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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.

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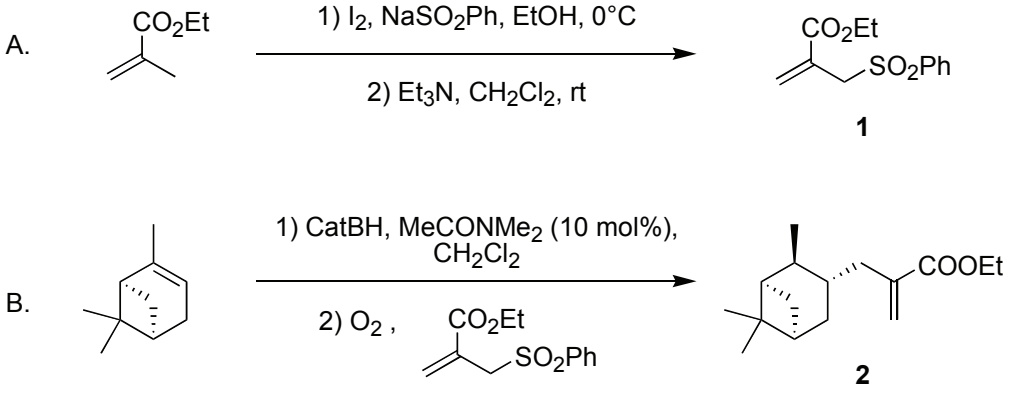
RADICAL ALLYLATION OF *B*-ALKYLCATECHOLBORANES [Ethyl 2-{[(1*S*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]methyl}acrylate]



Submitted by Vincent Darmency, Eoin Martin Scanlan, Arnaud Pierre Schaffner and Philippe Renaud.[1]
Checked by Bin Sui and Dennis P. Curran.

1. Procedure

A. 2-(Ethoxycarbonyl)prop-2-en-1-yl phenyl sulfone (**1**).[2] Ethyl methacrylate (7.50 mL, 60 mmol) (Note 1) and absolute ethanol (120 mL) are added to a 250-mL, three-necked, round-bottomed flask (Note 2) equipped with a magnetic stir bar, a glass stopper, a thermometer, and an argon inlet adaptor. The mixture is cooled to 0 °C in an ice bath, the stopper is removed, iodine (18.1 g, 71 mmol) and benzenesulfinic acid sodium salt (22.7 g, 126 mmol) are added with the aid of a plastic funnel, and the stopper is replaced. The temperature of the mixture increases to 6−7 °C upon addition of the sodium salt. The reaction mixture is recooled to 0 °C and stirred for 5 h, then allowed to warm to room temperature. Dichloromethane (100 mL) is added and the dark brown reaction mixture is transferred to a 500-mL separatory funnel. The organic layer is washed with water (2 x 100 mL) (Note 3), and the water is back-extracted with dichloromethane (2 x 25 mL). The combined organic layer is washed with saturated sodium hydrogen carbonate solution (100 mL) and sodium dithionite (5% solution, 2 x 100 mL). The resulting yellow solution is dried

over $MgSO_4$, filtered into a 250-mL, one-neck, round-bottomed flask and concentrated to dryness by rotary evaporation (40 °C, 500 mbar) to yield 22.58–22.68 g (98-99%) crude adduct as a dark oil (Note 4).

After addition of a magnetic stir bar, the flask is capped with a septum, placed under an argon atmosphere, and the crude adduct is diluted with dichloromethane (35 mL). Triethylamine (16.7 mL, 120 mmol) is added dropwise by syringe over 10 min (Note 5). The resulting orange-brown mixture is stirred for 9 h at room temperature (Note 6). The reaction mixture is concentrated by rotary evaporation (35 °C, bath temperature) to about half of its original volume (Note 7), and the concentrate is charged onto a column (8 x 18 cm) of 350 g of silica gel (Note 8). The column is eluted with 500 mL of *tert*-butyl methyl ether/cyclohexane (1:4), at which time the eluent is changed to *tert*-butyl methyl ether/cyclohexane (3:7). After elution with about 1 L of the solvent mixture, the product begins to emerge, as identified by TLC analysis (Note 6). The eluting solvent is changed to *tert*-butyl methyl ether/cyclohexane (1:1), and the product fractions are collected. Combination of the fractions, concentration by rotary evaporation (35 °C, bath temperature), and vacuum drying afforded 13.45–13.85 g of **1** as a colorless oil (88–90% yield) (Note 9).

