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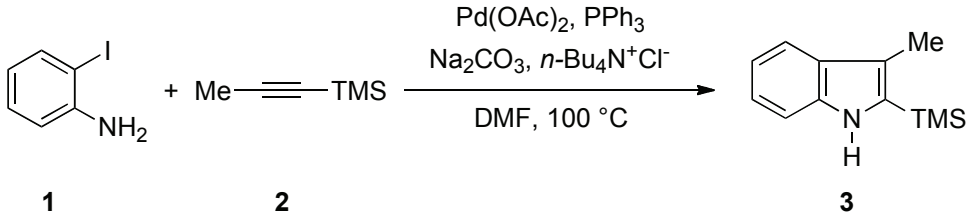
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

SYNTHESIS OF 2,3-DISUBSTITUTED INDOLES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALK YNES: 3-METHYL-2-(TRIMETHYLSILYL)INDOLE



1 **2** **3**

Submitted by Yu Chen, Nataliya A. Markina, Tuanli Yao, and Richard C. Larock.[1,2]
Checked by Kevin M. Allan and Viresh H. Rawal.

1. Procedure

3-Methyl-2-(trimethylsilyl)indole. A flame-dried 1-L, three-necked round-bottomed flask equipped with a 15 mm × 32 mm football-shaped magnetic stirring bar, a thermometer, a reflux condenser fitted with a nitrogen inlet, and a glass stopper is charged with 2-iodoaniline (**1**, 10.95 g, 50.0 mmol, 1.0 equiv) (Note 1), palladium(II) acetate (281 mg, 1.25 mmol, 0.025 equiv) (Note 2), triphenylphosphine (656 mg, 2.50 mmol, 0.050 equiv) (Note 3), sodium carbonate (13.25 g, 125.0 mmol, 2.5 equiv) (Note 4), tetra-*n*-butylammonium chloride (13.91 g, 50.0 mmol, 1.0 equiv) (Notes 5–8), and *N*,*N*-dimethylformamide (DMF, 500 mL) (Note 9). The mixture is stirred for 10 min at room temperature under a nitrogen atmosphere resulting in an orange suspension. 1-Trimethylsilyl-1-propyne (**2**, 16.98 g, 22.4 mL, 151.3 mmol, 3.0 equiv) (Note 10) is then added to the flask via syringe. The reaction flask is immersed in a preheated oil bath (at 110 °C) equipped with an external thermometer (Note 11). The reaction mixture is stirred at an internal temperature of 100 ºC for 20 h until the reaction is complete (Notes 12 and 13). The resulting dark brown suspension is cooled to room temperature. The glass stopper is replaced with a pressure-equalizing dropping funnel. Saturated aqueous NH_4Cl solution (100 mL) is added to the reaction mixture through the pressure-equalizing dropping funnel over 10 min with vigorous stirring (Note 14). The resulting two-phase mixture is transferred to a 2-L round-bottomed flask

equipped with a 15 mm × 32 mm football-shaped magnetic stirring bar. The original three-necked round-bottomed flask is rinsed with diethyl ether (2 × 30 mL) followed by saturated aqueous NH_4Cl solution (50 mL), and each rinse is transferred to the 2 L round-bottomed flask. The resulting mixture is sequentially treated with saturated aqueous NH_4Cl solution (220 mL) and diethyl ether (320 mL). The resulting two-phase mixture is stirred for 5 min at room temperature and transferred to a 2-L separatory funnel. The layers are separated and the aqueous phase is extracted three times with diethyl ether (3 × 150 mL) (Note 15). The combined organic phases are washed two times with water (2 × 100 mL), dried over anhydrous magnesium sulfate ($MgSO_4$) (Note 16), filtered through a medium porosity fritted glass funnel, rinsed with diethyl ether (50 mL), and concentrated by rotary evaporation (23 °C, 20 mmHg) to give a dark brown oil. The residue is purified by flash column chromatography on silica gel (Note 17) to afford 9.28 g (91%) of indole **3** as an orange oil (Notes 18 and 19).

2. Notes

1. The submitters purchased 2-iodoaniline (**1**, 98%) from TCI America and used it as received. The checkers purchased 2-iodoaniline (**1**, 98%) from Sigma-Aldrich and used it as received.

