Rhodium-Catalyzed Enantio- and Regioselective Allylation of Indoles with *gem*-Difluorinated Cyclopropanes

Hui Yang, Yaxin Zeng, Xiangyu Song, Ling Che, Zhong-Tao Jiang, and Ying Xia*

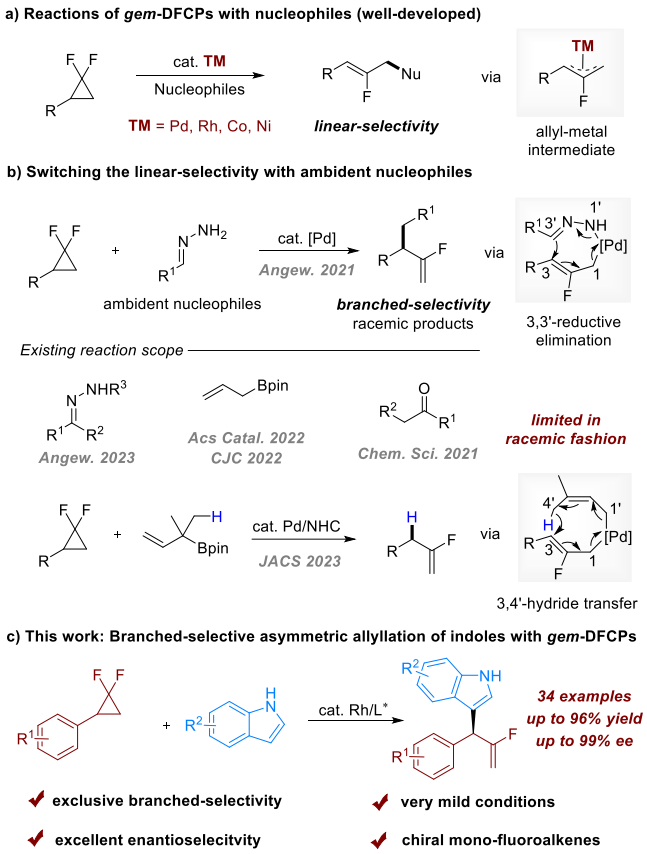
Supporting Information Placeholder

ABSTRACT: The use of *gem*-difluorinated cyclopropanes (*gem*-DFCPs) as fluoroallyl surrogates under transition-metal catalysis has drawn considerable attention recently but such reactions are restricted to producing achiral or racemic mono-fluoroalkenes. Herein, we report the first enantioselective allylation of indoles with *gem*-DFCPs under rhodium catalysis. This reaction shows exceptional branched regioselectivity towards rhodium catalysis with *gem*-DFCPs, which provides an efficient route to enantioenriched fluoroallylated indoles with wide substrate scope and good functional group tolerance.

Organofluorine compounds occupy a significant place in pharmaceutical chemistry[1] and material science[2], as evidenced by the ubiquity of fluorine-containing molecules in marketed pharmaceuticals and functional materials. Among the various fluorinated motifs, the mono-fluoroalkenes have consistently attracted attention from the synthetic community.[3] The pursuit of synthetic methods to access structurally diverse mono-fluoroalkenes stems from their potential as amide or enol mimics in the modification of bioactive molecules,[4] as well as their capacity to serve as molecular platform for further functionalization.[5]

Recently, *gem*-Difluorinated cyclopropanes (*gem*-DFCPs)[6] have garnered great attention in organic synthesis due to their powerful ability to transform into other fluorine-containing molecules, particularly mono-fluoroalkenes through transition-metal catalyzed allylic substitution reactions (Scheme 1a).[7] The pioneering work reported by Fu's group demonstrated that the Pd-catalyzed cross-coupling of *gem*-DFCPs with various nucleophiles to form linear-selective β-mono-fluoroalkenes.[8] Subsequently, the reaction scope has been extensively extended to access β-mono-fluoroalkenes integrated with the formation of C–C, C–N, C–S and C–P bonds.[9-11] Importantly, Lv and Li developed an elegant strategy to switch the regioselectivity from linear to branched in Pd/NHC-catalyzed cross-coupling of *gem*-DFCPs via inner-sphere 3,3'-reductive elimination process (Scheme 1b).[12] The employment of π-conjugated ambident nucleophiles (including hydrazones,[12,13a] ketones,[13b] and allylboronates[13c,13d]) has been the key to the success, delivering a series of racemic α-mono-fluoroalkene compounds. Very recently, an exceptional example is reported by the use of 3,3-dimethylallyl Bpin as an unusual hydride source, in which a branched-selective hydrodefluorination of *gem*-DFCPs was achieved to afford terminal α-mono-fluoroalkenes by Pd/NHC catalysis via an unusual 3,4'-hydride transfer mechanism.[14] Despite these significant achievements that have been made in the synthesis of racemic or achiral mono-fluoroalkenes, a strategy for the collection of enantioenriched α-mono-fluoroalkenes using *gem*-DFCPs as fluoroallyl surrogates has not been yet realized.

