1-Chlorotetradecane: 43% yield; NMR ($CDCl_3$) δ 3.54 (2 H, t, J = 6.9 Hz), 1.81 (2 H, q, J = 6.9 Hz), 1.26 (22 H, m), 0.88 (3 H, t, J = 6.3 Hz); IR (neat) 2924, 2853, 1628, 1466, 1377, 1287, 1090, 722 cm^{-1}.[12,15]

1-(2-Chloroethyl)-4-methoxybenzene (2b) via Tosylhydrazine 2a. 1-Tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine (**2a**) (100 mg, 0.314 mmol) was added to a solution of dry chloroamine in ether (100 mL) in one portion at 0 °C. A solution of KOH (100 mg) in MeOH (10 mL) was added immediately to the above mixture at 0 °C. The mixture was heated to reflux overnight under nitrogen. After the mixture was cooled to room temperature, water (80 mL) was added and the mixture was stirred for another 20 min. The organic layer was separated and concentrated. The residue was dissolved in hexanes (190 mL) and washed with saturated $NaHCO_3$ and brine. Drying and removal of hexanes afforded **2b** as a crude oil, 114 mg (51% purity by GC), 95% calculated yield. Spectra were identical to **2b** described above.

1-(2-Bromoethyl)-4-methoxybenzene (2c). Bromine (55.2 mg, 0.345 mmol) was added to a solution of 1-tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine (100 mg, 0.314 mmol) in dry ether (100 mL) at 0 °C. A solution of KOH (100 mg) in MeOH (10 mL) was added dropwise immediately to the above mixture at 0 °C. The mixture was heated to reflux overnight under nitrogen, and water (50 mL) was added after it cooled to room temperature. The ether layer was collected and washed with water, $NaHSO_3$, saturated $NaHCO_3$, and brine. Drying and removal of solvent afforded **2c** as a crude oil: 101 mg (58% purity by GC-MS); 85% calculated yield; GC-MS M^+ = 214 (1.2), 135 (7), 121 (100), 91 (6.7); NMR ($CDCl_3$) δ 7.14 (2 H, d, J = 8.3 Hz), 6.68 (2 H, d, J = 7.8 Hz), 3.80 (3 H, s), 3.53 (2 H, t, J = 7.9 Hz), 3.10 (2 H, t, J = 7.7 Hz); IR (neat) 3000, 2950, 2830, 1620, 1518, 1360, 1175, 1030, 990, 878, 765 cm^{-1}.[20]

1-(2-Iodoethyl)-4-methoxybenzene (2d). Iodine (159 mg, 0.628 mmol) was added to a solution of 1-tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine (100 mg, 0.314 mmol) in dry ether (100 mL) at 0 °C. A solution of KOH (100 mg) in MeOH (10 mL) was added dropwise immediately to the above mixture at 0 °C. The mixture was heated to reflux overnight under nitrogen, and water (50 mL) was added after it cooled to room temperature. The ether layer was collected and washed with water, $NaHSO_3$, saturated $NaHCO_3$, and brine. Drying and removal of solvent afforded **2d** as a crude oil: 76 mg (76% purity by GC-MS): 70% calculated yield; GC-MS M^+ = 262 (0.4), 135 (13), 121 (100), 91 (16), 77 (13); NMR ($CDCl_3$) δ 7.12 (2 H, d, J = 8.3 Hz), 6.85 (2 H, d, J = 8.7 Hz), 3.80 (3 H, s), 3.32 (2 H, t, J = 6.7 Hz), 3.11 (2 H, t, J = 7.4 Hz); IR (neat) 3000, 2958, 2834, 1611, 1512, 1463, 1247, 1177, 1036, 818, 755 cm^{-1}.[20]

Acknowledgment. We thank Professor Wolfgang Mueller for his assistance.

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Multifunctionalization of Imidazole via Sequential Halogen-Metal Exchange: A New Route to Purine-Ring Analogs†

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A new method for the synthesis of purine-ring analogs based upon the sequential halogen-metal exchange functionalization of 1-[(benzyloxy)methyl]-2,4,5-triiodoimidazole (1) has been developed and is illustrated by the synthesis of (1*H*)-imidazo[4,5-*d*]pyridazin-4(5*H*)-one (2-aza-3-deazahypoxanthine, 8). Treatment of 1 with BuLi followed by quench with PhSSPh afforded the 2-(phenylthio) derivative, which upon treatment with BuLi followed by quench with DMF gave the 5-carboxaldehyde. This aldehyde was converted into its ethylene acetal, which was treated with BuLi followed by quench with $ClCO_2CH_3$ to afford a 4-(methoxycarbonyl)imidazole. Removal of the phenylthio group with Al(Hg) and the (benzyloxy)methyl and ethylene acetal protecting groups concomitantly with 3 M HCl afforded methyl 5(4)-formylimidazole-4(5)-carboxylate, which underwent cyclocondensation with ethanolic NH_2NH_2 to give target 8. This synthetic approach was found amenable to modification by efficient "one-pot" multistep transformations. Thus, treatment of 1 with (a) BuLi, (b) $(CH_3)_3SiCl$, (c) BuLi, (d) $(CH_3)_2NN(CH_3)CHO$, (e) BuLi, and (f) $(CH_3OCO)_2O$ afforded the N-protected 4-(methoxycarbonyl)-imidazole-5-carboxaldehyde (13) in 25% yield *directly from* 1. Imidazole 13 was then elaborated to 8 in two steps. 1-Formyl-1,2,2-trimethylhydrazine is a recommended replacement for DMF as a tandem formylating/ortho-metalation directing agent.

