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A direct and sustainable synthesis of tertiary butyl esters enabled by flow microreactors

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Contents:

General

THF and 2-MeTHF was freshly distilled under a nitrogen atmosphere over Na/benzophenone ketyl. *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was distilled over finely powdered CaH_2, hexyllithium was purchased as a 2.3M hexane solution and was filtered on celite before using and title established by titration method.[1] All the other chemicals were commercially available and used without further purification.

Magnetic Resonance spectra were recorded using 400, 500 and 600 MHz spectrometers. For the ^{1}H, ^{13}C NMR spectra (^{1}H NMR 400, 500, 600 MHz, ^{13}C NMR 100, 125, 150 MHz), $CDCl_3$, methanol-d_4 or toluene-d_8 were used as the solvents.

MS-ESI analyses were performed on LC/MSD trap system VL. Melting points were uncorrected. GC-MS spectrometry analyses were carried out on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. sulphuric acid and heating to 200 °C for some time until blue spots appear. For flash chromathography silica Gel 60, 0.04-0.063 mm particle size was used. The high resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode. The sample solutions (CH_3OH or CH_3OH + 0.1%v/v HCOOH) were introduced by continuous infusion at a flow rate of 180 mL min^{-1} with the aid of a syringe pump. The instrument was operated with end-plate offset and capillary voltages set to −500 V and −4500 V respectively. The nebulizer pressure was 0.4 bar (N_2), and the drying gas (N_2) flow rate was 4.0 L min^{-1}. The capillary exit and skimmer 1 voltages were 90 V and 30 V, respectively. The drying gas temperature was set at 180 °C. The calibration was carried out with sodium formate: a solution made up of 10 μl of 98% formic acid, 10 μl of sodium hydroxide (1.0 M), 490 μl of *i*-propanol and 490 μl of deionized water. The software used for the simulations was Bruker Daltonics DataAnalysis (version 4.0). All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe septum cap technique. Three experiments were executed in each optimization run, and sample were collected after reaching the steady state. The steady state was achieved after flowing the solutions for three

[1] L. Degennaro, A. Giovine, L. Carroccia, R. Luisi *Practical Aspects of Organolithium Compounds in Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*, (R. Luisi, V. Capriati Eds.) **2014**, Ch. 18 Pages 513-538.

times the residence time. Chromatographic (TLC, GC) and spectroscopic analyses (^{1}H NMR) have been used for method's validation and ascertain yields and conversions.

Microfluidic components

For the microflow system, stainless steel (SUS304) T-shaped micromixer, with an internal diameter of 250µm, manufactured by Sanko Seiki Co., Inc. were used. Stainless steel (SUS 316) reaction microtubes, with an internal diameter of 1000 µm. Micromixer and reaction microtubes were connected with stainless steel fittings (1/16 O.D.). The microfluidic system was cooled by submersion in a cooling bath to control the temperature. The solutions were delivered in the microfluidic system by means of syringe pumps, Chemix, equipped with gas tight SGE or plastic Norm - Ject syringes.

General Procedure for the direct preparation of *tert*-butylesters from commercially available organolithiums. Synthesis of 1 is described.

A microfluidic system consisting of a T-shaped micromixer [M1], a microtube reaction (R1, length = 50 cm) and two pre-cooling units (P1, length = 100 cm; and P2, length = 100 cm) cooled at -50 °C was used (Figure 1). A solution of Boc_2O (0.1 M) in 2-MeTHF (flow rate: 2 mL/min) and a solution of HexLi (0.1 M) in hexane (flow rate: 2.2 mL/min) were introduced into M1 through syringe pumps. The resulting solution passes through R1 with a residence time of 5.6 s. After reaching the steady state (15 s), the out-coming solution of the product was collected for 60 s in a vial containing a saturated solution of NH_4Cl. Following extraction with Et_2O (3 x 10 mL), the collected organic phase were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/AcOEt 99:1) furnished pure ester **1** (95% yield). The same conditions were employed for ester **3** using PhLi (0.1 M hexane solution).

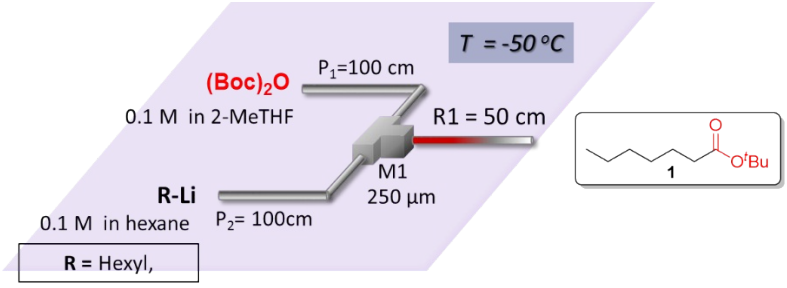
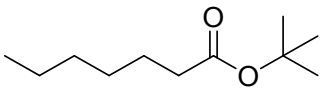


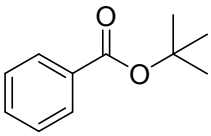
Figure 1

tert-butylheptanoate **1**. Data match that already reported.[2]



^{1}H-NMR (600 MHz, $CDCl_3$, ppm) δ: 2.20 (t, *J* = 7.52 Hz, 2H), 1.57 (s, *J* = 7.52 Hz, 2H), 1.44 (s, 9H), 1.31-1.27 (m, 6H), 0.88 (t, *J* = 6.98 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$, ppm) δ: 14.2, 22.64, 25.2, 28.2, 28.9, 31.7, 35.8, 80.0, 173.5. FT-IR (film, cm^{-1}): ν 1735, 1717.

tert-butylbenzoate **3**. Data match that already reported.[3]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 8.00 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 1.60 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 165.7, 132.4, 132.0, 129.4, 128.1, 80.9, 28.1. FT-IR (film, cm^{-1}): ν 2979, 2934, 2135, 1714, 1291, 1254, 1169, 1117, 712.

General procedure for the synthesis of *tert*-butyl esters from arylbromides and HexLi and trapping with Boc_2O. Synthesis of 6a is described.

A microfluidic system composed of two T-shaped micromixers [M1 and M2], two microtubes reaction (R1, length L = 6 cm and R2 length L = 200 cm) and three pre-cooling units (P1, length L = 100 cm, P2, length L = 50 cm, and P3, length L = 100 cm) cooled at 0 °C was used (Figure 2). A solution of arylbromide **5a** (0.12 M in 2-MeTHF) (flow rate: 2 mL/min) and a solution of HexLi (0.13 M in hexane) (flow rate: 2 mL/min) were introduced into M1 by syringe pumps. The resulting solution was transferred through R1 at M2 and mixed to a solution of $(Boc)_2O$ (0.16 M in 2-MeTHF) (flow: 1.5 mL/min). The resulting solution passes through R2 with a residence time of 17.38 s. After reaching the steady state (30 s), the out-coming solution of the product was collected for 120 s in a vial containing a saturated solution of NH_4Cl. Following extraction with AcOEt (3 x 10 mL), the collected organic phase were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/AcOEt 99:1 – 90/10) furnished pure ester **6a** (90% yield). Conditions reported in Table 1 were employed for bromides **5b-j**.

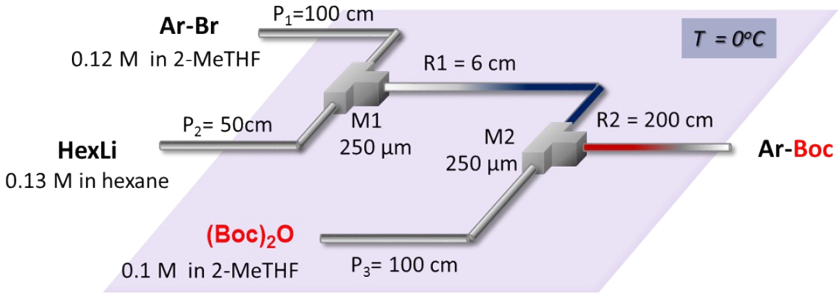
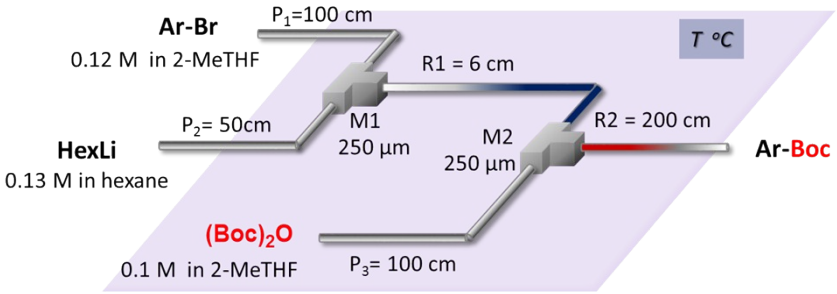
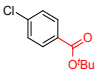
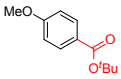
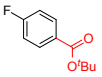
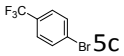
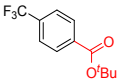
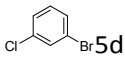
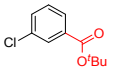
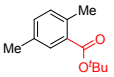
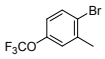
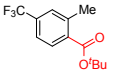
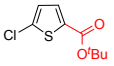
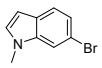
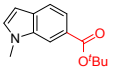
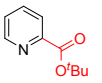


Figure 2

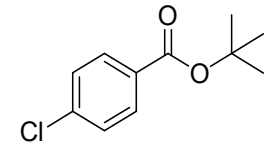
Table 1. Conditions for aryl and heteroaryl bromides.



R-Br **5**		T (°C)	t^{R1} (s)	t^{R2} (s)	Yield (%)	Ester **6**		Conditions[a]
	**5a**	0	0.7	17.1	90		**6a**	**A**
	**5b**	0	0.7	17.1	65		**6b**	**A**
	**5c**	0	0.7	17.1	75		**6c**	**A**[b]
	**5d**	0	0.7	17.1	65		**6d**	**A**
	**5e**	0	0.7	17.1	50		**6e**	**A**
	**5f**	0	2.04	20.9	80		**6f**	**B (A)**[c]
	**5g**	0	2.04	20.9	60		**6g**	**B (A)**[d]
	**5h**	-40	0.41	6.7	90		**6h**	**C**
	**5i**	0	0.41	6.7	65		**6i**	**C**
	**5j**	0	0.7	17.38	75		**6j**	**A**

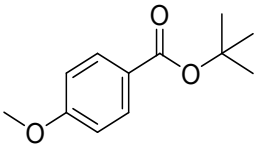
[a] **Condition A**. Flow rate: ArBr 2 mL/min; HexLi 2mL/min; Boc_2O 1.5 mL/min. **Condition B**. Flow rate: ArBr 2 mL/min; HexLi 2mL/min; Boc_2O 1.5 mL/min (R1 = 13 cm, R2 = 145 cm). **Condition C**. Flow rate: ArBr 2 mL/min (0.337 M); HexLi 2mL/min (0.337 M); Boc_2O 1.5 mL/min (0.27 M) (R1 = 13 cm, R2 = 145 cm). [b] To the solution of arylbromide (0:12 M) in 2-MeTHF (flow rate: 2 mL/min) was added 2 equivalent of TMEDA. [c] By using condition A the yield was 45%. [d] By using condition A the yield was 50%.

***tert*-butyl-4-chlorobenzoate 6a.** Data match that already reported.[4]



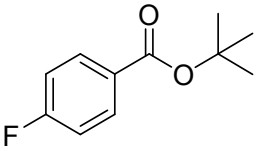
(90%, 92 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 1.58 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.9, 138.8, 130.9, 130.4, 128.4, 81.5, 28.2 (3C). FT-IR (film, cm^{-1}) ν: 2980, 1715, 1595, 1401, 1369, 1294, 1257, 1164, 1119, 850, 762.

