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Palladium-Mediated Arylation of 3-Aminopiperidines and 3-Aminopyrrolidines

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Received July 26, 2004

This paper describes the palladium-catalyzed arylation of 1-substituted 3-aminopyrrolidines or piperidines. Palladium(0) (1−2 mol %) in conjunction with "Buchwald's ligand" [2-(dimethylamino)-2′-(dicyclohexylphosphine)biphenyl] was shown to be the catalyst of choice for the coupling with aryl bromides or chlorides. When bromobenzene was used, a strong temperature effect was noticed. Whereas no reaction occurred at 100 °C, yields higher than 85% were obtained at 130 °C for each substrate. Such an effect was not observed when diphosphines were used. Whereas Xantphos and, to a lesser extent BINAP, were moderately efficient in the coupling of all diamines, the palladium-mediated arylation in the presence of monophosphines was strongly dependent on the substrate. The results suggest the participation of both nitrogens of the aminoheterocycle in the reactive intermediate. This participation could also account for the highly selective arylation of the endocyclic nitrogen of unsubstituted 3-aminopyrrolidine or piperidine. Optimal conditions were found for the arylation using 2- or 4-substituted electron-poor or enriched aryl halides.

Introduction

Aminopyrrolidine **1** and aminopiperidine **2** appended at heterocycles are building blocks or intermediates widely used in the drug discovery process. 3-(*N*-Arylamino)pyrrolidines are present in several potential or established biologically active compounds such as analgesics,[1] antivirals,[2] antidepressants,[3] antibacterials,[4] antiinflammatory drugs,[5] anti-ischemia,[6] antitumorals,[7] or ligands of central nervous system.[8] 3-(*N*-Arylamino)piperidines have found applications as psychotropic agents[9] or in the treatment of hormone deficiency[10] and neurological disorders related to β-amyloid production.[11] Optically enriched lithium amides are used as chiral auxiliaries in enantioselective organic synthesis,[12] and it has been shown that 3-(*N*-alkylamino)pyrrolidine lithium amides are able to form chiral noncovalent entities **3** with butyllithium (Figure 1).[13] Their condensation with aromatic aldehydes provides compounds with enantiomeric excesses (ee) up to 77%.[14]

With the aim of developing new ligands[15] and radioligands[16] for the serotoninergic system and to access to

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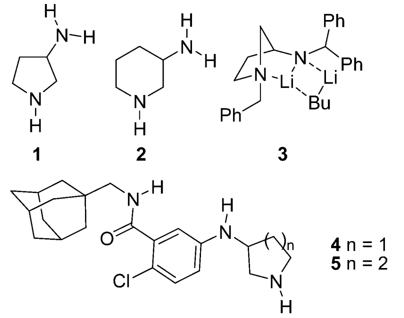

FIGURE 1. 3-Aminopiperidine and pyrrolidine and related complexes or compounds.

new chiral bases for asymmetric reactions,[17] we have undertaken a search for a reliable synthesis of 3-(*N*-arylamino)pyrrolidines and 3-(*N*-arylamino)piperidines. Numerous procedures have been reported for the preparation of these compounds including cyclization of amino acids[18] or cyclization of triols and related compounds,[19] reductive amination of pyrrolidinones or piperidinones,[1b,9,10,20] nucleophilic substitution of halides[21] or sulfonates,[3,22] Mitsunobu reaction,[1a] and SNAr reactions.[5d,7,23] Each synthesis has some limitations: (a) reductive amination requires either a costly ketone or a reactive amine, (b) nucleophilic substitution suffers from low yields or harsh reaction conditions, and (c) SNAr reactions are only possible with electron-poor arenes bearing a good leaving group (i.e., fluorine).

Migita and co-workers,[24] then Buchwald and Hartwig independently[25,26] have demonstrated the scope of the palladium-catalyzed arylation of amines, its mild conditions, and its tolerance for a wide range of functional groups. Although less studied, nickel-catalyzed arylaminations have received increasing attention over the past years and can offer an alternative to the use of costly palladium derivatives. Different nickel-based catalysts have been developed: Ni(COD)$_2$ (COD = cyclooctadiene) associated with 1,1′-bis(diphenylphosphino)ferrocene (DPPF) or 1, 10-phenanthroline,[27] Ni(0)/C-DPPF,[28] *N*-heterocyclic carbenes,[29] or Ni(0)-2,2′-bipyridine.[30] This latter was shown to be efficient for selective monoamination of aryl di- and trichlorides[31] and for sequential arylation of piperazines.[32] Copper-catalyzed aminations of aryl halides is another attractive method due to the low cost of copper salts. Recent works have shown that copper (I) iodide is the preferred catalyst to prepare enantiopure amino acid derivatives from amino acids and aryl halides.[33,34] In conjunction with potassium phosphate and glycol, it allowed the coupling of alkylamines and aryl iodides[35] whereas copper(I) oxide in a glycol solution of ammonia was more suitable for the amination of bromopyridines.[36]

The coupling of aryl halides with 3-aminopyrrolidines or 3-aminopiperidines has been only scarcely documented. To the best of our knowledge, the only described example concerns the synthesis of ligands **4** and **5** of gastrin and cholestokinin receptors (Figure 1).[5] The arylation of *N*-Boc-3-aminopyrrolidine **8** or *N*-Boc-3-aminopiperidine **10**, using the combination Pd(OAc)$_2$/BINAP/Cs$_2$CO$_3$/toluene, afforded the desired compounds in low yields (11% and 2.5% after removal of the Boc protection). 3-Aminopyrrolidines **6**−**8** or 3-aminopiperidines **9**−**10** (Figure 2) being easily available on a large scale,[37] we have envisaged the use of a cross-coupling methodology to access rapidly to 3-(*N*-arylamino)pyrrolidines **11**−**13** and piperidines **14** and **15** (Scheme 1 and Figure 3). In this paper, we report that arylation of the secondary cyclic amine of unprotected 3-aminopyrrolidine **1** and 3-aminopiperidine **2** is highly selective whatever

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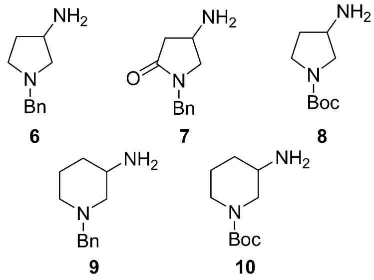


FIGURE 2. 3-Aminopyrrolidines and piperidines.

