Supporting Information Appendix

Development of a Practical, Biocatalytic Synthesis of *Tert*-Butyl (*R*)-3-Hydroxyl-5-Hexenoate: a Key Intermediate to Statin Side Chain

Chen Hu,[a, b] Minjie Liu,[a, b] Xiaoping Yue,[c] Zedu Huang,*[a, b] and Fener Chen*[a, b]

[a] Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University
220 Handan Road, Shanghai, 200433, P. R. China
E-mail: huangzedu@fudan.edu.cn, rfchen@fudan.edu.cn

[b] Shanghai Engineering Research Center of Industrial Asymmetric Catalysis of Chiral drugs
220 Handan Road, Shanghai, 200433, P. R. China

[c] West China School of Pharmacy, Sichuan University, Chengdu, 610041, P. R. China

*Authors to whom correspondence should be addressed

Amino acid sequence of ketoreductases used in this study

KRED-01
MSFHQQFFTLNNGNKIPAIAIIGTGTRWYKNEETDATFSNSLVEQIVYALKLPGIIHIDA
AEIYRTYPEVGKALSLTEKPRNAIFLTDKYSPQIKMSDSPADGLDLALKKMGTDYVDL
YLLHSPFVSKEVNGLSLEEAWKDMEQLYKSGKAKNIGVSNFAVEDLQRILKVAEVKP
QVNQIEFSPFLQNQTPGIYKFCQEHDILVEAYSPLGPLQKKTAQDDSQPFFEYVKELSE
KYIKSEAQIILRWVTKRGVLPVTTSSKPQRISDAQNLFSFDLTAEEVDKITELGLEHEPL
RLYWNKLYGKYNYAAQKV

KRED-02
MSVFVSGANGFIAQHIVDLLLKEDYKVIGSARSQEKAENLTEAFGNNPKFSMEVVPDI
SKLDAFDHVFQKHGKDIKIVLHTASPFCFDITDSERDLLIPAVNGVKGILHSIKKYAAD
SVERVVLTSSYAAVFDMAKENDKSLTFNEESWNPATWESCQSDPVNAYCGSKKFAEK
AAWEFLEENRDSVKFELTAVNPVYVFGPQMFDKDVKKHLNTSCELVNSLMHLSPEDK
IPELFGGYIDVRDVAKAHLVAFQKRETIGQRLIVSEARFTMQDVLDILNEDFPVLKGNI
PVGKPGSGATHNTLGATLDNKKSKKLLGFKFRNLKETIDDTASQILKFEGRI

KRED-03
MPATLKNSSATLKLNTGASIPVLGFGTWRSVDNNGYHSVIAALKAGYRHIDAAAIYL
NEEEVGRAIKDSGVPREEIFITTKLWGTEQRDPEAALNKSLKRLGLDYVDLYLMHWP
VPLKTDRVTDGNVLCIPTLEDGTVDIDTKEWNFIKTWELMQELPKTGKTKAVGVSNF
SINNIKELLESPNNKVVPATNQIEIHPLLPQDELIAFCKEKGIVVEAYSPFGSANAPLLKE
QAIIDMAKKHGVEPAQLIISWSIQRGYVVLAKSVNPERIVSNFKIFTLPEDDFKTISNLS
KVHGTKRVVDMKWGSFPIFQ

KRED-04
MKYTVITGASSGIGYETAKLLAGKGKSLVLVARRTSELEKLRDEVKQISPDSDVILKSV
DLADNQNVHDLYEGLKELDIETWINNAGFGDFDLVQDIELGKIEKMLRLNIEALTILSS
LFVRDHHDIEGTTLVNISSAGGYRIVPNAVTYCATKFYVSAYTEGLAQELQKGGAKLR
AKVLAPAATETEFADRSRGEAGFDYSKNVKKYHTAAEMAGFLHQLIESDAIVGIVDG
ETYEFELRGPLFNYAG

KRED-05
MNFTDKNVIITGGSAGIGLATAKKFIAKEANVLVTGRNTESLDKASVTINSPKFKTLAS
DISKLADIAALEKEVSESGKKVDVLVLNAGIAKQFSIEETTEEVFDDLFNINVKGLFFT
LQKLIPHLAEGASIILISSGVSVSGYAQMGAYAATKSAVDAIARTAAIELADRKIRVNTV
APGLTDTPMNQQTPEDIKNAIAAAVPLKRIGEAEEIANAIVFFASSEASYISGSYLSVDG
GVTIRR

KRED-06
MTDRLKGKVAIVTGGTLGIGLAIADKFVEEGAKVVITGRRADVGERAAKSIGGTDVI
RFIQHDASDEAGWTKLFDTTEEAFGPVTTVVNNAGIDVVKSVEDTTTEEWHKLLSVN
LDGVFFGTRLGIQRMKNKGLGASIINMSSIFGMVGDPTVGAYNASKGAVRIMSKSAA

LDCALKDYDVRVNTVHPGPIKTPMLDDVEGAEEMWSQRTKTPMGHIGEPNDIAWVC
VYLASGESKFATGAEFVIDGGWTAQ

KRED-07
MTYVVVTGASGYLAQHVIKQLLERNYKVIGTVRNQQKAEDIAKLFQNDNLTLELVP
DLLQADVFDDLFLKYTGQIKHVIHTASPCRFDTTEYENEMLLPAINGTKRVLESIKKYA
SETVETVVYTSSVSALANPAGILDSNLTLTEESWNPDSFEDGKKDVFSAYYVSKTFAE
RTAWDFWKENKDQVKFQLTTICPSYIFGPQAFEENAKGTLNFSTEIVNKILHSKPGDEL
DKNFAGAFVDVRDVARAHVLALEKPELKSKRLVLLNDVYALQDVADYINKHFPELR
GKIATGVPGEGKEIVKHIAHYDNSKTKKLLGFEFISFGQAITDTVAQILKANN

KRED-08
MKEYKYTVITGASSGIGYEAAKAFAKRGKNLIIIARRREKLEELKKEILHYNRSLKVIV
KSIDLSITSNVYSLYDELKNYNIETLVNNAGFGDYSKVNNQNLEKVESMLSLNIEALVI
LSSLFVRDYEKIEGTQLINISSAGGYTIVPNAVIYCATKFFVSSFTEGLARELIEAKSNLK
AKVLAPAATETEFGKVASDVKEYDYQEKFHKYHTSKQMAEFLIKLYDNDYIVGKVD
RNSFKFTLQNPIFDYA

KRED-09
MTDLFKPLPEPPTELGRLRVLSKTAGIRVSPLILGGASIGDAWSGFMGSMNKEQAFELL
DAFYEAGGNCIDTANSYQNEESEIWIGEWMASRKLRDQIVIATKFTGDYKKYEVGGG
KSANYCGNHKRSLHVSVRDSLRKLQTDWIDILYIHWWDYMSSIEEVMDSLHILVQQG
KVLYLGVSDTPAWVVSAANYYATSHGKTPFSVYQGKWNVLNRDFERDIIPMARHFG
MALAPWDVMGGGRFQSKKAMEERKKNGEGLRTFVGGPEQTELEVKISEALTKIAEE
HGTESVTAIAIAYVRSKAKNVFPLIGGRKIEHLKQNIEALSIKLTPEQIEYLESIVPFDVG
FPKSLIGDDPAVTKKLSPLTSMSARIAFDN

KRED-10
MYRLLNKTAVITGGNSGIGLATAKRFVAEGAYVFIVGRRRKELEQAAAEIGRNVTAVK
ADVTKLEDLDRLYAIVREQRGSIDVLFANSGAIEQKTLEEITPEHYDRTFDVNVRGLIF
TVQKALPLLRDGGSVILTSSVAGVLGLQAHDTYSAAKAAVRSLARTWTTELKGRSIRV
NAVSPGAIDTPIIENQVSTQEEADELRAKFAAATPLGRVGRPEELAAAVLFLASDDSSY
VAGIELFVDGGLTQV

KRED-11
MTTLPTVLITGASSGIGATYAERFARRGHDLVLVARDKVRLDALAARLRDESGVAVEA
LQADLTRPADLAAVEIRLREDARIGILINNAGMAQSGGFVQQTAEGIERLITLNTTALT
RLAAAVAPRFVQSGTGAIVNIGSVVGFAPEFGMSIYGATKAFVLFLSQGLNLELSPSGI
YVQAVLPAATRTEIWGRAGIDVNTLPEVMEVDELVDAALVGFDRRELVTIPPLHVAAR
WDALDGARQGLMSDIRQAQAADRYRPEA

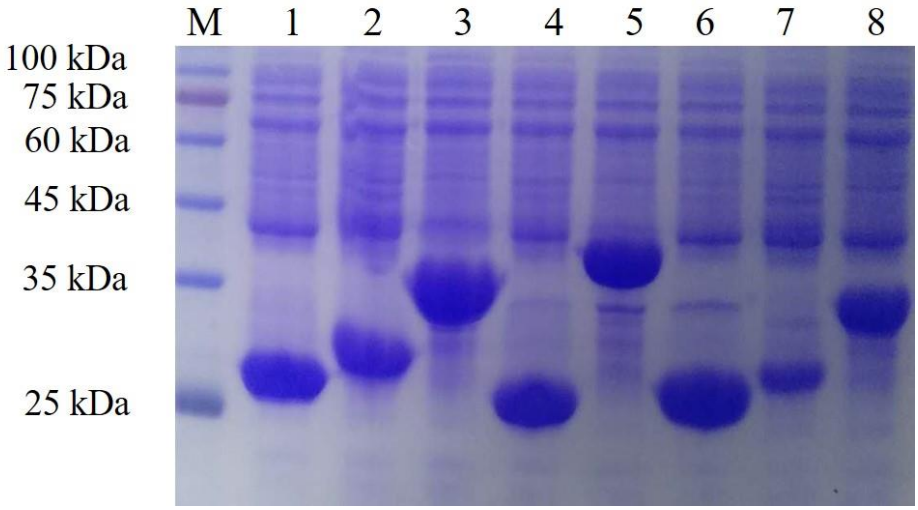


Figure S1. SDS-PAGE analysis of cell free lysate (crude enzyme extracts) of KREDs. Coomassie staining. M: RealBand 3-color Regular Range Protein Marker (Sangon Biotech, China). Lane 1: KRED-08. Lane 2: KRED-10. Lane 3: KRED-07. Lane 4: KRED-05. Lane 5: KRED-09. Lane 6: KRED-04. Lane 7: KRED-11. Lane 8: KRED-02.

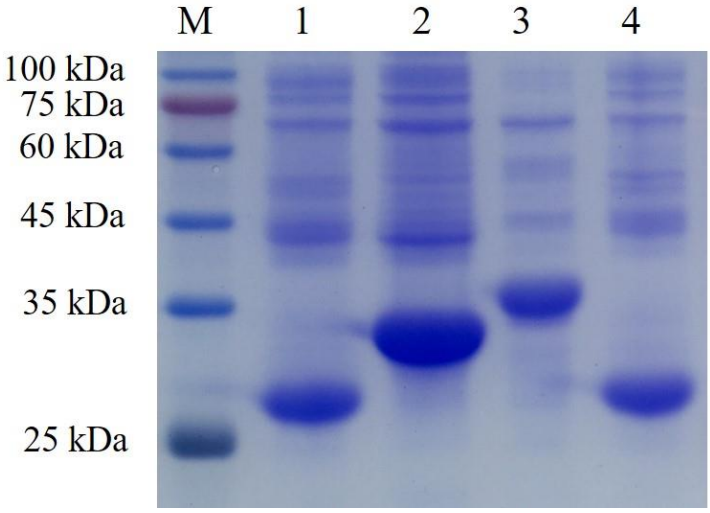


Figure S2. SDS-PAGE analysis of cell free lysate (crude enzyme extracts) of KREDs and LkADH. Coomassie staining. M: RealBand 3-color Regular Range Protein Marker (Sangon Biotech, China). Lane 1: KRED-06. Lane 2: KRED-03. Lane 3: KRED-01. Lane 4: LkADH.

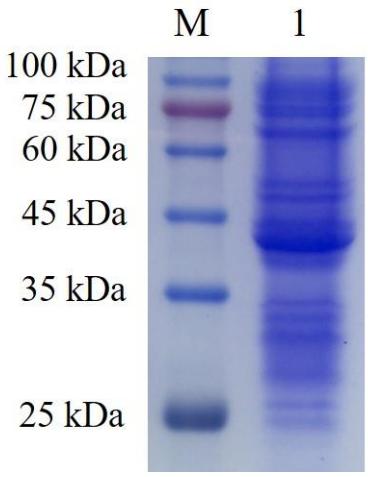
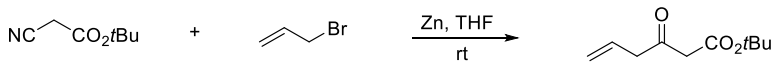


Figure S3. SDS-PAGE analysis of cell free lysate (crude enzyme extracts) of GDH. Coomassie staining. M: RealBand 3-color Regular Range Protein Marker (Sangon Biotech, China). Lane 1: GDH.

General procedure for the synthesis of ketone Substrates

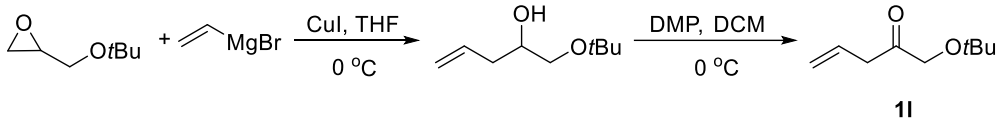
Method A



Scheme S1. General procedure for the synthesis of ketone substrates using method A.[1]

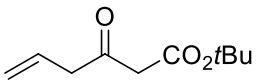
To an ice-cooled stirred solution of zinc powder (4.87 g, 75 mmol) and allylic bromide (7.26 g, 60 mmol) in anhydrous THF (21 mL) was dropwise added *tert*-butyl cyanoacetate (7.00 g, 50 mmol). The resulting mixture was warmed to room temperature and then stirred vigorously at room temperature for 1 h. The resulting mixture was then cooled in an ice-water bath, and aqueous HCl (4 M, 30 mL) was added dropwise. After stirring at room temperature for 30 minutes, the solution was extracted with EtOAc (120 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a yellow oil which was purified by vacuum distillation to yield colorless oil **1a** (7.76 g).

Method B



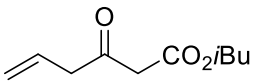
Scheme S2. General procedure for the synthesis of ketone precursors using method B.[2-3]

To a stirred solution of 1-*tert*-butoxy-2,3-epoxypropane (3.9 g, 30 mmol) and copper (I) iodide (0.57 g, 3 mmol) in Et_2O (100 mL) at -40 °C under N_2 was added vinyl magnesium bromide (45 mL of 1 M solution in THF, 45 mmol). After stirring at room temperature for 4 h, the reaction mixture was quenched with a solution of saturated aqueous ammonium chloride (100 ml). The resulting mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the corresponding homoallylic alcohol without further purification. To a DCM solution (20 mL) containing the above homoallylic alcohol (30 mmol) at 0 °C was added Dess-Martin periodinane (DMP, 13.99 g, 33 mmol). The resulting mixture was warmed to room temperature and then stirred at room temperature for 4 h. The mixture was concentrated *in vacuo* and purified via column chromatography on silica gel (eluent: petroleum ether/ethyl ether = 30/1) to give the product **1l** (3.82 g) in 75% yield over 2 steps.



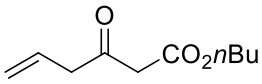
1a

***Tert*-butyl 3-oxohex-5-enoate (1a): synthesized by method A.** Colorless oil; actual mass 7.76 g, 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (m, 1H), 5.44 (m, 2H), 3.63 (s, 2H), 3.55 (d, J = 6.9 Hz, 2H), 1.71 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.2, 166.3, 129.8, 119.5, 82.0, 50.0, 47.5, 27.96. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{16}O_3Na$ 207.0992, found 207.0982.



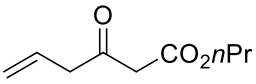
1b

***Iso*-butyl 3-oxohex-5-enoate (1b): synthesized by method A.** Colorless oil; actual mass 7.50 g, 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.77 (m, 1H), 5.17-5.06 (m, 2H), 3.84 (d, 2H), 3.42 (s, 2H), 3.29- 3.19 (d, 2H), 1.92-1.82 (m, 1H), 0.85 (d, J = 4.6 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.6, 167.0, 129.6, 119.5, 71.3, 48.5, 47.6, 27.5, 18.9. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{16}O_3Na$ 207.0992, found 207.0993.



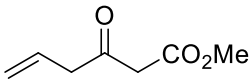
1c

Butyl 3-oxohex-5-enoate (1c): synthesized by method A. Colorless oil; actual mass 6.39 g, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22-6.10 (m, 1H), 5.50-5.41 (m, 2H), 4.39 (t, J = 6.7 Hz, 2H), 3.74 (s, 2H), 3.57 (d, J = 6.9 Hz, 2H), 1.91-1.86 (m, 2H), 1.64 (dd, J = 14.9, 7.5 Hz, 2H), 1.19 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.6, 167.1, 129.6, 119.5, 48.5, 47.5, 30.6, 30.4, 18.9, 13.5. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{16}O_3Na$ 207.0992, found 207.0985.



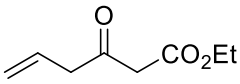
1d

Propyl 3-oxohex-5-enoate (1d): synthesized by method A. Colorless oil; actual mass 6.80 g, 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94-5.79 (m, 1H), 5.17 (dd, J = 19.9, 13.9 Hz, 2H), 4.06 (t, J = 6.7 Hz, 2H), 3.45 (s, 2H), 3.28 (d, J = 6.8 Hz, 2H), 1.64 (dd, J = 14.2, 7.1 Hz, 2H), 0.91 (t, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 201.2, 167.6, 130.1, 120.1, 67.4, 49.1, 48.1, 22.3, 10.7. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_9H_{14}O_3Na$ 193.0835, found 193.0834.



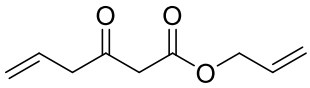
1e

Methyl 3-oxohex-5-enoate (1e): synthesized by method A. Known compound.[4] Colorless oil; actual mass 6.39 g, 90%.



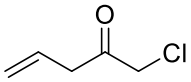
1f

Ethyl 3-oxohex-5-enoate (1f): synthesized by method A. Known compound.[5] Colorless oil; actual mass 7.17 g, 92%.



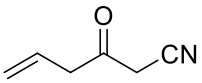
1g

Allyl 3-oxohex-5-enoate (1g): synthesized by method A. Colorless oil; actual mass 7.30 g, 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (m, 2H), 5.39-5.14 (m, 4H), 4.63 (d, J = 5.8 Hz, 2H), 3.51 (s, 2H), 3.31 (d, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.6, 166.7, 131.5, 129.5, 119.8, 118.9, 66.0, 48.5, 47.7. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_9H_{12}O_3Na$ 191.0679, found 191.0675.



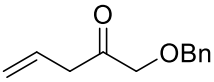
1h

1-Chloro-4-penten-2-one (1h): synthesized by method A. Known compound.[6] Colorless oil; actual mass 2.12 g, 60%.



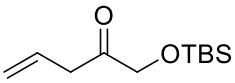
1i

3-Oxo-hex-5-enenitrile (1i): synthesized by method B. Known compound.[7] Colorless oil; actual mass 2.35 g, 72%.



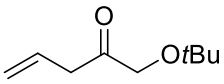
1j

1-(Benzyloxy)pent-4-en-2-one (1j): synthesized by method B. Known compound.[8] Colorless oil; actual mass 4.73 g, 83%.



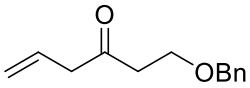
1k

1-(*tert*-Butyldimethylsilyloxy)pent-4-en-2-one (1k): synthesized by method B. Colorless oil; actual mass 3.85 g, 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, J = 9.2, 7.3 Hz, 1H), 5.19 (dd, J = 28.2, 8.9 Hz, 2H), 4.22 (s, 2H), 3.33 (d, 2H), 0.96 (s, 9H), 0.13 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 209.0, 130.5, 119.3, 69.3, 43.8, 26.2, 18.7, -5.0. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{11}H_{22}O_2SiNa$ 237.1281, found 237.1278.



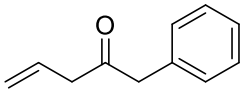
1l

1-*tert*-Butoxypent-4-en-2-one (1l): synthesized by method B. Colorless oil; actual mass 3.82 g, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.09 (dd, J = 21.3, 5.5 Hz, 2H), 3.91 (s, 2H), 3.24 (d, J = 6.9 Hz, 2H), 1.16 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 208.5, 130.6, 119.3, 74.5, 68.4, 44.5, 27.7. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_9H_{16}O_2Na$ 179.1043, found 179.1042.



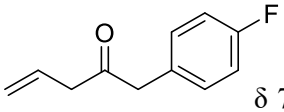
1m

1-(Benzyloxy)hex-5-en-3-one (1m): synthesized by method A. Known compound.[9] Colorless oil; actual mass 6.83 g, 67%.



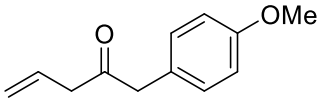
1n

1-Phenylpent-4-en-2-one (1n): synthesized by method A. Known compound.[10] Colorless oil; actual mass 6.48 g, 81%.



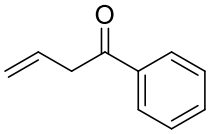
1o

1-(4-Fluorophenyl)pent-4-en-2-one (1o): synthesized by method A. Colorless oil; actual mass 8.1 g, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J = 5.5 Hz, 2H), 7.04 (t, J = 7.8 Hz, 2H), 6.00-5.86 (m, 1H), 5.18 (dd, J = 27.2, 13.7 Hz, 2H), 3.72 (s, 2H), 3.24 (d, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.8, 162.0 (d, J = 245.4 Hz), 131.1 (d, J = 8.0 Hz), 130.3, 129.7 (d, J = 3.2 Hz), 119.2, 115.6 (d, J = 21.4 Hz), 48.4, 46.9. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{11}H_{11}FONa$ 201.0686, found 201.0680.



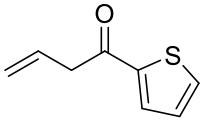
1p

3-*p*-Methoxy-phenyl-acetyl-thiopropen (1p): synthesized by method A. Known compound.[11] Colorless oil; actual mass 8.83 g, 93%



1q

1-Phenylbut-3-en-1-one (1q): synthesized by method A. Known compound.[12] Colorless oil; actual mass 6.50 g, 89%.



1r

1-Thiophen-2-yl-but-3-en-1-one (1r): synthesized by method A. Known compound.[13] Colorless oil; actual mass 6.41 g, 85%.

Optimization of biocatalytic process

Screening of ketoreductases

A reaction solution (9 mL) of **1a** (10 g/L), glucose (19.6 g/L), $NADP^+$ (0.0125 g/L), KRED (2.7 g/L), and GDH (1 g/L) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and 25 °C for 90 min. The reaction mixture was extracted with EtOAc (5 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis. The rest of the organic layer was concentrated *in vacuo*, and purified via column chromatography on silica gel (eluent: petroleum ether/ethyl ether = 10/1) to give the product. The product was benzoylated and its enantiomeric excess was determined by chiral HPLC analysis. The absolute configuration of the enzymatic product was assigned by comparing its optical rotation data to that of the literature data.

Effect of substrate concentration

A reaction solution (0.8 mL) of **1a** (25-200 g/L), IPA (2 equiv. relative to **1a**), $NADP^+$ (0.0125 g/L), KRED-06 (5 g/L), and LkADH (2.5 g/L) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and 25 °C for 12 h. The reaction mixture was extracted with EtOAc (1 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis. Each concentration point was assayed three times.

Effect of IPA concentration

A reaction solution (0.8 mL) of **1a** (125 g/L), IPA (1.0-4.0 equiv. relative to **1a**), $NADP^+$ (0.0125 g/L), KRED-06 (5 g/L), and LkADH (2.5 g/L) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and 25 °C for 12 h. The reaction mixture was extracted with EtOAc (1 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis. Each concentration point was assayed three times.

Effect of temperature

A reaction solution (0.8 mL) of **1a** (125 g/L), IPA (2.5 equiv. relative to **1a**), $NADP^+$ (0.0125 g/L), KRED-06 (5 g/L), and LkADH (2.5 g/L) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and different temperatures (25-50 °C) for 12 h. The reaction mixture was extracted with EtOAc (1 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis. Each temperature point was assayed three times.

Effect of thermal treatment

The crude enzyme extracts of KRED-06 and LkADH were incubated at temperatures of 25, 30, 35, 40 °C for different periods. Then, a reaction solution (0.8 mL) of **1a** (125 g/L), IPA (2.5 equiv. relative to **1a**), $NADP^+$ (0.0125 g/L), thermal treated KRED-06 (5 g/L), and thermal treated LkADH (2.5 g/L) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and different temperatures 30 °C for 2 h. The reaction mixture was extracted with EtOAc (1 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis. The initial enzymatic activity without thermal treatment was defined as 100%.

Effect of pH

A reaction solution (0.8 mL) of **1a** (125 g/L), IPA (2.5 equiv. relative to **1a**), $NADP^+$ (0.0125 g/L), KRED-06 (5 g/L), and LkADH (2.5 g/L) in different buffer solutions was shaking at 200 rpm and 30 °C for 12 h. The tested buffer solutions include 100 mM sodium citrate buffer (pH 5.0 or 6.0), 100 mM KPi buffer (pH 7.0 or 8.0), and 100 mM glycine buffer (pH 9.0). The reaction mixture was extracted with EtOAc (1 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis. Each pH point was assayed three times.

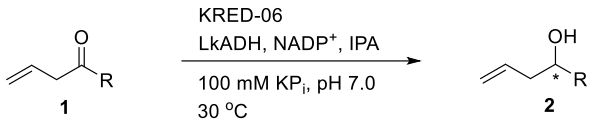
Effect of biocatalyst loading

A reaction solution (0.8 mL) of **1a** (125 g/L), IPA (2.5 equiv. relative to **1a**), $NADP^+$ (0.0125 g/L), KRED-06 (1-6 g/L), and LkADH (50% w/w relative to KRED-06) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and 30 °C for 12 h. The reaction mixture was extracted with EtOAc (1 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis. Each concentration point was assayed three times.

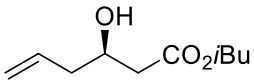
Effect of $NADP^+$ loading

A reaction solution (0.8 mL) of **1a** (125 g/L), IPA (2.5 equiv. relative to **1a**), $NADP^+$ (0-0.0125 g/L), KRED-06 (4 g/L), and LkADH (2 g/L) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and 30 °C for 1-17 h. The reaction mixture was extracted with EtOAc (1 mL), and an aliquot of the organic layer was taken for determining the reaction conversion by GC-MS analysis.

General procedure for KRED-06-catalyzed synthesis of chiral homoallylic alcohols 2

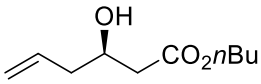


A reaction solution (3.2 mL) of **1** (125 g/L), IPA (2.5 equiv. relative to **1**), $NADP^+$ (0.0125 g/L), KRED-06 (5 g/L), and LkADH (2.5 g/L) in KP_i buffer (100 mM, pH 7.0) was shaking at 200 rpm and 30 °C. After certain amounts of time, the reaction mixture was extracted with EtOAc (5 mL) and the organic layer was concentrated *in vacuo* and the desired product was purified via column chromatography on silica gel (eluent: petroleum ether/ethyl ether = 10/1).



