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Remarkably Selective Palladium-Catalyzed Amination Process: Rapid Assembly of Multiamino Based Structures

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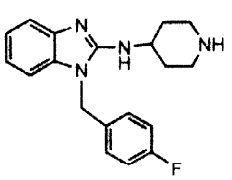
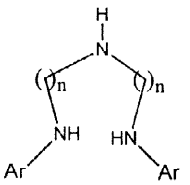
Abstract: Palladium-catalyzed selective amination by a primary amine in the presence of a secondary amine provided up to >99:1 selectivity with high yields. © 1998 Elsevier Science Ltd. All rights reserved.

Buchwald[1] and Hartwig[2] have independently developed palladium- and nickel-catalyzed amination reactions of aryl halides and triflates that have emerged as powerful tools for the preparation of aromatic amines. Because nitrogen protecting group manipulation is a difficult problem, synthetic applications of these reactions to the selective amination of aryl and heteroaromatic systems by polyamines would be an extremely important extension. The growing interest in the development of polyamine-based ligands[3] and complex polyamine-derived medicinally valuable targets[4] make such a task particularly rewarding. However, effective and selective amination processes have been limited in synthetic applications. Herein we disclose a practical entry for the preparation of polyamine-based structures using a palladium-catalyzed selective amination process.



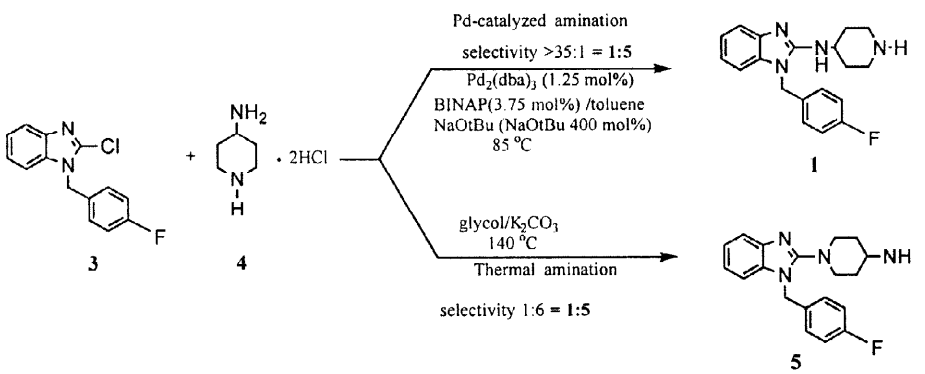
Norastemizole (1)



2

We recently demonstrated that palladium-catalyzed amination technology is extremely valuable in the synthesis of biologically active aminoazole derivatives.[4] During the development of a one step process for the synthesis of nonsedating antihistaminic norastemizole (**1**), the 4-fluorobenzyl-2-chlorobenzimidazole was selectively aminated by primary amine in the presence of a secondary amine using palladium catalysis. After a detailed inspection of this reaction, the selectivity was improved from 18:1 to >35:1 with an isolated yield of 84% (chemical purity > 99.5 A%) of **1**. The thermal reaction showed a higher degree of selectivity for the more nucleophilic secondary amine to produce **5** (Scheme 1).

Scheme 1



3 **4** **1** **5**

The viability of the palladium-catalyzed selective amination process was extended to acyclic diamine and triamine systems. The results are summarized in Table 1. In most cases, conversion of the 4-fluorobenzyl-2-chlorobenzimidazole to the corresponding primary aminated adducts exhibited high conversion, up to 99:1 selectivity and good yields (Table 1, entries 1-4). Under thermal conditions, reaction of one equivalent of amine **6** with imidazole **3** gave a 1:2 ratio of primary to secondary amine

