

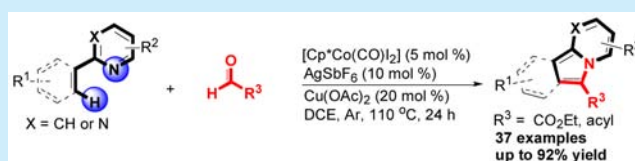
A [4 + 1] Cyclative Capture Access to Indolizines via Cobalt(III)-Catalyzed Csp²–H Bond Functionalization

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S Supporting Information

ABSTRACT: A Co(III)-catalyzed [4 + 1] cycloaddition of 2-arylpyridines or 2-alkenylpyridines with aldehydes through Csp²–H bond activation has been developed. This protocol provides a facile approach to structurally diverse indolizines including benzoindolizines with a broad range of functional group tolerance.



Indolizines and benzoindolizines are pervasive in natural products, pharmaceuticals, and functional materials (Figure 1).¹ In particular, 3-acylindolizines such as Rosabulin (STA-



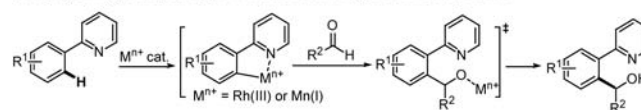
Figure 1. Selected examples of bioactive indolizines.

5312) exert a potential cytotoxic effect against multiple cancer cell lines.^{1c} Accordingly, substantial interest has been directed toward developing concise methods for the synthesis of diverse 3-acylindolizine skeletons.² Among the various methods, bromohydrocarbons and silylaryl triflates have been successively employed to construct indolizine heterocycles via photocyclization,^{2d} a multicomponent reaction,^{2e,f} and an aryne annulation process,²ⁱ but these methods are only limited to furnishing benzoindolizines. Therefore, developing efficient synthetic approaches to 3-substituted indolizines is desirable.³

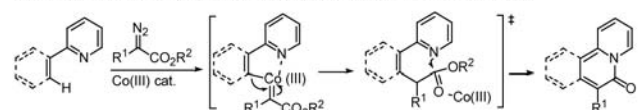
Recent, chelation-assisted C–H bond functionalizations provide an innovative strategy for direct Csp²–H addition to aldehydes.⁴ The pioneering report by Shi first described that a Rh(III)-catalyzed aryl C–H addition to aldehydes could produce diarylmethanols by using pyridine as a directing group (Scheme 1a).^{4b} More recently, employing the earth-abundant first-row metals such as manganese⁵ and cobalt⁶ catalysts to realize the C–H functionalization has aroused concerns due to their availability and low cost. In this regard, Wang took advantage of the directing character of the pyridine group to enable the manganese-catalyzed Grignard-type nucleophilic addition of Csp²–H bonds to aldehydes, but the corresponding alcohols could not undergo a subsequent intramolecular cyclization (Scheme 1a).^{4e} In contrast, Glorius found that a pyridine-directed aryl C–H coupling with diazo compounds could occur in the presence of Co(III) salts, in which Co(III) salts also played the role of Lewis acid catalyst to

Scheme 1. Dual Activation Strategy for Transition-Metal-Catalyzed Cascade Csp²–H Functionalization

a) Rh(III) or Mn(I)-catalyzed aryl C–H addition to aldehyde to access alcohols



b) Co(III)-catalyzed directed aryl C–H functionalization with carbene precursors



c) This work: Co(III)-catalyzed [4 + 1] cyclization of 2-alkenylpyridines with aldehydes

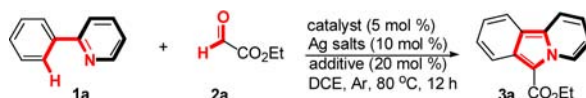


enhance the nucleophilic attack of pyridyl nitrogen on the carbonyl acceptor and resulted in furnishing polycyclic hydrocarbons (Scheme 1b).⁷ These results and our previous work⁸ encouraged us to speculate that pyridine-directed Csp²–H addition to aldehydes could also possibly occur to form alcohols by employing a Co(III) catalyst, and then a Co(III) species could activate the resulting hydroxymethylene group, leading to the formation of 3-substituted indolizines through a nucleophilic cyclization process (Scheme 1c).

