Palladium-Catalyzed Amination of Aryl Sulfoxides

G.Vanaja[1], V.S.Sangeetha[2], M.Deepa[3], C.Uma[4]

Assistant professor

[1] Department of chemistry,Dhanalakshmi Srinivasan College of arts and science for women, Perambalur, Tamil Nadu

ABSTRACT: Amination of diaryl sulfoxides with anilines and alkylamines has been accomplished under palladium/*N*-heterocyclic carbene (NHC) catalysis. Owing to its electron deficiency, the leaving arenesulfenate anion would be smoothly released from the palladium center to result in uneventful catalyst turnover under milder reaction conditions in comparison with previous C−S bond amination reactions. This amination accommodated a wider range of functional groups such as silyl, boryl, methylsulfanyl, and halogen moieties. Regioselective amination of unsymmetrical diaryl sulfoxides was also executed by means of steric bias.

Transition-metal-catalyzed amination of electrophilic aryl halides or triflates with amines, called Buchwald−Hartwig amination, has attained the central position for the preparation of aromatic amines.[1] Although aryl iodides or bromides have been widely utilized as substrates, the amination of less reactive aryl chlorides,[2] tosylates,[3] and mesylates[4] has been well established.[1c−h] Furthermore, significant efforts have been devoted to execute amination of more inert C−O[5−9] and C−C[10,11] bonds.

Recently, we became interested in the catalytic trans- formations of C−S bonds of aryl sulfides.[12,13] Due to their abundance and versatility, organosulfur compounds are expected to be prospective surrogates for aryl halides in transition-metal-catalyzed coupling reactions.[12,14] As a part of our research, we achieved palladium-catalyzed amination of aryl sulfides with anilines and alkylamines.[15] However, because strongly basic $KN(SiMe_3)_2$ is essential as a base, the amination suffered from poor functional group tolerance.

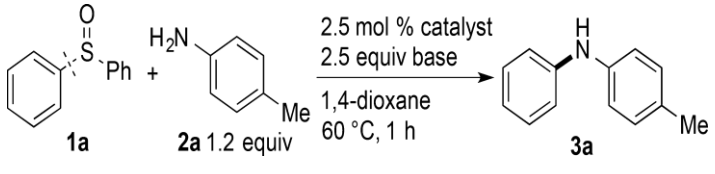
During the catalytic cycle of the amination, a thiolate anion derived from an aryl sulfide would tightly coordinate to the palladium center. We assume that $KN(SiMe_3)_2$ is indispensable to generate a highly reactive potassium amide from an amine for smooth transmetalation with an arylpalladium thiolate. We thus envisioned that a more electron-deficient and less catalyst- poisonous leaving sulfur anion would readily depart from the palladium center resulting in smooth catalyst turnover with milder bases. Based on these considerations, we have focused on amination of aryl sulfoxides. However, the transformation seemed to be challenging because a leaving sulfenate anion is valence-isoelectronic with a peroxide anion that potentially oxidizes metal catalysts as well as amines. Nevertheless, inspired by our recent achievement in catalytic transformation of aryl sulfoxides,[16] we tackled the development of amination of aryl sulfoxides.

Herein we report that amination of diaryl sulfoxides with anilines or alkylamines proceeds by means of a palladium/*N*-

wider variety of functional groups such as silyl, boryl, methylsulfanyl, and even halogen moieties.

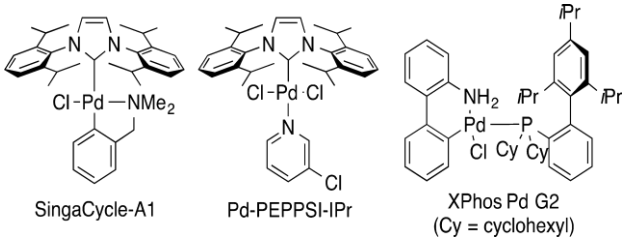
Our investigation began with the amination of diphenyl sulfoxide (1a) with *p*-toluidine (2a) under the optimal conditions for our amination of aryl sulfides[15b] with a SingaCycle-A1[17] precatalyst and $KN(SiMe_3)_2$ as a base. However, desired aminated product 3aa was obtained only in 7% yield accompanied by a 93% recovery of 1a (Table 1, entry

