Direct Preparation of N-Quaternized and N-Oxidized Polycyclic Azines by Palladium-Catalyzed Cross-Coupling. An Unequivocal Isomer Synthesis

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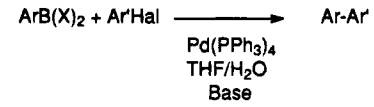
Quaternization and oxidation reactions of a nitrogen atom in polycyclic azines are subject to both steric and electronic control, steric factors being more important for the former[1,2] than for the latter preparation.[3] When several similarly reactive nitrogen atoms are present, selectively directing N-quaternization or N-oxidation to just one of these atoms is a synthetic challenge and generally is unsuccessful. Often mixtures are formed which may be hard to separate,[4] and identification of the resultant isomers may be difficult. Moreover, special methods are required to prepare selectively that isomer representing reaction at the less reactive site in a preformed polycyclic azine. We have, for example, employed in a multistep route a removable protecting group at the more reactive annular nitrogen atom in order to convert the less reactive nitrogen in 2,3′-bipyridine to the more sterically hindered mono N-methylated product, 1-methyl-2,3′-bipyridinium ion.[5] In the case of *N*-oxides of polyazines the traditional approach to prepare *N*-oxides of known structure has been based on cyclization reactions giving the *N*-oxide group on formation of an aromatic ring and not by direct oxidation.[3,6,7]

We report several examples of unequivocal isomer preparations using palladium-catalyzed cross-coupling to yield *N*-oxides and N-quaternized polycyclic azines. Our approach serves as a model for such syntheses where selective N-quaternization, N-oxidation, or other types of N-functionalization of several rings is now possible in a regiocontrolled manner.

Background

The number of recently reported transition metal-catalyzed cross-coupling reactions used to prepare polyaryl and polyhetaryl compounds has grown explosively, palladium being the metal of choice.[8–12] But the number of preparations of *N*-oxides by this means using preformed *N*-oxides in the coupling reaction has been very limited.[13–16] For example, the ability of a 2-bromopyridine *N*-oxide to undergo coupling without competing nucleophilic substitution to replace the bromine atom has been demonstrated,[13] and control over the location of the *N*-oxide group within a pyrazine ring by using a preformed chloropyrazine *N*-oxide in a cross-coupling reaction has been reported.[14–16] The preparation of N-quaternized polyhetaryls by such coupling reactions using quaternized starting materials seems not to have been exploited at all.

Scheme 1



We employ a boronic acid or a hetarylborane and a halogenated, N-oxidized or N-quaternized heteroaromatic compound to effect coupling under aqueous alkaline conditions along with a palladium reagent, now something of a standard procedure known as the Suzuki reaction, Scheme 1.[9,10,17] The use of an alkaline medium for such coupling reactions seems to be a necessary requirement in order to give an intermediate "ate" complex of the boron reagent on addition of hydroxide ion.[18] This "ate" complex then transfers its aromatic ligand to the palladium oxidative addition product of the halide prior to product formation in a final reductive elimination step.[19–22] Pyridylboronic acids have been made to cross-couple in a nonaqueous solvent such as DMF and triethylamine in the presence of a palladium catalyst.[23] Boranes couple with triflates in a suspension of Na_3PO_4 in dry dioxane containing a palladium catalyst.[18] Oxidative addition complexes of palladium and halogenated heterocycles have been isolated and characterized.[21,24,25]

Both N-oxidation and especially N-quaternization are known to activate enormously a halogenated hetarene for nucleophilic substitution on displacing the halogen atom,[26,27] and this knowledge may have prevented others from attempting the coupling reactions we now report. For example, methoxydechlorination of 2-chloro- and 4-chloropyridine *N*-oxides is some 10^{12} times faster than that of chlorobenzene, and the same reaction for 2-chloro- and 4-chloro-1-methylpyridinium ion is about 10^{21} and 10^{19} times faster, respectively, than substitution of chlorobenzene.[26,27] Moreover, under alkaline conditions, N-quaternized hetarenes may degrade by ring cleavage

