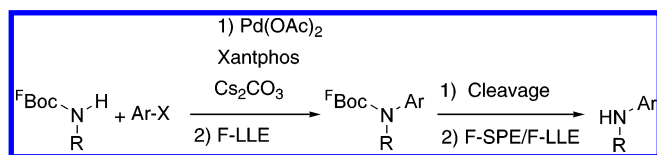## Fluorous-Tagged Carbamates for the Pd-Catalyzed Amination of Aryl Halides

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A novel fluorous-tagged ammonia surrogate has been synthesized and its application to the synthesis of anilines by Buchwald–Hartwig palladium-catalyzed amidation-hydrolysis protocol is described. Primary anilines were obtained in moderate to good yields after a sequence of two reaction steps involving fluorous separation techniques for their purification. Preliminary results indicate that N-substituted anilines can also be obtained using just N-substituted-^{F}Boc carbamates as the nitrogen source.
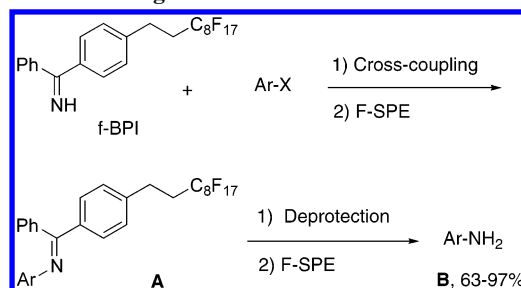
Anilines are valuable building blocks that are used as intermediates or additives for the production of dyes, pigments, and agrochemical or pharmaceutical products.[1] Their synthesis has always been a topic of interest in organic chemistry, and although many methods are available, the discovery of new and improved methodology is still of interest. Among others, the Buchwald–Hartwig palladium-catalyzed amination of aryl halides/triflates has emerged in the last decades as a powerful tool for the synthesis of arylamines.[2] While a large variety of amines and nitrogen nucleophiles undergo this reaction, the use of ammonia as the coupling partner does not afford the corresponding primary anilines.[3,4] Several ammonia surrogates

have been used to overcome this issue. Thus, allylamine,[5] benzophenone imine,[6,7] *tert*-butyl carbamate[8] Li[N(SiMe$_3$)$_2$],[9] and Zn[N(SiMe$_3$)$_2$][10] have been found as suitable masked forms of ammonia in cross-coupling amination reactions.

Solid-supported ammonia surrogates have also been used in Pd(0)-catalyzed amination reactions showing the advantage of an easy separation of the primary aniline precursors from the reaction byproducts. The final arylamines were obtained after the cleavage step with high purities and reasonable yields.[11]

Very recently a fluoroalkyl benzophenone imine reagent f-BPI has been used as an ammonia source (Scheme 1).[12,13]

SCHEME 1. Synthesis of Primary Anilines Using f-BPI as an Ammonia Surrogate

The use of this fluorous-tagged ammonia equivalent allowed the purification of both N-arylimine intermediates **A** and the final primary anilines **B** by fluorous solid-phase extraction (F-SPE).[14] To the best of our knowledge, this is the only reported example of Pd(0)-catalyzed amination reactions using fluorous-tagged amines.[15]

The synthesis of fluorous Boc (^{F}Boc) carbamates has been recently described by Curran et al., and it has been applied to the library production of amides, benzimidazoles, and quinoxalinones.[16]

With these precedents in mind, and with the aim of finding a fluorous tag that would allow a more general amination

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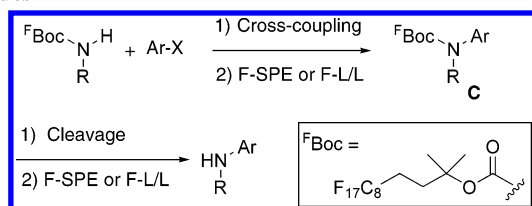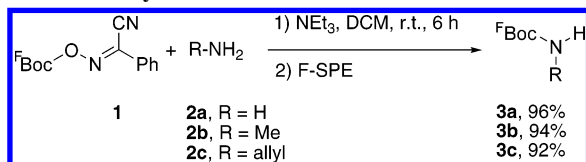
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SCHEME 2. ^{F}Boc Carbamates as Potential Coupling Partners in Pd(0) Cross-Coupling Aminations of Aryl Halides

