DOI: 10.1002/chem.200903225

Rhodium(I)-Catalyzed Enantioselective Activation of Cyclobutanols: Formation of Cyclohexane Derivatives with Quaternary Stereogenic Centers

Tobias Seiser and Nicolai Cramer*[a]

Dedicated to Professor Alexandre Alexakis on the occasion of his 60th birthday

Abstract: The activation of carbon–carbon σ bonds is a complementary method to access uncommon and difficult-to-prepare organometallic species. Herein, we describe the activation of *tert*-cyclobutanols through an enantioselective insertion of a chiral rhodium(I) complex into the C–C σ bond of the cyclobutane, forming a quaternary stereogenic center and an alkyl-rhodium functionality that initiates ring-closure reactions. This technology provides access to a variety of substituted cyclohexane derivatives with quaternary stereogenic centers. The formation of different product families can be controlled by the employed set of reaction conditions and additives. In general, high yields and excellent enantioselectivities of up to 99% *ee* are obtained.

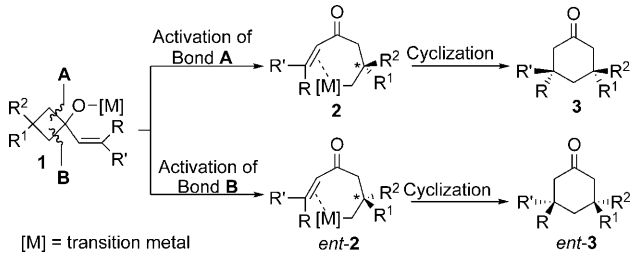
Keywords: asymmetric catalysis · C–C activation · cyclobutane · rhodium · ring expansion

Introduction

The selective and catalytic functionalization of carbon–hydrogen (C–H) and carbon–carbon (C–C) bonds by transition-metal complexes has a significant and broad impact on organic synthesis. The lack of pre-functionalization steps, required for traditional approaches, make such activation processes economically and ecologically highly attractive. C–H activations are a vibrant and very active research area that recently underwent impressive progress.[1] In comparison, the development of efficient C–C activation reactions largely lags behind and a practical implementation of this concept is still a major challenge for organometallic chemistry.[2] This can be attributed to the fact that C–C bonds are highly directed and even more inert than C–H bonds. Furthermore, reductive elimination, the reverse pathway, is most often the preferred reaction direction. Hartwig and Zhao recently demonstrated that triarylcarbinols and rhodium complexes are in an equilibrium with the corresponding diarylketones and aryl-rhodium species.[3] The site of the equilibrium is largely determined by the electronic properties and the steric bulk of the aromatic substituents. This report underscores the possibility to access organometallic species by β-carbon eliminations. Substrate classes that are more biased towards such fragmentation would provide an attractive entry into unusual organometallics with novel reactivities.[4] In this respect, small strained rings occupy a privileged position in C–C activation reactions, because of the additional driving force liberated by strain reduction in ring-opening reactions.[5] The inherent strain and their convenient accessibility make cyclobutane derivatives an attractive substrate class. Furthermore, a selective insertion into one of the two enantiotopic C–C bonds of a symmetrically substituted cyclobutane ring would open opportunities for enantioselective activations, a largely unmet challenge in transition-metal catalysis.[6] Pioneering studies from Uemura's group, who reported an asymmetric palladium-catalyzed ring-opening arylation of aryl-*tert*-cyclobutanols,[7] and reports from Murakami and co-workers, who used a highly enantioselective rhodium-catalyzed transformation to construct benzocyclopentanones and dihydrocoumarines from cyclobutanones,[8] underline the largely unexplored potential of this concept. We envisioned capitalizing on the potential of an enantioselective insertion in one of the two enantiotopic bonds of cyclobutanol **1** to form intermediate **2** bearing an alkyl-rhodium functionality next to a newly created quaternary stereogenic center (Scheme 1). As the chemical trans-

[a] T. Seiser, Dr. N. Cramer
ETH Zurich, Laboratory of Organic Chemistry
HCI H 304, Wolfgang-Pauli-Strasse 10
8093 Zurich (Switzerland)
Fax: (+41) 44-632-13-28
E-mail: Nicolai.cramer@org.chem.ethz.ch
Homepage: http://www.cramer.ethz.ch

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903225.



