Supporting Information

PALLADIUM ON CARBON–CATALYZED OXIDATIVE FUNCTIONALIZATION OF BENZYLIC ETHERS

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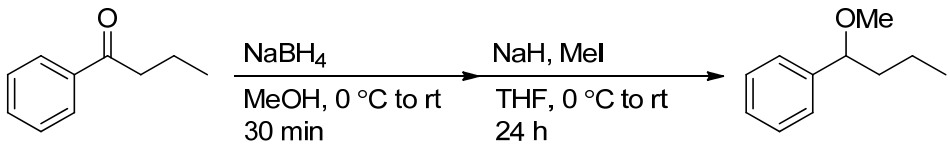
Contents

1. General information

10% Pd/C, 10% Pt/C, 10% Ru/C, 10% Rh/C, 10% Ir/C, 10% Ni/C and Au/C were supplied by N. E. Chemcat Corporation (Tokyo, Japan). Ethylene glycol was purchased from a commercial source and used without further purification. Flash column chromatography was performed with Silica Gel 60 N (Kanto Chemical Co., Inc., 63–210 μm spherical, neutral). ^{1}H NMR spectra were recorded on a JEOL ECZ 400 or ECA 500 spectrometer at room temperature in $CDCl_3$ as a solvent and internal standard (^{1}H NMR: δ= 7.26 for $CDCl_3$) with tetramethylsilane as an internal standard. Substrates (**1a**-**1i** and **3a**-**3d**) were prepared according to reference 1. Substrates (**1j** and **1k**) were prepared according to reference 2 and reference 3, respectively. Substrates (**3e**-**3g**) were prepared according to reference 4.

2. Preparation of substrates

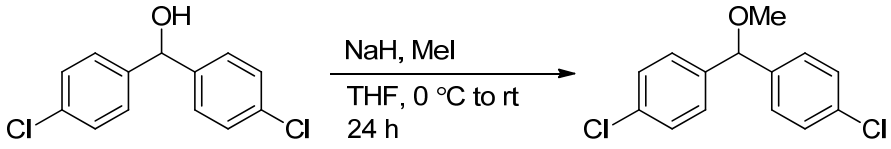
Preparation of methyl 1-phenylbutyl ether (1d)



To a solution of butyrophenone (1.53 g, 10.0 mmol) in MeOH (20 mL) was added sodium borohydride (0.76 g, 20.0 mmol) at 0 ºC under argon. After stirring for 30 min., the reaction mixture was quenched with H_2O (4.0 mL) and extracted with EtOAc (10 mL × 3). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. To the residue were added sodium hydride (0.60 g, 15.0 mmol) and THF (12 mL) at 0 ºC under argon. After stirring for 20 min., iodomethane (1.25 mL, 20.0 mmol) was added to the reaction mixture at 0 ºC. After further stirring for 24 h at room temperature, the reaction mixture was cooled to 0 ºC and quenched with H_2O (10 mL) and extracted with EtOAc (15 mL × 3). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography using *n*-hexane-EtOAc (50/1 to 10/1) as eluent to give methyl 1-phenylbutyl ether (788 mg, 4.80 mmol) in 48% yield.

1d; Colorless liquid; IR (ATR) cm^{-1}: 2958, 2932, 2872, 2820, 1492, 1453, 1356, 1201, 1093, 1069, 1027. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, J = 7.4 Hz, 2H), 7.29-7.25 (m, 3H), 4.09 (t, J = 6.8 Hz, 1H), 3.20 (s, 3H), 1.84-1.75 (m, 1H), 1.64-1.54 (m, 1H), 1.46-1.33 (m, 1H), 1.31-1.20 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5, 128.3, 127.4, 126.7, 83.9, 56.6, 40.3, 19.0, 14.0. ESI-HRMS m/z: 238.0812 ([M+K^+]). Calcd for $C_{11}H_{16}OK$: 203.0833.

Preparation of 1,1-bis(4-chlorophenyl)-methoxymethane (1i)



To the solution of 4,4'-dichlorobenzhydrol (2.50 g, 10.0 mmol) in THF was added sodium hydride (0.60 g, 15.0 mmol) at 0 ºC under argon. After stirring for 20 min., iodomethane (1.25 mL, 20.0 mmol) was added to the reaction mixture at 0 ºC. After stirring for 24 h at room temperature, the reaction mixture was cooled to 0 ºC and quenched with H_2O (10 mL) and extracted with EtOAc (15 mL × 3). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography using *n*-hexane-EtOAc (50/1 to 10/1) as the eluent to give 1,1-bis(4-chlorophenyl)-methoxymethane (782 mg, 3.20 mmol) in 32% yield.

1i; White Solid; M.p. 80-81 ºC; IR (ATR) cm^{-1}: 2988, 2928, 2822, 1589, 1483, 1459, 1404, 1346, 1191, 1111, 1084, 1013. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.8 Hz, 4H), 7.24 (d, J = 8.8 Hz, 4H),

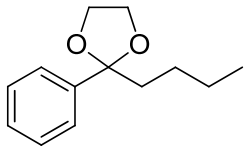
5.18 (s, 1H), 3.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.2, 133.4, 128.7, 128.2, 83.9, 57.0. ESI-HRMS m/z: 304.9919 ([M+K^+]). Calcd for $C_{14}H_{12}OCl_2K$: 304.9897.

3. Typical synthetic procedure for 2 and 4

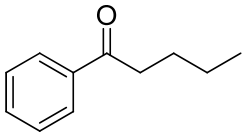
Alkyl benzyl ether (**1** or **3**; 0.2 mmol), 10% Pd/C (21.3 mg, 0.02 mmol, 10 mol%), and ethylene glycol (2 mL) were placed in a test tube, and then the test tube was sealed with a septum. The inside air was replaced with O_2 (balloon). The mixture was stirred with a ChemiStation (EYELA, Tokyo Rikakikai Co., Ltd., Tokyo, Japan) and heated at 80 °C for 24 h. After cooling to room temperature, the reaction mixture was passed through a pad of silica-gel and washed with *n*-hexane/EtOAc. The mixture was concentrated in vacuo. The residue was purified by silica-gel column chromatography using *n*-hexane/EtOAc as the eluent to give the corresponding product (**2** or **4**).

4. Spectroscopic data of synthesized products

2-Butyl-2-phenyl-1,3-dioxolane (2a) and valerophenone (5a)



2a



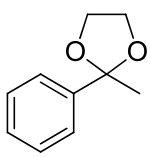
5a

Synthesized according to the typical synthetic procedure for **2**; **2a** and hydrolyzed **5a** were obtained as a mixture by the use of **1a** (35.7 mg, 0.20 mmol) as a substrate. However, **2a** and **5a** could not be separated as pure products after silica-gel column chromatography using *n*-hexane-EtOAc (20/1) as the eluent. Therefore, each yield (72% and 8%, repectively) was determined by the integral values of the ^{1}H NMR spectrum of the mixture.

