Supplementary Material (ESI) for Chemical Communications

Supporting Information

Regioselective Synthesis of Halohydrin Esters from Epoxides: Reaction with Acyl Halides and Rhodium-catalyzed Three-component Coupling Reaction with Alkyl Halides and Carbon Monoxide

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General Methods. All manipulations involving air- and/or moisture-sensitive compounds were carried out in a glove box under argon atmosphere or with the standard Schlenk technique under argon purified by passing through a hot column packed with BASF catalyst R3-11. Analytical thin-layer chromatography was performed on a glass plates coated with 0.25-mm 230–400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). For a silica gel column chromatography, Silica gel 60N (spherical neutral, particle size 63–210 μm, Kanto Kagaku Co., Ltd.) was used.

Apparatus. NMR spectra were recorded in deuteriochloroform on a 500 MHz (^{1}H 500 MHz; ^{13}C 125 MHz) or a 400 MHz (^{1}H 400 MHz; ^{13}C 100 MHz) spectrometer. Chemical shifts are reported in ppm from an internal standard: tetramethylsilane (0 ppm) for ^{1}H and deuteriochloroform (77.16 ppm) for ^{13}C. Data are presented in the following space: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet and/or multiplet resonances), coupling constant in hertz (Hz), and signal area integration in natural numbers. Optical rotations were measured on a JASCO P-1020 spectrometer using a 1-dm cell. IR spectra were recorded on a SHIMADZU FTIR-8400 spectrophotometer. HPLC analyses were carried out using a JASCO LC-2000Plus system (HPLC pump: PU-2080; gradient unit: LG-2080-02; degasser: DG-2080-53, column oven: CO-2060; UV detector: MD-2010) equipped with a DAICEL CHIRAPAK® IC column (4.6 mm × 250 mm). The recycling preparative gel-permeation chromatography (GPC) was performed with a JAI LC-928 chromatograph equipped with JAI GEL-1H and -2H columns (chloroform as an eluent). Elemental analyses were performed by the Microanalytical Laboratory of Department of Chemistry, Faculty of Science, The University of Tokyo.

Chemicals. All of alkyl halides and epoxides used for reactions were distilled under argon after drying over an appropriate drying reagent. $[PPN]^+[Rh(CO)_4]^-$, $[PPN]^+[Co(CO)_4]^-$, $[PPN]^+[Mn(CO)_5]^-$ were synthesized according to the literature.[1,2]

Synthetic Procedures and Characterization data

Representative procedure for the reaction of acetyl chloride with propylene oxide. A flame-dried 20-mL Schlenk tube was charged with acetyl chloride (0.4 mL, 5.6 mmol), propylene oxide (0.80 mL, 14 mmol), and 3-methoxypyridine (6 μL, 0.06 mmol). The mixture was degassed by freeze-pump-thaw cycles, and stirred at 75 °C for 12 h under argon atmosphere. Tetrachloroethane was added as an internal standard, and ^{1}H NMR analysis was performed to determine a NMR yield and a molar ratio between regio-isomers.[3]

Reaction of acetyl iodide with propylene oxide. A flame-dried 20-mL Schlenk tube was charged with propylene oxide (0.65 mL, 9.3 mmol), pyridine (0.10 mL, 1.24 mmol), CH_2Cl_2 (2.0 mL). To the mixture was added acetyl iodide (748 mg, 4.4 mmol) in CH_2Cl_2 (3.0 mL) via syringe pump over 1 h. The mixture was stirred at –78 °C for 3 h under argon atmosphere. After the resulting precipitate was filtered off, the filtrate was concentrated under the reduced pressure. Tetrachloroethane was added as an internal standard, and ^{1}H NMR analysis was performed to determine a NMR yield and a molar ratio between regio-isomers.[4]

General procedure for rhodium-catalyzed halohydrin-ester synthesis. A flame-dried 20-mL Schlenk tube was charged with alkyl halide (1 equiv.), epoxide (2 equiv. to alkyl halide) and pyridine derivatives (1 or 2 mol%, 2 equiv. to Rh). The mixture was degassed by freeze-pump-thaw cycles and transferred into a 50-mL autoclave containing $[PPN]^+[Rh(CO)_4]^-$ (0.5 or 1 mol%) and a magnetic stirring bar. After introduction of CO (6 MPa), the resulting mixture was stirred at 75 °C for the desired time. The reaction mixture was cooled to ambient temperature, and CO pressure was slowly released. Tetrachloroethane was added as an internal standard, and ^{1}H NMR analysis was performed to determine a NMR yield and a molar ratio between regio-isomers of the resulting halohydrin esters. The resulting reaction mixture was diluted with chloroform and washed with 1*M* aqueous HCl (15 mL × 3). The organic phase was dried over dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica-gel-column chromatography.

1-Bromopropan-2-yl phenylacetate (1c). The crude residue was obtained by using benzyl bromide (0.95 mL, 6.7 mmol) and propylene oxide (0.80 mL, 14 mmol). Purification by column chromatography (silica gel; AcOEt/hexane = 1/5 as an eluent; R_f 0.5) provided the title product **1c** as a colorless oil (1.56 g, 69% yield): IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.23 (m, 5H), 5.10–5.03 (m, 1H), 3.62 (s, 2H), 3.42 (dd, J = 10, 5 Hz, 1H), 3.38 (dd, J = 10, 5 Hz, 1H), 1.32 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8, 133.8, 129.3, 128.6, 127.2, 69.8, 41.4, 35.2, 18.6; Anal. Calcd for $C_{11}H_{13}BrO_2$ (%): C, 51.38; H, 5.10. Found: C, 51.19; H, 5.18.

(*S*)-1-Bromopropan-2-yl phenylacetate [(*S*)-1c]. The crude residue was obtained by using benzyl bromide (0.60 mL, 5.1 mmol) and (*S*)-propylene oxide (>99% ee, 0.70 mL, 10 mmol). Purification by column chromatography (silica gel; AcOEt/hexane = 1/20 as an eluent; R_f 0.23) provided the title product **(*S*)-1b** as a colorless oil (0.93 g, 71% yield). Enantiomeric excess of the title product (*S*)-**1c** was determined to be >99% by HPLC analysis (*rac*-**1c**: 10.8 min (*S*), 11.5 min (*R*), DAICEL CHIRAPAK® IC column (4.6 mm × 250 mm), Hexane/CH_2Cl_2/THF = 96/3/1 at 1.0 mL/min): $[\alpha]_D^{25}$ = –10° (c = 4.5, $CHCl_3$).

