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Pyrrolodiazines. 6. Palladium-Catalyzed Arylation, Heteroarylation, and Amination of 3,4-Dihydropyrrolo[1,2-*a*]pyrazines†

Isabel Castellote,‡ Juan J. Vaquero,*,‡ Javier Fernández-Gadea,§ and Julio Alvarez-Builla*,‡

Departamento de Química Orgánica, Universidad de Alcalá, 28871-Alcalá de Henares, Madrid, Spain, and Lab. Janssen-Cilag, C/Río Jarama s/n, Polígono Industrial, 45007-Toledo, Spain

juanjose.vaquero@uah.es

Received June 30, 2004

The palladium-catalyzed Suzuki cross-coupling reaction of arylboronic acids and 6-bromo- and 6,8-dibromo-3,4-dihydropyrrolo[1,2-*a*]pyrazines afforded 6-substituted and 6,8-disubstituted 3,4-dihydropyrrolo[1,2-*a*]pyrazines in good yields. Stille and Negishi coupling reactions have been used to prepare 6-heteroaryl-substituted derivatives in moderate yields by employing heteroaryl halides and 6-metalated 3,4-dihydropyrrolo[1,2-*a*]pyrazines as reaction partners. A variety of cyclic secondary amines have also been incorporated at position C-6 of 6-bromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine in the presence of the palladium catalyst $Pd_2(dba)_3$ in conjunction with BINAP as ligand. This amination reaction is one of the few reported examples of such a palladium-catalyzed transformation on a pyrrole ring, although the reaction could not be extended to less nucleophilic amines.

Introduction

The core structure of pyrrolodiazine **1**[1] is present in a variety of biologically active molecules including some natural alkaloids such as hinckdentine[2] and the variolin family[3] (Figure 1). In simple derivatives, the activity is strongly associated with the tetrahydro form of the diazine moiety. For example, 1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine derivatives **2** exhibit antihypertensive, ischemic, anxiolytic, and equistomicidal activities.[1b,4] To date, compounds with the core structure **2** have been prepared from the corresponding fully oxidized precursors or from the corresponding dihydro derivatives by standard reduction procedures.[1]

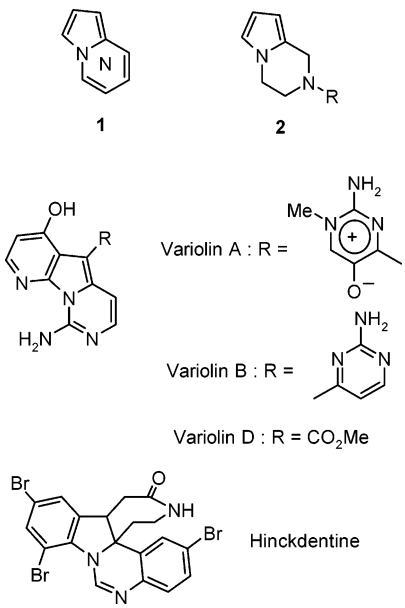

FIGURE 1. Structures of some natural alkaloids containing a pyrrolodiazine core.

In connection with our recent studies on the chemistry and biology of pyrrolodiazines,[5] we needed to develop a practical route to pyrrolo[1,2-*a*]pyrazine derivatives **6** and this would involve the prior preparation of **5**. Most of the reported methods for the synthesis of 1-substituted 3,4-dihydropyrrolo[1,2-*a*]pyrazines **5** are based on the con-

* To whom correspondence should be addressed.

† Dedicated to the memory of the organic chemist Dr. Juan C. del Amo, who was killed in the terrorist attack in Madrid, Spain, on March 11, 2004.

‡ Universidad de Alcalá.

§ Lab. Janssen-Cilag.

(1) (a) Amarnath, V.; Madhav, R. *Synthesis* **1974**, 837. (b) Kuhla, D. E.; Lombardino, J. G. *Adv. Heterocycl. Chem*. **1977**, *21*, 1. (c) Blewitt, H. L. *Chem. Heterocycl. Compd*. **1977**, *30*, 117. (d) Maury, G. *Chem. Heterocycl. Compd*. **1977**, *30*, 179. (e) Terenin, V. I.; Kabanova, E. S.; Feoktistova, E. S. *Chem. Heterocycl. Compd.* **1991**, *10*, 1037.

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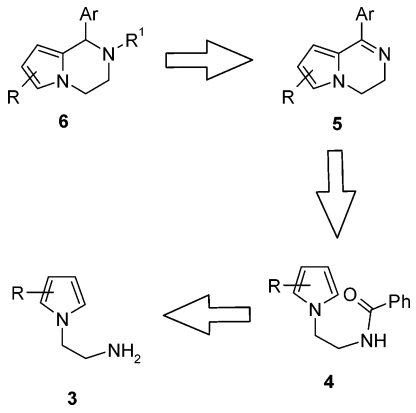
(4) (a) Jirkovsky, I. L. U.S. Patent 4188389, 1980. (b) Romero, G. S.; Franco, F.; Castaneda, A. C.; Muchowski, J. M.; U.S. Patent 5041442, 1991. (c) Rover, S. Eur. Patent 521368, 1993. (d) Seredenin, S.; Voronina, T. A.; Likhosherstov, A. M.; Peresada, V. P.; Moladavkin, G. M.; Halikas, J. A. U.S. Patent 5378846, 1995.