SCHEME 3. Synthesis of Novel ^{F}Boc-carbamates 3a−c

reaction, we decided to explore the viability of ^{F}Boc-protected amines as coupling partners in transition-catalyzed amination of aryl halides (Scheme 2). This would not only allow the synthesis of primary anilines, as is the case of f-BPI, but also secondary anilines could be synthesized after cleavage of the initially formed *N*-aryl-^{F}Boc carbamate intermediates **C**. Additionally, all purification steps would be suitable for either F-SPE or fluorous liquid−liquid extraction (F-LLE), making the protocol amenable for parallel synthesis if required.

In this way, we chose the commercially available ^{F}Boc derivative **1**[17] as the fluorous tag source (Scheme 3). Reaction of **1** with the amines **2a−c** occurred under standard conditions to give the corresponding ^{F}Boc carbamates **3a−c** in excellent yields after F-SPE purification using a Fluoro*Flash* cartridge.[18] Remarkable is the fact the corresponding diprotected ^{F}Boc carbamates were not detected in the ^{1}H NMR spectra of the reaction crudes, pointing in the direction that the ^{F}Boc derivative **1** could be an excellent group for the monoprotection of reactive primary amines.

Palladium-catalyzed coupling between the ^{F}Boc carbamate **3a** and different aryl halides (**4**) was successfully acomplished, applying standard conditions previously described by Buchwald et al.[9b] The results obtained are summarized in Table 1.

In general, reasonable yields were obtained for the palladium-catalyzed amination reaction of aryl halides and ^{F}Boc carbamate **3a**. The purification of the *N*-aryl-^{F}Boc carbamates **5** was easily achieved by means of F-LLE extraction with HFE-7100, being the corresponding carbamates **5** obtained with both high yield and purity. Different functionalized haloarenes, both bearing electron-donating (Table 1, entry 2) or electron-withdrawing groups (Table 1, entries 3−5), underwent the cross-coupling reaction. The coupling of 4-chlorobromobenzene (Table 1, entry 4) and 2-chlorobromobenzene (Table 1, entry 5) was successfully achieved in a chemoselective way, thus, the corresponding compounds **5d** and **5e** were obtained without any contamination of products derived from the cross-coupling reaction by the chlorine atom. The reaction with 2-halopyridine derivatives

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(17) ^{F}Boc derivative **1** is commercially available from Fluorous Technologies, Inc.

(18) FluoroFlash SPE cartridges are packed with silica gel with a stationary phase of $Si(Me)_2CH_2CH_2C_8F_{17}$. They are commercially available from Fluorous Technologies, Inc.

TABLE 1. Synthesis of Primary Anilines Using ^{F}Boc Carbamate 3a as an Ammonia Surrogate[a]

Entry	Substrate		5, Yield[b]	Aniline	Yield(%)[b]
1		X = Br	**5a**, 79[c]		**6a**, 89
		X = I	**5a**, 88		-
		X = Cl	**5a**, 65		-
2			**5b**, 83[d]		**6b**, 88
3			**5c**, 75		**6c**, 83
4			**5d**, 77		**6d**, 89
5			**5e**, 71		**6e**, 92
6			**5f**, 84		**6f**, 93
7			**5g**, 83		**6g**, 95
8			**5h**, 70		**6h**, 94
9		X = Br	**5i**, (50)[e]		**6i**, 40[f]
		X = I	**5i**, (58)[e]		-

