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SUPPLEMENTARY INFORMATION

Flow chemistry as a key parameter in reaction equilibrium control. Metal catalyzed cross-couplings under non-basic conditions

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Content:

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1. General Experimental:

Continuous-flow reactions were performed on reactor X-Cube™ (ThalesNano Inc., Hungary) at atmospheric pressure with flow rate 0.1-0.2 mL/min. NMR spectra (400 MHz for ^{1}H, 100 MHz for ^{13}C), (δ, ppm; *J*, Hz) were measured in hexadeuterated acetone or $CDCl_3$ and referenced to the solvent signal. Data are reported in the following order: chemical shifts; multiplicities are indicated br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Solvents were dried over 4 Å molecular sieves and titrated for water level with a Karl Fischer Coulometer (water content below 10 ppm). No degassing of solvents was necessary. Catalysts and were purchased from Aldrich, Acros Organics, Alfa-Aesar or Strem Chemicals and were used without further purification.

2. General Procedure for Sonogashira Coupling in Flow Regime

Continuous-flow reactions were performed on reactor X-Cube™ (ThalesNano Inc., Hungary; two CatCarts™ of 64 mm size, 4 mm i.d. in series connection, residence volume of the system was 6 mL). Substituted iodobenzene **1** (0.5 mmol) and aryl acetylene **2** (0.6 mmol) were dissolved in dried THF-DMA 9:1 (10 mL) and passed through the cartridges packed with commercially available Pd catalyst on a solid support[1] and 0.1% Cu_2O (Sigma-Aldrich) on alumina powder (made by evaporation of toluene suspension of both components) in the weight ratio of 17:1 (total amount of the catalyst was 1.9 g, average TON calculated from the total catalyst capacity was 120-150) at 80 °C in the same solvent composition with the flow rate 0.1 mL/min. GC yields were calculated from the correlated areas of reactant/product ratio. Isolation: To the eluate was added water (30 mL) and the mixture shaken with hexane (3x30 mL). The collected hexane portion was washed with brine and dried by $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (hexane:ether:acetone 30:1:2).

3. Continuous-Flow Preparation of Compounds 3a-3p:

4-(Phenylethynyl)toluene (**3a**): synthesized from 4-iodotoluene (**1a**, 0.109 g, 0.5 mmol) and phenylacetylene (**2a**, 0.062 g, 0.6 mmol), yield 0.0576 g (60%), m.p. 72.5-74.5 °C (ref.[2] 72.5-74 °C). ^{1}H NMR spectrum ($CDCl_3$): δ 7.55 – 7.50 (m, 2H), 7.43 (d, *J* = 8.1, 2H), 7.37 – 7.30 (m, 3H), 7.18 – 7.12 (m, 2H), 2.36 (s, 3H).

1,2-Diphenylethyne (**3b**): synthesized from iodobenzene (**1b**, 0.102 g, 0.5 mmol) and **2a** (0.062 g, 0.6 mmol), yield 0.0659 g (74%), m.p. 58.5-60.5 °C (ref.[3] 58-60 °C). ^{1}H NMR spectrum ($CDCl_3$): δ 7.55 – 7.50 (m, 4H), 7.37 – 7.30 (m, 6H).

2-Methyl-4-*p*-tolylbut-3-yn-2-ol (**3c**): synthesized from **1a** (0.109 g, 0.5 mmol) and 2-methylbut-3-yn-2-ol (**2b**, 0.050 g, 0.6 mmol), yield 0.0505 g (58%), m.p. 48.9-49.1 °C (ref.[4] 50-52 °C). ^{1}H NMR spectrum (cf. ref.[5]) ($CDCl_3$): δ 7.30 (d, *J* = 8.1, 2H), 7.11 (d, *J* = 7.8, 2H), 2.34 (s, 3H), 1.95 (br s, 1H), 1.61 (s, 6H). ^{13}C NMR spectrum ($(CD_3)_2CO$): δ 139.8 (C), 133.1 (2xCH), 130.9 (2xCH), 122.3 (C), 96.4 (C), 82.6 (C), 66.1 (C), 33.1 (2xCH_3), 22.3 (CH_3).

2-Methyl-4-nitro-1-(phenylethynyl)benzene (**3d**): synthesized from 1-iodo-2-methyl-4-nitrobenzene (**1c,** 0.132 g, 0.5 mmol) and **2a** (0.062 g, 0.6 mmol), LRMS (EI): m/z 237 (M^+). The product could not be obtained pure after column chromatography.

(Cyclopropylethynyl)benzene (**3e**): synthesized from **1b** (0.102 g, 0.5 mmol) and ethynylcyclopropane (**2c**, 0.040 g, 0.6 mmol), yield 0.0512 g (72%), oil. ^{1}H NMR spectrum (cf. ref.[6]) ($(CD_3)_2CO$): δ 7.35 (m, 2H), 7.30 (m, 3H), 1.48 (m, 1H), 0.89 (m, 2H), 0.73 (m, 2H). ^{13}C NMR spectrum ($(CD_3)_2CO$): δ 133.2 (2xCH), 130.1 (2xCH), 129.4 (CH), 125.9 (C), 95.2 (C), 77.3 (C), 9.8 (2xCH_2), 1.5 (CH).

3-(*p*-Tolylethynyl)pyridine (**3f**): synthesized from **1a** (0.109 g, 0.5 mmol) and 3-ethynylpyridine (**2d**, 0.062 g, 0.6 mmol), yield 0.0705 g (73%), colorless oil. ^{1}H NMR spectrum (cf. ref.[7]) ($CDCl_3$): δ 8.75 (d, 1H, *J* = 1.5 Hz), 8.53 (dd, 1H, *J* = 5.0, 1.5 Hz), 7.79 (dt, 1H, *J* = 1.75, 8.0 Hz), 7.44 (d, *J* = 8.1, 2H), 7.29-7.26 (m, 1H), 7.17 (d, *J* = 8.1, 2H).

1-Bromo-2-(phenylethynyl)benzene (**3g**): synthesized from **1b** (0.102 g, 0.5 mmol) and 1-bromo-2-ethynylbenzene (**2e**, 0.108 g, 0.6 mmol), catalyst: (5% Pd on alumina powder) : (0.1% Cu_2O on alumina powder) = 50:1; yield 0.0642 g (50%), isolated as colorless oil. ^{1}H NMR spectrum (cf. ref.[8]) ($(CD_3)_2CO$): δ 7.72 (m, 1H), 7.64 (m, 1H), 7.59 (m, 2H), 7.44 (m, 4H), 7.34 (m, 1H). ^{13}C NMR spectrum ($(CD_3)_2CO$): δ 135.2 (CH), 134.4 (CH), 133.3 (2xCH), 131.9 (2xCH), 130.8 (CH), 130.5 (CH), 129.5 (CH), 126.9 (C), 126.8 (C), 124.6 (C), 95.6 (C), 89.6 (C).

1-(4-(*p*-Tolylethynyl)phenyl)ethanone (**3h**): synthesized from **1a** (0.109 g, 0.5 mmol) and 1-(4-ethynylphenyl)ethanone (**2f**, 0.087 g, 0.6 mmol), yield 0.0714 g (61%), m.p. 122.7-123.0

°C (ref.[9] 126-127 °C). ^{1}H NMR spectrum (cf. ref.[9]) ($(CD_3)_2$)CO): δ 8.09 (d, *J* = 8.8, 2H), 7.67 (d, *J* = 8.6, 2H), 7.47 (d, *J* = 8.1, 2H), 7.27 (d, *J* = 7.8, 2H), 2.61 (s, 3H), 2.37 (s, 3H).

1-Fluoro-4-(phenylethynyl)benzene (**3i**): synthesized from **1b** (0.102 g, 0.5 mmol) and 1-ethynyl- 4-fluorobenzene (**2g**, 0.072 g, 0.6 mmol), yield 0.0716 g (73%), m.p. 107.8-109.7 °C (ref.[10] 108-111 °C). ^{1}H NMR spectrum (cf. ref.[10]) ($CDCl_3$): δ 7.53 (m, 4H), 7.35 (m, 3H), 7.05 (m, 2H). ^{13}C NMR spectrum ($(CD_3)_2$)CO): δ 165.7 (C), 135.5 (2xCH), 133.3 (2xCH), 130.4 (2xCH), 125.5 (C), 121.4 (C), 117.7 (2xCH), 117.5 (CH), 90.7 (C), 89.9 (C).

1-Fluoro-4-(*p*-tolylethynyl)benzene (**3j**): synthesized from **1a** (0.109 g, 0.5 mmol) and **2g** (0.072 g, 0.6 mmol), yield 0.0651 g (62%), m.p. 97.6-98.2 °C (ref.[11] 91-92 °C). ^{1}H NMR spectrum (cf. ref.[11]) ($(CD_3)_2$)CO): δ 7.58 (m, 2H), 7.42 (m, 2H), 7.19 (m, 4H), 2.90 (s, 3H). ^{13}C NMR spectrum ($(CD_3)_2$)CO): δ 165.6 (C), 140.6 (C), 135.4 (2xCH), 133.2 (2xCH), 131.1 (2xCH), 121.8 (C), 121.6 (C), 117.6 (2xCH), 90.9 (C), 89.2 (C), 22.4 (CH_3).

4-(Pyridin-3-ylethynyl)benzaldehyde (**3k**): synthesized from 4-iodobenzaldehyde (**1d**, 0.116 g, 0.5 mmol) and **2d** (0.062 g, 0.6 mmol), yield 0.0466 g (45%), m.p. 96.5-98.0 °C (ref.[12] 98.5-99.3 °C). ^{1}H NMR spectrum (cf. ref.[13]) ($CDCl_3$): δ 10.09 (s, 1H), 8.83 (br s, 1H), 8.66 (br s, 1H), 7.99 (d, *J* = 8.1, 2H), 7.95 (d, *J* = 6.1, 1H), 7.80 (d, *J* = 8.1, 2H), 7.49 (br m, 1H).

1-Bromo-2-(*p*-tolylethynyl)benzene (**3l**): synthesized from **1a** (0.109 g, 0.5 mmol) and **2e** (0.108 g, 0.6 mmol), catalyst: (5% Pd on alumina powder) : (0.1% Cu_2O on alumina powder) = 50:1; yield 0.0786 g (58%), isolated as colorless oil. ^{1}H NMR spectrum (cf. ref.[14]) ($(CD_3)_2$)CO): δ 7.70 (d, *J* = 8.1, 1H), 7.62 (d, *J* = 7.6, 1H), 7.48 (d, *J* = 8.1, 2H), 7.41 (m, 1H), 7.31 (m, 1H), 7.25 (d, *J* = 7.8, 2H), 2.36 (s, 3H). ^{13}C NMR spectrum ($(CD_3)_2$)CO): δ 141.1 (C), 135.1 (CH), 134.4 (CH), 133.3 (2xCH), 131.7 (2xCH), 131.2 (CH), 129.4 (CH), 127.2 (C), 126.8 (C), 121.6 (C), 95.9 (C), 89.0 (C), 22.5 (CH_3).

3-(Phenylethynyl)pyridine (**3m**): synthesized from **1b** (0.102 g, 0.5 mmol) and **2d** (0.062 g, 0.6 mmol), yield 0.0582 g (65%), m.p. 50.5-52 °C (ref.[15] 50-51 °C). ^{1}H NMR spectrum ($CDCl_3$): δ 8.77 (d, 1H, *J* = 1.5 Hz), 8.55 (dd, 1H, *J* = 5.0, 1.5 Hz), 7.81 (dt, 1H, *J* = 1.75, 8.0 Hz), 7.56-7.53 (m, 2H), 7.38-7.36 (m, 3H), 7.30-7.27 (m, 1H).

4-(Cyclopropylethynyl)toluene (**3n**): synthesized from **1a** (0.109 g, 0.5 mmol) and **2c** (0.040 g, 0.6 mmol), yield 0.0663 g (85%), oil. ^{1}H NMR spectrum (cf. ref.[6]) ($(CD_3)_2$)CO): δ 7.23 (d, *J* = 8.1, 2H), 7.11 (d, *J* = 7.8, 2H), 2.30 (s, 3H), 1.46 (m, 1H), 0.87 (m, 2H), 0.70 (m, 2H). ^{13}C

NMR spectrum ($(CD_3)_2$)CO): δ 139.2 (C), 133.2 (2xCH), 130.8 (2xCH), 122.9 (C), 94.3 (C), 77.4 (C), 22.3 (CH_3), 9.8 (2xCH_2), 1.6 (CH).

