Supporting Information

For

Hydrogen bonding-enabled gold catalysis: ligand effects in gold-catalyzed cycloisomerization of 1,6-Enynes in hexafluoroisopropanol (HFIP)

Yuan Zhao[‡a], Xinyuan Ma[‡a], Junying Wang[a], Vladislav A. Voloshkin[a] and Steven P. Nolan*[a]

[a]Department of Chemistry, Centre for Sustainable Chemistry, Ghent University, Krijgslaan 289, S-3, 9000 Ghent, Belgium. E-mail: Steven.Nolan@ugent.be

Table of Contents

1. General Information

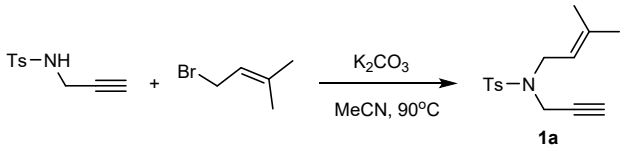
All reactions were carried out in air unless otherwise noted. All organic reagents were purchased and used as received without further purification unless otherwise stated.

All [M(NHC)Cl] and [Au(PR_3Cl] complexes were synthesized according to known procedures.[1–6]

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz spectrometers at 298 K. Chemical shifts (ppm) in ^{1}H and ^{13}C are referenced to the residual solvent peak ($CDCl_3$: $^{\delta}$H = 7.26 ppm, $^{\delta}$C = 77.16 ppm). Coupling constants (*J*) are given in hertz. Abbreviations used in the designation of the signals: s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, m = multiplet, q = quadruplet, br q = broad quadruplet, dq = doublet of quadruplets.

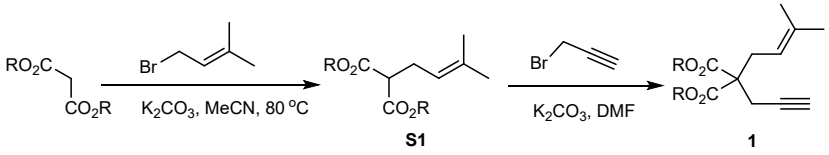
2. General procedures for the preparation of 1, 6-eneyne

General procedures I[7]:



1-bromo-3-methyl-2-butene (1.5 equiv.) was added dropwise to a mixture of *N*-propargyl-4-methylbenzenesulfonamide (1 equiv.) and K_2CO_3 (2.4 equiv.) in acetonitrile (0.4 M) at room temperature under argon atmosphere. The reaction mixture was then stirred at 90 °C overnight. After cooling to room temperature, the salts were filtered off, and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (petroleum ether (PE): EtOAc gradient) to give the corresponding product **1a**.

General procedures II[8]:



Step I:

1-bromo-3-methyl-2-butene (1.2 equiv.) was added dropwise to a mixture of malonate (1.0 equiv.) and K_2CO_3 (2.0 equiv.) in MeCN (0.4 M) at room temperature under argon

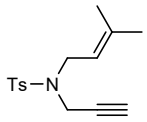
atmosphere. The reaction mixture was then stirred at 80 °C overnight. After cooling to room temperature, the salts were filtered off, and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (petroleum ether (PE): EtOAc gradient) to give the corresponding product **S1**.

Step II:

K_2CO_3 (2.0 equiv.), 3-bromoprop-1-yne (2.0 equiv.) were sequentially added to a stirred solution of **S1** (1.0 equiv.) in DMF. The resulting mixture was stirred at room temperature for 24 h. After completion, K_2CO_3 was removed by filtration. The resulting mixture was then extracted with ethyl ether, washed with a saturated aqueous solution of saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was further purified by chromatography on silica gel (petroleum ether (PE): EtOAc gradient) to afford **1**.

Characterization data of 1, 6-eneyne

4-Methyl-N-(3-methylbut-2-en-1-yl)-N-(prop-2-yn-1-yl) benzenesulfonamide (1a)

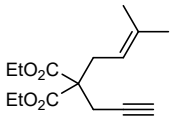


1a is a known compound[7] which was synthesized according to GP I as a yellowish solid (85% yield). $\mathbf{R_f}$ = 0.2 (PE: EA=20:1), Eluent: PE/EtOAc (95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73 (d, J = 8.3 Hz, 2H), 7.31–7.26 (m, 2H), 5.09 (ddq, J = 8.7, 5.8, 1.4 Hz, 1H), 4.06 (d, J = 2.4 Hz, 2H), 3.81 (d, J = 7.3 Hz, 2H), 2.42 (s, 3H), 1.98 (t, J = 2.5 Hz, 1H), 1.69 (dd, J = 21.0, 1.3 Hz, 6H).

Analytical data are in agreement with reported values.[7]

Diethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl) malonate (1b)

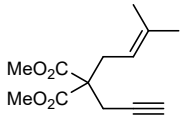


1b is a known compound[9] which was synthesized according to GP II as a colorless oil (74% yield). $\mathbf{R_f}$ = 0.4 (PE: EA = 20:1), Eluent: PE/EtOAc (95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.91 (tp, J = 7.7, 1.4 Hz, 1H), 4.26–4.11 (m, 4H), 2.80–2.73 (m, 4H), 1.99 (t, J = 2.7 Hz, 1H), 1.71–1.63 (m, 6H), 1.24 (t, J = 7.1 Hz, 6H).

Analytical data are in agreement with reported values.[9]

Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl) malonate (1c)

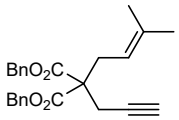


1c is a known compound[7] which was synthesized according to GP II as a colorless oil (86% yield). $\mathbf{R_f}$ = 0.5 (PE: EA = 20:1), Eluent: PE/EtOAc (95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.89 (ddq, J = 9.2, 5.8, 1.4 Hz, 1H), 3.73 (s, 6H), 2.82–2.72 (m, 4H), 2.00 (t, J = 2.7 Hz, 1H), 1.73–1.61 (m, 6H).

Analytical data are in agreement with reported values.[7]

Dibenzyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl) malonate (1d)

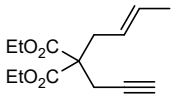


1d is synthesized according to GP II as a colorless oil (59% yield). $\mathbf{R_f}$ = 0.3 (PE: EA=20:1), Eluent: PE/EtOAc (95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32–7.28 (m, 6H), 7.26 (d, J = 3.5 Hz, 4H), 5.12 (d, J = 1.0 Hz, 4H), 4.83 (ddt, J = 7.8, 6.3, 1.4 Hz, 1H), 2.82 (q, J = 2.9 Hz, 4H), 1.96 (t, J = 2.7 Hz, 1H), 1.66–1.57 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.9, 137.1, 135.4, 128.6, 128.4, 128.3, 117.0, 79.3, 71.5, 67.4, 57.4, 26.1, 22.6, 18.1.

Diethyl (E)-2-(but-2-en-1-yl)-2-(prop-2-yn-1-yl) malonate (1e)

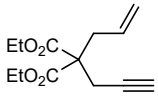


1e is a known compound[12] which was synthesized according to GP II as a colorless oil (70% yield). $\mathbf{R_f}$ = 0.4 (PE: EA=20:1), Eluent: PE/EtOAc (95:5). E: Z = 4.5:1.

^{1}H NMR (400 MHz, $CDCl_3$): for the E isomer, δ(ppm) 5.67 – 5.53 (m, 1H), 5.27–5.15 (m, 1H), 4.25–4.11 (m, 4H), 2.76 (d, J = 2.7 Hz, 2H), 2.72 (d, J = 7.5 Hz, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.67–1.60 (m, 3H), 1.24 (t, J = 7.1 Hz, 6H).

Analytical data agree with reported values.[12]

Diethyl 2-allyl-2-(prop-2-yn-1-yl) malonate (1f)

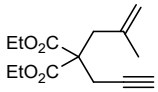


1f is a known compound[10] which was synthesized according to GP II as a colorless oil (56% yield). $\mathbf{R_f}$ = 0.4 (PE: EA=20:1), Eluent: PE/EtOAc (95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.67–5.52 (m, 1H), 5.21–5.05 (m, 2H), 4.18 (q, J = 7.1 Hz, 4H), 2.83–2.71 (m, 4H), 1.99 (t, J = 2.7 Hz, 1H), 1.22 (dd, J = 7.6, 6.9 Hz, 6H).

