Synthesis of 4- and 5-Substituted 1-Hydroxyimidazoles through Directed Lithiation and Metal−Halogen Exchange

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Electrophiles were introduced regioselectively at the 5-position of 1-(benzyloxy)imidazole by lithiation at C-5 after protection of C-2 with a chloro or a trimethylsilyl group. Subsequent treatment with an electrophile afforded 5-substituted 1-(benzyloxy)-2-chloroimidazoles **8**−**13** and 5-substituted 1-(benzyloxy)imidazoles **3**−**5**, the 2-(trimethylsilyl) group being lost during workup. Electrophiles were introduced regioselectively at the 4-position of 1-(benzyloxy)imidazole by bromine−lithium exchange of 4-bromo-2-chloro-1-(benzyloxy)imidazoles, protected at C-5 with chloro or trimethylsilyl groups, followed by reaction with an electrophile. The 5-(trimethylsilyl) group was removed via base-catalyzed desilylation. Chlorine at C-2 and *O*-benzyl groups were removed by palladium-catalyzed hydrogenolysis.

Introduction

1-Hydroxyimidazoles (parent compound **1a**) are gaining interest due to their biological activity, which encompasses antiviral,[1] antihypertensive,[2] angiotensin II antagonist activity,[3] bacteriostatic,[4] and insecticidal properties.[5] Only a few 1-hydroxyimidazoles with functional substituents have been described.[6]

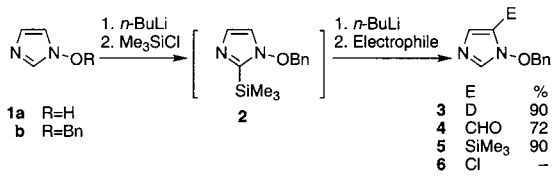
Recently we reported a method for the synthesis of a variety of 2-substituted 1-hydroxyimidazoles.[7] The method was based on lithiation of 1-(benzyloxy)imidazole (**1b**) followed by reaction with an electrophile and subsequent removal of the benzyl group by palladium-catalyzed hydrogenolysis or by hydrolysis with hydrochloric acid. This seems to be the only reported method for introduction of functional substituents in 1-hydroxyimidazoles per se. This strategy has now been extended to a protocol for the regioselective functionalization of the 4- and the 5-positions using lithiation followed by reaction with an electrophile.

Results and Discussion

Preparation of 5-Substituted 1-(Benzyloxy)imidazoles. As for other 1-substituted imidazoles[8] lithiation at C-5 in 1-(benzyloxy)imidazole is only possible when the 2-position is protected. As protection groups a trimethylsilyl group[9−11] and a chlorine[12,13] were tested.

When a trimethylsilyl group was used for protection of the 2-position, **1b** was lithiated at C-2 by treatment with *n*-butyllithium at −78 °C. Subsequent addition of trimethylsilyl chloride (TMSCl) gave rise to 1-(benzyloxy)-2-(trimethylsilyl)imidazole (**2**),[7] which was selectively metalated in situ at C-5 by treatment with a second equivalent of *n*-butyllithium at −78 °C in the presence of TMEDA. Subsequent addition of MeOD, DMF, or TMSCl followed by aqueous workup led to simultaneous loss of the 2-TMS group with formation of the 5-substituted 1-(benzyloxy)imidazoles **3**−**5** in 72−90% yield (Scheme 1). When hexachloroethane was used as an electrophile, the expected product **6** was contaminated with 2-chloro- and 2,5-dichloro-1-(benzyloxyimidazole) (**7** and **11**) due to loss of a protective trimethylsilyl group during the course of the reaction. The trimethylsilyl group was also lost when methyl iodide was used as an electrophile, giving rise to 2-methyl-substituted byproducts. Due to this limitation we therefore investigated the use of a 2-chloro substituent as protection group for the 2-position, since it can be removed by mild, palladium-catalyzed hydrogenolysis.[7] **7**[7] was then *ortho*-lithiated at C-5 using 1.2 equiv of *n*-butyllithium/TMEDA. Subsequent treatment with carbon, halogen, or tin electrophiles gave 5-substituted 1-(benzyloxy)-2-chloroimidazoles **8**−**13** in 88−99% yields (Scheme 2). By way of example the protective chloro substituent and the benzyl group of **9** could be removed simultaneously by palladium-catalyzed

Scheme 1



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(1) Harnden, M. R.; Jennings, L. J.; McKie, C. M. D.; Parkin, A. *Synthesis* **1990**, 893−895.
(2) Philipp, A. H.; Jirkovsky, I. L. U.S. Pat. 4,232,029, 1980; *Chem. Abstr.* **1981**, *94*, 103377.
(3) Kim, K. S. U.S. Pat. 5294722, 1994; *Chem. Abstr.* **1994**, *120*, 323571c.
(4) Abramovitch, R. A.; Cue, B. W. U.S. Pat. 4006160, 1977; *Chem. Abstr.* **1977**, *86*, 189707.
(5) Mamalis, P.; Croix, E. S. L.; Mhasalker, S. E. Ger. Offen. 2,254,474, 1973; *Chem. Abstr.* **1973**, *79*, 42507g.
(6) For a list of functionalized 1-hydroxyimidazoles see ref 7.
(7) Eriksen, B. L.; Vedsø, P.; Morel, S.; Begtrup, M. *J. Org. Chem.* **1998**, *63*, 12−16.
(8) Iddon, B.; Ngochindo, R. I. *J. Heterocycl. Chem.* **1994**, *38*, 2487.
(9) Jutzi, P.; Sakriss, W. *Chem. Ber.* **1973**, *106*, 2815.
(10) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351.
(11) Lipshutz, B. H.; Huff, B.; Hagen, W. *Tetrahedron Lett.* **1988**, *29*, 3411.
(12) Suzuki, M.; Tanaka, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1987**, *35*, 4056.
(13) Tanaka, H.; Hirayama, M.; Suzuki, M.; Miysaka, T.; Matsuda, A.; Ueda, T. *Tetrahedron* **1986**, *42*, 1971.