1-Benzyloxy-3-bromopropan-2-yl phenylacetate (1d). The crude residue was obtained by using benzyl bromide (0.40 mL, 3.4 mmol) and benzyl glycigyl ether (1.0 mL, 6.6 mmol). Purification by column chromatography (silica gel; AcOEt/hexane = 1/5 as an eluent; R_f 0.49) provided the title product **1d** as a colorless oil (851 mg, 70% yield): IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.25 (m, 10H), 5.19–5.14 (m, 1H), 4.53 (d, J = 12 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 3.68 (dd, J = 11, 5 Hz, 1H), 3.67 (s, 2H), 3.63 (dd, J = 11, 5 Hz, 1H), 3.60 (dd, J = 11, 5 Hz, 1H), 3.52 (dd, J = 11, 5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.9, 137.8, 133.7, 129.4, 128.7, 128.6, 128.0, 127.8, 127.3, 73.6, 72.0, 69.1, 41.4, 30.8; Anal. Calcd for $C_{18}H_{19}BrO_3$ (%): C, 59.52; H, 5.27. Found: C, 59.36; H, 5.25.

1,3-Dibromopropan-2-yl phenylacetate (1e). The crude residue was obtained by using benzyl bromide (0.60 mL, 5.1 mmol) and epibromohydrin (0.85 mL, 10 mmol). Purification by column chromatography (silica gel; AcOEt/hexane = 1/6 as an eluent; R_f 0.51) provided the title product **1e** as a

colorless oil (1.15 g, 68% yield): IR (neat) 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.26 (m, 5H), 5.16–5.12 (m, 1H), 3.68 (s. 1H), 3.59 (d, J = 5 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 170.5, 133.4, 129.4, 128.8, 127.5, 71.5, 41.2, 31.3; Anal. Calcd for $C_{11}H_{12}Br_2O_2$ (%): C, 39.32; H, 3.60. Found: C, 39.24; H, 3.65.

***trans*-2-Bromocyclohexyl phenylacetate (1f).** The crude residue was obtained by using benzyl bromide (0.30 mL, 2.5 mmol) and cyclohexene oxide (0.50 mL, 4.9 mmol). Purification by column chromatography (silica gel; AcOEt/hexane = 1/10 as an eluent, R_f 0.44) provided the title product **1f** as a colorless oil (632 mg, 84% yield): IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.23 (m, 5H), 4.94–4.87 (m, 1H), 3.96 (ddd, J = 11, 9, 4 Hz, 1H), 3.66 (d, J = 16 Hz, 1H), 3.64 (d, J = 16 Hz, 1H), 2.35–2.27 (m, 1H), 2.14–2.05 (m, 1H), 1.90–1.80 (m, 1H), 1.75–1.67 (m, 1H), 1.47–1.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 134.1, 129.4, 128.6, 127.2, 76.3, 52.7, 41.6, 35.6, 31.1, 25.5, 23.3; Anal. Calcd for $C_{14}H_{17}BrO_2$ (%):C, 56.58; H, 5.77. Found: C, 56.48; H, 5.795.

1-Iodopropan-2-yl acetate (1b). The crude residue was obtained by using methyl iodide (0.40 mL, 6.4 mmol) and propylene oxide (0.90 mL, 13 mmol). Purification by column chromatography (silica gel; chloroform as an eluent; R_f 0.71) provided the title product **1b** as a colorless oil (584 mg, 40% yield). The NMR spectral data was identical to that in the literature.[4]

1-Bromopropan-2-yl 3-butenoate (1g). The crude residue was obtained by using allyl bromide (0.60 mL, 6.9 mmol) and propylene oxide (1.0 mL, 14 mmol). Purification by a Kugelrohr bulb-to-bulb distillation and a recycling preparative GPC provided the title product **1g** as a colorless oil (589 mg, 41% yield): IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95–5.85 (m, 1H), 5.19–5.16 (m, 1H), 5.15–5.13 (m, 1H), 5.11–5.03 (m, 1H), 3.43 (dd, J = 11, 5 Hz, 1H), 3.41 (dd, J = 11, 5 Hz, 1H), 3.11–3.07 (m, 2H), 1.33 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8, 130.1, 118.8, 69.6, 39.2, 35.2, 18.7; Anal. Calcd for $C_7H_{11}BrO_2$ (%): C, 40.60; H, 5.35. Found: C, 40.31; H, 5.47.

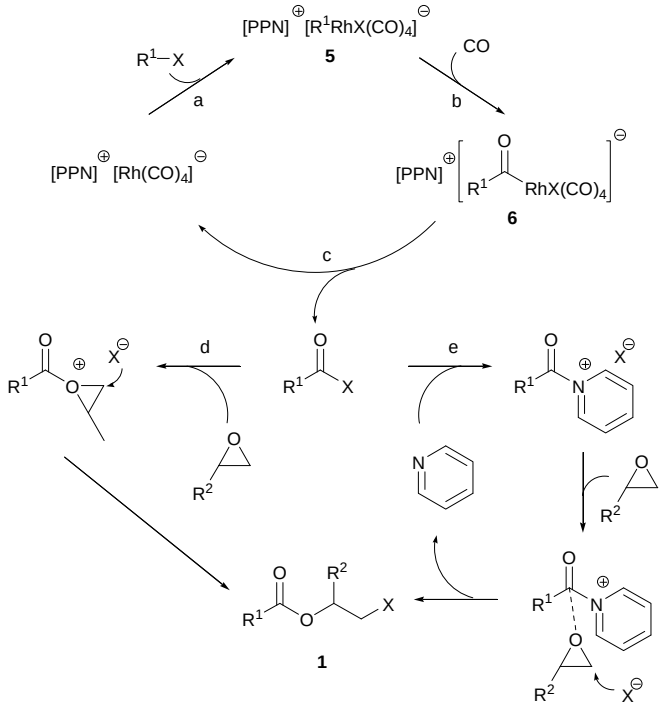
1-Bromopropan-2-yl methyl malonate (1h). The crude residue was obtained by using methyl bromoacetate (0.65 mL, 6.0 mmol) and propylene oxide (0.85 mL, 12 mmol). Purification by column chromatography (silica gel; AcOEt/hexane = 1/10 as an eluent, R_f 0.25) could not succeeded in the

complete separation of regio-isomers and provided the title product **1h** and its regio-isomer **2h** as a colorless oil (total: 1.0 g, 70% yield, **1h**/**2h** = 92/8): IR (neat) 1752, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18–5.10 (m, 1H), 3.76 (s, 3H), 3.47 (dd, J = 11, 5 Hz, 1H), 3.44 (dd, J = 11, 5 Hz, 1H), 3.41 (s, 2H), 1.39 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.8, 165.8, 70.7, 52.7, 41.5, 34.7, 18.6; Anal. Calcd for $C_7H_{11}BrO_4$ (%): C, 35.17; H, 4.64. Found: C, 34.93; H, 4.73.

1-Chloropropan-2-yl phenylacetate (1i). The crude residue was obtained by using benzyl chloride (0.65 mL, 5.7 mmol) and propylene oxide (0.80 mL, 11 mmol). Purification by column chromatography (silica gel; AcOEt/hexane = 1/5 as an eluent, R_f 0.32) and a recycling preparative GPC could not succeeded in the complete separation of regio-isomers and provided the title product **1i** and its regio-isomer **2i** as a colorless oil (total: 285 mg, 24 % yield, **1i**/**2i** = 96/4): IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.24 (m, 5H), 5.15–5.08 (m, 1H), 3.57 (dd, J = 11, 5 Hz, 1H), 3.54 (dd, J = 11, 5 Hz, 1H), 1.32 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0, 133.9, 129.4, 128.7, 127.3, 70.3, 46.9, 41.5, 17.7; Anal. Calcd for $C_{11}H_{13}ClO_2$ (%): C, 62.12; H, 6.16. Found: C, 61.96; H, 6.19.

