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

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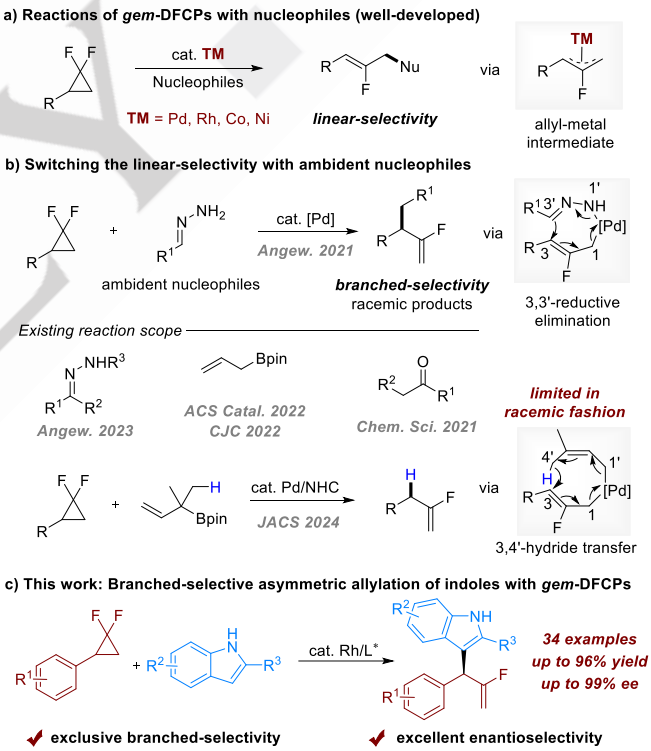
Abstract: The use of *gem*-difluorinated cyclopropanes (*gem*-DFCPs) as fluoroallyl surrogates under transition-metal catalysis has drawn considerable attention recently but such reactions are restricted to producing achiral or racemic mono-fluoroalkenes. Herein, we report the first enantioselective allylation of indoles under rhodium catalysis with *gem*-DFCPs. 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



Scheme 1. Regioselective ring-opening allylation reactions of *gem*-DFCPs.

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]

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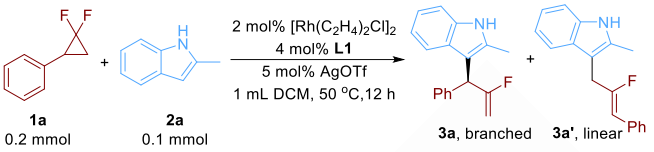
Despite these significant achievements that have been made in the synthesis of racemic or achiral mono-fluoroalkenes, a strategy for the collection of enantioenriched α-mono-fluoroalkenes using *gem*-DFCPs as fluoroallyl surrogates has not yet been realized.[15]

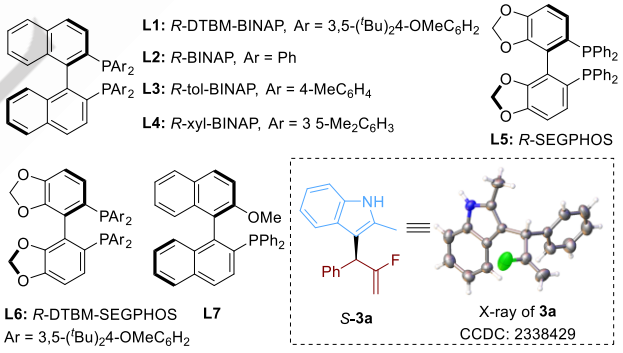
The development of such enantioselective reaction faces a significant challenge, which is that nucleophiles, other than ambident nucleophiles, often favor linear-selectivity because of the preferential nucleophilic attack at the less hindered carbon atom of the allyl-metal intermediate.[7-14] Accordingly, 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.[7c,10,16] 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).[17] 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.

