ChemPubSoc Europe

DOI: 10.1002/cctc.201501375

CHEMCATCHEM Full Papers

Room-Temperature Practical Copper-Catalyzed Amination of Aryl Iodides

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An efficient and highly practical procedure is reported for the Ullmann–Goldberg-type copper-catalyzed amination of aryl iodides. By using a combination of copper iodide and proline in the presence of an excess of an amine, a wide range of aryl iodides can be readily aminated at room temperature. The reaction proceeds well regardless of the electronic properties of the starting aryl iodide and the amination products can be obtained without the need for purification by column chromatography in most cases. Owing to its efficiency and the mildness of the reaction conditions, this amination could also be extended to the amination of complex aryl iodides at room temperature.

Introduction

Arylamines are key building blocks that are also at the core structure of an impressive number of natural products and biologically active molecules from the pharmaceutical and agrochemical industries. They have, in fact, applications in most areas of science where there is a need for small molecules and they are, for example, also used as dyes, pigments, or monomers for material sciences. As such, the development of efficient, robust, and practical methods for their synthesis is of significant importance in both industry and academia.

Besides their synthesis based on a nucleophilic aromatic substitution between an amine and a strongly activated arene, which is inherently restricted to the preparation of electron-poor arylamines, the classical routes to these building blocks have relied for years on reactions such as nucleophilic substitution or reductive amination, in which a C(sp^3)–N bond is formed. The development of metal-catalyzed reactions have enabled the design of new efficient routes to arylamines based on the formation of a C(sp^2)–N bond, a reaction which was actually first reported in the seminal work of Ullmann[1] and Goldberg[2] by using copper as the metal promoter. Indeed, a range of efficient procedures are now available to perform the amination of aryl halides or aryl–metal reagents, the former being usually more efficient and attractive because of the availability of the starting aryl halides. Over the years, many metals have been shown to efficiently catalyze the cross-coupling between amines and aryl halides, the palladium-catalyzed Buchwald–Hartwig amination—which is now a key tool in the organic chemist's toolbox—probably being the most famous example.[3] In addition to palladium, the amination of aryl halides can also be promoted by nickel,[4] cobalt,[5] rhodium,[6] or cadmium[7] complexes, even if their use is still somehow anecdotic. Indeed, palladium catalysis dominated this field until problems associated with substrate scope, harsh conditions, and the price of palladium sources and ligands motivated chemists to reconsider copper catalysis for the amination of aryl halides.

This eventually culminated in the discovery of efficient copper catalysts, which are now at least as efficient as their palladium counterpart, and even more in most cases.[8,9] The introduction of small chelating ligands for the copper-catalyzed amination of aryl halides, pioneered by the Buchwald[10] and Ma[11] groups who, respectively, introduced the use of diols, salicylamides, and amino acids as ligands for copper, resulted in dramatic improvements of the systems originally proposed by Ullmann and Goldberg. Following these reports, an impressive array of ligands, which mostly serve for the solubilization of copper(I) catalysts and the stabilization of key intermediates such as copper(III) complexes,[12] was next reported to enable the copper-catalyzed amination of aryl halides with high efficiency and broad substrate scope under milder conditions compared with the original Ullmann–Goldberg procedures.[8,13] Because of their efficiency and the availability/low cost of both copper sources and ligands, these developments, mostly reported during the last decade, clearly had a tremendous impact on many areas of organic synthesis, such as medicinal chemistry[14] or natural product synthesis,[15] not only in academia but also in industry where palladium catalysts are now often replaced with copper complexes for the amination of aryl halides.[16]

Despite these advances, some limitations still remain to be solved in order to access a fully practical and robust system for the amination of aryl halides. The three main limitations are: i) the need for thermal activation as most systems do not operate at room temperature, ii) the requirement for an inorganic base with limited solubility in organic solvents, which often results in lower yields and aggregation problems when scaling

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Supporting Information for this article can be found under http://dx.doi.org/10.1002/cctc.201501375.

up these reactions, and iii) tedious purifications by column chromatography to remove byproducts formed during the reaction. We report in this manuscript an efficient and practical copper-based procedure which addresses, at least in part, these limitations and enables the room-temperature amination of aryl iodides by using a fully homogenous system together with minimizing the efforts required for the purification step.

Results and Discussion

The model system that was chosen for the optimization relies on the use of *p*-iodoanisole **1a** as the model aryl iodide and pyrrolidine **2a** as the model amine. To avoid problems associated with an insoluble inorganic base, we chose to use two equivalents of this inexpensive amine, which would therefore serve both as the nucleophile and the base. Dimethylsulfoxide was chosen as the solvent for the reaction because of the excellent solubility of most copper(I) salts in this solvent, which can, in addition, act as a ligand for copper. Finally, we decided to use cuprous iodide, which is commonly employed in an array of copper-catalyzed cross-coupling reactions, as the source of copper(I) because of both its stability and low cost, and arbitrarily decided to use 10 mol% of this catalyst, a loading that is quite typical for such reactions. With this model system, the efficiency of different representative P,P-, N,N-, O,O-, and N,O-bidentate ligands L_1–L_8—used in a 1:1 stoichiometry relative to copper(I) iodide—to promote the amination was assessed. Results from these studies, shown in Figure 1, reveal that there is no background reaction in the absence of copper and that dppp (L_1, 1,3-bis(diphenylphosphino)propane), 1,10-phenanthroline (L_3), bipyridine (L_4), and deanol (L_6) were totally unable to promote the reaction. The expected amination product **3a** could, however, be observed, although in rather low yields, when switching to *N*,*N*′-dimethylethylenediamine (L_2), 2-isobutyrylcyclohexanone (L_5), picolinic acid (L_7), and proline (L_8), the latter being slightly superior in terms of efficiency. Assuming that the low conversion observed could be due to multiple coordination of the amine to the copper catalyst, which has been reported to generate catalytically inactive species, we decided to double the amount of the ligand, which indeed resulted in an improved yield (10% yield with a 1:1 ratio of CuI/proline vs. 24% yield with a 1:2 ratio). The reaction, however, remained rather sluggish, which could be overcome by increasing the catalyst loading; the use of 20 mol% of copper(I) iodide in combination with 40 mol% of proline resulted in the formation of **3a** in 71% yield. Finally, the use of 3 equivalents of pyrrolidine **2a** instead of two brought a further improvement as the amination product **3a** could now be isolated in 79% yield. Importantly, the use of an excess of the amine rather than an inorganic base (or even another organic base) enabled an especially clean amination as **3a** could be isolated in pure form by a simple extraction of the reaction mixture after addition of aqueous sodium hydroxide.

