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# Ligand-controlled regioselective and chemodivergent defluorinative functionalization of *gem*-difluorocyclopropanes with simple ketones†

Leiyang Lv, \* Huijun Qian, Yangyang Ma, Shiqing Huang, Xiaoyu Yan   
and Zhiping Li \*

Modulating the reaction selectivity is highly attractive and pivotal to the rational design of synthetic regimes. The defluorinative functionalization of *gem*-difluorocyclopropanes constitutes a promising route to construct  $\beta$ -vinyl fluorine scaffolds, whereas chemo- and regioselective access to  $\alpha$ -substitution patterns remains a formidable challenge. Presented herein is a robust Pd/NHC ligand synergistic strategy that could enable the C–F bond functionalization with exclusive  $\alpha$ -regioselectivity with simple ketones. The key design adopted enolates as  $\pi$ -conjugated ambident nucleophiles that undergo inner-sphere 3,3'-reductive elimination warranted by the sterically hindered-yet-flexible Pd-PEPPSI complex. The excellent branched mono-defluorinative alkylation was achieved with a sterically highly demanding IHept ligand, while subtly less bulky SIPr acted as a bifunctional ligand that not only facilitated  $\alpha$ -selective C(sp<sup>3</sup>)–F cleavage, but also rendered the newly-formed C(sp<sup>2</sup>)–F bond as the linchpin for subsequent C–O bond formation. These examples represented an unprecedented ligand-controlled regioselective and chemodivergent approach to various mono-fluorinated terminal alkenes and/or furans from the same readily available starting materials.

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## Introduction

Controlling reaction selectivity to outcompete the intrinsic bias and innate reactivity, to achieve a specific bond-forming mode is a formidable challenge.<sup>1</sup> Nature exquisitely exploits enzymes as powerful catalysts to achieve incredibly selective transformations.<sup>2</sup> Inspired by this phenomenon, synthetic chemists have devoted great effort to developing reliable and efficient approaches for the creative manipulation of inherent reactivity and selectivity.<sup>3</sup> In this context, transition-metal catalyzed regio- and chemoselective functionalization of inert C–F bonds is a synthetically useful yet challenging research topic.<sup>4,5</sup> For example, Pd-catalyzed ring-opening functionalization of *gem*-difluorocyclopropanes,<sup>6</sup> which acts as a novel and reliable fluorine-containing building block, predominantly proceeds through cleavage of a C–F bond to afford an intrinsically stable  $\beta$ -monofluorinated alkene structure, with linear selectivity (Scheme 1a).<sup>7–9</sup> Despite the flourishing advances, the deconstructive transformation of *gem*-difluorocyclopropanes that incorporate functionalities into the sterically hindered internal position, delivering kinetically favored  $\alpha$ -monofluorinated alkenes with branched selectivity, remains a challenging task.

In addition,  $\alpha$ -monofluorinated alkenes are attractive structures, which mimic amides and enols in drug discovery and medicinal chemistry,<sup>10</sup> particularly with the presence of synthetically versatile fluorinated terminal C=C bonds.<sup>11</sup> Therefore, an alternative strategy that allows for the incorporation of the functional group into the *gem*-difluorocyclopropanes with complementary regioselectivity and an innovative reaction manifold is highly desirable. Notably, the highly regioselective ring-opening cross-couplings of relevant aziridines have been elegantly realized by Doyle<sup>12</sup> and Takeda.<sup>13</sup>

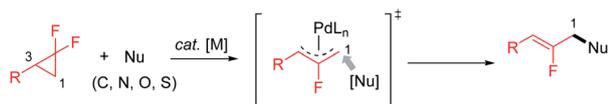
Motivated by the elegant accomplishments of Hou,<sup>14</sup> Echavarren<sup>15</sup> and Morken<sup>16</sup> *et al.* on allyl-allyl couplings, we aimed to take advantage of the flexible coordination character of ambident nucleophiles coupled with Pd/NHC ligand cooperative catalysis. According to the hard-soft-acid-base (HSAB) principle,<sup>17</sup> heteroatoms (*e.g.* nitrogen and oxygen) in such nucleophiles are harder Lewis bases that preferentially coordinate to the metal center, thus ensuring the softer carbon attack at the sterically more hindered internal position *via* inner-sphere 3,3'-reductive elimination warranted by the congested NHC ligand (Scheme 1b). Besides, the strong binding affinity of carbene to the metal center contributes to the thermal stability of the Pd–NHC complex, which renders a longer catalyst lifetime and consistent reactivity.<sup>18</sup> Guided by this concept, we have recently reported that simple hydrazones could act as ambident nucleophiles to realize the anticipated branched regioselectivity in

