Enantioselective metal-catalyzed activation of strained rings

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Activation of otherwise inert bonds has significant potential in the design of efficient and synthetically useful transformations. While general catalytic carbon–carbon single bond activations are still in their infancy, this emerging area examines recent developments in the activation of strained rings, focusing on enantioselective reactions.

Introduction

The catalytic activation of C–H bonds[1] and C–C bonds[2] has attracted considerable interest because of the potential economic and ecological advantages. These reactions have the potential to bring about a paradigm change in organic synthesis by simplifying and streamlining synthetic routes as pre-functionalization of the substrate and/or the reactant is no longer required. Translated to a practical sense, C–H and C–C bonds can be regarded as equivalent to C–Met bonds in organometallic reactions. Furthermore such activations can lead to the discovery of novel and potentially useful reaction pathways. The activation of C–C bonds is, compared to the activation of C–H bonds, rarely used in asymmetric catalysis. This can mainly be attributed to two obstacles which have to be addressed for successful C–C activations: 1) the inertness of C–C bonds and 2) energetically more favorable reverse pathways. Conceptually, two fundamental pathways of C–C σ bond cleavage are known (**A** and **B**, Fig. 1). The first involves an oxidative addition of the C–C bonds to a low valent transition metal. This process is the reversal of the reductive elimination, the terminal step in the catalytic cycle of an abundant number of transition metal-catalyzed reactions.

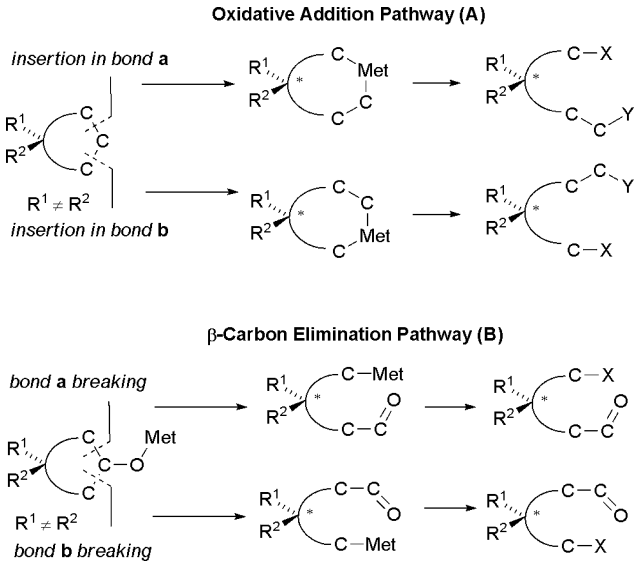

Fig. 1 The two major pathways for metal-catalyzed ring cleavage.

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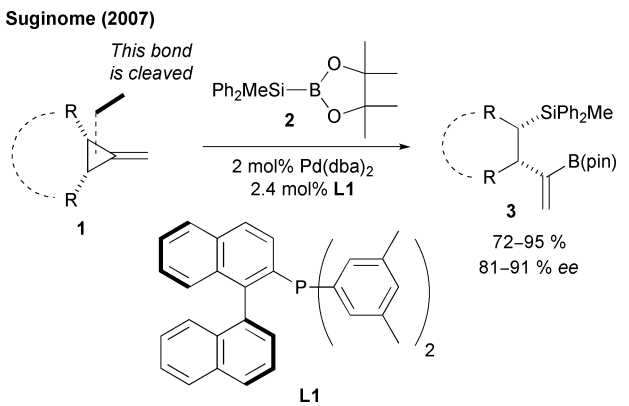
Nicolai Cramer

Nicolai Cramer received his diploma in chemistry from the University of Stuttgart, in 2003, and obtained his Ph.D. with Professor Sabine Laschat in 2005. After a research stay at Osaka University with the Professors Michio Murata and Sumihiro Hase, he joined the group of Professor Barry M. Trost at Stanford University as a Humboldt postdoctoral fellow. In fall 2007, he was awarded a Liebig-Fellowship and started his independent career as a Habilitant at the ETH Zurich. His research group focuses on natural product synthesis and transition metal catalysis.

