Organic Syntheses

Rhodium-Catalyzed Direct Amination of Arene C-H Bonds Using Azides as the Nitrogen Source

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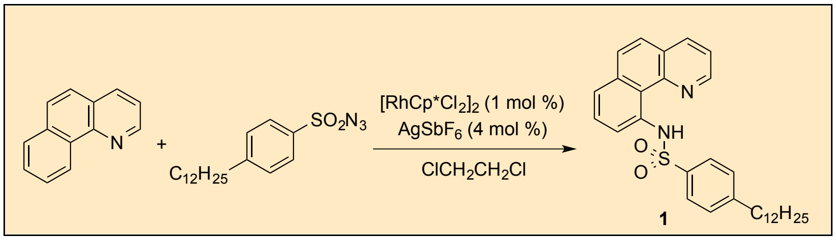
Checked by Kazuma Amaike, Kolby Lyn White, and Mohammad Movassaghi



Procedure

A. *N-(Benzo[h]quinolin-10-yl)-4-dodecylbenzenesulfonamide of compound (**1**).* A flame-dried, 100 mL, two-necked round-bottomed flask (Note 1) is equipped with a 3-cm football-shaped stir bar, dichloro(η^5-pentamethylcyclopentadienyl)-rhodium(III) dimer (124 mg, 0.20 mmol, 1.00 mol%), silver hexafluoroantimonate(V) (275 mg, 0.80 mmol, 4.00 mol%) (Note 2), and benzo[*h*]quinoline (3.58 g, 20 mmol) (Note 3). One neck of the flask is equipped with a reflux condenser (Note 1) and another neck is closed with a rubber septum. The flask is evacuated and then back-filled with dry N_2, a process that is performed three times. Distilled 1,2-dichloroethane (20 mL) (Note 4) and *p*-dodecylbenzenesulfonyl azide (7.36 mL, 22 mmol, 1.10 equiv) (Note 3) are added sequentially via syringe to the flask (Note 5). Under a continuous flow of N_2 gas by balloon (should not use balloons!), the mixture is placed in a preheated oil bath at 80 °C and stirred for 12 h (Note 6). After the reaction is complete as judged by TLC analysis (Note 7), the reaction mixture is cooled to room temperature and then filtered through a silica pad (19.0 g) washing with dichloromethane (5 x 20 mL) (Note 8) into a round-bottomed flask (Note 9). The filtrate is concentrated using a rotary evaporator (20 mmHg, water bath temperature 30 °C), and is purified by recrystallization from dichloromethane (5 mL) and *n*-hexane (100 mL) (Note 8) at 0 °C for 12 h (Note 10). Precipitate is filtered through a Büchner funnel (Whatman filter paper, 70 mm diameter) and washed with *n*-hexane (5 x 20 mL) at 25 °C to yield a yellowish solid. The filtered solid is transferred to a 20-mL glass vial with spatula and dried under vacuum at room temperature for 12 h to give an air stable yellow solid product **1** (7.74 g, 77%) (Note 11).

Notes

1. All glassware was flame-dried under vacuum and allowed to cool under an atmosphere of nitrogen.
2. Dichloro(η^5–pentamethylcyclopentadienyl)rhodium(III) dimer (99%) was purchased from Strem Chemicals Co., Ltd., and silver hexafluoroantimonate(V) (98%) was purchased from Aldrich Chemical Co., and both reagents were used as received.
3. Benzo[*h*]quinoline (99%) and *p*-dodecylbenzenesulfonyl azide (soft type, mixture) were purchased from Tokyo Chemical Industry Co., Inc and were used as received.
4. The checkers purchased 1,2-dichloroethane from Aldrich Chemical Co., and the liquid was distilled from calcium hydride before use.
5. The reflux condenser was used for heating the reaction mixture around the boiling point of 1,2-dichloroethane. However, the submitters obtained a similar range of product yields without using a reflux condenser, in which the flask was equipped with a rubber septum and kept under a N_2 atmosphere (balloon).
6. The reaction mixture was stirred at room temperature for 10 min before placing in a pre-heated oil bath (80 °C).
7. The progress of the reaction was monitored by TLC. For TLC analysis, silica gel 60 F_{254} TLC plates (EMD Chemicals, Inc.) were used.
8. The submitters purchased dichloromethane, ethyl acetate, and *n*-hexane from Junsei Chemical Co. Ltd. and used as received.

