20, 107144-39-8; 21, 24106-05-6; 22, 113162-47-3; 23, 113162-48-4; 24, 113162-49-5; $MeNH_2$, 74-89-5; $ClSO_2NCO$, 1189-71-5; MeNCO, 624-83-9; $HNMe_2$, 124-40-3; 2-Me-4-$BrC_6H_3NH_2$, 583-75-5; indoline, 496-15-1; 1-carbamoylindoline, 56632-33-8.

Supplementary Material Available: Tables of fractional atomic positional parameters, thermal parameters, interatomic distances and angles, and torsion angles for **7b** (6 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of Arylpyrazines and Bipyridines

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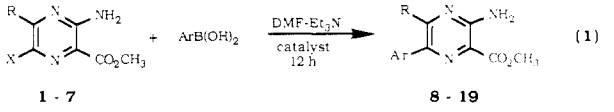
The coupling of chloro or bromo pyrazines and pyridines with areneboronic acids in the presence of palladium(0) catalysts is described. By use of the appropriate catalyst, the coupling of pyridineboronic acids was achieved. A convergent synthesis of the previously unknown 4-methyl derivative of the cardiotonic milrinone (**31**) is also described.

Substituted pyrazines occur widely in nature and are valuable heterocyclic nuclei for the design of pharmaceutical agents. In connection with our interest in the pyrazine congeners of the bipyridine cardiotonics amrinone and milrinone,[1-5] we examined the palladium(0)-catalyzed coupling reaction of areneboronic acids with 6-halo-2-aminopyrazinoate esters.[6,7] We report here that in the presence of [1,1'-bis(diphenylphosphino)ferrocene]palladium,[8] the method is generally useful for introducing substituted aryl and heteroaryl substituents, including the 3- and 4-pyridyl ring systems.[9] The utility of the method was further demonstrated as the key step in the synthesis of the novel 4-methyl derivative of milrinone.[10]



(1)

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The results from a variety of 2-amino-6-halopyrazinoates are summarized in Table I. The 6-bromopyrazinoate **1** underwent conversion to the 6-phenylpyrazinoate[8] utilizing the conditions employed for the synthesis of arylpyridines.[8] However, only traces of the coupled products **13-17** were obtained when the 6-halo-5-substituted-pyrazinoates **2** and **3** were used as starting materials. Substituting the more stable bis(tri-*o*-tolylphosphine)-ligated palladium catalyst ($Pd(totp)(OAc)_2$) for the tetrakis(triphenylphosphine)-palladium catalyst ($Pd(PPh)_4$) did not afford much improvement. We then found that the binuclear catalyst, 1,1'-bis(diphenylphosphino)ferrocene-ligated palladium ($Pd(dppf)(OAc)_2$)[9] formed in situ, was significantly more effective in promoting the desired transformation. One explanation to account for the greater efficiency of the $Pd(dppf)_2(OAc)_2$ catalyst relative to the others might be the decreased steric hindrance enforced by the rigid ferrocene backbone which acts to "stretch" the Pd-P bond distance from its usual length.[8] The catalyst was also found to be successful for 4-fluorobenzene-, 4-methoxybenzene-, 3-furan-, 2-furan-, 3-thianaphthylene-, and 3- and 4-pyridineboronic acids with 6-bromopyrazinoates as shown in Table I.[20]

The less reactive 6-chloropyrazinoates **2**, **4**, and **6** also underwent the coupling reaction with the $Pd(dppf)_2(OAc)_2$ catalyst, although a slower rate of conversion was observed

