Volume 50 | Number 49 | 21 June 2014 | Pages 6411–6544

ChemComm

Chemical Communications

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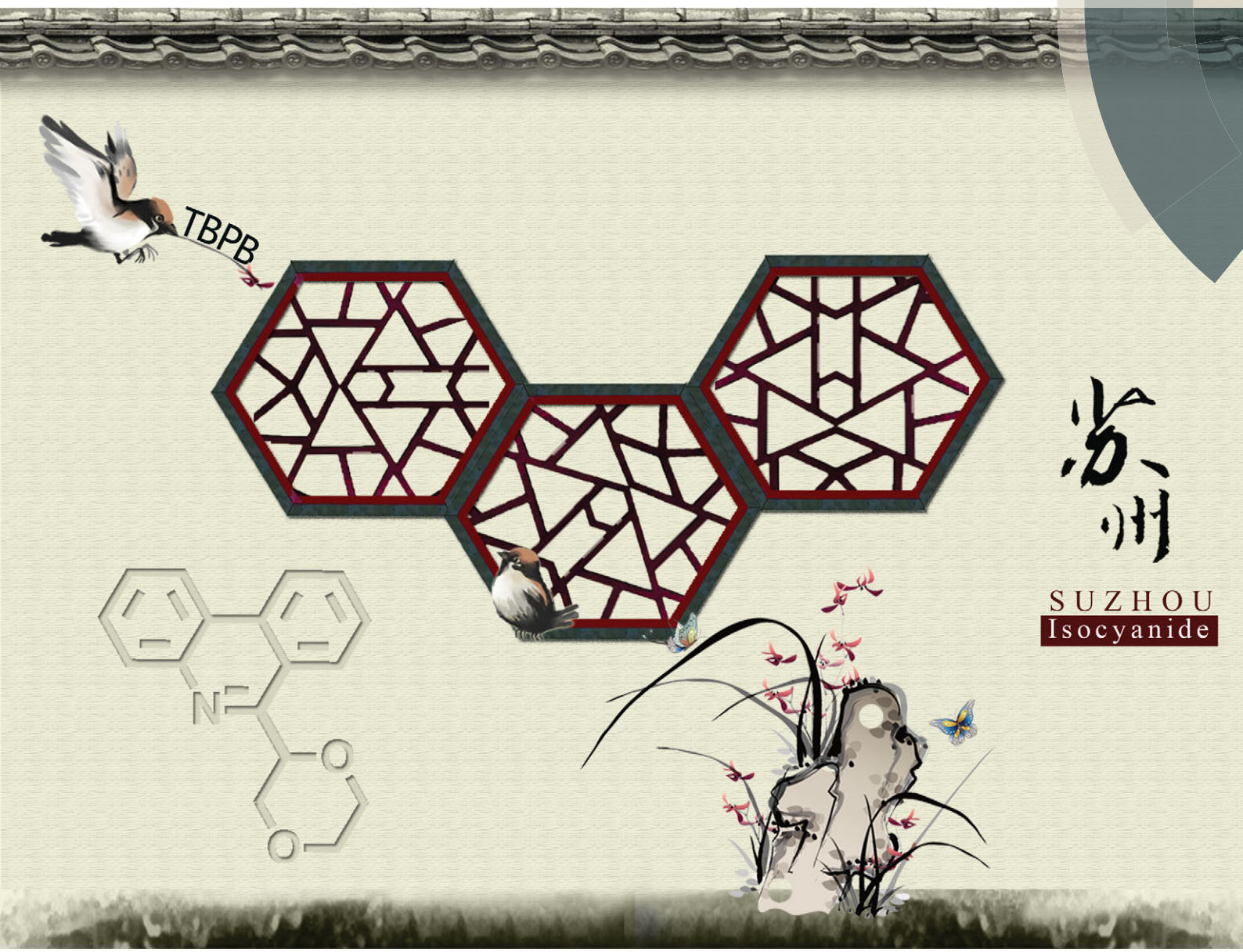

ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

Shun-Yi Wang, Shun-Jun Ji *et al.*

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Cite this: *Chem. Commun.*, 2014, **50**, 6439

