Palladium-Catalyzed Couplings of Heteroaryl Amines with Aryl Halides Using Sodium Phenolate as the Stoichiometric Base

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Abstract: Heteroaryl amines are efficiently coupled (in two hours) to aryl halides with catalytic $Pd_2(dba)_3$ and Xantphos to provide the corresponding biaryl amines under microwave and standard thermal conditions. The use of organic-soluble sodium phenolate (NaOPh) as the stoichiometric base promotes facile coupling of a variety of substrates in excellent yields.

Key words: palladium-catalyzed, sodium phenolate, C–N bond-forming, biaryl amine, heteroaryl amine

The Pd-catalyzed coupling of amines with aryl halides has become an important tool in the organic chemist's arsenal. As our knowledge of palladium chemistry increases, more of the shortcomings of classic Buchwald- and Hartwig-type reactions are being addressed. In particular, the coupling of heteroaryl amines with aryl halides has been problematic. Biaryl amines containing at least one heteroaromatic group have been used as cardiac stimulants, diuretics, for the inhibition of cyclin-dependant kinases, and for the treatment of cognition disorders.[1] A recent survey of the literature found few articles which demonstrate successful couplings of heteroaryl amines.[2–7] Typically, papers report C–N couplings which need to be tailored to individual substrates by changing the base, base equivalents, mol% of catalyst, ligand, mol% of ligand (Pd/L ratio), solvent, reaction concentration, equivalents of amine used, and additives (H_2O).[3] Others show limited substrate scope while suffering from long reaction times (15–23 h).[2,5,7] Improvements in the reaction rate by the use of microwave irradiation, as reported by Tundel et al., may be accomplished with nonaflates as coupling partners.[6] However, the use of nonaflates require an extra synthetic step since they are not readily available and only a few examples of coupling to heteroaryl amines were reported.[8]

The standard inorganic bases (Cs_2CO_3, Na_2CO_3, K_2CO_3, NaO*t*-Bu, K_3PO_4) used in palladium coupling chemistry are also a concern due to their limited solubility in typical organic reaction solvents. Sodium *tert*-butoxide in particular, although commonly used to increase reaction rate, is well known to have limited functional-group tolerance.[9] It was our goal to investigate these issues and develop a convenient and general method for the Pd-catalyzed C–N bond-forming reactions between heteroaryl amines and aryl halides without excessive tailoring of reaction parameters.

To establish the ideal reaction conditions, a limited study was performed employing five ligands (Figure 1) commonly used in Pd-catalyzed coupling reactions. We chose 2-aminothiazole as our intial coupling partner with 4-methylbromobenzene. Yin and coworkers have previously reported the difficulty of coupling 2-aminothiazoles/2-aminobenzothiazoles with aryl halides, which required up to 5 mol% of Pd catalyst and in some cases NaO*t*-Bu as the base.[3] Initially, we attempted standard C–N bond-forming thermal conditions [Cs_2CO_3, toluene/*t*-BuOH (5:1), 100–105 °C, 16–60 h] using either $Pd_2(dba)_3$ or $Pd(OAc)_2$ as the catalyst source and screened five different ligands [(*S*)-(–)-BINAP (**1**), Xantphos (**2**), X-Phos (**3**), 2-(di-*tert*-butylphosphino)biphenyl (**4**) and 2-(dicyclohexylphosphino)biphenyl (**5**)] to compare both monodentate and bidentate ligands. We did not have success in obtaining any appreciable amount of desired coupled product, likely due to our choice of base and the unreactive nature of our heteroaryl amine toward Pd-catalyzed coupling.

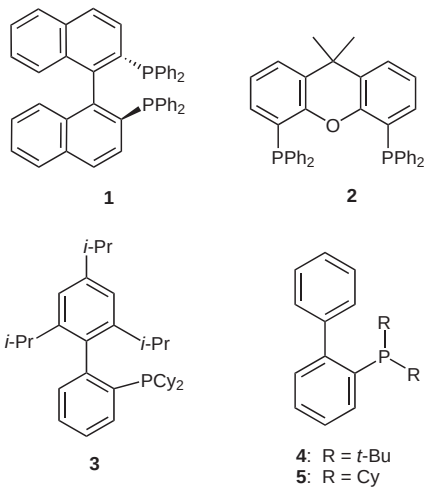

Figure 1 Ligands

We next attempted to couple 2-aminothiazole with an activated arylhalide, 4-bromobenzonitrile, using the microwave at 150–180 °C. For this study, we focused on comparing only three ligands [(*S*)-(–)-BINAP, Xantphos, X-Phos] in conjunction with $Pd_2(dba)_3$ as shown in Table 1. We also screened a variety of inorganic and

