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Regioselective One-Pot Bromination of Aromatic Amines[1]

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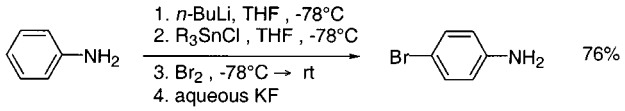
ABSTRACT

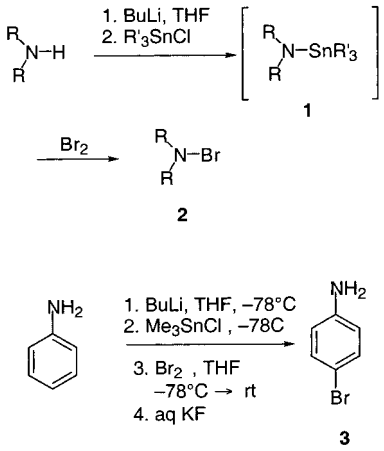


Treatment of aniline with *n*-butyllithium and then trimethyltin chloride gave the tin amide (PhNH-SnMe$_3$) in situ. Without isolation of the tin amide, reaction with bromine and workup with aqueous fluoride ion gave *p*-bromoaniline in 76% yield, with no dibromoaniline or *o*-bromoaniline. Application of this sequence to 11 different aromatic amines gave selective bromination in 36−91% yields, without formation of dibromides. This constitutes a good general method for the regioselective bromination of aromatic amines.

Electrophilic aromatic bromination is one of the older reactions known to organic chemists. Aryl halides are important synthetic intermediates for a variety of transformations that range from formation of functionalized aromatic compounds to aryl organometallic reagents that are used in other reactions. Despite the many halogenation methods that are available, activated aromatic compounds such as aniline derivatives remain a problem. Mixtures of ortho and para products and polybromination are problems that limit the synthetic utility of many procedures. There are a handful of selective bromination procedures, and we now report another that gives good yields of *p*-bromoaniline. The reaction is rather general in scope, and many monobrominated aromatic amines can be formed in good yield with high selectivity.

Tin amides such as **1** are known, formed by treating an amine with a strong base such as LDA, followed by addition of a trialkyltin halide (R$_3$SnCl). We became interested in these compounds as putative amino transfer agents in palladium-catalyzed coupling reactions but found that they also react with elemental bromine to give *N*-bromoamines (**2**), as shown in Scheme 1. When diisopropylamine was

Scheme 1



treated with butyllithium (ether, −78 °C) and then trimethyltin chloride, *i*-Pr$_2$N-SnMe$_3$ was formed in situ. Simple titration with elemental bromine at −78 °C gave **2** (R = *i*-Pr). We obtained a 45% isolated yield of **2**. *N*-Bromoamines

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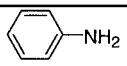
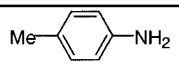
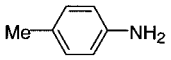
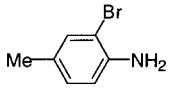
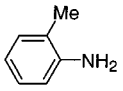
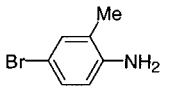
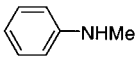
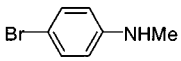
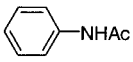
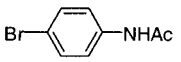
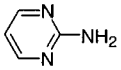
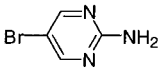
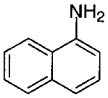
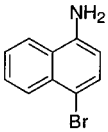
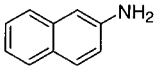
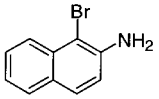
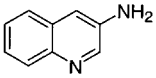
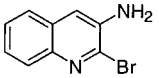
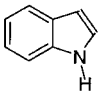
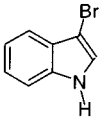
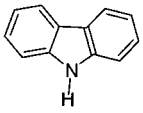
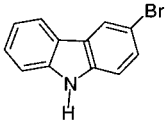
are known compounds but are rather unstable upon isolation. Although we prepared several different bromoamines **2**, the isolated yields were lower than those reported with other procedures. This process was not amenable to making large amounts, possibly as a result of residual tin compounds that promoted decomposition. Although we knew that *N*-bromoaniline was reported to be an unstable compound, we explored the possibility of generating this compound in situ for possible use. We therefore treated aniline with *n*-butyllithium and added trimethyltin chloride in ether, also at −78 °C. We presumably generated the tin amide in situ, and addition of bromine at −78 °C followed by warming at workup with aqueous KF to remove tin residues led to a 76% yield of *p*-bromoaniline, with no detectable *o*-bromo or dibromo compounds. Although the aromatic bromination is not surprising in itself, the selectivity of the reaction was notable.