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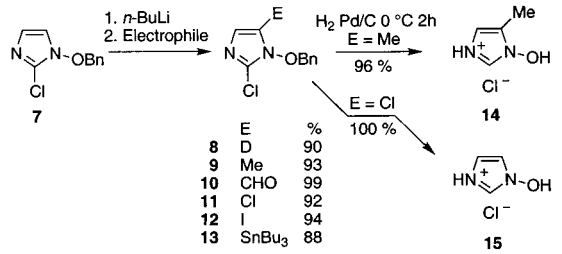
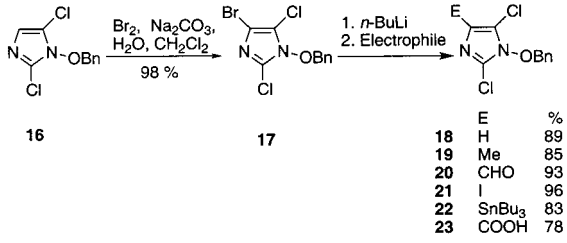
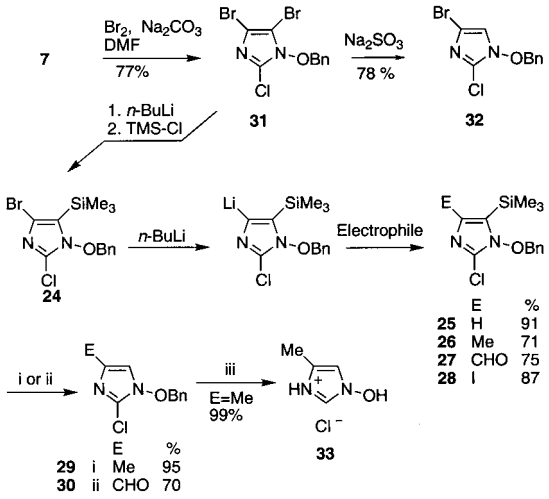
Scheme 2



Scheme 3



Scheme 4[a]



[a] Reagents and conditions: (i) NaOMe, MeOH, 20 °C, 3 h; (ii) K_2CO_3, MeOH, 20 °C, 1 h; (iii) H_2, Pd/C, 0 °C, 2 h.

hydrogenolysis at 0 °C for 2 h, affording the hydrochloride **14** in 96% yield. Similar hydrogenolysis of **11** caused loss of both chlorine substituents with production of 1-hydroxyimidazole hydrochloride (**15**) in quantitative yield, suggesting the 5-chloro substituent as protecting group for the 5-position.

Preparation of 4-Substituted 1-(Benzyloxy)imidazoles. Attempted deprotonation of **11** using 1.2 equiv of *n*-butyllithium/TMEDA failed as indicated by the fact that no deuterium incorporation was observed upon quenching with MeOD. Instead a 3:2 mixture of 1-(benzyloxy)-2-chloro-5-deuterioimidazole (**8**) and 1-(benzyloxy)-5-chloro-2-deuterioimidazole was formed presumably due to chlorine−lithium exchange at C-5 and C-2. As reported for other 1-substituted imidazoles[14] H-4 is not sufficiently acidic to be abstracted by butyllithium bases, and therefore bromine−lithium exchange was attempted.

In the first approach 1-(benzyloxy)-2,5-dichloroimidazole (**16**) was brominated at C-4 to give **17** in 98% yield. Subsequent bromine−lithium exchange at C-4 was then effected using 1.5 equiv of *n*-butyllithium. Quenching the putative 4-lithio intermediate with various electrophiles produced 4-substituted 2,5-dichloro-1-(benzyloxy)imidazoles **18**−**23** in 78−96% yields (Scheme 3). Unexpectedly, it was not possible to remove the 5-chloro substituent in **18**−**23** by palladium-catalyzed hydrogenolysis. Therefore, a more labile C-5 protecting group had to be developed. Thus, 4-substituted 1-(benzyloxy)imidazoles devoid of a 5-substituent could be prepared in an alternative approach by which 1-(benzyloxy)-2-chloroimidazole was first dibrominated to give 1-(benzyloxy)-4,5-dibromo-2-chloroimidazole (**31**) in 77% yield (Scheme 4). In a one-pot reaction **31** was then treated with 1.1 equiv of *n*-butyllithium to effect regioselective bromine−lithium exchange at the 5-position. Subsequent addition of 1.1 equiv of TMSCl gave the 5-silylated intermediate **24**, which upon treatment with a second equivalent of *n*-butyllithium and an electrophile produced 4-substituted 1-(benzyloxy)imidazoles **25**−**28** in 71−91% yields. If desired, **24** could be isolated after the first bromine−lithium exchange in 94% yield. This compound was then lithiated and quenched with methyl iodide, and **26** was obtained in 86% yield.