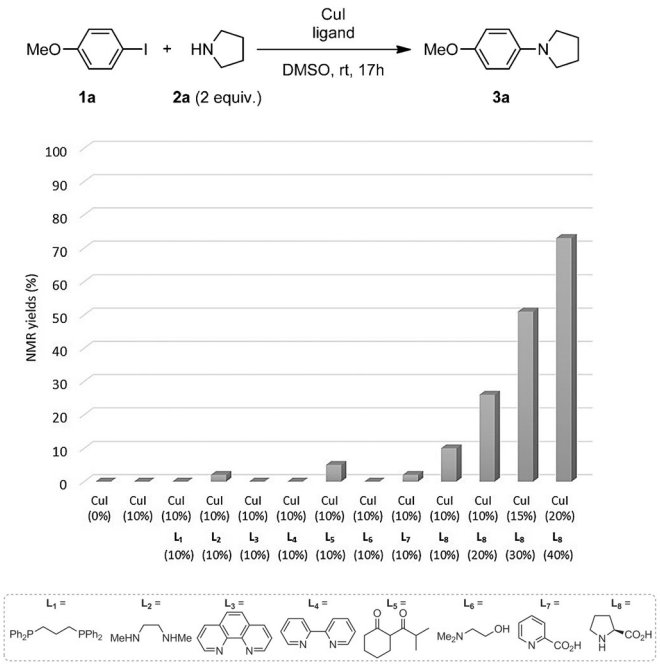
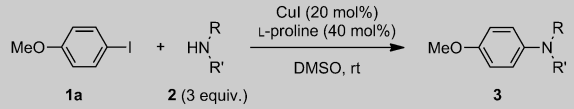


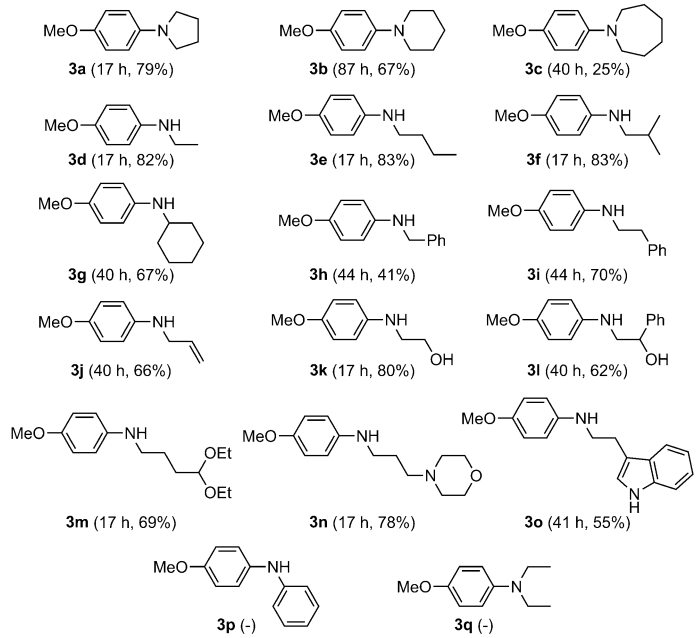
Figure 1. Optimization of the copper-catalyzed amination of *p*-iodoanisole with pyrrolidine.

Having in hand the optimized reaction conditions, we next moved to the scope and limitations studies by first evaluating the amines that could be used in our process. Results from these studies are shown in Table 1 and clearly demonstrate that a wide range of amines perform well for the amination, provided at least that they are inexpensive enough so that three equivalents can be used. Indeed, cyclic amines such as pyrrolidine, piperidine, or azepane provided the amination products **3a–c** in good yields, except in the case of azepane, which displayed a diminished reactivity. The amination involving primary amines was also successful, as demonstrated with the preparation of aniline derivatives **3d–o**, even in the presence of sensitive functional groups such as an acyclic acetal (**3m**). As an important note, bifunctional amines such as aminoalcohols[17] or tryptamine could be used without the need for protecting the alcohol or the indole, therefore providing an efficient access to polyfunctional aniline derivatives such as **3k**, **3l**, or **3o**. Here again, most aminated derivatives **3** could be readily obtained in a virtually pure form without purification by column chromatography; a simple acid–base extraction was totally sufficient in most cases. In contrast, the amination of aromatic amines (such as aniline) or acyclic secondary amines (such as diethylamine) did not proceed under our optimized conditions and the corresponding amination products **3p** and **3q** could not be detected in the crude reaction mixtures from which the starting aryl iodide **1a** could be fully recovered.

After examining the reactivity of different amines, we next studied the scope of the amination starting from different aryl iodides possessing representative electronic and steric properties (Table 2). As evident from the reactivity of these aryl iodides, the reactions, which were systematically performed by using three different amines (pyrrolidine **2a**, butylamine **2b**, and aminoethanol **2c**), smoothly gave the corresponding anilines **3** regardless the electronic properties or the substitution

Table 1. Scope of the copper-catalyzed amination of *p*-iodoanisole with different amines.

