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Pd-catalyzed amination in a polar medium: rate enhancement, convenient product isolation, and tandem Suzuki cross-coupling

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Abstract—A catalytic system utilizing a polar medium for the Pd-catalyzed amination reaction is described. This system utilizes $Pd[P(t\text{-}Bu)_3]_2$ and a weak base and displays a modest rate enhancement compared to similar existing protocols. Significant functional group tolerance is observed in both amine and aryl halide, including carboxylates, carbamates, nitriles, amides, and esters. Product isolation after filtration and automated reverse-phase chromatography readily permits parallel synthetic approaches if desired.

The palladium-catalyzed amination reaction has become an integral and valuable transformation within the pharmaceutical industry. Ongoing advances[1,2] for this process since the original landmark contributions utilizing amines with aryl bromides and iodides reported by Louie and Hartwig[3] and Wolfe and Buchwald[4] continue to allow milder conditions and the use of more diverse substrates. More specifically, catalytic conditions employing alkylmono-phosphines[5–7] or heterocyclic carbene ligands,[8,9] many now widely available, allow the amination of aryl chlorides. More recently ligand and reaction conditions have been optimized which greatly increase the scope for the amination of aryl tosylates[10] and allow room temperature coupling of unactivated aryl tosylates.[11]

Current C–N bond-forming methods which tolerate functionalized substrates typically utilize ether, *t*-BuOH, arene, or biphasic solvent systems which are incompatible with direct reverse-phase purification methods.[10,12–14] As part of a medicinal chemistry effort to develop catalytic amination conditions more suitable for both polar substrates and parallel synthetic strategies amenable to direct reverse-phase purification we found that the use of the commercially available $Pd[P(t\text{-}Bu)_3]_2$ (**1**) pre-catalyst in conjunction with a weak base and polar medium was highly effective toward the palladium mediated couplings of aryl bromides and aryl chlorides with amines.

The use of a polar medium in combination with a weak base and a sterically hindered phosphine was recently studied in detail using a high-throughput screening assay.[15] Although yields of coupled product using aqueous DMA and K_3PO_4 were not as high as those in less polar solvent mixtures, product yields using sterically hindered alkyl mono-phosphines were moderate. This observation, in addition to a recent study by Roy and Hartwig[11] demonstrating a rare medium rate enhancement for the oxidative addition of aryl tosylates, encouraged us to further evaluate the use of a polar medium-mild base combination in order to develop an optimal protocol for rapid parallel synthesis and purification.

A number of reaction parameters were investigated utilizing morpholine and 4-bromoanisole as coupling partners; beginning with a brief re-evaluation of the effect of catalyst structure on product yield. Initial studies were conducted with 2.0 equiv anhydrous powdered K_3PO_4 as base and DMF as solvent at elevated temperatures and included **1**, the Pd(I)-dimer $[P(t\text{-}Bu)_3PdBr]_2$, *rac*-BINAP, Xantphos, biphenyl-2-yl(di-*tert*-butyl)-phosphine, and a number of commercially available Solvias' Josiphos ligands using one or more Pd sources. In short,

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the results of these studies revealed that **1** was superior to all other ligand–metal combinations tested (>80% conversion versus <15% for all others). More significant and somewhat unexpected, was the observation that DMA and DMF were consistently the solvents that gave reaction rates 2-fold faster than those conducted in arene or ether solvents which are traditionally preferred for the Buchwald–Hartwig amination. Indeed, time–course experiments conducted in parallel (Fig. 1) comparing DMA versus toluene showed the relative rates for product formation under the optimal conditions were faster in DMA. After 5 h complete conversion occurred in DMA, whereas in toluene starting material remained even after 20 h. A second experiment comparing DMA and toluene was conducted with 4-chlorotoluene and morpholine (Fig. 1). Once again the rate of product formation was significantly faster in the more polar medium indicating the rate enhancement was not limited to aryl bromides.