10.1021/jo048898o CCC: $27.50 © 2004 American Chemical Society
Published on Web 11/11/2004

SCHEME 1



densation reaction between appropriately substituted furans or tetrahydrofurans and 1,2-diamino compounds to give 1-(2-aminoethyl)pyrroles **3**.[1e] Compounds **3** were reacted with carboxylic acids to afford the amides **4**, which are transformed into **5** under acid conditions (Scheme 1). In all cases, the R substituent on the pyrrole is incorporated in the starting material, a situation that limits the diversity in the pyrrole moiety and also suffers from the drawback of low to moderate global yields associated with this linear route.

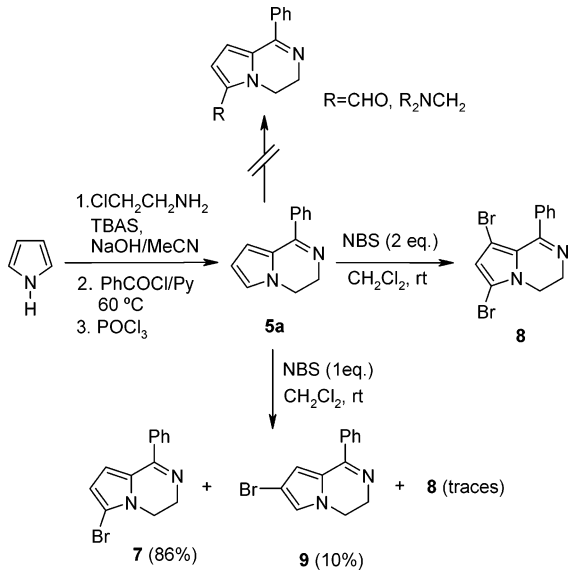
Herein, we report an easy and convergent method for the preparation of compounds **5** based on the use of palladium-catalyzed reactions (Suzuki, Stille, and Negishi) to introduce aryl, heteroaryl, and dialkylamino substituents in 1-aryl-substituted 3,4-dihydropyrrolo[1,2-*a*]pyrazines **5**.

Results and Discussion

Initial screening demonstrated the beneficial role, in terms of activity, of aryl substituents at the C1 position of compound **6**, and so our first target was the preparation of **5a** (R = H; Ar = Ph). This heterocycle was prepared following the procedure previously reported by us for an improved synthesis of 3,4-dihydropyrrolo[1,2-*a*]pyrazine.[5a] First, pyrrole was alkylated with 2-chloroethylamine under phase-transfer conditions,[6] and the resulting aminoethylpyrroles were treated with benzoyl chloride to give the desired amide. The amide was heated in the presence of $POCl_3$ to afford the desired cyclization product **5a** with a global yield of 36%.

It is worth noting that the attempted formylation of **5a** using Vilsmeier−Haack conditions resulted in recovery of the starting material when the reaction was carried out at room temperature and complex mixtures were obtained under more forcing conditions. Similarly, Mannich reaction with dimethylamine, di-*n*-propylamine, or

SCHEME 2



morpholine/formaldehyde also failed to give the expected substitution products (Scheme 2).

It was envisaged that a palladium-catalyzed coupling reaction would not only provide an efficient method to introduce substituents on the pyrrole ring but also constitute an extension of a known methodology in this field.[7] Investigation of this alternative process was initiated by studying the halogenation reaction of **5a**. Iodination using iodine provided only traces of the 6-iodo derivative. The reaction with *N*-iodosuccinimide (NIS), on the other hand, gave an unexpected 1:1 addition complex in equilibrium with starting materials.[8]

However, reaction of **5a** and 1 equiv of *N*-bromosuccinimide (NBS) afforded the 6-bromo-1-phenyl-3,4-dihydropyrrole **7** in 86% yield along with 10% of the 7-bromo compound **9** and traces of the 6,8-dibrominated derivative **8**. Compound **8** was obtained as the major reaction product when 2 equiv of NBS were used.

As palladium-promoted cross-coupling reactions have been successfully employed in the functionalization of some halopyrroles,[9] we therefore decided to explore various palladium-catalyzed C−C bond formation methods to achieve an efficient preparation of target compounds **5**. With this aim in mind, compound **7** was treated with ^{n}BuLi, and the metalated intermediate **10** was converted into the heteroarylboronic acid **11**, the heteroaryltin **12**, and the heteroarylzincate **13** to test the well-known Suzuki,[7,10] Stille,[7,11] and Negishi[7,12] reactions with a variety of commercially available aryl and heteroaryl halides (Scheme 3).

(5) (a) de Pablo, M. S.; Gandasegui, T.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J. *Tetrahedron* **1992**, *32*, 8793. (b) Minguez, J. M.; Vaquero, J. J.; García Navio, J. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1996**, *37*, 4263. (c) Minguez, J. M.; Castellote, I.; Vaquero, J. J.; García Navio, J. L.; Alvarez-Builla, J.; Castaño, O.; de Andrés, J. L. *J. Org. Chem*. **1996**, *61*, 1655. (d) Minguez, J. M.; Castellote, I.; Vaquero, J. J.; García Navio, J. L.; Alvarez-Builla, J.; Castaño, O.; de Andrés, J. L *Tetrahedron* **1997**, *53*, 9341. (e) Minguez, J. M.; Vaquero, J. J.; Alvarez-Builla, J.; Castaño, O.; de Andrés, J. L. *J. Org. Chem.* **1999**, *64*, 7788.