Scheme 1. Proposed activation and cyclization model of allylic *tert*-cyclobutanols.

formation does not take place directly at the hindered, asymmetrically substituted carbon atom, this approach should be well suited for demanding quaternary stereogenic centers.[9]

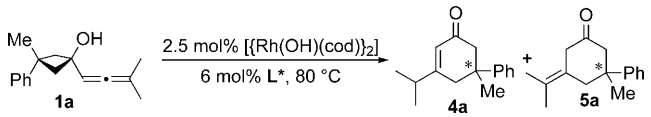
We expected that intermediate **2** would be prone to a 1,4-addition across the concomitantly formed activated olefin moiety of **2** to yield cyclohexanone **3**. Furthermore, the chelating environment created by the hydroxyl group and the π unsaturation in the form of an alkyne, allene, or olefin of **1** would not only facilitate an association with the metal complex, but also result in a structurally well-defined complex, the rigidity of which would allow an efficient imprint of the chirality of the ligand onto the substrate. We recently reported that especially allenyl-substituted cyclobutanols are a formidable starting point to access transient organometallic species that are difficult to prepare otherwise.[10] Herein, we report the full details and demonstrate further elaboration of these reactive intermediates into a host of structurally diverse, highly substituted cyclohexane derivatives under different sets of reaction conditions.

Results and Discussion

In a first experiment, the model substrate *trans*-1-(3,3-dimethylallenyl)-3-methyl-3-phenylcyclobutanol (**1a**) was heated to 80 °C in toluene in the presence of [{Rh(OH)(cod)}$_2$] (2.5 mol %; cod = 1,2-cyclooctadiene) and (*R*)-BINAP (6 mol %; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (**L1**); Table 1).

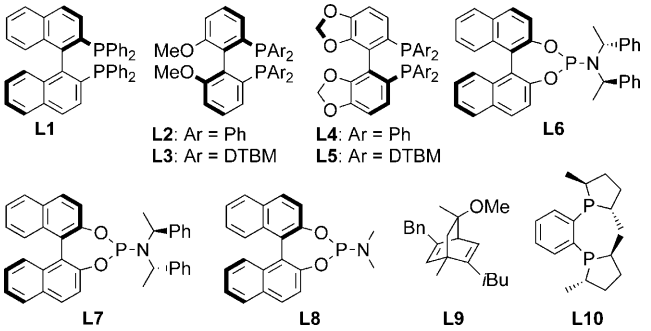
Methylene cyclohexanone **5a** was formed predominantly under these conditions with a promising enantiomeric excess of 76 % (entry 5). However, during the course of the reaction, **5a** isomerized in a variable amount to enone **4a** and also decomposed to more polar products (vide infra). To mitigate these side reactions, we screened auxiliary bases to promote the isomerization to the more stable enone **4a**. Weak organic bases like triethylamine were not competent (entry 6). Pleasingly, insoluble inorganic bases such as cesium carbonate or potassium phosphate accelerated the double-bond isomerization without interfering with the C–C bond-insertion event leading to a virtually quantitative yield and 80 % *ee* of the conjugated product (entries 7 and 8). The solvent has a significant impact on the reaction time as well as on the selectivity. Reactions in dioxane are slower and require higher temperatures to go to completion and are accompanied with lower selectivities (entries 1–4). Dry, nonpolar aromatic solvents (toluene or xylenes) turned out to be optimal. Screening of further chiral ligands showed that phosphoramidite (*RRR*)-**L6** and (*RSS*)-**L7** gave, in contrast to Monophos (**L8**), product **4a** in goods yields and in selectivities comparable to BINAP (entries 9–11). (−)-Dolefine (**L9**), a diene ligand, led to complete conversion and moderate yield (entry 12), whereas Me-Duphos (**L10**) was essentially inactive (entry 13). Biarylphosphines with a narrower dihedral angle[11] than BINAP (80 % *ee*, entry 8) increased the enantioselectivity slightly. Thus, (*R*)-MeOBiphep (**L2**)

Table 1. Optimization of the reaction conditions.[a]



