

Aqueous Hydroxide as a Base for Palladium-Catalyzed Amination of Aryl Chlorides and Bromides

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The amination of aryl halides in the presence of inexpensive and air-stable alkali metal hydroxide bases and Pd[P(*t*-Bu)₃]₂ as catalyst gave arylamines in high yields. The reactions were conducted with a catalytic amount of cetyltrimethylammonium bromide as phase-transfer agent and either aqueous hydroxide or solid hydroxide in the presence of water. This combination of alkali metal hydroxide base, H₂O, and the ammonium salt performed as well as NaO-*t*-Bu in the amination of *p*-chlorotoluene with dibutylamine. Hydroxide base was suitable for reactions of a wide range of aryl chlorides and bromides with aliphatic and aromatic amines. Some functional groups that were intolerant of *tert*-butoxide base, such as esters, enolizable ketones, nitriles, and nitro groups, were tolerated by the combination of hydroxide base, H₂O, and cetyltrimethylammonium bromide in toluene solvent.

Introduction

Arylamines are found in indole alkaloids,¹ pharmaceuticals,^{2–4} ligands for metal complexes,^{5–7} dendrimer frameworks,^{8,9} and materials with electronic^{10–17} and nonlinear optical properties.^{18–20} The importance of this

class of compound has led to extensive efforts toward the development of palladium catalysts for cross coupling of amines with aryl halides or sulfonates.^{21–29} The amination of aryl halides can now be conducted at room temperature,^{30–33} with high turnover numbers at elevated temperatures,^{31–35} in some cases in air,³⁶ and in other cases in reagent grade solvents without further purification.³¹ The reaction can show high functional group compatibility,^{33,37,38} and can be conducted with aryl

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chlorides,^{30–33,35,36,39–45} which are less expensive and more available than aryl bromides, iodides, and sulfonates.

With these developments, reactions that occur in the presence of inexpensive and air-stable bases have become more important. NaO-*t*-Bu must be stored in the absence of air, is more expensive than inorganic bases, and, in the amination chemistry, leads to a thick, gellike solution when the reactions are conducted under concentrated conditions. Concentrated aqueous NaOH or KOH would be the most desirable base.⁴⁶

In this paper, we show that inexpensive alkali metal hydroxides can serve as stoichiometric base for the palladium-catalyzed cross coupling of various amines with aryl chlorides and bromides with proper choice of catalyst, reaction medium, and phase-transfer catalyst to carry the hydroxide to the organic phase.⁴⁵ Rates and yields for these reactions were comparable to those with NaO-*t*-Bu as base in many cases. In addition, these data show that aqueous hydroxide, under the reaction conditions described here, is more compatible with base-sensitive functional groups than is *tert*-butoxide. In addition, these data demonstrate the remarkable tolerance of late transition metal amido intermediates toward water.^{47–51}

Results and Discussion

Optimization of Reaction Conditions. We evaluated a variety of common inorganic bases for the coupling of the unactivated aryl chloride, *p*-chlorotoluene, with the acyclic secondary amine dibutylamine in the presence of the phase-transfer catalyst, cetyltrimethylammonium bromide (**1**), which would assist in the rate of deprotonation of the intermediate amide by improving the solubility of the base (Table 1). Pd[P(*t*-Bu)₃]₂ was chosen as palladium catalyst because it is commercially available and was expected to be stable toward the hydroxide base and water byproduct. The reactions were conducted at 0.2 M concentration of aryl halide in toluene at 70 °C in the presence of 2 mol % of the palladium and 10 mol % of phase-transfer agent **1**. Yields of the desired *N,N*-dibutyl-*p*-toluidine were evaluated after 3 and 24 h by GC analysis. Reactions in the presence of KOH and NaOH were faster and occurred in higher yield than

TABLE 1. Amination of *p*-Chlorotoluene with Dibutylamine (Screening of Base)^a

| entry | base | GC yield at 3 h, % | GC yield at 24 h, % |
|-----------------|---------------------------------|--------------------|---------------------|
| 1 | KOH | 11 | 42 |
| 2 | NaOH | 4 | 55 |
| 3 | K ₃ PO ₄ | 0 | 6 |
| 4 | Na ₃ PO ₄ | 0 | <1 |
| 5 | K ₂ CO ₃ | 0 | 2 |
| 6 | Na ₂ CO ₃ | 0 | 3 |
| 7 | KF | 0 | <1 |
| 8 ^b | KOH | 15 | 94 |
| 9 ^b | NaOH | 6 | 61 |
| 10 ^c | NaO- <i>t</i> -Bu | 18 | 100 |

^a Reactions were conducted on a 0.1 mmol scale in toluene (0.5 mL) at 70 °C. Aryl chloride:amine:base:Pd[P(*t*-Bu)₃]₂:**1** = 100:110:150:2:10. ^b The reactions were carried out in the presence of 0.15 mmol of water. ^c The reaction was conducted in the absence of **1**.

those with various other inorganic bases we evaluated (entries 1 and 2). K₃PO₄, which is often used for the amination of functionalized aryl halides,^{33,37} was less effective than the alkali metal hydroxides (entry 3). Reactions conducted in the presence of other inorganic bases gave the arylamine product in only 0–3% yields (entries 4–7).

