



# Palladium-catalyzed intramolecular C–H bond functionalization of trifluoroacetimidoyl chloride derivatives: Synthesis of 6-trifluoromethyl-phenanthridines



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## ABSTRACT

Highly efficient approaches to obtain 6-trifluoromethyl-phenanthridine derivatives have been realized through the palladium-catalyzed intramolecular C–H bond functionalization of trifluoroacetimidoyl chlorides. The reaction allows the direct formation of C<sub>sp2</sub>–C<sub>sp2</sub> bonds via C–H bond functionalization and rapid access to phenanthridine ring systems in moderate to high yields with good functional group tolerance.

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## 1. Introduction

Phenanthridine is a ubiquitous framework found in many natural products [1–4], biologically active molecules [5–7], and optoelectronic materials [8–10]. Therefore, molecules containing this motif have attracted considerable attention in medicinal chemistry, and much effort has been focused on the synthetic methods of the phenanthridine ring system [11–17]. In particular, CF<sub>3</sub>-containing phenanthridines are of significant interest because trifluoromethyl group enhance biological and therapeutic activities of organic compounds. In 2013, Wu and co-workers reported rhodium-catalyzed [2 + 2 + 2] cycloaddition reaction between diynes and alkynes leading to CF<sub>3</sub>-containing phenanthridines [18]. Zhang and co-workers described the first example of a Pd-catalyzed tandem Suzuki/C–H arylation reaction of N-aryltrifluoroacetimidoyl chlorides with arylboronic acids [19]. More recently, another efficient strategy to build the phenanthridine scaffold was based on intermolecular radical addition/cyclization of 2-isocyanobiphenyls with CF<sub>3</sub> radicals developed by the groups of Studer and co-workers, Zhou and co-workers and Yu and co-workers, respectively [20–22].

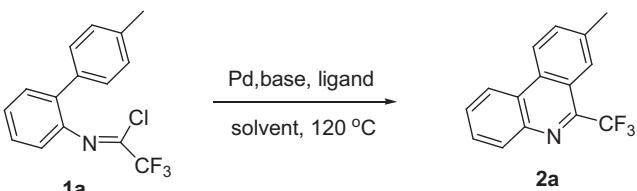
Trifluoroacetimidoyl chlorides, easily prepared from commercially available trifluoroacetic acid (TFA), amines, PPh<sub>3</sub>, and Et<sub>3</sub>N in CCl<sub>4</sub> in a one-pot manner [23], are one kind of the most important intermediates and versatile building blocks in organic synthesis [24–26]. For example, they are widely used as one of the coupling partners in transition-metal-catalyzed carbon–carbon bond formations via cross-coupling reactions [27–31]. Meanwhile, transition-metal-catalyzed C(sp<sup>2</sup>)–Cl bonds of trifluoroacetimidoyl chlorides were inserted into multiple bond have been explored [32]. Recently, transition-metal-catalyzed C–H bond functionalization has emerged as a useful, step-economical method for the direct conversion of C–H bonds to C–C and C–heteroatom bonds [33–38]. Inspired by recent advance on transition-metal-catalyzed direct C–H bond functionalizations and in parallel with our continuing efforts to develop synthetic methods of CF<sub>3</sub>-containing heterocycles [39–42], we report here an efficient protocol for the synthesis of 6-trifluoromethyl-phenanthridines via palladium-catalyzed intramolecular aromatic C–H bond functionalization of trifluoroacetimidoyl chlorides (Scheme 1).

## 2. Results and discussion

Initially, we started to evaluate the reaction parameters by employing N-biaryltrifluoroacetimidoyl chloride (**1a**) as model substrate. To our delight, the use of 10 mol% Pd(OAc)<sub>2</sub> as the catalyst, K<sub>2</sub>CO<sub>3</sub> (2.0 equiv) as the base and PPh<sub>3</sub> as the ligand in

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**Table 1**  
Reactions of **1a** under different conditions.<sup>a</sup>



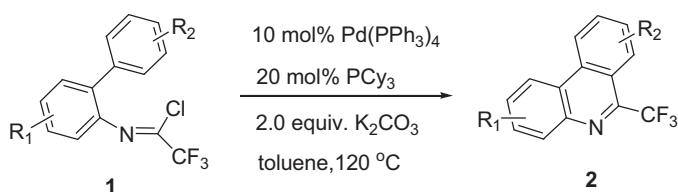
Entry	Catalyst	Base	Ligand	Solvent	Yield (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	PPh <sub>3</sub>	Toluene	48
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	PPh <sub>3</sub>	Toluene	62
3	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	PPh <sub>3</sub>	Toluene	38
4	Pd(CH <sub>3</sub> CN) <sub>2</sub> Cl <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	PPh <sub>3</sub>	Toluene	Trace
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	PCy <sub>3</sub>	Toluene	72
6	Pd(PPh <sub>3</sub> ) <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	P( <i>t</i> Bu) <sub>3</sub>	Toluene	64
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>	K <sub>3</sub> PO <sub>4</sub>	PCy <sub>3</sub>	Toluene	45
8	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Cs <sub>2</sub> CO <sub>3</sub>	PCy <sub>3</sub>	Toluene	54
9	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Na <sub>2</sub> CO <sub>3</sub>	PCy <sub>3</sub>	Toluene	37
10	Pd(PPh <sub>3</sub> ) <sub>4</sub>	KOAc	PCy <sub>3</sub>	Toluene	Trace
11	Pd(PPh <sub>3</sub> ) <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	PCy <sub>3</sub>	DMF	43
12	Pd(PPh <sub>3</sub> ) <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	PCy <sub>3</sub>	DMSO	Trace
13	Pd(PPh <sub>3</sub> ) <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	PCy <sub>3</sub>	CH <sub>3</sub> CN	Trace

<sup>a</sup> Reaction conditions: **1a** (0.4 mmol), [Pd] (10 mol%), ligand (20 mol%), base (0.8 mmol) in solvent (4.0 mL) at 120 °C under N<sub>2</sub> atmosphere for 12 h.

