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Enantioselective Rhodium-catalyzed C–C Bond Activation of Cyclobutanones

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Abstract: The activation of carbon–carbon bonds has attracted much attention in the past decade. Despite important progress, the development of asymmetric reactions lags behind. For the first time, asymmetric rhodium(I)-catalyzed direct oxidative additions into enantiotopic C–C bonds of cyclobutanones could be realized. Subsequent carboacylation of tethered olefins and carbonyl groups of the generated rhoda(III)cyclopentanone give an efficient access to complex polycyclic scaffolds in high yields. Despite operating at high reaction temperatures, the processes are characterized by outstanding enantioselectivities of generally greater than 99.5:0.5 *er*.

Keywords: Asymmetric catalysis · C–C bond activation · Cyclobutanone · Rhodium

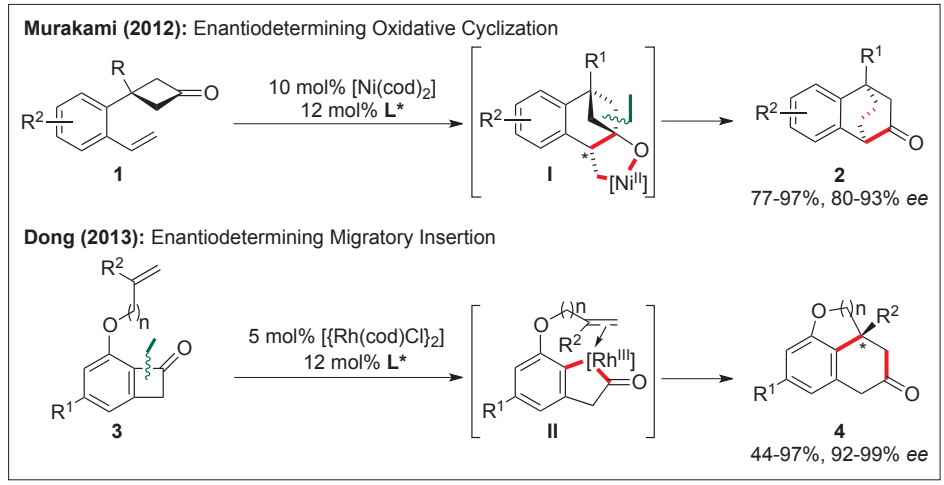
Introduction

The catalytic activation of carbon–carbon single bonds is a prime challenge in organometallic chemistry, since the lack of prefunctionalization steps opens the way to new, economically and ecologically attractive reaction pathways.[1] Strained ring substrates occupy a privileged role in C–C bond activations as the release of their ring strain facilitates the desired metal insertion. Important progress has been made in the field during the last decade.[2] However, the development of asymmetric variants lags behind. Transition metal-catalyzed C–C bond cleavages fall into two major mechanistic categories: oxidative addition or β-carbon elimination. Whereas examples for enantioselective β-carbon elimination processes have recently become more frequent,[3,4] asymmetric reactions of direct insertions into C–C bonds are scarce. For reactions involving oxidative additions of transition metals as the C–C cleavage mechanism, strained ketones such as cyclobutanones have proven versatile. So far, only two asymmetric transformations of cyclobutanones have been reported (Scheme 1). In 2012, Murakami disclosed an enantioselective nickel-catalyzed synthesis of benzobicyclo[2.2.2]octanones **2** from 3-styryl-substituted cyclobutanones **1**.[5] In the presence of [Ni(cod)$_2$] and a chiral phosphoramidite ligand, an enantioselective oxidative cyclization delivers nickel(II) cyclobutanolate **I**. Subsequent diastereoselective β-carbon elimination and reductive elimination close the catalytic cycle yielding benzobicyclo[2.2.2]octanone **2**. Dong reported rhodium(I)-catalyzed C–C bond activations of benzocyclobutanones **3**.[6] This process is initiated by an achiral oxidative insertion into the aryl–acyl C–C bond of benzocyclobutanone substrate **3** generating rhodacyclopentenone **II**. An enantioselective migratory insertion of the alkene moiety and reductive elimination affords fused tetralones **4**. In both of these examples, the C–C cleavage is not the enantiodetermining step. Processes in which the key oxidative addition into the C–C bond is the enantiodetermining step were elusive.[7] C–C bond activations require forcing reaction temperatures, rendering the development of enantioselective processes challenging. In the following, we demonstrate asymmetric oxidative additions of rhodium(I) complexes into enantiotopic C–C bonds of cyclobutanones, leading to efficient methods for the preparation of chiral bicyclic scaffolds.

