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Insertion of Arynes into *N*-Halo Bonds: A Direct Approach to *o*-Haloaminoarenes

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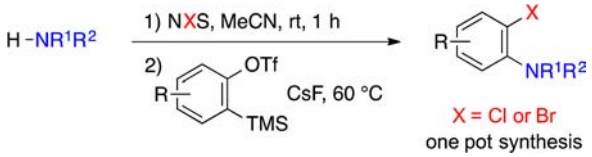
ABSTRACT



A new approach to access *o*-haloaminoarenes has been achieved by insertion of arynes into a nitrogen−halide bond (N−X). This transition-metal-free transformation displays a broad substrate scope of arynes, good compatibility with functional groups, and high regioselectivity. Representative transformations of the *o*-haloaminoarenes are described to highlight their utility for rapid access to diversely functionalized aminoarene derivatives.

o-Halo aminoarenes are an important class of compounds in drug discovery, agrochemicals, catalysis, and organic synthesis. The *o*-haloaminoarene functionality greatly influences pharmacological activities of bioactive molecules[1] such as Zanaflex, Abilify, and Levaquin. Furthermore, aryl halides (e.g., Cl, Br) are one of the most frequently used synthetic handles in cross-coupling reactions to construct a variety of functionalized arenes and heterocycles.[2] Therefore, efficient access to this class of molecules is highly valued and desired. The most commonly used methods are electrophilic *ortho*-halogenations of anilines,[3] which have been extended by recent development of transition-metal-catalyzed C−H functionalization[4] (Scheme 1). Yet, this approach has been limited by the requirement of an amino group present on arenes, the formation of undesired di-*ortho* halogenated byproducts, and the prolonged reaction times at elevated temperatures. It is desirable to develop more general methods for the selective formation of *o*-haloaminoarenes under mild conditions. Toward this end, here we report aryne insertion into a nitrogen−halide bond as a new approach to directly construct this important class of molecules under transition-metal-free conditions (Scheme 1).

A nitrogen−halide bond (N−X) possesses high reactivity and is known to readily undergo heterolytic or homolytic cleavage.[5] We envision that such a labile N−X bond could undergo an insertion reaction with highly reactive arynes to afford *o*-amino-functionalized arene derivatives

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(3) (a) Neale, R. S.; Schepers, R. G.; Walsh, M. R. *J. Org. Chem.* **1964**, *29*, 3390. (b) Gassman, P. G.; Campbell, G.; Frederick, R. *J. Am. Chem. Soc.* **1968**, *90*, 7377. (c) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 2567. (d) Nickson, T. E.; Rochedolson, C. A. *Synthesis* **1985**, 669. (e) Shen, H.; Vollhardt, K. P. C. *Synlett* **2012**, 208.

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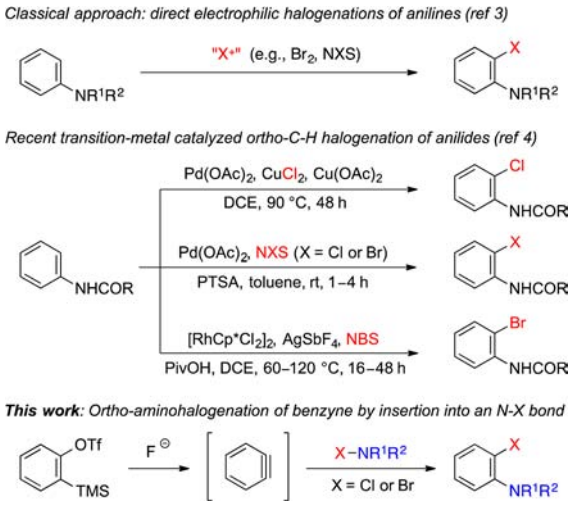
Scheme 1. Synthetic Strategies to Access *o*-Haloaminoarenes



in a single operation. Arynes are one of the oldest, most interesting, and useful reactive intermediates.[6] Aryne chemistry has proven extremely valuable for the synthesis of complex arene products, particularly evidenced by remarkable advances in the past decade.[7] Aryne insertions,[8] which allow for simultaneously functionalizing two carbon atoms of an arene, are of high synthetic significance and herald greater potentials of aryne intermediates. However, aryne insertion into N−X bonds remains unexplored, despite its promise in the synthesis of valuable aminoarene derivatives. Considering the instability of N−X bonds, we envision that mild reaction conditions would be critical to minimize decomposition of N−X bonds and to achieve compatibility with different functional groups. Therefore, our studies have focused on the in situ formation of arynes via 1,2-elimination of *o*-TMS-aryl triflates promoted by mildly basic fluoride (Scheme 1).[9] This paper describes our development of a one-pot protocol that begins with simple amines to directly prepare *o*-haloaminoarenes under transition-metal-free conditions. This transformation exhibits a good compatibility with functional groups and a broad substrate scope of arynes, including substituted arynes and heteroarynes. The observed regioselectivity for haloamination of arynes suggests the insertion may occur through a polar pathway directed by steric and electronic effects of both arynes and N−X bonds.