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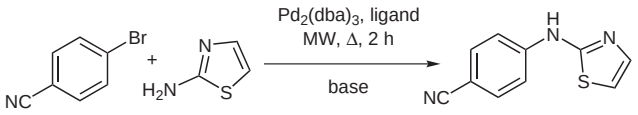
Table 1 Optimization of Conditions for the C–N Coupling of 2-Aminothiazole with 4-Bromobenzonitrile[a]



Entry	Base	Ligand	Solvent	Temp (°C)	Yield (%)[b]
1	DBU[c]	X-Phos	toluene	150	≤ 2[d]
2	MTBD[c]	Xantphos	toluene	175	≤ 2[d]
3	Cs_2CO_3[c]	X-Phos	toluene	150	≤ 2[d]
4	Na_2CO_3	Xantphos	dioxane	150	≤ 2[d]
5	K_3PO_4	Xantphos	dioxane	150	10[e]
6	K_3PO_4	Xantphos	dioxane	180	31[f]
7	NaOPh	(*S*)-(–)-BINAP	dioxane	170	9[f]
8	NaOPh	X-Phos	dioxane	170	≤ 2[f]
9	NaOPh	Xantphos	dioxane	170	53[f]

[a] Reaction conditions: 1.1 mmol of 4-bromobenzonitrile, 1.3 equiv of 2-aminothiazole, 1.4–1.5 equiv of base, 2.5 mol% Pd = 1.25 mol% $Pd_2(dba)_3$, 3–6 mol% of ligand, 6.5 mL of solvent, microwave.
[b] Yield estimated from HPLC results.
[c] Used 2.5 equiv of base.
[d] Reaction run for 30 min.
[e] Reaction run for 60 min.
[f] Reaction run for 90 min.

organic bases (K_3PO_4, Na_2CO_3, Cs_2CO_3, DBU, MTBD) found in the literature for Pd-catalyzed aryl amination reactions as well as sodium phenolate (NaOPh). The reactions were assayed by HPLC after 30–90 minutes to evaluate their progress. An earlier report indicated successful couplings of a few heteroaryl amines to aryl nonaflates using organic-soluble amine bases such as DBU {1,8-diazabicyclo[5.4.0]undec-7-ene} and MTBD {7-methyl-1,5,7-triazabicyclo [4.4.0]dec-5-ene} under microwave conditions.[6] We found little success in obtaining the desired coupled product under similar conditions (entries 1 and 2). Likewise, using the mild inorganic bases such as Cs_2CO_3 and Na_2CO_3 (entries 3 and 4) also proved disappointing, even when changing to a more polar organic solvent like dioxane to help solubilize the stoichiometric base. Employing a stronger base such as K_3PO_4 in combination with Xantphos (entries 5 and 6) did provide the requisite product, with a noticeable improvement in yield at higher temperatures and longer reaction times. Interestingly, after testing the organic-soluble sodium phenolate base (entries 7–9), we obtained the highest yield of the desired biaryl product when Xantphos was used as a ligand (entry 9). In comparison, neither (*S*)-(–)-BINAP nor X-Phos (entries 7 and 8) performed as well when used in concert with sodium phenolate.

Despite its high solubility in dioxane, a search in the recent literature showed that NaOPh was not widely used in Pd-catalyzed C–N bond-forming reactions.[10,11] It also has the advantage of being readily removed upon basic work-up, unlike the more commonly used soluble organic amine bases (DBU, MTBD, Et_3N, *i*-Pr_2NEt).

Table 2 Microwave-Mediated Pd-Catalyzed Couplings of Heteroaryl Amines with Aryl Halides Using NaOPh[a,b]

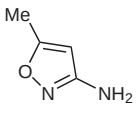
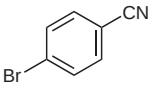
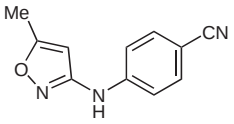
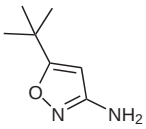
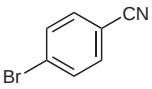
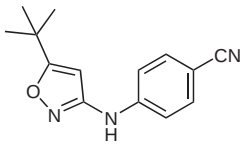
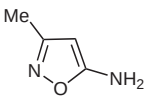
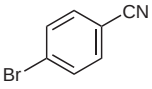
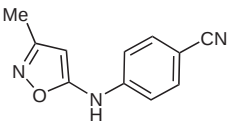
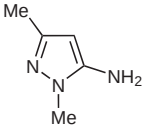
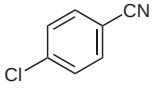
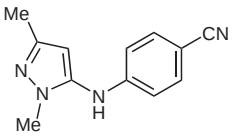
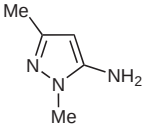
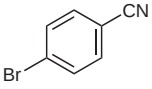
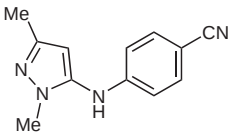
Entry	Amine	Aryl halide	Product	Yield (%)[c]
1				82
2				86
3				75
4				81
5				91

