

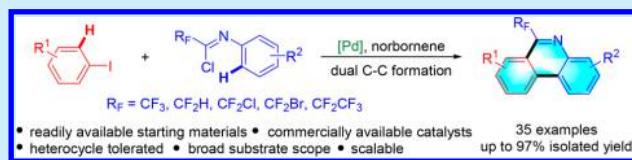
# Expedited Synthesis of 6-Fluoroalkyl-Phenanthridines via Palladium-Catalyzed Norbornene-Mediated Dehydrogenative Annulation

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## Supporting Information

**ABSTRACT:** A novel palladium-catalyzed, norbornene-mediated intermolecular dehydrogenative annulation approach for the synthesis of 6-fluoroalkyl-phenanthridines from aryl iodides and fluorinated imidoyl chlorides, which are important structural motifs for bioactive molecules, is reported. Fluorinated imidoyl chlorides served as a new type of electrophilic reagent in the Catellani-type reaction, which, in turn, could be readily prepared from various anilines and fluorinated carboxylic acids. Control experiments were carried out to study the mechanism of the reaction. This transformation is scalable and tolerates a broad range of functional groups.



**P**henanthridines represent a class of fused heteroaromatic<sup>1</sup> motifs found universally in many natural products,<sup>2</sup> biologically active molecules,<sup>3</sup> and in optoelectronic materials.<sup>3</sup> Well known members include trisphaeridine,<sup>4</sup> fagaronine,<sup>5</sup> and ethidium<sup>6</sup> (Figure 1). Moreover, the incorporation of a

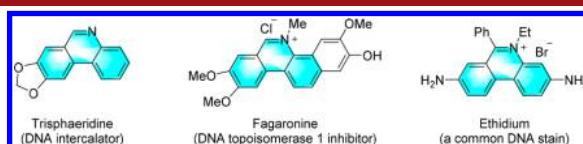
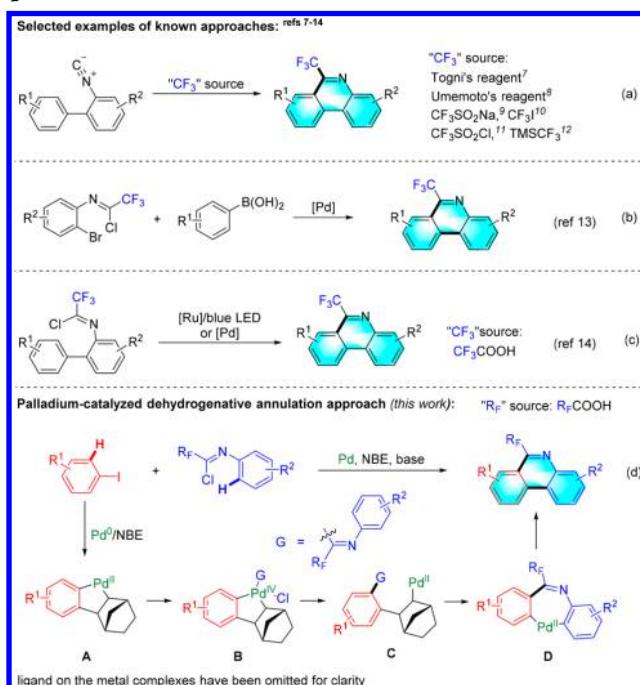


Figure 1. Biologically active phenanthridines.

fluoroalkyl group into phenanthridines often alters its physical and chemical properties, leading to improved biological functions, due to increased lipophilicity and metabolic stability. Therefore, the development of efficient methodologies to synthesize 6-fluoroalkyl-phenanthridines and their derivatives has become a subject of great interest during the past few years and many useful synthetic procedures have been explored. In one such transformation, trifluoromethylation of 2-arylisocyanides was carried out using radical trifluoromethylating reagents, such as Togni's reagent,<sup>7</sup> Umemoto's reagent,<sup>8</sup> Langlois' reagent,<sup>9</sup> CF<sub>3</sub>I,<sup>10</sup> CF<sub>3</sub>SO<sub>2</sub>Cl,<sup>11</sup> TMSCF<sub>3</sub>,<sup>12</sup> and others (Scheme 1a). In recent years, fluorinated imidoyl chlorides have proven to be good building blocks for the synthesis of 6-fluoroalkyl-phenanthridines using transition metal catalysts. For example, Zhang and co-workers<sup>13</sup> prepared 6-trifluoromethyl-phenanthridines through palladium-catalyzed tandem Suzuki/C–H arylation reactions of *N*-aryl trifluoroacetimidoyl chlorides with arylboronic acids (Scheme 1b).