B. Ethyl 2-{[(1S,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]methyl}acrylate (**2**).[3,4] (+)-α-Pinene (7.14 mL, 45 mmol), *N,N*-dimethylacetamide (0.42 mL, 4.5 mmol) (Note 10) and dichloromethane (30 mL) are added to a 100-mL, three-necked, round-bottomed flask equipped with a large, oblong magnetic stir bar, a reflux condenser with an argon inlet, a glass stopper, and a straight glass stopcock fitted with rubber septum. The stirred mixture is cooled to 0 °C in an ice bath, and catecholborane (12.0 mL, 113 mmol) (Note 11) is added dropwise via syringe by placing the syringe needle through the septum on the open stopcock. The stopcock is closed, the ice bath is removed and colorless reaction mixture is heated to reflux for 5 h (Note 12). The mixture is cooled to 0 °C, and methanol (3.0 mL, 74 mmol) is carefully added [*CAUTION: vigorous evolution of hydrogen gas*] to quench the excess of catecholborane, and the resulting mixture is warmed to room temperature and stirred for 15 min.

2-(Ethoxycarbonyl)prop-2-en-1-yl phenyl sulfone **1** from Step A (13.7 g, 54 mmol) is added via syringe, and the mixture is heated to reflux. Air (40 mL, 0.33 mmol O_2) (Note 13) is introduced over 1 h by a syringe pump with the needle of the syringe placed through the stopcock and immersed

just under the surface of the liquid. After 15–20 min, the clear yellow mixture turns black (Notes 12 and 14). After 1 h, the mixture is cooled and the solvent is removed by rotary evaporation (35 °C, bath temperature). The resulting black oil is dissolved in a minimum of dichloromethane (~20 mL). The solution is charged onto a column (8 x 9 cm) of 200 g silica gel, and the column is eluted with *tert*-butyl methyl ether/cyclohexane 1:19. Fractions containing the product (Note 15) are concentrated by rotary evaporation (35 °C, bath temperature) and dried under high vacuum to provide 8.70–8.75 g compound **2** (77–78%) as a colorless oil (Note 16).

2. Notes

1. The submitters purchased ethyl methacrylate (99%), iodine (99%) and benzenesulfinic acid sodium salt (97%) from Fluka Chemie GmbH. The checkers purchased ethyl methacrylate (99%) and benzenesulfinic acid sodium salt (98%) from Aldrich, and iodine (Certified A.C.S.) from Fischer Scientific. All reagents were used as received.

2. The apparatus is dried in an oven at 130 °C for 24 h, cooled in a dessicator, and maintained under an argon atmosphere during the course of the reaction.

3. Both layers are dark. Use of a flashlight helps to identify the phase boundary. Small additional amounts of water and dichloromethane can be added if the phases do not separate after the first extraction.

4. The intermediate adduct is $PhSO_2CH_2C(I)(CH_3)CO_2Et$: R_f = 0.58, 1/1 *tert*-butyl methyl ether/cyclohexane. ^1H NMR (300 MHz, $CDCl_3$): δ: 1.34 (t, J = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.95 (d, J = 13.8 Hz, 1H), 4.22−4.32 (m, 2 H), 4.51 (d, J = 13.8 Hz, 1 H), 7.60 (m, 2 H), 7.68 (m, 1 H), 7.92 (m, 2 H). The sample becomes a dark solid upon standing in the freezer.

5. The reaction mixture warms during the addition, so the rate of addition must be slow enough to keep the temperature well below the reflux point.

6. Reaction progress can be monitored by TLC analysis on silica eluting with 1/1 *tert*-butyl methyl ether/cyclohexane (UV lamp visualization): starting adduct R_f = 0.58; product **1** R_f = 0.35.

7. Salts may begin to precipitate towards the end of the concentration. These are loaded onto the column along with the residual liquid.

8. The submitters used SDS silica gel (40-63 mm). The checkers used standard grade silica gel (40-63 mm) from Sorbent Technologies, Inc.

