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# Rhodium Catalyzed Intramolecular [4+2] Cycloisomerization Reactions

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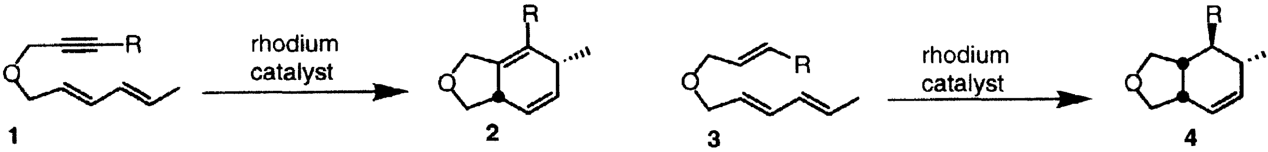
**Abstract:** A rhodium catalyst is reported that catalyzes the cycloisomerization of dieneynes and trienes. This cycloisomerization reaction, formally the equivalent of an unactivated Diels-Alder reaction, proceeds at room temperature with $[Rh(DIPHOS)(CH_2Cl_2)_2]\ SbF_6$ as the catalyst.

The rhodium catalyzed intramolecular [4 + 2] cycloisomerization reaction shown in Figure 1 is potentially an important addition to synthetic organic chemistry. This reaction, which is formally the equivalent of the Diels-Alder reaction between an unactivated diene and dienophile, cannot be performed under mild thermal conditions. The use of the correct transition metal catalyst should not only allow the reaction to be carried out at room temperature, but also presents the potential for asymmetric catalysis.[1] A number of workers have investigated intermolecular metal catalyzed [4 + 2] cyclodimerizaton reactions catalyzed by iron and rhodium.[2-10] Recently, researchers have begun to investigate the potential of nickel and rhodium as catalysts in the intramolecular variant of this reaction. (Figure 1).[11-15] To date, systems that have been used for this reaction have not been general in their reactivity and often require a temperature of 55°C or higher. In connection with our general interest in asymmetric catalysis we have begun to investigate this reaction in an attempt to find an active system that catalyzes this reaction on a number of substrates with a variety of different bisphosphine ligands.

**Figure 1**



In searching for better catalysts for this transformation, there are a number of factors that can be varied. Livinghouse found that the seven-membered rhodium phosphine chelates are more reactive than five atom chelates.[12] Since we ultimately desire to develop an asymmetric version of this reaction, we sought a system that had sufficient activity to catalyze this reaction at or below room temperature and ideally as a five-membered chelate, since many of the most successful chiral rhodium complexes have that structure. Initially, we chose to keep the ligand constant, diphenylphosphinoethane (DIPHOS), and study the effect of counterion and catalyst

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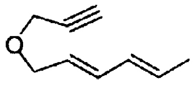
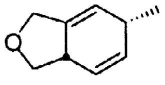
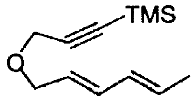
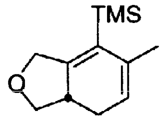
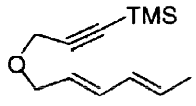
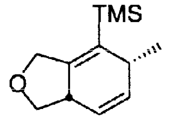
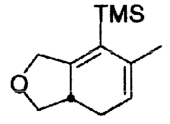
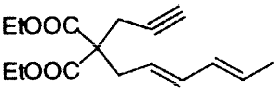
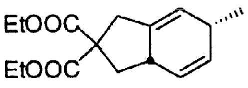
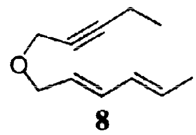
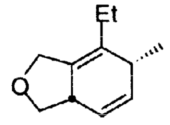
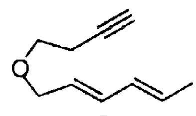
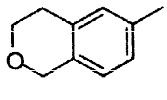
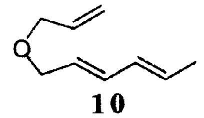
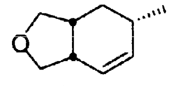
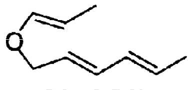
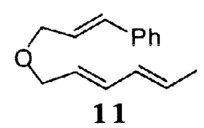
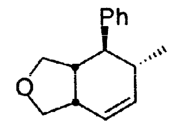
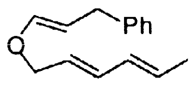
precursor. There are a number of examples in the literature where the counterion associated with the metal has an effect on the rate of catalyst turnover. Additionally, it is often possible to increase the rates of catalysis with diphosphine rhodium(I) complexes through removal of the dialkene coordinated to the metal by pretreatment with hydrogen. Recently, Bosnich et al. have demonstrated this with enhanced rates, conversions and selectivities in intramolecular hydroacylation reactions.[16] After screening complexes with a variety of counterions, we found that $Rh(DIPHOS)(CH_2Cl_2)_2]SbF_6$ catalyzed the [4 + 2] cycloisomerization of a number of substrates in good yield and at room temperature.

