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# *Communications*

## A New and Selective Catalyst for the [5 + 2] Cycloaddition of Vinylcyclopropanes and Alkynes

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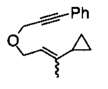
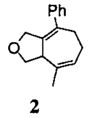
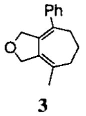
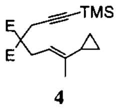
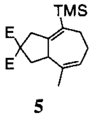
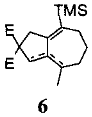
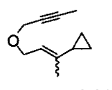
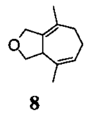
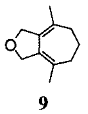
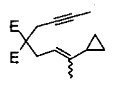
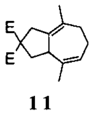
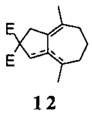
The design, discovery, and development of new reactions are essential for the further evolution of organic synthesis, particularly in connection with the preparation of increasingly complex targets in a simple, safe, and practical fashion.[1] In 1995, we reported the first examples of a new reaction for the formation of seven-membered rings based on the transition-metal-catalyzed [5 + 2] cycloaddition of vinylcyclopropanes and alkynes.[2] This reaction has been shown to work for internal, terminal, electron-rich, electron-poor, and conjugated alkynes. More recently, it has been extended to alkenes.[3] With the exception of preliminary studies on asymmetric catalysis,[4] our investigation of this reaction has centered on Wilkinson's catalyst ($(PPh_3)_3RhCl$). While this source of Rh(I) has performed efficiently for a wide range of substrates, we have uncovered several representative cases for which this catalyst is inefficient or does not work at all.

We describe herein investigations on $[Rh(CO)_2Cl]_2$, a new catalyst for the [5 + 2] cycloaddition of vinylcyclopropanes and alkynes that has proven to be impressively effective in many of the previously problematic cases and more generally allows for the reaction to proceed under mild conditions. Our interest in $[Rh(CO)_2Cl]_2$ was prompted in part by the expectation that it would be less sterically encumbered than Wilkinson's catalyst. The studies of Roundhill, Lawson, and Wilkinson have indeed shown that this catalyst is capable of oxidatively adding to a cyclopropane.[5] Moreover, related additions to activated C−C bonds have been found to occur under mild conditions as reported by the groups of Hogeveen,[6] Halpern,[7] Gassman,[8] and others.[9] More directly pertinent to the current study, vinylcyclopropanes have also been shown to react efficiently with $[Rh(CO)_2Cl]_2$, leading mainly to dienes[10] or cyclopentenes.[11]

**Table 1. Performance of $[Rh(CO)_2Cl]_2$ vs $(PPh_3)_3RhCl$ in [5 + 2] Cycloadditions of Substituted Alkyne−Vinylcyclopropanes**

| substrate/catalyst | products/yields (%) | | conditions[a] |
|---|---|---|---|
|  |  |  | |
| **1**, (*E*)/(*Z*)= 3.3/1 | **2** | **3** | |
| 5% $[RhCl(CO)_2]_2$ | 80 | 0 | 110 °C, 20 min, |
| 10% $(PPh_3)_3RhCl/AgOTf$ | 0[b] | 0 | 110 °C |
|  |  |  | |
| **4** | **5** | **6** | |
| 5% $[RhCl(CO)_2]_2$ | 81 | 0 | 30 °C, 2 d, $CDCl_3$ |
| 10% $(PPh_3)_3RhCl$ | 0 | 71 | 110 °C, 7 d,[c] |
|  |  |  | |
| **7**, (*E*)/(*Z*)= 3.3/1 | **8** | **9** | |
| 5% $[RhCl(CO)_2]_2$ | 78 | 0 | 110 °C, 20 min |
| 10% $(PPh_3)_3RhCl/AgOTf$ | 65 | 13 | 100 °C, 17 h, THF,[c] |
|  |  |  | |
| **10**, (*E*)/(*Z*)= 3.3/1 | **11** | **12** | |
| 5% $[RhCl(CO)_2]_2$ | 84 | 0 | 2 M, 110 °C, 3 h,[c] |
| 10% $(PPh_3)_3RhCl$ | 69 | 20 | 110 °C, 2 d,[d] |

[a] Unless otherwise noted, toluene is used as solvent. [b] Formation of a complex mixture of products.[c] See ref 2. [d] Slow addition of substrate.

The reaction of vinylcyclopropane **1** is illustrative of the performance of this new catalyst system (see Table 1). For reference, attempts to effect [5 + 2] cycloadditions with this substrate (**1**) and one of our previous catalyst systems, $(PPh_3)_3RhCl/AgOTf$, resulted only in the formation of complex product mixtures. In remarkable contrast, when this same substrate was treated with 5 mol % $[Rh(CO)_2Cl]_2$ for 20 minutes in toluene at 110 °C, the [5 + 2] cycloadduct **2** was obtained in 80% yield.

