ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 7124

Received 19th April 2021,
Accepted 17th June 2021

DOI: 10.1039/d1cc02079j

rsc.li/chemcomm

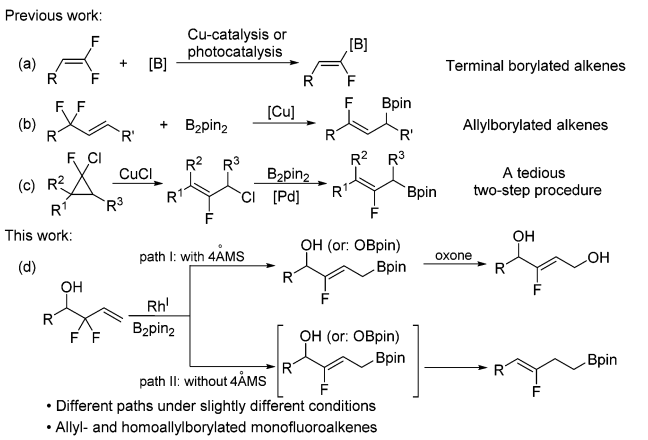
Rh-catalyzed tunable defluorinative borylation†

Fei Hao,[ab] Xueyun Shang,[a] Zhenwei Liu,[a] He Zhang,*[b] Jin-Hong Lin*[bc] and Ji-Chang Xiao*[b]

Described herein is a Rh-catalyzed tunable defluorinative borylation of allylic *gem*-difluorides to provide allylborylated monofluoroalkenes or homoallylborylated monofluoroalkenes with excellent *Z*/*E* selectivities. Completely different reaction paths were observed by slightly changing the reaction conditions. Allylborylated monofluoroalkenes were further converted into dihydroxyl-containing monofluoroalkenes.

Monofluoroalkene is a fluorinated motif which is of particular interest in medicinal chemistry because it has the potential to act as an amide bond isostere.[1] Many biologically active monofluoroalkene-containing molecules have been developed, such as Tezacitabine[2] and Rovafovir Etalafenamide,[3] both of which are being evaluated in clinical trials. Furthermore, monofluoroalkenes are also valuable intermediates in organic synthesis.[4,5] Significant efforts have thus been directed towards the development of efficient methods for the synthesis of monofluoroalkenes.[6–8] As organoboronic acids and their derivatives have become versatile building blocks in organic synthesis, particularly as nucleophilic coupling partners in the catalytic formation of C–C bonds,[9,10] the incorporation of an organoboryl group into a monofluoroalkene molecule may allow for convenient structural modifications. Therefore, the simultaneous installation of a monofluoroalkene moiety and an organoboryl group has thus received increasing attention recently.

Defluorinative borylation is the commonly used strategy, including defluorinative borylation of 1,1-difluoroalkenes *via* a S_NV process (nucleophilic vinylic substitution) (Scheme 1a) and S_N2'-type defluorinative borylation of allylic *gem*-difluorides (Scheme 1b). The S_NV process is usually achieved by Cu-catalysis,[11–15] and a photocatalyzed version was reported recently.[16] Although this S_NV protocol is quite efficient for stereoselective C–F bond cleavage and C–B bond formation, it is limited to the synthesis of terminal monofluoroalkenes (Scheme 1a). S_N2'-type defluorinative borylation can also occur smoothly by Cu-catlaysis.[17,18] High *Z*/*E* selectivity was observed, and enantioselective borylation was enabled by this protocol.[17] The S_N2'-type method could provide internal alkenes, but only allylborylated alkenes would be obtained (Scheme 1b). The borylated monofluoroalkenes could also be synthesized by a two-step process, CuCl-catalyzed ring-opening of *gem*-chlorofluorocyclopropanes and the subsequent Pd-catalyzed coupling with $B_2(pin)_2$ (Scheme 1c).[19] Although high yields and high *Z*/*E* selectivity could be obtained, the tedious two-step procedure may limit its wide applicability. Apparently, it is still highly desirable to develop mild and efficient methods for the synthesis of functionalized borylated monofluoroalkenes.