Plausible reaction pathways

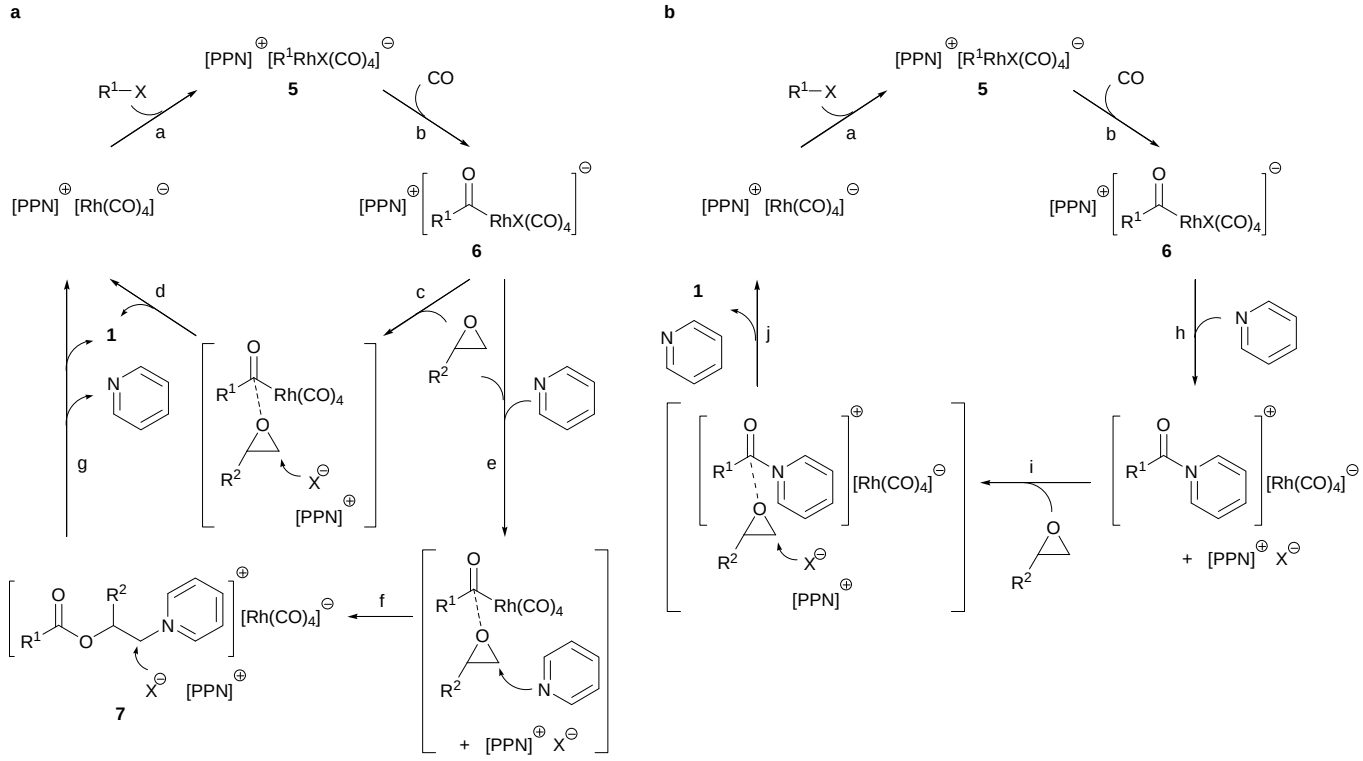
The possible reaction pathway via the formation of acyl halide is described in Scheme S1. The reaction of $[PPN]^+[Rh(CO)_4]^-$ with alkyl halide (R^1–X, R^1 = alkyl; X = halide) gives $[PPN]^+[R^1RhX(CO)_n]^-$ (**5**, step a).[5] The subsequent CO insertion into R^1–Rh bond affords $[PPN]^+[RC(=O)RhX(CO)_n]^-$ (**6**, step b), which gives acyl halide and regenerate $[PPN]^+[Rh(CO)_4]^-$ (step c). The resulting acyl halide reacts with epoxide to yield the corresponding halohydrin ester **1**. The reaction of acyl halide with epoxide in the absence of pyridine derivative may proceed via oxonium intermediate (step d), while the reaction in the presence of pyridine derivatives may involve the formation of pyridinium intermediate (step e).



Scheme S1 Plausible reaction pathway via the formation of acyl halide .

The reaction pathway without the formation of acyl halide is also plausible (Scheme S2a). In the absence of pyridine derivatives, the acylrhodium species **6** reacts with epoxide and a halide ion to give

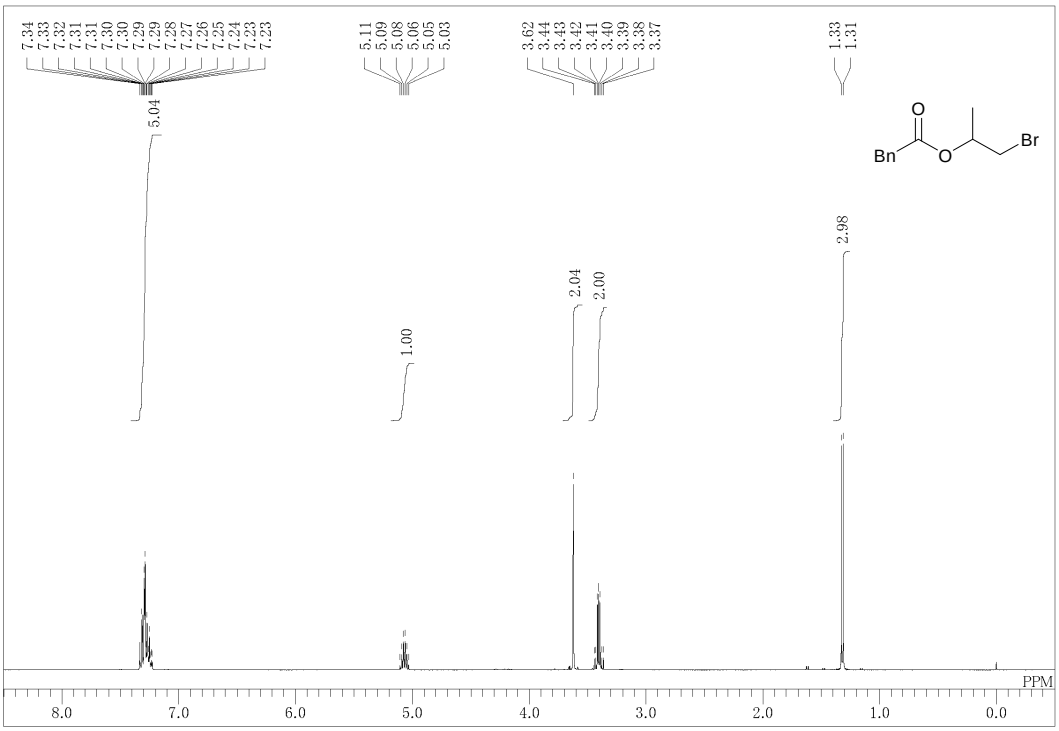
halohydrin ester **1** and regenerate $[PPN]^+[Rh(CO)_4]^-$ (steps c → d). On the other hand, in the presence of pyridine derivatives, the acylrhodium species is expected to react with epoxide and a pyridine derivative to give the pyridinium intermediate **7** (steps e → f),[6] which further reacts with a halide ion to afford halohydrin ester **1** and regenerate $[PPN]^+[Rh(CO)_4]^-$ (step g). Another possible pathway (Scheme 2b) involves the formation of acylpyridinium species from the acylrhodium species **6** and pyridine derivatives (steps h),[7] which further react with epoxide to give halohydrin ester **1** and regenerate $[PPN]^+[Rh(CO)_4]^-$ (steps i → j).



