Aminocyanation by the Addition of N−CN Bonds to Arynes: Chemoselective Synthesis of 1,2-Bifunctional Aminobenzonitriles

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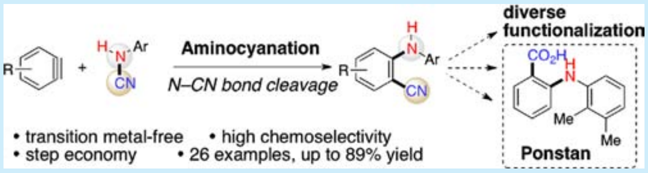
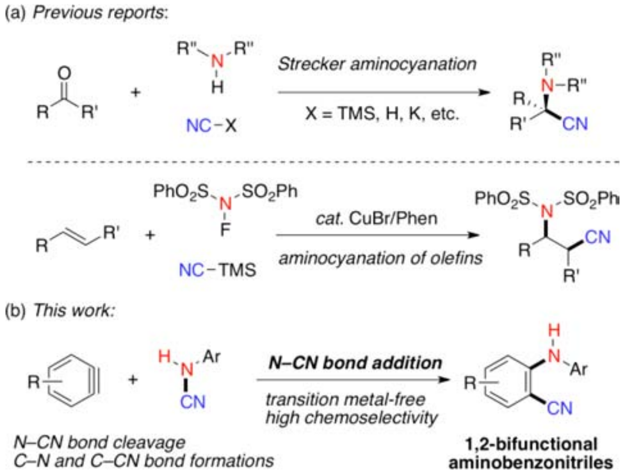
Supporting Information

ABSTRACT: An efficient aminocyanation by the direct addition of aryl cyanamides to arynes is described, enabling incorporation of highly useful amino and cyano groups synchronously via cleavage of inert N−CN bonds, affording synthetically useful 1,2-bifunctional aminobenzonitriles. The postsynthetic functionalization of the aminocyanation products allows diverse formation of synthetically important derivatives such as drug molecule Ponstan and fused heterocycles.



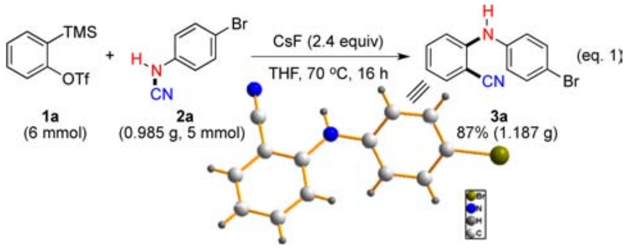
The amino and cyano groups are recognized as among the most important building blocks and are found in various bioactive molecules and functionalized materials.[1,2] Although dramatic advances have been achieved in transition-metal-catalyzed amination[3] and cyanation[4] for separate formation of these chemical subunits, a step-economic difunctionalization reaction that enables synchronous installation of amino and cyano fragments into one single molecule framework still remains a significant challenge[5] but is a practically useful strategy to rapid synthesis of important amino nitriles.[6] Current studies in the field focus on the Strecker aminocyanation of carbonyls[7] and the Cu-catalyzed reaction of olefins[8] by use of amine, amide, and cyanide partners (Scheme 1a); thus, limiting the scope of accessible compounds. Given the atom efficiency, the use of N−CN bond-containing cyanamides as single amino and cyano sources is highly attractive. However, because of the difficulty in cleavage of unreactive N−CN bonds,[9] such a practical aminocyanation has not been reported to date, despite the well-known examples of element−CN (E−CN) bond addition to unsaturated bonds.[10]

Scheme 1. Aminocyanation Reactions



Arynes are synthetically valuable intermediates and have been widely used in the construction of functionalized arenes.[11] In particular, Larock, Yoshida, Stoltz, and others proved that numerous σ bonds such as C−C, C−N, and C−O enable direct addition across the high-strain triple bonds of arynes, generally without the aid of transition metals.[11b,12] In an effort to develop a practically useful synthetic methodology, herein we describe the first example of aminocyanation by the direct addition of N−CN bonds of cyanamides to arynes, allowing introduction of highly useful amino and cyano groups simultaneously to give synthetically useful 1,2-bifunctional aminobenzonitriles, an important class of synthons,[13] and nonnucleoside reverse transcriptase inhibitor candidates for HIV-1 infection (Scheme 1b).[14]

A typical example of a gram-scale reaction by treating 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1a**) with *N*-(4-bromophenyl)cyanamide (**2a**) illustrates the simplicity of the protocol (eq 1). A mixture of **1a** (1.79 g, 6 mmol), **2a** (0.99 g, 5 mmol), and CsF (1.82 g, 12 mmol) was stirred in THF at 70 °C for 16 h, giving 2-aminobenzonitrile **3a** (1.19 g) in



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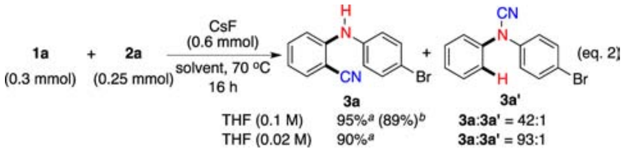
satisfactory yield (87%). The structure of **3a** was identified by single-crystal X-ray diffraction (see the Supporting Information).

