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Hypervalent iodine-mediated β-difluoroalkylboron synthesis *via* an unusual 1,2-hydrogen shift enabled by boron substitution†

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β-Difluoroalkylborons, featuring functionally important CF_2 moiety and synthetically valuable boron group, have great synthetic potential while remaining synthetically challenging. Herein we report a hypervalent iodine-mediated oxidative *gem*-difluorination strategy to realize the construction of *gem*-difluorinated alkylborons *via* an unusual 1,2-hydrogen migration event, in which the (*N*-methyliminodiacetyl) boronate (BMIDA) motif is responsible for the high regio- and chemoselectivity. The protocol provides facile access to a broad range of β-difluoroalkylborons under rather mild conditions. The value of these products was demonstrated by further transformations of the boryl group into other valuable functional groups, providing a wide range of difluorine-containing molecules.

Organofluorine compounds have been widely applied in medicinal chemistry and materials science.[1a–d] In particular, the *gem*-difluoro moiety featuring unique steric and electronic properties can act as a chemically inert isostere of a variety of polar functional groups.[2a–c] Therefore, the construction of *gem*-difluoro-containing compounds has received considerable attention in recent years. Efficient methods including deoxyfluorination of carbonyl compounds,[3a,b] photoredox difluorination,[4] radical difluorination,[5] and cross-coupling reactions with suitable CF_2 carriers[6a–f] are well developed. Alternatively, iodoarene-mediated oxidative difluorination reactions provide valuable access to these motifs by using simple alkenes as starting materials.[7a–i] Previously, these reactions were generally associated with a 1,2-aryl or 1,2-alkyl migration (Scheme 1a).[7a–f] Recent developments also allowed the use of heteroatoms as migrating groups, thereby furnishing *gem*-difluoro compounds equipped with easily transformable functional groups (Scheme 1b). In this regard, Bi and coworkers reported an elegant 1,2-azide migrative *gem*-difluorination of α-vinyl azides, enabling the synthesis of a broad range of novel β-difluorinated alkyl azides.[7g] Jacobsen developed an iodoarene-catalyzed synthesis of *gem*-difluorinated aliphatic bromides featuring 1,2-bromo migration with high enantioselectivity.[7h] Almost at the same time, research work from our group demonstrated that not only bromo, but also chloro and iodo could serve as viable migrating groups.[7i]

We have been devoted to developing new methodologies for the assembly of boron-containing building blocks by using easily accessible and stable MIDA (*N*-methyliminodiacetyl) boronates[8a–c] as starting materials.[9a–e] Recently, we realized a hypervalent iodine-mediated oxidative difluorination of aryl-substituted alkenyl MIDA boronates.[9d] Depending on the substitution patterns, the reaction could lead to the synthesis of either α- or β-difluoroalkylborons *via* 1,2-aryl migration (Scheme 1c). Recently, with alkyl-substituted branched alkenyl MIDA boronates, Szabó and Himo observed an interesting bora-Wagner–Meerwein rearrangement, furnishing β-difluorinated alkylboronates with broader product diversity (Scheme 1d).[10] While extending the scope of our previous work,[9d] we found that the use of linear alkyl-substituted alkenyl MIDA boronates also delivers β-difluoroalkylboron products. Intriguingly, instead of an alkyl- or boryl-migration, an unusual 1,2-hydrogen shift takes place. It should be noted that internal inactivated alkenes typically deliver the 1,2-difluorinated products, with no rearrangement taking place.[11a–d] Herein, we disclose our detailed study of our second generation of β-difluoroalkylborons synthesis (Scheme 1e). The starting linear 1,2-disubstituted alkyl-substituted alkenyl MIDA boronates, unlike the branched ones,[10] could be readily prepared *via* a two-step sequence consisting of hydroborylation of the terminal alkyne and a subsequent ligand exchange with *N*-methyliminodiacetic acid. This intriguing 1,2-H shift was found to be closely related to the boron substitution, probably driven thermodynamically by the

