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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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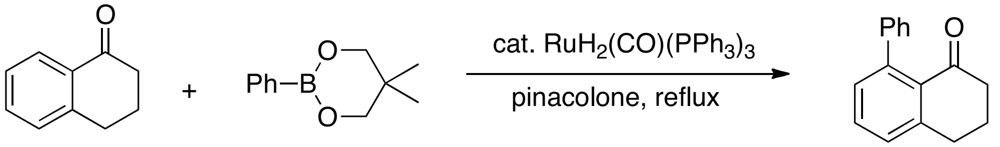
RUTHENIUM-CATALYZED ARYLATION OF ORTHO C-H BOND IN AN AROMATIC WITH AN ARYLBORONATE: 8-PHENYL-1-TETRALONE



Submitted by Kentaroh Kitazawa, Takuya Kochi, and Fumitoshi Kakiuchi.[1]
Checked by Somenath Chowdhury and Jonathan A. Ellman.

1. Procedure

8-Phenyl-1-tetralone (Note 1). All glassware and a magnetic stirring bar are oven-dried for about 0.5 h prior to use. A 100-mL three-necked round-bottomed flask is equipped with a reflux condenser connected to a vacuum/N_2 line, a thermometer, a rubber septum, and a Teflon coated octagonal magnetic stirring bar of dimension 8mm x 13mm. The flask is evacuated and backfilled with nitrogen three times. While the rubber septum is temporarily removed and a positive flow of nitrogen is maintained, the flask is charged with 5,5-dimethyl-2-phenyl[1,3,2]dioxaborinane, $PhB(OCH_2CMe_2CH_2O)$, (8.55 g, 45.0 mmol, 1.50 equiv) (Note 2) and carbonyldihydridotris(triphenylphosphine)ruthenium(II) ($RuH_2(CO)(PPh_3)_3$) (1.38 g, 1.50 mmol, 0.050 equiv) (Note 3). The flask is again evacuated and backfilled with nitrogen three times. 3,3-Dimethylbutan-2-one (pinacolone) (15 mL) (Note 4) and 1-tetralone (4.39 g, 4.00 mL, 30.0 mmol, 1.00 equiv) (Note 5) are added to the flask through the rubber septum via syringes in the order indicated at room temperature to give a white suspension (Note 6). The resulting mixture is heated at reflux in an oil bath (oil bath temperature 125 °C) (Note 7). The reaction mixture becomes a dark red solution within 5 min. After heating for 12 h, the mixture is cooled to room temperature (Notes 8 and 9). The resulting dark red solution is transferred to a 250-mL round-bottomed flask and concentrated by rotary evaporation (15 mmHg). The three-necked flask is rinsed with dichloromethane (50 mL) in two portions, and the combined rinse is transferred to the 250-mL flask, followed by concentration by rotary evaporation. The volatile materials are further removed under vacuum (1 mmHg) for 30 min. The residue is dissolved in dichloromethane (50 mL) and transferred to a 1-L Erlenmeyer flask. The round-bottomed flask is further rinsed with dichloromethane (2 x 125 mL) and the rinse is also transferred to the Erlenmeyer flask (Note 10). Basic alumina (250 g) (Note 11) is added to the solution, and the resulting mixture is stirred at room temperature for 30 min (Note 12). The mixture is filtered through Celite (20 g) (Note 13), and the filter cake is washed with dichloromethane (500 mL). After concentrating by rotary evaporation (15 mmHg), the resulting material is transferred to a 200-mL recovery flask using dichloromethane (50 mL). SiO_2 (9.0 g) (Note 14) is added to the dark red solution. The solvent is removed by rotary evaporation (15 mmHg) and then under vacuum (1 mmHg) for 2 h. Flash column chromatography is performed by charging the resulting solid onto the top of the column of SiO_2 (120 g) (Note 14) and eluting with 5% ethyl acetate in hexane (Note 15). The combined fractions containing the phenylated product are concentrated by rotary evaporation (15 mmHg). The resulting material is dissolved in a single-neck, open to air 1-L round-bottomed flask using methanol (90 mL) (Note 16) by heating in an oil bath with the bath temperature maintained at 90 °C. Distilled water (300 mL) is slowly added to the mixture to form a white precipitate, and then the oil bath is removed. After cooling the mixture to room temperature, water (600 mL) is slowly added. The precipitated white solid is collected by suction filtration on a Büchner funnel (Note 17) and washed with water (200 mL). Drying the solid under vacuum (1 mmHg) for 20 h gives 5.39-5.72 g (81-86% yield) of 8-phenyl-1-tetralone as a white solid (Note 18).