Table 1. Condition Screening



entry	catalyst	base	NMR yield (%)
1	SingaCycle-A1	$KN(SiMe_3)_2$	7
2	SingaCycle-A1	KOH	17
3	SingaCycle-A1	K_2CO_3	0
4	SingaCycle-A1	K_3PO_4	0
5	SingaCycle-A1	KO*t*Bu	91
6	SingaCycle-A1	NaO*t*Bu	>99
7	SingaCycle-A1	LiO*t*Bu	8
8[a]	SingaCycle-A1	NaO*t*Bu	>99 (97)[b] (87)[b,c]
9	Pd-PEPPSI-IPr	KO*t*Bu	11
10	$Pd(PPh_3)_4$	KO*t*Bu	0
11	XPhos Pd G2	KO*t*Bu	47
12	none	KO*t*Bu	0

[a]THF instead of 1,4-dioxane. [b]Isolated yield. [c]10 mmol of 1a.

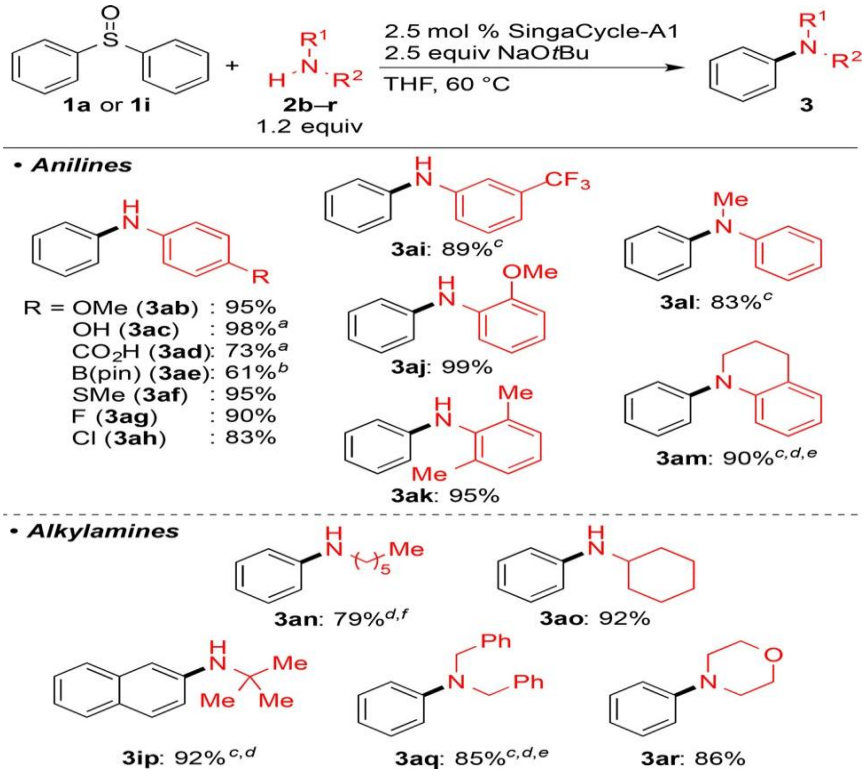


heterocyclic carbene (NHC) catalyst and NaO*t*Bu as a base.

1). We then screened a series of potassium bases. KOH as well as milder bases such as K_2CO_3 and K_3PO_4 were ineffective for the amination (entries 2−4). Fortunately, the yield of 3aa was greatly increased to 91% by means of KO*t*Bu (entry 5). When NaO*t*Bu was used instead of KO*t*Bu, 3aa was obtained quantitatively (entry 6). Since the aminated product is more acidic than 2a and should consume the base additionally, employment of 2.5 equiv of bases was required for smooth amination. The choice of countercation of the base is crucial, and the yield of 3aa was dramatically diminished with LiO*t*Bu (entry 7). Eventually, after solvent screening, 3aa was isolated in 97% yield in THF (entry 8). This amination was applicable to a gram-scale reaction; an 87% yield of 3aa was obtained from 10 mmol of 1a. Difficulty in removing some impurity by silica gel column chromatography led to the slight decrease in the yield of 3aa. We also tested other palladium precatalysts in the presence of KO*t*Bu. The reaction with Pd-PEPPSI-IPr[18] in place of SingaCycle-A1 gave a poor result although they have the same NHC ligand (entry 9). $Pd(PPh_3)_4$ was completely ineffective, and no product was obtained (entry 10). A moderate yield of 3aa was obtained when an XPhos-ligated palladium complex was used as a catalyst (entry 11). Naturally, no product was obtained without a palladium catalyst; thus, the possibility of S_NAr-type substitution was denied (entry 12).

