

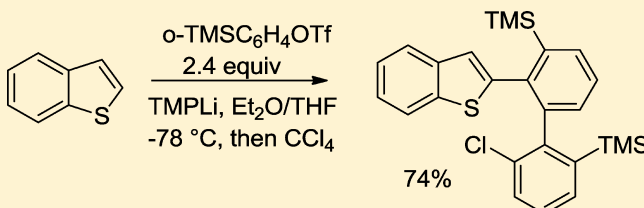
# General Method for Functionalized Polyaryl Synthesis via Aryne Intermediates

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**S** Supporting Information

**ABSTRACT:** A method for base-promoted arylation of arenes and heterocycles by aryl halides and aryl triflates is described. Additionally, in situ electrophilic trapping of ArLi intermediates generated in the reaction of benzyne with deprotonated arenes or heterocycles has been developed, providing rapid and easy access to a wide range of highly functionalized polyaryls. Base-promoted arylation methodology complements transition-metal-catalyzed direct arylation and allows access to structures that are not easily accessible via other direct arylation methods. The reactions are highly functional-group tolerant, with alkene, ether, dimethylamino, trifluoromethyl, ester, cyano, halide, hydroxyl, and silyl functionalities compatible with reaction conditions.

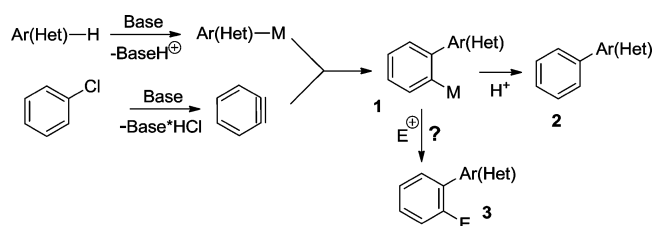


## 1. INTRODUCTION

The biaryl structure is a central building block in a large number of natural products, organic materials, and biologically active compounds.<sup>1</sup> Direct arylation through C–H bond cleavage represents an efficient alternative to classical methods for polyaryl preparation.<sup>2</sup> Second-row transition metals such as palladium, ruthenium, rhodium, and iridium have emerged as catalysts in direct arylation reactions. Excellent regioselectivity with respect to arene C–H bonds has been achieved for arylation of heterocycles as well as directing-group-containing and electron-poor arenes. In contrast, functionalization of other arenes often suffers from unsatisfactory selectivity. More recently, the use of inexpensive first-row metal catalysts has attracted substantial interest. Copper, nickel, and iron have been shown to catalyze direct arylation of  $sp^2$  C–H bonds.<sup>2d</sup> Several reports describe processes for the assembly of biaryl structures using aryl iodonium salts or photochemical methods.<sup>4</sup> Recently, direct arylation of arenes with the aid of organocatalysts has been reported.<sup>5</sup> Specifically, alkali metal alkoxide bases combined with amine bases were reported to promote formation of biaryls in the coupling of arenes with aryl halides. Reactions proceed by a homolytic aromatic substitution mechanism.<sup>5d</sup> However, arylation of simple compounds such as anisole or pyridine affords isomer mixtures, and the arene coupling component is often used in up to 100 equiv excess.

We have recently described direct base-promoted intermolecular arylation of heterocycle and arene C–H bonds.<sup>6</sup> In these reactions, less than 2.5 equiv of C–H bond coupling partner is used, and functionalization occurs at the most acidic carbon–hydrogen bond. In the presence of hindered amide bases, the (hetero)arene is deprotonated while the aryl halide forms aryne. Addition of aryl anion to the aryne affords the *o*-anionic biaryl intermediate **1**, which is subsequently protonated to form product **2** (Scheme 1). Trapping of **2** with electrophiles

## Scheme 1. Mechanism of Base-Promoted Arylation of Heterocycle and Arene C–H Bonds



other than  $H^+$  should be possible, leading to *o*-substituted biaryls of type **3**. Overall, the reaction product **3** can be thought of as a result of 2-fold C–H bond functionalization: C–H/C–Cl coupling followed by a C–H/electrophile reaction. In order for this sequence of reactions to be successful, arylmetal intermediate **1** has to be compatible with protonated base formed during formation of benzyne and **1**. Several examples of aryne reactions with nucleophiles followed by trapping of aryl metal intermediates with electrophiles have been reported.<sup>7</sup> A general procedure employing an accessible aryl halide or triflate aryne precursor, C–H bond nucleophiles, and diverse trapping reagents has not been demonstrated.

We report here (1) an expansion of scope of our previous methodology that allows a general, highly regioselective arylation of a wide range of arenes and heterocycles by aryl halides and triflates, and (2) trapping of intermediate aryl anions with a variety of electrophiles, resulting in *ortho*-functionalized biaryls and polyaryls.

