This article can be cited before page numbers have been issued, to do this please use: Y. Zeng, H. Yang, J. Du, Q. HUANG, G. Huang and Y. Xia, Chem. Sci., 2022, DOI: 10.1039/D2SC04118A.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Rh-Catalyzed Regio-Switchable Cross-Coupling of gem-Difluorinated Cyclopropanes with Allylboronates to Structurally Diverse Fluorinated Dienes

Yaxin Zeng, Hui Yang, Jiayi Du, Qin Huang, Guoliang Huang, and Ying Xia

The control of linear/branched selectivity is one of the major focuses in transition-metal catalyzed allyl-allyl cross-coupling reactions, in which the bond connection occurs at the terminal site of both the two 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 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 moiety in the products enable diversified downstream transformations. Typically, the allyl-allyl cross-coupling reactions proceed between allylic electrophiles and allylmetal reagents, and the two allyl moieties are connected together both at the terminal site of the allyl fragments through reductive elimination, resulting the formation of different types of 1,5-dienes via linear or branched selectivity (Scheme 1a). Furthermore, the introduction of chiral ligands in allyl-allyl cross-coupling reactions, mainly contributed by Morken and coworkers, allows the generation of enantioenriched 1,5-diene structures, which further enhances the importance of this methodology in synthetic chemistry.

On the other hand, gem-difluorinated cyclopropanes have been explored as novel fluoroalkyl surrogates to access fluoroalkenes through transition-metal catalyzed C−C bond activation. The pioneering work from Fu’s group showcased the Pd-catalyzed ring-opening functionalization of gem-difluorinated cyclopropanes with various nucleophiles, providing fluoroallylic skeletons with linear selectivity. Subsequently, the reaction scope was extensively expanded by Gong, Fu and other research groups, 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

Scheme 1

fluoroallylation of olefins (Scheme 1b, left). In addition, Lv and Li developed a branched selective allylation 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). During the preparation of this manuscript, Lv, Chen, Li and coworkers reported that the linear/branched selectivity in the reaction of gem-difluorinated cyclopropanes can be controlled by steric effects of Pd–N-heterocyclic carbene complex, which was also achieved by Wang and Shi using Pd-monophosphine complex, producing both linear and branched fluorinated 1,5-dienes in excellent regioselectivity (Scheme 1b).

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.

ARTICLE

Received 00th January 20xx, Accepted 00th January 20xx
DOI: 10.1039/x0xx00000x

Please do not adjust margins
aspect of allyl-allyl cross-coupling reaction, 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.\textsuperscript{1,4,12} While there are great advancements in the linear/branched control of allyl-allyl cross-coupling reactions, strategy that can render the bond connection at the internal site of an allyl moiety to achieve terminal/internal-switchable regioselectivity remains elusive.\textsuperscript{14} As a continuous research interest on the development of new reactivity of gem-difluorinated small rings,\textsuperscript{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\textsuperscript{16}, which provides a practical and modular approach to structurally diverse fluorinated 1,n-dienes (n = 3,4,5). 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\(_5\)H\(_4\))Cl\(_2\)] and 4 mol% monodentate phosphate 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-CIC\(_3\)H\(_4\))P turned out to be the best ligand in this transformation (entry 3). The reaction conversion was sharply increased with the addition of H\(_2\)O, 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 from [Rh(C\(_5\)H\(_4\))Cl\(_2\)] with [Rh(CO)\(_3\)]\(_2\) can improve the yield of 1,5-diene to some extent (entry 8). The yield of 4a could be further improved to 42% when DME (1,2-dimethoxyethane) was used as the solvent (entry 9). Taking more electronic-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 efficient approach for C=C bond migration in site- and stereoselective manner is highly demand in organic synthesis and has drawn considerable attention recently.\textsuperscript{17} [Rh(C\(_5\)H\(_4\))Cl\(_2\)] was proved to be 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 the 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 aryl also work well to provide the desired products in good yield (3j, 3k). Besides, 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 show in Table 3, the model fluorinated
Selective Synthesis of Fluorinated 1,4-Dienes*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>(0.1 mmol), [Rh(C11H15)Cl] (0.002 mmol), [4-CF2CH2]3P (0.004 mmol), PhO (30 µL) in 1,4-dioxane (0.3 mL) at 80 °C for 24 h. Isolated yields are 1 mmol scale: 58% (100 °C), 66% (120 °C)</td>
</tr>
<tr>
<td>2a</td>
<td>(0.2 mmol), [Rh(C11H15)Cl] (0.006 mmol), AgBF4 (0.005 mmol) in DME (0.5 mL) at 100 °C for 12 h. Isolated yields are 1 mmol scale: 72% (100 °C), 76% (120 °C)</td>
</tr>
</tbody>
</table>

