Carbocyclization

DOI: 10.1002/anie.201302496

Computational Studies and Experimental Results—An Example of Excellent Teamwork in Studying Carbocyclization**

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carbocyclization · computational chemistry · cyclopropane · metallacycles · rhodium

The vast possibilities of the cycloaddition reactions of unsaturated substrates like alkenes, alkynes, and heterocumulenes catalyzed by late transition metals have fascinated chemists for decades.[1] Beside unsaturated substrates also strained carbocycles like cyclopropanes and cyclobutanes and their derivatives were identified to be suitable participants in these formal "higher-order" cycloaddition reactions.[2] A well-known example for reactions tying together three different unsaturated reaction components (alkene, alkyne, and CO) in a defined manner is the Pauson–Khand reaction. The linkage of the single reaction participants in a chemo-, regio-, and stereoselective manner continues to display a significant challenge for preparative chemists since it provides the possibility to construct unusual structures difficult to assemble stepwise. Computational studies have more recently proven to be excellent tools for the investigation of these "formal" cycloaddition reactions, along with their mechanisms and the explanation of regioselectivities and unexpected reaction outcomes.[3]

In a recent publication Baik and Evans et al. followed a somewhat different approach.[4] They envisioned a novel rhodium-catalyzed [3+2+1] cycloaddition reaction of alkenylidenecyclopropanes (ACPs) with CO to form *cis*-fused bicyclohexenones and subsequently found theoretical evidence, by calculating suitable reactive intermediates and species, that the reaction can indeed occur. After they had established that the reaction involves reasonable energy barriers and should favor the generation of *cis*-fused bicyclohexenones in a feasible catalytic cycle, they performed the first experiments. Hitherto, [3+2+1] cycloaddition reactions have been developed, often based on the Pauson–Khand reaction, by purely experimental approaches only.[5]

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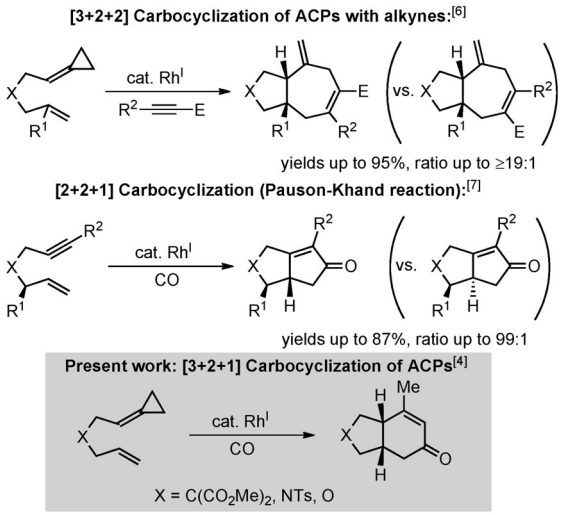
[**] We thank Prof. Uwe Rosenthal for his continuing support, helpful discussions, and insightful comments. M.H. thanks the DFG (HA3511/3-1) and the Leibniz-Gemeinschaft for financial support. I.T. thanks the Fonds der Chemischen Industrie for a Kekulé Fellowship.

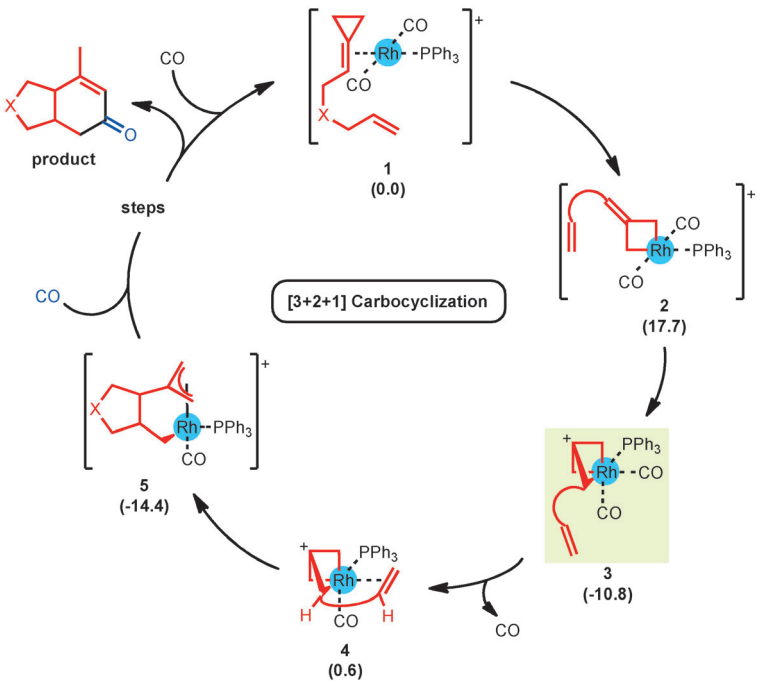
The highlighted work was preceded by a report on a rhodium-catalyzed [3+2+2] carbocyclization of ACPs with activated alkynes yielding *cis*-fused bicycloheptadienes[6] and the demonstration that the stereocontrol in the Pauson–Khand reaction is improved if a five-coordinate Rh complex is used.[7] Accordingly, an investigation based on the logical combination of these two principles was undertaken and resulted in the novel [3+2+1] carbocyclization of ACPs (Scheme 1).



