Concise Formation of 4-Benzyl Piperidines and Related Derivatives Using a Suzuki Protocol

Susan Vice,* Tom Bara, Annette Bauer, C. Anderson Evans, Jennifer Ford, Hubert Josien, Stuart McCombie,* Michael Miller, Dennis Nazareno, Anandan Palani, and Jay Tagat

Schering−Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539

sfvice@home.com

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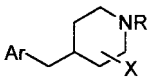
Introduction

During the course of a recent CNS program,[1] we were in need of a method to construct a family of 4-(substituted benzyl)piperidines, represented by **1**. We required a



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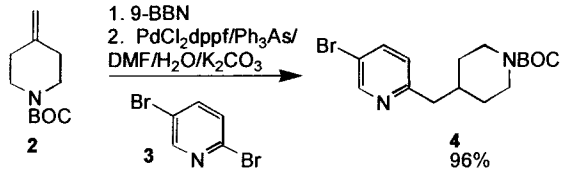
protocol that would tolerate variations in the aryl portion of the molecule including substituent patterns and heteroatom incorporation (for example, pyridyl). For the piperidine portion, we wished to vary −R, and ultimately to incorporate substituents −X into this ring. The "methylene spacer" would be the one constant in our design.

Although 4-benzyl piperidine derivatives possess an array of pharmacological properties,[1−6] methods for the concise construction of this class of molecules are few. Earlier methods use harsh conditions,[7] and, more importantly from our perspective, are limited to unsubstituted benzyl. Recently, Zhou and Keana have described[8] a much milder and more general Wittig olefination/reduction protocol to generate 4-(substituted benzyl) piperidines and pyrrolidines.

Scheme 1



The Suzuki reaction has enjoyed tremendous success in the area of C−C bond formation since its first description.[9] When hydroboration of an olefin is used[9b] to generate the metal species, an sp^3 hybridized carbon can be delivered in the cross-coupling step. Although Suzuki described this process for 1,1-disubstituted olefins, very few examples of this type have subsequently appeared in the literature,[10] in contrast to the reaction using monosubstituted ethylene derivatives.[9c−d] The hydroboration of heterocyclic, 1,1-disubstituted olefins and their subsequent Suzuki coupling with various aryl electrophiles for the formation of benzyl piperidines and related compounds is the subject of this Note.

Results and Discussion

Hydroboration of *N*-BOC 4-methylene piperidine **2**[11] followed by reaction with $PdCl_2$dppf, shown in Scheme 1, and 2,5-dibromopyridine **3** gave, after workup and chromatography, the desired piperidine derivative **4** in 96% yield.[12]

Neither the use of other bases (Cs_2CO_3, K_3PO_4) nor the absence of Ph_3As in the reaction notably changed the isolated yield of **4** (<5% variation).

As illustrated in Table 1, a variety of bromide, iodide, and triflate substrates couple under the given conditions. Differences in the electronic nature of the aryl component are well tolerated, as are other heterocycles (entry 9). Note that many of these examples contain functional groups that can be further transformed following the Suzuki coupling (entries 2 and 5), an important feature in the context of our drug discovery program.

As noted above, we also wished to vary the group on the piperidine nitrogen. BOC cleavage of **2** was effected with 6 N HCl in EtOAc to generate the hydrochloride salt **23**,[13] which was then converted under standard conditions to amine, sulfonamide, and amide derivatives, respectively (Scheme 2). These intermediates were subjected to the protocol described above for piperidine **2** to provide the anticipated products **25**, **26**, and **27**. Note that

* To whom correspondence should be addressed. (S.F.V.) Phone: (908)789-1206. Fax: (908)791-1992. E-mail: sfvice@home.com. (S.M.) Schering-Plough Research Institute, 2015 Galloping Hill Rd., Kenilworth, NJ, 07033-0593. Phone: (908)740-3544. Fax: (908)740-7512. E-mail: stuart.mccombie@spcorp.com.