Scheme 1 The synthesis of borylated monofluoroalkenes.

[a] *Shandong Provincial Key Laboratory of Molecular Engineering, Qilu University of Technology-Shandong Academy of Science, Ji'nan 250353, China*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: zhanghe07@gmail.com, jlin@sioc.ac.cn, jchxiao@sioc.ac.cn*
[c] *Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, P. R. China. E-mail: jlin@shu.edu.cn*

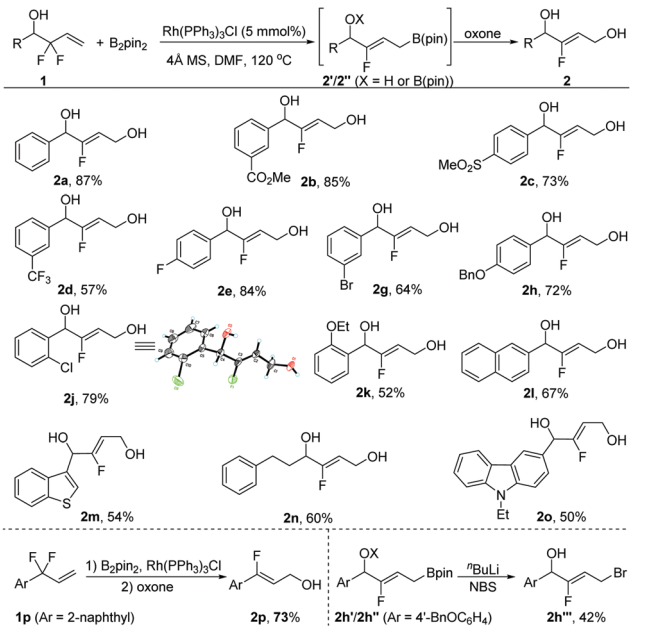
† Electronic supplementary information (ESI) available. CCDC 929444. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc02079j

We have been interested in the synthesis of fluoroalkenes.[20] Previously, we have described that allylic *gem*-difluorides could undergo a defluorination to afford trisubstituted monofluoroalkenes under the catalysis of $Rh(PPh_3)_3Cl$.[21] In contrast, herein we found that the presence of $B_2(pin)_2$ (bis(pinacolato) diboron) resulted in defluorinative borylation (Scheme 1d). Interestingly, two defluorinative borylation paths were observed, and the reaction paths were determined by slightly different conditions, the presence or absence of 4 Å MS (molecular sieves). Allylborylated monofluoroalkenes were obtained when using 4 Å MS (path I), and the absence of 4 Å MS led to sequential processes, including defluorination, dehydroxylation, borylation, and a double-bond shift, giving homoallylborylated monofluoroalkenes as products (path II). The tunable reactions occurred under mild conditions to give products with excellent *Z*/*E* selectivity.

Optimal reaction conditions were established for each path after screening the effects of numerous variants, such as solvents, additives and ligands (please see Table S1 in the ESI† for details). The use of 5 mol% of $Rh(PPh_3)_3Cl$ gave the expected products in good yields. Products **2a′** and **2a″** were usually obtained as mixtures. The **2a′**/**2a″** ratio was found to be different under the same conditions in different attempts, because the B–O bond may readily hydrolyze during isolation. We found that a one-pot procedure could oxidize the **2a′**/**2a″** mixture into a dihydroxyl-containing monofluoroalkene **2a** (Table 1). With the optimized reaction conditions in hand, we then investigated the substrate scope of the defluorinative borylation/oxidation reaction. As shown in Table 1, a variety of allylic *gem*-difluorides could be converted smoothly into the expected products, and excellent stereoselectivity was observed (*Z*/*E* > 98/2). Various functional groups could be tolerated, such as carboxylic ester, sulfonate ester and ether groups. For the substrate without the CH–OH moiety, the reaction also occurred smoothly (**2p**). The structure of product **2j** was determined by single crystal X-ray diffraction.[22] A hydroxyl group is commonly found in organic intermediates and biologically active molecules. In particular, 1,4-dihydroxyl monofluoroalkene derivatives have shown to be potent enzyme inhibitors,[23] meaning that the one-pot process may find great synthetic utility. The Bpin moiety could also be converted into a Br group (**2h‴**), a reactive functionality which is useful for further conversions.

