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for the Preparation
of Organic Compounds

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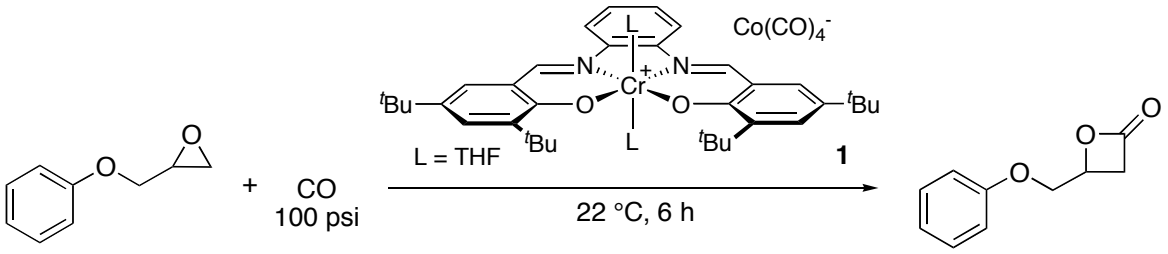
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.086.0287

LOW PRESSURE CARBONYLATION OF EPOXIDES TO β-LACTONES



Submitted by John W. Kramer, Daniel S. Treitler, and Geoffrey W. Coates.[1]
Checked by Scott E. Denmark and Andrew J. Hoover.

1. Procedure

Caution: Carbon monoxide is a highly toxic gas. All manipulations with carbon monoxide must be performed in a well-ventilated fume hood in the presence of a carbon monoxide detector.

In an argon-filled glove box, racemic 1,2-epoxy-3-phenoxypropane (5.00 g, 33.3 mmol) (Note 1) and dimethoxyethane (DME, 8.5 mL) (Note 2) are combined in an oven-dried, 85-mL Lab-Crest® Pressure Reaction Vessel (Note 3) equipped with a magnetic stir bar. The catalyst, $[(salph)Cr(THF)_2][Co(CO)_4]$ (**1**, 0.150 g, 0.166 mmol, 0.497 mol %) (Note 4) is weighed into an oven-dried, 20-mL vial and dissolved in 8.0 mL of DME. This catalyst solution is drawn into an oven-dried, 10-mL gastight syringe, and the syringe needle is embedded into a septum to exclude air upon removal from the glove box.

In a well-ventilated fume hood, the Lab-Crest® Pressure Reaction Vessel is connected to a cylinder of carbon monoxide (Notes 3 and 5). The reactor is then submerged into a water bath at 20 °C and concurrently pressurized with CO to 20 psi (Note 6). After five minutes in the water bath, the catalyst solution is added to the reactor through a septum over the injection port (Note 7). The reactor is then pressurized to 100 psi CO and the dark red solution is stirred while the temperature of the water bath is held between 20–26 °C (Note 8). The CO pressure is maintained by repressurizing the reactor to 100 psi when the pressure drops to 85 psi. After

6 h, the reactor is carefully vented in the fume hood and the reaction mixture is transferred to a 100-mL round-bottomed flask.

