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Direct Synthesis of 4-Arylpiperidines via Palladium/Copper(I)-Cocatalyzed Negishi Coupling of a 4-Piperidylzinc Iodide with Aromatic Halides and Triflates

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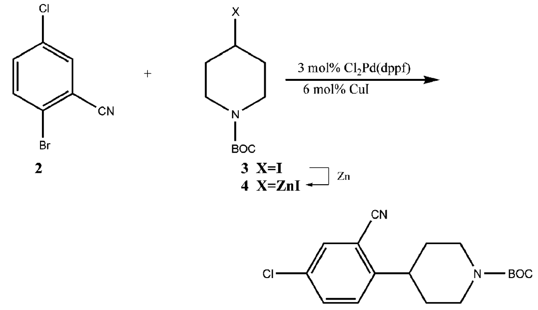
Abstract: A general procedure for the synthesis of 4-arylpiperidines via the coupling of 4-(*N*-BOC-piperidyl)zinc iodide with aryl halides and triflates is presented. The reaction requires cocatalysis with both $Cl_2Pd(dppf)$ and a copper(I) species. An improved, safer procedure for the activation of zinc dust is also presented.

The 4-arylpiperidine moiety is a structural feature which can be found in a wide variety of active pharmacologic agents.[1] Previously reported synthetic methods for their preparation include addition of an aryl Grignard to an N-protected piperidone followed by elimination and reduction.[2] Another protocol utilizes a copper-catalyzed coupling of aryl Grignards with an acylpyridinium species[3] followed by hydrogenation of the resulting dihydropyridine. Coupling of the enol triflate of *N*-BOC-piperidin-4-one with arylboronic acids[4a,b] and esters,[4c] stannanes,[4d] and aryl zinc chlorides[4e] provides the mono-unsaturated piperidine which can also be reduced to the desired saturated piperidine. These methods are somewhat limited by several issues including compatibility of functional groups with the Grignard reagents and sensitivity to reductive conditions. We recently required a scalable synthesis of **1**, an intermediate in an ongoing drug development program. The aforementioned Grignard coupling chemistry with an acylpyridinium (Comins reaction) was employed to make this intermediate.[5] While this allowed the preparation of kilogram quantities of the desired intermediate, it required multiple steps of moderate yield and use of the CBZ protecting group which then had to be converted to the BOC group before proceeding with subsequent chemistry.

Since a direct coupling of 2-bromo-5-chlorobenzonitrile (**2**) with 4-piperidylzinc iodide (**4**) was envisioned as a very efficient route to **1**, we decided to investigate this route toward the desired compound. An initial attempt at coupling the **4** with **2** using literature conditions ($Pd_2(dba)_3$, $P(2\text{-furyl})_3$) gave no reaction. However, it was demonstrated that the active zinc species had been formed from deuterium quenching experiments. Thus, we concluded that while the active species was present in solution, the metal mediated transfer was retarded. As a result, we set out to investigate this coupling and utilizing various palladium sources and cocatalysts. In this paper, we report the results of these studies along with a general and efficient protocol for the copper-cocatalyzed coupling of aryl bromides with alkylzinc reagents.



2

3 X=I

4 X=ZnI

1

The desired aryl bromide **(2)** was obtained by electrophilic bromination of 3-chlorobenzonitrile as previously reported.[5] 4-Iodo-1-BOC-piperidine **(3)** was obtained by iodination of 4-hydroxy-*N*-BOC-piperidine with iodine/triphenylphosphine.[6a] The zinc was activated by a modification of the Knochel procedure[6a,b] in which the zinc dust in dimethylacetamide (DMA) was treated with a 7/5 (v/v) mixture of chlorotrimethylsilane and 1,2-dibromoethane. In the literature procedure, the dibromoethane is added first, warmed briefly to 60 °C, cooled back to rt, and then treated with chlorotrimethylsilane. In our hands, we found that (in DMA) the dibromoethane often did not react with the zinc until the chlorotrimethylsilane was added. It would then react all at once giving a rather large exotherm and copious ethane release which, on a large scale, presented significant safety concerns. We found that premixing the activators provided a smoother, safer activation protocol. Addition of the premixed solu-

