Organofluorine compounds have been widely applied in medicinal chemistry and materials science. 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. Therefore, the construction of gem-difluoro-containing compounds has received considerable attention in recent years. Efficient methods including deoxygen-fluorination of carbonyl compounds, photoredox difluorination, radical difluorination, and cross-coupling reactions with suitable CF₂ carriers are well developed. Alternatively, iodoarene-mediated oxidative difluorination reactions provide valuable access to these moities by using simple alkennes as starting materials. Previously, these reactions were generally associated with a 1,2-aryl or 1,2-alkyl migration (Scheme 1a). 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. Jacobsen developed an iodoarene-catalyzed synthesis of gem-difluorinated aliphatic bromides featuring 1,2-bromo migration with high enantioselectivity. At almost the same time, research work from our group demonstrated that not only bromo, but also chloro and iodo could serve as viable migrating groups.

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 as starting materials. Recently, we realized a hypervalent iodine-mediated oxidative difluorination of aryl-substituted alkyn MIDA boronates. 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 alkyn MIDA boronates, Szabó and Himo observed an interesting boration-Michael addition-rearrangement taking place. Herein, we disclose our detailed study of our second generation of β-difluoroalkylborons synthesis (Scheme 1e). The starting linear 1,2-disubstituted alkyn MIDA boronates, unlike the branched ones, could be readily prepared via a two-step sequence consisting of hydroboration of the terminal alkyn 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
To start, we employed benzyl-substituted alkenyl MIDA boronate 1a as a model substrate (Table 1). In accordance with our previous observations, the use of F sources such as CsF, AgF and Et₃N·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)).

### 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     | Et₃N·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 1 Hypervalent iodine-mediated β-difluoroalkylboron synthesis.

**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)).

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\text{(1)}
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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 \( \text{H}_2\text{O}_2/\text{NaOH} \). 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).

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 difluorination 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.\(^{13a-d}\) 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.\(^{13a-d}\) 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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