The crude reaction mixture is concentrated by rotary evaporation (20 °C, 5 mmHg) and is then dissolved in 13 mL of dichloromethane (Note 9). This solution is poured into a medium-pore frit (9 cm diameter) packed with dry silica gel (4 cm) (Note 10). The lactone product is eluted with dichloromethane (1.1 L) and the filtrate is concentrated by rotary evaporation (15 ˚C, 14 mmHg) and then under high vacuum (26 °C, 0.33 mmHg) to afford 5.61–5.77 g (95–97%) of 4-phenoxymethyl-2-propiolactone as a white solid (Note 11). The lactone is dissolved in boiling diethyl ether (250 mL) in a 500-mL round-bottomed flask and the solution is allowed to cool at 25 °C for 15 min and is then submerged in a 10 °C water bath. Crystals formed within 7 min, and after 1 h in the bath the flask is placed in a freezer at –20 °C for 12 h. The supernatant is carefully decanted and the crystals are washed with 10 mL of cold (–40 °C) diethyl ether, which is decanted. The residual solvent is removed under vacuum (25 °C, 0.5 mmHg) to afford 5.13 g (86%) of 4-phenoxymethyl-2-propiolactone. The mother liquor is concentrated under vacuum (25 °C, 0.2 mmHg) to afford 568 mg of an off white solid, which is recrystallized in the same manner as described above except that 21 mL of boiling ether is used. The solution is cooled at –20 °C for 2.5 h and the crystals are washed with 3 mL of –40 °C diethyl ether to afford 0.48 g (8%) of 4-phenoxymethyl-2-propiolactone. The two crops are combined and residual solvent is removed under vacuum (25 °C, 0.325 mmHg) to afford 5.53 g (93%) of analytically pure 4-phenoxymethyl-2-propiolactone as colorless needles (Note 12).

2. Notes

1. 1,2-Epoxy-3-phenoxypropane is purchased from Aldrich Chemical Co., Inc. (99%) and is dried by stirring over CaH_2 under a nitrogen atmosphere for at least one week, degassed with three freeze-pump-thaw cycles, vacuum distilled, and transferred into an argon glove box prior to use. The submitters performed the reaction in a nitrogen-filled glove box.

2. DME is vacuum-distilled from a sodium/benzophenone ketyl and transferred into an argon glove box prior to use.

3. See Figures 1 and 2 for the assembly of the pressure apparatus. The Lab-Crest® pressure reaction vessel (**A**) and shield (**B**) are purchased from Andrews Glass Co. (part # 110207 0003, includes **A**, **B**, and fittings **C**-**F**)

and fitted with a needle valve adaptor (SS 1/8" NPT, Andrews Glass Co. part #110957 0001, **G**), which is fitted with a connector (male, SS, 1/8" NPT, 1/4" Swagelok Tube fitting, **H**). This connector is coupled to a union cross (SS, 1/4" Swagelok Tube fittings, **I**). Two of the union cross joints are coupled to two Swagelok needle valves (SS, 1/4" Swagelok Tube fittings, **J-K**). Valve **K** is fitted with a septum (**L**), and valve **J** is connected to a tube from a carbon monoxide tank. The last union cross joint is coupled to an elbow (SS, the two ends are 1/4" Swagelok tube fitting and 1/4" NPT male, **M**), which is connected to a tee-joint (SS, all female 1/4" joints, **N**). The tee-joint is connected to a pressure release valve (SS, 1/4" NPT, Swagelok part #SS-RL3M4-S4, **O**) and a pressure gauge (brass, 0-200 psi, Wika part #111.11.53, **P**). 1" SS tube sections (**Q**) were used to couple all Swagelok tube fittings. The threads of **H**, **M**, **O** and **P** were wrapped with Teflon tape. Always shield glass reactors when under pressure.

4. The submitters prepared catalyst **1** according to reference 5f. The checkers purchased catalyst **1** from Aldrich Chemical Co., Inc. (catalog # 674680), opened it only in an argon glove box, and used it as received.

5. The submitters purchased research-grade carbon monoxide (99.99% min) from Matheson and used it as received. The checkers purchased CP grade carbon monoxide (99.5%) from Matheson-Trigas and used it as received.

6. Pressurization of the cylinder is done by overpressurizing the apparatus, closing valve **J** and adjusting the internal pressure with the release valve **O**, Figure 3.

7. The catalyst solution is added via syringe through the septum covered port in valve **K**, Figure 4.

8. Pressurization of the cylinder is done by overpressurizing the apparatus, closing valve **J** and adjusting the internal pressure with the release valve **O**, Figure 5.

9. The submitters used dichloromethane without purification. The checkers purchased dichloromethane (ACS reagent grade, ≥99.5%) from Aldrich Chemical Co., Inc. and used it as received.

