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Copper-Catalyzed Synthesis of Phenanthridine Derivatives under an Oxygen Atmosphere Starting from Biaryl-2-carbonitriles and Grignard Reagents

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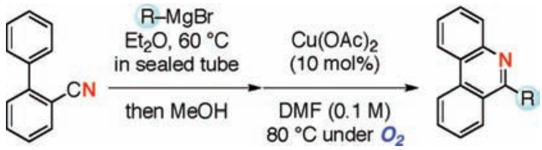
ABSTRACT



A copper-catalyzed synthesis of phenanthridine derivatives was developed starting from biaryl-2-carbonitriles and Grignard reagents. The present transformation is carried out by a sequence of nucleophilic addition of Grignard reagents to biaryl-2-carbonitriles to form *N*-H imines and their Cu-catalyzed C−N bond formation on the aromatic C−H bond, where molecular oxygen is a prerequisite to achieve the catalytic process.

Phenanthridines and their derivatives are of great interest in medicinal chemistry and material science due to their potent biological activities[1] and optoelectronic properties.[2] Although diverse approaches toward the construction of a phenanthridine skeleton have been reported so far,[3] versatile and efficient methodologies to synthesize phenanthridines with selective control of substitution patterns using readily accessible building blocks are still needed. Herein we wish to report a copper-catalyzed synthesis of phenanthridine derivatives under an oxygen atmosphere starting from biaryl-2-

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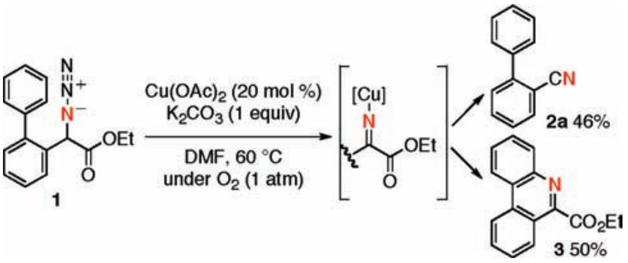
carbonitriles and Grignard reagents. The present transformation is carried out by a sequence of addition of Grignard reagents to biaryl-2-carbonitriles to form *N*-H imines and their Cu-catalyzed intramolecular cyclization including C−N bond formation on the aromatic C−H bond, where molecular oxygen is a prerequisite to achieve the catalytic process.

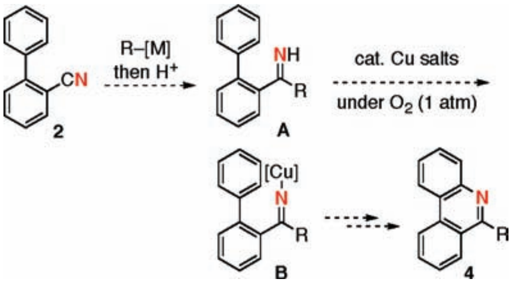
We have recently reported generation of iminyl copper species from α-azido carbonyl compounds and their copper-catalyzed C−C bond cleavage under an oxygen atmosphere, where nitriles were synthesized.[4,5] During the course of the study, it was found that a reaction of ethyl 2-azido-2-(biphenyl-2-yl)acetate (**1**) provided the desired biphenyl-2-carbonitrile (**2a**) in 46% yield along with 50% yield of phenanthridine **3**, which might be formed via aromatic C−H bond functionalization/C−N bond formation of the iminyl copper species (Scheme 1).

Scheme 1. Copper-Catalyzed Reaction of Ethyl 2-Azido-2-(biphenyl-2-yl)acetate (**1**)



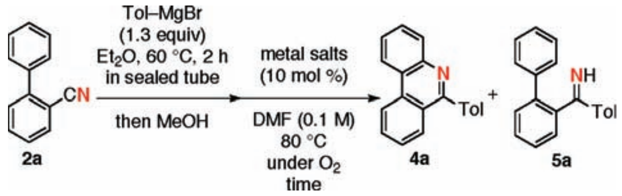
To explore an efficient synthetic method of phenanthridines via the iminyl copper species, we planned to use biaryl-2-carbonitriles and organometallic reagents as shown in Scheme 2, which commences with nucleophilic addition of R-[M] to biaryl-2-carbonitriles to afford *N*-H imines **A** after proper protonation. Consecutive treatment of resulting *N*-H imines with a catalytic amount of Cu salts under an oxygen atmosphere would give iminyl copper species **B**,[6] which could lead to formation of phenanthridines **4**.

Scheme 2. Synthetic Plan of Phenanthridines from Biaryl-2-carbonitriles and Organometallic Reagents



On the basis of this hypothesis, the formation of phenanthridines was investigated using biphenyl-2-carbonitrile (**2a**)[7] and *p*-tolylmagnesium bromide, and Table 1 lists the representative data. Addition of *p*-tolylmagnesium bromide to nitrile **2a** occurred smoothly in Et$_2$O at 60 °C (in sealed tube). After protonation with MeOH,[8] DMF (diluted to 0.1 M) and metal salts (10 mol %) were subsequently added, and the reaction mixture was stirred at 80 °C under an oxygen atmosphere (1 atm). It was found that several copper salts, either Cu(I) or Cu(II), exhibited good catalytic activity toward the formation of phenanthridine **4a** (entries 1−5). In contrast, the reaction using a stoichiometric amount of Cu(OAc)$_2$ without oxygen (under a N$_2$ atmosphere) provided phenanthridine **4a** in only 21% yield along with 36% yield of *N*-H imine **5a**, suggesting that molecular oxygen plays a vital role to achive the catalytic C−N bond formation process (entry 6).[9] Other metal complexes such as Pd(II), Co(II), Mn(III), and Fe(III) were not viable catalysts for this transformation (entries 7−10).