Alternative synthetic method of **2a** (isolation of pure 2a as a literature unknown compound for the collection of spectrum data); To a solution of valerophenone (1.62 g, 10.0 mmol) in toluene (20 mL) were added ethylene glycol (0.74 g, 12.0 mmol) and *p*-toluenesulfonic acid (0.20 g, 1.0 mmol) at room temperature under argon. The reaction mixture was refluxed under Dean-Stark conditions for 24 h. The reaction mixture was cooled to 0 ºC and quenched with sat. $NaHCO_3$ aq. (30 mL) and extracted with *n*-hexane (20 mL × 3). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. To the residue was added MeOH (20 mL) at 0 ºC under argon. After stirring for 10 min., sodium borohydride (0.76 g, 20.0 mmol) was added to the crude mixture at 0 ºC, to reduce unreacted valerophenone. After further stirring for 24 h at room temperature, the reaction mixture was cooled to 0 ºC and quenched with H_2O (10 mL) and extracted with EtOAc (20 mL × 3). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel column chromatography using *n*-hexane-EtOAc (10/1) as the eluent to give **2a** (782 mg, 3.79 mmol) in 38% yield.

2a; Colorless liquid; IR (ATR) cm^{-1}: 2954, 2874, 1447, 1262, 1216, 1174, 1111, 1043, 1028. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.43 (m, 2H), 7.35-7.26 (m, 3H), 4.04-3.97 (m, 2H), 3.98-3.73 (m, 2H), 1.89 (t, J = 7.0 Hz, 2H), 1.34-1.23 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.6, 128.0, 127.7, 125.7, 110.5, 64.4, 40.3, 25.7, 22.8, 14.0. ESI-HRMS m/z: 245.0952 ([M+K^{+}]). Calcd for $C_{13}H_{18}O_2K$: 245.0938. Spectroscopic data of ^{1}H NMR was identical to the prepared authentic sample.

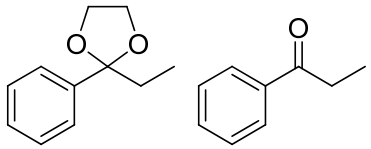
2-Methyl-2-phenyl-1,3-dioxolane (2b)



Synthesized according to the typical synthetic procedure for **2**; When using **1b** (27.2 mg, 0.20 mmol), **2b** was obtained in 44% after purification by silica-gel column chromatography using *n*-hexane-EtOAc (20/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 4.08-4.01 (m, 2H), 3.82-3.75 (m, 2H), 1.66 (s, 3H). Spectroscopic data of ^{1}H NMR was identical to that of reference 5.

2-Ethyl-2-phenyl-1,3-dioxolane (2c) and propiophenone (5c)

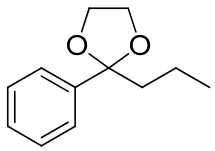


2c **5c**

Synthesized according to the typical synthetic procedure for **2**; **2c** and hydrolyzed **5c** were obtained as a mixture by the use of **1c** (30.0 mg, 0.20 mmol) as a substrate. However, **2c** and **5c** could not be separated as pure products after silica-gel column chromatography using *n*-hexane-EtOAc (20/1) as the eluent. Therefore, each yield (55% and 4%, repectively) was determined by the integral values of the ^{1}H NMR spectrum of the mixture.

2c; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.43 (m, 2H), 7.37-7.26 (m, 3H), 4.06-3.97 (m, 2H), 3.82-3.73 (m, 2H), 1.92 (q, *J* = 7.6 Hz, 2H), 0.88 (t, *J* = 7.6 Hz, 3H). Spectroscopic data of ^{1}H NMR was identical to that of reference 6.

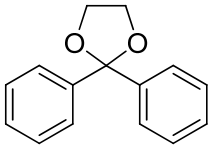
2-Phenyl-2-propyl-1,3-dioxolane (2d)



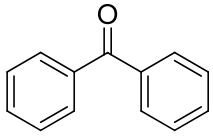
Synthesized according to the typical synthetic procedure for **2**; **2d** (34.6 mg, 0.18 mmol) was obtained in 90% yield by the use of **1d** (32.8 mg, 0.20 mmol) after purification by silica-gel column chromatography using *n*-hexane-EtOAc (50/1).

Colorless liquid; IR (ATR) cm^{-1}: 2959, 2875, 1448, 1266, 1220, 1180, 1053, 1026. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.45 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.30-7.26 (m, 1H), 4.04-3.97 (m, 2H), 3.80-3.73 (m, 2H), 1.89-1.86 (m, 2H), 1.38-1.30 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 142.6, 128.0, 127.7, 125.7, 110.5, 64.4, 42.7, 17.0, 14.2. ESI-HRMS m/z: 193.1208 ([M+H$^+$]). Calcd for $C_{12}H_{17}O_2$: 193.1223.

2,2-Diphenyl-1,3-dioxolane (2f) and benzophenone (5f)



2f

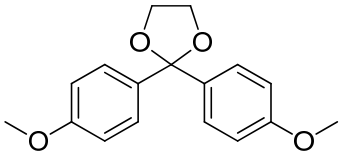


5f

Synthesized according to the typical synthetic procedure for **2**; **2f** and hydrolyzed **5f** were obtained as a mixture by the use of **1f** (39.7 mg, 0.20 mmol) as a substrate. However, **2f** and **5f** could not be separated as pure products after silica-gel column chromatography using *n*-hexane-EtOAc (20/1) as the eluent. Therefore, each yield (83% and 1%, respectively) was determined by the integral values of the ^{1}H NMR spectrum of the mixture.

2f; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.46 (m, 4H), 7.34-7.25 (m, 6H), 4.05 (s, 4H). Spectroscopic data of ^{1}H NMR was identical to that of reference 7.

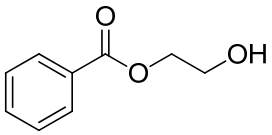
2,2-Bis(4-methoxyphenyl)-1,3-dioxolane (2g)



Synthesized according to the typical synthetic procedure for **2**; **2g** (25.8 mg, 0.09 mmol) was obtained in 45% yield by the use of **1g** (51.7 mg, 0.20 mmol) after purification by silica-gel column chromatography using *n*-hexane-EtOAc (10/1).

Colorless liquid; IR (ATR) cm^{-1}: 2954, 2890, 2836, 1609, 1584, 1509, 1463, 1415, 1301, 1245, 1207, 1170, 1078, 1032, 1020. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.4 Hz, 4H), 6.85 (d, J = 8.4 Hz, 4H), 4.04 (s, 4H), 3.79 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 134.3, 127.7, 113.4, 109.4, 64.7, 55.2. ESI-HRMS m/z: 287.1283 ([M+H^{+}]). Calcd for $C_{17}H_{19}O_4$: 287.1278.

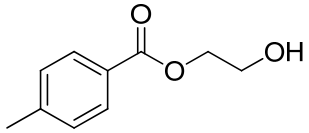
2-Hydroxyethyl benzoate (4a)



Synthesized according to the typical synthetic procedure for **4**; When using **3a** (24.4 mg, 0.20 mmol), **3e** (30.0 mg, 0.20 mmol), **3f** (32.8 mg, 0.20 mmol) or **3g** (55.3 mg, 0.20 mmol), **4a** was obtained in 78%, 78%, 81% and 65% yields, respectively after purification by silica-gel column chromatography using *n*-hexane-EtOAc (20/1 to 0/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 4.46 (t, J = 4.5 Hz, 2H), 3.95 (t, J = 4.5 Hz, 2H), 2.47 (brs, 1H). Spectroscopic data of ^{1}H NMR was identical to that of reference 8.

