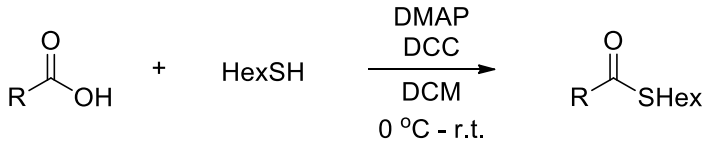


***N*-Phenylformamide**: By hydrogenation of **4a** using the general procedure A. Eluent: hexane/EtOAc = 2/1. 95% yield, behave as rotamers in $CDCl_3$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 – 8.90 (m, 0.5H), 8.78 – 8.63 (m, 0.5H), 8.45 – 8.21 (m, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.31 (dt, *J* = 15.1, 7.8 Hz, 2H), 7.21 – 7.07 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 159.7, 137.1, 136.8, 129.7, 129.0, 125.2, 124.7, 120.2, 118.8.

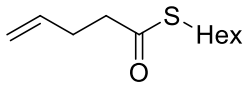


Diphenethylamine: By hydrogenation of **5c** using the general procedure A under 40 bar H_2 at 150 ^{o}C. Eluent: DCM/MeOH = 10/1. 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 6.98 (m, 10H), 2.89 (t, *J* = 6.5 Hz, 4H), 2.79 (t, *J* = 6.5 Hz, 4H), 1.40 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 128.7, 128.4, 126.1, 51.0, 36.3.

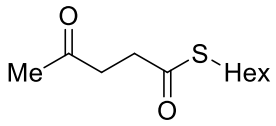
10. Synthetic procedures and characterization data of thioesters



To a stirred solution of the carboxylic acid (10 mmol) in dichloromethane (20 mL) was added hexanethiol (1.4 mL, 10 mmol) and 4-dimethylaminopyridine (0.12 g, 1 mmol) at 0 ℃. Then *N*,*N*-dicyclohexylcarbodiimide (2.06 g, 10 mmol) was added portionwise. The resulting thick white slurry was stirred rigorously for 24 h, at which point the reaction mixture was diluted with pentane (50 mL) and the resulting mixture were filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by flash column chromatography (eluent: hexane/EtOAc = 50/1, v/v).

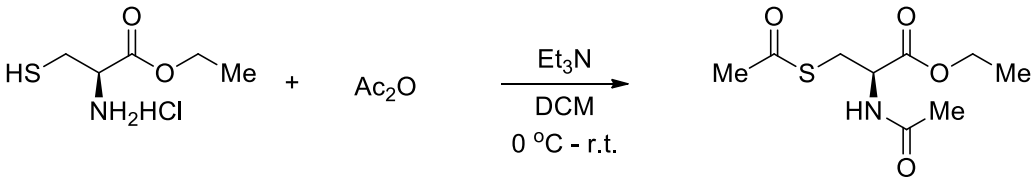


S-Hexyl pent-4-enethioate (1f): 76% yield. Colorless oil. IR (KBr): 2927, 1691, 1641, 1467, 1412, 1039, 915 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.09 – 4.93 (m, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.63 (dd, *J* = 8.2, 6.8 Hz, 2H), 2.40 (dt, *J* = 13.7, 6.8 Hz, 2H), 1.60 – 1.49 (m, 2H), 1.42 – 1.18 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 136.3, 115.8, 43.2, 31.4, 29.6, 29.6, 28.9, 28.6, 22.6, 14.1. GC-EI-MS *m/z* calcd. for $C_{11}H_{20}OS$ $[M]^+$: 200.1, found: 200.0.

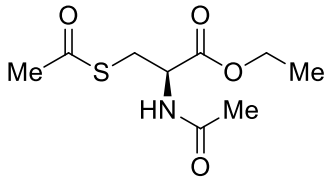


S-Hexyl 4-oxopentanethioate (1g): 76% yield. Colorless oil. IR (KBr): 2928, 1725, 1688, 1411, 1367, 1162, 1072 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 – 2.67 (m, 6H), 2.14 (s, 3H), 1.60 – 1.43 (m, 2H), 1.38 – 1.15 (m, 6H), 0.84 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 198.5, 38.1, 37.5, 31.3, 29.8, 29.5, 28.9, 28.5, 22.5, 14.0. GC-EI-MS *m/z* calcd. for $C_{11}H_{20}O_2S$ $[M]^+$: 216.1, found: 216.1.



To a stirred solution of L-cysteine ethyl ester hydrochloride (1.86 g, 10 mmol) in DCM (20 mL) was added Et_3N (5.0 mL, 36 mmol) and Ac_2O (2.1 mL, 22 mmol) at 0 ℃. The resulting mixture was stirred at 0 ℃ for 10 min, after which it was warmed up to 25 ℃ and stirred overnight. Then the reaction was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product which was purified by flash column chromatography (eluent: hexane/EtOAc = 1/2, v/v). The resulting solid was further recrystallized in EtOAc/hexane to remove the color, affording a pale white solid **1p** in 72% yield.