Scheme S2 Plausible reaction pathway without the formation of acyl halide .

The rhodium-catalyzed reaction of benzyl bromide, carbon monoxide, and propylene oxide in the absence of pyridine derivative (Table 2, entry 2) gave halohydrin ester **1c** in high regioselectivity. On the other hand, the reaction of acetyl chloride with propylene oxide in the absence of rhodium catalyst and pyridine derivative resulted in low regioselectivity (Table 1, entry 1). Accordingly, the reaction

pathway via acyl halide formation (Scheme S1) would not be the major pathway in the rhodium-catalyzed three-component coupling reaction without pyridine derivative. In the presence of pyridine derivative, the reaction of acetyl chloride with propylene oxide resulted in high regioselectivity (Table 1, entries 2 and 3). Thus, it is difficult to conclude whether the reaction pathway via acyl halide formation is the major pathway or not in the rhodium-catalyzed system.



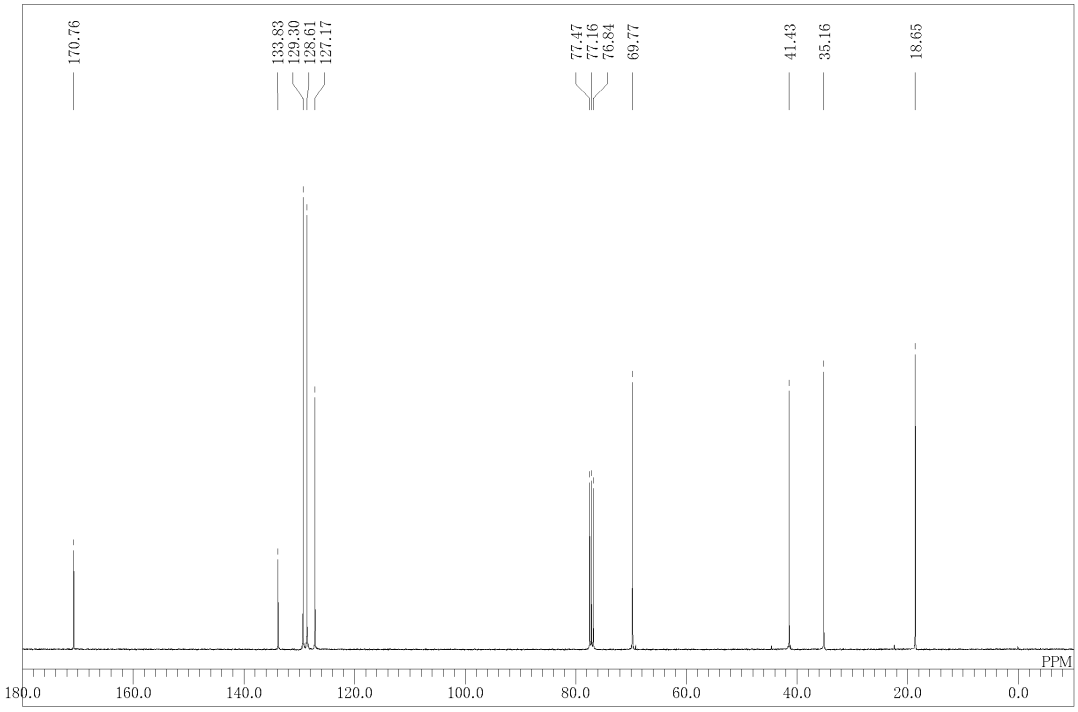
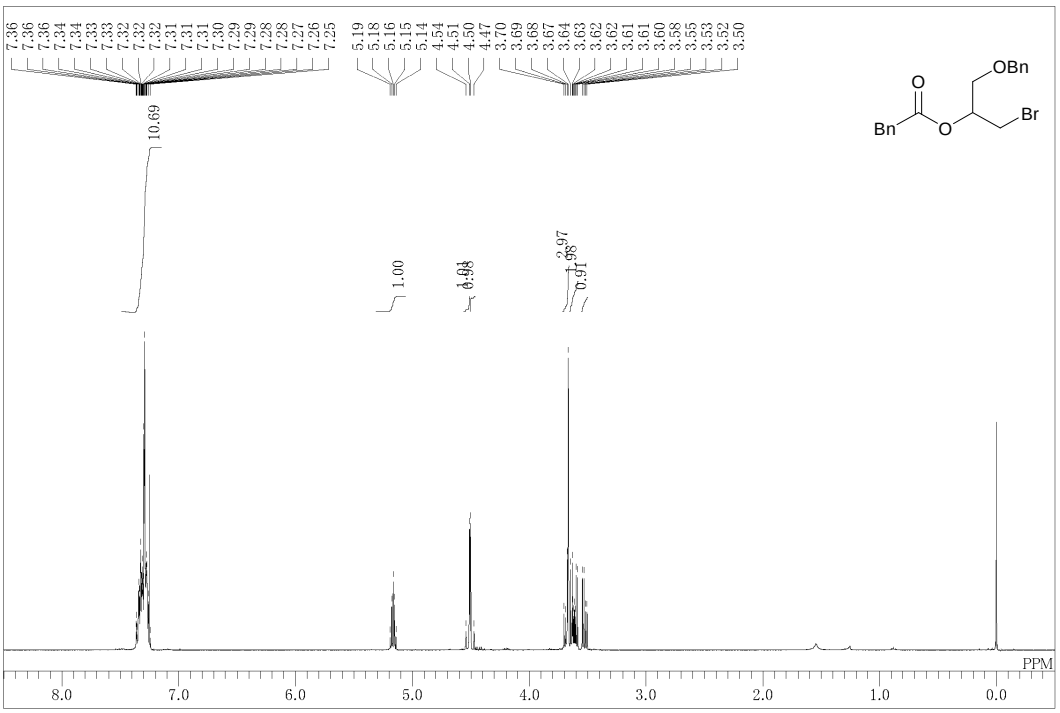


Figure S1. ^{1}H and ^{13}C NMR spectra of 1-bromopropan-2-yl phenylacetate (**1c**).



