doi:10.2533/chimia.2010.153 Chimia 64 (2010) 153–156

Enantioselective Rhodium-Catalyzed C–C Bond Activations

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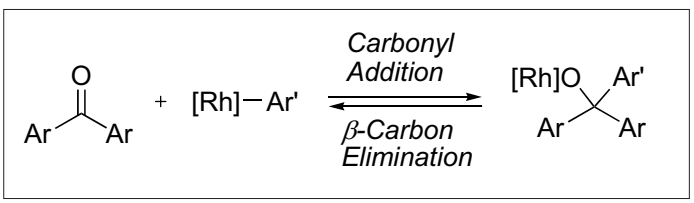
§SCS Mettler-Toledo Award Winner (Oral Presentation)

Abstract: The catalytic activation of carbon–carbon single bonds represents a major challenge in organometallic chemistry. Strained ring substrates occupy in this respect a privileged role as their inherent ring strain facilitates the desired metal insertion. Employing symmetrically substituted *tert*-cyclobutanols, an enantioselective rhodium(I)-catalyzed β-carbon elimination creates alkyl-rhodium species bearing all-carbon quaternary stereogenic centers. Downstream reactions enable access to a wide range of synthetically versatile products such as substituted cyclohexenones, lactones and indanols with excellent enantioselectivities of up to 99% *ee*.

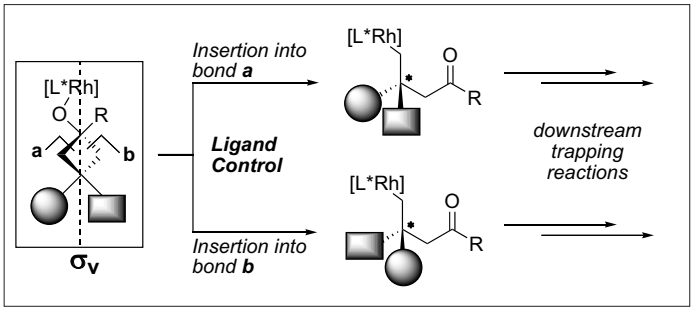
Keywords: Asymmetric catalysis · C–C activation · C–H activation · Rhodium · Ring expansion

1. Introduction

Facile and selective access to functionalized organometallic compounds is one of the aims of transition-metal catalysis. Conventional approaches always require pre-functionalization of the substrates in the form of halides and/or stoichiometric amounts of main group metal species. In contrast, the direct and catalytic activation of carbon–hydrogen (C–H) and carbon–carbon (C–C) bonds by transition metals opens an appealing and straightforward access to organometallic intermediates. Therefore such activations are more sustainable as the amount of waste is reduced. While the area of C–H bond activations underwent impressive progress within the last years,[1] the development of effective, catalytic C–C bond activations and their practical implementation largely lags behind. This can be traced back to the fact that C–C bonds are even more inert than C–H bonds and moreover the reverse pathway, reductive elimination, is most often the energetically preferred reaction direction.[2] Hartwig recently showed that the addition of aryl-rhodium species across aryl ketones is a reversible process (Scheme 1).[3] The mechanism follows a migratory insertion and elimination pathway that is typical for insertions of olefins and β-eliminations. The site of the equilibrium depends on the electronic properties and the steric bulk of the migrating aryl-group. These findings fuel the possibility to access organometallic species from the alkoxy-rhodium complexes by such β-carbon eliminations. We hypothesized that substrates which would be more susceptible towards this elimination can open an avenue to reactive organometallic species serving as versatile platform for further reactions. In particular, cyclic strained tertiary alcohols are intriguing as the additional energy, liberated by strain reduction in ring-opening reactions, is expected to shift the equilibrium in the desired direction.[4] In addition to this property, cyclobutane derivatives are an especially attractive substrate class due to their convenient accessibility. Symmetrically substituted cyclobutane rings furthermore offer the possibility for enantioselective catalysis, *via* a selective insertion into one of the two enantiotopic C–C σ-bonds of the cyclobutane (bond **a** or **b** in Scheme 2).[5] We expected that where R is an alkyne, allene or olefin, the chiral rhodium complex would potentially coordinate to both the hydroxyl group and the π-unsaturation. Such structurally well-defined complexes were expected to enable a more effective imprint of the chiral information from the ligand onto the substrate. The enantioselective β-carbon elimination generates then a reactive alkyl-rhodium species, bearing an all-carbon quaternary stereogenic center. Thereupon, one can design a myriad of intra- and intermolecular downstream reactions to exploit the high reactivity of this alkyl-rhodium intermediate and to convert it into synthetically valuable products.