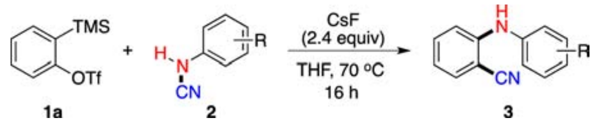
It is noteworthy that formation of the corresponding N−H adduct compound **3a**′ was also observed in the reaction (see the Supporting Information for specific information).[15] The fluoride sources, solvents, and concentration heavily influence the transformation and chemoselectivity. As compared with tetrabutylammonium difluorotriphenylsilicate (TBAT), KF/18-crown-6, and tetrabutylammonium fluoride (TBAF), cesium fluoride gives the best result, forming **3a** in good yield (89%) and satisfactory chemoselectivity (**3a**:**3a**′ = 42:1). The solvent screening shows that THF is superior to dimethyl ether, acetonitrile, dioxane, and toluene. Interestingly, low concentration favors the chemoselectivity, which can be significantly improved to 93:1 in 0.02 M THF (eq 2).

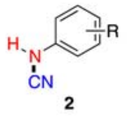
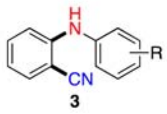
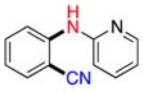
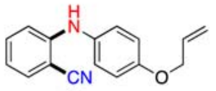
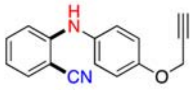


(eq. 2)

Subsequently, the scope of cyanamides was next explored by treatment with *o*-silyl aryl triflate **1a** (Table 1). Various electron-donating (entries 2−5) and electron-withdrawing (entries 6−16) substituted aromatic cyanamides are suitable with the formation of the corresponding aminocyanation products in good yields (64−86%). A broad range of functional groups, including fluoride, chloride, bromide, iodide, trifluoromethyl, alkoxyl, alkoxycarbonyl, nitro, and cyano, are well tolerated. Notably, pyridyl-substituted cyanamide can be employed in the reaction (entry 17). Interestingly, synthetically important allyl and propargyl are successfully introduced into the scaffolds of 2-aminobenzonitriles (entries 18 and 19). Unfortunately, the transformations using *N*-alkyl- and *N*,*N*-diaryl-substituted cyanamides, including *N*-benzylcyanamide, *N*-methyl-*N*-phenylcyanamide, and *N*,*N*-diphenylcyanamide, do not give the desired aminocyanation products.

Table 1. Scope of Aryl Cyanamides[a]



entry	aryl cyanamide	product		yield[b]
1	 2	 3	**3b**: R = H	70%
2			**3c**: R = *p*-Me	68%[c]
3			**3d**: R = *o*-Me, *m*-Me	70%[c]
4			**3e**: R = *p*-OMe	72%[c]
5			**3f**: R = *o*-OMe	65%[c]
6			**3g**: R = *p*-F	80%
7			**3h**: R = *p*-Cl	85%
8			**3i**: R = *o*-Cl	74%[c]
9			**3j**: R = *o*-Br	66%
10			**3k**: R = *m*-Br	74%
11			**3l**: R = *p*-I	86%
12			**3m**: R = *p*-CF_3	81%
13			**3n**: R = *p*-COMe	64%
14			**3o**: R = *p*-CO_2Me	79%
15			**3p**: R = *m*-NO_2	79%
16			**3q**: R = *p*-CN	70%
17	 2r	 3r		62%[c]
18	 2s	 3s		71%
19	 2t	 3t		65%

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.25 mmol), CsF (0.6 mmol), THF (2.5 mL), 70 °C, 16 h. [b]Isolated yield. [c]**1a** (0.5 mmol), **2** (0.25 mmol), CsF (1.0 mmol), THF (12.5 mL).

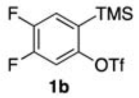
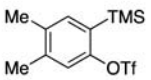
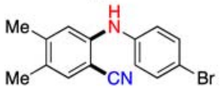
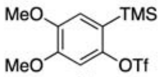
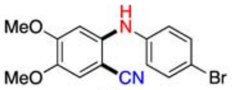
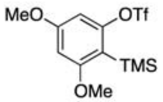
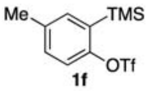
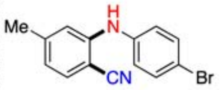
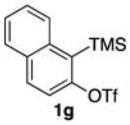
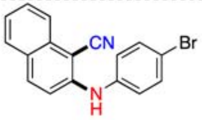
The influence of substituents on the arynes was then studied (Table 2). Both electron-poor (entry 1) and electron-rich (entries 2 and 3) symmetric arynes allow easy access to the desired products in moderate to good yields (42−75%). Interestingly, introducing the inductively electron-withdrawing methoxy group at the C3 and C5 positions of benzyne favors the nucleophilic attack at C1 site, giving the 2-aminobenzonitrile **3x** as a single product (entry 4).[11g] It should be mentioned that formation of a mixture in a nearly 1:1 regioisomeric ratio was observed using C4-methyl-substituted aryne (entry 5). In addition to benzynes, the reaction of 1,2-naphthalyne also takes place leading to two regioisomers (entry 6).

