Supporting Information

Mechanistic Analysis of a Copper-Catalyzed C–H Oxidative Cyclization of Carboxylic Acids

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Experimental Section

1. General

All chemicals were purchased from Sigma-Aldrich (St. Louis, MO). HPLC grade solvents were purchased from Fisher Scientific (Nepean, ON, Canada). Reactions were performed using glassware that was oven-dried. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (~15 Torr) by rotary evaporation. Solvents were purified by passage under 12 psi through activated alumina columns.

2. Desorption electrospray ionization mass spectrometric (DESI-MS) study

DESI-MS studies were performed on a high-resolution mass spectrometer (Thermo Scientific LTQ Orbitrap XL Hybrid Ion Trap-Orbitrap mass spectrometer) using a homebuilt DESI source. The source was constructed by using an inner fused silica capillary (100 μm i.d. and 360 μm o.d.) for solvent delivery, and an outer (coaxial) stainless steel capillary (0.5 mm i.d. and 1.6 mm o.d.) for nebulizing gas (nitrogen) flow as shown in Figures 1 and S1. A stream of charged microdroplets, produced from this DESI source at ambient temperature and atmospheric pressure, was directed to the analyte surface (on a glass plate) at an incident angle ~55^{o} with the spray tip-to-surface distance of ~5 mm, spray tip-to-mass spectrometric inlet distance of ~10 mm, and collection angle of ~5^{o}. The charged droplets were produced either in negative ion mode (–5 kV spray voltage) or at positive ion mode (+5 kV spray voltage), at 10 μL/min solvent (1:1 *v/v* acetonitrile and water) flow through silica tubing with the coaxial nebulizing gas flow (N_2 at 120 psi). The splashing of these charged microdroplets on the analyte surface resulted in the formation of secondary microdroplets encapsulating the analyte molecules (ions), which were then transferred to the mass spectrometer through a heated capillary causing the complete desolvation of the analyte ions. The heated capillary (MS inlet) temperature and voltage were maintained at 275°C and 44V respectively. Helium was used as the collision gas in the collision induced dissociation cell (CID cell; an ion trap). CID spectra (MS2) were acquired using an isolation width of 0.9 *m/z* unit with activation Q and activation time set to 0.25 and 30 ms respectively. The normalized collision energy was set to 18 % in the CID. All experiments were carried out under identical conditions,

unless otherwise stated. The ion optics were tuned to ensure maximum ion count. Data acquisition was performed using XCalibur software (Thermo Fisher Scientific).

3. Nuclear magnetic resonance (NMR) study

NMR spectra were acquired on either a Varian Inova-600 operating at 600 and 150 MHz, a Varian Inova-300 operating at 300 and 75 MHz, a Varian Mercury-400 operating at 400 and 100 MHz, or a Varian Inova-500 operating at 500 and 125 MHz, and are referenced internally according to residual solvent signals. $CDCl_3$ was used as solvent. Data for NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet), integration, coupling constant (Hz). Data are reported in terms of chemical shift (δ, ppm).

4. Reactionsfor the kinetic study

A 5 mL reaction vial was charged with 4-phenylbutyric acid (0.25 mmol), $Cu(OAc)_2•H_2O$(25μmol, 0.1 equiv), and $K_2S_2O_8$ (0.375 mmol, 1.5 equiv). To this mixture was added 1.2 mL of acetic acid and 1.2 mL of H_2O. The vial was sealed and immersed into an oil bath pre-heated to 105 °C, and the reaction mixture was stirred for the desired time (0, 0.5, 1.25, 1.75, 2, 3, 4, 5, and 10 min). The reaction contents were immediately transferred to a 60 mL separatory funnel filled with 10 mL of 1.0 M aqueous HCl and 10 mL of CH_2Cl_2. After vigorous shaking, the organic layer was collected and the aqueous fraction was extracted with 1 x 10 mL of CH_2Cl_2 and 1 x 10 mL of EtOAc. The combined organic fractions were dried over Na_2SO_4 and filtered. *p*-Nitrotoluene (0.25 mmol) was added as an internal standard and the solution was concentrated under reduced pressure; ^1H NMR was used to estimate reaction conversion and product ratios (Figure S2).

5. Reactions for DESI-MS studies

A 1-dram reaction vial was charged with the substrate (0.25 mmol), $Cu(OAc)_2•H_2O$ (25 μmol, 0.1 equiv), and $K_2S_2O_8$ (0.375 mmol, 1.5 equiv). To this mixture was added 1.2 mL of AcOH and 1.2 mL of H_2O. The vial was sealed, placed on a heating block preheated to 105 °C, and the reaction mixture was stirred for 2 min. Following this time, a 10 μL reaction aliquot was rapidly pipetted

and dispensed on a glass microscope slide placed under the charged microdroplet stream in the DESI probe (Figures 1 and S1).

6. Online ESI-MS study

The online ESI-MS experiment for real time monitoring of the Cu(I) species was performed using the pressurized infusion method originally described by McIndoe and coworkers (Vikse, K. L.; Woods, M. P.; McIndoe, J. S. Organometallics **2010**, 29, 6615–6618). A photograph of the setup used in this study is shown in Figure S12. The syringe flow rate (acetonitrile) was maintained at 5 μL/min and the nitrogen gas pressure in the Schlenk flask was kept at 4 psi. The reaction in the Schlenk flask was conducted at 0.25 mmol scale in 5 mL AcOH/H_2O (1:1 *v/v*) solvent at 75 °C. It should be noted that here we used double dilution and reduced temperature (75 °C) compared to the conditions used in the DESI-MS study or kinetics study (Figure S2). Dilution of the reaction mixture and reduction of the reaction temperature were essential to obtain good signal in the $[Cu^{I}(CH_3CN)_2]^+$ ion chronogram. The ion optics setup in the mass spectrometer (Thermo Scientific LTQ Orbitrap XL Hybrid Ion Trap-Orbitrap mass spectrometer) was identical to that used in the DESI-MS study described above. The voltage was applied at time zero. The dead time is approximately 30 s and does not account for the onset of the reaction seen in Figure 2c.

7. Reactions for Hammett analysis

A 5 mL reaction vial was charged with 4-phenylbutyric acid (0.25 mmol) and either 4-(4-methoxyphenyl)butyric acid (0.25 mmol), 4-(4-bromophenyl)butyric acid (0.25 mmol), 4-(4-acetamidophenyl)butyric acid (0.25 mmol), 4-(4-*tert*-butylphenyl)butyric acid (0.25 mmol) or 4-(4-nitrophenyl)butyric acid (0.25 mmol), $Cu(OAc)_2 \bullet H_2O$ (25 μmol, 0.1 equiv), and $K_2S_2O_8$ (0.375 mmol, 1.5 equiv). To this mixture was added 1.2 mL of AcOH and 1.2 mL of H_2O. The vial was sealed and immersed in an oil bath pre-heated to 105 °C, and the reaction mixture was stirred for 2 h. The reaction contents were transferred to a 60 mL separatory funnel to which 10 mL of 1.0 M aqueous HCl and 10 mL of CH_2Cl_2 were then added. The organic layer was collected and the aqueous fraction was extracted with 1 x 10 mL of CH_2Cl_2 and 1 x 10 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Product ratios were determined by integrating relevant signals in the ^1H NMR spectra.

8. Synthesis of Barton ester 7

Barton ester **7** was synthesized according to a modified procedure of Barton and Ferreira (Barton, D.H.R.; Ferreira, J.A. *Tetrahedron*, **1996**, *52*, 9347-9366). To a 100 mL round-bottom flask was added 2-phenethylbenzoic acid (2.0 g, 8.80 mmol) and 30 mL of CH_2Cl_2. The flask was wrapped in aluminum foil and placed in an ice bath. To the stirring solution was added 2-mercaptopyridine N-oxide sodium salt (1.36 g, 9.12 mmol, 1.03 equiv), N,N'-dicyclohexycarbodiimide (1.82 g, 8.82 mmol, 1.0 equiv), and 4-(dimethylamino)pyridine (0.10 g, 0.82 mmol, 0.09 equiv). The mixture was slowly warmed to room temperature and stirred for 12 h. Following this time, the contents were filtered through a small pad of Celite, and the flask and filter cake were rinsed with 30 mL of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (25% EtOAc/hexanes) yielded Barton ester **7** as a bright yellow oil.

9. Barton ester thermolysis (Scheme 3a)

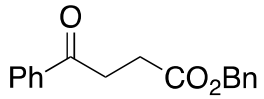
A 5 mL reaction vial was charged with Barton ester **7** (34 mg, 0.100 mmol) to which 2.5 mL of deoxygenated (N_2 sparged, 15 min) $BrCCl_3$ was then added. The vial was sealed and immersed in an oil bath pre-heated to 105 °C, and the mixture was stirred for 2 h, during which time the color of the reaction faded from bright yellow to pale yellow. The vial was then removed from the oil bath and allowed to cool to room temperature. The reaction contents were transferred to a 25 mL round bottom flask with 5 mL of CH_2Cl_2 and the solution was concentrated under reduced pressure to a yellow oil. Product ratios were determined by integrating relevant signals in the ^1H NMR against *p*-nitrotoluene as an internal standard.

10. Cyclization of 10 with $PhI(OAc)_2$ and I_2 (Scheme 3b)

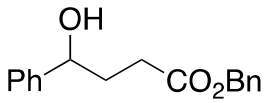
A 5 mL reaction vial was charged with 2-phenethylbenzoic acid (58 mg, 0.26mmol), $PhI(OAc)_2$ (89 mg, 0.28mmol, 1.1 equiv), and I_2 (70 mg, 0.28mmol, 1.1 equiv) to which 2.5 mL of dichloroethane was then added. The reaction vial was sealed, immersed in an oil bath preheated to 75 °C, and irradiated with a 500 W tungsten filament lamp for 1.5 h. The bath temperature increased to 85 °C during the course of the reaction. Following this time, the contents of the reaction vial were transferred to a 60 mL separatory funnel with 10 mL of CH_2Cl_2.The organic layer was washed with 1 x 15 mL of saturated aqueous $Na_2S_2O_3$ and 1 x 15 mL of 1.0 M aqueous NaOH. The organic fraction was collected, dried over Na_2SO_4, filtered, and concentrated under

reduced pressure to a yellow oil. Product ratios were determined by integrating relevant signals in the ^{1}H NMR spectra against *p*-nitrotoluene as an internal standard.

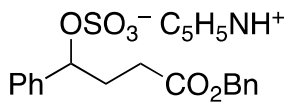
11. Synthesis of the pyridinium salt of 4-(benzyloxy)-4-oxo-1-phenylbutyl sulfate (11)



To a solution of 3-benzoylpropionic acid (2.0 g, 11.2 mmol) in 15 mL of DMF was added K_2CO_3 (1.86 g, 13.5 mmol, 1.2 equiv) and benzyl bromide (2.0 mL, 16.8 mmol, 1.5 equiv). After stirring for 2 h, the reaction mixture was diluted with 50 mL of Et_2O, transferred to a separatory funnel, and washed with 150 mL of saturated aqueous NaCl solution. The organic fraction was collected and concentrated under reduced pressure to a yellow oil. The material was determined by ^{1}H NMR to be sufficiently pure for use in the next step.

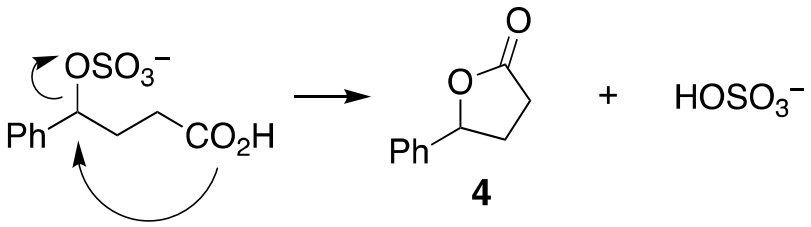


To an ice-cold solution of benzyl-4-oxo-4-phenylbutanoate (2.7 g, 10.0 mmol) in 30 mL of a 1:1 Et_2O/MeOH solution was added a single portion of $NaBH_4$ (0.2 g, 5.2 mmol, 0.5 equiv). After stirring for 1 h at 0 °C, the reaction was quenched by slow addition of 10 mL of saturated aqueous $NaHCO_3$. The reaction contents were transferred to a separatory funnel with 20 mL of CH_2Cl_2. The organic phase was collected and the aqueous phase was extracted with an additional 30 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (3:1 hexanes/EtOAc) afforded the benzyl-4-hydroxy-4-phenylbutanoate as a clear oil (2.05 g, 76% over 2 steps).



To a solution of benzyl-4-hydroxy-4-phenylbutanoate (2.05 g, 7.50 mmol) in 10 mL of pyridine was added a single portion of pyridine•SO_3 (1.33 g, 8.36 mmol, 1.1 equiv). After stirring the reaction mixture for 2h, silica gel (~0.5 g) was added and the yellow suspension was concentrated

under reduced pressure. Purification of the purple residue by chromatography on silica gel (gradient elution: 1:1 hexanes/EtOAc→MeOH) afforded the pyridinium salt of the sulfated alcohol as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, 2H, J = 4.0 Hz), 8.32 (t, 1H, J = 8.0 Hz), 7.82-7.79 (m, 2H), 7.35-7.18 (m, 10H), 5.47-5.44 (m, 1H), 5.07 (s, 2H), 2.57-2.52 (m, 2H), 2.27-2.15 (m, 2H) ppm; HRMS (ES^-) calcd for $C_{17}H_{17}O_6S^-$ 349.0751, found 349.0743 (Figure S10a).



Scheme S1. Putative displacement reaction of 3-carboxy-1-phenylpropyl sulfate to yield lactone **4**.