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) (see Supporting Information for details on how to determine the regioselectivity). Meanwhile, the major product **3a** was unambiguously confirmed as *S*-configuration by X-ray crystallography.[18] 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 (dichloromethane) 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*-tol-BINAP (**L3**), *R*-xyl-BINAP (**L4**), *R*-SEGPHOS (**L5**), *R*-DTBM-SEGPHOS (**L6**) resulted in decreased yields or selectivities of the product (entries 5-9). Interestingly, ligands with much smaller steric hindrance, including **L2**, **L3** and **L5**, favor the formation of product **3a** with *R*-configuration (entries 5, 6 and 8). As the steric hindrance on the bidentate ligand increases (**L1**, **L4** and **L6**), the product **3a** tends to be as *S*-configuration with low to excellent ee, depending on the steric hindrance of the ligand (entries 1, 7 and 9). No target product **3a** was observed in the presence of monodentate ligand (**L7**), which indicates that the use of a bidentate ligand was crucial in this transformation (entry 10). As for the solvent effect, chlorobenzene and DCE (1,2-dichloroethane) were less effective than DCM in this transformation (entries 11 and 12). When using THF (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 controlled by the reaction conditions (entry 13).

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/o AgOTf	0	-	-
3	$AgPF_6$	53	25:1	89
4	$AgBF_4$	56	25:1	69
5	**L2**	86	11:1	-31[e]
6	**L3**	82	9:1	-31[e]
7	**L4**	72	4:1	15
8	**L5**	86	10:1	-48[e]
9	**L6**	15	26:1	93
10	**L7**	0	-	-
11	PhCl	91	31:1	91
12	DCE	91	29:1	85
13	THF, **L2**	36	1:1.3	29[f]



[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] A negative ee value means that the configuration of **3a** is inversed with that obtained in entry 1. [f] $AgPF_6$ was used instead of AgOTf.

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*-DFCPs with 2-methylindole **2a** (Scheme 2A). The reaction of model substrate **1a** and **2a** provided the desired product **3a** in 92% yield with 93% ee. Para-electron-donating groups (**3b**-**3f**, R = Me, cyclopropyl, OPh, OAc, pyrrole) and para-electron-withdrawing groups (**3g**-**3j**, R = Ph, F, Cl, Br) on the phenyl ring of *gem*-DFCPs are all well-tolerated in the asymmetric allylation reaction, affording the corresponding α-mono-fluoroalkenes in moderate to

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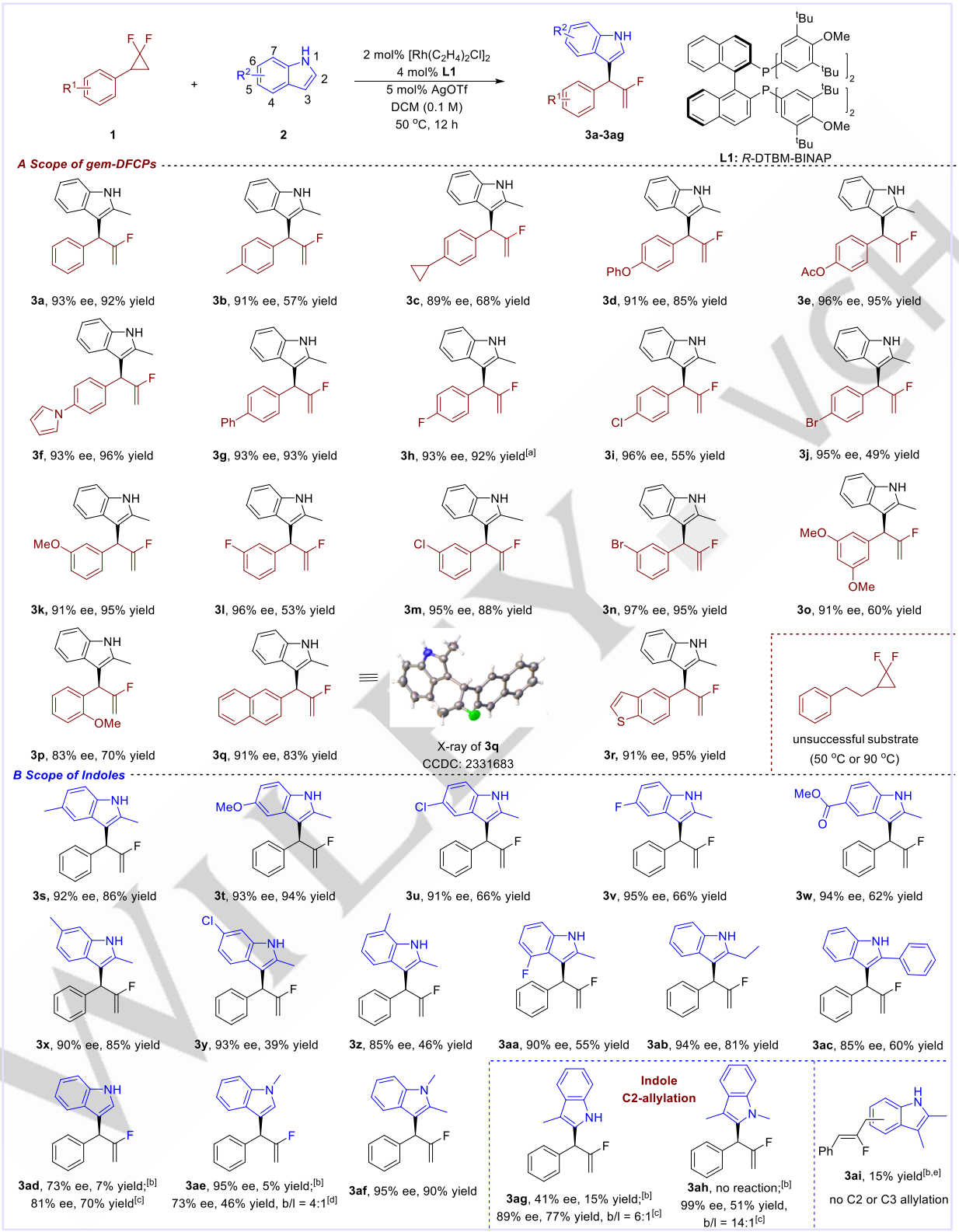