Entry	L*	Base	Solvent	Yield [%][b]	*ee* [%][c]
1[d]	**L1**	Cs_2CO_3	dioxane, 5 % H_2O	28	73 (*S*)
2[d]	**L1**	Cs_2CO_3	dioxane	99	73 (*S*)
3[d]	**L2**	Cs_2CO_3	dioxane	90	73 (*S*)
4[d]	**L5**	Cs_2CO_3	dioxane	97	92 (*R*)
5[d]	**L1**	–	toluene	79 (**5a**)	76 (*S*)
6	**L1**	NEt_3	toluene	71 (**5a**)	79 (*S*)
7	**L1**	K_3PO_4	toluene	79	79 (*S*)
8	**L1**	Cs_2CO_3	toluene	99	80 (*S*)
9[d,e]	**L6**	Cs_2CO_3	toluene	83	77 (*S*)
10[d,e]	**L7**	Cs_2CO_3	toluene	99	84 (*R*)
11[d,e]	**L8**	Cs_2CO_3	toluene	< 5	–
12[d,f]	**L9**	Cs_2CO_3	toluene	58	43 (*R*)
13[d]	**L10**	Cs_2CO_3	toluene	< 5	–
14	**L2**	Cs_2CO_3	toluene	99	83 (*S*)
15	*ent*-**L4**	Cs_2CO_3	toluene	92	85 (*S*)
16	**L3**	Cs_2CO_3	toluene	95	96 (*S*)
17	**L5**	Cs_2CO_3	toluene	92	95 (*R*)
18	**L5** (1 mol % [Rh])	Cs_2CO_3	toluene	99	91 (*R*)
19	**L5** (0.1 mol % [Rh])	Cs_2CO_3	toluene	99	90 (*R*)
20[d]	**L5** (0.01 mol % [Rh])	Cs_2CO_3	toluene	> 5	–

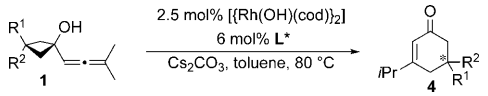
[a] Reaction conditions: 0.1 mmol **1a**, 1.5 equiv base, 2.5 mol % [{Rh(OH)(cod)}$_2$], 6.0 mol % **L***, 0.25 M, 80 °C, 3–5 h. [b] Yield of isolated product **4a**. [c] Enantioselectivities were determined by HPLC with a chiral stationary phase. [d] 100 °C, 24 h. [e] 12 mol % **L***. [f] With 2.5 mol % [{Rh(OAc)(C$_2$H$_4$)$_2$}$_2$].



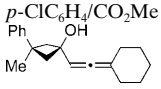
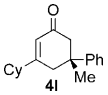
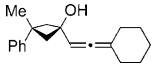
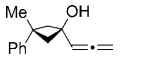
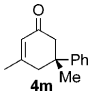
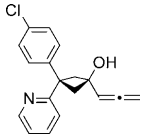
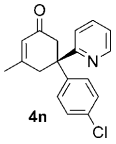
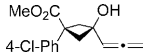
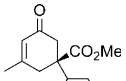
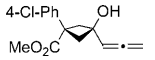
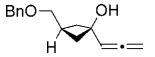
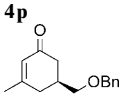
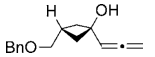
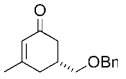
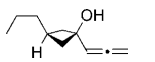
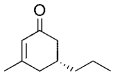
provided enone **4a** in 83% *ee* and (*R*)-Segphos (*ent*-**L4**) resulted in 85% *ee* (entries 14 and 15). A significant improvement was achieved with the sterically more demanding homologues (*R*)-DTBM-MeOBiphep (**L3**) and (*S*)-DTBM-Segphos (**L5**; DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl), affording now **4a** with an enantiomeric excess of 96% (**L3**) and 95% (**L5**) (entries 16 and 17). Noteworthy, the required catalyst loading—starting with a initial amount of 2.5 mol% [{Rh(OH)(cod)}$_2$]—could be reduced to 0.1 mol% rhodium without compromising the yield of the reaction and only slightly affecting the enantioselectivity (90% *ee* instead 95% *ee*, entry 19).