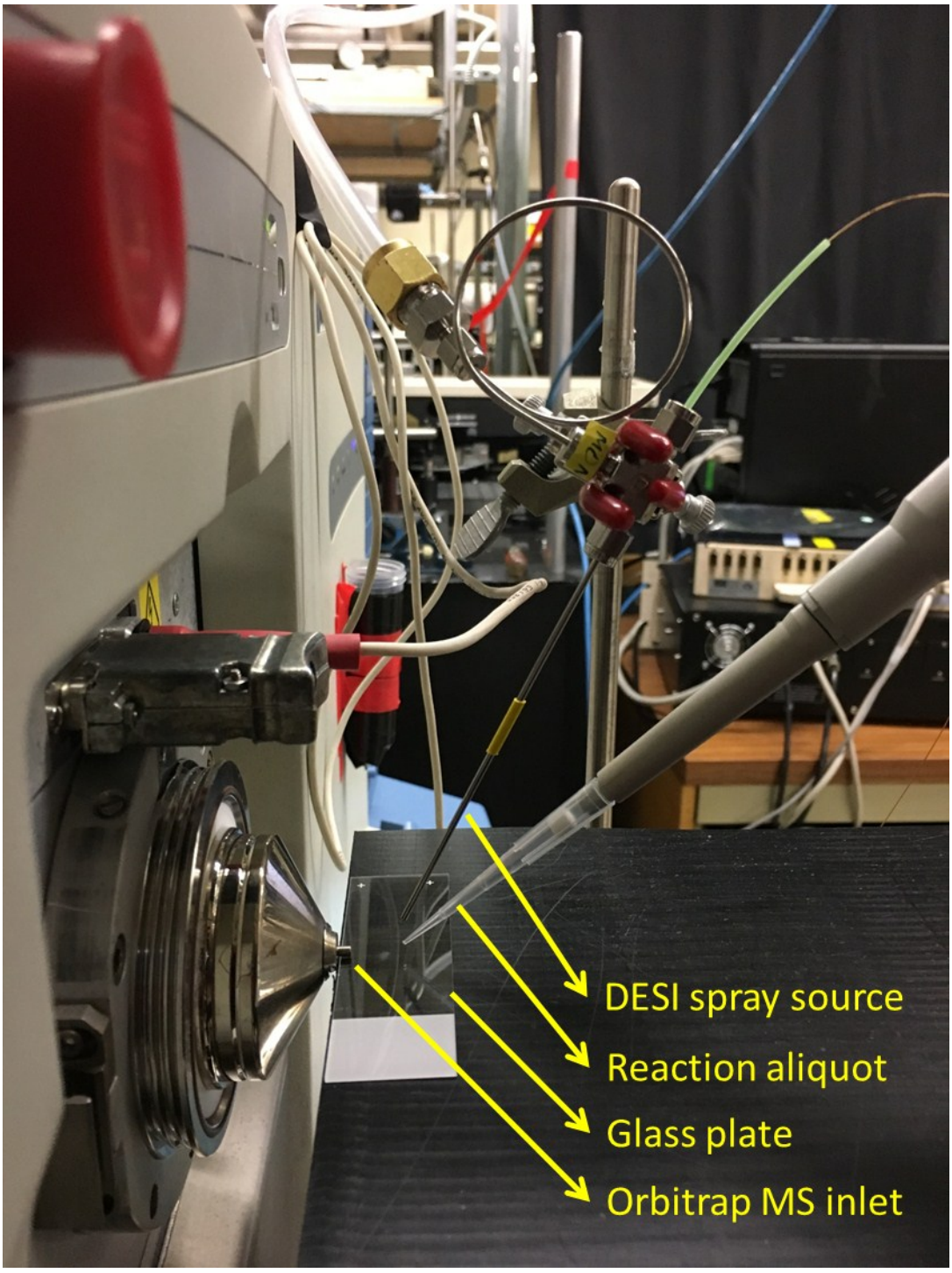


Figure S1. Photograph of the DESI setup showing the reaction aliquot dispensing under a stream of charged microdroplets.

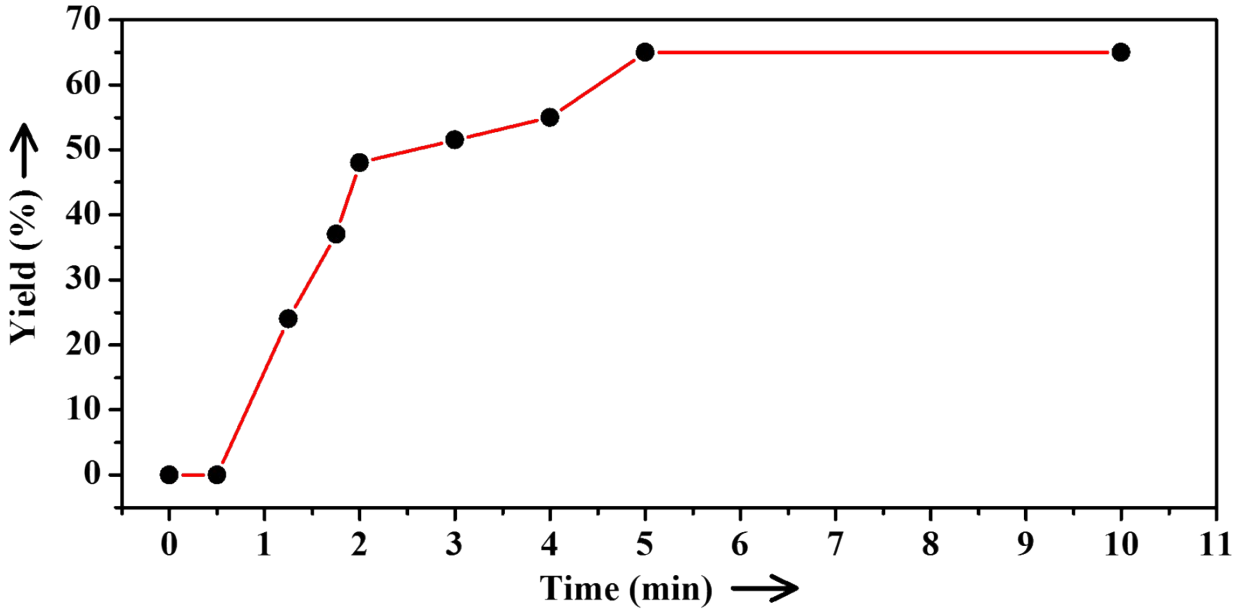


Figure S2. Kinetic study with 4-phenylbutyric acid showing a plot of percent yield of lactone *vs* reaction time. The initial induction period of 30 s is due to heat transfer. Products yields are estimated from ^{1}H NMR analysis.

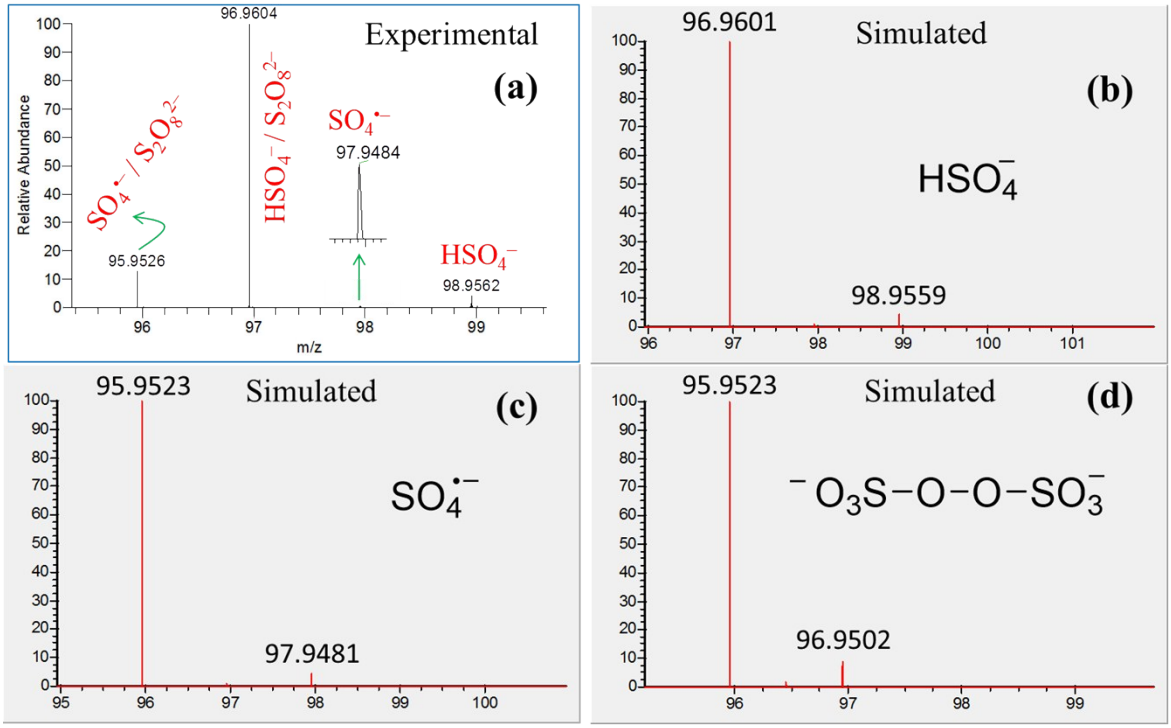


Figure S3. (a) Experimental ion signals of species HSO_4^-, $SO_4^{\bullet-}$, and $S_2O_8^{2-}$ obtained from Figure 2a showing their isotopic distributions, which match closely with the corresponding theoretical isotopic distributions of (b) HSO_4^-, (c) $SO_4^{\bullet-}$, and (d) $S_2O_8^{2-}$.

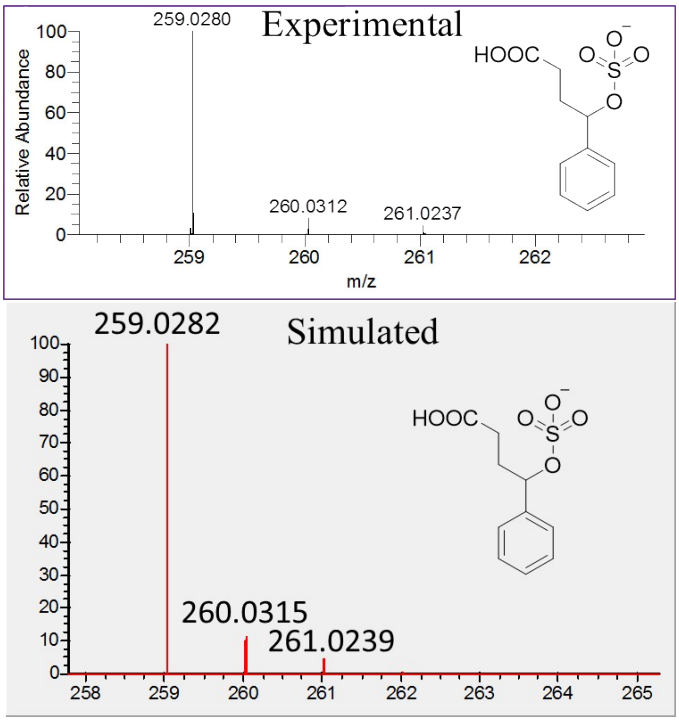


Figure S4. Isotopic distribution of the species detected at *m/z* 259.0280 (Figure 2a), which closely matches with the theoretical isotopic distribution of 3-carboxy-1-phenylpropyl sulfate.

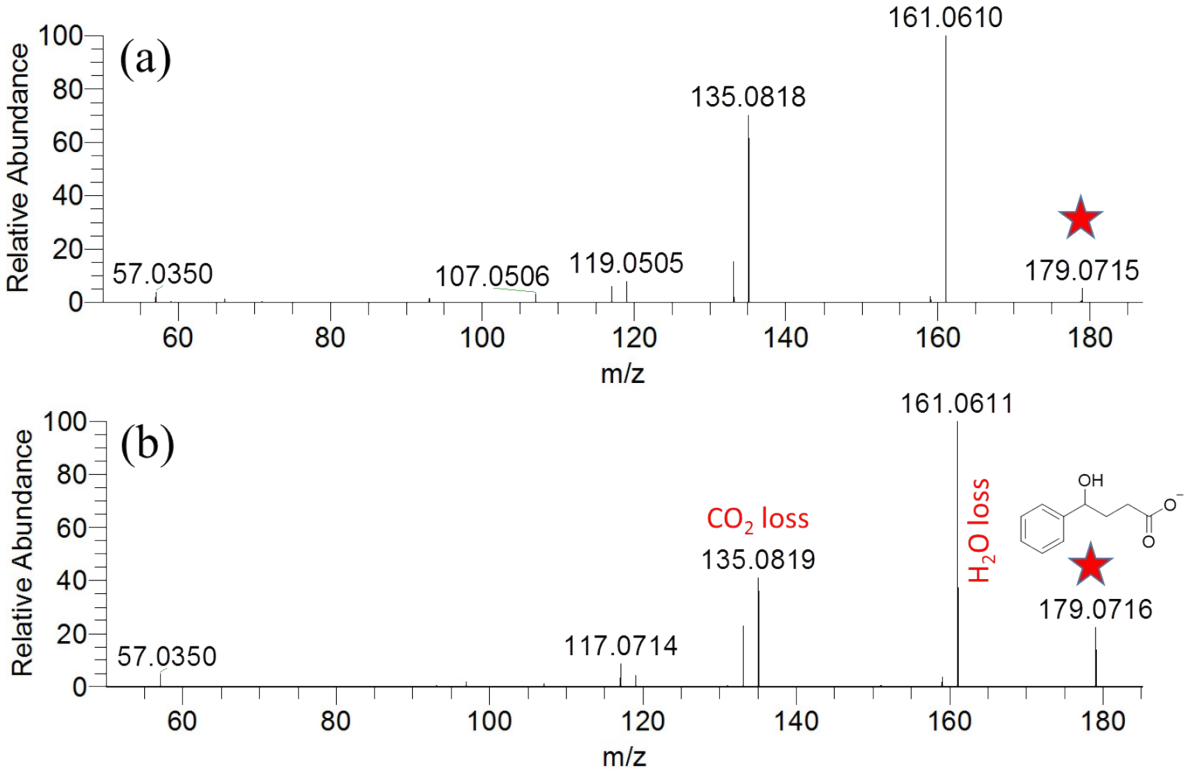


Figure S5. Negative ion mode (a) CID-MS^3 of the species at *m/z* 179.0716 mass selected from Figure 2b, and (b) CID-MS^2 of 4-hydroxy-4-phenylbutanoate / [**5**-H]$^-$ (Figure 2a).

