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# Co(III)-Catalyzed Annulative Vinylene Transfer via C−H Activation: Three-Step Total Synthesis of 8-Oxopseudopalmatine and Oxopalmatine

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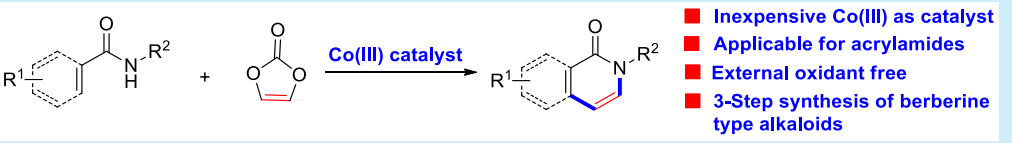


**ABSTRACT:** The Co(III)-catalyzed redox-neutral annulation of benzamides and acrylamides with vinylene carbonate for the synthesis of isoquinolinones and pyridinones has been developed. This protocol employing inexpensive Co(III) as the catalyst tolerated diverse functional groups and substitution patterns, affording the target products with good to excellent yields. The synthetic utility of this transformation was demonstrated by a three-step synthesis of gusanlung D, 8-oxopseudopalmatine, and oxopalmatine.



Isoquinolinones and pyridinones are privileged structural motifs found in natural products, biologically active compounds, and pharmaceuticals (Figure 1).[1] They are also useful reaction intermediates for the synthesis of berberine-type alkaloids bearing a tetrahydroisoquinoline scaffold and piperidine derivatives for drug discovery.[2] Consequently, the development of efficient accesses utilizing easily accessible starting materials to these heterocycles is of continuous interest to the synthetic communities. In this regard, extensive attention has been paid to second-row transition-metal-catalyzed C−H functionalization reactions and substantial progress has been made as well.[3] Specifically, Rh(III) was reported to be the adequate catalyst for converting benzamide analogs to nonsubstituted isoquinolinones by Raw and Bolm and co-workers, who respectively employed vinyl esters and α-chloroacetaldehyde as the acetylene equivalent.[4,5] During the course of our investigation, Miura's research group elegantly unveiled that vinylene carbonate was capable to serve as an acetylene surrogate for the synthesis of nonsubstituted isoquinolinones as well.[6] However, these transformations were mainly based on precious Rh(III) catalyst and limited to the activation of aryl C−H bond affording isoquinolinones. Versatile protocols that allow the rapid assembly of vinylene carbonate[7] to both isoquinolinone and pyridinone cores in a redox-neutral manner via base metal catalyst with latent applications to build complex molecules are still in demand (Figure 2).

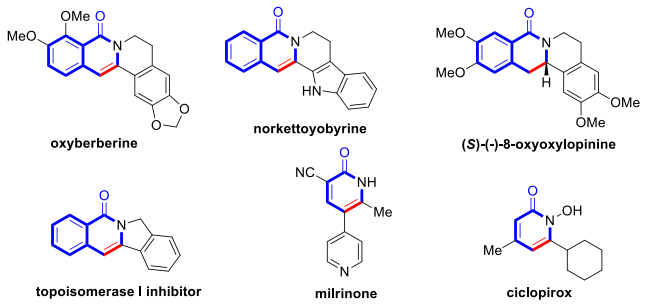


**Figure 1.** Selected important compounds containing isoquinolinone and pyridinone cores.

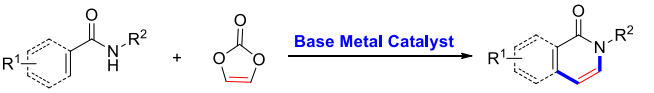


**Figure 2.** Base-metal-catalyzed synthesis of nonsubstituted isoquinolinones and pyridinones.

As an inexpensive first-row transition metal, high-valent cobalt catalyst has displayed enormous potential for the synthesis of heterocycles,[8] such as substituted indoles,[9] furans,[10] quinolines,[11] isoquinolines,[12] and others.[13] Despite these exquisite works, a Co(III)-catalyzed synthesis of nonsubstituted isoquinolinones and pyridinones via a