2. Notes

1. This procedure is a modification of that published by the submitters.[2]

2. The phenylboronate, 5,5-dimethyl-2-phenyl[1,3,2]dioxaborinane, can be synthesized according to the literature method.[3,4] This reagent is commercially available from chemical suppliers including Aldrich Chemical Company, Inc. and Wako Pure Chemical Industries, Ltd. The checkers purchased this reagent from Sigma-Aldrich.

3. The ruthenium complex, carbonyldihydridotris(triphenylphosphine)ruthenium(II), can be synthesized according to the literature method.[5,6] This complex is commercially available from various chemical suppliers including Aldrich Chemical Company, Inc., Strem Chemicals Inc.,

Acros Organics, Wako Pure Chemical Industries, Ltd., and Tokyo Chemical Industry Co., Ltd. The checkers purchased the reagent from Sigma-Aldrich.

4. Pinacolone was purchased from Sigma-Aldrich by the checkers and from Tokyo Chemical Industry Co., Ltd by the submitters. The reagent was dried over $CaSO_4$ and distilled (bp = 106 °C/760 mmHg).

5. 1-Tetralone was purchased from Sigma-Aldrich, dried over $CaSO_4$, and distilled under reduced pressure (bp = 117 °C/5 mmHg).

6. The ruthenium complex was only slightly soluble in pinacolone at room temperature.

7. Maintaining the oil bath temperature at 120–130 °C (preferentially around 125 °C) is necessary to effect the catalytic reaction with good reproducibility. Oil bath temperature was set to 125 °C and the internal temperature varied from 117–119°C.

8. The progress of the reaction can be followed by TLC analysis on silica gel (with 20% EtOAc-hexane as eluent and visualization with UV light (254 nm)). 1-Tetralone has an $R_f = 0.51$ and the phenylation product has an $R_f = 0.44$. TLC analysis was performed on Merck silica gel $60F_{254}$ pre-coated glass plates.

9. After the reaction, a yellow precipitate is sometimes observed. In this case, after cooling to room temperature, the reaction mixture is filtered through Celite. The Celite pad is then washed with diethyl ether (10 mL x 3) and the filtrates are combined. The checkers did not observe any yellow precipitate.

10. Dichloromethane was purchased from Fisher Scientific and used as received.

11. Merck aluminum oxide 90 active basic (0.063-0.200 mm, activity stage I) was used.

12. Basic alumina was added to remove the unreacted phenylboronate from the mixture, because the boronic ester exhibits significant tailing on silica gel column chromatography.

13. Celite® 545 was purchased from Kanto Chemical Co., Inc. and used as received.

14. Merck silica gel 60 (mesh 230-400) was added to the flask, which is the same batch of silica gel that was used to perform the chromatography.

15. The silica gel column (33 x 230 mm) was eluted with 3.5 L of 5% ethyl acetate in hexane at a flow rate of approximately 40 mL/min. 50 mL fractions were collected, and fractions 19 to 57, for which the product was observed by TLC analysis, were combined. In some cases, a small amount of

1-tetralone was also found in the early fractions that contained the product. These fractions can be combined with pure ones, which only contain the product, because 1-tetralone can be removed by a reprecipitation procedure following chromatography. Ethyl acetate (>99.0%) and hexane (>95.0%) were purchased from Fisher Scientific by the checkers and from Wako Pure Chemical Industries, Ltd. by the submitters and were used as received.

16. Methanol (>99.5%) was purchased from Fisher Scientific by the Checkers and from Kanto Chemical Co., Inc. by the submitters and was used as received.

