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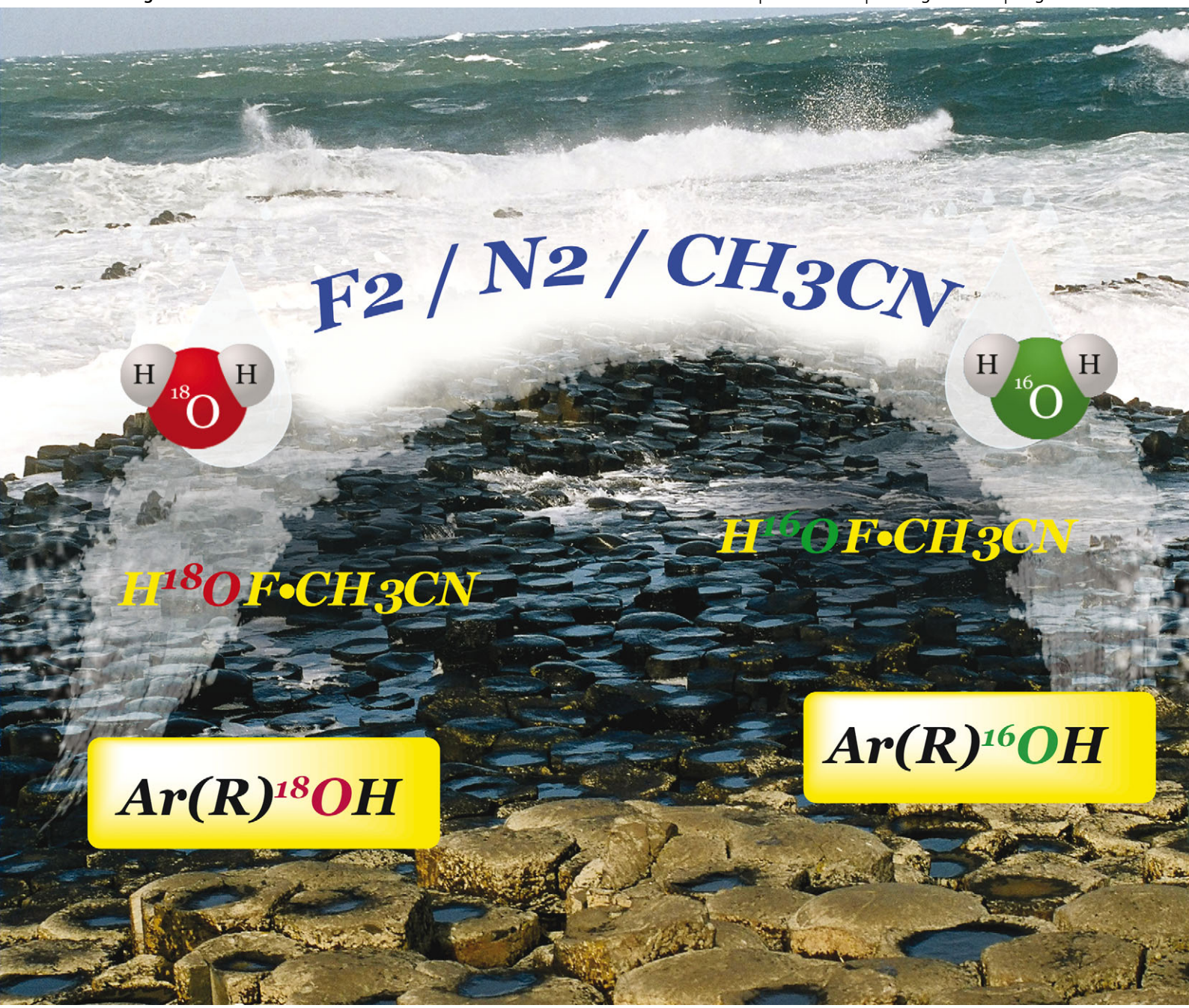


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# The first general route for efficient synthesis of $^{18}O$ labelled alcohols using the HOF·$CH_3CN$ complex†