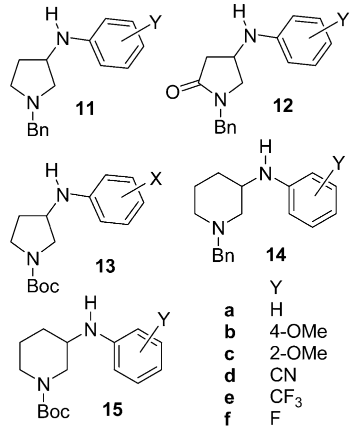
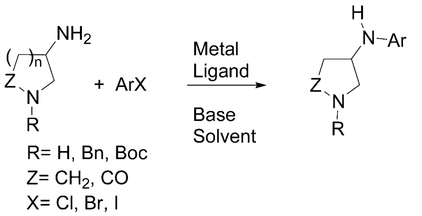


FIGURE 3. 3-(*N*-Arylamino)pyrrolidines and piperidines.

SCHEME 1. Arylaminations



palladium ligand used. We also present the first comparative study on metal-catalyzed arylations of these aminoheterocycles differing only by the substituent on the secondary cyclic amine. For a given substrate and aryl halide, the right choice of both the palladium ligand and the reaction temperature allowed for a high-yielding synthesis of the target compounds **11**–**15**.

Results and Discussion

Choice of the Transition-Metal Catalyst (Table 1, Figure 4). Preliminary experiments were carried out in order to choose the most efficient transition metal for the arylation of 1-benzyl-3-aminopyrrolidine **6** and 1-Boc-3-aminopiperidine **10**. Because palladium complexes are the most widely used catalysts in cross-coupling reactions, arylation of amines **6** and **10** with bromobenzene was first attempted in the presence of Pd_2dba_3/BINAP **B** under standard conditions (entries 1 and 2). Average to good yields (53 and 74%, respectively) of *N*-phenylamines **11a** and **15a** were obtained. The efficiency of the coupling reached 80% with pyrrolidine **6** by using chlorobenzene and Buchwald's ligand **F** (entry 3). Such an improvement was not observed with piperidine **9** (entry 4). Copper catalysis was next tested for the arylation. The first conditions we tried (data not shown) using iodobenzene with CuI (10%), a base (K_3PO_4 or Cs_2CO_3 or NaO-*t*-Bu), and a ligand (ethanediol at 80 or 100 °C[35] or *o*-hydroxybiphenyl,[38] cyclohexanediamine in toluene, at 100 °C)[39] failed. Similarly, no arylation was observed with bromobenzene in the presence of CuI (10%), diethylsalicylamide (20%), K_3PO_4, DMF, 100 °C.[38] The starting material was quantitatively recovered. However, copper iodide and proline in DMSO at 100 °C in the presence of potassium carbonate[33b] allowed the reaction to proceed with yields around 50% (entries 5 and 6). Copper(I)-2-thiophene carboxylate **A** (CuTC), a reagent initially developed by Liebeskind for the Ullmann,[40] Stille,[41] or Suzuki reactions,[42] was tested in the arylation of amine **6**. In toluene, without any base, the amine **11a** was formed (entry 7) in 10% yield. Addition of sodium *tert*-butoxide and replacement of toluene by *N*-methylpyrrolidone (NMP) improved significantly the yields (32 and 40%; entries 8 and 9). However, the same conditions used with piperidine **10** gave less than 10% of the coupling adduct **15a** (entry 10). To our knowledge, these results, although modest and using an excess of reagent, are the first examples of *N*-arylations of amines mediated by CuTC. Finally a few experiments were carried out in the presence of a nickel catalyst. When pyrrolidine **6** was treated (100 °C in toluene, 24 h) with chlorobenzene in the presence of (DPPF)$NiCl_2$/DPPF and NaO-*t*-Bu, no reaction was observed (data not shown). A similar disappointing result (less than 5% of the desired product) was obtained when the same amine **6** was allowed to react with bromobenzene in the presence of $Ni(COD)_2$/BINAP, NaO-*t*-Bu[27,43] (entry 11). Under the same conditions, no reaction was observed with piperidine **10**. All these data led us to use a palladium catalyst in the following experiments.

Arylation of Unprotected Aminopyrrolidine and Piperidine (Table 2). In contrast to anilines and simple alkylamines, the palladium-catalyzed arylation of only one nitrogen function of diamines is poorly documented.[44] In the synthesis of norastemizol, Senanayake et al.[45] observed selective arylations of primary amine functions of 4-aminopiperidine **16** and of acyclic diamines[46] with 4-fluorobenzyl-2-chlorobenzimidazole in the presence of NaO-*t*-Bu and Pd_2dba_3/BINAP as the catalyst system. Beletskaya and Guilard[47] and Schrock and co-workers,[48] when utilizing the BINAP/Pd combination, have also shown that arylation of acyclic polyamines takes place

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TABLE 1. Metal-Catalyzed *N*-arylation of 1-benzyl-3-aminopyrrolidine 6 and 1-Boc-3-aminopiperidine 10