Scheme I. Preparation of Methyl 3-Amino-5-alkyl-6-halopyrazinoates

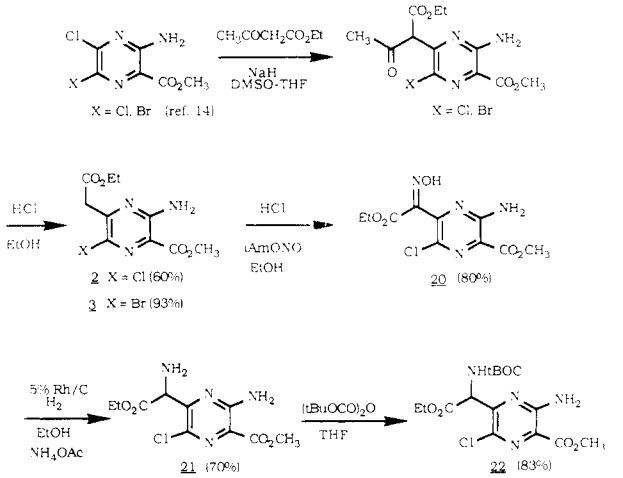

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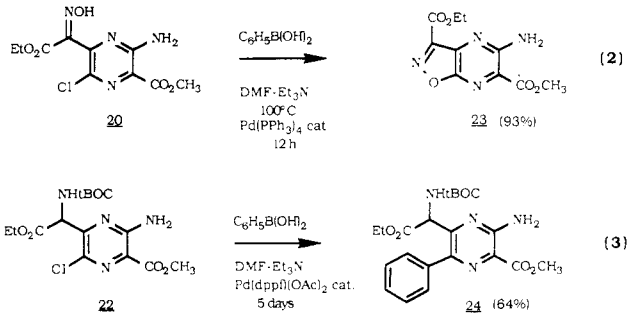
Table I. Synthesis of 3-Amino-6-arylpyrazines

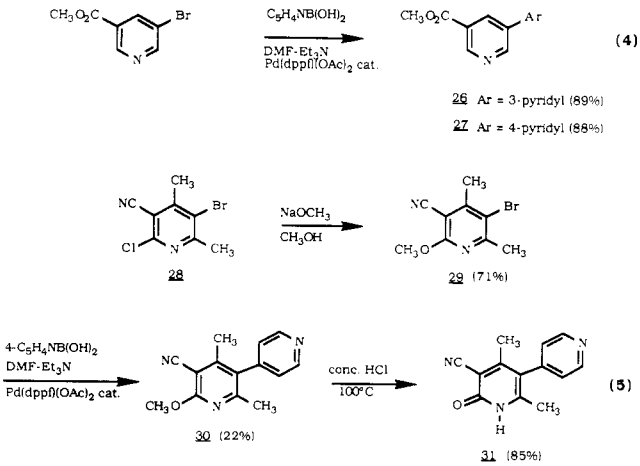
halopyrazine	R	X	Ar	catalysts[a]	product	yield (%)	mp (°C)
1	H	Br	C_6H_5	A	8	60	140–141
1	H	Br	C_6H_5	B	8	14	
1	H	Br	C_6H_5	C	8	82	
1	H	Br	4-$C_6H_4OCH_3$	C	9	94	146–147
1	H	Br	3-thianaphthyl	C	10	87	156–157
1	H	Br	3-furanyl	C	11	89	145–146
2	CH_2CO_2Et	Cl	C_6H_5	A	12	38	163–164
2	CH_2CO_2Et	Cl	C_6H_5	C	12	82	
3	CH_2CO_2Et	Br	C_6H_5	C	12	96	
3	CH_2CO_2Et	Br	4-FC_6H_4	C	16	80	163–164
3	CH_2CO_2Et	Br	2-furanyl	C	17	74	102–103
3	CH_2CO_2Et	Br	3-furanyl	A	13	22	123–124
3	CH_2CO_2Et	Br	3-furanyl	B	13	30	
3	CH_2CO_2Et	Br	3-furanyl	C	13	95	
3	CH_2CO_2Et	Br	3-pyridyl	C	14	67	186–187
3	CH_2CO_2Et	Br	4-pyridyl	C	15	65	160–161
4	$NH(CH_2)_2NMe_2$	Cl	3-furanyl	C	18	76	148–149
5	$NH(CH_2)_2NMe_2$	Br	3-furanyl	C	18	90	
7	NEt_2	Br	C_6H_5	A	19	90	86–87
7	NEt_2	Br	C_6H_5	C	19	93	

[a] A = $Pd(PPh_3)_4$; B = Pd(totp)$(OAc)_2$; C = Pd(dppf)$(OAc)_2$.