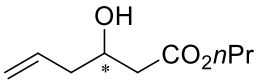
(*R*)-**2b**

(*R*)-*iso*-Butyl 3-hydroxyhex-5-enoate (2b)[14]: Colorless oil; actual mass 322 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.69 (m, 1H), 5.12 (d, *J* = 6.1 Hz, 1H), 5.08 (s, 1H), 4.07 (d, *J* = 2.8 Hz, 1H), 3.87 (d, *J* = 6.6 Hz, 2H), 3.00 (s, 1H), 2.47 (dd, *J* = 19.6, 6.1 Hz, 2H), 2.26 (dd, *J* = 11.9, 6.2 Hz, 2H), 1.91 (td, *J* = 13.3, 6.7 Hz, 1H), 0.91 (d, *J* = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.8, 134.01, 118.1, 70.8, 67.3, 40.9, 40.6, 27.6, 19.0. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1148, found 209.1145. $[\alpha]^{20}_D$ -11.21 (c 0.96, $CHCl_3$). lit. $[\alpha]^{25}_D$ − 17.6 (c 0.70, CH_2Cl_2).[14] HPLC (Chiracel® IC, Hexane **:** Isopropanol = 90 **:** 10, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) : t_1 = 8.3 min (major enantiomer), t_2 = 12.0 min. (82.1% ee)



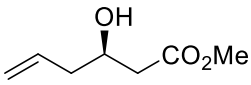
(*R*)-**2c**

(*R*)-Butyl 3-hydroxyhex-5-enoate (2c) [1]: Colorless oil; actual mass 351 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dd, *J* = 9.0, 7.5 Hz, 1H), 5.12 (d, *J* = 5.3 Hz, 1H), 5.08 (s, 1H), 4.09 (m, 2H), 4.05 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.03 (s, 1H), 2.45 (m, 2H), 2.26 (m, 2H), 1.65-1.55 (m, 2H), 1.40-1.32 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.9, 134.0, 118.1, 67.3, 64.6, 40.9, 40.6, 30.5, 19.1, 13.6. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1148, found 209.1146. $[\alpha]^{20}_D$ -13.41 (c 1.07, $CHCl_3$). lit. $[\alpha]^{20}_D$ -10.4 (c 0.9, $CHCl_3$).[1] HPLC (Chiracel® IC, Hexane **:** Isopropanol = 90 **:** 10, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) **:** t_1 = 6.2 min (major enantiomer), t_2 = 8.6 min. (98.1% ee)



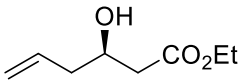
Enantioenriched-**2d**

Enantioenriched Propyl 3-hydroxyhex-5-enoate (2d): Colorless oil; actual mass 310 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.75 (m, 1H), 5.13 (d, *J* = 5.4 Hz, 1H), 5.09 (s, 1H), 4.10-3.98 (m, 3H), 3.00 (s, 1H), 2.54-2.48 (m, 1H), 2.46-2.36 (m, 1H), 2.27 (m, 2H), 1.64 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.9, 134.0, 118.1, 67.3, 66.3, 40.9, 40.6, 21.9, 10.3. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_9H_{16}O_3Na$ 195.0992, found 195.0987. $[\alpha]^{20}_D$ -13.34 (c 1.0, $CHCl_3$). HPLC (Chiracel® IC, Hexane **:** Isopropanol = 90 **:** 10, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) : t_1 = 5.1 min (major enantiomer), t_2 = 6.9 min. (97.3% ee)



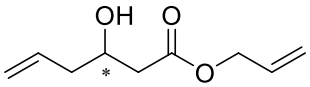
(*R*)-**2e**

(*R*)-Methyl 3-hydroxyhex-5-enoate (2e)[15]: Colorless oil; actual mass 230 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.14 (d, *J* = 4.6 Hz, 1H), 5.10 (s, 1H), 4.16-4.03 (m, 1H), 3.70 (s, 3H), 2.90 (s, 1H), 2.48 (m, 2H), 2.31-2.24 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.2, 133.9, 118.2, 67.3, 51.8, 40.9, 40.4. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_7H_{12}O_3Na$ 167.0679, found 167.0676. $[\alpha]^{20}_D$ -12.23 (c 1.13, $CHCl_3$). lit. $[\alpha]^{r.t.}_D$ -12.55 (c 1.3, $CHCl_3$).[15] HPLC (Chiracel® IC, Hexane **:** Isopropanol = 90 **:** 10, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) : t_1 = 7.4 min (major enantiomer), t_2 = 10.3 min. (97.5% ee)



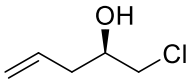
(*R*)-**2f**

(*R*)-Ethyl 3-hydroxyhex-5-enoate (2f)[16]: Colorless oil; actual mass 278 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.73 (m, 1H), 5.13 (d, *J* = 6.0 Hz, 1H), 5.09 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.12-4.03 (m, 1H), 3.05 (s, 1H), 2.46 (m, 2H), 2.27 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.8, 134.0, 118.2, 67.3, 60.7, 40.9, 40.6, 14.1. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_8H_{14}O_3Na$ 181.0835, found 181.0827. $[\alpha]^{20}_D$ -12.94 (c 1.08, $CHCl_3$). lit. $[\alpha]^{24}_D$ -14.8 (c 1.1, $CHCl_3$).[16] HPLC (Chiracel® IC, Hexane **:** Isopropanol = 90 **:** 10, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) : t_1 = 6.7 min (major enantiomer), t_2 = 9.7 min. (>99.9% ee)



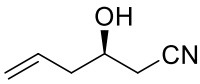
Enantioenriched-**2g**

Enantioenriched Allyl 3-hydroxyhex-5-enoate (2g): Colorless oil; actual mass 284 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08-5.76 (m, 2H), 5.30 (ddd, *J* = 14.8, 11.4, 0.9 Hz, 2H), 5.15 (dd, *J* = 9.9, 6.3 Hz, 2H), 4.74-4.54 (m, 2H), 4.19-4.03 (m, 1H), 2.97 (s, 1H), 2.61-2.45 (m, 2H), 2.30 (d, *J* = 2.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.3, 133.9, 131.8, 118.5, 118.2, 67.3, 65.3, 40.9, 40.6. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_9H_{14}O_3Na$ 193.0835, found 193.0835. $[\alpha]^{25}_D$ -26.2 (c 1.13, $CHCl_3$). HPLC (Chiracel® IC, Hexane **:** Isopropanol = 90 **:** 10, Flow rate = 0.5 mL/min, λ = 254 nm, 25 °C) : t_1 = 8.6 min, t_2 = 12.9 min (major enantiomer). (99.7% ee)



(*R*)-**2h**

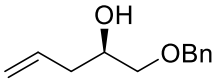
(*R*)-1-Chloropent-4-en-2-ol (2h)[17]: Colorless oil; actual mass 135 mg, 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.71 (m, 1H), 5.27-5.04 (m, 2H), 3.90 (s, 1H), 3.57 (ddd, *J* = 11.0, 8.7, 4.5 Hz, 2H), 2.54-2.28 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.3, 118.6, 70.6, 49.4, 38.7. $[\alpha]^{20}_D$ -4.3 (c 1.05, $CHCl_3$). lit. $[\alpha]^{23}_D$ -4.8 (c 1.0, $CHCl_3$).[17] HPLC (Chiracel® AD, Hexane **:** Isopropanol = 98 **:** 2, Flow rate = 0.3 mL/min, λ = 254 nm, 25 °C) : t_1 = 18.6 min, t_2 = 19.6 min (major enantiomer). (95.3% ee)



(*R*)-**2i**

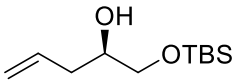
(*R*)-3-Hydroxyhex-5-enenitrile (2i)[18]: Colorless oil; actual mass 213 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.24-5.08 (m, 2H), 3.96 (m, 1H), 3.42 (s, 1H), 2.56 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.47 (dd, *J* = 16.7, 6.4 Hz, 1H), 2.32 (t, *J* = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 132.8, 119.2, 117.9, 66.6, 40.7, 25.1. HRMS(ESI) m/z $[M+Na]^+$ calcd for C_6H_9NONa 134.0576, found 134.0579. $[\alpha]^{20}_D$ -7.0 (c 1.13, $CHCl_3$). lit. $[\alpha]^{21}_D$ -6.8 (c 0.8, $CHCl_3$).[18] HPLC (Chiracel® AD, Hexane **:** Isopropanol = 99 **:** 1, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) : t_1 = 6.5 min,

t_2 = 7.2 min (major enantiomer). (91.3% ee)



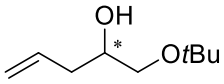
(*R*)-**2j**

(*R*)-1-(Benzyloxy)pent-4-en-2-ol (2j)[19]: Colorless oil; actual mass 259 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 5.91-5.77 (m, 1H), 5.11 (dd, *J* = 12.1, 10.8 Hz, 2H), 4.56 (s, 2H), 3.89 (s, 1H), 3.52 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.38 (dd, *J* = 9.3, 7.6 Hz, 1H), 2.43 (d, *J* = 2.2 Hz, 1H), 2.27 (t, *J* = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.9, 134.2, 128.5, 127.8, 127.7, 117.7, 73.9, 73.4, 69.7, 37.9. HRMS(ESI) m/z $[M+Na]^+$ calcd for $C_{12}H_{16}O_2Na$ 215.1043, found 215.1034. $[\alpha]^{20}_D$ -4.5 (c 1.0, $CHCl_3$). lit. $[\alpha]^{25}_D$ -3.8 (c 1.37, $CHCl_3$).[19] HPLC (Chiracel® OJ, Hexane **:** Isopropanol = 96 **:** 4, Flow rate = 1.0 mL/min, λ = 230 nm, 25 °C) : t_1 = 12.9 min (major enantiomer), t_2 = 15.0 min. (>99.9 % ee)



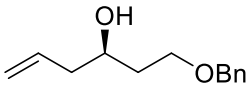
(*R*)-**2k**

(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-2-ol (2k)[1]: Colorless oil; actual mass 394 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91-5.76 (m, 1H), 5.08 (m, 2H), 3.69 (dt, *J* = 10.1, 4.9 Hz, 1H), 3.62 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.45 (m, 1H), 2.44 (s, 1H), 2.23 (t, *J* = 6.3 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.4, 117.3, 71.1, 66.5, 37.6, 25.8, 18.2, -5.3, -5.4. HRMS(ESI) *m/z* $[M+Na]^+$ calcd for $C_{11}H_{24}O_2SiNa$ 239.1438, found 239.1432. $[\alpha]^{20}_D$ -3.5 (c 1.1, $CHCl_3$). lit. $[\alpha]^{20}_D$ -3.7 (c 1.0, $CHCl_3$).[1] HPLC (Chiracel® AD, Hexane **:** Isopropanol = 99 **:** 1, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) : t_1 = 5.7 min, t_2 = 6.7 min (major enantiomer). (97.9 % ee)



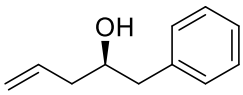
Enantioenriched-**2l**

Enantioenriched 1-(*tert*-Butoxy)pent-4-en-2-ol (2l): Colorless oil; actual mass 312 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.18-5.08 (m, 2H), 3.78 (d, *J* = 2.7 Hz, 1H), 3.41 (dd, *J* = 8.9, 3.4 Hz, 1H), 3.23 (dd, *J* = 8.8, 7.7 Hz, 1H), 2.51 (s, 1H), 2.28 (t, *J* = 6.7 Hz, 2H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.6, 117.2, 73.1, 70.0, 65.3, 37.9, 27.5. HRMS(ESI) *m/z* $[M+Na]^+$ calcd for $C_9H_{18}O_2Na$ 181.1199, found 181.1199. $[\alpha]^{20}_D$ -5.3 (c 1.1, $CHCl_3$). HPLC (Chiracel® AD, Hexane **:** Isopropanol = 98 **:** 2, Flow rate = 1.0 mL/min, λ = 254 nm, 25 °C) : t_1 = 4.6 min, t_R = 5.0 min (major enantiomer). (99.3 % ee)



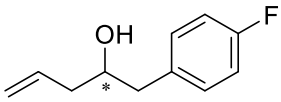
(*R*)-**2m**

(*R*)-1-(Benzyloxy)hex-5-en-3-ol (2m)[20]: Colorless oil; actual mass 150 mg, 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.86 (m, 1H), 5.27-5.06 (m, 2H), 4.55 (s, 2H), 4.01-3.85 (m, 1H), 3.78-3.63 (m, 2H), 3.07 (s, 1H), 2.28 (m, 2H), 1.84 -1.76 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.9, 134.9, 128.5, 127.8, 127.7, 117.6, 73.3, 70.3, 68.9, 41.9, 35.9. HRMS(ESI) *m/z* $[M+Na]^+$ calcd for $C_{13}H_{18}O_2Na$ 229.1199, found 229.1197. $[\alpha]^{25}_D$ -2.51 (c 0.53, $CHCl_3$). lit. $[\alpha]^{25}_D$ -3.33 (c 0.6, $CHCl_3$).[20] HPLC (Chiracel® OD, Hexane **:** Isopropanol = 97 **:** 3, Flow rate = 0.5 mL/min, λ = 254 nm, 25 °C) : t_R = 22.7 min, t_R = 23.8 min (major enantiomer). (60.3% ee)



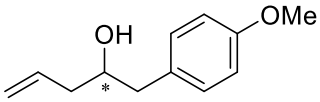
(*R*)-**2n**

(*R*)-1-Phenylpent-4-en-2-ol (2n)[21]: Colorless oil; actual mass 270 mg, 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.90 (dq, *J* = 10.8, 7.3 Hz, 1H), 5.22 (d, *J* = 5.3 Hz, 1H), 5.18 (s, 1H), 3.92 (s, 1H), 2.86 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.77 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.43-2.33 (m, 1H), 2.31-2.21 (m, 1H), 1.82 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.4, 134.7, 129.5, 128.6, 126.54 118.2, 71.7, 43.3, 41.2. $[\alpha]^{25}_D$ -17.3 (c 0.64, $CHCl_3$). lit. for (*S*)-enantiomer, $[\alpha]^{25}_D$ +13.6 (c 1.0, benzene).[21] HPLC (Chiracel® OD-H, Hexane **:** Isopropanol = 97 **:** 3, Flow rate = 0.5 mL/min, λ = 254 nm, 25 °C) : t_1 =16.8 min, t_2 =20.4 min (major enantiomer). (99.0 % ee)



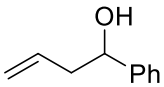
Enantioenriched-**2o**

Enantioenriched 1-(4-Fluorophenyl)pent-4-en-2-ol (2o)[22] Colorless oil; actual mass 181 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 2H), 6.99 (m, 2H), 5.94-5.75 (m, 1H), 5.22 -5.01 (m, 2H), 3.83 (s, 1H), 2.73 (m, 2H), 2.35-2.15 (m, 2H), 1.80 (d, *J* = 13.7 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7 (d, *J* = 244.3 Hz), 134.6, 134.1 (d, *J* = 3.2 Hz), 130.9 (d, *J* = 7.8 Hz), 118.4, 115.3 (d, *J* = 21.1 Hz), 71.6, 42.4, 41.2. $[\alpha]^{25}_D$ -15.15 (c 0.62, $CHCl_3$). HPLC (Chiracel® OD, Hexane **:** Isopropanol = 98 **:** 2, Flow rate =0.5 mL/min, λ = 254 nm, 25 °C) : t_1 = 16.2 min, t_2 = 17.9 min (major enantiomer). (88 % ee)



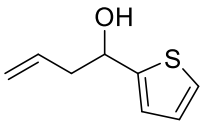
Enantioenriched-**2p**

Enantioenriched 1-(4-Methoxyphenyl)pent-4-en-2-ol (2p): Colorless oil; actual mass 234 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H), 6.87 (t, *J* = 8.3 Hz, 2H), 5.98-5.82 (m, 1H), 5.25-5.13 (m, 2H), 3.86 (s, 1H), 3.82 (s, 3H), 2.79 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.69 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.39-2.31 (m, 1H), 2.28-2.19 (m, 1H), 1.80 (d, *J* = 10.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.3, 134.8, 130.4, 130.3, 118.0, 113.9, 71.8, 55.2, 42.3, 41.1. HRMS(ESI) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{16}O_2Na$ 215.1043, found 215.1038. $[\alpha]^{25}_D$ -12.1 (c 1.03, $CHCl_3$). HPLC (Chiracel® OD, Hexane **:** Isopropanol = 98 **:** 2, Flow rate =0.5 mL/min, λ = 254 nm, 25 °C) : t_1 = 22.2 min, t_R = 23.9 min (major enantiomer). (>99.9 % ee)



2q

1-Phenylbut-3-en-1-ol (2q): Colorless oil; actual mass 162 mg, 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 4H), 7.31-7.24 (m, 1H), 5.81 (dq, *J* = 10.1, 7.4 Hz, 1H), 5.20-5.10 (m, 2H), 4.76-4.68 (m, 1H), 2.56-2.46 (m, 2H), 2.10 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.2, 134.8, 128.7, 127.9, 126.1, 118.8, 73.6, 44.1. HRMS(ESI) *m/z* $[M+Na]^+$ calcd for $C_{10}H_{12}ONa$ 171.0780, found 171.0777. HPLC (Chiracel® OJ, Hexane **:** Isopropanol = 96 **:** 4, Flow rate = 1.0 mL/min, λ = 230 nm, 25 °C) : t_1 = 13.1 min, t_2 = 15.2 min. (0% ee)



2r

1-(Thiphen-3-yl)but-3-en-1-ol (2r): Colorless oil; actual mass 100 mg, 30%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 4.2, 1.6 Hz, 1H), 6.98 (d, *J* = 4.1 Hz, 2H), 5.92-5.77 (m, 1H), 5.19 (dd, *J* = 20.6, 4.9 Hz, 2H), 4.98 (t, *J* = 6.4 Hz, 1H), 3.73 (s, 1H), 2.63 (t, *J* = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.2, 134.2, 126.9, 124.8, 124.0, 119.0, 69.7, 44.1. HRMS(ESI) *m/z* $[M+Na]^+$ calcd for $C_8H_{10}OS$ 177.0345, found 177.0337. HPLC (Chiracel® OJ,

Hexane **:** Isopropanol = 96 **:** 4, Flow rate = 1.0 mL/min, λ = 230 nm, 25 °C) : t_1 = 12.7 min, t_2 = 14.7 min. (0% ee)

References

(1) Huang, G.; Liu, M.; Xiong, F.; Meng, G.; Tao, Y.; Wu, Y.; Peng, H.; Chen, F. Chiral *Syn*-1,3-diol Derivatives *via* a One-Pot Diastereoselective Carboxylation/Bromocyclization of Homoallylic Alcohols. *iScience* **2018**, *9*, 513-520.

(2) Beattie, R. J.; Hornsby, T. W.; Craig, G.; Galan, M. C.; Willis, C. L. Stereoselective Synthesis of Protected *L*- and *D*-Dideoxysugars and Analogues *via* Prins cyclisations. *Chem. Sci.* **2016**, *7*, 2743-2747.

(3) Posevins, D.; Qiu, Y.; Backvall, J. E. Highly Diastereoselective Palladium-Catalyzed Oxidative Carbocyclization of Enallenes Assisted by a Weakly Coordinating Hydroxyl Group. *J. Am. Chem. Soc.* **2018**, *140*, 3210-3214.

(4) Theodore, T. E.; Vasileios, G.; Ioulia. S. An Efficient Chemoenzymatic Approach towards the Synthesis of Rugulactone. *Molecules* **2018**, *23*, 640-641.

(5) Almuth, S.; Juergen, M. First Synthesis of *α,β*-Unsaturated Lactones with High Diversity through the Passerini Reaction and Ring-Closing Metathesis. *Eur. J. Org. Chem.* **2011**, 4335-4344.

(6) Griesbaum, K.; Quinkert, R. O.; McCullough, K. J. C-C Bond Formation at Ozonide Rings by Substitution of Chlorinated Ozonides. *Eur. J. Org. Chem*. **2004**, 3657-3662.

(7) Adachi, I.; Yamamori, T.; Hiramatsu, Y.; Sakai, K.; Sato, H.; Kawakami, M.; Uno, O.; Ueda, M. Studies on Dihydropyridines. II. Synthesis of 4,7-Dihydropyrazolo [3,4-b]-pyridines with Vasodilating and Antihypertensive Activities. *Chem. Pharm. Bull.* **1987**, *35*, 3235-3252.

(8) Viktor, I.; Hans, S.; Ryan C. C. Synthesis of a Hominal Bis(difluoromethyl) Fragment. *ACS Omega* **2019**, *4*, 14140-14150.

(9) Ian, P.; Mark, J. C.; David, Y. K. C.; Renata, M. O.; Debra, J. W.; Roger, D. N. The Stereocontrolled Total Synthesis of Altohyrtin A/Spongistatin 1: the AB-Spiroacetal Segment. *Org. Biomol. Chem.* **2005**, *3*, 2399-2409.

(10) Lee, A. S. Y.; Lin, M. C.; Wang, S. H.; Lin, L. S. A Mild Isomerization Reaction for *β,γ*-Unsaturated Ketone to *α,β*-Unsaturated Ketone. *J. Chin. Chem. Soc.* **2004**, *51*, 371-376.

(11) Makoto, Y.; Makihiro, T.; Akio, B. A New Type of Allylation: Synthesis of *β,γ*-Unsaturated Ketones from *α*-Halogenated Aryl Ketones using an Allyltributyltin(IV)-tin(II) Dichloride-Acetonitrile System. *Chem. Commun.* **1998**, *5*, 563-564.

(12) Nikitas, N. F.; Tzaras, D. I.; Triandafillidi, I.; Kokotos, C. G. Photochemical Oxidation of Benzylic Primary and Secondary Alcohols Utilizing Air as the Oxidant. *Green Chem.* **2020**, *22*, 471- 477.

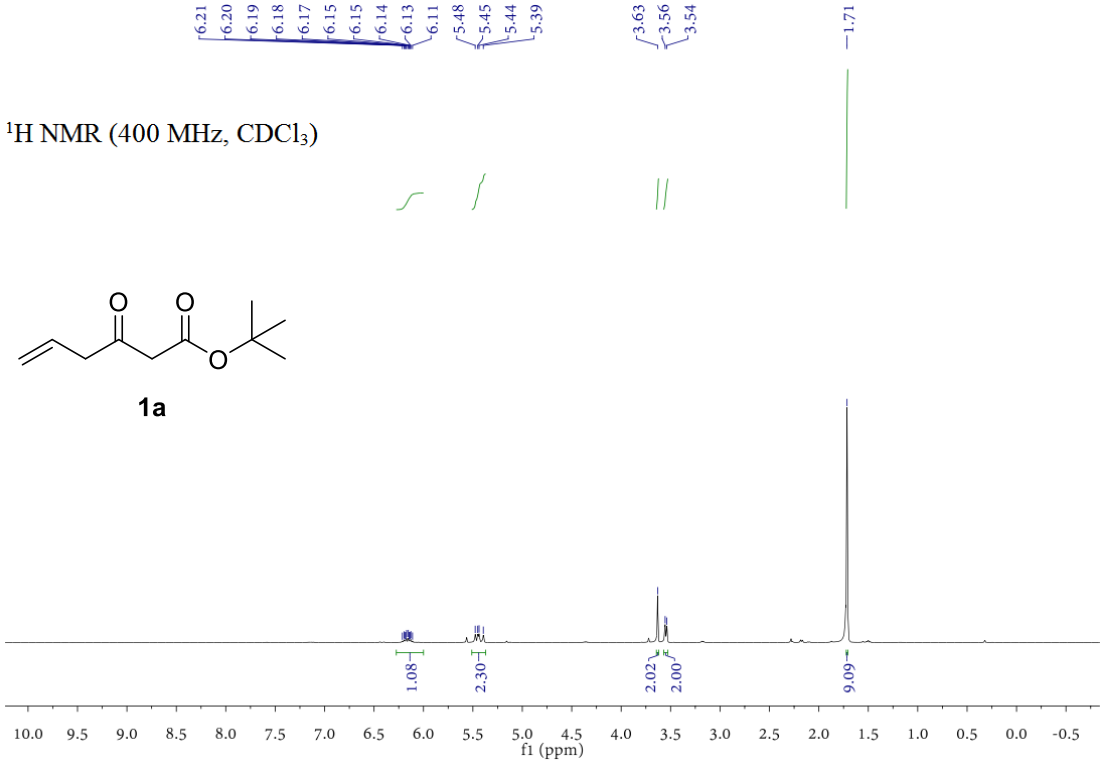
(13) Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. Alkyl, Unsaturated, (Hetero)aryl, and *N*-Protected *α*-Amino Ketones by Acylation of Organometallic Reagents. *J. Org. Chem.* **2006**, *71*, 9861-9864.

(14) Michael, T. C.; Elizabeth, A. O. B. Enantioselective Total Synthesis of Spirofungins A and B. *Org. Lett.* **2010**, *12*, 4416-4419.

(15) Mohr, P.; Roesslein, L.; Tamm, C. 3-Hydroxyglutarate and *β,γ*-Epoxy Esters as Substrates for Pig Liver Esterase (PLE) and *α*-Chymotrypsin. *Helv. Chim. Acta* **1987**, *70*, 142-152.

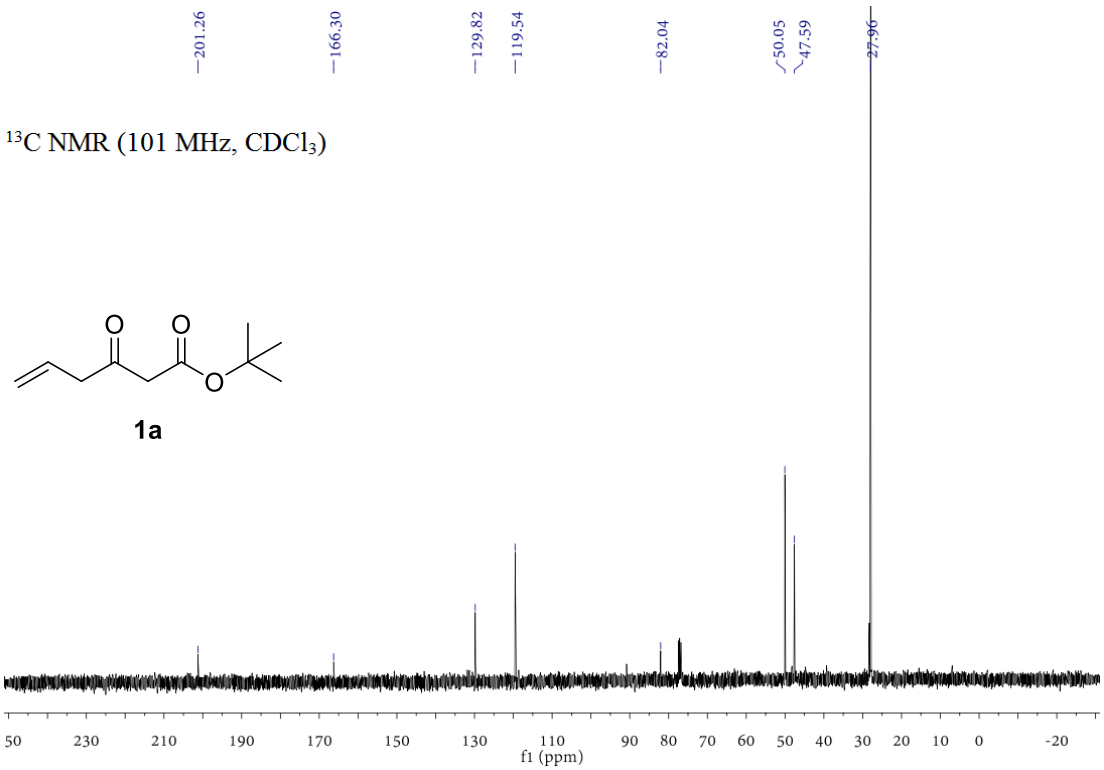
(16) Ema, T.; Moriya, H.; Kofukuda, T.; Ishida, T.; Maehara, K.; Utaka, M.; Sakai, T. High Enantioselectivity and Broad Substrate Specificity of a Carbonyl Reductase: Toward a Versatile Biocatalyst. *J. Org. Chem.* **2001**, *66*, 8682-8684.
(17) Spangenberg, T.; Aubry, S.; Kishi, Y. Synthesis and Structure Assignment of the Minor Metabolite Arising from the Frog Pathogen *Mycobacterium liflandii*. *Tetrahedron Letters* **2010**, *51*, 1782-1785.
(18) Saneyoshi, H.; Deschamps, J. R.; Marquez, V. Synthesis of Conformationally Locked l-Deoxythreosyl Phosphonate Nucleosides Built on a Bicyclo[3.1.0]hexane Template. *J. Org. Chem.* **2010**, 7659-7669.
(19) Jamieson, M. L.; Hume, P. A.; Furkert, D. P.; Brimble, M. A. Divergent Reactivity *via* Cobalt Catalysis: An Epoxide Olefination. *Org. Lett.* **2016**, *18*, 468- 471.
(20) Rauniyar, V.; Zhai, H.; G. Hall, D. Catalytic Enantioselective Allyl- and Crotylboration of Aldehydes Using Chiral Diol•$SnCl_4$ Complexes. Optimization, Substrate Scope and Mechanistic Investigations. *J. Am. Chem. Soc.* **2008**, *130*, 8481-8490.
(21) Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. Hydroxyl- Directed Stereoselective Diboration of Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 9264-9267.
(22) Jiang, N.; Hu, Q.-Y.; Reid, C. S.; Lu, Y.-F; Li, C.-J. A Novel Palladium-Catalyzed Coupling of Epoxides with Allyl Bromide Mediated by Indium(I) Chloride: a Cascade Epoxide Rearrangement–Carbonyl Allylation. *Chem. Commun.* **2003**, *18*, 2318-2319.