10. The submitters used MP SiliTech silica gel (neutral, 45-55 μm particle size, pore diameter of 60 Å) purchased from MP Biomedicals. The checkers used Merck silica gel (grade 9385, 60 mesh) purchased from Aldrich.

11. In one experiment, the checkers found that the product is contaminated with 1% of a ketone side product.

12. The product exhibits the following physicochemical properties: mp 75–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.57 (dd, *J* = 16.3, 4.8 Hz, 1 H), 3.61 (dd, *J* = 16.3, 5.8 Hz, 1 H), 4.23 (dd, *J* = 11.0, 4.5 Hz, 1 H), 4.34 (dd, *J* = 11.0, 3.5 Hz, 1 H), 4.86 (dddd, *J* = 5.0 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 7.01 (t, *J* = 7.3 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 40.4, 67.6, 68.6, 115.0, 122.1, 130.0, 158.3, 167.5; IR (CH_2Cl_2) cm^{-1}: 3063 (w), 3044 (w), 2925 (w), 2870 (w), 1833 (s), 1600 (m), 1591 (m), 1497 (m), 1453 (w), 1409 (w), 1366 (w), 1334 (w), 1303 (m), 1245 (s), 1175 (w), 1114 (s), 1052 (w), 972 (m), 926 (w), 887 (w), 838 (m), 739 (m), 692 (m); MS (EI), *m/z* (relative intensity): 179 (11), 178 (100), 176 (11), 136 (31), 108 (11), 107 (70), 94 (62), 85 (11), 79 (14), 77 (63), 65 (16); exact mass calcd for $C_{10}H_{10}O_3$: 178.0630. Found: 178.0632; Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.10; H, 5.62.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

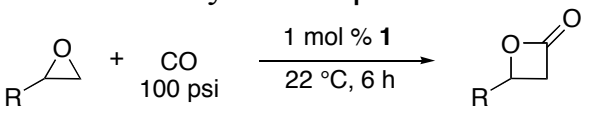
β-Lactones find a wide variety of uses in organic synthesis as both attractive intermediates[2] and natural product targets.[3] Since the initial report of epoxide carbonylation to β-lactones over a decade ago,[4] the method has emerged as a versatile synthetic route and has been elaborated to include a variety of catalyst systems applicable under a range of conditions.[5]

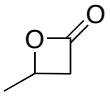
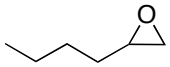
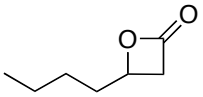
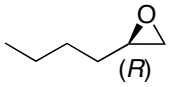
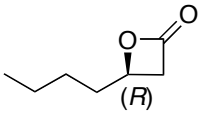
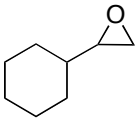
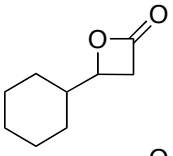
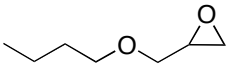
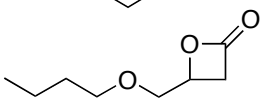
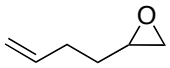
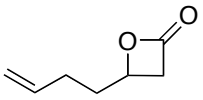
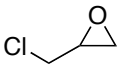
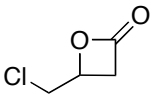
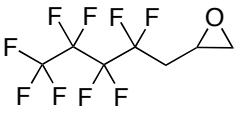
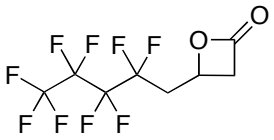
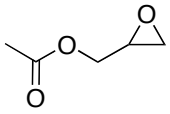
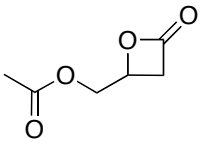
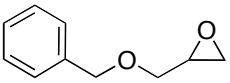
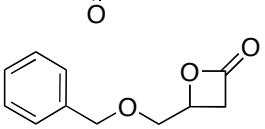
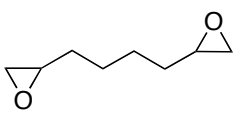
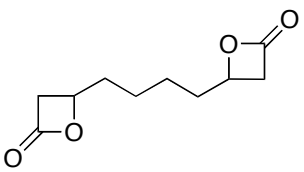
However, until recently[5f] all of these systems required high pressures of CO (>100 psi) for efficient carbonylation, necessitating the use of stainless steel reactors and other high-pressure equipment. The procedure presented herein allows for the carbonylation of epoxides to β-lactones with comparable efficiency to other systems but at significantly lower CO pressures.

