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Double strain-release enables formal C–O/C–F and C–N/C–F ring-opening metathesis†

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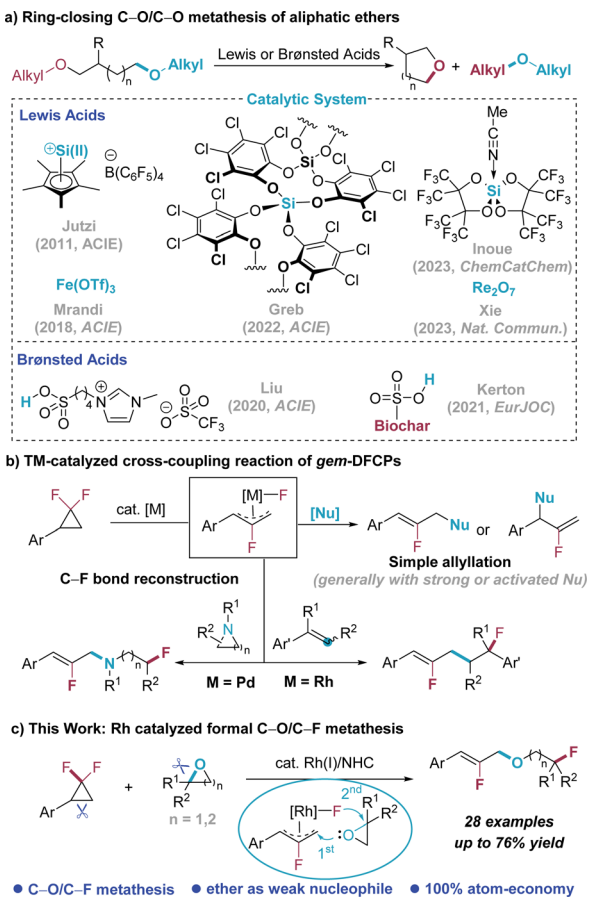
Metathesis reactions have been established as a powerful tool in organic synthesis. While great advances were achieved in double-bond metathesis, like olefin metathesis and carbonyl metathesis, single-bond metathesis has received less attention in the past decade. Herein, we describe the first C(sp^3)–O/C(sp^3)–F bond formal cross metathesis reaction between *gem*-difluorinated cyclopropanes (*gem*-DFCPs) and epoxides under rhodium catalysis. The reaction involves the formation of a highly electrophilic fluoroallyl rhodium intermediate, which is capable of reacting with the oxygen atom in epoxides as weak nucleophiles followed by C–F bond reconstruction. The use of two strained ring substrates is the key to the success of the formal cross metathesis, in which the double strain release accounts for the driving force of the transformation. Additionally, azetidine also proves to be a suitable substrate for this transformation. The reaction offers a novel approach for the metathesis of C(sp^3)–O and C(sp^3)–N bonds, presenting new opportunities for single-bond metathesis.

Introduction

The advent of metathesis reactions has promoted a revolution in synthetic chemistry and related areas,[1] offering innovative methodologies that are conceptually novel and strategically advanced for molecular construction. Among them, double-bond metathesis, typified by various types of olefin metathesis, has become an indispensable toolbox in modern organic chemistry. Besides, carbonyl-olefin metathesis has gradually drawn the attention of chemists and become a powerful technique for molecular backbone editing of carbonyl compounds.[2,3] In contrast, research on single-bond metathesis has not garnered sufficient attention and only limited examples were developed,[4,5] likely due to the less reactive σ-bonds compared with the π-bond. As for the metathesis of the C–O single bond, Jutzi disclosed that the pentamethylcyclopentadienyl silicon(II) cation ($Cp^*Si(II)^+$) expressed reactivity for the ring-closing C–O metathesis of ethers, which was applied in the degradation of oligo(ethyleneglycol) diethers (Scheme 1a).[6] The Morandi group reported that simple and cheap $Fe(OTf)_3$ was an efficient catalyst, providing an elegant and practical approach for the ring-closing C–O metathesis of aliphatic ethers.[7] Subsequently, other types of Lewis acids[8] and Brønsted acids[9] were also found to be capable catalysts in C–O/C–O



Scheme 1 Metathesis reactions involving the C–O single bond and their background.