^{1}H NMR (400 MHz, $CDCl_3$)



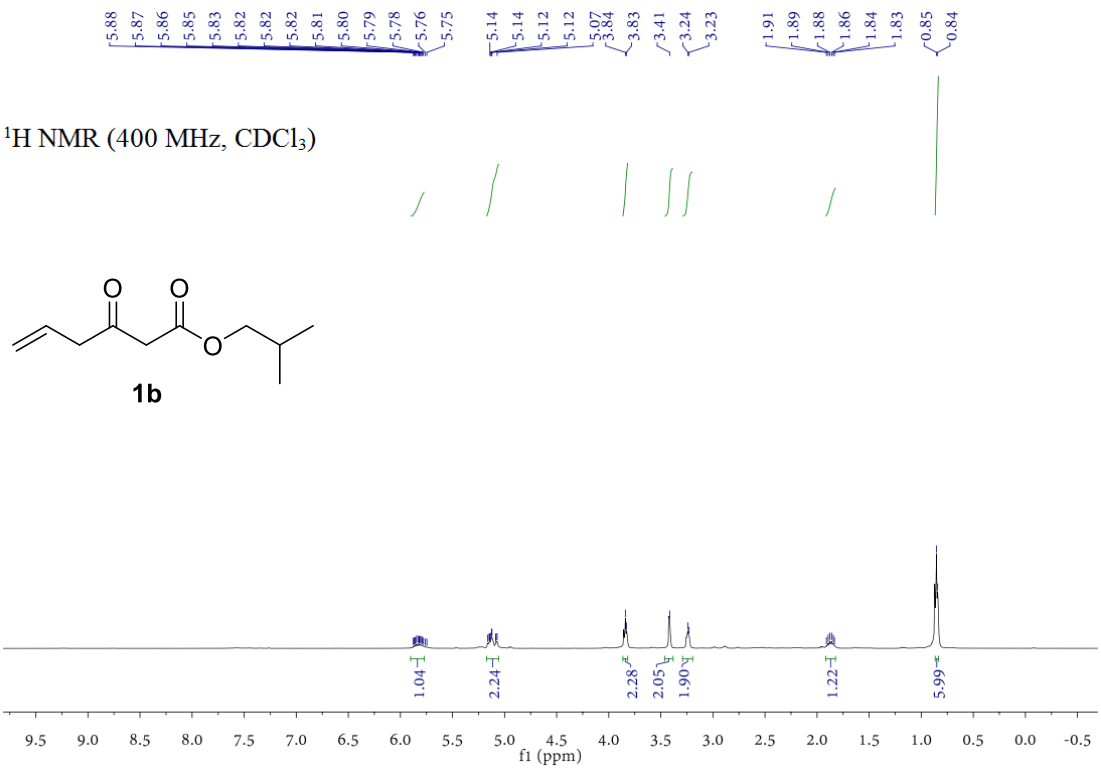
1a

^{13}C NMR (101 MHz, $CDCl_3$)



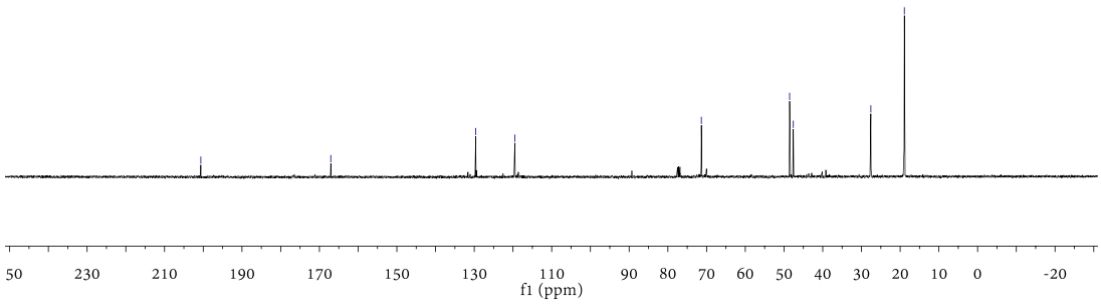
1a

^{1}H NMR (400 MHz, $CDCl_3$)



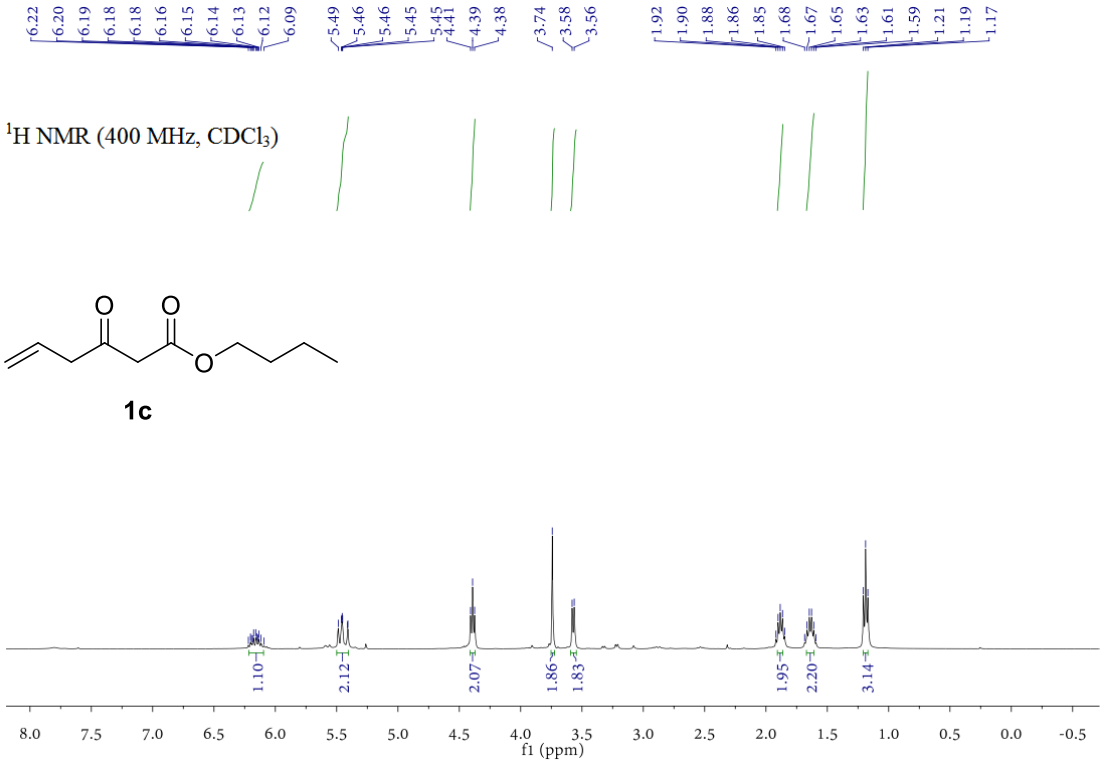
1b

^{13}C NMR (101 MHz, $CDCl_3$)



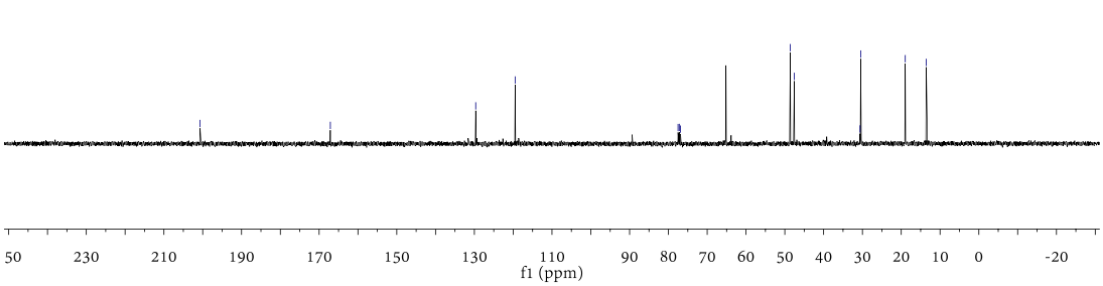
1b

^{1}H NMR (400 MHz, $CDCl_3$)



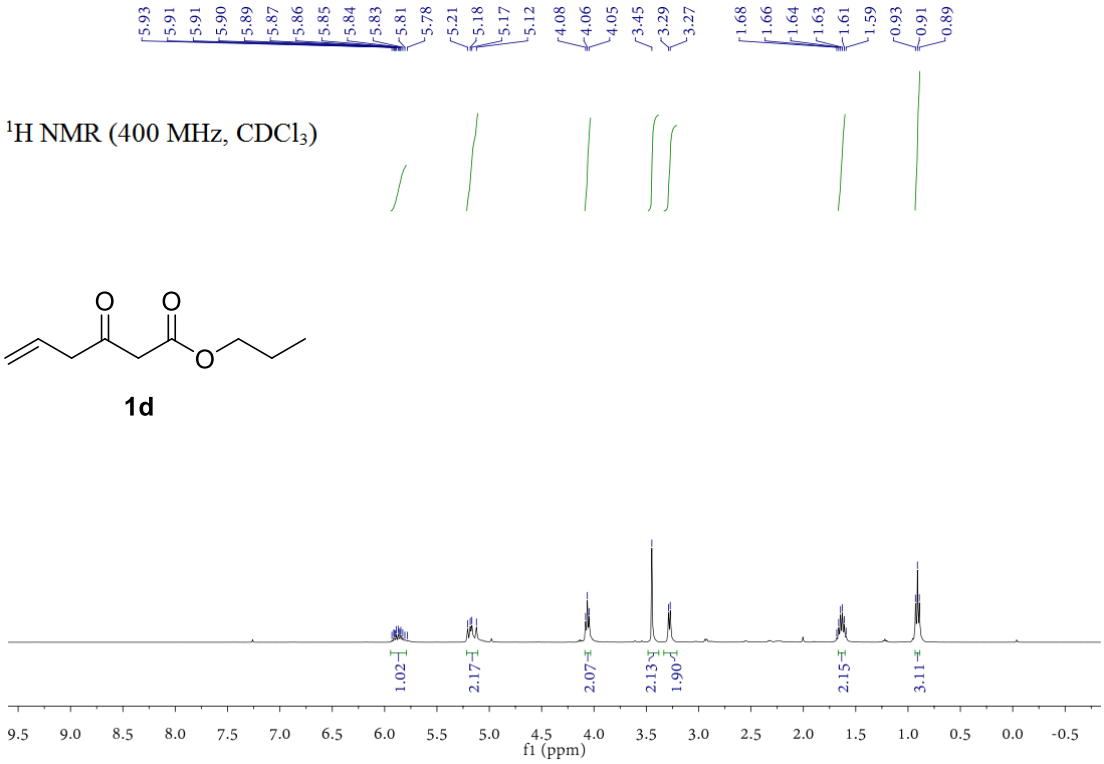
1c

^{13}C NMR (101 MHz, $CDCl_3$)



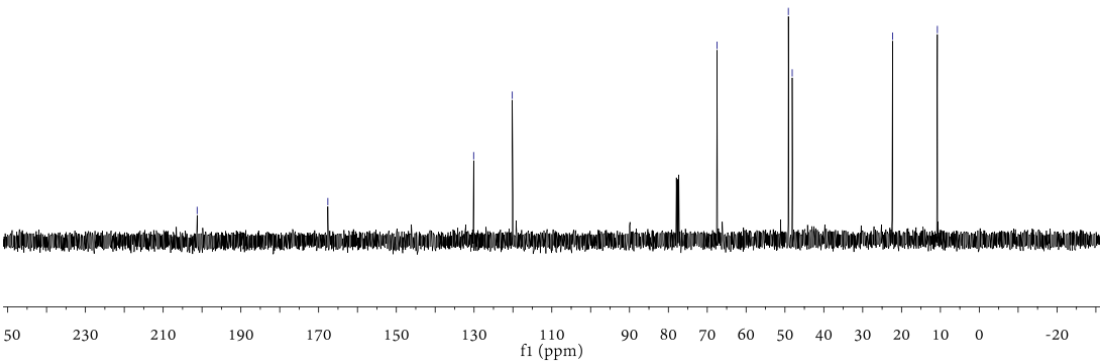
1c

^{1}H NMR (400 MHz, $CDCl_3$)



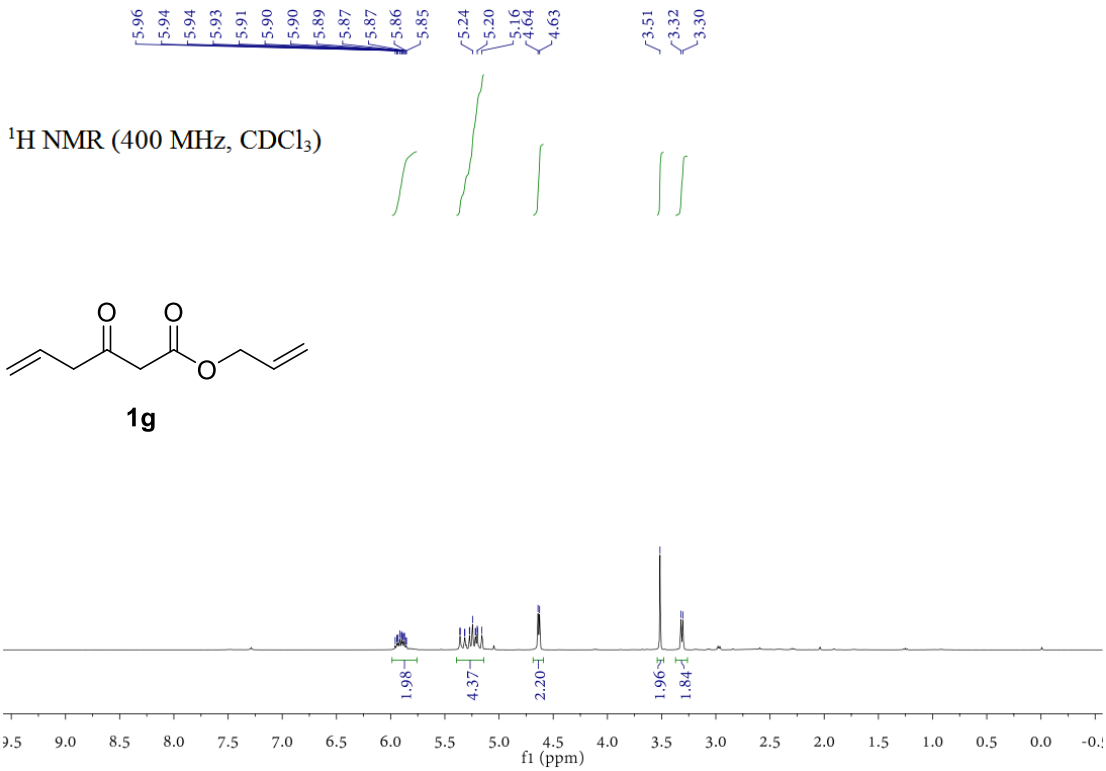
1d

^{13}C NMR (101 MHz, $CDCl_3$)



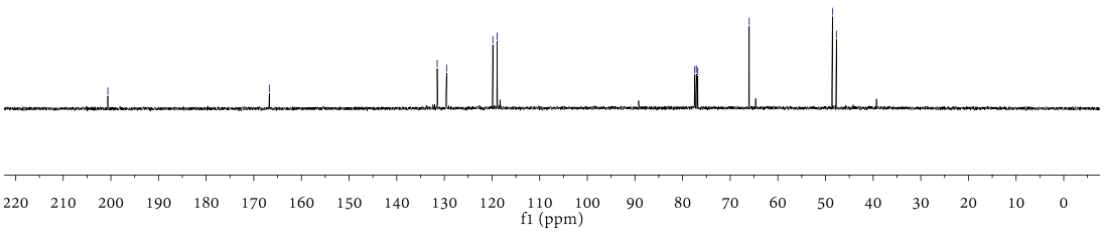
1d

^{1}H NMR (400 MHz, $CDCl_3$)



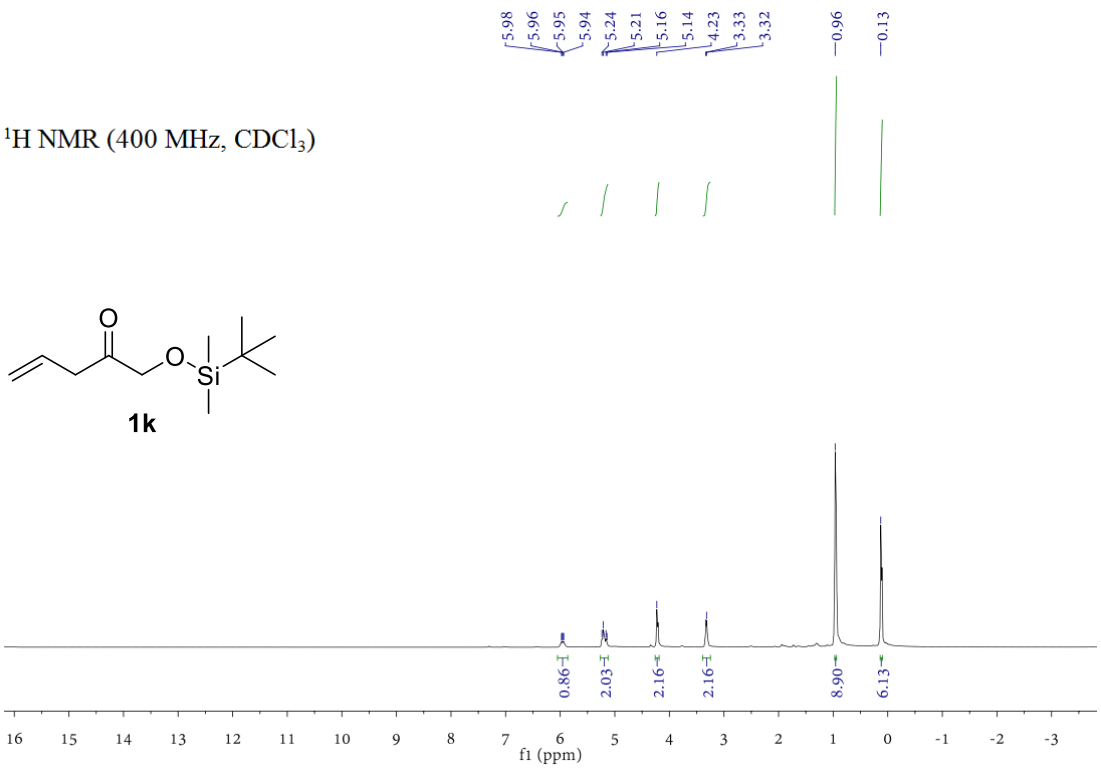
1g

^{13}C NMR (101 MHz, $CDCl_3$)

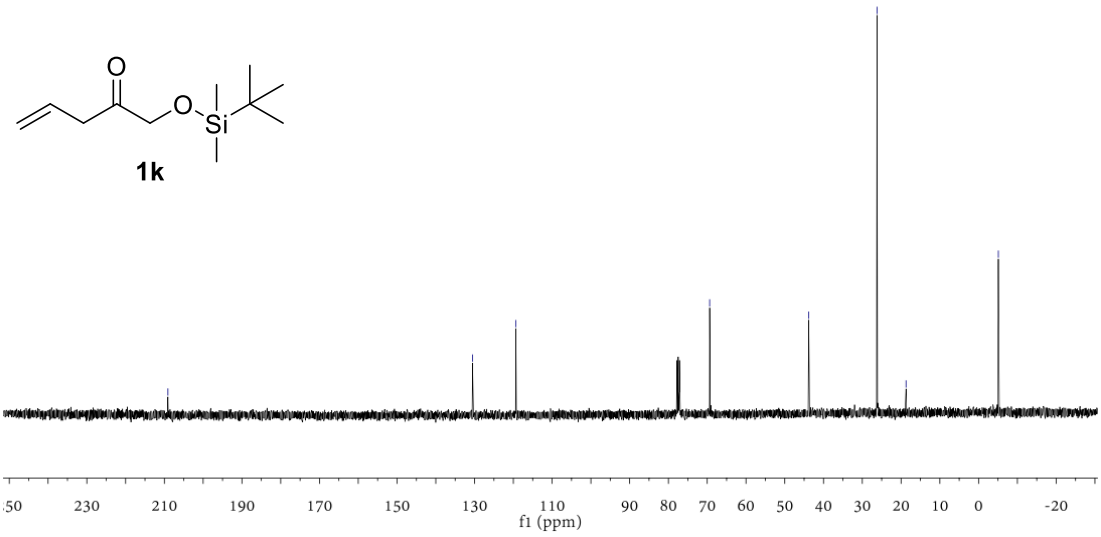


1g

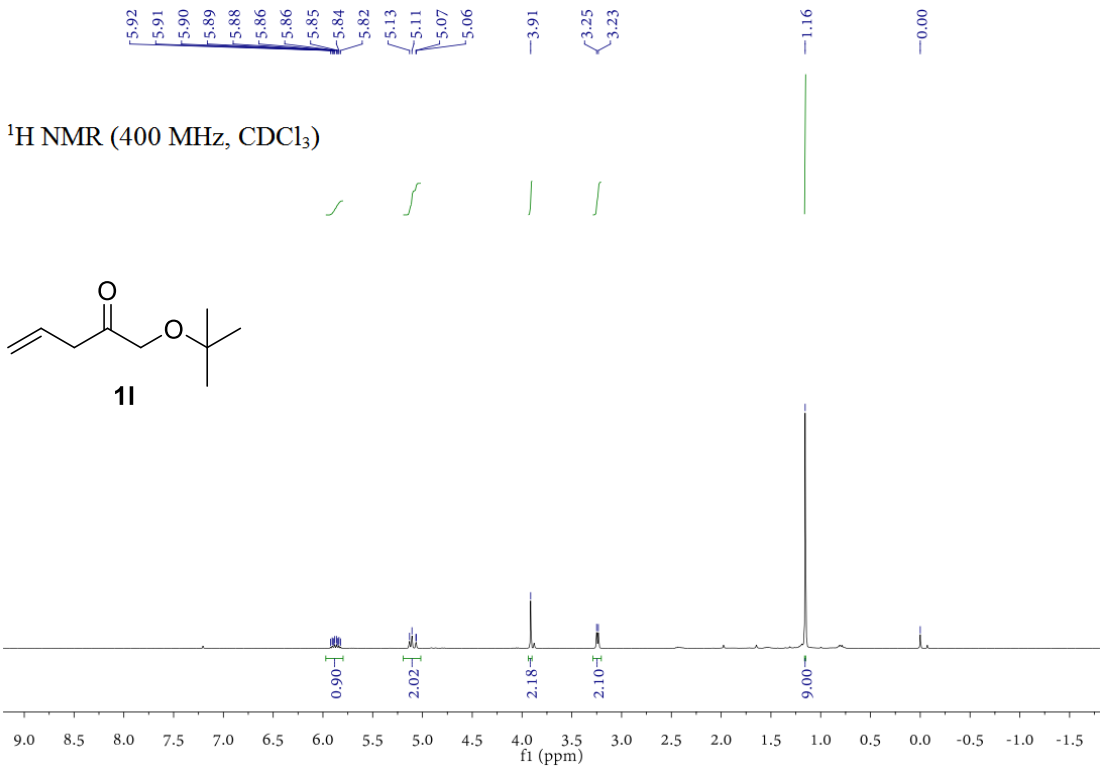
^{1}H NMR (400 MHz, $CDCl_3$)



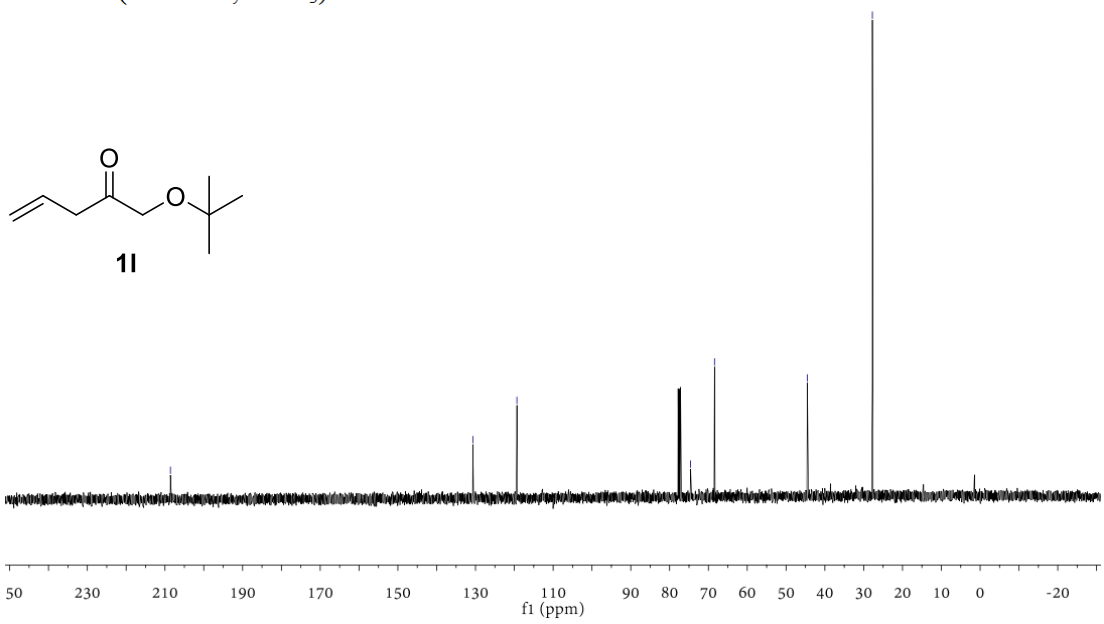
^{13}C NMR (101 MHz, $CDCl_3$)



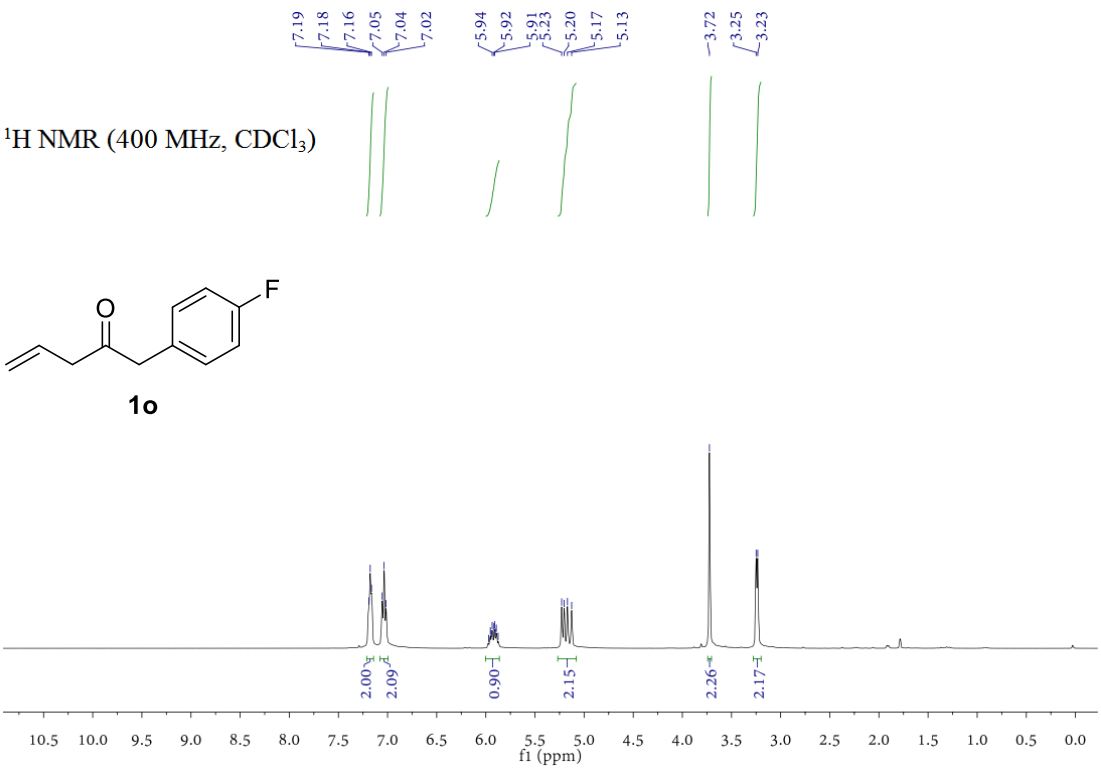
^{1}H NMR (400 MHz, $CDCl_3$)



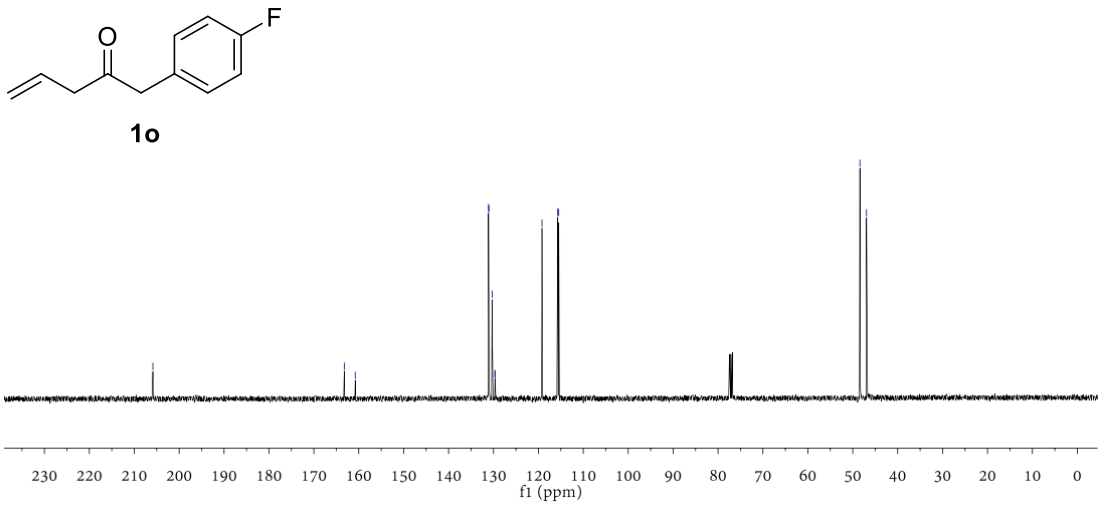
^{13}C NMR (101 MHz, $CDCl_3$)



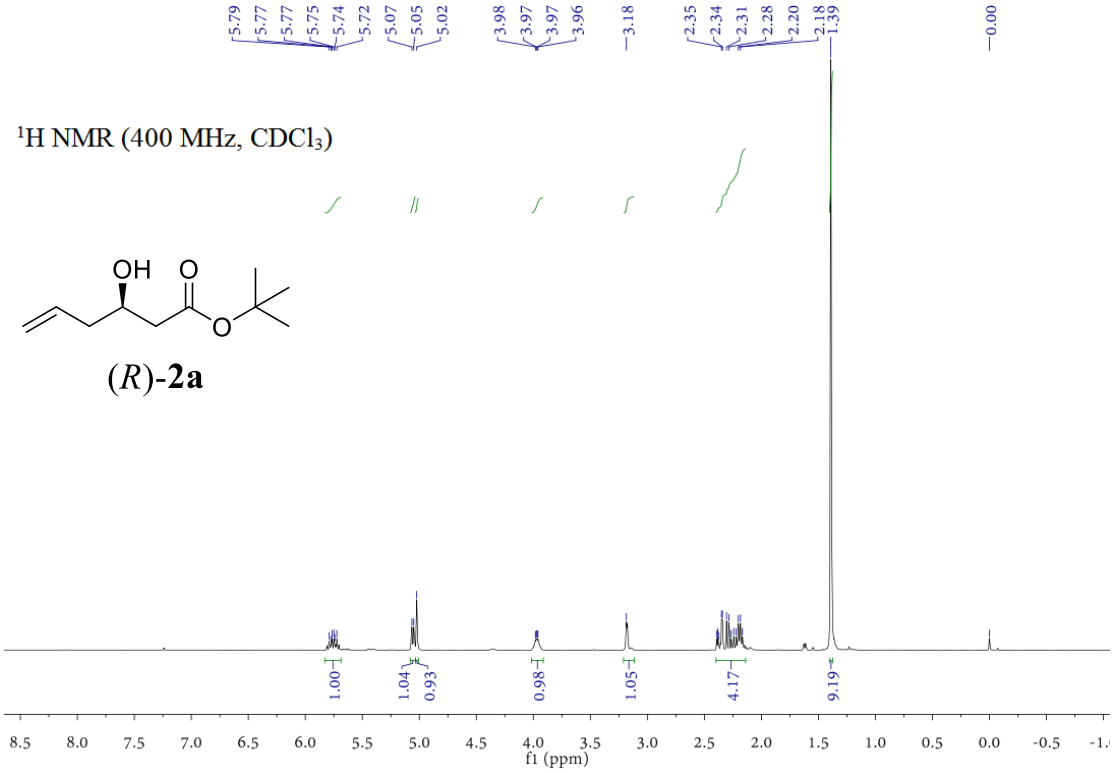
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