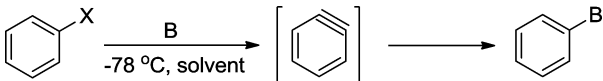
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## 2. RESULTS AND DISCUSSION

**2.1. Benzyne Formation.** We have previously used commercially available aryl halides as benzyne sources in direct arylation reactions.<sup>6</sup> Formation of arynes from halobenzenes was achieved by deprotonation affording 2-haloaryl anion followed by elimination of halide ion. A better leaving group than chloride would accelerate formation of benzyne, allowing generation of benzyne at low temperatures, avoiding competitive protonation by TMPH, and allowing electrophilic trapping of intermediate aryl metals. It is known that aryllithium protonation by tetramethylpiperidine is slow at low temperatures.<sup>8</sup> Aryl triflates have been used for deprotonative benzyne generation.<sup>9</sup> Comparison of aryl triflates and chlorides in benzyne generation is shown in Table 1. At

Table 1. Optimization of Benzyne Formation<sup>a</sup>



entry	X	base (B)	solvent	conv (%)
1	Cl	TMPLi	THF	trace
2 <sup>b</sup>	Cl	TMPLi	THF	41
3	Cl	TMPLi	Et <sub>2</sub> O	trace
4	OTf	LDA	Et <sub>2</sub> O	trace
5	OTf	TMPLi	Et <sub>2</sub> O	70
6	OTf	TMPLi	Et <sub>2</sub> O/THF (50/1)	89

<sup>a</sup>Total volume of solvent 1.5 mL, 0.25 mmol scale, PhX/base 1/2; 10 h; 6 h for entry 6. <sup>b</sup>Temperature: −62 °C, time: 12 h.

−78 °C, chlorobenzene is unreactive in THF and diethyl ether (entries 1 and 3). In THF, which facilitates the deprotonation/halide elimination sequence, chlorobenzene forms benzyne at −62 °C, albeit relatively slowly (entry 2). Thus, at least some chloroarenes should be usable for arylation/electrophilic quench sequences if solvent/temperature optimization is performed. Phenyl triflate does not form appreciable amounts of benzyne when treated with LDA in diethyl ether at −78 °C (entry 4). However, under the same conditions, TMPLi base was efficient (entry 5). Addition of a small amount of THF to diethyl ether solvent increases the yield of coupling product and decreases the reaction time (entry 6). Consequently, use of aryl triflates to generate benzyne at low temperatures should allow arylation of sensitive substrates. Trapping of aryl lithium intermediates with electrophiles should be feasible. The experiments also show that benzyne formation is most efficient in THF solvent.

### 2.2. Heterocycle and Arene Arylation by Aryl Triflates.

We have reported a method for base-mediated arylation of (hetero)arenes by aryl halides.<sup>6a</sup> The best results in arene arylation were obtained by employing LiTMP base in a pentane/THF solvent mixture. Arynes had to be generated at an appreciable rate to avoid prohibitively slow reactions. The rate of generation is highly dependent on the structure of the aryl halide. Simultaneously, aryl anions from the C–H bond coupling component had to be generated in appreciable concentrations. If aryl anions were present in low concentrations, aryne was consumed in side reactions. Consequently, the temperature for each reaction had to be optimized. Compounds possessing sensitive functional groups were either incompatible with the arylation conditions or relatively complex temperature regimes were required. In contrast, aryl triflates

can be used to generate arynes at −78 °C, allowing greater functional group tolerance and simplified temperature regimes (Table 1). The results of heterocycle and arene arylation by aryl triflates are presented in Table 2. All reactions were carried out at −78 °C in diethyl ether/THF mixed solvent. Dihalobenzenes such as 1,3-dichloro-, 1,3-difluoro-, 1,2-difluoro-, and 2-chloro-1-fluorobenzene afford products in good yields (entries 1–4). 2-Chloro-1,4-bis(trifluoromethyl)benzene is reactive, and the arylation product was obtained in 62% yield (entry 5). These examples show that formation of arynes from 2-lithiohalobenzenes (halogen = Cl, F) is slow on the time scale of benzyne formation from phenyl triflate. 1-Methyl-1,2,4-triazole and 1-phenylpyrazole are arylated efficiently (entries 6 and 7). 2,4,6-Trichloropyridine can be diarylated in 54% yield (entry 8). Triflates other than PhOTf can also be used. Interestingly, benzothiophene arylation by 2-trimethylsilylphenyl triflate, a common benzyne precursor,<sup>10</sup> affords the *ortho*-substituted product in good yield with the silyl group intact (entry 9). The regioselectivity can be explained by the inductive electron donating effect of silicon.<sup>11</sup> 2-Chlorophenyl triflate can be used to arylate benzothiophene in 53% yield (entry 10). The product contains a halogen functionality which can be used for further cross-coupling reactions. It can be concluded that aryl triflates can be used for arylation of substrates possessing DMSO pK<sub>a</sub>'s at or below 35.<sup>12</sup>