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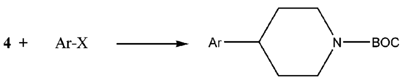
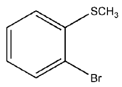
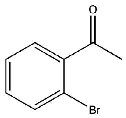
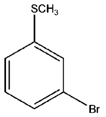
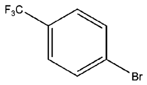
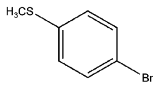
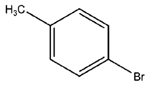
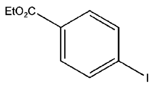
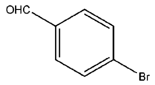
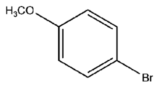
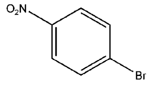
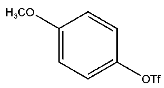
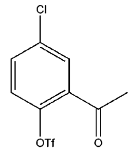
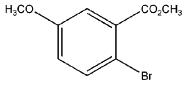
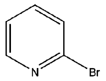
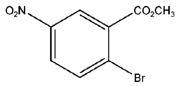
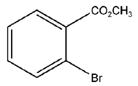
10.1021/jo049647i CCC: $27.50

TABLE 1. Coupling of 4 with Aryl Halides and Triflates



Ar-X	Assay Yield[a]	Product	Ar-X		Assay Yield[a]	Product
	62%	**5**[d]			88%	**12**
	85%	**6**			84%	**13**
	90%	**7**			66%	**14**[d]
 **21**	97%	**8**			99%	**15**
	38%	**9**[d]			88%[b]	**16**
	41%	**9**[d]	 **20**	note c	63%	**17**
	81%	**10**			97%	**18**
	60%	**11**			92%	**19**

[a] Assay yield of the coupled piperidine determined by HPLC using purified standards of the desired product. [b] Reaction complete in 0.5 h at 23 °C. [c] Prepared from the corresponding phenol (ref 10). [d] 6 mol % $Cl_2Pd(dppf)$; 12 mol % CuI used.

tion resulted in an exotherm after ca. 10−15% of the solution charge which was readily controlled by the rate of addition of the remainder of the activator solution. The resulting zinc slurry reacted exothermically with a gradually added solution of iodide **3** in DMA to provide the desired alkylzinc species. After filtration[7] of unreacted zinc metal, the resulting solution was stable at 22 °C under N_2 for >6 months.

With a reliable protocol for zinc insertion in hand, we next turned our attention to the palladium-catalyzed coupling. Since our initial attempts at coupling of **4** with the hindered aryl bromide **2** were unsuccessful, we tried the reaction with $Cl_2Pd(dppf)$, a catalyst known to be particularly suited for this type of coupling,[8] but only a trace of desired product was obtained. The literature had indicated that a similar coupling[6a] of **4** with the unhindered aryl iodide **21** proceeded, although in moderate (47%) yield. We next tried adding copper(I) iodide to the reaction mixture since it has been reported to have a significant rate-enhancing effect on some related cross-coupling reactions.[9−10] This proved to have a dramatic effect on the progress of this reaction. The reaction proceeded to completion overnight at 65 °C in THF. By using DMA in place of THF and running the reaction at 80 °C, the reaction was complete in 2−3 h. It should be noted that simply modifying the original conditions of $Pd_2(dba)_3$, $P(2\text{-furyl})_3$, even in the presence of copper iodide provided only 35% conversion after 16 h at 80 °C.

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(7) It is useful to remove the unreacted zinc dust from the zinc reaction mixture. The zinc metal undergoes a redox reaction with copper(I) to give copper(0) and zinc(I) resulting in a deficiency of copper(I) necessary for reaction. This could also be overcome by the use of a larger excess of copper iodide to make up for the amount lost to the redox reaction with zinc. Some fine white solids also form, possibly zinc hydroxide from extraneous water, which can slow the filtration process. The zinc activation/insertion can be performed in the presence of CelPure P-65, a pharmaceutical grade filter agent, to aid in the filtration of the zinc/zinc hydroxide mixture if desired.

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Optimization of reaction parameters showed that performing the reaction in DMA at 80 °C with 3 mol % $Cl_2Pd(dppf)$ and 6 mol % copper(I) iodide gave complete reaction in <2 h. Reductive homocoupling of the aryl bromide to form the symmetrical biphenyl was a minor byproduct (ca. 2%).