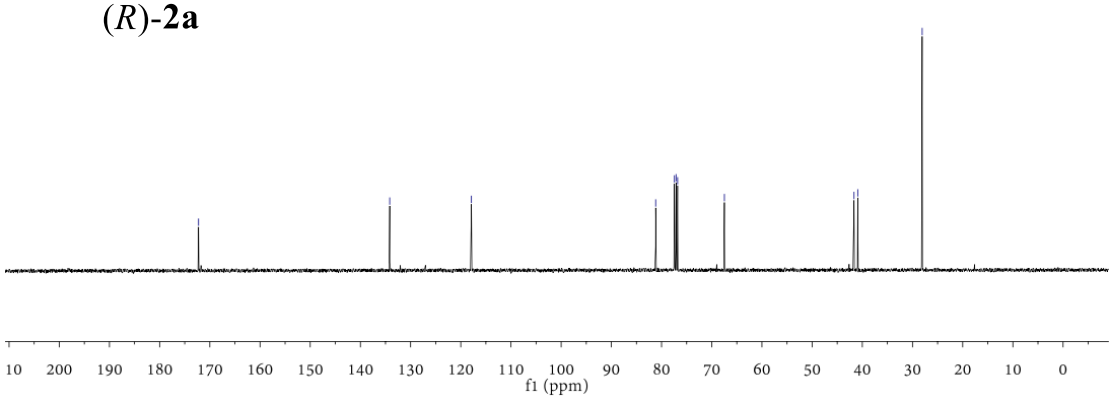


^{1}H NMR (400 MHz, $CDCl_3$)



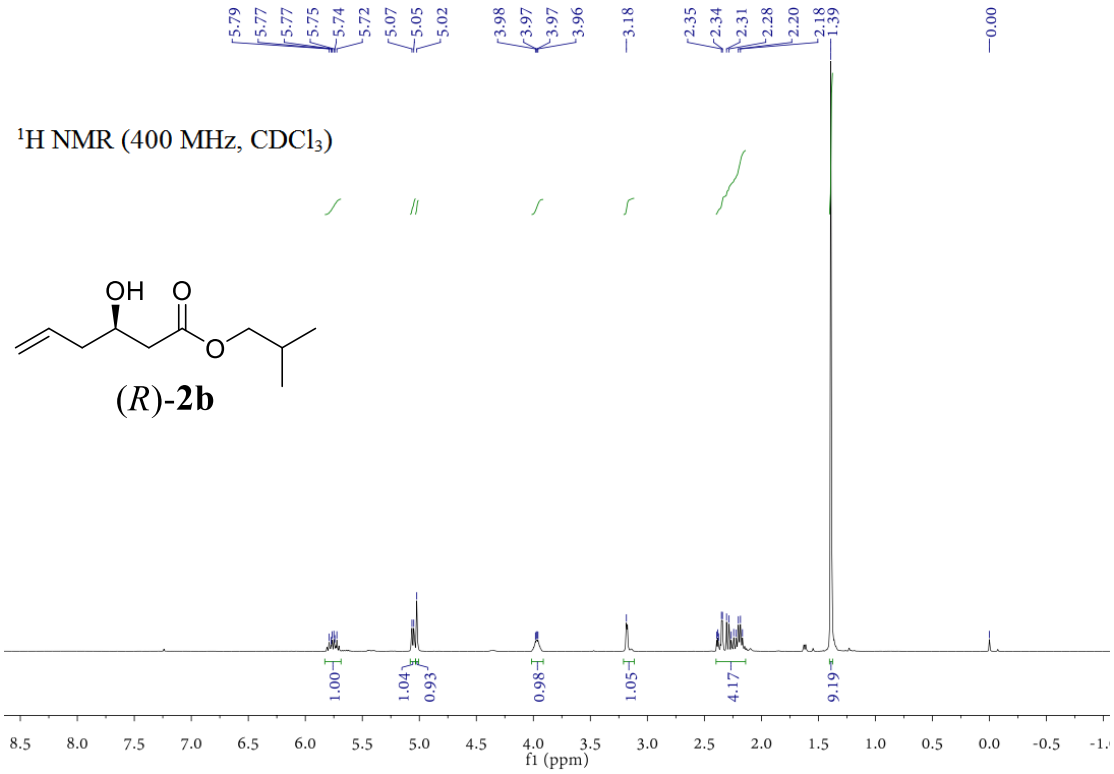
(*R*)-**2a**

^{13}C NMR (101 MHz, $CDCl_3$)

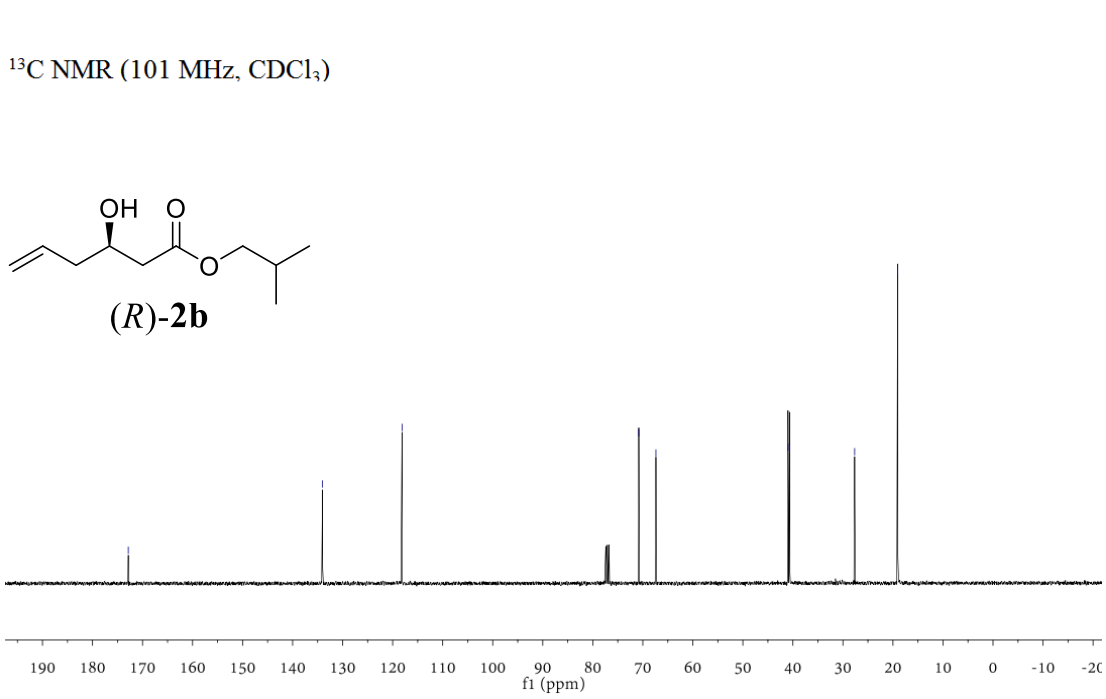


(*R*)-**2a**

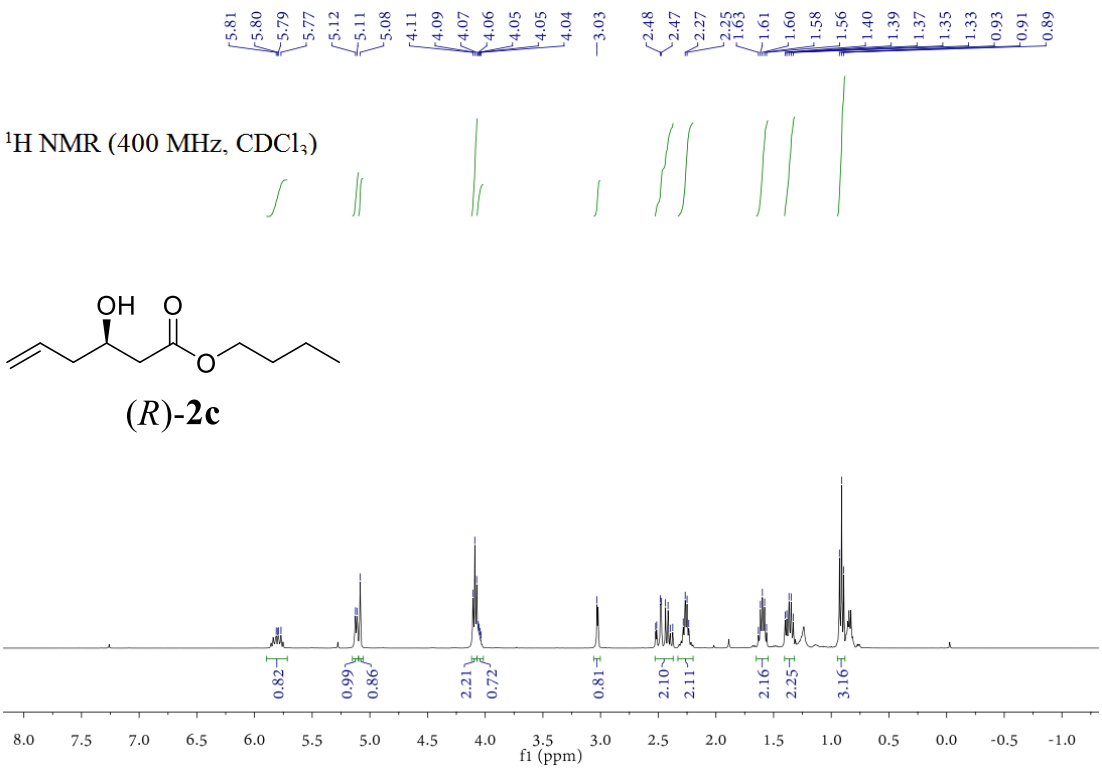
^{1}H NMR (400 MHz, $CDCl_3$)



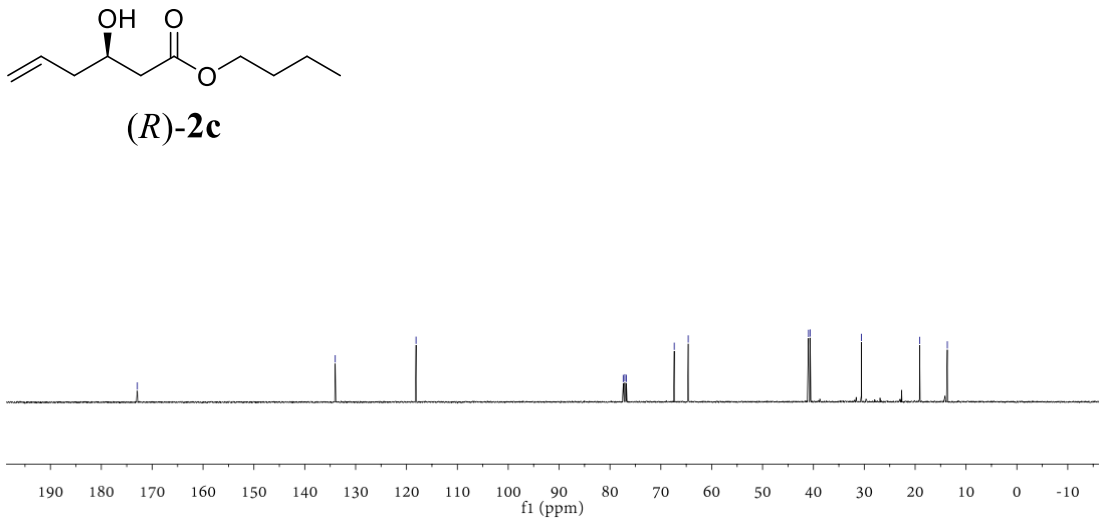
^{13}C NMR (101 MHz, $CDCl_3$)

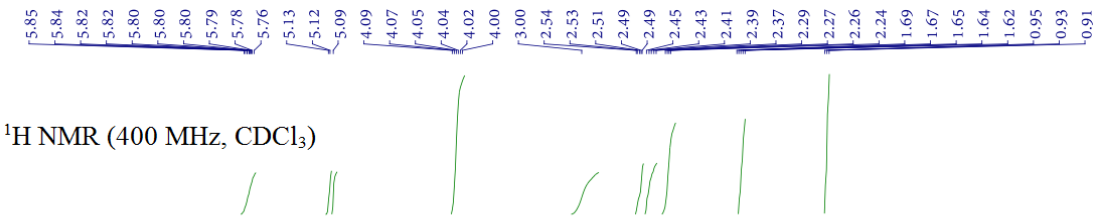


^{1}H NMR (400 MHz, $CDCl_3$)

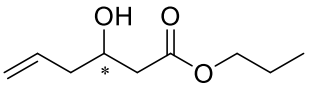


^{13}C NMR (101 MHz, $CDCl_3$)

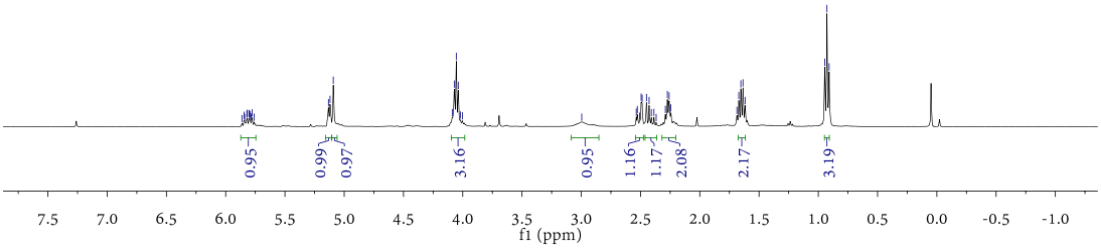




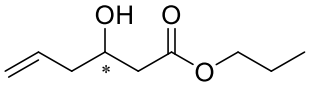
^{1}H NMR (400 MHz, $CDCl_3$)



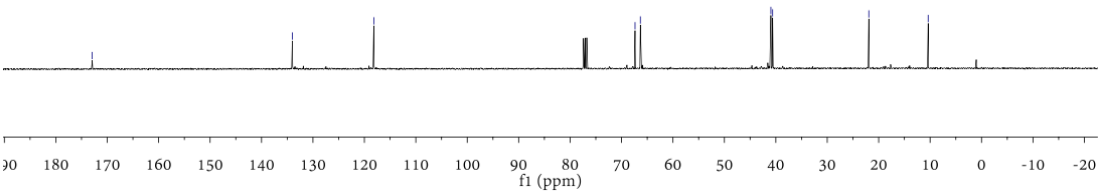
Enantioenriched-**2d**



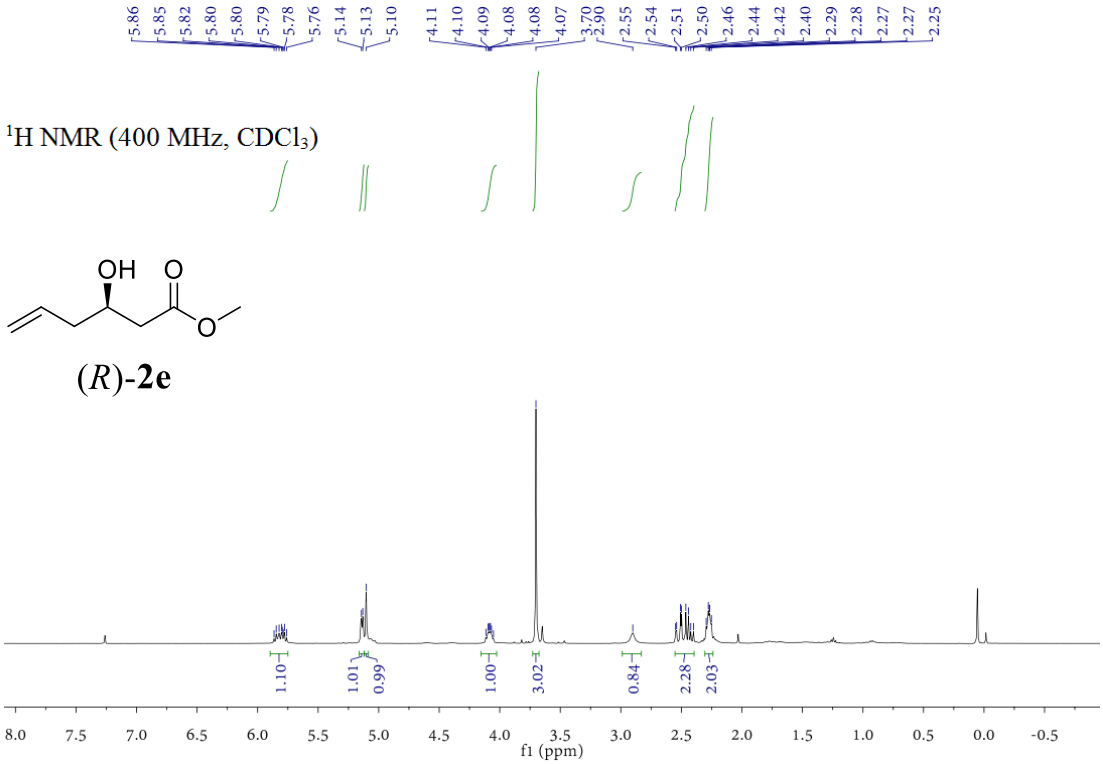
^{13}C NMR (101 MHz, $CDCl_3$)



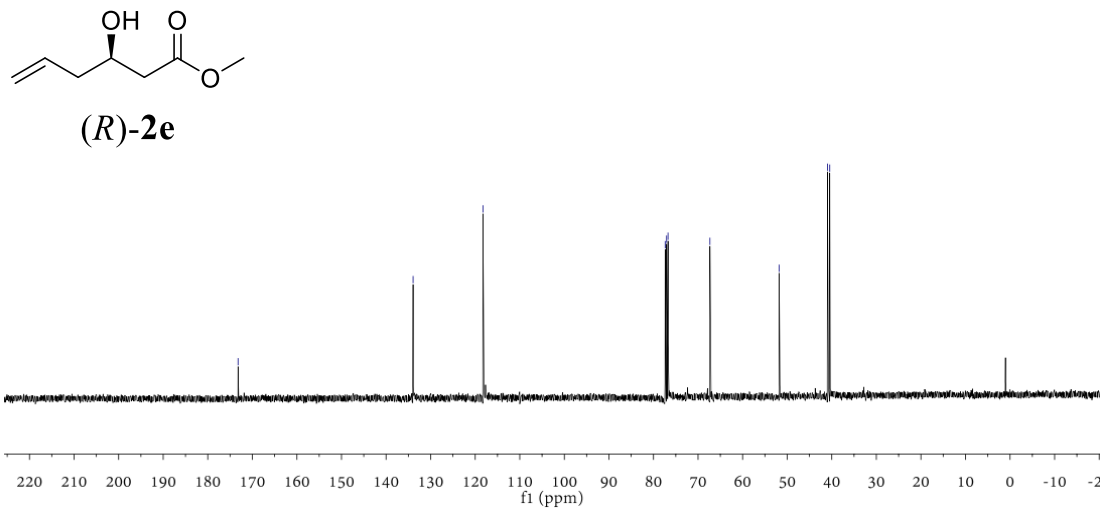
Enantioenriched-**2d**



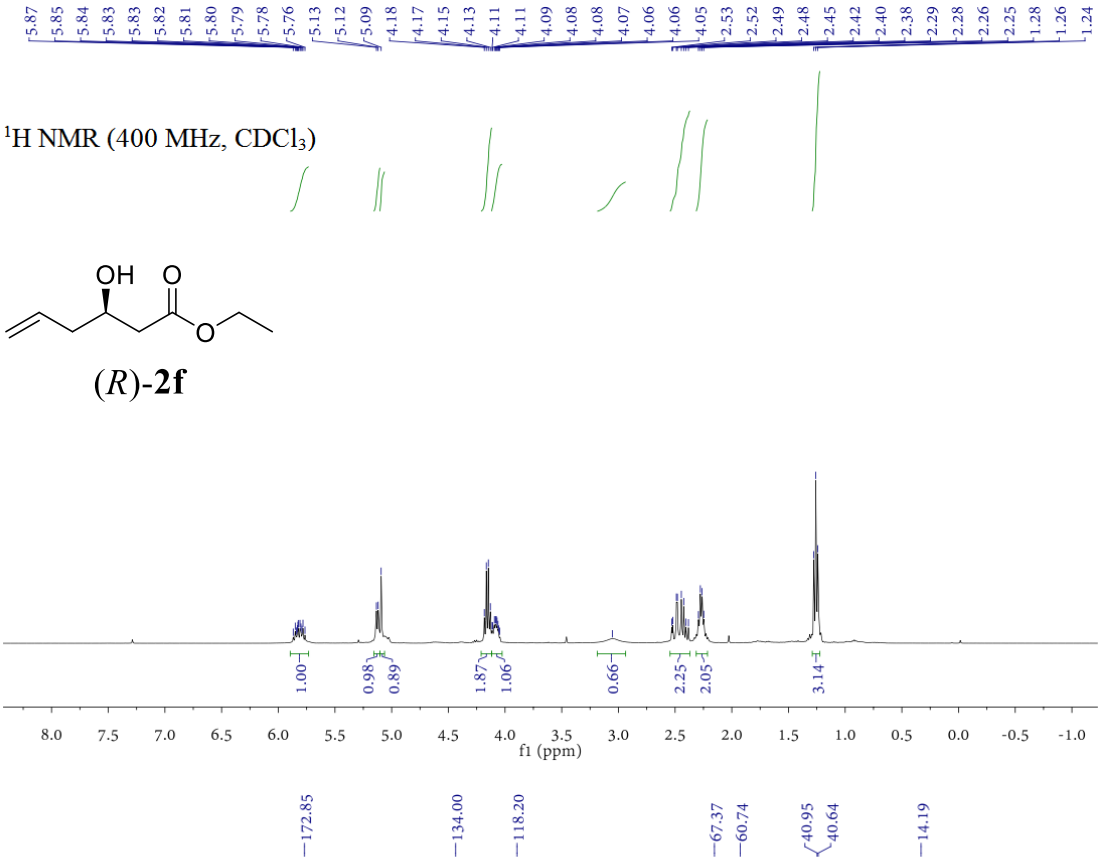
^{1}H NMR (400 MHz, $CDCl_3$)



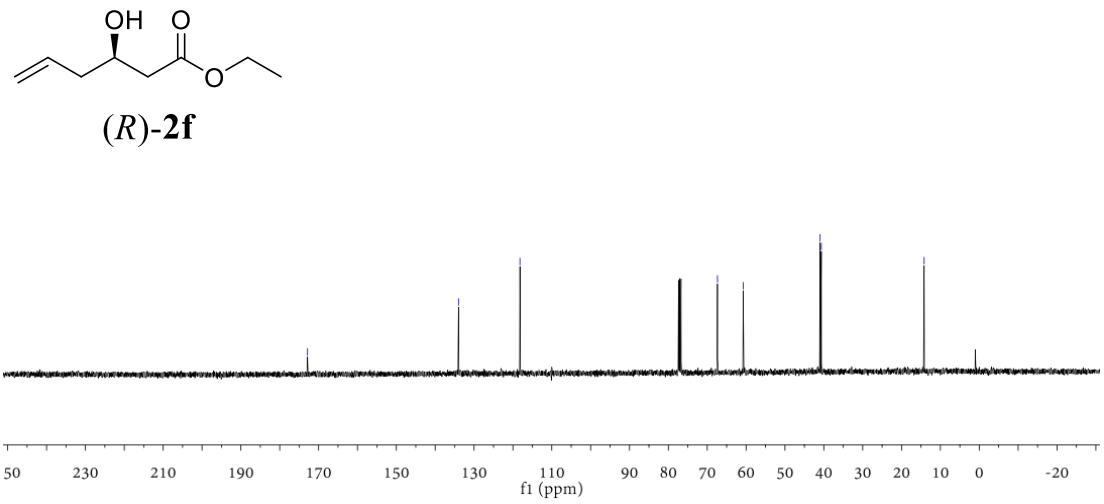
^{13}C NMR (101 MHz, $CDCl_3$)

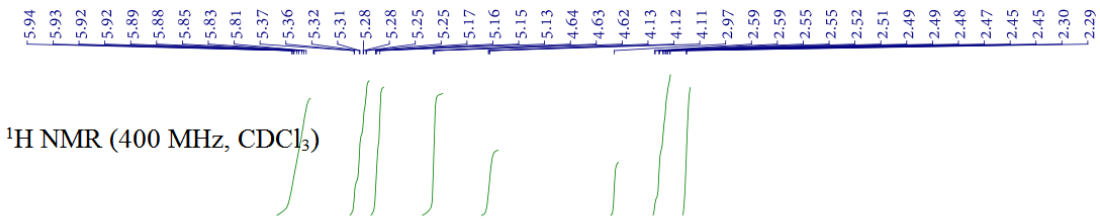


^{1}H NMR (400 MHz, $CDCl_3$)

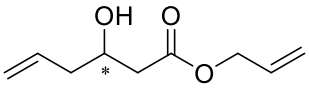


^{13}C NMR (101 MHz, $CDCl_3$)

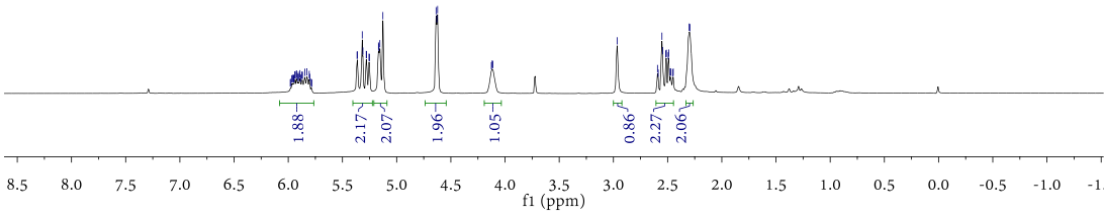




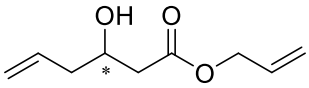
^{1}H NMR (400 MHz, $CDCl_3$)



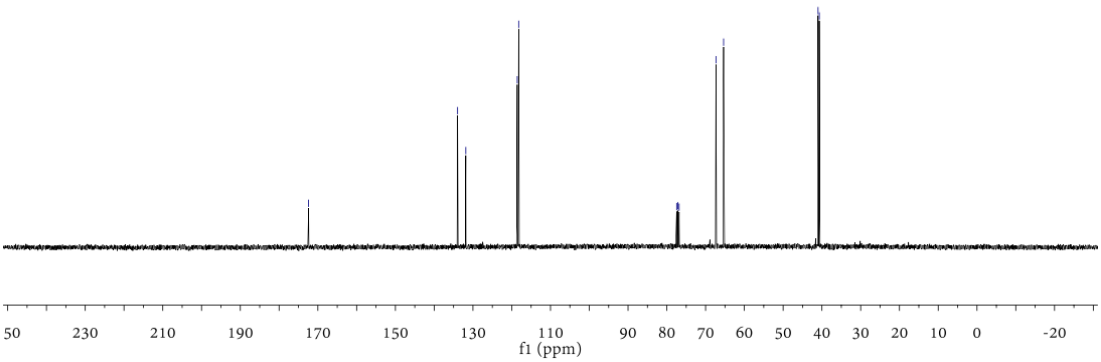
Enantioenriched-**2g**



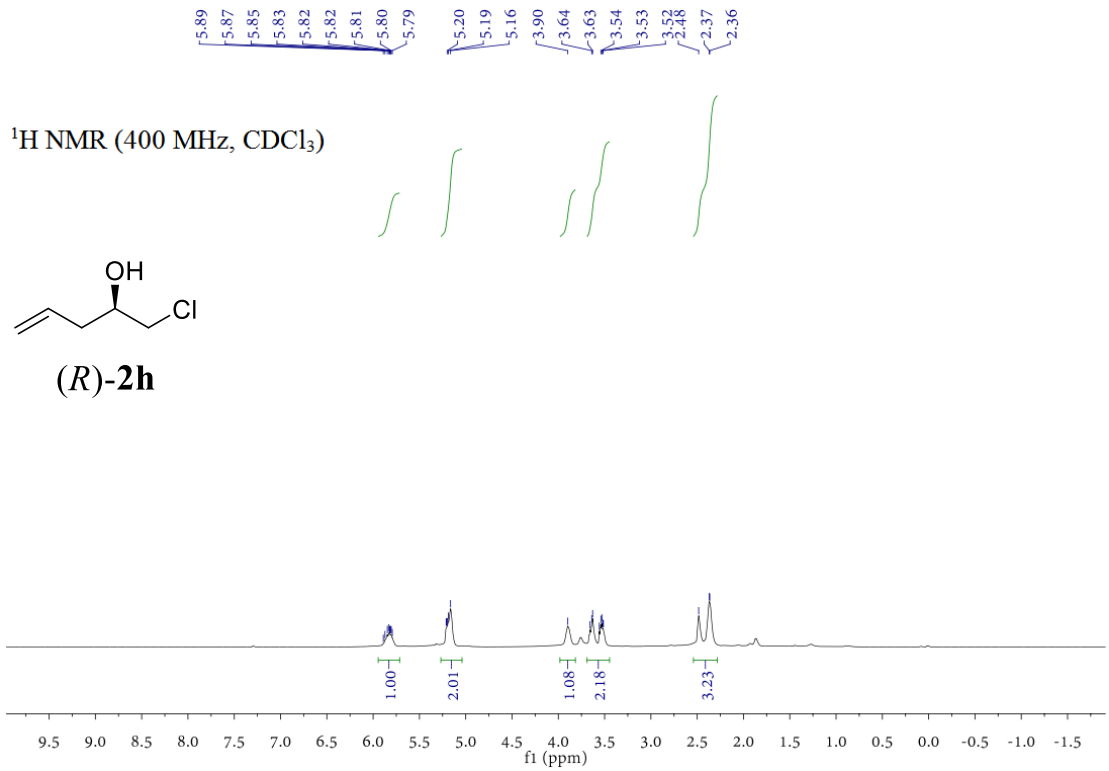
^{13}C NMR (101 MHz, $CDCl_3$)



Enantioenriched-**2g**

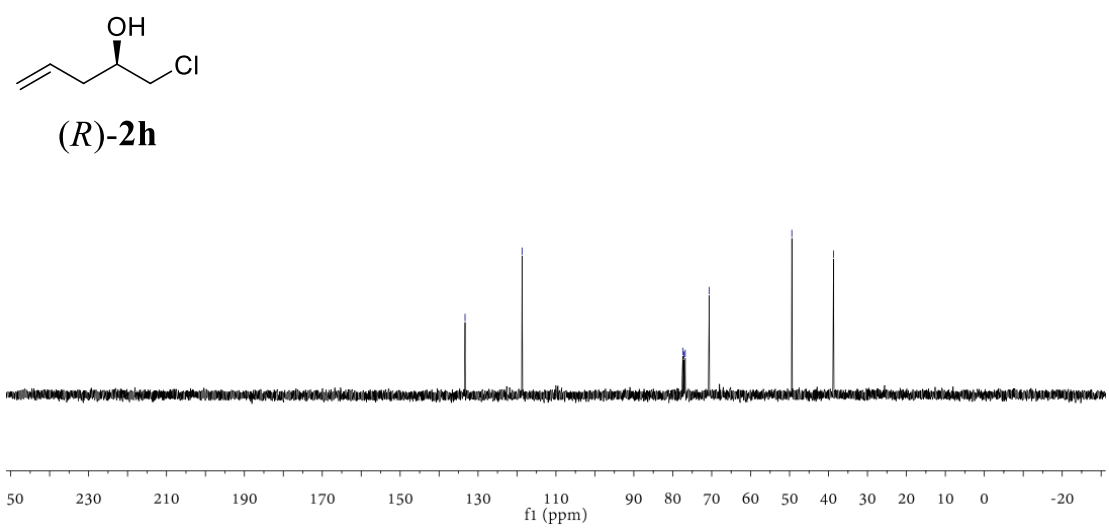


^{1}H NMR (400 MHz, $CDCl_3$)



