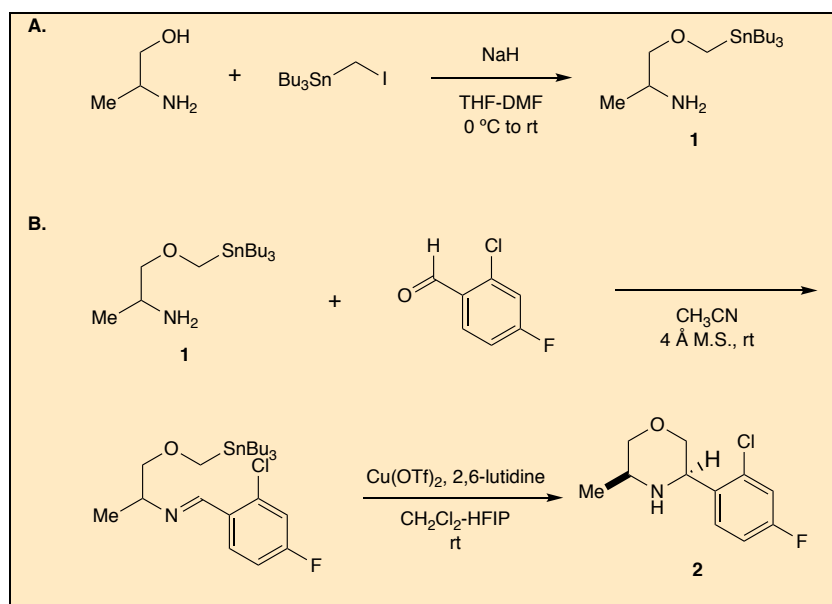


Stannylamine Protocol (SnAP) Reagents for the Synthesis of C-Substituted Morpholines from Aldehydes

Michael U. Luescher, Chalupat Jindakun, and Jeffrey W. Bode*¹

Laboratorium für Organische Chemie, ETH Zürich, HCI F315, Vladimir-Prelog-Weg 3, CH-8093 Zürich, Switzerland

Cedric Hervieu, Estibaliz Merino, and Cristina Nevado



Procedure (Note 1)

A. 1-((tributylstannyl)methoxy)propan-2-amine (**1**). Sodium hydride (1.12 g, 27.9 mmol, 1.1 equiv) (Note 2) is weighed out open to the air and added in one portion to an oven-dried 500-mL, pear-shaped recovery flask equipped with a 40 x 20 mm, Teflon-coated, oval magnetic stir bar, a rubber septum and a nitrogen inlet needle. Pentane (7.5 mL) (Note 3) is added via a syringe

through the septum and stirring is started to release the sodium hydride free from the mineral oil. Stirring is stopped after 10 min, the septum is removed, and the supernatant pentane is removed using a glass pipette. The septum is reattached, anhydrous THF (135 mL) (Note 4) is added via a syringe, and stirring with a rate of ca. 400 rpm is started. *N,N*-Dimethylformamide (30 mL) (Note 5) is added after 10 min via a syringe. The grey suspension is cooled to ca. 0–5 °C using an ice/water bath for 30 min before DL-alaninol (2.00 mL, 1.90 g, 25.3 mmol, 1.0 equiv) (Note 6) is added dropwise via syringe over 15 min. The ice/water bath is removed, and the grey suspension is stirred at 25–27 °C for 2 h to afford a yellow suspension that is re-cooled to 0–5 °C using an ice/water bath (Figure 1a and b). At this point, tributyl(iodomethyl)stannane (10.9 g, 25.3 mmol, 1.0 equiv) (Note 7) is added dropwise to the reaction flask over 1.5 h via a syringe pump using a 10-mL plastic syringe. The ice/water bath is removed and stirring at 25–27 °C is continued for 6 h to afford a colorless suspension (Figure 1c) (Notes 8 and 9).

The suspension is re-cooled to 0–5 °C using an ice/water bath and saturated NH_4Cl (25 mL) is added in one portion via a graduated cylinder. The cooling bath is removed and stirring is continued at 25–27 °C. After 10 min, the biphasic mixture is poured into a 500 mL separatory funnel containing ethyl acetate (50 mL) and water (50 mL). The aqueous layer is separated and extracted with ethyl acetate (3 x 25 mL). The combined organic layers are washed with saturated NaCl solution (3 x 25 mL), dried over anhydrous MgSO_4 (12.5 g), and filtered through a 100-mL sintered glass Büchner funnel (medium porosity, 66 mm diameter).

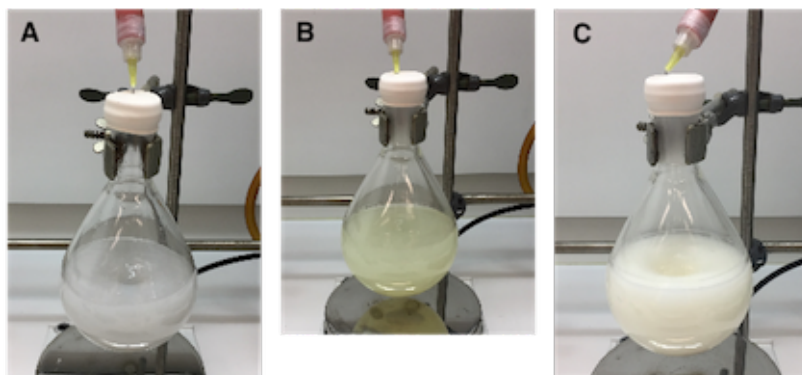


Figure 1. Color change through the course of the reaction

The MgSO_4 is washed with ethyl acetate (3 x 10 mL) and the combined filtrate is concentrated by rotary evaporation (40 °C, 20 mmHg) to afford ca. 11.7 g of a pale yellow oil. This material is diluted with ethyl acetate (2.5 mL) and deposited onto a column (90 mm diameter) of 410 g of silica gel (12 cm high) (Note 10) prepared as a slurry in 10:1 ethyl acetate-MeOH. Elution is carried out with 10:1 ethyl acetate-MeOH collecting 50-mL fractions. The desired product is obtained in fractions 18–34 (Note 11). Mixed fractions 11–17 are collected separately and concentrated by rotary evaporation (40 °C, 20 mmHg) (Note 12). The resulting colorless oil is diluted with ethyl acetate (1.5 mL) and loaded onto a column (60 mm diameter) of 200 g of silica gel (5.5 cm high) (Note 10) prepared as a slurry in 10:1 ethyl acetate-MeOH. Elution is carried out with 10:1 ethyl acetate-MeOH collecting 50-mL fractions. The desired product is obtained in fractions 11–23. All fractions containing pure product according to TLC (Note 11) are combined and concentrated by rotary evaporation (40 °C, 20 mmHg). Further concentration at 25 °C under 0.1 mmHg for 2 h provides 7.5 g (78%) of amino stannane **1** as a colorless oil (Notes 9, 13, 14 and 15).

B. (\pm)-*cis*-3-(2-Chloro-4-fluorophenyl)-5-methylmorpholine (**2**). An oven-dried 250-mL pear-shaped recovery flask equipped with a 40 x 20 mm, Teflon-coated, oval magnetic stir bar is charged with 4 Å molecular sieves (1.72 g) (Note 16) and acetonitrile (75 mL) (Note 17) via a syringe. The flask is fitted with a rubber septum and nitrogen inlet needle, after which the stir rate is set to ca. 375 rpm. 1-((Tributylstannyl)methoxy)propan-2-amine (**1**) (6.5 g, 17.2 mmol, 1.0 equiv) (Notes 13 and 14) prepared in step A is added in one portion via a syringe followed by 2-chloro-4-fluorobenzaldehyde (2.73 g, 17.2 mmol, 1.0 equiv) (Note 18) that is weighed in air and is added in one portion to the reaction flask. The pale-yellow suspension is stirred at 25 °C for 4 h (Note 19). The resulting yellow suspension is filtered over 2.5 g of Celite in a 30-mL sintered glass funnel (30 mm diameter, medium porosity) into a 250-mL pear-shaped recovery flask. The solid material is rinsed with acetonitrile (3 x 5 mL), and the filtrate is then concentrated by rotary evaporation (40 °C, 20 mmHg) to afford ca. 8.9 g of the imine as a clear yellow oil (Notes 20 and 21).