(Scheme I). Attempted arylation of the 5-[(ethoxycarbonyl)(hydroxyimino)methyl]-6-chloropyrazinoate **20** afforded the novel fused isoxazolopyrazinoate **23** in excellent yield. In the case of the severely hindered 6-chloropyrazine **22**, the rate of coupling was markedly slower than the other examples (67% conversion to **24** after 5 days).



The successful coupling with the pyridineboronic acids provides a new method for the synthesis of substituted bipyridines (**26** and **27**). Finally, the utility of the method was demonstrated by the synthesis of 4-methylmilrinone (**31**) from the readily available 6-bromo-3-chloro-2,4-dimethylpyridine-5-carbonitrile[7] (**28**).



Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 1420 spectrophotometer. Magnetic resonance spectra were taken on a Varian XL-300 or 90 MHz spectrophotometer. Ultraviolet absorption measurements were taken on a Beckman Acta MVI spectrophotometer. Thin layer chromatography (TLC) was performed on E. Merck silica gel 60F-254 (0.25 mm) analytical glass plates. E. Merck silica gel 60 (230–400 mesh) was used for flash chromatography.[15] Benzeneboronic acid was obtained from Aldrich Chemical Company and was recrystallized from water before use. All other reagents and solvents were reagent grade and were used without further purification.

Methyl 3-Amino-5-[(ethoxycarbonyl)methyl]-6-chloropyrazinoate (2). To an ice-cooled, stirred solution of 24 g (0.184 mol) of ethyl acetoacetate in 120 mL of freshly distilled tetrahydrofuran (THF) under a nitrogen atmosphere was added 9 g of sodium hydride as a 60% oil dispersion in portions, keeping the temperature of the reaction between 0 and 15 °C. When addition was complete, the reaction mixture was allowed to warm to 25 °C and 150 mL of dimethyl sulfoxide and 13.2 g (0.059 mol) of methyl 3-amino-5,6-dichloropyrazinoate[14] were added. The dark orange solution was allowed to stir overnight, then poured into 1.5 L of H_2O, and acidified with 3 N HCl. The mixture was extracted with three 300-mL portions of ethyl acetate, and the combined extracts were washed with 100 mL of H_2O and then concentrated to dryness on the rotary evaporater. The residue was extracted with three 30-mL portions of petroleum ether, taken up in EtOAc, dried over $MgSO_4$, and concentrated to dryness. After drying under reduced pressure, the residue (14.4 g) was suspended in 260 mL of absolute EtOH, and the mixture was acidified with 6.5 mL of 6.1 N HCl in EtOH and allowed to stir 1 h at reflux. The yellow solid was collected by filtration and the mother liquor concentrated. Repeated filtration of the slightly yellow solid following concentration of the mother liquor afforded two more crops of product homogeneous by TLC (2:3 EtOAc/hexanes development). Recrystallization of the combined solids (9.6 g, mp 110 °C) from EtOH gave 9.32 g (57.7%) of **2** after drying under vacuum: mp 115–116 °C, ^1H NMR (90 MHz, $CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz), 3.85 (s, 2 H), 3.93 (s, 3 H), 4.15 (q, 2 H, J = 7 Hz), 6.40 (br s, 2 H). Anal. Calcd for $C_{10}H_{12}N_3O_4Cl$: C, 43.89; H, 4.42; N, 15.35. Found: C, 43.78; H, 4.47; N, 15.41.