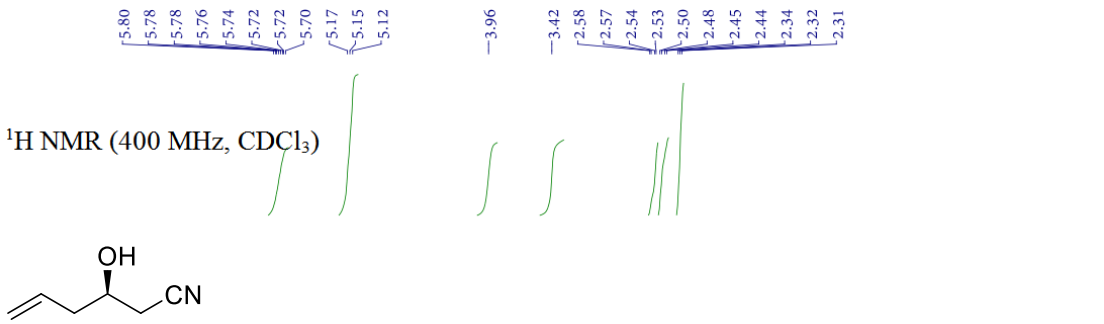
(*R*)-**2h**

^{13}C NMR (101 MHz, $CDCl_3$)



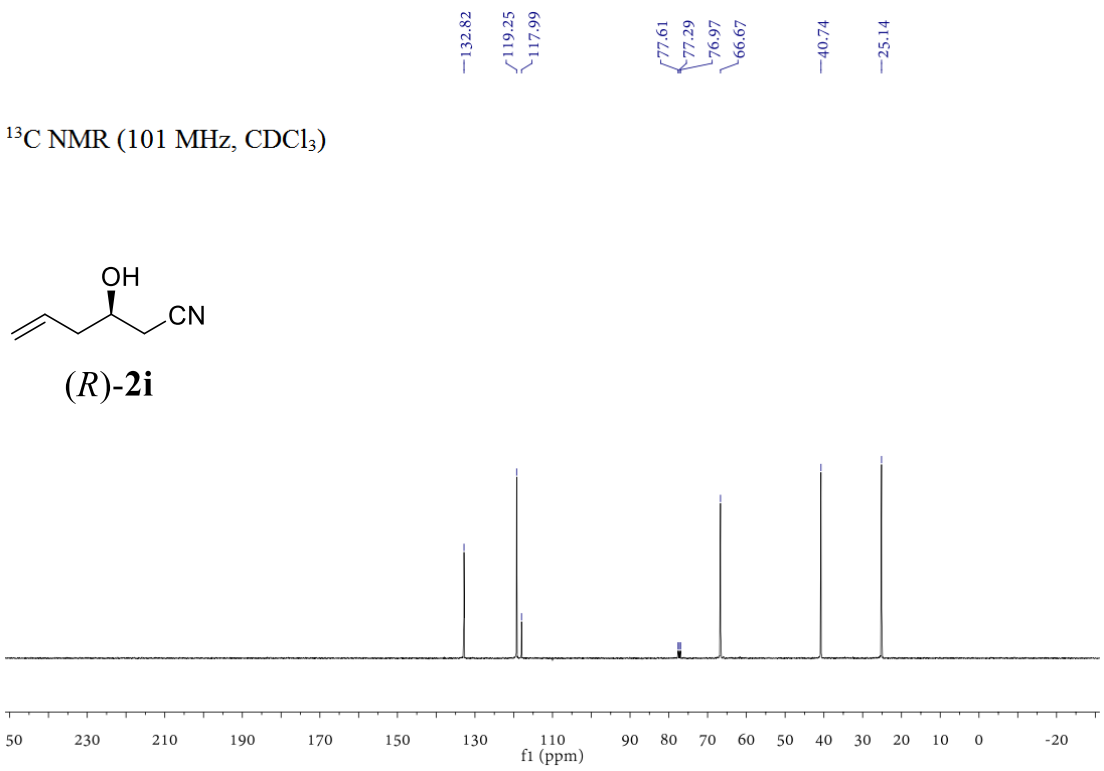
(*R*)-**2h**

^{1}H NMR (400 MHz, $CDCl_3$)



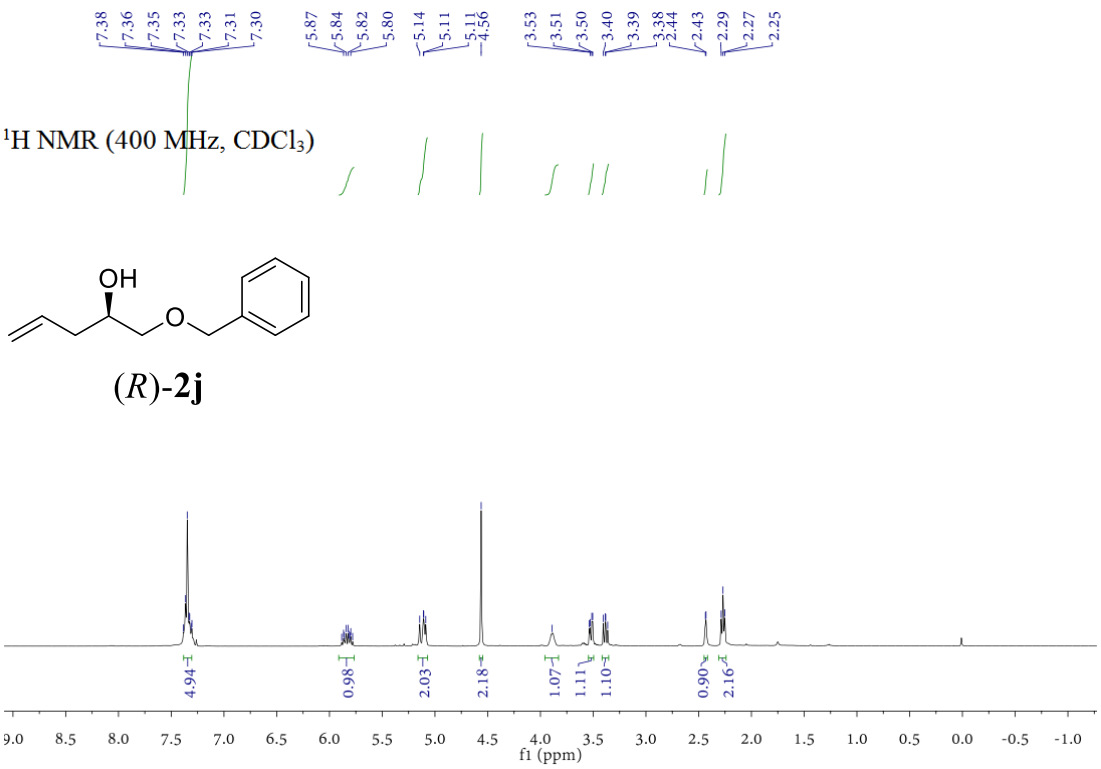
(*R*)-**2i**

^{13}C NMR (101 MHz, $CDCl_3$)



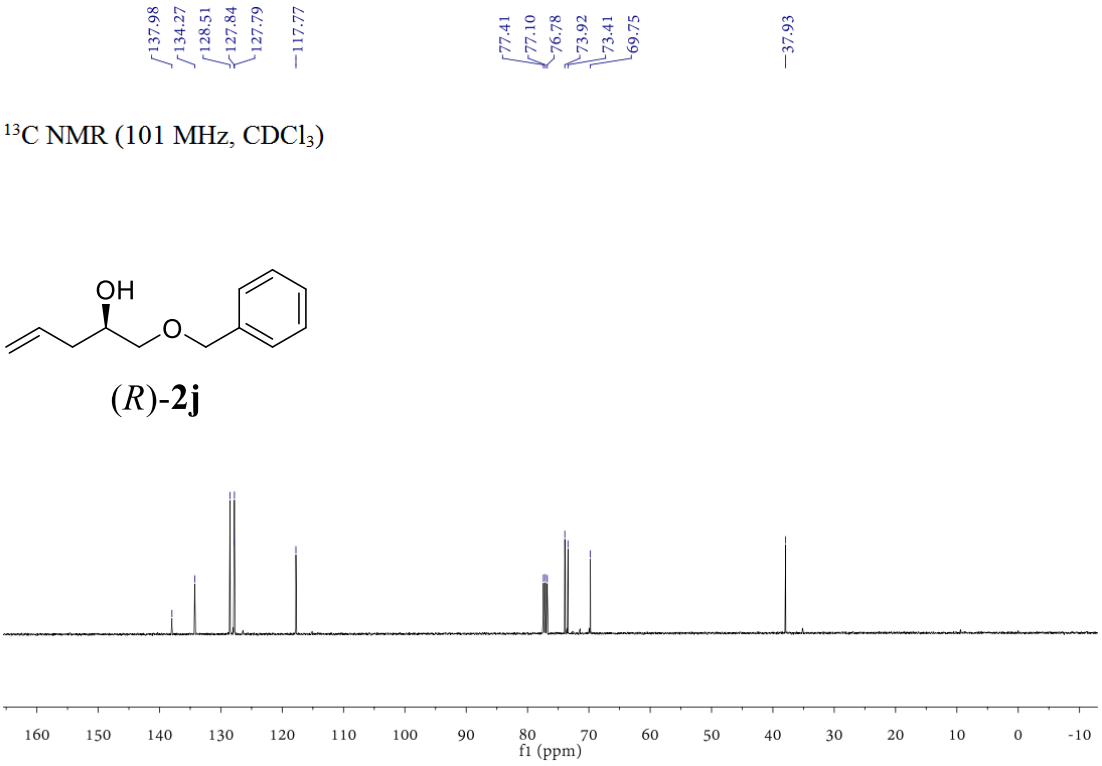
(*R*)-**2i**

^{1}H NMR (400 MHz, $CDCl_3$)



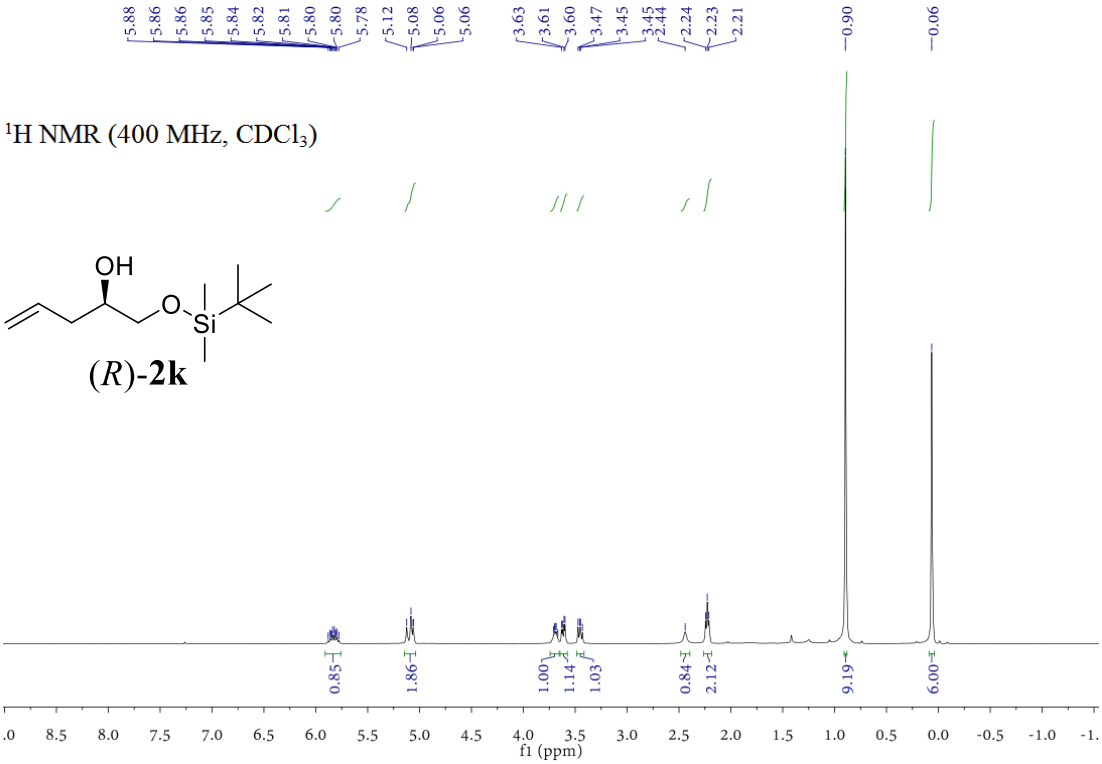
(*R*)-**2j**

^{13}C NMR (101 MHz, $CDCl_3$)

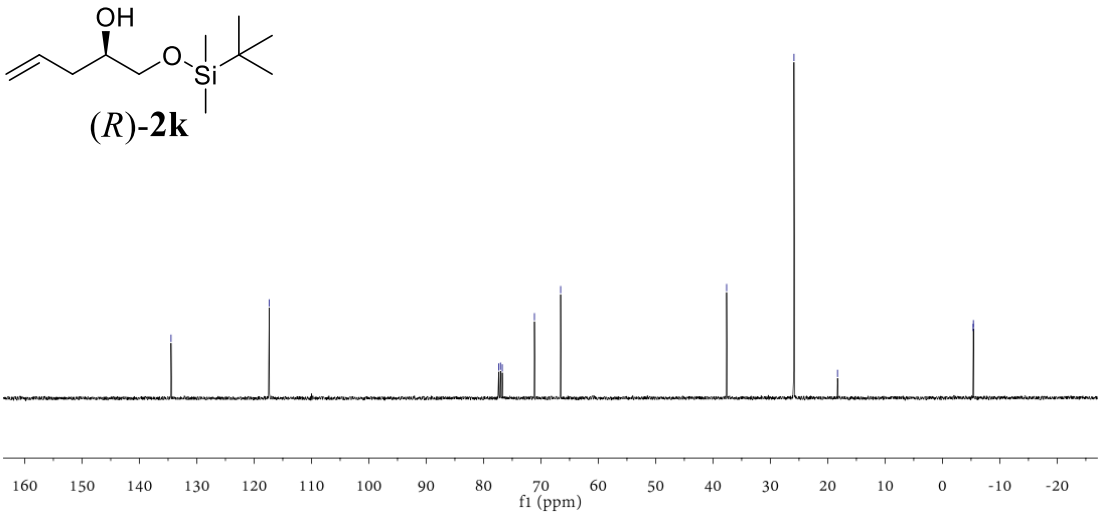


(*R*)-**2j**

^{1}H NMR (400 MHz, $CDCl_3$)

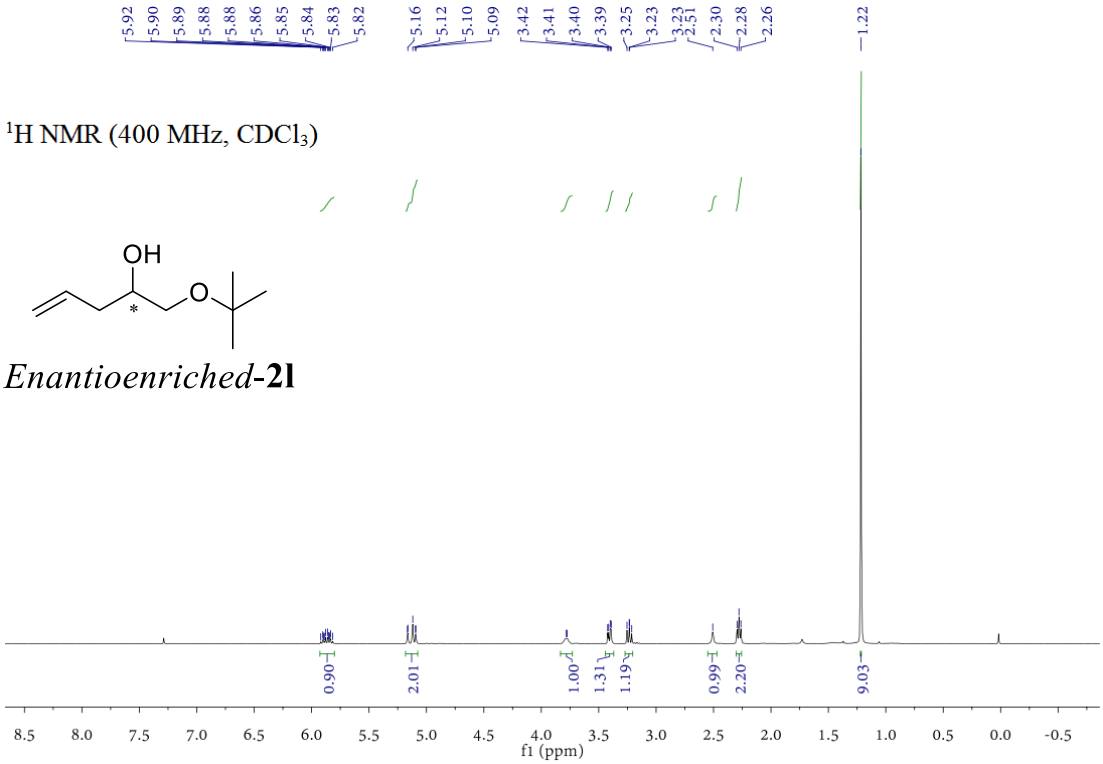


^{13}C NMR (101 MHz, $CDCl_3$)



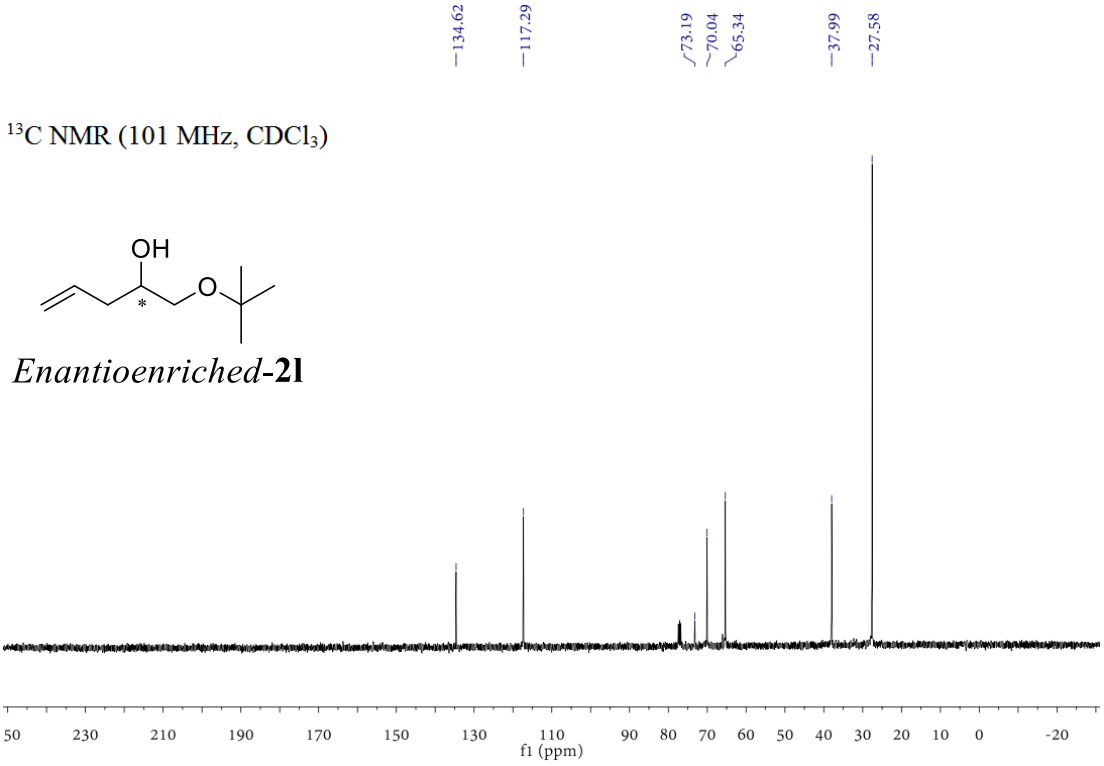
^{1}H NMR (400 MHz, $CDCl_3$)

Enantioenriched-**21**

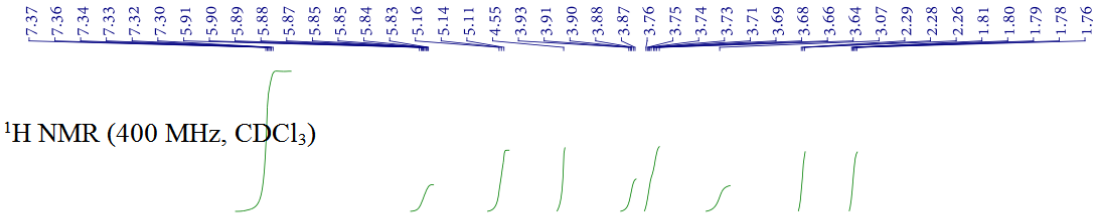


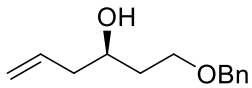
^{13}C NMR (101 MHz, $CDCl_3$)

Enantioenriched-**21**

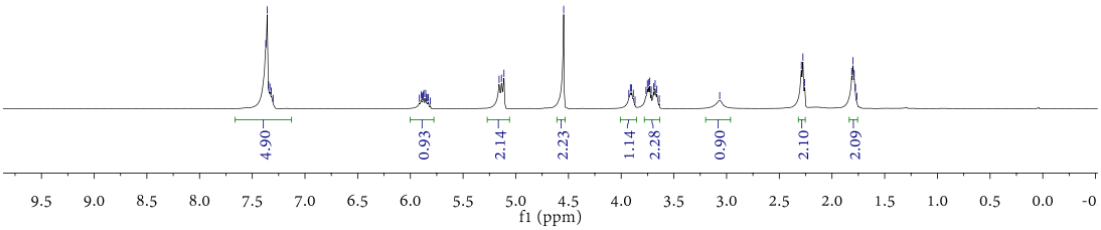


^{1}H NMR (400 MHz, $CDCl_3$)

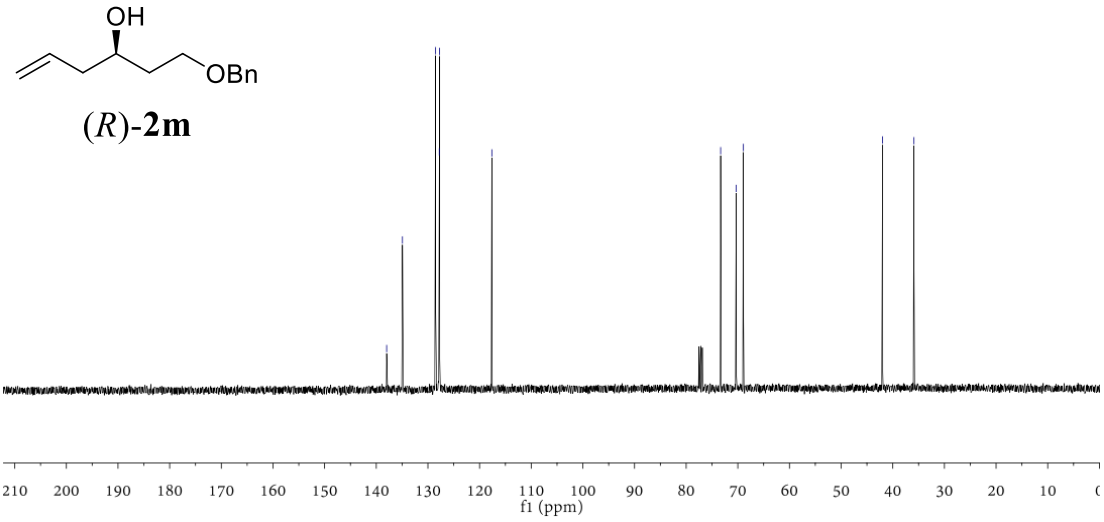




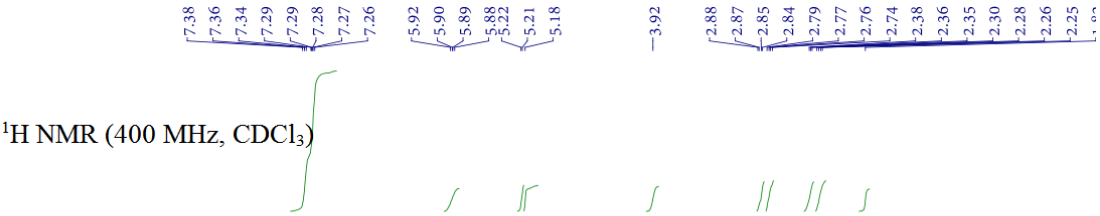
(*R*)-**2m**

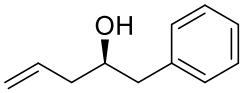


^{13}C NMR (101 MHz, $CDCl_3$)

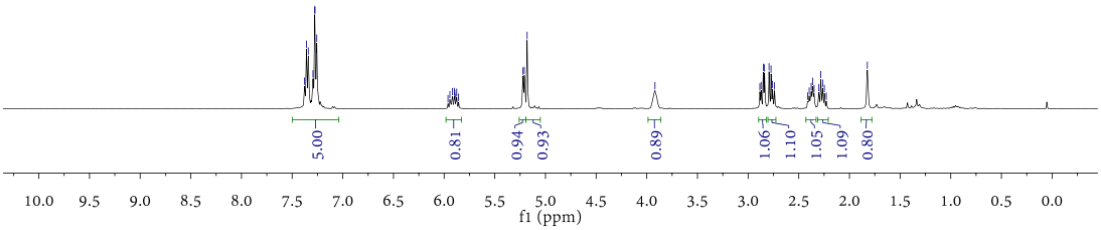


^{1}H NMR (400 MHz, $CDCl_3$)

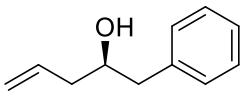




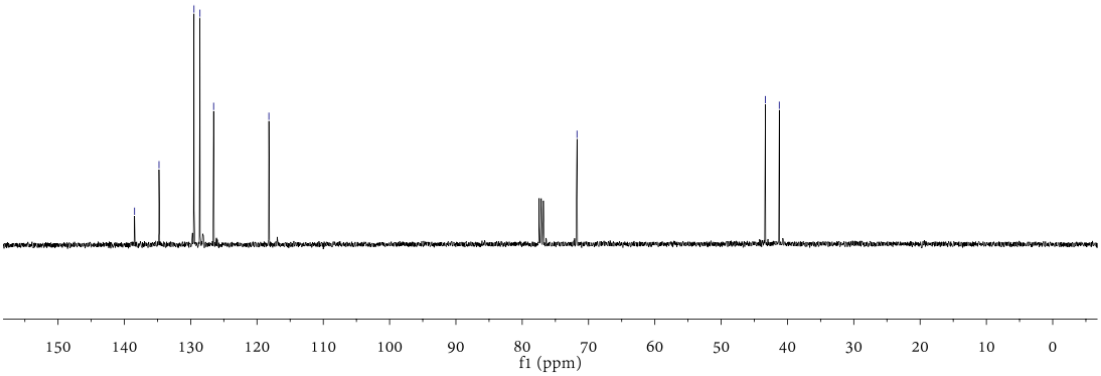
(*R*)-**2n**



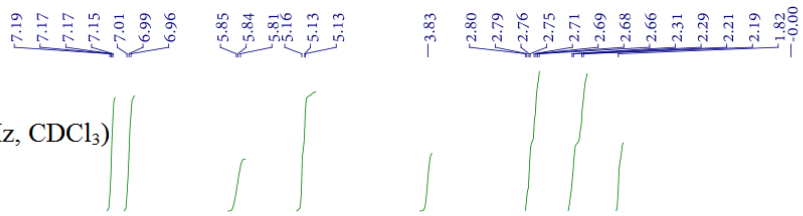
^{13}C NMR (101 MHz, $CDCl_3$)

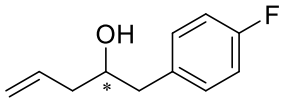


(*R*)-**2n**

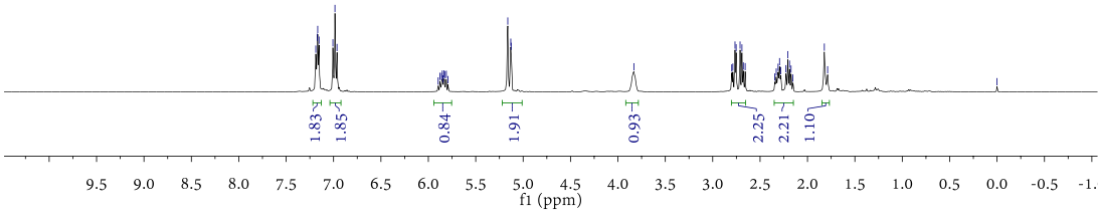


^{1}H NMR (400 MHz, $CDCl_3$)