## Scheme 1. Approaches To Access 6-Fluoroalkyl-phenanthridines



Later, Fu<sup>14</sup> achieved the intramolecular cyclization of *N*-biaryl trifluoroacetimidoyl chloride to obtain 6-trifluoromethyl-

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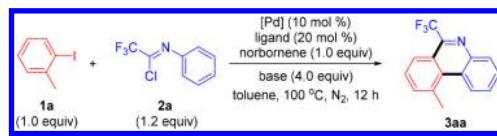
phenanthridines (**Scheme 1c**). Although many methods are available, the requirement of specific prefunctionalized starting materials and their low efficiencies limit the scope of these methods. Therefore, the development of expedited approaches for the synthesis of 6-fluoroalkyl-phenanthridines from readily available starting materials is necessary.

Pd/norbornene (NBE) chemistry represents a powerful strategy that allows the efficient construction of polyfunctional aromatic and heteroaromatic compounds,<sup>15</sup> which was pioneered by Catellani and co-workers in 1997.<sup>16</sup> Further explorations by Catellani's group,<sup>17</sup> Lautens' group,<sup>18</sup> and others<sup>19</sup> have enriched and expanded the scope of this method. Taking advantage of the palladium/NBE catalysis, *ortho* and *ipso* bis-functionalization products can be obtained by coupling with an electrophile and a nucleophile simultaneously. In recent years, different types of electrophilic reagents have been found to react with a key aryl-NBE palladacycle intermediate in reactions, such as amination,<sup>19e,g,20</sup> arylation,<sup>21</sup> alkylation,<sup>16,22</sup> and acylation,<sup>23</sup> which result in *ortho*-functionalized products. In order to broaden the scope of this reaction, it becomes crucial to explore new electrophilic reagents for the synthesis of divergent polysubstituted arenes.

In 2016, Jiao and co-workers<sup>24</sup> developed an efficient approach to synthesize phenanthridinone derivatives by employing palladium/NBE cooperative catalysis. This protocol was easy to handle, and aryl carbamic chloride served as the electrophilic reagent to realize *ortho*-acylation. As part of our continued interest in the development of practical methodologies for highly efficient construction of heterocyclic molecules from readily available building blocks<sup>25</sup> and inspired by Jiao's work,<sup>24</sup> we surmised that biologically relevant 6-fluoroalkyl-phenanthridines could be obtained from aryl iodides and fluorinated imidoyl chlorides through a palladium-catalyzed Catellani-type *one-pot* dehydrogenative annulation reaction. **Scheme 1d** depicts a convergent synthetic route to the aforementioned scaffolds. We hypothesize that the reaction is initiated by Pd(0), which undergoes oxidative addition with aryl iodide, followed by insertion of the norbornene and *ortho* C–H activation to form the key Pd(II) intermediate A. Subsequent oxidative addition of the fluorinated imidoyl chlorides with A provides the Pd(IV) complex B, which undergoes reductive elimination to afford Pd(II) intermediate C. The target 6-fluoroalkyl-phenanthridines and Pd(0) are obtained by elimination of the β-C with the removal of norbornene along with activation of the C–H bond to afford Pd(II) intermediate D, which finally undergoes another reductive elimination, thereby completing the Pd cycle. To the best of our knowledge, synthesis of 6-fluoroalkyl-phenanthridines by using this strategy is still unknown and is challenging due to two adjacent C–C bond formations via C–H bond cleavage.<sup>26</sup> Recently, Pd/NBE chemistry has proven to be an important protocol that allows activation of both the *ipso*- and *ortho*-positions of arenes.<sup>27–32</sup> These results encouraged us to test our dehydrogenative protocol.

