TITLE:

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CITATION:

Murai, Masahito ...[et al]. Gallium(III)-catalysed bromocyanation of alkynes: regio- and stereoselective synthesis of β -bromo- α,β -unsaturated nitriles.. Chemical communications 2011, 47(8): 2375-2377

ISSUE DATE:

2011-02

URL:

<http://hdl.handle.net/2433/156438>

RIGHT:

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Gallium (III)-catalysed Bromocyanation of Alkynes: Regio- and Stereoselective Synthesis of β -Bromo- α,β -unsaturated Nitriles

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Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

First published on the web Xth XXXXXXXXXX 20XX

Treatment of arylacetylenes and cyanogen bromide in $\text{ClCH}_2\text{CH}_2\text{Cl}$ with a catalytic amount of GaCl_3 afforded (Z)- β -bromoacrylonitriles with high regio- and stereoselectivity.

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The catalytic addition reactions of X-Y-type substrates to carbon-carbon multiple bonds are of continued interest due to the facile access to 1,2-difunctional units from simple alkenes or alkynes with ideal atom efficiency.¹ Among these transformations, addition reactions of X-CN to alkynes simultaneously form vinyl-X and vinyl-carbon bonds, both of which can be used to construct complex structures. Several notable examples of palladium- or nickel-catalysed regio- and stereoselective addition reactions to alkynes with several X-CN groups have been reported, such as X=H (hydrocyanation),² X=C (carbocyanation),³ X=Si (cyanosilylation),⁴ X=Ge (cyanogermylation),⁵ X=Sn (cyanostannylation),⁶ X=B (cyanoboration),⁷ X=S (cyanothiolation).⁸ However, much less attention has been paid to catalytic regio- and stereoselective halocyanation of alkynes⁹ or alkenes¹⁰ using cyanogen halides. Herein, we report on gallium-catalysed bromocyanation of alkynes with cyanogen bromide, providing an efficient route to (Z)- β -bromoacrylonitriles in a high regio- and stereoselective fashion (Scheme 1). Taking advantage of (Z)- β -bromoacrylonitriles, we can establish efficient routes to a wide range of α,β -unsaturated nitriles,¹¹ which are of synthetic value.

Scheme 1 Catalytic Addition Reactions of X-CN to Alkynes.

When we examined the reaction of cyanogen bromide¹² and phenylacetylene using palladium or nickel/phosphine complexes, which are effective catalysts in addition reactions of X-CN to alkynes (vide supra), no adducts were generated. Next, Lewis acids were screened for bromocyanation of alkynes, because there is a precedent for the haloacylation of alkynes in analogous reactions.¹³ Representative results of the reaction of cyanogen

bromide with phenylacetylene are shown in Table 1. We found that phenylacetylene underwent bromocyanation in the presence of AlCl_3 (10 mol%) in 1,2-dichloroethane at 80 °C to give β -bromocinnamionitrile **1a** in 42% yield as a mixture of Z- and E-isomers (Z:E = 89:11) (Table 1, entry 1). Interestingly, the use of GaCl_3 (10 mol%) instead of AlCl_3 led to **1a** in a high yield and stereoselectivity (81% chemical yield, Z:E = 92:8) (entry 2).¹⁴ This is in sharp contrast with the non-catalysed bromocyanation of ynamines, which gave a low stereoselectivity of the adducts (Z:E = 50:50, ~ 60:40).^{9a} The reaction using GaCl_3 at 70 °C led to a lower yield of **1a**, but with similar stereoselectivity (entry 3). 1,2-Dichloroethane was the most suitable solvent for bromocyanation, while other solvents, e.g., CHCl_3 , toluene, heptane, and 2-methyltetrahydrofuran gave a lower yield of the adducts (entries 4-6), or no adducts (entry 7).¹⁵ Using GaBr_3 as a catalyst afforded almost the same result as GaCl_3 (entry 8). Other Lewis acid catalysts, such as InCl_3 and InBr_3 , showed marginal catalytic activity and gave lower yields of **1a** (entries 9 and 10), while FeBr_3 , CuBr_2 , and ZnBr_2 exhibited no catalytic activity for bromocyanation (entries 11-13). It should be noted that

Table 1. Lewis Acid-catalysed Bromocyanation of Phenylacetylene Using BrCN^a

$\text{Ph—}\equiv + \text{BrCN} \xrightarrow[\text{solvent, 80 °C, 12 h}]{\text{catalyst}} \text{Ph—C(Br)=C(R)CN}$ <p style="text-align: center;">1a</p>				
entry	catalyst	solvent	yield ^b	Z : E ^c
1	AlCl_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	42%	89 : 11
2	GaCl_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	81% (72%)	92 : 8
3 ^d	GaCl_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	41%	91 : 9
4	GaCl_3	CHCl_3	62%	90 : 10
5	GaCl_3	toluene	61%	90 : 10
6	GaCl_3	heptane	25%	91 : 9
7	GaCl_3	2-MeTHF	0%	—
8	GaBr_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	75%	96 : 4
9	InCl_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	15%	93 : 7
10	InBr_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	32%	95 : 5
11	FeBr_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	0%	—
12	CuBr_2	$\text{ClCH}_2\text{CH}_2\text{Cl}$	0%	—
13	ZnBr_2	$\text{ClCH}_2\text{CH}_2\text{Cl}$	0%	—

^a Reaction conditions: Phenylacetylene (0.48 mmol) and BrCN (0.40 mmol) in solvent (1.6 mL) were heated in the presence of catalyst (10 mol%). ^b NMR yield (anisole as an internal standard). Isolated yield in parentheses. ^c Determined by NMR. ^d At 70 °C.