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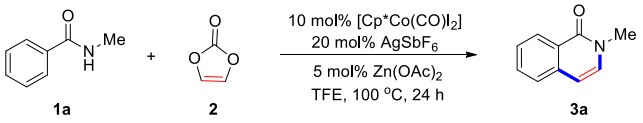
sequential C−H activation/annulative vinylene transfer reaction has not been reported yet. Herein, we describe the Co(III)-catalyzed redox-neutral synthesis of nonsubstituted isoquinolinones and pyridinones with vinylene carbonate. In contrast to the Rh(III) catalytic system,[6] this protocol is regioselective and applicable to acrylamides. Most importantly, by taking the advantage of the Co(III) technology, gusanlung D, 8-oxopseudopalmatine, and oxopalmatine, which are berberine-type alkaloid natural products, were conveniently synthesized through a three-step route.

Initially, the reaction of *N*-methylbenzamide (**1a**) and vinylene carbonate (**2**) catalyzed by Co(III) was selected as a model for the optimization studies. After substantial screening of the reaction conditions, we gratifyingly found that $[Cp^*Co(CO)I_2]$ (10 mol %) in combination of $AgSbF_6$ (20 mol %) was a proper catalytic system to effect the annulation reaction, furnishing the desired isoquinolinone product **3a** in 82% yield with the addition of 5 mol % $Zn(OAc)_2$ as the additive (Table 1, entries 1−2; see Table S1 for more details). Other frequently used additives in Co(III) chemistry, such as LiOAc and HOAc, were inferior (Table 1, entries 3 and 4). The reaction did not take place in most solvents, and TFE was proven to be the best choice (Table 1, entries 5−9). Lowering the catalyst loading to 5 mol % resulted in decreasing the yield to 50% (Table 1, entry 10). The reaction could work at 80 °C and 80% yield was obtained (Table 1, entry 11). The control experiment showed that $[Cp^*Co(CO)I_2]$ as well as $AgSbF_6$ were indispensable for the transformation (Table 1, entries 12 and 13).

