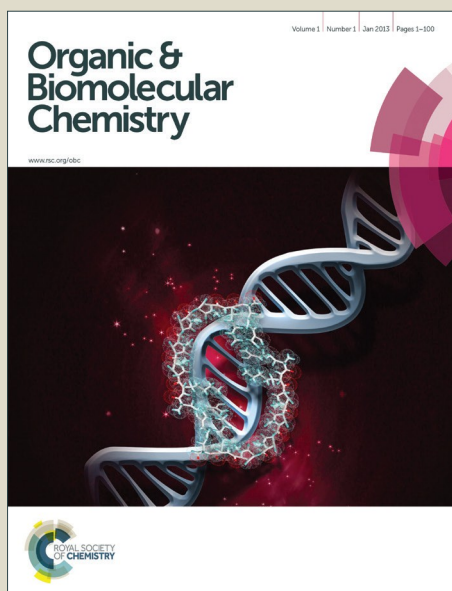


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Ni-Catalyzed Reductive Addition of Alkyl Halides to Isocyanides

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This paper highlights Ni-catalyzed reductive trapping of secondary and tertiary alkyl radicals with both electron-rich and electron-deficient aryl isocyanides using zinc as the terminal reductant, affording 6-alkylated phenanthridine in good yields. The employment of carbene ligand necessitates the alkyl radical process, and represents the first utility in the Ni-catalyzed reductive conditions for generation of unactivated alkyl radicals from the halide precursors.

Introduction

Phenanthridines are the important structures and building blocks widely persistent in naturally-occurring bioactive compounds, pharmaceutical drugs and synthetic optoelectronic materials.¹⁻⁶ For example, NK109 (Figure 1), which contains a phenanthridine as its core structure, shows great anti-tumor activities and proves to be against several drug-resistant human tumor cell lines.⁷

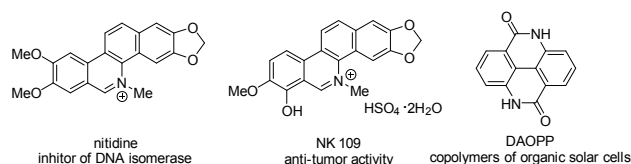
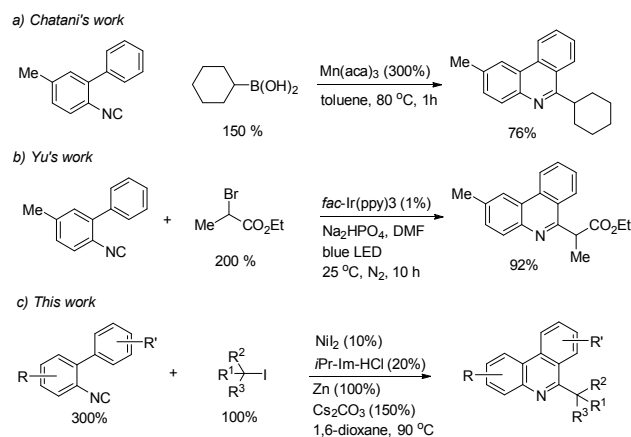


Fig. 1 Phenanthridines and related compounds

In the past few decades, numerous methods have been actively developed in the construction of the phenanthridines including classic Pictet–Hubert reaction⁸, radical cycloadditions⁹⁻¹², metal-catalyzed cross-coupling reactions¹³⁻¹⁷, C-H activation^{18, 19} and others²⁰⁻²⁴. In addition to these methods, recently aryl isocyanides

have regained many attentions because of their potency of building heterocycles by serving as good radical acceptors in cascade reactions. This synthetic strategy is particularly useful in the preparation of phenanthridine derivatives through efficient addition of radicals to aryl isocyanides followed by intramolecular cyclization.²⁵ The disclosed radicals include those arising from carbonyl^{26,27}, phosphoryl²⁸, carbazate²⁹, phenyl^{23, 30}, trifluoromethyl³¹⁻³³ and other fluoro sources^{34, 35}. By comparison, alkyl radicals are more active and likely to couple by itself. There are only rare examples involving alkyl radicals trapping with aryl isocyanides.³⁶⁻³⁸ For instance, in 2012, Chatani *et al* reported an approach using organoboron reagents catalyzed by Mn(acac)₃ to synthesize phenanthridine derivatives (Scheme 1a).³⁶ In 2013, Yu *et al.* developed a method to produce activated alkyl radicals from α -bromoesters which bears electron-withdrawing acyl groups to access 6-phenanthridine products (Scheme 1b).³⁷ Unactivated alkyl halides have not been reported for this type of reactions.