9. Silica gel 60 (0.040-0.063 mm) (230-400 mesh ASTM) was purchased from Aldrich Chemical Co. Inc., and used as received. A glass filter (60-mL) with a medium porosity fritted disc was used.
10. While a liquid product was first obtained upon rotary evaporation of solvent, crystallization of the crude residue yielded crystalline product.
11. The submitters and checkers obtained product yields in the range of 7.50~8.04 g (75~80%) without further purification. The product (a mixture of isomeric compounds in the dodecyl moiety) exhibits the following physicochemical properties, *N*-(benzo[*h*]quinolin-10-yl)-4-dodecylbenzenesulfonamide (**1**): R_f = 0.30 (20% ethyl acetate/*n*-hexane); mp 50–52 °C (decomp); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.50–1.58 (m, 24H), 2.21–2.60 (m, 1H), 6.98–7.10 (m, 2H), 7.46–7.60 (m, 4H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.72–7.82 (m, 2H), 7.84–7.93 (m, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.92 (d, *J* = 2.0 Hz, 1H), 15.06–15.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8, 13.7, 13.8, 13.89, 13.93, 14.0 (3C), 20.3, 21.6, 22.2, 22.39, 22.42, 22.45, 22.47, 22.52, 26.8, 27.1, 27.2, 27.3, 28.9, 29.0, 29.07, 29.13, 29.2, 29.27, 29.31, 29.36, 29.4 (2C), 31.4, 31.5, 31.6, 31.67, 31.7, 31.8, 35.9, 36.0, 36.28, 36.34, 37.8, 38.6, 39.6, 45.5, 45.7, 47.5, 116.0, 116.4, 116.6, 117.1, 117.3 (2C), 121.0, 122.6, 122.7, 122.8 (2C), 125.2 (2C), 126.99, 127.01, 127.1 (2C), 127.2 (2C), 127.8 (2C), 127.9, 128.4 (2C), 128.7 (2C), 134.9 (2C), 136.5 (2C), 137.4, 137.5 (2C), 138.4 (2C), 145.5, 146.96 (2C), 146.99, 151.3, 151.5, 151.62, 152.9. IR (NaCl) ν 2927, 2855, 1593, 1577, 1465, 1402, 1339 cm^{-1}; HRMS (EI) *m*/*z* calcd. for $C_{31}H_{38}N_2O_2S$ $[M+H]^+$: 503.2727, found: 503.2728; Elemental analysis; calcd. for $C_{31}H_{38}N_2O_2S$: C, 74.06; H, 7.62; N, 5.57; S, 6.38; Found: C, 74.05; H, 7.52; N, 5.52; S, 6.50.

Handling and Disposal of Hazardous Chemicals

The procedures in this article are intended for use only by persons with prior 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 www.nap.edu). 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.

Discussion

Aryl amines and aryl amides are a key synthetic building unit widely utilized in organic synthesis, coordination chemistry, materials science and pharmaceutical industry.[2] Currently, preparative routes to those compounds require either pre-functionalized reactants (aryl halides or haloamides) or external oxidants, and, therefore, the present procedures inevitably generate stoichiometric amounts of side products.[3] During the course of our efforts on developing new direct C-N bond formation reactions from arenes,[4] we found that an attractive nitrogen source are azides, which are able to be introduced into the arenes via direct C-H bond activation. We report herein a practical procedure of the direct C-H amination and amidation reaction of arenes using aryl sulfonyl azides as the source of the nitrogen functionality, which releases molecular nitrogen as the single by-product.[5]

This reaction is catalyzed under mild conditions by a cationic rhodium complex $[Cp^*Rh(III)]^{2+}(SbF_6)_2^{2-}$ (Cp*, η^5-pentamethylcyclopentadienyl) without requiring external oxidants. A broad range of chelate group-containing arenes were selectively aminated with excellent functional group tolerance. Preliminary mechanistic studies suggest that the carbon-nitrogen (C-N) bond formation proceeds via rate-limiting rhodium-mediated C-H bond activation of arenes followed by azide insertion into a rhodacycle intermediate.[5]

This procedure offers a very efficient and practical route to aryl amines and amides. Although additional optimization processes may be required for each substrate, synthetically acceptable product yields were obtained for wide range of arenes and azides investigated as demonstrated in Table 1.

