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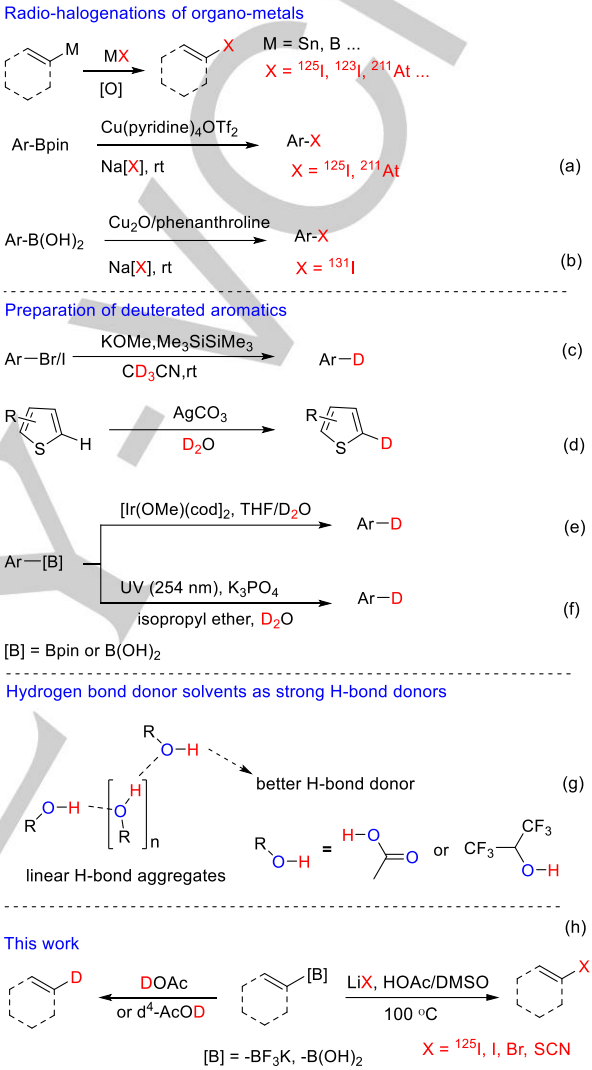
Hydrogen Bond Donor Solvents Enabled Catalyst-free (Radio)-Halogenation and Deuteration of Organoborons

Yi Yang,[a] Xinyan Gao,[b] Xiaojun Zeng,[a] Junbin Han,[b,*] Bo Xu[a,*]

Abstract: A hydrogen bond donor solvent assisted (radio)halogenation and deuteration of organoborons has been developed. The reactions exhibited high functional group tolerance and needed only an ambient atmosphere. Most importantly, compared to literature methods, our conditions are more consistent with the principals of green chemistry (e.g., metal-free, strong oxidant-free, more straightforward conditions).

Aromatic halides are one of the most important targets and also building blocks in synthesis.[1] However, their synthesis[2] are often based on the use of hazardous reagents (e.g., Cl_2, Br_2) or low atom-economy reagents (e.g., N-halo-succinimide).[3] More specifically, the radio-tracers containing radio-active halogens (e.g., ^{18}F, ^{76}Br, ^{82}Br, ^{131}I, ^{125}I, ^{211}At) play an essential role in the diagnosis and treatment of diseases such as tumor and nervous system degenerative diseases.[4][5] Radioiododestannylation and radio-iododeboronation are two commonly used radio-halogenation methods.[6] Notable examples include Makvandi and Mach's Cu-catalyzed radio-iodination of boronic esters (Scheme 1a)[7] and Chen and Zhang's Cu-mediated radioiodination of aryl boronic acids (Scheme 1b).[8] Although these methods are often very efficient, the use of strong oxidizing agents (e.g., Chloramine T) or a transition metal (e.g., $CuOTf_2$) might be problematic for the synthesis target molecular containing sensitive functional groups.

Similar to radio-active halogens labeled compounds, deuterium isotope-labeled compounds are also widely used in pharmaceutical chemistry.[9] Deuterium-substituted drugs have specific effects on improving pharmacokinetics and reducing toxic metabolism.[10] As a result, many efficient deuterium incorporation methods have been developed.[11] For example, Peris and coworkers reported an effective method of hydrogen-deuterium exchange using Cp^*IrCl_2(NHC) as the catalyst (NHC = N-Heterocyclic carbene).[12] Hlavac and coworkers reported an efficient transformation of aromatic amines to deuterium using sodium nitrite.[13] Liu and coworkers developed a deuterium-substituted reaction using CD_3CN as a deuterium reagent (Scheme 1c).[14] Recently, Huang and coworkers reported an Ag_2CO_3-catalyzed hydrogen isotope exchange reaction of heterocyclic aromatics (Scheme 1d).[15]



Scheme 1. Literature background.

