Convenient Palladium-Catalyzed Preparation of Primary Anilines Using a Fluorous Benzophenone Imine Reagent

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Abstract: A novel fluoroalkyl benzophenone imine reagent (f-BPI) serves as a convenient ammonia surrogate for the palladium-catalyzed Buchwald–Hartwig amination of aryl halides. The highly fluorinated imine moiety acts as a handle for rapid purification of intermediates using fluorous chromatographic techniques, and is removed in a subsequent stage by acid hydrolysis to provide the corresponding primary anilines.

Key words: amination, arylation, cross-coupling, palladium-catalyzed, fluorous

The last half-decade has seen tremendous advances in the development of useful and practical methods for palladium-catalyzed amination of aryl halides and triflates.[2] Early on in the course of these discoveries, however, it had become plain that alternative protocols were required for the direct generation of primary anilines, as ammonia was found not to participate. As a result, several methods have appeared in which various ammonia surrogates were found to undergo palladium-catalyzed coupling reactions with aryl halides to provide *N*-aryl amines.[3] One of the first methods developed by the Buchwald group utilized benzophenone imine as the ammonia equivalent in a cross-coupling reaction with aryl halides and triflates, to provide the corresponding *N*-aryl benzophenone imines.[3a] These adducts were then subjected to various deprotection conditions to unmask the amine functionality, either in a separate step or during the workup of the amination reaction, to provide primary anilines. In these cases, the intermediate *N*-aryl imines were found to crystallize directly following the aqueous workup, followed by chromatography after the hydrolysis step to provide clean material. In our experience we have found that larger molecules have not crystallized directly, leading to the necessity of purification at one or both stages of the transformation. However, with the advent of convenient fluorous techniques for the rapid purification of organic compounds,[4] we decided to investigate the possibility of combining a fluorine-containing tag into our ammonia surrogate. In this way, a fluorous handle would add to the value of Buchwald's amination procedure by taking additional advantage of the efficient purification method.

A discussion with the scientists at Fluorous Technologies, Inc. (FTI) led to the preparation of a fluorous version of benzophenone imine for evaluation in comparison to Buchwald's published method.[3a] As a result, FTI prepared the reagent 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)benzophenone imine (f-BPI, **2**) which we subjected to Buchwald's palladium-catalyzed cross coupling reaction conditions with some of the same aryl halides **1a**–**i** to provide a series of *N*-arylimine adducts **3** (Scheme 1). In this way we could compare a few yields directly with the original[3a] method. Following the cross-coupling reaction, the crude mixtures were purified by quick filtration through a plug of FluoroFlash silica gel (also referred to as a 'fluorous solid phase extraction' or 'fluorous SPE')[5] to provide the purified *N*-arylimine products **3a**–**i**, as shown in Table 1.[6] A slight excess of aryl substrate **1** to imine **2** was used to ensure efficient purification by the fluorous solid phase purification technique. In all cases the reactions were observed to achieve 100% conversion of the imine **2**.

To accomplish the fluorous SPE purification, the reaction mixture solvent was removed under reduced pressure and the residue was dissolved in a minimal amount of THF and applied to a plug of fluorous silica gel. The support was first flushed with a MeOH–water mixture (4:1) to remove the excess **1**, by-products, catalysts and inorganic salts. After discarding this fluorophobic organic wash, the plug was then flushed with a fluorophilic solvent (either MeOH or THF). This second wash was collected and the solvent was removed to provide the *N*-aryl products **3a**–**i** in good purity (>95% as determined by ^{1}H and ^{13}C NMR analyses).

Hydrolysis of the imine moiety of *N*-arylimines **3a**–**i** with aqueous HCl in THF at room temperature was achieved in a separate step. In most cases the hydrolyses were complete within fifteen minutes, after which the reaction mixtures were treated with macroporous triethylammonium methylpolystyrene carbonate (MP-carbonate) resin[7] and stirred for an additional five minutes. The basified contents were then loaded directly onto a FluoroFlash cartridge for a second fluorous separation to provide pure aniline products **4a**–**i** in good overall yields, as shown in Table 1. This time the fluorous solid phase was flushed with a MeOH–water mixture (4:1) to provide the anilines **4** as free bases in good purity (>95% as determined by ^{1}H and ^{13}C NMR analyses). The second wash of the fluorous silica gel with a fluorophilic mobile phase (MeOH or

