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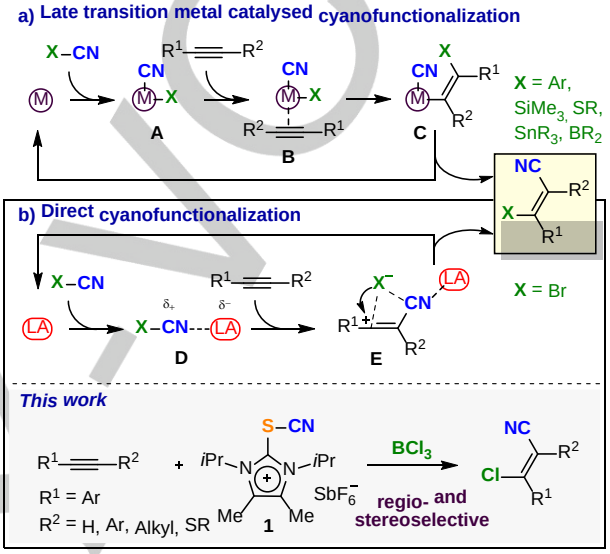
Regio- and Stereoselective Chlorocyanation of Alkynes

Alejandro G. Barrado,[a] Adam Zieliński,[a] Richard Goddard[b] and Manuel Alcarazo[a],*

Abstract: The regio- and stereoselective conversion of alkynes into (*Z*)-3-chloroacrylonitriles was achieved by treatment of a variety of terminal as well as internal alkynes with BCl_3 in the presence of stoichiometric amounts of imidazolium thiocyanates. These products can be easily functionalized into useful building blocks, demonstrating the synthetic value of the method. Preliminary mechanistic studies suggest initial activation of the cationic thiocyanate by the Lewis acid followed by electrophilic attack of the alkyne. *syn*-Addition of a chloride to the vinyl cation intermediate and final elimination of the thiourea unit afford the desired chloroacrylonitriles.

Acrylonitrile is a key monomer for the manufacture of plastics, rubbers and fibres, and substituted acrylonitriles are highly valuable precursors for the synthesis of fine chemicals in pharmaceutical and agrochemical industry.[1] This justifies the enormous attention that has been paid to reactions involved in the preparation, functionalization and transformation of acrylonitrile and its derivatives.[2] Among the methods known to gain acrylonitrile derivatives depicting well-defined substitution patterns, those based on the stereoselective cyano-functionalization of alkynes using X-CN type reagents are especially useful since two functionalities, the cyano and a second group X (which may be amenable to further transformation) are simultaneously installed in vicinal positions with ideal atom efficiency. This approach can be materialized in two different ways. In the majority of the cases an electron-rich late transition metal catalyst cleaves the X-CN bond forming intermediate **A** (Scheme 1a). This is followed by migratory insertion of the alkyne into the M-X bond **B**→**C**, and reductive elimination of the desired acrylonitrile from **C**. Transformations that are reported to follow this general mechanistic scheme include hydrocyanations,[3] carbocyanation,[4,5] cyanosilylation,[6] thiocyanation,[7] cyanostannations[8] and cyanoborations.[9] Most of the products thus obtained can be subsequently modified employing, for example, well-established coupling chemistry.

Much less attention has been paid to a complementary route: the synthesis of substituted acrylonitriles exploiting the inherent nucleophilicity of alkynes. In analogy to the well-documented addition of acids,[10] halogens or halogen derivatives,[11,12] reaction of alkynes with suitable CN^+ synthons **D** generates highly electrophilic vinyl species **E**, which after trapping by an appropriate nucleophile, renders the desired functionalized acrylonitriles (Scheme 1b). Making use of this approach, the halocyanation of (mainly terminal) alkynes has been achieved in moderate to good yields. Note however, that the number of electrophilic reagents able to perform this transformation, as well as their substrate scope, remains quite limited. In fact, to proceed satisfactorily these routes require the use of unpleasant cyanogen halides as CN^+ precursors.[13]



Scheme 1. Synthesis of substituted acrylonitriles from alkynes.