Methyl 3-Amino-5-[(ethoxycarbonyl)methyl]-6-bromopyrazinoate (3). To an ice-cooled, stirred suspension of 4.70 g of sodium hydride (60% oil dispersion) in 60 mL of freshly distilled THF was added 17 mL of ethyl acetoacetate over 15 min. After 15 min of stirring in the cold, a solution of 9.0 g (0.034 mol) of methyl 3-amino-5-chloro-6-bromopyrazinoate[14] in 30 mL of freshly distilled THF and 30 mL of DMSO (dried over activated 4A

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molecular sieves) was added dropwise over 15 min. The resulting mixture was allowed to warm to 25 °C and stir overnight and then was poured into a mixture of 200 mL of 0.1 N HCl and 200 mL of EtOAc. The mixture was shaken and separated. The aqueous layer was saturated with NaCl and extracted with two 50-mL portions of EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to dryness on a rotary evaporater. The residue was dissolved in 250 mL of EtOH, 1 mL of 4.7 N HCl in EtOH was added, and the mixture was heated to reflux for 1 h. After cooling to 25 °C, 1 mL of concentrated NH_4OH was added, and the mixture was cooled further in an ice bath at which point 8.0 g of crystals precipitated. Upon concentration and cooling, a second crop of crystalline product was obtained (2.0 g after drying under vacuum). Both crops were homogeneous by TLC (1:1 Et_2O/hexanes development) and were combined (92% of 3): mp 110–111 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 3.90 (s, 2 H), 3.98 (s, 3 H), 4.22 (q, 2 H, J = 7 Hz). Anal. Calcd for $C_{10}H_{12}BrN_3O_4$: C, 37.75; H, 3.80; N, 13.21. Found: C, 38.05; H, 3.79; N, 13.34.

Methyl 3-Amino-5-[[(dimethylamino)ethyl]amino]-6-bromopyrazinoate (5). A mixture of 9.9 g of methyl 3-amino-5-chloro-6-bromopyrazinoate[14] and 3.4 g of *unsym*-dimethylethylenediamine in 150 mL of 2-propanol was warmed to reflux for 24 h. Upon cooling to 25 °C, the hydrochloride of **5** was obtained as a crystalline solid (11.5 g, 87% after air drying): mp 261 °C dec; ^1H NMR (300 MHz, D_2O) δ 3.00 (s, 6 H), 3.45 (t, J = 7 Hz), 3.85 (t, J = 7 Hz), 4.85 (s, 3 H). Anal. Calcd for $C_{10}H_{17}BrClN_5O_2$: C, 33.87; H, 4.83; N, 19.75. Found: C, 34.16; H, 4.83; N, 19.72.

Methyl 3-Amino-5-(dimethylamino)-6-bromopyrazinoate (7). A solution of 1.2 g (4.6 mmol) of 3-amino-5-(diethylamino)-6-chloropyrazinoate[13] in 100 mL of absolute EtOH was shaken with 100 mg of 10% palladium on carbon and 714 mg of NH_4OAc under 50 psi of hydrogen on a Parr apparatus for 2 days. The reaction mixture was filtered through diatomaceous earth, concentrated to dryness, suspended in 50 mL of H_2O, and filtered. The resulting white crystalline solid (1.0 g) was dried, then dissolved in 5 mL of glacial AcOH, and stirred rapidly while 0.75 g of bromine in 2 mL of AcOH was added dropwise over 20 min. The reaction was diluted with 100 mL of CH_2Cl_2 and washed with dilute $NaHSO_3$ and 1 N NaOAc and then concentrated to dryness by azeotropic removal of AcOH with toluene. Flash chromatography with 1:4 EtOAc/hexanes and recrystallization from Et_2O–hexanes gave 1.28 g of **7** as white crystals: mp 55–56 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 6 H, J = 6.8 Hz), 3.63 (q, 4 H, J = 6.8 Hz), 3.89 (s, 3 H). Anal. Calcd for $C_{10}H_{15}BrN_4O_2$: C, 39.62; H, 4.99; N, 18.48. Found: C, 39.96; H, 5.10; H, 18.44.