Because aryl boronic acids and corresponding derivatives are readily available and both base or acid-promoted protodeboronation of arylboronic acids and esters have been reported,[16] their deboronative–deuteration is a straightforward method for the preparation of deuterated compounds. Notable examples include Ir-catalyzed deuteration of arylboronic esters with THF and D_2O (Scheme 1e)[17] and UV light-induced deboronation–deuteration of arylboronic acids with D_2O (Scheme 1f).[18] These above deuteration methods are often very efficient; however, strong bases, transition metals, or UV light, and relatively complex conditions are still needed in general.

Self-association of hydrogen bond donor solvent (e.g., hexafluoroisopropanol or acetic acid) molecular will lead to the

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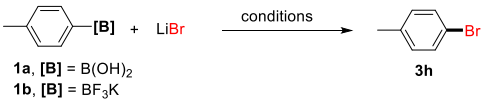
formation of linear aggregates at high concentrations, which are better hydrogen bond donors than monomers and cyclic hydrogen bond aggregates.[19] This high hydrogen-bond acidity could enable reactions that typically need strong Brønsted acids or Lewis acids. For example, we have developed hydrogen-bond donor solvents (e.g., HFIP, acetic acid) [20] enabled (radio)hydrofluorination of ynamides,[21] hydrofluorinations of alkenes,[22] addition of sulfonic acids to haloalkynes,[23] catalyst-free Friedel–Crafts acylations[24] and gold-catalyzed hydrochlorination of alkynes.[25] We envisioned that high hydrogen bond acidity might activate green and mild oxidants such as DMSO[26] for halo-deboronation (Scheme 1g). It could be a straightforward method for the production of high specific activity SPECT (single-photon emission computed tomography) imaging applications. In addition, the high hydrogen bond acidity could be used for deboronative–deuteration using the readily available d^1-AcOD or d^4-AcOD as deuteration reagents (Scheme 1g). Compared to literature methods, our conditions are more consistent with the principals of green chemistry [27](e.g., metal-free, strong oxidant-free, more straightforward conditions).

Table 1. Optimization of the reaction conditions.[a]



