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Tandem dual C(sp^3)–H/C(sp^2)–H functionalization: a radical cyclization of 2-isocyanobiphenyl with ether to 6-alkylated phenanthridine

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A simple and efficient radical coupling of 2-isocyanobiphenyl with ethers was developed, providing a variety of 6-alkylated phenanthridines. Both cyclic and acyclic ethers are suitable substrates for this transformation, which comprised the functionalization of two C–H bonds: the sp^3 C–H of ether and sp^2 C–H of phenyl group. The kinetic isotope effect (KIE) revealed that the cleavage of sp^3 C–H bond would be involved in the rate-determining step.

C–H functionalization, domino reaction, phenanthridine, 2-isocyanobiphenyl, ether

1 Introduction

Phenanthridine is an important skeleton present in many natural products and is of great interest in medicinal chemistry due to their remarkable biological activities, such as antitumor, antimicrobial, and antiviral (Figure 1(a)) [1]. Some members in this family also demonstrated optoelectronic properties and are receiving growing attention in material research [2]. As a consequence, a number of efficient and selective synthetic protocols have been developed for their synthesis [3]. Among many possible approaches to the phenanthridine scaffold, intramolecular cyclization via C–C or C–N bond formation of an *ortho*-functionalized biaryl precursor to construct the central ring are particularly attractive in virtue of ready accessibility of starting material by cross-coupling reaction. Homolytic aromatic substitution by an aryl radical and related process has been demonstrated as an efficient approach for the construction of biaryl motifs [4]. Recently, it was reported that phenanthridine skeleton could be formed through C-radical addition to 2-isocyanobiphenyls with subsequent homolytic aromatic substitution [5]. However, the development of simple and efficient method to access phenanthridine is still the pursuit of organic chemists.

Functionalization of unreactive C(sp^3)–H bonds is one of the most challenging issues in synthetic chemistry and continues to attract intensive efforts [6]. Tetrahydrofuran (THF) and 1,4-dioxane are important chemical raw materials. Such five- and six-membered ring moieties are widely present in natural organic substances and medicinal compounds (Figure 1(b)) [7]. Therefore, introduction of these simple ether molecules into complex organic compounds is very valuable in synthetic chemistry [8]. Due to their chemical inertness, direct sp^3 C–H bond functionalization of ethers is a challenging task. As a matter of fact, ethers can produce radicals under certain reaction conditions [9]. We postulate that radical **A** encounters radical acceptor aryl isonitrile can form imidoyl radical **B**, which then undergoes intramolecular homolytic aromatic substitution to afford 6-alkylated

Dedicated to Professor Qian Changtao on the occasion of his 80th birthday.
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phenanthridine (Scheme 1). In this way, difunctionalization of sp^3 C–H and sp^2 C–H could be achieved. Herein, we report a new oxidative 1,2-alkylarylation of 2-isocyanobiphenyl, through which an aryl C(sp^2)–H bond and a C(sp^3)–H bond adjacent to an oxygen atom can be activated for the selective synthesis of functionalized phenanthridines.

2 Results and discussion

Initially, we examined the reaction of biarylisonitrile (**1a**) with 1,4-dioxane (**2a**) in the presence of a radical initiator. Fortunately, the desired product 6-(1,4-dioxan-2-yl)phenanthridine **3aa** was obtained in 25% yield using TBHP as the radical initiator (Table 1, entry 1). The reaction yield was increased to 48% in the presence of DTBP, while no product was detected using DDQ. We attempted to promote the yields by adding inorganic salts, such as $FeCl_3$, $FeCl_2$, CuI. To our delight, **3aa** was isolated in 58% yield when 5 mol% of $FeCl_3$ was subjected to the procedure (Table 1, entry 5). Next, we explored the benefits from some ligands, such as DBU, DABCO, 2,2-dipyridine and TMDEA. Gratifyingly, the yield increased significantly to 75% when DBU was used as a ligand (Table 1, entry 9). With several rounds of optimization, the optimal reaction conditions were accomplished by using $FeCl_3$ (5 mol%), DBU (10 mol%) and DTBP (2 equiv) at 110 °C under N_2 (Table 1, entry 9).