2-Methyl-4-phenylbut-3-yn-2-ol (**3o**): synthesized from **1b** (0.102 g, 0.5 mmol) and **2b** (0.050 g, 0.6 mmol), yield 0.0504 g (63%), m.p. 53.5-53.8 °C (ref.[16] 52-54 °C). ^{1}H NMR spectrum (cf. ref.[16]) ($(CD_3)_2$)CO): δ 7.41 (m, 2H), 2.03 (br s, 1H), 1.62 (s, 6H). ^{13}C NMR spectrum ($(CD_3)_2$)CO): δ 133.2 (2xCH), 130.2 (2xCH), 129.9 (CH), 125.3 (C), 97.1 (C), 82.6 (C), 66.1 (C), 33.0 (2xCH_3).

4-(Phenylethynyl)benzaldehyde (**3p**): synthesized from **1d** (0.123 g, 0.5 mmol) and **2a** (0.062 g, 0.6 mmol), yield 0.0773 g (75%), m.p. 95.5-98 °C (ref.[17] 96.5-98 °C). ^{1}H NMR spectrum ($CDCl_3$): δ 10.02 (s, 1H), 7.87 (ddd, J = 0.4, 1.6, 8.1, 2H), 7.68 (ddd, J = 0.4, 1.6, 8.1, 2H), 7.58-7.54 (m, 2H), 7.36 – 7.40 (m, 3H).

4. Preparation of Compounds 5 and 6

Sonogashira cross-coupling of base-sensitive substrate (batch reaction): 1-Benzyltetrahydro-1*H*-thiophenium hexafluorophosphate[18] (**4**, 0.128 g, 0.4 mmol), phenylacetylene (**2a**, 0.042 g, 0.4 mmol) and potassium carbonate (0.5 g) were suspended in DMA (5 mL). The catalyst (5% Pd on alumina powder) : (0.1% Cu_2O on alumina powder) = 17:1; 0.040 g was added and the reaction mixture heated to 80 °C with stirring under Ar atmosphere. After 16 h, the UPLC analysis showed complete conversion of the starting sulfonium salt. The reaction mixture was poured to 5% HCl (30 mL) and shaken with ether (5x30 mL). The collected ether portion was washed with brine and dried by $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (hexane:ether:acetone (30:1:2). The obtained colorless oil (0.040 g) was identified as 2-*o*-tolyltetrahydrothiophene (**6**, Scheme 3), which is the usual product of the Sommelet-Hauser rearrangement of the starting sulfonium salt in the presence of bases[19]. Yield 57%, *m/z* (EI) 178, ^{1}H NMR spectrum ($CDCl_3$) (cf. ref.[19]): δ 7.61 (d, J = 7.0, 1H), 7.12-7.24 (m, 3H), 4.76 (dd, J = 8.0, 5.9, 1H), 3.12-3.18 (m, 1H), 3.00-3.08 (m, 1H), 2.40 (s, 3H), 2.25-2.39 (m, 2H), 1.93-2.09 (m, 2H).

Continuous flow reaction: 1-Benzyltetrahydro-1*H*-thiophenium hexafluorophosphate[18] (**4**, 0.128 g, 0.4 mmol) and phenylacetylene (**2a**, 0.042 g, 0.4 mmol) were dissolved in DMA (10 mL) and passed through the cartridges packed with (5% Pd on alumina powder) : (0.1% Cu_2O on alumina powder) = 17:1 at 80 °C at flow 0.3 mL/min. To the solution was then added water (30 mL) and the mixture shaken with hexane (3x30 mL). The collected hexane portion

was washed with brine and dried by $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (hexane:ether:acetone 30:1:2). The obtained colorless oil (0.052 g) was identified as the Sonogashira product, 1,3-diphenylpropyne (**5**). Yield 70%, *m/z* (EI) 192, ^{1}H NMR spectrum ($CDCl_3$) (cf. ref.[20]): δ 7.39-7.44 (m, 4H), 7.18-7.36 (m, 6H), 3.81 (s, 2H).

5. Control Experiments

Reaction of copper acetylide with HI in batch regime: Copper(I) phenylacetylide (0.033 g, 0.2 mmol), lithium chloride (0.0084 g, 0.2 mmol), 4-iodotoluene (**1a**, 0.044 g, 0.2 mmol), degassed dried DMA (4 mL), and $Pd(PPh_3)_4$ (0.002 g, cat.) were stirred at 90 °C for 3 h in the presence of 0.00, 0.25, 0.50, 0.75 and 1.00 equivalents of 48% hydriodic acid. The course of the reaction was monitored with GC-MS.

Control experiments in batch regime: **Sonogashira protocol:** 4-Iodotoluene (**1a**, 0.109 g, 0.5 mmol) and phenylacetylene (**2a**, 0.062 g, 0.6 mmol) were dissolved in THF-DMA 9:1 (10 mL). The catalyst (5% Pd on alumina powder) : (0.1% Cu_2O on alumina powder) = 17:1; 1.900 g was added and the reaction mixture heated to 75 °C with stirring under Ar atmosphere. After 72 h, less than 2 % of the Sonogashira product **3a** was formed in the reaction mixture (detection: UPLC-MS, GC-MS).

6. Optimization Procedures

The continuous flow Sonogashira reaction between 4-iodotoluene (**1a**) and phenylacetylene (**2a**) was optimized on catalyst (Table 1), Cu_2O content (Table 2), and solvent (Table 3).

Table 1. Optimization of the continuous flow Sonogashira reaction on catalyst[a]

	Catalyst	GC yield (%)
1	10% Pd/C	7
2	Polymer-bound $Pd(PPh_3)_4$	12
3	Polyurea-encapsulated palladium (Pd(0)EnCat™ 30)	50
4	Polyurea-encapsulated $Pd(OAc)_2$ (Pd(II)EnCat™ 30)	74
5	5% Pd/Al_2O_3 (EsCat™ 1241)	76
6	$Pd(OAc)_2$ on polymer fibre (FibreCat™ 1001)	84[b]

[a]Reaction conditions: mixed catalyst with 0.1% Cu_2O/Al_2O_3 (Pd:Cu catalyst 17:1); 0.1 mmol 4-iodotoluene (**1a**), 0.12 mmol phenylacetylene (**2a**), 2 mL DMA, flow 0.3 mL/min, 80 °C. [b]Strong Pd leaching was observed.

Table 2. Dependence of the Sonogashira/Glaser product ratio on the Cu_2O content[a]

	Cu_2O content on Al_2O_3 (%)	(EsCat™ 1241): (Cu_2O on Al_2O_3)	GC total yield (%)	Sonogashira/Glaser product
1	10	1:2	79	11/89
2	5	1:2	70	71/29
3	1	1:1	67	80/20
4	0.1	17:1	76	100/0

[a]Reaction conditions: mixed catalyst (Escat™ 1241) : (Cu_2O on alumina powder); 0.1 mmol 4-iodotoluene (**1a**), 0.12 mmol phenylacetylene (**2a**), 2 mL DMA, flow 0.3 mL/min, 80 °C.

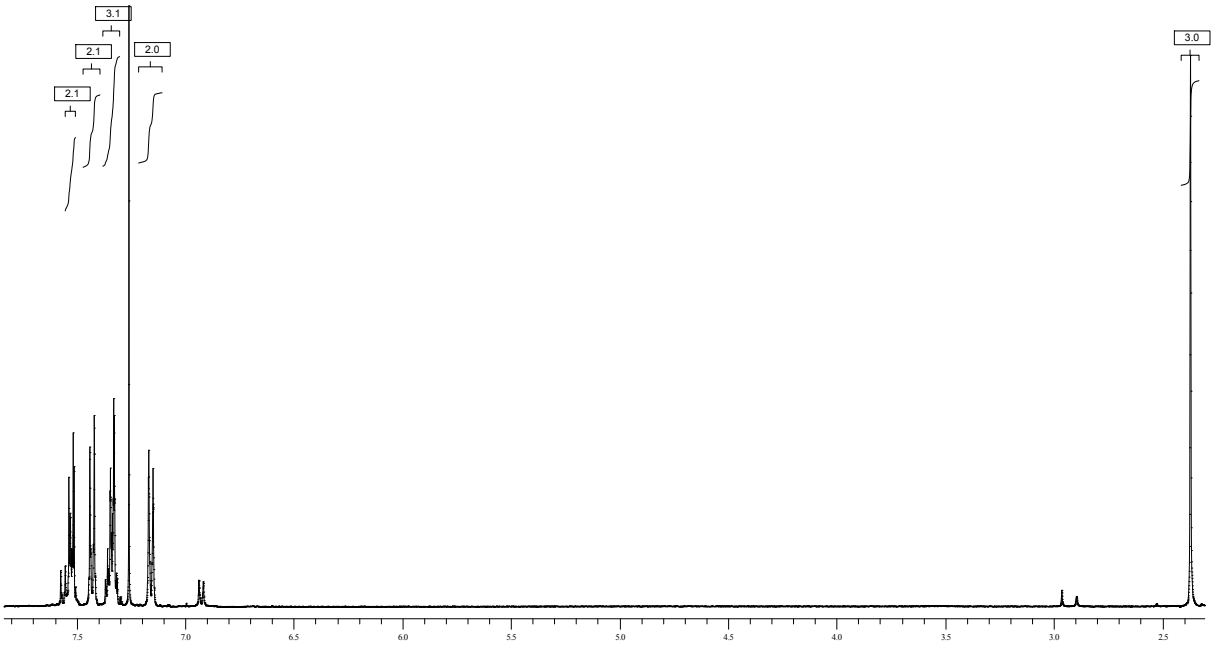
Table 3. Optimization of the continuous flow Sonogashira reaction on solvent[a]

	Solvent	GC yield (%)
1	THF	<1
2	EtOH	6
3	dioxane	8
4	DMF	15
5	NMP[b]	28
6	DMA	76
7	THF:DMA 9:1	76

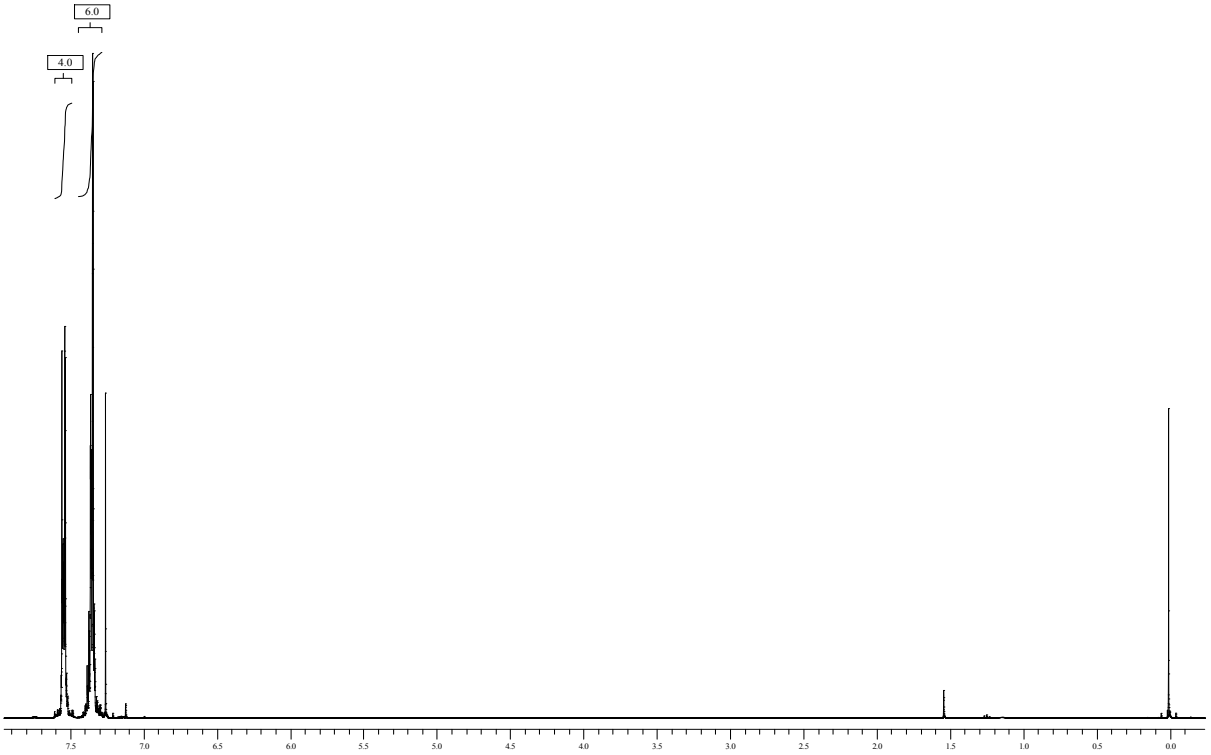
[a]Reaction conditions: mixed catalyst (Escat™ 1241) : (0.1% Cu_2O on alumina powder) = 17:1; 0.1 mmol 4-iodotoluene (**1a**), 0.12 mmol phenylacetylene (**2a**), 2 mL of solvent, flow 0.3 mL/min, 80 °C. [b]At 120 °C.

