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Rhodium Catalyzed [4 + 2 + 2] Cycloaddition and Alkyne Insertion: A New Route to Eight-Membered Rings

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Over the last 12 years there has been extensive development of rhodium-catalyzed cyclization reactions. A number of workers have reported catalyst systems that perform [4 + 2],[1-8] [5 + 2],[9-19] [6 + 2],[20] and [5 + 2 + 1][21] cyclizations in excellent yields. Additionally there have been a number of examples of rhodium-catalyzed Pauson−Khand-type reactions.[22-26] During this time we have been involved in the development of an asymmetric version of the [4 + 2] cycloisomerization.[7,8] Periodically in the reaction of dieneynes, we observe the formation of a product resulting from the insertion of a second equivalent of the alkyne (Scheme 1). This dimer results from a formal [4 + 2 + 2] cyclization. Herein we report a rhodium catalyst system that selectively yields the dimer product. Additionally, we report this catalyst system can be used to perform the [4 + 2 + 2] cyclization with incorporation of a second alkyne.

A wide variety of reaction conditions where examined in an attempt to reproducibly obtain the dimer product. Ultimately, we found that reaction of $[Rh(NBD)Cl]_2$ with 0.5 equiv or less (based on rhodium), of $AgSbF_6$ in the presence of Me-DuPHOS at 60 °C provides a catalyst system that gives the desired product in good-to-excellent yield. As illustrated in Table 1, both three- and four-atom tethers can be effective, giving either the [6.3.0]- or [6.4.0]-ring systems. Tethers containing either oxygen or nitrogen, as the sulfonamide, were found to be effective. With substrates where the diene does not have a terminal alkyl group, two regioisomers, resulting from the incorporation of the alkyne in two orientations, can be obtained (Table 1, entries 2 and 4). However in the case of entry 4 only one regioisomer was observed.

While dimer formation was used as a model to optimize the reaction conditions for the insertion of an alkyne, it would be desirable to insert a different alkyne during the reaction. Table 2 illustrates that such a cycloisomerization cross-coupling reaction is indeed possible. When the cycloisomerization reaction is run in the presence of 5 equiv of a second alkyne, the desired cross coupled-cyclized product is obtained (Table 2).

In addition to ether and sulfonamide tethers, carbon tethers, in the form of an aromatic ring, were also found to be useful. When the nitrogen in the tether is protected as its acetate, no product was observed. A number of different alkynes are accepted. While simple terminal alkyl acetylenes will provide the desired product (Table 2, entry 4), there appears to be a preference for propargyl ethers, with propargylbenzyl ether generally giving the highest yields. Toluenesulfonamide protected propargylamine also provided the desired product (Table 2, entry 7). Reaction with propargyl alcohol did not proceed. Attempted reaction with 3-hexyne or phenyl acetylene gave only product from dimerization of the dieneyne.

Scheme 1

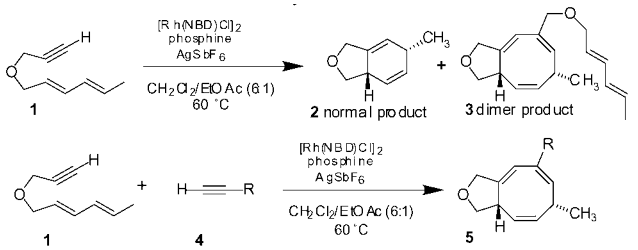
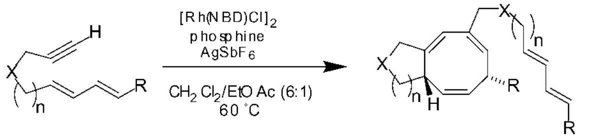
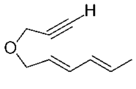
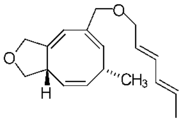
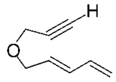
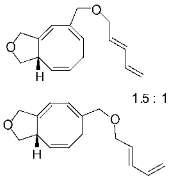
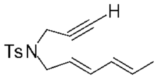
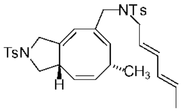
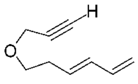
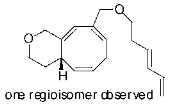


Table 1. Dimer Formation[a]



Entry No.	Dieneyne	Yield[c]	Product
1[a]		80%	
2[a]		44%	 1.5 : 1
3[b]		72%	
4[b]		58%	 one regioisomer observed

[a] The catalyst was generated from a ratio of 1:2:1 of $[Rh(NBD)Cl]_2$:phosphine:$AgSbF_6$ and run in CH_2Cl_2:EtOAc (6:1), Reaction was run at room temperature approximately 12 h. [b] Reaction was run at 60 °C, approximately 12 h. [c] The products were isolated as single diastereomers

In all the cases where the diene has a terminal methyl group only one diastereomer of the product has been observed. In our work with asymmetric [4 + 2] cycloisomerizations we have found that Me-DuPHOS is effective in transferring its chirality to the products of simple dieneynes.[7,8] This is not the case with the catalyst system developed here. The highest selectivity observed in these reactions was in entry 3, Table 2 (41% ee).