Table 2 Microwave-Mediated Pd-Catalyzed Couplings of Heteroaryl Amines with Aryl Halides Using NaOPh[a,b] (continued)

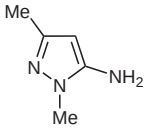
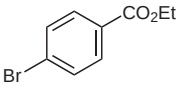
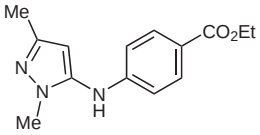
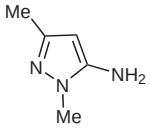
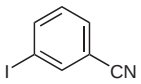
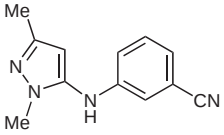
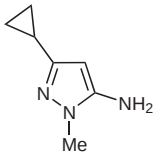
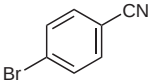
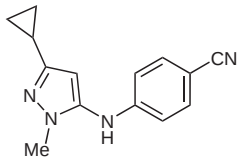
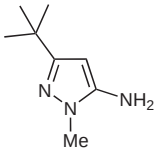
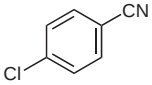
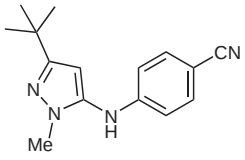
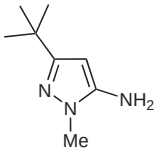
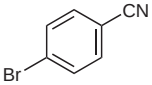
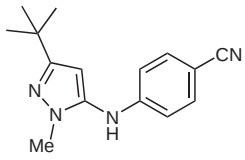
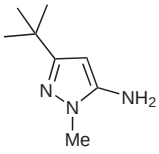
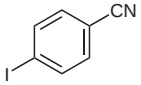
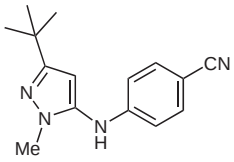
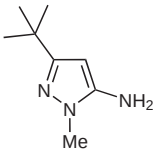
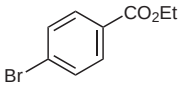
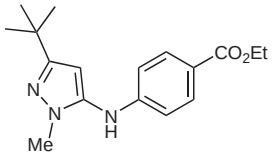
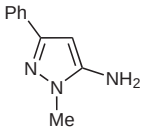
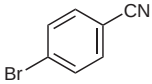
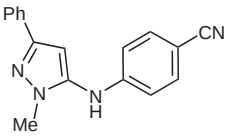
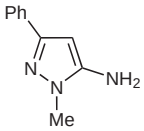
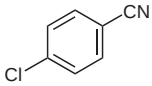
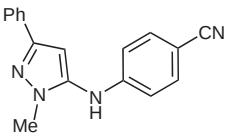
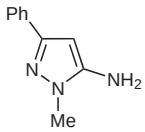
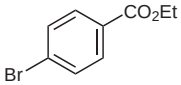
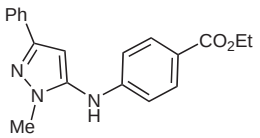
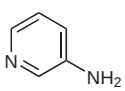
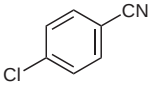
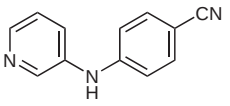
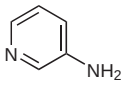
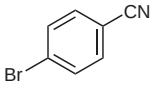
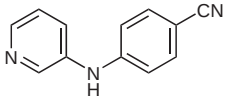
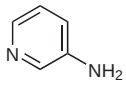
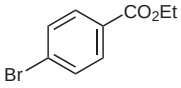
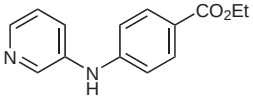
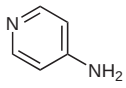
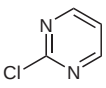
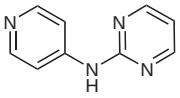
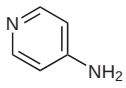
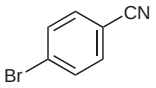
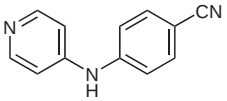
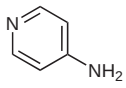
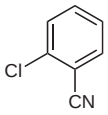
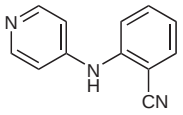
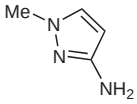
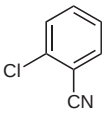
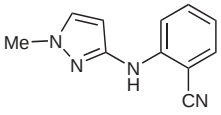
Entry	Amine	Aryl halide	Product	Yield (%)[c]
6				73
7				89
8				90
9				80
10				91
11				74
12				73 (75)[d]
13				93
14				68
15				71
16				68

