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Reverse the Diastereoselectivity of the Rh(I)-Catalyzed Pauson-Khand Cycloaddition

Mark Turlington and Lin Pu*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319, United States

lp6n@virginia.edu

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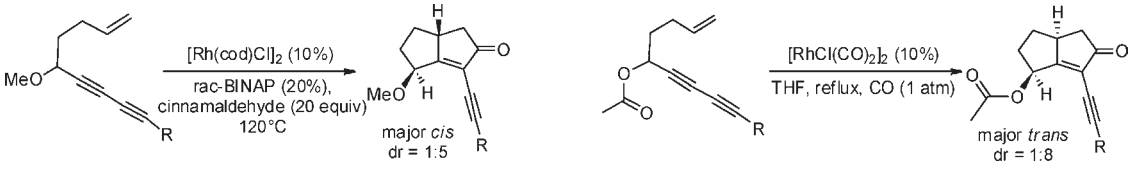
ABSTRACT



It is discovered that the diastereoselectivity of the Rh(I)-catalyzed Pauson–Khand cycloaddition of chiral enynes can be reversed to generate the *trans* diastereomer as the major product in the absence of a chelate phosphine ligand when the substrate contains an appropriate functional group capable of chelate coordination to the Rh(I) center. This expands the application of the Rh(I)-based catalytic processes to prepare both the *cis* and *trans* stereoisomers.

In recent years the metal catalyzed Pauson–Khand (PK) coupling of enynes with CO to generate cyclopentenones has become an increasingly popular alternative to the PK reaction employing stoichiometric $Co_2(CO)_8$.[1] A variety of transition metal complexes have been utilized including Ti,[2] Zr,[3] Ni,[4] Mo,[5] Ru,[6] Rh,[7] Ir,[8] and Pd[9] for the catalytic PK-type reactions in the presence of a CO source. Among the metals employed, the use of Rh has attracted considerable attention. The use of Rh to catalyze the PK-type reaction was first reported simultaneously by Jeong and Narasaka in 1998. Jeong tested a range of Rh catalysts bearing phosphine ligands, discovering that *trans*-$[RhCl(CO)dppp]_2$ [dppp = 1,3-bis(diphenylphosphino)propane] was a suitable catalyst for a variety of enynes.[7a] In contrast, Narasaka employed the phosphine-free $[RhCl(CO)_2]_2$ as a catalyst under CO.[7b,c] The Rh-catalyzed PK-type reaction was also shown to be viable using aldehydes and alcohols as the CO source.[10] In these

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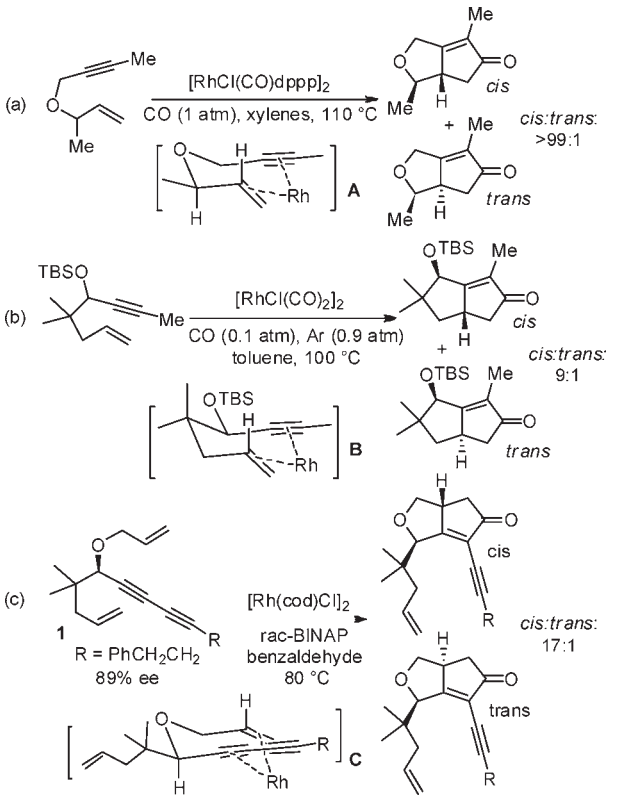
systems, Rh plays the dual role of decarbonylation of the aldehyde and facilitating enyne cyclization. The tandem allylic substitution and PK cycloadditions using a Rh catalyst only or in combination with a Pd complex were also developed.[11] A number of reports for the Rh-catalyzed enantioselective PK-cycloaddition with the use of chiral phosphine ligands have appeared.[12]