Received 28th January 2014,
Accepted 24th February 2014

DOI: 10.1039/c4cc00743c

www.rsc.org/chemcomm

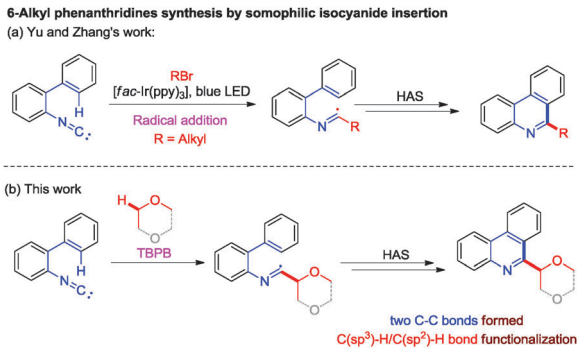
tert-Butyl peroxybenzoate (TBPB)-mediated 2-isocyanobiaryl insertion with 1,4-dioxane: efficient synthesis of 6-alkyl phenanthridines *via* C(sp^3)–H/C(sp^2)–H bond functionalization†

Jia-Jia Cao, Tong-Hao Zhu, Shun-Yi Wang,* Zheng-Yang Gu, Xiang Wang and Shun-Jun Ji*

An efficient method for the construction of 6-alkyl phenanthridines by *tert*-butyl peroxybenzoate (TBPB)-mediated 2-isocyanobiaryl insertion with 1,4-dioxane was established. Two new C–C bonds were formed in this reaction *via* a sequential C(sp^3)–H/C(sp^2)–H bond functionalization under metal-free conditions.

Over the past decades, significant attention has been focused on the transformation of an unactivated C–H bond to C–C and C–X bonds.[1–3] In particular, great progress has been achieved with respect to the functionalization of C(sp^3)–H bonds,[2] especially the functionalization of the C–H bonds of ethers.[3–8] For example, Li *et al.* reported iron/*tert*-butyl hydroperoxide (TBHP)-promoted C(sp^3)–H functionalization of ethers to construct new C–N bonds in DCE at 80 °C.[4] Wan *et al.*[5a] demonstrated a novel Bu_4NI-catalyzed C–O bond formation protocol for the synthesis of α-acyloxy ethers *via* C(sp^3)–H functionalization of ethers.[5b] Reddy, Kappe and co-workers established a $Cu(OAc)_2$-catalyzed C–O bond formation protocol in the reaction of ethers and β-ketoesters.[6] Very recently, Yuan and co-workers observed a C–S bond formation reaction of diaryl disulfides with ethers using di-*tert*-butyl peroxide (DTBP) as the oxidant under metal-free conditions.[7] Recently, Lei *et al.* described a Ni/DTBP-mediated C–C bond formation reaction of arylboronic acids and ethers.[8] However, a sequential C(sp^3)–H/C(sp^2)–H bond functionalization[9] of ethers gained less attention.

The phenanthridines have attracted much research attention because they are key skeleton compounds, which show several biological activities, such as antibacterial, antitumor and cytotoxic activity.[10] Recently, the somophilic isocyanide insertion strategy[11] has been successfully applied to construct a series of 6-substituted phenanthridines through the homolytic aromatic substitution (HAS) process.[12] More recently, Yu, Zhang and co-workers have reported photoredox neutral isocyanide insertions with functionalized alkyl bromide for the synthesis of 6-alkyl phenanthridines (Scheme 1, (a)).[13] However, there has been no report on the construction of 6-alkyl phenanthridines through the reaction of isocyanide with ethers. Herein, we report a TBPB-mediated 2-isocyanobiaryl insertion with ethers to access 6-alkyl phenanthridines under mild, metal-free conditions *via* a consecutive C(sp^3)–H/C(sp^2)–H bond functionalization based on somophilic isocyanide insertion and the cascade HAS strategy (Scheme 1, (b)).



Scheme 1 6-Alkyl phenanthridine synthesis *via* somophilic isocyanide insertion.

