Rh(I)-Catalyzed [5 + 1] Cycloaddition of Vinylcyclopropanes and CO for the Synthesis of α,β- and β,γ-Cyclohexenones

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ABSTRACT

Transition-metal-catalyzed cycloadditions (annulations) via coordination, oxidative addition, insertion, and reductive elimination processes provide powerful approaches to synthesize various sized ring compounds, which range from three- to nine-membered carbocycles. Despite this, developing new transition-metal-catalyzed cycloadditions that can expand, complement, or even surpass the reported ones is still highly demanded, considering the possible different skeletons, substitutions, and stereochemistry of the target molecules. Among them, developing metal-catalyzed cycloadditions to synthesize six-membered nonbenzenoid carbocycles is one of the most actively pursued research fields, because six-membered nonbenzenoid carbocycles are the most ubiquitous ring compounds in organic chemistry. Until now, some


(3) (a) See refs in 1a and 3b–3g. For selected examples, see: (b) Wender, P. A.; Jenkins, T. E.; Suzuki, S. J. Am. Chem. Soc. 1995, 117, 1843.


(9) For reports of hetero-[5 + 1] reactions, see: (a) Kamitani, A.; Chatani, N.; Morimoto, T.; Murai, S. J. Org. Chem. 2000, 65, 9230. (b) ref 4g.
elegant transition-metal-catalyzed cycloadditions, for example, the metal-catalyzed \([3 + 3]\),\(^2\) \([4 + 2]\),\(^3\) \([5 + 1]\),\(^4\) \([2 + 2 + 2]\),\(^5\) \([3 + 2 + 1]\),\(^6\) and \([4 + 1 + 1]\)\(^7\) reactions, have been developed for the synthesis of six-membered carbocycles. In particular, the metal-mediated or catalyzed \([5 + 1]\) reactions of vinylcyclopropanes (VCPs)\(^3\) or allenylcyclopropanes\(^5\) with CO are of synthetic significance, due to the easy preparation of the substrates and generation of various functionalized cyclohexenones. The \([5 + 1]\) reactions of vinylcyclopropanes and CO can be mediated by Fe(CO)\(_5\) under photoirradiation (developed by Sarel\(^8\)).\(^{4a}\) General cationic Rh(I) complex-catalyzed \([5 + 1]\) reactions of VCPs were reported by de Meijere’s group, only very special VCP substrates can be used.\(^{4a}\)\(^{,b}\) Elegant transition-metal-catalyzed cycloadditions, for example, metal-catalyzed \([2 + 2 + 2]\) cycloadditions, have been developed if CO was introduced to the reaction system.\(^{4c}\)\(^,d\)

The importance of the \([5 + 1]\) reaction of vinylcyclopropanes and CO to synthesize both allenylcyclopropanes, which then produce the \([5 + 1]\) cycloadducts, under the same catalytic condition. The importance of the \([5 + 1]\) reaction of vinylcyclopropanes and CO has been demonstrated by its application to the synthesis of various functionalized cyclohexenones.\(^{4f}\)\(^d\)\(^,e\) In particular, the metal-mediated or -catalyzed \([5 + 1]\) cycloaddition of allenylcyclopropanes and CO can be catalyzed by either Co catalyst (developed by Iwasawa\(^8\)) or Ir complex (developed by Murakami\(^9\)).\(^{4b}\) Very recently, Tang and co-workers developed a Rh-catalyzed tandem 1,3-acyloxy migration/\([5 + 1]\) cycloaddition reaction to produce highly functionalized cyclohexenones.\(^{5d}\) In Tang’s reaction, the key step is the Rh-catalyzed 1,3-acyloxy migration of propargyl esters to give allenylcyclopropanes, which then produce the \([5 + 1]\) cycloadducts under the same catalytic condition. The importance of the \([5 + 1]\) reaction of vinylcyclopropanes and CO has been demonstrated by its application in total synthesis by Taber’s group.\(^{13}\) Even though the Rh-catalyzed \([5 + 1]\) reaction of in situ generated allenylcyclopropanes and CO by Tang and co-workers has broad scope, the \([5 + 1]\) reaction of VCPs and CO catalyzed by Rh has not been developed into a general one. In the reported \([5 + 1]\) reaction of VCPs and CO catalyzed by [Rh(CO)\(_2\)]