The Rh(I)-catalyzed PK cycloadditions were found to exhibit high diastereoselectivity when chiral enynes were used. For example, Scheme 1a shows that [RhCl(CO)-(dppp)]$_2$ catalyzed the reaction of the enyne containing an allylic chiral center to generate the product with a >99:1 ratio of the *cis* and *trans* diastereomers.[13] In Scheme 1b, a chiral propargylic ether-based enyne underwent the Rh(I)-catalyzed PK reaction to give the *cis* stereoisomer as the major product.[7c] Recently, we have initiated a study on the PK cycloaddition of the chiral enynes derived from the 1,3-diyne-based propargylic alcohols because the products from these reactions contain additional enyne units for further structural elaboration. As shown in Scheme 1c, we found that with the use of benzaldehyde as the CO source a Rh(I) complex catalyzed the PK reaction of the optically active dienediyne **1** to generate the *cis* diastereomer with a 17:1 diastereomeric ratio.[14] This reaction was also found to be highly chemoselective with the double bond on the allylic ether group undergoing the cycloaddition much faster than the other one on the carbon chain. In the three examples of Scheme 1a–c, although three different Rh(I) catalysts were used under different reaction conditions, their diastereoselectivities could all be explained by proposing a preferred chairlike transition state for them. In each of the proposed transition states **A**, **B**, and **C**, the substituent at the chiral center is placed at the more favorable equatorial position. Coupling of the enynes in **A**–**C** followed by CO insertion and reductive elimination will produce the observed predominate *cis* diastereomer.

In these reactions, the formation of the *trans* diastereomer should involve a chairlike transition state such as **D** for the reaction in Scheme 1c in which the substituent Y needs to be at the higher energy axial position (Figure 1).[15] Therefore, when the desired product is the *trans* diastereomer, the application of the Rh(I) catalysts will be limited. It would be synthetically very useful if both the *cis* and *trans* diastereomers could be obtained from the

Scheme 1. Examples of Diastereoselective Rh-Catalyzed PK-Type Reactions of Enynes



Rh(I)-catalyzed PK reaction. In order to reverse the diastereoselectivity of the Rh(I)-catalyzed PK cycloadditions of the 1,3-diyne-based enynes, we propose to study the reaction of the chiral enynes that can generate a transition state like **E** in Figure 1. In **E**, the axial substituent Y is capable of coordinating to the Rh center to lower the

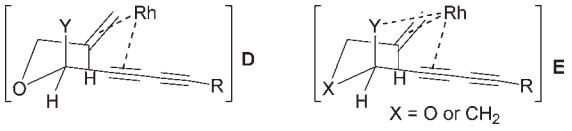


Figure 1. Proposed chair-like transition states for the formation of the *trans* diastereomers in the Rh(I)-catalyzed PK cycloaddition of the chiral enynes.

transition state energy in order to favor the formation of the *trans* diastereomer. Herein, our promising results toward this goal are reported.

