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Cyanation of aromatic/vinylic boronic acids with α-cyanoacetates†

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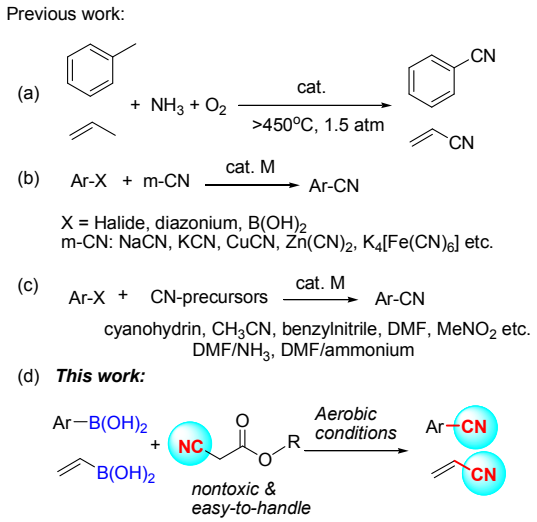
A friendly protocol is reported to achieve cyanation of aromatic and vinylic boronic acids using nontoxic and readily available α-cyanoacetates as cyano source under aerobic conditions. Many aryl/vinyl boronic acids (as well as some iodides and bromides) are amenable substrates to give aryl nitriles and acrylonitriles. This cyanation method provides a safe and operationally convenient alternative to traditional ones requiring toxic cyanide salts.

Aryl nitriles and acrylonitriles are important structural motifs occuring in pharmaceuticals and biologically active compounds. They also serve as versatile feedstock for organic synthesis and material science.[1,2] For instance, aryl nitriles are synthetic intermediates toward a range of compounds, including benzamides, ketones, amines and heterocycles. Acrylonitriles are particularly useful for the production of various polymeric commodities such as fibre, rubber, resin and etc. Therefore, nitriles synthesis has attracted tremendous interests from both academic and industrial community. A well-known industrial route to nitriles is oxidative amination of methyl arenes or propenes with ammonia/O_2 under high temperature and pressure (known as ammoxidation reaction, Scheme 1a). In laboratory, the synthesis of nitriles are dominated by cyanation of aryldiazonium salts or aryl halides using stoichiometric CuCN.[3,4] More recently, transition metal (especially Pd and Cu) catalyzed cyanation reactions have achieved significant progress which rely mainly on the cross-coupling of aryl halides or boronic acids with various cyanide salts (Scheme 1b).[5-7] Transition metal-mediated cyanation of vinyl halides or boronic acids has been much less studied.[8] The high toxicity of cyanide salts and the extremely volatile and flammable HCN gas easily generated during the use of cyanide salts however brings about great danger in storage and operation, and thus greatly limits the wide application of these reactions.

The quest for methods employing more friendly cyano sources has therefore been the focus of recent cyanation studies. Several CN-containing organic compounds have been studied as cyanating reagents to transfer a cyano group to aromatic ring, such as cyanohydrin,[9] CH_3CN,[10] and benzylnitriles[11] (Scheme 1c). Moreover, cyanation methods involving *de novo* generation of CN group during the reaction course have also been reported, from either an organic molecule (such as DMF[12] and nitromethane[13]) or an organic/inorganic combination (typically DMF with NH_3 or an ammonium salt[14,15]).

Despite the progress achieved, there are few examples describing ready access to both aryl and vinyl nitriles by a general and friendly synthetic method using nontoxic and easy-handling CN sources.[16] Considering that arylboronic acids are predominant and readily available aryl source and toxic cyanide salts generally used in most of arylboronic acids cyanation methods,[7] it will be highly desirable to achieve cyanation of aryl/vinyl boronic acids using nontoxic CN source. As part of our continuous effort,[17] we report herein a friendly protocol that achieves this goal by using α-cyanoacetates[18] to generate cyano group under aerobic oxidative conditions (Scheme 1d).



Scheme 1 Synthetic methods for the preparation of aryl/vinyl nitriles.