Table 1. Direct C-H amination of arenes with sulfonyl- and aryl azides [a]

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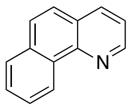
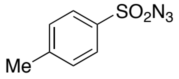
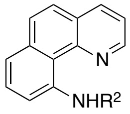
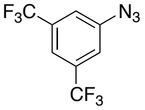
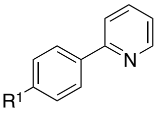
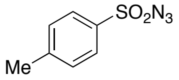
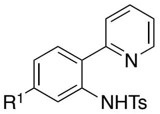
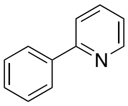
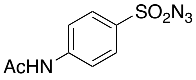
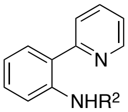
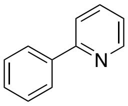
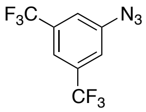
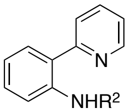
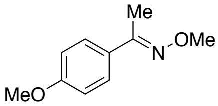
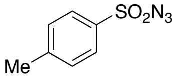
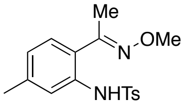
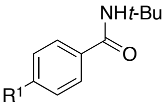
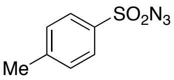
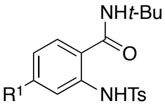
1[c]					89
2[d]					82
3		R^1 = H			83
4		Me			86
5		CHO			82
6		CF_3			82
7					71
8[d]					80
9					61
10		R^1 = H			60
11		Me			79

[a] Reaction conditions: arene (5.0 mmol), azide (5.5 mmol), $[RhCp^*Cl_2]_2$ (3.0 mol %), $AgSbF_6$ (12.0 mol %) in 1,2-dichloroethane (10 mL) at 80 °C for 24 h. [b] Isolated yield. [c] Scale of 20.0 mmol. [d] Scale of 1.0 mmol.

References

1. Center for Catalytic Hydrocarbon Functionalizations (IBS) and Department of Chemistry, Korea Advanced Institute of Science and

Technology (KAIST), Daejeon, 305-701, Republic of Korea, E-mail: sbchang@kaist.ac.kr.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

Silver hexafluoroantimonate(V) (26042-64-8)
Dichloro(η^5-pentamethylcyclopentadienyl)rhodium(III) dimer (12354-85-7)
Benzo[*h*]quinoline (230-37-3)
p-Dodecylbenzenesulfonyl azide (79791-38-1)