In the course of our investigation aimed at the development of new electrophilic reagents of synthetic interest, we recently demonstrated that imidazolium thiocyanates such as **1** act as efficient and easy to handle $[CN]^+$ synthons for the metal-free cyanation of non-prefunctionalized (hetero)aromatics, activated methylenes, thiols and amines.[14, 15] Hence, we reasoned that if this inherent electrophilicity could be further enhanced, for example by Lewis acid activation, then the scope of **1** as electrophilic cyanating reagent might be further extended to intrinsically less reactive substrates such as alkynes. Note, that to materialize this hypothesis a nucleophile compatible with the Lewis acid needs to be present in the reaction mixture in order to trap the transient vinyl cation **E** formed after attack of the electrophilic cyanating reagent. For this reason, we envisioned that metal halides would be appropriate promoters for such reaction: they possess well-known Lewis acid character and simultaneously could behave as latent source of halogenides. Herein, we report the realization of such a transformation using BCl_3 as an efficient promoter. The new chlorocyanation protocol is operationally simple, works with a variety of terminal as well as internal alkynes, and offers an exquisite route to fully substituted (*Z*)-3-chloroacrylonitriles in good yields and excellent regio- and stereoselectivities.

Initially, we tested the reaction of alkyne **2a** with thioimidazolium salt **1** in the presence of a range of Lewis acids such as $FeCl_3$, $TiCl_4$, $AlCl_3$ and $BF_3{\cdot}OEt_2$. No reaction was observed in any case with exception of $TiCl_4$, which was able to provide the desired product **4a**, albeit with a poor 14% yield

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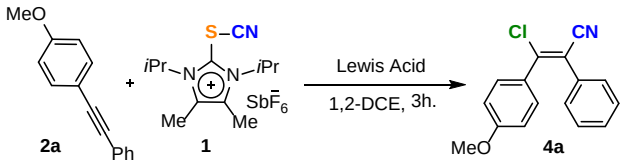
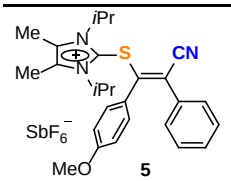
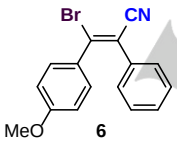
(Table 1, Entries 1-4). Interestingly, when $B(C_5F_6)_3$ was employed to activate **1**, the product of thiocyanation **5** was obtained in high yield as a 80:20 *Z*-, *E*-mixture (Table 1, Entry 5). This superior performance of $B(C_5F_6)_3$ made us speculate that BCl_3 or BBr_3 might promote the desired cynation event and avoid the undesired incorporation of the thiourea moiety to the product by providing nucleophilic halogenides to the medium. The product of bromocyanation **6** was unfortunately obtained in very low yield (Table 1, Entry 6); however, the chlorocyanation reaction was much more efficient and to our delight it proceeded with complete stereo- and regioselectivities (Table 1, Entry 7). Further optimization of the conditions (BCl_3, 2 equiv., r.t.) allowed the complete conversion of **2a** into **4a** and the isolation of this product with excellent yield (Table 1, Entry 9).

Table 1. Reaction optimization.



Entry	Lewis Acid	Equiv.	Temp. °C	Yield [a]
1	$FeCl_3$	1.0	50	n.r.[b]
2	$TiCl_4$	1.0	50	14%
3	$BF_3{\cdot}OEt_2$	1.0	50	n.r.
4	$AlCl_3$	1.0	50	traces
5	$B(C_6F_5)_3$	1.0	50	90% of **5**[c]
6	BBr_3	1.0	50	9% of **6**
7	BCl_3	1.0	50	37%
8	BCl_3	1.5	r.t.	65%
9	BCl_3	2.0	r.t.	97%





[a] Yields are of isolated products; [b] no reaction; [c] Obtained as a 80:20 mixture of the *Z*:*E* isomers respectively.

Having identified the optimal conditions, the scope and limitations of the transformation were explored. Terminal as well as internal alkynes are suitable substrates and afford the desired chloroacrylonitriles in moderate to excellent yields (Figure 1). This includes 1,2-diaryl alkynes, which are reluctant to participate in similar transformations.[12] Aliphatic groups of different steric demand (**4n-u**), halogens (**4c-f,s**), silyl groups (**4t**), heterocycles (**4l,m,u**), as well as thioether substituents (**4x**) were also tolerated. The practicability of the reaction is also demonstrated through the gram scale synthesis of **4a**. Unfortunately, 1,2-dialkyl alkynes did not react under the conditions developed; this still remains a limitation of the method.

