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Vicinal Diamination of Arenes with Domino Aryne Precursors

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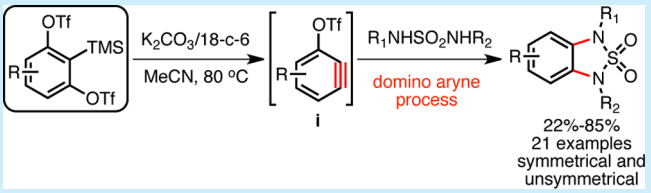
Supporting Information

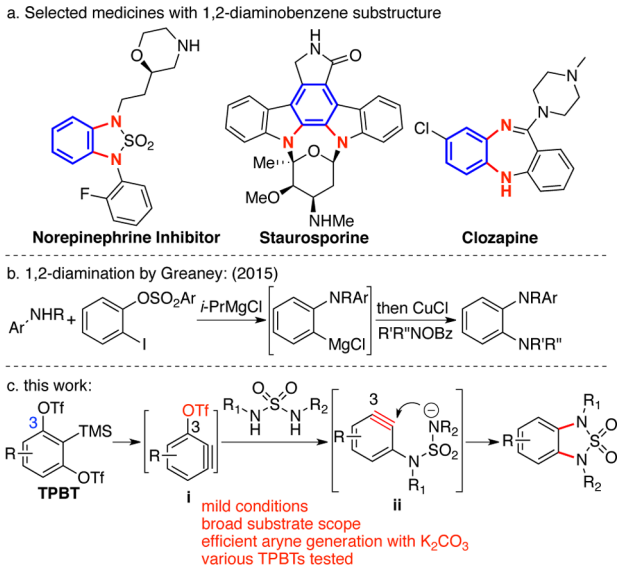
ABSTRACT: Vicinal diamination of domino aryne precursors was achieved with sulfamides. The reaction proceeds through a two-aryne pathway, accepting two N-nucleophiles at the 1,2-positions of an arene ring. Symmetrical and unsymmetrical diaminobenzenes were readily obtained.



Nucleophilic reactions are among the most prevalently investigated reaction types in aryne chemistry.[1] The formal triple-bond character of a standard aryne intermediate, however, can only accommodate a nucleophile as well as an electrophile in a nucleophilic reaction. Mechanistically, it is prohibited to accept *two* nucleophiles simultaneously at the vicinal positions of a standard aryne triple bond under traditional aryne reaction conditions. To overcome this drawback, a domino aryne precursor with the ability to sequentially generate two aryne intermediates has been conceived to fulfill this task under transition-metal-free conditions. Herein we report our discovery of a 1,2-diamination reaction of arenes from sulfamides and domino aryne precursors.

1,2-Diaminobenzenes are important substructures in both natural products and medicines, including a norepinephrine inhibitor,[2] a kinase inhibitor (staurosporine),[3] and an antipsychotic drug (clozapine) (Scheme 1a). Usually the construction of this structural motif, especially the unsymmetrical ones, requires multistep manipulation[4] or transition-metal-catalyzed processes.[5] The reaction via an aryne intermediate to reach this framework owns certain advantages, i.e., mild and transition-metal-free conditions. Recently, the Greaney group reported a protocol to prepare 1,2-heteroatom-functionalized arenes via three-component coupling of aryne with two heteroatoms (Scheme 1b).[6] Mechanistically, a one-pot, two-step procedure was applied in which the first N-nucleophile attacked the aryne intermediate and then the second amino group was incorporated through a Cu(I)-catalyzed coupling of an aryl Grignard intermediate with *O*-benzoyl *N*,*N*-dialkyl hydroxylamines. Our previous successes in employing a domino aryne precursor in the preparation of benzothiazole derivatives[7] and 1,3-diaminobenzenes[8] encouraged us to examine the possibility of vicinal diamination with our reagent (Scheme 1c).

