Organic Syntheses

Late-Stage Deoxyfluorination of Phenols with PhenoFluorMix

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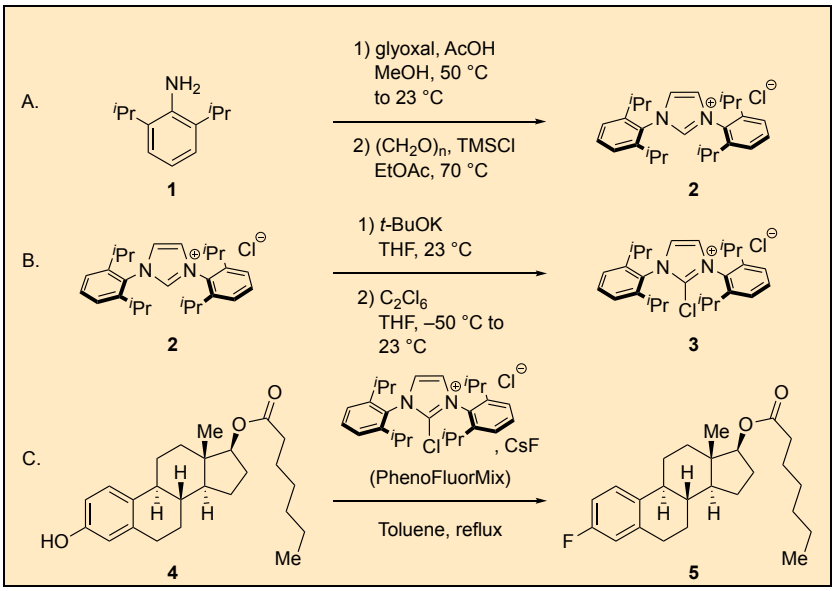
Checked by Shota Nagasawa and Richmond Sarpong



Procedure (Note 1)

A. *N,N′ -1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride* (**2**). In air, a 2000-mL one-necked, round-bottomed flask (24/40), equipped with a Teflon-coated egg-shaped magnetic stirbar (3/4″ × 2″), is charged with MeOH (250 mL) (Note 2), 2,6-diisopropylaniline (210 mL, 200 g, 1.0 mol, 2.0 equiv) (Note 2) and AcOH (1.0 mL, 1.1 g, 18 mmol, 0.035 equiv) (Note 2).

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In a 500-mL one-necked round-bottomed flask (24/40), glyoxal (60 mL, 73 g, 0.50 mol, 1.0 equiv) (Note 3) is dissolved in MeOH (250 mL). The resulting solution in the 500-mL flask is then added via a glass funnel to the 2000-mL flask over 2 min. The 2000-mL reaction flask is equipped with a reflux condensor, which is sealed with a rubber septum (Note 4) (Figure 1A) and placed into an oil bath (preheated at 50 °C). The reaction mixture is stirred (Note 5) at 50 °C (Note 6) for 15 min (Note 7), after which the oil bath is removed to allow the reaction mixture to cool to room temperature (Note 8) over 30 min. Subsequently, the reaction mixture is stirred (Note 5) at room temperature (Note 8) for an additional 10 h (Figure 1B), the resultant yellow solid is collected by filtration (Note 9) and rinsed with MeOH (3 × 200 mL) in a glass fritted funnel (Note 10) (Figure 1C). The resulting yellow solid is transferred to a 1000-mL one-necked round-bottomed flask (24/40) and volatiles are removed on a rotary evaporator (35 mmHg, 40 °C, 20 min) (Note 11) followed by further drying under vacuum (Note 12) at room temperature (Note 8) for 16 h to afford 167 g (89%) of *N,N′* -1,4-bis(2,6-diisopropylphenyl)-1,4-diazabutadiene as a yellow solid (Note 13).

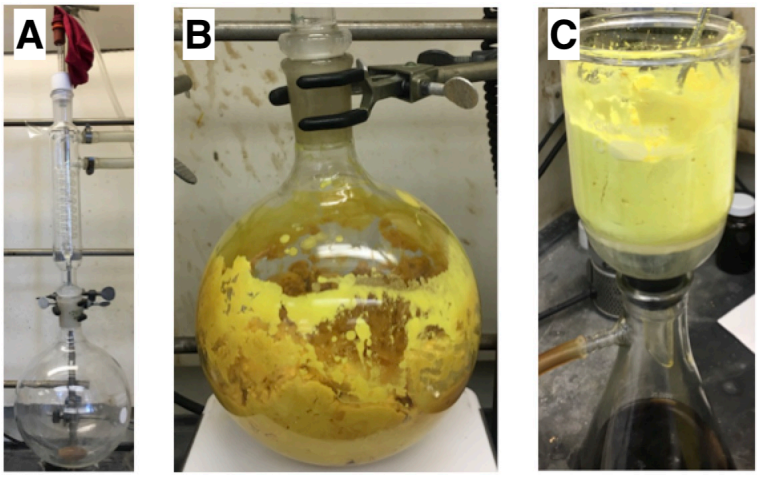


Figure 1. A) Reaction set-up for Step A, B) appearance of the reaction mixture after 10 h, and C) product from diazabutadiene synthesis

In air, two 2000-mL one-necked, round-bottomed flasks (24/40) (Note 14), equipped with a Teflon-coated egg-shaped magnetic stirbar (3/4" × 2"), are charged with a mixture of *N,N′* -1,4-bis(2,6-diisopropylphenyl)-1,4-diazabutadiene (2 × 43 g, 0.23 mol, 1.0 equiv) and paraformaldehyde

(2 × 3.4 g, 0.23 mol, 1.0 equiv) (Note 15) in EtOAc (2 × 1.0 L) (Note 15). Both reaction flasks are equipped with 50-mL pressure-equalizing addition funnels (Figure 2A), which are charged with a solution of TMSCl (2 × 15 mL, 2 × 13 g, 0.23 mol, 1.0 equiv) (Note 15) in EtOAc (2 × 15 mL) and sealed with a rubber septum (Note 4). The reaction flasks are placed in an oil bath, which is preheated at 70 °C (Note 6). After the reaction mixtures are stirred at 70 °C (Note 6) for 10 min, the TMSCl solutions are added dropwise over 45 min with the external temperature maintained between 65 °C and 75 °C (Note 6) (Figure 2B). The resulting mixtures are stirred (Note 5) at 70 °C (Note 6) for an additional 2 h (Figure 2C). The flasks are then removed from the oil bath and cooled in an ice-water bath (Note 16) for ca. 20 min to allow the internal temperature of the reaction mixture to reach 15 °C (Note 17).

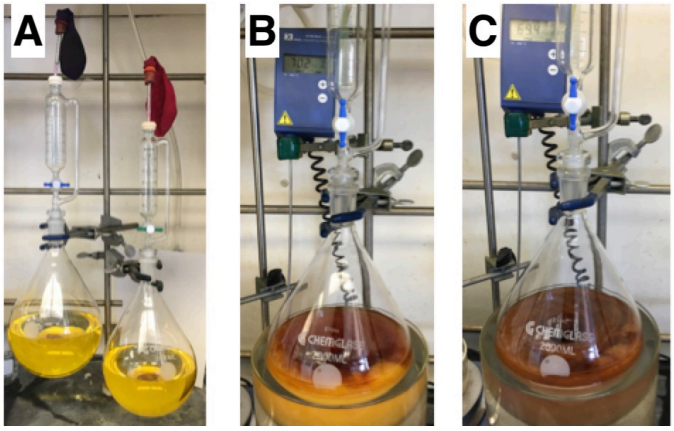


Figure 2. A) Reaction set-up, B) appearance after addition, and C) appearance after 2 h

The resulting solids in the two flasks are subsequently combined and collected by filtration (Note 9) (Figure 3A), rinsed with EtOAc (3 × 150 mL) in a glass fritted funnel and transferred into a 500-mL one-necked round-bottomed flask (24/40). After evaporation of the volatiles on a rotary evaporator (35 mmHg, 40 °C, 20 min) (Note 11), the solid is further dried by heating in an oil bath (preheated at 150 °C) at 150 °C (Note 6) under vacuum (Note 12) (Figure 3B) for 10 h to afford 73 g of compound **2** as a pinkish solid (75%) (Note 18) (Figure 3C).

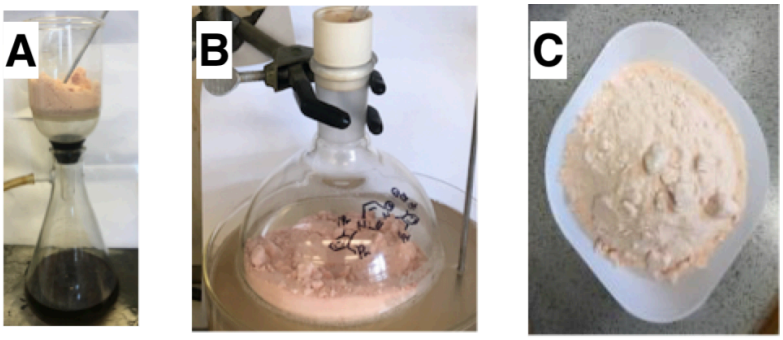


Figure 3. A) Filtration, B) drying of imidazolium salt, and C) appearance of imidazolium salt (2)

B. *N,N-1,3-Bis(2,6-diisopropylphenyl)-2-chloroimidazolium chloride (**3**)*. In air, a 1000-mL one-necked, round-bottomed flask (24/40), equipped with a Teflon-coated egg-shaped magnetic stirbar (3/4″ × 2″), is charged with *N,N′* -1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**2**) (52 g, 0.12 mol, 1.0 equiv) and *t*-BuOK (18 g, 0.15 mol, 1.25 equiv) (Note 19). The flask is evacuated (Note 12) at room temperature (Note 8) for 12 h, then backfilled with nitrogen (Note 20), subsequently sealed with a rubber septum and connected to a Schlenk line via a needle adapter (Figure 4A). The flask is evacuated (Note 12) for 3 min and then backfilled with nitrogen. The procedure is repeated three times, and the flask is filled with nitrogen and kept under a positive pressure of nitrogen via a gas inlet (Note 20) through the needle adapter. Anhydrous THF (240 mL) (Note 21) is then added via syringe (Note 22), and the resulting orange heterogeneous mixture (Note 23) is stirred (Note 5) under an atmosphere of nitrogen (Note 20) at room temperature (Note 8) for 10 h (Figure 4B and C). The reaction mixture is exposed to air and concentrated on a rotary evaporator (35 mmHg, 40 °C) (Note 11) to afford a yellow solid. Toluene (450 mL) (Note 24) is added to the flask, and the flask is then placed into an oil bath that is preheated to 55 °C (Note 6). After the orange heterogeneous mixture is stirred at 55 °C (Note 6) for 10 min (Figure 5A), the flask is removed from the oil bath, and the hot orange mixture in the flask is poured in 5 portions into a 350 mL funnel that is preloaded with a pad of Celite (Notes 9 and 25). Suction is

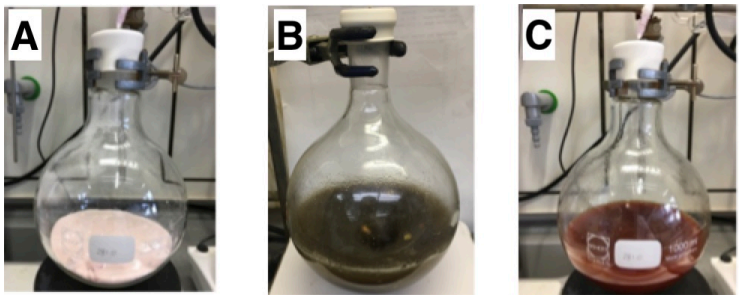


Figure 4. A) Step B reaction set-up, B) appearance after addition of THF, and C) appearance of the reaction mixture after 10 h

applied to dry the filter cake. The reaction flask is rinsed with toluene (100 mL), which is poured onto the Celite® pad, and suction is applied to dry the filter cake (Figure 5B). Elution with toluene (100 mL) is repeated twice. The filtrate is collected, transferred to a 1000-mL one-necked round-bottomed flask (24/40), and concentrated on a rotary evaporator (15 mmHg, 40 °C) (Note 11) to afford a beige solid (Note 26) (Figure 5C), which is immediately dissolved in THF (240 mL) (Note 27) to afford an orange solution, and the solution is transferred into a two-necked, 1000-mL round-bottomed flask.

