Cobalt/Rhodium-Catalyzed Diversified Amidation of Benzocyclobutenols via C–C Cleavage under Catalyst and Condition Control

Xingwei Li,* Runze Zhang, Zisong Qi,* Junwei Li, and Lingheng Kong

**ABSTRACT:** Cobalt(III) and rhodium(III)-catalyzed regio- and chemoselective amidation of benzocyclobutenols has been realized using dioxazolone as the amidating reagent to afford three classes of C–N-coupled products via β-carbon elimination of the benzocyclobutenol. The Co(III)-catalyzed coupling initially afforded an isolable o-(N-acylamino)aryl methyl ketone, which could further cyclize to the corresponding indole derivatives under condition control. In contrast, efficient stepwise diamidation has been achieved under Rh(III) catalyst control. The chemoselectivities are jointly controlled by the catalyst and reactions conditions.

In the past decades, increasing attention has been devoted to the selective cleavage and functionalization of C–C bonds because of the abundance of C–C bonds in almost every organic compound. Given the low reactivity and steric hindrance of common C–C bonds, the substrate activation strategy is typically adopted, as in metal-catalyzed C–C activation of strained three/four-membered-rings, which provides a feasible and powerful avenue toward rapid assembly of complicated new scaffolds because of facile scaffold reconstruction. Along this line, great efforts have been devoted to the functionalization of benzocyclobutane and derivatives. Dong and co-workers used the "cut-and-sew" strategy, which involved metal-catalyzed C–C bond functionalization by oxidative addition and coupling with unsaturated reagents. As a direct derivative of benzocyclobutane, benzocyclobutenol also reacted in high activity and regioselectivity in intermolecular reactions via selective cleavage of the C(sp²)–C(sp³) bond. To date, metal-catalyzed C–C activation of benzocyclobutenols has been carried out in three reaction modes (Scheme 1). First, the Orellana group reported Pd-catalyzed regioselective C(sp³)–C(sp³) coupling of benzocyclobutenols with aryl bromides (Scheme 1a-1). Second, Murakami et al. pioneered the Rh(I)-catalyzed C–C activation of benzocyclobutenols en route to intermolecular [4 + 2] annulation with various π-bonds, which affords six-membered ring alcohol (Scheme 1a-2). Since then, extensive studies on C1–C2 cleavage of benzocyclobutens has been realized by Rh(I) catalysis, and annihilation reactions with alkene, alkyl, allene, and isocyanate have been disclosed. This type of coupling has also been extended to intramolecular systems by taking advantage of the resulting ketone moiety. For example, Shi and Song et al. recently realized Rh(I)-catalyzed cyclization of alkene-tethered benzocyclobutenols followed by hydrogentransfer, which results in the formation of benzofurans bearing a 4-β-hydroxy or 4-β-keto moiety (Scheme 1a-3). In the third category, Wang reported in 2014 a Rh(I)-catalyzed [4 + 1] ring expansion of benzocyclobutenol, which utilizes diazoesters as a C1 precursors to afford indanols with an all-carbon quaternary center (Scheme 1a-4).

Most reported results in the C–C activation of benzocyclobutenols have focused on C(sp³)–C(sp³) or C(sp²)–C(sp³) bond formation. In this regard, the applications of benzocyclobutenols toward construction of C-heteroatom bonds would be of great interest. Given the nucleophilic nature of the benzocyclobutenol reagent, we hypothesized the employment of a heteroatom electrophilic reagent that matches the reactivity of the M–C(aryl) bond resulting from β-carbon elimination of a benzocyclobutenol. In that context, 1,4,2-dioxazol-5-one proved highly reactive as a nitrene transfer reagent under Co, Rh, and Ir. In addition, the initial coupling generates a nucleophilic NH group tethered to an electrophilic carbonyl, which may readily undergo cyclization–condensation. We now report the efficient synthesis of three classes of C–N-coupled products in excellent regio- and chemoselectivity that are under catalyst and condition control (Scheme 1b). Initially, the reaction of benzocyclobutenol (1a) with 1,4,2-dioxazol-5-one (2a) was screened to identify the optimal reaction conditions (Table 1). An optimal isolated yield of 91% of product 3aa was obtained when catalyzed by
Scheme 1. C–C Bond Cleavage of Benzocyclobutenols