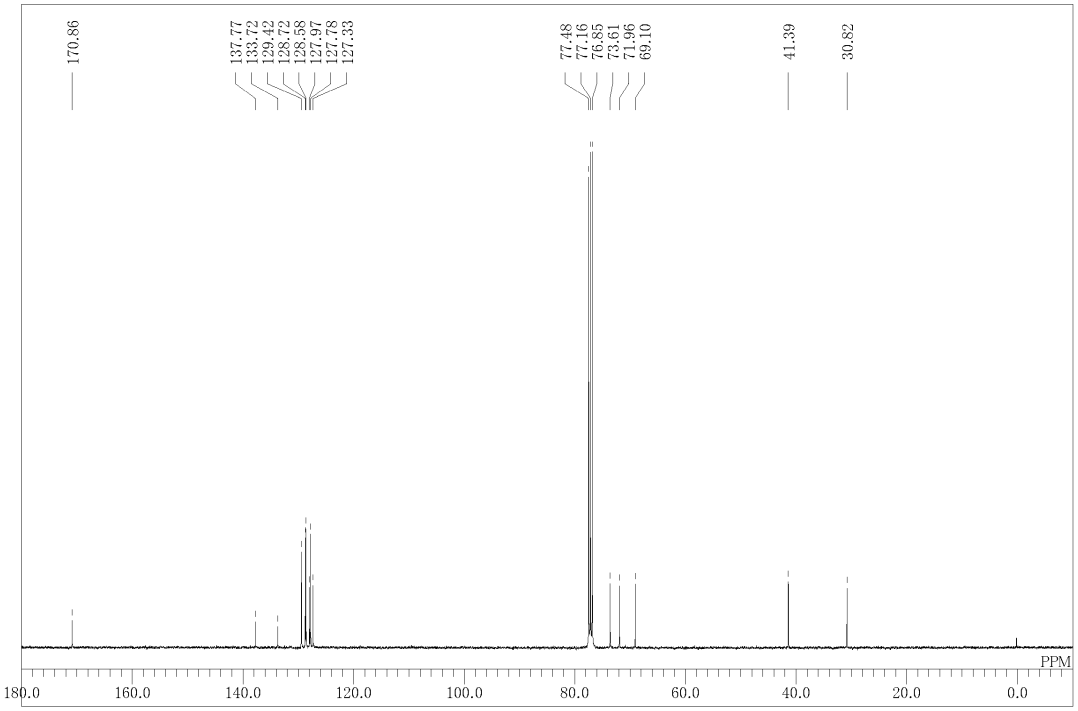
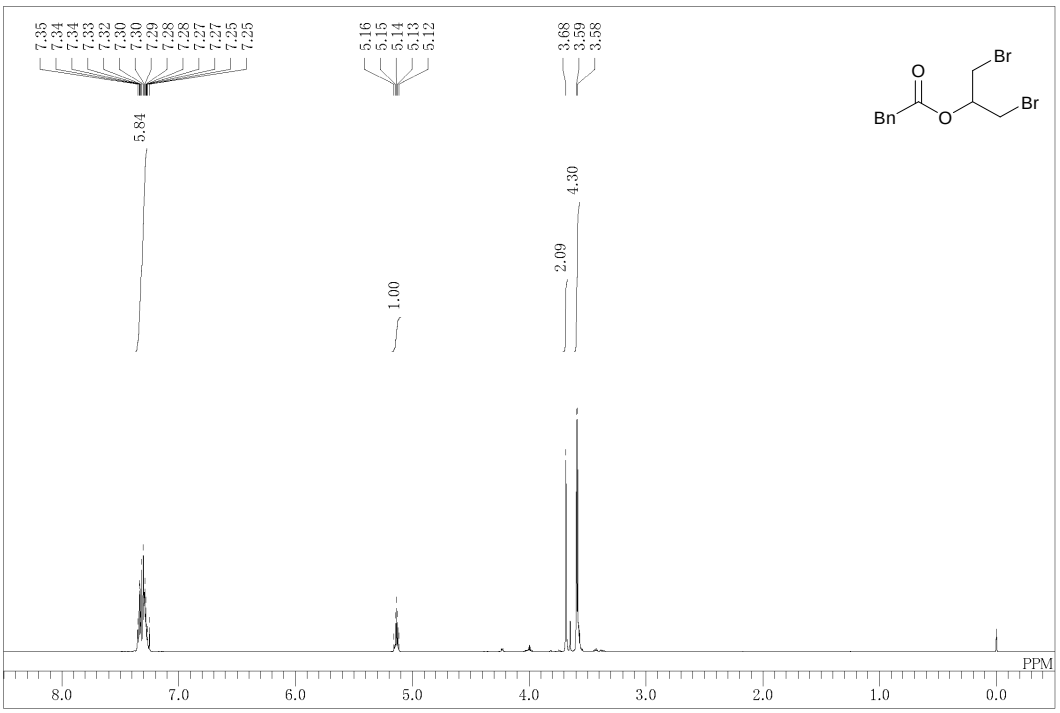


Figure S2. ^{1}H and ^{13}C NMR spectra of 1-benzyloxy-3-bromopropan-2-yl phenylacetate (**1d**).