***N*,S-diacetyl L-cysteine ethyl ester (1p)**: $[\alpha]^{25}_D$ = +63.3 (c = 2.6, $CHCl_3$). IR (KBr): 3275, 2984, 1742, 1698, 1662, 1538, 1132, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, *J* = 6.5 Hz, 1H), 4.75 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.47 – 3.20 (m, 2H), 2.32 (s, 3H), 1.98 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 195.1, 170.2, 170.0, 62.0, 52.1, 30.9, 30.5, 23.0, 14.1. GC-EI-MS *m/z* calcd. for $C_9H_{15}NO_4S$ $[M]^+$: 233.1, found: 233.1.

11. Selected NMR spectra

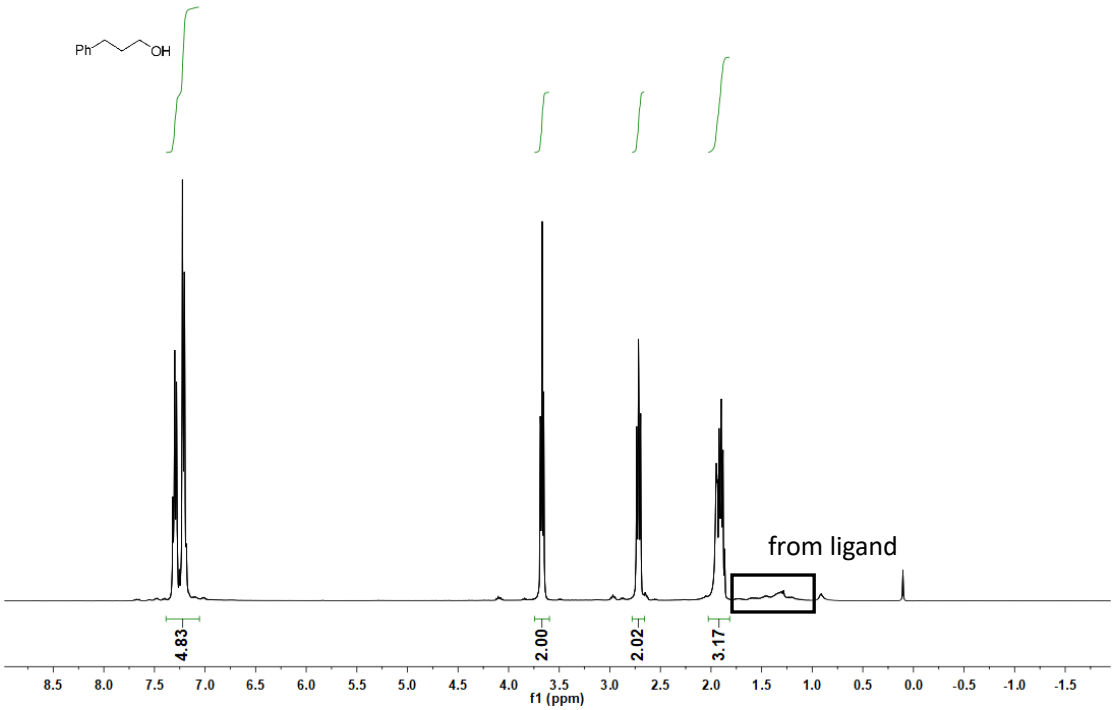


Figure S49. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 3-phenylpropan-1-ol without further purification.