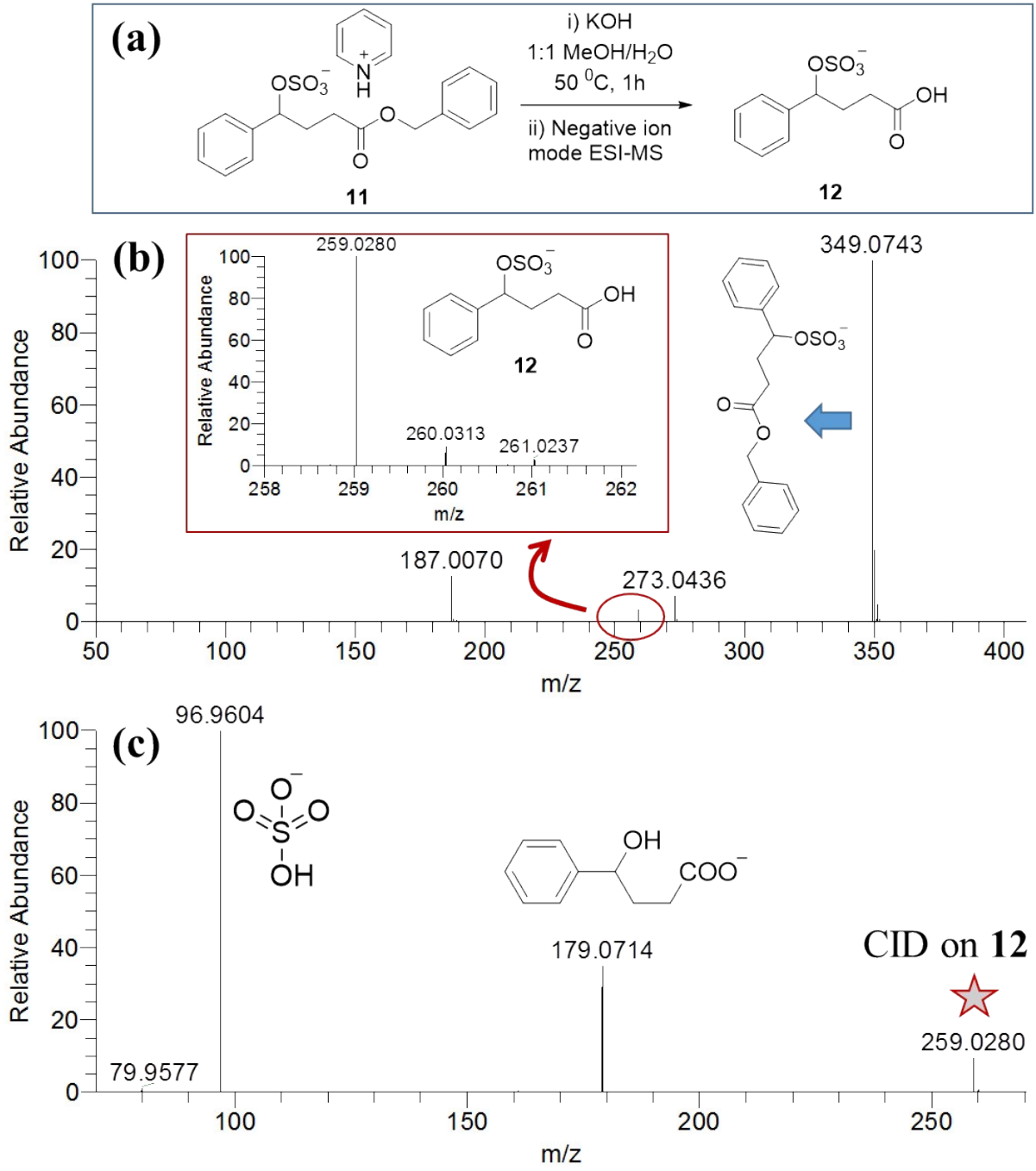


Figure S6. (a) Schematic presentation of the workflow for the synthesis and detection of 3-carboxy-1-phenylpropyl sulfate (**12**) by the hydrolysis of **11** (see Experimental section for the synthesis of **11**). (b) Negative ion mode ESI-MS of the reaction mixture shown in (a). The inset shows the isotopic distribution of **12** detected in the mass spectrum. (c) CID-MS^{2}of species **12** (m/z 259.0280) which was mass selected from (b).

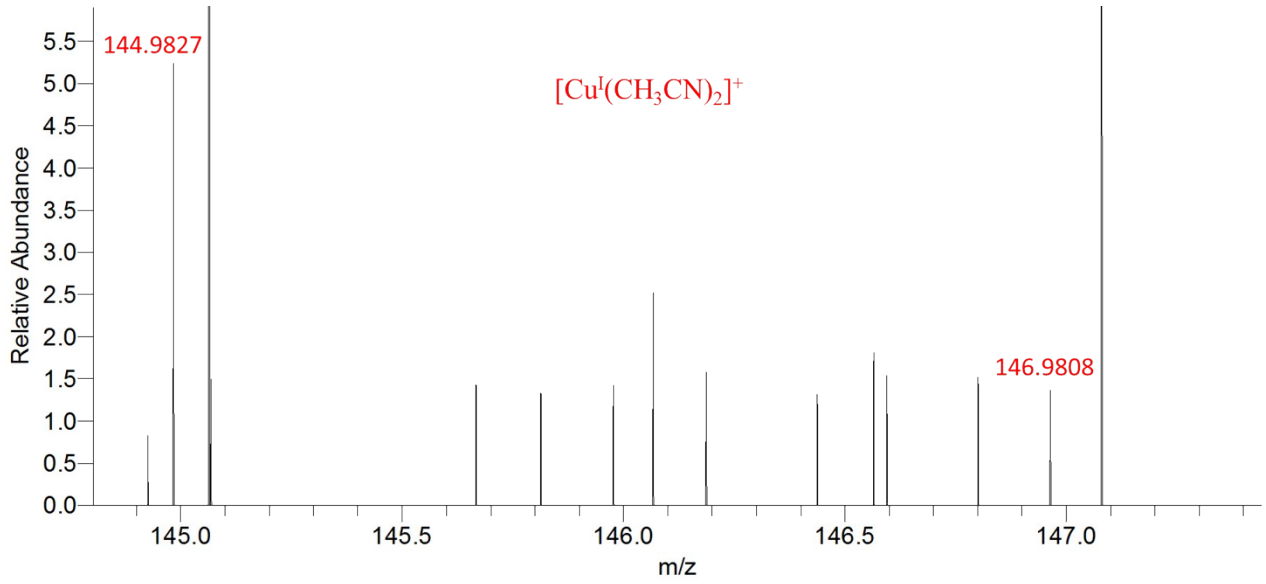


Figure S7. A trace ion signal at *m/z* 144 (attributed to $[Cu^{I}(CH_3CN)_2]^+$) is detected in the DESI mass spectrum (Figure 3a) of the Cu(II)-catalyzed oxidative cyclization of 4-phenylbutyric acid (Scheme 1).

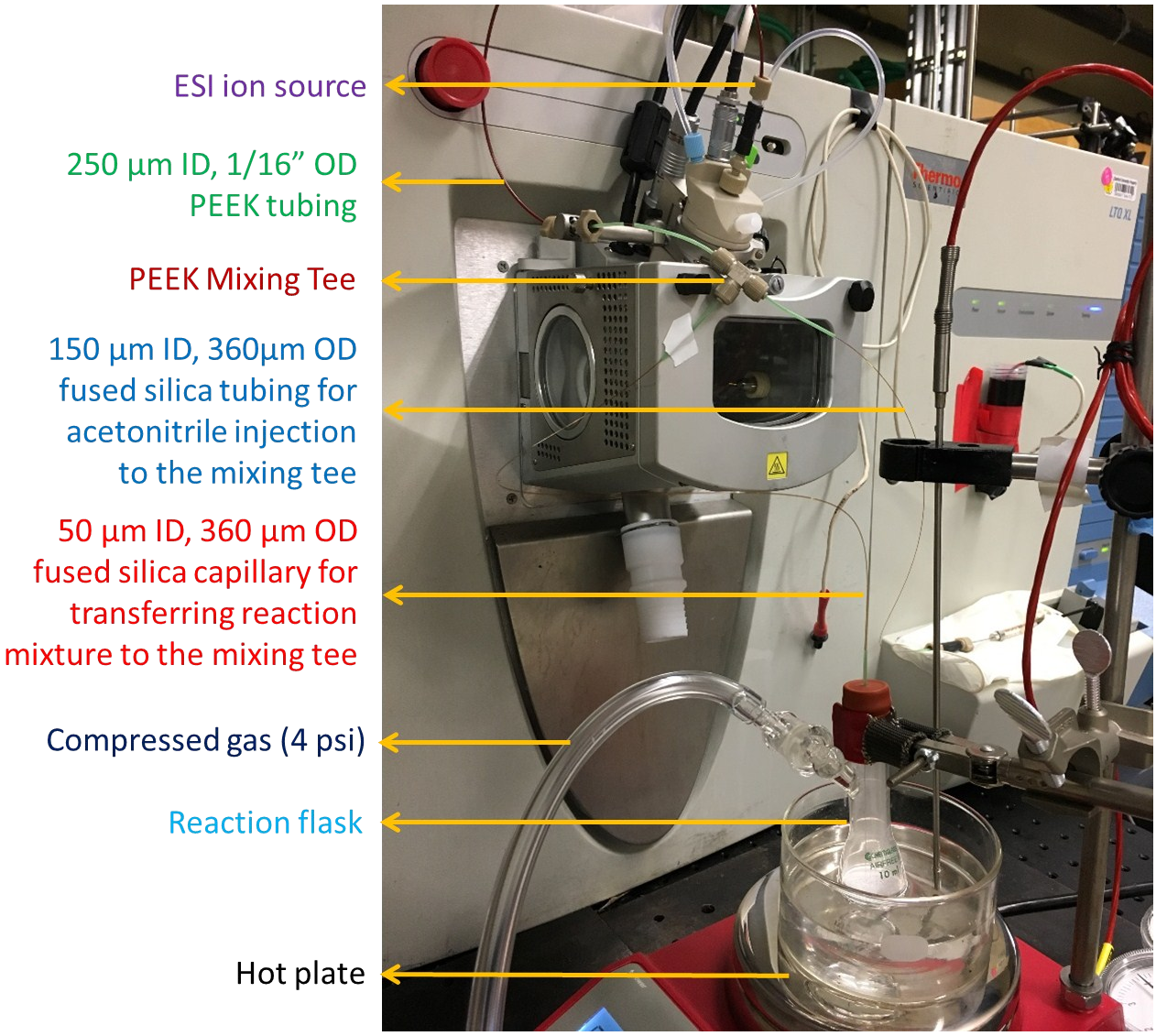


Figure S8. Pressurized infusion setup used in the online ESI-MS monitoring of Cu(I) formed during the Cu(II)-catalyzed oxidative cyclization of 4-phenylbutyric acid.

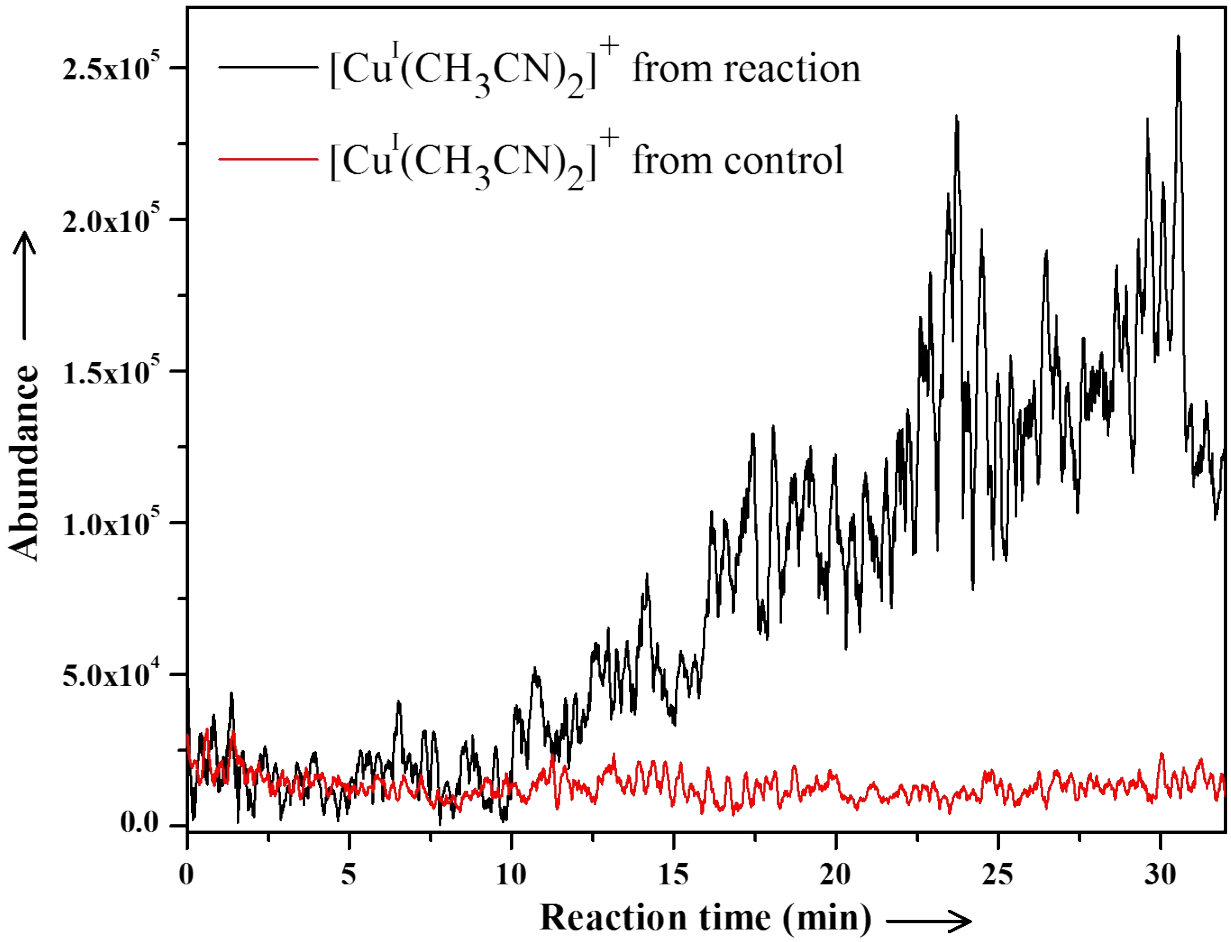


Figure S9. Online ESI-MS monitoring of the formation of Cu(I) species in real time from the reaction mixture (containing 4-methylvaleric acid substrate) and control (reaction mixture without substrate) at 75 °C. See the Experimental section for details.