The second pathway proceeds *via* a β-carbon elimination of a carbon–metal or a heteroatom–metal (*e.g.* a metal alkoxide) species. In this case, β-hydride elimination is most often the preferred pathway over β-carbon elimination. The generally observed and energetically often favored reverse step of the β-carbon elimination is addition of a carbon–metal species across a carbon–heteroatom or C–C multiple bond. Accordingly, small strained rings occupy a privileged position in C–C bond activation reactions because of the energy released by strain reduction in ring-opening reactions. Although the practical implementation of this concept is still a major challenge in organometallic chemistry, significant advances have been made over the past decade, mainly using palladium-, nickel-, rhodium- and iridium-complexes.[3] There have been significant efforts to develop asymmetric variants, leading in recent years to the development of a few enantioselective C–C bond activation reactions.[4]

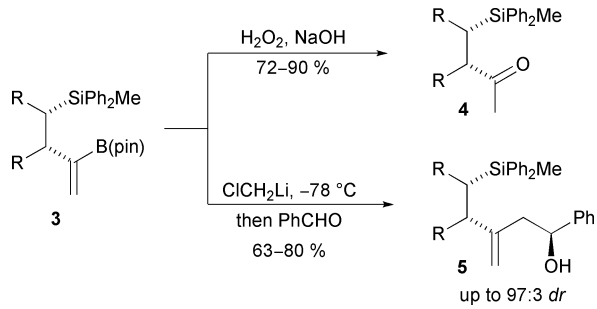
Palladium-catalyzed activations

The methylenecyclopropane moiety is an appreciably reactive functional group that undergoes, with a variety of transition metals, C–C bond activation reactions.[5] The cleavage of the cyclopropane ring can occur either at the proximal or the distal bond. Although this substrate class has found several synthetic applications, few enantioselective transformations have been achieved yet. A particular impressive example has been reported recently by Suginome and coworkers who disclosed an enantioselective palladium-catalyzed silaboration of such methylenecyclopropanes.[6] This reaction efficiently desymmetrizes *meso*-methylenecyclopropanes (**1**) to afford bifunctionalized products (**3**), bearing an alkyl silicon group and a vinyl boronate (Scheme 1).



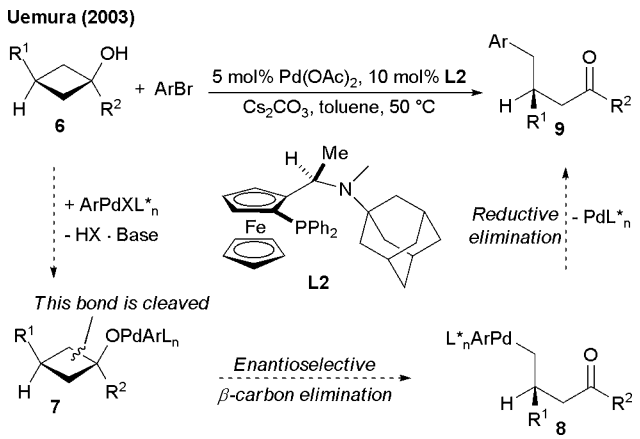
Scheme 1 Pd-catalyzed silaborative desymmetrization of methylenecyclopropanes.

A short survey of several monodentate phosphine ligands led to the identification of ligand **L1** as a suitable and uniquely selective ligand, providing, in combination with the silaborate donor **2**, the ring opened product **3** in excellent yield and up to 91% *ee*. Several cyclic *meso*-methylenecyclopropanes[7] of different ring sizes, as well as an acyclic derivative, undergo the reaction in comparable efficiency and selectivity. The resulting products are synthetically useful and versatile intermediates as they offer the possibility for a myriad of further elaborations by *e.g.* different cross coupling reactions (Suzuki–Miyaura coupling for *R*B(pin) and Hiyama coupling for *R*SiPh$_2$Me). Furthermore, methyl ketones (**4**) and homoallylic alcohols (**5**) can be obtained in good yields and selectivities (Scheme 2).



