Organic Syntheses

Palladium-catalyzed Buchwald-Hartwig Amination and Suzuki-Miyaura Cross-coupling Reaction of Aryl Mesylates

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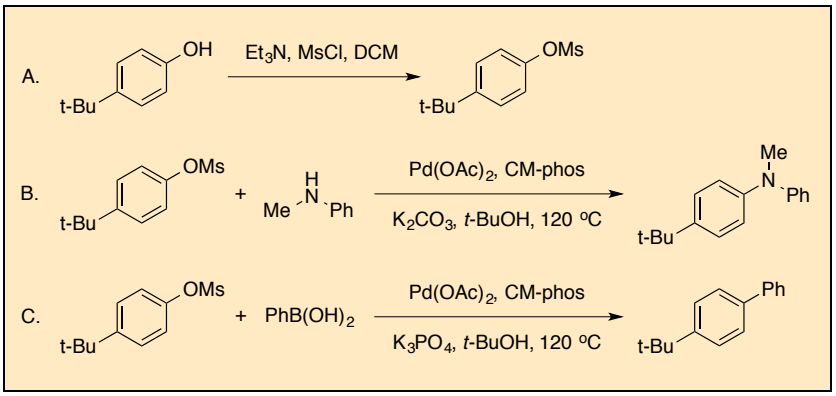
Checked by Kyohei Matsushita and Keisuke Suzuki



Procedure

A. *4-(tert-Butyl)phenyl methanesulfonate.* An oven-dried 500-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirbar (oval, 25 mm × 7 mm) is charged with 4-*tert*-butylphenol (15.0 g, 100 mmol) (Note 1), dichloromethane (120 mL) (Note 2), and stirring is started. Triethylamine (42 mL, 30.5 g, 300 mmol, 3.0 equiv) (Note 3) is added slowly over 5 min, and the mixture is stirred at room temperature for 5 min. Methanesulfonyl chloride (15.5 mL, 22.94 g, 200 mmol, 2.0 equiv) (Note 4) is added dropwise through a dropping funnel (Note 5), and the mixture is stirred at room temperature under an atmosphere of air until the

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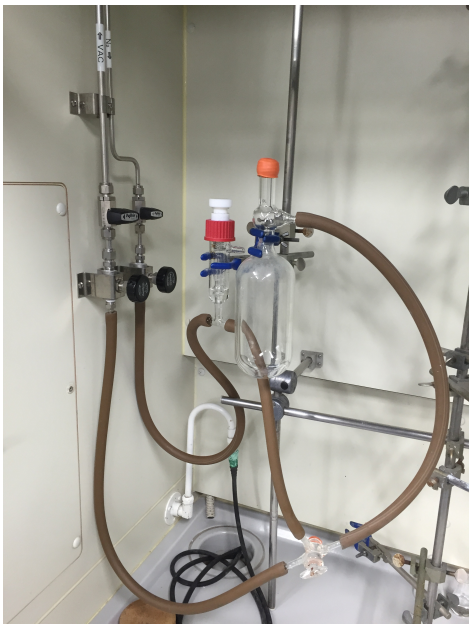
4-*tert*-butylphenol has been completely consumed as judged by TLC analysis (Note 6). The reaction mixture is transferred into a 2-L, separatory funnel. The reaction flask is rinsed with ethyl acetate (2 × 30 mL), water (20 mL), and with ethyl acetate (30 mL). All rinses, additional ethyl acetate (500 mL) and water (200 mL) are added to the separatory funnel, the funnel is shaken, and the layers are separated. The organic layer is washed sequentially with water (200 mL), 3.5 M hydrochloric acid (2 × 200 mL) (Note 7), water (200 mL), saturated aqueous sodium hydrogen carbonate (2 × 200 mL), and brine (2 × 200 mL). The organic layer is dried over anhydrous sodium sulfate (5 g) and the mixture is filtered. The sodium sulfate is washed with ethyl acetate (50 mL) and filtered. The combined organic solution is concentrated by rotary evaporation (36 °C, 20 mmHg) to afford a yellow oil. The oil is charged on a column of 100 g of silica gel (5.5-cm diameter × 9-cm packed height) (Note 8) and eluted with 50 mL of ethyl acetate–hexane (1:15). At this point, fraction collection (100-mL fractions) is begun, and elution is continued with 250 mL of ethyl acetate–hexane (1:15) and then 1500 mL of ethyl acetate–hexane (1:9). The eluent containing the product, as identified by TLC analysis, is concentrated by rotary evaporation (33 °C, 36 mmHg) to afford a pale yellow oil. The oil is dissolved in 5 mL of dichloromethane, and 200 mL of hexane is added. The solution is cooled in a freezer (–14 °C) for 8 h, and the resulting crystals are collected by suction filtration on a Büchner funnel, washed with ice-cold hexane (4 × 25 mL), and then transferred to a 100-mL, round-bottomed flask and dried overnight at 0.01 mmHg to provide 4-(*tert*-butyl)phenyl methanesulfonate (18.0–18.7 g, 79–82%) (Note 9) as white shiny crystals.

B. *4-(tert-Butyl)-N-methyl-N-phenylaniline.* An oven-dried 250-mL, resealable Schlenk flask (Note 10) equipped with a Teflon-coated magnetic stirbar (cylindrical, 45 mm × 7 mm) is charged with palladium(II) acetate (0.0393 g, 0.175 mmol, 1.0 mol%) (Note 11) and CM-phos (0.282 g, 0.700 mmol, 4.0 mol%) (Note 12). The Schlenk flask is capped with a rubber septum and then evacuated and backfilled with nitrogen three times. Dichloromethane (18 mL) (Note 13) and triethylamine (1.8 mL) (Note 14) are added via syringe through the septum, and stirring is started. The septum is replaced with a Teflon screwcap, and the Schlenk flask is sealed. The resulting dark orange mixture is placed in a 50 °C pre-heated oil bath with stirring for 5 min to afford a yellow reaction mixture. The flask is removed from the oil bath, allowed to cool to room temperature, and then the volatiles are stripped off at 0.01 mmHg for 1 h to afford a yellow solid. The flask is charged with potassium carbonate (6.05 g, 43.8 mmol, 2.5 equiv)

(Note 15), phenylboronic acid (0.0427 g, 0.350 mmol, 0.2 equiv) (Note 16), and 4-(*tert*-butyl)phenyl methanesulfonate (3.99 g, 17.5 mmol, 1.0 equiv). The Schlenk flask is capped with a rubber septum and then evacuated and backfilled with nitrogen three times. *N*-Methylaniline (2.85 mL, 26.3 mmol) (Note 17) and *tert*-butyl alcohol (70 mL) (Note 18) are added via syringe through



the septum, and stirring is started. The septum is replaced with a Teflon screwcap, and the Schlenk flask is sealed. The reaction flask is stirred at room temperature for 10 min, then placed in a 120 °C pre-heated oil bath (Note 19) with stirring for 24 h (Note 20). The flask is removed from the oil bath, allowed to cool to room temperature, and the mixture is transferred into a 500-mL, separatory funnel. The reaction flask is rinsed with ether (2 × 50 mL), brine (2 × 50 mL), water (50 mL), and again with ether (50 mL). All rinses are added to the separatory funnel, the funnel is shaken, and the layers are separated. The aqueous layer is extracted with ether (2 × 50 mL), and the combined organic extracts are dried over anhydrous sodium sulfate (5 g). The organics are separated by filteration. The sodium sulfate is washed with ether (50 mL) and the ether separated by filtration. The combined organic phase is concentrated by rotary evaporation (40 °C,

12 mmHg) to afford brown oil. The oil is charged on a column of 130 g of silica gel (4.5-cm diameter × 16-cm packed height) (Note 7) and eluted with 130 mL hexane. At this point, fraction collection (100-mL fractions) is begun, and elution is continued with dichloromethane–hexane (1:49) until all the desired product is eluted. The eluent containing the product is concentrated by rotary evaporation (39 °C, 14 mmHg) to afford pale-yellow liquid. The liquid is dried for 1 h at 0.01 mmHg to provide 4-(*tert*-butyl)-*N*-methyl-*N*-phenylaniline (3.60–3.85 g, 86–92%, Note 21) as a pale-yellow liquid.

