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Co(acac)$_2$/O$_2$-Mediated Oxidative Isocyanide Insertion with 2-Aryl Anilines: Efficient Synthesis of 6-Amino Phenanthridine Derivatives

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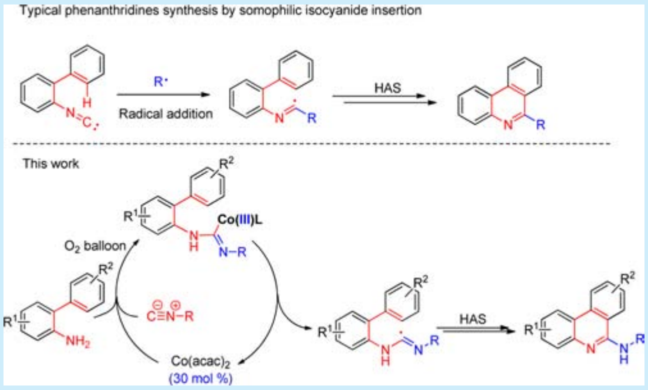
Supporting Information

ABSTRACT: A novel and efficient protocol for the creation of 6-amino phenanthridine derivatives by Co(acac)$_2$-catalyzed isocyanide insertion with 2-aryl anilines under an O$_2$ atmosphere via homolytic aromatic substitution (HAS) type C−H functionalization has been developed. This reaction not only proceeds smoothly utilizing O$_2$ as the oxidant but also provides a new approach to construct phenanthridine derivatives utilizing readily available 2-aryl anilines with isocyanides instead of 2-isocyanobiaryls with different radical precursors.



Phenanthridines have attracted much attention, because they show versatile biological activities such as antibacterial, antitumoral, cytotoxic, and DNA intercalator (Figure 1).[1,2] Therefore, it is important to develop new methods for the synthesis of these compounds.[3,4] Transition-metal-catalyzed isocyanide insertion reactions[5] and somophilic isocyanide insertion reactions[3,6] have been well developed for the construction of heterocycles via cascade reactions.[7] Recently, a series of 6-substituted phenanthridines were easily prepared by radical addition to 2-isocyanobiaryls followed by a homolytic aromatic substitution (HAS) process.[3,8] However, there has been no report on the construction of 6-amino phenanthridines utilizing a similar strategy. There are also no reactions of 2-aryl anilines with isocyanides to construct 6-amino phenanthridines. More recently, we have developed a cobalt-catalyzed isocyanide insertion reaction of aromatic amine derivatives to synthesize 2-aminobenzimidazoles, 2-aminobenzothiazoles, and 2-aminobenzoxazoles.[9]

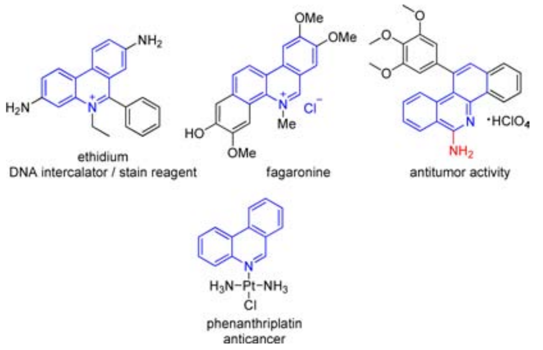
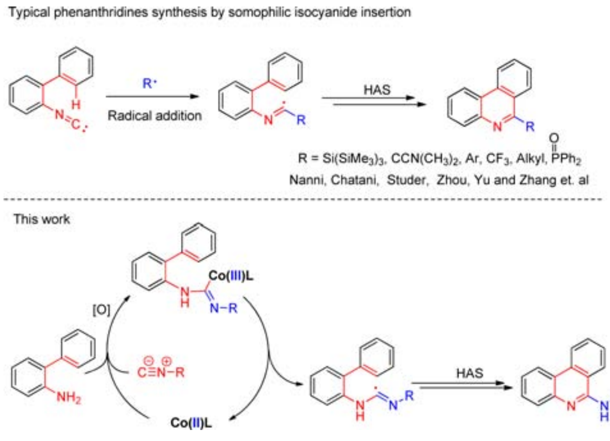


Figure 1. Biologically active phenanthridines.

As a continuation of our work on isocyanide insertion reactions,[9,10] herein, we plan to investigate the reaction of isocyanides with 2-aryl anilines catalyzed by a cobalt salt under oxidative conditions, which would concisely synthesize 6-amino phenanthridine derivatives via the formation of an imidoyl radical intermediate followed by HAS type C−H functionalization (Scheme 1). This reaction utilizes readily available 2-aryl anilines with isocyanides instead of 2-isocyanobiaryls with

Scheme 1. Phenanthridines Synthesis by Isocyanide Insertion



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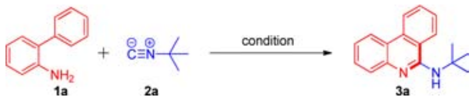
different radical precursors catalyzed by an inexpensive and low toxicity cobalt salt under oxidation conditions.