Scheme 1. Background and Proposal



Our previous study[7a,8] disclosed that the acidity of the NH proton is the key for the success of the initial nucleophilic attack on aryne intermediate **i**, which further warrants the generation of the second aryne intermediate **ii**, since protonation could be a competing side reaction after the nucleophilic attack. On the basis of these concerns, we started to look for two-amino subunits with a proper "linker". A carbonyl linker was first examined, and it was found that *N*,*N*′-diphenylurea did not react with the aryne intermediate at all. When benzamidine derivatives[9] were employed as thioamide analogues, no desired diamination products were obtained. These observations could be explained by the fact that the mismatched nucleophilic property/NH acidity tuned by the electron-withdrawing group on these substrates interrupted the desired domino aryne process. A similar phenomenon has also been previously reported by the Larock group.[10]

We then turned our attention to the sulfonyl group, a stronger electron-withdrawing group than the carbonyl group, as the electron-tuning factor on the amine, expecting that sulfonyl groups could be used to tune the pK_a of the NH to a

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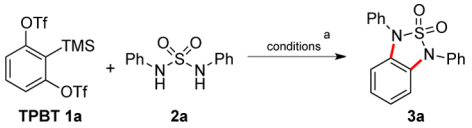
suitable range. With this assumption in hand, sulfonamide **2a** was prepared and examined (Table 1). Gratifyingly, when **2a**

Table 1. Optimization of 1,2-Diamination



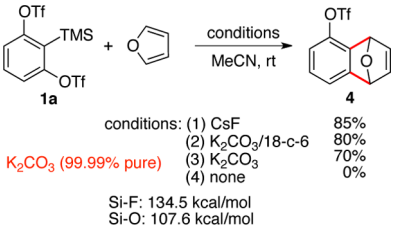
entry	"F"/base (equiv)	additive (equiv)	solvent	T (°C)	yield of **3a** (%)[b]
1	CsF (6.0)	no	MeCN	80	73
2	no	Cs_2CO_3 (6.0)	MeCN	80	48
3	CsF (4.0)	Cs_2CO_3 (3.0)	MeCN	80	54
4	TBAF (4.0)	no	MeCN	80	trace
5	KF (4.0)	18-c-6 (4.0)	MeCN	80	54
6	K_2CO_3 (3.0)	18-c-6 (2.0)	MeCN	80	80
7	**K_2CO_3 (4.0)**	**18-c-6 (4.0)**	**MeCN**	**80**	**85**
8	K_2CO_3 (4.0)	18-c-6 (4.0)	MeCN	50	73
9	K_2CO_3 (4.0)	18-c-6 (4.0)	MeCN	rt	68
10	K_2CO_3 (4.0)	18-c-6 (4.0)	PhMe	100	78
11	K_2CO_3 (4.0)	18-c-6 (4.0)	dioxane	80	77
12	K_2CO_3 (4.0)	18-c-6 (4.0)	DME	80	69
13	K_2CO_3 (4.0)	18-c-6 (4.0)	DCM	rt	trace
14	K_2CO_3 (4.0)	18-c-6 (4.0)	THF	65	trace

[a]Conditions: slow addition of **1a** (0.3 mmol) in solvent (10 mL) to **2a** (0.2 mmol) in solvent (10 mL) over 8 h. [b]Isolated yields.

was treated with 2-(trimethylsilyl)-1,3-phenylenebis-(trifluoromethanesulfonate) (TPBT) (**1a**) in MeCN in the presence of CsF, the 1,2-diaminated product **3a** was obtained in 73% isolated yield (entry 1). Further investigation revealed that Cs_2CO_3 itself could afford **3a** in 48% yield (entry 2). The combination of CsF and Cs_2CO_3 did not further enhance the yield (entry 3). Although the yield is low in entry 2, the reaction did not require fluoride ion to kick out the TMS group. When different fluoride sources were used, diminished yields were obtained (entries 4 and 5). Intriguingly, the reaction with K_2CO_3/18-crown-6 afforded **3a** in 85% yield at 80 °C (entry 7). Decreasing the reaction temperature only gave lower yields (entries 8 and 9). Other solvents were screened, such as toluene, dioxane, DME, DCM, and THF, and MeCN was found to be the best solvent (entries 10−14).

