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$MnBr_2$ catalyzed regiospecific oxidative Mizoroki-Heck type reaction

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ABSTRACT

Herein, we report an unprecedented regiospecific oxidative Mizoroki-Heck type reaction for the synthesis of α-difluoromethyl homoallylic alcohols. The reaction shows broad substrate scopes and high functional group tolerance. Late-stage functionalization of complex biologically active molecules demonstrates the synthetic potential of this transformation. Mechanistic study supports the involvement of $MnBr_2$ catalyzed radical 1,2-silyl transfer.

Olefins are not only one class of important synthetic building blocks in chemistry but also common structural motifs of pharmaceuticals, natural products, organic materials [1–4]. Therefore, preparation of functionalized alkenes is one synthetic transformation pursued by chemists for a long time [5–9]. Mizoroki-Heck reaction is a well-known C–C bond formation reaction involving carbometallation and β-hydride elimination pathway [10–18]. However, the key challenge remained is the regioselectivity control to generate terminal or internal alkenes, because both H^a and H^b are prone to be eliminated (Scheme 1a) [19–27]. Moreover, internal olefins are thermodynamically more stable, therefore the kinetically controlled synthesis of terminal olefins are extremely difficult because of possible post-isomerization [22,28-31]. Recent progress made by Nishikata group through Cu-catalyzed Mizoroki-Heck type reaction afforded mostly 91/9 (terminal alkene/ internal alkene) selectivity, but the *Z/E* selectivity in the synthesis tri-substituted olefin is low (64:36, *E/Z*) [32–34].

Fluorinated molecules often show improved lipophilicity, solubility, and metabolic stability than the parent compounds [35]. Among them, difluoromethylated compounds are of particular interests, because CF_2H could mimic OH and SH and it is also known to be a hydrogen donor through hydrogen bonding [36–42]. For example, difluoromethylated alcohols such as anti-tumor agent **A** [43] and cathepsin K inhibitor **B** [44] have gained increasing attention in pharmaceutical and life-related sciences (Scheme 1b). In 2020, our group [45] reported a synthesis of fluoroalkyl substituted homoallylic alcohol **C** enabled by radical 1,2-silyl transfer [46–52]. Although the yield is synthetically useful, the allylic sulfone substrate is needed to be synthesized from α-methyl styrene [45]. Herein, we disclose an efficient synthesis of difluoromethylated homoallylic alcohols directly from α-alkyl styrenes through $MnBr_2$ catalyzed regiospecific oxidative Mizoroki-Heck type reaction with our difluoromethylated organosilicon reagent (Scheme 1c). The new methodology is more step and atomic economical than the previous method [45]. The present allylic C–H alkylation reaction is operationally simple and shows broad substrate scopes along with high functional group tolerance. The late-stage functionalization of bioactive complex molecules and a gram scale reaction demonstrate the synthetic potential of our methodology.

We investigated the reaction with **1a** and α-methyl styrene **2a** as model substrates under catalytic system of $MnBr_2$/TBPB in DCM, and the target product **3a** was obtained in 48% yield after desilylation with TBAF (Table 1, entry 1). Encouraged by the result of selective formation of terminal alkene **3a**, we further investigated the influence of ligands on the efficiency of the reaction (Table 1, entries 2–5). The use of tridentate **L1** or bidentate **L2** as the ligand resulted in no formation of product **3a** (Table 1, entries 2 and 3). However, 2,2′-bipyridine type ligands are better choices. With **L3** as a ligand, 65% yield was observed (59% isolated yield, Table 1, entry 4). When **L4** was employed as the ligand, the yield of product **3a** increased to 68% (67% isolated yield, Table 1, entry 5). Altering silyl group from $SiMe_2Ph$ to $SiMePh_2$, the efficiency of reaction was further improved and **3a** was formed in 73% yield (isolated in 76% yield), but the yield could decrease to 53% without **L4** as the ligand (Table 1, entry 6). Other silyl group such as $SiPh_3$, $SiEt_3$, $SiMe_3$ substituted substrates **1c**∼**1e** afforded lower yield (Table 1,