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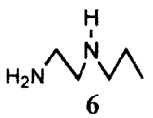
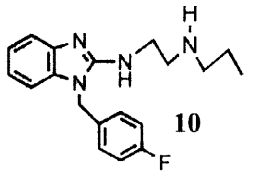
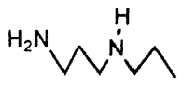
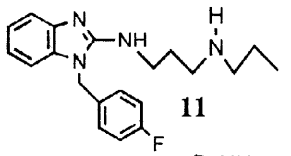
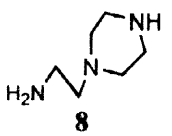
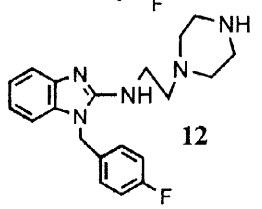
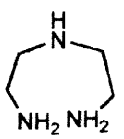
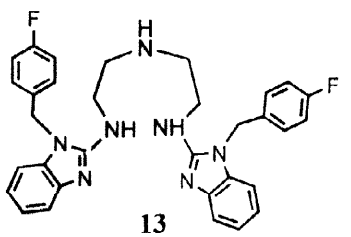
adducts. It is important to note that the imidazole-containing polyamine-based ligand **13** can be efficiently synthesized under the Pd-catalyzed amination conditions (entry 4).

Table 1

Entry	Amine	Major Product	Selectivity Primary:Secondary	$Pd_2(dba)_3$ mol% (Rn time, h)	Conversion% (Yield %)
1	 **6**	 **10**	>99:1	2(1)	>91 (77)[a]
2	 **7**	 **11**	>99:1	2(1)	>97 (81)[a]
3	 **8**	 **12**	>60:1	2(2)	>95 (80)[a]
4	 **9**	 **13**	>99:1	5(16)[c]	>91 (67)[b]

All reactions were conducted according to the procedure in note 5. The reactions were monitored by HPLC using μBondapak C-18 column eluted with 50 : 50 of pH=3 buffer/acetonitrile, flow rate 1.0 mL/min. The molar ratio of $Pd_2(dba)_3$:BINAP is 1:3. (a) Isolated yield; (b) HPLC wt% assay yield by comparing to the standard; (c) 300 mol% of NaO*t*Bu was used.

Due to the success of the selective amination of 4-fluorobenzyl-2-chlorobenzimidazole, our attention was drawn toward the development of the parent chlorobenzimidazole in the selective amination reaction. Unfortunately, attempts to couple 2-chororbenzimidazole with 4-aminopiperidine were unsuccessful, even when 5 equiv. of sodium *t*-butoxide were present. It was postulated that *t*-butoxide deprotonated the benzimidazole, generating an anion which strongly bound to palladium, shutting down the catalytic cycle. To test this hypothesis, the following competition experiment was designed. When a 1:1 mixture of 2-chlorobenzimidazole and **3** in the presence of amine **4** was subjected to the catalytic conditions (1.25 mol% $Pd_2(dba)_3$/3.75 mol% BINAP /$PhCH_3$) with 5 equivalents of NaO*t*Bu, <10% conversion was observed.

Knowing the importance of the coupling of benzimidazoles to amines, we envisaged a THP-protected analog as an ideal candidate for the coupling reaction. The THP group would provide easy attachment to and removal from the benzimidazole and should provide a new avenue to this amination process. In addition, THP-attached imidazoles can give access to combinatorial chemistry applications.[6] First, the utility of the palladium-catalyzed amination on a monoprotected amine, 4-aminopiperidine-1-ethyl carbamate, with freshly prepared 1-THP-2-chlorobenzimidazole (**14**) was examined.[7] As illustrated in Scheme 2, the Pd-catalyzed coupling proceeded in excellent yield. In this reaction, the THP protecting group can be removed straightforwardly by aqueous acidic (HCl) work-up to provide the corresponding

aminobenzimidazole.[8] Our attention was then focused on the selective Pd-catalyzed coupling process. As shown in the Scheme 2, the reaction between 1-THP-2-chlorobenzimidazole and 4-aminopiperidine dihydrochloride provided an 85% isolated yield of either compound **16** or **17** (depending on the work-up conditions) with remarkable selectivity for the primary amine (>37:1).