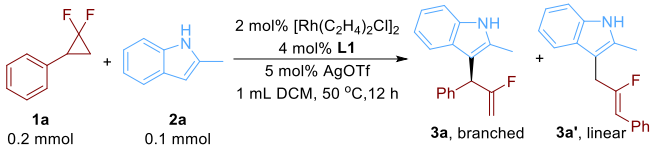
Scheme 1. Regioselective Ring-Opening Allylation Reactions of *gem*-DFCPs



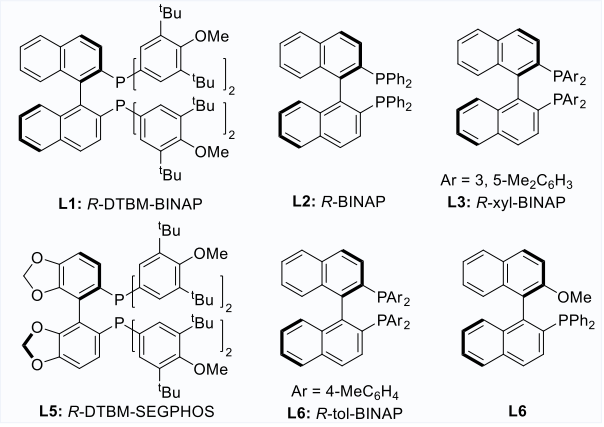
The development of such enantioselective reaction faces a significant challenge, which is that nucleophiles, other than ambident nucleophiles, often favor linear-selectivity because of the preferential nucleophilic attack at the less hindered carbon atom of the allyl-metal intermediate.[7-14] Therefore, overcoming the innate reactivity would potentially lead to the development of asymmetric allylic coupling

for constructing enantioenriched α-mono-fluoroalkenes. Our group has been continuously interested in the exploration of divergent reactivity of *gem*-DFCPs especially with rhodium catalysis.[10,15] However, the products were generally restricted to linear-selectivity from the allyl-Rh intermediate.[10] Herein, we disclosed the first Rh-catalyzed branched-regioselective and enantioselective allylic coupling between *gem*-DFCPs and indoles (Scheme 1c).[16] It was found that a catalytic system consisting of a cationic Rh complex and a bulky bidentate ligand ensures high efficiency, excellent branched-regioselectivity and enantioselectivity, thus providing an efficient and general approach to enantioenriched α-mono-fluoroalkenes.

Table 1. Optimization of Reaction Conditions[a]



entry	variations	yield (%)[b]	b/l[c]	ee (%)
1	none	93 (92[d])	38:1	93
2	w/oAgOTf	0	-	-
3	$AgPF_6$	53	25:1	89
4	$AgBF_4$	56	25:1	69
5	L2	86	11:1	31
6	L3	72	4:1	13
7	L4	66	11:1	29
8	L5	15	26:1	91
9	L6	0	-	-
10	PhCl	91	31:1	91
11	DCE	91	29:1	85
12[e]	THF, **L2**	36	1:1.3	29



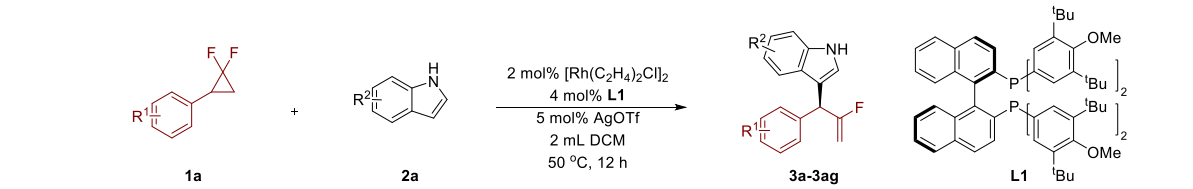
[a]Reactions were performed on 0.1 mmol scale. [b]Yield was determined by ^{19}F NMR using $PhCF_3$ as the internal standard. [c]The b/l refers to the ratio of branched to linear (**3a**:**3a'**), which was determined by ^{19}F NMR of the crude products. [d]Reaction was performed on 0.2 mmol scale and it was the isolated yield. [e]$AgPF_6$ was used instead of $AgBF_4$.

We first explored the branched allylation reaction by using (2,2-difluorocyclopropyl)benzene (**1a**) and 2-methylindole (**2a**) as the model substrates under rhodium catalysis. After extensive condition screening, we successfully obtained the desired branched fluoroallylation product **3a** in 93% yield with 93% ee and excellent branched-regioselectivity (b/l = **3a**:**3a'** = 38:1) (please see Supporting Information for details on how to determine the regioselectivity). The optimized reaction conditions feature with 2 mol% $[Rh(C_2H_4)_2Cl]_2$ as the pre-catalyst, 4 mol% *R*-DTBM-BINAP (**L1**) as the bulky ligand and 5 mol% AgOTf as the halide scavenger in DCM at 50 °C for 12 h (entry 1). Control experiment shows that the presence of silver salt was essential for this reaction (entry 2). It was proved that AgOTf was much better for the reaction than $AgPF_6$ and $AgBF_4$, not only on the yields but also the enantio- and regioselectivity (entries 3 and 4). Replacing **L1** with other types of bidentate phosphine ligands, including *R*-BINAP (**L2**), *R*-xyl-BINAP (**L3**), *R*-tol-BINAP (**L4**), *R*-DTBM-Segphos (**L5**), resulted in decreased yields and selectivities of the product **3a** (entries 5-8). No target product **3a** was observed in the presence of monodentate ligand (**L6**), which indicates that the use of a bidentate ligand was crucial in this transformation (entry 9). As for the solvent effect, 1,2-dichloroethane and chlorobenzene were less effective than DCM in this transformation (entries 10 and 11). When using tetrahydrofuran as the solvent, $AgPF_6$ as the silver salt, and **L2** as the ligand, the linear product **3a'** becomes the major one with a ratio of b/l = 1:1.3, suggesting the regioselectivity of the allylation reaction could be determined by the reaction conditions (entry 12).