17. Whatman grade 202 filter paper was used for the filtration.

18. The product exhibited the following physicochemical properties: Mp 97.0–97.5 ºC; IR (ATR): 1678 (C=O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.14 (tt, *J* = 6.6, 6.0 Hz, 2 H), 2.62 (t, *J* = 6.6 Hz, 2 H), 3.01 (t, *J* = 6.3 Hz, 2 H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.21–7.22 (m, 2 H), 7.24–7.26 (d, *J* = 7.8 Hz, 1 H), 7.31–7.33 (m, 1 H), 7.35–7.39 (m, 2 H), 7.43 (t, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.2, 30.8, 40.6, 126.7, 127.9, 128.2, 128.2, 130.4, 131.3, 131.9, 143.0, 144.1, 145.7, 198.5; HRMS (ESI) *m/z* calc. for $C_{16}H_{15}O$ ($[M+H]^+$) 223.1117; found 223.1110; Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35; found: C, 86.15; H, 6.52.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Transition metal-catalyzed functionalizations of C-H bonds are highly attractive research subjects in current organic synthesis.[7,8] Among these reactions, heteroatom-directed direct C-H arylations of aromatic compounds have been extensively studied. Almost all of these arylations involve electrophilic substitution at aromatic C-H bonds[9] or base-assisted proton abstraction from aromatic C-H bonds.[10] In these processes, relatively high valent transition metals, such as, Pd(II), Ru(II), and Rh(III), participate in the C-H bond cleavage step, and the hydrogen of the C-H bond is removed as a proton from the aromatic ring. In the C-H arylation described here, however, an ortho C-H bond in an aromatic ketone is cleaved via oxidative addition to a ruthenium(0) center and an (aryl)(H)Ru species is formed.[2,11] One of the key steps in the catalytic cycle is generation of a ruthenium-alkoxide intermediate which is essential for transmetalation with an arylboronate. The use of pinacolone as a solvent effectively generates an (aryl)(alkoxy)ruthenium intermediate without sacrificing much of the aromatic ketone substrate. Thus, pinacolone functions not only as a solvent but also as a hydride acceptor from the Ru-H species. Transmetalation between the ruthenium-alkoxide and the organoboronate provides a diarylruthenium intermediate, and subsequent reductive elimination yields the corresponding ortho-arylated aromatic ketone and regenerates the catalytically active species.

An important feature of the present ruthenium-catalyzed C-H arylation is that many functional groups, except for the ortho C-H bond, are tolerated in the reaction. A variety of aromatic ketones bearing an electron-donating or electron-withdrawing group can be used for this ruthenium-catalyzed arylation with arylboronates. Representative results concerning the $RuH_2(CO)(PPh_3)_3$-catalyzed C-H arylation are listed in the Table.

Table 1. Ruthenium-catalyzed C-H arylation of aromatic ketones with arylboronates.[a,b]

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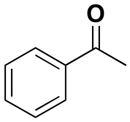
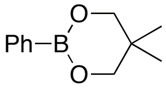
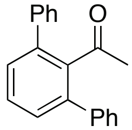
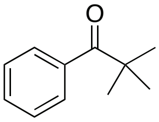
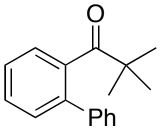
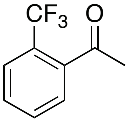
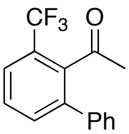
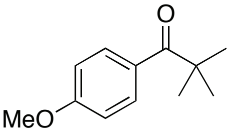
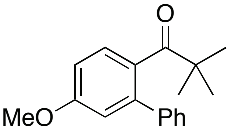
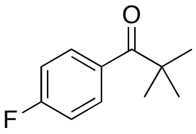
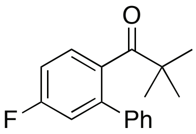
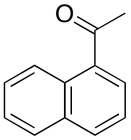
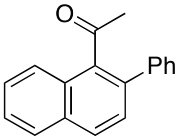
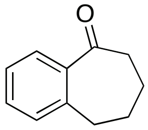
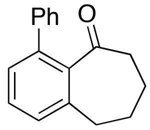
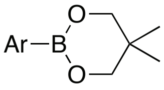
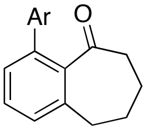
1[d]		 **1**	1 h		89%
2		**1**	1 h		76%
3		**1**	2 h		61%
4		**1**	1 h		81%
5		**1**	1 h		78%
6		**1**	3 h		78%
7[e]	 **2**	**1**	4 h	 **2**	98%
		 **3**		 **4**	
8[e]	**2**	**3a:** Ar = $\text{4-MeOC}_6\text{H}_4$	1 h	**4a**	88%
9[e]	**2**	**3b:** Ar = $\text{4-Me}_2\text{NC}_6\text{H}_4$	1 h	**4b**	84%
10[e]	**2**	**3c:** Ar = $\text{4-FC}_6\text{H}_4$	1 h	**4c**	75%
11[e]	**2**	**3d:** Ar = $\text{4-CF}_3\text{C}_6\text{H}_4$	1 h	**4d**	84%
12[e]	**2**	**3e:** Ar = $\text{2-MeC}_6\text{H}_4$	1 h	**4e**	96%
13[e]	**2**	**3f:** Ar = 1-naphthyl	1 h	**4f**	92%