Separately, an oven-dried 1-L pear-shaped recovery flask equipped with a 40 x 20 mm, Teflon-coated, oval magnetic stir bar, a rubber septum and a nitrogen inlet needle is charged with $\text{Cu}(\text{OTf})_2$ (6.2 g, 17.2 mmol, 1.0 equiv) (Note 22 and 23). Dichloromethane (250 mL) (Note 24) and 1,1,1,3,3,3-hexafluoro-2-propanol (65 mL) (Note 25) are added via a syringe. Stirring with a rate of ca. 400 rpm is started and 2,6-lutidine (1.99 mL, 1.84 g,

17.2 mmol, 1.0 equiv) (Note 26 and 27) is added over 5 min via a syringe to the grey suspension affording a green suspension containing scattered lumps of $\text{Cu}(\text{OTf})_2$ (Figure 2a). This suspension is stirred at 25 °C for 1 h affording a more homogeneous dark green suspension (Figure 2b) (Note 28).

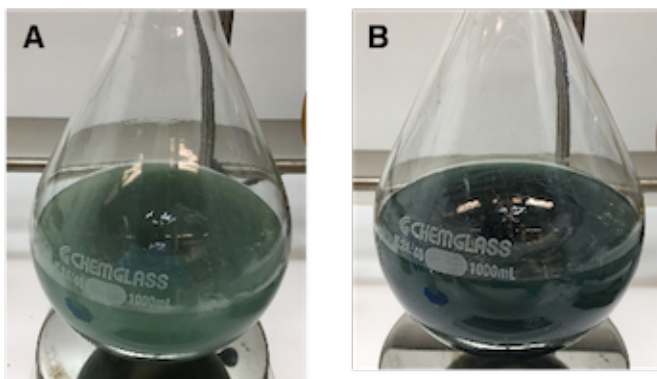


Figure 2. Color change through the course of the copper complex formation

A solution of the imine prepared earlier (ca. 8.9 g) (Notes 20 and 21) in dichloromethane (10 mL) (Note 24) is added dropwise via syringe over 5 min affording a brown reaction mixture. The flask that contained the imine is rinsed with dichloromethane (2 x 2.5 mL) (Note 24) that are added to the reaction mixture via syringe in one portion.

The resulting brown reaction mixture is stirred at 25 °C for 12 h affording a green suspension that is quenched with a pre-mixed solution of 1:1 water- NH_4OH solution (150 mL) (Note 29), which is added via a graduated cylinder in one portion (Notes 30 and 31). The biphasic mixture is stirred vigorously (ca. 800 rpm) for 30 min before being poured into a 1-L separatory funnel. The blue aqueous layer is separated and extracted with dichloromethane (2 x 25 mL). The combined organic layers are washed with a pre-mixed solution of 1:1 water- NH_4OH solution (2 x 40 mL) (Note 29) and saturated NaCl solution (2 x 40 mL), dried over anhydrous MgSO_4 (15 g), and filtered through a 150-mL sintered glass Büchner funnel (medium porosity, 66 mm diameter). The MgSO_4 is washed with dichloromethane (3 x 15 mL) and the combined filtrate is concentrated by rotary evaporation (40 °C, 20 mmHg). The resulting brown oil is further

concentrated at 40 °C and ca. 0.1 mmHg to remove most of the 2,6-lutidine (prior to chromatographic purification) affording ca. 13.0 g of brown oil (Note 32). This material is diluted with dichloromethane (5 mL) and deposited onto a column (90 mm diameter) of 340 g of silica gel (10 cm high) (Note 10) prepared as a slurry in 12:1 dichloromethane-ethyl acetate. Elution is carried out with 12:1 dichloromethane-ethyl acetate (2 L) and then 9:1 dichloromethane-ethyl acetate, collecting 50-mL fractions. The desired product is obtained in fractions 28–65 (Note 33). These fractions are combined, and the solvent is removed by rotary evaporation (40 °C, 20 mmHg). Further concentration at 25 °C under 0.1 mmHg for 2 h provides 2.55 g (65%) of morpholine **2** as a yellow oil (Figure 3) (Notes 9, 15, 34 and 35).



Figure 3. Product of Step B

Notes

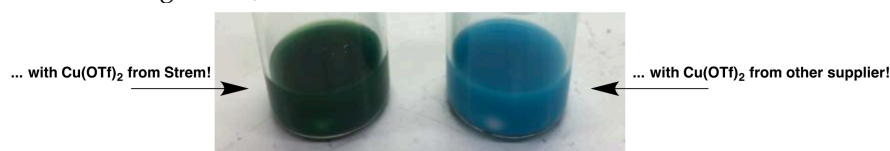
1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at <https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical>. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated

- website “Hazard Assessment in Research Laboratories” at <https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html>. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with sodium hydride, pentane, mineral oil, tetrahydrofuran, *N,N*-dimethylformamide, DL-alaninol, tributyl(iodomethyl)stannane, ammonium chloride, ethyl acetate, sodium chloride, magnesium sulfate (anhydrous), methanol, silica gel, molecular sieves, acetonitrile, 2-chloro-4-fluorobenzaldehyde, Celite, copper(II) triflate, dichloromethane, 1,1,1,3,3,3-hexafluoro-2-propanol, 2,6-lutidine, and ammonium hydroxide.
2. Sodium hydride (60% dispersion in mineral oil) was purchased from Sigma-Aldrich and used as received.
 3. Pentane (anhydrous, $\geq 99\%$) was purchased from Sigma-Aldrich and used as received.
 4. Tetrahydrofuran (low water inhibitor free HPLC grade) was purchased from Sigma-Aldrich and purified by pressure filtration through activated alumina immediately prior to use.
 5. *N,N*-Dimethylformamide (low water inhibitor free HPLC grade) was purchased from Sigma-Aldrich and purified by pressure filtration through activated alumina immediately prior to use.
 6. DL-Alaninol (98%) was obtained from Sigma-Aldrich and used as received.
 7. Tributyl(iodomethyl)stannane was prepared according to a modified procedure of Seitz et al² published in *Organic Syntheses* from Bode, et al, *Org. Synth.* **2018**, 95, 345.
 8. TLC analysis indicated that full conversion had occurred, as DL-alaninol was not visible at this point (10:1, ethyl acetate-MeOH with KMnO_4 stain visualization): DL-alaninol ($R_f = 0.08$) and 1-((tributylstannyl)methoxy)propan-2-amine (**1**) ($R_f = 0.18$).
 9. The KMnO_4 stain was prepared using 1.5 g of KMnO_4 and 10 g of K_2CO_3 dissolved in 200 mL of water and 1.25 mL of 10% m/v NaOH solution.
 10. High-purity Silica gel grade (9385), pore size 60 Å, 230–400 mesh particle size purchased from Sigma-Aldrich.
 11. Purification is followed using TLC analysis on Silica gel (10:1, ethyl acetate-MeOH with KMnO_4 stain visualization): 1-((tributylstannyl)methoxy)propan-2-amine (**1**) ($R_f = 0.18$).