To achieve this transformation, we made the starting material 2-phenylpyridine (1a) and investigated the effect of various cobalt catalysts (5 mol %) on the aryl C–H addition to ethyl oxoacetate (2a) in the presence of AgSbF₆ (10 mol %) and NaOAc (20 mol %) using 1,2-dichloroethane (DCE) as solvent at 80 °C for 12 h (Table 1, entries 1–4), and we soon found that the [Cp*Co(CO)I₂] catalyst provided the desired 3-

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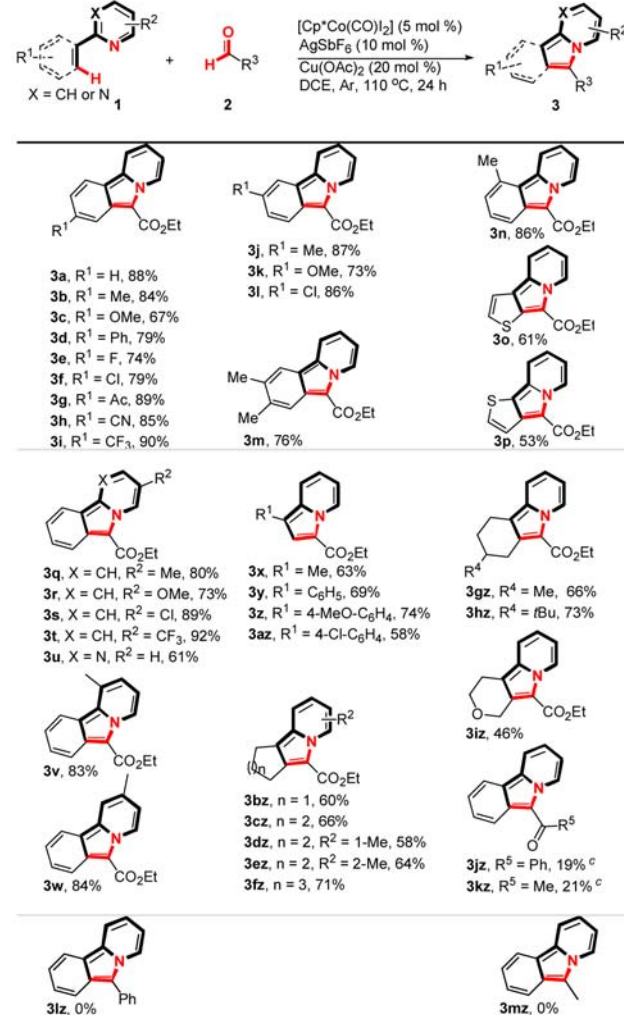
Table 1. Optimization of the Reaction Parameters^a


