Electronic Supplementary Material (ESI) for Green Chemistry.

Supplementary information

An ATP-Cu(II) catalyst efficiently catalyzes enantioselective Michael reactions in water

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1. General remarks

Circular Dichroism (CD) spectra were measured on a Chirascan Circular Dichroism Spectrometer (Applied Photophysics Ltd, England, UK). The CD spectra were performed using a quartz cell (1 mm optical path length), an instrument scanning speed of 100 nm/min and were accumulated by taking the average of three scans made from 200 to 320 nm at 4 °C. Ultraviolet-visible (UV-Vis) spectra were collected by Agilent Cary 3500 in a sealed quartz cell with a path length of 1.0 cm. The enantioselective Michael reactions were analyzed by high performance liquid chromatography (HPLC, Shimadzu Prominence-*i* LC-2030) with chiral stationary phase using hexane and *iso*-propanol as eluents. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AV 400 MHz spectrometers using residue solvent peaks as an internal standard (^{1}H NMR: $CDCl_3$ = 7.26, ^{13}C NMR: $CDCl_3$ = 77.16). Chemical shifts were reported in parts per million (ppm) with respect to the residual solvent signal. Peak multiplicities were reported as follows: s = singlet, m = multiplet. d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets. The coupling constant (*J*) were reported in hertz (Hz). High-resolution mass spectra (HRMS) were collected on a Bruker Maxis System.

ATP, UTP, GTP, CTP, dATP, ADP, AMP, 3',5'-Cyclic AMP and adenosine were purchased from Sangon (Shanghai, China). The substrates **2a**-**c**, metal salts and achiral ligands and buffers were purchased from Energy Chemical and J&K Scientific Ltd. The chemicals were used without further purification unless otherwise stated. Water used was distilled and deionized using a Milli-Q A10 water purification system. Compounds **1a**-**h** and racemates **3a**-**j** were prepared as the literatures reported[1-3].

2. Tables S1-S6

Table S1 Enantioselective Michael reactions catalyzed by ATP·Cu^{2+} with different copper(II) salts.

Entry[a]	Metal cofactor	Conversion (%)	ee (%)
1	$Cu(NO_3)_2$	63	75
2	$Cu(OTf)_2$	70	75
3	$CuSO_4$	58	75
4	$CuCl_2$	72	74

[a] Reaction conditions: **1a** (2 μmol), **2a** (200 μmol), ATP (250 μM), copper(II) salts (50 μM), MOPS (20 mM, pH 7.9), 4 °C, 72 h.

Table S2 Enantioselective Michael reactions catalyzed by ATP·Cu^{2+} with different molar ratios.

Entry[a]	ATP/μM	$Cu(OTf)_2$/μM	Conversion (%)	ee (%)
1	250	0	1	31
2	250	25	20	76
3	250	50	70	75
4	250	100	73	74
5	250	250	95	66
6	250	500	91	54

[a] Reaction conditions: **1a** (2 μmol), **2a** (200 μmol), ATP (250 μM), MOPS (20 mM, pH 7.9), 4 °C, 72 h.

Table S3 Enantioselective Michael reactions catalyzed by ATP·Cu^{2+} in different buffers.

Entry[a]	Buffer	pH	Conversion (%)	ee (%)
1	MOPS	7.4	48	74
2	MOPS	7.9	70	75
3	MOPS	9.0	83	74
4	CHES	8.0	70	75
5	CHES	9.0	89	74
6	CHES	9.5	96	74
7	CHES	10.0	94	70
8	Tris	7.4	4	60
9	PBS	7.4	28	68
10	MES	7.0	8	64

[a] Reaction conditions: **1a** (2 μmol), **2a** (200 μmol), ATP (250 μM), $Cu(OTf)_2$ (50 μM), 4 °C, 72 h.

Table S4 ATP·Cu^{2+} catalyzed Michael reactions of **1a** with different amount of **2a**.

Entry[a]	Molar ratios of **1a**/**2a**	Conversion (%)	ee (%)
1	1:2	16	72
2	1:5	34	72
3	1:10	58	73
4	1:20	78	74
5	1:50	90	74
6	1:100	97	74

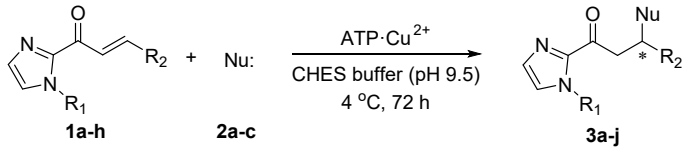
[a] Reaction conditions: **1a** (2 μmol), **2a** (4-200 μmol), ATP (250 μM), $Cu(OTf)_2$ (50 μM), CHES (20mM, pH 9.5), 4 °C, 72 h.

Table S5 Enantioselective Michael reactions catalyzed by ATP and different metal ions.

Entry[a]	Metal cofactor	Conversion (%)	ee (%)
1	$Ag(OTf)_2$	6	< 3
2	$Yb(OTf)_3$	8	< 3

[a] Reaction conditions: **1a** (2 μmol), **2a** (200 μmol), ATP (250 μM), metal cofactor (50 μM), CHES (20mM, pH 9.5), 4 °C, 72 h.

Table S6 ATP·Cu^{2+} catalyzed Michael reactions using different substrates in analytical scale.



1a-h **2a-c** **3a-j**

1a: R_1=Me, R_2=C_6H_5 **1e**: R_1=Me, R_2=4-$MeOC_6H_4$ **2a**: dimethyl malonate
1b: R_1=Me, R_2=4-ClC_6H_4 **1f**: R_1=Me, R_2=*iso*-propyl **2b**: diethyl malonate
1c: R_1=Me, R_2=4-BrC_6H_4 **1g**: R_1=Me, R_2=furyl **2c**: nitromethane
1d: R_1=Me, R_2=2-BrC_6H_4 **1h**: R_1=Et, R_2=C_6H_5

Entry[a]	**1**	**2**	**3**	Conversion (%)	ee (%)
1	**1a**	**2a**	**3a**	96	74
2[b]	**1b**	**2a**	**3b**	70	77
3[b]	**1c**	**2a**	**3c**	80	80
4[b]	**1d**	**2a**	**3d**	64	41
5	**1e**	**2a**	**3e**	83	80
6	**1f**	**2a**	**3f**	44	< 3
7	**1g**	**2a**	**3g**	85	55
8	**1h**	**2a**	**3h**	95	67
9	**1a**	**2b**	**3i**	98	77
10	**1a**	**2c**	**3j**	90	65

[a] Reaction conditions: **1** (2 μmol), **2** (200 μmol), ATP (250 μM), $Cu(OTf)_2$ (50 μM), CHES buffer (20 mM, pH 9.5), 4 °C, 72 h. The conversion of **1a** reacting with **2a** was calculated by HPLC analysis, while all other conversions of **1a-g** were determined by ^1H NMR. The ee values of **3a-j** were determined by chiral HPLC. All data were averaged by duplicated experiments with the reproducibility of ±5% conversion and ±3% ee. [b] Using ATP (1 mM) and $Cu(OTf)_2$ (200 μM).

3. Figures S1-S4

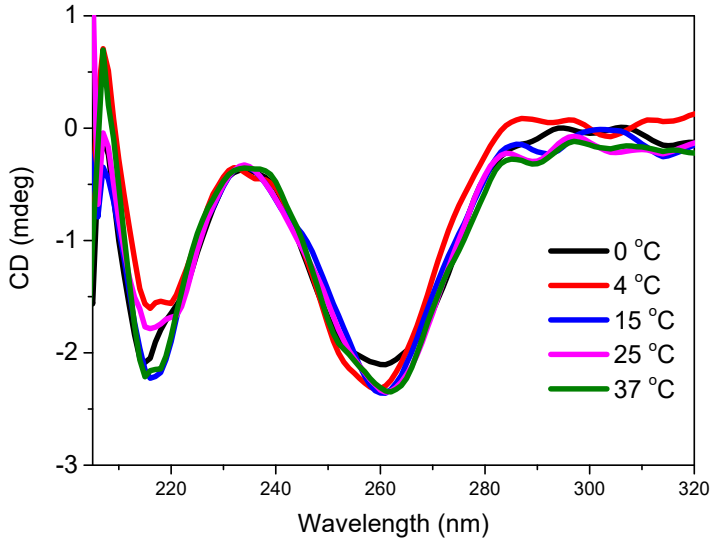


Figure S1 CD spectra of ATP (250μM) with $Cu(OTf)_2$ (50 μM) at different temperatures in CHES buffer (20 mM, pH 9.5).

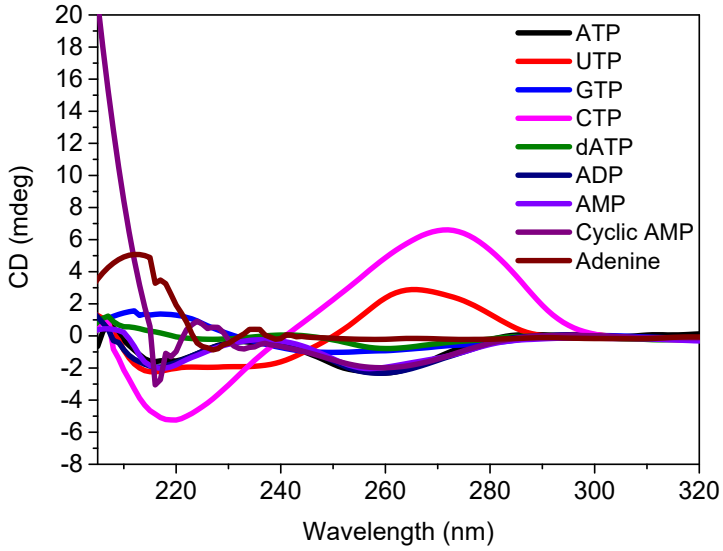


Figure S2 CD spectra of different ATP analogues (250 μM) with $Cu(OTf)_2$ (50 μM) in CHES buffer (20 mM, pH 9.5).

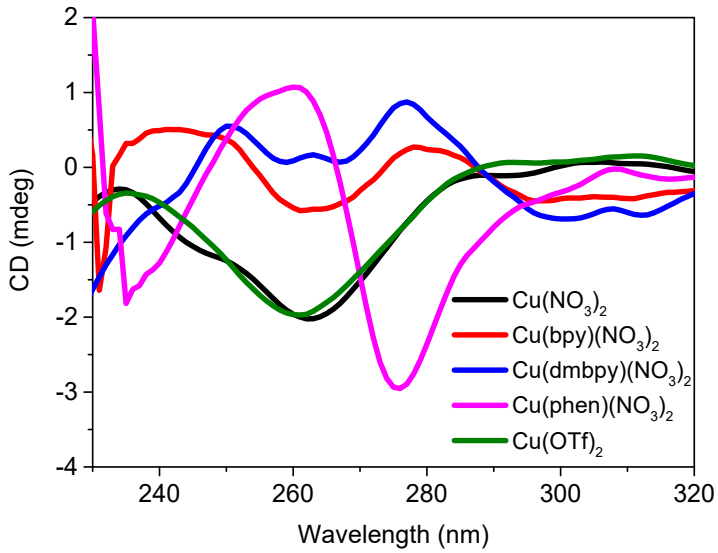


Figure S3 CD spectra of ATP (250 µM) with different copper(II) cofactors (50 µM) in CHES buffer (20 mM, pH 9.5).

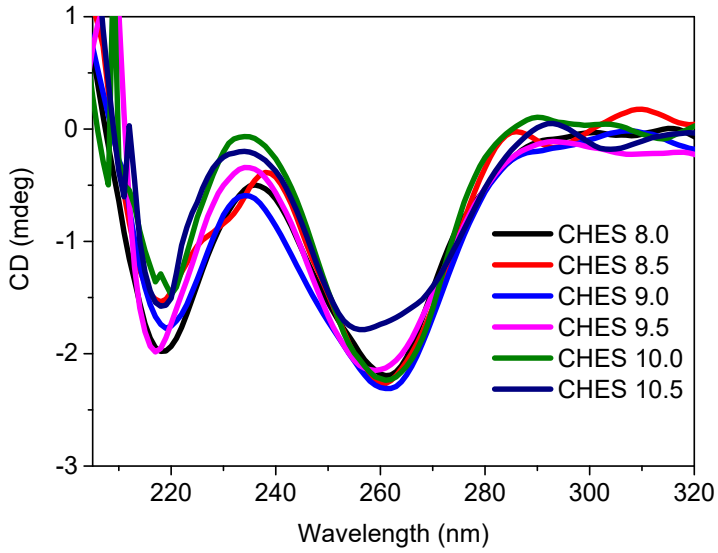


Figure S4 CD spectra of ATP (250 µM) with $Cu(OTf)_2$ (50 µM) in different CHES buffers (20 mM).

4. Determination of the absolute configuration of 3a

For the ATP·Cu^{2+} catalyzed enantioselective Michael reaction of **1a** and **2a**, the absolute configuration of the product **3a** was determined in comparison of the reported literature[4]. Roelfes et al. reported that the enantioselective Michael reaction of **1a** and **2a** was catalyzed by salmon testes DNA (st-DNA) and Cu(dmbpy)$(NO_3)_2$, yielding the chiral product **3a** at 96% ee in *R* configuration. The configuration of **3a** were assigned on the HPLC trace using Chiralpak AD column (hexane/*i*-PrOH = 80:20, 1.0 mL/min^{-1}, 254 nm). Using the same HPLC condition and Chiralpak AD column, we analyzed the product **3a** that was obtained from the enantioselective Michael reaction of **1a** and **2a** catalyzed by ATP·Cu^{2+}. By comparison to the reference, we determined that the major product **3a** generated by ATP·Cu^{2+} was in *R* configuration.

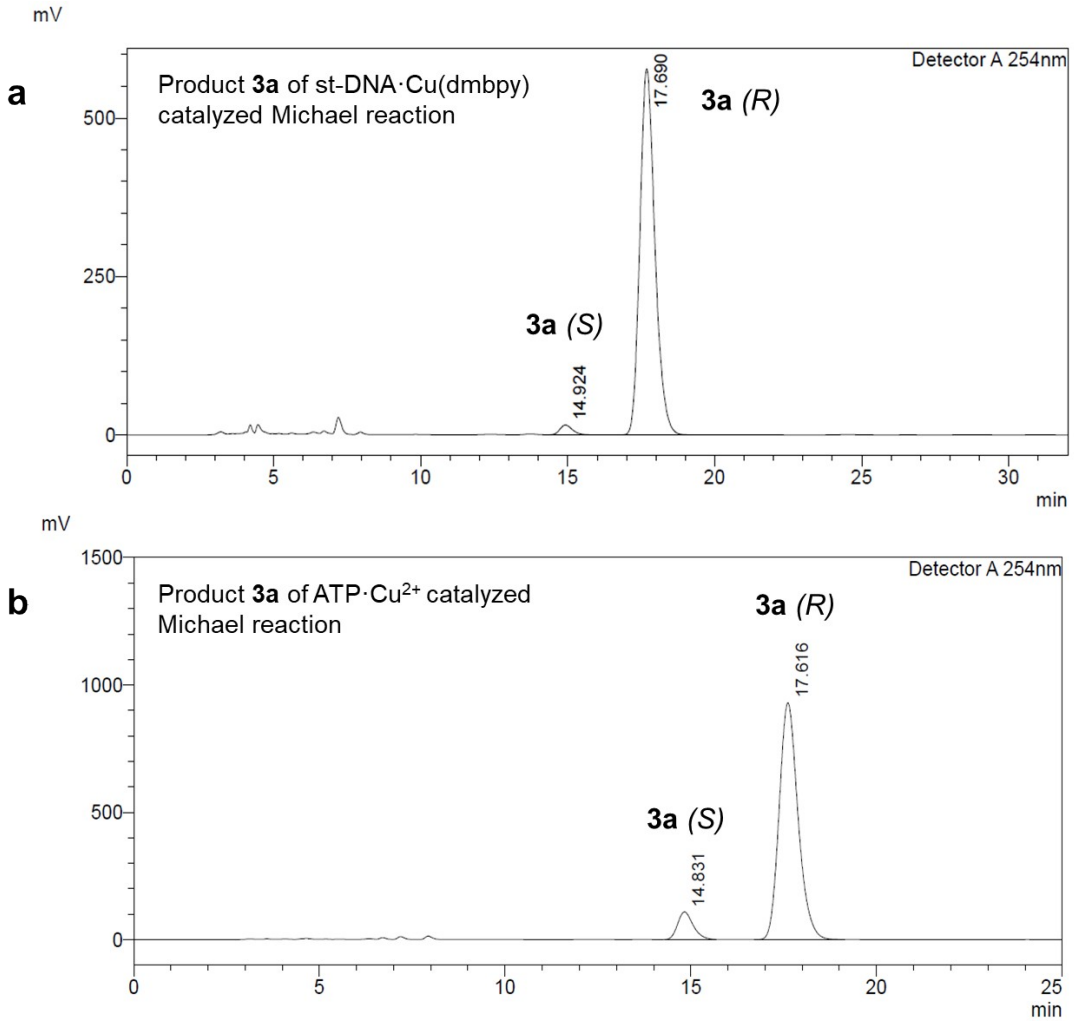


Figure S5 HPLC traces of product of **3a** from the enantioselective Michael reaction catalyzed by (a) st-DNA/Cu(dmbpy) and (b) ATP·Cu^{2+} using Chiralpak AD column. The major product **3a** generated by ATP·Cu^{2+} is *R* configuration.