Our studies began with exploring the direct benzyne insertion with *N*-chloramines, which are moderately stable and readily isolated.[10] We focused on the formation of 4-(2-chlorophenyl)morpholine **3a** from *N*-chloromorpholine **1a′** and 2-(trimethylsilyl)phenyl triflate **2** to identify optimal conditions for the proposed insertion reaction (Table 1). In a solvent screen employing CsF as the fluoride anion source, MeCN proved to be the optimal solvent (entry 1), leading to desired product **3a** in 50% yield while THF, 1,4-dioxane, toluene, and DMF were less effective.[11] Increasing the temperature accelerated the reaction (entries 2 and 3). In the subsequent studies where 60 °C was chosen as optimal temperature, other fluoride sources such as KF and TBAF (entries 4 and 5) were found to be less efficient than CsF while the reaction performed in lower concentration gave better reproducibility with a comparable yield of **3a** (entry 6 vs 3). Additional surveys of the reaction stoichiometry (entries 7−9) revealed that the instance with **1a′** as the limiting reagent, 1.5 equiv of benzyne precursor **2**, and 3.0 equiv of CsF afforded the highest yield of **3a** (entry 8). Based on these results, we next looked into a one-pot protocol starting from amine **1a,** as elimination of the *N*-chloramine isolation step would be attractive.[12] We first treated amine **1a** with *N*-chlorosuccinimide (NCS) to form *N*-chloromorpholine **1a′**, which was subsequently subjected to the insertion reaction with **2** (entry 10). Encouragingly, this one-pot protocol provided the desired product **3a** in 63% yield upon the complete consumption of *N*-chloromorpholine.[13]

With the developed one-pot insertion protocol, we examined the scope of this aryne insertion transformation (Table 2). First, the reactions of benzyne with different amines all delivered the *ortho*-chloroaminated arene products successfully (entries 2−6). A variety of functional groups were tolerated under the reaction conditions,

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(6) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502.

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(9) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

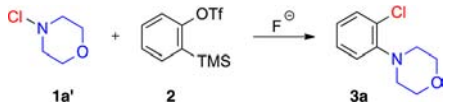
(10) Zhong, Y. L.; Zhou, H.; Gauthier, D. R.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett.* **2005**, *46*, 1099.

(11) See the Supporting Information for a detailed description.

(12) (a) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (b) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027. (c) Huang, H.-T.; Lacy, T. C.; Błachut, B.; Ortiz, G. X., Jr.; Wang, Q. *Org. Lett.* **2013**, *15*, 1818.

(13) Variations of these conditions (e.g., temperature, the equivalence of each reagent) led to inferior results. See these results in the Supporting Information.

Table 1. Optimizations for *o*-Amino Chlorination of Benzyne by Insertion into *N*-Chloromorpholine[a]



