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Palladium-Catalyzed Microwave-Assisted Amination of 1-Bromonaphthalenes and 5- and 8-Bromoquinolines

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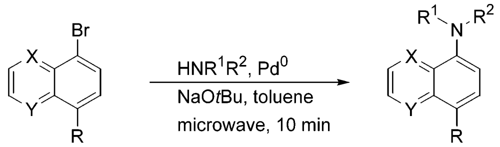
ABSTRACT



1-Aminonaphthalenes and 5- and 8-aminoquinolines were rapidly prepared from the respective aryl bromides in good yields by Pd-catalyzed aryl amination under microwave conditions. Consistent improvements in yields over those obtained under standard conditions were seen with quinoline substrates. In the cases where 5-bromo-8-cyanoquinoline was used as a substrate, no desired products were obtained under standard conditions with a number of different primary and secondary amines. However, microwave conditions provided the desired products in good to excellent yields.

Amination of aromatic halides has become a powerful methodology for the construction of arylamine intermediates useful for the synthesis of biologically active molecules.[1] Because of the ubiquitous presence of arylamine moieties within pharmaceutically relevant compounds, this methodology for the construction of a wide variety of mono- and polycyclic aromatic structures is of great utility. In particular, the technology is well-suited to applications where a more convergent approach and more sophisticated amines are desired to complement those attainable through reductive amination strategies. Microwave-assisted organic synthesis has also gained considerable attention over the past decade, and these advances have also found application in the pursuit of pharmaceutically active agents.[2,3] The power and complexity of reactions adapted to microwave methods has grown over the past few years in particular, expanding the scope of their use from simple acceleration of coupling reactions to include more elegant applications such as the acceleration of homogeneous metal-catalyzed transformations.[4]

Despite these advances, only two reports of microwave-assisted Pd-catalyzed aryl amination have appeared in the literature, and these accounts were limited to a demonstration of acceleration of the reaction times of simple phenyl and 2-naphthyl halides.[5,6] We report herein the use of microwave conditions to greatly accelerate the reactions of primary and secondary amines with 1-naphthyl bromides[7] where a limited number of examples exist. Furthermore, we report the application of Pd-catalyzed aryl amination under both conventional and microwave conditions to the preparation of 5- and 8-aminoquinolines, which have not been previously reported as substrates with this methodology.

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[1] (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

[2] Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

[3] (a) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406−416. (b) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251−1283.

[4] Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727.

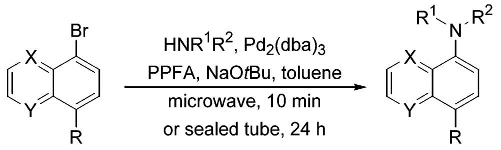
[5] Sharifi, A.; Hosseinzadeh, R.; Mirzaei, M. *Monatsh.* **2002**, *133*, 329−332.

[6] Wan, Y.; Alterman, M.; Hallberg, A. *Synthesis* **2002**, 1597−1600.

[7] (a) Loeppky, R. N.; Cui, W. *Tetrahedron* **2001**, *57*, 2953−2956. (b) Guilard, R.; Beletskaya, I. P.; Bessmertnykh, A. G. *Tetrahedron Lett.* **1997**, *38*, 2287−2290. (c) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (d) Thomas, G. H.; Kerrigan, F.; Martin, C. *Tetrahedron Lett.* **1998**, *39*, 2219−2222.

10.1021/ol034072h CCC: $25.00

Scheme 1. Amination of Naphthyl and Quinolinyl Bromides



In the course of our research, we sought to prepare a series of naphthyl or quinolinylamines where the amino substitution was located at either the 1 or 4 (5 or 8) position. Additionally, we desired a convergent route that would allow both maximum flexibility for variation of the amine moiety as well as the aryl scaffold. Our strategy focused on Pd-catalyzed aryl amination of naphthyl and quinolinyl bromide substrates, using simple primary or secondary aliphatic amines (Scheme 1). Because of the known propensity for interfering Pd chelation from pyridyl or quinolinyl substrates,[8] more powerful chelating ligands were chosen for these studies. Results from preliminary experimentation with several different ligands for the Pd catalyst showed satisfactory conversion to products using either BINAP[9] or (*S*)-(*R*)-PPFA.[10] However, as chromatographic elution times of the BINAP ligands frequently coincided with those of naphthyl and quinolinylamine reaction products under most standard solvent systems, the latter ligand was routinely employed. Not unexpectedly, comparable yields of desired amination products were obtained under microwave or sealed tube reaction conditions in initial experiments with 4-substituted-1-bromonaphthalenes (Table 1, entries **1**−**5**), though a marked rate acceleration was observed in the microwave reactions.[11] Typically, reactions performed under conventional heating conditions were still progressing after 16 h and were essentially complete by 24 h, whereas the microwave reactions appeared to be complete after 10 min of reaction time. In most cases, complete consumption of aryl bromide was observed by the end of the reaction time, and the reduced (H for Br) arene accounted for the vast predominance of the mass balance of starting aryl bromide.

