

Palladium-Catalyzed Amination of Aryl Sulfides with Anilines**

Tomohiro Sugahara, Kei Murakami,* Hideki Yorimitsu,* and Atsuhiko Osuka

Abstract: A combination of a palladium-NHC catalyst and potassium hexamethyldisilazide effects amination of aryl sulfides with anilines to afford a wide variety of diarylamines. The reaction conditions are versatile enough to convert even bulky ortho-substituted aryl sulfides. This amination is thus applicable to new modular synthesis of *N*-arylcarbazoles from ortho-bromothioanisoles. Since aryl sulfoxides undergo extended Pummerer reactions to afford ortho-substituted aryl sulfides, the Pummerer products are hence useful substrates for the amination to culminate in efficient syntheses of 2-anilinobenzothiophene and indole as proof-of-principle of the utility of extended Pummerer reaction/amination cascade.

Transition-metal-catalyzed amination of aryl halides^[1,2] has been attracting considerable attentions from material and medicinal chemists because a significant number of functional molecules^[3] and drugs^[4] contain arylamine 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] have been reported, it is still difficult to convert C–S bonds of aryl sulfides into C–N bonds.^[12,13] The difficulty would originate from reluctant transmetalation due to strong interaction between a cationic transition metal and an anionic thiolate.

Our recent studies showed that palladium and nickel catalysts having an *N*-heterocyclic carbene (NHC) ligand are sufficiently active for C–C bond forming cross-coupling reactions of aryl sulfides.^[14] We envisioned that such electron-donating and bulky ligands would also help catalytic amination of aryl sulfides. This

was indeed the case and here we report amination reactions of aryl sulfides with aryl amines using a Pd/NHC catalyst.

First, we optimized reaction conditions for the amination (Table 1). Treatment of thioanisole with *p*-toluidine (1.5 equiv) in the presence of Pd-PEPPSI-IPr^[15] (5 mol%) and K₂CO₃ (3 equiv) in dioxane at 100 °C for 12 h gave none of the corresponding diarylamine **1a** (entry 1). We speculated that this disappointing result would arise from sluggish transmetalation.^[15] We therefore screened stronger bases in order to accelerate the transmetalation step (entries 1–7). Although KOH and KO^{*t*}Bu were not effective, employment of KHMDS provided **1a** in 76% yield (entries 2–4). The choice of a counter cation was important: NaHMDS and LiHMDS only afforded 38% and 5% yields of **1a**, respectively (entries 5 and 6). The reaction did not proceed in the absence of a palladium catalyst, thereby eliminating a possible S_NAr pathway (entry 7).^[12] Palladium precursors also affected the efficiency (entry 8–13). SingaCycle-A3,^[16] which was commercially available from TCI, showed the higher catalytic activity than Pd-PEPPSI-IPr and **1a** was obtained in 84% yield. Further optimization revealed that the reaction gave the highest yield of 91% in the presence of 2.5 mol% of SingaCycle-A3, 1.2 equiv of *p*-toluidine, and 2.5 equiv of KHMDS under concentrated conditions (0.5 M) (entry 13). The choice of the Pd/IPr combination was crucial. Employment of the less bulky IMes ligand or the more bulky IPent ligand showed lower catalytic activity (entry 14 and 15). The reaction with SIPr ligand, which is an analog of IPr with a saturated imidazolium core, also resulted in low yield (entry 16). A combination of Ni salt and IPr ligand was not effective (entry 17).

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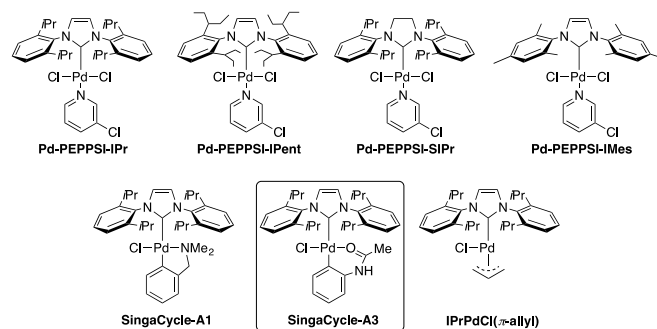
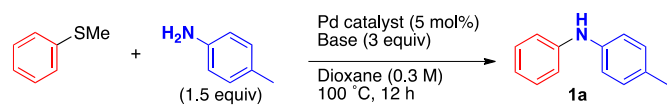


Figure 1. Palladium NHC catalysts used in this paper.

Table 1. Optimization of the reaction.