**Table 1 Catalysis with $[Rh(DIPHOS)(CH_2Cl_2)_2]SbF_6$**

| Substrate | Reaction conditions | Product | Secondary product |
|---|---|---|---|
|  **5** | 25°C,<br>$CH_2Cl_2$<br>6.5h |  **12** 75% | |
|  **6** | 25°C<br>acetone<br>6h |  **13** 80% | |
|  **6** | 25°C<br>$CH_2Cl_2$<br>30h |  **14** 76% |  **13** 16% |
|  **7** | 25°C<br>$CH_2Cl_2$<br>10h |  **15** 75% | |
|  **8** | 25°C<br>$CH_2Cl_2$<br>14h |  **16** 65% | |
|  **9** | 25°C<br>$CH_2Cl_2$<br>18h |  **17** 41% |  **20** 19% |
|  **10** | 25°C<br>$CH_2Cl_2$<br>3.5h |  **18** 42% |  **21** 25% |
|  **11** | 55°C<br>$CH_2Cl_2$<br>30h<br>10% catalyst |  **19** 59% |  **22** 10% |

The catalyst, $[Rh(DIPHOS)(CH_2Cl_2)_2]^+SbF_6^-$, was generated by treatment of $[Rh(NBD)(DIPHOS)]^+(SbF_6)^-$ with $H_2$ in $CH_2Cl_2$.

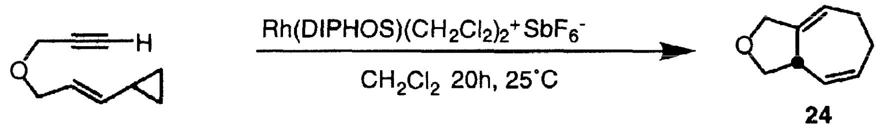
Except where noted all reactions were run with 6% catalyst formed in situ.

Our inital results with $Rh(DIPHOS)(CH_2Cl_2)_2]SbF_6$ as a catalyst for this reaction are shown in Table 1. In most cases, dieneynes react at room temperature to give the desired product in good yields and with high diastereoselectivity.[17] Terminal, internal and silyl-substituted alkynes undergo cyclization (Table 1). Silyl substituted dieneyne **6** cyclized in acetone to give the conjugated product **13**, while reaction in methylene chloride gave the expected product, **14**. Terminal alkynes **5** and **7** react to give cyclization products **12** and **15**. The reaction proceeds with both 3 and 4 atom tethers between the alkyne and the diene portion of the molecule. In the case of the 4 atom tether, aromatized by-product **20** is isolated after purification in 19% yield. Analysis of the NMR spectra of the crude reaction mixture revealed that the aromatized product (**20**) was not initally present in the reaction mixture, and consequently resulted from oxidation during silica-gel chromatography.

The reaction of trienes with this catalyst system proceeded under milder conditions than were previously reported, but was plagued by the formation of products from the isomerization of the isolated double bond toward the oxygen to give vinyl ethers **21** and **22**. The triene with a terminal olefin (**10**) cyclized at room temperature, while the substrate with a disubstituted double bond (**11**) required heating to 55° C and 30 hours to give the desired product.

We have also begun to examine this catalyst in the [5 + 2] isomerization reported by Wender. The $[Rh(DIPHOS)(CH_2Cl_2)_2]$ $SbF_6$ complex catalyzed the isomerization of substrate **23** at room temperature over 20 hours to yield **24**. The catalyst $[RhCl(PPh_3)_3]$ was reported to require 110°C to catalyze this transformation.[14] We are currently investigating the use of this catalyst in the [5 + 2] cycloisomerization of a variety of vinylcyclopropanes.

**Figure 2**



**23**

**24**
59%

In conclusion, we have found that in situ formation of the $[Rh(DIPHOS)(CH_2Cl_2)_2]$ $SbF_6$ complex results in a catalyst system that is more active than the systems used previously. This system catalyzes the cycloisomerization of both dieneynes and trienes in what is formally a Diels-Alder reaction of unactivated dienes and dienophiles. We are currently investigating catalysts based on this system with chiral bisphosphine ligands. We are also attempting to develop a catalyst system that performs the [4 + 2] cycloisomerization on triene substrates without forming the unwanted vinyl ether product.

*Catalyst Synthesis:* Under $N_2$ $[Rh(NBD)Cl]_2$ (305 mg, 0.6615 mmole) and 10 mL of acetone were placed into a 25 mL vial containing a stir bar. To this solution $AgSbF_6$ (455 mg, 1.323 mmole) was added. Silver chloride precipitated immediately from the light orange solution. After stirring for 10 minutes, the heterogeneous solution was drawn up into a 10 mL syringe and filtered airless via syringe filter into another vial containing a stirbar, diphenylphosphinoethane (527 mg, 1.323 mmole), and 5 mL acetone under $N_2$. An immediate color change from light orange to deep red was observed. This solution was stirred for 45 minutes, after which the volume of the reaction was reduced on a rotary evaporator until red crystals started to form. The solution was let stand at room temperature under $N_2$ for 5 hours. The dark red crystals were collected and washed with $Et_2O$. After drying invacuo they weighed 741 mg (67%).

*Sample procedure:* $[Rh(NBD)(DIPHOS)]^+ (SbF_6)^-$ (37 mg, 0.044 mmol) was placed in a Schlenk tube and dissolved in 6 mL of freshly distilled, deoxygenated $CH_2Cl_2$ to form a dark orange solution. $H_2$ gas was then bubbled through the solution for two minutes (solution color changed to dark red) followed by $N_2$ gas for two minutes. Substrate **5** (100 mg, 0.735 mmole) was added to the catalyst solution (immediate color change to yellow) along with 1 mL $CH_2Cl_2$. The Schlenk tube was then freeze-pump-thaw-degassed (3 cycles) and stirred under $N_2$ at ambient temperature. The course of the reaction was followed by TLC (5% ethyl acetate/hexane). After the reaction was deemed complete, the solvent was removed under reduced pressure. Flash column chromatography over silica gel (5% ethyl acetate/hexane) yielded 75 mg/75% after combination of product containing fractions and evaporation of their solvent.

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