2. The submitters received palladium(II) acetate donated by Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. and used it as received. The checkers purchased palladium(II) acetate (98%) from Sigma-Aldrich and used it as received.

3. The submitters and checkers each purchased triphenylphosphine (PPh_3, 99%) from Sigma-Aldrich and used it as received.

4. The submitters and checkers each purchased sodium carbonate (Na_2CO_3, 99.7%, anhydrous) from Fisher Scientific and used it as received.

5. The submitters purchased tetra-*n*-butylammonium chloride (*n*-Bu_4NCl, >97%) from TCI America and used it as received. The checkers purchased tetra-*n*-butylammonium chloride (*n*-Bu_4NCl, >97%) from Sigma-Aldrich and used it as received.

6. Due to its highly hygroscopic character, the submitters weighed tetra-*n*-butylammonium chloride in a glove box and added it quickly to the reaction flask. The checkers weighed tetra-*n*-butylammonium chloride on the bench top and added it quickly to the reaction flask.

7. In general, LiCl was observed to be more effective and reproducible than *n*-Bu_4NCl in the Larock indole synthesis; however, *n*-Bu_4NCl is superior in the current described reaction. A lower yield was obtained when LiCl was employed instead of *n*-Bu_4NCl.

8. The amount of *n*-Bu_4NCl is critical. More than 1 equiv of *n*-Bu_4NCl favors the formation of multiple insertion products and sharply lowers the yield of the annulation reaction.

9. The submitters purchased *N*,*N*-dimethylformamide (DMF, 99.8%, anhydrous) from Sigma-Aldrich and used it as received. The checkers purchased *N*,*N*-dimethylformamide (DMF, 99.8%) from Acros Organics and passed it over a column of activated alumina under positive nitrogen pressure prior to use. Dry DMF was collected from the column in a flame-dried 500-mL round-bottomed flask and transferred to the reaction flask via cannula under positive nitrogen pressure.

10. The submitters purchased 1-trimethylsilyl-1-propyne (**2**, 99%) from TCI America and used it as received. The checkers purchased 1-trimethylsilyl-1-propyne (**2**, 99%) from Sigma-Aldrich and used it as received. In order to achieve the best chemical yields, at least 3 equiv of 1-trimethylsilyl-1-propyne are required based on the submitters' experience (boiling point of **2** = 99–100 °C).

11. In order to maintain the internal reaction temperature at 100 °C, the temperature of the oil bath is set at 110 °C. Based on the submitters' experience, there is no significant effect on the result when the oil bath temperature fluctuates between 108 and 112 °C during the course of the reaction.

12. The submitters reported a 22 h reaction time.

13. The completeness of the reaction was judged by the disappearance of 2-iodoaniline by thin-layer chromatography performed on glass-backed pre-coated 60 Å silica gel plates (250 μm) with a UV254 indicator. The submitters obtained TLC plates from Sorbent Technologies and used 30:1 hexane/ethyl acetate as the eluent. (R_f of 2-iodoaniline (**1**) = 0.32; R_f of the product (**3**) = 0.51). The checkers obtained TLC plates from Dynamic Adsorbents and used 20:1 hexane/ethyl acetate as the eluent (R_f of 2-iodoaniline (**1**) = 0.21; the R_f of the product (**3**) = 0.36).

14. In order to dissolve all of the inorganic salts in the reaction mixture, a saturated aqueous NH_4Cl solution is added. The addition of aqueous NH_4Cl solution is a slightly exothermic process. A slow addition and vigorous stirring of the reaction mixture is recommended. Based on the

submitters' experience, the internal temperature of the two-phase mixture was below 30 °C when the aqueous solution was added over a period of ten minutes.

15. During aqueous work-up, the checkers noted fine black particulate matter suspended at the bottom of the organic phase. The organic layer was decanted away from these solids after each extraction. After washing the combined organic layers with water and decanting, the solids were rinsed with diethyl ether (20 mL), and the rinse was combined with the organic phase before drying over $MgSO_4$.

16. Anhydrous magnesium sulfate was purchased from Fisher Scientific and used as received. To ensure proper dryness, 55 g of $MgSO_4$ was added to the organic phase and the resulting mixture was kept at room temperature for 15 min with occasional swirling.