Table 1. Optimization of Reaction Conditions



entry	metal salts	time (h)	yield (%)[a] 4a	yield (%)[a] 5a
1	Cu(OAc)$_2$	26	91	0
2	CuCl2	19	88	6
3	Cu(OTf)$_2$	19	93	0
4	CuCl	18	89	0
5	CuTC	18	90	2
6[b]	Cu(OAc)$_2$	65	21	36
7	Pd(OAc)$_2$	24	2	72
8	Co(OAc)$_2$	24	1	99
9	Mn(OAc)$_3$	24	2	83
10	FeCl$_3$	24	0	71

[a] Isolated yields. [b] The reaction was carried out using 1 equiv of Cu(OAc)$_2$ under an N$_2$ atmosphere using degassed DMF. Tol = 4-methylphenyl; CuTC = copper(I) thiophene-2-carboxylate.

By utilizing Cu(OAc)$_2$ as the catalyst (entry 1 in Table 1), we examined the generality of this catalytic method for synthesis of substituted phenanthridines. First, scope of Grignard reagents were examined using biphenyl-2-carbonitrile (**2a**) (Table 2). Sterically hindered 2-methyl- and 2,6-dimethylphenyl moieties as well as an electron-deficient 4-chlorophenyl part could be installed with good to excellent

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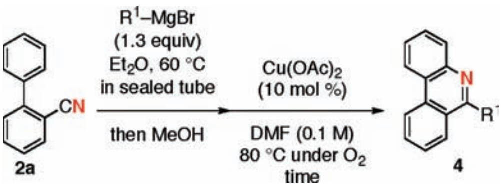
(6) For a report on formation of iminyl rhodium(I) complexes from *N*-H diarylimines, see: Zhao, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 11618.

Table 2. Reaction Scope of Grignard Reagents[a]

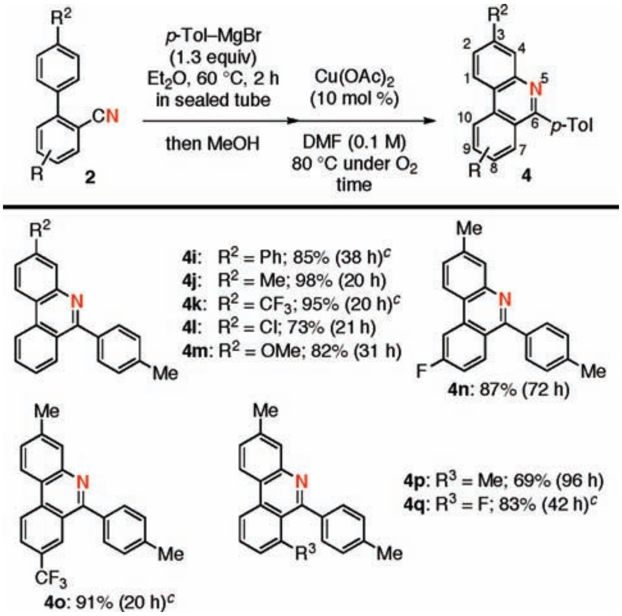


entry	R^1	time (h)	yield (%)[b]
1	2-Me-C_6H_4	19	**4b**, 99
2	2,6-Me_2-C_6H_3	20	**4c**, 88
3	4−Cl-C_6H_4	32	**4d**, 91
4	4-MeO-C_6H_4	36	**4e**, 5 (**5e**, 90)
5	2-thienyl	60	**4f**, 54 (**2a**, 41)
6[c]	CH_2CH_2Ph	31	**4g**, 76
7[d]	*i*-Pr	22	**4h**, 67

[a] Unless otherwise noted, reactions were carried out using 0.5 mmol of biaryl-2-carbonitriles **2a** with 1.3 equiv of Grignard reagents in Et_2O (0.5 mL) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), and $Cu(OAc)_2$ (10 mol %); the mixture was stirred at 80 °C under an O_2 atmosphere. [b] Isolated yields. [c] The reaction of **2a** with $Ph(CH_2)_2MgBr$ was completed in 24 h at 60 °C. [d] The reaction of **2a** with *i*-PrMgBr (2 equiv) was carried out at 80 °C for 24 h.

yields (entries 1−3). An electron-donating group such as methoxy on the benzene ring retarded the present cyclization, affording the corresponding phenanthridine **4e** in only 5% yield along with 90% yield of *N*-H imine **5e** even after stirring for 36 h (entry 4). When 2-thienylmagnesium bromide was utilized, the desired phenanthridine **4d** and biphenyl-2-carbonitrile (**2a**) were isolated in 54% and 41% yields, respectively, although nitrile **2a** was once consumed by the reaction with the Grignard reagent (entry 5). It was speculated that regeneration of nitrile **2a** might proceed via C−C bond cleavage of 2-thenyliminocopper species (see Supporting Information for more detail). Alkyl Grignard reagents also could be used, affording phenanthridines **4** in good yields (entries 6 and 7).

