An Efficient Method for the Protection of Aromatic Amines with Benzostabase and Its Utility in Anionic Aromatic Transformations

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In celebration of Professor Philip J. Parsons 60th birthday and his outstanding contributions to organic chemistry

Abstract: Herein we describe an efficient and generally applicable method of protecting a diverse series of aromatic amines with the 'benzostabase' group. We also demonstrate its efficient use in aromatic anionic chemistry including its utility in the anionic *ortho* Snieckus–Fries rearrangement.

Key words: benzostabase, stabase, in situ protection, directed *ortho* Metalation, anionic *ortho* Snieckus–Fries rearrangement

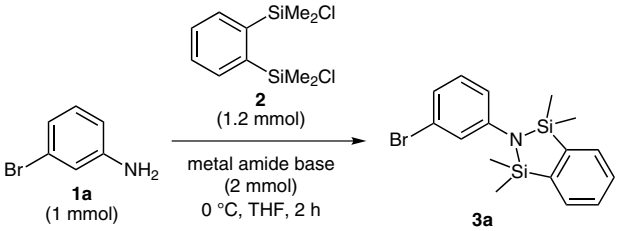
The synthesis of small-molecule libraries for lead optimization requires access to highly functionalized aromatic building blocks to obtain the desired target molecules with the requisite substitution patterns. Phenols, anilines, and nitro aromatics give rise to a rich and commercially available source of functionality, giving the medicinal chemist an advanced starting point for analogue synthesis and developing structural activity relationships within a series.

As part of our lead-optimization program of small-molecule inhibitors of amyloid $\beta_{40/42}$ and tau aggregation, we required a robust and reliable method to protect a variety of primary aromatic amines that would be inert to alkyl lithium, lithium amide bases, and Grignard reagents. Several protecting groups have been designed for this purpose and have effectively been installed onto primary amines, such as *N*,*N*-dibenzyl,[1] *N*,*N*-di-*tert*-butylcarbamate,[2] *N*-*tert*-butyl carbamate-*N*-trimethylsilyl,[2b] *N*,*N*-bistrimethylsilyl,[3] *N*,*N*-bistriethylsilyl,[3] 2,5-dimethylpyrrole,[4] 2,5-bis[(triisopropylsilyl)oxy]pyrole (BIPSOP),[5] bis[2-(*p*-toluenesulfonyloxy)ethyl]diphenylsilane (DPSide-),[6] stabase (SB),[7] benzostabase (BSB),[8] and 1,1,3,3-tetraethyl-1,3-disilasioindoline (TEDI).[9] Most importantly, these protecting groups ensure both amino hydrogens are masked, essential for preventing quenching in metal–halogen exchange reactions.[10]

For our synthetic sequence, we required a protecting group for primary aromatic amines that could be used in a metalation step of a sequence and then immediately removed. With this in mind, the protecting group needed to be easily installed, removed, commercially available, and utilized in situ or isolated before being subjected to alkyl lithium or magnesium reagents. The silicon-based protecting groups such as SB, BSB, and TEDI are ideal choices for these transformations, with numerous examples of easy installation onto primary alkyl amines under mild conditions.[7,11] However, protection of aromatic amines with these groups appears to be more challenging, requiring forcing and unfavorable conditions.[12] Furthermore, aromatic amines protected as their SB adducts appear to be less stable than the alkyl variants to both aqueous workup and silica gel.[8,9,13] The TEDI group offers the most stability of the cyclic silicon adducts, but is not commercially available.[14] Taking account of these factors, we opted to utilize the BSB group.

We first tested the protection of several aniline substrates under the mildest conditions reported with BSB. Treatment of 3-bromoaniline with triethylamine or Hünig's base and 1,2-bis(chlorodimethylsilyl)benzene (BSBCl)[15] in THF at room temperature and under prolonged refluxing conditions resulted in substantial amounts of starting material remaining. Due to the poor nucleophilicity of aromatic amines, we opted to test several stronger bases. Using modified conditions developed by Rizzo,[16] BSBCl

Table 1 Optimization of BSB Installation Conditions



Base[a]	Yield (%)[b]
KHMDS	70
NaHMDS	68
LiHMDS	79
LDA	64

[a] KHMDS: potassium bis(trimethylsilyl)amide; NaHMDS: sodium bis(trimethylsilyl)amide; LiHMDS: lithium bis(trimethylsilyl)amide; LDA: lithium diisopropylamide.
[b] Final product obtained in pure form by concentration of reaction mixture and filtration through a pad of basic alumina.

