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[Rh(CO)$_2$Cl]$_2$-Catalyzed Domino Reactions Involving Allylic Substitution and Subsequent Carbocyclization Reactions

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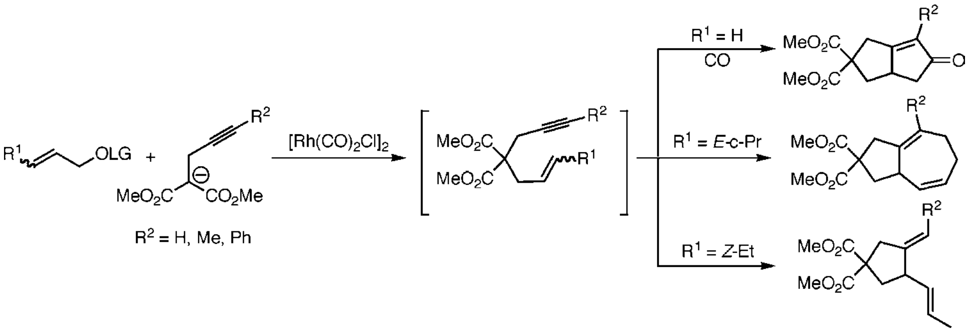
ABSTRACT



Three novel domino reaction processes have been discovered and developed that employ the regioselective and stereoselective [Rh(CO)$_2$Cl]$_2$-catalyzed alkylations of allylic trifluoroacetates with α-substituted sodiomalonates followed by an intramolecular Pauson–Khand annulation, a [5 + 2] cycloaddition, or a cycloisomerization. A unique aspect of the methodology is that a *single* catalyst is used to effect sequential transformations simply by increasing the temperature for the second reaction.

Transition-metal-catalyzed processes constitute a powerful class of reactions in the tool chest of organic chemists with new useful catalysts and transformations being reported at an impressive rate. Such reactions are now routinely employed for forming carbon−carbon and carbon−heteroatom bonds as a key step in the synthesis of more complex target molecules. Toward the goal of improving the efficiency and decreasing the waste associated with the production of organic compounds, the ability to execute one-pot, sequential reactions wherein the product of one reaction is the starting material for the next is particularly significant. Hence, in the arena of contemporary organometallic chemistry, the discovery and development of multifunctional catalysts that can be utilized to promote mechanistically distinct, cascade reactions has emerged as an exciting, albeit often elusive and challenging, objective.[1] The alkylation of carbon and heteroatom nucleophiles with symmetrical and unsymmetrical allylic substrates is arguably one of the more important transition metal-catalyzed reactions,[2] but there are only a few isolated reports of sequential processes in which such an allylic substitution serves as the first step.[3,4] We now report three novel cascade reactions that are catalyzed by the commercially available catalyst [Rh(CO)$_2$Cl]$_2$ and involve an initial allylic alkylation that is followed by one of three distinctly different carbocyclization reactions.

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[1] For a review, see: Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754.

[2] For reviews on transition metal-catalyzed allylic alkylations, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 395. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1996. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

[3] Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609.

[4] Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456. Yamamoto, Y.; Nakagai, Y.-i.; Itoh, K. *Chem. Eur. J.* **2004**, *10*, 231.

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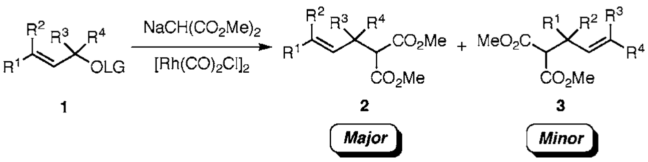
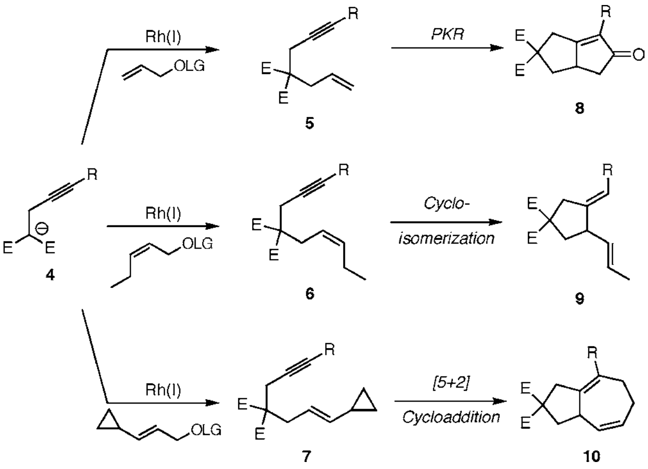
We recently discovered that $[Rh(CO)_2Cl]_2$ catalyzes highly regio- and stereoselective allylic alkylations to provide products arising from substitution at the carbon atom bearing the leaving group, *irrespective of the structure of the starting carbonate* (Scheme 1).[5] The potential of this discovery is greatly enhanced by the known ability of $[Rh(CO)_2Cl]_2$ and other rhodium(I) catalysts to catalyze a number of useful carbocyclization reactions, including intramolecular variants of the Pauson−Khand reaction (PKR),[6] cycloisomerizations of 1,6-enynes,[7,8] and [5 + 2] cycloadditions.[9] We thus reasoned that $[Rh(CO)_2Cl]_2$ might serve as a versatile multifunctional catalyst for a variety of domino reaction processes. Such transformations are highly attractive as synthetic constructs because they lead to the rapid assembly of complex molecular architectures **8**−**10** from simple starting materials according to the general strategy set forth in Scheme 2.