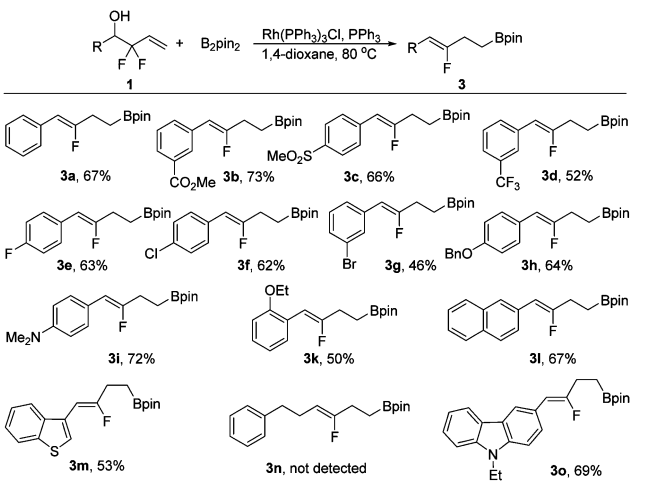
The successful defluorinative-borylation/oxidation encouraged us to further investigate the substrate scope of the dehydroxylative/defluorinative borylation process under the optimized reaction conditions (Table S1 (ESI†), entry 11). This transformation could be extended to a wide range of allylic *gem*-difluorides (Table 2). It is quite surprising that in all cases the shift of the double bond occurred smoothly. Excellent stereoselectivity was obtained (*Z*/*E* > 98/2), and good functional group tolerance was demonstrated. No obvious substituent electronic effect was observed, as evidenced by the moderate yields for the conversion of electron-rich, -neutral and -deficient aryl-containing substrates. No desired product was detected in the case of alkyl substrates even though the substrates were fully consumed (**3n**), reflecting the high importance of the aryl group. The aryl group may be favorable for the formation of a diene, which is a key intermediate for the dehydroxylative/defluorinative borylation reaction (please see the proposed mechanism).

Table 1 Defluorinative borylation/oxidation to dihydroxyl-containing monofluoroalkenes



Isolated yields are shown. Reaction conditions: **1** (0.5 mmol), B_2pin_2 (0.75 mmol), $Rh(PPh_3)_3Cl$ (0.025 mmol) and 4 Å MS (100 mg) in DMF (2 mL) at 120 °C for 70 min under a N_2 atmosphere. After the reaction mixture was cooled, water (2 mL), acetone (0.5 mL), Na_2CO_3 (0.8 g, 7.5 mmol), and oxone (308 mg, 0.5 mmol) were sequentially added. The mixture was stirred for another 15 min.

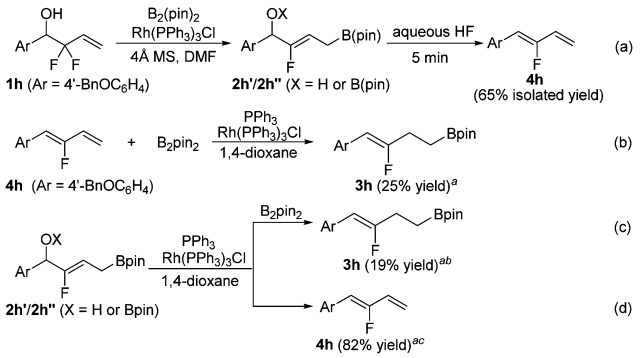
Table 2 Dehydroxylative/defluorinative borylation