We first used an \(\alpha\)-yne–VCP substrate to test this proposal. However, cycloisomerization still took place instead of the designed \([3 + 2 + 1]\) cycloaddition (Scheme 1a). To our surprise, when the standard \(\alpha\)-yne–VCP substrate 1a was tested in the presence of CO, \([5 + 1]\) cycloaddition occurred, affording both \(\beta,\gamma\)- and \(\alpha,\beta,\gamma\)-cyclohexenones.\(^{2b}\)\(^,\)\(^a\) To improve the \([5 + 1]\) reaction yield and the selectivity between \(\alpha,\beta\)- and \(\beta,\gamma\)-cyclohexenones, we further screened the reaction conditions, using the more easily accessible substrate 1b (Table 1). To our delight, under the catalysis of [Rh(dpdp)][SbF\(_6\)], the total yield was high, even though the selectivity was not very good. In this case, 41% of the \(\beta,\gamma\)-cyclohexenone 2b and 34% of the \(\alpha,\beta\)-unsaturated product 3b were generated (entry 1). Both neutral [Rh(CO)\(_2\)]\(_2\) (this is effective in some special substrates shown by de Meijere and Kurahashi\(^8\)) and cationic [Rh(CO)\(_2\)][SbF\(_6\)] failed to promote the desired cycloaddition (entries 2 and 3). We then tested a few other bidentate phosphine ligands and found that the yields became lower (entries 4–6). In particular, the standard reaction condition of the \([3 + 2]\) cycloaddition was not suitable for the \([5 + 1]\) reaction at all, giving no product (entry 4). We found that the presence of 4 \(\AA\) molecular sieves (MS) was essential to this reaction because the yield was much lower.

**Scheme 1.** (a) Our Previous Report of \(\alpha\)-Ene/Yne-VCP and (b) Observed \([5 + 1]\) Cycloaddition

(a) Our previous report

(b) This work

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without this additive (entry 7). Screening of the reaction temperature and the pressure of CO gave no better results (entries 8–11). Notably, 1 atm of CO is not beneficial to the [5 + 1] reaction (entry 10). To our delight, using AgOTf instead of AgSbF6 can improve the selectivity of the β,γ-unsaturated product 2b (66% yield), together with 12% of the α,β-unsaturated product 3b (entry 12). When the solvent was changed to DME or dioxane, the result became worse (entries 13 and 14). To obtain the α,β-cyclohexenone exclusively, DBU (1,8-diazabicyclo[5.4.0]undec-7-one) was added to the reaction system at room temperature after the accomplishment of the [5 + 1] cycloaddition. After 1 h, only a single product 3b was obtained in 73% yield through the isomerization procedure (entry 15). If the catalyst loading was reduced to 5 mol %, the reaction yield decreased sharply (entry 16).

We selected two conditions as the optimal conditions to explore the substrate scope of the [5 + 1] reaction: conditions A (using [Rh(dppp)]OTf as the catalyst to obtain the β,γ-unsaturated product 2 as the major product) and conditions B (using [Rh(dppp)]SbF6 for VCPs without substituents on the cyclopropyl rings) or [Rh(dppp)]OTf (for VCPs with substituents on the cyclopropyl rings) as the catalyst, and then treating the [5 + 1] system with DBU to obtain the α,β-unsaturated product 3 exclusively. See the Supporting Information for a detailed discussion (Tables 2 and 3). Besides the neutral phenyl group, both electron-donating and electron-withdrawing substituents can be tolerated in the cycloaddition (entries 2, 3 and 5). The more hindered substrates 1d and 1g also afforded the desired products in good yields (entries 4 and 7). In addition, a heterocyclic aryl-substituted substrate can also give a moderate yield (entry 6). Moreover, the R group could be alkyl substituents (entries 1 and 8–10). The [5 + 1] cycloaddition was not affected even if there was an alkene substituent or an acidic hydrogen in the substrates (entries 1 and 10). The [5 + 1] product of substrate 1j decompose; therefore, TsOH·H2O was used instead to give a good yield of the isomerized product (entry 10).
The substrates could have other different substitution patterns (Table 3). Both 1-phenyl- and benzyloxyethyl-VCP (1k, 1l) could afford the \( \beta,\gamma \)-unsaturated products exclusively under conditions A, in moderate to good yields (entries 1 and 2). At the same time, \( cis \)-2-benzyloxyethyl-VCP (1m) could be changed to a TBS (\( tert \)-butyldimethylsilyl) group, and even unprotected alcohols can be tolerated in the cycloadition (entries 4–6). In the reactions of substrates 1m–o, the cyclopropanes were cleaved on the less hindered monosubstituted C–C bonds; therefore, only one kind of [5 + 1] cycloaddition product was observed. Compared with substrate 1o, the [5 + 1] reaction of its \( trans \)-isomer 1o gave two cyclopropane cleavage products 2o and 2o with a total yield higher than that in the reaction of 1o. The reaction of the substrate 1p, which has a six-membered ring fused with the VCP and has the vinyl group at the bridgehead position, can also take place, affording a functionalized nonconjugated 6/6-bicyclic compound (entry 7). However, if the vinyl group is not at the bridgehead position (1r and 1s, Figure 1), the formation of the 6/6-cycloadducts was not observed and the reasons for this are not clear at this stage. We were pleased to find that for substrates 1q and 1q, which have a five-membered ring fused with the VCP and have the vinyl group at the nonbridgehead position, the expected [5 + 1] reaction can happen via two cyclopropane cleavage modes, giving two [5 + 1] cycloaducts 2q and 2q (the skeleton of the natural products of Taiwaniaquinoids\(^{16}\)) in moderate yields (entries 8 and 9, Table 3). Most \( \beta,\gamma \)-unsaturated products could isomerize to the \( \alpha,\beta \)-unsaturated ones quantitatively under reaction conditions B, except for 2k and 2p (Table 3). To our disappointment, the \( \beta \)-substituted VCPs (for example, 1t, Figure 1) were not suitable substrates for this [5 + 1] cycloaddition reaction.