We studied the Rh(I)-catalyzed PK cycloaddition of **2**, an analog of **1** but with a smaller substituent adjacent to the chiral propargylic carbon center, in the presence of two different Rh(I) catalysts (Scheme 2). In the presence of [Rh(cod)Cl]$_2$ (cod = 1,5-cyclooctadiene), *rac*-BINAP [racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl], and an aldehyde as the CO source (Method A), **2** gave the *cis*

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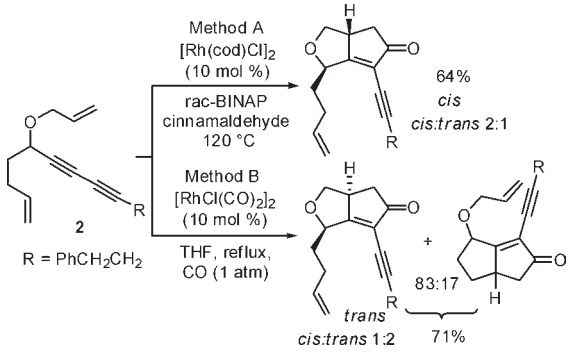
(15) A recent computational study focused on the effects of the electronics on the diastereoselectivity, but it is still consistent with the chairlike transition state proposed here: Baik, M.-H.; Mazumder, S.; Ricci, P.; Sawyer, J. R.; Song, Y.-G.; Wang, H.; Evans, P. A. *J. Am. Chem. Soc.* **2011**, *133*, 7621–7623.

cycloaddition product as the major product.[14] This is the same as that shown in Scheme 1c except for the reduced diastereoselectivity due to the reduced size of the substituent. However, when $[RhCl(CO)_2]_2$ was used as the catalyst under 1 atm of CO in the *absence* of a chelate phosphine ligand (Method B),[7b,16] the major product was the *trans* diastereomer. This reversal of the diastereoselectivity is significant since previously the Rh(I)-catalyzed PK cycloaddition of enynes with either an allylic or a propargylic chiral center normally gave the *cis* diastereomer as the major product except in special cases.[17] Using Method B also gave a small amount of the product from the cycloaddition of the double bond on the nonallylic ether chain. Thus, the chemoselectivity of **2** with Method B is much lower than that with Method A where no such product was observed.

Scheme 2. Two Different Rh(I) Catalysts Led to the Reversal of the Diastereoselectivity of the PK Cycloaddition of a Chiral Enyne



In a computational study on the mechanism of the $[RhCl(CO)_2]_2$-catalyzed PK cycloaddition of enynes,[13] Evans and Baik proposed that the reaction could involve both the four-coodinated square planar 16 electron complex **I** and the five-coordinated trigonal bipyrimidal 18-electron complex **II** (Figure 2). At low CO pressure complex **I** is more populated, and at high CO pressure complex

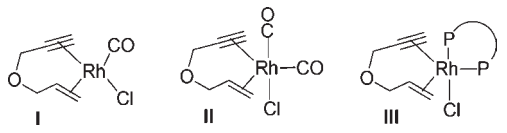
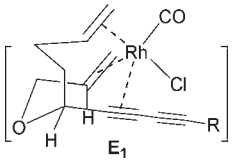


Figure 2. Four- and five-coordinated Rh-enyne complexes.

II is more populated. In the presence of a bisphosphine ligand such as dppp, because of the chelate coordination of the phosphine ligand, the five-coordinated electronically saturated complex **III** should be predominate.

On the basis of the above mechanistic analysis, we propose a hypothesis to explain our observed opposite diastereoselectivity of **2** for the reactions in Scheme 2 employing the two different Rh(I) catalysts. When $[RhCl(CO)_2]_2$ is used under 1 atm of CO, it could involve the four-coordinated intermediate **I** which makes the transition state $\mathbf{E_1}$ possible. In $\mathbf{E_1}$, the axial homoallyllic group could coordinate to the unsaturated Rh(I) center, leading to the formation of the major *trans* diastereomer.[18] However, in the presence of the chelate bisphosphine ligand *rac*-BINAP, the five-coordinated and electronically saturated intermediate **III** will be predominate. This makes the transition state like $\mathbf{E_1}$ less likely but a transition state like **C** with an equatorial homoallyl group more favorable, giving the major *cis* diastereomer. The smaller size of the substituent of **2** versus that of **1** makes the energy difference between the axial and equatorial smaller, leading to the reduced diastereoselectivity of **2** versus **1** in the reaction. The transition state $\mathbf{E_1}$ could also explain the lower chemoselectivity of **2** with the use of Method B since the coordinated double bond of the nonallyloxy group in $\mathbf{E_1}$ could also couple with the coordinated triple bond to give the corresponding PK cycloaddition product.



