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An efficient synthesis of a highly functionalized 4-arylpiperidine

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Abstract—In this manuscript, an efficient synthesis of a functionalized 4-arylpiperidine is disclosed. Several synthetic approaches towards formation of the key aryl-piperidine sp3 carbon–carbon bond are discussed, including a scalable route to the piperidine via reaction of acyl pyridinium ions with aryl Grignard reagents to form the corresponding dihydropyridines. Methods to access the BOC protected piperidine through dihydropyridine intermediates are described.
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1. Introduction

4-Arylpiperidines and their derivatives exhibit a diverse array of biological activity and as such are useful pharmacophores. 4-Arylpiperidines have been investigated as *N*-methyl-D-aspartate (NMDA) receptor antagonists, renin inhibitors, α_1 adrenergic receptor antagonists, beta-secretase inhibitors, and serotonin reuptake inhibitors, encompassing therapeutic areas including epilepsy and Parkinson's disease,[1a] heart and kidney insufficiency,[1b,c] hypertension and benign prostatic hyperplasia,[1d] Alzheimer's disease,[1e] and depression.[1f] The broad applicability of 4-arylpiperidines as structural scaffolds has generated considerable interest in general methods for their preparation.

We recently required a synthesis of 4-arylpiperidines containing multiple functional groups. A representative example, **1**, contains both aryl halide and benzonitrile functional groups. The nitrile is a versatile handle which can be further transformed to generate 4-arylpiperidines containing ketones, amines, aldehydes, and amides. Additionally, the aryl chloride moiety can provide functionalization through carbon–carbon or carbon–heteroatom bond formations accessed by various transition-metal-catalyzed cross-coupling reactions. The juxtaposition of both of these functional groups in the same molecule represents a challenge to existing methodology for preparing members of this class of compounds. While the nitrile is reactive to highly nucleophilic reagents, the halide is reactive towards reducing conditions which are frequently employed as a means of obtaining the saturated piperidine ring. In this manuscript, we disclose several routes towards the desired 4-aryl piperidines including a scalable route which utilizes the reaction of acyl pyridinium ions with aryl Grignard reagents to form the corresponding dihydropyridines.

1.1. Retrosynthetic analysis

Literature precedence suggested several possible approaches towards introducing the piperidine ring (Scheme 1). The piperidine ring could be accessed directly by coupling of a piperidyl zinc halide with an aryl bromide[2] or by stepwise reaction of an aryllithium or aryl Grignard species with a protected piperidinone followed by elimination and hydrogenation or deoxygenation.[1a,3] Alternatively, we envisioned formation of the aryl–piperidine bond either by Suzuki coupling of the aryl bromide (or aryl boronate) and suitable partner[4] or by the reaction of the aryl Grignard with an acyl pyridinium ion.[5] Access to the piperidine ring by these methods would further involve reduction of the resulting double-bond(s). Commonly performed via hydrogenation, such reductions could become complicated by dehalogenation. In each case, initial exploration of the route hinged on preparation of 2-bromo-5-chlorobenzonitrile **2b**, preferably by selective bromination of inexpensive chlorobenzonitrile **2a** at the 6 position (Scheme 2). In just 2–4 steps, these methods, if successful, would afford nitrile and halogen-containing 4-arylpiperidines ready for further functionalization.

2. Results and discussion

2.1. Bromination of 3-chlorobenzonitrile

In each of the proposed routes to arylpiperidines **1**, 2-bromo-5-chloro benzonitrile **2b** is a key intermediate.