***tert*-butyl-4-methoxybenzoate 6b.** Data match that already reported. [4]



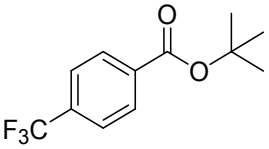
(65%, 65 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.93 (d, *J* = 7.4 Hz, 2H), 6.88 (d, *J* = 7.4 Hz, 2H), 3.84 (s, 3H), 1.57 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 165.6, 162.9, 131.3(2C), 124.5, 113.3, 80.5, 55.3, 28.2 (3C). FT-IR (film, cm^{-1}): ν 2979, 2936, 2135, 1757, 1702, 1607, 1510, 1461, 1253, 1162, 1119, 1033, 849, 775.

***tert*-butyl-4-fluorobenzoate 6c.** Data match that already reported.[5]



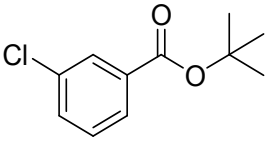
(75%, 60 mg) ^{1}H-NMR (400 MHz, 25°C, $CDCl_3$, ppm): δ 7.93 (m, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 1.58 (s, 9H). ^{13}C-NMR (100 MHz, 25°C, $CDCl_3$, ppm): δ 166.7, 164.3, 164.8, 131.8, 128.2, 115.2, 81.2, 28.1. ^{19}F-NMR (400 MHz, $CDCl_3$, ppm): δ -107.0. FT-IR (film, cm^{-1}): ν 2931, 2859, 1715, 1604, 1507, 1368, 1289, 1256, 1151, 1115, 853, 770.

***tert*-butyl-4-(trifluoromethyl)benzoate 6d.** Data match that already reported. [4]



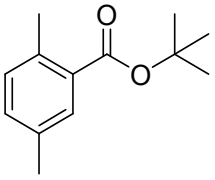
(65%, 76 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 8.10 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 1.61 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 164.5, 135.3, 133.9, 129.9, 125.2, 123.7, 82.0, 28.2. ^{19}F-NMR (400 MHz, $CDCl_3$, ppm): δ -63.1. FT-IR (film, cm^{-1}): ν 1709, 1121.

***tert*-butyl-3-chlorobenzoate 6e.** Data match that already reported.[6]



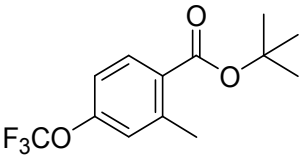
(50%, 50 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.95 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 1.59 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 164.7, 134.5, 134.0, 132.7, 129.8, 129.7 127.8, 81.9, 28.4. FT-IR (film, cm^{-1}): ν 3060, 1710.

***tert*-butyl-2,5-dimethylbenzoate 6f**



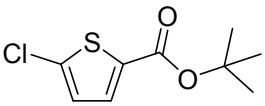
(80%, 79 mg) ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ 7.59 (s, 1H), 7.14 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 2.49 (s, 3H), 2.31 (s, 3H), 1.57 (s, 9H). ^{13}C-NMR (125 MHz, $CDCl_3$, ppm): δ 167.6, 136.1, 135.2, 132.1, 131.7, 131.6, 130.8, 81.1, 28.4, 21.4, 20.9 (3C). FT-IR (film, cm^{-1}): ν 2927, 1714, 1367, 1303, 1267, 1166, 1079, 853, 818, 785.HMRS $C_{13}H_{18}NaO_2$ [M+Na] calculated 2299.1199; found 229.1213.

***tert*-butyl-2-methyl-4-trifluoromethoxybenzoate 6g**



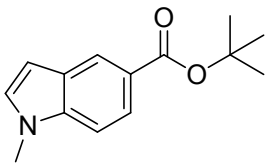
(60%, 80 mg) ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 8 Hz, 1H), 2.56 (s, 3H), 1.57 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$, ppm) δ 166.2, 151.1, 142.2, 132.4, 130.23, 123.4, 120.5 (q, *J* = 256.2 Hz, 1C OCF_3), 117.6, 81.73, 28.4, 22.7 (3C). FT-IR (film, cm^{-1}): ν 2918, 1720, 1368, 1256, 1171, 1084, 853, 783. HRMS $C_{13}H_{15}F_3NaO_3$ [M+Na] calculated 299.0866; found 299.0871.

***tert*-butyl 5-chlorothiophene-2-carboxylate 5h**



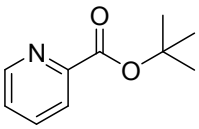
(90%, 94 mg) ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ 7.50 (d, *J* = 4.0 Hz, 1H), 6.89 (d, *J* = 4.0 Hz, 1H), 1.55 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$, ppm): δ 160.63, 136.56, 134.07, 132.32, 127.17, 82.43, 28.32 (3C). FT-IR (film, cm^{-1}): ν 2927, 1709, 1426, 1270, 1257, 1167, 1093, 747. HMRS $C_9H_{11}ClNaO_2S$ [M+Na] calculated 241.0060 found; 241.0074.

***tert*-butyl 1-methyl-1H-indole-6-carboxylate 5i**



(65%, 72 mg). ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ 8.34 (d, *J* = 1.2 Hz, 1H), 7.90 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 3.2 Hz, 1H). ^{13}C-NMR (126 MHz) δ 167.1, 139.0, 130.1, 128.0, 123.7, 123.4, 123.0, 108.7, 102.6, 80.3, 33.1, 28.5(3C). FT-IR (film, cm^{-1}): ν 2976, 1698, 1309, 1255, 1162, 751. HRMS $C_{14}H_{17}NNaO_2$ [M+Na] calculated 254.1151; found 254.1164.

***tert*-butyl picolinate 5j.** Data match that already reported.[7]



(75%, 64 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 8.71 (d, J = 4.8 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.77 (td, J = 7.8, 1.7 Hz, 1H), 7.39 (ddd, J = 7.8, 4.8, 1.2 Hz, 1H), 1.60 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 164.2, 149.7, 149.5, 136.8, 126.3, 124.7, 82.2, 28.0 (3C). FT-IR (film, cm^{-1}): ν 2940, 1734, 1713, 710.

General procedure for the synthesis of *tert*-butyl esters from alkenylbromide 5q. Synthesis of 6q is described.

A microfluidic system composed of two T-shaped micromixer [M1 and M2], two microtubes reaction (R1, length L = 6 cm and R2 length L = 400 cm) and three pre-cooling units (P1, length L = 100 cm, P2, length L = 50 cm, and P3, length L = 100 cm) cooled at -20 °C was used (Figure 3). A solution of bromide **5q** (0.12 M in 2-MeTHF) (flow rate: 7 mL/min) and a solution of sec-BuLi (0.13 M in hexane) (flow rate: 7 mL/min) were introduced into M1 by syringe pumps. The resulting solution was transfered through R1 at M2 and mixed to a solution of $(Boc)_2O$ (0.28 M in 2-MeTHF) (flow: 3 mL/min). The resulting solution passes through R2 with a residence time of 11.1 s. After reaching the steady state (10 s), the out-coming solution of the product was collected for 120 s in a vial containing a saturated solution of NH_4Cl. Following extraction with AcOEt (3 x 10 mL), the collected organic phase were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/AcOEt 99:1) furnished pure ester **6q** (95% yield).

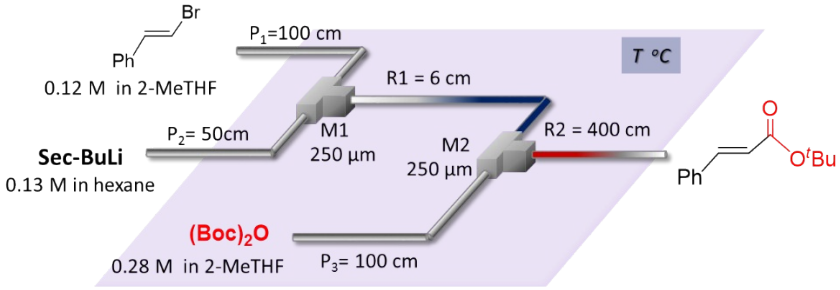
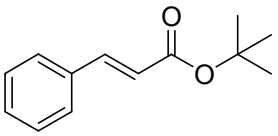


Figure 3

***tert*-butyl cinnamate 6q.** Data match that already reported [8]

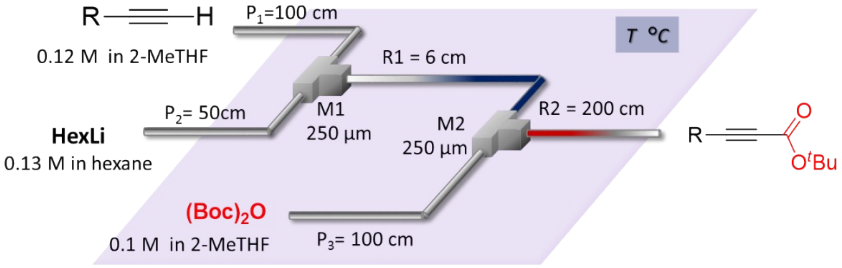


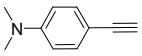
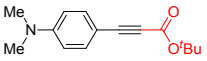
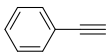
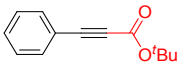
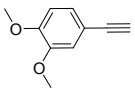
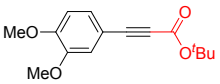
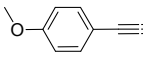
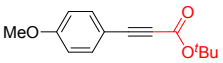
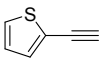
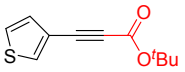
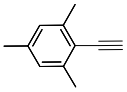
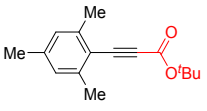
(95%, 93 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.59 (d, J = 16 Hz, 1H), 7.55-7.45 (m, 2H), 7.43-7.32 (m, 3H), 6.37 (d, J = 16 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 166.5, 143.7, 134.8, 130.1, 128.9, 128.1, 120.3, 80.6, 28.3. FT-IR (film, cm^{-1}): ν 1707, 1636, 1577, 1495, 1474, 1449, 1391, 1367, 1328, 1284, 1255, 1207, 1150.

General procedure for the synthesis of *tert*-butyl esters from alkynes. Synthesis of 6l is described.

A microfluidic system composed of two T-shaped micromixer [M1 and M2], two microtubes reaction (R1, length L = 6 cm and R2 length L = 200 cm) and three pre-cooling units (P1, length L = 100 cm, P2, length L = 50 cm, and P3, length L = 100 cm) cooled at 0 °C was used (Table 2). A solution of phenylacetylene **5l** (0.12 M in 2-MeTHF) (flow rate: 2 mL/min) and a solution of HexLi (0.13 M in hexane) (flow rate: 2 mL/min) were introduced into M1 by syringe pumps. The resulting solution was transfered through R1 at M2 and mixed to a solution of $(Boc)_2O$ (0.16 M in 2-MeTHF) (flow: 1.5 mL/min). The resulting solution passes through R2 with a residence time of 17.1 s. After reaching the steady state (30 s), the out-coming solution of the product was collected for 120 s in a vial containing a saturated solution of NH_4Cl. Following extraction with AcOEt (3 x 10 mL), the collected organic phase were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/AcOEt 99:1 – 90/10) furnished pure ester **6l** (50% yield). Conditions reported in Table 2 were employed for alkynes **5k-p**.

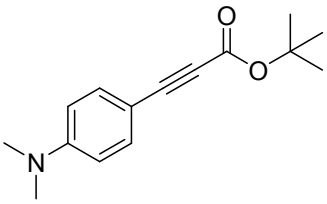
Table 2. Conditions for alkynes.



