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Coupling of carboxylic acids with internal alkynes by supported ruthenium catalysts: Direct and selective syntheses of multi-substituted phthalide derivatives

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Supported ruthenium catalysts promotes coupling of various kinds of aromatic carboxylic acids with internal alkynes, giving the corresponding multi-substituted phthalide derivatives in high yields. The supported Ru catalyst can be recycled at least five times with no loss of activity.

Isobenzofuranone, commonly termed as phthalide, often can be found in natural products that show a broad range of important bioactivities, such as antibacterial, anti-HIV, antifungal, antibiotic, antitumor and immunosuppressive activity.\textsuperscript{1} Various methodologies to obtain phthalides utilizing organic syntheses have been reported,\textsuperscript{2} many of them were, however, achieved through multistep reactions. Novel synthetic route that realizes facile and direct construction of phthalide moieties remains to be explored.

Carbon-carbon bond forming reactions involving cleavage of less-reactive carbon-hydrogen bonds has attracted much interest from the consideration of atom-economical synthesis.\textsuperscript{3} Thanks to recent remarkable progress in C-H bond functionalization by transition-metal catalysts, rapid and selective construction of carbon skeletons has become made available. So far, oxidative coupling of benzoic acids with electron-deficient alkenes pioneered by Miura and Satoh should be regarded as one of the most straightforward route to the syntheses of phthalides.\textsuperscript{4} The oxidative coupling of benzoic acids with internal alkynes is also reported to produce six membered lactones, namely, isocoumarins.\textsuperscript{5} Such dehydrogenative C-C coupling strategies, however, have an inevitable problem with the fact that they require the addition of stoichiometric oxidant, such as copper or silver salt. The development of novel method that can avoid the formation of unwanted byproduct is, therefore, highly desired. Also, efficient organic transformation with recyclable supported catalysts is important from the perspective of green and sustainable chemistry. This work introduces a novel, straightforward and recyclable synthesis of phthalide derivatives using supported ruthenium catalysts.

**Table 1.** Ru-catalysed reaction of o-toluic acid (1a) with 1-phenyl-1-propyne (2a)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>additive</th>
<th>3a</th>
<th>3a'</th>
<th>4a</th>
<th>4a'</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuZrO\textsubscript{2}</td>
<td>KOAc</td>
<td>93</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>RuCeO\textsubscript{2}</td>
<td>KOAc</td>
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<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>RuV\textsubscript{2}O\textsubscript{5}</td>
<td>KOAc</td>
<td>59</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>RuSiO\textsubscript{2}</td>
<td>KOAc</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>RuAl\textsubscript{2}O\textsubscript{3}</td>
<td>KOAc</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>RuTiO\textsubscript{2}</td>
<td>KOAc</td>
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<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>[RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}</td>
<td>KOAc</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>RuZrO\textsubscript{2}</td>
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<td>0</td>
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<td>1</td>
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<tr>
<td>9</td>
<td>RuZrO\textsubscript{2}</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
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<td>0</td>
<td>4</td>
<td>3</td>
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<tr>
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<td>RuZrO\textsubscript{2}</td>
<td>HCO\textsubscript{2}Na</td>
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<td>0</td>
<td>3</td>
<td>7</td>
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<tr>
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<td>RuCeO\textsubscript{2}</td>
<td>HCO\textsubscript{2}Na</td>
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<td>0</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>RuZrO\textsubscript{2}</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction conditions: (1) 1a (1.0 mmol), 2a (1.3 mmol, Ru catalyst (0.03 mmol as Ru), base (0.15 mmol), mesitylene (1.0 mL), at 170 °C, 24 h, under Ar. (2) MeI, K\textsubscript{2}CO\textsubscript{3}, DMF at rt. \textsuperscript{b} Yields were determined by GLC based on 1a.

**Scheme 1.** Transition-metal catalysed functionalization of benzoic acids.
Although Rh- or Ru-catalysed coupling of benzoic acids with potassium or sodium salts resulted in good yields of the products. A trace amount of CeO₂ was added to a methanol solution of [RuCl₂(p-cymene)]₂ at room temperature. After impregnation, the resulting powder was calcined at 400 °C in air to afford supported Ru catalyst. The loading of ruthenium was 2.0 wt%.

The reaction of o-toluic acid (1a) with 1-phenyl-1-propyne (2a) by the use of Ru/ZrO₂ with a catalytic amount of potassium acetate in mesitylene at 170 °C for 24 h produced phthalide 3a in the yield of 93%. A trace amount of o-alkenylated esters 4a and 4a' were formed as byproducts (Table 1, entry 1). The reaction was catalysed by CeO₂ and Y₂O₃-supported Ru catalysts, generating 3a in a moderate or a good yield (entries 2 and 3). However, Ru catalysts supported on SiO₂, Al₂O₃ or TiO₂ did not show sufficient activities [5]. The reaction with [RuCl₂(p-cymene)]₂ as a homogeneous catalyst could also produce 3a, but its yield was lower than one with Ru/ZrO₂ (entry 7). What is noteworthy is that regioisomer 3a' was not obtained at all in all cases. In the absence of base (entry 8), no product was obtained, which indicated that a catalytic amount of base was necessary for this reaction. Among the bases examined, potassium or sodium salts resulted in good yields of the products. Although Rh- or Ru-catalysed coupling of benzoic acids with internal alkynes in the presence of Cu(OAc)₂ as an external oxidant has been known to produce isocoumarin derivatives exclusively [6], no isocoumarins was observed under any conditions, in our supported Ru catalyst system.