entry	catalysts	Ag salts	additives	yield (%) ^b
1	Co(acac) ₃	AgSbF ₆	NaOAc	0
2	CoCl ₃	AgSbF ₆	NaOAc	0
3	[Cp*Co(CO)I ₂]	AgSbF ₆	NaOAc	28
4	A ^c	—	NaOAc	21
5	[Cp*Co(CO)I ₂]	AgBF ₄	NaOAc	19
6	[Cp*Co(CO)I ₂]	AgOAc	NaOAc	14
7	[Cp*Co(CO)I ₂]	AgNTf ₂	NaOAc	25
8	[Cp*Co(CO)I ₂]	AgClO ₄	NaOAc	0
9	[Cp*Co(CO)I ₂]	AgSbF ₆	CsOAc	24
10	[Cp*Co(CO)I ₂]	AgSbF ₆	AcOH	18
11	[Cp*Co(CO)I ₂]	AgSbF ₆	PivOH	22
12	[Cp*Co(CO)I ₂]	AgSbF ₆	AgOAc	16
13	[Cp*Co(CO)I ₂]	AgSbF ₆	Cu(OAc) ₂	47
14	[Cp*Co(CO)I ₂]	AgSbF ₆	Cu(OAc) ₂	36 ^d
15	[Cp*Co(CO)I ₂]	AgSbF ₆	Cu(OAc) ₂	18 ^e
16	[Cp*Co(CO)I ₂]	AgSbF ₆	Cu(OAc) ₂	0 ^f
17	[Cp*Co(CO)I ₂]	AgSbF ₆	Cu(OAc) ₂	71 ^{g,h}
18	[Cp*Co(CO)I ₂]	AgSbF ₆	Cu(OAc) ₂	88 ^{g,h,i}

^aUnless otherwise noted, all the reactions were carried out using 2-phenylpyridine (**1a**) (0.20 mmol) and ethyl glyoxylate (**2a**) (0.20 mmol) with catalysts (5 mol %) in the presence of silver salts (10 mol %) and additives (20 mol %) in solvent (2.0 mL) at 80 °C for 12 h under Ar in a sealed reaction tube. Followed by flash chromatography on SiO₂. ^bIsolated yield. ^cA refers to [Cp*Co(MeCN)₃(SbF₆)₂]. ^dTHF was used as solvent. ^eToluene was used as solvent. ^fDMF was used as solvent. ^gThe reaction time is 24 h. ^hThe reaction temperature is 110 °C. ⁱThe ratio of **1a**/**2a** is 1:2.

ethoxycarbonylbenzoindolizine **3a** in 28% yield (entry 3). The [Cp*Co(MeCN)₃(SbF₆)₂] catalyst also gave a 21% yield of **3a** (entry 4). It is worth noting that the further silver salt screening could not improve the reaction conversion (compare entries 5–8 with entry 3). However, after various additives including CsOAc, AcOH, PivOH, AgOAc, and Cu(OAc)₂ were evaluated for this transformation, the yield of product **3a** was moderately increased from 28% to 47% using Cu(OAc)₂ as an additive (compare entry 3 with 13). Meanwhile, the solvent screening also demonstrated that DCE was the optimal solvent (compare entries 14–16 with 13). Gratifyingly, extending the reaction time, increasing the reaction temperature, and changing the ratio of **1a**/**2a** to 1:2 could significantly improve the reaction yield to 71% and 88%, respectively (entry 17 vs 18).

With the optimized catalytic system in hand, we then turned our attention toward exploring the scope and limitation of the cobalt-catalyzed [4 + 1] cycloaddition of various 2-arylpyridines (**1**) with ethyl oxoacetate (**2a**). As shown in Scheme 2, this reaction protocol could smoothly convert 2-(4-substituted phenyl)-pyridines to the desired 3-ethoxycarbonylbenzoindolizines with good to excellent yields (67–90%), regardless of whether electron-deficient or -rich substituents were introduced into the phenyl rings (**3a–3i**). For example, 2-(4-methylphenyl)pyridine (**1b**) and 2-(4-trifluoromethylphenyl)pyridine (**1i**) could afford the desired 3-acylbenzoindolizines **3b** and **3i** in 84% and 90% yields, respectively. Moreover, 3- or 2-substitution on the benzene ring with an electron-donating group (Me, MeO) or electron-deficient group (Cl) could also give excellent yields of

Scheme 2. Substrate Scope^{a,b}

^aAll the reactions were carried out using 2-substituted pyridine (**1**) (0.20 mmol) and aldehyde (**2**) (0.40 mmol) with [Cp*Co(CO)I₂] (5 mol %) in the presence of AgSbF₆ (10 mol %) and Cu(OAc)₂ (20 mol %) in DCE (2.0 mL) at 110 °C for 24 h under Ar in a sealed tube. Followed by flash chromatography on SiO₂. ^bIsolated yield. ^cAnhydrous MgSO₄ (100 mg) was added.