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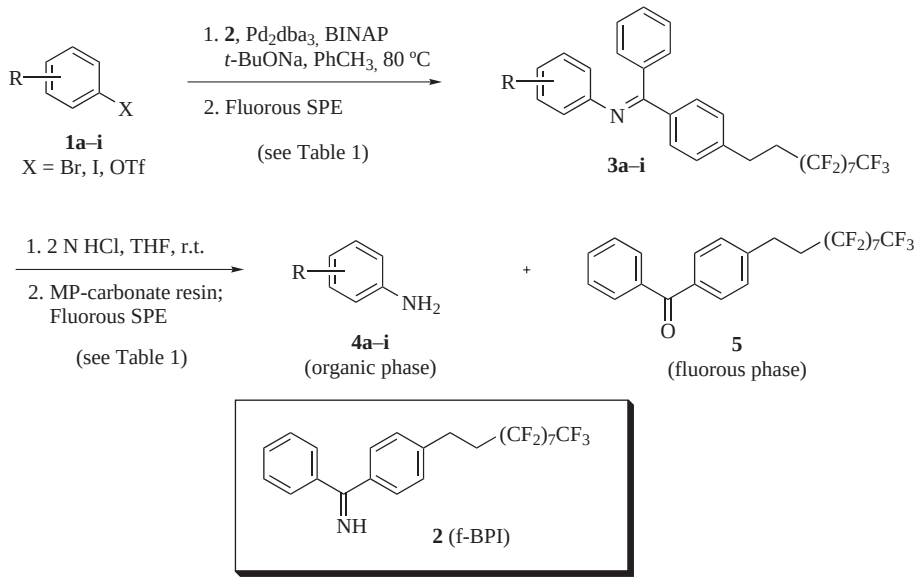


Scheme 1 General method for preparation of primary anilines **4** using f-BPI reagent **2**.

THF) then provided pure recovered fluorous benzophenone **5**, which was usually observed at >60% recovery for the two-step process.[17]

Examination of the results shows that these coupling and hydrolysis reactions are comparable to yields of the analogous reactions with benzophenone imine as reported by the Buchwald group.[3a] For example the cross-coupling of 1-bromo-4-*tert*-butylbenzene (**1d**) with f-BPI to provide **3d** was achieved in 95% yield (entry 4), which compares favorably to the 90% yield achieved by Buchwald's group for the analogous preparation of the adduct with benzophenone imine itself. Hydrolysis of **3d** to provide 4-*tert*-butylaniline (**4b**) was achieved in 97% yield (entry 4), which is similar to the throughput realized for Buchwald's equivalent benzophenone imine cleavage (84% yield). Similarly, the coupling of 4-bromobenzonitrile (**1a**) to f-BPI was achieved in 86% yield, and hydrolyzed to 4-aminobenzonitrile (**4a**) in 95% yield (entry 1). The overall yield of the two-step procedure (82%) is comparable to the two-step yield of 97% of **4a** from **1a** reported by Buchwald. We were therefore pleased to conclude that the fluorous tag imparts no adverse effects to the coupling reaction efficiency, so that f-BPI can be used as a general reagent to provide primary anilines (electron-rich and -deficient) and amino heterocycles without complication.

In conclusion, novel (now commercially available) heptadecafluorodecyl benzophenone imine reagent **2** (f-BPI) serves as a convenient ammonia equivalent in the palladium-catalyzed Buchwald–Hartwig amination of aryl halides and triflates. The highly fluorinated imine protecting group acts as a handle for rapid purification of non-crystalline intermediates using fluorous chromatographic techniques, and is removed in a subsequent stage by treatment with aqueous acid in THF to provide the pure corresponding primary anilines.

