ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: *Chem. Commun.*, 2017, 53, 6597

Received 14th April 2017,
Accepted 30th May 2017

DOI: 10.1039/c7cc02886e

rsc.li/chemcomm



# [$^{11}$C]Cyanation of arylboronic acids in aqueous solutions†

Longle Ma, [ab] Michael S. Placzek,[bcd] Jacob M. Hooker, [bd] Neil Vasdev*[ab] and Steven H. Liang *[ab]

**A copper-mediated $^{11}$C-cyanation method employing arylboronic acids and [$^{11}$C]HCN has been developed. This method was applied to the radiochemical synthesis of a wide range of aromatic $^{11}$C-nitriles in aqueous solutions. The use of readily accessible arylboronic acids as precursors makes this method complementary to the well-established $^{11}$C-cyanation methods that utilize aryl halide precursors.**

Positron Emission Tomography (PET) is a highly sensitive non-invasive molecular imaging modality, which can be used to monitor biochemical processes *in vivo*.[1] Carbon-11 ($^{11}$C; $t_{1/2}$ = 20.4 min) is a widely utilized radionuclide in radiotracer synthesis, particularly for labeling small organic, drug-like molecules. This is due to the breadth of functional groups (*e.g.*, $^{11}CH_3$, $^{11}$CN, $^{11}$C=O, *etc.*) into which carbon-11 could be incorporated. Furthermore, the relative short half-life of carbon-11 allows for repeated *in vivo* PET studies in animals or humans within short time intervals while maintaining a reasonable imaging window.[2,3] Carbon-11-labeled radiotracers are predominantly prepared by methylation reactions between –OH, –NH, or –SH groups and [$^{11}$C]$CH_3I$[4,5] or [$^{11}$C]$CH_3OTf$.[6] Driven by the need to expand beyond $^{11}$C-methylation reactions as a mainstay in PET radiopharmaceutical production, continued efforts towards employing a more diverse library of $^{11}$C-synthons remain a focus for several research laboratories,[7–12] and this topic has been reviewed by us[13–15] and others.[16] We are particularly interested in the development of new [$^{11}$C]HCN-labeling methods because nitriles are not only frequently present in biologically active agents but also represents a versatile functional group that can be readily converted into $^{11}$C-labeled amides, carboxylic acids or amines.[15] Historically, nucleophilic $^{11}$C-cyanation of aliphatic substrates was a subject that received long-term attention and is generally performed *via* the Strecker reaction[7] or by the ring-opening of activated aziridines.[17] The resulting $^{11}$C-labeled aliphatic nitriles have been used to prepare $^{11}$C-labeled amino acids such as [$^{11}$C]phenylalanine,[18] [$^{11}$C]tyrosine,[18] and [$^{11}$C]aspartic acid (Fig. 1A).[17] On the other hand, the existing methods for introducing [$^{11}$C]$CN^-$ into aromatic rings are focused on either nucleophilic aromatic substitution ($S_NAr$) reactions with $Cr(CO)_3$ activated arenes[19] or Pd-catalyzed $^{11}$C-cross-coupling reactions with ArBr,[20–22] ArI[23,24] or ArOTf[25] substrates (Fig. 1B). Alternatively, copper catalyzed transformation from aryl halide into aryl nitrile in the Rosenmund–von Braun reaction could be employed for $^{11}$C-aromatic cyanation (Fig. 1B).[26] This method

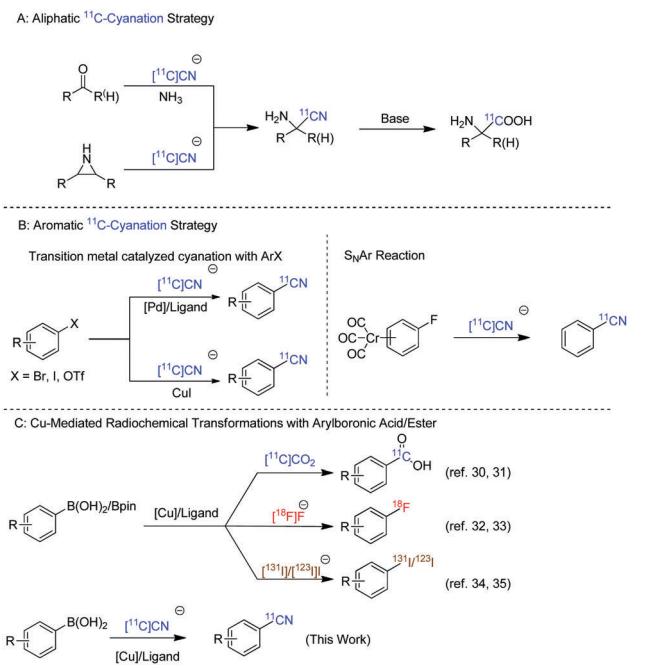



Fig. 1 Cyanation strategies and utility of boronic precursors in radiochemical transformations.