Scheme 2 Elaboration of the silaborated products **3** by oxidation or *via* Matteson-homologation/aldol.

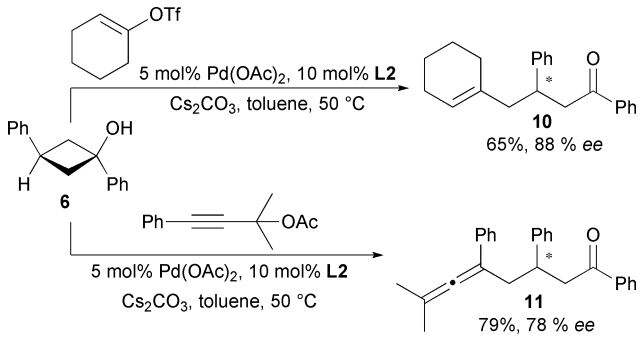
In addition to methylenecyclopropanes, the strain energy of the cyclobutane ring proved to be sufficient for C–C activation reactions. Pioneering work in this area,[3] and also the first enantioselective examples, were reported from Uemura and coworkers.[8] They have investigated a palladium-catalyzed arylation of *tert*-cyclobutanols[9] (**6**) resulting, *via* β-carbon elimination, in the formation of γ-arylated ketones (**9**) (Scheme 3).



Scheme 3 Pd-catalyzed asymmetric β-carbon cleavage/arylation of *tert*-cyclobutanols.

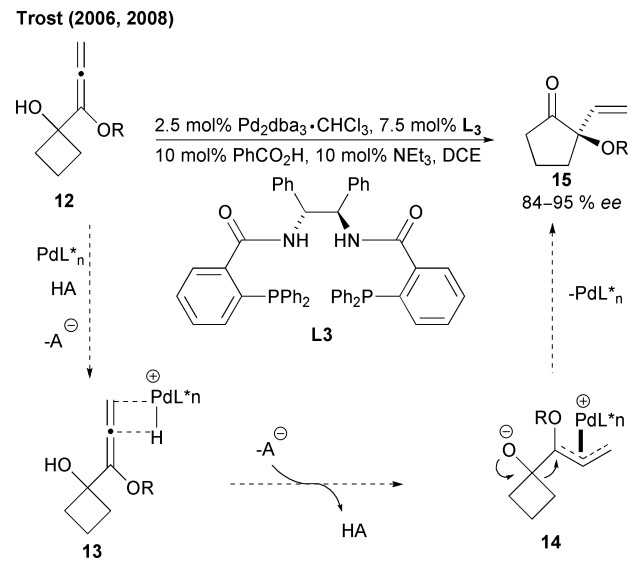
Mechanistically, an initial oxidative addition of the arylbromide forms an arylpalladium(II) intermediate, that subsequently undergoes a base promoted ligand exchange with the cyclobutanol to form palladium(II) alcoholate **7**. An enantioselective β-carbon cleavage opens the cyclobutane ring and gives rise to the alkylpalladium(II) species **8**. Reductive elimination is faster than β-hydride elimination and expels product **9** while regenerating the Pd(0)-catalyst. Although classical chiral bidentate phosphine ligands such as BINAP, DUPHOS and DIOP promoted the reaction, they provided almost no asymmetric induction. However, a suitable P,N-bidentate ligand family having a ferrocene backbone was identified (with **L2** being the most selective member) that provided high enantioselectivity. The planar chirality of the ferrocene ligand plays—compared to the stereochemistry of the amine—the dominant role in controlling the direction of the enantioselective C–C bond cleavage. A variety of different arylbromides works well under these conditions and products **9** were formed uniformly

in high yields and enantioselectivities (77–95% *ee*). Not only arylhalides are competent coupling partners, as couplings with vinylbromides and triflates as well as propargylic acetates have also been reported and give rise to alkenes **10** and allenes **11** (Scheme 4). However, the enantioselectivity as well as the reactivity of the rearrangement is sensitive towards the substituents of the cyclobutane core. An alkyl group as substituent R^2 (Scheme 3) or a disubstitution pattern in the 3-position of the cyclobutane lead to modest selectivities.