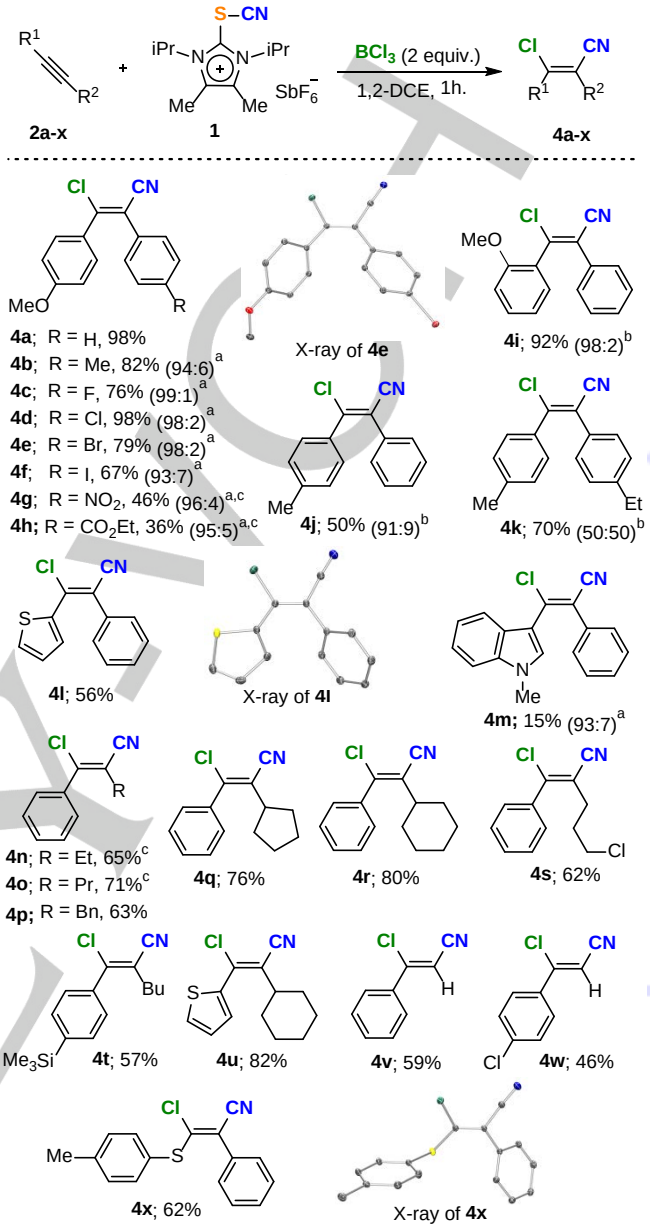


Figure 1. Substrate Scope of Alkyne Chlorocyanation. Reaction conditions: **2** (0.5 mmol, 1.0 equiv.), **1** (0.6 mmol, 1.3 equiv.), BCl_3 (1.0 M in DCM; 1.0 mmol 2 equiv.), 1,2-DCE (1 mL), rt, 1h.; yields are of isolated products; [a] *Z*:*E* ratios determined by ^{1}H-NMR; only the *Z*-alkene is detected in all other cases; [b] Obtained as mixtures of regioisomers, but only *Z*-isomers; [c] Reaction conducted at 60 °C during 3h.

The stereo- and regioselectivity observed are remarkable. The cyanide group is exclusively incorporated at the unsubstituted carbon in terminal alkynes, or at the alkyl-substituted one in 1-aryl-2-alkyl alkynes (**4n-w**), following a regioselectivity that is typical for an electrophilic mechanism. In both cases only the *Z*-isomer is formed, suggesting a *syn*-addition pathway for the reaction. When 1,2-bisarylalkynes are employed as substrates, again excellent Z-stereoselectivities are observed (**4a-i**); however, mixtures of regioisomers appear in

detectable amounts when both aromatic rings are electronically very similar (**4j,k**). It worth noting that slow isomerization of all original Z-products to the *E*-isomers takes place in solution until the thermodynamic equilibrium is achieved. [16,17]