The development and/or refinement of synthetic methods for functionalizing the carbon atom positions of imidazole[1-7] continues to be a central concern in the pursuit of bioactive synthetic analogs of naturally-occurring imidazole-based compounds. A major obstacle in carbanion-based versions of these efforts arises from the fact that the most readily-generated sp^2 carbanion, namely that at the C2 position,[2] is seldom the one desired. In the synthesis of analogs of the amino acid histidine, for example, one needs to achieve an efficient regioselective preparation of an imidazol-4(5)-yl carbanionic species. Both the latest imidazol-4-yl monoanion-based methodology developed by Turner et al.[1a] and the imidazole-1,4-diyl dianion-based one developed in Katritsky's laboratory[1b] address this need. In the pursuit of requisite imidazole precursors to

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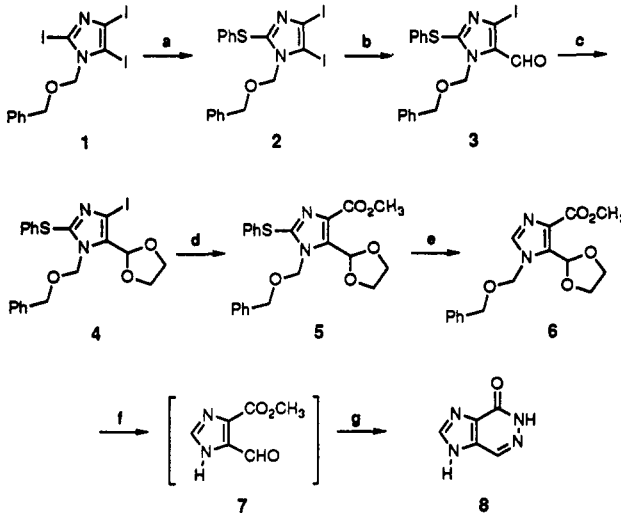
Scheme I[a]



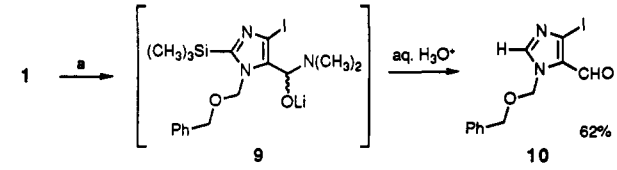
[a] Reagents and conditions: (a) BuLi, −78 °C, PhSSPh, −78 → 25 °C, 94%; (b) BuLi, −78 °C, DMF, 99%; (c) $HO(CH_2)_2OH$, pyr/TsOH, C_6H_6, 58%; (d) BuLi, −78 °C, $ClCO_2CH_3$, 80%; (e) Al(Hg), 25 °C, 6 h, 59%; (f) 3 M HCl, 74%; (g) NH_2NH_2, EtOH, reflux, 24 h, 59% from 6.

new purine-ring analogs, on the other hand, the task of obtaining 4,5-asymmetrically-disubstituted imidazoles presents additional difficulties in the regioselective control of carbanion generation and stabilization. Based upon the results of our recent study of the regioselective formation of imidazol-2-yllithium, imidazol-4-yllithium, and imidazol-5-yllithium species,[7] we saw the opportunity to develop a convenient route to certain 2-unsubstituted 4,5-asymmetrically-disubstituted imidazoles and, by doing so, illustrate a general synthetic strategy which should prove applicable to the preparation of an even wider variety of 2,4,5-trifunctionalized imidazole derivatives.

Results and Discussion

The purine analog 2-aza-3-deazahypoxanthine[8,9a] (imidazo[4,5-*d*]pyridazin-4(5)-one, **8**) is a parent heterocycle to a variety of nucleoside analogs,[9] some of which are of interest as potential inhibitors of cellular purine nucleoside-specific facilitated diffusion.[10] As shown in Scheme I, our first halogen–metal exchange-based synthetic approach to **8** involved the stepwise sequential functionalization of first the C2, then the C5, and finally the C4 position of 1-[(benzyloxy)methyl]-2,4,5-triiodoimidazole

Scheme II[a]



[a] Key: (i) BuLi, −78 °C; (ii) $(CH_3)_3SiCl$, −78 → 25 °C; (iii) BuLi, −78 °C; (iv) DMF, −78 → 25 °C.

