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1,2-Bis(arylthio)arene synthesis *via* aryne intermediates†

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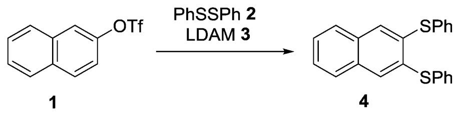
Lithium 1,1-diadamantylamide (LDAM) base-promoted insertion of arynes into disulfide S–S bonds is described. After generation of arynes from readily available aryl halides and triflates, reactions with diaryl and diisopropyl disulfides afford the insertion products in moderate to excellent yields. Use of 1-cyclohexenyl triflate gave an excellent yield of 1,2-bis(phenylthio)cyclohexene.

With few exceptions, 1,2-bis(arylthio)arenes are prepared from 1,2-dihaloarenes *via* nucleophilic aromatic substitution or transition-metal catalyzed or promoted pathways.[1] Three papers report aryne reactions with disulfides that result in the formation of 1,2-bis(arylthio)arenes.[2] In 1986, Nakayama disclosed the use of diphenyliodonium-2-carboxylate and diazotized anthranilic acid as aryne precursors in reaction with diaryl disulfides. 1,2-Bis(arylthio)arenes were isolated in 8–30% yields.[2a] More recently, Raminelli disclosed one example of 1,2-bis(phenylthio)benzene synthesis by treatment of diphenyl disulfide with *o*-(trimethylsilyl)phenyl triflate in the presence of CsF at room temperature.[2b] We have reported that arynes generated from silyl aryl triflates or halides react with bis(trifluoromethyl)disulfide to afford 1,2-bis-trifluoromethylthioarenes.[2c] However, in line with previous observations, the method is not compatible with diaryl disulfides providing low yields of products. Transition-metal catalyzed pathways leading to 1,2-bis(arylthio)arenes may require relatively harsh reaction conditions and use of 1,2-dihaloarenes, which have limited commercial availability. *o*-(Trimethylsilyl)aryl triflate starting materials for aryne reactions are even less available. Synthesis of 1,2-bis(arylthio)arenes from readily available aryl halides and aryl triflates would allow easy structural modifications and access to a more diverse set of ligands for transition metal catalysis and other applications.[3] We report here a base-promoted, efficient synthesis of 1,2-bis(arylthio)arenes from aryl halides and triflates by employing lithium 1,1-diadamantylamide (LDAM) base.

We have reported the preparation, characterization, and use of bulky lithium 1,1-diadamantyl amide in base-promoted insertion of arynes into Si–P, Si–S, Si–N, and C–C bonds.[4] Arynes were generated from aryl triflates and halides.[5] Reactions possess high functional group compatibility, with cyano, trifluoromethyl, vinyl, methoxy, chloro, fluoro, and even formyl moieties tolerated. The bulkiness of LDAM suppresses aryne reactions with base. We speculated that similar conditions could be used for base-promoted aryne generation and insertion into S–S bonds. The optimization of the reaction conditions is presented in Table 1. If 2-naphthyl triflate **1** is reacted with diphenyl disulfide **2** and LDAM base **3** in THF solvent, low yields of **4** were obtained (entries 1 and 2). The yields were somewhat variable, and unreacted aryl triflate was observed in a crude reaction mixture. Better results were obtained in diethyl ether/cyclohexane mixed solvent (entries 3 and 4). Use of a diethyl ether/THF mixture was successful as well (entries 5–9). The best results were obtained at 0 °C by employing a triflate/disulfide/LDAM ratio of 1/1.2/1.5, affording 80% NMR and 71% isolated

Table 1 Optimization conditions[a]



Entry	1/2/3	Solvent	T, °C, t, h	Yield,[b] %
1	1/1/1.2	THF	0, 38	35
2	1/1/1.2	THF	25, 38	25
3	1/1.2/2	Et_2O/C_6H_{12} (1/1)	0, 47	74
4	1/1.2/1.2	Et_2O/C_6H_{12} (1/1)	0, 47	69
5	1/2/2	Et_2O/THF (49/1)	0, 24	70
6	1/1/1.2	Et_2O/THF (49/1)	25, 38	20
7	1/1.2/1.2	Et_2O/THF (49/1)	0, 47	72
8	1/1.2/1.5	Et_2O/THF (49/1)	0, 47	80 (71[c])
9	1/1.2/2	Et_2O/THF (49/1)	0, 47	78

[a] Aryne precursor **1** (0.25 mmol), solvent (1.5 mL). [b] Yields determined by GC analysis, *n*-decane internal standard. [c] Isolated yield. LDAM = lithium 1,1-diadamantylamide (**3**).