Keywords: Arylpiperidine; Dihydropyridine; Catalytic hydrogenation.
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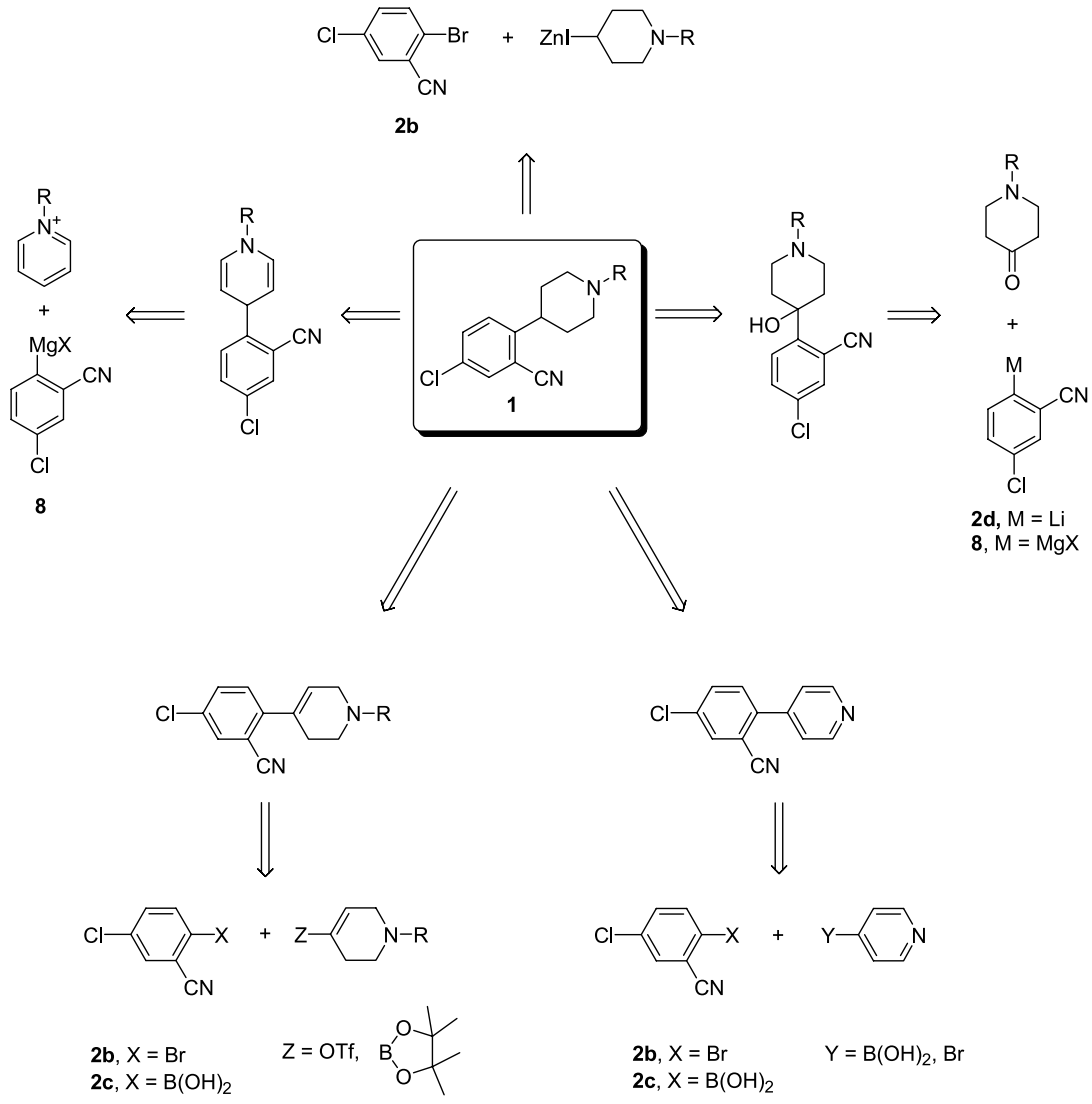
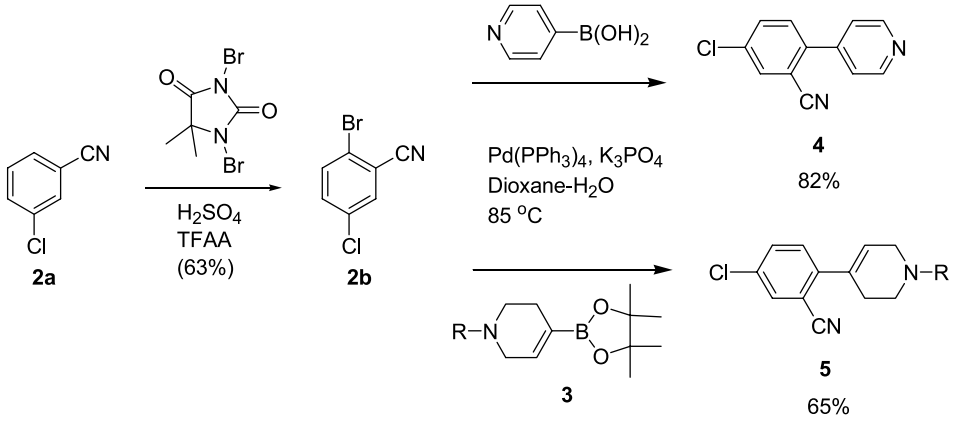


Scheme 1. Retrosynthetic analysis.



Scheme 2. Preparation and coupling of bromochlorobenzonitrile **2b**.

Preparations of this compound from 2-amino-5-chlorobenzonitrile via Sandmeyer reaction (formation of the diazonium salt and reaction with CuBr)[6] and from 2-bromo-5-chlorobenzoic acid via amide formation and dehydration[7] have been described. We desired a more direct synthesis using a readily available starting material and therefore decided to examine selective bromination of chlorobenzonitrile **2a**.[8] Using 1,3-dibromo-5,5-dimethylhydantoin (DBH) and H_2SO_4 in refluxing CH_2Cl_2, we obtained a 50% isolated yield of bromobenzonitrile **2b** after

crystallization. Attempts to improve the yield by varying solvent and brominating agent gave generally poor results, indicating that selective bromination could be affected only under a narrow range of conditions. Neat acids, however, emerged as the best solvents for the DBH bromination. The major by-products formed during the bromination were two mono-brominated regioisomers each occurring in approximately 10% and three dibrominated compounds, occurring in 3–4% each.[†]

An improved yield of 63% was obtained from reaction in trifluoroacetic acid with 1.3 equiv H_2SO_4.

