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LETTERS

Recent advances in Rh(I)-catalyzed carbocyclization reactions

John E. Robinson*

Department of Chemistry, Indiana University, Bloomington Indiana 47405. U.S.A.

Abstract—Transition metal-catalyzed annulations are among some of the most powerful transformations available for target directed synthesis. Rhodium(I)-catalyzed carbocyclization reactions have become particularly pertinent due to their immense synthetic utility. The following essay provides a critical account of some of the important mechanistic and stereoelectronic aspects of these reactions. © 2001 Elsevier Science. All rights reserved.

Introduction

Transition metal-catalyzed annulation reactions of tethered enyne or vinylallene derivatives provide some of the most powerful transformations in organic chemistry. Recent advances in rhodium(I)-catalyzed annulation reactions have attracted significant attention, primarily due to their immense synthetic versatility and the unique selectivities that are often obtained. The following review provides a critical account of recent developments in this area, as summarized below: (a) Enyne Cycloisomerization; (b) [2+2+1]; (c) [4+1]; (d) [4+2]; (e) [5+2]; (f) [6+2] (Fig. 1).

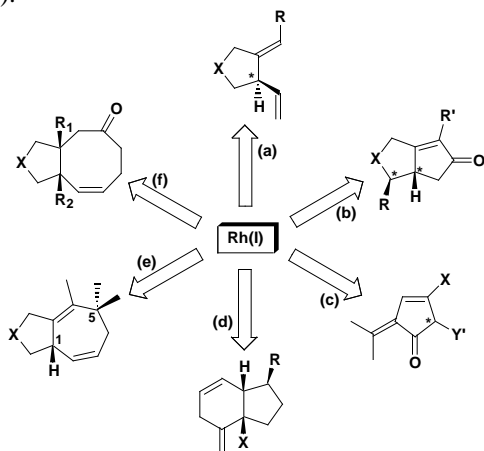


Figure 1

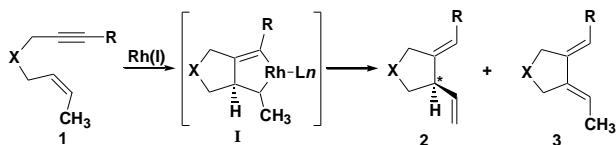
(a) Enyne Cycloisomerization: The transition metal-catalyzed *intramolecular* cycloisomerization of 1,6-enynes to 1,4-dienes allows the construction of intermediates which are not accessible *via* a classical Alder-ene process.¹ Recently, contributions by Buchwald² and Trost^{3,4} have demonstrated the feasibility of titanium, palladium, and ruthenium-catalyzed Alder-ene reactions.

The first rhodium-catalyzed cycloisomerization was described Zhang¹ and co-workers, in which they directly address the limitations of other transition metal-catalyzed processes. They demonstrated that the extreme reaction conditions necessary for carbocyclization with Ru and Ti catalysts could be alleviated through the use of the [Rh(diphos)Cl]₂, which proceeds at room temperature, and allows for catalyst tuning through diphosphine ligand exchange. The reaction presumably proceeds through a metallacyclopentene intermediate **I**, which then undergoes β -hydride/reductive elimination (**Scheme 1**). Treatment of the 1,6-enyne **1** (R=Ph; X=O) with [RhCl(dppb)]₂ furnished the 1,4-diene **2** in 84% yield. Interestingly, the coordinatively unsaturated Rh/AgSb₆ species is required to facilitate smooth elimination, as olefin isomerization products **3** are prevalent when more coordinatively saturated rhodium(I) catalysts are employed.

Furthermore, the *cis*-olefin reacts exclusively, which is the reverse of the Ti-catalyzed system.² A range of heteroatom tether/alkyne substituents are also tolerated

* John E. Robinson. Tel.: 1-812-855-4390; fax: 1-812-855-8300; e-mail: johjorob@indiana.edu.

(X=O, BsN), (R=Ar, CO₂Me, Me), in which the ether tethered enynes exhibit enhanced reaction rates, contrary to carbon-tethered systems which are inert to these conditions. This prompted the development of the following catalysts. Treatment of **1** (X=C(CO₂Et)₂, R=Me) with [Rh(BICPO)Cl]₂/AgSbF₆, furnished the desired product **2** in 90% yield (**Scheme 1**).



