Benchtop Delivery of Ni(cod)$_2$ using Paraffin Capsules

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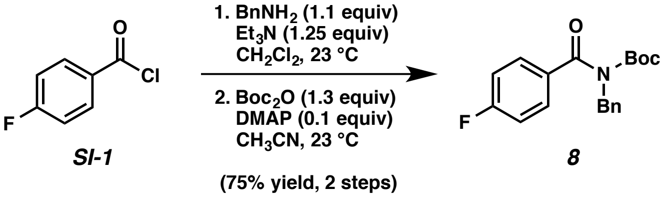
Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen and commercially obtained reagents were used as received. Non-commercially available substrates were synthesized following protocols specified in Section A in the Experimental Procedures. Prior to use, toluene and tetrahydrofuran were purified by distillation and taken through five freeze-pump-thaw cycles, and 1,4-dioxane was purified by distillation and sparged with nitrogen for 20 min. Iodine and morpholine (**6**) were obtained from Spectrum Chemical, and morpholine (**6**) was distilled before use. Paraffin wax (mp 53–57 °C ASTM D 87), iodocyclohexane, 2-naphthaldehyde (**22**), aniline (**26**), benzylamine, acid chloride **SI-1**, 2,2,2-trifluoroacetophenone, SIPr•HCl, and anhydrous 2-butanol were obtained from Sigma–Aldrich and used as received. Benzaldehyde (**25**) and 1,2-dibromoethane were obtained from Sigma–Aldrich and distilled before use. Phenylboronic acid pinacol ester (**9**) and 1-*N*-Boc-4-bromopiperidine (**16**) were obtained from Combi-Blocks. Ni(cod)$_2$, SIPr, IPr, and Zn powder (325 mesh, 99.9%) were obtained from Strem Chemicals and stored in a glove box. Triphenylphosphine was obtained from Strem Chemicals. Anhydrous lithium chloride (99%) was obtained from Alfa Aesar and stored in a glove box. Chlorotrimethylsilane, sodium *tert*-butoxide, and bathophenanthroline were obtained from Alfa Aesar, and chlorotrimethylsilane was distilled before use. Diphenylacetylene (**20**) and (–)-menthol (**3**) were obtained from Eastman Chemical Co., and (–)-menthol (**3**) was recrystallized before use. Phenylboronic acid (**17**) was obtained from Oakwood Products, Inc. K_3PO_4 was obtained from Acros. Isopropyl alcohol (**23**) was obtained from EMD and used as received. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm for analytical chromatography and 0.50 mm for preparative chromatography) and visualized using a combination of UV, iodine, anisaldehyde, and potassium permanganate staining techniques. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to residual solvent signals.

Experimental Procedures

A. Substrate Synthesis

Representative Procedure for the syntheses of amide substrates from Figure 3 (synthesis of amide 8 is used as an example).

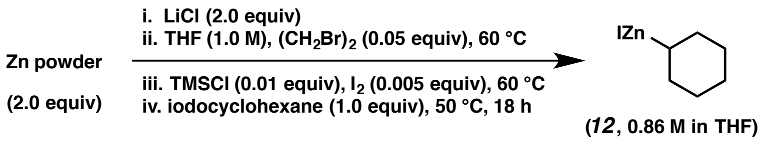


To a solution of acid chloride **SI-1** (1.14 g, 7.18 mmol, 1.0 equiv), triethylamine (1.24 mL, 8.97 mmol, 1.25 equiv), and dichloromethane (10.0 mL), was added dropwise a solution of benzylamine (0.861 mL, 7.89 mmol, 1.1 equiv) in dichloromethane (4.4 mL, 0.5 M in total) over 3 min. The reaction mixture was stirred at 23 °C for 4 h, diluted with EtOAc (10 mL), and then washed successively with 1.0 M HCl (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude solid material was used in the subsequent step without further purification.

To a flask containing the crude material from the previous step was added DMAP (76.9 mg, 0.630 mmol, 0.1 equiv), followed by acetonitrile (31.7 mL, 0.2 M). Boc_2O (1.80 g, 8.23 mmol, 1.3 equiv) was added in one portion and the reaction vessel was flushed with N_2. After stirring the reaction mixture at 23 °C for 25 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), transferred to a separatory funnel with EtOAc (10 mL) and H_2O (10 mL), and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting crude residue was purified by flash chromatography (19:1 Hexanes:EtOAc) to yield amide **8** (1.74 g, 75% yield, over two steps) as a white solid. Spectral data match those previously reported.[1c]

Note: Supporting information for the syntheses of substrates shown in Figures 3, 4, and 5 have previously been reported: **2**,[1a] **5**,[1b] **8**,[1c] **11**,[1c] **14**,[1d] and **19**.[1e]

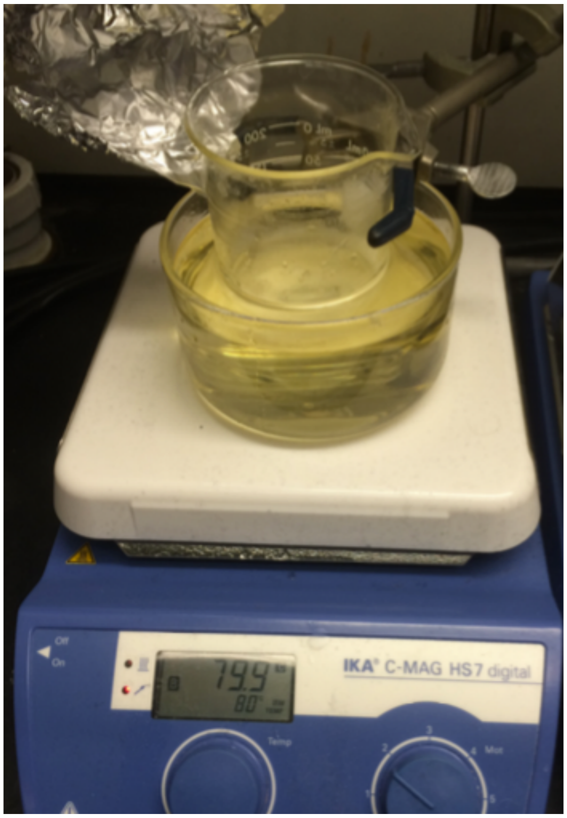
B. Preparation of Cyclohexylzinc Iodide (12)



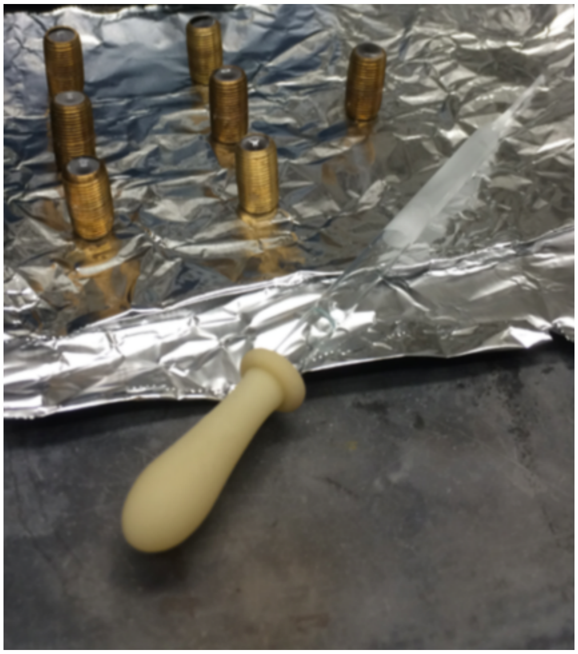
Following a modification of the procedure reported by Knochel,[2] a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar and rubber septum was brought into a glove box where Zn powder (1.30 g, 20.0 mmol, 2.0 equiv, Strem 325 mesh) and anhydrous LiCl (840 mg, 20.0 mmol, 2.0 equiv) were added. The flask was then removed from the glove box and heated with a heat gun for 10 min under high vacuum, cooled to room temperature, and then backfilled with N_2. Freshly distilled THF (10.0 mL) and 1,2-dibromoethane (43 µL, 0.50 mmol, 0.05 equiv) were added via syringe and the reaction mixture was heated at 60 °C for 20 min. After cooling to room temperature, freshly distilled TMSCl (12 µL, 0.10 mmol, 0.01 equiv) followed by a solution of I_2 (12.8 mg, 0.05 mmol, 0.005 equiv) in THF (50 µL, 1.0 M) were added via syringe and the reaction mixture was heated again at 60 °C for 20 min. After cooling to room temperature, iodocyclohexane (1.30 mL, 10.0 mmol, 1.0 equiv) was added dropwise via syringe over 1 min. A flame-dried air condenser was attached to the flask under N_2 and the reaction vessel was heated at 50 °C for 18 h. The reaction mixture was cooled to room temperature and allowed to stand for 1 h before the supernatant fluid was transferred to a flame-dried schlenk flask via syringe. The concentration of the organozinc halide was determined to be 0.86 M by iodometric titration using Knochel's procedure.[3]

C. Preparation of Paraffin–Ni(cod)$_2$ Capsules

Representative Procedure for the preparation of paraffin–Ni(cod)$_2$ capsules for Sections E–N in the Experimental Procedures (preparation of paraffin–Ni(cod)$_2$ capsules for use in section E in the Experimental Procedures is used as an example). Paraffin wax (mp 53–57 °C ASTM D 87) was melted in a 250 mL beaker suspended in an oil bath set to 80 °C.