7. NMR Spectra

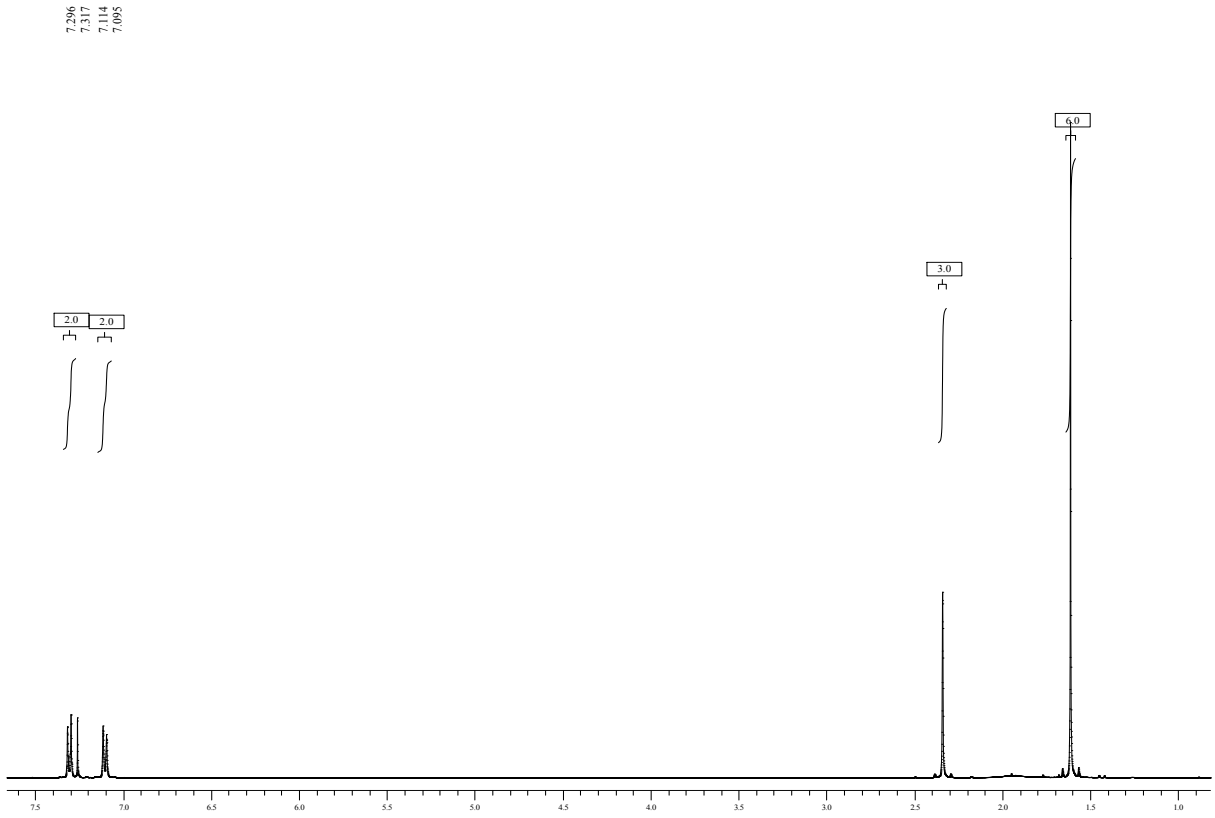
4-(Phenylethynyl)toluene (**3a**)



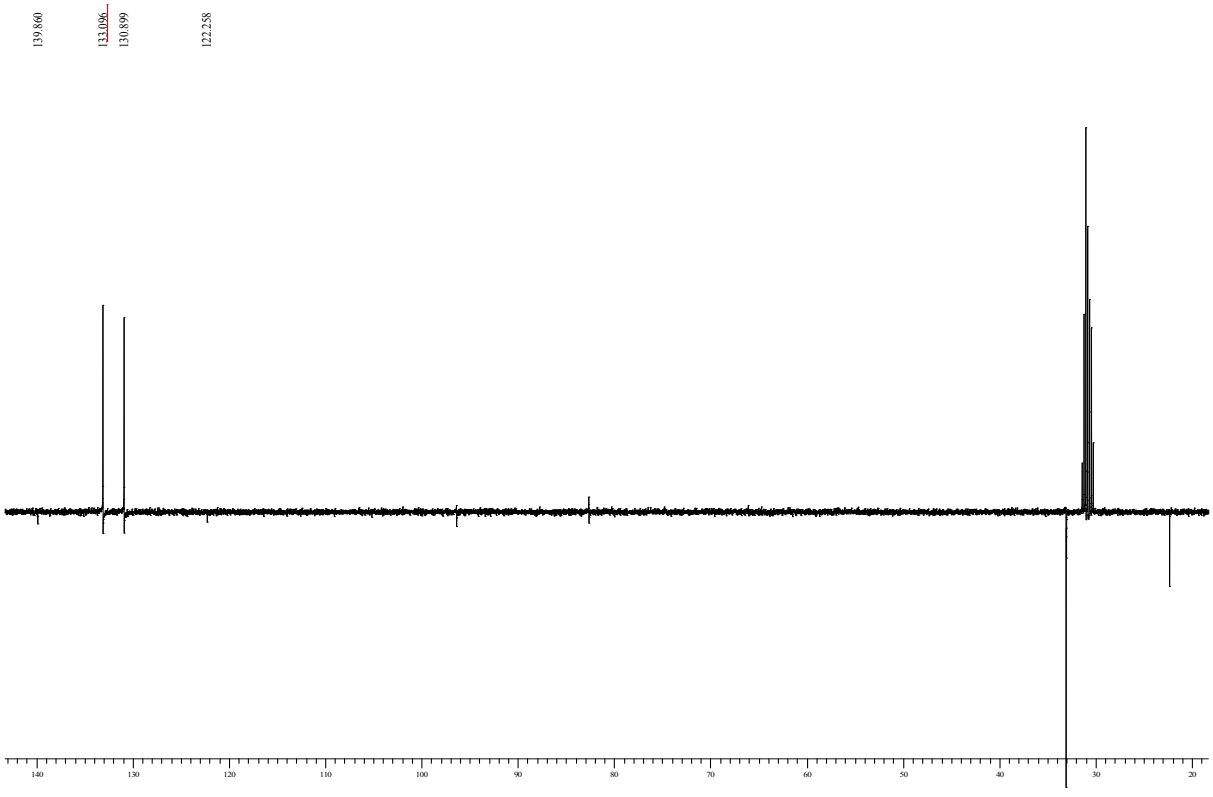
1,2-Diphenylethyne (**3b**)



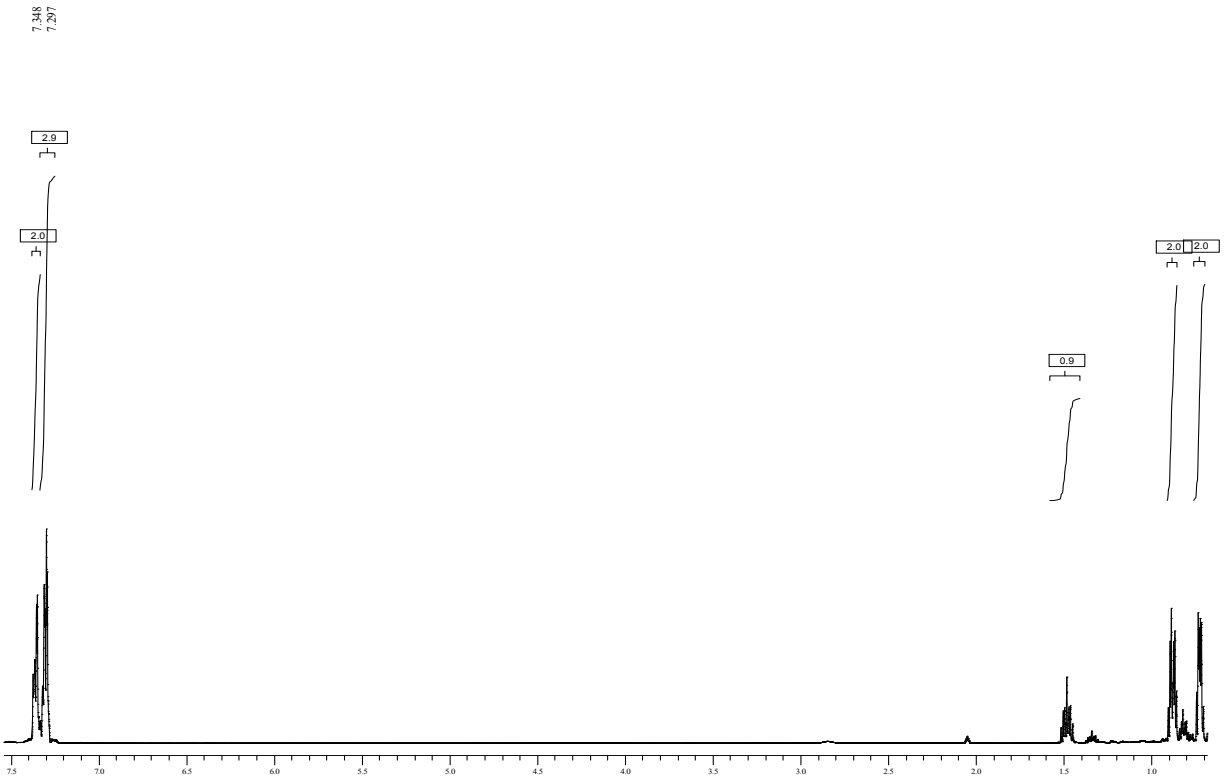
2-Methyl-4-*p*-tolylbut-3-yn-2-ol (**3c**)



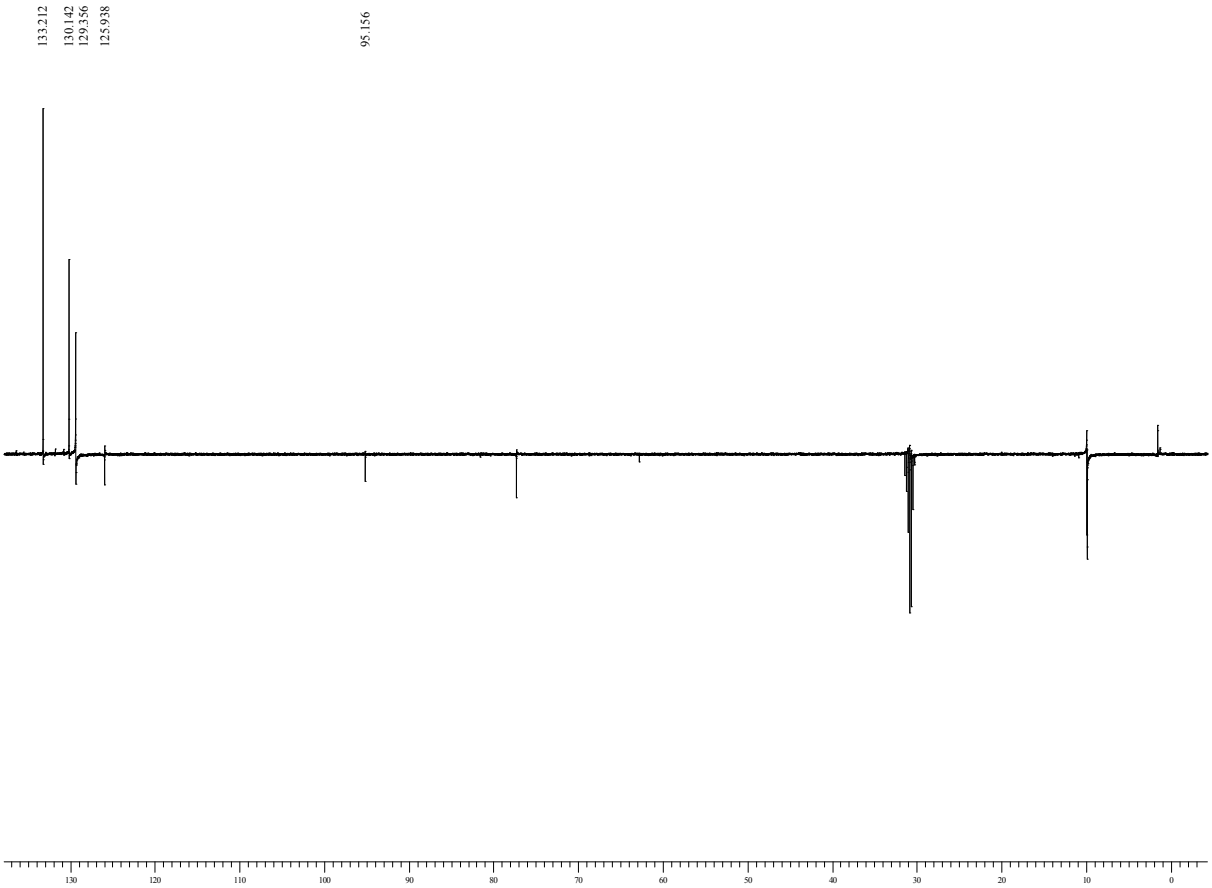
Compound **3c** (^{13}C NMR)