(6) Cuadro, A. M.; Matia, M. P.; García, J. L.; Vaquero, J. J.; Alvarez-Builla, J. *Synth. Commun*. **1991**, *21*, 535.

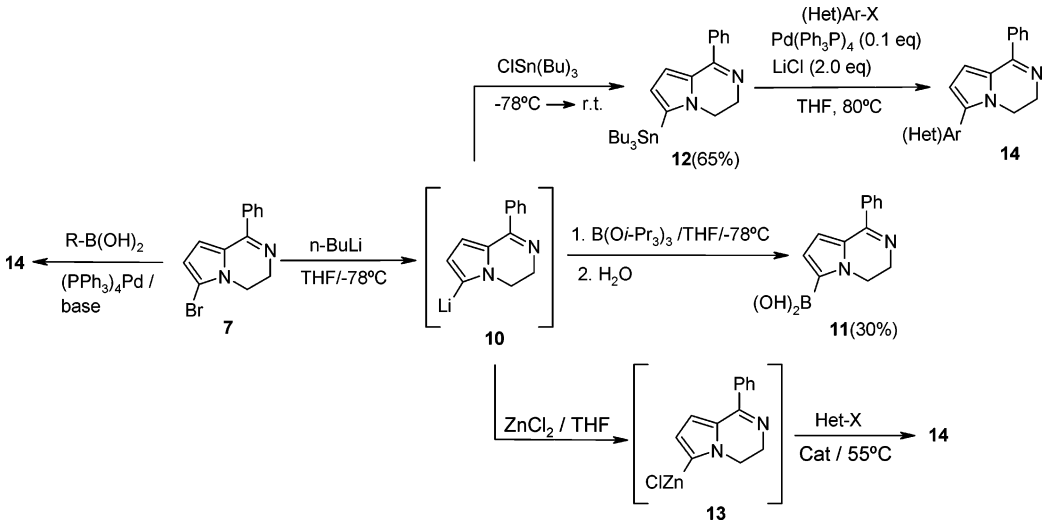
(7) (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (c) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry Series 219; Springer-Verlag: New York, 2002. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002.

(8) Analytical and spectral data are according with a NIS/**5a** (1:1) adduct. The unstability of this adduct precluded to date its structure determination by X-ray diffraction.

(9) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000.

(10) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miura, N.; Suzuki, A. *Chem. Commun*. **1979**, 866.

SCHEME 3



Stannane **12** was obtained in an acceptable 65% yield, but the boronic acid **11** was isolated in only 26% and 30% yield depending on the borate employed [$B(OMe)_3$ or B(O-*i*-Pr)$_3$]. These low yields are due to the low stability of **11**, which is prone to decomposition —a situation that precludes the use of this route as an efficient synthetic method. We therefore decided to study the Suzuki coupling reaction using halide **7** and commercially available arylboronic acids.

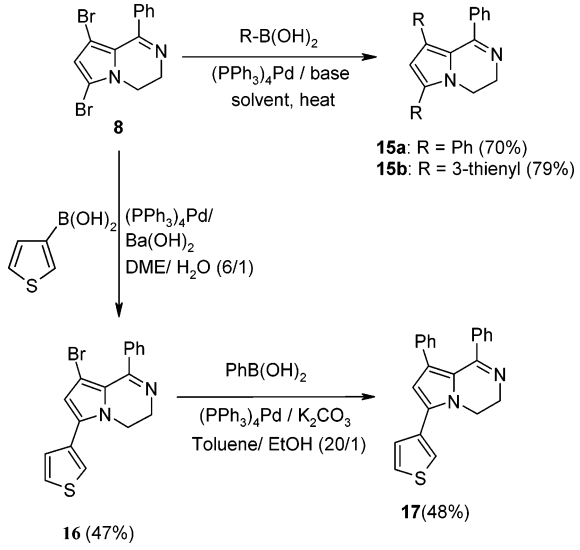
Initial attempts to couple **7** and representative arylboronic acids using $Pd(PPh_3)_3$ as a catalyst in toluene/K_2CO_3 gave the coupling product in low or moderate yield. The replacement of toluene by a mixture of toluene/EtOH led to a considerable improvement in the yields, and the best results for arylboronic acids (Table 1, entries 1−3) were obtained with a toluene/EtOH ratio of 20:1.

When these conditions were applied to the coupling of **7** and thienylboronic acid, the coupled compound was isolated in very low yield. Further attempts led to a remarkable increase in the yield by using $Ba(OH)_2$ as a base in a 6:1 mixture of DME/H_2O as solvent (Table 1, entry 4).

The conditions established for the coupling reaction of **7** and aryl- or thienylboronic acids also proved to be appropriate for a double-coupling reaction of the dibromo derivative **8** and these boronic acids. In this way, disubstituted compounds **15** (Table 1, entries 5 and 6) were obtained in high yields by using 2.5−3 equiv of the boronic acid (Scheme 4).