Analytical data are in agreement with reported values.[10]

Diethyl 2-(2-methylallyl)-2-(prop-2-yn-1-yl) malonate (1g)



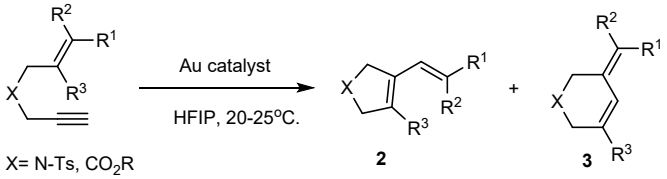
1g is a known compound[11] which was synthesized according to GP II as a colorless oil (68% yield). $\mathbf{R_f}$ = 0.4 (PE: EA=20:1), Eluent: PE/EtOAc (95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.85 (s, 1H), 4.78 (s, 1H), 4.17–4.10 (m, 4H), 2.79–2.74 (m, 4H), 1.95 (s, 1H), 1.60 (dd, J = 1.5, 0.8 Hz, 3H), 1.19 (t, J = 7.1 Hz, 6H).

Analytical data agree with reported values.[11]

3. General procedures for gold-catalyzed cycloisomerization of 1, 6-Enynes

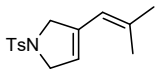
General procedures III



In a 4 mL vial equipped with a stirring bar and a septum-sealed cap, [Au] (1mol%), the substrate (0.5 mmol), and HFIP (0.5 mL) were added under air. The resulting clear solution was stirred at room temperature for the required time. When cationic gold catalysts were used, a drop of triethylamine was added to quench the reaction. The crude mixture was purified by silica gel column chromatography to afford the corresponding product (average of two runs). Product ratios reported were determined by ^{1}H NMR analysis of the crude reaction mixture prior to purification.

Characterization data of product 2 and 3

3-(2-methylprop-1-en-1-yl)-1-tosyl-2,5-dihydro-1H-pyrrole (2a)

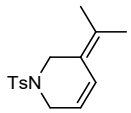


2a is synthesized according to GP III from **1a** (138.69 mg) and [Au(IPr)Cl] (3.1 mg) as a colorless oil (124 mg, 90% yield). Eluent: PE/EtOAc (9:1). **Selectivity ratio (2a:3a)**: 15:1

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 (d, J = 8.3 Hz, 2H), 7.34–7.29 (m, 2H), 5.65–5.57 (m, 1H), 5.38 (t, J = 2.3 Hz, 1H), 4.28–4.07 (m, 4H), 2.42 (s, 3H), 1.75 (d, J = 12.7 Hz, 6H).

Analytical data are in agreement with reported values.[7]

3-(propan-2-ylidene)-1-tosyl-1,2,3,6-tetrahydropyridine (3a)

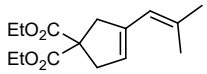


3a is synthesized according to GP III from **1a** (138.69 mg) and [Au(PPh$_3$)Cl] (2.6 mg) as a colorless oil (127.8 mg, 92% yield). Eluent: PE/EtOAc (9:1). **Selectivity ratio (2a:3a)**: 1:15

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.33 (dt, J = 10.3, 2.1 Hz, 1H), 5.52 (dt, J = 10.3, 3.5 Hz, 1H), 3.89 (s, 2H), 3.76 (s, 2H), 2.40 (s, 3H), 1.76 (s, 3H), 1.67 (s, 3H).

Analytical data are in agreement with reported values.[7]

Diethyl 3-(2-methylprop-1-en-1-yl)cyclopent-3-ene-1,1-dicarboxylate (2b)

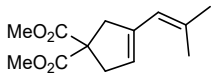


2b is synthesized according to GP III from **1b** (133.17 mg) and [Au(IPr)Cl] (3.1 mg) as a colorless oil (127.8 mg, 96% yield). Eluent: PE/EtOAc (20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.73 (s, 1H), 5.38 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.18 (d, *J* = 2.1 Hz, 2H), 3.03 (s, 2H), 1.82 (s, 3H), 1.78 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H).

Analytical data are in agreement with reported values.[12]

Dimethyl 3-(2-methylprop-1-en-1-yl)cyclopent-3-ene-1,1-dicarboxylate (2c)

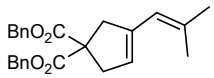


2c is synthesized according to GP III from **1c** (119.14 mg) and [Au(IPr)Cl] (3.1 mg) as a colorless oil (110 mg, 93% yield). Eluent: PE/EtOAc (20:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.74 (s, 1H), 5.38 (s, 1H), 3.73 (s, 6H), 3.20 (s, 2H), 3.04 (s, 2H), 1.82 (s, 6H).

Analytical data are in agreement with reported values.[7]

Dibenzyl 3-(2-methylprop-1-en-1-yl)cyclopent-3-ene-1,1-dicarboxylate (2d)

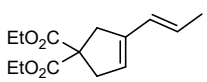


2d is synthesized according to GP III from **1d** (195.20 mg) and [Au(IPr)Cl] (3.1 mg) as a colorless oil (173 mg, 89% yield). Eluent: PE/EtOAc (20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32–7.28 (m, 6H), 7.26–7.22 (m, 4H), 5.72 (s, 1H), 5.39 (s, 1H), 5.12 (s, 4H), 3.22 (s, 2H), 3.07 (s, 2H), 1.79 (d, *J* = 8.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.8, 138.7, 135.7, 135.6, 128.5, 128.2, 128.0, 124.4, 120.6, 67.2, 59.5, 43.2, 40.3, 27.3, 19.8.

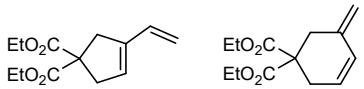
Dibenzyl 3-(2-methylprop-1-en-1-yl)cyclopent-3-ene-1,1-dicarboxylate (2e)



2e is synthesized according to GP III from **1e** (126.20 mg) and [Au(IPr)Cl] (3.1 mg) as a colorless oil (120 mg, 95% yield). Eluent: PE/EtOAc (20:1). E: Z = 5:1.

1H NMR (400 MHz, $CDCl_3$): for the E isomer, δ(ppm) 6.18 (d, J = 15.6 Hz, 1H), 5.66 – 5.53 (m, 1H), 5.41 (br s, 1H), 4.18 (q, *J* = 7.1 Hz, 4H), 3.09 – 3.02 (m, 4H), 1.78 (d, J = 6.7 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 6H).

Diethyl 3-vinylcyclopent-3-ene-1,1-dicarboxylate (2f and 3f)



2f **3f**

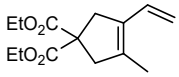
2f and **3f** are synthesized according to GP III from **1f** (119.14 mg) and [Au(IPr)Cl] (3.1 mg) as an inseparable colorless oil (85 mg, 71% yield). Eluent: PE/EtOAc (20:1). **Selectivity ratio (2f:3f)**: 1:1.7.

2f: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 6.50 (m, 1H), 5.62 – 5.54 (br s, 1H), 5.13–5.05 (m, 2H), 4.24–4.11 (m, 4H), 3.14–3.08 (m, 4H), (m, 4H), 1.24 (t, J = 7.1 Hz, 6H).

3f: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 6.14 (d, J = 9.8 Hz, 1H), 5.81–5.73 (m, 1H), 4.94 – 4.85 (m, 2H), 4.24–4.11 (m, 4H), 2.83 (s, 2H), 2.71–2.65 (m, 2H), 1.21 (t, J = 7.1 Hz, 6H).

Analytical data are in agreement with reported values.[12]

Diethyl 3-methyl-4-vinylcyclopent-3-ene-1,1-dicarboxylate (2g)

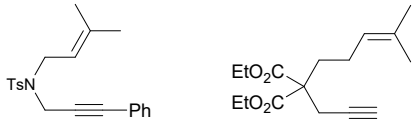


2g is synthesized according to GP III from **1g** (126.15 mg) and [Au(JohnPhos)Cl] (2.8 mg) as a colorless oil (97 mg, 77% yield). Eluent: PE/EtOAc (20:1). **Selectivity ratio (2g:3g)**: 28:1.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 6.62–6.48 (m, 1H), 5.07 (s, 1H), 5.03 (d, *J* = 6.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.13 (s, 2H), 3.05 (s, 2H), 1.75 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 7H).

Analytical data are in agreement with reported values.[12]

Substrates which failed to react



n.r. trace

4.Reference

1 P. De Frémont, N. M. Scott, E. D. Stevens and S. P. Nolan, *Organometallics*, 2005, **24**, 2411–2418.

2 N. V. Tzouras, A. Gobbo, N. B. Pozsoni, S. G. Chalkidis, S. Bhandary, K. V. Hecke, G. C. Vougioukalakis and S. P. Nolan, *Chem. Commun.*, 2022, **58**, 8516–8519.

