Organic Syntheses

Copper-Catalyzed Electrophilic Amination of Heteroaromatic and Aromatic C–H Bonds via TMPZnCl•LiCl Mediated Metalation

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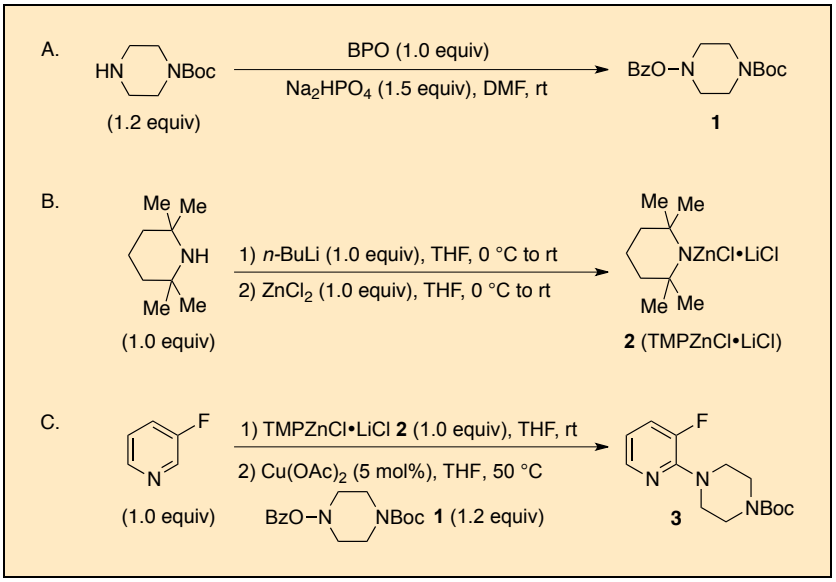

Procedure

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction

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mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414). [Note added January 2011].

A. *tert-Butyl-4-(benzoyloxy)piperazine-1-carboxylate* (***1***).[2] A 500-mL three-necked 24/40 round-bottomed flask is equipped with a 5 cm ellipsoid-shaped, Teflon-coated magnetic stirbar. Two necks are capped with rubber septa, and to the third neck is attached a nitrogen inline adapter. The flask is evacuated under high vacuum (~1 mmHg) and dried with a heat gun for 5 min. The flask is then allowed to cool to room temperature under vacuum. The flask is then back-filled with nitrogen and a thermocouple is charged through one of the necks. Under a slight positive pressure of nitrogen, and *without stirring*, one septum is removed, and solid benzoyl peroxide (24.2 g, 99.9 mmol, 1.0 equiv) (Note 1) and solid sodium phosphate dibasic (21.3 g, 150 mmol, 1.5 equiv) (Note 2) are added *via* a plastic powder funnel. Dimethylformamide (250 mL) (Note 3) is added (Note 4). The resulting heterogeneous white slurry is allowed to stir at room temperature and solid *N*-Boc-piperazine (22.3 g, 120 mmol, 1.2 equiv) (Note 5) is added in one portion *via* a plastic powder funnel. The septum is replaced and the reaction is allowed to stir at room temperature under nitrogen. Slight heat (Note 6) was evolved, and the reaction mixture gradually turned from a heterogeneous white slurry to a bright yellow slurry (Figure 1).

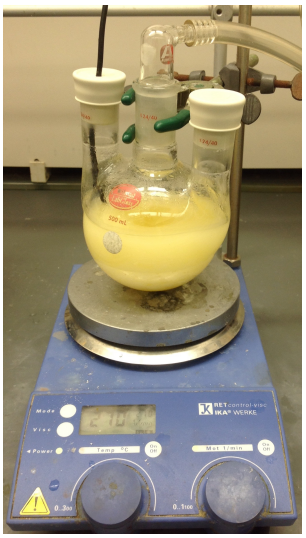


Figure 1. Yellow Slurry formed in Step A

After 1 h (Note 7), the reaction is poured directly into a 2-L Erlenmeyer flask containing deionized water (400 mL) and a 5 cm ellipsoid-shaped, Teflon-coated magnetic stirbar. The reaction flask is rinsed with additional deionized water (100 mL). To this solution is added ethyl acetate (350 mL) (Note 8). The resulting mixture is allowed to stir for 10 min. The organic and aqueous layers are decanted into a 2-L separatory funnel (Note 9), and the residue rinsed with an additional 100 mL of EtOAc. The organic layer is collected and washed with a saturated aqueous sodium bicarbonate solution (2 × 200 mL) (Note 10). The aqueous layers are combined and extracted with ethyl acetate (3 × 200 mL) (Notes 8 and 11). The combined organic portions are washed with deionized water (4 × 250 mL) (Note 12), followed by brine (200 mL). The organic layer is dried over anhydrous magnesium sulfate (50 g) (Note 13), and vacuum filtered through a pad of celite (25 g) in a 12 cm funnel with #1 filter paper, which was subsequently rinsed with ethyl acetate (2 x 100 mL) (Note 8). The filtrate is concentrated by rotary evaporation (22 °C, 70 – 30 mmHg) to give an off-white to yellow solid (Note 14). The crude residue is purified by flash chromatography on silica gel (Note 15) to afford *tert*-butyl-4-(benzoyloxy)piperazine-1-carboxylate as a crystalline white solid (22.2–22.8 g, 73 – 75%) (Note 16).

B. *2,2,6,6-Tetramethylpiperidyl–ZnCl•LiCl (TMPZnCl•LiCl) (**2**).*[3] An oven-dried 250-mL three-necked, 24/40 round-bottomed flask is equipped with a 4 cm ellipsoid-shaped, Teflon-coated magnetic stir bar. One neck is capped with a rubber septum, the center neck is equipped with a 50-mL addition funnel capped with a rubber septum, and the third neck is equipped with a nitrogen inline adapter. The apparatus is subjected to three cycles of evacuation and refilling with nitrogen, and a thermocouple is then added through one of the necks. Tetrahydrofuran (40 mL) (Note 17) and 2,2,6,6-tetramethylpiperidine (9.96 g, 11.9 mL, 70.5 mmol, 1.0 equiv) (Note 18) are added via a plastic syringe to the round-bottomed flask, and the flask is immersed in an ice-water bath. A solution of *n*-butyllithium (2.55 M in hexanes, 27.7 mL, 70.6 mmol, 1.0 equiv) (Note 19) is transferred to the addition funnel via cannula then added dropwise over ca. 20 min to the reaction mixture while maintaining an internal reaction temperature of < 10 °C (Note 20). The resulting solution turns golden in color immediately upon the addition of *n*-butyllithium. The resultant mixture is removed from the ice-water bath after 1 h and allowed to warm to room temperature over 30 min. The mixture is then allowed to stir an additional 1.5 h at room temperature.

