Supporting Information:

Direct Asymmetric Hydrogenation of α-Keto Acids by Using the Highly Efficient Chiral Spiro Iridium Catalysts

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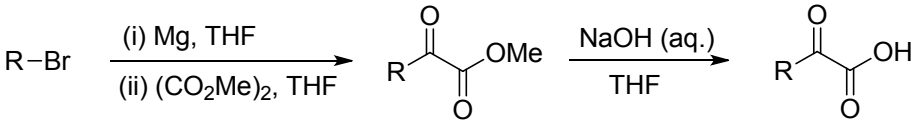
CONTENTS:

General. All reactions and manipulations which are sensitive to moisture or air were performed in an argon-filled glovebox (MIKROUNA *Super 1220/750*). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively. Chemical shifts were reported in ppm down field from internal Me_4Si. Melting points were determined on an open capillary apparatus (SG WRR) and uncorrected. Chiral separations for ee determinations were conducted on Chiracel OD-H (4.6 mm x 250 mm x 5 μm) or Chirapak AD-H (4.6 mm x 250 mm x 5 μm) column on an Agilent 1200 series instrument. Optical rotations were determined using a SG WZZ-2S automatic polarimeter. Mass spectra were recorded on Agilent 6530 Accurate-Mass Q-TOF LC/MS spectrometer with ESI resource. Hydrogen gas (99.999%) was purchased from Bao Qing Gas Int., Shanghai. ^{t}BuOK, α-keto acids **2a**, **2n**, **2p** were purchased from Adamas chemical company and used as received without further purification. Other α-keto acids were hydrolyzed from corresponding esters which were prepared as the reported method.[1] Anhydrous ^{i}PrOH, ^{n}PrOH and ^{n}BuOH were freshly distilled from calcium hydride. Anhydrous MeOH and EtOH were freshly distilled from magnesium. The catalyst (*R*)-**1** was prepared as the reported method.[2]

(A) General Procedure for the Preparation of α-Keto Acids



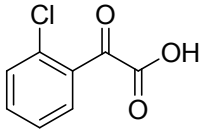
2-(2-Chlorophenyl)-2-oxoacetic acid (**2b**): A solution of *o*-bromochlorobenzene (25 g, 130.6 mmol) in dry THF (60 mL) was added dropwise to a mixture of Mg (3.3 g, 135.8 mmol) and I_2 (one piece) in dry THF (40 mL) at 25–35 ^{o}C over 1 h under N_2. To the Grignard reagent thus prepared was added a solution of dimethyl oxalate (10.2 g, 86.4 mmol) in dry THF (50 mL) at -70 ^{o}C. After the mixture had been stirred at -70 ^{o}C for 1 h, the reaction was quenched with 10% HCl. The product was extracted with ^{t}BuOMe, and the organic layer was dried over Na_2SO4 and concentrated. Purification by silica gel column chromatography (Hexane/EtOAc, 10:1) gave methyl *o*-chlorobenzoylformate as a pale yellow oil, yield: 20.3g (78%). The methyl *o*-chlorobenzoylformate was dissolved in THF (80 mL), to which the aqueous solution (80 mL) of NaOH (8.2 g, 205 mmol) was added at 0 ^{o}C. After stirring at 0 ^{o}C for 1 h, the reaction mixture was concentrated on a rotary evaporator. To the resulting residue was added 3 M HCl and extracted with ^{t}BuOMe. The extract was dried over Na_2SO_4 and concentrated to give the product 2-(2-chlorophenyl)-2-oxoacetic acid (**2b**), 16 g, yield: 85%.

[1] T. Ema, S. Ide, N. Okita, T. Sakai, *Adv. Synth. Catal*., 2008, **350**, 2039.

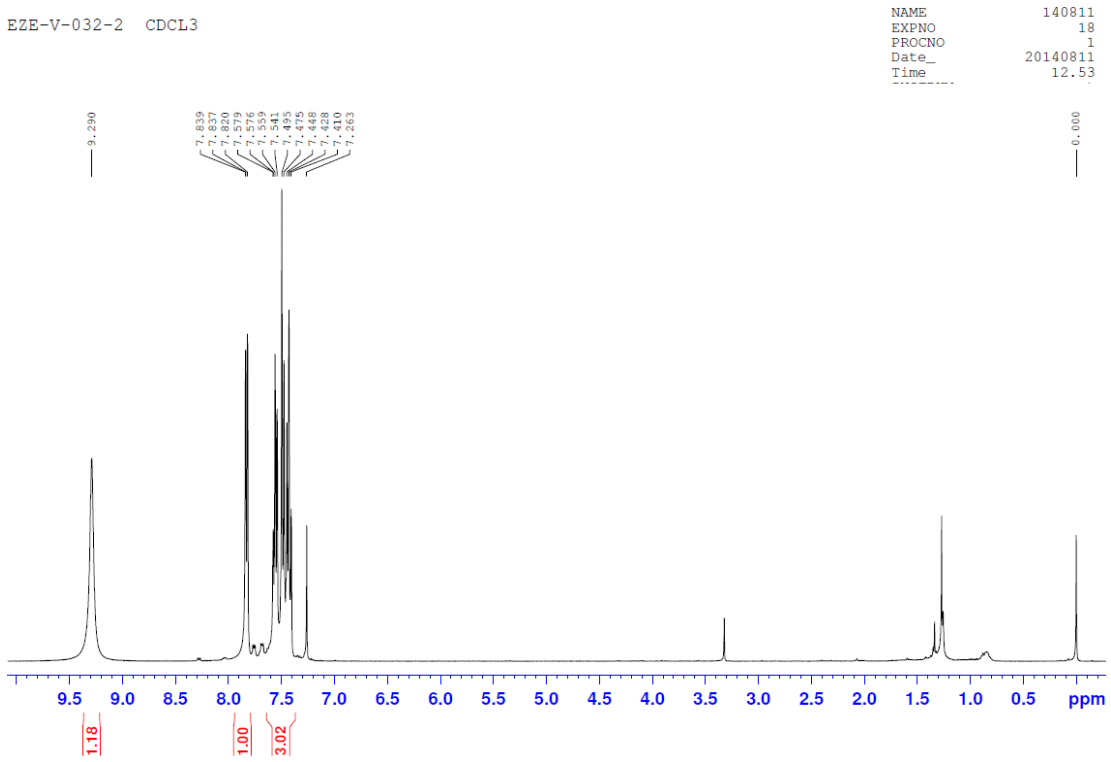
[2] J.-H. Xie, X.-Y. Liu, J.-B. Xie, L.-X. Wang, Q.-L. Zhou, *Angew. Chem., Int. Ed.,* 2011, **50**, 7329.

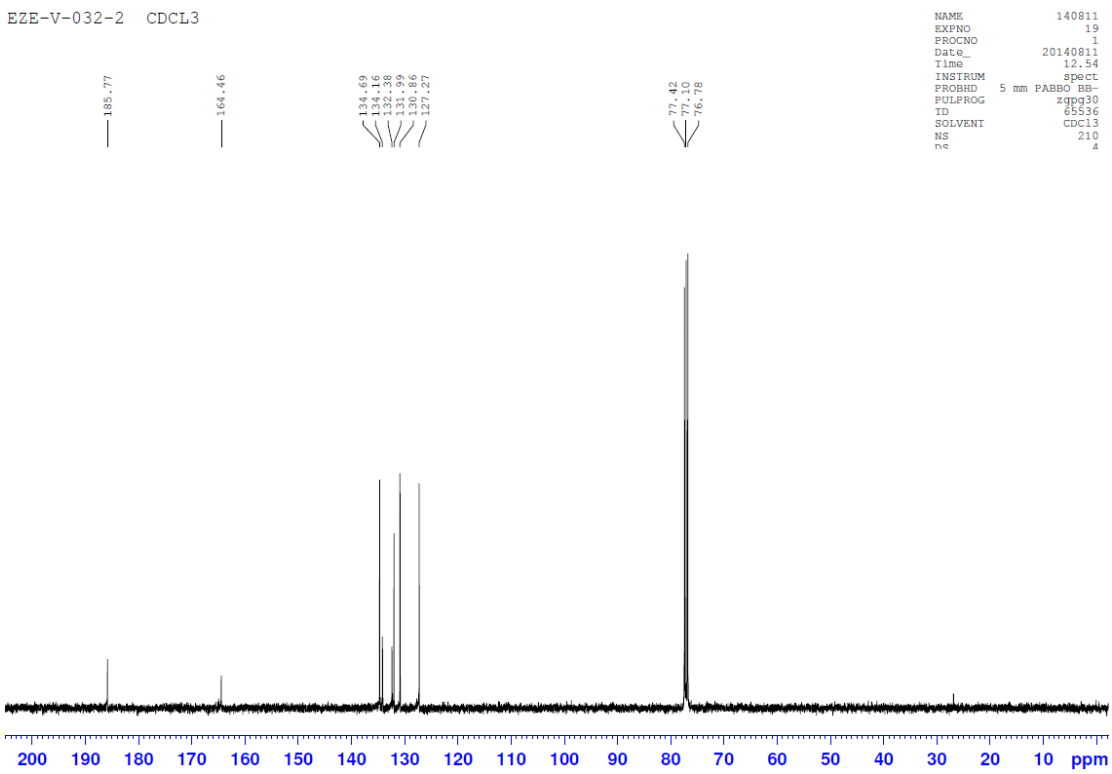
(B) Analytical Data and NMR Spectra of α-Keto Acids

2-(2-chlorophenyl)-2-oxoacetic acid (**2b**)

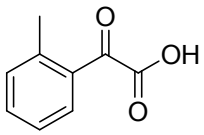


Pale yellow solid, mp: 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (brs, 1H), 7.84–7.82 (m, 1H), 7.58–7.41 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.8, 164.5, 134.7, 134.2, 132.4, 132.0, 130.9, 127.3. HRMS (ESI) calcd for $[M\text{-}H, C_8H_4ClO_3]^-$: 182.9849, Found 184.9845.

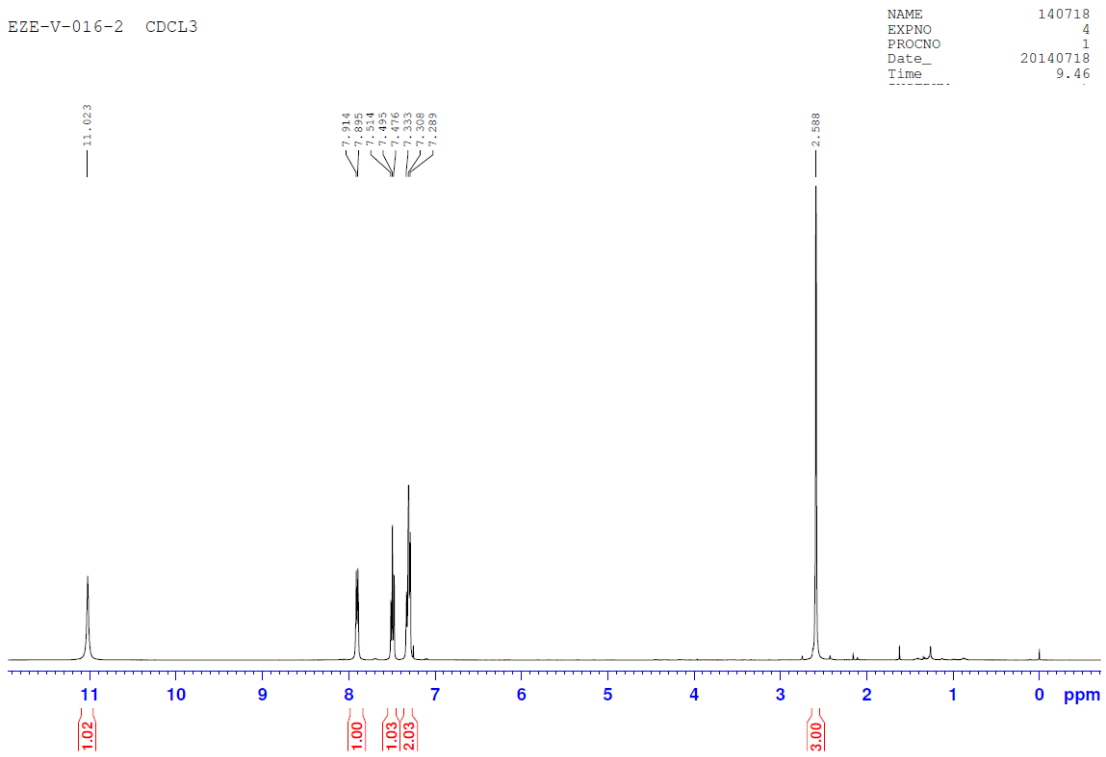


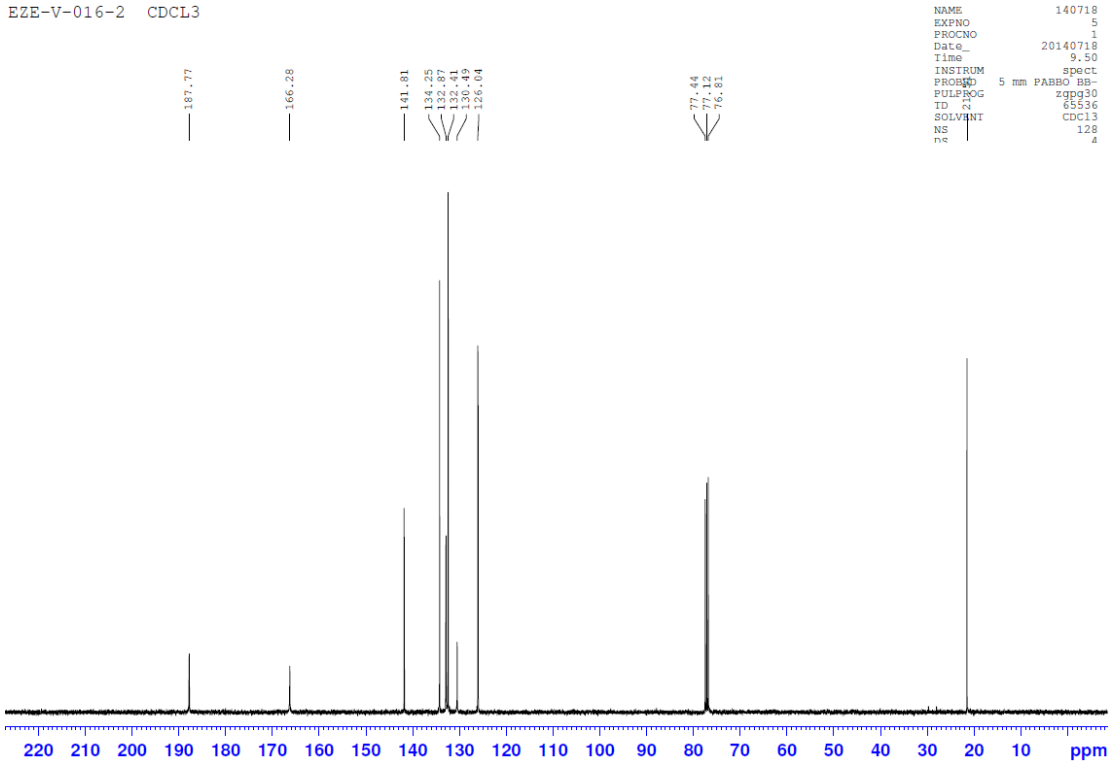


2-oxo-2-(o-tolyl)acetic acid (**2c**)

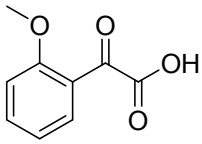


Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.02 (brs, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.33–7.29 (m, 2H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.8, 166.3, 141.8, 134.3, 132.9, 132.4, 130.5, 126.0, 21.5. HRMS (ESI) calcd for [M-H, $C_9H_7O_3$]$^{-}$: 163.0395, Found 163.0398.

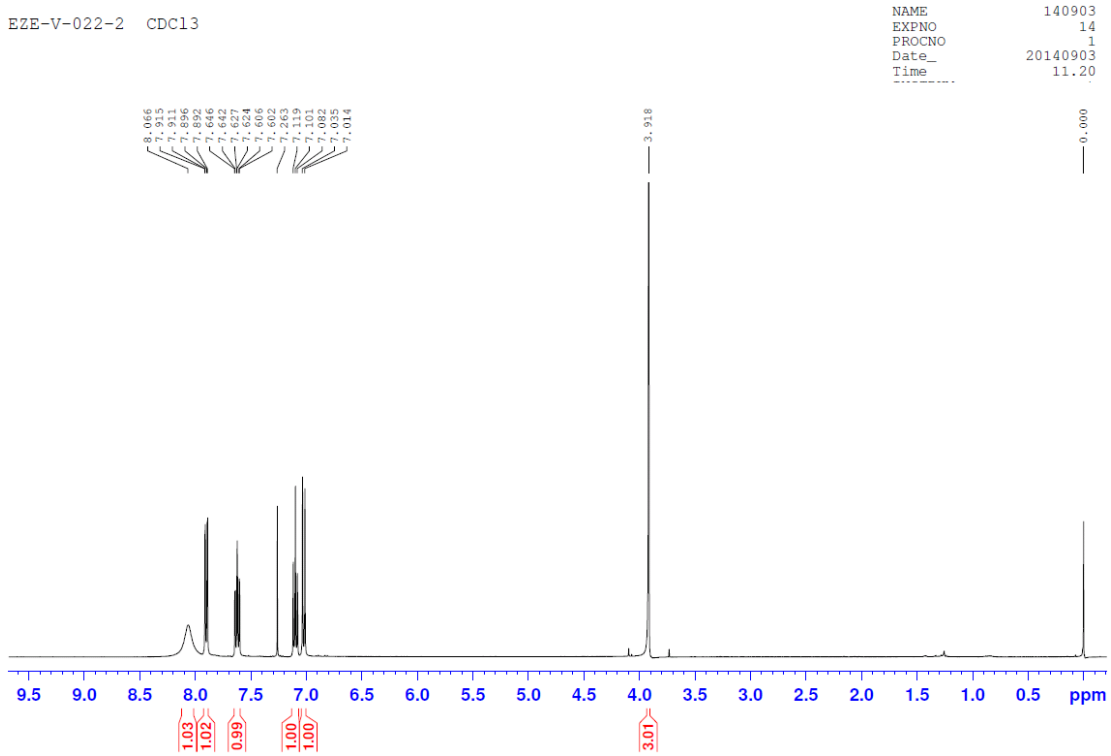


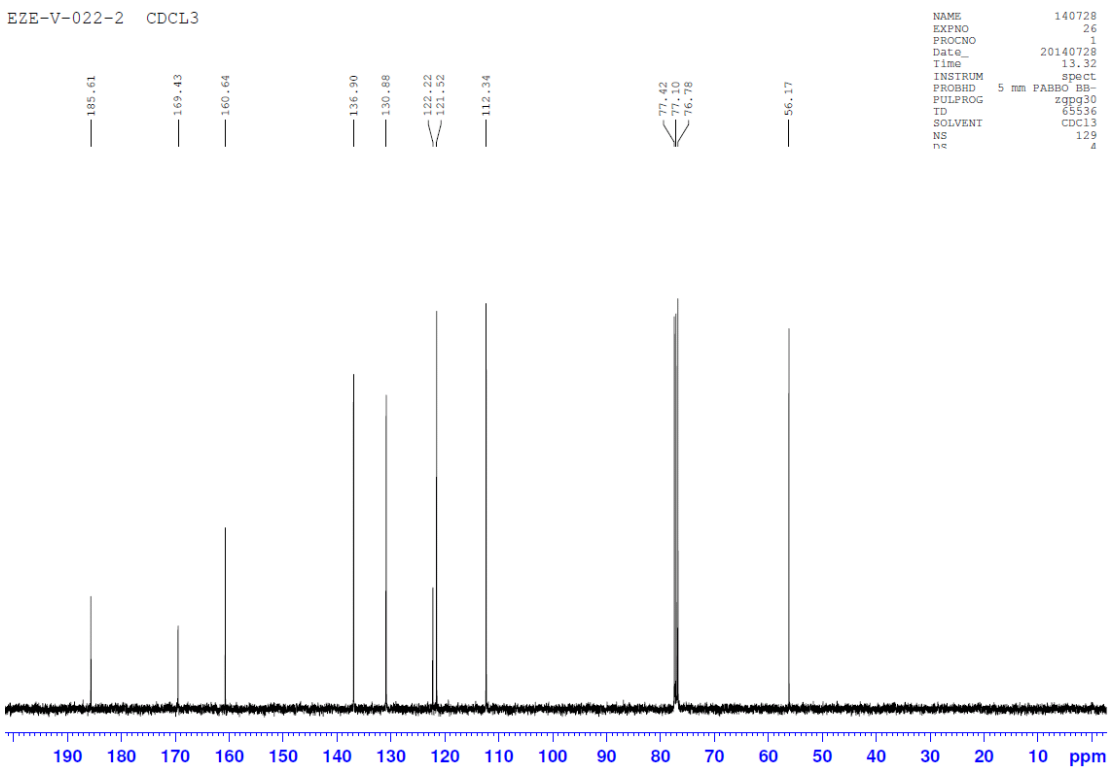


2-(2-methoxyphenyl)-2-oxoacetic acid (**2d**)

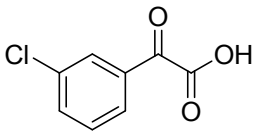


Pale yellow solid, mp: 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (brs, 1H), 7.90 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.65–7.60 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 169.4, 160.6, 136.9, 130.9, 122.2, 121.5, 112.3, 56.2. HRMS (ESI) calcd for $[M\text{-}H, C_9H_7O_4]^-$: 179.0344, Found 179.0347.

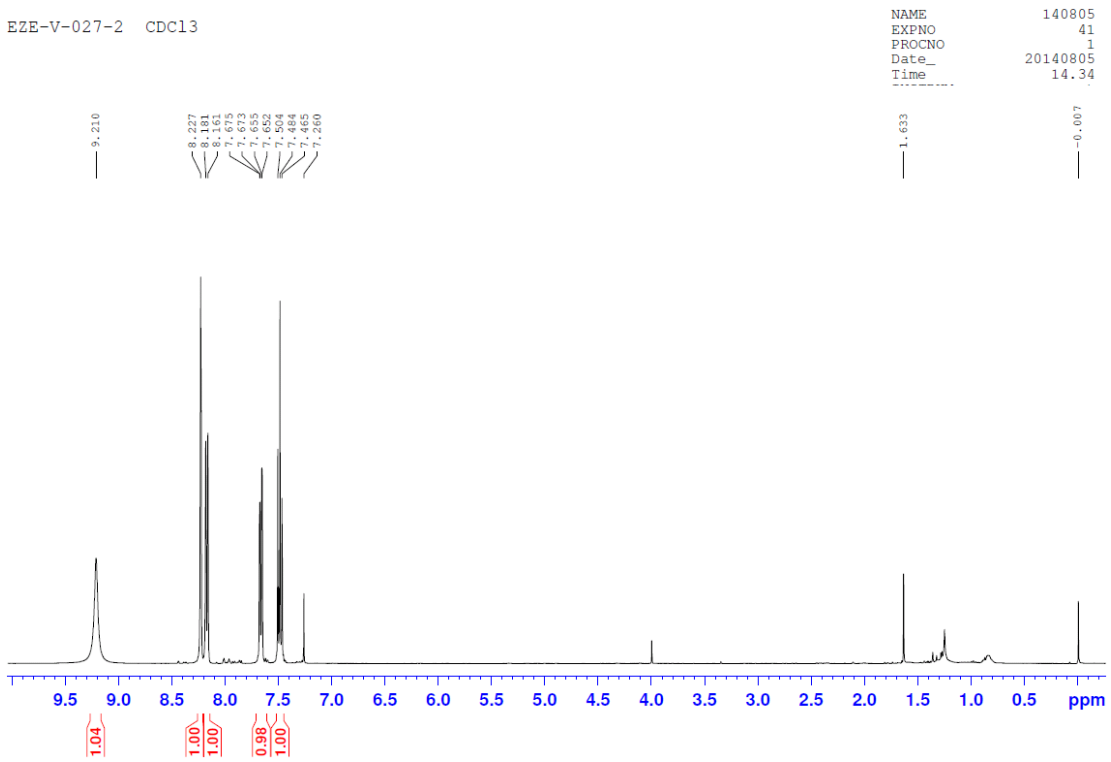


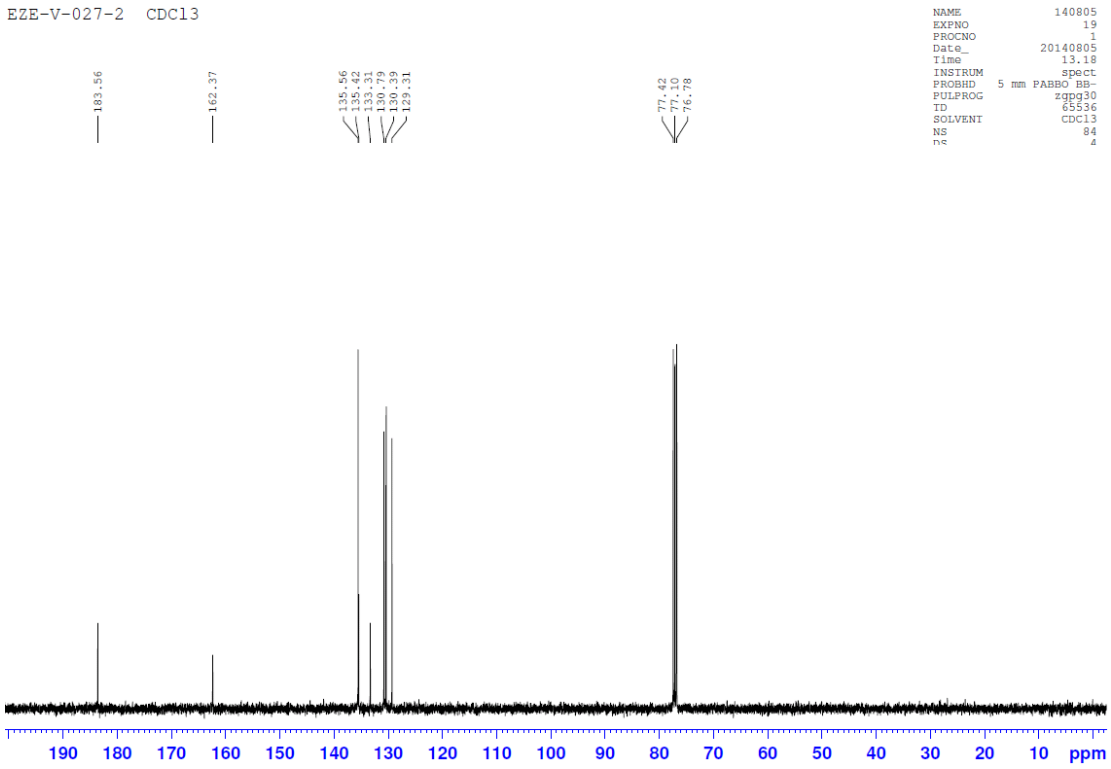


2-(3-chlorophenyl)-2-oxoacetic acid (**2e**)

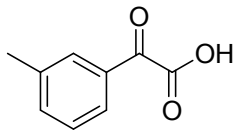


Pale yellow solid, mp: 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (brs, 1H), 8.23 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.68–7.65 (m, 1H), 7.48 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.6, 162.4, 135.6, 135.4, 133.3, 130.8, 130.4, 129.3. HRMS (ESI) calcd for [M-H, $C_8H_4ClO_3$]$^{-}$: 182.9849, Found 182.9842.