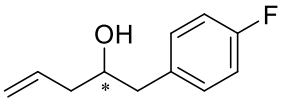




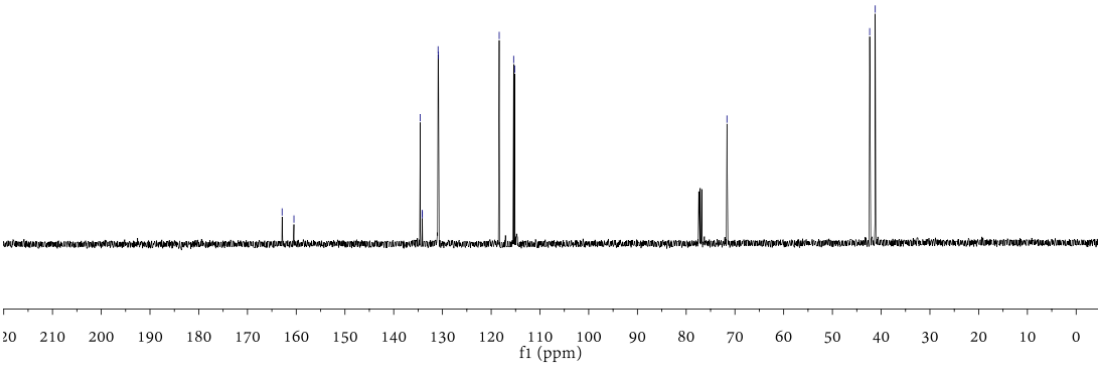
Enantioenriched-**2o**



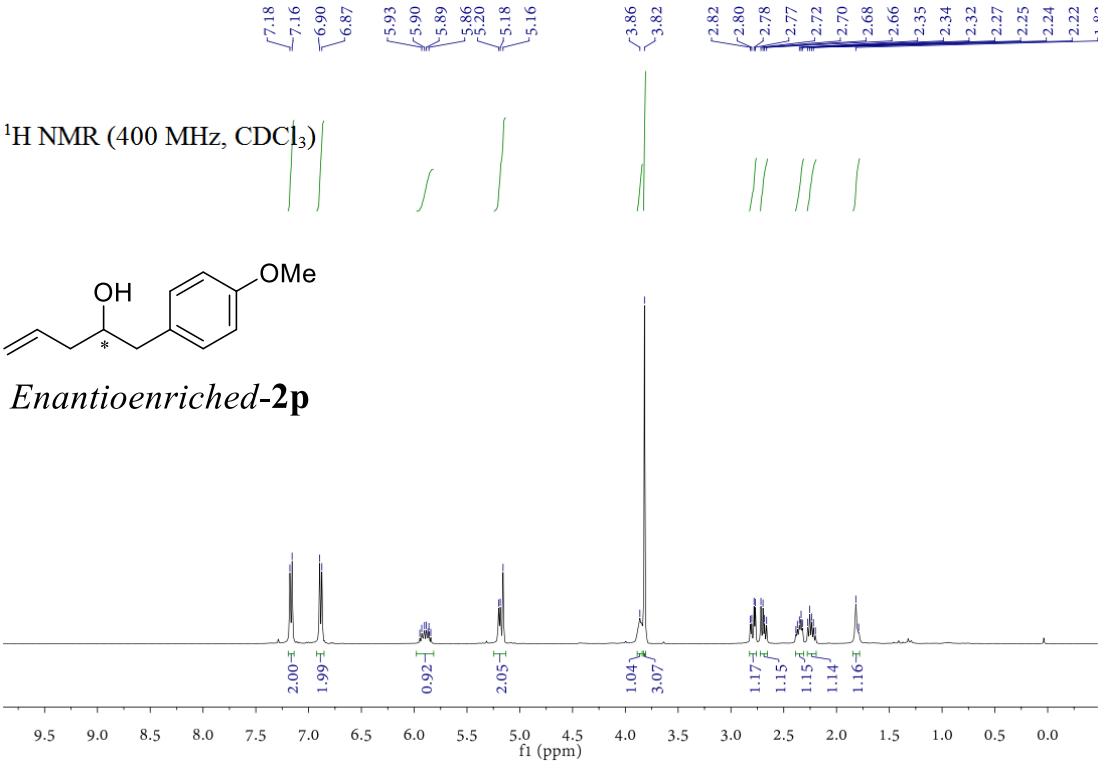
^{13}C NMR (101 MHz, $CDCl_3$)



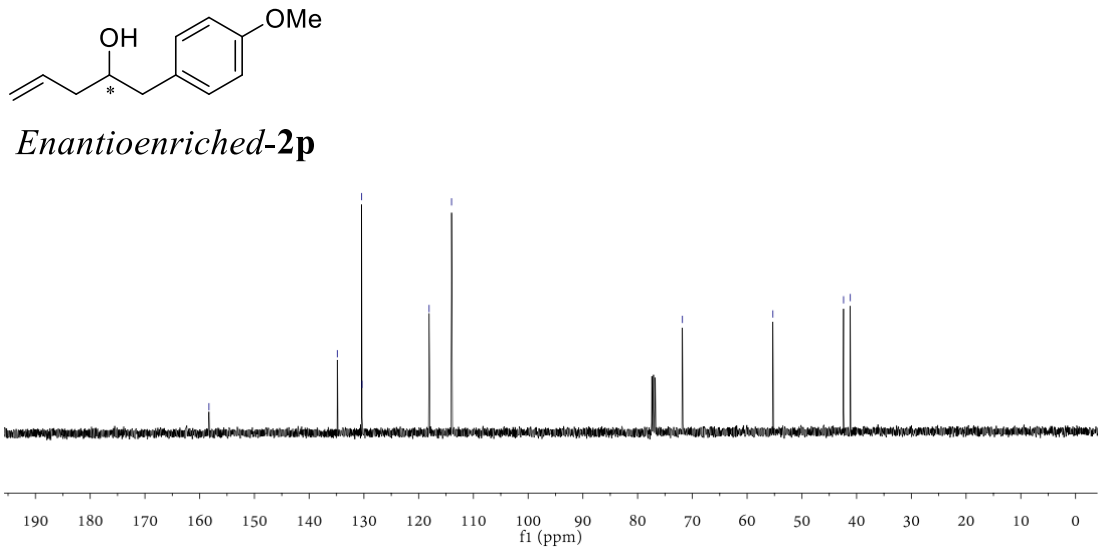
Enantioenriched-**2o**



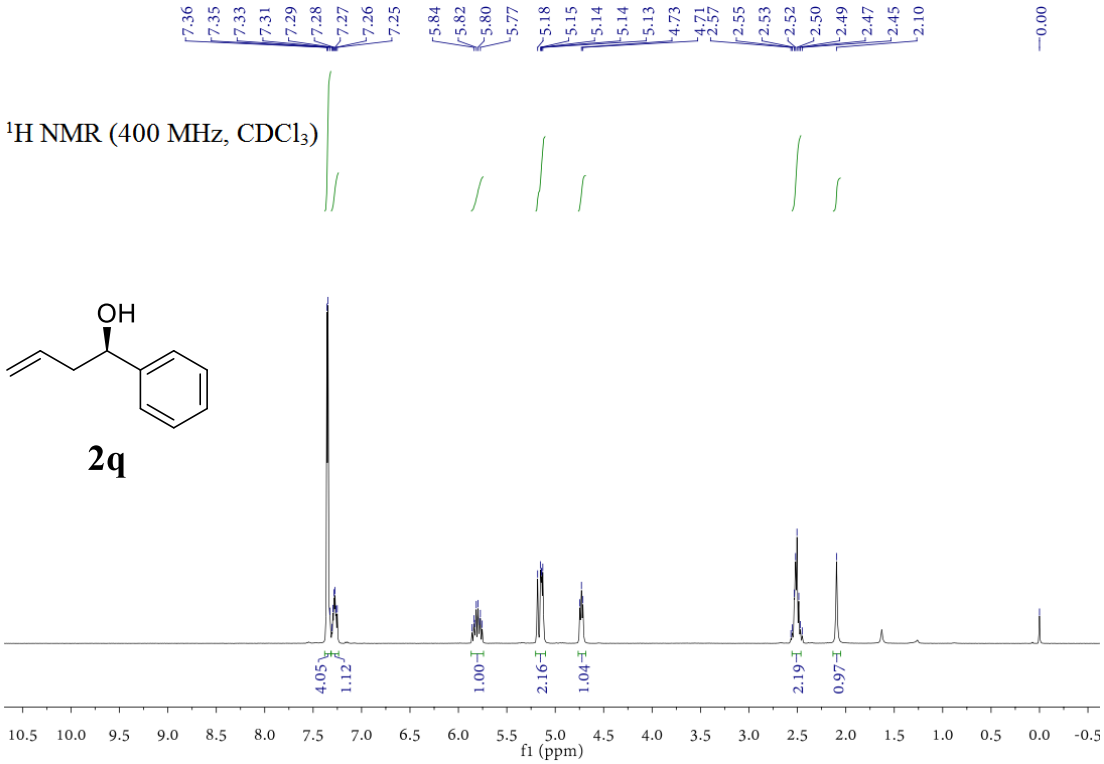
^{1}H NMR (400 MHz, $CDCl_3$)



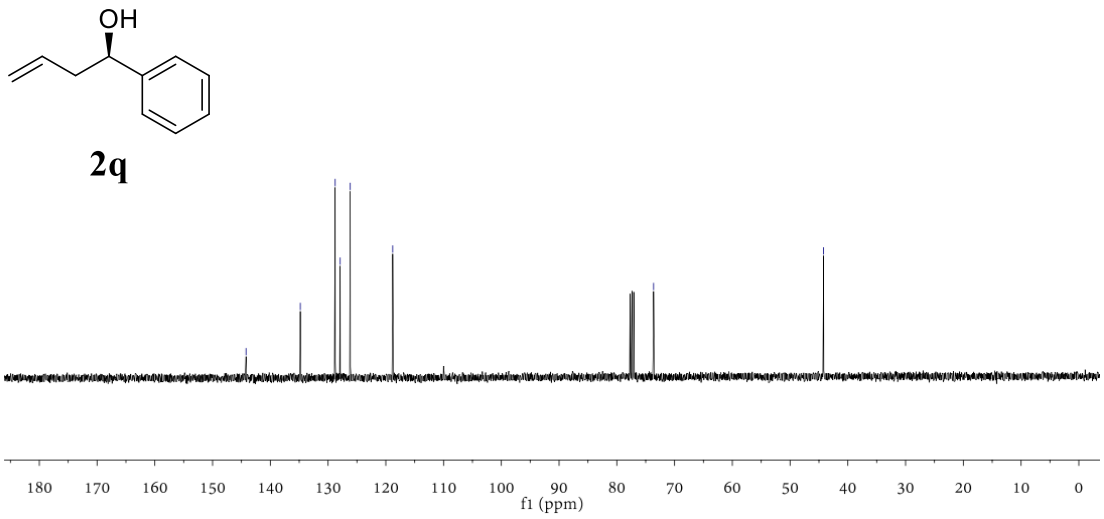
^{13}C NMR (101 MHz, $CDCl_3$)



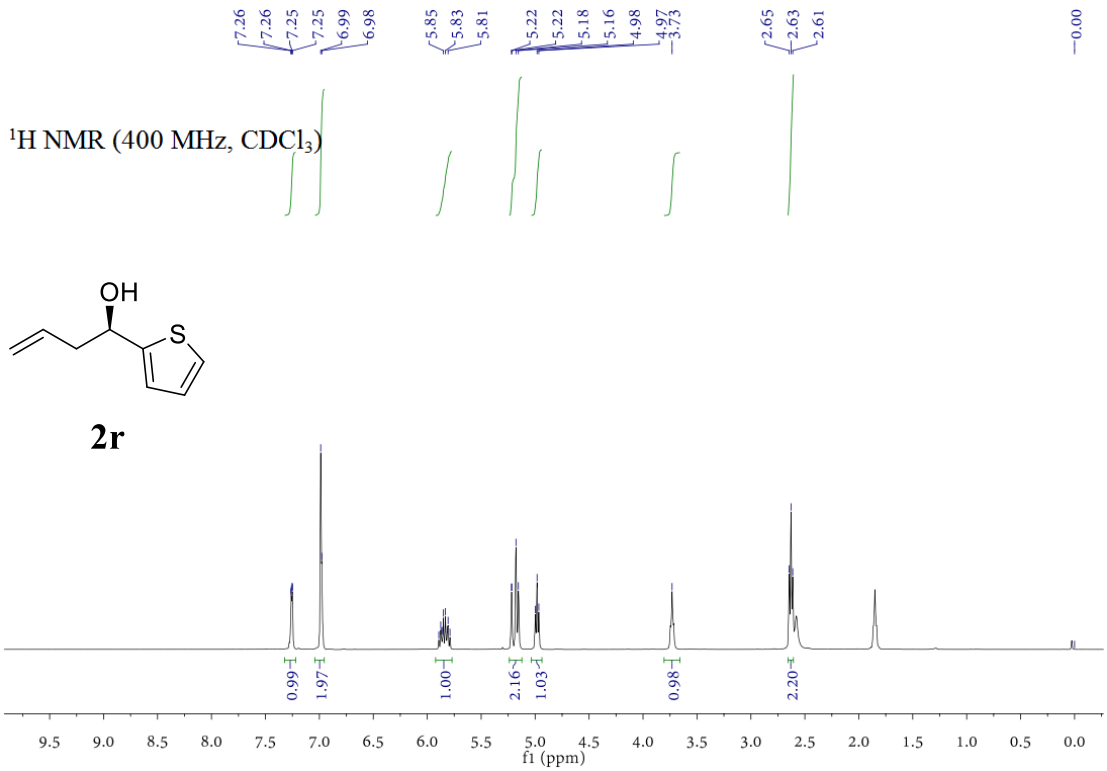
^{1}H NMR (400 MHz, $CDCl_3$)



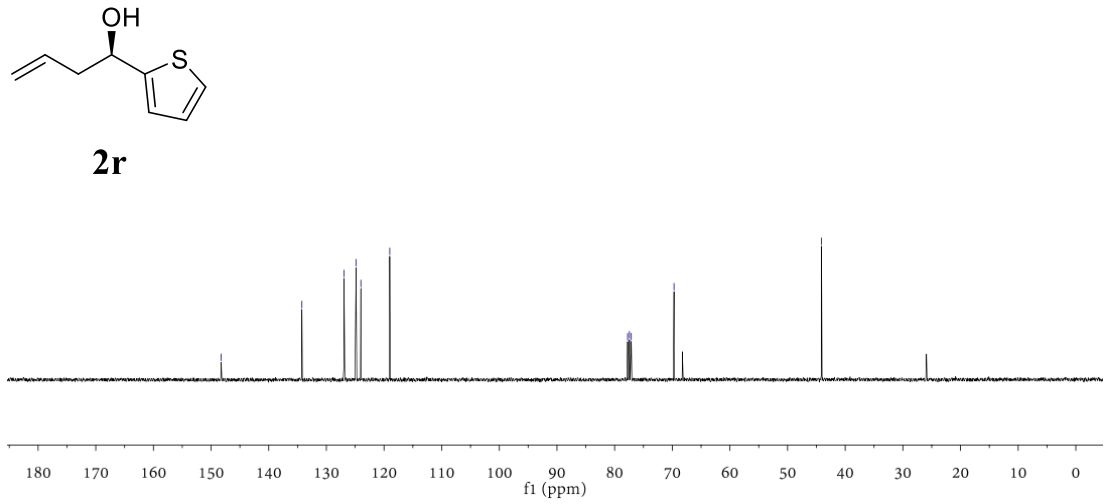
^{13}C NMR (101 MHz, $CDCl_3$)

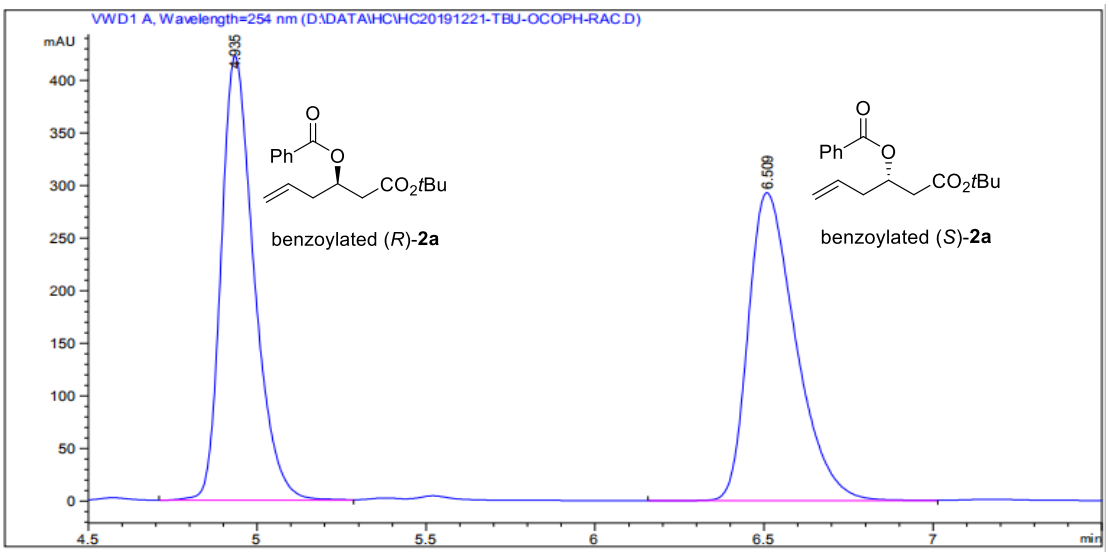


^{1}H NMR (400 MHz, $CDCl_3$)

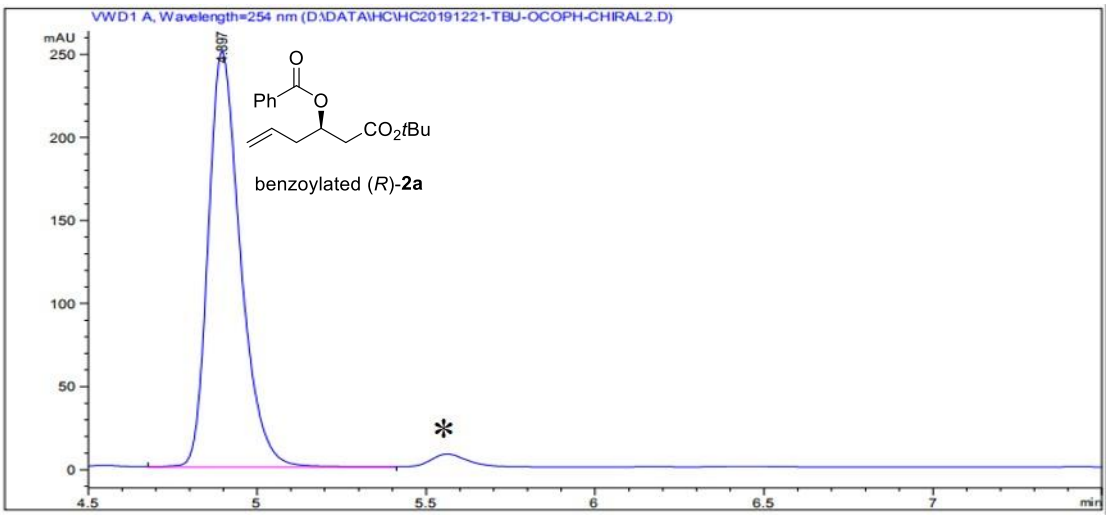


^{13}C NMR (101 MHz, $CDCl_3$)





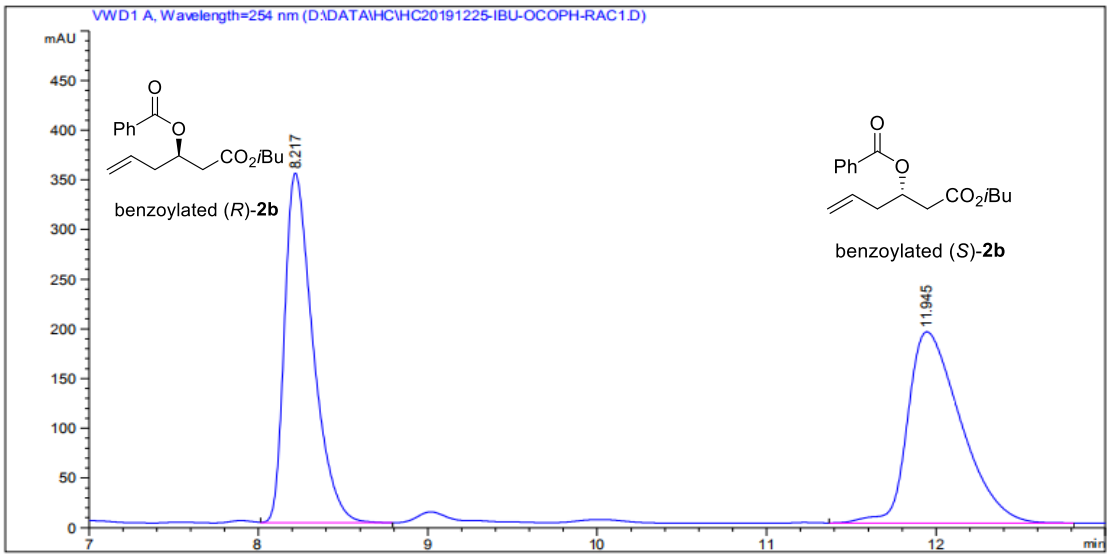
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.935	BV	0.1030	2862.27783	422.55313	50.0276
2	6.509	BV	0.1499	2859.11572	292.84491	49.9724



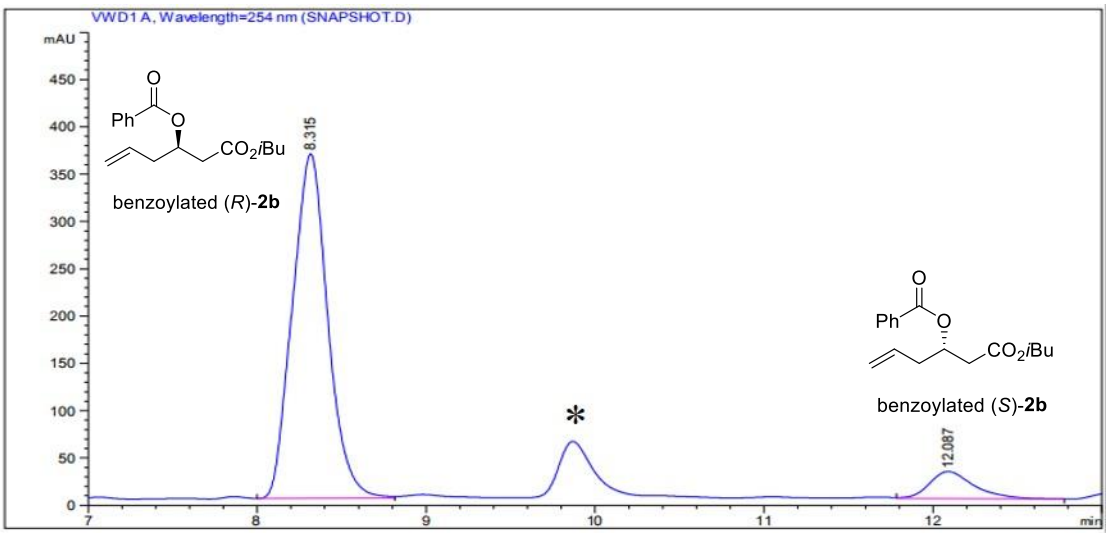
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.897	VV	0.1015	1660.32776	250.07681	100.0000

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

***Peak labeled with asterisk is impurity generated in the bioreduction or derivatization.**



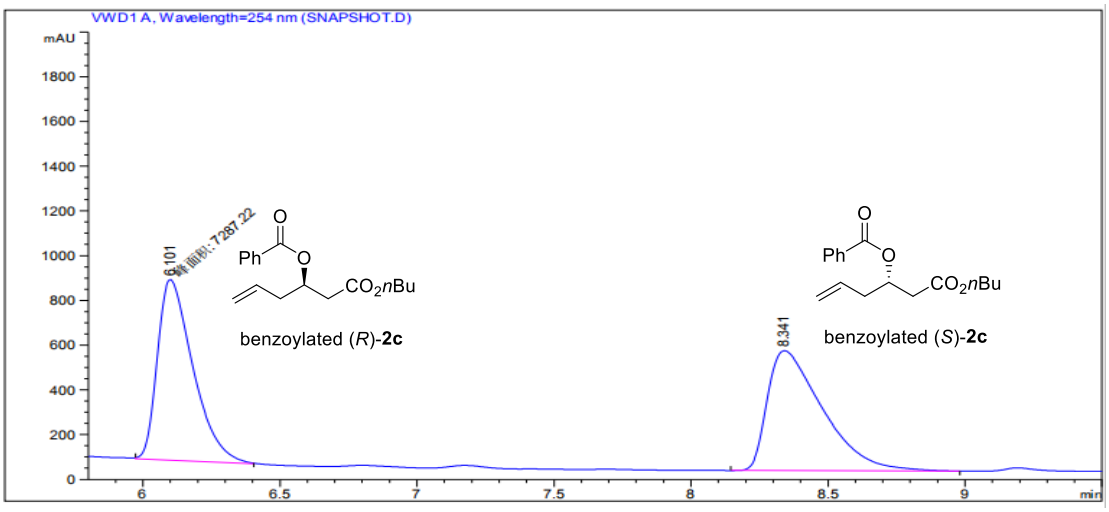
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.217	VB	0.1769	4100.83496	351.96143	49.5021
2	11.945	VB	0.3356	4183.33447	192.47890	50.4979



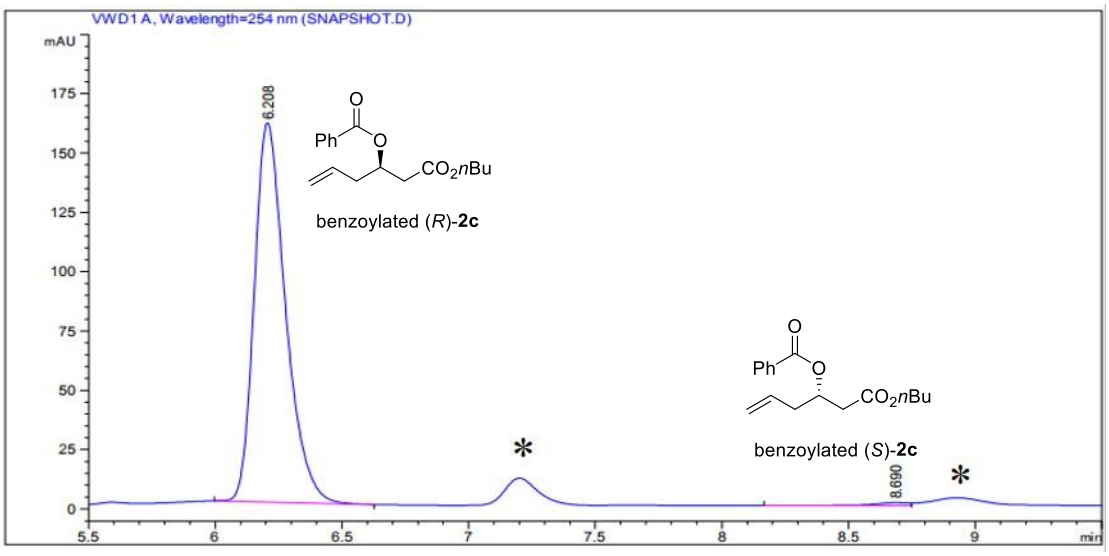
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.315	BV	0.2160	5308.48242	364.28256	91.0922
2	12.087	VB	0.2745	519.11334	28.50135	8.9078

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

***Peak labeled with asterisk is impurity generated in the bioreduction or derivatization.**



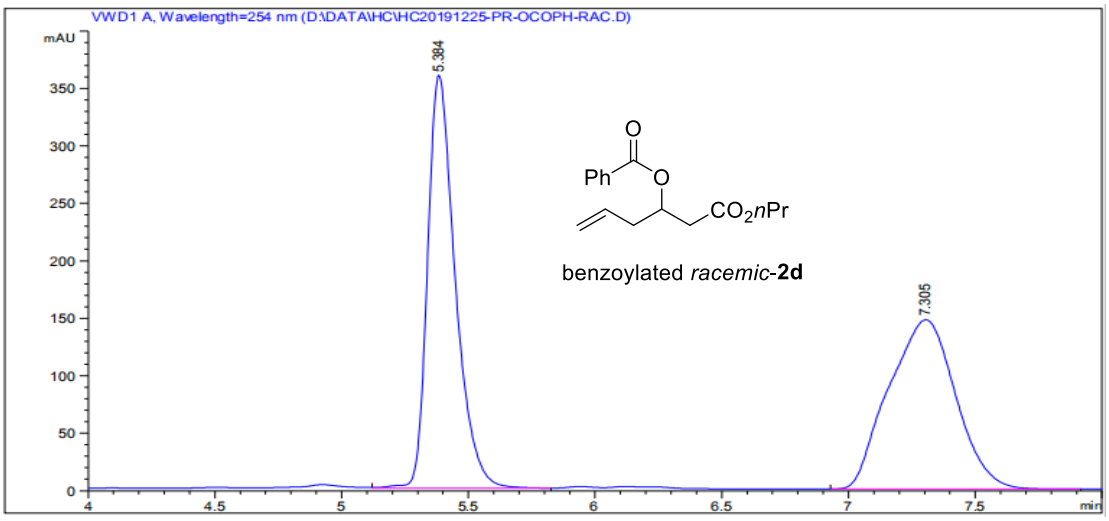
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.101	MM	0.1504	7287.21533	807.34143	49.3114
2	8.341	BB	0.2110	7490.73877	536.11902	50.6886



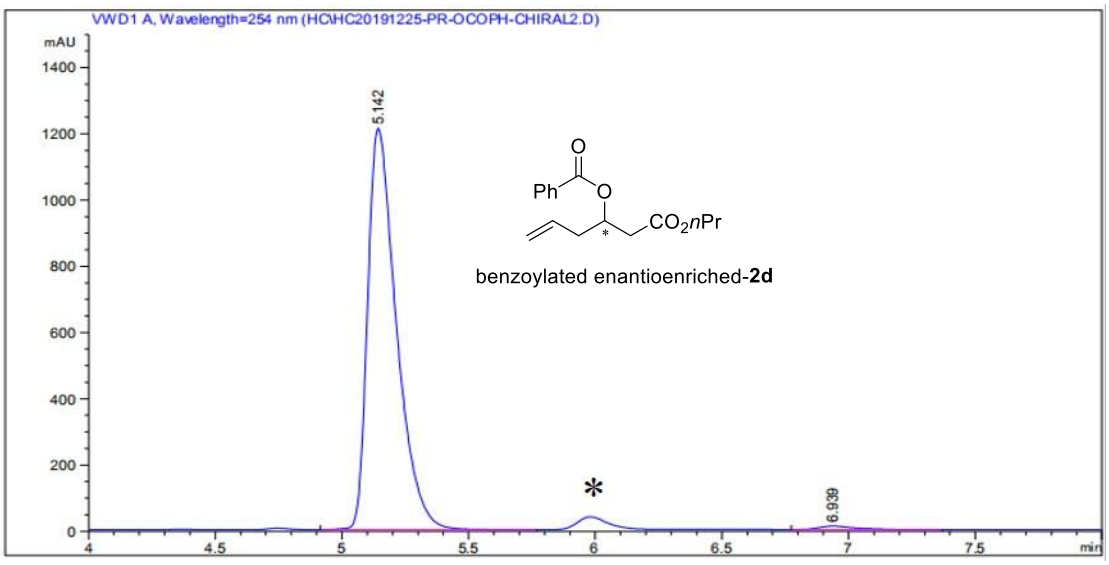
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.208	BB	0.1321	1369.81409	159.67963	99.0622
2	8.690	BV	0.1554	12.96755	1.22554	0.9378