Scheme 1. Reversibility in rhodium-catalyzed carbonyl additions.



Scheme 2. Enantioselective β-carbon elimination from *tert*-cyclobutanols.

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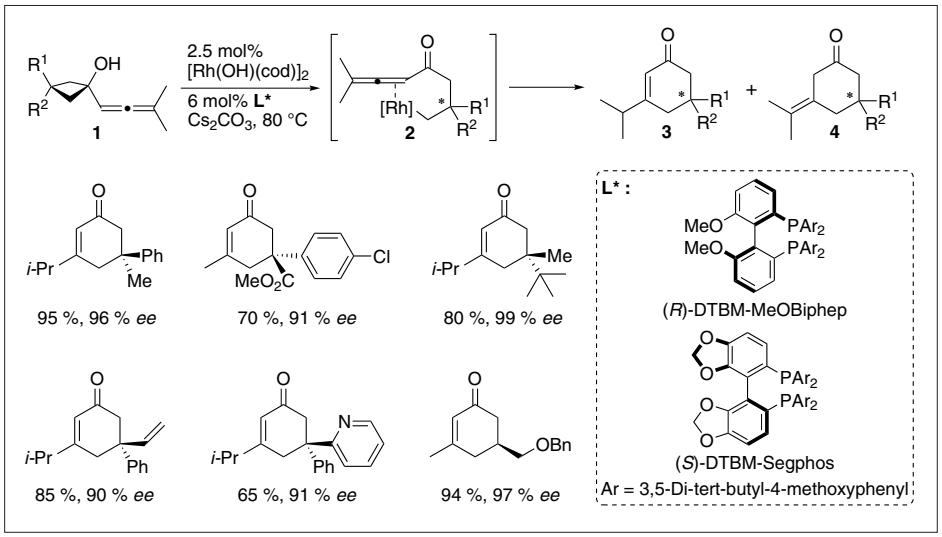
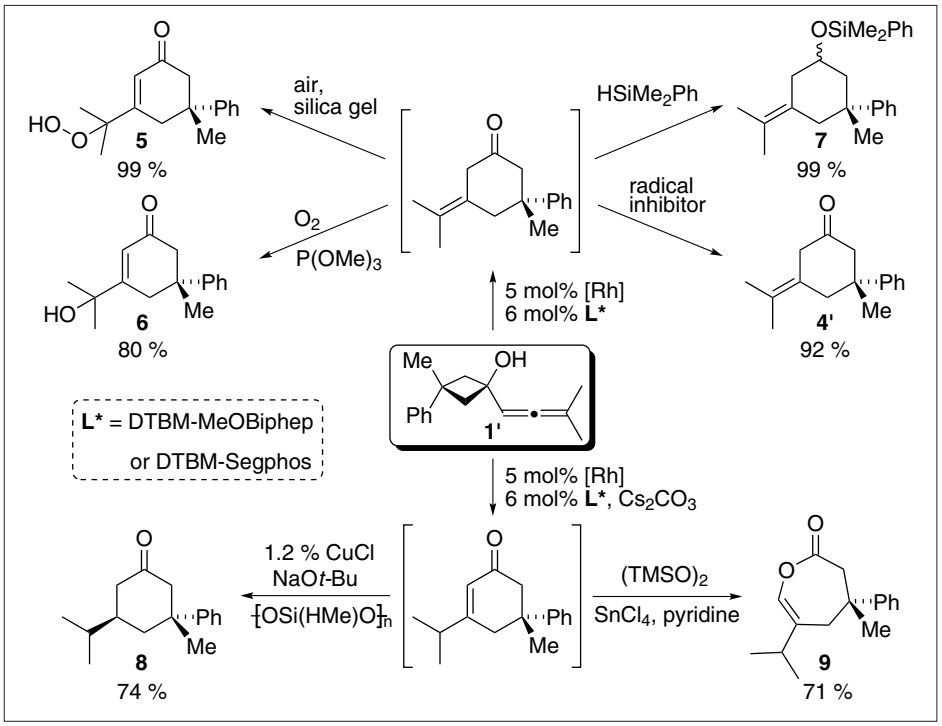
2. Formation of Cyclohexenones with Quaternary Stereogenic Centers through C–C Activation

