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$PhI(OAc)_2$-Mediated Synthesis of 6-(Trifluoromethyl)phenanthridines by Oxidative Cyclization of 2-Isocyanobiphenyls with CF_3SiMe_3 under Metal-Free Conditions

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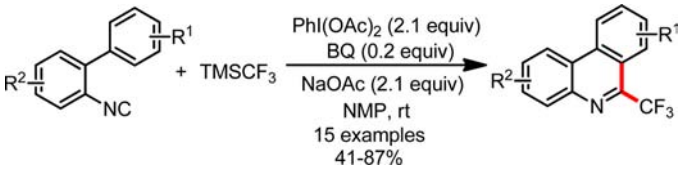
ABSTRACT



A mild and efficient method for the synthesis of 6-(trifluoromethyl)phenanthridines through oxidative cyclization of 2-isocyanobiphenyls with CF_3SiMe_3 under metal-free conditions was developed. The reaction allows the direct formation of C−CF_3 bonds and rapid access to phenanthridine ring systems in one catalytic cycle.

Phenanthridines are common structural units present in a wide variety of naturally occurring alkaloids[1] and exhibit interesting biological activities and potential pharmaceutical applications.[2] Substituted phenanthridines are also widely used in material science due to their significant optoelectronic properties.[3] For these reasons, diverse methods have been reported for their synthesis in the last decades.[4] Meanwhile, the development of new methodologies for preparing trifluoromethylated heterocyclic compounds has become a subject of great interest in organic synthesis, because the CF_3 group can often influence chemical and metabolic stability, lipophilicity, and binding selectivity.[5] Although the synthesis of phenanthridines has been largely described in the literature, methods leading to the trifluoromethylated substrates are still limited.[6] Only recently, Wu et al. reported a Rh-catalyzed [2 + 2+2] cycloaddition for

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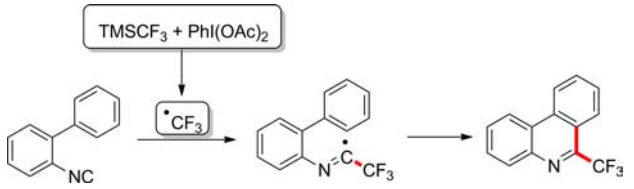
the construction of fluorine-containing phenanthridines.[6a] Zhang and co-workers developed a method for 6-trifluoromethyl phenanthridine via a palladium-catalyzed tandem Suzuki/C−H arylation reaction of *N*-aryltrifluoroacetimidoyl chlorides with arylboronic acids.[6b] However, the above-reported strategies remain associated with certain disadvantages such as harsh reaction conditions, use of transition-metal catalysts and difficult to obtain trifluoromethylated building blocks.

Undoubtedly, the ideal and promising route for the preparation of trifluoromethylated organic compounds is the direct generation of $C-CF_3$ bonds.[7] In the past decade, transition-metal catalyzed or -mediated cross-poupling reactions are widely applied for the formation of these bonds.[8] Another frequently used strategy is the utilization of high reactivity of CF_3 radical.[9,10] For example, Baran et al. reported direct C−H trifluoromethylation of nitrogen-containing heterocyclic compounds with the combination of $NaSO_2CF_3$ and ^tBuOOH.[10c] Shibata and co-workers developed a method for the oxidative trifluoromethylation of unsymmetrical biaryls.[10a] Unfortunately, these radical transformations always result in the trifluoromethylated products with poor regioselectivity, which make them have little application in the trifluoromethylation of polycyclic aromatic compounds. Thus, a more practical method for the synthesis of trifluoromethylated phenanthridines with high regioselectivity must be devised.

Recently, an elegant Mn(III)-mediated annulation of 2-isocyanobiphenyls with boronic acid under heating conditions was developed by Chatani et al.[11] In this reaction, an isocyano group was used as the radical acceptor, which followed by a radical cyclization to give phenanthridines. Inspired by these results, we envisioned bringing together the advantages of both strategies by combining 2-isocyanobiphenyls with CF_3 radicals (scheme 1). Herein, we report a $PhI(OAc)_2$-mediated synthesis of 6-trifluoromethyl phenanthridines by oxidative cyclization of 2-isocyanobiphenyls with CF_3SiMe_3 at room temperature under metal-free conditions. This transformation allows the direct formation of $C-CF_3$ bonds and phenanthridine ring systems in one reaction.