Next, we tested whether a small amount of water would improve the reaction rate because it has improved the efficiency of some reactions conducted with solid-liquid, phase-transfer catalysts.^{52,53} In the presence of added water, reactions conducted with KOH were superior to those conducted with NaOH (entries 8 and 9). Reactions containing 1 molar equiv of H₂O to KOH occurred in the highest yields. The amount of the ammonium salt affected the yield of arylamine. Reactions conducted with 20 mol % of phase-transfer agent **1** occurred at similar rates to those conducted with 10 mol % of **1** after 3 h, but the reaction did not proceed to completion with this larger amount of **1**, and only 23% yield was observed after 24 h. In contrast, reactions in the presence of KOH and 2 mol % of **1** occurred with similar rates and yields to those conducted in the presence of NaO-*t*-Bu. Reactions in the absence of the ammonium salt gave the coupled product in only 23% yield after 24 h, as determined by GC.

Table 2 shows results of the amination with different phase-transfer catalysts. Reactions in the presence of the series of tetraalkylammonium salts showed that both the ammonium cation and the counteranion influenced the rate and yield (entries 1–10). Reactions in the presence of cetyltrimethylammonium cation occurred at the fastest rates and in the highest yields, while those with cetylpyridinium bromide gave the product in only 5% yield. Reactions in the presence of tetraalkylammonium fluoride, chloride, or hydrogensulfate occurred at rates that were similar to those in the presence of **1** during the initial stages of the reaction, but they did not proceed to completion after 24 h, and they gave lower yields. Reactions in the presence of tetrabutylammonium iodide and pentafluorophosphate occurred slowly throughout.

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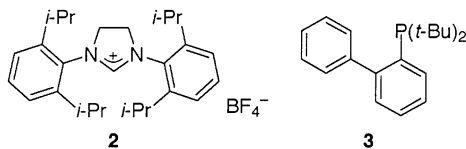
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TABLE 2. Amination of *p*-Chlorotoluene with Dibutylamine (Screening of Phase Transfer Catalyst)^a

| entry | phase transfer catalyst | GC yield at 3 h, % | GC yield at 24 h, % |
|-------|--|--------------------|---------------------|
| 1 | C ₁₆ H ₃₃ NMe ₃ Br | 18 | 100 |
| 2 | (C ₁₈ H ₃₇) ₄ NBr | 8 | 30 |
| 3 | Bu ₄ NBr | 9 | 57 |
| 4 | BnNEt ₃ Br | 4 | 21 |
| 5 | C ₁₆ H ₃₃ NC ₅ H ₅ Br ^b | 1 | 5 |
| 6 | Bu ₄ NF | 10 | 39 |
| 7 | Bu ₄ NCl | 11 | 39 |
| 8 | Bu ₄ NI | 2 | 22 |
| 9 | Bu ₄ NPF ₆ | 1 | 1 |
| 10 | C ₁₆ H ₃₃ NMe ₃ HSO ₄ | 20 | 68 |
| 11 | 15-crown-5 | 2 | 29 |
| 12 | 18-crown-6 | 5 | 27 |

^a Reactions were conducted on a 0.1 mmol scale in toluene (0.5 mL) at 70 °C. Aryl chloride:amine:KOH:H₂O:Pd[P(*t*-Bu)₃]₂:**1** = 100:110:150:150:2:2. ^b Cetylpyridinium bromide.

Crown ethers had no influence on the reactions (entries 11 and 12).