Results and Discussion

Development of an Enantioselective Olefin Carboacylation

Murakami and Ito reported rhodium(I)-catalyzed intramolecular olefin carboacylations.[8] The process converted cyclobutanone **1** (R = H) into symmetrical



Scheme 1. Asymmetric transformations of cyclobutanones involving a non-enantiodetermining C–C bond cleavage.

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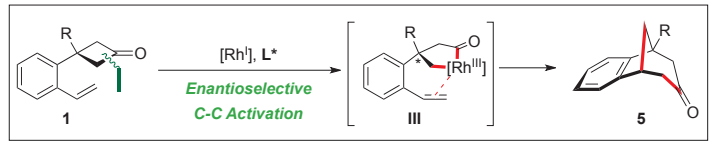
benzobicycloheptanone **5** *via* rhoda(III) cyclopentanone **III**. An efficient enantioselective access to the valuable benzobicycloheptanone scaffold **5** would be of great interest (Scheme 2). We thus selected cyclobutanone **1a** (R ≠ H) as model substrate for the development of the enantioselective methodology (Scheme 3). Executing the reaction in the presence of [{Rh(cod)Cl}$_2$] and BINAP (**L1**) in dioxane at 130 °C gave benzobicycloheptanone **5a** with an excellent enantiomeric ratio of 98.5:1.5. However, a moderate 50% yield was observed due to a limited conversion. The reactivity could be increased with ligands of the Segphos family. The bulkiest member DTBM-Segphos (L4) resulted in the most active catalyst. Under these conditions, product **5a** was obtained in 94% yield with an exceptionally high enantiomeric ratio of 99.7:0.3. Related DTBM-MeOBiphep (**L5**) was less reactive leading to moderate conversion. The counterion of the rhodium complex was found to be of critical importance. The use of other rhodium sources such as [{Rh(cod)OH}$_2$] or the cationic [{Rh(cod)}BF$_4$] was detrimental to the yield and the enantioselectivity.

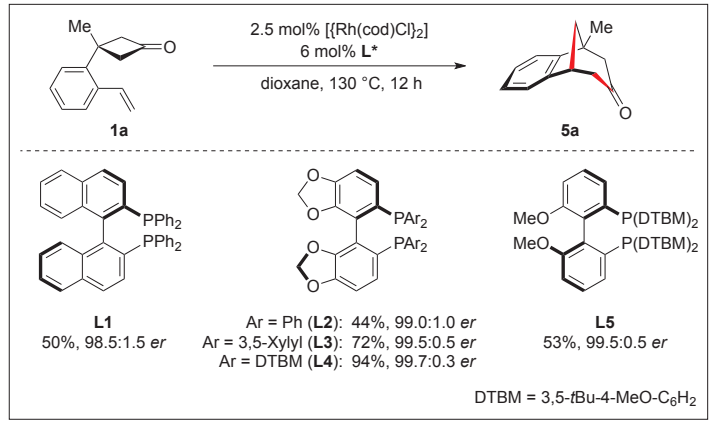
With the optimized reaction conditions, the generality of the process was explored (Scheme 4). The influence of different substituents (R^1) at the 3-position of the cyclobutanone including several aliphatic and aromatic groups as well as esters, nitriles and protected ethers were minimal and delivered the desired benzobicycloheptanones **5** with a variety of functionalized bridgeheads in high yields and enantioselectivities. Electronic modifications of the aryl moiety (R^2) has no influence on the reaction outcome. Importantly, 1,1-disubstituted alkenes (R^4, R^5 = H) provide benzobicycloheptanones **5j** and **5k** bearing quaternary stereogenic centers at both bridgehead positions in similar yields and enantioselectivities. Moreover, 1,2-disubstituted alkenes react well and fully maintain their stereochemical information. Cyclobutanones bearing a *trans*-olefin (R^3 and R^5 = H) deliver ketones **5l** and **5m** in excellent diastereomeric ratios (> 20:1). On the other hand, substrate bearing a *cis*-alkene (R^3, R^4 = H) did not yield the desired benzobicycloheptanone and slowly degrades under the reaction conditions. A tri-substituted olefin is well tolerated and provides a rapid and efficient access to tetracyclic ketone **5n**.