(**1**). This order of N-protected imidazolyl carbanion generation was established earlier by Iddon and Khan[3c] and has been confirmed by us.[7] After our initial attempts to utilize a *tert*-butyldiphenylsilyl protecting group for C2[1c] resulted in unavoidable protodesilylation occurring at the subsequent acid-catalyzed acetalation stage, we selected the same phenylthio protecting group for this position as has been utilized successfully by others.[3h,5b] Thus, the imidazol-2-yllithium species generated upon treatment of **1**[7] with butyllithium was quenched with PhSSPh to afford the 2-(phenylthio)imidazole **2** in high yield. With its C2 position blocked, **2** underwent butyllithium-mediated halogen–metal exchange exclusively at the C5 position, and the resulting imidazol-5-yllithium species afforded the 2-(phenylthio)imidazole-5-carboxaldehyde **3** in excellent yield upon quench with DMF. Subsequent protection of the aldehyde functionality of **3** then gave the ethylene acetal **4**, from which an imidazol-4-yllithium species was generated. Quench of this species with $ClCO_2CH_3$ gave the methyl imidazole-4-carboxylate **5**.[11] The C2 protecting group of this trifunctionalized imidazole derivative was removed under reductive conditions to give ester **6** in good yield. Next, concomitant removal of the (benzyloxy)methyl and ethylene acetal protecting groups of **6** was effected in 3 M HCl at room temperature, and the resulting methyl 5(4)-formylimidazole-4(5)-carboxylate **7**[9a] was promptly cyclized with ethanolic hydrazine to give **8** in 59% yield from **6**. According to the steps outlined in Scheme I, our preparation of **8** from **1** was accomplished in 15% overall yield.

For some applications, it may be possible to render a halogen–metal exchange-based imidazole multifunctionalization much more efficient by incorporating two or more steps into a "one-pot" multistep synthetic manipulation. In one such approach,[4a] C2 protection can be followed immediately by C5 functionalization if a trialkylsilyl moiety is employed as a base-stable *transient* protecting group[12] for C2. Silyl C2-protection of imidazoles has been utilized by others with varying degrees of success.[1b-c,2c,4a-b,d] Treatment of **1** with BuLi was followed by quench with chlorotrimethylsilane to afford a putative 2-TMS-protected intermediate, which was not isolated but instead immediately treated with another equiv of BuLi followed by quench with DMF to afford the 2,5-difunctionalized imidazole **9** (Scheme II). Aqueous workup of **9** then afforded, after chromatographic purification, the 4-iodoimidazole-5-carboxaldehyde **10**[7] in 62% yield directly from **1**. The often moisture-sensitive 2-(trialkylsily)imidazoles are known to hydrolyze readily under mildly acidic aqueous conditions, a property most likely due to the stability of the zwitterion initially produced by attack of water on the silicon atom of the 2-silyl-substituted imidazolium cation.[2a]

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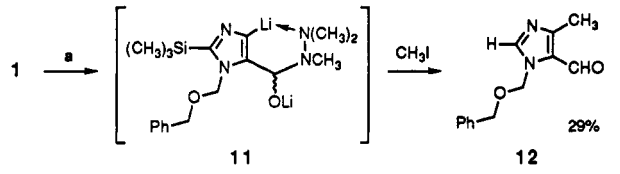
(11) An unsuccessful attempt to lithiate and functionalize the C4 position of an imidazole derivative quite similar to our compound **4** has been reported: see ref 3d.

(12) The concept of transient protection by trimethylsilylation applied to the synthesis of protected nucleosides has been described: Ti, G. S.; Gaffney, B. L.; Jones, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1316.

Scheme III[a]



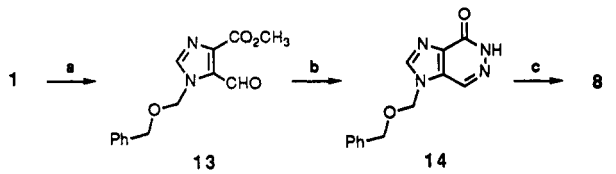
11 12

[a] Key: (i) BuLi, −78 °C; (ii) $(CH_3)_3SiCl$, −78 → 25 °C; (iii) BuLi, −78 °C; (iv) $(CH_3)_2NN(CH_3)CHO$, −78 → 25 °C; (v) BuLi, −78 °C.