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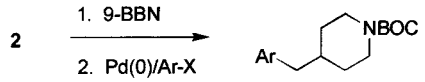
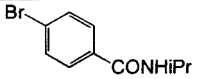
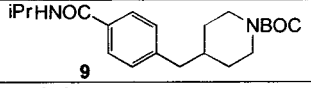
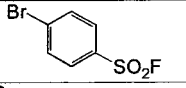
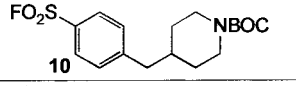
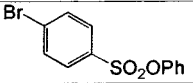
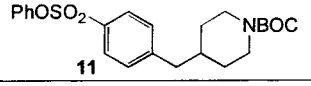
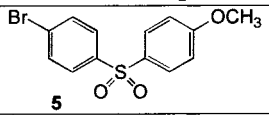
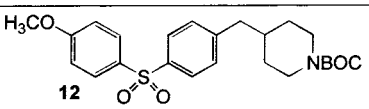
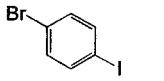
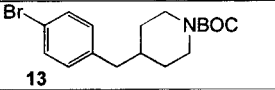
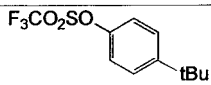
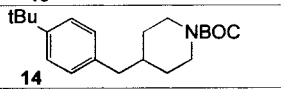
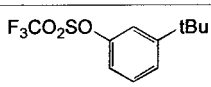
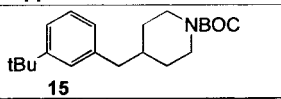
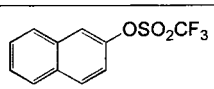
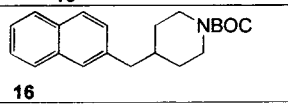
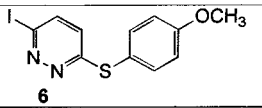
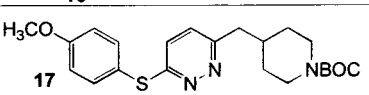
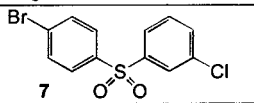
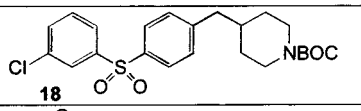
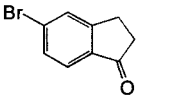
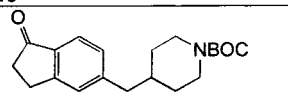
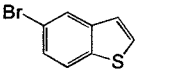
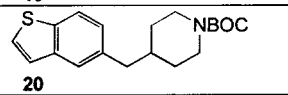
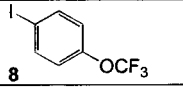
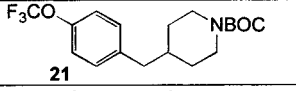
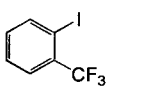
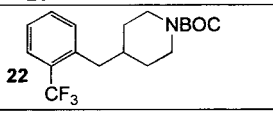
Table 1. Variation of Ar-X



Entry	Ar-X	Product	Isolated Yield (%)
1			98
2			82
3			80
4			94
5			60
6			90
7			90
8			82
9			88
10			87
11			77
12			80
13			62
14			72

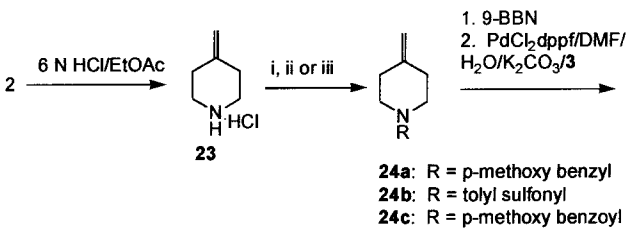
basic amines are tolerated, as exemplified by the formation of **25**, and this aspect of the reaction was further explored using the more complex systems described in Scheme 3.

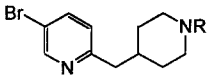
Thus, reductive amination of **23** with *N*-BOC 4-piperidone or, alternatively, formation of the methylated derivative via the reaction of methylmagnesium bromide with the corresponding cyano amine intermediate gave the desired olefin targets **28** and **29**, respectively.[1] These intermediates were hydroborated and coupled in fair to high yields (Table 2).