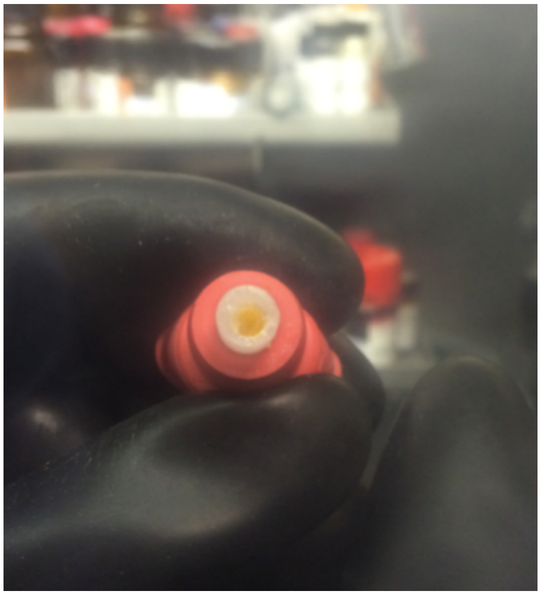
Approximately 1 mL of molten paraffin was then pipetted into a standard brass mold (Nipple Brass, 1/8 in x close) using a 5 3/4 in glass pipette and pipette bulb.



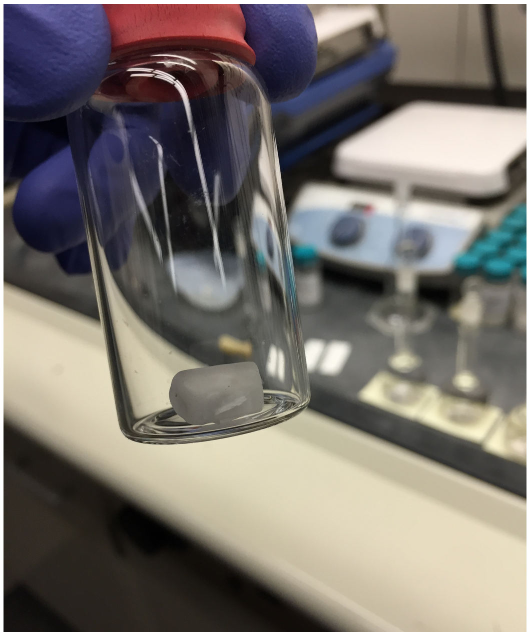
After cooling, the resulting wax cylinder was removed from the brass mold and trimmed to approximately 1 cm in length using a razor blade.

Next, a cavity was bored in the wax cylinder using a standard drill bit (5/32 in, black oxide), taking care not to bore through the entire cylinder.

The resulting hollow and open capsule was brought into a glove box, inserted into a 14/20 septum for ease of handling, and charged with Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 10 mol%) and SIPr (7.8 mg 0.020 mmol, 10 mol%).



After charging the capsule, a warm metal spatula (maintained at approximately 80 °C using a hot plate in the glove box) was used to melt the top of the capsule closed. Removal from the glove box and re-dipping in molten wax (to ensure a proper seal) gave the desired capsules that were ready for use on the benchtop (Sections E–N in the Experimental Procedures).

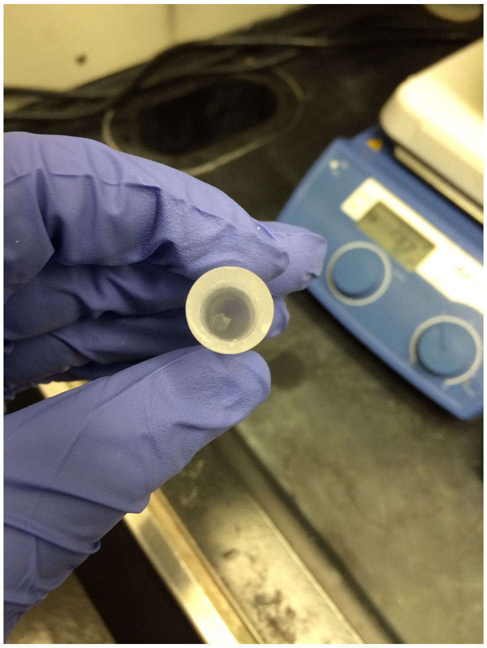


Note: Typically, paraffin–Ni(cod)$_2$ capsules generated in this way were used within 24 h of being prepared. For a detailed study of paraffin–Ni(cod)$_2$ capsule stability to air and moisture over prolonged periods of time, see Section N in the Experimental Procedures. For a detailed study of non-encapsulated Ni(cod)$_2$ and SIPr stability to air and moisture over prolonged periods of time, see Section O in the Experimental Procedures.

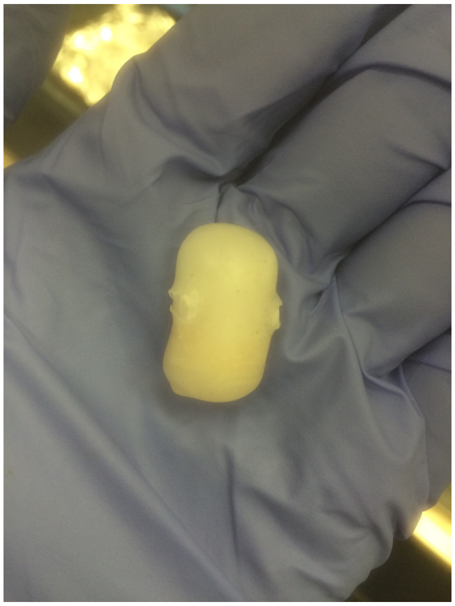
D. Preparation of Paraffin–Ni(cod)$_2$ Capsules for Gram-Scale Esterification

Representative Procedure for preparation of paraffin–Ni(cod)$_2$ capsules for Section P in the Experimental Procedures. Paraffin wax (mp 53–57 °C ASTM D 87) was melted in a 250 mL beaker suspended in an oil bath set to 80 °C. Approximately 9 mL of molten paraffin was then pipetted into a standard glass VWR culture tube (16 x 125 mm) using a 5 3/4 in glass pipette and pipette bulb. After cooling, the resulting wax cylinder was removed from the culture tube (by scoring and carefully breaking the glass away from the paraffin) and trimmed to approximately 2.5 cm in length using a razor blade.

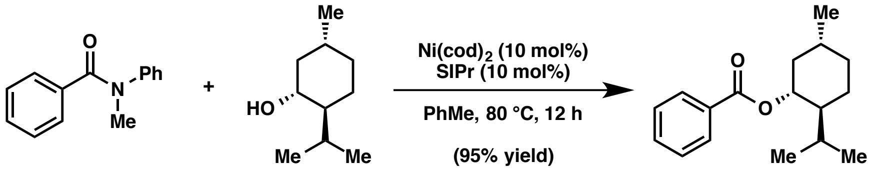
Next, a cavity was bored in the wax cylinder using a standard drill bit (3/8 in, black oxide), taking care not to bore through the entire cylinder.



The resulting hollow and open capsule was brought into a glove box and charged with Ni(cod)$_2$ (130 mg, 0.474 mmol, 10 mol%) and SIPr (185 mg, 0.474 mmol, 10 mol%). After charging the capsule, a warm metal spatula (maintained at approximately 80 °C using a hot plate in the glove box) was used to melt the top of the capsule closed. Removal from the glove box and re-dipping in molten wax (to ensure a proper seal) gave the desired capsules that were ready for use on the benchtop (Section P in the Experimental Procedures).



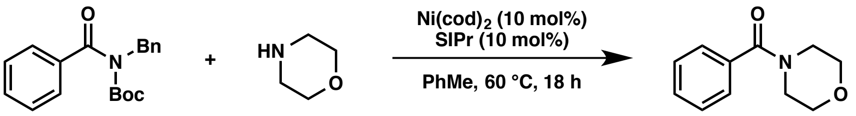
E. Esterification of Amide 2



2 (***3***, 1.2 equiv) ***4***

Ester 4. A 1-dram vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with amide substrate **2** (42.2 mg, 0.200 mmol, 1.0 equiv), (–)-menthol (**3**, 37.5 mg, 0.240 mmol, 1.2 equiv) and a paraffin capsule containing $Ni(cod)_2$ (5.5 mg, 0.020 mmol, 10 mol%) and SIPr (7.8 mg, 0.020 mmol, 10 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N_2, and subsequently toluene (0.20 mL, 1.0 M) was added. The vial was capped with a Teflon-lined screw cap under a flow of N_2 and the reaction mixture was stirred at 80 °C for 12 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 2.0 g of silica gel with hexanes (6.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (100 mL of hexanes eluent to remove paraffin, then 100 mL of 4:1 Hexanes:EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by preparative thin-layer chromatography (5:1 Hexanes:EtOAc) to yield ester **4** (95% yield, average of two experiments) as a white solid. Ester **4**: R_f 0.58 (5:1 Hexanes:EtOAc). The reported literature yield is 88%.[4] Spectral data match those previously reported.[5]

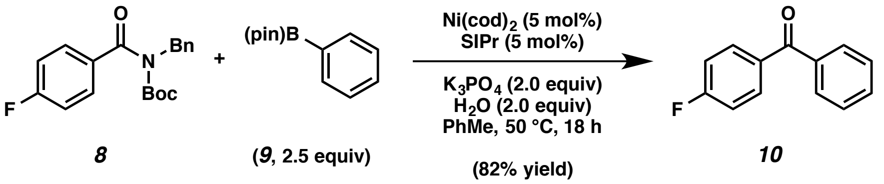
F. Transamidation of Amide 5



5 (***6***, 1.5 equiv) ***7***

Amide 7. A 1-dram vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with amide substrate **5** (62.2 mg, 0.200 mmol, 1.0 equiv), morpholine (**6**, 37.0 μL, 0.300 mmol, 1.5 equiv), and a paraffin capsule containing Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 10 mol%) and SIPr (7.8 mg, 0.020 mmol, 10 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N$_2$, and subsequently toluene (0.20 mL, 1.0 M) was added. The vial was capped with a Teflon-lined screw cap under a flow of N$_2$ and the reaction mixture was stirred at 60 °C for 18 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 2.0 g of silica gel with hexanes (6.0 mL) and CH$_2$Cl$_2$ (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (100 mL of hexanes eluent to remove paraffin, then 100 mL of 2:1 Hexanes:EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by preparative thin-layer chromatography (3:1 Hexanes:EtOAc) to yield amide **7** (87% yield, average of two experiments) as a colorless oil. Amide **7**: R$_f$ 0.24 (1:1 Hexanes:EtOAc). The reported literature yield is 91% when the reaction is run at 35 °C.[6] Spectral data match those previously reported.[7]

