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Ru-catalyzed decarboxylative cyclization of mandelic acids with acrylates: facile access to phthalide skeleton

Lili Chen, Hongji Li, Feng Yu, and Lei Wang

A new protocol for Ru-catalyzed decarboxylative cyclization of mandelic acids with acrylates was firstly established that allows the efficient construction of phthalide skeleton. Interestingly, this reaction underwent a decarboxylative process, in which only divinylation was observed and the subsequent cyclization led to the formation of phthalides.

Arguably, the decarboxylative couplings in recent years have emerged as one of the most attractive and powerful tools for the formation of C–C and C–heteroatom bonds in organic synthesis. Generally, the decarboxylative reaction often employ carboxylic acids as substrates, and the new C–C bonds would be formed with extrusion of CO$_2$ gas. Recently, much progress has been made on the transition metal-catalyzed decarboxylative couplings. Of them, the transition metal catalysts, such as Pd, Ni, Cu, Ag and Rh salts, have been demonstrated high efficiency in the decarboxylative coupling reactions and similar to the bimetal catalysts including Pd/Cu and Pd/Ag. For instance, Myers et al. firstly reported a Pd-catalyzed decarboxylative Heck-type coupling of olefin with arene carboxylic acids. Then Goossen, Glorius, Liu, Forgione, Crabtree, and others showed us a number of elegant results on the transition metal-catalyzed decarboxylative cross-coupling reactions. In addition, we found that the acidic substrates used in the above catalytic system mainly includes activated carboxylic acids, such as oxoacids, diphenylacetic acids, and polyfluorobenzoic acids, heteroaromatic carboxylic acids. Among these, the decarboxylative couplings of α-keto acids with other reagents have been extensively studied. For selected examples, Goossen et al. discovered the decarboxylative cross-coupling of α-ketone carboxylic acid with aryl bromides in Cu/Pd bimetallic system (Scheme 1, eq. 1). In 2010, Ge and co-workers reported a Pd-catalyzed intermolecular decarboxylative dehydrogenative cross-coupling of N-phenylacetamides with α-keto acids (eq. 2). Then a Ni-catalyzed decarboxylative cross-coupling of α-ketone carboxylic acid with benzoxazoles was developed by the same group (eq. 3). Inspired by these works, some recent results reported by Kim, Duan, Tan, Wang and our group also showed the high activity of α-ketone acid, and which presented an alternative way to synthesize ketone derivatives.

It should be noted that Lei and co-workers recently realized the first decarboxylation/oxidative amidation of α-keto acids with amines by taking the advantage of visible light with the assistance of photocatalyst (Scheme 1, eq. 4). To our knowledge, the Ru and its complexes have been rarely studied in the decarboxylative coupling reactions.

Scheme 1. Decarboxylation of α-keto acid and mandelic acids

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Mandelic acid and its derivatives are widely distributed in nature. As important materials, they have been broadly used as pharmaceuticals, agrochemicals, dyeing and flavouring agent in industry. Up to date, multiple methods have been established for the synthesis of mandelic acids, including traditional chemical synthesis, isolation from natural sources and preparation by using an enzymatic biochemical process. In light of the above facts, we envision that mandelic acids may undergo a normal decarboxylative process in particular environment, and the formed intermediate would react with other appropriate agents to realize some possible cross-coupling reactions. Based on our recent work on the transition metal-catalyzed decarboxylations, herein we will firstly report a Ru-catalyzed decarboxylative cyclization of mandelic acids with activated acrylics to generate phthalid derivatives in good yields (Scheme 1, eq. 5). It is important to note that the carbonyl group in mandelic acid acts as directing group, and subsequently as leaving group in the reaction.

Firstly, 2-hydroxy-2-phenylacetic acid (1a) and ethyl acrylate (2a) were chosen as model substrates for the optimization of reaction conditions, described in Table 1 (DMF should be dried and distilled prior to use in this investigation). It was found that the Ru salts, such as RuCl₃·nH₂O and Ru(PPh₃)₃Cl₂, did not work under the standard reaction conditions (entries 1 and 2). To our delight, employing [Cp*RuCl₃], as catalyst allows the efficient reaction of 1a with acrylates with low boiling point, such as ethyl acrylate and methyl acrylate, reacted with 2-hydroxy-2-phenylacetic acid (1a), providing the lower yields of corresponding products (3aa and 3ab). In contrast, most of the acrylics with high boiling point gave the satisfactory yields of the desired products (3ac–ag). Unfortunately, the reaction of phenyl acrylate and 4-chlorophenyl acrylate with 1a gave 3ah in 56%, and 3ai in 45% yields, respectively.