To explore the viability of our approach, different substituents R were evaluated. It turned out that especially allenyl-substituted cyclobutanols are promising substrates: Once alkyl-rhodium species **2** is formed by the insertion of the rhodium complex into the C–C bond, it can add intramolecularly across the allene moiety yielding a mixture of enone **3** and methylene cyclohexanone **4** (Scheme 3).[6] To circumvent this product mixture, the isomerization of **4** into the more stable enone **3** was accelerated by addition of auxiliary bases such as cesium carbonate. The bulky biarylphosphine ligands DTBM-MeOBiphep and DTBM-Segphos (DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl) give rise to the best enantioselectivity in this reaction. Noteworthy, the required catalyst loading could be lowered from initial 5 mol% to 0.1 mol% rhodium without affecting the yield and the enantioselectivity of the reaction. As illustrated, the reaction is applicable to a wide range of substrates including different aromatic, heteroaromatic and alkyl substituents with different steric bulk as well as several functional groups like benzyl ethers, olefins and esters (Scheme 3). Even substrates which are able to undergo β-hydride elimination of the organometallic intermediate are converted selectively to cyclohexenones with a tertiary stereogenic center in similar yields.



Scheme 3. Enantioselective C–C activation and formation of substituted cyclohexenones.



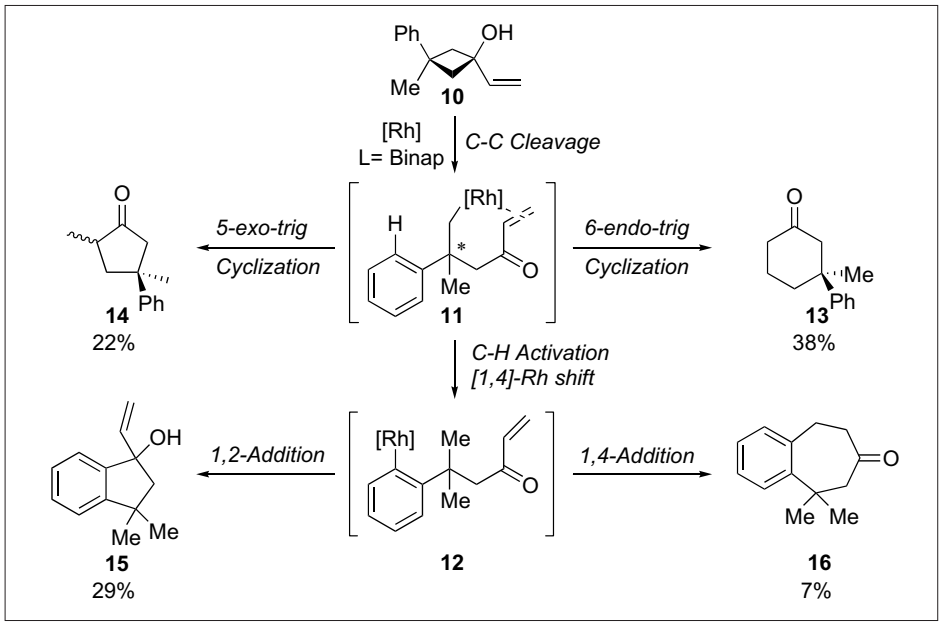
Scheme 4. Sequential reactions open access to a broad product scope.