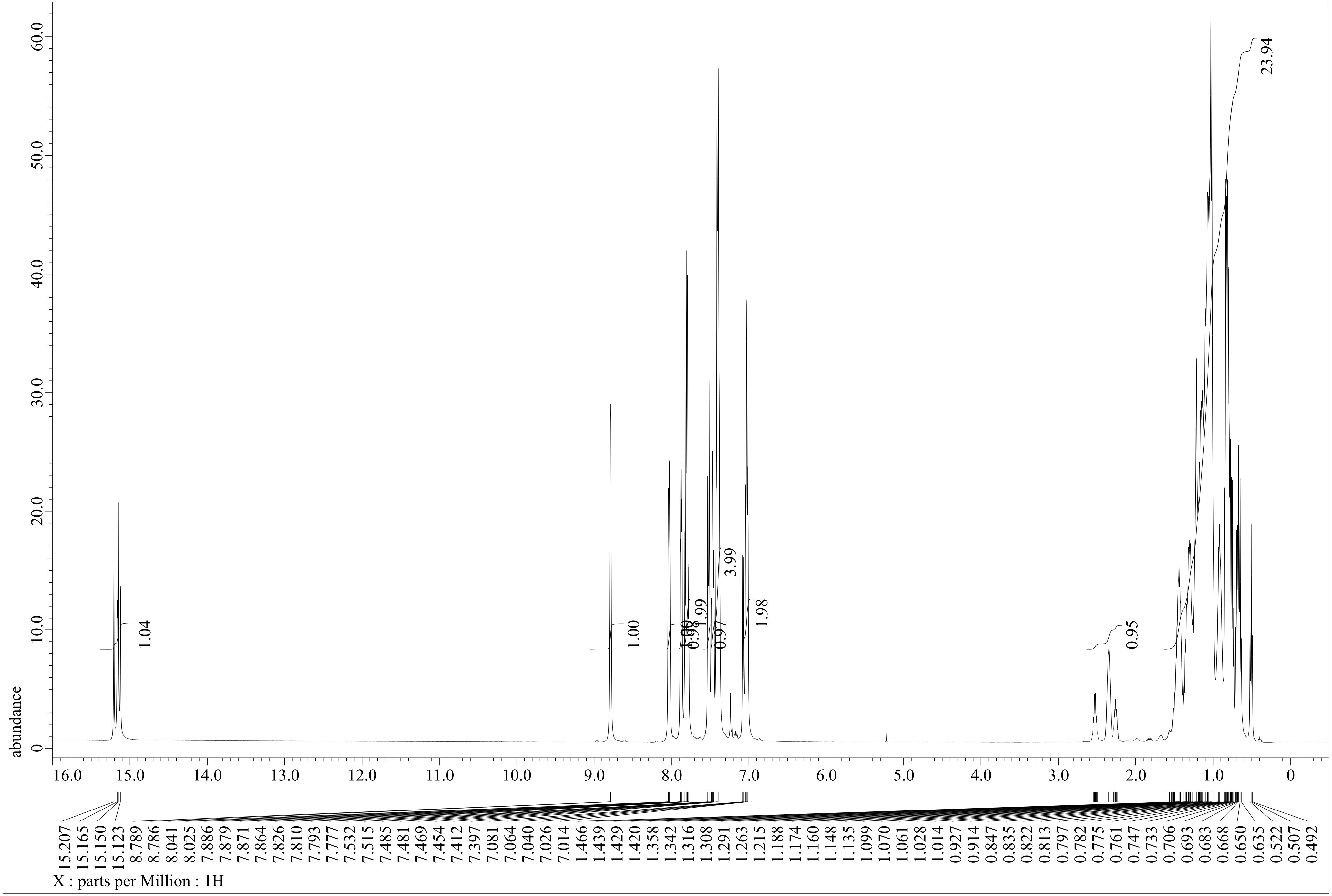
Professor Sukbok Chang received his B.S. degree from Korea University (1985), M.S. from KAIST (1987) and Ph.D. from Harvard University (1996) under the guidance of Professor Eric N. Jacobsen. He was a postdoctoral fellow in the lab of Professor Robert H. Grubbs at California Institute of Technology from 1996 to 1998, and became an assistant professor at Ewha Womans University (Seoul, Korea) in 1998. In 2002, he moved to the present position at KAIST and was promoted to professor 2007. He received the Award for Young Chemists (KCS-Wiley) of the Korea Chemical Society (2002), Organic Chemistry Division Award (2005), and Korean Chemical Society Academic Award (2010). His recent research interests include the development of new synthetic methods via metal catalysis.

Sae Hume Park was born in Princeton, New Jersey, United States of America, in 1985. He received his B.S. degree in chemistry from Sungkyunkwan University (2008). He is now in M.S.-Ph.D. joint course at Korea Advanced Institute of Science and Technology (KAIST) under the guidance of Professor Sukbok Chang. Currently, he is focused on researching metal-catalyzed oxidative C-H bond activation to make C-C and C-N bond formation.

Yoonsu Park was born in Suwon, Korea, in 1992. He is an undergraduate student in Korea Advanced Institute of Science and Technology (KAIST), and now performing undergraduate research at KAIST under the guidance of Professor Sukbok Chang. Currently, he is interested in discovering C-H bond activation reactions to make biologically active compounds

Kazuma Amaike is pursuing his graduate studies in Professor Kenichiro Itami's group at Nagoya University, Nagoya, Japan. His studies focus on a range projects related to C–H activation and the synthesis of natural products. In 2013, he joined the laboratory of Professor Mohammad Movassaghi at MIT as a visiting graduate student via the National Science Foundation CCI Center for selective C–H functionalization.