We began our study by reaction of biphenyl boronic acid (**1a**) with ethyl α-cyanoacetate (**2a**), aiming to produce cyanation product **3a**. Initial examination of a set of reaction conditions developed for cyanation of aryl iodides[17a] gave aryl nitrile **3a** in trace amounts (Table 1, entries 1, 2). After great efforts, it was found that using a stoichiometric amount of CuI and 20 mol% PPh_3 in the presence of tertbutylhydroperoxide (TBHP) in NMP (*N*-methylpyrrolidin-2-one) at 130 °C produced **3a** in a moderate yield of 49% (entry 3). Gratifyingly, addition of 2 equivalents of acetic acid further improved the yield to 68% (entry 4). Interestingly, when PPh_3 was used in one equivalent instead of 20 mol%, a much lower yield of 40% was however obtained (entry 5). Attempts to reduce the amount of CuI led to much lower yields (entries 9, 10), suggesting a failure of turnover of active copper species. When lowering down the reaction temperature to 100 °C, **3a** was obtained in only 34% yield (entry 17), highlighting the importance of reaction temperature probably for the C-CN bond cleavage in cyanoacetate.

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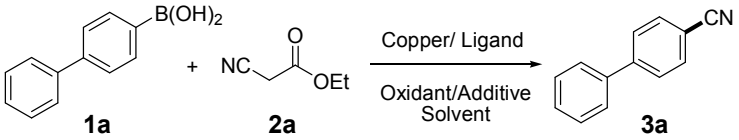
Table 1 Optimization of the reaction conditions for cyanation of arylboronic acids with α-cyanoacetate [a]



1a 2a 3a

Entry	Copper	Ligand	Solvent	Oxidant/Additive	Yield (%)[b]
1	Cu_2O (0.1 mmol)	PPh_3 (0.1 mmol)	NMP	$AgNO_3$	trace
2	CuI (0.1 mmol)	PPh_3 (0.1 mmol)	NMP	$AgNO_3$	10
3 [c]	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	NMP	TBHP	49
4	**CuI (0.5 mmol)**	**PPh_3 (0.1 mmol)**	**NMP**	**TBHP/HOAC**	**68**
5	CuI (0.5 mmol)	PPh_3 (0.5 mmol)	NMP	TBHP/HOAc	40
6	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	NMP	TBHP/K_2CO_3	18
7	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	NMP	TBTP/KF	23
8	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	NMP	TBHP/HOTf	55
9	CuI (0.25 mmol)	PPh_3 (0.1 mmol)	NMP	TBHP/HOAc	36
10	CuI (0.1 mmol)	PPh_3 (0.1 mmol)	NMP	TBHP/HOAc	34
11	CuI (0.5 mmol)	PCy_3 (0.1 mmol)	NMP	TBHP/HOAC	58
12	CuI (0.5 mmol)	DPPE (0.1 mmol)	NMP	TBHP/HOAC	47
13	CuI (0.5 mmol)	Xantphos (0.1mmol)	NMP	TBHP/HOAC	40
14	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	Toluene	TBHP/HOAC	NR
15	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	DMF	TBHP/HOAC	45
16	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	DMA	TBHP/HOAC	60
17 [d]	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	NMP	TBHP/HOAC	34
18	CuI (0.5 mmol)	PPh_3 (0.1 mmol)	NMP	HOAc	22
19	—	PPh_3 (0.1 mmol)	NMP	TBHP/HOAC	0
20	CuI (0.5 mmol)	—	NMP	TBHP/HOAC	27

[a] Reaction conditions: biphenylboronic acid (**1a**, 0.5 mmol), ethyl cyanoacetate (**2a**, 1.0 mmol), copper, ligand, oxidant/additive (1:1, 1.0 mmol) in solvent (2 mL) stirred at 130 °C under oxygen balloon for 18 hours. [b] Isolated yields of **3a** after column chromatography. [c] TBHP, tertbutylhydroperoxide, was used as a 65% aqueous solution. [d] Reaction performed at 100 °C.