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metathesis reactions, which greatly enriched the reactions implemented for ether synthesis.

While there are noticeable advances in the area of single-bond metathesis regarding the C–O bond, these reactions are mainly restricted in C–O/C–O bond metathesis with the use of Lewis/Brønsted acid-activation mode.[6–9] Given the significance of cross metathesis in structural editing of molecular backbones, as an analogue of carbonyl–olefin metathesis in the double-bond metathesis area,[2,3] extending C–O/C–O single bond metathesis to C–O/C–X (X is an element other than oxygen) metathesis would substantially enrich the diversity of the reaction pattern. However, the development of C–O/C–X metathesis is a challenging task and there has been no reported method to the best our knowledge.

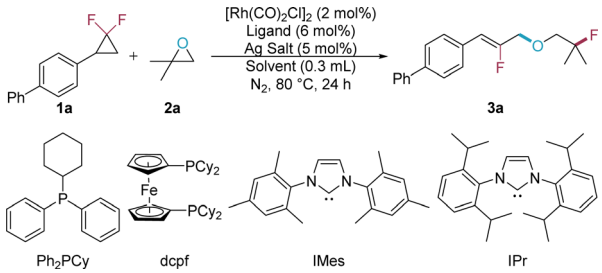
On the other hand, the development of new strategies to introduce fluorine into organic molecules has emerged as one of the primary research focuses, as the introduction of the fluorine can endow the organic molecules with distinct properties.[10] Recently, the use of *gem*-difluorinated cyclopropanes (*gem*-DFCPs)[11] as a new type of reagents to synthesize fluorine-containing compounds has caught considerable attention, most of which involve a fluoroallyl intermediate under transition-metal catalysis.[12–14] Our group has been continuously interested in the development of new reaction modes of *gem*-DFCPs especially using rhodium catalysis.[15] It was found that the fluoroallyl-Rh intermediate can be highly electrophilic that is able to react with weak or non-polar nucleophiles, like simple arenes[15a] and olefins,[15b–d] which is distinct from other transition-metal catalized reactions with *gem*-DFCPs that generally necessitate strong or activated nucleophiles (Scheme 1b, top).[13] Meanwhile, Liu and co-workers disclosed that the use of cyclic amines as strong nucleophiles can allow C–F bond reconstruction[16] with *gem*-DFCPs as bifunctional reagents under Pd catalysis;[17a] our group also revealed the unique usage of *gem*-DFCPs in the Rh-catalyzed olefin fluoroallylation reaction[17b] (Scheme 1b, bottom).

Along this line and considering the importance and challenges in C–O/C–X metathesis, we envisage that the highly electrophilic fluoroallyl-Rh intermediate can also be captured by using epoxide as an unusual nucleophile (1st bond formation), though epoxides are generally used as electrophiles in organic synthesis,[18] and the following reconstruction of the C–F bond (2nd bond formation) would eventually lead to the formal C–O/C–F ring-opening metathesis (Scheme 1c). Herein, we discover that the formal C–O/C–F ring-opening metathesis can be realized between *gem*-DFCPs and epoxides by using Rh catalysis that consists of $[Rh(CO)_2Cl]_2$ as the pre-catalyst and N-heterocyclic carbene (NHC) as the ligand. The strain release from the two strained three-membered substrates[19,20] provides the driving force for the whole transformation, with cleavage and formation of many inert chemical bonds including C–C, C–O and C–F bonds (Scheme 1c). In addition, this strategy can also be applied to the reaction with azetidine to achieve formal C(sp^3)–N/C(sp^3)–F ring opening metathesis.