In addition to the facility and efficiency of the reaction of **1** with this new catalyst, it is noteworthy that this reaction proceeded without secondary isomerization of the product alkene (**2** → **3**), a problem previously encountered with some cycloadducts. In order to more fully explore the generality of this finding, we have examined the reactions of several other substrates which produce cycloadducts prone to secondary rhodium-catalyzed alkene isomerization. For example, substrate **4**, an exceptionally problematic case, reacts with Wilkinson's catalyst to provide only the product of secondary isomerization (**6**, 71%), a catalytic cascade of value

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(1) (a) Wender, P. A.; Miller, B. L. In *Organic synthesis: theory and applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1993; Vol 2, pp 27−66. (b) Wender, P. A.; Handy, S.; Wright, D. L. *Chem. Ind.* **1997**, 765−9.

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(9) Many transition metals have since been observed to react with strained C−C bonds. For a review, see: Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245−69.

(10) For lead references, see: (a) Doyle, M. P.; Van Leusen, D. *J. Org. Chem.* **1982**, *47*, 5326−38. (b) Doyle, M. P.; Van Leusen, D. *J. Am. Chem. Soc.* **1981**, *103*, 5917−9. (c) Salomon, R. G.; Salomon, M. F.; Kachinski, J. L. C. *J. Am. Chem. Soc.* **1977**, *99*, 1043−54. (d) Voigt, H. W.; Roth, J. A. *J. Catal.* **1974**, *33*, 91−7. (e) Salomon, M. F.; Salomon, R. G. *J. Chem. Soc., Chem. Commun.* **1976**, *3*, 89−90. For transformations of vinylcyclopropanes in the presence of Rh-, as well as Fe-, Co-, Ni-, and Pd-complexes, see: Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, *471*, 1−18.

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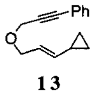
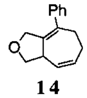
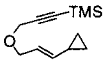
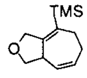
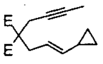
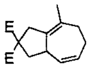
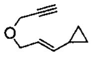
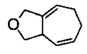
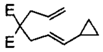
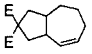
**Table 2. Performance of $[Rh(CO)_2Cl]_2$ vs $(PPh_3)_3RhCl$ in [5 + 2] Cycloadditions of Unsubstituted Alkyne−Vinylcyclopropanes**

| substrate/catalyst | product/yield (%) | conditions[a] |
|---|---|---|
|  |  | |
| **13** | **14** | |
| 5% $[RhCl(CO)_2]_2$ | 78 | 65 °C, 15 min, $CDCl_3$ |
| 5% $[RhCl(CO)_2]_2$ | 80 | 30 °C, 14 h, $CDCl_3$ |
| 10% $(PPh_3)_3RhCl$ | 80 | 110 °C, 1.5 h,[b] |
|  |  | |
| **15** | **16** | |
| 5% $[RhCl(CO)_2]_2$ | 78 | 30 °C, 14 h, $CDCl_3$ |
| 10% $(PPh_3)_3RhCl$ | 83 | 110 °C, 3.5 h,[b] |
|  |  | |
| **17** | **18** | |
| 1% $[RhCl(CO)_2]_2$ | 89 | 2 M, 110 °C, 3 h,[c] |
| 5% $[RhCl(CO)_2]_2$ | 79 | 30 °C, 16 h, $CDCl_3$ |
| 5% $[RhCl(CO)_2]_2$ | 82 | 110 °C, 20 min |
| 0.5% $(PPh_3)_3RhCl/AgOTf$ | 83 | 1 M, 110 °C, 20 min,[b] |
| 10% $(PPh_3)_3RhCl$ | 90-95 | 65 °C, 19 h, $CF_3CH_2OH$,[b] |
| 10% $(PPh_3)_3RhCl$ | 84 | 110 °C, 2 d,[b] |
|  |  | |
| **19** | **20** | |
| 5% $[RhCl(CO)_2]_2$ | 0 | 30 °C |
| 10% $(PPh_3)_3RhCl$ | 50[d] | 110 °C, 2 d,[b] |
|  |  | |
| **21** | **22** | |
| 5% $[RhCl(CO)_2]_2$ | 0 | 110 °C, 48 h |
| 0.1% $(PPh_3)_3RhCl/AgOTf$ | 90 | 110 °C, 15 h,[e] |

[a] Unless otherwise noted, toluene is used as solvent. [b] See ref 2. [c] Slow addition of substrate. [d] The low yield is due to product volatility. [e] See ref 3.