Next, other oxidant/additive combinations were evaluated (entries 6-8), such as TBHP/K_2CO_3, TBHP/HOTf and TBHP/KF, but all showed much less efficiency compared with TBHP/HOAc. Further efforts were directed to examine ligand and solvent effects for this reaction. It was found that PCy_3, DPPE and Xantphos were also shown to be effective and give **3a** in moderate yields, but are inferior to PPh_3 (entries 11-13). Nonpolar toluene was completely ineffective while polar DMF and DMA could produce the desired **3a** in lower yields than NMP (entries 14-16). Finally, control experiments confirmed the crucial roles of CuI, PPh_3 and TBHP for promoting this reaction; without them, the reaction could not occur or led to very low yields (entries 18-20).

The substrate scope was next studied for this cyanation reaction (Table 2). Arylboronic acids with either electron-rich or electron-deficient substituents on the aryl ring were compatible with the optimized reaction condition. Phenyl, methoxyl, phenoxide and ester were tolerated on the aromatic ring, giving the desired aryl nitriles in good yields. Furthermore, heteroaryl boronic acids, such as 3-quinolyl, 2-thiophenyl and dibenzofuryl boronic acids, gave the desired products **3i-k** in moderate to satisfying yields. However, for boronic acids with methylthio, acetyl and fluoro, the desired products were unable to be obtained or in very low yield (**3f-h**), possibly due to low reactivity or competitive side reaction (eg, oxidation of arylboronic acids to phenols) for these substrates.

To further show the synthetic compatibility, other commercially available cyanoacetates were examined to react with biphenyl boronic acid (**1a**) under the optimized reaction conditions (Table 3). It was pleasing to see that methyl cyanoacetate (**2b**) gave the desired product **3a** in 79% yield (entry 2). Cyanoacetates **2c** and **2d** with either one phenyl or two methyl substituents on the α-C atom also gave **3a** in very good yields (entries 3,4). These results demonstrate the feasibility of a range of cyanoacetates as the CN source.

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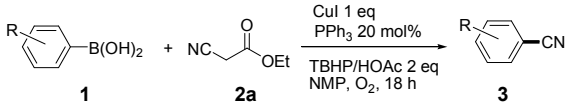
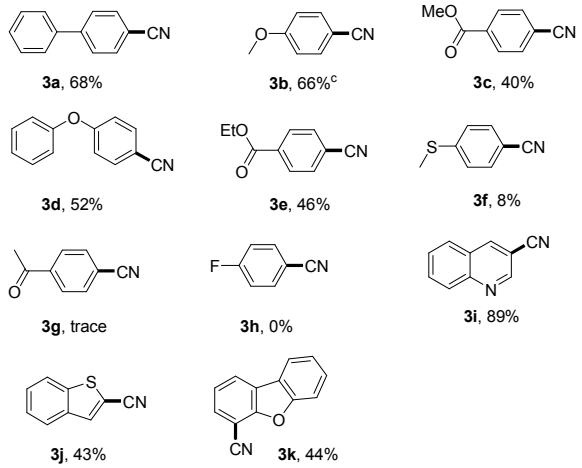
Table 2 Substrate scope for copper-mediated aromatic cyanation of arylboronic acids [a,b]

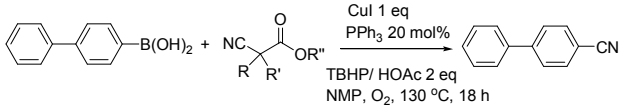


1 2a 3

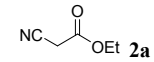
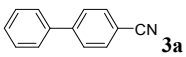
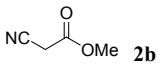
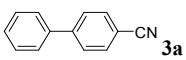
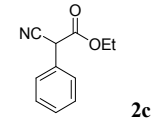
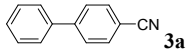
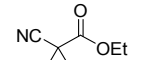
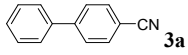


[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), CuI (0.5 mmol), PPh_3 (0.1 mmol), TBHP/HOAc (1.0 mmol), NMP (2 mL), 130 °C, under O_2 (balloon) for 18h. [b] Isolated yields using column chromatography. [c] 5 hours for **3b**.

