Integrated redox-active reagents for photoinduced regio- and stereoselective fluorocarboborylation

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Vinylboronates and alkylboronates are key components in variegated transformations in all facets of chemical science. The synthesis of vinylboronates and alkylboronates suffers from step-tedious and poor stereoselective procedures. We have developed a regulated radical difunctionalization strategy for the construction of fluorine-containing vinylboronates and alkylboronates with an integrated redox-active reagent IMDN-SO₂RF. This bench-stable imidazolium sulfonate cationic salt offers a scalable and operational protocol for the fluoroalkylation-borylation of unsaturated hydrocarbons in a high regio- and stereoselective manner. The products can be further transformed into valuable fluorinated building blocks.

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**Results**

**Reaction optimization.** To validate the above hypothesis, we selected phenylacetylene (2a) as pilot substrate to test the trifluoromethylborylation reaction (Table 1). After extensive screening
Table 1 Optimization of the reaction conditions.

| Entry | Variation from the conditions | Yield of 3a (%) | Z/E of 3a \(^b\) |
|-------|-------------------------------|-----------------|-----------------|
| 1     | None                          | 82 (65)\(^c\)   | >20:1           |
| 2     | 1b instead of 1a               | 67              | >20:1           |
| 3     | 1c instead of 1a               | 69              | >20:1           |
| 4     | 1d instead of 1a               | 53              | >20:1           |
| 5     | 1e instead of 1a               | 76              | >20:1           |
| 6     | 1f instead of 1a               | 60              | >20:1           |
| 7     | 1g instead of 1a               | 32              | >20:1           |
| 8     | 1h instead of 1a               | 0               | —               |
| 9     | B\(_2\)pin\(_2\) instead of B\(_2\)cat\(_2\) | 0               | —               |
| 10    | B\(_2\)neop\(_2\) instead of B\(_2\)cat\(_2\) | 0               | —               |
| 11    | 2.0 equiv of pyridine          | 58              | >20:1           |
| 12    | 2.0 equiv of 1-methylimidazole | 47              | >20:1           |

\(^a\)Yield determined by \(^{19}\)F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. \(^b\) The Z/E ratio was determined by \(^{19}\)F NMR. \(^c\) Isolated yield.

Fig. 2 Substrate scope of the alkynes. \(^a\)Crude yields determined by \(^{19}\)F NMR spectroscopy using benzo trifluoride or trifluoromethoxybenzene as an internal standard. \(^b\)Values in parentheses are of isolated yields. \(^c\)The E/Z ratio was determined by \(^{19}\)F NMR. \(^d\)The E/Z ratio was determined by \(^1\)H NMR. \(^e\)Crude yields determined by \(^1\)H NMR spectroscopy using dibromomethane as an internal standard. \(^f\)2.0 mmol of 2p was used.
of conditions (see Supplementary Tables 1 and 2), we found that when using 2.5 equivalents of IMDN-SO2CF3 (1a) (E1/2\text{red} = −1.385 V vs SCE), 2 mol% of fac-Ir(ppy)3 (E1/2\text{III}/\text{II} = −1.73 V vs SCE)17, 2.5 equivalents of B2cat2 in a mixed solvent of MeCN and EtOAc (1:3 v/v) at room temperature under the irradiation of 30 W blue LEDs, the vinylboronate product 3a could be obtained in 82% yield (determined by 19F NMR) with over 20:1 Z/E ratio. Different imidazolium sulfonate reagents 1b–1h were then examined (Table 1). The yield of 3a descended when the benzoimidazolium reagents 1b and 1c were used (entries 2 and 3). The counterion was found to be important for this transformation, as evidenced by the low yield (53%) obtained when using BF4− salt (1d, entry 4). The reaction proceeded with 2-phenylimidazolide reagents 1e and 1f in 76% and 60% yield, respectively (entries 5–6). The dimethylated reagent 1g resulted in a lower conversion (entry 7). The electro-neutral reagent 1h failed to produce the desired product under irradiation, which may due to the low reduction potential (E1/2\text{red} = −1.080 V vs SCE) (entry 8). This result validated the precedent presumption that the cationic reagent can serve as a better electron acceptor to furnish N-centered neutral radicals.48–51 Other diboron reagents, such as bis(pinacolato)diboron (B2pin2) and bis(neopentylglycolato)-diboron (B2neop2), did not provide the corresponding borylated products (entries 9–10). Addition of excess bases such as imidazole and pyridine resulted in much lower yields (entries 11–12).