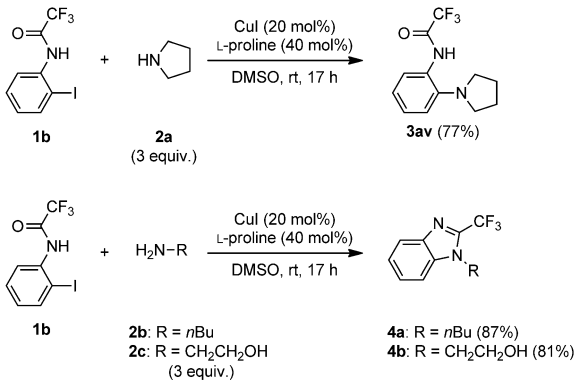




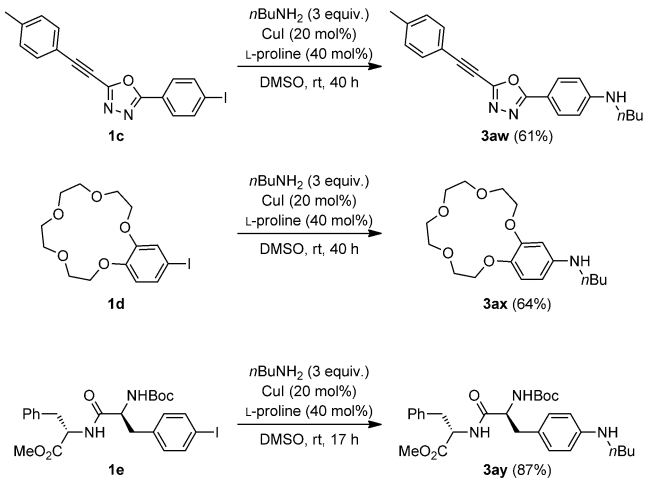
pattern of the starting aryl iodide. Indeed, electron-neutral, electron-rich, and electron-poor aryl iodides gave the corresponding anilines in fair to good yields and the total chemoselectivity observed during the amination of 4-bromo-iodobenzene—which only took place at the more reactive C–I bond—is worth noticing. A methyl ester or a primary *tert*-butyldimethylsilyl (TBS) ether were well tolerated and, importantly, the reaction can also be easily performed on a multigram scale as demonstrated with the synthesis of **3 s** starting from 10 g of iodobenzene and in 77% yield. On such a scale, the isolation of the amination product by a simple acid–base extraction and without column chromatography is especially appreciable. The mildness of the reaction conditions also enabled the amination of more sensitive aryl iodides bearing, for example, a boronate, which was well tolerated, and whose presence in the corresponding amination products **3 aj**, **3 ak**, or **3 al** provides a handle for further functionalization by metal-catalyzed cross-coupling reactions. Finally, heteroaryl iodides were also found to be suitable starting materials as evident from the preparation of indolylamines **3 am**–**3 ao**. In contrast, the use of an aryl iodide bearing an unprotected aniline or a non-chelating group (such as a methyl group) *ortho* to the reacting center did not yield the corresponding amination products (**3 ap**–**3 au**), which might be attributed to the sensitivity of the corresponding bis-amino-arenes and steric hindrance, respectively.

The outcome of the amination of 2-trifluoroacetamido-iodobenzene **1 b** was found to depend on the amine used for the amination, as shown in Scheme 1. Indeed, although the use of a secondary amine such as pyrrolidine **2 a** gave the amination product **3 av** in 77% yield, the arylation of **1 b** with primary amines such as butylamine **2 b** and aminoethanol **2 c** did not stop at the amination step. The amination was followed by addition of the amine to the activated trifluoroacetamide, leading to the trifluoromethylated benzimidazoles **4 a** and **4 b**, a reaction that has been previously reported by using either high temperatures or a two-step process.[18]

Finally, and in an effort to push our system to its limits, we briefly examined the possibility of using our procedure for the amination of complex systems for which the use of a high temperature or an inorganic base could be problematic. The amination of aryl iodides possessing an unsaturated oxadiazole substituent **1 c**, a benzocrown ether **1 d**, or embedded in a more complex and sensitive dipeptide such as in **1 e** was therefore tested by using butylamine as the nucleophile (Scheme 2). To our delight, the corresponding amination prod-

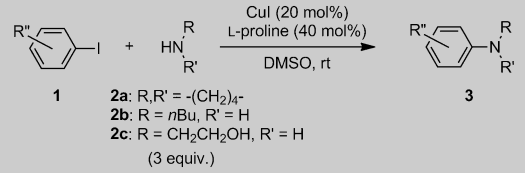


Scheme 1. Copper-catalyzed amination of 2-trifluoroacetamido-iodobenzene.

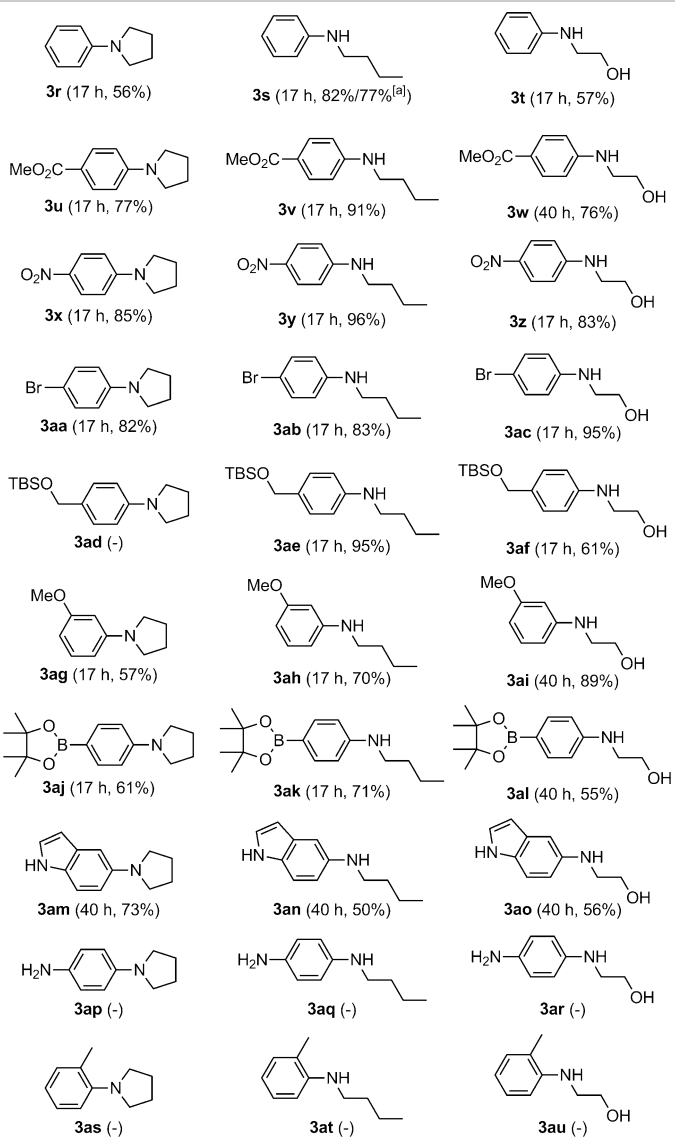


Scheme 2. Copper-catalyzed amination of complex substrates.

