Synthetic Methods

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Palladium-Catalyzed Amination of Aryl Sulfides with Anilines**

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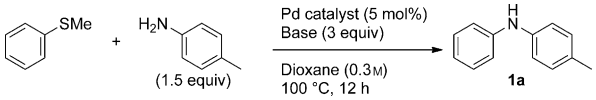
Abstract: *A combination of a palladium–NHC catalyst and potassium hexamethyldisilazide enables the amination of aryl sulfides with anilines to afford a wide variety of diarylamines. The reaction conditions are versatile enough for the reaction of even bulky ortho-substituted aryl sulfides. This amination can be applied to the modular synthesis of N-aryl carbazoles from the corresponding ortho-bromothioanisoles. As aryl sulfoxides undergo extended Pummerer reactions to afford ortho-substituted aryl sulfides, the Pummerer products are thus useful substrates for the amination to culminate in efficient syntheses of a 2-anilinobenzothiophene and an indole as proof-of-principle of the utility of the extended Pummerer reaction/amination cascade.*

The transition-metal-catalyzed amination of aryl halides[1,2] has attracted considerable attention from material and medicinal chemists because a significant number of functional molecules[3] and drugs[4] contain aryl amine structures. Although aminations of inert C–O bonds of phenol derivatives, such as mesylate,[5] tosylates,[6] carbamates,[7] sulfamates,[7a,8] pivalate esters,[9] phosphate,[10] and methyl ethers,[11] are established, it is still difficult to convert C–S bonds of aryl sulfides into C–N bonds.[12,13] The difficulty originates from a difficult transmetalation step, which is caused by the strong interaction between a cationic transition-metal center and an anionic thiolate moiety. Although many conversions of C–S bonds into C–C bonds are known,[14,15] no catalytic conversion of C–S into C–N bonds has been reported.

Our recent studies showed that palladium and nickel catalysts bearing an N-heterocyclic carbene (NHC) ligand are sufficiently active for C–C bond-forming cross-coupling reactions of aryl sulfides.[16] We envisioned that such electron-donating and bulky ligands would also aid the catalytic amination of aryl sulfides. Herein, we report amination reactions of aryl sulfides with aryl amines using a Pd–NHC catalyst.

The reaction conditions were first optimized for the amination reaction (Table 1; for details of the catalysts used, see Figure S1 in the Supporting Information). Treatment of thioanisole with *p*-toluidine (1.5 equiv) in the presence of the catalyst Pd-PEPPSI-IPr[1c,d,h] (5 mol%; PEPPSI = pyridine-enhanced pre-catalyst preparation, stabilization, and initiation; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and K_2CO_3 (3 equiv) in dioxane at 100 °C for 12 h gave none of the expected diaryl amine **1a** (entry 1). We speculated that this disappointing result is caused by a sluggish transmetalation step.[17] The same reaction was tested using stronger bases to accelerate the transmetalation step (entries 2–6). Although KOH and KO*t*Bu were not effective, employment of KHMDS (potassium hexamethyldisilazide) provided **1a** in 76% yield (entries 2–4). The choice of countercation was important: analogues NaHMDS and LiHMDS afforded **1a** in only 38% and 5% yields, respec-

Table 1: Optimization of the amination reaction conditions.



Entry	Catalyst	Base	Yield [%][a]
1	Pd-PEPPSI-IPr	K_2CO_3	0
2	Pd-PEPPSI-IPr	KOH	0
3	Pd-PEPPSI-IPr	KO*t*Bu	7
4	Pd-PEPPSI-IPr	KHMDS/Toluene	76[b]
5	Pd-PEPPSI-IPr	NaHMDS/THF	38
6	Pd-PEPPSI-IPr	LiHMDS/THF	5
7	None	KHMDS/Toluene	0
8	SingaCycle-A1	KHMDS/Toluene	84
9	SingaCycle-A3	KHMDS/Toluene	88[b]
10	[IPrPdCl(π-allyl)]	KHMDS/Toluene	72
11	$[Pd_2(dba)_3]$/IPr·HCl	KHMDS/Toluene	50
12	$[\{(\pi\text{-allyl})PdCl\}_2]$/IPr·HCl	KHMDS/Toluene	84
13	**SingaCycle-A3**	**KHMDS/Toluene**	**91**[b,c]
14	Pd-PEPPSI-IMes	KHMDS/Toluene	0
15	Pd-PEPPSI-IPent	KHMDS/Toluene	5
16	Pd-PEPPSI-SIPr	KHMDS/Toluene	25
17	$NiBr_2$·diglyme/IPr·HCl	KHMDS/Toluene	0

[a] Product yield calculated from ^{1}H NMR experiments. Diphenylmethane was used as an internal standard. [b] Yield of isolated product. [c] *p*-Toluidine (1.2 equiv), SingaCycle-A3 (2.5 mol%), KHMDS/toluene (2.5 equiv), dioxane (0.5 M). Highlighted line indicates optimum reaction conditions.