Scheme 1

This transformation was also amenable to asymmetric catalysis, as illustrated in the cycloisomerization of **1** (X=O, R=Ph) with [Rh((*R,R*)-Me-DuPHOS)Cl]₂/AgSbF₆, furnishing the enantiomerically enriched product **2** in 62% yield with excellent enantioselectivity (96% *ee*). Although a model for the origin of enantioselectivity was not provided, it is consistent with the explanation summarized in **Figure 2**.

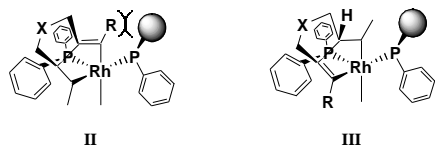
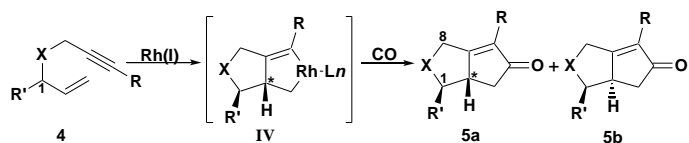


Figure 2

The steric interaction of the **R** group with the bulky phenyl ring of the bidentate phosphorus ligand **II** could presumably account for facial discrimination in initial metallacycle formation, consistent with observed products. Additionally, it appears that the electron-deficient alkynes (R=Ar), undergo the asymmetric transformation with greater efficiency with the more electron-donating (Me-DuPHOS) ligands. Electron-rich alkynes require less π -acidic BICP ligand, whereas the nitrogen-containing tethers require the original (BCPO) ligand conditions. Therefore, the rhodium-catalyzed cycloisomerization reaction proceeds under mild reaction conditions, allowing for efficient catalyst tuning through ligand exchange, and is also applicable to *cis*-substituted ene-alkenes.

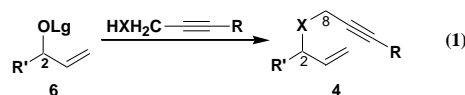
(b) Pauson-Khand Annulation: The development of the first rhodium-catalyzed Pauson-Khand annulation was a direct result of the necessity to have a more practical catalyst, which facilitates this transformation under less forcing conditions.⁵ Treatment of **4** (R'=H, X=O, R=Ph) with [RhCl(CO)₂]₂ and one atmosphere of CO, effected carbocyclization to **5** in 89% yield. This represents one of the first examples of a [2+2+1] using 1 atmosphere of CO (**Scheme 2**). This method also tolerates carbon, oxygen, and nitrogen tethers, in addition to alkyl and aryl substituted alkynes. Simultaneously, Jeong and co-workers⁶ investigated multiple Rh(I) catalysts for the [2+2+1], but found an alternate catalyst to be optimum, *trans*-[RhCl(CO)(dppp)]₂. Treatment of the aforementioned **4** with *trans*-[RhCl(CO)(dppp)]₂ produced the carbocyclization product **5** in 82% yield. The new

catalyst was also compatible with unsubstituted alkynes, as demonstrated by the conversion **4** (R'/R=H, X=C(CO₂Et)₂) to the bicycle **5** in 55% yield.



Scheme 2

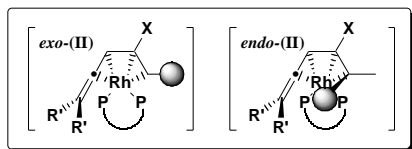
Asymmetric induction in simple tethered enynes was also investigated employing the catalyst derived from [RhCl(CO)₂]₂, (*S*)-BINAP, and AgOTf under an atmosphere of CO,⁷ which furnished the carbocyclization product **5** in 88% yield (81% *ee*). A steric model for predicting enantiomeric outcome resembles that illustrated in (**Fig. 2**), which is again proposed to proceed through the incipient metallacycle **IV**.