3 F. Nahra, N. V. Tzouras, A. Collado and S. P. Nolan, *Nat Protoc*, 2021, **16**, 1476–1493.

4 A. Collado, A. Gómez-Suárez, A. R. Martin, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.*, 2013, **49**, 5541.

5 P. De Frémont, N. M. Scott, E. D. Stevens, T. Ramnial, O. C. Lightbody, C. L. B. Macdonald, J. A. C. Clyburne, C. D. Abernethy and S. P. Nolan, *Organometallics*, 2005, **24**, 6301–6309.

6 O. Santoro, A. Collado, A. M. Z. Slawin, S. P. Nolan and C. S. J. Cazin, *Chem. Commun.*, 2013, **49**, 10483.

7 A. Cervantes-Reyes, F. Rominger, M. Rudolph and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2020, **362**, 2523–2533.

8 Y.-N. Zheng, X.-E. Cai, H.-L. Wu, Y. Zhou, W.-C. Tian, Y. Ruan, H. Liu and W.-T. Wei, *Chem. Asian J.*, 2023, **18**, e202201149.

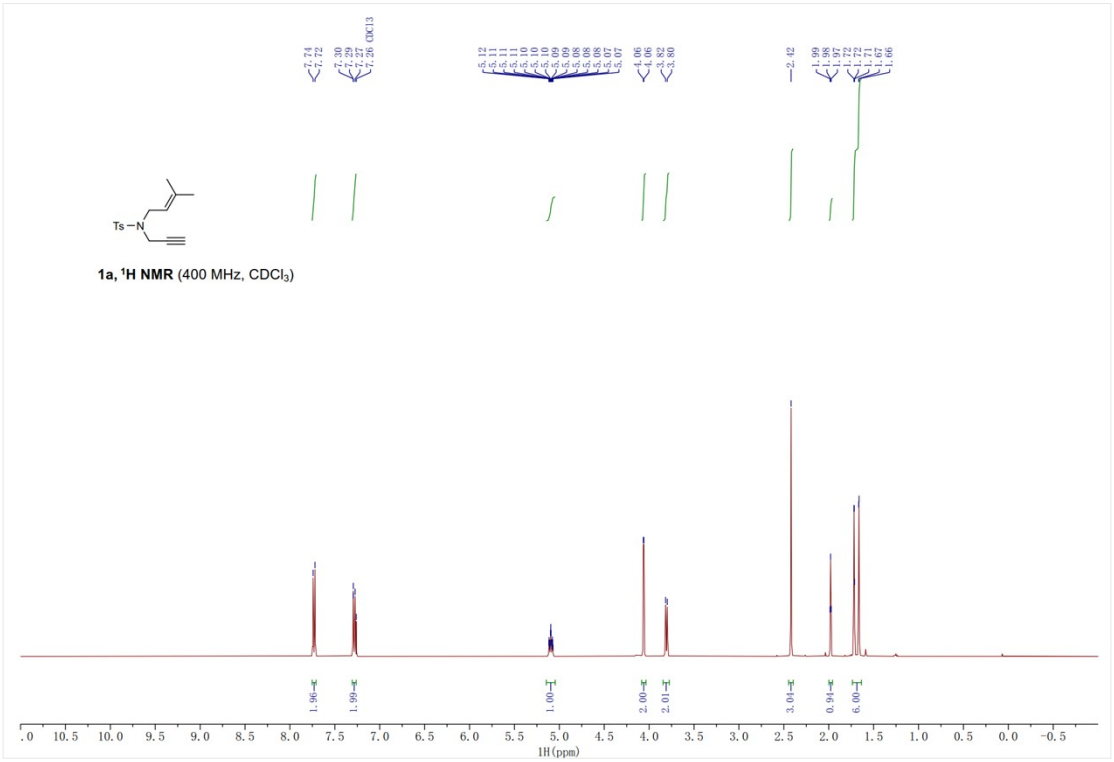
9 A. López-Rodríguez, G. Domínguez and J. Pérez-Castells, *J. Org. Chem.*, 2019, **84**, 924–933.

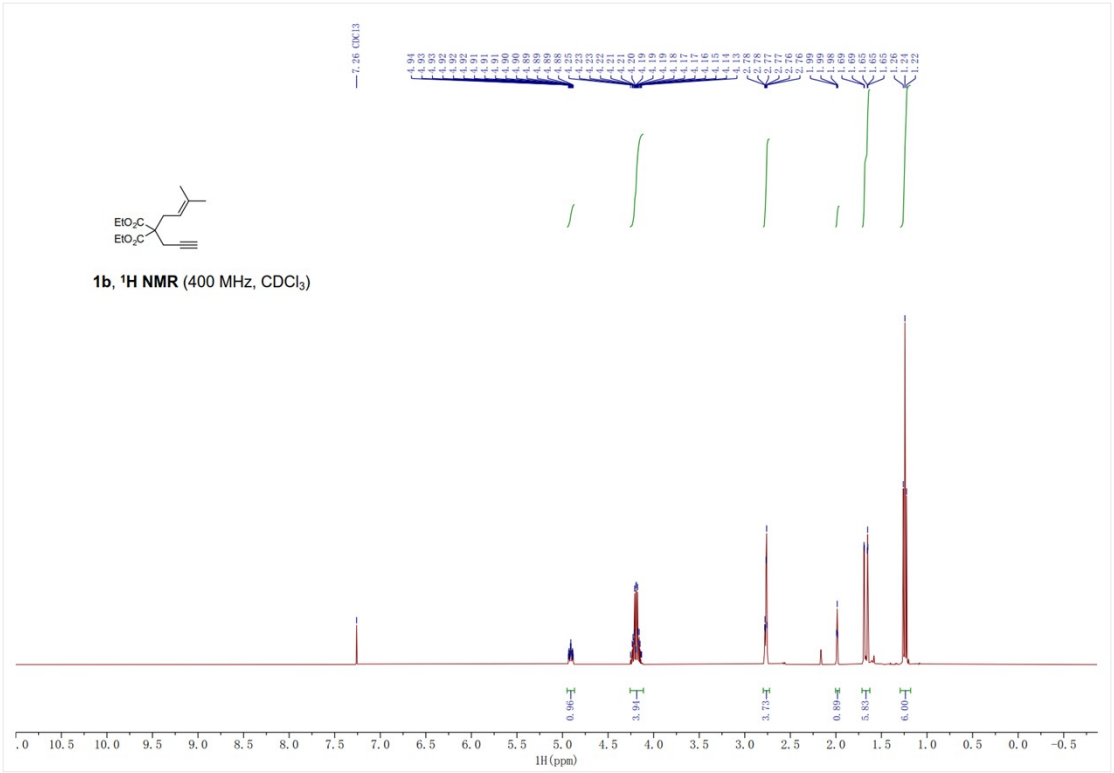
10 B. M. Trost, A. Breder, B. M. O'Keefe, M. Rao and A. W. Franz, *J. Am. Chem. Soc.*, 2011, **133**, 4766–4769.