Pd[P(*t*-Bu)₃]₂ is air stable and commercially available,⁵⁵ but it is less active for the amination reactions in the presence of NaO-*t*-Bu than are catalysts generated from a 1:1 mixture of palladium precursor and P(*t*-Bu)₃. Thus, we evaluated catalysts based on a combination of Pd(dba)₂ and P(*t*-Bu)₃,³⁰ carbene precursor **2**,³¹ or biphenyl ligand **3**,^{32,33} in a 1:1 ratio. The reactions conducted in the presence of these catalysts and hydroxide base gave the arylamine in low yield (<30%). To our surprise, reactions conducted with the palladium catalyst generated in situ from Pd(dba)₂ and 2 equiv of P(*t*-Bu)₃, a combination that should generate Pd[P(*t*-Bu)₃]₂,⁵⁵ also showed lower activity than did reactions conducted with catalytic amounts of the isolated Pd[P(*t*-Bu)₃]₂. To determine if dibenzylideneacetone (DBA) deactivated the catalyst we added 2 equiv of DBA to reactions catalyzed by isolated Pd[P(*t*-Bu)₃]₂. Indeed, the reaction rate was much slower, and only 15% yield was observed after 24 h.

Further optimization of the reaction conditions showed that the fastest rates and highest yields were accomplished by performing the amination at 90 °C in the presence of a half-molar amount of **1** to palladium. *N,N*-Dibutyl-*p*-toluidine was obtained in 91% isolated yield from the reaction conducted with 1 mol % of Pd[P(*t*-Bu)₃]₂ and 0.5 mol % of **1** in toluene solvent (1 M concentration) for 21 h. Reaction of these substrates with NaO-*t*-Bu formed a thick suspension or gel as the reaction proceeded to completion. This thick medium is generally observed during aminations of aryl halides conducted under concentrated conditions with NaO-*t*-Bu base. In contrast, no such gel was observed during the reactions in the presence of KOH and H₂O.

Scope of the Amination of Aryl Chlorides in the Presence of KOH. The amination of various aryl

chlorides in the presence of the combination of KOH, H₂O, and a catalytic amount of **1** is summarized in Table 3. Under these conditions, a wide range of aryl halide aminations occurred in high yield. Ortho-substituted aryl chlorides were suitable for aminations conducted with the present base system (entries 7–10). Even the sterically congested combination of *o*-chlorotoluene and diphenylamine gave the corresponding triaryamine in high yield (entry 8). Reactions with electron-rich aryl chlorides conducted with this base system were much slower than reactions of *p*-chlorotoluene. For example, the reactions of *p*-chloroanisole with 1 mol % of palladium produced the *p*-anisidine derivatives in 45–70% yields, even after 48 h. The reaction of *N*-methylaniline with *p*-chloroanisole did, however, give the coupled product in high yield (entry 11).

Dialkylamines, secondary arylamines, and primary arylamines were all suitable substrates for reactions conducted with H₂O, **1**, and KOH. The reaction of an unhindered aryl chloride with aniline gave the diarylamine in high yield. Less than 2% (determined by GC) of the triaryamine was formed as side product (entry 5). Reaction of aniline with *o*-chlorotoluene occurred in high yield without formation of any triaryamine (entry 9). Reaction of hexylamine with *o*-chlorotoluene provided the desired monoarylated product in high yield without formation of the tertiary amine (entry 10). However, the reaction of hexylamine, even when conducted with 2 equiv of amine, formed a mixture of mono- and diarylamine products (entry 6). Unfortunately, benzophenone imine,^{56,57} *tert*-butyl carbamate,³⁰ and indole^{30,45,56,58} did not react with aryl chlorides under these new conditions.

The strong basicity of NaO-*t*-Bu limits the functional group tolerance of the aryl halide amination chemistry conducted with this reagent. Buchwald and Wolfe have shown that reactions conducted with K₃PO₄ or Cs₂CO₃ can allow for the chemistry to be conducted with base-sensitive substrates such as those bearing esters, nitro groups, and enolizable hydrogens.^{33,37,38} Although potassium hydroxide is nearly as basic as NaO-*t*-Bu,⁵⁹ water and **1** can modulate the strength of hydroxide base. In addition, the deprotonation of palladium amine complexes to form palladium amides is unlikely to be turnover-limiting, and a lower concentration of base will, therefore, have less of an effect on the rate of amination than it has on the rate of substrate decomposition. Thus, the combination of KOH, H₂O, and **1** was suitable as base for the amination of a wide range of functionalized aryl chlorides.

