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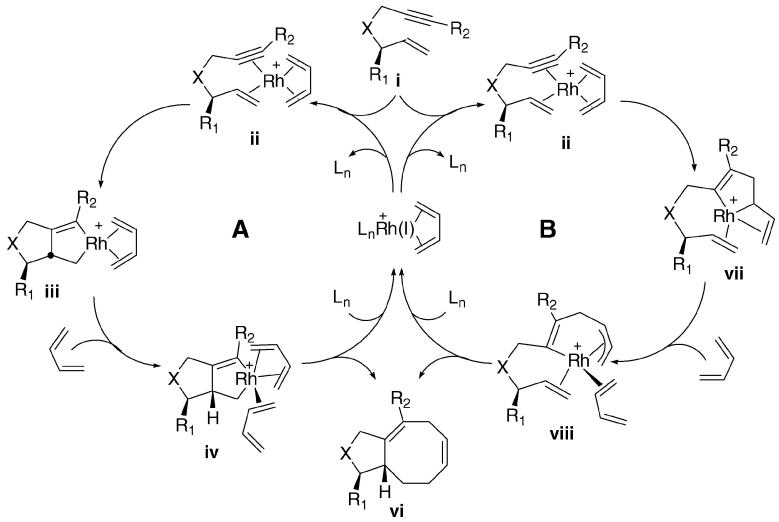

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Diastereoselective Intermolecular Rhodium-Catalyzed [4 + 2 + 2] Carbocyclization Reactions: Computational and Experimental Evidence for the Intermediacy of an Alternative Metallacycle Intermediate

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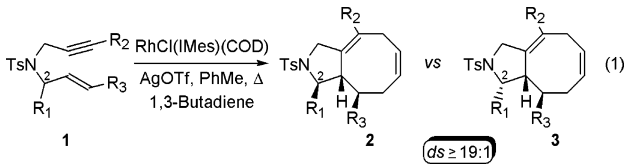
*Inter*molecular rhodium-catalyzed [$m + n + o$] reactions of 1,6-enynes and various π-components (carbon monoxide, alkynes, 1,3-butadienes, *etc.*) provide an expeditious approach for the construction of polycyclic fragments that represent important synthons for target-directed synthesis.[1] We recently reported a diastereoselective intermolecular rhodium-catalyzed [4 + 2 + 2] carbocyclization reaction of the substituted 1,6-enyne **1** (R_1/R_2 = Me, R_3 = H) with 1,3-butadiene to afford the corresponding bicyclic octanoid **2** in high yield (eq 1).[2]



(1)

Excellent diastereoselectivity was obtained irrespective of the nature of the C-2 or alkyne substituents (R_1/R_2 when R_3 = H), in sharp contrast to the related Pauson−Khand reaction,[3] where the nature of these substituents governs the level of diastereocontrol.[4] To elucidate the origin of the excellent stereocontrol obtained in this new transformation, we explored a number of possible mechanisms using high-level density functional theory (DFT) calculations.[5,6] The most intuitive mechanism that is widely assumed for similar reactions[1] is a Pauson−Khand-type mechanism, illustrated as path A in Figure 1. The computed reaction profile of this path is shown in Figure 2 (broken line). The initial binding of the 1,6-enyne **i** with the rhodium catalyst results in adduct **ii**, formally a 16-electron complex with a Rh(I)-d^8 center, which cycloisomerizes oxidatively to afford a Rh(III)-d^6 metallacyclopentene **iii**. Binding of 1,3-butadiene gives intermediate **iv**, which presumably undergoes migratory insertion and reductive elimination to give a product−catalyst complex **v** (not shown in Figure 1). The catalytic cycle closes upon release of the bicyclic product **vi**, and the catalyst is recovered. Our calculations suggest that this generic mechanism[1] is associated with a rate-determining activation barrier of 43.4 kcal/mol when the π-component is 1,3-butadiene. A high barrier of this magnitude is not consistent with a reaction that reaches completion at 110 °C within 6−12 h. The transition state **iv-TS** (Figure 2) is characterized by concerted formation of the two C−C bonds to give the eight-membered cycle.