Table 3 Aromatic cyanation using various α-cyanoacetate sources [a]



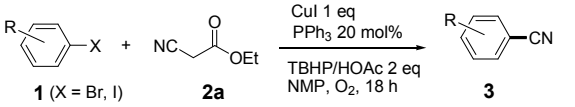
1a 2 3a

entry	*Cyanoacetate*	*Product*	*Yield (%)[b]*
1	 **2a**	 **3a**	68
2	 **2b**	 **3a**	79
3	 **2c**	 **3a**	67
4	 **2d**	 **3a**	70

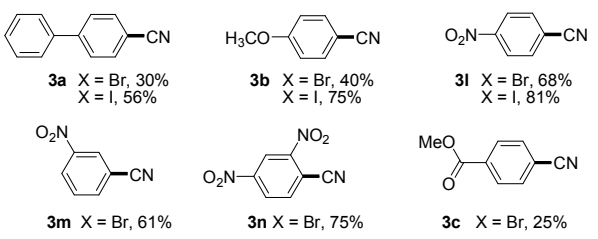
[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), CuI (0.5 mmol), PPh_3 (0.1 mmol), TBHP/HOAc (1.0 mmol), NMP (2 mL), 130 °C, under O_2 balloon for 18h. [b] Isolated yields using column chromatography.

Gratifyingly, this protocol is also applicable to the cyanation of aryl iodides and bromides (Table 4). Aryl bromides were found to perform poorly in our previous report.[17a] As shown in Table 4, aryl halides with a para, meta or ortho substituent can all be compatible. Aryl iodides are generally more reactive than aryl bromides. For aryl bromides with a strong electron-withdrawing nitro group, the yields can

Table 4 Substrate scope for copper-mediated aromatic cyanation of aryl halides [a,b]

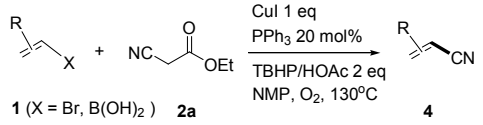


1 (X = Br, I) 2a 3

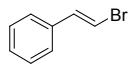
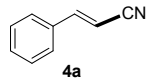
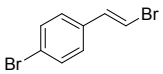
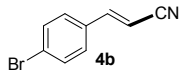
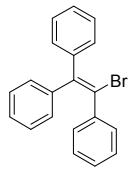
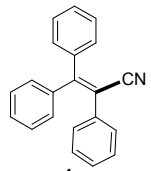
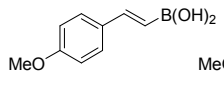
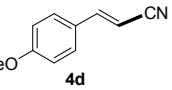


[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), CuI (0.5 mmol), PPh_3 (0.1 mmol), TBHP/HOAc (1.0 mmol) and NMP (2 mL), 130 °C, under O_2 (balloon) for 18h. [b] Isolated yields using column chromatography.

Table 5 Copper-mediated vinylic cyanation of vinyl boronic acids or halides [a,b]



1 (X = Br, B(OH)2) 2a 4

Reactant	*Product*	*Yield*
	 **4a**	56% (74%)[c]
	 **4b**	56%
	 **4c**	74% (81%)[c]
	 **4d**	60%

[a] Reaction conditions: vinyl halide or boronic acid (0.5 mmol), **2a** (1.0 mmol), CuI (0.5 mmol), PPh_3 (0.1 mmol), TBHP/HOAc (1.0 mmol), NMP (2 mL), 130 °C, under O_2 balloon for 18h. [b] Isolated yields using column chromatography. [c] Yields in parentheses were obtained using Cu_2O (0.1 mmol), PPh_3 (0.1 mmol), $AgNO_3$ (0.5 mmol).

be greatly improved. Aryl chlorides were still unreactive. These results suggest a rate-limiting activation of aryl halide for this cyanation reaction.

Finally, vinyl bromides and boronic acids are also compatible with the optimized conditions to give cinnamonitriles in good yields (Table 5). For example, reaction of 2-styryl bromide with α-cyanoacetae **2a** gave (*E*)-cinnamonitrile **4a** in a yield of 56% with the retention of double bond configuration. When a *para*-bromo is present on the aryl ring of styryl bromide, reaction selectively occurred

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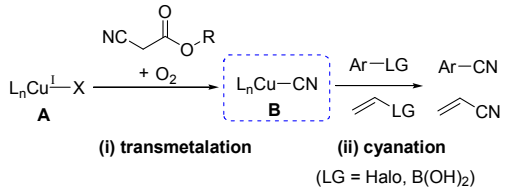
at the vinylic C-Br bond to give **4b** as the major product in a yield of 56%. A triphenyl substituted vinyl bromide was also reactive with **2a**, affording a highly conjugated acylonitrile **4c** in a sastisfying yield of 74%. Finally, vinyl boronic acid is also feasible for this reaction to prepare **4d** in an isolated yield of 60%.