C. *4-(tert-Butyl)-1,1′-biphenyl*. An oven-dried 250-mL, resealable Schlenk flask (Note 10) equipped with a Teflon-coated magnetic stirbar (cylindrical, 45 mm × 7 mm) is charged with palladium(II) acetate (0.0393 g, 0.175 mmol, 1.0 mol%, Note 11) and CM-phos (0.282 g, 0.700 mmol, 4.0 mol%) (Note 12). The Schlenk flask is capped with a rubber septum and then evacuated and backfilled with nitrogen three times. Dichloromethane (18 mL) (Note 13) and triethylamine (1.8 mL, 1.31 g, 12.9 mmol, 0.74 equiv) (Note 14) are added *via* syringe through the septum, and stirring is started. The septum is replaced with a Teflon screwcap, and the Schlenk flask is sealed. The resulting dark orange mixture is placed in a 50 °C pre-heated oil bath with stirring for 5 min under reflux, affording a yellow reaction mixture. The flask is removed from the oil bath, allowed to cool to room temperature, then the volatiles are stripped off at 0.01 mmHg for 1 h to afford a yellow solid. The flask is charged with potassium phosphate (11.1 g, 52.5 mmol, 3.0 equiv) (Note 22), phenylboronic acid (4.27 g, 35.0 mmol, 2.0 equiv) (Note 16), and 4-(*tert*-butyl)phenyl methanesulfonate (3.99 g, 17.5 mmol, 1.0 equiv). The Schlenk flask is capped with a rubber septum and then evacuated and backfilled with nitrogen three times. *tert*-Butyl alcohol (88 mL) (Note 18) is added *via* syringe through the septum, and stirring is started. The septum is replaced with a Teflon screwcap and the Schlenk flask is sealed. The reaction flask is stirred at room temperature for 10 min, then placed in a 120 °C (Note 19) pre-heated oil bath with for 24 h (Note 20). The flask is removed from the oil bath, allowed to cool to room temperature, and the mixture is transferred into a 500-mL, separatory funnel. The reaction flask is rinsed with ether (2 × 50 mL), brine (2 × 50 mL), water (50 mL), and again with ether (50 mL). All rinses are added to the separatory funnel, the funnel is shaken, and the layers are separated. The aqueous layer is extracted with ether (2 × 50 mL), and the combined organic extracts are dried over anhydrous sodium sulfate (5 g). The mixture is filtered and the sodium sulfate is washed with ether (50 mL).

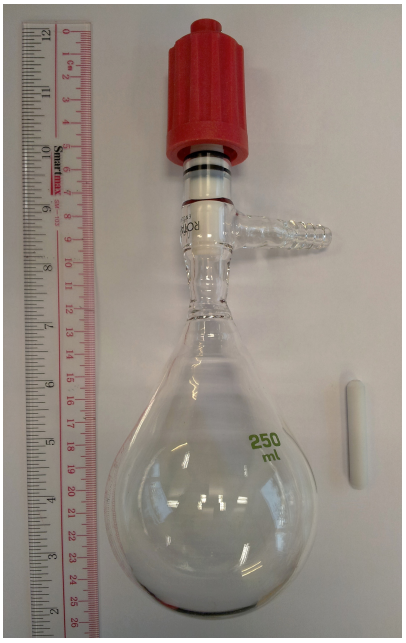
The organic solution is concentrated by rotary evaporation (40 °C, 15 mmHg) to afford a brown oil. The oil is charged on a column of 100 g of silica gel (4.5-cm diameter × 12-cm packed height) (Note 7) and eluted with 75 mL hexane. At this point, fraction collection (100-mL fractions) is begun, and elution is continued with hexane until all the desired product is eluted. The eluent containing the product is concentrated by rotary evaporation (40 °C, 15 mmHg) to afford a colorless oil. The oil is dried for 2 h at 0.01 mmHg to provide 4-(*tert*-butyl)-1,1'-biphenyl (2.20–2.90 g, 60–79%) (Note 23) as a white solid.

Notes

1. The checkers used 4-*tert*-butylphenol (>98%) as received from Tokyo Chemical Industry Co., Ltd. (TCI). The submitters used 4-*tert*-butylphenol (97%) as received from Acros Organics.
2. The checkers used dichloromethane (anhydrous) as received from KANTO CHEMICAL Co., Inc.. The submitters obtained dichloromethane (GR Grade) from DUKSAN and used it as received.
3. Triethylamine (≥99.5%) was obtained from Aldrich Co., Inc., and used as received.
4. Two equiv of methanesulfonyl chloride were used to ensure the reaction could be completed within 3 h. The checkers obtained methanesulfonyl chloride from Tokyo Chemical Industry Co., Ltd. (TCI) and used it as received. The submitters used methanesulfonyl chloride as obtained from Merck Millipore.
5. Upon addition of methanesulfonyl chloride, vapor and heat were released.
6. Ethyl acetate–dichloromethane-–hexane (1:2:7) [SM (R_f = 0.43), product (R_f = 0.50)] Thin layer chromatography was performed on pre-coated TLC-plates (Merck Co., Inc. TLC silica gel 60 F_{254}, Art 5715, 0.25 mm). n-Hexane (≧95% grade) from Kanto Chemical Co. was used.
7. Hydrochloric acid (reagent grade, 35%–37%) was obtained from Koso Chemical Co., Inc. and diluted with water to the desired concentration.
8. The checkers used silica gel 60N (Spherical, neutral, 63–210 μm) obtained from KANTO CHEMICAL Co., Inc. The submitters used silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM) obtained from Merck Millipore.

9. The analytical data of 4-(*tert*-butyl)phenyl methanesulfonate are as follows mp = 53–54 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.32 (s, 9 H), 3.12 (s, 3 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 7.42 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 31.5, 34.8, 37.3, 121.5, 127.1, 147.1, 150.7; MS (EI): *m*/*z* (relative intensity) 228 (M^+, 16), 213 (100), 135 (70), 91 (41), 79 (47); HRMS calcd. for $C_{11}H_{16}O_3S^+$: 228.0820, found 228.0811; Anal. calcd for $C_{11}H_{16}O_3S$: C, 57.87; H, 7.06; S, 14.04. Found: C, 57.86; H, 6.93; S, 13.88.
10. The resealable Schlenk flask used by the checkers was tailor-made with a Rotaflo stopcock and a 250–300-mL round-bottomed flask. The key bore of the Rotaflo stopcock was 10-mm. In order to have effective stirring during the reaction, Teflon-coated magnetic stirbar (cylindrical, 45 mm × 7 mm) was chosen. The resealable Schlenk flask used by the submitters was tailor-made with a Rotaflo stopcock and a 250-mL, round-bottomed flask. The key bore of the Rotaflo stopcock was 10-mm. In order to have effective stirring during reaction, Teflon-coated magnetic stirbar (cylindrical, 50 mm × 8 mm) was chosen. Photographs of the Schlenk flasks are shown below.

