DOI: 10.1002/adsc.200900323

# Aminations of Aryl Bromides in Water at Room Temperature

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Received: May 9, 2009; Published online: July 16, 2009

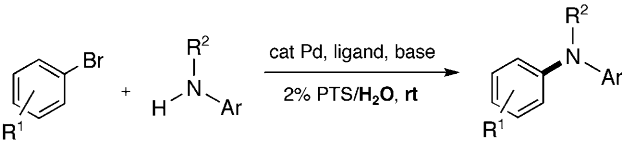
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900323.

**Abstract:** Unsymmetrical di- and triarylamines can be formed under green chemistry conditions, taking advantage of micellar catalysis leading to palladium-catalyzed aminations at ambient temperatures in water as the only medium.

**Keywords:** aminations; amphiphiles; micellar catalysis; surfactants

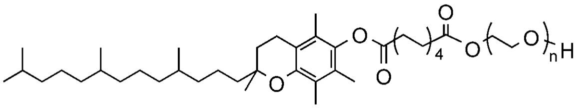
The direct amination of aromatic rings *via* palladium-catalyzed processes could be considered among the most important of the advances in synthesis within the past two decades. A wide range of C–N bond-forming reactions are available; a variety of aryl-,[1] heteroaryl-,[2] and alkylamines[3] can be introduced onto an aromatic or heteroaromatic ring. The nature of the leaving group also varies widely (e.g., halides, pseudo-halides, etc.), made possible by the impressive range of ligands developed that allow for fine-tuning of the reactivity of this group 10 metal.[4] Notwithstanding these impressive advances, there remain opportunities to further this science, in particular concerning the "greening" of existing procedures;[5] that is, finding new inroads to net aminations of aromatic rings that may be environmentally more appealing relative to existing methodologies. One such approach is to eliminate the up-front use of organic solvents, as well as the need to invest energy in the form of heat. A literature precedent for such amination reactions that fulfill these criteria (i.e., reactions in water only, at room temperature) is unknown.

Aminations in water at reflux, on the other hand, have been reported,[6] as have such couplings in toluene/water using a phase-transfer catalyst,[7] and in "water-containing solvent."[8] Very recently, a limited amount of water has been found to assist with Pd catalyst pre-activation, although the catalysis was conducted in *t*-BuOH or dioxane at 110 °C.[9] In this communication we describe the first amination technology for preparing unsymmetrical di- and triarylamines that relies on water exclusively as the medium at ambient temperatures (Scheme 1).



**Scheme 1.** Aminations in water at room temperature.

Prior work has led to the finding that micellar catalysis,[10] based on the commercially available[11] "designer" surfactant PTS (polyoxyethanyl α-tocopheryl sebacate, **1**; Figure 1),[12] allows for several cross-couplings to occur in pure water at room temperature. Thus, low percentages of PTS/$H_2O$ (usually 1–3% by weight) enable olefin metathesis,[13a] Suzuki–Miyaura,[13b] Heck,[13c] and Sonogashira[13d] couplings under these mild and eco-friendly conditions.

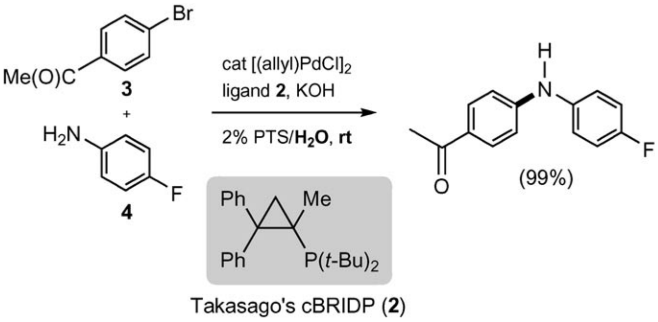


**1**

PTS: composed of α-**T**ocopherol, **S**ebacic acid, and **P**EG-600 (n = *ca.* 13)