Our initial work focused on epoxide carbonylation at 100 psi CO which allows the use of a glass-sealed reactor, a significantly cheaper and more accessible alternative to a stainless steel reactor. This method worked well under optimized conditions on a 2-mmol scale for a variety of functionally diverse epoxides (Table 1, entries 1-11). In each case, β-lactone

is formed as the exclusive product and is isolated from the catalyst in high yield using the method described in the Procedure. Further, the reaction proceeds with retention of stereochemistry (entry 3),[6] so enantiopure β-lactones can be prepared from enantiopure epoxides.

Table 1. Synthesis of functionally diverse β-lactones at 100 psi CO[a]



Entry	Epoxide	β-Lactone	Yield[b] (%)
1[c]			63[e]
2[d]			93
3[d]			92[f]
4[d]			92
5[d]			98
6[d]			94
7			94
8			84
9			82[g]
10[d]			99
11			86

[a] All reactions performed on a 2 mmol scale with 1 mol % **1**. [b] Isolated yields of β-lactones. [c] Diethyl ether is reaction solvent and reaction time is 2 h. [d] 10 mL Hexanes added to crude reaction mixture before filtering through silica. [e] The volatility of BBL caused the anomalously low isolated yield upon purification. [f] Both epoxide and β-lactone >99% ee; determined by chiral GC. [g] Contains 3% γ-lactone.[7]