entry[a]	substrate	PhX	metal source (mmol)	ligand	ratio M/L[b]	conditions	product	yield[c] (%)
1	**6**	PhBr	Pd_2dba_3 (0.005)	(±)-**B**	1/1.5	NaO-*t*-Bu (1.4 equiv), toluene, 100 °C	**11a**	53
2	**10**	PhBr	Pd_2dba_3 (0.005)	(±)-**B**	1/1.5	NaO-*t*-Bu (1.4 equiv), toluene, 100 °C	**15a**	74
3	**6**	PhCl	Pd_2dba_3 (0.005)	**F**	1/1.5	NaO-*t*-Bu (1.4 equiv), toluene, 100°C	**11a**	80
4	**9**	PhCl	Pd_2dba_3 (0.005)	**F**	1/1.5	NaO-*t*-Bu (1.4 equiv), toluene, 100 °C	**15a**	(34)
5	**6**	PhI	CuI (0.1)	proline	1/2	K_2CO_3 (2 equiv), DMSO, 100 °C	**11a**	59
6	**10**	PhI	CuI (0.1)	proline	1/2	K_2CO_3 (2 equiv), DMSO, 100 °C	**15a**	41
7	**6**	PhI	CuTc (3)	no		toluene, 100 °C	**11a**	10
8	**6**	PhI	CuTc (3)	no		NaO-*t*-Bu (1.4 equiv), toluene, 110 °C	**11a**	32
9	**6**	PhI	CuTc (3)	no		NaO-*t*-Bu (1.4 equiv), NMP, 110 °C	**11a**	40
10	**10**	PhI	CuTc (3)	no		NaO-*t*-Bu (1.4 equiv), NMP, 110 °C	**15a**	(10)
11	**6**	PhBr	$Ni(COD)_2$ (0.05)	(±)-**B**	5/8.5	NaO-*t*-Bu (1.4 equiv), toluene, 80 °C then 100 °C	**11a**	(5)

[a] Reaction conditions: halobenzene (1 mmol), amine (1.2 mmol except entry 4 (1.5 mmol)). All of the reactions were carried out for 24 h except entry 11 (12 h at 80 °C then 36 h at 100 °C). Reaction times have not been minimized. [b] Ratio M/L. [c] Yields represent isolated yields after purification by flash chromatography (average of two or more experiments). In parentheses are given the yields deduced from ^1H NMR spectra of the crude product, using 1, 4-bis(trichloromethyl)benzene as an internal standard.

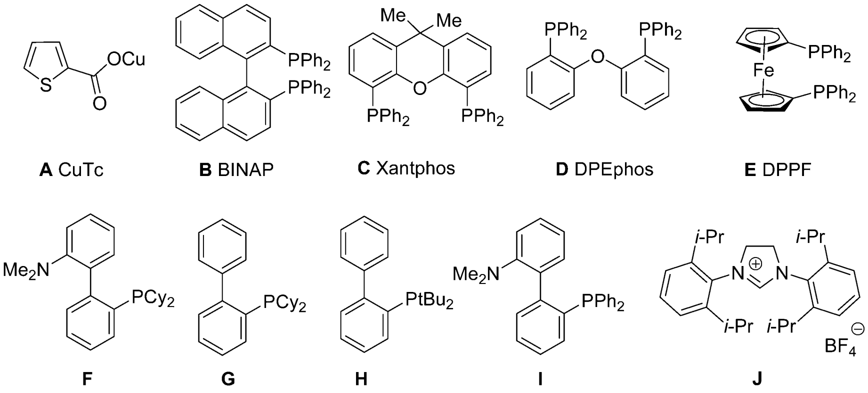

FIGURE 4. Reagent and ligands used in the aryl aminations.

on the primary amino group. Such a selectivity also noticed in heteroarylations using $(DPPF)PdCl_2$[49] led us to attempt the palladium-catalyzed arylation of unprotected 3-aminopyrrolidine **1** or piperidine **2**. 3-(Aminophenyl)pyrrolidine **18**, (aminophenyl)piperidine **21**, and diphenylamine **19** were independently synthesized[50] for unambiguous spectral characterizations.

Reaction of pyrrolidine **1** was carried out using bromobenzene, Pd_2dba_3, and BINAP **B** under standard conditions (NaO-*t*-Bu, toluene, 100 °C). To our surprise, 1-phenylpyrrolidine **17** was the sole compound isolated in 68% yield (entry 1). 3-(*N*-Phenylamino)pyrrolidine **18** and the diarylated compound **19** were not detected in the ^1H NMR spectrum of the crude reaction mixture. Although less efficient in terms of yields, Xantphos **C** or DPPF **E** (entry 3) reacted also selectively with the cyclic secondary amine. No reaction (data not shown) was observed when attempting to couple amine **1** and chlorobenzene in the presence of ligand **F** known to be efficient with aryl chlorides.[51] Ligands **F** (entry 2) and to a less extent **G** or **H** (data not shown; yields of the coupled product: 16 and 10%, respectively) catalyzed the arylation of amine **1** with the same selectivity when bromobenzene was used.

N-Arylation of 3-aminopiperidine **2** was also attempted. Whatever the palladium ligand used for the coupling, reaction of the secondary amino group was largely favored (entry 4), 1-phenyl-3-aminopiperidine **20** and 3-(*N*-phenylamino)piperidine **21** being formed in 85/15 molar ratio. No amine **22** arising from arylation of both primary and secondary amine functions was observed. For comparison, we also submitted 4-aminopiperidine **16** to the same arylation conditions. 1-Phenyl-4-aminopiperidine **23** was obtained in 58% isolated yield. However, it was accompanied by 1-phenyl-4-(*N*-phenylamino)piperidine **25** (isolated yield: 27%) (entry 5) without any traces of 4-(phenylamino)piperidine **24**.

In the next set of experiments (entries 6−9), we subjected diamines **1** and **2** to the coupling conditions with ortho-substituted bromobenzenes. Mono- and diarylation were observed with both substrates. With piperidine **2**, results were in better agreement with the literature data (arylation of the primary amine) whereas

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(47) (a) Beletskaya, I. P.; Bessmertnykh A. G.; Guilard, R. *Tetrahedron Lett.* **1997**, *38*, 2287−2290. (b) Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Synlett* **1999**, 1459−1461. (c) Beletskaya, I. P.; Averin, A. D.; Bessmertnykh, A. G.; Denat, F.; Guilard, R. *Tetrahedron Lett.* **2002**, *43*, 1193−1196.