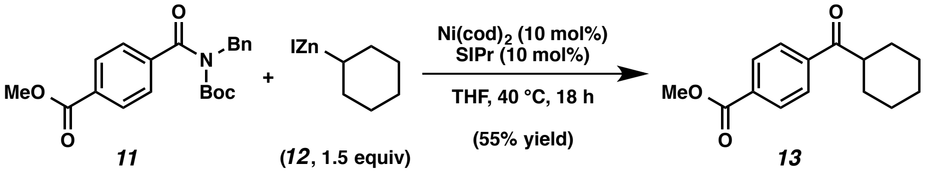
G. Suzuki–Miyaura Coupling of Amide 8



Ketone 10. A 1-dram vial was charged with anhydrous powdered K$_3$PO$_4$ (84.8 mg, 0.400 mmol, 2.0 equiv) and a magnetic stir bar. The vial and contents were flame-dried under reduced pressure, and then allowed to cool under N$_2$. The vial was charged with amide substrate **8** (65.8 mg, 0.200 mmol, 1.0 equiv), phenylboronic acid pinacol ester (**9**, 102.0 mg, 0.500 mmol, 2.5 equiv), and a paraffin capsule containing Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol%) and SIPr (3.9 mg, 0.010 mmol, 5 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N$_2$, and subsequently water (7.2 μL, 0.400 mmol, 2.0 equiv) and toluene (0.20 mL, 1.0 M) were added. The vial was capped with a Teflon-lined screw cap under a flow of N$_2$ and the reaction mixture was stirred vigorously (1,000 rpm) at 50 °C for 18 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 2.0 g of silica gel with hexanes (6.0 mL) and CH$_2$Cl$_2$ (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (50 mL

of hexanes eluent to remove paraffin, then 50 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by preparative thin-layer chromatography (8:1:1 Hexanes:Et_2O:CH_2Cl_2) to yield ketone **10** (82% yield, average of two experiments) as a white solid. Ketone **10**: R_f 0.58 (5:1 Hexanes:EtOAc). The reported literature yield is 90% when the reaction is run using 1.2 equiv boronate **9**.[1c] Spectral data match those previously reported.[8]

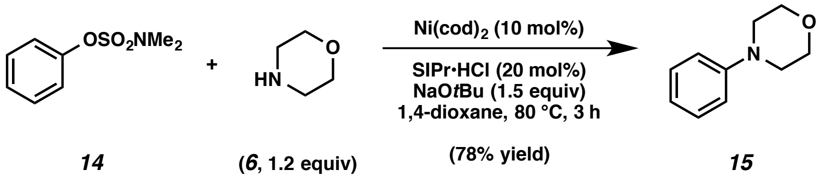
H. Negishi Coupling of Amide 11



Ketone 13. A 1-dram vial was charged with a magnetic stir bar and flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with amide substrate **11** (73.8 mg, 0.200 mmol, 1.0 equiv) and a paraffin capsule containing Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 10 mol%) and SIPr (7.8 mg, 0.020 mmol, 10 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N_2, and subsequently THF (0.50 mL, 0.40 M) was added. The reaction mixture was allowed to stir at 40 °C for 1 h, over which time a red-orange color developed. Concurrently, the cyclohexylzinc iodide solution (**12**) was heated in a water bath at 50 °C for 1 h. A portion of the preheated solution of **12** (349 µL, 0.300 mmol, 1.5 equiv, 0.86 M in THF) was then added to the reaction mixture at 40 °C dropwise via syringe over 3 sec. The vial was capped with a Teflon-lined screw cap under a flow of N_2, and the reaction mixture was allowed to stir at 40 °C for 18 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 2.0 g of silica gel with hexanes (6.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (50 mL of hexanes eluent to remove paraffin, then 50 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (24:1 Hexanes:EtOAc) to yield ketone **13** (55% yield, average of two experiments) as an off-white solid. Ketone **13**: R_f 0.50 (5:1

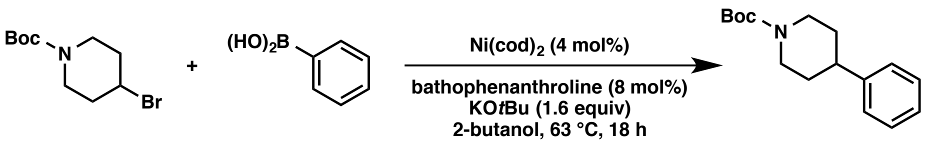
Hexanes:EtOAc). The reported literature yield is 71% when the reaction is run at 23 °C and 1.0 M.[9] Spectral data match those previously reported.[10]

I. Amination of Sulfamate 14



Amine 15. A 20 mL vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with morpholine (**6**, 52.4 µL, 0.600 mmol, 1.2 equiv), sulfamate **14** (100.5 mg, 0.500 mmol, 1.0 equiv), anhydrous powdered NaO*t*Bu (72.0 mg, 0.750 mmol, 1.5 equiv), SIPr•HCl (42.7 mg, 0.100 mmol, 20 mol%), and a paraffin capsule containing Ni(cod)$_2$ (13.8 mg, 0.050 mmol, 10 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N_2, and subsequently 1,4-dioxane (2.5 mL, 0.20 M) was added. The vial was capped with a Teflon-lined screw cap under a flow of N_2 and the reaction mixture was stirred at 80 °C for 3 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 3.0 g of silica gel with hexanes (6.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (100 mL of hexanes eluent to remove paraffin, then 100 mL of 1:1 Hexanes:EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by preparative thin-layer chromatography (19:1 PhH:EtOAc) to yield amine **15** (78% yield, average of two experiments) as a white solid. Amine **15**: R_f 0.30 (9:1 Hexanes:EtOAc). The reported literature yield is 95% when the reaction is run using 5 mol% Ni(cod)$_2$ and 10 mol% SIPr•HCl.[11] Spectral data match those previously reported.[12]

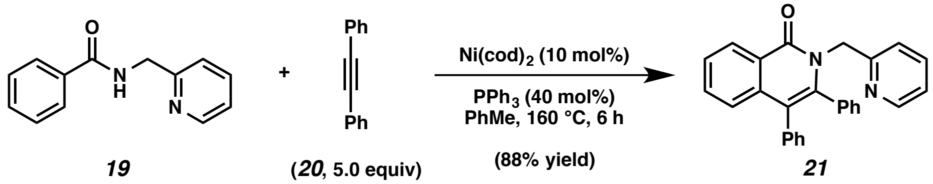
J. Suzuki–Miyaura Coupling of Alkyl Halide 16



16 (*17*, 1.2 equiv) (77% yield) *18*

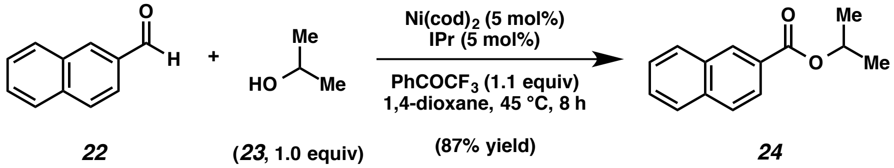
Carbamate 18. A 1-dram vial was charged with a magnetic stir bar and flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with anhydrous powdered KO*t*Bu (89.6 mg, 0.800 mmol, 1.6 equiv), phenylboronic acid (**17**, 73.2 mg, 0.600 mmol, 1.2 equiv), bathophenanthroline (13.2 mg, 0.040 mmol, 8 mol%), and a paraffin capsule containing Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 4 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N_2, and subsequently anhydrous 2-butanol (2.8 mL, 0.20 M) was added. The reaction mixture was allowed to stir at 63 °C for 10 min, over which time a deep purple color developed. A solution of alkyl halide **16** (132.0 mg, 0.500 mmol, 1.0 equiv, 2.5 M in anhydrous 2-butanol) was then added to the reaction mixture at 63 °C rapidly via syringe. The vial was capped with a Teflon-lined screw cap under a flow of N_2, and the reaction mixture was allowed to stir at 63 °C for 18 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 2.0 g of silica gel with hexanes (6.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (50 mL of hexanes eluent to remove paraffin, then 50 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (24:1 Hexanes:EtOAc → 14:1 Hexanes:EtOAc) to yield carbamate **18** (77% yield, average of two experiments) as a colorless oil. Carbamate **18**: R_f 0.42 (5:1 Hexanes:EtOAc). The reported literature yield is 88%.[13] Spectral data match those previously reported.[14]