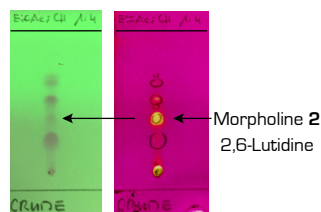
12. The impurities in those mixed fractions do not affect the subsequent imine formation and annulation reaction. Mixed fractions that contain mostly product can be combined with the pure material in order to avoid a second column purification and save solvent.
13. A second reaction performed on half-scale provided 3.65 g (78%) of the same colorless oil. 1-((Tributylstannyl)methoxy)propan-2-amine (**1**) decomposes over time when stored neat at ambient temperature. This reagent should be stored as a degassed 1 M solution in dry dichloromethane at $-10\text{ }^{\circ}\text{C}$ in which it is stable for months.
14. 1-((Tributylstannyl)methoxy)propan-2-amine (**1**) has the following physical and spectroscopic properties: $R_f = 0.18$ (10:1 ethyl acetate-MeOH; KMnO_4 visualization; Merck Millipore TLC Silica gel 60 F254 plates); ^1H NMR (CDCl_3 , 400 MHz) δ : 0.88–0.93 (m, 15H), 1.03 (d, $J = 6.3$ Hz, 3H), 1.26–1.35 (m, 6H), 1.41–1.62 (m, 6H), 1.76 (bs, 2H), 3.01–3.14 (m, 2H), 3.25 (td, $J = 3.1, 1.5$ Hz, 1H), 3.70 (d, $J = 10.3$ Hz, 1H), 3.76 (d, $J = 10.3$ Hz, 1H); ^{13}C (CDCl_3 , 101 MHz) δ : 9.0, 13.7, 19.6, 27.3, 29.1, 46.5, 62.3, 82.4; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{38}\text{NOSn}$ $[\text{M} + \text{H}]^+$ 380.19699, found 380.19654; IR (film): 2955, 2924, 2871, 2853, 1463, 1376, 1086, 864, 726, 688, 664, 594, 504 cm^{-1} . Purity was assessed as 95% by Q NMR using 4'-nitroacetophenone as the internal standard.
15. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl_3 peak at 7.26 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl_3 at 77.00 ppm used as a standard) and $^{117}/^{119}\text{Sn}$ – ^{13}C couplings are not reported.
16. 4 Å Molecular sieves (powder, activated, 325 mesh particle size) was purchased from Sigma-Aldrich. The sieves are activated at $120\text{ }^{\circ}\text{C}$ and 0.1 mmHg for 12 h.

17. Acetonitrile ($\geq 99.5\%$ HPLC gradient grade) was purchased from Fisher Scientific and purified by pressure filtration through activated alumina immediately prior to use.
18. 2-Chloro-4-fluorobenzaldehyde (98.0%) was purchased from Fluorochem and used as received.
19. A small aliquot was taken and filtered to remove the molecular sieves. Concentration using a rotavap (40 °C, 20 mmHg) afforded an orange oil which upon ^1H NMR measurement indicated full conversion.
20. The imine is stable neat at ambient temperature. No special precautions need to be taken.
21. The intermediate imine has the spectroscopic properties: ^1H NMR (CDCl_3 , 400 MHz) δ : 0.84 (t, $J = 7.3$ Hz, 15H), 1.17–1.29 (m, 9H), 1.37–1.54 (m, 6H), 3.38 (d, $J = 3.1$ Hz, 1H), 3.40 (d, $J = 0.7$ Hz, 1H), 3.53–3.65 (m, 1H), 3.67 (d, $J = 10.3$ Hz, 1H), 3.75 (d, $J = 10.3$ Hz, 1H), 6.99 (dddd, $J = 8.7, 7.9, 2.5, 0.7$ Hz, 1H), 7.10 (dd, $J = 8.5, 2.5$ Hz, 1H), 8.06 (dd, $J = 8.8, 6.4$ Hz, 1H), 8.61 (s, 1H); ^{13}C (CDCl_3 , 101 MHz) δ : 8.9, 13.7, 18.7, 27.2, 29.1, 62.3, 65.7, 79.8, 114.5 (d, $J_{\text{CF}} = 21.4$ Hz), 116.8 (d, $J_{\text{CF}} = 24.8$ Hz), 129.9 (d, $J_{\text{CF}} = 3.5$ Hz), 130.1 (d, $J_{\text{CF}} = 9.1$ Hz), 135.8 (d, $J_{\text{CF}} = 10.6$ Hz), 155.8, 163.6 (d, $J_{\text{CF}} = 253.5$ Hz).
22. $\text{Cu}(\text{OTf})_2$ (98%) was purchased from Strem Chemical and dried at 115 °C at 0.1 mmHg for 2 h before use. The dried $\text{Cu}(\text{OTf})_2$ can be stored in a desiccator and be used for weeks without a negative impact on the reaction outcome.
23. $\text{Cu}(\text{OTf})_2$ from other suppliers gave inferior results. A 1:1 $\text{Cu}(\text{OTf})_2$ - 2,6-lutidine complex in HFIP (0.1 M) of a suitable copper source affords a green suspension within 0.5–1 h (see picture below - left side) while inferior $\text{Cu}(\text{OTf})_2$ sources afford blue or purple suspensions (see picture below - right side).

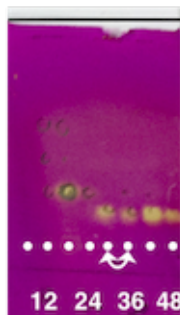


24. Dichloromethane (HPLC grade) was purchased from Fisher Scientific and purified by pressure filtration through activated alumina immediately prior to use.

25. 1,1,1,3,3,3-Hexafluoro-2-propanol, also known as 1,1,1,3,3,3-hexafluoroisopropanol or HFIP (99.9%) was purchased from Fluorochem and was used as received.
26. 2,6-Lutidine (ReagentPlus, 98%) was purchased from Sigma-Aldrich and used as received.
27. This is a slightly endothermic reaction.
28. Different colors at this point in time, other than various shades of green, often result in lower yields. This phenomenon was observed using $\text{Cu}(\text{OTf})_2$ from suppliers other than Strem Chemicals (Note 23).
29. Ammonium hydroxide solution (ACS reagent, 28.0–30.0% NH_3 basis) was purchased from Sigma-Aldrich and used as received.
30. This is a slightly exothermic reaction.
31. The reaction progress was not monitored.
32. TLC analysis (9:1, dichloromethane-ethyl acetate with KMnO_4 stain visualization): Side product ($R_f = 0.38$), (\pm)-*cis*-3-(2-chloro-4-fluorophenyl)-5-methylmorpholine (**2**) ($R_f = 0.31$), and 2,6-lutidine ($R_f = 0.18$). The morpholine **2** is barely visible using UV 254 nm as the visualization technique. In general, product heterocycles are detected by TLC in the unpurified reaction mixture using both, potassium permanganate and ninhydrin stains. The product is visible with both developing agents while 2,6-lutidine is only visible using UV 254 nm and does not stain using KMnO_4 or ninhydrin (see pictures below in which 4:1 hexanes-ethyl acetate was used as the eluent for better separation on the TLC plate).



33. Purification is followed using TLC analysis on silica gel (9:1 dichloromethane-ethyl acetate; KMnO_4 visualization; Merck Millipore TLC Silica gel 60 F254 plates): (\pm)-*cis*-3-(2-Chloro-4-fluorophenyl)-5-methylmorpholine (**2**) ($R_f = 0.31$). The morpholine **2** is barely visible using UV 254 nm as the visualization technique.



34. (±)-*cis*-3-(2-Chloro-4-fluorophenyl)-5-methylmorpholine (**2**) has the following physical and spectroscopic properties: R_f = 0.31 (9:1, dichloromethane-ethyl acetate; KMnO_4 visualization; Merck Millipore TLC Silica gel 60 F254 plates) and R_f = 0.45 (4:1 hexanes-ethyl acetate; KMnO_4 visualization; Merck Millipore TLC Silica gel 60 F254 plates); ^1H NMR (CDCl_3 , 400 MHz) δ : 1.03 (d, J = 5.9 Hz, 3H), 1.72 (bs, 1H), 3.09–3.18 (m, 3H), 3.78 (d, J = 8.2 Hz, 1H), 3.90 (ddd, J = 10.8, 3.1, 0.7 Hz, 1H), 4.42 (ddd, J = 9.9, 5.0, 0.3 Hz, 1H), 6.98 (dddd, J = 8.6, 7.9, 2.6, 0.4 Hz, 1H), 7.09 (dd, J = 8.5, 2.6 Hz, 1H), 7.67 (dd, J = 8.7, 6.3 Hz, 1H); ^{13}C (CDCl_3 , 101 MHz) δ : 17.8, 50.9, 56.0, 71.2 (d, J_{CF} = 1.3 Hz), 73.06, 114.2 (d, J_{CF} = 20.6 Hz), 116.6 (d, J_{CF} = 24.6 Hz), 129.5 (d, J_{CF} = 8.7 Hz), 133.6 (d, J_{CF} = 10.1 Hz), 133.7 (d, J_{CF} = 3.4 Hz), 161.5 (d, J_{CF} = 249.4 Hz); HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{14}\text{ClFNO}$ [$\text{M} + \text{H}$] $^+$ 230.07425, found 230.07385; IR (film): 3015, 2970, 2960, 2949, 1740, 1488, 1436, 1366, 1229, 1216, 1102, 910, 588, 539, 527, 515 cm^{-1} . Purity was assessed as 97% by Q NMR using 4'-nitroacetophenone as the internal standard.
35. A second reaction performed on half-scale provided 1.31 g (66%) of the same yellow oil. In general, the reaction is not very sensitive to oxygen or H_2O and can be conducted without extra dry solvents or without pre-dried $\text{Cu}(\text{OTf})_2$ with only slightly diminished yields.