Another potential shortcut approach involves the merging of C4 and C5 functionalizations into a one-pot multistep sequence. For the specific purpose of preparing 4-functionalized imidazole-5-carboxaldehydes, an α-(dimethylamino)alkoxide moiety (such as that in **9** generated upon addition of DMF to an imidazol-5-yllithium species) can be employed as an in situ ortho-metalation directing group[13] for the C4 position. However, we considered that the use of a formyl*hydrazine* reagent in place of a formylamine as a tandem formylating/ortho-metalation directing agent would have certain advantages. As an "α-effect" nucleophilic species, the terminal amino group of an α-hydrazinoalkoxide should form a stronger chelate than does that of an α-aminoalkoxide. In addition, an α-hydrazinoalkoxide group would form a 6-membered cyclic chelate to an *o*-lithio substituent, in contrast to the 5-membered one formed by an α-aminoalkoxide. Since 5,6-fused bicyclic chelation complexes have a geometry-derived thermodynamic advantage over their 5,5-fused counterparts, we reasoned that the use of a formylhydrazine reagent might have a markedly favorable impact especially upon ortho-difunctionalizations of 5-membered ring heterocycles. We now report that the use of 1-formyl-1,2,2-trimethylhydrazine, prepared in three steps from 1,1-dimethylhydrazine,[14] in place of DMF does indeed provide for cleaner one-pot ortho-difunctionalizations in the limited number of cases examined thus far (e.g., vide infra).[15]

If a merged C4/C5 imidazole difunctionalization sequence were to be preceded by a transient C2 silylation, we considered that a one-pot 2,4,5-*trifunctionalization* of an N-protected imidazole could be accomplished. We have done this by first treating **1** with BuLi followed by TMS–chloride to silylate C2 and then treating the silylated imidazole intermediate with BuLi followed by $(CH_3)_2NN(CH_3)CHO$ to functionalize C5, next generating the chelated imidazol-4-yllithium species **11** by treatment with yet another equiv of BuLi, and finally alkylating **11** with CH_3I to afford the 4-methylimidazole-5-carboxaldehyde **12** in 29% yield *directly from* **1** (Scheme III). A much lower yield of **12** was realized upon replacement of $(CH_3)_2NN(CH_3)CHO$ with DMF. A definitive structural assignment of aldehyde **12** was made possible in part by an analysis of its short- and long-range HETCOR NMR spectral data. In a similar fashion, the desired 4-(methoxycarbonyl)-imidazole-5-carboxaldehyde **13** was obtained in 25% yield directly from **1** upon substitution of dimethylpyrocarbonate[16] for the iodomethane as the final electrophilic reagent in this procedure (Scheme IV). Cyclocondensation of **13** with hydrazine proceeded smoothly to afford the N-protected 2-aza-3-deazahypoxanthine derivative **14** in high yield. Removal of the (benzyloxy)methyl group of **14** then afforded **8**, thereby completing a more efficient synthesis than the stepwise approach outlined in Scheme I. Our successful conversions of **1** → **12** and of **1** → **13** represent the first one-pot 2,4,5-trifunctionalizations of an N-protected imidazole resulting in the preparation of 2-unsubstituted 4,5-asymmetrically-disubstituted imidazole products. We note here that both reaction time and temperature appear to be of critical importance to the success of these one-pot imidazole trifunctionalizations.

Scheme IV[a]



13 14

[a] Reagents and conditions: (a) (i) BuLi, −78 °C; (ii) $(CH_3)_3SiCl$, −78 → 25 °C; (iii) BuLi, −78 °C; (iv) $(CH_3)_2NN(CH_3)CHO$, −78 → 25 °C; (v) BuLi, −78 °C; (vi) $(CH_3OCO)_2O$, 25% from **1**; (b) NH_2NH_2, EtOH, reflux, 80%; (c) 3 M HCl, 98%.

In summary, the sequential halogen–metal exchange approach to multifunctionalized imidazoles illustrated by our synthesis of 2-aza-3-deazahypoxanthine should prove quite useful for the preparation of purine analogs and other biologically-important 2,4,5-trifunctionalized imidazole derivatives. The approach is regioselective in carbanion generation and is amenable to modification with one-pot multistep synthetic transformations.

Experimental Section

Materials and Methods. Melting points were determined on a capillary tube apparatus and are uncorrected. Radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA) using Merck silica gel-60 (with fluorescent indicator) as adsorbent. Flash column chromatography was performed using 70–230 mesh Merck silica gel-60. Tetrahydrofuran was dried by distillation from sodium under argon, using benzophenone ketyl as indicator. DMF was predried over P_2O_5 and then distilled from the same under argon in vacuo. ^1H, ^{13}C, and short- and long-range 2D ^1H–^{13}C heteronuclear correlation (HETCOR) NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C. These spectra were recorded with tetramethylsilane (δ = 0.0 for ^1H) or $CDCl_3$ (δ = 77.0 for ^{13}C) as internal reference. All compounds prepared in this study were judged to be at least 95% pure by NMR analysis. A majority of the compounds were found to exist as oils; thus, high-resolution mass spectral analyses were obtained in lieu of elemental microanalyses. Diphenyl disulfide, methyl chloroformate, chlorotrimethylsilane, 97% hydrazine, iodomethane, butyllithium in hexanes, and poly(2-vinylpyridine-co-styrene) were purchased from the Aldrich Chemical Co. Benzyl chloromethyl ether was purchased from Fluka. Chlorotrimethylsilane was purified by distillation from CaH_2 and was stored over poly(2-vinylpyridine-co-styrene). Butyllithium was titrated with diphenylacetic acid in dry THF solution at 0 °C. Elemental microanalyses were performed by Tom McCarthy at the University of Illinois, and mass spectral analyses were obtained from Richard Milberg and his staff at the Mass Spectrometry facility at the University of Illinois.