Alkyne **5**		T (°C)	t^{R1} (s)	t^{R2} (s)	Yield (%)	Ester **6**		*Conditions*[a]
	**5k**	20	0.7	17.1	95		**6k**	*A*
	**5l**	0	0.7	17.1	50		**6l**	*A*
	**5m**	20	0.7	17.1	75		**6m**	*A*
	**5n**	0	0.7	17.1	70		**6n**	*A*
	**5o**	0	2.94	17.1	87		**6o**	*D*
	**5p**	20	0.7	17.1	95		**6p**	*A*

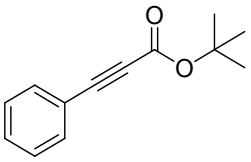
[a] **Condition A**. Flow rate: Alkyne 2 mL/min; HexLi 2mL/min; Boc_2O 1.5 mL/min. **Condition D**. Flow rate: Alkyne 2 mL/min; HexLi 2mL/min; Boc_2O 1.5 mL/min (R1 = 25 cm).

(4-Dimethylamino-phenyl)-propynoic acid *tert*-butyl ester 6k



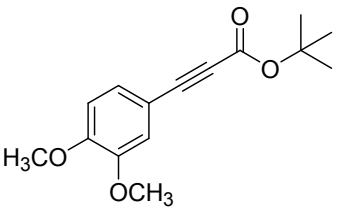
(95%, 112 mg). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 7.45 (d, *J* = 9 Hz, 2H), 6.61 (d, *J* = 9 Hz, 2H), 3.01 (s, 6H), 1.54 (s, 9H). ^{13}C-NMR (126 MHz): δ 154.0, 151.5, 134.8 (2C), 111.5 (2C), 105.8, 87.0, 82.9, 81.5, 40.1 (2C), 28.3 (3C). FT-IR (film, cm^{-1}) ν 2918, 2190, 1687, 1606, 1315, 1145, 823, 748. HMRS $C_{15}H_{19}NaO_2$ [M+Na] calculated 268.1308; found 268.1316.

***tert*-butyl 3-phenylpropiolate 6l [5]**



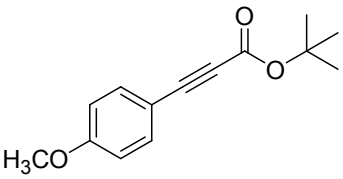
(50%, 92 mg) ^{1}H-NMR (600 MHz, $CDCl_3$, ppm): δ 7.55 - 7.53 (m, 2 H), 7.41 - 7.38 (m, 1 H), 7.34 - 7.31 (m, 2 H), 1.52 (s, 9 H). ^{13}C-NMR (150 MHz, $CDCl_3$, ppm): δ 153.1, 132.8, 130.3, 128.5, 120.0, 83.8, 83.4, 82.0, 28.0. FT-IR (film, cm^{-1}): ν 2982, 844.

(3,4-Dimethoxy-phenyl)-propynoic acid *tert*-butyl ester 6m



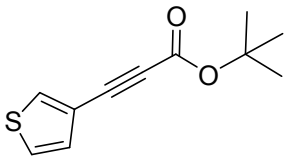
(75%, 94 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 7.21 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 1.54 (s, 9H). ^{13}C-NMR (100 MHz) δ 153.4, 151.3, 148.8, 127.2, 115.4, 112.0, 111.1, 84.8, 83.5, 81.4, 56.1 (2C), 28.2 (3C). FT-IR (KBr, cm^{-1}) ν 2201, 1689, 1515, 1485, 1237, 1137, 1028, 842, 820, 750. HRMS $C_{15}H_{18}NaO_4$ [M+Na] calculated 285.1097; found 285.1107.

(4-Methoxy-phenyl)-propynoic acid *tert*-butyl ester 6n



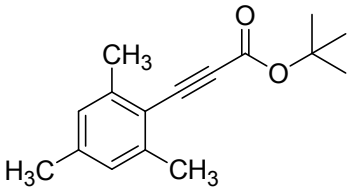
(70%, 78 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 7.52 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 1.54 (s, 9H). ^{13}C-NMR (126 MHz) δ 161.3, 153.5, 134.9(2C), 114.3 (2C), 111.8, 84.6, 83.3, 81.5, 55.4, 28.2 (3C). FT-IR (film, cm^{-1}) ν 2980, 2206, 1718, 1605, 1252, 1145, 833, 727. HRMS $C_{14}H_{16}NaO_3$ [M+Na] calculated 255.0992; found 255.1001.

***tert*-butyl 3-(thiophen-3-yl)propiolate 6o**



(87%, 87 mg) ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.71 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.30 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.21 (dd, *J* = 5.0, 1.1 Hz), 1.54 (s, 9H). ^{13}C-NMR (100 MHz): δ 153.1, 133.2, 130.1, 125.8, 119.1, 83.5, 81.9, 79.2, 28.0 (3C). FT-IR (film, cm^{-1}): ν 2917, 2217, 1704, 1370, 1279, 1147, 787. HRMS $C_{11}H_{12}NaO_2S$ [M+Na] calculated 231.0450; found 231.0459.

(2,4,6-Trimethyl-phenyl)-propynoic acid *tert*-butyl ester 6p



(95%, 111 mg). ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ 6.86 (d, *J* = 0.5 Hz, 2H), 2.42 (s, 6H), 2.28 (s, 3H), 1.54 (s, 9H). ^{13}C-NMR (126 MHz): δ 153.76, 142.38 (2C), 140.23, 127.96 (2C) 116.94, 89.68, 83.11, 82.39, 28.24 (3C), 21.61, 20.9 (2C). FT-IR (film, cm^{-1}): ν 2980, 2204, 1704, 1282, 1142, 848, 750, 727. HRMS $C_{16}H_{20}NaO_2$ [M+Na] calculated 267.1356; found 267.1366.

Synthesis of tetrahydroisoquinoline 8.

A microfluidic system composed of two T-shaped micromixer [M1 and M2], two microtubes reaction (R1, length L = 6 cm and R2 length L = 200 cm) and three pre-cooling units (P1, length L = 100 cm, P2, length L = 50 cm, and P3, length L = 100 cm) cooled at 0 °C was used (Table 2). A solution of isoquinoline **7** (0.12 M in 2-MeTHF) (flow rate: 2 mL/min) and a solution of HexLi (0.13 M in hexane) (flow rate: 2 mL/min) were introduced into M1 by syringe pumps. The resulting solution was transfered through R1 to M2 and mixed to a solution of $(Boc)_2O$ (0.16 M in 2-MeTHF) (flow: 1.5 mL/min). The resulting solution passes through R2 with a residence time of 17.1 s. After reaching the steady state (30 s), the out-coming solution of the product was collected for 120 s in a vial containing a saturated solution of NH_4Cl. Following extraction with AcOEt (3 x 10 mL), the collected organic phase were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/AcOEt 70/30) furnished pure **8** (82% yield).

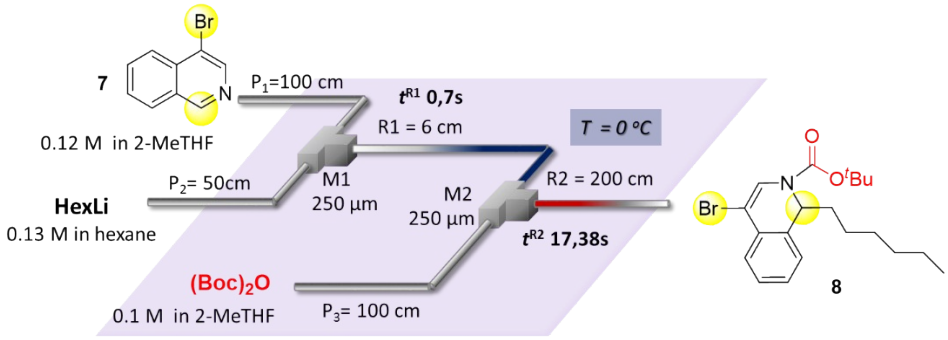
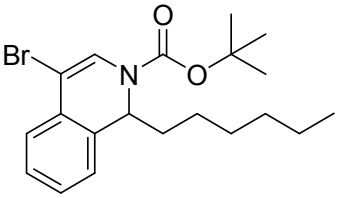


Figure 4

***tert*-butyl 4-bromo-1-hexylisoquinoline-2(1H)-carboxylate 8**



(82%, 155 mg) ^{1}H-NMR (500 MHz, $CDCl_3$, ppm) 7.47-7.44 (m, 2H), 7.30-7.27 (m, 3H), 7.24-7.21 (m, 2H), 7.10 (s, 1H), 7.04-7.01 (m, 2H), 5.28 (t, J = 7.35 Hz, 1H), 5.11 (t, J = 6.75 Hz, 1H), 1.66-1.56 (m, 4H), 1.54 (s, 9H) 1.52 (s, 9H), 1.25-1.23 (m, 16H,) 0.88-0.83 (6H,). ^{13}C-NMR (126 MHz, $CDCl_3$, ppm) δ 151.1, 133.3, 128.0, 127.8, 126.3, 126.3, 125.9, 124.5, 102.9, 82.1, 55.3, 35.1, 31.9, 29.2, 28.3 (3C), 25.5, 22.7, 14.2. FT-IR (film, cm^{-1}): ν 2929, 2856, 1712, 1617, 1453, 1391, 1332, 1162, 1132, 857, 761, 685. HRMS $C_{20}H_{28}O_2NNaBr$ $[M+Na]^+$ calculated 416.1196; found 416.1213.

General procedure for the synthesis of a *tert*-butyl ester, starting from a substituted aryliodide by an ester group through an exchange reaction with PhLi.

A microfluidic system consisting of two T-shaped micromixer [M1 and M2], two microtubes reaction (R1, L = 3.5 cm, R2, L = 100 cm) and three pre-cooling units (P1, length L = 100 cm, P2, length L = 50 cm and P3, length L = 100 cm) at -40 °C was used. A solution of ethyl 4-iodobenzoate **9** (0.12 M in THF) (flow rate: 4.5 mL/min) and a solution of PhLi (0.675 M in THF) (flow rate: 1 mL/min) were introduced into M1 by syringe pumps. The resulting solution transferred through R1 to M2 and mixed with a solution of Boc_2O (0.27 M in THF) (flow rate: 3 mL/min). The resulting solution passes through R2 with a residence time of 5.4 s. After reaching the steady state (15 s), the out-coming solution of the product was collected for 120 s in a vial containing a saturated solution of NH_4Cl. Following extraction with AcOEt (3 x 10 mL), the collected organic phase were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/AcOEt 90/10) furnished pure di-ester **10**.

