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Palladium-Mediated N-Arylation of Heterocyclic Diamines: Insights into the Origin of an Unusual Chemoselectivity

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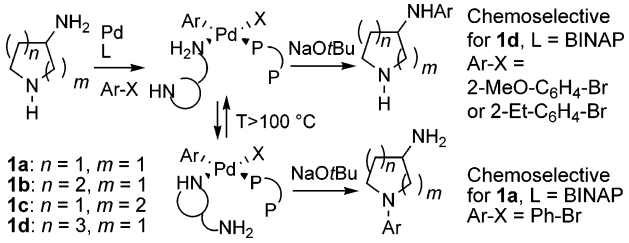

The chemoselectivity of the palladium-mediated reaction of bromobenzene with various heterocyclic diamines was studied. Whatever the ligand used, 3-aminopyrrolidine underwent arylation of the secondary amine function (>82%), whereas the more flexible 3-aminoazepinine was arylated on its primary function (>70%). The ratio "arylation of primary amine versus arylation of secondary amine" of 3-aminopiperidine with bromobenzene varied from 90:10 (BINAP, electron-enriched and hindered biphenyls **L2** or **L3**) to 32:68 with the Josiphos-type ligand **L10**. The same trend was observed when 4-aminopiperidine was used (82:18 with **L2** and 17:83 with **L10**). This selectivity can be tuned by the choice of aryl halide partners having different steric and electronic properties. A cooperative effect of both nitrogens of diamines during the reaction was deduced from competitive experiments. Finally, ^{13}C and ^{31}P NMR experiments, carried out with 3-aminopyrrolidine at room temperature, support a fast coordination of the primary amine to the metal. Indeed, a palladium complex resulting from the unusual displacement of one phosphane group of the intermediate ArPdX(BINAP) by the primary amino group was characterized.

Introduction

The 3-(*N*-arylamino)-pyrrolidine and -piperidine backbones are frequently encountered in molecules of pharmaceutical or biological interest.[1] Recently, we reported[2] the synthesis of these conformationally restricted 1,2-diamines using the attractive methodology developed by Buchwald and Hartwig,[3] based on palladium-mediated coupling reactions. From *N*-protected 3-aminopyrrolidines or -piperidines, a library of compounds bearing various aromatic rings was prepared. Attempts to use the unprotected heterocycles led to the exclusive or preferential arylation of the secondary amine (Scheme 1).[2] Indeed, arylation of 3-aminopyrrolidine **1a**, under the conditions described in Scheme 1, afforded *N*-phenyl-3-aminopyrrolidine **2a** as the sole product in 68% isolated yield. When 3-aminopiperidine **1b** was employed as the substrate, the reaction was incomplete. A mixture of monoarylated compounds **2b** and **3b** was isolated in 40% yield, with a 85:15 ratio of **2b**/**3b** in favor of the arylation of the secondary amine. Finally, the palladium-

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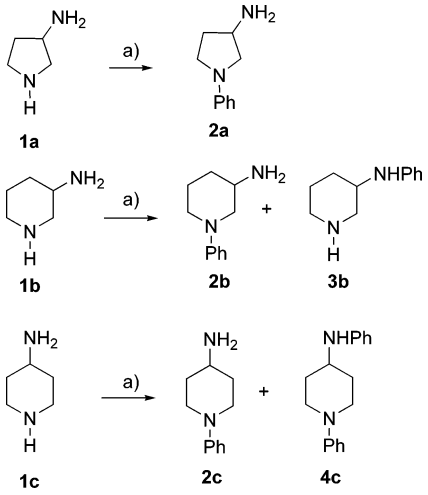
SCHEME 1[a]



[a] Reagents and conditions: diamine (1.2 equiv), PhBr (1 equiv), NaO*t*Bu (1.4 equiv), Pd_2dba_3 (1% mol in Pd), BINAP (1.5 mol), 100 °C, toluene, 24 h.

mediated coupling of bromobenzene with 4-aminopiperidine **1c** afforded *N*-phenyl-4-aminopiperidine **2c** as the major component of the reaction (ratio **2c**/**4c** 68:32, overall yield 85%) in contradiction with previous results.[4]

The selective arylation of a secondary amine in the presence of a primary one was unexpected from literature reports dealing with palladium-mediated arylations of polyamines. Compared to secondary amines, the less hindered primary amines are more easily coupled. Moreover, the formation of stable palladium complexes with polyamines can be observed, these inhibiting the catalytic reaction.[5] Although N-arylations catalyzed by Cu, Ni, or Pd complexes were performed on a variety of substrates such as monoamines,[6] amides,[7] aminoalcohols,[8] and N-H heterocycles,[9] only a few papers described the arylation of di- or polyamines. In most of the cases, one of the nitrogen atoms was protected.[10] Senanayake et al.,[4] in their synthesis of norastemizole requiring the reaction of 1-(4-fluorobenzyl)-2-(chlorobenzyl)imidazole with 4-aminopiperidine, reported the first example of a palladium-catalyzed (Pd_2dba_3, BINAP) selective coupling of a primary amine in the presence of a secondary amine. This selectivity was in contrast with the thermal coupling reaction.[4] This preferential arylation was confirmed in the reaction of the same imidazole substrate with acyclic polyamines or in the coupling of methyl- or cyano-substituted bromobenzenes with 4-aminopiperidine and acyclic polyamines. Hibert et al. described similar results with (*N*-ethyl)-ethylenediamine.[11] Beletskaya et al.[12] have extensively studied the arylation of linear polyamines using Pd_2dba_3 in conjunction with DPPF (bis(diphenylphosphino)ferrocene) or BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphtyl). They observed the exclusive reaction of primary amines versus secondary amines. Recently, Thommen and Blaser, tuning the substituents of the "Josiphos"-type ligand, observed a high chemoselectivity of palladium-mediated arylation of the primary amine in polyamines with no protection of the secondary amine.[13] However, the examples presented did not show the structures of substrates and catalysts used, and overall the chemoselectivity in C−N bond-forming processes has not been explored in great detail.

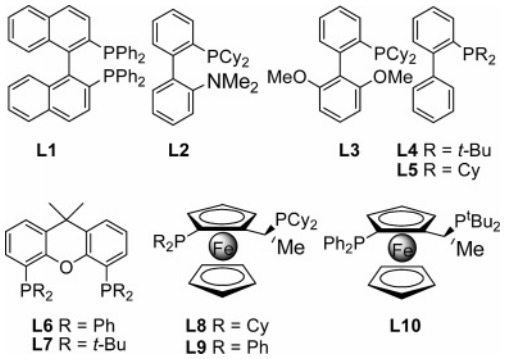


FIGURE 1. Ligands tested in the arylaminations.

To explain our previous results, we suspected that the structure of the ligands were not the sole factors governing the chemoselectivity. We envisaged that structure of the diamine substrate could play an important role on the issue of the reaction. To test this hypothesis, we studied or revisited the palladium-mediated reaction of aryl halides with heterocyclic 1,2-diamines **1a**, **1b** (Scheme 1), and **1d** (Scheme 2), differing only by the size of their ring, and 1,3-diamine **1c** (Scheme 1). We describe here the role of the different partners of the reaction (diamine, ligand, aryl halide) on the chemoselectivity of palladium-catalyzed arylation of compounds **1a**−**1d**. Our results are supported by competitive experiments and NMR data.