Finally, we chose to look at variations in the hydroborated component, including ring size and ring substituents. Reaction of **2** with selenium dioxide[15] gave the carbinol **34**, and silylation afforded the TBDMS ether **35** as shown in Scheme 4. The four- and five-membered ring systems (**38** and **39**, respectively; see Table 3) were prepared using published procedures.[13,14]

The results for the hydroboration/palladium-mediated bond forming reactions of these olefins are summarized in Table 3. The products **40** and **41** were isolated as a 1:1 mixtures of diastereoisomers, indicating a lack of

Scheme 2





25: R = p-methoxy benzyl: 38%[a]
26: R = tolyl sulfonyl: 52%[a]
27: R = p-methoxy benzoyl: 55%[a]

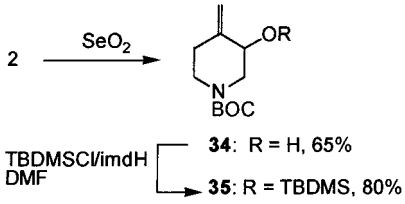
(i) p-methoxy benzyl chloride/iPr_2EtN/CH_3CN, 94%;
(ii) $K_2CO_3/H_2O/CH_2Cl_2$/toluene sulfonyl chloride, 45%;
(iii) $K_2CO_3/H_2O/CH_2Cl_2$/p-methoxy benzoyl chloride, 79%
[a]represents a single experiment

Scheme 3

28: R = H
29: R = CH_3

(i) **23**/DBU/CH_2Cl_2 then $NaBH(OAc)_3$/acetic acid, 97%
(ii) (a) **23**/$Ti(OiPr)_4/CH_2Cl_2$ (b) Et_2AlCN (c) CH_3MgBr, 60%

Scheme 4



facial selectivity in the hydroboration step for olefin **34** or **35**. In the case of the monomethylated olefin **36**, a measurable, but moderate, preference for one isomer was noted in the final products (entry 3). The moderate yield for the formation of **45** (entry 6) may be due to complexation of the product amine with boron residues.[9b]

The product mixtures, **40** and **41**, could be separated into their respective cis and trans components. The specific stereochemical assignments of these isomers were based on detailed ^1H and COSY NMR experiments, at both room and lower temperatures, used to distinguish line broadening effects due to rotational isomerization about the N−C bond of the BOC group. The coupling patterns and total widths of the methine proton resonances were the primary basis for the structural assignments. For example, the oxy methine proton of **40trans** had a total line width of 23 Hz, consistent with two large (9 Hz) and one small (4 Hz) couplings. The corresponding proton in **40cis** had a total line width of 8 Hz due to three small (3 Hz) couplings. The assignment of **40trans** was confirmed by a series of difference NOE experiments in which the close axial−axial interaction between the oxy methine and the 5-axial protons was observed.

In summary, an efficient method of constructing 4-benzyl piperidines and related substances is described. This protocol tolerates a wide variation in both reaction partners and complements the related process of Zhou and Keana.[8] The concise formation of a variety of building blocks, such as those described here, has found wide applicability in our drug discovery programs. Adapting this C−C bond forming reaction to solid-phase applications[16] will further extend the utility of this method, and experiments designed to address this are ongoing in our laboratories.

Experimental Section

Compounds **5**, **6**, **7**, **23**, **28**, and **29** were prepared as described in ref 1. Compound **38** was prepared as described in ref 13, and compound **39** was prepared as described in ref 14.

General Procedure: 1-Piperidinecarboxylic Acid, 4-[(5-Bromo-2-pyridinyl)methyl] 1,1-Dimethylethyl Ester (4). To a degassed sample of **2** (7.93 mL, 46 mmol) was added 9-BBN (92 mL of a 0.5 M solution in THF, 46 mmol). The resulting solution was refluxed for 1 h. After cooling to room temperature, the solution was added to a mixture of the dibromide **3** (10 g, 42 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.03 g, 3 mol %), DMF (95 mL), water (9.1 mL), and K_2CO_3 (7.62 g). The resulting mixture was heated at 60 °C for 3 h. After the mixture was cooled to room temperature and poured into water, the pH was adjusted to 11 with 10% aqueous NaOH and the mixture was extracted with EtOAc. The combined organic extracts were dried with brine and Na_2SO_4, filtered, and evaporated to give a crude oil, which was further purified by column chromatography (silica adsorbent; 8:1 then 4:1 hexanes:EtOAc eluant) to give the product **4** as a waxy solid (14.3 g) in 96% yield. Mp 66 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (qd, J = 11.3 and 4.5 Hz, 2H), 1.45 (s, 9H), 1.52−1.70 (m, 2H), 1.77−1.99 (m, 1H), 2.55−2.75 (m, 4H), 3.94−4.20 (b, 2H), 7.00 (d, J = 7.5 Hz, 1H), 7.70 (dd, J = 7.5, 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 28.4 (3C), 31.9 (2C), 36.7, 43.9 (b 2C), 44.5, 79.3, 118.1, 124.9, 138.7, 150.4, 154.8, 158.8. MS (ESI) *m*/*z* (relative intensity) 358 (11), 357 (40), 356 (10), 355 (43). Anal. Calcd for $C_{16}H_{23}N_2O_2Br$: C, 54.09; H, 6.53; N, 7.88; Br, 22.49. Found: C, 54.46; H, 6.69; N, 7.67; Br, 22.42.