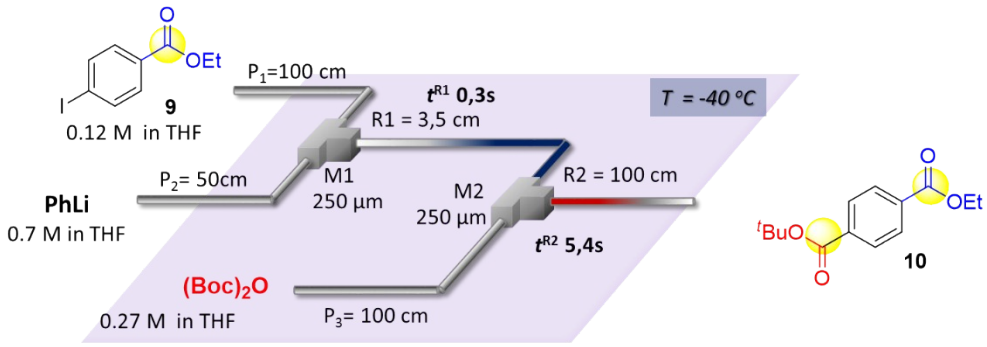
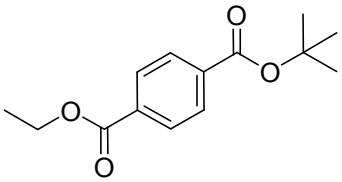
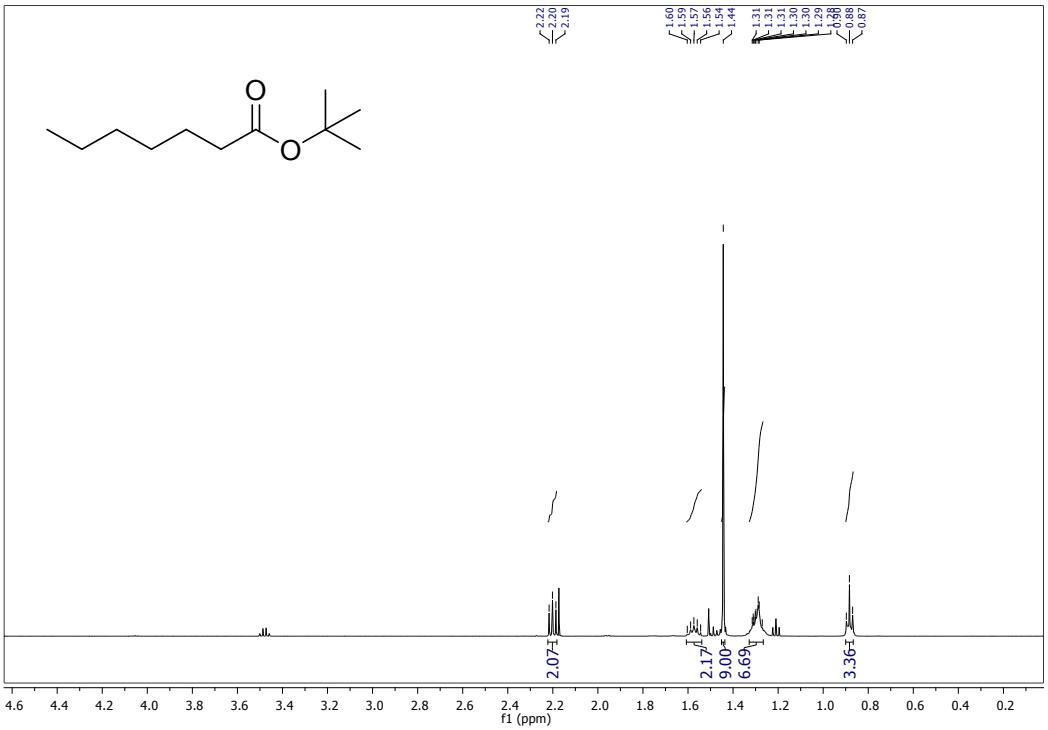


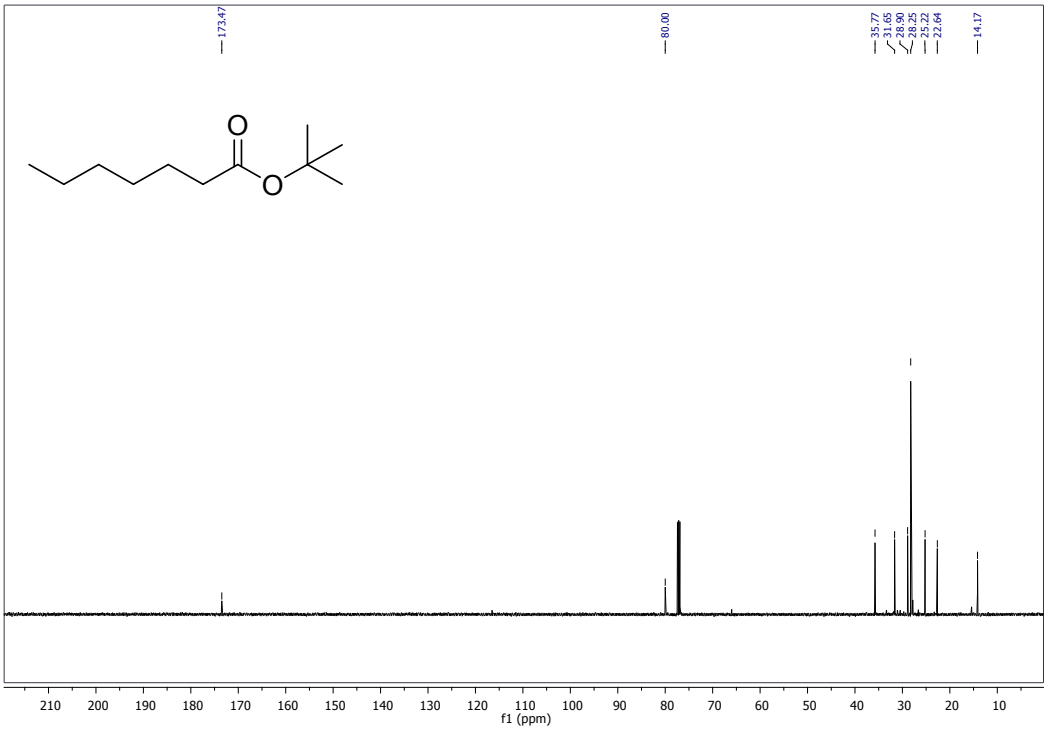
Figure 5

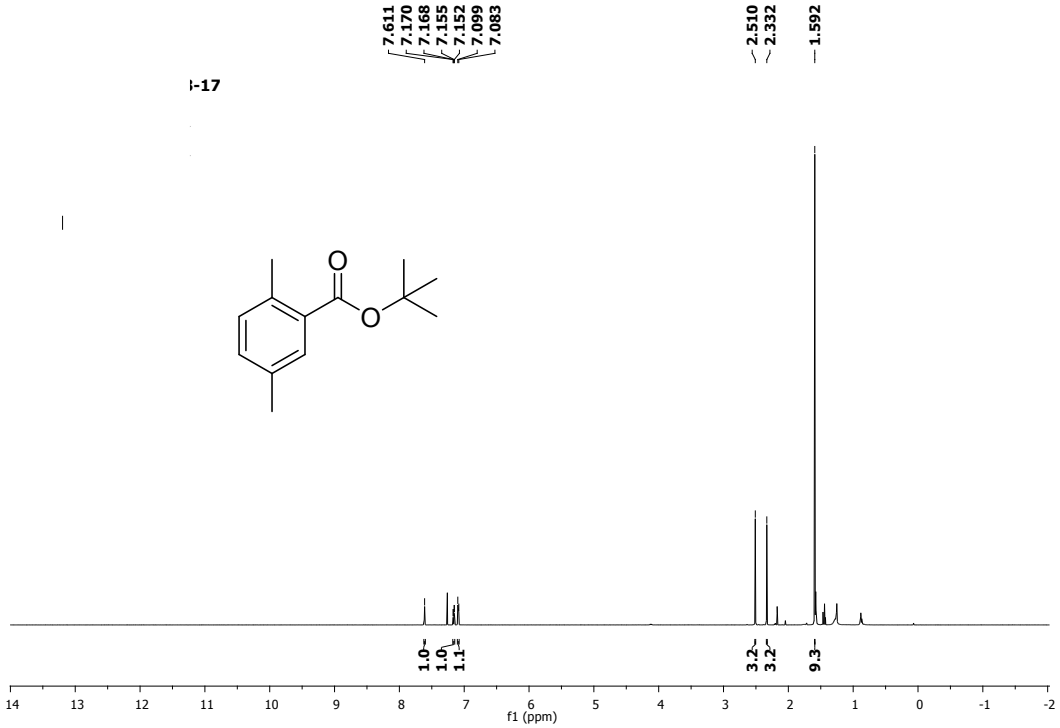
***tert*-butyl ethyl-terephtalate 10**

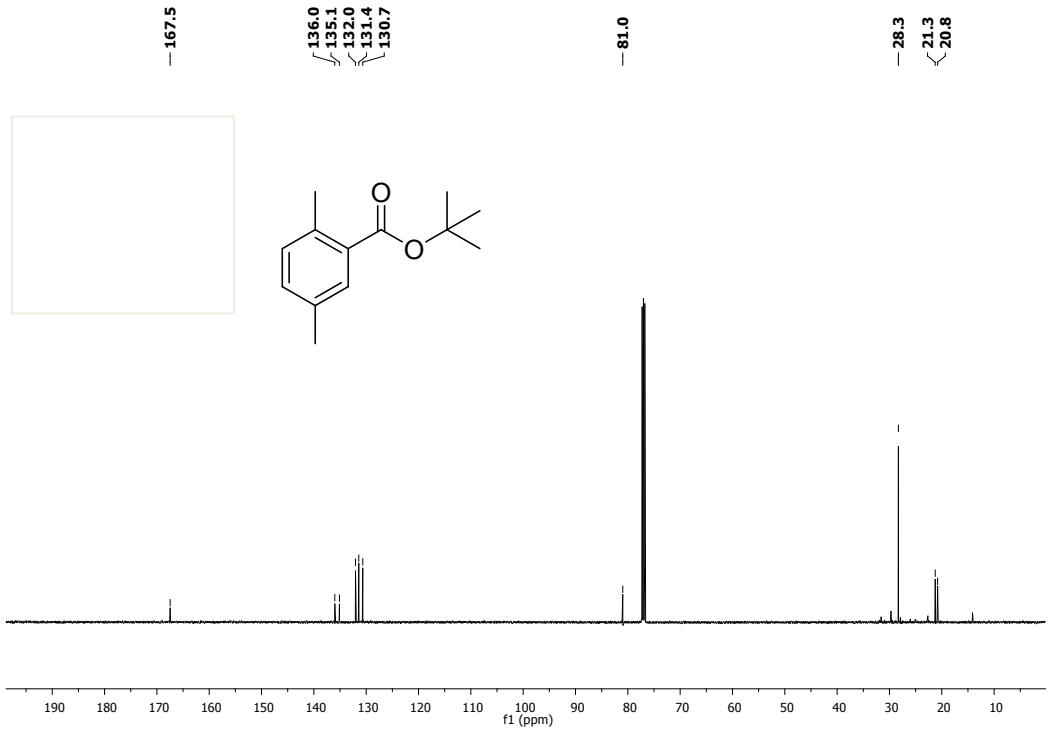


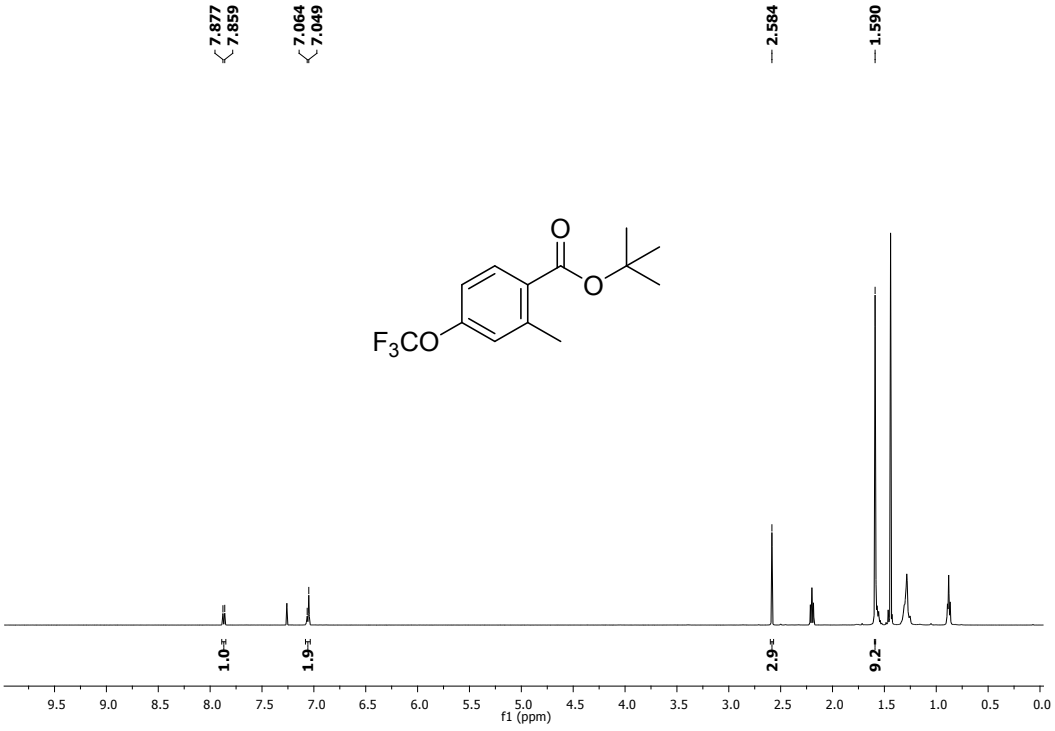
(65%, 78 mg) ^{1}H-NMR (500 MHz, $CDCl_3$, ppm) δ 8.07 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 8.6 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.60 (s, 9H), 1.4 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$, ppm) δ 166.07, 165.06, 135.83, 133.90, 129.44 (4C), 81.81, 61.47, 28.26 (3C), 14.41. FT-IR (film, cm^{-1}) ν 2980, 1716, 1368, 1247, 1164, 1119, 1019, 876, 844. HRMS $C_{14}H_{18}O_4Na$ [M+Na$^+$] calculated 273.1097; found 273.1109.