5. Detailed procedures of ATP·Cu^{2+} catalyzed enantioselective Michael reactions in different reaction scales

5.1 Analytical scale

*Using enone **1** in a 2 μmol scale*: To a CHES buffer (2.0 mL, 20 mM, pH 9.5), an aqueous solution of ATP (final conc. 250 μM) was added. After stirred for twenty minutes at 4 °C, a solution of $Cu(OTf)_2$ (final conc. 50 μM) was added. After stirred for another twenty minutes at 4 °C. Then, the mixture of **1** in DMSO (20 μL of a 0.1 M solution) and nucleophile **2** (200 μmol, 100 eq.) were added. The above reaction media was stirred for 72 h followed by the extraction with ethyl acetate (3 × 2 mL) and removal of the solvent under reduced pressure. After a short flash chromatography, the residue was directly analyzed by chiral HPLC with the eluents of hexane and *iso*-propanol (*i*-PrOH), using a Daicel Chiralpak AD or ODH column column (250 × 4.6 mm). The conversion of **1a** was calculated by HPLC with a correction factor and the conversions of **1b-h** were estimated by ^{1}H NMR from the crude products.

The conversion of **1a** was calculated by the following equation as described in the literature[3].

$$\text{Conversion of } \mathbf{1a}\ (\%) = \frac{PA_{\mathbf{3a}}}{PA_{\mathbf{3a}} + PA_{\mathbf{1a}}/f}$$

Where $PA_{\mathbf{1a}}$ and $PA_{\mathbf{3a}}$ are the peak areas of **1a** and **3a**, respectively. And *f* is the correction factor determined to be 0.520 from a fitting curve (Figure S6).

*Using enone **1** in a 0.1 mmol scale*: In order to obtain the isolated yields of the Michael products **3a-j**, the ATP·Cu^{2+} catalyzed enantioselective Michael reactions were carried out using enone **1** in a 0.1 mmol scale. The typical procedure is as follows: ATP (0.05 mmol) and $Cu(OTf)_2$ (0.01 mmol) was dissolved in a CHES buffer (15 mL, 20 mM, pH 9.5). After stirring for 30 min at 4 °C, a mixture of **1** (0.1 mmol) and **2** (5 mmol, 50 eq.) in DMSO (0.5 mL) were added. The mixture was stirred for 72 h followed by the extraction with ethyl acetate (2 × 10 mL). The combined organic fractions were dried by Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 6:1, v/v) and the isolated yields of **3a-j** were obtained. The enantioselectivities of pure **3a-j** were analyzed by chiral HPLC with the eluents of hexane and *i*-PrOH using Daicel Chiralpak AD or ODH column (250 × 4.6 mm).

5.2 Preparative scale

*Using enone **1** in a 0.5 mmol scale*: To a CHES buffer (60 mL, 20 mM, pH 9.5) in a round-bottom flask, ATP (0.5 mmol) and $Cu(OTf)_2$ (0.1 mmol) were added. After stirring for 30 min at 4 °C, a mixture of **1** (0.5 mmol, **1a** = 106 mg, **1c** = 145 mg, **1e** = 121 mg) and **2a** (25 mmol, 50 eq.) in DMSO (1.2 mL) were added. The reaction was stirred for 72 h and monitored by TLC, followed by the extraction with ethyl acetate (2 × 30 mL). The combined organic fractions were dried by Na_2SO_4 and concentrated under reduced pressure. The crude products of **3a, 3c** and **3e** were purified by silica gel chromatography using petroleum ether and ethyl acetate as eluents with a volume ratio of 6:1. The enantioselectivities of **3a, 3c** and **3e** were analyzed by chiral HPLC with the eluents of hexane and *i*-PrOH, using Daicel Chiralpak AD column (250 × 4.6 mm).

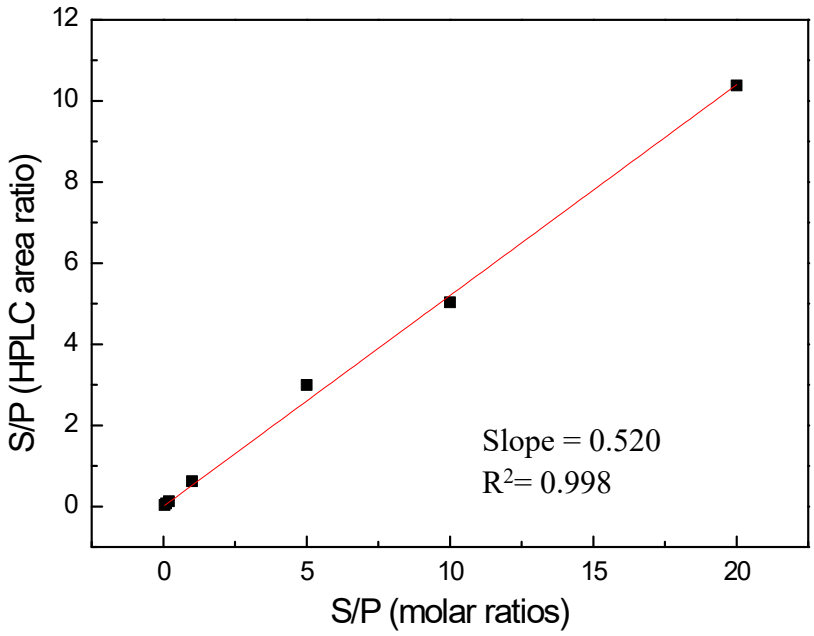


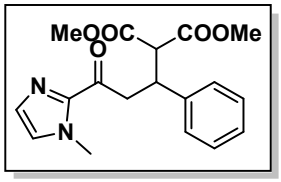
Figure S6 Determination of the correction factor between **1a** and **3a** on HPLC. The HPLC ratios of peak areas (PA_{1a}/PA_{3a}) were determined with the standard molar ratios (n_{1a}/n_{3a}) of 1/20, 1/10, 1/5, 1, 5, 10, 20. The correction factor (f = 0.520) was estimated from the fitting curve (R^2 = 0.998).

6. References

1. C. Wang, G. Jia, Y. Li, S. Zhang and C. Li, *Chem. Commun.*, 2013, **49**, 11161-11163.
2. Y. Li, C. Wang, G. Jia, S. Lu and C. Li, *Tetrahedron*, 2013, **69**, 6585-6590.
3. C. Wang, M. Hao, Q. Qi, J. Dang, X. Dong, S. Lv, L. Xiong, H. Gao, G. Jia, Y. Chen, J. S. Hartig and C. Li, *Angew. Chem. Int. Ed.*, 2020, **59**, 3444-3449.
4. D. Coquière, B. L. Feringa and G. Roelfes, *Angew. Chem. Int. Ed.*, 2007, **46**, 9308-9311.

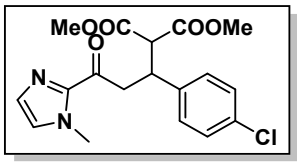
7. NMR and HRMS data

2-[3-(1-Methyl-1*H*-imidazol-2-yl)-3-oxo-1-phenyl-propyl]-malonic acid dimethyl ester (3a).



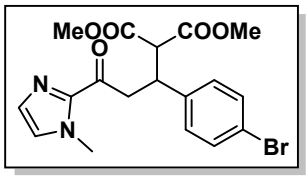
White solid (94% yield), R_f = 0.2 (petroleum ether: ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 2H), 7.22 (d, *J* = 13.1 Hz, 2H), 7.17 – 7.15 (m, 1H), 7.12 (s, 1H), 6.97 (s, 1H), 4.14 (td, *J* = 10.0, 4.3 Hz, 1H), 3.91 – 3.80 (m, 5H), 3.71 (s, 3H), 3.50 (dd, *J* = 17.5, 4.4 Hz, 1H), 3.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.61 (s), 168.63 (s), 168.18 (s), 142.78 (s), 140.49 (s), 128.91 (s), 128.41 (d, *J* = 13.1 Hz), 127.33 – 127.21 (m), 127.08 (d, *J* = 21.6 Hz), 57.70 (s), 52.82 (s), 52.47 (s), 42.89 (s), 40.33 (s), 36.22 (s). HRMS (ESI) calcd. For $[C_{18}H_{20}N_2O_5]\cdot Na^+$ $(M+Na)^+$: *m/z* 367.1264, found 367.1263.

2-[1-(4-Chloro-phenyl)-3-(1-methyl-1*H*-imidazol-2-yl)-3-oxo-propyl]-malonic acid dimethyl ester (3b).



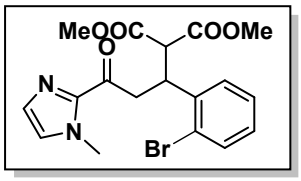
White solid (59% yield), R_f = 0.25 (petroleum ether: ethyl acetate = 2:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 22.8, 8.5 Hz, 4H), 7.08 (s, 1H), 6.96 (s, 1H), 4.15 – 4.11 (m, 1H), 3.86 (s, 3H), 3.84 – 3.76 (m, 2H), 3.71 (s, 3H), 3.48 (s, 3H), 3.41 (dd, *J* = 17.5, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.37 (s), 168.30 (s), 167.90 (s), 142.75 (s), 139.05 (s), 132.83 (s), 129.74 (s), 129.04 (s), 128.53 (s), 127.02 (s), 57.34 (s), 52.73 (s), 52.43 (s), 42.61 (s), 39.75 (s), 36.03 (s). HRMS (ESI) calcd. For $[C_{18}H_{19}N_2O_5Cl]\cdot H^+$ $(M+H)^+$: *m/z* 379.1055, found 379.1052.

2-[1-(4-Bromo-phenyl)-3-(1-methyl-1*H*-imidazol-2-yl)-3-oxo-propyl]-malonic acid dimethyl ester (3c).

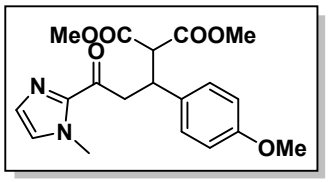


White solid (63% yield), R_f = 0.2 (petroleum ether: ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (q, *J* = 8.5 Hz, 4H), 7.03 (s, 1H), 6.93 (s, 1H), 4.09 (td, *J* = 10.1, 4.3 Hz, 1H), 3.82 (s, 3H), 3.79 – 3.67 (m, 2H), 3.67 (s, 3H), 3.44 (s, 3H), 3.37(dd, *J* = 17.5, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.38 (s), 168.36 (s), 167.96 (s), 139.63 (s), 131.56 (s), 130.18 (s), 129.08 (s), 127.11 (s), 121.08 (s), 57.33 (s), 52.84 (s), 52.55 (s), 42.63 (s), 39.85 (s), 36.15 (s). HRMS (ESI) calcd. For $[C_{18}H_{19}N_2O_5Br]\cdot Na^+$ $(M+Na)^+$: *m/z* 445.0370, found 445.0363.

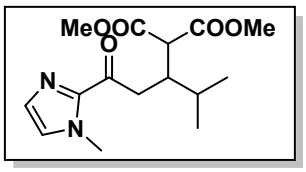
2-[1-(3-Bromo-phenyl)-3-(1-methyl-1*H*-imidazol-2-yl)-3-oxo-propyl]-malonic acid dimethyl ester (3d).



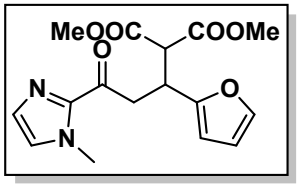
White solid (51% yield), R_f = 0.2 (petroleum ether: ethyl acetate = 2:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 15.3, 7.5 Hz, 2H), 6.96 (s, 1H), 4.12 (td, *J* = 9.9, 4.4 Hz, 1H), 3.86 (d, *J* = 14.3 Hz, 3H), 3.78 (dd, *J* = 17.6, 9.7 Hz, 2H), 3.71 (s, 3H), 3.50 – 3.44 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.27 (s), 168.24 (s), 167.83 (s), 142.98 (s), 131.41 (s), 130.27 (s), 129.90 (s), 129.09 (s), 127.02 (d, *J* = 8.3 Hz), 122.32 (s), 57.27 (s), 52.70 (s), 52.42 (s), 42.52 (s), 39.96 (s), 36.00 (s). HRMS (ESI) calcd. For $[C_{18}H_{19}N_2O_5Br]\cdot Na^+$ $(M+Na)^+$: *m/z* 445.0370, found 445.0376.

2-[1-(4-Methoxy-phenyl)-3-(1-methyl-1*H*-imidazol-2-yl)-3-oxo-propyl]-malonic acid dimethyl ester (3e). 

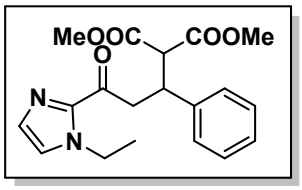
White solid (80% yield), R_f = 0.15 (petroleum ether: ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.16 (m, 2H), 7.04 (d, *J* = 0.8 Hz, 1H), 6.92 (s, 1H), 6.75 – 6.72 (m, 2H), 4.08 (td, *J* = 10.0, 4.3 Hz, 1H), 3.82 (d, *J* = 3.8 Hz, 3H), 3.76 (dd, *J* = 20.0, 9.0 Hz, 2H), 3.69 (d, *J* = 6.9 Hz, 6H), 3.44 (s, 3H), 3.38 (dd, *J* = 17.4, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.83 (s), 168.65 (s), 168.21 (s), 158.49 (s), 142.95 (s), 132.47 (s), 129.35 (s), 128.99 (s), 126.95 (s), 113.76 (s), 57.85 (s), 55.17 (s), 52.69 (s), 52.40 (s), 42.94 (s), 39.68 (s), 36.09 (s). HRMS (ESI) calcd. For $[C_{19}H_{22}N_2O_6]\cdot Na^+$ $(M+Na)^+$: *m/z* 397.1370, found 397.1363.

2-{2-Methyl-1-[2-(1-methyl-1*H*-imidazol-2-yl)-2-oxo-ethyl]-propyl}-malonic acid dimethyl ester (3f). 

White solid (37% yield), R_f = 0.2 (petroleum ether: ethyl acetate = 3:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 7.00 (s, 1H), 3.98 (s, 3H), 3.71 (s, 3H), 3.60 (d, *J* = 6.7 Hz, 4H), 3.23 (t, *J* = 5.8 Hz, 2H), 2.93 -2.89 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.50 (s), 169.61 (s), 169.41 (s), 143.06 (s), 128.96 (s), 126.93 (s), 54.37 (s), 52.48 (d, *J* = 13.3 Hz), 38.98 (s), 37.65 (s), 36.25 (s), 30.16 (s), 20.89 (s), 18.15 (s). HRMS (ESI) calcd. For $[C_{15}H_{22}N_2O_5]\cdot Na^+$ $(M+Na)^+$: *m/z* 333.1421, found 333.1429.

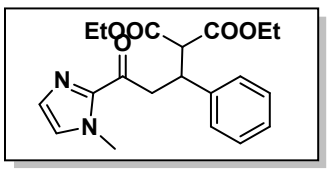
2-[1-Furan-2-yl-3-(1-methyl-1*H*-imidazol-2-yl)-3-oxo-propyl]-malonic acid dimethyl ester (3g). 

Yellow oil (95% yield), R_f = 0.2 (petroleum ether: ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.0 Hz, 1H), 7.08 (s, 1H), 6.98 (s, 1H), 6.19 – 6.17 (m, 1H), 6.10 (d, *J* = 3.2 Hz, 1H), 4.25 (td, *J* = 9.2, 4.4 Hz, 1H), 3.90 (s, 3H), 3.82 (dd, *J* = 19.2, 9.1 Hz, 2H), 3.68 (s, 3H), 3.58 (s, 3H), 3.41 (dd, *J* = 17.7, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.49 (s), 168.25 (d, *J* = 7.6 Hz), 153.62 (s), 142.73 (s), 141.78 (s), 129.12 (s), 127.07 (s), 110.25 (s), 107.00 (s), 55.27 (s), 52.70 (d, *J* = 8.5 Hz), 40.35 (s), 36.18 (s), 34.01 (s). HRMS (ESI) calcd. For $[C_{16}H_{18}N_2O_6]\cdot Na^+$ $(M+Na)^+$: *m/z* 357.1057, found 357.1055.

2-[3-(1-Ethyl-1H-imidazol-2-yl)-3-oxo-1-phenyl-propyl]-malonic acid dimethyl ester (3h). 

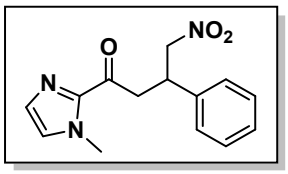
White solid (90% yield), R_f = 0.25 (petroleum ether: ethyl acetate = 3:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.28 (m, 2H), 7.25 – 7.21 (m, 2H), 7.16 – 7.12 (m, 1H), 7.09 (s, 1H), 7.02 (s, 1H), 4.34 - 4.24 (m, 2H), 4.18 (td, *J* = 10.0, 4.6 Hz, 1H), 3.87 – 3.80 (m, 2H), 3.72 (s, 3H), 3.51 - 3.46 (m, 1H), 3.45 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.50 (s), 168.50 (s), 168.06 (s), 142.25 (s), 140.46 (s), 129.14 (s), 128.27 (d, *J* = 4.0 Hz), 127.01 (s), 125.12 (s), 57.63 (s), 52.59 (s), 52.25 (s), 43.57 (s), 42.90 (s), 40.51 (s), 16.20 (s). HRMS (ESI) calcd. For $[C_{19}H_{22}N_2O_5]\cdot Na^+$ $(M+Na)^+$: *m/z* 381.1434, found 381.1431.

