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Rh-catalyzed regio-switchable cross-coupling of *gem*-difluorinated cyclopropanes with allylboronates to structurally diverse fluorinated dienes†

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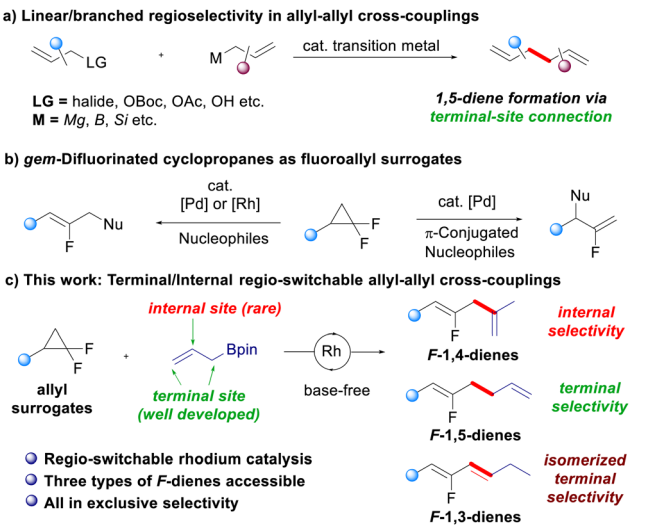
The control of linear/branched selectivity is one of the major focuses in transition-metal catalyzed allyl–allyl cross-coupling reactions, in which bond connection occurs at the terminal site of both the allyl fragments forming different types of 1,5-dienes. Herein, terminal/internal regioselectivity is investigated and found to be switchable in allyl–allyl cross-coupling reactions between *gem*-difluorinated cyclopropanes and allylboronates. The controlled terminal/internal regioselectivity arises from the fine-tuning of the rhodium catalytic system. Fluorinated 1,3-dienes, 1,4-dienes and 1,5-dienes are therefore produced in good yields with respectively isomerized terminal, internal, and terminal regioselectivity.

Introduction

Allyl–allyl cross-coupling reactions catalyzed by a transition-metal complex play an important role in organic synthesis, not only because they constitute a robust and efficient method for the construction of C(sp^3)–C(sp^3) bonds, but also because the two olefin moieties in the products enable diversified downstream transformations.[1–4] Typically, allyl–allyl cross-coupling reactions proceed between allylic electrophiles and allylmetal reagents, and the two allyl moieties are connected together at the terminal site of the allyl fragments through reductive elimination, resulting in the formation of different types of 1,5-dienes *via* linear[2] or branched[3,4] selectivity (Scheme 1a). Furthermore, the introduction of chiral ligands in allyl–allyl cross-coupling reactions,[4] mainly contributed by Morken and coworkers,[4a–4f] allows the generation of enantioenriched 1,5-diene structures, which further enhances the importance of this methodology in synthetic chemistry.[5]

On the other hand, *gem*-difluorinated cyclopropanes[6] have been explored as novel fluoroallyl surrogates to access fluoroalkenes through transition-metal catalyzed C–C bond activation.[7–12] The pioneering work from Fu's group showed the Pd-catalyzed ring-opening functionalization of *gem*-difluorinated cyclopropanes with various nucleophiles, providing fluoroallyllic skeletons with linear selectivity.[7] Subsequently, the reaction scope was extensively expanded by Gong, Fu[8] and other research groups,[9] including our work using rhodium catalysis that realized the fluoroallylation of simple arenes *via* aryl C–H activation and the site-divergent alkenyl C–H fluoroallylation of olefins[10] (Scheme 1b, left). In addition, Lv and Li developed a branched selective alkylation of *gem*-difluorinated cyclopropanes with π-conjugated ambident nucleophiles (including hydrazones and ketones), which may involve 3,3′-reductive elimination to deliver α-fluoroalkene skeletons (Scheme 1b, right).[11] During the preparation of this manuscript, Lv, Chen, Li and coworkers reported that the linear/branched selectivity in



Scheme 1 Regioselectivity in transition-metal catalyzed allyl–allyl cross-coupling reactions and its background.