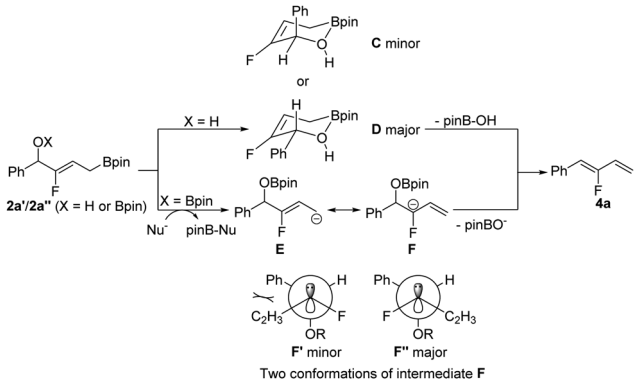
Isolated yields are shown. Reaction conditions: **1** (0.5 mmol), B_2pin_2 (1.0 mmol), $Rh(PPh_3)_3Cl$ (0.025 mmol) and PPh_3 (0.1 mmol) in 1.4-dioxane (2 mL), at 80 °C for 18 h under a N_2 atmosphere.

As shown in Table S1 (ESI†), entry 11, under the optimal conditions for the formation of product **3a**, compounds **2a′/2a″** were also produced as side products. GC–MS analysis revealed that there was another side product whose molecular weight was 148, which should correspond to diene **4a**, PhCH = CF–CH = CH_2. This species could also be produced slowly from the isolated **2a′/2a″** mixture under an air atmosphere at room temperature. Therefore, we speculated that **3a** was produced *via* the sequential formation of **2a′/2a″** and diene **4a**. Since it is hard to isolate the diene due to its low yield and high volatility, the reaction of the BnO-substituted substrate, **1h**, was then examined in detail (Scheme 2). We first collected evidence to find out if diene **4h** is a key intermediate. After substrate **1h** was converted into **2h′/2h″**, the addition of a few drops of aqueous HF solution into the reaction system led to the formation of diene **4h** (Scheme 2, eqn (a)). Diene **4h** could be successfully converted into the desired product **3h** by Rh-catalysis (Scheme 2, eqn (b)). The low yield was mainly because no proton source was present in the reaction system. We have examined various proton sources such as MeOH, $PhCO_2H$ and H_2O, but the yield was still quite low (18%–23%). The use of an extra proton source may have side effects because the conjugate base of the source may deactivate the catalyst by coordination. A suitable proton source may favor the reaction, but our efforts failed to identify the good choice. Next, we then examined the conversion of **2h′/2h″** into **3h** under dehydroxylative/defluorinative borylation conditions (Scheme 2, eqn (c)). Only a 19% yield of **3h** was obtained, because there was not enough proton present. The similar conditions without B_2pin_2 led to the formation of diene **4h** in a high yield, further supporting that diene **4h** is a key intermediate for the formation of **3** (Scheme 2, eqn (d)).

A question arises regarding how products **2′/2″** are transformed into diene **4** and how the 4 Å MS determines the reaction paths. As shown in Scheme 3, two possibilities may exist for the conversions of **2′/2″** into **4** depending on the identity of the X group. If X = H, the hydroxyl group may coordinate to the terminal B(pin) group to generate a six-membered ring. Apparently, configuration **D** is preferred over configuration **C** because in configuration **D** the steric Ph group is in the equatorial position. The elimination of (pin)B–OH



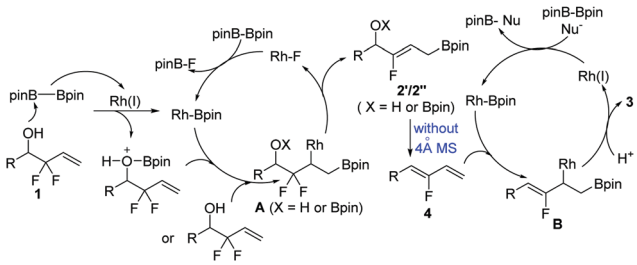
Scheme 2 Experimental evidence. [a]The yield was determined by ^{19}F NMR spectroscopy; [b]0.2 equiv. of PPh_3 was used; [c]1 equiv. of PPh_3 was used.