A second oven-dried, 250-mL, 24/40 three-necked round-bottomed flask equipped with a 2 cm ellipsoid-shaped stir bar is charged with zinc chloride ($ZnCl_2$) (9.55 g, 70.0 mmol, 1.0 equiv) (Note 21). Two necks are capped with rubber septa. The third neck is equipped with a nitrogen inline adapter. The flask is then evacuated using high vacuum (~1 mmHg) and dried using a heat gun for 5 min. The flask was then allowed to cool to ambient temperature under vacuum. This drying procedure was repeated two more times. After the final cooling to room temperature, the flask is refilled with nitrogen, and a thermocouple is added through one of the necks. Tetrahydrofuran (60 mL) (Note 17) is then added *via* a plastic syringe. The resulting white suspension is cooled in an ice-water bath. The LiTMP solution is then added dropwise via cannula transfer over ca. 10 min to the $ZnCl_2$ suspension (Figure 2) while maintaining an internal batch temperature of 10–15 °C.

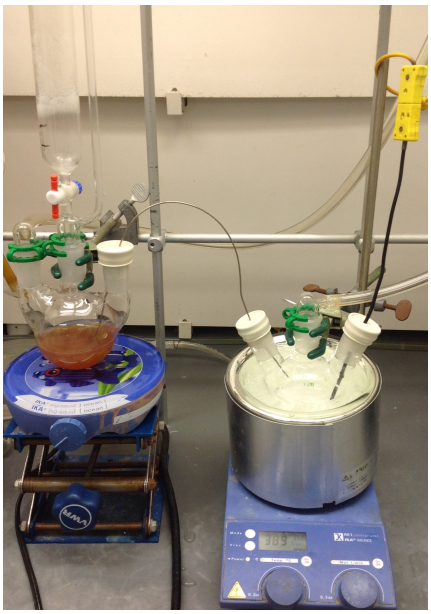
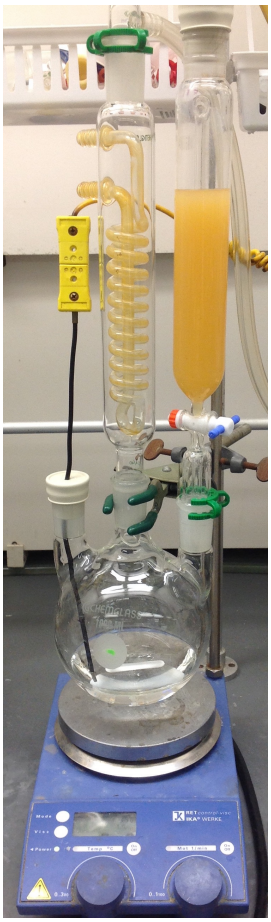


Figure 2. Addition of LiTMP solution to $ZnCl_2$

After complete addition of the LiTMP, the batch is stirred for 30 min, and the gold colored reaction mixture is warmed to room temperature over 30 min and allowed to stir continuously at room temperature under a slight positive pressure of nitrogen. After 14 h, the agitation is stopped to allow



solids to settle. The resulting brown-orange solution is titrated (Note 22) (0.40–0.41 M).

C. *tert-Butyl-4-(3-fluoropyridin-2-yl)piperazine-1-carboxylate (**3**)*. An oven-dried, 1-L three-necked, 24/40 round-bottomed flask is equipped with a 5 cm ellipsoid-shaped, Teflon-coated magnetic stir bar. One neck is capped with a rubber septum. The second neck is equipped with a 125-mL addition funnel that is capped with a rubber septum. The third neck is equipped with a reflux condenser with a nitrogen inline adapter. The apparatus is subjected to three cycles of evacuation and refilling with nitrogen. A thermocouple is then added to the flask through one of the necks. Tetrahydrofuran (125 mL) is added to the round-bottomed flask by cannula and 3-fluoropyridine (4.3 mL, 4.9 g, 50.0 mmol, 1.0 equiv) (Note 23) is added *via* a plastic syringe. 2,2,6,6-Tetramethylpiperidyl–ZnCl•LiCl (**2**) (0.41 M, 122 mL, 112.0 g, 50 mmol, 1.0 equiv) is transferred by cannula to the addition funnel and then slowly added dropwise over ca. 15 min to the reaction at room temperature (Note 24) (Figure 3). The resulting orange solution is stirred at room temperature for 4 h.

Figure 3. Addition of 2,2,6,6-tetramethylpiperidyl–ZnCl•LiCl

An oven-dried, 250-mL, 24/40 pear-shaped flask equipped with a 2 cm ellipsoid-shaped Teflon-coated magnetic stir bar is charged *tert*-butyl-4-(benzoyloxy)piperazine-1-carboxylate (**1**) (18.4 g, 60.0 mmol, 1.2 equiv) and copper(II) acetate (454 mg, 2.50 mmol, 0.05 equiv) (Note 25). The flask is capped with a rubber septum and subjected to three cycles of evacuation and refilling with nitrogen. Tetrahydrofuran (125 mL) (Note 17) is transferred by cannula to the flask. The resulting mixture is stirred at room temperature for 10 min and is then cannula transferred over ca. 10 min to the aryl zincate mixture at room temperature (Note 26). The reaction flask is inserted into an oil bath at 50 °C. The reaction is allowed to stir at 50 °C for

18.5 h and is then removed from heat and cooled to room temperature over 20 min (Notes 26 and 27). The orange-brown solution is directly vacuum filtered (Note 28) through neutral alumina (166 g) (Note 29) in a medium porosity fritted glass funnel, washed with ethyl acetate (500 mL) (Note 8), and concentrated by rotary evaporation (Note 30) to give a thick brown oil. The crude residue is purified by flash chromatography on silica gel (Note 31) to afford *tert*-butyl-4-(3-fluoropyridin-2-yl)piperazine-1-carboxylate (**3**) (7.05–7.77 g, 50–53%) as a yellow oil that crystallizes very slowly at 4 °C (Notes 32 and 33).