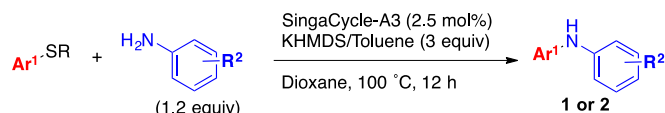
Entry	Catalyst	Base	Yield ^[a]
1	Pd-PEPPSI-IPr	K ₂ CO ₃	0%
2	Pd-PEPPSI-IPr	KOH	0%
3	Pd-PEPPSI-IPr	KOtBu	7%
4	Pd-PEPPSI-IPr	KHMDS/Toluene	76%^[b]
5	Pd-PEPPSI-IPr	NaHMDS/THF	38%
6	Pd-PEPPSI-IPr	LiHMDS/THF	5%
7	None	KHMDS/Toluene	0%
8	SingaCycle-A1	KHMDS/Toluene	84%
9	SingaCycle-A3	KHMDS/Toluene	88%^[b]
10	[IPrPdCl(π-allyl)]	KHMDS/Toluene	72%
11	Pd ₂ (dba) ₃ /IPr•HCl	KHMDS/Toluene	50%
12	[(π-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] ¹H NMR yield. [b] Isolated yield. [c] *p*-Toluidine (1.2 equiv), SingaCycle-A3 (2.5 mol%), KHMDS/toluene (2.5 equiv), dioxane (0.5 M).

The scope of this amination was then investigated (Table 2). We first studied the effect of alkylthio leaving groups. Not only odorless 1-dodecylthio group^[17] but also bulky *t*-butylthio and phenylthio groups participated in the reaction (entries 1–4). The scope of anilines was also reasonably wide. Bulky *o*-toluidine reacted smoothly to give **1c** in high yield (entry 6). Anilines having an electron-donating or -withdrawing group engaged in the amination (entries 7–9). Amination with 2-pyridylamine proceeded albeit with a longer reaction time (entry 10). A variety of aryl sulfides were also applicable to the reaction (entries 11–23). Aryl sulfides having various substituents such as *o*-methyl (entry 13), electron-withdrawing fluoro and trifluoromethyl (entries 14 and 16), electron-donating methoxy (entry 17), protected hydroxy (entry 18), and protected formyl (entry 19) underwent the amination. Unfortunately, 4-trifluoromethylaniline derivative **2e** was not obtained due to the instability of **2e** under the basic conditions. Gratifyingly, the reaction conditions were applicable to bulky polyaromatic sulfides such as 1-naphthyl, 9-phenanthryl, and 9-anthracenyl sulfides (entries 20–22). 2-Biphenylamine **2m** was obtained in good yield, which was easily transformed into the corresponding carbazole (*vide infra*, Table 3).

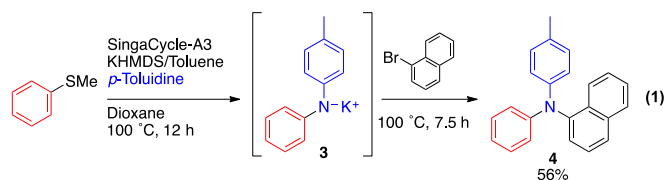
Since the amination provided potassium diarylamides such as **3** before aqueous work-up, one-pot synthesis of triarylamine **4** was accomplished by the subsequent reaction of **3** with 1-bromonaphthalene (eq. 1).^[18]

Table 2. 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	<i>t</i> 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	4-MeO	1d	90%
8	Ph	Me	4-F	1e	88%
9	Ph	Me	3-CF ₃	1f	65% ^[b]
10	Ph	Me	(2-Pyridyl)	1g	75% ^[c,d]
11	4-MeC ₆ H ₄	Me	4-Me	2a	72% ^[c]
12	3-MeC ₆ H ₄	Me	4-Me	2b	80% ^[c]
13	2-MeC ₆ H ₄	Me	4-Me	2c	64%
14	4-FC ₆ H ₄	Me	4-Me	2d	65% ^[c]
15	4-CF ₃ C ₆ H ₄	C ₁₂ H ₂₅	4-Me	2e	0%
16	3-CF ₃ C ₆ H ₄	C ₁₂ H ₂₅	4-Me	2f	83%
17	4-MeOC ₆ H ₄	Me	4-Me	2g	73% ^[e]
18	4-THPOC ₆ H ₄	Me	4-Me	2h	60% ^[b,d]
19		Me	4-Me	2i	76% ^[b]
20		Me	4-Me	2j	68% ^[b]
21		C ₁₂ H ₂₅	4-Me	2k	80% ^[f]
22		C ₁₂ H ₂₅	4-Me	2l	81% ^[b]
23		Me	4-Me	2m	73% ^[b]