3. Expanding the Reaction Scope: Sequential Catalysis

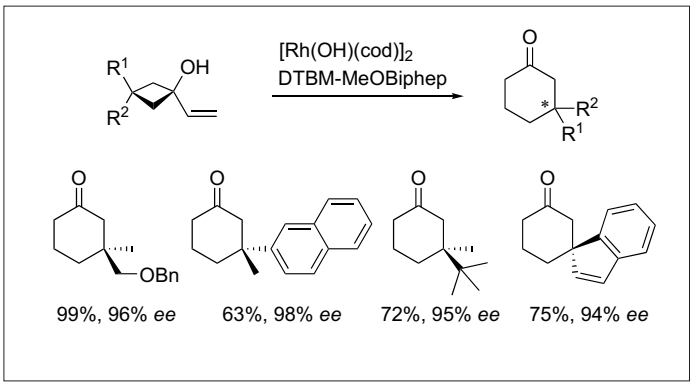
To enhance the synthetic value of this transformation, we investigated conditions to optimize the reaction for the sensitive methylene cyclohexanone **4**, formed when base-free reaction conditions are used.[7] Its isolation appeared to be challenging as in addition to its propensity to isomerize to the enone **3** it also converted to another product during purification. Isolation and X-ray crystallographic analysis confirmed the formation of hydroperoxide **5** (Scheme 4), generated by oxidation under atmospheric conditions. An advantage of this oxidation is the access to additional functionalized substrates. Treatment of the reaction mixture with oxygen and trimethylphosphite after the catalytic cycle provides the corresponding tertiary alcohol **6** in 80% yield. However, isolation of methylene cyclohexanone **4** is feasible by addition of radical inhibitors during the purification procedure. The oxidation and/or isomerization of the *exo*-double bond can as well be circumvented by an *in situ* conversion of the ketone functionality, preventing the formation of the more stable enone. For that purpose, ketone **4** can be directly reduced to the protected alcohol by a rhodium-catalyzed hydrosilylation using dimethylphenylsilane, yielding silyl ether **7** in a virtually quantitative yield. Enone **3** is as well suited for such sequential catalysis. For example, the formation of a second stereogenic center is realized by a conjugate reduction subsequent to the ring expansion furnishing cyclohexanone **8.** A copper(I) source in combination with a silane as terminal reductant and the small excess of DTBM-Segphos present in the reaction mixture as steering ligand proved to be sufficient for a complete ligand-controlled reduction, yielding **8** exclusively as a single diastereomer. Alternatively, a Baeyer-Villiger oxidation of **3** gives rise to lactones. Under the employed conditions ε-enol-lactone **9** is obtained as sole product, thereby providing access to linear quarternary stereogenic centers.

4. Alternatives to Allene-substituted Cyclobutanols

Although the chelating environment offered by the allene functionality of the cyclobutanol facilitates the C–C insertion reaction, it clearly represents a limitation. Therefore its substitution by other functional groups is desirable. For



Scheme 5. Product mixture obtained from vinyl *tert*-cyclobutanol.



Scheme 6. Rearrangement of vinylcyclobutanol into cyclohexanone.

example, it should be possible to employ olefin-substituted *tert*-cyclobutanols for the rhodium-catalyzed rearrangement. To explore this possibility, vinylcyclobutanol **10** was submitted to the standard set of reaction conditions using Binap as ligand (Scheme 5).[7] Besides the expected cyclohexanone **13**, other products (**14**–**16**) were formed in significant amounts, suggesting the following reaction pathways: Alkyl-rhodium species **11** adds not only in a *6-endo-trig* fashion across the enone functionality, but forms also cyclopentanones **14** by a *5-exo-trig* cyclization. Furthermore, due to the longer lifetime of **11**, an additional pathway becomes operative, initiated by formation of aryl-rhodium **12** *via* a 1,4-rhodium shift. An intramolecular 1,4-addition yields cycloheptanone **16**, whereas an 1,2-addition across the ketone gives rise to indanol **15**. Despite these multiple potential reaction pathways and products, it is possible to convert vinyl-cyclobutanols selectively into the corresponding cyclohexanones (Scheme 6). Usage of the DTBM-MeOBiphep ligand mitigates the side reactions. Irrespectively of an aryl-substituent in 3-position, cyclobutanols react selectively to the corresponding cyclohexanones, including spirocyclic compounds, in good yields and excellent enantiomeric excess.

5. Capitalizing on the C–C/C–H Activation Sequence for a Selective Synthesis of Indanols

The second observed branch of the proposed mechanism in Scheme 5, the 1,4-rhodium shift, seemed to have synthetic potential and was therefore examined further. Removal of the vinyl group from the substrate was expected to shut down the other reaction pathways and result in a selective formation of the indanol. While the C–C cleavage proceeds equally well without the chelating vinyl group, the enantioselectivity in the carbonyl addition step was only modest with the previously successful chiral ligands. A ligand screening revealed that Josiphos-ligand A works best for this reaction and results in excellent enantioselectivities for the intramolecular carbonyl addition, furnishing the 3,3-dimethyl substituted indanols in excellent yields (Scheme 7).[8] Again, the catalyst loading could be reduced to 0.5 mol% rhodium without affecting the reaction outcome. To explore the possibility of an enantioselective C–H activation step, 3,3-diphenyl-substituted cyclobutanol **17** was exposed to the reaction conditions (Scheme 7). While selectivity in the C–C activation is irrelevant, the employed ligand had to provide a differentiation between the two enantiotopic phenyl groups in the 1,4-rhodium shift and subsequently control the selectivity for the carbonyl addition. The Difluorphos ligand reliably fulfilled these requirements, producing diastereomer **18** in high enantio- and diastereoselectivity. Indanols bearing a second stereogenic center are also accessible using this technique. The best results were obtained for these substrates with Difluorphos as ligand, promoting *both* selectivity-determining steps (the C–C insertion and the carbonyl addition) in good selectivities, yielding the indanols in good diastereo- and excellent enantioselectivity (Scheme 7). Once again the reaction is well tolerant to benzyl ethers, esters and aryl halides. Furthermore, substrates having heteroaromatic substituents like pyridines or thiophenes can be equally employed. The selective formation of the phenyl-substituted 6-aza-indanol suggests that electron-poor aromatic groups preferentially participate in the C–H activation.