Table 2. Scope of substrates

![Image](334x298 to 557x449)

Under the optimized reaction conditions, the coupling of various kinds of aromatic acids with internal alkynes was investigated by using Ru/ZrO₂ or Ru/CeO₂ catalysts (Table 2). The reactions of benzoic acids having methyl substituent at ortho-position proceeded efficiently to produce the corresponding phthalides 3b-3e in a good or a high yield. 1-Naphthoic acid and 2-biphenylcarboxylic acid could participate in the present catalytic system to produce 3f and 3g in high yields. The reaction of benzoic acid having fluoro substituent at ortho-position resulted in a moderate yield of 3h. The reactions of meta- or para methyl substituted benzoic acids were also carried out and the corresponding products (3i and 3j) were obtained in moderate to good yields. Furthermore, unsymmetrical internal alkynes other than 2a were employed in this reaction to produce the corresponding phthalide (3k-3m) in moderate to good yields. Note that the reactions of unsymmetrical internal alkynes proceeded with high regioselectivities and only a trace amount of byproducts (4 or 4', < ca. 5% yield) were formed in each reaction. Even if longer period of reaction was required, desired product 3n was obtained from bisarylacetylene in a high yield.

Figure 1 shows the time course of the coupling reaction of 1a with 2a by the use of Ru/ZrO₂ under the condition shown in the table 1, entry 1. At the initial stage of the reaction, 4a was rapidly formed. After 3 h, the formation of final product 3a and the decreasing yield of 4a were observed. These results clearly indicate that the formation of phthalide 3a was achieved through regioselective addition of aromatic C-H bond to internal alkynes followed by nucleophilic intramolecular cyclization [4,13]. Although a small amount of 4a' was formed, subsequent cyclization leading to 3a' did not occur.

![Image](356x380)

Figure 1. Time-course of the reaction of 1a with 2a; yield of 3a(○), 4a(□) and 4a'(▲)

To get information about the reaction mechanism, deuterium labeling experiment was carried out. When aromatic acid 1d was treated with D₂O in mesitylene at 170 °C for 24 h, significant deuterium incorporation at ortho-position of 1d was observed.

![Image](409x167 to 438x183)

Scheme 2. Deuterium labeling experiment

![Image](420x468)
Scheme 3. Intermolecular competition experiment with alkyne 2a.
(Scheme 2, eq 1). This suggests that the reaction includes reversible ortho-ruthenation step. When the reaction of 1b with 2a was performed by the use of D2O, desired product 3b was obtained in 58% isolated yield, and 68% of methylene group hydrogen of the formed phthalide 3b was deuterated (Scheme 2, eq 2). Intermolecular competition experiment was also conducted. As is shown in Scheme 3, benzoic acid with electron-donating substituent was preferentially converted to corresponding phthalide, suggesting that electrophilic C-H bond cleavage was the rate-determining step. From these results, a possible reaction mechanism shown in Scheme 4 is proposed. Our previous study revealed the formation of a RuIV-oxo species after the reactions. After the reaction of 1a with 2a for 24 h by the fresh Ru/ZrO2 catalyst, the amount of ruthenium species leaching into the solution was only 1.17 μmol as Ru (3.9% of the ruthenium species in the fresh catalyst).

Table 3. Recyclability of Ru/ZrO2

<table>
<thead>
<tr>
<th>cycle</th>
<th>amount of Ru/ZrO2 (ng)</th>
<th>3a</th>
<th>4a</th>
<th>4a'</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>88</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>291</td>
<td>89</td>
<td>0</td>
<td>4</td>
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<tr>
<td>3</td>
<td>285</td>
<td>91</td>
<td>1</td>
<td>3</td>
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</tr>
<tr>
<td>5</td>
<td>271</td>
<td>94</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

* Reaction conditions: (1) 1a (2.0 mmol), 2a (2.6 mmol), Ru/ZrO2 (0.060 mmol as Ru), KOAc (0.30 mmol), mesitylene (2.0 mL), at 170 °C, 24 h, under Ar. (2) MeI, K2CO3, DMF at rt.

Conclusions

We have developed direct and regioselective synthesis of multi-substituted phthalide derivatives through Ru/ZrO2-catalysed addition of aromatic carboxylic acid to internal alkynes and subsequent intramolecular cyclization. The reaction requires no addition of metallic oxidant. The supported Ru catalyst shows excellent activities and environmental compatibility resulting from their high recyclability and low contamination of products by metallic species. Further investigation of mechanistic insight and development of novel catalytic reaction are underway in our laboratory.

Notes and references

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After catalytic runs, products were esterized using methyl iodide and potassium carbonate to quantitate the resulting acids by flame ionization detector (FID) gas chromatography.

Similar trends were observed in our previous studies on organic transformations with supported Ru catalysts. Detailed analyses of supported Ru catalysts are shown in Supplementary information.


Removal of the supported ruthenium catalyst by the hot filtration through a polytetrafluoroethylene (PTFE) filter (pore size 0.45 µm) after the reaction for 3 h partly retarded further progress of reaction of 1a and 2a (Figure S1 in the Supplementary information), which indicates that a small contribution of soluble ruthenium species to the catalysis.

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