General Procedure for the Aryl Coupling Reactions with Pd(dppf)(OAc)$_2$ Catalyst. A stirred mixture of 0.3 mmol of $Pd(OAc)_2$ and 0.4 mmol of 1,1′-bis(diphenylphosphino)ferrocene (dppf) in 30 mL of dimethylformamide (DMF) was warmed to 50 °C for 0.25 h. After cooling, 10 mmol of the halopyrazine or halopyridine, 11 mmol of the areneboronic acid, and 2.0 mL of Et_3N were added, and the mixture was heated to 90 °C for 12 h. (TLC of the crude reaction mixture usually indicated complete conversion after 2–6 h.) After cooling, the black mixture was concentrated to dryness on the rotary evaporator (bath temperature 55 °C), then taken up in 50 mL of chloroform, washed with 25 mL of dilute NH_4OH, and concentrated to dryness. The "crude product" was taken up in ether or chloroform, filtered through a 100-mL column of silica gel with 1 L of ether, and recrystallized. In the case of the more basic pyrazines and pyridines, purification by flash chromatography on silica gel in the designated solvent, followed by recrystallization, gave the pure product.

With Pd(totp)$_2$(OAc)$_2$ Catalyst. The same procedure as abbove was followed, with the exception that 0.8 mmol of tri-*o*-tolylphosphine was substituted for the dppf ligand.

With Pd(PPh$_3$)$_4$ Catalyst. The same procedure as above was followed, with the exception that 0.3 mmol of tetrakis(triphenylphosphine)palladium(0) was substituted as catalyst.

Methyl 3-Amino-5-[(ethoxycarbonyl)(hydroxyimino)methyl]-6-chloropyrazinoate (20). To an ice-cold suspension of 22 g of **2** in 1 L of absolute EtOH was added 17 mL of 4.87 N HCl in EtOH. The bath was removed and after stirring for 15 min 12 mL of isoamyl nitrite was added. After being stirred at 25 °C overnight, the mixture was concentrated to dryness under reduced pressure and the residue extracted with 200 mL of CH_2Cl_2. Concentration of this extract gave 4.0 g of solid homogeneous by TLC. The insoluble solids from the extraction were further purified by flash chromatography with 1:4 EtOAc/hexanes as eluant and gave an additional 15.5 g of product (homogeneous by TLC), as well as 2.9 g of product contaminated with starting material. The combined yield of **20** was 19.5 g (80%): mp 172 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.23 (9, J = 7 Hz, 3 H), 3.87 (s, 3 H), 4.27 (q, 2 H, J = 7 Hz), 7.73 (br s, 2 H); IR ($CHCl_3$) 3550, 3510, 3380, 3000, 1710, 1600, 1520, 1450, 1410, 1380, 1330, 1250, 1190, 1120, 1025, 990 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_4O_5Cl$: C, 39.68; H, 3.66; N, 18.51. Found: C, 40.02; H, 3.58; N, 18.31.

Methyl 3-Amino-5-[(ethoxycarbonyl)aminomethyl]-6-chloropyrazinoate (21). A mixture of 3.0 g of **20**, 2.78 g of NH_4OAc, 0.5 g of 5% rhodium on carbon, and 3.0 mL of glacial AcOH was shaken under 50 psi of hydrogen for 2.5 h on a Parr apparatus. The catalyst was filtered off and the solution concentrated to dryness, dissolved in 300 mL of $CHCl_3$, and NH_3 gas was bubbled in. The solid (NH_4OAc) was filtered off and the solution concentrated to dryness. Purification by flash chromatography with 5:1 EtOAc/hexanes followed by recrystallization from EtOH gave 7.21 g (70%) of **21**: mp 110 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 2.10 (br s, 2 H), 3.99 (s, 3 H), 4.20 (m, 2 H), 5.00 (s, 1 H); IR ($CHCl_3$) 3500, 3395, 3000, 1740, 1700, 1600, 1530, 1445, 1410, 1370, 1320, 1210, 1190, 1125, 1040, 1020, 725, 665 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClN_4O_4$: C, 41.75; H, 4.55; N, 19.48. Found: C, 41.84; H, 4.63; N, 19.38.

Methyl 3-Amino-5-[(ethoxycarbonyl)[(*tert*-butoxycarbonyl)amino]methyl]-6-chloropyrazinoate (22). A solution of 8.64 g of **21** and 7.4 g of di-*tert*-butyl dicarbonate (1.1 equiv) in 90 mL of THF was warmed to reflux for 3 h. After being cooled to 25 °C, the solution was concentrated to dryness and the residue recrystallized from EtOAc. After drying, 9.48 g of **22** (81.3%) was obtained: mp 157–158 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 1.47 (s, 9 H), 3.98 (s, 3 H), 4.20 (m, 2 H), 5.83 (br s, 1 H), 6.50 (br s, 1 H). Anal. Calcd for $C_{15}H_{21}ClN_4O_6$: C, 46.34; H, 5.44; N, 14.41. Found: C, 46.08; H, 5.52; N, 14.25.