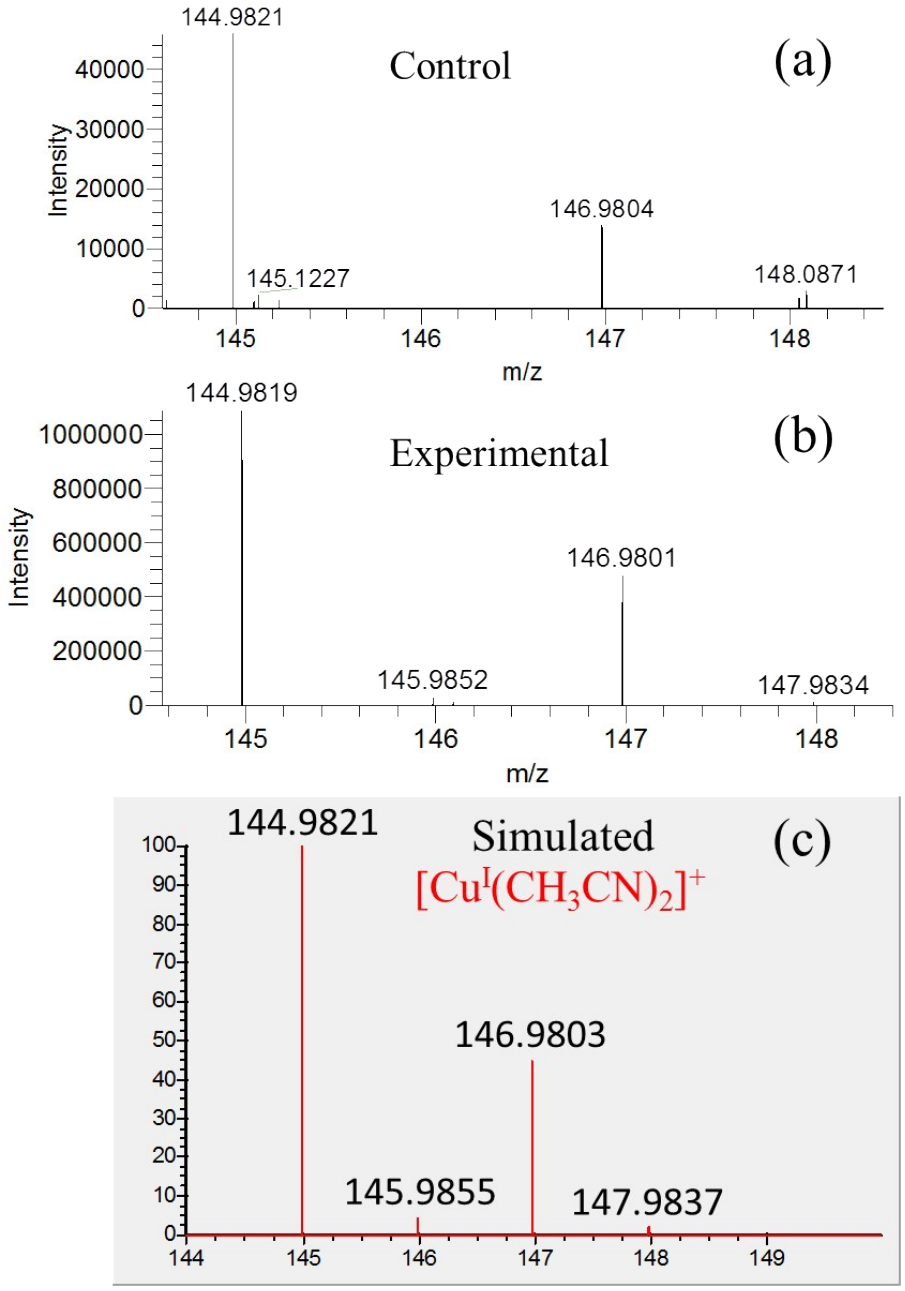


Figure S10. Average ion signal of $[Cu^{I}(CH_3CN)_2]^+$ species detected by online ESI-MS from (a) control study (reaction mixture without substrate), (b) reaction mixture at 75 °C. The lower panel (c) shows the theoretical isotopic distribution of $[Cu^{I}(CH_3CN)_2]^+$ species.

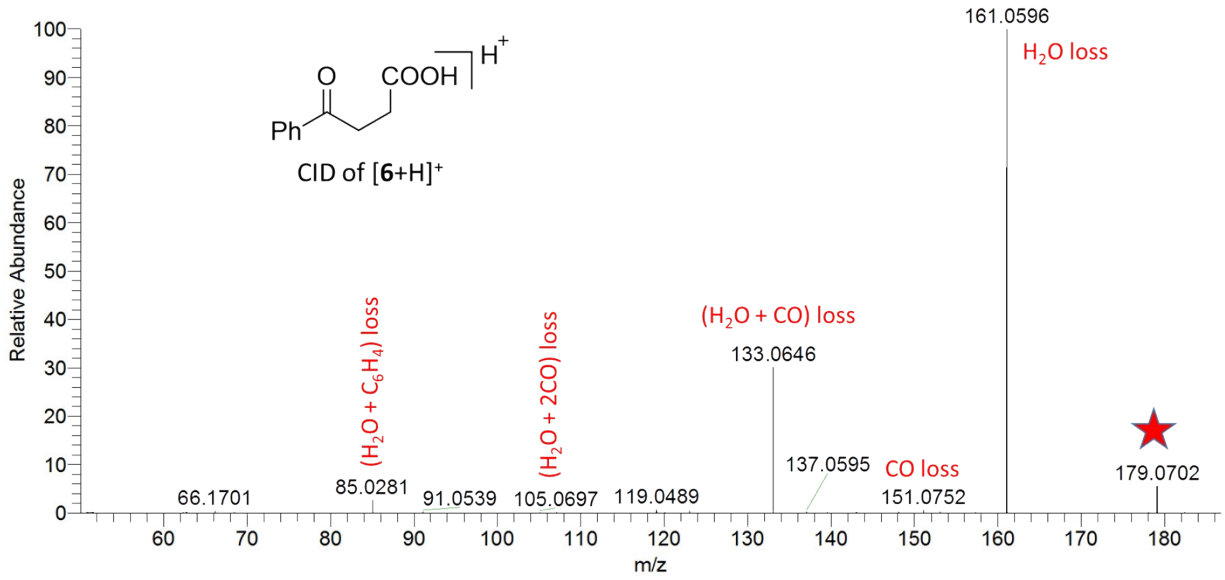


Figure S11. CID-MS^2 spectrum of mass selected protonated species **6** observed at *m/z* 179.0706 (Figure 3a).

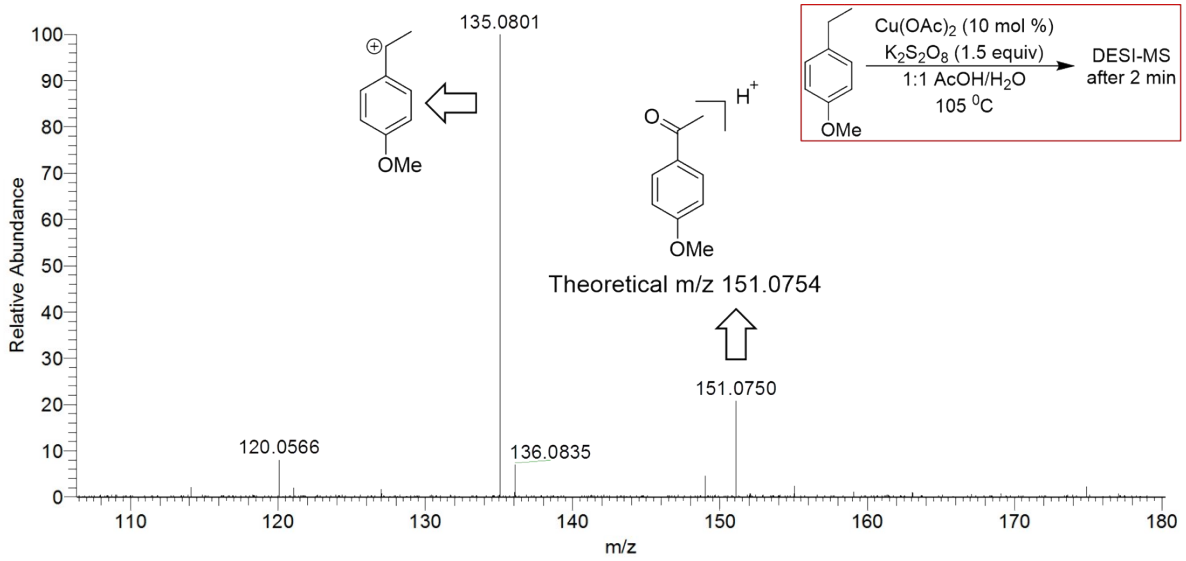


Figure S12. Positive ion mode DESI mass spectrum for the Cu(II)-catalyzed oxidation of 4-ethylanisole. Formation of its benzylic carbocation is indicated by the ion signal at *m/z* 151.0754 with high mass accuracy (2.6 ppm).

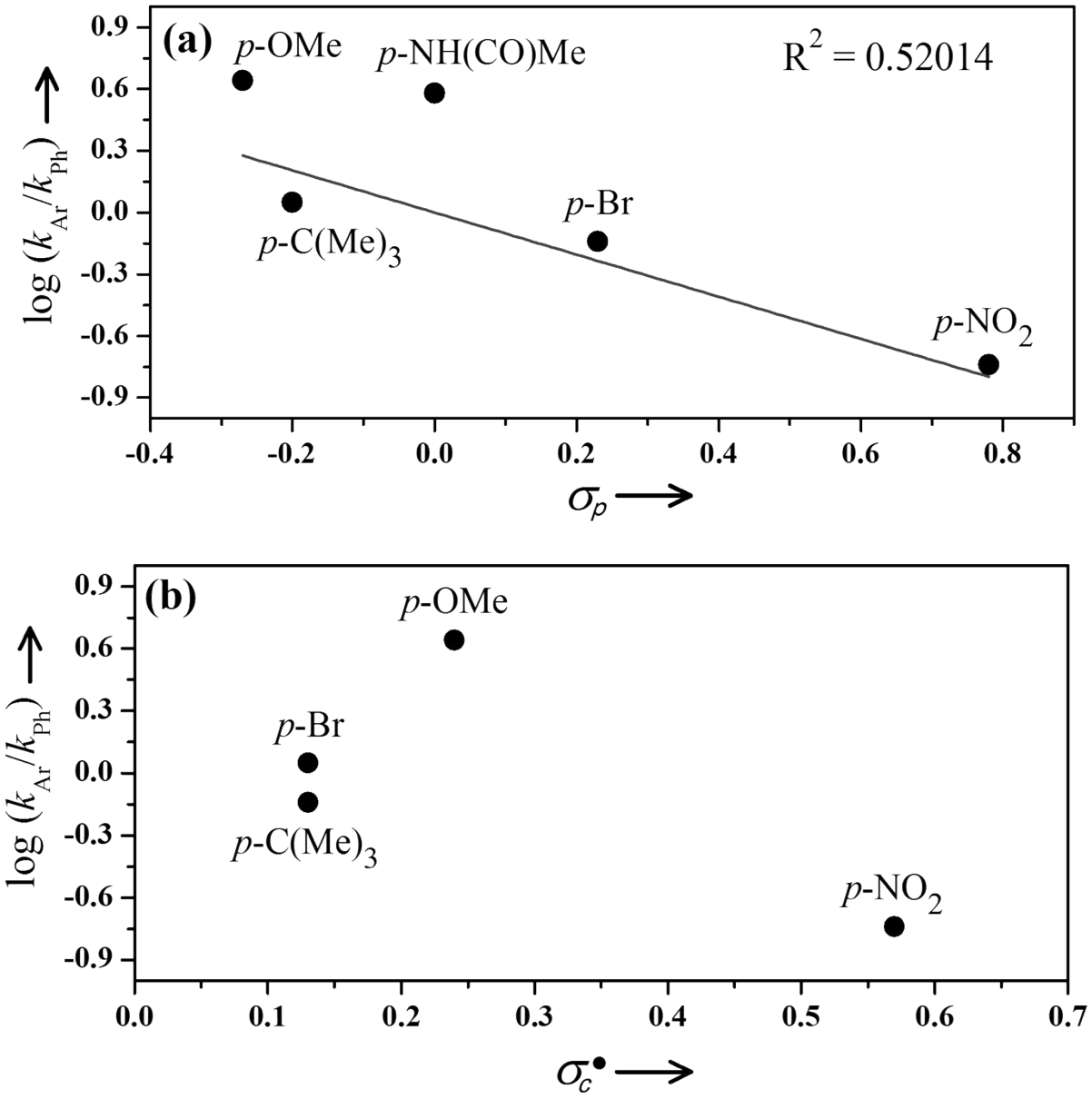
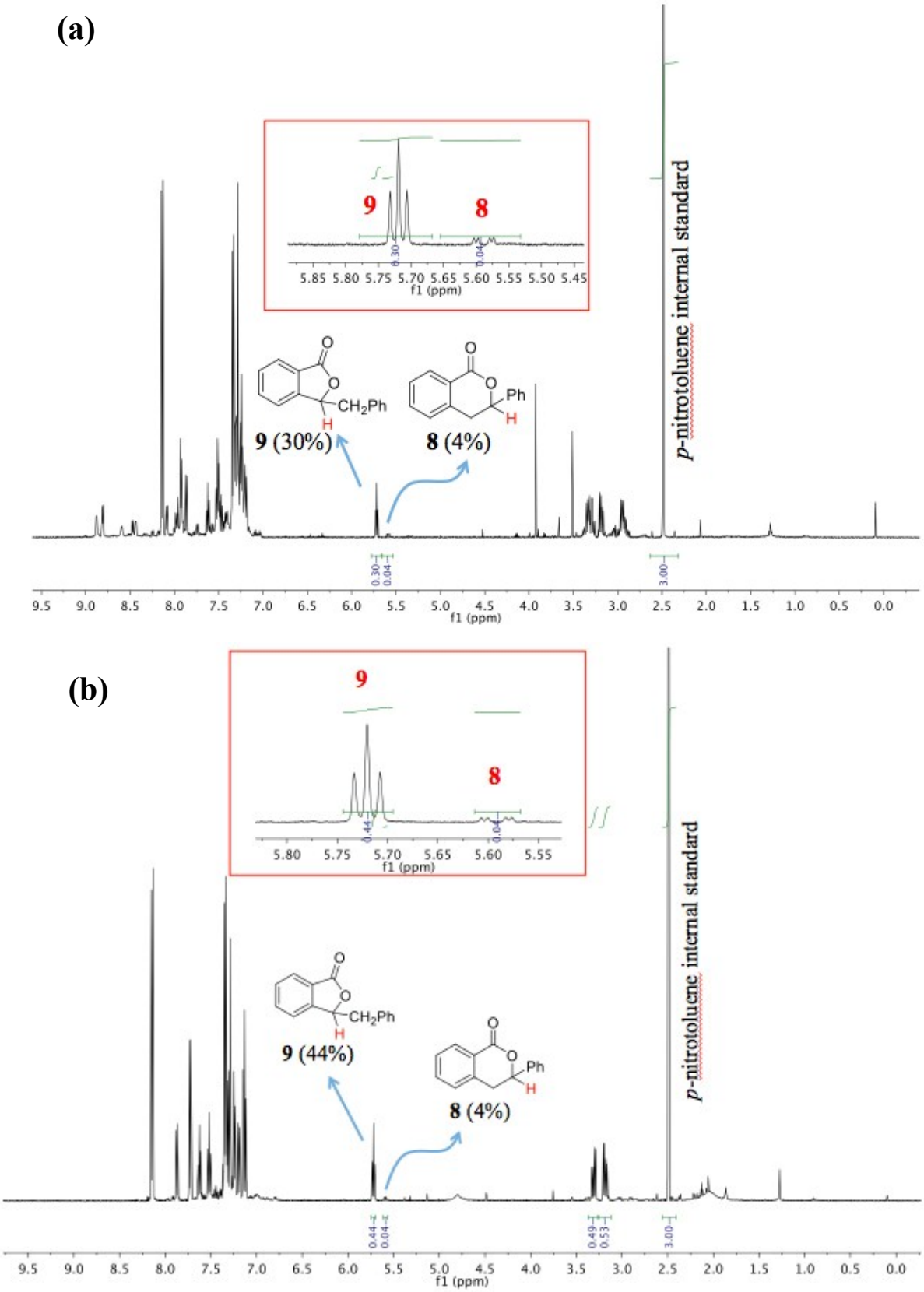


Figure S13. Plots of (a) log (k_{Ar}/k_{Ph}) *vs.* Hammett substituent constant σ_p, and (b) log (k_{Ar}/k_{Ph}) *vs.* Creary radical constant $\sigma_c^{\cdot}$ from competition experiments between 4-phenylbutyric acid (Ph) and *para*-substituted 4-phenylbuytric acids (Ar). See the Experimental section for details. A $\sigma_c^{\cdot}$ value for p-NH(CO)Me was not found in the literature.