Development of an Enantioselective Carbonyl Carboacylation

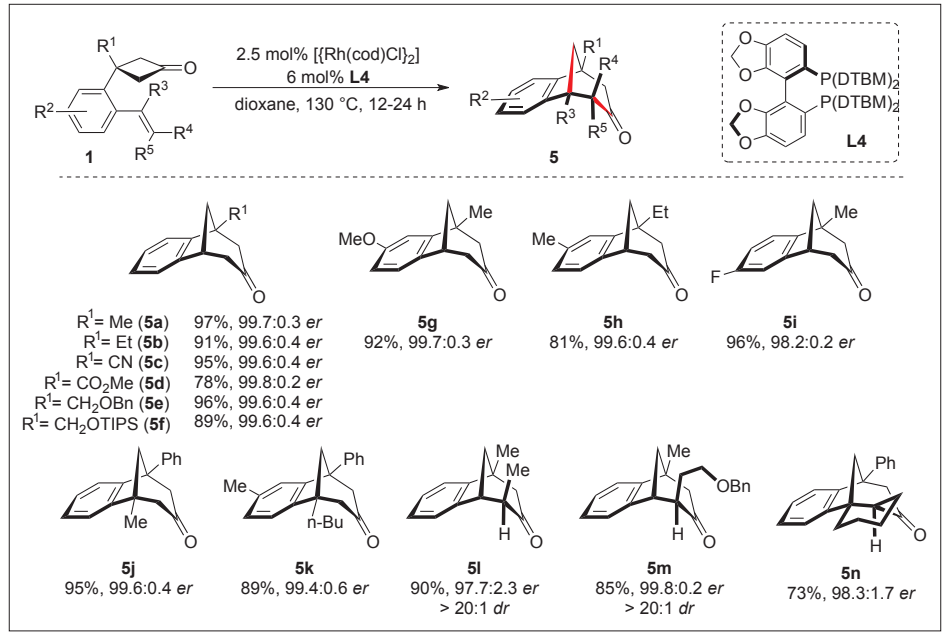
The utility of the asymmetric C–C bond activation process could be extended to carbonyl carboacylations, thus expanding the accessible scaffold range. In this case, the reaction provides an efficient access to lactones – a ubiquitous and im-



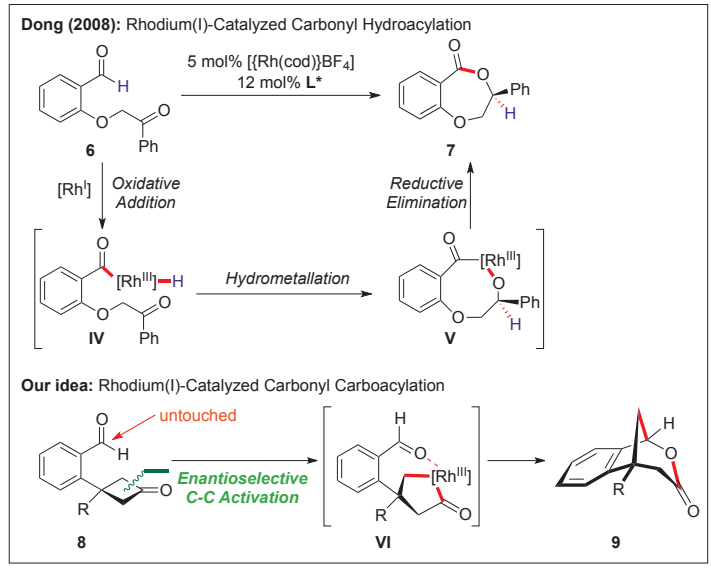
Scheme 2. Envisioned enantiotopic C–C bond activation followed by an olefin carboacylation.



Scheme 3. Optimization of the enantioselective C–C bond activation of cyclobutanone **1a**.



Scheme 4. Scope of the enantioselective C–C bond activation of cyclobutanones **1**.