9. ^{1}H NMR (300 MHz, $CDCl_3$)[2] δ: 1.15 (t, *J* = 7.1 Hz, 3 H), 4.00 (q, *J* = 7.1 Hz, 2 H), 4.15 (d, *J* = 0.8 Hz, 2 H), 5.89 (narrow q, *J* = 0.8, 0.6 Hz, 1 H), 6.49 (d, *J* = 1 Hz, 0.6 H), 7.52 (m, 2 H), 7.62 (m, 1 H), 7.84 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 57.4, 61.4, 128.6, 128.9, 129.0, 133.2, 133.8, 138.2, 164.6. The submitters report that the product can be further purified by distillation in a Kugelrohr oven; bp 90−95 °C (6 mmHg).

10. The submitters purchased α-pinene (97%) and *N*,*N*-dimethylacetamide (99%) from Fluka Chemie GmbH. The checkers purchased (*R*)-(+)-α-pinene (98%, 91% ee) from Aldrich and *N*,*N*-dimethylacetamide (99%) from J. T. Baker. These were used as received.

11. The quality of the catecholborane is crucial for success. The submitters purchased catecholborane from BASF corporation, Mount Olive, NJ, USA and distilled it (bp 50 °C, 50 mmHg) prior to use. The checkers used catechol borane (98%) directly from a fresh bottle purchased from Aldrich.

12. The progress of the hydroboration reaction and the radical allylation reaction can be monitored by GC analysis on an Agilent MP-1 methyl siloxane capillary column (19091Z-413E, 30 m x 0.32 mm); temperature ramp, 10 °C per min from 50 °C to 315 °C. T_R; pinene, 3.59 min; hydroboration adduct, 15.21 min; **1**, 15.29 min; **2**, 12.68 min. The submitters used a CE instrument, MEGA Series HRGC fitted with an Optima delta-3 0.25 μm fused silica capillary column from Macherey-Nagel, 30 m x 0.25 mm; temperature ramp, 6 °C per min from 60 °C to 280 °C; T_R pinene, 7.38 min; **1**, 31.53 min; **2** = 24.86 min.

13. The submitters report that initiation with di-*tert*-butyl hyponitrite in refluxing dichloromethane afforded a similar reaction yield.[3]

14. GC analysis at this point (Note 12) indicates that the reaction is complete. The checkers observed the black color after 15−20 min, while the submitters observed the color change after about 1 h.

15. Thin layer chromatography (TLC) analysis is used to identify product fractions. TLCs are performed by using Merck silica gel 60 F_{254} analytical plates; detection with UV or by dipping in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH 5% (5 mL) in H_2O (300 mL) and subsequent heating. Product R_f 0.62 in *tert*-butyl methyl ether/cyclohexane (1:9).

16. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 0.74 (d, *J* = 9.5 Hz, 1 H), 0.97 (s, 3 H), 1.00 (d, *J* = 7.1 Hz, 3H), 1.16 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.40 (ddd, *J* = 13.3, 5.9, 2.6 Hz, 1 H), 1.66 (quintd, *J* = 7.1, 1.9 Hz, 1 H), 1.75 (td, *J* = 5.7, 1.9 Hz, 1 H), 1.82–1.97 (m, 2 H), 2.04 (tdd, *J* = 11.4, 3.5, 2.1 Hz, 1 H), 2.13 (ddd, *J* = 13.5, 9.3, 0.7 Hz, 1 H), 2.27 (dtd, *J* = 9.5, 6.2, 2.1 Hz, 1 H), 2.51 (ddd, *J* = 13.5, 5.1, 1.0 Hz, 1 H), 4.19 (m, 2 H), 5.52 (dd, *J* = 1.7, 1.0 Hz, 1 H), 6.11 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 14.1, 21.4, 22.9, 28.0, 34.0, 34.2, 34.6, 38.8, 41.9, 43.4, 43.5, 48.2, 60.4, 125.3, 139.8, 167.3; MS (EI): *m/z* (%): 250 [M^+], 235, 207, 194, 176, 137, 121, 107, 93, 81, 67, 55; $[\alpha]_D^{20}$ –31.5 (c, 1.0, $CHCl_3$). If desired, the product can be further purified by vacuum distillation (bp 113–114 °C, 0.45 mmHg) to provide a clear oil; Anal. calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.77; H, 10.41.