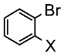
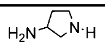
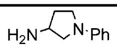
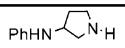
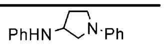
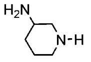
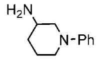
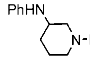
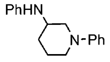
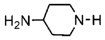
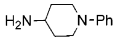
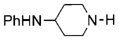
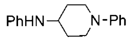
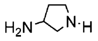
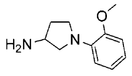
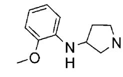
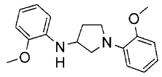
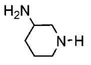
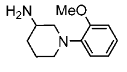
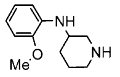
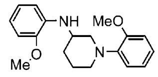
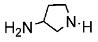
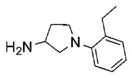
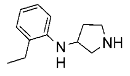
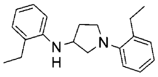
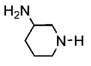
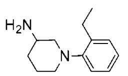
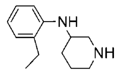
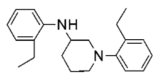
(48) (a) Greco, G. E.; Popa, A. I.; Schrock, R. R. *Organometallics* **1998**, *17*, 5591−5593. (b) Liang, L.-C.; Schrock, R. R.; Davis, W. M.; McConville, D. H. *J. Am. Chem. Soc.* **1999**, *121*, 5897−5798. (c) Schrock, R. R.; Casado, A. L.; Goodman, J. T.; Liang, L.-C., Bonitatebus, P. J. *Organometallics* **2000**, *19*, 5325−5341.

(49) Parrot, I.; Ritter, G.; Wermuth, C. G.; Hibert, M. *Synlett* **2002**, 1123−1127.

(50) Compounds **18** and **21** were prepared by arylation of Boc pyrrolidine **8** and piperidine **10** according to the procedure described in Table 3 followed by TFA deprotection (cf. the Supporting Information). Diphenylamine **19** was obtained by diarylation of 3-aminopyrrolidine **1**.

(51) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.

TABLE 2. Arylation of Unsubstituted 3-Aminopyrrolidine 1, 3-Aminopiperidine 2, and 4-Aminopiperidine 16

Entry	amine		L[a]	Yield (%)[b]	Products (relative ratio,[c] %)		
		X					
	1				**17**	**18**	**19**
1		H	**B**	68	100	0	0
2		H	**F**	49	100	0	0
3		H	**C** or **E**	40	100	0	0
							
	2				**20**	**21**	**22**
4		H	**B** or **C**[d]	40	85	15	0
							
	16				**23**	**24**	**25**
5		H	**B**	85	68	0	32
							
	1				**26**	**27**	**28**
6		OMe	**B**	74	74	0	26
							
	2				**29**	**30**	**31**
7		OMe	**B**	48	15	29	56
							
	1				**32**	**33**	**34**
8		Et	**B**	83	61	12	27
							
					35	**36**	**37**
9	**2**	Et	**B**	45	2.5	48.5	49

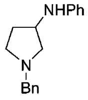
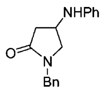
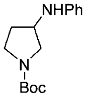
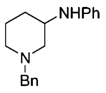
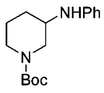
[a] Reaction conditions: bromobenzene (1 mmol), amine (1.2 mmol), NaO-*t*-Bu (1.4 mmol), Pd_2dba_3 (0.005 mmol), L (0.015 mmol), toluene, 100 °C, 24 h. Reaction times have not been minimized.
[b] Isolated yields (average of two or more experiments) of compounds.
[c] Ratio in the mixture determined by ^{1}H NMR.
[d] Chlorobenzene (1 mmol) was used in conjunction with ligand **C**.

arylation of 3-aminopyrrolidine **1** still resulted in the coupling with the secondary amino group. The structure of these heterocycles seemed responsible for the observed peculiar chemoselectivity and a more complete study is needed to clarify these data.

The overall discrepancy in the chemoselectivity of this palladium-mediated arylation of these diamines led us to protect with a benzyl or a *tert*-butoxycarbonyl (Boc) group the endocyclic nitrogen atom. For comparison, arylation of 1-benzyl-3-aminolactam **7** was also studied. The results will be presented according to the substitution on the endocyclic nitrogen before discussion.

Arylation of 1-Benzyl-3-aminopiperidine 9 and Pyrrolidine 6 (Table 3). Reactions of bromobenzene with diamines **6** and **9** were initially carried out under standard conditions (Pd_2dba_3, BINAP **B**, toluene, 100 °C, 24 h). The coupled products **11a** and **14a**, respectively, were isolated in moderate yields (entry 1, 53 and 36%). These yields were slightly improved by using Xantphos (entry 3, 60 and 46%, respectively). Similar or lower yields were obtained when the reaction was carried out with the diphosphines **B** and **C** (entries 2 and 4) in xylene at 130 °C. DPEphos[52] **D** and DPPF[53] **E** did not allow the reaction to proceed (entries 5 and 6). Monophosphine

TABLE 3. Arylation of 1-Protected 3-Aminopyrrolidines 6–8 and Piperidines 9 and 10

					 **11a**	 **12a**	 **13a**	 **14a**	 **15a**
Entry[a]	PhX	Ligand	Pd/L[b]	temp .(°C)			Yield[c] (%)		
1	PhBr	**B**	1/1.5	100	53	21	39	36	74
2	PhBr	**B**	1/1.5	130	(62)	(50)	(34)	(42)	(77)
3	PhBr	**C**	1/1.5	100	60	58	(63)	46	80
4	PhBr	**C**	1/1.5	130	36	56		42	(71)
5	PhBr	**D**	1/1.5	100	0	(28)	(5)	0	(52)
6	PhBr	**E**	1/1.5	100	0	(31)	0	(7)	(10)
7	PhBr	**F**	1/1.5	100	0	(44)	80	12	69
8	PhBr	**F**	3/4.5	100	(92)				
9	PhBr	**F**	2/3	130	85	(92)		88	90
10	PhBr	**G**	1/1.5	100	0	(35)		(15)	98
11	PhBr	**G**	1/1.5	130	84 (96)		84	(97)	
12	PhBr	**H**	1/1.5	100	0			(0)	(76)
13	PhBr	**H**	1/1.5	130			(17)		
14	PhCl	**F**	1/1.5	100	80	49	0	(34)	(100)
15	PhCl	**F**	1/1.5	130	80 (90)	81	(49)	76	(100)
16	PhCl	**F**	2/3	100	79	71		-	-
17[d]	PhCl	**F**	2/3	100	46	-		-	-
18	PhCl	**G**	1/1.5	100	75	(44)	(0)	(14)	(100)
19	PhCl	**G**	1/1.5	130			(12)		
20	PhCl	**H**	1/1.5	100	77	(0)	(0)	(0)	(97)
21	PhCl	**J**	1/1	100	(0)			(0)	46