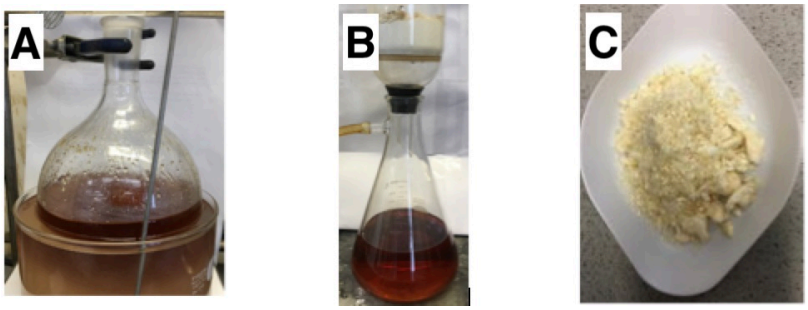


Figure 5. Appearance of the A) toluene solution while heating, B) filtration set-up, and C) carbene intermediate

While exposed to air, the 1000-mL flask is equipped with a glass thermometer and a Teflon-coated egg-shaped magnetic stirbar (3/4″ × 2″) is added. The orange solution is stirred (Note 5) and cooled in a dry ice-MeOH/H_2O bath to between −55 °C and −45 °C (bath temperature) (Note 28) for 10 min (Figure 6A). 1,1,1,2,2,2-Hexachloroethane (29 g,

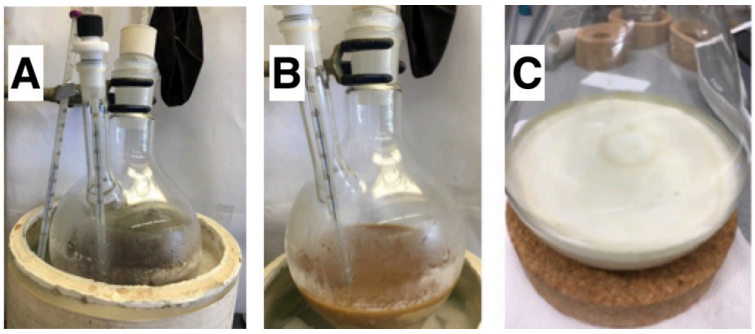


Figure 6. A) Reaction set-up, B) appearance after addition of Cl_3CCCl_3, and C) appearance after 20 h

0.12 mol, 1.0 equiv) (Note 29) is then added to the reaction flask in 5 roughly equal portions over 5 min with the internal temperature maintained between −45 °C and −40 °C. After addition, the reaction flask is sealed with a rubber septum (Note 4), and the reaction mixture is stirred (Note 5) between −55 °C and −45 °C (bath temperature) (Note 28) for an additional 30 min (Note 30) (Figure 6B). The dry ice-MeOH/H_2O bath is then removed. The reaction mixture is stirred (Note 5) and allowed to warm to room temperature (Note 8) over the course of 45 min and then stirred (Note 5) at room temperature (Note 8) for an additional 20 h (Figure 6C). The resulting heterogeneous mixture is filtered through a fritted funnel (Note 9), and the resulting filter cake is rinsed with THF (3 × 100 mL) (Note 31) and then with toluene (3 × 100 mL) (Note 31) (Figure 7A). The resultant colorless solid is ground into a fine powder in a porcelain mortar (Figure 7B). The

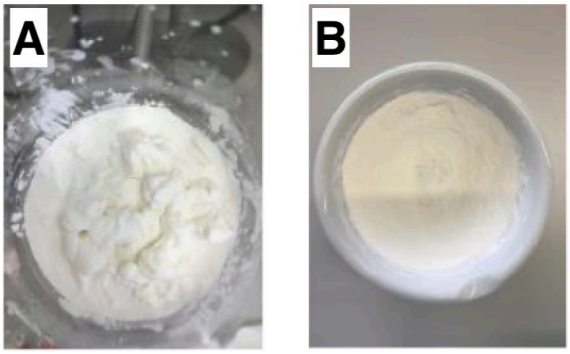


Figure 7. A) Appearance of chloroimodazolium chloride (3) during filtration, and B) appearance of 3 after grinding

resulting powder is transferred into a 500-mL one-necked, round-bottomed flask (24/40), heated to 180 °C (Note 32) under vacuum (Note 12) for 24 h using a heating mantle connected to a variac, (Figure 8A) to afford 45 g of the title compound (**3**) as a colorless powder (80%) (Note 33) (Figure 8B).

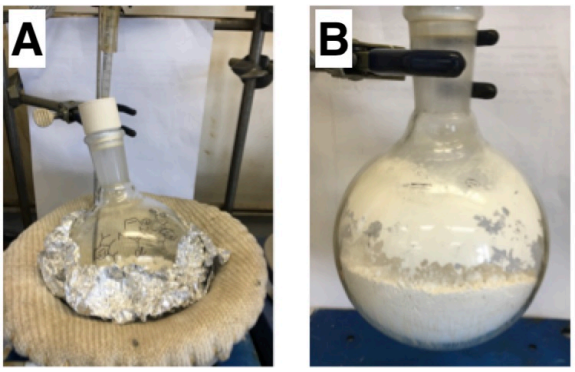


Figure 8. A) Drying of the product and B) appearance of chloroimodazolium chloride (3)

C. *3-Fluoro-estradiol-enanthate (**5**).* In air, a 500-mL round-bottomed Schlenk flask (24/40), with a side arm fitted with a T-bore glass stopcock, is equipped with a Teflon-coated egg-shaped magnetic stirbar (3/4″ × 2″). *N*,*N*-1,3-Bis(2,6-diisopropylphenyl)-2-chloroimidazolium chloride (**3**) (14 g, 31 mmol, 1.5 equiv) and CsF (25 g, 0.17 mol, 8.0 equiv) (Note 34) are added to the Schlenk flask. The flask is subsequently shaken manually for 30 sec to afford PhenoFluorMix as a colorless powder. The flask is then equipped with a glass stopper (24/40), connected to a Schlenk line via the side arm, evacuated (Note 12) and heated in an oil bath (preheated at 140 °C) at 140 °C (Note 6) for 1 h. The oil bath is then removed to allow the flask to cool to room temperature (Note 8) over the course of 45 min. The flask is backfilled with nitrogen and left under an atmosphere of nitrogen via a nitrogen inlet (Note 20) through the side arm. The glass stopper is removed, and estradiol-enanthate (8.00 g, 20.8 mmol, 1.00 equiv) (Note 35) is added in one portion within 1 min. The flask is subsequently equipped with a Dimroth condenser, which is connected to the Schlenk line via a glass adaptor (hose connection, vacuum/gas) (Note 36). The side arm is subsequently closed, and the entire reaction apparatus is evacuated (Note 12) for 3 min via the glass adaptor and then backfilled with nitrogen.

After the evacuation-backfilling procedure is repeated three times, the reaction apparatus remains under a positive pressure of nitrogen (Note 20) via a nitrogen inlet through the glass adaptor (Figure 9A). Anhydrous toluene (300 mL) (Note 21) is subsequently added through the side arm via syringe (Notes 22 and 37). The resulting colorless heterogeneous mixture is stirred at 600 rpm (Note 5) at room temperature (Note 8) for 30 min (Figure 9B), and the reaction flask is subsequently transferred into an oil bath,

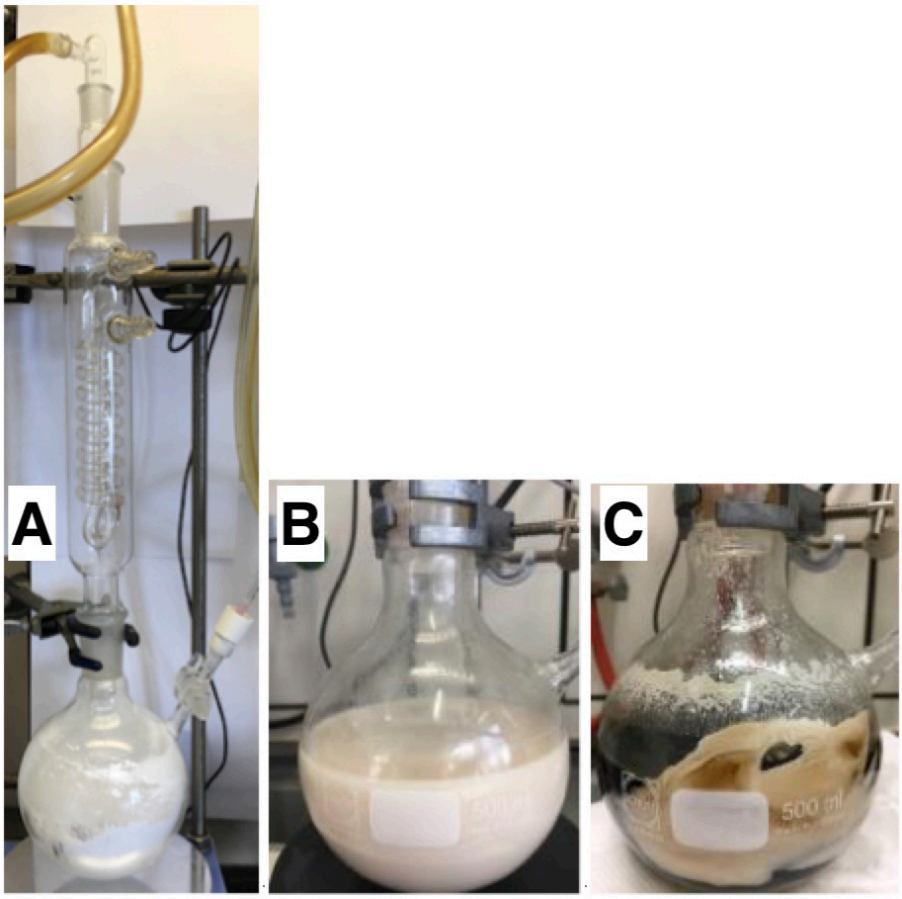


Figure 9. A) Reaction set-up for Step C, B) appearance of the reaction mixture before heating, and C) appearance of the reaction mixture after heating

which is preheated to 120 °C (Note 6). After the reaction mixture is heated with stirring (Note 5) at 120 °C (Note 6) for 24 h, the oil bath is removed to allow the reaction mixture to cool to room temperature (Note 8) over the course of 45 min (Figure 9C). Upon exposure to air, the Dimroth condenser is removed, and the resulting brown heterogeneous mixture in the flask is filtered using a glass-fritted funnel with 150-mL capacity (Note 9) to give a colorless filter cake and a brown filtrate. The reaction flask is rinsed with dichloromethane (20 mL) (Note 38), and the resulting mixture is poured onto the filter cake, and suction is applied to dry the filter cake. The dichloromethane rinse procedure is repeated three times. The collected filtrate is transferred into a 1000-mL one-necked, round-bottomed flask (24/40) and concentrated on a rotary evaporator (35 mmHg, 42 °C) (Note 11) to afford a brown solid. Hexanes (100 mL) (Note 39) is added to the flask, which is subsequently shaken manually for 2 min. The resulting heterogeneous mixture is filtered through a glass-fritted funnel with 150-mL capacity (Note 9) to give a brown filter cake and a light brown filtrate. The flask is rinsed with hexanes (20 mL), and subsequently the resulting mixture is poured onto the filter cake, and suction is applied to dry the filter cake (Figure 10A). The hexanes rinse procedure is repeated three times. The filtrate is then transferred into a 250-mL one-necked, round-bottomed flask