(a)
9
8
5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45
f1 (ppm)
CH2Ph
H
9 (30%)
Ph
H
8 (4%)
p-nitrotoluene internal standard
0.30
0.04
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
(b)
9
8
5.80 5.75 5.70 5.65 5.60 5.55
f1 (ppm)
CH2Ph
H
9 (44%)
Ph
H
8 (4%)
p-nitrotoluene internal standard
0.44
0.04
0.49
0.53
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

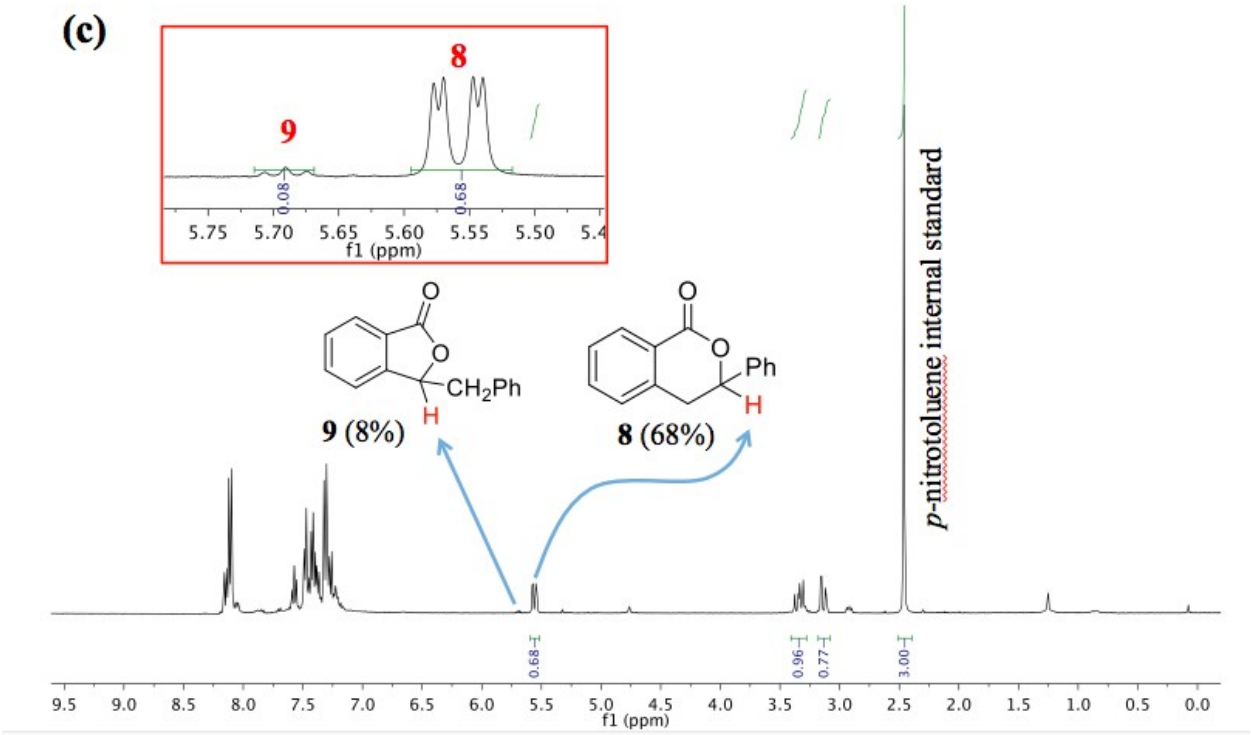
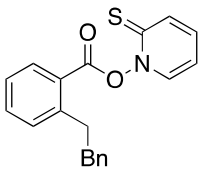


Figure S14. ^{1}H NMR quantification of products (from unpurified reaction mixture) obtained from (a) the Barton ester **7** as shown in Scheme 3a. (b) Cyclization with $PhI(OAc)_2/I_2$ as shown in Scheme 3b. (c) 2-phenethylbenzoic acid (**10**) as shown in Scheme 3c.

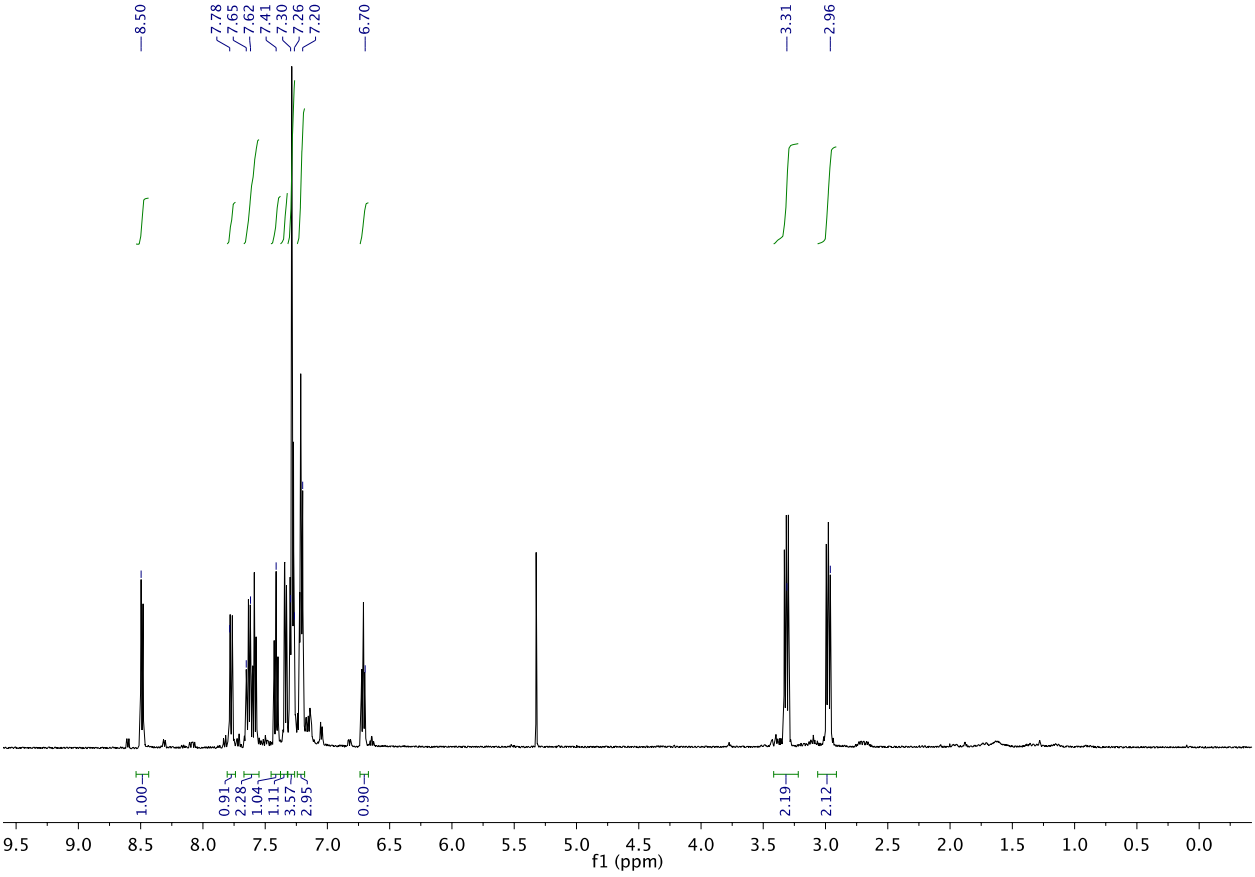
Characterization of Barton ester 7



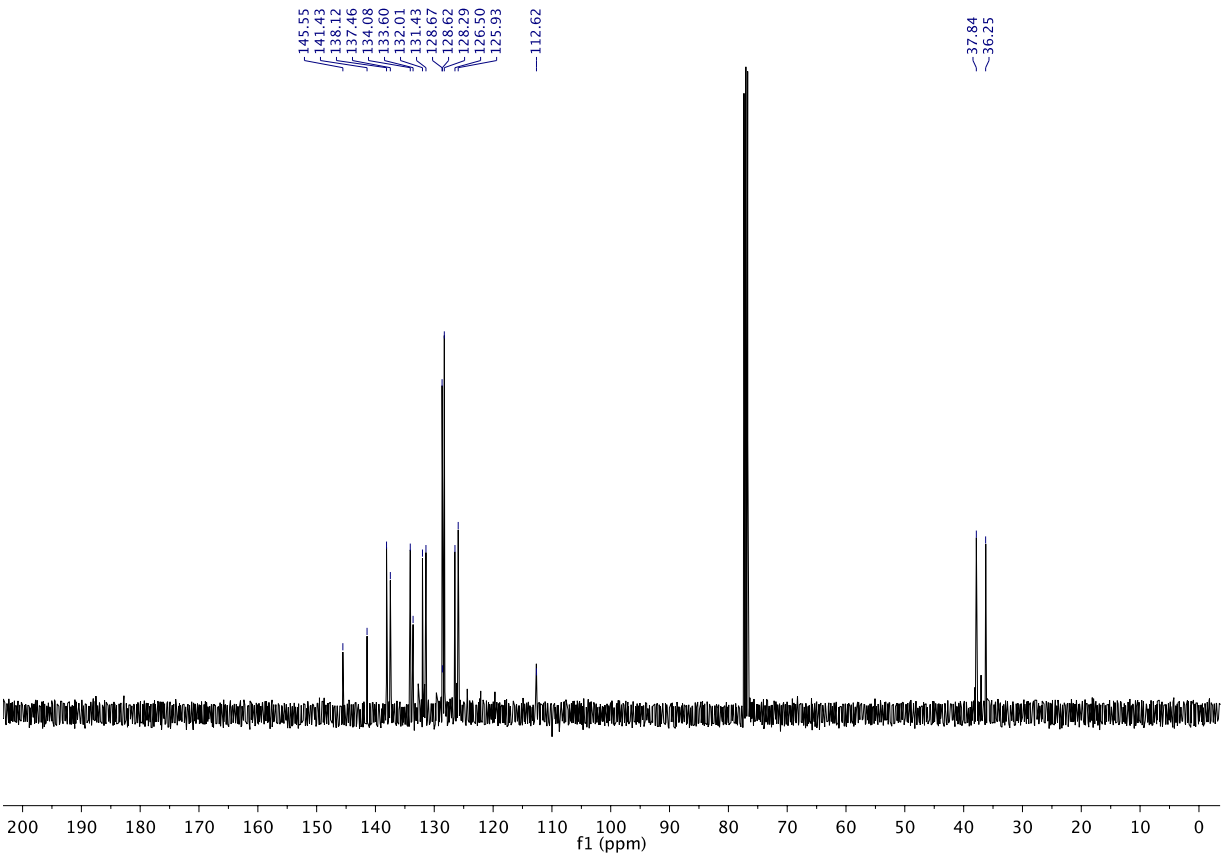
7

Bright yellow oil: TLC R_f = 0.11 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (d, 1H, J = 10.0 Hz), 7.78 (d, 1H, J = 10.0 Hz), 7.66-7.62 (m, 1H), 7.58 (t, 1H, J = 7.6 Hz), 7.42 (t, 1H, J = 7.7, 1.7 Hz), 7.33 (d, 1H, J = 5.0 Hz), 7.32-7.26 (m, 3H), 7.24-7.18 (m, 3H), 6.74-6.68 (dd, 1H, J = 6.2 Hz, 1.8 Hz), 3.31 (t, 2H, J = 10.0 Hz), 2.96 (t, 2H, J = 10.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.6, 141.4, 138.1, 137.5, 134.1, 133.6, 132.0, 131.4, 128.7, 128.6, 128.3, 126.5, 125.9, 112.6, 37.8, 36.3 ppm; IR (thin film) ν 3061, 1776, 1234, 1135, 842 cm^{-1}; HRMS (ES$^+$) calcd for $C_{20}H_{17}NO_2SNa^+$ 358.0878, found 358.0868 (MNa^+).

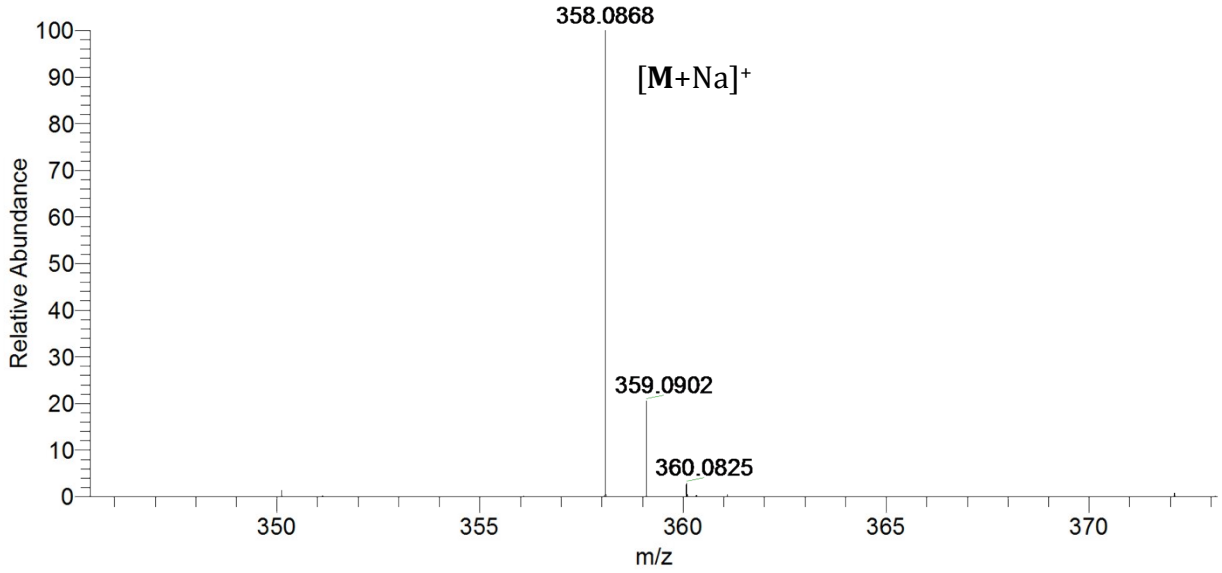
^{1}H NMR ($CDCl_3$, 500 MHz) of **7**



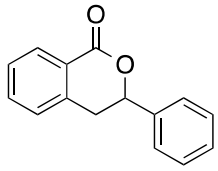
^{13}C NMR ($CDCl_3$, 100 MHz) of **7**



HRMS (ES^+) of 7

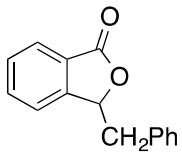


Characterization of 8 and 9



8 (3-phenylisochroman-1-one)

This compound has been previously characterized. See Sathyamoorthi, S.; Du Bois, J. *Org. Lett.* **2016**, *18*, 6308-6311.