2.2. Initial routes to arylpiperidine 1: Negishi and Suzuki coupling approaches

With the arylbromide in hand, we began investigation of the four potential routes to arylpiperidines **1**. We first attempted the most direct route: coupling of the arylbromide with 4-iodo-*N*-BOC-piperidyl zinc. Billotte has reported that coupling of a protected iodopiperidine with an unhindered aryl iodide provided 47% of the 4-arylpiperidine.[2] Unfortunately, employing these conditions did not provide the desired product. However, we demonstrated by direct quench with DCl/MeOD that the active zinc species was formed in solution. In addition, employing the commercially available cyclohexyl zincate with **2b** under the literature conditions provided the coupled product in 65% yield. Thus, we concluded that while the zinc reagent had been formed, and the conditions were competent with known zincate nucleophiles, the coupling was not a viable route to the desired compound.

An alternate route would be condensation of the aryllithium or aryl Grignard with a protected piperidinone. However, with our substrate, the reported literature methods for these condensations resulted in complex reaction mixtures and only trace amounts of desired product.[‡,1a,3]

We subsequently investigated the Suzuki reaction of the arylbromide **2b** with appropriate coupling partners including 4-pyridylboronic acid and boronate ester **3** (Scheme 2).[9] Coupling of bromide **2b** with pyridylboronic acid using $Pd(PPh_3)_4$ and K_3PO_4 in dioxane–H_2O at 85 °C resulted in a 82% yield of **4**. Under the same conditions, reaction of the boronate ester **3** with bromide **2b** afforded **5** in 65% yield. Due to the limited availability of the pyridyl boronic acid and boronate ester **3**,[10] we decided to switch the coupling partners (Scheme 3). Synthesis of boronic acid **2c** was performed by adding *n*-BuLi dropwise to a −70 °C solution of bromobenzonitrile **2b** and $B(O\text{-}i\text{-}Pr)_3$ in THF.[11] The isolated solid (69% yield) was used without further purification in coupling reactions with both 4-bromopyridine HCl and triflate **6**.[12] The bromopyridine coupling proved problematic as incomplete consumption of the arylbromide was observed even in the presence of 3 equiv of boronic acid. Reaction with triflate **6** exhibited similar limitations and gave the desired product in only moderate conversion under the unoptimized conditions.

Turning our attention to the hydrogenation of arylpyridine **4** and tetrahydropyridine **5**, we found that using the literature protocols[13] (PtO_2, Pd/C, Pt/C, Rh/C, $RhClPPh_3$ in solvents including MeOH, EtOH, AcOH/H_2O, with and without acid) 5–15% of the dechlorinated product **7** was always detected. The presence of this by-product in the reaction mixture complicated purification of the piperidines **1**. In addition, controlling the levels of these impurities as a function of increasing scale could become problematic. These results made clear to us the need for a method of installing the piperidine ring that would avoid highly reducing conditions and subsequent dechlorination.

2.3. Comins approach to arylpiperidine 1

Given the issues associated with the Suzuki approach outlined above, we next focused on construction of the dihydropyridine by reaction of an acyl pyridinium ion with aryl Grignard **8** (Scheme 4). The preparation of dihydropyridines by this method has been well documented by Comins[5,14] and precedent existed for reduction to the piperidine under milder conditions than needed for substrates **4** and **5**.[15] We envisioned that using milder reducing conditions might decrease or eliminate formation of the dechlorinated by-product and thereby facilitate recovery of **1**.

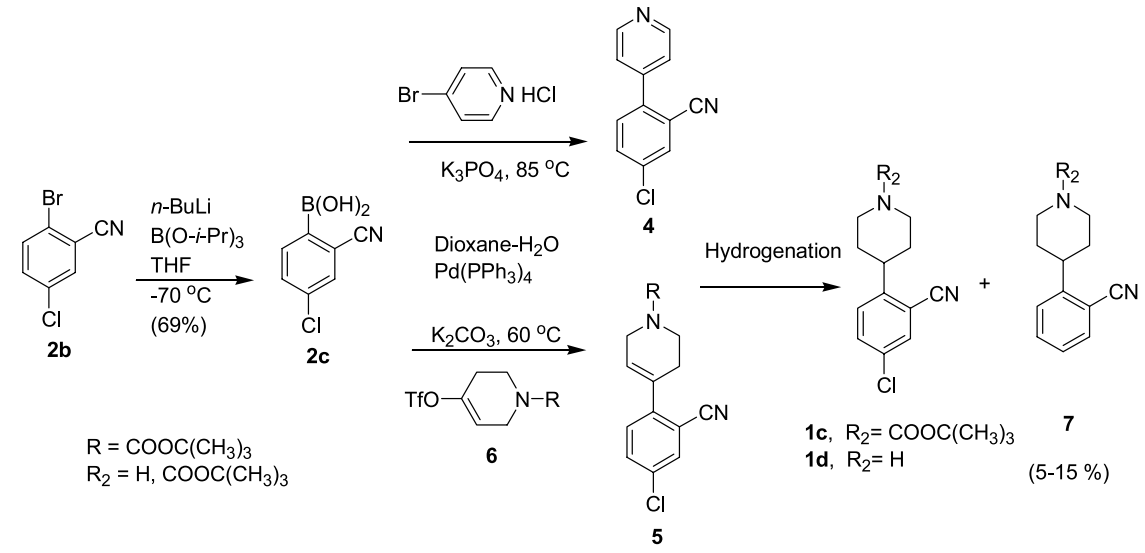
Formation of the aryl Grignard **8** was accomplished by addition of *i*-PrMgCl to bromobenzonitrile **2b** in THF at −20 °C. In parallel, the acyl pyridinium was formed by addition of either benzyl or phenyl chloroformate to a solution of pyridine and CuI (2 mol%) in THF at −10 °C. The aryl Grignard **8** was then transferred to the acyl pyridinium mixture and the reaction was allowed to warm to rt. In the course of probing this reaction, we found that Grignard **8** decomposes at temperatures above 0 °C. We also observed that maintaining an inert atmosphere was critical in preventing the formation of Ullmann dimerization product **10**. The resulting dihydropyridine **9** was formed in good yields although recovery via crystallization was not optimized (assay yield 70–80%, isolated yield 45–57%).[§]