Table 2 Microwave-Mediated Pd-Catalyzed Couplings of Heteroaryl Amines with Aryl Halides Using NaOPh[a,b] (continued)

Entry	Amine	Aryl halide	Product	Yield (%)[c]
17				99 (94)[d]
18				81 (78)[e]
19				74
20				83
21				69 (50)[f]
22				(58)[d]

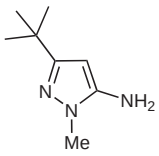
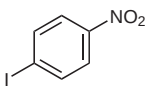
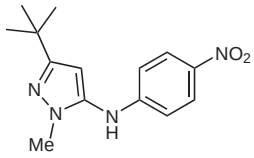
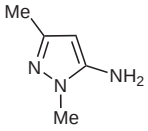
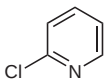
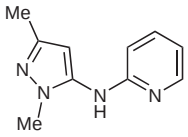
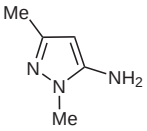
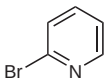
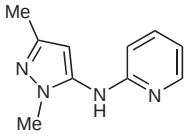
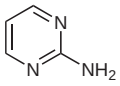
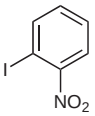
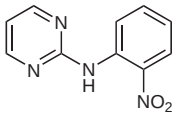
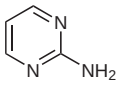
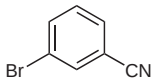
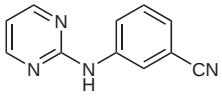
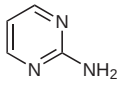
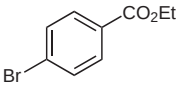
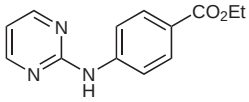
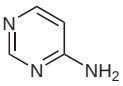
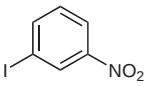
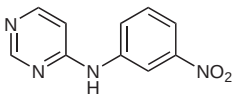
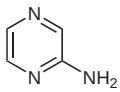
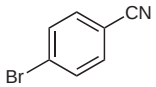
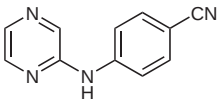
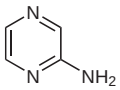
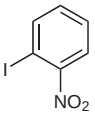
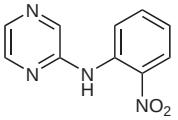
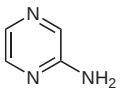
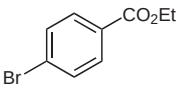
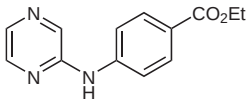
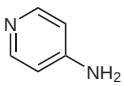
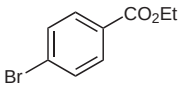
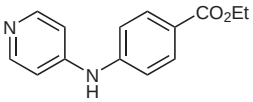
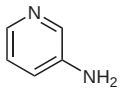
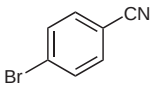
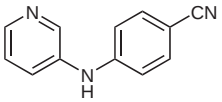
[a] Reaction conditions: 1.1 mmol of aryl halide, 1.1 equiv of heteroaryl amine, 2.5 mol% Pd = 1.25 mol% of $Pd_2(dba)_3$, 3.0 mol% of Xantphos (L/Pd = 1.2), 1.5 equiv of NaOPh, dioxane, 170 °C, 2 h, microwave.
[b] Conditions were not optimized for reaction temperature, time, nor catalyst loading.
[c] Isolated yield, yields in parentheses indicate lower reaction temperatures.
[d] Reaction run for 1 h at 120 °C.
[e] Reaction run for 30 min at 120 °C.
[f] Reaction run for 2 h at 120 °C.