Results and discussion

In our initial experiments, 4-(2,2-difluorocyclopropyl)-1,1′-biphenyl (**1a**) was selected as the model substrate to investigate its reactivity with 1,1-dimethyloxirane (**2a**) using Rh catalysis (Table 1). Under previously established reaction conditions where olefins were used as the nucleophiles,[15b] the desired product **3a** was obtained, albeit in low yield (entry 1). The widely used ligand in the Rh-catalyzed reaction of *gem*-DFCPs, binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl),[12d] only results in decomposition of the substrate **1a** (entry 2). The bidentate phosphine ligand dcpf (1,1′-bis(dicyclohexylphosphino)ferrocene) also yielded an unsatisfactory outcome (entry 3). In contrast, the utilization of NHC ligands notably improved the reaction efficiency, producing the product **3a** in 43% or 60% yield with IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) or IPr (1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidene) as the ligand, respectively (entries 4 and 5). Subsequent solvent screening revealed that a switch to fluorobenzene slightly decreased the reaction yield (entry 6). The use of DCM as the solvent totally shut down the C–O/C–F ring-opening metathesis, leading to the decomposition of the substrate **1a** (entry 7). A remarkable improvement was observed when $PhCF_3$ was chosen as the reaction solvent, delivering the desired product with a yield of 56% (entry 8). The influence of the silver salt was then investigated, and it was found that other silver salts were less efficient than $AgBF_4$ in this transformation (entries 9–11). Similar to our previous work,[15b] a great promotion in yield was observed when the catalytic amount of MeCN

Table 1 Optimization of the reaction conditions[a]



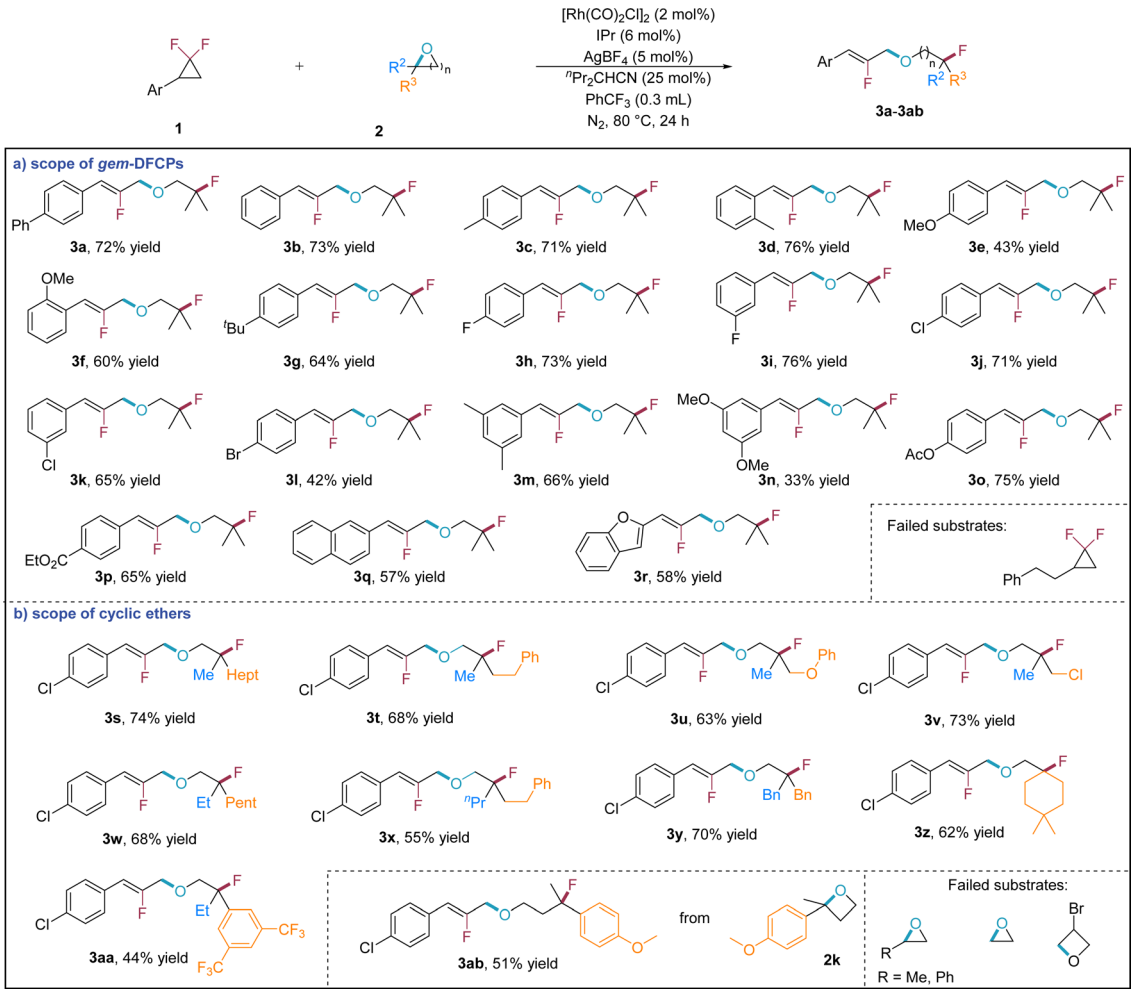
Entry	Ligand	Solvent	Ag salt	Yield[b]
1	Ph_2PCy	PhCl	$AgBF_4$	17%
2	Binap	PhCl	$AgBF_4$	0%
3	dcpf	PhCl	$AgBF_4$	19%
4	IMes	PhCl	$AgBF_4$	37%
5	IPr	PhCl	$AgBF_4$	45%
6	IPr	PhF	$AgBF_4$	44%
7	IPr	DCM	$AgBF_4$	0%
8	IPr	$PhCF_3$	$AgBF_4$	56%
9	IPr	$PhCF_3$	$AgSbF_6$	24%
10	IPr	$PhCF_3$	$AgPF_6$	0%
11	IPr	$PhCF_3$	AgOTf	41%
12[c]	IPr	$PhCF_3$	$AgBF_4$	68%
13[d]	IPr	$PhCF_3$	$AgBF_4$	76%(72%)[e]