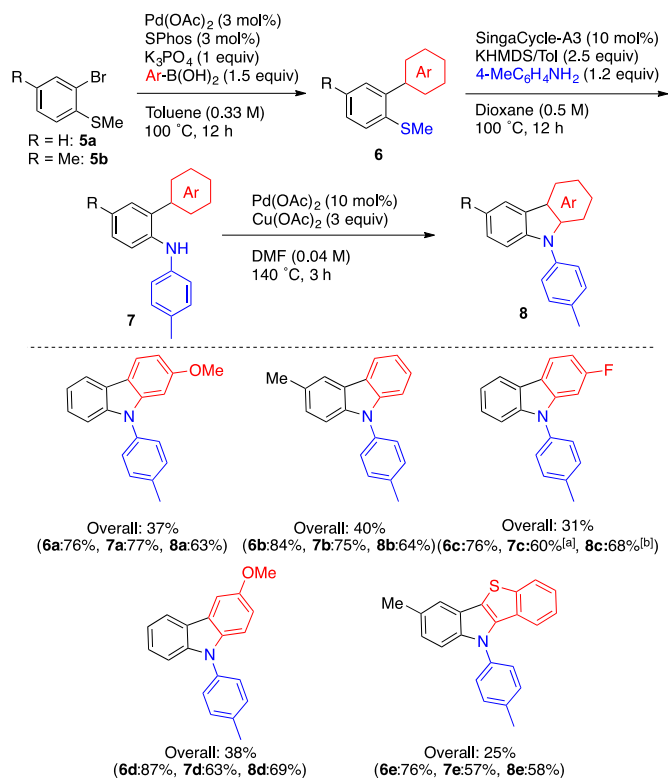
[a] Isolated yield. ¹H NMR yields are in the parentheses. [b] SingaCycle-A3 (10 mol%). [c] SingaCycle-A3 (5 mol%). [d] 18 h. [e] SingaCycle-A3 (2.5 mol% x 3). [f] SingaCycle-A3 (7.5 mol%).



Taking advantage of the efficient amination of bulky aryl sulfides (e.g., Table 2, entry 23), we tried to achieve modular synthesis of carbazoles. Compounds **6** were obtained through palladium-catalyzed Suzuki reaction of 2-bromoaryl methyl sulfide **5a** or **5b**, which are readily available through bromination of aryl methyl sulfide. The amination of **6** provided the corresponding amine **7**. Although a variety of direct oxidative C–N bond formation to construct carbazoles have been reported,^[19,20] the substituents on nitrogen were limited to alkyl,^[20a] acyl,^[20b–d] sulfonyl^[20e–g] or pyridyl^[20h,i] groups. We therefore developed new conditions for *N*-aryl substrates **7**. After extensive screening, we found Cu(OAc)₂ was the best oxidant to furnish carbazole **8** in high

yield (See SI for optimization). A wide variety of carbazoles including a ladder-type molecule **8e**, were obtained through this three-step strategy in 24–40% overall yield from **5**. Interestingly, the ring-closing reaction of **7d** proceeded regioselectively at the *ortho* position of the methoxy group to give **8d**.

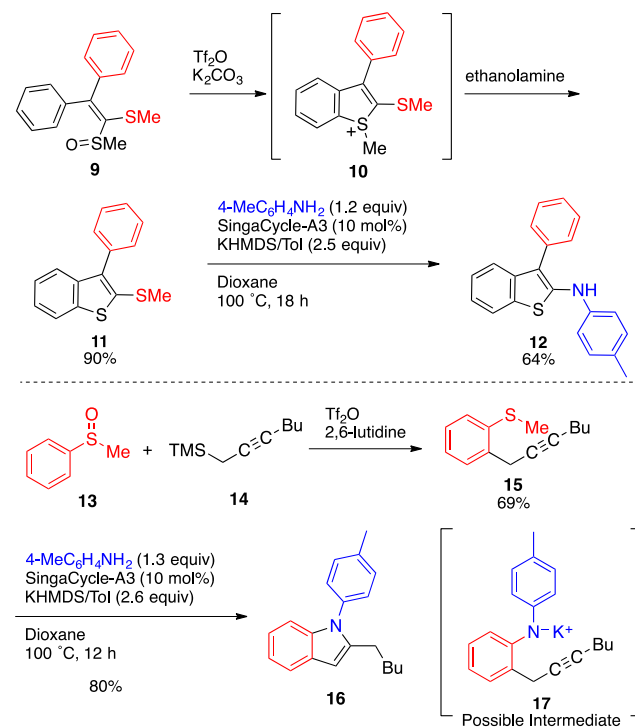
Table 3. Modular synthesis of *N*-arylcarbazoles.