(a) C–C bond cleavage of benzocyclobutenols for C–C bond formation

(b) This work: C–C bond cleavage of benzocyclobutenols for C–N bond formation

Table 1. Optimization Studies of the Amidation Reaction*

<table>
<thead>
<tr>
<th>entry</th>
<th>variations from conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>91 (91)</td>
</tr>
<tr>
<td>2</td>
<td>[Cp<em>Co(H2)Cl] instead of [Cp</em>CoCl2]</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>[Cp<em>IrCl2] instead of [Cp</em>CoCl2]</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>[p-cymene]RuCl2 instead of [Cp*CoCl2]</td>
<td>N.D.</td>
</tr>
<tr>
<td>5</td>
<td>without [Cp*CoCl2]</td>
<td>N.D.</td>
</tr>
<tr>
<td>6</td>
<td>without additive</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>without Na2CO3</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>Ag2O (0.2) as additive</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>Ag2CO3 (0.2) as additive</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>AgOAc (0.2) as additive</td>
<td>33</td>
</tr>
<tr>
<td>11</td>
<td>without B(OH)3</td>
<td>37</td>
</tr>
<tr>
<td>12</td>
<td>MeCN as solvent</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>THF as solvent</td>
<td>38</td>
</tr>
<tr>
<td>14</td>
<td>DCM as solvent</td>
<td>74</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.1 mmol), 2a (0.15 mmol), [Cp*CoCl2] (4 mol %), and an additive in a solvent (1.0 mL) at 80 °C for 1 h under N2. *The yield was determined by crude 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard; isolated yield is indicated in parentheses. N.D. = not detected.
prolonged reaction time, which suggested that the \(\text{o-}-(\text{N-acylamino})\text{arylmethyl ketones} \) might undergo further cyclization via condensation. The scope of this indole synthesis was then explored (Scheme 3). This transformation was successfully extended to several other dioxazolones and benzocyclobutenols. Dioxazolones with different 3-alkyl groups all reacted well (\(4\text{aa}−4\text{ae}\), \(8−36\) h). Benzocyclobutenol bearing a 1-ethyl group afforded the corresponding indole derivative in 43% yield (\(4\text{ba}\)). Benzocyclobutenols with 6-Cl, 6-Me, and a fused ring all quickly delivered the desired product in satisfactory yield (\(4\text{la}−4\text{na}\), \(3−5\) h). We postulated that this facile condensation was facilitated by the steric effect of these substituents (steric assistance). Significantly, a ring-fused benzocyclobutenol also reacted to deliver the desired product in excellent yield (\(4\text{oa}\)). A phenyl-substituted dioxazolone could also afford the corresponding product \(4\text{af}\), albeit under harsh conditions.

Because of the powerful role of rhodium catalyst in amidation reactions, \(16,18\) an efficient diamidation reaction was realized when catalyzed by \([\text{Cp}^\ast\text{RhCl}_2]\) under rather mild reaction conditions with \(\text{Ag}_2\text{O}\) (0.1 equiv) as an additive (see Scheme 4 and Table S1). With dioxazolone as the limiting reagent, diamidation product \(5\text{aa}\) was isolated in 80% yield.

The formation of this product is interesting because it involved sequential cleavage of a C−C bond and a C(sp\(^3\))−H bond. Variation of the dioxazolones to different 3-alkyl groups (Me, Et, and cyclopropyl) was successful, which afforded the products \(5\text{aa}, 5\text{ab}, \) and \(5\text{ae}\). The presence of alkyl, halo, and fused rings was also well-tolerated (\(5\text{ha}, 5\text{ja}, 5\text{la}, \) and \(5\text{ma}\)) (Scheme 4).

We next performed a series of experimental investigations to explore possible reaction mechanisms (Scheme 5). Control experiments using propiophenone as a substrate failed to give any amidating product under the standard Co-catalyzed conditions. These results indicated that the key cobalt aryl species was formed via C−C bond cleavage rather than C−H bond activation, and no reversible ortho-C−H activation should be involved. The role of the catalyst and/or the additive during the cyclization−condensation process was next examined. Heating a solution of \(3\text{aa}\) in the presence of \([\text{Cp}^\ast\text{CoI}_2]\) or both \([\text{Cp}^\ast\text{CoI}_2]\) and \(\text{B(OH)}_3\) gave product reagent, diamidation product \(5\text{aa}\) was isolated in 80% yield. The formation of this product is interesting because it involved sequential cleavage of a C−C bond and a C(sp\(^3\))−H bond. Variation of the dioxazolones to different 3-alkyl groups (Me, Et, and cyclopropyl) was successful, which afforded the products \(5\text{aa}, 5\text{ab}, \) and \(5\text{ae}\). The presence of alkyl, halo, and fused rings was also well-tolerated (\(5\text{ha}, 5\text{ja}, 5\text{la}, \) and \(5\text{ma}\)) (Scheme 4).

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**Scheme 2. Substrate Scope of the Amidation of Benzocyclobutenols with Dioxazolones**

- **Reactions conditions:**
  - 1 (0.2 mmol), 2 (0.3 mmol), \([\text{Cp}^\ast\text{CoI}_2]\) (4 mol %), \(\text{B(OH)}_3\) (1.0 equiv), and \(\text{Na}_2\text{CO}_3\) (1.0 equiv) in DCE at 80 °C under \(\text{N}_2\); isolated yield.
  - 1 (0.1 mmol), 2 (0.15 mmol), \([\text{Cp}^\ast\text{CoI}_2]\) (4 mol %), and \(\text{Na}_3\text{PO}_4\) (0.2 mmol) at 60 °C in DCM under \(\text{N}_2\); isolated yield.