9 (3-benzylisobenzofuran-1(3*H*)-one)

This compound has been previously characterized. See Sueki, S.; Wang, Z.; Kuninobu, Y. *Org. Lett.* **2016**, *18*, 304-307.

^{1}H NMR of sulfated alcohol 11

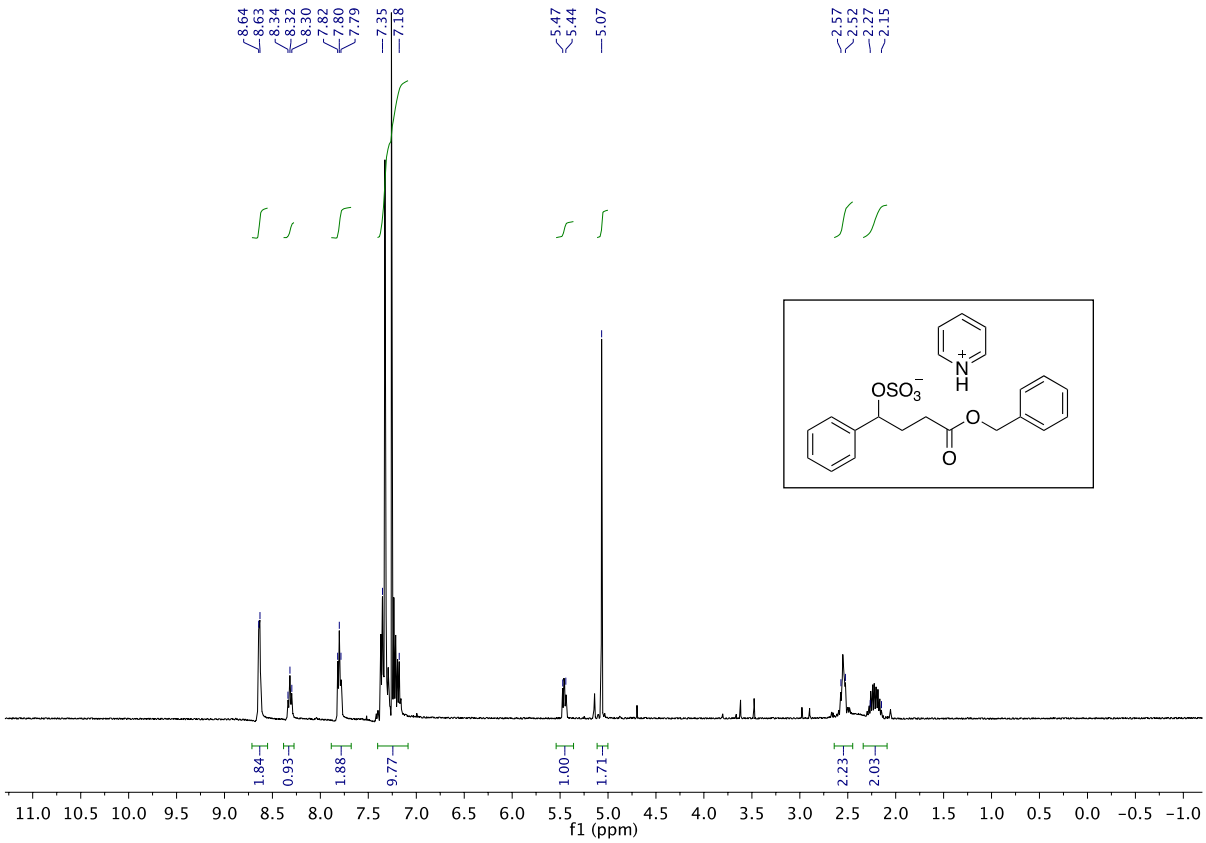


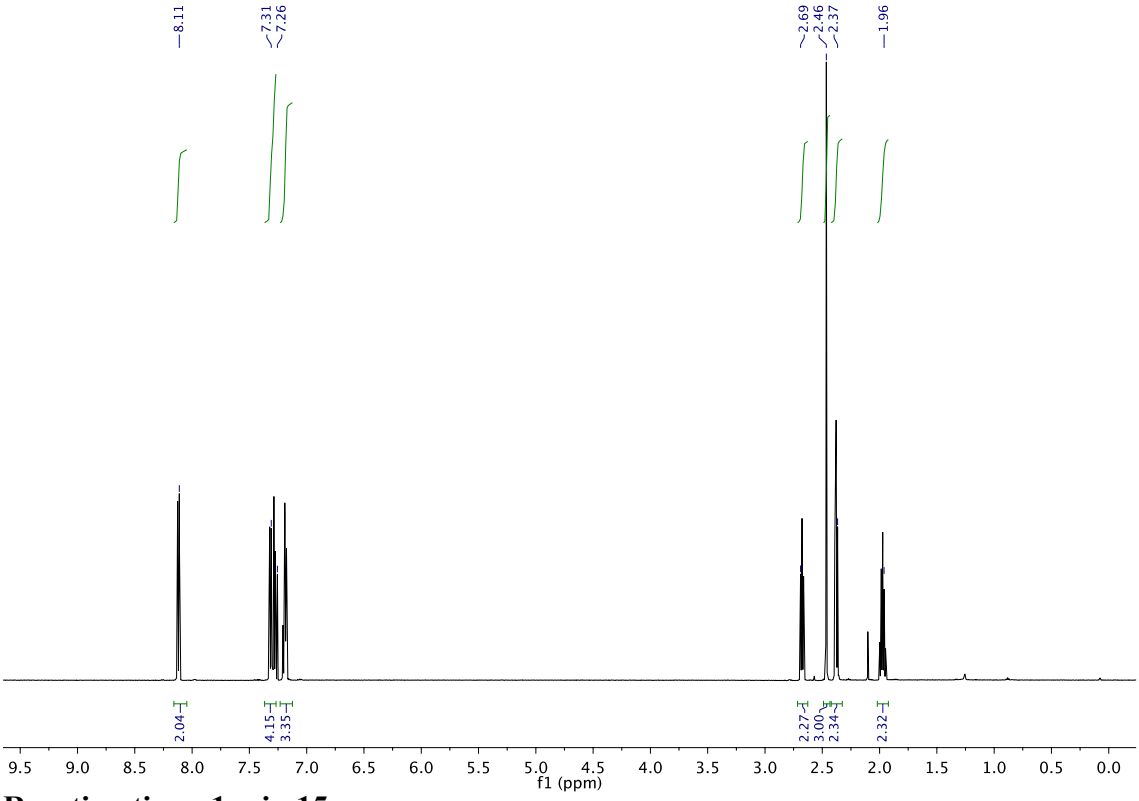
Table S1. List of species and their *m/z* values, representing the accuracy* in their mass measurements

Species detected	Observed *m/z*	Theoretical *m/z*	Deviation	Error (ppm)
[**1**-H]$^-$	163.0765	163.0765	0	0
[**5**-H]$^-$	179.0714	179.0714	0	0
[**6**-H]$^-$	177.0558	177.0557	0.0001	0.6
HSO_4^-	96.9604	96.9601	0.0003	3.1
$S_2O_8^{2-}$	95.9526	95.9523	0.0003	3.1
$SO_4^{\bullet-}$	95.9526	95.9523	0.0003	3.1
Adduct of **2** with $SO_4^{\bullet-}$	259.0280	259.0282	0.0002	-0.8
$[Cu^I(CH_3CN)_2]^+$	144.9819	144.9822	-0.0003	-2.1
3 / [**4**+H]$^+$	163.0756	163.0754	0.0002	1.2
[**6**+H]$^+$	179.0704	179.0703	0.0001	0.6
[**4**+Na]$^+$	185.0576	185.0573	0.0003	1.6
[**4**+K]$^+$	201.0316	201.0312	0.0004	2.0
[**6**+Na]$^+$	201.0525	201.0522	0.0003	1.5
[**6**+K]$^+$	217.0265	217.0262	0.0003	1.4
Benzyl cation of 4-ethylanisole	135.0801	135.0804	-0.0003	-2.2
Benzyl cation of ethylbenzene	105.0694	105.0698	-0.0004	-3.8

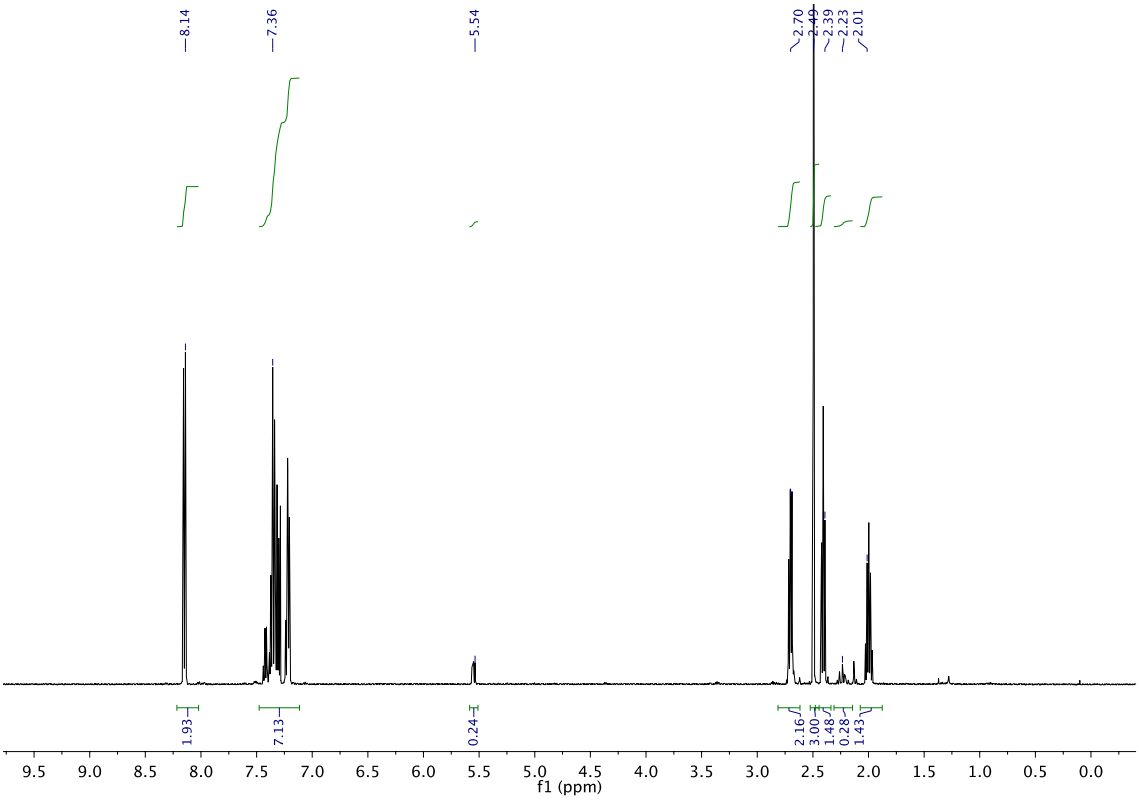
*Verified further by using standards of reactants **1**, $S_2O_8^{2-}$, $[Cu^I(CH_3CN)_2]^+$, and the product **4**.