1-(4-Methoxybenzyl)-4-methylenepiperidine (24a). Acetonitrile (4.2 mL), diisopropylethylamine (3.3 mL), and **23** (1.00 g, 7.49 mmol) were mixed at room temperature, and *p*-methoxybenzyl chloride (0.96 mL) was added. After the mixture was stirred overnight, the volatile materials were removed, and the resulting oil was diluted with EtOAc (40 mL) and washed with 6 N HCl_{aq}. The aqueous layer was cooled in an ice bath, and the pH was adjusted to 11 with solid NaOH.The resulting aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered, and evaporated to give the product **24a** as a gold oil (1.52 g) in 94% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (t, J = 6.0 Hz, 4H), 2.44 (t, J = 6.0 Hz, 4H), 3.47 (s, 2H), 3.81 (s, 3H), 4.66 (d, J = 0.9 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 Hz, $CDCl_3$) δ 34.5, 54.8, 55.2, 62.2, 107.5, 113.5, 130.3, 130.4, 146.7, 158.6. MS (FAB) *m*/*z* (relative intensity) 218 ($M + H^+$, 100), 217 (M^+, 75), 216 ($M - H^+$, 49). HRMS (FAB, $[M + 1]^+$): calcd for $C_{14}H_{20}NO$, 218.1545; found 218.1542. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.34; H, 8.88; N, 6.37.

4-Methylene-1-(4-methyl)phenylsulfonylpiperidine (24b). To a cooled (0 °C) mixture of amine hydrochloride **23** (4.00 g, 30 mmol), CH_2Cl_2 (60 mL), water (40 mL), and K_2CO_3 (12.4 g) was added a solution of 4-methylphenylsulfonyl chloride (5.43 g, 28.5 mmol) and CH_2Cl_2 (20 mL). After stirring at room temperature for 2 h, **23** (1.57 g, 11.8 mmol) and 4-methylphenylsulfonyl chloride (2.00 g, 10.5 mmol) were added, and the resulting mixture was stirred for 18 h at room temperature. The CH_2Cl_2 layer was removed and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, filtered, and evaporated to give a crude solid which was stirred with 2:1 hexanes:EtOAc (50 mL) for 2 h. Filtration and washing with hexanes gave the product **24b** as a white solid (4.44 g) in 45% yield (the filtrate was evaporated and found to

(14) Morimoto, A.; Okutani, T.; Masuda, K. *Chem. Pharm. Bull.* **1973**, *21*, 228−231.
(15) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526−5528. (b) Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404−1412.
(16) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581.

Table 2. Synthesis of 4-(Substituted aryl methyl)piperidines

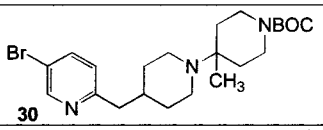
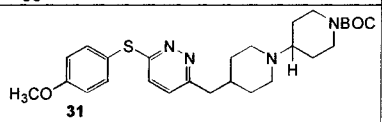
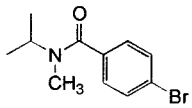
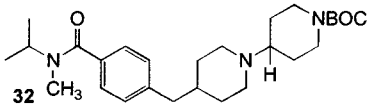
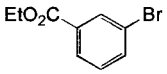
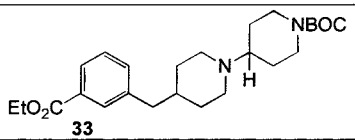
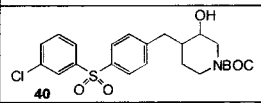
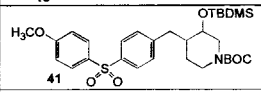
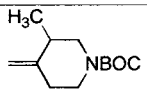
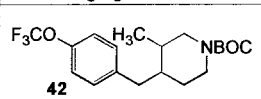
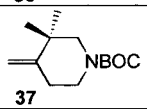
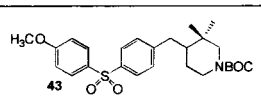
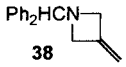
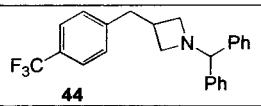
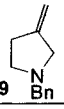
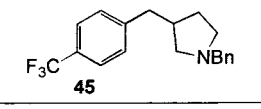
Entry	ArX	Olefin	Product	Yield (%)
1	**3**	**29**	 **30**	56
2	**6**	**28**	 **31**	54
3		**28**	 **32**	60
4		**28**	 **33**	85