[a] Reaction conditions: halobenzene (1 mmol), amine (1.2 mmol), NaO-*t*-Bu (1.4 mmol), Pd_2dba_3, ligand, solvent (2 mL/mmol halide, toluene for reactions conducted at 100 °C, xylene for reactions conducted at 130 °C), reaction time 24 h. Reaction times have not been minimized. [b] Ratio Pd/Ligand, mol %. [c] Yields represent isolated yields (average of two or more experiments) after purification by flash chromatography. In parentheses are the yields determined from ^1H NMR, using 1, 4-bis(trichloromethyl)benzene as an internal standard. The difference between NMR and isolated yields is around 10%. [d] $Pd(OAc)_2$ used in place of Pd_2dba_3.

ligands were then tested in conjunction with bromo- or chlorobenzene. Under the best conditions, 1-benzyl 3-aminopyrrolidine **6** afforded compound **11a** in 80% yield when it reacted with chlorobenzene in the presence of aminophosphine **F**,[54] at 100 °C (entry 14). Dicyclohexylphosphine **G**[55] or di-*tert*-butylphosphine **H**[56] displayed a slightly lower efficiency (entries 18 and 20). Ligand **F** was also an excellent partner in the palladium-mediated coupling of pyrrolidine **6** with bromobenzene provided that the reaction was carried out at a higher catalyst

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(52) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leewen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089. (b) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327–5330. (c) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432–4438.

(53) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119,* 8232–8245. (c) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618–4630.

(54) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.

(55) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560–2565

(56) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416.

loading at 100 °C (entry 8) or 130 °C (entry 9). In these reactions, Pd_2dba_3 was the preferred palladium source (comparison of entries 16 and 17).

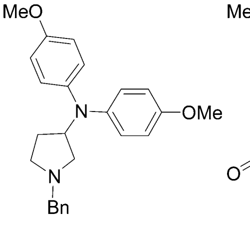
Arylation of the primary amine function of 1-benzyl-3-aminopiperidine **9** appeared more difficult. The Pd(0)/BINAP **B** or Pd(0)/Xantphos **C** catalytic system in combination with bromobenzene, at 100 °C, afforded the expected coupled 1-benzyl 3-aminopiperidine **14a** in yields lower than those obtained with the pyrrolidine analogue **6** (entries 1 and 3). No significant improvement was observed by using chlorobenzene in the presence of aminophosphine **F** (entry 14). The highest yields in amine **14a** were obtained when the C−N bond-forming reaction used bromobenzene at 130 °C in the presence of the electron-rich phosphines **F** or **G** (entries 9, 11). All the other phosphines, tested with chlorobenzene at 100 °C, gave poor or no reaction with piperidine **9**. This contrasts with the behavior of pyrrolidine **6** which was transformed in phenylamine **11a** in good yields (comparison of entries 14, 18, and 20 for phosphines **F**, **G**, and **H**, respectively).

Arylation of 1-Boc-3-aminopiperidine 10, 1-Boc-3-aminopyrrolidine 8, and lactam 7 (Table 3). 1-Boc-3-aminopiperidine **10** and pyrrolidine **8** were submitted to the previously used conditions for their arylation. The results are displayed in Table 3. Boc piperidine **10** appeared to be the most reactive substrate whatever the ligand used. Ligands **F** and **G** with chlorobenzene at 100 or 130 °C (entries 14, 15, and 18) or with bromobenzene at 130 °C (entries 9, 10) afforded *N*-Boc piperidine **15a** in yields higher than 95%. Di-*tert*-butylphosphine **H** was more efficient with chlorobenzene (entry 20 compared to entry 12). The coupling using bromobenzene and BINAP **B** or Xantphos **C** at 100 °C reached 80% (entries 1 and 3). Finally, even the carbene **J**[34,57] allowed the reaction to proceed but with a moderate yield (46%, entry 21).

The reactivity of *N*-Boc pyrrolidine **8** was very different: under the best conditions described for piperidine **10**, no (entries 14, 18, 20) or modest coupling (entry 15) was observed. Whereas ligand **H** and bromobenzene gave piperidine **15a** in 76% at 100 °C (entry 12), even at 130 °C the arylation of *N*-Boc pyrrolidine **8** was poor (entry 13, 17%). The highest yields of pyrrolidine **13a** were obtained when using bromobenzene in combination with ligand **F** at 100 °C (80%, entry 7) or with ligand **G** at 130 °C (84%, entry 11). Among the diphosphines screened (**B**, **C**, **D**, **E**), Xantphos was the most efficient (entry 3). BINAP **B**, DPEphos **D**, and DPPF **E** displayed a moderate to poor reactivity in this reaction (entries 1, 2, 5, 6).

The optimum yields obtained in the arylation of lactam **7** were obtained at 130 °C, using aminophosphine **F** and bromo- or chlorobenzene (entries 9 and 15). The other ligands (diphosphines **B**, **C**, entries 1−4 at 100 °C or 130 °C; monophosphine **G** at 100 °C, entry 15) gave poor or moderate yields.

Arylation of 3-Aminopyrrolidines and Piperidines with Substituted Aryl Halides (Table 4). The scope of the arylation of piperidines and pyrrolidines **6**−**10** was next studied. The couplings were evaluated with electron-rich and electron-poor aryl halides. Reaction of amines **6**−**10** with 4-bromoanisole under the standard conditions (temperature: 100 °C, toluene, 24 h) using BINAP **B** (ratio Pd/ligand: 1/1.5) or aminophosphine **F** (ratio Pd/ligand: 1/1.5) failed. The use of ligand **F** with high catalyst loading (Pd/L: 2/3) and temperature (130 °C) allowed the reaction to proceed with good to high yield using either bromo- (entry 1) or chloroanisole (entry 2). Under these conditions, *N*,*N*-diarylamines **38** or **39** were isolated in less than 10% yield from pyrrolidine **1** or lactam **7** (Figure 5). No reaction was observed with iodoanisole (mol % Pd_2dba_3/BINAP: 1/1.5, NaO-*t*-Bu, toluene, 110 °C, 48 h, data not shown). For comparison, the cross-coupling reaction of 2-chloroanisole with amines **6**−**10** was studied. Under the conditions described in entry 3, the *N*-arylamines were obtained in 63−96%yields. Due to the steric hindrance of the aryl halide, no diarylation was observed in good agreement with previous works. No homocoupling of the aryl halide was observed.