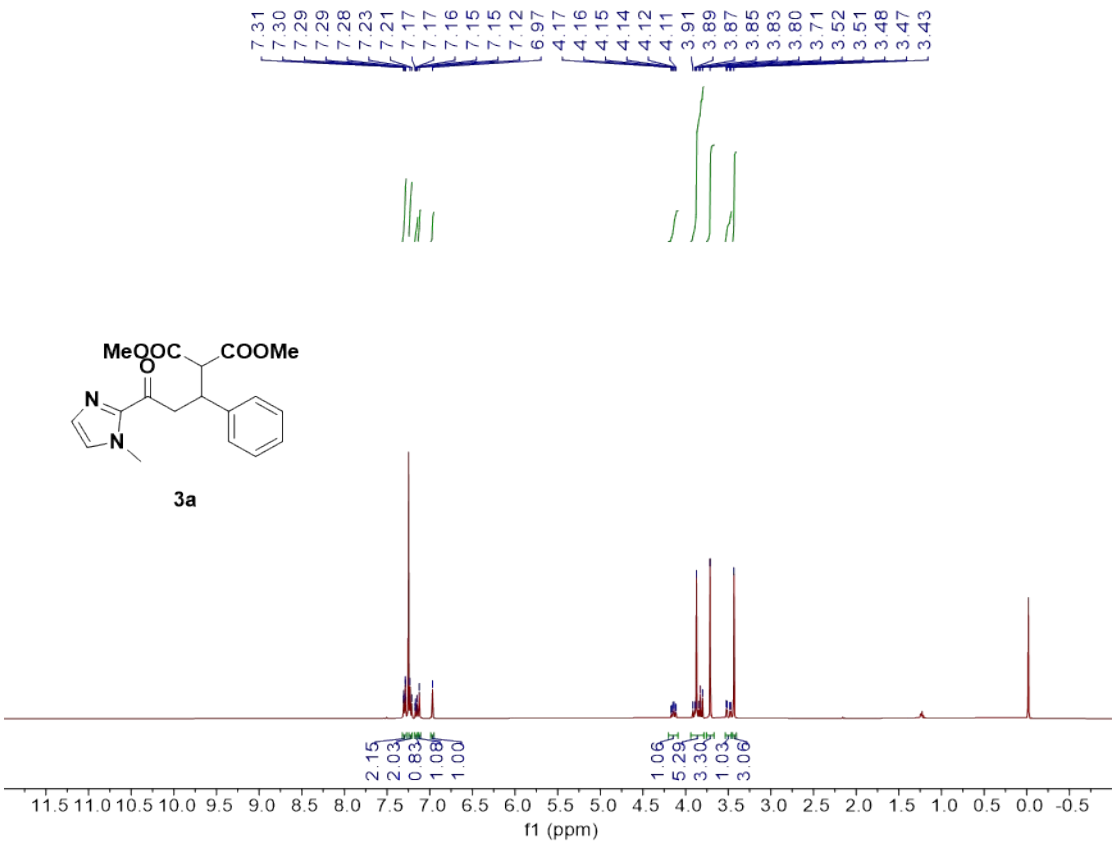
2-[3-(1-Methyl-1*H*-imidazol-2-yl)-3-oxo-1-phenyl-propyl]-malonic acid diethyl ester (3i).



White solid (91% yield), R_f = 0.3 (petroleum ether: ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.13 (m, 5H), 7.06 (d, *J* = 0.6 Hz, 1H), 6.93 (s, 1H), 4.19 – 4.11 (m, 3H), 3.90 – 3.74 (m, 7H), 3.44 (dd, *J* = 17.4, 4.1 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.73 (s), 168.22 (s), 167.79 (s), 142.89 (s), 140.66 (s), 128.71 (d, *J* = 33.0 Hz), 128.34 (s), 126.97 (d, *J* = 18.4 Hz), 61.71 (s), 61.31 (s), 57.90 (s), 43.19 (s), 40.35 (s), 36.12 (s), 14.11 (s), 13.80 (s). HRMS (ESI) calcd. For $[C_{20}H_{24}N_2O_5]\cdot Na^+$ (M+Na)$^+$: *m/z* 395.1577, found 395.1571.

1-(1-Methyl-1*H*-imidazol-2-yl)-4-nitro-3-phenyl-butan-1-one (3j). White solid (89% yield), R_f = 0.25 (petroleum ether: ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.3 Hz, 4H), 7.25 – 7.21 (m, 1H), 7.14 (s, 1H), 7.02 (s, 1H), 4.73 (dd, *J* = 12.7, 6.9 Hz, 1H), 4.63 (dd, *J* = 12.4, 8.2 Hz, 1H), 4.24 – 4.15 (m, 1H), 3.93 (s, 3H), 3.74 (dd, *J* = 17.4, 7.3 Hz, 1H), 3.53 (dd, *J* = 17.5, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.14 (s), 139.03 (s), 129.29 (s), 128.96 (s), 127.68 (d, *J* = 19.8 Hz), 79.91 (s), 41.90 (s), 39.33 (s), 36.12 (s), 29.70(s). HRMS (ESI) calcd. For $[C_{14}H_{15}N_3O_3]\cdot Na^+$ (M+Na)$^+$: *m/z* 296.1006, found 296.1001.