Scheme 1. Regiochemical Trends in Transition Metal-Catalyzed Allylic Alkylations

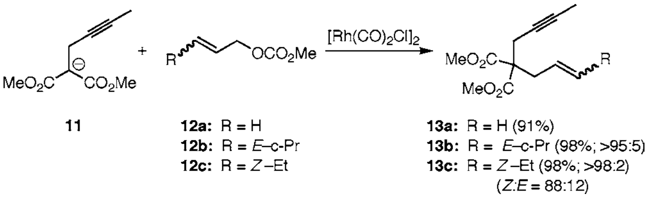


Scheme 2. Domino $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation/Carbocyclization Reactions



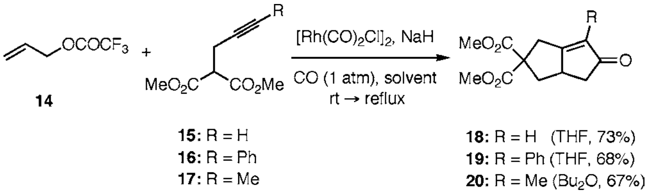
The first step in evaluating the feasibility of the transformations outlined in Scheme 2 was to establish that α-alkynyl-substituted malonates were viable substrates in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation. Toward this end, we examined the allylic substitution reactions of the sodiomalonate anion **11** with carbonates **12a**−**c** in the presence of $[Rh(CO)_2Cl]_2$ (5 mol %, THF or DMF, rt, 1−2 h) (Scheme 3). In each case, the desired alkylation occurred giving the expected enynes **13a**−**c** in excellent yields. As anticipated from previous experience,[5] **13b** and *Z*-enyne **13c** were obtained with high regioselectivity (>95:5) and stereoselectivity (*Z*/*E*-**13c** = 88:12).

Scheme 3. Direct, Stereoselective $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylations



Having thus established that $[Rh(CO)_2Cl]_2$ catalyzed the alkylation of allylic carbonates with α-alkynyl substituted malonates, we turned our attention toward developing domino allylic alkylation/carbocyclization reactions. Although allylic carbonates and acetates may be used as substrates in these processes, we discovered that it was necessary to employ the corresponding allylic trifluoroacetates for the domino reactions to proceed with high efficiency. Thus, the allyl trifluoroacetate **14** reacted smoothly with the anion of malonates **15**−**17** in the presence of $[Rh(CO)_2Cl]_2$ (10 mol %) under an atmosphere of CO in either THF or Bu_2O to yield bicyclic enones **18**−**20** in good overall yields (Scheme 4). The allylic substitution reactions proceeded rapidly at room temperature, whereas the subsequent intramolecular PKRs simply required heating at reflux temperatures to complete the reaction in a reasonable period of time (12−24 h). This transformation represents a convenient complement to a related tandem Rh(I)-catalyzed allylic alkylation/Pauson−Khand annulation protocol reported by Evans.[3]

Scheme 4. Domino $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation/Pauson−Khand Reaction



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(6) Jeong, N.; Lee, S.; Sung, B. K. *Organometallics* **1998**, *17*, 3642. Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771. Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. Park, K. H.; Son, S. U.; Chung, Y. K. *Tetrahedron Lett.* **2003**, *44*, 2827. Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795.

