Dual cobalt(II)/silver catalysis: Synthesis of aryliminated pyrrolo[2,3-*b*]indoles via multicomponent bicyclization cascades

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ABSTRACT

Dual cobalt(II)/silver catalysis enables multicomponent bicyclization cascades of 2-ethynylanilines, *tert*-butyl isocyanide and arylamines, resulting in subsequent multiple bond-forming events to rapidly build up aryliminated pyrrolo[2,3-*b*]indoles. The reaction pathway involves bimetal-catalyzed isocyanide insertion/1,3-dipolar cycloaddition/ imination substitution sequence.

Keywords:

Dual bimetallic catalysis

Bicyclization

Pyrrolo[2,3-*b*]indoles

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Dual catalysis has become a very useful synthetic strategy for the assemble of unusual functional molecules which are difficult to obtain through traditional methods. During these processes, both the nucleophile and the electrophile are respectively activated by two different catalysts, facilitating their sequential coupling to prepare the desired compounds and remarkably improving reaction efficiency and selectivity. As a result, considerable effort has been devoted to synergistic catalysis in organic community.¹ However, the exploration of dual catalysis is challenging due to the fact that different catalysts may interfere with each other in one pot, thereby weakening their catalytic activities. To overcome this limitation, during the past few years the chemists have developed several compatible co-catalyst systems including a combination of transition-metal and organocatalysis,² transition-metal and photoredox catalysis,³ and prevalent bimetallic catalysis.⁴ Despite these high synthetic potential, the success of synergistic catalysis remains immature and there is a strong demand to develop new synergistic catalysis, especially those with perfectly compatible catalytic system.

Figure 1. Representative pyrrolo[2,3-*b*]indole alkaloids
 Pyrrolo[2,3-*b*]indoles are an important class of aza-heterocycles⁵ that are widely distributed in numerous natural products such as

pysostigmine,⁶ pseudophrvnaminol⁷ and flustramine C⁸ (Figure 1). Accordingly, many methods for the synthesis of this structural skeleton have been developed, which mainly involved the following three categories: i) tandem cyclization of tryptophan derivatives;⁹⁻¹³ ii) copper-catalyzed coupling of iodo-tryptophans;¹⁴ iii) aza-Pauson-Khand cyclocarbonylations.¹⁵ Despite these limited advances, the development of a direct and general catalytic protocol toward pyrrolo[2,3-*b*]indoles, especially through synergistic catalysis, has been an attractive target.

Our previous work

Zhang's work

This work

Scheme 1. Double insertion reaction of isocyanides

On the other hand, isocyanides have been served as powerful building blocks, which are extensively used in multicomponent reactions,¹⁶ insertion reactions,¹⁷ and oligo-/polymerization

processes.¹⁸ Very recently, we have reported an interesting Co/Ag synergistic catalysis of isocyanides and 2-ethynylanilines, enabling isocyanide insertion/1,3-dipolar cycloaddition to access pyrrolo[2,3-*b*]indoles (Scheme 1a).¹⁹ Later on, Zhang and co-workers presented Rh(I)-catalyzed cascade reaction of 2-azidoalkynylbenzenes with two different isocyanides by two steps, affording pyrrolo[2,3-*b*]indoles (Scheme 1b).²⁰ During this project, we found that when *tert*-butyl isocyanide **2** was subjected with reaction of 2-ethynylanilines and aromatic amines, this dual cobalt(II)/silver catalysis could occur, delivering aryliminated pyrrolo[2,3-*b*]indoles *via* multicomponent bicyclization cascades (Scheme 1c). Herein, we would like to report this interesting observation.