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7.12
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4.16
4.15
4.14
4.12
4.11
3.91
3.89
3.87
3.85
3.83
3.80
3.71
3.52
3.51
3.48
3.47
3.43
MeOOC
COOMe
O
N
N
3a
2.15
2.03
0.83
1.08
1.00
1.06
5.29
3.30
1.03
3.06
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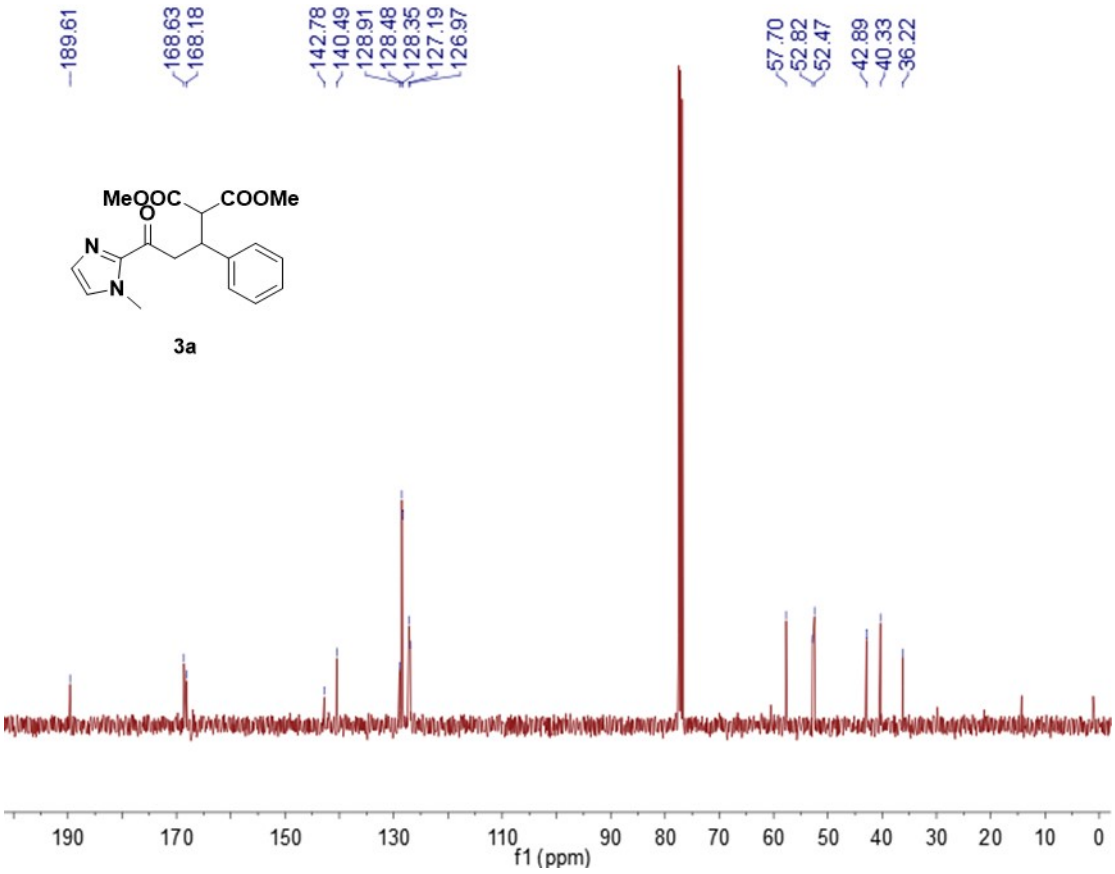
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52.47
42.89
40.33
36.22
MeOOC
COOMe
O
N
N
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150
130
110
90
80
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60
50
40
30
20
10
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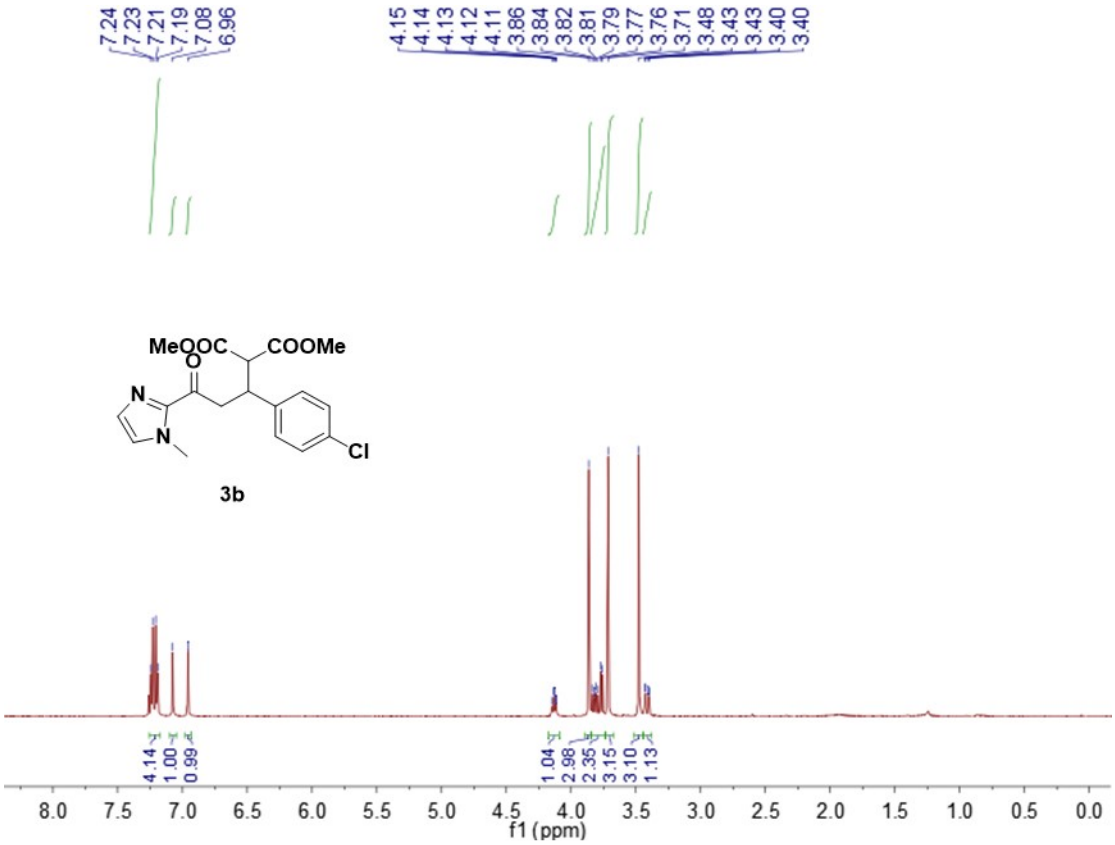
f1 (ppm)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COOMe
O
N
N
Cl
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3.15
3.10
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7.0
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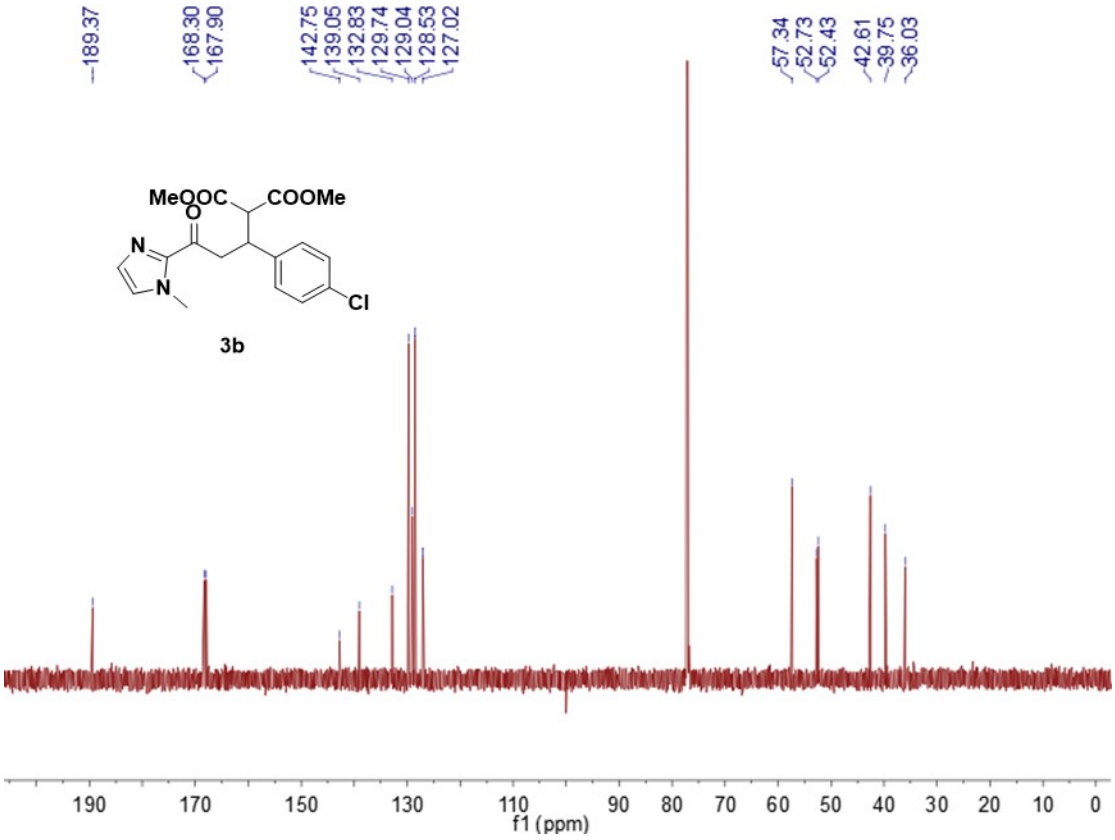
f1 (ppm)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O
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50
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30
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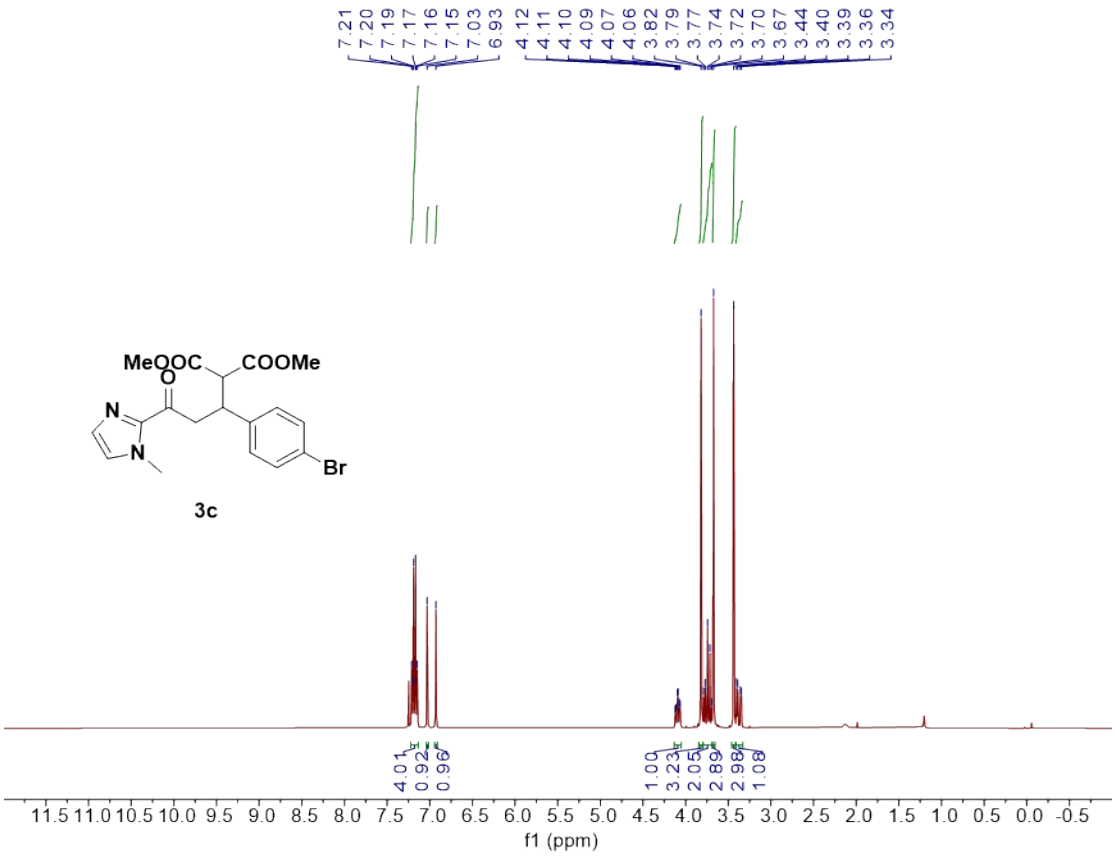
10
0
f1 (ppm)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3.40
3.39
3.36
3.34
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COOMe
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N
Br
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0.96
1.00
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2.05
2.89
2.98
1.08
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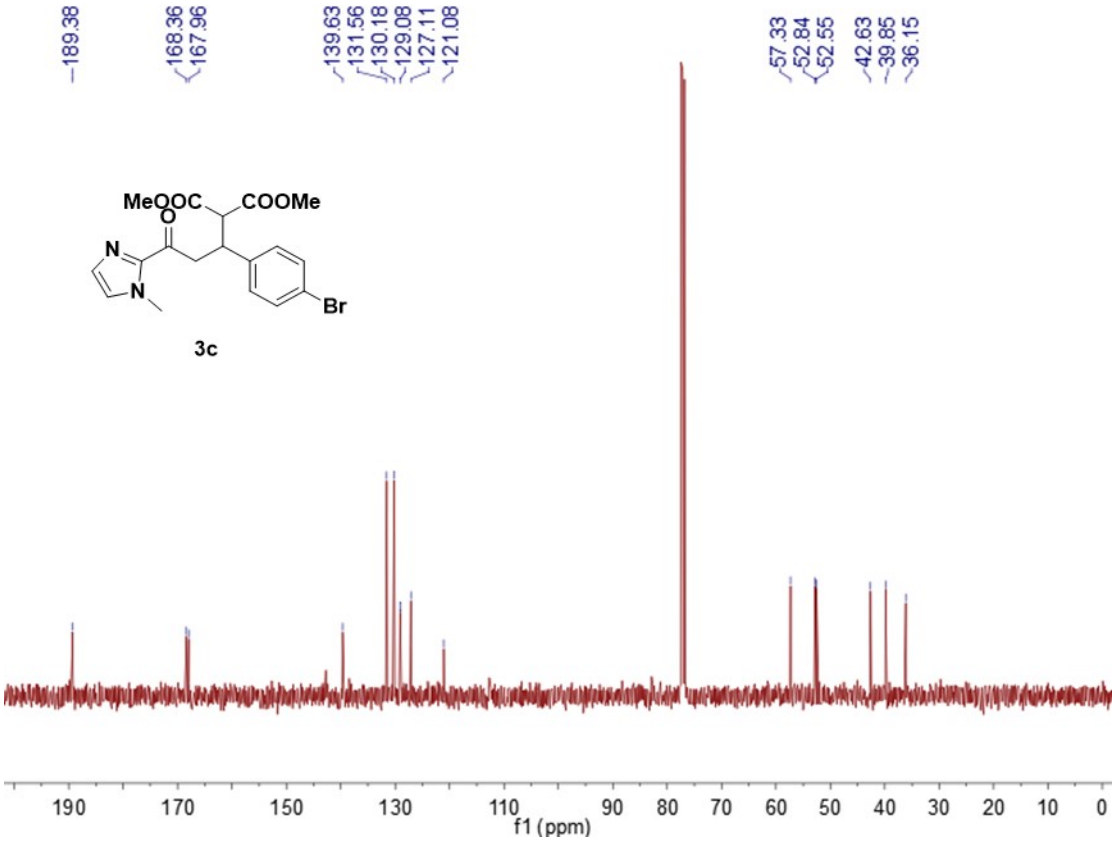
f1 (ppm)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39.85
36.15
MeOOC
COOMe
O
N
N
Br
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130
110
90
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50
40
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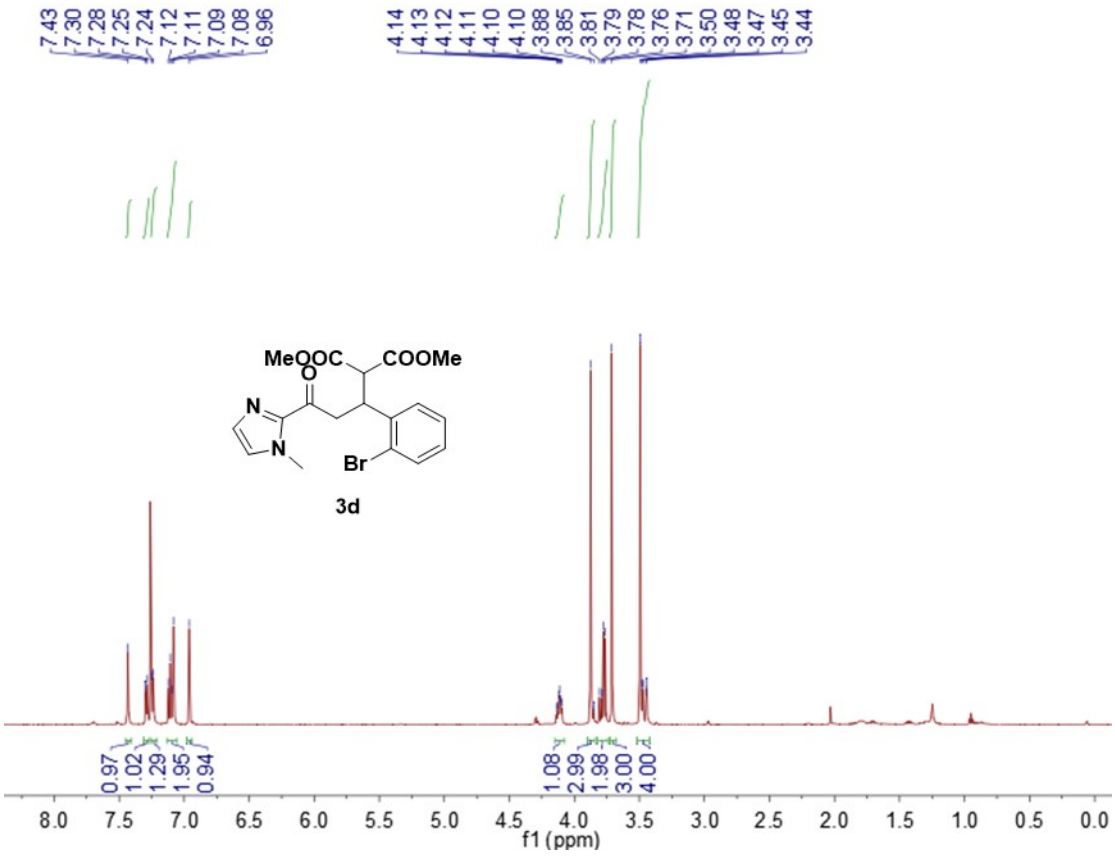
20
10
0
f1 (ppm)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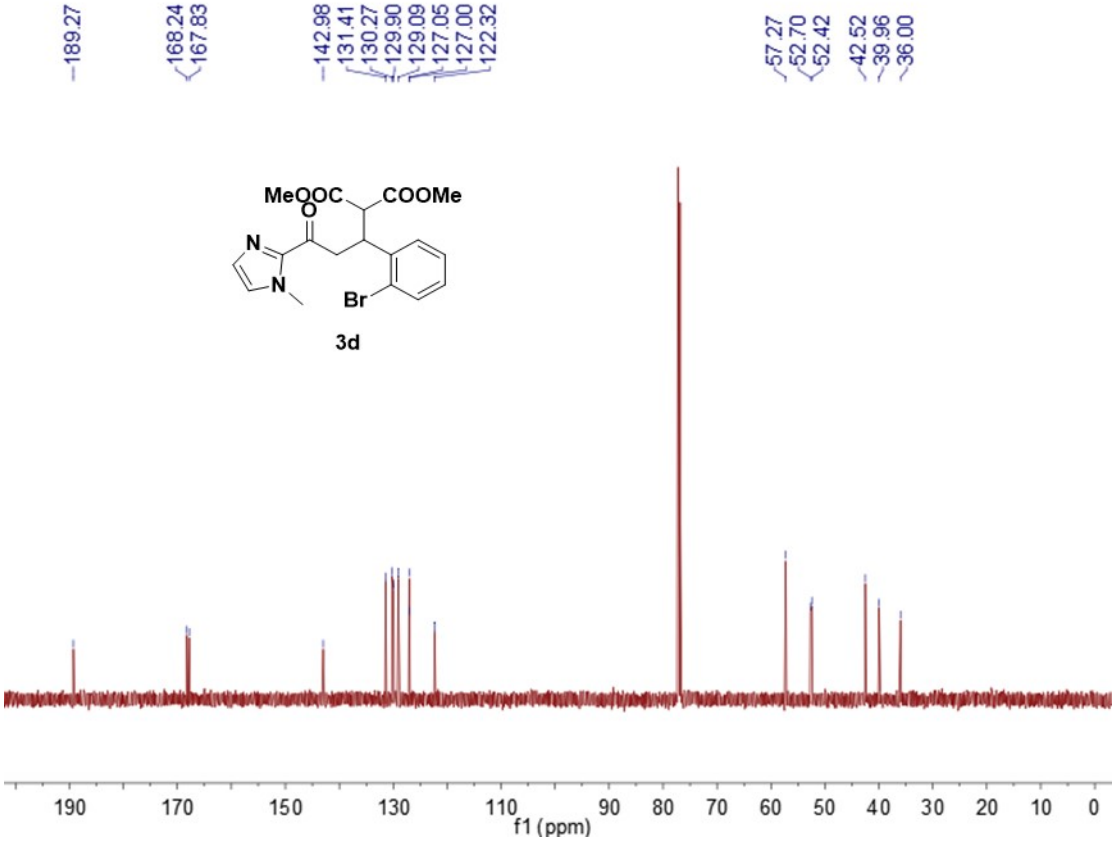
f1 (ppm)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42.52
39.96
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COOMe
O
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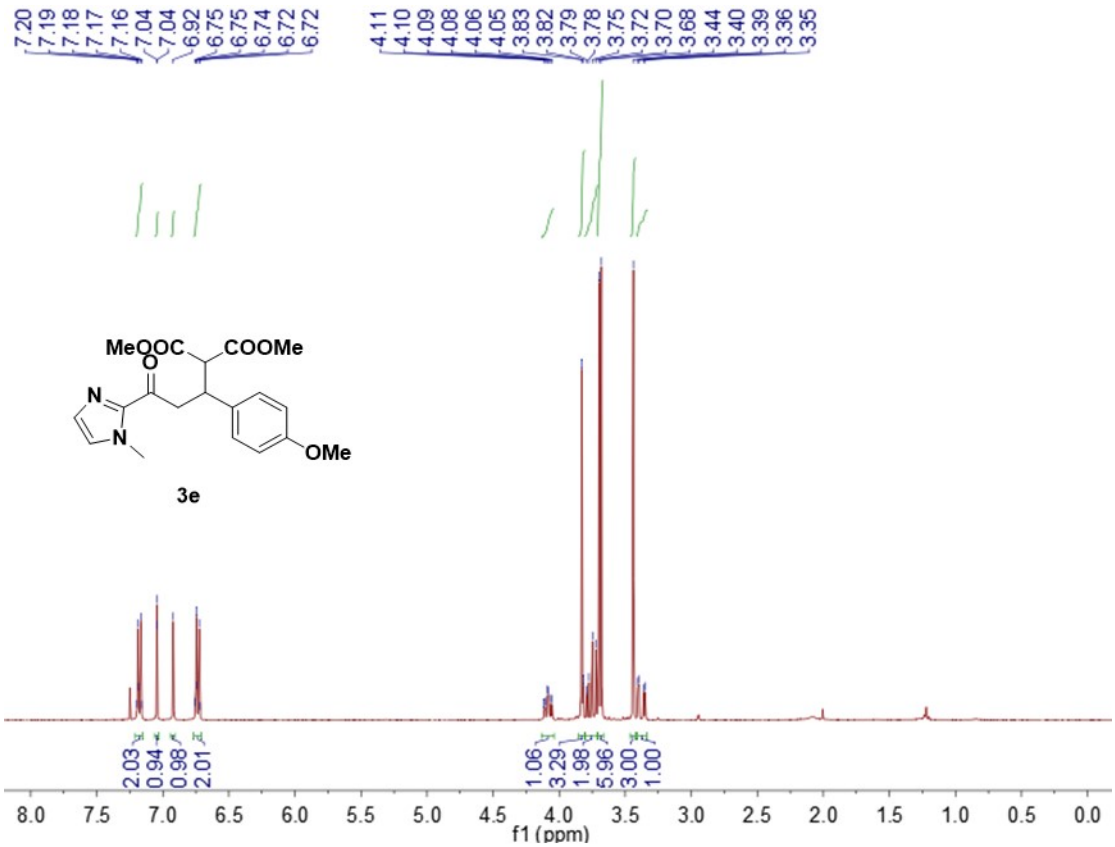
f1 (ppm)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4.08
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COOMe
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N
OMe
3e
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1.06
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7.0
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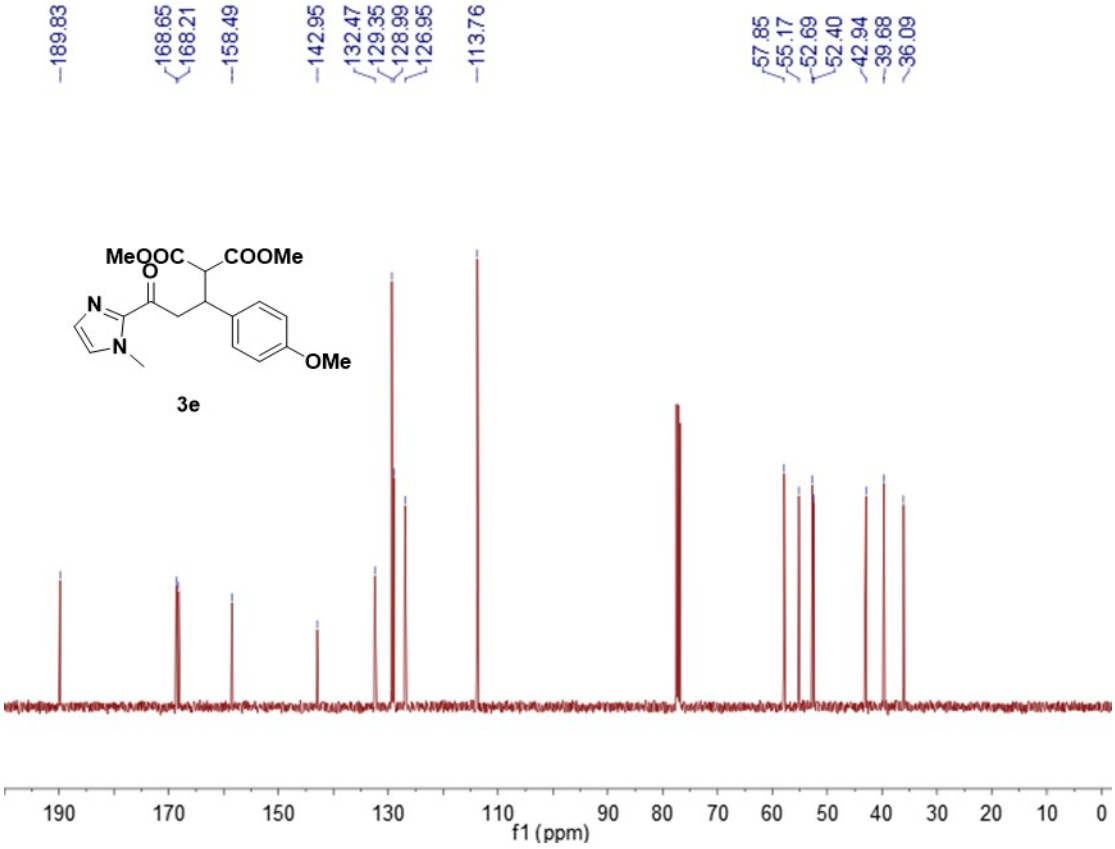
f1 (ppm)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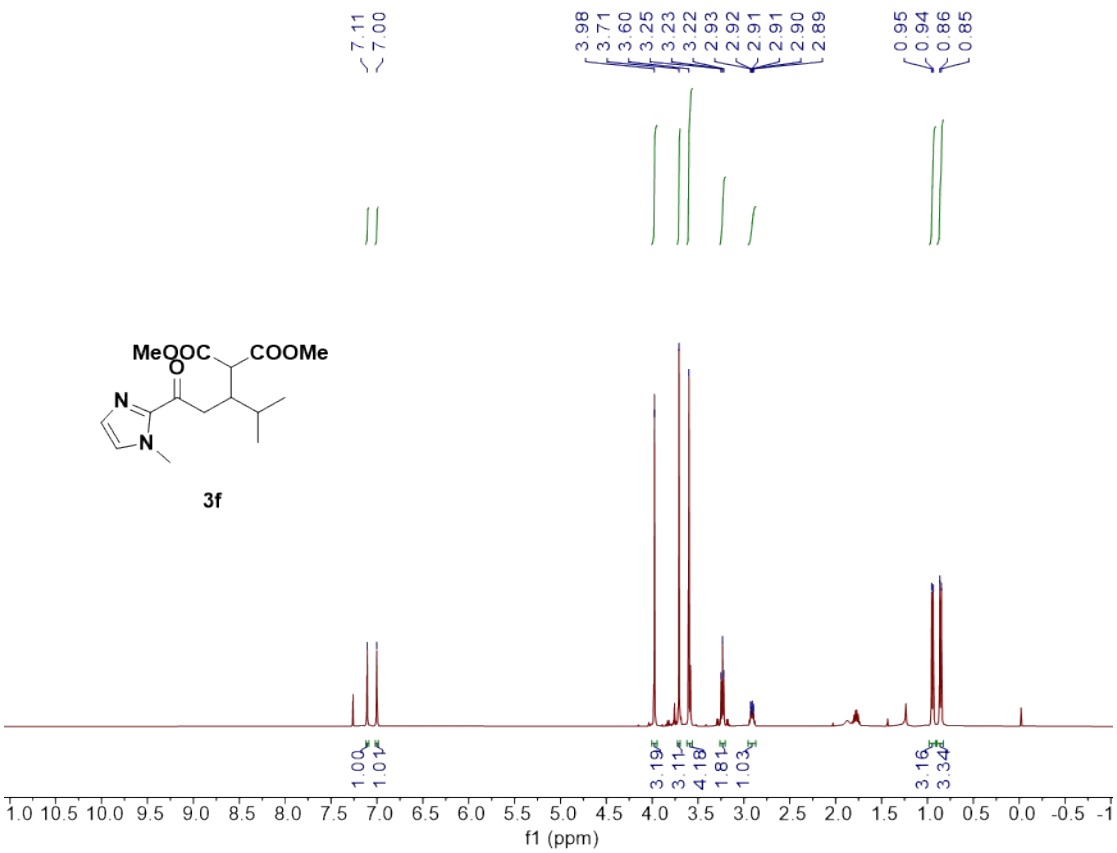
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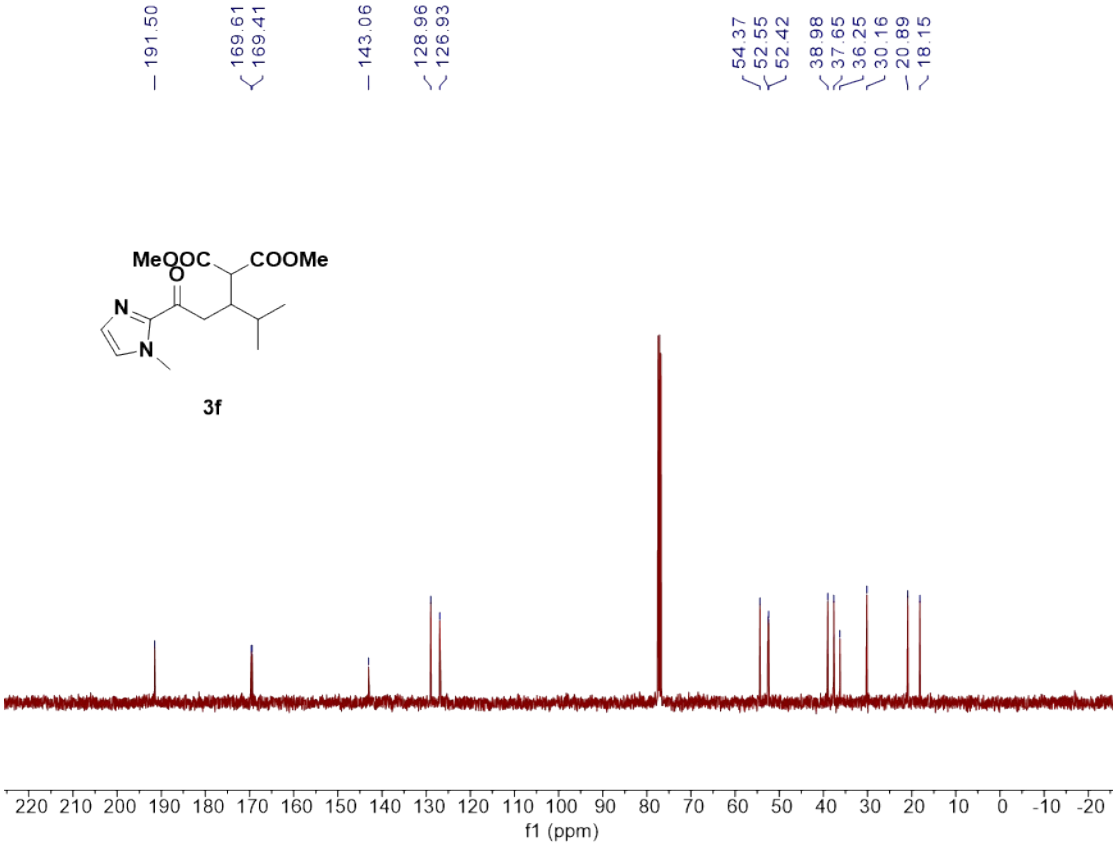
f1 (ppm)