### 2.3. Heterocycle and Arene Arylation by Aryl Halides.

Aryl triflates allow for uniform C–H bond arylation conditions at low temperature. In contrast, use of aryl chloride reagents requires substantial optimization of reaction temperature, solvents, and stoichiometry. In many cases, however, there are advantages in using aryl chlorides. First, aryl chlorides are substantially cheaper than aryl triflates. Second, aryl triflates cannot be used for the arylation of nonacidic arenes (pK<sub>a</sub> > 35, DMSO solvent)<sup>12</sup> due to fast aryne formation relative to deprotonation of ArH, resulting in low product yields. We have previously reported aryl chloride use in heterocycle and arene arylation.<sup>6</sup> Additional examples are presented in Table 3 showing several other arene and heterocycle classes that are reactive. Diphenyl ether can be arylated by chlorobenzene in 53% yield (entry 1). Aryl ethers can not be arylated by aryl triflates in acceptable yields. Dibenzofuran arylation by 2-bromocumene and 2-chloronaphthalene affords the *m*-substituted products in good yields (entries 2 and 3). 2,4-Dimethoxybenzonitrile can be arylated in 42% yield, showing that nitrile functionality is compatible with the reaction conditions (entry 4). The C-arylation of NH-containing heterocycles such as 2-methyl- and 2,3-dimethylindoles is possible under the conditions developed for aniline arylation (entries 5 and 6).<sup>6c</sup> Interestingly, 4- and 5-hydroxybenzofurans are arylated at the 2-position (entries 7 and 8). The *O*-arylation product was not observed in the crude reaction mixture for entry 8. This experiment shows that heterocycle C-arylation is compatible with a phenolic hydroxyl group, in contrast to related copper-catalyzed reactions where *O*-arylation of phenols is observed.<sup>13</sup> Methoxypyridines can also be arylated in good yields (entries 9 and 10). For these substances, arylation regioselectivity is determined by the methoxy group.<sup>6a,14</sup> Reactions are typically run at −15 to −65 °C, with the exception of indole arylation (entries 5 and 6), which occurs at room temperature. Most reactions give the best yields in THF/diethyl ether mixtures (entries 1–3, 7, 8). However, more sensitive substrates such as nitriles (entry 4) require low

Table 2. Arylation with Aryl Triflates<sup>a</sup>

$\text{Het}(\text{Ar})\text{-H} + \text{Ar-OTf} \xrightarrow[\text{Et}_2\text{O/THF, -78 } ^\circ\text{C}]{\text{TMPLi}} \text{Het}(\text{Ar})\text{-Ar}$				
entry	Ar-H	Ar-X	product	yield, %
1	1,3-Dichlorobenzene	PhOTf		70
2	1,3-Difluorobenzene	PhOTf		74
3	1,2-Difluorobenzene	PhOTf		61
4	2-Chloro-1-fluorobenzene	PhOTf		54
5	2-Chloro-1,4-bis-(trifluoromethyl)benzene	PhOTf		62
6 <sup>b</sup>	1-Me-1,2,4-triazole	PhOTf		50
7	1-Ph-pyrazole	PhOTf		55
8	2,4,6-Trichloropyridine	PhOTf		54
9 <sup>c</sup>	Benzothiophene	2-TMSC <sub>6</sub> H <sub>4</sub> OTf		66
10 <sup>c</sup>	Benzothiophene	2-ClC <sub>6</sub> H <sub>4</sub> OTf		53

<sup>a</sup>Conditions: ArOTf (2–4 equiv), Ar–H (1 equiv), TMPLi (4–6 equiv), Et<sub>2</sub>O/THF solvent (30–40/1), –78 °C, 18 h, 0.25 mmol scale. Yields are isolated yields. See Supporting Information for details. <sup>b</sup>Base: LDA, THF solvent. <sup>c</sup>Time: 12 h in THF at –85 °C.

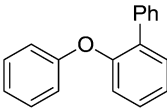
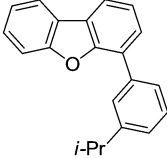
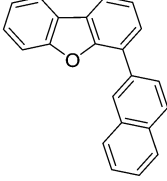
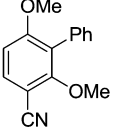
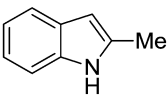
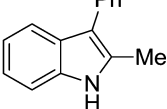
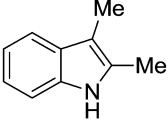
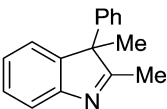
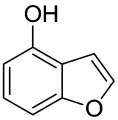
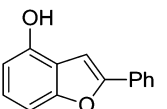
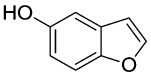
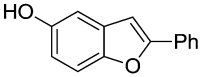
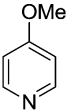
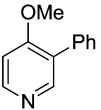
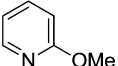
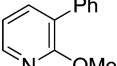
temperatures. Thus, THF solvent, where benzyne generation occurs even at –65 °C, is optimal.