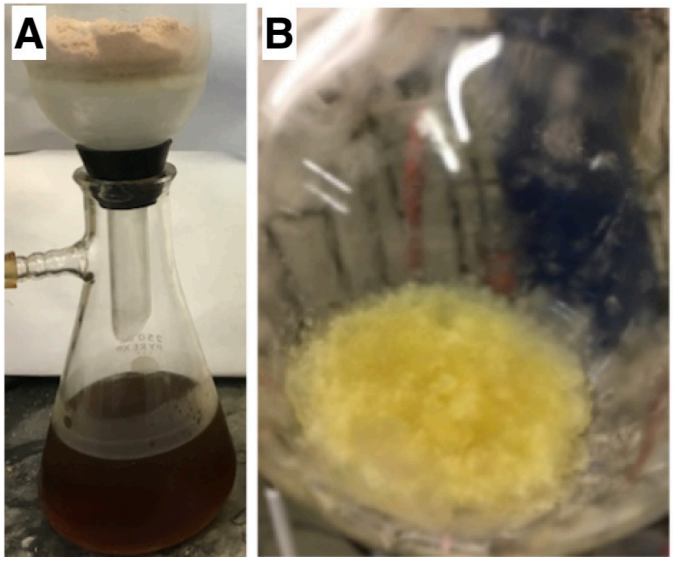


Figure 10. A) Filtration set-up and B) fluorinated compound 5

(24/40) and concentrated on a rotary evaporator (35 mmHg, 40 °C) (Note 11) to afford a brown oil, which is purified by flash column chromatography on silica gel (Note 40). The fractions containing the product are collected, concentrated on a rotary evaporator (35 mmHg, 40 °C) (Note 11) and dried under vacuum (Note 12) at room temperature (Note 8) for 16 h to afford 7.39 g (92%) of the title compound as a yellow solid (Note 41) (Figure 10B).

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 *2,6-diisopropyl analine, glyoxal, acetic acid, methanol, paraformaldehyde, trimethylsilyl chloride, potassium tert-butoxide, tetrahydrofuran, hexachloroethane, cesium fluoride, toluene* as well as the proper procedures for setting up *experimental operations*.
2. MeOH (certified ACS) was obtained from Fisher Scientific. 2,6-Diisopropylaniline (technical grade, 90%) was obtained from Sigma Aldrich. Acetic acid (90–100%) was obtained from J. T. Baker VWR. These reagents were used as received.
3. Glyoxal solution (40 wt. % in water) was obtained from Sigma Aldrich and used as received.

4. The rubber septum was equipped with a balloon via a needle adaptor to prevent over-pressure. The reaction was performed under air.
5. Submitter purchased a stir plate from Heidolph Instruments GmbH & Co. KG. It has an input power of 230–240 V (50–60 Hz, 825 W), and the stirring range is from 100 rpm to 1400 rpm. Checker used IKA RET basic hot plate stirrer (115V, 620W, 50-60 Hz) and Corning PC-420 stir plate (120V, 60 Hz, 5.9 A) Unless specified differently, 500 rpm was used for stirring.
6. The Submitter purchased the silicone oil for the oil bath from abcr GmbH & Co. KG. The boiling point is over 205 °C. Checker used silicone oil (PSF-100cSt Silicone fluid) purchased from Clearco Products Co., Inc. Unless specified differently, the oil in the oil bath should cover the reaction mixture in the reaction flask while heating. Unless otherwise reported, the temperatures throughout this manuscript refer to temperatures of oil in oil baths which were detected by the stirring plates' temperature detectors.
7. If the precipitate prevented stirring within 15 min of heating, it needed to be crushed manually to facilitate the stirring.
8. The room temperature throughout this manuscript refers to temperature between 23 °C and 25 °C.
9. Glass fritted funnels (supplied by Synthware; 29/32) with code C were used for most cases, while funnels with code M were used in specified cases. Unless otherwise clarified, the capacity for the funnel was no less than 350 mL.
10. To rinse the impurities out of the flask, manual stirring with a stainless spatula or stirring rod was applied to thoroughly mix the rinse solvent with the solid.
11. The submitter used a BUCHI Vacuum Controller V-850 in combination with evaporator R-210 for rotary evaporation. Checker used a Heidolph "The Collegiate" rotary evaporator (Heidolph Instruments GmbH & Co.) without vacuum controller. Water was used in the heating bath. Unless otherwise clarified, the pressure and temperature were read from the controller.
12. The submitter and checker used a vacuum pump supplied by Vacuubrand GmbH & Co. KG. The lowest pressure achieved was 1×10^{-3} mbar. In this context, vacuum refers to pressure lower than 0.1 mbar.
13. The yellow solid has the following characteristics: mp = 106 °C; ^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ: 1.23 (d, J = 6.8 Hz, 24H), 2.96 (hept,

J = 6.8 Hz, 4H), 7.15–7.22 (m, 6H), 8.12 (s, 2H). ^{13}C NMR (101 MHz, 298K, $CDCl_3$) δ: 23.4, 28.0, 123.2, 125.1, 136.7, 148.0, 163.1. ESI-HRMS (m/z) calcd $[M+H]^+$ for $C_{26}H_{37}N_2$: 377.2957, found: 377.2953. IR (ATR): 2958, 2927, 2887, 1626, 1457, 1433, 1383, 1362, 1241, 1162, 1096, 1061, 1043, 923, 818, 805, 794. Quantitative NMR (400 MHz, 2:1 DMSO-d_6-$CDCl_3$) using 4-nitrophenylacetic acid (≥ 99% purity, Sigma Aldrich) as an internal standard was used to assess purity at 87 wt. %. The checkers also ran a half-scale reaction and obtained 80 g (85%) of the desired compound at 86% purity.

14. The submitters used a single 4000 mL flask for the reaction.
15. Paraformaldehyde (97%) was purchased from Alfa Aesar and used as received. The molar calculation in the context was based on monomer $(CH_2O)_1$. EtOAc (certified ACS) was purchased from Fisher Scientific and used as received. Chlorotrimethylsilane (≥ 98%, GC) was purchased from Sigma Aldrich and used as received.
16. The cooling mixture (ice/water) in the ice-water bath covered the flask to the level of the reaction mixture.
17. The addition funnel was removed after 20 min. A thermometer was used to detect the internal temperature of the reaction mixture.
18. The pinkish product has the following characteristics: mp > 260 °C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 1.23 (d, J = 6.8 Hz, 12H), 1.26 (d, J = 6.8 Hz, 12 H), 2.41 (hept, J = 6.8 Hz, 4H), 7.37 (d, J = 8.0 Hz, 4H), 7.60 (t, J = 8.0 Hz, 2H), 7.81 (s, 2H), 11.13 (s, 1H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ: 23.7, 24.8, 29.5, 125.0, 126.0, 130.5, 132.3, 141.0, 145.5. ESI-HRMS: $[M-Cl]^+$ calcd for $C_{27}H_{37}N_2$: 389.2957. Found: 389.2945. IR (ATR): 2965, 2897, 1533, 1466, 1252, 1060, 812, 760, 746 cm^{-1}. Quantitative NMR (500 MHz, DMSO-d_6) using 4-nitrophenylacetic acid (≥ 99% purity, Sigma Aldrich) as an internal standards assessed purity of the product as 97 wt. %. A second reaction that was run on full scale provided 69 g (71%) of the identical product with 98% purity.
19. *t*-BuOK (98+%) was purchased from Acros Organics and used as received.
20. Unless indicated otherwise, a positive pressure of nitrogen with a minimum of 0.1 bar (read from the control valve regulator) was used. Other inert gases could be used as well. The submitters used argon instead of nitrogen.
21. Anhydrous solvents were obtained from a Phoenix Solvent Drying System and used without further purification. THF was obtained with

less than 5 ppm of water content, and toluene was obtained with less than 10 ppm. All anhydrous solvents were argon saturated.

22. Syringes with 60-mL capacity were equipped with stainless steel needles, which were dried in an oven at 120 °C for at least 16 h before use.
23. After the addition of THF, the checkers observed a (deep) green heterogeneous solution. The color of the solution gradually turned into a brown-orange.
24. Toluene (certified ACS) was purchased from Fisher Scientific and used as received.
25. The Celite (filter aid, treated with sodium) was obtained from Fisher Scientific and used as received (Submitter obtained it from Sigma Aldrich). A Celite pad with 5 cm minimum height should be used for this filtration. A 350-mL glass fritted funnel was used. A layer of orange precipitate appeared on the top of the Celite pad. The layer was manually cracked to facilitate filtration and shorten the filtration time to less than 15 min.
26. The beige carbene intermediate has the following characteristics: ^{1}H NMR (400 MHz, 298K, CD_2Cl_2) δ: 1.18 (d, J = 6.6 Hz, 12H), 1.21 (d, J = 6.6 Hz, 12H), 2.69 (hept, J = 6.6 Hz, 4H), 7.19 (s, 2H), 7.30 (d, J = 7.6 Hz, 4H), 7.45 (t, J = 7.6 Hz, 2H).
27. THF (HPLC grade) for this purpose was purchased from Fisher Scientific and used as received.
28. A dewar was charged with 1:1 (v/v) mixture of MeOH/H_2O, and dry ice was added to lower the temperature to between −55 °C and −45 °C. A thermometer (with a range from −100 °C to 30 °C) was placed in the dry ice–solvent mixture to measure the temperature. Dry ice was added timely to maintain the temperature between −55 °C and −45 °C. The submitter used acetone instead of MeOH/H_2O mixture.
29. Hexachloroethane (99%) was obtained from Sigma Aldrich and used as received.
30. As needed, dry ice was added to the cooling bath within the next 30 min to maintain the temperature between −55 °C and −45 °C.
31. Due to the viscosity of the filter cake, it took 10–20 min to dry the filter cake via suction. Manual thorough mixing of the filter cake with the rinse solvent is crucial to wash impurities out. To make sure the filter cake was dry enough for grinding, the filter cake was firstly left under suction for roughly 30 min after the last toluene rinse; the roughly dried filter cake was then transferred into a 500-mL one-necked, round-

bottomed flask and dried further on a rotary evaporator (35 mmHg, 40 °C) (Note 11).