A variety of other aryl halides and triflates were examined to determine the scope of the reaction (Table 1). Copper(I) thiocyanate may be substituted for copper iodide with equivalent results. The procedure appears to have general utility, although as expected, electron-rich substrates tended to give decreased yields and require a higher catalyst loading presumably due to a slower rate of oxidative insertion of the palladium(0) active catalyst (entries 5, 9, 14, and 15).

In conclusion, an improved method for the direct synthesis of 4-arylpiperidines has been developed. The method is compatible with a wide variety of sensitive functional groups including aldehydes, ketones, and esters. We have not attempted to extend this reaction to other saturated heterocyclic zinc reagents at this time. (For a discussion of the coupling of alkylzinc reagents with aryl halides, see Weichert.[9b]) The combination of $Cl_2Pd(dppf)$ and a copper(I) species is critical for a successful reaction especially with hindered halides. The method is amenable to scale-up (it has been run on a 160 mol scale). Additionally, a stock solution of **4** can be used to readily produce a wide variety of Boc-protected 4-arylpiperidines. Since the Boc group is stable to many subsequent transformations, yet can be readily removed with HCl, this method is of general utility for the synthesis of many biologically active piperidine containing substrates.

Experimental Section

All NMR data is 400 MHz ^{1}H, 100 MHz ^{13}C in $CDCl_3$. All aryl substrates are from commercial suppliers with the exception of **2** and **20**. DMA (dimethylacetamide) was dried over 3 Å molecular sieves to <200 μg/mL of H_2O as determined by Karl Fischer titration, prior to use.

***tert*-Butyl 4-Iodopiperidine-1-carboxylate (3).** Imidazole (9.84 g, 145 mmol), triphenylphosphine (37.93 g, 145 mmol), and *N*-BOC-piperidin-4-ol (25 g, 120.5 mmol) were combined in 62.5 mL of THF and cooled in an ice bath to 2−3 °C. A freshly prepared solution of iodine (36.7 g, 145 mmol) in 62.5 mL of THF was then added dropwise maintaining the internal temperature below 12 °C. After the addition was complete, the reaction was allowed to warm to room temperature and aged for 6 h. The reaction was then cooled to 8 °C, and 20 mL of 10 wt % $NaHSO_3$ was added in one portion. *n*-Heptane (125 mL) was added and the mixture transferred to a separatory funnel. The bottom layer was cut and then back-extracted with 125 mL of *n*-heptane. The combined organic layers were washed with 75 mL of water. The organic layer was solvent-switched to ethanol to a final product concentration of 330−340 g/L. The ethanol solution was cooled to 0 °C, and 22.5 mL of water was added dropwise. The solution was seeded with 0.1 wt % dry seed and then aged until a thin slurry formed. An additional 67.5 mL of water was added dropwise and the slurry aged at −5 °C for 1 h. The solids were filtered, washed with precooled 1:1 ethanol/water, and then dried in vacuo to give 31 g of **3** as a white, crystalline solid (83% yield): mp 47−48 C; NMR δ ^{1}H 4.43 (m, 1H), 3.57 (dt, $J = 3.6$, 13.6 Hz, 2H), 3.26 (dt, $J = 6.0$, 3.6 Hz, 2H), 2.01 (m, 4H), 1.44 (s, 9H); ^{13}C 154.5, 79.6, 43.6, 37.2, 28.3, 27.6. Anal. Calcd for $C_{10}H_{18}INO_2$: C, 38.60; H, 5.83; N, 4.50. Found: C, 38.61; H, 5.71; N, 4.46.

(1-*tert*-Butoxycarbonylpiperidin-4-yl)(iodo)zinc (4). Zinc activation. Into a 100 mL round-bottom flask was charged dry DMA (10.4 mL), zinc dust (4.22 g, 64.5 mmol), and Celpure P65 (0.83 g). The mixture was stirred at 20−25 °C while the 7:5 v/v mixture of TMS-Cl/1,2-dibromoethane (1.25 mL) was added at a rate to maintain the temperature below 65 °C (5−10 min at this scale). The resulting slurry was aged for 15 min.