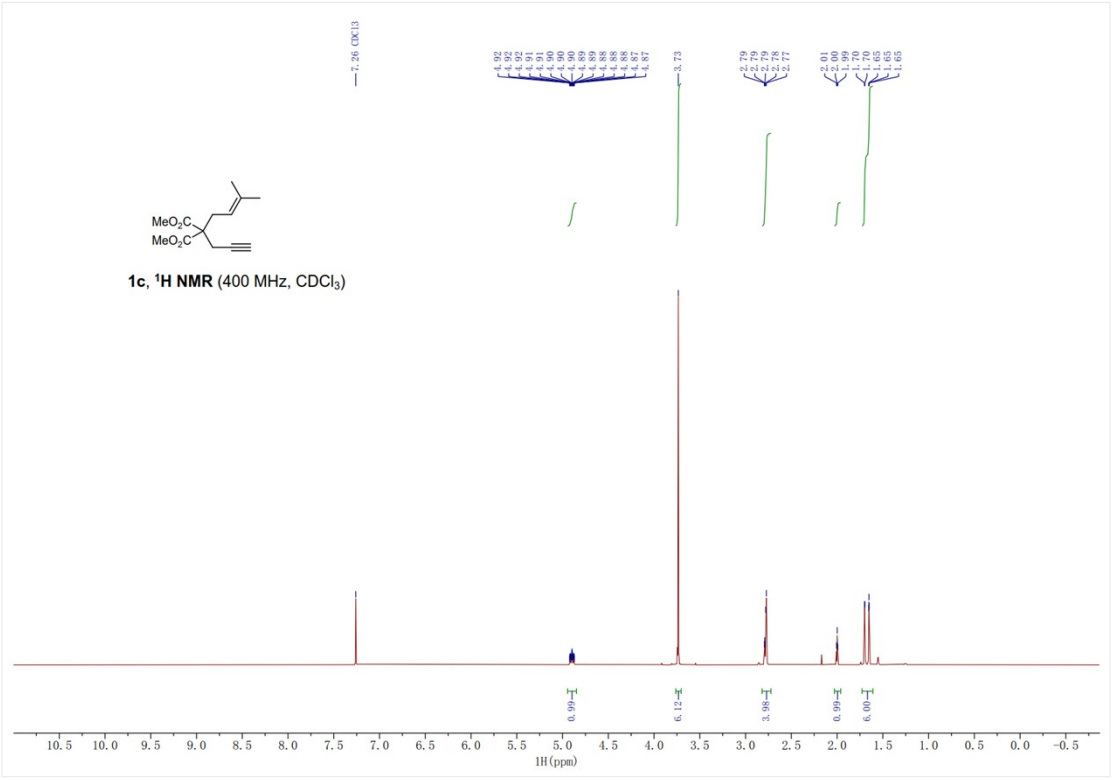
11 M. Gao, Q. Gao, X. Hao, Y. Wu, Q. Zhang, G. Liu and R. Liu, *Org. Lett.*, 2020, **22**, 1139–1143.