Scheme 3 The formation of diene **4a**.

from intermediate **D** furnishes diene **4a**. If X = B(pin), the terminal C–B(pin) bond would be easily cleaved by a nucleophile to produce intermediate **E**. The nucleophile could be trace water present in the reaction system, a fluoride anion generated *in situ*, or a hydroxyl group in another substrate molecule. Elimination of $(pin)BO^-$ from the resonance intermediate **F** would readily occur. There are two conformations of intermediate **F**, conformations **F′** and **F″**. Obviously, conformation **F″** is favorable because of steric effects. The elimination of $(pin)BO^-$ from intermediate **F″** then provides diene **4a**. Now it is clear that why 4 Å MS can determine the reaction paths. A nucleophile, such as a fluoride anion and the hydroxyl group, is necessary for the transformation of **2′/2″** into diene **4**. If 4 Å MS, which can act as a Lewis acid,[24] is added, the nucleophiles in the reaction system would coordinate to 4 Å MS, suppressing the further conversion of **2′/2″**.

On the basis of the above results, we propose the plausible reaction mechanism as shown in Scheme 4. The coordination of substrate **1** to B_2pin_2 leads to the cleavage of the B–B bond, and the subsequent ligand exchange gives a Rh-Bpin complex. The addition of Rh-Bpin to the double bond in the substrate or pinB-substrate complex generates intermediates **A**, and the following reductive elimination affords Rh-F species and products **2′/2″**. The *Z*-isomer is favored due to steric effects. The reaction of Rh-F with B_2pin_2 re-produces the Rh-Bpin complex. If 4 Å MS is used, compounds **2′/2″** would be obtained as the final products. Without 4 Å MS, **2′/2″** would be further transformed into diene **4**. The aryl group in the substrate may favor the formation of diene **4** due to conjugation effects. A further addition of Rh-Bpin to the terminal double bond forms



Scheme 4 The plausible reaction mechanism.

intermediate **B**, protonation of which furnishes the final product **3** and releases the Rh(I) complex. The proton may come from the hydroxyl group in the substrate. The activation of B_2pin_2 by a nucleophile in the presence of Rh(I) forms Rh-Bpin. The nucleophile can be a fluoride anion, the additive Ph_3P, or the hydroxyl group in the substrate. Reaction progress kinetic analysis (RPKA) revealed that the conversion of **1** into **3** is zero order in both substrate **1** and $Bpin_2$ (please see the ESI† for details). During the course of the reaction, diene **4** was detected after 0.5 h. Since it was consumed quite slowly, we believe that the transformation of **4** into intermediate **B** is the rate-determining step for the formation of **3**.

In summary, we have described a Rh-catalyzed tunable defluorinative borylation of allylic *gem*-difluorides. Interestingly, slightly different conditions led to completely different reaction paths. The presence of 4 Å MS resulted in defluorinative borylation to give allylborylated monofluoroalkenes, which were further converted into dihydroxyl-containing monofluoroalkenes. However, in the absence of 4 Å MS, sequential processes occurred, including dehydroxylation, defluorination, borylation, and a double-bond shift. High *Z*/*E* selectivity was observed in each reaction path. Since the boryl group can be further transformed, this protocol may find utility in the synthesis of biologically active monofluoroalkenes.

F. Hao and H. Zhang conducted most of the experiments and analyzed the data. X.-Y. Shang and Z.-W. Liu helped conduct the experiments. J.-H. Lin wrote the manuscript and analyzed the data. J.-C. Xiao designed the experiments and wrote the manuscript.