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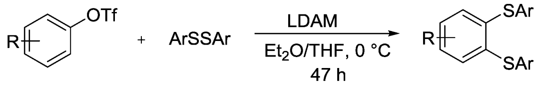
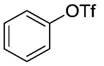
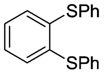
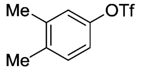
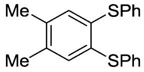
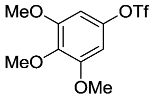
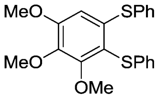
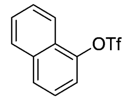
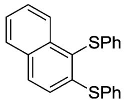
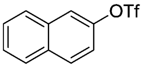
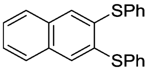
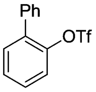
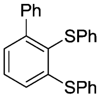
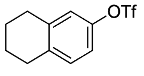
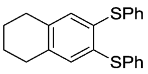
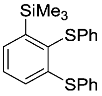
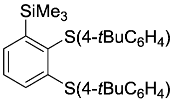
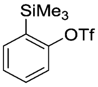
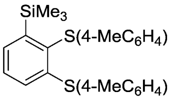
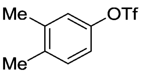
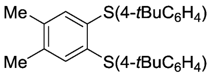
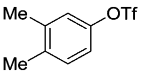
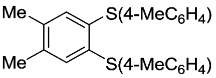
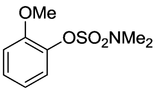
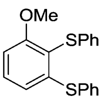
yields of **4** (entry 8). The room-temperature reaction gave a 20% NMR yield (entry 6). An increased amount of **3** did not improve the yield (entry 9).

The reaction scope with respect to aryl triflates is presented in Table 2. Reaction of phenyl triflate with diphenyl disulfide gives the product in 91% isolated yield (entry 1). Methyl- and methoxy-substituted aryl triflates are reactive as well, and acceptable to excellent yields of 1,2-bis(arylthio)arenes were obtained (entries 2 and 3). 1-Naphthyl and 2-naphthyl triflates afford products in 61 and 71% yields, respectively (entries 4 and 5). Notably, 2-naphthyl triflate gives one isomer of bis(phenylthio)-naphthalene, showing selective formation of one isomer of naphthalyne. Phenyl, alkyl, and silyl substituents are tolerated as well (entries 6–8). Several reactions were performed with substituted diaryl disulfides. Bis(4-*t*-butylphenyl)disulfide and bis(4-tolyl)disulfide react with silyl- and methyl-substituted aryl triflates giving products in good yields (entries 9–12). Interestingly, dimethylsulfamate can be employed as a leaving group (entry 13). The advantage of sulfamate relative to triflate is its lower cost.

Table 2 Reaction scope with respect to aryl triflates[a]



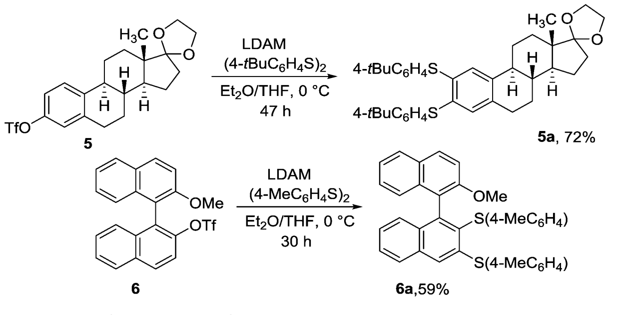
Entry	Aryne precursor	Product	Yield, %
1			91
2			84
3			56
4			61
5			71
6			68
7			82
8			91
9[b]			94
10[c]			68
11[b]			94
12[c]			>99
13			55

[a] Reaction conditions: aryne precursor (0.25 mmol), ArSSAr (0.3 mmol), LDAM (0.5 mmol), Et_2O/THF (49/1), 47 h, 0 °C. Yields are isolated yields. [b] Bis(4-*tert*-butylphenyl)disulfide was used. [c] Di(*p*-tolyl)disulfide was used. Please see the ESI for details.