Initial studies were focused on the model reaction of 2-isocyanobiphenyl (**1a**) and 1,4-dioxane (**2a**) in the presence of a catalytic amount of $AgNO_3$ and different oxidants under argon atmosphere (Table 1, entries 1–9). It was found that 6-(1,4-dioxan-2-yl)phenanthridine (**3a**) could be obtained in a 70% LC yield by the reaction of **1a** and **2a** under a $AgNO_3$ (20 mol%)/TBPB (2.0 equiv.) catalytic system (Table 1, entry 5). The structure of **3a** was confirmed by IR and NMR spectroscopy and HRMS. To our delight, the LC yield of **3a** could be increased to 75% when the reaction was mediated by TBPB (2.0 equiv.) only, without any metal salt (Table 1, entry 10). Further screening regarding the amount of TBPB used, the reaction temperature and the reaction time established the optimized conditions as follows: 2-isocyanobiphenyl (**1a**) and 1,4-dioxane (**2a**) in the presence of a 1.0 equiv. of TBPB under reflux conditions. **3a** could be obtained in an 88% LC yield (89% isolated yield) (Table 1, entry 17).

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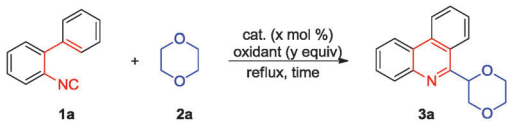
† Electronic supplementary information (ESI) available: Experimental section, spectroscopic data and other supplementary information. See DOI: 10.1039/c4cc00743c

Table 1 Screening of reaction conditions[a]



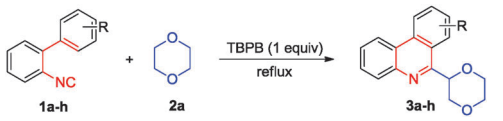
1a 2a 3a

Entry	Cat. (mol%)	Oxidant (equiv.)	Time (h)	Yield[b] (%)
1	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	3	18
2	$AgNO_3$ (20)	O_2 (1 atm)	3	Trace
3	$AgNO_3$ (20)	TBHP (2)	3	39
4	$AgNO_3$ (20)	DTBP (2)	3	21
5	$AgNO_3$ (20)	TBPB (2)	3	70
6	$AgNO_3$ (20)	CHP (2)	3	38
7	$AgNO_3$ (20)	DDQ (2)	3	Trace
8	$AgNO_3$ (20)	$PhI(OAc)_2$ (2)	3	28
9	$AgNO_3$ (20)	$Cu(OAc)_2$ (2)	3	Trace
10	—	TBPB (2)	3	75
11	—	TBPB (1)	3	79
12	—	TBPB (3)	3	74
13[c]	—	TBPB (1)	3	35
14[d]	—	TBPB (1)	3	4
15	—	TBPB (1)	2	54
16	—	TBPB (1)	4	72
17	—	TBPB (1)	3	88[e] (89[f])
18[g]	—	TBPB (1)	3	36

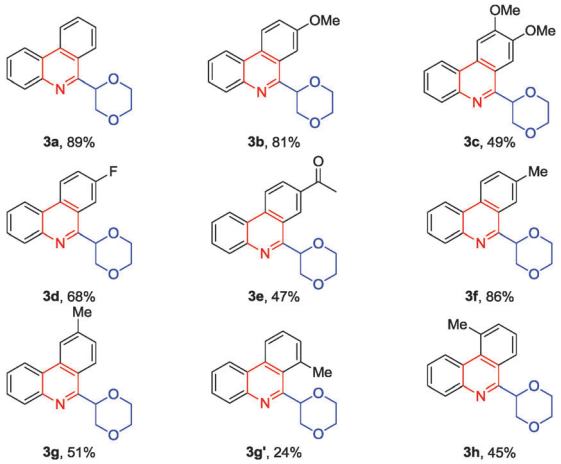
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 mL), under argon atmosphere and reflux conditions. [b] Yields were determined through LC analysis with an internal standard (benzophenone) by calculating the ratio between the formed products and the initial amount of the limiting reactant **1a**. [c] At 90 °C. [d] At 80 °C. [e] **1a** (0.5 mmol), **2a** (3 mL). [f] Isolated yield. [g] **1a** (0.5 mmol), **2a** (10 mmol) in 2 mL EtOAc. DTBP = di-*tert*-butyl peroxide, CHP = cumene hydroperoxide.