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

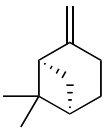
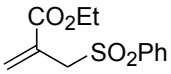
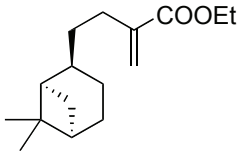
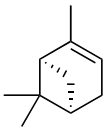
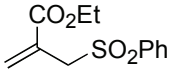
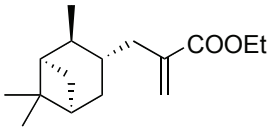
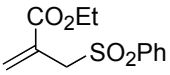
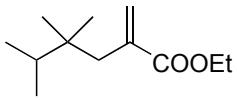
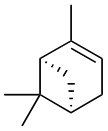
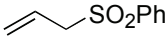
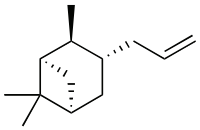
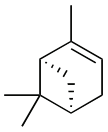
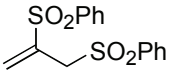
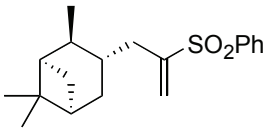
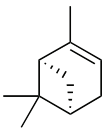
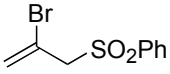
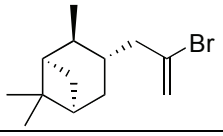
Here we describe an efficient one-pot radical hydroallylation of an alkene under tin-free conditions.[3,4] *B*-Alkylcatecholboranes are easily prepared by hydroboration of alkenes with catecholborane according to the efficient and cost-effective conditions developed by Fu.[5] These are used as radical precursors in a fragmentation process where the resulting benzenesulfonyl radical can sustain the radical chain. This methodology has proven to be an effective alternative to radical reactions mediated by toxic tin reagents. Interestingly, this radical approach complements nicely Knochel's procedure for the allylation of organoboranes, which requires transmetalation to organozinc derivatives.[6]

Oxygen-centered radicals react efficiently with *B*-alkylcatechol-boranes.[7] The use of oxygen from air as the radical initiator is efficient for a large-scale reaction. Care is always required when oxygenating warm organic solvents. In this reaction, slow syringe pump addition of air is a suitable way to continuously provide the small amounts of oxygen needed

for initiation. This transformation can be carried out under mild conditions and is tolerant of a wide range of organic functionalities.

Typical results of this reductive allylation (hydroallylation) of alkenes are shown in Table 1. The allylated products were obtained in satisfactory

Table 1

Entry	Alkene	Trap	Product	Yield	dr
1				62 %[a]	90/10
2				80 %[b]	>98/2
3				65 %[a]	-
4				52 %[a]	95/5
5				89 %[a]	96/4
6				58 %[a]	96/4

a) 2-3 mmol scale b) 45 mmol scale

to excellent yields by using only 1.2 equivalents of the allyl sulfones with primary, secondary and tertiary alkyl radicals (Entries 1-3). The unsubstituted allyl sulfone also reacts under these conditions and provides the volatile allylated product in moderate isolated yield (Entry 4). Finally, allylic sulfones bearing a sulfonyl group (Y = $PhSO_2$) and a bromine atom (Y = Br) reacted equally well (Entries 5-6). The stereochemical outcome of all these reactions is rationalized in a straightforward manner, both the hydroboration and the radical reaction occur from the less hindered face of the alkene and of the radical, respectively.