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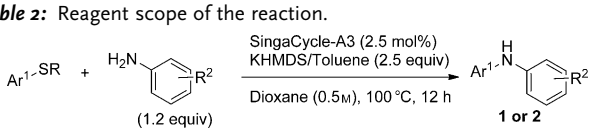
tively (entries 5,6). The reaction did not proceed in the absence of a palladium catalyst, thereby eliminating a possible S_NAr (nucleophilic aromatic substitution) pathway (entry 7).[12] Palladium precursors also affected the efficiency (entries 8–13). Palladium compound SingaCycle-A3[18] showed higher catalytic activity than Pd-PEPPSI-IPr to obtain **1a** in 88% yield (entry 9). Further optimization revealed that the highest yield (91%) for the reaction was obtained in the presence of SingaCycle-A3 (2.5 mol%), *p*-toluidine (1.2 equiv), and KHMDS (2.5 equiv) under concentrated conditions (0.5 M; entry 13). The choice of the Pd–IPr catalyst combination was crucial. Employment of the less bulky IMes ligand (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) or the more bulky IPent ligand (IPent = 1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene) showed lower catalytic activity (entries 14,15). The reaction with the SIPr ligand, which is an analogue of the IPr ligand with a saturated imidazolium core, also resulted in a lower product yield (entry 16). A combination of a nickel salt ($NiBr_2$·diglyme) and the IPr ligand was not effective (entry 17).

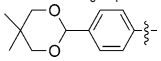
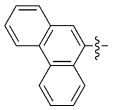
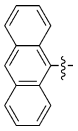
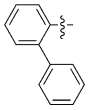
The scope of the amination reaction was then investigated (Table 2). We first studied the effect of alkylsulfanyl leaving groups. The odorless 1-dodecylsulfanyl group[19] and bulky *tert*-butylsulfanyl and phenylsulfanyl groups participated in the reaction (entries 1–4). A wide scope of anilines was also successfully employed in this reaction. Bulky *o*-toluidine reacted smoothly to give **1c** in high yield (entry 6). Unsubstituted aniline (entry 7) as well as anilines having an electron-donating group (entries 8,11) or an electron-withdrawing group (entries 9,10) were successfully used in the amination reaction. By protection of the NH_2 substituent using benzyl groups, the reagent survives under the basic reaction conditions (entry 11).[20] Amination with 2-pyridylamine was also successful but required a longer reaction time (entry 12). A variety of aryl sulfides were also tested in the reaction (entries 13–25). Aryl sulfides having various substituents, such as *o*-methyl (entry 15), electron-withdrawing fluoro and trifluoromethyl (entries 16,18), electron-donating methoxy (entry 19), THP-protected hydroxy[20] (entry 20, THP = tetrahydropyran), and acetal-protected formyl[20] (entry 21), underwent the amination. Unfortunately, 4-trifluoromethylaniline derivative **2e** could not successfully isolated from the reaction as a result of its instability under basic conditions (entry 17). The reaction conditions were also applicable to bulky polyaromatic sulfides, such as 1-naphthyl, 9-phenanthryl, and 9-anthracenyl sulfides (entries 22–24). 2-Biphenylylamine **2m** was obtained in good yield (73%) and was easily transformed into the corresponding carbazole (see below, Scheme 1).

Since the amination provided potassium diarylamides, such as **3**, before aqueous work-up, the one-pot synthesis of triarylamine **4** was achieved by the subsequent reaction of **3** with 1-bromonaphthalene [Eq. (1)].[21]