Having established the optimized conditions, we investigated the scope and limitations of this rhodium catalyzed asymmetric allylation reaction. Firstly, we examined the scope of *gem*-difluorinated cyclopropanes with 2-methylindole **2a**. The reaction of model substrate **1a** and **2a** provided the desired product **3a** in 92% yield with 93% ee. The substrates bearing an electron-donating group (R = -Me, -pyrrole, -cyclopropyl, -OPh, -OAc, -OMe) of the phenyl ring provided the corresponding products in moderate to good yields and enantioselectivities (**3b**-**3g**, **3q**) in 12 h. The substrates with an electron-withdrawing group (R = -Br, -Cl, -F, -Ph, -Naphthalene, -pyrrole) of the phenyl ring providing products with moderate to good yields and excellent enantioselectivity (**3g**-**3o**), in which the absolute configuration of **3h** was unambiguously confirmed by X-ray crystallography. The reaction is slightly sensitive to the substituent at the ortho-position, as the enantioselective yield was decreased when the steric group (R = -OMe) in that position (**3p**). *gem*-Difluorinated cyclopropanes with benzothiophene substituent deliver the product in high yield and ee (**3r**).

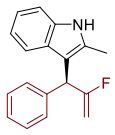
After that, the reactivity of indole was then evaluated. As shown in Scheme 2B, a wide array of substituted indole were studied in moderate to good yields with excellent regioselectivity and enantioselectivity. A variety of electron-donating (**3u**-**3ab**) and electron-withdrawing groups (**3w**-**3aa**) were found to be all tolerated, providing the corresponding products in moderate to good yields and excellent enantioselectivity. Substituting the ethyl or phenyl groups on indole at the position 2 afforded the branched product in high yield with high ee (**3ab**, **3ac**). The steric hindrance may result in a decrease in the enantioselectivity of the reaction.

Scheme 2. Substrate Scope of Indole Fluoroallylation[a,b]

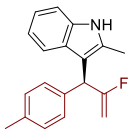


1a + 2a → 3a-3ag; L1

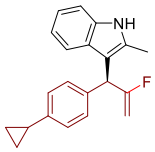
A Scope of gem-DFCPs



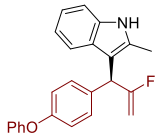
3a, 93% ee, 92% yield



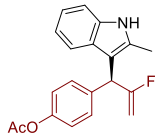
3b, 91% ee,57% yield



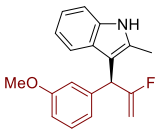
3c, 89% ee ,68% yield



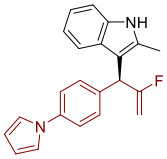
3d, 91% ee, 85% yield



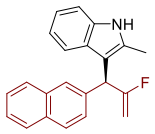
3e, 96% ee, 95% yield



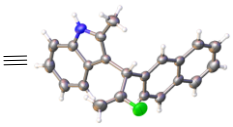
3f, 91% ee,95% yield



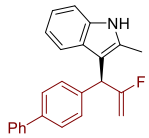
3g, 93% ee, 96% yield



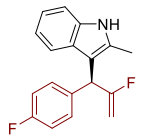
3h, 91% ee, 83% yield



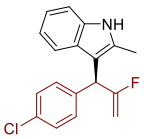
X-ray of **3h**
CCDC: 2331683



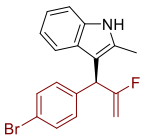
3i, 93% ee, 93% yield



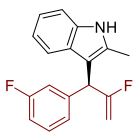
3j, 93% ee, 92% yield[c]