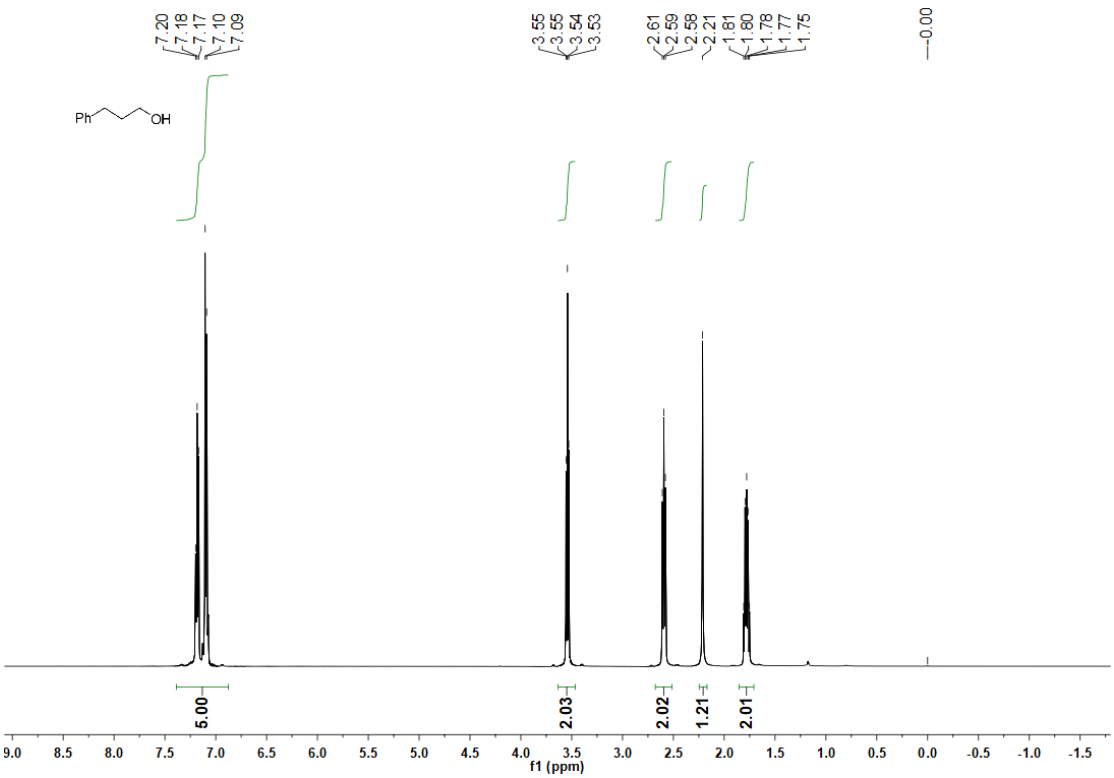


Figure S50. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 3-phenylpropan-1-ol after purification.

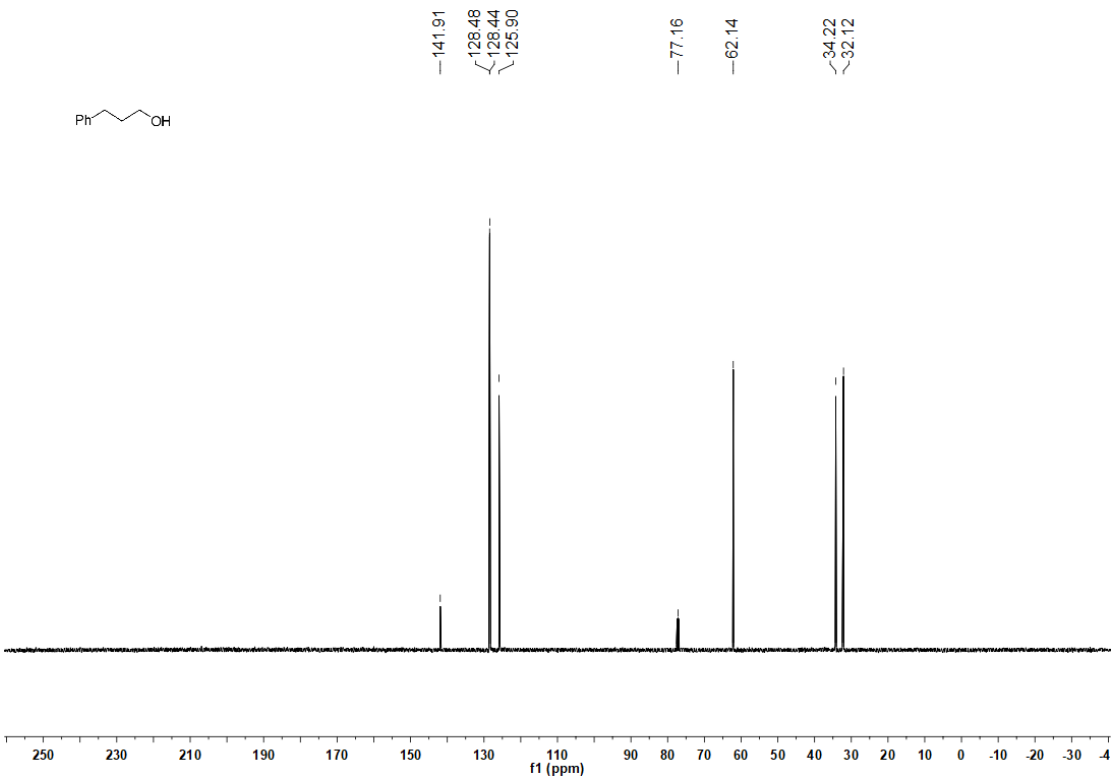


Figure S51. ^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of 3-phenylpropan-1-ol after purification.

