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## COMMUNICATION

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## [4+2+2] Cycloaddition Catalyzed by a New Cationic Rhodium-Bisphosphine Monooxide Complex

Gino Martin, R. Canlas and Scott R. Gilbertson\*<sup>c</sup>

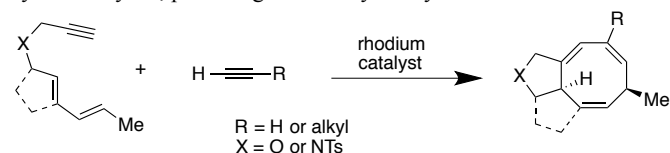
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**A rhodium-BozPHOS based complex is reported. This complex is competent in catalyzing the [4+2+2] cycloisomerization of cyclooctatrienes in moderate to good yields. The x-ray crystal structure of this complex is reported, along with formation of both bicyclic and tricyclic cyclooctatrienes.**

Over the last few years a wide variety of higher-order cycloadditions have been developed. These methods have provided access to a number of medium sized ring sizes with eight member rings being one of the most common.<sup>1-18</sup> Structurally complex cyclooctanoid systems with interesting bioactivities are present in numerous natural products (Figure 1). Many of these cyclooctane systems are embedded within fused polycyclic frameworks complicating their synthesis. A number of strategies have been developed to synthesize these structures.<sup>19-35</sup> We previously reported an efficient, diastereoselective rhodium-catalyzed [4+2+2] cycloaddition method which provides a functionally versatile bicyclic [6.3.0] core with a variety of substrates (Scheme 1).<sup>36, 37</sup> The original system was discovered while developing rhodium catalyzed [4+2] cycloisomerizations.<sup>38, 39</sup> As the catalyst aged, a [4+2+2] product was observed. Eventually a catalyst system was prepared using a [Rh(nbd)Cl]<sub>2</sub> (1.0 equiv.), (S,S)-Me-DuPHOS (2.0 equiv.) and AgSbF<sub>6</sub> (1.0 equiv.) (note this is ½ an equivalent of Ag relative to

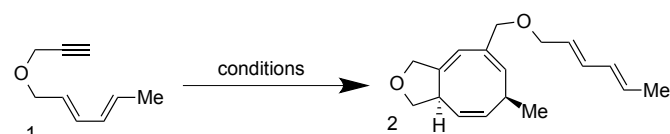
Cl) that selectively provided the [4+2+2] product.<sup>36</sup> Despite its effectiveness in the reaction, the exact composition of the catalyst was never identified. Furthermore, the lack of a discrete species hindered making improvements in stereoselectivity and substrate scope. Reported here is a rhodium-bisphosphine monooxide complex that is catalytically comparable to the previously reported system and is likely to be the same species. The complex is characterized by single crystal X-ray diffraction and NMR. Additionally, the substrate scope for the reaction was expanded with this catalyst to include cyclic dienynes, providing fused tricyclic cyclooctanoids.



**Scheme 1.** General scheme for the rhodium-catalyzed synthesis of fused polycyclic cyclooctatriene systems.

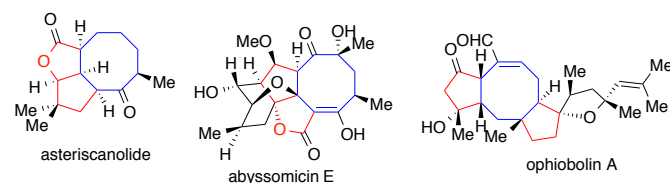
Since the initial catalyst was formed by a reaction that did not provide a discrete, isolable complex, a range of reaction conditions were investigated. Temperature, solvent, ligand and metal were varied. Reactions were attempted with both bis and monophosphine

**Table 1:** Exploratory conditions in trying to obtain a discrete catalyst for the [4+2+2] dimerization with acyclic substrate.



Entry	Complex/Catalyst Mixture	Solvent, Conditions	%Yield (2) <sup>a</sup>
1	Rh/nbd/DuPHOS/SbF <sub>6</sub> <sup>b</sup>	CH <sub>2</sub> Cl <sub>2</sub> , 60 °C, 24 h	83
2	Rh/nbd/dppf/SbF <sub>6</sub> <sup>b</sup>	CH <sub>2</sub> Cl <sub>2</sub> , 65 °C, 24 h	12
3	[Rh(cod)]{(S,S)-Me-DuPHOS}BF <sub>4</sub>	6:1 CH <sub>2</sub> Cl <sub>2</sub> :EtOAc, rt, 24 h	30
4	[Rh(nbd)]{(S,S)-Me-BozPHOS}SbF <sub>6</sub> <sup>c</sup>	CH <sub>2</sub> Cl <sub>2</sub> , 60 °C, 24 h	80

<sup>a</sup> Isolated yield of 2. <sup>b</sup> Catalyst mixture was formed with ½ equivalent of AgSbF<sub>6</sub> relative to Cl. <sup>c</sup> Complex was synthesized using full equivalent of AgSbF<sub>6</sub> relative to Cl.