**Scheme 3. Substrate Scope of Co-Catalyzed Annulation between Benzocyclobutenols and Dioxazolones**

- **Reactions conditions:**
  - 1 (0.2 mmol), 2 (0.3 mmol), \([\text{Cp}^\ast\text{CoI}_2]\) (4 mol %), \(\text{B(OH)}_3\) (1.0 equiv), and \(\text{Na}_2\text{CO}_3\) (1.0 equiv) in DCE at 80 °C under \(\text{N}_2\); isolated yield.

**Scheme 4. Substrate Scope of Diamidation of Benzocyclobutenols with Dioxazolones**

- **Reactions conditions:**
  - 1 (0.2 mmol), 2 (0.2 mmol), \([\text{Cp}^\ast\text{RhCl}_2]\) (2 mol %), and \(\text{Ag}_2\text{O}\) (10 mol %) in DCM at 30 °C under \(\text{N}_2\); isolated yield.

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**Scheme 5. Substrate Scope of Diamidation of Benzocyclobutenols with Dioxazolones**

- **Reactions conditions:**
  - 1 (0.2 mmol), 2 (0.2 mmol), \([\text{Cp}^\ast\text{RhCl}_2]\) (2 mol %), and \(\text{Ag}_2\text{O}\) (10 mol %) in DCM at 30 °C under \(\text{N}_2\); isolated yield.
3aa in 100% yield, while the employment of B(OH)₃ alone only gave cyclization product 4aa in 55% yield (Scheme 5b). No conversion was observed when Na₂CO₃ alone was used. These observations highlighted the primary Lewis acidic nature of the Co catalyst in the cyclization of o-(N-acylamino)-aryl methyl ketones. To further explore the mechanistic details of the cyclization, we graphed the yield-time distribution curves of 3ae and 4ae by ¹H NMR analysis (Supporting Information). Initially, 3ae was generated in a short time. As the reaction proceeded, it subsequently decayed with the increase in the amount of 4ae, thereby indicating the intermediacy of 3ae.

To further explore the mechanistic details of the diamidation system, an equimolar mixture of 3aa and 2aa was allowed to react under the standard conditions, from which complex 5aa was isolated in 43% yield. This result indicated a sequential diamidation approach (Scheme 5c). In contrast, no diamidation product was detected in the absence of [Cp²*RhCl₂]₂, which suggested the important role of Rh(III) in the second amidation. A crossover experiment using benzocyclobutenol 1a and two distinguishable dioxazolones verified that the diamidation reaction is stepwise because two corresponding crossover products (8 and 9) were generated (see Figure S1, Supporting Information).

Synthetic applications have been performed (see the Supporting Information for details). Scale-up reaction of 1a and 2a afforded the corresponding product 3aa in 73% yield. Transformations of indole 4aa were also conducted to showcase its synthetic utility. The C–H alkenylation reaction of 4aa with an alkynyl bromide afforded 6 in 97% yield, and the oxidation reaction of 4aa provided nitrile 7 in 58% yield.

A catalytic cycle is proposed in Scheme 6 on the basis of the above reaction results and related reports. An alkoxide intermediate A is generated via ligand exchange between Cp²*Co(III) and 1a in the presence of a base, which is then proposed to undergo regioselective β-C elimination to give a Co–C(sp²) species B. Coordination of 2aa and subsequent decarboxylation deliver a nitrene intermediate C, possibly with the assistance of B(OH)₃. Migratory insertion of the Co–C bond into the nitrene unit is proposed to give intermediate D, again with possible assistance of the B(OH)₃₃ additive. Protonolysis of intermediate D furnishes the final product and regenerates the catalyst.

In conclusion, we disclosed diversified amidation reactions between benzocyclobutenol and dioxazolone via Co(III)- or Rh(III)-catalyzed C–C bond cleavage. Three classes of C–N-coupled products have been selectively obtained in moderate to excellent efficiency via β-carbon elimination of the benzocyclobutenol. The Co(III)-catalyzed coupling initially afforded an isolable o-(N-acylamino)aryl methyl ketone, which could further cyclize to the corresponding indole derivatives under condition control. In contrast, efficient stepwise diamidation has been attained under Rh(III) catalyst control. Overall, the chemoselectivities are jointly controlled by the catalyst and reaction conditions. The generation of reactive metal–carbon species using other common substrates is underway in our laboratories, which may offer new possibilities for the synthesis of complex scaffolds.

### ASSOCIATED CONTENT

#### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01788.

Detailed experimental procedures, characterization of new compounds, and copies of NMR spectra (PDF)

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Notes
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References