[a] *Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital, Boston, MA, USA. E-mail: liang.steven@mgh.harvard.edu, vasdev.neil@mgh.harvard.edu; Fax: +1-617-726-6165; Tel: +1-617-726-6107*
[b] *Harvard Medical School, Boston, MA, USA*
[c] *McLean Hospital, Belmont, USA*
[d] *Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, USA*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cc02886e

takes advantage of the robust nature and environmentally-benign characteristics of the copper catalyst and obviates the limitation imposed by air/moisture sensitive ligands which are required by Pd-catalyzed reactions. With the increased demand for developing rapid and highly efficient syntheses for $^{11}$C-CN-labeled PET tracers, we herein report a novel copper(I)-mediated $^{11}$C-cyanation of arylboronic acids in aqueous solutions.

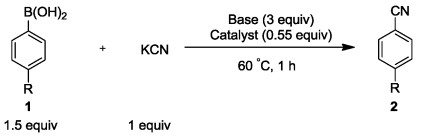
Copper-mediated Rosenmund–von Braun type transformations between arylboronic precursors and various coupling partners have been the subject of extensive investigation[27–29] and their translations into radiochemistry have gained increasing attention. For example, Riss *et al.*[30] and our laboratory[31] developed $^{11}$C-carboxylation reactions with arylboronic esters using copper(I) catalysts (Fig. 1C). Mossine *et al.*[32] and Preshlock *et al.*[33] reported aromatic $^{18}$F-fluorinations using boronic acid/ester precursors, respectively (Fig. 1C). Moreover, Zhang *et al.*[34] and Wilson *et al.*[35] disclosed aromatic $^{131}$I/$^{123}$I-iodination reactions involving copper catalysts and boronic acids/esters (Fig. 1C). Inspired by their pioneering work, we envisioned that $^{11}$C-aromatic cyanation could be achieved using widely available and easily-handled arylboronic acid[36] precursors, $^{11}$C-cyanide and copper catalysts.

To evaluate several reaction parameters including copper catalysts, bases, and solvents, we initiated our preliminary studies by selecting phenylboronic acids and KCN under non-radioactive conditions. After a survey of copper catalysts, we found that CuI and CuBr outperformed $Cu_2O$ and $Cu(OTf)_2$ in cyanation reactions (Table 1, entries 1–4). When 0.55 equiv. of the CuI catalyst was added to the reaction mixture, 13% and 36% cyanated products were obtained for *para*-Br- and *para*-OMe-phenylboronic acids, respectively (Table 1, entries 1 and 16). Further increasing the temperature did not improve the yield within the 1 hour reaction window (Table 1, entry 5). The presence of bases such as $n$Bu$_4$NOH was essential to this transformation (Table 1, entry 6); therefore, we evaluated a variety of inorganic and organic bases. We found that $K_2CO_3$ and $Et_3N$ were both ineffective for CuI catalyzed reactions. However, NaOH and $Cs_2CO_3$ promoted the reaction and yielded 13% and 18% desired aryl nitrile, respectively (Table 1, entries 7–10). We next screened different solvents and found DMF to be the optimal solvent for this model reaction (Table 1, entries 11–14). It is noteworthy that when a DMF/water mixture was used, a nearly identical yield of the cyanated product was observed (Table 1, entry 15). The use of the DMF/water mixture as the solvent was beneficial to the development of our $^{11}$C-cyanation reaction, because with increased $Cs_2CO_3$ solubility in aqueous solution, we were able to carry out the trapping of [$^{11}$C]HCN gas in a basic solution of $Cs_2CO_3$ directly.