3f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COOMe
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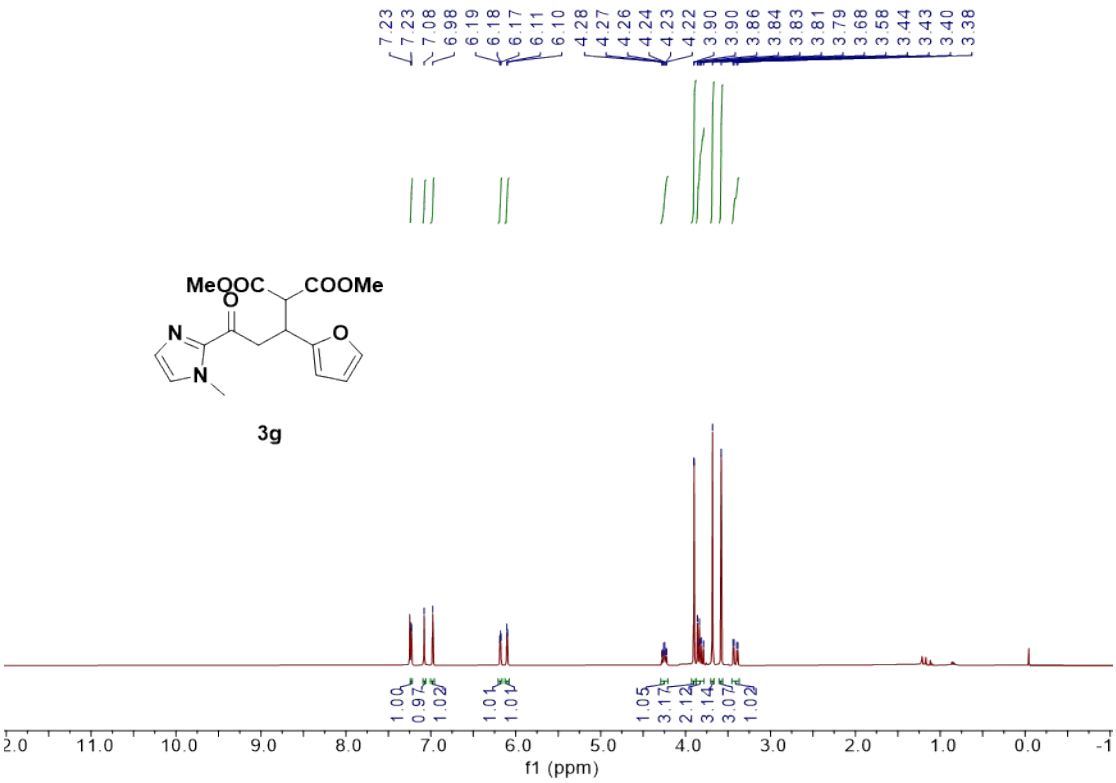
N
f1 (ppm)

3f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COOMe
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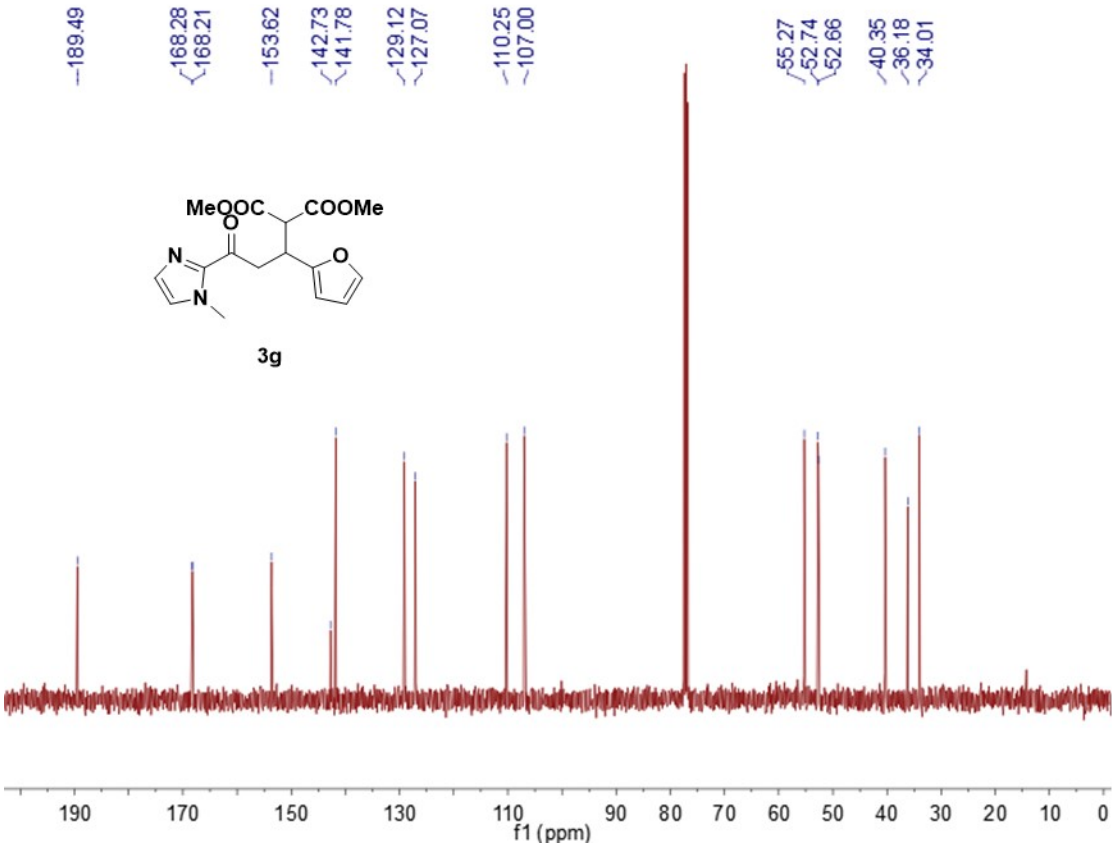
1.02
f1 (ppm)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COOMe
O
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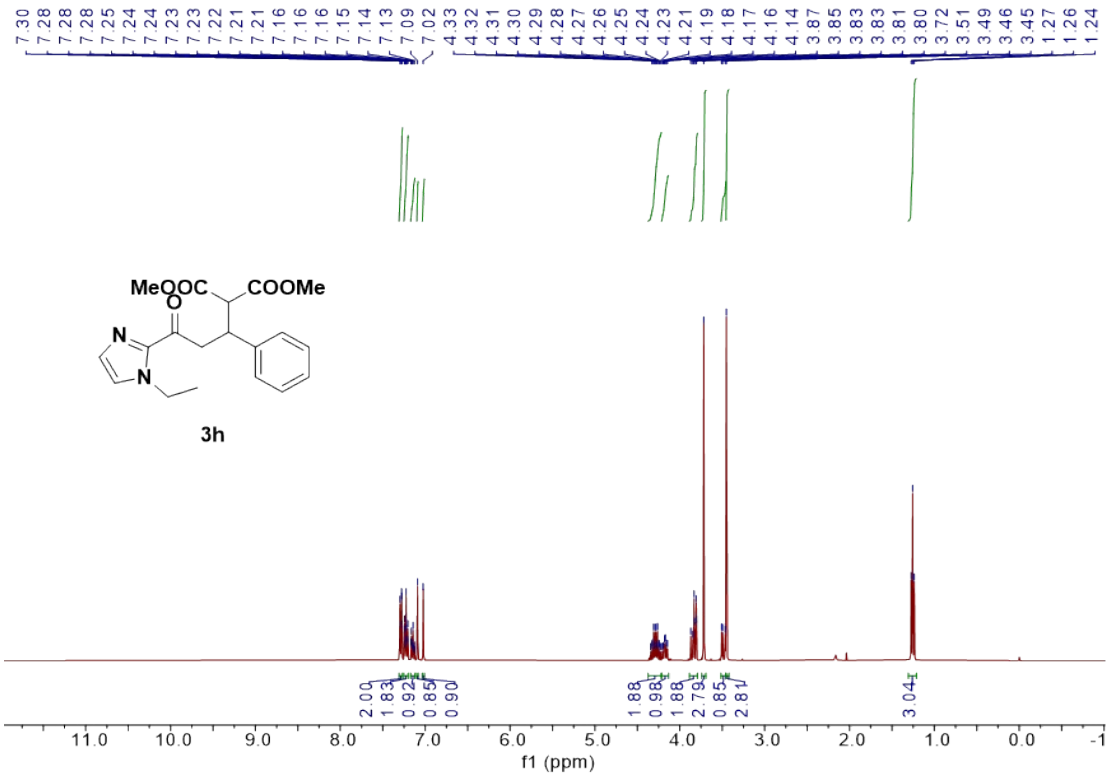
N
O
3g
f1 (ppm)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4.33 4.32 4.31 4.30 4.29 4.28 4.27 4.26 4.25 4.24 4.23 4.21 4.19 4.18 4.17 4.16 4.14 3.87 3.85 3.83 3.83 3.81 3.80 3.72 3.51 3.49 3.46 3.45 1.27 1.26 1.24
MeOOC
COOMe
O
N
N
3h
2.00 1.83 0.92 0.85 0.90 1.88 0.98 1.88 2.79 0.85 2.81 3.04
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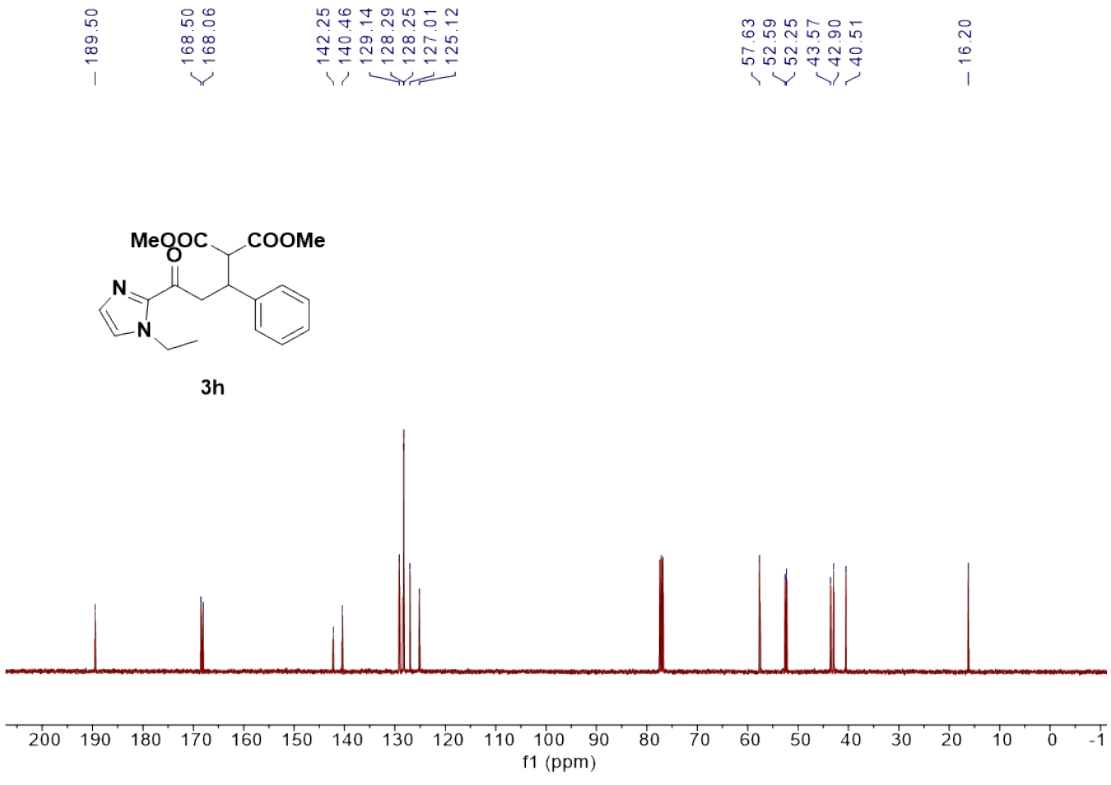
f1 (ppm)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O
N
N
3h
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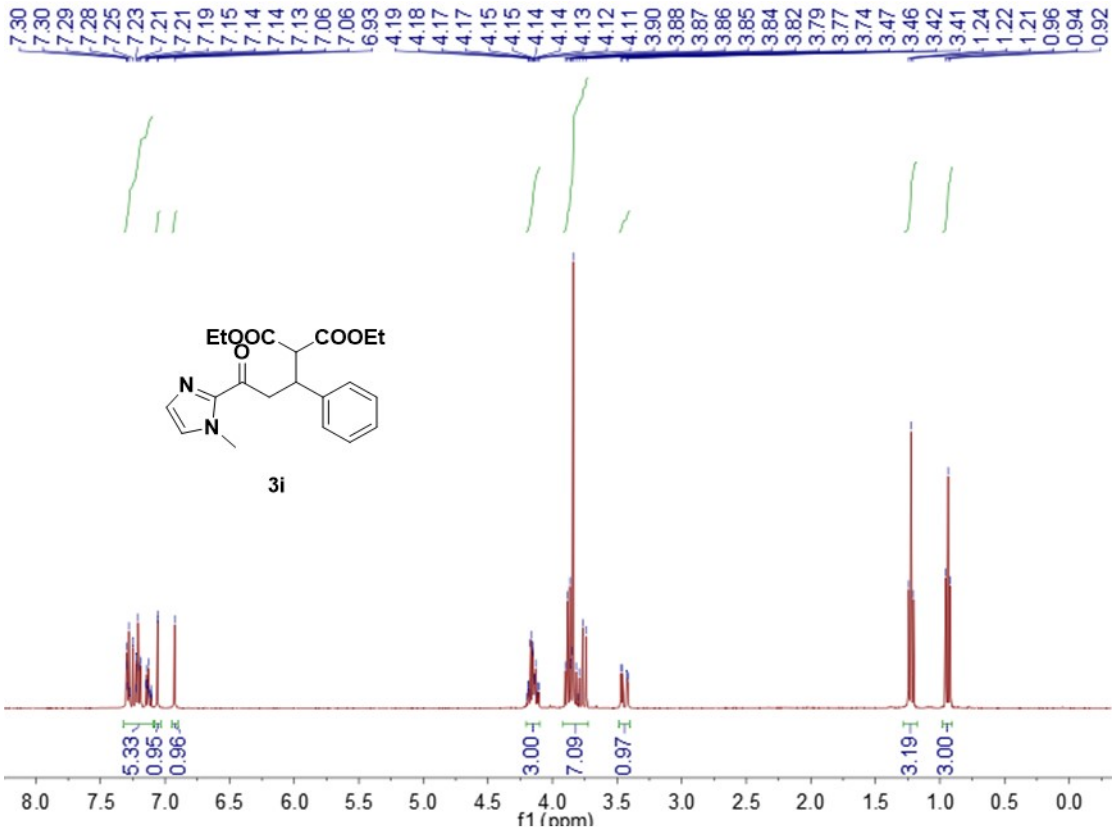
f1 (ppm)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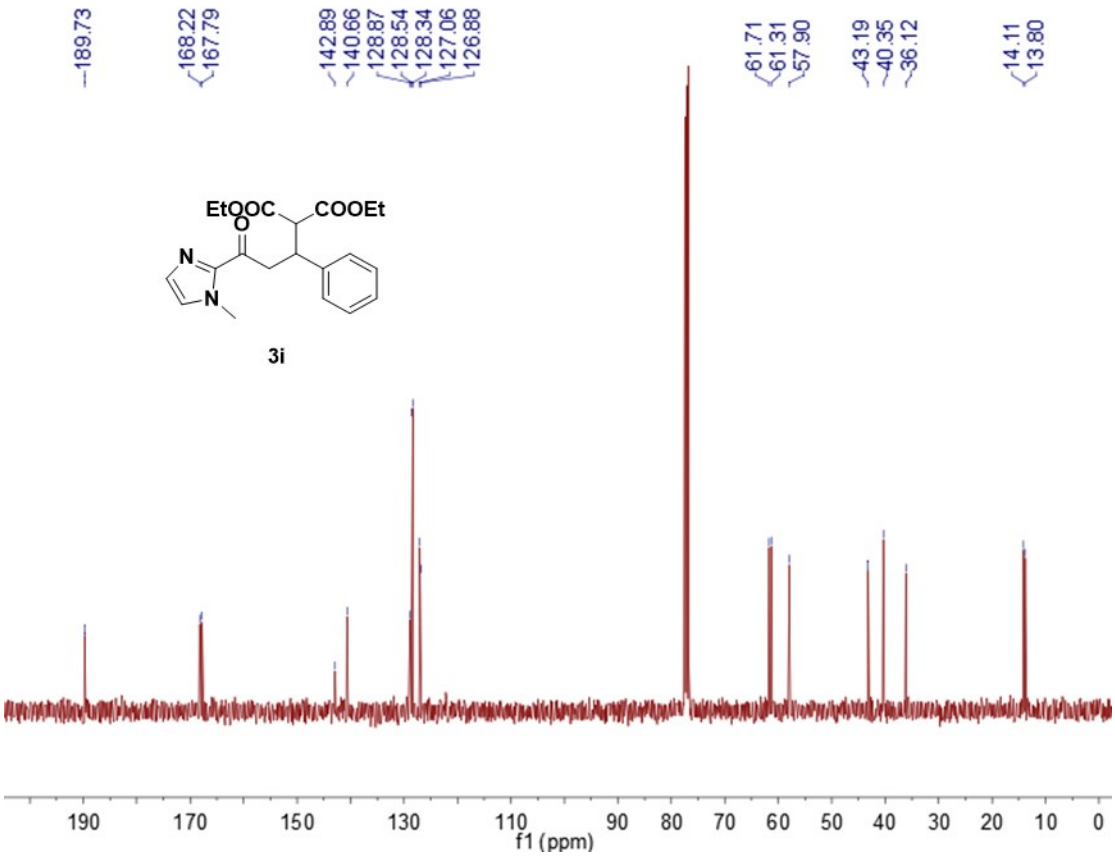
7.30
7.29
7.28
7.25
7.23
7.21
7.21
7.19
7.15
7.14
7.14
7.13
7.06
7.06
6.93
4.19
4.18
4.17
4.17
4.15
4.15
4.14
4.14
4.13
4.12
4.11
3.90
3.88
3.87
3.86
3.85
3.84
3.82
3.79
3.77
3.74
3.47
3.46
3.42
3.41
1.24
1.22
1.21
0.96
0.94
0.92
EtOOC
COOEt
O
N
N
3i
5.33
0.95
0.96
3.00
7.09
0.97
3.19
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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168.22
167.79
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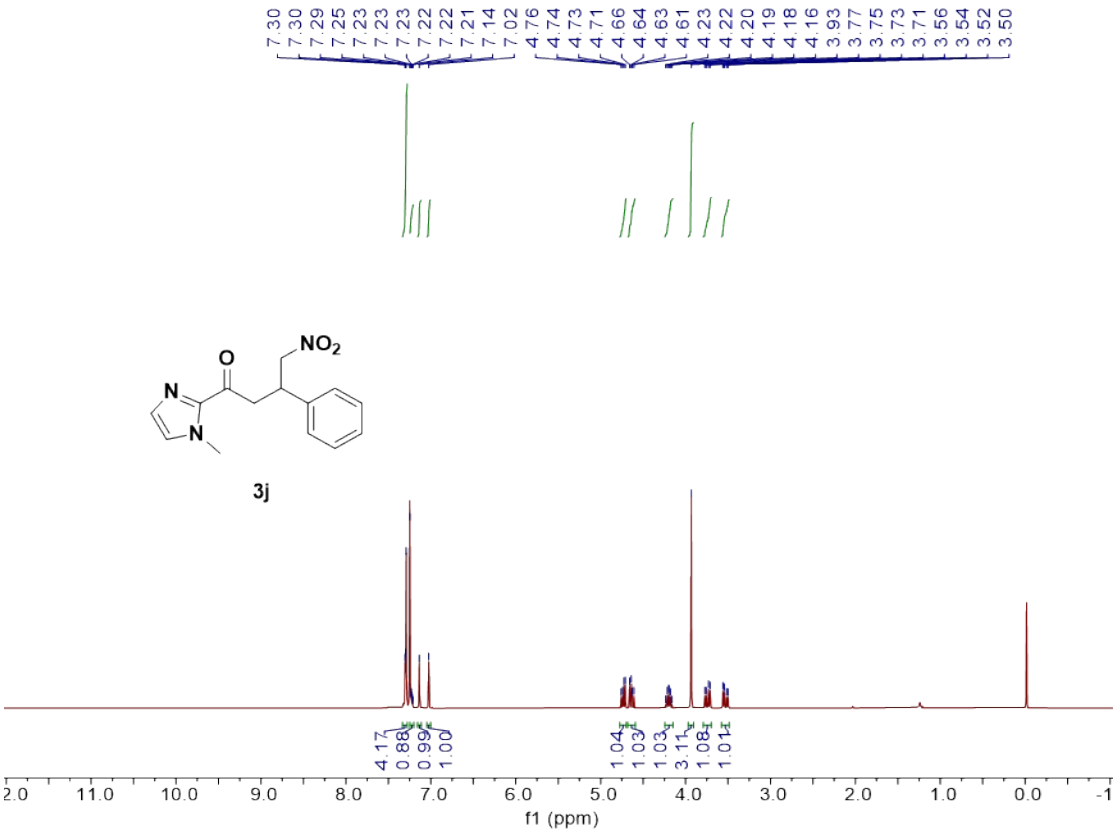
140.66
128.87
128.54
128.34
127.06
126.88
61.71
61.31
57.90
43.19
40.35
36.12
14.11
13.80
EtOOC
COOEt
O
N
N
3i
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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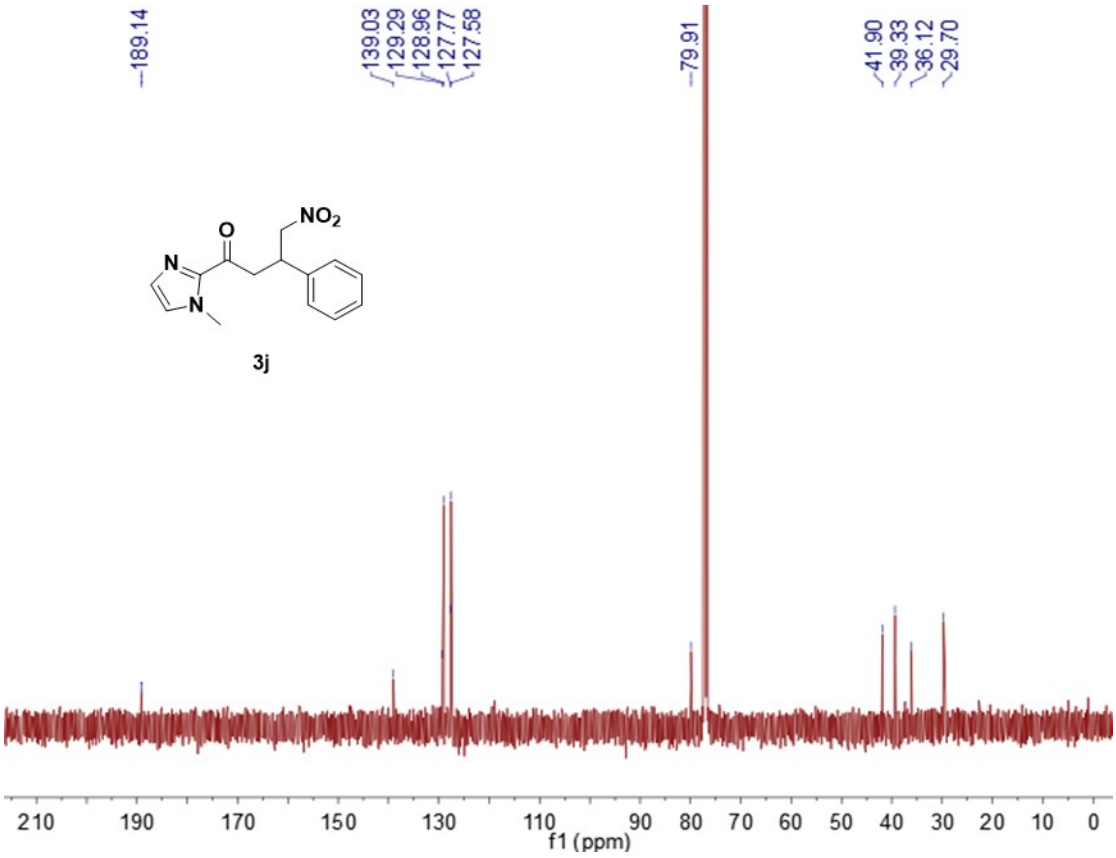
7.21
7.14
7.02
4.76
4.74
4.73
4.71
4.66
4.64
4.63
4.61
4.23
4.22
4.20
4.19
4.18
4.16
3.93
3.77
3.75
3.73
3.71
3.56
3.54
3.52
3.50
O
NO2
N
N
3j
4.17
0.88
0.99
1.00
1.04
1.03
1.03
3.11
1.08
1.01
f1 (ppm)