1,5-diene 4a can be produced in good yield in 1 mmol scale reaction. It was found that fluorinated 1,5-dienes bearing aryls substituted with phenyl (4c), alkyl (4d, 4e, 4g, 4l), phenoxyl (4f), acetoxy (4h), methoxy (4i, 4q), halogen (4j, 4n, 4o), ester (4k), trifluoromethyl (4l) or nitro (4m) group were produced in 52%-80% yields. Among them, increasing the loading of the rhodium catalyst was generally adopted to gain a satisfactory result for gem-difluorinated cyclopropanes bearing an electron- withdrawing group. 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 methyal (4r), phenyl (4s), benzyl (4t) or amyl (4u) group 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 supporting information).

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, 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, 5p) on 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). Deuterium experiment using D2O as the additive under the standard conditions can deliver deuterated 1,4-diene 3a-D in excellent yield with 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 2d). 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 the process of this alkene isomerization, deuterium labeling 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 exchanges 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.

Table 4 Selective synthesis of fluorinated 1,3-dienes

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mol% [Rh(CO)₂Cl]₂</td>
<td>6a, observed by HRMS</td>
</tr>
<tr>
<td>5 mol% AgBF₄</td>
<td></td>
</tr>
<tr>
<td>0.5 mL THF</td>
<td></td>
</tr>
<tr>
<td>80 °C, 12 h, N₂</td>
<td></td>
</tr>
<tr>
<td>1a, 0.1 mmol</td>
<td></td>
</tr>
<tr>
<td>2a, 0.2 mmol</td>
<td></td>
</tr>
<tr>
<td>5a-5q</td>
<td></td>
</tr>
</tbody>
</table>

Based on our mechanistic investigations and previous reports, a plausible mechanism is proposed (Scheme 3a). Firstly, the oxidative addition of gem-difluorinated cyclopropane with 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, the allyl-Bpin serves as an alkene functionality that inserts to the Rh-allyl bond to afford intermediate C, followed by β-H elimination to give dienyl-Bpin-bonded rhodium complex D. The dissociation of rhodium complex D would give dienyl-Bpin E and F=Rh–H species. 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

Scheme 2 Mechanistic investigations.

a) Pathway a: oxidative addition followed by β-F elimination and reductive elimination.

b) Pathway b: transmetalation followed by β-H elimination and protodeboronation.
intramolecular transmetallation and reductive elimination via intermediate F. The rationalization for 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, allyl-Rh(III) complex B would undergo transmetallation with allyl-Bpin to give di-allyl rhodium complex I, and allyl-Rh reductive elimination furnishes fluorinated 1,5-diene 4a. When using BINAP as the ligand, further C=C double migration can occur in 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 allylic site to form a π3-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, 10b). A Pd-catalyzed oxygenation of allylic C-H bond was performed with 3a to generate fluorinated alkenyl aldehyde 8a in 58% yield (Scheme 4a). Furthermore, Wacker oxidation of 4a in the presence of Pd/Cu under air gave fluorinated y,6-unsaturated ketone 9a in 68% yield. The fluorinated 1,5-diene 4a underwent a highly regioselective hydroboronation with 9-BBN, which was followed by oxidation with NaBO$_3$ or Suzuki coupling with methyl 4-bromobenzoate to deliver 9d or 9e in moderate to good yields, respectively (Scheme 4b). Finally, Diels–Alder reactions of conjugated diene 5a with 1-phenyl-1H-pyrrole-2,5-dione or dimethyl but-2-yne-dioate 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 appropriate choice of 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. The terminal selectivity gives fluorinated 1,5-dienes, while the use of cationic rhodium catalyst and monodentate phosphine ligand ensures terminal selectivity in the 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 the regio-switchable allyl-allyl coupling reactions is also demonstrated by a series of downstream transformations of the three types dienes for the synthesis of polysubstituted and fluorine-containing molecules. Future work will focus on understanding the origin of how the combination of Rh/ligand controls the regioselectivity.

Data availability

All experimental data in this manuscript are available in the ESI.$^\dagger$

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

This work is supported by "Thousand Young Talents Program" (Grant 15-YINGXIA), the National Natural Science Foundation
(Grant 22001180), the Key Research and Development Program of Sichuan Province (Grant 2021YFQ00060), the start-up funding from Sichuan University (Grant YJ201965), and Tsinghua Laboratory Innovation Fund (100020019).

References