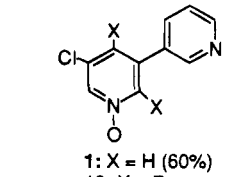
(1) Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* **1988**, *43*, 173.
(2) Zoltewicz, J. A.; Deady, L. W. *Adv. Heterocycl. Chem.* **1978**, *22*, 71.
(3) Grimmett, M. R.; Keene, B. R. T. *Adv. Heterocycl. Chem.* **1988**, *43*, 127.
(4) Moran, D. B.; Morton, G. O.; Albright, J. D. *J. Heterocycl. Chem* **1986**, *23*, 1071.
(5) Zoltewicz, J. A.; Bloom, L. B.; Kem, W. R. *J. Org. Chem.* **1992**, *57*, 2392.
(6) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic Press: New York, 1971.
(7) Katritzky, A. R.; Lam, J. N. *Heterocycles* **1992**, *33*, 1011.
(8) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(9) Terashima, M.; Ishikura, M. *Adv. Heterocycl. Chem.* **1989**, *46*, 143.
(10) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.
(11) Abramovitch, R. A.; Barton, D. H. R.; Finet, J. P. *Tetrahedron* **1988**, *44*, 3039.
(12) Undheim, K.; Benneche, T. *Heterocycles* **1990**, *30*, 1155.
(13) Malm, J.; Hörnfeldt, A.-B.; Gronowitz, S. *Heterocycles* **1993**, *35*, 245.
(14) Ohta, A.; Inoue, A.; Ohtsuka, K.; Watanabe, T. *Heterocycles* **1985**, *23*, 133.
(15) Ohta, A.; Ohta, M.; Watanabe, T. *Heterocycles* **1986**, *24*, 785.
(16) Watanabe, T.; Hayashi, K.; Sakurada, J.; Ohki, M.; Takamatsu, N.; Hirohata, H.; Takeuchi, K.; Yasa, K.; Ohta, A. *Heterocycles* **1989**, *29*, 123.
(17) Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scripta* **1984**, *23*, 120.
(18) Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
(19) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.
(20) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.
(21) Isobe, K.; Kawaguchi, S. *Heterocycles* **1981**, *16*, 1603.
(22) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.
(23) Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Theis, J. E. *J. Org. Chem.* **1988**, *53*, 2052.
(24) Benneche, T. *Acta Chem. Scand.* **1990**, *44*, 927.
(25) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 2003.
(26) Illuminati, G. *Adv. Heterocycl. Chem.* **1964**, *3*, 285.
(27) Oae, S.; Furukawa, N. *Adv. Heterocycl. Chem.* **1989**, *48*, 1.

0022-3263/95/1960-0264$09.00/0

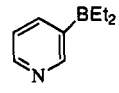
reactions.[28] While nucleophilic substitution by the S_NAr mechanism is largely insensitive to the identity of the halogen nucleofuge,[26] cross-coupling rates decrease in the order I > Br > Cl. Clearly then, the choice of a halogen atom and the reaction conditions, especially pH, are expected to be quite important for the success of the cross-coupling reaction of hydrolytically labile substrates.

Results and Discussion

The compounds we selected to be prepared were designed to illustrate the power of our approach and to establish some of its scope and limitations. Consider our synthesis of 5-chloro-3,3'-bipyridine 1-oxide (**1**) from 3,5-dichlorpyridine 1-oxide[29] and diethyl-3-pyridylborane (**2**). The position of the oxide ligand with respect to the chlorine atom is unequivocal because the *N*-oxide group was present on the chlorinated ring at the start. By contrast, attempts to N-oxidize 5-chloro-3,3'-bipyridine following a similar coupling reaction to prepare the unoxidized material would not be expected to provide the 1-oxide as the major product. Mixed mono-*N*-oxides are likely because the electron-withdrawing chlorine atom would have caused N-oxidation to take place at the more reactive unsubstituted ring to give the isomeric 1'-oxide as the major product and **1** as the minor product. The N-oxidation of 3,3'-bipyridine itself is known to give a mixture of mono- and di-*N*-oxides that are hard to separate.[4]



1: X = H (60%)
10: X = D



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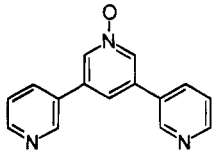
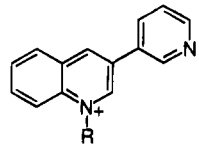
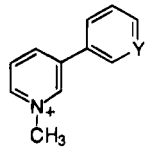


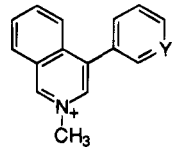
3 (50%)



4: R = O⁻ (63%)
7: R = CH_3 (34%)