[a] Reaction conditions: 1.2 equiv of the aryl halide, 1.0 equiv of **3a**, xantphos/Pd(OAc)$_2$ = 2/1, 1.5 equiv of Cs$_2$CO$_3$, 1,4-dioxane (1 mL/mmol halide), 100 °C, 24 h. [b] Yields refer to isolated yields of compounds estimated to be >95% pure, as determined by ^{1}H NMR and LCMS/GCMS. [c] When Pd$_2$(dba)$_3$ was used in place of Pd(OAc)$_2$, the corresponding coupling product was obtained in 70% yield; 10 mol % Pd refers to 5 mol % Pd$_2$(dba)$_3$. [d] When the reaction was heated for 12 h, conversion of 69% was determined by ^{1}H NMR analysis of the reaction crude. [e] Conversion determined by ^{1}H NMR analysis of the reaction crude. [f] Yield based in 2-bromopyridine.

(Table 1, entry 9) did not occur to completion and only conversions of 50 and 58% were achieved.[19]

Finally, primary anilines **6** were isolated with good yields and excellent purities after hydrolysis of the fluorous carbamate function in **5** with DCM/TFA and subsequent F-SPE purification. The yield obtained for aniline **6c** compares well with that reported by Herr et al. in the case of 4-bromoacetophenone when using the fluorous imine f-BPI as an ammonia equivalent.[12]

To our delight, *N*-substituted-^{F}Boc carbamates underwent cross-coupling with different arylbromides to give the corresponding secondary anilines after the cleavage step and F-SPE purification. The results obtained are shown in Table 2.
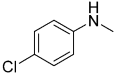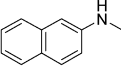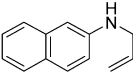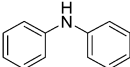
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(19) When the reaction beween 2-bromoaniline and **3a** was carried out in the absence of the catalytic system (Xantphos/Pd(OAc)$_2$), the starting materials were recovered.

TABLE 2. Synthesis of Secondary Anilines Using *N*-substituted-[F]Boc Carbamates as Amine Sources[a]

Entry	3	Ar	Aniline	6, Yield(%)[b]
1	3b	Ph		6j, 74
2	3b	4-Cl-Ph		6k, 70
3	3b	2-naphtyl		6l, 76
4	3c	Ph		6m, 38
5	3c	2-naphtyl		6n, 65
6	5a	Ph		6o, 49

[a] Reaction conditions: 1.0 equiv of the aryl halide, 1.1 equiv of [F]Boc carbamate, xantphos/Pd(OAc)$_2$ = 2/1, 1.5 equiv of Cs$_2$CO$_3$, 1,4-dioxane (1 mL/mmol halide), 100 °C, 24 h. [b] Yields refer to isolated yields of compounds estimated to be >95% pure, as determined by ^{1}H NMR and LCMS analysis or combustion analysis.

N-Methyl- and *N*-allyl-[F]Boc carbamates **3b** and **3c** reacted with different aryl bromides under the same reaction conditions as described above for the synthesis of primary anilines. Thus, the corresponding secondary anilines **6j−n** (Table 2, entries 1−5) were obtained with good purities and moderate yields after F-SPE purification. When *N*-phenyl-[F]Boc carbamate **5a** was used, the reaction was not successful under our standard reaction conditions, and the use of a stronger base such as NaO*t*-Bu was necessary to obtain the corresponding aniline **6o** (Table 2, entry 6).

In summary, we have described the preparation the novel fluorous-tagged ammonia surrogate **3a** and its application to the synthesis of anilines by Buchwald−Hartwig palladium-catalyzed amidation-hydrolysis protocol. Primary anilines were obtained in moderate to good yields and excellent purities after a sequence of two reaction steps involving fluorous separation techniques for their purification. Preliminary results indicate that *N*-substituted anilines can also be obtained just using *N*-substituted-[F]Boc carbamates as a nitrogen source. Studies toward the use and scope of [F]Boc carbamates in Buchwald−Hartwig palladium-catalyzed amination reactions are currently ongoing in our laboratories and will be reported in due course.

