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COMMUNICATION

Directed nucleophilic aromatic substitution reaction

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In this study, we discovered a directed nucleophilic aromatic substitution reaction, "directed SNAr (dSNAr)", in the reaction of ortho-iodobezamides and amine in the presence of pyridine. The reaction proceeded ortho-specifically and did not require a strong electron-withdrawing group on the arene substrate. Most reactions proceeded at room temperature in the presence of Py, and a wide range of amine nucleophiles can be applied. Furthermore, the reactions with benzamide substituted with multiple halogens were found to be 100% ortho-selective.

Aromatic amines are one of the most important molecules, which can be seen in pharmaceuticals, agrochemicals, and bioactive molecules [1]. There are many methodologies to construct aryl mines (Figure 1A). One of the most frequent reactions to synthesize aromatic ammines is a transition-metal catalyzed or mediated cross-coupling reaction (such as Ullmann,[2] Buchwald−Hartwig,[3] and Chan−Lam[4] cross-couplings). However, the problem of metal residues in the products[5] has led to a demand for transition metal-free amination. In this context, the S_NAr reaction, which is one of the most classical organic reaction[6], is again attracting attention as a transition metal-free amination method. However, there are several problems with the S_NAr reaction that need to be solved. For example, via the Meisenheimer complex[7,8], a strong electron-withdrawing group (EWG) (NO_2 (ρ=0.78), CN (ρ=0.66)) to stabilize the anionic intermediate[9] is required on the aromatic ring. Reactions via benzyne require either a very strong base or a fairly low reaction temperature, and there are also regioselectivity problems[10]. For S_NAr reactions via pi-metal complexes, strong EWG is not required, but stoichiometric transition metal salts are needed to form electron-deficient haloarenes in most cases [11]. On the other hand, there are some reports on S_NAr under mild conditions. Wu, Kuniyil and Mandal's group developed photocatalyst or super electron donor for C-N couplings via anion radical species[12]. Previous S_NAr reactions via anion radicals required high reaction temperatures [13]. However, efficient reactions can be achieved with the use of an efficient electron donor catalyst. Li and Nicewicz were able to successfully generate cation radical species in the presence of an organocatalyst or mediator [14]. In this reaction, electron-deficient (pseudo)haloarenes generated in situ can smoothly react with various nucleophiles. Concerted nucleophilic aromatic substitution (cS_NAr)[15] is a reaction that partially eliminates the need for a strong EWG, which is a drawback of the classical S_NAr reaction. Chiba and Sanford's group accomplished aromatic C-O bond activation via cS_NAr [16,17]. A recent highlight in this area is the unprecedented reaction to the upgraded EWG concept. Bird and Knowles's group discovered oxyl radical is very strong EWG for the electronic activation of inert fluorinated arenes [18]. The reaction of p-F-Ar-OH reacted with carboxylates to produce p-(RCO_2)-Ar-OH under the mild conditions. In this reaction, formal homolysis of the aryl O-H bond generates oxyl radical and oxyl radical make

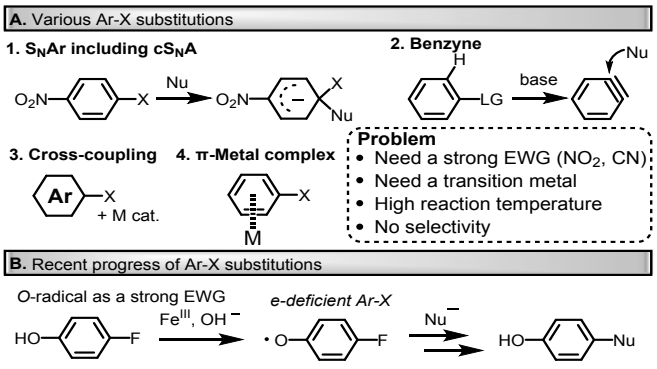

Fig. 1 Various type of S_NAr reactions.

the arene ring electron-deficient. Extended Hammett substituent constants (σ_p^-) of oxyl radical is much higher than cyano or nitro group (CN(σ_p^-)=1.00, NO_2(σp^-)=1.27, oxyl radical(σp^-)=2.79). Consequently, SNAr reaction of F-Ar-OH with carboxylate

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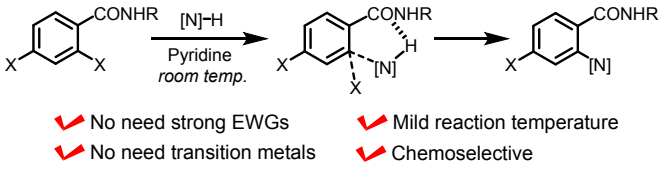
†Electronic Supplementary Information (ESI) available: Details of experimental procedures, full characterization data, and copies of NMR spectra. See DOI: 10.1039/x0xx00000x

accelerate.