In addition to K_3PO_4, Cs_2CO_3 is also effective as a base; however, Cs_2CO_3 tended to generate heterogeneous solutions that were more difficult to filter prior to reverse-phase purification. Attempts to use either biphasic or monophasic aqueous DMF with carbonate or phosphate solutions proved ineffective and tended to generate arene. The use of $[HP(t\text{-}Bu)_3][BF_4]$[16] in combination with either $Pd(OAc)_2$, $PdCl_2$, or Pd_2dba_3 in the place of **1** gave comparable yields of (4-methylphenyl)morpholine.

Table 1 summarizes the results from reactions using a variety of aryl bromide substrates under our optimized conditions, which consisted of 2.5 mol% of **1** as catalyst, K_3PO_4 as base, and DMA as solvent.[17] The examples shown were performed in parallel. The crude reactions were simply filtered using a nylon or glass frit and the resulting eluent purified directly by reverse-phase chromatography. A number of trends in Table 1 with regard to substrate scope are similar to those reported for this catalyst using toluene and NaO-*t*Bu.[5] For example, anilines and cyclic secondary amines were among the more effective amine substrate partners and gave conversions

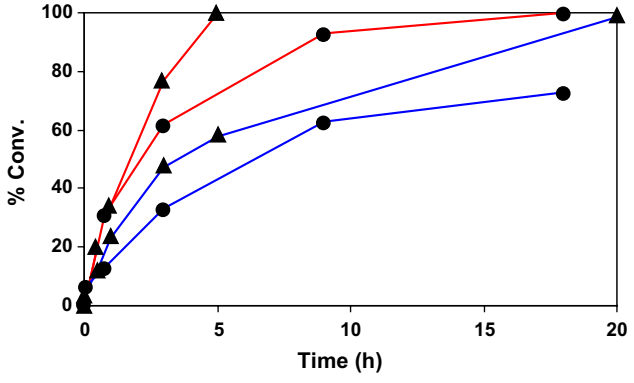


Figure 1. Comparison of DMA (red) versus toluene (blue) as solvent in the coupling of 4-bromoanisole and morpholine (80 °C, ▲) and 4-chlorotoluene and morpholine (100 °C, ●): 2.5 mol% **1**, 2 equiv K_3PO_4, 1.0 M substrate concentration.

>90% when using 4-bromotoluene. In contrast to previous studies[5] simple acyclic secondary amines were poor substrates (entry 6) and simple primary amines gave low to moderate yields of coupled products (entries 4 and 11). Remarkably, for couplings with primary amines no diarylated material was detected when using 1.5 equiv of amine. In the case of morpholine and 4-bromoanisole (entry 8) the reaction occurred within 1 h using 2.5 mol% of **1**. The yield of the product from the coupling of morpholine and 2-bromoanisole, a sterically and electronically demanding aryl bromide, occurred in only 11% yield. However, both aniline and 2,6-dimethylaniline underwent coupling with 2-bromoanisole smoothly giving >80% conversion and good isolated yields (entries 10 and 12).

In a few cases (entries 1, 4, 6, 8, and 11) the isolated yields via reverse-phase purification were unexpectedly low due to poor retention characteristics for those particular low molecular weight compounds.[18] In these instances the reactions were repeated on a 1 mmol scale and the product was purified on silica gel by flash chromatography.

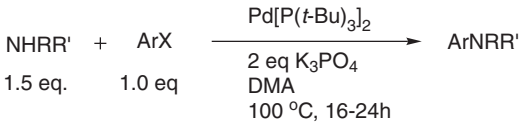
The use of K_3PO_4 in arene or ether solvents has previously been shown to permit base-sensitive functionality to be tolerant in the amination reaction;[5,19] despite this advance in substrate scope carboxyl groups and amides have until recently remained problematic.[20] By using **1** and K_3PO_4 in DMA in the coupling reaction of 4-amino-acetanilide with 4-bromotoluene (entry 7, Table 1) product was obtained in 58% isolated yield.