The reactivities of the C6 and C8 positions in the dibromo compound **8** are different toward the palladium-catalyzed coupling reaction. Evidence for this was provided by the fact that 8-aryl or heteroaryl subtitution products were not detected when 1 equiv of the boronic acid was reacted with **8**. Under these conditions, however,

SCHEME 4



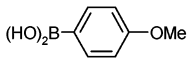
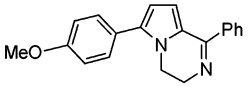
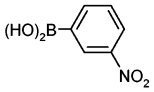
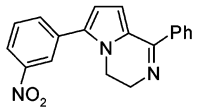
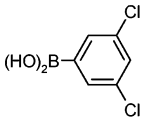
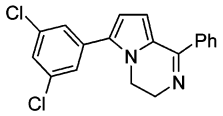
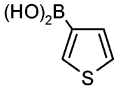
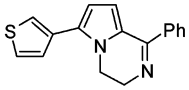
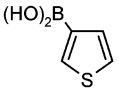
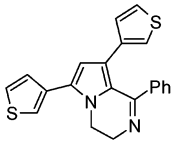
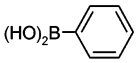
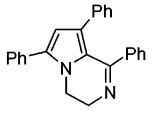
a significant decrease in the yield of the monocoupled compound **16** was found in comparison to the corresponding coupling reaction of the monobromo compound **7**. This chemoselective coupling process allowed the preparation of the disubstituted compound **17** bearing a 3-thienyl and a phenyl substituents at C6 and C8 respectively by employing consecutive coupling reactions with two different boronic acids (Scheme 4).

As anticipated, the low stability and yield of boronic acid **11** precluded its use as a convenient partner in the Suzuki reaction. This situation limited the preparation of 6-heteroaryl-substituted derivatives to those derived from commercially available heteroaryl halides. In contrast to **11**, stannane **12** provides a good alternative for an investigation into the Stille reaction using a variety of heteroaryl halides such as those shown in Table 2. Using conditions similar to those reported for the palladium-catalyzed coupling reaction of pyrrolestannanes and aryl and heteroaryl halides,[12] we successfully obtained the coupled products using haloazines (Table 2, entries 1−3) and haloazoles (Table 2, entries 4−11) although moderate or low yields were obtained in all

(11) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508. (d) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; John Wiley & Sons: New York, 1998.

(12) See, inter alia: (a) Bailey, T. R. *Tetrahedron Lett*. **1986**, *27*, 4407. (b) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapiro, J. *J. Org. Chem*. **1990**, *45*, 5833. (c) Hoffmann, H. M. R.; Gerlach, K.; Lattmann, E. *Synthesis* **1996**, 164.

TABLE 1. Suzuki Coupling of Aryl and Heteroarylboronic Acids and Halides 7 and 8

entry	organoboronic	halide	conditions[a]	coupling product (**14/15**)	yield (%)
1		**7**	Toluene/EtOH (20/1)/ K_2CO_3	 **14a**	84
2		**7**	Toluene/EtOH (20/1)/ K_2CO_3	 **14b**	82
3		**7**	Toluene/EtOH (20/1) /K_2CO_3	 **14c**	87
4		**7**	DME/H_2O (6/1)/ $Ba(OH)_2.8H_2O$	 **14d**	90
5		**8**	DME/H_2O (6/1)/ $Ba(OH)_2.8H_2O$	 **15a**	79
6		**8**	Toluene/EtOH (20/1) /K_2CO_3	 **15b**	70

[a] $Pd(Ph_3)_4$ (0.05 mmol).

cases. It was found that a catalyst combination of 0.1 equiv of $(PPh_3)_4Pd$ and 2.0 equiv of LiCl in THF as solvent and heating at 80 °C generally provided the best results, except in the case of 3-iodopyrazole (Table 2, entry 4).

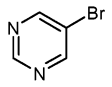
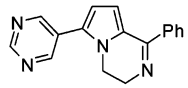
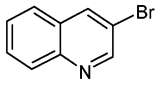
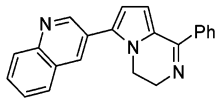
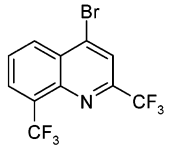
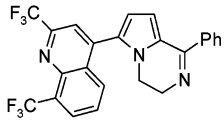
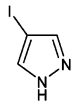
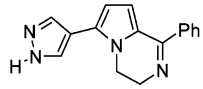
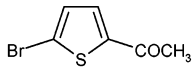
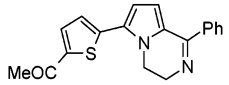
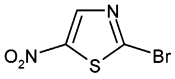
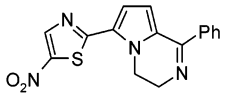
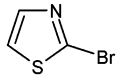
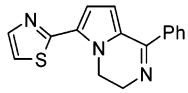
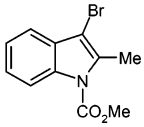
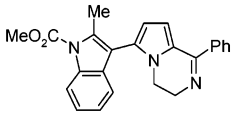
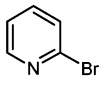
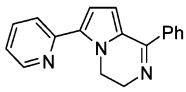
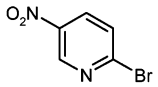
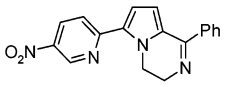
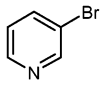
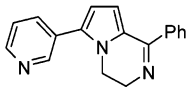
In an attempt to improve these yields, we turned our attention to the Negishi methodology since there are literature precedents for coupling reactions involving pyrrolezincates that give high yields of coupled products.[13,14] The required zincate **13** was generated in situ by metalation of **7** with ^{n}BuLi followed by addition of $ZnCl_2$ in THF. A slight modification of the reported conditions for the palladium-catalyzed arylation of pyrrolezincates gave no reaction with haloazoles, but bromopyridines (Table 2, entries 9−11) provided the coupled compounds with better yields than those obtained in the Stille reaction using stannane **12**. While 2-bromopyridines reacted in the presence of $(PPh_3)_4Pd$ to afford moderate yields of the coupled products (Table 2, entries 9 and 10), the less reactive 3-bromopyridine could only be coupled using $Pd_2(dba)_3$ dppf as palladium catalyst, and in this case the yield was lower (Table 2, entry 11).