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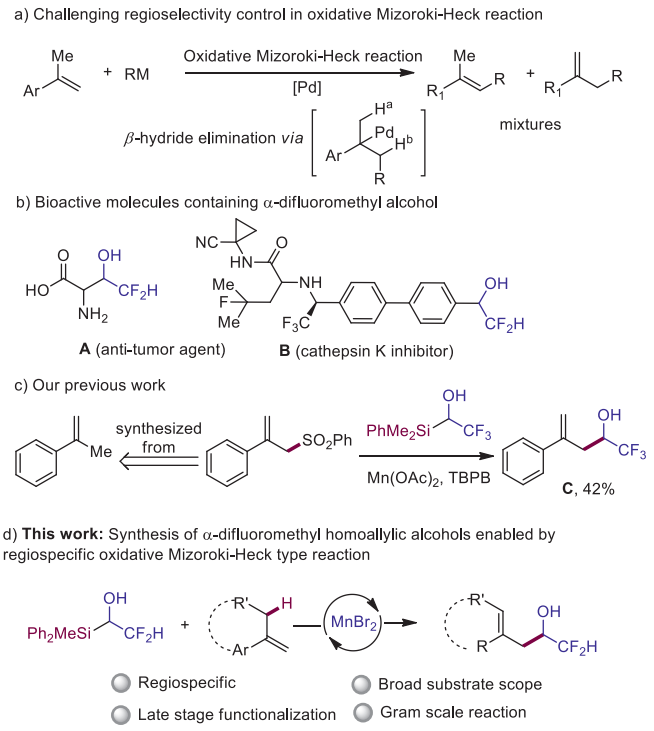
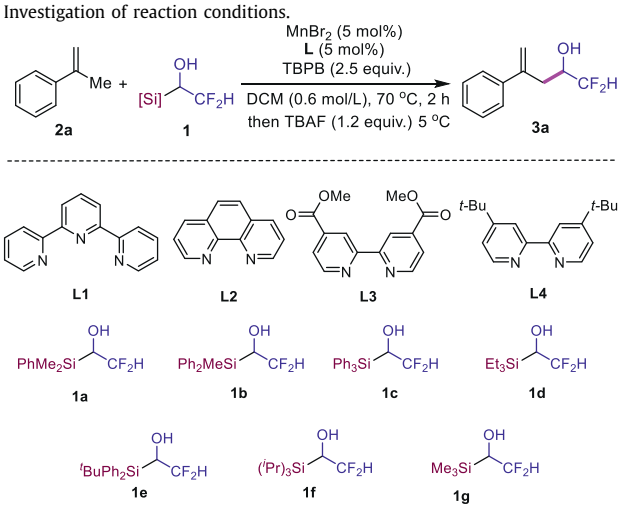


Scheme 1. Background and our strategy in the synthesis of difluoromethyl homoallylic alcohols.

Table 1
Investigation of reaction conditions.



Entry	1	L	Yield of **3a** (%)[a]	Conversion of **1** (%)
1	**1a**	–	48	100
2	**1a**	**L1**	0	100
3	**1a**	**L2**	0	100
4	**1a**	**L3**	65 (59)	100
5	**1a**	**L4**	68 (67)	95
6	**1b**	**L4**	73 (76) (53)[b]	100
7	**1c**	**L4**	58 (57)	100
8	**1d**	**L4**	43	100
9	**1e**	**L4**	47	100
10	**1f**	**L4**	0	92
11	**1g**	**L4**	0	100
12 [c]	**1b**	**L4**	0	0
13 [d]	**1b**	**L4**	0	0