3-(Ethoxycarbonyl)-5-amino-6-(methoxycarbonyl)-pyrazino[2,3-*d*]isoxazole (23). A mixture of 0.273 g (1 mmol) of **20**, 0.116 g of benzeneboronic acid (1 mmol), 25 mg (0.02 mmol) of $Pd(Ph_3P)_4$, 1 mL of Et_3N, and 5 mL of DMF was warmed to 100 °C for 2 h. The mixture was concentrated to dryness and purified by flash chromatography using 1:9 EtOAc/CH_2Cl_2. Recrystallization from CH_2Cl_2–hexanes gave 0.247 g (93%) of **23** as bright yellow crystals: mp 225 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (t, 3 H, J = 7 Hz), 4.08 (s, 3 H), 4.58 (q, 2 H, J = 7 Hz), 7.0 (br s, 2 H). Anal. Calcd for $C_{10}H_{10}N_4O_5$: C, 45.12; H, 3.79; N, 21.05. Found: C, 44.86; H, 3.80; N, 20.87.

Methyl 3-Amino-5-[(ethoxycarbonyl)[(*tert*-butoxycarbonyl)amino]methyl]-6-phenylpyrazinoate (24). A mixture of 23 mg (0.10 mmol) of $Pd(OAc)_2$ and 84 mg (0.15 mmol) of 1,1′-bis(diphenylphosphino)ferrocene in 4 mL of DMF was warmed to 50 °C for 10 min. To this dark mixture were added 0.233 g (1 mmol) of **22**, 0.235 g (2 mmol) of benzeneboronic acid, and 0.5 mL of Et_3N. The stirred mixture was warmed to 95 °C for 5 days under nitrogen atmosphere and then concentrated to dryness under reduced pressure. The crude product was taken up in 100 mL of Et_2O and filtered through a 100-mL column of silica gel using another 200 mL of Et_2O as eluant. The combined filtrates were concentrated to dryness and purified by flash chromatography using 1:1 EtOAc/hexanes as eluant. Further purification by preparative HPLC on a Whatman Magnum 20, Partisil 10 m ODS-3 (22.1 mm × 25 cm) column with an isocratic solvent mixture of 55:45 MeOH/H_2O (pH adjusted to 2.5 with HCO_2H) monitored at 254 nm, followed by recrystallization from EtOAc–hexanes and drying, gave 0.290 g (67%) of **24**: mp 126–127 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3 H, J = 7 Hz), 1.45 (s, 9 H), 4.00 (s, 3 H), 4.15 (m, 2 H), 5.72 (s, 1 H), 6.5 (br s, 2 H), 7.4–7.5 (m, 3 H), 7.6–7.7 (m, 2 H). Anal. Calcd for $C_{21}H_{26}N_4O_6$: C, 58.60; H, 6.09; N, 13.01. Found: C, 58.58; H, 5.98; N, 12.67.

Methyl [3,3′-bipyridine]-5-carboxylate (26): from 2.2 g of methyl 5-bromonicotinate **25** and 2.5 g of 3-pyridineboronic acid[18]

(18) Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bays* **1965**, *84*, 439.

using $Pd(dppf)(OAc)_2$ as catalyst. Filtration of the crude product through silica gel (300 mL) using EtOAc (500 mL) as solvent and flash chromatography using EtOAc as eluant followed by sublimation at 0.01 mm (bath temperature 80 °C) gave 1.90 g (89%) of **26** as white needles: mp 98–99 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.0 (s, 3 H), 7.46 (dd, 1 H, J = 5 Hz, J = 9 Hz), 7.95 (d, 1 H, J = 9 Hz), 8.5 (t, 1 H, J = 2 Hz), 8.7 (d, 1 H, J = 5 Hz), 8.9 (d, 1 H, J = 2 Hz), 9.02 (d, 1 H, J = 2 Hz), 9.25 (d, 1 H, J= 2 Hz). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71, N, 13.08. Found: C, 67.58; H, 4.74; N, 13.05.