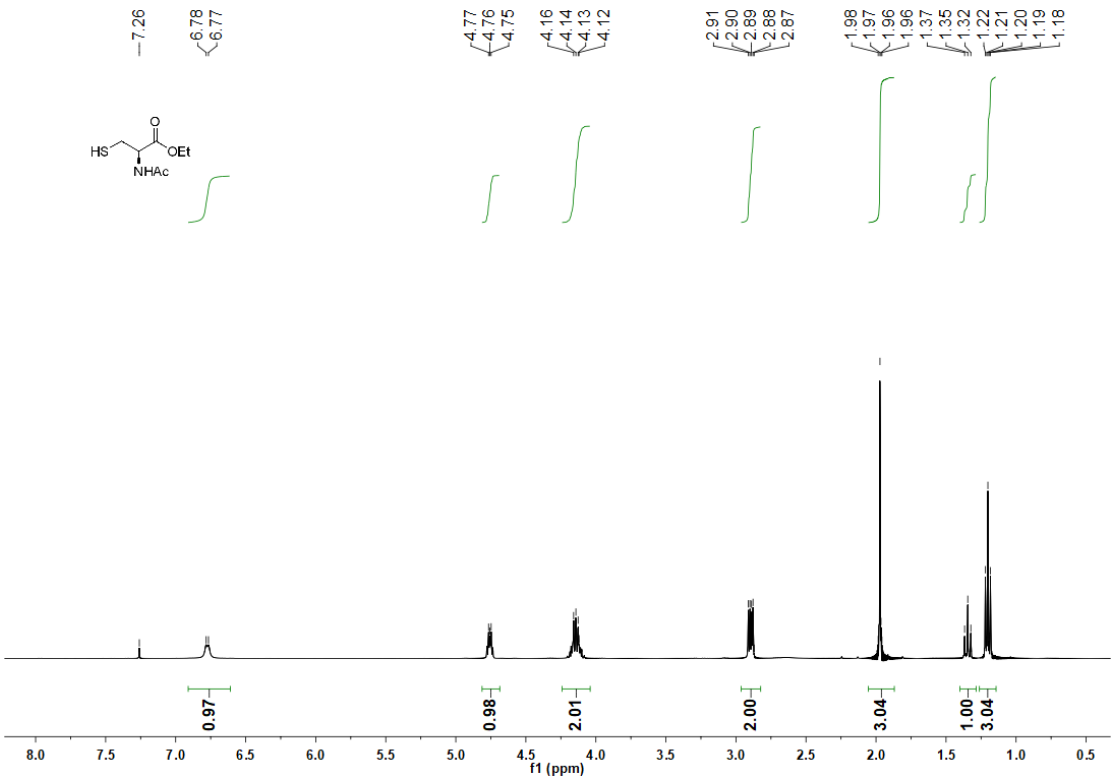


Figure S52. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-acetyl L-cysteine ethyl ester after purification.

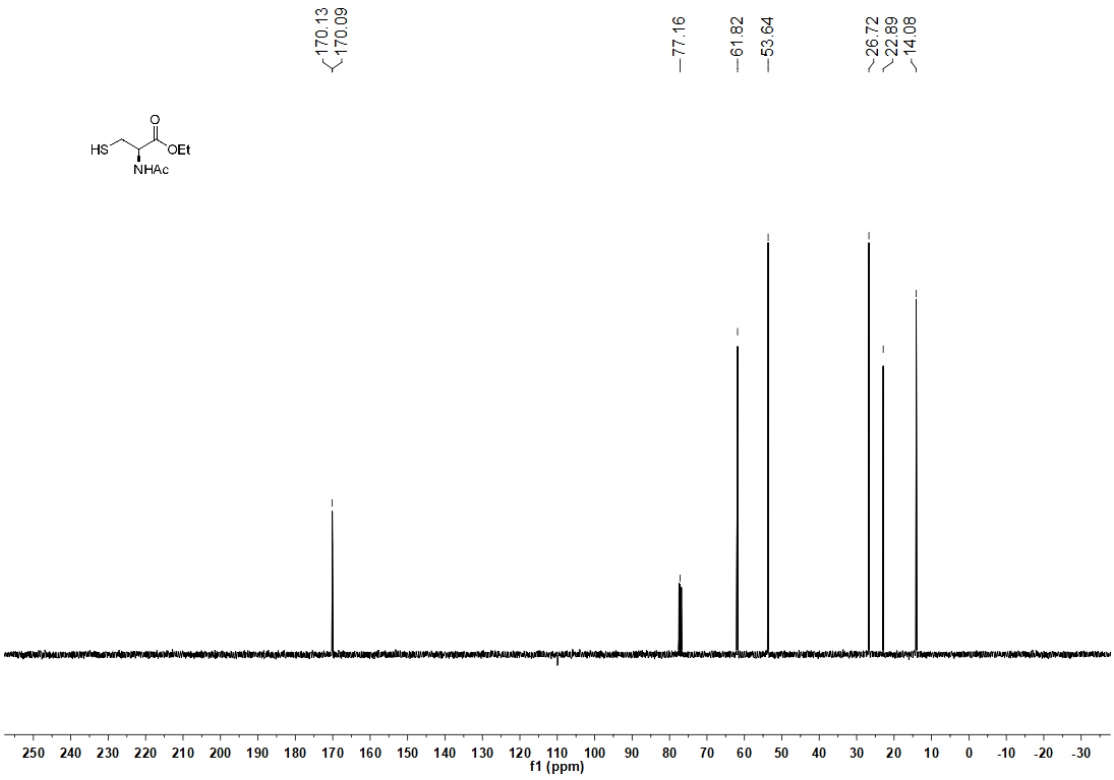


Figure S53. ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of *N*-acetyl L-cysteine ethyl ester after purification.