32. The heater temperature was controlled by adjusting the variac and was monitored by digital thermometer. The submitter used a sand bath as a heat source.
33. Compound **3** has the following characteristics: mp > 260 °C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 1.21 (d, *J* = 6.6 Hz, 12H), 1.30 (d, *J* = 6.6 Hz, 12H), 2.34 (hept, *J* = 6.6 Hz, 4H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.67 (t, *J* = 7.8 Hz, 2H), 8.85 (s, 2H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ: 23.6, 24.4, 29.8, 125.6, 128.4, 128.9, 133.2, 133.9, 145.5. ESI-HRMS: $[M\text{-}Cl]^+$ calcd for $C_{27}H_{36}ClN_2$: 423.2567. Found: 423.2556. IR (ATR): 2963, 2928, 2870, 1547, 1486, 808, 761, 747 cm^{-1}. Quantitative NMR (500 MHz, DMSO-d_6) using 4-nitrophenylacetic acid (≥ 99% purity, Sigma Aldrich) as an internal standard assessed purity of the product as 97 wt. %. A second reaction performed on full scale provided 45 g (80%) of the identical product with 97% purity.
34. CsF (99%) was obtained from Sigma Aldrich and used as received. The reagent must be used in excess, possibly due to its low solubility in toluene. For PhenoFluorMix-mediated deoxyfluorination, 8.0 to 10 equivalents of CsF are required to achieve good and reproducible yields.
35. Estradiol-enanthate (95%) was purchased from Haihang Industry Co., Ltd. and dried at room temperature (Note 7) under vacuum (Note 10) in a one-necked, 100-mL round-bottomed flask (24/40) for 1 h before use.
36. The Dimroth condenser (24/40) was dried in an oven at 120 °C for at least 16 h before use. On the top of the condenser, an adaptor (24/40) with hose connection was used to connect the condenser to the Schlenk line. The side arm stopcock of the Schlenk flask was closed before evacuation/backfilling.
37. The stir plate was turned on to 600 rpm. before solvent addition to ensure stirring. In case the stirring bar doesn't stir before/after solvent addition, it is necessary to shake the reaction apparatus manually to enable stirring. Syringes (with 60-mL capacity) were equipped with stainless steel needles which were dried in an oven at 120 °C for at least 16 h before use. The side arm stopcock was closed after solvent addition.
38. The checkers used dichloromethane (certified ACS), which was purchased from Fisher Scientific and used as received.

39. The checkers used hexanes (certified ACS) instead of *iso*-hexane, which was utilized by the submitters. Hexanes was purchased from Fisher Scientific and used as received.
40. Flash column chromatography: A column (supplied by Synthware; Column O.D.: 60 mm, column I.D.: 53 mm, column length: 457 mm, reservoir: No) was charged with 180 g of silica (Geduran Si 60 with pore size 40–63 μm; purchased from Merck KGaA) and *iso*-hexane. The brown oil was dissolved in 50 mL of *iso*-hexane, and 15 g of silica was added to the resulting solution. The resulting heterogeneous mixture was concentrated on a rotary evaporator (35 mmHg, 40 °C) (Note 10) to dryness and the residue was transferred to the column. Sand with 5 cm minimum height (50–70 mesh particle size; purchased from Fisher Scientific) was added to the top of the column (sand was used to assist packing). The product was eluted with 1 L of hexanes : DCM = 9 : 1, followed by 2.5 L of hexanes : DCM = 7 : 3 (v/v). TLC analysis of the product was done on silica TLC plates coated with fluorescent indicator F_{254} (purchased from Merck) with hexanes : DCM = 3 : 1 (v/v) as eluent and visualized with 254 nm UV and $KMnO_4$ stain. The product has R_f = 0.2 (Figure 11). Tubes (25 mm × 180 mm) 26–65 were collected and

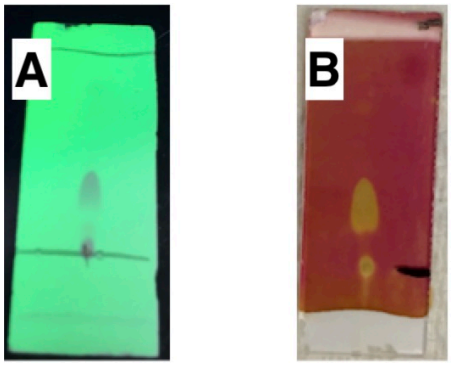


Figure 11. TLC for crude reaction mixture of deoxyfluorination step (hexanes : DCM = 3 : 1 (v/v) as eluent), A) UV visualization, and B) $KMnO_4$ visualization

concentrated on a rotary evaporator (35 mmHg, 40 °C) (Note 10) to afford the fluorinated compound **5** as a sticky yellow oil which solidified upon drying under vacuum.

41. Compound **5** has the following characteristics: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.84 (s, 3H), 0.89 (t, *J* = 6.6 Hz, 3H), 1.26–1.49 (m, 12H), 1.51–1.58 (m, 1H), 1.61–1.65 (m, 2H), 1.72–1.78 (m, 1H), 1.86–1.91 (m, 2H), 2.19–2.29 (m, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.84–2.87 (m, 2H), 4.71 (t, *J* = 8.4 Hz, 1H), 6.77 (dd, *J* = 9.6, 2.9 Hz, 1H), 6.82 (td, *J* = 8.7, 2.9 Hz, 1H), 7.22 (dd, *J* = 8.7, 5.7 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ : 12.1, 14.0, 22.5, 23.3, 25.1, 26.2, 27.0, 27.6, 28.8, 29.6, 31.5, 34.6, 36.9, 38.3, 42.9, 43.8, 49.8, 82.3, 112.3 (d, *J* = 20.5 Hz), 115.0 (d, *J* = 20.2 Hz), 126.7 (d, *J* = 8.0 Hz), 135.8 (d, *J* = 2.7 Hz), 138.8 (d, *J* = 7.1 Hz), 160.9 (d, *J* = 243.7 Hz), 173.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ : –117.7 (q, *J* = 8.0 Hz). IR (ATR): 2927, 2857, 1731, 1611, 1589, 1495, 1467, 1234, 1170, 1100, 1008, 816, 783 cm^{-1}. MS (EI) *m*/*z* = 386 (M^+, 100%), HRMS: [M^+] calcd for $C_{25}H_{35}FO_2$: 386.2621. Found: 386.2623. m. p. 41 °C. Elemental Analysis: Calcd for $C_{25}H_{35}FO_2$: C, 77.68; H, 9.13. Found: C, 77.32; H, 9.16 (1st run), C, 77.61; H, 8.99 (2nd run). A second reaction run on the same scale provided 7.27 g (90%) of compound **5**.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; 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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment

and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Deoxyfluorination accesses organofluorides directly from hydroxyl-containing substrates. Several SF_4 derivatives have been available for deoxyfluorination of alcohols, for example DAST[2] and Deoxy-Fluor[3]. Typically, chemist associate drawbacks like low functional group compatibility and hazards of reagent exotherms with these conventional reagents. Some new reagents like Pyfluor[4] are safer to handle and very practical; the reactivity with more hindered alcohols, such as secondary alcohols, is typically lower than with PhenoFluor[5b]. PhenoFluor was the first reagent that could also be used for practical deoxyfluorination of phenols[5a]. The advantages of deoxyfluorination with PhenoFluor are a broader substrate scope and larger functional group tolerance than any other deoxyfluorination reagent. The disadvantages of PhenoFluor are its cost and weight, together with the associated waste that comes with it, as well as its instability toward moisture upon long-term storage. We have developed two related reagents, PhenoFluorMix[6] for the deoxyfluorination of phenols and Alkylfluor[7] for the deoxyfluorination of alcohols, that are both stable toward long-term storage and do not hydrolyze. Sulfuryl fluoride[8] has also been shown for deoxyfluorination of phenols; the reagent is much less expensive than PhenoFluor but has not yet been applied to molecules of the complexity that are accessible with PhenoFluor-based reagents. More broadly speaking, aryl fluorides can also be accessed via a variety of other methods[9], for example transition-metal catalyzed[10] nucleophilic substitution that, depending on the application, can be advantageous when compared to PhenoFluor. The obvious advantage of nucleophilic aromatic substitution, transition-metal-catalyzed or not, is the lower cost of the fluoride source. When the arene is sufficiently electron-poor, simple Halex[11] (halogen

exchange) reaction with inexpensive fluoride salts are the method of choice due to simplicity and low cost.

In our opinion, PhenoFluor-based reagents PhenoFluorMix and Alkylfluor are useful, practical reagents that can be used for reliable deoxyfluorination of substrates that are too complex for other deoxyfluorination reagents. PhenoFluor-based reagents are also easier and safer to handle than most SF_4-based reagents, and can access organofluorides when other reagents fail. In particular, PhenoFluor-based reagents seem to be the method of choice for deoxyfluorination of highly functionalized complex molecules on relatively small scale (up to grams). For large-scale applications, or deoxyfluorination that can be accomplished with other reagents, the cost of PhenoFluor is likely going to render it a suboptimal choice. The next breakthrough in the field of deoxyfluorination would combine aspects of the various fluorination methods that are available now: catalysis like in the Pd-catalyzed fluorination of aryl bromides[10e]; low cost of a reagent, like Pyfluor, if a fluorine source other than fluoride must be used, and functional group tolerance and substrate scope as for PhenoFluor-mediated reactions.

References

1. Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470, Muelheim an der Ruhr, Germany, E-mail: ritter@mpi-muelheim.mpg.de. Generous support by the Max-Planck-Society is gratefully acknowledged. We specially thank the members of our NMR, MS departments and Mikroanalytical Laboratory Kolbe for their excellent support. We would also like to thank Dr. Fabien Serpier for generously checking this procedure.
2. Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574−578.
3. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999,** *64*, 7048−7054.
4. Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9571−9574.
5. (a) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482−11484. (b) Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 2470−2473.
6. Fujimoto, T.; Ritter, T. *Org. Lett.* **2015**, *17*, 544−547.