With the aforementioned optimized conditions, we then explored the substrate scope and limitations of this process with a host of different cyclobutanol substrates **1**. We first examined the opposite isomer *cis*-**1a** yielding in full accordance with the hypothesized mechanism *ent*-**4a** in comparable yield and selectivity (Table 2, entry 1). Different aromatic substitutions (entries 1–9) as well as alkyl substituents (entries 12–15) are well tolerated. Irrespective of the substitution pattern, the rearranged products were generally obtained with high fidelity in excellent yields and selectivities. The process also proved to be tolerant to functional groups that can potentially interfere with transition-metal-catalyzed processes: Terminal olefins (entries 10 and 11) and pyridines (entry 16 and 23) coordinate to the rhodium complex and require higher temperature and reaction times to go to completion. Aryl halides, benzyl groups, and esters are perfectly stable under these reaction conditions (entries 4 and 5; 17 and 18; 19 and 24–25, respectively). The dimethylallene can be exchanged for cyclic (entries 20 and 21) and for terminal allenes (entries 22–25 and 27–29) to yield the corresponding products **4**, once again, in excellent yields and selectivities. It is noteworthy, that in the 3-position mono-substituted cyclobutanols rearranged smoothly to cyclohexenones **4** (entries 26–29). Surprisingly, no trace of products arising from β-hydride elimination was observed with these substrates, which sug-

Table 2. Scope of the rhodium(I)-catalyzed C–C activation.[a]



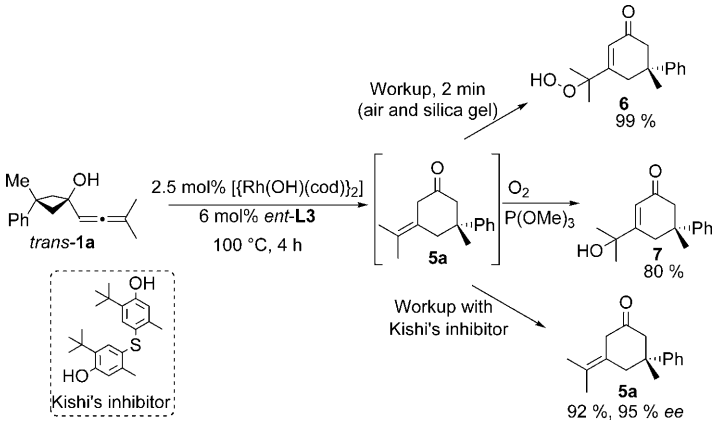
1 → 4

Entry	L*	1	R^1/R^2	4	Yield [%][b]	*ee* [%][c]
1	**L3**	*cis*-**1a**	Ph/Me	**4a**	97	96 (*R*)
2	**L3**	*cis*-**1b**	Ph/Et	**4b**	99	97 (*R*)
3	**L5**	*trans*-**1b**	Et/Ph	**4b**	99	96 (*R*)
4	**L3**	*cis*-**1c**	*p*-ClC_6H_4/Me	**4c**	88	95 (*R*)
5	**L5**	*trans*-**1c**	Me/*p*-ClC_6H_4	**4c**	99	96 (*R*)
6	**L3**	*cis*-**1d**	*p*-MeC_6H_4/Me	**4d**	87	94 (*R*)
7	**L5**	*trans*-**1d**	Me/*p*-MeC_6H_4	**4d**	99	95 (*R*)
8	**L3**	*cis*-**1e**	2-Naph/Me	**4e**	85	94 (*R*)
9	**L5**	*trans*-**1e**	Me/2-Naph	**4e**	97	94 (*R*)
10[d]	**L3**	*cis*-**1f**	Ph/Vinyl	**4f**	85	90 (*R*)
11[d]	**L5**	*trans*-**1f**	Vinyl/Ph	**4f**	74	90 (*R*)
12	**L3**	*cis*-**1g**	*i*Pr/Me	**4g**	80	94 (*R*)
13	**L5**	*trans*-**1g**	Me/*i*Pr	**4g**	91	97 (*R*)
14	**L3**	*cis*-**1h**	*t*Bu/Me	**4h**	81	96 (*R*)
15	**L5**	*trans*-**1h**	Me/*t*Bu	**4h**	80	99 (*R*)
16[d]	**L5**	**1i**	Ph/2-pyridyl	**4i**	65	91 (*R*)
17[d]	**L3**	*trans*-**1j**	Ph/CH_2OBn	**4j**	89	97 (*S*)
18	**L5**	*cis*-**1j**	CH_2OBn/Ph	**4j**	99	94 (S)
19	*ent*-**L3**	*trans*-**1k**	*p*-ClC_6H_4/CO_2Me	**4k**	78	90 (*R*)
20[d]	**L3**	*cis*-**1l**		 **4l**	91	93 (*R*)
21	**L5**	*trans*-**1l**			93	92 (*R*)
22[d]	**L5**	**1m**		 **4m**	93	93 (*R*)
23[d]	**L3**	**1n**		 **4n**	57	89 (*S*)
24	*ent*-**L3**	*cis*-**1o**			70	91 (*S*)
25	**L3**	*trans*-**1o**		**4o**	52	87 (*S*)
26	**L5**	**1p**	Ph/H	**4p**	94	85 (*S*)
27	*ent*-**L3**	*cis*-**1q**		 **4q**	85	88 (*S*)
28	*ent*-**L3**	*trans*-**1q**		 *ent*-**4q**	94	97 (*R*)
29	*ent*-**L5**	*cis*-**1r**		 **4r**	88	93 (*R*)