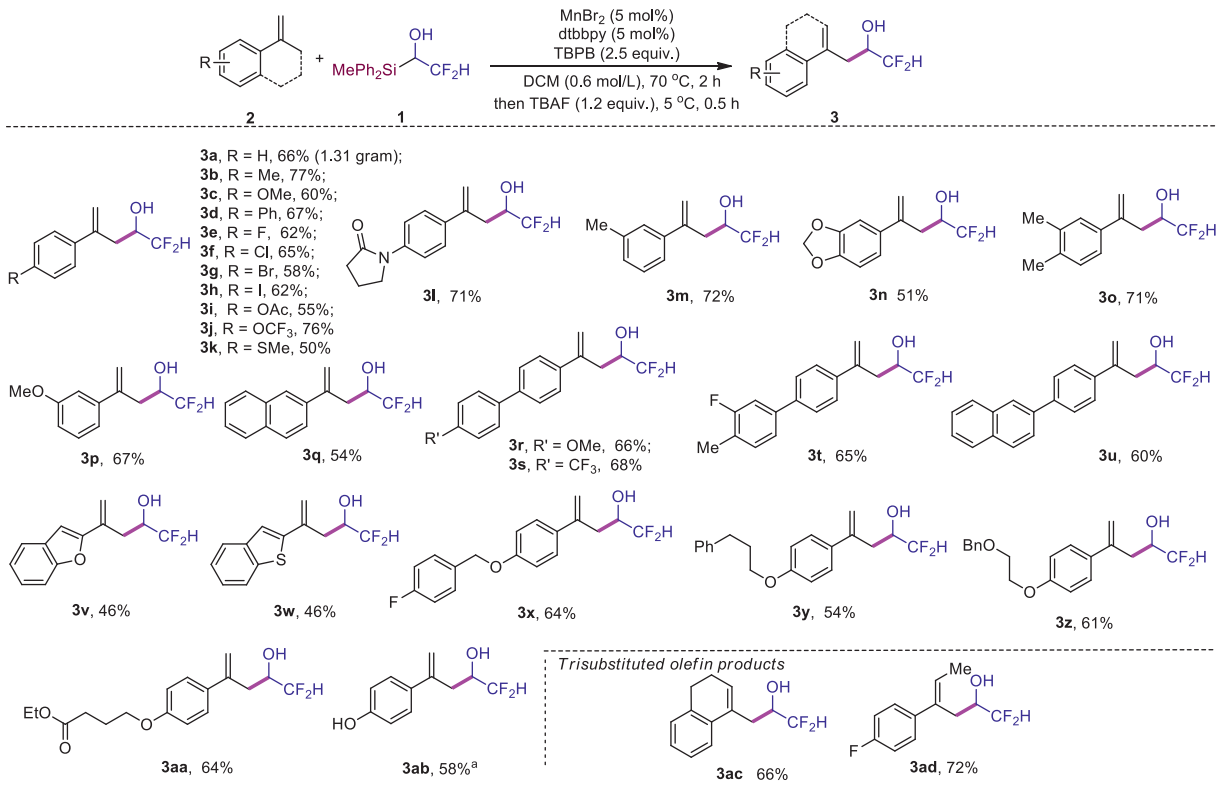
TBPB: *tert*-buty peroxybenzoate; TBAF: tetrabutylammonium fluoride.
[a] Yield of **3a** and conversion of **1** were determined by ^{19}F NMR with $PhCF_3$ as the internal standard. Yield in parentheses is isolated yield.
[b] Without **L4**.
[c] Reaction without $MnBr_2$/**L**.
[d] Reaction without TBPB.

entries 7–9), but Si^iPr_3 and $SiPh_2{}^tBu$ substituted reagents **1f** and **1g** could not afford product **3a** owing to the steric hindrance of the silyl groups (Table 1, entries 10 and 11). Control experiments showed both catalyst and oxidant are important for the success of this reaction, since no conversion of the organosilicon reagent was observed without either $MnBr_2$/**L4** or TBPB (Table 1, entries 12 and 13).