Our initial studies focused on developing a more efficient catalytic system by investigating the reaction of aniline **1a** and *tert*-butyl isocyanide **2a** as a model system. When the reaction of **1a** and **2a** was carried out in toluene at 100 °C without a catalyst under sealed tube conditions, no desired product was observed (Table 1, entry 1). To our surprise, the desired *N*-(*tert*-butyl)phenanthridin-6-amine **3a** could be obtained in 53% GC-yield by the reaction of **1a** and **2a** catalyzed by 20 mol % $Co(acac)_2$ in toluene at 100 °C under sealed tube conditions (Table 1, entry 2). However, other cobalt salts such as $Co(OAc)_2$, $CoCl_2{\cdot}6H_2O$, $Co(NO_3)_2{\cdot}9H_2O$, and $CoSO_4{\cdot}7H_2O$ could not promote this reaction (Table 1, entries 3−6). The results of screening for solvent, catalyst loading, and reaction temperature conditions indicated that 1,4-dioxane, 30 mol % $Co(acac)_2$, and 100 °C were optimal for this reaction (Table 1, entries 7−16). When the reaction was carried out under an argon atmosphere, it was found that almost no desired product was formed (Table 1, entry 17). This result indicated that O_2 was critical for this reaction. To our delight, the reaction of **1a** and **2a** catalyzed by 30 mol % $Co(acac)_2$ in 1,4-dioxane at 100 °C could react smoothly under 1 atm of O_2 atmosphere (O_2 balloon) to afford the desired product **3a** in 66% GC-yield (60% isolated yield) (Table 1, entry 18).

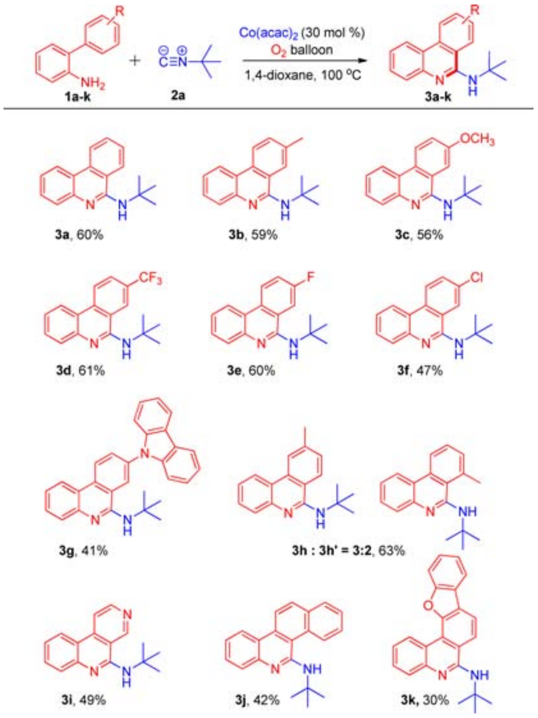
Table 1. Optimization of Isocyanide Insertion with 2-Aryl Anilines[a]



entry	catalyst (mol %)	temp (°C)	solvent	yield (%)[b]
1	–	100	toluene	0
2	$Co(acac)_2$ (20)	100	toluene	53
3	$Co(OAc)_2$ (20)	100	toluene	trace
4	$CoCl_2{\cdot}6H_2O$ (20)	100	toluene	trace
5	$Co(NO_3)_2{\cdot}9H_2O$ (20)	100	toluene	trace
6	$CoSO_4{\cdot}7H_2O$ (20)	100	toluene	trace
7	$Co(acac)_2$ (20)	100	benzene	39
8	$Co(acac)_2$ (20)	100	DMSO[e]	trace
9	$Co(acac)_2$ (20)	100	anisole	56
10	$Co(acac)_2$ (20)	100	1,4-dioxane	58
11	$Co(acac)_2$ (20)	100	DCE[f]	41
12	$Co(acac)_2$ (20)	100	DME[g]	53
13	$Co(acac)_2$ (10)	100	1,4-dioxane	24
14	$Co(acac)_2$ (30)	100	1,4-dioxane	63
15	$Co(acac)_2$ (30)	110	1,4-dioxane	44
16	$Co(acac)_2$ (30)	130	1,4-dioxane	43
17[c]	$Co(acac)_2$ (30)	100	1,4-dioxane	trace
18[d]	$Co(acac)_2$ (30)	100	1,4-dioxane	66