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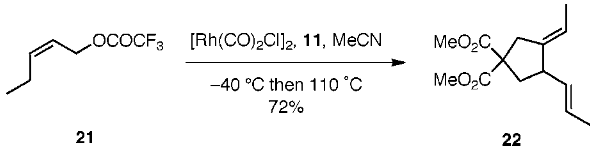
During the course of our studies we discovered somewhat surprisingly that $[Rh(CO)_2Cl]_2$ catalyzed the facile isomerization of 1,6-enynes to yield 1,4-dienes as vinyl alkylidene cyclopentanes. Although cationic Rh(I) catalysts are well-known to promote these reactions,[7] neutral Rh(I) species are not known to be efficient catalysts for such transformations.[10] Inasmuch as the Rh(I)-catalyzed cycloisomerizations of *Z*-enynes proceed more efficiently than the corresponding *E*-enynes,[7] *the ability of* $[Rh(CO)_2Cl]_2$ *to catalyze allylic substitution of Z-substrates with minimal Z/E-isomerization is especially noteworthy.*[5] To establish the efficacy of a domino allylic alkylation and cycloisomerization sequence, the allylic trifluoroacetate **21** was treated with the malonate anion **11** (−40 °C, MeCN, 6 h) in the presence of $[Rh(CO)_2Cl]_2$ (10 mol %), and the resultant 1,6-enyne (*Z*/*E* >95:5) underwent cycloisomerization upon heating (110 °C, sealed tube, 4 h) to provide diene **22** in excellent overall yield (Scheme 5).[11]

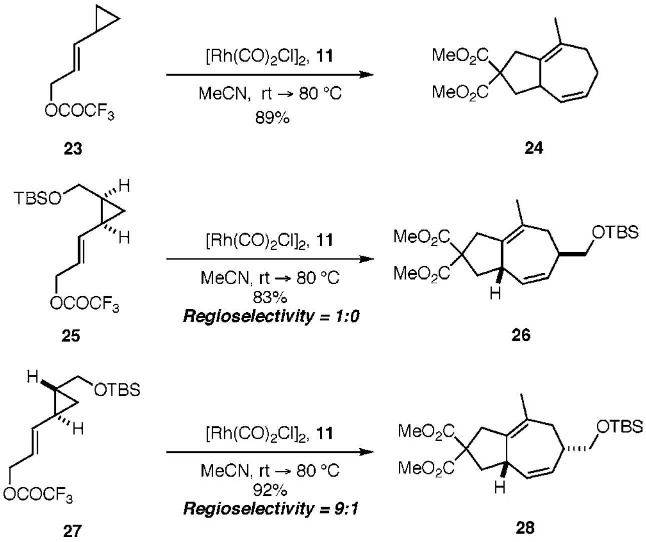
Scheme 5. Domino $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation/Cycloisomerization



In parallel studies, we discovered that a domino $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation followed by a [5 + 2] cycloaddition also proceeded smoothly using a variety of different cyclopropyl-substituted allylic trifluoroacetates as starting substrates. For example, reaction of **23** with the malonate anion **11** in the presence of $[Rh(CO)_2Cl]_2$ (5 mol %) at room temperature gave an intermediate cyclopropyl 1,6-enyne that underwent facile [5 + 2] cycloaddition to give **24** (89%) when the reaction temperature was simply raised to 80 °C (bath temperature) (Scheme 6). Similarly, subjecting allylic trifluoroacetates **25** and **27** to the same conditions provided cycloadducts **26** and **28**, respectively, in excellent overall yields. The diastereoselectivity and regiochemical trends we observed in these [5 + 2] cycloadditions are in accord with precedent established by Wender.[12]

In summary, we have discovered that the commercially available complex $[Rh(CO)_2Cl]_2$ is a multifunctional catalyst that efficiently promotes a variety of mechanistically different reactions in novel domino reaction sequences, of which the tandem allylic alkylation/enyne cycloisomerization and allylic alkylation/[5 + 2] cycloaddition cascade reactions are the first of their kind. These processes commence with a regioselective and stereoselective allylic alkylation followed by one of three different carbocyclizations, including an intramolecular Pauson−Khand reaction, an enyne cycloisomerization, and a [5 + 2] cycloaddition. A notable feature of this new methodology is that the experimental procedure is operationally simple as only a change in temperature is necessary to promote the second step of the overall transformation. The importance of these findings is underscored by the fact that there are few transition-metal catalysts capable of promoting two sequential reactions in a single chemical operation.[1] Moreover, such processes have significant synthetic potential for the rapid assembly of structurally complex targets from relatively simple starting materials. Studies to explore and develop these and other $[Rh(CO)_2Cl]_2$-catalyzed cascade reactions are in progress and will be reported in due course.

Scheme 6. Domino $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation/[5 + 2] Cycloaddition



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Supporting Information Available: General experimental procedures and copies of ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Cycloisomerization of an enyne has been observed as a side reaction in a PKR catalyzed by $[Rh(CO)_2Cl]_2$. See ref 8.

[11] The conjugated diene (4%) was also isolated as a side product.

[12] Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089.