Another significant limitation of the Pauson-Khand is the requirement for substrate *intramolecularity*, to minimize side product formation. The first solution to this problem was the employment of a dual catalytic system, Pd₂(dba)₃(CHCl₃) and [RhCl(CO)(dppp)]₂, to effect allylic alkylation (**Eq. 1**; R'=H), followed by the Pauson-Khand (**Scheme 2**), respectively.⁸ This method is limited in so much that the palladium-catalyzed allylic alkylation is restricted to simple allylic fragments. More recently, the development of the tandem regio- and diastereoselective Rh(I)-catalyzed allylic alkylation/Pauson-Khand strategy provides a significant improvement over the dual catalyst method,⁹ in which temperature was used to modulate catalytic activity.¹⁰ This system allows for the incorporation of substituents at C-2 (**Eq. 1**; R'=alkyl, aryl, *et al.*) *via* the regioselective alkylation of unsymmetrical allylic carbonates.¹¹ Furthermore, retention of absolute configuration in Rh(I)-catalyzed allylic alkylation reactions allows for control of absolute configuration at C-2. Treatment of the (*S*)-chiral non-racemic allylic carbonate **6** (**Eq. 1**; R'=2-Np; 99% *ee*) with the lithium anion of tosylpropargylamine, furnished **4** as a >99:1 mixture of regioisomers (98% *cee*), which is then converted to the desired carbocycle **5** in 82% yield, (**5a/5b** = 43:1). The high degree of diastereoselectivity may be attributed to the steric bulk of the C-2 substituent, which facilitates diastereofacial selection in enyne complexation prior to metallacycle formation, in direct agreement with the diastereotopic binding observed in [5+2] and [4+2] annulation strategies.¹²

Therefore the Rh(I)-catalyzed Pauson-Khand proceeds under mild reaction conditions and with minimal substrate limitations. Furthermore, the tandem processes promises to provide a versatile and diastereoselective method for construction of 2-substituted-5,5-bicyclic systems.

(c) **[4+1] Annulation:** The [4+1] carbocyclization reaction was initiated as a study into $\text{exo-}^2/\text{endo-}^4$ bound rhodium(I) intermediates. The tendency for conjugated diene-transition metal complexes to exhibit multiple binding modes, and a general lack of knowledge surrounding vinyl-allene complexation prompted the examination of a series



Scheme 3

of differentially substituted allenes.¹³ This study resulted in the isolation of the first stable rhodium(III) metallacycles. Treatment of an *E/Z*-mixture of **7** with Wilkinson's catalyst, afforded a mixture of the *endo*-II ($Y'=\text{TMS}$) and *exo*-II ($Y=\text{TMS}$) derivatives,¹⁴ which undergo gradual equilibration to furnish the exo-^4 isomer exclusively. This was attributed to the formation of the 5-membered metallacycle **V** (Scheme 3), which can undergo thermal flip-envelop inversion and reductive elimination to give back the isomerized endo-^4 -intermediate. The isolation of the metallacycle prompted the development of a catalytic process, in which the *endo*-II/Rh(I) complex, under an atmosphere of carbon monoxide, produced the carbonyl insertion product **8** in 98% yield.

Unfortunately, treatment of the vinyl-allene with $\text{RhCl}(\text{PPh}_3)_3$ under CO did not furnish any of the desired product. However, the increasingly coordinatively unsaturated catalysts, $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{PF}_6$ and $[\text{Rh}(\text{cod})(\text{dppb})]\text{BF}_4$, proved effective for the conversion of **7** to **8** with a variety of different alkene derivatives. In all examples, a mixture of geometrical isomers were obtained (<3:1). However, treatment of the *mono*-substituted allenes ($R=\text{H}$, $R'=n\text{-propyl}$, $X/Y'=\text{Me}$) led to retention of alkene geometry about the allene. This may be rationalized through the facial selective binding of the vinylallene followed by disrotary ring closure. This result is in direct agreement with the stereochemical induction observed in other Rh(I) catalyzed transformations.