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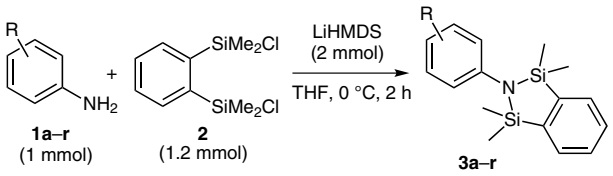
(**2**, 1.2 mmol) and aromatic amine **1** (1 mmol) were premixed in THF at 0 °C to which was added the metal amide base (2 mmol). Screening several metal amide bases (Table 1) under these in situ quench/'Martin conditions'[17] resulted in clean and facile transformation to the protected BSB adduct **3** in good yields. All of the bases shown in Table 1 performed adequately in the reaction, delivering the isolated protected compounds in 64–79% yields. Lithium bis(trimethylsilyl)amide, which is commercially available, delivered the protected adduct in the highest yield of 79% and therefore became the reagent of choice for this reaction.[18]

Table 2 Protection of Functionalized Anilines as BSB Adducts



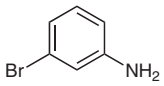
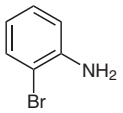
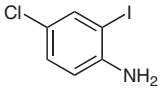
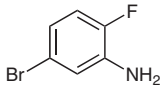
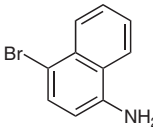
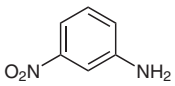
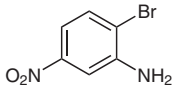
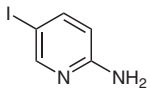
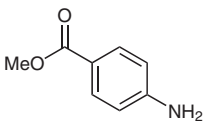
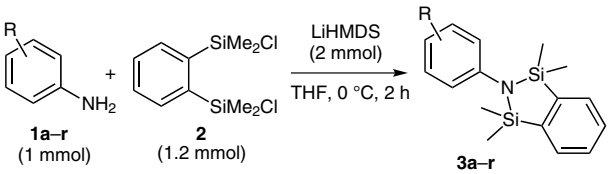
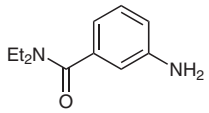
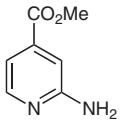
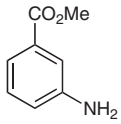
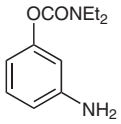
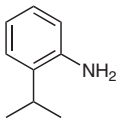
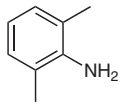
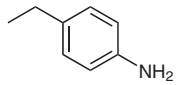
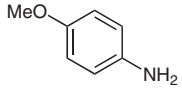
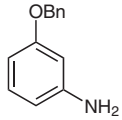
Entry	Aniline	Product	Yield (%)
1		**3a**	79[a]
2		**3b**	92[b]
3		**3c**	71[a]
4		**3d**	79[b]
5		**3e**	82[b]
6		**3f**	72[a]
7		**3g**	84[a]
8		**3h**	62[a]
9		**3i**	88[a]

Table 2 Protection of Functionalized Anilines as BSB Adducts (continued)



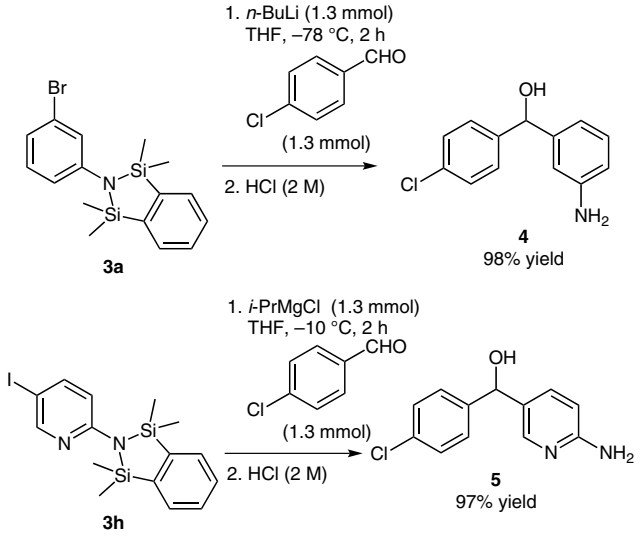
Entry	Aniline	Product	Yield (%)
10		**3j**	76[a]
11		**3k**	57[a]
12		**3l**	73[a]
13		**3m**	72[a]
14		**3n**	61[a]
15		**3o**	95[b]
16		**3p**	77[a]
17		**3q**	94[b]
18		**3r**	70[a]