Scheme 2 Proposed mechanism for this cyanation reaction.

Radical trapping experiment showed that **3a** was obtained in only 10% yield in the presence of 2 equivalents of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinyloxy) (68% without TEMPO), suggesting the involvement of radical species during the reaction course.[19] Based on this finding and insights gained from closely related reactions,[17b] a plausible mechanism is suggested to comprise two stages: transmetalation and cyanation. A key L_nCu-CN intermediate **B** may be formed by transmetalation of CN group from α-cyanoacetate via oxidative C-CN bond cleavage[17,20] promoted by TBHP/O_2 during which radical species are possibly involved. A rate-limiting reaction of **B** with aryl/vinyl boronic acid or halide would install the cyano group on the aromatic or vinylic C_{ipso} position.

In summary, a protocol for aromatic and vinylic cyanation is described to prepare aryl nitriles and acrylonitriles using readily available and nontoxic α-cyanoacetates as the cyanating reagents. This reaction is mediated by CuI/PPh_3 in the presence of TBHP/HOAc under oxygen, and is compatible with aryl/vinyl boronic acids and halides. The reaction is potentially attractive for practical synthesis of various aryl nitriles and acrylonitriles.

Conflicts of interest

There are no conflicts of interest to declare.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, copies of ^1H and ^{13}C NMR spectra for all the products. See DOI: 10.1039/b000000x/

1 (a) A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substance: Synthesis Patents, Applications*, 4th ed., Georg Thieme, Stuttgart, 2001; (b) J. S. Miller and J. L. Manson, *Acc. Chem. Res.*, 2001, **34**, 563; (c) F. F. Fleming and Q. Wang, *Chem. Rev.*, 2003, **103**, 2035.

2 (a) Z. Rappoport, *Chemistry of the Cyano Group*, Wiley, London, 1970; (b) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, VCH, New York, 1989.

3 T. Sandmeyer, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1633.

4 K.W. Rosenmund and E. Struck, *Ber. Dtsch. Chem. Ges.*, 1919, **2**, 1749.

5 For reviews on transition metal-catalyzed cyanation reactions, see: (a) G. P. Ellis and T. M. Romney-Alexander, *Chem. Rev.*, 1987, **87**, 779; (b) J. Kim, H. J. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 11948; (c) P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049; (d) Q. Wen, J. Jin, L. Zhang, Y. Luo, P. Lu and Y. Wang, *Tetrahedron Lett.*, 2014, **55**, 1271.

6 Aryl halides with cyanides: (a) J. Zanon, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 2890; (b) H.-J. Cristau, A. Ouali, J.-F. Spindler and M. Taillefer, *Chem.–Eur. J.*, 2005, **11**, 2483; (c) T. Schareina, A. Zapf and M. Beller, *Tetrahedron Lett.*, 2005, **46**, 2585; (d) T. Schareina, A. Zapf, W. Magerlein, N. Müller and M. Beller, *Chem.–Eur. J.*, 2007, **13**, 6249; (e) D. Wang, L. Kuang, Z. Li and K. Ding, *Synlett*, 2008, 69; (f) P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 648; (g) P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2010, **49**, 8918; (h) P. Y. Yeung, C. P. Tsang and F. Y. Kwong, *Tetrahedron Lett.*, 2011, **52**, 7038.

7 For Cu-mediated cyanation of aryl boronic acids: see: (a) G. Zhang, L. Zhang, M. Hu and J. Cheng, *Adv. Synth. Catal.*, 2011, **353**, 291; (b) C. W. Liskey, X. Liao and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 11389; (c) G. Zhang, S. Chen, H. Fei, J. Cheng and F. Chen, *Synlett*, 2012, 2247; (d) Y. Luo, Q. Wen, Z. Wu, J. Jin, P. Lu and Y. Wang, *Tetrahedron*, 2013, **69**, 8400; (e) Z. Zhang and L. S. Liebeskind, *Org. Lett.*, 2006, **8**, 4331. For more examples of Pd-mediated cyanation of boronic acids, see: ref 5c.