**Figure 1.** Cyclooctanoid natural products containing an eight-membered ring (blue) embedded in a fused polycyclic system.

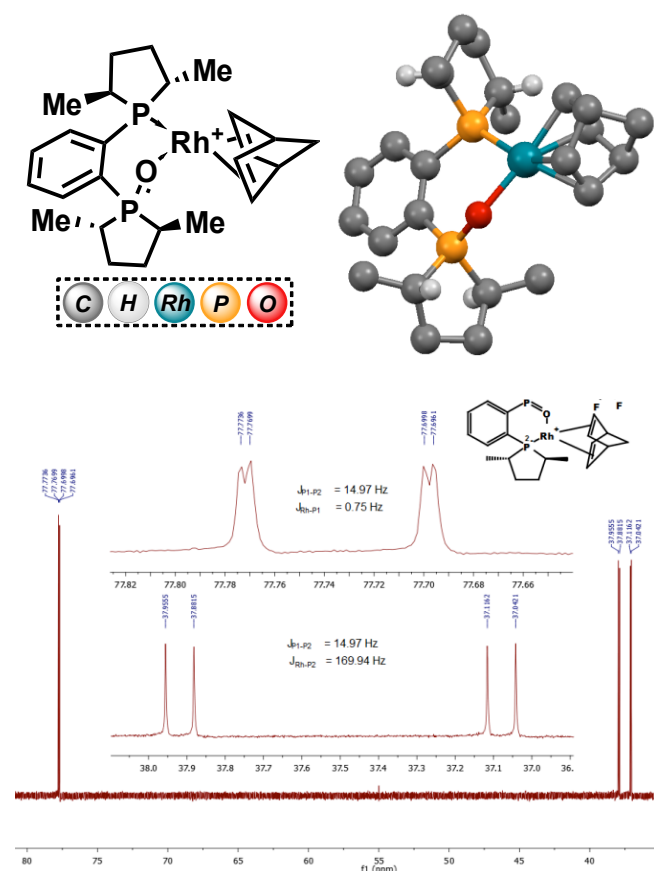
Department of Chemistry, University of Houston, Houston TX 77204

Electronic supplementary information (ESI) available: Experimental procedure, characterization data, <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra of compounds

ligands, CHIRAPHOS, triphenylphosphine, DuPhos, BINAP, RajPHOS, dppf, DPPP and MOP. An N-heterocyclic carbene as well as rhodium with no donor ligand present were also tested. (Details of the systems investigated can be found in the supplemental material.) In the original rhodium catalyzed [4+2] cycloisomerization, it was observed that as the  $[\text{Rh}(\text{cod})\{(\text{S,S})\text{-Et-DuPHOS}\}]\text{OTf}$  complexes “aged”, [4+2+2] product was formed. This observation led to using a DuPHOS-monooxide (BozPHOS) as a ligand in the system.<sup>40-44</sup> This rhodium complex resulted in the formation of the desired product in good yield (Table 1).

The structure of the BozPHOS complex was analyzed by NMR. Two sets of  $^{31}\text{P}$  doublets of doublets corresponding to the Rh-bound ligand were observed, with a P-P coupling of 14.97 Hz and Rh-P coupling constants of 0.75 and 169.94 Hz. These values are consistent with the phosphine directly bound to rhodium and the phosphine oxide bound through the oxygen. Single crystal X-ray analysis revealed a structure consistent with the NMR data, with the phosphine and the oxygen for phosphine oxide directly bound to the rhodium.

**Figure 2.** Structure of the Rh-BozPHOS complex,  $[\text{Rh}(\text{nbd})\{(\text{S,S})\text{-Me-BozPHOS}\}]\text{SbF}_6$ , **3**.



The counterion and hydrogen atoms (except those in stereogenic centers) were omitted for clarity. The  $^{31}\text{P}$  NMR spectrum for the compound shows the two distinct phosphorus atoms and the expected P-O as the ligating atoms to Rh, as shown by the coupling constants. The complex obtained after crystallization was catalytically competent in the dimerization, further supporting its activity for the [4+2+2] cycloaddition.