The introduction of a chiral ligand (*R,R*)-Me-DuPHOS to the aforementioned catalyst, produced the chiral complex $[\text{Rh}\{(\text{R,R})\text{-Me-DuPHOS}\}(\text{cod})]\text{PF}_6$.¹⁵ Treatment of **7** ($X/Y=n\text{-propyl}$, $R/R'=\text{Me}$) with the chiral complex under an atmosphere of carbon monoxide, furnished an equal mixture of the enantiomerically enriched product **8** (42% *ee*) and -^4 -hydride elimination product **9**. This is consistent with products observed in the enyne cycloisomerization reaction. Additional studies demonstrated that side-

reactions could be minimized by increasing the CO pressure to 5 atm (62% *ee*), which presumably increases the rate of migratory insertion.

Although a similar trend of reactivity was obtained over a range of alkyl substitutions, the reactions generally afforded products with low enantiomeric excess. Additional improvement in rate and asymmetric induction were obtained for the ester-substituted alkene ($X=\text{CO}_2\text{Bn}$, $Y=\text{Ph}$, $R/R'=\text{Me}$). In this case, the reaction proceeds in excellent yield (94%) and with high enantioselectivity (95% *ee*). The origin of asymmetric induction in these examples may be attributed to the binding of the catalyst to the vinyl-allene, as illustrated in Fig. 3, in which there is an unfavourable steric interaction between **X** and the methyl group of the ligand in **VI**.

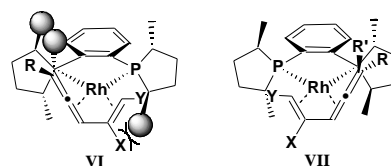


Figure 3

Facial exchange of the vinyl-allene leads to a less sterically hindered derivative **VII**, which is consistent with the absolute configuration of the product, assuming bond formation from the face of the metal. Furthermore, the degree of asymmetric induction should be dictated, at least to some extent, by the size of the **X** substituent, which is in agreement with experimental observations.¹⁶ These results indicate that enantio-differentiation occurs prior to rhodacycle **V** formation, which is further substantiated with observation that the opposite terminal olefin geometry results in the opposite enantiomer, albeit with decreased yield and enantiomeric excess.¹⁷

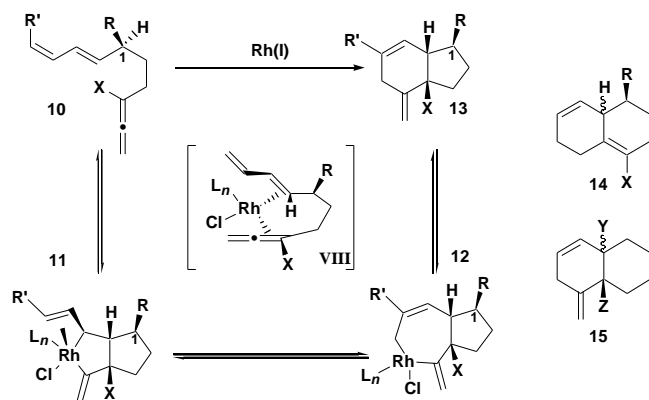
Hence, the rhodium(I)-catalyzed [4+1] cycloaddition reaction provides a convenient method for the enantioselective construction of non-conjugated 5 member enones, which would be difficult to access through classical methods. Furthermore, stereoelectronic influences are well precedented in the mechanistically similar enyne cycloisomerization, and may be amenable this particular method.

(d) **[4+2] Annulations:** Owing to the fact that many different transition-metal catalysts have been applied to the [4+2], and significant contributions have been made toward diastereocontrol and asymmetric induction, recent applications involving Rh(I)-catalysts have focused on non-classical substrates and problems associated with other catalyst systems.

Extrapolation of existing [4+2] methodology has now produced the first examples of tethered allenes in Rh(I)-catalyzed Diels-Alder reactions. The treatment of **10** ($R=\text{CH}_2\text{OTBS}$, $R'=\text{H}$, $X=\text{Me}$) with catalytic $[\text{Rh}(\text{COD})\text{Cl}]_2$ and $\text{P}(\text{O}-o\text{-BiPh})_3$ in THF, produces the 5,6-fused bicyclic **13** as a single diastereoisomer, in 90% yield (Scheme 4).¹⁸ The high degree of stereoselectivity can be accounted for through the facial selective binding of the initial ene-allene complex **VIII**, producing a single metallacycle **11**, as seen

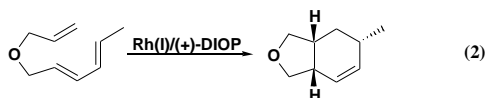
in related systems. The alkene then rotates, and positional isomerization occurs, followed by reductive elimination.

