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Diamination of Domino Aryne Precursor with Sulfonamides

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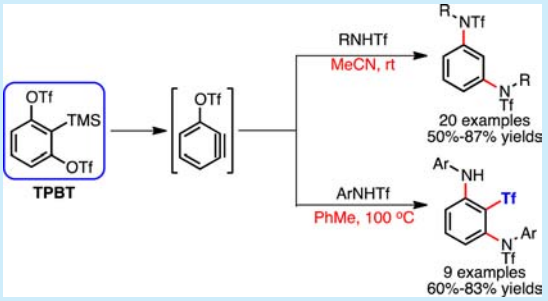
Supporting Information

ABSTRACT: The reaction of a domino aryne precursor with sulfonamides efficiently afforded both 1,3-diaminobenzenes and trisubstituted 1,3-diaminobenzenes by simply varying the reaction conditions. Mechanistic study supports the sequential formation of two transient aryne intermediates involved in the reaction.



1,3-Diaminoarenes are privileged subunits in both natural products and medicines, including anticancer drug (Gleevec), antibiotics (Ciprofloxacin, Levofloxacin, Rufloxacin, and Tigecycline), and the natural indolo[3,2-*a*]carbazole Ancorinazole (Figure 1).[1] Synthetically, the most commonly utilized diamination approaches involve transition-metal catalyzed amination of halobenzenes (e.g., Buchwald−Hartwig[2] or Ullman[3] reactions). The restricted usage of transition metals in the late stage of drug synthesis prompts people to seek transition-metal-free as well as environmentally friendly manipulation conditions.

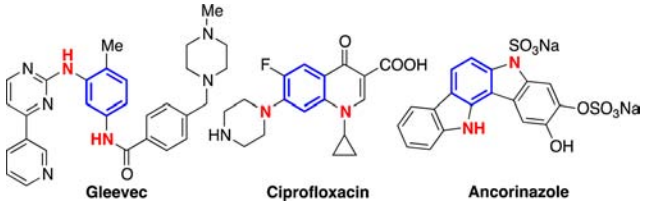
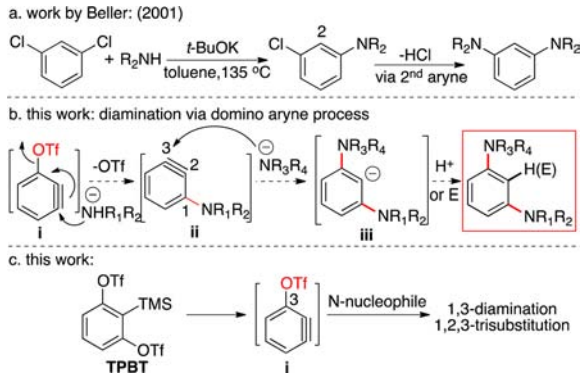


Figure 1. Selected 1,3-diaminobenzene structures.

As an alternative approach to transition metal catalysis, arynes can be directly trapped by a wide range of dienes, dipoles, and nucleophiles to generate substituted aromatics.[4] The advantage of employing aryne intermediate in the C−N bond formation resides primarily in its high efficiency as well as instant incorporation of two vicinal functional groups.[5] As for diamination reaction, however, only limited approaches are known via aryne chemistry.[6] For example, the Beller group reported the construction of 1,3-diaminobenzenes from 1,3-dichlorobenzene, where they used a strong base (*t*-BuOK) under high temperature (Scheme 1a).[6a] A stepwise generation of two aryne intermediates was proposed, and the regioselective formation of the 1,3-diaminobenzene was explained by "the higher acidity of the hydrogen in position 2 of the aromatic ring". Although this approach could gain 1,3-diaminobenzenes via aryne intermediates, its harsh conditions restrict the application of this method.