With the optimal conditions in hand, we investigated the substrate scope using various 1-isocyano-2-arylbenzene derivatives. The results are listed in Table 2. The utilization of 2-isocyano-4′-methoxy-1,1′-biphenyl (**1b**) bearing an electron-donating group results in the formation of 6-substituted phenanthridine **3b** in an 81% yield. The reaction of halide-substituted 4′-fluoro-2-isocyano-1,1′-biphenyl

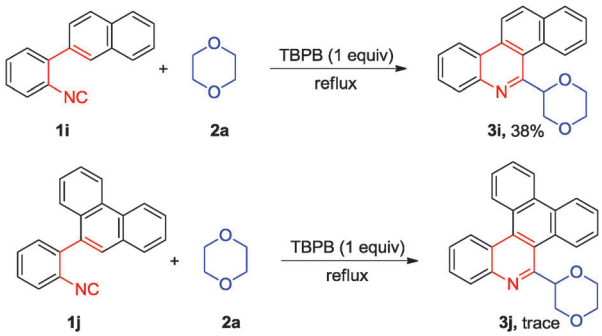
Table 2 The reaction of **1a–h** with **2a**[a]



1a-h 2a 3a-h



[a] Reaction conditions: **1** (0.5 mmol) in 3 mL 1,4-dioxane (**2a**) under argon atmosphere and reflux conditions.



Scheme 2 The reaction of **1i** and **1j** with **2a**.

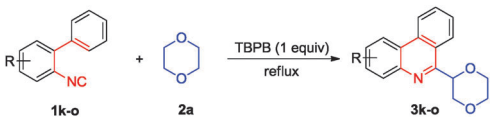
(**1d**) with **2a** also proceeded smoothly, which furnished the desired product **3d** in a 68% yield. When 1-(2′-isocyano-[1,1′-biphenyl]-4-yl)ethanone (**1e**) containing an electron-withdrawing group was subjected to the reaction, the desired product **3e** could also be obtained in a 47% yield. It should be noted that the reaction of 2-isocyano-3′-methyl-1,1′-biphenyl (**1g**) proceeded well to afford two regioisomers **3g** and **3g′** in yields of 51% and 24%, respectively.

Next, we explored the reaction of **1i** and **1j** with **2a**. It was found that the reaction could be extended to 2-(2-isocyanophenyl)-naphthalene (**1i**) with **2a**, furnishing the desired product **3i** in a 38% yield. Unfortunately, only a trace amount of product **3j** was detected when 9-(2-isocyanophenyl)phenanthrene (**1j**) was used in the reaction (Scheme 2).

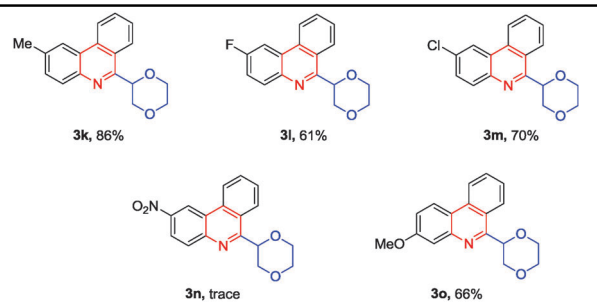
We further explored the effects of different substituents on the aromatic ring bearing the isocyano group. The results are summarized in Table 3. 2-Isocyano-5-methyl-1,1′-biphenyl (**1k**) showed good applicability to this reaction, which afforded the desired product **3k** in an 86% yield. The reactions of the halide-substituted 5-fluoro-2-isocyano-1,1′-biphenyl (**1l**) and 5-chloro-2-isocyano-1,1′-biphenyl (**1m**) led to the formation of the phenanthridines **3l** and **3m** in 61% and 70% yields, respectively. 2-Isocyano-4-methoxy-1,1′-biphenyl (**1o**) bearing a methoxy group also successfully underwent the reaction to afford **3o** in a 66% yield. The reaction of 2-isocyano-5-nitro-1,1′-biphenyl **1n** did not proceed under identical conditions.