**Table 1. Optimization of Reaction Conditions**[a]



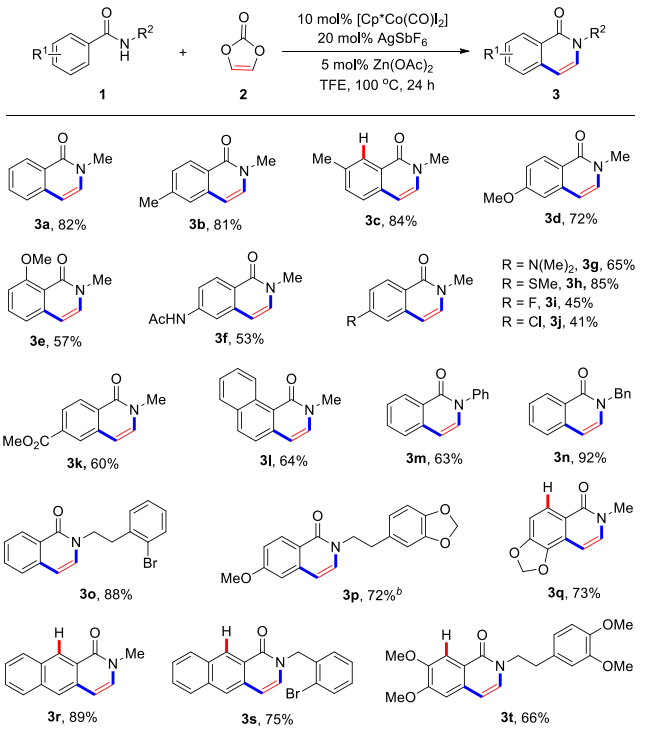

1a 2 3a

| entry | variation from the standard conditions | yield[b] (%) |
|---|---|---|
| 1 | none | 82 |
| 2 | without $Zn(OAc)_2$ | 47 |
| 3 | 20 mol % HOAc instead of $Zn(OAc)_2$ | 70 |
| 4 | 20 mol % LiOAc instead of $Zn(OAc)_2$ | 65 |
| 5 | DCE instead of TFE | 0 |
| 6 | toluene instead of TFE | 0 |
| 7 | dioxane instead of TFE | 0 |
| 8 | EtOH instead of TFE | 0 |
| 9 | DMF instead of TFE | 0 |
| 10 | 5 mol % $[Cp^*Co(CO)I_2]$, 10 mol % $AgSbF_6$, and 2.5 mol % $Zn(OAc)_2$ | 50 |
| 11 | 80 °C instead of 100 °C | 80 |
| 12 | without $AgSbF_6$ | 0 |
| 13 | without $[Cp^*Co(CO)I_2]$ | 0 |

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $[Cp^*Co(CO)I_2]$ (10 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2$ (5 mol %), TFE (2 mL), 100 °C, 24 h. [b]Isolated yields. TFE = 2,2,2-trifluoroethanol.

With the optimized reaction conditions in hand, benzamides bearing different substituents or substitution patterns were examined to clarify the substrate scope of the reaction. As depicted in Table 2, methyl- and methoxy-substituted benzamides were smoothly transformed into the desired products in satisfactory yields (**3b−3e**). The reaction conditions were also compatible with a weak coordinating

**Table 2. Substrate Scope of Benzamides**[a]




[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $[Cp^*Co(CO)I_2]$ (10 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2$ (5 mol %), TFE (2 mL), 100 °C, 24 h. Average of two runs. [b]1 mmol scale, 48 h.

acetamido group, affording the corresponding product in 53% yield (**3f**). The presence of other electron-donating groups in the aryl ring of benzamides, namely *N*,*N*-dimethyl and methylthio substituents, did not affect the transformation (**3g** and **3h**). Benzamides with fluoro, chloro, or ester substituents could participate in the reaction as well, and the target products were obtained in moderate yields (**3i−3k**). Conversion of 1-naphthamide to the annulation product was viable (**3l**). Variation of the substituents on the nitrogen atom of benzamides from methyl to phenyl, benzyl, and substituted phenethyl groups turned out to be successful, providing the designed products in good to excellent yields (**3m−3p**). In addition, the regioselectivity of this transformation was achieved when two reaction sites were available, and eletron-rich or less hindered positions were of priority (**3q−3t**). An indole derivative could not be synthesized from acetanilide under the standard reaction conditions.

This transformation was also applicable to acrylamides (Table 3). Acrylamides having phenyl and fluoro-, chloro-, or bromo-substituted phenyl groups were ideal substrates for the Co(III)-catalyzed annulative vinylene transfer reaction, and pyridinone derivatives were satisfyingly prepared (**4a−4d**). In addition, the reaction was feasible to achieve vinyl amides with two substituents in their double bond, respectively, giving the annulated products in 65% and 64% yields (**4e**, **4f**).

The successful preparation of compound **3o** prompted us to envision the feasibility of the concise synthesis of berberine-type alkaloids from cheap and readily available starting materials using the Co(III)-catalyzed annulative vinylene-transfer reaction (Scheme 1). Benzoylation of 2-(benzo[*d*]-[1,3]dioxol-5-yl)ethanamine followed by the annulation reaction were applied to obtain the key intermediate **5b** for