When the crude 4,5-dibromo compound **31** was treated with aqueous sodium sulfite, regioselective reduction took place at C-5 to give the 4-bromo compound **32** in 78% overall yield. When 1-(benzyloxy)-4-bromo-2-chloroimidazole was treated with *n*-butyllithium followed by reaction with MeOD, a 1:1 mixture of 1-(benzyloxy)-2-chloro-5-deuterio-4-bromoimidazole and **8** was obtained. This indicated poor chemoselectivety and thermodynamical instability of the initially formed 4-lithio-1-(benzyloxy)-2-chloroimidazole. This experiment confirms that selective C-4 lithiation requires a 4-bromoimidazole protected at the 5-position. Removal of the protective 5-silyl group of **26** and **27** could be effected under mild basic conditions. Thus, 1-(benzyloxy)-2-chloro-4-formyl-5-(trimethylsilyl)-imidazole (**27**) was desilylated using K_2CO_3 in methanol to give 1-(benzyloxy)-2-chloro-4-formylimidazole (**30**) in 70% yield. Likewise, 1-(benzyloxy)-2-chloro-4-methyl-5-(trimethylsilyl)imidazole (**26**) was desilylated by treatment with sodium methoxide to give 1-(benzyloxy)-2-chloro-4-methylimidazole (**29**) in 95% yield. The feasibility of the debenzylation dechlorination protocol described above was demonstrated by the quantitative palladium-catalyzed hydrogenolysis at 0 °C for 2 h of compound **29** to give 1-hydroxy-4-methylimidazole, isolated as its hydrochloride (**33**).

In conclusion, methods for regioselective introduction of electrophiles into the 4- and the 5-positions of 1-(benzyloxy)imidazole have been developed. In the 5-position the method is based on proton−lithium exchange and in the 4-position on halogen−lithium exchange. During these reactions chloro and trimethylsilyl serve as protecting groups for the 2-position and a trimethylsilyl group serves as protecting group for the 5-position.

Experimental Section

General Methods and Materials. See ref 7. *The compounds were never distilled. Violent decomposition of imidazole 1-oxides has been reported to take place at ca. 150 °C.*[15]

(14) Katritzky, A. R.; Slawinski, J. J.; Bunner, F.; Gorun, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1139.

(15) Flynn, A. P. *Chem. Br.* **1984**, *20*, 30.

Preparation of 5-Substituted 1-(Benzyloxy)imidazoles. In Situ Protection of C-2 Using Trimethylsilyl as Protecting Group. Standard Procedure. Under nitrogen, a solution of 1-(benzyloxy)imidazole (**1b**)[7] (174 mg, 1.0 mmol) in tetrahydrofuran (8 mL) was cooled to −78 °C. *n*-Butyllithium (1.48 M in hexanes) (0.81 mL, 1.2 mmol) was added with stirring over 2 min. After the resulting mixture was stirred for a further 5 min, trimethylchlorosilane (133 μL, 1.05 mmol) was added. Stirring was continued for 1 h, and TMEDA (0.3 mL, 2 mmol) and *n*-butyllithium (1.35 mL, 2 mmol) were added. After the resulting mixture had been stirred for 1 h, the electrophile was added. Stirring was continued at −78 °C for 1 h, and the reaction mixture was allowed to warm to 20 °C over the course of 1 h. Stirring was continued for a further 0.5 h. The mixture was worked up by addition of saturated aqueous sodium hydrogen carbonate (10 mL), extraction with dichloromethane (3 × 10 mL), drying ($MgSO_4$), filtration, and removal of the solvents to give the crude product.

1-(Benzyloxy)[5-^{2}H]imidazole (3). After addition of monodeuteriomethanol (MeOD; 0.3 mL, 7.4 mmol), the mixture was stirred and worked up as described above to give a residue which upon flash chromatography (heptanes−ethyl acetate, 2:1 → 0:1) gave 156 mg (90%) of 1-(benzyloxy)[5-^{2}H]imidazole. The ^{1}H NMR spectrum was identical with that of the starting material except that the signal from H-5 was absent and the signal from H-4 collapsed to a doublet. The signal from C-5 at 115.1 ppm appeared as a triplet (J_{CD} = 28.2 Hz).

1-(Benzyloxy)-5-formylimidazole (4). After addition of dimethylformamide (0.39 mL, 5 mmol) and stirring as described above, 2 M aqueous hydrochloric acid (5 mL) was added, and the mixture was stirred for 1 h. Addition of saturated aqueous sodium hydrogen carbonate until pH 8 and extractive workup with dichloromethane as described above gave a residue which by flash chromotography (heptanes−ethyl acetate, 2:1 → 0:1) afforded 145 mg (72%) of **4** as a yellow oil which crystallized from heptane−ethyl acetate. Mp: 52−54 °C (heptanes−ethyl acetate). Anal. Found: C, 65.63; H, 5.24; N, 13.87. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. NMR: δ_H ($CDCl_3$) 9.73 (1H, d, J = 0.78 Hz, HCO), 7.67 (1H, d, J = 0.95 Hz, H-4 or H-2), 7.41−7.18 (6H, m, Ph and H-4 or H-2), 5.22 (2H, s, CH_2); δ_C ($CDCl_3$) 177.0 (d), 137.9 (d), 137.4 (d), 132.4 (s), 129.8 (d), 129.6 (d), 128.6 (d), 127.7 (s), 82.3 (t).

1-(Benzyloxy)-5-(trimethylsilyl)imidazole (5). After addition of trimethylchlorosilane (0.25 mL, 2 mmol), the mixture was stirred and worked up as described above to give a residue which upon flash chromotography (heptanes−ethyl acetate, 2:1 → 0:1) gave 221.4 mg (90%) of **5** as a yellow oil. Anal. Found: C, 63.51; H, 7.39; N, 11.24. Calcd for $C_{13}H_{18}N_2OSi$: C, 63.37; H, 7.36; N, 11.37. NMR: δ_H ($CDCl_3$) 7.36−7.29 (6H, m, Ph and H-4 or H-2), 6.92 (1H, d, J = 1.0 Hz, H-4 or H-2), 5.04 (2H, s, CH_2), 0.30 (9H, s, $SiMe_3$); δ_C ($CDCl_3$) 134.1 (d), 133.3 (d), 133.3 (s), 129.0 (d), 128.8 (d), 128.4 (d), 126.0 (s), 82.0 (t) −1.4 (q).