To test our hypothesis as shown in **Scheme 1d**, compounds **1a** and **2a** were initially chosen as the model substrates, which were reacted in the presence of Pd(OAc)<sub>2</sub> (10 mol %), PPh<sub>3</sub> (20 mol %), norbornene (1.0 equiv), and Cs<sub>2</sub>CO<sub>3</sub> (4.0 equiv) in toluene (2.0 mL) at 100 °C under a nitrogen atmosphere. Gratifyingly, after 12 h, the expected product **3aa** was indeed obtained in 40% isolated yield (**Table 1**, entry 1). Inspired by this result, first, a range of solvents were tested, of which toluene was found to be the most efficient (**Table 1**, entries 2–

**Table 1. Optimization of Reaction Conditions<sup>a</sup>**

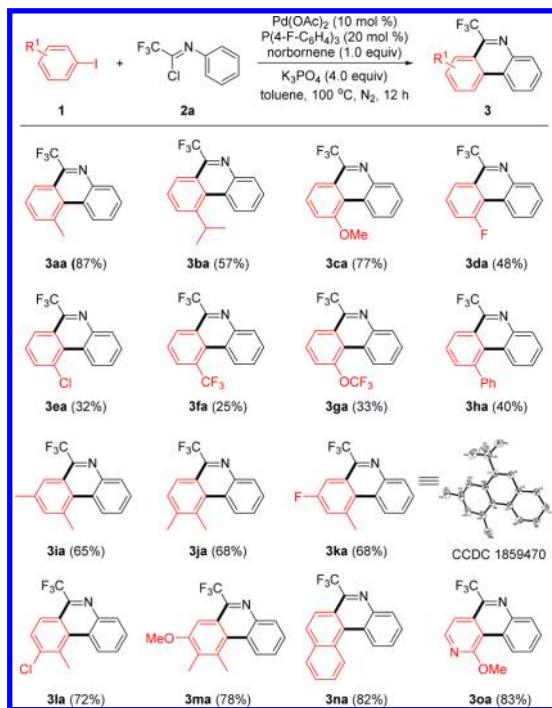


entry	[Pd]	ligand	base	yield <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	40%
2 <sup>c</sup>	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	15%
3 <sup>d</sup>	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	trace
4 <sup>e</sup>	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	trace
5	Pd(OAc) <sub>2</sub>	S-Phos	Cs <sub>2</sub> CO <sub>3</sub>	22%
6	Pd(OAc) <sub>2</sub>	P(2-furyl) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	36%
7	Pd(OAc) <sub>2</sub>	P(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	52%
8	Pd(OAc) <sub>2</sub>	P(4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	50%
9 <sup>f</sup>	Pd(OAc) <sub>2</sub>	dppe	Cs <sub>2</sub> CO <sub>3</sub>	45%
10 <sup>f</sup>	Pd(OAc) <sub>2</sub>	dppf	Cs <sub>2</sub> CO <sub>3</sub>	43%
11 <sup>f</sup>	Pd(OAc) <sub>2</sub>	DPE-Phos	Cs <sub>2</sub> CO <sub>3</sub>	23%
12	PdCl <sub>2</sub>	P(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	42%
13	Pd(cod)Cl <sub>2</sub>	P(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	32%
14	Pd(OAc) <sub>2</sub>	P(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	KOH	45%
15	Pd(OAc) <sub>2</sub>	P(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	87%
16 <sup>g</sup>	Pd(OAc) <sub>2</sub>	P(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	50%
17 <sup>h</sup>	Pd(OAc) <sub>2</sub>	P(4-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	45%

<sup>a</sup>Reaction conditions: the reactions were carried out with **1a** (0.2 mmol), **2a** (0.24 mmol), [Pd] (0.02 mmol), ligand (0.04 mmol), norbornene (0.2 mmol), base (0.8 mmol), toluene (2.0 mL), nitrogen atmosphere, 12 h. <sup>b</sup>Isolated yield. <sup>c</sup>Xylene 2.0 mL. <sup>d</sup>PhCF<sub>3</sub> 2.0 mL. <sup>e</sup>MeCN 2.0 mL. <sup>f</sup>Ligand (0.02 mmol). <sup>g</sup>Norbornene (0.1 mmol). <sup>h</sup>5 mol % Pd(OAc)<sub>2</sub>.