Scheme 1. Development of Rh-catalyzed carbocyclization reactions.

Initial studies dealt with the most plausible cationic Rh^I complex as the starting point of the catalytic cycle. The computational studies included the calculation of the solution-phase Gibbs free energies $\Delta G(Sol)$ for different square-planar Rh^I complexes. It was found that a complex composed of two *trans*-coordinated CO ligands, together with the coordinated olefin moiety of the alkylidenecyclopropane and finally a PPh_3 ligand was the most stable species (**1**; Scheme 2).

The proposed reaction mechanism starting from complex **1** involves first the opening of the cyclopropane moiety and the oxidative addition to the metal center (**2**). A spontaneous rearrangement to form the unanticipated Rh^{III} trimethylene-



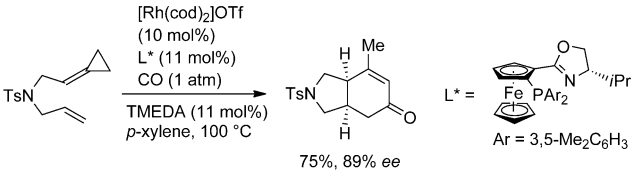
Scheme 2. Significant steps of the proposed reaction mechanism; ΔG(Sol) (in kcal mol^{-1}) values are given in parentheses below.

methane (TMM) complex results in the more stable intermediate **3**, which is proposed to be the resting state of the catalytic cycle (Scheme 2, highlighted structure). The C–C distances show the symmetric bonding of the TMM group to the metal, providing a piano-stool-type coordination mode. The TMM fragment acts as a formally trianionic ligand, while it is normally considered to be dianionic.[8] Upon dissociation of one of the CO ligands in the course of the reaction, the ACP's pendant vinyl group can coordinate to the metal center (**4**). The cycle passes through three allylic intermediates starting with complex **5**, already possessing the newly formed five-membered ring, leading to the coordination and subsequent insertion of the second CO ligand (not shown).[9] After reductive elimination and 1,3-hydride shift, the exocyclic double bond is isomerized and the final product released. In contrast to other cyclization reactions the rate-determining step has been proposed to be the insertion of the vinyl group (**3**→**5**) rather than the oxidative addition, which is energetically very favorable due to release of energy upon ACP ring opening. Hereby, the stereocontrol for the formation of the stereocenters is delayed to a later stage of the catalytic cycle, when substrate control of the stereochemistry prevails.

To evaluate the accuracy of the proposed active catalyst species, different Rh^{I} precursor complexes were screened. All three tested catalyst systems—[{Rh(CO)$_2$Cl}$_2$]/PPh$_3$, [Rh(CO)(PPh$_3$)$_2$Cl], and [Rh(PPh$_3$)$_3$Cl]—displayed good to excellent activity and furnished the *cis*-fused bicyclohexenones in high stereoselectivity (*cis*/*trans* ≥ 19:1). In agreement with the computational studies, cationic Rh^{I} complexes achieved higher conversions than the corresponding neutral complexes. The use of either bidentate ligands or 2 equivalents of monophosphines resulted in a decrease in yield, while the addition of the less frequently used silver salt AgCO$_2$CF$_3$ proved to be optimal for the abstraction of the chloride ion. A large array of different ACPs were transformed into the corresponding *cis*-fused bicyclohexenones with high yields and stereoselectivities by application of the optimized catalyst system consisting of [Rh(PPh$_3$)$_3$Cl] and silver trifluoroacetate.

As a final highlight the authors anticipated that even though enantioselective [3+2+1] carbocyclizations with ACPs have been very rare,[10] consistent with previous results indicating the preference of monodentate over bidentate ligands, their computational and experimental results hinted that certain chelating ligands may be tolerated in the decisive stereochemistry-determining step of the catalytic cycle (**2**→**3**). Indeed, in a representative reaction, when [Rh(cod)$_2$]OTf (cod = 1,5-cyclooctadiene, OTf$^-$ = trifluoromethanesulfonate) and a chiral P,N ligand were applied, a bicyclohexenone was isolated with high enantiomeric excess (Scheme 3).

Baik and Evans et al. experimentally established a highly stereoselective as well as enantioselective Rh-catalyzed [3+2+1] carbocyclization with ACPs after they had assessed the catalyst's



Scheme 3. Enantioselective version of the [3+2+1] carbocyclization. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Ts = *p*-toluenesulfonyl

requirements and reaction conditions and discerned the rate-determining steps in the catalytic cycle with the help of computational studies. The authors demonstrate the increasing predicting value of calculations. This comprehensive investigation proved that even though experimental results as well as computational studies can provide great results on their own, merging the two strategies in the initial phase of a research project leads to results with much greater impact for the development of synthetic methods.

Received: March 25, 2013
Published online: May 6, 2013

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