Scheme 4 Pd-catalyzed cleavage/vinylation and allenylation.

Another palladium-catalyzed activation of *tert*-cyclobutanols has been reported by Trost and Xie (Scheme 5).[10] They found that alkoxyallenyl substituted *tert*-cyclobutanols (**12**) can be rearranged with a catalytic amount of a chiral palladium complex into cyclopentanones with α-chiral *O*-tertiary centers (**15**). Although the substrate class is closely related to the previously described reaction, its mechanistic picture is completely different. In this case, the suggested mechanism starts with a hydropalladation of the starting alkoxy allene moiety (**13**) to form π-allyl palladium intermediate **14** (Scheme 5). Upon deprotonation, this intermediate participates in a facile Wagner–Meerwein shift to give, under optimized conditions with Trost ligand **L3**, the observed ring expanded cyclopentanone **15** in excellent yields (78% to quantitative) and enantioselectivities (84–95% *ee*). A careful control of

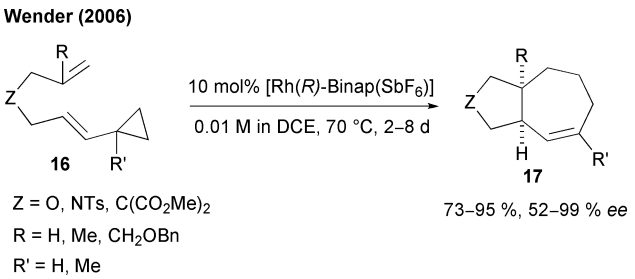


Scheme 5 Pd-catalyzed enantioselective Wagner–Meerwein shift of allenyl *tert*-cyclobutanols.

the pH of the reaction (addition of benzoic acid/triethylamine) proved to be key to good conversion and a high selectivity. The method was extended to substrates having additional substituents in the 3-position of the cyclobutanol, thus providing access to richly functionalized cyclopentanones in high enantio- as well as diastereoselectivities, given that the starting cyclobutanol is not a mixture of *cis*/*trans* isomers.[11] The remarkable diastereoselectivity of the rearrangement process demonstrates that the employed ligand not only dictates the configuration of the newly formed *O*-tertiary stereogenic center but also influences the migrating aptitude of the two prochiral C–C bonds of the cyclobutanol.