Estrone-derived aryl triflate **5** was converted to bis(arylthio) derivative **5a** in 72% yield, showing relevance of the methodology to the modification of biologically active compounds (Scheme 1). One isomer of the product was obtained, demonstrating regioselective formation of an aryne intermediate. Additionally, we performed reaction of a BINOL-derived triflate **6** with bis(4-methylphenyl)disulphide, and product **6a** was isolated in 59% yield.

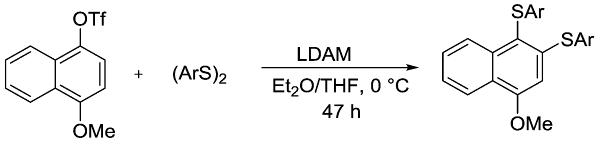
The reaction scope with respect to disulfides is shown in Table 3. The reaction conditions are similar to the ones used in Table 2. The aryne generated from 4-methoxy-1-naphthyl triflate was reacted with a selection of disulfides. 4-Methoxy-1,2-bis(phenylthio)naphthalene was synthesized in 89% isolated yield (entry 1). When bis(4-methylphenyl) and bis(4-*tert*-butylphenyl)disulfides were employed, products were isolated in 88% and 95% yields (entries 2 and 3). A chloro substituent on the disulfide is compatible with reaction conditions and the product was isolated in 72% yield (entry 4). Three isomeric dimethoxyphenyl disulfides were reacted with 4-methoxy-1-naphthyl triflate in the presence of base to afford the products in 68%, 64%, and 62% isolated yields, respectively (entries 5–7). Heterocycles are compatible with the reaction conditions as well. 4-Methoxy-1,2-bis(5-methyl-2-thienylthio)naphthalene was synthesized in 58% isolated yield (entry 8).

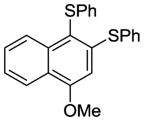
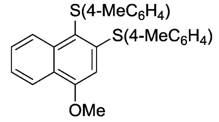
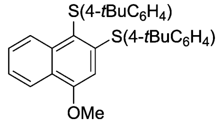
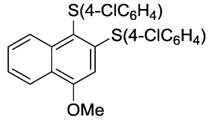
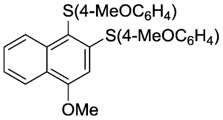
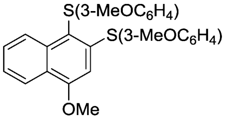
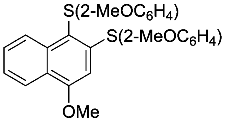
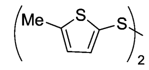
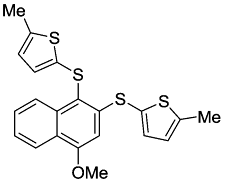
Aryl halides are often cheaper or more readily available than aryl triflates. Unfortunately, use of an aryl chloride as the aryne source gave only a modest yield of the product (Scheme 2, **8**). If aryl bromide was employed, the yield was increased to 65%. Trimethoxyphenyl bromide is reactive as well, and **11** was isolated in 78% yield. Aryl bromide possessing an electron-withdrawing trifluoromethyl substituent afforded **13** in 72% yield.



Scheme 1 Bis(arylthiolation) of estrone and BINOL derivatives.