Aromatic $^{11}$C-cyanation was optimized using **1a** as the model substrate. A 1 : 2 ratio (mass ratio) of a CuI : **1a** mixture was reacted with [$^{11}$C]HCN/[$^{11}$C]CsCN trapped in a solution of $Cs_2CO_3$ in a 3 : 1 DMF/water (v/v) mixture at 120 °C for 5 min. A 13% radiochemical conversion (RCC) of **2a** was determined by radioTLC (Table 2, entry 1). Increasing the loading of the CuI catalyst (Table 2, entries 2 and 3) did not affect the RCC of **2a**. However, by elevating the reaction temperature from 120 °C to 150 °C, the RCC of **2a** was increased to 22% (Table 2, entry 4). The amount of the boronic acid substrate was also found to influence the reaction outcome (Table 2, entry 5) and a 37% RCC was achieved when the substrate loading was doubled. Further increasing the quantity of the boronic acid substrate was expected to lead to insoluble materials given the limited amount of the solvent (200 μL) under the present conditions; therefore, we varied alternative parameters to further improve the yield. For example, when the amount of $Cs_2CO_3$ was doubled from 4 mg to 8 mg, a significant increase of RCC from 37% to 61% was achieved (Table 2, entry 6). Shorter reaction times were apparently not sufficient for a satisfactory RCC (Table 2, entries 7 and 8). Lastly, a variety of copper ligands were tested and DMEDA was shown to benefit the radiochemical transformation by further improving the RCC to 65% (Table 2, entries 9–13). In addition, we found that an additional amount of $Cs_2CO_3$ increased the RCC to 70% (Table 2, entry 14). This experimentation led us to determine the optimal molar ratio for the reactants as follows: 1 : 5 : 4.5 : 4 for CuI/boronic acid/$Cs_2CO_3$/DMEDA.

Arylboronic acids with different functional groups were reacted with [$^{11}$C]HCN/[$^{11}$C]CsCN under the optimized conditions established in Table 2 to explore the substrate scope of this transformation. Substrates bearing electron-donating groups such as methoxy and phenyl groups on the *para*-position gave rise to the desired products in good RCCs (Fig. 2, **2a** and **2b**), making this method complementary to existing $S_NAr$ methods where electron-withdrawing groups are necessary to activate the aromatic ring. However, 2,4,6-trimethlyphenyl boronic acid is less reactive and afforded an

Table 1 Preliminary screening of aromatic cyanation

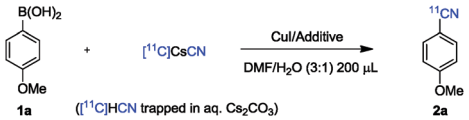



| Entry | R | Base | Cu catalyst | Solvent | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | Br | $n$Bu$_4$NOH | CuI | DMF | 13 |
| 2 | Br | $n$Bu$_4$NOH | CuBr | DMF | 12 |
| 3 | Br | $n$Bu$_4$NOH | $Cu_2O$ | DMF | Not observed |
| 4 | Br | $n$Bu$_4$NOH | $Cu(OTf)_2$ | DMF | Not observed |
| 5[b] | Br | $n$Bu$_4$NOH | CuI | DMF | 11 |
| 6 | Br | None | CuI | DMF | Trace |
| 7 | Br | NaOH | CuI | DMF | 13 |
| 8 | Br | $Et_3N$ | CuI | DMF | Not observed |
| 9 | Br | $K_2CO_3$ | CuI | DMF | Not observed |
| 10 | Br | $Cs_2CO_3$ | CuI | DMF | 18 |
| 11 | Br | $Cs_2CO_3$ | CuI | 1,4-Dioxane | Not observed |
| 12 | Br | $Cs_2CO_3$ | CuI | MeCN | Not observed[c] |
| 13 | Br | $Cs_2CO_3$ | CuI | DMA | 9 |
| 14 | Br | $Cs_2CO_3$ | CuI | DMSO | 4 |
| 15 | Br | $Cs_2CO_3$ | CuI | DMF : $H_2O$ = 1 : 1 | 18 |
| 16 | OMe | $n$Bu$_4$NOH | CuI | DMF | 36 |
| 17 | OMe | $Cs_2CO_3$ | CuI | DMF | 33 |
| 18 | OMe | $Cs_2CO_3$ | CuI | DMF : $H_2O$ = 1 : 1 | 36 |

[a] The reactions were carried out at 60 °C and stopped at 1 h; isolated yields are reported. [b] The reaction was carried out at 90 °C. [c] The desired cyanated product was not observed, but the homocoupling product of the boronic acid was isolated instead.