**2.4. (Hetero)Arene Arylation with Subsequent Aryl Lithium Intermediate Trapping.** **2.4.1. Considerations and Reaction Optimization.** The synthesis of highly functionalized polyaryls has been extensively investigated due to their widespread applications.<sup>1</sup> Additional complexity could be introduced in hetero(arene) arylation products if the intermediate aryllithium reagent, formed in the reaction of arylmetal with benzyne, was trapped by an electrophile

(Scheme 1, structure 3). In this way, structures inaccessible by other direct arylation methods could be accessed. In essence, a three-component coupling between ArX, ArH, and electrophile would be realized.

Optimization of trapping conditions is shown in Table 4. Three major products were formed—the desired iodophenylbenzothiophene 4, 2-phenylbenzothiophene 5, and biphenylated compound 6 formed in the reaction of 2-lithiobenzothiophene with 2 equiv of benzyne. Slow generation of benzyne from chlorobenzene was observed in THF at –65 °C when

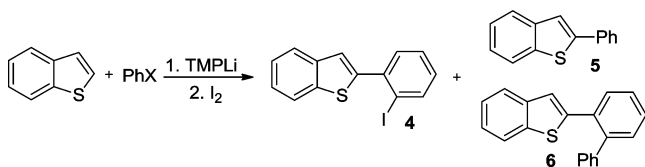
Table 3. Arylation with Aryl Halides<sup>a</sup>

$\text{Ar}^1\text{-H} + \text{Ar}^2\text{-Cl(Br)} \xrightarrow[\text{solvent, T}]{\text{TMPLi}} \text{Ar}^1\text{-Ar}^2$				
entry	arene (Ar <sup>1</sup> H)	Ar <sup>2</sup> Cl(Br)	product	yield, %
1	Ph <sub>2</sub> O	PhCl		53
2	Dibenzofuran	2-Bromo cumene		57
3	Dibenzofuran	2-Chloro naphthalene		59
4	2,4-Dimethoxybenzonitrile	PhCl		42
5 <sup>b</sup>		PhCl		66
6 <sup>b</sup>		PhCl		64
7		PhCl		59
8		PhCl		53
9		PhCl		61
10		PhCl		63

<sup>a</sup>Conditions: arene (0.25 mmol), ArX (0.375–0.75 mmol), TMPLi (1–1.25 mmol), Et<sub>2</sub>O/THF, pentane/THF, THF, or Et<sub>2</sub>O solvent, –65 to –15 °C. Yields are isolated yields. See Supporting Information for details. <sup>b</sup>Heterocycle (1 mmol), PhCl (0.5 mmol), TMPLi (1.8 mmol), cyclohexane/Et<sub>2</sub>O solvent, 23 °C.

TMPLi was used. Attempts to trap *o*-anionic biaryl intermediates with I<sub>2</sub> at this temperature failed to give a good yield of **4** (entry 1). Instead, **5** and **6** were formed predominately, showing that ArLi protonation by TMPH is relatively fast under those conditions. Changing solvent from THF to diethyl ether gave an improved 15/1 ratio of **4**/(**5** + **6**).

However, only 5% conversion was observed, showing inefficient formation of benzyne under these conditions (entry 2). At –20 °C in diethyl ether, 75% conversion was observed, but the iodinated **4** was formed as a minor product due to aryllithium protonation by TMPH (entry 3). Reaction at –45 °C resulted in slow benzyne formation, but good selectivity for **2**-

Table 4. Reaction Optimization<sup>a</sup>

entry	PhX	solvent	T (°C)	yield (%)	4/(5 + 6)
1	PhCl	THF	-65	78	1/2
2	PhCl	Et <sub>2</sub> O	-65	5	15/1
3	PhCl	Et <sub>2</sub> O	-20	74	1/22
4	PhCl	Et <sub>2</sub> O	-45	10	16/1
5	PhCl	Et <sub>2</sub> O/THF (9/1)	-45	87	10/1
6 <sup>b</sup>	PhOTf	Et <sub>2</sub> O/THF (50/1)	-78	91	12/1

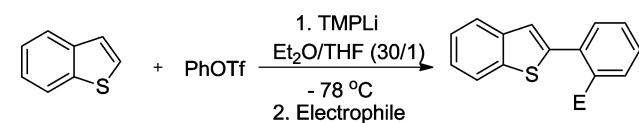
<sup>a</sup>PhX/benzothiophene 1.8/1; 24 h, 0.25 mmol scale. Yields determined by GC analysis. <sup>b</sup>Reaction time: 10 h.

iodobenzothiophene **4** was observed (entry 4). As expected, addition of THF facilitated benzyne formation and **4** was obtained in 80% yield when reaction was performed at -45 °C in a 9/1 Et<sub>2</sub>O/THF mixture. Use of PhOTf under the conditions employed in Table 2 afforded an excellent yield of **4** in short reaction times (entry 6). Thus, two sets of conditions can be applied for arylation with subsequent electrophilic trapping of aryl lithium intermediates. The first set of conditions involves the use of aryl chlorides in a Et<sub>2</sub>O/THF mixture at about -45 °C. The second set involves the use of aryl triflates in a Et<sub>2</sub>O/THF mixture at -78 °C. The latter set of conditions is beneficial for sensitive substrates.