The combination of water, **1**, and KOH proved useful for the syntheses of *p*-nitroanilines, some of which can have nonlinear optical^{18–20} and solvatochromic properties.⁶⁰ Reactions of 1-chloro-4-nitrobenzene with various amines rapidly produced the corresponding *N*-substituted *p*-nitroanilines in 93–99% isolated yields (entries 12–16). Substrates bearing methyl esters, enolizable hydrogens, and cyano groups all reacted with anilines in the

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TABLE 3. Amination of Aryl Chlorides in the Presence of KOH, Water, and Catalytic Phase-Transfer Agent **1** and Catalytic Pd[P(*t*-Bu)₃]₂^a

| Entry | Aryl Chloride | Amine | Time | Product (3) | Yield ^b | Entry | Aryl Chloride | Amine | Time | Product (3) | Yield ^b |
|-----------------|---------------|-------------------|------|-------------|--------------------|-----------------|---------------|-------------------|------|-------------|--------------------|
| 1 | | HNBu ₂ | 21 h | | 91% | 13 | | | 3 h | | 94% |
| 2 | | | 24 h | | 90% | 14 | | | 2 h | | >99% |
| 3 | | | 19 h | | 99% | 15 ^f | | | 6 h | | 98% |
| 4 | | | 24 h | | 82% | 16 | | | 1 h | | 96% |
| 5 | | | 24 h | | 91% | 17 | | | 1 h | | 92% |
| 6 ^c | | | 48 h | | 62% ^d | 18 | | HNBu ₂ | 6 h | | 98% |
| 7 | | | 24 h | | 84% | 19 | | | 6 h | | >99% |
| 8 | | | 24 h | | 88% | 20 | | | 6 h | | 92% |
| 9 | | | 24 h | | 90% | 21 | | | 6 h | | 84% ^g |
| 10 ^e | | | 24 h | | 95% | 22 | | | 2 h | | 87% |
| 11 | | | 48 h | | 92% | 23 | | | 4 h | | 86% |
| 12 | | HNBu ₂ | 6 h | | 93% | | | | | | |

^a Reactions were conducted on a 1 mmol scale in toluene (1 mL) at 90 °C. Aryl chloride:amine:KOH:H₂O:Pd[P(*t*-Bu)₃]₂:**1** = 100:105:150:150:1.0:0.5. ^b Isolated yield. ^c Aryl chloride:amine:KOH:H₂O:Pd[P(*t*-Bu)₃]₂:**1** = 100:200:150:150:5.0:2.5. ^d Estimated by ¹H NMR. Diarylated product was obtained in 22% yield. ^e Aryl chloride:amine:KOH:H₂O:Pd[P(*t*-Bu)₃]₂:**1** = 100:120:150:150:2.0:1.0. ^f Aryl chloride:amine = 105:100. ^g **4** was obtained in 8% yield.

presence of hydroxide, water, and **1** (entries 17, 22, and 23). Low yields of coupled products were observed for reactions of other amines with these same aryl chlorides, however. Substrates with a *tert*-butyl instead of methyl ester did couple efficiently (entries 18–20). Reactions of *p*-chloroacetophenone gave the desired *p*-aminoacetophenones in 64–87% yield. During reactions of amines other than aniline, this coupled product was accompanied by a small amount of bis(4-acetylphenyl)methane (**4**) side product (entry 21). Most likely, the diarylmethane was formed by a double arylation of the α -position of the acetyl group^{61–64} and hydrolysis of the resulting diary-

lated ketone in the presence of KOH and H₂O (Scheme 1).^{65–67} Hydrolysis of triarylmethyl ketones can generate carboxylic acids,⁶⁷ but hydrolysis of a ketone with enolizable hydrogens is unusual. This hydrolysis may occur in the present case because the electron-deficient diarylmethyl group can act as a suitable leaving group. To test this hypothesis, diarylated ketone **5** was prepared by a palladium-catalyzed arylation of the substituted acetophenone. Ketone **5** underwent hydrolysis in the pres-

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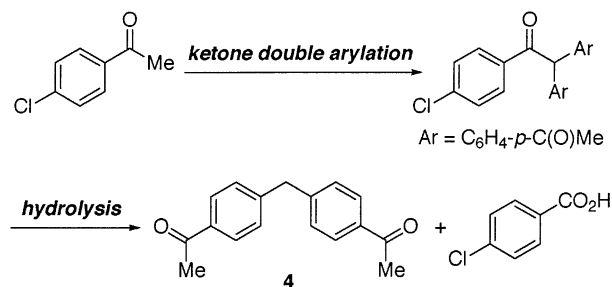
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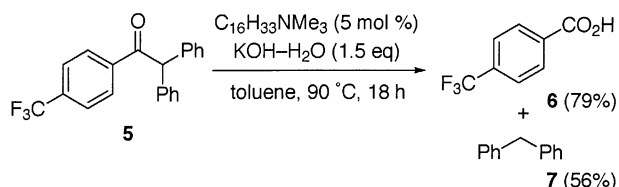
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SCHEME 1



SCHEME 2



ence of KOH, H₂O, and a catalytic amount of C₁₆H₃₃-NMe₃Br to form *p*-trifluoromethylbenzoic acid (**6**) and diphenylmethane (**7**) (Scheme 2).

