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Palladium-Catalyzed Amination of Aryl Sulfides with Aliphatic Amines

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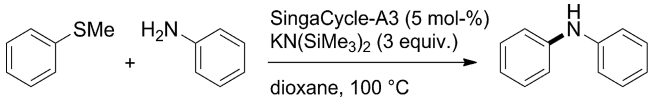
Keywords: Synthetic methods / Homogeneous catalysis / Amination / Arylation / Sulfur / Carbene ligands / Palladium

Conditions for the palladium–NHC-catalyzed amination of aryl sulfides with aliphatic as well as aromatic amines were established. The KHMDS-mediated amination of heteroaryl sulfides could proceed without palladium. Based on the distinct difference in reactivity of C–Br and C–S bonds, a sequential amination of bromothioanisole can take place to install two different alkylamino groups onto the aromatic ring in one pot.

Introduction

The great relevance of aniline derivatives in pharmaceutical, agrochemical, and materials sciences has been an inspiration for organic chemists to develop efficient methods for carbon–nitrogen bond formation.[1] After Buchwald's and Hartwig's breakthrough on the palladium-catalyzed amination of aryl halides with anilines, a number of catalytic amination reactions of aryl halides/pseudohalides have been reported.[2,3] Recently, a series of stable and low-cost phenol derivatives[4] such as carbamates,[5] sulfamates,[5b,6] pivalate esters,[7] phosphates,[8] and even challenging methyl ethers[9] have been introduced as substrates for amination reactions. This situation encouraged us to discover new coupling partners for amination reactions other than oxygen-based molecules.

Although the reactivities of carbon–sulfur bonds are comparable to those of carbon–halogen bonds, they have been used much less frequently in transition-metal-catalyzed cross-coupling reactions, due to the strong affinity of the sulfur atom for transition metals.[10] The development of new catalytic reactions of C–S bonds would be an important challenge, since C–S bonds are found widely in organic feedstocks, synthetic intermediates, and useful products. As a part of our recent research into catalytic C–S bond cleavage,[11] we reported the first palladium-catalyzed amination of aryl sulfides (Scheme 1).[11c] A palladium–NHC (N-heterocyclic carbene) precatalyst, SingaCycle-A3, showed excellent reactivity for C–S bond cleavage. However, the amination of aliphatic amines was not successfully achieved. In this paper, we report a more general protocol for the catalytic amination of aryl sulfides with both aliphatic and aromatic amines.



Scheme 1. Previously reported palladium-catalyzed amination of aryl sulfides with anilines.

Results and Discussion

For the optimization of the reaction conditions, we chose thioanisole (**1a**) and morpholine (**2a**) as model substrates. Since only NHC ligands had been shown to be effective for the previously reported amination through C–S bond cleavage, the modification of NHC ligands was our first strategy to achieve the amination. Thus, a variety of NHC ligands were synthesized to screen reaction conditions. However, all the modified NHC ligands other than IPr·HCl [1,3-bis(2,6-diisopropylphenyl)imidazolium chloride] were less effective (Table S1).[12] Therefore, we then screened various Pd–IPr precatalysts for the amination reaction. The results are summarized in Table 1. SingaCycle-A3[13] in combination with $KN(SiMe_3)_2$ (KHMDS), which worked previously in the amination with anilines,[11c] gave the corresponding amination product (i.e., **3aa**) in only 18% yield (Table 1, entry 1). In the presence of SingaCycle-A1,[14] the yield of the desired product increased to 29% (Table 1, entry 2). Other palladium precatalysts such as [IPrPdCl(π-allyl)][15] and Pd–PEPPSI-IPr (PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation)[16] were less effective (Table 1, entries 3 and 4). The choice of the base, KHMDS, is critical for the reaction, as other organic and inorganic bases, including Grignard reagents, KO*t*Bu, and K_2CO_3, gave only trace amounts of **3aa** or were totally ineffective. Importantly, nonpolar solvents worked much better than polar solvents (Table 1, entries 5–7). The reaction gave **3aa** in 98% yield in toluene

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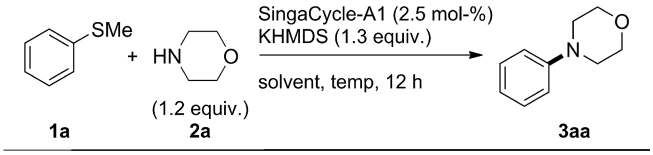
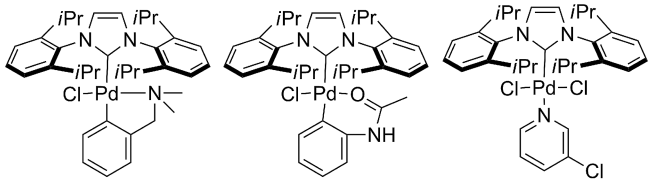
(Table 1, entry 7). Furthermore, we were delighted to find that the reaction could take place even at 60 °C to give **3aa** in 99% isolated yield (Table 1, entry 8). SingaCycle-A3 was not as efficient as SingaCycle-A1 when the reactions were run in toluene (Table 1, entry 9).

