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Synthesis of Polysubstituted Phenanthridines via Ligand-Free Copper-Catalyzed Annulation

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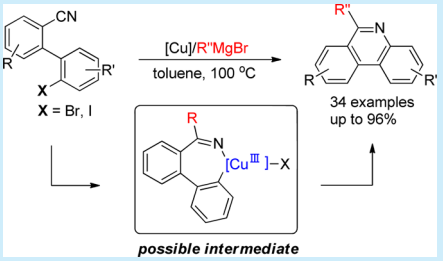
Supporting Information

ABSTRACT: A novel procedure for the cascade reaction of the addition of a Grignard reagent to a nitrile with a copper-catalyzed C−N bond coupling was developed, which afforded various polysubstituted phenanthridines in moderate to good yields with tolerance for a wide variety of substrates. Experimental data demonstrated that the reaction proceeded more likely through a Cu(I/III) catalytic cycle.



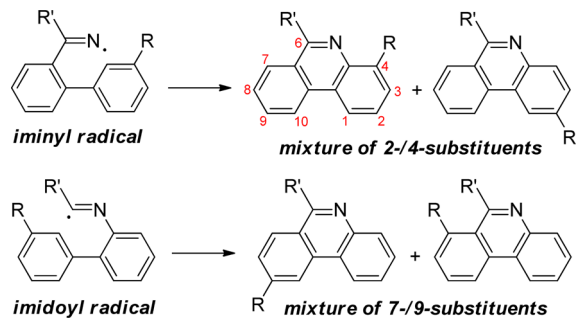
Phenanthridine derivatives are important compounds for organic synthesis since they were often discovered in a wide variety of natural alkaloids,[1] bioactive compounds, and pharmaceuticals.[2] In addition, some structures also possess electronic and optical properties.[3] Therefore, numerous methods were developed to prepare phenanthridine fragments such as transition-metal-catalyzed imine cyclization,[4] oxidation of 5,6-dihydrophenanthridine,[5] cyclization of aryne,[6] [2 + 2 + 2] cycloaddition,[7] aza-Wittig reaction,[8] intramolecular condensation of 2′-aminobiphenyl-2-carbaldehyde,[9] modified Pictet−Spengler[10]/Bischler−Napieralski[11] reactions, anionic ring closure reaction,[12] and stepwise addition of Grignard reagents to a nitrile with copper-catalyzed oxidative C−N coupling.[13] However, these strategies could only be applied to some specific phenanthridines with limitation of the substrate scope.

Syntheses of phenanthridines through cyclization reactions of iminyl and imidoyl radicals are the most common methods and have been developed over two decades.[14−21] Besides photolysis,[14,15] current development has progressed to oxidant-induced[16] and transition-metal-mediated generation of imidoyl or iminyl radicals. For example, Mn,[17] Ag,[18] Fe,[19] Co,[20] and Cu[13,21] have been successfully applied to generate the corresponding iminyl or imidoyl radicals which then cyclize to form the desired phenanthridines.

Although strategies for the syntheses of phenanthridines are dominated by using an iminyl or imidoyl radical as a key intermediate, the difficulty in controlling the steric position of 2-/4- or 7-/9-substituents after cyclization was often observed (Scheme 1). Therefore, development of novel methods to provide the corresponding products with a clearly steric position such as the coupling reaction through the cleavage of a carbon−halide bond is still desirable.

The copper-catalyzed carbon−heteroatom coupling reaction can be an alternative approach for phenanthridines with the advantages of low cost, air stability, and easy operation. Although this Ullmann type reaction was developed and widely

Scheme 1. Cyclization via Iminyl and Imidoyl Radicals



applied for over than one century, the mechanism still exists big dispute. Until recently, direct evidence for the oxidative addition of Cu(I) to aryl halides and formation of Ar−Cu(III)−Br was first revealed by Ribas.[22] Many research groups supported the Cu(I/III) catalytic cycle and provided more evidence to advocate this mechanism.[23] Our experience in the copper catalytic coupling reactions and the reactions involving a nitrile[24] encouraged us to explore the possibility for the synthesis of phenanthridines via a copper-catalyzed annulation reaction with a nitrile. Herein, we report the first example for the synthesis of phenanthridines through the Cu(I/III) catalytic cycle.

Our initial studies used 2′-bromo-[1,1′-biphenyl]-2-carbonitrile (**1a**) as a model substrate (Table 1, entry 1), which was treated with 5 mol % $Cu(OAc)_2$ and 2 equiv of EtMgBr in 0.5 mL of benzene at 100 °C for 18 h; the corresponding 6-ethylphenanthridine (**3a**) was obtained in 61% NMR yield. Product **3a** was confirmed by the ^1H NMR, ^{13}C NMR, and HRMS analysis. We also observed some undefined side products and substrate after working up the reaction.