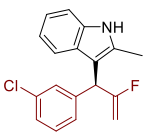
3k, 96% ee, 55% yield



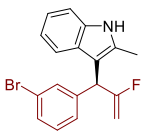
3l, 95% ee, 49% yield



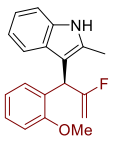
3m, 96% ee, 53% yield



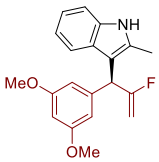
3n, 95% ee, 88% yield



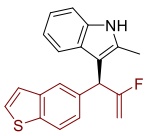
3o, 97% ee, 95% yield



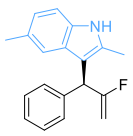
3p, 83% ee, 70% yield



3q, 91% ee, 60% yield

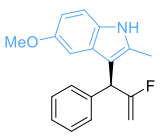


3r, 91% ee, 95% yield

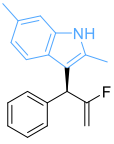


3s, 92% ee, 86% yield

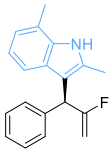
B Scope of Indoles



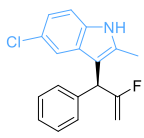
3t, 93% ee, 94% yield



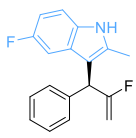
3u, 90% ee, 85% yield



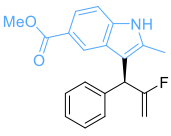
3v, 85% ee, 46% yield



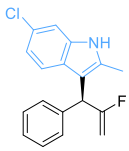
3w, 91% ee, 66% yield



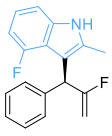
3x, 95% ee, 66% yield



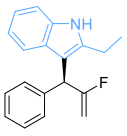
3y, 94% ee, 62% yield



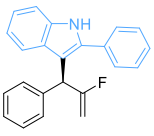
3z, 93% ee, 39% yield



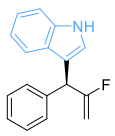
3aa, 90% ee, 55% yield



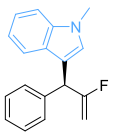
3ab, 94% ee, 81% yield



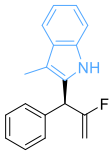
3ac, 85% ee, 60% yield



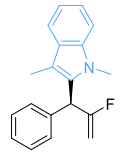
3ad, 81% ee, 70% yield[e]



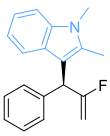
3ae, 73% ee, 46% yield[d]
4:1(b/l)



3af, 89% ee, 77% yield[e]
6:1(b/l)



3ag, 99% ee, 51% yield[e]
14:1(b/l)

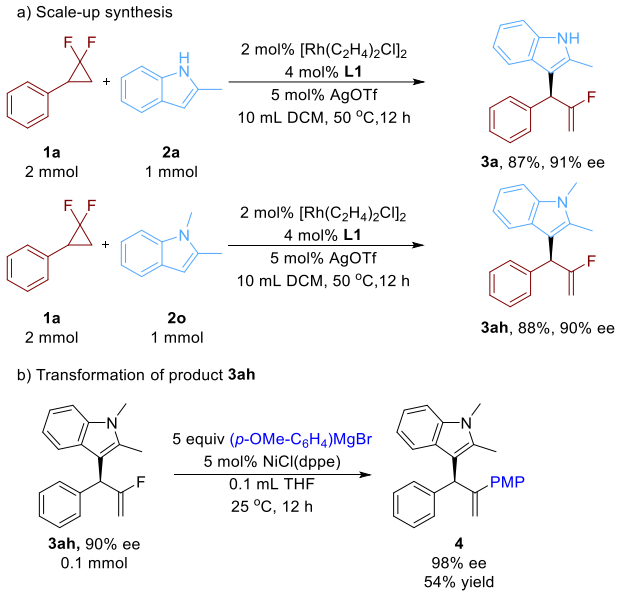


3ah, 95% ee, 90% yield

[a]General conditions: **1a** 0.2 mmol, **2a** 0.1 mmol, 2 mol% $[Rh(C_2H_4)_2Cl]_2$, 4 mol% **L1**, 5 mol% AgOTf, 50 °C, 1 mL DCM, 12 h. [b]Isolated yields are presented. The regioselectivity was over 20>1 if not noted. [c]3 mol% $[Rh(C_2H_4)_2Cl]_2$, 6 mol% **L1.** [d]4 mol% *S*-SEGPHOS, 40 °C. [e]4 mol% *R*-BINAP, 40 °C.

Motivated by the broad functional group tolerance demonstrated above, we explored the applicability in more complex settings. Under standard conditions, the use of ordinary indole resulted in low conversion of the substrates. However, replacing the ligand with a conventional ligand **L2** significantly enhances both enantioselectivity and reactivity (**3ad**). With *N*-Me-indole, the enantioselectivity was slightly enhanced with moderate regioselectivity, in which the branched selectivity was still the major reaction pathway, and the yield was moderate with *S*-SEGPHOS (**3ae**). When a methyl group is introduced at the 3-position, the reaction performs well with moderate regioselectivity by *R*-BINAP (**3af**). In cases where dimethyl substitution is employed, it has been observed that the indole substituted with methyl groups at the 1 and 3 positions demonstrates exceptional performance in enantiomeric excess and moderate yield albeit with a slight decrease in branched selectivity (**3ag**). It is worth noting that 3-methyl-substituted indoles (**3af**, **3ag**) undergo allylation at position 2 instead of dearomatization.[9g] Conversely, indole substituted with 1,3-dimethyl groups slightly decreased reactivity with excellent enantiomeric excess (**3ah**).