Checker's flask



Submitter's flask

11. Palladium(II) acetate (≥99.9% trace metals basis) was obtained from Aldrich Co., Inc., and used as received.
12. CM-Phos (98%) is available commercially from Strem Chemical, Co. and can be used for the reaction described above. The checkers used material produced in their laboratory based on a procedure that has been submitted for checking by *Organic Syntheses*.
13. The checkers used dichloromethane (anhydrous) as received from KANTO CHEMICAL Co., Inc. The submitters used dichloromethane (GR Grade) obtained from DUKSAN, and the solvent was distilled from calcium hydride under nitrogen prior to use.
14. Triethylamine (≥99.5%) was obtained from Aldrich Co., Inc., and distilled from potassium hydroxide under nitrogen prior to use.
15. Potassium carbonate (ACS reagent, ≥99.0%) was obtained from Aldrich Co., Inc., and used as received.
16. Two equiv of phenylboronic acid were used in order to obtain the desired yield of the coupling reaction. The checkers used phenylboronic acid from Aldrich Co., Inc., and the submitters used phenylboronic acid from Soochiral Chemical Science & Technology Co., Ltd. Phenylboronic acid was recrystallized from dichloromethane and hexane prior to use.
17. *N*-Methylaniline (98%) was obtained from Aldrich Co., Inc., and distilled under nitrogen.
18. *tert*-Butyl alcohol (ACS reagent, ≥99.0%) was obtained from Aldrich Co., Inc., and distilled from sodium under nitrogen.
19. The oil bath temperature was higher when run on a large scale than previously published examples because of the lower internal temperature of the large-scale reactions. A blast shield was used since the boiling point of *tert*-butyl alcohol is 82 °C and the reaction was run at 120 °C under a closed system.
20. Reaction times are longer when run on a large scale than the previously published reaction times for smaller scale reactions. Efficient stirring is very important for these large-scale reactions, otherwise, very sticky and glutinous reaction mixtures form, and lower product yields are obtained.
21. The analytical data of 4-(*tert*-butyl)-*N*-methyl-*N*-phenylaniline are as follows: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.32 (s, 9 H), 3.30 (s, 3 H), 6.89 (t, J = 7.8 Hz, 1 H), 6.97 (d, J = 7.8 Hz, 2 H), 7.00 (brd, J = 8.7 Hz, 2 H), 7.24 (brt, 7.8 Hz, 2 H), 7.30 (brd, J = 8.7 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 31.6, 34.4, 40.4, 119.1, 120.4, 121.4, 126.2, 129.2, 145.0, 146.5, 149.4; MS (EI): *m*/*z* (relative intensity) 239 (M^+, 31), 224 (100); HRMS

calcd. for $C_{17}H_{21}NH^+$: 240.1752, found 240.1743; Anal. calcd for $C_{17}H_{21}N$: C, 85.30; H, 8.84; N, 5.85. Found: C, 85.21; H, 8.59; N, 5.92. R_f = 0.5, in dichloromethane–hexane (1:19) solvent system.

22. The checkers used potassium phosphate as received from Aldrich Co., Inc. The submitters use potassium phosphate (97%) as obtained from Strem Chemicals, Inc.
23. The analytical data of 4-(*tert*-butyl)-1,1'-biphenyl are as follows: mp = 47–49 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.36 (s, 9 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.42 (t, *J* = 7.2 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 31.5, 34.7, 125.9, 126.9, 127.12, 127.17, 128.8, 138.5, 141.2, 150.4; MS (EI): *m*/*z* (relative intensity) 210 (M^+, 34), 195 (100), 167 (25); HRMS calcd. for $C_{16}H_{18}^+$: 210.1409, found 210.1402; Anal. calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.06; H, 8.47. R_f = 0.3, in hexane solvent system.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

Discussion

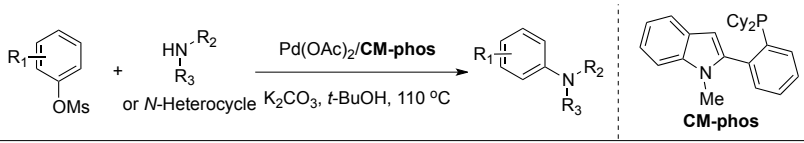
Palladium-catalyzed cross-coupling reactions have become an extremely versatile tool in organic synthesis for the construction of carbon-carbon as well as carbon-heteroatom bonds.[2] Notably, it evolves into a synthetically attractive transformation in targeting pharmaceutically useful intermediates.[3] In particular, the Buchwald-Hartwig amination and Suzuki-Miyaura cross-coupling reaction represent an effective method for the construction of $C(sp^2)$-N and $C(sp^2)$-$C(sp^2)$ linkages, respectively.

In 2008, we reported the synthesis and applications of **CM-phos**,[4] which showed excellent catalytic activities towards the first palladium-catalyzed amination and Suzuki coupling reaction of aryl mesylates. Aryl mesylates can be easily accessed from phenols, owing to their lower molecular mass, and cross-coupling reactions utilizing these reagents have the advantage of higher atom economy than those employing the corresponding aryl tosylates.[5] However, their relatively inert leaving-group activity, with respect to tosylates, has limited their applications in coupling reactions. Thus, this area remains highly challenging as mesylates are regarded as the least active sulfonate leaving group.

The examples described here demonstrate that a variety of aryl mesylates with differing substitution patterns, electronic properties, and functional groups can be coupled with differing amines and arylboronic acids in high yield on large scale up to 40 mmol (Tables 1 and 2).

As shown in Tables 3 to 6, the $Pd(OAc)_2$/**CM-phos** catalyst is highly effective for both amination and Suzuki coupling reactions of aryl mesylates. The examples showed that the catalytic system is applicable to couple a range of aryl/heteroaryl mesylate substrates with amine and arylboronic acid nucleophiles in high yield with low to moderate levels of catalyst loading (0.5-4 mol% Pd). Notably, the reactions require no special techniques and are amenable to large-scale synthesis.

Table 1. Palladium-catalyzed amination of aryl mesylates with amines or *N*-heterocycles on large scale[a]



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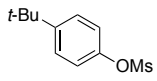
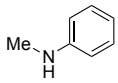
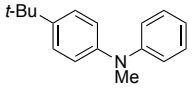
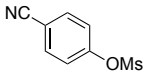
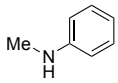
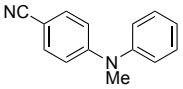
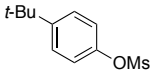
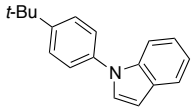
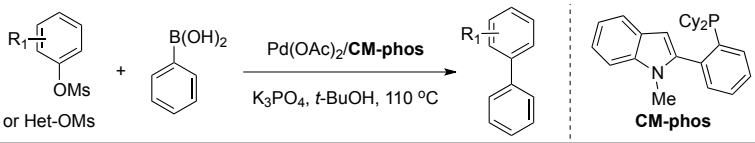
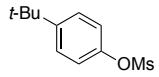
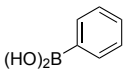
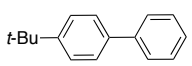
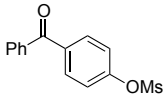
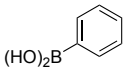
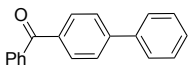
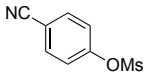
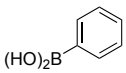
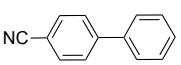
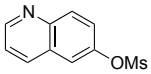
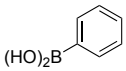
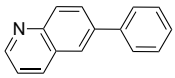
1[c]				1	24	72
2				1	24	83
3				1	24	74

[a] Reaction condtions: ArOMs (40 mmol), amine or *N*-heterocycle (60 mmol), K_2CO_3 (100 mmol), $Pd(OAc)_2$:**CM-phos** = 1:4 (mol% as indicated), $PhB(OH)_2$ (0.8 mmol), *t*-BuOH (160 mL), at 110 °C under N_2 for indicated period of time. [b] Yields of isolated product. [c] ArOMs (35 mmol), amine (52.5 mmol), K_2CO_3 (87.5 mmol), $Pd(OAc)_2$:**CM-phos** = 1:4 (mol% as indicated), $PhB(OH)_2$ (0.7 mmol), *t*-BuOH (140 mL), at 120 °C under N_2 for indicated period of time.