This first example of a stereoselective Rh(I) catalyzed vinylallene Diels-Alder reaction also exhibits chemoselective binding to the internal bond of the allene, which is opposite to the Ni-catalyzed [4+2] process. By altering the electronic nature of the catalyst, using $P(OCH(CF_3)_2)_3$, the 6,6- product **14** is obtained in excellent yield, albeit with diminished diastereocontrol. Additional atoms within the tether allow the formation of 6,7-fused systems, which are uncommon in transition-metal catalyzed processes.



Scheme 4

Further investigation into asymmetric induction of ether-tethered diene/dieneophiles probed the steric and electronic effects of the bridging bidentate DIOP ligand, as well as “bite angle” influence through modification its C-2 bridgehead position.¹⁹ Extensive studies demonstrated that simple electronic effects are not operating in this system, as the increasingly electron deficient *bis*-3,5-(trifluoromethyl) phenyl phosphine modified ligand exhibited minimal change in asymmetric induction. The highest degree of enantioselectivity was obtained with terminally substituted alkenes (**Eq. 2**; 73% *ee*), which is attributed to enhanced facial differentiation in transition state binding.

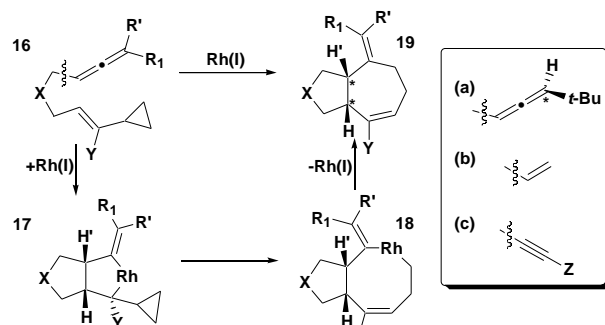


In addition, this substrate did not undergo cyclization with increasingly bulky ligands, suggesting that asymmetric induction may be substrate dependent. Extensive counter-ion studies were performed and suggest that halogens and other counter-ions have little effect on enantiospecificity.²⁰ Progress has also been made in the intermolecular cycloaddition. Various applications utilizing cationic Rh(I) species with non-activated substrates,^{21,22} promoting the regioselective formation of various products and avert common [2+2+2] products.²³

Therefore, recent advances in the Rh(I)-catalyzed Diels-Alder reactions provide the first chemo- and stereoselective carbocyclizations of a tethered diene-allene. Although steric and electronic influences in the intramolecular

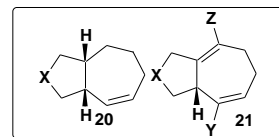
cyclization have been addressed, a general solution is not yet been forthcoming. New applications in *intermolecular* cyclizations have also been achieved, providing access to new classes of carbocycles with unactivated substrates.

(e) [5+2] Annulation: Development of the [5+2] intramolecular cyclization²⁴ relied on extensive background research in the Rh(I)-catalyzed [4+2] annulations reactions.²⁵ Formation of the seven-membered ring was envisioned to arise from a strain-induced cyclopropane opening of the incipient metallacycle, followed by reductive elimination to yield the desired products (**Scheme 5**). To this end, **16c** ($X=C(CO_2Me)_2$, $Y=Me$, $Z=H$) was readily converted to the 5,7-fused bicycle **21** in 82% yield, utilizing AgOTf modified Wilkinson’s catalyst. The Rh(I) system was then applied to range of differentially substituted vinyl cyclopropanes, which all undergo cyclization in good to excellent yield (71-92%).