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the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

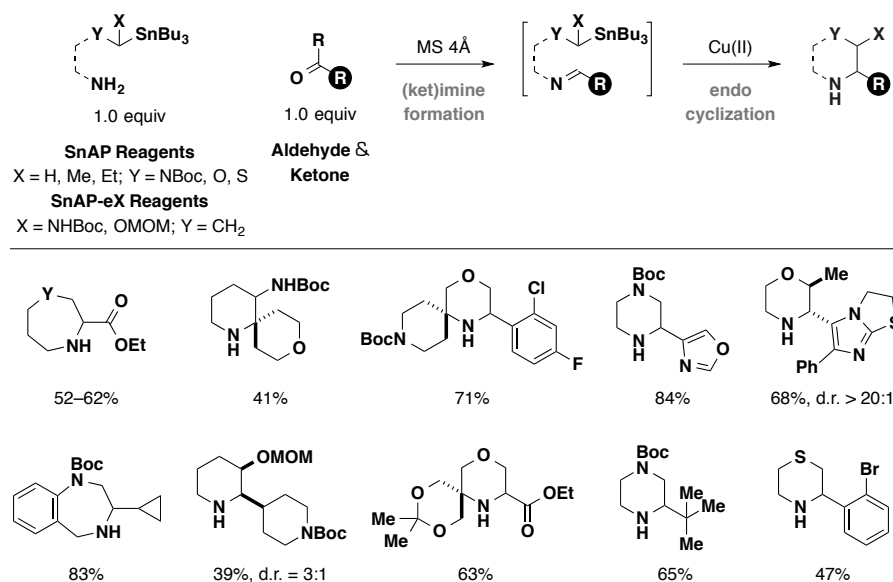
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Discussion

Functionalized saturated N-heterocycles, such as piperidines, piperazines, or morpholines, can be found with increasing prevalence in small molecule pharmaceuticals, despite their limited commercial abundance and challenging routes for their preparation.³ Enormous efforts have been made on the synthesis of such cyclic amines, but a direct extension of cross-coupling methods to include saturated N-heterocycles remains elusive. Recent efforts to address this well-known limitation have provided promising methodologies for the derivatization of simple N-heterocycles.^{4,5} However, these methods still have considerable shortcomings as a restricted substrate in terms of classes of N-heterocycles, substitution patterns, the requirement of protection-deprotection steps or the limited access of more complex N-heterocycles for further modifications.

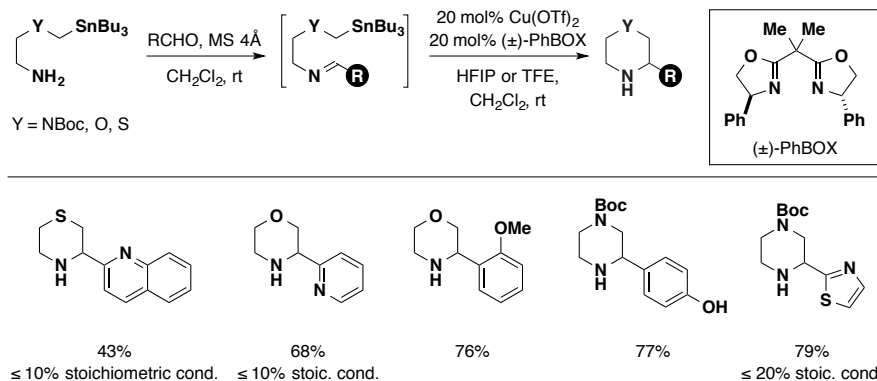
As an alternative to traditional cross-coupling approaches, our group developed SnAP (stannyl (Sn) amine protocol) reagents as a versatile, predictable method for the preparation of functionalized, NH-free saturated nitrogen heterocycles, using widely available aromatic, heteroaromatic, and aliphatic aldehydes or ketones to access spirocyclic scaffolds (Scheme 1).^{6,7}



Scheme 1. SnAP reagent concept and substrate scope

Following our first report on SnAP reagents for the preparation of thiomorpholines,^{7a} we have extended the line of air- and moisture stable SnAP reagents to include ones suitable for the preparation of functionalized morpholines and piperazines,^{7b, d–f} pyrrolidines and piperidines,^{7f} as well as medium-sized N-heterocycles.^{7c} This process has an excellent substrate scope and tolerates electronically and sterically diverse (hetero)aromatic and aliphatic aldehydes and ketones as well as a good functional group tolerance accepting various heterocycles, aryl halides, nitriles, or unprotected phenols. Furthermore, it offers the advantage of affording unprotected products, which obviates the need to cleave the often-difficult-to-remove protecting groups. A further advantage of the SnAP protocol is that the reaction protocol described herein can be used for all SnAP reagents with no substrate specific optimization needed; although substrate-specific

optimization might allow to improve isolated yields of the desired N-heterocyclic products. As an example, catalytic amounts of $\text{Cu}(\text{OTf})_2$ in combination with a bisoxazoline ligand proved to be beneficial for aldehydes containing proximal heteroatoms (Scheme 2).^{7d}



Scheme 2. Catalytic synthesis of 6-membered thiomorpholines, morpholines, and piperazines

The main drawback of the SnAP protocol, however, is its dependence on tin and its suspected toxicity.⁸ The large difference in polarity between the NH-free product heterocycles and the tin products, however, simplifies the purification and methods to remove most of the tin species prior to column purification, for example, through extraction with acetonitrile and hexanes further facilitate purification to access products containing trace amounts of tin at most.^{8,9} Furthermore, the unprotected N-heterocycles can be converted into their salts to remove last traces of tin impurities,^{7c} and we hope that the procedure disclosed herein further simplifies access to various functionalized N-heterocycles currently challenging to prepare, and in great demand in drug development approaches.

References

1. Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zurich, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland. Email: bode@org.chem.ethz.ch. We thank the European

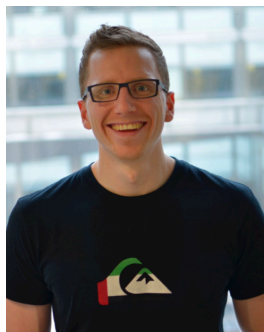
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Appendix

Chemical Abstracts Nomenclature (Registry Number)

Sodium hydride; (7646-69-7)
 DL-Alaninol: (±)-2-Amino-1-propanol; (6168-72-5)
 Tributyl(iodomethyl)stannane; (66222-29-5)
 2-Chloro-4-fluorobenzaldehyde; (84194-36-5)
 Cu(OTf)₂: Copper(II) trifluoromethanesulfonate (34946-82-2)
 HFIP: 1,1,1,3,3,3-Hexafluoro-2-propanol; (920-66-1)
 2,6-Lutidine: 2,6-Dimethylpyridine; (108-48-5)
 NH₄OH: Ammonium hydroxide; (1336-21-6)



Michael U. Luescher was born in 1985 in Switzerland and was trained as a medicinal chemistry laboratory technician at the Novartis Pharma AG (Switzerland). He then moved on to earn a BSc and MSc degree in chemistry in 2010 and 2012 from the University of Basel under the supervision of Professor Karl Gademann. Afterwards, he joined Professor Jeffrey W. Bode at ETH Zurich (Switzerland) investigating SnAP reagents where he received his Ph.D. in 2017. He is currently a post-doctoral fellow in the laboratory of Professor Emily Balskus at Harvard University.