To overcome the 1,2-difunctionalization limitation by a standard aryne intermediate, we recently developed a domino aryne precursor, which can feature a sequential formation of two aryne intermediates during the reaction.[7] The nature of this aryne precursor to accept two nucleophiles via a domino aryne process inspired us to explore the synthetic application of this compound with other nucleophiles. Herein, we report our study on diamination reactions of this domino aryne precursor with sulfonamides.

Scheme 1. Previous and Current Work



As shown in Scheme 1b, when the second nucleophile attacks aryne intermediate **ii** intermolecularly, a regioselective amination could be conceived and 1,3-diaminobenzenes would be produced via nucleophilic attack of the second amine species on the 3-position of intermediate **ii**. The origin of the selectivity relies on the electron-withdrawing inductive effect of the amino

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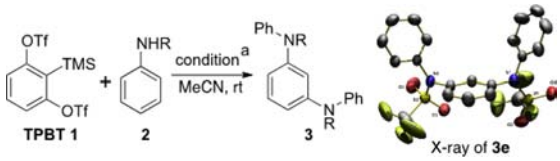
group on aryne **ii**, which has been well-studied previously.[4c,8] Furthermore, in the absence of a proton source, intermediate **iii** would be trapped by an electrophile, resulting in a trisubstituted 1,3-diaminobenzene derivative.

Table 1. Varying EWGs on Aniline



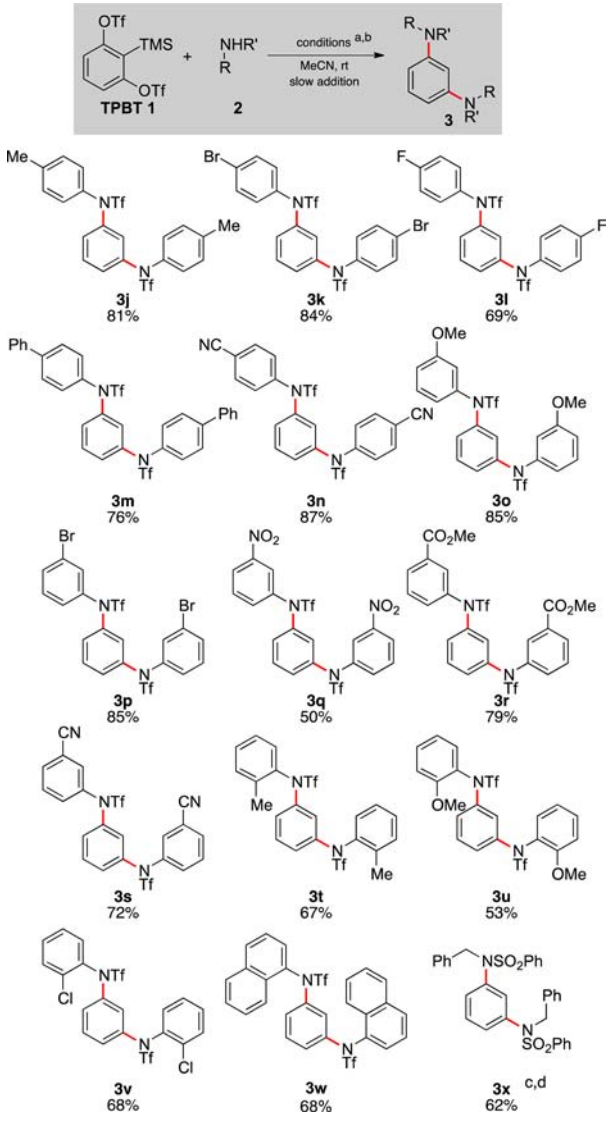
entry	R-	product	yield[b] (%)
1	4-$MeC_6H_4SO_2$- (**2a**)	**3a**	67
2	$PhSO_2$- (**2b**)	**3b**	57
3	4-$ClC_6H_4SO_2$- (**2c**)	**3c**	75
4	$MeSO_2$- (**2d**)	**3d**	60
5	CF_3SO_2- (**2e**)	**3e**	87
6	Ac- (**2f**)		0
7	CF_3CO- (**2g**)		0
8	Bz- (**2h**)		0
9	Boc- (**2i**)		0

[a]Conditions: slow addition of TPBT **1** (0.3 mmol) in MeCN (10 mL) to **2** (0.4 mmol) and CsF (1.2 mmol) in MeCN (10 mL) over 8 h at room temperature. [b]Isolated yield.