K. Oxidative Annulation of Amide 19



Isoquinolinone 21. A 1-dram vial was charged with a magnetic stir bar and flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with amide substrate **19** (106.0 mg, 0.500 mmol, 1.0 equiv), diphenylacetylene (**20**, 445.0 mg, 2.500 mmol, 5.0 equiv), triphenylphosphine (52.4 mg, 0.200, 40 mol%), and a paraffin capsule containing $Ni(cod)_2$ (13.8 mg, 0.050 mmol, 10 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N_2, and subsequently toluene (2.0 mL, 0.25 M) was added. The vial was capped with a Teflon-lined screw cap under a flow of N_2 and the reaction mixture was stirred at 160 °C for 6 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 2.0 g of silica gel with hexanes (6.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (50 mL of hexanes eluent to remove paraffin, then 50 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (2:1 Hexanes:EtOAc → 1:1 Hexanes:EtOAc) to yield isoquinolinone **21** (88% yield, average of two experiments) as a tan solid. Isoquinolinone **21**: R_f 0.64 (100% EtOAc). The reported literature yield is 92%.[15] Spectral data match those previously reported.[15]

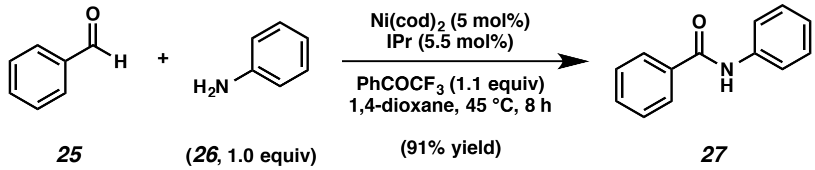
L. Esterification of Aldehyde 22



Ester 24. A 1-dram vial was charged with a magnetic stir bar and flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with a paraffin capsule

containing Ni(cod)$_2$ (6.9 mg, 0.025 mmol, 5 mol%) and IPr (9.7 mg, 0.025 mmol, 5 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N$_2$, and subsequently 1,4-dioxane (1.0 mL) was added. The reaction mixture was allowed to stir at 45 °C for 20 min, over which time a black color developed. A solution of isopropyl alcohol (**23**, 38.2 μL, 0.500 mmol, 1.0 equiv) in 1,4-dioxane (0.5 mL) was then added to the reaction mixture at 45 °C rapidly via syringe, followed by a solution of aldehyde **22** (78.0 mg, 0.500 mmol, 1.0 equiv) and 2,2,2-trifluoroacetophenone (76.6 μL, 0.550 mmol, 1.1 equiv) in 1,4-dioxane (1.0 mL, 0.20 M in total) in the same manner. The vial was capped with a Teflon-lined screw cap under a flow of N$_2$, and the reaction mixture was allowed to stir at 45 °C for 8 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 3.0 g of silica gel with hexanes (6.0 mL) and CH$_2$Cl$_2$ (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (100 mL of hexanes eluent to remove paraffin, then 100 mL of 2:1 Hexanes:EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by preparative thin-layer chromatography (5:1 Hexanes:EtOAc) to yield ester **24** (87% yield, average of two experiments) as a colorless oil. Ester **24**: R$_f$ 0.64 (5:1 Hexanes:EtOAc). The reported literature yield is 98% when the reaction is run at 30 °C.[16] Spectral data match those previously reported.[16]

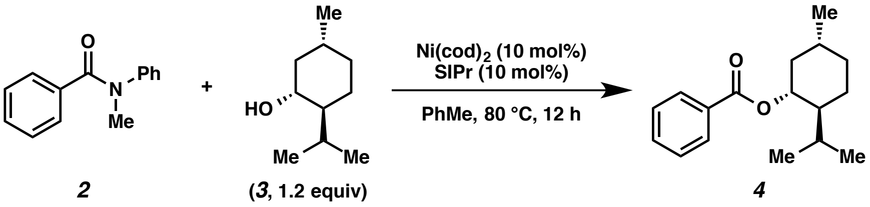
M. Amidation of Aldehyde 25



Amide 27. A 1-dram vial was charged with a magnetic stir bar and flame-dried under reduced pressure, and then allowed to cool under N$_2$. The vial was charged with a paraffin capsule containing Ni(cod)$_2$ (6.9 mg, 0.025 mmol, 5 mol%) and IPr (10.7 mg, 0.028 mmol, 5.5 mol%) prepared as described in Section C in the Experimental Procedures. The vial was flushed with N$_2$, and subsequently 1,4-dioxane (1.0 mL) was added. The reaction mixture was allowed to stir at 45 °C for 20 min, over which time a black color developed. A solution of aniline (**26**, 45.5 μL,

0.500 mmol, 1.0 equiv) in 1,4-dioxane (0.5 mL) was then added to the reaction mixture at 45 °C rapidly via syringe, followed by a solution of benzaldehyde (**25**, 50.7 μL, 0.500 mmol, 1.0 equiv) and 2,2,2-trifluoroacetophenone (76.6 μL, 0.550 mmol, 1.1 equiv) in 1,4-dioxane (1.0 mL, 0.20 M in total) in the same manner. The vial was capped with a Teflon-lined screw cap under a flow of N_2, and the reaction mixture was allowed to stir at 45 °C for 8 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 3.0 g of silica gel with hexanes (6.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (100 mL of hexanes eluent to remove paraffin, then 100 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (9:1 Hexanes:EtOAc → 7:3 Hexanes:EtOAc → 1:1 Hexanes:EtOAc) to yield amide **27** (91% yield, average of two experiments) as an off-white solid. Amide **27**: R_f 0.19 (5:1 Hexanes:EtOAc). The reported literature yield is 96% when the reaction is run at 40 °C.[16] Spectral data match those previously reported.[16]

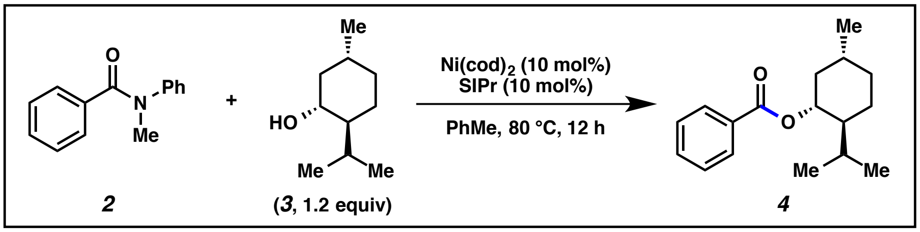
N. Air and Moisture Stability Tests of Paraffin–Ni(cod)$_2$ Capsules



Representative Procedure for air and moisture stability tests of paraffin–Ni(cod)$_2$ capsules from Table S1 (coupling of amide 2 and (–)-menthol (3) is used as an example). A 1-dram vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with amide substrate **2** (42.2 mg, 0.200 mmol, 1.0 equiv), (–)-menthol (**3**, 37.5 mg, 0.240 mmol, 1.2 equiv) and a paraffin capsule containing Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 10 mol%) and SIPr (7.8 mg, 0.020 mmol, 10 mol%) prepared as described in Section C in the Experimental Procedures that had been stored on the benchtop under the indicated conditions. The vial was flushed with N_2, and subsequently toluene (0.20 mL, 1.0 M) was added. The vial was capped with a Teflon-lined screw cap under a flow of N_2 and the reaction mixture was stirred at 80 °C for 12 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 2.0 g of silica gel with hexanes (6.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (100 mL of hexanes eluent to remove paraffin, then 100 mL of 4:1 Hexanes:EtOAc eluent). 1,3,5-trimethoxybenzene (10.1 mg, 0.060 mmol, 30 mol%) was then added to the crude mixture, the volatiles were removed under reduced pressure, and the yield was determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as an external standard.

Any modifications of the conditions shown in the representative procedure above are specified below in Table S1.

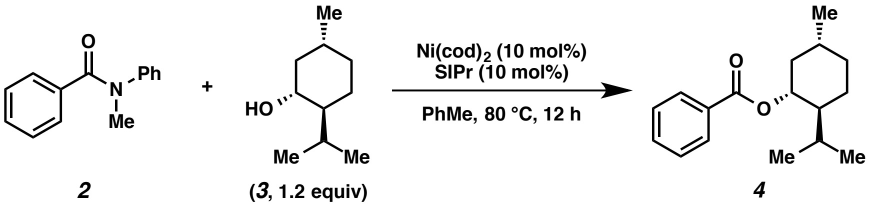
Table S1. Air and Moisture Stability Tests of Paraffin–Ni(cod)$_2$ Capsules[a]



Reaction Conditions	***Experimental Results*** *2*	*4*
Paraffin capsule containing Ni(cod)$_2$ (10 mol%) and SIPr (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 24 hours before use	0%	96%
Paraffin capsule containing Ni(cod)$_2$ (10 mol%) and SIPr (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 2 weeks before use	0%	97%
Paraffin capsule containing Ni(cod)$_2$ (10 mol%) and SIPr (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 1 month before use	0%	99%
Paraffin capsule containing Ni(cod)$_2$ (10 mol%) and SIPr (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 2 months before use	0%	95%
Paraffin capsule containing Ni(cod)$_2$ (10 mol%) and SIPr (10 mol%) submerged under water for 1 hour before drying and use	0%	97%

[a] Yields were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

O. Air Stability Tests of Non-encapsulated Ni(cod)$_2$ and SIPr

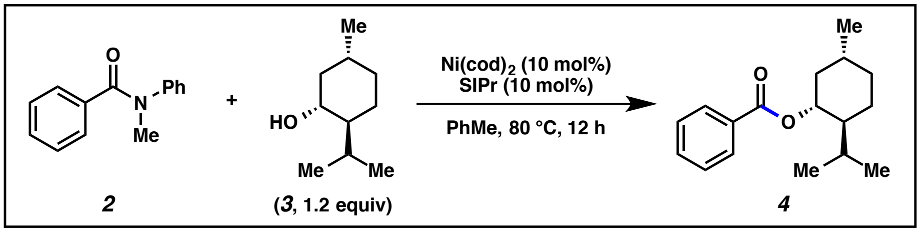


2 (3, 1.2 equiv) 4

Representative Procedure for air and moisture stability tests of non-encapsulated Ni(cod)$_2$ and SIPr from Table S2 (coupling of amide 2 and (–)-menthol (3) is used as an example). A 1-dram vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with amide substrate **2** (42.2 mg, 0.200 mmol, 1.0 equiv), (–)-menthol (**3**, 37.5 mg, 0.240 mmol, 1.2 equiv) and Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 10 mol%) that had been stored on the benchtop under ambient conditions for the indicated amount of time. The vial was flushed with N_2, taken into a glove box, and charged with SIPr (7.8 mg, 0.020 mmol, 10 mol%). The vial was then removed from the glove box, and subsequently toluene (0.20 mL, 1.0 M) was added. The vial was capped with a Teflon-lined screw cap under a flow of N_2 and the reaction mixture was stirred at 80 °C for 12 h. After cooling to 23 °C, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL of EtOAc eluent). 1,3,5-trimethoxybenzene (10.1 mg, 0.060 mmol, 30 mol%) was then added to the crude mixture, the volatiles were removed under reduced pressure, and the yield was determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an external standard.