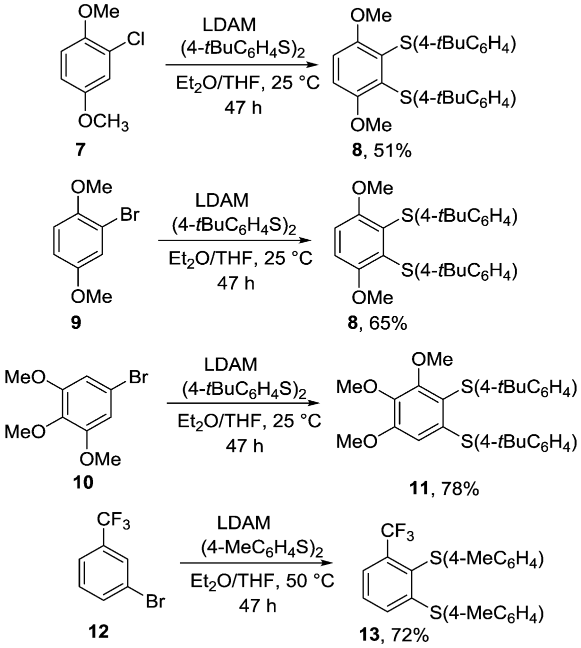
Table 3 Reaction scope with respect to ArSSAr[a]



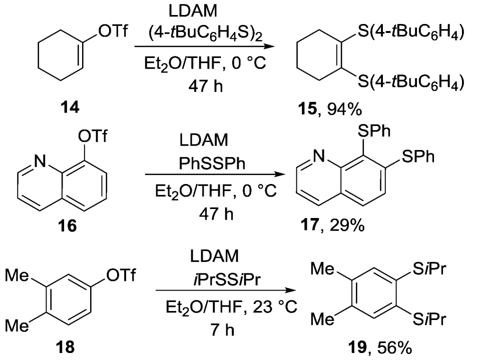
Entry	$(ArS)_2$	Product	Yield, %
1	$(PhS)_2$		89
2	$(4\text{-}MeC_6H_4S)_2$		88
3	$(4\text{-}tBuC_6H_4S)_2$		95
4	$(4\text{-}ClC_6H_4S)_2$		72
5	$(4\text{-}MeOC_6H_4S)_2$		68
6	$(3\text{-}MeOC_6H_4S)_2$		64
7	$(2\text{-}MeOC_6H_4S)_2$		62
8			58

[a] Reaction conditions: aryne precursor (0.25 mmol), ArSSAr (0.3 mmol), LDAM (0.5 mmol), Et_2O/THF (19/1), 47 h, 0 °C. Yields are isolated yields. Please see the ESI for details.

Some reactions involving cyclohexyne and quinolyne, as well as diisopropyl disulfide were also investigated (Scheme 3).[6] We were pleased that the reaction of 1-cyclohexenyl triflate with diphenyl disulfide was successful. Under the conditions employed previously, 1,2-bis(4,4′-*t*-butylphenylthio)cyclo-hexene **15** was synthesized in 94% isolated yield. Reactions with 1-cyclopentenyl and 1-cycloheptenyl triflates were not successful. 8-Quinolinyl triflate reacts with diphenyl disulfide to afford the product **17** in 29% isolated yield. Additionally, dialkyl disulfides, such as diisopropyl disulfides, are reactive as well and **19** was isolated in 56% yield.

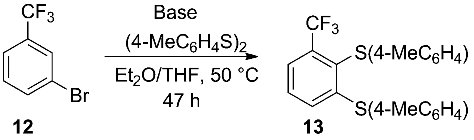


Scheme 2 Aryl halides as aryne precursors.



Scheme 3 Reactions of cyclohexyne, 8-quinolyne, and diisopropyl disulfide.

The performance of LiTMP and LDAM bases in aryne reactions with diaryl disulfide was studied (Scheme 4). Identical conditions were used for comparison. Bromide **12** was reacted with bis(*p*-tolyl)disulfide in the presence of LiTMP or LDAM. The crude NMR yields were measured by using a benzotrifluoride internal standard. Reaction promoted by LiTMP afforded 42% NMR yield of **13**, while use of LDAM gave 77% NMR and 72% isolated yield of **13**.



LDAM base: 77% NMR yield
Lithium tetramethylpiperidide base: 42% NMR yield

Scheme 4 Base comparison.

In summary, a general method for the synthesis of 1,2-bis(arylthio)arenes is described. Arynes generated from aryl triflates and aryl halides by treatment with bulky 1,1-diadamantylamide base react with diaryl disulfides to afford 1,2-bis(arylthio)arenes. Use of 1-cyclohexenyl triflate gave an excellent yield of 1,2-bis(phenylthio)cyclohexene.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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