With the optimized conditions (Table 1, entry 8) in hand, we then investigated the scope of anilines (Scheme 1). *p*-Anisidine smoothly underwent the amination to afford 3ab in 95% yield. By means of 4 equiv of KO*t*Bu, the amination with anilines bearing an unprotected hydroxy or carboxy moiety afforded the target diarylamines 3ac and 3ad. Although the reaction conditions are significantly basic, the pinacolatoboryl moiety

Scheme 1. Scope of Anilines and Alkylamines



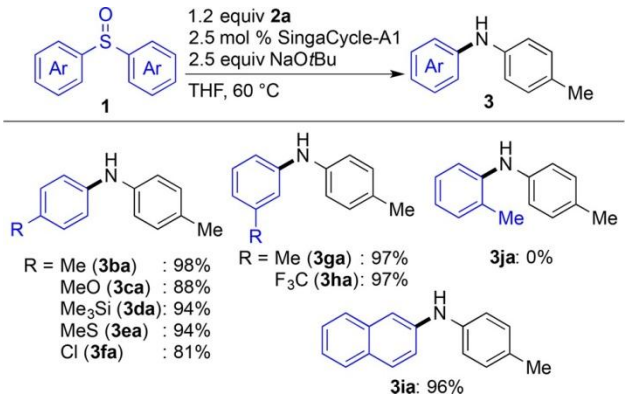
[a]4 equiv of NaO*t*Bu. [b]95% NMR yield. [c]At 80 °C. [d]KO*t*Bu instead of NaO*t*Bu. [e]2.4 equiv of 2. [f]3 equiv of 2. At 40 °C.

on 3ae stayed intact during the amination. Notably, the reaction did not deteriorate a methylsulfanyl or chloro moiety that is potentially reactive under palladium−NHC catalysis. Electron-deficient 3-trifluoromethylaniline (2i) uneventfully underwent the amination. Other electron-deficient anilines having a cyano or sulfonyl moiety at their *ortho*- or *para*- positions were not involved in the amination resulting in recovery of substrates (not shown). Methoxycarbonyl function- ality was degraded via amidation with anilines (not shown).

Steric congestion around the amino group did not hamper the amination, and the desired products 3aj and 3ak were successfully obtained from *o*-anisidine (2j) and 2,6-xylidine (2k), respectively. The reactions with *N*-alkylanilines 2l and 2m gave tertiary amines 3al and 3am, respectively, in high yields. Besides anilines, alkylamines could also be subjected to this reaction. The reaction of 1a with hexylamine (2n) was carried out with 3 equiv of 2n at 40 °C in order to suppress diphenylation, affording *N*-hexylaniline (3an) in 79% yield along with a diphenylated byproduct in 13% NMR yield. Cyclohexylamine (2o) and *tert*-butylamine (2p) successfully participated in the amination without formation of the corresponding diarylated byproducts probably due to the bulkiness of their alkyl moieties. The amination with secondary alkylamines easily proceeded to yield the corresponding tertiary amines 3aq and 3ar.

We then conducted the amination of a series of diaryl sulfoxides 1b–j (Scheme 2). Diaryl sulfoxides bearing an

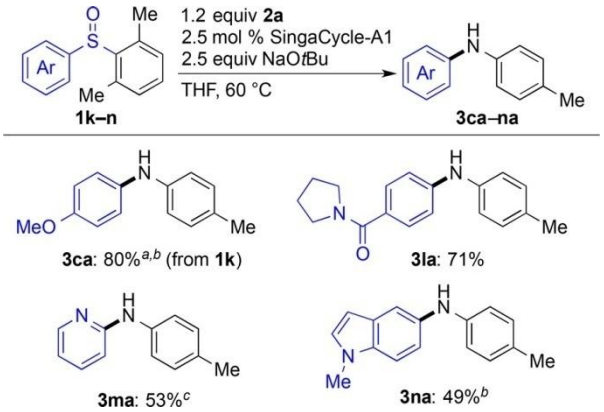
Scheme 2. Scope of Diaryl Sulfoxides



electron-donating or -withdrawing group reacted smoothly to provide the corresponding diarylamines in high yields. The trimethylsilyl moiety on 3da remained intact under the reaction conditions. Again, a methylsulfanyl or chloro moiety on 1e or 1f was compatible with the amination. The electron deficiency of the sulfoxide unit would promote the selective cleavage of the C−S(O) bond over that of the C−S or C−Cl bond. As a π-extended diaryl sulfoxide, dinaphthyl sulfoxide 1i also underwent the reaction to furnish 3ia in excellent yield. Unfortunately, attempted amination of *ortho*-substituted diaryl sulfoxide 1j failed to give the product 3ja and 89% of 1j was recovered.