Table 3

Entry	Ar-X	Olefin	Product[a]	Yield (%)
1	**7**	**34**	 **40**	78
2	**5**	**35**	 **41**	65
3	**8**	 **36**	 **42**	73
4	**5**	 **37**	 **43**	93
5	**8**	 **38**	 **44**	70
6	**8**	 **39**	 **45**	35

[a] Products **40** and **41** are formed as 1:1 mixtures of isomers; product **42** is formed as a 1.4:1 mixture of isomers.

contain 3.23 g of product **24b** that was 85% pure). Mp 128−129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (t, J = 5.7 Hz, 4H), 2.43 (s, 3H), 3.05 (t, J = 5.7 Hz, 4H), 4.69 (s, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 21.5, 33.8 (2C), 47.6 (2C), 109.9, 127.6, 129.6, 133.5, 143.4 (2C). MS (ESI) *m/z* (relative intensity) 252 (M + H^+, 100). Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.23; H, 6.77; N, 5.34.

(4-Methylenepiperidin-1-yl) 4-Methoxyphenyl Methanone (24c). To a cooled (0 °C) mixture of amine hydrochloride **23** (4.00 g, 30 mmol), CH_2Cl_2 (60 mL), water (40 mL), and K_2CO_3 (12.4 g) was added *p*-methoxybenzoyl chloride (4.86 g, 28.5 mmol) as a solid in five portions over five min. After the mixture was stirred at room temperature for 18 h, the CH_2Cl_2 layer was removed and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, filtered, and evaporated to give a crude oil. Purification by silica gel chromatography (4:1 hexanes:EtOAc eluant) gave the product **24c** as an oil (5.21 g) in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15−2.32 (b, 4H), 3.40−3.76 (b, 4H), 3.84 (s, 3H), 4.80 (s, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 34.6 (b), 44.0 (b), 47.0 (b), 55.3, 109.7, 113.7, 128.2, 128.9, 144.6, 160.7, 170.4. MS (ESI) *m/z* (relative intensity) 234 (M + $2H^+$, 57), 232 (M + H^+, 100). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.49; H, 7.38; N, 5.80.

Using the general procedure described for **4**, the following compounds were prepared.

1-(4-Methoxy)benzyl-4-[(5-bromo-2-pyridinyl)methyl]piperidine (25): as an oil in 38% yield. R_f = 0.33 (76:19:5 hexanes:EtOAc:Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.48 (m, 2H), 1.55−1.80 (m, 2H), 1.68−1.85 (m, 1H), 1.99 (t, J = 12.0 Hz, 2H), 2.65 (d, J = 6.9 Hz, 2H), 2.87 (bd, J = 12.0 Hz, 2H), 3.49 (s, 2H), 3.76 (s, 3H), 6.83 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 7.69 (dd, J = 8.4, 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H). ^{13}C NMR (75 Hz, $CDCl_3$) δ 31.5, 36.3, 44.2, 53.1, 55.1, 62.2, 113.5 (2C), 117.9, 124.9, 128.6, 130.4,

130.6, 138.5, 150.2, 158.8, 158.9. MS (FAB) *m/z* (relative intensity) 377 (M^+, ^{81}Br, 96), 375 (M^+, ^{79}Br, 100). HRMS (FAB, $M^+ + 1$): calcd for $C_{19}H_{24}N_2O_{Br}$, 375.1072; found, 375.1069.