in synthesis, but an undesired product in the current study. In contrast, when **4** is treated with 5 mol % $[Rh(CO)_2Cl]_2$, only cycloadduct **5** is obtained (81%). Less dramatic but equally important results were obtained with substrates **7** and **10**. With Wilkinson's catalyst and AgOTf, the former reacts to give a mixture of cycloadduct **8** (65%) and the product of its secondary isomerization, bicycle **9** (13%). In contrast, reaction of **7** with $[Rh(CO)_2Cl]_2$ gives only cycloadduct **8** (78%). Similar results were obtained with substrate **10**. Interestingly, with $[Rh(CO)_2Cl]_2$, (*E*)-vinylcyclopropanes react more readily than (*Z*)-vinylcyclopropanes. The former undergoes cycloaddition at 30 °C while the latter reacts only at higher temperatures (110 °C). With Wilkinson's catalyst, both stereoisomers react at similar rates.[12]

It is of further note that in all cases discussed thus far cycloadditions occur more rapidly with $[Rh(CO)_2Cl]_2$ than with Wilkinson's catalyst. Given the operational advantages of shorter reaction times and the potential for milder conditions, our attention was focused next on the relative merit of the new catalyst system in cases where Wilkinson's catalyst works but only at elevated temperatures. Our findings are summarized in Table 2. While general and efficient cycloadditions of internal alkynes are observed with $[Rh(CO)_2Cl]_2$ as well as with Wilkinson's catalyst, the former generally works well even at lower reaction temperatures. At 65 °C, for example, the cyclization of **13** takes place in less than 15 min to give **14** (78%) as a single product. *This reaction (**13** → **14**) proceeds even at 30 °C to give **14** in 80% yield.* In contrast, the same substrate with Wilkinson's catalyst requires higher temperatures and longer times to achieve complete conversion. Bulky substituents on the alkene moiety such as is found in **15** do not adversely effect the facility of this reaction: full conversion is observed within 14 h at 30 °C. With Wilkinson's catalyst, a higher temperature is again required. While the performance of Wilkinson's catalyst can be improved either by using $CF_3CH_2OH$ as solvent (substrate **17**, 65 °C, 19 h) or by addition of AgOTf to the reaction mixture (substrate **17**, 1 M, 110 °C, 20 min), both procedures are less practical. The use of $[Rh(CO)_2Cl]_2$ also allows for reactions to be conducted at concentrations of up to 2 M.[13] With Wilkinsons's catalyst, significant polymerization is observed when the concentration exceeds 1 M.

From a practical point of view, $[Rh(CO)_2Cl]_2$ appears to be a general and useful catalyst for the intramolecular cycloaddition of alkyne−vinylcyclopropanes.[14] Interestingly, however, terminal alkynes (**19**) and alkenes (**21**) give no [5 + 2] product. Not surprisingly, the highly electron-deficient nature of Rh leads to insertion into the terminal alkyne C−H bond of the former, altering the course of the reaction. For the latter, no reaction is observed even under forcing conditions (110 °C, 48 h).

The higher reactivity of $[Rh(CO)_2Cl]_2$ relative to Wilkinson's catalyst could be attributed to both electronic and steric differences. The lower ligand count of $Rh(CO)_2Cl$, presumably the active species, might also play an important role, facilitating coordination and subsequent cleavage of the three-membered ring.[15] The selectivity, efficiency, and mild conditions obtained with this new catalyst greatly enhance the utility of this new class of cycloadditions. Further studies on the scope, mechanism, and asymmetric catalysis are in progress.

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**Supporting Information Available:** Full experimental data and complete spectral data for new compound **2** (2 pages).

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(12) The time-course of the reaction was monitored by $^1H$ NMR ($[Rh(CO)_2Cl]_2$) or by GC (Wilkinson's catalyst).

(13) Addition of the substrate over 3 h is required to keep the substrate concentration below 0.5 M. Substrate concentrations over 0.5 M reduce the rate of conversion.

(14) In a representative procedure, $[Rh(CO)_2Cl]_2$ (5 mol %) was dissolved in toluene (4 mL) under a nitrogen atmosphere. Substrate **17** (0.2 mM) was added neat, and the resulting solution was heated at 110 °C for 20 min. After cooling, hexane was added (5 mL), and the reaction mixture was passed through silica gel (0.5 g). The product was eluted with hexane/AcOEt = 20/1. Concentration in vacuo gives **18** in 82% as a colorless oil.

(15) Studies of Lehmkuhl showed that coordinatively unsaturated (cycloalkylmethyl)bis(cyclopentadienyl)titanium and nickel complexes rearrange by ring opening: (a) Lehmkuhl, H.; Rufinska, A.; Benn, R.; Schroth, G.; Mynott, R. *Liebigs Ann. Chem.* **1981**, 317−32. (b) Lehmkuhl, H.; Fustero, S. *Liebigs Ann. Chem.* **1980**, 1361−70. For an excellent rewiew about organometallic derivatives of cyclopropanes and their reactions, see: Goldschmidt, Z. In *The chemistry of the cyclopropyl group*; Rappoport, Z., Ed.; John Wiley: London, 1995; Vol 2; pp 498−647. For a theoretical study of the activation of C−C bonds by transition-metal atoms, see: Siegbahn, E. M.; Blomberg, M. R. A. *J. Am. Chem. Soc.* **1992**, *114*, 10548−56.