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Construction of Pyrrolo[1,2-*a*]indoles via Cobalt(III)-Catalyzed Enaminylation of 1-(Pyrimidin-2-yl)-1*H*-indoles with Ketenimines and Subsequent Base-Promoted Cyclization

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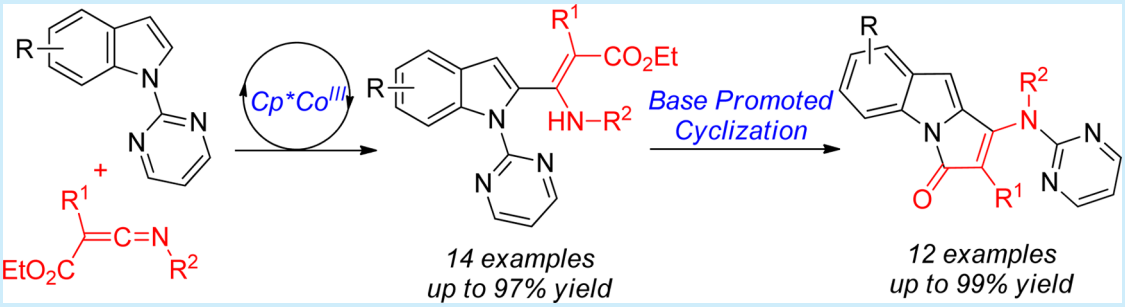
Supporting Information



ABSTRACT: A cobalt(III)-catalyzed cross-coupling reaction of 1-(pyrimidin-2-yl)-1*H*-indoles with ketenimines is reported. The reaction provided 2-enaminylated indole derivatives in moderate to excellent yields with a broad substrate scope. The prepared 2-enaminylated indoles could be conveniently converted into pyrrolo[1,2-*a*]indoles, which are an important class of compounds in medicinal chemistry.

Transition-metal-catalyzed C−H activation of arenes has attracted much attention and has become an effective way to build C(sp^2)−C and C(sp^2)−N bonds in modern organic synthesis.[1] With respect to the transition metals used in this kind of reaction, cobalt deserves to be explored because it is relatively cheaper in comparison with other noble metals, such as rhodium, platinum, gold, ruthenium, palladium, and iridium. Hence, several cobalt-catalyzed reactions recently appeared. In this burgeoning area, direct alkylation,[2] alkenylation,[3] cyanation,[4] amidation,[5] and phosphoramidation[6] on arenes have been disclosed. Although various coupling partners, such as alkenes,[3a] alkynes,[3b−g] imines,[7] azides,[5a,6] α-diazo esters,[8] 1,4,2-dioxazol-5-ones,[5d−f,9] *N*-cyano-*N*-phenyl-*p*-toluenesulfo-amides (NCTS),[4a,b] acetoxycarbamates,[5c] aldehydes,[10] and isocyanides,[5b] have been applied in this transformation, ketenimine, as an important intermediate in organic synthesis,[11] has never been used as a cobalt-catalyzed coupling partner.

Pyrrolo[1,2-*a*]indole is a distinctive substructure in many natural products and bioactive drugs.[12] Several representatives containing the pyrrolo[1,2-*a*]indole core are listed in Figure 1. Consequently, the development of new methodology for the construction of pyrrolo[1,2-*a*]indole ring systems continues to attract significant attention owing to their importance medicinal chemistry. Published approaches to the 3*H*-pyrrolo[1,2-*a*]-indol-3-one core include the thermal cascade rearrangement of 1- or 2-substituted indole (Scheme 1, routes a[13] and b[14]), Pd(II)-catalyzed C-2 alkenylation of 1-acryloylindole (Scheme 1, route c[15]), and Rh(III)- or Co(III)-catalyzed C−H activation/annulation sequence of 1-carbamoylindole with

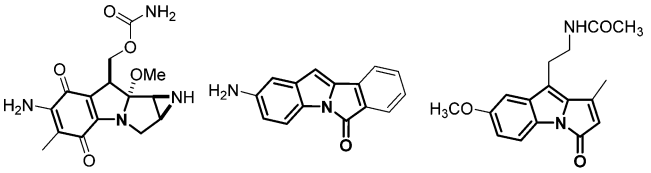


Figure 1. Representative biologically active pyrrolo[1,2-*a*]indole derivatives.

alkyne (Scheme 1, routes d[16] and e[3b]). Herein, we report an alternative route leading to the 3*H*-pyrrolo[1,2-*a*]indol-3-one core from 1-pyrimidinylindole and ketenimine (Scheme 1, this work).