Chalupat Jindakun received his BSc and MSc in Organic Chemistry from Mahidol University in Bangkok (Thailand). In 2016, he received a Royal Thai Government Scholarship to pursue his doctoral studies in organic chemistry under the guidance of Professor Jeffrey W. Bode at ETH Zurich (Switzerland) where he is currently investigating SnAP reagents for the preparation functionalized, of NH-free N-heterocycles.



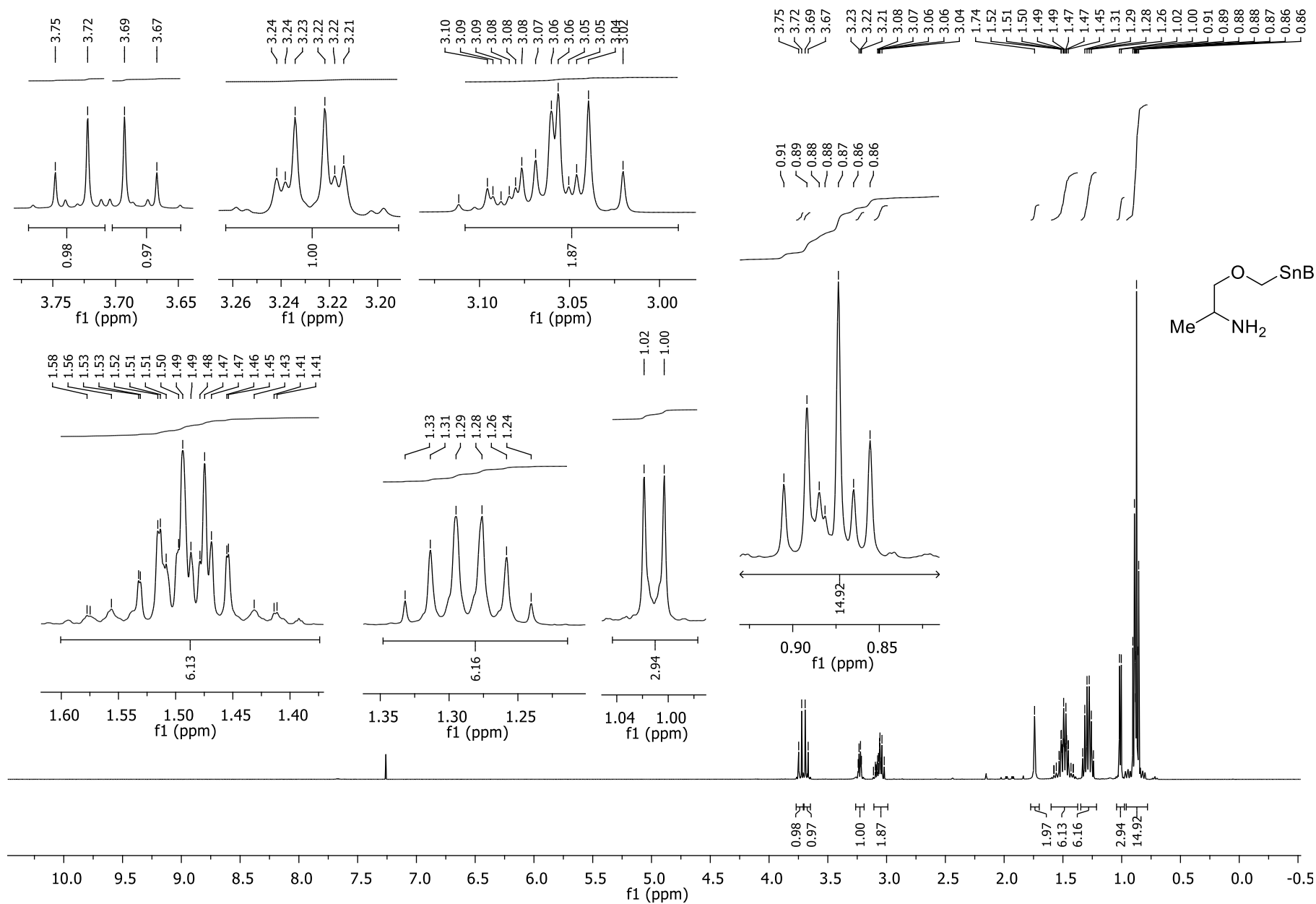
Jeffrey W. Bode studied at Trinity University in San Antonio, TX (USA). Following doctoral studies at the California Institute of Technology (USA) and ETH Zurich and postdoctoral research at the Tokyo Institute of Technology (Japan), he began his independent academic career at UC Santa Barbara (USA) in 2003. He moved to the University of Pennsylvania as an Associate Professor in 2007 and to ETH Zurich as a Full Professor in 2010. Since 2013, he is also a Principal Investigator and Visiting Professor at the Institute of Transformative Biomolecules (WPI-ITbM) at Nagoya University (Japan).

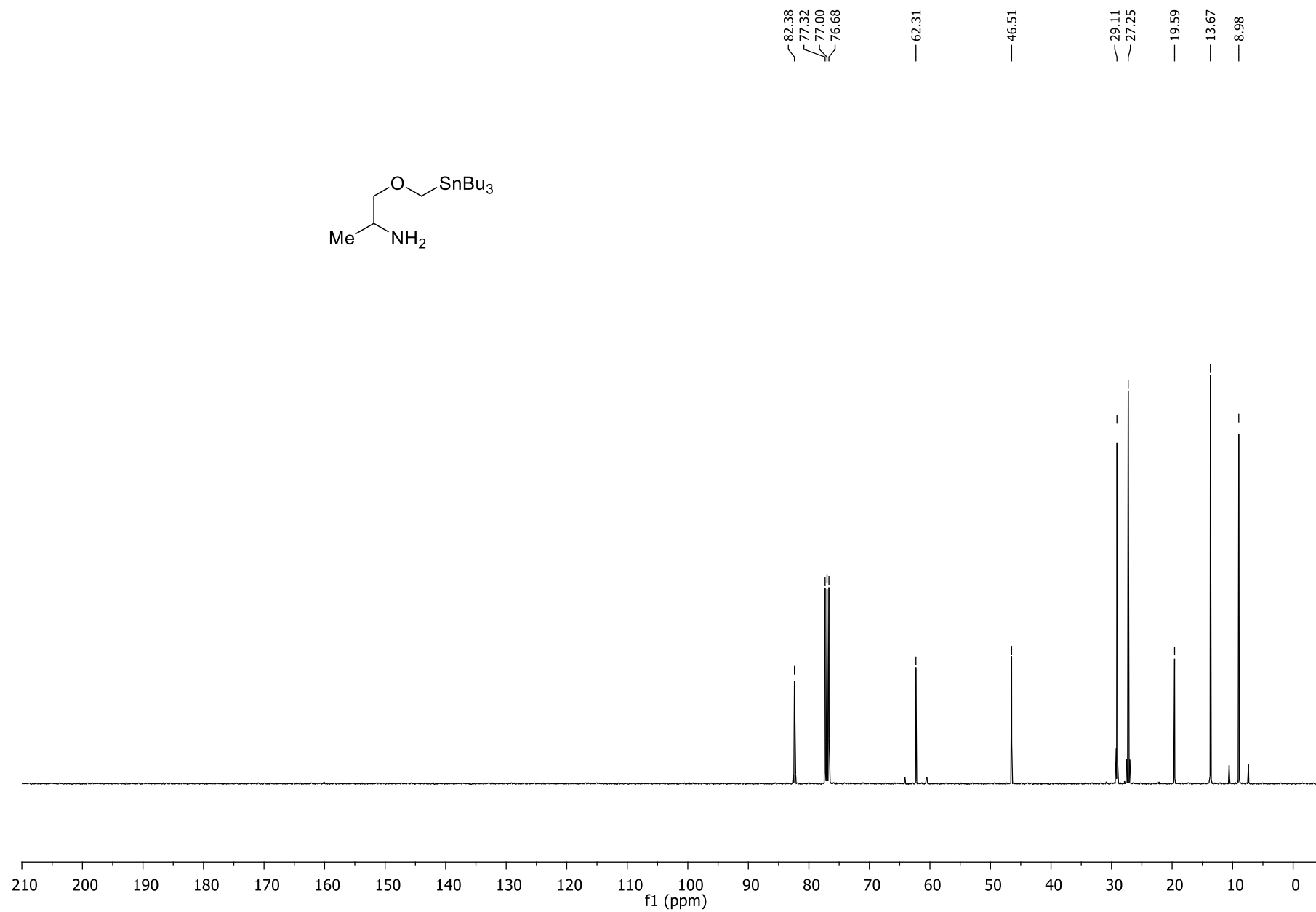
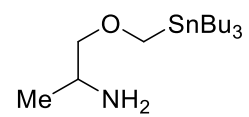