Zinc Insertion. A solution of **3** (16.5 g, 52 mmol) in DMA (26 mL) was slowly added to the mixture described above at a rate to maintain a temperature <65 °C. The resulting mixture was then aged for 30 min while slowly cooling to rt. The reaction was monitored by GC/MS by quenching an aliquot into DCl/MeOD. The starting iodide was typically completely consumed, and deuterium incorporation (mass 186) could be used as an indicator of active zinc species. The mixture was then transferred via cannula to an air-free sintered Schlenk funnel to remove all solids. The resulting solution (ca. 1 M) could be stored at room temperature under nitrogen until needed for the coupling reaction.

2-(1-*tert*-Butoxycarbonylpiperidin-4-yl)-5-chlorobenzonitrile (1). Into a 500 mL flask were charged 2-bromo-5-chlorobenzonitrile (8.04 g, 37 mol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)−dichloromethane complex (0.908 g, 1.11 mmol), cuprous iodide (0.423 g, 2.22 mmol), and DMA (52 mL). The resulting mixture was degassed with alternating vacuum/nitrogen purges. The filtered piperidylzinc iodide solution (52 mmol, prepared as described above) was then added. The mixture was degassed one more time and then heated to 80 °C. The reaction was aged at that temperature until the starting benzonitrile had been consumed (1−5 h). The reaction mixture was then cooled to 20 °C and treated with MTBE (methyl *tert*-butyl ether, 130 mL) and 1 N ammonium chloride (130 mL). The mixture was stirred at 20−30 °C for 30 min and then filtered through Solka Floc to remove solids. The lower aqueous layer was drawn off, and the remaining organic layer was treated with saturated aqueous NH_4Cl (50 mL) and stirred for 30 min. After settling, the lower aqueous layer was removed and the organic layer was collected. The resulting MTBE solution was treated with Ecosorb C-941 (5.35 g) and stirred for 30 min. The mixture was then filtered through a small pad of SolkaFloc. The cake was washed with MTBE (25 mL). The solvent was evaporated, and the residue was treated with absolute ethanol (40 mL). The ethanol solution was treated with water (10 mL) and aged for 30 min at 20 °C to allow the product to begin crystallizing. An additional 6 mL of water was then added slowly, and the mixture was cooled to −12 °C, aged for 1 h, and filtered. The cake was washed with cold, 2:1 ethanol/water (15 mL) and sucked dry under a nitrogen stream to give 8.80 g of **1** as a light yellow solid (74% yield). An analytical sample was prepared by recrystallization from ethanol with a 50 wt % EcoSorb C-941 treatment: white solid; mp 105−108 °C; NMR ^{1}H δ 7.59 (d, $J = 2.0$ Hz, 1H), 7.52 (d of d, $J = 8.8$, 2.4 Hz, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 4.27 (broad d, $J = 13.6$ Hz, 2H), 3.10 (t of t, $J = 12.4$, 3.6, 1H), 2.85 (m, 2H), 1.83 (d, $J = 13.2$ Hz, 2H), 1.60 (q of d, $J = 12.4$, 2.0 Hz, 2H), 1.47 (s, 9H); ^{13}C 154.6, 147.6, 133.4, 132.6, 132.4, 127.8, 116.5, 113.3, 79.6, 43.9, 40.4, 32.3, 28.3. Anal. Calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.72; H, 6.47; N, 8.64.

General Procedure for Coupling. The experimental procedure as described for **1** through the ammonium chloride washes was used for the remainder of examples. The MTBE was then evaporated and the residue chromatographed on silica gel, eluting with 3:1 hexanes/ethyl acetate. The purified product was then used as a standard to determine reaction yield by HPLC.