[a] Reactions were performed with **1a** (0.1 mmol), **2a** (0.3 mmol), $[Rh(CO)_2Cl]_2$ (2 mol%), ligand (6 mol%), Ag salt (5 mol%) in 0.3 mL of solvent at 80 °C for 24 h. [b] The yield was determined by ^1H NMR using 1,1,2,2-tetrachloroethane (TCE) as an internal standard. [c] MeCN (25 mol%) was added. [d] $^nPr_2CHCN$ (25 mol%) was added. [e] Isolated yield is shown in parentheses.

was added as an additive (entry 12). After systematically screening the nitrile additives, the yield of **3a** was further improved to 76% (72% isolated yield) in the presence of a bulky nitrile $^{n}Pr_2CHCN$ (entry 13).

Upon establishing the optimized reaction conditions, we advanced to investigate the substrate scope of the formal C–O/C–F ring-opening metathesis reaction (Scheme 2). For *gem*-DFCPs (Scheme 2a), simple phenyl *gem*-DFCP (**3b**) yielded a satisfactory result. Aryl *gem*-DFCPs with varying positional methyl group (**3c**, **3d**) were well tolerated, in which the *ortho*-substituted one (**3d**) even contributes a slightly enhanced yield. Aside from the methyl group, the methoxy group at different positions of the aromatic ring is also well tolerated (**3e**, **3f**). Other electron-donating groups such as *tert*-butyl (**3g**) were tested, in which the substrate furnishes the corresponding product in 64% yield. In the case of halogen-substituted substrates, both fluorine- (**3h**, **3i**) and chlorine-containing (**3j**, **3k**) *gem*-DFCPs present good reactivity; while the bromine-substituted one (**3l**) gives a diminished yield. The substrate with two substitutions provides the corresponding products (**3m**, **3n**) in moderate to good yields. Furthermore, ester groups (**3o**, **3p**) were capable of preservation under these reaction conditions. Naphthyl (**3q**) and benzofuryl (**3r**) *gem*-DFCPs are qualified substrates for this transformation, forming the desired products in modest yields. Finally, alkyl *gem*-DFCP is unreactive under the current reaction conditions.