12 K. Muratov and F. Gagosz, *Angew. Chem. Int. Ed.*, 2022, **61**, e202203452.

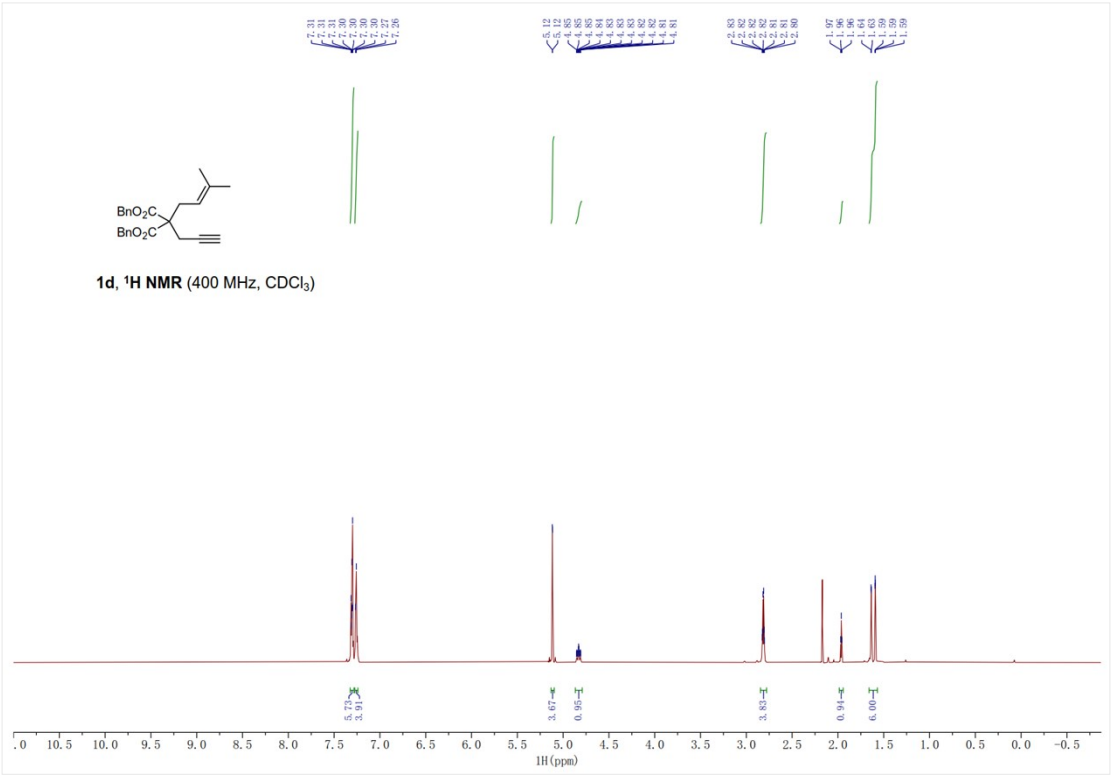
5.NMR Spectra



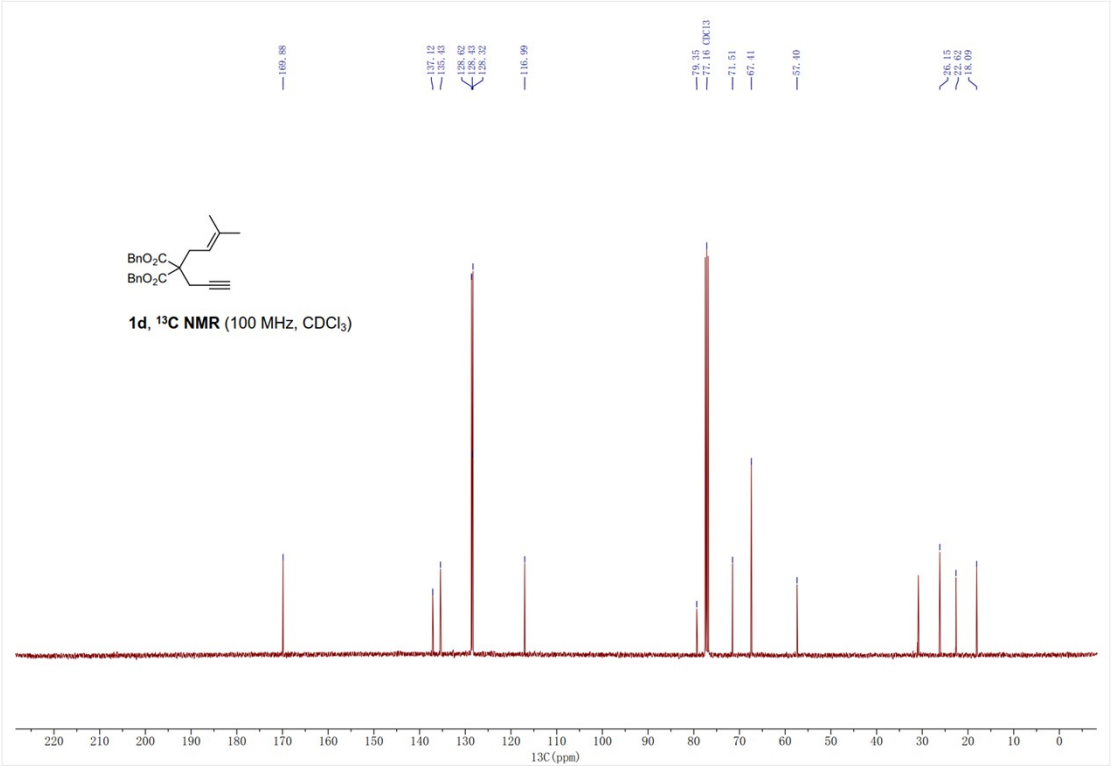




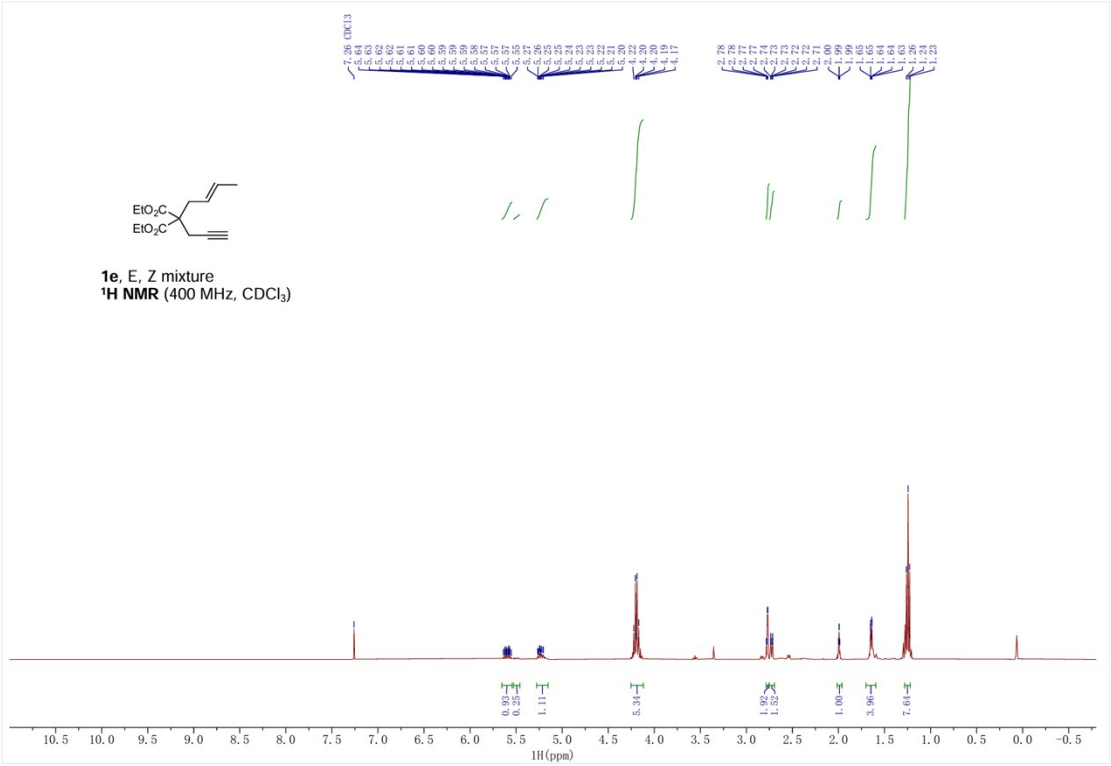
1c, **^{1}H NMR** (400 MHz, $CDCl_3$)



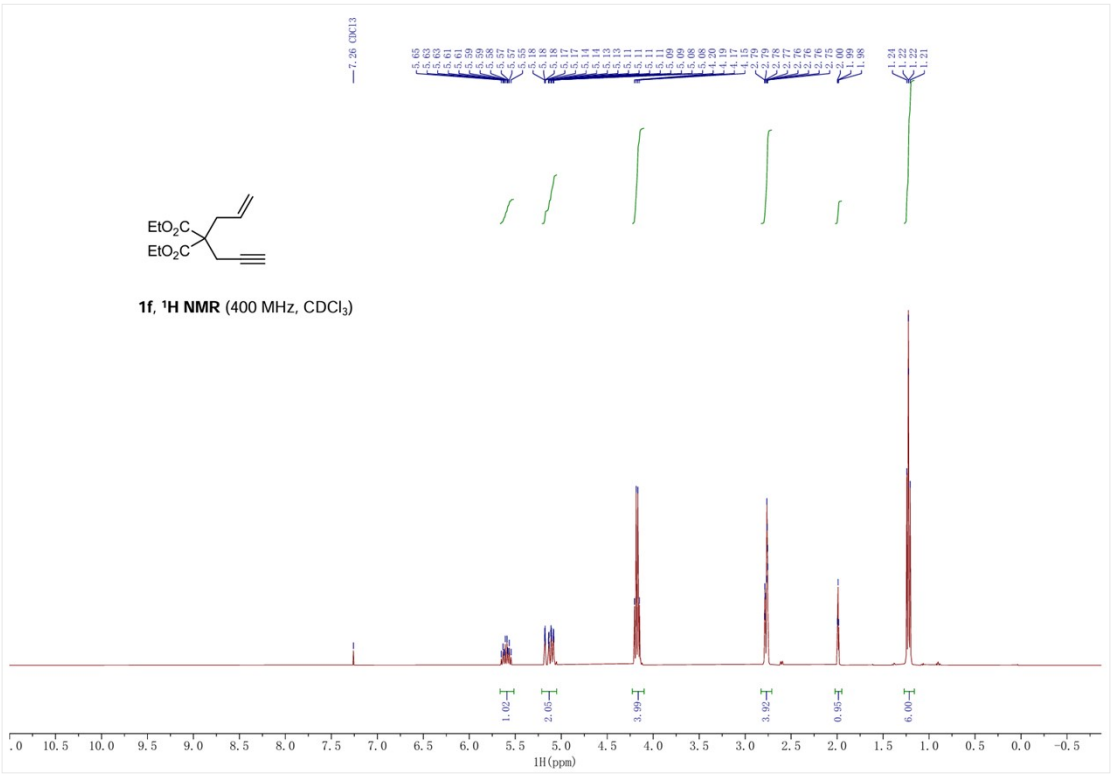
1d, **^{1}H NMR** (400 MHz, $CDCl_3$)