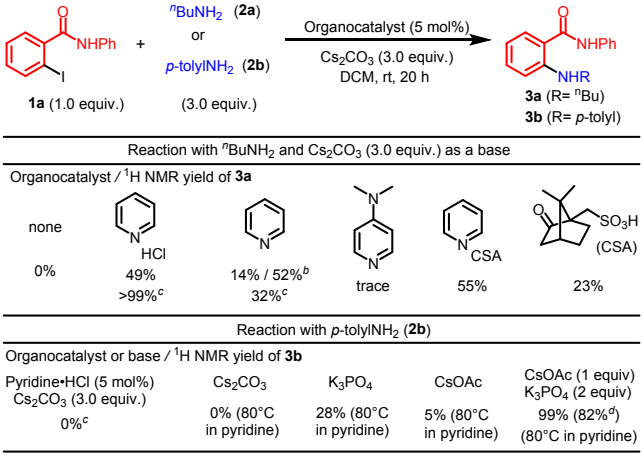
However, we still need an efficient S_NAr methodology under mild reaction conditions which avoids low chemoselectivity, high reaction temperature, transition-metal catalysts or harsh reagents. Herein, we describe an unprecedented chemoselective S_NAr reaction under mild conditions that does not require strong EWGs (NO_2 (ρ=0.78) vs CONHPh (ρ=0.41)) [9] on the arene substrate. In this study, we found that multi-halogenated benzamides can efficiently react with amines in the presence of pyridine (Scheme 1). We call our reaction system as "Directed S_NAr (dS_NAr)".



Scheme 1. This work-Directed SNAr (dS_NAr).

Generally, the S_NAr reaction does not occur under mild conditions without a strong electron-withdrawing group, such as a nitro group, on haloarenes. Therefore, the reaction of ortho-iodo-N-phenylbenzamide (**1a**) with n-butylamine (**2a**) was carried out at various temperatures. However, no products were obtained at all and the starting materials were recovered. During the course of this investigation, we found that the addition of an additional amine hydrochloride salt yielded the product **3a** at room temperature. Therefore, various amine hydrochlorides

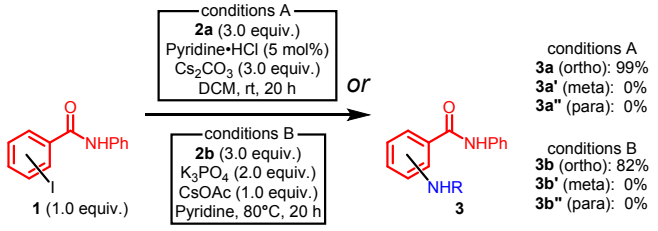
Table 1. Optimization[a]



[a]All reactions were conducted with **1** (1.0 equiv.), **2** (3.0 equiv.), organocatalyst (5 mol%), and Cs_2CO_3 (3.0 equiv.) in DCM (dichloromethane) (0.5 M) for 20 h at room temperature. ^1H NMR yields are shown. [b] The reaction was conducted in pyridine without a catalyst. [c] 5 equiv. of **2** was used. [d] Isolated yield.

were examined (Table 1). Although pyridine hydrochloride gave 49%, simple pyridine and pyridine derivatives, such as DMAP and 4-cyanopyridine, gave no effect. Interestingly, the yield of **3a** increased significantly to 52% when pyridine was used as the solvent. Py·CSA salt was also effective. When CSA was used, **3a** was 23%. We also tested other acids, but not effective. Various pyridine or aliphatic amine salts were subsequently examined, but pyridine was the best (See SI). Finally, using 5 equiv. of **2a** gave the highest yield of **3a** (99%) when Py·HCl was used. The use of **2a** at 5 equivalents tended to increase yields in all cases. The reaction was found to be chemoselective.