multisubstituted benzoindolizines in excellent yields, in which no significant effect of steric hindrance was observed in this transformation (**3i–3n**, 73%–87% yields). Note that, 2-(3-thienyl)pyridine (**1o**) and 2-(2-thienyl)pyridine (**1p**) are also allowed for this transformation to assemble the corresponding 3-substituted thieno[3,2-*α*]indolizine (**3o**) and thieno[2,3-*α*]indolizine (**3p**) in good yields. Meanwhile, the reaction scope with respect to 2-phenyl-3- or 4- or 5-substituted pyridines was further evaluated, and it was found that these substrates with electron-poor and -rich pyridine moieties were reactive, and could produce the corresponding benzoindolizines in 61–92% yields (**3q–3w**). Among them, the structure of **3s** was already unambiguously assigned by single crystal X-ray analysis [see Supporting Information (SI) for more details].

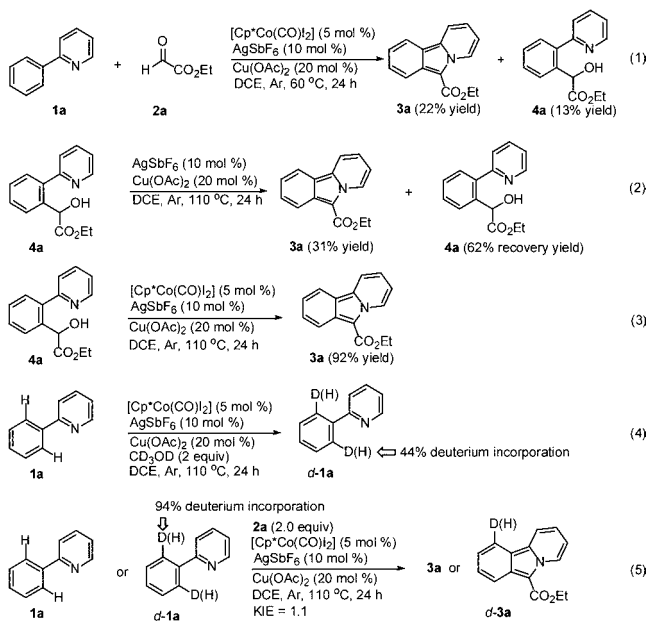
More importantly, the reactions are not limited to 2-arylpyridines. 2-Alkenylpyridines could also smoothly undergo a [4 + 1] cycloaddition with ethyl oxoacetate (**2a**) to furnish 3-ethoxycarbonylindolizines, in which 2-pyridyl substituted

terminal alkenes and internal alkenes are compatible with the reaction conditions, and produce the corresponding structurally diverse indolizines (**3x–3iz**) in moderate to good yields (46–74%).

Finally, the reaction scope with respect to aldehydes was further investigated. In addition to ethyl oxoacetate, oxo-aryl-acetaldehyde, and oxo-alkyl-acetaldehyde could give the desired 3-acylindolizines (**3jz** and **3kz**) in accepted yields.⁹ In contrast, other aldehydes such as benzaldehyde and acetaldehyde were not allowed for this transformation, and the starting materials were recovered completely.