As shown in Table 1, when *N*-tosylated aniline **2a** reacted with TPBT **1** in the presence of CsF, 1,3-diaminobenzene **3a** was obtained in 67% isolated yield (entry 1) (see Table S1 in the Supporting Information for its detailed optimization conditions). We hypothesized that different electron-withdrawing groups (EWGs) on aniline nitrogen could tune both the pK_a of the N−H proton and the nucleophilicity of the aniline nitrogen.[5e] Indeed, drastic reactivity change was observed by varying the R group on aniline (Table 1). When sulfonamides were employed, the yields varied from 57% to 87% (entries 1−5), and triflate **3e** was found to be the best substrate. The *meta*-diaminated structure of **3e** could be confirmed by X-ray single crystallographic analysis (Table 1). In contrast, amides with other protecting groups, such as acetyl (Ac), trifluoroacetyl, benzoyl (Bz), and *t*-butoxycarbonyl (Boc), gave no desired products (entries 6−9).

After identifying triflyl (Tf) as the best EW group, we further explored the substrate scope. As shown in Scheme 2, when Tf-protected anilines were employed, 1,3-diaminated products could be obtained in good to excellent yields. This reaction is highly efficient and tolerates various functional groups, such as halogen (**3k**, **3l**, **3p**, and **3v**), cyano (**3n** and **3s**), nitro (**3q**), and methoxycarbonyl (**3r**) groups, which are incompatible with either Grignard reagents or strong bases.[6] In addition, a substituent on the *ortho*-, *meta*-, and *para*-position of aniline could all afford the corresponding 1,3-diaminobenzenes. When *ortho*-substituted substrates were employed, diminished yields were obtained. The trend for these decreased yields is parallel with the increased size of the substituents. For instance, when the sizes of the substituents on aniline follow a OMe > Me ≈ Cl trend, the yields would contrastingly change. Moreover, this transformation can be scaled up on gram scale. At last, when benzylamine analogue **2x** was used with CsF as the activating reagent, there was no desired product observed. Interestingly, by using both CsF and Cs_2CO_3 as the bases, diaminobenzene **3x** was obtained in 62% NMR yield. This observation could be

Scheme 2. Substrate Scope of 1,3-Diamination



[a]Conditions: slow addition of TPBT **1** (0.3 mmol) in MeCN (10 mL) to **2** (0.4 mmol) and CsF (1.2 mmol) in MeCN (10 mL) over 8 h at room temperature. [b]Isolated yield. [c]Both CsF and Cs_2CO_3 were used. [d]Yield was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

explained by a lower acidity of the NH on benzyl analogue and hence stronger base Cs_2CO_3 is needed to deprotonate **2x**. Further investigation on other aliphatic amines, however, failed to give the desired products.

Moreover, we could prepare unsymmetrical diaminobenzene with a modified protocol. When a 1:1 mixture of triflated *p*-methylaninline **2j** and *p*-cyanoaninline **2n** was used under diamination conditions, an unsymmetrical diamine **3y** could be obtained in 42% yield, along with two symmetrical 1,3-diaminobenzenes **3j** and **3n** in ∼20% yield each (eq 1). This example exhibits a potential of TPBT **1** in the preparation of unsymmetrical 1,3-diaminobenzene analogues. To identify the source of the proton on the 2-position, a deuterium-labeling experiment was conducted. By employing deuterated acetonitrile as the solvent, TPBT **1** reacted with **2j** to give the deuterated product **3j−d** with 25% deuteration, suggesting that