[a] Reaction conditions: biphenyl-2-amine **1a** (0.5 mol), *tert*-butyl isocyanide **2a** (0.6 mol, 1.2 equiv), cobalt catalyst, and solvent (3 mL) mixed in a 25 mL sealed tube with a magnetic stirrer for 12 h. [b] Yields were determined by GC analysis with biphenyl as the internal standard. [c] The atmosphere was argon. [d] The O_2 balloon was used, and a Schlenk tube was used instead of a sealed tube. [e] DMSO = dimethyl sulfoxide. [f] DCE = 1,2-dichloroethane. [g] DME = ethyleneglycol dimethyl ether.

Scheme 2. Cobalt-Catalyzed Insertion Reactions of *tert*-Butyl Isocyanides 2a with Substituted 2-Phenyl Aniline 1a−k[a,b]

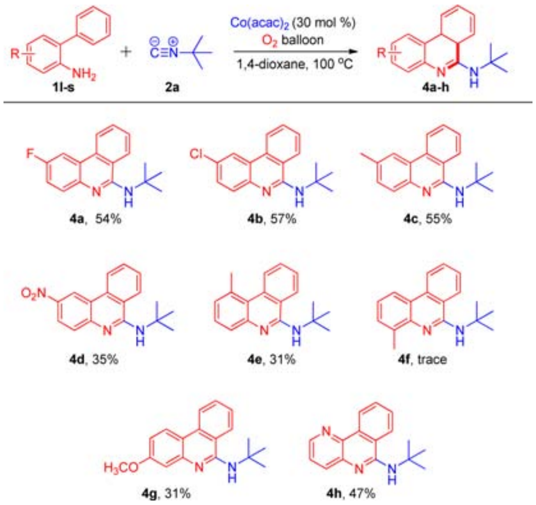


[a] Reaction conditions: substituted 2-phenyl aniline **1a−k** (0.5 mol), *tert*-butyl isocyanide **2a** (0.6 mol, 1.2 equiv), $Co(acac)_2$ (30 mol %), and 1,4-dioxane (3 mL) mixed in a Schlenk tube at 100 °C under O_2 balloon conditions. [b] Isolated yields.

With the optimized conditions in hand, the reaction scope of the 2-aryl anilines was investigated. The results are summarized in Schemes 2 and 3. The substituted 2-aryl anilines (**1a−k**) reacted well with *tert*-butyl isocyanide **2a** (Scheme 2), giving the desired products **3a−k** in moderate yields. It is noteworthy that not only the 2-aryl group bearing electron-donating groups could offer the desired products in moderate yields but also the 2-aryl group bearing electron-withdrawing groups could afford the desired products in moderate yields (30%-63%). When 3′-methylbiphenyl-2-amine **1h** was applied to the reaction, a mixture of the two isomers *N*-*tert*-butyl-9-methylphenanthridin-6-amine **3h** and *N*-*tert*-butyl-7-methylphenanthridin-6-amine **3h′** in the ratio 3:2 was obtained. 2-(Pyridin-4-yl)aniline could also react well and lead to the desired product **3i** in 49% yield. It should be noted that **3j** could also be observed in 42% yield with excellent regioselectivity, determined by NMR.

Then, we investigated the subtituent effects on the aniline aromatic ring. The results are listed in Scheme 3. The 2-aryl substituted anilines (**1l−s**) reacted well with *tert*-butyl isocyanide **2a**, furnishing the desired products **4a−h** in moderate yields. It is worth noting that the reaction of aniline bearing electron-donating groups (Me, OMe) could lead to the desired products in 31%−55% yields. When an aniline bearing an electron-withdrawing group such as NO_2 was applied to the reaction, the desired product **4d** could also be obtained in 35% yield. The reactions of halo-substituted anilines **1l** and **1m** afforded the products **4a** and **4b** in 54% and 57% yields, respectively. Furthermore, relatively bulky substrate **1p** could also undergo the transformation, generating the desired product **4e** in 31% yield. Unfortunately, when 3-methylbiphenyl-2-amine **1q** reacted with **2a**, only a trace of product was formed. To our delight, *N*-(*tert*-butyl)benzo[*c*][1,5]naphthyridin-6-amine **4h** could also be observed in 47% yield by the

Scheme 3. Cobalt-Catalyzed Insertion Reactions of *tert*-Butyl Isocyanides 2a with Substituted 2-Phenyl Aniline 1l−s[a,b]