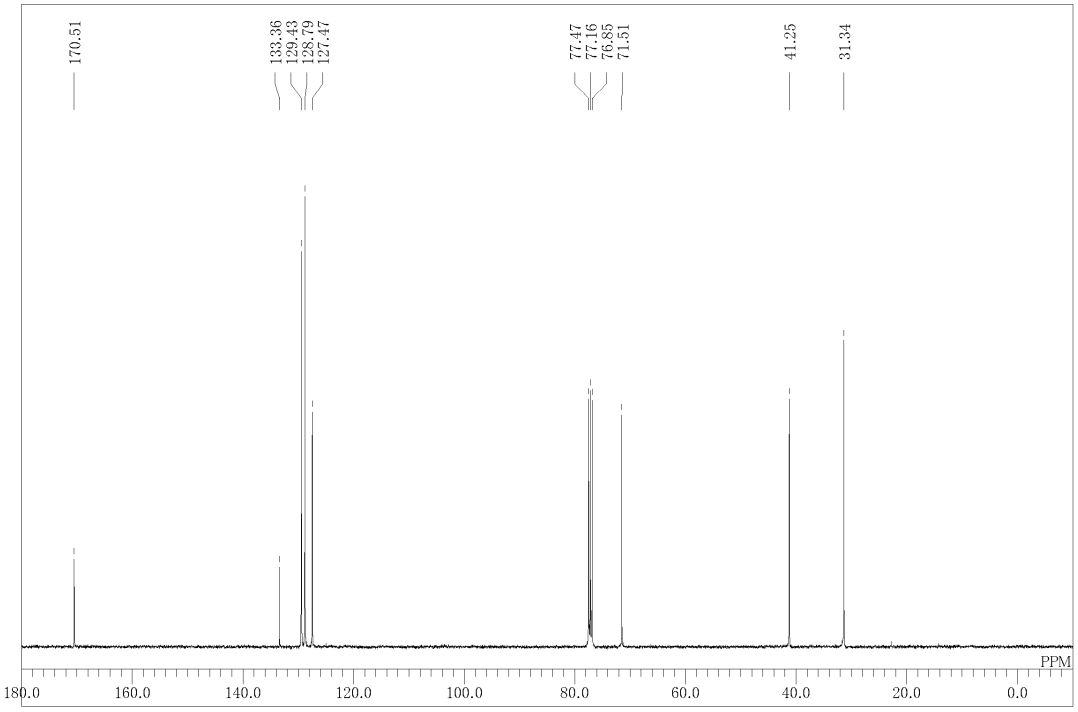


Figure S3. ^{1}H and ^{13}C NMR spectra of 1,3-dibromopropan-2-yl phenylacetate (**1f**).

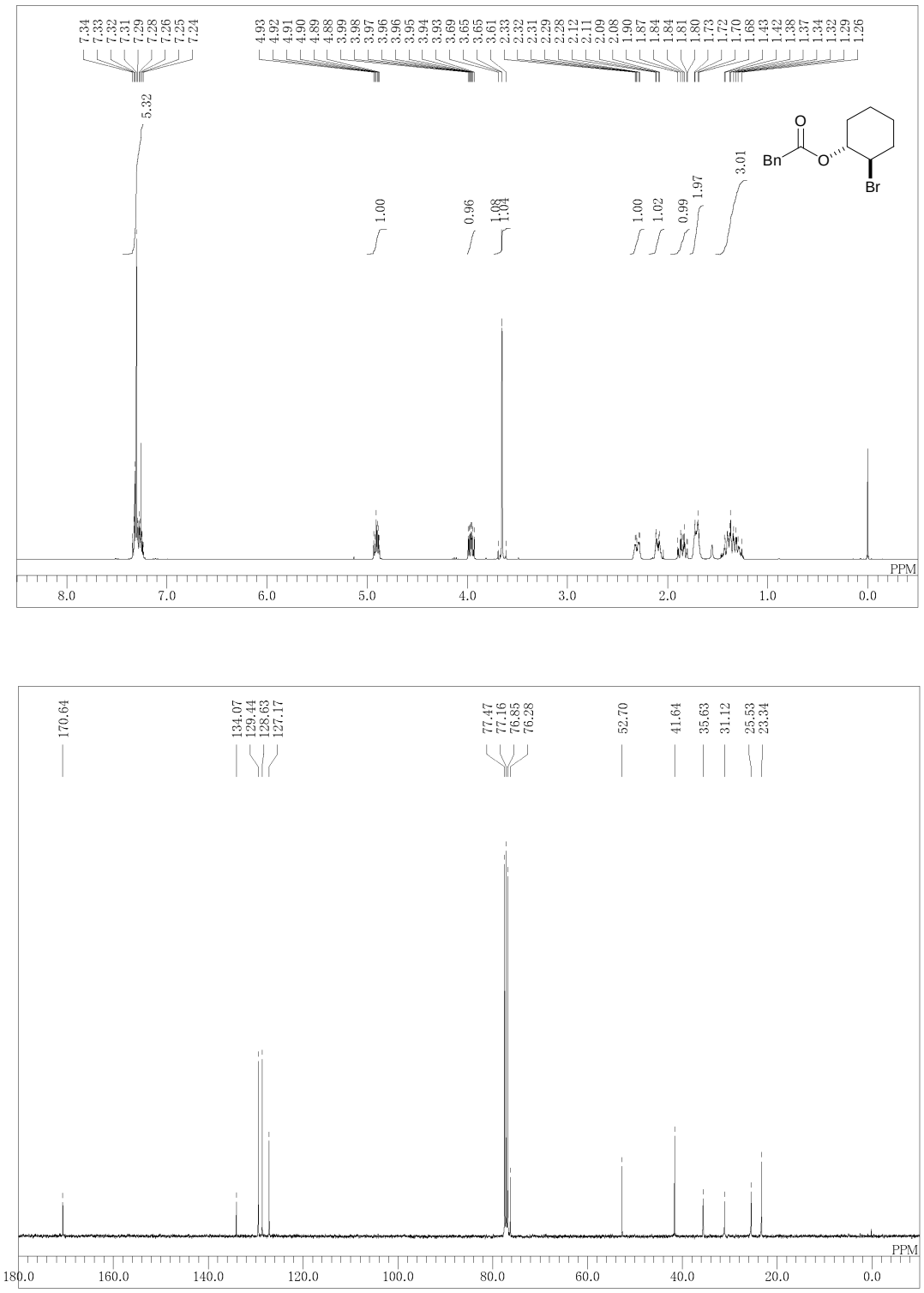
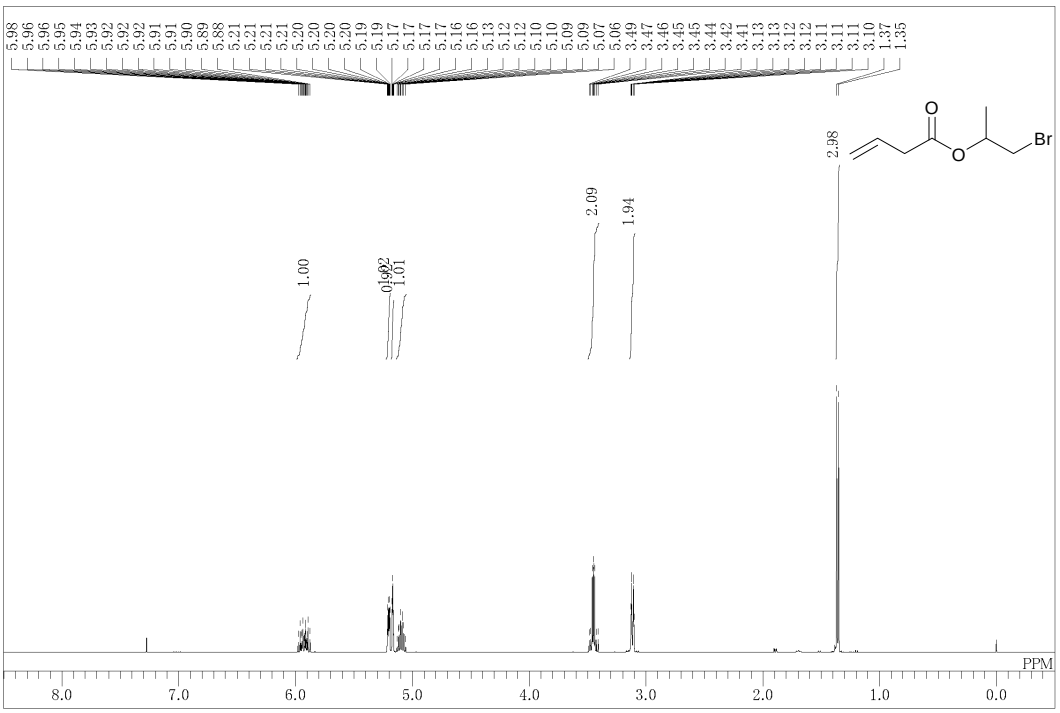


Figure S4. ^{1}H and ^{13}C NMR spectra of *trans*-2-bromocyclohexyl phenylacetate (**1f**).