Table 2. Scope of the copper-catalyzed amination of representative amines with different aryl iodides.



1 2a: R,R' = -$(CH_2)_4$- 2b: R = *n*Bu, R' = H 2c: R = CH_2CH_2OH, R' = H (3 equiv.) 3



[a] Reaction performed on a 10 g scale.

ucts **3aw**, **3ax**, and **3ay** could be isolated in 61, 64, and 87% yield, respectively, which demonstrates the efficiency of our system for the amination of structurally complex and/or sensitive aryl iodides.

Conclusions

We have developed an efficient and highly practical procedure for the Ullmann–Goldberg-type copper-catalyzed amination of aryl iodides with amines. By using a combination of copper iodide and proline in the presence of an excess of the amine, a wide range of aryl iodides can be readily aminated at room temperature. The reaction proceeds well regardless of the electronic properties of the starting aryl iodide and the amination products can be obtained without the need for purification by column chromatography in most cases, which is most certainly the main advantage of our process, especially on a large scale. Owing to its efficiency and the mildness of the reaction conditions, this amination could also be extended to the amination of complex aryl iodides at room temperature, which should be especially useful for diversity-oriented synthesis or medicinal chemistry. Further studies to better understand the activation mode of the aryl iodide by the copper catalyst, which readily proceeds at room temperature, are ongoing.

Experimental Section

General remarks

All reactions were carried out in oven-dried glassware under an argon atmosphere. All solvents were reagent grade. Anhydrous DMSO (>99.5% purity, stored over molecular sieves) was purchased from Aldrich and used as supplied. Copper(I) iodide (99.999% purity) was purchased from Aldrich and used as supplied. All other reagents were used as supplied. Reactions were magnetically stirred and monitored by thin layer chromatography by using Macherey–Nagel Pre Coated TLC-sheets Alugram Xtra Sil/UV254. Flash chromatography was performed with silica gel 60 (particle size 35–70 μm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds. Proton NMR spectra were recorded by using an internal deuterium lock at ambient temperature on Bruker 300 MHz spectrometers. An internal reference of $\delta_H = 7.26$ was used for $CDCl_3$. Data are presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{TMS} = 0$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, m = multiplet, br. = broad, app. = apparent), coupling constant (*J* [Hz]) and integration. Resonances that are either partially or fully obscured are denoted obscured (obs.). Carbon-13 NMR spectra were recorded at 75 MHz by using $CDCl_3$ ($\delta_C = 77.16$) as the internal reference. Melting points were recorded with a Stuart Scientific Analogue SMP11. Infrared spectra were recorded with a Bruker Alpha (ATR). High-resolution mass-spectra were obtained with an Agilent Technologies GC-Q-TOF or with a Waters Xevo-QTOF spectrometer.

General procedure for the copper-catalyzed amination of aryl iodides

An oven-dried flask was charged with copper iodide (38 mg, 0.2 mmol) and L-proline (46 mg, 0.4 mmol); if solid, the aryl iodide (1.0 mmol) was also introduced at this stage. The flask was evacuated under high vacuum and backfilled with argon three times, then fitted with a rubber septum. DMSO (1.0 mL) was next added, as well as the aryl iodide, which was added at this stage if liquid.

The resulting blue solution was stirred for 5 min before adding the amine (3.0 mmol). The resulting mixture was stirred under argon at room temperature until completion (see below for reaction times). The workup used is indicated below for each arylation product.

***N*-(4-Methoxyphenyl)pyrrolidine 3a**: Obtained according to the general procedure from 4-iodoanisole (234.0 mg, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3a** as a beige solid (139 mg, 0.79 mmol, 79%). This compound has been previously reported.[11b]

***N*-(4-Methoxyphenyl)piperidine 3b**: Obtained according to the general procedure from 4-iodoanisole (233.9 mg, 1.0 mmol) and piperidine (295 μL, 3.0 mmol) at room temperature for 87 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3b** as a pale-yellow solid (128 mg, 0.67 mmol, 67%). This compound has been previously reported.[19]

***N*-(4-Methoxyphenyl)azepane 3c**: Obtained according to the general procedure from 4-iodoanisole (234.2 mg, 1.0 mmol) and azepane (340 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3c** as a pale-brown oil (75.7 mg, 0.37 mmol, 37%). This compound has been previously reported.[20]

***N*-Ethyl-4-methoxyaniline 3d**: Obtained according to the general procedure from 4-iodoanisole (234.0 mg, 1.0 mmol) and ethylamine (70% in water, 285 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3d** as a pale-brown oil (124 mg, 0.82 mmol, 82%). This compound has been previously reported.[21]

***N*-Butyl-4-methoxyaniline 3e**: Obtained according to the general procedure from 4-iodoanisole (234.1 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3e** as a pale-yellow oil (150 mg, 0.83 mmol, 83%). This compound has been previously reported.[11b]

***N*-Isobutyl-4-methoxyaniline 3f**: Obtained according to the general procedure from 4-iodoanisole (234.2 mg, 1.0 mmol) and isobutylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3f** as a pale-yellow solid (148 mg, 0.83 mmol, 83%). This compound has been previously reported.[22]

***N*-Cyclohexyl-4-methoxyaniline 3g**: Obtained according to the general procedure from 4-iodoanisole (234.1 mg, 1.0 mmol) and cyclohexylamine (345 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3g** as a dark oil (138 mg, 0.67 mmol, 67%). This compound has been previously reported.[23]