Department of Chemistry, Renmin University of China, Beijing 100872, China. E-mail: lvleiyang2008@ruc.edu.cn; zhipingli@ruc.edu.cn

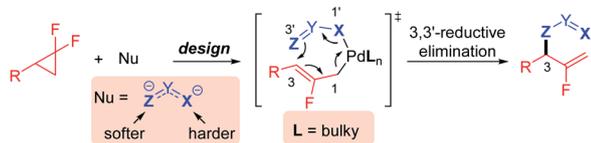
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc05451a



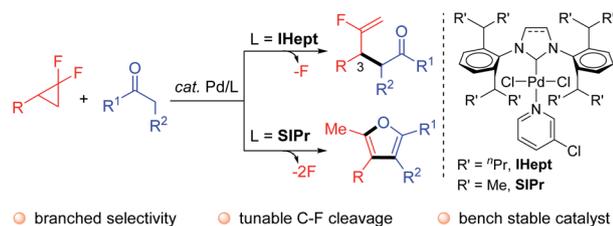
## (a) Previous work: linear selectivity



## (b) Design: branched selectivity enabled by ambident nucleophile



## (c) This work: Pd/ligand modulates both regioselectivity and chemoselectivity



Scheme 1 Strategies for the regio- and chemoselective C–F bond functionalization of *gem*-difluorocyclopropanes.

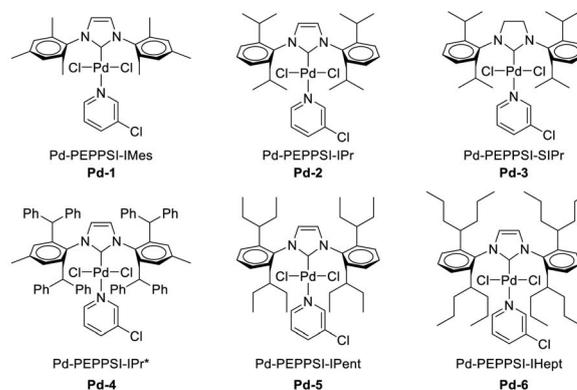
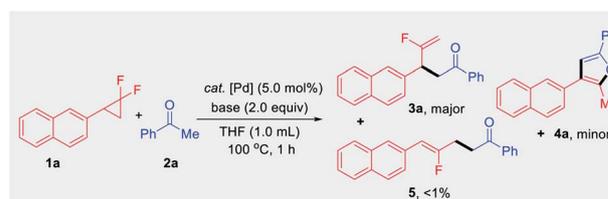
the Pd-catalyzed mono-defluorinative alkylation reactions facilitated by denitrogenation.<sup>19</sup>

Ketones are a cheap and naturally abundant feedstock that have been widely used in both academia and industry.<sup>20</sup> Inspired by the inner-sphere allylic alkylations, and given the ketone–enolate tautomerization, we envisioned that if enolates could serve as  $\pi$ -conjugated ambident nucleophiles (*e.g.* oxygen as the harder coordination anchor, carbon as the softer coupling site) to couple with *gem*-difluorocyclopropanes under Pd/NHC catalysis. The advantage of the incorporated carbonyl functionality may allow for further interconversions. However, compared with stabilized carbon nucleophiles (*e.g.* malonates or  $\beta$ -ketoesters), destabilized simple ketone enolates, especially methyl ketones [ $pK_a \approx 25$  (DMSO)],<sup>21</sup> are challenging coupling partners in such transformations<sup>22</sup> due to: (1) direct outer-sphere attack *vs.* inner-sphere coordination to afford competitive linear products; (2) overalkylation of the ketone commonly occurring due to the mono-alkylated ketones featuring more acid C–H bonds; (3) aldol-type condensations prevailing in the case of destabilized enolates. Herein, our strategy to circumvent these challenges takes advantage of the cooperative Pd catalysis with tunable, sterically hindered yet flexible NHC ligands. The excellent branched regioselective mono-defluorinative alkylation was achieved with the bulky IHept ligand, while sterically less hindered SIPr acted as an unexpected bifunctional ligand,<sup>23</sup> that not only enabled the exquisitely branched selective C(sp<sup>3</sup>)–F cleavage, but also facilitated further manipulation of the newly-formed C(sp<sup>2</sup>)–F bond. This powerful ligand-controlled regio- and chemoselective strategy afforded a variety of mono-fluorinated terminal alkenes or advantageous furans from the same readily available *gem*-difluorocyclopropanes and ketones.