In a final attempt to improve the yields of compounds **14** (Table 2) by a Stille reaction, we also tested the reaction between **7** and tributyl 2-pyridylstannane. Results obtained with different catalysts demonstrate that although the coupling reaction did occur, isolated yields were clearly disappointing when compared with those obtained using the alternative combination of reactants shown in Scheme 3. The coupling products and best yields

(13) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.; Matsushita, H.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* **1983**, *24*, 3823. (c) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683. (d) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (e) *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999. (f) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boston, 1996. (g) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414−4435.

(14) (a) Luo, F.-T.; Wang, R.-T. *Heterocycles* **1990**, 2181. (b) Takahashi, K.; Gunji, A. *Heterocycles* **1996**, 941.

TABLE 2. Stille and Negishi Coupling of Heteroaryl Halides 12 and 13

entry	halide	organometallic/ conditions[a]	coupling product (**14**)		yield (%)
1		**12**/A		**14e**	32
2		**12**/A		**14f**	49
3		**12**/A		**14g**	56
4		**12**/A		**14h**	Traces
5		**12**/A		**14i**	67
6		**12**/A		**14j**	41
7		**12/A**		**14k**	45
8		**12**/A		**14l**	35
9		**13**/B		**14m**	57
10		**13**/B		**14n**	60
11		**13**/C		**14o**	30

[a] Conditions: A = $Pd(Ph_3P)_4$ (0.01 mmol), LiCl, THF; B = $Pd(PPh_3)_4$ (0.05 mmol), THF; C = $Pd_2(dba)_3$ (0.01 mmol), dppf (0.01 mmol), THF.

achieved by Stille and/or Negishi reactions are summarized in Table 2.

Although the Pd-catalyzed amination of some azoles have been reported,[15] the amination of pyrroles had not previously been reported until our recent publication[16] describing the conditions for the amination of protected 2-acetyl-5-bromopyrrole with primary and cyclic secondary amines using $Pd_2(dba)_3$ as catalysts with BINAP as the ligand. Under these conditions, morpholine was successfully coupled with **7** to give the desired 6-morpholino-1-phenyl-3,4-pyrrolo[1,2-*a*]pyrazine **18a** by using ^{t}BuONa as a base and toluene as the solvent at 100 °C. These conditions proved to be general for the amination of **7** with a variety of secondary cyclic amines (Table 3). However, all our attempts to extend the scope of this amination reaction to primary and secondary acyclic amines such as 4-methoxybencilamine, *n*-propylamine, cyclobutylamine and di-*n*-butylamine failed, and unaltered **7** was recovered in most cases or the debrominated compound was formed as the main reaction product when $Pd_2(dba)_3$ was used in the presence of different ligands such as dppf, P^tBu_3 and biphenylP^tBu_2.

SCHEME 5

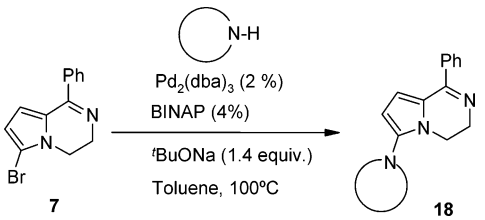
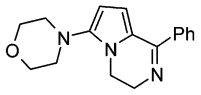
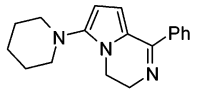
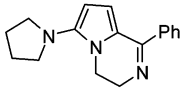
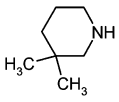
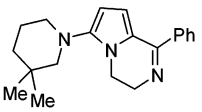
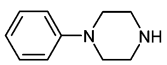
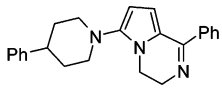
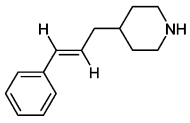
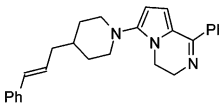


TABLE 3. Palladium-Catalyzed Amination of 7 with Cyclic Secondary Amines

entry	amine	coupling product (**18**)[a]		yield (%)
1			**18a**	69
2			**18b**	64
3			**18c**	69
4			**18d**	45
5			**18e**	43
6			**18f**	51

[a] Conditions: $Pd_2(dba)_3$ (0.02 mmol), BINAP (0.04 mmol), NaO^{t}Bu, toluene, 100 °C.

Conclusions

The palladium-catalyzed arylation and heteroarylation of 6-bromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**7**) using aryl and heteroaryl halides has proven to be a practical means for introducing aromatic and heteroaromatic diversity on the pyrrole ring. The Suzuki reaction is particularly useful with aryl or 3-thienyl boronic acids and 6-bromo- or 6,8-dibromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine as reaction partners. Stille and Negishi reactions gave rise to heteroaromatic substitution with moderate yields on using heteroaryl halides and 1-phenyl-3,4-dihydro[1,2-*a*]pyrazine as the C6 metalated substrate. Exceptions to this general applicability include 3-iodopyrazole, which did not react with either the stannane or the zincate. Comparatively, the Stille reaction produced better yields than the Negishi coupling except in the cases of bromopyridines, which were the only heterocycles that could be incorporated using this latter reaction. The Pd-catalyzed amination of the pyrrole ring was successfully achieved using BINAP as the ligand and $Pd_2(dba)_3$ a catalysts, although this amination was only successful with cyclic secondary amines.