Table 2 Optimization of aromatic $^{11}$C-cyanation of boronic acids




| Entry | CuI (mg) | *p*MeOPhB(OH)$_2$ (mg) | $Cs_2CO_3$ (mg) | Additive | $T$ (°C) | Time (min) | RCC[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 2 | 4 | None | 120 | 5 | 13 |
| 2 | 2 | 2 | 4 | None | 120 | 5 | 13 |
| 3 | 4 | 2 | 4 | None | 120 | 5 | 10 |
| 4 | 1 | 2 | 4 | None | 150 | 5 | 22 |
| 5 | 1 | 4 | 4 | None | 150 | 5 | 37 |
| 6 | 1 | 4 | 8 | None | 150 | 5 | 61 |
| 7 | 1 | 4 | 8 | None | 150 | 1 | 13 |
| 3 | 1 | 4 | 8 | None | 150 | 3 | 23 |
| 9 | 1 | 4 | 8 | Pyridine (2 μL) | 150 | 5 | 24 |
| 10 | 1 | 4 | 8 | 1,10-Phenanthroline (2 mg) | 150 | 5 | 64 |
| 11 | 1 | 4 | 8 | Bis-pyridine (2 μL) | 150 | 5 | 37 |
| 12 | 1 | 4 | 8 | TMEDA[b] (2 μL) | 150 | 5 | 45 |
| 13 | 1 | 4 | 8 | DMEDA[c] (2 μL) | 150 | 5 | 65 |
| **14**[d] | **1** | **4** | **16** | **DMEDA (2 μL)** | **150** | **5** | **70** |

[a] Radiochemical conversion and product identity were determined by radioTLC and radioHPLC, respectively. [b] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. [c] DMEDA = *N*,*N*′-dimethylethylenediamine. [d] Molar ratio for the optimal reaction conditions: CuI (5.25 μmol): boronic acid (26 μmol): $Cs_2CO_3$ (24 μmol): DMEDA (19 μmol) = 1 : 5 : 4.5 : 4.

8% RCC (Fig. 2, **2c**). This is possibly due to steric hindrance exerted by the *ortho*-substituents. Parent phenylboronic acid and substrates bearing electron-withdrawing groups on the *para*-position were less favored and showed moderate RCCs ranging from 34 to 50% (Fig. 2, **2d–2g**). We were pleased to see halogen-substituted arylboronic acid afforded a good RCC of the corresponding nitrile (Fig. 2, **2e**), a significant advantage over the Pd-catalyzed methods (*i.e.*, a multi-halogen bearing precursor utilized with the Pd-catalyzed method would raise regioselectivity concerns). Furthermore, *meta*-substituents on the phenyl ring are well tolerated with the radiochemical conditions established herein. Substrates bearing *meta*-amino and *meta*-$CF_3$ groups both proceed smoothly to afford the $^{11}$C-cyanated product (Fig. 2, **2h** and **2i**). Under our reaction conditions, the unprotected benzamide and aniline (Fig. 2, **2g** and **2h**) did not interfere with the copper-mediated transformation. This observation holds true for heteroaromatic boronic acid substrates as well. Pyridine-3-boronic acid produced [$^{11}$C]3-pyridine nitrile with good conversion (Fig. 2, **2j**; >50% RCC). Both quinoline and furan based boronic acids are radiolabeled with $^{11}$C-cyanide, albeit in lower RCCs (Fig. 2, **2k** and **2i**). As proof-of-concept, we selected **1a** as the substrate and carried out the radiosynthesis and isolation of **2a**. A slightly modified procedure using the reaction mixture (DMF/water) as the [$^{11}$C]HCN trapping solution was adopted in order to improve the operational-simplicity (see the ESI†). We isolated 0.455 GBq (12.3 mCi) of **2a**, after semi-preparative HPLC purification which resulted in an RCY of 4.2% ($n$ = 2, non-decay corrected, relative to starting [$^{11}$C]HCN) and the specific activity was determined to be 16 GBq μmol$^{-1}$ (433 mCi μmol$^{-1}$) with a total synthesis time of 26 min.

The mechanism of the [$^{11}$C]cyanation of arylboronic acids is proposed as follows: CuI underwent ligand exchange with $^{11}$C-cyanide in the presence of the ligand to afford Cu(I) intermediate **3**. Intermediate **3** was subsequently converted into Cu(III) intermediate **4** under aerobic oxidative conditions. Intermediate **4** participated in a transmetallation reaction with the borate complex to give rise to intermediate **5**. After reductive elimination, cyanated product **2d** was formed and Cu(I) species were regenerated to complete the catalytic cycle (Scheme 1).