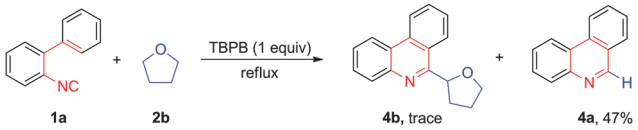
In order to expand the applicability of this reaction, we tried reacting **1a** with **2b**. However, no desired products was observed

Table 3 The reaction of **1k–o** with **2a**

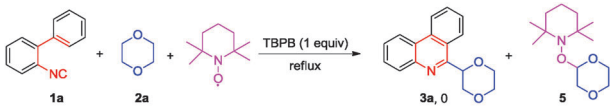


1k-o 2a 3k-o





Scheme 3 The reaction of **1a** with **2b**.

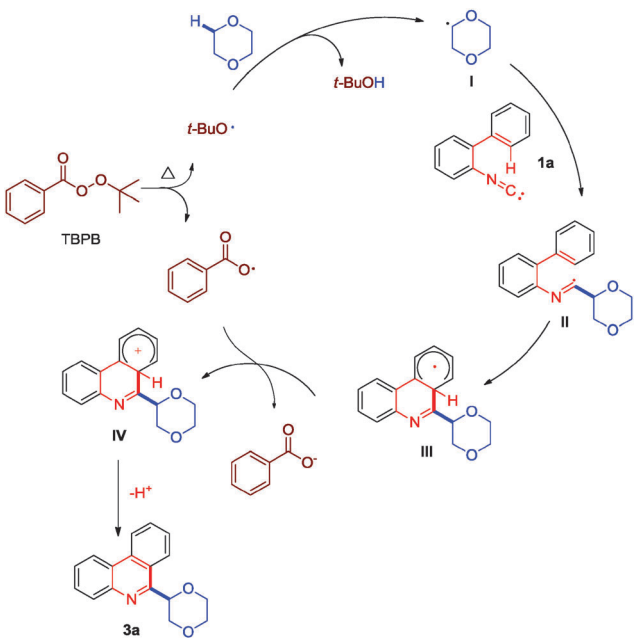


Scheme 4 Control experiment.

and only the phenanthridine **4a** was obtained in 47% yields (Scheme 3).

To understand the mechanism of this reaction, a control experiment reacting **1a** with **2a** in the presence of TEMPO was carried out. As expected, the desired product 6-(1,4-dioxan-2-yl)-phenanthridine (**3a**) was not detected; instead, only the formation of a TEMPO-1,4-dioxane (**5**) adduct was observed (Scheme 4). This result indicated that TBPB-mediated 2-isocyanobiaryl insertion with 1,4-dioxane involves a radical process.

Based on the literature and the above observations, a plausible mechanism is proposed in Scheme 5. Firstly, TBPB decomposes to a *tert*-butoxyl radical and a benzoate radical. Then, the *tert*-butoxyl radical reacts with 1,4-dioxane to activate the C–H bond adjacent to the oxygen atom, furnishing the active intermediate **I**, which can be trapped by TEMPO to give **5**. Addition of **I** to **1a** affords the imidoyl radical intermediate **II**. The intermediate **IV** and benzoate are formed by the subsequent intramolecular aromatic substitution of **II** and further oxidation by the benzoate radical. Finally, the desired phenanthridine is delivered after deprotonation.



Scheme 5 Plausible mechanism.

In conclusion, we have developed an efficient method to construct 6-alkyl phenanthridines by a *tert*-butyl peroxybenzoate (TBPB)-mediated 2-isocyanobiaryl insertion reaction with 1,4-dioxane. Two new C–C bonds were formed in this reaction *via* cascade C(sp^3)–H/C(sp^2)–H bond functionalization under metal-free conditions.

We gratefully acknowledge the Natural Science Foundation of China (No. 21172162, 21372174), the PhD Programs Foundation of Ministry of Education of China (2013201130004), the Young National Natural Science Foundation of China (No. 21202111), the Young Natural Science Foundation of Jiangsu Province (BK2012174), the Key Laboratory of Organic Synthesis of Jiangsu Province (KJS1211), PAPD, and Soochow University for financial support.

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