5: Y = CH (57%)
6: Y = N (62%)



8: Y = CH (31%)
9: Y = N (43%)

The direct preparation of the symmetrical 3,3':5'3''-terpyridine having the center ring N-oxidized as in **3** by direct N-oxidation is an even greater challenge because all three pyridyl rings are expected to have similar reactivities. Our synthesis of **3** is both trivial and unequivocal in that the same 3,5-dichloropyridine 1-oxide[29] used to prepare **1** was employed to synthesize **3** but now 2 equiv of borane **2** was present along with a carbonate buffer. Surprisingly, the nonoxidized form of **3** was prepared from 3,5-dibromopyridine in 1936 by a palladium on $CaCO_3$ coupling reaction under heterogeneous conditions[30] that substantially predates its recent synthesis using the complexed palladium metal.[31]

3-(3-Pyridyl)quinoline 1-oxide (**4**) was easily synthesized from **2** and 3-bromoquinoline 1-oxide[32] in the presence of a bicarbonate buffer. Here the *N*-oxide unit is located on a nitrogen atom highly sterically hindered by the peri position[2] and so **4** would have been formed only as a minor product on N-oxidation of the preformed pyridylquinoline.

A substrate even more activated for nucleophilic substitution and ring cleavage by hydroxide ion is found in 3-iodo-1-methylpyridinium ion.[33] 3-Phenyl-1-methylpyridinium ion[34] (**5**) was prepared now using phenylboronic acid and the 3-iodide. Similarly, 1-methyl-3,3'-bipyridinium ion (**6**) was formed from the same 3-iodide and **2**. While in alternate syntheses the quaternizations of 3-phenylpyridine to give **5** or of 3,3'-bipyridine to yield **6** are simple and unequivocal reactions, our coupling method illustrates the important principle that even quaternized substrates very highly activated for nucleophilic substitution and ring cleavage may be employed in the cross-coupling under aqueous alkaline conditions. This approach would be useful, for example, to prepare unsymmetrically carbon-substituted derivatives of **6** of known and controlled structure as in the case of **1**. Phenyl-substituted derivatives of the unquaternized form of **5** have been prepared by palladium coupling.[35]

The reactivity of halogenated *N*-methylquinolinium and *N*-methylisoquinolium salts also were examined. These bicyclic materials are still more activated than the pyridinium ions for nucleophilic substitution[36] and for pseudobase formation by the addition of hydroxide ion, often accompanied by ring cleavage.[28,37] Several attempts were necessary to find the proper alkaline buffer to minimize side reactions. Borate, phosphate, and bicarbonate buffers were examined in order to lower successively the reaction pH.

3-Pyridylated quinolinium ion **7** was recovered as product in moderate yield when bicarbonate was used to buffer the reaction mixture consisting of **2** and 3-bromo-1-methylquinolinium ion[38] and the palladium catalyst. This is a useful preparation because quaternization of preformed 3-(3-pyridyl)quinoline is not expected to yield **7** directly, owing to considerable steric hindrance by the peri position.[2] Replacing the aqueous solvent by anhydrous DMF did not lead to an increase in the yield of product. Bicarbonate has been used in palladium-induced coupling reactions of thiopheneboronic[17] and pyridylboronic acids,[39] for example.

By employing 4-bromo-2-methylisoquinolinium ion[40] and benzeneboronic acid it was possible to prepare the 4-phenylated isoquinolinium ion **8** with borate base, but

(28) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1.
(29) Zoltewicz, J. A.; Kauffman, G. M. *J. Org. Chem.* **1969**, *34*, 1405.
(30) Busch, M.; Weber, W.; Darboven, C.; Renner, W.; Hahn, H. J.; Mathauser, G.; Stratz, F.; Zitmann, K.; Engelhardt, H. *J. Prakt. Chem.* **1936**, *146*, 1.
(31) Ishikura, M.; Ohta, T.; Terashima, M. *Chem. Pharm. Bull.* **1985**, *33*, 4755.
(32) Murray, J. G.; Hauser, C. R. *J. Org. Chem.* **1954**, *19*, 2008.
(33) Zoltewicz, J. A.; Cross, R. E. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1363.
(34) Krumholtz, P. *J. Am. Chem. Soc.* **1951**, *73*, 3487.
(35) Ishikura, M.; Kamada, M.; Terashima, M. *Heterocycles* **1984**, *22*, 265.
(36) Shepherd, R. G.; Fedrick, J. L. *Adv. Heterocycl. Chem.* **1965**, *4*, 145.
(37) Bunting, J. W. *Tetrahedron* **1987**, *43*, 4277.
(38) La Costa, W. *Chem. Ber.* **1881**, *14*, 915.
(39) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117.
(40) Bunting, J. W.; Chew, V. S. F.; Sindhuatmadja, S. *Can. J. Chem.* **1981**, *59*, 3195.

