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Synthesis of fluorinated amphoteric organoborons *via* iodofluorination of alkynyl and alkenyl MIDA boronates†

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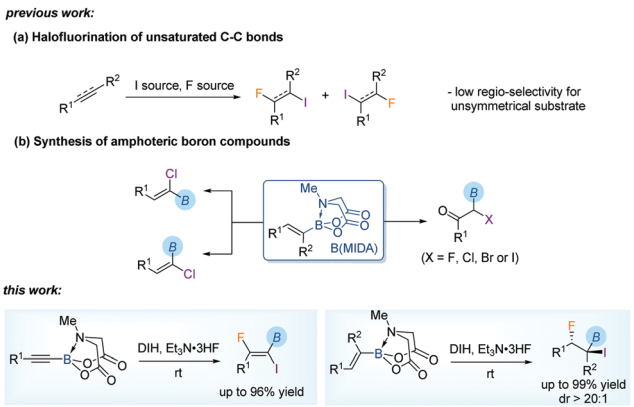
The iodofluorination of alkynyl and alkenyl MIDA (*N*-methyliminodiacetyl) boronates led to the synthesis of two types of fluorinated organoborons bearing a valuable C–I bond. The B(MIDA) moiety confers exclusive regioselectivity to the reaction, and the products were formed in generally good yields. Preliminary utility of the products was demonstrated.

There has been considerable interest in the synthesis and chemistry of organofluorines due to their often desirable pharmacokinetic and metabolic properties in pharmaceuticals and agrochemicals.[1] One useful approach for the introduction of fluorine to organic molecules is the halofluorination of unsaturated C–C bonds, leading to vicinal halofluorides.[2,3] By related methods not only a fluorine atom but also a halogen (chlorine, bromine or iodine) functionality could be incorporated simultaneously. The latter could then serve as a valuable handle for downstream transformations. An important feature of a typical halofluorination reaction is the high stereoselectivity, arising from the initial formation of a three-membered halonium cation intermediate[3d] and thereafter anti S_N2 nucleophilic substitution by a fluoride anion in the mechanism. Nevertheless, the regioselectivity may be problematic when unsymmetrical alkenes or alkynes are used as substrates, although Markovnikov's rule is generally applicable.

We have been interested in the synthetic transformations of alkenyl MIDA (*N*-methyliminodiacetyl) boronates[4] towards the step-economic construction of structurally complex organoborons.[5] The reaction of alkenyl MIDA boronates[6,7] with different halogen sources allowed us to prepare several halogenated organoborons. These include α-boryl-α-haloketones[5a] and α-chloroalkenyl boronates,[5b] both of which are traditionally challenging targets in organic synthesis. Particularly, in line with the importance of fluorine-containing molecules in functional molecules, our attention was also drawn to the synthesis of fluorinated organoborons *via* a similar late-stage fluorination of a pre-borylated starting material.[5c] In continuation with these studies, herein, we report an efficient iodofluorination of alkenyl and alkynyl MIDA boronates. The MIDA boron moiety tolerated strong oxidizing reaction conditions and was retained in the product, bringing about additional value to these new fluorinated amphoteric synthons.[8] Furthermore, in addition to the high stereoselectivity, an exclusive regioselectivity was observed, thanks to the directing effect of MIDA boron (Scheme 1).

We first explored the iodofluorination of alkynyl MIDA boronates, anticipating to obtain a fluoroalkene bearing a valuable C–B and C–I bond within the same molecule. It should be noted that fluoroalkene has been recognized as an important structural motif in medicinal chemistry.[9] Thus, the development of a synthetic method towards multi-functionalized fluoroalkenes



Scheme 1 Iodofluorination and late-stage modification of alkenyl MIDA boronates.