Cedric Hervieu obtained his master's Degree in chemistry from the Joseph Fourier University (Grenoble-France), in 2017. He joined Prof. Liming Zhang group at the University of California, Santa Barbara in United States to work as a visiting student (2016), followed by a stay at University of Zürich in Prof. Cristina Nevado's group. In August 2017, he started his Ph.D. at the University of Zurich where he is working in Prof. Cristina Nevado's group. His research interests focus on the development and application of new photo redox catalysis based synthetic methods.



Estíbaliz Merino obtained her Ph.D. degree from the Autónoma University (Madrid-Spain). After a postdoctoral stay with Prof. Magnus Rueping at Goethe University Frankfurt and RWTH-Aachen University in Germany, she worked with Prof. Avelino Corma in Instituto de Tecnología Química-CSIC (Valencia) and Prof. Félix Sánchez in Instituto de Química Orgánica General-CSIC (Madrid) in Spain. At present, she is research associate in Prof. Cristina Nevado's group in University of Zürich. She is interested in the synthesis of natural products using catalytic tools and in the development of new materials with application in heterogeneous catalysis.





OS-QNMR-Step-1

8.33
8.31
8.12
8.10

7.26

3.76
3.74
3.70
3.68
3.25
3.24
3.23
3.07
3.06
3.05
1.53
1.52
1.50
1.50
1.49
1.49
1.47
1.33
1.32
1.31
1.29
1.28
1.26
1.04
1.02
0.91
0.90
0.89
0.88
0.87
0.85

Int = Average of normalized integrals values

MW = Molecular weight

P = Purity (as percent value)

m = mass

n = number of protons giving rise to a given NMR signal (The total number of protons is set to one because an average of all normalized integrals is carried out)

$$n_{IS} = 1$$

$$Int_{IS} = 1.03$$

$$MW_{IS} = 165.15 \text{ g/mol}$$

$$m_{IS} = 2.53 \text{ mg}$$

$$P_{IS} = 98\%$$

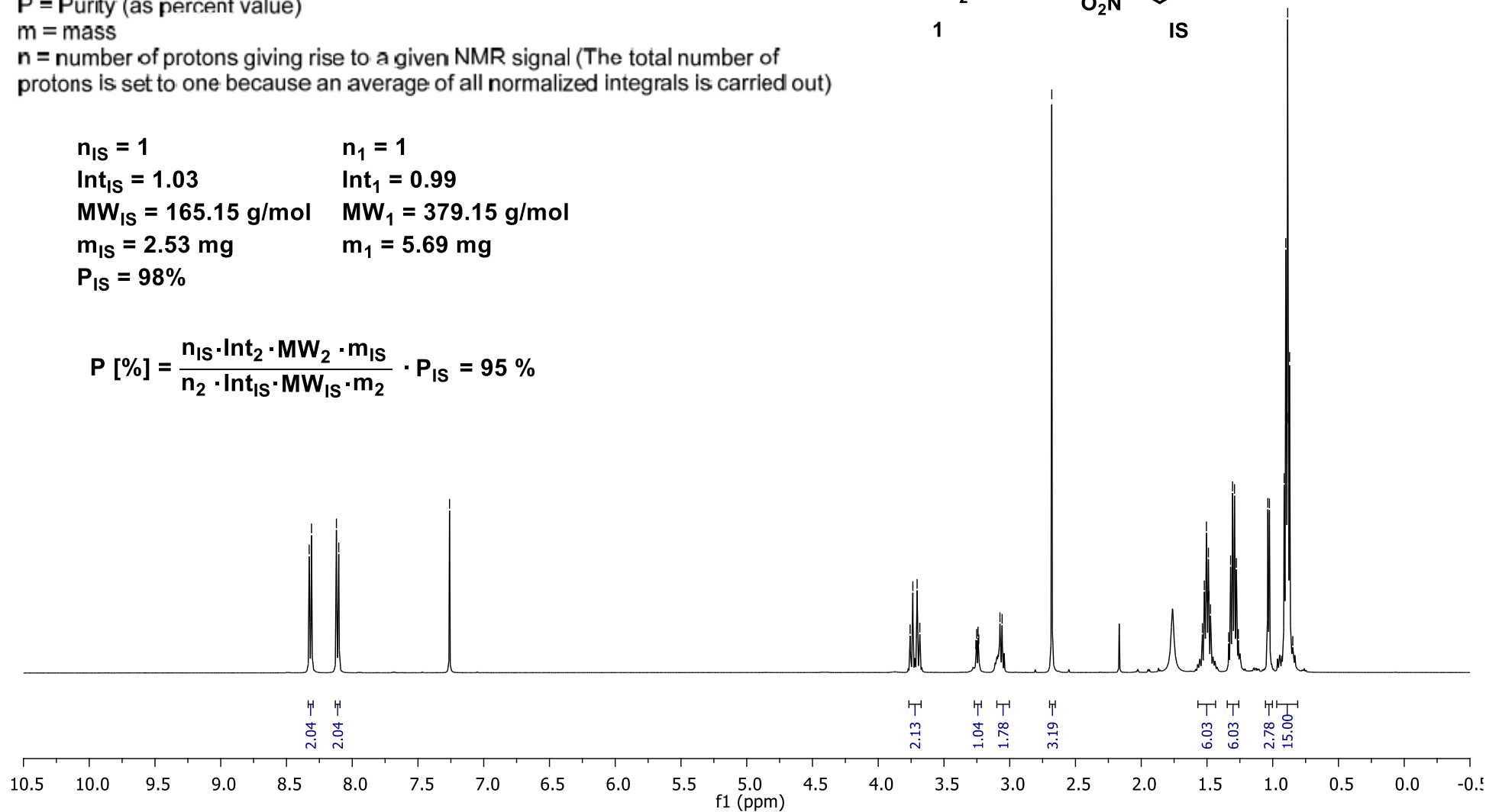
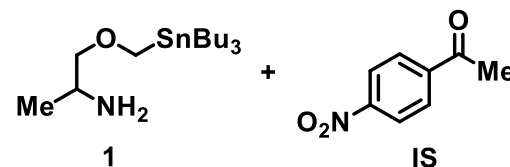
$$n_1 = 1$$