In our efforts to find literature precedence for Pd-catalyzed aryl amination of substituted quinolines, we observed that no reports describing application of this methodology for 5- or 8-bromoquinolines existed. As observed with the naphthyl substrates, a marked rate acceleration was observed under the microwave conditions relative to standard heating (Table 1, entries **6**−**11**). In addition, yields for microwave conditions were reproducibly enhanced in all cases under the microwave-assisted conditions (the magnitude of this effect ranged from 15−75% improvement).

Certain substrates failed to provide the desired amination products under conventional heating, even after prolonged reaction times. In our hands, under the standard conditions employed previously, we did not observe any appreciable reaction with 5-bromo-8-methoxyquinoline and piperidine or with the strongly electron-deficient 5-bromo-8-cyanoquinoline with any of the primary or secondary amines tested. Unlike the previous examples where reduced arene byproducts predominated, recovery of aryl bromide was high (65−90%), indicating failure of Pd insertion for these substrates. However, under microwave-assisted conditions, these reactions proceeded reproducibly without event in the usual 10 min reaction time in yields ranging from 50−90% (Table 1, entries **12**−**16**). To rule out a possible shift in mechanism, specifically for the 5-bromo-8-cyanoquinoline substrate due to the perceived potential for microwave-assisted nucleophilic aromatic substitution para to the electron-withdrawing cyano group, an additional investigation was initiated. Thus, the microwave-promoted aryl amination was carried out under identical conditions in the absence of Pd catalyst and PPFA ligand with piperidine as the amine component. As previously observed, these conditions provided solely the recovered starting aryl bromide, demonstrating the requirement for Pd in the reaction and ruling out involvement of a potentially competing mechanism under these conditions.

Because the conditions employed in our studies with both conventional and microwave-assisted reactions were otherwise identical (temperature, concentration, pressure, reaction vessel), these results suggest an opportunity to consider historically debated potential nonthermal effects of microwave reactions.[12] One possible factor contributing to enhanced yields for non-cyano-(5- or 8-)-bromoquinoline substrates relates to the potential for catalyst degradation over the extended reaction times required for conventional methods, which are obviated under the rapid microwave protocol. This is consistent with the observed findings where reduced arenes comprise the majority of the remainder of the mass balance of product, though contribution from other microwave-specific effects cannot be definitively ruled out.

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[8] Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240−7241.

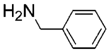
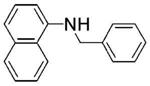
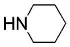
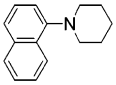
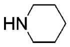
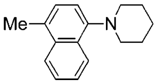
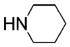
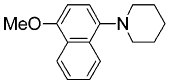
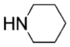
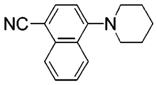
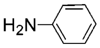
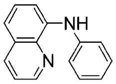
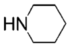
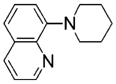
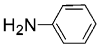
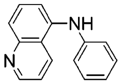
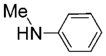
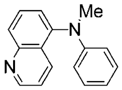
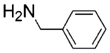
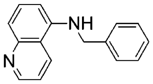
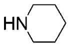
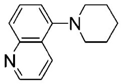
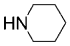
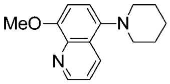
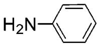
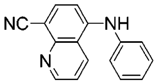
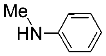
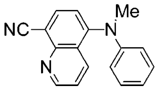
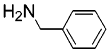
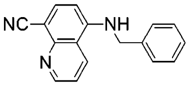
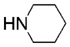
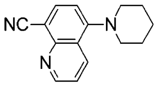
[9] Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157.

[10] Marcoux, J.-F.; Wagaw, S.; Buchwald, S. W. *J. Org. Chem.* **1997**, *62*, 1568−1569.