attempts to make the 4-pyridylated isoquinolinium ion **9** using borate, phosphate, or bicarbonate buffers were unsuccessful due to degradation of the heterocyclic cation when the reaction was run with two phases, the alkaline layer containing the isoquinolinium ion. However, the addition of some methanol to make the mixture homogeneous allowed **9** to be isolated in 43% yield in the presence of a borate buffer. The unquaternized precursor of **9** has been made by a palladium coupling route.[41]

Having demonstrated that weakly basic buffers are sufficient to induce cross-coupling, a perdeuterated substrate was examined in order to learn whether it is possible to employ an isotopically labeled reagent in the coupling process. The deuterium isotopes at the equivalent 2,6 positions in 3,5-dichloropyridine-*2,4,6-d*$_3$ 1-oxide are known to be removed easily with dilute alkali[42] and their presence therefore serves as a sensitive test of reaction conditions. Partially deuteriated product **10** was prepared in the presence of bicarbonate from the essentially completely labeled (95%) dichloride.[29] No deuterium was found at position 6, 65% D at position 2, and the original amount at 4. Unequal labeling of the 2 and 6 positions of **10** indicates that some of the hydrogen isotope was removed both during and following the formation of coupling product, the former site being more activated for isotope exchange than the latter in the product. The coupling conditions are mild enough to allow selected sites to retain their hydrogen label.

Conclusions

Palladium-catalyzed cross-coupling may be used successfully to prepare N-oxidized and N-quaternized polycyclic azines of unequivocal structure under aqueous conditions. An isotopically labeled substrate may be employed as a reactant when the buffer is selected judiciously so that a hydrogen isotope at carbon will be retained. It seems likely that other types of N-functionalized compounds such as *N*-amines can be prepared by our method.

The synthesis of isomers having a bond to the 2 or 4 position of N-quaternized materials is still more challenging due to the enhanced ease of nucleophilic substitution of the halogenated precursors. Such studies are in progress.

Experimental Section

3-Diethylpyridylborane (**2**), 3,5-dichloropyridine, 4-bromoisoquinoline, 3-bromoquinoline, and benzeneboronic acid were from Aldrich. The N-oxidized and N-methylated starting materials are known compounds. Flash column chromotography[43] made use of either Kieselgel 60 or silica gel 60, 230–400 mesh. Attempts were not made to maximize the yields of isolated products.

5-Chloro-3,3′-bipyridine 1-Oxide (1). A mixture of 3,5-dichloropyridine *N*-oxide[29] (0.400 g, 2.44 mmol), diethyl-3-pyridylborane (0.36 g, 2.4 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.25 mmol) in 20 mL of degassed THF was allowed to stir at room temperature for 5 min. After the addition of potassium carbonate (0.66 g, 4.8 mmol) in 10 mL of water, the mixture was heated at reflux while being stirred. After 12 h, the reaction was allowed to cool and then was diluted with 30 mL of EtOAc and 30 mL of water. The layers were separated, and the aqueous layer was concentrated to give a solid consisting of product and buffer which was extracted three times by shaking with 20 mL of MeOH. The MeOH washes were combined and concentrated in the presence of 20 g of silica gel. Flash chromotography using 70/30 EtOAc/MeOH gave 350 mg of an off-white solid which was recrystallized with EtOAc and isopropyl alcohol to yield 300 mg (1.4 mmol) of a white solid (60% yield, mp 168–170 °C). ^{1}H NMR (DMSO-d_6): δ 8.98 (1H, d, J = 2 Hz), 8.70 (1H, s), 8.65 (1H, dd, J = 2 and 5 Hz), 8.56 (1H, s), 8.20 (1H, dt, J = 2, 2 and 9 Hz), 7.94 (1H, s), 7.53 (1H, dd, J = 5 and 9 Hz). The compound was dried under vacuum at 100 °C, and repeated analyses gave results indicating the presence of variable amounts of water (0.25 and 0.5 equiv). Anal. Calcd for $C_{10}H_7N_2OCl{\cdot}0.5H_2O$: C, 55.70; H, 3.74; N, 12.99. Found: C, 55.63; H, 3.54; N, 12.73.