#### 2.4.2. Scope of Aryllithium Intermediate Trapping.

Arylation of benzothiophene followed by electrophilic trapping is presented in Table 5. Trapping by I<sub>2</sub>, CBr<sub>4</sub>, CCl<sub>4</sub>, and *N*-fluorobenzenesulfonimide afforded the corresponding 2-(2-halophenyl)benzothiophenes in good to excellent yields (entries 1–4). These products can be further functionalized by cross-coupling reactions.<sup>15</sup> When DMF was used as electrophile, aldehyde was obtained in 65% yield (entry 5). Reaction with pivaldehyde yielded a secondary alcohol (entry 6). Trapping of reaction mixture with methyl chloroformate or CO<sub>2</sub> followed by MeI/NaH afforded carboxylate ester in good yield (entry 7). Both TMSCl and 4-chlorobenzoyl chloride are reactive, and functionalized products were obtained in reasonable yields (entries 8 and 9). Treating the reaction mixture with chlorodiphenylphosphine generates corresponding triarylphosphine in good yield (entry 10). The reaction could be used for efficient preparation of arylphosphine ligands. Other electrophiles such as PhSSPh can be used (entry 11).

Arylation of various (hetero)arenes by aryl halides and triflates with subsequent trapping of aryl lithium intermediates is presented in Table 6. Arylation of benzothiophene by 2-bromocumene followed by quenching with I<sub>2</sub> reagent afforded *o*-iodinated product in good yield (entry 1). When 9-bromophenanthrene was used and reaction mixture was quenched with pivaldehyde, 1-aryl-2,2-dimethylpropanol was obtained in 77% yield (entry 2). Arylation of benzothiophene by *o*-TMSC<sub>6</sub>H<sub>4</sub>OTf followed by addition of CCl<sub>4</sub> afforded chlorobiaryl product (entry 3). Interestingly, increasing the amount of *o*-TMSC<sub>6</sub>H<sub>4</sub>OTf from 1.25 to 2.4 equiv relative to benzothiophene allows trapping the first aryne addition product with a molecule of another aryne, affording triaryl in a good yield (entry 4). This reaction was repeated on 2.5 mmol scale, and product was isolated in 69% yield. Trapping of double-

Table 5. 2-(2-Lithiophenyl)benzothiophene Trapping with Electrophiles<sup>a</sup>

entry	electrophile	product	yield, %
1	I <sub>2</sub>		66
2	CBr <sub>4</sub>		79
3	CCl <sub>4</sub>		69
4	(PhSO <sub>2</sub> ) <sub>2</sub> NF		50
5	DMF		65
6	Pivaldehyde		75
7	MeOCOCi or CO <sub>2</sub> , MeI		67 62
8	TMSCl		55
9	4-ClC <sub>6</sub> H <sub>4</sub> COCl		55
10	ClPPh <sub>2</sub>		48
11	PhSSPh		69

<sup>a</sup>Benzothiophene (0.25 mmol), PhOTf (0.5 mmol), TMPLi (1.0 mmol), Et<sub>2</sub>O/THF, -78 °C, 12 h; then electrophile. Yields are isolated yields. Please see Supporting Information for details.

addition product with CCl<sub>4</sub> is also possible, affording a highly functionalized triaryl in 74% yield (entry 5). Similarly, double



Table 6. Arylation of (Hetero)arenes and Trapping of Aryllithium Intermediates<sup>a</sup>