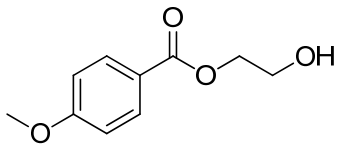
2-Hydroxyethyl 4-methylbenzoate (4b)



Synthesized according to the typical synthetic procedure for **4**; **4b** (15.9 mg, 0.09 mmol) was obtained in 44% yield by the use of **3b** (27.2 mg, 0.20 mmol) after purification by silica-gel column chromatography using *n*-hexane-EtOAc (10/1 to 0/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 4.45 (t, J = 4.5 Hz, 2H), 3.95 (t, J = 4.5 Hz, 2H), 2.41 (s, 3H), 2.26 (brs, 1H). Spectroscopic data of ^{1}H NMR was identical to that of reference 9.

2-Hydroxyethyl 4-methoxybenzoate (4c)



Synthesized according to the typical synthetic procedure for **4**; **4c** (29.0 mg, 0.15 mmol) was obtained in 74% yield by the use of **3c** (30.4 mg, 0.20 mmol) after purification by silica-gel column chromatography using *n*-hexane-EtOAc (2/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 7.5 Hz, 2H), 6.92 (d, J = 7.5 Hz, 2H), 4.44 (t, J = 4.5 Hz, 2H), 3.95 (t, J = 4.5 Hz, 2H), 3.86 (s, 3H). Spectroscopic data of ^{1}H NMR was identical to that of reference 8.

5. References

1) H. T. Dao, U. Schneidera, S. Kobayashi, *Chem. Commun.*, **2011**, *47*, 692-694.

2) F. Ke, Z. Li, H. Xiang, X. Zhou, *Tetrahedron Lett.*, **2011**, *52*, 318-320.

3) L. Zhao, B. Liu, Q. Tan, C. -H. Ding, B. Xu, *Org. Lett.*, **2019**, *21*, 9223-9227.

4) N. Yasukawa, T. Kanie, M. Kuwata, Y. Monguchi, H. Sajiki, Y. Sawama, *Chem. Eur. J.,* **2017**, *23*, 10974-10977.

5) A. Ugo, C. Massimo, D. M. Ashenafi, M. Irene, P. Luisa, Z. Giuseppe, *Green Chem*., **2015**, *17*, 3281-3284.

6) H. Suzuki, S. Yonezawa, T. Mori, *Bull. Chem. Soc. Jpn*., *1995*, **68**, 1535-1544.

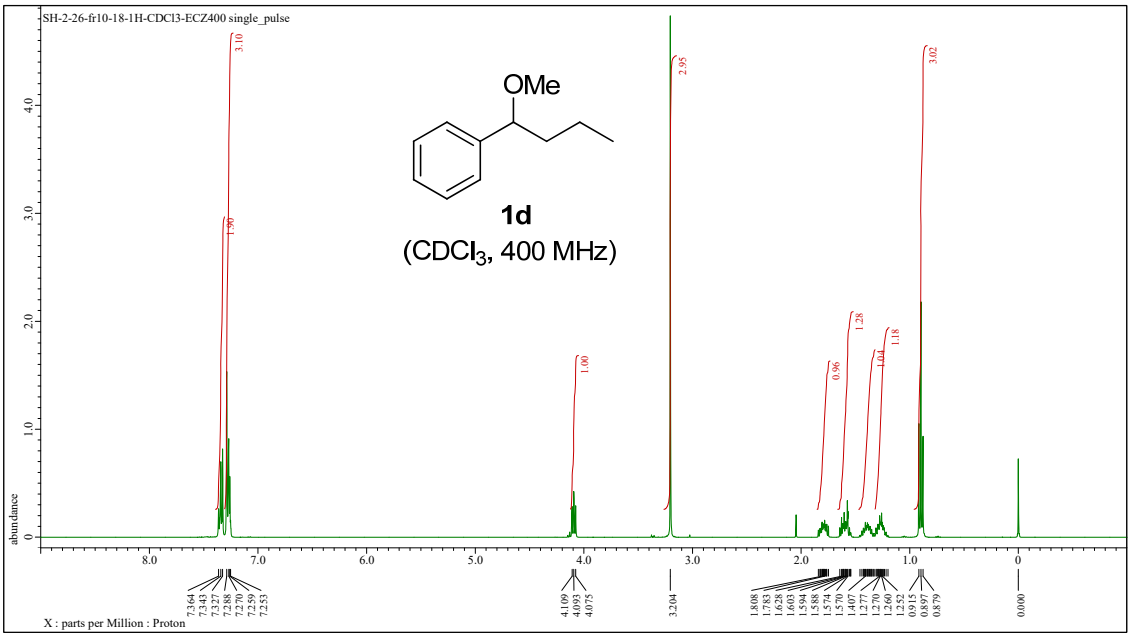
7) S. Ueno, T. Oshima, T. Nagai, *J. Org. Chem*., **1984**, *49*, 4060-4063.

8) N. Yasukawa, S. Asai, M. Kato, Y. Monguchi, H. Sajiki, Y. Sawama, *Org. Lett.*, **2016**, *18*, 5604-5607.

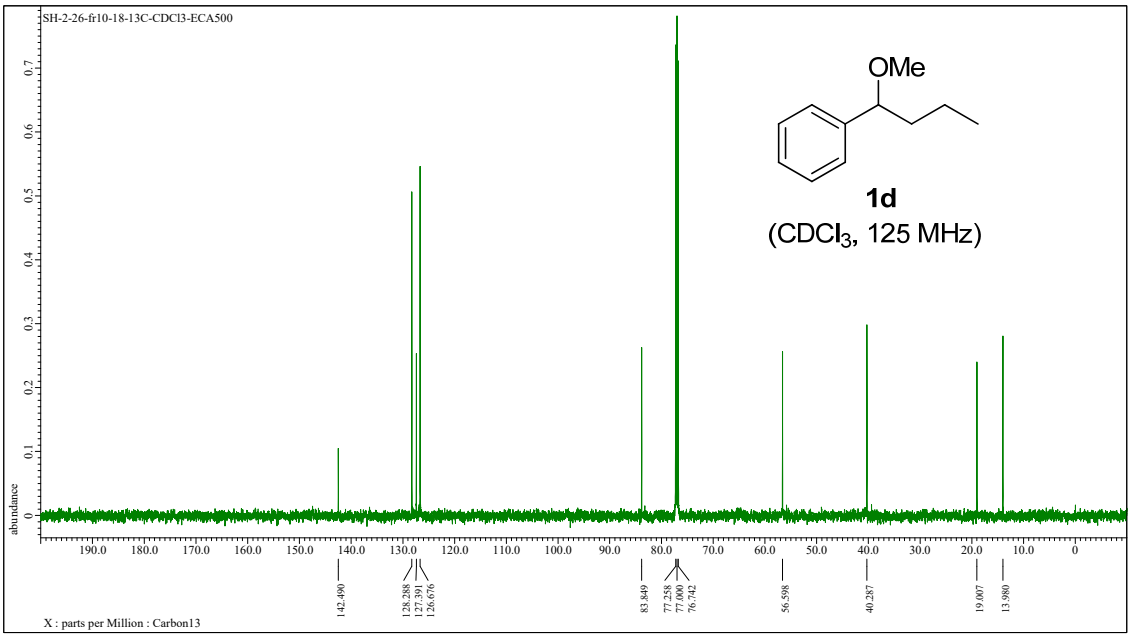
9) R. Ritwika, D. J. Rahul, B. Mayukh, M. Debabrata, K. L. Goutam, *Chem. Eur. J*., **2014**, *20*, 1-8.