3,3′:5′,3″-Terpyridine 1′-Oxide (3) and Trihydrochloride. A mixture of 3,5-dichloropyridine *N*-oxide[29] (0.200 g, 1.22 mmol), diethyl-3-pyridylborane (0.360 g, 2.44 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.25 mmol) in 20 mL of degassed THF was allowed to stir at room temperature for 5 min. Following the addition of potassium carbonate (0.505 g, 3.65 mmol) in 10 mL of water, the reaction was heated at reflux while being stirred. After 12 h, the reaction was allowed to cool and then was diluted with 30 mL of EtOAc and water. The aqueous layer was separated and concentrated. The resultant white solid was extracted three times with 20 mL of MeOH to remove product from buffer. The MeOH washes were combined and concentrated onto 20 g of silica gel. Flash chromotography using an eluant of 70/30 EtOAc/MeOH gave 190 mg (0.76 mmol) of an off-white solid which was recrystallized with EtOAc and isopropyl alcohol to yield 150 mg (0.60 mmol) of a white solid (50% yield, mp >220 °C). ^{1}H NMR (DMSO-d_6): δ 8.98 (2H, d, J = 2 Hz), 8.70 (2H, s), 8.65 (2H, dd, J = 2 and 5 Hz), 8.10 (2H, dt, J = 2, 2 and 9 Hz), 7.94 (1H, s), 7.53 (2H, dd, J = 5 and 9 Hz). Anal. Calcd for $C_{15}H_{11}N_3O{\cdot}0.75H_2O$: C, 68.56; H, 15.99; N, 4.79. Found: C, 68.77; H, 15.64; N, 4.30. Addition of the product to ether-hydrogen chloride gave a precipitate, mp >220 °C. Anal. Calcd for $C_{15}H_{11}N_3O{\cdot}3HCl$: C, 50.23; H, 3.93; N, 11.72. Found: C, 50.10; H, 3.53; N, 11.29.

3-Bromoquinoline 1-Oxide. To a solution of 3-bromoquinoline (2.0 mL, 14.7 mmol) in chloroform (35 mL) was added 50% *m*-chloroperoxybenzoic acid (7.6 g, 44 mmol). The solution was allowed to stir at room temperature overnight. The insoluble *m*-chlorobenzoic acid was filtered off, and the filtrate was washed twice with saturated $NaHCO_3$. The $CHCl_3$ was dried and concentrated to a brown solid. A flash silica gel column using 80% hexanes/20% EtOAc gave 1.4 g (6.2 mmol) of an off-white solid (43% yield, mp 192–195 °C (lit.[32] mp 194–196 °C)). ^{1}H NMR (DMSO-d_6): δ 8.85 (1H, s), 8.45 (1H, d, J = 9 Hz), 8.28 (1H, s), 8.04 (1H, d, J = 8 Hz), 7.80 (2H, m).

3-(3-Pyridyl)quinoline 1-Oxide (4). A mixture of 3-bromoquinoline 1-oxide (1.2 g, 5.4 mmol), diethyl-3-pyridylborane (0.79 g, 5.4 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.25 mmol) in 30 mL of degassed tetrahydrofuran was stirred at room temperature for 5 min. Following the addition of sodium bicarbonate (2.3 g, 27 mmol) in 15 mL of water the reaction was heated at reflux while being stirred. When starting material was consumed (TLC) after 36 h the reaction was cooled to 0 °C, and the insoluble catalyst was removed. To the filtrate water (30 mL) and EtOAc

(41) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936.
(42) Zoltewicz, J. A.; Kauffman, G. M. *Tetrahedron Lett.* **1967**, 337.
(43) Still, W. C. *J. Org. Chem.* **1978**, *43*, 2923.