Scheme 1. $PhI(OAc)_2$-Mediated Oxidative Cyclization of 2-Isocyanobiphenyls with CF_3SiMe_3



Initially, the reaction was carried out by using 2-isocyanobiphenyl **1a** and CF_3SiMe_3 (4 equiv) in NMP (0.4 mL) with $PhI(OAc)_2$ (2.1 equiv) as the oxidant at room temperature.[12] Gratifyingly, the desired phenanthridine **2a** was obtained as the major product in 43% yield as determined by ^1H NMR spectroscopy (Table 1, entry 1). It was observed that the use of inorganic bases such as K_2CO_3, Cs_2CO_3, and NaOAc promoted the reactions, and NaOAc gave the best result (Table 1, entries 2−4). H_2O_2 and ^{t}-BuOOH (TBHP) were also attempted as the oxidants, but only a trace of the desired product was detected (Table 1, entries 5 and 6). Among various solvents examined, DMF provided a slightly lower yield (Table 1, entry 7). Other solvents such as MeCN, 1,4-dioxane, THF, toluene, and EtOH were all less efficient compared with NMP (Table 1, entries 8−12). These results indicated poorly nucleophilic polar solvents are crucial for this transformation. Notably, the reaction could also proceed smoothly in

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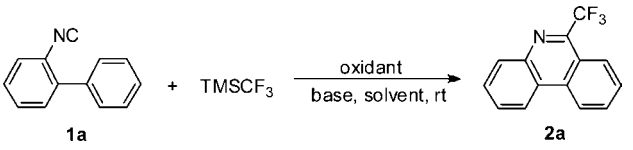
(12) The concentration of CF_3SiMe_3 is highly important in this reaction. The yield of **2a** decreased sharply when 2 mL of NMP was used as the solvent under the standard reaction conditions.

Table 1. Optimization of Reaction Conditions[a]



entry	base	oxidant	solvent	yield[b] (%)
1		$PhI(OAc)_2$	NMP	43
2	K_2CO_3	$PhI(OAc)_2$	NMP	74
3	Cs_2CO_3	$PhI(OAc)_2$	NMP	60
4	NaOAc	$PhI(OAc)_2$	NMP	85
5	NaOAc	H_2O_2	NMP	trace
6	NaOAc	TBHP	NMP	trace
7	NaOAc	$PhI(OAc)_2$	DMF	81
8	NaOAc	$PhI(OAc)_2$	MeCN	29%
9	NaOAc	$PhI(OAc)_2$	1,4-dioxane	17%
10	NaOAc	$PhI(OAc)_2$	THF	ND[c]
11	NaOAc	$PhI(OAc)_2$	toluene	ND
12	NaOAc	$PhI(OAc)_2$	EtOH	ND
13[d]	NaOAc	$PhI(OAc)_2$	NMP	63
14[e]	**NaOAc**	**$PhI(OAc)_2$/BQ**	**NMP**	**91**
15[f]	NaOAc	$PhI(OAc)_2$/BQ	NMP	26
16[g]	NaOAc	$PhI(OAc)_2$/BQ	NMP	9

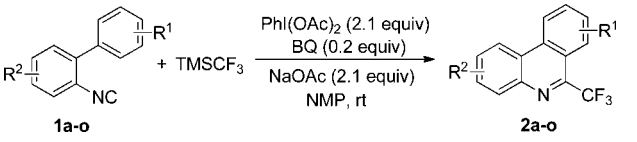
[a] Reaction conditions if not otherwise noted: **1a** (0.2 mmol), $TMSCF_3$ (4 equiv), oxidant (2.1 equiv), base (2.1 equiv) in 0.4 mL of solvent for 4 h under N_2. [b] Yields determined by ^1H NMR analysis using CH_2Br_2 as internal standard. [c] ND: not detected. [d] The reaction was carried out in the open air. [e] 0.2 equiv of BQ was added. [f] 2 equiv of $TMSCF_3$ was used. [g] 1 equiv of $TMSCF_3$ was used.