Any modifications of the conditions shown in the representative procedure above are specified below in Table S2.

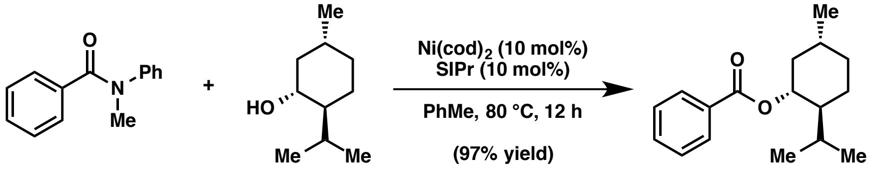
Table S2. Air Stability Tests of Non-encapsulated Ni(cod)$_2$ and SIPr[a]



Reaction Conditions	*Experimental Results* 2	4
Ni(cod)$_2$ (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 1 hour before use	13%	87%
Ni(cod)$_2$ (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 24 hours before use	8%	92%
Ni(cod)$_2$ (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 1 week before use	99%	0%
Ni(cod)$_2$ (10 mol%) and SIPr (10 mol%) stored on the benchtop under ambient temperature, oxygen, and moisture for 1 hour before use	96%	0%

[a] Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

P. Gram-Scale Esterification of Amide 2 Using a Paraffin–Ni(cod)$_2$ Capsule



2 (***3***, 1.2 equiv) ***4***

Ester 4. A 20 mL vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under N_2. The vial was charged with amide substrate **2** (1.00 g, 4.74 mmol, 1.0 equiv), (–)-menthol (**3**, 887 mg, 5.69 mmol, 1.2 equiv), and a paraffin capsule containing Ni(cod)$_2$ (130 mg, 0.474 mmol, 10 mol%) and SIPr (185 mg, 0.474 mmol, 10 mol%) prepared as described in Section D in the Experimental Procedures. The vial was flushed with N_2, and subsequently toluene (4.74 mL, 1.0 M) was added. The vial was capped with a Teflon-lined screw cap under a flow of N_2 and the reaction mixture was stirred at 80 °C for 12 h. After removing the vial from heat, the reaction mixture was transferred to a 100 mL round bottom flask containing 8.0 g of silica gel with hexanes (12.0 mL) and CH_2Cl_2 (12.0 mL). The mixture was adsorbed onto the silica gel under reduced pressure and filtered over a plug of silica gel (500 mL of hexanes eluent to remove paraffin, then 1,000 mL of 100:1 Hexanes:EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (100:1 Hexanes:EtOAc) to yield ester **4** (1.20 g, 97% yield) as a white solid. Spectral data match those previously reported.[5]

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^{1}H NMR Spectra

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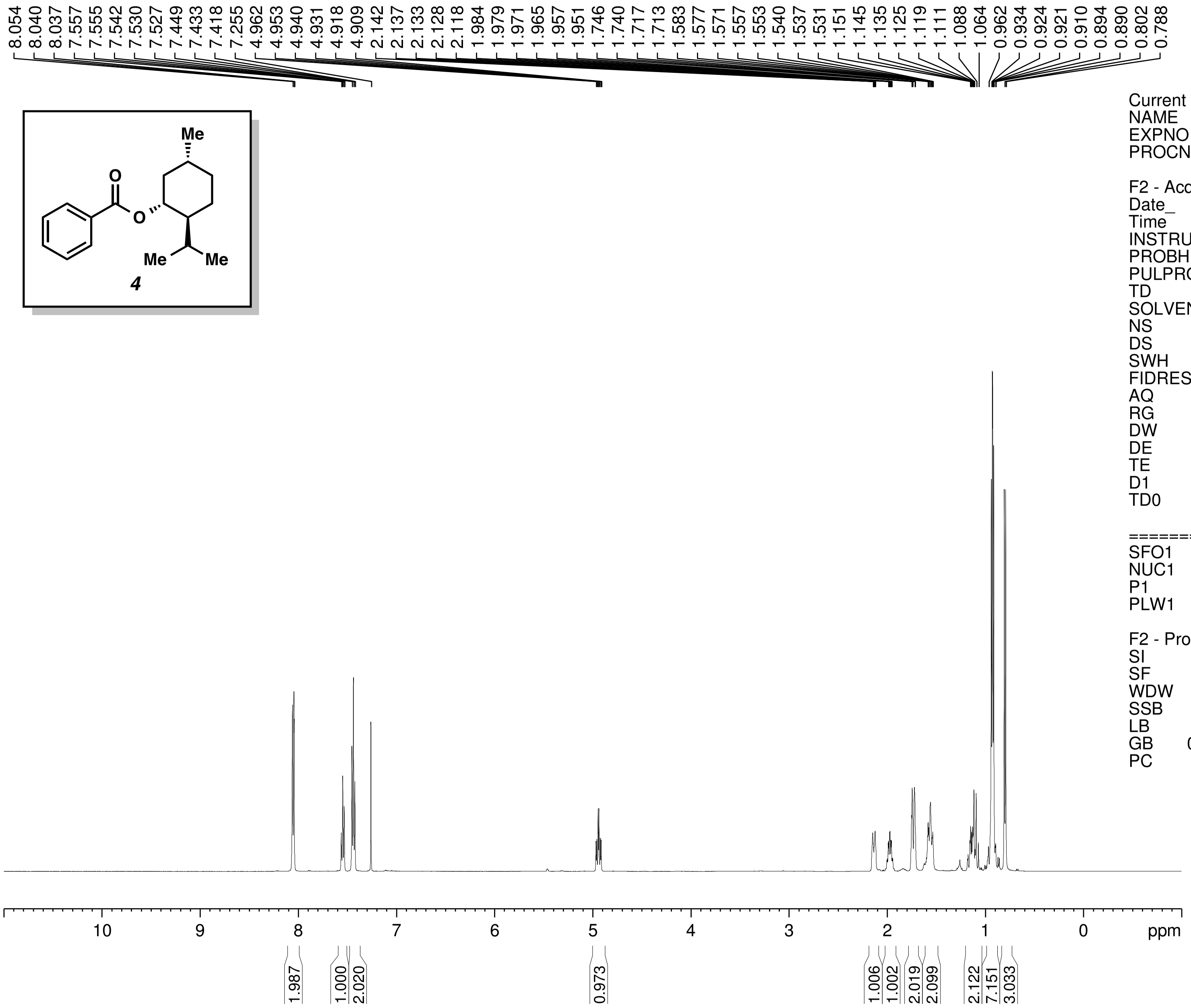

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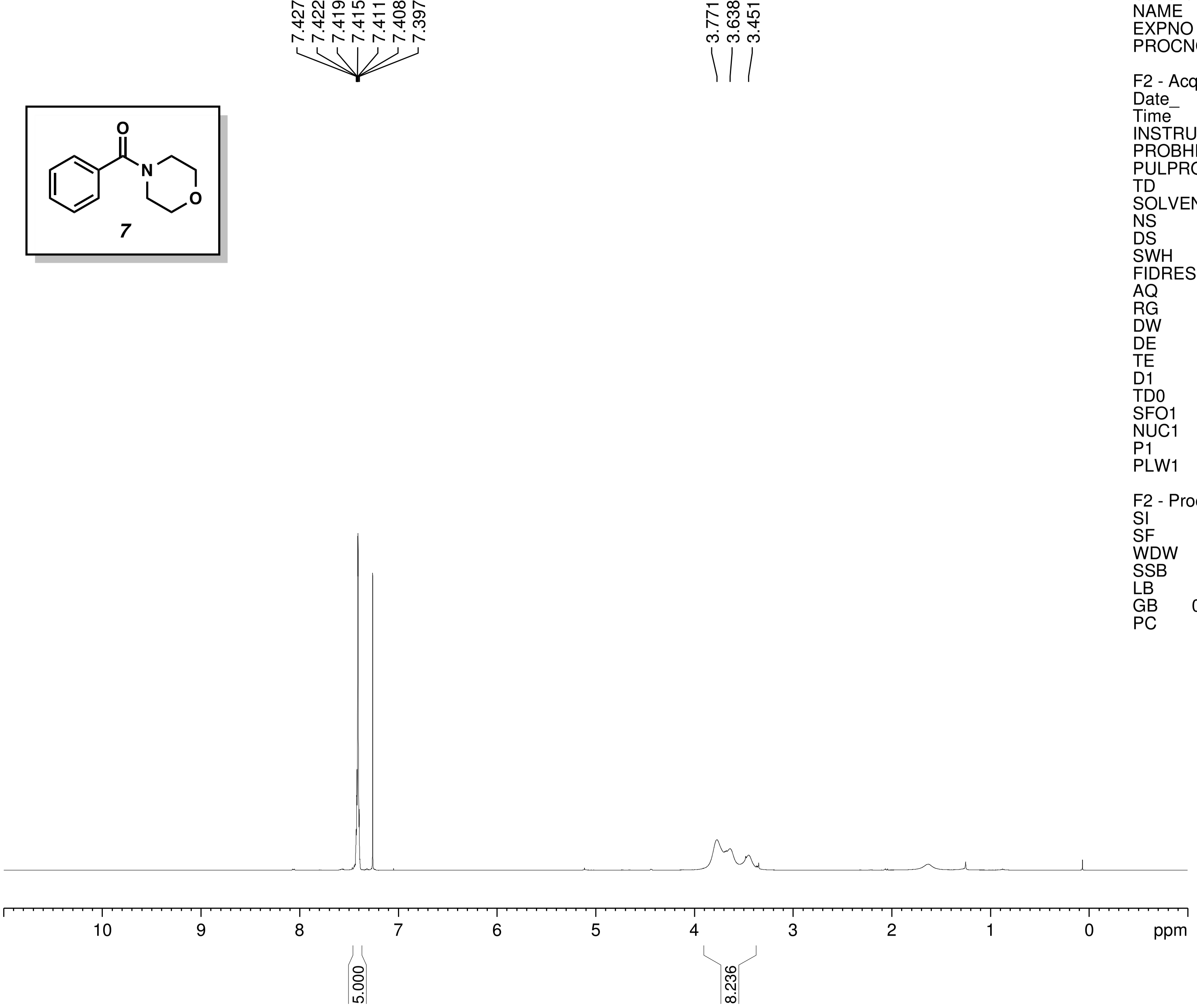
Purified Product, 1H NMR