(30 mL) were added; after separation the water layer was concentrated to a brown solid. The material was triturated with 50 mL of methanol, and the insolubles were filtered off. The methanol was concentrated in the presence of 20 g of silica gel. A flash column was run with an eluant of 85% EtOAc and 15% methanol to give 750 mg (3.4 mmol) of off-white solid (63% yield, mp 132–134 °C). ^{1}H NMR (DMSO-d_6): δ 9.25 (1H, s), 8.73 (1H, d, J = 5 Hz), 8.67 (1H, s), 8.53 (1H, d, J = 10 Hz), 8.2 (2H, m), 7.98 (1H, dd, J = 7 and 9 Hz), 7.8 (2H, m), 7.46 (1H, dd, J = 5 and 7 Hz). Anal. Calcd for $C_{14}H_{10}N_2O{\cdot}0.25H_2O$: C, 74.15; H, 4.67; N, 12.35. Found: C, 73.77; H, 4.71; N, 12.11.

1-Methyl-3-phenylpyridinium Hexafluorophosphate (5). A mixture of 3-iodo-1-methylpyridinium perchlorate[33] (0.500 g, 1.59 mmol), phenylboronic acid (0.200 g, 1.64 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.184 g, 0.159 mmol) in 15 mL of degassed tetrahydrofuran was allowed to stir at room temperature for 15 min. To this was added potassium carbonate (0.330 g, 2.36 mmol) in 15 mL of water, and the suspension was heated at reflux under a nitrogen atmosphere. After 6 h, the reaction was cooled to room temperature, and the precipitated catalyst was collected by filtration. To the filtrate was added 10 mL of EtOAc and 10 mL of water. The aqueous layer was separated, and to it was added an excess of saturated KPF_6 solution. Upon stirring, product precipitated to give 285 mg (0.90 mmol) of a white solid (58% yield, mp 131–135 °C (lit.[34] mp no mp)). ^{1}H NMR (DMSO-d_6): δ 9.38 (1H, s), 8.93 (1H, d, J = 6 Hz), 8.86 (1H, d, J = 8 Hz), 8.17 (1H, dd, J = 6 and 8 Hz), 7.88 (2H, m), 7.58 (3H, m), 4.39 (3H, s, CH_3). Anal. Calcd for $C_{12}H_{12}NPF_6$: C, 45.73; H, 3.84; N, 4.44. Found: C, 45.78; H, 3.80; N, 4.38.

1-Methyl-3-(3-pyridyl)pyridinium Hexafluorophosphate (6). A mixture of 3-iodo-1-methylpyridinium perchlorate[33] (0.500 g, 1.59 mmol), diethyl-3-pyridylborane (0.240 g, 1.63 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.184 g, 0.159 mmol) in 15 mL of degassed tetrahydrofuran was allowed to stir at room temperature for 15 min. To this was added potassium carbonate (0.330 g, 2.36 mmol) in 15 mL of water, and the suspension was heated at reflux under a nitrogen atmosphere. After 7 h, the reaction was cooled to room temperature, and the precipitated catalyst was collected. To the filtrate was added 10 mL of EtOAc and 10 mL of water. The aqueous layer was separated, and to it was added an excess of saturated KPF_6 solution. Upon stirring, product precipitated to give 310 mg (0.98 mmol) of an orange solid (62% yield, mp 210–213 °C (lit.[44] mp iodide)). ^{1}H NMR (DMSO-d_6): δ 9.47 (1H, s), 9.07 (1H, d, J = 1 Hz), 8.95 (2H, 2d, J = 6 and 8 Hz), 8.73 (1H, d, J = 5 Hz), 8.25 (2H, m), 7.63 (1H, dd, J = 5 and 8 Hz), 4.39 (3H, s, CH_3). Anal. Calcd for $C_{11}H_{11}N_2PF_6$: C, 41.79; H, 3.51; N, 8.86. Found: C, 41.68; H, 3.47; N, 8.70.

1-Methyl-3-(3-pyridyl)quinolinium Iodide (7). A mixture of 3-bromo-1-methylquinolinium iodide[38] (0.75 g, 2.1 mmol), diethyl-3-pyridylborane (0.47 g, 3.2 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.25 mmol) in 20 mL of degassed THF was allowed to stir at room temperature for 5 min. To this was added sodium bicarbonate (0.54 g, 6.4 mmol) in 10 mL of water, and the suspension was heated at reflux. After 8 h, the reaction was cooled to 0 °C with ice and the precipitated catalyst was filtered off. To the filtrate was added 30 mL of EtOAc and 30 mL of water. The aqueous layer was separated and concentrated to an orange solid/oil. This material was washed with 10 mL of MeOH and the insolubles filtered away. The product was precipitated from the MeOH with 20 mL of EtOAc to yield 250 mg (0.72 mmol) of an orange solid (33% yield, mp 208–212 °C, dec). ^{1}H NMR (DMSO-d_6): δ 10.05 (1H, s), 9.71 (1H, s), 9.22 (1H, d, J = 2 Hz), 8.76 (1H, dd, J = 2 and 5 Hz), 8.53 (1H, d, J = 10 Hz), 8.47 (1H, d, J = 10 Hz), 8.42 (1H, dt, J = 2, 2 and 9 Hz), 8.29 (1H, dd, J = 8 and 10 Hz), 8.09 (1H, t, J = 8 and 10 Hz), 7.68 (1H, dd, J = 5 and 9 Hz), 4.71 (3H, s, CH_3). Anal. Calcd for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76; N, 8.05. Found: C, 51.89; H, 3.75; N, 7.77.