Hydrogenation of the dihydropyridine to the piperidine proved to be highly sensitive to the reaction conditions. A screen of catalysts including Pd/C, PtO_2, Pt/C, $Pd/CaCO_3$, Ru/C activated, Rh/C, $Pd/BaSO_4$, and Rh/alumina resulted in either dechlorination or incomplete reaction. Interestingly, the intermediate isolated from incomplete reactions was monohydrogenated product **11** and we did not observe any isomerization of the double-bond to the more substituted position in conjugation with the aryl ring. Eventually we were able to reduce the dihydropyridine to the desired product **1** in 80–85% yield by using Wilkinson's catalyst ($RhCl(PPh_3)_4$) (10 mol%) in toluene at 70 °C,

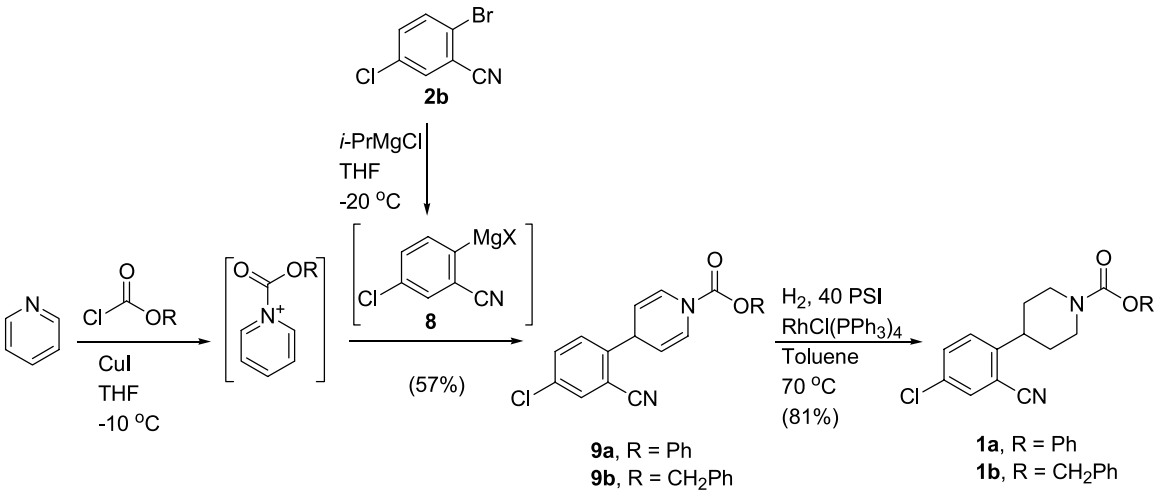
[†] Percents reported are liquid chromatograph area percents (LCAP).

[‡] Reaction conditions included use of aryl Grignard and aryllithium in THF and toluene, temperatures from −70 to 0 °C, and additives including TMEDA. We believe the complex mixtures are due in part to reaction at the nitrile as evidenced by absence of the nitrile signal in IR and ^{13}C NMR.

[§] The isolated yields are obtained using direct crystallization from the crude organic layer after the aqueous work-up. Higher yields can be obtained if column chromatography is performed after the aqueous extraction.



Scheme 3. Preparation and coupling of boronic acid **2c**; hydrogenation of coupling products **4** and **5**.



Scheme 4. Formation and hydrogenation of dihydropyridines **9** to prepare 4-arylpiperidines **1a**,**b**.

40 psi H_2. Under these conditions, the dechlorinated product was not detected. With this method, the phenyl and CBZ carbamate protected piperidines (**1a** and **1b**, respectively) could be obtained as crystalline solids in good yields after a simple silica gel filtration of the reaction mixture to remove $O(PPh_3)_3$ (Fig. 1).