Table 1 Amination of Aryl Halides and Triflates **1** with f-BPI **2** and Subsequent Hydrolysis to Primary Anilines **4**

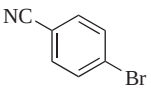
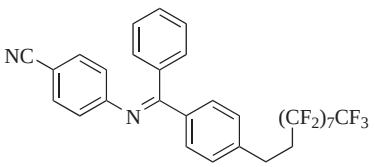
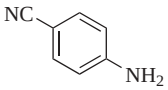
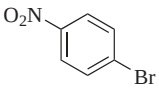
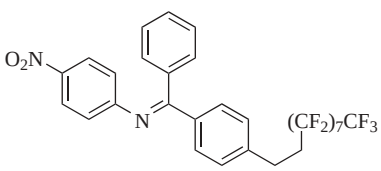
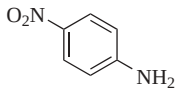
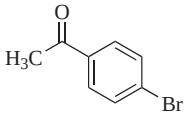
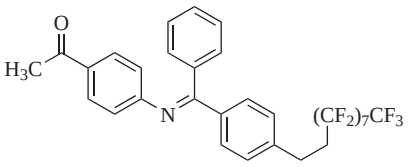
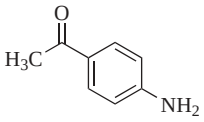
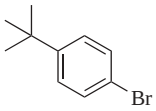
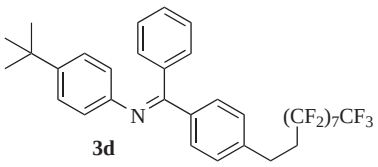
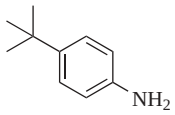
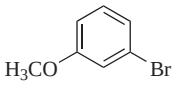
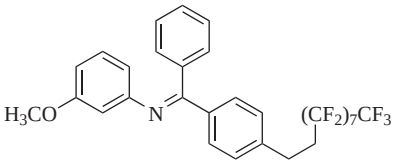
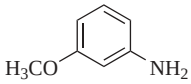
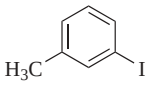
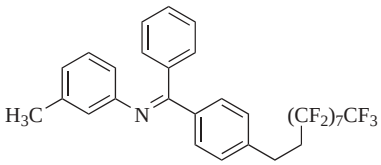
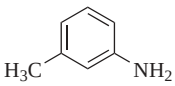
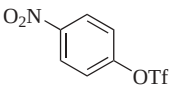
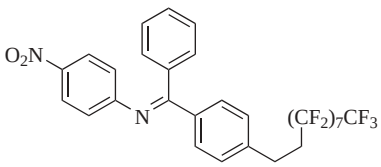
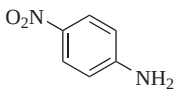
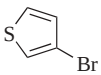
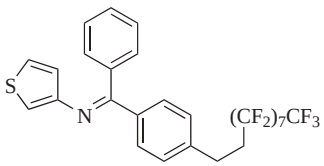
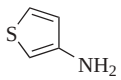
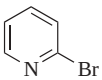
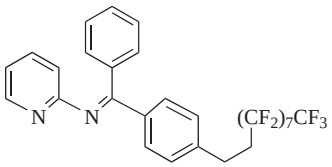
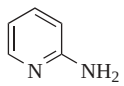
Entry	Aryl Substrate 1	*N*-Aryl Imine 3	Yield[a] (%)	Aniline 4	Yield[a,b] (%)
1	 **1a**	 **3a**	86	 **4a**	95[8,9]
2	 **1b**	 **3b**	79	 **4b**	91[8,10]

Table 1 Amination of Aryl Halides and Triflates **1** with f-BPI **2** and Subsequent Hydrolysis to Primary Anilines **4** (continued)

Entry	Aryl Substrate 1	*N*-Aryl Imine 3	Yield[a] (%)	Aniline 4	Yield[a,b] (%)
3	 **1c**	 **3c**	79	 **4c**	90[8,11]
4	 **1d**	 **3d**	95	 **4d**	97[8,12]
5	 **5e**	 **3e**	94	 **4e**	63[8,13]
6	 **1f**	 **3f**	65	 **4f**	88[8,14]
7	 **1g**	 **3b**	65	 **4b**	90
8	 **1h**	 **3h**	97	 **4h**	92[15]
9	 **1i**	 **3i**	93	 **4i**	96[8,16]

[a] Isolated yields after fluorous solid phase extraction (chromatography).
[b] Superscripted numbers are literature references for the known compounds.