The allylation chemistry described here has been extended to a tandem radical process involving conjugate addition of a *B*-alkylcatecholborane to an activated alkene followed by allylation. The whole process can be considered as a unique and selective coupling of three different alkenes.[8]

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6. Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 2748.
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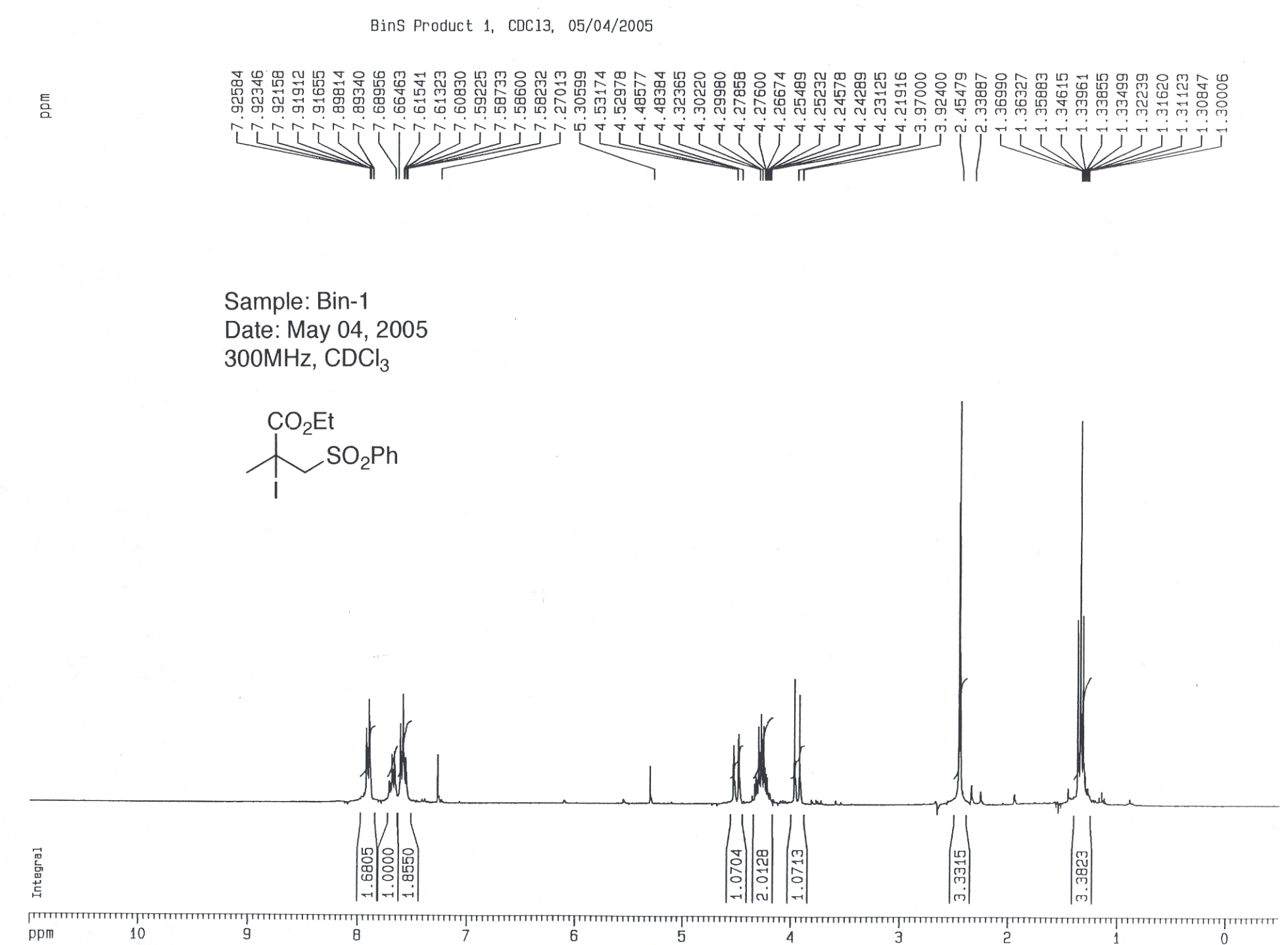
Appendix
Chemical Abstracts nomenclature; (Registry Number)