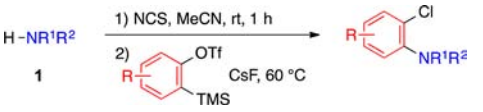
1a′ 2 3a

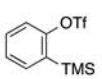
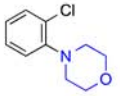
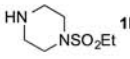
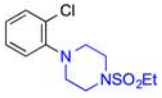
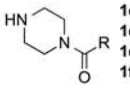
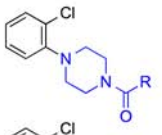
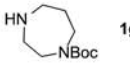
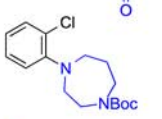
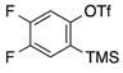
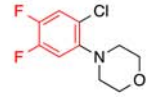
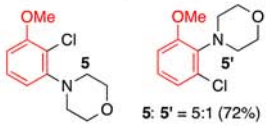
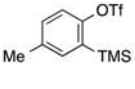
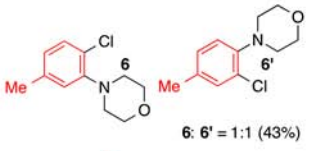
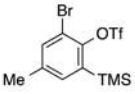
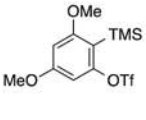
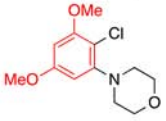
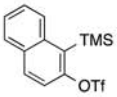
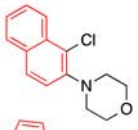
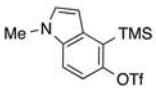
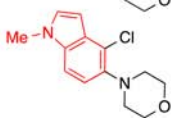
entry	1a′/2 (equiv)	F⁻ (equiv)	concn (M)	temp (°C)	time[b] (h)	3a[c] (%)
1	2.0/1.0	CsF (3.0)	0.2	24	96	50
2	2.0/1.0	CsF (3.0)	0.2	40	24	63
3	2.0/1.0	CsF (3.0)	0.2	60	5	63
4	2.0/1.0	KF (3.0)	0.2	60	24	16
5	2.0/1.0	TBAF (3.0)	0.2	24	0.1	[d]
6	2.0/1.0	CsF (3.0)	0.1	60	4	63
7	1.0/1.0	CsF (3.0)	0.1	60	1.5	53
8	1.0/1.5	CsF (3.0)	0.1	60	2.5	65
9	1.0/2.0	CsF (6.0)	0.1	60	12	62
10[e]	**1.0/1.5**	**CsF (3.0)**	**0.1**	**60**	**1.5**	**63**

[a] Reactions run on 0.1 mmol scale in MeCN. [b] Reaction time required for the complete consumption of the limiting reagent. [c] Yield determined by ^{1}H NMR spectroscopy with DMF as a quantitative internal standard. [d] **2** was consumed within 10 min while no **3a** was observed. [e] **1a′**was formed in situ from the treatment of **1a** with 1.0 equiv of *N*-chlorosuccinimide (NCS) for 1 h at rt.

including sulfonamide, carbamate, amide, and urea groups on piperazine skeletons (**3b**–**f**). In all cases, the insertion was selective toward the N–Cl bond over the C–N bond in urea[8c] or carbamate,[8o] which are known to react with benzyne. These conditions were effective for other cyclic amines[14] such as diazepane (entry 7). The lower efficiency observed in the reactions with electronically rich cyclic amines and acyclic amines suggests that the insertion is impeded by the competing decomposition of more reactive or more sterically hindered intermediates.[15] We next examined the scope of arynes by their insertion reactions with amine **1a**. The results suggest that both electron-donating and electron-withdrawing groups on arynes are well tolerated in this transformation (entries 8–14). Furthermore, the substitutions can affect the regioselectivity of the insertion for aminochlorination of arynes. For example, an aryne bearing an *o*-methoxy led to the chloro aminoarene products in a regioselective manner (entry 9), while an aryne containing a *p*-methyl group provided a 1:1 ratio of both isomers (entry 10). For unsymmetrically disubstituted arynes and the napthyl aryne derivative, only one isomer was observed in the insertion reactions (entries 11–13). Additionally, a heteroaryne was also a viable substrate, providing the chloroaminated indole derivatives in a 8:1 ratio of two isomers (entry 14). Note that the

Table 2. One-Pot Protocol for *o*-Amino Chlorination of Arynes[a,b]



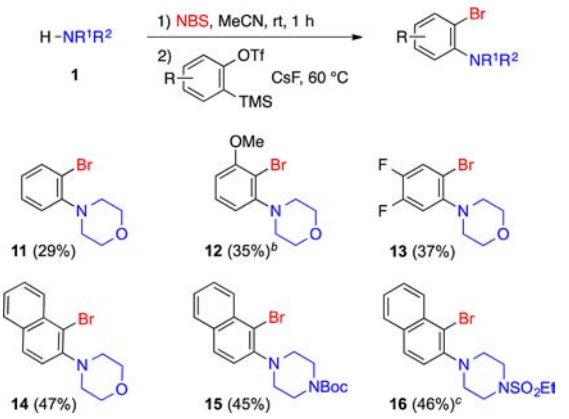
entry	amine	aryne precursor	products (yield)[b]
1	 **1a**	 **2**	 **3a** (67%)
2	 **1b**	**2**	 **3b** (66%)
3 4 5 6	 **1c** R = O*t*-Bu **1d** R = Ph **1e** R = Cyclopropyl **1f** R = NEt_2	**2**	 **3c** (63%) **3d** (44%) **3e** (53%) **3f** (53%)
7	 **1g**	**2**	 **3g** (32%)
8	**1a**		 **4** (54%)
9	**1a**		 **5**: **5′** = 5:1 (72%)
10	**1a**		 **6**: **6′** = 1:1 (43%)
11	**1a**		 **7** (59%)
12	**1a**		 **8** (34%)
13	**1a**		 **9** (63%)
14	**1a**		 **10** (25%)[c]