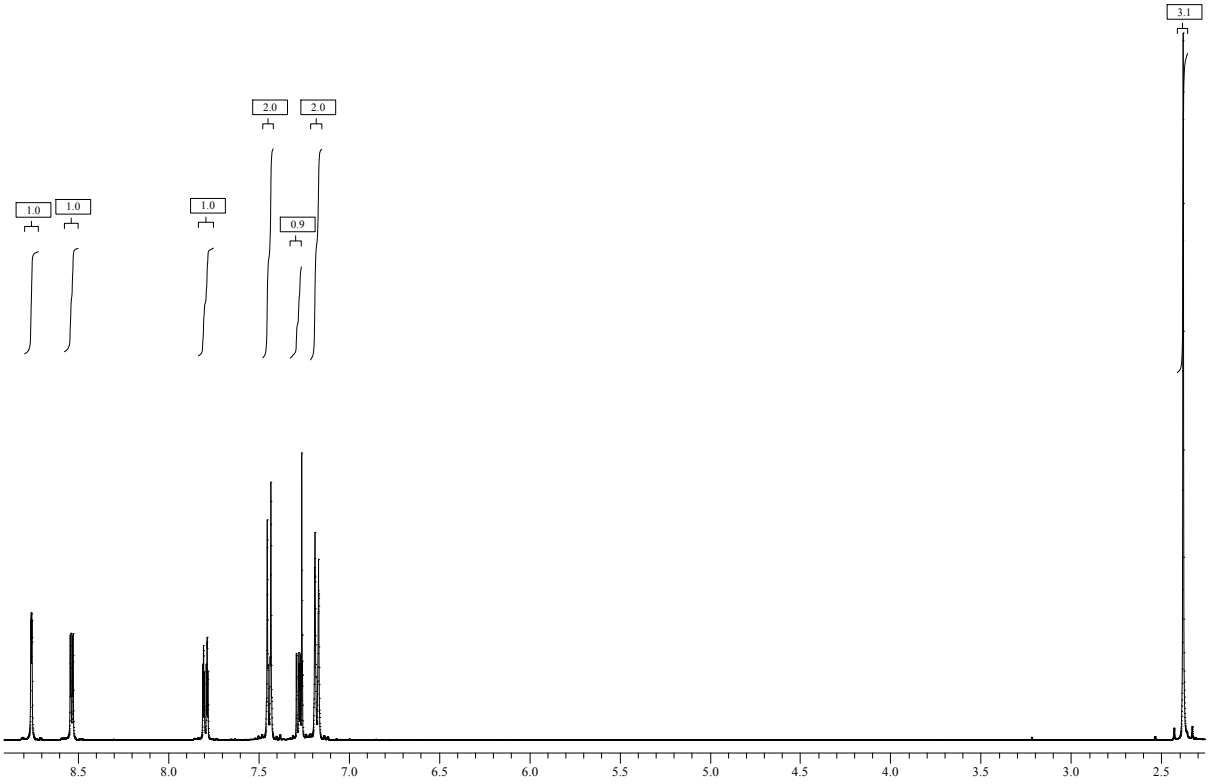
(Cyclopropylethynyl)benzene (**3e**)



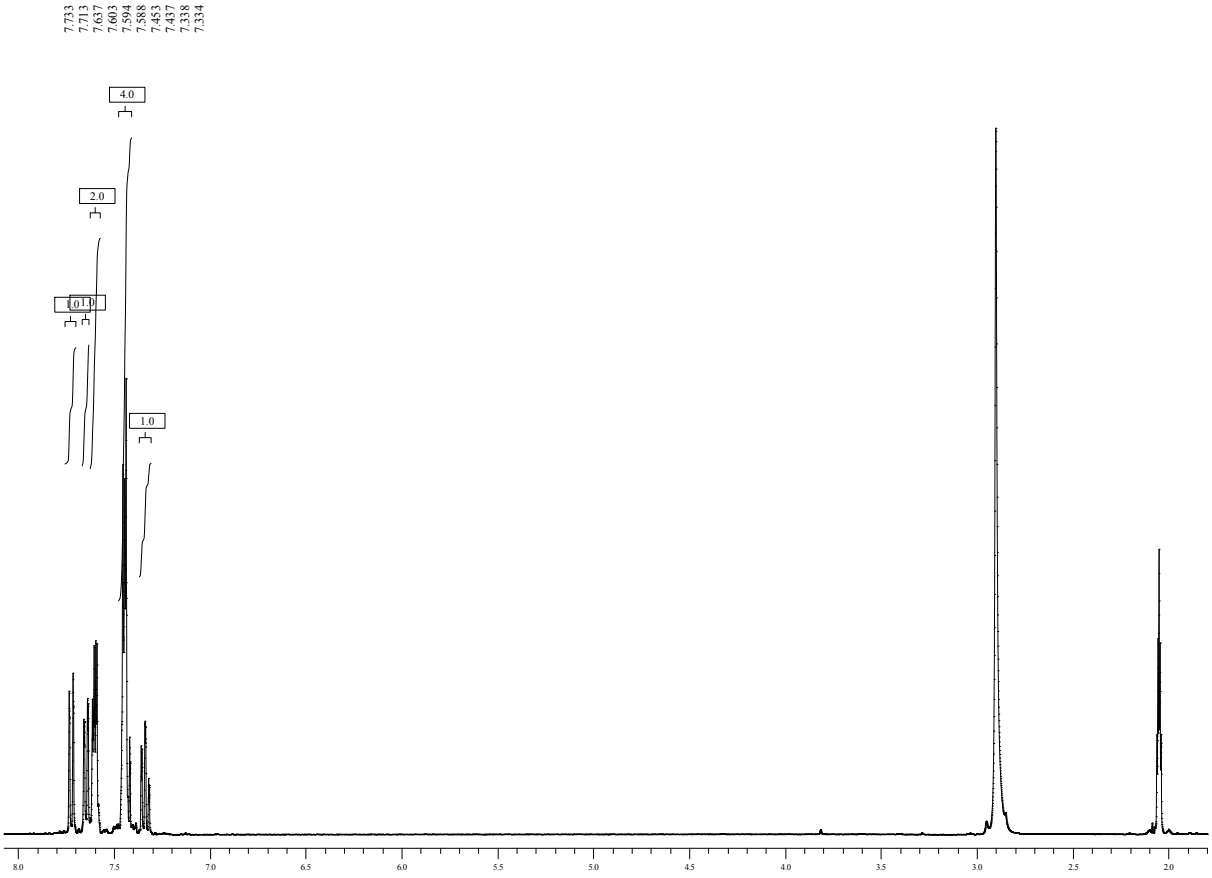
Compound **3e** (^{13}C NMR)



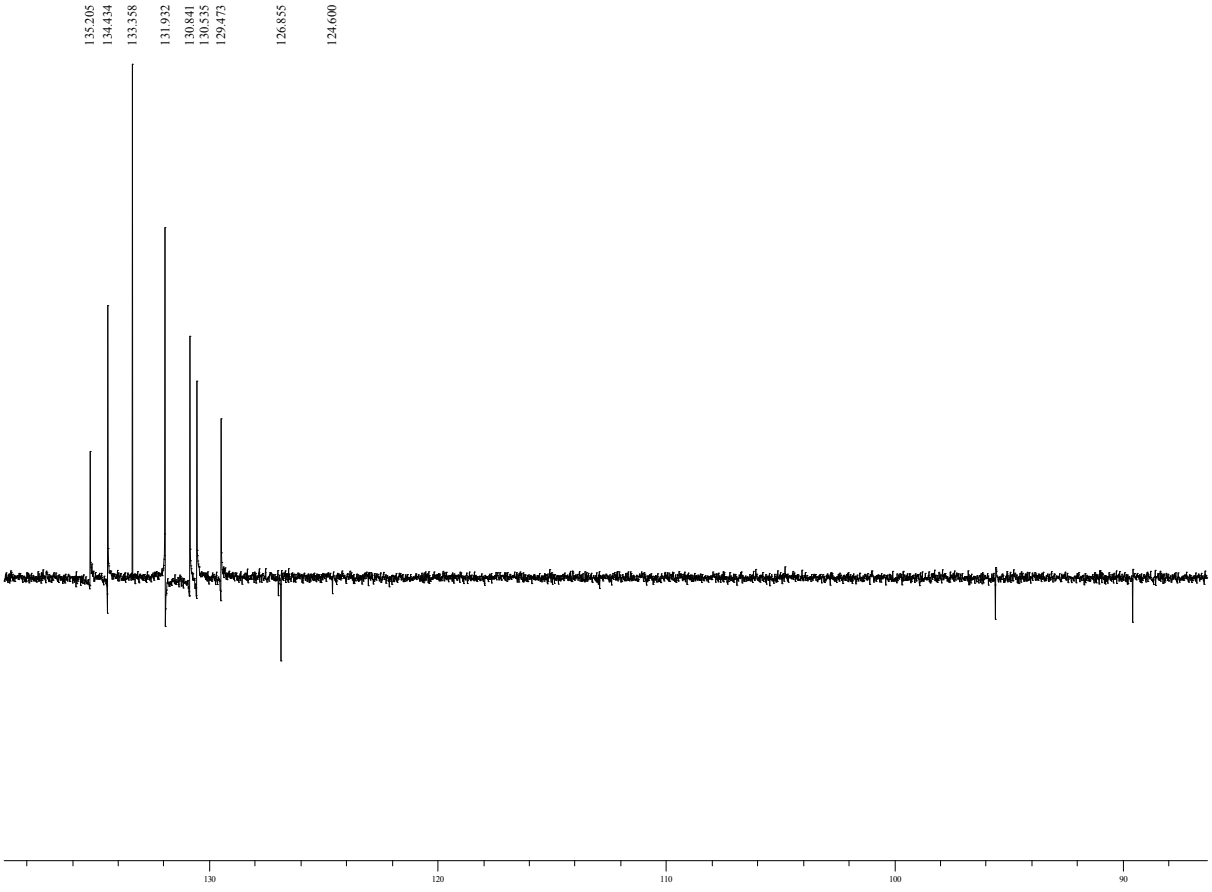
3-(*p*-Tolylethynyl)pyridine (**3f**)



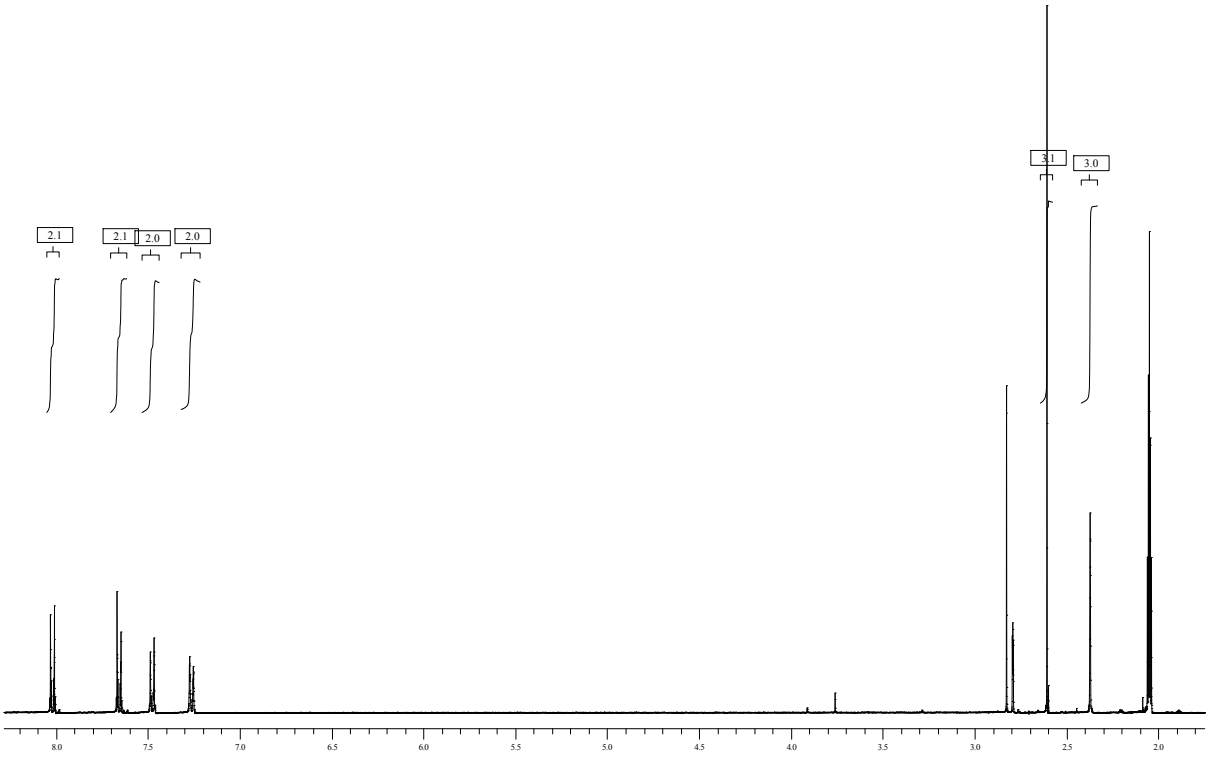
1-Bromo-2-(phenylethynyl)benzene (**3g**)