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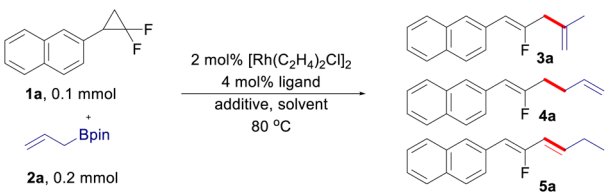
the reaction of *gem*-difluorinated cyclopropanes can be controlled by the steric effects of the Pd–N-heterocyclic carbene complex, which was also achieved by Wang and Shi using a Pd-monophosphine complex, producing both linear and branched fluorinated 1,5-dienes with excellent regioselectivity (Scheme 1b).[12]

Switchable reactivity allows the production of two or more structurally diverse products starting from the same substrates, which has been a constant quest in synthetic chemistry.[13] In the aspect of allyl–allyl cross-coupling reactions, the control of linear and branched selectivity has been well-developed, in which the C–C bond was formed at the terminal site of the allyl moiety.[1–4,12] While there are great advancements in the linear/branched control of allyl–allyl cross-coupling reactions, a strategy that can form a bond connection at the internal site of an allyl moiety to achieve terminal/internal-switchable regioselectivity remains elusive.[14] As continuous research interest on the development of new reactivity of *gem*-difluorinated small rings,[10,15] we envisioned that this challenge can be potentially addressed by the use of *gem*-difluorinated cyclopropanes as fluoroallyl surrogates under rhodium catalysis. Herein, we developed regio-switchable rhodium-catalyzed cross-coupling reactions between *gem*-difluorinated cyclopropanes and allylboronates,[16] which provides a practical and modular approach to structurally diverse fluorinated 1,*n*-dienes (n = 3, 4, and 5). The internal selectivity gives fluorinated 1,4-dienes, while the terminal selectivity furnishes fluorinated 1,3-dienes and 1,5-dienes respectively, depending on whether the C=C bond migrates or not (Scheme 1c). Remarkably, fine-tuning the rhodium precursor and the ligand enables the diversity-oriented synthesis of fluorinated dienes in excellent regioselectivity.

Results and discussion

At the outset of the study, (2,2-difluorocyclopropyl)benzene **1a** and allyl-Bpin **2a** were selected as the model substrates to optimize the reaction conditions (Table 1). With a combination of 2 mol% $[Rh(C_2H_4)_2Cl]_2$ and 4 mol% monodentate phosphine ligand as the catalytic system, internal-selective fluorinated 1,4-diene **3a** was observed in 8–15% yield with low conversion of the substrates (entries 1–3), in which $(4\text{-}ClC_6H_4)_3P$ turned out to be the best ligand in this transformation (entry 3). The reaction conversion was sharply increased with the addition of H_2O, in which the product **3a** can be isolated in 88% yield with exclusively internal selectivity (entries 4–5). It is noteworthy that the regioselectivity can be totally reversed when $AgBF_4$ was used as the additive, leading to the formation of fluorinated 1,5-diene **4a** in 20% yield with exclusively terminal selectivity (entry 6). While increasing the reaction temperature can push the substrate **1a** to full conversion, the yield of **4a** was only slightly improved (entry 7). Replacing the pre-catalyst of $[Rh(C_2H_4)_2Cl]_2$ with $[Rh(CO)_2Cl]_2$ can improve the yield of 1,5-diene to some extent (entry 8). The yield of **4a** could be further improved to

Table 1 Selected optimization of reaction conditions[a]