Considering the failure in utilizing *ortho*-substituted diaryl sulfoxide 1j, we anticipated that regioselective amination of unsymmetrical diaryl sulfoxide would be feasible by means of steric bias (Scheme 3). Indeed, the amination of sterically biased 2,6-dimethylphenyl 4-methoxyphenyl sulfoxide (1k) with 2a proceeded at the less hindered C−S(O) bond exclusively to afford 3ca in 80% yield. In analogous fashion,

Scheme 3. Regioselective Amination of Unsymmetrical Diaryl Sulfoxides

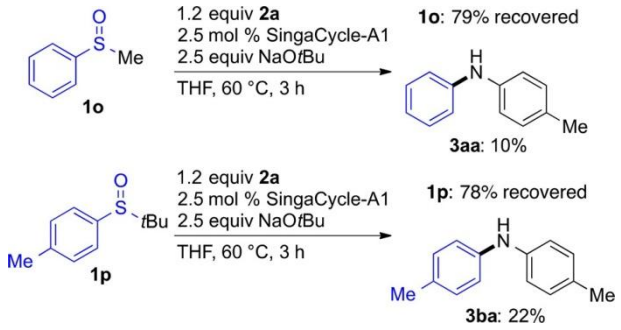


[a]KO*t*Bu instead of NaO*t*Bu. [b]80 °C. [c]10 mol % of catalyst.

amide-substituted 1l and heteroaryl sulfoxides 1m and 1n furnished the desired diarylamines 3la−na.

Although we applied this amination to more accessible alkyl aryl sulfoxides such as methyl phenyl sulfoxide (1o) and *tert*- butyl *p*-tolyl sulfoxide (1p), the reactions proceeded sluggishly and the sulfoxides were recovered (Scheme 4). The more

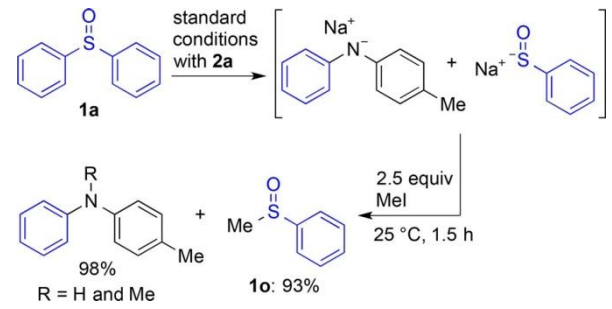
Scheme 4. Amination of Alkyl Aryl Sulfoxides



electron-donating alkylsulfinyl groups would slow down the oxidative addition and transmetalation steps. In addition, alkanesulfenate anions generated through the amination would be labile and catalyst-poisonous to interfere with the catalyst turnover.[16a,c,19]

The amination would proceed via a pathway similar to general Buchwald−Hartwig amination: oxidative addition of 1 to low-valent palladium, formation of the arylpalladium amide species through substitution of the arenesulfenate anion on the palladium center, and C−N bond forming reductive elimination. To confirm the generation of the arenesulfenate anion, we conducted an electrophilic trapping experiment (Scheme 5). After the amination of 1a with 2a under the standard reaction conditions (Table 1, entry 12), the reaction mixture was treated with 2.5 equiv of iodomethane. As a consequence, desired methyl phenyl sulfoxide 1o was obtained in 93% yield accompanied by a mixture of 3aa and its methylated product in 98% total yield. This result clearly indicates that the arenesulfenate anions are surely generated and remain intact in the reaction system without any inhibition of the amination as opposed to the behavior of alkanesulfenate anions.[19]

Scheme 5. Electrophilic Trapping of Arenesulfenate Anion



In summary, we have developed palladium-catalyzed amination of aryl sulfoxides with anilines and alkylamines. Owing to its electron deficiency, the leaving arenesulfenate anion would be readily released from the palladium center, which results in smooth catalyst turnover under milder reaction conditions in comparison with our previous C−S bond amination. According to its mild reaction conditions, the present amination was compatible with important yet potentially reactive functional groups such as silyl, boryl, methylsulfanyl, and halogen moieties. Regioselective amination of unsymmetrical diaryl sulfoxides was also accomplished by means of steric bias. Further investigation of metal-catalyzed transformations of aryl sulfoxides is ongoing in our laboratory.

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