Employing our best conditions, we evaluated a series of heteroaryl amines (Table 2) with respect to their ability to couple with a variety of activated aryl halides.[12] A wide assortment of five- and six-membered heteroaryl amines were readily coupled to substituted aryl halides in good to excellent yield (68–99%) at 170 °C. The method was general for various aminoisoxazoles (entries 1–3), aminopyrazoles (entries 4–15) and aminopyridines (entries 16–21). In a direct comparison of halide coupling partners, we tested the reaction between 3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-amine with 4-halobenzonitriles (entries 9–11) and discovered they all went to completion within two hours. The 4-bromobenzonitrile reactant gave a superior yield (91%) to the corresponding 4-chloro and 4-iodo analogues. The couplings were successful with *para*-, *meta*-, and *ortho*-substituted aryl halides. We also tested a handful of examples (entries 12, 17, 18, 21, and 22) at a lower temperature (120 °C) and shorter reaction times (0.5–2 h) in the microwave. In general, those reactions performed equally well, with the exception of *ortho*-chlorobenzonitrile coupling to 4-aminopyridine (entry 21) and 1-methyl-1*H*-pyrazol-3-amine (entry 22) to give the corresponding products in less than 60% yield.

Finally, we also tested our method under standard thermal conditions at 80–120 °C (Table 3) for a reaction time of two hours.[13] Various heteroaryl amines including aminopyrazole, aminopyrimidine, aminopyrazines, and aminopyridines were coupled to phenyl- and pyridinyl halides in 41–99% yield. We observed a substantial improvement in yield when comparing 2-chloropyridine (entry 2) and 2-bromopyridine (entry 3) as coupling partners with the same heteroaryl amine. In general, the yields were good to excellent, but some reactions did require higher temperature (120 °C) to go to completion (entries 6, 7, 8, 10, and 11). Also, we were pleased to note that the potential formation of a phenoxide-coupled byproduct was not realized to any appreciable extent.[14] In comparison, we believe that microwave assistance is not necessary for this reaction to perform well.

In conclusion, we have developed a general set of thermal conditions, which provide an efficient method for the Pd-catalyzed C–N coupling of heteroaryl amines with arylchlorides, arylbromides, aryliodides, halopyrimidines, and halopyridines in short reaction times (2 h). We did not observe a significant difference in microwave versus thermal reaction conditions, and several reactions tested at lower temperature (80 °C) also worked well. The use of NaOPh as the stoichiometric base improved the product

Table 3 Pd-Catalyzed Couplings Under Thermal Conditions[a]

Entry	Amine	Halide	Product	Yield (%)[b]
1				90
2				41
3				81
4				96
5				71
6				75[c]
7				83[c]
8				87[c]
9				99
10				81[c]
11				79[c]
12				92

[a] Reaction conditions: 1.1 mmol of aryl halide, 1.1 equiv of heteroaryl amine, 2.5 mol% Pd = 1.25 mol% of $Pd_2(dba)_3$, 3.0 mol% Xantphos (L/Pd = 1.2), 1.5 equiv of NaOPh, dioxane, 2 h, 80 °C.
[b] Isolated yield.
[c] Reaction run at 120 °C for 2 h.

yield, enabled tolerance of sensitive functional groups such as nitrile, nitro, and ester moieties, and allowed for much shorter reaction times than previously reported. It also has the added advantage of being easily removed from the amine product by basic work-up techniques.

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(12) All microwave reactions were conducted in a 2–5 mL Biotage Microwave Vial Kit with sealable cap (code no. 351521) using a magnetic stirbar. Microwave heating was performed with a single-mode cavity Emrys SmithCreator.

(13) **General Procedure for Compounds Shown in Table 3** A 2–5 mL Biotage microwave vial was charged with the aryl halide (1.10 mmol), sodium phenolate (191 mg, 1.65 mmol), $Pd_2(dba)_3$ (12.6 mg, 0.0137 mmol, 2.5 mol% of Pd), and Xantphos (19.1 mg, 0.0330 mmol, 3.0 mol%) followed by degassed 1,4-dioxane (6.50 mL). The mixture was stirred while degassing with argon for 1 min. The heteroaryl amine (1.21 mmol) was added last, the vial was immediately capped and sealed, then heated at 80 °C for 2 h. After cooling to r.t., the mixture was diluted with EtOAc (400 mL), washed with 1 N aq NaOH (3 × 100 mL) and brine (100 mL), dried over anhyd Na_2SO_4, filtered, and the solvent removed under vacuum. The resulting residue was purified over silica gel (12 g, hexanes–EtOAc) and the product was freeze-dried from MeCN–H_2O to provide the pure product.

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