Ethyl 2-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)methyl]propenoate; (183623-93-0)
2-(Ethoxycarbonyl)prop-2-en-1-yl phenyl sulfone; (89295-32-9)
Ethyl methacrylate: 2-Methyl-2-propenoic acid, ethyl ester; (97-63-2)
Benzenesulfinic acid, sodium salt: Sodium benzenesulfinate; (873-55-2)
(+)-α-Pinene: (1*R*)-2,6,6-Trimethyl-bicyclo[3.1.1]hept-2-ene; (7785-70-8)
Catecholborane: 1,3,2-Benzodioxaborole; (274-07-7)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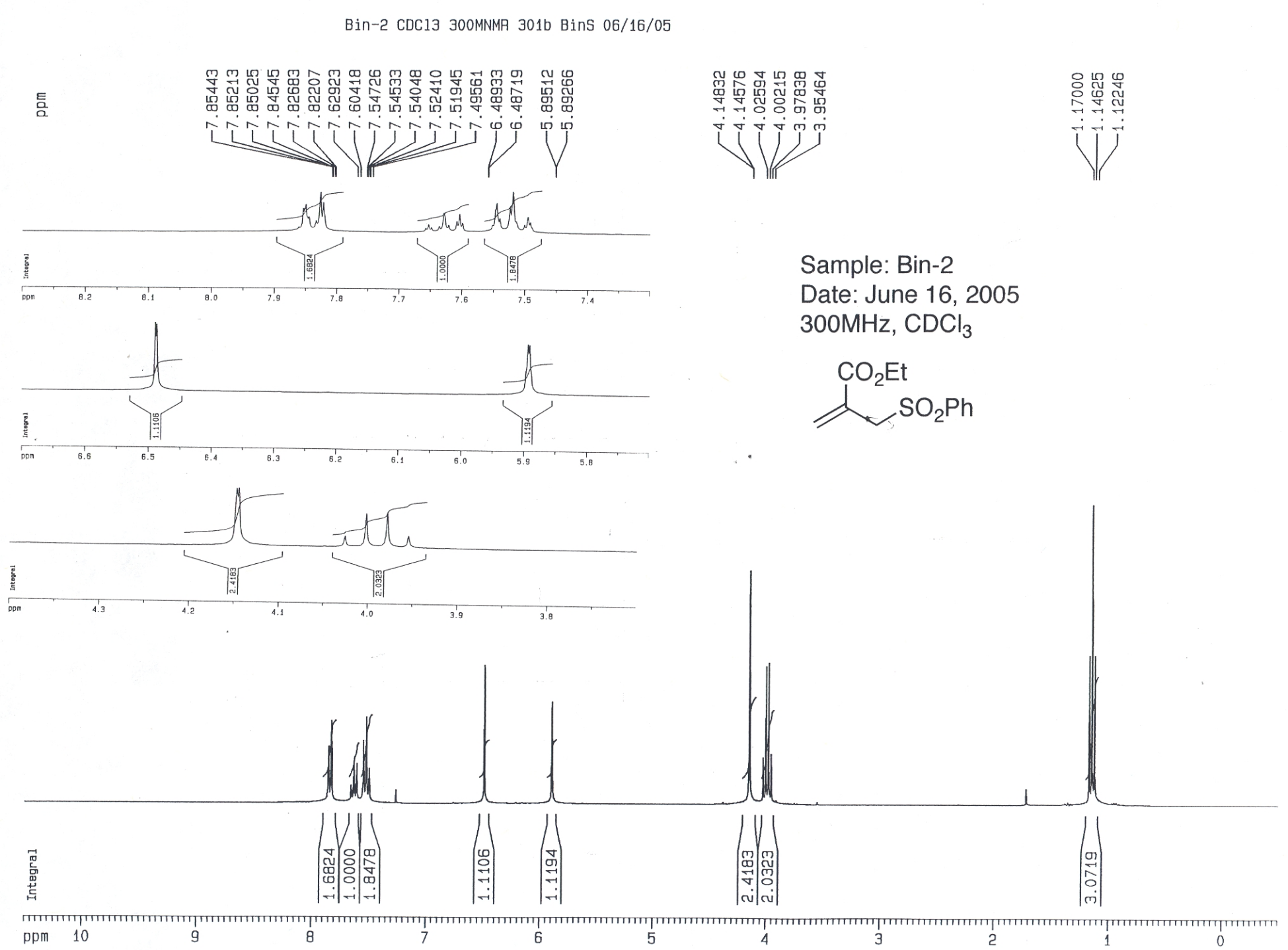
Bin-2 CDCl3 300MNMR 301b BinS 06/16/05



Bin-3 1HNMR CDCl3 301b BinS 06/11/05