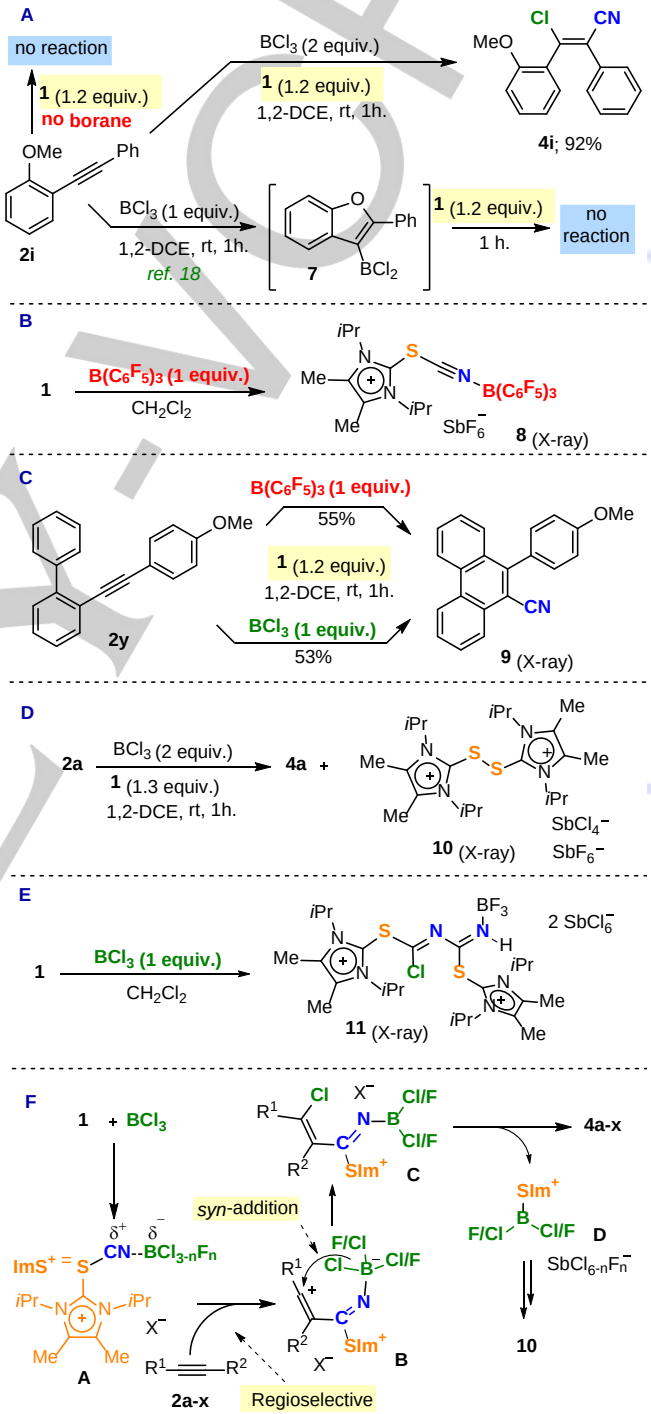
To learn more about the mechanism governing the chlorocyanation reaction, a series of control experiments were performed (Scheme 2). We first turned our attention to the recently reported cyclization of **2i** to the borylated benzofuran **7** (Scheme 2A).[18] The authors propose that alkyne activation by BCl_3 is followed by nucleophilic attack of the oxygen atom and formation of chloromethane. Interestingly, when BCl_3 is added to a mixture of **1** and **2i**, the only product detected is the one of chlorocyanation **4i.** Moreover, if **1** is added to solutions of **7** generated *in situ*, no cyanation is observed. Hence, **4i** is not likely to be formed by addition of Cl_2B-Cl to **2a**, followed by BCl_2/CN displacement. We also conclude from this experiment that BCl_3 preferentially activates **1** (and not the alkyne). This is additionally supported by the isolation of the Lewis adduct **8** in crystalline form by cooling to -80 °C an equimolar solution of **1** and $B(C_6F_5)_3$ (Scheme 2B and the Supporting Information).[19]

Also very informative is the formation of cyanated phenanthrene **9** when the biphenyl decorated substrate **2y** is made react with a solution of *in situ* prepared **8** (Scheme 2C). In this case, the electrophilic cyanation and subsequent cyclisation takes place without the participation of any chloride, excluding cyanogen chloride as the actual cyanating reagent. Product **9** is also obtained when BCl_3 is used as promotor, indicating that intramolecular trapping of the vinyl cation intermediate by the hanging phenyl ring is faster than the attack of the chloride.

We also analyzed the very insoluble orange powder that is formed during the chlorocyanation reaction,**10**. ^{1}H and ^{13}C NMR spectra pointed to the formation of a bis(imidazolium)disulphide, presumably formed by oxidation of the thiourea byproduct. However, the key information could only be obtained from X-ray diffraction (See Scheme 2D and the Supporting Information). This analysis indicated that one of the two counteranions of **10** corresponds to a tetrachloroantimonate $[SbCl_4]^-$ unit. Hence, the hexafluoroantimonate anions from **1** do not remain innocent; they participate in fluoride/chloride exchange with BCl_3 and act as oxidants transforming the urea side-product into disulphide **10**. This additionally hinders the adventitious formation of **5**.

Intrigued by this result we cooled to -80 °C the complex mixture formed after mixing **1** and BCl_3 obtaining some colourless plates, which were analysed by X-ray diffraction (See Scheme 2E and the Supporting Information). Although by no mean representative of the reaction bulk, the dimeric structure of **11** well serves to illustrate the different processes involved in the chlorocyanation reaction; namely, halogen exchange between BCl_3 and $[SbF_6]^-$, activation of **1** by Lewis acids, and addition of chloride to electrophilic carbon centres.