17. Column chromatography is performed on an 8 cm diameter column, wet-packed with 400 g of silica gel (SiliCycle Silia*Flash* P60 40–63 μm 60Å) in hexanes. The length of silica gel is 25 cm. A gradient of 30:1 hexane/ethyl acetate (2 L) followed by 20:1 hexane/ethyl acetate (2 L) is used as the eluent. Three 200 mL fractions are collected and set aside. The next sixty-four 65 mL fractions are collected. Among the 65 mL fractions, fractions 35–56 contained the desired product and were concentrated by rotary evaporation (23 °C bath, 20 mm Hg), and dried under vacuum (1.0 Torr) at 23 °C for 18 h until a constant weight (9.28 g) was obtained.

18. The physical properties of **3** follow: R_f = 0.36 (TLC analysis performed on glass-backed pre-coated 60 Å silica gel plates (250 μm) with a UV254 indicator obtained from Dynamic Adsorbents; 20:1 hexane/ethyl acetate is used as the eluent; the product is visualized with a 254 nm UV lamp and basic $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.40 (s, 9 H), 2.44 (s, 3 H), 7.12 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.20 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1 H), 7.37 (app d, *J* = 8.1 Hz, 1 H), 7.59 (app d, *J* = 7.9 Hz, 1 H), 7.88 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –0.7, 10.6, 110.9, 118.8, 119.2, 120.5, 122.4, 129.7, 133.1, 138.2; IR (neat film, NaCl) 3440, 2954, 1250 cm^{-1}; HRMS *m/z* calcd. for $C_{12}H_{17}NSi$ $[M+H]^+$ 204.1203, found 204.1189. Anal. calcd. for $C_{12}H_{17}NSi$: C, 70.88; H, 8.43; N, 6.89. Found: C, 70.73; H, 8.39; N, 6.94.

19. The product 3-methyl-2-(trimethylsilyl)indole (**3**) is generally stable under the current described work-up and separation conditions. However, significant decomposition (>90%) of **3** was observed after storing as a dichloromethane solution for four weeks. In case long term storage is

needed, it is recommended that this compound be evaporated to complete dryness before storage and that it be stored at a low temperature (–20 °C).

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

Palladium-catalyzed annulation processes have proven to be very powerful for the synthesis of a wide variety of heterocycles and carbocycles.[3] The preparation of 3-methyl-2-(trimethylsilyl)indole described here illustrates a general protocol for the palladium-catalyzed coupling of *ortho*-iodoaniline and its derivatives with internal alkynes to produce 2,3-disubstituted indoles.[4] Since this process was first communicated in 1991, it has been subsequently employed by others in the synthesis of potential migraine headache drugs and other indole heterocycles.[5] This approach to 2,3-disubstituted indoles is very versatile. *ortho*-Iodoanilines with a variety of substituents on the nitrogen moiety, such as methyl, acetyl, and tosyl groups, undergo the annulation process successfully (Table 1). On the other hand, 2-bromoaniline and its derivatives are unreactive under our general annulation conditions. However, improved procedures for less reactive halides have more recently been reported.[6] A wide variety of internal alkynes bearing alkyl, aryl, silyl, ester and alcohol-containing groups, and hindered or unhindered substituents have been successfully employed in this process.

Table 1. Palladium-catalyzed annulation of internal alkynes with 2-iodoanilines or *N*-substituted derivatives[a]