On the other hand, when the use of aniline derivative **2b** gave no product **3b** under the optimized conditions. The difference in nucleophilicity between **2a** and **2b** may have affected this S_NAr reaction. To overcome this limitation, we screened various bases. The results show that the inorganic base system in pyridine as a solvent increases the chemical yield of **3b**. The highest yield of **3b** was obtained in the presence of CsOAc:K_3PO_4 (1:2). Pyridine plays an important role in this reaction. Under the optimized conditions, the reaction of *meta*- and *para*-2-iodo-*N*-phenylbenzamide (**1**) with **2a** or **2b** did not proceed at all (Scheme 2).

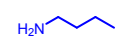
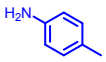
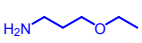
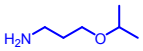
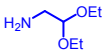
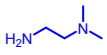
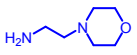
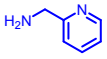
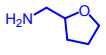
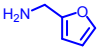
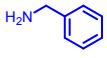
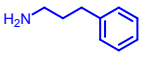
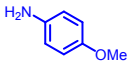
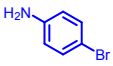


Scheme 2. The reaction with *o*-, *m*-, and *p*-iodobenzamides **1**.

Reactions of various amines with **1a** were attempted using optimized conditions A and B. Condition A was effective mainly for alkylamines, while condition B was effective for aniline derivatives (**2b**, **2q**, **2r**) and less reactive alkylamines (**2k**, **2n**, **2o**, **2p**, **2s**). For example, primary alkylamines (**2c-f**, **2h-j**, **2m**) showed good reactivity and gave products **3** in high yields. The **2g** diamine showed better reactivity in diluted solvent system. 2-Furyl-substituted alkylamine **2k** is primary alkylamines and their structure is similar to **2j**, but its reactivity was quite different. Under the condition A, the **3k** yield was 22%, whereas under condition B, the yield was 94%. The reasons for these are unclear. On the other hand, secondary alkyl substituted amines and secondary amines (**2o**, **2p**) and hindered amine (**2n**) showed good yields under condition B. Aniline derivatives (**2q**, **2r**) gave products **3** under condition B, but in moderate yields. The reaction is sensitive to the steric hindrance of amine nucleophiles. For example, pyrrolidine reacts, but not dibutylamine.A noteworthy aspect of this reaction is that it proceeded directly with ammonia. For example, **1a** reacted with an ammonia/MeOH solution under the condition B to give **3t** in 70% yield.

Various iodoarenes were then examined (Table 3). For example, **1g-1i** with a sterically large substituent reacted smoothly at room temperature, giving the corresponding products (**4g-4i**) in high yields. In cases of **1l, 1n, 1o**, and **1p**, the reactions were effective in diluted DCM solvent. In these systems, the solubility of the substrate may have affected the reaction. Reactions requiring condition B were electronically and sterically less reactive

Table 2. The reaction with *o*-, *m*-, and *p*-iodobenzamides **1**.

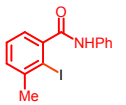
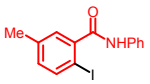
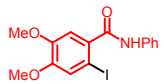
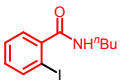
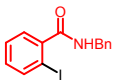
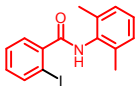
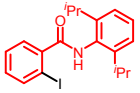
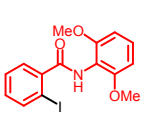
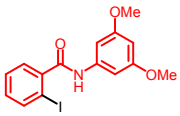
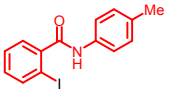
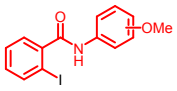
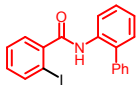
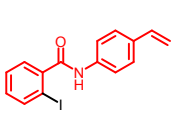
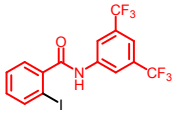
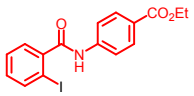
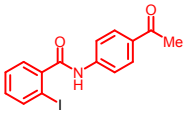
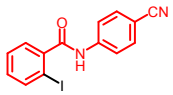
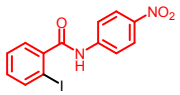
Amine **2** / Isolated yield of **3** (conditions)			
 **2a** / **3a**: 99%[b] (A) 97% (B)	 **2b** / **3b**: 0%[b] (A) 82% (B)	 **2c** / **3c**: 91% (A)	 **2d** / **3d**: 98% (A)
 **2e** / **3e**: 97% (A)	 **2f** / **3f**: 97% (A)	 **2g** / **3g**: 96%[b] (A)	 **2h** / **3h**: 90% (A)
 **2i** / **3i**: 99% (A)	 **2j** / **3j**: 99% (A)	 **2k** / **3k**: 22% (A) 94% (B)	 **2l** / **3l**: 52% (A)
 **2m** / **3m**: 76% (A)	 **2n** / **3n**: 22% (A) 88% (B)	 **2o** / **3o**: 1% (A) 68% (B)	 **2p** / **3p**: 18% (A) 85% (B)
 **2q** / **3q**: 47% (B)	 **2r** / **3r**: 68% (B)	 **2s** / **3s**: 2% (A) 75% (B)	7 N NH_3 in methanol **2t** / **3t**: 70% (B)