Preparation of 5-Substituted 1-(Benzyloxy)-2-chloroimidazoles 8−13. Standard Prodedure. Under nitrogen, a solution of 1-(benzyloxy)-2-chloroimidazole (**7**)[7] (208.5 mg, 1.0 mmol) in tetrahydrofuran (8 mL) was cooled to −78 °C. TMEDA (0.18 mL, 1.2 mmol) and *n*-butyllithium (1.33 M in hexanes) (0.90 mL, 1.2 mmol) were added with stirring over 2 min. After the resulting mixture was stirred for a further 3 min, the electrophile was added. Stirring was continued at −78 °C for 1 h, and the reaction mixture was allowed to warm to 20 °C over the course of 1 h. Stirring was continued at 20 °C for a further 0.5 h. The mixture was worked up by addition of saturated aqueous sodium hydrogen carbonate (10 mL), extraction with dichloromethane (3 × 10 mL), drying ($MgSO_4$), filtration, and removal of the solvents to give the crude product.

1-(Benzyloxy)-2-chloro[5-^{2}H]imidazole (8). After addition of MeOD (0.3 mL, 7.4 mmol), the mixture was stirred and worked up as described above to give a residue which upon flash chromotography (heptanes−ethyl acetate, 2:1 → 0:1) gave 187.6 mg (90%) of **8**. The ^{1}H NMR spectrum was identical with that of the starting material except that the signal from H-5 was absent and the signal from H-4 collapsed to a singlet. The signal from C-5 at 117.8 ppm appeared as a triplet (J_{CD} = 31.1 Hz).

1-(Benzyloxy)-2-chloro-5-methylimidazole (9). Methyl iodide (0.32 mL, 5 mmol) was added, and the mixture was stirred at −78 °C for 1 h. To destroy excess methyl iodide, 33% dimethylamine in ethanol (5 mL) was added. The mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:1), affording 207 mg (93%) of **9**. Anal. Found: C, 59.54; H, 5.09; N, 12.58. Calcd for $C_{11}H_{11}N_2OCl$: C, 59.33; H, 4.98; N, 12.58. NMR: δ_H ($CDCl_3$) 7.44−7.36 (5H, m, Ph), 6.54 (1H, q, J = 1.0 Hz, H-4), 5.10 (2H, s, CH_2), 1.98 (3H, d, J = 1.0, Me); δ_C ($CDCl_3$) 132.6 (s), 129.8 (d), 129.6 (d), 128.6 (d), 126.8 (s), 125.7 (s), 121.1 (d), 80.9 (t), 8.4 (q).

1-(Benzyloxy)-2-chloro-5-formylimidazole (10). After addition of dimethyformamide (0.15 mL, 2 mmol), the mixture was stirred as in the standard procedure. Then 2 M aqueous hydrochloric acid (5 mL) was added, and the mixture was stirred for 1 h. Addition of saturated aqueous sodium hydrogen carbonate until pH 8 and extractive workup with dichloromethane as described above gave a residue which by flash chromatography (heptanes−ethyl acetate, 1:1) afforded 234 mg (99%) of **10** as a yellow oil which crystallized from pentane−ethyl acetate. Recrystallization (pentane−ethyl acetate) gave mp 50−51 °C. Anal. Found: C, 55.95; H, 3.64; N, 11.83. Calcd for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.84. NMR: δ_H ($CDCl_3$) 9.59 (1H, d, J = 1.1 Hz, HCO), 7.59 (1H, d, J = 0.95 Hz, H-4), 7.48−7.39 (5H, m, Ph), 5.26 (2H, s, CH_2); δ_C ($CDCl_3$) 176.4 (d), 136.2 (d), 135.5 (s), 131.9 (s), 130.3 (d), 129.9 (d), 129.5 (s), 128.7 (d), 82.1 (t).

1-(Benzyloxy)-2,5-dichloroimidazole (11). After addition of hexachloroethane (710 mg, 3 mmol) dissolved in THF (2 mL), the mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:0 → 2:1) to afford 224 mg (92%) of **11**. Mp: 38−40 °C (pentane). Anal. Found: C, 49.27; H, 3.39; N, 11.65. Calcd for $C_{10}H_8N_2OCl_2$: C, 49.41; H, 3.32; N, 11.52. NMR: δ_H ($CDCl_3$) 7.42 (s, 5H, Ph) 6.77 (s, 1H, H-4), 5.16 (s, 2H, CH_2); δ_C ($CDCl_3$) 132.1 (s), 130.0 (d), 129.8 (d), 128.6 (d), 126,9 (s), 121.4 (d), 116.1 (s), 81.76 (t).

1-(Benzyloxy)-2-chloro-5-iodoimidazole (12). After addition of iodine (508 mg, 2 mmol), the mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 3:1) to give 314 mg (94%) of **12**. Mp: 63−64 °C. Anal. Found: C, 36.10; H, 2.28; N, 8.31. Calcd for $C_{10}H_8N_2OClI$: C, 35.90; H, 2.41; N, 8.37. NMR: δ_H ($CDCl_3$) 7.49−7.41 (m, 5H, Ph), 6.95 (s, 1H, H-4), 5.16 (s, 2H, CH_2); δ_C ($CDCl_3$) 131.9 (s) 131.5 (d) 130.0 (d), 129.8 (d), 128.7 (d), 128.2 (s), 81.8 (t), 66.3 (s).