A number of possible alternatives can be imagined, including stepwise formation of the two C−C bonds. We explored various pathways and identified a mechanism outlined as path B in Figure 1 that not only provides a lower activation barrier, but suggests a distinctively different sequence of reaction steps. After initial complexation of the 1,6-enyne and 1,3-butadiene to the metal center giving **ii**, an oxidative coupling step follows that results in metallacycle **vii**, formally a 14-electron Rh(III) complex. Although a similar metallacyclopentene motif was invoked previously in the intramolecular [2 + 2 + 1] cyclization manifold,[7] the existence of

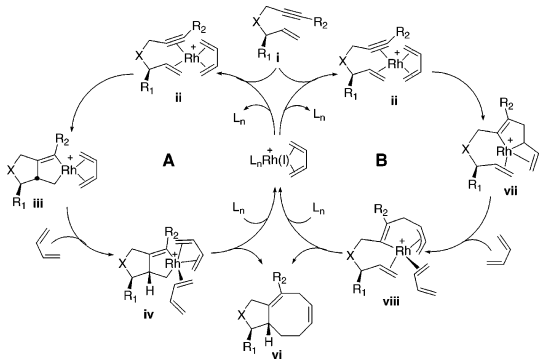


Figure 1. Proposed catalytic cycles for the diastereoselective intermolecular rhodium-catalyzed [4 + 2 + 2] carbocyclization reactions. (L_n = solvent or spectator ligand.)

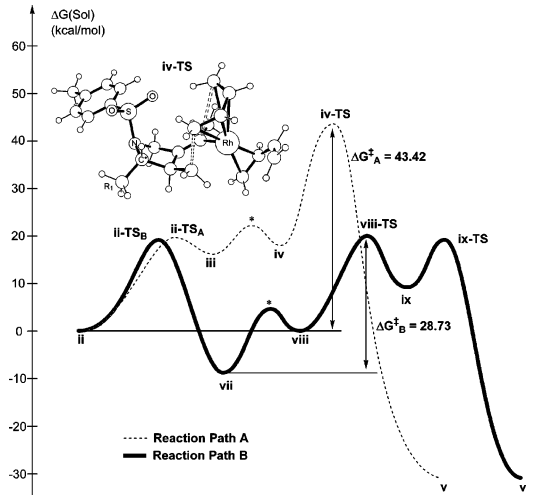


Figure 2. Computed reaction free energy profiles in benzene. The free energy of activation for the rate-determining steps are labeled as $\Delta G^{\ddagger}_A$ and $\Delta G^{\ddagger}_B$, for reaction paths A and B, respectively.

competition between the inter- and intramolecular metallacyclopentene formation was not addressed. The key feature of reaction path B is the intermolecular cyclization that gives **vii**, which is preferred over the cyclization of the 1,6-enyne moiety that yields **iii** (path A). Coordination of an additional butadiene ligand in η^2-fashion forms complex **viii** (Figure S1, Supporting Information), which is a transient 16-electron intermediate leading directly to the rate-determining transition state **viii-TS** (Figure 3) to give the 11-membered heterocycle intermediate complexed with the Rh center, **ix**. Reductive elimination and C−C bond formation across the ring give the desired bicyclic product−catalyst complex **v** after traversing the low barrier transition state **ix-TS**. Interestingly, this transition state is practically isoenergetic with **viii-TS**, having a relative energy of 19.3 kcal/mol compared to that of the initial adduct **ii**, whereas 20.1 kcal/mol was found for **viii-TS**.[8] Another distinctive charac-

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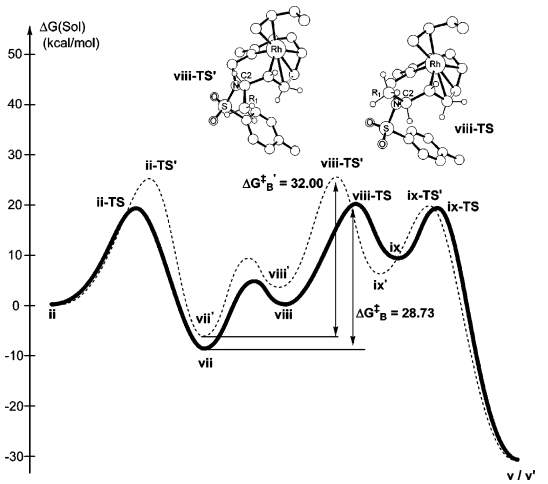

Figure 3. Reaction free energy profiles for the formation of the two diastereomers.

teristic of path B is that it suggests a thermodynamically stable intermediate, **vii**. All intermediates in path A are higher in energy than the initial adduct **ii**.