[a] Reactions typically run on 0.2–0.3 mmol scale. Conditions: **1** (1.0 equiv, 0.1 M), NCS (1.0 equiv), MeCN, 1 h; aryne precursor (1.5 equiv), CsF (3.0 equiv), 60 °C. [b] Isolation yield. Regioselectivity determined by ^{1}H NMR spectroscopy. [c] Major isomer shown (8:1).

observed regioselectivity in our studies is consistent with with that reported for nucleophilic additions of unsymmetrical arynes,[7c,16] suggesting the insertion may occur in a

(14) See the Supporting Information for additonal amine substrates.
(15) Base-promoted dehydrochlorination of *N*-chloramines. See, for example: Bartsch, R. A.; Cho, B. R. *J. Am. Chem. Soc.* **1979**, *101*, 3587.
(16) (a) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A. *J. Org. Chem.* **2008**, *73*, 5452. (b) Cheong, P. H. Y.; Paton, R. S.; Bronner, S. M.; Im, G. Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267. (c) Garr, A. N.; Luo, D. H.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96.

Scheme 2. *o*-Amino Bromination of Arynes by Insertion into N−Br Bonds[a]



[a] Results listed as product and isolation yield. Reactions typically run on 0.2−0.3 mmol scale. Conditions: **1** (1.0 equiv, 0.1 M), NBS (1.0 equiv), MeCN, 1 h; aryne precursor (1.5 equiv), CsF (3.0 equiv), 60 °C. [b] Major isomer shown (5:1). [c] Major isomer shown (3:1). Regioselectivity determined by ^{1}H NMR spectroscopy.

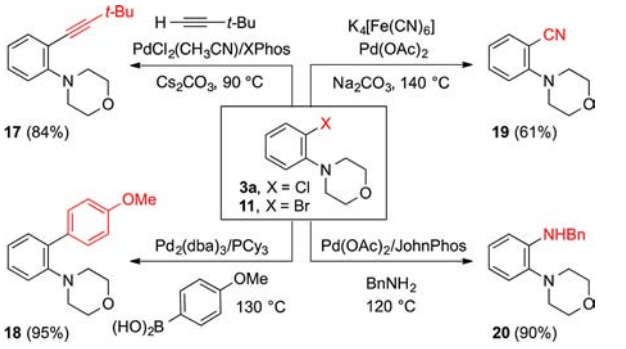
polar pathway directed by steric and electronic effects of both arynes and N−X bonds.[17]

We further explored benzyne insertion into more reactive N−Br and N−I bonds (Scheme 2). Following the one-pot protocol, the analogous reactions of *N*-morpholine **1a** and benzyne precursor **2** led to *o*-bromo amination product **11** in 29% yield but no *o*-iodoamination product. This was consistent with our observations that less stable N−X bonds tend to undergo decomposition and led to lower efficiency of aryne insertion under these conditions. Nonetheless, albeit with moderate yields, aryne insertion into N−Br bonds has proven to be an effective strategy to rapidly access various *o*-bromoaminoarenes (e.g., **11**−**16**).

To highlight the utility of *o*-haloaminoarenes (e.g., **3a** and **11**), we undertook their conversion to a variety of *o*-functionalized derivatives as outlined in Scheme 3. Several palladium-catalyzed carbon−carbon coupling reactions have been successfully achieved, including the alkynylation of aryl chloride **3a** with *tert*-butylacetylene, the arylation reaction with (4-methoxyphenyl)boronic acid, and cyanation of **11** with potassium ferrocyanide. The amination of aryl chloride **3a** with benzylamine also occurred effectively, providing *o*-diaminated arene **20** in 90% yield.

(17) See the Supporting Information for additonal mechanistic studies.

Scheme 3. Diverse *Ortho*-Substituted Anilines Derived from 4-(2-Halophenyl)morpholine



In summary, a new approach to directly access *o*-chloro- and *o*-bromoaminoarenes has been achieved by aryne insertion into N−Cl and N−Br bonds under transition-metal-free conditions. This transformation displays a broad substrate scope of arynes, good compatibility with functional groups, and high regioselectivity. Furthermore, this method allows for a rapid access to diversely functionalized aminoarenes through versatile cross-coupling reactions of the halo group.

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Supporting Information Available. Experimental procedures, additional screening data, and characterization data for new compounds including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.