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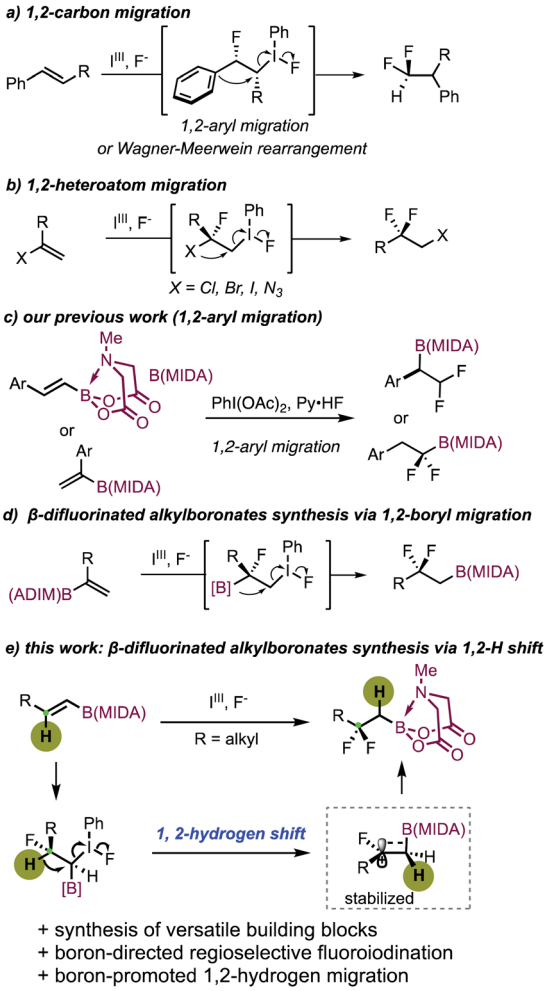


Scheme 1 Hypervalent iodine-mediated β-difluoroalkylboron synthesis.

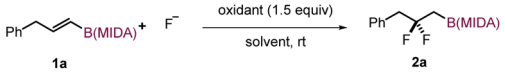
formation of the β-carbon cation stabilized by a σ(C–B) bond *via* hyperconjugation.[12a–d]

To start, we employed benzyl-substituted alkenyl MIDA boronate **1a** as a model substrate (Table 1). In accordance with our previous observations,[9d] the use of F sources such as CsF, AgF and $Et_3N{\cdot}HF$ in association with $PhI(OAc)_2$ (PIDA) as the oxidant and DCM as the solvent led to no reaction (entries 1 to 3). The use of Py·HF (20 equiv) successfully provided β-difluorinated alkylboronate **2a**, derived from an unusual 1,2-hydrogen migration, in 39% yield (entry 4). By simply increasing the loading of Py·HF to 40 equivalents, a higher conversion and thus an improved yield of 61% was obtained (entry 5). No further improvement was observed by using a large excess of Py·HF (100 equiv) (entry 6). Other hypervalent iodine oxidants such as PhIO or PIFA were also effective but resulted in reduced yields (entries 7 and 8). A brief survey of other solvents revealed that the original DCM was the optimal one (entries 9 and 10).

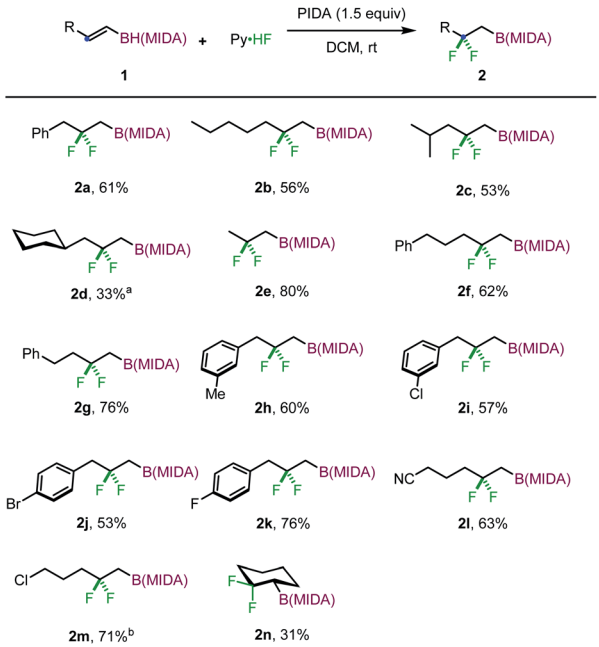
With the optimized reaction conditions in hand, we set out to investigate the scope and limitation of this *gem*-difluorination reaction. The reaction of a series of *E*-type 1,2-disubstituted alkenyl MIDA boronates were first examined. As shown in Scheme 2, the reaction of substrates with primary alkyl (**1b**, **1e–g**), secondary alkyl (**1c**, **1d**), or benzyl (**1h–k**) groups proceeded efficiently to give the corresponding *gem*-difluorinated alkylboronates in moderate to good yields. Halides (**1i–k**, **1m**) and cyano (**1l**) were well tolerated in this reaction. Of note, cyclic alkene **1n** is also a viable substrate, affording an interesting *gem*-difluorinated cyclohexane product (**2n**).