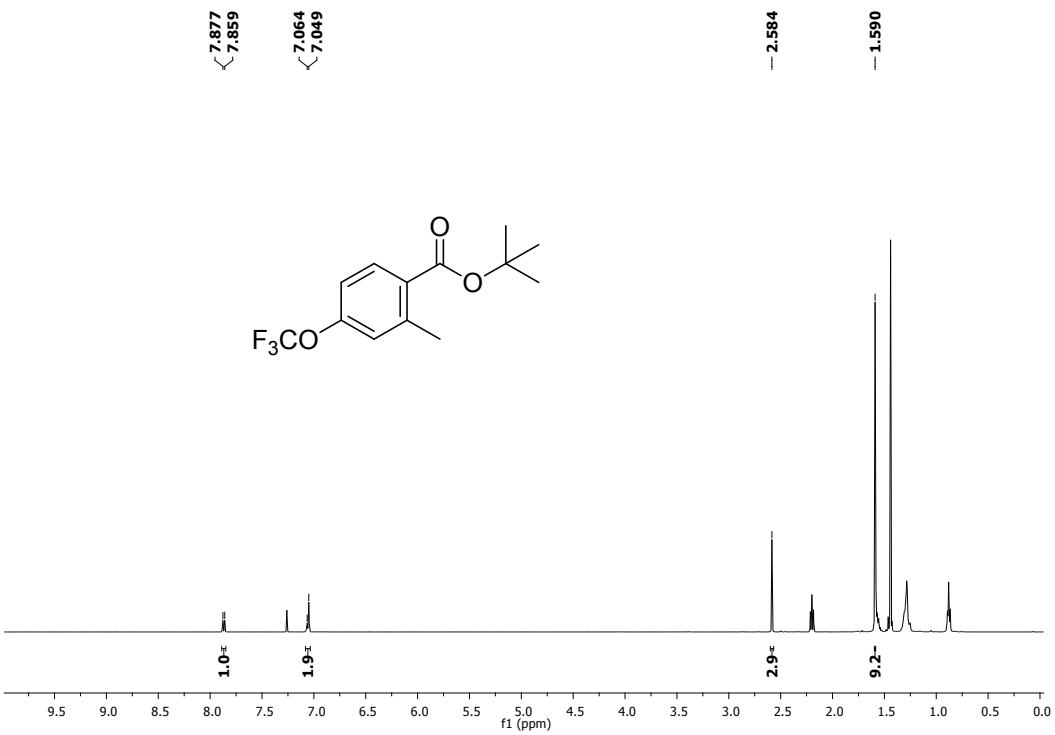

2.22
2.20
2.19
1.60
1.59
1.57
1.56
1.54
1.44
1.31
1.31
1.31
1.30
1.29
0.88
0.88
0.87
O
O
2.07
2.17
9.00
6.69
3.36
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)

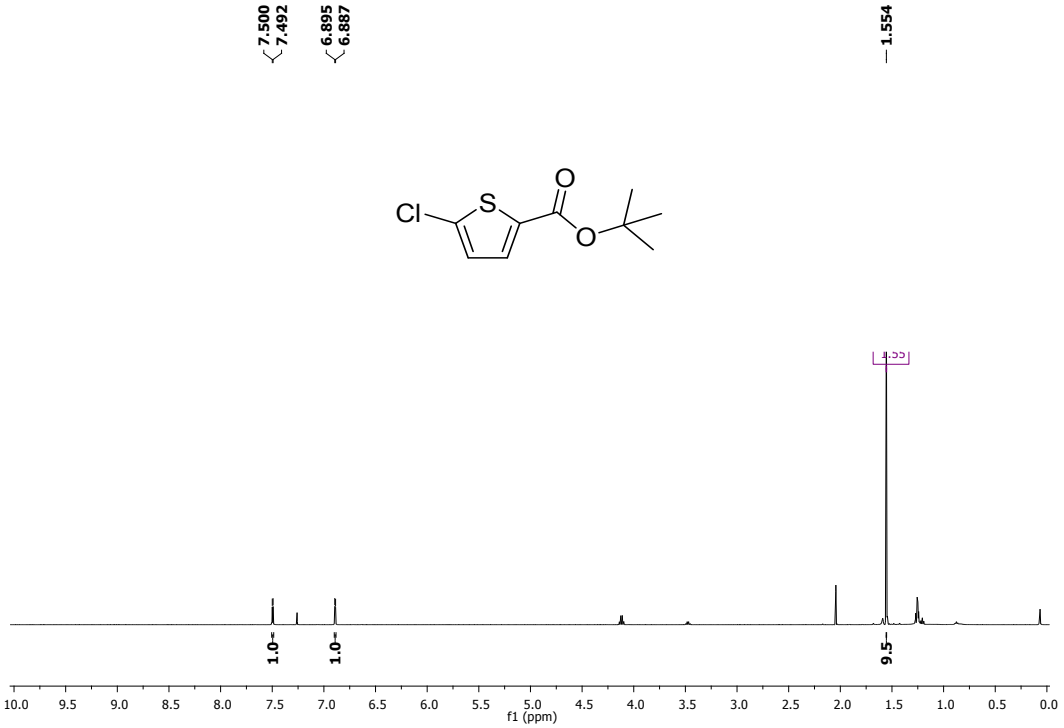

173.47
80.00
35.77
31.65
28.90
28.25
25.22
22.64
14.17
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

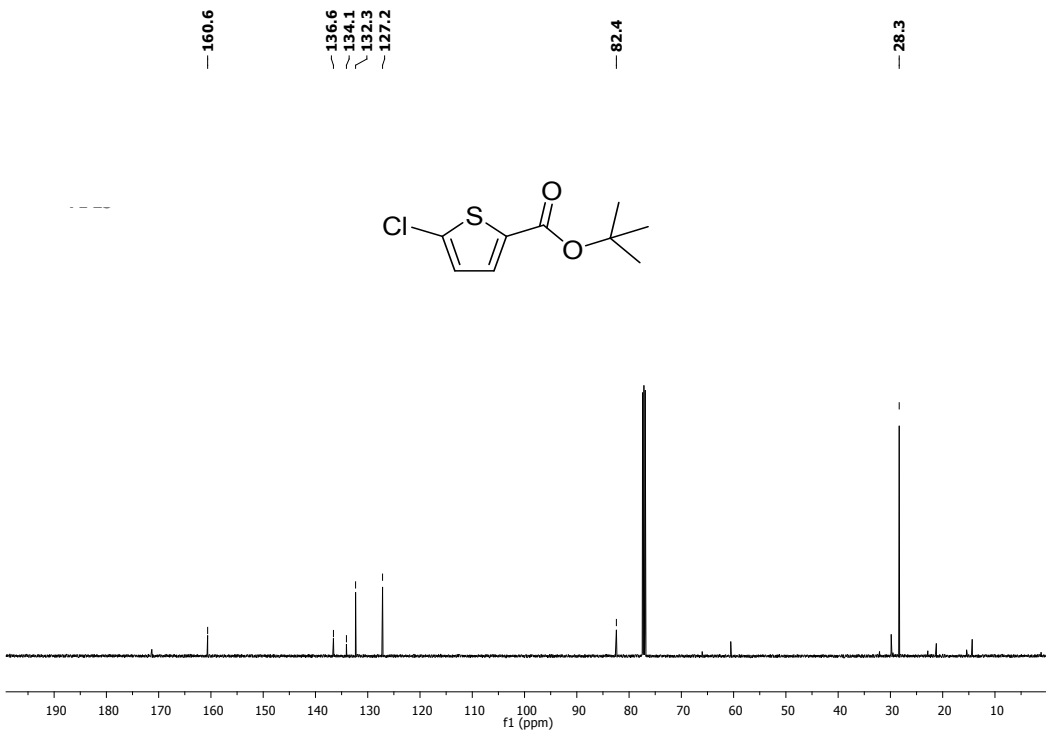

7.611
7.170
7.168
7.155
7.152
7.099
7.083
2.510
2.332
1.592
1.0
1.0
1.1
3.2
3.2
9.3
f1 (ppm)

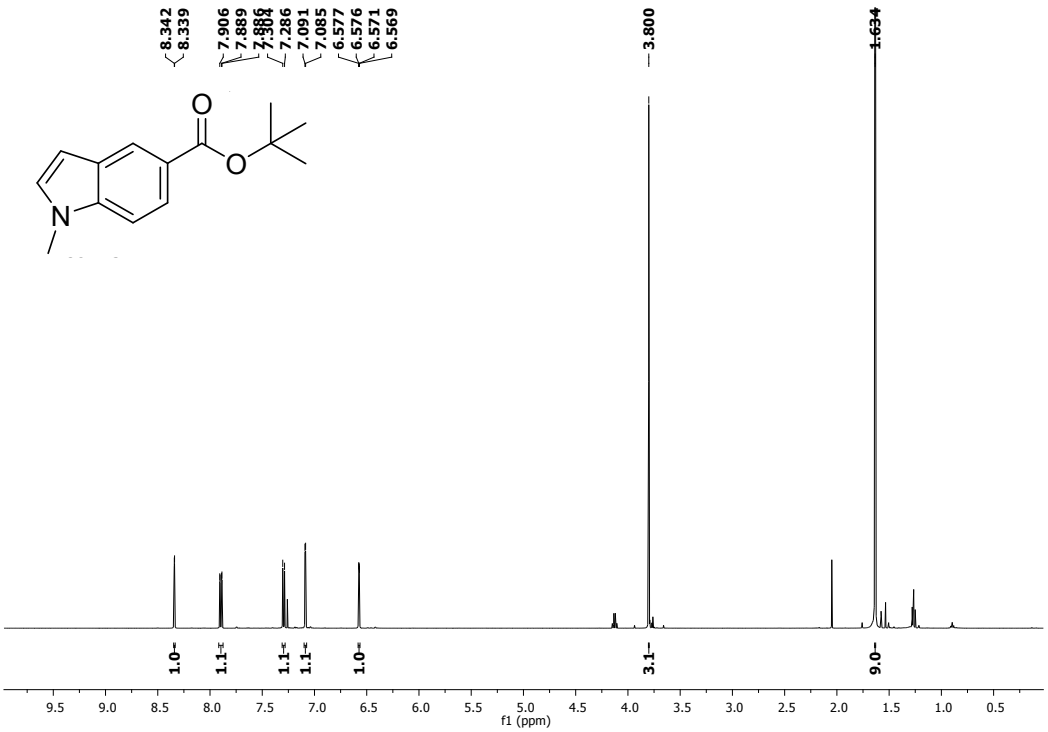

167.5
136.0
135.1
132.0
131.4
130.7
81.0
28.3
21.3
20.8
f1 (ppm)