To start with, we probed the direct coupling reaction between 1-(pyrimidin-2-yl)-1*H*-indole (**1a**) and ketenimine **2a** using Cp*Co(CO)I_2 as catalyst (Table 1). In our initial trial, we did not detect the envisioned product **3a** with the recovery of **1a** after the reaction mixture was refluxed in the presence of KOAc in dichloroethane (DCE) under nitrogen atmosphere for 10 h (Table 1, entry 1). After the additive was altered from KOAc to $AgSbF_6$, **3a** was obtained in 70% yield.[17] Delighted by this result, we then screened other silver salts, including $AgSbF_6$, $AgBF_4$, $AgPF_6$, AgOTf, AgOAc, AgO_2CCF_3, and $AgNTf_2$ (Table 1, entries 2−8), and $AgNTf_2$ gave the best yield

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Scheme 1. Construction of 3*H*-Pyrrolo[1,2-*a*]indol-3-one Core

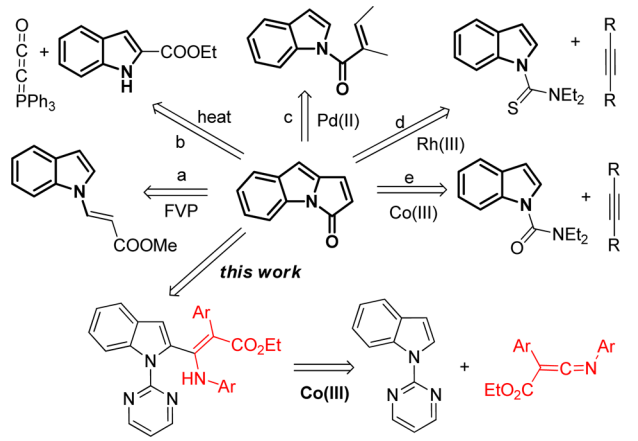
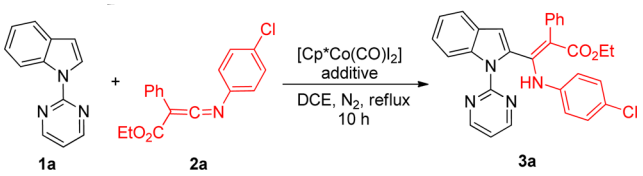


Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

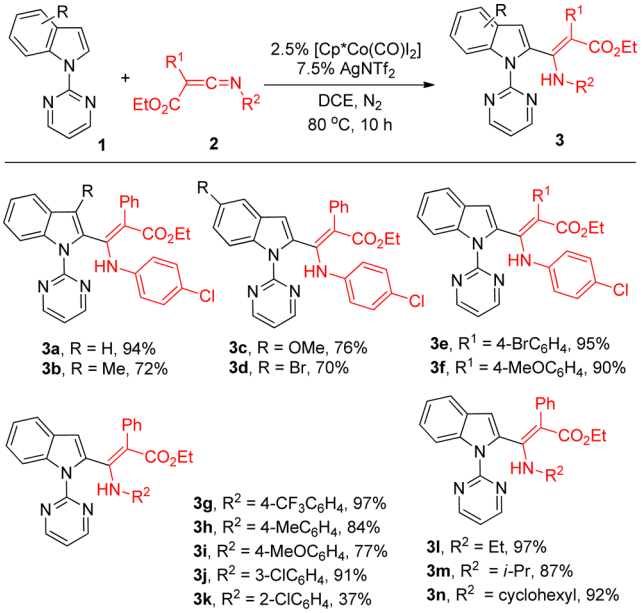
entry	additive (mol %)	catalyst (mol %)	yield[b] (%)
1	KOAc (30)	5	ND
2	$AgSbF_6$ (15)	5	70
3	$AgBF_4$ (15)	5	71
4	$AgPF_6$ (15)	5	77
5	AgOTf (15)	5	85
6	AgOAc (15)	5	NR
7	AgO_2CCF_3 (15)	5	NR
8	$AgNTf_2$ (15)	5	86
9	$AgNTf_2$ (15)	5	55[c]
10	$AgNTf_2$ (15)	o	NR
11	$AgNTf_2$ (7.5)	2.5	94
12	$AgNTf_2$ (3)	1	90