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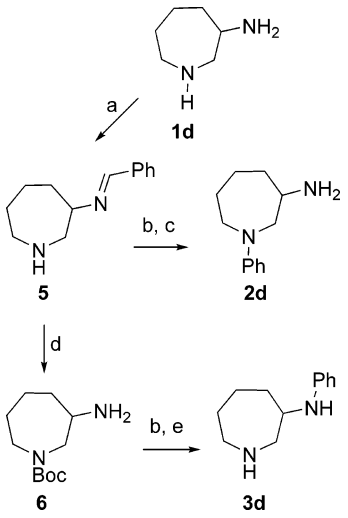
SCHEME 2. Synthesis of 2d and 3d[a]



[a] Reagents and conditions: (a) PhCHO, Na_2SO_4, CH_2Cl_2, room temperature, overnight; (b) Pd_2dba_3 (2% mol Pd), **L2** (3% mol), PhBr, NaO*t*Bu, xylene, 130 °C, 24 h; (c) SiO_2, flash chromatography; (d) Boc_2O, Et_3N, CH_2Cl_2, room temperature, 48 h, then acetic acid (3 M), room temperature, 3 days; (e) TFA, CH_2Cl_2, room temperature, overnight.

Results

Since we suspected the rigid structure of our amines to be responsible for the unusual selectivity, we chose to compare arylations of amines **1a**−**1c** with the seven-membered ring heterocyclic diamine **1d**.[14] Products **2a**−**c** to **4a**−**c** are known compounds,[2] whereas **2d** and **3d** were synthesized independently (Scheme 2). Condensation of diamine **1d** with benzaldehyde in the presence of Na_2SO_4 afforded imine **5**, which was directly subjected to palladium-mediated arylation with bromobenzene. Hydrolysis of the *N*-phenyl imine on silica gel during the purification step afforded **2d** in 24% overall yield (not optimized). Alternatively, protection of the endocyclic amine of **5** with Boc_2O followed by acetic acid treatment led to compound **6**. Palladium-mediated arylation of amine **6**, followed by deprotection, yielded compound **3d** in 54% overall yield.

Palladium-mediated arylation of the diamines **1** can provide at least three compounds: two monoarylamines (**2** and/or **3**) and a diarylamine **4** (Table 1). Yields of the reactions were accurately determined by two different methods: GC (wt %, authentic sample) and ^{1}H NMR using a known amount of an internal standard. Both methods afforded similar values. The yields of the monoarylated products **2** and **3** were determined by GC analysis, in comparison with authentic samples.

To improve the modest yield of our previous arylations (Pd_2dba_3/BINAP 1/1.5 mol %), the amounts of Pd and ligand were increased to 2 and 3 mol %, respectively. Starting with piperidine **1b**, GC analysis showed the formation of the expected monoarylated products **2b** and **3b** albeit in a different ratio (93:7, Table 1, entry 1), but the conversion was still poor. By increasing the temperature to 130 °C (replacing toluene by xylene, Table 1, entry 2) the conversion into monoarylated products reached 47%. Therefore different monophosphines, diphosphines, and aminophosphines were tested as ligands under these conditions, and the results for the four diamines are displayed in Table 1. The last column of the table represents the efficiency of the coupling reaction (sum of mono and double arylations).

Arylation of **1b**, in the presence of BINAP **L1**, afforded three compounds arising from mono- (**2b** and **3b)** and diarylation (**4b**) with a high selectivity of arylation of the secondary amine (**2b**/**3b** 92:8, entry 2). Whatever the ligand (**L1**, **L2**, **L3**) or the halobenzene used, arylation of the secondary amine was largely favored (entries 2−6), although the total arylation decreased to 71% with PhCl and 36% with PhI (entries 3 and 5). The phosphine ligand had a strong influence on the monoarylation/diarylation ratio for **1b**, ranging from 100:0 with **L8** (entry 7) to 45:55 with **L2** (entry 3). Important variations of the ratio of monoarylated products **2b/3b** were observed with other ligands. It varied from 91:9 with **L3** to 32:68 with **L10** (entries 6 and 8). Bulkier substituents on the phosphorus atom of the ligand still increased the arylation on the primary amine, as shown with **L8** (ratio **2b/3b** 63:37, entry 7). Xantphos **L6** and **L7** appeared a backbone not adapted for arylation of **1b** (Table 1, entries 9 and 10). Monophosphines **L4** and **L5** (entries 11 and 12) without any electron-donating group on the phenyl ring were inefficient as well.[15] In all of these reactions, no reduction of bromobenzene to benzene was observed.

An apparent discrepancy between our results and those from the literature appeared when we submitted 4-aminopiperidine **1c** to an arylation under the standard conditions.[4] Indeed, in our hands, in the presence of BINAP **L1**, **L2**, or **L9**, the major product resulted from the arylation on the secondary amine (**2c**/**3c** 93:7 entry 14, 82:18 entry 15, 90:10 entry 17 for **L1**, **L2**, and **L9**, respectively). **L2** was the best ligand tested, affording selectively monoarylated amine **2c** in good yields (entry 15). However, using ligand **L8**, arylation of both nitrogens occurred without any selectivity (52:48, entry 16), whereas **L10** led mainly to arylation of the primary amine (**2c**/**3c** 17:83, entry 18). This tendency was further increased with the seven-membered ring **1d**. The palladium coupling reaction carried out with BINAP **L1** afforded a ratio **2d**/**3d** of 31:69, in favor of the arylation on the exocyclic nitrogen atom (entry 19). With **L8** and **L10**, the selectivity toward the arylation of the same amine reached 81% (entries 20 and 21).

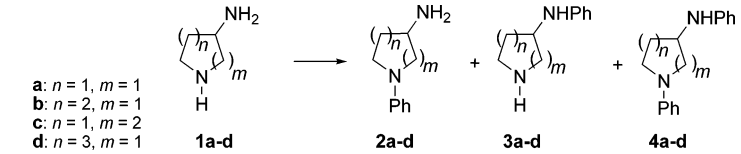
In contrast, arylamination of 3-aminopyrrolidine **1a** in the presence of BINAP yielded only both products **2a** and **4a** arising respectively from arylation of the endocyclic nitrogen and to a smaller extent from diarylation (entries 22 and 23). The compound **3a** was detected neither by GC nor by ^{1}H NMR. Although selective for the arylation of the primary amine of **1d** (entry 20), the ligand **L8** afforded **2a** selectively and in excellent yield in toluene at 100 °C and quantitatively in xylene at 130 °C (entries 24 and 25). Josiphos **L10**, bearing *tert*-butyl instead of cyclohexyl groups, was the sole ligand to afford from **1a** any amount of arylation on the primary amine, although diarylated amine **4a** was the major product with this ligand (entry 26).

Comparison of the results obtained at 110 and 130 °C for amines **1b** (entries 1 and 2) and **1a** (entries 22 and 23) shows that the temperature improved only the yields without modifying the selectivity and the ratio of monoarylation to diarylation.