Notes

1. Benzoyl peroxide (Luperox® A98, reagent grade, 98%) was purchased from Sigma Aldrich and used as received. The reaction was not stirred until solvent was added due to shock sensitivity of benzoyl peroxide.
2. Sodium phosphate dibasic (BioReagent, ≥99%) was purchased from Sigma Aldrich and used as received.
3. Dimethylformamide (anhydrous, 99.8%) was purchased from Sigma Aldrich and used as received. The submitters used dimethylformamide (ACS grade, ≥99.8%) purchased from Sigma Aldrich and used it directly.
4. The internal reaction temperature decreases from 20 °C to 15 °C upon the addition of dimethylformamide.
5. *N*-Boc-piperazine (≥98.0%) was purchased from Sigma Aldrich and used as received. The submitters purchased this material from ArkPharm, Inc. (98%) and used it directly.
6. The internal reaction temperature reached a maximum of 37 °C in ~10 min and then began to slowly cool back to room temperature.
7. Completeness of reaction is judged by the disappearance of benzoyl peroxide by thin-layer chromatography (TLC), performed on glass backed pre-coated silica gel plates (DC-Kieselgel 60 F_{254}) with a UV254 indicator, using 20% ethyl acetate–hexanes as the eluent (R_f of benzoyl peroxide = 0.43; R_f of the product = 0.19). The product is visualized with a 254 nm UV lamp and $KMnO_4$ stain. The submitter's utilized TLC plates on aluminum backed pre-coated

silica gel plates (250 μm, Agela Technologies) with a UV254 indicator.

8. Ethyl acetate (ACS reagent, ≥99.7%) was purchased from Sigma Aldrich and used as received. The submitters used ethyl acetate (Chromasolv®, for HPLC, ≥99.7%) purchased from Sigma Aldrich and used it directly.
9. A portion of solid material would not dissolve in the organic or aqueous phases. This insoluble material was not transferred to the separatory funnel.
10. Sodium bicarbonate (ACS reagent grade, 99.7–100.3%) was purchased from Sigma Aldrich and used as received.
11. During the ethyl acetate extraction, a solid began to crystallize in the aqueous layer. After shaking the separatory funnel, the aqueous portion containing this solid was removed from the funnel quickly to avoid this solid material settling to the bottom, which results in clogging of the separatory funnel.
12. The first water wash gave fast layer separation. The remaining three water washes gave slow phase separations (~30 min needed to obtain good phase cuts).
13. Magnesium sulfate (ACS reagent, >99.5%, anhydrous) was purchased from Sigma Aldrich and used as received. The submitters dried the material using sodium sulfate (131 g, ACS reagent, >99.0%, anhydrous, granular, Sigma Aldrich).
14. The organic layer (and the aqueous layer) is tested for the presence of peroxides using a peroxide test strip before concentration (or disposal of the aqueous layer). No evidence for peroxides was observed.
15. The crude solid is dissolved in 20% ethyl acetate/hexanes with enough methylene chloride added to dissolve all the solids. This material is then dry-loaded onto 56 g (125 mL) of silica gel. The volatile organics are then removed by rotary evaporation (35 mmHg, bath temperature = 22 °C). Chromatography is then performed using a 6 cm diameter flash chromatography column packed with 208 g (400 mL) of silica gel (Grade 60, 230–400 mesh, Fisher Scientific). The column is eluted using 20% ethyl acetate/hexanes (1700 mL) followed by 35% ethyl acetate/hexanes (700 mL) by collecting 100 mL fraction sizes using 125 mL Erlenmeyer flasks. The product is typically found in fractions 6–21.

TLCs were eluted with 35% ethyl acetate-hexanes (product R_f = 0.35).

16. The physical properties of *tert*-butyl-4-(benzoyloxy)piperazine-1-carboxylate (**1**) are: mp 103–105 °C; R_f = 0.19 (Note 7); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (s, 9H), 2.92 (br s, 2H), 3.32 (br s, 2H), 3.44 (br s, 2H), 4.04 (br s, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.58 (tt, *J* = 7.4, 1.4 Hz, 1H), 8.03–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 41.9 (br s), 55.7, 80.1, 128.4, 129.0, 129.3, 133.1, 154.3, 164.4; IR (thin flim): cm^{-1} 2977, 2905, 2864, 2848, 1737, 1691, 1599, 1583, 1447, 1409, 1363, 1274, 1248, 1228, 1169; HRMS (ESI) [M + H] calcd for $C_{16}H_{22}N_2O_4$: 307.1658; found 307.1651; QHMNR (400 MHz, $CDCl_3$, dimethyl fumarate standard (Sigma-Aldrich, 96.9%)): 97–99%.
17. Anhydrous tetrahydrofuran was purchased from Sigma Aldrich and used as received. The submitter's used tetrahydrofuran (Chromasolv®, for HPLC, 99.9%) purchased from Sigma Aldrich and dried the solvent using an Innovative Technologies solvent purification system before use.
18. 2,2,6,6-Tetramethylpiperidine (≥99%) was purchased from Sigma Aldrich and used as received. The submitters used 2,2,6,6-tetramethylpiperidine (98%) purchased from Matrix Scientific, and distilled the material over calcium hydride under nitrogen atmosphere (152 °C) prior to use.
19. *n*-Butyllithium solution (*n*-BuLi) (2.5 M in hexanes) was purchased from Sigma Aldrich. The *n*-BuLi was titrated at 2.55 M prior to use using the following protocol. A 2-necked, 14/20 round-bottomed flask with a 2-cm ellipsoid shaped Teflon coated magnetic stir-bar, a nitrogen inlet adapter and a septum was evacuated using high vacuum (~1 mmHg) and dried using a heat gun for ~3 min. The flask was allowed to cool to ambient temperature under vacuum. The flask was refilled with nitrogen, the septum was removed, and 223.8 mg (1.016 mmol) of 2,6-di-*tert*-butyl-4-methylphenol (BHT, 99.0%, Sigma-Aldrich) and 3 mg of 1,10-phenanthroline (>99%, Sigma-Aldrich) were charged to the flask under a positive pressure of nitrogen. The septum was replaced, and anhydrous THF (3.0 mL, Note 17) was charged. The resultant solution was agitated at ambient temperature, and the *n*-BuLi solution was charged dropwise by syringe until the color of the mixture changed from

yellow to black indicating the endpoint (0.398 mL). The submitters titrated *n*-BuLi using an alternate literature procedure.[4]