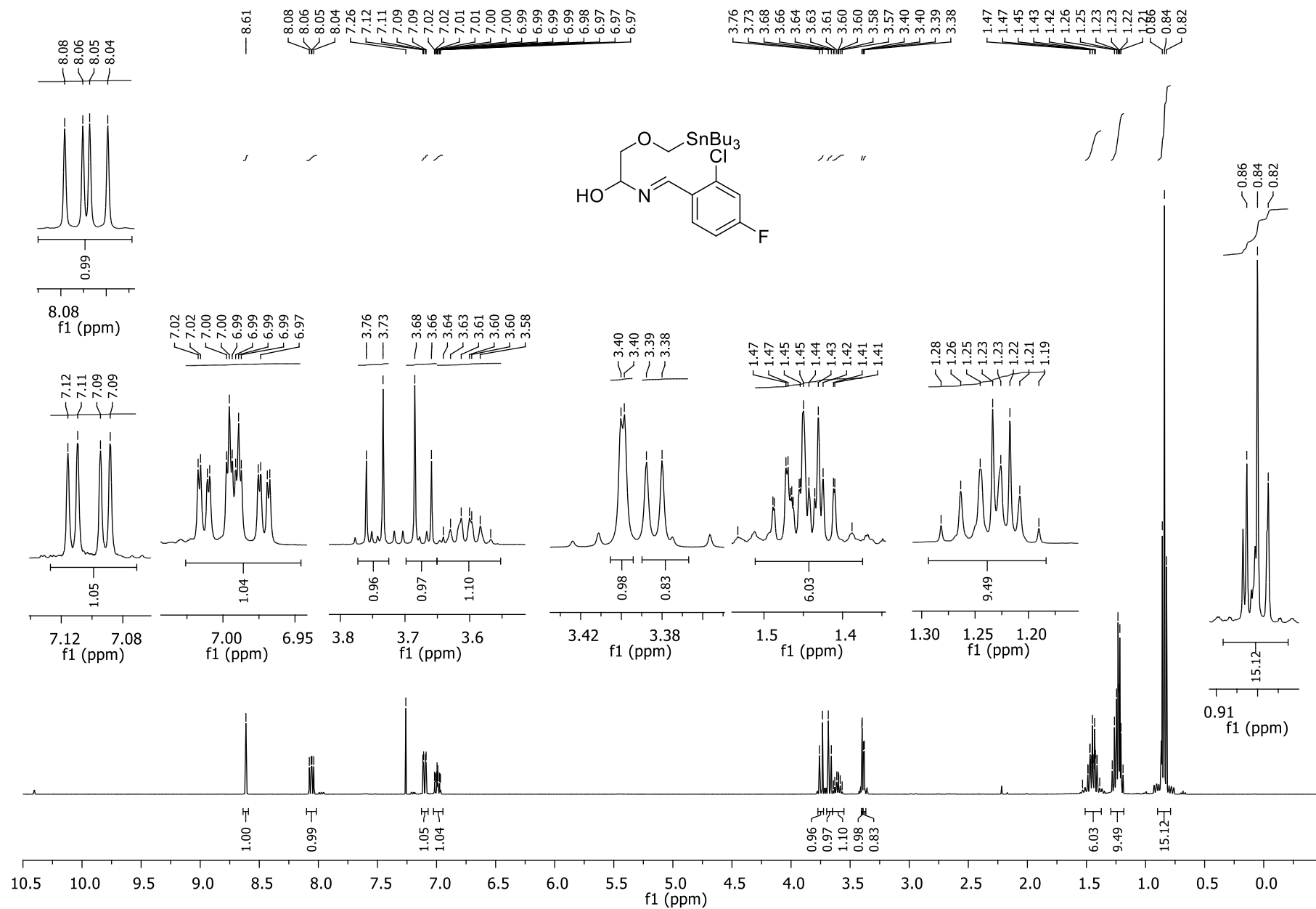
$$Int_1 = 0.99$$

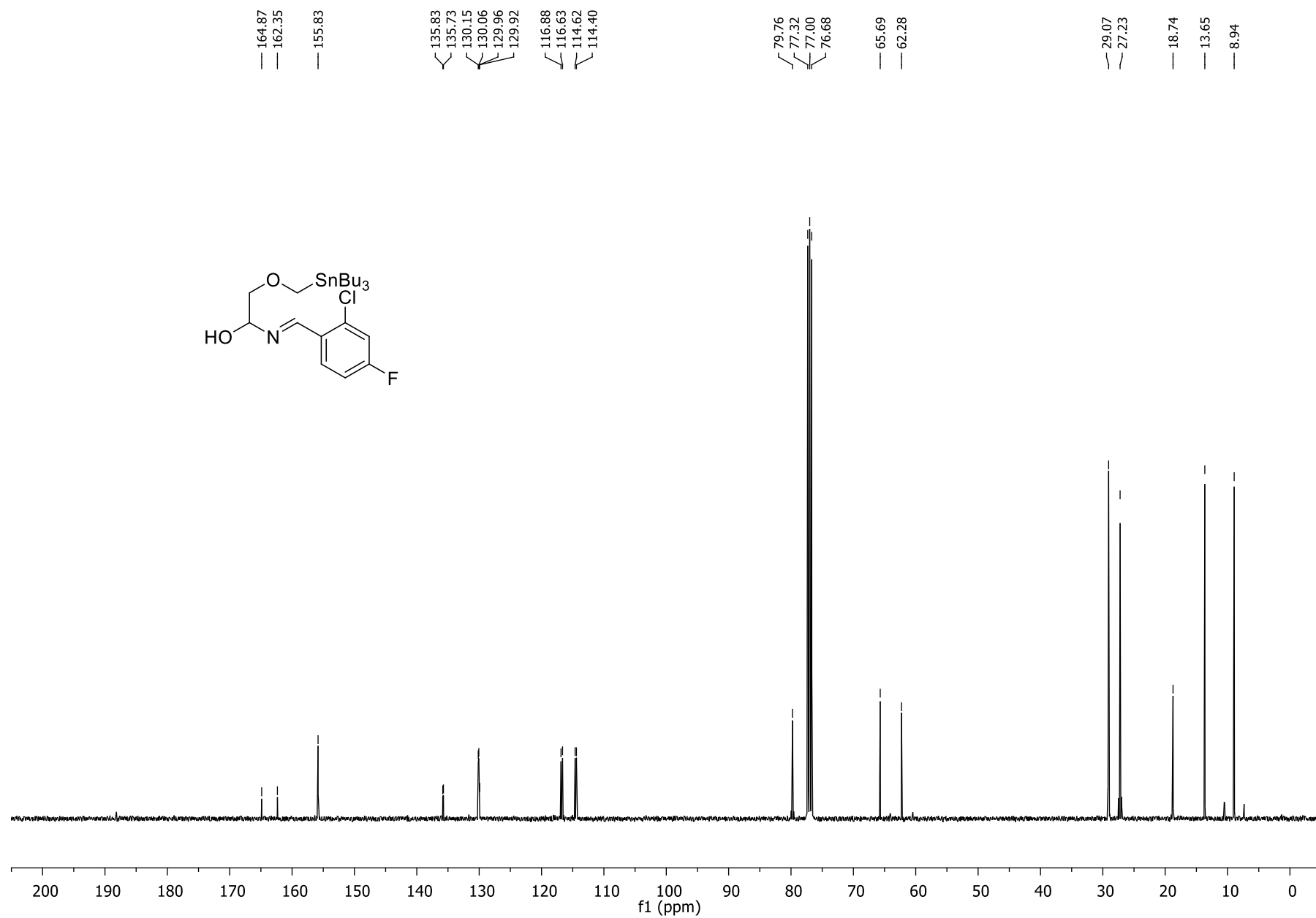
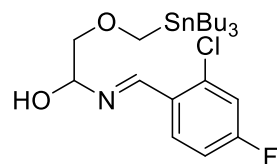
$$MW_1 = 379.15 \text{ g/mol}$$