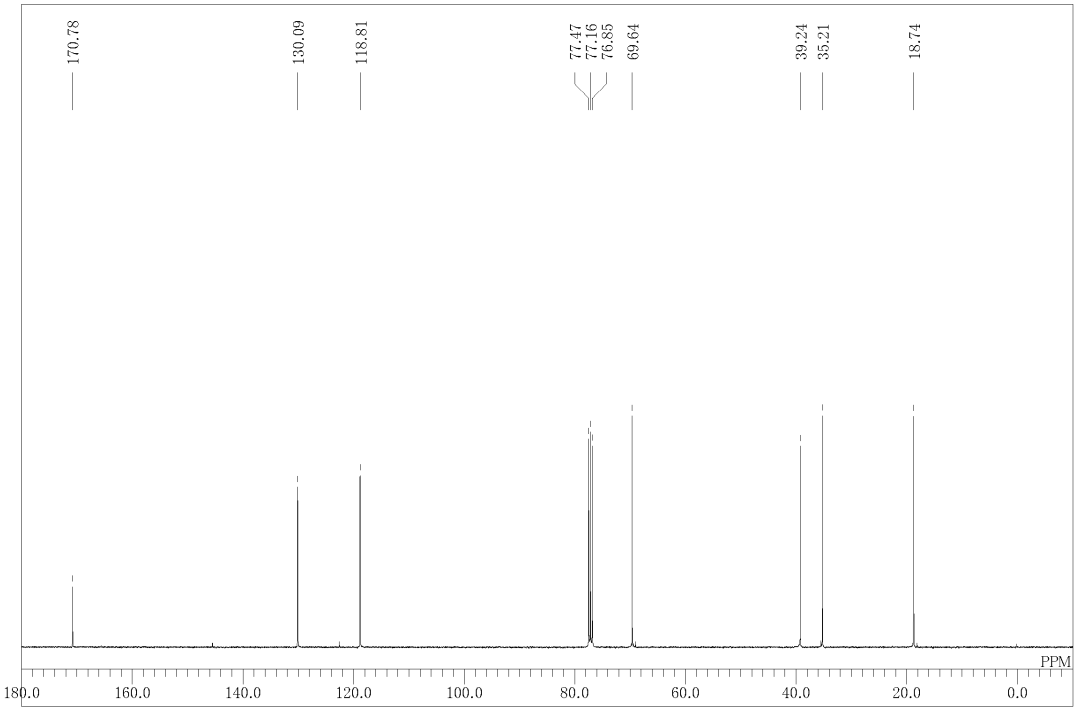
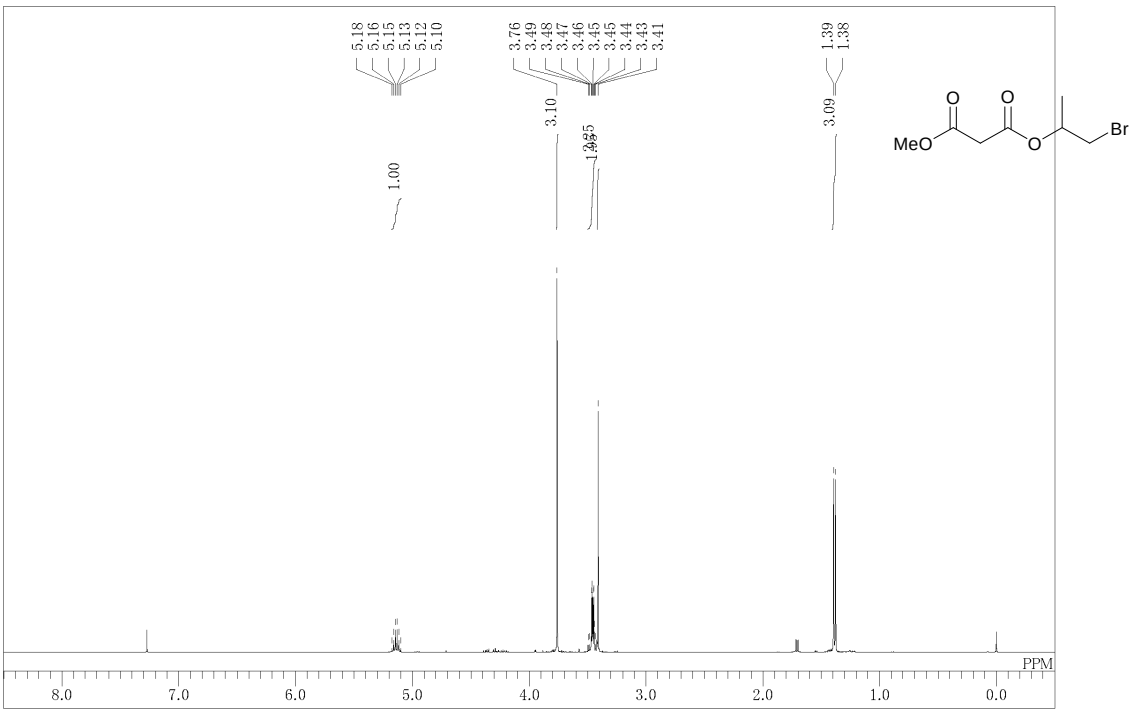


Figure S5. ^{1}H and ^{13}C NMR spectra of 1-bromopropan-2-yl 3-butenoate (**1g**).