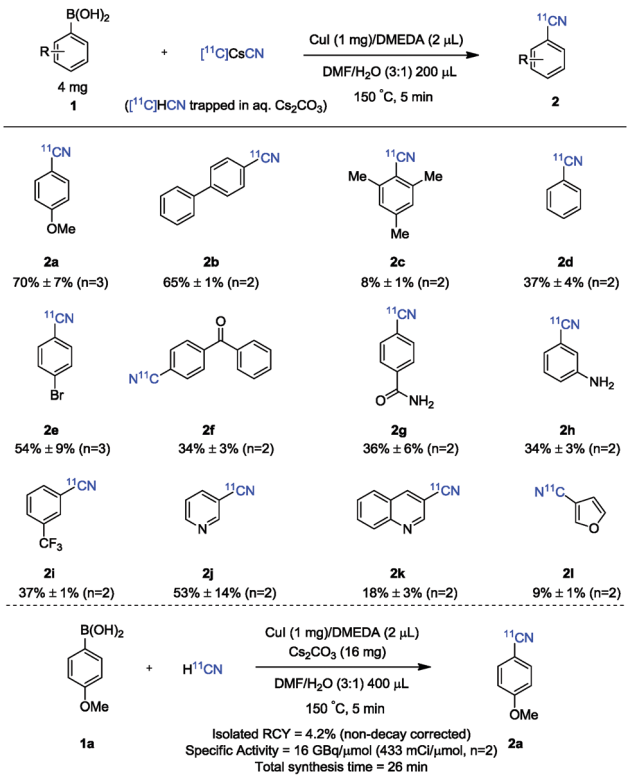
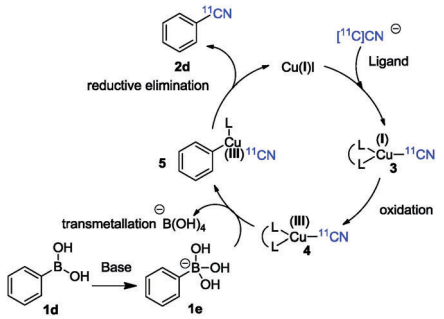



Fig. 2 Substrate scope of the $^{11}$C-aromatic cyanation reactions.




Scheme 1 Proposed mechanism for copper-mediated $^{11}$C-aromatic cyanation.

In conclusion, we have developed a copper-mediated $^{11}$C-aromatic cyanation reaction using readily available boronic acids in aqueous solutions. This method is applicable to a broad range of arylboronic acids and complementary to existing methods for $^{11}$C-aromatic cyanation. Carbon-11 labeled **2a** was synthesized and isolated using this approach as proof-of-concept. Efforts towards improving the specific activity and application of this method to the synthesis of other $^{11}$CN-labeled radiotracers are underway.