7



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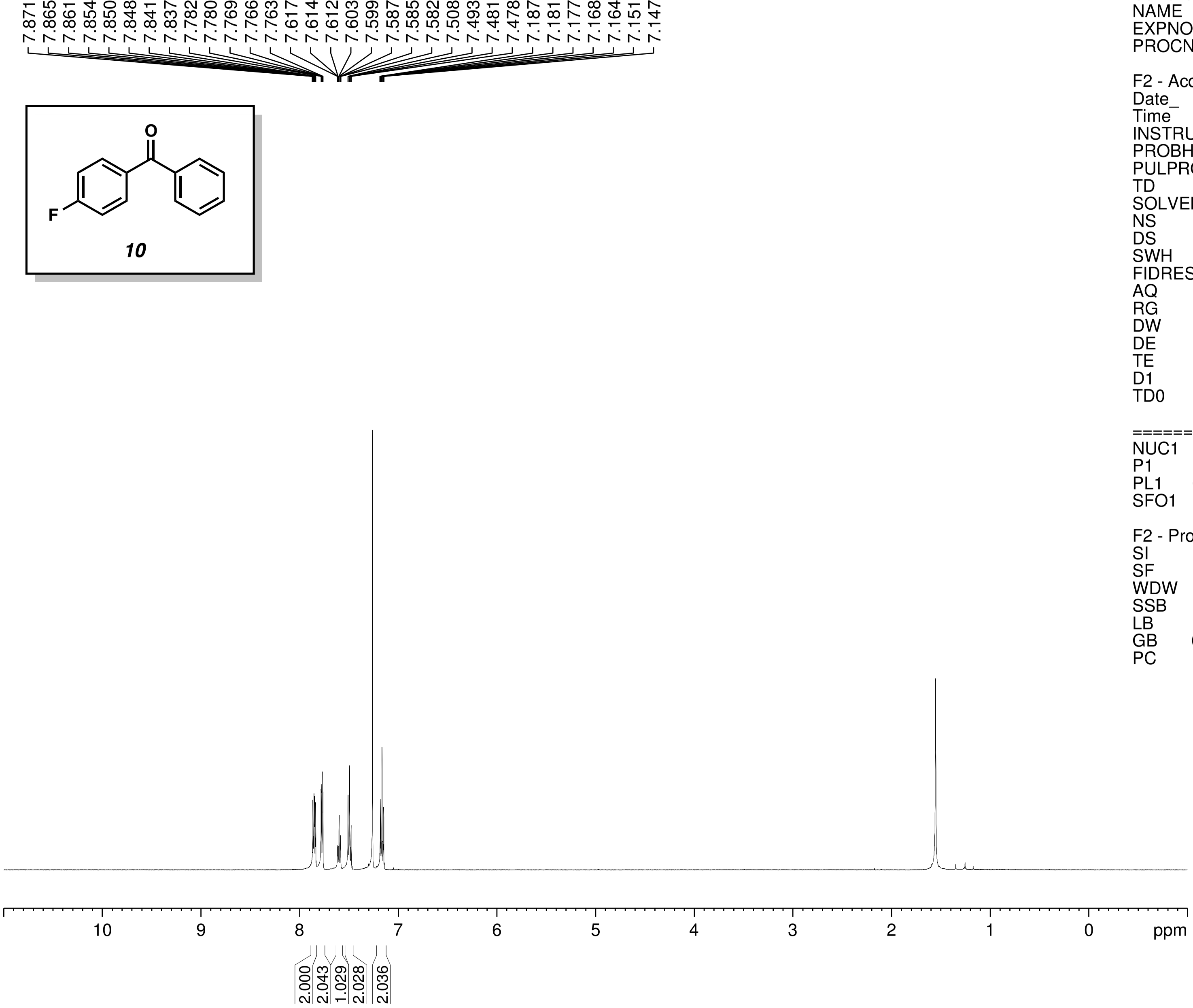

10

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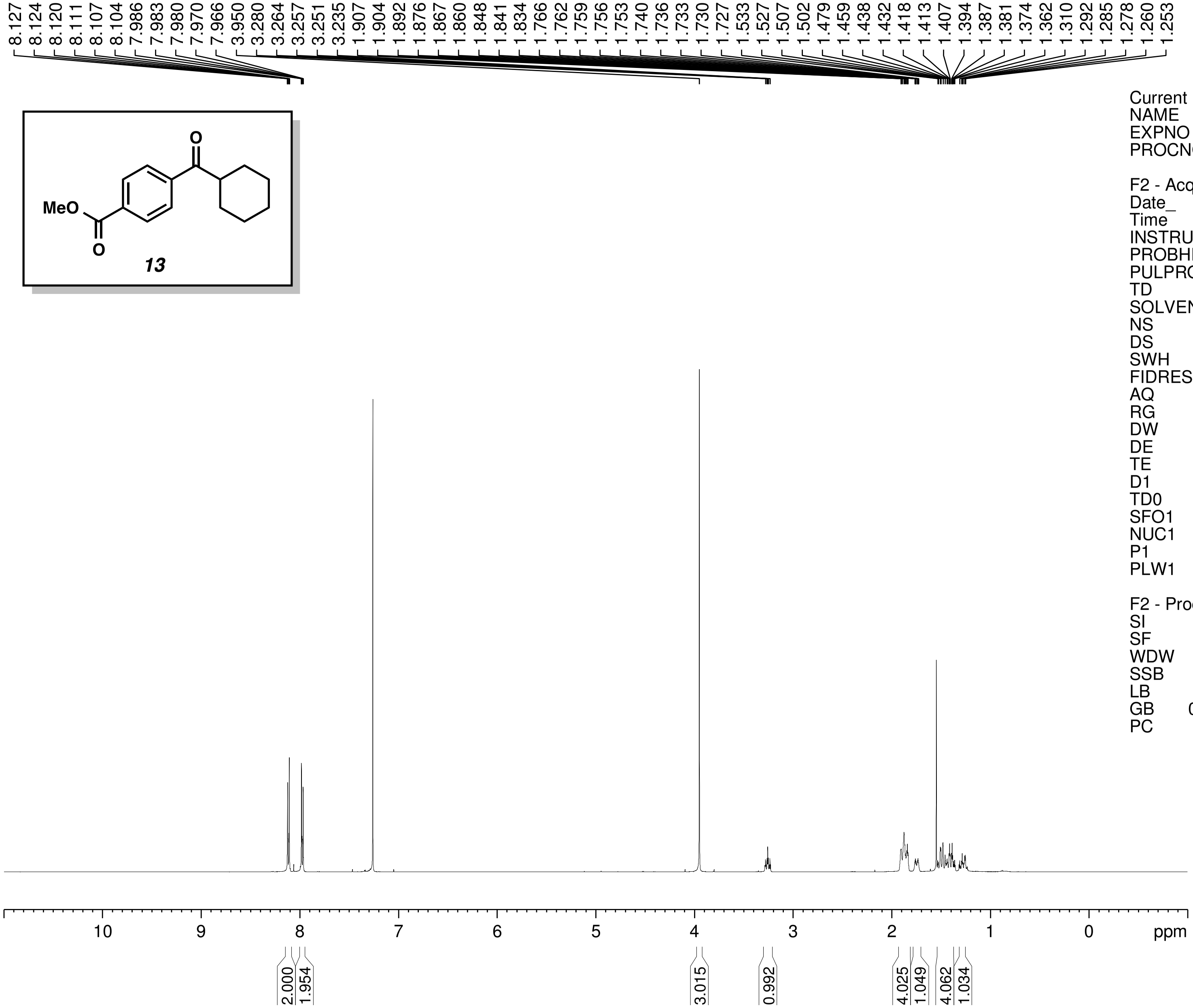
Purified Product, 1H NMR