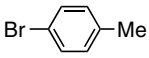
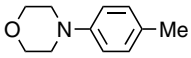
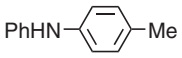
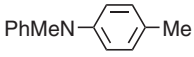
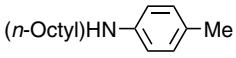
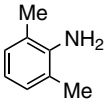
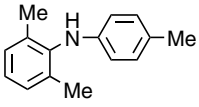
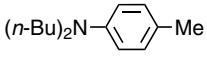
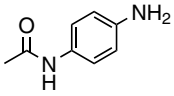
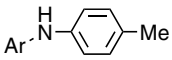
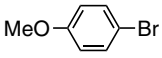
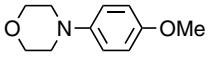
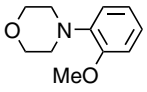
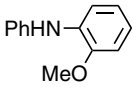
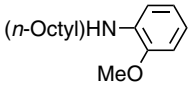
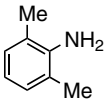
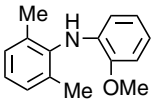
Table 2 summarizes examples which contain additional functionality and polarity. In addition to the secondary amide as exemplified in Table 1, carbamate (entry 1), ester (entries 2–7), and carboxylate functionalities (entry 5) are tolerant to these conditions and give isolated products in yields ranging from 35% to 62%. Interestingly, the use of a primary alkyl amine bearing a β-*t*-butylester (entry 3) was moderately effective in the coupling with *p*-bromobenzonitrile[21] to give, in 57% isolated yield, the *N*-arylated product, which is a useful intermediate toward the synthesis of *N*-arylated β-lactams.

A variety of activated heteroaromatic halides were evaluated and found to generate products with varying levels of success. For example, 2,6-dichloropyridine (entry 4) coupled with 3-ethoxycarboxyl-piperidine to give pure product in 55% isolated yield. Reaction with 2-chloropyrazine (entry 7) gave a low yield of isolated product. Lastly, unprotected 6-bromopurine (entry 6), when exposed to the polar amination conditions gave coupled product in moderate isolated yield.

The rate enhancement in a polar medium using a weak base led us to propose that perhaps other cross-couplings conducive to a polar medium might permit a selective tandem amination–cross-coupling. Such a process would offer an efficient means to access modular compounds using a single catalyst in a one pot fashion. Preliminary efforts toward utilizing the differential aryl

Table 1. Amination of aryl bromides using **1** and polar media[a]



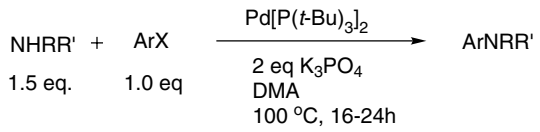
Entry	Aryl bromide	Amine	Product	Yield (%)
1				67[b]
2	$PhNH_2$			68
3	PhNHMe			59
4	*n*-OctylNH_2			36[b]
5				70
6	$(n\text{-Bu})_2NH$			28[b]
7				58
8				95[b]
9				11
10		$PhNH_2$		55
11		*n*-OctylNH_2		63[b]
12				73

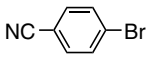
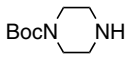
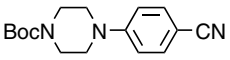
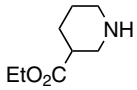
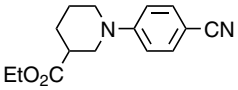
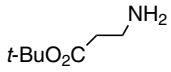
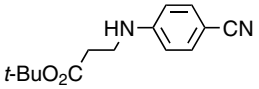
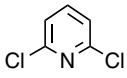
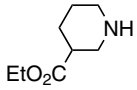
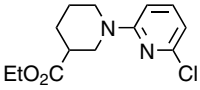
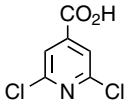
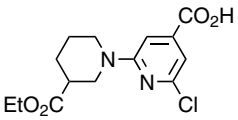
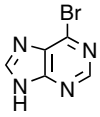
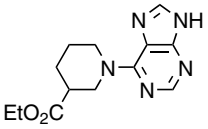
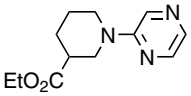
[a] Performed at 2.5 mol% **1**, see Ref. 17 for further details. Isolated yields average of two runs; products >95% pure as judged by ^1H NMR spectroscopy and HPLC.
[b] Performed on 1.0 mmol scale and purified by SiO_2 chromatography.