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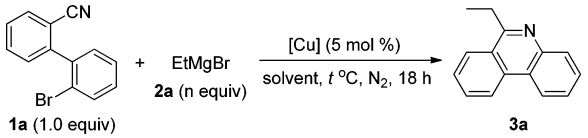
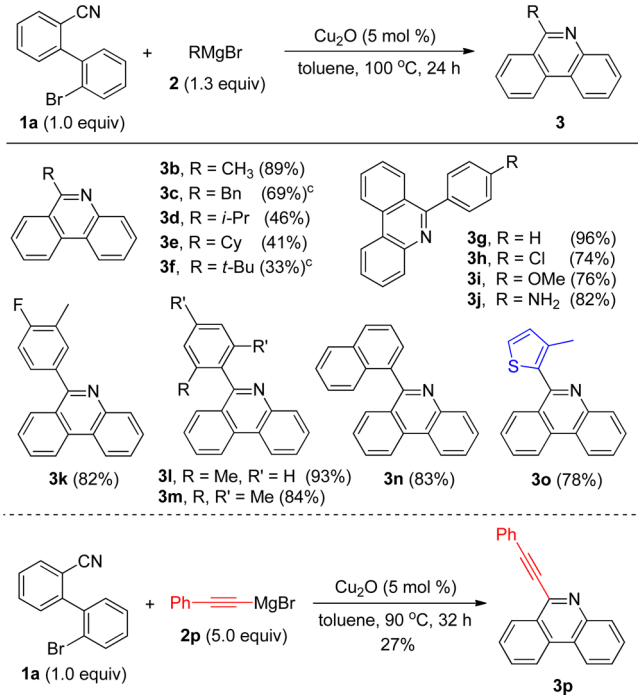
Table 1. Optimization of Reaction Conditions[a]



entry	[Cu]	*n*	solvent	temp (°C)	yield (%)[b]
1	$Cu(OAc)_2$	2	benzene	100	61
2	$Cu(TFA)_2$	2	benzene	100	52
3	$Cu(OTf)_2$	2	benzene	100	49
4	CuI	2	benzene	100	69
5	CuBr	2	benzene	100	76
6	Cu_2O	2	benzene	100	89
7	Cu_2O	2	toluene	100	92
8	Cu_2O	2	xylene	100	31
9	Cu_2O	2	hexane	100	19
10	Cu_2O	2	THF	100	11
11	Cu_2O	2	DME	80	6
12	Cu_2O	2	polar solvent[c]	100	0
13	Cu_2O	1.3	toluene	100	95 (86)[d]
14[e]	Cu_2O	1.3	toluene	120	96
15[f]	Cu_2O	1.3	toluene	80	84
16[g]	Cu_2O	1.3	toluene	100	81
17	none	1.3	toluene	100	13

[a]Reactions were carried out using 0.1 mmol (1.0 equiv) of 2′-bromo-[1,1′-biphenyl]-2-carbonitrile (**1a**) with 5 mol % [Cu] and EtMgBr (**2a**, *n* equiv) in 0.5 mL of solvent at *t* °C for 18 h. [b]^{1}H NMR yield based on internal standard mesitylene. [c]DMF, DMSO, and NMP were used. [d]Isolated yield in 0.4 mmol scale. [e]10 h. [f]28 h. [g]Under air.

Scheme 2. Scope of Grignard Reagents[a,b]



[a]Reactions were carried out using 0.4 mmol (1.0 equiv) substrate **1a** with 5 mol % Cu_2O, 1.3 equiv RMgBr (**2**) in 2.0 mL toluene at 100 °C for 24 h. [b] Isolated yield. [c] RMgCl was used.

To optimize the reaction conditions, the effect of solvents, amount of EtMgBr, reaction temperatures, and copper sources were investigated (Table 1). We first examined the copper source for this reaction (entries 2−6). Among the various copper sources employed, Cu_2O was found to be the most effective catalyst, providing an 89% NMR yield of the desired product **3a** (entry 6). The effect of solvent is very significant, and it was found that only nonpolar solvents such as benzene, toluene, xylene, and hexane allowed the reaction to proceed (entries 6−9), but the reactions in polar solvents gave <10% of the product (entries 10−12). A slightly excess amount (1.3 equiv) of EtMgBr was found to be sufficient for this cyclization (entry 13). The reaction proceeded smoothly at 80 to 120 °C with different reaction times (entries 13−15). However, the reaction could not proceed when the reaction temperature was lower than 80 °C. If the reaction temperature was higher than 120 °C, the reaction became very complicated and provided **3a** in a lower yield. The copper catalytic cyclization could also proceed under air with a lower yield (entry 16). This is probably due to the moisture interference in the reaction. Moreover, when the copper source was absent, product **3a** could be afforded in low yield via anionic ring closure reaction (entry 17).