## Results and discussion

As a proof of concept, we began our investigations with the reaction of *gem*-difluorocyclopropane **1a** as a limiting reagent in the presence of 2.0 equiv. of acetophenone **2a**, base, and 5 mol% of bench-stable Pd-PEPPSI catalyst at 100 °C for 1 h (Table 1). Among the various Pd **1–6** complexes examined, the desired branched product **3a** and unexpected furan product **4a** were obtained, in which the yields and proportions were sensitive to the steric hindrance of the side chain of the NHC ligands. Notably, the thermodynamically stable linear product **5** was

Table 1 Optimization of the reaction conditions (N.D. = not detected)<sup>a</sup>



Entry	Cat. [Pd]	Base	<b>3a</b> <sup>b</sup> (%)	<b>4a</b> <sup>b</sup> (%)	<b>3a/4a</b> <sup>c</sup>
1	<b>Pd-1</b>	NaOH	N.D.	N.D.	—
2	<b>Pd-2</b>	NaOH	<1	32	<1 : 32
3	<b>Pd-3</b>	NaOH	<1	31	<1 : 31
4	<b>Pd-4</b>	NaOH	65	6	11 : 1
5	<b>Pd-5</b>	NaOH	82	7	12 : 1
6	<b>Pd-6</b>	<b>NaOH</b>	<b>95</b>	<b>3</b>	<b>32 : 1</b>
7	<b>Pd-6</b>	LiO <sup>t</sup> Bu	84	3	28 : 1
8	<b>Pd-6</b>	KOH	65	17	3.8 : 1
9	<b>Pd-6</b>	Cs <sub>2</sub> CO <sub>3</sub>	34	1	34 : 1
10 <sup>d</sup>	<b>Pd-6</b>	Cs <sub>2</sub> CO <sub>3</sub>	91	3	30 : 1
11	<b>Pd-6</b>	K <sub>3</sub> PO <sub>4</sub>	N.D.	N.D.	—
12	<b>Pd-6</b>	K <sub>2</sub> CO <sub>3</sub>	N.D.	N.D.	—
13	<b>Pd-6</b>	—	N.D.	N.D.	—
14	—	NaOH	N.D.	N.D.	—
15 <sup>e</sup>	<b>Pd-6</b>	NaOH	93	3	30 : 1