Although drybox procedures were used to assemble the nonaqueous components of the reactions in Table 3, a drybox is, of course, not required to perform these reactions. For example, the amination of activated aryl chlorides was also conducted by weighing all solids in air in a flask that had not been dried. Powdered KOH

that had been stored in a screw-capped vial in air over 1 month and Pd[P(*t*-Bu)₃]₂ that was stored at -30 °C in air over 1 month were used for the reactions in this work. The flask was evacuated, filled with nitrogen, and then charged with toluene that had been stored in air and was simply degassed by bubbling with nitrogen for a few minutes. Under these conditions, the reaction of 1-chloro-4-nitrobenzene and aniline gave *N*-phenyl-4-nitroaniline in 93% yield. When distilled amine and deoxygenated toluene (sodium/benzophenone ketyl) was used with KOH, water, and **1** as base, the reaction of *p*-chlorotoluene with morpholine provided 85% isolated yield.

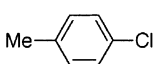
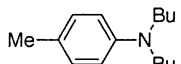
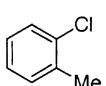
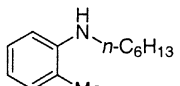
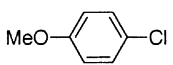

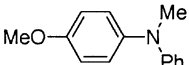
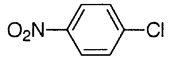
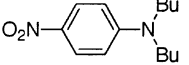
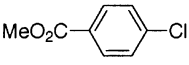
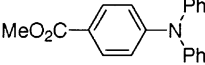
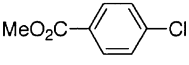
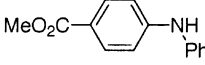
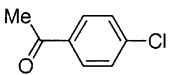

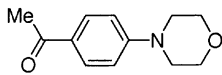
Scope of the Amination of Aryl Bromides in the Presence of KOH. As shown in Table 4, the combination of KOH, H₂O, and a catalytic amount of **1** was suitable for the aminations of various aryl bromides. Aminations of unactivated and electron-rich aryl bromides were complete in shorter reaction times than those of aryl chlorides. In most cases, these aryl bromides were consumed completely within 6 h. As exceptions, reactions of dibutylamine (entries 1 and 10) and the sterically congested reaction of *o*-bromotoluene and diphenylamine (entry 7) required longer reaction times. The reaction of hexylamine with bromobenzene required 3 equiv of amine to suppress the formation of diphenylhexylamine and required 2 mol % of palladium catalyst because the excess amine seemed to retard the reaction rate (entry 6). Reactions of aryl bromides having ester and cyano groups provided the desired products in high yields but, for

TABLE 4. Amination of Aryl Bromide in the Presence of KOH, Water, and Catalytic Phase-Transfer Agent **1** and Catalytic Pd[P(*t*-Bu)₃]₂^a

| Entry | Aryl Bromide | Amine | Time | Product | Yield ^b | Entry | Aryl Bromide | Amine | Time | Product | Yield ^b |
|----------------|--------------|--|------|---------|--------------------|-------|--------------|--------------------|------|---------|--------------------|
| 1 | | HNBu ₂ | 20 h | | 92% | 9 | | H ₂ NPh | 6 h | | 98% |
| 2 | | | 3 h | | 95% | 10 | | HNBu ₂ | 24 h | | 81% |
| 3 | | | 1 h | | 94% | 11 | | | 3 h | | >99% |
| 4 | | HNPh ₂ | 3 h | | 96% | 12 | | | 3 h | | 93% |
| 5 | | H ₂ NPh | 3 h | | 94% | 13 | | HNPh ₂ | 6 h | | 99% |
| 6 ^c | | H ₂ N(<i>n</i> -C ₆ H ₁₃) | 6 h | | 79% ^d | 14 | | H ₂ NPh | 2 h | | 90% |
| 7 | | HNPh ₂ | 18 h | | 92% | 15 | | H ₂ NPh | 2 h | | 92% |
| 8 | | H ₂ NPh | 3 h | | 97% | 16 | | H ₂ NPh | 9 h | | 70% |

^a Reactions were conducted on a 1 mmol scale in toluene (1 mL) at 90 °C. Aryl bromide:amine:KOH:H₂O:Pd[P(*t*-Bu)₃]₂:**1** = 100:105:150:150:1.0:0.5. ^b Isolated yield. ^c Aryl bromide:amine:KOH:H₂O:Pd[P(*t*-Bu)₃]₂:**1** = 100:300:150:150:2.0:1.0. ^d Diarylated product was obtained in 6% yield.