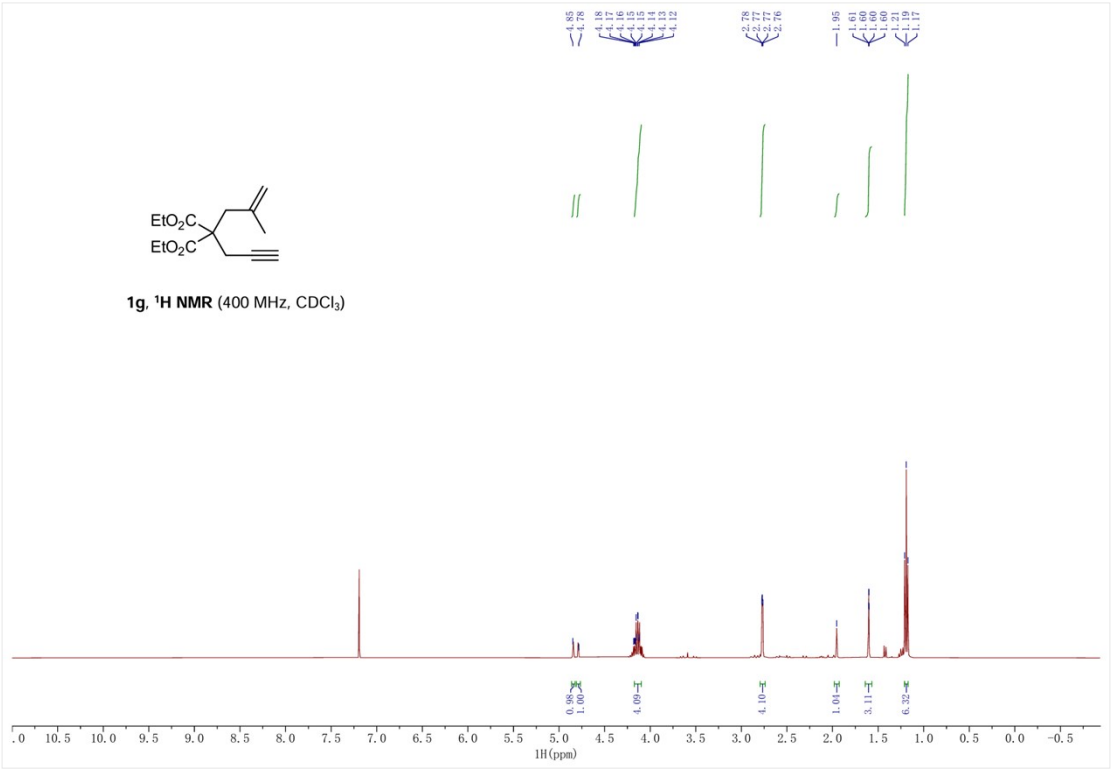


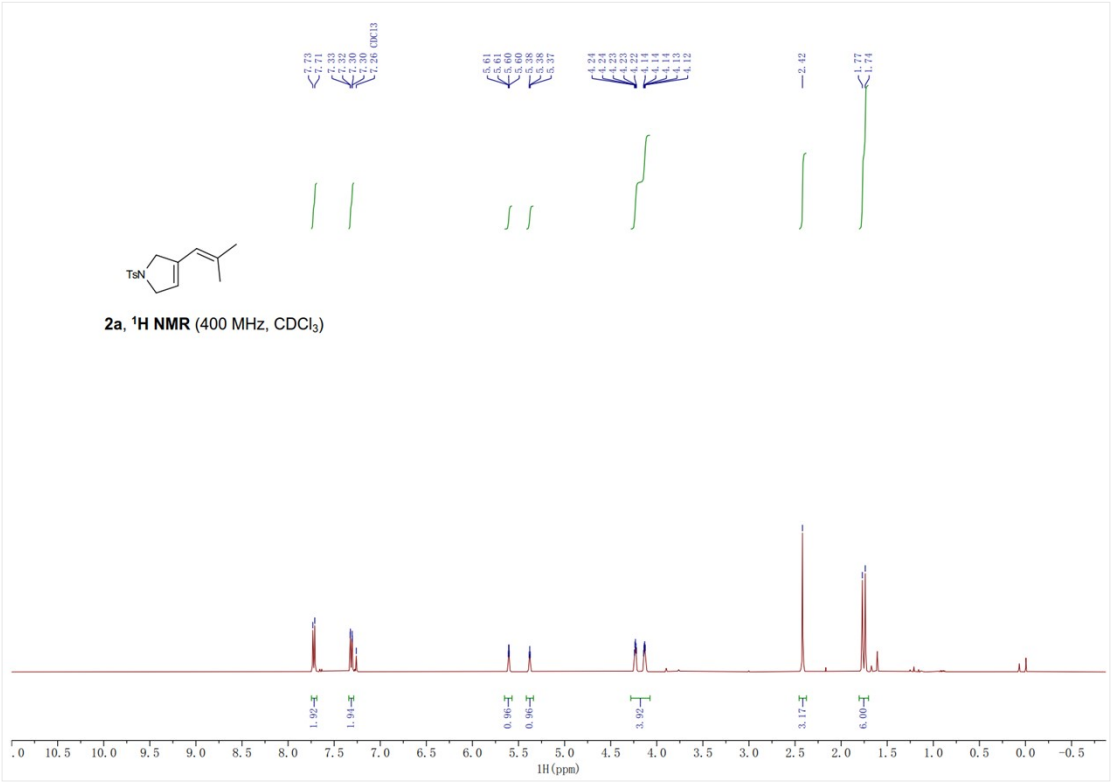
1d, **^{13}C NMR** (100 MHz, $CDCl_3$)



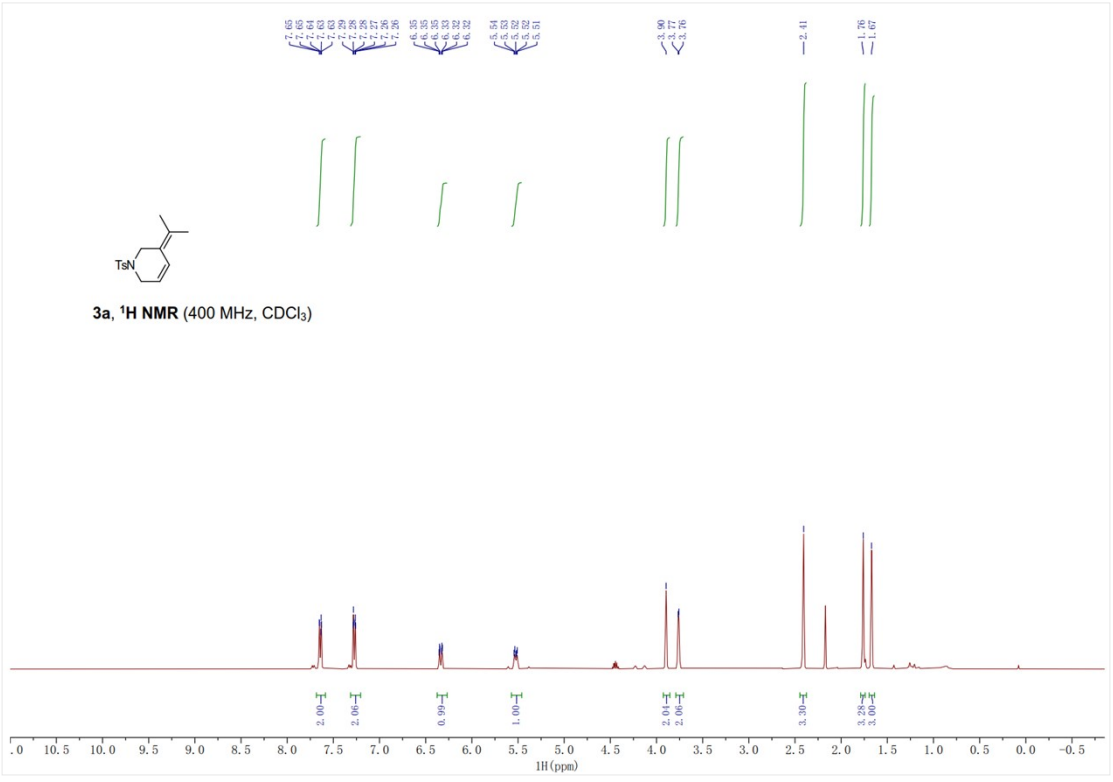
1e, E, Z mixture
^{1}H NMR (400 MHz, $CDCl_3$)


EtO2C
EtO2C
1f, 1H NMR (400 MHz, CDCl3)
1H (ppm)

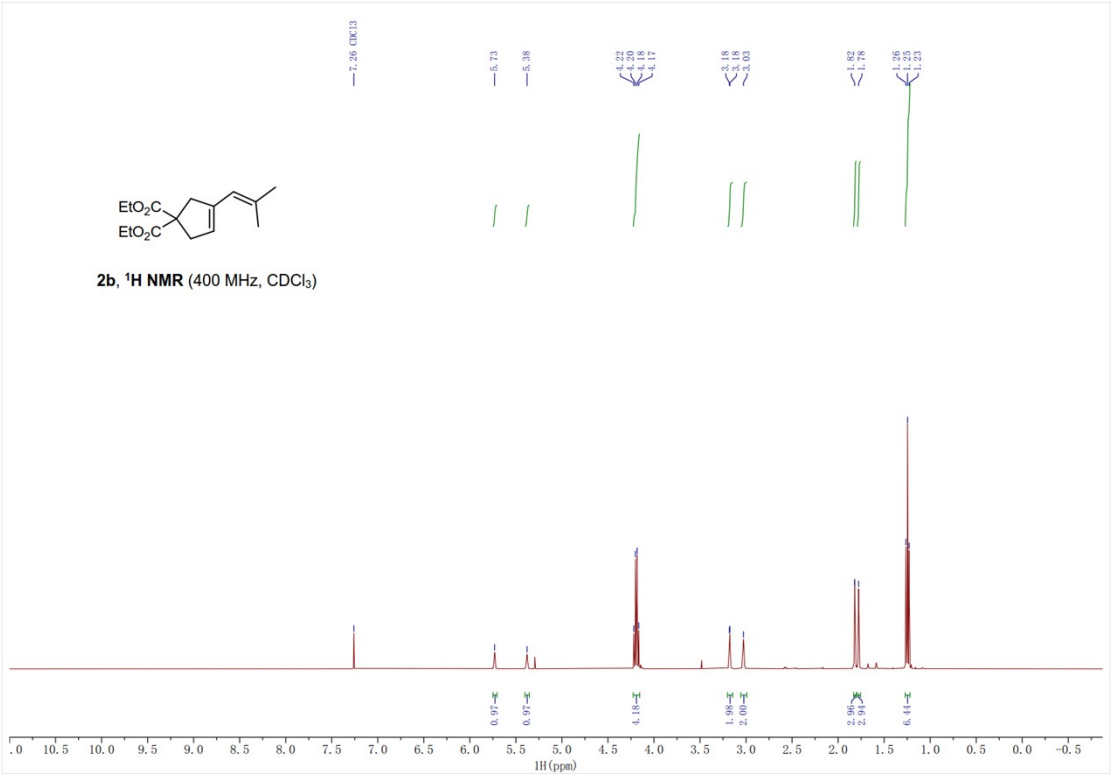

EtO2C
EtO2C
1g, 1H NMR (400 MHz, CDCl3)
1H (ppm)