Table 1. Optimization of conditions.[a]



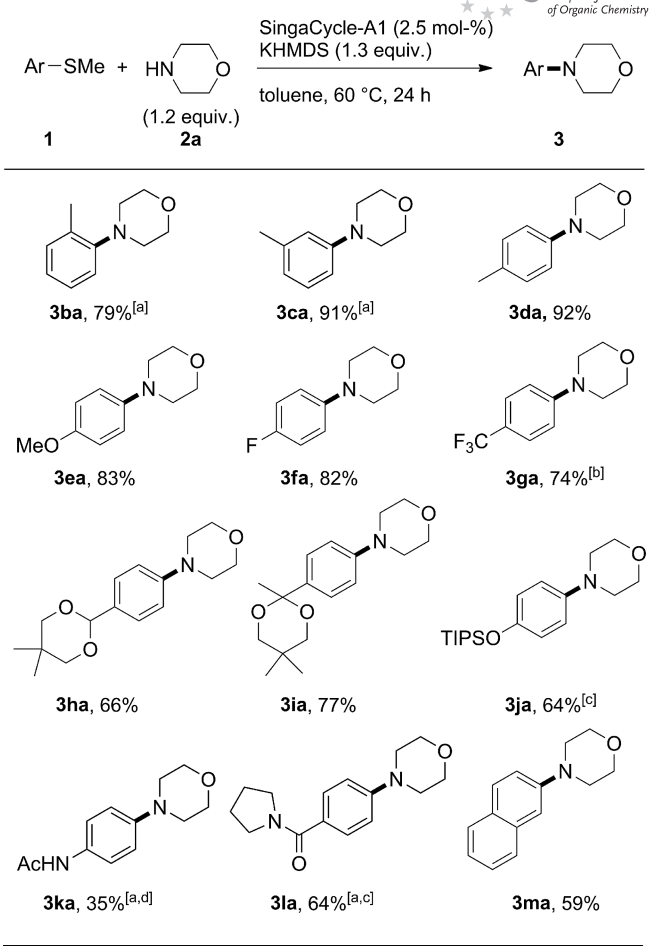
1a 2a 3aa

Entry	Catalyst	Temp. [°C]	Solvent	Yield [%][b]
1	SingaCycle-A3	100	dioxane	18
2	SingaCycle-A1	100	dioxane	29
3	[IPrPdCl(π-allyl)]	100	dioxane	17
4	Pd-PEPPSI-IPr	100	dioxane	13
5	SingaCycle-A1	100	thf	52
6	SingaCycle-A1	100	hexane	73
7	SingaCycle-A1	100	toluene	98[c]
8	SingaCycle-A1	60	toluene	99[c]
9	SingaCycle-A3	60	toluene	77



SingaCycle-A1 SingaCycle-A3 Pd-PEPPSI-IPr

[a] The reaction was carried out on a 0.5 mmol scale. [b] Determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.

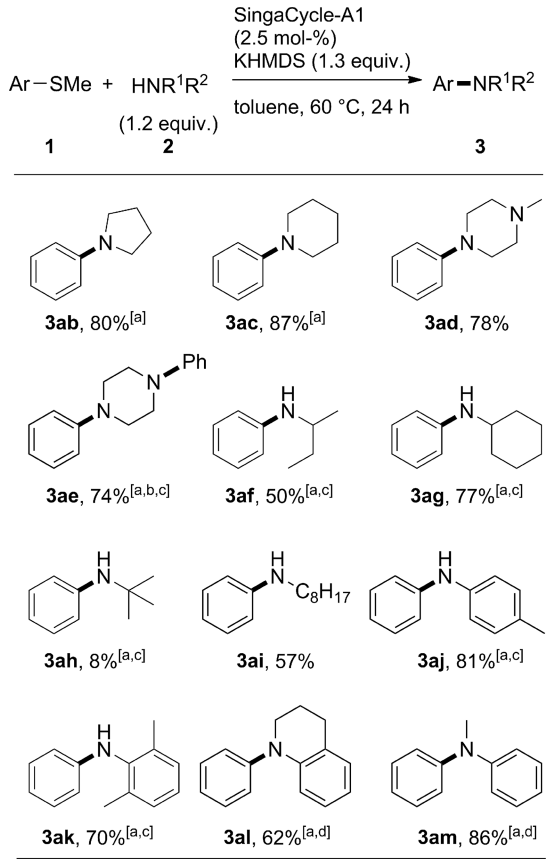


Scheme 2. Palladium-catalyzed amination of aryl sulfides with morpholine. The reaction was carried out on a 0.5 mmol scale. [a] The reaction was carried out at 80 °C. [b] *p*-$CF_3C_6H_4SC_{12}H_{25}$ was used. [c] 5 mol-% SingaCycle-A1 was used; TIPS = triisopropylsilyl. [d] 10 mol-% SingaCycle-A1 and 2.3 equiv. of KHMDS were used.