To gain insight into the reaction pathway, a preliminary mechanistic study was performed by treatment of *N*-(2-bromophenyl)-*N*-phenylcyanamide (**4**) with *n*-BuLi and then quenching with water (Scheme 2). The reaction furnishes the 2-aminobenzonitrile **3b** in 62% yield. This indicates that a phenyl anion derived from a nucleophilic attack of deprotonated cyanamide to benzyne can be considered in the transformation,[16] which may undergo a cyclization leading to the four-membered intermediate **B**, followed by a ring-opening and protonation giving the final product.[17] On the other hand, a direct nucleophilic attack of cyanamide to benzyne without the deprotonation cannot be excluded.

In view of the easily modified feature of the aminocyanation products, the postsynthetic functionalization was explored. Diversely functionalized derivatives, including 2-amino-substituted benzylamine (**5**), benzamide (**6**), ketone (**7**), and benzaldehyde (**8**), can be readily accessed by the transformation of the cyano scaffold while leaving NH and bromide intact (Scheme 3). In particular, the application of our method in transition-metal-free synthesis of the nonsteroidal anti-inflammatory drug molecule Ponstan (**9**) was successfully through two-step operations.[18] The synchronous difunctionalization of the cyano and amino moieties was realized giving diphenylamino-substituted benzamide derivative **10**.[19] In addition, fused heterocyclic carbazole **11** and bioactive acridanone **12** can also be easily produced. Obviously, the diversely functionalization of the resulting 2-aminobenzonitriles dramatically improves the practicality of the synthetic methodology.

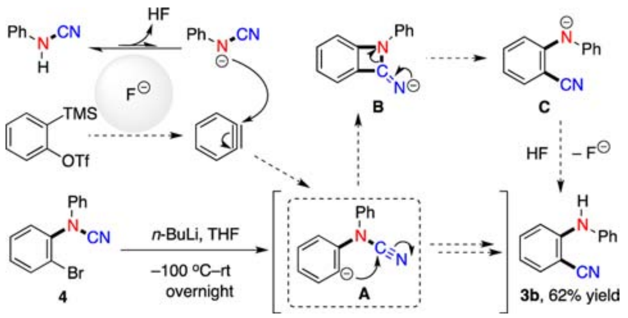
In summary, we have developed an operationally simple, transition-metal-free, and highly efficient aminocyanation of arynes through the direct addition of N−CN bonds of aryl cyanamides. The protocol enables facile access to synthetically and biologically interesting 1,2-bifunctional aminobenzonitriles

Table 2. Variation of Substituents on the Arynes[a]

entry	1	product	yield[b]
1	 **1b**	 **3u**	42%
2	 **1c**	 **3v**	54%
3	 **1d**	 **3w**	75%
4	 **1e**	 **3x**	58%
5	 **1f**	 **3y** +  **3y'**	66% (**3y**:**3y'** = 55:45)[c]
6[d]	 **1g**	 **3z** +  **3z'** (X-ray)	40% 30%

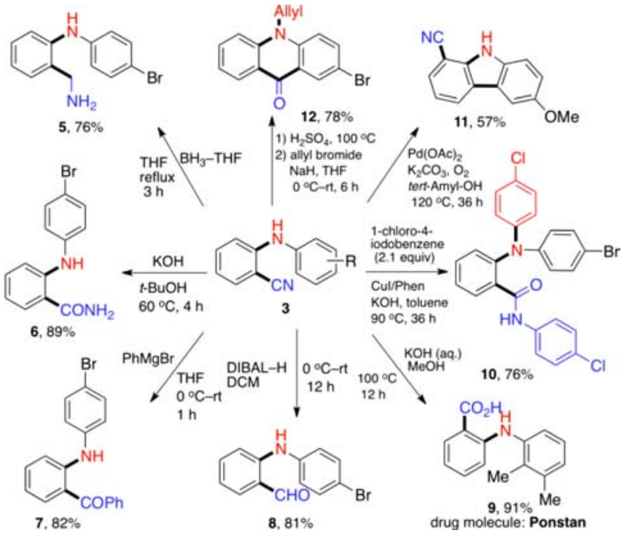
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.25 mmol), CsF (0.6 mmol), THF (2.5 mL), 70 °C, 16 h. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR analysis. [d] **1g** (0.5 mmol), **2a** (0.25 mmol), CsF (1.0 mmol), THF (12.5 mL).

Scheme 2. Proposed Mechanism



by simultaneously introducing highly useful amino and cyano groups. The postsynthetic functionalization of the amino-cyanation products allows diverse formation of important derivatives. Further applications and mechanistic studies are in progress in our laboratory.

Scheme 3. Postsynthetic Functionalization



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed optimization data; experimental procedures; characterization data of all new compounds; ORTEP drawing of **3a** and **3z'**; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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