20. The addition takes ca. 20 min.
21. Zinc chloride ($ZnCl_2$) (anhydrous, >97%, ACS, Redi-Dri™) was purchased from Sigma Aldrich. The submitters purchased $ZnCl_2$ (anhydrous, 97%, ACS) from Strem Chemicals, Inc.
22. 2,2,6,6-Tetramethylpiperidyl–ZnCl•LiCl was titrated according to the following literature procedure.[3] A 2-necked, 14/20 round-bottomed flask with a 2 cm ellipsoid shaped Teflon coated magnetic stir-bar, a nitrogen inlet adapter and a septum was evacuated using high vacuum (~1 mmHg) and dried using a heat gun ~3 min. The flask was then allowed to cool to ambient temperature under vacuum. The flask was refilled with nitrogen, the septum was removed, and 217.6 mg (1.782 mmol) of benzoic acid (Sigma-Aldrich, >99.5%) and 3 mg of 4-(phenylazo)diphenylamine (Sigma-Aldrich, 97%) were charged to the flask under a positive pressure of nitrogen. The septum was replaced, and anhydrous THF (3.0 mL, Note 17) was charged. The resultant orange solution was stirred at 0 °C, and the TMPZnCl•LiCl solution was charged dropwise by syringe until the color of the mixture changed from orange to a persistent red color indicating the endpoint (4.35 mL).
23. 3-Fluoropyridine (99%) was purchased from Oakwood Chemicals and fractionally distilled (107 °C) before use. The submitters used material from Matrix Scientific and also purified the material by distillation prior to use.
24. The internal reaction temperature remained at 21 °C throughout the addition.
25. Copper(II) acetate (anhydrous, 97%) was purchased from Strem Chemicals, Inc. and used as received.
26. Completeness of reaction is judged by the disappearance of *tert*-butyl-4-(benzoyloxy)piperazine-1-carboxylate by thin-layer chromatography (TLC), on glass backed pre-coated silica gel plates (DC-Kieselgel 60 F_{254}) with a UV254 indicator, using 20% ethyl acetate–hexanes as the eluent (R_f of *tert*-butyl-4-(benzoyloxy)piperazine-1-carboxylate = 0.19; R_f of the product = 0.35). The product is visualized with a 254 nm UV lamp and $KMnO_4$ stain. The submitter's utilized TLC plates on aluminum backed pre-

coated silica gel plates (250 μm, Agela Technologies) with a UV254 indicator.

27. Conversion of the limiting reagent (3-fluoropyridine) was determined by ^{19}F NMR spectroscopy by dissolving an aliquot of the reaction mixture in $CDCl_3$ followed by analysis. Despite the fact that the *tert*-butyl-4-(benzoyloxy)piperazine-1-carboxylate is consumed, 3-fluoropyridine is present as determined by ^{19}F NMR spectroscopy.
28. The reaction mixture is poured slowly.
29. Aluminum oxide (activated, neutral, Brockman grade I, 58 Å) was purchased from Alfa Aesar and used as received.
30. Crude mixture was dried on high vacuum (1 mmHg) for ~20 min after rotary evaporation (bath temperature = 22 °C, 35 mmHg) to remove excess ethyl acetate and 2,2,6,6-tetramethylpiperidine.
31. The crude oil is dissolved in methylene chloride and then dry-loaded onto 54 g (~125 mL) of silica gel. The volatile organics are then removed by rotary evaporation (35 mmHg, bath temperature = 22 °C). Chromatography is then performed using a 6 cm diameter flash chromatography column packed with 223 g (~450 mL) of silica gel (Grade 60, 230–400 mesh, Fisher Scientific). The column is eluted using 15% ethyl acetate/hexanes (1200 mL) followed by 22% ethyl acetate/hexanes (825 mL) followed by 27% ethyl acetate/hexanes (525 mL) by collecting 75 mL fraction sizes using 125 mL Erlenmeyer flasks. The product is typically found in fractions 11-26. TLC's were eluted with 20% ethyl acetate-hexanes (product R_f = 0.35). The submitter's used the following chromatography conditions: Column diameter: 8 cm, silica: 800 mL (Silicycle, SiliaFlash® P60, 230–400 mesh, 60 Å), eluent: 3500 mL (20% ethyl acetate–hexanes), fraction size: 25 mL, 18 x 150 mm test tubes. The crude product was dry-loaded on 100 mL of silica and 800 mL eluent flushed through column before collecting fractions. The product is typically found in fractions 17–60.
32. The product solidified very slowly after isolation. However, by adding a small amount of product seeds to subsequent batches of the product, the material solidified rapidly at room temperature.
33. The physical properties of *tert*-butyl-4-(3-fluoropyridin-2-yl)piperazine-1-carboxylate are: mp 54–55 °C; R_f = 0.35 (TLC, Note 26); ^1H NMR (500 MHz, $CDCl_3$) δ: 8.00 (dt, J = 4.8, 1.5 Hz, 1H), 7.24 (ddd, J = 13.0, 8.0, 1.5 Hz, 1H), 6.77 (ddd, J = 8.0, 4.8, 3.0 Hz,

1H), 3.58–3.53 (m, 4H), 3.47–3.41 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.8, 150.1 (d, J = 255.1 Hz), 149.8 (d, J = 6.4 Hz), 142.8 (d, J = 5.5 Hz), 123.2 (d, J = 18.8 Hz), 116.1 (d, J = 2.6 Hz), 79.8, 47.5 (d, J = 5.2 Hz), 43.6 (br s), 28.4; the submitters reported the following ^{13}C NMR values: (125 MHz, $CDCl_3$, 60 °C) δ: 154.6, 149.8 (J_{C-F} = 255.0 Hz), 149.6 (J_{C-F} = 6.2 Hz), 142.6 (J_{C-F} = 5.2 Hz), 122.9 (J_{C-F} = 18.9 Hz), 115.7, 79.5, 47.3 (J_{C-F} = 5.0 Hz), 43.6, 28.3; IR (thin film): 2976, 2929, 2859, 1692, 1605, 1469, 1453, 1417, 1365, 1266, 1238, 1216, 1165 cm^{-1}; HRMS (ESI) [M + H] calcd for $C_{14}H_{20}FN_3O_2$: 282.1618; found 282.1624; QHMNR (500 MHz, $CDCl_3$, dimethyl fumarate standard (Sigma-Aldrich, 96.9%)): 96–98%.

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.

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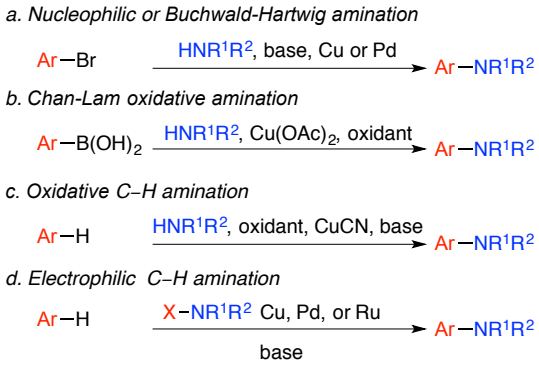
Discussion

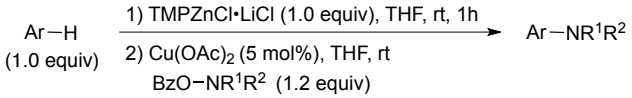
Heteroaromatic and aryl amines are functionally and biologically important molecules.[5] The importance of nitrogen-containing compounds continues to drive the development of new C–N bond-forming transformations.[6] Among different amination strategies (Scheme 1),[7] C–H amination offers a direct method to introduce amino groups into molecules without stepwise functional group manipulations. It would be greatly desirable to develop a catalytic amination system effective for sp^2 C–H bonds with broader applications in complex molecule synthesis. For example, a range of catalyst systems have been developed, including Pd, Ru, and Cu.[8]