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.25 mmol) [Cp*Co(CO)I_2], additive, DCE (2 mL), N_2, reflux, 10 h. [b]Isolated yield refers to **1a**. [c]Under air atmosphere.

(86%). A decreased yield (55%) was observed when the reaction was conducted under air atmosphere (Table 1, entry 9). Without cobalt catalyst, no reaction occurred (Table 1, entry 10). Finally, the optimal loading amounts of $AgNTf_2$ and Cp*Co(CO)I_2 were determined to be 7.5 and 2.5 mol %, respectively (Table 1, entry 11).

With the optimized reaction conditions in hand, we investigated the substrate scope (Scheme 2). 3-Methyl-1-(pyrimidin-2-yl)indole (**1b**), 5-methoxy-1-(pyrimidin-2-yl)-indole (**1c**), and 5-bromo-1-(pyrimidin-2-yl)indole (**1d**) afforded **3b**, **3c**, and **3d** in 72%, 76%, and 70% yields, respectively. For **1b**, substitution on the 3-position of the indole ring might retard the reaction because of steric hindrance. Subsequently, the scope of ketenimines was studied. The substituent (R^1) on the terminal carbon of ketenimine could be either 4-bromophenyl (**2b**) or 4-methxoyphenyl (**2c**). In this case, **3e** and **3f** were isolated in 95% and 90% yields, respectively. A significant electronic effect was observed for the substituent (R^2) on the nitrogen of ketenimine. The electron-withdrawing group substituted **3g** and **3j** were

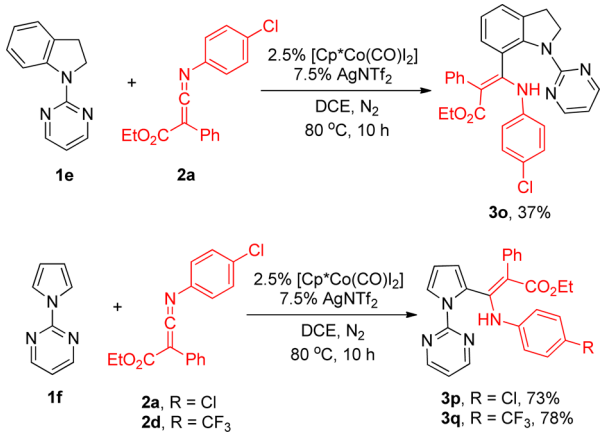
Scheme 2. Scope of Indoles and Ketenimines in the C–H Bond Activation[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.25 mmol), [Cp*Co(CO)I_2] (0.005 mmol), $AgNTf_2$ (0.015 mmol), DCE (2 mL), N_2, 80 °C, 10 h. Isolated yields refer to **1**.

obtained in excellent yields, while the electron-donating group substituted **3h** and **3i** were generated in decreased yields. For ethyl 3-(2-chlorophenylimino)-2-phenyl acrylate (**2h**), **3k** was obtained in very low yield due to steric hindrance. The substituent on the nitrogen of ketenimine could be an alkyl group. Thus, the reaction of ethyl 3-(ethylimino)-2-phenyl acrylate (**2i**), ethyl 3-(isopropylimino)-2-phenyl acrylate (**2j**), and ethyl 3-(cyclohexylimino)-2-phenyl acrylate (**2k**) with **1a** gave **3l**, **3m**, and **3n** in excellent yields, respectively. When 1-(pyrimidin-2-yl)indoline (**1e**) was used as the substrate, C–H on the 7-position of indole ring was activated. As a result, **3o** was isolated in 37% yield (Scheme 3). In comparison with **1a**, 1-(pyrimidin-2-yl)pyrrole (**1f**) was also tested for this transformation. In this case, **3p** and **3q** were isolated in 73% and 78% yields, respectively.