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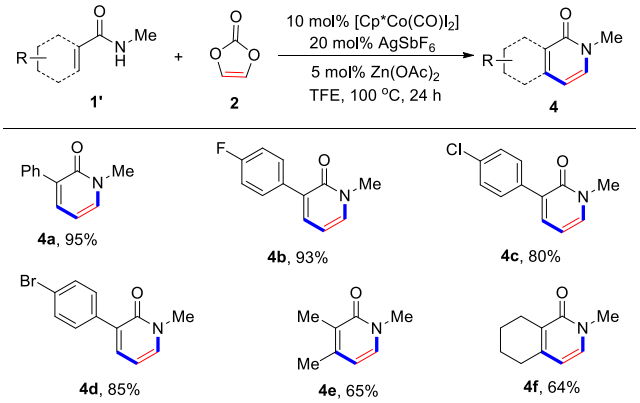
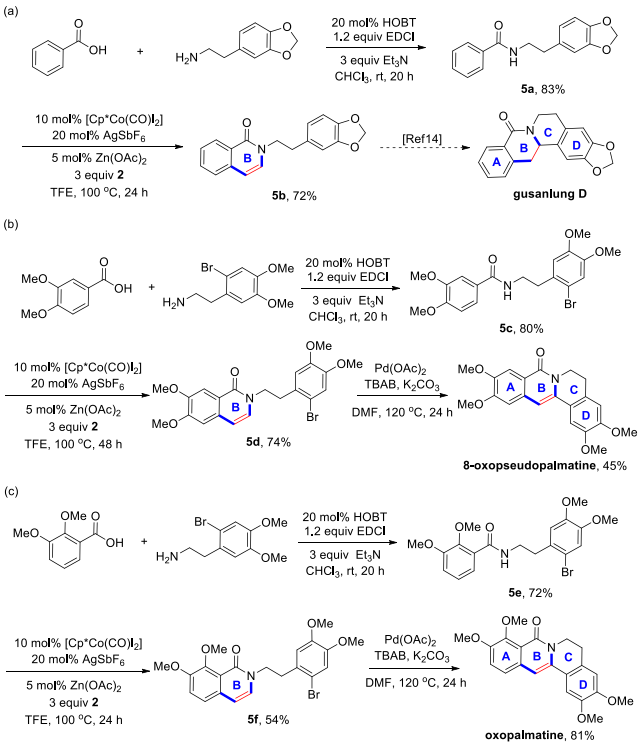
**Table 3. Substrate Scope of Acrylamides**[a]




[a]Reaction conditions: **1′** (0.2 mmol), **2** (0.6 mmol), [Cp*Co(CO)$I_2$] (10 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2$ (5 mol %), TFE (2 mL), 100 °C, 24 h. Average of two runs.

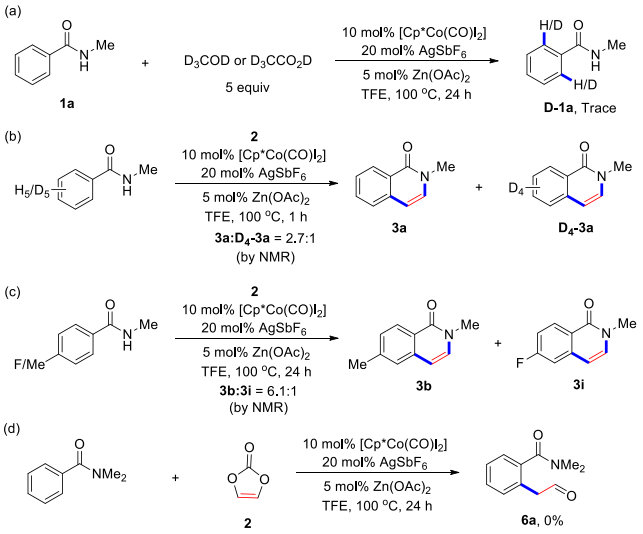
**Scheme 1. Three-Step Synthesis of Gusanlung D, 8-Oxopseudopalmatine, and Oxopalmatine**




gusanlung D synthesis (Scheme 1a).[14] Next, total syntheses of 8-oxopseudopalmatine and oxopalmatine were investigated. We utilized the Co(III) protocol for the construction of B ring again (**5d** and **5f**) and the intramolecular Heck reaction for C-ring closure, and 8-oxopseudopalmatine and oxopalmatine were successfully synthesized by the two-step, sequential ring-closure strategy (Scheme 1b,c). Previously, lengthy synthetic sequences were generally required to access these alkaloids.[2b,6,15]