We thank the financial support from the Program for Scientific Research Innovation Team in Colleges and Universities of Shandong Province, Jinan Science and Technology Bureau (2019GXRC021), the National Natural Science Foundation (21971252 and 21991122), Key Research Program of Frontier Sciences, Chinese Academy of Sciences (CAS) (QYZDJSSW SLH049), and Youth Innovation Promotion Association CAS (2019256).

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880.
2 A.-M. Tsimberidou, Y. Alvarado and F. J. Giles, *Expert Rev. Anticancer Ther.*, 2002, **2**, 437–448.
3 M. Berg and Z. Temesgen, *Drugs Future*, 2020, **45**, 459–469.
4 D. Guérin, I. Dez, A.-C. Gaumont, X. Pannecoucke and S. Couve-Bonnaire, *Org. Lett.*, 2016, **18**, 3606–3609.
5 K. Rousée, C. Schneider, J.-P. Bouillon, V. Levacher, C. Hoarau, S. Couve-Bonnaire and X. Pannecoucke, *Org. Biomol. Chem.*, 2016, **14**, 353–357.
6 G. Landelle, M. Bergeron, M.-O. Turcotte-Savard and J.-F. Paquin, *Chem. Soc. Rev.*, 2011, **40**, 2867–2908.
7 P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme and J.-F. Paquin, *Chem. Rev.*, 2015, **115**, 9073–9174.
8 M. Drouin, J.-D. Hamel and J.-F. Paquin, *Synthesis*, 2018, 881–955.
9 S. Darses and J.-P. Genet, *Chem. Rev.*, 2008, **108**, 288–325.
10 L. T. Pilarski and K. J. Szabo, *Angew. Chem., Int. Ed.*, 2011, **50**, 8230–8232.
11 H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi and T. Hosoya, *J. Am. Chem. Soc.*, 2017, **139**, 12855–12862.
12 R. Kojima, K. Kubota and H. Ito, *Chem. Commun.*, 2017, **53**, 10688–10691.
13 J. Zhang, W. Dai, Q. Liu and S. Cao, *Org. Lett.*, 2017, **19**, 3283–3286.
14 H. Ito, T. Seo, R. Kojima and K. Kubota, *Chem. Lett.*, 2018, **47**, 1330–1332.
15 D.-H. Tan, E. Lin, W.-W. Ji, Y.-F. Zeng, W.-X. Fan, Q. Li, H. Gao and H. Wang, *Adv. Synth. Catal.*, 2018, **360**, 1032–1037.
16 W. Xu, H. Jiang, J. Leng, H.-W. Ong and J. Wu, *Angew. Chem., Int. Ed.*, 2020, **59**, 4009–4016.
17 S. Akiyama, K. Kubota, M. S. Mikus, P. H. S. Paioti, F. Romiti, Q. Liu, Y. Zhou, A. H. Hoveyda and H. Ito, *Angew. Chem., Int. Ed.*, 2019, **58**, 11998–12003.
18 T. W. Butcher, J. L. Yang and J. F. Hartwig, *Org. Lett.*, 2020, **22**, 6805–6809.
19 M. A. Novikov and O. M. Nefedov, *Org. Biomol. Chem.*, 2018, **16**, 4963–4967.
20 J.-H. Lin and J.-C. Xiao, *Acc. Chem. Res.*, 2020, **53**, 1498–1510.
21 H. Zhang, J.-H. Lin, J.-C. Xiao and Y.-C. Gu, *Org. Biomol. Chem.*, 2014, **12**, 581–588.
22 Summary of Data CCDC 929444.
23 M. Frederickson, J. R. Coggins and C. Abell, *Chem. Commun.*, 2002, 1886–1887.
24 V. Verdoliva, M. Saviano and S. De Luca, *Catalysts*, 2019, **9**, 248.