Scheme 3. Reaction of 1-(Pyrimidin-2-yl)indoline (1e) and 1-(Pyrimidin-2-yl)pyrrole (1f) with Ketenimines



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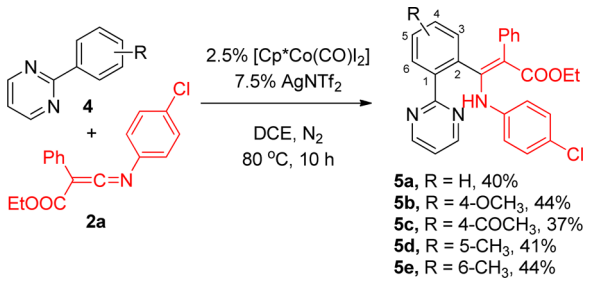
Moreover, to illustrate the practical utility of this methodology, a gram-scale experiment was performed. Accordingly, when **1a** (4 mmol), **2a** (5 mmol), [Cp*Co(CO)I_2] (0.1 mmol), and $AgNTf_2$ (0.3 mmol) in DCE (30 mL) were subjected to the optimized reaction conditions, 1.785 g of **3a** was isolated in 90% yield.

A possible mechanism for this reaction is proposed in Scheme S1 (see the Supporting Information). First, the catalyst reacts with $AgNTf_2$ to form $[Cp^*Co]^{2+}$. Then, the C−H activation and subsequent enaminylation occur to give 2-functionalized indoles.

In order to extend the substrate scope, 2-phenylpyrimidine (**4a**) was used for the C−H bond activation/enaminylation. Under the established reaction conditions for the formation of **3**, the coupling between **4** and **2a** afforded the enaminylation product **5a** in 40% yield (Scheme 4). Efforts to improve the yield of **5a** failed. Substituted 2-phenylpyrimidines **4b−e** could also be used to give the corresponding products **5b−e** in 37−44% yields.

