C–C Activation

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Rhodium(I)-Catalyzed Enantioselective C–C Bond Activation

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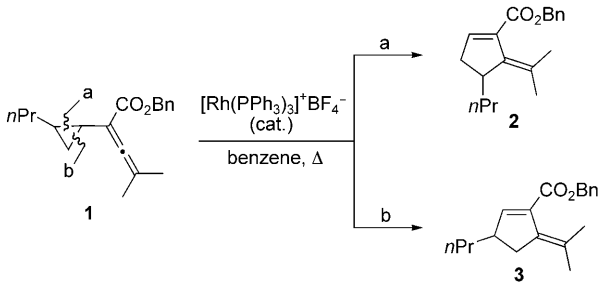
asymmetric catalysis · C–C activation · cyclobutanes · rhodium · ring expansion

Transition-metal-catalyzed reactions have become powerful tools in preparative organic chemistry and enable a variety of transformations.[1] Normally, such reactions lead to the formation of a carbon–carbon bond by the reductive elimination of two carbon substituents linked to the metal center. The driving force for these transformations is the formation of a strong C–C σ bond (ca. 350 kJ mol^{-1}) at the expense of two relatively weak carbon–metal bonds (each 80–120 kJ mol^{-1}).[2] Despite the large difference in bond strength, the reverse reaction is also feasible. Such oxidative additions to a transition metal cause the cleavage of a C–C σ bond and result in reactive organometallic reagents which can be used for the subsequent formation of a new carbon–carbon bond.[3]

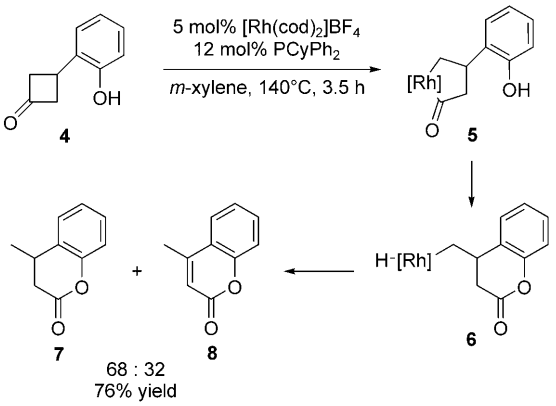
Small strained ring systems are particularly suitable for C–C activation reactions of this type, as their cleavage releases the strain energy. For example, the insertion of a transition metal into vinyl or allenyl cyclopropanes, such as **1**, leads to the formation of cyclopentenes, such as **2** or **3** (Scheme 1). The substitution pattern of the ring-expansion



Scheme 1. Rhodium(I)-catalyzed ring opening of the allenyl cyclopropane **1** to give cyclopentenes **2** and **3**. Bn = benzyl.

product depends on the regioselectivity of the insertion (into bond a or b).[4] With cationic rhodium complexes, the metal insertion can take place with high regioselectivity (> 99:1) in favor of cyclopentene **3**, which results from the cleavage of the sterically less hindered bond (b).

The strain energy of cyclobutanes is also sufficient for C–C σ-bond cleavage, which activates the molecule for further transformations. As early as 1994, Murakami, Amii, and Ito reported the rhodium(I)-catalyzed ring opening of cyclobutanones.[5] The resulting acylrhodium intermediate can be trapped in an intramolecular fashion by a nucleophile (Scheme 2). In the case of the *o*-hydroxyphenyl-substituted



Scheme 2. Rhodium(I)-catalyzed C–C activation of cyclobutanone **4**. Cy = cyclohexyl, cod = cycloocta-1,5-diene.

cyclobutanone **4**, the C–C activation is facilitated by precoordination of the catalyst, and the acylrhodium species **5** formed is trapped by the phenolic hydroxy group to give the lactone **6**, which undergoes either reductive elimination to give dihydrocoumarin **7** or β-hydride elimination and subsequent isomerization to give coumarin **8**.[6] When the *o*-hydroxyphenyl group is in the 2-position, carbon monoxide extrusion also occurs to produce the corresponding cyclopropyl-substituted phenol after reductive elimination. This side reaction can be suppressed by conducting the transformation under a CO atmosphere.