***N*-Benzyl-4-methoxyaniline 3h**: Obtained according to the general procedure from 4-iodoanisole (234.0 mg, 1.0 mmol) and benzylamine (330 μL, 3.0 mmol) at room temperature for 44 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were filtered through a short plug of silica gel, which was washed with a mixture of petroleum ether and ethyl acetate (80:20). The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3h** as a brownish solid (87 mg, 0.41 mmol, 41%). This compound has been previously reported.[11b]

***N*-Phenethyl-4-methoxyaniline 3i**: Obtained according to the general procedure from 4-iodoanisole (234.1 mg, 1.0 mmol) and phenethylamine (380 μL, 3.0 mmol) at room temperature for 44 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were filtered through a short plug of silica gel, which was washed with a mixture of petroleum ether and ethyl acetate (90:10). The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to

give the desired pure product **3i** as a colorless oil (159 mg, 0.70 mmol, 70%). This compound has been previously reported.[24]

***N*-Allyl-4-methoxyaniline 3j**: Obtained according to the general procedure from 4-iodoanisole (234.0 mg, 1.0 mmol) and allylamine (225 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3j** as a brownish oil (107 mg, 0.66 mmol, 66%). This compound has been previously reported.[25]

2-(4-Methoxyphenyl)aminoethanol 3k: Obtained according to the general procedure from 4-iodoanisole (234.2 mg, 1.0 mmol) and aminoethanol (180 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of ethyl acetate. The organic layers were combined and filtered through a short plug of silica gel, which was washed with ethyl acetate. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3k** as a pale-yellow solid (134 mg, 0.80 mmol, 80%). This compound has been previously reported.[26]

2-[(4-Methoxyphenyl)amino]-1-phenylethanol 3l: Obtained according to the general procedure from 4-iodoanisole (233.9 mg, 1.0 mmol) and 2-amino-1-phenylethanol (412.3 mg, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3l** as a brownish oil (151 mg, 0.62 mmol, 62%). This compound has been previously reported.[27]

***N*-(4,4-Diethoxybutyl)-4-methoxyaniline 3m**: Obtained according to the general procedure from 4-iodoanisole (234.0 mg, 1.0 mmol) and 4,4-diethoxybutylamine (520 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography over triethylamine-deactivated silica gel (petroleum ether/EtOAc = 90:10) to afford the desired pure product **3m** as a pale-orange oil (184 mg, 0.69 mmol, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.86$ (d, $J = 9.0$ Hz, 2H), 6.55 (d, $J = 8.7$ Hz, 2H), 4.52 (t, $J = 5.1$ Hz, 1H), 3.74 (s, 3H), 3.65 (app. quint., $J = 7.7$ Hz, 2H), 3.50 (app. quint., $J = 7.6$ Hz, 2H), 3.09 (t, $J = 6.5$ Hz, 2H), 1.78–1.60 (m, 4H), 1.21 ppm (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.1$, 142.8, 115.0, 114.1, 102.8, 61.3, 55.9, 44.9, 31.4, 25.0, 15.5 ppm; IR (ATR): $\tilde{\nu}_{max} =$ 2973, 1513, 1235, 1123, 1039, 818 cm^{-1}; ESI HRMS *m/z* calcd for $C_{15}H_{25}NO_3$: 268.1907 $[M+H]^+$; found: 268.1896.

4-Methoxy-*N*-(3-morpholinopropyl)aniline 3n: Obtained according to the general procedure from 4-iodoanisole (234.0 mg, 1.0 mmol) and *N*-(3-aminopropyl)morpholine (440 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of diethyl ether. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3n** as a pale-yellow solid (196 mg, 0.78 mmol, 78%). M.p.: 50 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.76$ (d, $J = 8.7$ Hz, 2H), 6.55 (d, $J = 9.0$ Hz, 2H), 3.73 (s, 3H), 3.76–3.69 (m, 4H), 3.11 (t, $J = 6.4$ Hz, 2H), 2.48–2.44 (m, 6H), 1.73 ppm (app. quint., $J = 6.6$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.4$, 142.4, 114.4, 113.5, 66.5, 57.1, 55.3, 53.3, 43.6, 25.2 ppm; IR (ATR): $\tilde{\nu}_{max} = 3360$, 2949, 2859, 1515, 1232, 1115, 1033, 865, 523 cm^{-1}; ESI HRMS *m/z* calcd for $C_{14}H_{22}N_2O_2$: 251.1754 $[M+H]^+$; found: 251.1757.

***N*-(4-Methoxyphenyl)-tryptamine 3o**: Obtained according to the general procedure from 4-iodoanisole (233.9 mg, 1.0 mmol) and tryptamine (480.9 mg, 3.0 mmol) at room temperature for 41 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of diethyl ether. The crude was purified by column chromatography on silica gel (EtOAc/petroleum ether gradient from 10:90 to 50:50) to afford the desired pure product **3o** as a brownish solid. (145.7 mg, 0.55 mmol, 55%). M.p.: 85–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.18$ (br. s, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.22–7.34 (m, 2H), 7.05 (br. s, 1H), 6.90 (dt, $J =$ 6.9, 2.6 Hz, 2H), 6.70 (d, $J = 8.1$ Hz, 2H), 3.86 (s, 3H), 3.53 (t, $J =$ 6.8 Hz, 2H), 3.17 ppm (t, $J = 6.9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.2$, 142.5, 136.5, 127.5, 122.2, 119.4, 118.8, 115.0, 114.6, 113.3, 111.3, 55.9, 45.1, 25.2 ppm; IR (ATR): $\tilde{\nu}_{max} = 3344$, 1508, 1457, 1439, 1079, 823, 682, 667 cm^{-1}; ESI HRMS *m/z* calcd for $C_{17}H_{18}N_2O$: 267.1492 $[M+H]^+$; found: 267.1496.