Entry	Ligand	Solvent (mL)	Additive (mol%)	Yield[b] (%) of dienes **3a**/**4a**/**5a**
1	PPh_3	Dioxane (0.3)	—	8/0/0
2	$(4\text{-}MeC_6H_4)_3P$	Dioxane (0.3)	—	11/0/0
3	$(4\text{-}ClC_6H_4)_3P$	Dioxane (0.3)	—	15/0/0
4	$(4\text{-}ClC_6H_4)_3P$	Dioxane (0.3)	H_2O (10 μL)	56/0/0
5	$(4\text{-}ClC_6H_4)_3P$	Dioxane (0.3)	H_2O (30 μL)	88[c]/0/0
6	$(4\text{-}ClC_6H_4)_3P$	Dioxane (0.3)	$AgBF_4$ (5)	0/20/0
7[d]	$(4\text{-}ClC_6H_4)_3P$	Dioxane (0.3)	$AgBF_4$ (5)	0/26/0
8[d,e]	$(4\text{-}ClC_6H_4)_3P$	Dioxane (0.3)	$AgBF_4$ (5)	0/35/0
9[d,e]	$(4\text{-}ClC_6H_4)_3P$	DME (0.3)	$AgBF_4$ (5)	0/42/0
10[d,e]	$(4\text{-}CF_3C_6H_4)_3P$	DME (0.3)	$AgBF_4$ (5)	0/51/0
11[d,e]	$(4\text{-}CF_3C_6H_4)_3P$	DME (0.5)	$AgBF_4$ (5)	0/63/0
12[d,e,f]	$(4\text{-}CF_3C_6H_4)_3P$	DME (0.5)	$AgBF_4$ (5)	0/72[c]/0
13[d,e]	BINAP	DME (0.5)	$AgBF_4$ (5)	0/0/10
14[d]	BINAP	DME (0.5)	$AgBF_4$ (5)	0/0/27
15[d]	BINAP	THF (0.5)	$AgBF_4$ (5)	0/0/50
16[g]	BINAP	THF (0.5)	$AgBF_4$ (5)	0/0/68[c]

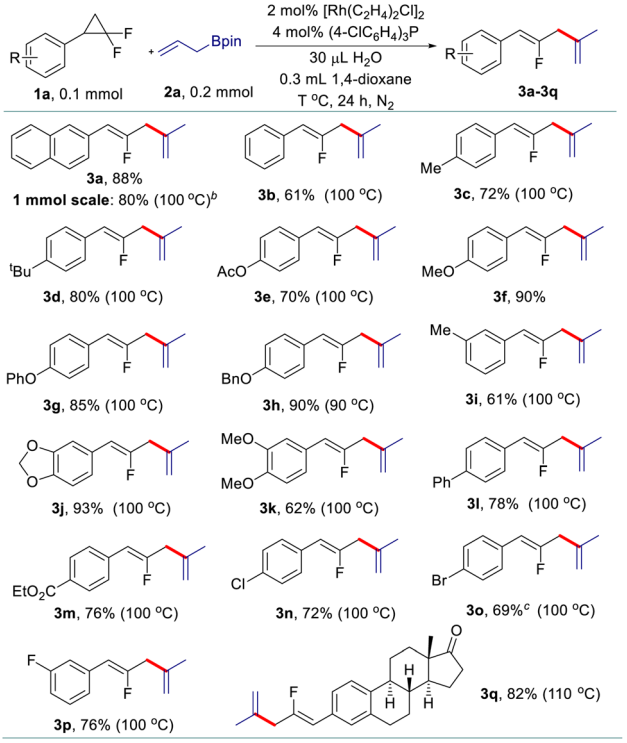
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Rh(C_2H_4)_2Cl]_2$ (2 mol%), ligand (4 mol%), and additive (x mol%) in solvent (x mL) at 80 °C for 24 h. [b] Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c] Isolated yield. [d] Reaction was carried out at 100 °C for 12 h. [e] $[Rh(CO)_2Cl]_2$ was used instead of $[Rh(C_2H_4)_2Cl]_2$. [f] 6 mol% ligand was used. [g] Reaction was carried out at 80 °C for 12 h. BINAP, 1,1′-binaphthyl-2,2′-diphenyl phosphine; DME, 1,2-dimethoxyethane.

42% when DME (1,2-dimethoxyethane) was used as the solvent (entry 9). Taking a more electron-deficient ligand and reducing the reaction concentration to 0.2 M are both beneficial to the reaction (entries 10 and 11). The best result can be gained by modulating the loading of the ligand to 6 mol%, in which the terminal-selective product **4a** can be isolated in 72% yield (entry 12). Interestingly, it was found that the use of BINAP (1,1′-binaphthyl-2,2′-diphenyl phosphine) as the ligand can lead to the formation of a conjugated diene **5a** (entry 13), which is likely generated through C=C bond isomerization from the terminal coupling product **4a**. The development of an efficient approach for C=C bond migration in a site- and stereoselective manner is highly demanded in organic synthesis and has drawn considerable attention recently.[17] $[Rh(C_2H_4)_2Cl]_2$ was proved to be a more efficient pre-catalyst for the generation of 1,3-diene (entry 14). The yield of **5a** can be further improved by using THF (tetrahydrofuran) as the solvent (entry 15), and finally lowering the reaction temperature to 80 °C led to the optimized conditions for isomerized terminal selectivity (entry 16).