Scheme 2. Cascade reaction between 2-ethynylanilines and *tert*-butyl isocyanide²²

In our previous report, the cobalt(II)/silver-co-catalyzed bicyclization cascades of 2-ethynylanilines with cyclohexyl isonitrile (adamantanyl (Ada) and 4-bromophenyl) in a 1:2 molar ratio in 1,4-dioxane at 120 °C gave access to a range of functionalized pyrrolo[2,3-*b*]indoles.¹⁹ To expand the synthetic utility of this methodology, *tert*-butyl isocyanide (**2**) was selected and subjected to the reaction of 2-(*p*-tolylethynyl)aniline (**1a**) under the aforementioned reaction conditions, the reaction proceeded to generate the unexpected pyrrolo[2,3-*b*]indoles **4a**, albeit with 28% yield; this may be caused by the strong steric hindrance of 2-ethynylanilines. During this process, two molecule of arylethynylanilines and isocyanides were merged into the final pyrrolo[2,3-*b*]indoles (Scheme 2). In view of these useful results, we made our efforts to evaluate the feasibility of the synthesis of pyrrolo[2,3-*b*]indoles by replacing a molecule of arylethynylanilines with small steric aryl amines **3**. As per our expectation, the four-component reaction of **1** with **2** and aryl amines **3** under the above-described conditions provided poly-substituted 2-aryliminated pyrrolo[2,3-*b*]indoles **4** in good yields (Scheme 3). In the beginning, upon repeating the reaction with 2-(*p*-tolylethynyl)aniline (**1a**) and *tert*-butyl isocyanide (**2**), we were pleased to find that aryl amines **3** bearing electron-donating, -neutral, and -withdrawing substituents at the *para*-positions of the phenyl ring participated well in this synergistic bimetallic catalysis, delivering the collection of highly substituted pyrrolo[2,3-*b*]indoles **4b-f** in 53%-67% yields. Next, the scope of arylalkynes **1** was next explored, employing *tert*-butyl isocyanide **2** and *p*-toluidine **3a** as model substrates. Various 2-ethynylanilines possessing arylvinyl moiety attached by electron-donating (Me and MeO), neutral (H), or withdrawing (F and Cl) groups were compatible, and the target pyrrolo[2,3-*b*]indoles **4g-4j** were obtained in synthetically useful yields. The sterically more demanding 1-naphthyl (1-Np) counterpart was an adaptable component, enabling dual Co/Ag catalysis to access the desired product **4k** in a 72% yield under the standard conditions. Similarly, 2-ethynylanilines with various functional groups (Me, CN, F, and Cl) located at the 4-position of the internal arene ring would be accommodated, confirming the reaction efficiency, as **4m-4q** were afforded in 50%-62% yields.

Note that this is the special procedure for the assemble of these new imino-functionalized pyrrolo[2,3-*b*]indoles through Co/Ag-catalyzed double isocyanide insertion/ 1,3-dipolar cycloaddition/ imination substitution. Besides, the NMR and HR-MS spectroscopic analysis for inden o[1,2-*d*]pyridazine **4**, the X-ray diffraction for product **4a** has been performed as shown in Figure 1.

Scheme 3. Scope of cobalt/silver-co-catalyzed multicomponent bicyclization reaction.²² Yields of isolated products after column chromatography on silica gel are given. **1** (0.5 mmol) and *tert*-butyl isocyanide (1.2 mmol), aromatic amines (0.6 mmol), catalyst (10 mol %), dry 1,4-dioxane (4.0 mL), under N₂ atmosphere, 24 h; after completion, all the reaction mixtures were stirred at room temperature under air conditions for 5 h

Figure 1. The ORTEP drawing of **4a**²³

Although the detailed mechanism of this reaction has not been fully confirmed at this point, on the basis of our previous report,²⁰ a possible reaction pathway for forming pyrrolo[2,3-*b*]indoles **4**

is proposed in Scheme 4. The insertion of the ligated isonitrile into N-H bond of arylethynylanilines **1** affords enyne-imine specie **B**,²¹ which is converted into 1,3-dipoles **C**. In the presence of silver triflate, intramolecular 1,3-dipolar cycloadditions leads to pyrrolo[2,3-*b*]indole intermediate **D**, followed by imination substitution with arylamines **3** (**D** to **F**) to access aryliminated pyrrolo[2,3-*b*]indoles **4** through dehydrogenation.

Scheme 4. The proposed mechanism

In summary, a facile cobalt(II)/silver co-catalyzed bicyclization of arylethynylanilines with isonitriles and arylamines has been established, by which a range of aryliminated pyrrolo[2,3-*b*]indoles with high stereoselectivity were prepared in a convergent manner. The reaction also features dual Co/Ag catalysis and flexible structural modification. A detailed application of resulting pyrrolo[2,3-*b*]indoles is currently underway in our laboratory.