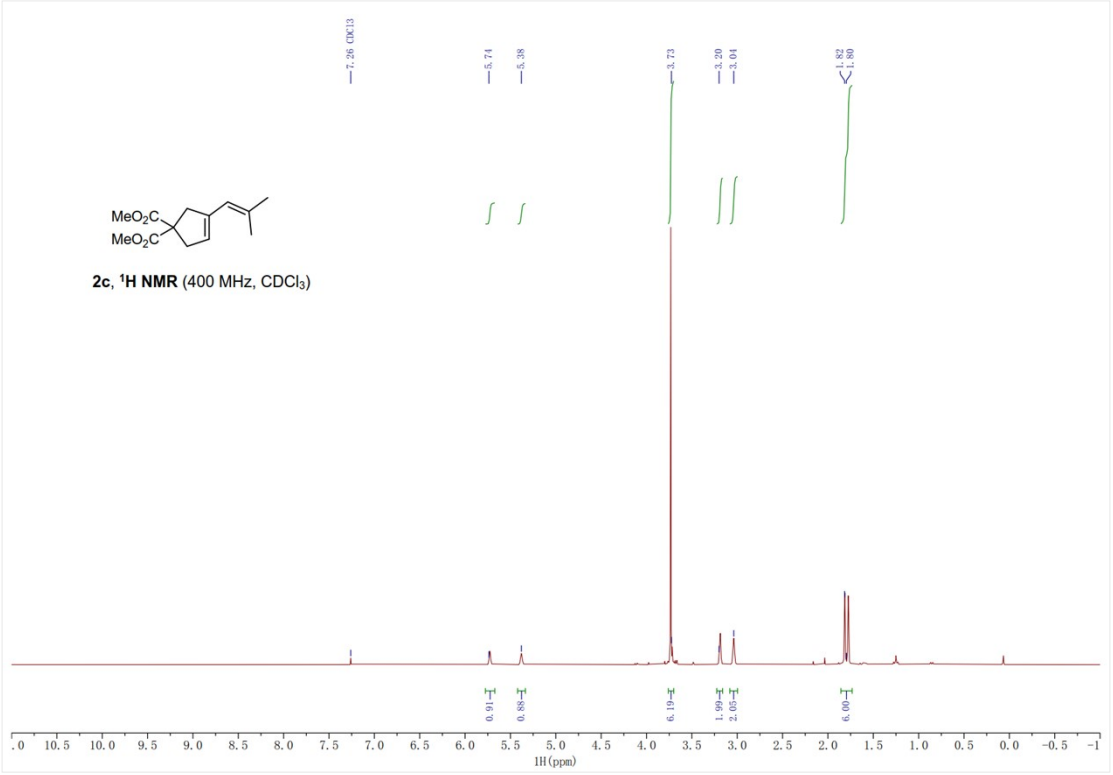
2a, **^{1}H NMR** (400 MHz, $CDCl_3$)



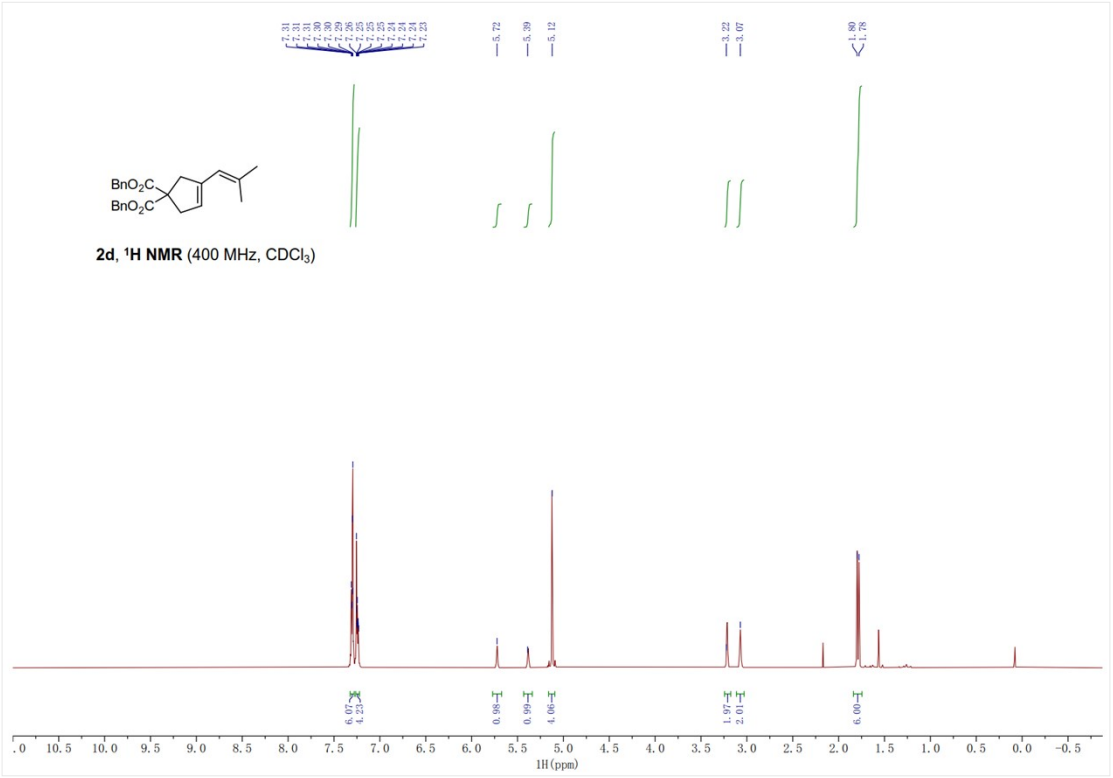
3a, **^{1}H NMR** (400 MHz, $CDCl_3$)



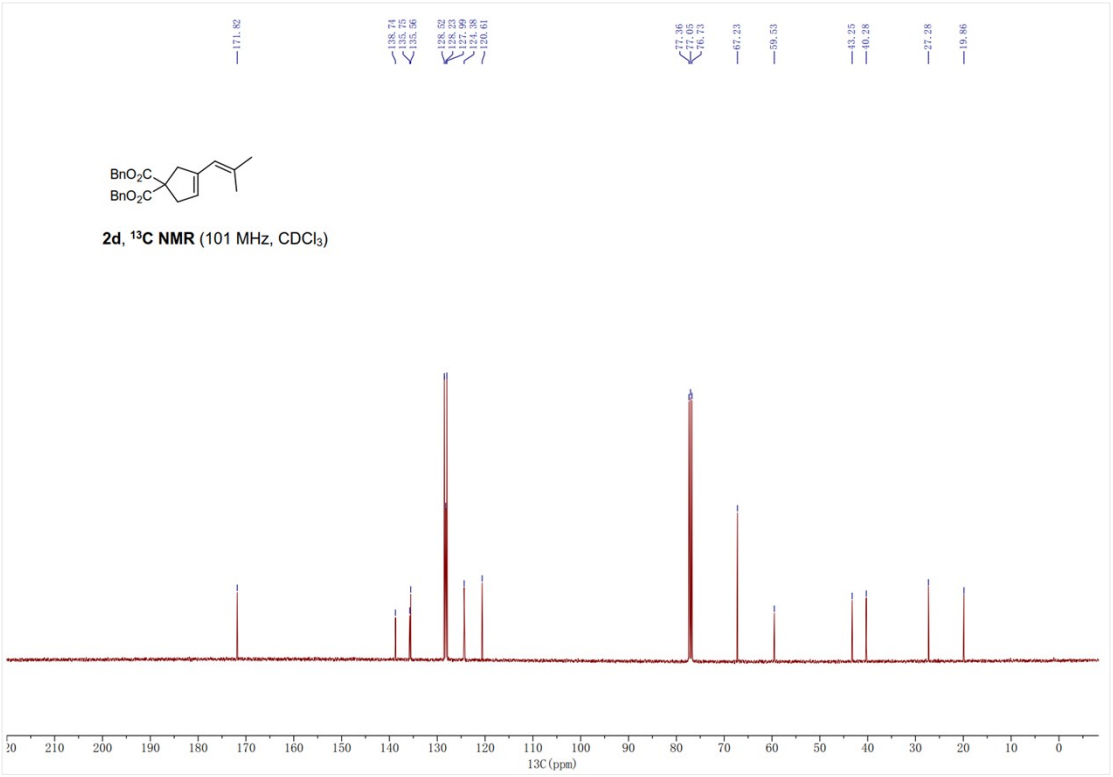
2b, **^{1}H NMR** (400 MHz, $CDCl_3$)