Having identified the three sets of optimized reaction conditions, we then evaluated the generality of the allyl–allyl cross-coupling reactions with different regioselectivity. Firstly, we tested the substrate scope for the synthesis of fluorinated 1,4-dienes with internal selectivity (Table 2). The model product **3a** can be obtained in 80% yield in a scale-up reaction. A variety of *gem*-difluorinated cyclopropanes bearing electron-donating (**3a–3i**) or electron-withdrawing (**3l–3p**) aryl moieties all react smoothly, delivering the corresponding fluorinated 1,4-dienes in good to excellent yields with internal selectivity. *gem*-Difluorinated cyclopropanes containing di-substituted aryls also work well to provide the desired products in good yield (**3j** and **3k**). Besides, a *gem*-difluorinated cyclopropane derived from estrone can be successfully transformed into the complex 1,4-diene (**3q**) in 82% yield. Overall, substrates with electron-donating groups showed relatively better reactivity than those bearing electron-withdrawing groups.

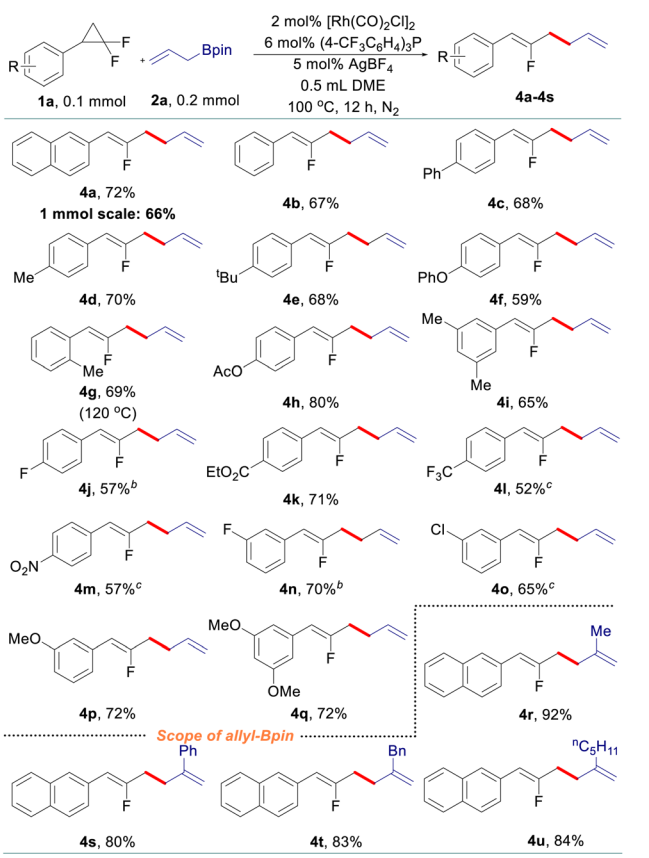
After that, various *gem*-difluorinated cyclopropanes were employed for the construction of fluorinated 1,5-dienes with terminal selectivity. As shown in Table 3, the model fluorinated 1,5-diene **4a** can be produced in good yield in a 1 mmol scale reaction. It was found that fluorinated 1,5-dienes bearing aryls substituted with phenyl (**4c**), alkyl (**4d**, **4e**, **4g**, and **4i**), phenoxy (**4f**), acetoxy (**4h**), methoxy (**4p** and **4q**), halogen (**4j**, **4n**, and **4o**), ester (**4k**), trifluoromethyl (**4l**) or nitro (**4m**) groups were produced in 52–80% yields. Among them, increasing the loading of the rhodium catalyst was generally adopted to gain

Table 2 Selective synthesis of fluorinated 1,4-dienes[a]



[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.002 mmol), $(4\text{-}ClC_6H_4)_3P$ (0.004 mmol), and H_2O (30 μL) in 1,4-dioxane (0.3 mL) at 80 °C for 24 h. Isolated yields are presented. [b] H_2O (100 μL) was used. [c] $[Rh(C_2H_4)_2Cl]_2$ (0.004 mmol) and $(4\text{-}ClC_6H_4)_3P$ (0.008 mmol) were used.