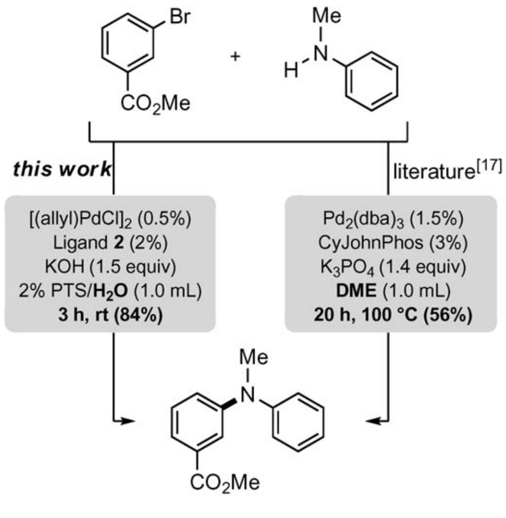
**Figure 1.** PTS: composed of α-**T**ocopherol, **S**ebacic acid, and **P**EG-600 (n = *ca.* 13).

Although PTS accommodates normally water-insoluble substrates within its *ca.* 25 nm nanoreactors formed spontaneously upon dissolution in water, the remaining parameters of (1) source of palladium catalyst; (2) ligand; (3) base; and (4) global reaction concentration, required study. Screening several Pd catalysts[14] indicated that [(π-allyl)PdCl]$_2$ (0.5%), together with Takasago's newly introduced ligand (**2**; 2%)[15] gave the highest level of conversion using partners **3** and **4** (1.2 equiv.) as a representative amination (Scheme 2).[16] KOH was initially determined to be a



**Scheme 2.** Model amination using KOH as base.

satisfactory base.[6,7] Reactions run at 1.0 M in degassed 2% PTS/$H_2O$ afforded good results in several cases examined, as illustrated in Table 1 (entries **A–J**). Importantly, these basic conditions did not lead to any saponification of the diester linkages that characterize PTS. Tertiary amine **5** could be fashioned at room temperature in three hours using these green conditions (water, 2% PTS) in good isolated yield (84%; Scheme 3). By way of comparison, the identical coupling using the most recent literature procedure for such aminations calls for a 20-hour timeframe in hot (100 °C) organic solvent (DME).[17]



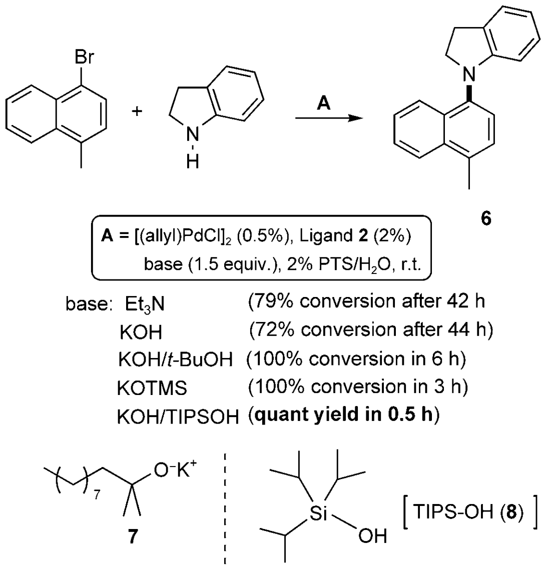
**5**

**Scheme 3.** Comparison of conditions for a known amination.[17]

A simple switch from KOH to *tert*-butoxide[18] or *t*-amylate[19] (either $K^+$ or $Na^+$) had a dramatic impact on the rates of these aminations. At first, this might seem odd, given the leveling effect in water. However, these more lipophilic bases, to the extent present in water, would be expected to have far greater solubility than hydroxide within the lipophilic core of PTS micelles where the couplings are occurring under homogeneous conditions. Hence, as also shown by several examples in Table 1 (entries **I–R**, **T–V**), this single modification provides good results in shorter reaction times. Noteworthy aspects include (a) considerable flexibility as to the nature of the aniline with respect to both steric and electronic effects; (b) both carboalkoxy (entry **K**) and nitro (entry **O**) groups in the amine readily participated; (c) highly electron-rich aryl bromides (entries **M**, **N**) gave an excellent yield of product in each case, seemingly independent of the nature of the amine; (d) 1-naphthylamines (entries **I**, **Q**) could be formed in either direction; (e) amination using 3-aminopyridine (entry **L**) worked well at room temperature; (f) certain activated cases (e.g., a nitrile, entry **T**, and **U**) were uncharacteristically sluggish and required mild heating.