Rhodium catalyzed reactions

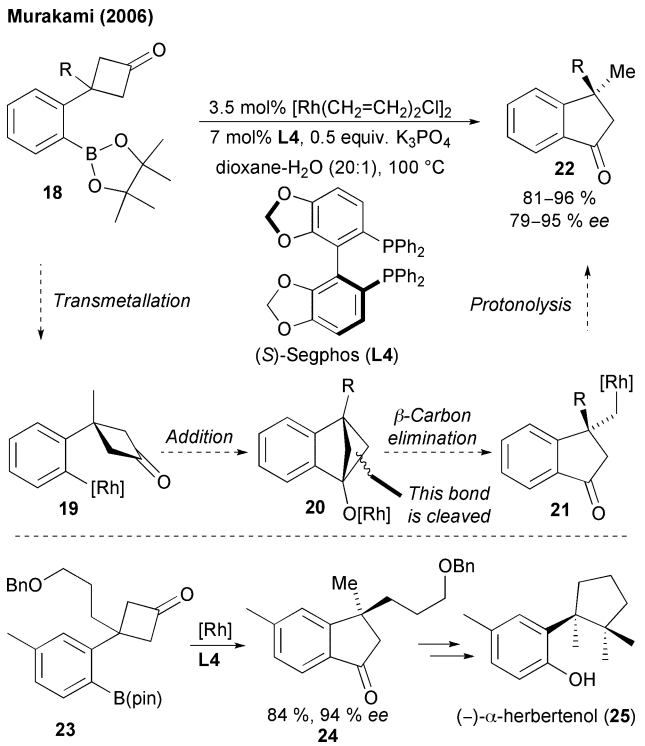
Vinylcyclopropanes (VCPs) are an intriguing class of compounds that enjoy a variety of metal-catalyzed activation reactions. Their propensity to form metalla-cyclohexene intermediates has been exploited by Wender and coworkers in their seminal work on the rhodium-catalyzed [5 + 2] cycloaddition of tethered alkyne-VCPs, alkene-VCPs and allene-VCPs.[12] Although highly reactive rhodium-catalysts have been devised, an asymmetric variant of the reaction remained elusive for a long period. This contrasts with the high enantioselectivities obtained in related rhodium-catalyzed [4 + 2] cycloadditions of tethered ene-dienes.[13] Recent investigations led to the identification of the cationic rhodium complex [Rh(Binap)SbF_6] that effects for the first time an efficient enantioselective [5 + 2] cycloaddition of a VCP and a tethered alkene (**16**) to afford the bicycle **17** (Scheme 6).[14]



Scheme 6 Rh-catalyzed asymmetric [5 + 2]-cycloaddition of ene-vinylcyclopropanes.

High yields and selectivities (up to >99% *ee*) are obtained with ether, sulfonamide and malonodiester tethers. A substituent in the R and/or R′ position of **16** is beneficial for the enantioselectivity of the reaction, but reduces, on the other hand, the reactivity of the substrate significantly, reflected by long reaction times of 2–8 days.

In addition to cyclopropanes, Murakami and coworkers demonstrated for the first time that 4-membered rings are also suitable substrates for asymmetric ring cleavage reactions. They disclosed, in a pioneering contribution, a rhodium(I)-catalyzed rearrangement of functionalized cyclobutanones (**18**) into benzocyclopentanones bearing a quaternary stereogenic center (**22**) (Scheme 7).[15] The reaction is thought to operate through a cascade of steps initiated by a transmetallation of the boronic ester to rhodium. Subsequently, the aryl-rhodium intermediate **19** adds intramolecularly to the carbonyl-group forming the highly strained bicyclic rhodium alcoholate **20**. This reactive intermediate fragment leads, *via* a selective cleavage of one of the two prochiral C–C σ-bonds, to the alkyl-rhodium species **21**. Protonolysis ultimately provides



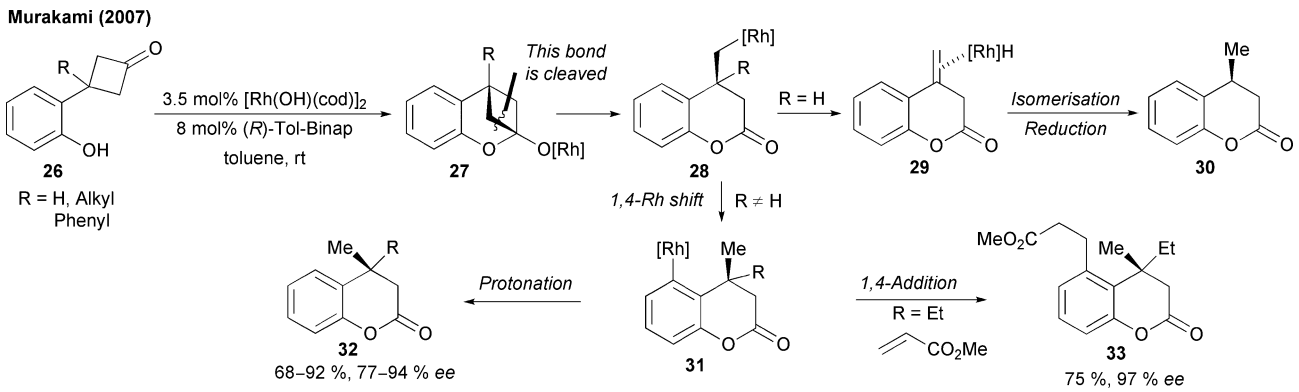
Scheme 7 Rh-catalyzed asymmetric C–C cleavage of cyclobutanones.