An intriguing character of this TPBT reagent emerged at this stage: the fluoride-free conditions provided the best yields in 1,2-diamination reactions (Table 1). In contrast, it has been generally recognized that the activation of a standard Kobayashi aryne precursor requires the use of a fluoride source to "kick out" the TMS group.[11] What species is responsible for the generation of 3-triflyloxybenzyne (**i**) from TPBT **1a**? Indeed, when high-purity K_2CO_3 (99.99% from Aldrich)/18-crown-6 was used in the reaction of TPBT **1a** with furan, the adduct **4** was obtained in 80% yield, which is comparable with that using CsF (85% yield) as the activating reagent (Scheme 2). Without 18-crown-6, **4** could still be obtained in 70% yield with K_2CO_3. In contrast, in the absence of both activating reagents, no cycloaddition product **4** was observed. Because there were no other possible nucleophiles in the reaction system, especially when high-purity K_2CO_3 was utilized, carbonate had to be responsible for the nucleophilic species to activate TPBT **1a**. The weakened C2−Si bond of TPBT **1a** can be attributed to the two electron-withdrawing OTf groups, which could pull more electron density away from the phenyl carbon−silicon

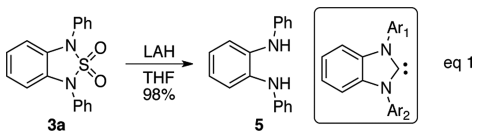
Scheme 2. Reactions of TPBT 1a with Furan



bond. Hence, the TMS group on TPBT **1a** would become more vulnerable to nucleophilic attack, allowing nucleophiles other than fluoride (i.e., oxygen) to generate aryne **i**. This observation is essential, since it indicates that our TPBT reagent does not necessarily have to rely on the traditional fluoride-based aryne generation method. The advantage of using potassium carbonate as the activating species is that it allows TPBT to adapt broader functional group scope than under fluoride-based conditions, such as the presence of commonly used trialkylsilyl protecting groups in complex molecule synthesis.

The reaction scope of 1,2-diamination was then explored. As shown in Scheme 3, functional groups on aniline, such as methyl (**3b**), halogens (**3c** and **3d**), nitrile (**3e**), methoxy (**3f**), and methoxycarbonyl (**3g**) groups, are well-tolerated under the reaction conditions, no matter if they are electron-withdrawing or electron-donating groups. Unsymmetrical diaryl substrates could afford unsymmetrical diaminobenzenes (**3h** and **3i**) as well. Moreover, a dibenzyl substrate works well, giving **3j** in 73% yield. Unsymmetrical aryl alkyl substrates were tested as well. When phenyl−benzyl substrate **2k** was used, **3k** was obtained in 68% yield. Functional groups on the benzyl subunit, such as 4-F and 4-Me substituents, could also produce the diaminobenzenes **3l** and **3m**, respectively. Slightly enhancing the steric hindrance did not affect the reaction efficiency, and **3n** was obtained in 45% yield. However, phenyl cyclopentyl sulfamide gave no desired product **3o** at all, primarily because of the steric repulsion of the cyclopentyl group.

It is worth mentioning that the diaminobenzene framework with unsymmetrical aryl and aliphatic amine subunits has recently emerged in norepinephrine inhibitors (see Scheme 1a).[2] Our approach could quickly construct a series of SO_2-bridged unsymmetrical 1,2-diaminobenzenes, where other methods would require multistep manipulation. Another advantage of using sulfamides to prepare 1,2-diaminobenzenes is their potential conversion to other useful compounds, such as benzimidazoles or N-heterocyclic carbenes (NHCs). Our approach also provides an alternative way to synthesize unsymmetrical 1,2-diaminobenzenes under transition-metal-free conditions.[12] As an example, the diamination product **3a** can be readily converted to 1,2-diamine **5** via LAH reduction, exhibiting the potential of using **3** to prepare a variety of NHCs (eq 1).[12,13]