6. ^{1}H and ^{13}C NMR spectra of substrates

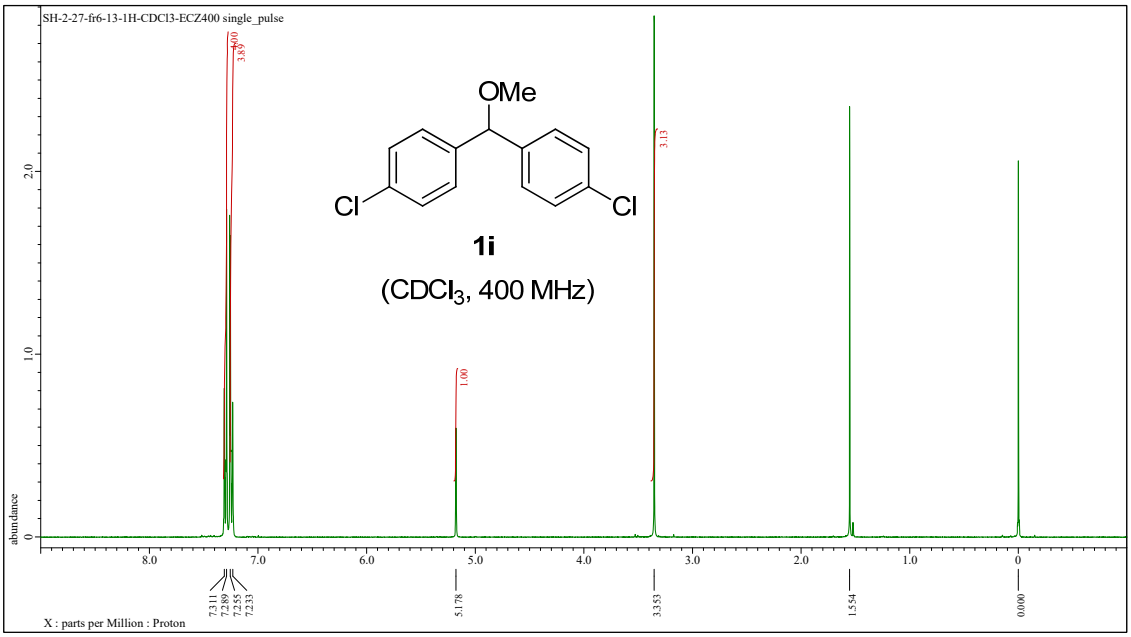
^{1}H NMR of methyl 1-phenylbutyl ether (1d)



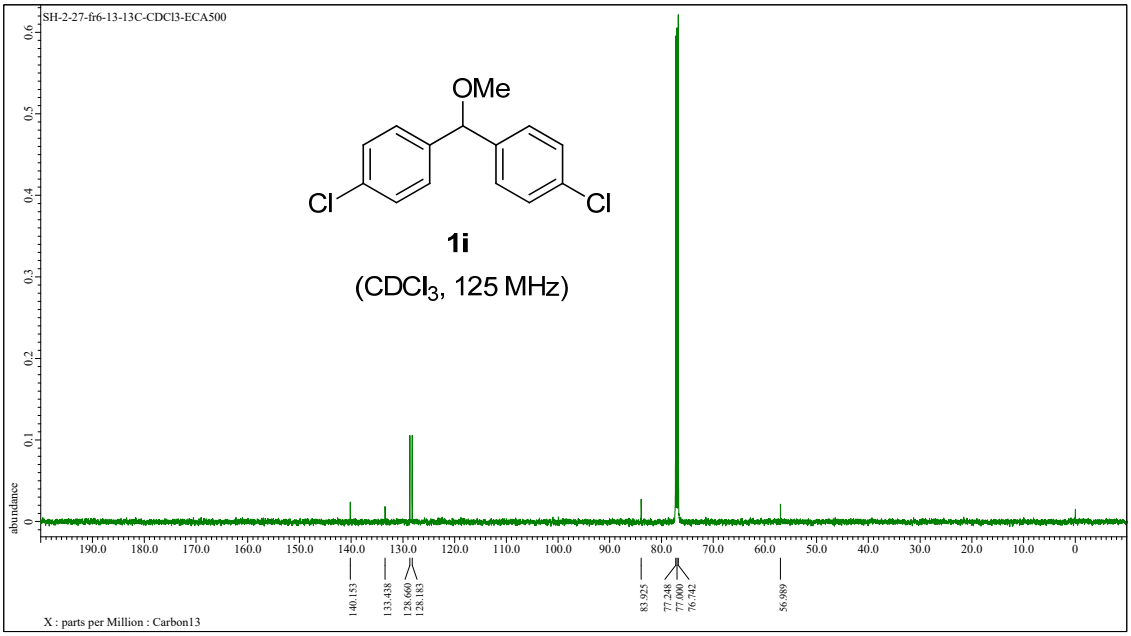
^{13}C NMR of methyl 1-phenylbutyl ether (1d)



^{1}H NMR of 1,1-bis(4-chlorophenyl)-methoxymethane (1i)