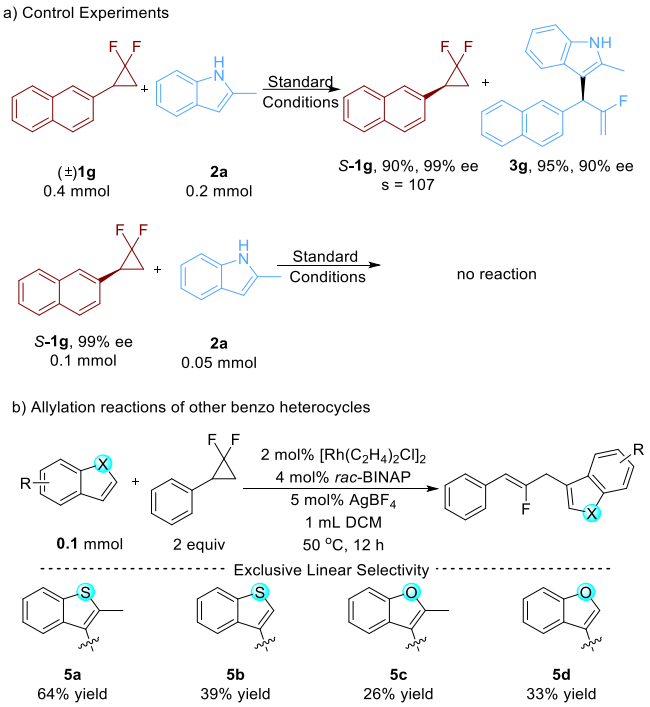
Scheme 3. Scale-up Synthesis and Transformation



To demonstrate the synthetic functionality of the fluoroallylated indoles, we performed the scale up experiments, furnishing the expected product **3a** in 87% isolated yield with 91% ee and **3ah** 88% isolated yield with 90% ee (Scheme 3a). We further conducted synthesis experiments to show the synthetic utility of this method (Scheme 3b). In the nickel-catalyzed cross-coupling of **3ah** with the Grignard reagent, the allylic product **4** was produced. Predictably, the configuration of **4** was retained during the fluorine transformation in the Kumada coupling (Scheme 3b).

In control experiment (Scheme 4a), we recycled the remaining **1g** when **2a** was consumed in the standard reaction, the HPLC analysis showed that the recycled *S*-**1g** (the absolute configuration of the recovered **1g** was confirmed by comparing with the reported data[10d]) up to 99% ee, coupled with an isolated yield of 90%. Upon employing the recycled *S*-**1g** as substrate under the standard reaction conditions, no subsequent reaction was observed. These results conclude the involvement of a kinetic resolution pathway. Furthermore, given the high branched selectivity of indoles as the nucleophiles, we explored other aromatic heterocycles. We found that substituting sulfur or oxygen for the heteroatom resulted in an exclusive linear selectivity (Scheme 4b). These observations underscore the privileged nucleophilicity of indoles in controlling the regioselectivity.

Scheme 4. Control Experiments



In conclusion, we have developed an efficient access to a highly branched and enantioselective allylic substitution of indoles with *gem*-difluorinated cyclopropanes using rhodium catalysis. This reaction is the first example with high enantioselectivity and high branched-regioselectivity in the ring opening of DFCPs, exhibiting a broad substrate scope with a wide array of substituted indoles to afford C2 and C3 allylated products. The scale-up experiments and application demonstrated the potential of this method in synthetic application. Further study on the understanding of the origin of the branched regioselectivity is currently underway in our laboratory.

ASSOCIATED CONTENT

Detailed experimental procedures, characterization data, copies of ^{1}H, ^{13}C, ^{19}F NMR and HPLC spectra of products are reported in the Supporting Information.

AUTHOR INFORMATION

Corresponding Author

Ying Xia – West China School of Public Health and West China Fourth Hospital, and State Key Laboratory of Biotherapy Sichuan University, Chengdu 610041, China

E-mail: xiayingscu@scu.edu.cn

Author Contributions

Hui Yang – West China School of Public Health and West China Fourth Hospital, and State Key Laboratory of Biotherapy Sichuan University, Chengdu 610041, China

Yaxin Zeng – West China School of Public Health and West China Fourth Hospital, and State Key Laboratory of Biotherapy Sichuan University, Chengdu 610041, China

Xiangyu Song – West China School of Public Health and West China Fourth Hospital, and State Key Laboratory of Biotherapy Sichuan University**,** Chengdu 610041, China

Lin Che – School of Chemistry and Chemical Engineering, Linyi University, Linyi 276000, China

Zhong-Tao Jiang – West China School of Public Health and West China Fourth Hospital, and State Key Laboratory of Biotherapy Sichuan University**,** Chengdu 610041, China

ACKNOWLEDGMENT

This work is supported by the National Natural Science Foundation (Grant 22371189 and 22001180) and the "Thousand Young Talents Program of China" (Grant 15 YINGXIA). Dr. Xuejiao Song, Dr. Xunxun Deng and Dr. Tianli Zheng in Public Health and Preventive Medicine Provincial Experiment Teaching Center at Sichuan University are acknowledged for the support for instrument management.

REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science*. **2007**, *317*, 1881–1886. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev*. **2014**, *114*, 2432–2506. (c) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422–518.

(2) (a) Vincent, J.-M. Recent Advances of Fluorous Chemistry in Material Sciences. *Chem. Commun.* **2012**, *48*, 11382–11391. (b) Zhang, C.; Yan, K.; Fu, C.; Peng, H.; Hawker, C. J.; Whittaker, A. K. Biological Utility of Fluorinated Compounds: from Materials Design to Molecular Imaging, Therapeutics and Environmental Remediation. *Chem. Rev.* **2022**, *122*, 167–208.