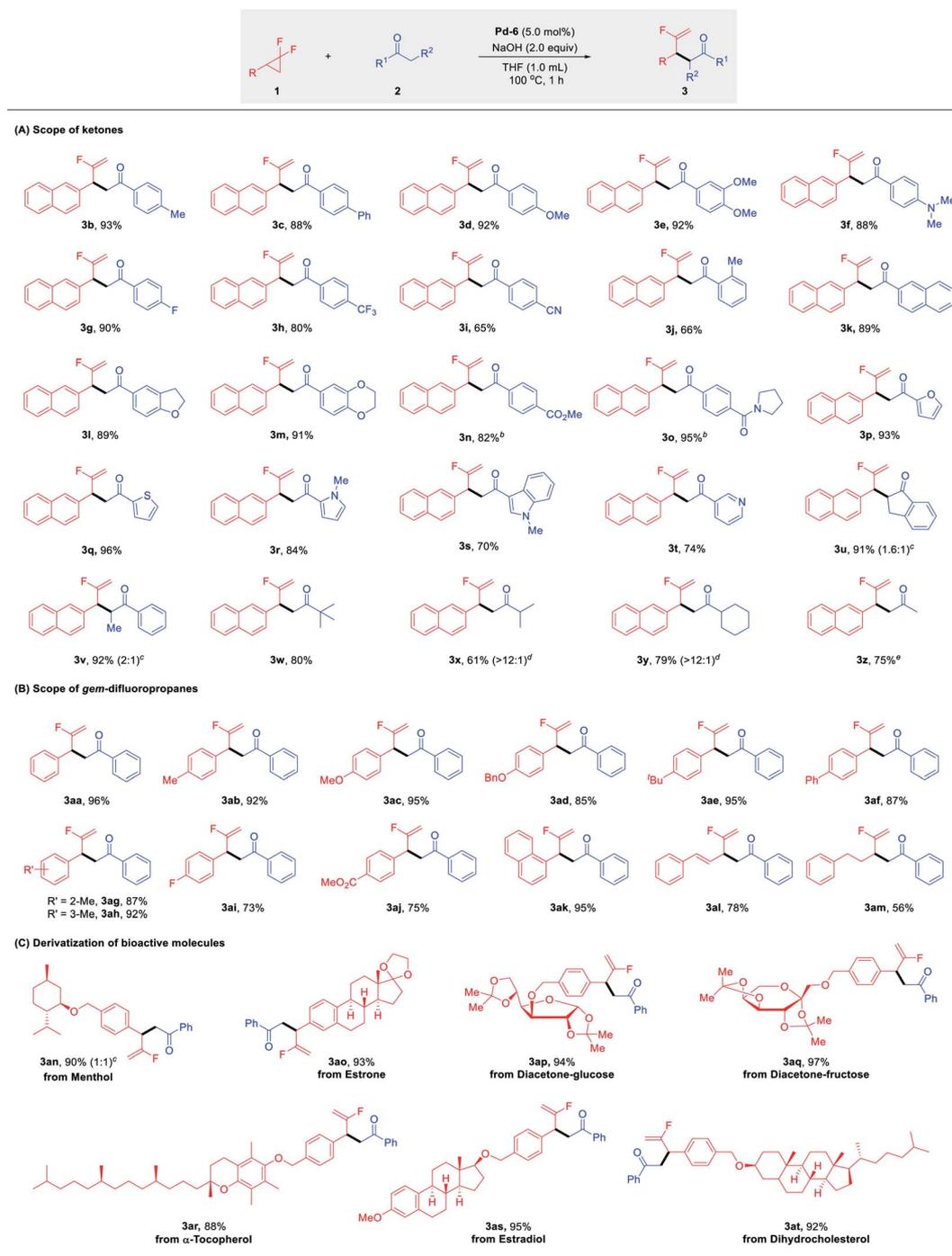
<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd-PEPPSI catalyst (5.0 mol%), base (0.2 mmol), THF (1.0 mL), 100 °C, 1 h under N<sub>2</sub> unless otherwise noted. <sup>b</sup> NMR yields were based on **1a** and determined by <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. <sup>c</sup> The **3a/4a** ratio was determined by <sup>1</sup>H NMR analysis of the crude mixtures. <sup>d</sup> 6 h. <sup>e</sup> **1a** (1.0 mmol), **2a** (2.0 mmol), **Pd-6** (2.5 mol%), NaOH (1.5 mmol), THF (6.0 mL).



detected in only trace amounts (<1%) in all cases. The *gem*-difluorocyclopropane **1a** was recovered quantitatively when **Pd-1** was tested (entry 1). In the case of bulkier **Pd-2** and **Pd-3**, furan **4a** was obtained selectively in calc. ~30% yields *via* twofold defluorinative functionalization (entries 2 and 3). With further

increase of the ligand steric hindrance (*e.g.* **Pd-4** to **Pd-6**), an intriguing complete shift of the chemoselectivity was observed, and the branched mono-defluorination product **3a** was afforded predominantly (entries 4–6). The best result was for the branched fluoroalkene product **3a** which was selectively