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

***Peak labeled with asterisk is impurity generated in the bioreduction or derivatization.**



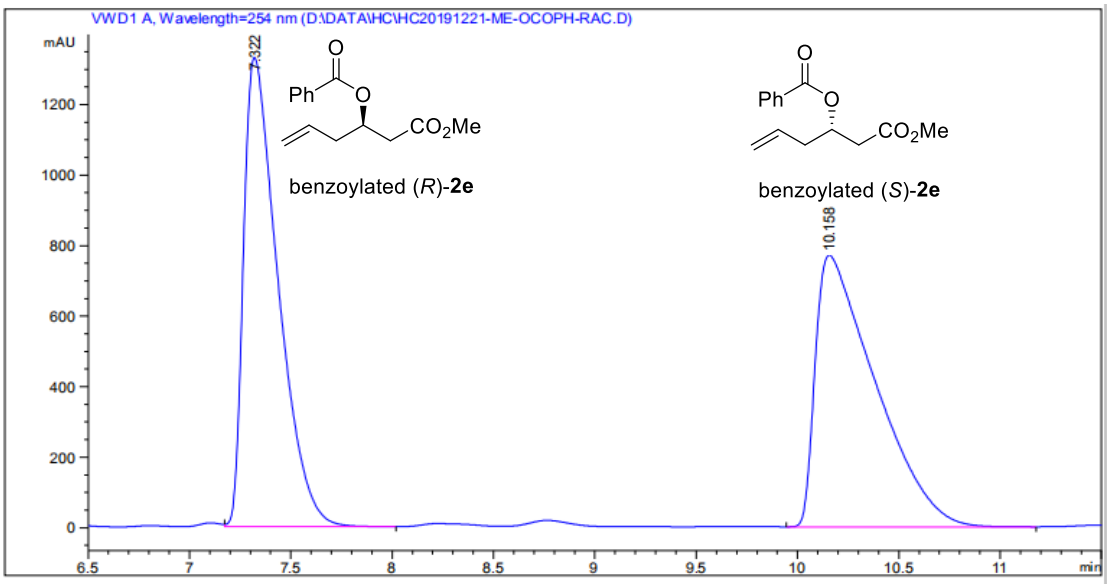
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.384	VB	0.1144	2722.54883	359.13177	50.1555
2	7.305	VB	0.2693	2705.66895	147.29071	49.8445



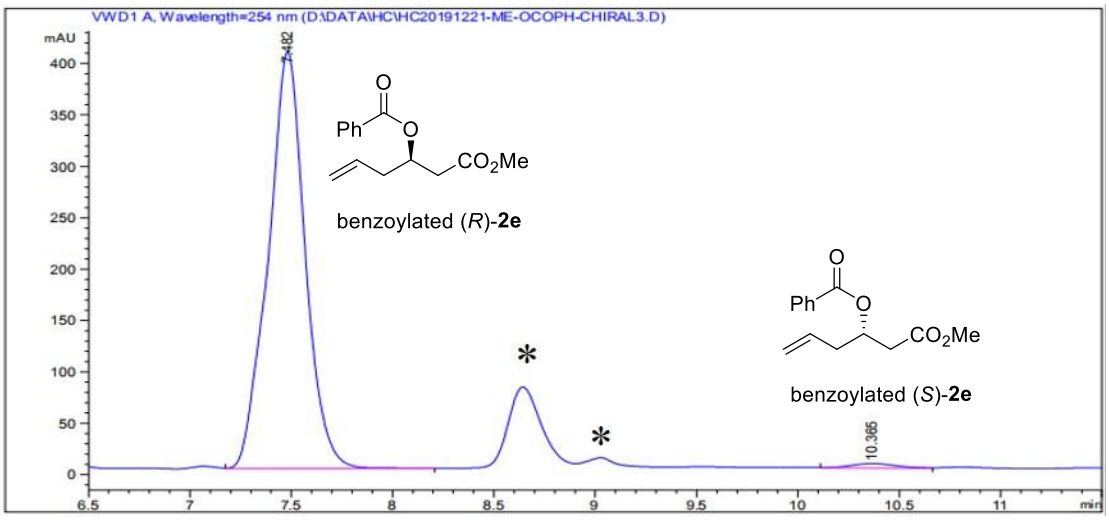
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.142	VB	0.1201	9563.86719	1211.92139	98.6537
2	6.939	VB	0.1618	130.51370	11.63877	1.3463

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

***Peak labeled with asterisk is impurity generated in the bioreduction or derivatization.**



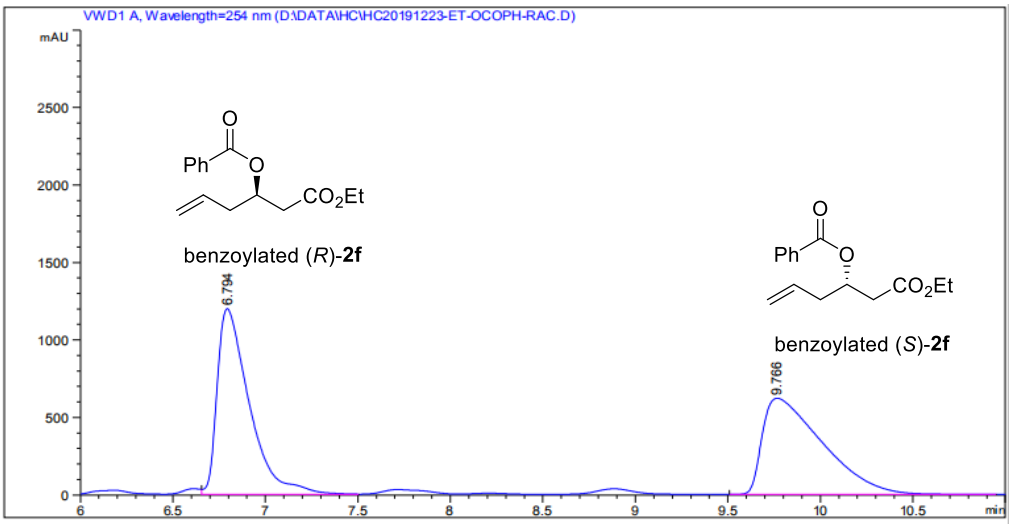
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	7.322	VB	0.1782	1.57561e4	1330.02991	49.8924
2	10.158	VV	0.2977	1.58241e4	770.34662	50.1076



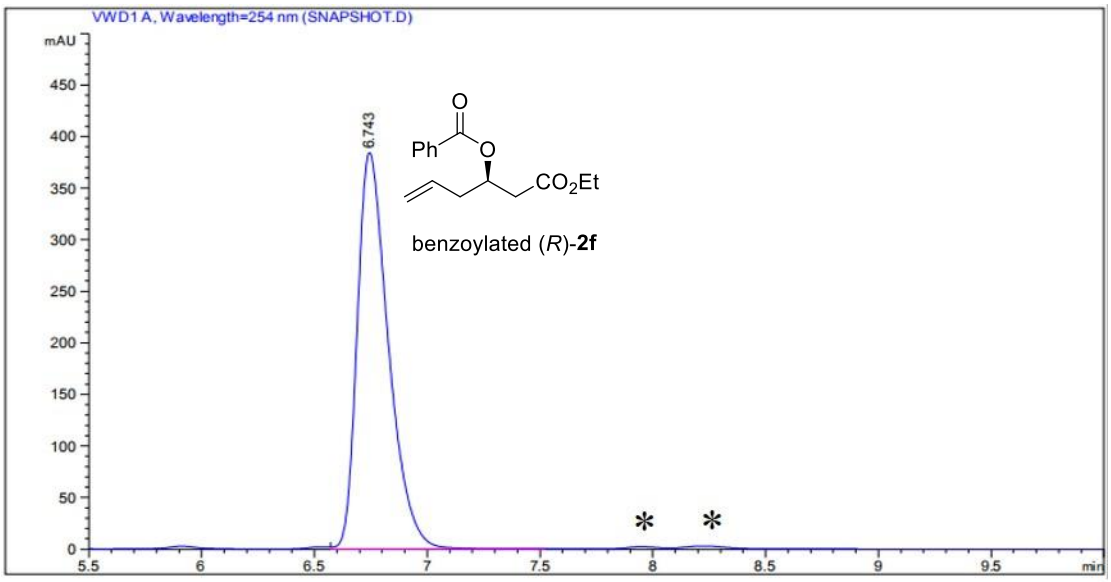
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	7.482	VB	0.1847	5135.32666	405.64032	98.7212
2	10.365	VV	0.2338	66.52149	4.31686	1.2788

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

***Peak labeled with asterisk is impurity generated in the bioreduction or derivatization.**



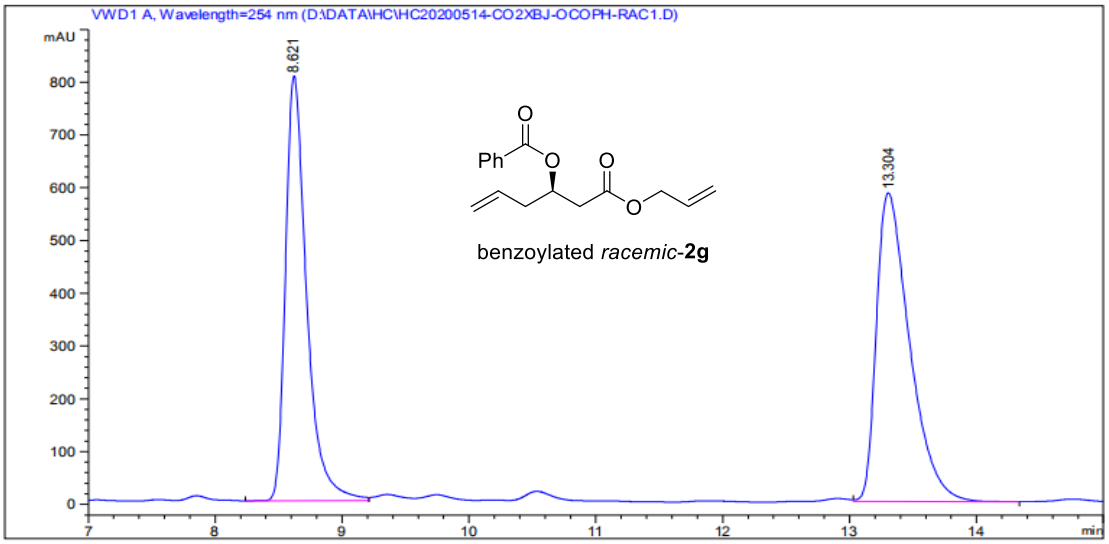
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.794	VB	0.1795	1.44149e4	1197.06714	50.6623
2	9.766	VV	0.3468	1.40380e4	620.87091	49.3377



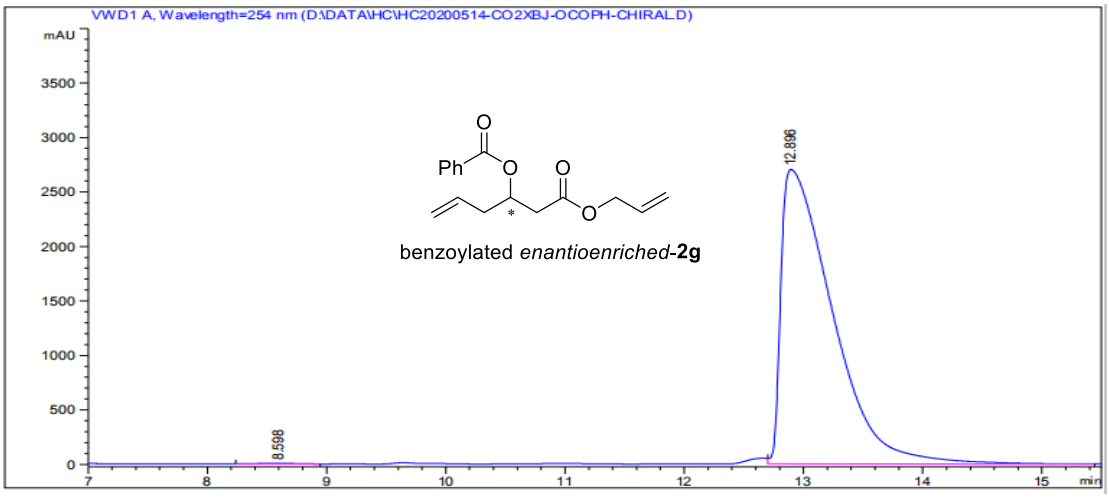
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.743	VB	0.1462	3699.15234	384.66833	100.0000

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

***Peak labeled with asterisk is impurity generated in the bioreduction or derivatization.**

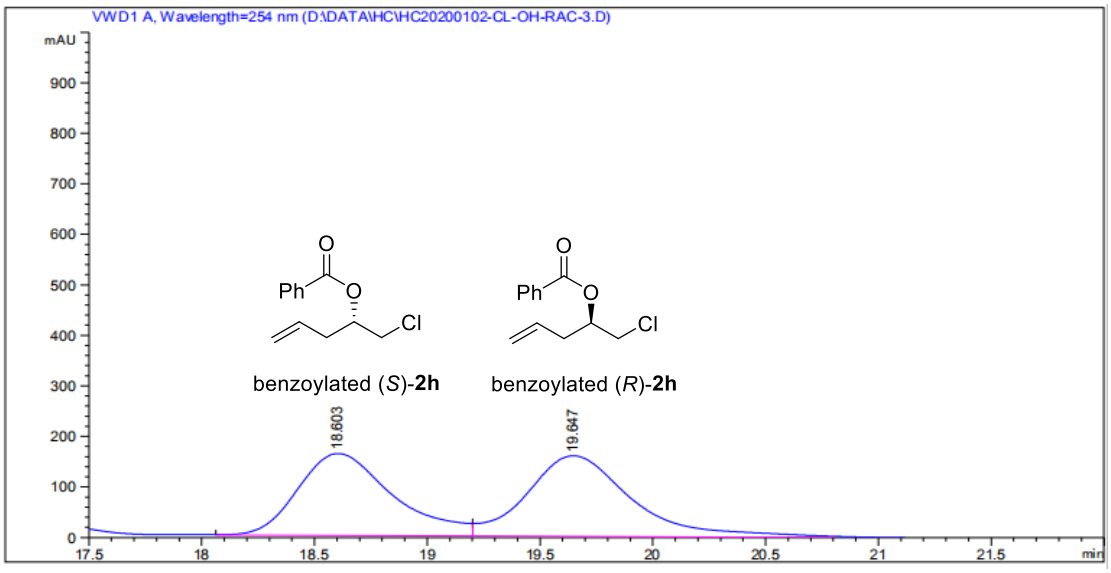


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.621	BV	0.1741	9318.39453	804.79492	46.7306
2	13.304	VB	0.2739	1.06223e4	584.74506	53.2694

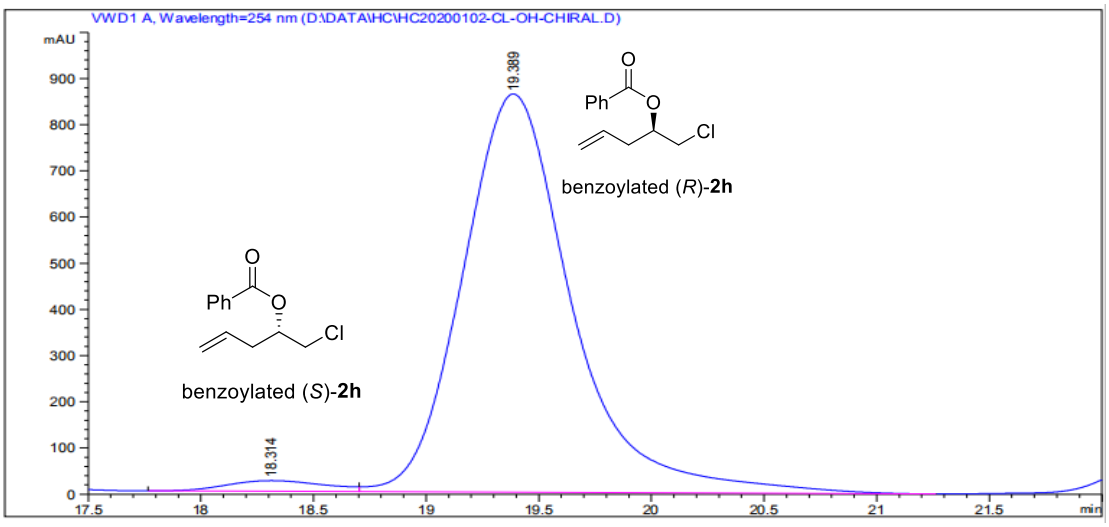


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.598	BB	0.2541	113.73392	6.40741	0.1402
2	12.896	VV	0.4607	8.09956e4	2702.04907	99.8598

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

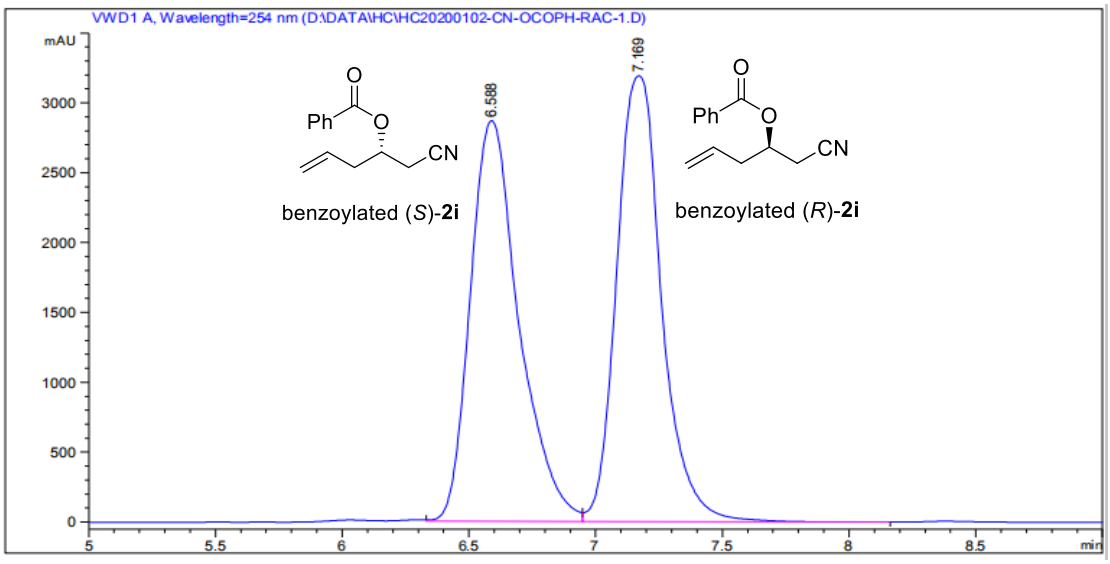


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	18.603	VV	0.4463	4728.51025	162.12004	47.6995
2	19.647	VB	0.4807	5184.60352	159.73410	52.3005

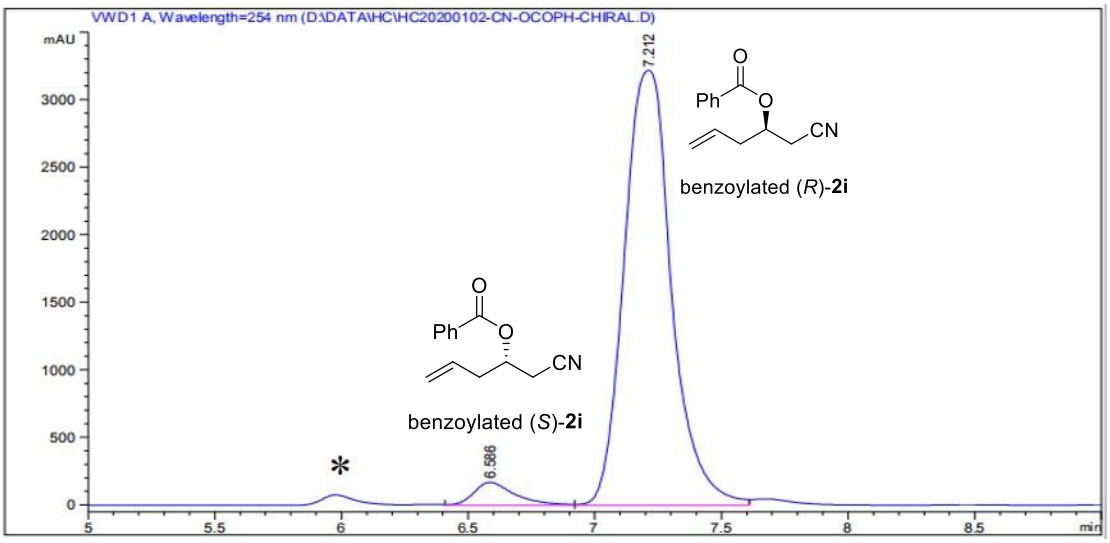


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	18.314	BV	0.4667	705.57910	23.27259	2.3620
2	19.389	VB	0.5115	2.91670e4	862.49249	97.6380

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.



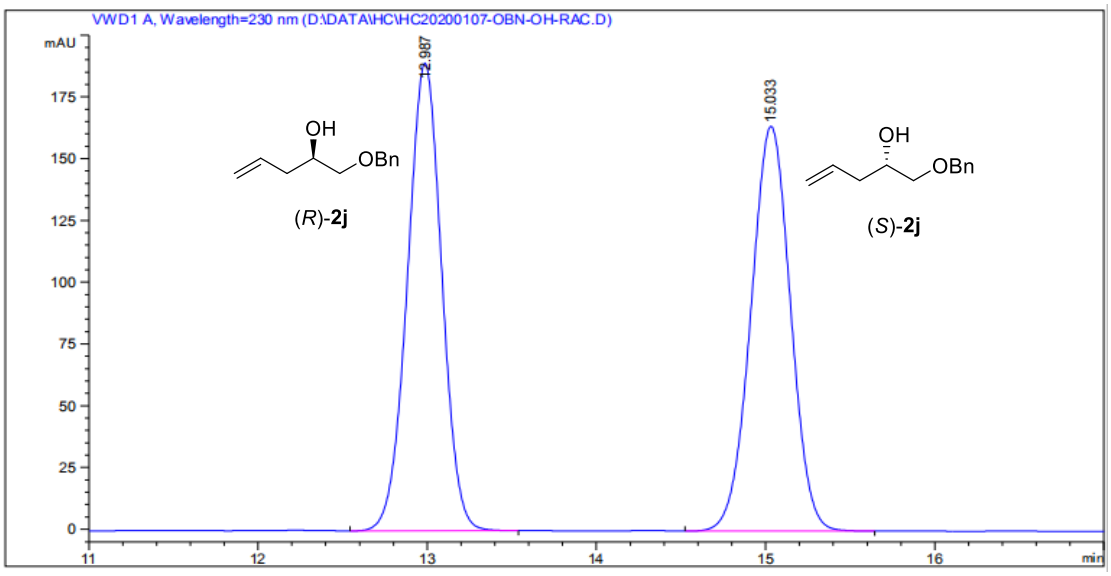
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.588	VV	0.2017	3.82515e4	2866.79956	49.3560
2	7.169	VB	0.1885	3.92496e4	3189.96582	50.6440



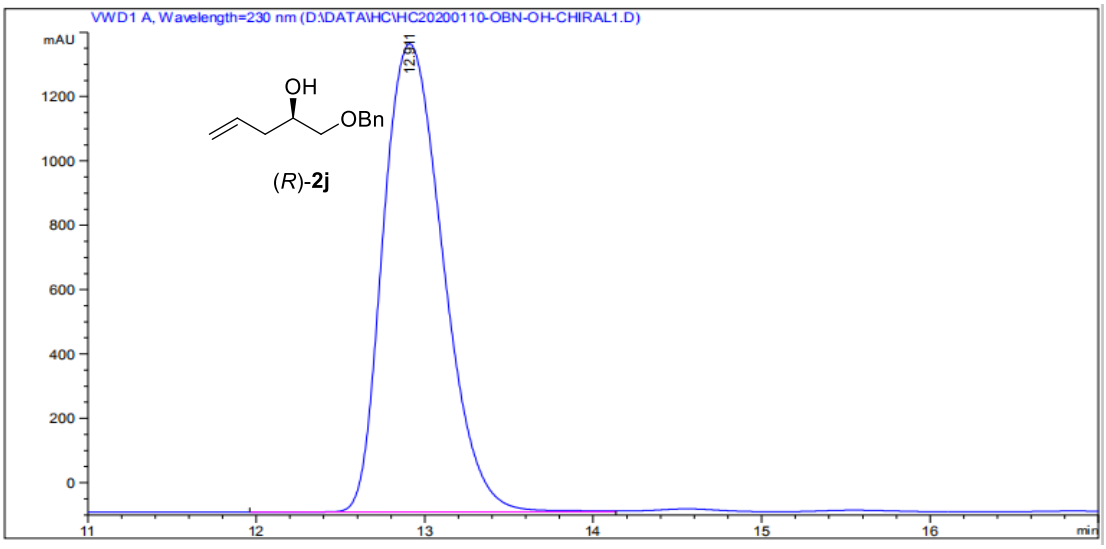
peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.586	VV	0.1666	1909.17639	169.31525	4.3638
2	7.212	VV	0.1987	4.18409e4	3217.51880	95.6362

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

***Peak labeled with asterisk is impurity generated in the bioreduction or derivatization.**

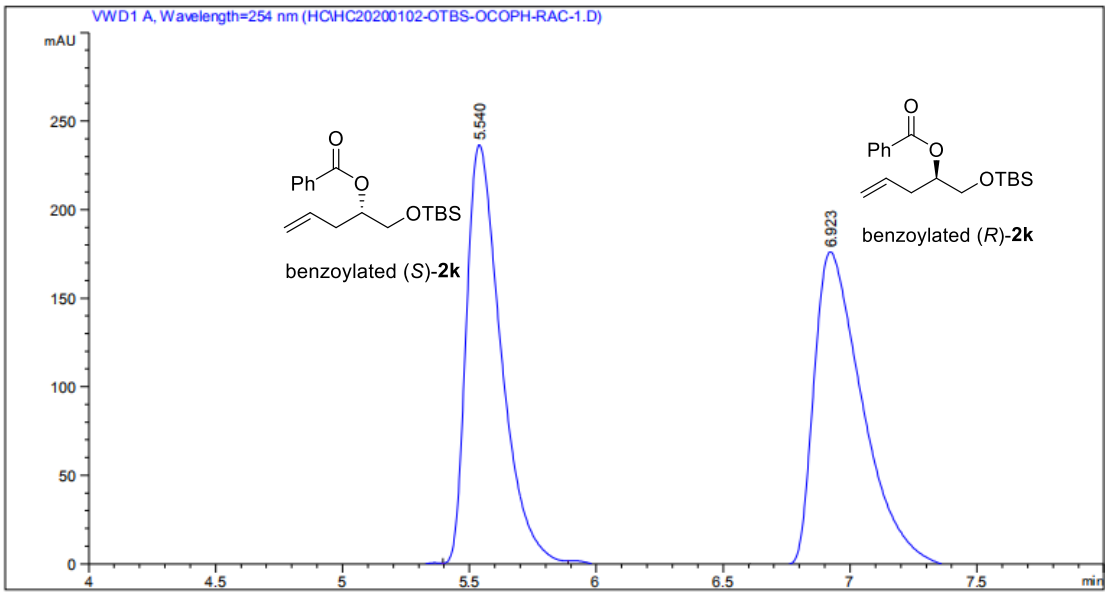


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	12.987	BB	0.2187	2670.86475	189.18336	50.0267
2	15.033	BB	0.2540	2668.01636	163.78847	49.9733

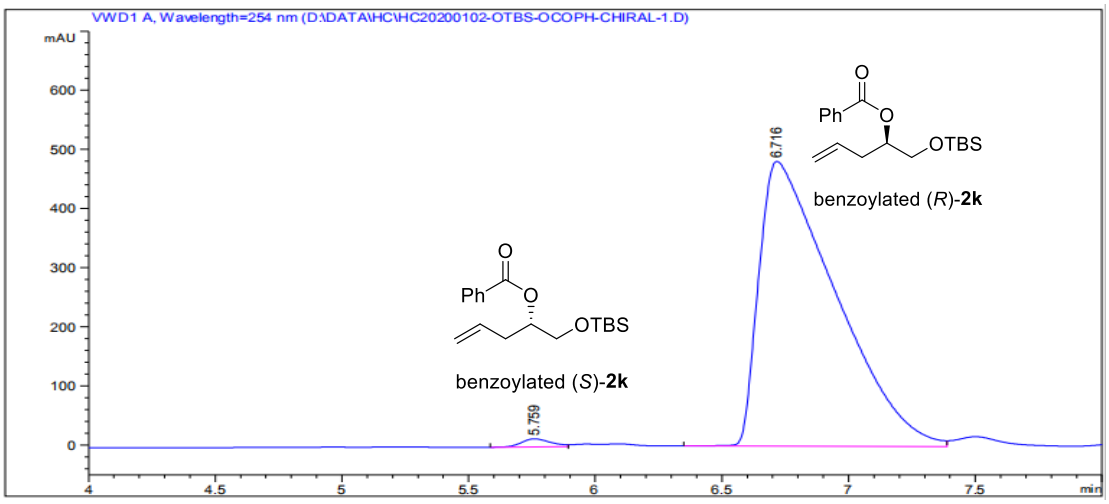


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	12.911	BV	0.3926	3.58641e4	1455.02771	100.0000