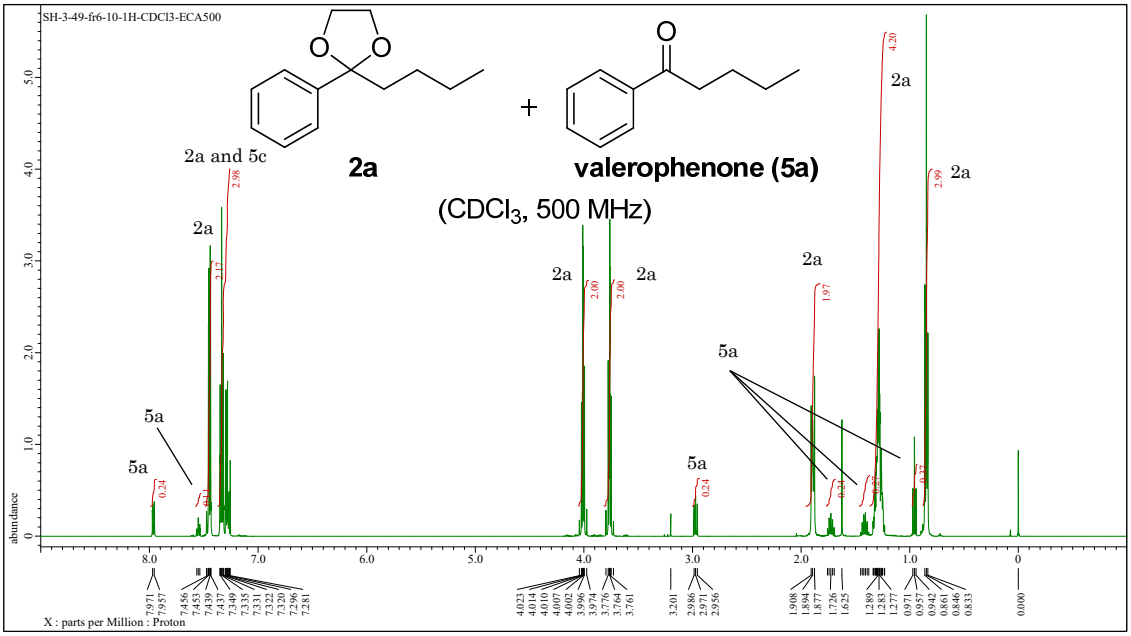


^{13}C NMR of 1,1-bis(4-chlorophenyl)-methoxymethane (1i)

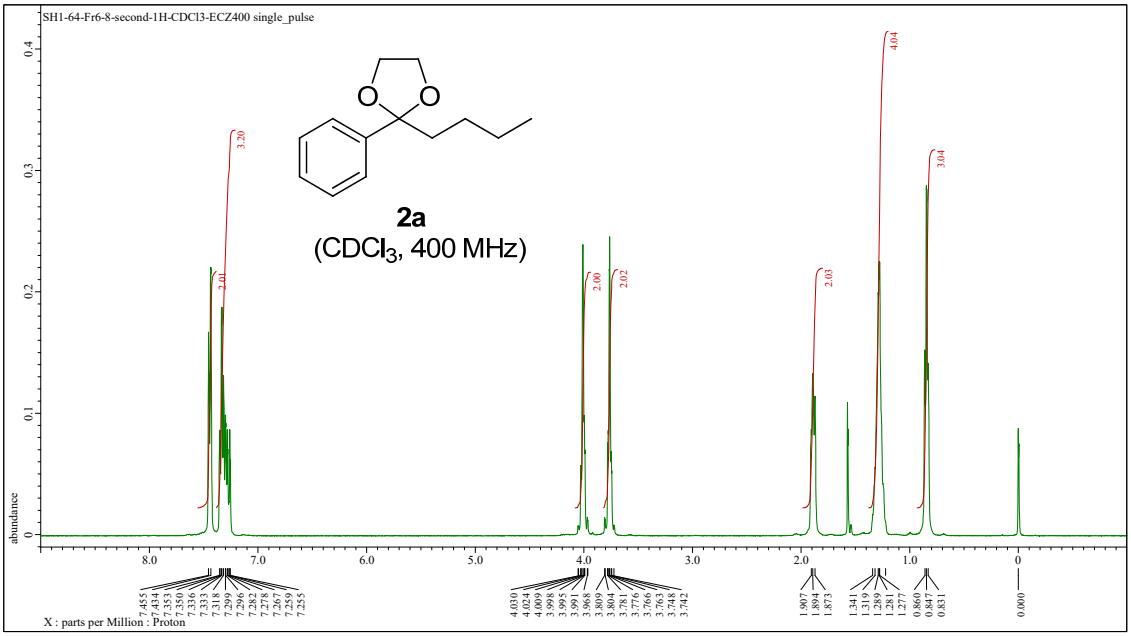


7. ^{1}H and ^{13}C NMR spectra of products

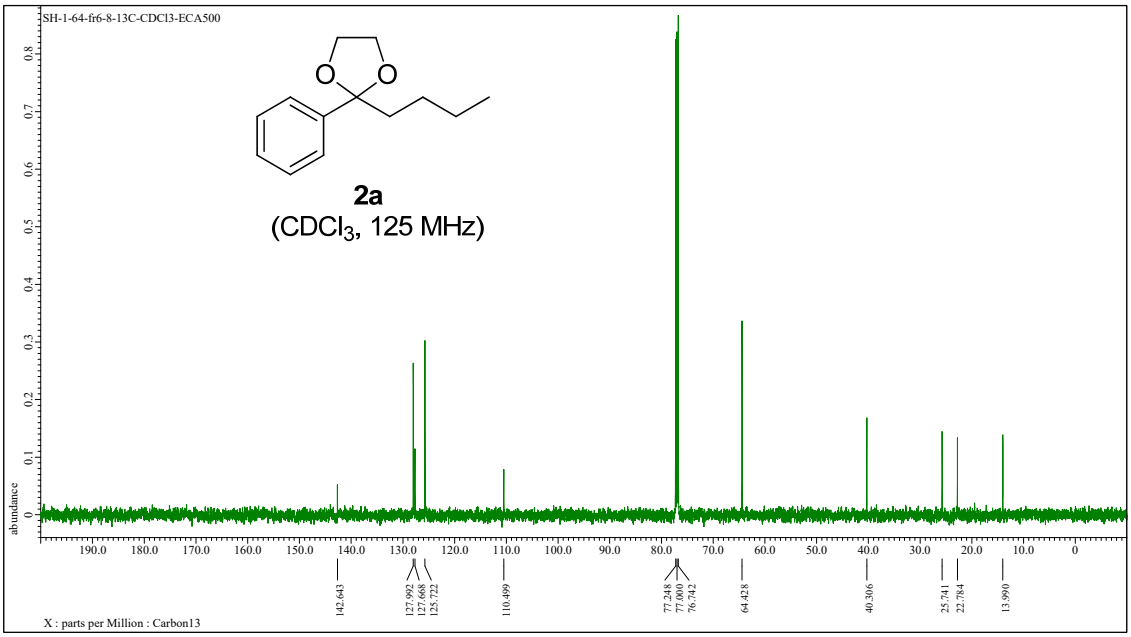
^{1}H NMR of 2-butyl-2-phenyl-1,3-dioxolane (2a) and valerophenone (5a) as inseparable products