^{1}H NMR data for the kinetic study

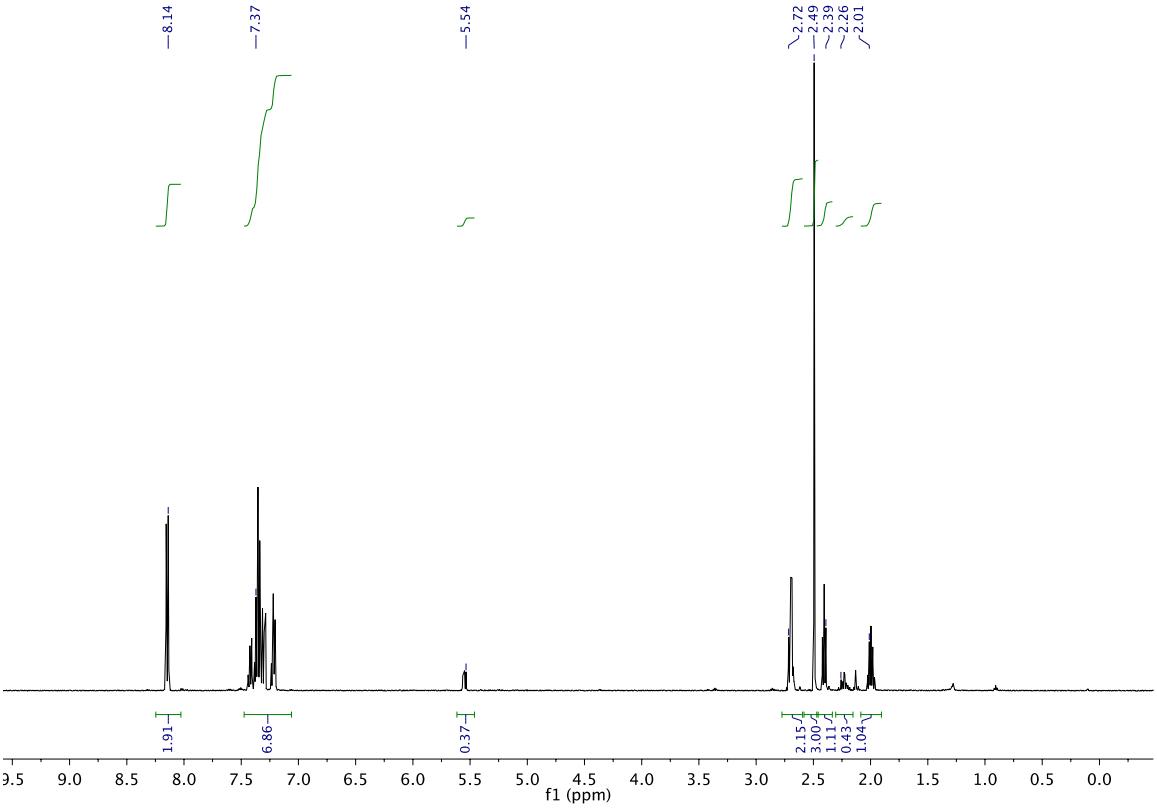
Reaction time: 30 sec



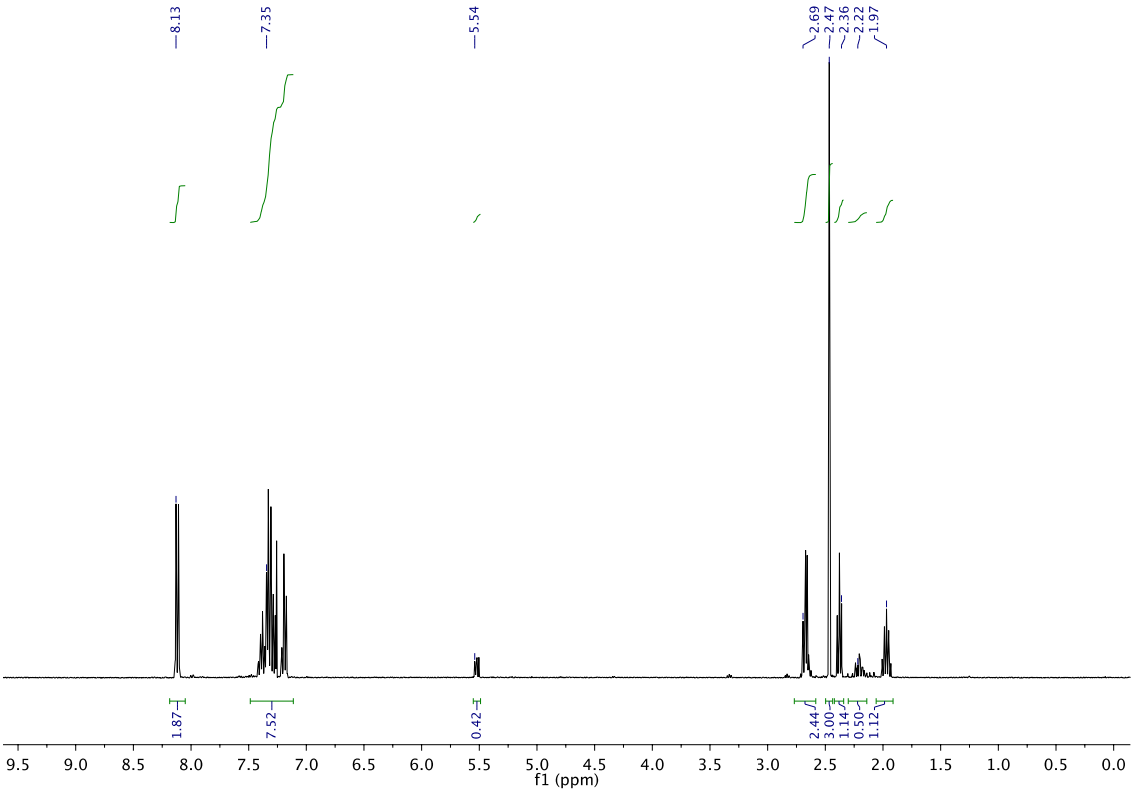
Reaction time: 1 min 15 sec



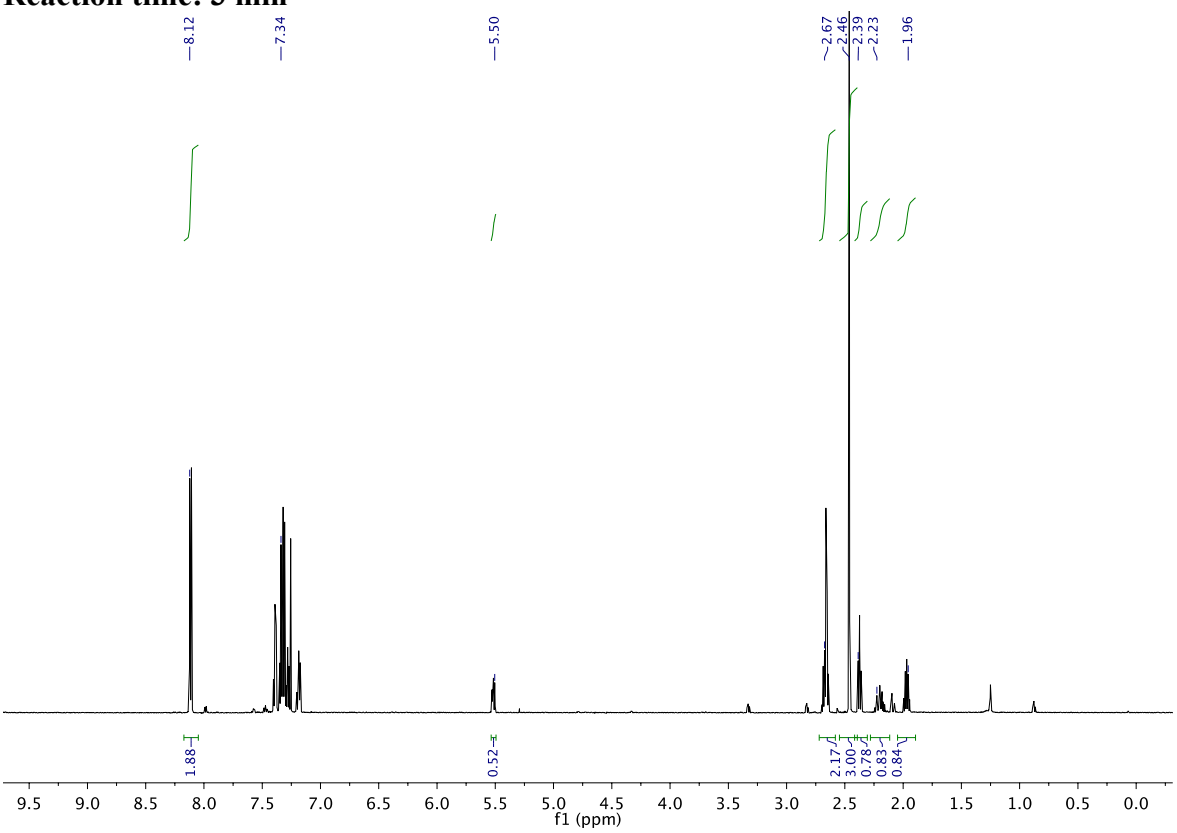
Reaction time: 1 min 45 sec



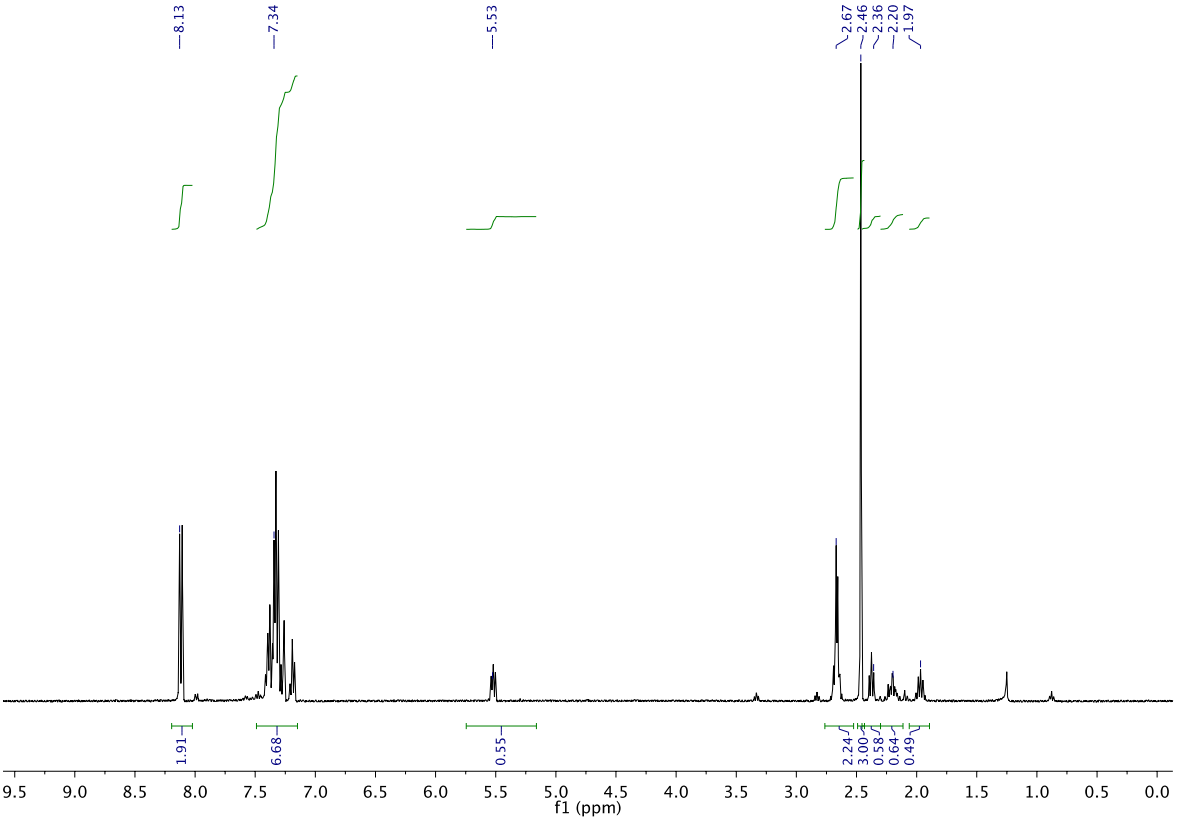
Reaction time: 2 min



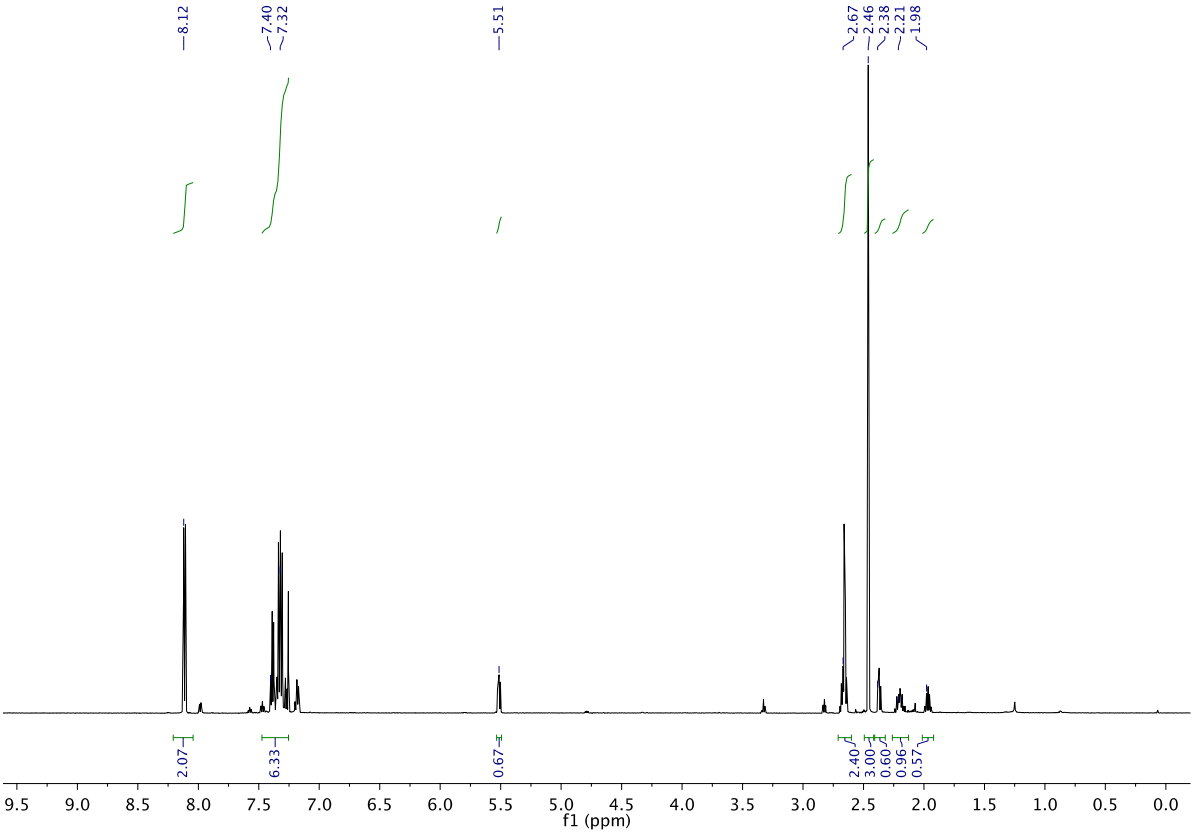
Reaction time: 3 min



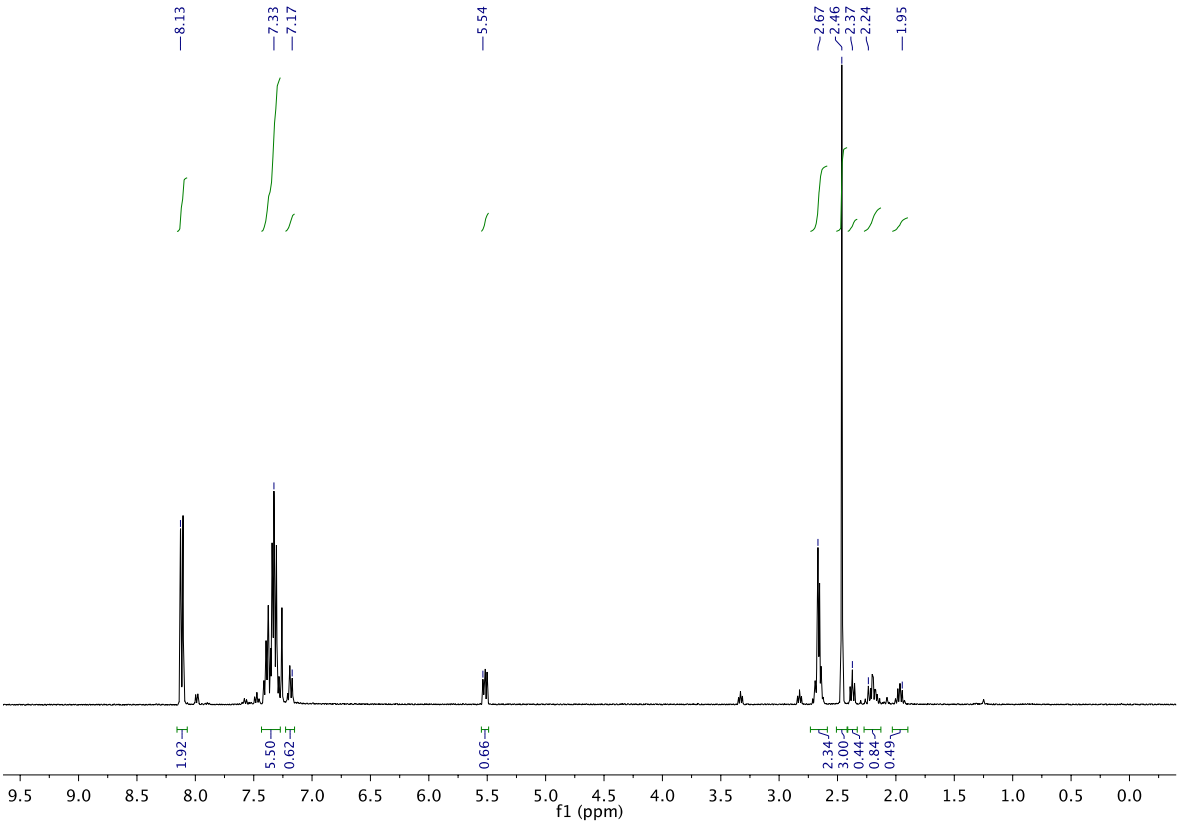
Reaction time: 4 min