[a]See ref. [b]Reaction conditions: aromatic ketone (1 mmol), phenylboronate (1.1 mmol), RuH$_2$(CO)(PPh$_3$)$_3$ (0.02 mmol), pinacolone (1.0 mL, 8 mmol), reflux. [c]Isolated yield. [d]**1** (2.2 mmol), [e]**1**(1.2 mmol), pinacolone (0.5 mL).

1. Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan. E-mail: kakiuchi@chem.keio.ac.jp.
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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

$RuH_2(CO)(PPh_3)_3$: Ruthenium, carbonyldihydrotris(triphenylphosphine); (25360-32-1)

1-Tetralone: 1(2H)-Naphthalenone, 3,4-dihydro-; (529-34-0)

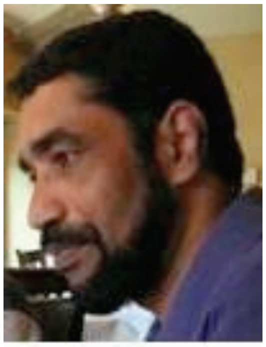
pinacolone: 2-Butanone, 3,3-dimethyl-; (75-97-8)

Phenylboronate: 1,3,2-Dioxaborinane, 5,5-dimethyl-2-phenyl-; (5123-13-7)

Fumitoshi Kakiuchi was born in Hyogo, Japan, in 1965 and received his B.Sc. in 1988 and Ph.D. in 1993 from Osaka University under the guidance of Professor Shinji Murai. He was appointed as an Assistant Professor at Osaka University in 1993. He did his postdoctoral work with Prof. E. N. Jacobsen at Harvard University in 1996-1997. In 2000, he was promoted to an Associate Professor at Osaka University. In 2005, he moved to Keio University as a Professor. His research interests include the development of new transition metal-catalyzed reactions.