halide reactivity in a one-pot tandem amination–Suzuki cross-coupling using 1-bromo-3-chlorobenzene were successful giving the *meta* substituted biphenyl **2** in 30% isolated yield after RP-HPLC (Scheme 1). Upon completion of the initial amination step as evident by LC–MS, boronic acid was added and the reaction continued until disappearance of the intermediary product.[22]

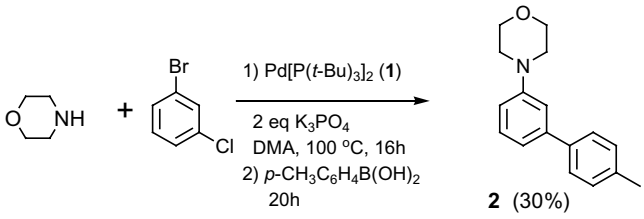
Mechanistically we suggest the observed rate enhancement could perhaps involve solvent coordination at events early in the catalytic cycle leading to an increased

Table 2. Amination of functionalized substrates using **1**[a,17]



Entry	Aryl bromide	Amine	Product	Yield (%)
1				50
2				62
3				57
4				55
5				35
6				55
7				35

[a] Isolated yields average of two runs; products >95% pure as judged by ^{1}H NMR spectroscopy and HPLC.



Scheme 1. One-pot tandem amination–Suzuki coupling.

concentration of either the active catalyst **3a**, or a solvent coordinated complex **3b**, both of which could participate in the subsequent oxidative addition step (Fig. 2). This proposal is consistent with studies involving P(*t*-Bu)$_3$ as a supporting ligand[5,23–25] which have demonstrated that factors, such as pre-catalyst source and ligand stoichiometry, can significantly alter the reaction rate by effecting the concentration of the active palladium-mono-phosphane adduct. Additionally, the observed rate increase could be related to a 'base effect', which has recently been suggested for a BINAP–toluene

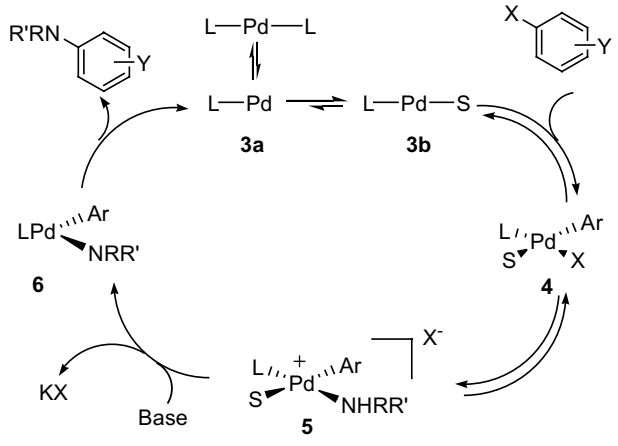


Figure 2. Potential pathways for amination in polar medium.

system studied by Maes and co-workers[26] and Dommisse and co-workers.[14] These studies imply that the solvent is enhancing or increasing a proposed interphase pathway via the generation of **6**. This later proposal is

also consistent with the observation that finely ground K_3PO_4 gives better yields than unground phosphate.

In summary, we have developed a mild and convenient method for the synthesis of functionalized amines using a polar medium which allows products to be purified in a rapid fashion using reverse-phase chromatography. In addition, the polar amination conditions demonstrate the potential for a novel tandem amination–Suzuki cross-coupling. The relative enhancement in catalyst activity for **1** by simply modifying the medium is significant from the standpoint of implications for future high-throughput catalysis screening efforts and our current understanding of existing protocols and substrate scope for other cross-couplings utilizing **1**. Applications of these modified conditions toward other such processes in addition to the use of microwave technology as a means to shorten reaction times and expand substrate scope are currently under investigation.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.095.

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2. Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041.
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