***tert*-Butyl 4-[2-(methylthio)phenyl]piperidine-1-carboxylate (5):** white solid; mp 59−61 °C; 62% assay yield; NMR ^{1}H δ 7.20 (m, 4H), 4.26 (br m, 2H), 3.14 (tt, $J = 12.4$, 3.6 Hz, 1H), 2.85 (t, $J = 12.4$ Hz, 2H), 2.47 (s, 3H), 1.83 (d, $J = 13.0$ Hz, 2H), 1.59 (qd, $J = 13.0$, 4.0 Hz, 2H), 1.49 (s, 9H); ^{13}C 154.8, 143.3, 136.6, 126.7, 125.9, 125.6, 125.3, 79.3, 44.4, 38.8, 32.1, 28.4, 16.0. Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.46; H, 8.27; N, 4.52

***tert*-Butyl 4-[3-(methylthio)phenyl]piperidine-1-carboxylate (6:** white solid; mp 54−55 °C; 85% assay yield; NMR ^{1}H

δ 7.25 (m, 1H), 7.11 (m, 2H), 6.98 (m, 1H), 4.24 (br m, 2H), 2.79 (t, $J = 12.4$ Hz, 2H), 2.62 (tt, $J = 12.4$, 3.6 Hz, 1H), 2.49 (s, 3H), 1.81 (d, $J = 13.0$ Hz, 2H), 1.62 (qd, $J = 13.0$, 4.4 Hz, 2H), 1.49 (s, 9H); ^{13}C 154.7, 146.4, 138.4, 128.9, 125.1, 124.4, 123.5, 79.4, 44.2, 42.6, 33.0, 28.4, 15.7. Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.57; H, 8.32; N, 4.55.

***tert*-Butyl 4-[4-(methylthio)phenyl]piperidine-1-carboxylate (7):** white solid; mp 80−81 °C; 90% assay yield; NMR ^{1}H δ 7.22 (m, 2H), 7.13 (m, 2H), 4.24 (br m, 2H), 2.79 (t, $J = 12.4$), 2H), 2.61 (tt, $J = 12.4$, 3.6, 1H), 2.47 (s, 3H), 1.80 (d, $J = 12.8$, 2H), 1.59 (qd, $J = 12.4$, 4.0, 2H), 1.49 (s, 9H); ^{13}C 154.7, 154.7, 142.8, 135.9, 127.2, 127.0, 79.3, 44.3, 42.1, 33.1, 28.4, 16.1. Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.51; H,8.25, N, 4.39.

***tert*-Butyl 4-[4-(ethoxycarbonyl)phenyl]piperidine-1-carboxylate (8):** colorless oil; 97% assay yield; NMR ^{1}H 7.97 (m, 2H), 7.25 (m, 2H), 4.35 (q, $J = 6.80$ Hz, 2H), 4.25 (br m, 2H), 2.79 (t, $J = 12.4$ Hz, 2H), 2.69 (tt, $J = 12.4$, 3.6 Hz, 1H), 1.81 (d, $J = 12.8$ Hz, 2H), 1.62 (qd, $J = 12.8$, 4.0 Hz, 2H), 1.47 (s, 9H), 1.37 (t, $J = 6.8$ Hz, 3H); ^{13}C: 166.3, 154.7, 150.8, 129.7, 128.6, 126.7, 79,4m 60.7, 44.1, 42.7, 32.8, 28.4, 14.2. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.35; H, 8.30; N, 4.20.

***tert*-Butyl 4-(4-methoxyphenyl)piperidine-1-carboxylate (9):** white solid; mp 36−38 °C; 38% assay yield; NMR ^{1}H δ 7.13 (m, 2H), 6.86 (m, 2H), 4.23 (br m, 2H), 3.79 (s, 3H), 2.79 (t, $J =$ 12.4 Hz, 2H), 2.60 (tt, $J = 12.4$, 3.6 Hz), 1H), 1.80 (d, $J = 13.0$ Hz, 2H), 1.58 (qd, $J = 13.0$, 3.6 Hz, 2H), 1.49 (s, 9H); ^{13}C 158.0, 154.8, 137.9, 127.5, 113.8, 79.3, 55.1, 44.4, 41.7, 33.3, 28.4. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81; O, 16.47. Found: C, 70.09; H, 8.73; N, 4.81.