1-(4-Methyl)benzenesulfonyl-4-[(5-bromo-2-pyridinyl)methyl]piperidine (26): as a white solid in 52% yield. Mp 149−150 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (dq, J = 3.6 and 12.0 Hz, 2H), 1.60−1.78 (m, 2H), 1.84−1.1.99 (m, 1H), 2.19 (dt, J = 2.1, 11.7 Hz, 2H), 2.41 (s, 3H), 2.62 (d, J = 6.6 Hz, 2H), 3.73 (d, J = 11.7 Hz, 2H), 6.97 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.68 (dd, J = 8.4, 2.7 Hz, 1H), 8.52 (d, J = 2.7 Hz, 1H). ^{13}C NMR (75 Hz, $CDCl_3$) δ 21.4, 31.1, 35.5, 43.8, 46.3, 118.1, 124.9, 127.6 (2C), 129.5 (2C), 132.9, 138.8, 143.4, 150.2, 158.3. MS (ESI) *m/z* (relative intensity) 410 (M + 1, 100). MS (FAB) *m/z* (relative intensity) 411 (M^+, ^{81}Br, 96), 409 (M^+, ^{79}Br, 100). HRMS (FAB, $M^+ + 1$): calcd for $C_{18}H_{22}N_2O_2SBr$, 409.0585; found, 409.0591.

4-[(5-Bromo-2-pyridinyl)methyl]piperidin-1-yl-(4-methoxy)phenyl Methanone (27): as a white solid in 55% yield. Mp 101−104 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15−1.39 (bm, 2H), 1.55−1.76 (bm, 2H), 1.97−2.17 (m, 2H), 2.54 (d, J = 7.2 Hz, 0.25H), 2.70 (d, J = 7.2 Hz, 1.75H), 2.75−3.01 (bm, 2H), 3.82 (s, 3H), 4.03−4.80 (b, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.7 Hz, 2H), 7.72 (dd, J = 8.4, 2.4 Hz, 1H), 8.59 (d, J = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 32.5, 36.8, 44.2, 55.3, 113.6, 118.2, 125.0, 127.7, 128.3, 128.9, 138.9, 150.3, 158.4, 160.5, 170.3. MS (ESI) *m/z* (relative intensity) 391 (M^+, ^{81}Br, 96), 389 (M^+, ^{79}Br, 100). HRMS (FAB, M^+ ^{81}Br): calcd for $C_{19}H_{21}N_2O_2Br$, 391.0844; found, 391.0838. Anal. Calcd for $C_{19}H_{21}BrN_2O_2$: C, 58.62; H, 5.44; N, 7.20. Found: C, 58.29; H, 5.45; N, 6.88.

1-Piperidinecarboxylic Acid, 3-Hydroxy-4-methylene 1,1-Dimethylethyl Ester (34). A mixture of SeO_2 (563 mg), CH_2Cl_2 (40 mL), and *t*-BuOOH (90% in decane, 2 mL) was cooled to 0 °C and stirred for 20 min. A solution of olefin **2** (2.00 g, 10.15 mmol) and CH_2Cl_2 (5 mL) was added dropwise, the cooling bath was removed, and the mixture was stirred for 90 min. A 10% $NaHSO_3$ solution was added, and the aqueous layer was removed and extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to give an orange oil, which was further purified by silica gel chromatography (3:1 hexanes:EtOAc) to give **34** as an oil (1.41 g) in 65% yield. R_f = 0.24 (3:1 hexanes:EtOAc). ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.70−1.90 (b, 1H), 2.10−2.22 (m, 1H), 2.41−2.49 (m, 1H), 3.12−3.32 (m, 2H), 3.46−3.61 (m, 1H), 3.75 (dd, J = 12.8, 4.1 Hz, 1H), 4.09−4.14 (bm, 1H), 4.88 (s, 1H), 5.02 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 32.2, 45.3 (b), 51.3, 69.7, 79.9, 108.0, 147.0, 155.0. HRMS (FAB, $M^+ + 1$): calcd for $C_{11}H_{20}NO_3$, 214.1443; found, 214.1441.

1-Piperidinecarboxylic Acid, 3-[Dimethyl(1,1-dimethylethyl)siloxy]-4-methylene 1,1-Dimethylethyl Ester (35). Alcohol **34** (64 mg, 0.30 mmol), TBDMSCl (60 mg, 0.36 mmol), and imidazole (31 mg, 0.45 mmol) were dissolved in DMF (3 mL) and stirred for 18 h at room temperature. A second portion of TBDMSCl (54 mg) was added, and the solution was heated at 45 °C for 24 h. After the mixture was cooled to room temperature, Et_2O and H_2O were added. The aqueous layer was removed and extracted with Et_2O. The organic extracts were combined, washed with water and brine, dried with Na_2SO_4, filtered, and evaporated to give a crude yellow oil. Purification by silica gel column chromatography (4:1 hexanes:Et_2O) gave **35** as a clear oil (78 mg) in 80% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.47 (s, 9H), 2.06−2.18 (m, 1H), 2.37 (td, J = 3.80, 13.7 Hz, 1H), 2.80−2.90 (m, 1H), 2.92−3.01 (m, 1H), 3.74−4.05 (m, 3H), 4.82 (s, 1H), 5.02 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9 (2C), 18.3, 25.8 (3C), 28.5 (3C), 32.9, 44.8, 52.5, 70.5 (b), 79.5, 107.3, 147.4, 154.3.