1a, **[B]** = $B(OH)_2$
1b, **[B]** = BF_3K

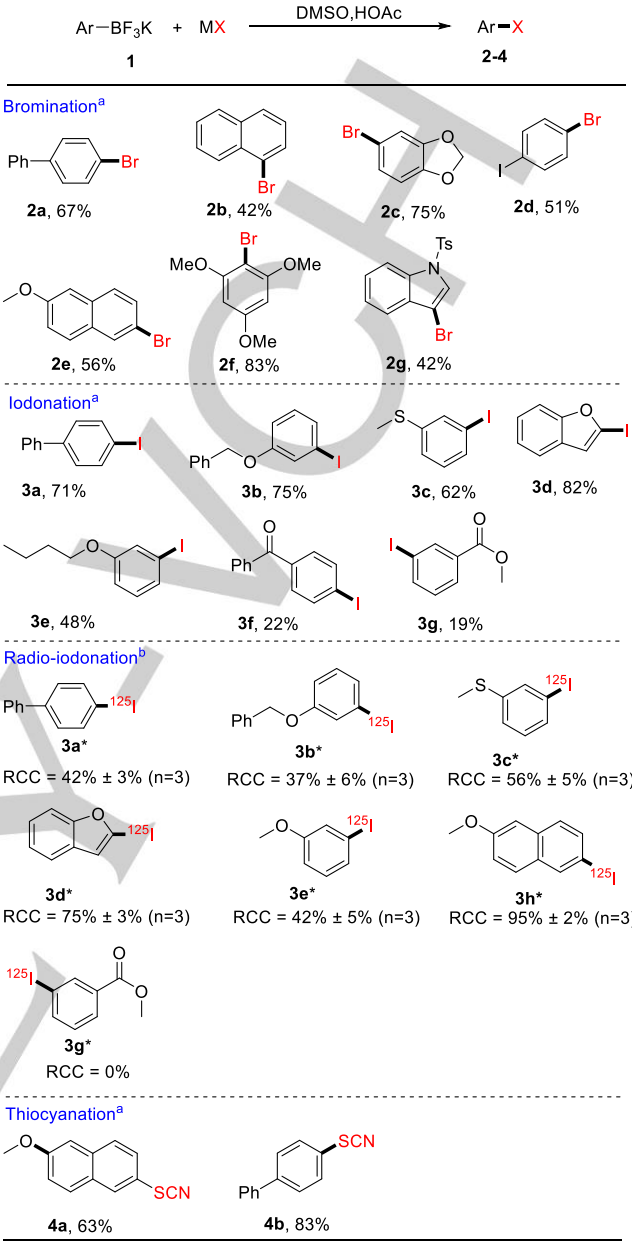
3h

Entry	**1**	DMSO (mL)	Co-solvent (mL)	Temp/°C	**3h**/%[b]
1	**1a**	0.4	HOAc (0.4)	100	38
2	**1a**	0.4	DCM (0.4)	100	14
3	**1a**	0.4	CH_3CN (0.4)	100	<5
4	**1a**	0.4	dioxane (0.4)	100	<5
5	**1b**	0.4	HOAc (0.4)	100	99
6	**1b**	0.4	HOAc (0.4)	80	76
7	**1b**	0.4	HOAc (0.4)	50	54
8	**1b**	0.4	HOAc (0.4)	25	41
9	**1b**	0.2	HFIP (0.6)	25	93
10[c]	**1b**	-	HOAc (0.8)	100	0

[a] Conditions: **1** (0.2mmol), LiBr (0.8 mmol), DMSO (0.4 mL), HOAc (0.4 mL), 100 °C, 8 h. [b] Yields were determined by GC analysis. [c] No DMSO was used.

The bromination of organoborons **1a** and **1b** served as our model reactions for methodology development (Table 1). Using DMSO as the oxidant, hydrogen bond donor solvent AcOH gave the best results compared to other solvent systems such as DCM, CH_3CN, and dioxane (Table 1, entries 1-4). We were glad to observe nearly quantitative when $ArBF_3K$ **1b** was used instead of $ArB(OH)_2$ **1a** (Table 1, entry 5). At lower temperatures, the reaction became sluggish (Table 1, entries 6-8). Hydrogen bond donor solvent – HFIP also gave good results (Table 1, entry 9) at a lower temperature. In the absence of oxidant – DMSO, the reaction did not proceed (Table 1, entry 10). We think that DMSO functions as a mild oxidant as it does in Kornblum oxidation, Pfitzner-Moffatt oxidation, or Swern Oxidation.

Table 2. The substrate scope.[a]



[a] Reaction conditions: **1** (0.2 mmol), MX (LiBr, LiI, NaSCN) (0.8 mmol), DMSO (0.4 mL), HOAc (0.4 mL), 100 °C, 8 h. All yields are isolated yields. [b] $Na^{125}I$ aqueous solution was used for radio-iodonations, please see SI for detailed conditions for radio-iodonations.

With the optimized conditions in hand, we explored the substrate scope of this new methodology (Table 2). First, we investigated the reaction of bromo-deboronation (Table 2, **2a**-**2g**). Good to moderate yields of bromide products were obtained. We also evaluated the substrate scope of iodo-deboronation (Table 2, **3a-3g**). In general, the reaction worked well for electron-rich substrates (Table 2, **3a-3e**). Moreover, for aryl $ArBF_3K$ substituted with electron-withdrawing groups such as ketone, ester (Table 2, **3f-3g**), more reduced yields were obtained.

We are glad to find that this transition-metal-free and strong oxidant-free conditions could be used for radio-iodonations (Table 2, **3a*-3g***). When $Na^{125}I$ aqueous solution was used as the radio-

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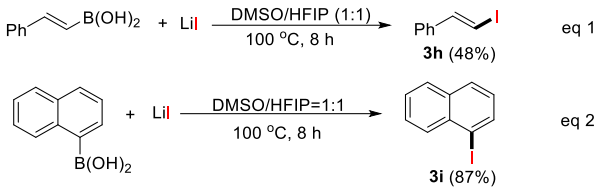
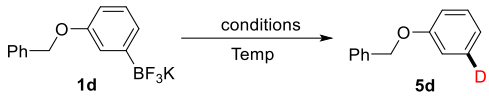
active iodine source, good radiochemistry conversion of starting materials were obtained. Similarly, this protocol did not work well for electron-deficient substrates. To our delight, our conditions even worked beyond halogenations. For example, the same protocol could be applied to thiocyanation (Table 3, **4a**-**4b**).



Our iodo-deboronation conditions only gave low yields of the products when less reactive organoboronic acids were uased as the starting materials. After optimizations, we found the yields could be improved by replacing the acetic acid solvent with a stronger hydrogen bond donor solvent - HFIP (eqs 1-2).

Table 3. Optimization of the deuteration reaction.