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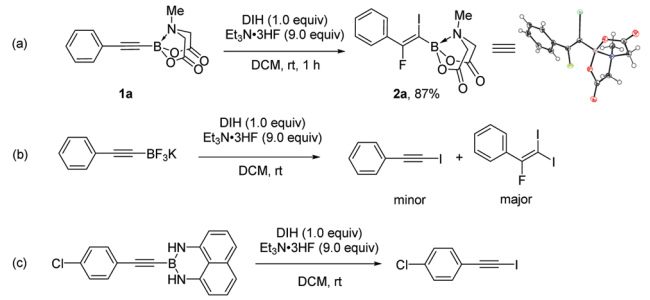


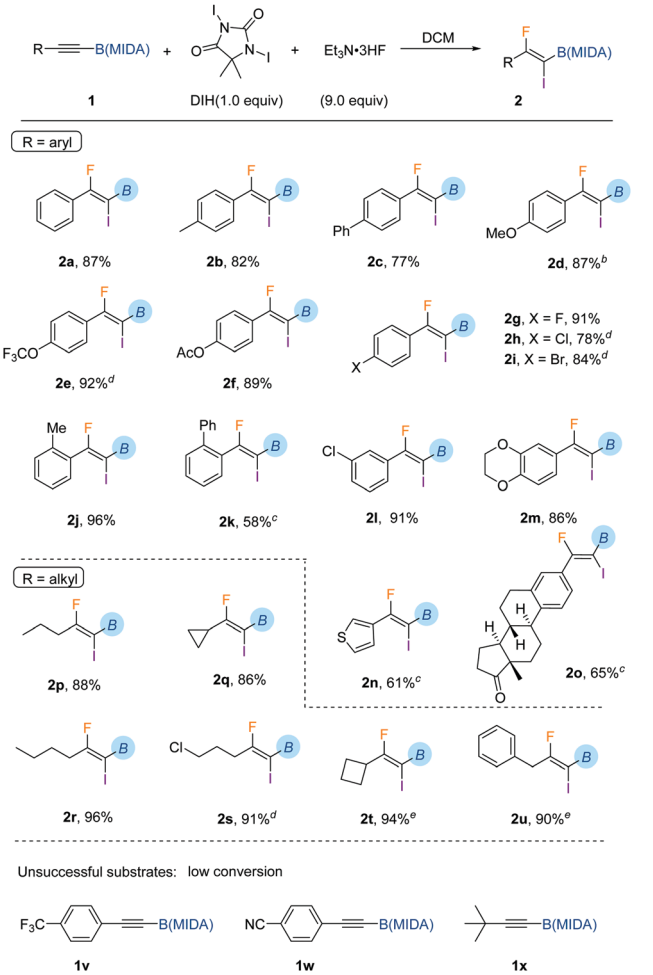
Scheme 2 Exploration of different alkynyl boronates in the iodofluorination reaction.

is highly desirable. By using analogous conditions of Gouverneur,[3k] which consists of the use of DIH (1,3-diiodo-5,5,-dimethylhydantoin) as an electrophilic iodo source and $Et_3N{\cdot}3HF$ as a nucleophilic fluorine source in DCM at room temperature, the reaction of phenylethynyl MIDA boronate **1a** delivered a *trans* iodofluorination product **2a** in 87% yield (Scheme 2a). The iodo atom was found to be attached α to the C–B bond as clearly defined by X-ray diffraction analysis (CCDC 1942792†).[9] The replacement of B(MIDA) moiety with its sp^3-B congener BF_3K, or sp^2-B B(dan), all led to an oxidative deboryliodination reaction, indicating the importance of stability of B(MIDA) in this reaction (Schemes 2b and c).

To determine the generality and limitations of this reaction, diverse aryl-substituted alkynyl MIDA boronates were applied. As shown in Table 1, a number of functional groups on the aryl ring were well tolerated under the standard conditions. These include methyl (**2b** and **2j**), phenyl (**2c** and **2k**), methoxy (**2d**), acetoxyl (**2f**), trifluoromethoxy (**2e**), and halogens (**2g–2i**, **2l**). Besides, a thiophenyl substituted substrate was amenable for iodofluorination (**2n**). And an estrone-derived substrate could also be smoothly converted to the corresponding product **2o** in good yield. Strong electron-withdrawing substituents, such as trifluoromethyl (**1v**), and cyano (**1w**), retard the reaction, leading to low conversion of the corresponding starting materials. The protocol was applicable to alkyl-substituted alkynyl MIDA boronates as well (**2p–2u**). And only one regioisomer was detected, indicating the strong directing effect of B(MIDA). Another limitation of the reaction is the incompatibility of *tert*-butyl groups (**1x**), probably due to steric reasons. In all these cases, no column chromatography was needed. A simple quenching with aqueous sodium thiosulfate and extraction generally led to a chemically pure product.