To probe the reaction mechanism, H/D exchange experiments were carried out first. We did not observe any H/D exchange when 5 equiv of $D_3COD$ or $D_3CO_2D$ was added (Scheme 2a). The KIE value of the reaction was measured to be 2.7, indicating that C−H activation might be the rate-

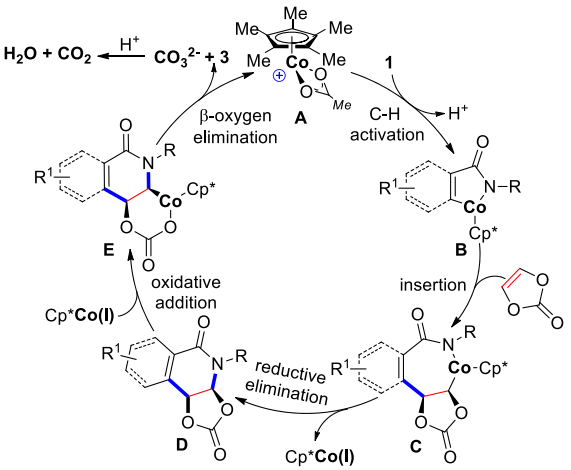
**Scheme 2. Mechanistic Studies**




determination step (Scheme 2b).[16] An intermolecular competition experiment between **1b** and **1i** revealed that the electron-rich benzamide was more reactive than its electron-deficient counterpart, which implied an electrophilic substitution mechanism for C−H cyclocobaltation (Scheme 2c).[17] Finally, under the standard reaction conditions, *N*,*N*-dimethylbenzamide was found to be unreactive (Scheme 2d), and therefore, we excluded the tandem C−H 2-oxoethylation/annulation pathway.

Based on the above observations and previously reported works,[6,7a,8] we proposed a plausible catalytic cycle for the annulative vinylene transfer reaction catalyzed by Co(III) (Scheme 3). Cationic cobalt **A** coordinated with amide **1** and

**Scheme 3. Proposed Mechanism for the Co(III)-Catalyzed Vinylene Transfer Reaction**




an electrophilic attack of the active cobalt to the $sp^2$ C−H bond subsequently occurred, bringing about the formation of a cyclocobaltation intermidiate **B**. Then, a seven-membered metallacycle complex **C** was generated via the insertion of vinylene carbonate into the Co−C bond within **B**. Complex **C** underwent reductive elimination to form intermediate **D** and Cp*Co(I). The presence of two heteroatoms connecting to the same carbon atom in **D** made the carbonate C−O bond adjacent to nitrogen atom fragile, which caused oxidative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addition of the C−O bond to Cp*Co(I), affording fused metallacycle **E**.[18] The product **3** was eventually obtained through $\beta$-oxygen elimination of metallacycle **E** with the concomitant release of the Co(III) catalyst and $CO_3^{2-}$. On protonation, $CO_3^{2-}$ decomposed into $CO_2$ and $H_2O$.

In conclusion, we have devised a straightforward and efficient method to access isoquinolinones and pyridinones via a Co(III)-catalyzed C−H activation/annulative vinylene-transfer reaction. Both aryl ring and nitrogen atom bearing a broad range of functional groups and substitution patterns of amides were found to be proper substrates, affording the target products in good to excellent yields. By using the Co(III) methodology and Heck reaction as the key, the concise three-step total syntheses of 8-oxopseudopalmatine and oxopalmatine were realized. Further applications of this method to facilely prepare key intermediates for the enantioselective total synthesis of other berberine-type alkaloids with a chiral carbon center will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02016.

Detailed experimental procedures, characterization data for all compounds and copies of $^1H$, $^{13}C$ and $^{19}F$ NMR spectra (PDF)

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### Author Contributions

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### Notes

The authors declare no competing financial interest.

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