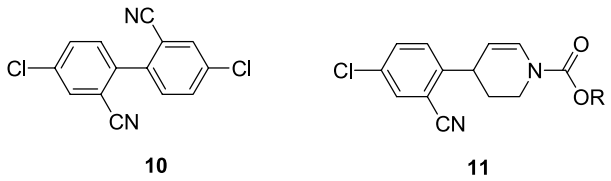
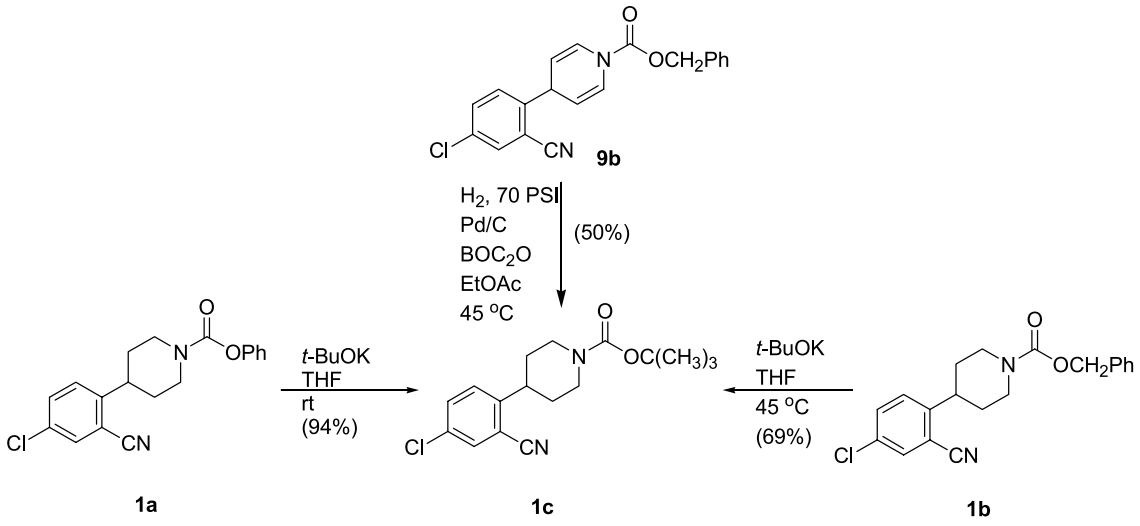


Figure 1. Dimer and monohydrogenated piperidine.

To increase the synthetic potential of **1**, we also needed access to the BOC protected piperidine. As the acyl pyridinium chemistry cannot be performed directly incorporating the BOC moiety, we synthesized the desired BOC protected piperidine from the CBZ and phenyl carbamates (Scheme 5). While CBZ to BOC transformation under hydrogenation conditions (H_2/Pd–C, $(BOC)_2O$) is well known,[16] it resulted in significant amounts of dechlorination and other by-products when attempted with piperidine **1b**. We next contemplated a stepwise approach, with combined hydrogenation of the dihydropyridine and removal of the CBZ group preceding subsequent BOC protection. Unfortunately, when we submitted dihydropyridine **9b** to hydrogenation (Pd/C(10%), H_2, EtOAc) the reaction gave almost exclusively dechlorination.

However, in the presence of BOC_2O, hydrogenation of dihydropyridine **9b** with Pd/C 10 wt%) 50% wet, H_2, in EtOAc gave minimal dechlorination and yielded BOC piperidine **1c** as the major product. The major by-product was monohydrogenated BOC compound. Screens of pressure, temperature, solvent, and catalyst loading failed to drive the reaction to completion, as did resubmission of



Scheme 5. Preparation of BOC protected 4-arylpiperidine **1c**.

the product mixture to reaction conditions.[¶] Under optimized conditions (1 equiv BOC_2O, 15 wt% catalyst, 70 psi H_2, 45 °C) **1c** was obtained in 50% yield after crystallization.

While this procedure was effective to replace the CBZ protecting group of the dihydropyridine, a different method was needed for the phenyl carbamate protecting group. In the literature, phenyl carbamate protected dihydropyridines have been treated with *t*-BuOK in THF to affect the desired protecting group switch.[17] However, in our hands, the dihydropyridine quickly oxidized to the corresponding pyridine when treated with *t*-BuOK. We found instead that the protective group switch could be efficiently performed on the fully hydrogenated piperidine. Adding 1.1 equiv of *t*-BuOK (1 M in THF) to a rt solution of phenyl carbamate protected piperidine **1a** in THF afforded BOC protected piperidine **1c** in 94% yield. We were delighted to find that by modifying the procedure to run at 45 °C in THF/hexanes we were also able to transform CBZ piperidine **1b** to BOC piperidine **1c** in 69% yield.

3. Conclusion

In conclusion, several routes towards the desired 4-aryl piperidines were investigated. The optimum route (Scheme 4) is a 3-step synthesis of **1** which involves selective bromination of 3-chlorobenzonitrile **2a** at the 6-position followed by reaction of the corresponding aryl Grignard with an acyl pyridinium under Cu(I) catalysis to form an *N*-protected dihydropyridine. The dihydropyridine can then be hydrogenated under mild conditions to produce the desired 4-arylpiperidines in 29% overall yield. Introduction of a BOC protecting group is possible in good yields in one step from either piperidines **1a**,**b** or dihydropyridine **9b**. The synthesis utilizes readily available and inexpensive starting materials (pyridine and 3-chlorobenzonitrile) and eliminates the dechlorination side product which often accompanies hydrogenation of unsaturated compounds **9**.

[¶] This suggests that reduction of the double bonds is occurring prior to BOC protection and we believe that steric hindrance prevents the reduction of the final double bond.

4. Experimental

4.1. General methods

Reagents and solvents were obtained from commercial suppliers and were used without further purification or drying unless otherwise noted. Chromatography was done on silica gel (70–230 mesh). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2,-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **3**,[11] *tert*-butyl 4 {[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2*H*)-carboxylate **6**,[13] were previously described in the literature.