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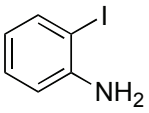
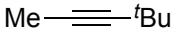
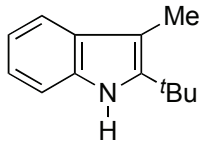
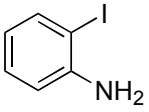
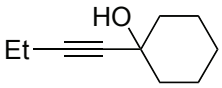
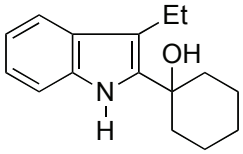
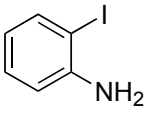
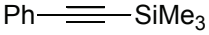
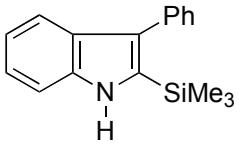
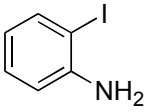
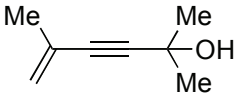
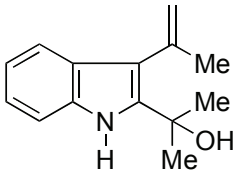
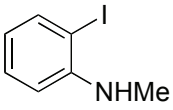
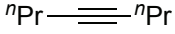
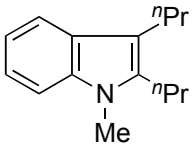
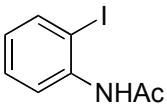
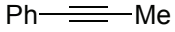
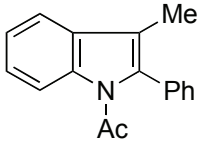
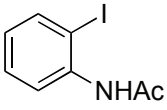
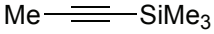
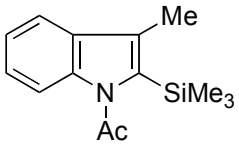
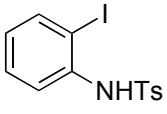
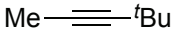
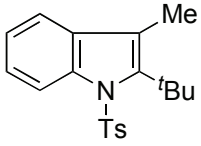
1				82
2				85
3				68
4				70
5				71
6				75
7				70
8				86

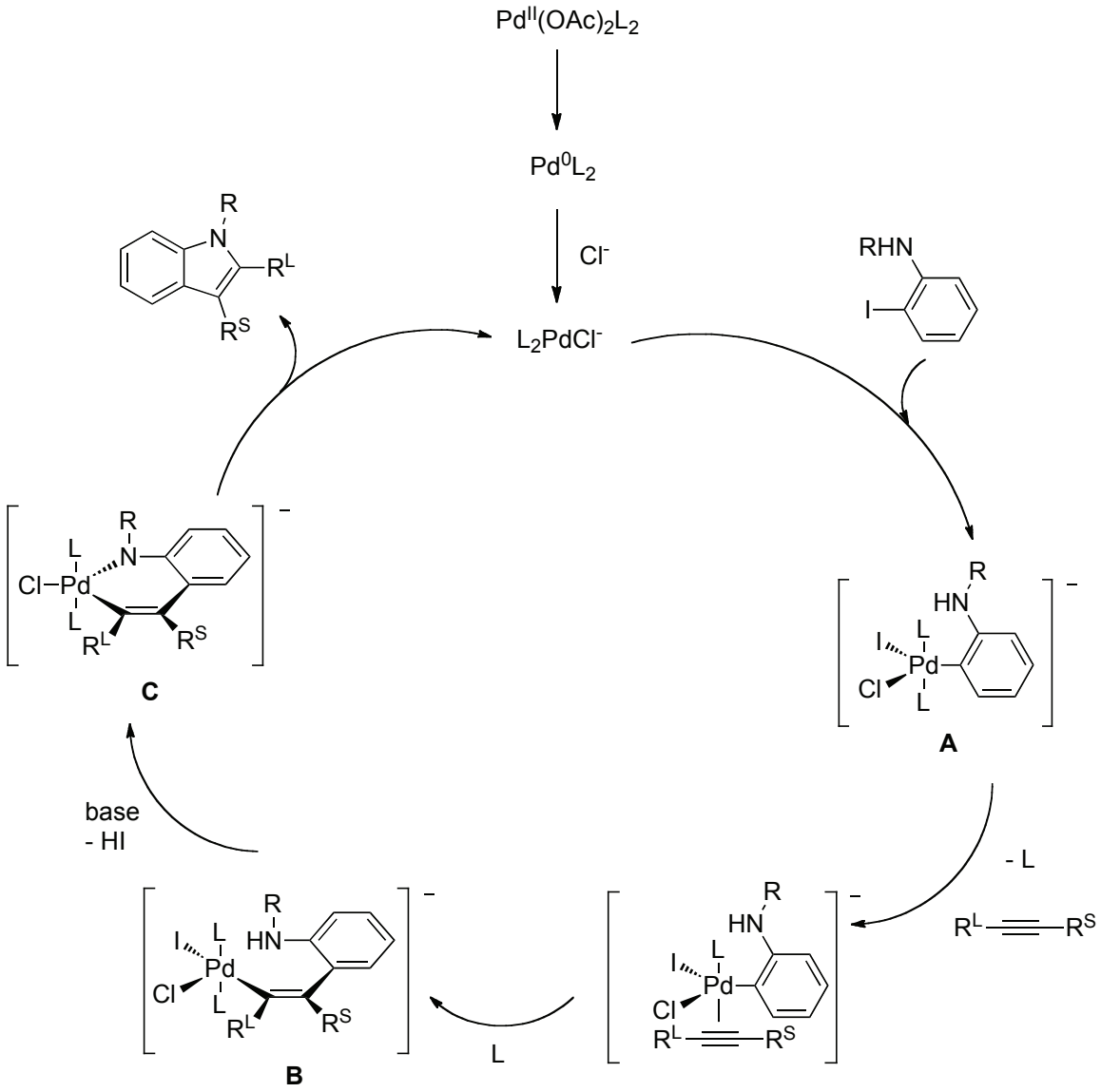
a. All reactions were run at 100 °C in DMF with 5 mol % of $Pd(OAc)_2$, 1 equiv of $^nBu_4NCl$ or LiCl, 5 equiv of base, and where appropriate, 5 mol % of PPh_3. For details, see reference 4b.