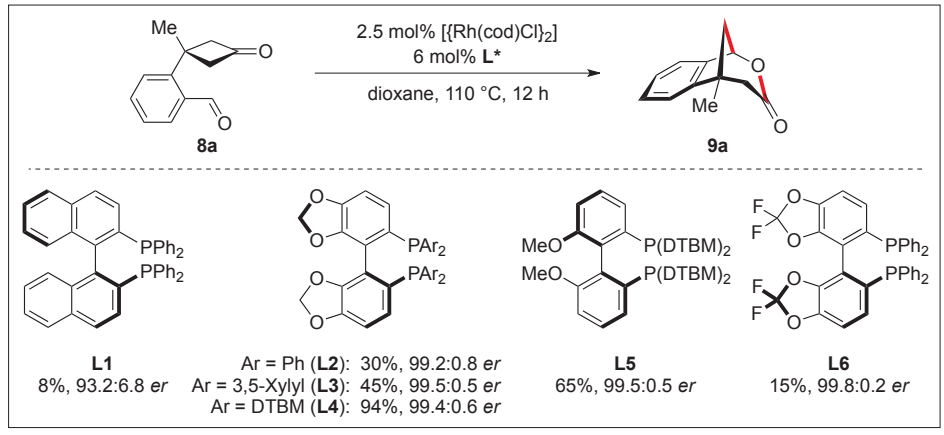


Scheme 5. Selective C–C bond activations in the presence of aldehydes for asymmetric carbonyl carboacylations.

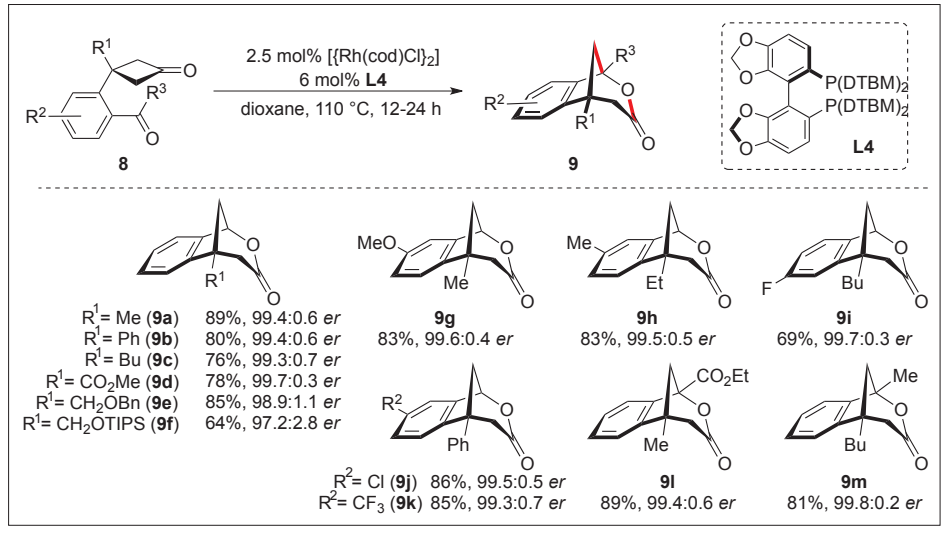
portant structural motif – from uncommon synthetic precursors. A related rhodium(I)-catalyzed intramolecular asymmetric carbonyl hydroacylation from **6** providing Tishchenko-type lactone products **7** was reported by Dong (Scheme 5).[9] The major limitation is that carbonyl hydroacylations are strictly limited to the transfer of a hydride to the accepting carbonyl group. In contrast, our envisioned carbonyl carboacylation would allow for the formation of C–C bonds during the lactonization event. From a mechanistic point, these carbonyl *carbo*acylations require the opposite reaction order compared to the carbonyl *hydro*acylations. In the latter case, the reaction is initiated by oxidative addition of rhodium(I) into the aldehyde C–H bond leading to the acyl rhodium(III)hydride intermediate **IV**. Ketone hydrometallation then delivers acyl rhodium(III) species **V**. Finally, a C–O bond forming reductive elimination closes the catalytic cycle. In our case, the enantioselective C–C bond activation of the cyclobutanone **8** giving rhodium(III) intermediate **VI** must proceed first, leaving the generally more reactive aldehyde untouched. We envisioned that the superior reactivity of the strained cyclobutanone would enable such reactivity reversal.

The evaluation of this hypothesis was conducted on model substrate **8a**. Again, the chloride counteranion was critical for the reactivity. Different chiral ligands were examined using [{Rh(cod)Cl}$_2$] as rhodium source (Scheme 6). Similar trends as for the olefin carboacylation were observed. BINAP (**L1**) as chiral ligand gave lactone **9a** in a promising enantiomeric ratio of 93.2:6.8, however in a very poor yield of 8%. Ligands of the Segphos family resulted in higher reactivity as well as enantioselectivities. DTBM-Segphos (**L4**) proved to be the most efficient and afforded lactone **9a** in 94% yield and excellent enantiomeric ratio of 99.4:0.6. The related DTBM-MeOBiphep (**L5**) was less reactive. Despite outstanding enantioselectivity of 99.8:0.2 *er*, Difluorphos (**L6**) gives a poorly reactive catalyst.