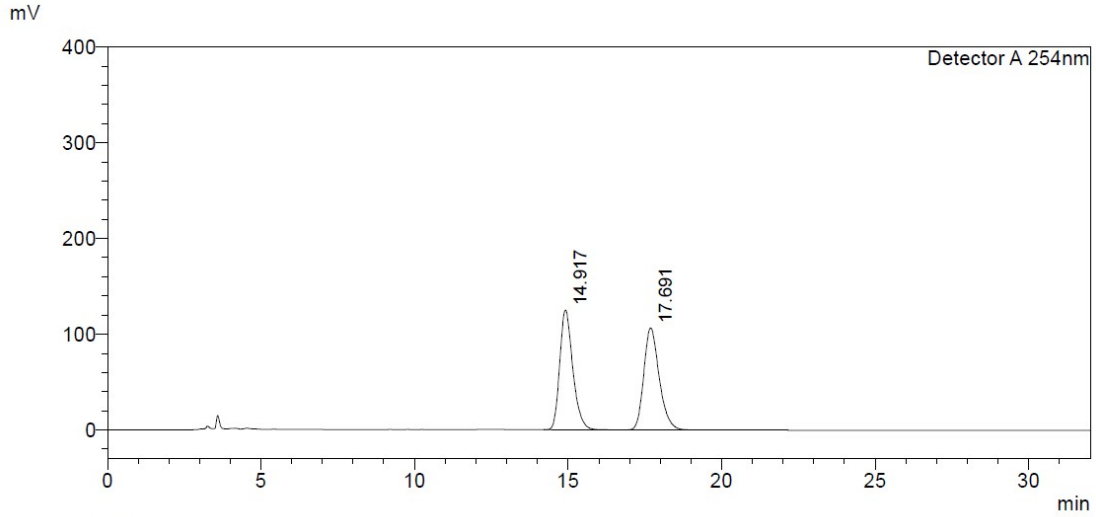

189.14
139.03
129.29
128.96
127.77
127.58
79.91
41.90
39.33
36.12
29.70
O
NO2
N
N
3j
f1 (ppm)

8. HPLC traces

3a racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 80:20, 1.0 mL/min, 254 nm).

Retention times: 14.9 min and 17.7 min.



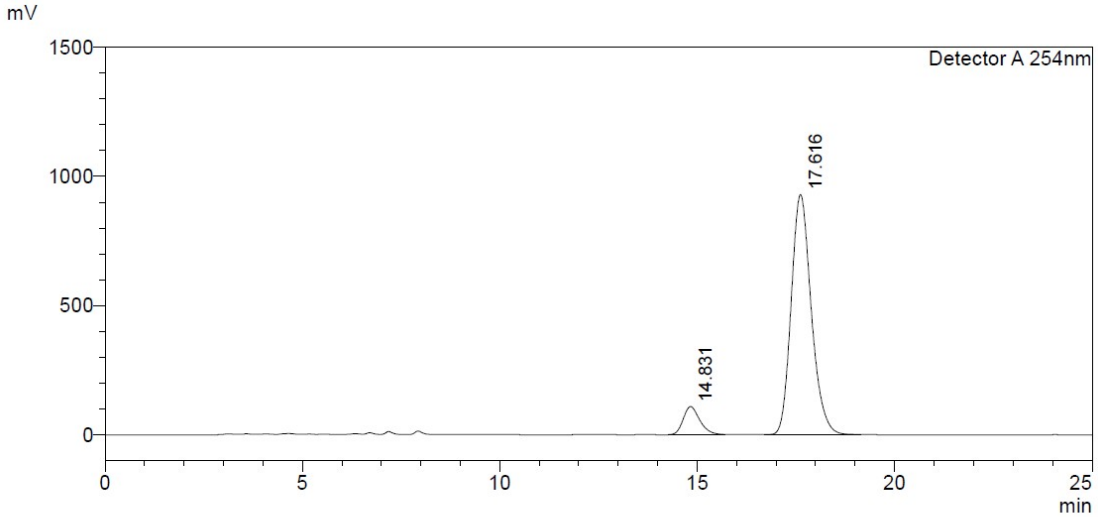
<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.917	3714146	125128	49.953			
2	17.691	3721117	106520	50.047			
Total		7435263	231647				

Product **3a** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1a** in a 0.5 mmol scale (83% ee).

Retention times: 14.8 min and 17.6 min.



<Peak Table>

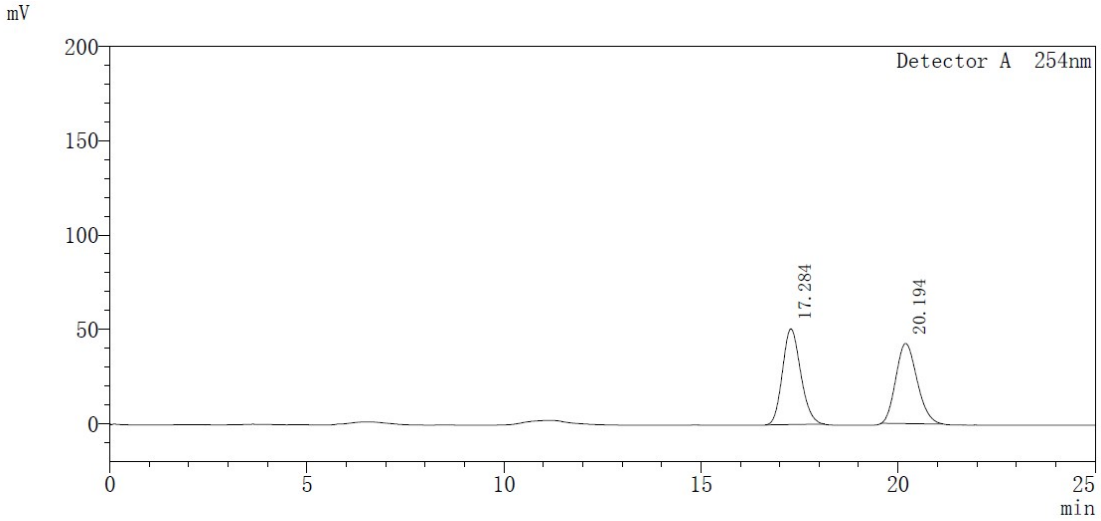
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.831	3142245	108368	0.000		M	
2	17.616	32844655	929661	0.000		M	
Total		35986901	1038029				

3b racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 80:20, 1.0 mL/min, 254 nm).

Retention times: 17.3 min and 20.2 min.