It is worth noting that this annulation process is often highly regioselective in the case of unsymmetrical internal alkynes, placing the aryl group of the aniline on the less sterically hindered end of the triple bond and the nitrogen moiety on the more sterically hindered end (Figure 1). Complete regioselectivity is observed in the current example. 3-Methyl-2-(trimethylsilyl)indole is the sole product obtained. It is noteworthy that the 2-silyl-substituted indoles generated by this annulation process can undergo a variety of other synthetically useful substitution processes, such as halogenation, protonolysis, and the Heck reaction, providing a convenient entry into various other substituted indoles.[4] The present procedure is a slight modification of that previously reported by the Larock group.[4] This general process has also been used to prepare indoles tethered to a polymer support.[7]

Figure 1. Steric effects on the regiochemistry of alkyne insertion.

This indole synthesis presumably proceeds via the mechanism displayed in Scheme 1: (1) reduction of the $Pd(OAc)_2$ to Pd(0), (2) coordination of the chloride to form a chloride-ligated zerovalent palladium species, (3) oxidative addition of the aryl iodide to Pd(0) to form intermediate **A**,[8] (4) coordination of the alkyne to the palladium atom of intermediate **A** and subsequent regioselective *syn*-insertion into the arylpalladium bond to form the vinylic palladium intermediate **B**, (5) nitrogen displacement of the halide in intermediate **B** to form a six-membered, heteroatom-containing palladacycle **C**, and (6) reductive elimination to form the indole and regenerate Pd(0).

Scheme 1. Proposed mechanism for the palladium-catalyzed annulation of internal alkynes by 2-iodoanilines or *N*-substituted derivatives.



1. Department of Chemistry, Iowa State University, Ames, IA 50011; larock@iastate.edu. We gratefully acknowledge the National Institutes of Health and National Science Foundation for their generous financial support; and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Inc., for the palladium reagents.

2. The non-corresponding authors' names are in alphabetical order.

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8. It has been noted by Board members that an alternative role for the chloride may be to displace the iodide in intermediate **A**.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Palladium acetate; (3375-31-3)
Triphenylphosphine; (603-35-0)
Sodium carbonate; (497-19-8)
Tetra-*n*-butylammonium chloride; (1112-67-0)
N,N-Dimethylformamide; (68-12-2)
1-Trimethylsilyl-1-propyne; (6224-91-5)

Richard C. Larock received his B.S. at the University of California, Davis in 1967. He then joined the group of Prof. Herbert C. Brown at Purdue University, where he received his Ph.D. in 1972. He worked as an NSF Postdoctoral Fellow at Harvard University in Prof. E. J. Corey's group and joined the Iowa State University faculty in 1972. His current research interests include aryne chemistry, electrophilic cyclization, palladium catalysis, and polymer chemistry based on biorenewable resources.