[a] Reaction conditions: 0.1 mmol **1**, 1.5 equiv Cs_2CO_3, 2.5 mol% [{Rh(OH)(cod)}$_2$], 6.0 mol% **L3** or **L5**, toluene (0.25 M), 80 °C, 3 h. [b] Yield of isolated product **4**. [c] Enantioselectivities were determined by HPLC with a chiral stationary phase. [d] 100 °C, 16 h.

gests that either a mechanism involving rhodacyclic intermediates[12] or a very fast addition to the allenone is operative. This somewhat unexpected tolerance allowed determination of the absolute configuration by a synthesis of the celery ketone (**4r**),[13] and was additionally confirmed by the optical rotation of the known compound **4q**.[14]

The initial observation of the formation of the nonconjugated cyclohexanone isomer **5** prompted us to devise reaction conditions for its selective formation. It was apparent from the optimization studies that **5** is the initially predominantly formed product, and not being the thermodynamically stable isomer, it is converted under base or metal catalysis over time to the more stable enone **4**. Omitting the base and performing the reaction for 4 h at 100 °C forms cleanly the nonconjugated isomer **5**. However, even this compound is the only observable product by ^{1}H NMR spectroscopy of the reaction mixture, and its isolation proved to be delicate. Surprisingly, it turned out to be significantly more sensitive towards oxidation than to base-catalyzed isomerization reactions. Even under carefully controlled workup and purification conditions, minimizing its exposure time to air and silica gel, we only obtained hydroperoxide **6** in a virtually quantitative yield (Scheme 2). The same, but significantly



Scheme 2. Facile autoxidation of nonconjugated isomer **5a**.

slower, process is observed when solutions of **5** are exposed to air. The identity of the obtained hydroperoxide **6** was confirmed by X-ray crystallographic analysis (Figure 1).[15]

We regard this surprisingly facile autoxidation[16] as being responsible for the difficulties of our initial attempts to trace the nonconjugated product **5**. When the reaction mixture was stirred after the completed rhodium-catalyzed rearrangement at ambient temperature under an atmosphere of oxygen, and was subsequently treated with trimethylphosphite, alcohol **7** was produced in 80 % yield. Despite these obstacles, we succeeded in isolating the exocyclic olefinic isomer **5a** in 92 % yield and 95 % *ee* by adding Kishi's radical inhibitor[17] during the workup and purification procedure, which mostly suppressed the oxidative isomerization. Applying these conditions and precautions to a range of substrates, the corresponding 3-isopropylidene cyclohexanones **5** were obtained in moderate to good yields and excellent enantiomeric excesses matching those obtained for enones **4** (Table 3). The somewhat fluctuating and reduced yields relative to those obtained using the standard isomerizing conditions are a reflection of the lability of this compound class.

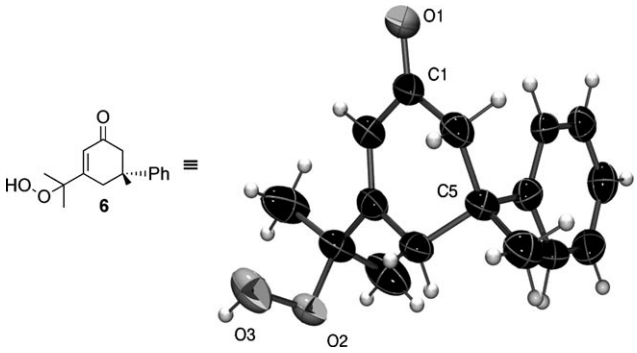
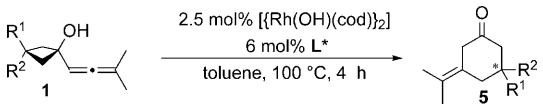


Figure 1. ORTEP representation of hydroperoxide **6** (probability ellipsoids at 60 %).