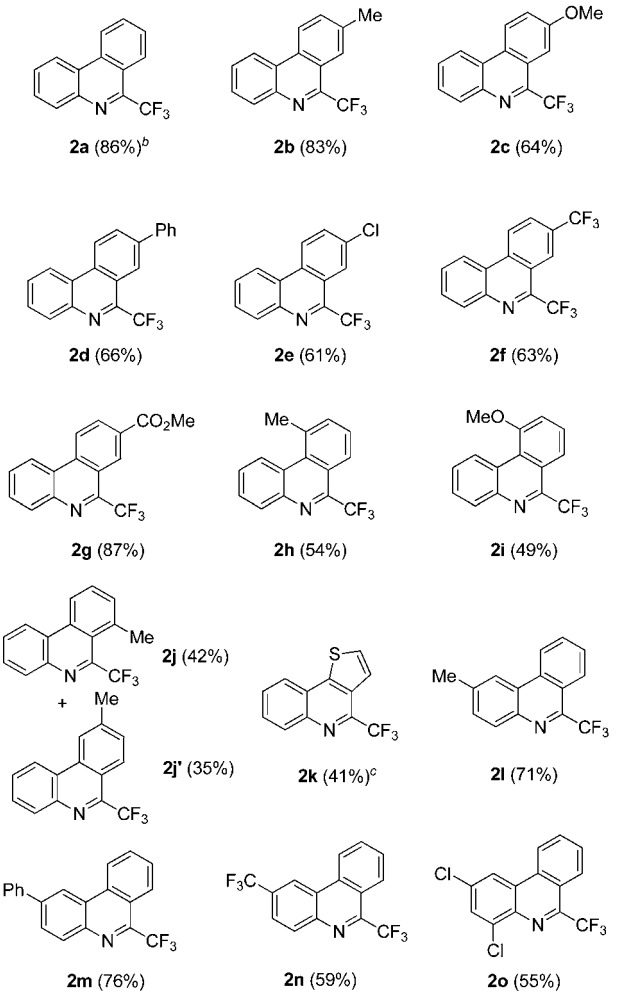
the open air conditions, albeit affording the product with slightly diminished yield (Table 1, entry 13). It is reported that catalytic amount of benzoquinone (BQ) could improve the reaction efficiency,[13] we were pleased to find that the yield of the desired product could be increased to 91% with the addition of 0.2 equiv of BQ (Table 1, entry 14). However, the role of BQ in the reaction is not clear at this stage. Finally, the amount of $TMSCF_3$ was optimized (Table 1, entries 15 and 16). Unfortunately, we found the yield of **2a** decreased sharply when a lower amount of $TMSCF_3$ was used.

With the optimized reaction conditions in hand, the present oxidative cyclization method was applied to a series of 2-isocyanobiaryl compounds, which can be readily prepared from corresponding anilines. As shown in Table 2, the isocyanides bearing either electron-rich or electron-deficient substituents on 4′-position of the aromatic ring all underwent the reactions smoothly to afford the corresponding 6-(trifluoromethyl)phenanthridines **2b**–**g** in good yields. A wide range of functional groups, such as phenyl (**2d**), chloro (**2e**), and ester (**2g**), were tolerated under the present oxidative conditions. The reaction also worked well when only one ortho hydrogen atom was available in the biaryl isocyanides, albeit giving the products in moderate yields (**2h** and **2i**). When two nonequivalent ortho hydrogen atoms were available, this reaction suffered from poor regioselectivity, and two isomers **2j** and **2j′** were isolated in yields of 42% and 35%, respectively. In addition, we found

(13) Wu, X.; Chu, L.; Qing, F.-L. *Tetrahedron Lett*. **2013**, *54*, 249.