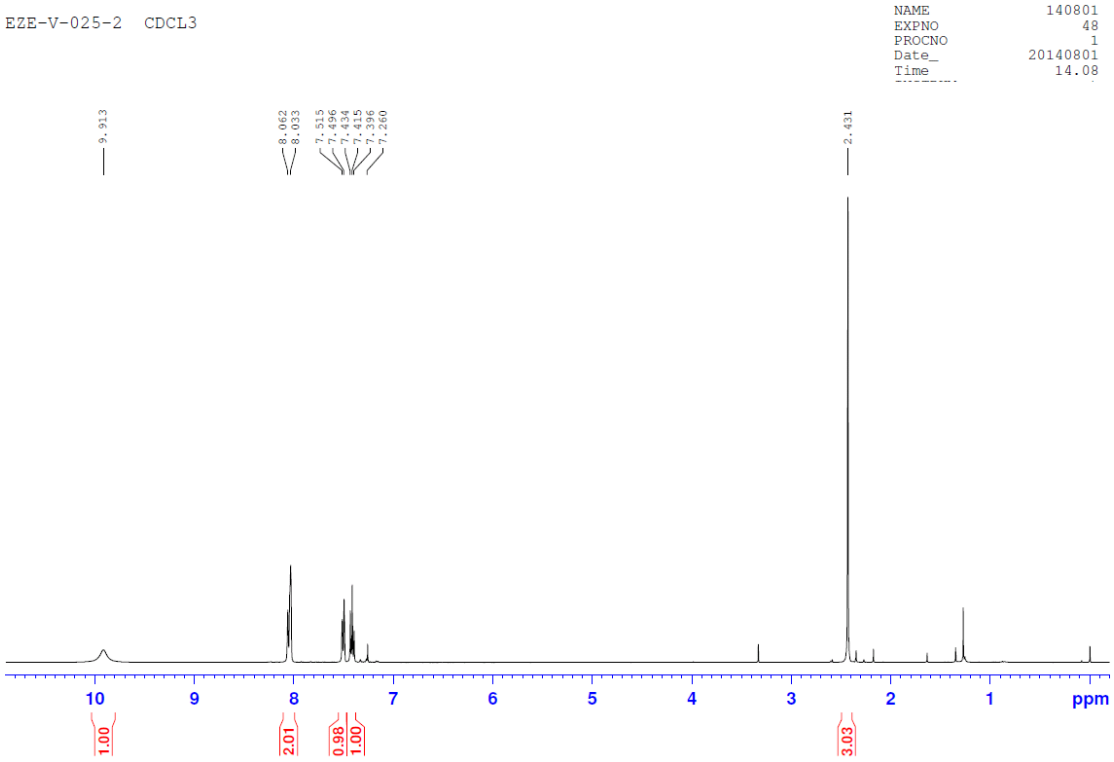


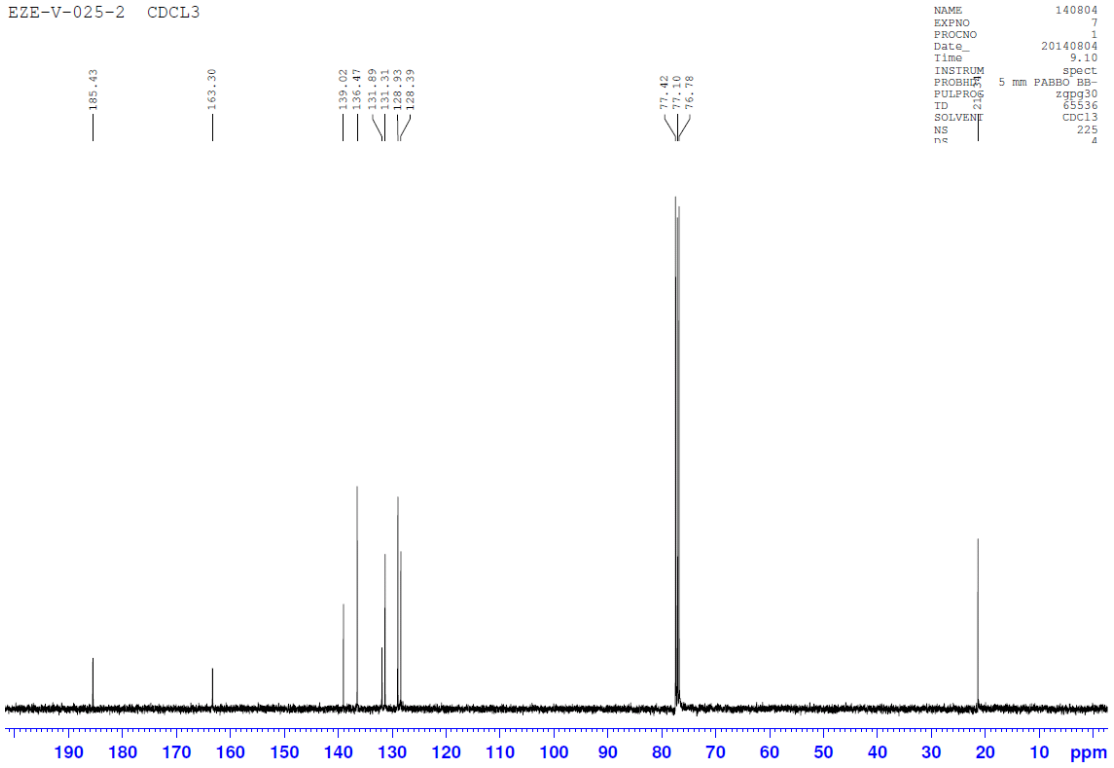


2-oxo-2-(m-tolyl)acetic acid (**2f**)

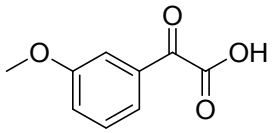


Pale yellow solid, mp: 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.03 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 6.71 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ185.4, 163.3, 139.0, 136.5, 131.9, 131.3, 128.9, 128.4, 21.3. HRMS (ESI) calcd for [M-H, $C_9H_7O_3$]$^{-}$: 163.0395, Found 163.0398.

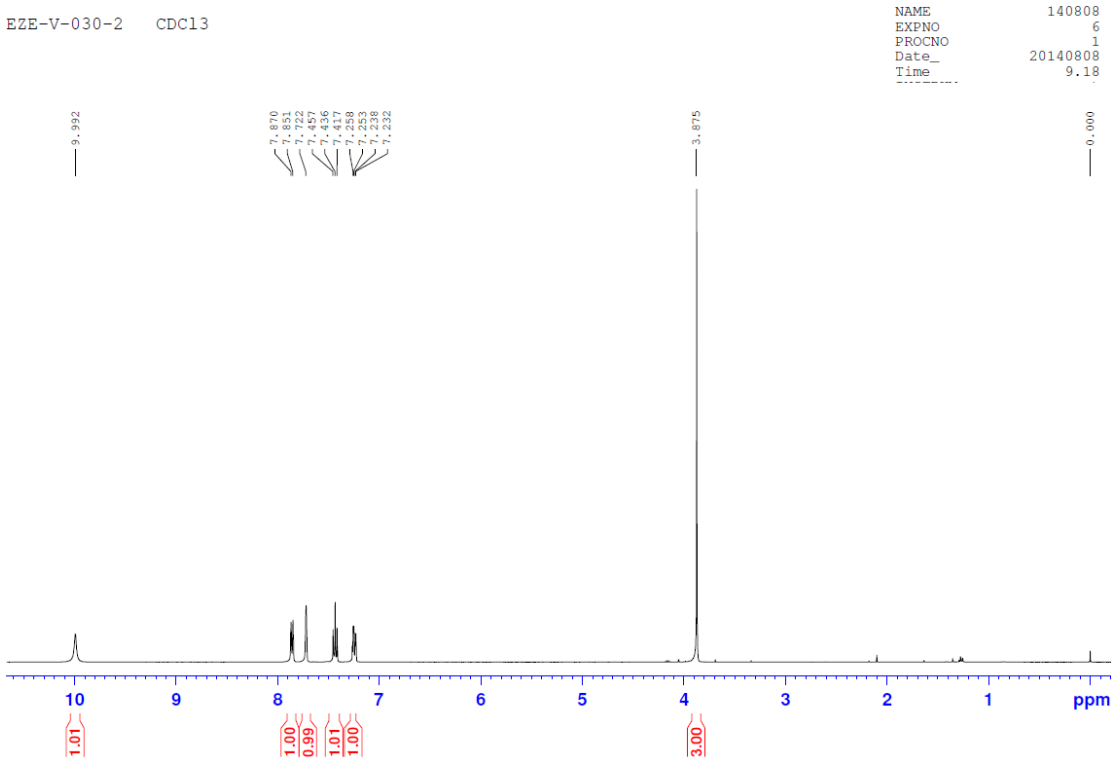


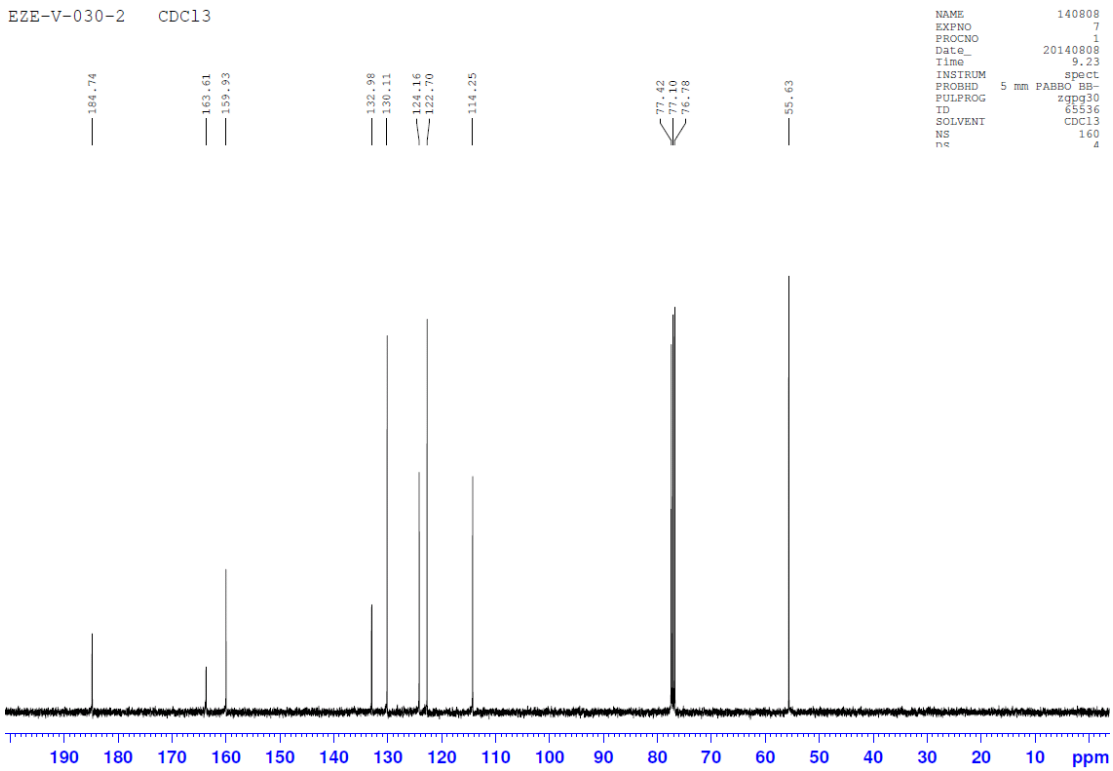


2-(3-methoxyphenyl)-2-oxoacetic acid (**2g**)

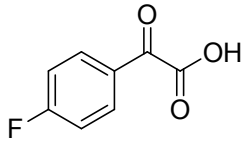


Yellow solid, mp: 63–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (brs, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.25 (dd, J = 2.0, 8.0 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7, 163.6, 159.9, 133.0, 130.1, 124.2, 122.7, 114.3, 55.6. HRMS (ESI) calcd for [M-H, $C_9H_7O_4$]$^-$: 179.0344, Found 179.0340.

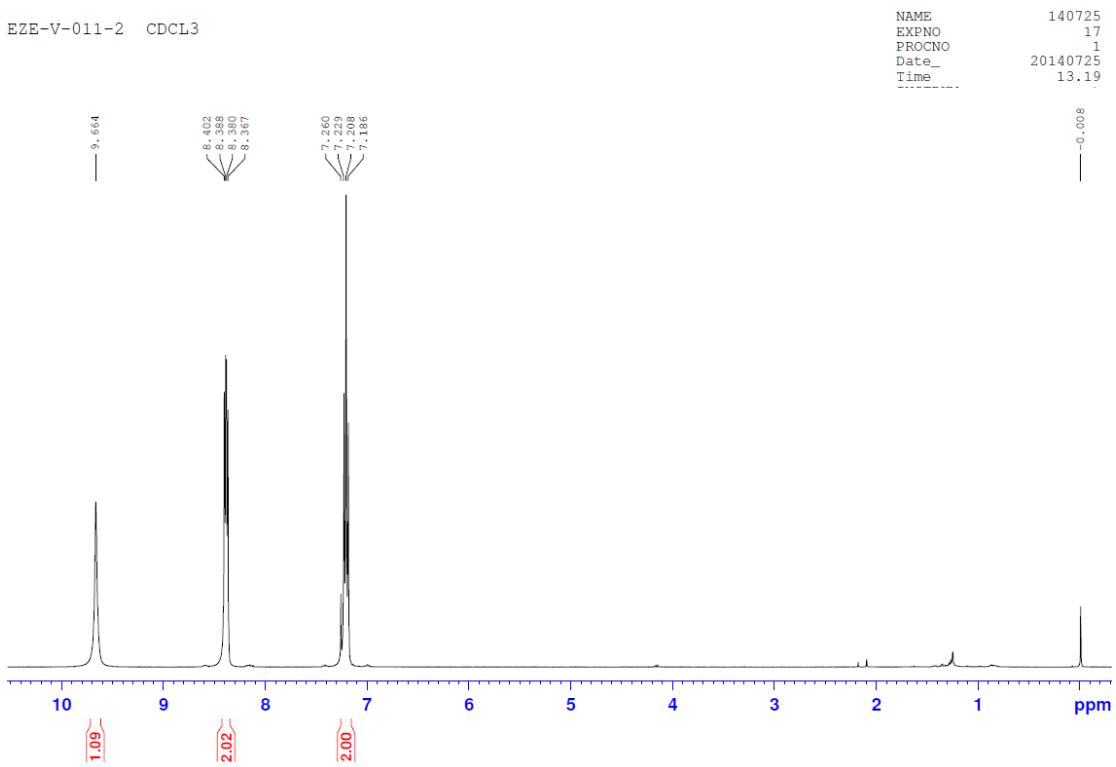




2-(4-fluorophenyl)-2-oxoacetic acid (**2h**)



Pale yellow solid, mp: 93–94 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (brs, 1H), 8.40–8.37 (m, 2H), 7.23–7.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 168.7, 166.1, 162.2, 134.5, 134.4, 128.3 (d), 116.6, 116.4. HRMS (ESI) calcd for [M-H, $C_8H_4FO_3$]$^{-}$: 167.0144, Found 167.0150.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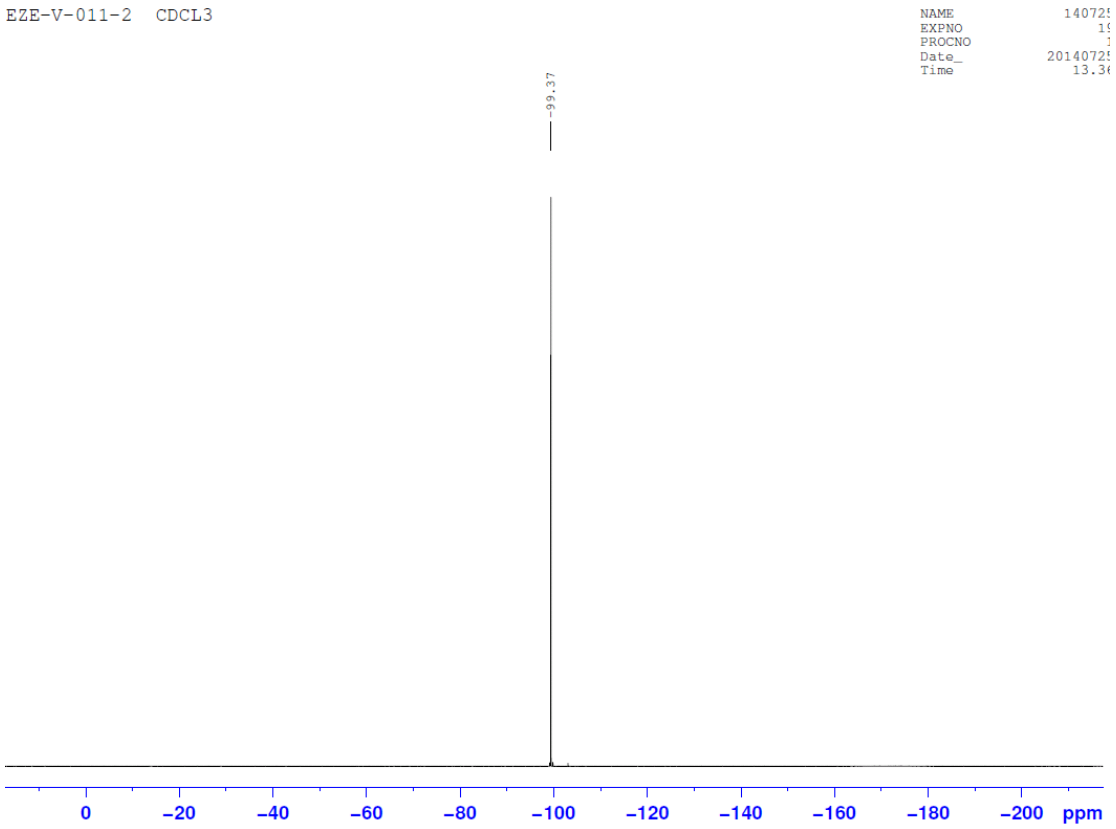
2.00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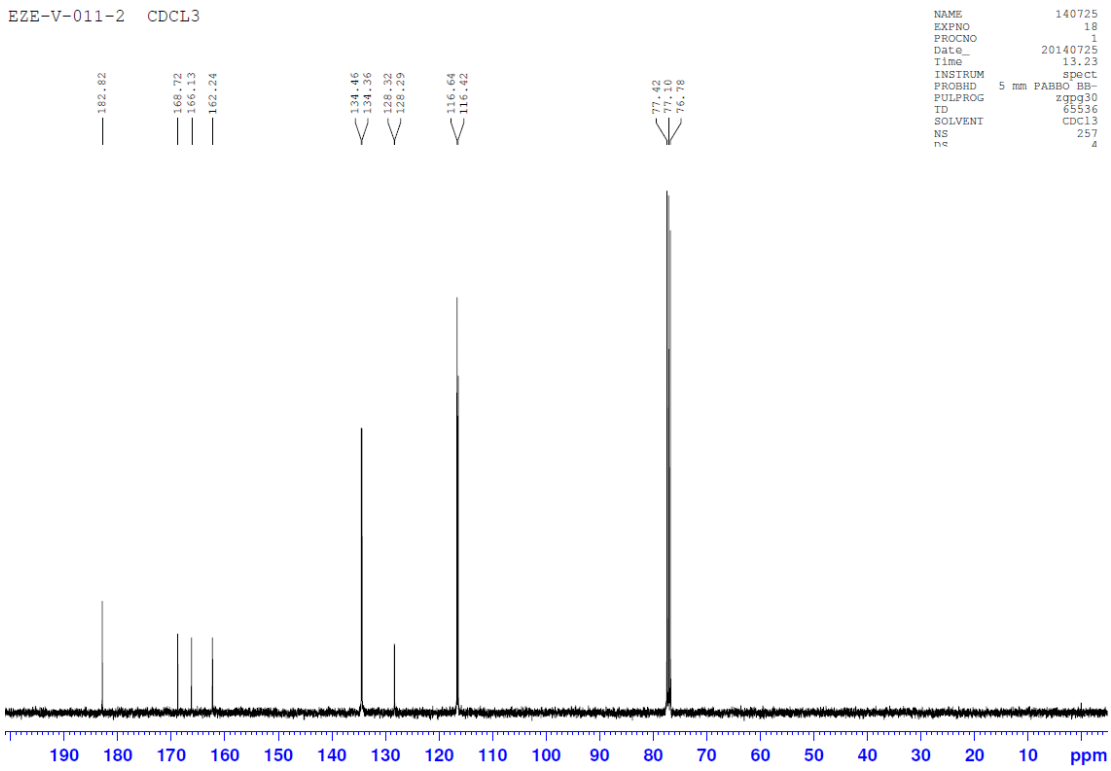
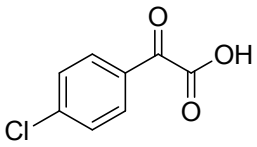
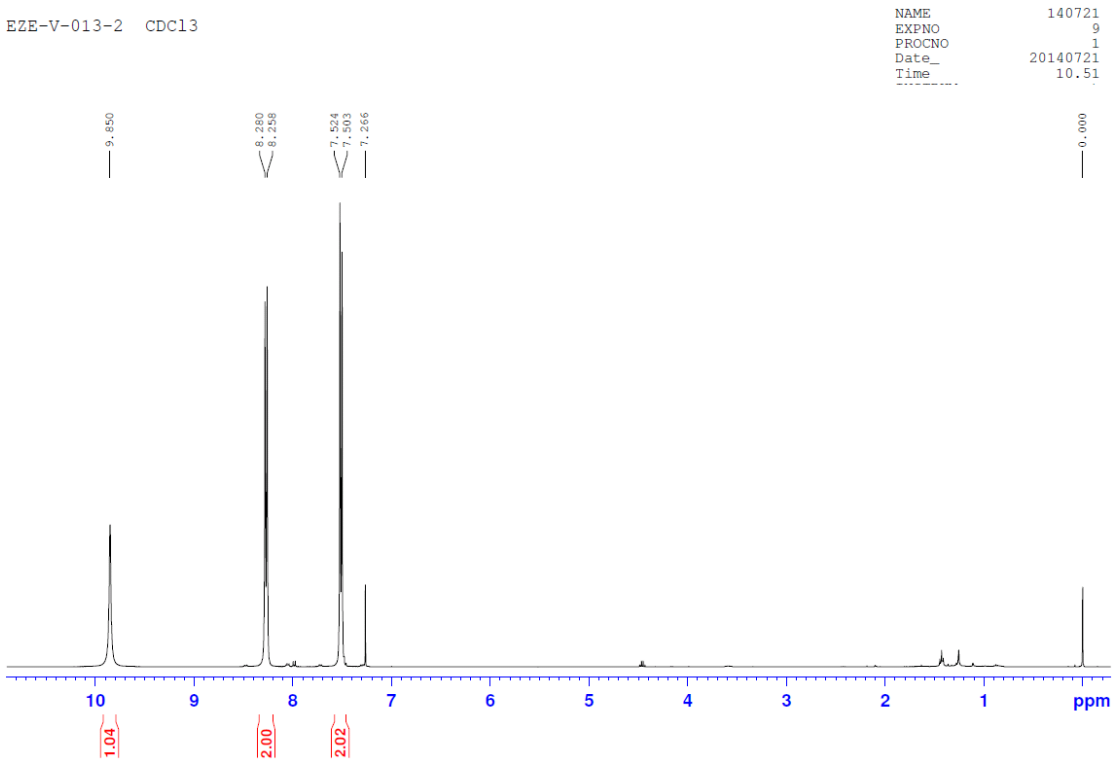


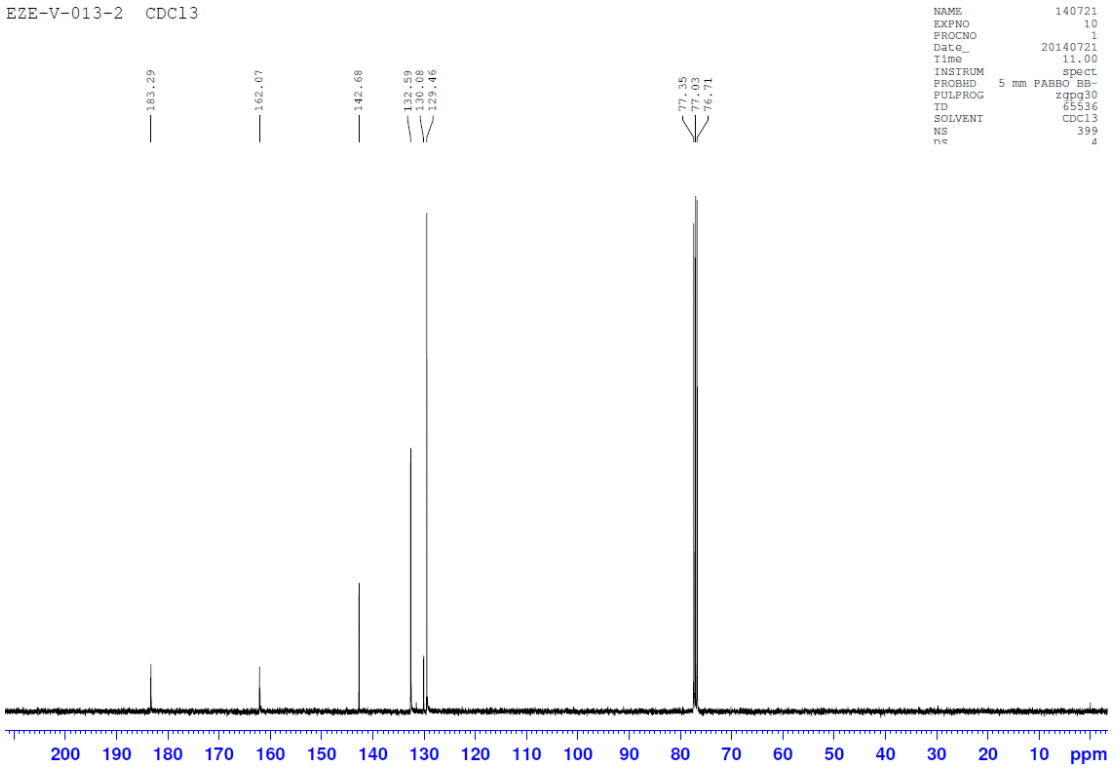
2-(4-chlorophenyl)-2-oxoacetic acid (**2i**)[3]



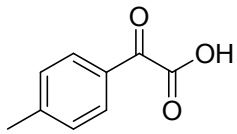
Pale yellow solid, mp: 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (brs, 1H), 8.27 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.3, 162.1, 142.7, 132.6, 130.1, 129.5.