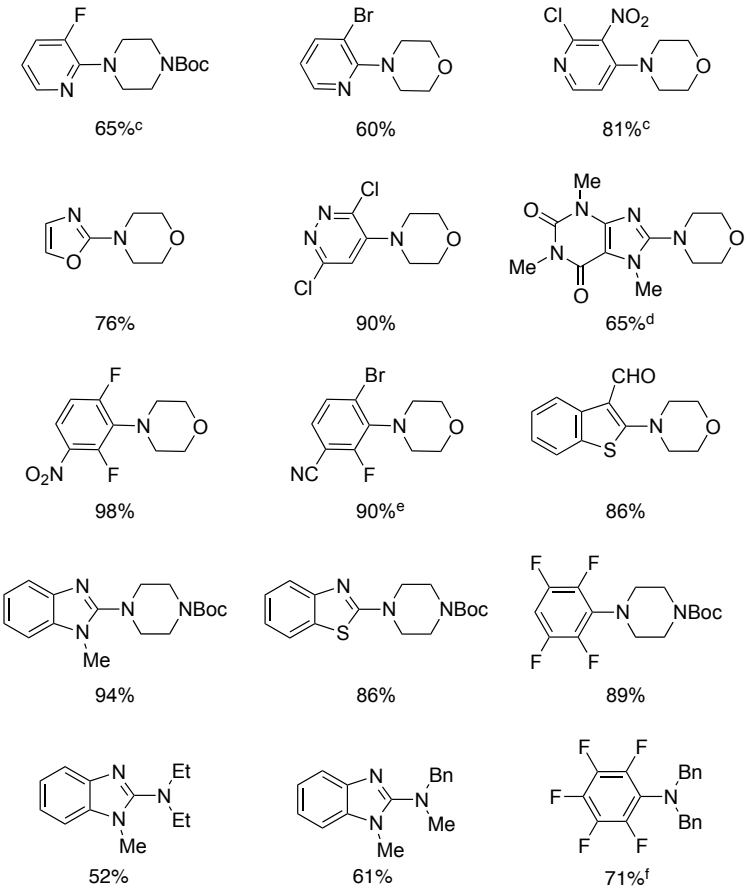


Scheme 1. Amination Strategies to Access Ar–NR^1R^2

We have recently developed a facile electrophilic C–H amination that can be achieved *via* organozinc intermediates derived from C–H bonds,[9] including a broad range of heteroaromatic and aryl substrates (Table 1). Such organozinc reagents can be generated *in situ* using the strong and non-nucleophilic base TMPZnCl•LiCl.[3] Additionally, readily available *O*-benzoylhydroxylamines have been demonstrated as an effective electrophilic nitrogen source in this C–H amination reaction, similar to those electrophilic aminations of organometallic reagents reported previously.[2,8,10]

Table 1. Direct amination of heteroaromatic and aryl amines using TMPZnCl·LiCl base[a,b]





[a]Isolated yields. [b]All reactions run at a 0.20 mmol scale and 10 mol% $Cu(OAc)_2$ used. [c]Amination run at 50 °C. [d]Reaction run in CH_2Cl_2 due to low solubility of starting material in THF. [e]Deprotonation run at 65 °C. [f]Deprotonation run for 1.5 h.

In summary, this H−Zn exchange/amination strategy offers a rapid and powerful way to access a variety of highly functionalized complex aromatic

amines. It is especially attractive with the use of a low cost copper catalyst and readily available reagents. Additionally, the mild reactivity of organozinc reagents allows for good compatibility with different functional groups, such as esters, amides, and halides.

References

1. Department of Chemistry, Duke University, Durham, NC 27708, qiu.wang@duke.edu. The authors thank Duke University for financial support to the research. Fellowships from the Burroughs Wellcome Endowment (S.L.M.) and Duke University Pharmacological Sciences Training Program (C.E.H.) are gratefully acknowledged. The authors thank Dr. George R. Dubay for performing HRMS experiments.
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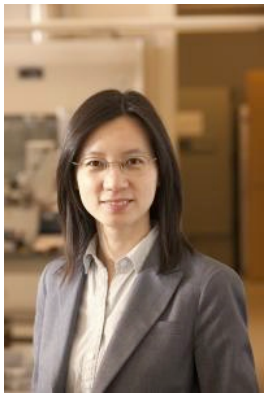
Appendix

Chemical Abstracts Nomenclature (Registry Number)

Benzoyl peroxide; (94-36-0)
Sodium phosphate dibasic; (7558-79-4)
N-Boc-piperazine: *tert*-Butyl piperazine-1-carboxylate; (57260-71-6)
2,2,6,6-Tetramethylpiperidine; (768-66-1)
n-Butyllithium; (109-72-8)
Zinc chloride; (7646-85-7)
3-Fluoropyridine; (372-47-4)
Copper(II) acetate: Cupric acetate (142-71-2)



Qiu Wang received her Ph.D. in organic chemistry from Emory University under the direction of Professor Albert Padwa (2005). She undertook postdoctoral training with Professor Andrew Myers at Harvard University (2005–2007) and Professor Stuart Schreiber at the Broad Institute of Harvard and MIT (2007–2011). She started her independent career in 2011 as an assistant professor of chemistry at Duke University. Her research interests focus on the synthesis and studies of biologically important nitrogen-containing molecules.