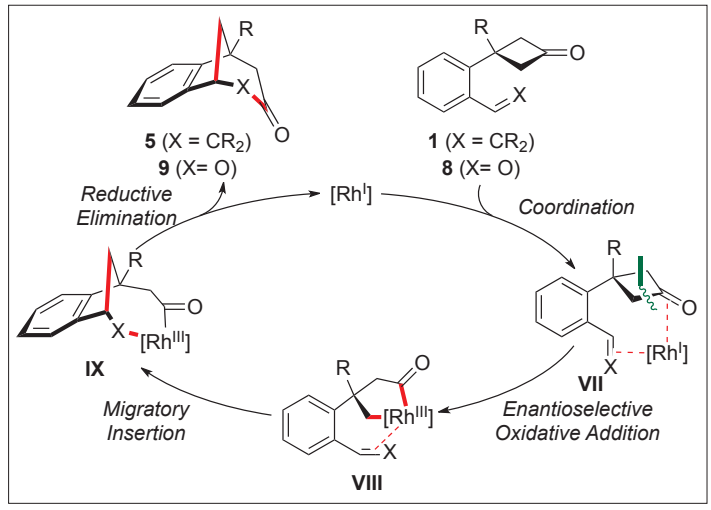
The generality of the process for the carbonyl carboacylation was subsequently investigated (Scheme 7). The influence of different substituents at the 3-position of cyclobutanones **8** (R^1) including aliphatic and aromatic groups, methyl ester or protected alcohols was limited and the desired polycyclic lactones **9** were obtained in good yields and excellent enantioselectivities. Modification of the electronic properties of the aryl moiety with electron-withdrawing or -donating groups (R^2) did not influence the reaction outcome. The reactivity of ketones as accepting group was also investigated (R$^3 \neq$ H). Due to their lower electrophilicity, ketones are less reactive towards migratory insertion. Very activated ketones, such as α-ketoester **8l** gave benzo[*c*]oxepinone **9l** bearing two different quaternary stereogenic centers at the bridgehead positions with no erosion of the high enantiomeric ratio. By increasing both the catalyst loading and the reaction time, a simple methyl ketone reacted as well and provided lactone **9m** in good yields.



Scheme 6. Optimization of the asymmetric carbonyl carboacylation.



Scheme 7. Scope for the asymmetric synthesis of bicyclic lactones **9**.



Scheme 8. Proposed mechanistic picture.

Mechanistic Picture

The proposed mechanism for both presented carboacylations is depicted in Scheme 8. An initial coordination of rhodium(I) to the carbonyl group as well as to the unsaturated acceptor (X = CR$_2$ or X = O) of the cyclobutanone would lead to complex **VII**. This double coordination induces a relatively rigid transition state, enabling a good enantiodiscrimination in

the C–C cleavage step. Oxidative addition of rhodium into the acyl-carbon bond of cyclobutanone would deliver rhoda(III) cyclopentanone species **VIII**. Subsequent migratory insertion of either the appended olefin or the carbonyl group would form acyl rhodium species **IX**. In turn, reductive elimination would give the polycyclic scaffold **5** (X = CR_2) or **9** (X = O).

Conclusion

Whereas enantioselective β-carbon elimination processes are well precedented, the enantioselective direct oxidative addition into C–C bonds remained a long standing challenge. We now demonstrated the possibility for rhodium(I) complexes to undergo such enantioselective oxidative additions into enantiotopic C–C bonds of cyclobutanones. Despite the high reaction temperatures, this reactivity was exploited for an enantioselective rhodium(I)-catalyzed C–C bond activation of 3-styryl cyclobutanones giving an efficient access to bicycloheptanones.[10] Moreover, we reported an enantioselective rhodium(I)-catalyzed carbonyl carboacylation reaction of cyclobutanones providing an efficient access to the benzo[*c*]oxepinone skeleton.[11] Both developed methodologies proceed with outstanding enantioselectivities and are giving an efficient access to complex polycyclic scaffolds in high yields. Ongoing research is focused on the development of further asymmetric C–C bond activations.

Acknowledgments

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