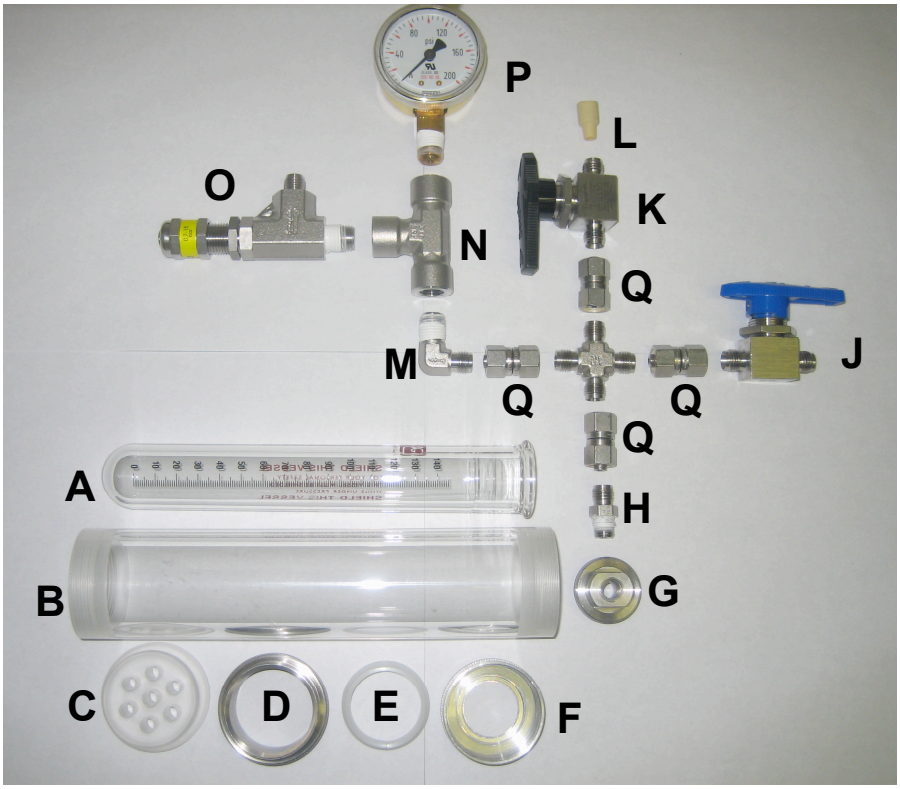


Figure 1. Components of pressure reactor.

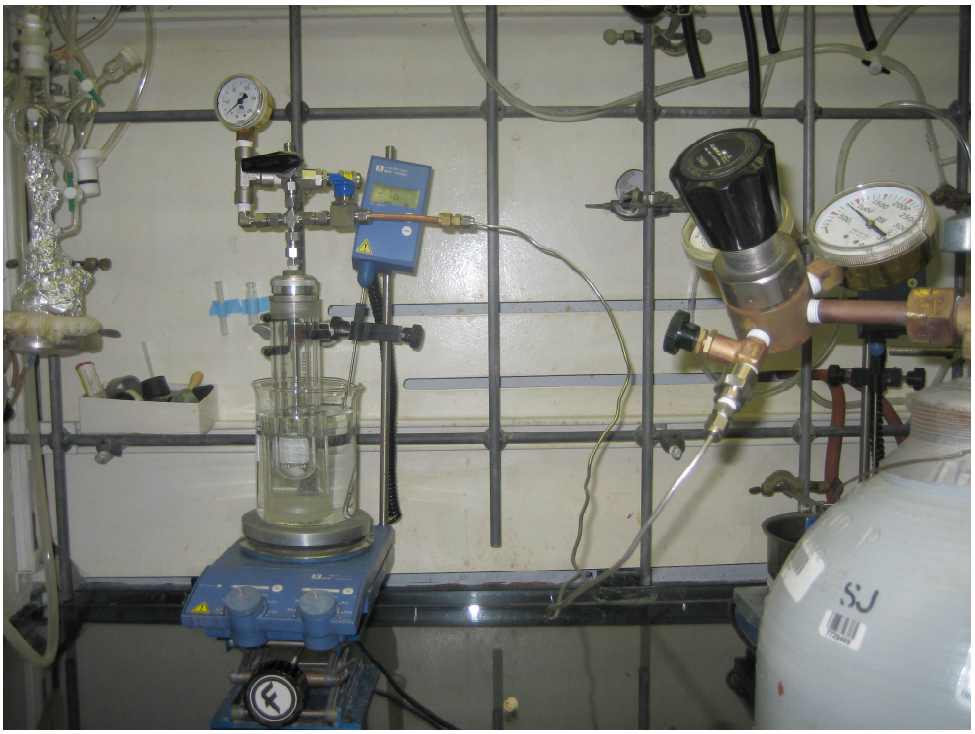


Figure 2. Assembled pressure reactor with CO cylinder.

Figure 3. Adjusting pressure to 20 psi.