1-[(Benzyloxy)methyl]-4,5-diiodo-2-(phenylthio)imidazole (2). A suspension of **1**[7] (9.0 g, 15.8 mmol) in 70 mL of anhyd THF at −78 °C under argon was treated dropwise with BuLi (11.65 mL of a 1.36 M solution in hexanes, 15.8 mmol) and was stirred for 1 h at −78 °C. A solution of diphenyl disulfide (3.44 g, 15.8 mmol) in 10 mL of THF was then added dropwise to the resulting imidazol-2-yllithium solution maintained at −78 °C. The reaction mixture was allowed to warm to room temperature and was kept overnight before it was quenched with saturated aqueous NH_4Cl. The mixture was then extracted with EtOAc (3 × 30 mL), and the combined organic extracts were dried (Na_2SO_4) and rotary

(13) For α-aminoalkoxide-directed ortho-deprotonations, see: (a) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104 and references contained therein. For reviews on directed ortho-deprotonations, see: (b) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (c) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (d) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(14) Beltrami, R. T.; Bissell, E. R. *J. Am. Chem. Soc.* **1956**, *78*, 2467.

(15) A detailed comparison of these two reagents will be reported separately: Groziak, M. P.; Kongsjahju, A.; Wei, L. Unpublished results.

evaporated to dryness. The residue was dissolved in 10 mL of EtOAc and applied to a silica gel chromatography column. Elution with hexanes afforded diphenyl disulfide, and further elution with 1:5 EtOAc/hexanes gave 8.15 g (94%) of **2** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.19–7.34 (m, 10, PhH), 5.53 (s, 2, CH_2N), 4.43 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 143.0 (C2), 136.2 and 133.3 (Ph-quaternary C), 129.3–127.3 (each PhC), 97.9 (C4), 86.1 (C5), 76.9 (CH_2N), 70.6 ($PhCH_2$); low-resolution ACE (alternating CI/EI)-mass spectrum, EI m/z 547.9 (M^+); CI(NH_3) m/z 548.4 (MH^+). Anal. Calcd for $C_{17}H_{14}N_2I_2SO$: C, 37.25; H, 2.57; N, 5.11; I, 46.30. Found: C, 37.55; H, 2.61; N, 5.08; I, 46.15.

1-[(Benzyloxy)methyl]-4-iodo-2-(phenylthio)imidazole-5-carboxaldehyde (3). A solution of **2** (2.06 g, 3.75 mmol) in 20 mL of anhyd THF at −78 °C under argon was treated dropwise with BuLi (2.78 mL of a 1.35 M solution in hexanes, 3.75 mmol) and was stirred for 1 h. Neat DMF (1.85 mL, excess) was added in one portion to this imidazol-5-yllithium solution maintained at −78 °C, and the reaction mixture was then allowed to warm to room temperature and was stirred for 1 h. The mixture was quenched with saturated aqueous NH_4Cl and then was extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and rotary evaporated to give a residue which was purified by column chromatography (1:5 EtOAc/hexanes as eluent) to give 1.40 g (99%) of **3** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 9.49 (s, 1, CHO), 7.29–7.26 (m, 10, PhH), 5.84 (s, 2, CH_2N), 4.56 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 179.9 (CHO), 152.2 (C2), 136.4 and 132.1 (Ph-quaternary C), 130.8–127.3 (each Ph-C), 102.0 (C4), 86.1 (C5), 73.5 (CH_2N), 71.1 ($PhCH_2$); low-resolution ACE-mass spectrum, EI m/z 450.0 (M^+); CI(NH_3) m/z 451.0 (MH^+); high-resolution EI-mass spectrum 449.9899 ($C_{18}H_{15}N_2ISO_2$ requires 449.9901).

1-[(Benzyloxy)methyl]-4-iodo-2-(phenylthio)imidazole-5-carboxaldehyde Ethylene Acetal (4). A solution of **3** (254 mg, 0.56 mmol) in 40 mL of dry C_6H_6 was treated with $HOCH_2CH_2OH$ (0.14 mL, 2.52 mmol), pyridine (25 μL, 0.32 mmol), and *p*-TsOH (58 mg, 0.32 mmol), and the mixture was heated at reflux in a 20-mL-capacity Dean-Stark trap-equipped apparatus for 6 h. The mixture was allowed to cool to room temperature and then was rotary evaporated to dryness in vacuo. The residue was purified by radial chromatography (1:8 EtOAc/hexanes) to afford 160 mg (58%) of **4** as a white solid: mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 7.32–7.21 (m, 10, PhH), 5.93 (s, 1, acetal-CH), 5.58 (s, 2, CH_2N), 4.41 (s, 2, $PhCH_2$), 4.06–3.97 (m, 4, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 136.8 (C2), 133.2 (C5), 130.8 (Ph-quaternary C), 129.3–127.4 (each Ph-C), 98.4 (acetal-CH), 88.0 (C4), 74.0 (CH_2N), 70.4 ($PhCH_2$), 65.2 (CH_2CH_2); low-resolution ACE-mass spectrum, EI m/z 494.0 (M^+); CI(NH_3) m/z 495.0 (MH^+). Anal. Calcd for $C_{20}H_{19}N_2ISO_3$: C, 48.59; H, 3.87; N, 5.67; I, 25.67. Found: C, 48.54; H, 3.84; N, 5.74; I, 25.49.