〈Peak Table〉

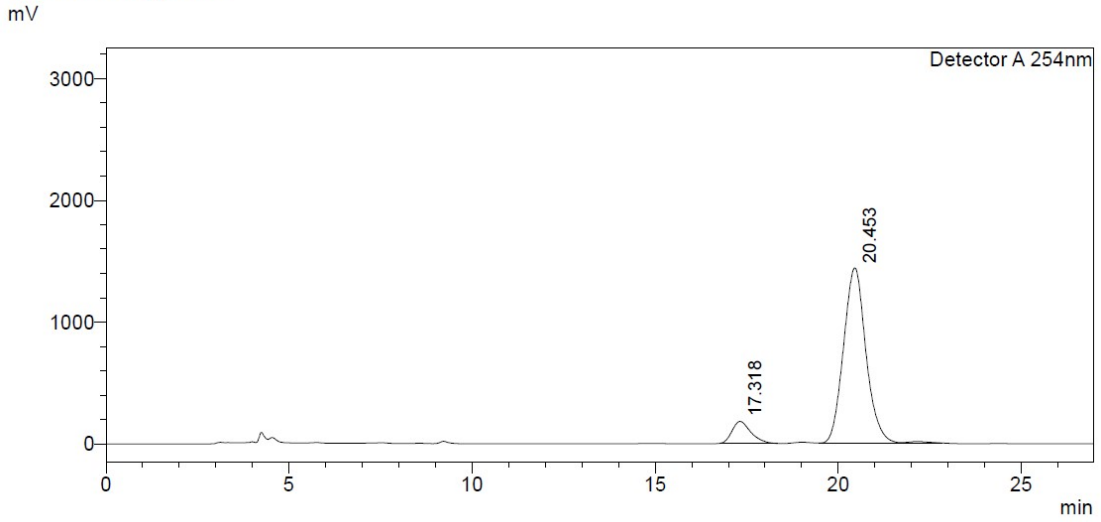
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	17.284	1636515	50706	50.737		M	
2	20.194	1588994	42456	49.263		M	
Total		3225509	93162				

Product **3b** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1b** in a 0.1 mmol scale (81% ee).

Retention times: 17.3 min and 20.5 min.

<Chromatogram>



<Peak Table>

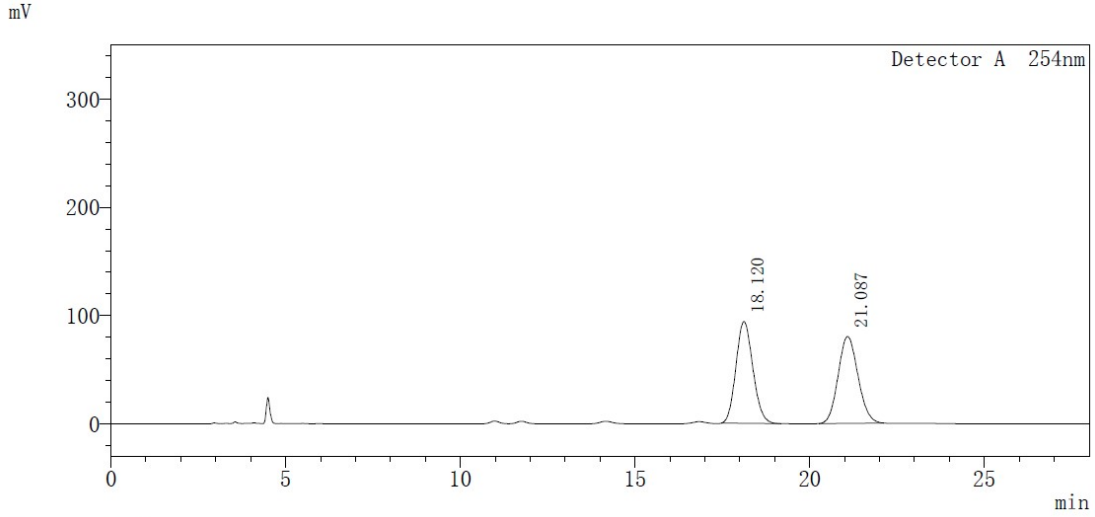
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	17.318	6459870	180458	9.489		M	
2	20.453	61617645	1438868	90.511		M	
Total		68077515	1619326				

3c racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 80:20, 1.0 mL/min, 254 nm).

Retention times: 18.1 min and 21.1 min.



〈Peak Table〉

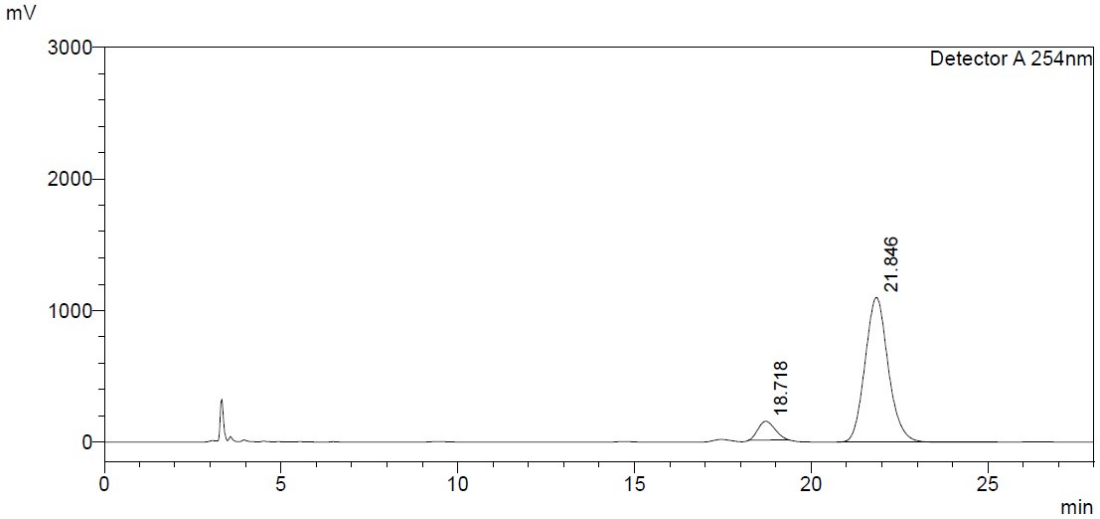
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	18.120	3166447	93982	0.000		M	
2	21.087	3167019	80217	0.000		M	
Total		6333467	174199				

Product **3c** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1c** in a 0.5 mmol scale (83% ee).

Retention times: 18.7 min and 21.8 min.

<Chromatogram>



<Peak Table>

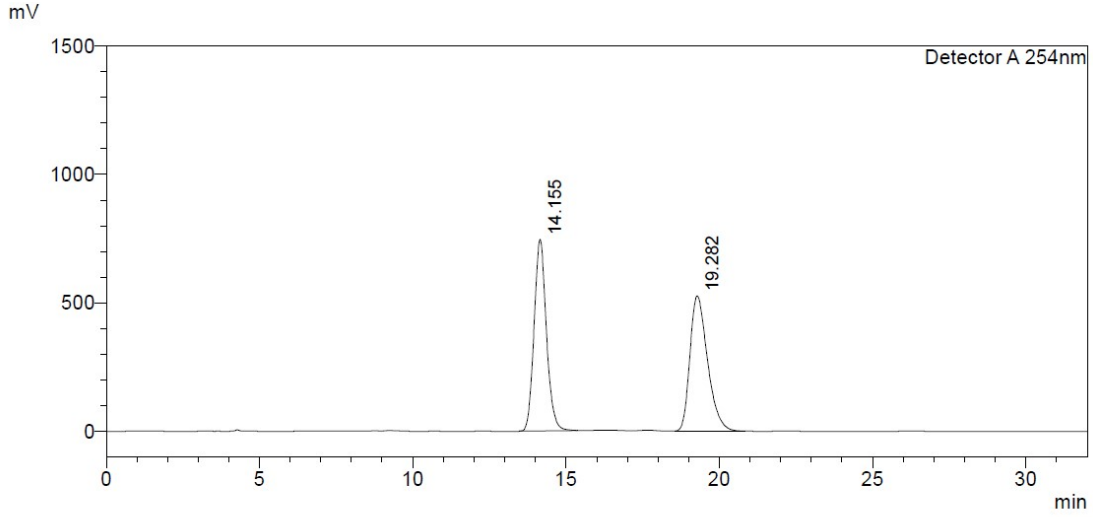
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	18.718	4753918	142281	8.679		M	
2	21.846	50022999	1098712	91.321		M	
Total		54776917	1240993				

3d racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 80:20, 1.0 mL/min, 254 nm).

Retention times: 14.2 min and 19.3 min.



<Peak Table>

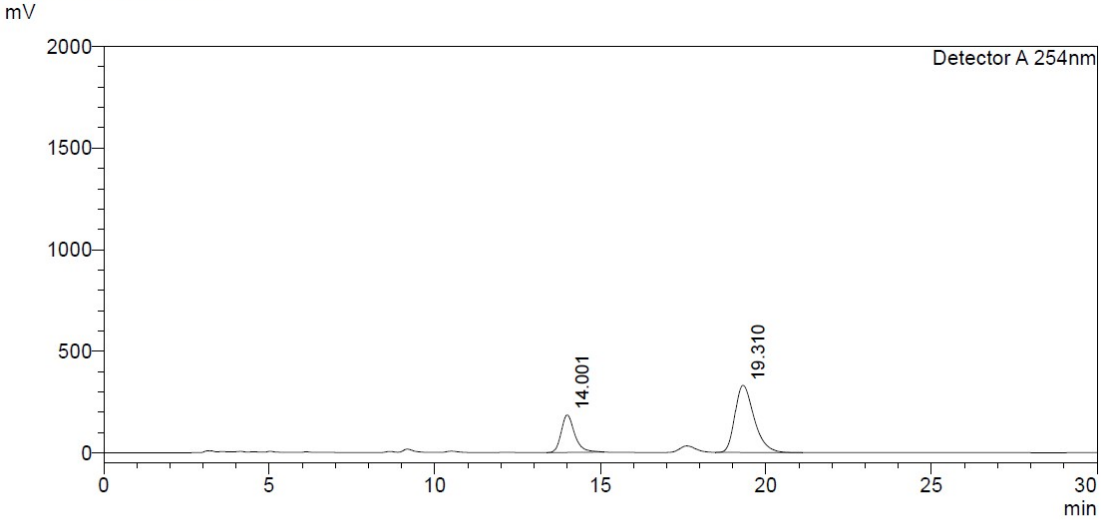
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.155	20855447	745233	49.789		M	
2	19.282	21032277	526221	50.211		M	
Total		41887724	1271454				

Product **3d** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1d** in a 0.1 mmol scale (44% ee).

Retention times: 14.0 min and 19.3 min.

<Chromatogram>



<Peak Table>

Detector A 254nm

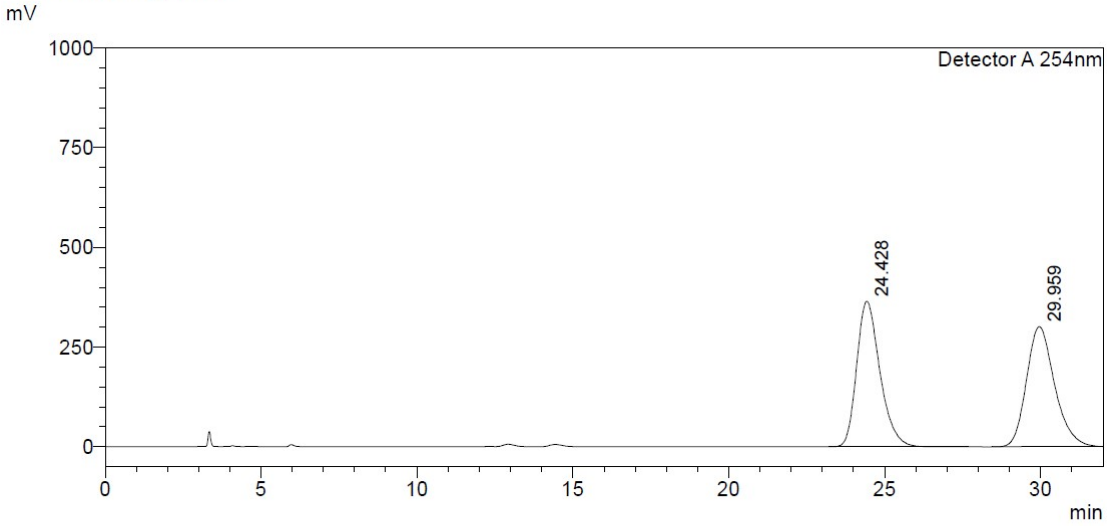
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.001	5246579	184508	28.248		M	
2	19.310	13326511	330981	71.752		M	
Total		18573089	515489				

3e racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 80:20, 1.0 mL/min, 254 nm).

Retention times: 24.4 min and 30.0 min.

<Chromatogram>



<Peak Table>

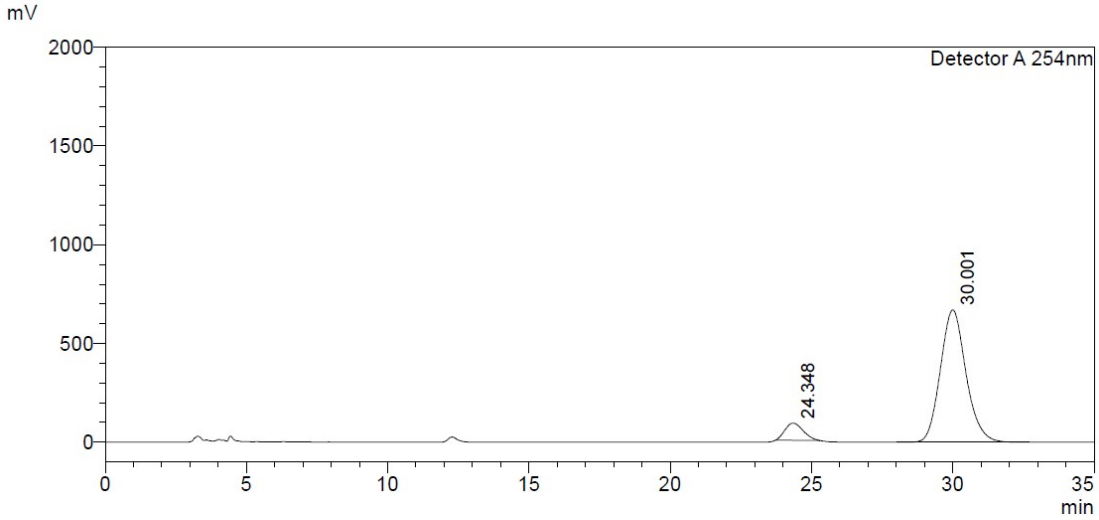
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	24.428	18903008	364743	50.076			
2	29.959	18845723	301003	49.924			
Total		37748731	665746				

Product **3e** from the enantioselective Michael reactions catalyzed by ATP-Cu(II) catalyst using **1e** in a 0.5 mmol scale (83% ee).

Retention times: 24.3 min and 30.0 min.

<Chromatogram>



<Peak Table>

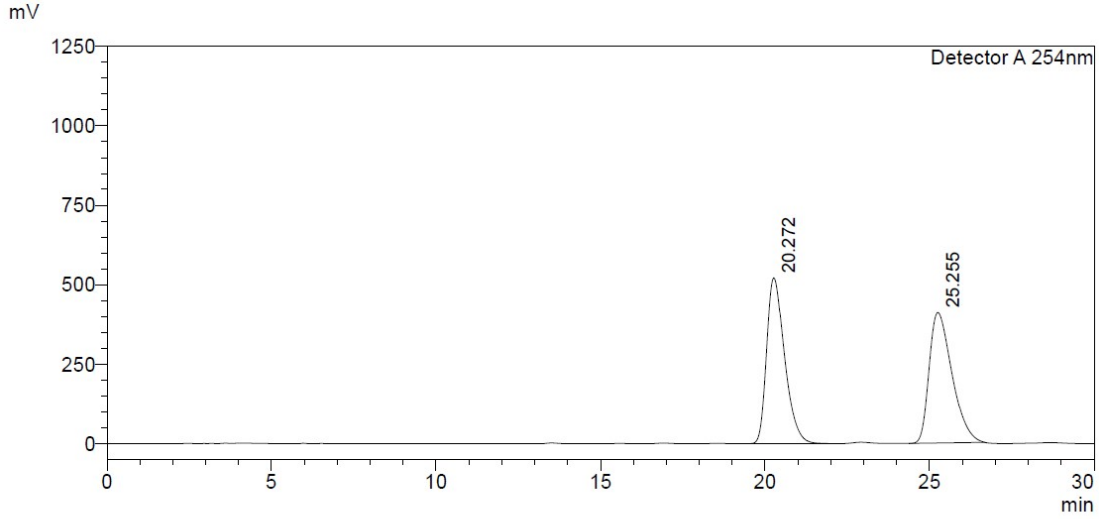
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	24.348	3913978	87168	8.498		M	
2	30.001	42144975	669604	91.502		M	
Total		46058953	756772				

3f racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 95:5, 1.0 mL/min, 254 nm).

Retention times: 20.3 min and 25.3 min.



<Peak Table>

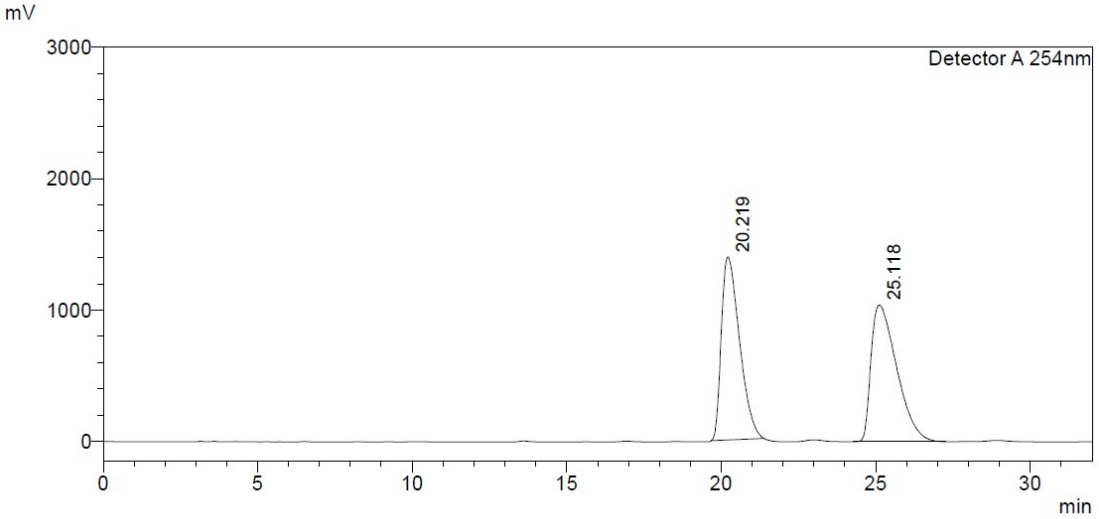
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	20.272	19775133	521163	49.823		M	
2	25.255	19915983	410648	50.177		M	
Total		39691117	931810				

Product **3f** from the enantioselective Michael reactions catalyzed by ATP-Cu(II) catalyst using **1f** in a 0.1 mmol scale (3% ee).