**Substrate scope with respect to the alkynes.** Using 2 mol% of fac-Ir(ppy)3, IMDN-SO2CF3 (1a) (2.5 equiv), and B2cat2 (2.5 equiv) at ambient temperature, a range of alkynes underwent fluoroalkylation-borylation with good efficiency. As shown in Fig. 2, the reaction can be performed at a gram scale to give 3a in 61% yield and high stereoselectivity. Aromatic alkynes with electro-donating or electro-withdrawing substituents afford the desired products 3b–3j in good to excellent yields (60–93%) with high regio- and stereoselectivity (Z:E > 20:1).

Functionalities including halides (3b, 3m, 3n), nitrile (3d), ester (3g), and boronate (3j) are tolerated. Naphthyl- and thienyl-substituted alkynes also readily transformed into the Z-products 3h and 3l in good yields. The reaction could also be applied to alkynyl deuterium to produce the (Z)-selective deuterated vinylboronates 3k–3l in 52–72% yields. An attempt of more challenging internal alkyne substrate resulted in the tetrasubstituted olefin in high regio- and stereoselectivity (3o, 45%).
standard carboxylation conditions. Perfluoro-butyl (1I), hexyl (I1), and octanyl (1K) reagents could furnish the corresponding products 3q–3s in good yields (81–87%). Using a perhalogenated ether-derived sulfonate (1I), the vinylboronate 3t was formed in high yield. To demonstrate the scalability of such radical carboxylation protocol, the reaction was carried out on 10 mmol scale to afford 3a in 61% yield with equally high Z/E ratio. Under the standard reaction conditions, alkyl-substituted alkenes could not transform to the desired products. DFT calculations illustrate that the energy barrier of CF3 radical addition to aliphatic alkenes is higher than that to aromatic alkenes. Furthermore, a competing pathway of CF3 radical addition to B2Cat2 leads to other trifluoromethylated products. Therefore, an excess amount of alkyl alkyne substrate is needed to facilitate the main reaction pathway. By using four equivalents of the alkyne, the desired product 3p can be obtained in 26% yield. For internal aliphatic alkenes, the computed barrier with the CF3 radical is much higher than that for the reaction of B2Cat2 with the CF3 radical. Therefore, no desired product is obtained using internal aliphatic alkenes as substrate.

Substrate scope with respect to the olefins. The α-fluoroalkylated boronates are also useful fluorine-containing synthons for further elaboration. By slight variation of the standard reaction conditions (see Supplementary Tables 3–10), we have extended this carboxylation protocol to a range of unactivated alkenes (Fig. 3). Using IMDN-SO2CF3 (1e), alkenes bearing ester and amide functionalities underwent radical 1,2-carbonboration to afford trifluoromethylated boronates (5a–5h) in good yields. Heteroaryl (5i–5j), sulfonyl (5k), and oxygenated alkyl groups (5l–5n) at various positions of the alkenes were also found effective. Cyclic alkenes could also transform into the desired products 5q and 5y. Noteworthy, biorelevant molecules, such as boldenone, lanosterol, (+)-α-tocopherol, and estrone-derived terminal alkenes afforded β-trifluoromethylboronates (5r–5u) in good yields. Additionally, fluoroalkyl radicals including CF3F3 (1i), CF3F7 (1k), and CF3CF2O(CF2)7CF2Cl (1l) were successfully stitched to unactivated olefins to afford fluoroalkylborylated products in moderate yields (5v–5dd). The reaction with styrene failed to afford the desired product due to inert reactivity of benzylic radical.

Synthetic applications. The synthetic utility of the method was demonstrated in a number of transformations of the highly functionalized alkylboronates and alkylalkenylboronates20,52,53 (Fig. 4). Oxidation of β-CF3 boronate 5a afforded hydroxylated product 6 in 62% yield. Silver-catalyzed radical deboronofluorination of 5a in aqueous solution provided the alkyl fluoride 7 in 76% yield. Vinylation, oxidative coupling, and homologation of 5p afforded functionalized products 8–10 in good yields. Halogenation of vinylboronic ester 3a resulted in the formation of β-CF3-vinyl bromide 11 (53%). Palladium-catalyzed Suzuki–Miura cross-coupling of 3a with (hetero)aryl iodides afforded the corresponding trisubstituted alkenes 12 (90%) and 15 (88%). Olefination and alkynylation using vinyl bromide or alkynyl bromide also proceeded smoothly to generate 13 and 14 in 73% and 96% yields, respectively. The coupling of 3a with bioactive estrone-derived trifluorate the corresponding product 16 with high stereoselectivity.