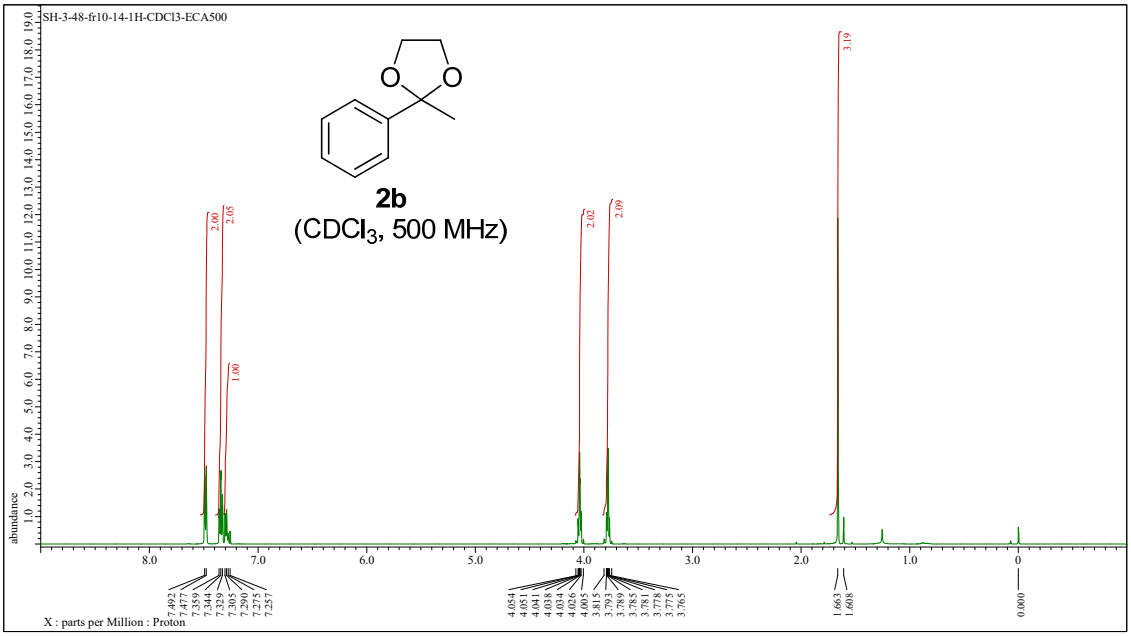
^{1}H NMR of 2-butyl-2-phenyl-1,3-dioxolane (Authentic sample)



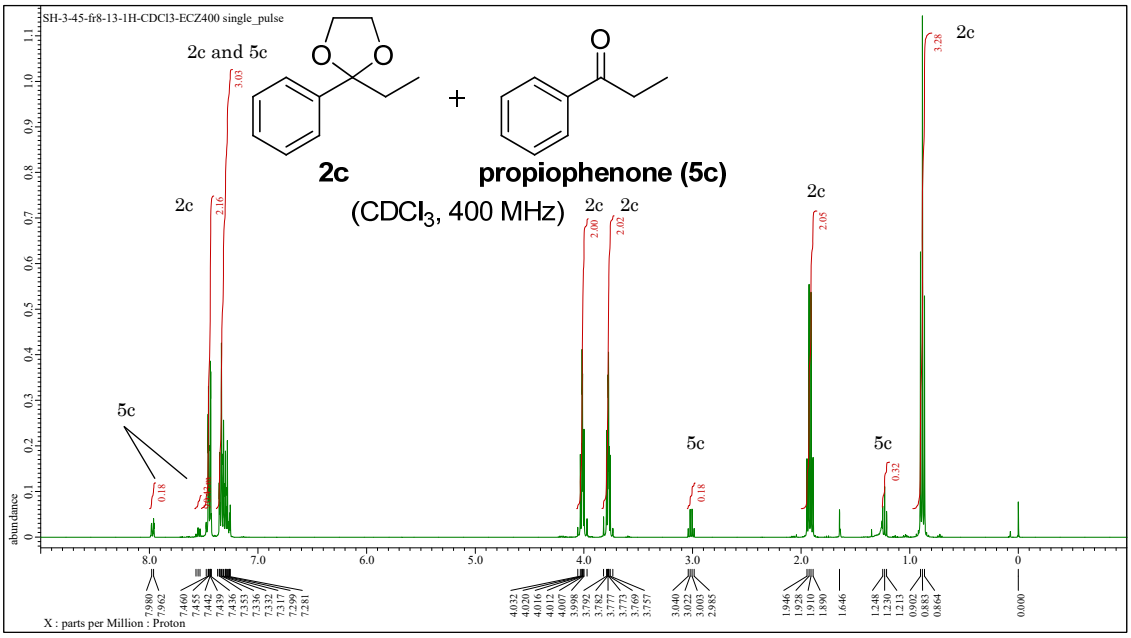
^{13}C NMR of 2-butyl-2-phenyl-1,3-dioxolane (2a)



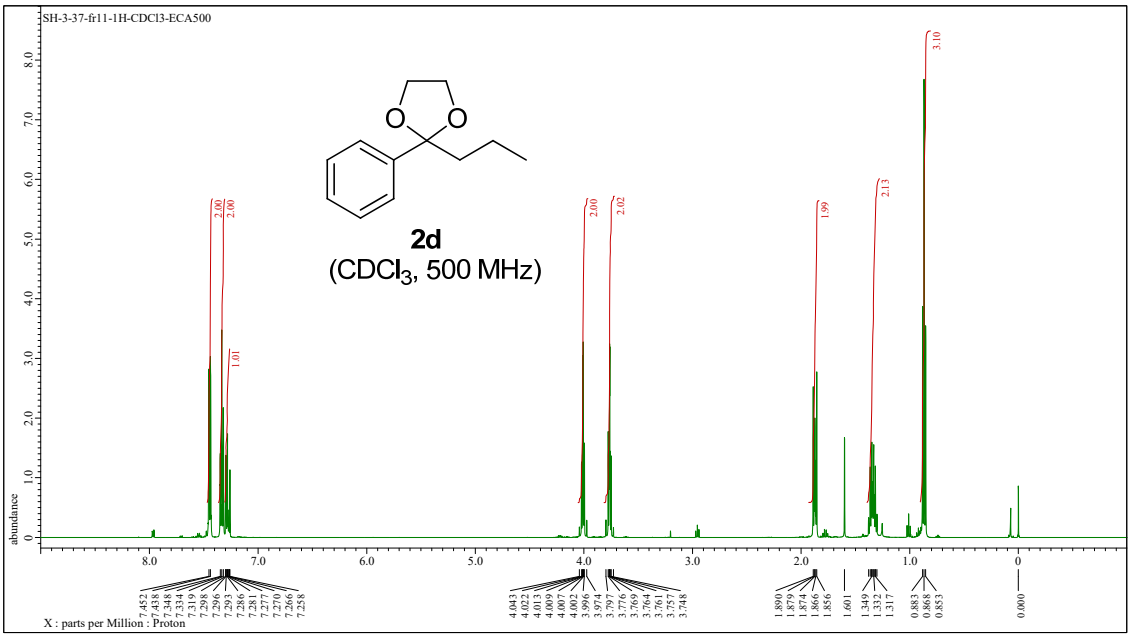
^{1}H NMR of 2-methyl-2-phenyl-1,3-dioxolane (2b)