Experimental Section

6-Bromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (7) and 7-bromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (9). To a solution of **5a**[5a,17] (0.295 g, 1.5 mmol) in CH_2Cl_2 (6 mL) was added a solution of N-bromosuccinimide (0.267 g, 1.5 mmol) in CH_2Cl_2 (3 mL). After the mixture was stirred at room temperature for 30 min, a 2% solution of NaOH was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL).The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure, yielding a residue which was purified by column chromatography (hexane/EtOAc, 3:7) to yield 355 mg (86%) of compound **7** and 40 mg (10%) of compound **9**. **7**: mp 84−86 °C (pale powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (m, 2H), 7.43−7.40 (m, 3H), 6.37 (d, 1H, J = 4.0 Hz), 6.23 (d, 1H, J = 4.0 Hz), 4.04−3.92 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.8, 137.5, 129.9, 128.4, 128.3, 125.8, 113.2, 110.8, 106.4, 48.0, 40.2; IR (KBr) ν_{max} 2947, 1589, 1566, 1408, 1036 cm^{-1}. Anal. Calcd for $C_{13}H_{11}BrN_2$: C, 56.75; H, 4.03; N, 10.18. Found: C, 56.49; H, 4.23; N, 10.11. **9**: mp 94−95 °C (pale powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.40 (m, 5H), 6.82 (d, 1H, J = 1.5 Hz), 6.39 (d, 1H, J = 1.5 Hz), 4.06−3.96 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.5, 136.6, 130.4, 128.3, 128.2, 124.3, 123.5, 114.7, 96.8, 47.1, 42.0; IR (KBr) ν_{max} 1715, 1593, 1567, 1409, 1333 cm^{-1}. Anal. Calcd for $C_{13}H_{11}BrN_2$: C, 56.75; H, 4.03; N, 10.18. Found: C, 56.49; H, 4.24; N, 10.07.

6,8-Dibromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (8). To a solution of **5a** (0.295 g, 1.5 mmol) in CH_2Cl_2 (6 mL) was added a solution of *N*-bromosuccinimide (0.534 g, 3.0 mmol) in CH_2Cl_2 (6 mL). After the mixture was stirred at room temperature for 1 h, a solution of NaOH 2% was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography (hexane/EtOAc, 2:8) yielding 418 mg (79%) of the title compound as a pale powder: mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.66 (m, 2H), 7.45−7.41 (m, 3H), 6.45 (s, 1H), 4.02−3.95 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 136.8, 130.2, 128.4, 128.3, 125.9, 114.6, 108.2, 99.3, 47.6, 41.1; IR (KBr) ν_{max} 2946, 1590, 1567, 1407, 1326 cm^{-1}. Anal. Calcd for $C_{13}H_{10}Br_2N_2$: C, 44.10; H, 2.85; N, 7.91. Found: C, 43.97; H, 2.76; N, 8.06.

(1-Phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-6-yl)boronic Acid (11). To a −78 °C cooled solution of **5a** (687 mg, 2.5 mmol) in dry THF (6 mL) was added ^{n}BuLi (1.72 mL, 2.75 mmol, 1.6 M in hexane) dropwise under argon. After the mixture was stirred for 45 min at this temperature, B(O^{i}Pr)$_3$ (0.63 mL, 2.75 mmol) was added, and the reaction mixture was stirred for another 30 min at the same temperature and then allowed to warm to room temperature. The reaction mixture was treated with 20 mL of a solution of THF/HCl (10%) (1/1) and H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was evaporated under reduced pressure to obtain a solid that was treated with EtOH. Filtration and evaporation of the solvent gave a residue that

(15) For aminations of thiophenes, see: (a) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Chem. Commun.* **2000**, 133. (b) Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731. (c) Ogawa, K.; Radke, K. R.; Rothstein, S. D.; Rasmussen, S. C. *J. Org. Chem.* **2001**, *66*, 9067. For amination of thiazoles and imidazoles, see: (b) Hong, Y.; Tanoury, G. J.; Wilkinson, S. H.; Bakale, R. P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **1997**, *38*, 5607. (c) Wang, Z.; Rizzo, C. J. *Org. Lett.* **2001**, *3*, 565. (d) Schoffers, E.; Olsen, P. D.; Means, J. C. *Org. Lett.* **2001**, *3*, 4221. For amination five-membered heterocyclic halides, see: Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861.

(16) Castellote, I.; Vaquero, J. J.; Alvarez-Builla, J. *Tetrahedron Lett.* **2004**, *45*, 769−772

(17) Likhosherstov, A. M.; Peresada, V. P.; Vinokurov, V. G.; Skoldinov, A. P. *J. Org. Chem. USSR* **1986**, *22*, 2341.

was triturated with Et_2O to yield 180 mg (30%) of the title compound (yellow unstable powder). ^1H NMR (300 MHz, $CDCl_3$): δ 7.84−7.61 (m, 5H), 7.03 (d, 1H, J = 4.4 Hz), 6.82 (d, 1H, J = 4.4 Hz), 4.65−4.61 (m, 2H), 4.03−3.98 (m, 4H).