38

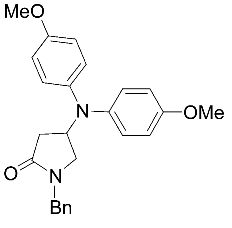

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FIGURE 5. 3-(Diarylamino)pyrrolidine and -pyrrolidinone.

The electron-poor aryl halides, bromobenzonitrile, or trifluorobromobenzene gave successful couplings using BINAP **B** as the ligand (entries 4 and 5). Under the same conditions, using Xantphos **C** instead of BINAP, no improvement was observed in the coupling of lactam **7** with bromobenzonitrile (yield: 57%, data not shown). Aminophosphine **F** was not a suitable ligand in the coupling of 1-benzyl-3-aminopyrrolidine **6** with bromobenzonitrile, whereas low yields were obtained with chlorobenzonitrile (15% and 33%, respectively, at 100 and 130 °C, data not shown).

Finally, arylation of amines **6**, **7**, **9**, and **10** with bromofluorobenzene or chlorofluorobenzene was evaluated. With bromofluorobenzene at 100 °C, the ligands BINAP **B** or aminophosphine **F** afforded the expected phenylamines **11f**, **12f**, **14f**, and **15f**, respectively, although in moderate or low yields (entries 6 and 7). At 130 °C (entry 9) and with a higher ratio Pd/ligand, yields higher than 70% were obtained. Chlorofluorobenzene was equally efficient in the coupling of lactam **7** and piperidine **9**.

Discussion

Arylations were first attempted with bromobenzene, the most common and general halide used in these reactions.[25,26] To compare the efficiency of its palladium-mediated cross-coupling with amines **6**−**10** in the presence of different ligands (Figure 4), some parameters of the couplings were fixed. Based on literature data, Pd_2dba_3 and toluene were chosen as the palladium source and the solvent, respectively. Among the bases tested[58] (NaO-*t*-Bu, Cs_2CO_3, K_3PO_4), NaO-*t*-Bu was the sole base able to promote the arylation of pyrrolidine **6** at 100 °C

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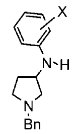
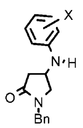
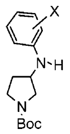
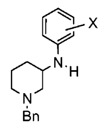
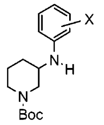
TABLE 4. Synthesis of 3-(*N*-Arylamino)pyrrolidines and -piperidines

Entry[a]	X-C_6H_4-Y	Ligand	Pd/L[b]	T (°C)	 Yields (%)[c]				
					11b	**12b**	**13b**	**14b**	**15b**
1	4-BrC_6H_4OMe	**F**	2/3	130	57[d]	73[e]	50	98	77
2	4-ClC_6H_4OMe	**F**	2/3	130	83[e]	75[f]	77	(100)	(100)
					11c		**13c**	**14c**	**15c**
3	2-ClC_6H_4OMe	**F**	2/3	130	81		63	70	96
					11d	**12d**	**13d**	**14d**	**15d**
4	4-BrC_6H_4CN	**B**	1/1.5	100	70	55	75	71	87
					11e	**12e**	**13e**	**14e**	**15e**
5	4-$BrC_6H_4CF_3$	**B**	1/1.5	100	91	84	65	97	92
					11f	**12f**	**13f**	**14f**	**15f**
6	4-BrC_6H_4F	**B**	1/1.5	100	44	24		30	(29)
7	4-BrC_6H_4F	**F**	1/1.5	100	35	25		traces	
8	4-BrC_6H_4F	**F**	1/1.5	130	(47)	(27)		(74)	92
9	4-BrC_6H_4F	**F**	2/3	130	70		79	74	
10	4-ClC_6H_4F	**F**	1/1.5	130		(17)			63
11	4-ClC_6H_4F	**F**	2/3	130	(44)	74		71	

[a] Conditions: ArX (1 mmol), amine (1.2 mmol), NaO-*t*-Bu (1.4 mmol), toluene (100 °C) or xylene (130 °C), 2 mL/mmol, 24 h. [b] Palladium source: Pd_2dba_3. Ratio Pd/ligand, mol %. [c] Isolated yields; in parentheses are the yields determined from ^1H NMR. [d] **38**: 5%. [e] **39:** 6%. [f] **39:** 10%.

(ligand: BINAP **B**) and thus, was used in all our attempts. As bromobenzene did not react at room temperature, the couplings were first carried out at 100 °C. Finally, based on the evolution of the reaction as a function of time (cf. Supporting Information), the arylations were quenched after 24 h. The crude reaction mixture was then analyzed by ^1H NMR after addition of a known amount of 1,4-bis(trichloromethyl)benzene. This compound was chosen as a standard due to its chemical shift (^1H NMR: singlet at 8.00 ppm), its physical properties (bp 312 °C, mp 110 °C) and its good solubility in organic solvents. The reduction of the aryl halide cannot be completely ruled out although GC analysis of the crude product in some experiments with amine **6** using DPEphos **D** or DPPF **E** as ligands (Table 3, entries 5 and 6, respectively) showed that bromobenzene was not reduced.