Examining the literature revealed several previous methods for selective bromination of aniline. Tetrabutylammonium tribromide,[5] DBUH·Br_3[6] cetyltrimethylammonium tribromide,[7] and pyridinium bromide perbromide[8] have been reported as mild brominating agents. Aniline reacted with tetrabutylammonium tribromide, for example, to give an 82% yield of **3**, along with some dibrominated products. However, acetanilide and pyridine did not react with this reagent.[9] This contrasts with pyridinium bromide perbromide, which brominated pyridine, aniline, and its derivatives, although reaction with aniline gave a 19:68 ratio of *o*- to *p*-bromoaniline.[10] A recent study used LiBr/ceric ammonium nitrate as a brominating agent, converting *N*,*N*-dimethylaniline to a 2:3 mixture of *o*- and *p*-bromo derivatives in 70% yield.[11] Majetich and co-workers, who showed that aniline reacted with HBr/DMSO to give a 76% yield of **3** after 6 h, in a remarkably selective reaction, reported one of the most useful methods.[12]

We were pleased to find that conversion of aniline to the corresponding tin amide, followed by directed bromination, led to good yields of monobrominated product, 4-bromoaniline,[13] with excellent selectivity (entry 1 in Table 1). We were interested in expanding this reaction to other aromatic amines, with the hope that monobrominated products could be obtained. Our results are presented in Table 1, and it is clear that this technique is both general and selective.

We examined the reactivity of both 4-methylaniline and 2-methylaniline. 2-Methylaniline (entry 3) reacted much like aniline, giving a 73% yield of 4-bromo-2-methylaniline.[14] We were particularly interested in the reaction of 4-methylaniline (entry 2), in which bromination was forced to the ortho position or there would be no reaction. Although a 30% yield of 2-bromo-4-methylaniline[15] was obtained, it is clear that reactivity is greatly diminished. We have not clearly determined the source of this para selectivity. Two possibilities are a steric effect or an electronic effect of the N−Sn unit. If the brominating agent were coordinated to the tin, one might expect delivery of bromine to the ortho position. This was not observed. We also observed that 2-methylaniline reacted rapidly to give the 4-bromo product but 4-methylaniline reacted sluggishly to give a poor yield of the 2-bromo derivative. These results are consistent with a steric effect that inhibits delivery to the ortho position but do not prove it. Another report involves coordination of aniline to a metal, in which aniline was converted to the

Table 1. Selective Bromination of Aromatic Amines via Tin Amides

entry	amine	product	% yield
1			76
2			30
3			73
4			83
5			58
6			88
7			40
8			91
9			36
10			80
11			69

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N-magnesium compound (PhNHMgBr), and upon reaction with oxygen, *p*-bromoaniline was obtained.[16] It was suggested that Br^+ was formed in situ, but no *o*-bromoaniline was reported. The authors did not comment on the selectivity, and we believe that bromination of the tin amides proceeds by a different mechanism.

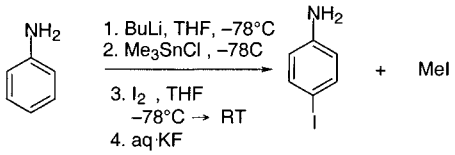
The bromination of aminonaphthalenes shows that the steric argument may be too simplistic. While 2-aminonaphthalene (entry 8) gave a 91% yield of 1-bromo-2-aminonaphthalene,[17] 1-aminonaphthalene (entry 7) gave only a 40% yield of 4-bromo-1-aminonaphthalene.[18] Although the "para" position is blocked in entry 8, there are two ortho positions, with bromination at C_1 favored. Although ortho attack is forced, the reaction proceeds in excellent yield in contrast to that of 4-methylaniline (entry 2). 1-Aminonaphthalene has an open para position, but the reaction is very sluggish and gives a poor yield of product. Without additional work, including internal competition experiments, we cannot further speculate on a mechanism.

The bromination proceeded normally when there were substituents on nitrogen. *N*-Methylaniline gave an 83% yield of 4-bromo-*N*-methylaniline.[19] Acetanilide gave a 58% yield of the 4-bromo derivative,[14b] without formation of other isomers.

Attempts to extend this methodology to other useful aromatic systems were successful. The tin amide vehicle for bromination showed great selectivity for the reaction of indole, 3-aminoquinoline, carbazole, and 2-aminopyrazole. In all cases, the bromination gave a single product in good yield. Indole (entry 10) gave an 80% yield of 3-bromoindole,[20] and 3-aminoquinoline (entry 9) gave 2-bromo-3-aminoquinoline[21] but in only 36% yield. Presumably, this is due to the difficulty inherent to electrophilic substitution on a pyridine ring. Carbazole (entry 11) gave a 69% yield of 4-bromocarbazole,[22] and 2-aminopyrazole (entry 6) gave an 88% yield of 4-bromo-1-aminopyrazole.[23] Bromination of carbazole with *N*-bromosuccinimide has been reported, but with only modest selectivity for monobromination.[24]

We were also interested in the scope of this halogenation reaction. When iodine replaced bromine in the sequence, shown in Scheme 2 using aniline as the starting material,

Scheme 2



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we obtained a 45−50% yield of 4-iodoaniline, **4**.[25] Although the reaction was selective, showing no 2-iodoaniline or diiodination products, the yield was poor. In addition, we found that iodine (or iodide) attacked the methyl group attached to tin, producing iodomethane. This was confirmed when we used tri-*n*-butyltin chloride to form the tin amide. Subsequent reaction with iodine led to **4** as well as a good yield of iodobutane. We did not attempt the reaction with chorine gas.

We have discovered a remarkably selective bromination technique that works well for a variety of aromatic amines, including substituted aniline derivatives. Although there are four distinct steps, including the aqueous fluoride workup, it is a one-pot reaction. The tin byproducts are easily removed and separable from the brominated products by using the fluoride ion workup, making this an excellent synthetic route to monobrominated aromatic amines.

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Supporting Information Available: Experimental procedures and characterization data for new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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