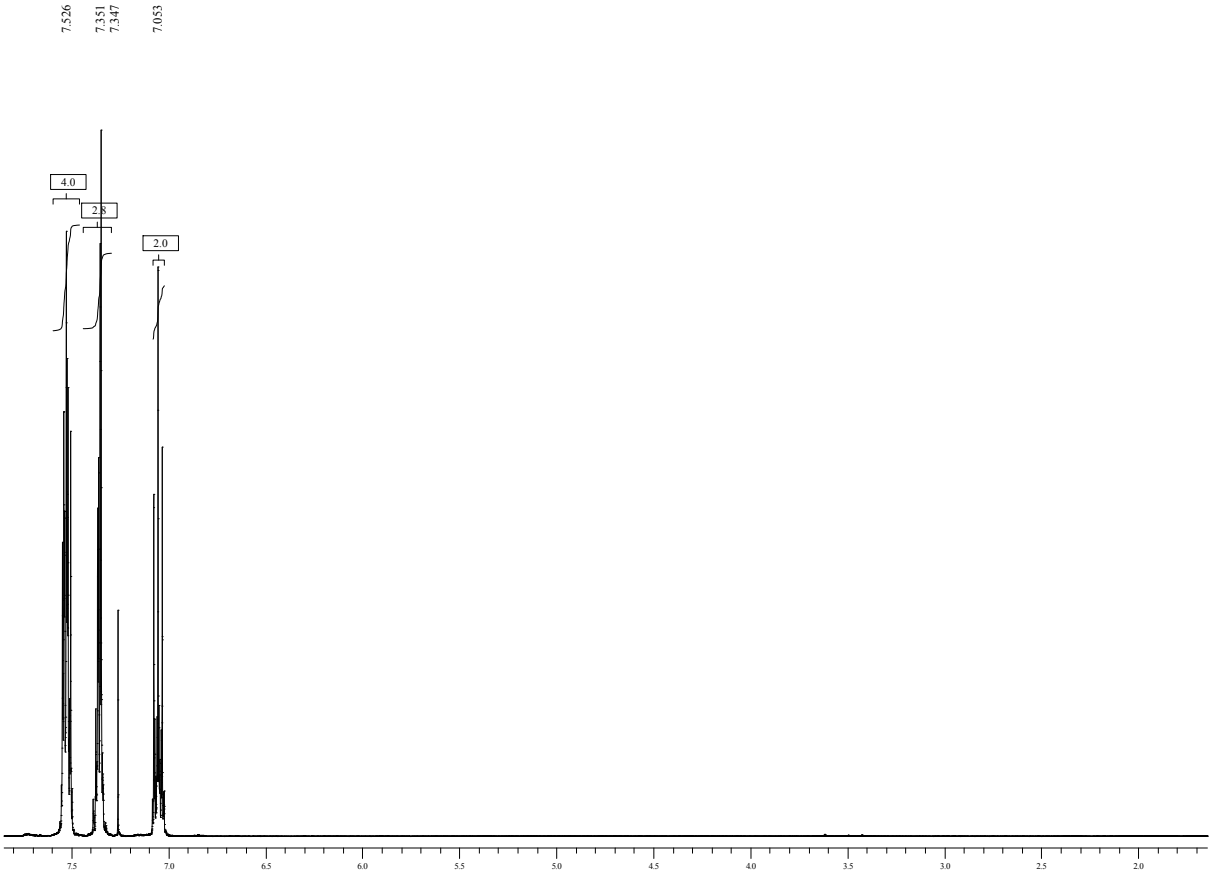
Compound **3g** (^{13}C NMR)



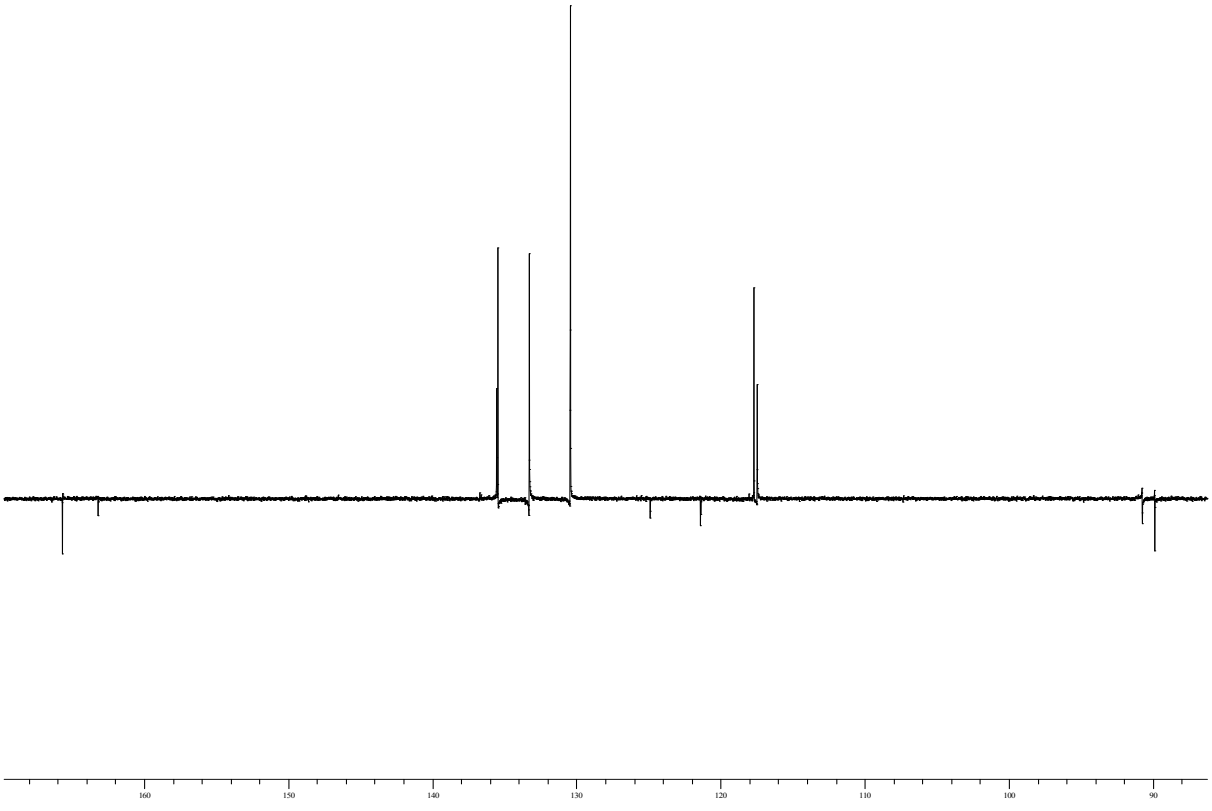
1-(4-(*p*-Tolylethynyl)phenyl)ethanone (**3h**)



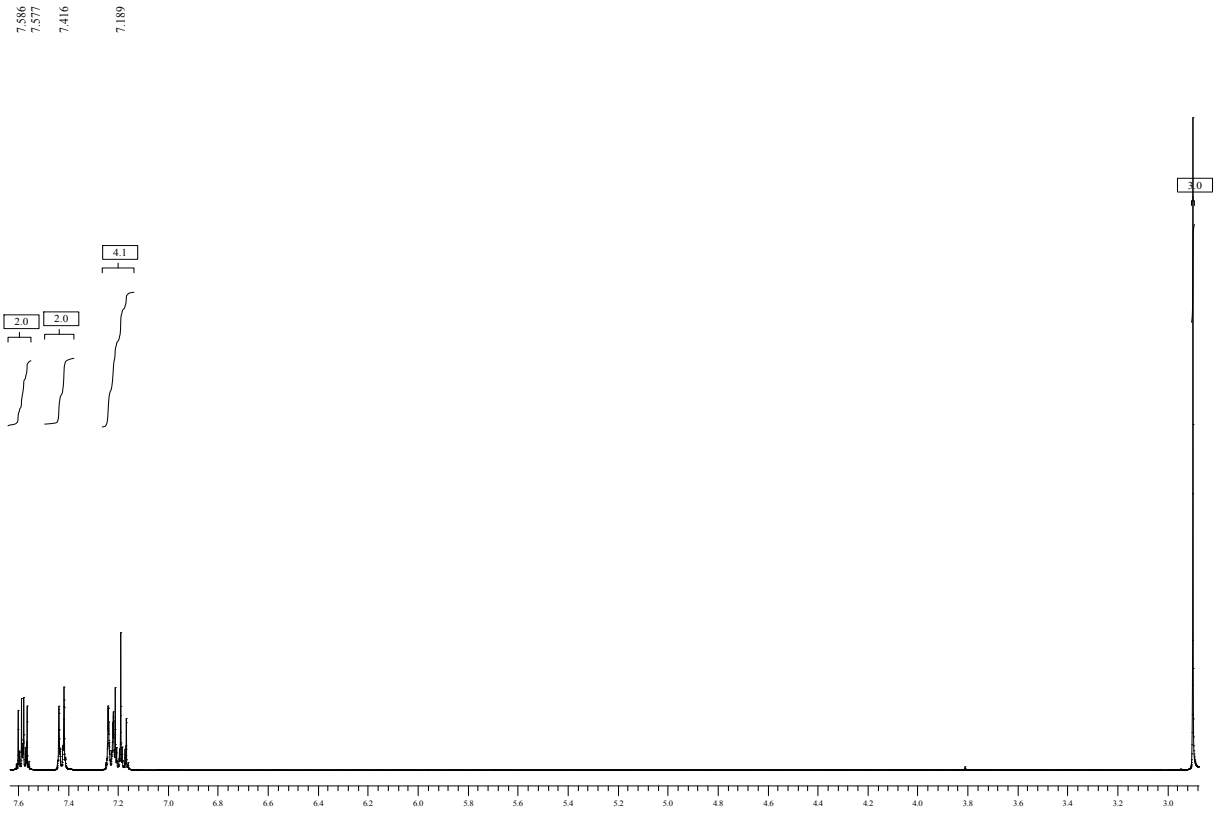
1-Fluoro-4-(phenylethynyl)benzene (**3i**)



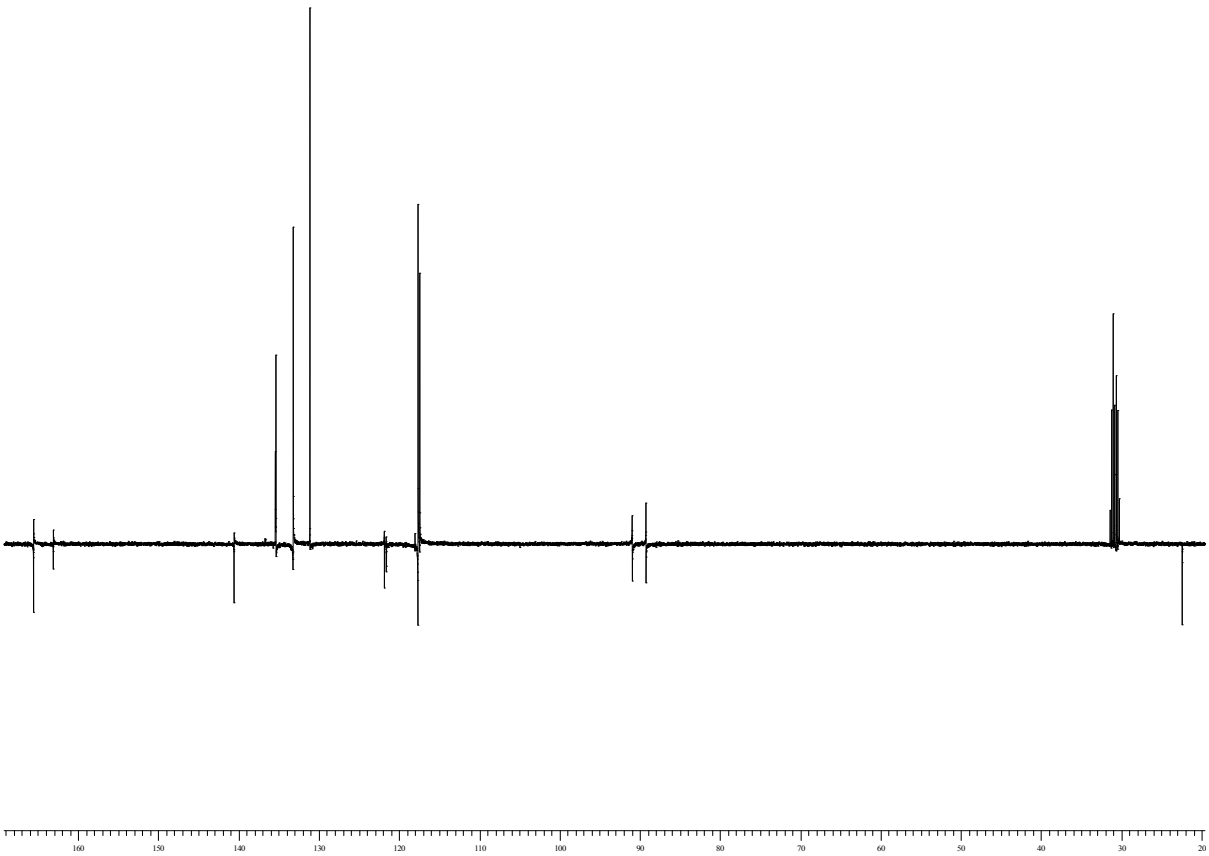
Compound **3i** (^{13}C NMR)