TABLE 5. Amination of Aryl Chlorides in the Presence of Aqueous NaOH or Aqueous KOH^a

| Entry | Aryl Chloride | Amine | Base ^b | Time | Product | Yield ^c |
|----------------|---|---|-------------------|------|--|--------------------|
| 1 |  | HNBu ₂ | KOH | 18 h |  | 81% |
| 2 | | | NaOH | 20 h | | 82% |
| 3 ^d |  | H ₂ N(<i>n</i> -C ₆ H ₁₃) | KOH | 24 h |  | 91% |
| 4 ^d | | | NaOH | 24 h | | 92% |
| 5 |  |  | KOH | 28 h |  | 92% |
| 6 | | | NaOH | 28 h | | 92% |
| 7 |  | HNBu ₂ | KOH | 3 h |  | 97% |
| 8 | | | NaOH | 3 h | | 93% |
| 9 |  | HNPh ₂ | KOH | 1 h |  | 97% |
| 10 | | | NaOH | 1 h | | 90% |
| 11 |  | H ₂ NPh | NaOH | 1 h |  | 90% |
| 12 |  |  | KOH | 3 h |  | 86% |
| 13 | | | NaOH | 3 h | | 84% |

^a Reactions were conducted on a 0.8 mmol scale in toluene (1 mL) at 90 °C. Aryl chloride:amine:base:Pd[P(*t*-Bu)₃]₂:**1** = 100:105:150:1.0:0.5. ^b KOH = 45 wt % aqueous solution; NaOH = 50 wt % aqueous solution. ^c Isolated yield. ^d Aryl chloride:amine:base: Pd[P(*t*-Bu)₃]₂:**1** = 100:120:150:2.0:1.0.

reasons we do not understand, were slower than the reaction of the corresponding aryl chlorides (entries 15 and 16).

The Amination of Aryl Chlorides with Aqueous Alkali Metal Hydroxide Solutions. As described above, solid alkali metal hydroxide bases were effective in the presence of 1 equiv of H₂O, but not in the absence of added water. Thus, we tested whether the reactions would occur if we simply used a solution of concentrated aqueous sodium or potassium hydroxide and phase-transfer catalyst. As shown in Table 5, reactions conducted with commercially available concentrated aqueous NaOH occurred in high yields in the presence of palladium and phase-transfer catalyst, despite the increased amount of water in this system. Reactions conducted with 50 wt % aqueous NaOH and a catalytic amount of **1** occurred in essentially the same fashion as the reactions conducted with powdered KOH and added water as described above. Reactions conducted with commercially available 45 wt % aqueous KOH also occurred in a similar fashion. In comparison with reactions conducted

with solid base and small amounts of water, reactions with the concentrated aqueous hydroxide occurred in slightly shorter reaction times. Similarly high functional group tolerance was observed. Amination again occurred in the presence of base-sensitive functionality such as esters, enolizable ketones, nitriles, and nitro groups. In fact, the diphenylmethane **4** that is formed in competition with the product from amination of *p*-chloroacetophenone was generated in 3% yield or less when the concentrated aqueous hydroxide was used (entries 12 and 13). Excess amounts of water with hydroxide base do not adversely affect the amination process, as long as the hydroxide is added as an aqueous solution.

Conclusion

In summary, we have found conditions that allow the inexpensive, air-stable inorganic bases KOH and NaOH to be used in the palladium-catalyzed amination of aryl halides. The combination of a phase-transfer catalyst, 1 equiv of water, and KOH or the combination of phase-

transfer catalyst and concentrated aqueous NaOH or KOH led to acceptable reaction rates and high yields for the formation of arylamines. The new base system performed as well as NaO-*t*-Bu in certain reactions. However, reactions catalyzed by Pd[P(*t*-Bu)₃]₂ gave the arylamine in higher yield than those conducted with other catalysts tested. Other catalysts that are active for aminations in the presence of NaO-*t*-Bu failed to give high conversions of aryl chloride in the presence of hydroxide as base. The hydroxide base was suitable for reactions of substrates bearing reactive functionality such as methyl esters, enolizable ketones, nitro groups, and cyano groups. Aryl chlorides bearing nitro and *tert*-butyl esters reacted with various amines in high yields. The procedure developed is simple to conduct. The palladium catalyst Pd[P(*t*-Bu)₃]₂ is commercially available, and a batch of catalyst that had been stored in air at -30 °C reacted similarly to a batch of catalyst that had been stored in a nitrogen-filled drybox. Although removal of oxygen from solvent was required, bubbling of nitrogen through reagent grade toluene for a few minutes removed enough oxygen from the solvent to obtain the product in high yield. Most remarkable was the tolerance of the system to added water. Phosphine-ligated palladium hydroxides are known to generate phosphine oxide,⁶⁸ and one might expect the amido intermediates in the catalytic process to be hydrolyzed. Yet, the reactions occurred in high yield in the presence of excess water.