Table 2 Substrate scope of mono-defluorinative alkylations<sup>a,b</sup>



<sup>a</sup> Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Pd-PEPSI-Hept (5.0 mol%), NaOH (0.2 mmol), THF (1.0 mL), 100 °C, 1 h under N<sub>2</sub>, isolated yields. <sup>b</sup> Cs<sub>2</sub>CO<sub>3</sub> used instead of NaOH. <sup>c</sup> The diastereomeric ratio was determined by <sup>1</sup>H NMR analysis of the crude mixtures. <sup>d</sup> Coupling at CH<sub>3</sub>/CH ratio. <sup>e</sup> Acetone (0.5 mmol).



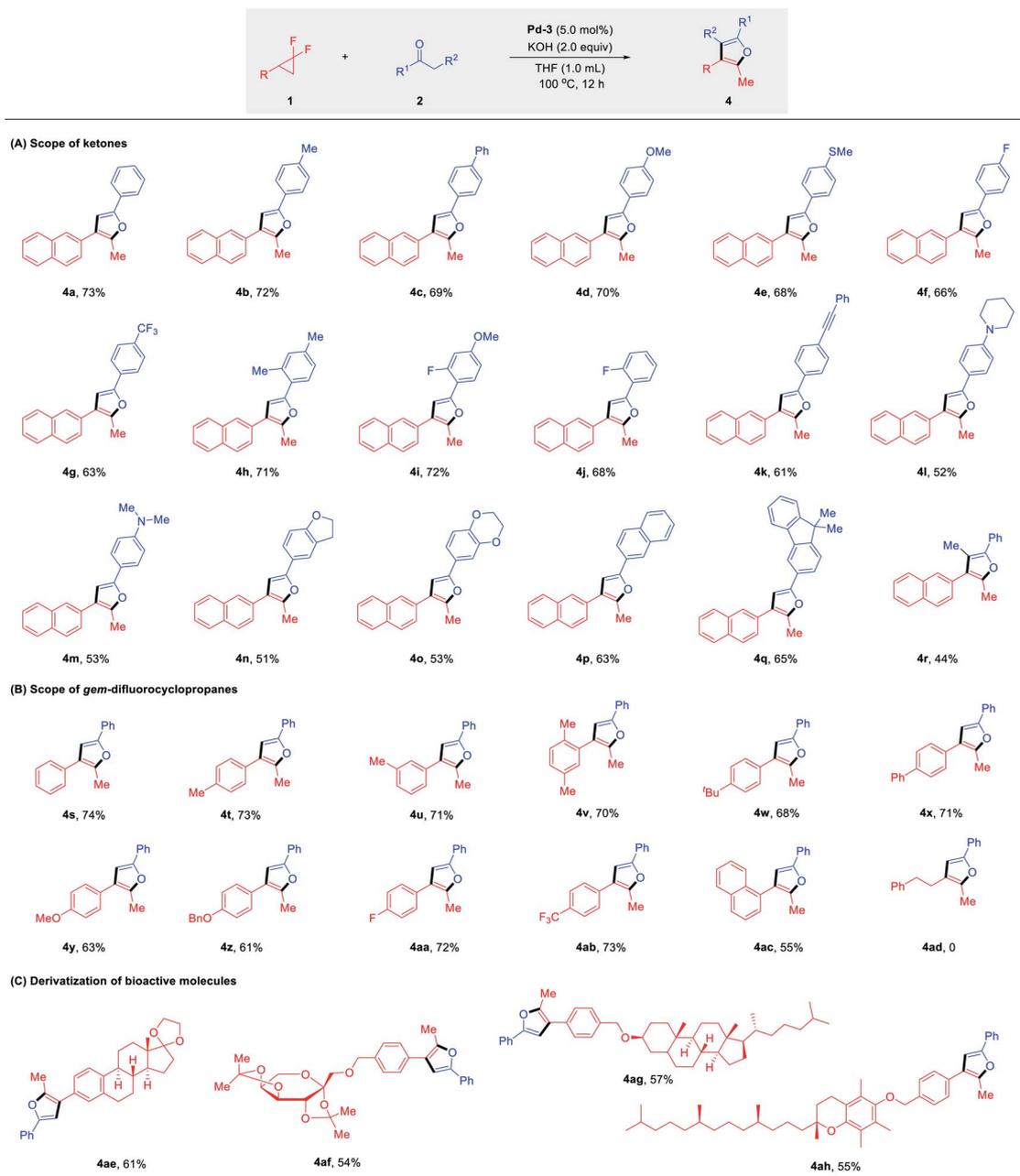


such as naphthalene and fluorene also reacted smoothly with **1a** to deliver furan products **4p** and **4q** in 63% and 65% yields, respectively. Notably, propiophenone could undergo the transformation as well, affording the desired fully-substituted furan **4r** in 44% yield.

The compatibility of *gem*-difluoro cyclopropanes in this transformation was examined accordingly. As shown in Table 3, B, the substitution patterns of the substrates proved to be versatile. Good yields were obtained ranging from 61–74% in the case of the electron-donating (–Me, –<sup>t</sup>Bu, –Ph, –OMe, –OBn)

and electron-withdrawing groups (–F, –CF<sub>3</sub>) tested. 1-Naphthalene substituted *gem*-difluorocyclopropane was also identified as a suitable reaction partner, affording the desired product **4ac** as a suitable reaction partner, affording the desired product **4ac** in 55% yield. Moreover, *gem*-difluoro cyclopropanes derived from bioactive molecules – estrone, diacetone-fructose, dihydrocholesterol and  $\alpha$ -tocopherol – were successfully converted to the corresponding furan products **4ae–ah** in moderate yields (Table 3, C). These examples demonstrated that by employing different ligands or bases, diverse products could be

Table 3 The substrate scope of two fold defluorinative functionalizations<sup>a,b</sup>



<sup>a</sup> Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Pd-PEPPSI-SIPr (5.0 mol%), KOH (0.2 mmol), THF (1.0 mL), 100 °C, 12 h under N<sub>2</sub>. <sup>b</sup> Isolated yields.



implemented selectively from the identical starting materials under similar reaction conditions.