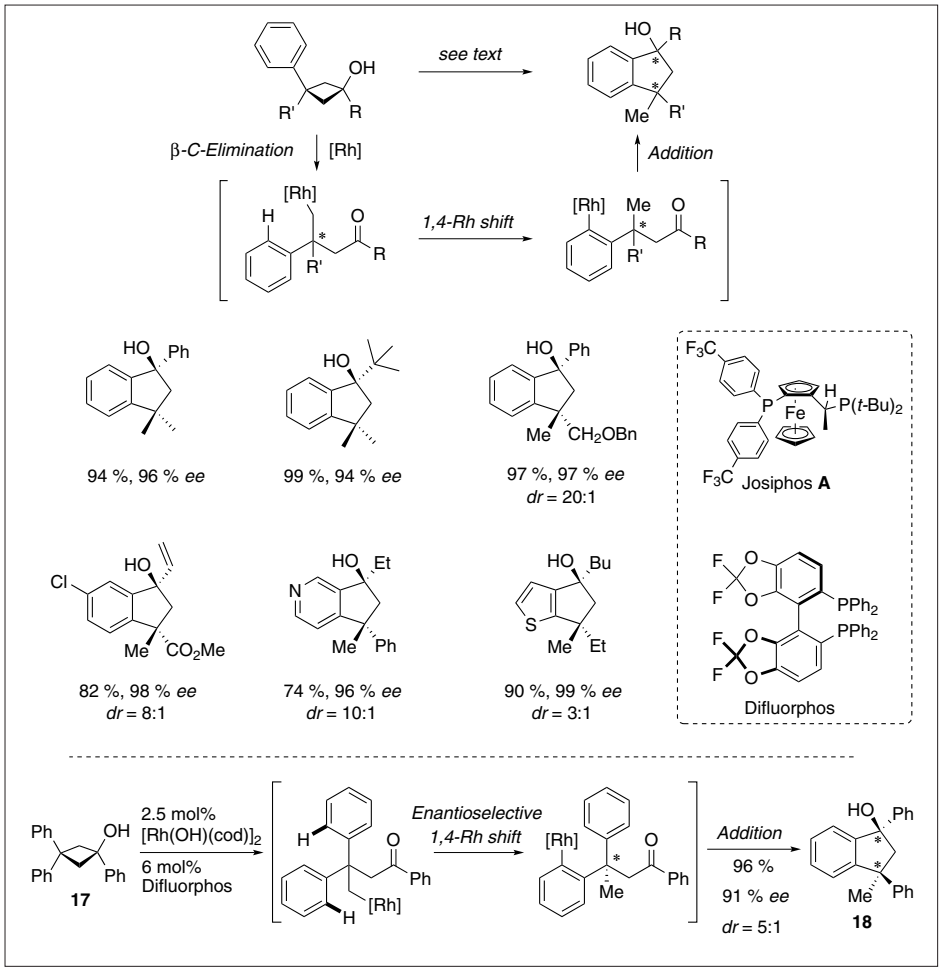
6. Conclusion

In summary, we have underlined the potential of catalytic enantioselective C–C bond activations. The described cleavage reactions of cyclobutanols and the formed alkyl-rhodium species enable access to a host of novel reactivities. The resulting products are structurally diverse and bear all-carbon quaternary stereogenic centers. We believe that further research in the area of catalytic activation of inert bonds holds the promise to discover novel chemical reactivity that might allow for more efficient and environmentally benign synthetic processes.

Acknowledgments

T. S. would like to cordially thank Mettler-Toledo and the Swiss Chemical Society for the SCS-Mettler-Toledo award. We are grateful to the Swiss National Foundation (21-119750.01) as well as to Solvias AG and Takasago Int. Corp. for ligands. The Fonds der Chemischen Industrie is acknowledged for a Liebig-Fellowship (N. C.) and a Kekulé-Fellowship (T. S.).

Received: January 11, 2010



Scheme 7. Enantioselective synthesis of indanols by a C–C/C–H activation sequence.

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