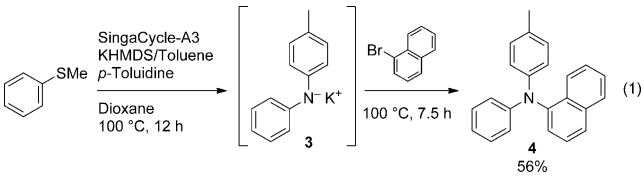
Taking advantage of the efficient amination of bulky aryl sulfides (for example Table 2, entry 25), we undertook the modular synthesis of carbazoles. Compounds **6** (**6a**–**6e**; Scheme 1) were obtained through the palladium-catalyzed Suzuki reaction of 2-bromoaryl methyl sulfide (**5a**) or its methyl derivative **5b**, which are readily available through bromination of aryl methyl sulfide. Amination of the compound **6** derivatives provided the corresponding amines **7**. The resulting diarylamines **7** can be employed as the key precursors of substituted carbazoles **8** through direct oxidative C–N bond formations.[22,23] Treatment of **7** in the presence

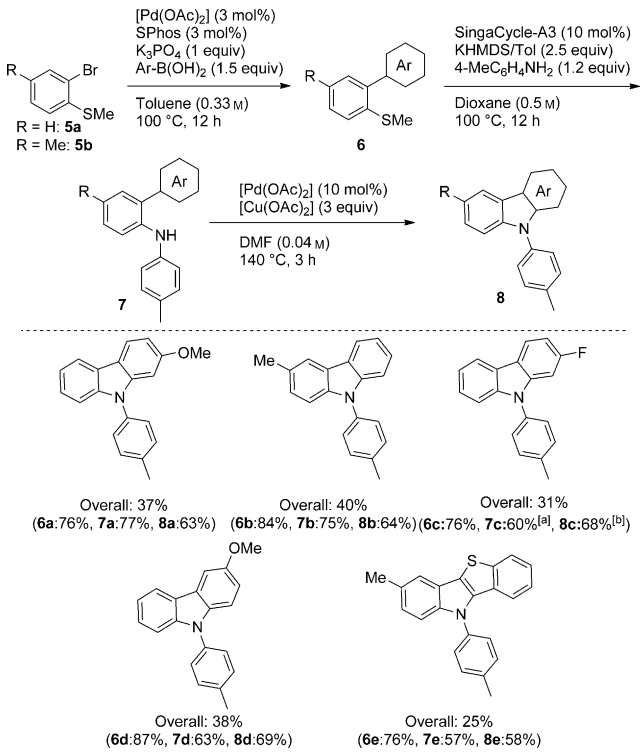
Table 2: Reagent scope of the reaction.



Entry	Ar^1	R	R^2	**1** or **2**	Yield [%][a]
1	Ph	Me	4-Me	**1a**	91
2	Ph	$C_{12}H_{25}$	4-Me	**1a**	(73)
3	Ph	*t*Bu	4-Me	**1a**	(65)
4	Ph	Ph	4-Me	**1a**	(99)
5	Ph	Me	3-Me	**1b**	92[b]
6	Ph	Me	2-Me	**1c**	75
7	Ph	Me	H	**1d**	85
8	Ph	Me	4-MeO	**1e**	90
9	Ph	Me	4-F	**1f**	88
10	Ph	Me	3-CF_3	**1g**	65[b]
11	Ph	Me	4-Bn_2N	**1h**	74[b]
12	Ph	Me	(2-Pyridyl)	**1i**	75[c,d]
13	4-MeC_6H_4	Me	4-Me	**2a**	72[c]
14	3-MeC_6H_4	Me	4-Me	**2b**	80[c]
15	2-MeC_6H_4	Me	4-Me	**2c**	64
16	4-FC_6H_4	Me	4-Me	**2d**	65[c]
17	4-$CF_3C_6H_4$	$C_{12}H_{25}$	4-Me	**2e**	0
18	3-$CF_3C_6H_4$	$C_{12}H_{25}$	4-Me	**2f**	83
19	4-$MeOC_6H_4$	Me	4-Me	**2g**	73[e]
20	4-$THPOC_6H_4$	Me	4-Me	**2h**	60[b,d]
21		Me	4-Me	**2i**	76[b]
22		Me	4-Me	**2j**	68[b]
23		$C_{12}H_{25}$	4-Me	**2k**	80[f]
24		$C_{12}H_{25}$	4-Me	**2l**	81[b]
25		Me	4-Me	**2m**	73[b]

[a] Yield of isolated product. Product yield calculated from ^{1}H NMR experiments are in parentheses. [b] SingaCycle-A3 (10 mol%). [c] SingaCycle-A3 (5 mol%). [d] 18 h. [e] SingaCycle-A3 (2.5 mol% ×3). [f] SingaCycle-A3 (7.5 mol%).