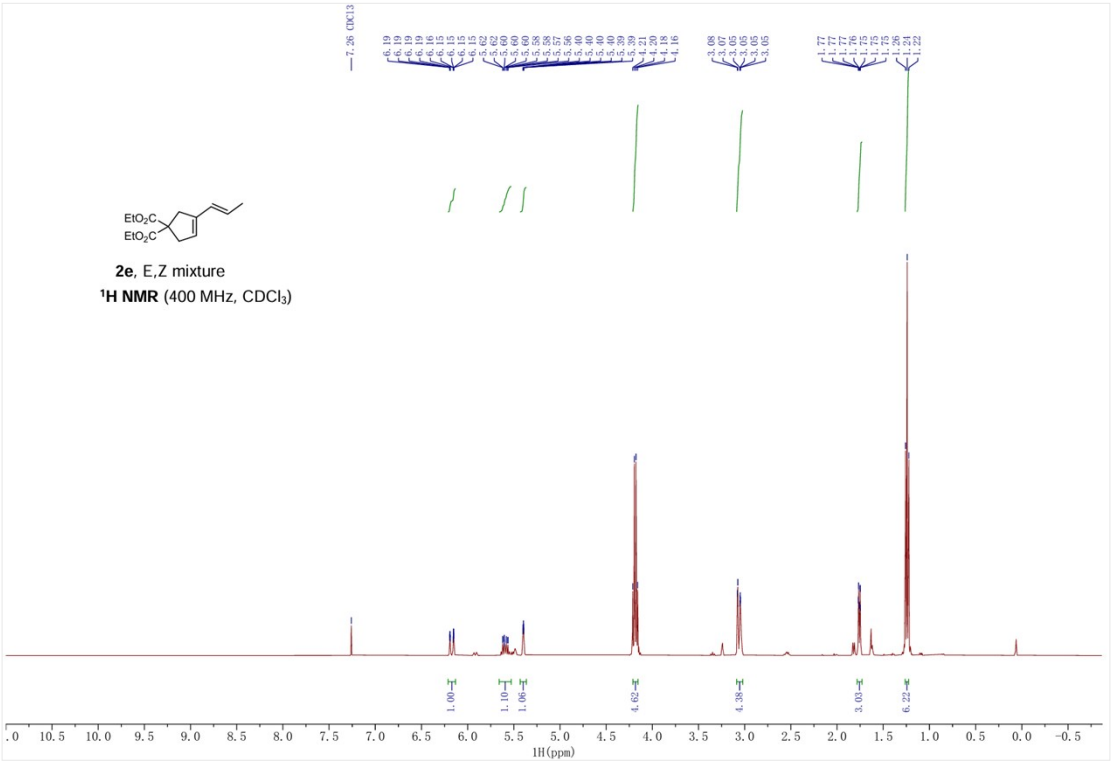
2c, **^{1}H NMR** (400 MHz, $CDCl_3$)

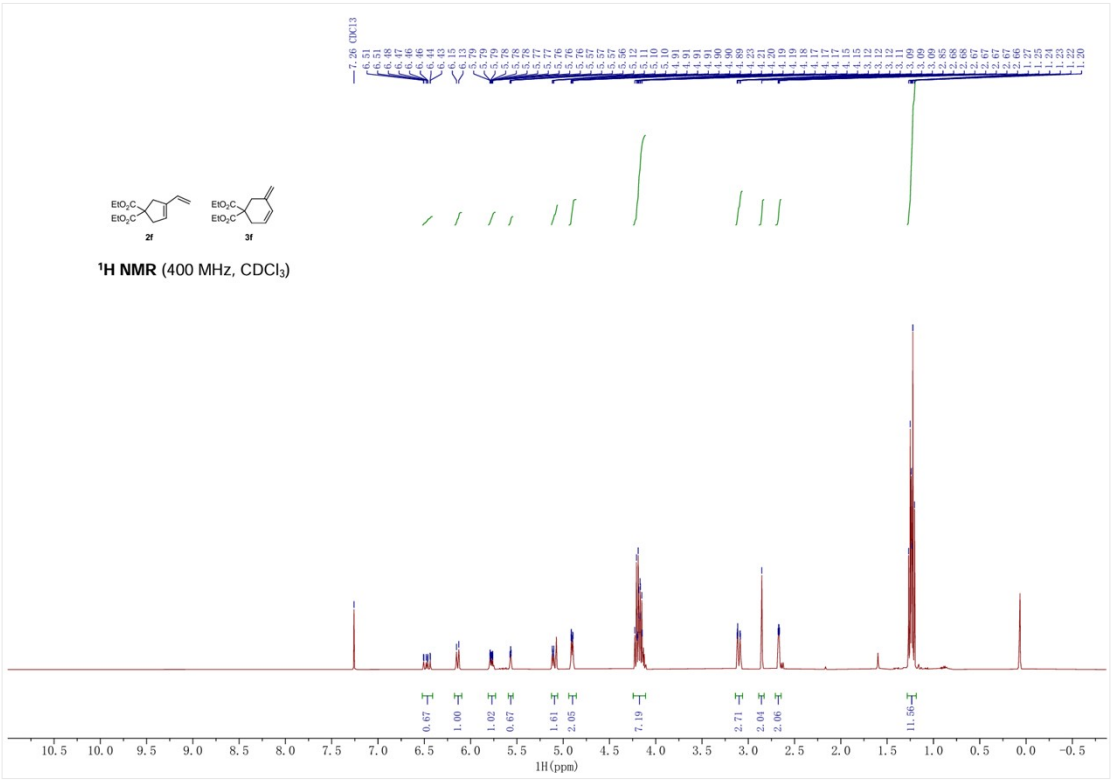


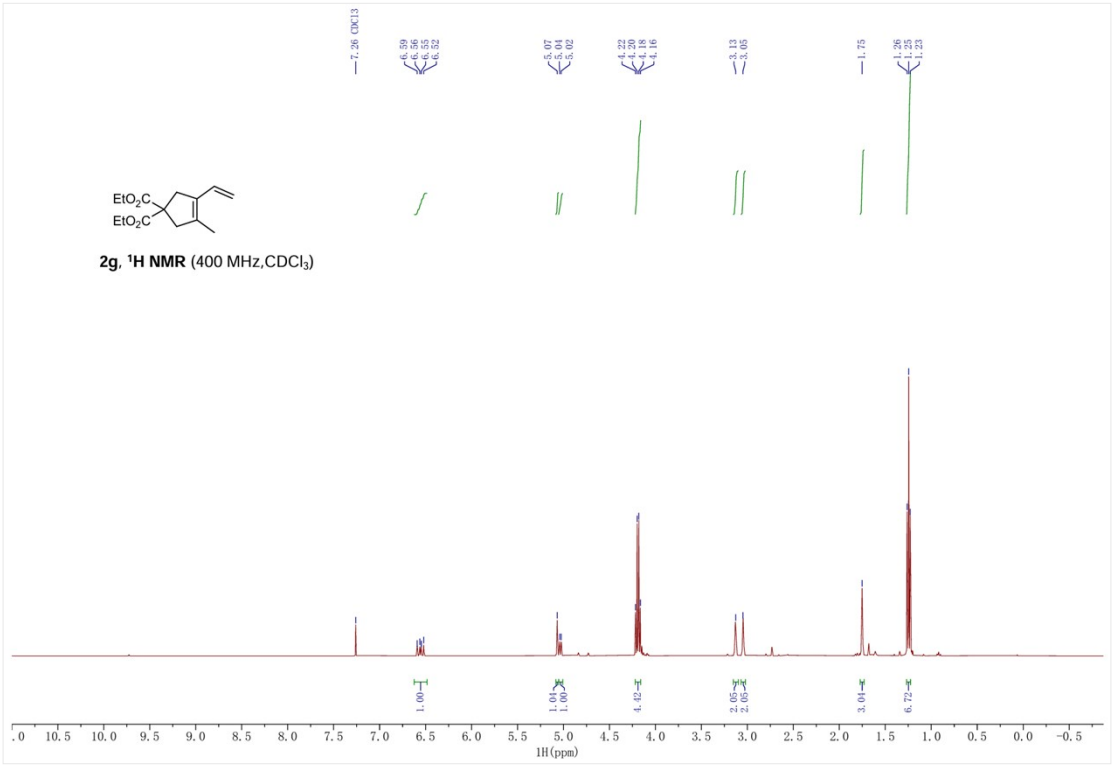
2d, **^{1}H NMR** (400 MHz, $CDCl_3$)



2d, **^{13}C NMR** (101 MHz, $CDCl_3$)


EtO2C
EtO2C
2e, E,Z mixture
1H NMR (400 MHz, CDCl3)
1H(ppm)


EtO2C
EtO2C
2f
3f
1H NMR (400 MHz, CDCl3)
1H(ppm)


7.26 CDCl3
6.59
6.58
6.55
6.52
5.07
5.04
5.02
4.22
4.20
4.18
4.16
3.13
3.05
1.75
1.26
1.25
1.23
EtO2C
EtO2C
2g, 1H NMR (400 MHz,CDCl3)
1.00
1.04
1.00
4.42
2.05
2.05
3.04
6.72
1H(ppm)