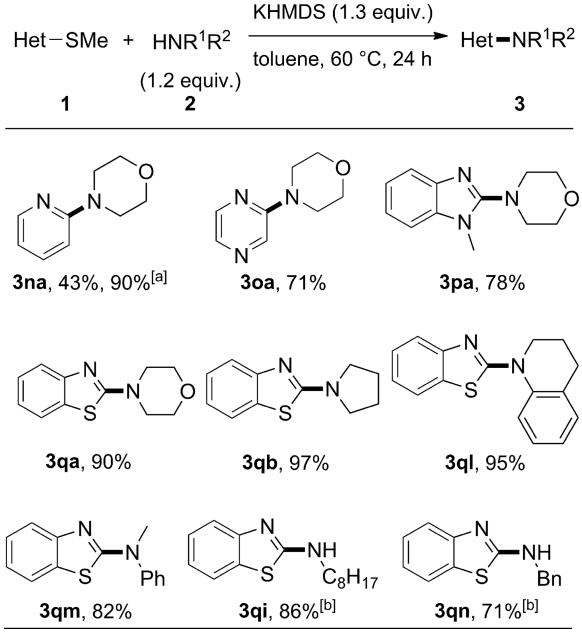
Having established optimized reaction conditions, we examined the amination of various aryl sulfides with morpholine (Scheme 2). Sterically hindered *ortho*-methylphenyl sulfide (**1b**) gave the desired product (i.e., **3ba**) in 79% yield at 80 °C. Neither electron-donating nor electron-withdrawing groups at the *para* position of aryl sulfides had a significant effect on the efficiency of the reaction (**3da**–**3la**). *para*-Trifluoromethylphenyl sulfide was aminated with morpholine to give **3ga** − an attempted amination of this compound with aniline failed in our previous work.[11c] The reaction showed a reasonable compatibility with functional groups, including a protected aldehyde (**3ha**) and ketone (**3ia**), a TIPS-protected phenol (**3ja**), an acetanilide (**3ka**), and an amide (**3la**).

We went on to explore the amination reactions of an aryl sulfide with various amines (Scheme 3). Cyclic amines including piperidine, pyrrolidine, and 1-methylpiperazine reacted smoothly with thioanisole to give the corresponding amination products (i.e., **3ab**–**3ad**) in good yields. The reaction of piperazine gave diarylation product **3ae** in good yield with 2.2 equiv. of thioanisole. *sec*-Butylamine and cyclohexylamine also reacted in the presence of 5 mol-% SingaCycle-A1 at 80 °C to give secondary amines **3af** and **3ag** without any formation of the diphenylated tertiary amines. Bulky *tert*-butylamine gave product **3ah** in a poor yield. The reaction of the sterically less demanding octylamine gave the desired product (i.e., **3ai**) in 57% yield, along with a diarylation product in 11% yield. These conditions could also be used for amination with aromatic *p*-toluidine to give **3aj** in 81% yield at 80 °C, which is comparable to the result obtained under the previous conditions.[11c] Moreover, sterically hindered 2,6-dimethylaniline, 1,2,3,4-tetrahydroquinoline, and *N*-methylaniline underwent the amination reaction to give the corresponding products (i.e., **3ak**, **3al** and **3am**, respectively) in good yields.

The amination of heteroaryl sulfides was also examined (Scheme 4). We were delighted to find that the reaction proceeded in the absence of SingaCycle-A1. The catalyst-free amination of 2-pyridyl sulfide gave product **3na** in 43% yield, and the yield increased to 90% in the presence of SingaCycle-A1. Other heteroaryl sulfides such as 2-pyrazyl sulfide, 2-(1-methylbenzimidazolyl), and 2-benzothiazolyl sulfide were smoothly aminated with morpholine to give the corresponding products (i.e., **3oa**, **3pa**, and **3qa**, respectively). Primary and secondary amines both reacted with 2-benzothiazolyl sulfide to give the amination products (i.e.,