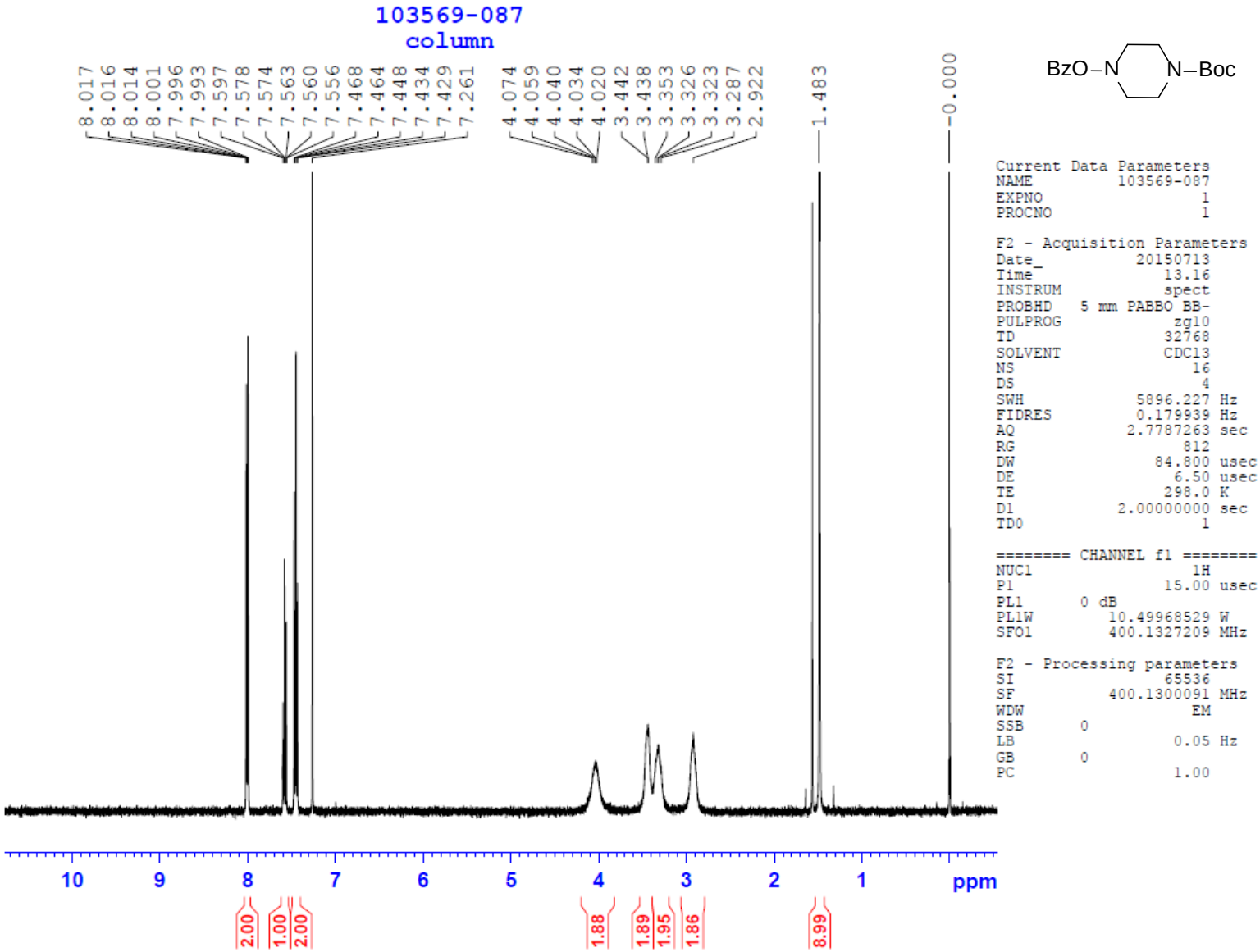
Stacey L. McDonald is originally from Fort Mill, SC. In 2009, she received her B.S. in chemistry from Wofford College in Spartanburg, SC. She received her Ph.D. in 2015 from Duke University under the direction of Professor Qiu Wang. Her graduate studies focused on the copper-catalyzed electrophilic amination of sp^2 and sp^3 C–H bonds.

Charles E. Hendrick hails from Kernersville, NC. He received his B.S. in chemistry in 2011 from Wake Forest University under the supervision of Professor Lindsay Comstock-Ferguson. He is currently a graduate student in the Wang group at Duke University where his research focuses on aryl amination strategies employing nitrogen-heteroatom bonds.

Katie J. Bitting originates from Elizabethtown, PA. She received her B.S. in biochemistry and molecular biology from Sweet Briar College in 2013. She is currently a graduate student at Duke University where she works on zincate-mediated functionalization of arenes in the Wang group.

Dr. Joshua D. Sieber obtained a B.S. in chemistry from Penn State University with honors in chemistry in 2003. He then received a Ph.D. from Boston College in 2008 where he worked under the direction of Professor James P. Morken and was an ACS Division of Organic Chemistry Fellow. Subsequently, he was an American Cancer Society postdoctoral fellow in the laboratory of Professor Barry M. Trost. After this period, he joined Chemical Development at Boehringer Ingelheim Pharmaceuticals in 2011 where he is currently a Senior Scientist. His research interests include the development and application of catalytic asymmetric reactions.

tert-Butyl-4-(benzoyloxy)piperazine-1-carboxylate



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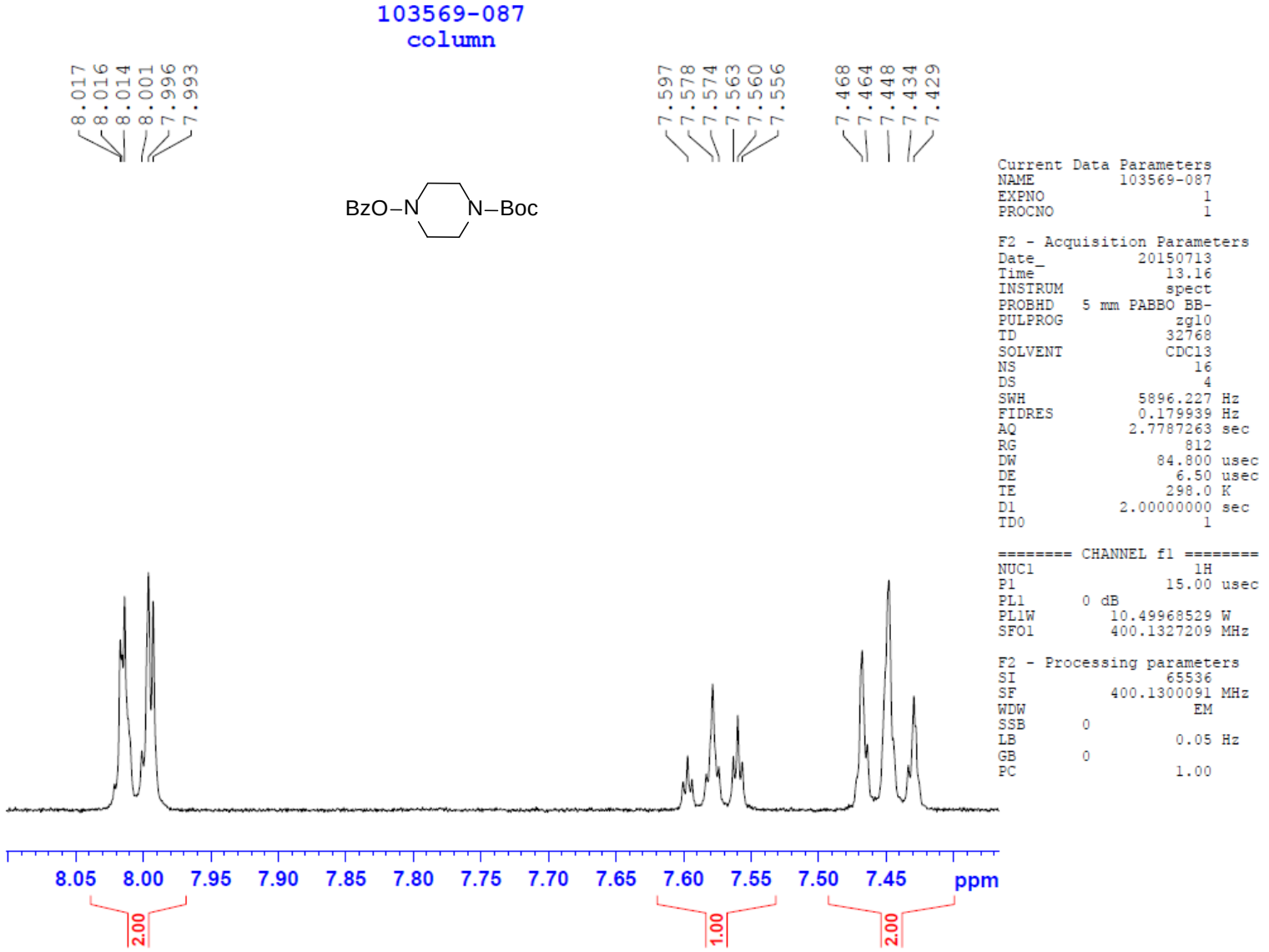