(14) Diamine **1d** was synthesized in two steps starting from commercially available (+)-lysine according to literature procedures: (a) Bladé-Font, A. *Tetrahedron Lett.* **1980**, *21*, 2443−2446. (b) Fenton, R. R.; Easdale, W. J.; Er, H. M.; O'Mara, S. M.; McKeage, M. J.; Russell, P. J.; Hambley, T. W. *J. Med. Chem.* **1997**, *40*, 1090−1098.

(15) No palladium-mediated arylation of 1-benzyl-3-aminopyrrolidine was observed when triphenylphosphine, tricyclohexylphosphine, or diphenylphosphineferrocene was tested as ligand.

TABLE 1. Arylation of Diamines[a]



			yields[b,d] (%)			ratios		
entry	amine	ligand	**2**[b,d]	**3**[b,d]	**4**[c,d]	**2**/**3**[b]	**(2 + 3)**/**4**[i]	total arylation[j] (%)
1[e]	**1b**[f]	**L1**	23	2	10	93:7	71:29	45
2	**1b**	**L1**	43	4	17	92:8	73:27	81
3[g]	**1b**	**L2**	19.5	1.5	25 (23)	92:8	45:55	71
4	**1b**	**L2**	47	5	23 (23)	90:10	69:31	98
5[h]	**1b**	**L2**	20	4	6	84:16	80:20	36
6	**1b**	**L3**	39	4	22	91:9	66:34	87
7	**1b**	**L8**	24.5	14.5	0	63:37	100:0	39
8	**1b**	**L10**	15.5	32.5	17	32:68	74:26	82
9	**1b**	**L6**	26	8	3	77:23	92:8	40
10	**1b**	**L7**	1		nd	nd	nd	1
11	**1b**	**L4**	3		nd	nd	nd	3
12	**1b**	**L5**	8.5	2.5	nd	79:21	nd	11
13	**1b**	**L9**	27.5	4.5	10	86:14	76:24	52
14	**1c**	**L1**	37	3	7	93:7	85:15	54
15[g]	**1c**	**L2**	68 (60)	15	7 (7)	82:18	92:8	97
16	**1c**	**L8**	26.5	25.5	10 (8)	52:48	83:17	71
17	**1c**	**L9**	49.5	5.5	11 (9)	90:10	83:17	77
18	**1c**	**L10**	3.5	16.5	0	17:83	100:0	20
19	**1d**	**L1**	17.5	38.5	(17)	31:69	76:24	90
20	**1d**	**L8**	4	16	0	19:81	100:0	20
21	**1d**	**L10**	8	32	0	19:81	100:0	40
22[e]	**1a**[f]	**L1**	(48)	0	(16)	100:0	75:25	80
23	**1a**	**L1**	(60)	0	(20)	100:0	75:25	100
24[e,h]	**1a**	**L8**	90 (75)	0	0	100:0	100:0	90
25	**1a**	**L8**	100 (85)	0	0	100:0	100:0	100
26	**1a**	**L10**	21.5	4.5	22	82:18	54:46	70

[a] Conditions unless otherwise stated: PhBr (1 equiv), diamine (1.2 equiv), Pd_2dba_3 (2% mol in Pd), ligand (3% mol), and NaO*t*Bu (1.4 equiv when the free diamine was employed, 4.5 equiv when the dihydrochloride salt was employed) in xylene at 130 °C for 24 h. [b] Determined by GC by comparison with authentic samples. [c] Determined by ^{1}H NMR, using 1,4-bis(trichloromethyl)benzene as internal standard. [d] Value in parentheses is the isolated yield after flash chromatography. [e] Carried out in toluene at 110 °C. [f] Used as its dihydrochloride salt. [g] Reaction carried out with PhCl. [h] Reaction carried out with PhI. [i] Ratio of monoarylation versus diarylation. [j] Total arylamination yields = **2** + **3** + (2 × **4**).

The influence of the substitution pattern of the aryl halide on the chemoselectivity of the coupling reaction was next studied using different *ortho*- and *para*-substituted bromobenzenes. We chose conditions similar to those used in our original study,[2] in particular BINAP **L1**, which was highly selective for the arylation of the secondary amine of our heterocycles (Table 2, entries 1−3). The steric hindrance induced by the presence of *ortho* substituents on the aryl halide led to a preferential or total arylation of the exocyclic amine of piperidines **1b** (entries 4 and 5) and **1c** (entries 7 and 8) or azepinine **1d** (entries 10 and 11). An electron-withdrawing substituent on the *para* position of the aryl halide influenced the chemoselectivity of the coupling reaction with amines **1b** and **1c** in the same way (entries 6 and 9). However, the low yield observed in the coupling of 4-bromobenzonitrile with **1b** (20%, Table 2, entry 6) compared to the one obtained with **1c** (68%, Table 2, entry 9) could result from a decomposition of the cyano derivative at 130 °C. It is noteworthy that the results obtained with *p*-bromobenzonitrile and 4-aminopiperidine **1c** are, with this aryl halide, in good agreement with those described.[4]

3-Aminopyrrolidine **1a** remains reluctant to arylation of the primary amine, although some arylation of this function could be detected with *o*-ethylbromobenzene and *p*-bromobenzonitrile (entries 13 and 14).

The restricted conformations of the heterocyclic skeleton implies the close proximity between amine functions and suggests that both nitrogens can be involved in the coupling process. Indeed, it is known that diamine **1a**, in the presence of a metal, may adopt a rigid aza-norbornyl conformation.[16] According to this hypothesis, palladium-mediated arylation of diamines **1** could be facilitated over that of monoamines of similar structures, thanks to a cooperative effect of both amino groups. With the aim at finding evidence on the role of the structure of the substrates in the abnormal chemoselectivity observed for the arylamination, we thus performed a set of competitive experiments. The results are presented in Table 3.

The reactions were carried out using a 1/1/1 mixture of monoamine, diamine, and bromobenzene. GC analysis of the crude mixtures after 1.5 h showed the preferential arylation of the diamines, either on the endocyclic or on the exocyclic nitrogen (Table 3), versus the monoamines, beyond the possible statistical distribution in the three reactions tested. These results were not modified by a longer reaction time (17 h). Because an excess of amines with respect to bromobenzene was employed, no diphenylamine **4a**−**c** was observed. A similar competitive

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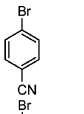
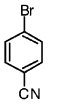
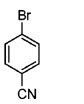
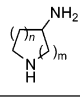
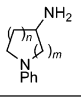
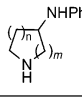
TABLE 2. Palladium-Catalyzed Coupling with Substituted Aryl Bromides[a]

entry	amine	ArBr	yield (%)[b]	ratios[c]		
						
1	**1a**	PhBr		**2a**	**3a**	**4a**
			68	100	0	0
2	**1b**	PhBr		**2b**	**3b**	**4b**
			40	85	15	0
3	**1c**	PhBr		**2c**	**3c**	**4c**
			58	68	0	32
4[d]	**1b**[e]			**16**	**17**	**18**
			21	15	29	56
5[d]	**1b**[e]			**19**	**20**	**21**
			23	3	48	49
6[f]	**1b**[e]			**22**	**23**	**24**
			20	0	100	0
7	**1c**			**25**	**26**	**27**
			62	0	100	0
8[f]	**1c**			**28**	**29**	**30**
			65	0	88	12
9	**1c**			**31**	**32**[g]	**33**
			68	0	89	11
10[f]	**1d**			**34**	**35**	**36**
			23	0	100	0
11[f]	**1d**			**37**	**38**	**39**
			99	0	100	0
12[d]	**1a**[e]			**7**	**8**	**9**
			55	74	0	26
13[d]	**1a**[e]			**10**	**11**	**12**
			61	61	12	27
14	**1a**[e]			**13**	**14**	**15**
			21	88	3	9