4). A subsequent survey of a series of ligands indicated that P(4-F-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub> was the most efficient ligand, giving a 52% yield of the product. In contrast to P(4-F-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>, other ligands including diphosphines and monophosphines failed to show better catalytic reactivities (**Table 1**, entries 5–11). Among the catalysts investigated, Pd(OAc)<sub>2</sub> was found to be the most efficient one (**Table 1**, entries 12 and 13). To further improve the yield, various bases were examined, and to our delight, K<sub>3</sub>PO<sub>4</sub> exhibited the best performance and afforded the product in 87% yield (**Table 1**, entries 14 and 15). Additionally, when the loading of norbornene was decreased to 50 mol %, the yield was only 50% (**Table 1**, entry 16). Moreover, use of 5 mol % Pd(OAc)<sub>2</sub> decreased the yield to 45%, due to the low conversion of starting materials (**Table 1**, entry 17). Finally, the reaction of **1a** (1.0 equiv) with **2a** (1.2 equiv) in the presence of Pd(OAc)<sub>2</sub> (10 mol %), P(4-F-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub> (20 mol %), norbornene (1.0 equiv), and K<sub>3</sub>PO<sub>4</sub> (4.0 equiv) in toluene (2.0 mL) under nitrogen atmosphere at 100 °C for 12 h was considered to be the most optimal.

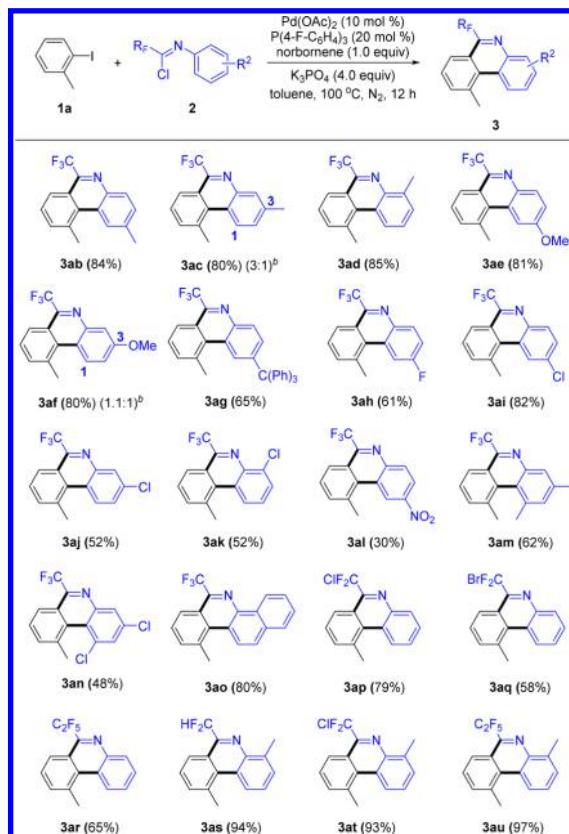
With optimal reaction conditions in hand, the scope of this methodology with respect to substituted aryl iodides was first examined. As shown in **Scheme 2**, a variety of iodoarenes were tested, all of which proved to be competent substrates for reaction with **2a**. In addition, regarding **1a**, a variety of *ortho*-substituents on the iodoarenes were tolerated in the reaction, which included isopropyl, methoxyl, fluoro, chloro, trifluoromethyl, trifluoromethoxyl, and phenyl groups, and the corresponding products **3aa**–**3ha** were isolated in moderate to excellent yields. Both electron-withdrawing and -donating groups on iodoarenes were tolerated, although substrates with electron-withdrawing groups gave products with relatively lower yields. Furthermore, multisubstituted aryl iodides with