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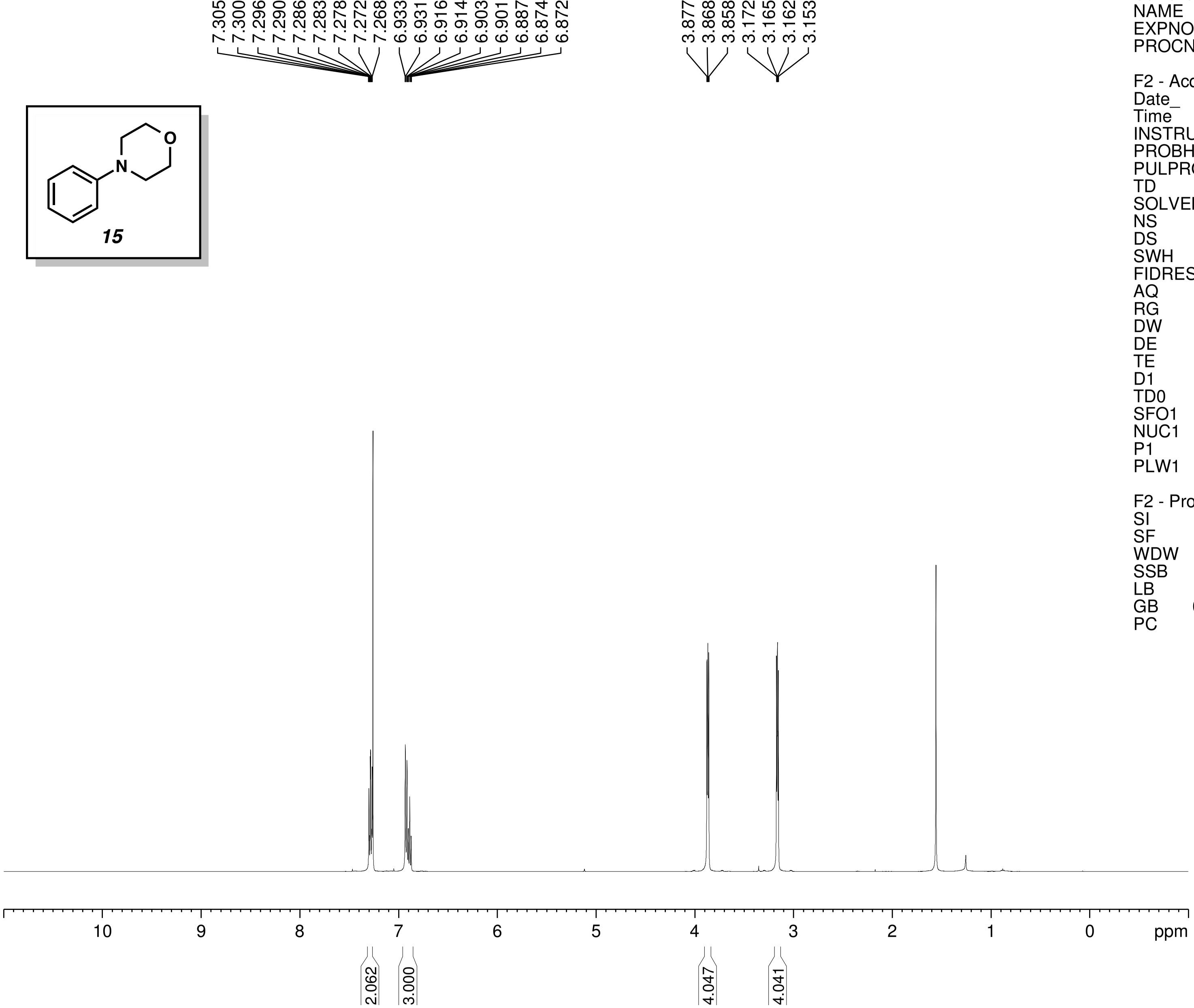

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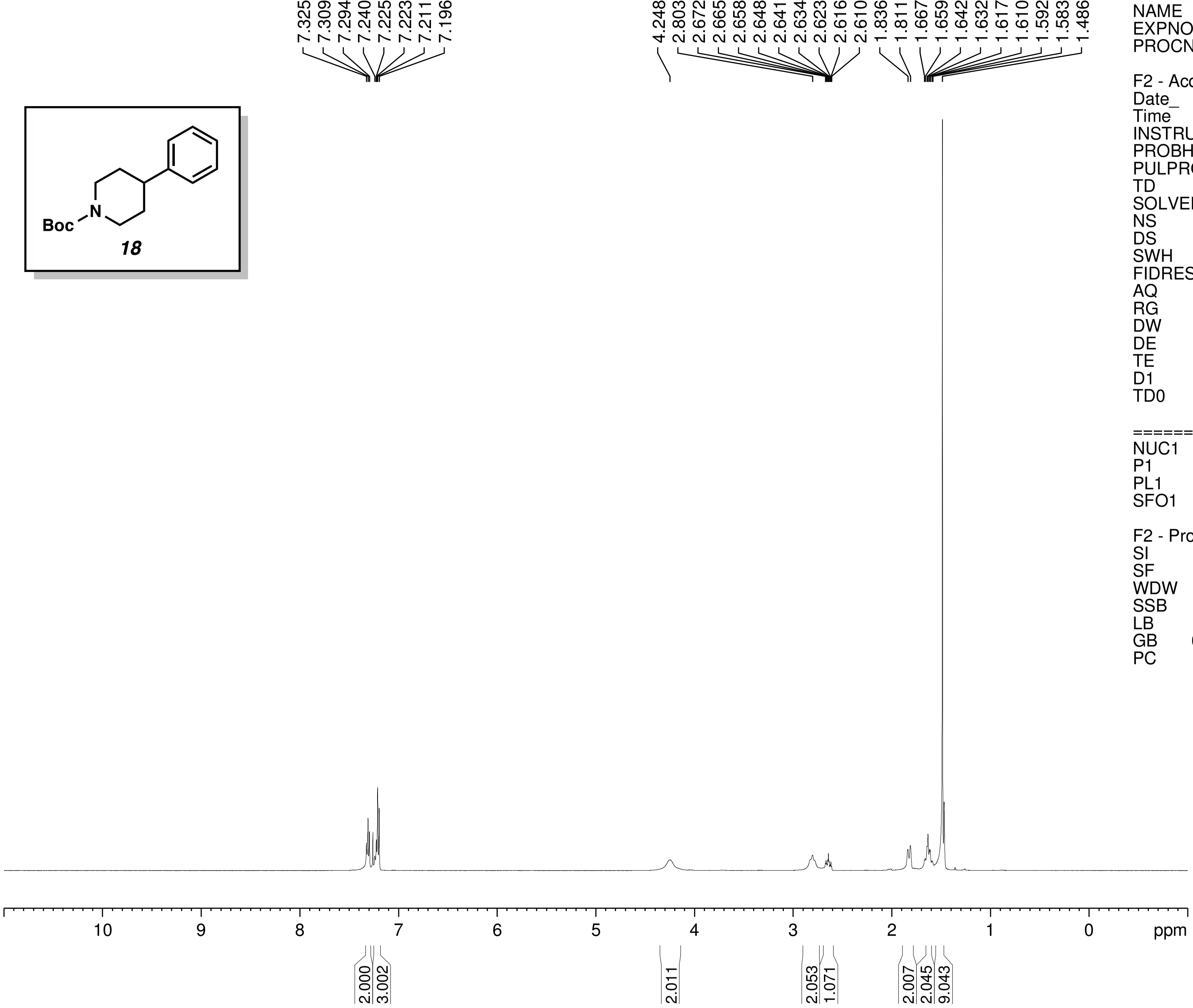
Purified Product, 1H NMR

18



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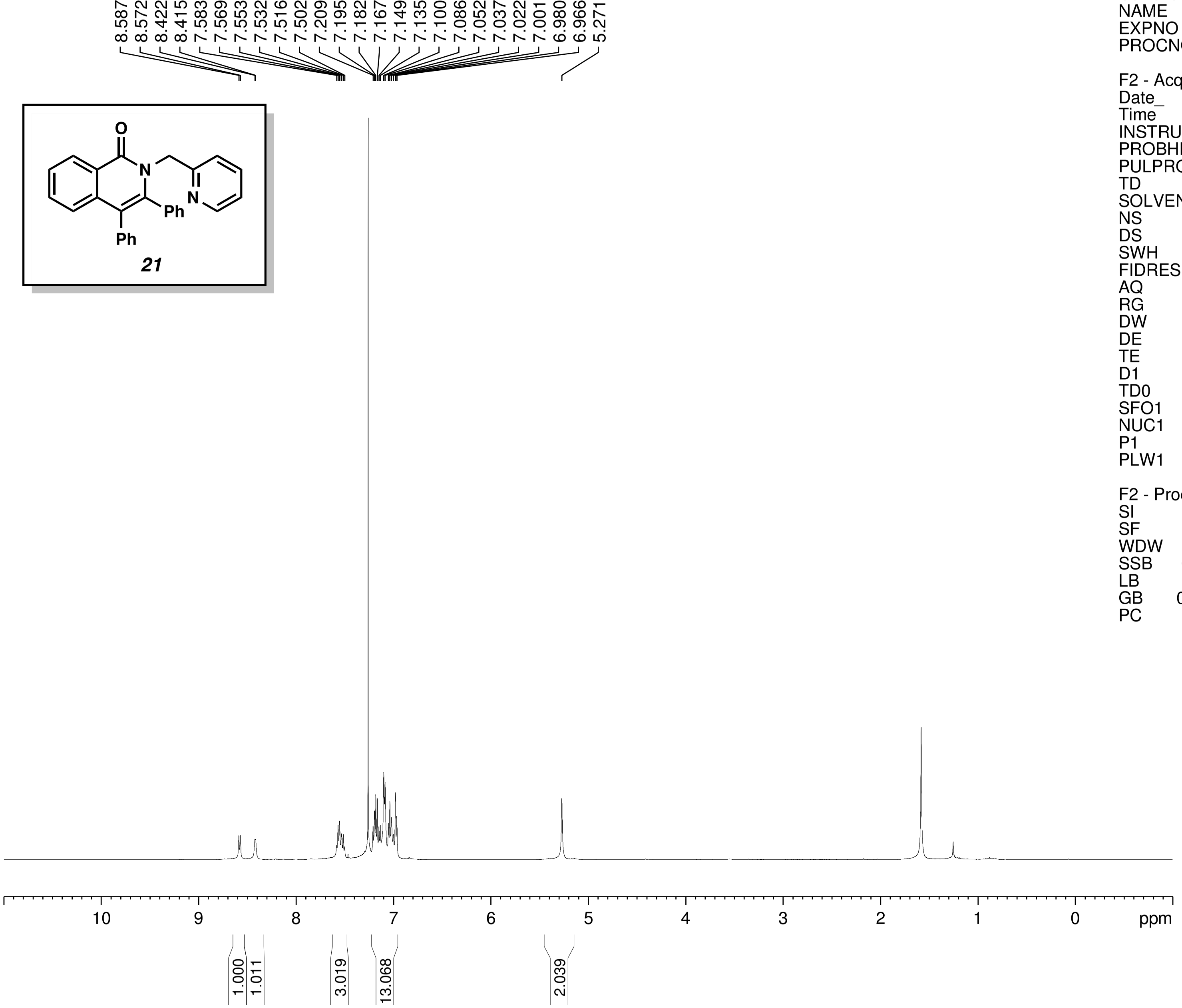
Purified Product, 1H NMR