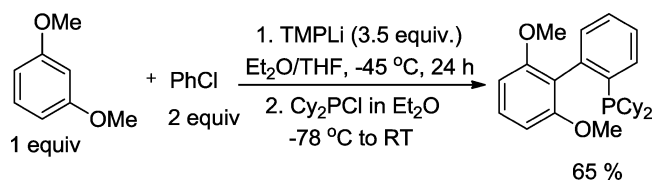
$\text{Ar-H} + \text{R} \begin{array}{c} \text{---} \text{X} \\ \text{---} \end{array} \xrightarrow[2. \text{ Electrophile}]{1. \text{ TMPLi}} \text{R} \begin{array}{c} \text{---} \text{Ar} \\ \text{---} \text{E} \end{array}$									
entry	ArH	ArX/electrophile	product	yield,%	entry	ArH	ArX/electrophile	product	yield,%
1	Benzothiophene	2-Bromocumene/I <sub>2</sub>		61	7	Benzofuran	PhOTf/DMF		62
2	Benzothiophene	9-Bromophenanthrene/pivaldehyde		77	8	3-Methoxy pyridine	PhCl/I <sub>2</sub>		53
3	Benzothiophene	<i>o</i> -TMS-C <sub>6</sub> H <sub>4</sub> -OTf/CCl <sub>4</sub>		59	9	3-Methoxybenzonitrile	PhCl/none		71
4	Benzothiophene	<i>o</i> -TMS-C <sub>6</sub> H <sub>4</sub> -OTf		71 69 <sup>b</sup>	10	3-Methoxybenzonitrile	2-Chloroanisole/none		59
5	Benzothiophene	<i>o</i> -TMS-C <sub>6</sub> H <sub>4</sub> -OTf/CCl <sub>4</sub>		74	11	1,3-Dimethoxy benzene	PhCl/DMF		64
6	Benzothiophene	PhOTf/TMSCl		66	12	1,3-Dimethoxy benzene	2-Bromocumene/I <sub>2</sub>		57

<sup>a</sup>Hetero(arene) (0.25 mmol), ArX (0.3–1.0 mmol), TMPLi (1.0–1.75 mmol), THF/Et<sub>2</sub>O or THF solvent, –35 to –78 °C, 12–39 h; then quench with an electrophile. Yields are isolated yields. Please see Supporting Information for details. <sup>b</sup>Scale: 2.5 mmol.

addition of benzyne to benzothiophene followed by trapping with TMSCl is successful if a 1/3 ratio of benzothiophene/PhOTf is employed (entry 6). These examples allow efficient syntheses of highly functionalized polyaryls which cannot be easily made by any other means. Other arenes can also be used for the arylation/electrophilic trapping sequence. Thus, arylation of benzofuran followed by trapping with DMF gives 2-(benzofuran-2-yl)benzaldehyde in a yield comparable to the one obtained for benzothiophene (entry 7). Six-membered ring heterocycles are reactive. 3-Methoxypyridine was treated with chlorobenzene followed by trapping with iodine, and 4-(2-iodophenyl)-3-methoxypyridine was obtained in acceptable yield (entry 8). Simple arenes can be used in both inter- and intramolecular trapping reactions. Thus, 3-methoxybenzonitrile was reacted with benzyne generated from chlorobenzene. Intermediate aryllithium was trapped by a cyano group, forming 4-methoxy-9-fluorenone after hydrolysis (entry 9). 2-Chloroanisole can also be used as an aryne source (entry 10). 1,3-Dimethoxybenzene is reactive, and 2',6'-dimethoxybiphenyl-2-carbaldehyde was prepared in 64% yield by reaction with benzyne followed by trapping with DMF (entry 11). A polysubstituted biaryl was produced in the reaction between dimethoxybenzene and aryne derived from 2-bromocumene followed by quench with iodine (entry 12).

The methodology allows for an efficient synthesis of Buchwald's SPhos ligand in a one-pot reaction from simple and readily accessible starting materials (Scheme 2). While the current synthesis of SPhos is highly efficient and uses cheap

#### Scheme 2. Buchwald's SPhos Ligand Synthesis



starting materials, it requires 1,2-dihalobenzene reactants that might be less available if SPhos analogues are prepared.<sup>16</sup>

An important use of organolithium reagents is in the preparation of other organometallic complexes through transmetalation. Among those, organocopper complexes have found wide use in synthetic organic chemistry. Thus, transmetalation of biaryl lithium intermediates to aryl copper reagents and their further reactivity was investigated (Table 7). Biaryl lithium was generated by reaction of benzothiophene, phenyl triflate, and TMPLi. Transmetalation of the reaction mixture with CuCN·2LiCl followed by addition of electrophiles results in functionalized arylation products. Thus, reaction with MeI electrophile afforded 2-*o*-tolylbenzothiophene in excellent yield (entry 1). Allyl bromide is reactive (entry 2). Bromomethyl acrylate ester can be used, and product was obtained in good yield (entry 3) showing compatibility of the reaction conditions with ester functionality. Epoxide opening is possible, and substitution takes place at the less hindered position (entry 4). Reactions without added CuCN·2LiCl gave substantially lower yields of products. We have previously reported a method for copper-catalyzed deprotonative arene dimerization.<sup>17</sup> When oxygen is