The first unexpected result was the selective coupling of the secondary amine function of the unprotected substrates **1**, **2**. The discrepancy between our results and those described in the literature for diamines[45−49] could arise from the particular structure of our substrates. 3-Aminopiperidine and 3-aminopyrrolidine[13,59] can coordinate the metal with their primary and/or secondary amino groups and therefore can compete with the phosphine ligand mostly in the case of monophosphines. From kinetic studies, Buchwald et al. predicted that the amine group is also able to activate the catalyst[60] and that primary amines bind faster to the catalyst than do secondary amines.[61] A possible explanation for the observed selectivity could be the formation of a strained aza bicyclic intermediate **M**[61,62] (Figure 6). Since reductive elimination is accelerated by steric crowding in the palladium complex, one would expect a faster reductive elimination from a coordinated secondary amine compared to a coordinated primary amine. Moreover, with primary amines, one cannot exclude the formation of the

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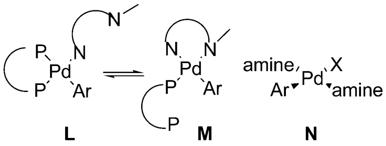

FIGURE 6. Possible palladium reactive intermediates.

palladium bis(primary amine) complex **N** which is known to be inefficient in the arylations (Figure 6).[63]

The arylation with bromobenzene of *N*-protected aminopyrrolidines or piperidines **6**−**10** was studied in the presence of several diphosphines (**B**, **C**, **D**, **E**) (Table 3, entries 1−6). Among them, DPEphos[52b] **D** (Table 3, entry 5) or DPPF[64] **E** (Table 3, entry 6) gave no or poor yields whereas BINAP **B** and Xantphos[52a,65] **C** led to the corresponding *N*-phenyl derivatives **11**−**15** within 36−80% yields (Table 3, entries 1 and 3). Xantphos **C**, a less used ligand, appeared slightly superior to BINAP **B**, with isolated yields higher than 58% for each substrate. Such an efficiency of Xantphos has been previously reported in the arylation of 2-aminoheterocycles,[66] of unreactive amides,[67] and in the C−N bond-forming reaction involving alkylamines.[68] The formation of a trans-chelating bis(phosphine)Pd(II) complex with a bite angle much larger than the angle of the cis complex and larger than that of most commonly used bidentate phosphine ligands (BINAP, DPPF, DPEphos) could explain this high reactivity.[67b,69]

With bromobenzene, palladium-catalyzed reaction of amines **6**−**10** in the presence of monophosphines, at 100 °C, was also studied. No cross-coupling reaction occurred when tris(*o*-tolyl)phosphine, tricyclohexylphosphine or monophosphine **I** were used (data not shown). However, with the electron-enriched aminophosphine **F**, pyrrolidine **8** and its piperidine analogue **10** led, respectively, to 3-(*N*-phenylamino)amines **13a** and **15a** in 80% and 69% yields (Table 3, entry 7). Dicyclohexylphosphine **G** was also efficient either at 100 °C for the arylation of piperidine **10** or at 130 °C for its five-membered ring analogue **8** (Table 3, entries 10 and 11), whereas di-*tert*-butylphosphine **H** gave poor transformations (Table 3, entries 12 and 13). Under the conditions described for *N*-Boc derivative **8**, the benzylamine **6** had no reactivity (Table 3, entry 7). The same difference in the reactivity toward the cross-coupling was observed with the Boc and benzyl piperidines **10** and **9**: piperidine **15a** and 1-benzyl piperidine **14a** were formed in 69 and 12% yields respectively (Table 3, entry 7).

A substantial influence of the temperature of the reaction or of the mol % of catalyst employed on the efficiency of the arylation involving monophosphine ligands and aryl bromides was observed. For example, when the arylations of 1-benzylaminopyrrolidine **6** with bromobenzene were carried out at 100 °C, low conversions were observed (Table 3, entries 7, 10, and 12). Under the same conditions but heating at 130 °C, the amine **6** was arylated in yields higher than 84%. The use of 1 mol % of Pd at 100 °C gave no *N*-phenylamine **11a** whereas with 3 mol % catalyst loading, the yield reached 92%. The lower reactivity of *N*-benzyl 3-aminopiperidine and pyrrolidine compared to their Boc analogues could be due to the ability of the endocyclic nitrogen to coordinate strongly the palladium thereby decreasing the rate of one or more steps in the catalytic cycle due to competition with the phosphine ligand. However, this sole coordination of the diamine to the palladium is not efficient for the cross coupling as no reaction was observed when bromobenzene was allowed to react with the pyrrolidine **6** in the presence of Pd_2dba_3 without phosphine ligand. The fact that arylations of amines **6**−**10** proceed effectively at 130 °C suggests that the basic phosphine ligand is able to displace the amine from the metal.

Monophosphines **F**, **G**, and **H**, known for their efficiency in the palladium-mediated arylations of amines with aryl chlorides,[54b] were tested as ligands in the reaction of chlorobenzene with diamines **6**−**10**. The conditions used for the coupling reaction were similar to those previously employed. Pd_2dba_3 was preferred over $Pd(OAc)_2$ as the palladium source (Table 3, comparison of entries 16 and 17) even at high catalyst loading. As can be seen in Table 3, monophosphine **F** was the most general ligand among the three tested (**F**, **G**, and **H**). At 100 °C, arylation of benzyl aminopyrrolidine **6** with chlorobenzene (Table 3, entry 14) led to 3-(*N*-phenylamino)pyrrolidine **11a** in a yield comparable to that obtained with bromobenzene at 130 °C (Table 3, entry 8). However, at 100 °C, chlorobenzene appeared less suitable for the arylation of benzyl aminopiperidine **9** (Table 3, entry14) and detrimental (80% with PhBr, 0% with PhCl) to the arylation of 1-Boc aminopyrrolidine **8** (Table 3, entries 14 and 18 compared to entries 7 and 11). The influence of the temperature on the coupling with chlorobenzene was also studied. A higher temperature (130 °C instead of 100 °C, entries 15) led to a more efficient coupling particularly with lactam **7** and Boc-protected amine **8**. A high loading catalyst (Table 3, entries 16) had no influence on the arylation of pyrrolidine **6** but improved significantly that of **7**. Dicyclohexylphosphine **G** (Table 3, entries 18 and 19) can be compared to ligand **F** but is less efficient, even at 130 °C, in the arylation of 1-Boc-pyrrolidine **8** and benzyl aminopiperidine **9**. Di-*tert*-butylphosphine **H** (Table 3, entries 12 and 20) appeared as a selective ligand for the arylation of benzyl aminopyrrolidine **6** or Boc aminopiperidine **10**.