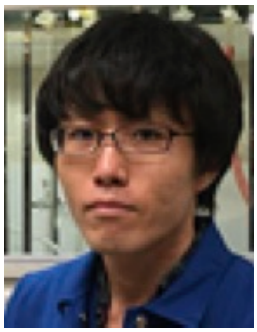
7. Goldberg, N. W.; Shen, X.; Li, J.; Ritter, T. *Org. Lett*. **2016**, *18*, 6102−6104.
8. Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 1452−1455.
9. For selected fluorination of diaryliodonium salts, see: (a) Van Der Puy, M. *J. Fluorine Chem.* **1982**, *21*, 385−392. (b) Wang, B.; Cerny, R. L.; Uppaluri, S.; Kempinger, J. J.; DiMagno, S. G. *J. Fluorine Chem*. **2010**, *131*, 1113−1121.
10. For selected transition-metal-mediated nucleophilic C−F bond formation, see: (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661−1664. (b) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795−10798. (c) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342−9345. (d) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292−16295. (e) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 3792–3795.
11. Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034–6037.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

2,6-Diisopropylaniline: 2,6-Bis(1-methylethyl)-benzenamine; (24544-04-5)
Glyoxal: 1,2-ethanedione; (107-22-2)
Paraformaldehyde: Polyoxymethylene; (30525-89-4)
Chlortrimethylsilane: Trimethylsilyl chloride; (75-77-4)
Potassium *tert*-butoxide: Potassium 2-methylpropan-2-olate; (865-47-4)
Hexacholoroethane: 1,1,1,2,2,2-Hexachloroethane; (67-72-1)
Estradiol-enanthate: estra-1,3,5(10)-triene-3,17-diol (17β)-17-heptanoate; (4956-37-0)

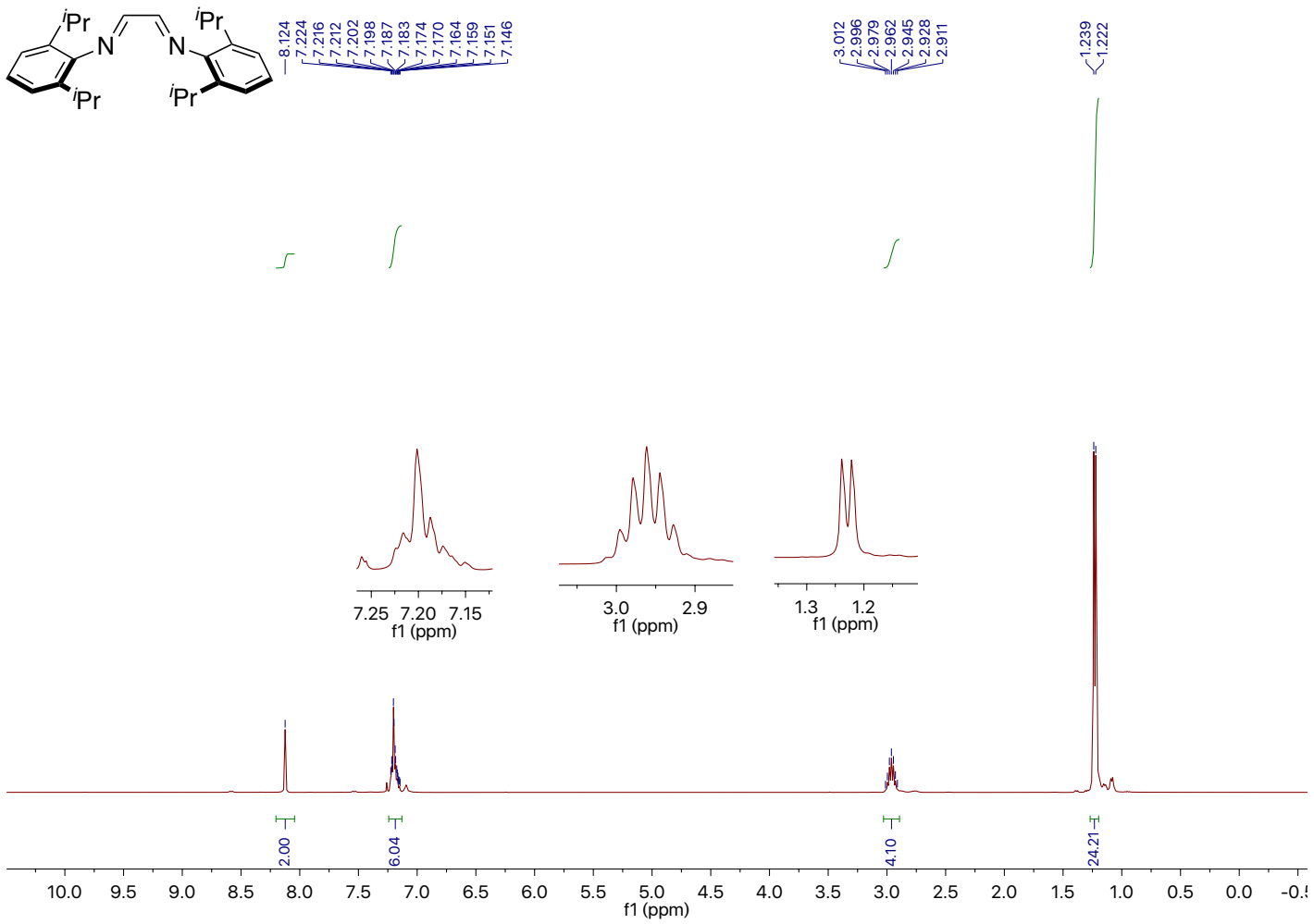
Junting Chen obtained her B.S. in chemistry in 2016 from Nankai University under the supervision of Professor Pingping Tang. She did her undergraduate thesis research on late-stage deoxyfluorination in the Ritter group at Harvard University. She is currently pursuing her Ph.D. degree in the Ritter group at the Max-Planck-Institut fuer Kohlenforschung, Muelheim an der Ruhr, Germany.

Tobias Ritter received his undergraduate education in Braunschweig, Bordeaux, Lausanne, and Stanford. He has performed undergraduate research with Prof. Barry M. Trost, obtained his Ph.D. with Prof. Erick M. Carreira at ETH Zurich in 2004, and was a postdoc with Prof. Robert H. Grubbs at Caltech. In 2006, Tobias was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard, promoted to Associate Professor in 2010, and to Professor of Chemistry and Chemical Biology in 2012. Since 2015 he is director at the Max-Planck-Institut fuer Kohlenforschung. In 2011, Tobias founded SciFluor LifeScience, a pharmaceutical development company.

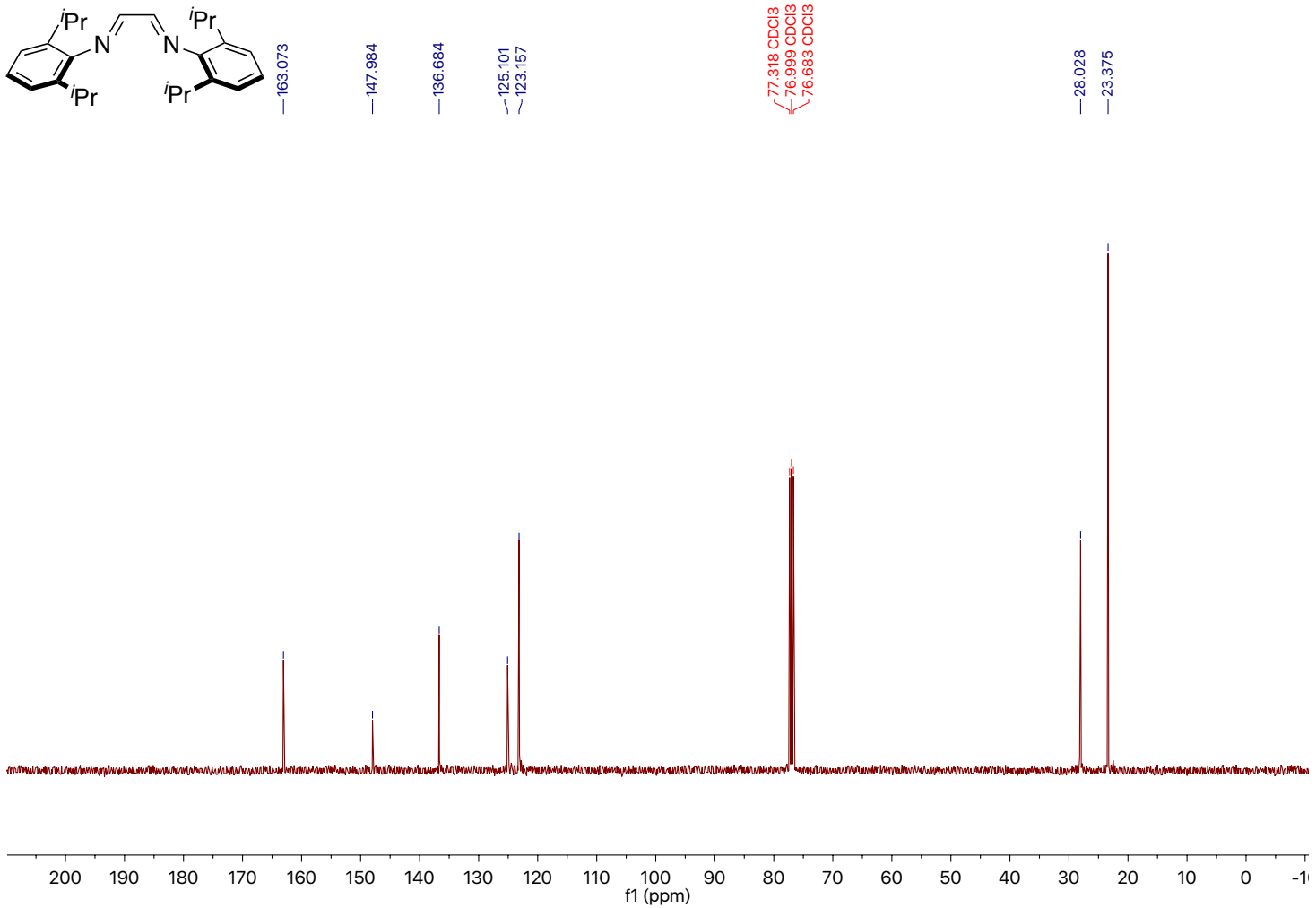


Shota Nagasawa obtained his Ph.D. in 2017 under the supervision of Prof. Yoshiharu Iwabuchi at Tohoku University, Japan. His Ph.D. work focused on oxidative molecular transformations. He is currently a postdoctoral scholar with Prof. Richmond Sarpong at University of California, Berkeley, working on total synthesis of natural terpenoid.