To probe the preliminary insight into the reaction mechanism, several control experiments were carried out (Scheme 2). The yield of **3a** was not affected when radical inhibitors such as butylated hydroxytoluene (BHT) or 1,1-diphenylethylene were added under the standard conditions, which ruled out the involvement of a radical pathway (eqn (1) and (2)). Besides, silyl enol ether **6** also reacted with **1a** to afford the desired product **3a** in comparable yield (eqn (3)). Moreover, a time-course reaction indicated that there was a short induction period related to activation of the Pd precatalyst (calc. 10 min), after which the transformation was faster and could be completed in 1 h (see ESI† for details).

Taking the above results and literature reports together, a plausible reaction mechanism was proposed to illustrate the regioselectivity and chemodivergent reactivity of this transformation (Scheme 3). Initially, the Pd(0) catalyst reacts with *gem*-difluorocyclopropane via C–C bond activation and C–F bond cleavage to generate the allyl-Pd(II) complex **B**. The two fluorine atoms on the cyclopropane ring make the C1–C2–C3 bond angle increase and distal (C1–C3) bond lengthen, thus leading to the distal bond in the *gem*-difluorocyclopropane more easily cleaving during the ring-opening process.<sup>26</sup> This highly selective ring-

opening mode was also calculated by Fu and coworkers with the lower energy barrier of the oxidative addition of the C1–C3 bond (7.9 kcal mol<sup>-1</sup>) versus oxidation of the C2–F bond (46.5 kcal mol<sup>-1</sup>).<sup>7</sup> Also, considering alkyl substrates such as **1m** are also active in the mono-defluorinative alkylation, we suspected that it was less possible for the current ring-opening of *gem*-difluorocyclopropane in the S<sub>N</sub>2 fashion, where the interactions existed between the aryl unit of the aziridines and Pd catalyst.<sup>13b</sup> Then, the transmetalation of **B** with enolate as the π-ambident nucleophile derived from deprotonated ketone **2**, affords the crucial bis(η<sup>1</sup>-allyl) intermediate **C**, which undergoes inner-sphere 3,3'-reductive elimination,<sup>25</sup> guaranteed by the sterically encumbered NHC ligand to deliver the branched product **3** and regenerate the Pd(0) catalyst. The furan product **4** was formed via the base-mediated enolization/nucleophilic substitution/rearomatization sequence promoted by the less-congested Pd-3 catalyst. Therefore, the elaborate design of ligand structure and modification of reaction conditions (e.g. base, reaction time) could enable the exquisitely chemodivergent synthesis of β-monofluorinated alkenes and/or corresponding furan products via selective C–F bond cleavage.