Conclusions

In summary, we have described the palladium-catalyzed arylation of 3-aminopyrrolidines and piperidines which are key-building blocks in medicinal chemistry. Optimal conditions were determined for each substrate; nickel, copper, and palladium in conjunction with a number of ligands were screened, and the complex

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palladium-Buchwald's ligand [2-(dimethylamino)-2′-(dicyclohexylphosphine)biphenyl] consistently achieved the best yields (over 70%). In certain cases with monophosphines and aryl bromides, a strong temperature effect was observed. Among bisphosphines, Xantphos was the best ligand tried, although it afforded moderate to good yields. This method is a strong alternative to the previously described (mainly in the patent literature) procedures, allowing a rapid access to a library of compounds with a variety of aryl groups appended on the primary amino group of readily available substrates. It should find wide application among synthetic and medicinal chemists. When performing the coupling reaction on the unprotected heterocycles with bromobenzene, a selective arylation on the secondary amine occurred, in contrast with all previous literature data, and mixed results were obtained using ortho-substituted bromobenzenes. Work is currently underway to determine the parameters governing the chemoselectivity of the arylation of unprotected 3-aminopyrrolidine and -piperidine.

Experimental Section

General Procedure for *N*-Arylation of 1-(Un)substituted 3-Aminopyrrolidines and 3-Aminopiperidines. Palladium-Catalyzed Reaction. To a Schlenk tube were added Pd_2dba_3 (4.6 mg, 0.005 mmol, 1 mol % Pd) or $Pd(OAc)_2$ (2.4 mg, 1 mol % Pd), the ligand (0.015 mmol, 1.5 mol %), NaO-*t*-Bu (134 mg, 1.4 mmol), and degassed solvent (2 mL, toluene or xylene). The reaction vessel was fitted with a rubber septum, evacuated, and back-filled with nitrogen. The aryl halide (1 mmol) and the amine (1.2 mmol) were successively added through the septum (solid aryl halides or amines were added after the addition of NaO-*t*-Bu). The reaction mixture was stirred while heating at 100 °C (in toluene) or 130 °C (in xylene). After 24 h, it was cooled to ambient temperature.

For ^1H NMR analysis, methanol and then 1,4-bis(trichloromethyl)benzene as a standard (156 mg, 0.5 mmol) were added. The mixture was concentrated and the residue analyzed before purification by flash chromatography on a silica gel column.

For GC analysis, the crude product was injected directly on the column (5% phenyl methylpolysiloxane column, 0.32 mm Internal Diameter, 30 m length, 1 μm film thickness), with nitrogen as gas carrier, oven temperature from 180 °C to 250 °C; gas carrier: N_2). Retention times: benzene, 1.6 min; toluene, 1.7 min; bromobenzene, 2.1 min).

Copper Iodide-Catalyzed Reaction. A Schlenk tube was charged with CuI (19 mg, 0.1 mmol, 10 mol % Cu), ligand (0.2 mmol, 20 mol %), base (1.4 mmol), and degassed solvent (2 mL). The tube was capped with a rubber septum, evacuated, and flushed with nitrogen. Bromobenzene (105 μL, 1 mmol) or iodobenzene (112 μL, 1 mmol) and the amine (1.2 mmol) were added through the septum. The mixture was heated to the temperature as indicated in Table 1 for 24 h. The solvent was removed under vacuum and the crude product purified by flash chromatography on a silica gel column.

CuTC-Catalyzed Reaction. A Schlenk tube was charged with CuTC (580 mg, 3 mmol), NaO-*t*-Bu (134 mg, 1.4 mmol), and degassed solvent (2 mL). The flask was capped with a rubber septum, evacuated, and flushed with nitrogen. Iodobenzene (112 μL, 1 mmol) and the amine (1.2 mmol) were added through the septum. The mixture was heated to the temperature as indicated in Table 1 for 24 h. After cooling, dichloromethane (20 mL) was added, and the organic layer was washed with ammonia (28% in water, 20 mL). The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The solvent was removed under vacuum, and the crude product was purified by flash chromatography on a silica gel column.

Ni(COD)-Catalyzed Reaction. A Schlenk tube was charged with $Ni(COD)_2$ (14 mg, 0.05 mmol, 5 mol % Ni), (±)-BINAP (53 mg, 0.085 mmol, 8.5 mol %), NaO-*t*-Bu (134 mg, 1.4 mmol), and degassed toluene (2 mL). The flask was capped with a rubber septum, evacuated, and flushed with nitrogen. Bromobenzene (105 μL, 1 mmol) and the amine (1.2 mmol) were added through the septum. The mixture was heated to the temperature indicated in Table 1. After 24 h, the mixture was diluted with methanol and concentrated under reduced pressure. The crude product was analyzed by TLC and ^1H NMR.

$(DPPF)NiCl_2$-Catalyzed Reaction. A Schlenk tube was charged with $(DPPF)NiCl_2$ (14 mg, 0.02 mmol, 2 mol % Ni), DPPF (11 mg, 0.02 mmol, 2 mol %), and NaO-*t*-Bu (134 mg, 1.4 mmol). The flask was capped with a rubber septum, evacuated, and flushed with nitrogen. Dry toluene (2 mL) was added, followed by methylmagnesium bromide (3.0 M in diethyl ether, 20 μL, 0.06 mmol). The mixture was stirred at rt for 15 min before adding chlorobenzene (102 μL, 1 mmol) and 1-benzyl-3-aminopyrrolidine 1 (211 mg, 1.2 mmol). The mixture was heated to 100 °C for 24 h and then cooled before addition of methanol. After evaporation of the volatile compounds, the crude product was analyzed by TLC and ^1H NMR.

Acknowledgment. We gratefully acknowledge the CNRS (Centre National de la Recherche Scientifique), the Région Basse-Normandie for a fellowship to L.J., PunchOrga Network (Pôle Universitaire Normand de Chimie Organique), the Ministère de la Recherche et des Nouvelles Technologies, and the European Union (FEDER funding) for financial support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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