indanones **22**, having a benzylic quaternary stereogenic center. The reaction proceeds in good to excellent enantioselectivities (79–95% *ee*) with (*S*)-SEGPHOS (**L4**) as a chiral ligand. The utility of the products obtained was further demonstrated by the synthesis of the sesquiterpene (–)-α-herbertenol (**25**).

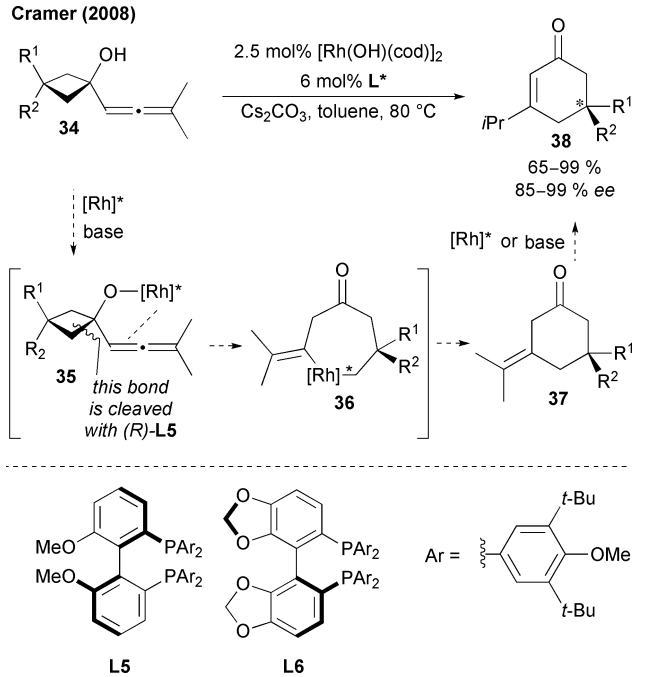
The Murakami group also reported a related reaction with *o*-hydroxyphenyl-substituted cyclobutanones[9] (**26**) which provide, upon treatment with a chiral rhodium complex, access to dihydrocoumarins (Scheme 8).[16] Presumably, the phenolic OH of **26** forms a rhodium alcoholate, promoting the generation of the bicyclic species **27** *via* hemiketalization.

This strained intermediate is activated enough to undergo facile β-carbon elimination even at ambient temperature. The resulting carbon–rhodium species (**28**) provides, after a series of β-hydride elimination/readdition events, dihydrocoumarin **30** with a tertiary methyl stereogenic center in 77% yield and >99% *ee*. Substrates where this β-hydride elimination pathway is blocked by a second substituent undergo a 1,4-rhodium shift generating the aryl-rhodium species **31**. These intermediates undergo either a protodemetallation reaction to form the corresponding dihydrocoumarins with quaternary stereogenic center (**32**) or react in the presence of a competently activated olefin in a Michael type fashion to give rise to substituted dihydrocoumarins (**33**). The different pathways of this transformation highlight the power and versatility of such an activation to obtain useful compounds that are difficult to access by common synthetic methods. Surprisingly, when the same reaction was conducted in the presence of an arylhalide and a palladium catalyst instead of rhodium, the reaction still proceeds and the corresponding palladium intermediate of **28** is trapped to form the arylated product.[17] However, the enantioselectivity is virtually completely lost (15% *ee* reported for Binap).