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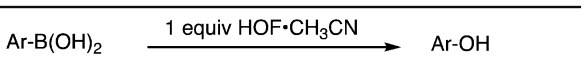
**A mild and very efficient method for converting boronic acids to alcohols has been developed using the acetonitrile complex of hypofluorous acid HOF·$CH_3CN$. Employing $^{18}O$-labeled water results in alcohols containing a heavy oxygen isotope. The reactions were performed at room temperature, within a few minutes and in excellent yields.**

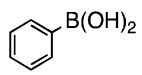
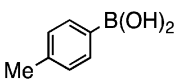
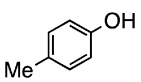
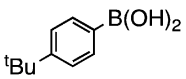
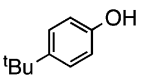
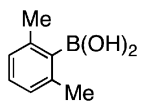
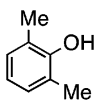
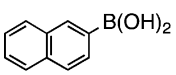
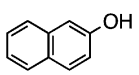
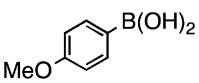
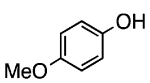
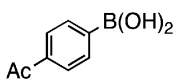
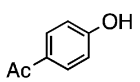
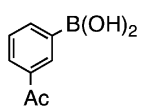
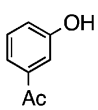
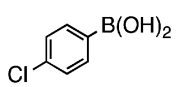
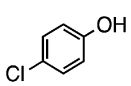
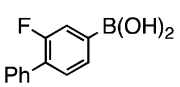
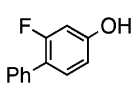
Phenols are ubiquitous in medicinal and natural product chemistry whereas the hydroxyl function is essential in numerous aromatic ring functionalizations as well as in biological activities.[1] Despite their importance, classical phenolation methods, which include various nucleophilic aromatic substitutions of aryl halides, can be limited by the harsh reaction conditions required for non-activated substrates which may cause incompatibility with sensitive functions.[2] Needless to say, numerous aliphatic and alicyclic alcohols also play very important roles in natural and synthetic organic chemistry. Labeling all these alcohols with the heavy $^{18}O$ isotope can be very useful in tracking their fate in living cells.

Aromatic boronic acids are readily available either commercially or through the corresponding halides and have found broad applications in synthetic chemistry. Several procedures for hydroxylation of arylboronic acids using transition metal catalysts or a copper/strong base combination have recently been introduced, providing mild and efficient access to phenols.[3,4] A base free or palladium-catalyzed environment was developed as well.[5] As the pharmaceutical industry prefers metal free processes, aromatic hydroxylation *via* hydrogen peroxide,[6] oxone[7] and *N*-oxides was also developed.[8] It should be pointed out that none of those methods is suitable for introducing the heavy $^{18}O$ isotope in the aromatic hydroxyl function.

The hydroxylation with alkylboronic acids is less accessible as only two or three works deal with their conversion to alcohols. An old paper describes the transformation of very few alkylboronic acids with 30% $H_2O_2$ using a quite cumbersome procedure, which the authors admit is mainly suitable for

**Table 1** Hydroxylation of arylboronic acids




| | Substrate (**1**) | Product (**2**) | Yield (%) |
|---|---|---|---|
| **a** |  |  | 95 |
| **b** |  |  | >95 |
| **c** |  |  | >95 |
| **d** |  |  | 92 |
| **e** |  |  | 90 |
| **f** |  |  | 93 |
| **g** |  |  | >95 |
| **h** |  |  | >95 |
| **i** |  |  | >95 |
| **j** |  |  | 90 |

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† Electronic supplementary information (ESI) available: Working with $F_2$ and HOF·$CH_3CN$ including the synthesis of alcohols with the $^{18}O$ isotope is described. Preparation and characterisation of all alcohols is presented. See DOI: 10.1039/c3cc42337a

liquid materials such as propanol and butanol.[9] A recent work describes the conversion of cyclohexylboronic acid (the only non-aromatic example in this paper) to cyclohexanol in 60% yield by an electrochemical method.[10] Another procedure made use of oxone as an oxidant, but the starting materials were the trifluoroborates, R-$BF_3K$,[11] imposing an additional synthetic step since they are usually prepared from the corresponding boronic acids. Here again, it should be pointed out that none of the above methods is suitable for synthesizing alcohols with the heavy $^{18}O$ isotope.