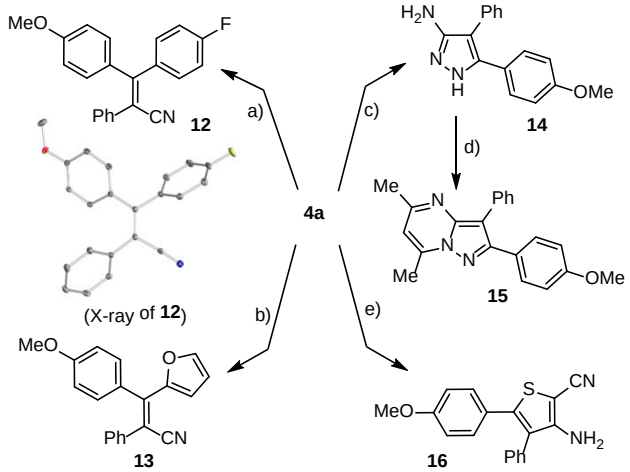
On the basis of literature precedents[20] and our own investigation, we preliminarily propose the following mechanism for the chlorocyanation reaction (Scheme 2F). First, activation of the cyanating reagent **1** takes place by formation of Lewis adduct **A**, which could be already partially fluorinated at boron. This is followed by regioselective attack of the corresponding alkyne **2a-x** and concomitant generation of vinyl cation **B**. *syn*-Transfer of one chloride from boron to the carbocationic center affords iminoborane **C,** which generates the desired chlorocyanated products **4a-x** by elimination of the imidazolium-thioborane fragment **D**.[21] Finally, a redox process transforms **D** into disulfide **10**.[22]



Scheme 2. Control experiments and proposed mechanism.

Willing to underscore the synthetic utility of the method, we tested the expedite conversion of the chloroacrylonitriles

prepared into more complex products using **4a** as model substrate. Suzuki coupling with aryl boronic acids affords the corresponding triaryl substituted acrylonitriles **12** and **13** with high stereocontrol.[23] Not less interesting is the reaction of **4a** with hydrazine to produce pyrazole **14**, which could be further transformed into the corresponding pyrazolo[1,5-*a*]pyrimidine **15** by condensation with acetylacetone. A similar synthetic procedure renders thiophene **16** in only two steps. [24]



Scheme 3. Further transformations of **4a**. Reaction conditions: a) *p*-(F)C_6H_4 $B(OH)_2$ (1.0 equiv.), $Pd_2(dba)_3$ (5 mol%), (tBu)$_3$P (20 mol%), THF:H_2O (9:1), 60 °C, 92%, *Z*:*E* = 30:1; b) 2-furylboronic acid (1.0 equiv.), $Pd_2(dba)_3$ (5 mol%), (tBu)$_3$P (20 mol%), THF:H_2O (9:1), 60 °C, 68%, *Z*:*E* = 12:1); c) NH_2-NH_2, EtOH reflux, 12h, 90%; d) acetylacetone (3.0 equiv.), piperidine (2 equiv), EtOH, 85°C, 80 min., 81%; e) $Na_2S{\cdot}9H_2O$, DMF, 50 min. and then, $ClCH_2CN$ (1 equiv.), NaOEt (1 equiv.) 23%.

In conclusion, we disclose here the use of **1**/BCl_3 mixtures for the chlorocyanation of alkynes, thereby providing a straightforward access to synthetically useful 3-chloroacrylonitriles of very different substitution patterns. Reactions proceed at room temperature, are scalable and occur with excellent regio- and stereoselectivities. The extension of the newly developed method to other substrates is currently under investigation in our research group.

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Keywords: Electrophilic cyanation • alkynes • nitriles • chlorocyanation • stereoselectivity

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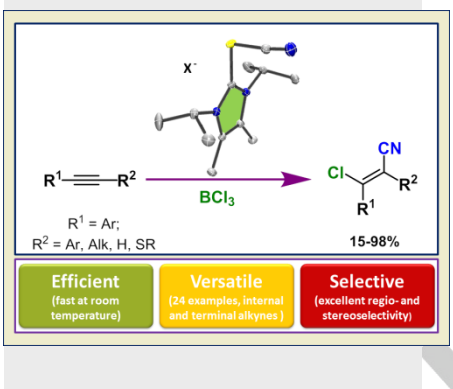
The conversion of alkynes into Z-(3)-chloroacrylonitriles has been achieved employing imidazolium thiocyanates as electrophilic cyanating reagents.



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