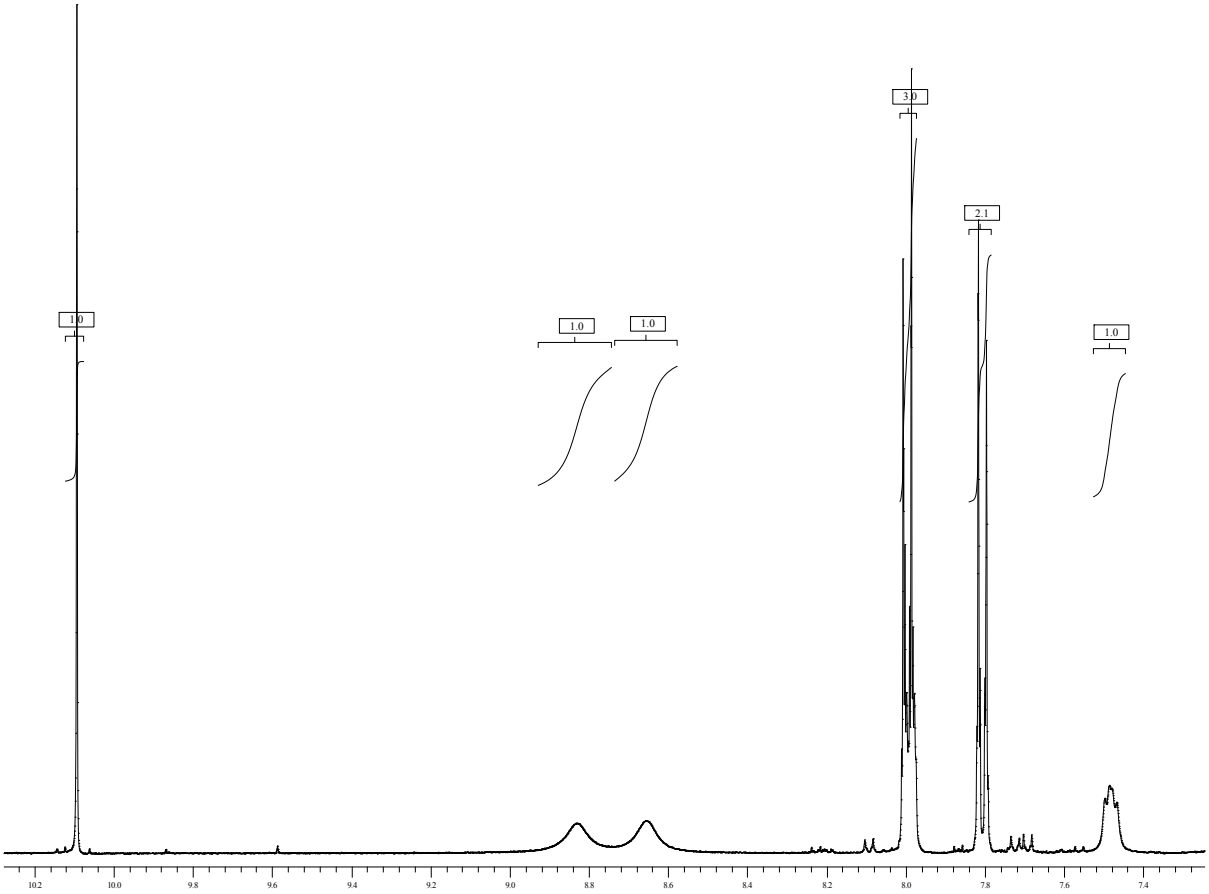
1-Fluoro-4-(*p*-tolylethynyl)benzene (**3j**)



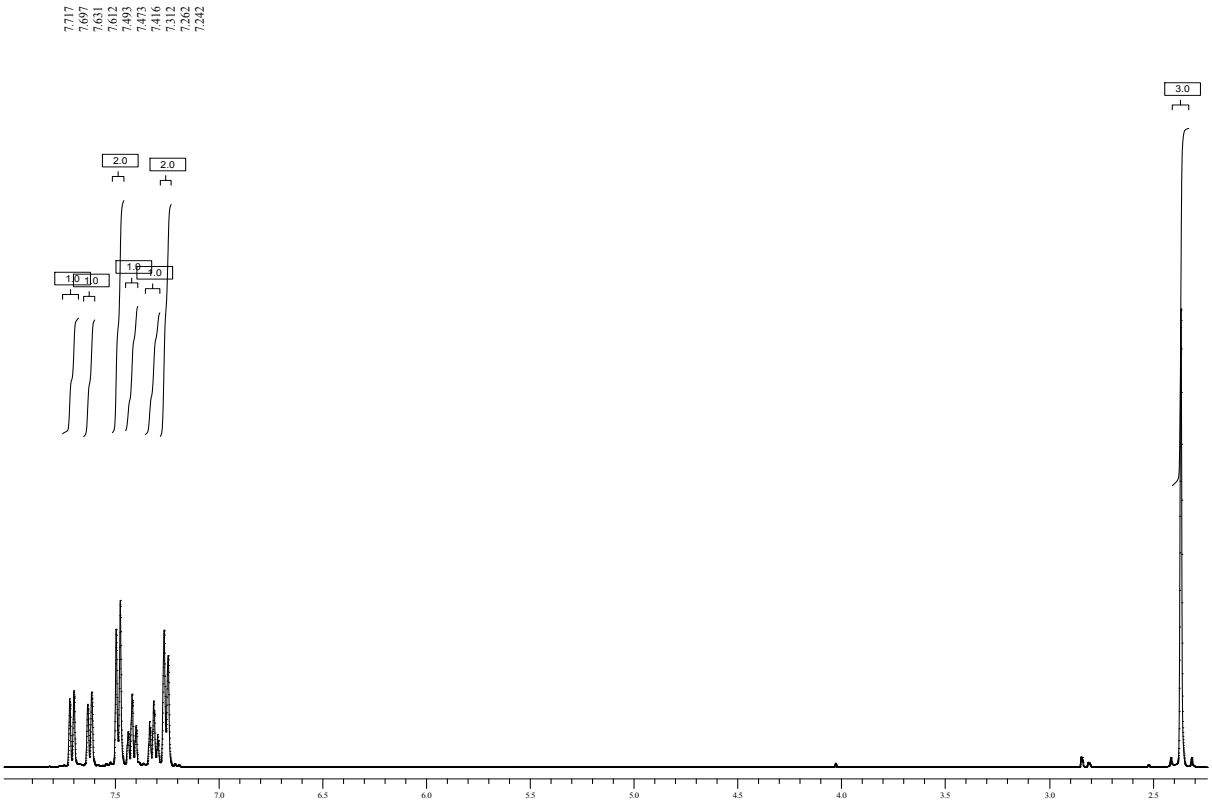
Compound **3j** (^{13}C NMR)



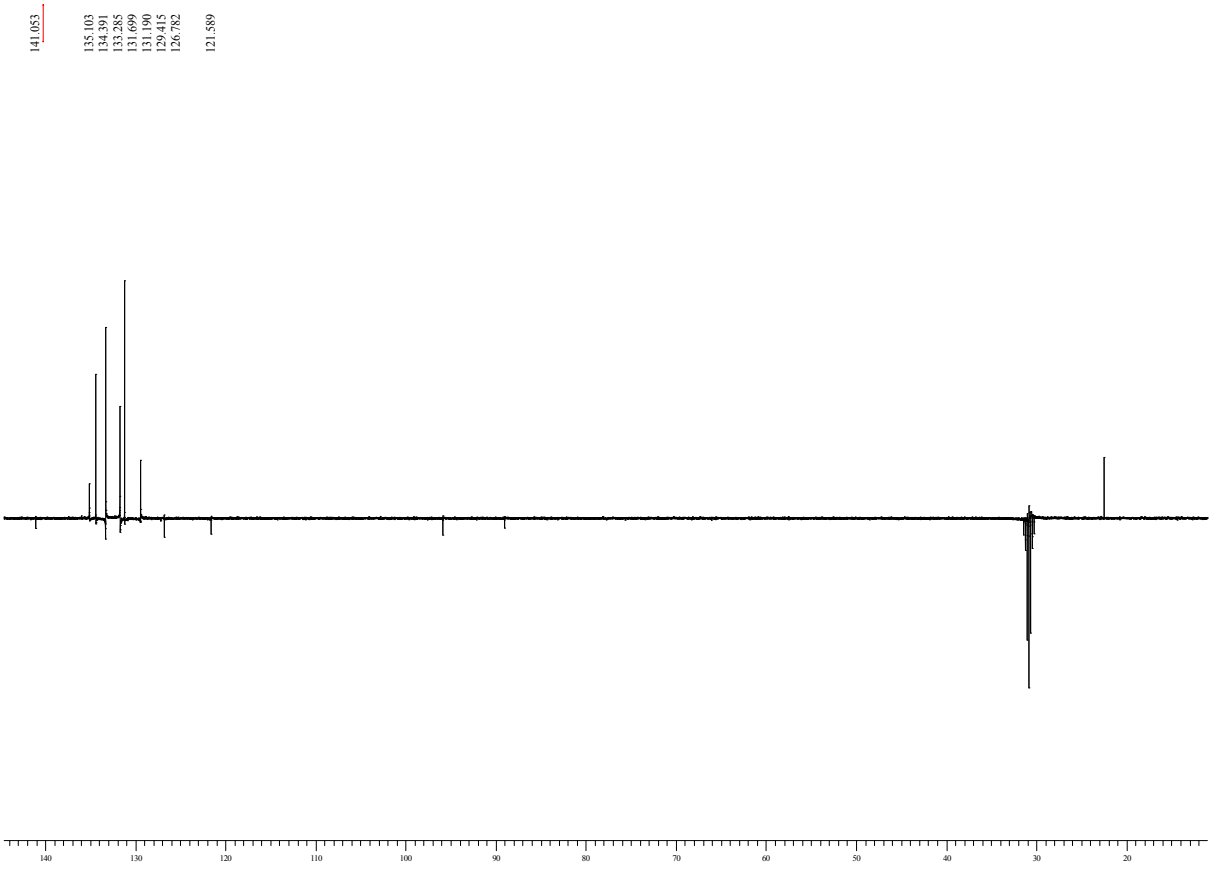
4-(Pyridin-3-ylethynyl)benzaldehyde (**3k**)