To expand the scope of domino aryne reagents, TPBT analogues **1b−1g** were prepared with different substituents on the arene ring (see the Supporting Information for the

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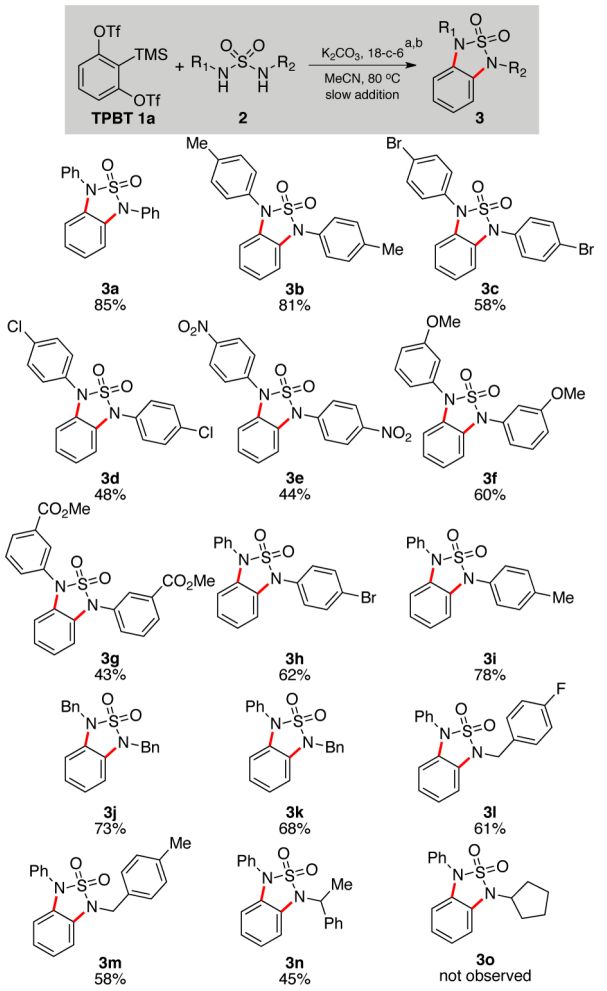
Scheme 3. 1,2-Diamination of TPBT

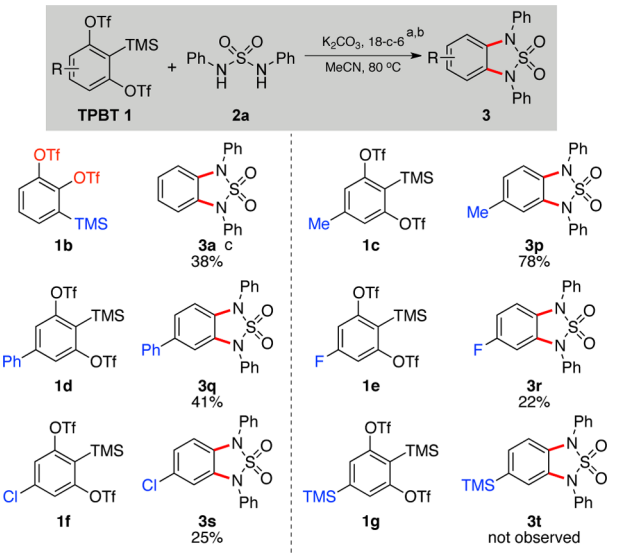


[a]Conditions: slow addition of **1a** (0.3 mmol) in MeCN (10 mL) to **2** (0.2 mmol), K_2CO_3 (0.8 mmol), and 18-crown-6 (0.8 mmol) in MeCN (10 mL) over 8 h. [b]Isolated yields are shown.

preparation procedures for these reagents). Because there are two topological arrangements of TPBT reagents, namely symmetrical **1a** and unsymmetrical **1b**, we wondered whether the unsymmetrical TPBT **1b** could exhibit similar reactivity as **1a**. As shown in Scheme 4, to our surprise, unsymmetrical TPBT **1b** acts quite differently from TPBT **1a**. A significant amount of TPBT **1b** was found decomposed at elevated temperature in the reaction. When the reaction temperature was decreased, diaminobenzenes **3a** could be obtained in 38% yield, which is still less efficient than the reaction with TPBT **1a** (Table 1). Since both TPBTs **1a** and **1b** could afford the same aryne intermediate, 3-triflyloxybenzyne (**i**), the low reaction efficiency with **1b** should come from the inadequate aryne generation step. The different aryne generation efficiencies of these two TPBTs might be explained by their different electron distribution patterns of the benzyne rings, which substantially increases the side reaction for TPBT **1b** before aryne **i** could be generated.