Methyl 1-[(Benzyloxy)methyl]-5-(1,3-dioxolan-2-yl)-2-(phenylthio)imidazole-4-carboxylate (5). A solution of **4** (128 mg, 0.26 mmol) in 10 mL of anhyd THF at −78 °C under argon was treated dropwise with BuLi (0.22 mL of a 1.36 M solution in hexanes, 0.30 mmol) and kept at −78 °C for 1 h. The resulting imidazol-4-yllithium solution was treated with $ClCO_2CH_3$ (24 μL, 0.30 mmol), and the mixture was allowed to warm slowly to ambient temperature and then was stirred at this temperature overnight. The mixture was quenched with aqueous NH_4Cl and was then extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), and rotary evaporated. The residue was purified by radial chromatography (1:2 EtOAc/hexanes) to afford 86 mg (80% yield) of **5** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.30–6.70 (m, 10, two PhH), 6.70 (s, 1, acetal-CH), 5.64 (s, 2, CH_2N), 4.41 (s, 2, $PhCH_2$), 3.99 (m, 4, CH_2CH_2), 3.92 (s, 3, OCH_3); ^{13}C NMR ($CDCl_3$) δ 163.0 (CO_2CH_3), 134.1 (C2), 132.9 (Ph-quaternary C), 129.4–127.4 (each Ph-C), 116.7 (C5), 99.0 (C4), 96.2 (acetal-CH), 7.48 (CH_2N), 70.4 ($PhCH_2$), 65.2 (CH_2CH_2), 52.1 (CO_2CH_3); high-resolution EI-mass spectrum 426.1249 ($C_{22}H_{22}N_2SO_5$ requires 426.1249).

Methyl 1-[(Benzyloxy)methyl]-5-(1,3-dioxolan-2-yl)-imidazole-4-carboxylate (6). Amalgamated aluminum strips were prepared according to a literature procedure.[16] A solution of **5** (1.0 g, 2.34 mmol) in 150 mL of 50% aqueous EtOH was stirred while freshly prepared Al(Hg) strips (8.15 g, excess) were added in 1.0–1.5 g portions over 5 h. The mixture was filtered through Celite, and the Celite was washed with the absolute EtOH. The filtrate and wash were combined and rotary evaporated. Purification of the residue by radial chromatography (EtOAc as eluent) gave 372 mg of **6** (50%, 59% based on recovered starting material) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1, H2), 7.33–7.31 (m, 5, PhH), 6.66 (s, 1, acetal-CH), 5.50 (s, 2, CH_2N), 4.50 (s, 2, $PhCH_2$), 4.01–3.99 (m, 4, CH_2CH_2), 3.91 (s, 3, OCH_3). ^{13}C NMR ($CDCl_3$) δ 163.0 (CO_2CH_3), 138.8 (C2), 129.2 (Ph-quaternary C), 128.4–126.9 (each Ph-C), 97.1 (C4), 96.1 (acetal-CH), 76.6 (CH_2N), 73.8 (C5), 70.4 ($PhCH_2$), 65.0 (CH_2CH_2), 51.8 (CO_2CH_3); high-resolution CI(CH_4)-mass spectrum 319.1298 ($C_{16}H_{19}N_2O_5$ requires 319.1294).

(1*H*)-Imidazo[4,5-*d*]pyridazin-4(5*H*)-one (8). A solution of **6** (160 mg, 0.50 mmol) in a mixture of 10 mL of 3 M HCl and 5 mL of Me_2CO was stirred at room temperature for 0.5 h and then was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated, and the residue was purified by radial chromatography (1:5 EtOAc/hexanes) to afford 57.5 mg (74%) of **methyl 5-formylimidazole-4-carboxylate (7)** as a pale yellow solid which was used immediately in the next step. A mixture of this sample of **7** and 97% NH_2NH_2 (150 μL, 4.8 mmol) in 10 mL of absolute EtOH was heated at reflux for 24 h. The reaction mixture was allowed to cool, and the excess solvent was removed by rotary evaporation in vacuo. An aqueous solution of the resulting solid was carefully acidified to pH 4 by the addition of 0.1 M HCl. The white precipitate which formed was collected by filtration, was washed with cold water, and was air dried to give 40 mg (79% from **7**, 59% from **6**) of **8** as a white solid: mp >300 °C (lit.[8a] mp >300 °C; lit.[8b] mp >340 °C); ^{1}H NMR ($NaOD/D_2O$) δ 8.60 (s, 1, H8), 8.01 (s, 1, H2); high-resolution CI(CH_4)-mass spectrum 137.0463 ($C_5H_5N_4O$ requires 137.0463).