4.1.1. Phenyl 4-(4-chloro-2-cyanophenyl)piperidine-1-carboxylate (1a). To a solution of **9a** (12.0 g, 35.6 mmol) in toluene (160 mL) was added $RhCl(PPh_3)_3$ (3.3 g, 3.6 mmol). The reaction mixture was submitted to H_2 (40 psi) and heated to 70 °C. After 8 h, the reaction stream was filtered through silica gel (100 g) and the silica gel was washed with 1:2 EtOAc/hexanes (800 mL). The filtrate was concentrated and solvent switched to toluene. Crystallization from 2:1 toluene/heptane followed by a wash of the filtercake (1:1 toluene/heptane) afforded a white solid (9.82 g, 81%). Mp 157–159 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, $J=2.2$ Hz, 1H), 7.57 (dd, $J=8.5$, 2.3 Hz, 1H), 7.40–7.32 (m, 3H), 7.23 (app t, $J=7.4$ Hz, 1H), 7.14 (dd, $J=8.4$, 1.2 Hz, 2H), 4.49 (br s, 2H), 3.24–2.93 (m, 3H), 1.96 (app d, $J=12.5$ Hz, 2H), 1.76 (dq, $J=12.4$, 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 151.3, 147.1, 133.5, 132.8, 132.5, 129.2, 127.8, 125.2, 121.6, 116.5, 113.4, 44.7, 44.4, 40.2, 32.5, 31.9; IR (thin film) 3065, 2934, 2858, 2228, 1722 cm^{-1}. Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 67.08; H, 4.86; N, 8.15.

4.1.2. Benzyl 4-(4-chloro-2-cyanophenyl)piperidine-1-carboxylate (1b). To a solution of **9b** (9.18 kg, 27.2 mol)

in toluene (55.3 kg) was added $RhCl(PPh_3)_3$ (2.42 kg, 2.5 mol) as a slurry in toluene (20 kg). The reaction mixture was submitted to H_2 (40 psi) and heated to 70 °C. After 6 h, the reaction stream was filtered through silica gel (27.5 kg) and the silica gel was washed with 1:9 EtOAc/toluene (84 L). The filtrate was solvent switched to toluene and concentrated to a volume of 18 L. Heptane (7.5 kg) was added to the rt solution. The solution was seeded and aged overnight. Additional heptane (41.8 kg) was added over 2 h. The resulting slurry was cooled to 0 °C, filtered, and the product cake washed with 1:4 toluene/heptane affording a yellow solid (7.1 kg, 81%). Mp 85–87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, J=2.2 Hz, 1H), 7.54 (dd, J=8.5, 2.2 Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (d, J=8.5 Hz, 1H), 5.17 (s, 2H), 4.37 (br s, 2H), 3.14 (tt, J=12.1, 3.5 Hz, 1H), 2.95 (br s, 2H), 1.87 (br d, J=12.3 Hz, 2H), 1.62 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1, 147.3, 136.6, 133.4, 132.7, 132.4, 128.4, 128.0, 127.9, 127.8, 116.5, 113.3, 67.1, 44.2, 40.3, 32.2; IR (thin film) 3065, 2934, 2844, 2221, 1695 cm^{-1}. Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; N, 7.89. Found: C, 67.56; H, 5.22; N, 7.71.

4.1.3. *tert*-Butyl 4-(4-chloro-2-cyanophenyl)piperidine-1-carboxylate (1c). *Method A*. To a solution of **1b** (3.27 kg, 9.2 mol) in hexanes (3 L) and THF (3 L) was added *t*-BuOK (1 M in THF, 28.0 L, 28.0 mol). The reaction was heated to 45 °C, aged 4 h, and then cooled to 5 °C. Water (14 L) and hexanes (28 L) were added and the mixture was stirred for 30 min. The aqueous layer was cut and the organic layer was washed twice with water (2×24 L). The organic layer was treated with Ecosorb C-941 (1.14 kg). After aging overnight, the mixture was filtered through Solka Floc followed by hexanes (3 L). The resulting solution was solvent switched to EtOH and concentrated to 14 L. Water (4.5 L) was added slowly and the resulting slurry was cooled to −10 °C and filtered. The filtercake was washed with 0 °C 2:1 EtOH/H_2O to afford, after drying, a yellow solid (2.22 kg, 69%).

Method B. To a heterogeneous mixture of **1a** (5.10 g, 15.0 mmol) in THF (17 mL) was added *t*-BuOK (1.0 M in THF, 15.0 mL, 15.0 mmol). After an overnight age and assay for completeness, *t*-BuOK (2.0 mL, 2.0 mmol) was added. After 5 h, 1 M NaOH (30 mL) was added and the resulting layers were separated. The organic layer was washed with 9 wt% NaCl (aq) (30 mL), dried over Na_2SO_4, and concentrated to afford an oil that solidified upon standing (4.54 g, 94%).