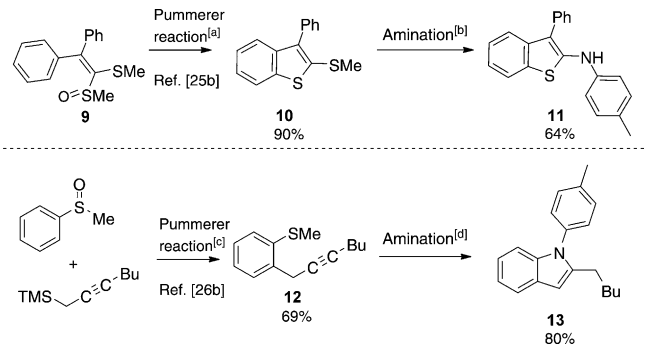




Scheme 1. Top: Modular synthesis of *N*-arylcarbazole derivatives **8** from bromoaryl methyl sulfide reagents **5**. Bottom: Structures and overall cumulative yields of final *N*-arylcarbazole products **8a**–**8e**. Yields for individual reaction steps to form intermediates **6a**–**6e** and **7a**–**7e** and final products **8a**–**8e** given in parentheses. [a] 2 h. [b] 150 °C.

of a catalytic amount of $[Pd(OAc)_2]$ with $[Cu(OAc)_2]$ as an oxidant in DMF for 3 h at 140 °C furnished carbazole compounds **8** in high yields. A wide variety of carbazoles, including a ladder-type molecule **8e**, were obtained through this three-step strategy in 25–40 % overall yields from **5**. Interestingly, the ring-closing reaction of **7d** proceeded regioselectively at the *ortho* position of the methoxy group to give carbazole **8d**.

We have regarded sulfur as a halogen surrogate of higher functionality because of the relatively recent advancements in extended Pummerer reactions,[16,24–26] where sulfoxide moieties are converted into the corresponding sulfides with intriguing C–C bond formation. As a limited variety of transformations of the resulting alkylsulfanyl moieties are available,[14] we have been striving after new methods for transformations of C–S bonds to expand the potential of the Pummerer products. We envisioned that combining extended Pummerer reactions with our catalytic amination would provide a new method to synthesize nitrogen-containing aromatic compounds. For example, we employed our benzothiophene synthesis from the readily available compound, ketene dithioacetal monoxide **9**[25b] (Scheme 2). The Pummerer cyclization of **9** with trifluoromethanesulfonic anhydride (Tf_2O) followed by demethylation with ethanolamine afforded 2-methylsulfanyl-3-phenylbenzothiophene (**10**) in 90 % yield. The resulting methylsulfanyl group of **10** was replaced with *p*-toluidine using the amination method.



Scheme 2. Extended Pummerer/amination reaction sequences. [a] Tf_2O (1.4 equiv), K_2CO_3 (3 equiv), toluene, 25 °C, 1 h, then ethanolamine (5 equiv), 25 °C, 3 h. [b] *p*-Toluidine (1.2 equiv), SingaCycle-A3 (10 mol %), KHMDS/toluene (2.5 equiv), dioxane (0.5 M), 100 °C, 18 h. [c] Tf_2O (1.5 equiv), MeCN, 25 °C, 0.5 h, then 2,6-lutidine (2.5 equiv), 80 °C, 20 h. [d] *p*-Toluidine (4-$MeC_6H_4NH_2$; 1.3 equiv), SingaCycle-A3 (10 mol %), KHMDS/toluene (2.6 equiv), dioxane (0.5 M), 100 °C, 12 h.

Another example includes the method of Eberhart and Procter for the *ortho*-propargylation of aryl sulfoxides, which afforded methyl-2-propargylphenyl sulfide (**12**).[26b] When compound **12** was used under the amination conditions, a tandem amination/cyclization reaction occurred to yield the corresponding indole **13** in 80 % yield.[27]

In summary, we have developed new amination of aryl sulfides by using a state-of-the-art palladium–IPr catalyst. The wide scope of the reaction means that various aryl sulfides and anilines, including bulky *ortho*-substituted substrates and substrates with base-proof protection, can be employed. A new route to the modular synthesis of *N*-arylcarbazoles can be achieved through amination of 2-biphenylyl sulfides followed by intramolecular C–N bond formation under oxidative conditions. We have also demonstrated that extended Pummerer reaction/amination sequences are highly efficient for the rapid synthesis of complex molecules. Our work will be an important milestone to disseminate carbon–sulfur-based organic synthetic methods that complement carbon–halogen-based syntheses. The development of more general aminations of aryl sulfides under mild conditions is ongoing in our laboratory.

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