1-Piperidinecarboxylic Acid, 3,3-Dimethyl-4-methylene 1,1-Dimethylethyl Ester (37). To a solution of *N*-BOC 4-piperidone (15.95 g, 80 mmol) in anhydrous THF (400 mL) at 10 °C were successively added NaH (60% in hexanes; 6.72 g, 0.17 mol) and iodomethane (12.5 mL, 0.20 mol). The resulting solution was allowed to warm to room temperature and stirred for 2 days. The residue obtained after evaporation was taken up in diethyl ether, washed with brine, dried over Na_2SO_4, and concentrated. Two recrystallizations from pentane gave 6.60 g of a white solid which was used directly in the next step (^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 6H), 1.49 (s, 9H), 2.48 (t, J = 6.8 Hz, 2H), 3.41 (bs, 2H), 3.70 (t, J = 6.9 Hz, 2H)). To a suspension of methyltriphenylphosphonium bromide (13.22 g, 37 mmol) in anhydrous THF (200 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes; 14.8 mL, 37 mmol). After stirring for 15 min, the intermediate described above (4.55 g, 20 mmol) and THF (200 mL) were added. The resulting solution was warmed to room temperature, stirred for 18 h, poured into ice-cooled water, and extracted with diethyl ether. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography over silica gel (3:1 CH_2Cl_2:hexanes eluant) afforded **37** (2.40 g) as an oil in 19% yield over two steps. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 6H), 1.46 (s, 9H), 2.27 (bt, J = 6.0 Hz, 2H), 3.12 (bs, 2H), 3.43 (t, J = 5.8 Hz, 2H), 4.71 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8 (2C), 28.4 (3C), 32.1, 37.6, 45.2, 56.4, 79.3, 106.7, 152.9, 155.0.

1-Piperidinecarboxylic Acid, 4-[[4-[(3-Chlorophenyl)-sulfonyl]phenyl]methyl]-3-hydroxy 1,1-Dimethylethyl Ester (40). The general procedure for the formation of **4** above was used, except K_3PO_4 was used instead of K_2CO_3. Purification of the crude oil was carried out using silica gel chromatography (4:1 hexanes:EtOAc eluant) to give **40** as a colorless oil in 78% yield as a 1:1 mixture of isomers. A second treatment by silica gel chromatography led to the collection of a small sample of each isomer. **40cis:** ^1H NMR (300 MHz, $CDCl_3$) δ 1.34−1.44 (m (obscured by singlet at 1.49), 1H), 1.49 (s, 9H), 1.55−1.75 (m, 2H), 1.78−1.93 (b, 1H), 2.59−2.68 (m, 2H), 2.79−2.88 (m, 2H), 3.60 (bs, 1H), 4.06−4.21(m, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.44 (t, J = 8.3 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.81−7.88 (m, 3H), 7.93 (bs, 1H). Treatment of **40cis** with 5:1 CH_2Cl_2:TFA produced a derivative with the following properties. Mp (HCl salt) 155−165 °C (with decompostion). ^1H NMR (300 MHz, $CDCl_3$) (free base) δ 1.33−1.41 (m, 1H), 1.46−1.59 (m, 1H), 1.60−1.68 (m, 1H), 1.85 (b, 2H), 2.51 (dt, J = 2.1 Hz; J = 8.7 Hz, 1H), 2.56−2.64 (m, 2H), 2.81(dd, J = 6.0 Hz; J = 9.9 Hz, 1H), 2.94−3.04 (m, 2H), 3.47 (bs, 1H), 7.36 (d, J = 6.6 Hz, 2H), 7.44 (t, J = 5.7 Hz, 1H), 7.49−7.53 (m, 1H), 7.80−7.86 (m, 3H), 7.91 (t, J = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) (free base form) δ 28.4, 40.4, 43.6, 47.6, 54.1, 67.0, 126.7, 128.6 (2C), 128.8, 131.3, 131.6 (2C), 134.2, 136.4, 139.3, 144.6, 148.3. HRMS (FAB, $M^+ + 1$): calcd for $C_{18}H_{21}NO_3SCl$, 366.0931; found, 366.0936.