[a] Conditions A: Reactions were conducted with **1a** (1.0 equiv.), **2** (5.0 equiv.), PyHCl (5 mol%), and Cs_2CO_3 (3.0 equiv.) in DCM (dichloromethane) (0.5 M) for 20 h at room temperature. Conditions B: Reactions were conducted with **1a** (1.0 equiv.), **2** (5.0 equiv.), PyHCl (5 mol%), and Cs_2CO_3 (3.0 equiv.) in pyridine (1.0 M) for 20 h at 80ºC. Isolated yields were shown. [b] The reaction was conducted in 0.25 M DCM.

substrates. Sterically hindered **1b**, electron rich **1d**, *N*-alkyl substituted **1e** and **1f**, and cyanophenyl substituted **1t** showed low yields of products **4** under the condition A, but the reaction proceeded smoothly under the condition B. Nitrophenyl substituted **1u** reacted at room temperature but required Py solvent. In these cases, the low-yield conditions only resulted in a surplus of substrate, and no significant side reactions occurred. It is conceivable that the interaction of the amine with the nucleophile or catalyst and the formation of transition states leading to the product may impede the main reaction. However, the underlying reason for this phenomenon remains unclear.

The highlight of this reaction is the chemoselective reaction. The reaction of haloarenes **5** and **2a** with multiple halogen-substituted **5** was performed to test the chemoselectivity (Table 4). Substrates with C-X bonds on the N-aryl (**5a-5g**, **5l**) did not react due to electronic factors and smoothly gave the desired product **6** in high yield (**6a-6g, 6l**). **5a** gave moderate yields under condition A, but higher yields in pyridine solvent at room temperature. Interesting results were for substrates (**5h-5k,5m,5n**) with C-X bonds in the same aromatic ring as the reaction site. In all cases, the reactions proceeded ortho-selectively. In nucleophilic aromatic substitution reactions, the C-F bond is generally more reactive than the C-I bond due to the steric or electronic reason (much more polarized bond and much weaker pi-back-donation into the pi system). But, the order of reactivity in this reaction was: ArI>>ArF, which is the reverse of the order often found in classical S_NAr reactions.

Table 3. The reactivities of iodoarenes **1**.[a]

Iodoarenes **1** / Isolated yield of **4** (conditions)		
 **1b** / **4b**: 11% (A) 99% (B)	 **1c** / **4c**: 71% (A)	 **1d** / **4d**: 91% (B)
 **1e** / **4e**: 1% (A) 92% (B)	 **1f** / **4f**: 41% (A) 99% (B)	 **1g** / **4g**: 98% (A)
 **1h** / **4h**: 84% (A)		
 **1i** / **4i**: 99% (A)	 **1j** / **4j**: 99% (A)	 **1k** / **4k**: 96% (A)
 ortho, **1l** / **4l**: 84%[b] (A) meta, **1m** / **4m**: 86% (A) para, **1n** / **4n**: 99%[b] (A)	 **1o** / **4o**: 96%[b] (A)	
 **1p** / **4p**: 81%[b] (A)	 **1q** / **4q**: 68% (A)	 **1r** / **4r**: 95% (A)
 **1s** / **4s**: 76% (A)	 **1t** / **4t**: 22%[c] (A) 88% (B)	 **1u** / **4u**: 85%[c](A)