(3) (a) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. Synthetic Approaches to Monofluoroalkenes. *Chem. Soc. Rev.* **2011**, *40*, 2867–2908. (b) Zhang, X.-J.; Cheng, Y.-M.; Zhao, X.-W.; Cao, Z.-Y.; Xiao, X.; Xu, Y. Catalytic Asymmetric Synthesis of Monofluoroalkenes and *gem*-Difluoroalkenes: Advances and Perspectives. *Org. Chem. Front.* **2021**, *8*, 2315–2327. For an example of synthesis of optically active monofluoroalkenes: Marhold, M.; Wittmann, U.; Grimme, S.; Takahashi, T.; Haufe, G. Synthesis of Optically Active 2-Fluoroalk-1-En-3-Yl Esters and Chirality Transfer in Their Claisen-Type Rearrangements. *J. Fluor. Chem.* **2007**, *128*, 1306–1317.

(4) (a) Couve-Bonnaire, S.; Cahard, D.; Pannecouke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157. (b) Van der Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A. M.; Maes, M. B.; Scharpé, S.; Haemers, A.; Augustyns, K. Fluoro-Olefins as Peptidomimetic Inhibitors of Dipeptidyl Peptidases. *J. Med. Chem.* **2005**, *48*, 1768–1780.

(5) (a) Chelucci, G. Synthesis and Metal-Catalyzed Reactions of *gem*-Dihalovinyl Systems. *Chem. Rev.* **2012**, *122*, 1344–14462. (b) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation to Access Fluorinated Building Blocks. *Chem. Rev.* **2015**, *115*, 931–972. (c) Zhang, X.; Cao, S. Recent Advances in The Synthesis and C–F Functionalization of *gem*-Difluoroalkenes. *Tetrahedron Lett.* **2017**, *58*, 375–392. (d) Li, Y.; Liu, W.; Liu, Z.-Y.; Wang, C.-Y.; Bian, K.-J.; Sheng, J.; Wang, X.-S. Development of Monofluoroalkenes as Molecular Platform for Diversity-Oriented Syntheses of Tertiary Aliphatic Fluorides via Nickel/Manganese-Dual Catalysis. *CCS Chem.* **2022**, *4*, 2888–2896.

(6) (a) Dolbier, W. R.; Battiste, M. A. Structure, Synthesis, and Chemical Reactions of Fluorinated Cyclopropanes and Cyclopropenes. *Chem. Rev.* **2003**, *103*, 1071–1098. (b) Fedoryński, M. Syntheses of *gem*-Dihalocyclopropanes and Their Use in Organic Synthesis. *Chem. Rev*. **2003**, *103*, 1099–1132. (c) Wang. F.; Luo. T.; Hu. J.; Wang. Y.; Krishnan. H. S.; Jog. P. V.; Ganesh. S. K.; Prakash. G. K. S., Olah, G. A. Synthesis of *gem*-Difluorinated Cyclopropanes and Cyclopropenes: Trifluoromethyltrimethylsilane as a Difluorocarbene Source. *Angew. Chem. Int. Ed*. **2011**, *50*, 7153–7157; (d) García-Domínguez, A.; West, T. H.; Primozic, J. J.; Grant, K. M.; Johnston, C. P.; Cumming, G. G.; A, G. Leach; Lloyd-Jones, G. C.; Difluorocarbene Generation from TMSCF3: Kinetics and Mechanism of NaI-Mediated and Si-Induced Anionic Chain Reactions. *J. Am. Chem. Soc.* **2020**, *142*, 14649–14663. (e) Adekenova, K. S.; Wyatt, P. B.; Adekenov, S. M.; The preparation and properties of 1,1-difluorocyclopropane derivatives. *Beilste J. Org. Chem.* **2021**, *17*, 245–272.

(7) (a) Lv, L.; Qian, H.; Li, Z.; Catalytic Diversification of gem-Difluorocyclopropanes: Recent Advances and Challenges. *ChemCatChem*. **2022**, *14*, e202200890. (b) Zhu, Y.; Zeng, Y.; Jiang, Z.-T; Xia, Y., Recent Advances in Transition-Metal-Catalyzed Cross-Coupling Reactions of gem-Difluorinated Cyclopropanes. *Synlett*. **2023**, *34*, 1-13.

(8) Xu, J.; Ahmed, E.-A. M. A.; Xiao, B.; Lu, Q. Q.; Wang, Y. L.; Yu, C. G.; Fu, Y. Pd-Catalyzed Regioselective Activation of *gem*-Difluorinated Cyclopropanes: A Highly Efficient Approach to 2-Fluorinated Allylic Scaffolds. *Angew. Chem. Int. Ed*. **2015**, *54*, 8231–8235.