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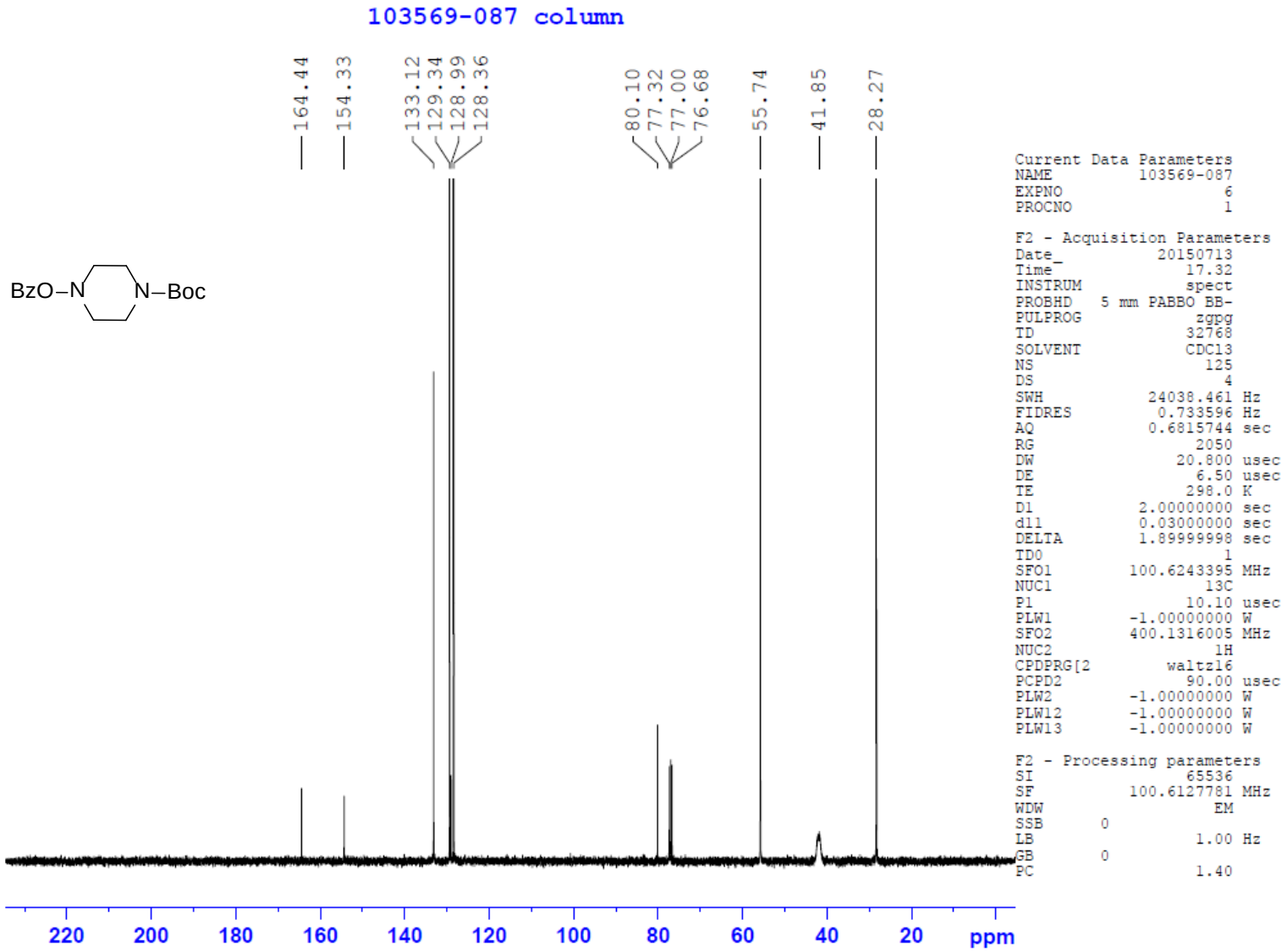