Retention times: 20.2 min and 25.1 min.

<Chromatogram>



<Peak Table>

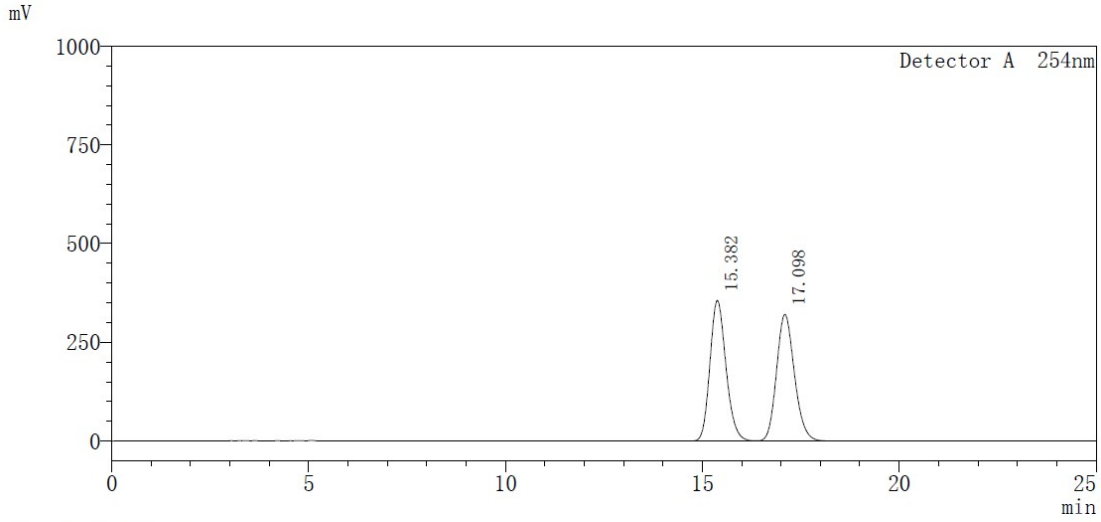
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	20.219	57019400	1391921	48.663		M	
2	25.118	60153242	1039830	51.337		M	
Total		117172642	2431751				

3g racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 80:20, 1.0 mL/min, 254 nm).

Retention times: 15.4 min and 17.1 min.



〈Peak Table〉

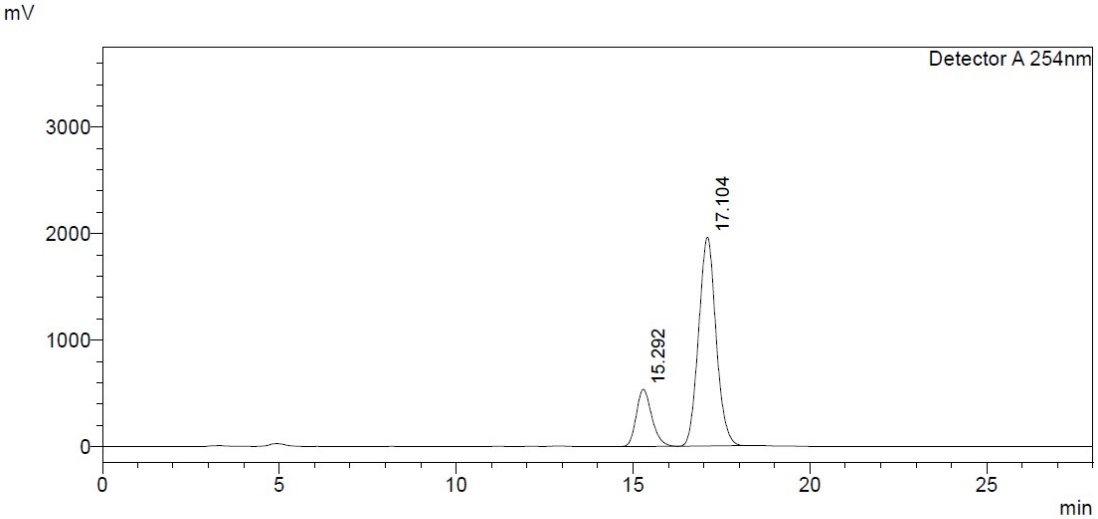
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	15.382	10096928	355861	49.999		M	
2	17.098	10097318	320464	50.001		V M	
Total		20194246	676325				

Product **3g** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1g** in a 0.1 mmol scale (61% ee).

Retention times: 15.3 min and 17.1 min.

<Chromatogram>



<Peak Table>

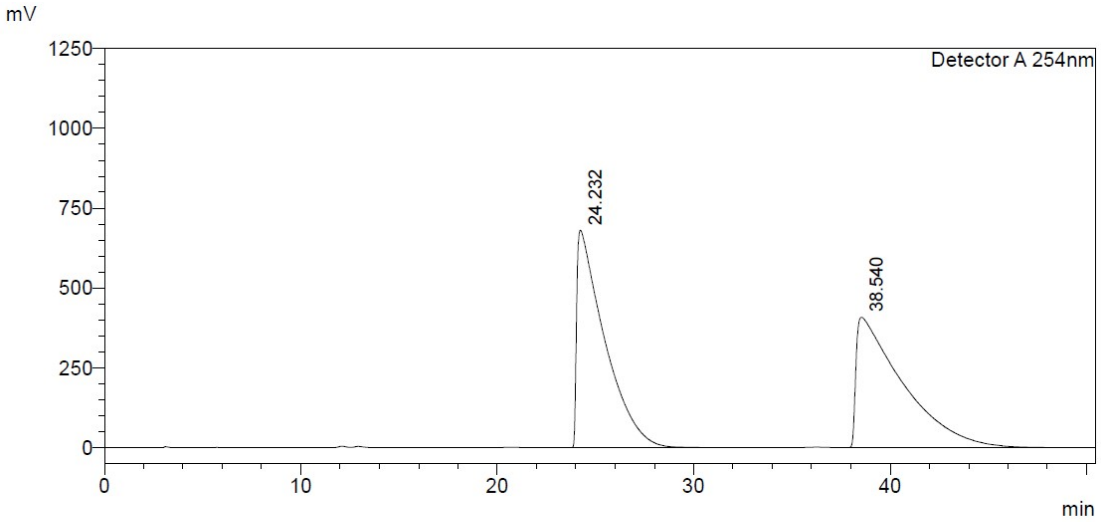
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	15.292	16343143	536656	19.544		M	
2	17.104	67280192	1960423	80.456		M	
Total		83623334	2497079				

3h racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-ODH, hexane/*i*-PrOH 95:5, 1.0 mL/min, 254 nm).

Retention times: 24.2 min and 38.5 min.



<Peak Table>

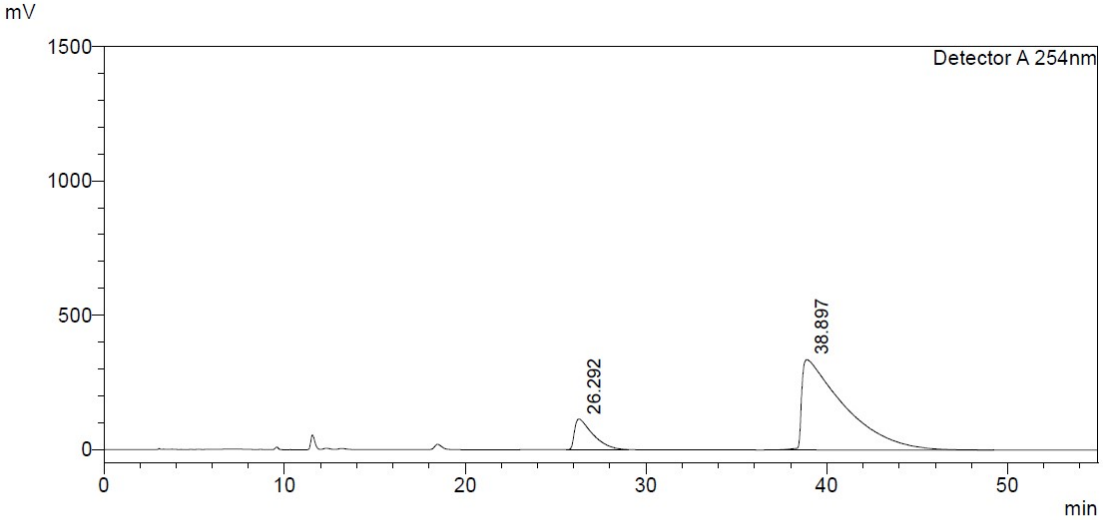
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	24.232	66874472	681126	49.761		M	
2	38.540	67516213	408577	50.239		M	
Total		134390685	1089704				

Product **3h** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1h** in a 0.1 mmol scale (75% ee).

Retention times: 26.2 min and 38.9 min.

<Chromatogram>



<Peak Table>

Detector A 254nm

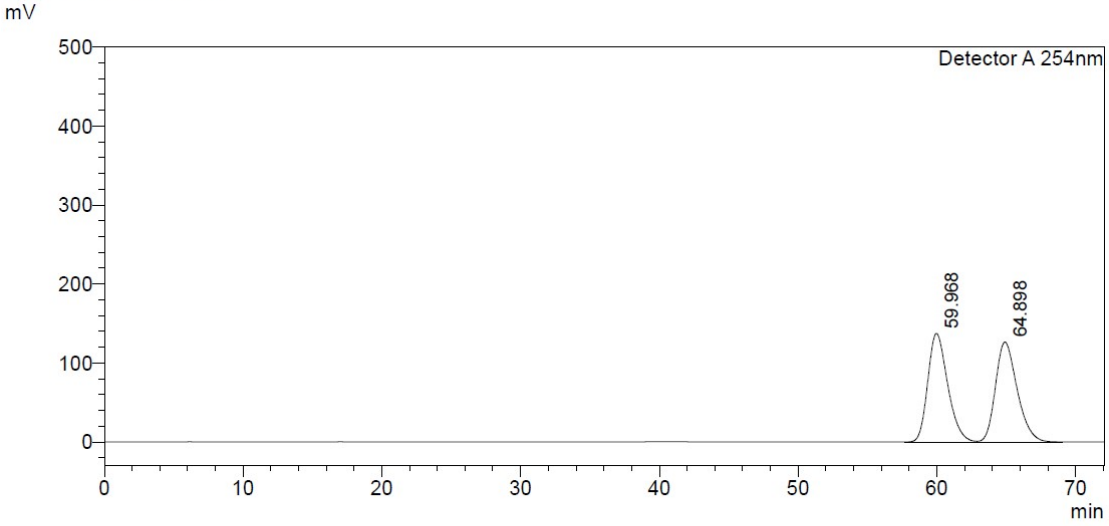
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	26.292	7946610	113957	12.669		M	
2	38.897	54779826	336001	87.331		M	
Total		62726437	449958				

3i racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 90:10, 0.5 mL/min, 254 nm).

Retention times: 60.0 min and 64.9 min.

<Chromatogram>



<Peak Table>

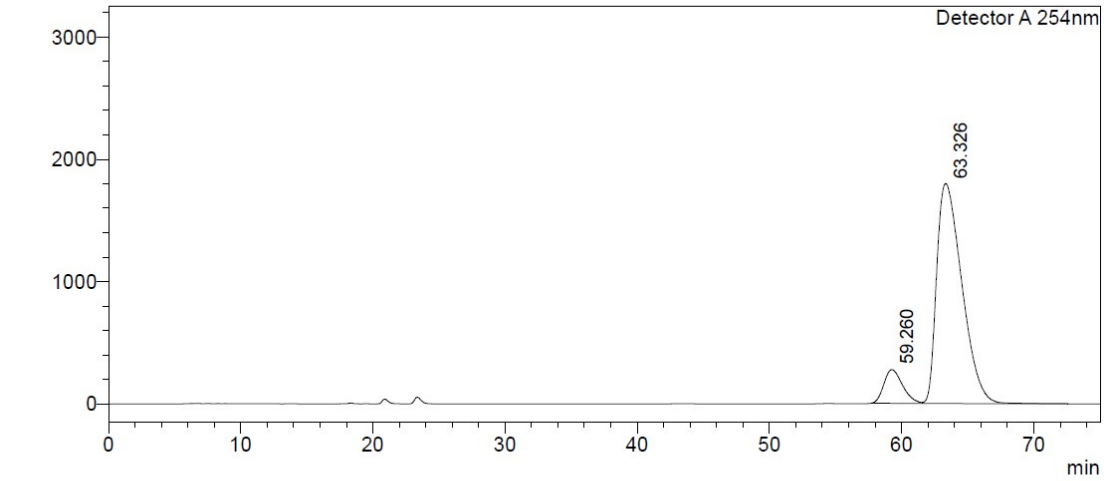
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	59.968	13740774	137407	49.971			
2	64.898	13756745	126508	50.029		V	
Total		27497519	263916				

Product **3i** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1a** in a 0.1 mmol scale (80% ee).

Retention times: 59.3 min and 63.3 min.

<Chromatogram>



<Peak Table>

Detector A 254nm

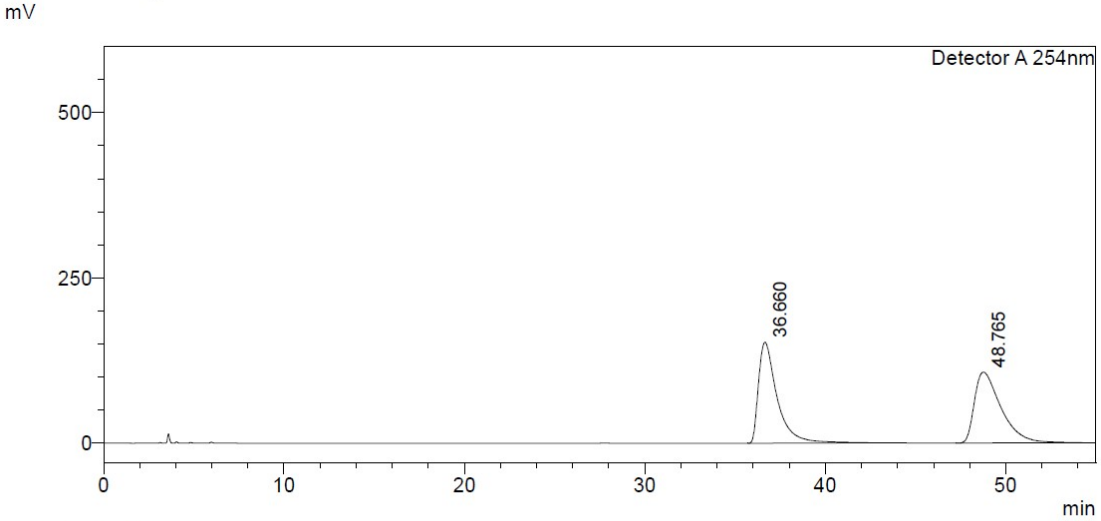
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	59.260	27004652	275689	10.158		M	
2	63.326	238832474	1798483	89.842		V M	
Total		265837126	2074172				

3j racemate

The ee were determined by chiral-phase HPLC (Daicel chiralpak-AD, hexane/*i*-PrOH 95:5, 1.0 mL/min, 254 nm).

Retention times: 36.7 min and 48.8 min.

<Chromatogram>



<Peak Table>

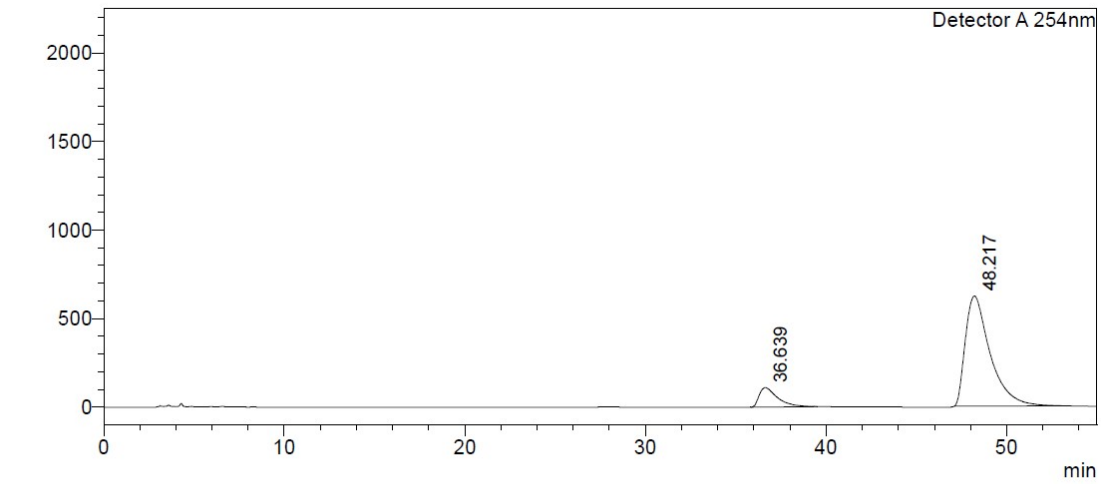
Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	36.660	11013399	152793	49.944		M	
2	48.765	11038284	107356	50.056		M	
Total		22051683	260149				

Product **3j** from the enantioselective Michael reaction catalyzed by ATP-Cu(II) catalyst using **1a** in a 0.1 mmol scale (77% ee).

Retention times: 36.6 min and 48.2 min.

<Chromatogram>



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	36.639	7719177	109352	11.482		M	
2	48.217	59509963	621217	88.518		M	
Total		67229140	730569				