[3] K. Wadhwa, C. Yang, P. R. West, K. C. Deming, S. R. Chemburkar, R. E. Reddy, *Synth. Commun.,* 2008, **38**, 4434.

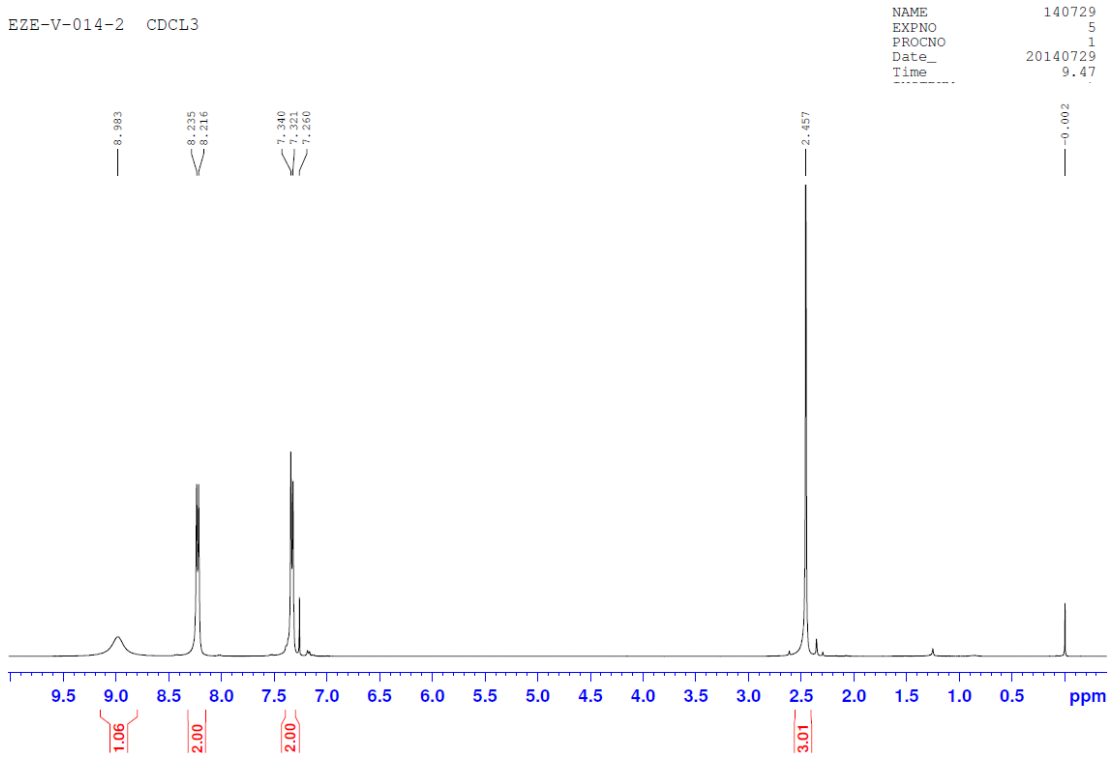


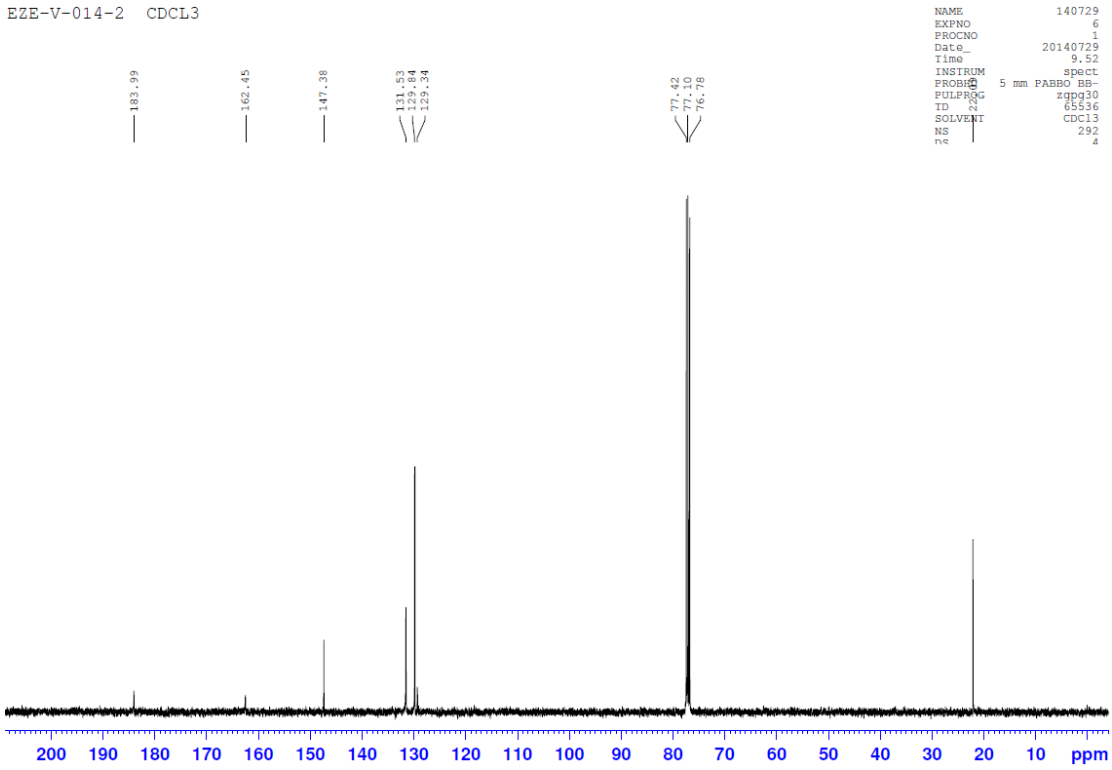


2-oxo-2-(p-tolyl)acetic acid (**2j**)

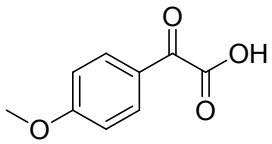


Pale yellow solid, mp: 94–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (brs, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.0, 162.5, 147.4, 131.5, 129.8, 129.3, 22.1. HRMS (ESI) calcd for [M-H, $C_9H_7O_3$]$^{-}$: 163.0395, Found 163.0398.

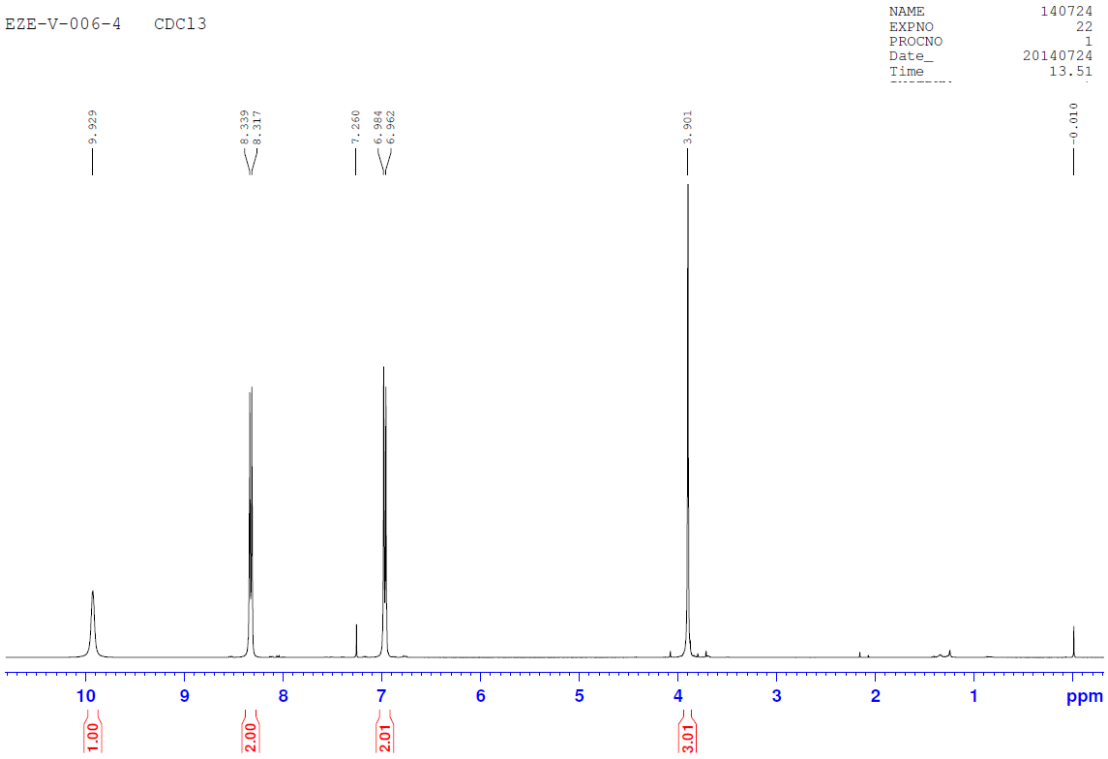




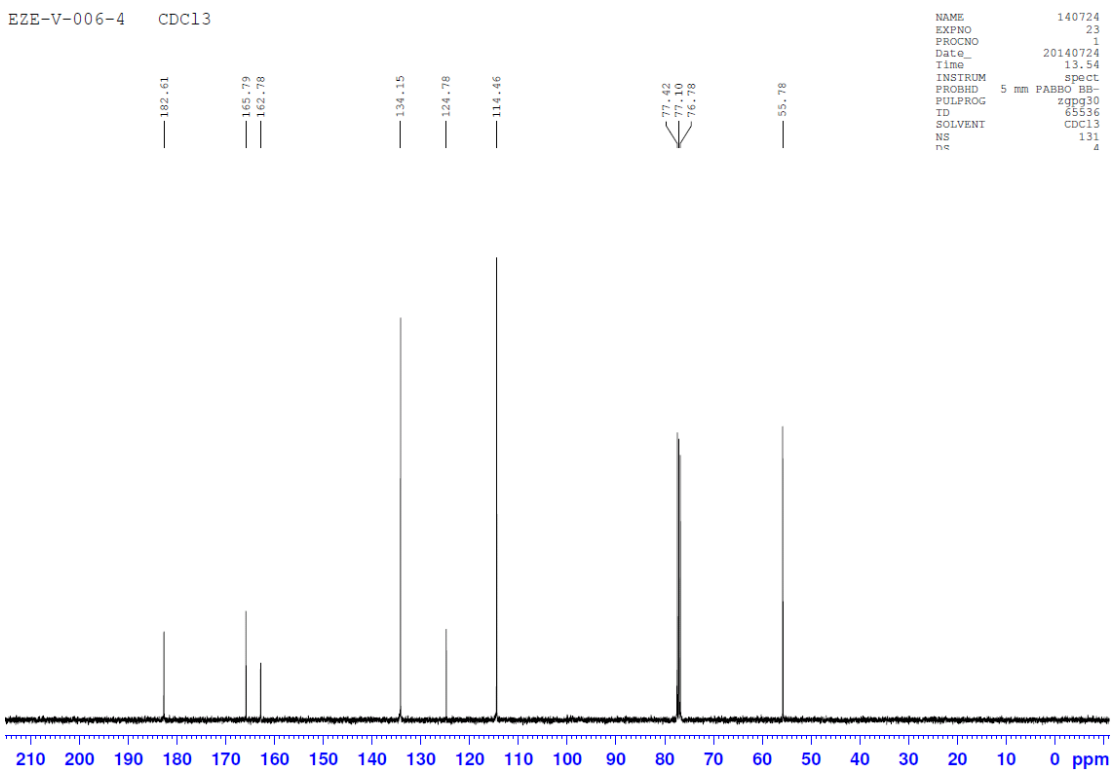
2-(4-methoxyphenyl)-2-oxoacetic acid (**2k**)[4]



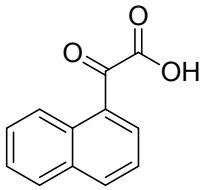
Pale yellow solid, mp: 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (brs, 1H), 8.33 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.6, 165.8, 162.8, 134.2, 124.8, 114.5, 55.8.



[4] M.-L. Yang, P.-C. Kuo, A. G. Damu, R.-J. Chang, W.-F. Chiou, T.-S. Wu, *Tetrahedron,* 2006, **62**, 10900.

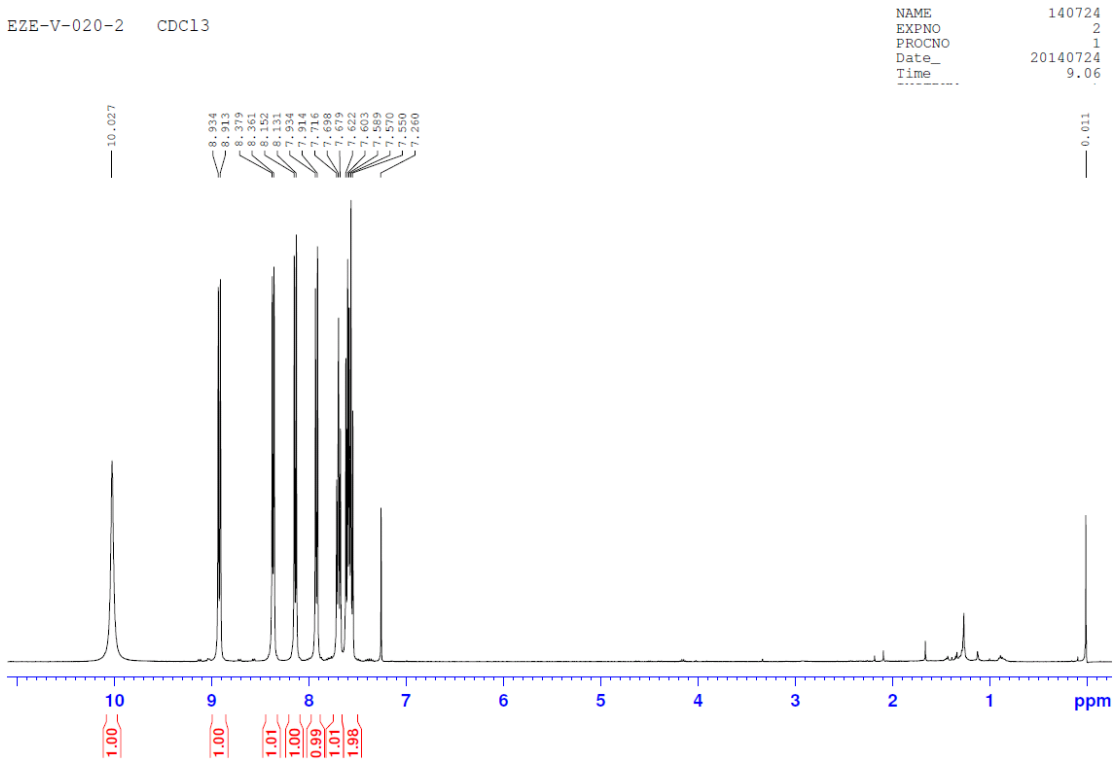


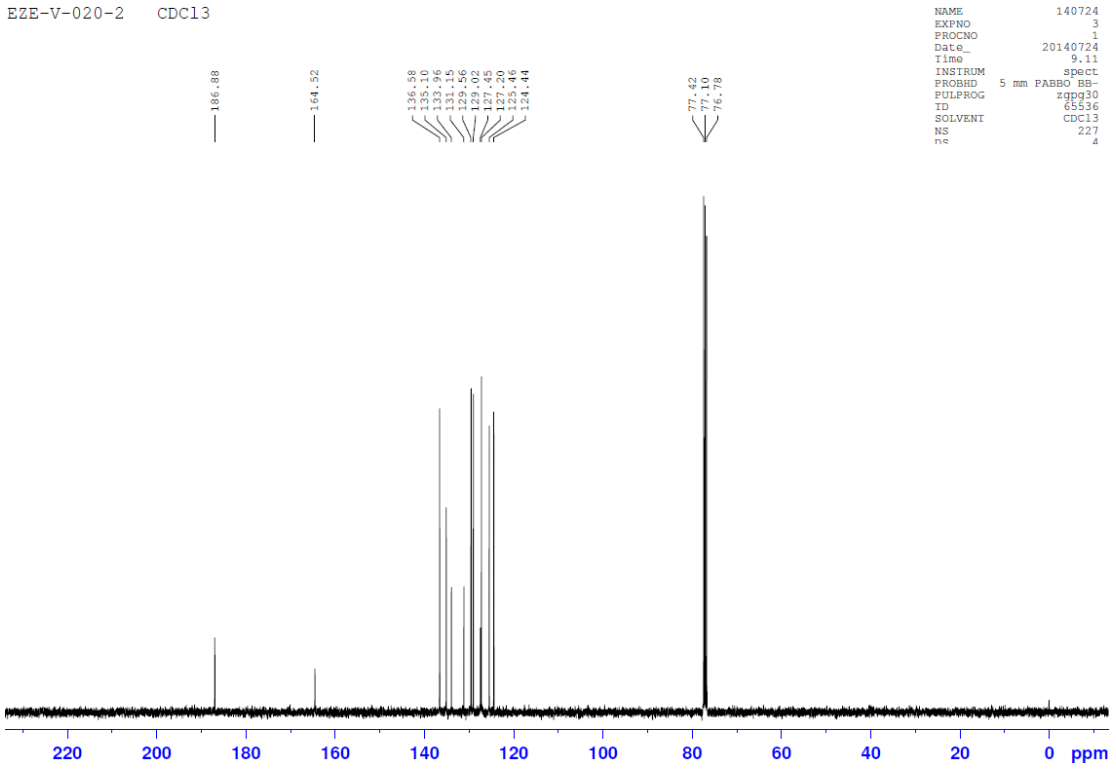
2-(naphthalen-1-yl)-2-oxoacetic acid (**2l**)[5]



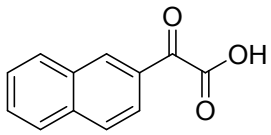
Yellow solid, mp: 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (brs, 1H), 8.92 (d, J = 8.4 Hz, 2H), 8.37 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.72–7.55 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9, 164.5, 136.6, 135.1, 134.0, 131.2, 129.6, 129.0, 127.5, 127.2, 125.5, 124.4.

[5] D. Crich, Y. Zou, *J. Org. Chem.,* 2005, **70**, 3309.

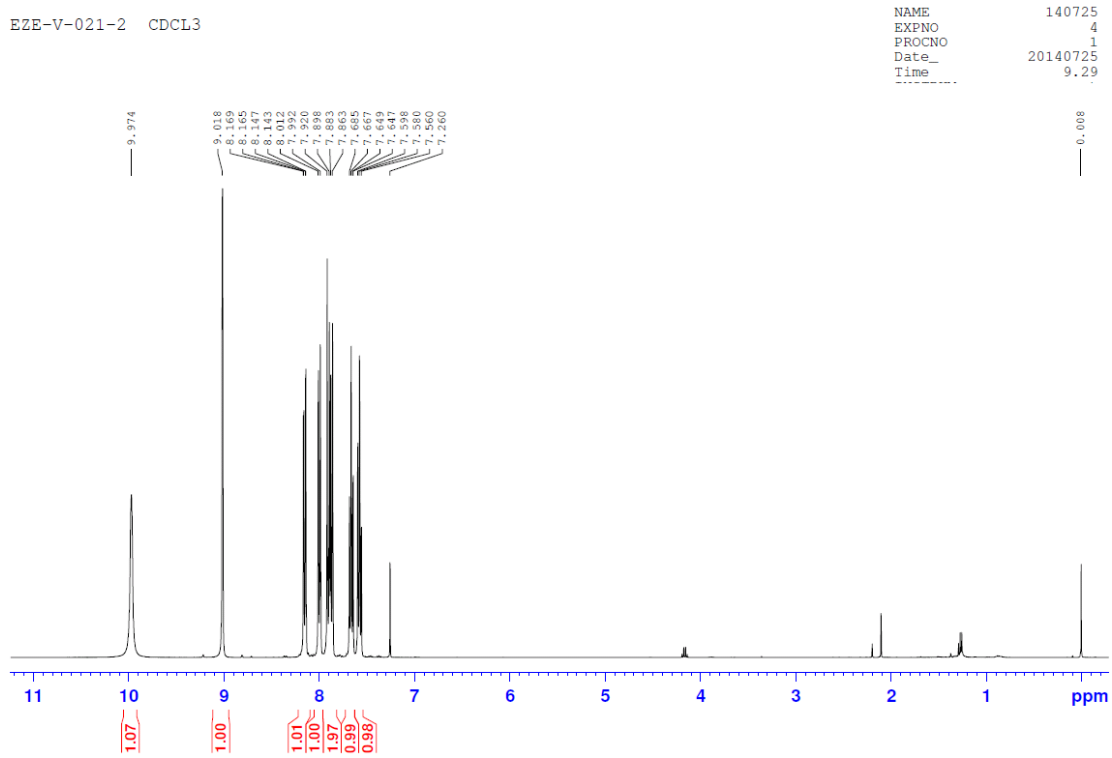


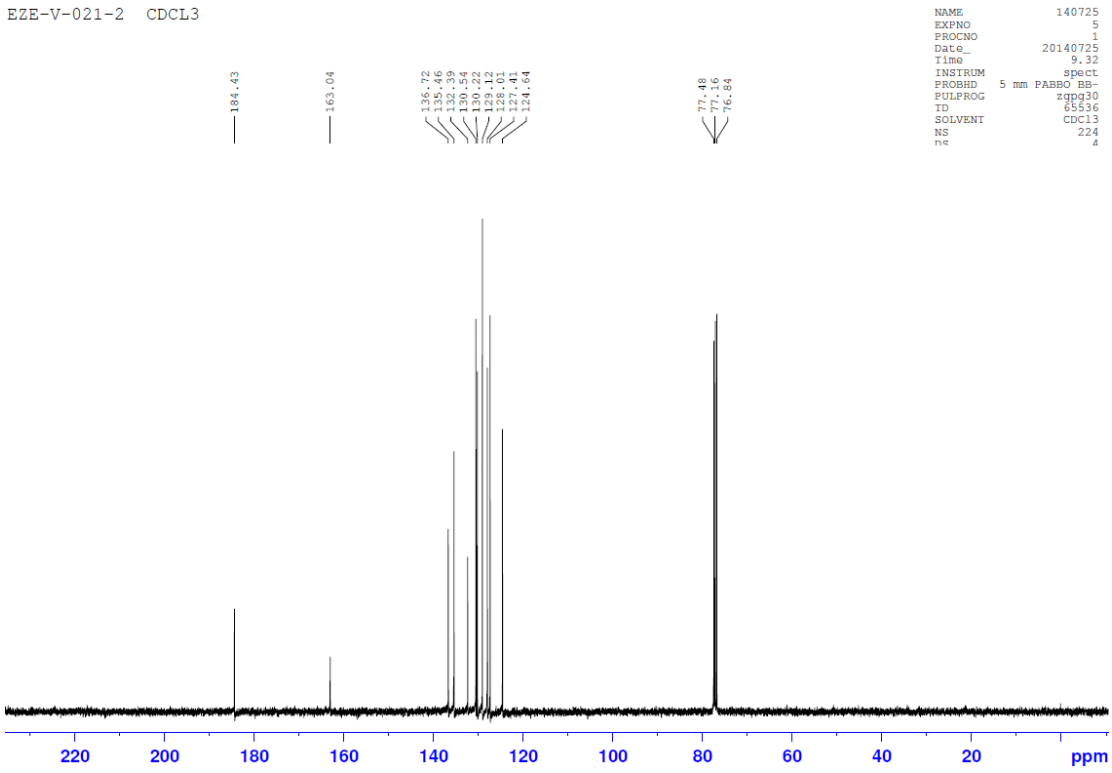


2-(naphthalen-2-yl)-2-oxoacetic acid (**2m**)

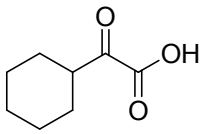


Yellow solid, mp: 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (brs, 1H), 9.02 (s, 1H), 8.16 (dd, J = 8.8, 1.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.92–7.86 (m, 2H), 7.69–7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.4, 163.0, 136.7, 135.5, 132.4, 130.5, 130.2, 129.1, 128.0, 127.4, 124.6. HRMS (ESI) calcd for [M-H, $C_{12}H_7O_3$]$^{-}$: 199.0395, Found 199.0399.