A series of TPBT **1a** analogues **1c**−**1g** were then examined (Scheme 4). Under the optimal reaction conditions achieved in Table 1, TPBTs **1c**−**1f** afforded the desired products in various yields, demonstrating that these reagents could be commonly utilized in domino aryne processes. In general, TPBTs with an

Scheme 4. Reactions with Various TPBTs

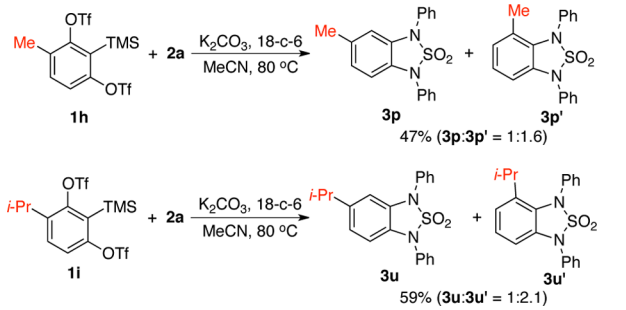


[a]Conditions: slow addition of **1** (0.3 mmol) in MeCN (10 mL) to **2a** (0.2 mmol), K_2CO_3 (0.8 mmol), and 18-crown-6 (0.8 mmol) in MeCN (10 mL) over 8 h. [b]Isolated yields are shown. [c]The reaction was performed at rt.

electron-donating substituent, i.e., a methyl group (**1c**), gave relatively high yields, whereas electron-withdrawing substituents, i.e., phenyl (**1d**), fluoride (**1e**), and chloride (**1f**), resulted in diminished yields. It is worth noting that the halogens on TPBTs **1e** and **1f** could be further transformed to other functional groups via cross-coupling reactions, exhibiting a potential for these products in further manipulation. In the case of TPBT **1g**, however, there was no observation of the desired products. This study reveals that the additional functional group on TPBT dramatically affects the reaction efficiency.

To study the regioselectivity issue of domino aryne precursors whenever the additional substituents make the framework unsymmetrical, TPBTs **1h** and **1i** were prepared (Scheme 5). When TPBT **1h** with a vicinal methyl group was

Scheme 5. Regioselectivity Study with Unsymmetrical TPBTs



used in the 1,2-diamination reaction, the product ratio of **3p** and **3p′** was 1:1.6 with an overall yield of 47%. Moreover, when TPBT **1i** with a vicinal isopropyl group was utilized, the reaction gave a mixture of **3u** and **3u′** in 59% yield with a ratio of 1:2.1, which was only slightly enhanced compared with the product ratio for TPBT **1h** (Scheme 5). The low product ratios in these reactions indicate that both the methyl and isopropyl groups on TPBT framework do not significantly affect the

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preference for which OTf departs during the course of generating the first aryne intermediate **i**. Moreover, these results also indicate that the steric hindrance imposed by them is ignorable.

In conclusion, vicinal diamination of arenes has been achieved using sulfamides and domino aryne precursors. The reaction proceeds under mild and transition-metal-free conditions with a broad substrate scope. K_2CO_3 was found to be efficient in generating the aryne intermediate from TPBT. Both symmetrical and unsymmetrical diaminobenzenes were obtained with high efficiency. TPBTs with additional substituents on the benzene ring were also studied. Future work includes the development of other applications of domino aryne precursors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01747.

Experimental details for all chemical reactions and measurements (PDF)

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†L. L. and D. Q. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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