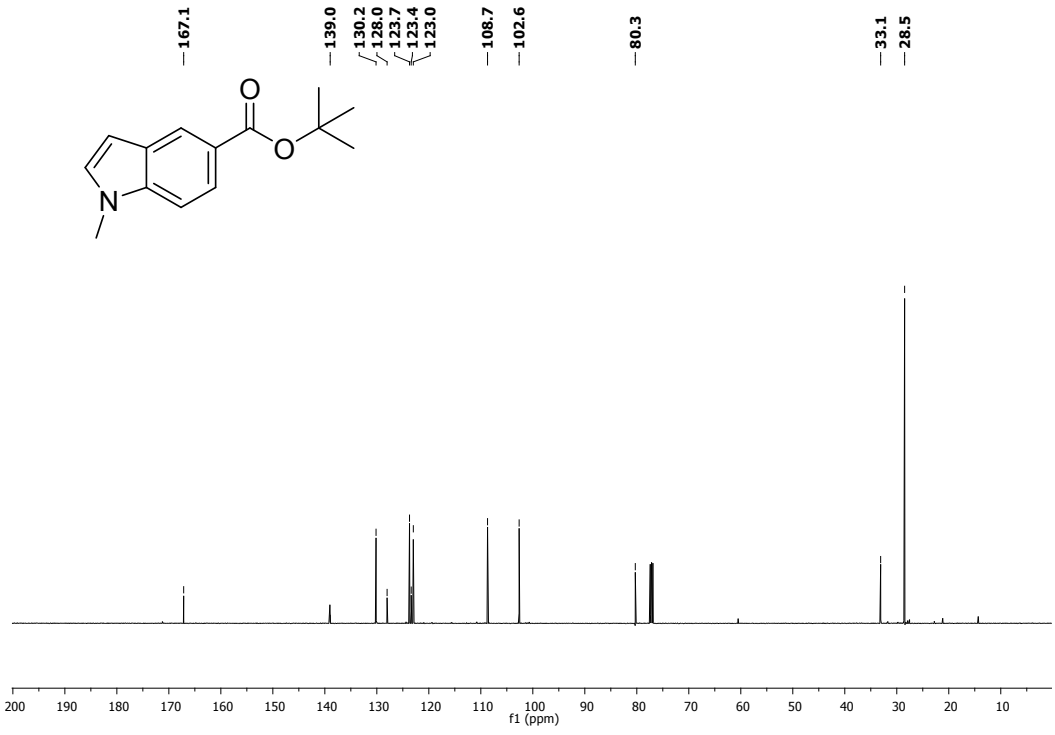

7.877
7.859
7.064
7.049
2.584
1.590
O
O
F3CO
1.0
1.9
2.9
9.2
f1 (ppm)

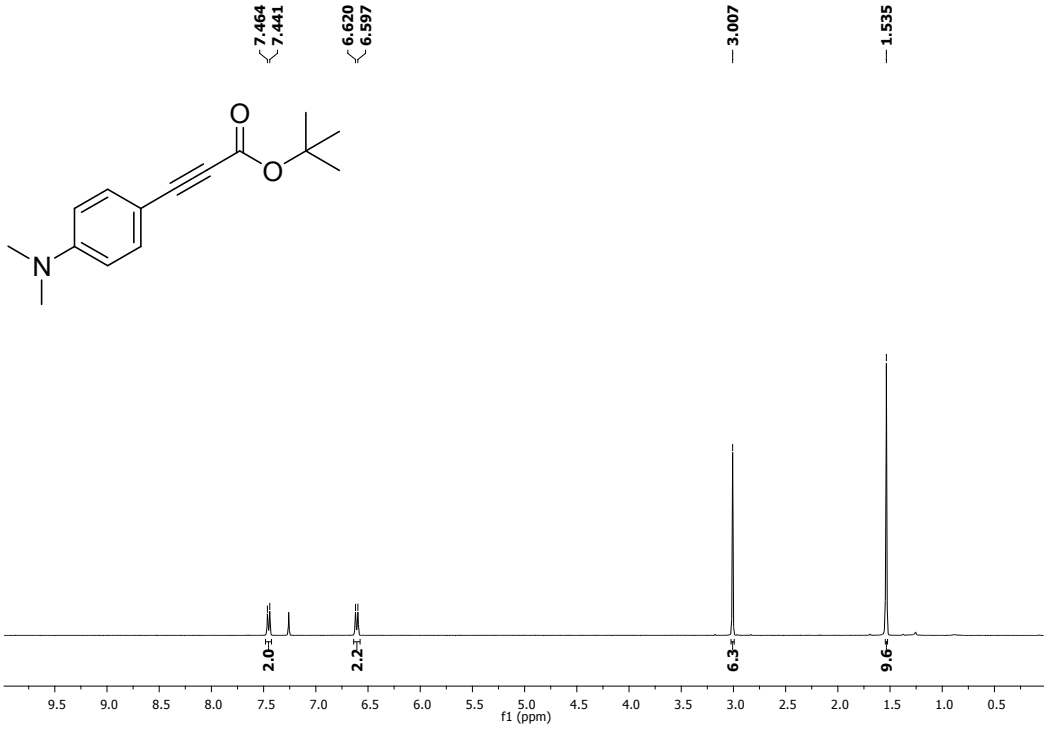

7.877
7.859
7.064
7.049
2.584
1.590
O
O
F3CO
1.0
1.9
2.9
9.2
f1 (ppm)

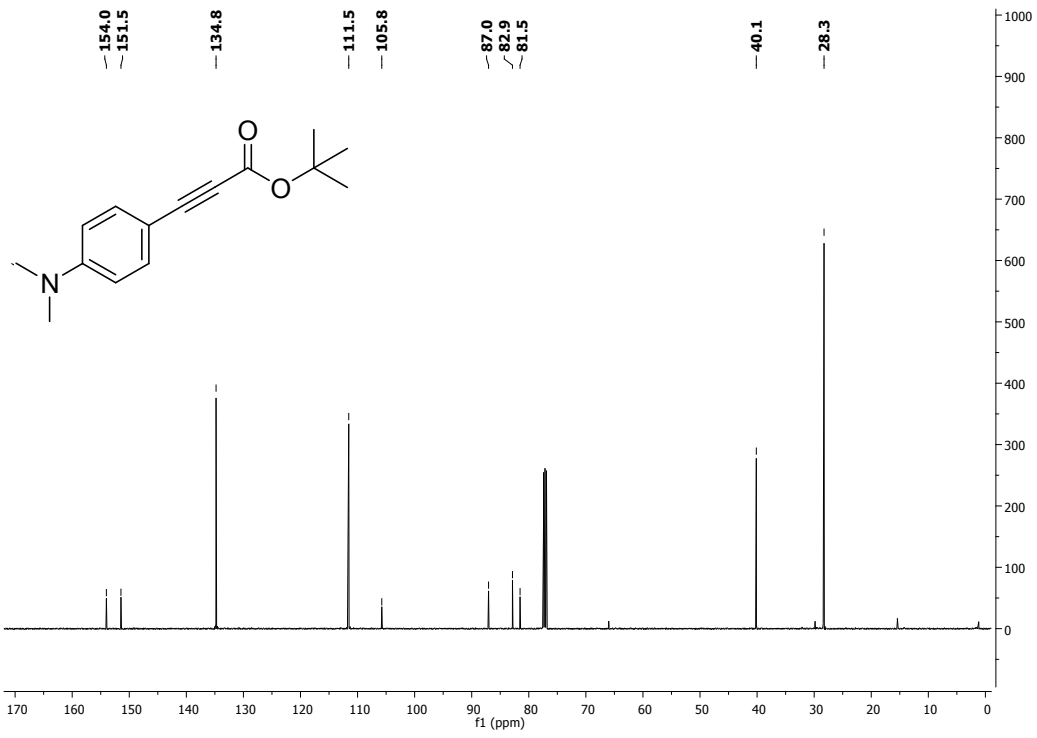

7.500
7.492
6.895
6.887
1.554
Cl
S
O
O
1.0
1.0
9.5
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

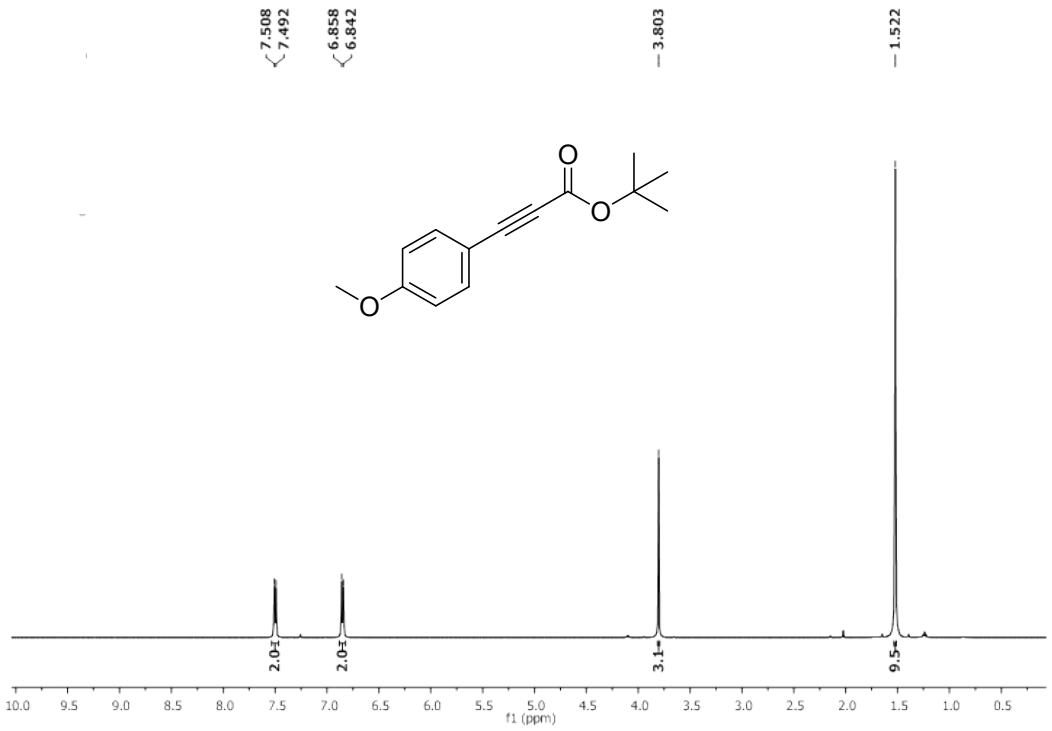

160.6
136.6
134.1
132.3
127.2
82.4
28.3
Cl
S
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

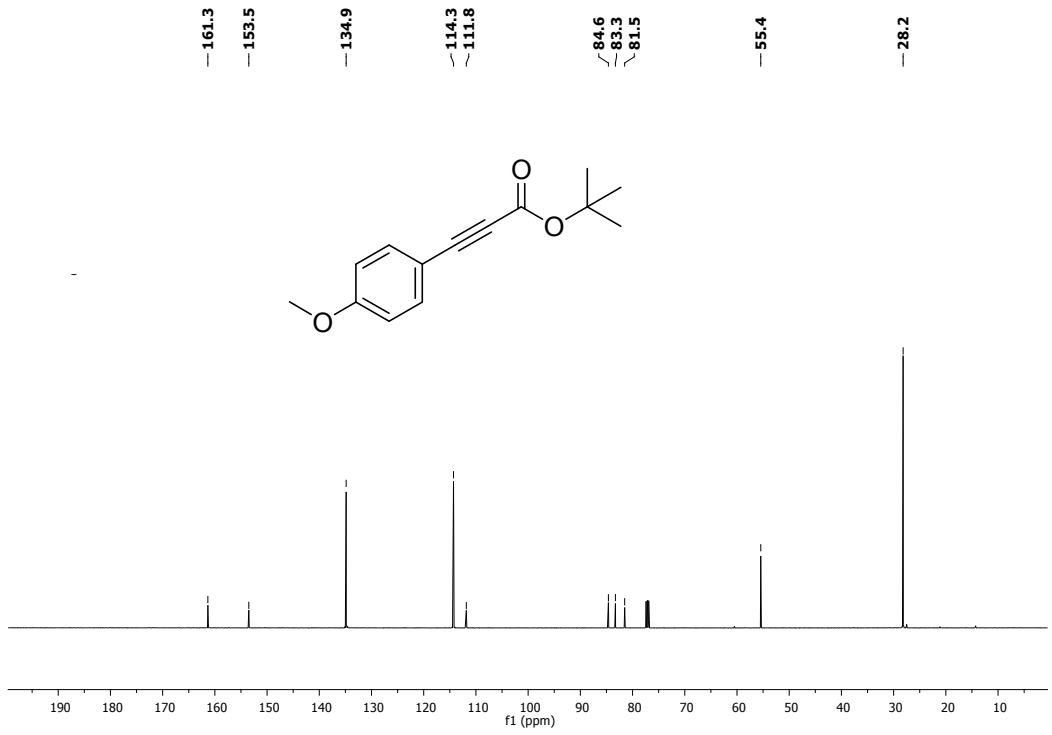

8.342
8.339
7.906
7.889
7.304
7.286
7.091
7.085
6.577
6.576
6.571
6.569
3.800
1.634
1.0
1.1
1.1
1.1
1.0
3.1
9.0
f1 (ppm)