We studied the effect of the chain length of the substituent of **2** on the Rh(I)-catalyzed PK cycloaddition. As shown in Scheme 3a, when the chain of the substituent at the chiral propargylic center is extended in **3**, Method B gave only a 1:1 mixture of the *cis* and *trans* diastereomers. This demonstrates that the increased chain length of the substituent in **3** makes the axial chelate coordination of the substituent less favorable than that shown in $\mathbf{E_1}$ for **2**, giving the reduced *trans* isomer formation. However, because there is little difference in the size of the substituents between **2** and **3** at the propargylic chiral center, when Method A was used their diastereoselectivity is the same. Compound **4** has a reduced chain length versus **2** for the substituent at the propargylic chiral center. As shown in Scheme 3b, with the use of Method B, the diastereoselectivity for the formation of the *trans* isomer is increased to 3:1. This could be explained by a better coordination of the allyl group of **4** to the Rh(I) center than that of the homoallyl group of **2** shown in $\mathbf{E_1}$. However, because the size of an allyl group is also not significantly different from those of the substituents in **2** and **3**, the diastereoselectivity of **4** with the use of Method A is the same as those of **2** and **3**. Here, all the reactions of **3** and **4** showed high chemoselectivity without the cycloaddition of the double bonds on

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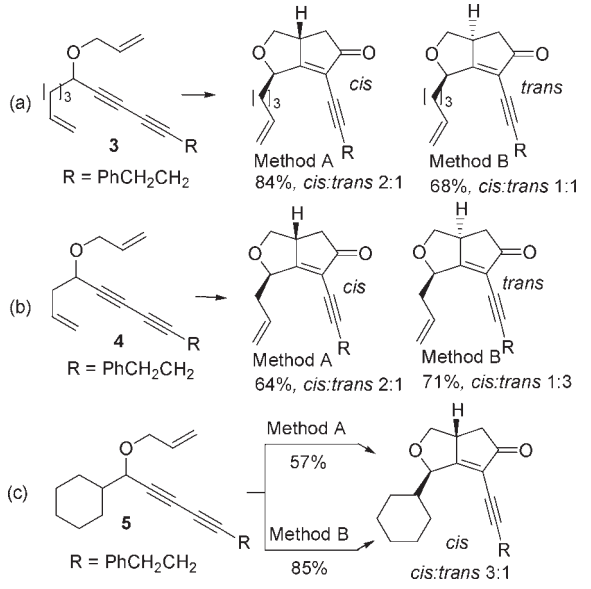
(18) For a reversal of the diastereoselectivity of a $Mo(CO)_6$-mediated PK cycloaddition by an additional substituent coordination, see: Brummond, K. M.; Curran, D. P.; Mitasev, B.; Fischer, S. *J. Org. Chem.* **2005**, *70*, 1745–1753.

the nonallyloxy group. The much greater chemoselectivity of **3** and **4** compared to **2** with the use of Method B could be attributed to the slower rate of formation for the six- or four-membered ring than the five-membered ring.