Scheme 1 Phenanthridine synthesis *via* a radical process

Our recent discovery of Ni-catalyzed reductive coupling of alkyl halides with other electrophiles indicated that the reactions generally involve conversion of unactivated alkyl halides to alkyl radicals in the presence of terminal of reductants, particularly Zn.³⁹⁻

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⁴⁴ In line with this feature, we envision that the alkyl radicals generated under the Ni/Zn conditions can be trapped with electron-deficient unsaturated bonds. Indeed, our previous studies disclosed that trapping glycosyl bromides with α,β -unsaturated double bonds is viable.^{45,46} In this work, we describe the success in the coupling of isocyanides with both secondary and tertiary alkyl iodides under the Ni-catalyzed reductive conditions, which resulted in efficient synthesis of 6-alkyl substituted phenanthridine derivatives (Scheme 1c). To the best of our knowledge, this is the first example that carbene ligands are utilized in the Ni-catalyzed reductive reactions for generation of unactivated alkyl radicals from the halide substrates.

Results and discussion

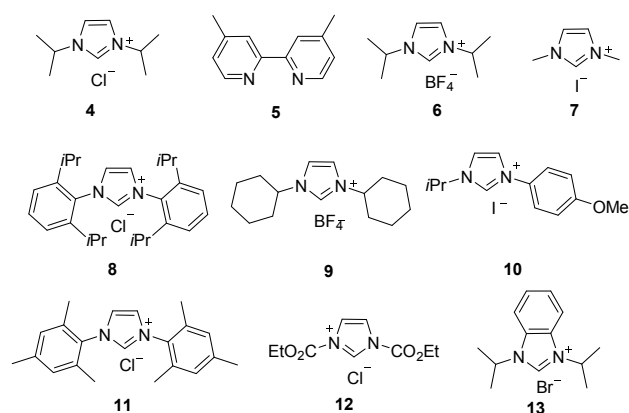
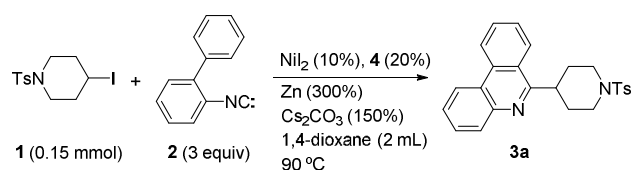


Fig. 2 Structures of ligands

Our studies commenced with the coupling of 4-iodo-1-tosylpiperidine (**1**) with 1,1'-biphenyl-2-isocyanide (**2**) as the model reactions. With significant optimization efforts, we eventually identified under $\text{NiI}_2/\mathbf{4}/1,4\text{-dioxane}$ catalytic conditions. The reaction generated phenanthridine product **3a** in 88% yield at 90°C (Table 1, entry 1), wherein the alkyl iodide was used as the limiting reagent and the isocyanide was 3 equiv in excess (see Figure 2 for the ligand structures). Lowering the loading for **2** or use of **2** as the limiting reagents resulted in reduced yields (entries 2–6). Without addition of the carbene precursor **4** or Cs_2CO_3 , no product was detected (entry 7–8), suggesting that the imidazolium salt served as the ligand after deprotonation.⁴⁷ Use of 0.5 equiv. of Zn still generated the product in 52% yield (entry 9). Other ligands **5–12** (entries 10–18), nickel sources and solvents⁴⁸ were inferior (see the ESI for details). Without Ni precatalyst, no product was obtained based on the control experiment (entry 19). In general, the major side reactions account for the ring closure of isocyanide **2** without incorporating the alkyl group, and hydrodehalogenation of **1**

Table 1 Optimization for the reaction of **1** and **2**.