All non-aqueous reactions were performed under a dry atmosphere of nitrogen unless otherwise specified. Commercial grade reagents and anhydrous solvents were used as received from vendors and no attempts were made to purify or dry these components further. Removal of solvents under reduced pressure was accomplished with a Buchi rotary evaporator at approximately 28 mm Hg pressure using a Teflon-linked KNF vacuum pump. TLC was performed using 1'' × 3'' AnalTech No. 02521 silica gel plates with fluorescent indicator. Visualization of TLC plates was made by observation with either short wave UV light. Solid phase extractions were carried out using FluoroFlash™ silica gel or pre-packed 10 g FluoroFlash™ silica gel columns, purchased from Fluorous Technologies, Inc. ^{1}H and ^{13}C NMR spectra were obtained on a 300 MHz NMR spectrometer and are reported in ppm δ values, using TMS as an internal reference. Melting points are uncorrected. API Mass spectroscopic analyses were performed using atmospheric pressure chemical ionization (APCI).

_N_-Aryl Imines 3a–i; General Procedure

To an oven-dried round-bottom flask charged with tris(dibenzylidene)dipalladium(0) [$Pd_2(dba)_3$, 1 mol%], racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, 3 mol%), sodium *tert*-butoxide (1.4 mmol) and anhyd toluene (2 mL) at r.t. under nitrogen were added aryl halide or triflate **1** (1.1 mmol) and the fluorous benzophenone imine reagent **2** (f-BPI, 1.0 mmol) and the mixture was heated at 80 ºC. When the conversion was judged as complete (by TLC analysis), the mixture was cooled to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in THF (1 mL) and placed onto a column containing FluoroFlash™ silica gel (5 g), which was pre-treated with a MeOH–water mixture (4:1, 20 mL). The column was initially flushed with a MeOH–water mixture (4:1, 30 mL, fluorophobic fraction) to remove non-fluorous organic components, followed by elution with either MeOH or THF (30 mL, fluorophilic fraction). The collected fluorophilic fraction was concentrated under reduced pressure to provide the desired imine adducts **3** in >95% purity in all cases. Final products were characterized by APCI MS, ^{1}H NMR and ^{13}C NMR spectroscopy. The reaction conditions were not optimized, and selected examples are shown.

4-({[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)phenyl]phenylmethylene}amino)benzonitrile (3a)

From 4-bromobenzonitrile (**1a**, 64 mg, 0.35 mmol); light yellow gum (200 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (m, 2 H), 7.71 (m, 1 H), 7.36 (m, 3 H), 7.24 (m, 2 H), 7.15 (m, 2 H), 7.06 (m, 1 H), 6.55 (m, 2 H), 2.93 (m, 2 H), 2.41 (m, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 26.77, 33.03, 106.71, 119.59, 121.73, 128.64, 129.57, 130.31, 131.01, 131.76, 133.14, 155.81, 169.39.

APCI MS: *m*/*z* = 728 [$C_{30}H_{17}F_{17}N_2$ + H]$^+$.

1-[4-({[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)phenyl]phenylmethylene}amino)phenyl]ethanone (3c)

From 4′-bromoacetophenone (**1c**, 70 mg, 0.35 mmol); yellow gum (190 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (m, 2 H), 7.75 (m, 1 H), 7.40 (m, 3 H), 7.30 (m, 2 H), 7.15 (m, 2 H), 7.06 (m, 1 H), 6.60 (m, 2 H), 2.93 (m, 2 H), 2.53 (s, 3 H), 2.41 (m, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 26.63, 32.99, 120.97, 127.70, 128.61, 129.67, 130.31, 131.02, 132.62, 132.75, 156.26, 168.72, 197.51.

APCI MS: *m*/*z* = 745 [$C_{31}H_{20}F_{17}NO$ + H]$^+$.

{[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)phenyl]phenylmethylene}-*m*-tolylamine (3f)

From 3-iodotoluene (**1f**, 84 mg, 0.35 mmol); light yellow gum (84 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (m, 2 H), 7.71 (m, 1 H), 7.57 (m, 2 H), 7.48 (m, 3 H), 7.33 (m, 1 H), 7.26 (m, 3 H), 7.09 (m, 1 H), 2.98 (m, 2 H), 2.36 (m, 2 H), 2.21 (s, 3 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 24.26, 26.23, 29.52, 33.12, 68.37, 118.58, 122.54, 124.69, 128.49, 128.62, 128.86, 128.91, 128.99, 129.27, 130.03, 130.17, 130.51, 130.70, 130.79, 131.41.