Scheme 2

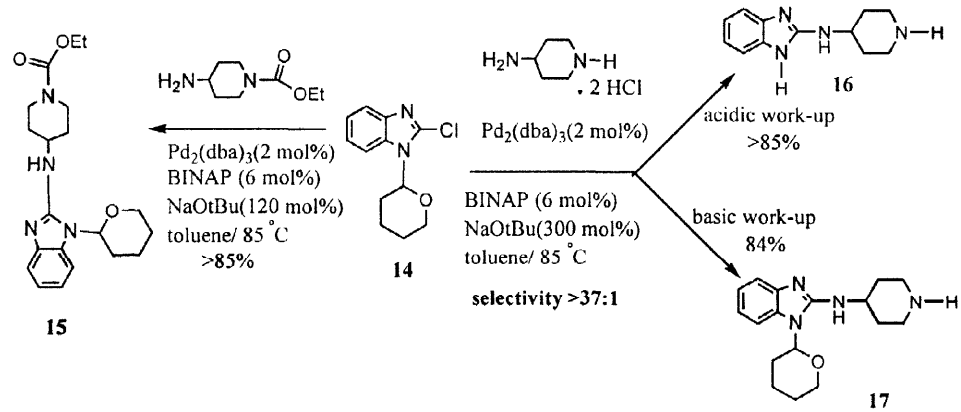
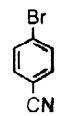
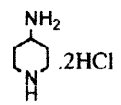
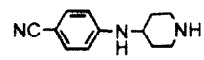
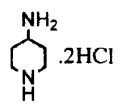
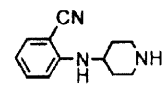
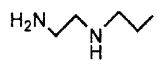
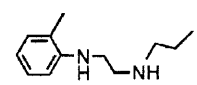
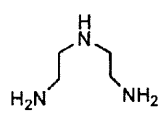
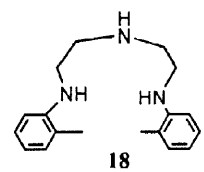
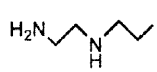
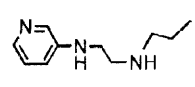
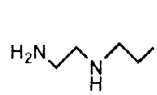
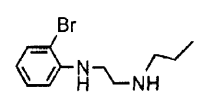


Table 2

Entry	Aryl Bromide	Amine	Product	Selectivity (Rn time, h)	$Pd_2(dba)_3$ mol%	Yield% (Conversion%)
1				27:1	0.5(0.5)[c]	84[a] (93)
2				59:1	0.5(0.5)[c]	87[a](99)
3				>99:1	1.5(2)	81[a](>99)
4			 18	>99:1	1.5(7)[c]	95[b] (>95)
5				>9:1	1.5(10)	85[b](>99)
6			 19	>99:1[d]	4(3)	58[a](>99)

All reactions were conducted according to the procedure in note 5. The reactions were monitored by HPLC using μBondapak C-18 column eluted with 50 : 50 of pH=3 buffer/acetonitrile, flow rate 1.0 mL/min. The molar ratio of $Pd_2(dba)_3$:BINAP is 1:3. (a) Isolated yield; (b) HPLC wt% assay yield by comparing to the standard; (c) 300 mol% of NaO*t*Bu was used; (d) The coupling was performed with 3 equivalents amine with standard reaction condition according to reference 5.