2-Methyl-4-phenylisoquinolinium Hexafluorophosphate (8). A mixture of 4-bromo-2-methylisoquinolinium iodide[40] (0.500 g, 1.43 mmol), phenylboronic acid (0.292 g, 2.40 mmol), and tetrakis(triphenylphosphine)palladium-(0) (0.277 g, 0.240 mmol) in 15 mL of degassed tetrahydrofuran was allowed to stir at room temperature for 15 min. To this was added sodium borate (1.83 g, 4.80 mmol) in 15 mL of water, and the suspension was heated at reflux under a nitrogen atmosphere. After 6 h, the reaction was cooled to room temperature and the precipitated catalyst and sodium borate were filtered away. To the filtrate was added 10 mL of EtOAc and 10 mL of water. The aqueous layer was separated, and to it was added an excess of saturated KPF_6 solution. Upon stirring, product precipitated to give 160 mg (0.44 mmol) of a white solid (31% yield, mp 182–184 °C). ^{1}H NMR (DMSO-d_6): δ 10.00 (1H, s), 8.78 (1H, d, J = 1 Hz), 8.55 (1H, dd, J = 1 and 8 Hz), 8.23 (1H, td, J = 1 and 7 Hz), 8.09 (2H, td, J = 1 and 7 Hz), 7.65 (5H, m), 4.50 (3H, s, CH_3). Anal. Calcd for $C_{16}H_{14}NPF_6$: C, 52.61; H, 3.86; N, 3.83. Found: C, 52.48; H, 3.84; N, 3.70.

2-Methyl-4-(3-pyridyl)isoquinolinium Iodide (9). A mixture of 4-bromo-2-methylisoquinolinium iodide[40] (0.500 g, 1.43 mmol), diethyl-3-pyridylborane (0.250 g, 1.70 mmol), and tetrakis(triphenylphosphine)palladium-(0) (0.165 g, 0.143 mmol) in 15 mL of degassed tetrahydrofuran was allowed to stir at room temperature for 15 min. To this was added 7 mL of MeOH, followed by sodium borate (1.09 g, 2.86 mmol) in 15 mL of water, and the suspension was heated at reflux under a nitrogen atmosphere. After 6 h, the reaction was cooled to room temperature, and the precipitated catalyst and sodium borate were collected. To the filtrate was added 10 mL of EtOAc and 10 mL of water. The aqueous layer was separated and concentrated to an orange solid/oil which was washed with 10 mL of MeOH. The insolubles were filtered away. The product precipitated from MeOH on addition of 20 mL of EtOAc to give 215 mg (0.62 mmol) of an orange solid (43% yield, mp 200–203 °C, dec). ^{1}H NMR (DMSO-d_6): δ 10.07 (1H, s), 8.85 (3H, m), 8.58 (1H, d, J = 9 Hz), 8.26 (1H, m), 8.10 (3H, m), 7.72 (1H, dd, J = 6 and 9 Hz), 4.51 (3H, s, CH_3). Anal. Calcd for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76; N, 8.05. Found: C, 51.42; H, 3.71; N, 7.68.

Partially Deuteriated 5-Chloro-3,3′-bipyridine 1-Oxide (10). The 3,5-dichloropyridine 1-oxide[29] contained 95% D at all positions.[29] The conditions were the same as those used for the preparation of **1**. The reaction mixture stood for 20 h at room temperature and then was heated at reflux for 28 h. ^{1}H NMR (DMSO-d_6): 0% D at C-6, 95% D at C-4, and 65% D at C-2.

(44) Lukes, R.; Pliml, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 1356.

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