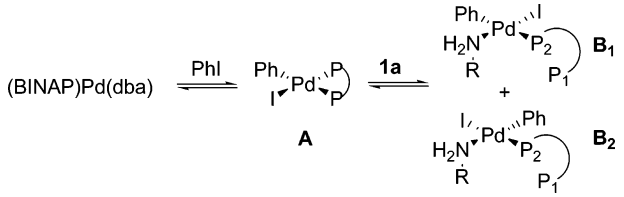
[a] Conditions: ArBr (1 equiv), diamine (1.2 equiv), Pd_2dba_3 (1% mol in Pd), BINAP (1.5% mol), and NaO*t*Bu (1.4 equiv when the free diamine was employed, 4.5 equiv when the dihydrochloride salt was employed) in toluene at 110 °C for 24 h. [b] Isolated yields of the mixture of monoaryled products. [c] Ratios were determined by ^{1}H NMR. [d] Reported in ref 2. [e] Employed as the dihydrochloride salt. [f] Reaction carried out in xylene at 130 °C with 2% mol Pd and 3% BINAP. [g] Literature value for **32**:**31**, 27/1 under slightly different conditions (Pd, 1% mol; BINAP 3% mol; in toluene at 85 °C).[4]

TABLE 3. Competitive Palladium-Mediated Arylations of Mixtures of Diamine and Monoamine[a]

entry	substrates					ratios[b]		
	m,n		p					
1	1, 1	**1a**[c]	1	**40**	**2a**	**3a**	**42**	
					73	8	19	
2	1,2	**1b**[c]	2	**41**	**2b**	**3b**	**43**	
					41	35	25	
3	2,1	**1c**	2	**41**	**2c**	**3c**	**43**	
					15	74	10	

[a] Conditions: diamine **1a**−**1c** (1 equiv), monoamine (1 equiv), PhBr (1 equiv), Pd_2dba_3 (2% mol Pd), ligand **L10** (3% mol), and NaO*t*Bu (2.5 equiv) in toluene at 100 °C for 17 h. [b] Ratios were determined by GC. [c] Employed as its dihydrochloride salt, 4.5 equiv of NaO*t*Bu was used.

SCHEME 3. Palladium Complexes Formed at Room Temperature in the Absence of Base



coupling between diamines **1a** and **1b** with bromobenzene revealed a large proportion of products arising from the arylation of pyrrolidine **1a** versus piperidine **1b** (ratio (**2a** + **3a**)/(**2b** + **3b**) 80:20, see Experimental Section). The whole data confirmed our hypothesis on the faster arylation of our diamines **1a**−**1c** in the presence of pyrrolidine or piperidine. Moreover, aminopyrrolidine **1a** is a better substrate for the arylation than aminopiperidine **1b**, but its strong ability to chelate metals[16] was detrimental in certain cases to the efficiency of the coupling reaction.

Finally, NMR experiments were carried out in the absence of base to elucidate the nature of the complexes formed with diamine **1a** and mainly to underline which amino group from this diamine was first involved in the arylation. The reactions were performed in benzene-d_6 to have a medium similar to the one employed in the palladium-catalyzed reactions. The complex (BINAP)Pd(dba) was generated after mixing and stirring Pd_2dba_3 with 1 equiv of BINAP for 4 h at room temperature. Its ^{31}P NMR spectrum in C_6D_6 exhibited two broad singlets at δ 26.6 and 27.9 ppm, values close to those observed in $CDCl_3$[17] or THF.[18] Addition of an excess of PhI to (BINAP)Pd(dba) yielded after stirring for 2 days PhPdI(BINAP) **A** as a brown precipitate (Scheme 3), which was filtered off and then washed with pentane. It was characterized in ^{31}P NMR by two doublets at δ 10.6 and 22.4 ppm with J_{pp} = 40 Hz, values in good agreement with the literature data.[18] When a stoichiometric amount of (*S*)-**1a** was added to this complex in C_6D_6, a precipitate appeared that could be partially redissolved upon

(17) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.

(18) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176−5185.