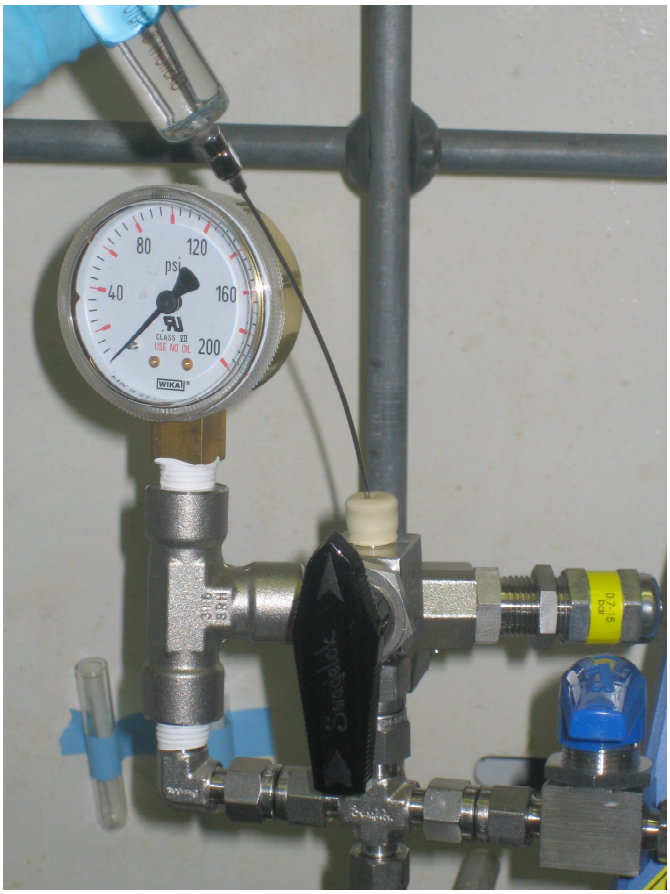


Figure 4. Valve orientation for injecting the catalyst solution.

Figure 5. Pressure maintained at 100 psi throughout the procedure.

1. Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301. Email: gc39@cornell.edu
2. For a review of β-lactones in organic chemistry, see: Wang, Y.; Tennyson, R. L.; Romo. D. *Heterocycles* **2004**, *64*, 605-658.
3. Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729-744.
4. Drent, E.; Kragtwijk, E. European Patent Application EP 577206; *Chem. Abstr*. **1994**, *120*, 191517c.
5. (a) Lee, J. T.; Thomas, P. J.; Alper, H. *J. Org. Chem*. **2001**, *66*, 5424-5426. (b) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc*. **2002**, *124*, 1174-1175. (c) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed*. **2002**, *41*, 2781-2784. (d) Allmendinger, M.; Zintl, M.; Eberhardt, R.; Luinstra, G. A.; Molnar, F.; Rieger, B. *J. Organomet. Chem*. **2004**, *689*, 971-979. (e) Schmidt, J. A. R.; Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Org. Lett*. **2004**, *6*, 373-376. (f) Kramer, J. W.; Lobkovsky, E. B.; Coates, G. W. *Org. Lett*. **2006**, *8*, 3709-3712. (g) Rowley, J. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc*. **2007**, *129*, 4948-4960.
6. A thorough mechanistic study of a closely related catalyst system hasbeen completed. See: Church, T. L.; Getzler, Y. D. Y. L.; Coates, G. W. *J. Am. Chem. Soc*. **2006**, *128*, 10125-10133.
7. γ-Lactones are observed as rearranged side products during the carbonylation of glycidyl esters. For mechanistic insight, see: Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc*. **2005**, *127*, 11426-11435.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

1,2-Epoxy-3-phenoxypropane: oxirane, 2-(phenoxymethyl)-; (122-60-1)
[*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-phenylenediamino-chromium-di-tetrahydrofuran]tetracarbonylcobaltate (**1**); (909553-60-2)
Carbon monoxide; (630-08-0)

Geoffrey W. Coates obtained a B.A. degree in chemistry from Wabash College in 1989 and a Ph.D. in organic chemistry from Stanford University in 1994. He was an NSF Postdoctoral Fellow with Robert H. Grubbs at the California Institute of Technology. In 1997 he joined the faculty of Cornell University as an Assistant Professor of Chemistry. He was promoted to Associate Professor in 2001, and to Professor in 2002. He was Associate Chair of Chemistry from 2004 to 2008 and was appointed as the first Tisch University Professor in 2008. His research focuses on the development of catalysts for organic and polymer synthesis.