***N*-Phenyl-pyrrolidine 3r**: Obtained according to the general procedure from iodobenzene (110 μL, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3r** as a pale-yellow oil (82 mg, 0.56 mmol, 56%). This compound has been previously reported.[19]

***N*-Butyl-aniline 3s**: Obtained according to the general procedure from iodobenzene (110 μL, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3s** as a colorless oil (123 mg, 0.82 mmol, 82%). Alternatively, this compound was prepared from iodobenzene (5.5 mL, 49 mmol) and butylamine (14.5 mL, 147 mmol) under the same reaction conditions to afford **3s** (5.6 g, 38 mmol, 77%). This compound has been previously reported.[11b]

2-(Phenylamino)ethanol 3t: Obtained according to the general procedure from iodobenzene (110 μL, 1.0 mmol) and aminoethanol (180 μL, 3.0 mmol) at room temperature for 17 h. Upon comple-

tion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The combined organic layers were successively washed with 30 mL of water and 15 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3t** as a pale-yellow oil (79 mg, 0.57 mmol, 57%). This compound has been previously reported.[28]

Methyl 4-(pyrrolidin-1-yl)benzoate 3u: Obtained according to the general procedure from methyl 4-iodobenzoate (262.1 mg, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3u** as a white solid (159 mg, 0.77 mmol, 77%). This compound has been previously reported.[29]

Methyl 4-(butylamino)benzoate 3v: Obtained according to the general procedure from methyl 4-iodobenzoate (231.8 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3v** as a pale-orange solid (189 mg, 0.91 mmol, 91%). This compound has been previously reported.[30]

Methyl 4-[(2-hydroxyethyl)amino]benzoate 3w: Obtained according to the general procedure from methyl 4-iodobenzoate (261.8 mg, 1.0 mmol) and aminoethanol (180 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The combined organic layers were successively washed with 30 mL of water and 15 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3w** as a pale-orange solid (153 mg, 0.76 mmol, 76%). This compound has been previously reported.[31]

1-(4-Nitrophenyl)pyrrolidine 3x: Obtained according to the general procedure from 4-iodonitrobenzene (248.9 mg, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3x** as a yellow solid (164 mg, 0.85 mmol, 85%). This compound has been previously reported.[29]

***N*-Butyl-4-nitroaniline 3y**: Obtained according to the general procedure from 4-iodonitrobenzene (249.0 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3y** as a yellow solid (187 mg, 0.96 mmol, 96%). This compound has been previously reported.[32]

2-[(4-Nitrophenyl)amino]ethanol 3z: Obtained according to the general procedure from 4-iodonitrobenzene (249.2 mg, 1.0 mmol) and aminoethanol (180 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The combined organic layers were successively washed with 30 mL of water and 15 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3z** as a yellow solid (151 mg, 0.83 mmol, 83%). This compound has been previously reported.[33]

1-(4-Bromophenyl)pyrrolidine 3aa: Obtained according to the general procedure from 1-bromo-4-iodobenzene (282.9 mg, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3aa** as a brownish solid (185 mg, 0.82 mmol, 82%). This compound has been previously reported.[19]

4-Bromo-*N*-butylaniline 3ab: Obtained according to the general procedure from 1-bromo-4-iodobenzene (282.9 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3ab** as a brownish oil (189 mg, 0.83 mmol, 83%). This compound has been previously reported.[11b]

2-[(4-Bromophenyl)amino]ethanol 3ac: Obtained according to the general procedure from 1-bromo-4-iodobenzene (283.1 mg, 1.0 mmol) and aminoethanol (180 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The combined organic layers were successively washed with 30 mL of water and 15 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3ac** as a brownish solid (160 mg, 0.95 mmol, 95%). This compound has been previously reported.[34]

***N*-Butyl-4-(*tert*-butyldimethylsilyloxymethyl)aniline 3ae**: Obtained according to the general procedure from 4-(*tert*-butyldimethylsilyloxymethyl)iodobenzene (348.5 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3ae** as a pale-yellow oil (239.6 mg, 0.95 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 8.4$ Hz, 2H), 6.63 (d, $J = 8.4$ Hz, 2H), 4.71 (s, 2H), 3.71 (t, $J = 7.1$ Hz, 2H), 1.66 (app. quint., $J = 7.4$ Hz, 2H), 1.50 (app. sext., $J = 7.5$ Hz, 2H), 1.02 (obs. t, 3H) 1.02 (s, 9H), 0.17 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.9$, 130.1, 127.9, 112.7, 65.3, 44.0, 31.9, 26.2, 20.5, 18.6, 14.1, −4.9 ppm; IR (ATR): $\tilde{\nu}_{max} = 2955$, 2929, 1616, 1521, 1073, 836, 755 cm^{-1}; ESI HRMS *m/z* calcd for $C_{17}H_{32}NOSi$: 294.2248 $[M+H]^+$; found: 294.2250.

2-{[4-(*tert*-Butyldimethylsilyloxymethyl)phenyl]amino}ethan-1-ol 3af: Obtained according to the general procedure from 4-(*tert*-butyldimethylsilyloxymethyl)iodobenzene (348.1 mg, 1.0 mmol) and aminoethanol (181 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography over silica gel (petrole-

um ether/EtOAc = 90:10 to 50:50)) to afford the desired pure product **3af** as a colorless oil (171.5 mg, 0.61 mmol, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 8.4 Hz, 2H), 4.64 (s, 2H), 3.77 (t, J = 5.2 Hz, 2H), 3.25 (t, J = 5.2 Hz, 2H), 0.95 (s, 9H), 0.10 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.4, 130.9, 127.9, 113.3, 65.2, 61.2, 46.4, 26.1, 18.6, −5.0 ppm; IR (ATR): $\tilde{\nu}_{max}$ = 2952, 2929, 1665, 1523, 1063, 836, 775 cm^{-1}; ESI HRMS *m/z* calcd for $C_{15}H_{28}NO_2Si$: 282.1884 $[M+H]^+$; found: 282.1879.