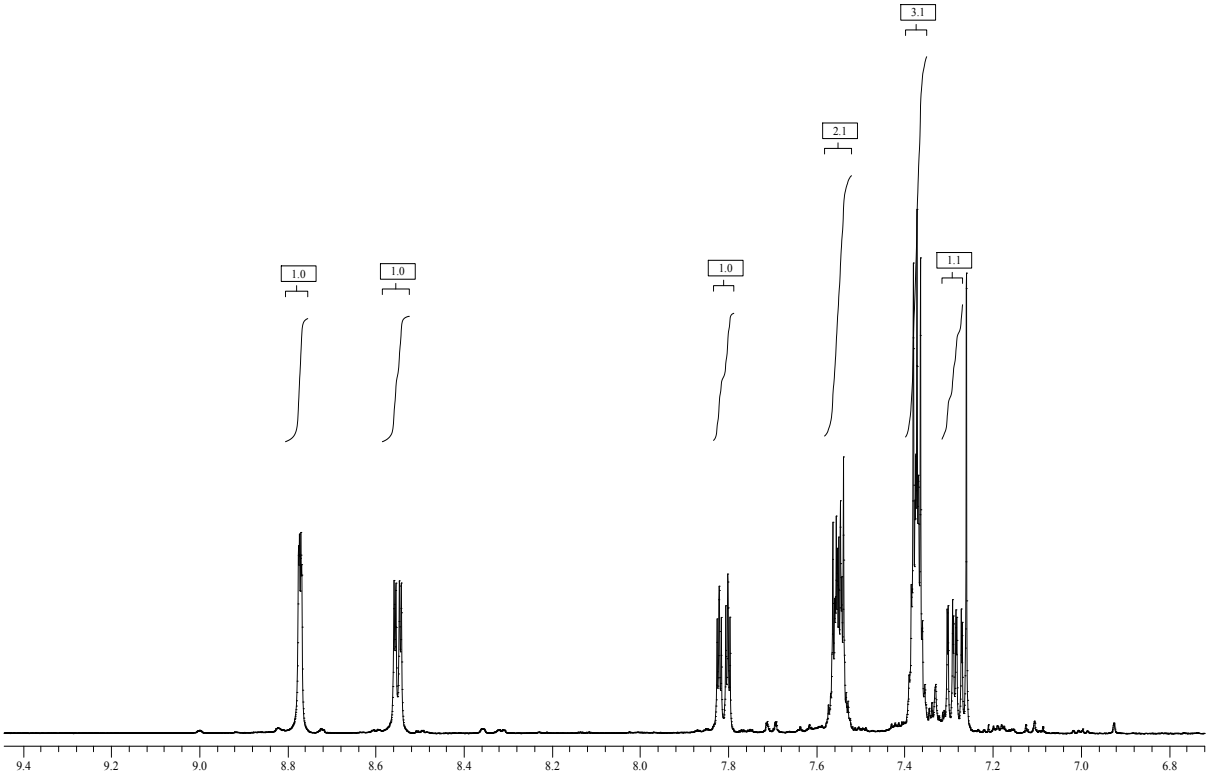
1-Bromo-2-(*p*-tolylethynyl)benzene (**3l**)



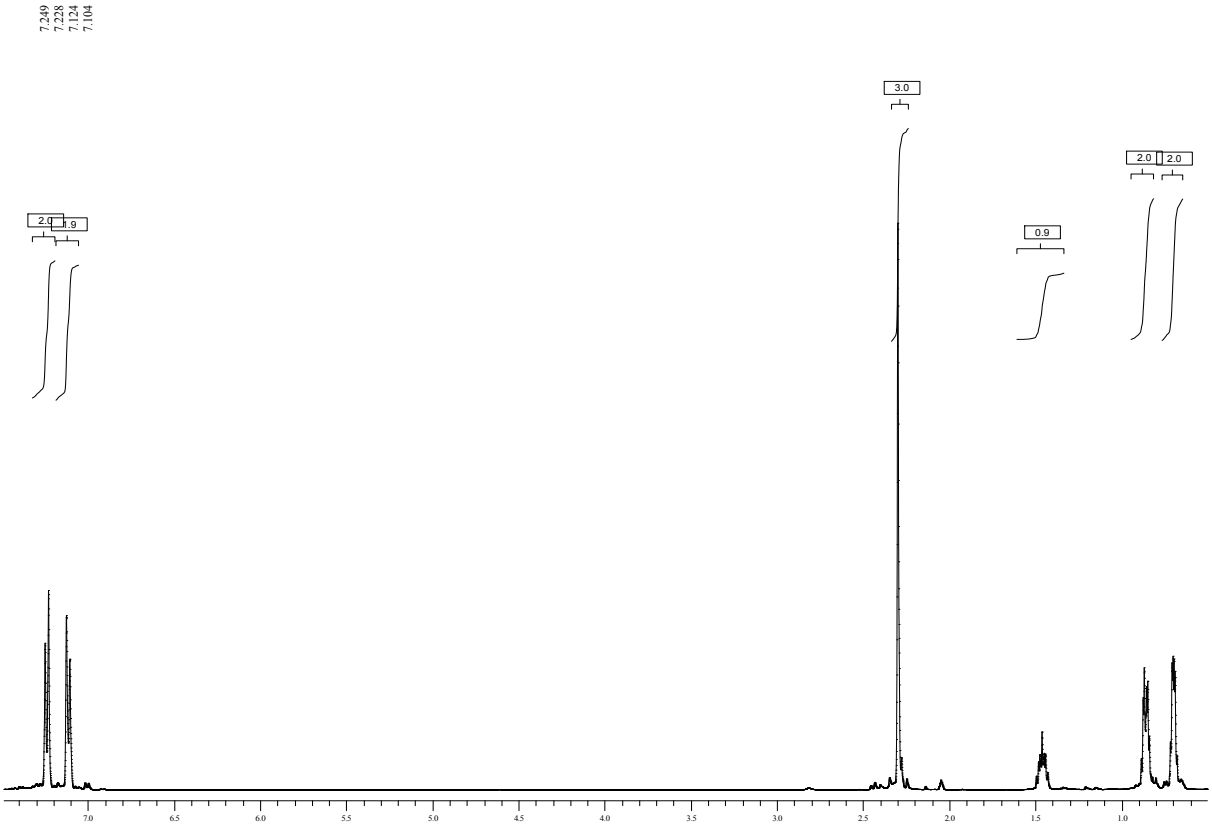
Compound **3l** (^{13}C NMR)



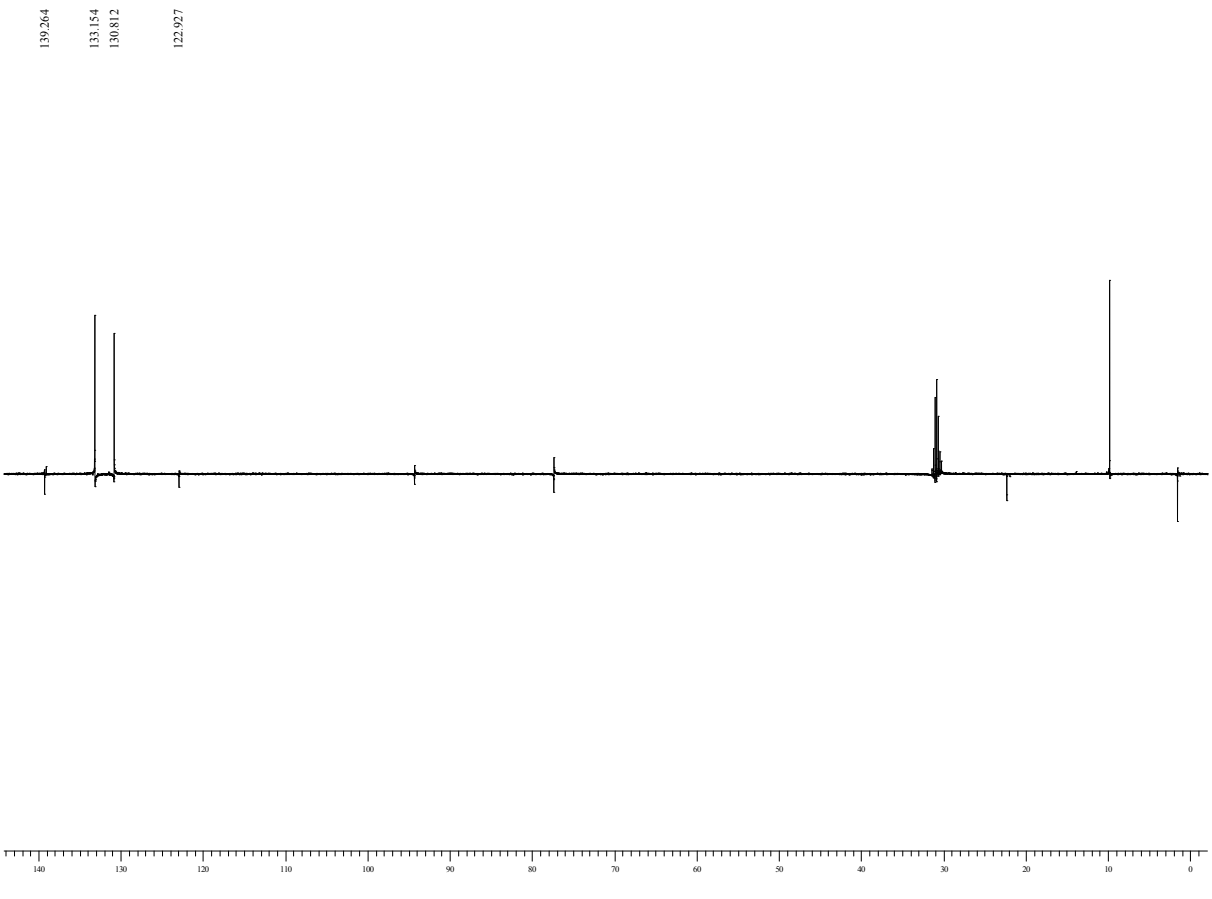
3-(Phenylethynyl)pyridine (**3m**)



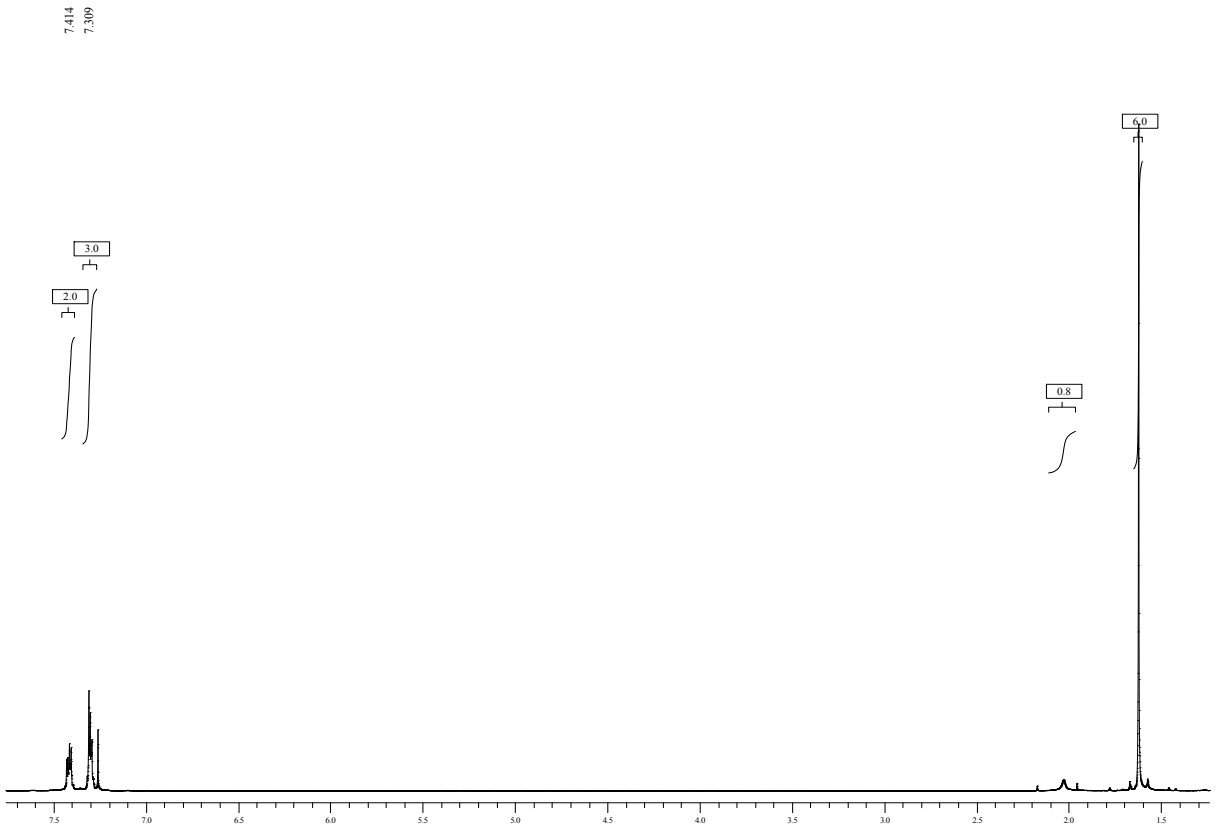
4-(Cyclopropylethynyl)toluene (**3n**)