Reaction time: 5 min

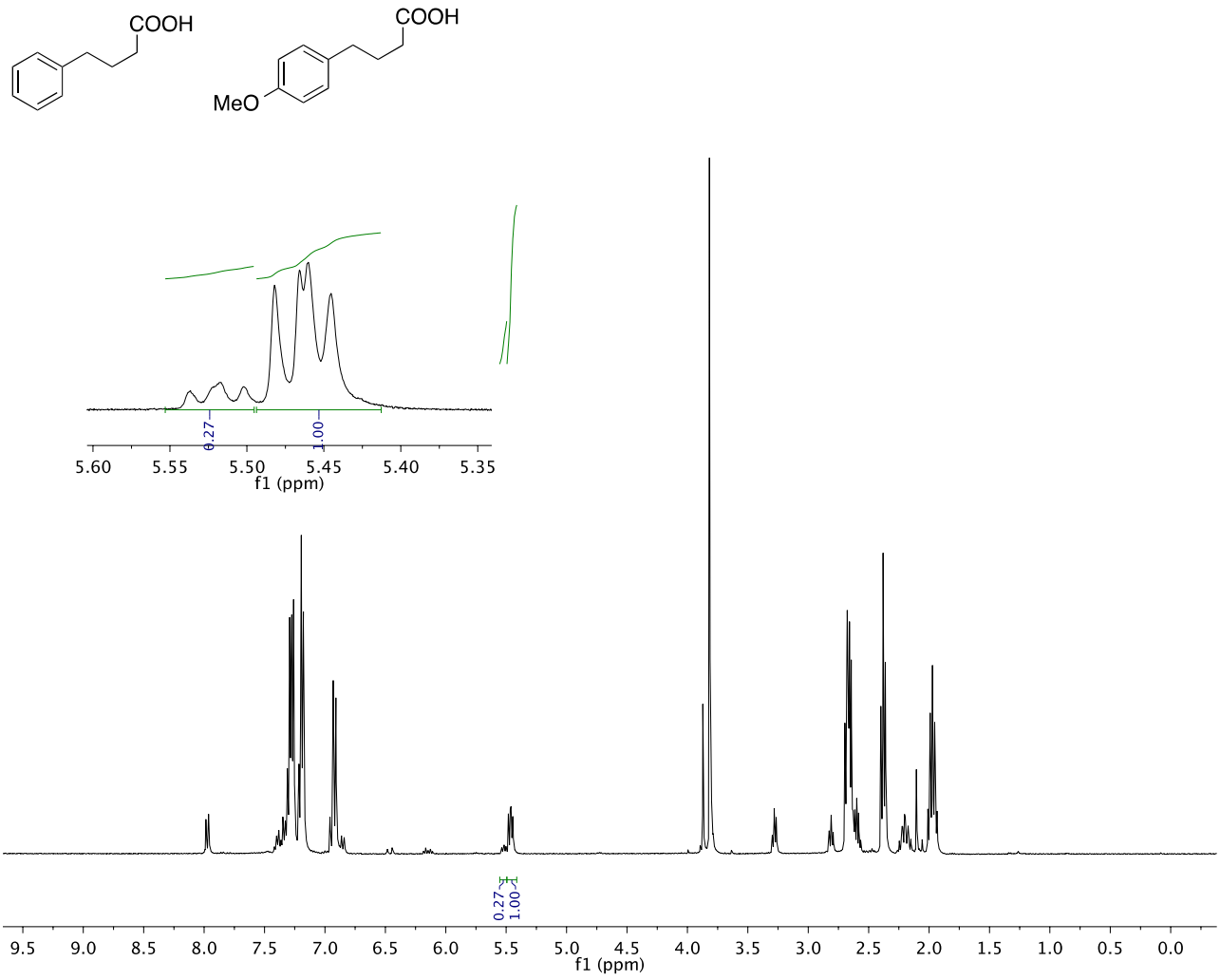


Reaction time: 10 min

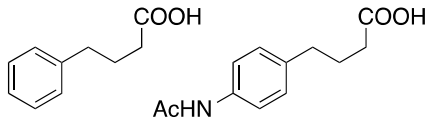


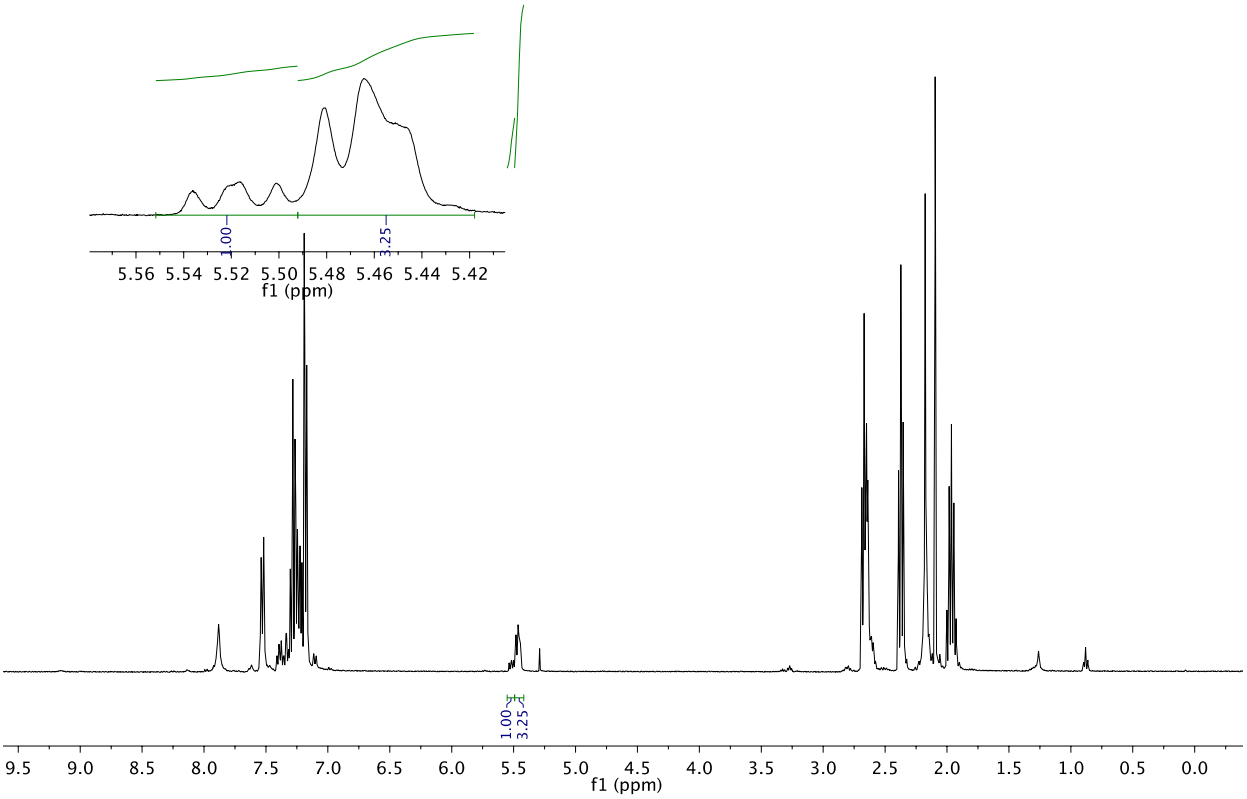
^{1}H NMR data for the Hammett analysis

(a) ($CDCl_3$, 400 MHz)

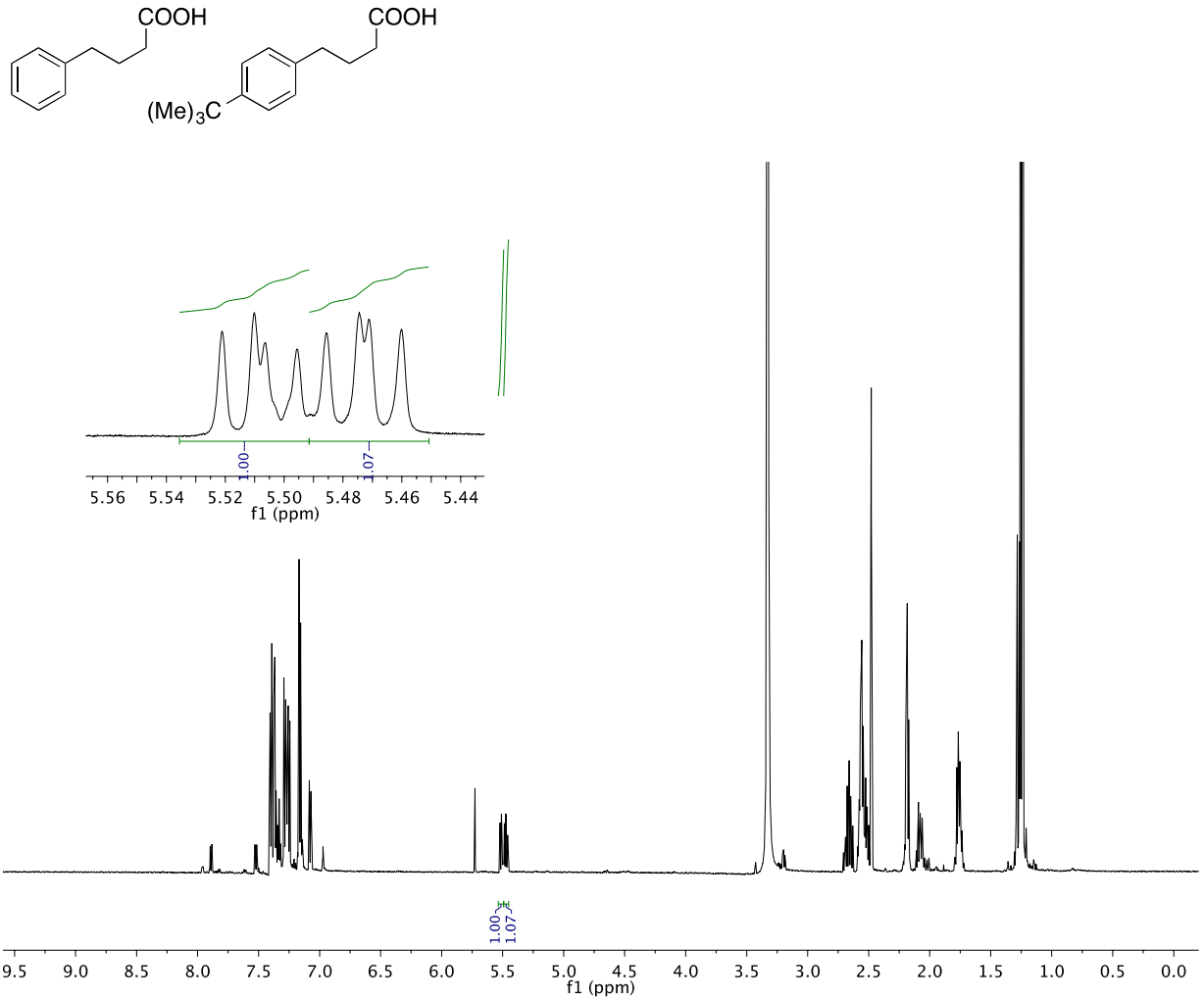


(b) ($CDCl_3$, 400 MHz)

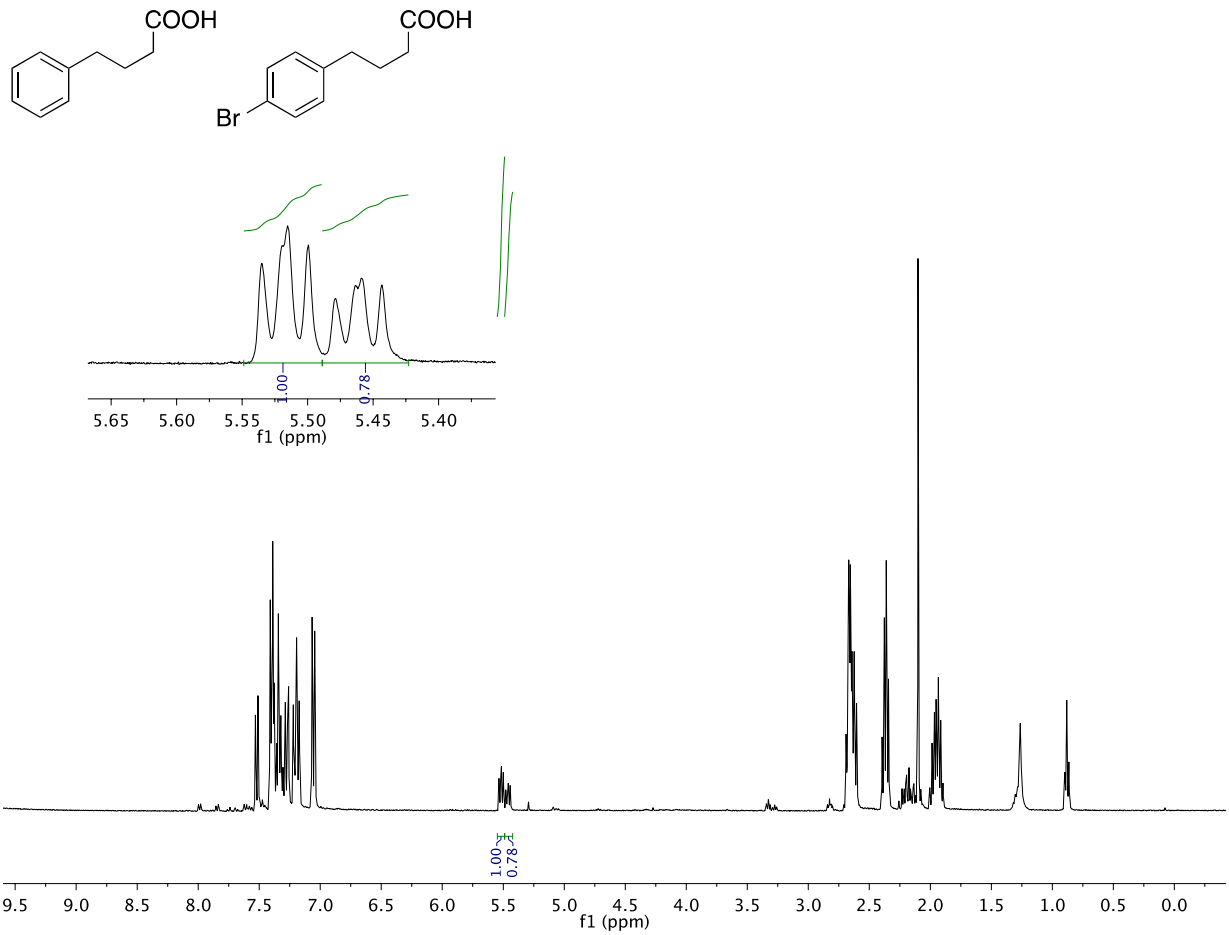




(c) ($(CD_3)_2SO$, 600 MHz)



(d) ($CDCl_3$, 400 MHz)



(e) ($CDCl_3$, 400 MHz)