[a] Final product was obtained by concentration of reaction mixture followed by filtration through a pad of basic alumina to obtain spectroscopically pure BSB adduct.
[b] The reaction mixture was subjected to aqueous workup followed by extraction with EtOAc and concentration.

Using these optimized conditions, we subjected a variety of functionalized amines (Table 2) to the BSB protection reaction. In general, the majority of substrates were converted into products in moderate to high yield. Several products (Table 2, entries 2, 4, 5, 15, and 17) did not require purification and were subjected to aqueous workup

only. Due to the silica gel instability of several examples, the remaining products shown in Table 2 were all directly filtered through a pad of basic alumina and concentrated to give the pure compounds. Both electron-rich and electron-deficient substrates were converted in good yield, with a wide range of functionality such as aromatic nitro, iodide, fluoride, and esters being tolerated under these reaction conditions. Pyridine examples (Table 2, entries 8 and 11) were converted in moderate yield but required chromatography purification over basic alumina.

We next examined the utility of the BSB group in metal–halogen exchange reactions (Scheme 1). Illustrating lithiation, **3a** was subjected to *n*-BuLi at –78 °C in THF followed by addition of 4-chlorobenzaldhyde and acidic workup, delivered the carbinol **4** in 98% yield. In a similar manner, we subjected **3h** to isopropoyl magnesium chloride[19] at –10 °C in THF and quenched with the same electrophile to deliver the compound **5** in excellent yield (97%).



Scheme 1 Metal–halogen exchange of BSB-protected anilines followed by reaction with 4-chlorobenzaldeyde

We next explored the use of BSB protection in a series of directed *ortho* metalation (DoM) reactions.[20] With supportive evidence that the cyclic silicon-based protecting groups are not themselves directing groups,[12a] we postulated that due to its steric bulk it could behave as a 'deflecting' group, having an anticooperative effect on lithiation between itself and the *meta*-substituted directed metalation group (DMG, Figure 1).

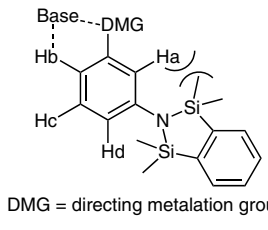
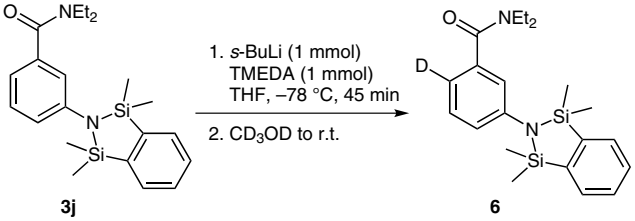


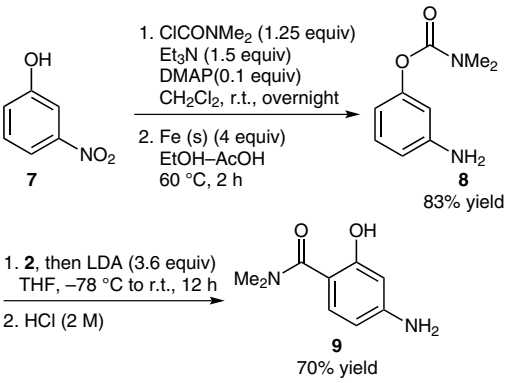
Figure 1 Proposed anticooperative effect of BSB-protected anilines

To test this hypothesis, we subjected the *N*,*N*-diethylamide **3j** to *s*-BuLi at –78 °C in THF, followed by addition of CD_3OD (Scheme 2). Analysis of the ^1H NMR spectra of the crude reaction mixture showed clean conversion to a single product **6** which clearly demonstrated a powerful 'deflecting' group effect of the BSB group in this DoM reaction.