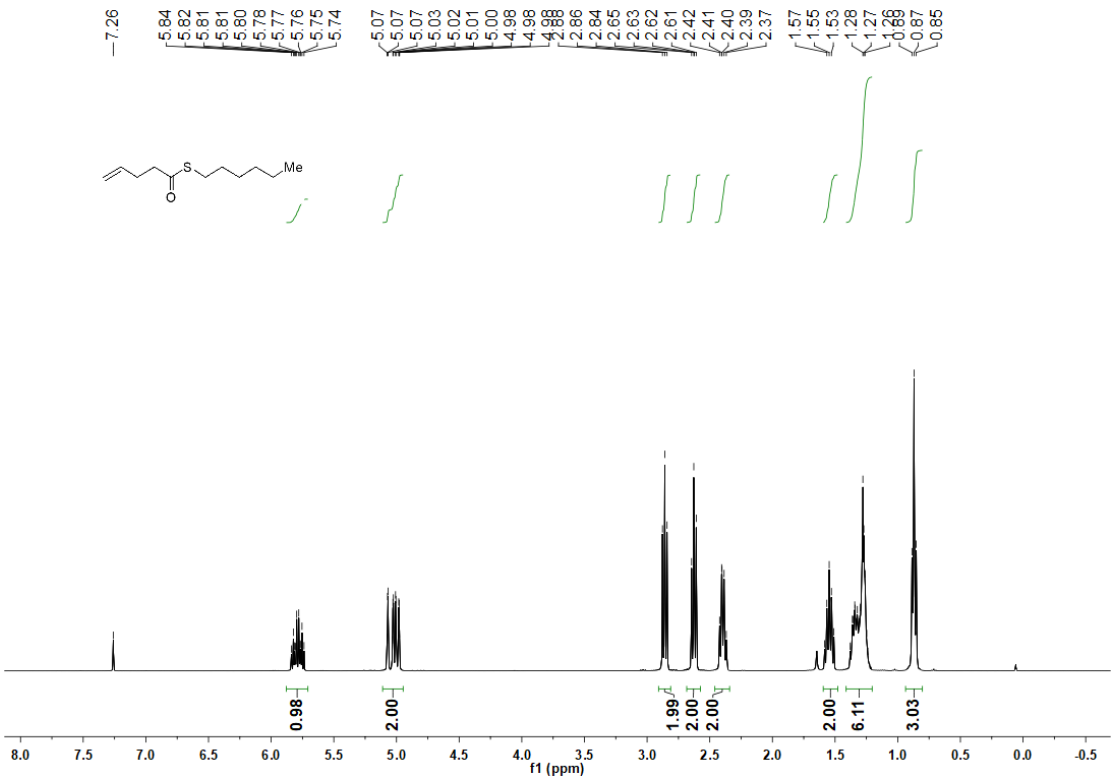


Figure S54. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of **1f**.

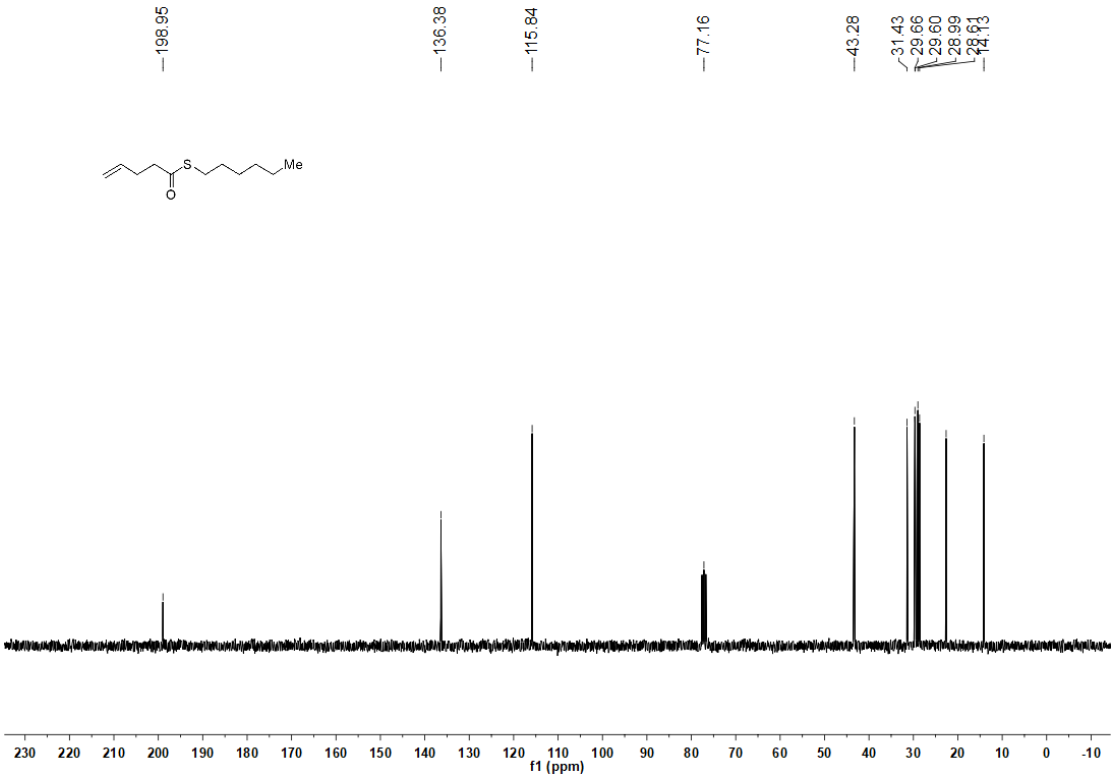


Figure S55. ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of **1f**.