Table 3 Selective synthesis of fluorinated 1,5-dienes[a]



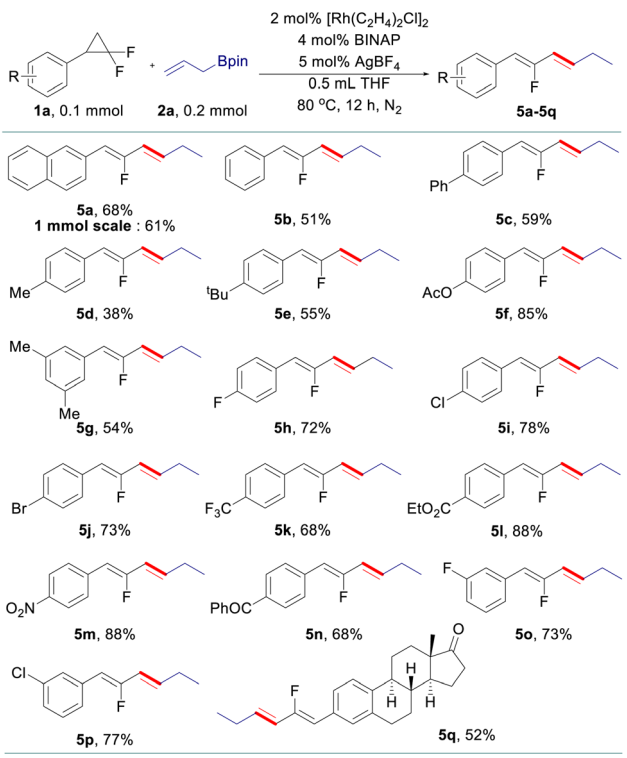
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Rh(CO)_2Cl]_2$ (0.002 mmol), $(4\text{-}CF_3C_6H_4)_3P$ (0.006 mmol), and $AgBF_4$ (0.005 mmol) in DME (0.5 mL) at 100 °C for 12 h. Isolated yields are presented. [b] $[Rh(CO)_2Cl]_2$ (0.003 mmol), $(4\text{-}CF_3C_6H_4)_3P$ (0.009 mmol), and $AgBF_4$ (0.0075 mmol) were used. [c] $[Rh(CO)_2Cl]_2$ (0.004 mmol), $(4\text{-}CF_3C_6H_4)_3P$ (0.012 mmol), and $AgBF_4$ (0.01 mmol) were used.

a satisfactory result for *gem*-difluorinated cyclopropanes bearing an electron-withdrawing group. A sterically hindered substrate with an *ortho*-substituted aryl moiety also works well by elevating the reaction temperature to 120 °C (**4g**). Besides, we also tested the reactivity of different allylboronate derivatives under the optimized reaction conditions. Allylboronates with methyl (**4r**), phenyl (**4s**), benzyl (**4t**) or amyl (**4u**) groups at the 2-position undergo this transformation to afford the corresponding fluorinated 1,5-dienes in excellent yields. Meanwhile, unsymmetric 1-methyl-substituted allylboronate could provide two different 1,5-dienes in 58% combined yields with 3.3 : 1 site-selectivity; 1,1-disubstituted and 3-substituted allylboronates did not react under the reaction conditions (see details in the ESI†).