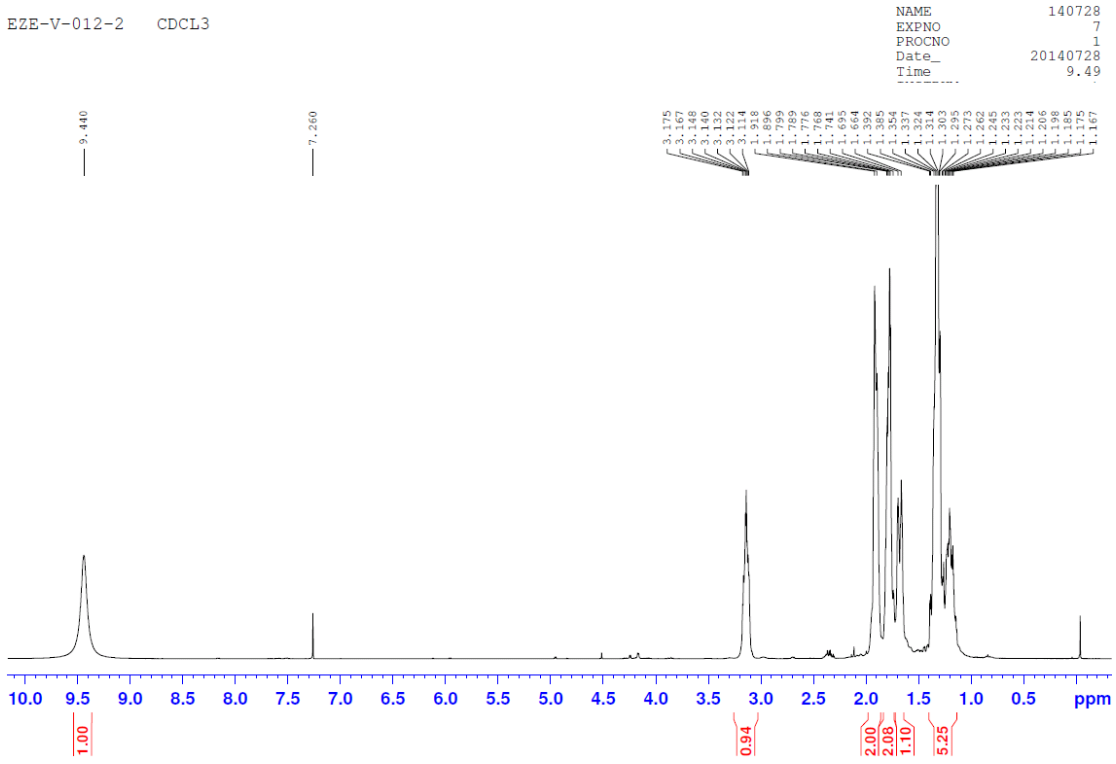


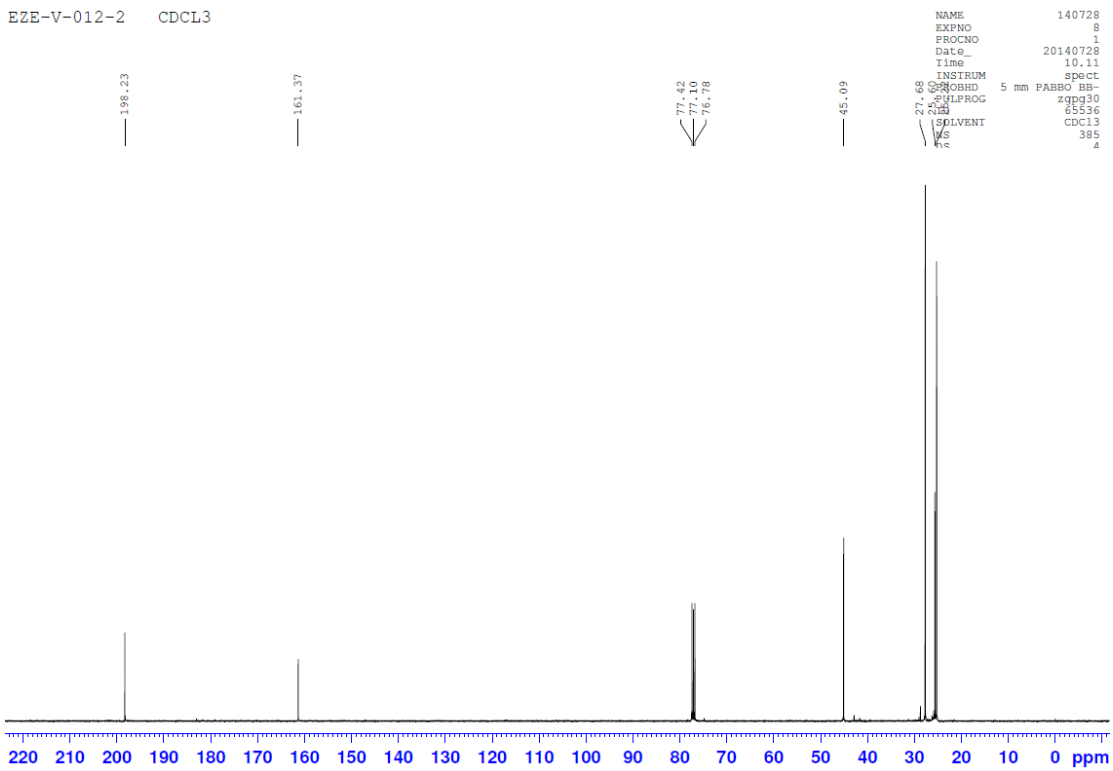


2-cyclohexyl-2-oxoacetic acid (**2o**)

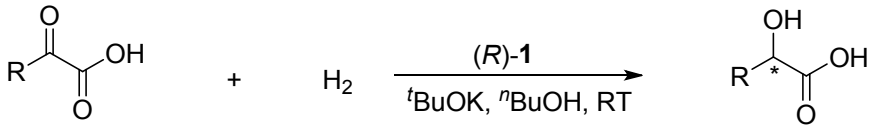


Yellow solid, mp: 48~49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (brs, 1H), 3.18–3.11 (m, 1H), 1.92–1.66 (m, 5H), 1.39–1.17 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 161.4, 45.1, 27.7, 25.6, 25.2. HRMS (ESI) calcd for $[M\text{-}H, C_8H_{11}O_3]^-$: 155.0708, Found 155.0711.





(C) General Procedure for Asymmetric Hydrogenation



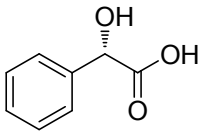
2 **3**

(S/C = 1000): To a 30 mL hydrogenation vessel were added ^{t}BuOK (242 mg, 2.16 mmol), α-keto acid **2** (2 mmol), the catalyst (*R*)-**1** (2 mg, 0.002mmol) and anhydrous ^{n}BuOH (5 mL) under nitrogen atmosphere. The vessel was then placed in an autoclave. The air in the autoclave was replaced with hydrogen for five times. Then the autoclave was charged with hydrogen to 15 atm, and the reaction mixture was stirred at room temperature for a certain time. After releasing the hydrogen pressure, the reaction mixture was acidified with 3 M HCl and extracted with ^{t}BuOMe. The extract was dried over Na_2SO_4 and concentrated on a rotary evaporator. The conversion of substrate was determined by ^{1}H NMR analysis. The crude product was purified by flash chromatography on silica gel column to give the pure product **3**. The product was esterfied to afford the corresponding ester which was analyzed on HPLC with a chiral column to determined *ee* value.

(D) Analytical Data, NMR Spectra and HPLC Charts of α-Hydroxy Acids

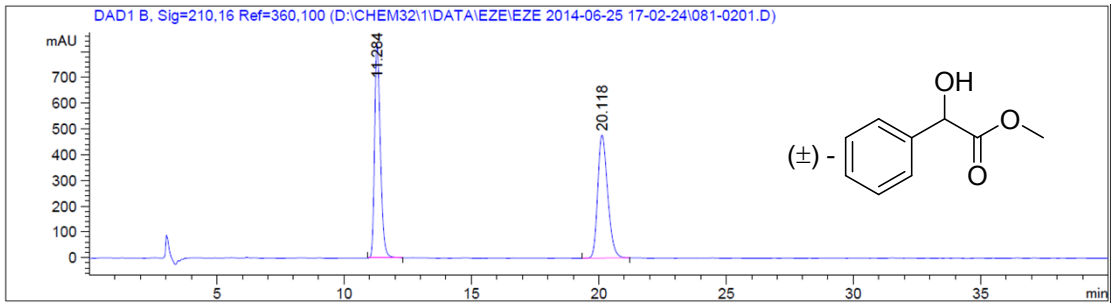
(*S*)-2-hydroxy-2-phenylacetic acid (**3a**)[6]

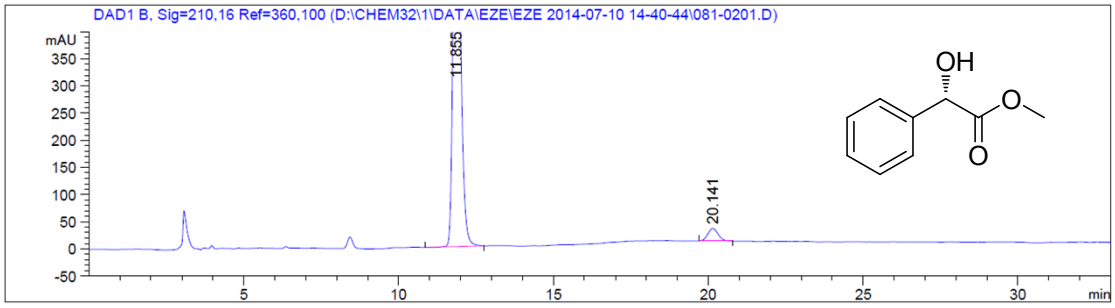
[6] P. D. Gennaro, S. Bernasconi, F. Orsini, E. Corretto, G. Sello, *Tetrahedron: Asymmetry,* 2010, **21**, 1885.



Yield: 95%, white solid. 93% ee, $[\alpha]_D^{28}$ +148.0 (*c* 0.5, H_2O), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 11.86 min for (*S*)-enantiomer and t_R = 20.14 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, CD_3OD): δ 7.46 (d, *J* = 7.2 Hz, 2H), 7.30–7.19 (m, 3H), 4.84 (s, 1H).

methyl 2-hydroxy-2-phenylacetate



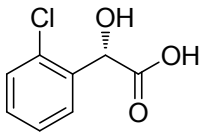


Signal 1: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.855	VB	0.2496	1.36085e4	846.38763	96.2531
2	20.141	BBA	0.3590	529.74707	22.97806	3.7469
Totals :				1.41382e4	869.36569	

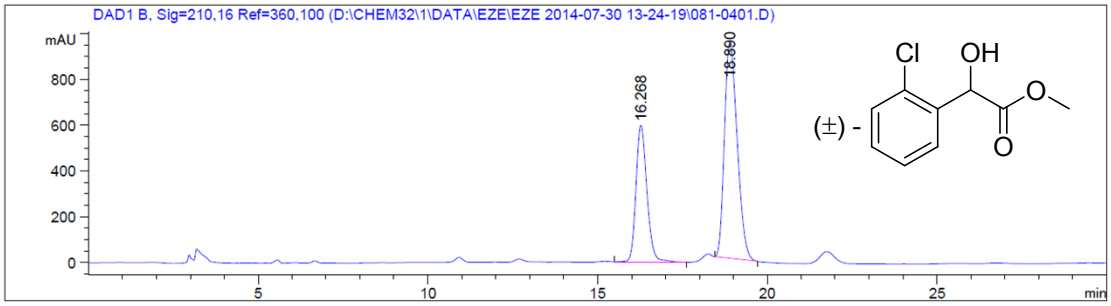
(*S*)-2-(2-chlorophenyl)-2-hydroxyacetic acid (**3b**)[7]

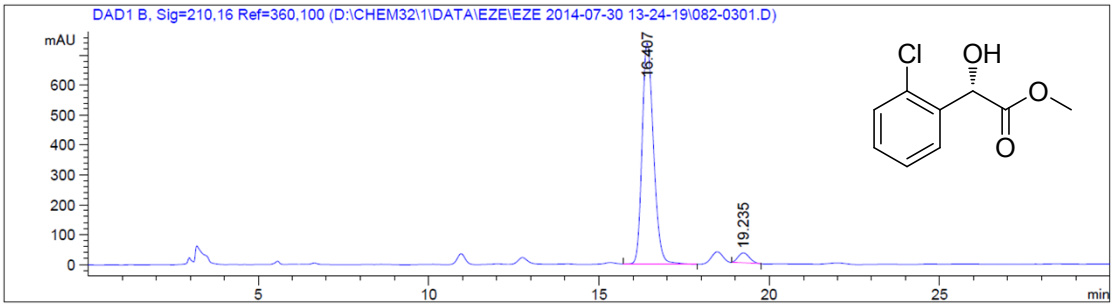
[7] N. Kurono, K. Arai, M. Uemura, T. Ohkuma, *Angew. Chem., Int. Ed.*, 2008, **47**, 6643.



Yield: 93%, white solid. 91% ee, $[\alpha]_D^{28}$ +137.1 (*c* 0.5, EtOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 97:3, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 16.41 min for (*S*)-enantiomer and t_R = 19.24 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, CD_3OD): δ 7.52–7.50 (m, 1H), 7.42–7.39 (m, 1H), 7.33–7.29 (m, 2H), 5.57 (s, 1H).

methyl 2-(2-chlorophenyl)-2-hydroxyacetate

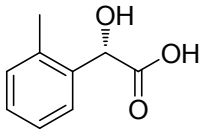




Signal 1: DAD1 B, Sig=210,16 Ref=360,100

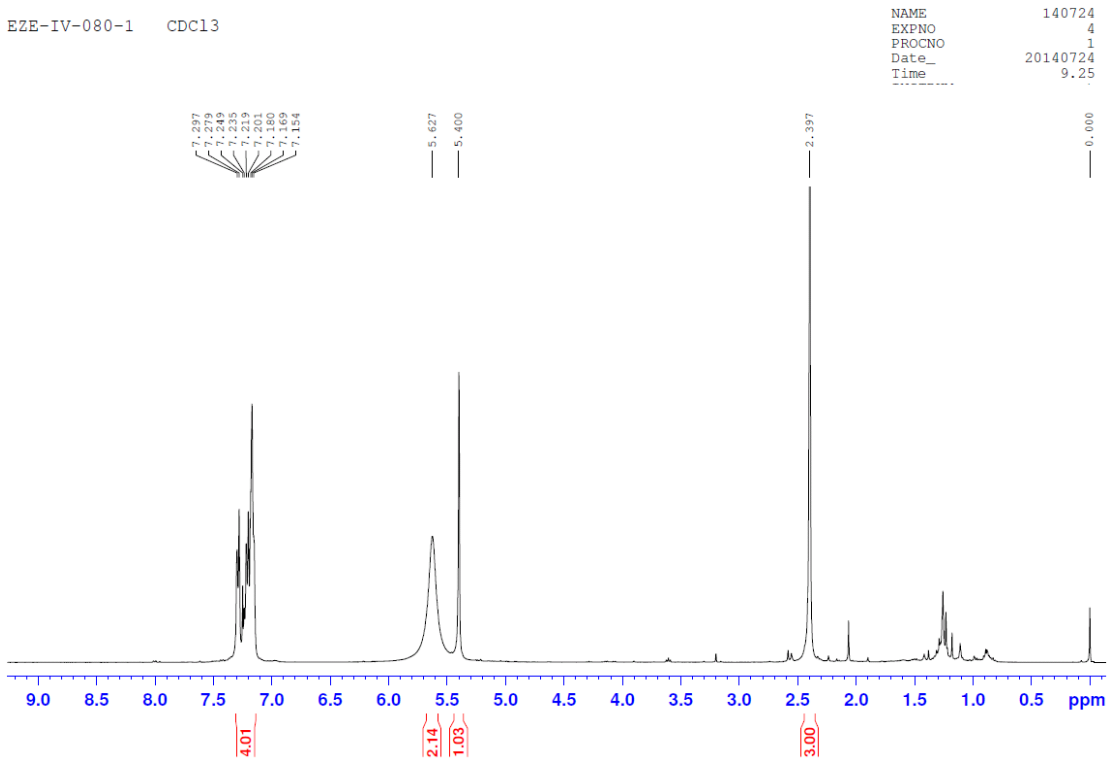
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.407	VB	0.3601	1.72843e4	741.08130	95.6767
2	19.235	BBA	0.3703	781.02588	33.71489	4.3233
Totals :				1.80653e4	774.79618	

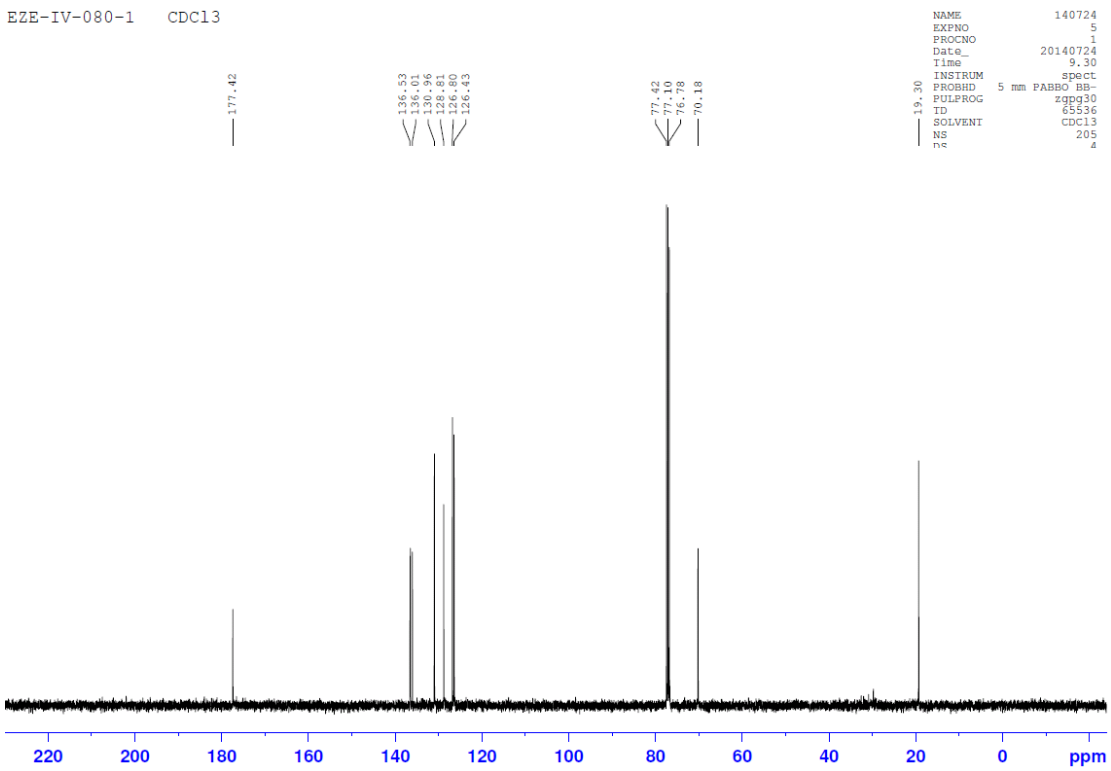
(*S*)-2-hydroxy-2-(o-tolyl)acetic acid (**3c**)[8]



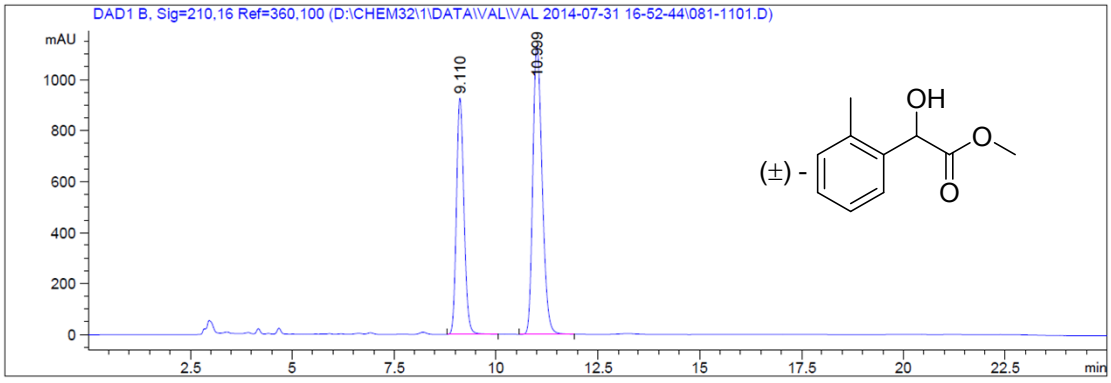
[8] H. Vázquez-Villa, S. Reber, M. A. Ariger, E. M. Carreira, *Angew. Chem., Int. Ed.,* 2011, **50**, 8979.

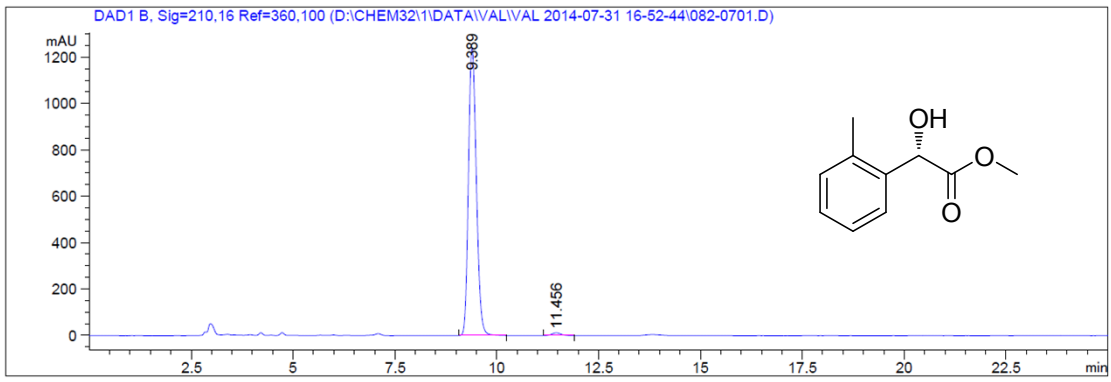
Yield: 98%, pale yellow oil, 98% ee, $[\alpha]_D^{28}$ +175.1 (*c* 0.5, EtOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 92:8, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 9.39 min for (*S*)-enantiomer and t_R = 11.46 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.15 (m, 4H), 5.63 (brs, 2H), 5.40 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 136.5, 136.0, 131.0, 128.8, 126.8, 126.4, 70.2, 19.3.





methyl 2-hydroxy-2-(o-tolyl)acetate

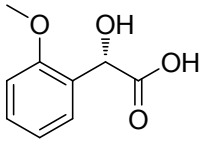




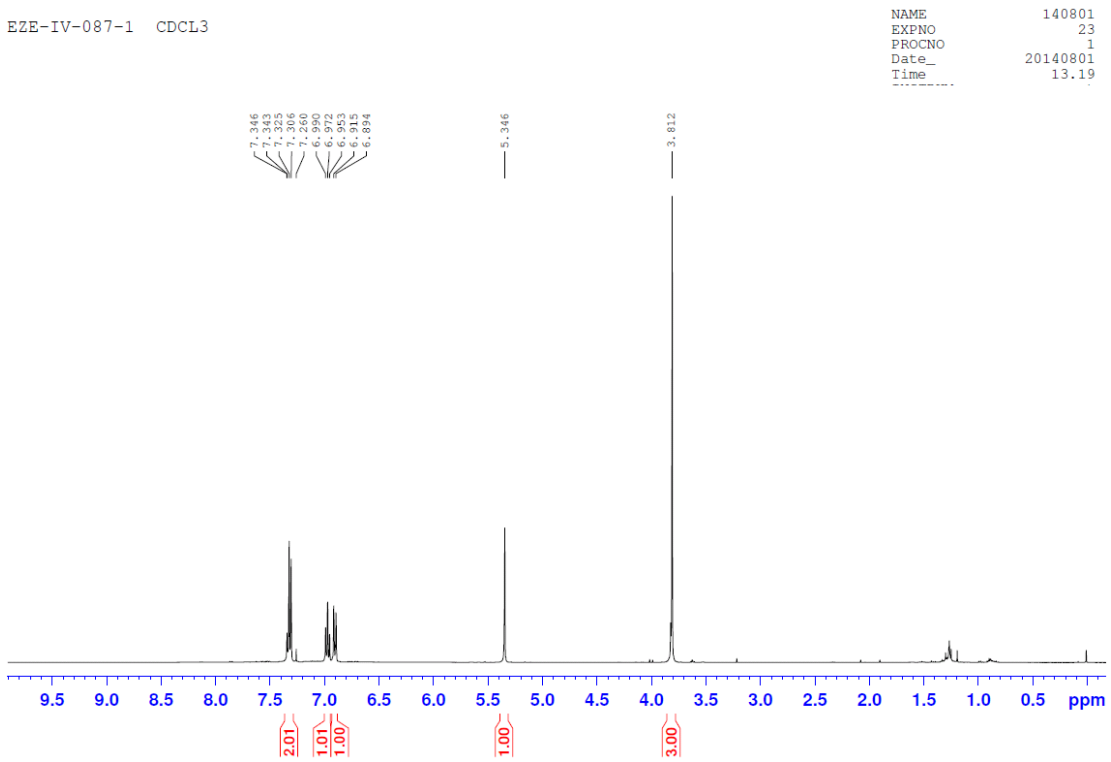
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