In conclusion, we have developed a useful Rh(I)-catalyzed [5 + 1] cycloaddition of vinylcyclopropanes (VCPs) and CO. This reaction provides a new strategy for the assembly of six-membered carbocycles. Application of this reaction in synthesis is ongoing in our laboratory.

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**Supporting Information Available.** Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Table 3. Scope of the [5 + 1] Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Conditions A</th>
<th>Conditions B</th>
<th>yield of 2</th>
<th>yield of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1k</td>
<td>( \text{Ph} )</td>
<td>2k</td>
<td>80% ({}^6)</td>
<td>80% ({}^6)</td>
</tr>
<tr>
<td>2'</td>
<td>1l</td>
<td>2l-OBn</td>
<td>3l-OBn</td>
<td>42%</td>
<td>39% ({}^6)</td>
</tr>
<tr>
<td>3'</td>
<td>1m</td>
<td>2m-OBn</td>
<td>3m-OBn</td>
<td>63%</td>
<td>56% ({}^6)</td>
</tr>
<tr>
<td>4</td>
<td>1n</td>
<td>2n-OTBS</td>
<td>3n-OTBS</td>
<td>64%</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td>1o</td>
<td>2o-OTBS</td>
<td>3o-OTBS</td>
<td>64%</td>
<td>65%</td>
</tr>
<tr>
<td>6</td>
<td>1p</td>
<td>2p-OTBS</td>
<td>3p-OTBS</td>
<td>68%</td>
<td>54%</td>
</tr>
<tr>
<td>7</td>
<td>1q</td>
<td>2q-OTBS</td>
<td>3q-OTBS</td>
<td>68%</td>
<td>54%</td>
</tr>
<tr>
<td>8</td>
<td>1r</td>
<td>2r-OTBS</td>
<td>3r-OTBS</td>
<td>68%</td>
<td>54%</td>
</tr>
<tr>
<td>9</td>
<td>1s</td>
<td>2s-OTBS</td>
<td>3s-OTBS</td>
<td>68%</td>
<td>54%</td>
</tr>
</tbody>
</table>

\(^{a}\) Conditions A: 10 mol % of [Rh(dppp)OTf], 4 Å MS (100 mg), 0.2 atm of CO, DCE as solvent (0.05 M), 85 °C, 24 h. Conditions B: 10 mol % of [Rh(dppp)OTf] (VCPs with substituents on the cyclopropyl rings), 4 Å MS (100 mg), 0.2 atm of CO, DCE as solvent (0.05 M), 85 °C, 24 h; then DBU (1 equiv), rt, 1 h. DCE = 1,2-dichloroethane.

\(^{b}\) Isolated yield after column chromatography.

\(^{c}\) The \( \beta,\gamma \)-cyclohexenone 2 could not isomerize to \( \alpha,\beta \)-cyclohexenone 3 after some attempts. The reaction time was 36 h. 3% of 2l was also isolated. 75 °C was used, and the reaction time was 48 h. The reaction time was 48 h. 6% of 3q was also isolated. Because of the instability of the product to DBU, and the presence of 4 Å MS, 5 equiv of TsOH-H\(_2\)O was used instead of DBU, and the mixture reacted at 50 °C for 4 h.

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**Figure 1.** Unsuccessful substrates for the [5 + 1] reaction.

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