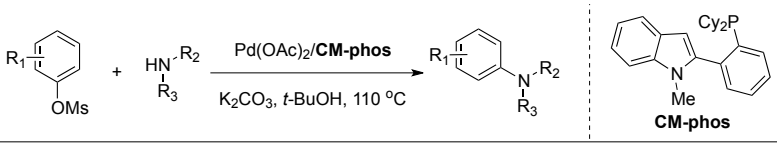
Table 2. Palladium-catalyzed Suzuki-Miyaura coupling of aryl/heteroaryl mesylates with arylboronic acids on large scale[a]

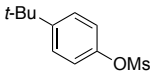
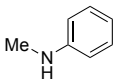
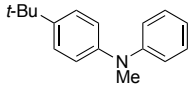
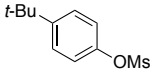
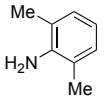
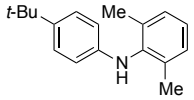
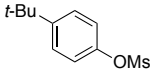
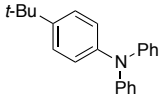
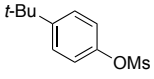
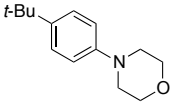
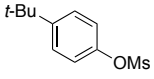
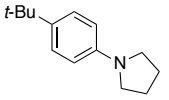
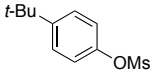
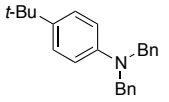
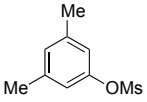
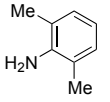
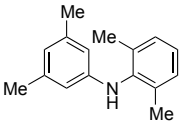
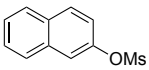
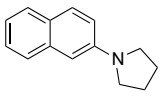
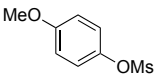
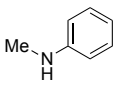
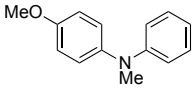


Entry	ArOMs or Het-OMs	$Ar'B(OH)_2$	Product	Pd (mol%)	Time (h)	Yield (%)[b]
1[c]				1	24	96
2				1	12	97
3				1	17	92
4				1	12	95

[a] Reaction conditions: ArOMs or Het-OMs (40 mmol), $Ar'B(OH)_2$ (80 mmol), K_3PO_4 (120 mmol), $Pd(OAc)_2$:**CM-phos** = 1:4 (mol% as indicated), *t*-BuOH (180 mL), at 110 °C under N_2 for indicated period of time. [b] Yields of isolated product. [c] Reaction conditions: ArOMs (35 mmol), $Ar'B(OH)_2$ (70 mmol), K_3PO_4 (105 mmol), $Pd(OAc)_2$:**CM-phos** = 1:4 (mol% as indicated), *t*-BuOH (175 mL), at 120 °C under N_2 for indicated period of time.

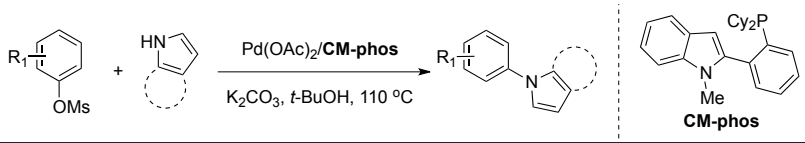
Table 3. Palladium-catalyzed amination of aryl mesylates[a]

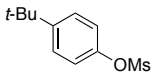
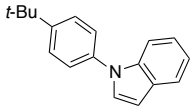
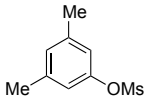
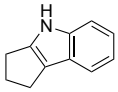
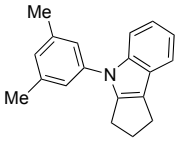
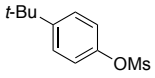
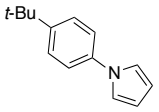
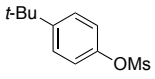
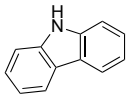
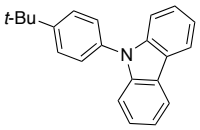
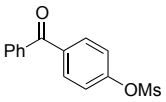
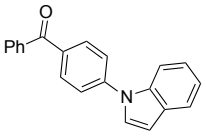
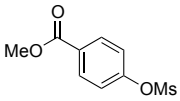
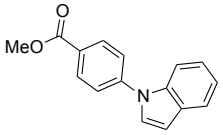


Entry	ArOMs	Amine	Product	Pd (mol%)	Time (h)	Yield (%)[b]
1				2	4	93
2				0.5	24	96
3				1	24	90
4				4	24	80
5				1	18	90
6[c]				2	24	93
7[c]				4	24	81
8				1	24	87
9				2	24	85
10				2	24	78

[a] Reaction condtions: ArOMs (1.0 mmol), amine (1.5 mmol), K_2CO_3 (2.5 mmol), $Pd(OAc)_2$:**CM-phos** = 1:4 (mol% as indicated), $PhB(OH)_2$ (0.04 mmol), *t*-BuOH (4.0 mL), at 110 °C under N_2 for indicated period of time. [b] Yields of isolated product. [c] K_3PO_4 was used instead of K_2CO_3.

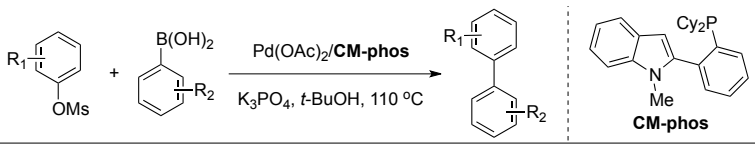
Table 4. Palladium-catalyzed *N*-arylation of nitrogen heterocycles with aryl mesylates[a]

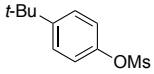
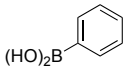
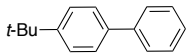
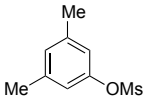
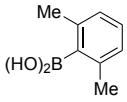
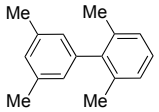
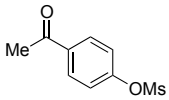
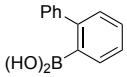
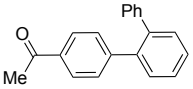
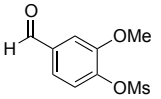
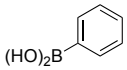
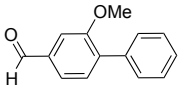
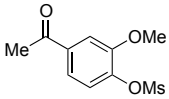
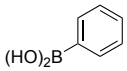
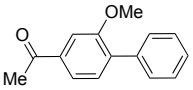
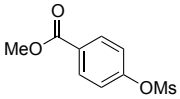
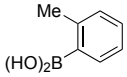
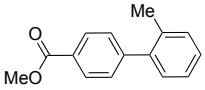
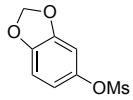
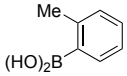
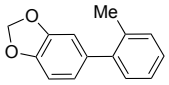
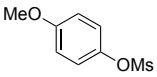
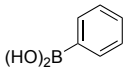
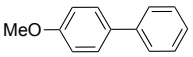


Entry	ArOMs	*N*-Heterocycle	Product	Pd (mol%)	Time (h)	Yield (%)[b]
1				1	24	93
2				2	24	84
3				1	24	80
4[c]				2	24	98
5				1	24	88
6				1	24	79

[a] Reaction condtions: ArOMs (1.0 mmol), *N*-heterocycle (1.5 mmol), K_2CO_3 (2.5 mmol), $Pd(OAc)_2$:**CM-phos** = 1:4 (mol% as indicated), $PhB(OH)_2$ (0.04 mmol), *t*-BuOH (4.0 mL), at 110 °C under N_2 for indicated period of time. [b] Yields of isolated product. [c] ArOMs (1.0 mmol), carbazole (1.0 mmol) were used.