1-(Benzyloxy)-2-chloro-5-(tributylstannyl)imidazole (13). After addition of tributylchlorostannane (0.41 mL, 1.5 mmol), the mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:0 → 4:1), affording 438 mg (88%) of **13** as an oil. The compound was unstable, and a correct elemental analysis could not be obtained. NMR: δ_H ($CDCl_3$) 7.42 (s, 5H, Ph), 6.81 (s, 1H, H-4), 5.09 (s, 2H, CH_2), 1.55−0.84 (m, 27H, 3Bu); δ_C ($CDCl_3$) 132.6, 132.5, 129.1, 128.9, 128.4, 127.3, 81.07, 28.47 (J_{C-Sn} = 9 Hz), 26.8 (J_{C-Sn} = 34 Hz), 13.2, 10.0 (J_{C-Sn} = 179 Hz).

Bromination of 1-(Benzyloxy)-2,5-dichloroimidazole (16). 1-(Benzyloxy)-4-bromo-2,5-dichloroimidazole (17). Bromine (0.5 mL, 9.7 mmol) was added slowly with stirring at 0 °C to a mixture of 1-(benzyloxy)-2,5-chloroimidazole (2.0 g, 8.23 mmol), dichloromethane (15 mL), water (15 mL), and sodium carbonate (2.82 g, mmol). After the resulting mixture was stirred for 16 h, sodium sulfite (ca 2 g) dissolved in water (5 mL) was added. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 15 mL). Drying of the combined organic phases followed by filtration, evaporation, and flash chromatography (heptanes−ethyl acetate, 1:0 → 4:1) gave 2.61 g (98%) of **17**. Mp: 51−52 °C (pentane). Anal. Found: C, 37.44; H, 2.08; N, 8.59. Calcd for $C_{10}H_8N_2OCl_2Br$: C, 37.30; H, 2.19; N, 8.70. NMR: δ_H ($CDCl_3$)

7.44 (s, 5H, Ph), 5.20 (s, 2H, CH_2); δ_C ($CDCl_3$) 131.5, 130.1, 130.0, 128.7, 126.0, 115.3, 107.9, 82.1.

Preparation of 4-Substituted 1-(Benzyloxy)-2,5-dichloroimidazoles 18−23. Standard Procedure. Under nitrogen, a solution of **17** (323 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was cooled to −78 °C. *n*-Butyllithium (1.61 M in hexanes) (0.93 mL, 1.5 mmol) was added with stirring over 2 min. After the resulting mixture was stirred for a further 1 min, the electrophile was added. Stirring was continued at −78 °C for 1 h, and the reaction mixture was allowed to warm to 20 °C over the course of 1 h. Stirring was continued at 20 °C for a further 0.5 h. The mixture was worked up by addition of saturated aqueous sodium hydrogen carbonate (10 mL), extraction with dichloromethane (3 × 10 mL), drying ($MgSO_4$), filtration, and removal of the solvents to give the crude product.

1-(Benzyloxy)-2,5-dichloroimidazole (18). After addition of methanol (0.2 mL, 4.9 mmol), the mixture was worked up as described above to give a residue which upon flash chromatography (heptanes−ethyl acetate, 1:0 → 2:1) gave 217 mg (89%) of **18**, identical with the material described above.

1-(Benzyloxy)-2,5-dichloro-4-methylimidazole (19). Methyl iodide (0.32 mL, 5 mmol) was added, and the mixture was stirred at −78 °C for 1 h. To destroy excess methyl iodide, 33% dimethylamine in ethanol (5 mL) was added. The mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:1), affording 219 mg (85%) of **19**. Mp: below room temperature. Anal. Found: C, 51.67; H, 3.91; N, 11.02. Calcd for $C_{11}H_{10}N_2OCl_2$: C, 51.39; H, 3.92; N, 10.90. NMR: δ_H ($CDCl_3$) 7.43 (s, 5H, Ph), 5.15 (s, 2H, CH_2), 2.14 (s, 3H, Me); δ_C ($CDCl_3$) 131.1 (s), 130.0 (d), 129.7 (d), 129.5 (s), 128.6 (d), 125.2 (s), 112.0 (s), 81.6 (t), 12.5 (q).

1-(Benzyloxy)-2,5-dichloro-4-formylimidazole (20). After addition of dimethylformamide (0.15 mL, 2 mmol), the mixture was stirred as in the standard procedure. Then 2 M aqueous hydrochloric acid (5 mL) was added, and the mixture was stirred for 1 h. Addition of saturated aqueous sodium hydrogen carbonate until pH 8 and extractive workup with dichloromethane as described above gave a residue which upon flash chromatography (heptanes−ethyl acetate, 1:1) afforded 252 mg (93%) of **20** as a yellow oil which crystallized from pentane−ethyl acetate. Recrystallization (pentane) gave mp 85−86 °C. Anal. Found: C, 48.84; H, 2.93; N, 10.37. Calcd for $C_{11}H_8N_2O_2Cl_2$: C, 48.73; H, 2.97; N, 10.33. NMR: δ_H ($CDCl_3$) 9.74 (s, 1H, CHO), 7.47−7.27 (m, 5H, Ph), 5.27 (s, 2H, CH_2); δ_C ($CDCl_3$) 182.7 (d), 131.2 (s), 130.3 (d), 130.3 (d), 129.8 (s), 128.9 (d), 122.1 (s), 82.5 (t). One signal was hidden by another absorption.