Mechanistically most significant is the fact that path B does not require a transition state facilitating the concerted formation of two C−C bonds. Instead, the three C−C bonds are formed in separate steps.[9] A detailed molecular-orbital-based explanation of the high activation barrier associated with reaction path A in comparison to that in path B and the classical Pauson−Khand reaction will be reported elsewhere, but the following intuitive rationalization can be constructed. The complexed ligand fragments of the rate-determining transition state of reaction path A, **iv-TS**, are reminiscent of a thermally forbidden [4 + 4] cyclization, whereas there are no orbital symmetry concerns with the alternative transition state **viii-TS**. This rationalization, albeit qualitative, provides an explanation for why reaction path A is allowed for the original Pauson−Khand reaction, where the additional ligand to be coupled is a carbon monoxide ligand and thus constitutes a [4 + 1] cyclization process.

Having established the feasibility of the reaction path B, we explored the diastereoselectivity of path B by inverting the stereocenter and re-evaluating all intermediates and transition states. The alternative path that gives the diastereomer **3** is similar to that resulting in **2** but is associated with higher energies. In particular, the diastereomeric isomer of the key intermediate **vii**, labeled **vii′** in Figure 3, is 2.5 kcal/mol higher in energy. Similarly, the rate-determining transition states **viii-TS** and **viii-TS′** display a solution-phase free-energy difference of 3.3 kcal/mol in our calculations, predicting approximately 3 orders of magnitude faster reaction kinetics for the ring expansion step, **viii** → **ix**, for **2** over its diastereomeric analogue **3**. Inspection of the transition states **viii-TS** and **viii-TS′** offers two intuitive reasons for the energy difference. (i) An energetically unfavorable steric interaction between the tosylamide group and the R_1 moiety exists in **viii-TS′**, whereas the R_1 group points away from the sterically crowded region of the **viii-TS** complex (Figure 3). (ii) The *anti*-disposition of the R_1 group relative to the alkene moiety gives rise to a thermodynamic preference over the *syn*-arrangement of the two functionalities in **viii-TS′**.

On the basis of the proposed new mechanism, we envisioned that a *trans*-1,2-substituted alkene **1** ($R_3 \neq H$) would provide an experimental probe to further distinguish between the two mechanisms. (*E*)-Alkenes are generally poor substrates in related carbocyclization reactions, which are also thought to proceed

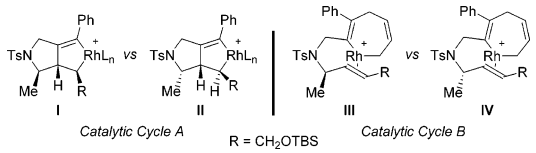

Figure 4. Potential diastereomeric metallacycle intermediates that provide a predictive model for diastereocontrol.

through metallacycle **iii**. The alternative metallacycle **vii**, however, should not be restricted to the same criteria given that the alkene is involved in the penultimate step of catalytic cycle B. Examination of the proposed diastereomeric metallacycle intermediates, derived from computed structure of **viii-TS**, reveals that whereas **III** is clearly favored over **IV**, unfavorable steric interactions in both **I** (Me/R) and **II** (Me/H) increase the potential for the formation of both stereoisomers.[10] Interestingly, treatment of the enyne **1b** (eq 1; R_1 = Me, R_2 = Ph, R_3 = CH_2OTBS) under standard [4 + 2 + 2] reaction conditions furnished the expected cycloadduct **2** in 90% yield with excellent diastereoselectivity (*ds* ≥ 19:1), providing strong experimental support for the calculated mechanism.

In conclusion, we have provided computational and experimental evidence for the existence of a previously undescribed reaction pathway for the rhodium-catalyzed [4 + 2 + 2] reaction involving a 1,6-enyne. This model clearly demonstrates the origin of the excellent diastereoselectivity in this type of reaction and remarkable tolerance of both (*E*)- and (*Z*)-isomers[2] within the 1,6-enyne, which is generally prone to competitive ene-cycloisomerization.

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Supporting Information Available: X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative of **2b** (where R_1 = Me, R_2 = Ph, R_3 = $CH_2OCOC_6H_3(NO_2)_2$), computational details, computed structures, alternative reaction profiles, and energies. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(10) Treatment of the enyne **1b** (eq 1; R_1 = Me, R_2 = Ph, R_3 = CH_2OTBS) under the [2 + 2 + 1] reaction conditions furnished the corresponding bicyclopentenones in 30% yield, as a 2:1 mixture of diastereoisomers.

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