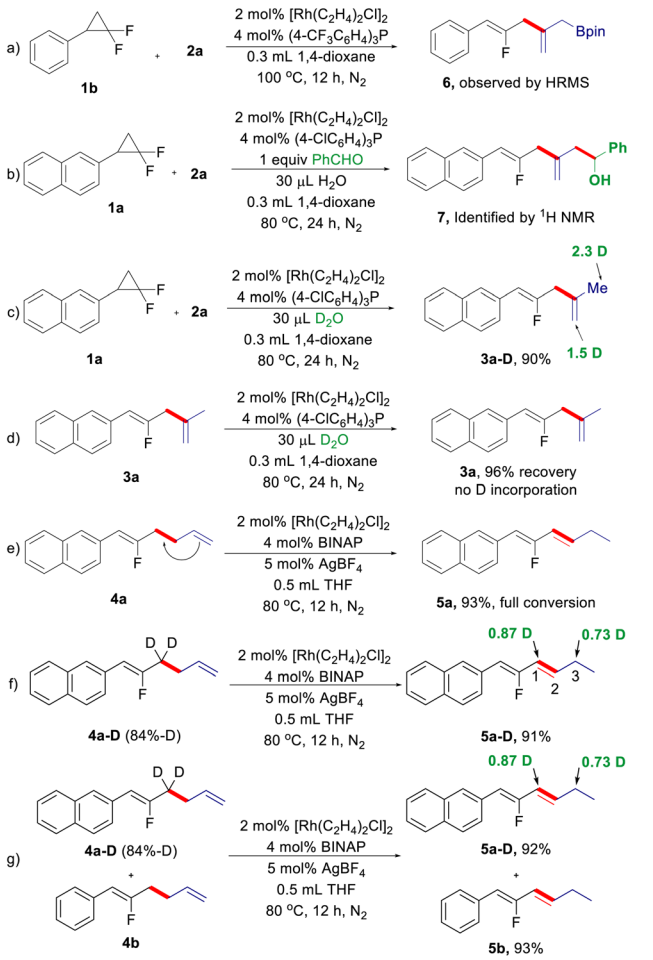
The scope of allyl–allyl cross-coupling in isomerized terminal selectivity was then explored to produce a wide range of fluorinated 1,3-dienes (Table 4). Our protocol tolerates the presence of a variety of functional groups, including alkyl (**5d** and **5e**), phenyl (**5c**), halogen (**5h–5j**), ester (**5l**), nitro (**5m**), and benzoyl (**5n**). In general, substrates bearing electron-withdrawing groups exhibit better reactivity than those with electron-donating groups. *gem*-Difluorinated cyclopropanes with di-substituted (**5g**) and meta-substituted groups (**5o** and **5p**) on the benzene ring are also suitable substrates in this reaction, giving the desired products in moderate to good yields with isomerized terminal selectivity. Again, the synthesis of estrone-derived 1,3-diene **5q** can be smoothly conducted *via* this coupling reaction.

Next, we turned our attention to the reaction mechanism, particularly regarding the process of 1,4-diene formation *via* internal selectivity (Scheme 2). During the optimization of the reaction conditions for 1,4-dienes, the putative dienyl-Bpin **6** can be detected by GC-MS analysis, which was further supported by HRMS (Scheme 2a). Benzaldehyde was used to capture the dienyl-Bpin intermediate under the optimized conditions, and the allylation product **7** was indeed produced (Scheme 2b). A deuterium experiment using D_2O as the additive under the standard conditions can deliver deuterated 1,4-diene **3a-D** in excellent yield with a high degree of deuterium incorporation at the allyl moiety derived from allyl-Bpin, while 1,4-diene **3a** cannot be deuterated under the same reaction conditions (Scheme 2c and d). The above results suggest that a Heck-type process followed by protodeboronation of the resulting dienyl-Bpin accounts for the internal selectivity. Then, we also investigated the origin of the 1,3-diene formation (Scheme 2d). As expected, 1,5-diene **4a** can be smoothly isomerized to give 1,3-diene **5a** under the reaction conditions for isomerized-terminal selectivity, indicating that 1,3-diene is generated by C=C double bond migration from **4a** (Scheme 2e). To elucidate

Table 4 Selective synthesis of fluorinated 1,3-dienes[a]



[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Rh(CO)_2Cl]_2$ (0.002 mmol), BINAP (0.004 mmol), and $AgBF_4$ (0.005 mmol) in THF (0.5 mL) at 80 °C for 12 h.