1-(Benzyloxy)-2,5-dichloro-4-iodoimidazole (21). After addition of iodine (508 mg, 2 mmol), the mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:0 → 4:1), affording 352 mg (96%) of **21**. Mp: 56 °C (pentane). Anal. Found: C, 32.85; H, 1.96; N, 7.54. Calcd for $C_{10}H_7N_2OCl_2I$: C, 32.55; H, 1.91; N, 7.59. NMR: δ_H ($CDCl_3$) 7.42 (s, 5H, Ph), 5.20 (s, 2H, CH_2); δ_C ($CDCl_3$) 131.7, 130.3, 130.2, 128.9, 127.6, 121.1, 82.2, 75.4.

1-(Benzyloxy)-2,5-dichloro-4-(tributylstannyl)imidazole (22). After addition of tributylchlorostannane (0.41 mL, 1.5 mmol), the mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:0 → 4:1), affording 441 mg (83%) of **22** as an oil. Anal. Found: C, 49.60; H, 6.63; N, 5.27. Calcd for $C_{22}H_{34}N_2OCl_2Sn$: C, 49.66; H, 6.44; N, 5.26. NMR: δ_H ($CDCl_3$) 7.45−7.42 (m, 5H, Ph), 5.17 (s, 2H CH_2),1.6−0.8 (m, 27H, 3 Butyl); δ_C ($CDCl_3$) 133.4, 132.2, 129.9, 129.5, 128.5, 123.6, 81.3, 28.5 (J_{C-Sn} = 10 Hz), 27.0 (J_{C-Sn} = 28 Hz), 13.5, 9.6. (t, J_{C-Sn} = 180 Hz).

1-(Benzyloxy)-2,5-dichloroimidazole-4-carboxylic Acid (23). Lithiation was performed as described above. Then the septum was removed, and solid CO_2 (1.5 g) was added. Stirring was continued for 1 h at −78 °C, and the mixture was allowed to warm to room temperature over the course of 1 h. HCl (1 M, 10 mL) was added, and stirring was continued for a further 1 h. The THF was removed, which induced precipitation. Filtration, washing with HCl (1 M), and drying gave 252 mg (78%) of **23**. Anal. Found: C, 46.13; H, 3.07; N, 9.54. Calcd for $C_{11}H_8N_2O_3Cl_2$: C, 46.02; H, 2.81; N, 9.75. NMR: δ_H (DMSO) 7.52−7.45 (m, 5H, Ph), 5.34 (s, 2H, CH_2); δ_C (DMSO) 161.6, 132.6, 130.8, 130.3, 129.1, 127.7, 123.9, 122.3, 82.3.

Bromination of 7. 1-(Benzyloxy)-4,5-dibromo-2-chloroimidazole (31). Bromine (0.79 mL, 15.37 mmol) was added to a mixture of 1-(benzyloxy)-2-chloroimidazole (916.9 mg, 4.39 mmol) and sodium carbonate (1.67 g, 15.8 mmol) in DMF (10 mL). The mixture was stirred for 20 h at room temperature and quenched with saturated aqueous sodium sulfite (10 mL). Extraction with diethyl ether (3 × 20 mL), drying, filtration, and evaporation followed by flash chromatography (heptanes−ethyl acetate, 1:0 → 4:1) gave 1.25 g (77%) of **31**. Mp: 65−66 °C. Anal. Found: C, 33.00; H, 2.19; N, 7.56. Calcd for $C_{10}H_7N_2OClBr_2$: C, 32.78; H, 1.93; N, 7.64. NMR: δ_H ($CDCl_3$) 7.46−7.42 (m, 5H, Ph), 5.16 (s, 2H, CH_2); δ_C ($CDCl_3$) 131.6, 130.1, 130.0, 128.8, 127.0, 111.8, 101.6, 82.1.

Sulfite Reduction of 31. 1-(Benzyloxy)-4-bromo-2-chloroimidazole (32). Bromine (0.71 mL, 13.8 mmol) was added to a mixture of **7** (826 mg, 3.96 mmol) and sodium carbonate (1.57 g, 14.2 mmol) in DMF (4 mL). The mixture was stirred for 20 h at room temperature and quenched with saturated aqueous sodium sulfite (5 mL). Extraction with diethyl ether (3 × 20 mL), drying, filtration, and evaporation gave **31**, which, without further purification, was dissolved in methanol (40 mL). Sodium sulfite·$7H_2O$ (10 g, 39.6 mmol) and water (20 mL) were added, and the mixture was refluxed for 24 h. Extraction with dichloromethane (3 × 50 mL), drying, filtration, and evaporation followed by flash chromatography (heptanes−ethyl acetate, 1:0 → 4:1) gave 891 mg (78%) of **32**. Mp: 71 °C (ethyl acetate−pentanes). Anal. Found: C, 42.06; H, 2.98; N, 9.65. Calcd for $C_{10}H_8N_2OClBr$: C, 41.77; H, 2.80; N, 9.74. NMR: δ_H ($CDCl_3$) 7.43 (s, 5H, Ph), 5.16 (s, 2H, CH_2); δ_C ($CDCl_3$) 131.6, 130.1, 130.0, 128.8, 127.0, 111.8, 101.6, 82.1.

Preparation of 4-Substituted 1-(Benzyloxy)-2-chloro-5-(trimethylsilyl)imidazoles 25−28. Standard Procedure. Under nitrogen, a solution of **31** (367 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was cooled to −78 °C. *n*-Butyllithium (1.62 M in hexanes) (0.68 mL, 1.1 mmol) was added with stirring over 2 min. After the resulting mixture was stirred for a further 1 min, trimethylchlorosilane (0.138 mL, 1.1 mmol) was added. After the resulting mixture was stirred for 0.5 h at −78 °C, *n*-butyllithium (1.62 M in hexanes) (0.68 mL, 1.1 mmol) was added over 2 min. After the resulting mixture was stirred for a further 1 min, the electrophile was added. Stirring was continued at −78 °C for 1 h, and the reaction mixture was allowed to warm to 20 °C over the course of 1 h. Stirring was continued at 20 °C for a further 0.5 h. The mixture was worked up by addition of saturated aqueous sodium hydrogen carbonate (10 mL), and extraction with dichloromethane (3 × 10 mL), drying ($MgSO_4$), filtration, and removal of the solvents gave the crude product.