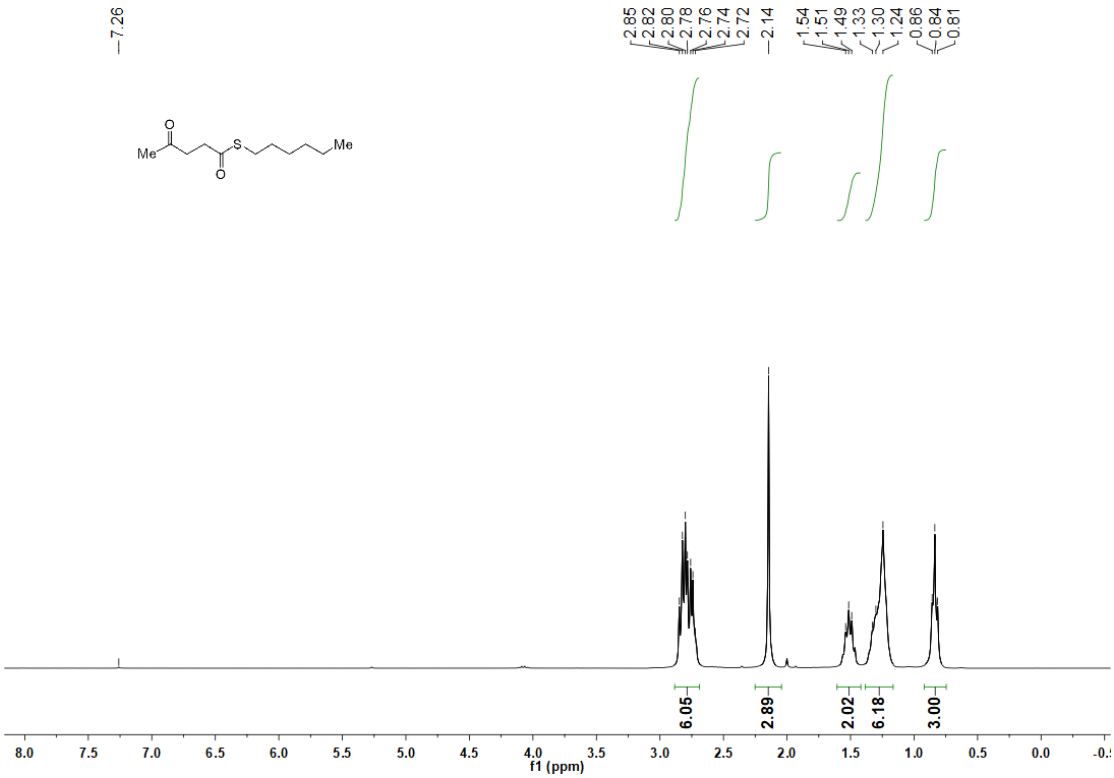


Figure S56. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **1g**.