Experimental Section

General Methods. Toluene was distilled from sodium-benzophenone ketyl under nitrogen. Aryl halides except *tert*-butyl *p*-chlorobenzoate were purchased from commercial sources and were used without further purification. *tert*-Butyl *p*-chlorobenzoate was prepared according to the literature.^{69,70} Amines were purchased from commercial sources and were distilled from CaH₂ under nitrogen before use with the exception of diphenylamine, which was used without further purification. KOH powder was made from KOH pellets with a pestle and mortar in a nitrogen-filled drybox, and the powder was stored in the drybox. Cetyltrimethylammonium bromide (1), 45 wt % aqueous KOH, and 50 wt % aqueous NaOH were purchased from Aldrich Chemicals. Pd[P(*t*-Bu)₃]₂ was purchased from Strem Chemicals.

General Procedure for Aminations of Liquid Aryl Halides with KOH powder. In a drybox, aryl halide (1.0 mmol) and amine (1.05 mmol) were added to a suspension of Pd[P(*t*-Bu)₃]₂ (5.1 mg, 10.0 μmol), cetyltrimethylammonium bromide (1.8 mg, 5.0 μmol), and KOH powder (84 mg, 1.5 mmol) in toluene (1.0 mL) in a screw-capped vial. A small stirbar was added, and the vial was sealed with a cap containing a PTFE septum and removed from the drybox. Water (27 μL, 1.5 mmol) was added to the mixture by syringe. The reaction mixture was then stirred *vigorously* at 90 °C. The reaction was monitored by GC. After the reaction, the mixture was absorbed onto the silica gel and purified by flash column chromatography on silica gel to give the desired arylamine in the yield shown. Procedures for the reactions of solid materials are described in the Supporting Information.

General Procedure for Aminations of Aryl Chlorides with Aqueous Hydroxide. In a drybox, aryl chloride (0.8 mmol) and amine (0.84 mmol) were added to a suspension of Pd[P(*t*-Bu)₃]₂ (4.1 mg, 8.0 μmol) and cetyltrimethylammonium bromide (1.5 mg, 4.0 μmol) in toluene (0.8 mL) in a screw-

capped vial. A small stirbar was added, and the vial was sealed with a cap containing a PTFE septum before removing it from the drybox. KOH (45 wt % in water, 150 μL, KOH 1.2 mmol, H₂O 4.57 mmol) or NaOH (50 wt % water solution, 96 μL, NaOH 1.2 mmol, H₂O 2.65 mmol) was added to the mixture by syringe. The reaction mixture was then stirred *vigorously* at 90 °C. The reaction was monitored by GC. After the reaction, the mixture was absorbed onto the silica gel and purified by flash column chromatography on silica gel to give the desired arylamine in the yield shown.

Procedure for the Amination of 1-Chloro-4-nitrobenzene (Activated Aryl Chloride) with Aniline without the Use of a Drybox. Pd[P(*t*-Bu)₃]₂ (5.1 mg, 10 μmol), cetyltrimethylammonium bromide (1.8 mg, 5.0 μmol), 1-chloro-4-nitroaniline (159 mg, 1.01 mmol), KOH (84 mg, 1.50 mmol), and a small stirbar were placed in a Schlenk-type flask (not oven-dried) in air. The flask was sealed with a septum, evacuated, backfilled with nitrogen, and charged with reagent-grade toluene (1.0 mL) that had been bubbled with nitrogen for a few minutes. Aniline (98 mg, 1.05 mmol) and water (27 μL, 1.50 mmol) were added by syringe. The reaction mixture was stirred *vigorously* at 90 °C for 1 h, at which time the mixture was absorbed onto the silica gel and purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to give 4-nitro-*N*-phenylaniline⁷¹ (205 mg, 95%) as an orange solid. In another experiment, the title compound was obtained in 91% yield: ¹H NMR (400 MHz, CDCl₃, TMS) δ 6.26 (br s, 1H), 6.94 (d, *J* = 9.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 8.13 (d, *J* = 9.4 Hz, 2H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 113.6, 121.9, 124.6, 126.2, 129.7, 139.4, 139.7, 150.1.