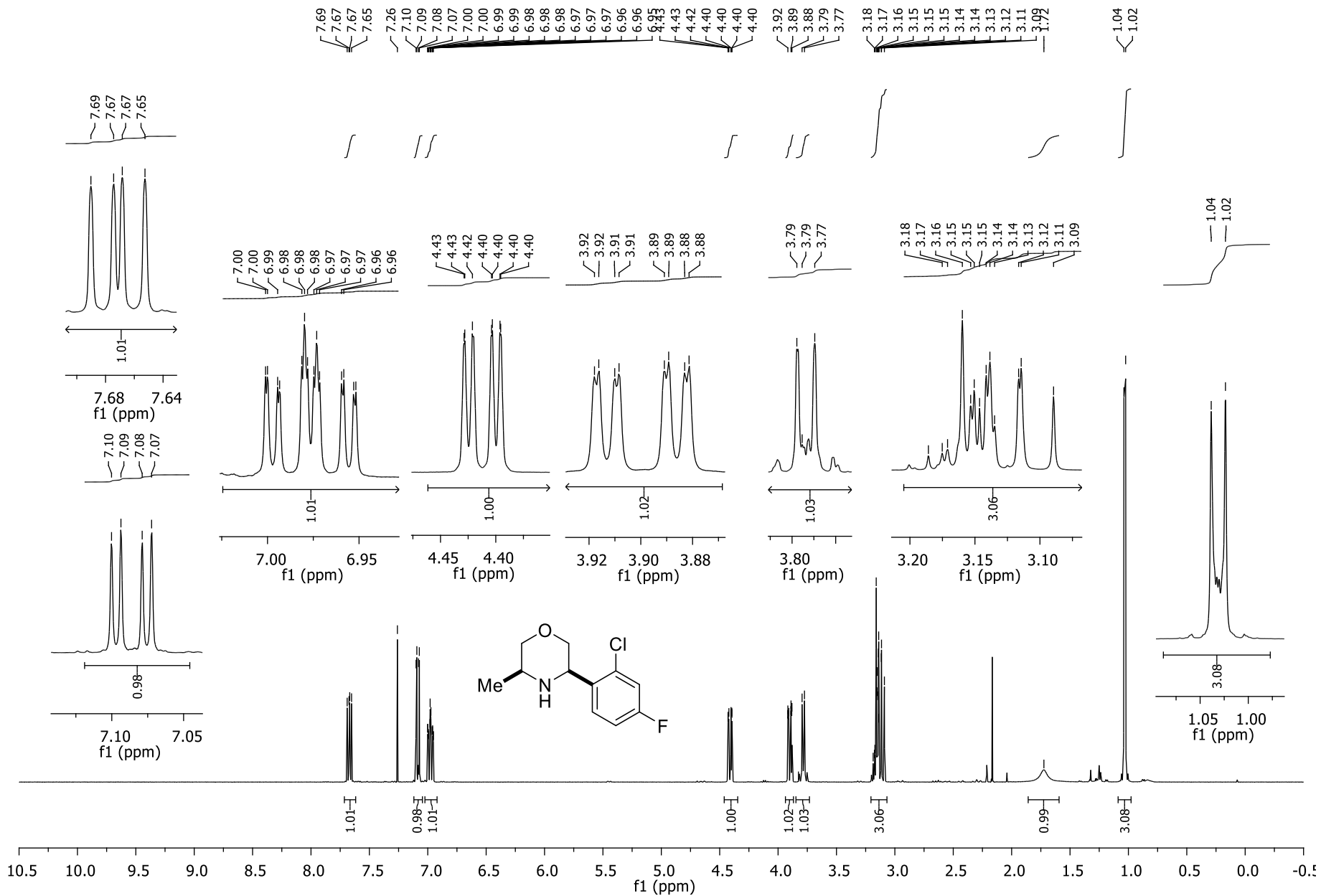
$$m_1 = 5.69 \text{ mg}$$

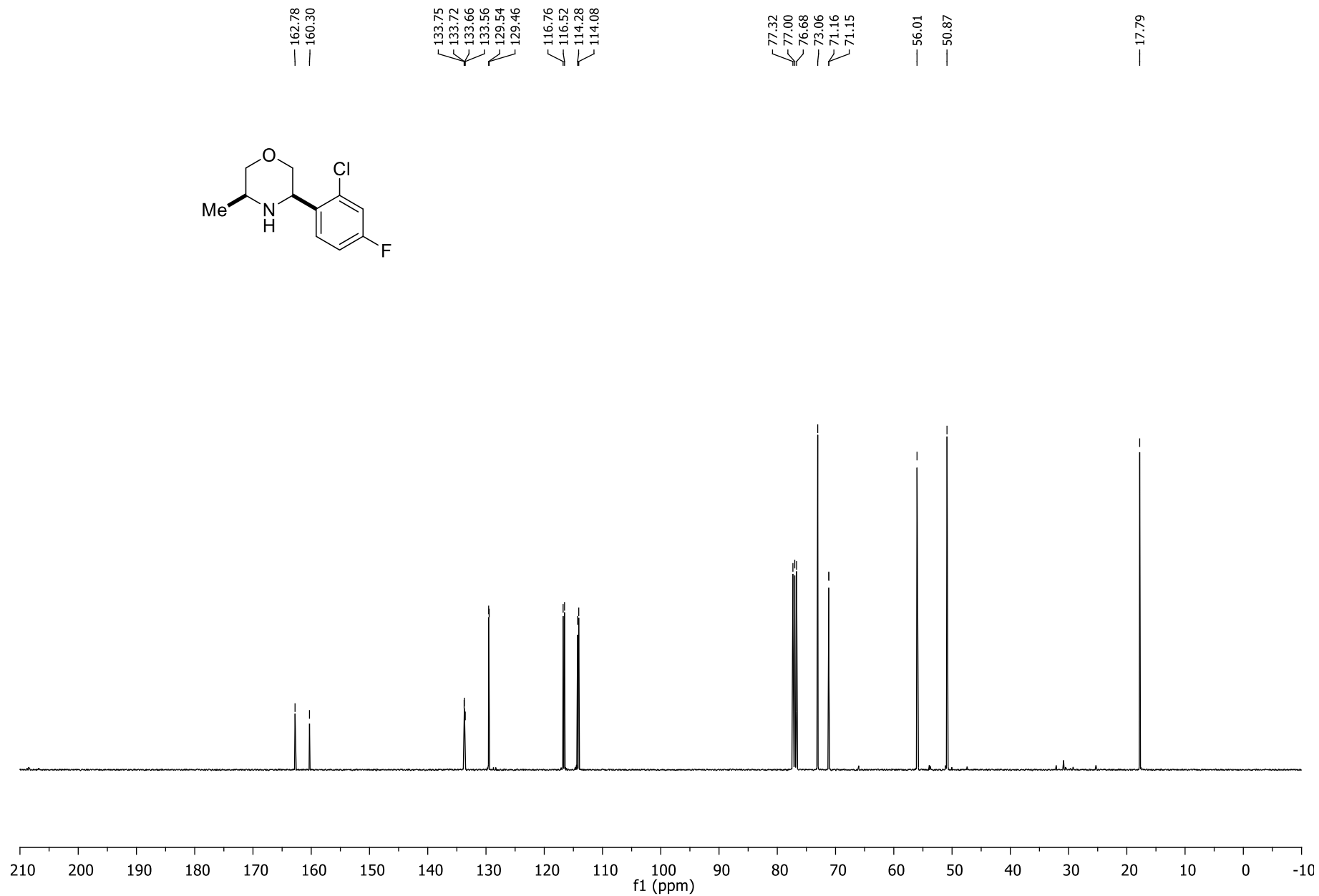
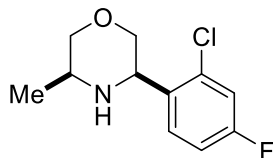
$$P [\%] = \frac{n_{IS} \cdot Int_2 \cdot MW_2 \cdot m_{IS}}{n_2 \cdot Int_{IS} \cdot MW_{IS} \cdot m_2} \cdot P_{IS} = 95 \%$$



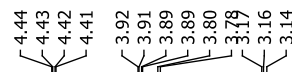
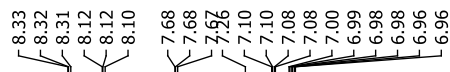








OS-QNMR-Step-2



Int = Average of normalized integrals values

MW = Molecular weight

P = Purity (as percent value)

m = mass

n = number of protons giving rise to a given NMR signal (The total number of protons is set to one because an average of all normalized integrals is carried out)

$$n_{IS} = 1$$

$$Int_{IS} = 1.01$$

$$MW_{IS} = 165.15 \text{ g/mol}$$

$$m_{IS} = 2.47 \text{ mg}$$

$$P_{IS} = 98\%$$

$$n_2 = 1$$

$$Int_2 = 1.005$$

$$MW_2 = 229.68 \text{ g/mol}$$

$$m_2 = 3.44 \text{ mg}$$

$$P [\%] = \frac{n_{IS} \cdot Int_2 \cdot MW_2 \cdot m_{IS}}{n_2 \cdot Int_{IS} \cdot MW_{IS} \cdot m_2} \cdot P_{IS} = 97 \%$$