This copper-catalyzed annulation reaction was successfully extended to various Grignard reagents (**2**), and the results are listed in Scheme 2. For most cases, the reaction required at least 24 h to fully consume the substrates (**1**). As indicated, reactions worked well for both alkyl and aryl Grignard reagents. Primary (**3b** and **3c**), secondary (**3d** and **3e**), and tertiary (**3f**) alkyl groups were all well tolerated, but secondary and tertiary alkyl groups provided their corresponding products in lower yields. Aryl groups (**3g**−**3n**) and a heterocyclic aromatic group such as the thiophenyl group (**3o**) were also well tolerated, and the desired products were afforded in high yields. The reaction for the 6-phenylphenanthridine (**3g**) proceeded very smoothly and gave an excellent yield. However, the yields were slightly lower when there were heteroatoms on the *para* position of aryl Grignard reagents (**3h**−**3k**). When **1a** was treated with 4-$(TMS)_2$NPhMgBr (**2j**), the two TMS groups were lost in the workup procedure, and 4-(phenanthridin-6-yl)aniline (**3j**) was isolated. When more hindered aryl groups such as *o*-tolyl, mestyl, and 1-naphthyl were introduced into the reaction, the yields of corresponding products (**3l**−**3n**) remained high. The stereo effect of the Grignard reagents appeared to not significantly affect the cyclization reaction. The 6-phenylethynyl substituted product (**3p**) was also obtained by using 5.0 equiv of **2p** at 90 °C. It is noteworthy that product **3p** is a very unique and challenging compound; the phenanthridine with the 6-ethynyl group was not yet reported by any literature related to the catalytic reaction.

The developed protocol allowed the reaction to be carried out with various substrates **1**, and the results are shown in Scheme 3. We first investigated the effect of electron density on the moiety of benzonitrile and of aryl bromide by using EtMgBr with various substrates **1**. It was found that the electron density of both the benzonitrile and aryl bromide moieties significantly affected the reactions. Reactions utilizing the substrate with an electron-withdrawing group on the moiety of aryl bromide afforded their corresponding products (**3A**−**3C**) in better yields than in the case with an electron-donating group (**3D**). A similar tendency was also observed for the effect of electron density on the moiety of benzonitrile (**3E**−**3H**). When an electron-rich substrate was introduced into the reaction, a homocoupling compound of the Grignard reagent was often detected. This catalytic reaction could well tolerate heterocyclic

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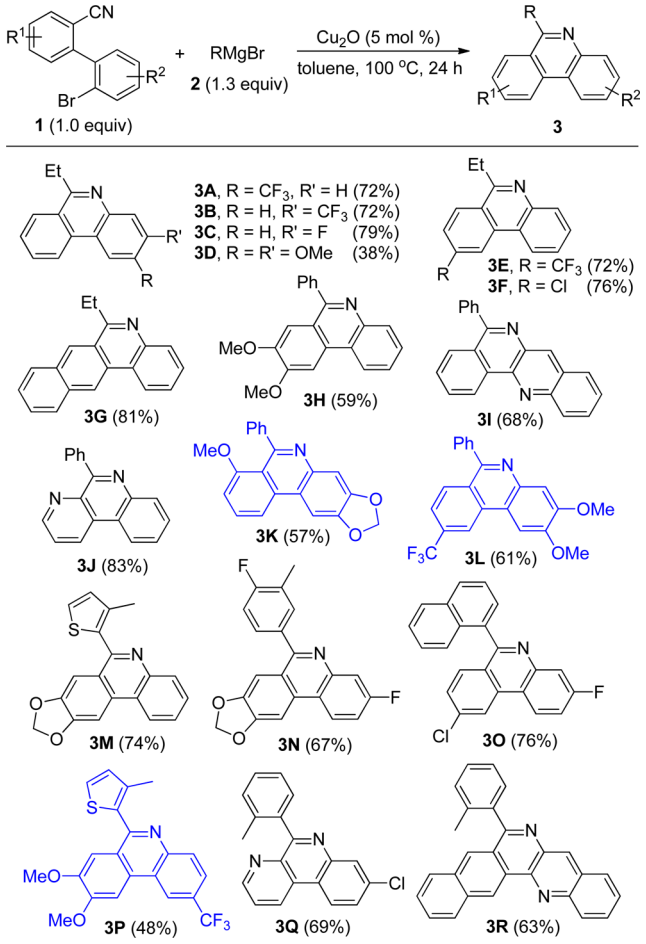
Scheme 3. Scope of Polysubstituted Phenanthridines[a,b]