Method C. To a slurry of **9b** (5.0 g, 14.2 mmol) in EtOAc (150 mL) was added BOC anhydride (3.4 g, 15.5 mol). 50% wet 10% Pd/C (0.78 g, 15.6 wt%) was added and the mixture was aged at 45 °C under 70 psi of H_2 for 8 h. The solution was cooled to rt, filtered through Solka Floc, and solvent switched to MeOH. After addition of 2:1 MeOH/H_2O and an overnight age the resulting slurry was filtered. The solid was recrystallized from heptane yielding 2.26 g (50%). Mp 97–99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, J=2.2 Hz, 1H), 7.55 (dd, J=8.6, 2.2 Hz, 1H), 7.29 (d, J=8.6 Hz, 1H), 4.28 (br s, 2H), 3.11 (tt, J=12.2, 3.5 Hz, 1H), 2.87 (app t, J=12.0 Hz, 2H), 1.85 (app d, J=13.1 Hz, 2H), 1.66–1.54 (m, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 147.5, 133.3, 132.5, 132.4, 127.8, 116.5, 113.3, 79.6, 43.9, 40.4, 32.2, 28.3; IR (thin film) 3072, 2975, 2929, 2858, 2235, 1681 cm^{-1}. Anal. Calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.85; H, 6.49; N, 8.60.

4.1.4. 2-Bromo-5-chlorobenzonitrile (2b). To a solution of 3-chlorobenzonitrile (50 g, 360 mmol) in trifluoroacetic acid (180 mL) was added sulfuric acid (24 mL) and then 1,3-dibromo-5,5-dimethylhydantoin (67 g, 234 mmol) in portions over 8 min. The reaction temperature was allowed to reach 31 °C and then cooling was applied to bring the temperature to 24 °C. After a 6 h age the heterogeneous reaction was cooled to 10 °C and water (250 mL) was added. Following a 10 min ages, the reaction was filtered and the product cake was washed twice with water (250 and 100 mL) to afford a white solid (52.4 g, 63%). Mp 137–140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.62 (m, 2H), 7.44 (dd, J=8.6, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.2, 134.1, 133.9, 133.8, 123.3, 117.2, 115.8; IR (thin film) 3086, 3052, 2228 cm^{-1}. Anal. Calcd for C_7H_3BrClN: C, 38.84; H, 1.40; N, 6.47. Found: C, 38.64; H, 1.18; N, 6.35.

4.1.5. (4-Chloro-2-cyanophenyl)boronic acid (2c). To a −72 °C heterogeneous mixture of **2b** (1.5 g, 6.9 mmol) and triisopropyl borate (1.9 mL, 8.3 mmol) in THF (40 mL) was added *n*-BuLi (2.5 M in hexanes, 2.9 mL, 7.2 mmol) at a rate such that the temperature <-69 °C. The reaction was aged 20 min, allowed to warm to −20 °C and quenched with 1 M HCl (40 mL). EtOAc was added (20 mL), the aqueous layer was cut and the organic layer extracted with 1.25 M NaOH (2×50 mL). The aqueous extracts were combined and EtOAc (75 mL) was added. HCl (2 M) was added until the pH=4.8. The layers were separated and the organic was concentrated to give a pale yellow solid (0.86 g, 69%). The solid decomposes above 285 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.77 (d, J=1.8 Hz, 1H), 7.70 (d, J=8.1 Hz, 1H), 7.65 (dd, J=8.2, 1.9 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 135.5, 135.3, 132.2, 131.7, 117.8, 117.1, the boron bearing carbon is not observed due to signal broadening; IR (thin film) 3356, 2927, 2234 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_7H_5BClNO_2$ 181.0216 (M+H), found 181.0219 (M+H).

4.1.6. 5-Chloro-2-pyridin-4-ylbenzonitrile (4). A flask under N_2 was charged with 2-bromo-5-chlorobenzonitrile **2b** (2.1 g, 9.6 mmol), pyridine-4-boronic acid (2.0 g, 16.3 mmol), K_3PO_4 (4.7 g, 22.1 mmol), $Pd(PPh_3)_4$ (0.55 g, 0.5 mmol), dioxane (90 mL), and H_2O (18 mL). The reaction mixture was heated to 85 °C. A second charge of pyridine-4-boronic acid (0.1 g, 0.8 mmol) was added after 5 h. After 6 h, the reaction mixture was cooled to rt. Saturated $NaHCO_3$(aq) (80 mL) and EtOAc (90 mL) were added and the resulting layers were separated. The aqueous layer was extracted with EtOAc (40 mL) and the combined organic layers were dried over Na_2SO_4. The organic layer was concentrated to a golden oil. Purification by silica gel chromatography (2:1 EtOAc/hexanes to 100% EtOAc) afforded the product as an off-white solid (1.69 g, 82%). Mp 143–145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (dd, J=4.5, 1.7 Hz, 2 H), 7.79 (d, J=2.1 Hz, 1H), 7.68 (dd, J=8.4, 2.1 Hz, 1H), 7.49–7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 144.4, 140.7, 135.3, 133.50, 133.48,

131.0, 123.0, 116.5, 112.5; IR (thin film) 3350, 3065, 2228, 1598 cm^{-1}. Anal. Calcd for $C_{12}H_7ClN_2$: C, 67.15; H, 3.29; N, 13.05. Found: C, 67.04; H, 2.96; N, 12.86.