### Table 1. Optimization of Ru catalyst, oxidant and additive

<table>
<thead>
<tr>
<th>entry</th>
<th>Ru source</th>
<th>oxidant</th>
<th>additive</th>
<th>yield [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>RuCl₃·nH₂O</td>
<td>Cu(OAc)₂</td>
<td>/</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Ru(PPh₃)₃Cl₂</td>
<td>Cu(OAc)₂</td>
<td>/</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>[Cp*RuCl₃]</td>
<td>Cu(OAc)₂</td>
<td>/</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>[RuCl₃]₂</td>
<td>Cu(OAc)₂</td>
<td>/</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>[RuCl₃]₂</td>
<td>Cu(OAc)₂</td>
<td>/</td>
<td>n.r.</td>
</tr>
<tr>
<td>6</td>
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<td>nH₂O</td>
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</tr>
<tr>
<td>7</td>
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<td>AgSbF₅</td>
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<tr>
<td>8</td>
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<td>Cu(OAc)₂</td>
<td>KPF₆</td>
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<tr>
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<td>Cu(OAc)₂</td>
<td>NaBF₄</td>
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<tr>
<td>10</td>
<td>[RuCl₃]₂</td>
<td>/</td>
<td>/</td>
<td>n.r.</td>
</tr>
<tr>
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<td>[RuCl₃]₂</td>
<td>TBHP</td>
<td>/</td>
<td>n.r.</td>
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<td>BQ</td>
<td>/</td>
<td>n.r.</td>
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<tr>
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<td>Ag₂CO₃</td>
<td>/</td>
<td>n.r.</td>
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<tr>
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<td>AgOAc</td>
<td>/</td>
<td>n.r.</td>
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<tr>
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<td>Ag₂O</td>
<td>/</td>
<td>n.r.</td>
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<tr>
<td>16</td>
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<td>PhI(OAc)₂</td>
<td>/</td>
<td>n.r.</td>
</tr>
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<td>17</td>
<td>[RuCl₃]₂</td>
<td>Cu(OAc)₂</td>
<td>1.1 equiv</td>
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<td>Cu(OAc)₂</td>
<td>1 equiv</td>
<td>37%</td>
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<tr>
<td>19</td>
<td>[RuCl₃]₂</td>
<td>Cu(OAc)₂</td>
<td>0.22 mmol</td>
<td>68%</td>
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<tr>
<td>20</td>
<td>[RuCl₃]₂</td>
<td>Cu(OAc)₂</td>
<td>0.01 mmol</td>
<td>36%</td>
</tr>
</tbody>
</table>

a. Reaction conditions: 2-hydroxy-2-phenylacetic acid (1a, 0.20 mmol, excess), ethyl acrylate (2a, 0.20 mmol), Ru complex (0.01 mmol, containing Ru 5.0 mol%), Cu(OAc)₂ (0.22 mmol), DMF (1.0 mL), 110°C in air for 12 h. b. Isolated yield. c. N₂, 90 °C, 130 °C. d. 1a/2a = 1:2. e. 1a/2a = 2:1. Cp* = pentamethylcyclopentadienyl, L = p-cymene. n.r. = no reaction.

Scheme 2. Substrate scope of acrylates

![Scheme 2. Substrate scope of acrylates](image-url)

**Reaction conditions:** 2-hydroxy-2-phenylacetic acid (1a, 0.20 mmol), acrylate (2, 0.20 mmol), [Ru] = [Ru(p-cymene)Cl₂]. (0.01 mmol, containing Ru 5.0 mol%), Cu(OAc)₂ (0.22 mmol, 1.1 equiv), DMF (1.0 mL), 110°C, air, 12 h. **Isolated yields.**
the in situ formed CO decarboxylative cyclization. In addition, we successfully detected carboxylic and hydroxyl group is extremely important to realize this application of decarboxylative reactions is currently underway. We have demonstrated a new route to construct the phthalide skeleton from the reaction of mandelic acids with acrylates. To the best of our knowledge, this work is a first example referring to Ru-species I, forming Ru-complex II. The migratory insertion of ethyl acrylate (2a) with II and reductive elimination twice led to the formation of intermediate III, IV, V and I [Ru(O2CMe)2(p-cymene)]. On the other hand, the V lost CO2 and resulted into the formation of VI.6 Although VI was not isolated, a significant molecular ion peak presented the possible structural information (Fig. S2, ESI†). Finally, intramolecular cyclization of VI afforded the product 3aa.

We have demonstrated a new route to construct the phthalide skeleton from the reaction of mandelic acids with acrylates. To the best of our knowledge, this work is a first example referring to Ru-catalyzed decarboxylative reaction, which features the only divinylation and final cyclization. Control experiments, CO2 detection by IR and trapping intermediate by high resolution mass spectrum support this decarboxylative cyclization process. Further application of decarboxylative reactions is currently underway.

This work was financially supported by the National Science Foundation of China (No. 21172092).

Notes and reference

Thus, a possible mechanism for the reaction was proposed in Scheme 5. 2-Hydroxy-2-phenylacetic acid (1a) was initially oxidized into 2-oxo-2-phenylacetic acid,40 which next coordinated to Ru-species I, forming Ru-complex II. The migratory insertion of ethyl acrylate (2a) with II and reductive elimination twice led to the formation of intermediate III, IV, V and I [Ru(O2CMe)2(p-cymene)]. On the other hand, the V lost CO2 and resulted into the formation of VI.6 Although VI was not isolated, a significant molecular ion peak presented the possible structural information (Fig. S2, ESI†). Finally, intramolecular cyclization of VI afforded the product 3aa.

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‡ Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/