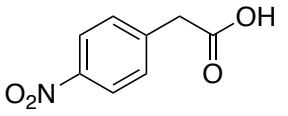
^{1}H-NMR for *N,N'*-1,4-bis(2,6-diisopropylphenyl)-1,4-diazabutadiene (400 MHz, $CDCl_3$)



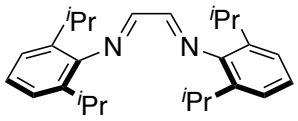
^{13}C-NMR for *N,N'*-1,4-bis(2,6-diisopropylphenyl)-1,4-diazabutadiene (101 MHz, $CDCl_3$)



qNMR for *N,N'*-1,4-bis(2,6-diisopropylphenyl)-1,4-diazabutadiene (400 MHz, d_6-DMSO :$CDCl_3$ = 2:1)



16.4 mg

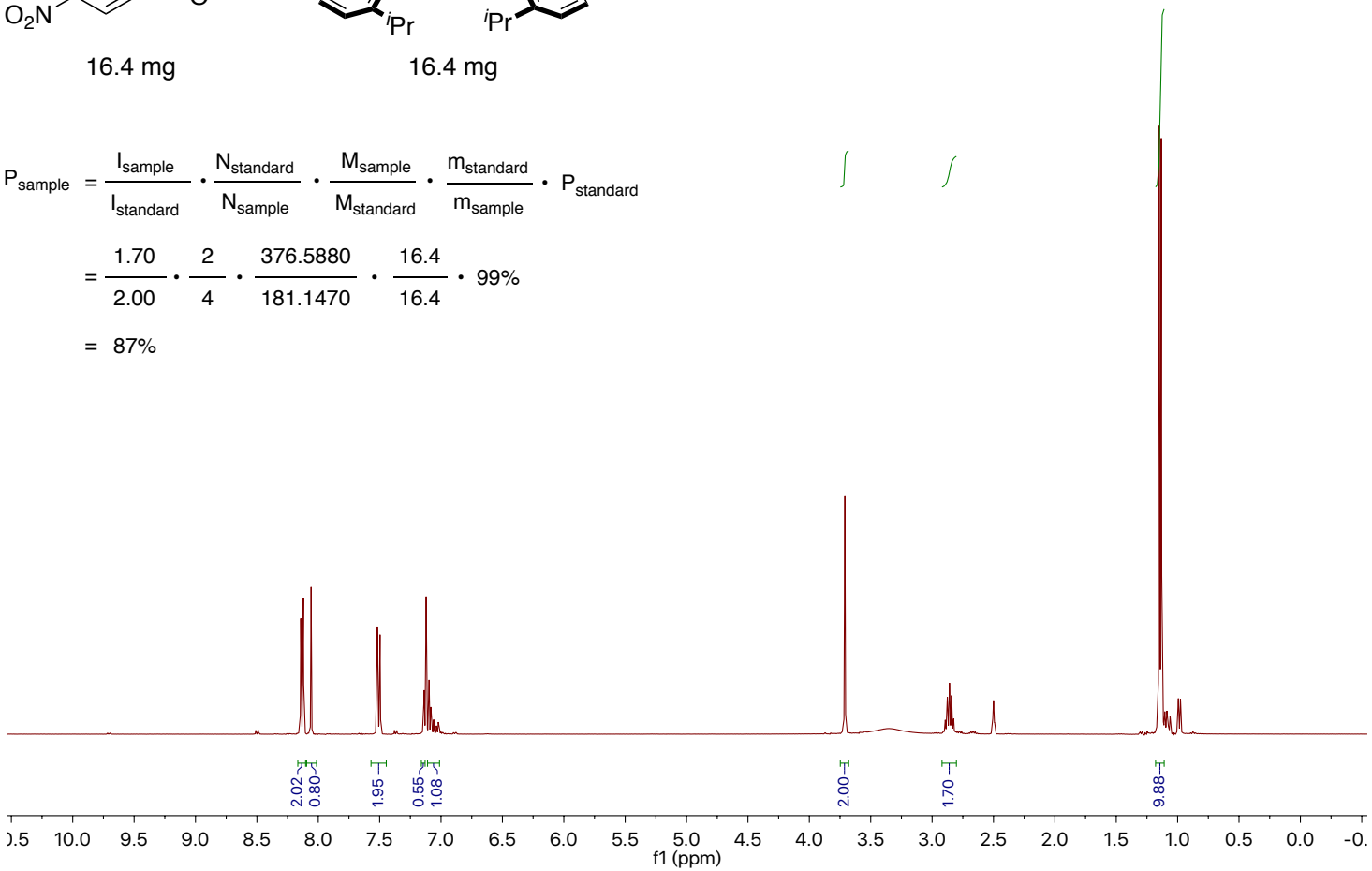


16.4 mg

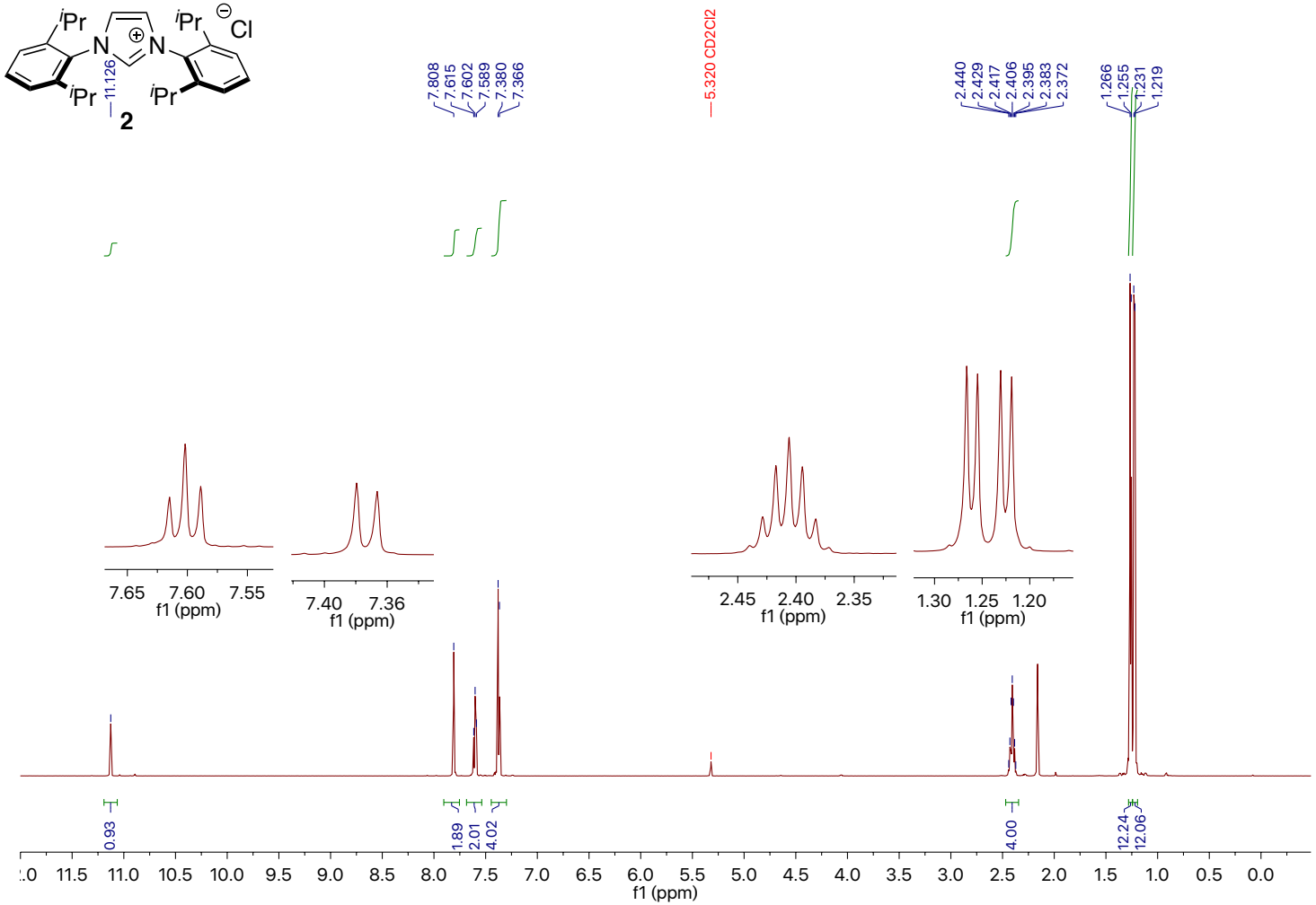
$$P_{sample} = \frac{I_{sample}}{I_{standard}} \cdot \frac{N_{standard}}{N_{sample}} \cdot \frac{M_{sample}}{M_{standard}} \cdot \frac{m_{standard}}{m_{sample}} \cdot P_{standard}$$

$$= \frac{1.70}{2.00} \cdot \frac{2}{4} \cdot \frac{376.5880}{181.1470} \cdot \frac{16.4}{16.4} \cdot 99\%$$

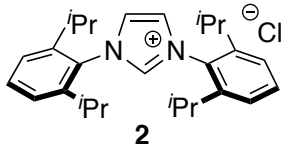
$$= 87\%$$



^{1}H-NMR for *N,N'*-1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**2**) (600 MHz, CD_2Cl_2)

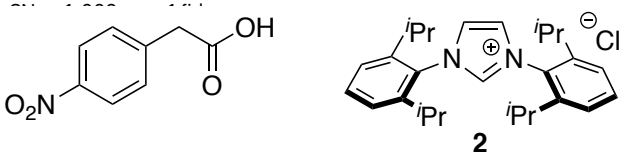


^{13}C-NMR for *N,N'*-1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**2**) (151 MHz, CD_2Cl_2)



2

qNMR for *N,N'*-1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**2**) (500 MHz, d_6-DMSO)