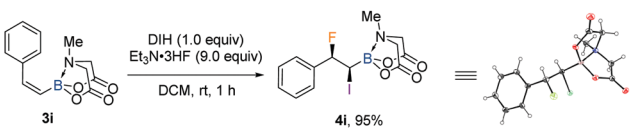
With the iodofluorination of alkynyl MIDA boronates established, we then explored a similar iodofluorination by using alkenyl MIDA boronate as a substrate (Table 2). As expected, by using the identical reaction conditions, phenylvinyl MIDA boronate **3a** underwent a reaction smoothly to deliver an *anti*-iodofluorination adduct **4a**. The relative stereochemistry is determined by the X-ray diffraction analysis of **4b** (CCDC 1953148†).[10] It is worth mentioning that the tri-substituted alkene (**4e**) was also a good substrate, giving the desired product in 96% yield without erosion of either regio- or stereoselectivity. The alkyl substrates also provided the desired products in good yields and selectivity (**4f–4h**). The *anti*-addition nature of the protocol also allowed us to synthesise

Table 1 Iodofluorination of alkynyl MIDA boronates[a]



[a] General reaction conditions: alkynyl MIDA boronate (0.2 mmol, 1.0 equiv.), DIH (0.2 mmol, 1.0 equiv.), $Et_3N{\cdot}3HF$ (9.0 equiv.), DCM (1.0 mL), rt, 5 min to 1 h. Isolated yield. [b] Reaction was conducted at 0 °C. [c] Yield after recrystallization. [d] 0.1 mL DCM was used. [e] 0.5 mL DCM was used.

the *cis* iodofluorination product (CCDC 1956650†)[10] by simply using a Z-type starting material (eqn (1)).



(1)

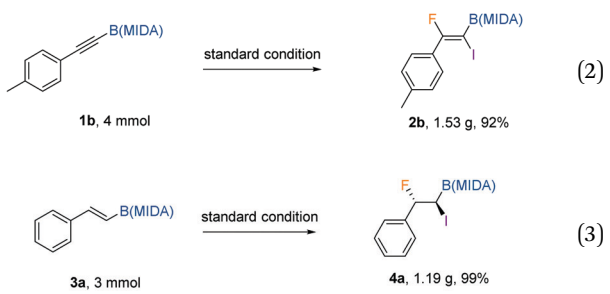
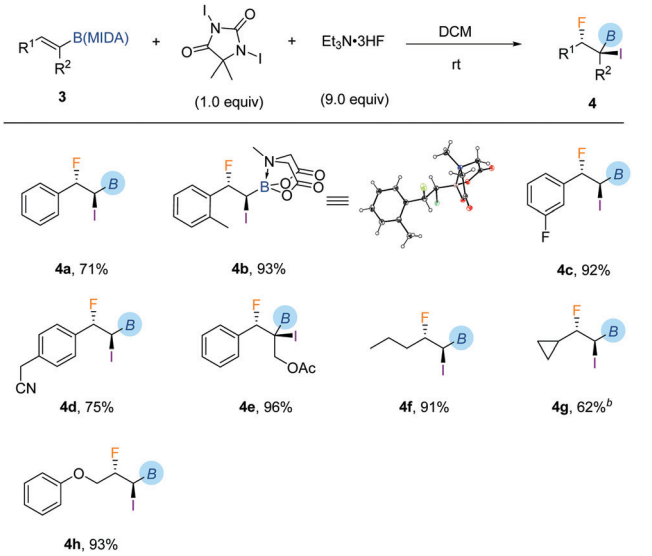
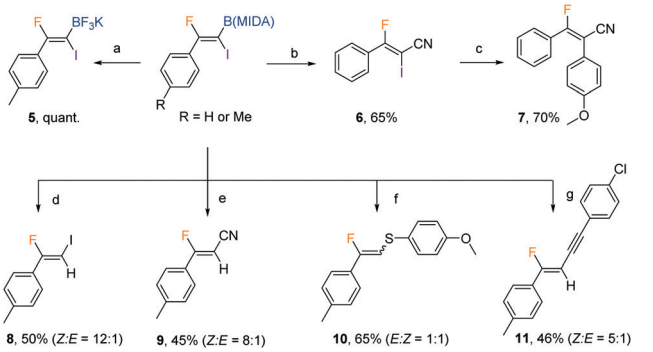