We then tested the reaction scope of epoxide substrates (Scheme 2b). The reaction proceeds smoothly when one of the methyl groups in the epoxide substrate is replaced with different types of alkyl groups (**3s–3v**), of which electron-rich arene (**3u**) and primary alkyl chloride (**3v**) can be tolerated in this transformation. Similarly, a wide range of epoxides that are substituted with two alkyl groups perform very well, producing the corresponding products in 55–70% yields (**3w–3z**). Beyond alkyl substitution, the reaction protocol exhibits compatibility with aryl substitution directly on the epoxide substrate, exemplified by 3,5-bis(trifluoromethyl)phenyl oxirane (**3aa**). Apart from epoxides, it was found that the range of nucleophiles can be further extended to oxetane, providing the corresponding product (**3ab**) with modest yield by using 2-(4-methoxyphenyl)-

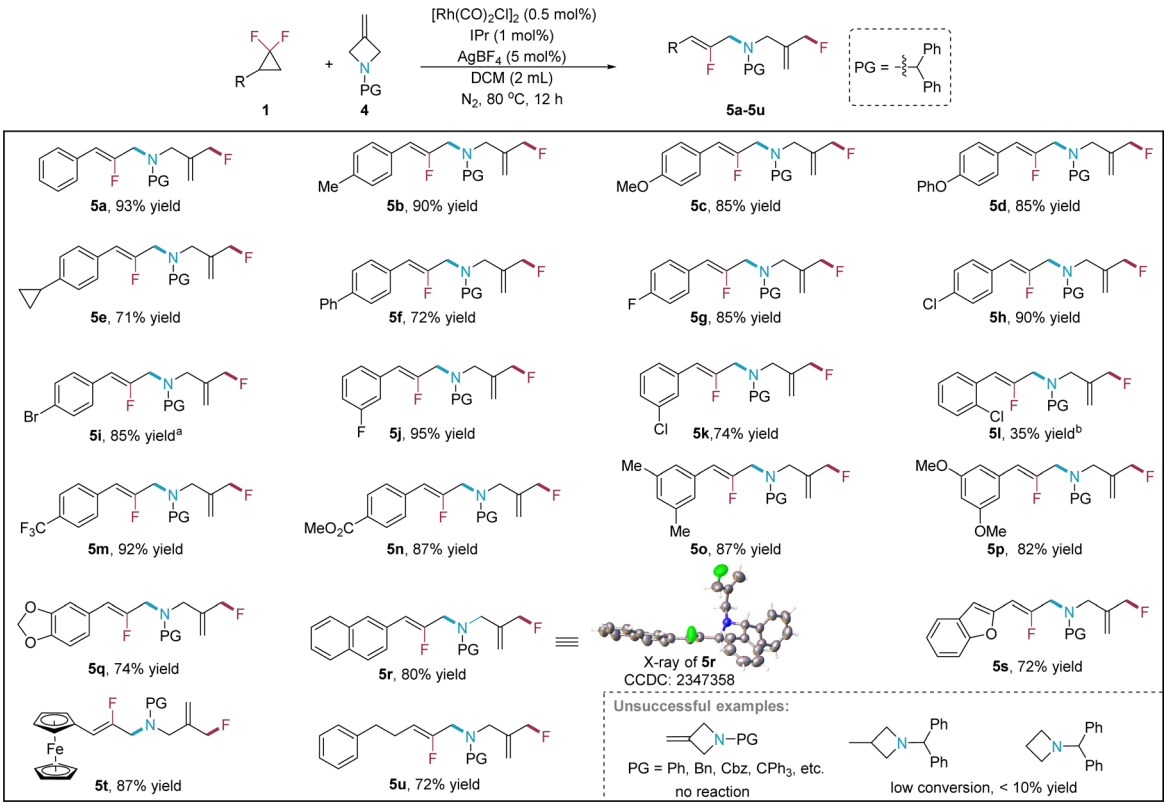


Scheme 2 Scopes of the Rh-catalyzed ring-opening C–O/C–F cross metathesis reaction. Reactions were performed with **1** (0.1 mmol), **2** (0.3 mmol), $[Rh(CO)_2Cl]_2$ (2 mol%), IPr (6 mol%), $AgBF_4$ (5 mol%), $^{n}Pr_2CHCN$ (25 mol%) in 0.3 mL of $PhCF_3$ at 80 °C for 24 h, and isolated yields were provided.