Alcohols labeled with $^{18}O$ are very valuable as biological probes for a variety of studies which are often limited by the availability of labeled precursors for the preparation of the compounds of interest. Low oxygen-18 enrichment of phenols by an isotopic exchange reaction under drastic conditions has been reported.[12] Using the prohibitively expensive $^{18}O_2$ was also reported for phenols.[13] Some specific compounds bearing an aromatic nitro group undergo exchange of the phenolic oxygen atom with $^{18}O$-labeled water in basic solution.[14] As a matter of fact there is no good general method available for obtaining $^{18}O$ containing alcohols.

The HOF·$CH_3CN$ complex is one of the several reagents produced from $F_2$. By itself fluorine has been used to activate remote tertiary CH bonds,[15] while trifluoroacetyl hypofluorite and acetyl hypofluorite, $CF_3COOF$ and $CH_3COOF$, two secondary reagents, were employed for various fluorination processes.[16] Elemental fluorine is also the source of reagents leading to fluorine free products, the unique MeOF[17] and IF[18] being only two examples. The most useful reagent, however, was found to be the HOF·$CH_3CN$ complex, easily prepared by bubbling dilute fluorine through aqueous acetonitrile,[19] and which is considered to be one of the best oxygen transfer agents in chemistry today.[20] Unlike all other oxygen transfer reagents, HOF·$CH_3CN$ is a unique source of a permanent electrophilic oxygen species since it is bound to the only atom more electronegative than itself – fluorine. This facilitates the transfer of the oxygen atom to most nucleophilic sites under mild conditions (*e.g.*, room temperature and reaction times of seconds or minutes).

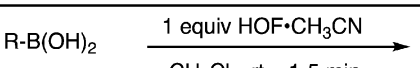
The present study offers easy and convenient access to both aromatic and aliphatic alcohols *via* readily performed, high yield and fast reactions between any boronic acid and HOF·$CH_3CN$. The same procedure leads to oxygen-18 labeled alcohols by using the most readily available source of this isotope, namely $H_2{}^{18}O$, which is used for producing $H^{18}OF{\cdot}CH_3CN$ in very good yield based on the $H_2{}^{18}O$ used.

Hydroxylations with the HOF·$CH_3CN$ complex were applied to a wide selection of aromatic and aliphatic boronic acids forming the corresponding alcohols in a few seconds to a few minutes in almost quantitative yields. Tables 1 and 2 summarize these results.

Reacting phenylboronic acid (**1a**) with HOF·$CH_3CN$ at room temperature produced the corresponding phenol (**2a**) in a few seconds and in 95% yield. Similar results were observed with *p*-tolylboronic acid (**1b**) and *p-t*-butylphenylboronic acid (**1c**), which are converted to the corresponding phenols **2b** and **2c** in quantitative yields. The reaction provided excellent yields also for substrates containing *meta* or *ortho* substituents as in 2,6-dimethylphenylboronic acid (**1d**) and 2-naphthylboronic acid (**1e**), which are transformed into 2,6-dimethylphenol (**2d**) and 2-naphthol (**2e**). Electron-donating or withdrawing groups on the aromatic ring did not affect the efficiency of the reaction. 4-Methoxyphenol (**2f**), 4-hydroxyacetophenone (**2g**) and 3-hydroxyacetophenone (**2h**) were obtained from the corresponding boronic acids **1f**, **1g** and **1h** in a few seconds in 93%, >95% and >95% yields, respectively. Halogenated boronic acids **1i** and **1j** also provide the corresponding phenols in excellent yields (Table 1).