To define the scope further, the substrates with *Z* configuration were also employed under the standard reaction conditions (eqn (1) and (2)). The same type of products were isolated with comparable efficiency, suggesting that the reaction outcome is independent of the substrate configuration and substrates with *Z* configuration also have a profound aptitude of 1,2-hydrogen migration. Nevertheless, the reaction of *t*-butyl substituted alkenyl MIDA boronate (**1p**) delivered a normal 1,2-difluorinated alkylboron product (eqn (3)). The 1,2-hydrogen

Table 1 Optimization of reaction conditions

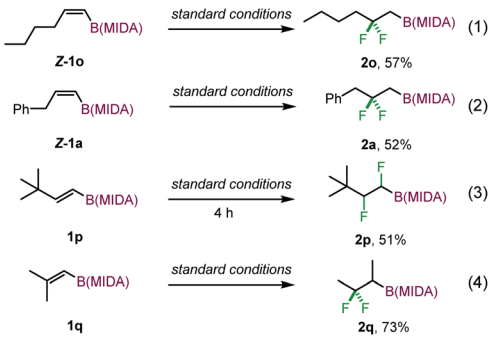


Entry	F^- (equiv)	Oxidant	Solvent	Yield (%)
1	CsF (2.0)	PIDA	DCM	0
2	AgF (2.0)	PIDA	DCM	0
3	$Et_3N{\cdot}HF$ (40.0)	PIDA	DCM	0
4	Py·HF (20.0)	PIDA	DCM	39
5	**Py·HF (40.0)**	**PIDA**	**DCM**	**61**
6	Py·HF (100.0)	PIDA	DCM	55
7	Py·HF (40.0)	PIFA	DCM	52
8	Py·HF (40.0)	PhIO	DCM	26
9	Py·HF (40.0)	PIDA	DCE	49
10	Py·HF (40.0)	PIDA	Toluene	46



Scheme 2 Scope of 1,2-H migratory *gem*-difluorinations. [a] 4 h. [b] PIFA was used.

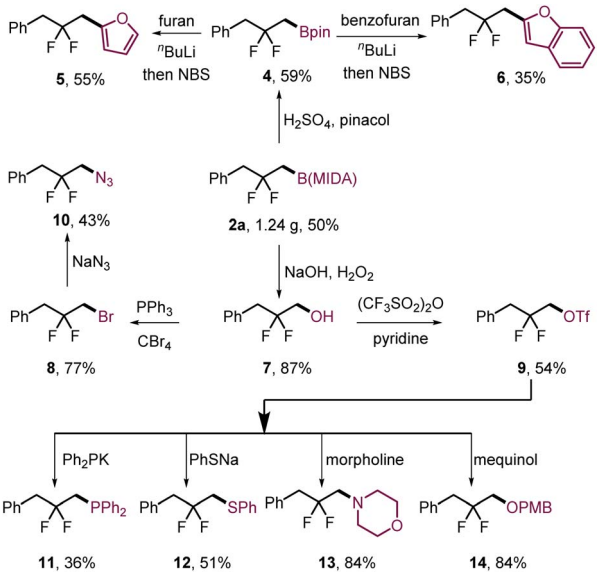
migration was completely suppressed probably due to unfavorable steric perturbation. With an additional alkyl substituent introduced, a 1,2-alkyl migrated product was formed as expected (eqn (4)).