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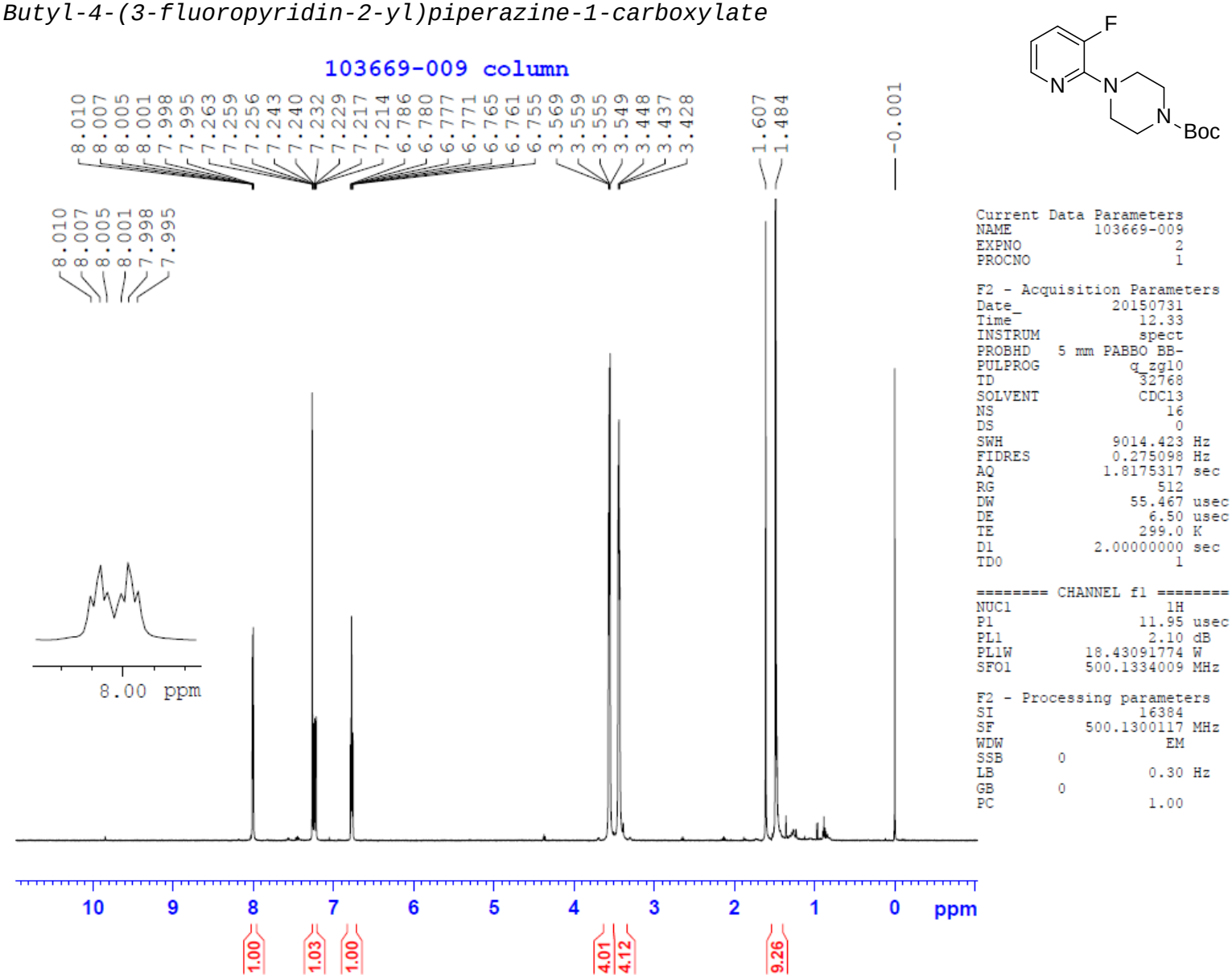


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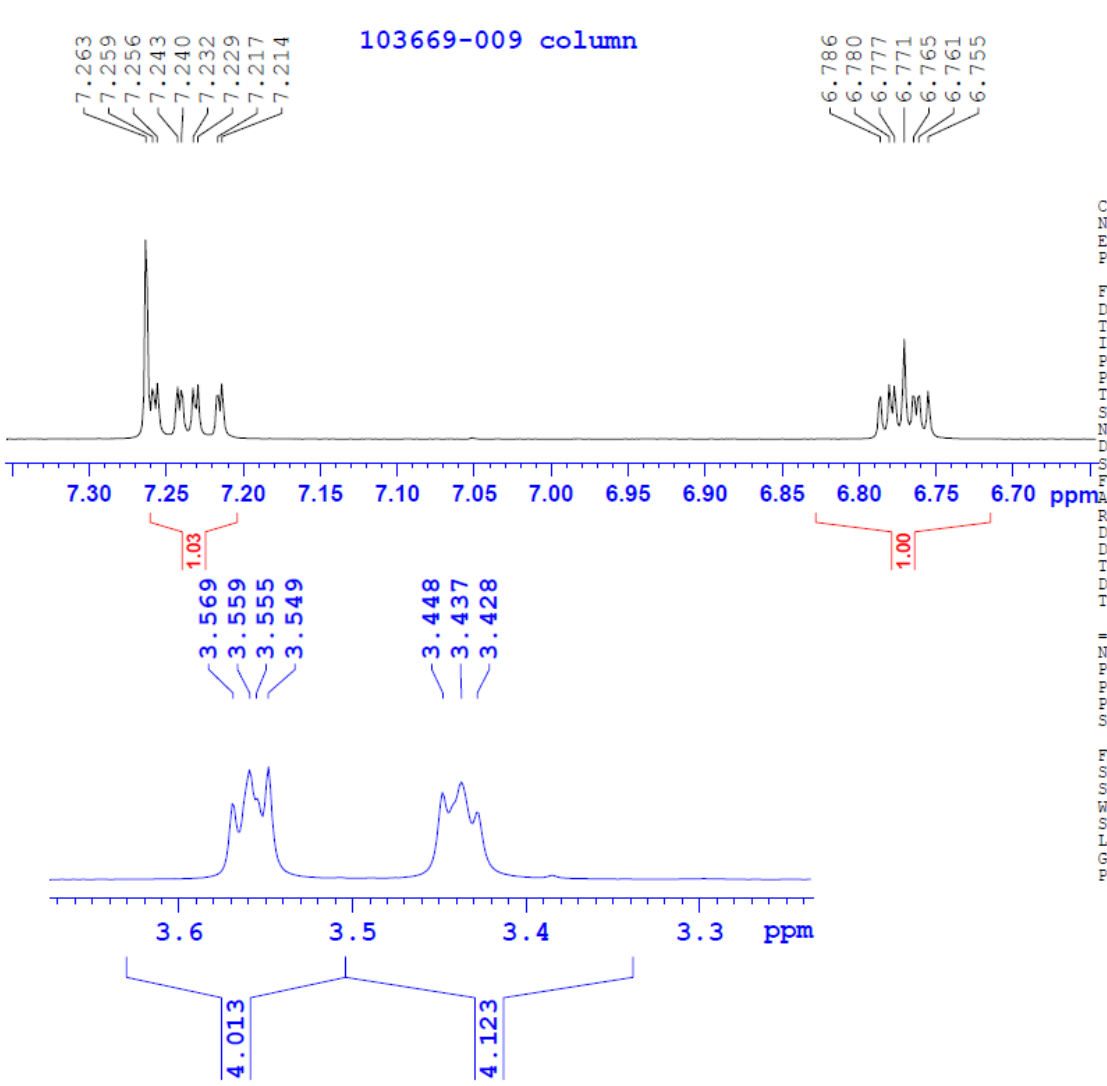

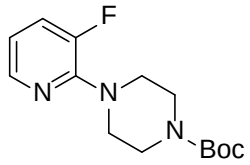


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DW               55.467 usec
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TE                299.0 K
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======== CHANNEL f1 ========
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PL1                2.10 dB
PL1W        18.43091774 W
SFO1        500.1334009 MHz

F2 - Processing parameters
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tert-Butyl-4-(3-fluoropyridin-2-yl)piperazine-1-carboxylate