To explore the substrate scope of this protocol, the optimized reaction conditions were applied to a series of 2-isocyanobiaryl compounds. As shown in Table 2, various functional groups such as methoxy, chloro, fluoro, trifluoromethoxy and trifluoromethyl groups were well tolerated

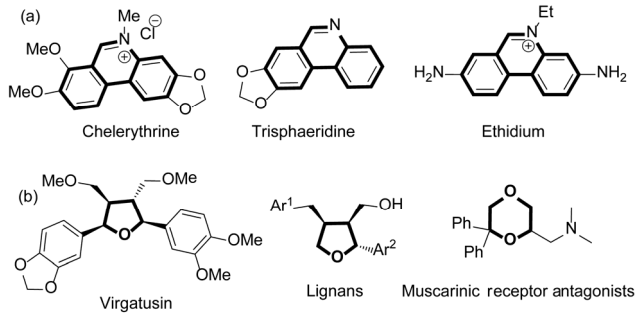
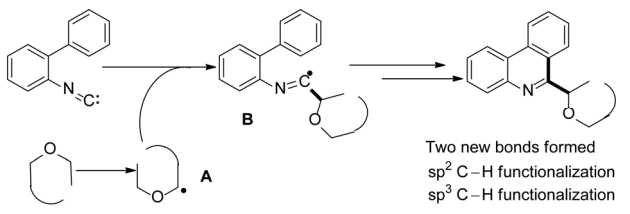
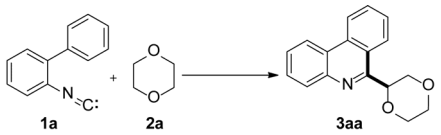


Figure 1 Phenanthridine and ether moieties in biologically active compounds.



Scheme 1 Our strategy via radical cyclization.

Table 1 Screening for optimal reaction conditions [a)]



Entry	[M]	Ligand	Radical initiator	Yield(%) [b)]
1	–	–	TBHP [c)]	25
2	–	–	DTBP	48
3	–	–	Dicumyl peroxide	31
4	–	–	DDQ	0
5	$FeCl_3$	–	DTBP	58
6	$FeCl_2$	–	DTBP	52
7	CuI	–	DTBP	50
8	Bu_4NI	–	DTBP	43
9	$FeCl_3$	DBU	DTBP	75
10	$FeCl_3$	DABCO	DTBP	66
11	$FeCl_3$	2,2-dipyridine	DTBP	40
12	$FeCl_3$	TMDEA	DTBP	46