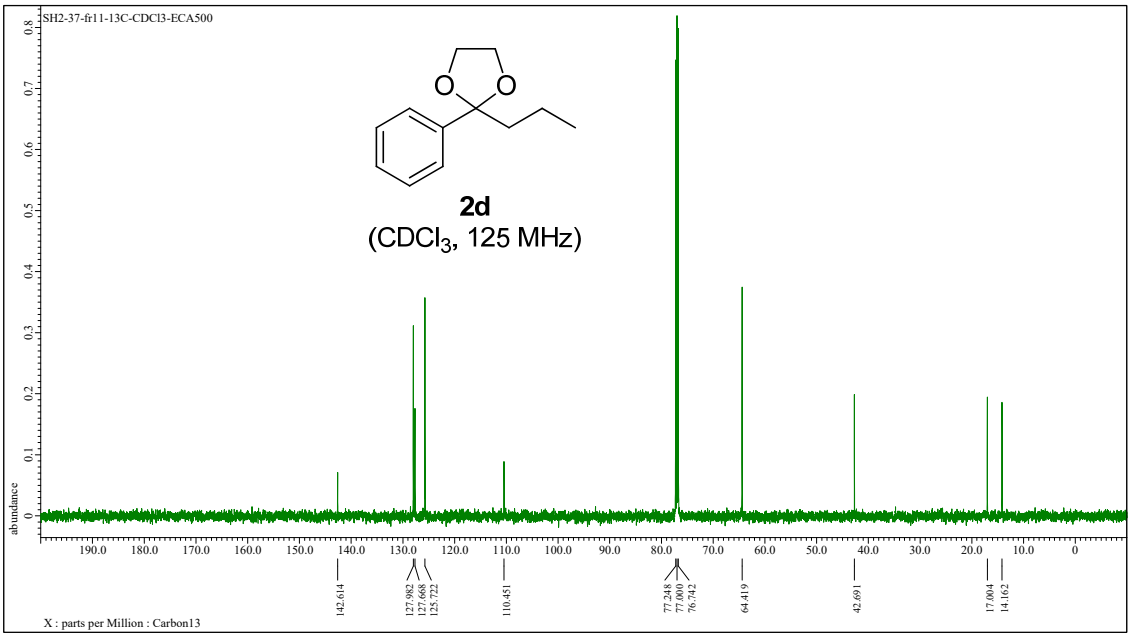
^{1}H NMR of 2-ethyl-2-phenyl-1,3-dioxolane (2c) and propiophenone (5c) as inseparable products



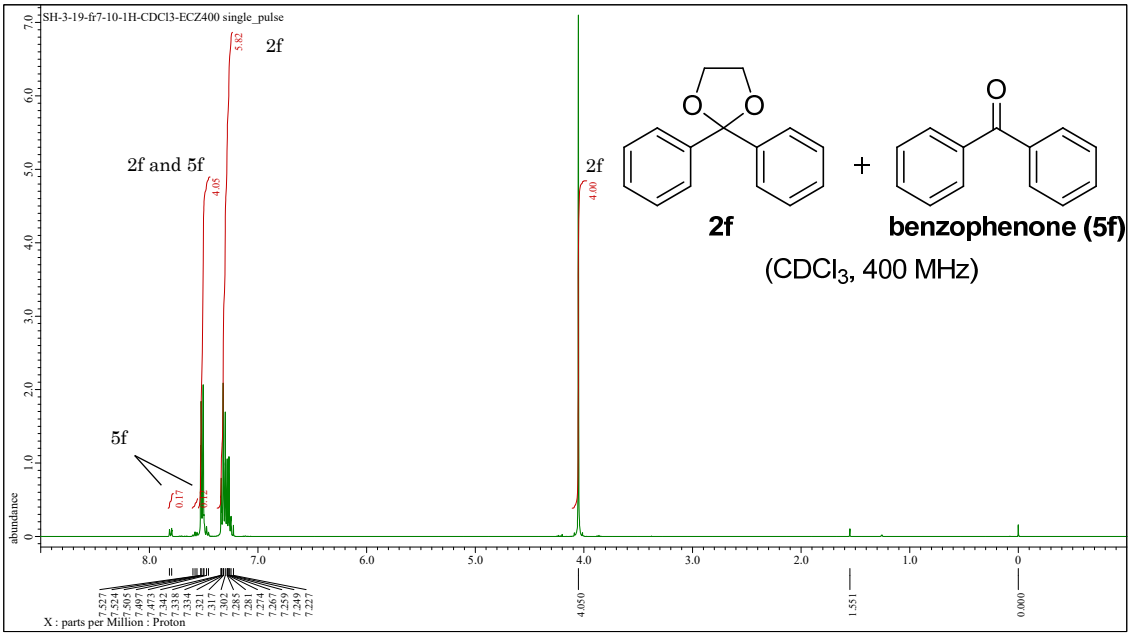
^{1}H NMR of 2-phenyl-2-propyl-1,3-dioxolane (2d)



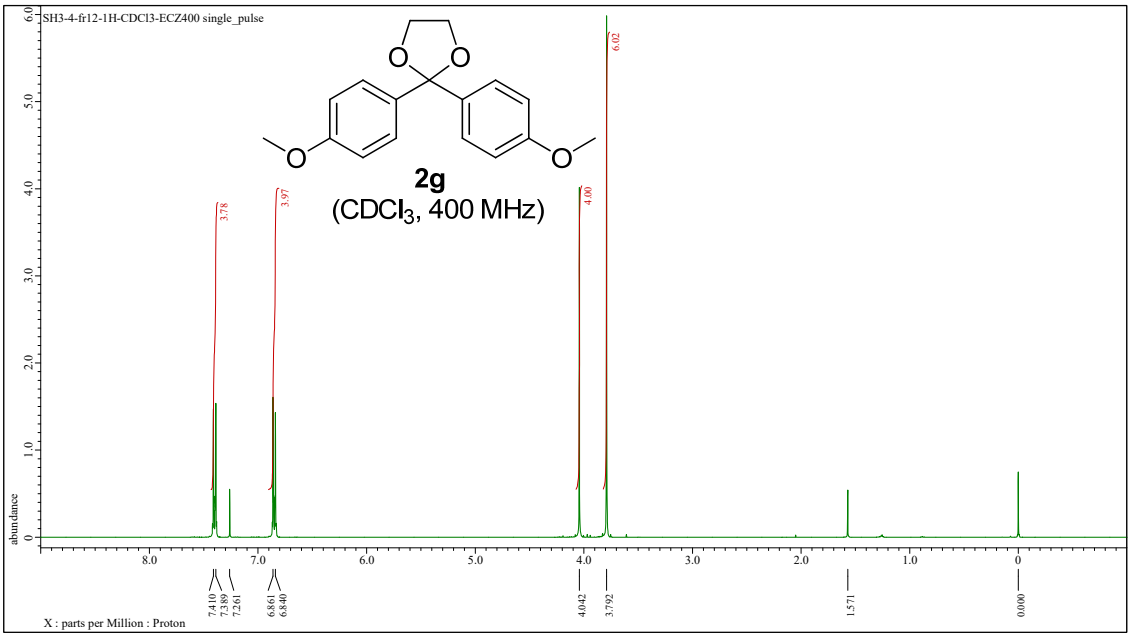
^{13}C NMR of 2-phenyl-2-propyl-1,3-dioxolane (2d)