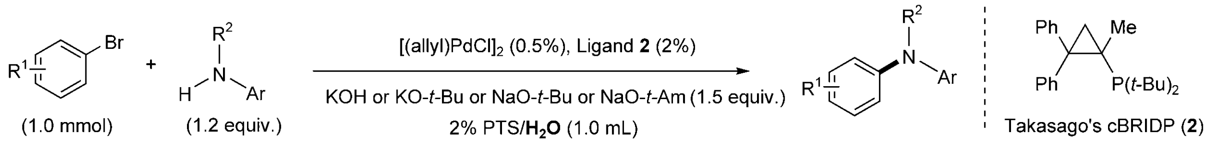
Steric congestion associated with the aryl bromide in the form of di-*ortho*-substitution can be problematic (entry **G**). On the other hand, an aniline bearing substituents at the same 2,6-positions appears to be more forgiving (entry **C**). Selected activated aryl bromides were unexpectedly among the *least* reactive substrates; thus, both *para*-nitrobromobenzene and *para*-bromobenzonitrile required mild heating (*ca.* 45 °C) to reach completion (entries **T**, **U** and **V**). Such was not the case with an acetophenone (entry **E**) or benzophenone (entry **R**) derivative, or a methyl benzoate (Scheme 3) that underwent amination at room temperature.

The case of a 1-bromonaphthalene and indoline (Scheme 4) was used to extend the study on the effect of base on these aminations. While $Et_3N$ was surprisingly ineffective,[20] as was KOH, essentially full conversion could be realized with KOH in the presence of *t*-BuOH (1.5 equiv.) in six hours at room temperature. Also equally effective is the addition of limited

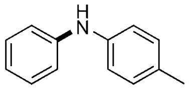


**Scheme 4.** Impact of base on aminations in PTS/$H_2O$.

**Table 1.** Representative aminations of aryl bromides in PTS/$H_2O$ at room temperature.[a,b]

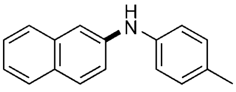


**A**



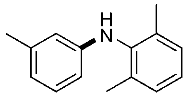
KOH: 85%, 4.5 h, r.t.

**B**



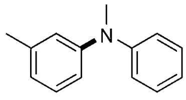
KOH: 84%, 25 h, r.t.
KO-*t*-Bu: 98%, 3 h, r.t.

**C**



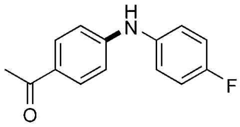
KOH: 81%, 19 h, r.t.

**D**



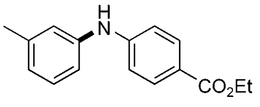
KOH: 98%, 4 h, r.t.

**E**



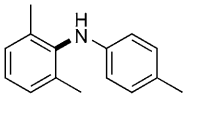
KOH: 99%, 3 h, r.t.

**F**



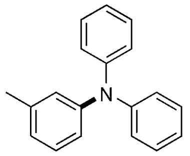
KOH: quant., 3 h, r.t.

**G**



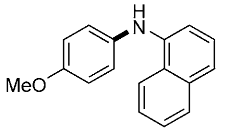
KOH: 31%, 72 h, r.t. to 50 °C

**H**



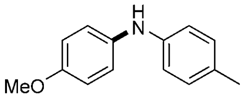
KOH: 83%, 23 h, r.t.

**I**



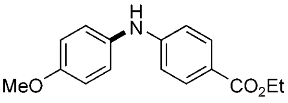
KOH: 90%, 4 h, 40 °C
KO-*t*-Bu : 94%, 3 h, r.t.
NaO-*t*-Bu: quant., 3 h, r.t.
NaO-*t*-Am: 91%, 1.5 h, r.t.

**J**



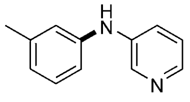
KOH: 93%, 9.0 h, 40 °C
KO-*t*-Bu: 99%, 21.0 h, r.t.
NaO-*t*-Am: 93%, 23 h, r.t.