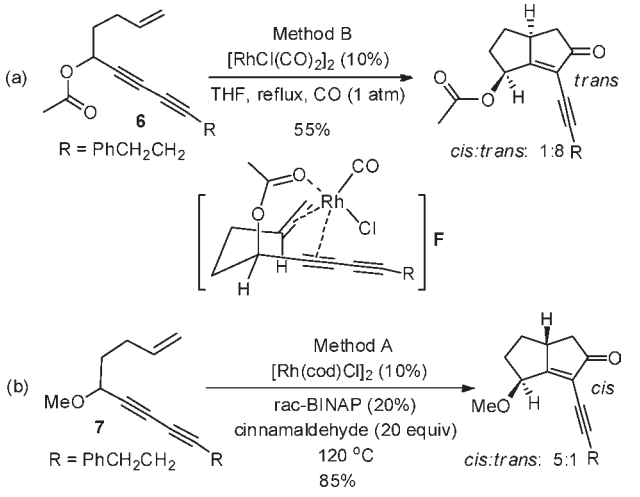
We also studied the reaction of compound **5** that contains no additional coordinating group for a transition state like $\mathbf{E_1}$. For this compound, both Methods A and B gave the *cis* diastereomer as the major product with the same diastereoselectivity of 3:1. This is because **5** cannot provide additional coordination to the Rh(I) center in Method B to stabilize the axial orientation of its substituent and the transition state like **C** is more favorable. The study of compounds **2**–**5** in the Rh(I)-catalyzed PK cycloadditions with and without a chelate phosphine ligand supports our proposed approach to reverse the diastereoselectivity of this catalytic process.

Scheme 3. Two Different Rh(I) Catalysts Led to the Opposite Diastereoselectivity for the PK Cycloaddition of the Chiral Enynes



In order to further develop this diastereoselectivity reversal strategy, we studied the Rh(I)-catalyzed PK cycloaddition of the enyne **6** by incorporating an ester group for potential chelate coordination (Scheme 4a). With the use of Method B, we were pleased to find that **6** underwent the PK cycloaddition to give the corresponding *trans* product with a greatly enhanced diastereomeric ratio of 8:1. This significantly improved diastereoselectivity indicates that, in the transition state **F**, the chelate coordination of the ester carbonyl oxygen should be more favorable than the double bond coordination in $\mathbf{E_1}$. Steric factors may be important here since the lone pair electrons of the carbonyl oxygen in **F** should be more sterically accessible than the π electrons of the double bond in $\mathbf{E_1}$. When the AcO group of **6** was replaced with a MeO group (compound **7**), the diastereoselectivity with the use of Method B was decreased to 3:1 (*trans*/*cis*) since the coordination of the MeO to the Rh(I) center is both sterically and electronically less favorable in a transition state like **F**. The stronger chelate coordination of **6** as shown in **F** can be also used to explain the reduced diastereoselectivity of **6** when Method A was applied which gave a *cis*/*trans* ratio of 1.5:1 for the product. Here, the chelate coordination of the ester group to the Rh(I) might be in competition with that of the phosphine ligand. In contrast, with the use of Method A, **7** was converted to its PK cycloaddition product with a much better diastereoselectivity of 5:1 (*cis*/*trans*) due to the less favorable MeO coordination (Scheme 4b). Therefore, by properly choosing the functional groups on the chiral enynes and matching them with the catalysts, both *cis* and *trans* diastereomers can be obtained as the major products from the Rh(I)-catalyzed PK cycloaddition.

Scheme 4. Matching the Functional Groups of the Chiral Enynes with the Catalytic Conditions to Obtain Both the *trans* and *cis* Diastereomers of the PK Cycloaddition Products



In conclusion, we have demonstrated that the generally observed diastereoselectivity of the Rh(I)-catalyzed PK cycloaddition of chiral enynes can be reversed through a judicious choice of substrates and catalysts. It was found that when an appropriate functional group capable of chelate coordination to a coordinatively unsaturated Rh(I) center is incorporated into the chiral enyne substrates, the previously unfavorable *trans* diastereomer can be obtained as the major product for the PK cycloaddition of chiral enynes. This study should expand the application of the Rh(I)-catalyzed diastereoselective PK cycloadditions in organic synthesis.

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Supporting Information Available. Synthesis and characterization of the new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.