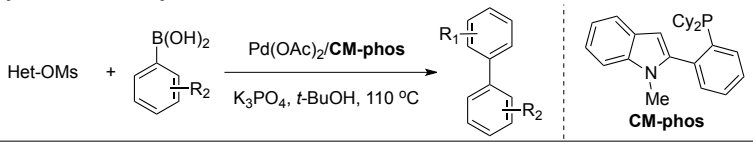
Table 5. Palladium-catalyzed Suzuki-Miyaura coupling of aryl mesylates with arylboronic acids[a]



Entry	ArOMs	Ar'B(OH)$_2$	Product	Pd (mol%)	Time (h)	Yield (%)[b]
1				1	19	91
2				0.5	24	88
3				4	8	70
4				2	3	92
5				2	3	81
6				2	3	95
7				2	3	97
8				2	3	89
9				4	8	89

[a] Reaction conditions: ArOMs (1.0 mmol), Ar'B(OH)$_2$ (2.0 mmol), K_3PO_4 (3.0 mmol), Pd(OAc)$_2$:**CM-phos** = 1:4 (mol% as indicated), *t*-BuOH (3.0 mL), at 110 °C under N_2 for indicated period of time. [b] Yields of isolated product.

Table 6. Palladium-catalyzed Suzuki-Miyaura coupling of heteroaryl mesylates with arylboronic acids[a]



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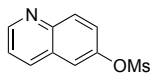
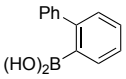
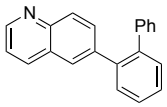
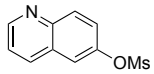
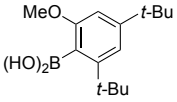
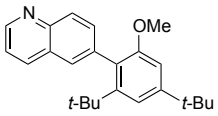
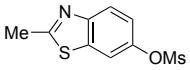
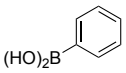
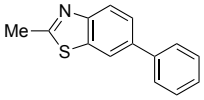
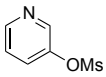
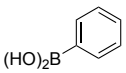
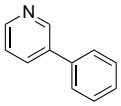
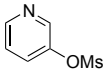
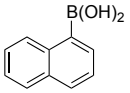
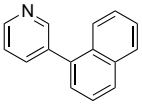
1				2	3	91
2				2	3	77
3				2	3	84
4				2	3	84
5				2	3	85

[a] Reaction conditions: Het-OMs (1.0 mmol), Ar'B(OH)$_2$ (2.0 mmol), K_3PO_4 (3.0 mmol), Pd(OAc)$_2$:**CM-phos** = 1:4 (mol% as indicated), *t*-BuOH (3.0 mL), at 110 °C under N_2 for indicated period of time. [b] Yields of isolated product. Het-OMs = heteroaryl mesylate

References

1. State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong. E-mail: chau.ming.so@polyu.edu.hk, fuk-yee.kwong@polyu.edu.hk; Fax: +852-2364-9932. We thank the Research Grants Council of Hong Kong (PolyU153008/14P) for financial support.

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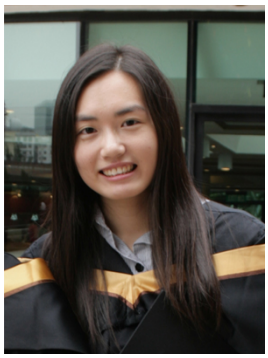
5. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 259.

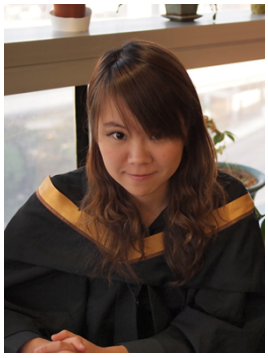
Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-*tert*-Butylphenol; (98-54-4)
Triethylamine; (121-44-8)
Methanesulfonyl chloride; (124-63-0)
Palladium(II) acetate; (3375-31-3)
CM-phos: 2-(2-(Dicyclohexylphosphino)phenyl)-1-methyl-1*H*-indole, (1067883-58-2)
Phenylboronic acid; (98-80-6)
N-Methylaniline; (100-61-8)
tert-Butanol; (75-65-0)
Potassium phosphate; (7778-77-0)

Shun Man Wong received his B.Sc. in Chemical Technology from The Hong Kong Polytechnic University in 2010. He pursued his postgraduate study at the same university and obtained his Ph.D. degree in 2014. He is currently a research associate under the supervision of Prof. Fuk Yee Kwong, researching the synthesis of new heterocyclic phosphine ligands and their potential applications.

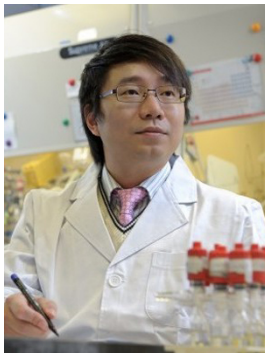


Pui Ying Choy received her B.Sc. in Chemical Technology in The Hong Kong Polytechnic University in 2010. She pursued her postgraduate study at the same university and obtained her Ph.D. degree in 2014. She is currently a research associate under the supervision of Prof. Fuk Yee Kwong, researching the synthesis of new heterocyclic phosphine ligands and their potential applications in transition-metal catalysis.

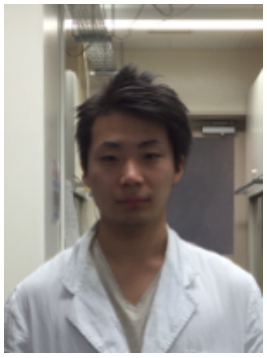


On Ying Yuen received her B.Sc. (1st class honors) in Chemical Technology from the Hong Kong Polytechnic University in 2011. Currently, she is pursuing her Ph.D. under the guidance of Prof. Fuk Yee Kwong. Her main research focuses on palladium-catalyzed direct functionalization of aromatics: process and catalyst design.

Chau Ming So is currently a Visiting Assistant Professor in the Department of Applied Biology and Chemical Technology of The Hong Kong Polytechnic University. He received his B.Sc. (1st class honor) from PolyU in 2006. He pursued his postgraduate study at the same university and obtained his Ph.D. degree in 2010. He received the Hong Kong Young Scientist Award in the same year. Moreover, he was the winner of Eli Lilly the Best Thesis Award (1st Prize). In 2012-2013, he moved to Institute of Materials Research and Engineering (IMRE) as postdoctoral fellow in Prof. Tamio Hayashi's research group.