[a] 2 h. [b] 150 °C.

We have regarded sulfur as a halogen surrogate of higher functionality because of the recent drastic boost in extended Pummerer reactions^[14,21–23] where sulfoxide moieties are converted to the corresponding sulfides along with intriguing C–C bond formation. Since the limited variety of transformations of the resulting alkylthio moieties are available,^[24] we have been striving after new repertoires for transformations of C–S bonds to expand the potential of the Pummerer products.^[14] Naturally, we envisioned that a combination of extended Pummerer reactions with our catalytic amination would provide a new tool for synthesizing nitrogen-containing aromatic compounds. For example, we indeed employed our benzothiophene synthesis from readily available ketene dithioacetal monoxide **9**^[22b] (Scheme 1). The Pummerer cyclization of **9** with Tf₂O followed by demethylation with ethanolamine afforded 2-methylthio-3-phenylbenzothiophene (**11**) in 90% yield. The resulting methylthio group of **11** was replaced with *p*-toluidine through our technology. Another example includes Procter's *ortho*-propargylation of aryl sulfoxides, which afforded methyl 2-propargylphenyl sulfide **15**.^[23b] Exposure of **15** under the amination conditions beneficially led to tandem amination/annulation to yield the corresponding indole **16** in 81% yield, probably via possible intermediate **17**.^[25]

In summary, we have developed new amination of aryl sulfides by using a state-of-the-art Pd/IPr catalyst. The scope is wide enough to employ various aryl sulfides and anilines including bulky *ortho*-substituted substrates. Amination of 2-biphenyl sulfides followed by intramolecular C–N bond formation under our modified oxidative conditions has opened a door to modular synthesis of *N*-arylcarbazoles. We have also demonstrated that extended Pummerer reaction/amination sequences are highly efficient for rapid synthesis of complex molecules. Our work will be an important milestone to trigger a paradigm shift from C–X-based synthesis to C–S-based synthesis.



Scheme 1. Extended Pummerer/amination sequences.

Experimental Section

Synthesis of **1a** is representative (Table 1, entry 13). *p*-Toluidine (64 mg, 0.6 mmol) and SingaCycle-A3 (8.3 mg, 0.013 mmol) were added to a Schlenk tube under argon. Dioxane (1 mL) and thioanisole (59 μ L, 0.50 mmol) were added successively to the tube. After an addition of KHMDS (2.5 mL, 1.25 mmol, 0.5 M in toluene), the mixture was heated at 100 °C for 12 h. After the reaction, the mixture was cooled to 25 °C. The reaction was then quenched with water (5 mL). The organic compounds were extracted with EtOAc (5 mL) three times. The combined organic part was then washed with brine. The mixture was filtered through a pad of silica-gel and Na₂SO₄ and concentrated in vacuo. Purification by chromatography on silica-gel (*n*-hexane/EtOAc = 20/1) provided **1a** (83 mg, 0.45 mmol, 91%).

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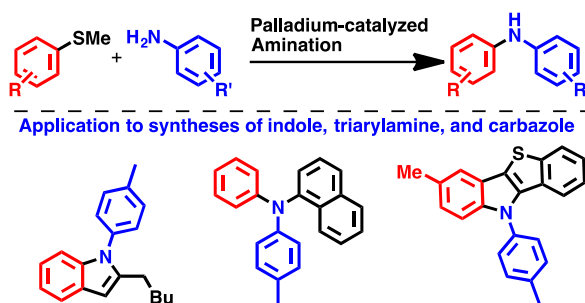
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Synthetic Method

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Palladium-Catalyzed Amination of Aryl
Sulfides with Anilines



Transformation of inert C–S bonds of aryl sulfides into C–N bonds has been accomplished by using a palladium complex having an N-heterocyclic carbene ligand. A wide range of aryl sulfides and anilines are applicable to the reaction. Thanks to the efficient conditions for amination of bulky sulfides, modular syntheses of carbazoles from 2-biphenylamine products were achieved through our newly modified oxidative C–N bond formation. When combined with extended Pummerer reactions that afforded useful aryl sulfides, the amination led to highly efficient construction of intriguing nitrogen-containing molecules.