***tert*-Butyl 4-[4-methoxy-2-(methoxycarbonyl)phenyl]piperidine-1-carboxylate (10):** colorless oil; 81% assay yield; NMR ^{1}H δ 7.30 (d, $J = 2.8$, 1H), 7.24 (d, $J = 8.8$ Hz, 1H), 7.00 (dd, $J = 8.8$, 2.8 Hz, 1H), 4.22 (br d, $J = 13.2$ Hz, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.44 (tt, $J = 12.0$, 3.2 Hz, 1H), 2.81 (m, 2H), 1.79 (d, $J = 10.8$ Hz, 2H), 1.57 (qd, $J = 12.4$, 2.0 Hz, 2H), 1.48 (s, 9H); ^{13}C 168.1, 157.2, 154.8, 138.8, 130.4, 127.8, 118.1, 114.8, 79.2, 55.3, 52.0, 44.5, 37.7, 33.2, 28.4. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.32; H, 7.88; N, 4.06.

***tert*-Butyl 4-[2-(methoxycarbonyl)-4-nitrophenyl]piperidine-1-carboxylate (11):** white solid; mp 90−91.5 °C; 60% assay yield; NMR ^{1}H δ 8.68 (d, $J = 2.8$ Hz, 1H), 8.30 (dd, $J =$ 8.8, 2.4 Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 4.27 (br d, $J = 12.8$ Hz, 2H), 3.97 (s, 9H), 3.69 (tt, $J = 12.0$, 3.2 Hz, 1H), 2.85 (m, 2H), 1.84 (bd, $J = 13.2$ Hz, 2H), 1.63 (qd, $J = 8.4$, 4.0 Hz, 2H), 1.48 (s, 9H); ^{13}C 166.1, 154.6, 154.2, 145.8, 130.7, 128.2, 126.3, 125.6, 79.6, 52.6, 44.1, 38.6, 32.7, 28.4. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.41; H, 6.48; N, 7.63.

***tert*-Butyl 4-(3-acetylphenyl)piperidine-1-carboxylate (12):** white solid; mp 67−69 °C; 95% assay yield (80% isolated by silica gel chromatography); NMR ^{1}H δ 7.77−7.83 (m, 2H), 7.40−7.43 (m, 2H), 4.27 (d, $J = 12.8$ Hz, 2H), 2.81 (m, 2H), 2.72 (tt, $J = 12.4$, 3.6 Hz), 2.60 (s, 3H), 1.84 (d, $J = 13.2$ Hz, 2H), 1.65 (qd, $J = 12.4$, 4.4 Hz, 2H), 1.49 (s, 9H); ^{13}C 198.1, 154.7, 146.2, 137.3, 131.5, 128.7, 126.5, 126.4, 79.4, 44.2, 42.5, 33.0, 28.4, 26.6. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.32; H, 8.30; N, 4.62.

***tert*-Butyl 4-[4-(trifluoromethyl)phenyl]piperidine-1-carboxylate (13):** colorless oil; 84% assay yield; NMR ^{1}H 7.57 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 4.27 (br m, 2H), 2.82 (t, $J = 12.4$ Hz, 2H), 2.72 (tt, $J = 12.4$, 3.6 Hz, 1H), 1.83 (d, $J = 12.8$ Hz, 2H), 1.63 (qd, $J = 12.8$, 4.0 Hz, 2H), 1.49 (s, 9H); ^{13}C 154.8, 149.7, 128.6 (q, $J_{CF} = 32.0$ Hz), 127.1, 125.4 (q, $J_{CF} =$ 3.2 Hz), 124.2 (d, $J_{CF} = 271.5$ Hz), 79.6, 44.1, 42.6, 32.9, 28.4. Anal. Calcd for $C_{17}H_{22}F_3NO_2$: C, 61.99; H, 6.73; N, 4.25. Found: C, 62.16; H, 6.59; N, 4.29.

***tert*-Butyl 4-(4-methylphenyl)piperidine-1-carboxylate (14):** colorless oil; 66% assay yield; NMR ^{1}H δ 7.12 (m, 4H), 4.24 (m, 2H), 2.80 (td, $J = 13.0$, 2.4 Hz, 2H), 2.61 (tt, $J = 12.0$, 3.6 Hz, 1H), 2.33 (s, 3H), 1.81 (bd, $J = 13.0$ Hz, 2H), 1.61 (qd, $J =$ 13.0, 4.4 Hz, 2H), 1.49 (s, 3H); ^{13}C δ 154.8, 142.8, 135.7, 129.1, 126.5, 79.3, 44.4, 42.2, 33.2, 28.4, 20.9. Anal. Calcd for $C_{17}H_{25}NO_{2:}$ C, 74.14; H, 9.15; N, 5.09. Found: C, 74.03; H, 9.24; N, 5.08.