Cyclobutanones with an achiral substituent in the 3-position contain enantiotopic C–C σ bonds. The selective activation of one of these bonds is of particular interest, since it provides access to enantiomerically enriched or enantiomerically pure carbo- or heterocycles, which are valuable substrates for organic synthesis. This concept was implement-

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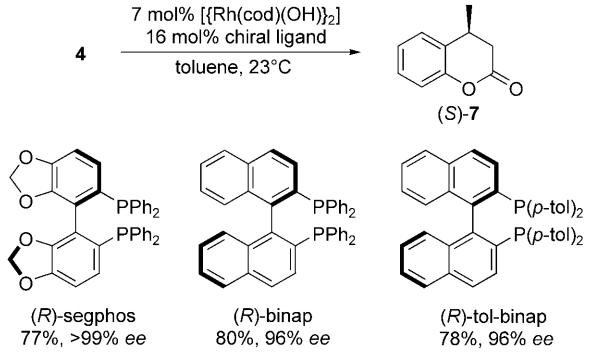
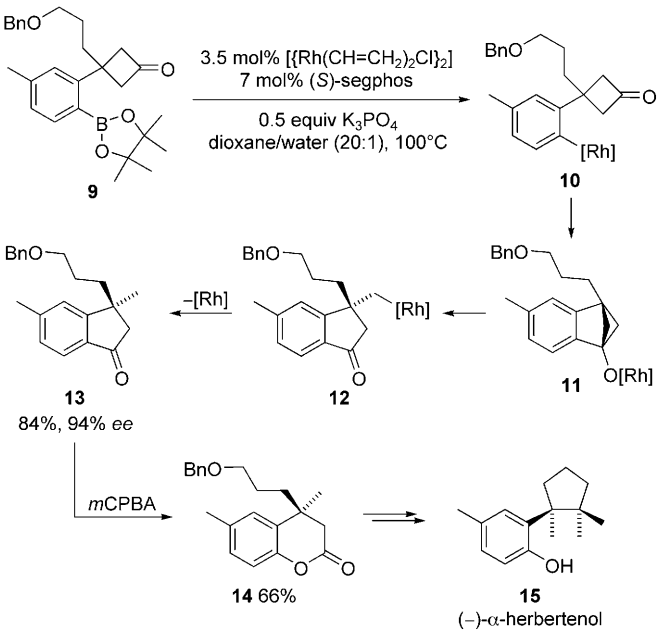
ed by Murakami and co-workers[7] in the synthesis of dihydrocoumarin **7** by the treatment of the achiral cyclobutanone **4** with a chiral rhodium(I) catalyst (Scheme 3). When a C_2-symmetric bisphosphine ligand of the segphos or binap type was used, the chiral rhodium complex was generated in situ, and dihydrocoumarin (*S*)-**7** was produced with high enantioselectivity.



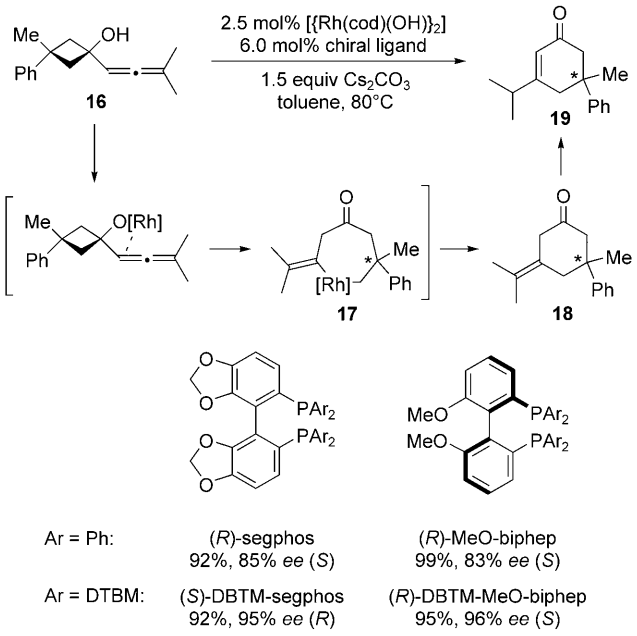
Scheme 3. Synthesis of dihydrocoumarin (*S*)-**7** by the selective activation of enantiotopic C–C σ bonds in cyclobutanone **4**. Tol = tolyl.