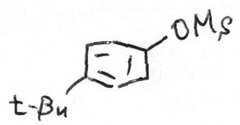


Fuk Yee (Michael) Kwong is currently a Professor of the Department of Applied Biology and Chemical Technology at The Hong Kong Polytechnic University. He received his B.Sc. in 1996, and completed his Ph.D. at The Chinese University of Hong Kong in 2000 under the supervision of Professor Kin Shing Chan. In 2001–2003, he was at the Massachusetts Institute of Technology (MIT), USA, as a Croucher Foundation postdoctoral fellow in Professor Stephen L. Buchwald's research group. Kwong's research interests are new cross-coupling methodologies, carbon–hydrogen bond functionalization, and catalytic enantioselective transformations.



Kyohei Matsushita was born in 1989 in Chiba, Japan. He received his B.Sc. degree in 2012 at Chuo University under the supervision of Prof. Shin-ichi Fukuzawa. In the same year, he joined the research group of Prof. Keisuke Suzuki at Tokyo Institute of Technology. In 2014, he received his M.Sc., and currently, is pursuing his Ph.D.

4-(tert-butyl)phenyl methansulfonate
1H CDCl3



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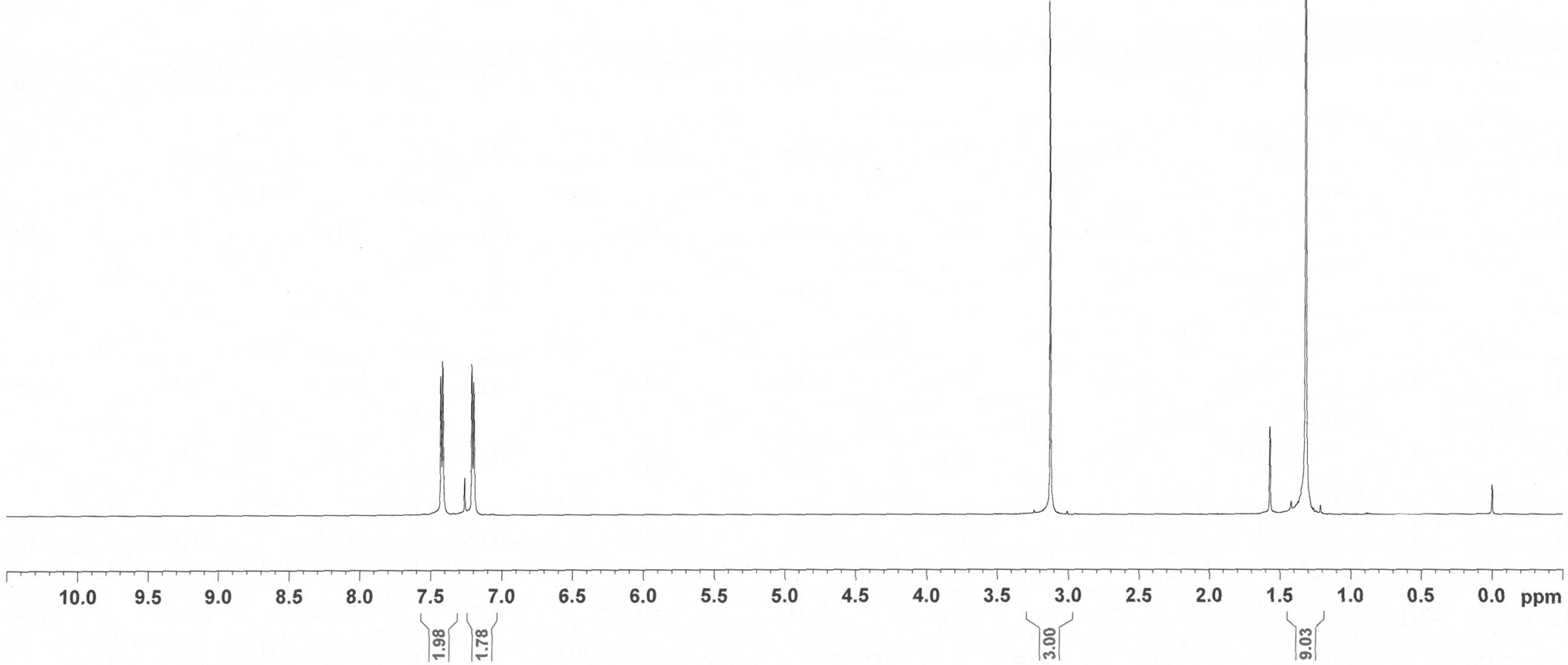

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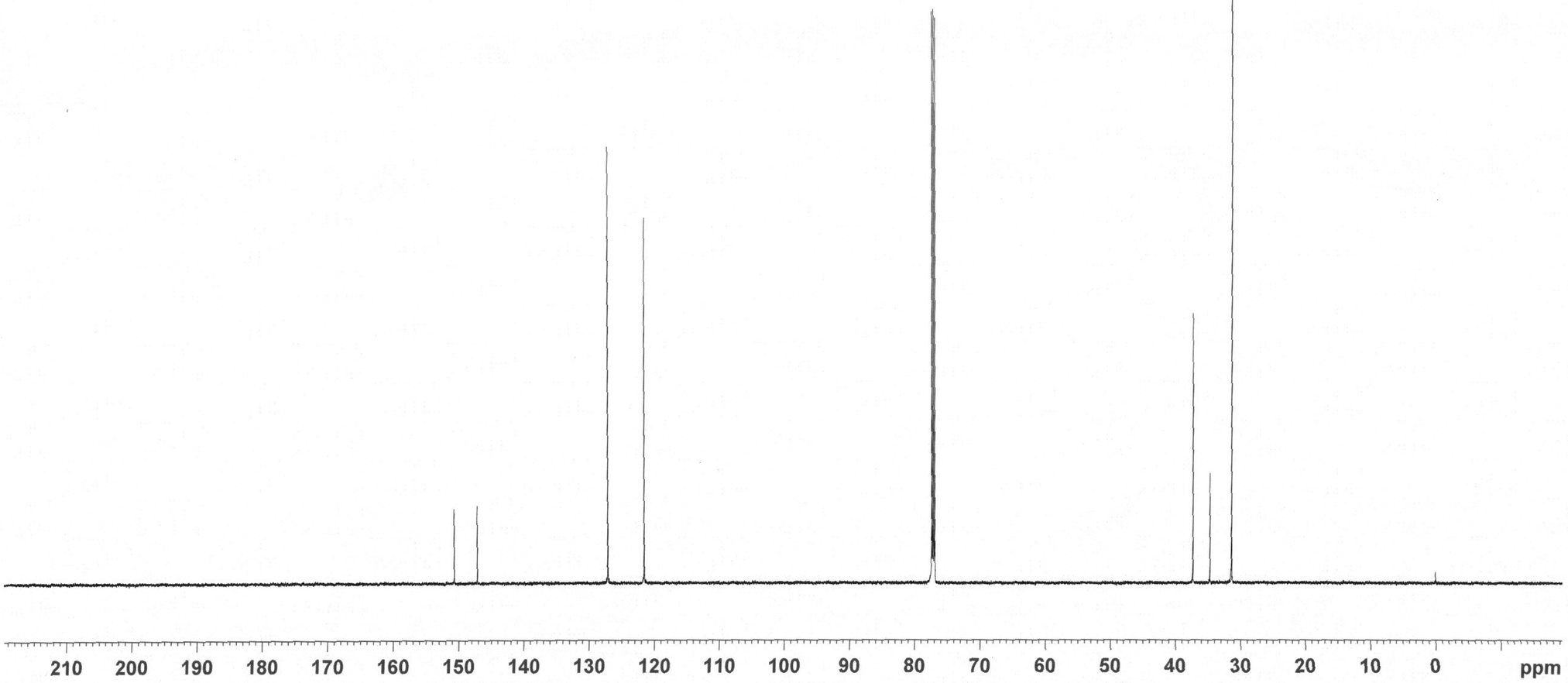
NS                   16
DS                    2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7262976 sec
RG                18.96
DW               41.600 usec
DE               10.00 usec
TE               300.0 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        600.1337060 MHz
NUC1                  1H
P1               12.00 usec
PLW1       23.00000000 W