Experimental Section

Typical Procedure: Aniline 6a (Table 1, entry 1). To a round flask was added **1** (2 g, 2.94 mmol) in dichloromethane (30 mL) followed by NH$_3$ (7 N in MeOH) (2.52 mL, 17.64 mmol) and Et$_3$N (0.067 mL, 0.47 mmol). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue thus obtained was placed onto a FluoroFlash silica gel cartridge (10 g) that was pretreated with a MeOH/H$_2$O (4/1) mixture (30 mL). The cartridge was initially eluted with MeOH/H$_2$O (4/1) (100 mL) to remove nonfluorinated organic components. This fraction was discarded. Then the elution was done with pure with MeOH (200 mL), and the resulting fraction was collected and concentrated under reduced pressure to afford the corresponding pure ammonia surrogate **3a** in high purity as a white solid (1.95 g, 96%); mp = 110 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.47 (br s, 2H), 2.22−1.96 (m, 4H), 1.48 (s, 6H); MS (ES) *m/z* (M + 1) calcd, 550.23; found, 550.22; Anal. Calcd. for C$_{14}$H$_{12}$F$_{17}$NO$_2$: C, 30.62; H, 2.20; N, 2.55. Found, C, 30.60; H, 2.21; N, 2.55.[20] A dried, sealed tube under a nitrogen atmosphere was charged with Pd(OAc)$_2$ (0.016 g, 0.072 mmol), xantphos (0.082 g, 0.14 mmol), and Cs$_2$CO$_3$ (0.17 g, 0.54 mmol) in a previously deoxygenated dioxane (4 mL). After 1 min of stirring, PhBr (0.046 mL, 0.43 mmol) and **3a** (0.2 g, 0.36 mmol) were added and the mixture was stirred at 100 °C for 24 h. The mixture was filtered through celite and concentrated under reduced pressure. The solid was partitioned between MeOH/H$_2$O (4/1) and HFE-7100 (2 × 30/30 mL). The fluorous fractions were collected and concentrated under reduced pressure to achieve **5a** as a white solid (0.34 g, 79%); mp = 156 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38−7.27 (m, 4H), 7.06 (t, *J* = 8 Hz, 1H), 6.49 (br s, 1H), 2.26−2.05 (m, 4H), 1.52 (s, 6H); MS (ES) *m/z* (M + 1) calcd, 626.09; found, 626.10; Anal. Calcd. for C$_{20}$H$_{16}$F$_{17}$NO$_2$: C, 38.41; H, 2.58; N, 2.24. Found, C, 38.38; H, 2.57; N, 2.24.[20] To a round flask was added **5a** (0.34 g, 0.54 mmol) and a mixture of dichloromethane/trifluoroacetic acid (1/2; 15 mL). The sample was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was partitioned between NaHCO$_3$ and dichloromethane (2 × 20 mL). The organic layers were collected, the solvent was removed under reduced pressure, and the resulting residue was partitioned between NaHCO$_3$ and dichloromethane (2 × 20 mL). The organic layers were combined and the volatiles were removed under vacuum. The residue thus obtained was placed onto a FluoroFlash silica gel cartridge (10 g) that was pretreated with a MeOH/H$_2$O (4/1) mixture (30 mL). The cartridge was eluted with MeOH/H$_2$O (4/1; 100 mL), and the resulting fraction was collected and concentrated under reduced pressure to provide the desired aniline **6a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.16−7.05 (m, 2H), 6.75−6.60 (m, 3H) 3.55 (br s, 2H). ^{1}H NMR data were identical to the ones obtained from the commercially available product.

Supporting Information Available: Detailed experimental procedures and spectroscopic data, elemental analysis. and ^{1}H NMR data for all new compounds described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Elemental analyses were performed on HPLC-purified samples of compounds.