Scheme 2. Substrate scope of indole fluoroallylation. General conditions: **1a** 0.2 mmol, **2a** 0.1 mmol, 2 mol% $[Rh(C_2H_4)_2Cl]_2$, 4 mol% **L1**, 5 mol% AgOTf, 50 °C, 1 mL DCM, 12 h. Isolated yields are presented. The regioselectivity was over 20>1 if not noted. [a] 3 mol% $[Rh(C_2H_4)_2Cl]_2$, 6 mol% **L1**. [b] Determined by ^{1}H NMR; under standard reaction conditions. [c] 4 mol% *R*-BINAP (**L2**), 40 °C. [d] 4 mol% *R*-SEGPHOS (**L5**), 40 °C. [e] The branched regioselectivity was suggested by ^{1}H and ^{19}F NMR of the crude product.

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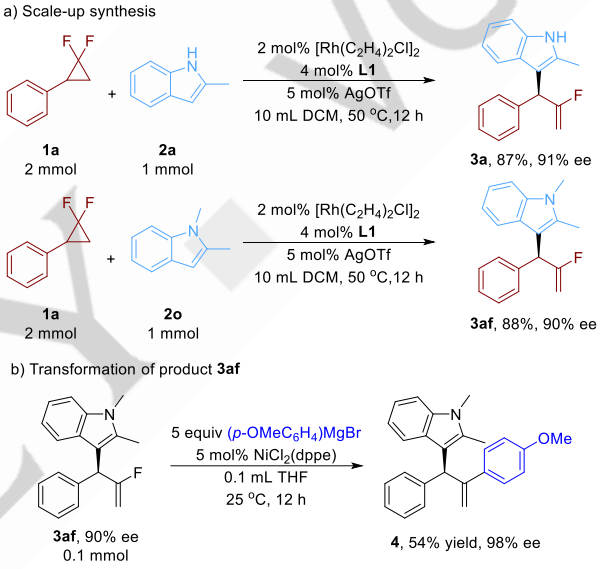
good yields with excellent branched-regioselectivity and enantioselectivity. Note that *gem*-DFCP **1c**, which contains another cyclopropyl moiety, worked smoothly in this reaction, indicating the privileged reactivity of this catalytic system on *gem*-DFCP over simple cyclopropane. *gem*-DFCPs bearing meta-substituted groups (**3k**-**3n**) with different electronic properties on the benzene ring or di-substituted aryl (**3o**) are also suitable substrates in this reaction. It is worth noting that the good compatibility of the aryl halides (**3i**, **3j**, **3m**, **3n**) provides a handle of the products for further transformations. The reaction is slightly sensitive to the substituent at the ortho-position, as the enantioselectivity was decreased in the case of **3p**. In addition, *gem*-DFCPs substituted with fused aromatic ring are also compatible in this reaction, producing **3q** and **3r** with good yields and enantioselectivities, in which again the product (**3q**) was confirmed as *S*-configuration by X-ray crystallography.[18] Meanwhile, alkyl substituted *gem*-DFCP showed no reactivity under the standard reaction conditions, even at increased reaction temperature.