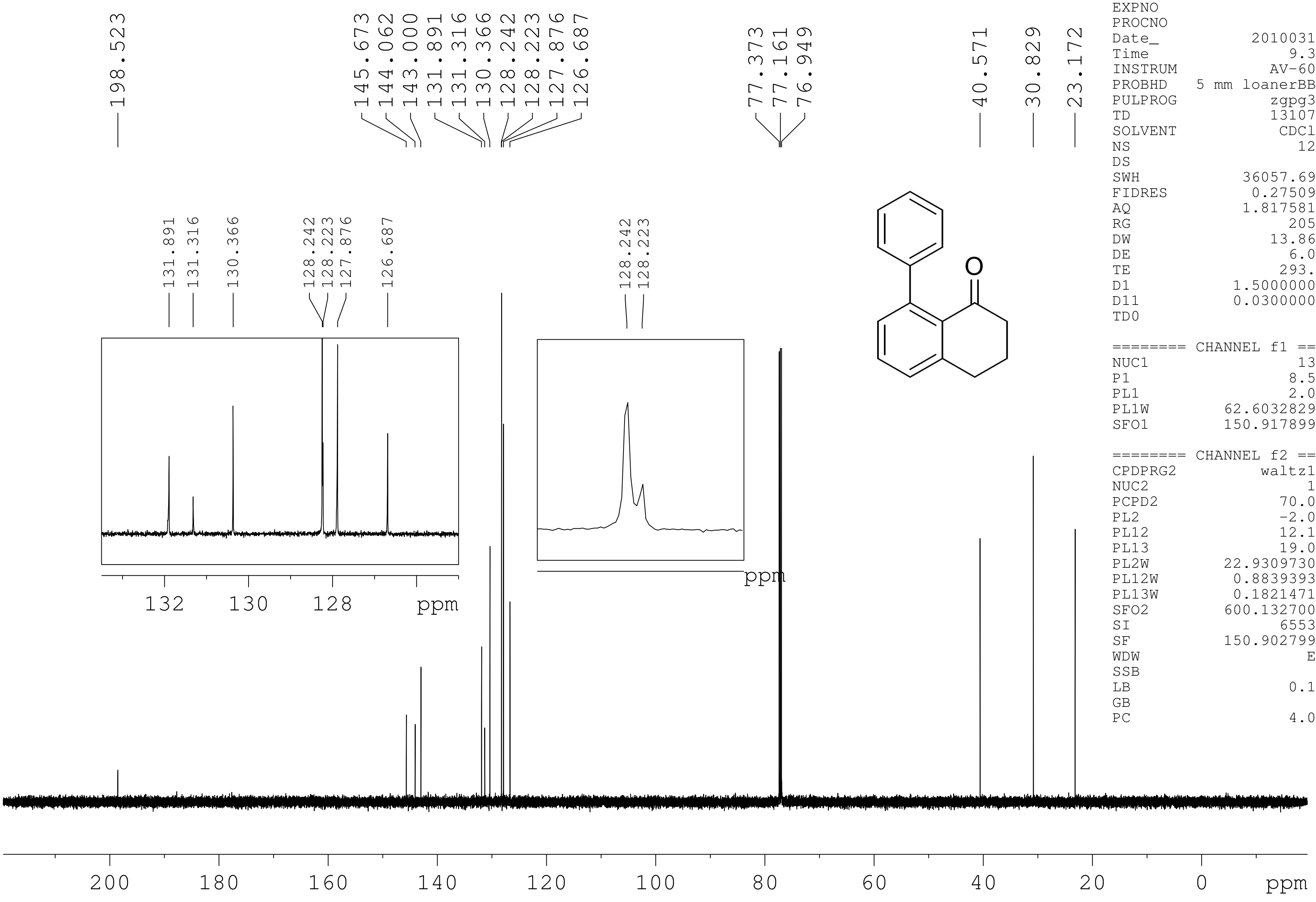
Kentaroh Kitazawa was born in Nagano, Japan in 1983. B. Sc. in 2006 and M.Sc. in 2008 from Keio University, working with Professor Fumitoshi Kakiuchi. He is currently a Ph.D. student in Professor Kakiuchi's group at Keio University. His research interest is catalytic C-H functionalization.

Takuya Kochi was born in Tokyo, Japan in 1975. He received his undergraduate and master's degree from the University of Tokyo, working with Professors Masanobu Hidai and Youichi Ishii, and his Ph.D. in chemistry from the University of California at Berkeley, working with Professor Jonathan A. Ellman. After carrying out postdoctoral research with Professor Kyoko Nozaki at the University of Tokyo, he joined the group of Professor Fumitoshi Kakiuchi at Keio University as an Assistant Professor in 2007. His research interests include development of new reactions and their application to the synthesis of a wide range of organic molecules.



Somenath Chowdhury grew up in Majirdanga, India. He obtained his M.Sc. degree in Chemistry from the Indian Institute of Technology, Kharagpur, India and his Ph. D. degree from the University of Saskatchewan, Canada. In his Ph.D. research he worked on the design and synthesis of peptide beta sheet mimics under the supervision of Professor Heinz-Berhard Kraatz. After finishing his Ph.D. he carried out research with Professor Giuseppe Melacini's group at McMaster University, Canada for one and a half years where he studied protein ligand interactions by NMR spectroscopy. He then joined Professor Jonathan Ellman's lab at the University of California, Berkeley in Sept 2008 as an NSERC postdoctoral fellow. His current research focuses on developing small molecule protease inhibitors.