At the present time, we do not know the exact nature of the catalyst system. In our previous work on rhodium-catalyzed cycloisomerization systems, we have generated the catalyst by treatment of $[Rh(NBD)Cl]_2$ with 1 equiv of $AgSbF_6$ in acetone

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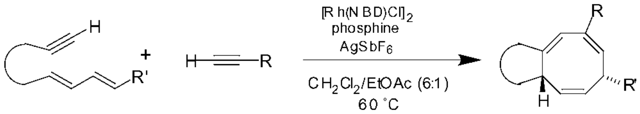
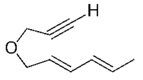
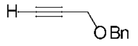
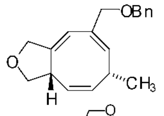
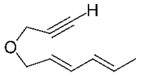
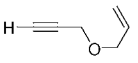
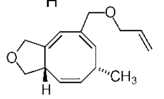
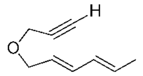
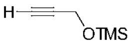
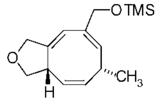
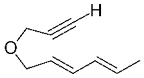
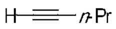
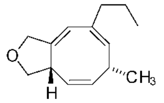
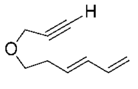
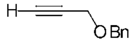
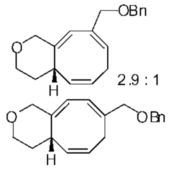
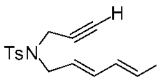
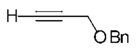
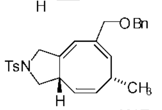
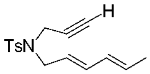
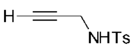
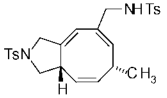
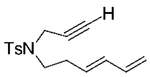
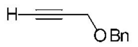
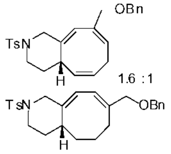
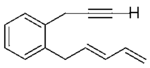
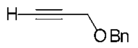
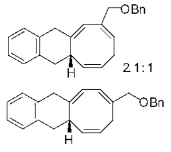
Table 2. [4 + 2 + 2] Cyclization with Incorporation of a Second Alkyne



No.	Dieneyne	Alkyne[b]	Yield	Product
1[a]			73%[c]	
2[a]			36%[c]	
3[a]			63%[c]	
4[a]			41%[c]	
5[a]			55%	
6[a]			70%[c]	
7[a]			49%[c]	
8[a]			69%	
9[a]			43%	

[a] Catalyst was generated from a ratio of 1:2:1 of $[Rh(NBD)Cl]_2$: phosphine: $AgSbF_6$ and run in CH_2Cl_2:EtOAc (6:1), 60 °C approximately 12 h. [b] Reactions were run with 5 equiv of alkyne [c] The products were isolated as single diastereomers.

which is then added to the appropriate phosphine. This procedure provides a yellow homogeneous solution that is then treated with H_2 or used as is to catalyze the desired reaction. In the system reported here, the catalyst is generated by treatment of a solution of $[Rh(NBD)Cl]_2$ and a Me-DuPHOS with 0.5 equiv or less of $AgSbF_6$ in THF. Following exchange of the solvent, the catalyst is used after treatment with H_2 gas. After approximately 1 h a dark brown precipitate forms on the walls of the reaction vessel. Formation of the heterogeneous material appears to be a requirement for the formation of the desired product. Given that the reaction takes place in a heterogeneous environment, we tested the ability of rhodium in the absence of a phosphine to catalyze the reaction. When $[Rh(NBD)Cl]_2$ is treated with $AgSbF_6$, a brown heterogeneous mixture is formed. In these cases the only product observed was the normal [4 + 2] cycloisomerization product. There are currently a number of different reaction conditions that have been used to generate rhodium catalysts.[20,27] The Wender system of $[Rh(CO)Cl]_2$ was tested separately and in the presence of triphenylphosphine. In both cases, the normal [4 + 2] cycloisomerization product was obtained as the major product. The catalyst system reported by Zhang[6] also gave the [4 + 2] product, but in this case some of the eight-membered ring product was formed. In addition to DuPHOS, other rhodium phosphine complexes have been found to carry out this reaction. Catalysts made with DPPE, DPPB, and 1 or 2 equiv of triphenylphosphine were found to catalyze the reaction shown in Table 2, entry 1, giving 19, 25, 50, and 34% of the product from insertion of a second alkyne, respectively.

In the area of rhodium-catalyzed cyclizations, there are a number of different reaction manifolds that can be accessed. In this case, we have found that through the treatment of rhodium dimer with less than 1 equiv $AgSbF_6$ a new product can be obtained. This reaction represents a new diastereoselective approach to eight-membered rings. We are currently attempting to determine the catalytically active species and to develop an enantioselective version of this reaction.

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Supporting Information Available: Sample procedures and NMR data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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