F2 - Processing parameters
SI                65536
SF          600.1300181 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

4-(tert-butyl)phenyl methansulfonate
13C CDCl3

150.67
147.12
127.07
121.51
77.37
77.16
76.95
37.34
34.75
31.46



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```
Current Data Parameters
NAME      km1-917-1-cdcl3
EXPNO                  11
PROCNO                  1

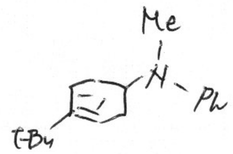
F2 - Acquisition Parameters
Date_            20140704
Time                20.37
INSTRUM             spect
PROBHD   5 mm CPPBBO BB
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH          36057.691 Hz
FIDRES        0.550197 Hz
AQ            0.9087659 sec
RG               175.56
DW               13.867 usec
DE                18.00 usec
TE                300.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1       150.9178981 MHz
NUC1               13C
P1               10.00 usec
PLW1        70.00000000 W

======== CHANNEL f2 ========
SFO2       600.1324005 MHz
NUC2               1H
CPDPRG[2        waltz16
PCPD2            70.00 usec
PLW2        26.00000000 W
PLW12        0.76407999 W
PLW13        0.37439999 W

F2 - Processing parameters
SI                 32768
SF         150.9027901 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

4-(tert-butyl)-N-methyl-N-phenylaniline
1H CDCl3



7.310
7.307
7.299
7.295
7.253
7.242
7.240
7.231
7.228
7.012
7.007
7.004
6.996
6.993
6.973
6.972
6.959
6.900
6.888
6.876

3.297
1.316
0.000

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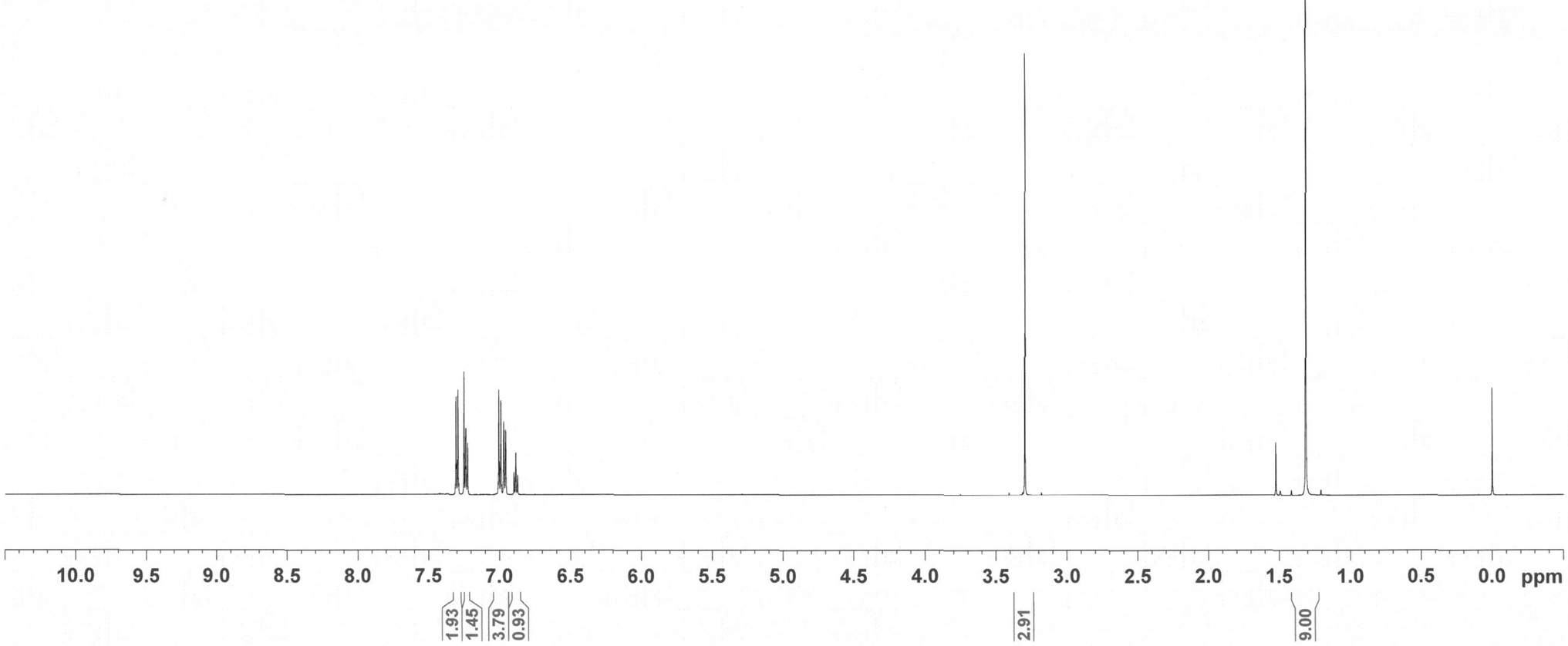
```
Current Data Parameters
NAME      km1-1018-1-cdcl3
EXPNO                   10
PROCNO                   1

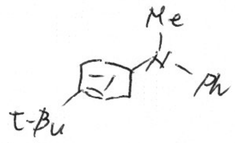
F2 - Acquisition Parameters
Date_             20141205
Time                 15.04
INSTRUM              spect
PROBHD    5 mm CPPBBO BB
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              12019.230 Hz
FIDRES            0.183399 Hz
AQ                2.7262976 sec
RG                   31.94
DW                  41.600 usec
DE                  10.00 usec
TE                  300.0 K
D1               1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1           600.1337060 MHz
NUC1                   1H
P1                  12.00 usec
PLW1           23.00000000 W

F2 - Processing parameters
SI                    65536
SF            600.1300220 MHz
WDW                     EM
SSB       0
LB                   0.30 Hz
GB        0
PC                    1.00
```



4-(tert-butyl)-N-methyl-N-phenylaniline
13C CDCl3



149.36
146.53
144.95
129.19
126.22
121.39
120.35
119.12
77.37
77.16
76.95
40.37
34.35
31.61
0.15

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```
Current Data Parameters
NAME      km1-1018-1-cdcl3
EXPNO                   11
PROCNO                   1

F2 - Acquisition Parameters
Date_           20141205
Time               15.39
INSTRUM            spect
PROBHD   5 mm CPPBBO BB
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           36057.691 Hz
FIDRES         0.550197 Hz
AQ            0.9087659 sec
RG               175.56
DW               13.867 usec
DE                18.00 usec
TE                300.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

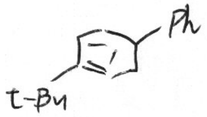
======== CHANNEL f1 ========
SFO1        150.9178981 MHz
NUC1                13C
P1                10.00 usec
PLW1        70.00000000 W

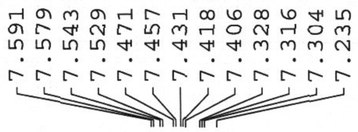
======== CHANNEL f2 ========
SFO2        600.1324005 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             70.00 usec
PLW2        26.00000000 W
PLW12        0.76407999 W
PLW13        0.37439999 W