**K**



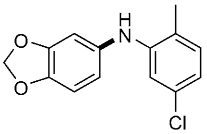
KO-*t*-Bu: 97%, 3 h, r.t.

**L**



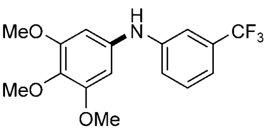
KO-*t*-Bu: 83%, 20 h, r.t.

**M**



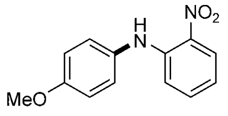
KO-*t*-Bu: quant., 4 h, r.t.

**N**



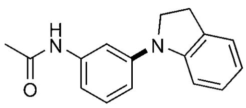
KO-*t*-Bu: quant., 3 h, r.t.

**O**



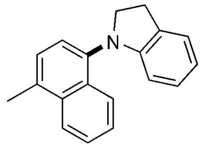
KO-*t*-Bu: quant., 23 h, r.t.

**P**



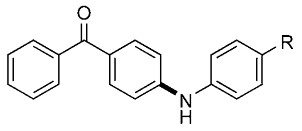
KO-*t*-Bu: 94%, 22 h, r.t.

**Q**



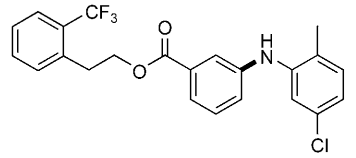
KO-*t*-Bu: 95%, 3 h, r.t.
NaO-*t*-Am: quant., 3 h, r.t.

**R**



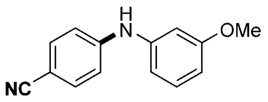
R = F: NaO-*t*-Am: quant., 30 min, r.t.
R = Me: $Et_3N$, 95%, 1 h, r.t.

**S**



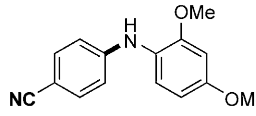
KOH/TIPS-OH: 94%, 6 h, r.t.[c]
KOH/TIPS-OH: 97%, 45 min, r.t.[d]

**T**



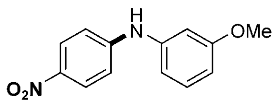
KO-*t*-Bu: 91%, 3.5 h, 40 °C
KOH/TIPS-OH: 97%, 3 h, r.t.[d]

**U**



KO-*t*-Bu: 86%, 50 h, 40 – 50 °C[e]

**V**



KO-*t*-Bu: 76%, 68 h, 40 °C

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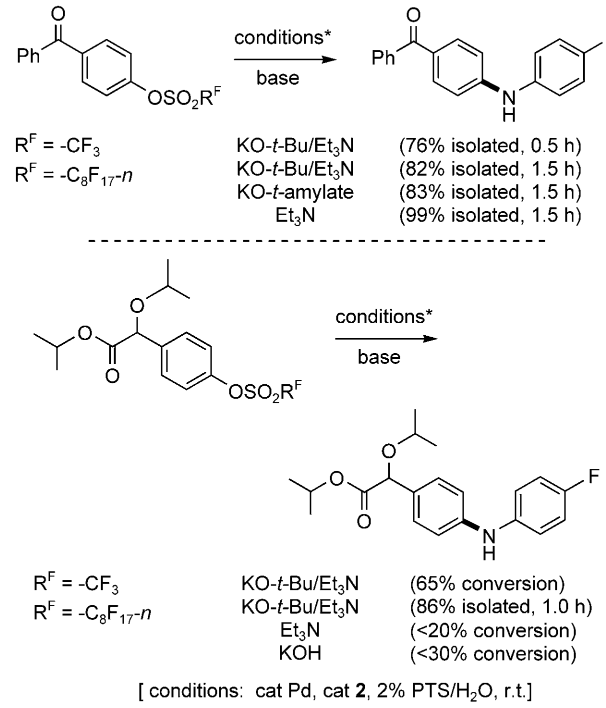
[a] Products were fully characterized by NMR and HR-MS data.
[b] Yields refer to isolated, chromatographically purified materials.
[c] Only 0.5 equiv. TIPS-OH used.
[d] 1.5 equiv. TIPS-OH used.
[e] Josiphos analog (CyPF-*t*-Bu) used as ligand.