Although these enantioselective desymmetrization reactions enable an elegant approach to chiral target molecules which are difficult to access otherwise, applications in organic synthesis are scarce.[8] The stereoselective formation of quaternary stereogenic centers is a crucial challenge that can be solved by rhodium(I)-catalyzed desymmetrization.[9] Thus, Murakami and co-workers[10] utilized the enantioselective C–C bond activation of prochiral cyclobutanones in a synthesis of the sesquiterpene (−)-α-herbertenol (**15**; Scheme 4). The starting point was the boronic ester **9**, which was transmetalated to give the chiral acylrhodium intermediate **10** in the presence of (*S*)-segphos. The formation of **10** induces a cascade reaction consisting of an intramolecular nucleophilic addition (to give **11**), desymmetrization by cleavage of one of the enantiotopic C–C σ bonds (to give **12**), and reductive elimination to afford the enantiomerically enriched benzocyclopentanone **13**. Subsequent oxidation leads to the chiral lactone **14**, which can be transformed into the target molecule **15**.

The scope of C–C activation reactions is not limited to the use of strained carbonyl compounds as substrates. Recently, Seiser and Cramer[11] used a similar desymmetrization approach for the synthesis of chiral cyclohexenones from C_2-symmetric allenyl cyclobutanols. In analogy to the ring expansion of allenyl cyclopropanes **1** (Scheme 1), this transformation leads to a ring-expanded carbocycle with an exocyclic double bond. A representative example is the enantioselective C–C bond activation of the prochiral cyclobutanol **16**: The initially formed metallacycle **17** undergoes reductive elimination to give the cyclohexanone **18** (Scheme 5). This product turned out to be unstable under the reaction conditions, but the addition of a base induces isomerization of the exocyclic double bond to give the more stable cyclohexenone **19**. The use of a chiral rhodium(I) complex generated from [{Rh(cod)(OH)}$_2$] and an appropriate chiral bisphosphine ligand resulted in excellent chemical yields and high stereoselectivities.



Scheme 4. Enantioselective synthesis of the sesquiterpene (−)-α-herbertenol (**15**) by a rhodium(I)-catalyzed desymmetrization of cyclobutanone **9**. *m*CPBA = *m*-chloroperbenzoic acid.



Scheme 5. Rhodium(I)-catalyzed desymmetrization of the allenyl *tert*-cyclobutanol **16** to give cyclohexenone **19**. DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl.

Whereas the product **19** was formed with only 80% *ee* using the ligand (*R*)-binap, bisphosphines with a smaller dihedral angle (e.g., segphos or MeO-biphep) provided better results (Scheme 5). Particularly suitable are the sterically demanding biaryl phosphines DTBM-segphos (95% *ee*) and DTBM-MeO-biphep (96% *ee*). The use of *R*-configured

ligands leads to products with an *S*-configured quaternary stereogenic center and vice versa. In contrast to the synthesis of the benzocyclopentanone **13**, which proceeds best in polar solvent mixtures consisting of dioxane and water, the use of polar solvents for the desymmetrization of **16** gave poor stereoselectivities; in this case, the best results were attained with toluene. Remarkably, the catalyst loading of initially 2.5 mol% $[\{Rh(cod)(OH)\}_2]$ could be decreased drastically to 0.05 mol% without a significant loss of selectivity (90% *ee* instead of 95% *ee*). A wide range of substituted cyclobutanols can be transformed under these conditions, which are compatible with a variety of functional groups (chlorinated aryl groups, pyridines, benzyl ethers).

This remarkably selective ring expansion enables access to highly substituted cyclohexenones with a quaternary stereogenic center and is the first rhodium(I)-catalyzed ring opening of a cyclobutanol by activation of a carbon–carbon σ bond.[12] In contrast, a related palladium-catalyzed reaction of alkoxy-substituted allenyl *tert*-cyclobutanols results in the formation of cyclopentanones with a vinylic side chain.[8b] With their contributions, the research groups of Murakami and Cramer have made a breakthrough in the field of enantioselective C–C activation and demonstrated the tremendous potential of this methodology for the synthesis of highly enantiomerically enriched building blocks from prochiral starting materials. Moreover, their approach paves the way for the synthesis of compounds with quaternary stereogenic centers that are not accessible by alternative transformations. Further intriguing examples of transition-metal-catalyzed desymmetrization reactions and their application in preparative chemistry can be expected in the near future.

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