After that, the reactivity of indoles was then evaluated (Scheme 2B). First, a variety of electron-donating (**3s**, **3t**) and electron-withdrawing groups (**3u**-**3w**) in the para position of the indole nitrogen atom were found to be all tolerated, providing the allylated indole products in 62-94% yields with >90% ee. Indoles bearing substituents on other position of the arene ring participated in this reaction to deliver the corresponding products **3x**-**3aa** in moderate to good yields. Thus, the allylation coupling reaction can occur successfully with indoles bearing substituents at any position of the indolyl benzene ring.

On the other hand, we evaluated the influence of the nitrogen-containing moiety of the indoles on the reaction. It was found that the substitution of the 2-methyl group with ethyl (**3ab**) or phenyl (**3ac**) resulted in the formation of the branched products with good enantioselectivity. Notably, while simple indole without the 2-methyl group (**3ad**) only gave the product with moderate enantioselectivity and poor yield under the standard conditions (with **L1**), the ee value can be increased to 81% by using *R*-BINAP (**L2**) as the ligand, in which the configuration of the major enantiomer in **3ad** is the same from these two ligands. When substituting the nitrogen atom of indole with a methyl group (**3ae**), the allylation product was obtained with excellent enantioselectivity but poor yield; the yield of **3ae** was increased but with diminished ee when using *R*-SEGPHOS (**L5**) as the ligand, in which again the configuration of the major enantiomer in the product is the same compared with that from **L1**. Nevertheless, the branched-regioselective allylation remains the major reaction pathway, indicating the NH moiety is not necessary for the branched regioselectivity. Moreover, 1,2-dimethylindole performed very well with excellent yield and ee (**3af**), which further excludes the possible role of the NH moiety on both the branched-regioselectivity and enantioselectivity. When blocking the 3-position of the indole substrates, C2-allylated products with branched-selectivity (**3ag**, **3ah**) were exclusively obtained with **L2** as the ligand.[19] Note that the configuration of the major enantiomer from **L1** and **L2** is the same in the case of **3ag**. Finally, 2,3-dimethylindole fails to deliver the corresponding dearomatized C2 or C3 allylation product under the standard reaction conditions; instead, partial conversion with allylation occurring at the benzene ring with linear selectivity was observed (**3ai**). It is worth noting that 3-methyl-substituted indoles (**3ag**, **3ai**) undergo allylation at 3-position with dearomatization under Pd-catalysis.[9g]

To demonstrate the synthetic utility of the asymmetric allylation reaction, we then performed scale-up experiments, furnishing the expected product **3a** in 87% yield with 91% ee and **3af** in 88% yield with 90% ee (Scheme 3a). We further conducted downstream transformation of the enantioenriched allylated products. In the nickel-catalyzed cross-coupling of **3af** with aryl Grignard reagent via C−F activation, the allylic product **4** was produced in moderate yield, wherein the ee of **4** was slightly increased during the F-based Kumada coupling reaction (Scheme 3b).



Scheme 3. Scale-up synthesis and transformation.

To gain some understanding of the reaction mechanism, preliminary mechanistic studies were then conducted. First, we recycled the remaining *gem*-DFCP when the indole was consumed in the standard reaction between **1q** and **2a**, in which the recycled *S*-**1q** (the absolute configuration was confirmed by comparing with the reported data[10d]) was up to 99% ee (Scheme 4a). The desired allylation product was isolated in 90% yield, giving a *S*-factor of 107. Second, the recycled *S*-**1q** was then subjected to the standard reaction conditions, and no conversion of *S*-**1q** was observed (Scheme 4b-1). When using *rac*-**L1** as the ligand under otherwise the standard reaction conditions, *S*-**1q** was converted to *R*-**3q** with 91% ee in 89% yield, which is in excellent stereospecificity (Scheme 4b-2). These results conclude the involvement of a kinetic resolution pathway and a net stereoretention (*R*-**1q** to *S*-**3q**) in the allylation reaction when using the bulky **L1** as the ligand.