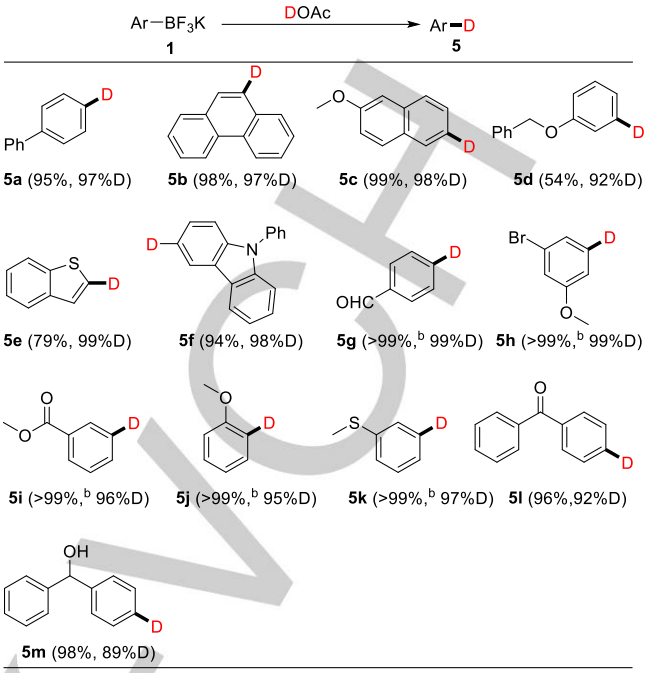


Entry[a]	D_2O /mL	DOAc/mL	Temp/ °C	Yield /%[b]
1	0.4	0.4	25	Trace
2	0.2	0.6	25	Trace
3	0.6	0.2	25	Trace
4	-	0.8	25	10
5	-	0.8	80	75
6	-	0.8	100	>99

[a] Conditions: **1d** (0.2 mmol), DOAc (0.8 mL), 100 °C, 8 h. [b] Yields of **5d** were determined by GC analysis.

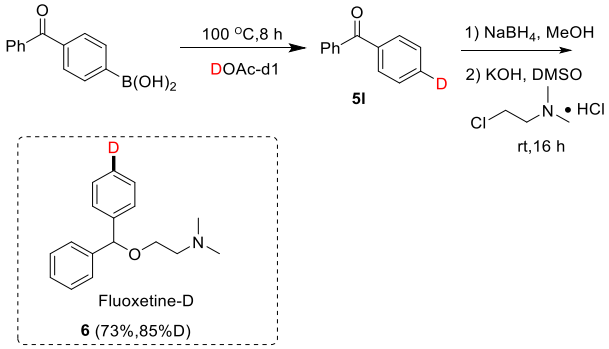
We then moved our attention to the deboronation–deuteration reaction. We used deboronation–deuteration of $ArBF_3K$ **1d** as our model system (Table 3). Only trace amount of product was obtained using D_2O/AcOD mixture as the solvent (Table 3, entries 1-3). The reaction became significantly faster when pure AcOD was used as the solvent (Table 3, entry 4). The yields were greatly improved by rasing to higher temperatures (80 °C or 100 °C) (Table 3, entries 5-6).

Table 4. Substrate scope studies of deuterium reactions.



[a] Conditions: **1d** (0.2 mmol), DOAc (0.8 mL), 100 °C, 8 h. Yields are isolated yields unless stated otherwise. The percentage of deuterium is determined by ^{1}H-NMR. [b] The yield is determined by ^{1}H-NMR due to the high volatility of products.

With the optimized conditions in hand, we explored the substrate scope of this new methodology (Table 4). This protocol works for diverse types of aromatic and heteroaromatic substrates (naphthalene, thiophene, benzothiophene, benzoindole). Both electron-rich and electron-poor substrates worked very well. Diverse functional groups such as ketone, ester, nitrile, alcohol, amide were well-tolerated. The percentage of deuterium (D%) could be slightly improved using well-dried starting material (in a vacuum oven) and a more strict anhydrous condition.



Scheme 2. Synthesis of deuterium-substituted fluoxetine.

To demonstrate the utility of our protocol, we synthesized a deuterium-substituted drug molecular - Fluoxetine-D (Scheme 2). Fluoxetine-D was obtained from **5l** in excellent yield (2 steps).

Conclusions

We have developed a hydrogen bond donor solvents assisted (radio)-halogenation and deuteration of organoborons. Compared to literature methods, our conditions are metal-free, strong oxidant-free. Our straightforward conditions are especially beneficial in radio-halogenation.

Acknowledgments

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Keywords: Hydrogen Bond Donor Solvents, Radio-Halogenation, Deuteration, Organoborons

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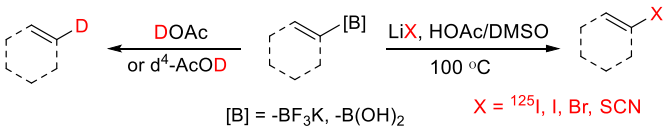

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