4.1.7. *tert*-Butyl 4-(4-chloro-2-cyanophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (5). A flask under N_2 was charged with 2-bromo-5-chlorobenzonitrile **2b** (0.9 g, 4.2 mmol), boronate **3** (1.7 g, 5.6 mmol), K_3PO_4 (1.8 g, 8.4 mmol), $Pd(PPh_3)_4$ (0.24 g, 0.2 mmol), dioxane (60 mL), and H_2O (15 mL). The reaction mixture was heated to 85 °C. After 21 h, the reaction mixture was cooled to rt. Purification of the concentrated reaction mixture by silica gel chromatography (1:3 CH_2Cl_2/Hex) afforded the product as a pale yellow oil that solidified upon standing (0.87 g, 65%). Mp 93–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J=2.2 Hz, 1H), 7.52 (dd, J=8.4, 2.4 Hz, 1H), 7.27 (d, J=8.4, 1H), 6.00 (br s, 1H), 4.10 (d, J=2.8 Hz, 2H), 3.66 (t, J=5.6 Hz, 2H), 2.53–2.48 (m, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 144.4, 133.2, 133.1, 132.93, 132.90, 129.4, 126.9, 117.2, 111.7, 79.9, 43.5, 39.5, 28.8, 28.4; IR (thin film) 2968, 2228, 1688 cm^{-1}. Anal. Calcd for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79. Found: C, 64.33; H, 5.88; N, 8.61.

4.1.8. Phenyl 4-(4-chloro-2-cyanophenyl)pyridine-1(4*H*)-carboxylate (9a). General procedure for dihydropyridines. To a −30 °C solution of **2b** (835 g, 3.86 mol) in THF (10 L) was added *i*-PrMgCl (1.71 M in THF, 2.5 L, 4.25 mol) at a rate such that the temperature <-20 °C. Meanwhile, to a −10 °C solution of CuI (36 g, 190 mmol) in THF (10 L) was added pyridine (624 mL, 7.72 mol) and then phenyl chloroformate (532 mL, 4.25 mmol) such that the temperature <0 °C. To this heterogeneous mixture was added the previously formed Grignard at a rate such that temperature <0 °C. The resulting solution was aged at 0 °C for 30 min and allowed to warm up to rt. The reaction was then quenched with 10% aqueous NH_4Cl (20 L). EtOAc (20 L) was added and the blue aqueous layer was removed. The organic layer was washed with 10% aqueous NH_4Cl (20 L), 1 N HCl (20 L), and finally an aqueous 20% NaCl solution (20 L). The organic layer was then concentrated, solvent switched to MeOH and crystallized. The slurry was filtered and the filtercake washed with MeOH, yielding an off-white solid (584 g, 43%). Mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.59 (m, 2H), 7.50 (d, J=8.4 Hz, 1H), 7.41 (app t, J=7.8 Hz, 2 H), 7.27 (t, J=7.2 Hz, 1H), 7.20–7.11 (m, 4H), 5.05 (br d, J=15.5 Hz, 2H), 4.70 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5, 149.7, 146.9, 133.7, 133.1, 132.3, 131.2, 129.5, 126.1, 123.7, 123.4, 121.4, 116.3, 112.3, 107.9, 107.3, 36.9; IR (thin film) 3065, 2228, 1736, 1688 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H^{13}ClN_2O_2$ 337.0744 (M+H), found 337.0740 (M+H).

4.1.9. Benzyl 4-(4-chloro-2-cyanophenyl)pyridine-1(4*H*)-carboxylate (9b). The general procedure for dihydropyridines was followed, using **2b** (5.71 kg, 26.4 mol), THF (114 L) and *i*-PrMgCl (1.74 M in THF, 23.9 L, 41.6 mol), CuI (250 g, 1.31 mol), THF (114 L), pyridine (4.25 L, 52.5 mol) and benzylchloroformate (5.83 L, 40.9 mol), 10% aqueous NH_4Cl (55 L), MTBE (55 L), 10% aqueous NH_4Cl (55 L), 1 N HCl (55 L), and finally an aqueous 5% $NaHCO_3$/5% NaCl solution (55 L). The organic layer was then concentrated, solvent switched to MeOH, and further concentrated to 60 L. The solution was aged and the resulting slurry was cooled to 0 °C, filtered and the filtercake washed with MeOH to afford an off-white solid (5.31 kg, 57%). Mp 98–100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, J=2.2 Hz, 1H), 7.57 (dd, J=8.5, 2.2 Hz, 1H), 7.44–7.35 (m, 6H), 7.01 (br d, J=44.4 Hz, 2H), 5.27 (s, 2H), 4.93 (br d, J=36.4 Hz, 2H), 4.65–4.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.0, 147.2, 135.2, 133.6, 133.0, 132.1, 131.2, 128.6, 128.5, 128.3, 123.8, 123.3, 116.3, 112.1, 107.0, 106.5, 68.4, 36.8; IR (thin film) 3058, 2955, 2221, 1729, 1681 cm^{-1}. Anal. Calcd for $C_{20}H_{15}ClN_2O_2$: C, 68.48; H, 4.31; N, 7.99. Found: C, 68.32; H, 4.12; N, 7.89.

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Supplementary data

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