40trans: ^1H NMR (300 MHz, $CDCl_3$) δ 1.05−1.20 (m, 2H), 1.44 (s, 9H), 1.55−1.70 (m, 1H), 2.05−2.20 (b, 1H), 2.38−2.48 (m, 1H), 2.52−2.66 (m, 2H), 3.25−3.38 (m, 2H), 3.94 (bd, J = 13.0 Hz, 1H), 4.22 (bd, J = 13.0 Hz, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.44 (t, J = 6.5 Hz, 1H), 7.53 (d, J = 6.5 Hz, 1H), 7.80−7.89 (m, 3H), 7.92 (bs, 1H). Treatment of **40trans** with 5:1 CH_2Cl_2:TFA produced a derivative with the following properties. Mp (HCl salt) 130−140 °C (with decompostion). ^1H NMR (300 MHz, $CDCl_3$) (free base) δ 1.06−1.17 (m, 1H), 1.50−1.66 (m, 2H), 1.70−1.82 (bs, 2H), 2.39−2.52 (m, 3H), 2.87−2.94 (m, 1H), 3.14−3.24 (m, 2H), 3.33 (ddd, J = 3.3, 7.2, 7.2 Hz, 1H), 7.31−7.35 (m, 2H), 7.44 (t, J = 6.0 Hz, 1H), 7.50−7.54 (m, 1H), 7.81−7.85 (m, 3H), 7.92 (t, J = 1.2 Hz, 1H). ^{13}C (75 MHz, $CDCl_3$) (free base form) δ 31.4, 39.6, 46.6, 46.9, 54.8, 72.7, 126.7, 128.6, 128.8, 131.3 (2C), 131.5, 131.6, 134.3, 136.4, 139.3, 144.5, 148.1. HRMS (FAB, M^+ + 1): calcd for $C_{18}H_{21}NO_3SCl$, 366.0931; found, 366.0928.

1-Piperidinecarboxylic Acid, 4-[[4-[(4-Methoxyphenyl)-sulfonyl]phenyl]methyl]-3- dimethyl(1,1-dimethylethyl)-siloxy, 1,1-Dimethylethyl Ester (41). The general procedure for the formation of **4** above was used, except K_3PO_4 was used instead of K_2CO_3. Purification of the crude oil was carried out using silica gel chromatography (5:1 then 1:1 hexanes:EtOAc eluant) to give **41** as a yellow oil (R_f = 0.18 (5:1 hexanes:EtOAc))-in 65% yield as a 1:1 mixture of isomers. A second treatment by silica gel chromatography led to the collection of a small sample of each isomer. **41cis:** ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.11 (s, 3H), 0.99 (s, 9H), 1.12−1.27 (m, 1H), 1.43 (s, 9H), 1.50−1.75 (m, 2H), 2.47−2.60 (m, 1H), 2.62−2.96 (m, 3H), 3.75 (bs, 1H), 3.83 (s, 3H), 3.85−4.05 (m, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H), 7.86 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.1, 18.2, 24.7, 25.9 (3C), 28.5 (3C), 38.2, 42.4, 42.8, 48.7, 50.0, 55.7, 68.2, 114.3 (2C), 127.2 (2C), 129.6 (2C), 129.7 (2C), 133.2, 139.8, 146.2, 154.7, 163.0. **41trans:** ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 0.99−1.14 (m, 1H), 1.44 (s, 9H), 1.50−1.63 (m, 2H), 2.09 (t, J = 10.5 Hz, 1H), 2.42−2.56 (bm, 2H), 3.20−3.36 (bm, 2H), 3.83 (s, 3H), 3.87−4.00 (bm, 1H), 4.06 (bm, 1H),

6.95 (d, J = 8.9 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6 (2C), 18.2, 22.1, 25.8 (3C), 26.3, 28.5 (3C), 32.1, 38.5, 46.4, 55.7, 71.9, 79.6, 114.3 (2C), 127.2 (2C), 129.6 (2C), 129.8 (2C), 133.2, 139.8, 146.2, 154.0, 163.0. Further characterization of **41cis** and **41trans** as their amino carbinol derivatives is given in the Supporting Information.

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Supporting Information Available: Characterization data (^{1}H, ^{13}C NMR, and mass spectral data) for all new compounds and elemental analyses for several new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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