1-(Benzyloxy)-4-bromo-2-chloro-5-(trimethylsilyl)imidazole (24). Instead of addition of the second equivalent of *n*-butyllithium, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (10 mL), and the reaction mixture was allowed to warm to 20 °C. Addition of water (10 mL), extraction with dichloromethane (3 × 20 mL), drying ($MgSO_4$), filtration, and removal of the solvents gave the crude product. Chromatography (ethyl acetate−heptanes, 0:1 → 1:4) provided 338 mg (94%) of **24**. Mp: 65 °C (heptanes). R_f (EtOAc−heptanes, 1: 4): 0.56. Anal. Found: C, 43.65; H, 4.49; N, 7.77. Calcd for $C_{13}H_{16}N_2OBrClSi$: C, 43.41; H, 4.48; N, 7.79. NMR: δ_H ($CDCl_3$): 7.43 (s, 5H, Ph), 5.13 (s, 2H, CH_2), 0.42 (s, 9H, $SiMe_3$); δ_C ($CDCl_3$) 132.2, 129.7, 129.5, 128.9, 128.5, 127.3, 118.9, 81.9, −0.24.

1-(Benzyloxy)-2-chloro-5-(trimethylsilyl)imidazole (25). After addition of methanol (0.2 mL, 4.9 mmol), the mixture was worked up as above to give a residue which was flash chromatographed (heptanes−ethyl acetate, 1:0 → 4:1) to produce 255.3 mg (91%) of **25**. Mp: 53−54 °C. Anal. Found: C, 55.88; H, 6.12; N, 9.98. Calcd for $C_{13}H_{17}N_2OClSi$: C, 55.60; H, 6.10; N, 9.98. NMR: δ_H ($CDCl_3$): 7.48−7.42 (m, 5H, Ph), 6.91 (s, H-4), 5.15 (s, 2H, CH_2), 0.34 (s, 9H, $SiMe_3$); δ_C ($CDCl_3$)

132.8 (s), 132.4 (d), 129.9 (s), 129.5 (d), 129.3 (d), 128.8 (d), 81.3 (t), −1.3 (q). One signal was hidden by another absorption.

1-(Benzyloxy)-2-chloro-4-methyl-5-(trimethylsilyl)imidazole (26). Method a. Methyl iodide (0.32 mL, 5 mmol) was added, and the mixture was stirred at −78 °C for 1 h. To destroy excess methyl iodide, 33% dimethylamine in ethanol (5 mL) was added. The mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:0 → 4:1), affording 215 mg (71%) of **26**. Anal. Found: C, 57.03, H, 6.51, N, 9.51. Calcd for $C_{14}H_{19}N_2OClSi$: C,57.35; H, 6.50; N, 9.50. NMR: δ_H ($CDCl_3$) 7.47−7.40 (m, 5H, Ph), 5.10 (s, 2H, CH_2), 2.24 (s, 3H, Me), 0.35 (s, 9H, $SiMe_3$); δ_C ($CDCl_3$) 141.6 (s), 132.8 (s), 129.4 (d), 129.2 (d), 128.7 (d), 127.7(s), 123.8 (s), 81.1 (t), 15.8 (q), −0.4 (q).

Method b. *n*-Butyllithium (1.58 M in hexanes) (2.28 mL, 3.60 mmol) was added with stirring over 2 min to a solution of **24** (1079 mg, 3 mmol) in dry tetrahydrofuran (15 mL) at −78 °C. After the resulting mixture was stirred for a further 2 min, methyl iodide (0.29 mL, 4.5 mmol) was added. Stirring was continued for a further 1 h at −78 °C. After addition of 33% dimethylamine in ethanol (5 mL), the reaction mixture was allowed to warm to 20 °C. Addition of saturated aqueous sodium hydrogen carbonate (15 mL) and water (15 mL), extraction with dichloromethane (3 × 30 mL), drying ($MgSO_4$), filtration, and removal of the solvents gave the crude product, which was flash chromatographed (heptanes−ethyl acetate, 1:0 → 4:1), affording 761 mg (86%) of **26**, identical with the material above.

1-(Benzyloxy)-2-chloro-4-formyl-5-(trimethylsilyl)imidazole (27). After addition of dimethylformamide (0.2 mL, 2.6 mmol), the mixture was stirred as in the standard procedure. Then 2 M aqueous hydrochloric acid (5 mL) was added, and the mixture was stirred for 1 h. Addition of saturated aqueous sodium hydrogen carbonate until pH 8 and extractive workup with dichloromethane as described above gave a residue which upon flash chromatography (heptanes−ethyl acetate, 1:0 → 4:1) afforded 231 mg (75%) of **27**.[16] Mp: 45 °C. R_f (ethyl acetate−heptanes, 1:4): 0.36. Anal. Found: C, 54.30; H, 5.44; N, 9.16. Calcd for $C_{14}H_{17}N_2O_2ClSi$: C, 54.45; H, 5.55; N, 9.07. NMR: δ_H ($CDCl_3$) 9.80 (s, CHO) 7.45 (s, 5H, Ph), 5.16 (s, 2H, CH_2), 0.46 (s, 3H, $SiMe_3$); δ_C ($CDCl_3$) 186.4, 142.1, 136.8, 132.0, 131.9, 129.9, 129.6, 128.9, 82.2, −1.0.