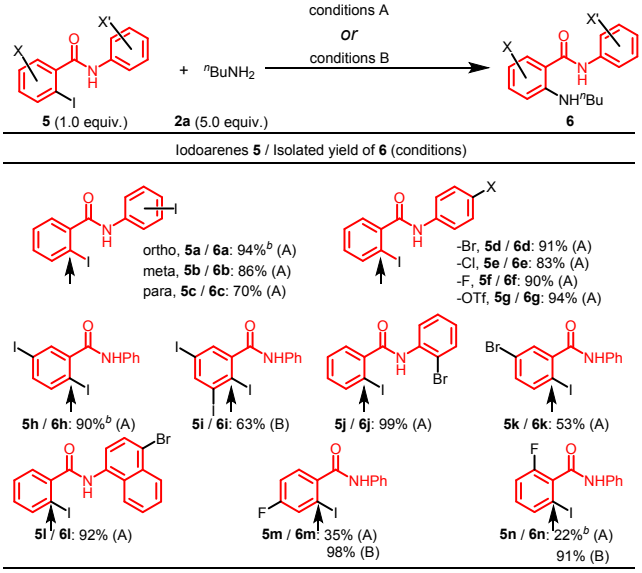
[a] Conditions A: Reactions were conducted with **1** (1.0 equiv.), **2a** (5.0 equiv.), PyHCl (5 mol%), and Cs_2CO_3 (3.0 equiv.) in DCM (dichloromethane) (0.5 M) for 20 h at room temperature. Conditions B: Reactions were conducted with **1** (1.0 equiv.), **2a** (5.0 equiv.), PyHCl (5 mol%), and Cs_2CO_3 (3.0 equiv.) in pyridine (1.0 M) for 20 h at 80ºC. Isolated yields were shown. [b] The reaction was conducted in 0.25 M DCM. [c] The reaction was conducted in pyridine (0.5 M) without catalyst.

One interesting application is the transition metal-free synthesis of Mebroqualone by this reaction (Scheme 3) [19]. In the case of the corresponding haloarene **5j**, it is difficult to proceed chemoselectively in transition-metal catalyzed amination due to steric and electronic effects. Using our dS_NAr reaction, **5j** and ammonia reacted smoothly to give the corresponding aniline derivative **7** in 94% yield. Compound **7** can then be cyclized to obtain the desired Mebroqualone.

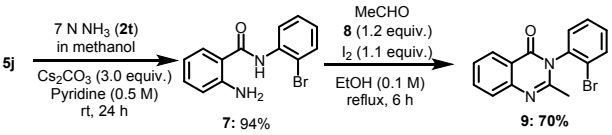
In this study, we have discovered an ortho-specific nucleophilic aromatic substitution reaction, "Directed S_NAr (dS_NAr)," in which Py is the activator. Our discovery of dS_NAr is unique in that it can use haloarenes substituted with a weak electron-withdrawing group, carboxamide, and the reaction proceeds chemoselectively. Since this reaction reacts with ammonia and aniline as well as alkylamines, a wide range of aniline derivatives can be synthesized. Furthermore, in the reaction with polyhalogenated arenes, the amination reaction proceeds only at the ortho-position, making it easy to synthesize halogenated aniline derivatives, which are difficult to synthesize by

Buchwald-Hartwig coupling. There are many unknowns about the reaction mechanism, but one thing is clear: Py plays an important role. Detailed analysis of the reaction mechanism will be performed by theoretical chemical experiments in due course.

Table 4. Chemoselective S_NAr reaction.[a]



[a] Conditions A: Reactions were conducted with **5** (1.0 equiv.), **2a** (5.0 equiv.), PyHCl (5 mol%), and Cs_2CO_3 (3.0 equiv.) in DCM (dichloromethane) (0.5 M) for 20 h at room temperature. Conditions B: Reactions were conducted with **5** (1.0 equiv.), **2a** (5.0 equiv.), PyHCl (5 mol%), and Cs_2CO_3 (3.0 equiv.) in pyridine (1.0 M) for 20 h at 80ºC. Isolated yields were shown. [b] The reaction was conducted in pyridine (0.5 M) without catalyst.



Scheme 3. Synthesis of Mebroqualone.

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Data availability

The data supporting this article have been included as part of the ESI.†

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Data availability statements

The data supporting this article have been included as part of the Supplementary Information.