1-Phenyl-6-tributylstannyl-3,4-dihydropyrrolo[1,2-*a*]-pyrazine (12). To a −78 °C cooled solution of **5a** (550 mg, 2.0 mmol) in dry THF (10 mL) was added ^{n}BuLi (1.54 mL, 2.2 mmol, 1.6 M in hexane). After the mixture was stirred for 45 min, a solution of tributyltin chloride (0.61 mL, 2.2 mmol) in dry THF (2 mL) was added. The reaction mixture was stirred at this temperature for another 45 min and then allowed to warm to room temperature, treated with a saturated $NaHCO_3$ (10 mL) solution, and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with aqueous KF (10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 8:2) to give 705 mg (66%) of **12** as a yellow pale oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.80−7.71 (m, 2H), 7.48−7.41 (m, 3H), 6.38 (d, 1H, J = 3.6 Hz), 6.24 (d, 1H, J = 3.6 Hz), 4.02−3.96 (m, 4H), 1.60−1.25 (m, 18H), 0.83 (t, 9H, J = 8.1 Hz). Anal. Calcd for $C_{25}H_{38}N_2Sn$: C, 61.88; H, 7.89; N, 5.77. Found: C, 62.02; H, 7.96; N, 5.99.

General Procedure for Suzuki Coupling of Aryl- and Heteroarylboronic Acids and 7. Method A (Compounds 14a−c). To a suspension of **7** (1.00 mmol) and $Pd(Ph_3)_4$ (58 mg, 0.05 mmol) in a mixture of toluene/EtOH (20/1,16 mL) under argon were added K_2CO_3 (152 mg, 1.10 mmol) and the corresponding boronic acid (1.10 mmol). The reaction mixture was refluxed for 24 h, and the cooled suspension was extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was washed with a saturated solution of NaCl (20 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography. Compounds **14a** and **14d** were isolated and identified as the oxalate salt.

Method B (Compound 14d). The reaction was carried out as described in method A, but the mixture of solvents and the base were changed to DME/H_2O (6/1.7, 16 mL) and $Ba(OH)_2\cdot 8H_2O$ (473 mg, 1.50 mmol). Compound **14d** was isolated and identified as the oxalate salt.

General Procedure for Stille Coupling of 12 and Heteroaryl Halides (Compounds 14e−l). A solution of the stannane **12** (242 mg, 0.50 mmol), the heteroaryl halide (0.75 mmol), LiCl (42 mg), and $Pd(Ph_3P)_4$ (12 mg, 0.01 mmol) in dry THF (7 mL) was refluxed for 20 h. The mixture was cooled, filtered over Celite, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel.

General Procedure for Negishi Coupling of 13 and Heteroaryl Halides. Method A (Compounds 14m,n). To a solution of **7** (275 mg, 1.00 mmol) in dry THF (5 mL), under an atmosphere of argon, was added ^{n}BuLi (0.69 mL, 1.6 M in hexane, 1.10 mmol) at −78 °C. After the mixture was stirred for 45 min, a solution of $ZnCl_2$ (2.2 mL, 1.10 mmol, 0.5 M in THF) was added, and stirring was continued while warming up to rt. A solution of the halide (1.00 mmol) in THF (3 mL) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) were added, and the mixture was heated at 55 °C until completion. After being cooled to rt, the solution was diluted with EtOAc (30 mL) and washed with saturated $NaHCO_3$ (10 mL) solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/MeOH satd NH_3, 96:4).

Method B (Compound 14o). To a solution of **7** (275 mg, 1.00 mmol) in dry THF (5 mL), under argon, was added ^{n}BuLi (0.69 mL, 1.10 mmol, 1.6 M in hexane) at −78 °C. After the mixture was stirred for 45 min, a solution of $ZnCl_2$ (2.2 mL, 1.10 mmol, 0.5 M in THF) was added, and stirring was continued with warming to rt. A solution of the halide (1.00 mmol) in THF (3 mL), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), and dppf (10 mg, 0.01 mmol) were added, and the mixture was heated at 55 °C for 10 h. After being cooled to rt, the reaction mixture was diluted with EtOAc (30 mL) and washed with saturated $NaHCO_3$ (10 mL) solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/MeOH satd NH_3, 96:4).

General Procedure for Suzuki Coupling of Aryl- and Heteroarylboronic Acids and Halides 8. Over a stirring solution of **8** (354 mg, 1.0 mmol), the boronic acid (2.5 mmol), and $Ba(OH)_2\cdot 8H_2O$ (1.10 g, 3.50 mmol) in DME/H_2O (6/1, 14 mL) or toluene/EtOH (20:1, 21 mL) was added $Pd(Ph_3)_4$ (116 mg, 0.10 mmol) under argon. The reaction mixture was refluxed for 24 h, cooled to rt, poured into a saturated NaCl solution, and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue obtained was triturated with EtOAc to yield compounds **15a**,**b**.