**Table 2:** Synthesis of [4+2+2] cycloadducts

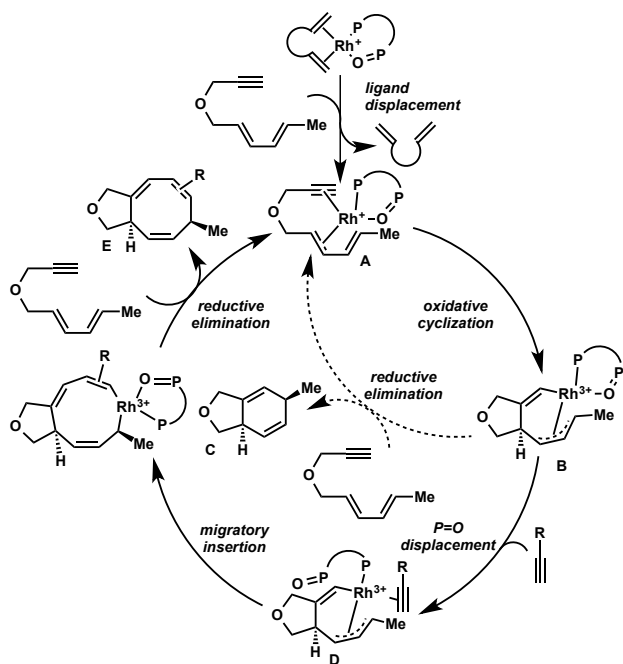
Entry	Substrate	Secondary Alkyne	Product	%Yield
1		none		80
2		none		57
3		$\text{H} \equiv \text{H}$		45
4		$\text{H} \equiv \text{H}$		71
5				53
6		$\text{H} \equiv \text{H}$		97
7		$\text{Me} \equiv \text{H}$		65 6:1 <sup>d</sup>
8				16
9				21
10		$\text{H} \equiv \text{H}$		82
11		$\text{H} \equiv \text{H}$		67
12		$\text{H} \equiv \text{H}$		85

<sup>a</sup> Numbers refer to isolated yields for each entry. Reactions were performed in  $\text{CH}_2\text{Cl}_2$  using 4 mol% complex **3** as catalyst. The solutions were degassed using freeze-pump-thaw degassing method. <sup>b</sup> Acetylene and propyne were bubbled onto the solution right after degassing, wherein the solutions were still partially frozen. The reaction mixture was then allowed to warm up to 0 °C before sealing the storage tube. <sup>c</sup> Nongaseous secondary alkynes were added in five-fold excess before degassing. <sup>d</sup> 6:1 regioisomers at the alkyne addition, based in  $^1\text{H}$  NMR integration of an inseparable mixture.

As seen in Table 2, the Rh-BozPHOS ligand complex provides the [4+2+2] products with a number of substrates. Both acyclic and cyclic dieneynes, where the diene is part of a five-member ring, provide the cyclooctatriene products, with the latter case providing tricyclic hexahydro-2-oxa-1*H*-cycloocta[*cd*]pentalene core. Both terminal alkynes and acetylene proceed to give desired product with acetylene providing the higher yields. The yields were comparable to those obtained with the previously system.

The initial system was optimized by following the formation of the [4+2+2] dimer product that is observed when a second alkyne is not present. Following that, reactions with a second alkyne were run. The alkynes used were terminal as well as acetylene gas. We have observed that internal alkynes will not participate in the reaction. The reaction with propyne (Table 2 entry 7) appears to provide two regioisomers where the alkyne inserts in two orientations.

While the complex used for the cycloaddition is chiral the reaction with the acyclic achiral substrates gave the corresponding cycloaddition dimers with modest enantiomeric excess (~30 % *ee*). While the reaction does not proceed with high *ee*, the products are routinely obtained in greater than 20:1 diastereomeric excess. Six-membered ring-containing substrates provided the [4+2+2] products however the reactions were not as clean, with aromatic by products being isolated on workup.



**Scheme 2.** Working mechanism for the bimolecular Rh-catalyzed [4+2+2] cycloaddition and the competing intramolecular [4+2] cycloaddition

While specific mechanistic work has not been undertaken, our working view of the reaction pathway is illustrated in Scheme 2. Displacement of the bisolefin ligand on rhodium by the alkyne and one of the double bonds provides **A** which undergoes oxidative cyclization to yield a vinyl rhodium  $\pi$ -allyl intermediate **B**. Reductive elimination from this species provides the [4+2] type

products (**C**) observed in our previous work. Alternatively, the weakly coordinating phosphine oxide can be displaced with a second alkyne to give complex **D** which following migratory insertion and reductive elimination yields the cyclooctatriene product **E**.

In addition to providing a catalyst system for the [4+2+2] reaction discussed above, the discovery of a new catalyst based on the phosphine-phosphine oxide combination illustrates the potential for this type of ligand system, where the dative phosphine oxide can fill the role as a labile ligand that can provide an open coordination site as needed. We have begun to investigate this ligand type in a number of other ligand and reaction systems, including other versions of this type of cycloisomerization.

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