Scheme 5

Olefin isomerization is observed in the presence of the $Z = \text{Methyl}$ substituted alkyne, and is the exclusive product in the silylated derivative. This synthetic limitation was overcome through the introduction of a less sterically encumbering Rh(I) catalyst, $[RhCl(CO)_2]_2$, which has good precedent for the opening of vinyl-cyclopropanes.²⁶ Treatment of **16(c)** ($X=C(CO_2Me)_2$, $Y/Z=Me$) with $[RhCl(CO)_2]_2$ selectively formed the fused bicycle **21** in 84% yield. Interestingly, it appears that the (*E*)-vinyl-cyclopropanes react more readily, opposite the original catalyst system. Investigation

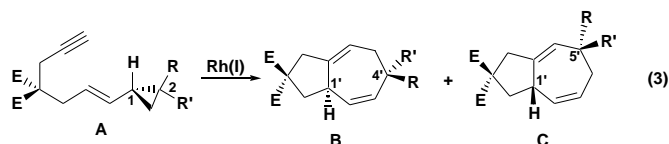


into the scope of the [5+2] first led to the examination of alkene acceptors **16(b)**.²⁷ Under the previously optimized reaction conditions, carbocyclization of the ene-vinyl cyclopropane **16(b)** ($X=C(CO_2Me)_2$) proceeded smoothly to produce the *cis*-diastereoisomer **20** in 86% yield. The *cis*-diastereoisomer is produced exclusively in all cases of fused 5,7-bicycles, though corresponding methyl (*quaternary* bridgehead) substituted products require the addition of AgOTf to prevent decomposition. Increasing the length of the tether by one methylene furnished the *trans*-diastereoisomer as the exclusively product, though the rate of the reaction is decreased drastically, possibly indicating a thermal process. Further methyl substitution of the terminal olefins produced only β -hydride elimination

products, which are constant with the *ene*-cycloisomerization route presented earlier.

Attention then shifted toward allenic functionality in the hopes that β -hydride elimination products could be averted. As expected, both catalyst systems proved effective in the cycloaddition reaction, with a general preference for the formation of the *cis*-diastereoisomer over a range of differentially substituted allenic vinylcyclopropanes. The stereospecificity of this reaction was also examined with a chiral allene. Treatment of **16(a)** (91% *ee*) with Wilkinson's catalyst furnished the cycloaddition product **19** with complete retention of stereochemistry (92% *ee*). This was facilitated through facial selective binding of the vinyl-allene analogous to the [4+2] methodology **VIII**, **Scheme 4**.

The latent stereochemical effects of substitution about the cyclopropane were next addressed.²⁸ Initial findings suggest that the relative chemistry about the 1,2-disubstituted cyclopropane dictates diastereoselectivity in cleavage, as both geometrical isomers **A** (R=Me, R'=H) and (R=H, R'=Me) produced single regioisomers **B** but opposite diastereoisomers upon cleavage (**Eq. 3**).



Alternatively, 1,1-disubstituted analogues are also amenable to this methodology, and the alkoxy substituted system exhibits an enhanced rate. Additional investigation into possible mechanistic implications of the 2-substituent was then undertaken.²⁹ Generally speaking, Rh(PPh₃)₃OTf catalyzed carbocyclizations of free and protected *trans* 2-hydroxy methyl groups **A** (R'=H) produce **B** exclusively. However the dimeric Rh(I) catalyst produces mixtures of regioisomers **B/C**, but in good yield. Electron withdrawing substituents exhibit unique behaviour, as the dimeric catalysts produces the opposite regioisomer **C** selectively, but maintains stereochemical integrity, which is consistent with the relative electron density of the two species.³⁰ Similar investigation into *cis*-disubstituted cyclopropanes produced the expected product, with retention of cyclopropane stereochemistry. Electron withdrawing substituents produced mixtures of regioisomers, in all but one case, where the **B** was isolated as the exclusive product. The combination of these studies provides a general trend in regio- and diastereocontrol through substituent and catalyst tuning. The synthetic utility of this transformation was then highlighted in the synthesis of (+)-Dictamnol³¹ and (+)-Amphanamol.³²

Initial attempts at the *intermolecular* (5+2) carbocyclization (*via* Wilkinson's catalyst) of simple vinylcyclopropanes were unsuccessful, due to competing cyclotrimerization, and vinyl-cyclopropane isomerization.³³ Employment of the 1,1-oxosubstituted vinyl cyclopropanes alleviated the rate dependant competing reactions. Treatment of **22** (R=OTBS, Z=H) and **23** (R'=Ac) with