(9) For selected examples of palladium catalysis with linear selectivity, see: (a) Ahmed, E.-A. M. A.; Suliman, A. M. Y.; Gong, T.-J.; Fu, Y. Palladium-Catalyzed Stereoselective Defluorination Arylation/Alkenylation/Alkylation of *gem*-Difluorinated Cyclopropanes. *Org. Lett.* **2019**, *21*, 5645–5649. (b) Ni, J.; Nishonov, B.; Pardaev, A.; Zhang, A. Palladium-Catalyzed Ring-Opening Coupling of *gem*-Difluorocyclopropanes for the Construction of 2-Fluoroallylic Sulfones. *J. Org. Chem.* **2019**, *84*, 13646–13654. (c) Ahmed, E.-A. M. A.; Suliman, A. M. Y.; Gong, T.-J.; Fu, Y. Access to Divergent Fluorinated Enynes and Arenes via Palladium-Catalyzed Ring-Opening Alkynylation of *gem*-Difluorinated Cyclopropanes. *Org. Lett.* **2020**, *22*, 1414–1419. (d) Zhou, P.-X.; Yang, X.; Wang, J.; Ge, C.; Feng, W.; Liang, Y.-M.; Zhang, Y. Palladium-Catalyzed C–H Allylation of Electron-Deficient Polyfluoroarenes with *gem*-Difluorinated Cyclopropanes. *Org. Lett.* **2021**, *23*, 4920–4924. (e) Xiong, B.; Chen, X.; Liu, J.; Zhang, X.; Xia, Y.; Lian, Z. Stereoselective *gem*-Difluorovinylation of *gem*-Difluorinated Cyclopropanes Enabled by Ni/Pd Cooperative Catalysis. *ACS Catal.* **2021**, *11*, 11960–11965. (f) Suliman, A. M. Y.; Ahmed, E.-A. M. A.; Gong, T.-J.; Fu, Y. Cu/Pd-Catalyzed cis-Borylfluoroallylation of Alkynes for the Synthesis of Boryl-Substituted Monofluoroalkenes. *Org. Lett.* **2021**, *23*, 3259–3263. (g) Fu, Z.; Zhu, J.; Guo, S.; Lin, A. Palladium-Catalyzed Allylic Alkylation Dearomatization of β-naphthols and Indoles With *gem*-Difluorinated Cyclopropanes. *Chem. Commun.* **2021,** *57*, 1262–1265. (h) Yuan, W.; Li, X.; Qi,

Z.; Li, X. Palladium-Catalyzed Synthesis of Functionalized Indoles by Acylation/Allylation of 2-Alkynylanilines with Three-Membered Rings. *Org. Lett.* **2022,** *24*, 2093−2098. (i) Li, D.; Shen, C.; Si, Z.; Liu, L. Palladium-Catalyzed Fluorinative Bifunctionalization of Aziridines and Azetidines with gem-Difluorocyclopropanes. *Angew. Chem. Int. Ed.* **2023**, *62*, e2023102. (j) Ahmed, E.-A. M. A.; Zhang, H.; Cao, W.-G.; Gong, T.-J. Palladium-Catalyzed Cross-Coupling of gem-Difluorocyclopropanes with gem-Diborylalkanes for the Synthesis of Boryl-Substituted Fluorinated Alkenes. *Org. Lett.* **2023**, *25*, 9020−9024. (k) Sun, J.; Ye, H.; Sun, F.; Pan, Y.-Y.; Zhu, X.-W.; Wu, X.-X., Palladium-Catalyzed Allylation of P(O)H Compounds: Access to 2-Fluoroallylic Phosphorus Compounds. *Org. Lett.* **2023**, *25*, 5220−5225.

(10) For rhodium catalysis with linear selectivity, see: (a) Jiang, Z.-T.; Huang, J.; Zeng, Y.; Hu, F.; Xia, Y. Rhodium Catalyzed Regioselective C−H Allylation of Simple Arenes via C−C Bond Activation of *gem*-Difluorinated Cyclopropanes. *Angew. Chem. Int. Ed.* **2021,** *60*, 10626−10631. (b) Zeng, Y.; Gao, H.; Zhu, Y.; Jiang, Z.-T.; Lu, G.; Xia, Y. Site-Divergent Alkenyl C−H Fluoroallylation of Olefins Enabled by Tunable Rhodium Catalysis. *ACS Cat.* **2022,** *12*, 8857−8867. (c) Zeng, Y.; Yang, H.; Du, J.; Huang, Q.; Huang, G.; Xia, Y. Rh-Catalyzed Regio-switchable Cross-coupling of *gem*-Difluorinated Cyclopropanes with Allylboronates to Structurally Diverse Fluorinated Dienes. *Chem. Sci.* **2022,** *13*, 12419−12425. (d) Jiang, Z.-T.; Chen, Z.; Zeng, Y.; Shi, J.; Xia, Y. Enantioselective Formation of All-Carbon Quaternary Stereocenters in *gem*-Difluorinated Cyclopropanes via Rhodium-Catalyzed Stereoablative Kinetic Resolution. *Org. Lett*. **2022**, *24*, 6176−6181.

(11) For selected examples of other transition-metal catalysis with linear selectivity, see: (a) Ai, Y.; Yang, H.; Duan, C.; Li,. X.; Yu, S. Cobalt-Catalyzed Fluoroallyllation of Carbonyls via C−C Activation of *gem*-Difluorocyclopropanes. *Org. Lett.* **2022**, *24*, 5051−5055. (b) Qi, S.; Hua,Y.; Pan, L.; Yang, J.; Zhang, J. Nickel-Catalyzed Regio- and Stereoselective Defluorinative Arylation of *gem*-Difluorinated Cyclopropanes. *Chin. J. Chem.* **2024**, *42*, 823-828. (c) Wenz. J., Rettenmeier, C.; Wadepohl, H.; Gade, L. Catalytic C−F bond activation of geminal difluorocyclopropanes by nickel(I) complexes via a radical mechanism. *Chem. Commun*. **2016**, *52*, 202.