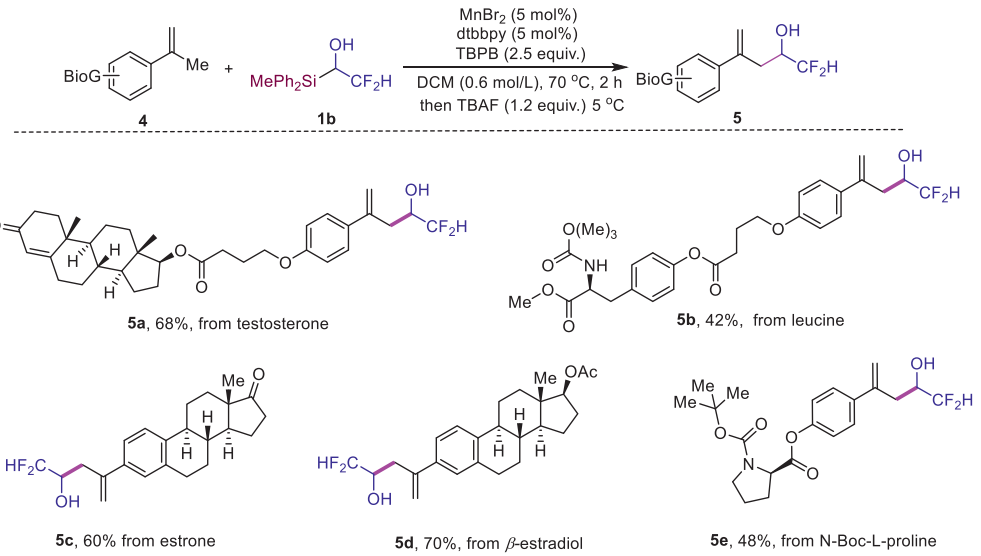
With the optimized condition in hand, we next explored the scope of reaction. We found a variety of α-alkylstyrenes bearing different functional groups could be used as substrates, affording the α-difluoromethyl substituted homoallylic alcohols **3b-3ad** in 46%–77% yields (Scheme 2). This reaction can be scaled up, and compound **3a** was obtained in yield of 66% (1.31 g isolated). Many functional groups could be tolerated. Csp^2-X (X = F, Cl, Br, I) bond was maintained after the reaction, affording product **3e-3h** in 58%–65% yields. Moreover, OMe, OAc, OCF_3 and SMe could be tolerated, giving corresponding products **3c, 3i-3k** in 50%–76% yields. An amide containing product **3l** was also isolated in 71% yield. Mutiple substituted styrenes were used as substrates to generate products **3n** and **3o** in 51% and 71% yield. Biaryl and naphthlenyl substituted olefins are also suitable substrates, resulting in products **3q-3u** in 54%–68% yields. Heterocyclic groups, such as benzofuryl, benzothienyl groups were also tolerated by the current oxidative reaction conditions (**3v**, 46%, **3w**, 46%). A variety of ethers could also generate desired products (**3x** 64%, **3y** 54%, **3z** 61%, **3aa** 64%). It was worth noting that phenol product **3ab** could be obtained in 58% yield with 4-OTBS substituted styrene as starting material. To our delight, tri-substituted alkene containing hydroxyl difluoroalkyl group such as **3ac** was successfully synthesized in 66% yield. Notebly, compounds **3ad** was isolated in 72% yield as single regioisomer and stereoisomer, indicating the excellent regio and stereoselectivity of our reaction.

To further evaluate the efficiency of the regiospecific oxidative Mizoroki-Heck type reaction, we next applied this protocol in late-stage synthesis of relatively more complex molecules. When testosterone derived terminal olefin **4a** was emplyed as the substrate in the formal C–H alkylation reaction, corresponding product **5a** was obtained in 68% yield (Scheme 3). It was worth noting that N–H bond in substrate **4b** could also be tolerated in the reaction, affording product **5b** in 42% yield, which is an obvious advancement over our previous work, because N–H bonds were detrimental to the reaction of allylic sulfones [45]. Moreover, estrone and estradiol derived α-methyl styrenes were also effective in present condition, affording desired alcohols **5c** and **5d** in 60%–70% yields. In addition, the reaction of proline derived ester **4e** was also efficient, affording product **5e** in the yield of 48% (Scheme 3).

Several control experiments were conducted to probe possible mechanism. Firstly, we found that the $MnBr_2$ catalyzed oxidative Mizoroki-Heck type reaction was inhibited by the addition of radical trapping agent 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), and compound **6** was detected by HRMS (Scheme 4a). Therefore, radical process is likely involved in current reaction. The detection of compound **7** (Scheme 4a) and homo-coupling product **8** in the reaction of **2a** under standard condition (Scheme 4b) led us to consider the possibility of the radical-radical coupling between allyl radical and ketyl radical (for details, see Supporting information). However, the deuterium-incorporation experiment did not support this possibility because compound **3q-d_2** was isolated in 51% yield, when compound **2q-d_3** was used as the substrate (Scheme 4c). There was no deuterium-incorporation in the allylic position of compound **3q-d_2** (Scheme 4c). Moreover, competitive reaction between **2q** and **2q-d_3** showed that KIE was 1.04, which implied the deprotonation-elimination process was not the rate-determining step (Scheme 4d) [52]. We have shown that Mn(II) catalyst is important for the success of the reaction (Table 1,