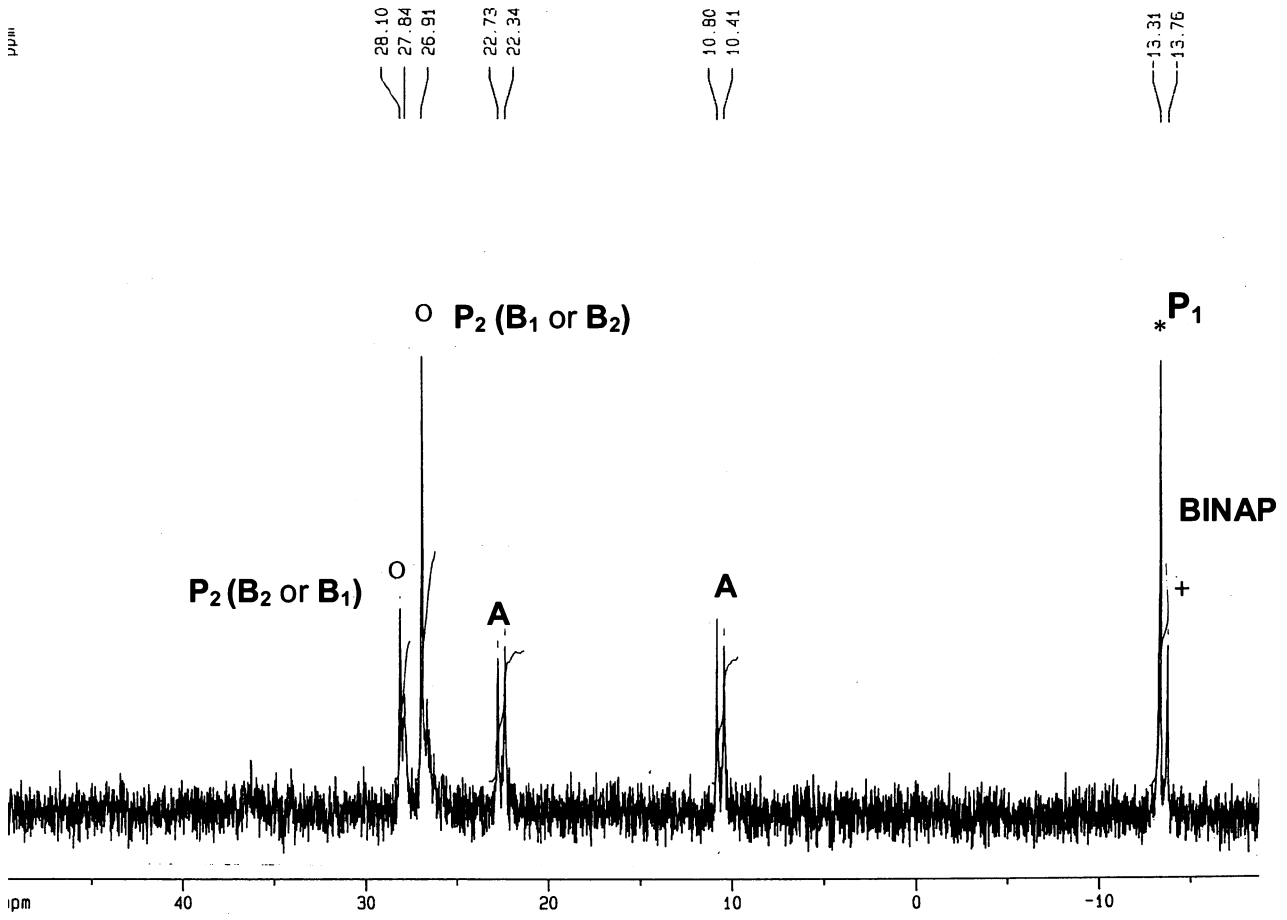


FIGURE 2. ^{31}P NMR spectrum (101 MHz, C_6D_6) of an equimolecular mixture of PhPdI(BINAP) **A** and (*S*)-3-aminopyrrolidine **1a**, contaminated with free BINAP (+). New signals observed after the addition of the amine: two singlets (○) tentatively assigned to the Pd-coordinated phosphorus (P_2) of both isomers of PhPdI(BINAP)(**1a**) (**B**$_1$ and **B**$_2$) and one singlet (∗) tentatively assigned to the free phosphane group (P_1) of PhPdI(BINAP)-(**1a**) (**B**$_1$ and **B**$_2$).

addition of one drop of acetone-d_6.[19] The ^{31}P NMR spectrum showed the formation of new signals at 26.9 and 28.1 ppm as broad singlets (overlapping the signals of a minor amount of remaining (BINAP)Pd(dba)), similar to those expected for tetra-coordinated Pd-amino complexes.[20] A sharp singlet was also observed at δ −13.3 ppm close to the peak of free BINAP (−13.7 ppm) (Figure 2). This signal suggested the presence of an uncoordinated phosphorus atom (**P$_1$**) and thus the displacement of one phosphine of BINAP by the diamine. The signals at δ 26.9 and 28.1 ppm were thus assigned to **P$_2$** as the phosphorus atom of BINAP still coordinated to the metal. The observation of two signals could be attributed of the presence of two stereoisomers **B$_1$** and **B$_2$** of the complex [PhPdI(P−P)(**1a**)] (Scheme 3).[21] Attempts to monitor the behavior of the postulated intermediate when increasing the temperature failed. Indeed, in the absence of a base at 70 °C in benzene-d_6, the ^{31}P NMR spectrum of the previous complex displayed a large number of signals probably due to its instability.

The ^{13}C NMR spectrum (Figure 3), recorded immediately after addition at room temperature of the diamine **1a** to the palladium complex PhPdI(BINAP) **A**, in the absence of base, revealed a sharp shift in the resonance due to the tertiary carbon of the diamine (*C*H goes from ca. 52.6 to 61.4 ppm), while the corresponding resonances for the three *C*H$_2$ varied only slightly (by ca. 1.5 ppm). These data suggested that a rapid coordination occurred only between the primary amino group of diamine **1a** and the metal with the displacement of one phosphane of the bidentate ligand. The substitution of one phosphane group by an amino group in square planar d^8 complexes like **A** is unusual,[22] particularly with a bidentate ligand such as BINAP.[23]

Discussion

The above results (Tables 1 and 2) indicate that the arylation of polyamines is not as straightforward as previously sug-

(19) The addition of one drop of acetone-d_6 was necessary to partially dissolve the new complex **B** produced upon addition of (*S*)-**1a** on **A**, thus reducing the acquisition time mainly in the ^{13}C NMR. No change of the chemical shifts of the signals was detected, only the intensities of the peaks were increased for this new complex. A clear difference is observed by comparing ^{13}C NMR spectra (b) and (c) of Figure 3.

(20) (a) Widenhoefer, R. A.; Zong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745−2754. (b) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755−2763. (c) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794−2805. (d) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534−3542. (e) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030−3039.

(21) Monteiro, A. L.; Davis, W. M. *J. Braz. Chem. Soc.* **2004**, *15*, 83−95.

(22) (a) Jutand, A.; Négri, S.; Principaud, A. *Eur. J. Inorg. Chem.* **2005**, 631−635. (b) Tougerti, A.; Negri, S.; Jutand, A. *Chem. Eur. J.* **2007**, *13*, 666−676.

(23) The displacement of one phosphane group of DPPF by a thiol was observed. See: Moreau, X.; Campagne, J.-M.; Meyer, G.; Jutand, A. *Eur. J. Org. Chem.* **2005**, 3749−3760.