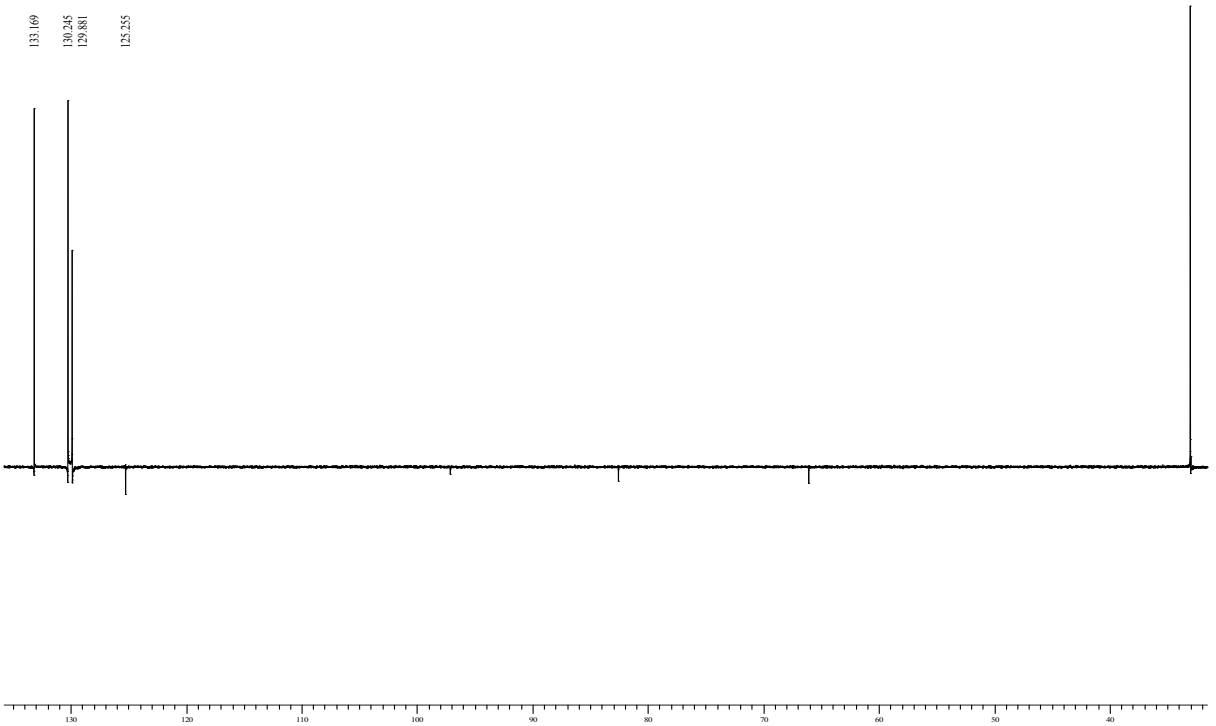
Compound **3n** (^{13}C NMR)



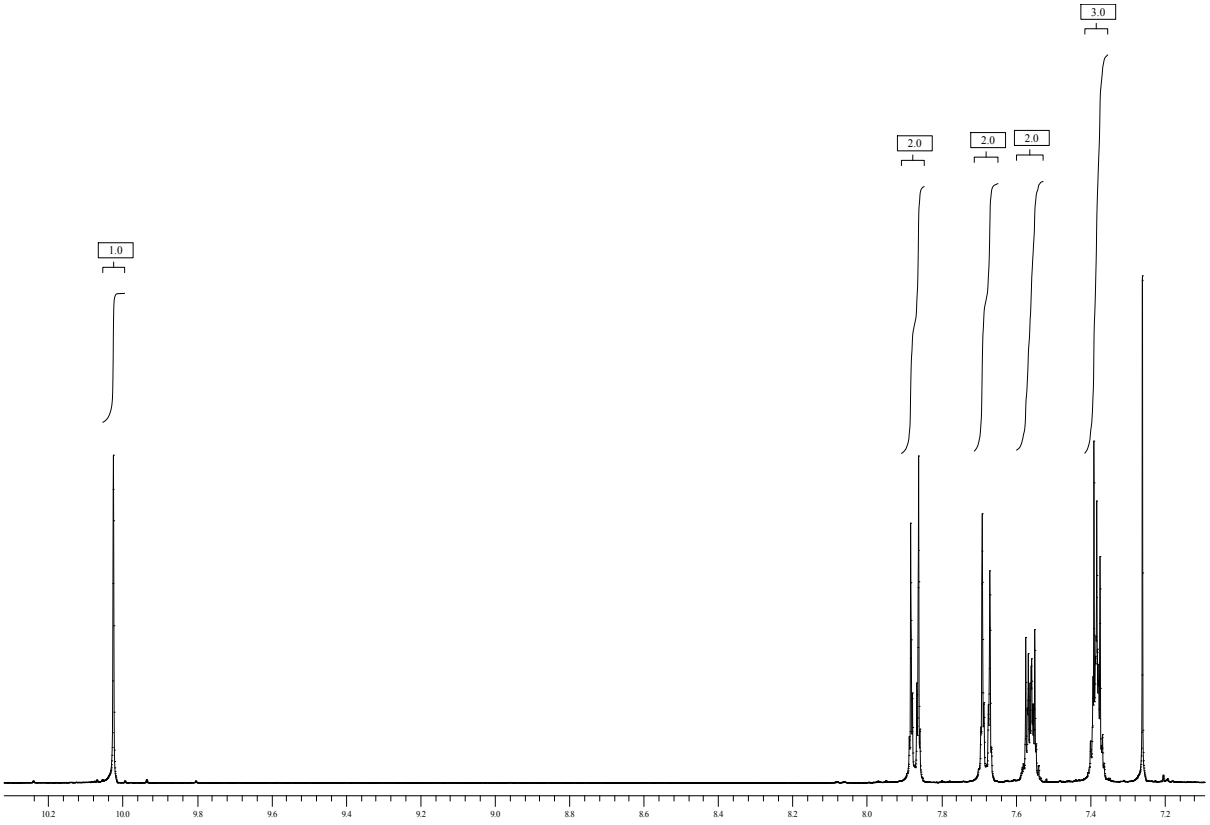
2-Methyl-4-phenylbut-3-yn-2-ol (**3o**)



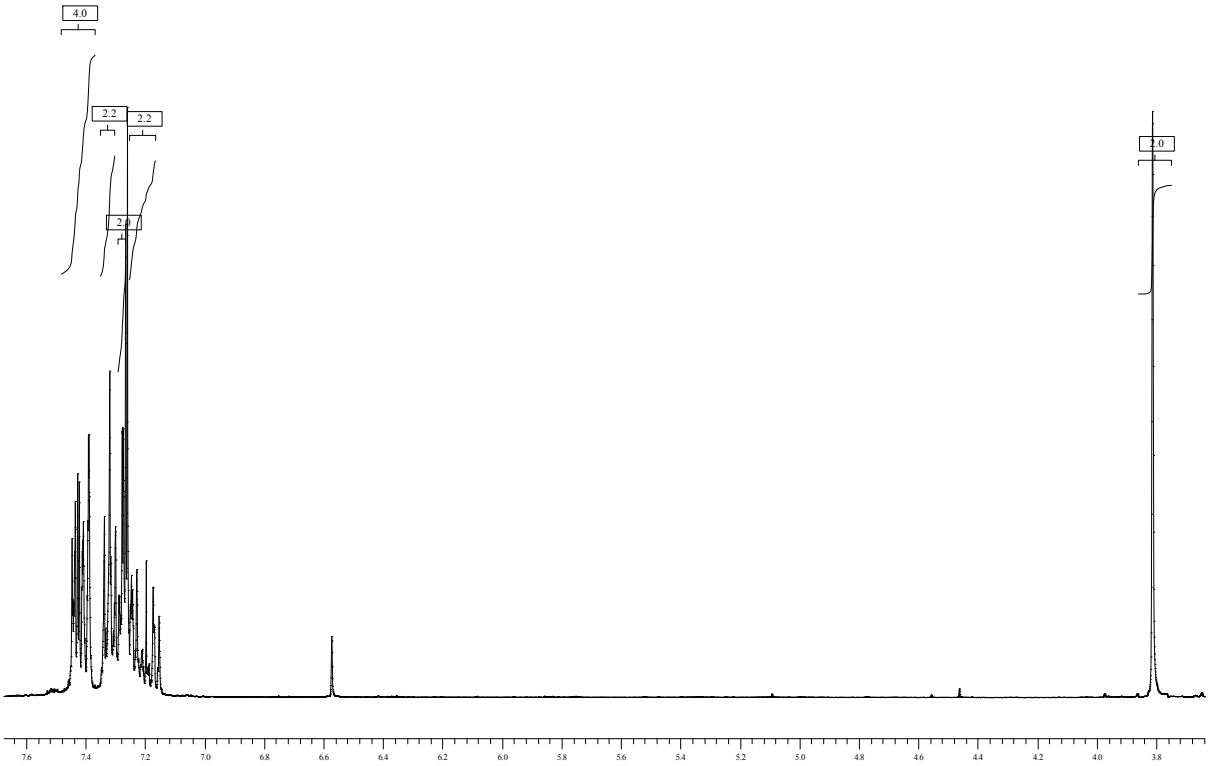
Compound **3o** (^{13}C NMR)



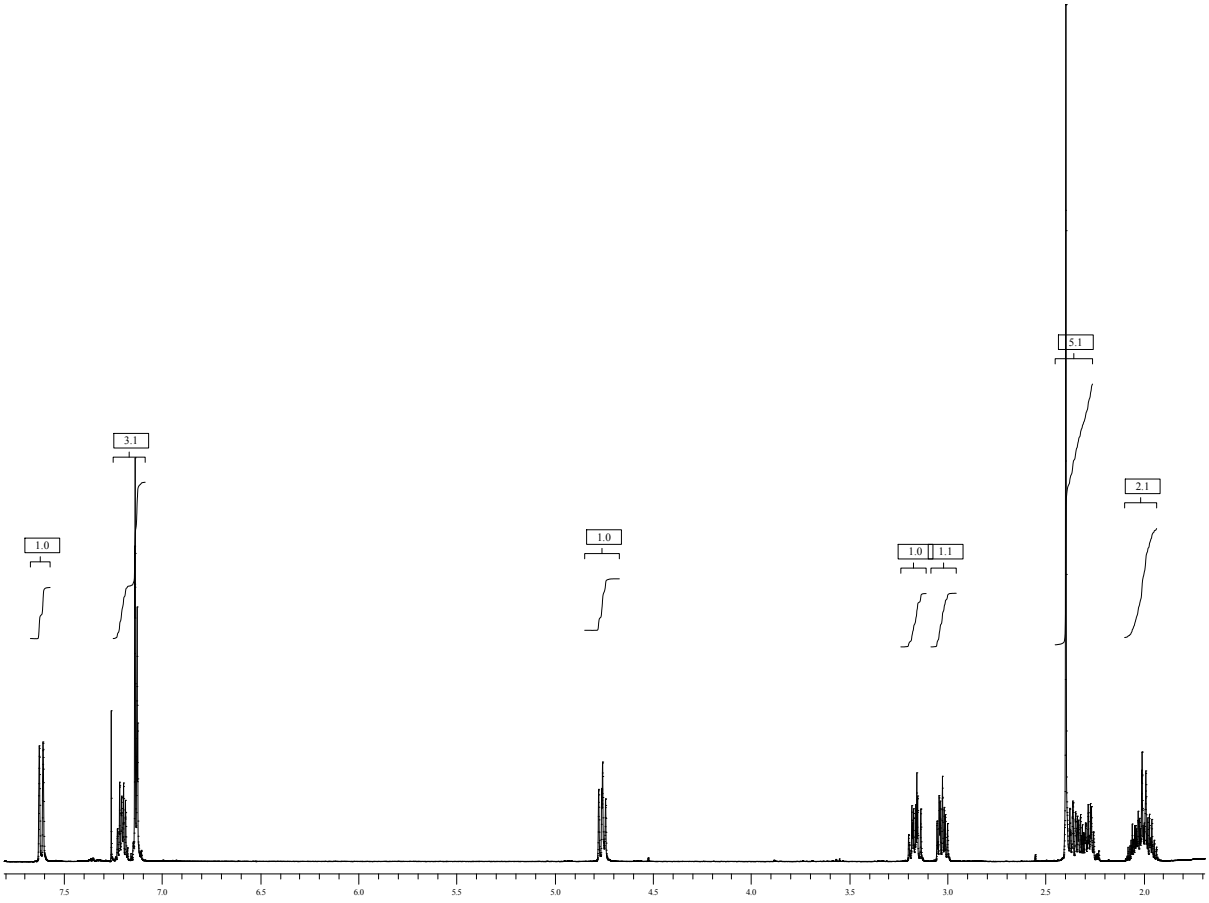
4-(Phenylethynyl)benzaldehyde (**3p**)



1,3-Diphenylpropyne (**5**)



2-*o*-Tolyltetrahydrothiophene (**6**)



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