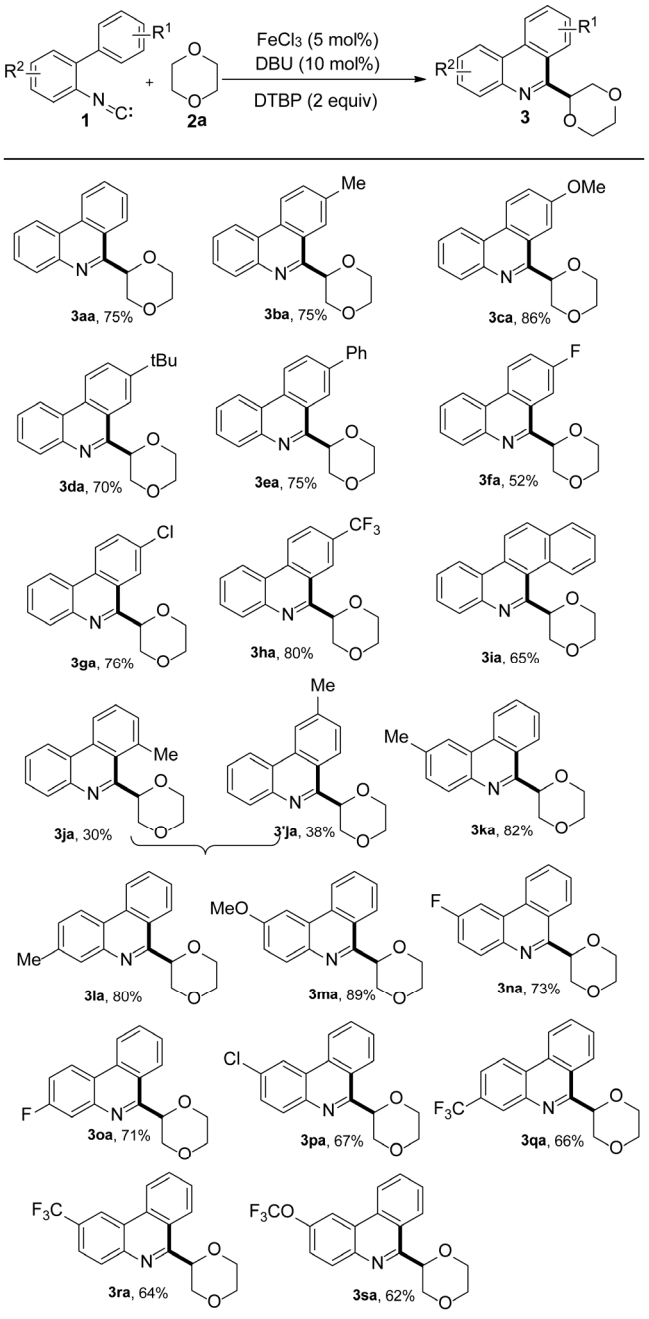
a) Reaction conditions: **1a** (0.2 mmol), [M] (5 mol%), ligand (10 mol%), oxidant (0.4 mmol) and **2a** (1 mL) under N_2 atmosphere for 12 h at 110 °C; b) isolated yield; c) TBHP (anhydrous, 5M in decane) = *tert*-butyl hydrogenperoxide, DTBP = di-*tert*-butyl peroxide, TMDEA = tetramethylethylenediamine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.

under the oxidative conditions. The isocyanides **1b**–**h** bearing either electron-donating or electron-withdrawing substituents on 4-position of the aromatic ring all underwent smoothly to provide the corresponding 6-(1,4-dioxan-2-yl) phenanthridines **3ba**–**3ha** in moderate to good yields. To investigate the regioselectivity of the cyclization, we studied *meta*-substituted biphenyls (**1j**). This reaction resulted in poor regioselectivity, and both isomers **3ja** and **3'ja** were isolated in 30% and 38% yields, respectively. Subsequently, we studied the effect of substituents on the aromatic ring attached to isocyanide. As expected, the corresponding 6-(1,4-dioxan-2-yl)phenanthridines **1k**–**s** were afforded upon oxidative cyclization of isocyanides with 1,4-dioxane in good yields.

Encouraged by the above results, we further investigated the scope of ethers. Cyclic ethers such as THF (**2b**), 1,3-dioxolane (**2c**) and tetrahydro-2*H*-pyran (**2d**) were also good partners (Table 3, **3ab**–**3ad**). Gratifyingly, moderate yields were obtained when acyclic ethers such as diethyl ether (**2e**), *tert*-butyl methyl ether (**2f**) and 1,2-dimethoxyethane (**2g**) were subjected to the procedure. Two isomers **3ag** and **3'ag** were isolated in 44% and 31% yields, respectively when 1,2-dimethoxyethane was tested.

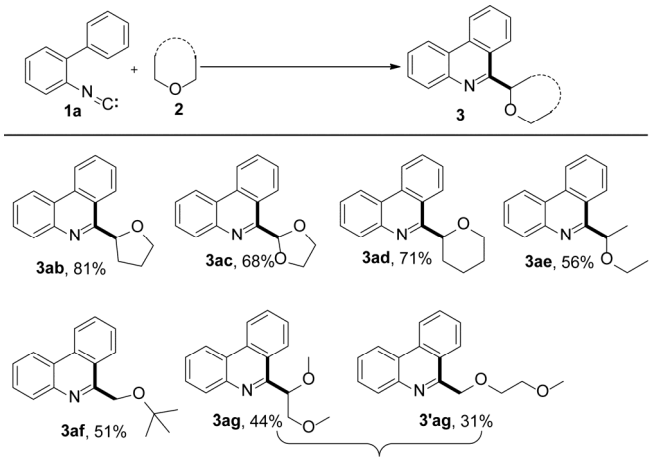
To understand the mechanism for difunctionalization of a 2-isocyanobiphenyls, some isotopic experiments were carried out. A mixture of substrates **1a** and **1a'** in a 1:1 ratio was used to determine the intermolecular kinetic isotope effect (KIE) (Scheme 2, Eq. (1)). The result demonstrated that there is no kinetic isotope effect (k_H/k_D = 1) in intermolecular experiments, suggesting that the arylation step may