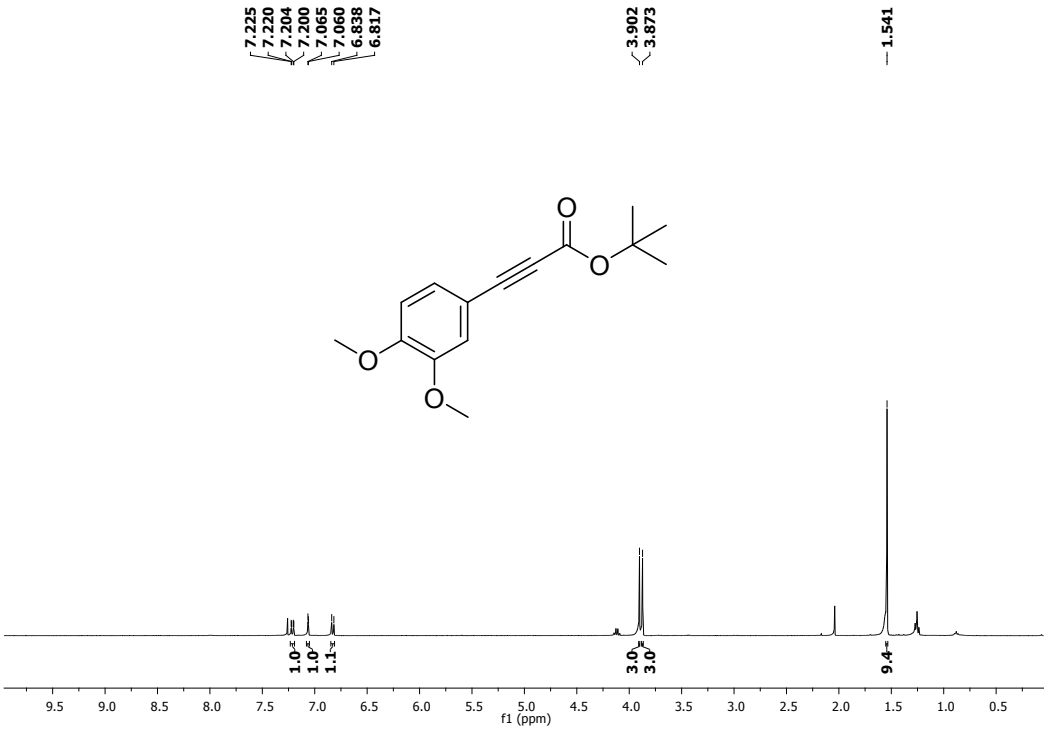

167.1
139.0
130.2
128.0
123.7
123.4
123.0
108.7
102.6
80.3
33.1
28.5
f1 (ppm)

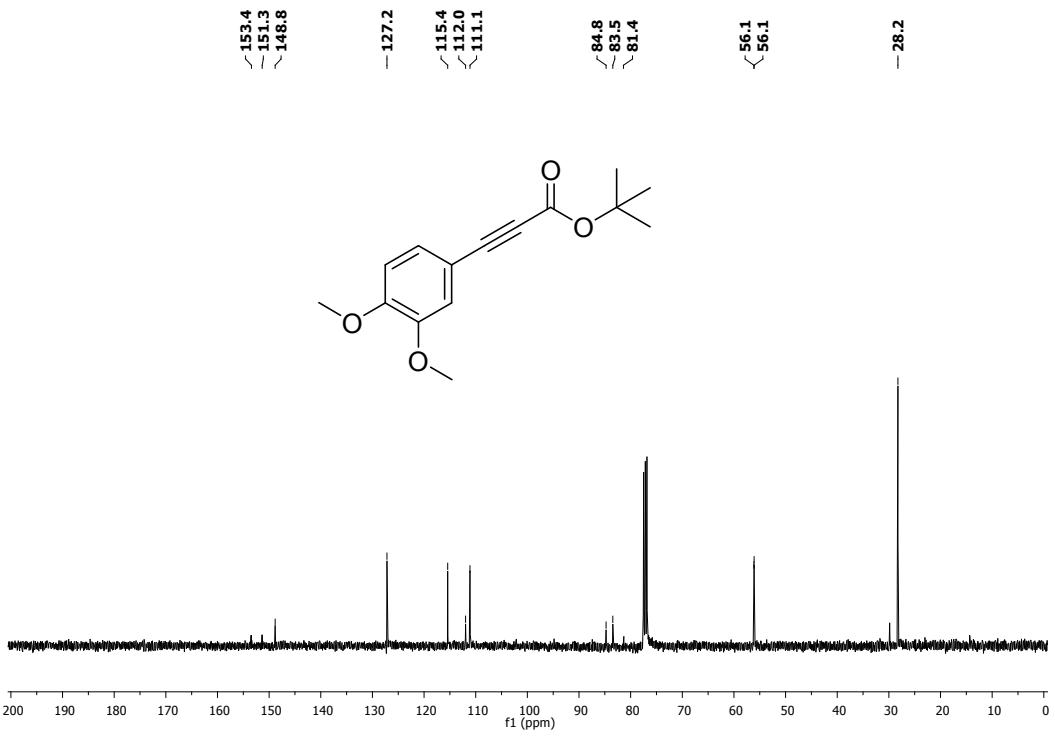

7.464
7.441
6.620
6.597
3.007
1.535
O
O
N
2.0
2.2
6.3
9.6
f1 (ppm)

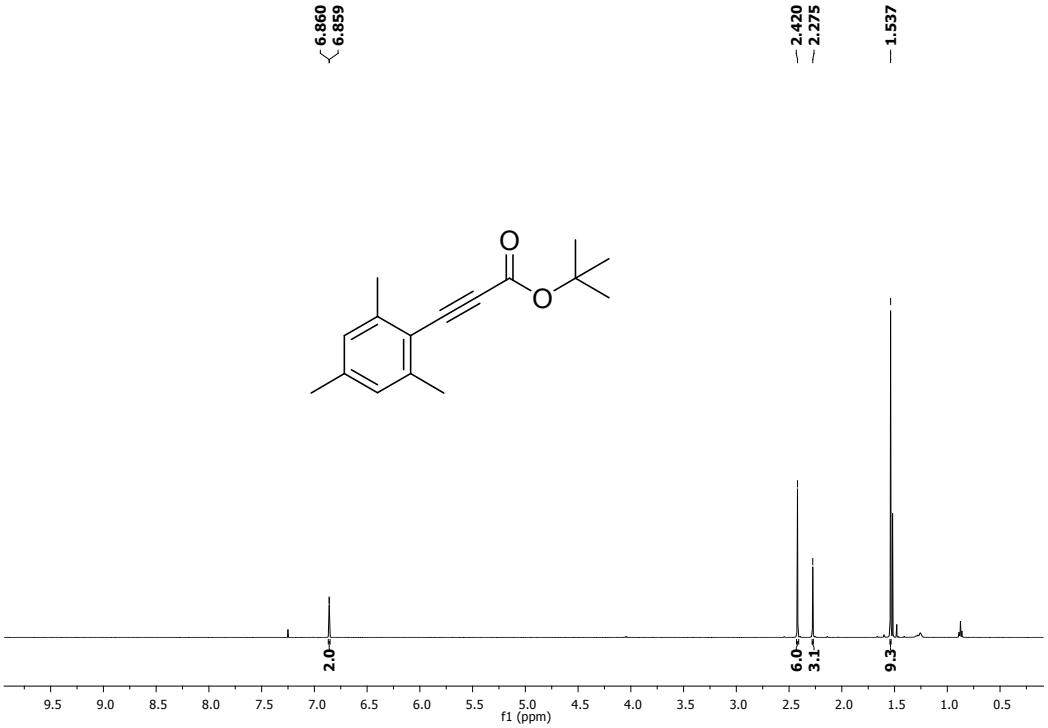

154.0
151.5
134.8
111.5
105.8
87.0
82.9
81.5
40.1
28.3
O
O
N
f1 (ppm)

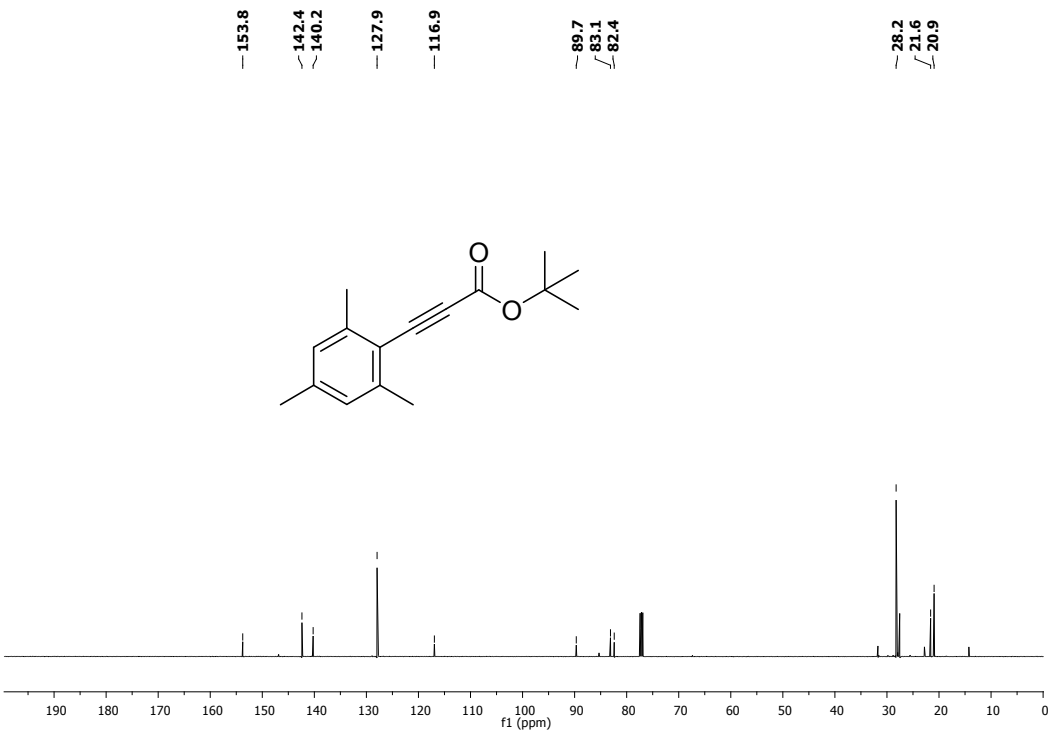

7.508
7.492
6.858
6.842
3.803
1.522
O
O
O
2.0
2.0
3.1
9.5
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