(12) Lv, L.; Li, C. J. Palladium-Catalyzed Defluorinative Alkylation of *gem*-Difluorocyclopropanes: Switching Regioselectivity via Simple Hydrazones. *Angew. Chem. Int. Ed.* **2021**, *60*, 13098-13104.

(13) For other examples with branched selectivity, see: (a) Qian, H.; Nguyen. H. D.; Lv, L.; Chen, S.; Li, Z. Chemo-, Stereo-and Regioselective Fluoroallylation/Annulation of Hydrazones with gem-Difluorocyclopropanes via Tunable Palladium/NHC Catalysis. *Angew. Chem. Int. Ed.* **2023**, *62*, e202303271. (b) Lv, L.; Qian, H.; Ma, Y.; Huang, S.; Yan, X.; Li, Z. Ligand-Controlled Regioselective and Chemodivergent Defluorinative Functionalization of *gem*-Difluorocyclopropanes with Simple Ketones. *Chem. Sci.* **2021,** *12*, 15511−15518. (c) Lv, L.; Qian, H.; Crowell, A. B.; Chen, S.; Li, Z. Pd/NHC-Controlled Regiodivergent Defluorinative Allylation of gem-Difluorocyclopropanes with Allylboronates. *ACS Cat.* **2022**, *12*, 6495−6505. (d) Wu, L.; Wang, M.; Liang, Y.; Shi, Z. Ligand-Controlled Palladium-Catalyzed Regiodivergent Defluorinative Allylation of *gem*-Difluorocyclopropanes via σ-Bond Activation. *Chin. J. Chem.* **2022**, *40*, 2345−2355.

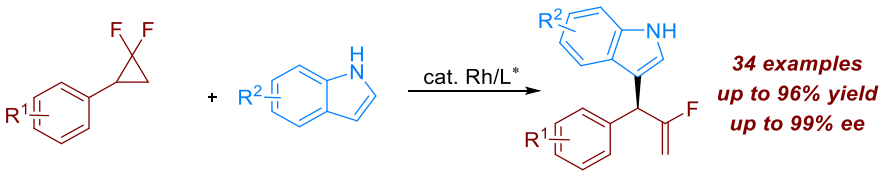
(14) Qian, H.; Cheng, Z. P.; Luo, Y.; Lv, L.; Chen, S.; Li, Z. Pd/IPr-BIDEA-Catalyzed Hydrodefluorination of *gem*-Difluorocyclopropanes: Regioselective Synthesis of Terminal Fluoroalkenes. *J. Am. Chem. Soc.* **2023**,146, 24-32.

(15) (a) Zeng, Y.; Xia, Y. Rhodium-Catalyzed Regio- and Diastereoselective [3 + 2] Cycloaddition of *gem*-Difluorinated Cyclopropanes with Internal Olefins. *Angew. Chem., Int. Ed.* **2023**, 62, e202307129. (b)Jiang, Z.-T.; Chen, Z.; Xia, Y. Modular Synthesis of Fully-Substituted and Configuration-Defined Alkyl Vinyl Ethers Enabled by Dual-Functional Copper Catalysis. *Angew. Chem. Int. Ed*. **2024**, e202319647.

(16) For recent examples of transition-metal-catalyzed asymmetric allylation of indoles, see (a) Panda, S.; Ready, J. M.; Palladium Catalyzed Asymmetric Three-Component Coupling of Boronic Esters, Indoles, and Allylic Acetates. *J. Am. Chem. Soc.* **2017**, *139*, 6038-6041. (b) Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M. Alkyne Hydroheteroarylation: Enantioselective Coupling of Indoles and Alkynes via Rh-Hydride Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 10641. (c) Pesciaioli, F.; Dhawa, U.; Oliveira, J.; Yin, R.; John, M.; Ackermann, L. Enantioselective Cobalt(III)-Catalyzed C−H Activation Enabled by Chiral Carboxylic Acid Cooperation. *Angew. Chem. Int. Ed.* **2018**, *57*, 15425−15429. (d) Kim, S. W.; Schempp, T. T.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Regio- and Enantioselective Iridium-Catalyzed *N*-Allylation of Indoles and Related Azoles with Racemic Branched Alkyl-Substituted Allylic Acetates. *Angew. Chem. Int. Ed.* **2019**, *58*, 7762−7766. (e) Ashton, J.; Clarke, A.; Donald, J.; Zheng, C.; Taylor, R.; Unsworth, W.; You, S.-l. Iridium-Catalyzed Enantioselective Intermolecular Indole C2-Allylation. *Angew. Chem. Int. Ed*. **2020**, *59*, 7598-7604. (g) Sun, M.; Liu, M.; Li, C. Rhodium-Catalyzed Chemodivergent Regio- and Enantioselective Allylic Alkylation of Indoles. *Chem. Eur. J.* **2021**, *27*, 3457−3462.

Entry for the Table of Contents

The first example of enantioselective allylation with *gem*-difluorinated cyclopropanes



34 examples
up to 96% yield
up to 99% ee

- ✔ **exclusive branched-selectivity**
- ✔ **very mild conditions**
- ✔ **excellent enantioselecitvity**
- ✔ **chiral mono-fluoroalkenes**