Procedure for the Amination of *p*-Chlorotoluene (Unactivated Aryl Chloride) with Morpholine without the Use of a Drybox. Pd[P(*t*-Bu)₃]₂ (5.1 mg, 10 μmol), cetyltrimethylammonium bromide (1.8 mg, 5.0 μmol), KOH (84 mg, 1.50 mmol), and a small stirbar were placed in a Schlenk-type flask (not oven-dried) in air. The flask was sealed with a septum, evacuated, backfilled with nitrogen, and charged with toluene (1.0 mL) that had been distilled from sodium-benzophenone ketyl. *p*-Chlorotoluene (124 mg, 0.98 mmol), morpholine (91 mg, 1.04 mmol), and water (27 μL, 1.50 mmol) were added by syringe. The reaction mixture was stirred *vigorously* at 90 °C for 30 h, at which time the mixture was absorbed onto the silica gel and purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to give *N*-(4-methylphenyl)morpholine⁷² (153 mg, 88%) as a white solid. In another experiment, the title compound was obtained in 81% yield: ¹H NMR (400 MHz, CDCl₃, TMS) δ 2.28 (s, 3H), 3.10 (t, *J* = 4.8 Hz, 4H), 3.86 (t, *J* = 4.8 Hz, 4H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 20.4, 49.9, 67.0, 116.0, 129.6, 129.7, 149.2.

2,2-Diphenyl-1-[4-(trifluoromethyl)phenyl]-1-ethanone (5). In a drybox, phenyl bromide (378 mg, 2.41 mmol) was added to a mixture of 4'-(trifluoromethyl)acetophenone (193 mg, 1.03 mmol), NaO-*t*-Bu (231 mg, 2.4 mmol), Pd(OAc)₂ (4.4 mg, 20 μmol), and P(*t*-Bu)₃ (4.9 mg, 20 μmol) in THF (2.0 mL) in a screw-capped vial. A small stirbar was added, and the vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at room temperature for 1 h, and then at 60 °C for 2 h. The mixture was diluted with H₂O and was extracted with EtOAc. The organic layer was washed with 2 N aqueous HCl, dried with MgSO₄, and then evaporated. The residue was purified by flash column chromatography on silica gel (1% EtOAc in hexanes) to give **5** (294 mg, 84%) as a white solid: mp 139–140 °C; ¹H NMR (400 MHz, CDCl₃, TMS) δ 6.00 (s, 1H), 7.23–7.29 (m, 6H), 7.31–7.37 (m, 4H), 7.66 (d, *J* = 8.0 Hz, 2H), 8.80 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 59.9, 123.5

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(q, $J = 271$ Hz), 125.7 (q, $J = 4$ Hz), 127.4, 128.9, 129.1, 129.3, 134.2 (q, $J = 33$ Hz), 138.3, 139.3, 197.2; IR (KBr disk) 1687 cm^{-1} . Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{F}_3\text{O}_2$: C, 74.11; H, 4.44. Found: C, 74.24; H, 4.51.

Hydrolysis of 5. Water was added to a mixture of **5** (69 mg, 0.20 mmol), KOH (17 mg, 0.30 mmol), and **1** (3.6 mg, 10 μmol) in toluene (1.0 mL) in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum. The reaction mixture was stirred at 90 °C for 18 h. The mixture was diluted with 10% aqueous NaOH and extracted with EtOAc. The organic layer was washed with brine, dried with MgSO_4 , and then evaporated. The residue was purified by flash column chromatography on silica gel. Diphenylmethane (**7**) (19 mg, 56%) was eluted with hexanes, and the starting material **5** (14 mg, 20%) was eluted with 2% EtOAc in hexanes. The aqueous layer was acidified (pH < 1) with concentrated aqueous HCl and extracted with CH_2Cl_2 . This organic layer was dried with MgSO_4 and evaporated to give 4-(trifluoromethyl)benzoic acid (**6**; 30 mg, 79%). **6**:⁷³ white solid; ^1H NMR (400 MHz, acetone- d_6) δ 7.87 (d, $J = 8.0$ Hz, 2H), 8.24 (d, $J = 8.0$ Hz, 2H), 10.6–13.0 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ

124.4 (q, $J = 272$ Hz), 125.9 (q, $J = 4$ Hz), 130.6, 134.0 (q, $J = 32$ Hz), 134.6, 165.9; IR (KBr disk) 3300–2200, 1697 cm^{-1} . **7**:⁷⁴ colorless oil; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 3.98 (s, 2H), 7.16–7.22 (m, 6H), 7.25–7.31 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 41.9, 126.0, 128.4, 128.9, 141.1.

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Supporting Information Available: Details of experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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