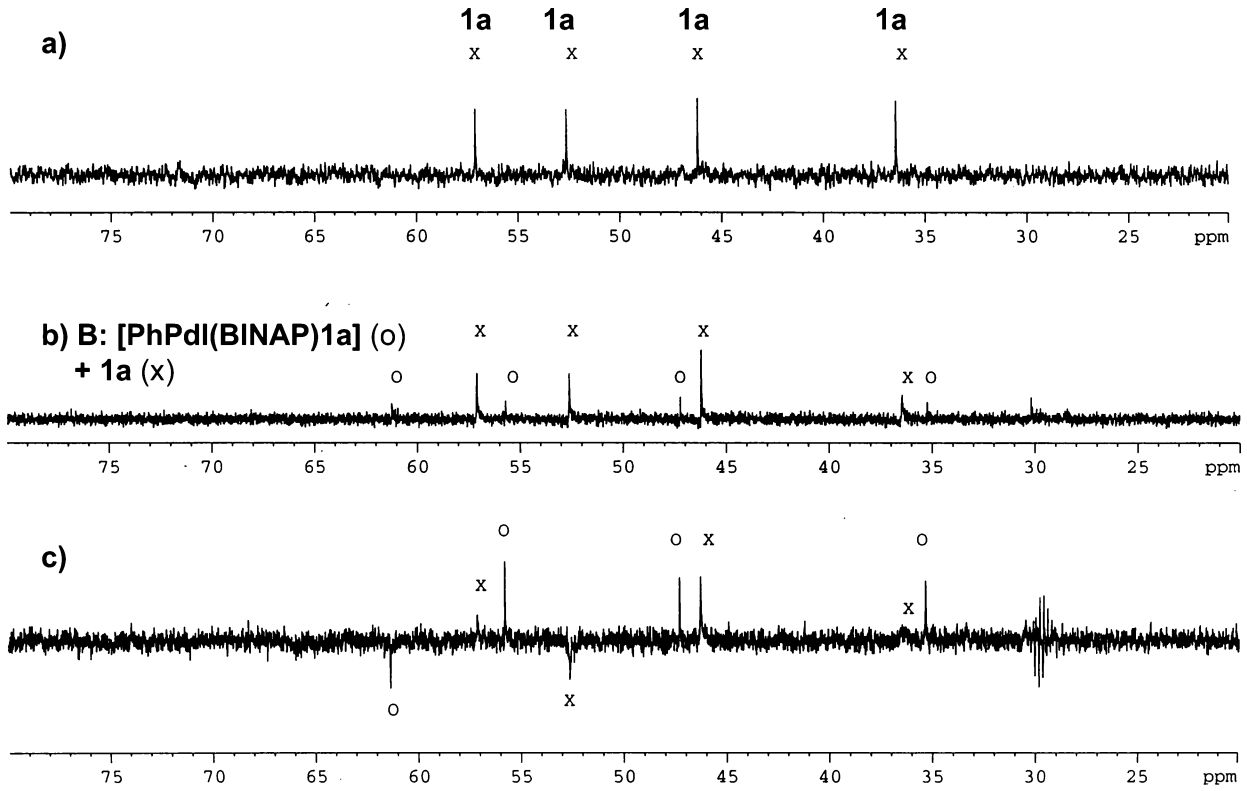


FIGURE 3. ^{13}C NMR spectra (100.6 MHz, C_6D_6) of (*S*)-3-aminopyrrolidine **1a**: (a) free diamine **1a** (x), (b) equimolar mixture of **1a** and PhPdI(BINAP) **A** forming the new complex **B**, [PhPdI(BINAP)(**1a**)] (○) with some remaining free **1a** (x), (c) JMOD spectrum of (b) recorded with one drop of acetone-d_6 showing CH_2 (up), *C*H (down) of the diamine.[19]

gested[5,12] and that it requires the search for efficient partners (ligands and halobenzenes). Since simple monophosphines are usually poor ligands in arylaminations[3] and particularly in the arylation of 1-protected heterocycles **1a** and **1b**,[15] monophosphines **L2**−**L4** derived from biphenyl and known to promote the arylations[24] were tested. The data reported in Table 1 (comparison of entries 5, 7, 11, 12) showed that a high yielding coupling required a ligand substituted on the 2′,2′-positions of the lower aromatic ring. The efficiency of the catalysis probably resulted from the tight chelation of **L2** or **L3** to the Pd center, thus decreasing the chance for displacement of the ligand by a chelating diamine, which may deactivate the catalyst.[25,26]

The chemoselectivity of the reaction was controlled by the ligand (steric and electronic factors), the ring size of the substrate, and its coordination characteristics. With the less flexible five-membered ring diamine **1a**, arylation occurred almost exclusively on the secondary amine, whereas with six-membered ring compounds **1b** and **1c** modulation of the selectivity was possible using different ligands or aryl halides. By using the large and more flexible cyclic diamine **1d**, arylation on the primary amine became the major reaction whatever the ligand or aryl halide used. These results are in good agreement with the literature data on the preferential arylation of primary amines of linear diamines (bearing primary and secondary amino groups).[11,12] The presence of bulky substituents on the phosphorus atom of the ligand and *ortho* substitution or the presence of electron-withdrawing groups on the aryl halide increased the arylation on the exocyclic nitrogen of these diamines. Because these parameters are known to increase the rate of the reductive elimination,[27] the proportion of the monoarylated products might reflect the faster coordination of primary amines over secondary ones before an equilibration between both amines.[20b]

A plausible mechanism is presented in Scheme 4. From palladium complex **A** (result of the oxidative addition of aryl halide on Pd^0), the coordination of the primary amine occurs first to afford complex **B** by substituting one phosphane of the bidentate ligand, as shown by the NMR experiments at room temperature. At higher temperature, an equilibrium between **B** and **C** could take place. The combination of the temperature of the reaction (110 °C) and the higher nucleophilicity of the secondary amine are probably sufficient to overcome the high steric demand generated at the metal center by the coordination of a secondary amine. The amine exchange in the palladium complex could involve a pentacoordinate intermediate such as **D** already mentioned by Beletskaya in the case of diamines[12d] or a cationic four-coordinated intermediate such as **D′**. The competitive experiments suggest a cooperative effect between both amines of the heterocycles during the palladium-mediated arylation, which supports the presence of such intermediates **D** or **D′**. This effect, particularly important for **1a**, could be

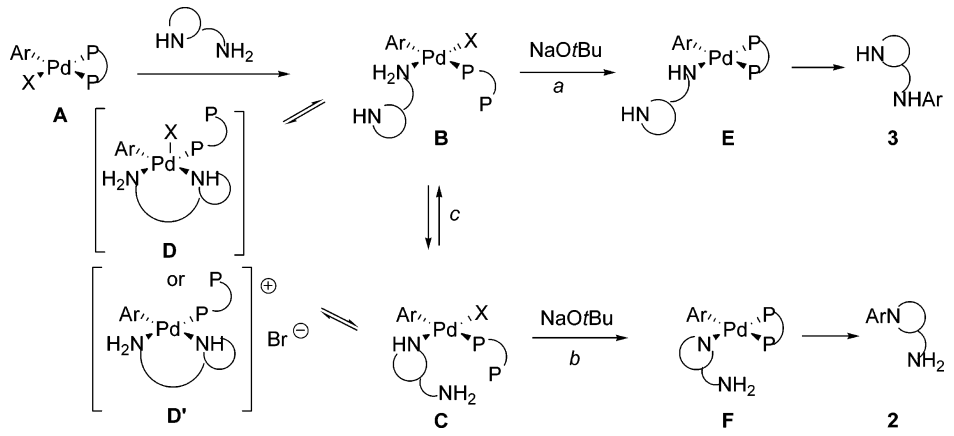
(24) (a) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560−2565. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 14, 1871−1876.

(25) Ross, A.; Widenhoefer, R. A., Buchwald, S. L *Organometallics* **1996**, *15*, 3534−3542.

(26) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523−6527.

(27) (a) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775−2789. (b) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533−1541.

SCHEME 4. Plausible Mechanism of the Palladium-Mediated Arylation of 1a−d



attributed to the propensity of the diamine **1a** to adopt a norbornanyl structure around a metal, allowing both nitrogen atoms to participate in the palladium-mediated arylation. The involvement of intermediates such as **B**, **C**, and **D** postulated in this mechanism raised the question whether a tightly Pd-coordinated bidentate phosphane ligand was necessary for successful reactions with substrates **1**. From recent literature reports, it appears that this question is still open for discussion.[28] We believe in our case that a ligand with nonsymmetrical chelating properties is necessary: one basic phosphane group to firmly anchor the ligand to the metal and another softer group (an electron-enriched aromatic ring as in **L2** or **L3** or a diphenylphosphine group as in **L10**) that could be easily displaced by the amine but will be rapidly recoordinated to the metal after the reductive elimination step to stabilize the palladium center during the resting state of the catalytic cycle.

The presence of a base generates palladium-amido complexes **E** and **F** from **B** and **C**, respectively, to yield products **3** and **2** after reductive elimination. This last step could be the rate-limiting step.[29] On the one hand, when increasing the rate of reductive elimination (hindered phosphines, steric and electronic factors of the aryl halide), the arylation on the primary amine is increased or even favored with flexible diamines (**1b−d**) because path *a* occurs faster than equilibration *c*. On the other hand, the highly restricted conformation of diamine **1a** forces the proximity of the secondary amine to the metal center in complex **B**. Thus, one can suppose that equilibrium *c* is moved in favor of complex **C**. Once this complex is generated, reaction *b* should occur faster than reaction *a*, the reductive elimination yielding product **2** being easier because of the steric constraint introduced by the secondary amine at the metal center and the high nucleophilic amido group.[30] Linear polyamines used in previous studies bearing primary and secondary amines were probably too flexible to uncover this aspect of the mechanism and their arylations occur exclusively according to path *a*. Moreover, the results (Table 1, entries 1 and 2 for **1b**, entries 22 and 23 for **1a**) show that the temperature improved significantly the yields but did not modify the selectivities. This confirms that the steps *a* or *b* (deprotonation step, displacement of the halogen and formation of complexes such as **E** or **F**, Scheme 4) play an important role in the efficiency of the coupling.