1-(Benzyloxy)-2-chloro-4-formylimidazole (30). The crude product present in the dichloromethane solution was dissolved in methanol (10 mL). Addition of potassium carbonate (290 mg), stirring for 1 h at room temperature, addition of water (20 mL), extraction with dichloromethane (3 × 20 mL), drying ($MgSO_4$), filtration, and removal of the solvents gave the crude product, which after chromatography (heptanes−ethyl acetate, 10:1 → 4:1) afforded 167 mg (70%) of **30**. Mp: 83 °C (ethyl acetate−pentane). R_f (EtOAc−heptanes 1:4): 0.19. Anal. Found: C, 56.05; H, 3.88; N, 11.79. Calcd for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.84. NMR: δ_H ($CDCl_3$) 9.65 (s, CHO) 7.49−7.35 (m, 6H, Ph), 5.20 (s, 2H, CH_2); δ_C ($CDCl_3$) 184.9, 135.4, 131.9, 130.3, 130.0, 129.9, 129.1, 122.5, 82.4.

1-(Benzyloxy)-2-chloro-4-iodo-5-(trimethylsilyl)imidazole (28). After addition of iodine (508 mg, 2.0 mmol), the mixture was worked up as above to give the crude product, which was flash chromatographed (heptanes−ethyl acetate, 4:1), affording 354 mg (87%) of yellow **28**. Mp: 50−51 °C. Anal. Found: C, 38.67; H, 3.83; N, 6.76. Calcd for $C_{13}H_{16}N_2OClISi$: C, 38.38; H, 3.96; N, 6.88. NMR: δ_H ($CDCl_3$) 7.44 (s, 5H, Ph), 5.11 (s, 2H, CH_2), 0.44 (s, 3H, $SiMe_3$); δ_C ($CDCl_3$) 132.2, 132.0, 130.2, 129.7, 129.4, 128.8, 85.5, 81.9, −0.43.

Desilylation with Sodium Methoxide. 1-(Benzyloxy)-2-chloro-4-methylimidazole (29). To a mixture of sodium (160 mg, 7 mmol) in methanol (2 mL) was added **26** (166 mg, 0.56 mmol) in methanol (2 mL). Stirring for 3 h, addition of saturated aqueous sodium hydrogen carbonate (5 mL) and water (5 mL), extraction with dichloromethane (3 × 10 mL), drying, filtration, and evaporation followed by flash chromatography (heptanes−ethyl acetate, 4:1) afforded 119 mg (95%) of **29** as a white crystalline compound. Mp: 50−51 °C (ethyl acetate−pentane). Anal. Found: C, 59.60; H, 4.95; N, 12.55. Calcd for $C_{11}H_{11}N_2OCl$: C, 59.33; H, 4.98; N, 12.58. NMR: δ_H ($CDCl_3$) 7.43−7.37 (m, 5H, Ph), 6.61 (q, J = 0.9 Hz, 1H, H-5) 5.10 (s, 2H, CH_2), 2.11 (d, J = 0.6 Hz, 3H, Me); δ_C ($CDCl_3$) 133.3 (s), 133.0 (s), 129.8 (d), 129.6 (d), 128.8 (d), 125.9 (s), 114.0 (d), 81.7 (t), 14.1 (q).

Debenzylation with Hydrogen/Palladium on Carbon. 1-Hydroxyimidazole Hydrochloride (15). 18 (182 mg, 0.75 mmol), 10% palladium on carbon (50 mg), and methanol (6 mL) were stirred under hydrogen at 1 bar and 0 °C for 2 h. Filtration through kieselguhr and removal of the solvent gave 90 mg (100 %) of **15**, identical with the material described previously.[7,17]

1-Hydroxy-5-methylimidazole Hydrochloride (14). 9 (348 mg, 1.56 mmol), 10% palladium on carbon (65 mg), and methanol (10 mL) were stirred under hydrogen at 1 bar and 0 °C for 2 h. Filtration through kieselguhr and removal of the solvent gave 201.1 mg (96%) of **14**. Mp: 159−160 °C. Anal. Found: C, 35.51; H, 5.03; N, 20.56. Calcd for $C_4H_7N_2OCl$: C, 35.70; H, 5.24; N, 20.82. NMR: δ_H (D_2O) 8.65 (d, J = 1.93 Hz, 1H), 7.08 (s, 1H), 2.24 (d, J = 1.93 Hz); δ_C (D_2O) 131.0, 130.7, 115.3, 8.0.

1-Hydroxy-4-methylimidazole Hydrochloride (33). 29 (167 mg, 0.75 mmol), 10% palladium on carbon (38 mg), and methanol (4 mL) were stirred under hydrogen at 1 bar and 0 °C for 2 h. Filtration through kieselguhr and removal of the solvent followed by addition of 4 M HCl and removal of the solvent gave 100 mg (99%) of **33** as a semicrystalline compound. Anal. Found: C, 33.63; H, 4.87; N, 19.41. Calcd for $C_4H_6N_2O$, 1.25 mol of HCl: C, 33.44; H, 5.09; N, 19.50. NMR: δ_H (D_2O) 8.65 (s, 1H), 7.19 (s, 1H), 2.22 (s, 3H); δ_C (D_2O) 129.7, 129.1, 117.3, 10.1.

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Supporting Information Available: Spectral data of compound **13**. This material is available free of charge via the Internet: http://pubs.acs.org.

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(16) The compound slowly desilylates to **30** on silica gel.

(17) Baus, U.; Reuther, W. Eur. Pat. Appl. EP, 1991; *Chem. Abstr.* **1991**, *115*, 29334.