Scheme 3. Reaction Scope on Substituents of Biaryl-2-carbonitriles **2**[a,b]

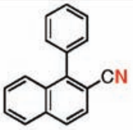
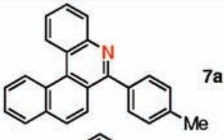
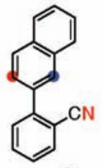
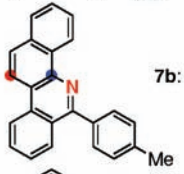
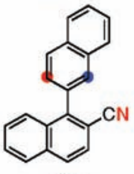
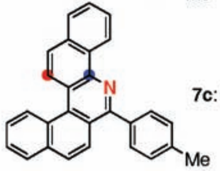
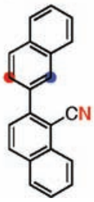
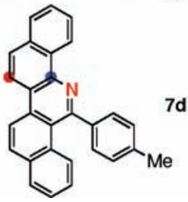


[a] Unless otherwise noted, reactions were carried out using 0.5 mmol of biaryl-2-carbonitriles **2** with 1.3 equiv of *p*-tolylmagnesium bromide in Et_2O (0.5 mL) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), and $Cu(OAc)_2$ (10 mol %), and the mixture was stirred at 80 °C under an O_2 atmosphere. [b] Isolated yields and reaction times on copper-catalyzed cyclization are recorded in parentheses. [c] 20 mol % of $Cu(OAc)_2$ was used.

Next, various biaryl-2-carbonitriles **2** were utilized to prepare substituted phenanthridines (Scheme 3). By varying substituent R^2 on C(3) of phenanthridine **4**, both electron-donating and -withdrawing groups could be installed (for **4i−4m**). Several substituents such as F, CF_3, and Me were also successfully introduced at the C(7), C(8), and C(9) of phenanthridines (for **4n−4q**).

This catalytic method allowed accessing polycyclic aza-aromatic hydrocarbons (aza-PAHs)[10] (Table 3). The reaction of 1-phenyl-2-naphthonitrile (**6a**) with *p*-tolylmagnesium bromide provided tetracyclic benzo[*k*]phenanthridine **7a** in good yield (entry 1). Aza-chrysene (benzo[*c*]phenan-

Table 3. Synthesis of Polycyclic Aza-Aromatic Compounds (aza-PHAs)[a]

entry	nitriles 6		time (h)[b]	aza-PHAs 7	yield (%)[c]
1		**6a**	46		**7a**: 86%
2		**6b**	21		**7b**: 86%
3		**6c**	64		**7c**: 81%
4[d]		**6d**	70		**7d**: 68%

[a] Reactions were carried out using 0.5 mmol of biaryl-2-carbonitriles **6** with 1.3 equiv of *p*-tolylmagnesium bromide in Et_2O (0.5 mL) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), and $Cu(OAc)_2$ (10 mol %); the mixture was stirred at 80 °C under an O_2 atmosphere. [b] Reaction times on copper-catalyzed cyclization. [c] Isolated yields. [d] The reaction of **6d** (0.3 mmol) with *p*-tolylmagnesium bromide (2 equiv) was carried out in toluene (1 mL) at 80 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), and $Cu(OAc)_2$ (20 mol %); the mixture was stirred at 120 °C under an O_2 atmosphere.

thridine) **7b** could be accessed selectively from 2-(naphthalen-2-yl)benzonitrile (**6b**) (entry 2). Pentanuclear aza-aromatic hydrocarbons, dibenzo[*c*,*k*]phenanthridine **7c** and dibenzo[*c*,*i*]phenanthridine (aza-picene) **7d**, were also synthesized starting from binaphthyl-2-carbonitriles **6c** and **6d**, respectively, although longer reaction time and higher temperature (120 °C for **7d**) were required (entries 3 and 4). In the cases of **6b**, **6c**, and **6d**, C−H functionalization occurred exclusively on the α-carbon (marked in blue) of the naphthalene ring, which suggested that an electrophilic aromatic substitution pathway[11] might be involved in the mechanism of the copper-catalyzed C−N bond formation (see Supporting Information for putative reaction mechanisms).[12−14]

In conclusion, a facile synthetic method of phenanthridine derivatives has been developed starting from biaryl-2-carbonitriles and Grignard reagents via Cu-catalyzed C−N bond formation on the aromatic C−H bond under an O_2 atmosphere. Continuous studies on the scope, mechanistic evaluation, and synthetic applications of the present method toward various polynuclear aza-aromatic hydrocarbons are in progress.

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Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) No C−N bond formation was observed without Cu catalysts.

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