14.2 mg

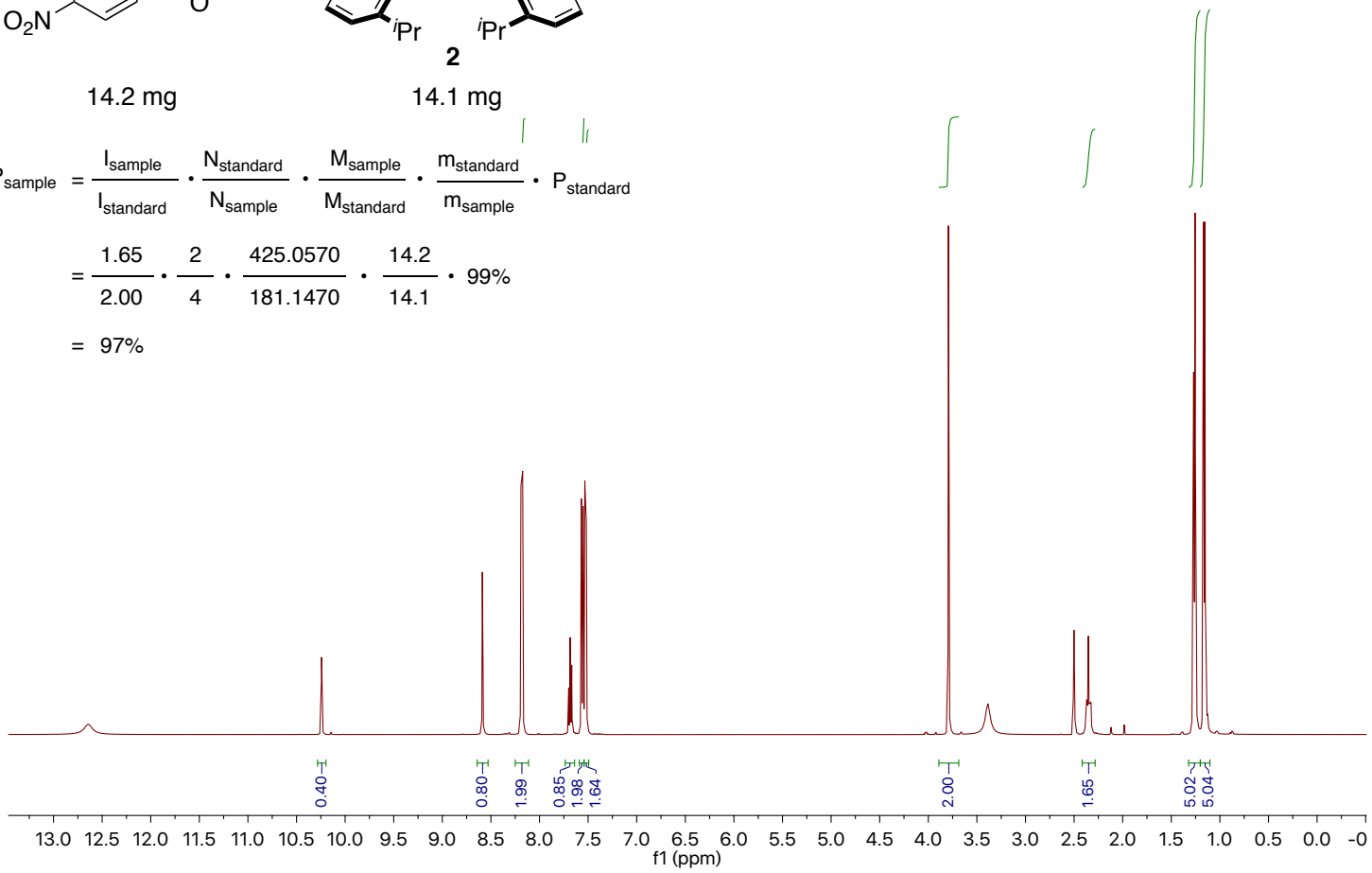
2

14.1 mg

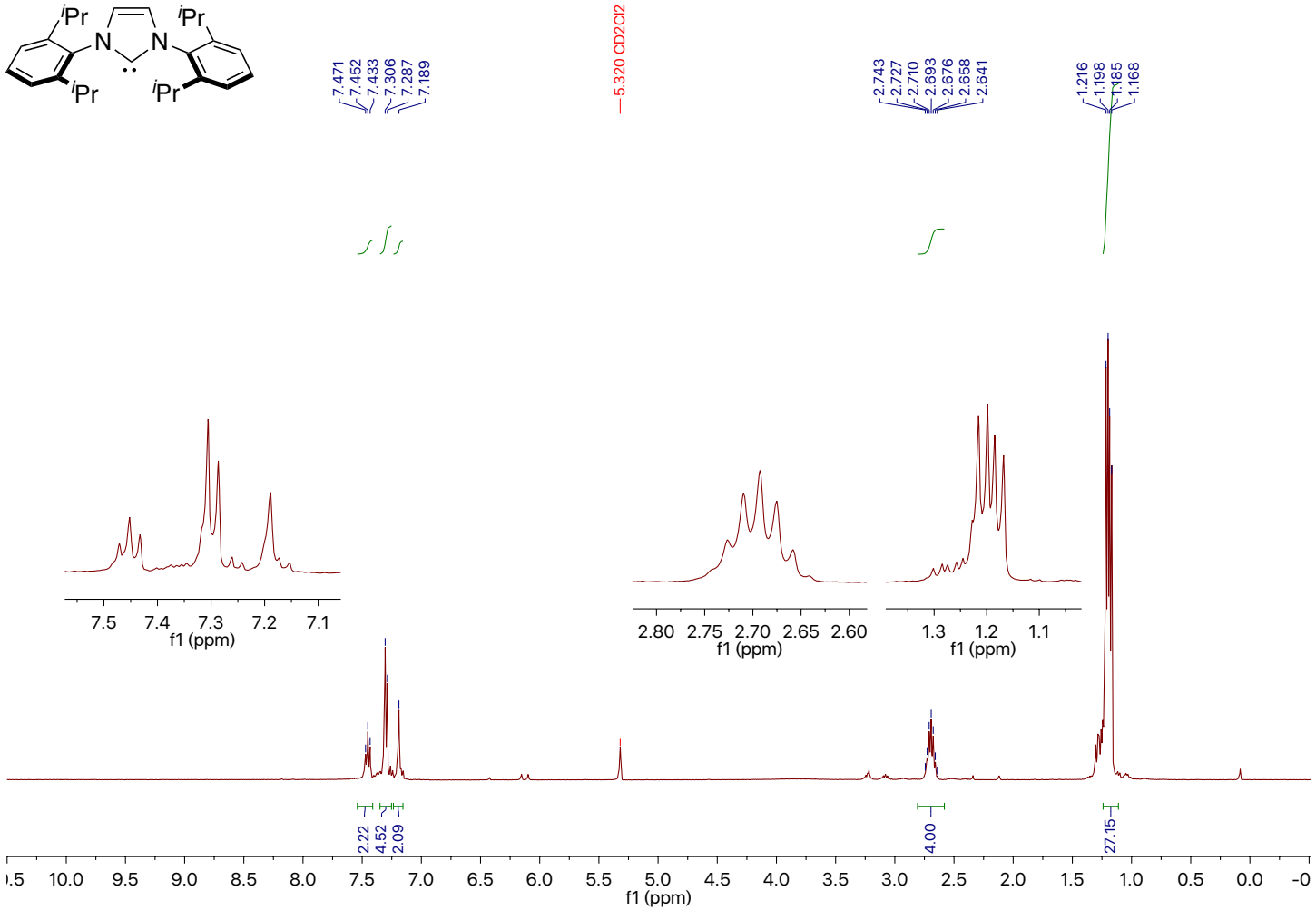
$$P_{sample} = \frac{I_{sample}}{I_{standard}} \cdot \frac{N_{standard}}{N_{sample}} \cdot \frac{M_{sample}}{M_{standard}} \cdot \frac{m_{standard}}{m_{sample}} \cdot P_{standard}$$

$$= \frac{1.65}{2.00} \cdot \frac{2}{4} \cdot \frac{425.0570}{181.1470} \cdot \frac{14.2}{14.1} \cdot 99\%$$

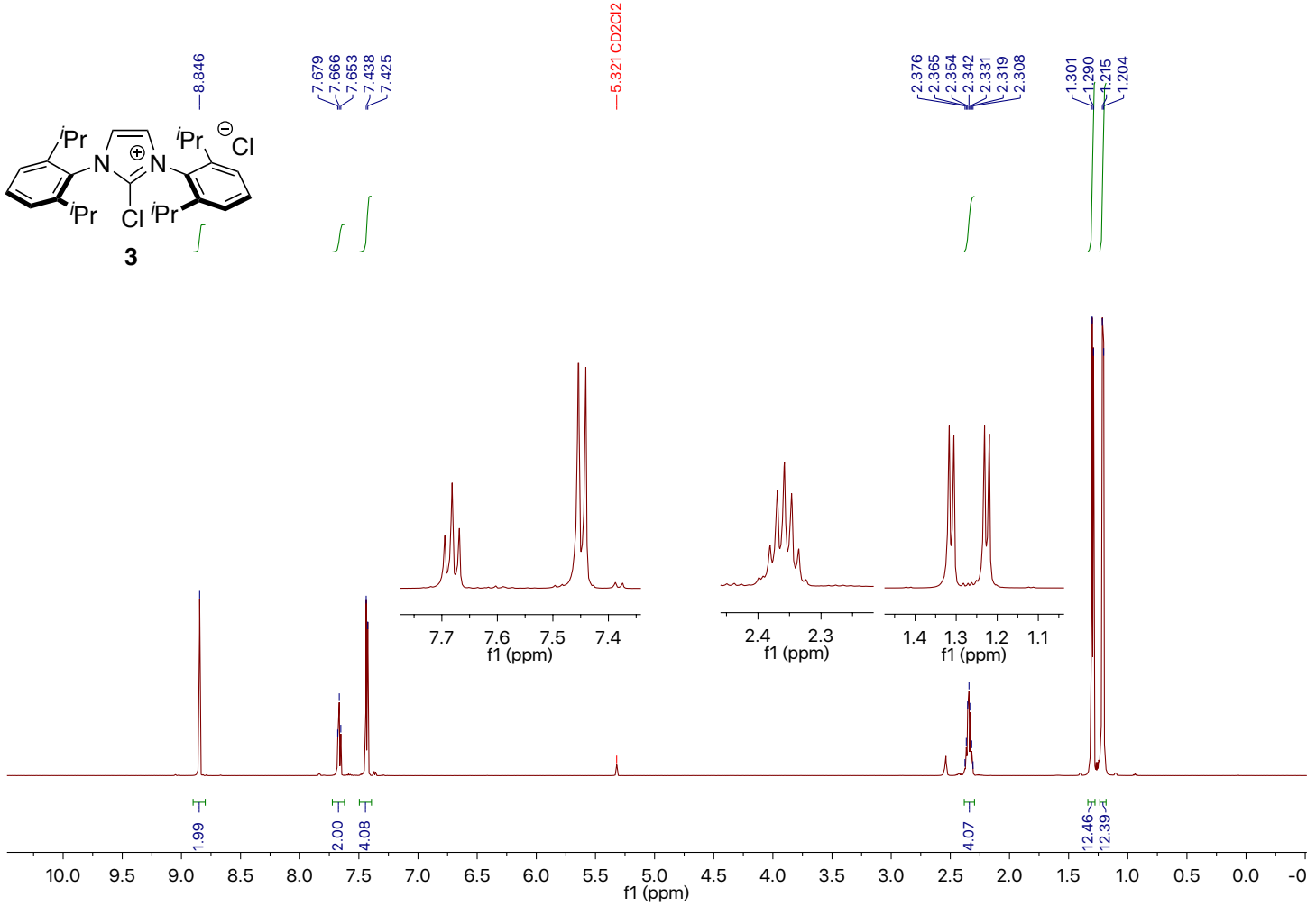
$$= 97\%$$



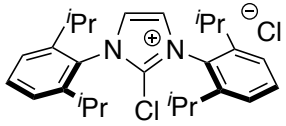
^{1}H-NMR for carbene intermediate (400 MHz, CD_2Cl_2)



^{1}H-NMR for *N,N'*-1,3-bis(2,6-diisopropylphenyl)-2-chloroimidazolium chloride (**3**) (600 MHz, CD_2Cl_2)

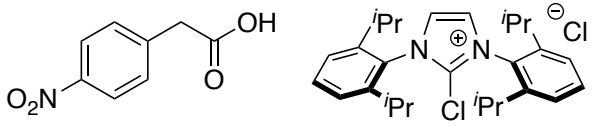


^{13}C-NMR for *N,N'*-1,3-bis(2,6-diisopropylphenyl)-2-chloroimidazolium chloride (**3**) (151 MHz, CD_2Cl_2)



3

qNMR for *N,N'*-1,3-bis(2,6-diisopropylphenyl)-2-chloroimidazolium chloride (**3**) (500 MHz, d_6-DMSO)