With aliphatic and alicyclic alcohols the picture is similar. 2-Methylpropylboronic acid (**3a**) was converted to 2-methyl-

**Table 2** Hydroxylation of alkylboronic acids




**3** **4**

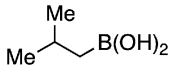
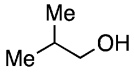
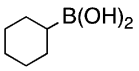
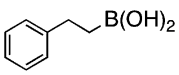
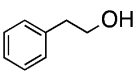
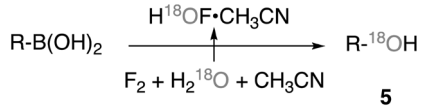
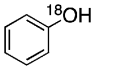
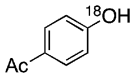
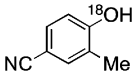
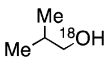
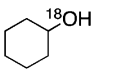
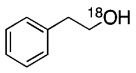
| | Substrate (**3**) | Product (**4**) | Yield (%) |
|---|---|---|---|
| **a** |  |  | 80 |
| **b** |  |  | 90 |
| **c** |  |  | 92 |
| **d** | $Br(CH_2)_6B(OH)_2$ | $Br(CH_2)_6OH$ | 93 |

**Table 3** Synthesis of oxygen-18 labeled alcohols




**5**

| | Product (**5**) | MS $m/z$[a] |
|---|---|---|
| **a** |  | Calcd. for $C_6H_5{}^{18}O$: 95.0383<br>[M−H]-found: 95.0384 |
| **b** |  | Calcd. for $C_8H_7{}^{16}O^{18}O$: 137.0483<br>[M−H]-found: 137.0487 |
| **c** |  | Calcd. for $C_8H_6N^{18}O$: 134.0492<br>[M−H]-found: 134.0499 |
| **d** |  | Calcd. for $C_4H_{10}{}^{18}O$: 76.1<br>[M−H]-found: 76.1 |
| **e** |  | Calcd. for $C_6H_{12}{}^{18}O$: 102.1<br>[M−H]-found: 102.1 |
| **f** |  | Calcd. for $C_8H_{10}{}^{18}O$: 124.1<br>[M−H]-found: 124.1 |
| **g** | $Br(CH_2)_6{}^{18}OH$ | Calcd. for $C_6H_{14}Br^{18}O$: 183.0<br>[M−H]-found: 183.1 |

[a] HRMS of phenols was measured under ESI (negative mode) conditions. MS of aliphatic alcohols was measured *via* a methanol cluster-based chemical ionization method through a supersonic molecular beam interface.[21]

propanol (**4a**) in 80% isolated yield. The yield of the less volatile cyclohexanol (**4b**) obtained from cyclohexylboronic acid (**3b**) was 90% and the 2-phenylethylboronic acid (**3c**) produced 2-phenylethanol (**4c**) in higher than 90% yield. The reaction is tolerant of halogens as evident from the reaction of 6-bromohexylboronic acid (**3d**) which upon treatment with $HOF{\cdot}CH_3CN$ resulted in 6-bromohexanol (**4d**) (Table 2).

As stated above, the origin of the electrophilic oxygen in the $HOF{\cdot}CH_3CN$ complex is water. This allowed us to prepare any alcohol we wished, be it aromatic (**5a–5c**) or aliphatic (**5d–5g**), with the $^{18}O$ isotope using $H^{18}OF{\cdot}CH_3CN$ prepared readily by bubbling dilute $F_2$ through acetonitrile and $H_2{}^{18}O$. When this labeled reagent was reacted with a variety of boronic acids it produced the corresponding oxygen-18 labeled alcohols with identical yields to the reactions with the oxygen-16 isotope. MS of the final product indicates the expected isotopic enrichment (Table 3). It should be noted that although during the reaction the solution is somewhat acidic (HF is released when $F_2$ reacts with water) the hydroxylic $^{18}O$ was not exchanged with the common $^{16}O$ found in air and water even after several days.

In conclusion, this work offers for the first time a general route for producing various alcohols, and in particular $^{18}O$ labelled alcohols. It is done with the help of dilute fluorine (10% $F_2$ in $N_2$) which, for example, is much less dangerous and easier to work with than chlorine (it is less toxic than $Cl_2$ (ref. 22)). Diluted fluorine is commercially available, requiring a simple soda-lime trap at the reaction outlet, or technical (>95%) $F_2$ could be diluted on the spot to whatever degree desired by using a simple vacuum line.[23]

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