Table 7. Transmetalation/Cross-Coupling Reactions<sup>a</sup>

$\text{ArH} + \text{PhOTf} \xrightarrow[\substack{-78\text{ }^\circ\text{C} \\ \text{2. CuCN}\cdot\text{2LiCl} \\ \text{then E}^+}]{\substack{\text{1. TMPLi} \\ \text{Et}_2\text{O/THF (50/1)}}} \text{Ar}-\text{C}_6\text{H}_4-\text{E}$				
entry	ArH	reagent	product	yield, %
1	Benzothiophene	MeI		87
2	Benzothiophene	Allyl bromide		75
3	Benzothiophene	Ethyl-2-(bromomethyl)acrylate		57
4	Benzothiophene	2-Ethyloxirane		72
5	1,3-Dichlorobenzene	O <sub>2</sub>		44
6 <sup>b</sup>	1,3-Dichlorobenzene	O <sub>2</sub>		43
7 <sup>c</sup>	<i>n</i> -Butylthiophene	O <sub>2</sub>		30

<sup>a</sup>Hetero(arene) (0.25 mmol), PhOTf (0.5 mmol), TMPLi (1.0 mmol),  $-78\text{ }^\circ\text{C}$ , 12 h; then CuCN·2LiCl followed by electrophile or O<sub>2</sub>. Yields are isolated yields. Please see Supporting Information for details. <sup>b</sup>1,3-C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub>/PhOTf = 4; 4.8/1 ratio of product/2,2',6,6'-tetrachlorobiphenyl. <sup>c</sup>PhCl as benzyne source; *n*-butylthiophene/PhCl = 1/1; 4.3/1 ratio of product/butylthiophene dimer.

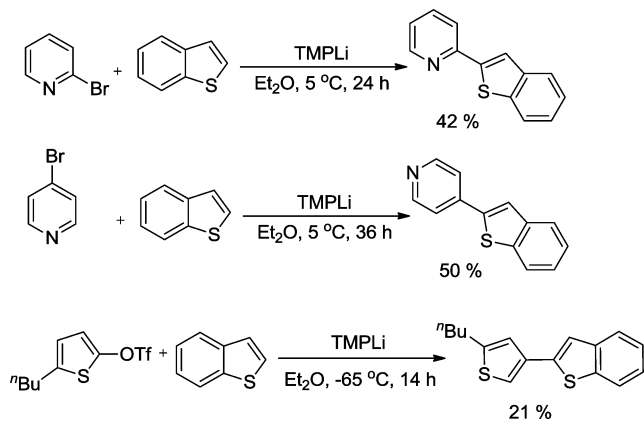
used as oxidant, a variety of arene and heterocycles can be efficiently dimerized. By employing this methodology, dimerization of aryl copper reagents was achieved in good yields. Dichlorobenzene was reacted with phenyl triflate in the presence of TMPLi to afford 2-arylphenyllithium reagent. Following lithium-to-copper transmetalation, oxygen was introduced into the reaction mixture and tetraaryl product was isolated in 44% yield (entry 5). Interestingly, when C–H

bond coupling component is used in excess, cross-dimerization between biaryl copper and starting aryl copper species can be achieved. For example, if excess of 1,3-dichlorobenzene is used under the conditions of entry 5, cross-dimerization product was obtained in moderate yield (entry 6). About 4.8/1 ratio of cross- to homodimerization was observed. Similarly, *n*-butylthiophene can be reacted with PhCl in the presence of TMPLi followed by cross-dimerization affording a 1,2-

difunctionalized arene (entry 7). In this case, a 4.3/1 ratio of cross- vs homocoupling was observed. Essentially, this method allows for 1,2-diarylation of aryl triflates.

**2.5. Heterocyclic Arynes.** Benzyne and its derivatives have been well-explored.<sup>18</sup> In contrast, relatively few heterocyclic arynes have been investigated. Pyridynes and indolynes have been employed in the synthesis of complex natural products.<sup>19</sup> Several attempts were made to investigate the formation and reactivity of heterocyclic arynes. The reaction of benzothiophene with 2-bromopyridine in the presence of TMPLi afforded 42% of coupling product (Scheme 3). The

Scheme 3. Reactions of Heterocyclic Arynes



regioselectivity of the reaction is consistent with the one reported previously for 2,3-pyridynes.<sup>20</sup> Formation of arynes from five-membered ring heterocycles is difficult, and use of five-membered ring arynes for synthetic purposes is exceedingly rare.<sup>21</sup> The challenging thiophyne generation requires use of a triflate leaving group, as 2,5-dilithiodichlorothiophene has been described as a free-flowing, white powder that decomposes slowly at 115–120 °C.<sup>22</sup> Reaction of 2-butylthiophenyl triflate with benzothiophene afforded a single product in 21% yield (Scheme 3). Analysis of product indicates that substitution occurred at the C3 position of thiophene. Functionalization of thiophene C–H bonds at the 3-position is challenging.<sup>23</sup>