Apart from cyclobutanones, Cramer and Seiser have demonstrated that *tert*-cyclobutanol derivatives[9] are also susceptible towards rhodium-catalyzed ring cleavage.[18] They reported a rearrangement of allenyl-*tert*-cyclobutyl alcohols into substituted cyclohexenones having a quaternary stereogenic center in the β-position. The anticipated mechanism of the reaction envisions an allenyl-*tert*-cyclobutyl alcohol (**34**) as a chelating group that favors the formation of a well defined adduct **35** with a chiral rhodium complex, ensuring an efficient imprint of the chiral information of the ligand onto the substrate in the enantiodiscriminating C–C activation step (Scheme 9). A putative enantioselective insertion into one of the two prostereogenic C–C σ-bond of the cyclobutane leads to the metallacycloheptanone **36**. A subsequent reductive elimination results in the formation of methylene cyclohexanone **37** as the primary product. An isomerization of the exocyclic double bond converts **37** into the more stable conjugated enone **38**. Their optimization study revealed that both compounds, **37** and **38**, are formed in various ratios. This product mixture was avoided by the addition of caesium carbonate which provided a virtually quantitative yield of enone **38** and additionally improved the reaction rates. Ligand screening revealed that (*R*)-DTBM-MEOBIPHEP (**L5**) and (*S*)-DTBM-SEGPHOS (**L6**), both bulky biaryl diphosphine ligands with a narrow dihedral angle,[19] were well suited to promote the rearrangement in high enantioselectivity (96% *ee* with **L5** and 95% *ee* with **L6**). The efficiency of the catalyst system was further demonstrated by lowering the initial catalyst loading of 2.5 mol% to 0.05 mol% $[Rh(OH)(cod)]_2$



Scheme 8 Rh-catalyzed hemiketalization and enantioselective C–C bond cleavage of cyclobutanones.



Scheme 9 Rhodium catalyzed activation of *tert*-cyclobutanols and rearrangement into cyclohexenones.

without any deterioration of yield and only a slight drop in enantioselectivity to 90% *ee.* The reaction is tolerant to functional groups that might be problematic with transition metal complexes such as aryl halides, benzyl ethers and vinyl groups and is mostly insensitive to the substitution pattern in the 3-position of the cyclobutane. Apart from various aromatic substituents, bulky alkyl and heteroaromatic groups, different substitutions of the allene are also tolerated.

The reactions proceeded generally in high yields (65–99%) and enantioselectivities ranging from 85 to 99% *ee.* Remarkably, even cyclobutanol derivatives that possess a hydrogen at the 3-position of the cyclobutane do not suffer from a β-hydride elimination and are smoothly converted into the cyclohexenones in comparable yields and selectivities. From a mechanistic point of view, it remains unsolved whether a direct β-carbon cleavage of a rhodium(I) alcoholate (**35**) or a hydro-rhodation/elimination pathway is operative. Further research in this area should shed more light on the catalytic cycle. This will not only provide a more concrete knowledge of the activation, but should also enable the design of new reactions to further exploit reactive intermediates.

Conclusions

There is an increasing body of work that underlines the potential of the enantioselective activation of carbon–carbon single bonds. Most of the work has been done on small strained rings such as cyclopropanes and cyclobutanes. Although the reported reactions are so far focused on this relatively small set of substrate classes, the diversity of the generated products is broad and the observed selectivities have already reached synthetically useful levels. However, for a further understanding of the reaction pathways, detailed mechanistic studies are required to allow the prediction of activation sites and further propel the development of more sophisticated and better performing catalyst systems. Further research in this direction might lead to the discovery of methods for the activation of unstrained carbon–carbon bonds enabling transformations that are otherwise difficult to achieve and would therefore offer new horizons for streamlining synthesis.

Acknowledgements

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