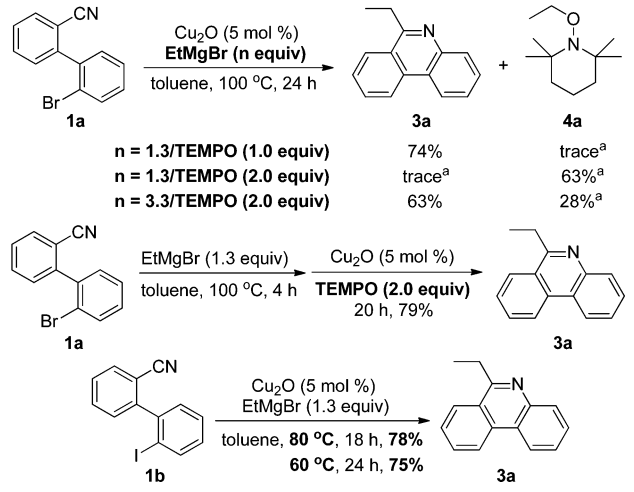


[a]Reactions were carried out using 0.4 mmol (1.0 equiv) of substrate **1** with 5 mol % Cu_2O, and 1.3 equiv of RMgBr (**2**) in 2.0 mL of toluene at 100 °C for 24 h. [b] Isolated yield.

aromatic substrates as well, and the corresponding products **3I** and **3J** could be obtained in good yields. Moreover, because of the natural limitation of Grignard reagents, various subunits except the electrophilic substituents could be freely combined to provide a wide scope of polysubstituted phenanthridines. Thus, products with an extended ring system or complicated structures can be established in moderate to good yields (**3K**–**3R**). It is very important to understand that products **3E**–**3G** and **3J**–**3Q** could not be obtained in a regiochemically pure form via an imidoyl radical pathway, and products **3K**, **3L**, and **3P** were very difficult to afford in a single isomer by the existing radical procedures (Scheme 1).

To study the reaction mechanism, some control experiments were conducted to understand the reaction pathway (Scheme 4). We utilized additional TEMPO and found that when 1.0 equiv of TEMPO was introduced into the reaction, the reaction was only slightly influenced and product **3a** was provided in 74% yield. However, when the amount of TEMPO was increased to 2.0 equiv, we could only detect a trace amount of **3a** by GC-MS and the major product was found to be the coupling product of TEMPO with EtMgBr (**4a**). If the amount of EtMgBr was increased to 3.3 equiv, we could again isolate **3a** in 63% yield. Upon further reaction in a stepwise process, we observed that the yield of **3a** did not significantly reduce after completing the addition of the Grignard reagent to the nitrile.

Scheme 4. Control Experiments

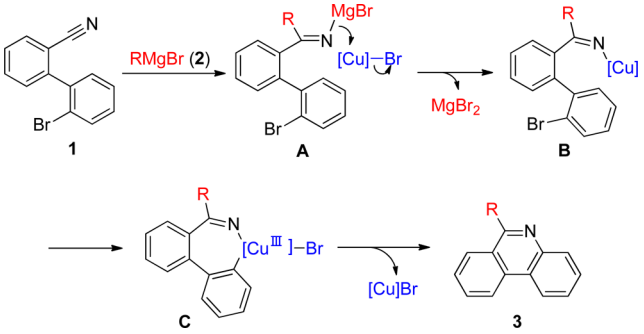


[a]Determined by GC–MS.

That means TEMPO as a radical scavenger is functionless in this copper catalysis. In addition, the reaction rate for the iodo compound **1b** was compared as well. The reaction rates between **1a** and **1b** at low temperature were very different. These results do not support the formation of radicals by the homolysis of aryl halide.[23c,25]

According to the above results and previous reports, a tentative mechanism can be proposed (Scheme 5).[22−25] The

Scheme 5. Proposed Mechanism



catalytic reaction is likely to be initiated by the nucleophilic addition of a Grignard reagent to the nitrile of compound **1** (complex **A**). The following transmetalation of the Mg(II) to Cu(I) complex then occurs to generate $MgBr_2$ and complex **B**. Oxidative addition of complex **B** in an intramolecular manner takes place to form a Cu(III) species (complex **C**). The subsequent reductive elimination provides compound **3** and regenerates the Cu(I) species.

In conclusion, we have developed a novel method for the copper-catalyzed annulation reaction involving the addition of the Grignard reagent to the nitrile and C–N bond coupling. This method efficiently provides polysubstituted phenanthridines in moderate to good yields with tolerance for a very wide variety of substrates. The mechanism study demonstrated that the reaction is more likely via an oxidative addition of Cu(I) to aryl halide, but not a radical pathway. Further studies to explore the possibility for the synthesis of natural alkaloids are currently underway.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, spectral data, and copies of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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