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

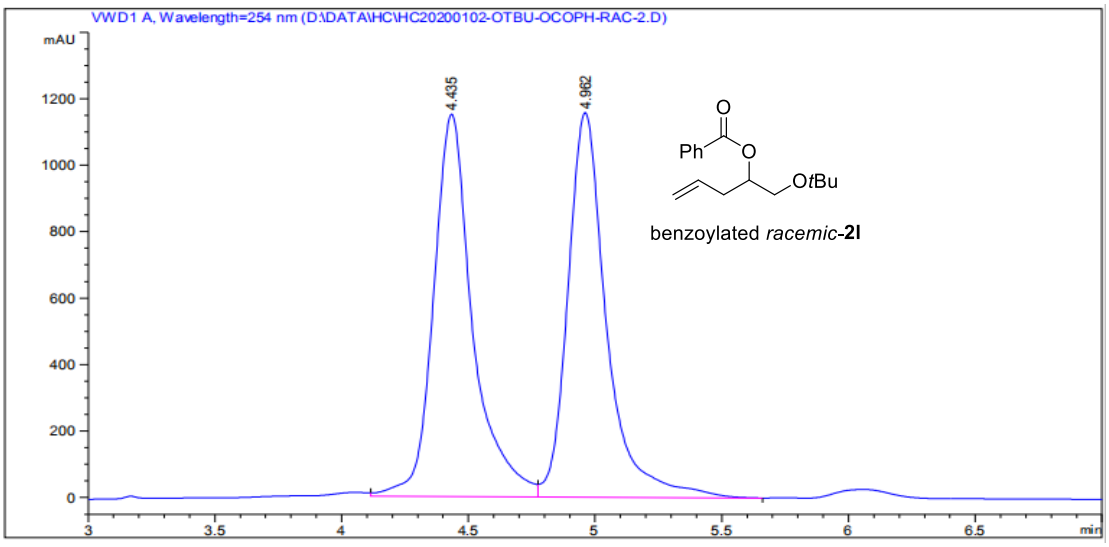


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.540	VV	0.1460	2286.08569	238.18317	48.2315
2	6.923	VV	0.2076	2453.73682	179.35674	51.7685

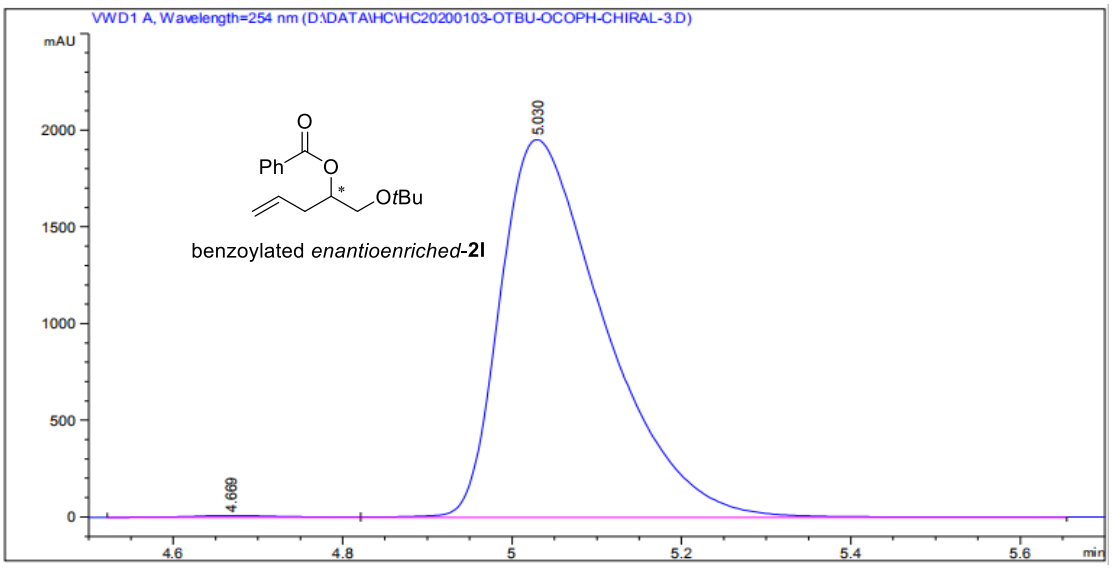


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.759	BV	0.1239	111.26965	13.67590	1.0904
2	6.716	BV	0.3175	1.00928e4	481.66348	98.9096

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

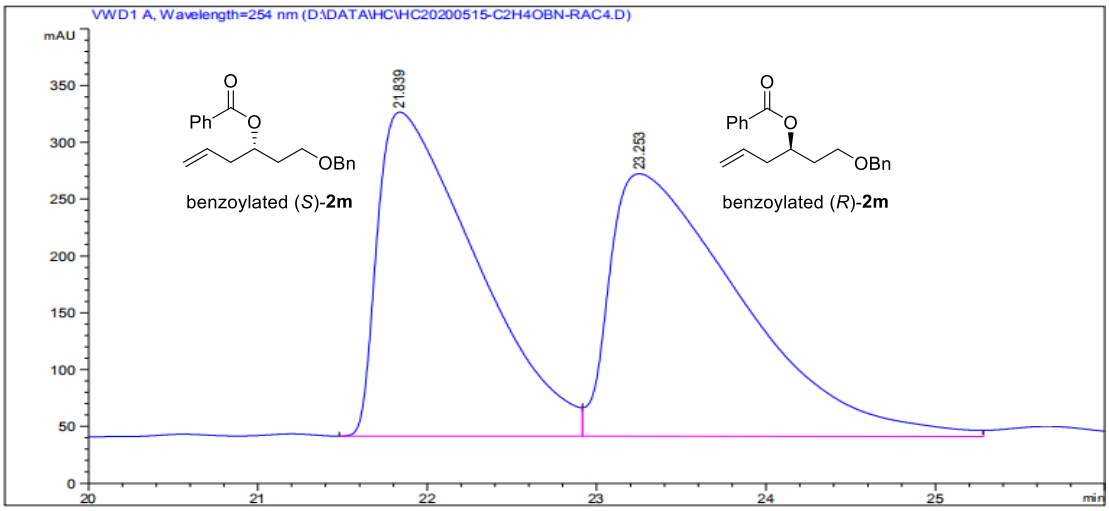


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.435	VV	0.1605	1.23769e4	1150.37976	50.1653
2	4.962	VB	0.1580	1.22954e4	1157.21497	49.8347

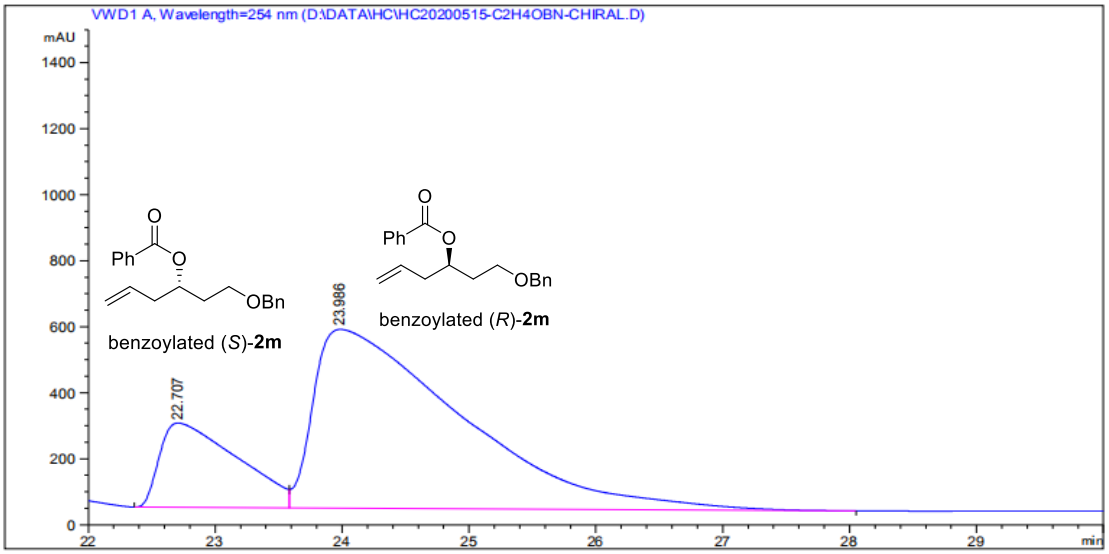


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.669	BV	0.1017	58.69129	8.81029	0.3492
2	5.030	VV	0.1301	1.67508e4	1953.20605	99.6508

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

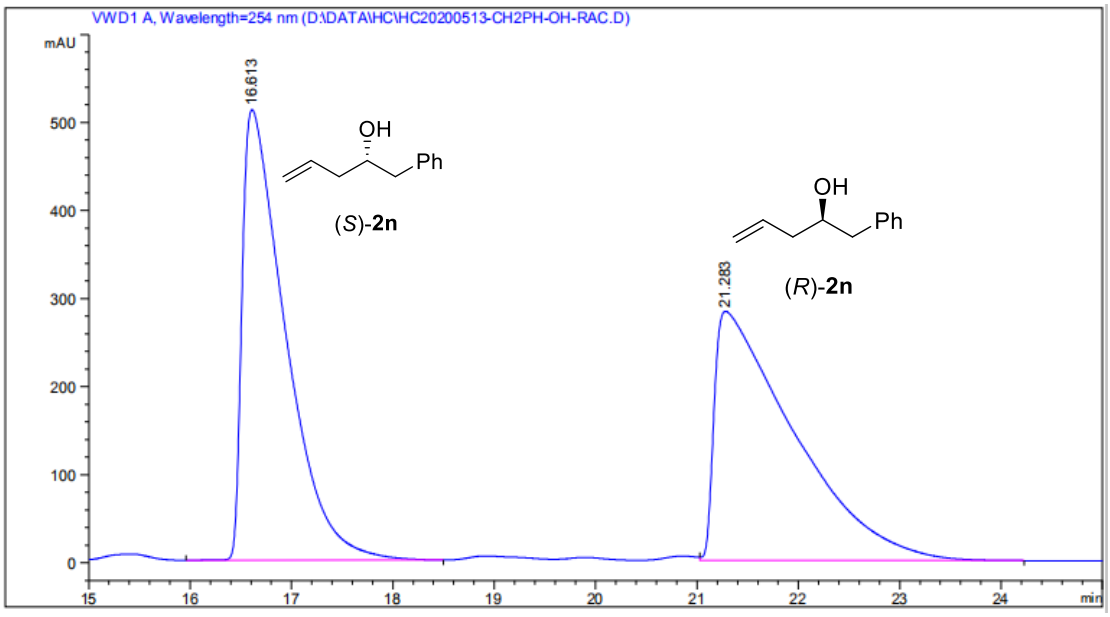


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	21.839	BV	0.5896	1.15243e4	285.12384	47.9219
2	23.253	VV	0.8606	1.25239e4	230.98405	52.0781

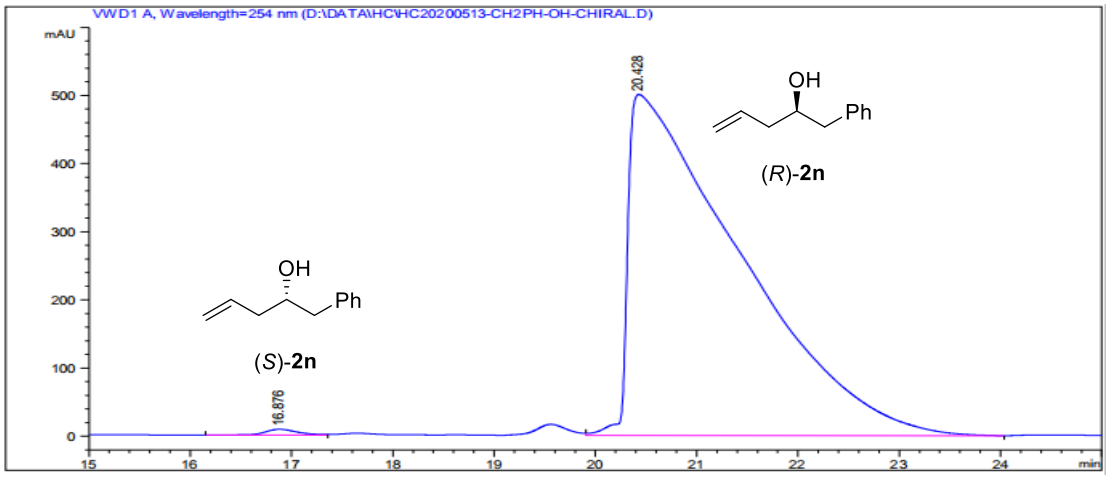


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	22.707	BV	0.6396	1.08934e4	255.42453	19.8481
2	23.986	VB	1.1705	4.39902e4	541.64801	80.1519

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

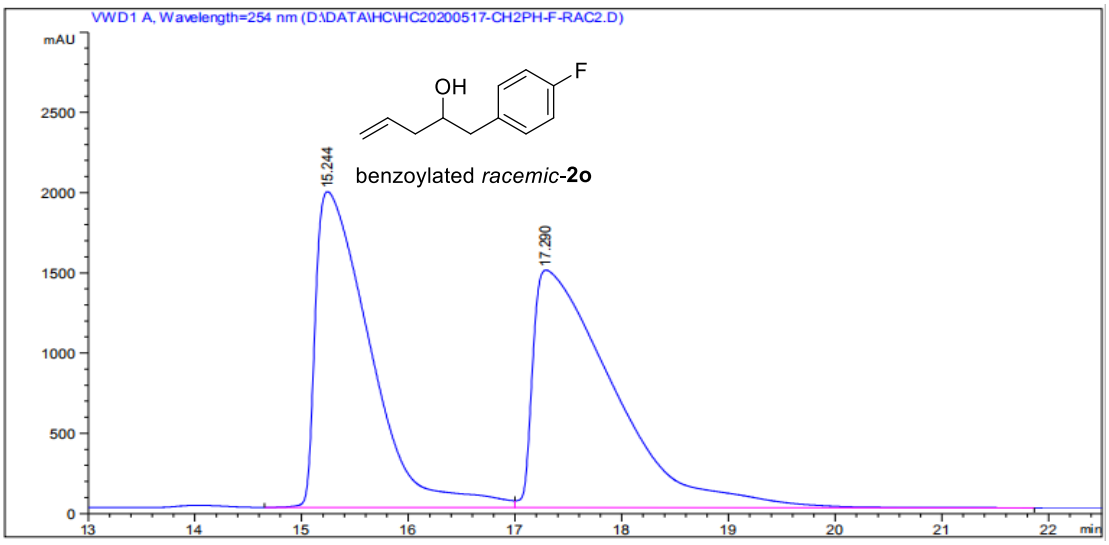


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	16.613	BB	0.4281	1.51938e4	512.17120	49.6099
2	21.283	VB	0.8044	1.54327e4	282.93237	50.3901

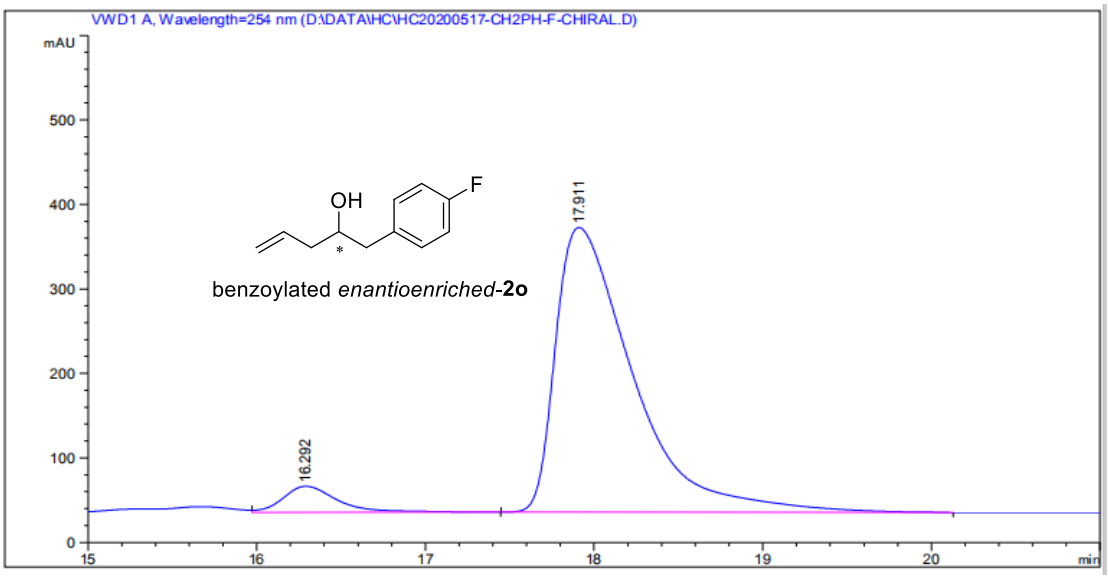


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	16.876	BV	0.3354	186.82227	8.43376	0.4816
2	20.428	VB	1.0588	3.86070e4	500.56708	99.5184

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

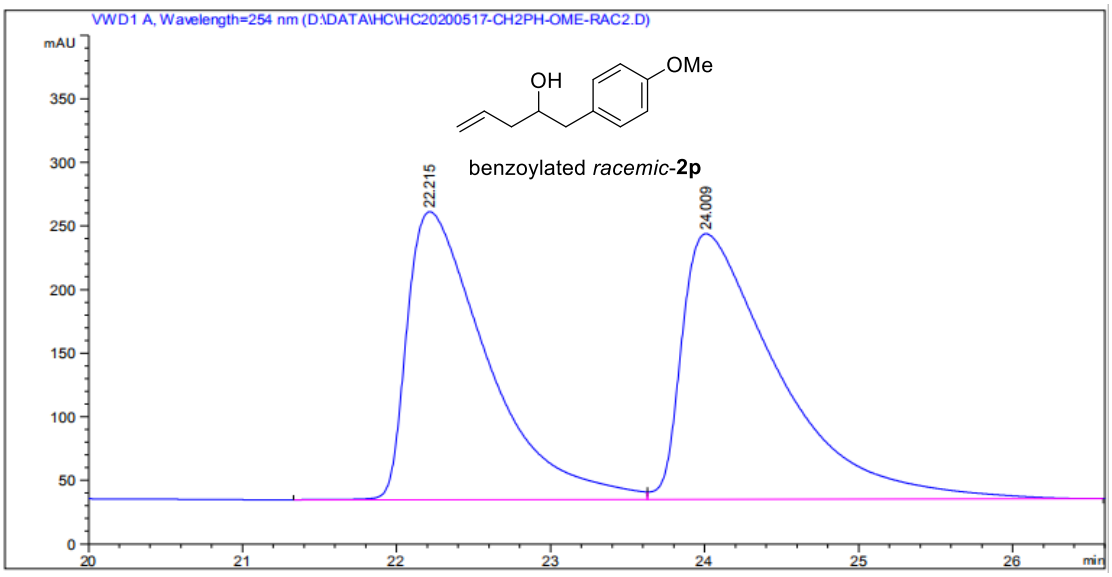


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	15.244	VV	0.5520	6.98829e4	1969.10046	47.4358
2	17.290	VB	0.7763	7.74382e4	1480.43481	52.5642

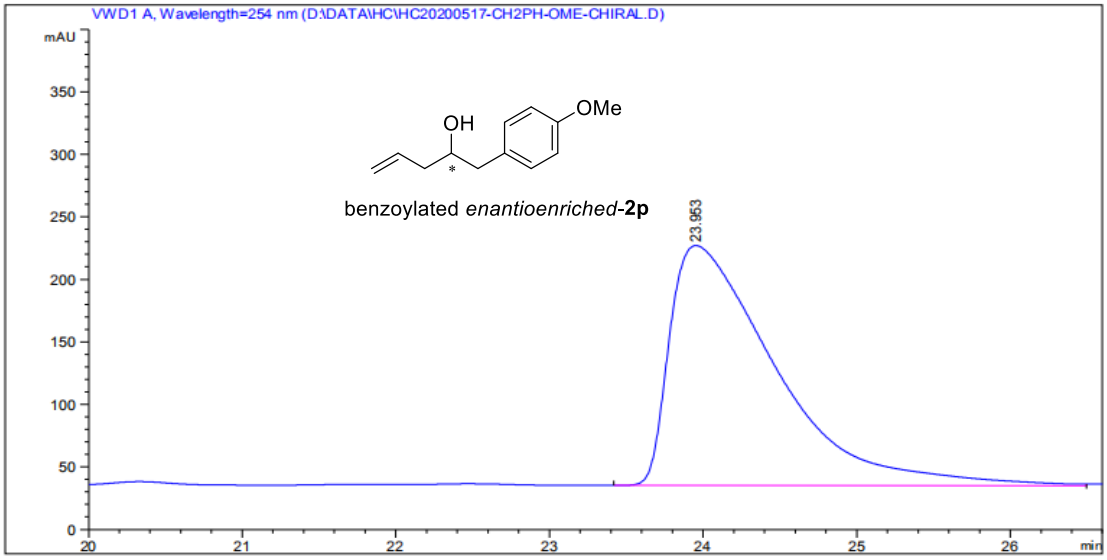


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	16.292	VB	0.3387	685.54712	30.67464	5.9849
2	17.911	BB	0.4810	1.07690e4	336.84494	94.0151

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

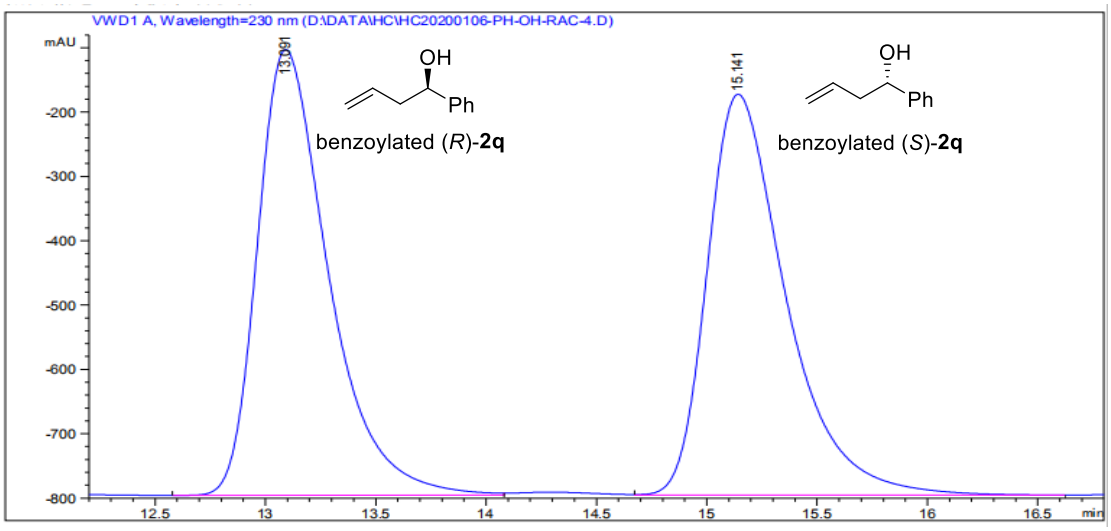


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	22.215	BV	0.5355	8216.09277	226.32632	47.4643
2	24.009	VB	0.6253	9093.96875	208.71684	52.5357

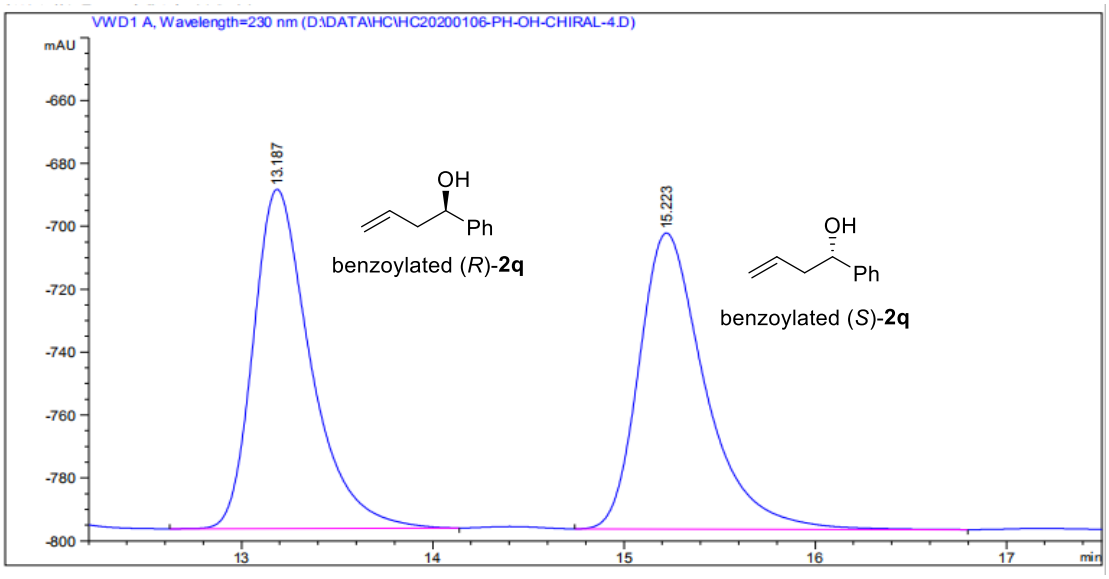


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	23.953	BV	0.7363	9195.09570	191.79260	100.0000

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.

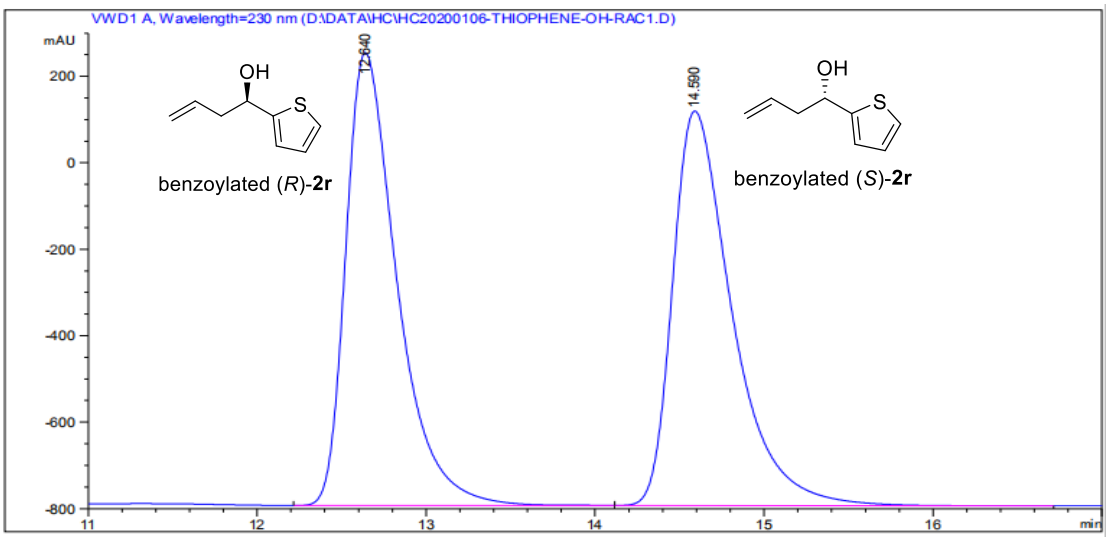


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	13.091	BV	0.3395	1.55261e4	692.75970	50.0463
2	15.141	VB	0.3762	1.54974e4	623.07031	49.9537

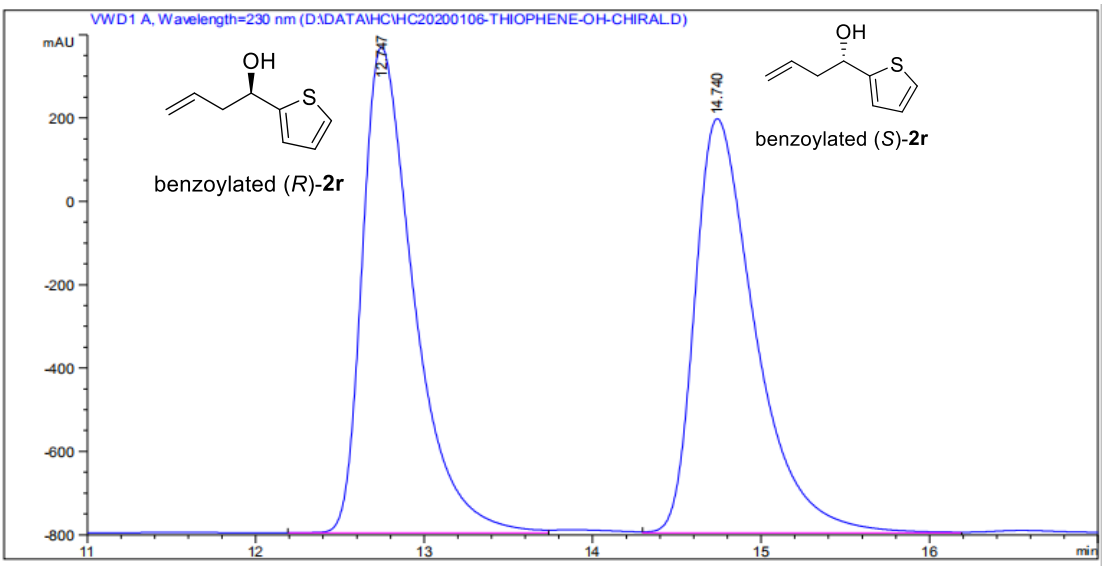


peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	13.187	BB	0.3139	2244.91577	107.83353	49.8515
2	15.223	BB	0.3620	2258.29248	94.09634	50.1485

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.



peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	12.640	BB	0.3189	2.20805e4	1047.77625	49.7212
2	14.590	BB	0.3684	2.23282e4	912.74042	50.2788



peak retention time	type	peak width	peak area	peak height	peak area
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	12.747	BV	0.3205	2.47306e4	1165.66174	49.9854
2	14.740	VV	0.3756	2.47451e4	993.50385	50.0146

The top spectrum is the chiral HPLC analysis of the racemic synthetic standard. The bottom spectrum is the chiral HPLC analysis of KRED-06-catalyzed biotransformation.