## Conclusion

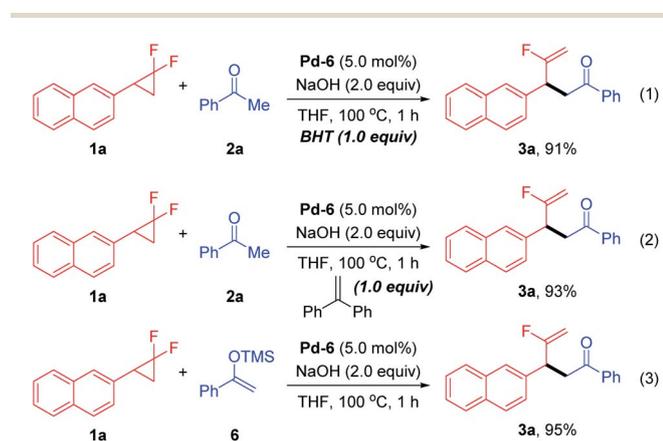
In summary, we have developed a powerful ligand-controlled regioselective and chemodivergent defluorinative functionalization of *gem*-difluorocyclopropanes to deliver mono-fluorinated terminal alkenes and/or furans. This potent Pd/NHC ligand synergistic strategy enabled the C–F bond functionalization in an exclusive α-regioselectivity with simple ketones as π-conjugated ambident nucleophiles, which was difficult to access by conventional approaches. The excellent branched regioselective mono-defluorinative alkylations were achieved with sterically highly demanding IHept ligands, while less bulky SIPr acted as an unexpected bifunctional ligand that not only enabled the exquisitely branched selective C(sp<sup>3</sup>)–F cleavage, but also facilitated further manipulation of the newly-formed C(sp<sup>2</sup>)–F bond. The robustness of this protocol was demonstrated by the wide substrate scope, excellent regio- and chemoselectivity, good functional group compatibility, efficient modification of bioactive molecules and natural products as well as stable and user-friendly precatalysts. Further efforts will be made to develop the enantioselective version. Our study is dedicated to the art of tuning ligands to achieve selective catalysis by utilizing identical starting materials to produce different products, and also enriches the toolbox of chemists enabling cross-couplings with destabilized carbon nucleophiles.

## Data availability

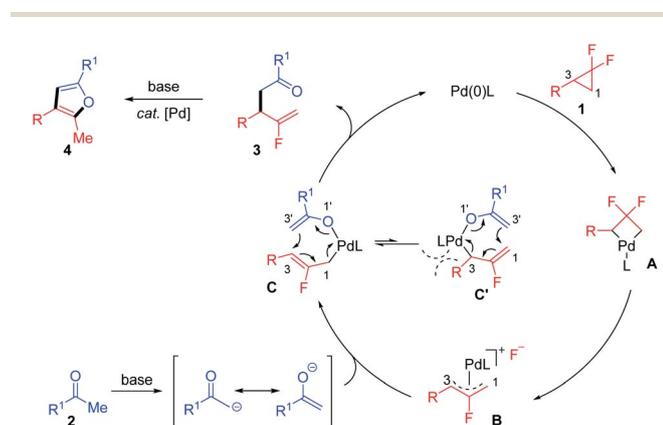
All experimental data in this manuscript are available in the ESI.†

## Author contributions

L. L. conceived the idea for this work, supervised and designed the experiments. L. Z. co-supervised the project. L. L. and Q. H.



Scheme 2 Control experiments.



Scheme 3 Proposed reaction mechanism.



performed the experiments and analyzed the data. Ma, Y. synthesized some of the catalysts. L. L. wrote the manuscript. All authors discussed the experimental results and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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