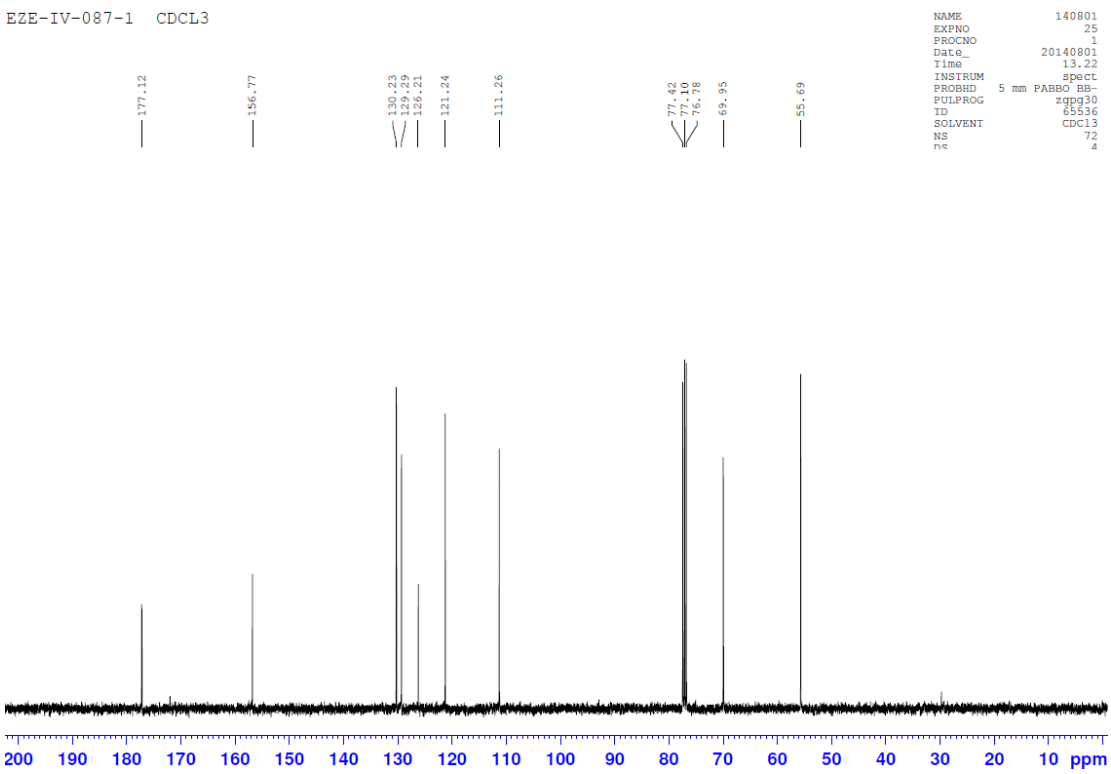
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.389	BB	0.2109	1.67179e4	1242.99023	98.9050
2	11.456	BB	0.2425	185.08586	11.83152	1.0950
Totals :				1.69030e4	1254.82176	

(*S*)-2-hydroxy-2-(2-methoxyphenyl)acetic acid (**3d**)

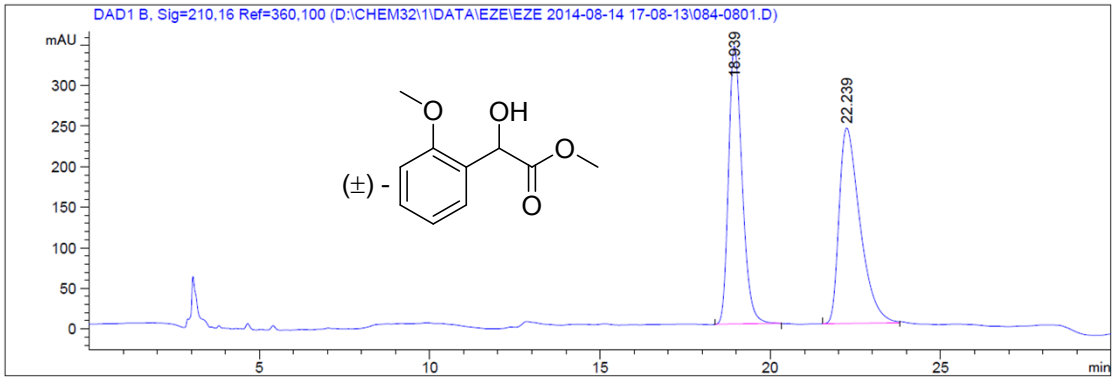


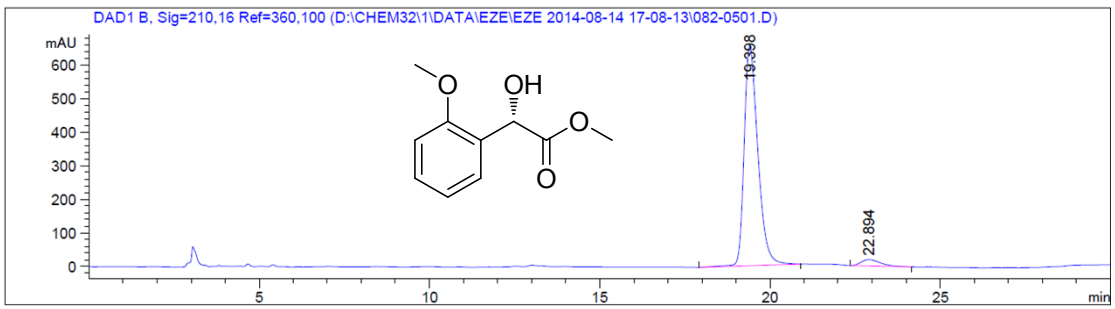
Yield: 97%, colorless oil, 92% ee, $[\alpha]_D^{28}$ +124.2 (*c* 0.51, EtOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 19.40 min for (*S*)-enantiomer and t_R = 22.89 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.31 (m, 2H), 6.99–6.89 (m, 2H), 5.35 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 156.8, 130.2, 129.3, 126.2, 121.2, 111.3, 70.0, 55.7; HRMS (ESI) calcd for $[M\text{-}H, C_9H_9O_4]^-$: 181.0501, Found 181.0504.





methyl 2-hydroxy-2-(2-methoxyphenyl)acetate

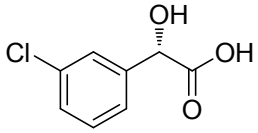




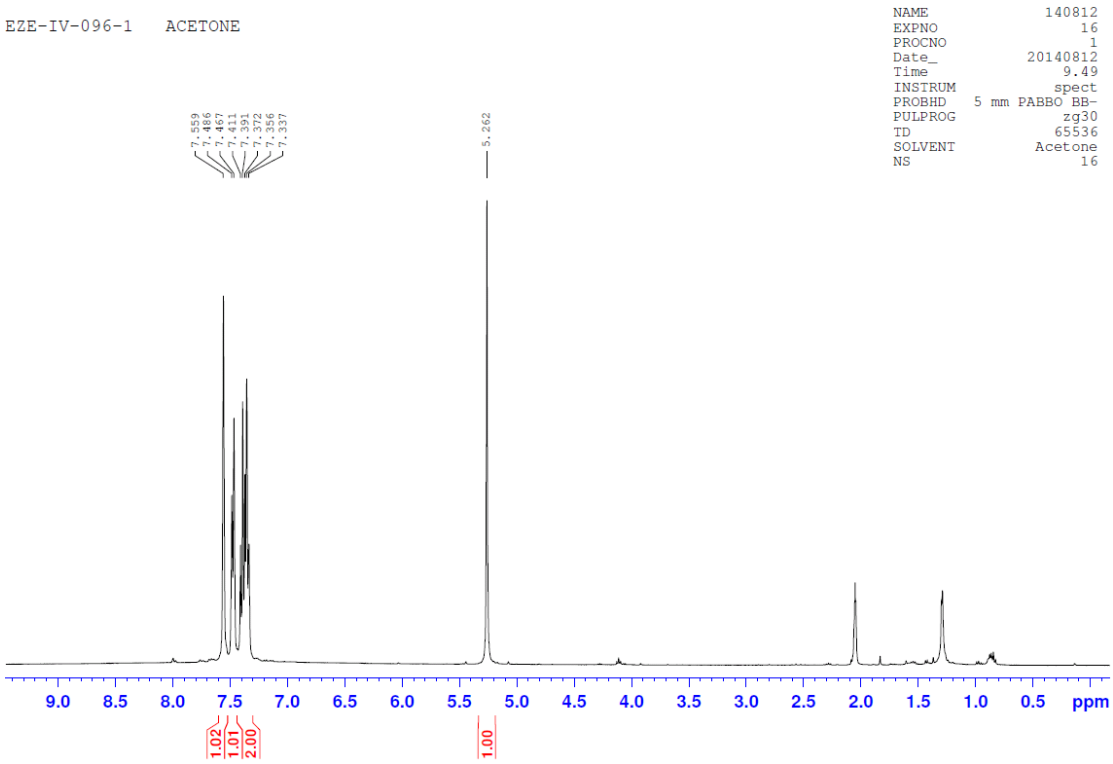
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.398	BB	0.4331	1.83758e4	655.45667	95.9851
2	22.894	BB	0.5856	768.62891	19.25933	4.0149
Totals :				1.91444e4	674.71600	

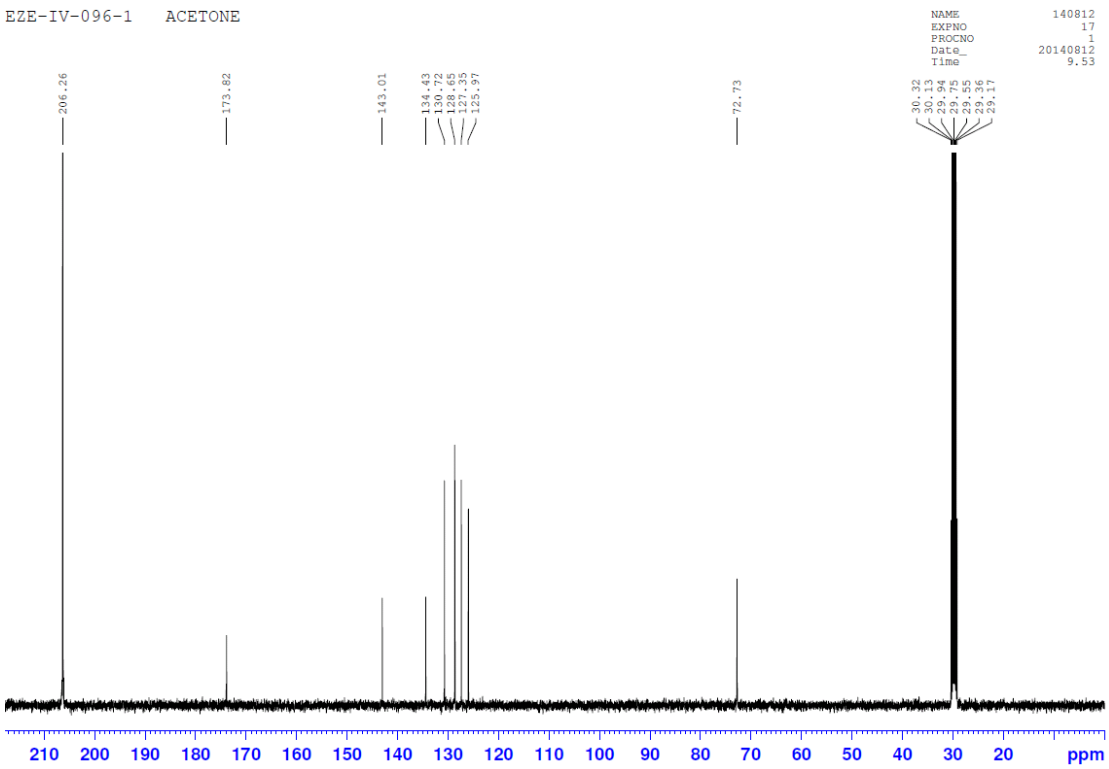
(*S*)-2-(3-chlorophenyl)-2-hydroxyacetic acid (**3e**)[9]



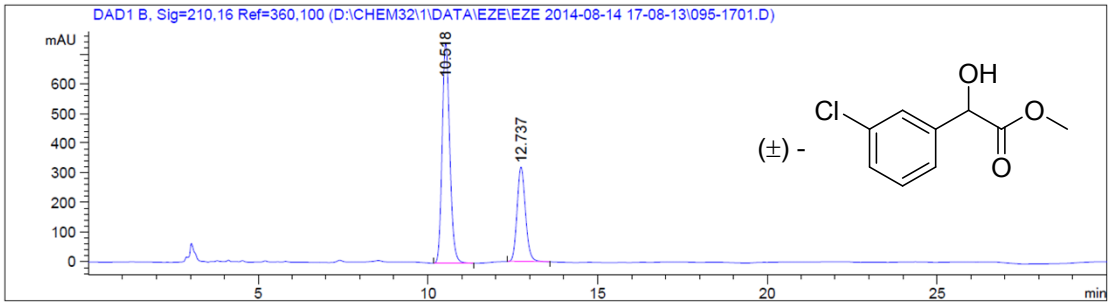
Yield: 94%, white solid, 91% ee, $[\alpha]_D^{28}$ +117.3 (*c* 0.5, H_2O), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 11.43 min for (*S*)-enantiomer and t_R = 13.74 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 7.56 (s, 1H), 7.49–7.34 (m, 3H), 5.26 (s, 1H). ^{13}C NMR (100 MHz, Acetone-d6): δ 173.8, 143.0, 134.4, 130.7, 128.7, 127.4, 126.0, 72.7; HRMS (ESI) calcd for [M-H, $C_8H_6ClO_3$]$^-$: 185.0005, Found 185.0010.

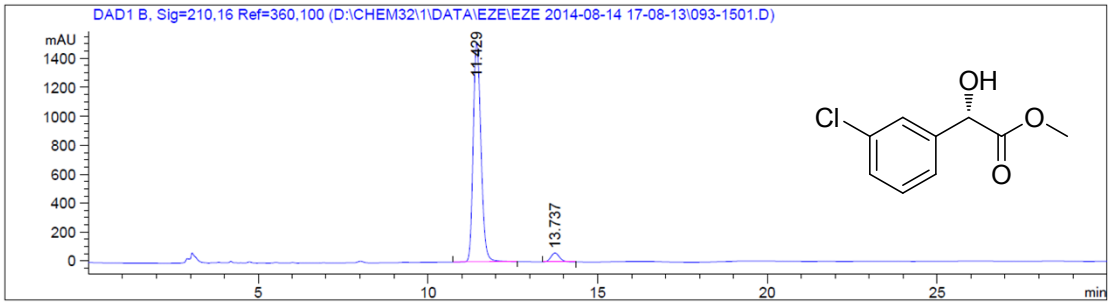


[9] H.-R. Huang, J.-H. Xu, Y. Xu, J. Pan, X. Liu, *Tetrahedron: Asymmetry,* 2005, **16**, 2113.



methyl 2-(3-chlorophenyl)-2-hydroxyacetate

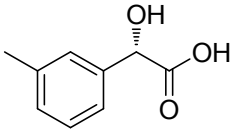




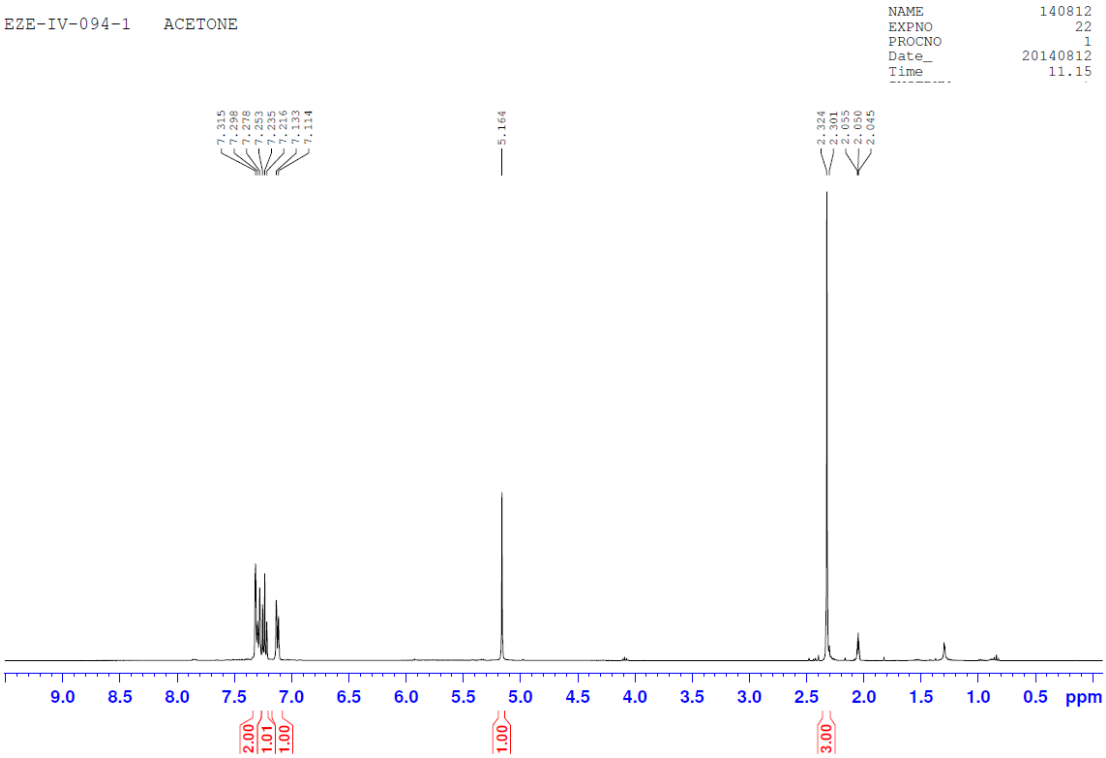
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

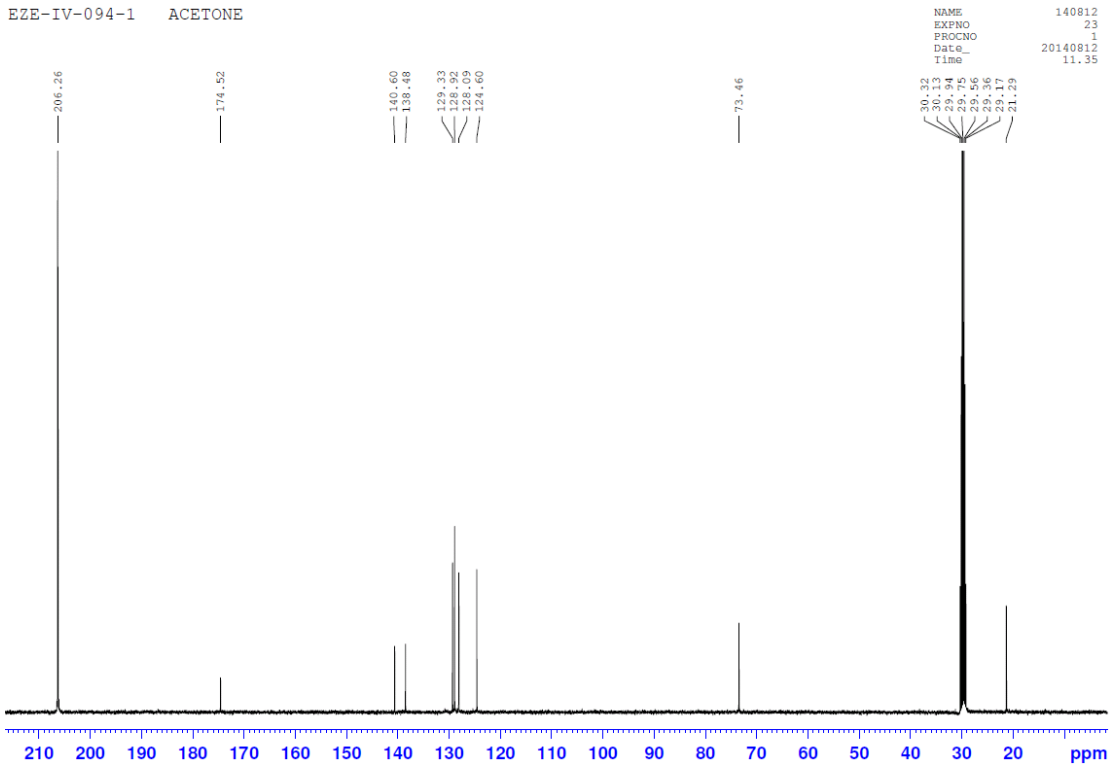
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.429	VB	0.2501	2.41473e4	1514.10461	95.6381
2	13.737	BB	0.2739	1101.30994	61.79673	4.3619
Totals :				2.52486e4	1575.90134	

(*S*)-2-hydroxy-2-(m-tolyl)acetic acid (**3f**)

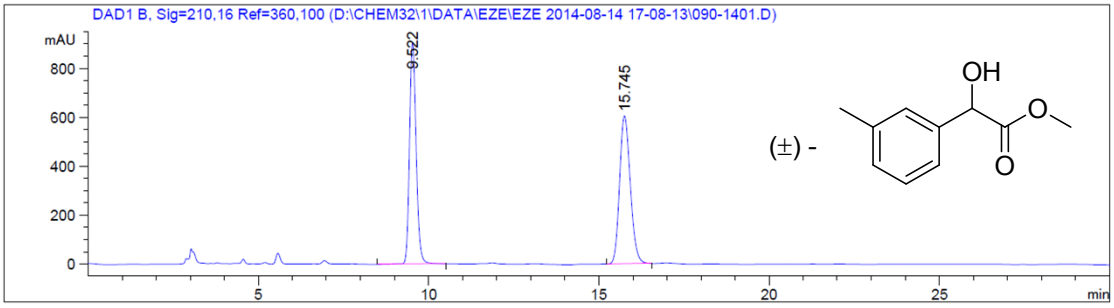


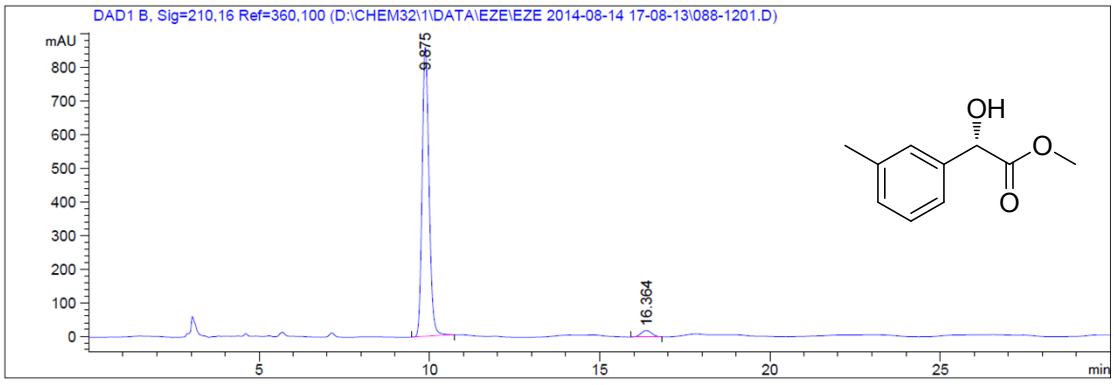
Yield: 95%, white solid, 92% ee, $[\alpha]_D^{28}$ +132.3 (*c* 0.5, EtOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 9.88 min for (*S*)-enantiomer and t_R = 16.36 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 7.32–7.22 (m, 3H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.16 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d6): δ 174.5, 140.6, 138.5, 129.3, 128.9, 128.1, 124.6, 73.5, 21.3; HRMS (ESI) calcd for [M-H, $C_9H_9O_3$]$^-$: 165.0552, Found 165.0557.





methyl 2-hydroxy-2-(m-tolyl)acetate

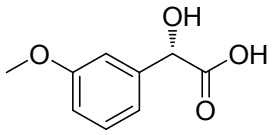




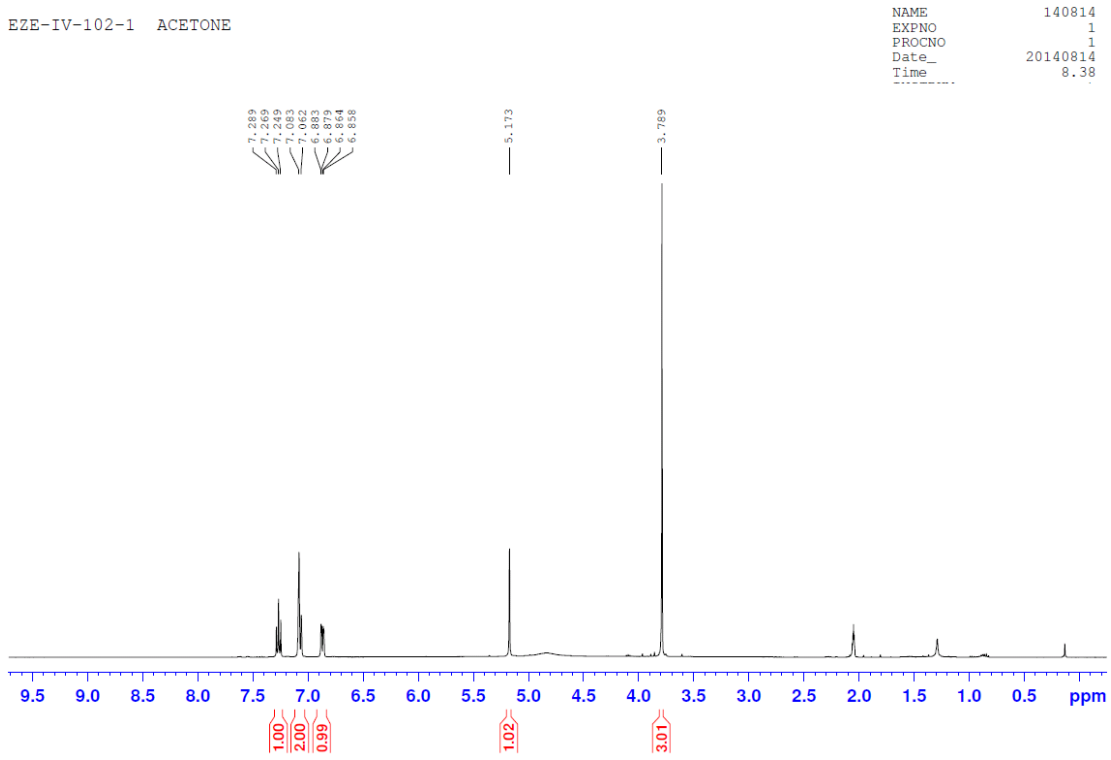
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