Since the selective amination process of imidazole derivatives proceeded extremely well, we studied the scope and limitations of the process with several aryl halide under these conditions. As depicted in Table 2, *para-* and *ortho*-bromobenzonitrile can be selectively aminated under palladium catalysis in high yields and excellent selectivities (entry 1 and 2). The coupling of triamine **9** with *ortho*-bromotoluene could provide a straightforward entry for the synthesis of polydentate ligands. As shown in Table 2, entry 4, compound **18** can be prepared in >99 % selectivity and in high yield. Also, 3-bromopyridine proved to be an excellent candidate for the selective amination process (entry 5). The selective amination process was examined with 1,2-dibromobenzene. Interestingly, compound **19** can be prepared in unoptimized 58% yield with a >99% selectivity. No double coupling was observed even with 3 equivalents of amine **6** and excess NaO*t*Bu.

The palladium-catalyzed selective amination by primary amines in the presence of secondary amines with aryl and heteroaromatic halides provides an expedient avenue to the preparation of synthetically complex and pharmacologically useful polyamine systems. The scope and limitations of the reaction are being explored further.

References and notes

(1) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, L. S. *J Am. Chem. Soc.* **1996**, *118*, 7215. (b) Wagaw, S.; Buchwald, L. S. *J. Org. Chem.* **1996**, *61*, 7240. (c) Wolfe, J. P.; Buchwald, L. S. *J. Org. Chem.* **1996**, *61*, 1133.

(2) (a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708. (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118, 7217.*

(3) Togni, A.; Venanzi, L. M. *Ang. Chem., Int. Ed. Eng.* **1994**, *33*, 497.

(4) Hong, Y.; Tanoury, G. T.; Wilkinson, H. S.; Bakale, R. P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **1997**, *38*, 5607.

(5) A selective amination procedure is as follows: Anhydrous toluene was degassed with argon for 20 min. prior to use. A dry 25 mL 2-neck flask was charged with N-propylethylenediamine (0.432 mL, 3.51 mmol), tris(dibenzylideneacetone)-dipalladium(0) [$Pd_2(dba)_3$] (40.1 mg,0.044 mmol), 2,2'-Bis(diphenylphosphino)-1-1'-binaphthyl (81.6 mg, 0.131 mmol) [BINAP], sodium tert-butoxide (309 mg, 3.21 mmol), and 2-bromotoluene (500 mg, 2.92 mmol). The resulting mixture was evacuated and purged with argon, followed by the addition of anhydrous toluene (10 mL). The solution was degassed with argon for 5 minutes, at which time it was heated to 85 °C for 2 h (at this point, the conversion was >99% monitored by HPLC). The reaction was cooled to room temperature, quenched with 0.1N NaOH and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography was performed using EtOAc:MeOH (8:2, v/v) to afford the desired product in 81% yield (see Table 2, Entry 3).

(6) Chen, S.; Junda, K.D. *J. Am. Chem. Soc.* **1997**, *119, 8724.*

(7) THP protected chlorobenzoimidazole (**14**) is prepared as follows: 2-chlorobenzimidazole (3.15 g, 20.7 mmol), THF (50 mL) and 3,4-dihydro-2H-pyran (5.7 mL, 62 mmol) were charged to a 250 mL, 3-neck flask equipped with a reflux condenser, a thermometer, and an overhead-stirrer under N_2. The mixture was heated to 50 °C over 15 min with stirring. To this reaction mixture was added $TsOH.H_2O$ (0.11 g) with stirring. The resulting mixture was heated at 55 °C for 3 h (monitored by HPLC). After cooling to 0-5 °C, NaH (100 mg, 60%) was added and stirred for 10 min. Heptane (100 mL) was added and stirred for 10 min at 0-10 °C. The mixture was passed through a pad of silica gel to remove insolubles. The filtrate was concentrated under vacuum at 30-40 °C to provide crude product, which was dried at 30-40 °C/5-10 mmHg for 10 h to afford 5 g of the desired prodcut **14** in essentially quantitative yield.

(8) Under thermal conditions the coupling was sluggish, and the THP group was partially cleaved to provide a mixture of **15**, THP deprotected **15, 14**, THP deprotected **14**, and the corresponding urea analogue.