Discussion

In summary, we have described an air-stable redox-active reagent IMDN-SO2R2, 1 with high reactivity and scalability. A key design feature of this dual functional imidazolium sulfonate reagent is the cationic nature that favors the progressive formation of fluoroalkyl radicals by SET reduction under photocatalytic conditions. Meanwhile, the in situ-generated Lewis basic imidazole residue promotes the B–B bond cleavage. The integrated reagent is applicable to regulate the reaction sequence of carbon and boron-centered radicals to access various fluorine-bearing vinylboronates and alkylalkenylboronates with high stereo- and regioselectivities. Further study of this reagent is underway in our laboratory.

Methods

General procedure for the synthesis of imidazolium salts 1. To a one-necked 1000 mL flask equipped with a magnetic stirrer, the corresponding imidazol (100 mmol), Et3N (150 mmol), and 600 mL DCM were added. The flask was then cooled in an ice bath, and 130 mmol (36.8 g) (CF3SO2)2O was bubbled into the flask slowly. The mixture was stirred at room temperature for 2 h and evaporated in vacuo, quenched with water, and extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed over Na2SO4, filtered, and concentrated. The product was purified by flash column chromatography on silica gel with n-pentane/ethyl acetate as eluent to give the imidazolyl sulfonamide. Under argon, to a solution of the imidazolyl sulfonamide in dried DCM (400 mL) was added dropwise MeOTf (or Me3OBF4) (130 mmol at 0 °C). Then, the mixture was stirred at room temperature for 24 h. After the reaction was completed as monitored by TLC or GC-MS analysis. A solution of pinacol (236 mg, 2 mmol) in MeCN (1.0 mL) was added dropwise to the mixture at 0 °C. After that, the mixture was concentrated under rotary evaporation to give a white solid (or a viscous liquid) crude product, to which Et2O (300 mL) was added. With vigorous stirring, a solid precipitate was formed and washed with Et2O (200 mL × 3) and dried in vacuo to yield the imidazolium salt 1 as a white solid.

General procedure for the synthesis of vinylboronates 3. Under argon, to a solution of 1 (0.50 mmol, 2.5 equiv), B2Cat2 (0.5 mmol, 2.5 equiv) and fac-Ir(ppy)3 (2 mol%) in MeCN/EtOAc (1:3) (3 mL) was added corresponding alkenes 2 (0.2 mmol) at room temperature. After that, the tube was exposed to 30 W blue LEDs at room temperature about 30 h until the reaction was completed as monitored by TLC or GC-MS analysis. A solution of pinacol (236 mg, 2 mmol) in MeCN (1.0 mL) was added dropwise to the mixture at 0 °C. After that, the mixture was concentrated under rotary evaporation to give a white solid. The product was purified by flash column chromatography on silica gel with n-pentane/ethyl acetate as eluent to give the vinylboronates 3.
General procedure for the synthesis of alkyloboranes. Under argon, to a solution of $\text{CF}_3\text{H}_2\text{C}=$ (0.50 mmol, 2.5 equiv), $\text{B}2\text{Cat}_2$ (0.6 mmol, 3.0 equiv) and $\text{fac-Ir}(ppy)_3$ (2 mol%) in 1:1 MeCN/acetonitrile (0.2 ml) was added Et$_3$B (0.6 mmol, 3.0 equiv, 1 mol%/l in THF) and corresponding alkene 4 (0.2 mmol) at room temperature. After that, the tube was exposed to 30 W blue LEDs at room temperature for 30 h until the reaction was completed as monitored by TLC or GC-MS analysis. A solution of pinacol (142 mg, 1.2 mmol) in Et$_3$N (1.1 ml) was added to the mixture. After 1 h, the reaction mixture was evaporated in vacuo. The product was purified by flash column chromatography on silica gel with n-pentane/ethyl acetate as eluent to give the alkyloboranes.

Data availability

The authors declare that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its Supplementary Information files. X-ray structural data of compound 1a, which are available free of charge from the Cambridge Crystallographic Data Center under the deposition number CCDC 1958307. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions
Y.W. designed and guided this project. W. Zhang, Z.Z., Z.W., and M.H. are responsible for the plan and implementation of the experimental work. Y.L., W. Zhao, and S.L. are responsible for the calculation studies. Y.W., X.W., Y.L., Y. Zha, Y. Zheng, and Y.P. co-wrote the manuscript, analyzed the data, discussed the results, and commented on the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
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