14.9 mg

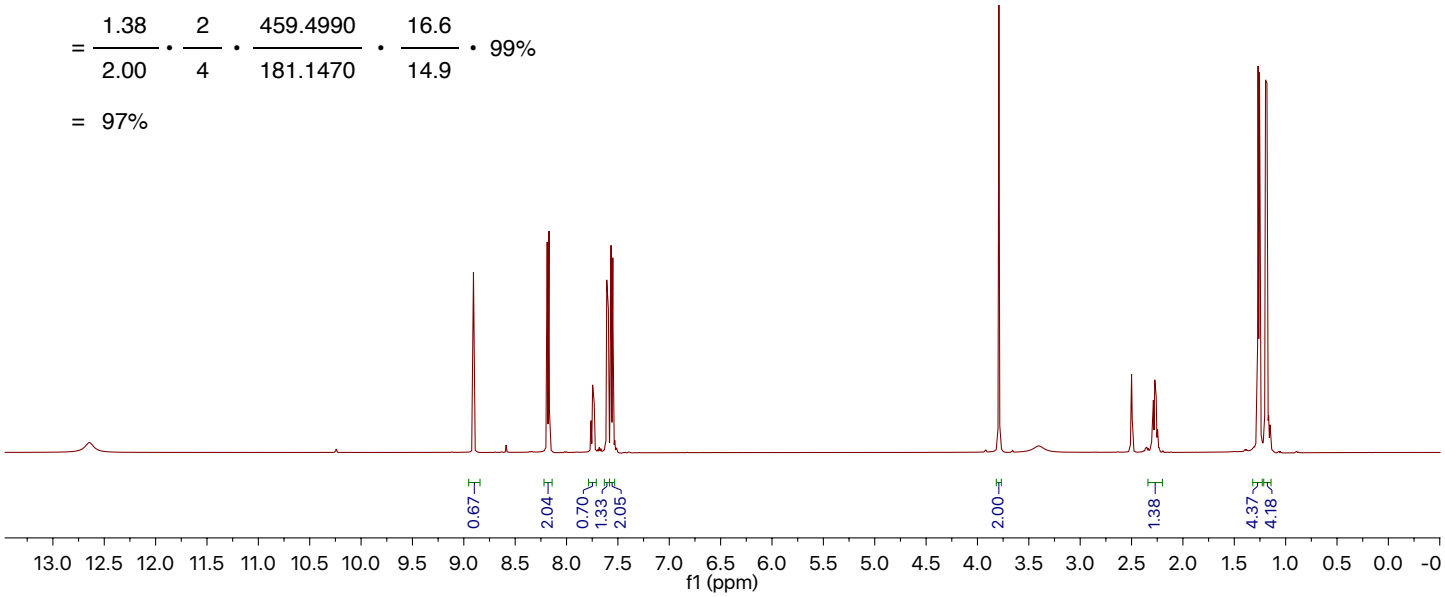
3

16.6 mg

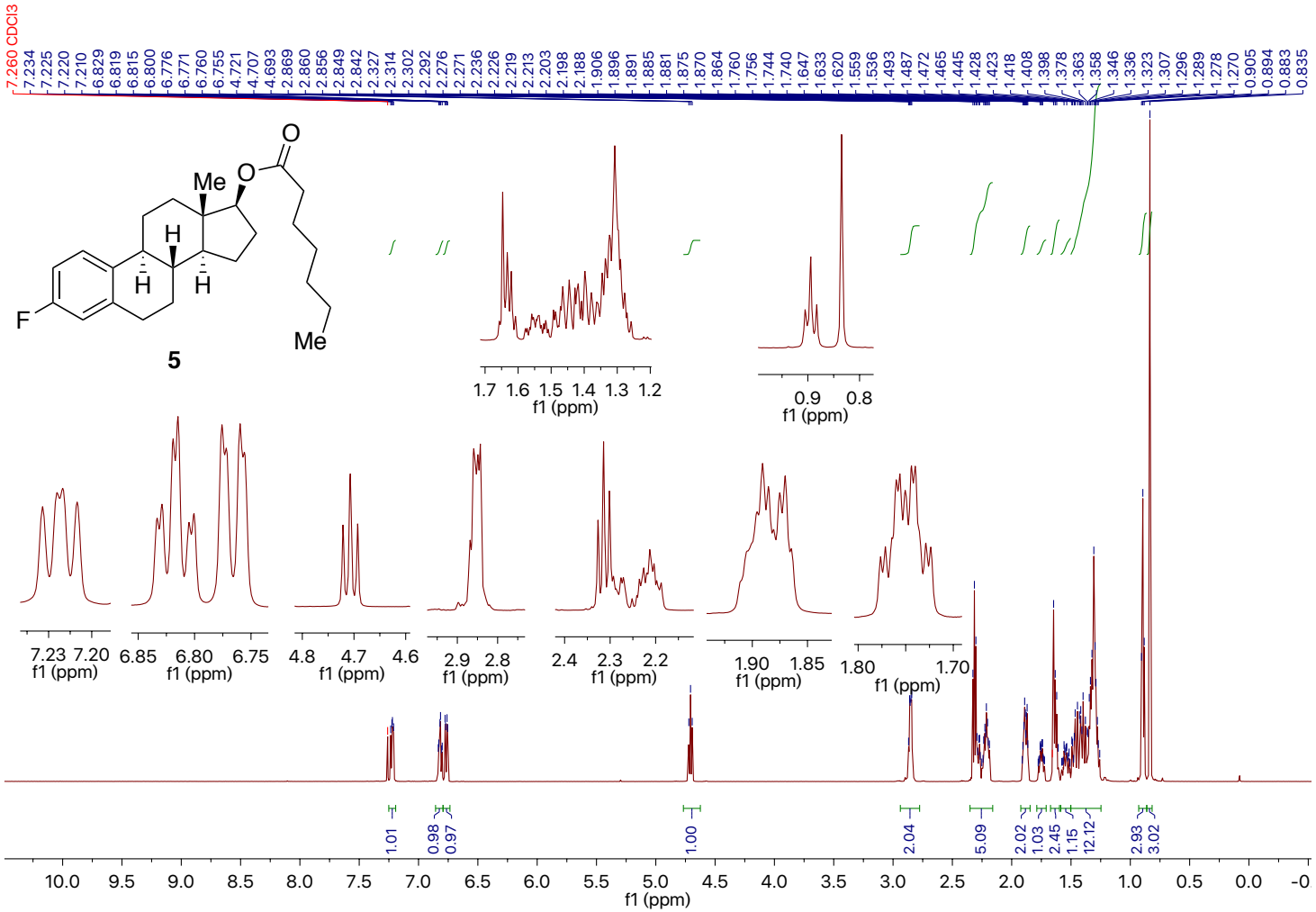
$$P_{sample} = \frac{I_{sample}}{I_{standard}} \cdot \frac{N_{standard}}{N_{sample}} \cdot \frac{M_{sample}}{M_{standard}} \cdot \frac{m_{standard}}{m_{sample}} \cdot P_{standard}$$

$$= \frac{1.38}{2.00} \cdot \frac{2}{4} \cdot \frac{459.4990}{181.1470} \cdot \frac{16.6}{14.9} \cdot 99\%$$

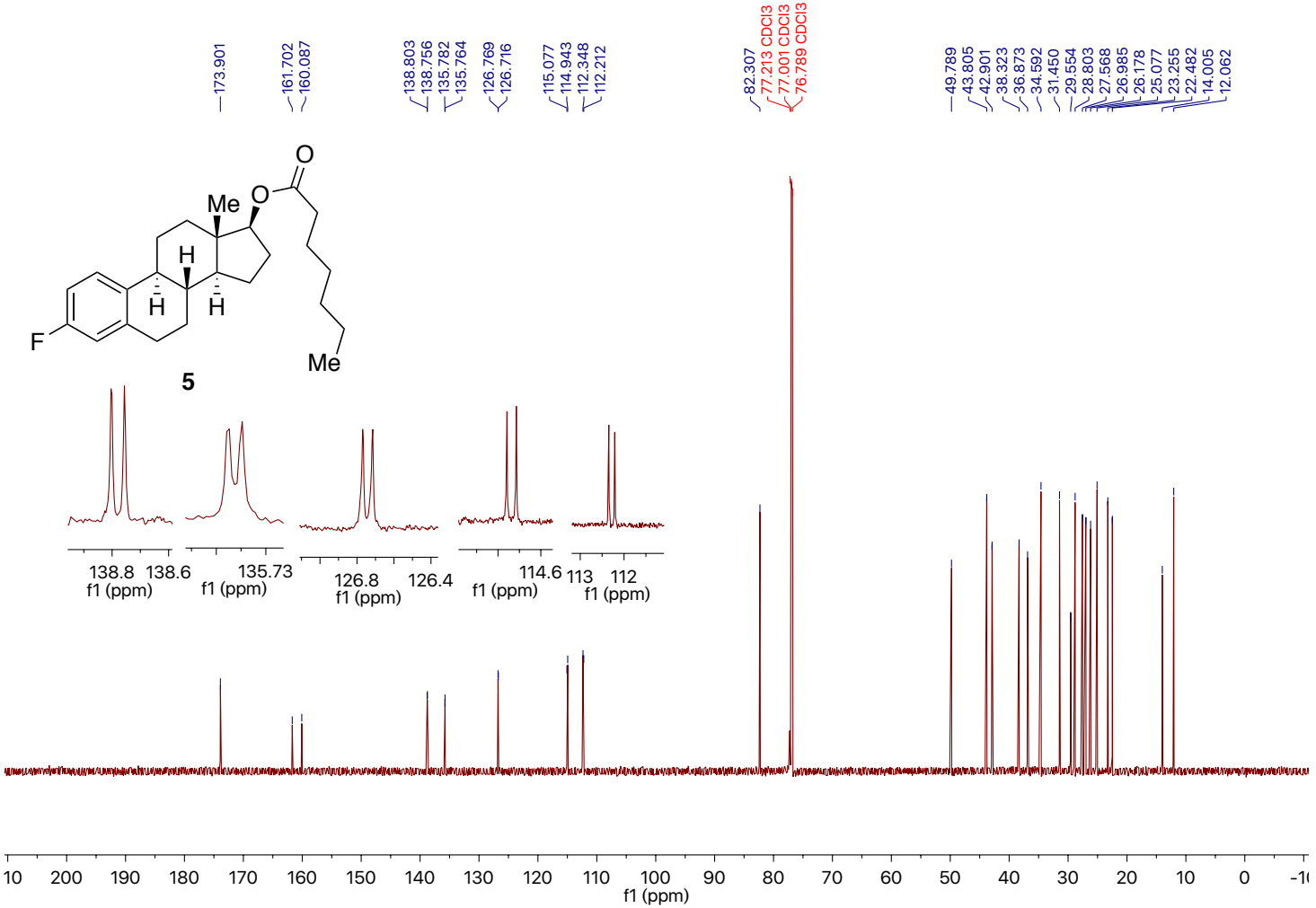
$$= 97\%$$



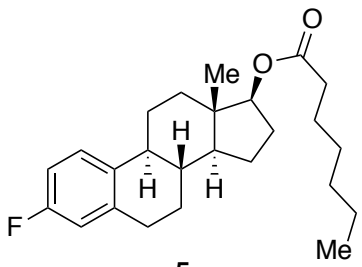
^{1}H-NMR for 3-fluoro estradiol enanthate (**5**) (600 MHz, $CDCl_3$)



^{13}C-NMR for 3-fluoro estradiol enanthate (**5**) (151 MHz, $CDCl_3$)



^{19}F-NMR for 3-fluoro estradiol enanthate (**5**) (376 MHz, $CDCl_3$, internally referenced to $CFCl_3$ (0.00 ppm))



5