Scheme 2. Variation of Aryl Iodides<sup>a</sup>

<sup>a</sup>Reaction conditions: the reactions were carried out with **1** (0.2 mmol), **2a** (0.24 mmol),  $\text{Pd}(\text{OAc})_2$  (0.02 mmol),  $\text{P}(4\text{-F-C}_6\text{H}_4)_3$  (0.04 mmol), norbornene (0.2 mmol),  $\text{K}_3\text{PO}_4$  (0.8 mmol) in toluene (2.0 mL) under a nitrogen atmosphere for 12 h.

versatile groups reacted smoothly to give the corresponding products in 65%–78% yields (**3ia**–**3ma**). Meanwhile the molecular structure of **3ka** was unambiguously confirmed by X-ray crystallographic analysis (CCDC 1859470; for other details, see the Supporting Information). Reaction with 1-iodonaphthalene provided **3na** in 82% yield. Notably, heteroaryl iodide **1o** was also found to be a suitable substrate, which reacted with **2a** to afford **3oa** in 83% yield.

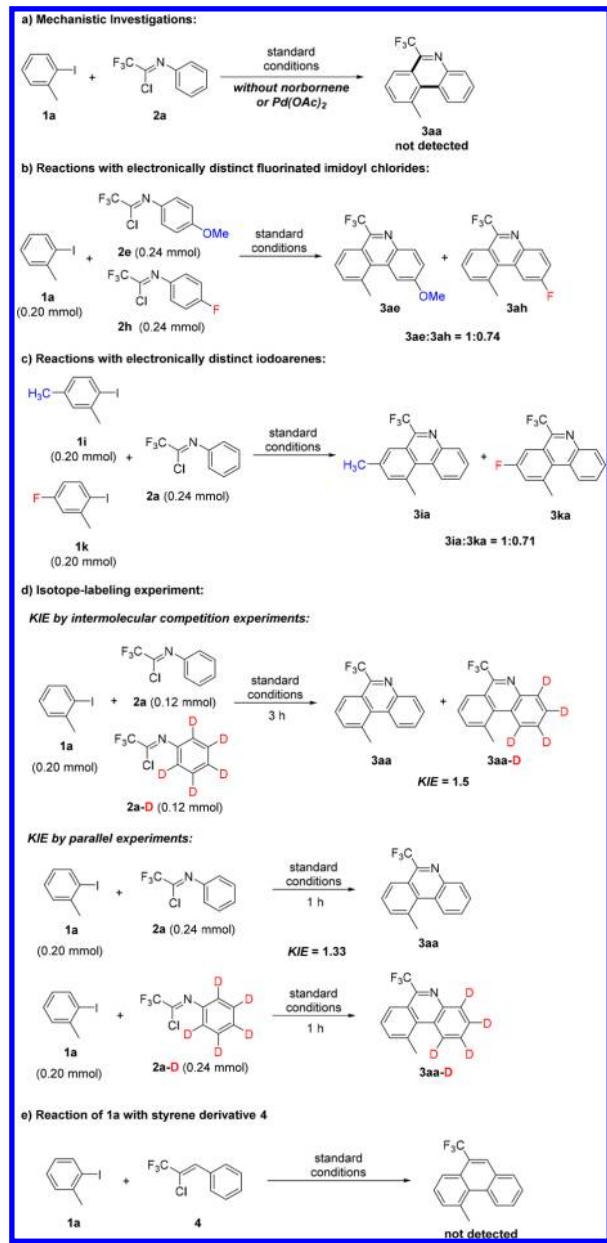
The catalytic dehydrogenative annulation methodology was then extended to other fluorinated imidoyl chlorides, which could be easily prepared from the corresponding aniline and fluorinated carboxylic acids. As shown in Scheme 3, *p*-, *m*-, and *o*-methyl substituents on the aryl ring of **2** were well tolerated and the desired products **3ab**–**3ad** were obtained in 80–85% yields. Among them, *meta*-substituted substrate **2c** with **1a** resulted in a mixture of the products **3ac** with moderate regioselectivity (3:1). Different derivatives of **2** with electron-withdrawing and -donating groups on the phenyl ring were tested, which showed good performance, affording the corresponding products in moderate yields (**3ae**–**3al**). Moreover, multisubstituted fluorinated imidoyl chlorides were also compatible under these reaction conditions (**3am** and **3an**). Likewise, other fluorinated substrates **2p**–**2u** were also tested, wherein the corresponding 6-fluoroalkyl-phenanthridines **3ap**–**3au** were formed smoothly in moderate to excellent yields. Different  $\text{CF}_2\text{X}$  ( $\text{X} = \text{Cl}, \text{Br}, \text{H}, \text{CF}_3$ ) groups could also be introduced into phenanthridines through these reactions. Notably, this transformation could very well introduce the  $\text{CF}_2\text{Br}$  group, which is potentially useful for the further elaboration of more valuable molecules through cross-coupling reactions.<sup>33</sup>