1-[(Benzyloxy)methyl]-4-iodoimidazole-5-carboxaldehyde (10). A solution of **1** (556 mg, 1.0 mmol) in 20 mL of anhyd THF under argon was cooled to −78 °C and was treated dropwise with BuLi (0.70 mL of a 1.43 M solution in hexanes, 1.0 mmol). The reaction mixture was stirred for 20 min at −78 °C and then was treated dropwise with $(CH_3)_3SiCl$ (0.13 mL, 1.0 mmol). The reaction mixture was allowed to warm slowly to room temperature and was stirred for 4 h. After the mixture was cooled to −78 °C, BuLi (0.70 mL of a 1.43 M solution in hexanes, 1.0 mmol) was added dropwise, and the reaction mixture was stirred for 0.5 h at −78 °C, followed by addition of DMF (0.5 mL, excess). The reaction mixture was allowed to warm slowly to room temperature over 20 min and then was quenched by the addition of 20 mL of saturated aqueous NH_4Cl. The product was isolated by extraction (EtOAc) and purified by radial chromatography (50% EtOAc/hexanes) to afford 210 mg (62%) of **10** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) identical to that of an authentic sample.[7]

1-[(Benzyloxy)methyl]-4-methylimidazole-5-carboxaldehyde (12). A solution of **1** (2.28 g, 4.0 mmol) in 50 mL of anhyd THF at −78 °C under argon was treated dropwise with BuLi (3.08 mL of a 1.30 M solution in hexanes, 4.0 mmol). The reaction mixture was stirred for 1 h at −78 °C and then was treated in one portion with $(CH_3)_3SiCl$ (0.51 mL, 4.0 mmol). The reaction mixture was allowed to warm slowly to room temperature and was stirred overnight. The solution was cooled back down to −78 °C and was treated once again with BuLi (3.08 mL of a 1.30 M solution in hexanes, 4.0 mmol). Stirring was continued for 0.5 h at −78 °C, and then $(CH_3)_2NN(CH_3)CHO$[14] (0.43 mL, 4.0 mmol) was added in one portion. The reaction mixture was allowed to warm slowly to room temperature over 20 min and then was cooled to −78 °C. BuLi (3.08 mL of a 1.30 M solution in hexanes, 4.0 mmol) was added dropwise, and the reaction mixture was stirred for 0.5 h at −78 °C, followed by addition of CH_3I (0.25 mL, 4.0 mmol). The reaction mixture was allowed to warm slowly to room temperature and was stirred overnight. Quench with saturated aqueous NH_4Cl (20 mL) was followed by extraction (EtOAc), and the product was purified by radial chromatography (EtOAc as eluent) to afford 0.27 g (29%) of **12** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1, CHO), 7.69 (s, 1, H2), 7.35–7.27 (m, 5, PhH), 5.71 (s, 2, CH_2N), 4.57 (s, 2, $PhCH_2$), 2.52 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.5 (CHO), 153.2 (C4), 142.1 (C2), 136.2 (Ph-quaternary C), 128.2–127.4 (each Ph-C), 126.0 (C5), 74.6 (CH_2N), 70.6

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($PhCH_2$), 13.0 (CH_3). Correlations observed in a long-range (10 Hz-optimized) HETCOR NMR experiment were *H*2/*C*4, *H*2/*C*5, Ph*H*/Ph-quaternary *C*, Ph*H*/Ph*C*, Ph*H*/Ph*C*H_2, *C*H_2N/*C*2, *C*H_2N/*C*5, *C*H_2N/Ph*C*H_2, Ph*C*H_2/Ph-quaternary *C*, Ph*C*H_2/Ph*C*, Ph*C*H_2/*C*H_2N, *C*H_3/*C*4, *C*H_3/*C*5. High-resolution CI(CH_4)-mass spectrum: 231.1152 ($C_{13}H_{15}N_2O_2$ requires 231.1133).