Methyl [3,4′-bipyridine]-5-carboxylate (27): from 2.2 g of methyl 5-bromonicotinate **25** and 2.5 g of 4-pyridineboronic acid[18] using $Pd(dppf)(OAc)_2$ as catalyst. Filtration of the crude residue through 200 mL of silica gel using 2 L of EtOAc and flash chromatography using EtOAc as eluant followed by sublimation at 0.01 mm (bath temperature 100 °C) gave 1.58 g (74%) of **27**: mp 122–124 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.0 (s, 3 H), 7.56 (d, 1 H, M = 7 Hz), 8.55 (t, 1 H, J = 2 Hz), 8.75 (d, 1 H, J = 7 Hz), 9.08 (d, 1 H, J = 2 Hz), 9.3 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{12}H_{10}N_2O_2 \cdot 0.1H_2O$: C, 66.72, H, 4.67; N, 12.98. Found: C, 66.73; H, 4.69; N, 12.75.

3-Bromo-2,4-dimethyl-6-methoxypyridine-5-carbonitrile (29). To a stirred solution of 0.98 g of sodium in 25 mL of absolute MeOH at 25 °C was added 6.63 g of 6-chloro-3-bromo-2,4-dimethylpyridine-5-carbonitrile[7] in 150 mL of absolute MeOH. After stirring at 25 °C for 16 h, 4 mL of glacial AcOH was added. The mixture was concentrated to dryness, taken up in 200 mL of CH_2Cl_2, washed with H_2O (50 mL) and saturated NaCl (50 mL), and dried over $MgSO_4$. After concentrating to dryness, the crude orange solid (6.81 g) was purified by flash chromatography eluting with 1:3 $CHCl_3$/hexanes. Recrystallization from Et_2O–hexanes gave 3.35 g (71%) of white prisms: mp 95–98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3 H), 2.65 (s, 3 H), 4.01 (s, 3 H). Anal. Calcd for $C_9H_9BrN_2O$: C, 44.84; H, 3.76; N, 11.62. Found: C, 45.04; H, 3.65; H, 11.41.

2,4-Dimethyl-6-methoxy-[3,4′-bipyridine]-5-carbonitrile (30). To a solution of $Pd(dppf)(OAc)_2$ (from 115 mg of $PdOAc_2$ and 276 mg of dppf) in 8 mL of DMF under N_2 atmosphere were added 1.2 g of **29**, 1.12 g of 4-pyridineboronic acid,[18] and 2.1 mL of Et_3N. The mixture was warmed to 90 °C for 27 h and then concentrated to dryness by short path distillation of the solvents. The black residue was dissolved in $CHCl_3$, washed with dilute aqueous NH_3 and saturated brine, and dried over Na_2SO_4. The crude product (1.56 g) was purified by flash chromatography, eluting with 2:3 Et_2O/hexanes. Recrystallization from heptane gave 263 mg (22%) of colorless crystals: mp 143–144 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3 H), 2.22 (s, 3 H), 4.07 (s, 3 H), 7.10 (dd, 2 H, J = 5 Hz. J = 1 Hz), 8.74 (dd, 2 H, J = 5 Hz, J = 1 Hz); UV (MeOH) max 237 (ϵ 13 600) and 296 nm (ϵ 9100).