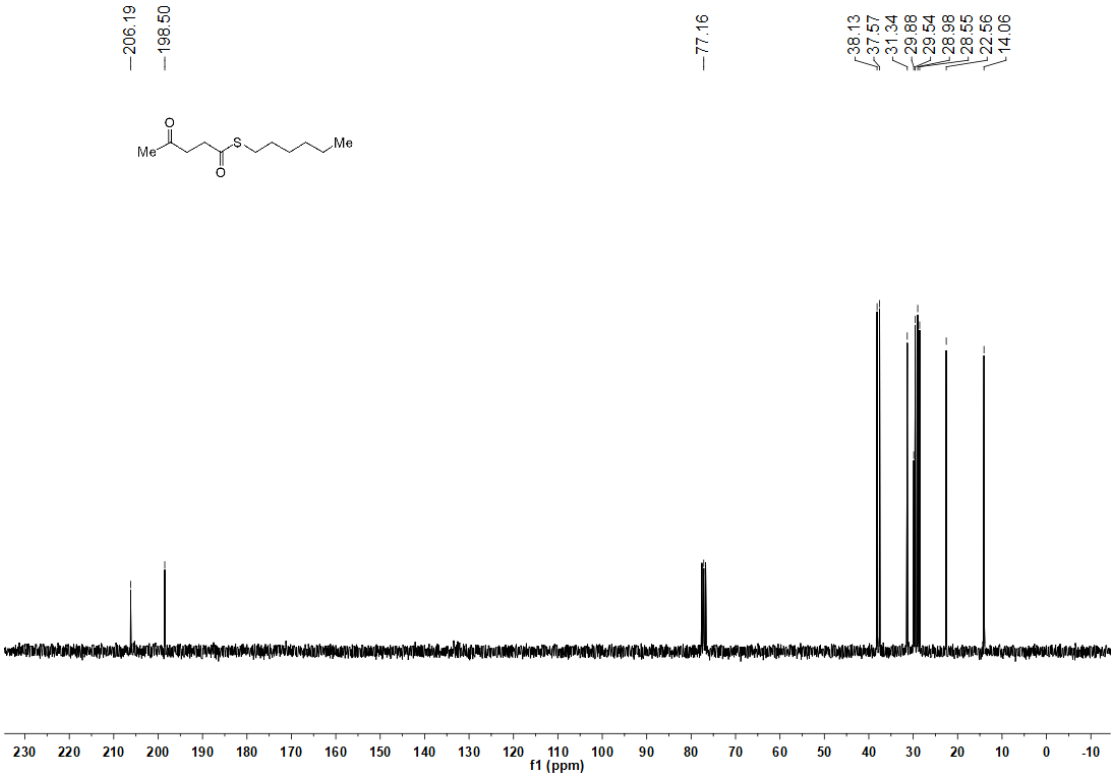


Figure S57. ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of **1g**.

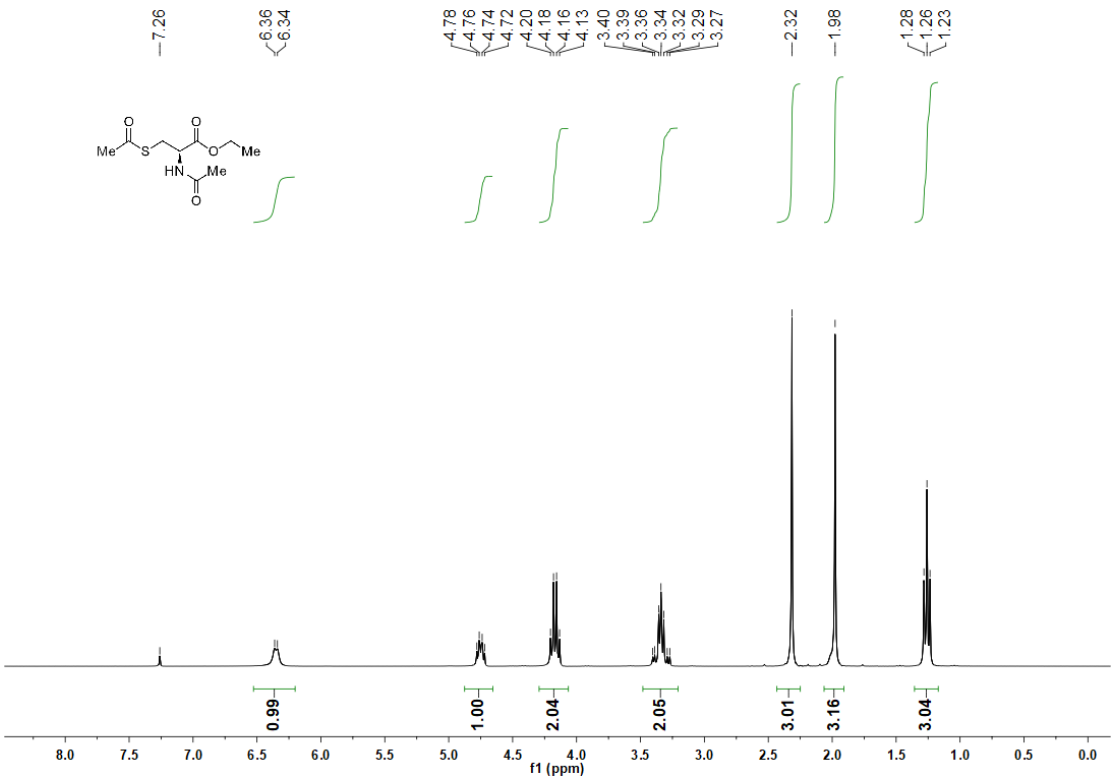


Figure S58. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **1p**.