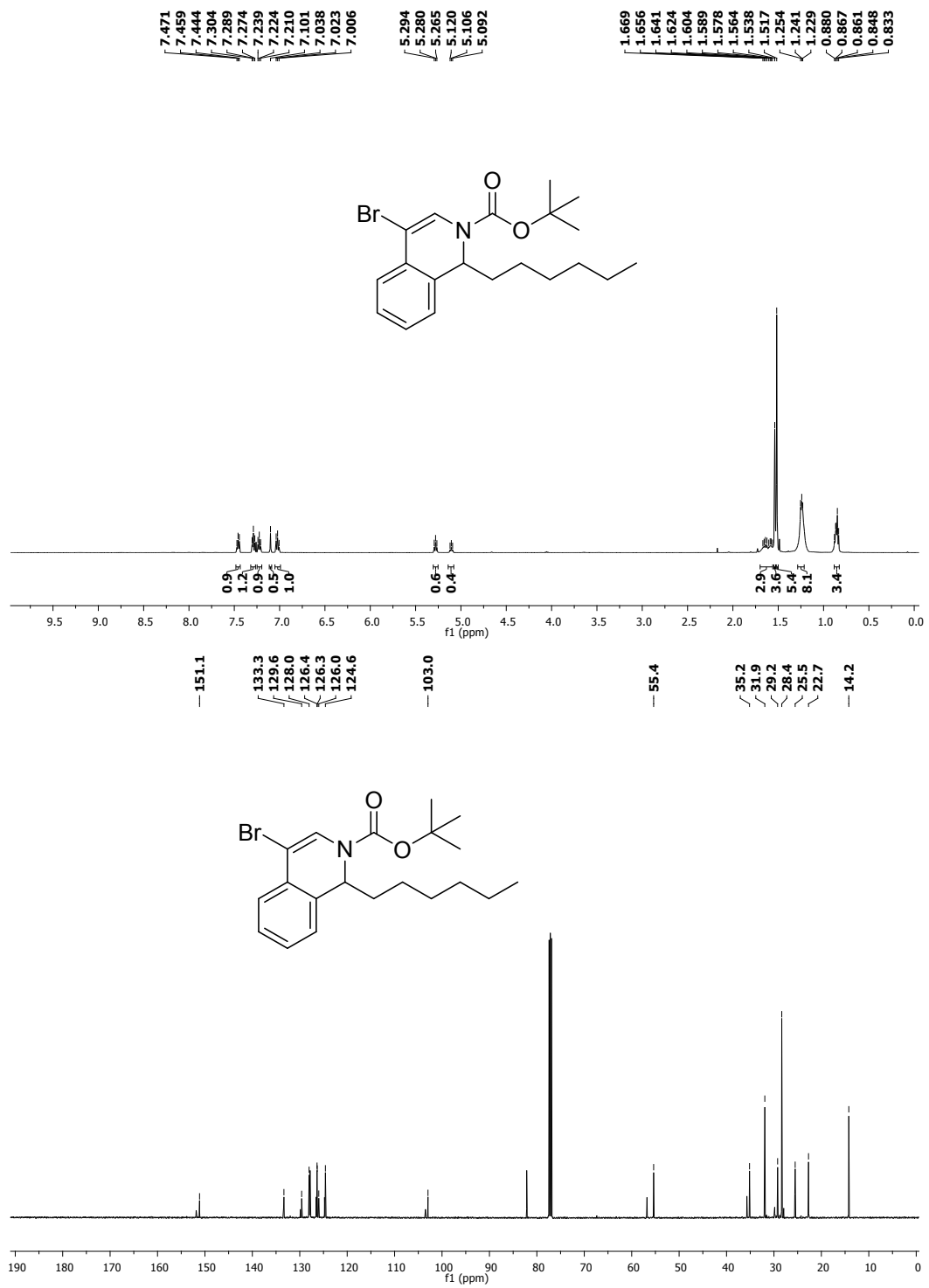

161.3
153.5
134.9
114.3
111.8
84.6
83.3
81.5
55.4
28.2
O
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

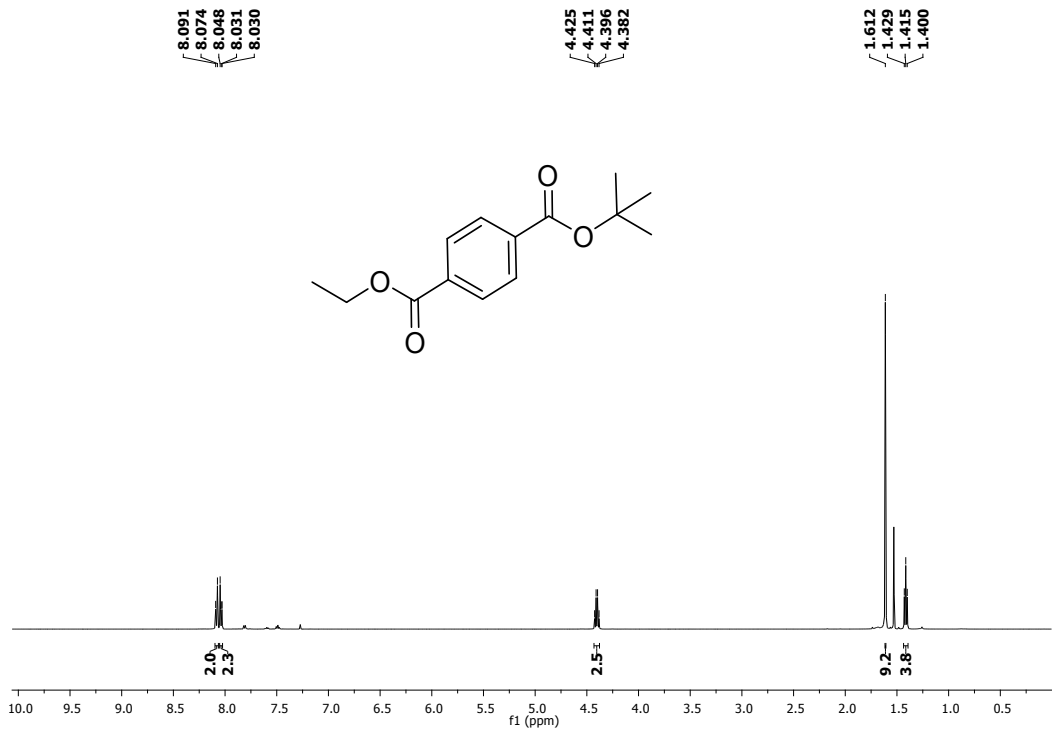

7.225
7.220
7.204
7.200
7.065
7.060
6.838
6.817
3.902
3.873
1.541
1.0
1.0
1.1
3.0
3.0
9.4
f1 (ppm)

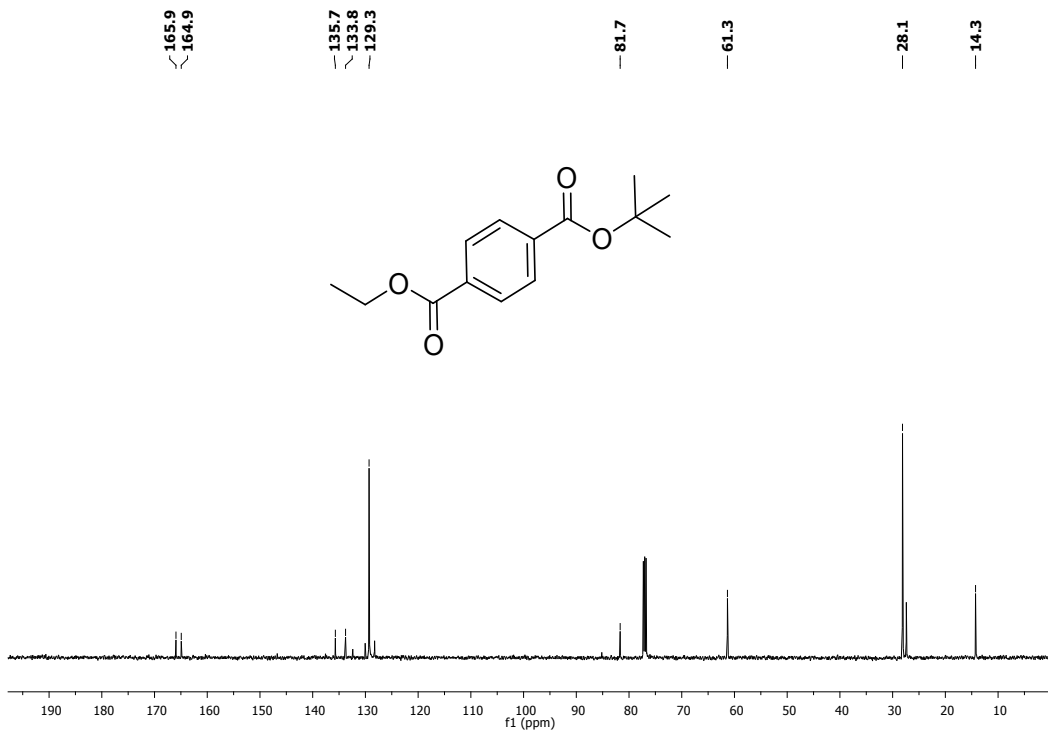

153.4
151.3
148.8
127.2
115.4
112.0
111.1
84.8
83.5
81.4
56.1
56.1
28.2
f1 (ppm)


6.860
6.859
2.420
2.275
1.537
O
O
2.0
6.0
3.1
9.3
9.5 9.0 8.5 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
f1 (ppm)


153.8
142.4
140.2
127.9
116.9
89.7
83.1
82.4
28.2
21.6
20.9
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.471
7.459
7.444
7.304
7.289
7.274
7.239
7.224
7.210
7.101
7.038
7.023
7.006
5.294
5.280
5.265
5.120
5.106
5.092
1.669
1.656
1.641
1.624
1.604
1.589
1.578
1.564
1.538
1.517
1.254
1.241
1.229
0.880
0.867
0.861
0.848
0.833
Br
N
O
O
0.9
1.2
0.9
0.5
1.0
0.6
0.4
2.9
3.6
5.4
8.1
3.4
f1 (ppm)
151.1
133.3
129.6
128.0
126.4
126.3
126.0
124.6
103.0
55.4
35.2
31.9
29.2
28.4
25.5
22.7
14.2
f1 (ppm)


8.091
8.074
8.048
8.031
8.030
4.425
4.411
4.396
4.382
1.612
1.429
1.415
1.400
O
O
O
O
2.0
2.3
2.5
9.2
3.8
10.0 9.5 9.0 8.5 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
f1 (ppm)


165.9
164.9
135.7
133.8
129.3
81.7
61.3
28.1
14.3
O
O
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

References

1. Degennaro L., Giovine A., Carroccia L., Luisi R. Practical Aspects of Organolithium Compounds in Lithium Compounds in Organic Synthesis: From Fundamentals to Applications, (R. Luisi, V. Capriati Eds.) 2014, Ch. 18 Pages 513-538.
2. Dinca E., Hartmann P., Smrček J., Dix I., Jones P. G., Jahn U. *Eur. J. Org. Chem*., **2012** , 24, 4461 – 4482.
3. Duguet, N.; Harrison-Marchand, A.; Maddaluna, J.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5745 – 5748.
4. Ghosh, K.; Molla, R. A.; Iqubal, Md. A.; Islam, S. M. *Green Chem.* **2015**, *17*, 3540 – 3551.
5. Nagaki, A.; Uesugi, Y.; Kim, H.; Yoshida, J.-ichi *Chem. Asian J.*, **2013**, *8*, 705-708.
6. Zhang H.; Renyi S.; Ding A.; Lu L.; Chen B.; Lei A. *Angew. Chem. Int. Ed.* **2012**, *51*, 12542 – 12545.
7. Wu, Y.; Li, X.; Zou, D.; Zhu, H.; Wang, Y.; Li, J.; Wu, Y. *Org. Lett*., **2014**, *16*, 7, 1836 – 1839.
8. Tyagi, V.; Fasan, R. *Angew. Chem. Int. Ed*., **2016**, *55*, 7, 2512 – 2516.