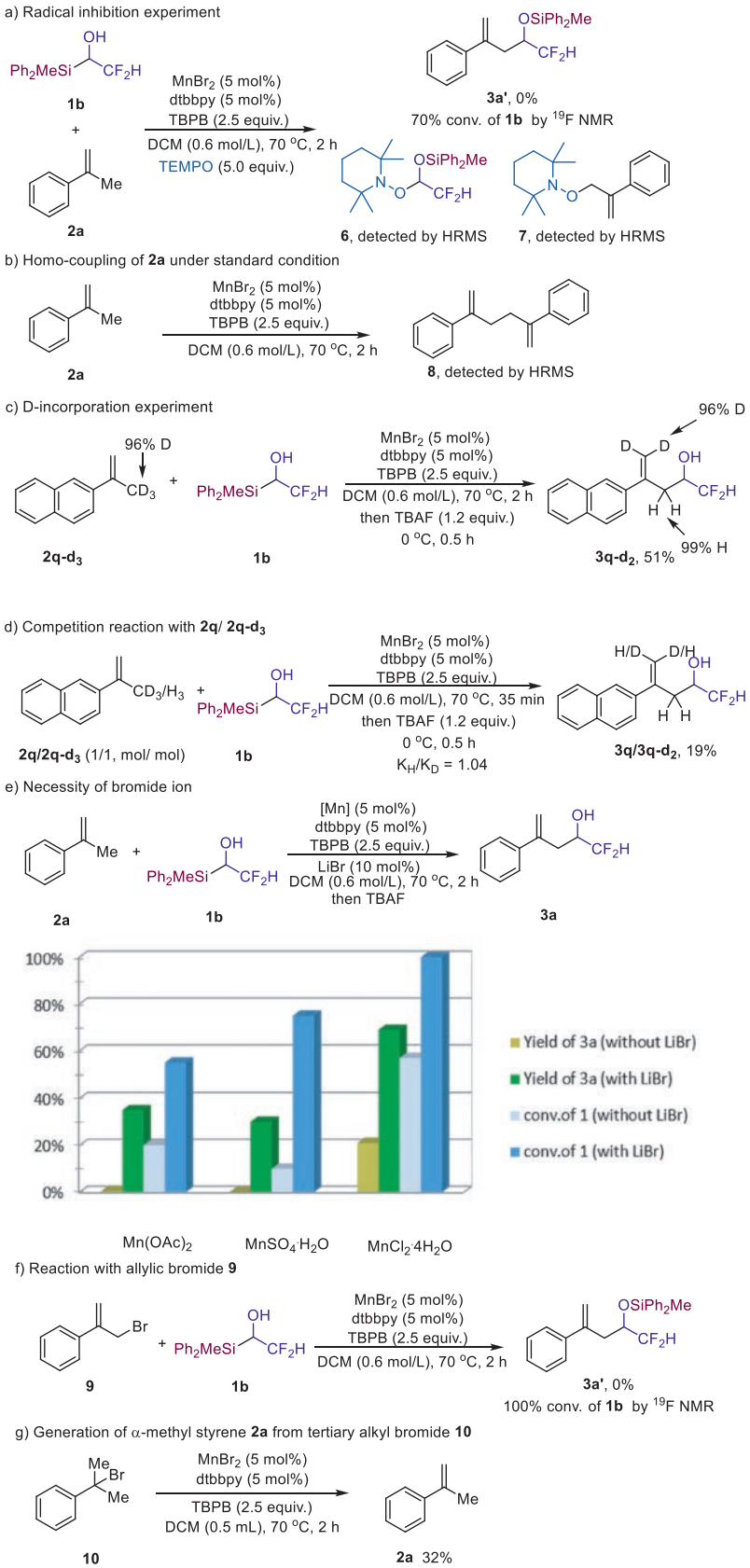
Scheme 2. Investigation of substrate scopes. Reactions were conducted under standard condition and isolated yield was provided for each product. [a] 4-OTBS substituted reagent **2aa** was used.