Scheme 3. Variation of Fluorinated Imidoyl Chlorides<sup>a</sup>

<sup>a</sup>Reaction conditions: the reactions were carried out with **1a** (0.2 mmol), **2** (0.24 mmol),  $\text{Pd}(\text{OAc})_2$  (0.02 mmol),  $\text{P}(4\text{-F-C}_6\text{H}_4)_3$  (0.04 mmol), norbornene (0.2 mmol),  $\text{K}_3\text{PO}_4$  (0.8 mmol) in toluene (2.0 mL) under a nitrogen atmosphere for 12 h. <sup>b</sup>Regioselectivity ratio (the major isomer is substituted at the 3-position as indicated).

To gain insight into the mechanism, several control experiments were carried out. In order to understand the role of each component, when the reactions were carried out by excluding either norbornene or the Pd catalyst, desired dehydrogenative annulation product **3aa** was not obtained (Scheme 4a). Competing reactions with fluorinated imidoyl chloride substrates bearing different electronic properties were investigated. <sup>1</sup>H NMR analysis indicated that the more electron-rich substrate **2e** had a higher reaction rate (**3ae**:**3ah** = 1:0.74) probably due to the fact that the C–H activation process occurs easily (Scheme 4b). Next, an equimolar mixture of **1i** and **1k** that differed in electronic effects was also examined. The <sup>1</sup>H NMR analysis of this product mixture revealed a slight preference for more electron-rich iodoarenes (**3ia**:**3ka** = 1:0.71) (Scheme 4c). Then, to study the kinetic isotope effects (KIE) in the reactions, intermolecular competition experiments were performed under standard conditions for 3 h. The reaction of **1a** with **2a** and **2a-D** provided a mixture of the products **3aa** and **3aa-D** in 20% combined yield, and the ratio of **3aa**:**3aa-D** was 1.5. Furthermore, a parallel experiment was also performed under standard conditions for 1 h. The KIE was 1.33 (for details, see the Supporting Information). The KIE values suggested that the C–H bond activation step is not the rate-determining step of this reaction (Scheme 4d). It is noteworthy that the cyclization product was not detected with styrene derivative **4** as the substrate under the standard conditions, which

## Scheme 4. Control Experiments



demonstrated that the imine group probably played a key role in this transformation (**Scheme 4e**). Moreover, scale-up of **1a** to 4 mmol (872 mg) with 4.8 mmol (996 mg) of **2a** provided the corresponding 6-trifluoromethyl-phenanthridines **3aa** in 84% yield (878 mg).<sup>34</sup>

In conclusion, we developed a useful strategy to synthesize 6-fluoroalkyl-phenanthridines from simple aryl iodides and fluorinated imidoyl chlorides, through dual C–H bond activations. Fluorinated imidoyl chlorides served as a new type of electrophilic reagent in Pd/NBE catalysis, which, in turn, could be readily prepared from various anilines and fluorinated carboxylic acids. The good tolerance for functional groups on fluorinated imidoyl chlorides and aryl iodides indicated its high potential for constructing biologically active fluorinated phenanthridine heterocycles. Further applications of this method to synthesize various other heterocycles are underway in our laboratory.

## ■ ASSOCIATED CONTENT

## ■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.8b02588](https://doi.org/10.1021/acs.orglett.8b02588).

Experimental procedures and full spectroscopic data for all new compounds (**PDF**)

## Accession Codes

CCDC 1859470 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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(34) Scalability of 6-trifluoromethyl-phenanthridines **3aa** was described in the [Supporting Information](#).