Scheme 2 Regioselective directed *ortho* lithiation–deuteration of **3j**

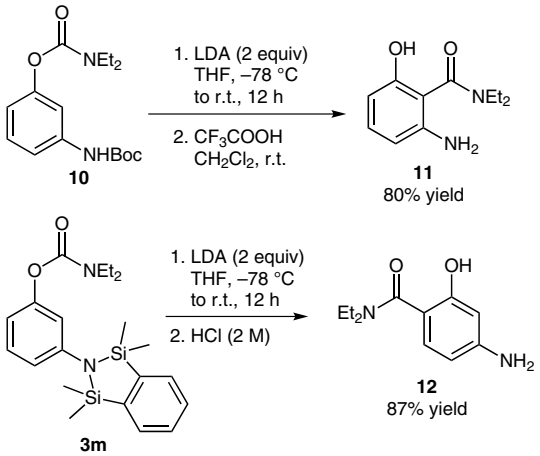
To expand this observation, we investigated the effect of the BSB group in the anionic *ortho* Snieckus–Fries rearrangement.[21] To demonstrate its ability to 'deflect' lithiation from its *ortho* site, we prepared the *N*,*N*-dimethyl carbamate **8** from 3-nitro phenol (**7**) through carbamoylation followed by iron-mediated reduction of the nitro group. In a 'one-pot' reaction, the protected aniline **8** was premixed with BSBCl in THF at –78 °C followed by addition of 3.6 equivalents of LDA[22] (Scheme 3). Allowing the solution to warm to room temperature followed by acidic workup delivered exclusively the *N*,*N*-dimethylbenzamide **9** in 70% yield.



Scheme 3 Regioselective anionic Snieckus–Fries rearrangement of BSB-protected anilines

Finally, to complement the observed anticooperative regioselectivity in this reaction, we exchanged the BSB group for a known DMG, the *tert*-butoxycarbonyl amino group.[23] Using the more common and useful *N*,*N*-diethylcarbamate DMG[20a,24] the aniline **1m**[25] was treated with di-*tert*-butyl dicarbonate to give 3-[(*tert*-butoxycarbonyl)amino]phenyl diethylcarbamate (**10**, Scheme 4). Treatment of **10** with LDA at –78 °C followed by warming to room temperature and acidic workup delivered selectively the migrated product **11**, presumably resulting from a cooperative effect of the two DMG groups (Scheme 4). Analogous to the transformation **8** → **9**, treatment of the

BSB-protected aniline **3m** with LDA followed by acidic workup delivered selectively the amide **12** in excellent yield.



Scheme 4 Bimodal translocation of diethylamide using NHBoc and BSB group

In conclusion, we have described a generally applicable method for installing the BSB group onto a diverse set of primary anilines and demonstrated its use in several anionic transformations. Most notably, in the anionic *ortho* Snieckus–Fries rearrangement, we have demonstrated for the first time the complimentary use of both a directed metalation group and a benzostabase to induce two regioselective translocation modes of the diethylamide.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) HMPA, elevated temperature, and long reaction times required to install the 'benzostabase' group, see ref. 8. For elevated temperatures, long reaction times, see: (a) Zhichkin, P. E.; Krasutsy, S. G.; Beer, C. M.; Rennells, W. M.; Lee, A. J.; Xiong, J.-M. *Synthesis* **2011**, 1604. (b) Guggenheim, T. L. *Tetrahedron Lett.* **1984**, *25*, 1253.
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(22) Note: For the anionic *ortho* Snieckus–Fries rearrangement, LDA was used in place of LHMDS due to the ability of LHMDS to affect efficient *ortho* lithiation.
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(24) For transformation of the aromatic diethylamide into the more versatile aldehyde group, see: Zhao, Y.; Snieckus, V. US 0145060, **2010**.
(25) Note: Aniline **1m** was synthesized in a fashion analogous to that of compound **8**, see the Supporting Information for the synthesis of **8**, **10**, and **3m**.