Acknowledgments

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- Typical procedure for the synthesis of **4a**: Under a nitrogen atmosphere, 2-(*p*-tolylethynyl)aniline (**1a**, 207 mg, 1.0 mmol), Co(acac)₃ (25.7 mg, 0.1 mmol, 10 mol %) and AgOTf (25.7 mg, 0.1 mmol, 10 mol %) were introduced into a 25-mL Schlenk reaction flask, *tert*-butyl isocyanide (**2**, 99.6 mg, 1.2 mmol, 1.2 equiv) and dry 1,4-dioxane (4.0 mL) were then successively added into this reaction mixture. The reaction system was stirred at 120 °C for 12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was continuously stirred at room temperature under air conditions for 5 h until the reaction solution turned red. Next, the solvent was removed under vacuum. The residue was separated by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate) to afford the pure red solid **4a**. Red solid, mp 194–195 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.33 (d, *J* = 8.0 Hz,

- 2H, Ar-H), 7.15-7.07 (m, 6H, Ar-H), 7.00 (d, $J = 8.0$ Hz, 2H, Ar-H), 6.85-6.80 (m, 3H, Ar-H), 6.71-6.65 (m, 2H, Ar-H), 6.52 (d, $J = 8.0$ Hz, 1H, Ar-H), 2.33 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 1.87 (s, 9H, CH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 172.6, 157.3, 148.8, 141.4, 138.2, 137.9, 132.1, 131.6, 131.2, 130.1, 129.9, 129.1, 128.3, 128.2, 128.1, 127.9, 123.6, 122.7, 122.5, 120.8, 120.4, 119.0, 114.5, 110.1, 93.1, 87.3, 58.8, 29.8, 21.5, 21.2. HRMS (APCI): m/z calcd for: C₃₆H₃₃N₃, 508.2753 [M+H]⁺; found: 508.2776. Typical procedure for the synthesis of products **4b**: Under a nitrogen atmosphere, 2-(phenylethynyl)aniline (**1b**, 96.5 mg, 0.5 mmol), *p*-toluidine (**3a**, 64.2 mg, 0.6 mmol, 1.2 equiv), Co(acac)₃ (12.8 mg, 0.05 mmol, 10 mol %) and AgOTf (12.8 mg, 0.05 mmol, 10 mol %) were introduced into a 25-mL Schlenk reaction flask, *tert*-butyl isocyanide (**2**, 99.6 mg, 1.2 mmol, 2.4 equiv) and 1,4-dioxane (4.0 mL) were then successively added into this reaction mixture. The reaction system was stirred at 120 °C for 24 h. After the completion of the reaction (monitored by TLC), the reaction mixture was continuously stirred at room temperature under air conditions for 5 h until the reaction solution turned red. Next, the solvent was removed under vacuum. The residue was separated by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate) to afford the pure red solid **4b**. Red solid, mp 149-150 °C. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.19$ -6.95 (m, 8H, Ar-H), 6.71 (s, 1H, Ar-H), 6.68-6.43 (m, 4H, Ar-H), 2.10 (s, 3H, CH₃), 1.84 (s, 9H, CH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 172.4, 163.2, 156.3, 144.1, 142.5, 132.8, 132.3, 131.9, 128.4, 128.2, 128.2, 127.7, 127.3, 123.6, 123.4, 122.5, 121.2, 118.9, 58.8, 29.8, 20.6. HRMS (APCI): m/z calcd for: C₂₇H₂₅N₃, 392.2127 [M+H]⁺; found: 392.2154.$$
- (23) Crystal data for **4a** (CCDC 1499409): C₃₆H₃₁N₃, $M_r = 505.64$, Monoclinic, space group $P2(1)/c$ with $a = 9.1198(9)$, $b = 17.4080(16)$, $c = 19.2261(18)$ Å, $\alpha = 90.00^\circ$, $\beta = 111.966(3)^\circ$, $\gamma = 90.00^\circ$, $V = 2830.7(5)$ Å³, $Z = 4$, $D_c = 1.186$ g/cm³, $\mu(\text{MoK}\alpha) = 0.534$ mm⁻¹, $F(000) = 1072$, the final $R = 0.0732$ and $wR = 0.0836$.

Graphical Abstract

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