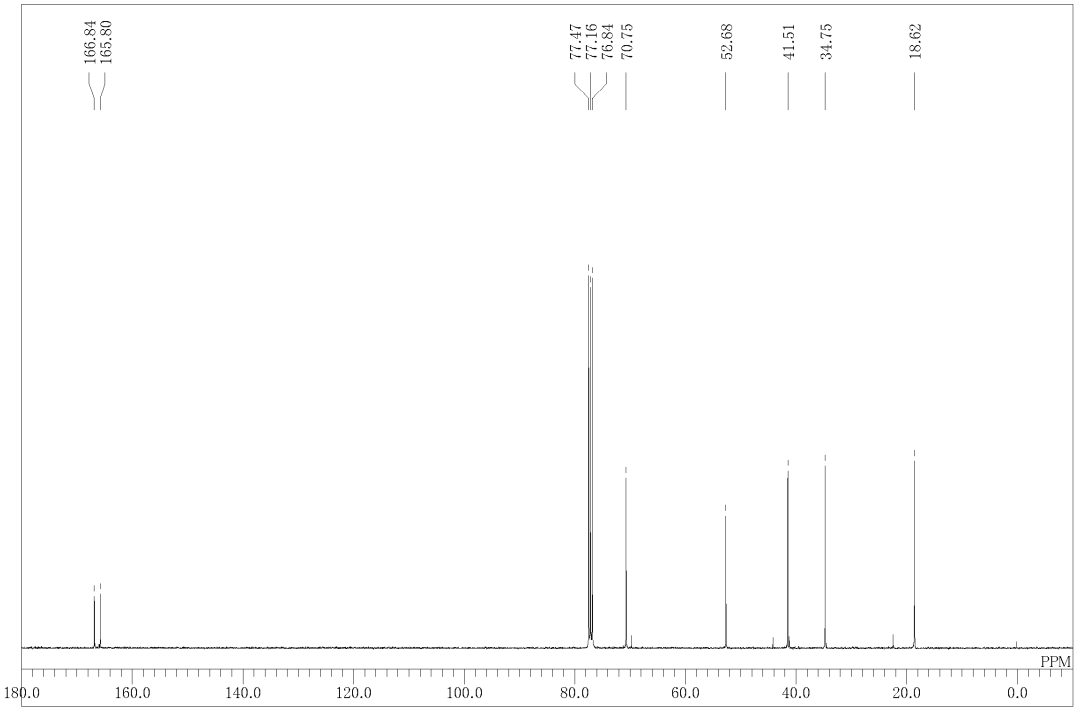
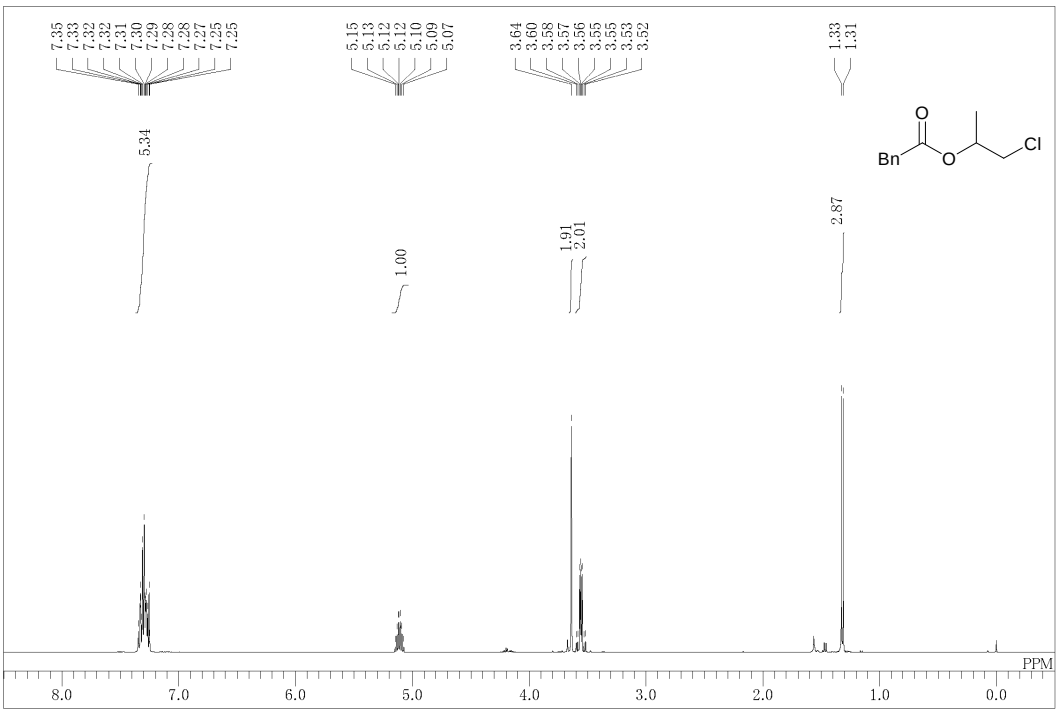


Figure S6. ^{1}H and ^{13}C NMR spectra of 1-bromopropan-2-yl methyl malonate (**1h**).



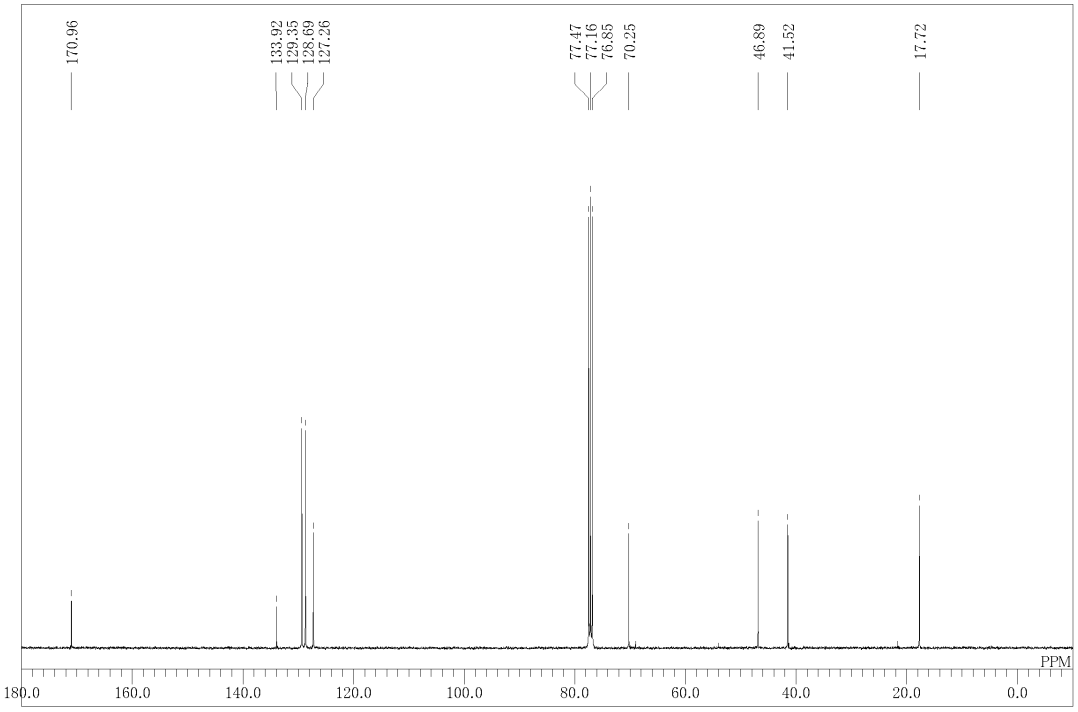


Figure S7. ^{1}H and ^{13}C NMR spectra of 1-chloropropan-2-yl phenylacetate (**1i**).

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