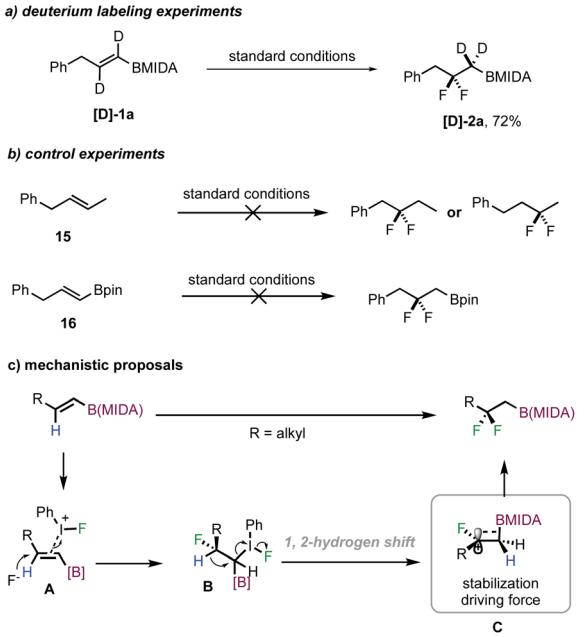
(1)

The *gem*-difluorination protocol was amenable to gram-scale synthesis of **2a** (Scheme 3, 8 mmol scale of **1a**, 1.24 g, 50%). To assess the synthetic utility of the resulting β-difluorinated alkylborons, transformations of the C–B bond were carried out (Scheme 3). Ligand exchange of **2a** furnished the corresponding pinacol boronic ester **4** without difficulty, which could be ligated with electron-rich aromatics to obtain **5** and **6** in moderate yields. On the other hand, **2a** could be oxidized with high efficiency to alcohol **7** using H_2O_2/NaOH. The hydroxyl group of **7** could then be converted to bromide **8** or triflate **9**. Both serve as useful electrophiles that can undergo intermolecular S_N2 substitution with diverse nitrogen- (**10**, **13**), oxygen- (**14**), phosphorus- (**11**) and sulfur-centered (**12**) nucleophiles.

To gain insight into the reaction mechanism, preliminary mechanistic studies were conducted. The reaction employing deuterated alkenyl MIDA boronate **[D]-1a** efficiently afforded difluorinated product **[D]-2a** in 72% isolated yield, clearly demonstrating that 1,2-H migration occurred (Scheme 4a). However, when the MIDA boronate moiety was replaced with a methyl group (**15**), no difluorinated product (derived from 1,2-migration) was detected at all, suggesting an indispensable role of boron for promoting the 1,2-migration event (Scheme 4b). Also, with a Bpin congener of **1a**, the reaction led to large decomposition of the starting material, with no desired product being formed (Scheme 4b).



Scheme 3 Product derivatizations. PMB = *p*-methoxyphenyl.



Scheme 4 Mechanistic studies and proposals.

Based on the literature precedent and these experiments, a possible reaction mechanism is proposed in Scheme 4c. With linear alkenyl MIDA boronates, the initial coordination of the double bond to an iodium ion triggered a regioselective fluoroiodination to deliver intermediate **B**. The regioselectivity could arise from an electron-donating inductive effect from boron due to its low electronegativity, consistent with previous observations.[13a,b] Thereafter, a 1,2-hydrogen shift, rather than the typical direct fluoride substitution of the C–I bond, provides carbon cation **C**. The formation of a hyperconjugatively stabilized cation is believed to be the driving force for this event.[12a–d] The trapping of this cation finally forms the product.

In conclusion, we demonstrated herein our second generation of β-difluoroalkylboron synthesis *via* oxidative difluorination of easily accessible linear 1,2-disubstituted alkenyl MIDA boronates. An unexpected 1,2-hydrogen migration was observed, which was found to be triggered by a MIDA boron substitution. Mild reaction conditions, moderate to good yields and excellent regioselectivity were achieved. The applications of these products allowed the facile preparation of a wide range of *gem*-difluorinated molecules by further transformations of the boryl group.

Data availability

Data for this work, including experimental procedures, characterization data for all new compounds are provided in the ESI.†

Author contributions

W.-X. L. and H. W. conceived the project. W.-X. L., Y. L., Y.-H. C., D.-H. T., Z. L. and J.-L. L. analysed the experimental results. W.-X. L., Q. L. and Y. L. performed the derivatizations and mechanistic studies. H. W. directed the project and composed the manuscript with input from all the authors.

Conflicts of interest

The authors declare no competing financial interests.

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