1-[(Benzyloxy)methyl]-4-(methoxycarbonyl)imidazole-5-carboxaldehyde (13). A solution of 1 (566 mg, 1 mmol) in 20 mL of anhyd THF under argon was cooled to −78 °C and was treated dropwise with BuLi (0.7 mL of a 1.43 M solution in hexanes, 1.0 mmol). The reaction mixture was stirred for 20 min at −78 °C and then was treated dropwise with $(CH_3)_3SiCl$ (0.13 mL, 1.0 mmol). The reaction mixture was allowed to warm slowly to room temperature and stirred for 4 h. After the mixture was cooled to −78 °C, BuLi (0.7 mL of a 1.43 M solution in hexanes, 1.0 mmol) was added dropwise and the reaction mixture was stirred for 0.5 h at −78 °C, followed by addition of $(CH_3)_2NN(CH_3)CHO$[14] (110 μL, 1.0 mmol). The reaction mixture was allowed to warm slowly to room temperature over 20 min and then was cooled to −78 °C immediately. BuLi (0.7 mL of a 1.43 M solution in hexanes, 1.0 mmol) was then added dropwise, and the reaction was stirred for 0.5 h at −78 °C, followed by addition of $(CH_3OCO)_2O$ (110 μL, 1.0 mmol). The reaction mixture was allowed to warm slowly to −35 °C (dry ice/anisole bath) and was kept at this temperature for 4 h. The mixture was then allowed to rise to room temperature and was quenched by the addition of 20 mL of saturated aqueous NH_4Cl. The product was isolated by extraction (EtOAc) and was purified by radial chromatography (1:1 EtOAc/hexanes) to afford 68 mg (25%) of 13 as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 10.52 (s, 1, CHO), 7.82 (s, 1, H2), 7.33–7.27 (m, 5, PhH), 5.80 (s, 2, CH_2N), 4.60 (s, 2, $PhCH_2$), 4.00 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 182.8 (CHO), 162.1 (CO_2), 141.6 (C2), 135.9 (Ph-quaternary C), 128.6–127.8 (each Ph-C), 75.9 (CH_2N), 71.6 ($PhCH_2$), 52.5 (OCH_3). Prolonged storage in $CDCl_3$ solution apparently promoted a D-for-H exchange (presumably at C2) of the sample of 13 ultimately submitted for HRMS: high-resolution EI-mass spectrum 275.1041 ($C_{14}H_{13}DO_4N_2$ requires 275.1015).

1-[(Benzyloxy)methyl]imidazo[4,5-*d*]pyridazin-4(5*H*)-one (14). A mixture of 13 (50 mg, 0.18 mmol) and 97% NH_2NH_2 (150 μL, 4.8 mmol) in 10 mL of abs EtOH was heated at reflux for 12 h. The reaction mixture was allowed to cool to room temperature and was rotary evaporated in vacuo. An aqueous solution of the residue obtained was acidified to pH 4 by the addition of 0.1 M HCl. The product was isolated by extraction (EtOAc) and was purified by radial chromatography (10% CH_3OH/CH_2Cl_2) to afford 54 mg (80%) of 11 as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 8.26 (s, 1, H7), 8.00 (s, 1, H2), 7.35–7.23 (m, 5, PhH), 5.61 (s, 2, CH_2N), 4.52 (s, 2, $PhCH_2$); high-resolution CI(CH_4)-mass spectrum 256.0959 ($C_{13}H_{12}O_2N_4$ requires 256.0960).

8 from 14. A solution of 14 (45 mg, 0.18 mmol) in 4 mL of 1:1 3 M HCl/Me_2CO was stirred at room temperature for 0.5 h. The Me_2CO was then rotary evaporated and the resulting aqueous solution was neutralized to pH 7 by the dropwise addition of 3 M NaOH. The precipitate which formed was collected by filtration and was recrystallized from EtOH to afford 24 mg (98%) of 8 as a white solid: ^1H NMR spectrum identical to that of 8 obtained by the route outlined in Scheme I.

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Structural Features of 1,1′-Bis(azaaryl)-Substituted Ferrocenes

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The Friedländer condensation of acetyl- and propionylferrocene with various aromatic *o*-amino aldehydes results in the formation of azaaryl-substituted ferrocenes. The same reaction carried out on the 1,1′-diacetyl- and 1,1′-dipropionyl analogs provides the corresponding 1,1′-bis(azaaryl)-substituted derivatives. In solution, ^1H NMR shielding effects indicate π-stacking of the azaaryl rings with the pyrido moieties overlapped and pointing in opposite directions. These observations are supported by a single-crystal X-ray analysis.

There is considerable current interest in the design of molecular systems possessing two or more sites capable of interacting in a productive fashion.[1] Such systems might bring together a catalyst and a substrate and often are modeled after naturally occurring prototypes. We have designed several polyaza cavity shaped molecules where conformational effects controlled by polymethylene bridging have been used to mediate the interaction of various species bound in the cavity.[2] In a similar fashion, two "active sites" can be oriented in parallel planes by using appropriate spacer groups.[3] The relative orientation of the sites in these two parallel planes could be varied if the spacer group demonstrated the appropriate axial conformational mobility.

As a spacer group ferrocene shows excellent mobility about the organometallic bond, possessing a low rotational barrier which interconverts syn and anti isomers of a 1,1′-disubstituted derivative.[4] In the event that substituents A and B are planar aromatic species, rotation about the A/B–Cp bond also becomes important. Kasahara and co-workers have reported a variety of 1,1′-diaryl-substituted ferrocenes (aryl = phenyl, 1′-naphthyl, or 4-bi-

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