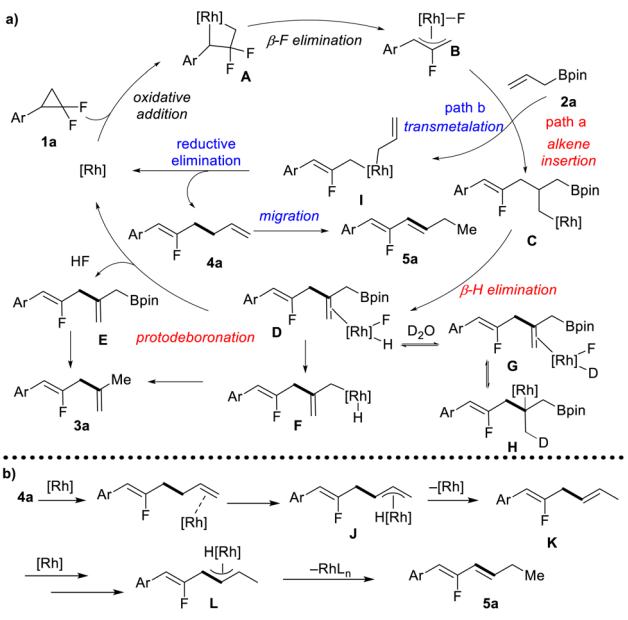


Scheme 2 Mechanistic investigations.

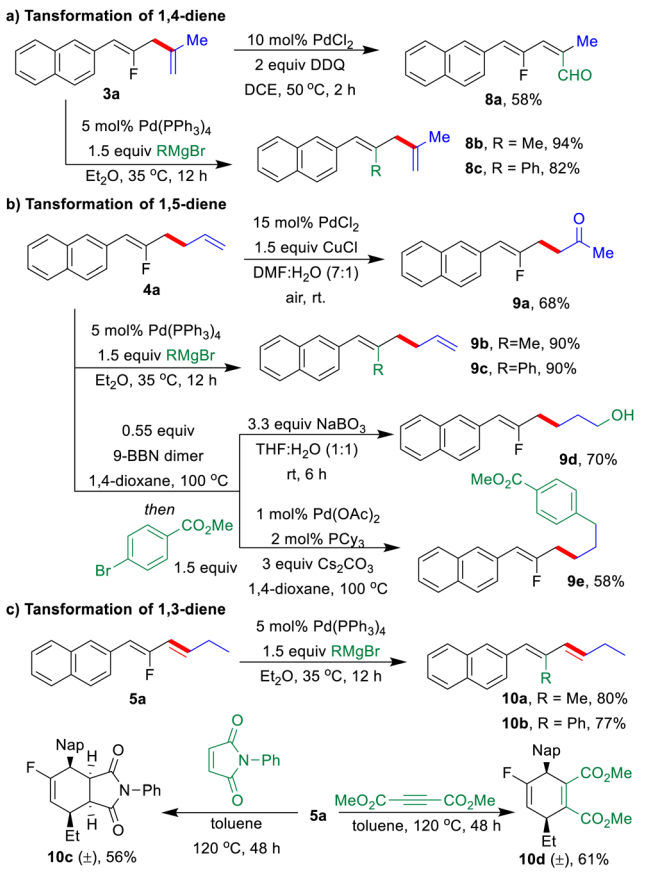
the process of this alkene isomerization,[18] deuterium labelling experiments were conducted. When isotopically labelled fluorinated 1,5-diene **4a-D** was treated under cationic rhodium/BINAP conditions, a 1,3-deuterium shift was observed (Scheme 2f). Furthermore, a H/D crossover experiment shows that no intermolecular deuterium is exchanged between **4a-D** and **4b**, which indicates that the 1,3-hydrogen migration is exclusively intramolecular (Scheme 2g). These results suggest that a π-allyl mechanism may be involved in this alkene isomerization.