John W. Kramer was born in 1980 in East Troy, Wisconsin. In 2002 he earned his B.A. in Chemistry and Environmental Studies from Grinnell College, working under the guidance of Professor T. Andrew Mobley. In 2003 he began his graduate studies at Cornell University and joined the laboratory of Geoffrey W. Coates. His work in the Coates group has focused on the ring-expanding carbonylation of heterocycles for the synthesis of biologically relevant molecules. He is currently a Research Scientist at Dow Chemical in Midland, Michigan.

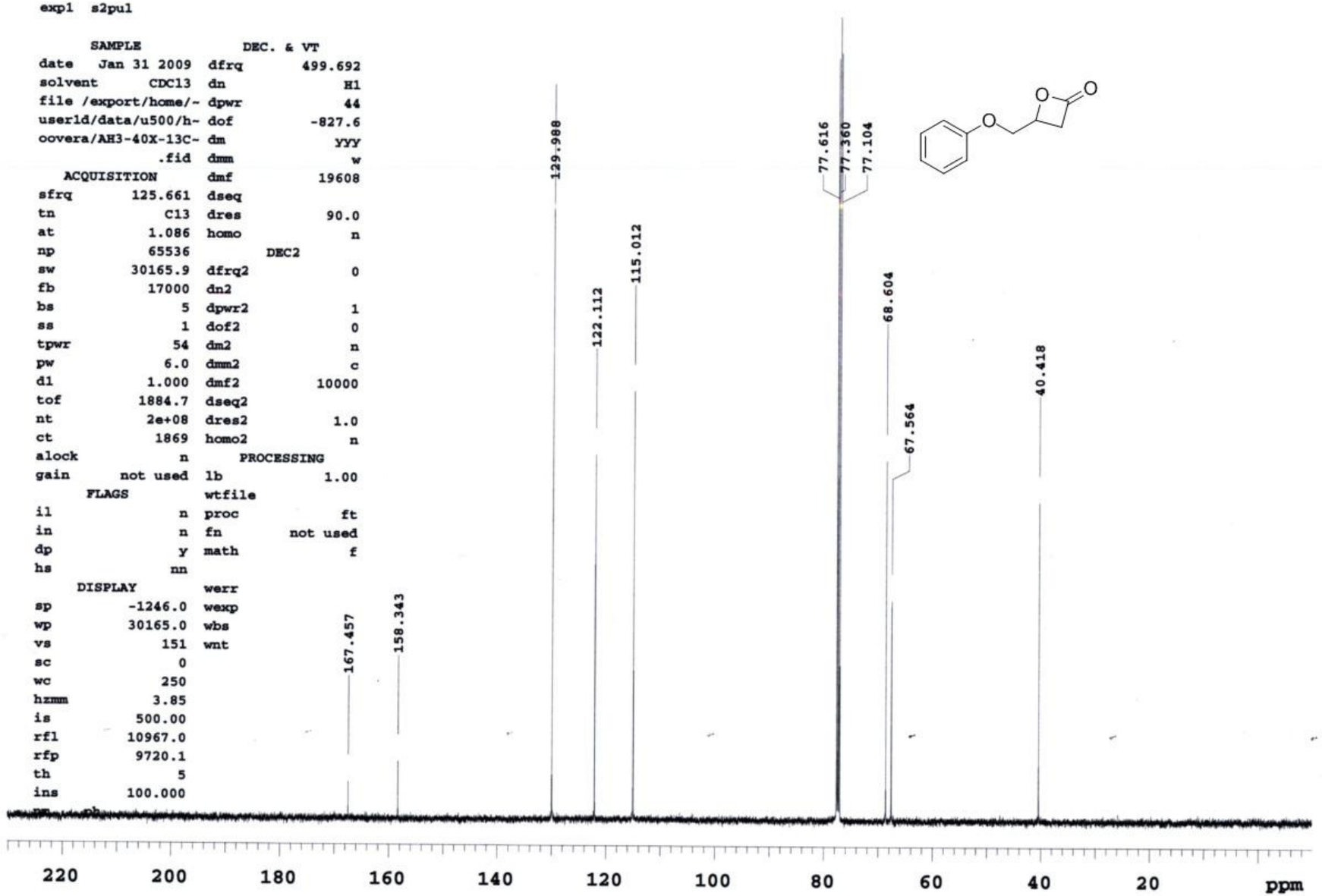
Daniel S. Treitler was born in Denville, New Jersey, in 1985. He joined the Coates group in 2005 as a sophomore at Cornell University. His research focused on the synthesis of substituted β-lactones and their polymerization to form new polyesters. From 2006 to 2007, he worked for Novomer, LLC where he optimized the large-scale synthesis of catalyst **1**. Dan is currently pursuing his Ph.D. in organic chemistry at Columbia University.