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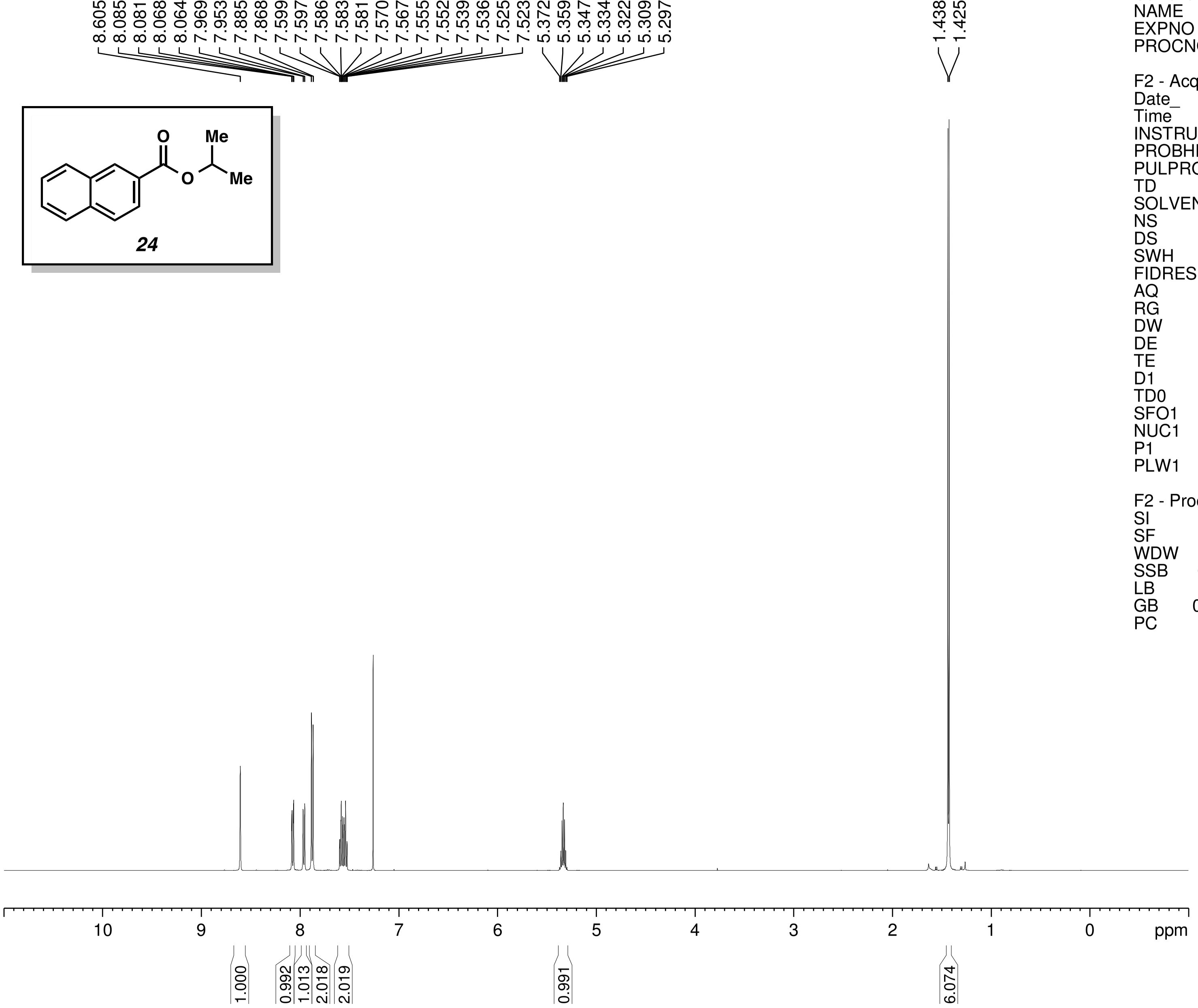
Purified Product, 1H NMR



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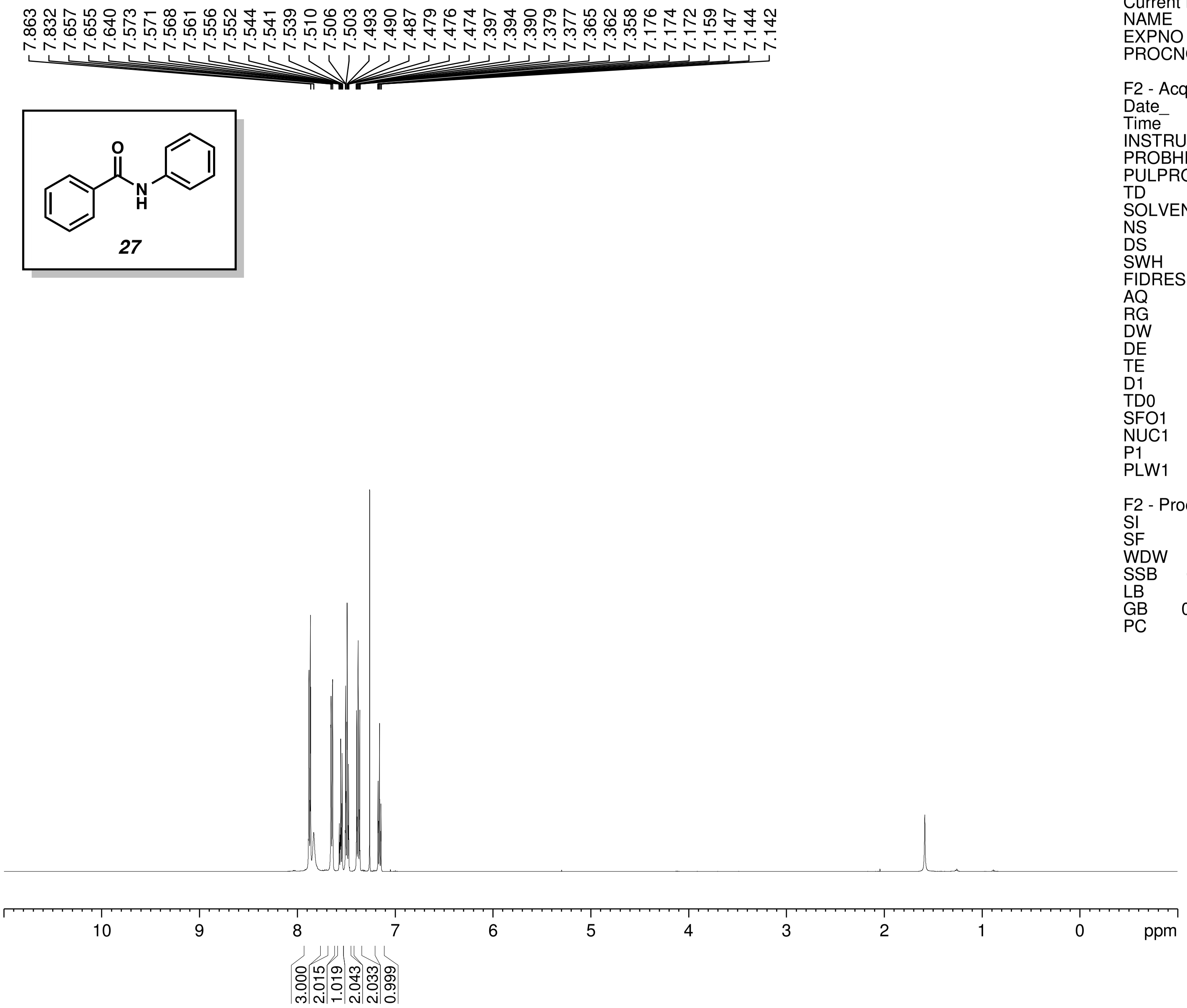
Purified Product, 1H NMR



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