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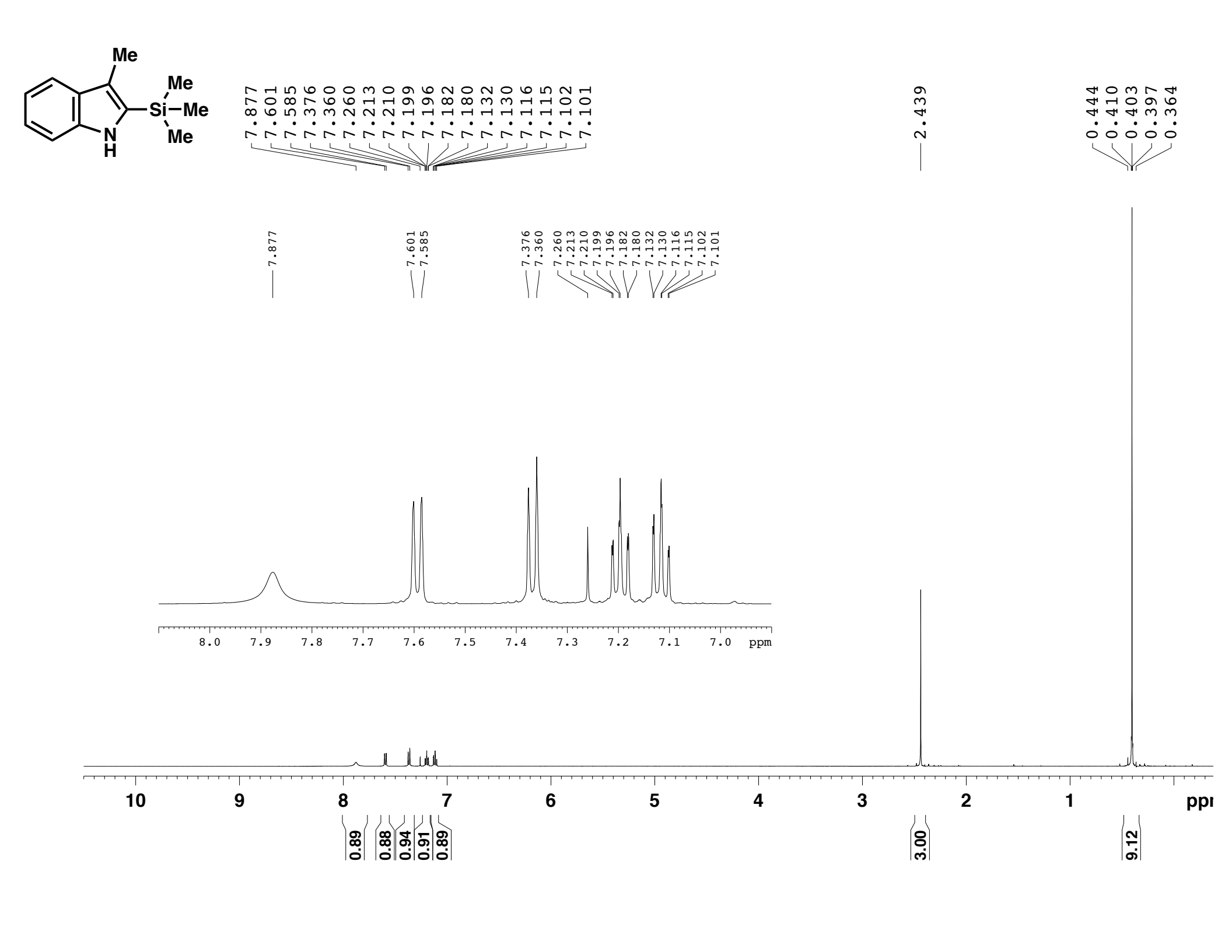
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Me
Si—Me
Me
N
H
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7.585
7.376
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7.260
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7.210
7.199
7.196
7.182
7.180
7.132
7.130
7.116
7.115
7.102
7.101
2.439
0.444
0.410
0.403
0.397
0.364
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
ppm
10
9
8
7
6
5
4
3
2
1
0.89
0.88
0.94
0.91
0.89
3.00
9.12