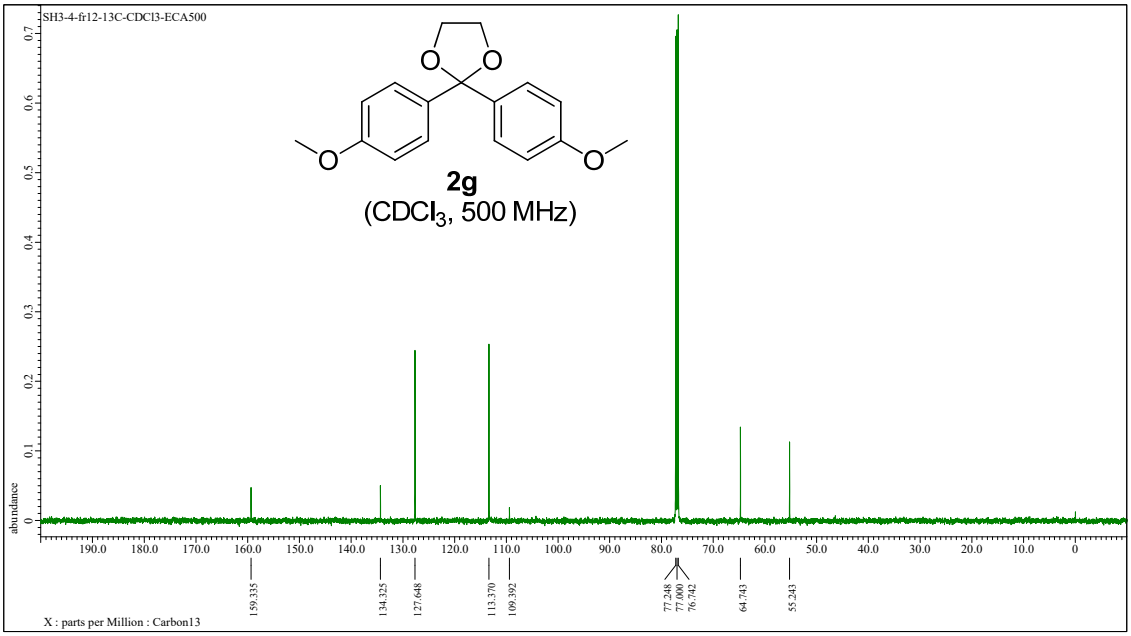
^{1}H NMR of 2,2-diphenyl-1,3-dioxolane (2f) and benzophenone (5f) as inseparable products



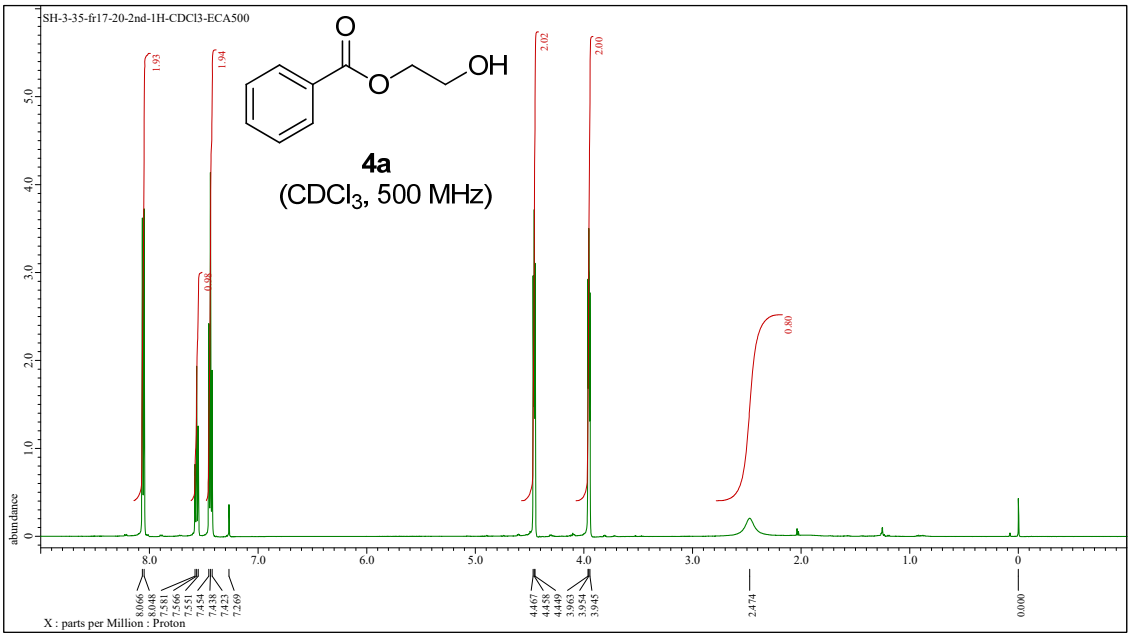
^{1}H NMR of 2,2-bis(4-methoxyphenyl)-1,3-dioxolane (2g)



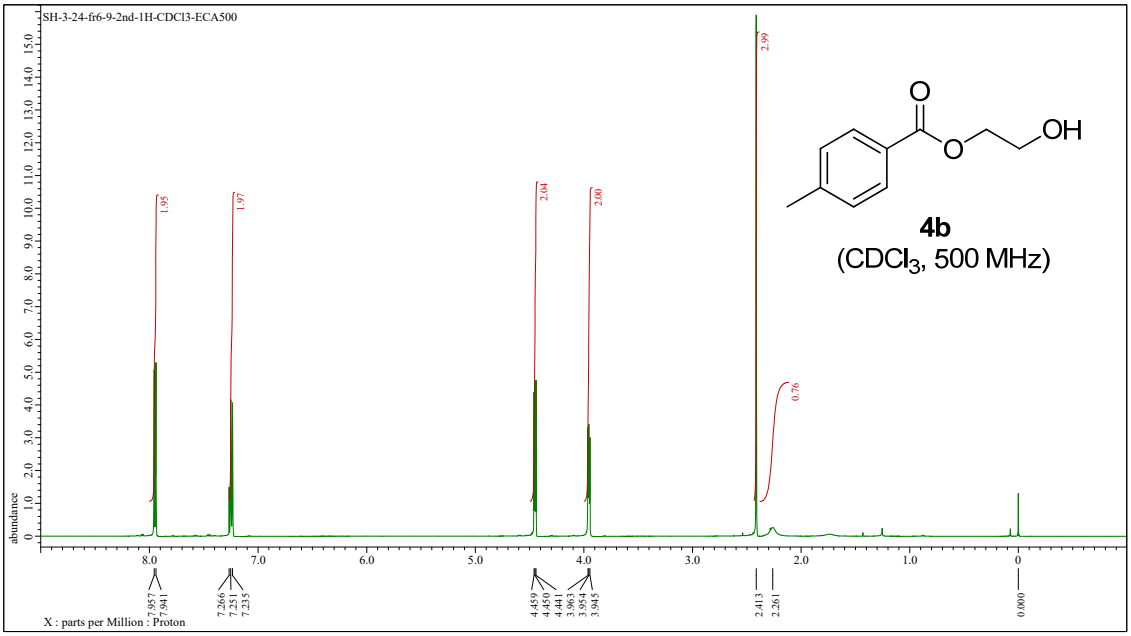
^{13}C NMR of 2,2-bis(4-methoxyphenyl)-1,3-dioxolane (2g)



^{1}H NMR of 2-hydroxyethyl benzoate (4a)



^{1}H NMR of 2-hydroxyethyl 4-methylbenzoate (4b)



^{1}H NMR of 2-hydroxyethyl 4-methoxybenzoate (4c)