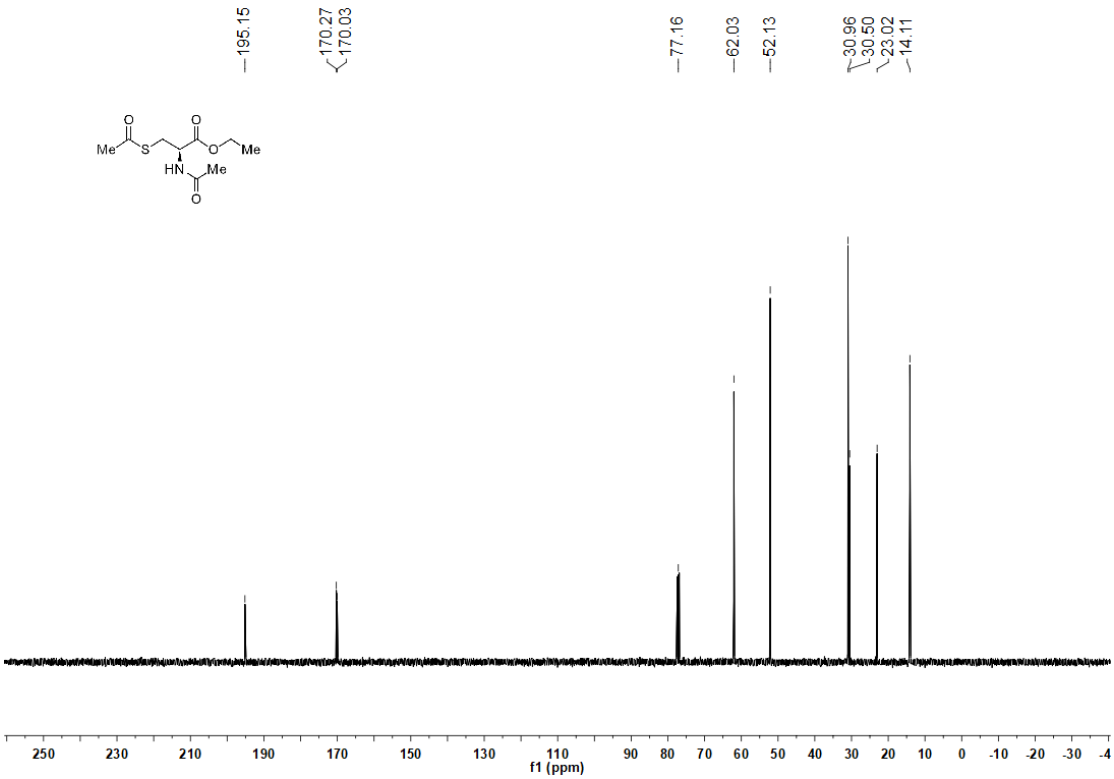


Figure S59. ^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of **1p**.

12. References

1. Zou, Y.-Q.; Wolff, N. v.; Anaby, A.; Xie, Y.; Milstein, D. Ethylene glycol as an efficient and reversible liquid-organic hydrogen carrier. *Nat. Catal.* **2019**, *2*, 415-422.
2. Luo, J.; Rauch, M.; Avram, L.; Diskin-Posner, Y.; Shmul, G.; Ben-David, Y.; Milstein, D. Formation of Thioesters by Dehydrogenative Coupling of Thiols and Alcohols with H_2 Evolution. *Nat. Catal.* **2020**, *3*, 887–892.
3. Gnanaprakasam, B.; Zhang, J.; Milstein, D. Direct Synthesis of Imines from Alcohols and Amines with Liberation of H_2. *Angew. Chem. Int. Ed.* **2010**, *49*, 1468-1471.
4. Balaraman, E.; Gnanaprakasam, B.; Shimon, L. J. W.; Milstein, D. Direct Hydrogenation of Amides to Alcohols and Amines under Mild Conditions. *J. Am. Chem. Soc.* **2010**, *132*, 16756-16758.
5. Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. Facile Conversion of Alcohols into Esters and Dihydrogen Catalyzed by New Ruthenium Complexes. *J. Am. Chem. Soc.* **2005**, 127, 10840-10841.
6. Roberts, D.M.; Bartel, C.; Scott, A.; Ivison, D.; Simpsona, T. J.; Cox, R. J.; Substrate Selectivity of An Isolated Enoyl Rductase Catalytic Domain from An Iterative Highly Reducing Fungal Polyketide Synthase Reveals Key Components of Programming. *Chem. Sci.*, **2017**, *8*, 1116-1126.
7. Thielman, J. R.; Sherman, D. H.; Williams, R. M. Stereoselective Synthesis of Baulamycin A. *J. Org. Chem.* **2020**, *85*, 3812-3823.
8. Tarantino, K, T.; Miller, D. C.; Callon, T. A.; Knowles, R. R. Bond-Weakening Catalysis: Conjugate Aminations Enabled by the Soft Homolysis of Strong N-H Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 6440-6443.
9. Chen, S.; Li, Y.; Chen, J; Xu, X.; Su, L.; Tang, Z.; Au, C.-T.; Qiu, R. Iodine-Promoted Synthesis of Thioamides from 1,2-Dibenzylsulfane and Difurfuryl Disulfide. *Synlett* **2016**, *27*, 2339-2344.

10. Nguyen, T. B.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. Three-Component Reaction between Alkynes, Elemental Sulfur, and Aliphatic Amines: A General, Straightforward, and Atom Economical Approach to Thioamides. *Org. Lett.* **2014**, *16*, 310-313.
11. Xie, Y; Milstein, D. Pd Catalyzed, Acid Accelerated, Rechargeable, Liquid Organic Hydrogen Carrier System Based on Methylpyridines/Methylpiperidines. *ACS Appl. Energy Mater*. **2019**, *2*, 4302-4308.
12. Tsikas, D.; Dehnert, S.; Urban, K.; Surdacki, A.; Meyer, H. H. GC-MS Analysis of S-Nitrosothiols after Conversion to S-Nitroso-*N*-acetylcysteine Ethyl Ester and In-Injector Nitrosation of Ethyl Acetate. *J. Chromatogr. B* **2009**, *877*, 3442-3455.