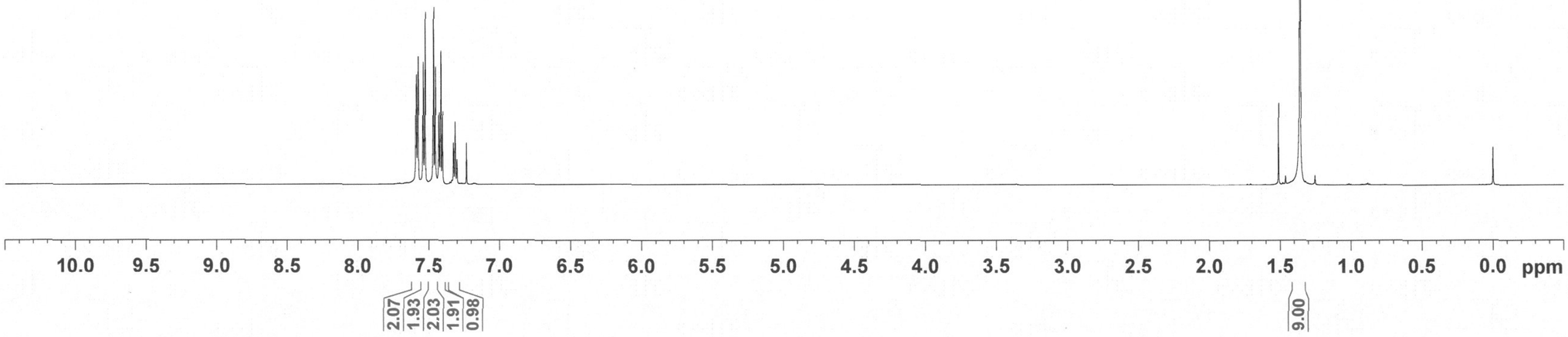
F2 - Processing parameters
SI                32768
SF          150.9027880 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

4-(tert-butyl)-1,1`-biphenyl
1H CDCl3







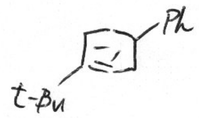

```
Current Data Parameters
NAME      km1-949-1-cdcl3
EXPNO                  10
PROCNO                  1

F2 - Acquisition Parameters
Date_           20140808
Time              15.19
INSTRUM           spect
PROBHD   5 mm CPPBBO BB
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ             2.7262976 sec
RG                 17.5
DW                41.600 usec
DE                10.00 usec
TE                300.0 K
D1           1.00000000 sec
TD0                   1

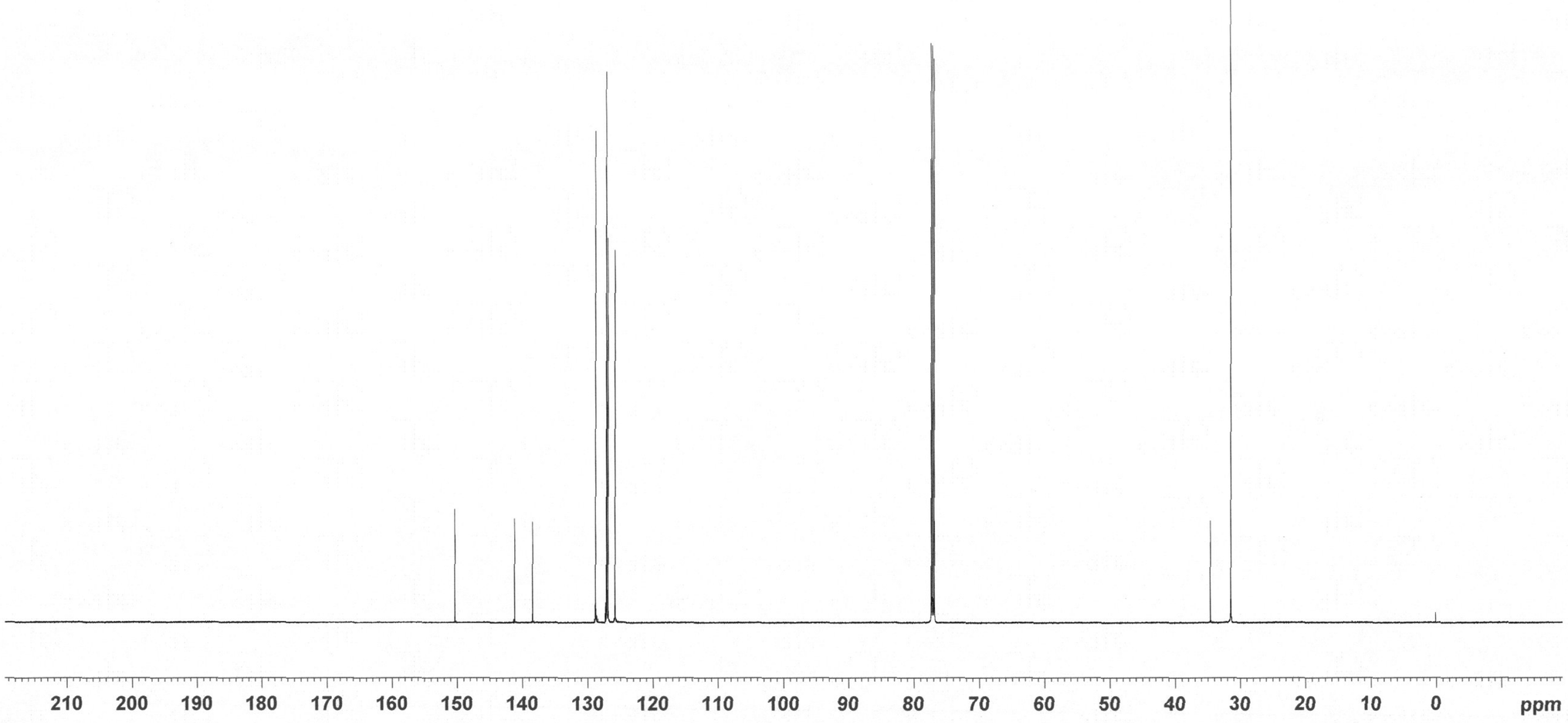
======== CHANNEL f1 ========
SFO1        600.1337060 MHz
NUC1                1H
P1                12.00 usec
PLW1        23.00000000 W

F2 - Processing parameters
SI                65536
SF          600.1300327 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

4-(tert-butyl)-1,1`-biphenyl
13C CDCl3



150.40
141.22
138.47
128.83
127.17
127.12
126.93
125.85
77.37
77.16
76.95
34.68
31.52
0.15



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```
Current Data Parameters
NAME      km1-949-1-cdcl3
EXPNO                  21
PROCNO                  1

F2 - Acquisition Parameters
Date_           20140827
Time               9.03
INSTRUM           spect
PROBHD   5 mm CPPBBO BB
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1200
DS                    4
SWH           36057.691 Hz
FIDRES         0.550197 Hz
AQ            0.9087659 sec
RG               175.56
DW               13.867 usec
DE                18.00 usec
TE                300.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        150.9178981 MHz
NUC1               13C
P1               10.00 usec
PLW1        70.00000000 W

======== CHANNEL f2 ========
SFO2        600.1324005 MHz
NUC2               1H
CPDPRG[2        waltz16
PCPD2            70.00 usec
PLW2        26.00000000 W
PLW12        0.76407999 W
PLW13        0.37439999 W

F2 - Processing parameters
SI                32768
SF          150.9027898 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```