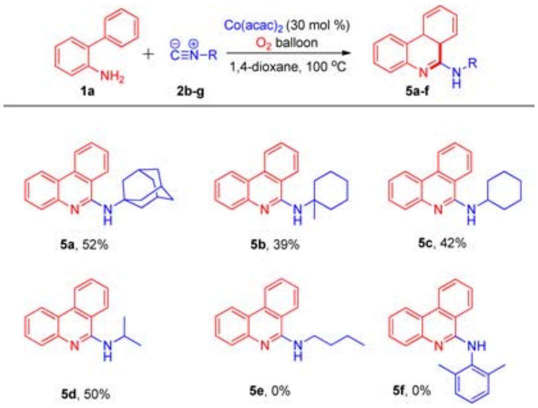


[a] Reaction conditions: substituted 2-phenyl aniline **1l−1s** (0.5 mol), *tert*-butyl isocyanide **2a** (0.6 mol, 1.2 equiv), Co(acac)$_2$ (30 mol %), and 1,4-dioxane (3 mL) mixed in a Schlenk tube at 100 °C under O$_2$ balloon conditions. [b] Isolated yields.

reaction of 2-phenylpyridin-3-amine **1k** with **2a** under the optimal conditions.

We further studied the reaction of several isocyanides with **1a** under identical conditions. When other secondary or tertiary aliphatic isocyanides **2b−e** were employed, the reactions also proceeded smoothly to give the desired products in moderate yields (39%−52%) (Scheme 4). However, the reactions of primary aliphatic isocyanide *n*-butyl isocyanide **2f** and aromatic isocyanide **2g** failed to give the desired products.

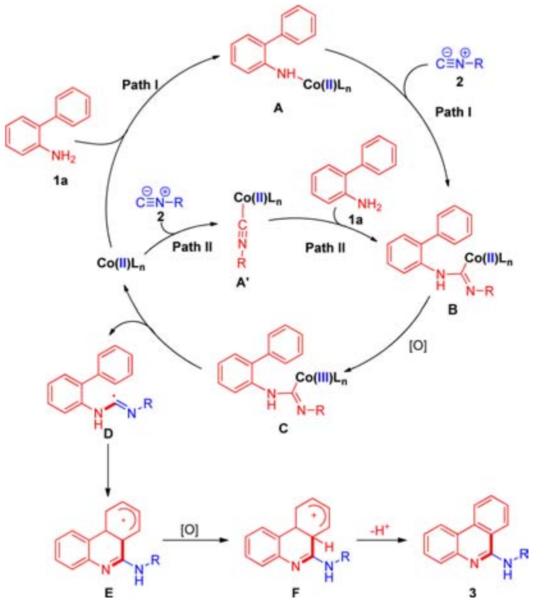
Scheme 4. Cobalt-Catalyzed Insertion Reactions of Substituted Isocyanides 2b−g with Biphenyl-2-amine 1a[a,b]



[a] Reaction conditions: substituted biphenyl-2-amine **1a** (0.5 mol), isocyanide **2b−g** (0.6 mol, 1.2 equiv), Co(acac)$_2$ (30 mol %), and 1,4-dioxane (3 mL) mixed in a Schlenk tube at 100 °C under O$_2$ balloon conditions. [b] Isolated yields.

Based on the literature reports[11−16] and the above results, we proposed a plausible mechanism via two possible pathways as shown in Scheme 5. Path I consists of a Co(II) salt reacting with **1a** to give cobalt(II) complex **A**.[11] **A** undergoes addition with **2**[12] to provide cobalt(II) carbene complex **B**[13] (Scheme 5, path I). The other possible pathway involves the Co(II) salt reacting with isocyanide **2** to furnish complex **A′**.[14,15] Then, **1a** adds to **A′** to give cobalt(II) carbene complex **B** (Scheme 5, path II). After the oxidation of **B**,[16] cobalt(III) complex **C** is formed, which may be cleaved homolytically to afford the active imidoyl radical **D** and the Co(II) catalyst. After the intramolecular cyclization of **D**, further oxidation, and subsequently deprotonation, the desired phenanthridine is formed.

Scheme 5. Proposed Mechanism



In conclusion, we have developed a new, simple, and efficient Co(acac)$_2$-catalyzed cascade isocyanides insertion with 2-aryl anilines under an O$_2$ atmosphere to construct 6-amino phenanthridine derivatives in moderate to good yields via homolytic aromatic substitution (HAS) type C−H functionalization. In view of the important biological properties of phenanthridines, 6-amino substituted phenanthridines have potential biological properties. The mechanism of this reaction is different from the mechanisms of the Pd-catalyzed isocyanide insertion reaction and radical isocyanide insertion reaction, and further mechanism studies are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new 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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