Andrew J. Hoover was born in New London, Connecticut in 1987. He enrolled at the University of Illinois in 2005, and beginning in 2006 he conducted research on deoxyribozyme catalysis with Professor Scott Silverman. As an Amgen scholar during the summer of 2007 he worked with Professor Richmond Sarpong at UC Berkeley on efficient syntheses of cyclopentenones, and in the fall of 2007 he joined the research group of Scott Denmark, where he currently is investigating the use of Lewis bases as catalysts for enantioselective functionalization of alkenes. He will graduate in December 2008 with a chemistry B.S. degree, and will enroll in graduate school in 2009.

AH3-40X-13C

exp1 s2pul

SAMPLE		DEC. & VT	
date	Jan 31 2009	dfrq	499.692
solvent	CDC13	dn	H1
file	/export/home/~	dpwr	44
userId/data/u500/h~		dof	-827.6
oovera/AH3-40X-13C~		dm	YYY
	.fid	dmm	w
ACQUISITION		dmf	19608
sfrq	125.661	dseq	
tn	C13	dres	90.0
at	1.086	homo	n
np	65536	DEC2	
sw	30165.9	dfrq2	0
fb	17000	dn2	
bs	5	dpwr2	1
ss	1	dof2	0
tpwr	54	dm2	n
pw	6.0	dmm2	c
d1	1.000	dmf2	10000
tof	1884.7	dseq2	
nt	2e+08	dres2	1.0
ct	1869	homo2	n
alock	n	PROCESSING	
gain	not used	lb	1.00
FLAGS		wtfile	
il	n	proc	ft
in	n	fn	not used
dp	y	math	f
hs	nn		
DISPLAY		werr	
sp	-1246.0	wexp	
wp	30165.0	wbs	
vs	151	wnt	
sc	0		
wc	250		
hzmm	3.85		
is	500.00		
rfl	10967.0		
rfp	9720.1		
th	5		
ins	100.000		



AH3-40X

exp1 s2pul

SAMPLE		DEC. & VT	
date	Jan 31 2009	dfrq	499.693
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	20
	user1d/data/u500/h~	dof	0
	oovera/AH3-40X.fid	dm	nnn
ACQUISITION		dmm	c
sfrq	499.693	dmf	200
tn	H1	dseq	
at	4.665	dres	1.0
np	65536	homo	n
sw	7024.9	DEC2	
fb	4000	dfrq2	0
bs	4	dn2	
tpwr	63	dpwr2	1
pw	6.5	dof2	0
d1	15.000	dm2	n
tof	2.0	dmm2	c
nt	10	dmf2	200
ct	10	dseq2	
alock	n	dres2	1.0
gain	not used	homo2	n
FLAGS		PROCESSING	
il	n	lb	0.30
in	n	wtfile	
dp	y	proc	ft
hs	nn	fn	not used
DISPLAY		math	f
sp	-250.0		
wp	5246.6	werr	
vs	109	wexp	
sc	0	wbs	
wc	250	wnt	
hzmm	20.99		
is	33.57		
rf1	4639.5		
rfp	3627.8		
th	4		
ins	1.000		
ai	ph