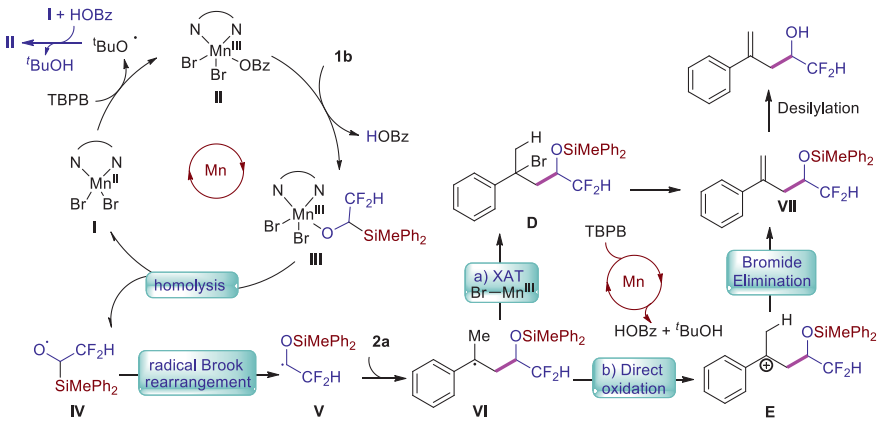
Scheme 3. Late-stage functionalization of alkenes derived from bioactive complex molecules.

entry 12). Further investigation indicates that bromide ion is also crucial (Scheme 4e). We found that when $Mn(OAc)_2$ was used as the catalyst, no product **3a** was generated although the organosilicon reagent was consumed in about 20%. However, the addition of LiBr (10 mol%) led to the formation of compound **3a** in 35% yield, while $Mn(OAc)_2$ (5 mol%) was used as the catalyst. Similar trend was found for the catalysis with $MnSO_4{\cdot}H_2O$ (without LiBr, 0% yield of **3a**, 10% conversion of **1b**; with 10 mol% LiBr, 30% yield of **3a**, 75% conversion of **1b**). While there is 21% yield of **3a** formed when $MnCl_2{\cdot}4H_2O$ was employed as the catalyst, the addition of LiBr also significantly increased the efficiency of the reaction (69% yield of **3a**, 100% conversion of **1b**). Allylic bromide was ruled out as the intermediate in the present protocol because no product **3a** was detected when **9** was added to the reaction (Scheme 4f).

Since bromide is important for the success of the reaction, we propose that intermediate **D** might be involvement in the reaction (Scheme 5). We indeed found that α-methyl styrene **2a** could be easily generated from tertiary alkyl bromide under the standard reaction (Scheme 4g). The KIE experiment indicate that the deprotonation-elimination step might not the rate-determining step which could explain why we could not isolate intermediate **D**. Based on the above experimental results and previous report



Scheme 4. Control experiments and mechanism study.



Scheme 5. Plausible mechanism for product formation.

[32-34,45,53], a plausible mechanism was proposed (Scheme 5). Mn(II) could be oxidized to Mn(III) by TBPB, and intermediate **III** might be formed by an anion exchange process, which could undergo homolysis to generate the alkoxyl radical **IV**. The *in-situ* generated flourinated ketyl radical **V** *via* radical Brook rearragement was added to styrene to form the new benzyl radical **VI**, and intermediate **D** could be generated through halogen atom abstraction (XAT) from liganted Mn(III) bromide. The selective deprotonative bromide elimination process from the less sterically hindered side would afford the olefin product (Scheme 5). However, we could not rule out the possibility of the formation of product *via* intermediate **E** which would be generated through direct oxidation by hypervalent Mn species.

In conclusion, we have developed a $MnBr_2$ catalyzed regio- and stereo-selective oxidative Mizoroki-Heck type reaction. Various difluoromethylated homoallylic alcohols have been produced in synthetically useful yield. The broad applicability and general utility of this formal C–H alkylation reaction is demonstrated by the wide substrate scopes and highlighted by the late-stage introduction of the difluoroalkyl group to natural product derived olefins. The observed selectivity was proposed to be resulted from the bulky alkylation reagent. We believe that the finding of the selectivity control in this work will attract chemists' interest in the application of oxidative Mizoroki-Heck type reaction in the synthesis of functionalized terminal alkenes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.10.083.

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