Table 2 The scope of 2-isocyanobiaryl compounds [a]

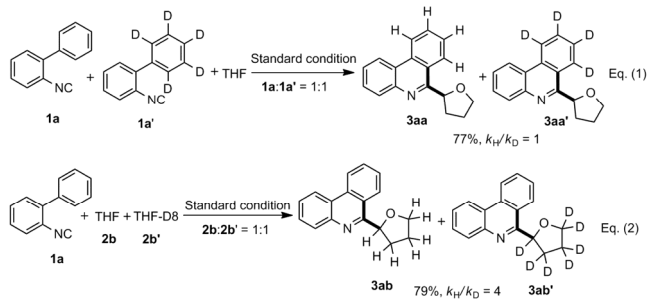


a) Reaction conditions: **1** (0.2 mmol), $FeCl_3$ (5 mol%), DBU (10 mol%), DTBP (0.4 mmol) and **2a** (1 mL) under N_2 atmosphere for 12 h at 110 °C; b) isolated yield.

Table 3 The scope of ethers [a]



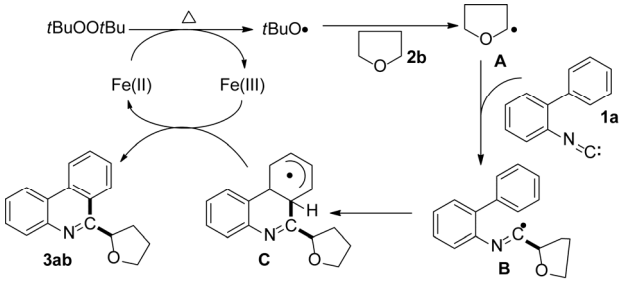
a) Reaction conditions: **1a** (0.2 mmol), $FeCl_3$ (5 mol%), DBU (10 mol%), DTBP (0.4 mmol) and **2** (1 mL) under N_2 atmosphere for 12 h at 110 °C. Isolated yield.



Scheme 2 Deuteration experiments.

be compatible with either SEAr or free radical mechanism [10]. When 2.0 equiv. of 2,2,6,6-tetramethylpiperidine oxide (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added as a radical inhibitor, no desired product was observed, which supported the free radical mechanism. However, the KIE result of the experiment between THF **2b** and [D8]THF **2b'** ($k_H/k_D = 4$) showed that the sp^3 C–H bond cleavage should be involved in the rate-determining step of this oxidative cyclization (Scheme 2, Eq. (2)).

On the basis of the above experimental results, a possible mechanism (Scheme 3) is proposed. Initially, homolysis of DTBP is assisted by Fe(II) into a *tert*-butoxy radical and Fe(III) [11]. Substrate **2b** with C(sp^3)–H bonds adjacent to an oxygen atom is readily transformed into radical intermediate **A** in the presence of a *tert*-butoxy radical. Then, radical **A** attacks the N=C bond of 2-isocyanobiaryl **1a** to form the imidoyl radical **B**, which upon intramolecular cyclization with an aryl ring gives radical intermediate **C**. Finally,



Scheme 3 The proposed mechanism.

hydrogen abstraction of radical intermediate **C** by Fe(III) takes place to provide 6-(tetrahydrofuran-2-yl)phenanthridine **3ab**.

3 Conclusions

In summary, we have developed a novel cascade radical bimolecular C–C coupling of 2-isocyanobiaryls with ethers to afford 6-alkylated phenanthridines. This reaction comprised functionalization of two C–H bonds, including the sp^3 C–H of ether and the sp^2 C–H of phenyl group. In addition, cheap and commercially available DTBP was used as an oxidant for this procedure.

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