Conclusion

This study brings new elements regarding the chemoselectivity of the palladium-catalyzed arylation of polyamines. It puts into evidence a clear relationship between the structure of the substrate bearing both types of amino groups (primary and secondary) and the selectivity of the coupling. Bulky ligands associated with the metal as well as steric and electronic properties of the aryl halide partner are also parameters likely to tune the site of these arylaminations. This work uncovers the presence of a probable amino-palladium intermediate **B** having a ligand monocoordinated to the metal. This complex arose immediately at room temperature upon mixing PhPdI(BINAP) **A** with 3-aminopyrrolidine **1a**. Although this type of amino-palladium species is well-known in literature,[20] this is the first example, to our knowledge, of generation of such a complex by the displacement by an amine of one phosphane group of the bidentate BINAP ligand. Hence, the use of strongly chelating ligands may not be an absolute requirement to achieve high and efficient chemoselective palladium-mediated arylamination. As suspected in previous studies, we have shown that coordination of the diamine to the palladium center occurred through the primary amino group at room temperature. Depending on the size of the heterocycle and on factors accelerating the reductive elimination step, arylation takes place either on the primary or on the secondary amines via a plausible equilibration of the intermediates **B** and **C** at higher temperature. Overall, the heterocyclic diamines used in this study, which are important building blocks in the pharmaceutical industry, appeared as key substrates to unveil the decisive factors governing the chemoselectivity of the arylamination reactions. Finally, as pointed out in our previous report,[2] the diamines **1a−1d** should be monoprotected for best results in the palladium-catalyzed monoarylation, although efficient chemoselective couplings were observed in specific cases (with **1a** and **1d**). Designing specific ligands that mediate high yields and high chemoselectivities of monoarylations of these diamines remains a challenge.

Experimental Section

General Procedure for the Pd-Catalyzed Arylation of Unprotected Diamines with Unsubstituted Aryl Halides. A Schlenk flask backfilled with nitrogen was charged with the diamine or its

(28) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371−1375.

(29) Although we cannot exclude that the deprotonation of the amine/recoordination of the phosphine is the rate-limiting step, the deprotonation of amino-palladium complexes similar to **B** or **C** occurs at room temperature very rapidly to form arylamines in high yields. See ref 20c.

(30) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232−8245. (b) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626−3633.

hydrochloride (0.6 mmol), NaO*t*Bu (67 mg, 0.70 mmol, 1.4 equiv; or 212 mg, 2.2 mmol, 4.5 equiv when the dihydrochloride was employed), ligand (0.015 mmol, 3% mol), Pd_2dba_3 (0.005 mmol, 4.6 mg, 2% mol in Pd), and degassed toluene or xylene (3 mL). Then, the aryl halide (0.5 mmol) was added, and the mixture was heated under nitrogen at 110 or 130 °C for 24 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, filtered over a celite pad, and analyzed by GC to determine the conversion and the ratio of monoarylated compounds by comparing with authentic samples. After evaporation of the volatile compounds, the crude mixture was analyzed by ^{1}H NMR by using 1,4-bis-(trichloromethyl)benzene as internal standard. Flash chromatography on SiO_2 afforded the pure arylation products when necessary.

Arylation of 3-Aminopiperidine (1b). Arylation of 3-aminopiperidine **1b**·2HCl (0.6 mmol) was carried out according to the general procedure by using **L2** and PhBr (80 mg, 0.5 mmol) in xylene at 130 °C. After purification of the crude mixture by flash chromatography using CH_2Cl_2/MeOH/NH_3 (v/v/v 95:5:1) as eluent, 1-phenyl-3-(phenylamino)piperidine **4b** was obtained as a yellow oil (30 mg, 0.12 mmol, 23% yield). Further elution afforded 3-amino-1-phenylpiperidine **2b** and 3-phenylaminopiperidine **3b** as a mixture (28 mg, 0.16 mmol, 32% yield). Comparison of the retention times [t_R (**2b**) 11.5 min, t_R (**3b**) 13.0 min] and NMR spectra with authentic samples and the literature data[2] allowed an unambiguous characterization of both monoarylated products.

General Procedure for the Pd-Catalyzed Arylation of Unprotected Diamines with Substituted Aryl Halides (unless otherwise stated, see Table 2). A Schlenk flask backfilled with nitrogen was charged with the diamine or the diamine dihydrochloride (0.6 mmol), NaO*t*Bu (212 mg, 2.2 mmol, 4.5 equiv; or 67 mg, 0.75 mmol, 1.2 equiv when the free amine was employed), (±)-BINAP **L1** (0.007 mmol, 4.6 mg, 1.5% mol), Pd_2dba_3 (0.0025 mmol, 2.3 mg, 1% mol in Pd), and 3 mL of degassed toluene. The aryl halide (0.5 mmol) was then added, and the mixture was heated under nitrogen at 110 °C for 24 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and filtered over a celite pad, and the volatile compounds were evaporated under reduced pressure. The crude product was analyzed by ^{1}H NMR, using 1,4-bis(trichloromethyl)benzene as an internal standard to determine the composition of the reaction mixture. Flash chromatography on SiO_2 afforded the arylation products when necessary.

4-[(2-Ethylphenyl)amino]piperidine (29) and 1-(2-Ethylphenyl)-4-[(2-ethylphenyl)amino]piperidine (30). Arylation of 4-aminopiperidine **1c** with 2-bromo-ethylbenzene was carried out in toluene at 110 °C according to the general procedure. Purification of the crude mixture by flash chromatography by using CH_2Cl_2/MeOH/NH_3 (v/v/v 95:5:1) as eluent afforded **30** as a yellow oil (16 mg, 0.05 mmol, 10% yield). Further elution of the chromatographic column afforded **29** as a yellow oil (40 mg, 0.2 mmol, 40% yield).

4-[(2-Ethylphenyl)amino]piperidine (29). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.14−7.05 (m, 2H), 6.71−6.64 (m, 2H), 3.44 (m, 2H), 3.12 (dt, J = 3.5, 12.7, 2H), 2.73 (td, J = 2.3, 11−13 Hz, 2H), 2.47 (q, J = 7.5 Hz, 2H), 2.10 (d, J = 11.8 Hz, 2H), 2.03 (s, 1H), 1.36 (qd, J = 3.5, 10−12 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 144.1 (C), 128.1 (CH), 127.5 (C), 126.9 (CH), 116.9 (CH), 110.6 (CH), 49.9 (CH), 45.3 (CH), 33.7 (CH), 23.8 (CH), 12.8 (CH_3). MS (EI) *m*/*z* (%): 206 (M+2, 15), 205 (M+1, 100), 204 (M, 70), 188 (17), 187 (88), 186 (38), 172 (36), 160 (9), 159 (8), 158 (16), 146 (17), 145 (8), 144 (19), 134 (11), 133 (8), 132 (30), 131 (7), 130 (16), 119 (8), 118 (24), 117 (13), 103 (5), 91 (9), 77 (9), 56 (8), 43 (5), 42 (9). HRMS (ESI) calcd for $C_{13}H_{21}N_2$ (M + H) 205.1705, found 205.1711. IR (neat, cm^{-1}) 3038, 2932, 2851, 1603, 1584, 1507, 1451, 1413, 1306, 1262, 1238, 1149. R_f (CH_2Cl_2/MeOH/NH_3, 95:5:1) 0.24.