1-(3-Methoxyphenyl)pyrrolidine 3ag: Obtained according to the general procedure from 3-iodoanisole (120 μL, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3ag** as a pale-yellow oil (102 mg, 0.57 mmol, 57%). This compound has been previously reported.[19]

***N*-Butyl-3-methoxyaniline 3ah**: Obtained according to the general procedure from 3-iodoanisole (120 μL, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3ah** as a colorless oil (125 mg, 0.70 mmol, 70%). This compound has been previously reported.[11b]

2-[(3-Methoxyphenyl)amino]ethanol 3ai: Obtained according to the general procedure from 3-iodoanisole (120 μL, 1.0 mmol) and aminoethanol (180 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The combined organic layers were successively washed with 30 mL of water and 15 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3ai** as a brownish solid (160 mg, 0.95 mmol, 95%). This compound has been previously reported.[35]

***N*-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine 3aj**: Obtained according to the general procedure from 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (330.1 mg, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3aj** as a brownish solid (166 mg, 0.61 mmol, 61%). This compound has been previously reported.[36]

***N*-Butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 3ak**: Obtained according to the general procedure from 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (329.6 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3ak** as a reddish solid (197 mg, 0.71 mmol, 71%). M.p.: 54–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 3.90 (br.s, 1H), 3.14 (t, J = 6.9 Hz, 2H), 1.60 (app. quint., J = 7.2 Hz, 2H), 1.42 (app. sext., J = 7.3 Hz, 2H), 1.35 (s, 12H), 0.98 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 136.3, 111.7, 83.1, 43.1, 31.5, 24.9, 20.3, 13.9 ppm; IR (ATR): $\tilde{\nu}_{max}$ = 3361, 2976, 1607, 1396, 1360, 1330, 1310, 1280, 1182, 1142, 1089, 861, 824, 658 cm^{-1}; ESI HRMS *m/z* calcd for $C_{16}H_{26}BNO_2$: 276.2132 $[M+H]^+$; found: 276.2156.

***N*-{[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}-ethanol 3al**: Obtained according to the general procedure from 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (330.0 mg, 1.0 mmol) and aminoethanol (180 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The combined organic layers were successively washed with 30 mL of water and 15 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3al** as a brownish oil (146 mg, 0.55 mmol, 55%). This compound has been previously reported.[37]

5-(Pyrrolidin-1-yl)-indole 3am: Obtained according to the general procedure from 5-iodoindole (243.1 mg, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the desired pure product **3am** as a brownish solid (136.3 mg, 0.73 mmol, 73%). M.p.: 67–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (br. s, 1H), 7.23 (d, J = 9.3 Hz, 1H), 7.09 (t, J = 2.9 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.72 (dd, J = 9.0, 2.4 Hz, 1H), 6.43–6.45 (m, 1H), 3.36 (t, J = 6.6 Hz, 4H), 2.06 ppm (app. quint, J = 3.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5, 129.3, 129.1, 124.6, 111.5, 110.4, 101.7, 101.6, 48.9, 25.4 ppm; IR (ATR): $\tilde{\nu}_{max}$ = 3398, 1624, 1578, 1137, 901, 790, 755, 637 cm^{-1}; ESI HRMS *m/z* calcd for $C_{12}H_{14}N_2$: 187.1230 $[M+H]^+$; found: 187.1235.

***N*-Butyl-indol-5-amine 3an**: Obtained according to the general procedure from 5-iodoindole (243.1 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the desired pure product **3an** as a viscous brownish oil (94.9 mg, 0.50 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (br. s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.06 (app. t, J = 2.6 Hz, 1H), 6.90 (d, J = 2.1 Hz, 1H), 6.64 (dd, J = 8.7, 2.4 Hz, 1H), 6.40–6.42 (m, 1H), 3.19 (t, J = 7.2 Hz, 2H), 1.68 (app. quint., J = 7.4 Hz, 2H), 1.48 (app. sext., J = 7.3 Hz, 2H), 1.01 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.6, 130.3, 128.9, 124.7, 112.5, 111.8, 102.6, 101.6, 45.5, 32.0, 20.6, 14.2 ppm; IR (ATR): $\tilde{\nu}_{max}$ = 3398, 3243, 1625, 1582, 1169, 1133, 1066, 833, 795, 757 cm^{-1}; ESI HRMS *m/z* calcd for $C_{12}H_{16}N_2$: 189.1386 $[M+H]^+$; found: 189.1394.

2-[(Indol-5-yl)amino]ethan-1-ol 3ao: Obtained according to the general procedure from 5-iodoindole (243.0 mg, 1.0 mmol) and

aminoethanol (180 μL, 3.0 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 15 mL of ethyl acetate. The organic layers were combined and extracted with 30 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded, and the aqueous layer was basified by addition of 40 mL of a 1 M aqueous solution of sodium hydroxide, then extracted twice with 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the desired pure product **3 ao** as a viscous brownish oil (98.7 mg, 0.58 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (br. s, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.16 (t, J = 2.9 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 6.71 (dd, J = 8.7, 2.4 Hz, 1H), 6.44–6.46 (m, 1H), 3.88 (t, J = 5.3 Hz, 2H), 3.37 (t, J = 5.1 Hz, 2H), 2.88 ppm (br.s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 142.1, 130.6, 128.8, 127.7, 112.8, 111.8, 103.3, 101.9, 61.5, 47.8 ppm; IR (ATR): $\tilde{\nu}_{max}$ = 3401, 2933, 1723, 1373, 1168, 1137, 843, 799 cm^{-1}; ESI HRMS *m/z* calcd for $C_{10}H_{12}N_2O$: 177.1022 $[M+H]^+$; found: 177.1023.

2,2,2-Trifluoro-*N*-[2-(pyrrolidin-1-yl)phenyl]acetamide 3 av: Obtained according to the general procedure from 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (314.7 mg, 1.0 mmol) and pyrrolidine (250 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of an aqueous solution of hydrochloric acid (pH 5) and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **3 av** as a brown solid (193 mg, 0.77 mmol, 77%). M.p.: 53–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.26 (s, 1H), 8.15 (dd, J = 7.8, 1.4 Hz, 1H), 7.21–7.06 (m, 3H), 3.01 (t, J = 6.3 Hz, 4H), 1.96 ppm (t, J = 6.3 Hz, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 155.2, 154.7, 154.2, 153.7, 141.1, 130.5, 126.2, 124.3, 121.8, 120.5, 120.0, 117.9, 114.1, 110.3, 52.7, 24.5 ppm; IR (ATR): $\tilde{\nu}_{max}$ = 1698, 1541, 1501, 1455, 1225, 1160, 754 cm^{-1}; ESI HRMS *m/z* calcd for $C_{12}H_{13}F_3N_2O$: 259.1053 $[M+H]^+$; found: 259.1056.