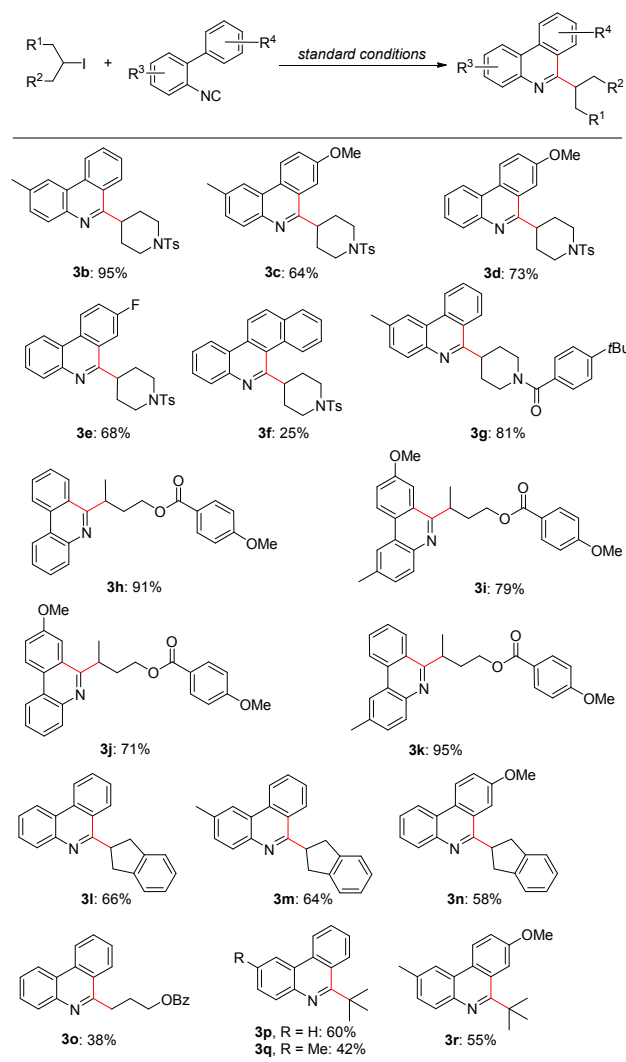
entry	Variation from the standard conditions	yield
1	none	88%
2	2.5 equiv. of isocyanide 2	65%
3	2 equiv. of isocyanide 2	57%
4	1 equiv. of isocyanide 2	52%
5	2 equiv. of 1 , 1 equiv. of isocyanide 2	51%
6	1.5 equiv. of 1 , 1 equiv. of isocyanide 2	48%
7	no ligand	ND ^c
8	no Cs_2CO_3	trace
9	50% Zn instead of 3 equiv	52%
10	5 (10%) instead of 4	63%
11	6 instead of 4	75%
12	7 instead of 4	73%
13	8 instead of 4	55%
14	9 instead of 4	55%
15	10 instead of 4	56%
16	11 instead of 4	56%
17	12 instead of 4	62%
18	13 instead of 4	65%
19	no Ni salt	ND

^a Reaction conditions: **1** (100 mol%, 0.75 M in 1,4-dioxane), **2** (300 mol%), NiI_2 (10 mol%), Zn (300 mol%), ligand (20 mol%), Cs_2CO_3 (150 mol%), 1,4-dioxane (2 mL). ^b Isolated yields. ^c not detected.