Table 2. Reaction of $TMSCF_3$ with Various Isocyanides[a]





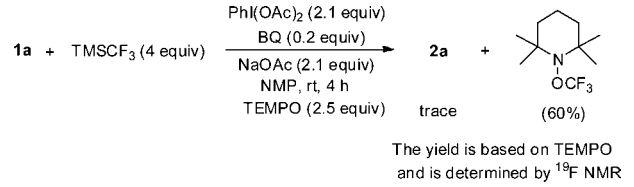
[a] Reaction conditions: isocyanides **1** (0.2 mmol), $TMSCF_3$ (4 equiv), $PhI(OAc)_2$ (2.1 equiv), NaOAc (2.1 equiv) and BQ (0.2 equiv) in 0.4 mL of NMP for 4 h under N_2. [b] Isolated yield. [c] The reaction was carried out at 0 °C.

that 2-(2-thienyl)phenyl isocyanide (**1k**) was also a suitable substrate in this annulation reaction to generate a thieno-[3,2-*c*]quinoline system (**2k**). Subsequently, we studied the effect of the substituents on the aromatic ring attached to isocyanide and were pleased to find that the oxidative cyclization of CF_3SiMe_3 with isocyanides **1l**–**o** afforded the corresponding 6-(trifluoromethyl)phenanthridines **2l**–**o** in moderate to goods yields, respectively. The sensitive

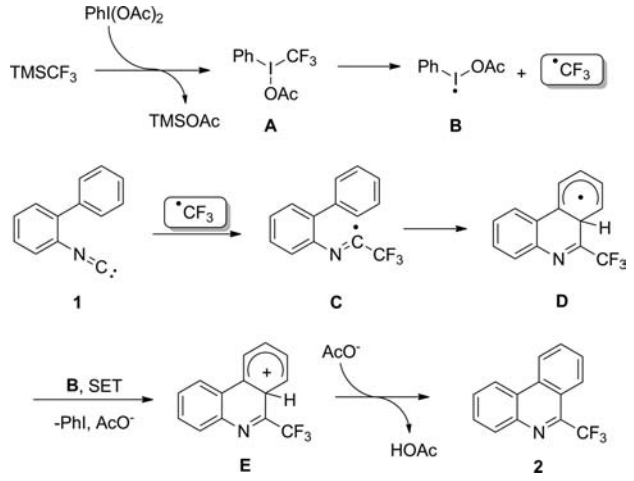
(14) See the Supporting Information for evidence for the in situ formation of intermediate **A**.

(15) For use of an isocyano group as the acceptor of a CF_3 radical, see: (a) Tsuchii, K.; Imura, M.; Kamada, N.; Hirao, T.; Ogawa, A. *J. Org. Chem*. **2004**, *69*, 6658. (b) Tordeux, M.; Wakselman, C. *Tetrahedron* **1981**, *37*, 315.

Scheme 2. Experiment for Mechanistic Study



Scheme 3. Mechanistic Rationale



chlorine in isocyanides **1o** was also compatible with the reaction conditions, providing potential possibility for further functionalization.

To gain insight into the reaction mechanism, we investigated the reaction in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), which is known as an effective radical scavenger. When 2.5 equiv of TEMPO was added in the reaction of **1a** under identical conditions, the reaction was almost shut down, while the TEMPO–CF_3 adduct was formed in 60% yield as estimated by ^{19}F NMR analysis (Scheme 2). This result indicates that the CF_3 radical may be involved in the transformation.

On the basis of this result, a plausible reaction pathway is proposed in Scheme 3. Initially, PIDA reacts with CF_3SiMe_3 to give intermediate **A** upon release of TMSOAc.[14] The following homolysis generates the hypervalent iodine(III)-centered radical **B** and CF_3 radical.[10a] Intermolecular addition of CF_3 radical to isocyanide **1**,[15] followed by intramolecular aromatic substitution of the resulting imidoyl radical **C**, generated the intermediate **D**. Subsequently, **D** is oxidized to cyclohexadienyl cation **E** through a single electron transfer (SET) by the intermediate **B**.[16] Finally, deprotonation of **E** by the acetate anion leads to the desired 6-(trifluoromethyl)phenanthridines 2.

In conclusion, we have developed a mild and efficient method for the synthesis of 6-(trifluoromethyl)phenanthridines through oxidative cyclization of 2-isocyanobiphenyls with CF_3SiMe_3 under metal-free conditions. The reaction allows the direct formation of C–CF_3 bonds and rapid access to phenanthridine ring systems in one catalytic cycle. Diversified phenanthridines bearing a CF_3 group at the C6 position were obtained in good yields with high regioselectivity at ambient temperature. Further investigations on the substrate scope and related cascade radical processes are currently underway in our laboratory.

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Supporting Information Available. Procedures for synthesis and characterization of products (^1H and ^{13}C NMR data). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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