1-Phenyl-6,8-di(thiophen-3-yl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (15a): yellow powder; 284 mg (79%); mp 235−236 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84−7.80 (m, 2H), 7.50−7.45 (m, 3H), 7.43 (dd, 1H, J = 4.8, 2.9 Hz), 7.31 (dd, 1H, J = 2.9, 1.1 Hz), 7.20 (dd, 1H, J = 4.8, 2.9 Hz), 7.07 (dd, 1H, J = 4.8, 1.1 Hz), 6.95 (dd, 1H, J = 2.9, 1.1 Hz), 6.91 (dd, 1H, J = 4.8, 1.1 Hz), 6.62 (s, 1H), 4.05−3.90 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.5, 138.0, 135.8, 131.0, 129.9, 129.1, 128.5, 128.2, 127.6, 127.4, 126.0, 125.7, 124.9, 124.1, 119.6, 119.1, 111.9, 48.3, 39.7; IR (KBr) ν_{max} 1589, 1564, 1461, 1418, 1349, 1332, 1286, 1168 cm^{-1}. Anal. Calcd for $C_{21}H_{16}N_2S_2$: C, 69.97; H, 4.47; N, 7.77. Found: C, 70.02; H, 4.61; N, 7.91.

1,6,8-Triphenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (15b): pale powder; 243 mg (70%); mp 233−234 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.83 (m, 2H), 7.47−7.38 (m, 6H), 7.34−7.30 (m, 2H), 7.22−7.10 (m, 5H), 6.66 (s, 1H), 4.02−3.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 138.1, 135.4, 132.5, 130.8, 130.6, 129.9, 128.6, 128.5, 128.2, 128.2, 128.1, 128.1, 125.8, 124.3, 123.4, 111.5, 48.5, 40.0; IR (KBr) ν_{max} 1586, 1562, 1457, 1436, 1415, 1181 cm^{-1} . Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.18; H, 5.79; N, 8.04. Found: C, 86.32; H, 5.77; N, 8.01.

8-Bromo-1-phenyl-6-(thiophen-3-yl)-3,4-dihydropyrrolo-[1,2-*a*]pyrazinium Oxalate (16). Over a stirring solution of **8** (354 mg, 1.0 mmol), thiophen-3-yl-boronic acid (128 mg, 1.0 mmol), and $Ba(OH)_2\cdot 8H_2O$ (1.50 mmol, 473 mg) in DME/H_2O (6/1, 7 mL) was added $Pd(Ph_3)_4$ (0.05 mmol, 58 mg) under argon. The reaction mixture was refluxed for 24 h, cooled to rt, poured into saturated NaCl solution, and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography (CH_2Cl_2/acetone) to give the coupling product **16** (168 mg, 47%) as a yellow oil that was transformed into the corresponding oxalate: mp 174−175 °C; ^1H NMR (200 MHz, CD_3OD) δ 7.90 (dd, 1H, J = 4.2, 1.3 Hz), 7.87−7.77 (m, 3H), 7.75−7.64 (m, 3H), 7.47 (dd, 1H, J = 5.2, 1.3 Hz), 7.25 (s, 1H), 4.44 (t, 2H, J = 6.3 Hz), 4.08 (t, 2H, J = 6.3 Hz); IR (KBr) ν_{max} 1713, 1597, 1540, 1436, 1338, 1230, 1131 cm^{-1}. Anal. Calcd for $C_{19}H_{15}BrN_2O_4S$: C, 51.02; H, 3.38; N, 6.26. Found: C, 51.23; H, 3.54; N, 6.17.

1,8-Diphenyl-6-(thiophen-3-yl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (17). Over a stirring solution of **16** (178 mg, 0.50 mmol), phenylboronic acid (67 mg, 0.55 mmol), and K_2CO_3 (76 mg, 0.55 mmol) in toluene/EtOH (20/1, 12 mL) was added $Pd(Ph_3)_4$ (0.025 mmol, 30 mg) under argon. The reaction mixture was refluxed for 24 h, cooled to rt, poured into a saturated NaCl solution, and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography (hexane/EtOAc, 6:4) to give **17** (85 mg, 48%) as a yellow powder: mp 179−180 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.80 (dd, 2H, J = 7.7, 1.8 Hz); 7.48−7.42 (m, 3H), 7.40−7.27 (m, 5H), 7.23 (dd, 1H, J = 2.9, 1.1 Hz), 7.20−7.11 (m, 2H), 6.99 (dd, 1H, J = 5.1, 1.1 Hz), 6.58 (s, 1H), 3.99 (m, 4H); IR (KBr) ν_{max} 1589, 1564, 1460, 1416, 1172 cm^{-1}. Anal. Calcd for $C_{23}H_{18}N_2S$: C, 77.93; H, 5.12; N, 7.90. Found: C, 77.87; H, 5.21; N, 7.95.

General Procedure for Palladium-Catalyzed Aminations of 7. An oven-dried glass vial was charged with **7** (275 mg, 1.00 mmol), 1.2 equiv of the amine, NaO^{t}Bu (135 mg, 1.40 mmol), $Pd_2(dba)_3$ (19 mg, 0.02 mmol), and BINAP (25 mg, 0.04 mmol) in dry toluene (7 mL) under argon. The flask was immersed in an oil bath, heated at 100 °C, and stirred overnight. The solution was then allowed to cool to room temperature, taken up in CH_2Cl_2 (10 mL), filtered over Celite, and concentrated under reduced pressure. Column chromatography of the residue on silica gel gave pure products **18**.

Acknowledgment. We acknowledge support of this work from Lab. Janssen and the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Dirección General de Investigación, Ministerio de Ciencia y Tecnología through projects BQU2002-03578 and BQU2001-1508 and a grant from Lab. Janssen (I.C.).

Supporting Information Available: Complete experimental procedures for the synthesis and characterization data for compounds **14** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048898O