Based on our mechanistic investigations and previous reports,[10] a plausible mechanism is proposed (Scheme 3a). Firstly, the oxidative addition of *gem*-difluorinated cyclopropane with a Rh(I) complex gives four-membered rhodacycle **A**, followed by β-F elimination to form the key allyl-Rh(III) complex **B**. At this stage, there are two reaction pathways for the Rh-complex **B**. In path a, allyl-Bpin serves as an alkene functionality that inserts into the Rh-allyl bond to afford intermediate **C**, followed by β-H elimination to give a dienyl-Bpin-bound rhodium complex **D**. The dissociation of the rhodium complex **D** would give dienyl-Bpin **E** and F-[Rh]-H species. The reductive elimination of F-[Rh]-H would regenerate the rhodium catalyst and release one molecule of HF. Finally, dienyl-Bpin **E** would undergo protodeboronation with *in situ* generated HF to form 1,4-diene **3a** as the coupling product. Meanwhile, the protodeboronation can also occur through a sequence of intramolecular transmetallation and reductive elimination *via* intermediate **F**. The rationalization of the high degree of deuterium incorporation may include deuterium exchange from **D** to **G**, multiple times of olefin migratory insertion and β-H elimination (**G** to **H**), and protodeboronation with *in situ* generated DF. In path b, the allyl-Rh(III) complex **B** would undergo transmetallation with allyl-Bpin to give a di-allyl rhodium complex **I**, and allyl–allyl reductive elimination furnishes fluorinated 1,5-diene **4a**. When using BINAP as the ligand, further C=C double migration can occur in a site- and stereoselective manner forming conjugated diene **5a** as the final product. Mechanistic studies support that this alkene migration follows the π-allyl pathway, as shown in Scheme 3b. The terminal olefin coordinates to the rhodium catalyst, followed by C–H bond addition at the allylic site to form a η^3-allyl rhodium intermediate **J**. Then, C–H bond reductive elimination at the terminal site gives 1,4-diene **K**, and a second migratory process would provide the thermodynamically more stable 1,3-diene **5a**.

The synthetic practicability of the regio-switchable allyl–allyl coupling strategy was further demonstrated by a series of post-functionalization of three types of fluorinated dienes (Scheme 4). Under palladium catalysis, F-based Kumada-coupling between 1,*n*-dienes (**3a**, **4a**, and **5a**) with Grignard reagents as the nucleophiles gave highly functionalized 1,*n*-dienes in excellent yields, in which the configuration of the double bonds remain unchanged (**8b**, **8c**, **9b**, **9c**, **10a**, and **10b**).[19] A Pd-catalyzed oxygenation of the allylic C–H bond was performed with **3a** to generate fluorinated alkenyl aldehyde **8a** in 58% yield (Scheme 4a).[20] Furthermore, Wacker oxidation of **4a** in the presence of Pd/Cu under air gave fluorinated γ,δ-unsaturated ketone **9a** in 68% yield.[21] The fluorinated 1,5-diene **4a** underwent a highly regioselective hydroboration with 9-BBN, followed by oxidation with $NaBO_3$ or Suzuki coupling with methyl 4-



Scheme 3 Proposed mechanism for the formation of fluorinated 1,*n*-dienes.



Scheme 4 Synthetic applications.

bromobenzoate to deliver **9d** or **9e** in moderate to good yields, respectively (Scheme 4b).[22] Finally, Diels–Alder reactions of conjugated diene **5a** with 1-phenyl-1*H*-pyrrole-2,5-dione or dimethyl but-2-ynedioate produced fluorinated cyclic compounds **10c** and **10d** in moderate yields (Scheme 4c).

Conclusions

In conclusion, we have developed a facile protocol to access structurally diverse fluorinated dienes through rhodium-catalyzed region-switchable cross-coupling of *gem*-difluorinated cyclopropanes with allylboronates. The regioselectivity pattern could be dominated by an appropriate choice of the rhodium catalyst and phosphine ligand. The internal selectivity that gives fluorinated 1,4-dienes can be achieved in the presence of a neutral rhodium catalyst and a monodentate phosphine ligand, while the use of a cationic rhodium catalyst and monodentate phosphine ligand ensures terminal selectivity to produce fluorinated 1,5-dienes. When BINAP serves as the ligand, the terminal-selective transformation undergoes an additional C=C bond migration to give conjugated dienes. Mechanistic investigations indicate that the internal selectivity comes from a Heck-type process/protodeboronation sequence, while 1,3-dienes are derived from the isomerization from 1,5-dienes *via* the π-allyl mechanism. The practicability of regio-switchable allyl–allyl coupling reactions is also demonstrated by a series of downstream transformations of three types of dienes for the synthesis of polysubstituted and fluorine-containing molecules. Future work will focus on understanding how the combination of Rh/ligand controls the regioselectivity.

Data availability

All experimental data in this manuscript are available in the ESI.†

Author contributions

Y. Z. and Y. X. conceived and designed the experiments. Y. Z., H. Y., J. D., and Q. H. performed the experiments, compound characterization, and data analysis. Y. Z., G. H. and Y. X. co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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