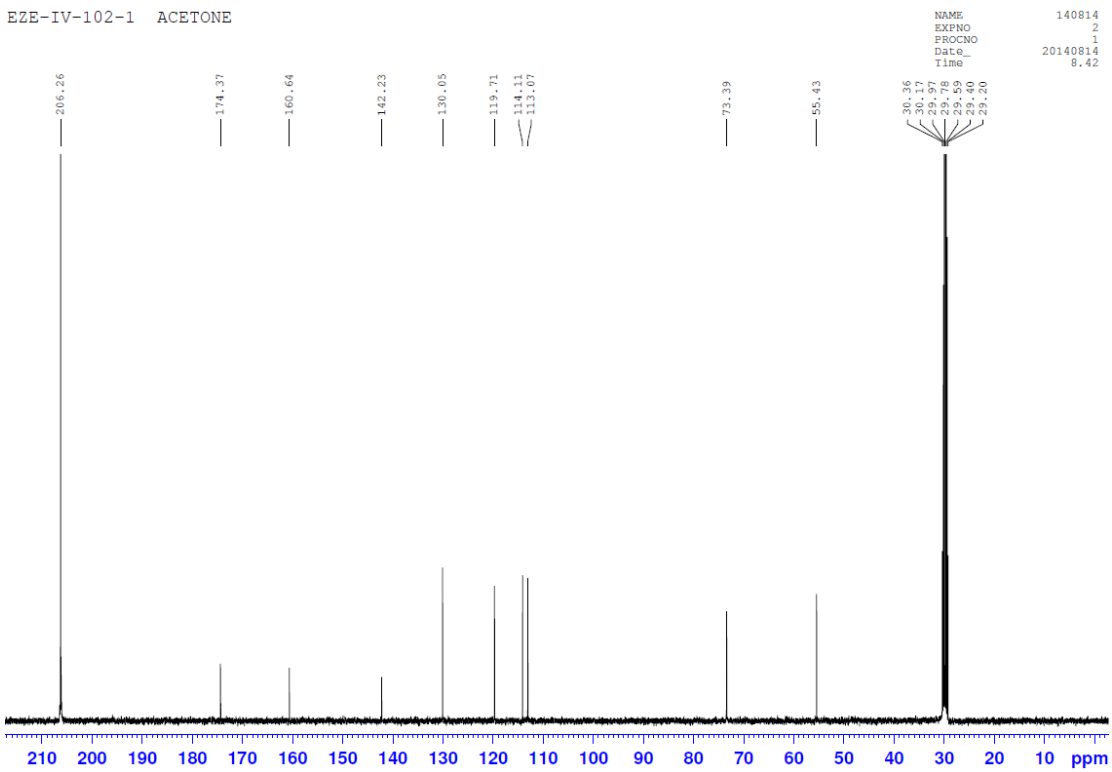
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.875	BB	0.2177	1.20792e4	860.73804	96.1747
2	16.364	VV	0.3666	480.44095	20.41241	3.8253
Totals :				1.25596e4	881.15045	

(*S*)-2-hydroxy-2-(3-methoxyphenyl)acetic acid (**3g**)

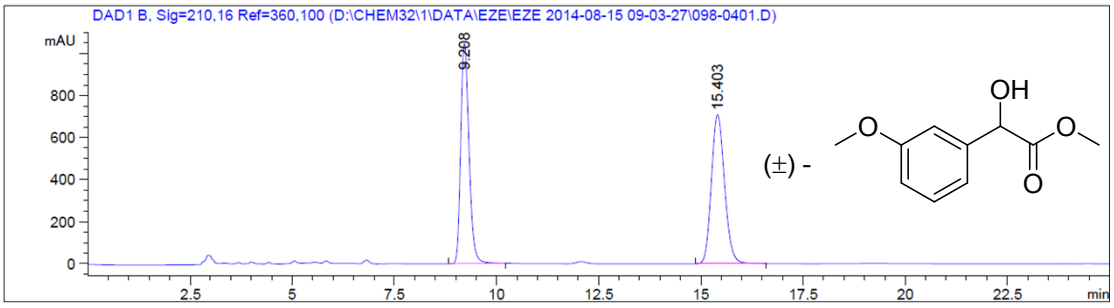


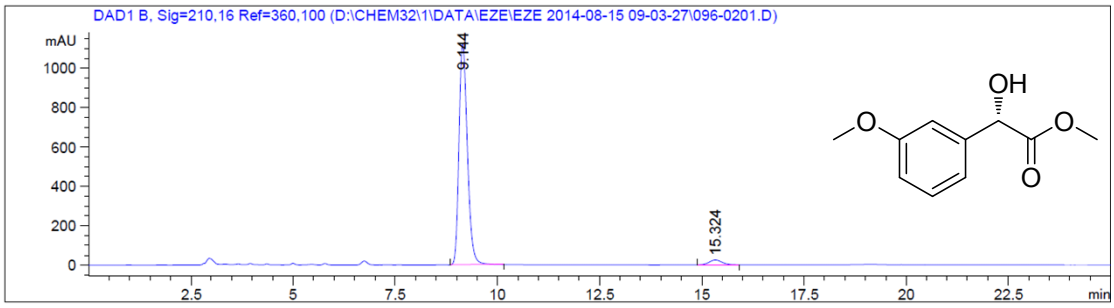
Yield: 97%, colorless oil, 94% ee, $[\alpha]_D^{28}$ +106.6 (*c* 0.5, EtOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 90:10, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 9.14 min for (*S*)-enantiomer and t_R = 15.32 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 7.27 (t, *J* = 8.0 Hz, 1H), 7.08–7.06 (m, 2H), 6.88–6.86 (m, 1H), 5.17 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d6): δ 174.4, 160.6, 142.2, 130.1, 119.7, 114.1, 113.1, 73.4, 55.4; HRMS (ESI) calcd for[M-H, $C_9H_9O_4$]$^-$: 181.0501, Found 181.0506.





methyl 2-hydroxy-2-(3-methoxyphenyl)acetate

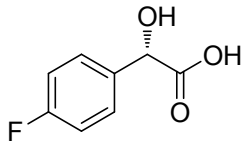




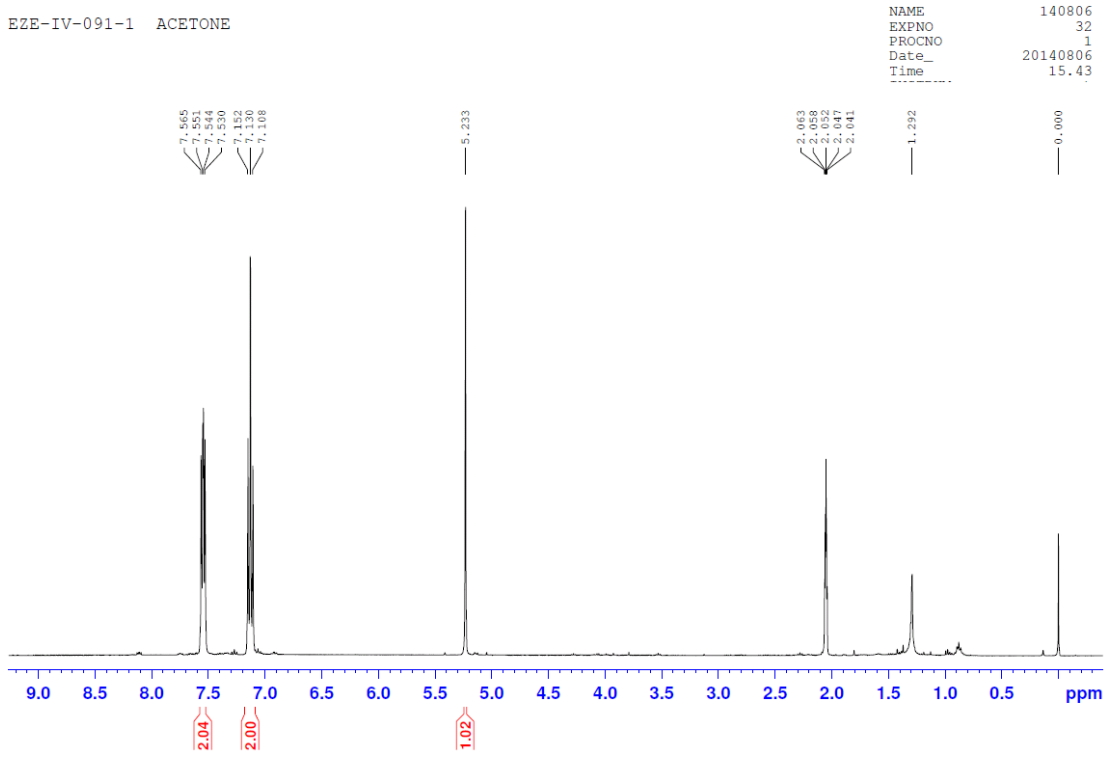
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

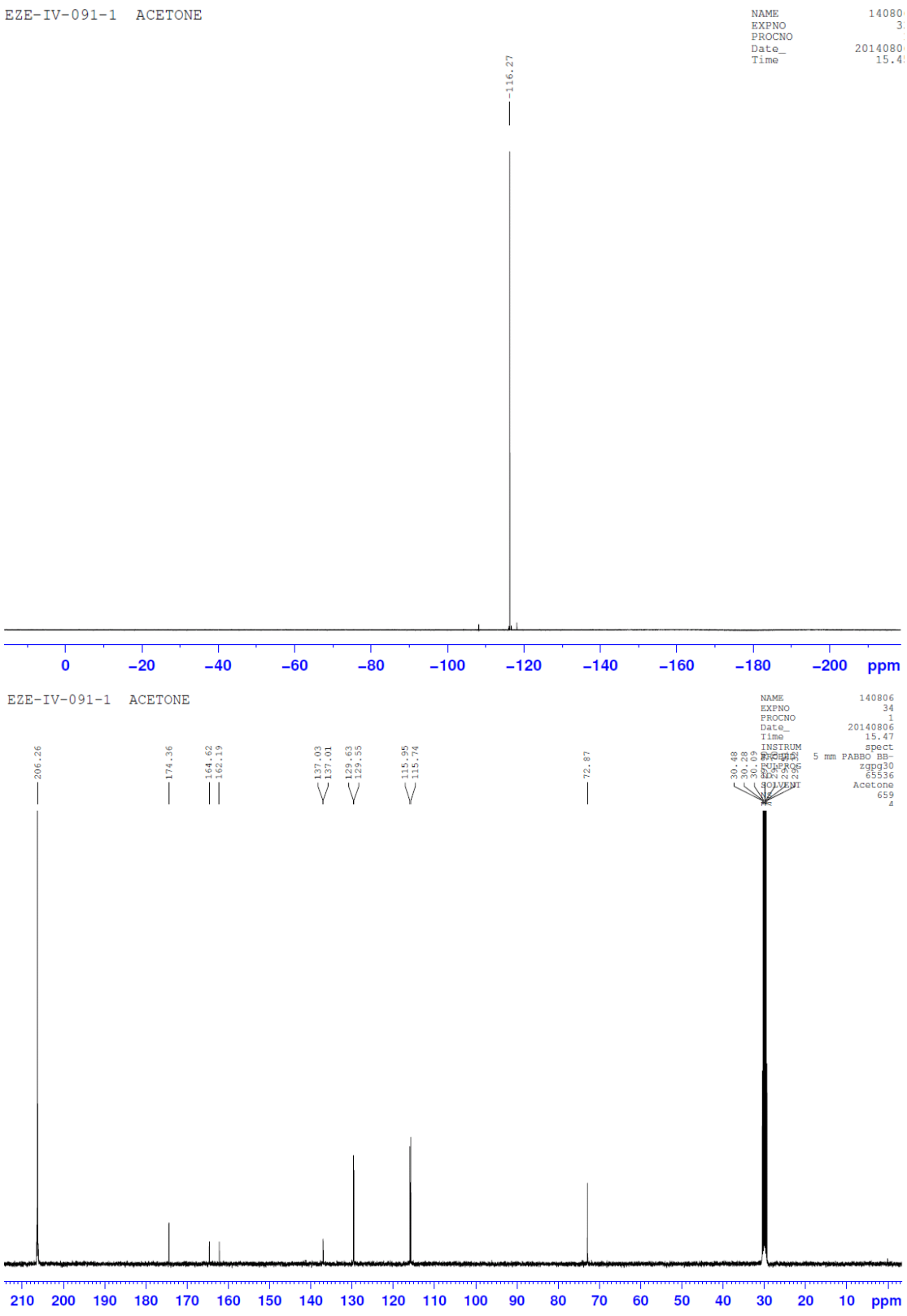
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.144	BB	0.2230	1.60726e4	1122.86279	96.7622
2	15.324	BB	0.3399	537.80792	24.71538	3.2378
Totals :				1.66104e4	1147.57817	

(*S*)-2-(4-fluorophenyl)-2-hydroxyacetic acid (**3h**)

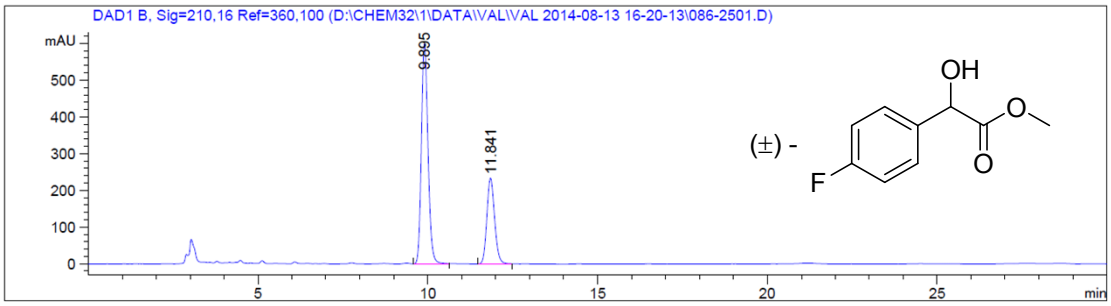


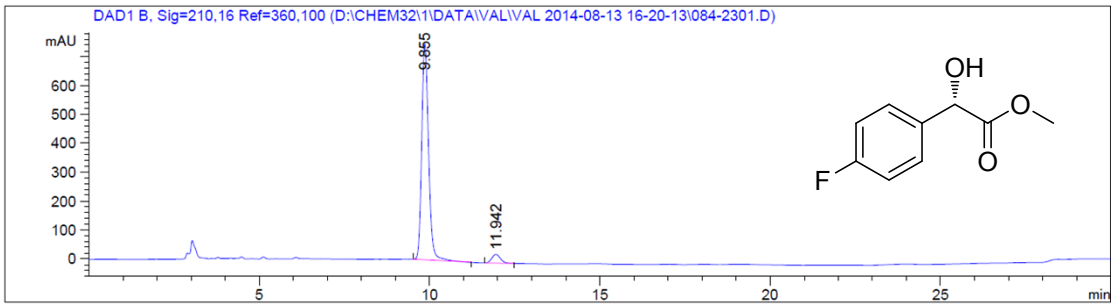
Yield: 94%, colorless oil, 90% ee, $[\alpha]_D^{28}$ +137.3 (*c* 0.5, EtOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 9.86 min for (*S*)-enantiomer and t_R = 11.94 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 7.57–7.53 (m, 2H), 7.15–7.11 (m, 2H), 5.23 (s, 1H). ^{19}F NMR (376 MHz, Acetone-d6): δ –116.3. ^{13}C NMR (100 MHz, Acetone-d6): δ 174.4, 164.6, 162.2, 137.0 (d), 129.6 (d), 115.8 (d), 72.9; HRMS (ESI) calcd for[M-H, $C_8H_6FO_3$]$^-$: 169.0301, Found 169.0305.





methyl 2-(4-fluorophenyl)-2-hydroxyacetate

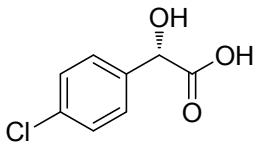




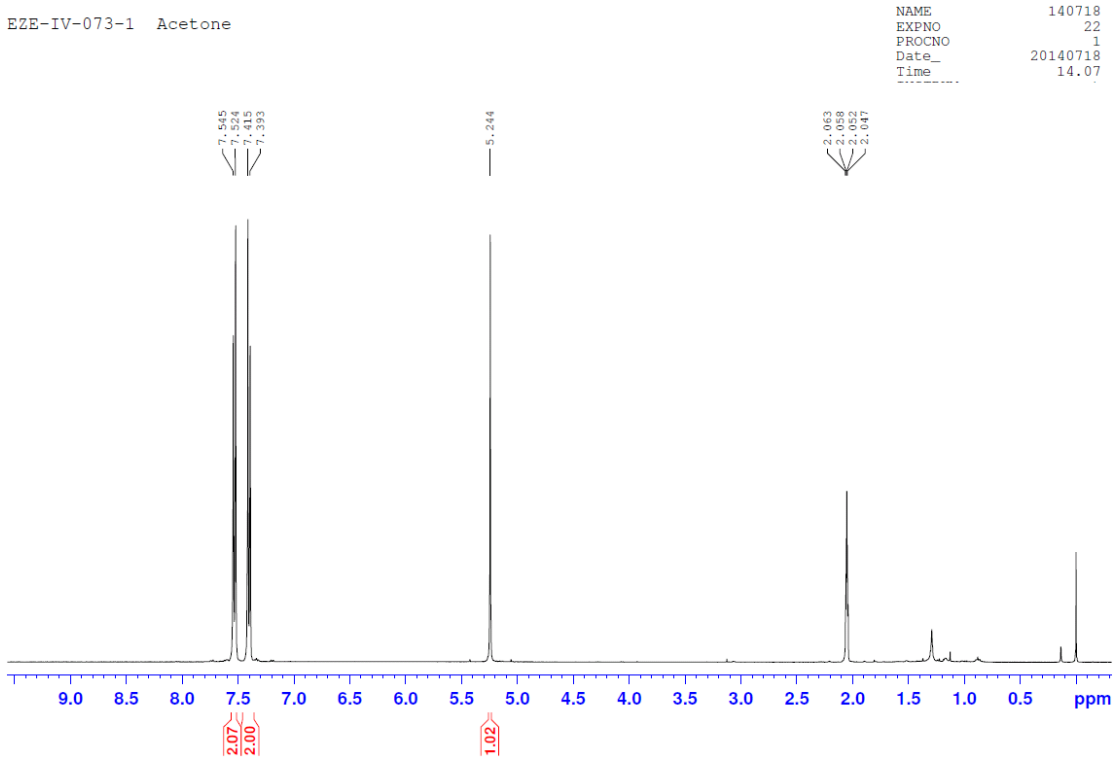
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

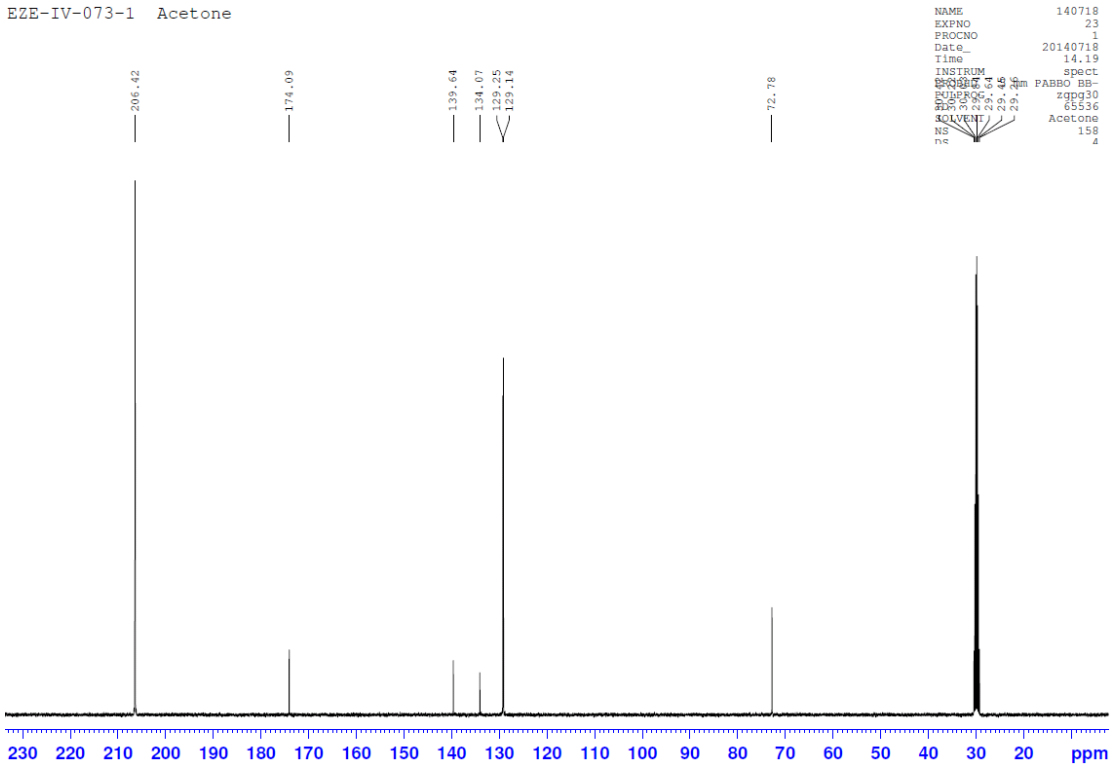
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.855	BB	0.2148	1.04407e4	748.19348	95.1700
2	11.942	BB	0.2729	529.87708	30.17592	4.8300
Totals :				1.09706e4	778.36940	

(*S*)-2-(4-chlorophenyl)-2-hydroxyacetic acid (**3i**)[9]

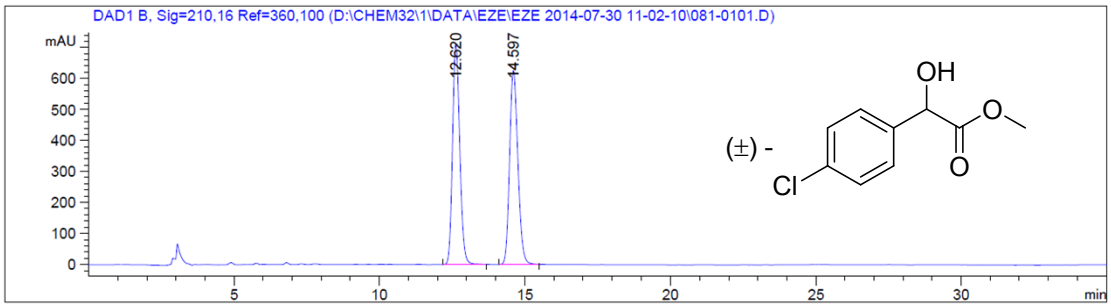


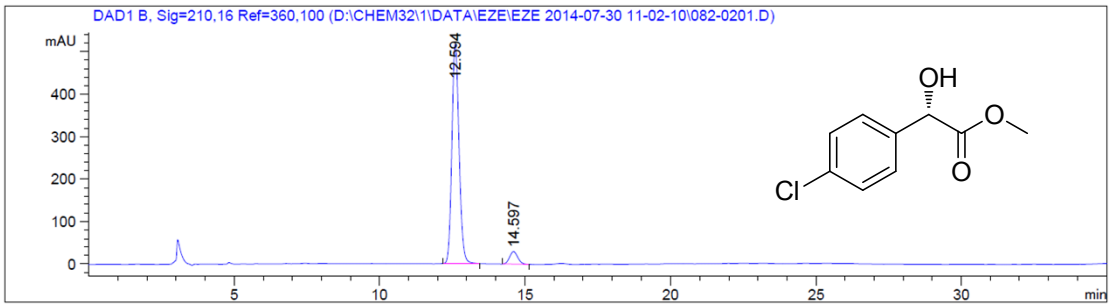
Yield: 97%, white solid, 88% ee, $[\alpha]_D^{28}$ +110.2 (*c* 0.5, H_2O), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 96:4, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 12.59 min for (*S*)-enantiomer and t_R = 14.60 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 5.24 (s, 1H). ^{13}C NMR (100 MHz, Acetone-d6): δ 174.1, 139.6, 134.1, 129.3, 129.1, 72.8.





methyl 2-(4-chlorophenyl)-2-hydroxyacetate

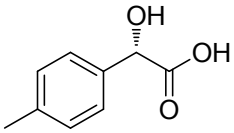




Signal 1: DAD1 B, Sig=210,16 Ref=360,100

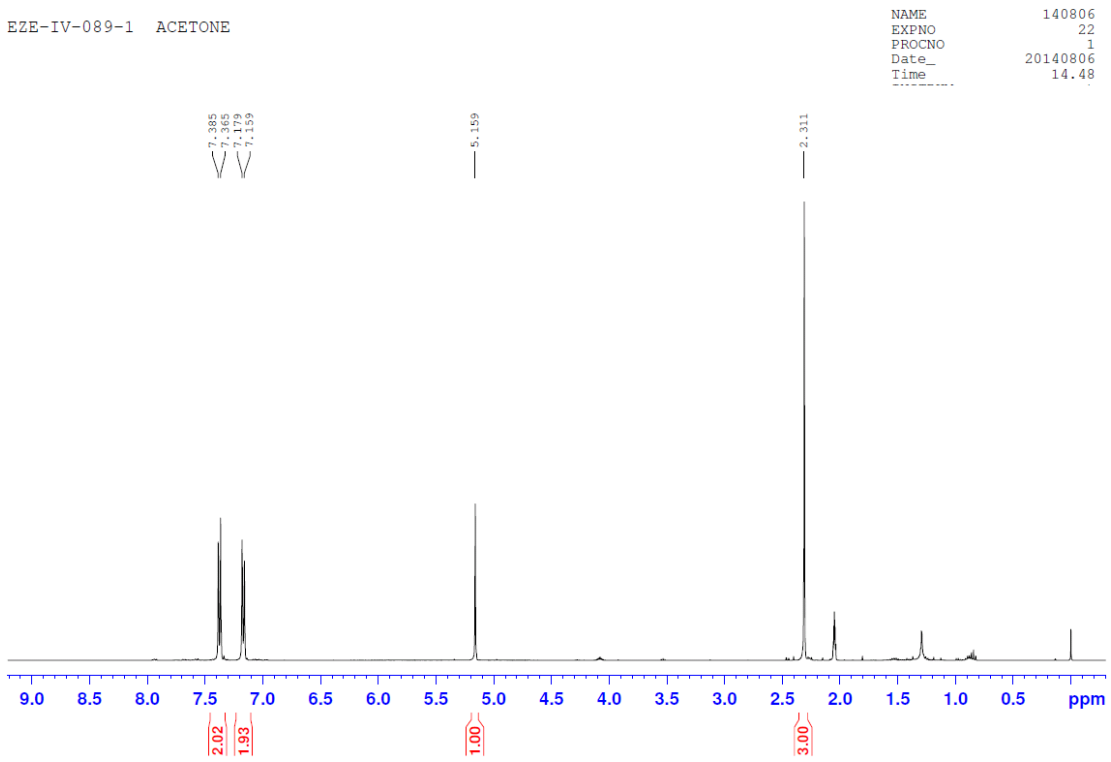
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.594	BB	0.2632	8827.68066	517.05139	93.8373
2	14.597	BB	0.3040	579.75293	29.66323	6.1627
Totals :				9407.43359	546.71462	