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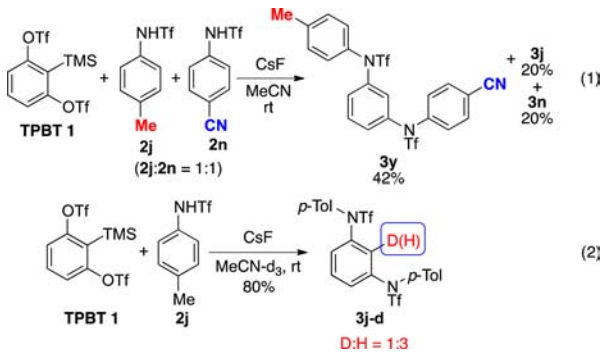
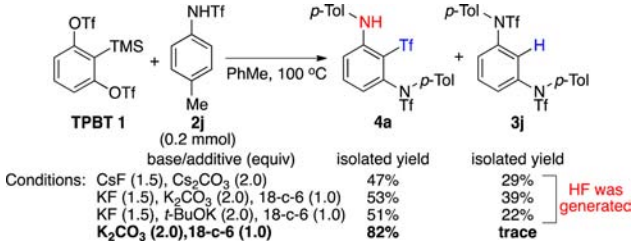


the proton sources are from both the N−H of **2j** and the solvent (eq 2).

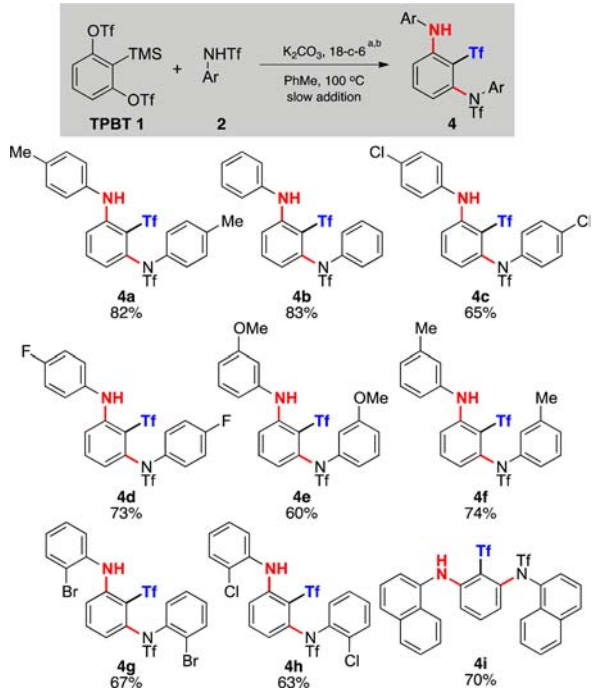
An extended application of TPBT **1** was also pursued, namely the introduction of three functional groups on the consecutive positions of a benzene ring, which could be accomplished by capturing an electrophile other than a proton in the final stage of the transformation (intermediate **iii** in Scheme 1b). The Larock group previously exhibited a 1,3-migration of trifluoroacetyl ($-COCF_3$) as well as trifluoromethanesulfinyl ($-SOCF_3$) groups via aryne chemistry, when the corresponding aniline derivatives were used.[5e] Although thia-Fries rearrangement has been reported with Tf migration from the oxygen of an OTf group,[9] as a competing side reaction in the aryne generation process, there is no precedent for Tf migration from NTf. To fulfill our goal to migrate one of the Tf groups to the 2-position in intermediate **iii**, we decided to extrude the proton sources within the reaction system. Satisfyingly, toluene was found to be the ideal solvent. As shown in Scheme 3, several activating reagents were tested, and K_2CO_3/18-c-6 was found to be the best one with exclusive formation of product **4a**. All the other conditions employing the fluoride anion, however, gave a significant amount of 1,3-diaminobenzene **3j** (Scheme 3). Intriguingly, fluoride ion was found to be no longer necessary in this transformation. This observation could be explained by the fact that the HF produced during the reaction would protonate intermediate **iii** before Tf migration. Although aryl amine gave products in good to high yields under the reaction conditions, aliphatic amine could not afford the desired product (Scheme 4).