## Notes and references

1 S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.*, 2008, **108**, 1501–1516.
2 D. Jolly, R. Hopewell, M. Kovacevic, Q. Y. Li, J.-P. Soucy and A. Kostikov, *Appl. Radiat. Isot.*, 2017, **121**, 76–81.
3 P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem., Int. Ed.*, 2008, **47**, 8998–9033.
4 B. Långström and H. Lundqvist, *Int. J. Appl. Radiat. Isot.*, 1976, **27**, 357–363.
5 D. Comar, C. Crouzel and M. Maziere, International Atomic Energy Agency, Vienna (Austria); World Health Organization, Geneva (Switzerland); Proceedings series; 1973, pp. 461–469.
6 K. Någren, C. Halldin, L. Müller, C.-G. Swahn and P. Lehikoinen, *Nucl. Med. Biol.*, 1995, **22**, 965–970.
7 R. Iwata, T. Ido, T. Takahashi, H. Nakanishi and S. Iida, International Journal of Radiation Applications and Instrumentation, *Part A. Appl. Radiat. Isot.*, 1987, **38**, 97–102.
8 P. Landais and C. Crouzel, *Int. J. Rad. Appl. Instrum. Part A. Appl. Radiat. Isot.*, 1987, **38**, 297–300.
9 J. M. Hooker, M. Schönberger, H. Schieferstein and J. S. Fowler, *Angew. Chem., Int. Ed.*, 2008, **47**, 5989–5992.
10 J. M. Hooker, A. T. Reibel, S. M. Hill, M. J. Schueller and J. S. Fowler, *Angew. Chem., Int. Ed.*, 2009, **48**, 3482–3485.
11 T. L. Andersen, S. D. Friis, H. l. n. Audrain, P. Nordeman, G. Antoni and T. Skrydstrup, *J. Am. Chem. Soc.*, 2015, **137**, 1548–1555.
12 T. Haywood, S. Kealey, S. Sánchez-Cabezas, J. J. Hall, L. Allott, G. Smith, C. Plisson and P. W. Miller, *Chem. – Eur. J.*, 2015, **21**, 9034–9038.
13 B. H. Rotstein, S. H. Liang, J. P. Holland, T. L. Collier, J. M. Hooker, A. A. Wilson and N. Vasdev, *Chem. Commun.*, 2013, **49**, 5621–5629.
14 S. H. Liang and N. Vasdev, *Aust. J. Chem.*, 2015, **68**, 1319–1328.
15 B. H. Rotstein, S. H. Liang, M. S. Placzek, J. M. Hooker, A. D. Gee, F. Dollé, A. A. Wilson and N. Vasdev, *Chem. Soc. Rev.*, 2016, **45**, 4708–4726.
16 P. J. H. Scott, *Angew. Chem., Int. Ed.*, 2009, **48**, 6001–6004.
17 N. Gillings and A. Gee, *J. Labelled Compd. Radiopharm.*, 2001, **44**, 909–920.
18 A. R. Studenov, D. E. Szalda and Y.-S. Ding, *Nucl. Med. Biol.*, 2003, **30**, 39–44.
19 J. A. Balatoni, M. J. Adam and L. D. Hall, *J. Labelled Compd. Radiopharm.*, 1989, **27**, 1429–1435.
20 Y. Andersson and B. Långström, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1395–1400.
21 H. G. Lee, P. J. Milner, M. S. Placzek, S. L. Buchwald and J. M. Hooker, *J. Am. Chem. Soc.*, 2015, **137**, 648–651.
22 A. J. Airaksinen, J. Andersson, P. Truong, O. Karlsson and C. Halldin, *J. Labelled Compd. Radiopharm.*, 2008, **51**, 1–5.
23 I. Bennacef, C. A. Salinas, T. A. Bonasera, R. N. Gunn, H. Audrain, S. Jakobsen, N. Nabulsi, D. Weinzimmer, R. E. Carson and Y. Huang, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5056–5059.
24 W. B. Mathews, J. A. Monn, H. T. Ravert, D. P. Holt, D. D. Schoepp and R. F. Dannals, *J. Labelled Compd. Radiopharm.*, 2006, **49**, 829–834.
25 J. Sandell, C. Halldin, H. Hall, S.-O. Thorberg, T. Werner, D. Sohn, G. Sedvall and L. Farde, *Nucl. Med. Bio.*, 1999, **26**, 159–164.
26 M. Ponchant, F. Hinnen, S. Demphel and C. Crouzel, *Appl. Radiat. Isot.*, 1997, **48**, 755–762.
27 H. Yang, Y. Li, M. Jiang, J. Wang and H. Fu, *Chem. – Eur. J.*, 2011, **17**, 5652–5660.
28 G. Zhang, L. Zhang, M. Hu and J. Cheng, *Adv. Synth. Catal.*, 2011, **353**, 291–294.
29 K. Sanjeeva Rao and T.-S. Wu, *Tetrahedron*, 2012, **68**, 7735–7754.
30 P. J. Riss, S. Lu, S. Telu, F. I. Aigbirhro and V. W. Pike, *Angew. Chem., Int. Ed.*, 2012, **51**, 2698–2702.
31 B. H. Rotstein, J. M. Hooker, J. Woo, T. L. Collier, T. J. Brady, S. H. Liang and N. Vasdev, *ACS Med. Chem. Lett.*, 2014, **5**, 668–672.
32 A. V. Mossine, A. F. Brooks, K. J. Makaravage, J. M. Miller, N. Ichiishi, M. S. Sanford and P. J. Scott, *Org. Lett.*, 2015, **17**, 5780.
33 S. Preshlock, S. Calderwood, S. Verhoog, M. Tredwell, M. Huiban, A. Hienzsch, S. Gruber, T. C. Wilson, N. J. Taylor and T. Cailly, *Chem. Commun.*, 2016, **52**, 8361–8364.
34 P. Zhang, R. Zhuang, Z. Guo, X. Su, X. Chen and X. Zhang, *Chem. – Eur. J.*, 2016, **22**, 16783–16786.
35 T. C. Wilson, G. McSweeney, S. Preshlock, S. Verhoog, M. Tredwell, T. Cailly and V. Gouverneur, *Chem. Commun.*, 2016, **52**, 13277–13280.
36 J. Qiao, P. Lam and D. Hall, *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, Wiley, 2011.