8-Phenyl-1-tetralone



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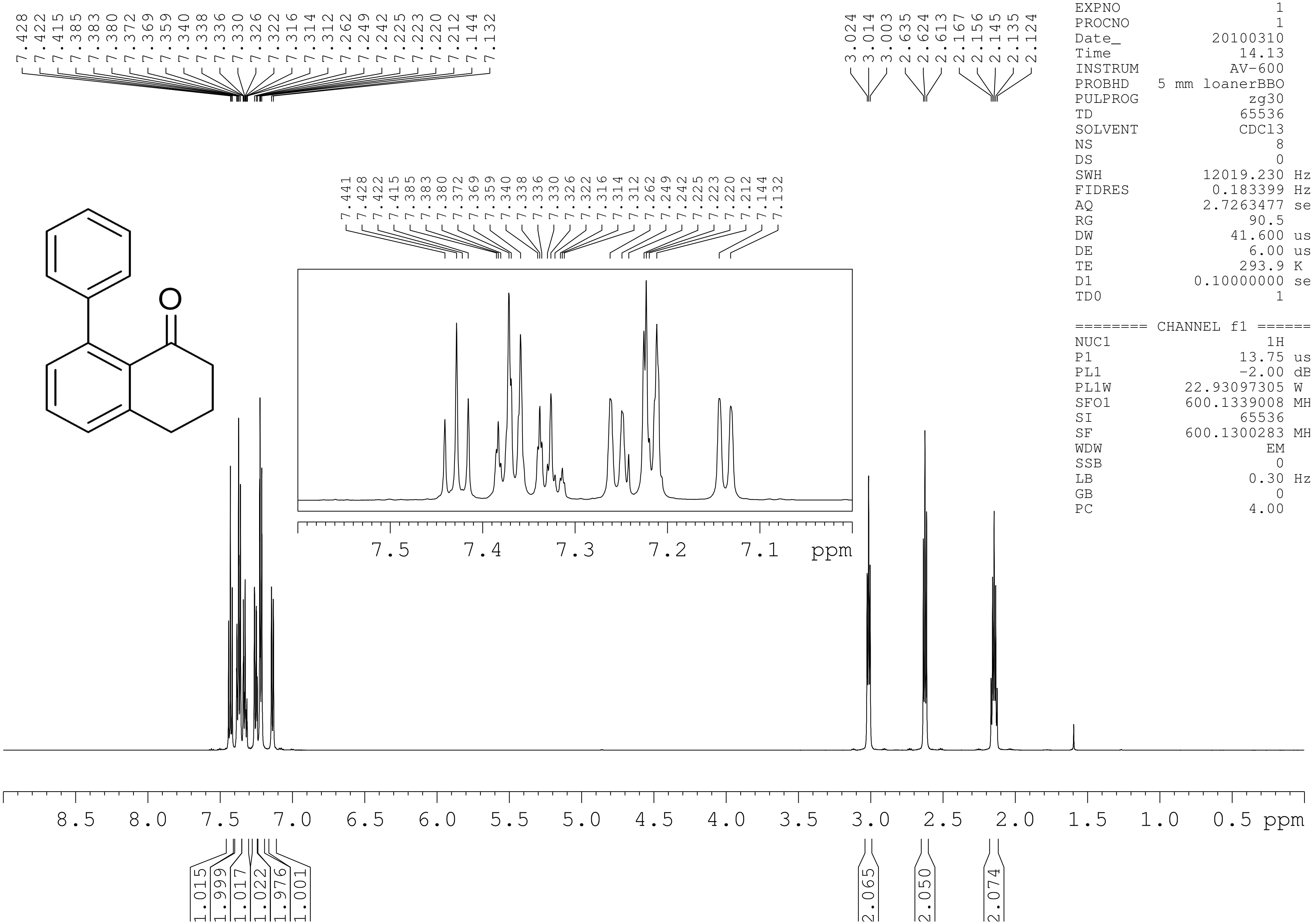
8-Phenyl-1-tetralone



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