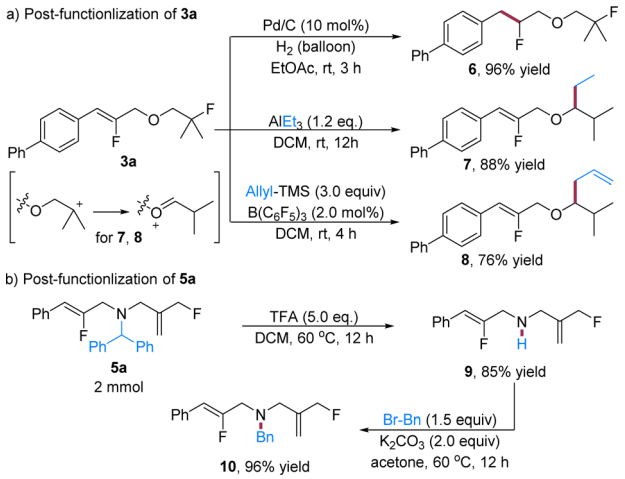
2-methyloxetane (**2k**) as the substrate. However, mono-substituted and simple epoxides as well as mono-substituted oxetane show no reactivity in this formal C–O/C–F ring-opening metathesis reaction.

With the success of the formal C–O/C–F bond metathesis under Rh catalysis, we are wondering whether this Rh-catalyzed protocol can be extended to other C–heteroatom single bond metathesis reactions. It was found that 3-methyleneazetidine **4** can be employed as the nucleophile to couple with *gem*-DFCPs, which leads to the formal C(sp^3)–N/C(sp^3)–F bond metathesis (Scheme 3). The reaction is very efficient, in which only 0.5 mol% of $[Rh(CO)_2Cl]_2$ is required to achieve 93% yield of the product **5a** for the model reaction (see ESI† for more details on the condition optimization). The reaction scope of *gem*-DFCPs is then thoroughly investigated. A wide range of aryl *gem*-DFCPs, including those with electron-donating (**5b–5d**), electron-neutral (**5d**, **5e**) and electron-withdrawing (**5g–5n**) substituents regardless of the position, furnish the target products in good yields, except for the *ortho*-substituted case (**5l**) which is in diminished yield. Besides, disubstituted variants(**5o–5q**), naphthyl (**5r**), benzofuryl (**5s**) and ferrocenyl (**5t**) substrates all work very well under the optimized reaction conditions, in which the structure of product **5r** is confirmed by X-ray crystallographic analysis.[21] Note that the reaction of alkyl *gem*-DFCP (**5u**) proceeds smoothly under the same reaction conditions, affording the corresponding product in 72% yield. During our investigation on finding suitable *N*-protecting groups of 3-methyleneazetidine in this reaction, it is found that several candidates with *N*-protecting groups including phenyl, benzyl, triphenylmethyl and Cbz (benzyloxycarbonyl) show no reactivity, indicating a big influence of the *N*-protecting group on the efficiency of the reaction. It is speculated that nitrogen with a smaller protecting group would poison the rhodium catalyst by strong coordination, while substrates with a bulkier (CPh_3) or carbonyl (Cbz) protecting group would decrease the nucleophilic ability of the nitrogen. Finally, 3-methyl and simple azetidines express some reactivity but afford the target products with very low yields.

After investigating the reaction scope, we then move to explore the synthetic utility of these fluorine-containing ether and amine products (Scheme 4). The reduction of **3a** under a hydrogen atmosphere with Pd/C gives ether **6** in 96% yield, in which the two fluorine substituents can be retained in the transformation. Furthermore, the alkyl fluoride moiety in **3a** can smoothly undergo alkylation (**7**)[22] and allylation (**8**)[23] in the presence of a Lewis acid, wherein the substitution shifts to the α-carbon of the oxygen, possibly *via* an arrangement of the carbon cation (Scheme 4a). As for the fluorine-containing amine products, while the *N*-protecting group is restricted as diphenylmethyl, it can facilely undergo deprotection with trifluoroacetic acid (TFA) to liberate the free amine 9 in 85% yield. The facile deprotection allows the installation of other