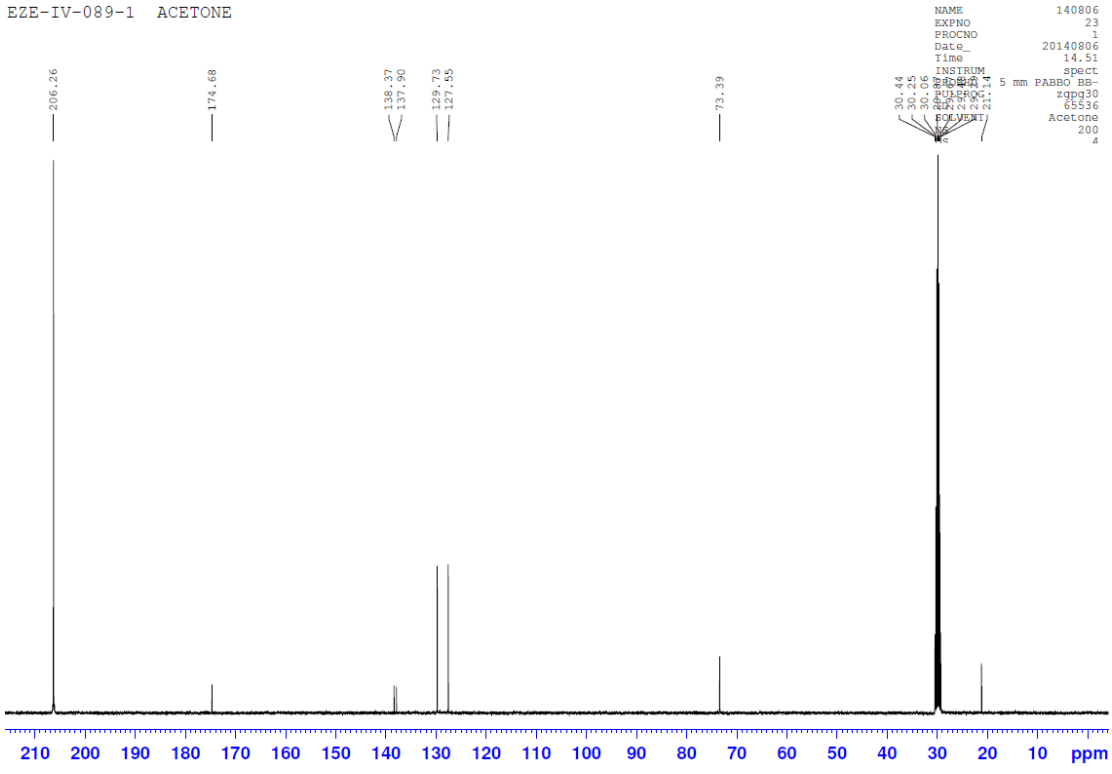
(*S*)-2-hydroxy-2-(p-tolyl)acetic acid (**3j**)[10]



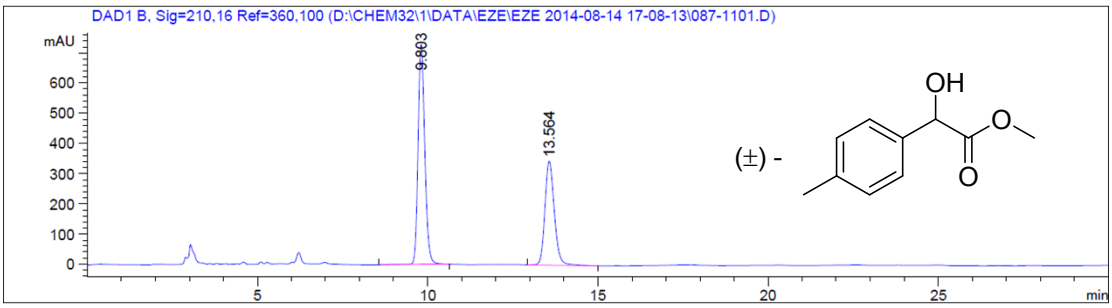
Yield: 97%, white solid, 90% ee, $[\alpha]_D^{28}$ +135.1 (*c* 0.5, MeOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 10.42 min for (*S*)-enantiomer and t_R = 14.14 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.16 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d6): δ 174.7, 138.4, 137.9, 129.7, 127.6, 73.4, 21.1.

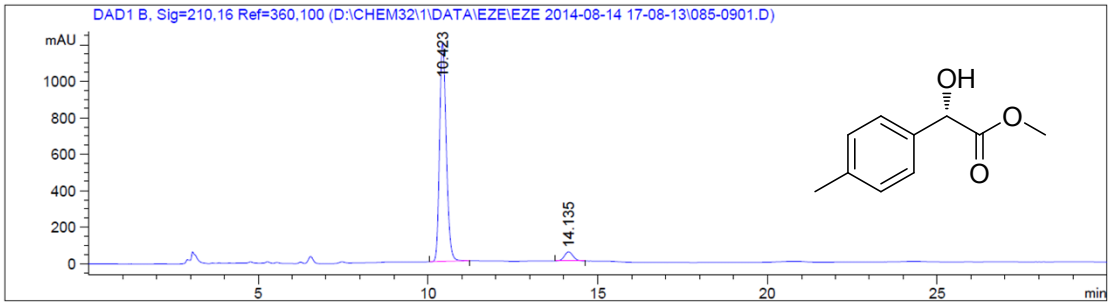
[10] (a) T. Ziegler, B. Hörsch, F. Effenberger, *Synthesis,* 1990, **7**, 575; (b) D. F. Colon, S. T. Pickard, H. E. Smith, *J. Org. Chem.,* 1991, **56**, 2322.





methyl 2-hydroxy-2-(p-tolyl)acetate

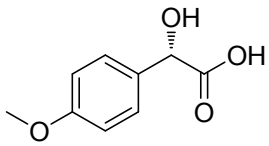




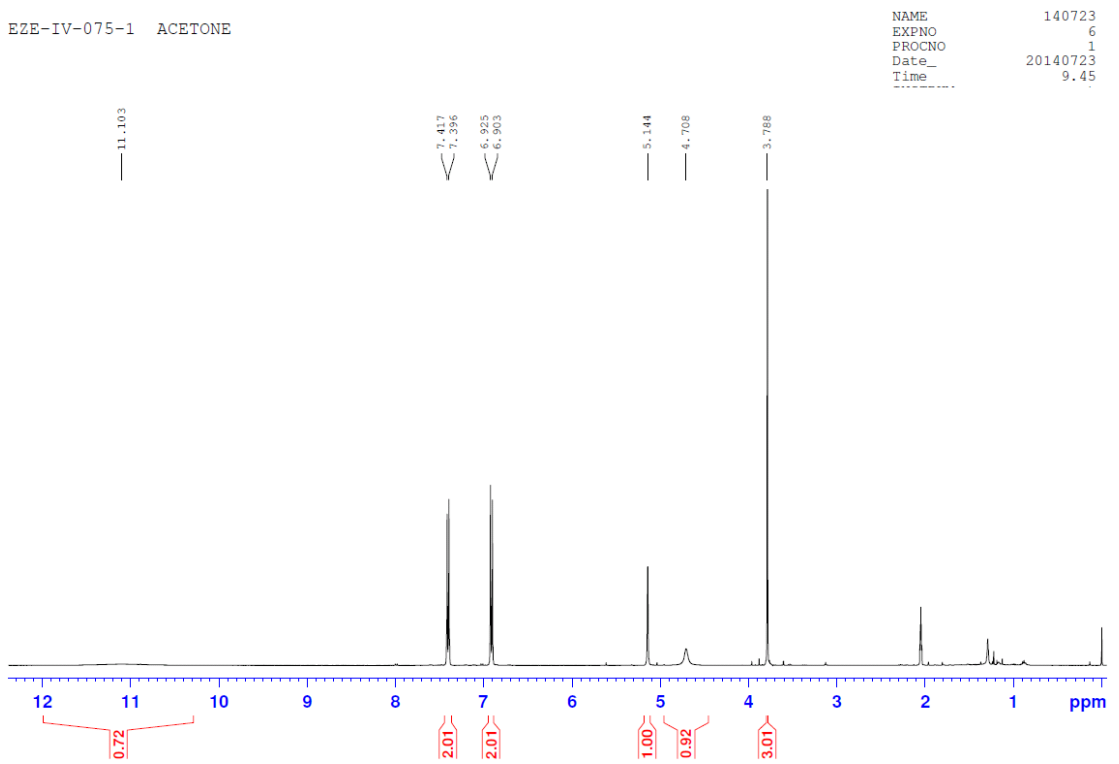
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

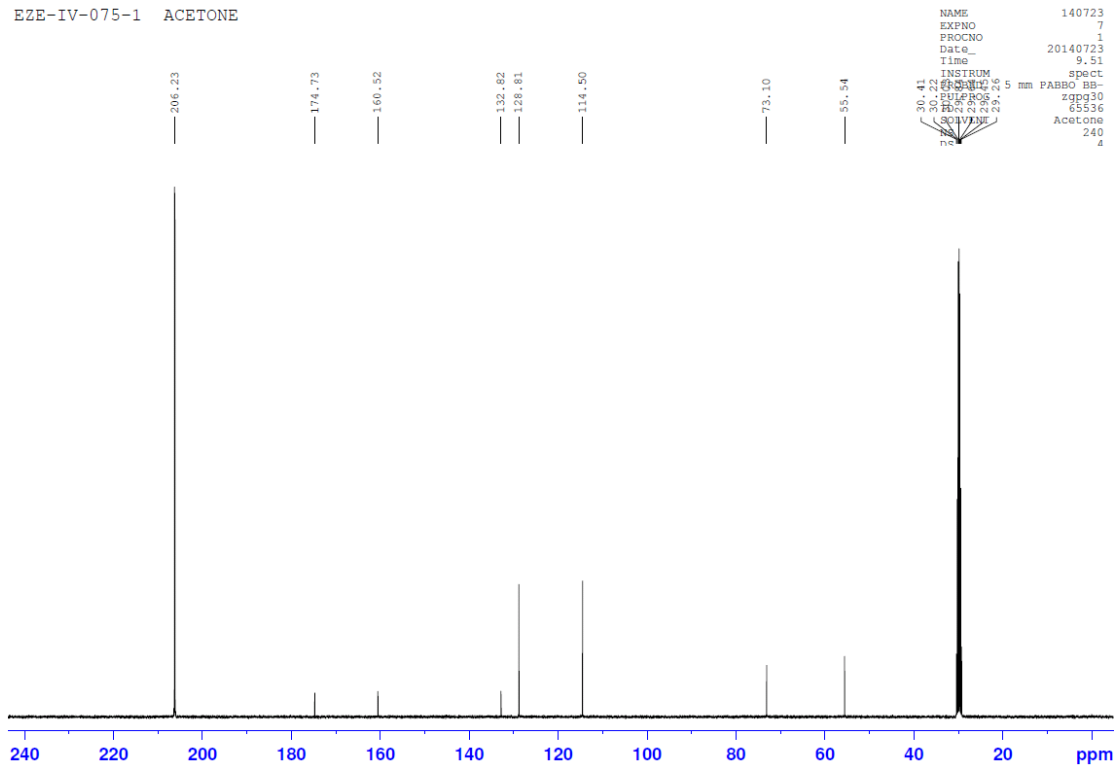
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.423	BB	0.2137	1.66223e4	1199.29419	94.9006
2	14.135	BBA	0.2782	893.18469	50.05350	5.0994
Totals :				1.75155e4	1249.34769	

(*S*)-2-hydroxy-2-(4-methoxyphenyl)acetic acid (**3k**)

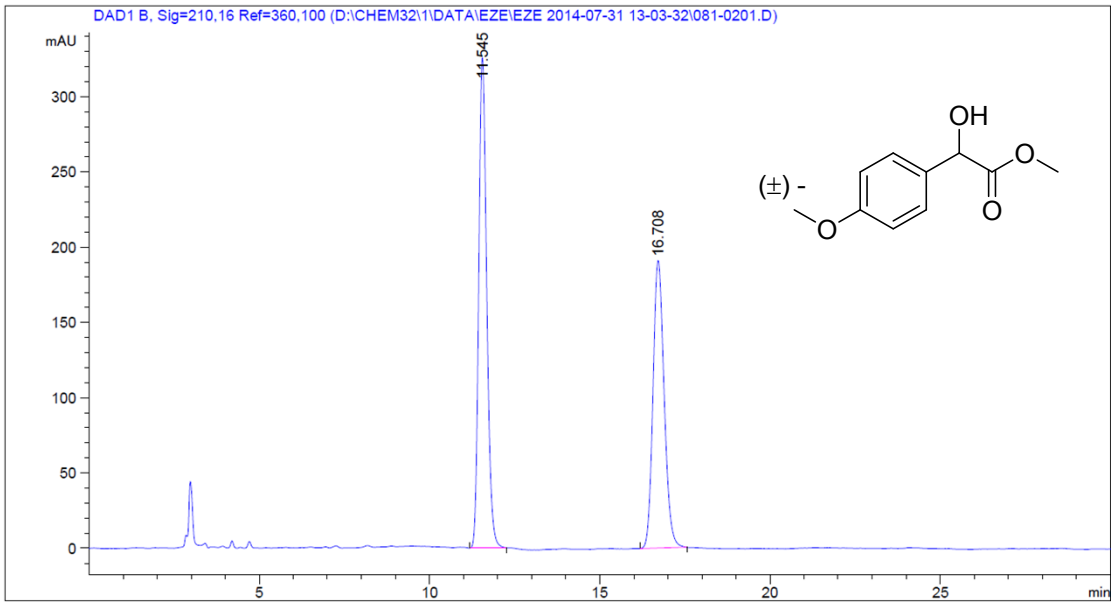


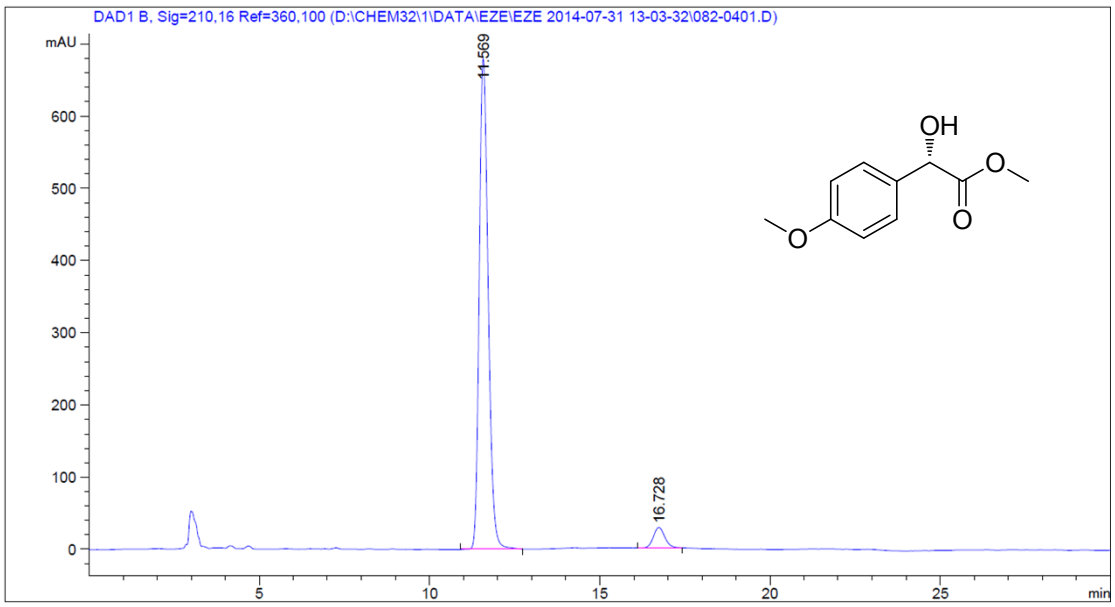
Yield: 96%, white solid, 90% ee, $[\alpha]_D^{28}$ +125.1 (*c* 0.5, H_2O), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 92:8, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 11.57 min for (*S*)-enantiomer and t_R = 16.73 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 11.10 (brs, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 1H), 4.71 (brs, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d6): δ 174.7, 160.5, 132.8, 128.8, 114.5, 73.1, 55.5. HRMS (ESI) calcd for[M-H, $C_9H_9O_4$]$^-$: 181.0501, Found 181.0504.





methyl 2-hydroxy-2-(4-methoxyphenyl)acetate

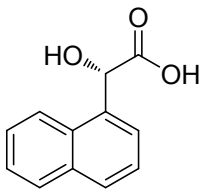




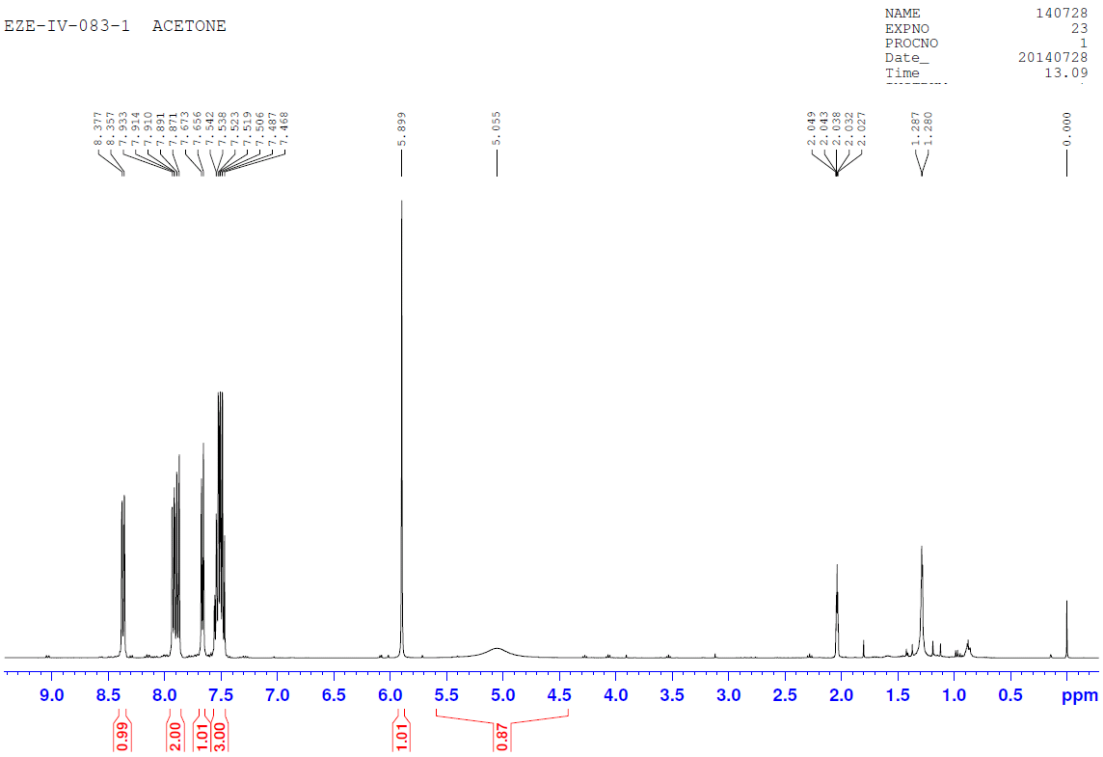
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.569	BB	0.2823	1.24893e4	680.02960	94.9257
2	16.728	BB	0.3518	667.61395	28.44955	5.0743
Totals :				1.31569e4	708.47915	

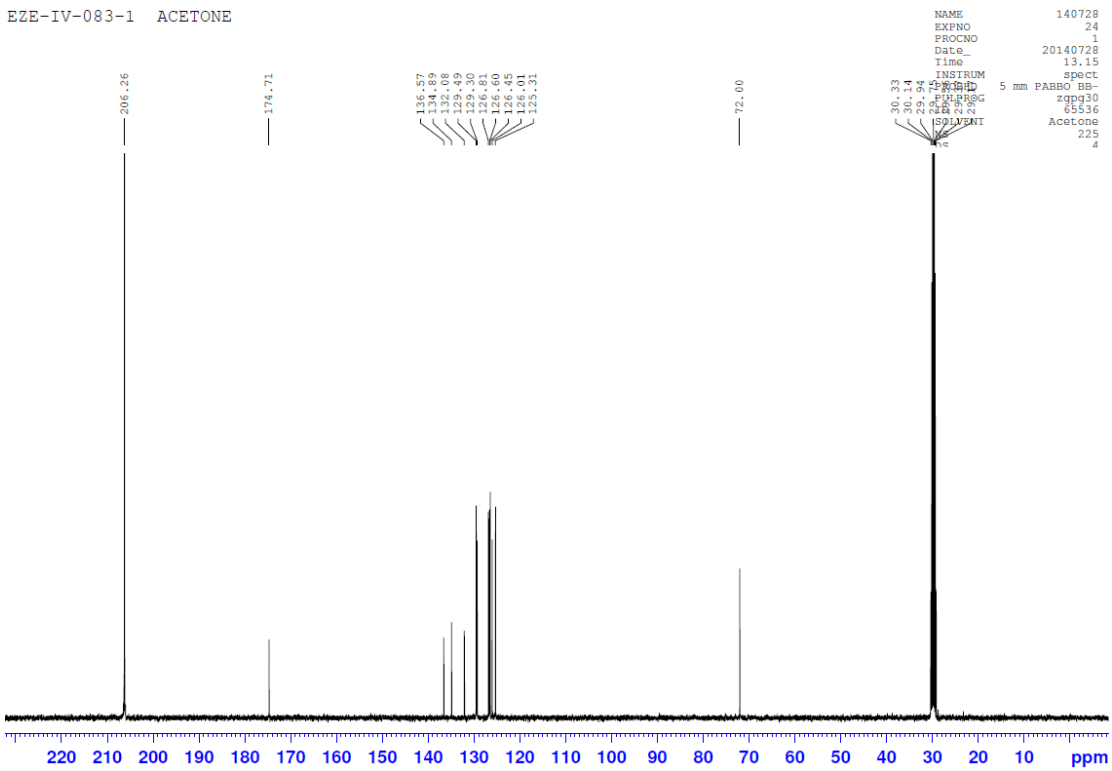
(*S*)-2-hydroxy-2-(naphthalen-1-yl)acetic acid (**3l**)[11]



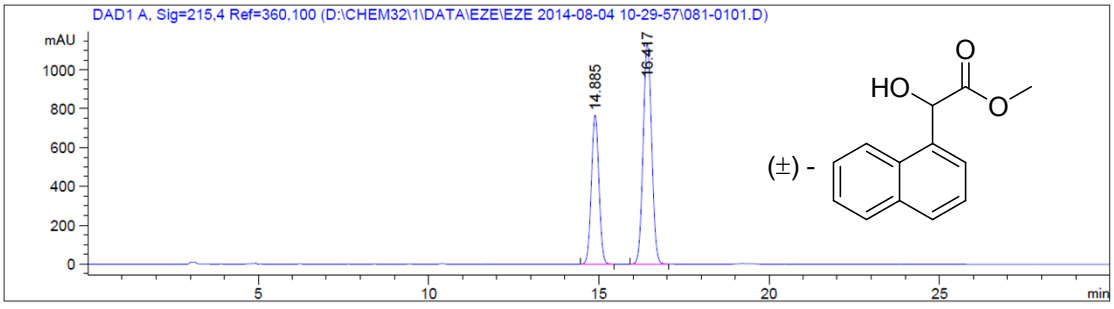
Yield: 98%, white solid, 99.2% ee, $[\alpha]_D^{28}$ +157.7 (*c* 0.5, EtOH), HPLC condition for corresponding methyl ester: Chiralpak AD-H column, *n*-Hexane/EtOH = 92:8, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 14.73 min for (*R*)-enantiomer and t_R = 16.22 min for (*S*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 8.37 (d, *J* = 8.0 Hz, 2H), 7.93–7.87 (m, 2H), 7.66 (d, *J* = 6.8 Hz, 1H), 7.54–7.47 (m, 3H), 5.90 (s, 1H), 5.06 (brs, 1H). ^{13}C NMR (100 MHz, Acetone-d6): δ 174.7, 136.6, 134.9, 132.1, 129.5, 129.3, 126.8, 126.6, 126.5, 126.0, 125.3, 72.0.