***tert*-Butyl 4-(4-formylphenyl)piperidine-1-carboxylate (15):** white solid; mp 70−72 °C; 99% assay yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.82 (m, 2H), 7.36 (m, 2H), 4.26 (br m, 2H), 2.76 (m, 3H), 1.83 (d, $J = 12.6$, 2H), 1.64 (qd, $J = 12.6$, 4.4, 2H), 1.48 (s, 9H); ^{13}C 191.7, 154.7, 152.8, 134.9, 130.0, 127.4, 79.5, 44.4, 41.7, 33.3, 28.4. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.41; H, 8.06; N, 4.78.

***tert*-Butyl 4-(4-nitrophenyl)piperidine-1-carboxylate (16):** white solid; mp 69−70 °C; 88% assay yield; NMR ^{1}H 8.18 (m, 2H), 7.37 (m, 2H), 4.29 (br m, 2H), 2.81 (m, 3H), 1.85 (d, $J =$ 13.0 Hz, 2H), 1.64 (qd, $J = 4.4$, 13.0 Hz, 2H), 1.49 (s, 9H); ^{13}C 154.6, 153.2, 146.5, 127.6, 123.7, 79.6, 44.0, 42.6, 32.7, 28.4. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.70; H, 7.04; N, 9.04.

***tert*-Butyl 4-(2-acetyl-4-chlorophenyl)piperidine-1-carboxylate (17):** white solid; mp 80−81 °C; 63% assay yield; NMR ^{1}H δ 7.52 (d, $J = 2.40$ Hz, 1H), 7.40 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 4.22 (br d, $J = 13.2$ Hz), 3.22 (tt, $J =$ 12.0, 3.6 Hz), 2.79 (m, 2H), 2.58 (s, 3H), 1.77 (d, $J = 13.2$ Hz, 2H), 1.56 (qd, $J = 12.4$, 4.4 Hz, 2H), 1.48 (s, 9H); ^{13}C 201.4, 154.7, 143.3, 139.8, 131.6, 131.2, 128.7, 128.1, 79.4, 44.2, 37.7, 33.1, 30.3, 28.4. Anal. Calcd for $C_{18}H_{24}ClNO_3$: C, 63.99; H, 7.16; N, 4.15. Found: C, 64.17; H, 7.01; N, 4.02.

***tert*-Butyl 4-pyridin-2-ylpiperidine-1-carboxylate (18):** colorless oil; 63% assay yield; NMR ^{1}H 8.52 (m, 1H), 7,61 (m, 1H), 7.11 (m, 2H), 4.24 (br m, 2H), 2.83 (m, 3H), 1.90 (d, $J =$ 13.0 Hz, 2H), 1.70 (qd, $J = 13.0$, 4.4 Hz, 2H), 1.46 (s, 9H); ^{13}C 164.3, 154.7, 149.2, 136.4, 121.4, 120.8, 79.3, 44.5, 44.0, 31.6, 28.4. Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.59; H, 8.55; N, 10.70.

***tert*-Butyl 4-[2-(methoxycarbonyl)phenyl]piperidine-1-carboxylate (19):** colorless oil; 92% assay yield; NMR ^{1}H δ 7.80 (dd, $J = 7.6$, 1.6 Hz, 1H); 7.47 (td, $J = 7.6$, 1.6 Hz, 1H), 7.35 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.26 (td, $J = 7.6$, 1.2 Hz, 1 H), 4.25 (br d, $J = 13.2$ Hz, 1H), 3.91 (s, 3H), 3.55 (tt, $J = 12.0$, 3.6 Hz, 2H), 2.84 (td, $J = 13.2$, 2.4 Hz, 2H), 1.83 (br d, $J = 13.2$ Hz, 2H), 1.64 (q of d, $J = 12.4$, 4.4 Hz, 2H), 1.49 (s, 9H); ^{13}C 168.3, 154.8, 146.7, 131.9, 130.2, 129.6, 126.7, 125.8, 79.3, 51.9, 44.5, 38.3, 33.0, 28.4. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.64; H, 7.97; N, 4.38.

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