8 For cyanation of vinyl halides, see: (a) A. Pradal and G. Evano, *Chem. Commun.*, 2014, **50**, 11907; (b) K. J. Powell, L.-C. Han, P. Sharma and J. E. Moses, *Org. Lett.*, 2014, **16**, 2158; (c) M. Shevlin, *Tetrahedron Lett.*, 2010, **51**, 4833; (d) D. Saha, L. Adak, M. Mukherjee and B. C. Ranu, *Org. Biomol. Chem.*, 2012, **10**, 952.

9 Cyanohydrin: (a) M. Sundermeier, A. Zapf and M. Beller, *Angew. Chem., Int. Ed.*, 2003, **42**, 1661; (b) T. Schareina, A. Zapf, A. Cott, M. Gotta and M. Beller, *Adv. Synth. Catal.*, 2011, **353**, 777; (c) K. Ouchaou, D. Georgin and F. Taran, *Synlett* 2010, 2083; (d) E. J. Park, S. Lee and S. Chang, *J. Org. Chem.*, 2010, **75**, 2760.

10 CH_3CN: (a) F.-H. Luo, C.-I. Chu and C.-H. Cheng, *Organometallics* 1998, **17**, 1025; (b) Y. Zhu, L. Li and Z. Shen, *Chem.–Eur. J.*, 2015, **21**, 13246.

11 Benzyl nitrile: a) Q. Wen, J. Jin, B. Hu, P. Lu, Y. Wang, *RSC Adv.*, 2012, **2**, 6167; b) J. Jin, Q. Wen, P. Lu, Y. Wang, *Chem. Commun.*, 2012, **48**, 9933; c) O. Y. Yuen, P. Y. Choy, W. K. Chow, W. T. Wong and F. Y. Kwong, *J. Org. Chem.*, 2013, **78**, 3374.

12 DMF: S. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374.

13 CH_3NO_2: X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790.

14 J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272.

15 (a) J. Kim, J. Choi, K. Shin and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 2528; (b) K. V. V. K. Mohan, N. Narender and S. J. Kulkarni, *Tetrahedron Lett.*, 2004, **45**, 8015; (c) J. Kim, H. Kim and S. Chang, *Org. Lett.*, 2012, **14**, 3924; (d) X. Ren, J. Chen, F. Chen and J. Cheng, *Chem. Commun.*, 2011, **47**, 6725; (e) G. Zhang, X. Ren, J. Chen, M. Hu and J. Cheng, *Org. Lett.*, 2011, **13**, 5004.

16 Z. Wang and S. Chang, *Org. Lett.*, 2013, **15**, 1990.

17 (a) S.-L. Zhang and L. Huang, *Org. Biomol. Chem.*, 2015, **13**, 9963. (b) S.-L. Zhang and X.-J. Wang, *Org. Lett.*, 2017, **19**, 3139; (c) S.-L. Zhang, L. Huang and W.-F. Bie, *Organometallics*, 2014, **33**, 3030.

18 For a pioneering study using α-cyanoacetates, see: (a) S. Zheng, C. Yu and Z. Shen, *Org. Lett.*, 2012, **14**, 3644. For a related study leading to different products, see: (b) P. Y. Yeung, K. H. Chung and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 2912.

19 Efforts to determine the fate of TEMPO were unsuccessful.

20 For a review on C−CN bond cleavage, see: M. Tobisu and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300.

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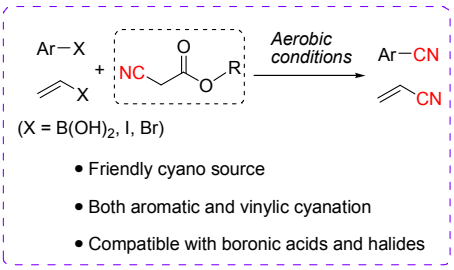

A protocol is reported to achieve safe and convenient aromatic and vinylic cyanation of boronic acids (as well as halides) with α-cyanoacetates, avoiding the use of toxic cyanide salts.