1-Butyl-2-(trifluoromethyl)-benzimidazole 4 a: Obtained according to the general procedure from 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (315.0 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of an aqueous solution of hydrochloric acid (pH 5) and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **4 a** as a dark oil (210 mg, 0.87 mmol, 87%). This compound has been previously reported.[38]

2-[2-(Trifluoromethyl)-benzimidazol-1-yl]ethan-1-ol 4 b: Obtained according to the general procedure from 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (314.8 mg, 1.0 mmol) and aminoethanol (300 μL, 3.0 mmol) at room temperature for 17 h. Upon completion, the reaction mixture was diluted with 70 mL of an aqueous solution of hydrochloric acid (pH 5) and extracted twice with 15 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give the desired pure product **4 b** as a brown solid (187 mg, 0.81 mmol, 81%). This compound has been previously reported.[38]

***N*-Butyl-4-[5-(*p*-tolylethynyl)-1,3,4-oxadiazol-2-yl]aniline 3 aw**: Obtained according to the general procedure from 2-(4-iodophenyl)-5-(*p*-tolylethynyl)-1,3,4-oxadiazole (20.1 mg, 0.052 mmol) and butylamine (15 μL, 0.15 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 10 mL of a 1 M aqueous solution of sodium hydroxide and extracted twice with 7 mL of diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc = 90:10) to afford the desired pure product **3 aw** as a yellow solid (10.5 mg, 0.032 mmol, 61%). M.p.: 98–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 3.19 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.68–1.58 (m, 2H), 1.46 (app. sext., J = 7.4 Hz, 2H), 0.98 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 152.0, 141.5, 132.8, 130.0, 129.4, 117.7, 112.8, 111.9, 110.2, 97.4, 73.7, 43.7, 32.0, 22.3, 20.8, 14.4 ppm; IR (ATR) $\tilde{\nu}_{max}$ = 1652, 1520, 1472, 1182, 1166, 1033, 817, 742 cm^{-1}; ESI HRMS *m/z* calcd for $C_{21}H_{21}N_3O$: 331.1757 $[M+H]^+$; found: 332.1759.

15-Butylamino-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]-pentaoxacyclopentadecane 3 ax: Obtained according to the general procedure from 15-iodo-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecane (49.8 mg, 0.013 mmol) and butylamine (37 μL, 0.38 mmol) at room temperature for 40 h. Upon completion, the reaction mixture was diluted with 10 mL of a 25% aqueous solution of tetramethylammonium hydroxide (TMAOH) and extracted twice with 5 mL of ethyl acetate. The organic layers were combined and extracted with 10 mL of a 1 M aqueous solution of hydrochloric acid. The organic layer was discarded and the aqueous layer was basified by addition of 15 mL of a 25% aqueous solution of TMAOH, then extracted twice with 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford the desired pure product **3 ax** as a brownish solid (28 mg, 0.083 mmol, 64%). M.p.: 61–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (d, J = 8.7 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 6.14 (dd, J = 5.7, 2.6 Hz, 1H), 4.12–4.05 (m, 4H), 3.91–3.85 (m, 4H), 3.74 (br.s, 8H), 3.05 (t, J = 7.1 Hz, 2H), 1.58 (app. quint., J = 7.1 Hz, 2H), 1.41 (app. sext., J = 7.3 Hz, 2H), 0.94 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4, 143.7, 140.9, 117.4, 104.5, 100.5, 70.7, 70.6 (2C), 70.5, 70.2, 69.7, 69.4, 68.5, 44.3, 31.4, 20.0, 13.6 ppm; IR (ATR) $\tilde{\nu}_{max}$ = 2929, 1518, 1454, 1251, 1236, 1200, 1136, 1087, 1056, 976, 937, 819, 789 cm^{-1}; ESI HRMS *m/z* calcd for $C_{18}H_{29}NO_5$: 340.2118 $[M+H]^+$; found: 340.2117.

Methyl {(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-(butylamino)phenyl]propanoyl}-L-phenylalaninate 3 ay: Obtained according to the general procedure from methyl {(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-iodophenyl)propanoyl}-L-phenylalaninate (552.4 mg, 1.0 mmol) and butylamine (300 μL, 3.0 mmol) at room temperature for 17 h in 2.5 mL of DMSO. Upon completion, the reaction mixture was diluted with 70 mL of water and extracted twice with 50 mL of ethyl acetate. The organic layers were combined and washed successively with 50 mL of water and 30 mL of brine. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the desired pure product **3 ay** as a yellow solid (433.3 mg, 0.87 mmol, 87%). M.p.: 88–90 °C; $[\alpha]_D^{25}$ +44.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.43 (m, 4H), 7.25 (d, J = 7.8 Hz, 4H), 6.80 (d, J = 8.1 Hz, 2H), 6.56 (d, J = 7.8 Hz, 1H), 5.21 (br.s, 1H), 5.03 (q, J = 6.6 Hz, 1H), 4.51 (br. s, 1H), 3.95 (s, 3H), 3.36–3.13 (m, 6H), 1.85 (app. quint., J = 7.0 Hz, 2H), 1.67 (obs. app. sext., 2H), 1.67 (br. s, 9H), 1.21 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 171.5, 155.4, 147.6, 136.0, 130.2, 129.5, 129.4, 128.5, 127.1, 124.6, 112.9, 53.5, 52.3, 43.8, 38.1, 37.6, 31.7, 28.3, 20.4, 14.0 ppm; IR (ATR): $\tilde{\nu}_{max}$ = 3325, 2957, 2930, 1731, 1454, 1331, 1244, 1170, 1043, 817, 697 cm^{-1}; ESI HRMS *m/z* calcd for $C_{28}H_{39}N_3O_5$: 498.2962 $[M+H]^+$; found: 498.2981.

Acknowledgements

Our work was supported by the Université Libre de Bruxelles and the FNRS (Incentive Grant for Scientific Research no. F.4530.13). C.D. acknowledges the Fonds pour la formation à la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A.) for a graduate fellowship.

Keywords: amination · anilines · aryl halides · C–N bond formation · copper catalysis

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Received: December 17, 2015
Published online on March 8, 2016