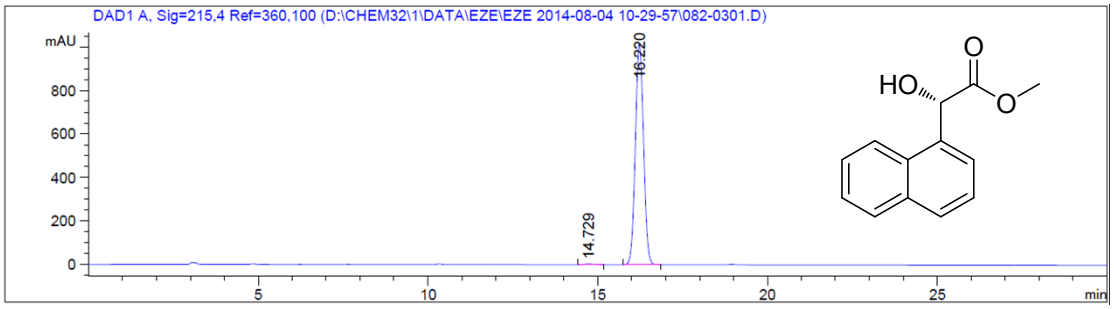


[11] G. Massolini, G. Fracchiolla, E. Calleri, G. Carbonara, C. Temporini, A. Lavecchia, S. Cosconati, E. Novellino, F. Loiodice, *Chirality,* 2006, **18**, 633.



methyl 2-hydroxy-2-(naphthalen-1-yl)acetate

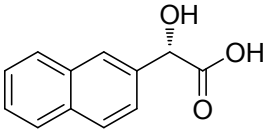




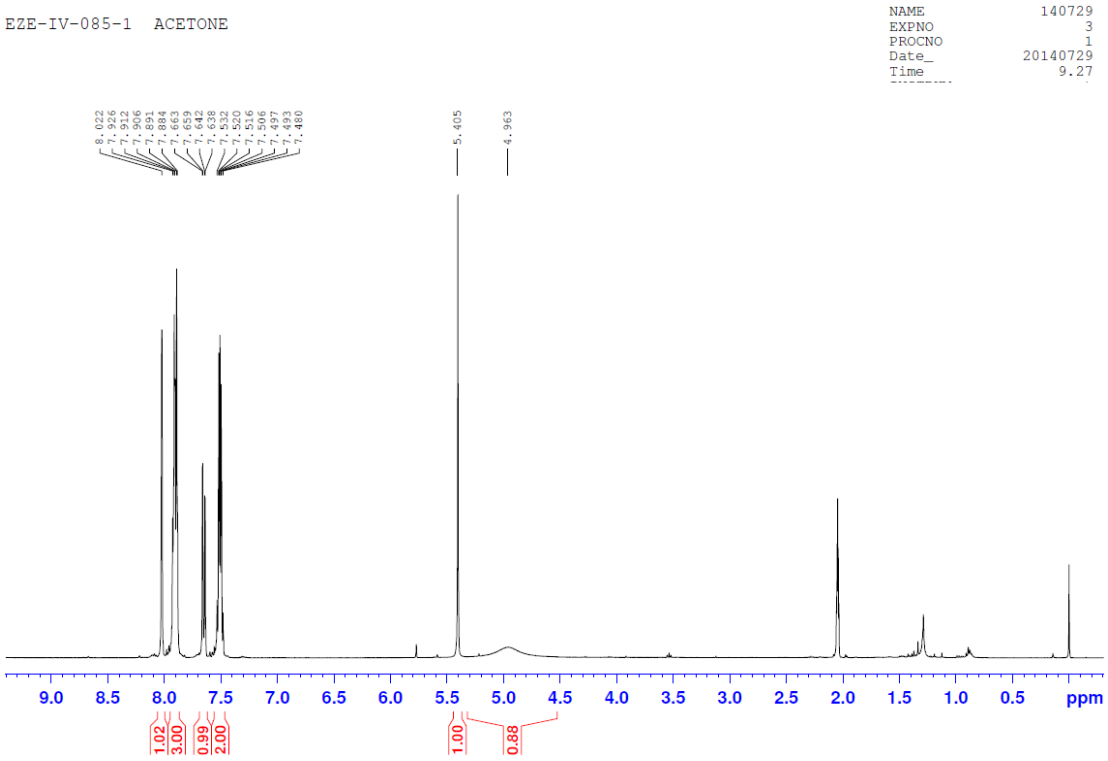
Signal 1: DAD1 A, Sig=215,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.729	BB	0.2629	68.90124	3.96143	0.4014
2	16.220	BB	0.2621	1.70977e4	1017.05078	99.5986
Totals :				1.71666e4	1021.01221	

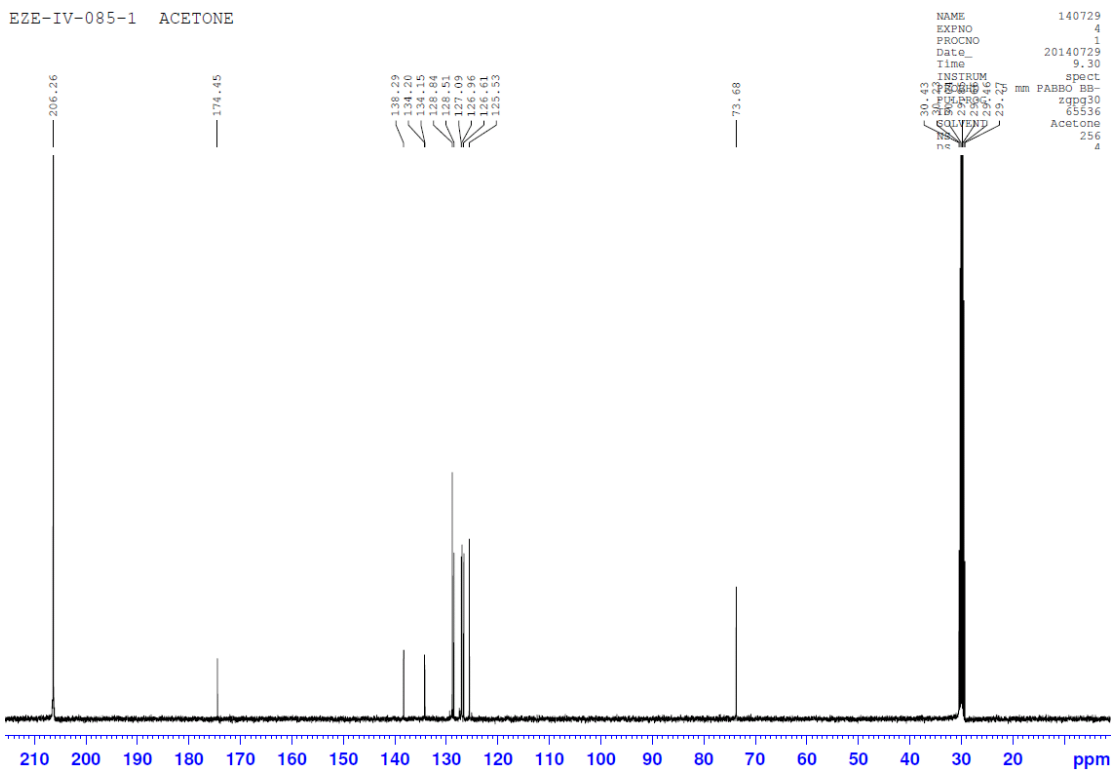
(*S*)-2-hydroxy-2-(naphthalen-2-yl)acetic acid (**3m**)[12]



Yield: 98%, white solid, 91% ee, $[\alpha]_D^{28}$ +137.1 (*c* 0.5, EtOH), HPLC condition for corresponding methyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 92:8, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 13.34 min for (*S*)-enantiomer and t_R = 15.71 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, Acetone-d6): δ 8.02 (s, 1H), 7.93–7.88 (m, 3H), 7.65 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.53–7.48 (m, 2H), 5.41 (s, 1H), 4.96 (brs, 1H). ^{13}C NMR (100 MHz, Acetone-d6): δ 174.5, 138.3, 134.2 (d), 128.8, 128.5, 127.1, 127.0, 126.6, 125.5, 73.7.

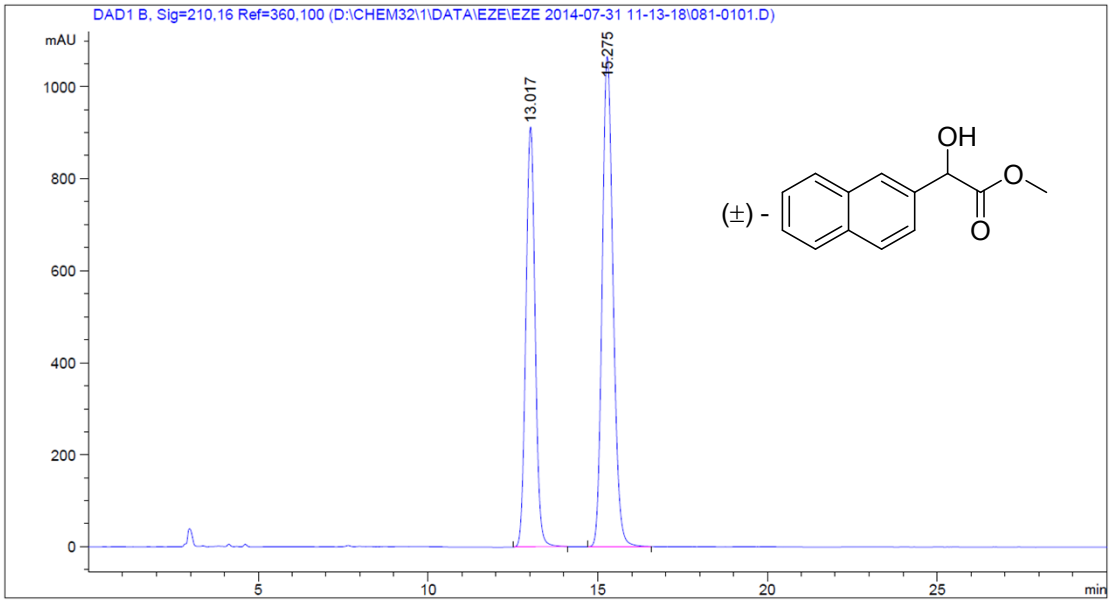


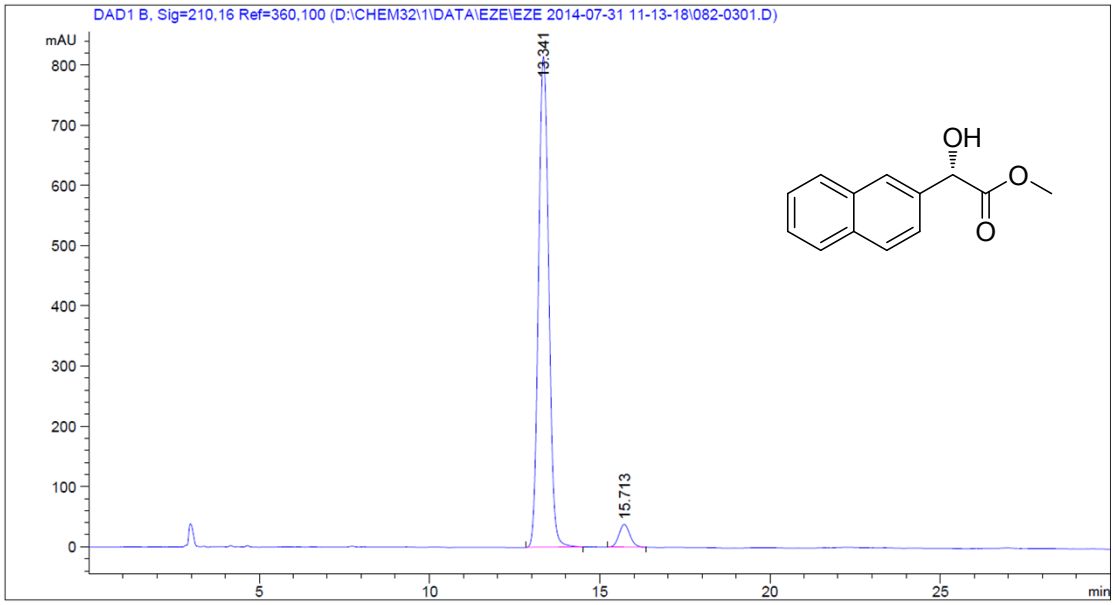
[12] M. St. Maurice, S. L. Bearne, *Biochemistry,* 2004, **43**, 2524.



methyl 2-hydroxy-2-(naphthalen-2-yl)acetate

1c was used as catalyst:

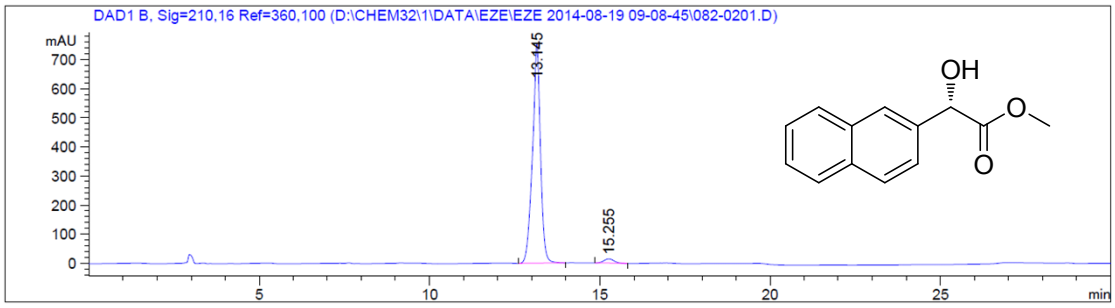




Signal 1: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.341	BB	0.3326	1.70857e4	814.84875	95.2550
2	15.713	BB	0.3419	851.09479	37.90898	4.7450
Totals :				1.79368e4	852.75773	

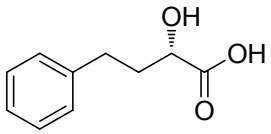
1b was used as catalyst:



Signal 1: DAD1 B, Sig=210,16 Ref=360,100

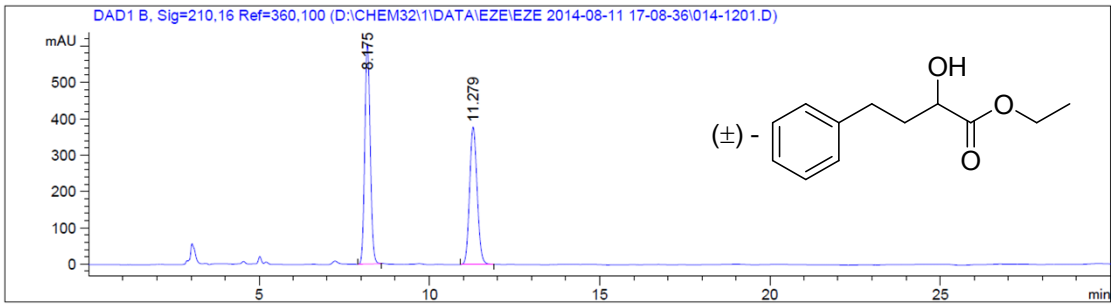
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.145	BB	0.2269	1.22257e4	755.02460	97.4511
2	15.255	BB	0.3261	319.76462	15.16102	2.5489
Totals :				1.25454e4	770.18562	

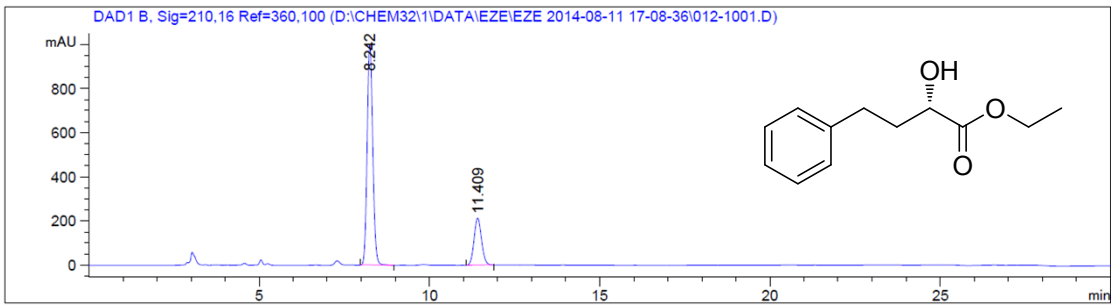
(*S*)-2-hydroxy-4-phenylbutanoic acid (**3n**)[13]



Yield: 96%, white solid, 56% ee, $[\alpha]_D^{28}$ +5.3 (*c* 0.5, EtOH), HPLC condition for corresponding ethyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 8.24 min for (*S*)-enantiomer and t_R = 11.41 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.18 (m, 5H), 4.26 (dd, *J* = 4.0, 8.0 Hz, 1H), 2.83–2.78 (m, 2H), 2.22–2.14 (m, 1H), 2.06–1.96 (m, 2H).

ethyl 2-hydroxy-4-phenylbutanoate



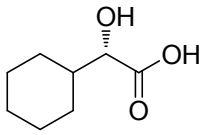


Signal 1: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.242	BB	0.1804	1.14958e4	998.21069	77.9436
2	11.409	BB	0.2383	3253.06372	212.87833	22.0564
Totals :				1.47488e4	1211.08902	

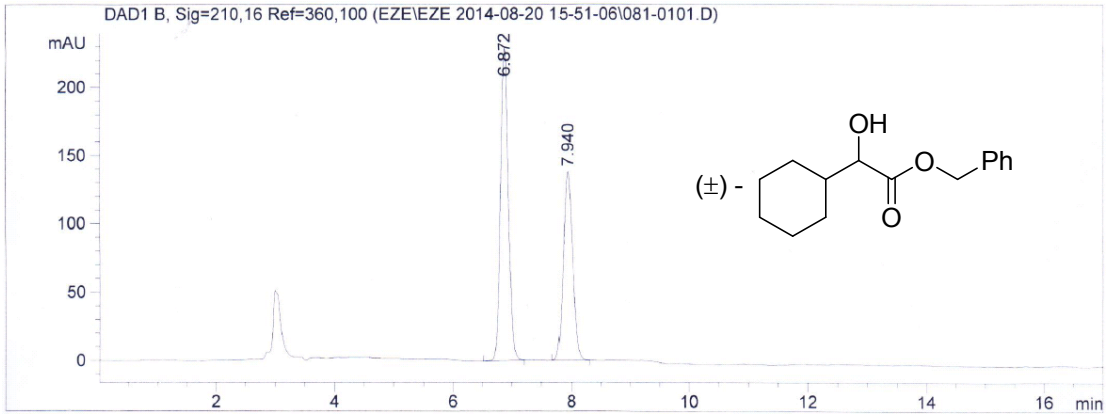
[13] (a) Q. Meng, L. Zhu, Z. Zhang, *J. Org. Chem.,* 2008, **73**, 7209; (b) B. Larissegger-Schnell, W. Kroutil, K. Faber, *Synlett,* 2005, **12**, 1936.

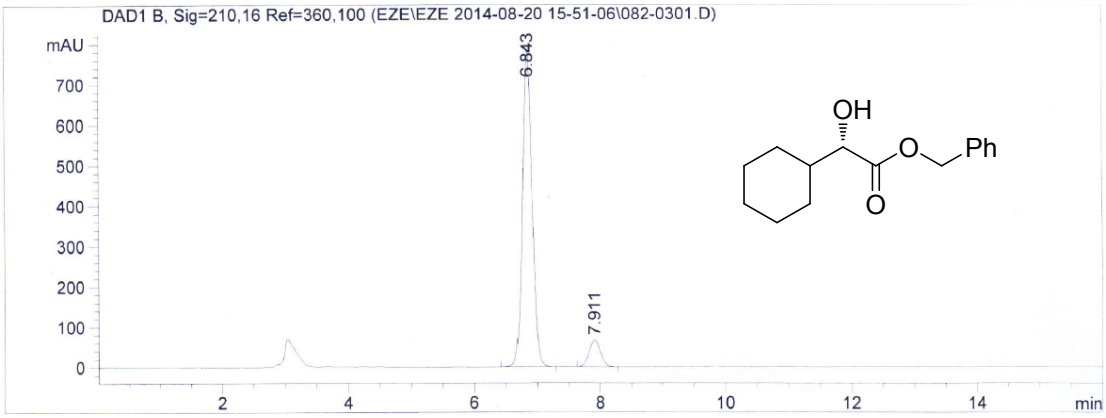
(*S*)-2-cyclohexyl-2-hydroxyacetic acid (**3o**)[14]



Yield: 95%, white solid, 82% ee, $[\alpha]_D^{28}$ +18.1 (*c* 0.5, Acetic acid), HPLC condition for corresponding benzyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 95:5, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 6.84 min for (*S*)-enantiomer and t_R = 7.91 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (d, *J* = 3.6 Hz, 1H), 1.80–1.66 (m, 5H), 1.54–1.52 (m, 1H), 1.36–1.13 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 74.8, 41.8, 29.2, 26.3, 26.0.

benzyl 2-cyclohexyl-2-hydroxyacetate



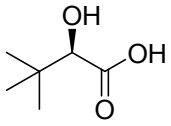


Signal 1: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.843	BB	0.1625	8388.33496	786.07605	90.9171
2	7.911	BB	0.1974	838.02167	66.33637	9.0829
Totals :				9226.35663	852.41242	

[14] N. Yamagiwa, J. Tian, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.,* 2005, **127**, 3413.

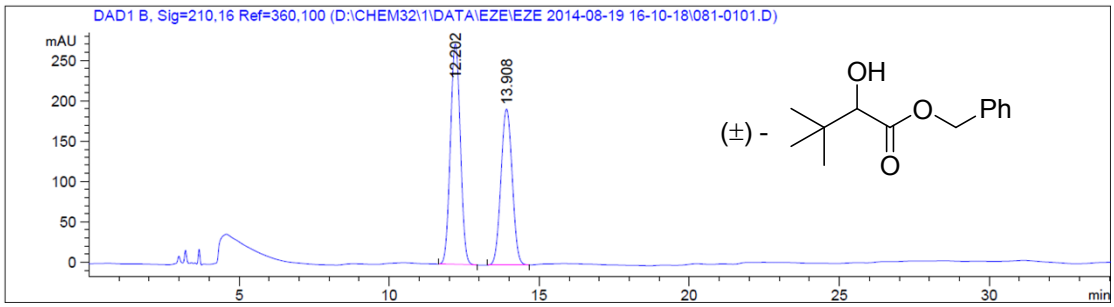
(*R*)-2-hydroxy-3,3-dimethylbutanoic acid (**3p**)[15]

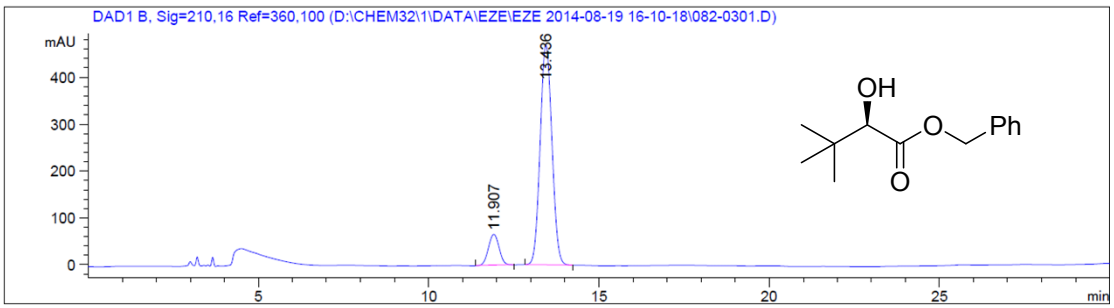


Yield: 92%, yellow oil, 85% ee, $[\alpha]_D^{25}$ –3.8 (*c* 0.5, MeOH), HPLC condition for corresponding benzyl ester: Chiralcel OD-H column, *n*-Hexane/IPA = 99:1, 1.0 mL/min, 35 °C, 210 nm UV detector, t_R = 7.87 min for (*S*)-enantiomer and t_R = 8.45 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 1H), 1.02 (s, 9H).

benzyl 2-hydroxy-3,3-dimethylbutanoate

1c was used as catalyst:



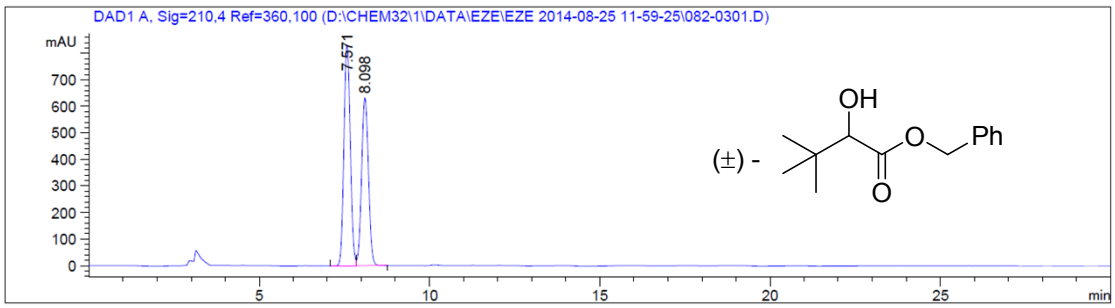


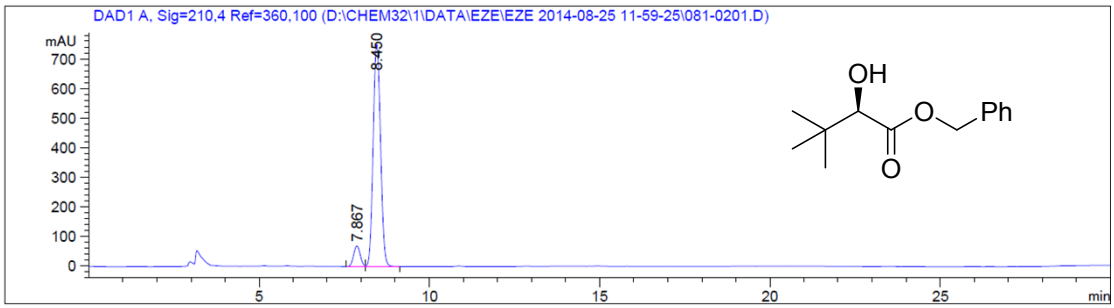
Signal 1: DAD1 B, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.907	BB	0.3452	1444.68518	66.05718	11.3084
2	13.436	BB	0.3817	1.13306e4	469.25998	88.6916
Totals :				1.27753e4	535.31716	

[15] N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, C. H. Heathcock, *J. Org. Chem.,* 1991, **56**, 2499.

1b was used as catalyst:





Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.867	BV	0.2146	947.40387	69.67858	7.7099
2	8.450	VB	0.2378	1.13408e4	752.82141	92.2901
Totals :				1.22882e4	822.49999	