Kolby Lyn White pursued her undergraduate studies at Northwestern University, where she received her B.A./M.S. degree in Chemistry in 2011. While an undergraduate, she worked in the laboratory of Professor Karl Scheidt. In 2011, she joined the laboratory of Professor Mohammad Movassaghi at MIT for her graduate studies, which is focused on the total syntheses of alkaloid natural products.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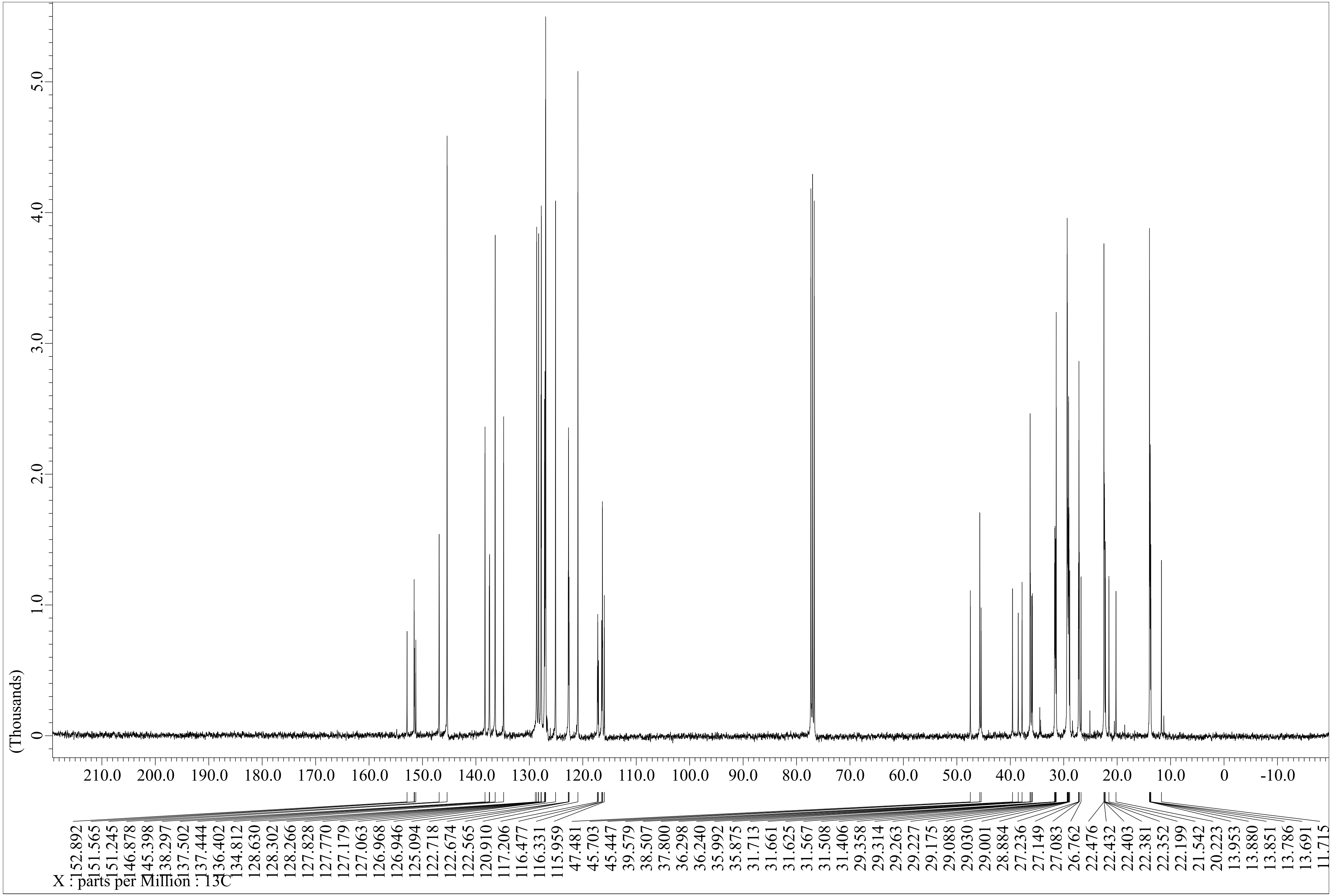
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X : parts per Million : 13C