1,6-Dihydro-2,4-dimethyl-6-oxo-[3,4′-bipyridine]-5-carbonitrile (31). A solution of the methoxybipyridine **30** (101 mg, 0.424 mmol) in 2 mL of concentrated HCl was warmed to 100 °C for 1 h. The mixture was filtered, diluted with EtOH, and allowed to cool. The white solid which precipitates was collected by vacuum filtration and dried. Recrystallization from 1 N ethanolic HCl gave 95 mg (85%) of white crystalline **31** as the hydrochloride salt: mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6)[19] δ 2.06 (s, 3 H, C_2-methyl), 2.09 (s, 3 H, C_4-methyl), 7.82 (d, 2 H, J = 6.4 Hz), 8.92 (d, 2 H, J = 6.4 Hz); IR (KBr) 3450, 3100, 2920, 2860, 2220 (CN, s), 1660, 1620, 1540, 1510, 1450, 1380, 1300, 1240, 1210, 1080, 960, 810 cm^{-1}, ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.22, 20.11, 100.41, 115.76, 115.84, 128.27, 144.06, 149.52, 150.61, 157.80, 159.92; UV (MeOH) max 270 (ϵ 6700) and 345 nm (ϵ 10 300). Anal. Calcd for $C_{13}H_{11}N_3O \cdot HCl$: C, 59.66; H, 4.62; N, 16.06. Found: C, 60.00; H, 4.52; N, 16.25.

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Supplementary Material Available: Full experimental details including NMR data for compounds **8–19** (4 pages). Ordering information is given on any current masthead page.

(19) The methyl resonances at 2.06 and 2.09 ppm were assigned on the basis of long range heteronuclear correlations using 2-dimensional carbon–proton correlation experiments. The 2.06-ppm methyl group correlated with two carbons (115.76 and 149.52 ppm) while the 2.09-ppm methyl group correlated with three carbons (100.41, 115.76, and 157.80 ppm). Thus, the 2.06-ppm resonance is due to the C_2-methyl group, and the 2.09-ppm resonance is due to C_4-methyl group. The authors thank Drs. Steve M. Pitzenberger and Sandor L. Varga for both providing these spectral assignments and performing the NMR experiments.

(20) For a detailed experimental section, see the paragraph at the end of the paper about supplementary material.

Synthesis and Complexing Properties of Macrocycles Incorporating 2,2′-Biindazolyl Binding Subunits

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Substituted 2,2′-biindazoles **4** and **19–23** were prepared in 80–90% yields by thermal decomposition of *o,o′*-diazido azines **13–18**, which in turn were readily obtained from the corresponding 2-azidobenzaldehydes or 2-azidobenzophenones. The preference of these N,N′-linked azolyl dimers for an almost orthogonal conformation was clearly demonstrated by the strong deshielding of the H-3 signal in ^1H NMR spectra. Appropriate substituted indazolyl models were used for the full assignment of ^1H and ^{13}C NMR signals. The chemistry of 2,2′-biindazoles appears to be mainly governed by the ease of cleavage of the interconnecting N–N bond under reducing or strongly acidic conditions. Analogously, cine substitution to position 3 of one ring, with simultaneous loss of the other moiety, acting as a leaving group, was observed in 7,7′-dinitro derivatives. Despite these limitations, dimethyl derivatives **21**, **23**, and **38** were useful starting materials for 2,2′-biindazolyl-containing macrocycles **50–60** via NBS bromination (50–68% yield) and reaction with the disodium salt of tetraethylene glycol (9–17% yield). The sodium cryptate of the macrobicycle **61** was similarly obtained from the bis(bromomethyl) derivative **56** in a 63% yield, without high dilution techniques. ^1H NMR techniques and ion-transport experiments across a bulk $CHCl_3$ phase were used to evaluate the coordination properties of macrocycles **58–60**. Na^+ and K^+ ions coordinate on the crown moiety of **58**, as well as Hg^{2+}, whereas the $PdCl_2$ complex showed the expected coordination by the indazolyl nitrogen atoms. Alkali-metal ions were transported at moderate rates by **58–60**, and a high Na^+/Li^+ selectivity was observed for **60**. An allosteric effect was demonstrated on the complex **58**·$PdCl_2$, in which conformational changes induced by complexation caused transport rates by the crown to be lowered, without inversion of the K^+/Na^+ selectivity.

It is well-known that substitution of donor atoms in macrocyclic ligands causes important changes in their complexation behavior. In particular, introduction of nitrogen atoms belonging to heteroaromatic subunits

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