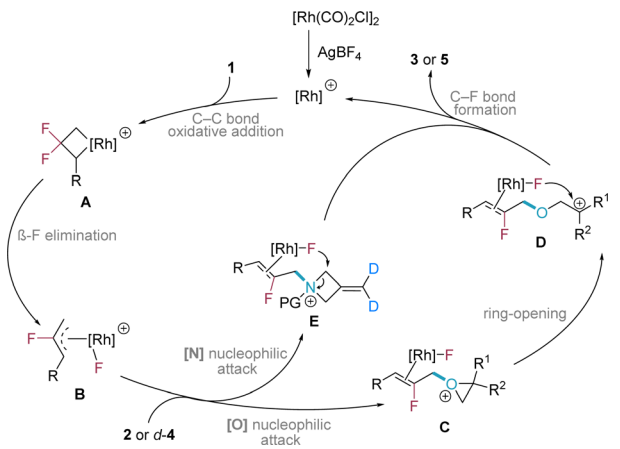
Scheme 3 Substrate scope of the Rh-catalyzed ring-opening C–N/C–F metathesis reaction. Reaction conditions: **1** (0.3 mmol), **4** (0.2 mmol), $[Rh(CO)_2Cl]_2$ (0.5 mol%), IPr (1 mol%), $AgBF_4$ (5 mol%) in 2 mL of solvent at the indicated temperature for 12 h, isolated yields were provided. [a]Reaction was performed with $[Rh(CO)_2Cl]_2$ (2 mol%), IPr (4 mol%). [b]Reaction was performed for 24 h.



Scheme 4 Synthetic applications.

functionalities on the nitrogen on demand. For example, the free amine 9 undergoes benzylation with benzyl bromide (BnBr), efficiently producing the desired molecule 10 in 96% yield (Scheme 4b). These reactions further enrich the diversity and complexity of the formal single bond metathesis products.

We proposed a simplified catalytic cycle for the formal single bond metathesis reaction (Scheme 5). In the initial stage, a highly active cationic Rh(I) species is generated from the neutral Rh precatalyst in the presence of $AgBF_4$. The *gem*-DFCP subsequently undergoes C–C bond oxidative addition to form rhodium complex **A**, which then experiences β-fluoride elimination to form the key intermediate fluoroallyl Rh(III) species **B**. Owing to the highly electrophilic properties of the species **B**, it can be attacked by a weak nucleophile of the oxygen in the epoxide, which generates an oxonium intermediate **C**. Following ring-opening, the resulting carbon cation of species **D** is trapped by the fluoride (from Rh–F or BF_4),[17b,24] which yields the product 3 and releases the rhodium catalyst to complete the catalytic cycle. For 3-methyleneazetidine as the coupling partner, the fluoroallyl Rh(III) species **B** undergoes nucleophilic attack by the nitrogen to give ammonium intermediate **E**, which



Scheme 5 Proposed mechanism.

is then trapped by the fluoride[17b,24] at the methylene site in the ring (see ESI† for more details).

Conclusions

In conclusion, we have successfully developed a rhodium-catalyzed method for the formal C(sp^3)–O/C(sp^3)–F cross metathesis reaction between *gem*-DFCPs and epoxides. The reaction features the use of ether oxygen as a weak nucleophile and a remarkable 100% atom economy. The use of two strained three-membered substrates *via* double-strain release offers the driving force for the formal single-bond metathesis, which involves the cleavage and formation of many inert chemical bonds including C–C, C–O and C–F bonds. The developed method can also be applied to the formal C(sp^3)–N/C(sp^3)–F cross metathesis between *gem*-DFCPs and 3-methyleneazetidine. We believe such advancements will not only contribute to the research area of single-bond metathesis, but also provide efficient and versatile synthetic methods for the construction of complex fluorine-containing compounds.

Data availability

All the data have been presented in the manuscript and ESI.†

Author contributions

Y. Z. and J. J. contributed equally to this work. Y. X. conceived the project. Y. Z., J. J. and X. S. carried out the experiments. Y. Z., J. J., Y. X. and C. G. co-wrote the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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