Table 2 Iodofluorination of alkenyl MIDA boronates[a]

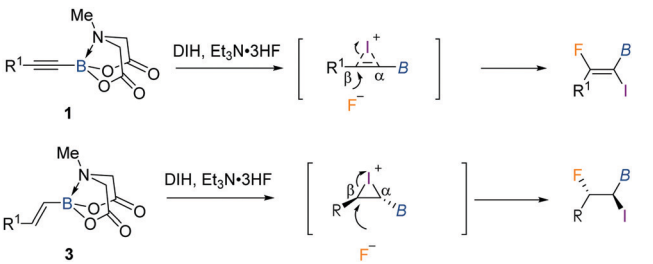


[a] General reaction conditions: alkenyl MIDA boronate (0.2 mmol, 1.0 equiv.), DIH (0.2 mmol, 1.0 equiv.), $Et_3N{\cdot}3HF$ (9.0 equiv.), DCM (1.0 mL), rt, 1–5 min. Isolated yields. [b] Yield after recrystallization.

Table 3 Derivatization of products



[a] KHF_2, MeOH, 60 °C. [b] $Zn(CN)_2$, CsF, $Cu(NO_3)_2{\cdot}H_2O$, MeOH/H_2O, 70 °C. [c] (4-Methoxyphenyl)boronic acid, $Pd_2(dba)_3$, PPh_3, K_2CO_3, toluene/EtOH/H_2O, 80 °C. [d] CuI, KF, DMPU; 80 °C. [e] CuCN, KF, DMPU, 80 °C. [f] 4-Methoxybenzenethiol, CuCl, KF, DMPU, 80 °C. [g] Ethynylbenzene, CuCl, KF, DMPU, 80 °C.



Scheme 3 Proposed mechanism.

The protocol was amenable to gram-scale synthesis, as evidenced by the excellent yield obtained when multiple millimoles of the alkynyl or alkenyl substrate was employed in the reaction (eqn (2) and (3)). The synthetic utility of the products was preliminarily investigated. The B(MIDA) moiety could be converted to the corresponding potassium trifluoroboronate (**5**) in quantitative yield upon ligand exchange with KHF_2 in MeOH.[11] A copper-mediated Chan–Lam-type cyanation[5b] yielded fluoroalkenyl cyanide (**6**) in good yield. The C–I bond in **6** could then be used in Suzuki–Miyaura coupling to give a fully substituted fluoroalkene in a stereospecific fashion. Intriguingly, synthetic manipulation on the C–I bond in **2b** in the presence of copper all resulted in the formation of deborylation products. The newly introduced functional groups are predominantly located *trans* to the aryl ring. A metal vinylidene species might be formed as intermediates in these reactions (Table 3).[12]

The regio- and stereoselectivity is worthy of mention (Scheme 3). Initially, the reaction of DIH with alkynyl MIDA boronates **1** or alkenyl MIDA boronates **3** would form relatively stable three-membered halonium cation intermediates.[3d] The S_N2 nucleophilic ring-opening from the opposite side of iodine accounts for the observed anti stereochemistry of the reaction. The hemilabile nature of the MIDA B–N dative bond makes the boron atom an electron acceptor to some extent.[5e,6i] For this reason, the development of more cations at the β position is expected, thus leading to a regioselective fluoride substitution. On the other hand, the bulky nature of the B(MIDA) moiety may also dictate the nucleophilic attack at the β position.

In summary, by taking advantage of the notable stability of MIDA boronates, we realized an iodofluorination reaction of alkynyl and alkenyl borons. The reaction led to the synthesis of two types of borylated organofluorines bearing a valuable C–I bond. The B(MIDA) confers exclusive regioselectivity to the reaction. Both aryl and alkyl substituents are well compatible and the products were formed in generally good yields. Preliminary utility of the products was demonstrated.

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Conflicts of interest

There are no conflicts to declare.

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