Several control experiments were designed to elucidate the possible mechanism of this transformation (Scheme 3). When

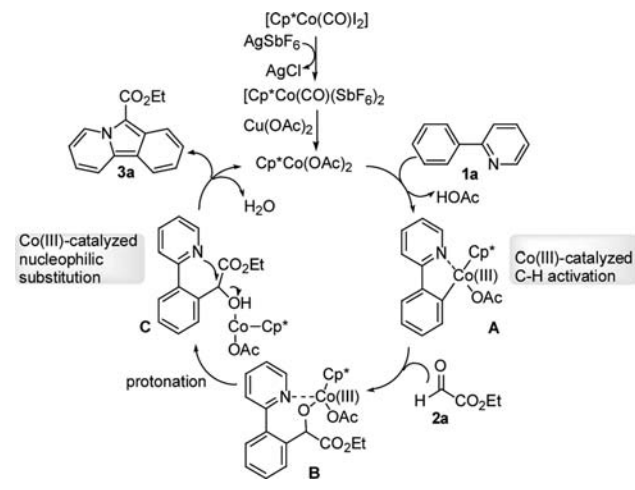
Scheme 3. Preliminary Mechanistic Studies



the cobalt-catalyzed [4 + 1] cycloaddition of 2-phenylpyridine (**1a**) with ethyl oxoacetate (**2a**) was conducted in the Co(III)/Cu(OAc)₂/AgSbF₆ system at 60 °C for 24 h, 3-acylindolizine **3a** and alcohol **4a** were produced in 22% and 13% yields, respectively (eq 1). Considering that the alcohol **4a** was the possible intermediate for this cycloaddition, alcohol **4a** was then subjected to the AgSbF₆/Cu(OAc)₂ system in the absence of a cobalt catalyst at 110 °C for 24 h, and **3a** was formed in 31% yield; the starting material **4a** could be recovered in 62% yield (eq 2). However, treating the alcohol **4a** with the Co(III)/Ag(I)/Cu(II) catalytic system at 110 °C for 24 h afforded a 92% yield of **3a** (eq 3). Moreover, deuterium incorporation at the phenyl C2- and C6-position of 2-pyridylbenzene (**1a**) was also observed in the presence of CD₃OD (eq 4). These results implied that alcohol **4a** belonged to the intermediate for this transformation in which Co(III) salts also played a dual role of transition metal catalyst and Lewis acid. Subsequently, the parallel kinetic experiments from **1a** and **d-1a** ($k_{\text{H}}/k_{\text{D}} = 1.1$) further indicated that aryl C–H bond-breaking was not involved in the rate-limiting step of this transformation (eq 5) (see SI for more details).

Based on the preliminary mechanistic investigations, a plausible mechanism is proposed in Scheme 4. First, [Cp*Co(CO)I₂] catalysts are activated by additives AgSbF₆/Cu(OAc)₂ to form the Co(III) species Cp*Co(OAc)₂^{7,10} which

Scheme 4. Proposed Mechanism



coordinate to pyridine “N” of **1a** to form a five-membered cobaltacycle intermediate **A** via a concerted metalation/deprotonation (CMD) process.¹¹ Subsequently, an insertion of α -keto aldehyde **2a** to a Co–carbonyl bond of intermediate **A** forms the seven-membered Co(III) intermediate **B**, and then intermediate **B** undergoes protonation to give alcohol **C** in which the hydroxymethylene group is activated by a Co(III) Lewis acid. Finally, Co(III)-catalyzed nucleophilic attack of the pyridine nitrogen on the hydroxymethylene carbon leads to the formation of 3-acylindolizine (**3a**) with release of the Co(III) catalyst.

In conclusion, we have developed a novel cobalt-catalyzed [4 + 1] cycloaddition of 2-arylpyridines with aldehydes via a Cp*²–H activation process, in which cobalt catalysts play a dual role as a metal catalyst and Lewis acid. A wide range of 2-arylpyridines and 2-alkenylpyridines are allowed for this transformation, and this method provides concise access to 3-acylindolizines. Excellent functional group tolerance from 2-substituted pyridines is observed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02421.

Detailed experimental procedures, characterization data, copies of ¹H NMR and ¹³C NMR spectra for all isolated compounds (PDF)

Crystallographic data for **3s** (CIF)

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Notes

The authors declare no competing financial interest.

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