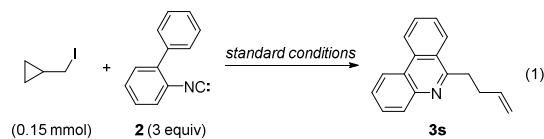
With the optimized conditions in hand (Table 1, entry 1), a range of alkyl iodides and aryl isocyanides were examined, and the results were illustrated in Table 2. The Coupling of 4-iodo-1-tosylpiperidine (**1**) with both electron deficient and electron rich isocyanides all gave phenanthridine products in fairly good yields (**3b** to **3e**). The addition of alkyl radical to 1-naphthyl isocyanide resulted in relatively low yield (**3f**), possibly due to steric and electronic effects of 1-naphthalene. Moreover, other cyclic and open-chain secondary iodides were efficient as well, providing corresponding products **3g** to **3n** in moderate to good yields. It was interesting to note that unstable iodides such as 2-iodoindanes also delivered the desired product in reasonably good results even though it is prone to decompose under air as evident in **3l** to **3n**. The coupling of primary alkyl iodides was not satisfactory. This is possibly due to the difficulty of trapping the less stable primary alkyl radical in the reactions which in turn favors formation of homocoupling byproducts.⁴⁹ In contrast, *tertiary* butyl iodide worked more efficiently, as evident in generating **3p** in a 60% yield, although it is

bulky in terms of steric factor. Likewise, under the standard conditions, moderate yields were obtained for **3q** and **3r** (42% and 55%, respectively). In general, the mild reaction conditions tolerate a wide arrange of functional groups such as ethers, esters, fluoride, etc.

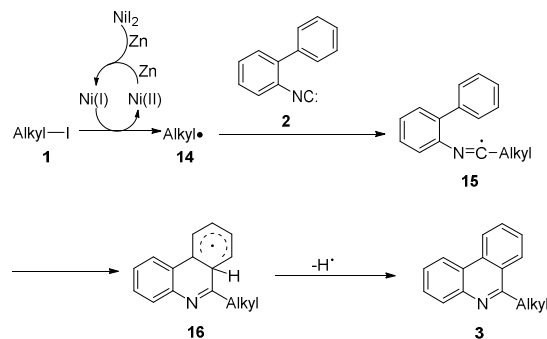
Table 2. Scope of the alkyl iodides and aryl isocyanides



To verify a possible radical mechanism for alkyl halides, the coupling of (iodomethyl)cyclopropane with isocyanide **2** was carried out under the standard conditions (equation 1). We only observed **3s**, which should involve ring-opening of an alkyl radical arising from the iodide substrate, followed by a radical addition process, although a Ni-insertion process cannot be excluded.⁵⁰ Addition of TEMPO completely shut down the reaction, which may further support a radical process is involved in this process.



Based on the present observation, a possible mechanistic pathway for this Ni-catalyzed annulation of 2-isocyanobiphenyl with alkyl iodide is depicted in Scheme 2. First, L_n-NiI_2 is reduced to Ni(I) complex by zinc, which may undergo halide abstraction or one electron transfer to alkyl halides to produce alkyl radical species **14** and a Ni(II) complex. A second reduction of the resultant Ni(II) by zinc will allow regeneration of the catalytic Ni(I) complex. The addition of radical **14** to aryl isocyanide **2** produces the imidoyl radical intermediate **15**, and the following intramolecular radical cyclization produces the radical intermediate **16**. After losing the hydrogen radical, the 6-phenanthridine product is finally obtained. Since the major side reactions for isocyanide arise from hydrogen-addition/ring-closure process. It is likely that isocyanide (3 equiv. in excess) may also serve as an intermolecular hydrogen acceptor. Meanwhile, the Ni(I) or Ni(II) could also serve as the hydrogen-atom acceptor, which generates Ni(n+1)-H. Reductive elimination of H-X gives Ni(0) or Ni(I) which continues to generate alkyl radicals without Zn reduction. This may partially be supported by the observation that 50% Zn could result in 52% yield, even if NiI_2 is initially used.



Scheme 2 Proposed reaction mechanism

Conclusions

In conclusion, we have developed a Ni-catalyzed radical addition method for efficient synthesis of 6-alkylated phenanthridine using carbene complex **4** as the ligand. The reactions are easy-to-operate, which display excellent functional group tolerance and demonstrates broad substrate scope enabling various aryl isocyanides and alkyl halides including secondary and tertiary alkyl iodides. The present work may be useful for the synthesis of phenanthridine derivatives of interest, in particular avoiding the typical use of toxic tin reagents for generation of alkyl radicals.

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