### 3. SUMMARY

We describe here a method for base-promoted arylation of arenes and heterocycles by aryl halides and aryl triflates. Despite the use of lithium amide bases, the reaction is highly functional-group tolerant, with alkene, ether, dimethylamino, trifluoromethyl, ester, cyano, halide, hydroxyl, and silyl functionalities compatible with reaction conditions. Moreover, *NH*-containing indole arylation at the 3-position by aryl chlorides was achieved. Additionally, we describe a general method for electrophilic trapping of ArLi intermediates that are generated in the reaction of benzyne with deprotonated arenes or heterocycles. The trapping provides rapid and easy access to a wide range of highly functionalized polyaryls from readily available starting materials. Furthermore, generation and use of thiophyne is disclosed. The base-promoted arylation methodology complements conventional direct arylation processes, possesses high functional group tolerance, and allows access to structures that are not easily accessible via other direct arylation methods.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
- (2) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (g) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 677. (h) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res.* **2008**, *41*, 1512. (i) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (j) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (k) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (l) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495. (m) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269.
- (3) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.
- (4) (a) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668. (b) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713. (c) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458. (d) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154. (e) Wetzel, A.; Ehrhardt, V.; Heinrich, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 9130.
- (5) (a) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673. (b) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. J. *Am. Chem. Soc.* **2010**, *132*, 16737. (c) Shirakawa, E.; Itoh, K.-I.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537. (d) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018. (e) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044.
- (6) (a) Truong, T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 4243. (b) Truong, T.; Daugulis, O. *Org. Lett.* **2011**, *13*, 4172. (c) Truong, T.; Daugulis, O. *Org. Lett.* **2012**, *14*, 5964. (d) Truong, T.; Daugulis, O. *Chem. Sci.* **2013**, *4*, 531. (e) Bajracharya, G.; Daugulis, O. *Org. Lett.* **2008**, *10*, 4625.
- (7) (a) Hart, H.; Harada, K.; Du, C.-J. *J. Org. Chem.* **1985**, *50*, 3104. (b) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334. (c) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789. (d) Hamura, T.; Chuda, Y.; Nakatsuji, Y.; Suzuki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3368. (e) Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.*



2006, 128, 14042. (f) Lin, W.; Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, 44, 4258.

(8) Podraza, K. F.; Bassfield, R. L. *J. Org. Chem.* **1988**, 53, 2643.

(9) Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, 56, 2045.

(10) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 8, 1211.

(11) (a) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.-i.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angew. Chem., Int. Ed.* **2011**, 50, 5674.

(b) Akai, S.; Ikawa, T.; Takayanagi, S.-i.; Morikawa, Y.; Mohri, S.; Tsubakiyama, M.; Egi, M.; Wada, Y.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, 47, 7673. (c) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, 134, 13966.

(12) (a) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, 63, 1568. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, 21, 456.

(13) Maiti, D.; Buchwald, S. L. *J. Org. Chem.* **2010**, 75, 1791.

(14) Gros, Ph.; Fort, Y.; Queguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, 36, 4791.

(15) Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, 127, 17978.

(16) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, 127, 4685.

(17) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, 131, 17052.

(18) (a) Huisgen, R.; Sauer, J.; Hauser, A. *Chem. Ber.* **1958**, 91, 2366.

(b) Meyers, A. L.; Pansegrau, P. D. *J. Chem. Soc., Chem. Commun.* **1985**, 690. (c) Leroux, F.; Schlosser, M. *Angew. Chem., Int. Ed.* **2002**, 41, 4272. (d) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, 9, 5589. (e) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, 46, 2535. (f) Becht, J.-M.; Gissot, A.; Wagner, A.; Mioskowski, C. *Chem.—Eur. J.* **2003**, 9, 3209. (g) Abboud, M.; Mamane, V.; Aubert, E.; Lecomte, C.; Fort, Y. *J. Org. Chem.* **2010**, 75, 3224. (h) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, 12, 1224. (i) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, 132, 17933. (j) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, 112, 3550. (k) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, 51, 3766. (l) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, 42, 502. (m) Sanz, R. *Org. Prep. Proced. Int.* **2008**, 40, 215.

(19) (a) Hutters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, 133, 15797. (b) May, C.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1984**, 926. (c) Enamorado, M. F.; Ondachi, P. W.; Comins, D. L. *Org. Lett.* **2010**, 12, 4513. (d) Goetz, A. E.; Garg, N. K. *Nature Chem.* **2013**, 5, 54.

(20) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 24, 4093. The reaction of 4-bromopyridine in the place of 2-bromopyridine gave a mixture of regioisomeric products. However, direct nucleophilic substitution cannot be rigorously excluded at this point.

(21) (a) Reinecke, M. G. *Tetrahedron* **1982**, 38, 427. (b) Ye, X.-S.; Wong, H. N. C. *J. Org. Chem.* **1997**, 62, 1940.

(22) Smith, M. R., Jr.; Gilman, H. J. *Organomet. Chem.* **1972**, 42, 1.

(23) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, 49, 8946.