Interestingly, the stereospecificity was not observed when a less steric hindered achiral ligand, bis(2-(diphenylphosphanyl)phenyl)methanone (dpbp), was used in the reaction of *S*-**1q**, providing *S*-**3q** with inversed configuration and low ee (Scheme 4b-3). This result matches with the outcomes

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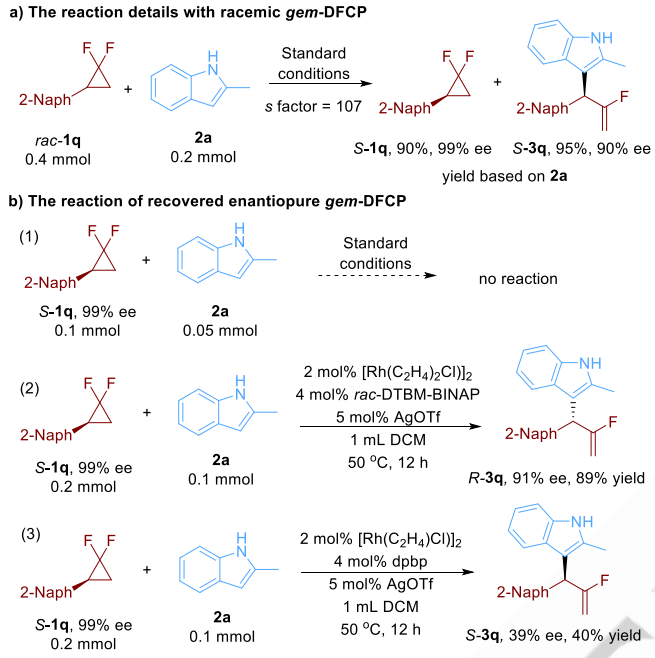
presented in Table 1, which collectively demonstrates that the use of highly bulky bidentate ligand, such as **L1**, is crucial for the high stereospecificity of this allylation reaction. Taking together, the efficient kinetic resolution process (via oxidative addition)[10d] and the high stereospecificity of the allylation process with **L1** as the bulky ligand account for the observed high enantioselectivity of the reaction.



Scheme 4. Preliminary mechanistic studies.

Furthermore, encouraged by the high branched selectivity of indoles in the allylation reaction with *gem*-DFCPs, we then explored the reactivity of other aromatic heterocycles. It was found that these sulfur- and oxygen-containing heteroarenes provided the corresponding allylation products with exclusively linear selectivity (Scheme 4c). While more investigations are required to understand the origin of the branched selectivity, this observation underscores the privileged nucleophilicity of indoles in controlling the regioselectivity.

Based on these observations and the previous investigations on allylation chemistry,[20] we presented a simplified mechanism for the asymmetric allylation reaction, which includes three processes: C−C activation via oxidative addition, C−F activation via β-F elimination and C−C formation via allylic coupling (Scheme 4d). As the oxidative addition and β-F elimination should be stereoretentive, and net stereoretention was observed for the reaction, we speculate that the third step (allylic coupling) should also be also in net stereoretention. The net stereoretentive allylation process can occur via an inner-sphere electrophilic C−H metalation/reductive elimination sequence that is similar with our previous study,[10a] or via a stereoinversion of the allyl Rh species followed by an outer-sphere allylic substitution.

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

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Keywords: *gem*-difluorinated cyclopropanes • rhodium catalysis • allylation reactions • enantioselectivity • regioselectivity

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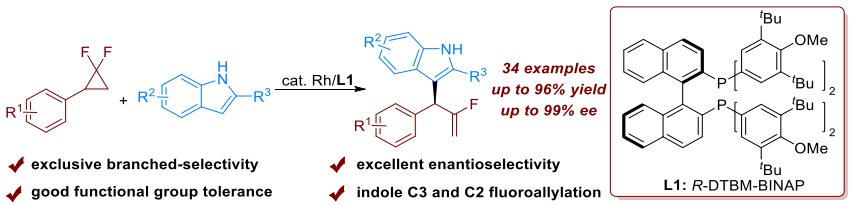

The first enantioselective allylation of indoles with *gem*-difluorinated cyclopropanes is developed under rhodium catalysis. The reaction shows exceptional branched regioselectivity and excellent enantioselectivity with a bulky ligand, which provides an efficient route to enantioenriched C2 and C3 fluoroallylated indoles with wide substrate scope and good functional group tolerance.