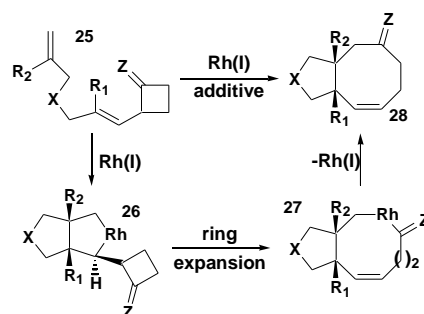
Wilkinson's catalyst, yielded the carbocyclization product **24** in 88% (**Scheme 6**).

The apparent need for activated vinyl-cyclopropanes thus prompted the re-examination of this strategy.³⁴ Conformational analysis suggested that the energy difference between **22** and **22'** could be minimized through the introduction of bulky substituents at C-1'. This intermediate can then form the Z₃-intermediate **IX**, which can presumably undergo cycloaddition with the alkyne. This hypothesis accounts for the lack of reactivity in the unsubstituted systems, as the activation barrier is too high. Treatment of **22** (R=CO₂Me, Z=CH₂OTBS) with **23** (R'=cProp) and the dimeric [RhCl(CO)₂]₂ catalyst produced **24** in 93%. Various 1'-substituents were explored, elucidating a rate increase with substituent size. Additionally, two acceptable mechanistic routes are proposed by the author.

Therefore, the development of the *intra*- and *inter*-molecular [5+2]

annulation reactions has lead to the delineation of the stereoelectronic and catalyst requirements needed to facilitate the stereoselective construction of various highly functionalized 5,7-fused bicyclic systems.

(f) [6+2] Annulation: The previously developed [5+2] methodology has been further extended to the [6+2] intramolecular cyclization.³⁵ Initial attempts at cyclization of **25** (R₁/R₂/Z=H/H) using unsubstituted cyclobutanes proved unsuccessful (**Scheme 7**). However, precedent for the opening of cyclobutanones existed,³⁶ and focus was shifted toward utilizing this type of 6-carbon component. Treatment of **25** (R₁/R₂=H, X=TsN, Z=O) with Wilkinson's catalysts produced the fused bicycle **28** in 95% yield, as a single diastereoisomer.



Scheme 7

As in all of the previously described reactions herein, the reaction is proposed to proceed through a metallacyclic

26, which then cleaves the neighboring cyclobutanone ring, and reductively eliminates. Both Wilkinson's/AgOTf and the dimeric $[\text{RhCl}(\text{CO})_2]_2/\text{AgOTf}$ catalysts perform well, but for the first time a phosphine source ($\text{P}(n\text{-Bu})_3$) is needed for the dimeric species. Additionally, substitution is tolerated about either alkene, facilitating the construction of quaternary bridgehead carbons. Unfortunately alkynes are not applicable, however allenes similar to those employed in **Scheme 5** ($\text{R/R}'=\text{Me}$, $\text{X}=\text{TsN}$) proceed in excellent yield.

Therefore, the Rh(I)-catalyzed [6+2] carbocyclization reaction allows for the construction of fused 5,8-bicyclic systems. The subtle electronic and steric influences from each of the other system presented herein are harnessed in optimizing this reaction.

Conclusions:

The rhodium(I)-catalyzed carbocyclizations of enyne and vinylallene derivatives presented herein, are representative of the true synthetic diversity of Rh(I)-catalysis toward the preparation of highly substituted, mono- and bicyclic systems. Furthermore, it is rather intriguing that these transformations are all related through the proposed intermediacy of a 5-membered metallacycle. Hence, the formation of the metallacycle provides a common theme in understanding the origin of enantio- and diastereoselectivity in annulation reactions of this type.

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¹⁰ Standard reaction conditions employ 10 mol% $[\text{RhCl}(\text{CO})(\text{dppp})]_2$, MeCN, and 1 (atm) CO.

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¹⁴ Note: In the absence of steric hindrance about the terminal allene bonds, preferential π - π binding occurs.

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¹⁶ As the size of the ester group increases (i.e. ethyl vs. benzyl) enantiomeric excess also increases (91 vs. 95% ee).

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