[11] Typical procedure. All aryl amination reactions were conducted in Personal Chemistry 2 mL Smith Process thick-walled borosilicate glass conical vials that were degassed, filled with argon, and sealed with a cap containing a PTFE septum. Aryl bromides were either obtained commercially or prepared by known methods. $Pd_2(dba)_3$, (*S*)-(*R*)-PPFA, NaO*t*-Bu, aniline, benzylamine, *N*-methylaniline, and piperidine were obtained from Aldrich Chemical Co. and were used as received. Anhydrous toluene was purchased from VWR. Yields reported are for isolated compounds of greater than 98% purity as determined by HPLC. All reactions were run at an approximately 0.25 M aryl bromide concentration. Standard conditions combined 2 mol % $Pd_2(dba)_3$ with 6 mol % PPFA in 0.50 mL of toluene under argon with addition of aryl bromide (1.0 equiv) and then amine (1.2 equiv), followed by NaO*t*-Bu (1.5 equiv). The system was degassed and back-filled with argon. In the conventional method, the reaction mixture was stirred in an oil bath at 120 °C for a maximum time of 24 h, and most reactions proceeded to completion (consumption of aryl bromide) in this period. Microwave reactions were carried out in a Personal Chemistry Emrys Optimizer model microwave reactor. Typical reactions were run using 150 W of power for the initial 250−400 s until the temperature reached 120 °C as measured with an IR probe, and this temperature was then maintained using approximately 100 W of power until the final experiment time reached 900 sec. In each method, after completion of the reaction time, the mixture was diluted with EtOAc and filtered. The volatiles were removed by rotary evaporation, and the resulting residue was purified using standard silica gel flash chromatography with hexanes/EtOAc as eluents.

[12] (a) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863−1866. (b) Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589−3590. (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223. (d) Strauss, R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (e) Raner, K. D.; Strauss, C. R.; Vyskoc, F.; Mokbel, L. *J. Org. Chem.* **1993**, *58*, 950−953. (f) Pagnotta, M.; Pooley, C. L. F.; Gurland, B.; Choi, M. *J. Phys. Org. Chem.* **1993**, *6*, 407−411.

Table 1. Pd-Catalyzed Amination of 1-Bromonaphthalenes and 5- and 8-Bromoquinolines under Standard and Microwave Conditions

entry	amine	X	Y	R	product	yield (%)[a] microwave[b]	yield (%)[a] standard[c]
1		CH	CH	H		80	78
2		CH	CH	H		85	83
3		CH	CH	Me		62	64
4		CH	CH	OMe		47	45
5		CH	CH	CN		62	57
6		N	CH	H		69	58
7		N	CH	H		83	60
8		CH	N	H		83	68
9		CH	N	H		67	47
10		CH	N	H		50	40
11		CH	N	H		63	53
12		CH	N	OMe		46	4
13		CH	N	CN		92	<2
14		CH	N	CN		79	0
15		CH	N	CN		86	<2
16		CH	N	CN		72	0

[a] Isolated yields of compounds determined to be of >98% purity by ^{1}H NMR and LC/MS. [b] Temperature = 120 °C, 10 min, microwave. [c] Temperature = 120 °C, 24 h.

In contrast, in the case of the strongly dipolar 5-bromo-8-methoxyquinoline and 5-bromo-8-cyanoquinoline, where no Pd insertion or subsequent product formation was observed under conventional heating conditions, this argument is not persuasive. It has been previously observed that certain conditions and reaction types are more readily subject to potential nonthermal effects of microwave heating of chemical reactions. It has been specifically noted that in the case of nonpolar solvents such as toluene, which are essentially transparent to microwave energy, that energy transfer may occur from highly polar reactants (such as the methoxy- and cyanoquinoline substrates), which may differ between conventional and microwave heating.[13] This phenomenon is thought to be particularly true in bimolecular reactions where a significant dipole develops in the transition state,[12c] such as would be expected in the present Buchwald/Hartwig aryl amination chemistry. The nature of the observed results with the reaction type, solvent, and substrates in our studies are consistent with those where favorable nonthermal effects have been most readily demonsrated and may lend further support to the potential of microwave reactions to expand the scope of Pd-catalyzed transformations. In all cases studied, the present results demonstrate an efficient means of rapidly generating naphthyl and quinolinylamines with reasonably wide tolerance for variation in functional group substitution. Further application of microwave technology to Pd-catalyzed *N*-aryl bond construction is under investigation in these laboratories.

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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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(13) (a) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363−2366. (b) Bogdal, D. *Monogr. Politech. Kirakow* **1999**, *248*, 1−134; *Chem Abst.* **2000**, *133*, 58369.