Scheme 3. Optimization for Tf Migration



By exploring the reaction scope, a list of the Tf migration products **4** could be obtained in good to high yields (Scheme 4). Efforts to migrate a Ts group when aniline **2a** was employed, however, gave solely the 1,3-diamination product **3a**, presumably because of the weak migration ability of the Ts group. This transformation is, to some extent, important, since triflylbenzene (aryl triflone) is known as the substructure of medicines, such as Ponazuril and anticancer drug Navitoclax (ABT-263). The success of this operation not only allows us to

Scheme 4. Intramolecular Sulfonyl Group Migration

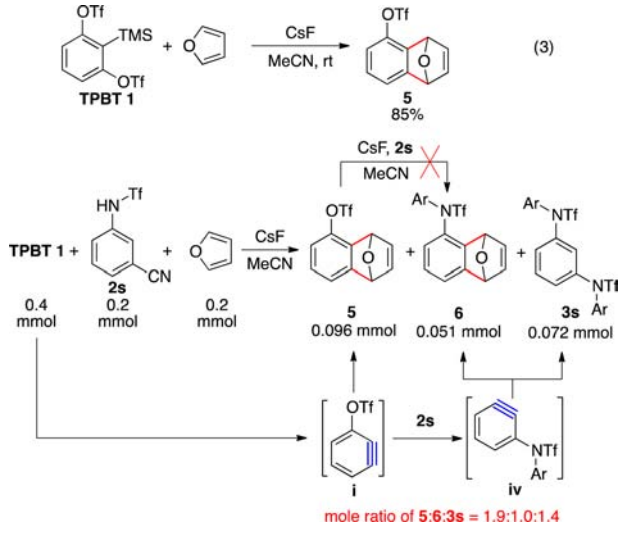


[a]Conditions: slow addition of **1** (0.3 mmol) in toluene (5 mL) to **2** (0.4 mmol), K_2CO_3 (0.8 mmol), and 18-c-6 (0.4 mmol) in toluene (5 mL) over 10 h at 100 °C. [b]Isolated yield.

incorporate two nitrogen- and one sulfur-based functional groups on a benzene ring at the same time with a strict N, S, N sequence but also extends the reaction pattern of the domino aryne precursor to a different adding sequence (1,3,2- vs 1,2,3-) toward 1,2,3-trisubstituted arenes.

We are curious whether the diamination reactions indeed undergo the domino aryne process or not. Several observations could support the proposed pathways in Scheme 1b: (a) the formation of adduct **5** from TPBT **1** and furan suggests the generation of 3-triflyloxybenzyne (**i**) (eq 3); (b) the reaction of TPBT **1** with both aniline **2s** and furan in the same pot gave a mixture of **5**, **6**, and **3s** in a 1.9:1.0:1.4 mol ratio (Scheme 5),

Scheme 5. Mechanistic Studies



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whereas **5** could not be converted to **6** in the presence of CsF and **2s**. These results indicate that the formation of **6** must proceed through the second aryne intermediate **iv**. Moreover, the high consumption of **2s** (98%) and furan (74%), based on the amounts of the products, suggests that the sequential aryne process is indeed a major path in this transformation.

In summary, as an alternative, mild, and efficient transition-metal-free strategy, diamination reactions of a domino aryne precursor with sulfonamides were reported. This TPBT reagent is unique and unprecedented in the preparation of both 1,3-diaminobenzene and trisubstituted 1,3-diaminobenzene by simply varying the reaction conditions. Mechanistic study reveals that the reaction proceeds through a sequential aryne pathway. Our ongoing work includes the development of new domino aryne transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01334.

Experimental details for all chemical reactions and measurements (PDF)

X-ray single crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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