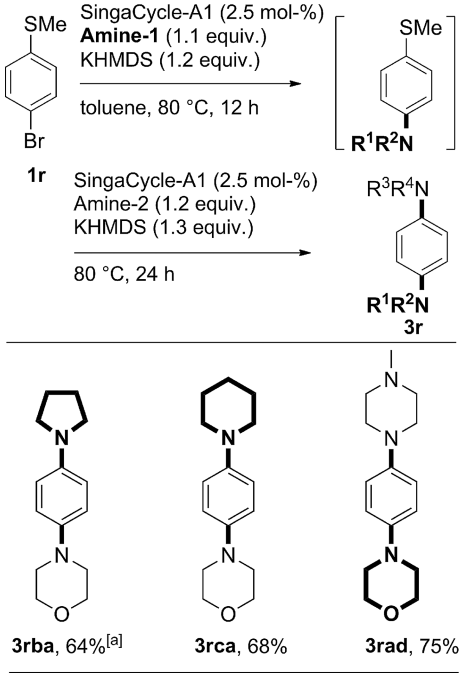
Scheme 3. Palladium-catalyzed amination of aryl sulfides with various amines. The reaction was carried out on a 0.5 mmol scale. [a] The reaction was carried out at 80 °C. [b] 2.2 equiv. of **1a** was used. Piperazine is the limiting substrate. [c] 5 mol-% SingaCycle-A1 was used. [d] 10 mol-% SingaCycle-A1 was used.



Scheme 4. Catalyst-free amination of heteroaryl sulfides with various amines. The reaction was carried out on a 0.5 mmol scale. [a] In the presence of SingaCycle-A1 (2.5 mol-%). [b] 2.2 equiv. of amine and 2.3 equiv. of KHMDS were used.

3qb–**3qm**) in good to excellent yields. The reaction proceeds by nucleophilic aromatic substitution of heteroaryl sulfides with deprotonated amines in the presence of KHMDS. Similar displacement of heteroaryl sulfones and sulfoxides with amines is known.[17,18] However, reports of the direct displacement of heteroaryl sulfides with amines are rare, and only limited examples are known.[19] The KHMDS-mediated amination of heteroaryl sulfides provides a more general protocol for the functionalization of heteroaryl sulfides.

We found that the amination reactions of *p*-bromothioanisole proceeded preferentially at the C–Br bond, while the C–S bond remained untouched (Scheme 5). The exclusive conversion of the C–Br bond allowed us to install two different amino groups onto the aromatic ring in one pot. The second amination was highly selective, and gave diaminobenzenes **3rba**, **3rca**, and **3rad** in high yields.



Scheme 5. The amination of heteroaryl sulfides with various amines. The reaction was carried out on a 0.5 mmol scale. [a] 5 mol-% SingaCycle-A1 was used in the second amination.

Conclusions

We have developed a method for the palladium-catalyzed amination of aryl sulfides with aliphatic amines. The reaction proceeded under milder conditions than the previously reported amination with aromatic amines. The amination of heteroaryl sulfides could proceed in the absence of a palladium catalyst. The different reactivities of a C–S bond and a C–Br bond allowed us to install different amino groups onto an aromatic ring in one pot, which could be a useful protocol for organic synthesis.

Experimental Section

General Remarks: All reactions dealing with air- or moisture-sensitive compounds were carried out using standard Schlenk techniques in oven-dried reaction vessels under a nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 silica-gel plates. Flash chromatography was carried out on silica gel (Wako gel C-200). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded with a JEOL ECA-600 NMR spectrometer. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane. Tetramethylsilane was used as an internal standard in ^{1}H spectra (δ = 0 ppm), and residual $CHCl_3$ was used in in ^{13}C spectra (δ = 77.0 ppm). High-resolution APCI-TOF mass spectra were obtained with a Bruker micrOTOF instrument.

Materials: SingaCycle-A1, -A2, and -A3 were purchased from TCI Japan. Pd–PEPPSI-IPr was purchased from Aldrich. KHMDS was purchased from TCI. Unless otherwise noted, commercially supplied reagents were purchased from Aldrich, TCI, and Wako Pure Chemical Industries, Ltd., and were used as received.

General Procedure for the Palladium-Catalyzed Amination of Aryl Sulfides with Aliphatic Amines: SingaCycle-A1 (8.3 mg, 0.0125 mmol), thioanisole (**1a**; 62.1 mg, 0.50 mmol), and morpholine (**2a**; 52.3 mg, 0.60 mmol) were put into a Schlenk tube. A toluene solution of $KN(SiMe_3)_2$ (0.5 M; 1.3 mL, 0.65 mmol) was then added to the mixture. The resulting mixture was stirred at 60 °C for 12 h. The reaction was quenched by the addition of saturated NH_4Cl solution (1.0 mL), and then the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc, 10:1–5:1) to give compound **3aa** (82.2 mg, 0.50 mmol, 99%) as an orange solid.

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