APCI MS: *m*/*z* = 717 [$C_{30}H_{20}F_{17}N$ + H]$^+$.

{[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)phenyl]phenylmethylene}thiophen-3-ylamine (3h)

From 3-bromothiophene (**1h**, 62 mg, 0.35 mmol); light yellow gum (220 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (m, 1 H), 7.71 (m, 1 H), 7.36 (m, 3 H), 7.24 (m, 2 H), 7.15 (m, 2 H), 7.06 (m, 1 H), 6.53 (m, 1 H), 6.51 (m, 1 H), 2.93 (m, 2 H), 2.41 (m, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 23.76, 26.21, 28.99, 67.53, 107.80. 112.74, 113.00, 123.86, 123.96, 124.02, 124.08, 127.98, 128.04, 128.21, 128.70, 128.98, 129.34, 129.46, 130.50.

APCI MS: *m*/*z* = 709 [$C_{27}H_{16}F_{17}NS$ + H]$^+$.

Anilines 4a–i; General Procedure

To a solution of the imine adduct **3** in THF (0.3 M solution) at r.t. was added aqueous 2.0 M HCl solution (approximately 5% by volume with THF). When the conversion was judged as complete (by TLC analysis), the mixture was made alkaline by addition of MP-carbonate resin (150 mg). The mixture was then placed directly onto a cartridge of FluoroFlash™ silica gel (5 g), which was pretreated with a MeOH–water mixture (4:1, 20 mL). The column was initially flushed with a MeOH–water mixture (30 mL, fluorophobic fraction) to collect the organic product, followed by elution with MeOH or THF (30 mL, fluorophilic fraction) to collect the fluorous benzophenone byproduct. The fluorophobic fraction was concentrated under reduced pressure to provide the desired aniline free bases **4** in >95% purity in all cases. The fluorophilic fraction was concentrated under reduced pressure to provide recovered fluorous benzophenone **5**. Final products were characterized by APCI MS, ^{1}H NMR and ^{13}C NMR spectroscopy. The reaction conditions were not optimized, and selected examples are shown.

4-Aminobenzonitrile (4a)[8,9]

From 4-{[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl]phenylmethylene}-amino)benzonitrile (**3a**, 130 mg, 0.18 mmol); yellow oil (20 mg, 95%); mp 84–87 ºC (Lit[9a] mp 86–87 ºC).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.57 Hz, 2 H), 6.65 (d, *J* = 8.61 Hz, 2 H), 4.10 (br s, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 112.71, 125.66, 151.83.

APCI MS: *m*/*z* = 154 [$C_7H_6N_2$ + H]$^+$.

4′-Aminoacetophenone (4c)[8,11]

From 1-[4-({[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl]phenylmethylene}-amino)phenyl]ethanone (**3c**, 160 mg, 0.22 mmol); white solid (26 mg, 90%); mp 100–102 ºC (Lit[11a] mp 104–105 ºC).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 2.48 Hz, 2 H), 6.66 (d, *J* = 2.52 Hz, 2 H), 4.11 (br s, 2 H), 2.50 (s, 3 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 31.97, 34.33, 115.37, 126.46, 141.22, 144.25.

APCI MS: *m*/*z* = 136 [C_8H_9NO + H]$^+$.

***m*-Toluidine (4f)[8,14]**

From {[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl]phenylmethylene}-*m*-tolylamine (**3f**, 140 mg, 0.20 mmol); yellow oil (18 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (m, 1 H), 6.56 (m, 1 H), 6.44 (m, 1 H), 3.49 (br s, 2 H), 2.22 (s, 3 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 22.46, 113.33, 116.99, 120.42, 130.20, 140.20, 147.55.

APCI MS: *m*/*z* = 107 [C_7H_9N + H]$^+$.

2-Aminothiophene (4h)[15]

From {[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl]phenylmethylene}-thiophen-3-ylamine (**3h**, 200 mg, 0.28 mmol); white solid (26 mg, 92%); mp 140–145 ºC (Lit[15a] mp 146 ºC).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (m, 1 H), 6.58 (m, 1 H), 6.10 (m, 1 H), 3.61 (br s, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 99.95, 121.15,125.20, 145.19.

APCI MS: *m*/*z* = 100 $[C_4H_5NS + H]^+$.

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