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† Electronic Supplementary Information (ESI) is available: Experimental details and analytical data are provided. See DOI: XXXXXXXX

no chlorocyanation adducts were obtained even when Lewis acid catalysts bearing chloride ligands were used (entries 1-7 and 9).

With the optimized reaction conditions established (10 mol% GaCl₃ in 1,2-dichloroethane at 80 °C), we then examined the substrate scope of alkynes (Table 2). Arylacetylenes having a range of aromatic rings underwent bromocyanation of the alkyne moieties to give the corresponding (*Z*)-adducts, **1b-h**¹⁶ in good yields with high regio- and stereoselectivity (entries 1-7), while 1-octyne and 1-(trimethylsilyl)acetylene gave no adducts. Reactions with internal aliphatic or alicyclic alkynes, such as 4-octyne and cyclooctyne, gave complex mixtures, while internal alkynes substituted by a phenyl ring produced bromocyanation adducts **1i**¹⁷ and **1j**, having a cyano group at the β position to the phenyl group in good yields with high regio- and stereoselectivities (entries 8 and 9). Although the reaction of diphenylacetylene was sluggish, and required an elevated temperature (100 °C), the corresponding bromocyanation adduct **1k** was obtained in a 56% yield with excellent stereoselectivity (entry 10).

Table 2. GaCl₃-catalysed Bromocyanation of Alkynes Using BrCN^a

entry	R ¹	R ²	product	isolated yield	Z : E ^b
1	4-CH ₃ C ₆ H ₄	H	1b	70%	95 : 5
2	2-CH ₃ C ₆ H ₄	H	1c	61%	98 : 2
3	2-naph	H	1d	55%	95 : 5
4	4-FC ₆ H ₄	H	1e	71%	91 : 9
5	4-ClC ₆ H ₄	H	1f	68%	90 : 10
6	4-BrC ₆ H ₄	H	1g	68%	91 : 9
7	4-CF ₃ C ₆ H ₄	H	1h	20%	92 : 8
8	Ph	CH ₃	1i	70%	95 : 5
9	Ph	<i>n</i> -Bu	1j	72%	91 : 9
10 ^c	Ph	Ph	1k	56%	99 : 1

^a Reaction conditions: Alkynes (0.48 mmol) and BrCN (0.40 mmol) in ClCH₂CH₂Cl (1.6 mL) were heated in the presence of GaCl₃ (10 mol%). ^b Determined by NMR. ^c Reaction carried out in toluene at 100 °C.

The alkynophilicity¹⁸ of trivalent GaX₃ leading to the formation of cationic vinylgallium species is well known, and some notable synthetic applications have been demonstrated.¹⁹ To gain insight into the present bromocyanation of alkynes, we carried out an NMR study on a stoichiometric reaction. When GaCl₃ was added to a solution of BrCN in CDCl₃ at room temperature, the signal of CN (δ 76.1 ppm) in BrCN shifted to a new peak at δ 88.2 ppm. The downfield shift of the CN peak suggested the possibility of the formation of a complex between BrCN and GaCl₃.²⁰ When an equimolar amount of 1-phenyl-1-hexyne was added to a CDCl₃ solution of this complex at room temperature, the quantitative formation of the bromocyanation product **1j** (Z:E = 98:2) coordinated with GaCl₃ was observed, with the signal of the CN moiety being observed at δ 149.5 ppm. This result clearly shows that electrophilic addition of the BrCN

and GaCl₃ complexes to alkynes²¹ occurs, even at room temperature, and a high temperature is required in the catalytic reaction conditions to release GaCl₃ from cyano moiety of the adduct.

The synthetic utility of (*Z*)-β-bromo-α,β-unsaturated nitriles obtained from the bromocyanation of alkynes was demonstrated by the cross-coupling reactions of the representative product **1a** (Scheme 2). The Stille coupling reactions of **1a** with organostannanes afforded the stereo-defined structures **2** or **3** in good yields. The Sonogashira coupling reaction of **1a** with phenylacetylene gave enyne **4** quantitatively, with complete stereoselectivity. The nickel-catalysed reductive homo-coupling of **1a** produced 3,4-diphenyl-2,4-hexadiene-1,6-dinitrile **5**.²² Moreover, we demonstrated the synthetic utility of **1a** and its derivative **3** in the preparation of the biologically active heterocycles **6**²³ and **7**.¹¹

(a) (4-CH₃C₆H₄)SnBu₃, Pd(PPh₃)₄, CuI, dioxane, 100 °C, 8h. (b) BzSnBu₃, Pd(OAc)₂, PPh₃, dioxane, 100 °C, 12 h. (c) Phenylacetylene, Pd(PPh₃)₄, CuI, Et₃N, THF, rt, 5 h. (d) NiBr₂(PPh₃)₂, PPh₃, Zn, dioxane, 80 °C, 6 h. (e) Ethyl thioglycolate, NaOEt, EtOH, 70 °C, 12 h. (f) 1,3-Dimethoxybenzene, Cu(OTf)₂, ClCH₂CH₂Cl, H₂O, 80 °C, 15 h. Ar = 2,4-(MeO)₂C₆H₃.

Scheme 2 Transformation of **1a**.

In summary, we developed gallium(III)-catalysed bromocyanation of alkynes using cyanogen bromide. This method enables the regio- and stereoselective introduction of the synthetically useful Br and cyano functionalities to carbon-carbon triple bonds in single operation. Further investigations into the reaction mechanism, substrate scope, and the synthetic application are currently underway in our laboratory.

Acknowledgment. This work is financially supported by a Grant-in-Aid for Scientific Research from MEXT. M. M. thanks the JSPS Research Fellowships for Young Scientists.

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