<sup>b</sup> Isolated yield.

toluene at 120 °C could give the corresponding 6-trifluoromethylphenanthridine **2a** in 48% yield (Table 1, entry 1). Then we tried other palladium source, such as Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub>. The results indicated that Pd(0) was more effective than Pd(II) species and Pd(PPh<sub>3</sub>)<sub>4</sub> displayed the highest reactivity in the model reaction (Table 1, entries 1–4). Then, we investigated the effect of ligands [PPh<sub>3</sub>, PCy<sub>3</sub>, and P(*t*Bu)<sub>3</sub>] on the reaction and observed that the addition of PCy<sub>3</sub> or P(*t*Bu)<sub>3</sub> as ligand afforded better yields of 72% and 64%, respectively (Table 1, entries 5–6). The base also plays an important role in the cyclization reaction. K<sub>2</sub>CO<sub>3</sub> was found to be the best one among the bases investigated. Other bases such as K<sub>3</sub>PO<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>, and Na<sub>2</sub>CO<sub>3</sub> were inferior and generated **2a** in 37–54% yields (Table 1, entries 7–9). Only a trace amount of **2a** was detected when KOAc was used as a base (Table 1, entry 10). Polar solvents such as DMF, DMSO and CH<sub>3</sub>CN were unfavorable for this transformation (Table 1, entries 11–13).

With the optimized conditions in hand, we then explored the scope and generality of the present process, and the results are summarized in Table 2. As shown in Table 2, a variety of substituents (such as Me, OMe, F, Cl, and CF<sub>3</sub>) on the 4'-position of the aromatic ring were applicable, affording the cyclized products in good yields (Table 2, entries 1–7). The reaction also worked well with 2'-substituted substrate, albeit giving the products in moderate yields (Table 2, entries 8–9). As expected, 3'-substituted substrate **1k** gave a mixture of two regioselective products (products **2k/2k'**). In addition, 2-thiophenyl trifluoroacetimidoyl chloride **1l** were also viable substrate to provide a thieno-[3,2-*c*]quinoline system (**2l**). Subsequently, the effect of the substituents on the aromatic ring attached to trifluoroacetimidoyl

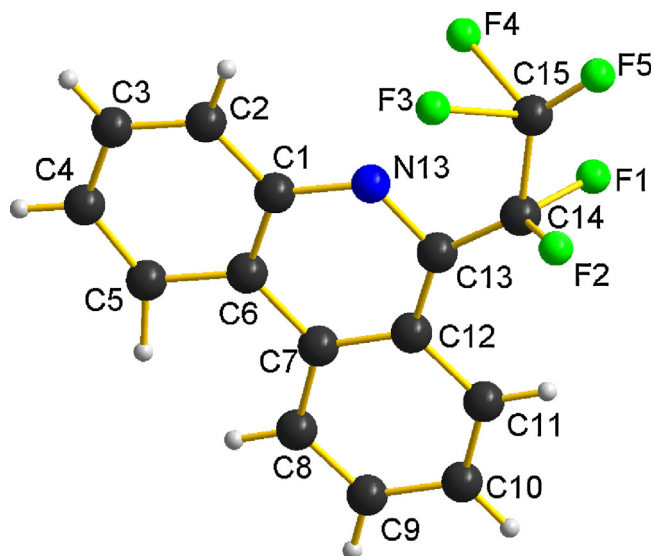


**Scheme 1.** Palladium-catalyzed intramolecular C–H bond functionalization of trifluoroacetimidoyl chlorides.

chloride was screened. In all cases, substrates **1m–q** proceeded smoothly to give the corresponding products **2m–q** in moderate to good yields (Table 2, entries 12–16). Likewise, the perfluoroalkylated substrate **1r** was also tested in this cyclization reaction, and the corresponding 6-perfluoroalkylated phenanthridine **2r** was formed smoothly. The structure of **2r** was unequivocally confirmed by single-crystal X-ray analysis (Fig. 1) [43].

To gain insight into the mechanism, we tried the TEMPO-trapping experiment. That is, treatment of **1a** in the presence of TEMPO (1.2 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol%), PCy<sub>3</sub> (20 mol%), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv) in toluene at 120 °C for 12 h afforded the cyclized product **2a** in 70% yield (Scheme 2). This result indicated that radical pathway can be ruled out.

A proposed reaction mechanism was shown in Scheme 3. The oxidative addition of trifluoroacetimidoyl chloride **1** to Pd(0) species afforded intermediate **A**. Subsequently, **A** underwent an intramolecular electrophilic aromatic palladation through C–H



**Fig. 1.** X-ray crystal structure of **2r**.

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