1-(2-Ethylphenyl)-4-[(2-ethylphenyl)amino]piperidine (30). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.24−7.01 (m, 6H), 6.71−6.66 (m, 2H), 3.55−3.45 (m, 2H), 3.08 (br d, $J \approx$ 12 Hz, 2H), 2.83 (d, $J \approx$ 11 Hz, 2H), 2.71 (q, J = 7.5 Hz, 2H), 2.49 (q, J = 7.5 Hz, 2H), 2.18 (br d, $J \approx$ 11 Hz, 2H), 1.65 (qd, J = 3.4, 11 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H), 1.25 (t, overlapped, J = 7.5, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 151.7 (C), 144.4 (C), 139.2 (C), 128.8 (CH), 128.1 (CH), 127.5 (C), 126.9 (CH), 126.3 (CH), 123.8 (CH), 119.8 (CH), 116.8 (CH), 110.7 (CH), 52.1 (CH_2), 49.7 (CH), 33.5 (CH_2), 23.9 (CH_2), 23.4 (CH_2), 14.8 (CH_3), 12.9 (CH_3). MS (EI) *m*/*z* (%): 309 (M+1, 22), 308 (M, 53), 188 (19), 187 (100), 186 (26), 173 (6), 172 (35), 160 (9), 159 (9), 158 (13), 146 (20), 145 (8), 144 (15), 134 (6), 133 (8), 132 (28), 131 (7), 130 (12), 119 (8), 118 (19), 117 (14), 91 (10), 77 (11). HRMS (ESI) calcd for $C_{21}H_{29}N_2$ (M + H) 309.2331, found 309.2333. IR (neat, cm^{-1}) 2967, 2790, 1603, 1585, 1509, 1451, 1381, 1297, 1143, 923. R_f (CH_2Cl_2) 0.92.

Competitive Experiments. General Procedure. A Schlenk flask was backfilled with nitrogen and charged with 0.4 mmol of each amine, PhBr (0.4 mmol, 65 mg), ligand **L10** (0.012 mmol, 6.5 mg), NaO*t*Bu, Pd_2dba_3 (3.6 mg, 0.004 mmol), and 3 mL of degassed toluene. This mixture was heated at 100 °C, and its composition was analyzed by GC after 1 and 17 h. The results are summarized in the text (Table 3).

Competitive Experiment between 3-Aminopyrrolidine Dihydrochloride (1a·2HCl) and 3-Aminopiperidine Dihydrochloride (1b·2HCl). The reaction was carried out according to the general procedure by using **1a**·2HCl (65 mg, 0.4 mmol), **1b**·2HCl (69 mg, 0.4 mmol), PhBr (65 mg, 0.4 mmol), NaO*t*Bu (245 mg, 2.6 mmol), Pd_2dba_3 (3.6 mg, 0.004 mmol), **L10** (6.5 mg, 0.012 mmol), and 3 mL of degassed toluene. The reaction was monitored by GC (aliquots after 1 and 17 h). GC t_R: **2a**, 11.3 min; **3a**, 10.9 min; **2b**, 11.5 min; **3b**, 13.0 min. Ratio (**2a** + **3a**)/(**2b** + **3b**) = 80/20.

Competitive Experiment between 3-Aminopyrrolidine Dihydrochloride (1a·2HCl) and Pyrrolidine (40). The reaction was carried out according to the general procedure by using **1a**·2HCl (65 mg, 0.4 mmol), pyrrolidine **40** (28 mg, 0.4 mmol), PhBr (65 mg, 0.4 mmol), NaO*t*Bu (173 mg, 1.8 mmol), Pd_2dba_3 (3.6 mg, 0.004 mmol), **L10** (0.012 mmol, 6.5 mg), and 3 mL of degassed toluene. The reaction was monitored by GC (aliquots after 1 and 17 h). GC t_R: **2a**, 11.3 min; **3a**, 10.9 min; 1-phenylpyrrolidine, 6.9 min. The results are summarized in the text (Table 3).

Competitive Experiment between 3-Aminopiperidine Dihydrochloride (1b·2HCl) and Piperidine (41). The reaction was carried out according to the general procedure by using **1b**·2HCl (69 mg, 0.4 mmol), piperidine **41** (34 mg, 0.4 mmol), PhBr (65 mg, 0.4 mmol), NaO*t*Bu (173 mg, 1.8 mmol), Pd_2dba_3 (3.6 mg, 0.004 mmol), **L10** (0.012 mmol, 6.5 mg), and 3 mL of degassed toluene. The reaction was monitored by GC (aliquots after 1 and 17 h). GC t_R: **2b**, 11.5 min; **3b**, 13.0 min; 1-phenylpiperidine, 7.1 min. The results are summarized in the text (Table 3).

Competitive Experiment between 4-Aminopiperidine (1d) and Piperidine (41). The reaction was carried out according to the general procedure by using **1d** (40 mg, 0.4 mmol), piperidine **41** (34 mg, 0.4 mmol), PhBr (65 mg, 0.4 mmol), NaO*t*Bu (96 mg, 1.0 mmol), Pd_2dba_3 (3.6 mg, 0.004 mmol), **L10** (6.5 mg, 0.012 mmol), and 3 mL of degassed toluene. The reaction was monitored by GC (aliquots after 1 and 17 h of reaction). GC t_R: **2d**, 12.0 min; **3d**, 13.2 min; 1-phenylpiperidine, 7.1 min. The results are summarized in the text (Table 3).

Synthesis of (BINAP)Pd(Ph)I (A) and Study of Its Complexation with 3-Aminopyrrolidine (1a). A Schlenk flask was backfilled with nitrogen and charged with Pd_2dba_3 (58.6 mg, 0.065 mmol), (±)-BINAP **L1** (73.5 mg, 0.12 mmol), and 0.5 mL of degassed acetone. This mixture was stirred for 4 h at room temperature, and then an excess of PhI was added (1.2 mmol, 0.13 mL). The resulting solution was stirred for a further 48 h. A precipitate appeared that was filtered and washed with pentane to afford 40 mg (0.04 mmol, 31% yield) of a brown solid, corresponding to the complex **A** (BINAP)Pd(Ph)I.[18] A part of this solid (28.6 mg, 0.03 mmol) was dissolved under nitrogen in degassed C_6D_6, (*R*)-3-aminopyrrolidine **1a** was added (0.03 mmol, 2.6 μL), and a precipitate appeared. The ^{31}P NMR spectrum recorded after 1 h showed the appearance of new peaks at −13.7 (free BINAP),

−13.3, 26.9, and 28.1 ppm. ^{13}C NMR was then recorded. Finally, the ^{13}C NMR JMOD spectrum was recorded after addition of one drop of acetone-d_6 to the same sample, still maintained under nitrogen. The results are summarized in the text and in Figures 3 and 4.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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