amounts of *tert*-butyl alcohol to a reaction mixture containing KOH. Attempts to extend the effect of increased lipophilicity associated with the alkoxide base using the potassium salt **7** of the corresponding 12-carbon tertiary alcohol, did not improve the rate of the same model amination (Scheme 4). Use of commercially sold KOTMS,[21] however, decreased the reaction time with KOH/*t*-BuOH from six to three hours. A more remarkable result was observed upon addition of branched silanol **8**[22] (i.e., TIPS-OH, also an item of commerce):[23] coupling to the desired diarylamine **6** was complete in <30 min. The pronounced effect of this additive, in anion form (Table 1, entries **S**, **T**), appears to be due to its potential as a phase-transfer agent according to Soderquist,[22] in this case shuttling protons between the inside of the micelle (from the amine) to the excess KOH in the water surrounding the nanoparticles.

Lastly, phenolic derivatives as leaving groups were also investigated. Both triflates and less expensive, more lipophilic perfluorooctanesulfonates[24] could be aminated at room temperature in PTS/$H_2O$ using *p*-fluoroaniline as a model amine (Scheme 5). $Et_3N$ as base appeared to minimize competing hydrolysis of either type of sulfonate ester, seen to varying extents in the presence of KO-*t*-Bu alone. Higher yields were obtained with the more highly fluorinated derivative in both cases.



**Scheme 5.** Aminations of fluorosulfonate derivatives.

In summary, a new method has been developed that allows for aminations of aryl bromides with arylamines to be conducted in the absence of both heat and organic solvent. These mild conditions arise in part due to micellar effects based on PTS,[11] an amphiphile that continues to demonstrate considerable applicability to transition metal-catalyzed cross-couplings.[25] Further work on aminations with alkylamines is ongoing, as are studies on related couplings with aryl chlorides.

## Experimental Section

### Representative Procedure A for Aryl Aminations: *N*-(4-Methoxyphenyl)-*p*-toluidine (Table 1, Entry J)

Inside a dry box, to a 5-mL round-bottom flask equipped with a stir bar and fitted with a rubber septum under argon were sequentially charged with $[(\pi\text{-allyl})PdCl]_2$ (2.1 mg, 0.006 mmol), cBRIDP (**2**) (7.6 mg, 0.022 mmol), 95% KO-*t*-Bu (184 mg, 1.56 mmol), and *p*-toluidine (137 mg, 1.23 mmol). Outside the dry box, under a positive flow of argon were added *via* syringe sequentially, *degassed* water (0.8 mL), *degassed* 10 wt% PTS solution (0.2 mL) (to give a *degassed* 2 wt% PTS solution (1.0 mL)), and 4-bromoanisole (130 μL, 1.04 mmol). The milky reaction mixture was stirred under argon at room temperature. After complete consumption of the aryl bromide was observed by GC analysis (21 h), the mixture was diluted with brine and extracted with EtOAc (4×). The combined organic extracts was dried over anhydrous $Na_2SO_4$, filtered, and concentrated by rotary evaporation to give the crude residue. Purification by silica gel chromatography (eluent: gradient from hexanes to 3% EtOAc/hexanes) afforded the titled product as an off-white solid; yield: 218 mg (99%); mp 83–84 °C. $^1H$ NMR (400 MHz, $CDCl_3$) values match previously reported spectra data.[3] The polar PTS is completely separated at the top of the silica column.

## Acknowledgements

*Financial support provided by Zymes, LLC is warmly acknowledged with thanks. We are indebted to Takasago for a generous supply of the cBRIDP ligand (**2**).*

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[14] Other catalysts, including Umicore's CX-32, Pd-PEPPSI-IPr, and $Pd[P(t\text{-}Bu)_3]_2$ were less effective.

[15] K. Suzuki, Y. Hori, T. Kobayashi, *Adv. Synth. Catal.* **2008**, *350*, 652–656. Ligand **2** is stored in a glove box to avoid exposure to oxygen.

[16] Other ligands screened include: X-Phos, Takasago's Cy-cBRIDP, and Takasago's Cy-vBRIDP. None were as effective as **2**.

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[21] Sigma–Aldrich catalog # 324868.

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