Scheme 4. Coupling Reaction of 2-Phenylpyrimidines and Ketenimines

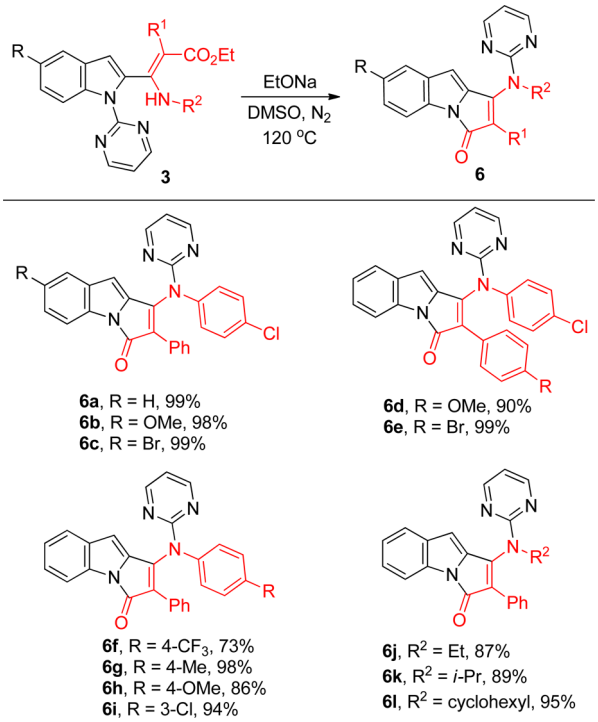


When we shifted our attention to the derivation of enaminylation products **3**, pyrrolo[1,2-*a*]indoles **6** were efficiently constructed by simple treatment of **3** with sodium ethoxide in DMSO at 120 °C. The structure of **6** was established by the single-crystal analysis of **6a**.[17] Compared with the *Z*-configuration in **3a**, the double-bond configuration changed. Interested by the bioactivities of compounds containing pyrrolo[1,2-*a*]indole core as described above, we studied the substrate scope of **3** (Scheme 5). Variation of the substituent on the indole ring did not affect the yield. 3*H*-Pyrrolo[1,2-*a*]indol-3-ones **6a−e** and **6g−i** were obtained in quantitative or excellent yields, whereas the strong electron-withdrawing group substituted **6f** was isolated in relatively low yield (73%). The substituent on nitrogen could be not only aryl but also alkyl. Thus, **6j**, **6k**, and **6l** were obtained in 87%, 89%, and 95% yields, respectively.

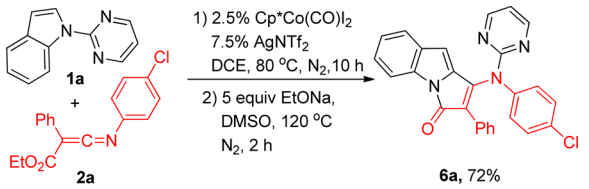
We then tried to combine the formation and cyclization of **3a** in one pot after the C−H bond activation reaction of **1a** and **2a**. As shown in Scheme 6, the two-step one-pot procedure successfully provided **6a** with a total yield up to 72%.

In order to understand the formation of **6**, a rearrangement mechanism is proposed (Scheme 7). Treatment of **6** with a base leads to deprotonation to form anion **A**, which can be stabilized by the ester group and the aryl group. A good indication is that the yield for the formation of **6e** is higher than that of **6d**. Then, **A** undergoes a sequence of nucleophilic aromatic substation (S_NAr) and aminolysis of ester to provide pyrrolo[1,2-*a*]indole **6**. During this process, a change of the

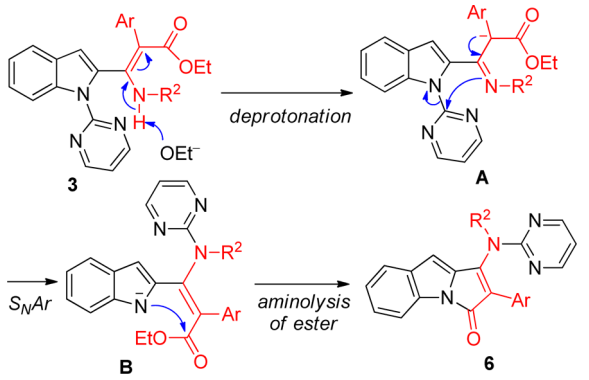
Scheme 5. Preparation of 3*H*-Pyrrolo[1,2-*a*]indol-3-ones 6



Scheme 6. One-Pot Preparation of 6a



Scheme 7. Proposed Rearrangement Mechanism for the Formation of 6



configuration of C=C bond of enamine occurs through intermediate **A**.

In conclusion, we have demonstrated that ketenimines could be used as the coupling partner in Co(III)-catalyzed cross-coupling reactions through the *ortho* C−H activation of some pyrimidinyl-substituted arenes. The Co-catalyzed reaction of 1-(pyrimidin-2-yl)indoles and ketenimines furnished 2-enaminylated indoles in moderate to excellent yields. The substrates are readily available. Moreover, the synthesized indole derivatives could be conveniently converted into 3*H*-pyrrolo[1,2-*a*]indol-

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3-ones, which are an important class of heterocyclic compounds in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02353.

Detailed synthetic procedures and characterization data for all products (PDF)
Crystallographic information for compound **3a** (CIF)
Crystallographic information for compound **5a** (CIF)
Crystallographic information for compound **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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(17) For ORTEPs of products **3a**, **5a**, and **6a** see the Supporting Information. CCDC 1491448 (**3a**), 1491447 (**5a**), and 1491449 (**6a**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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