Table 3. Synthesis of 3-isopropylidene cyclohexanones **5**.[a]



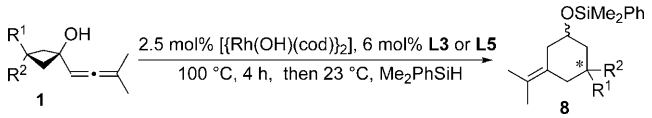
Entry	L*	1	R^1/R^2	5	Yield [%][b]	*ee* [%][c]
1	*ent*-**L3**	*trans*-**1a**	Me/Ph	**5a**	92	95 (*R*)
2	**L3**	*cis*-**1a**	Ph/Me	**5a**	71	96 (*R*)
3	**L3**	*cis*-**1b**	Ph/Et	**5b**	84	97 (*R*)
4	*ent*-**L3**	*trans*-**1e**	Me/2-Naph	**5e**	69	94 (*R*)
5	*ent*-**L5**	*cis*-**1j**	CH_2OBn/Ph	**5j**	42	92 (*R*)
6	*ent*-**L3**	*trans*-**1k**	*p*-Cl-Ph/CO_2Me	**5k**	49	90 (*R*)

[a] Reaction conditions: 0.1 mmol **1**, 2.5 mol % [{Rh(OH)(cod)}$_2$], 6.0 mol % **L***, toluene (0.25 M), 100 °C, 4 h. [b] Yield of isolated product **5**. [c] Enantioselectivities were determined after base-catalyzed isomerization to enones **4** by HPLC with a chiral stationary phase.

The inherent lability of products **5** prompted us to investigate the possibility of sequential catalytic reactions that would 1) avoid any isolation of this sensitive compound class and 2) would take advantage of the additionally generated functionalities. For example, treatment of the reaction mixture with dimethylphenylsilane promoted a rhodium-catalyzed hydrosilylation[18] and directly formed silyl-protected secondary alcohols **8** in high yields (Table 4). Although the rhodium complex very efficiently promoted the reduction, the observed diastereoselectivities of the hydrosilylation event are only modest, slightly favoring the *syn* product. As shown for *cis*-**1a** and *trans*-**1a**, the obtained products **8** are enantiomers of each other, which indicates that the substrate and not the chiral phosphine ligand governs the facial selectivity of the reduction.

Furthermore, we investigated the possibility of a sequential conjugate reduction pathway of the obtained enones **4** to address the direct synthesis of ketones **3**, one of our ini-

Table 4. Activation/cyclization/1,2-reduction cascade.[a]

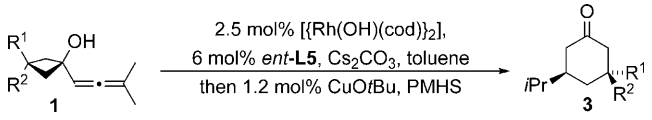


Entry	L*	1	R^1/R^2	8	Yield [%][b]	*ee* [%][c]	*syn*/*anti*[d]
1	**L3**	*cis*-**1a**	Ph/Me	**8a**	80	96 (3*R*)	1.3:1
2	**L3**	*trans*-**1a**	Me/Ph	**8a**	99	96 (3*S*)	1.2:1
3	**L3**	*cis*-**1b**	Ph/Et	**8b**	80	97 (3*R*)	1.3:1
4	**L5**	*trans*-**1e**	Me/2-Naph	**8e**	94	94 (3*R*)	1.2:1
5	**L5**	*cis*-**1p**	Ph/H	**8p**	85	85 (5*S*)	1.9:1

[a] Reaction conditions: 0.1 mmol **1**, 2.5 mol% [{Rh(OH)(cod)}$_2$], 6.0 mol% **L***, toluene (0.25 M), 100 °C, 4 h. [b] Yield of isolated product **8**. [c] Enantioselectivities were determined on an aliquot before silane addition by HPLC with a chiral stationary phase. [d] Diastereomeric ratios were determined by proton NMR spectroscopy.

tial aims. Unfortunately, the utilized rhodium complex did not prove to be a competent catalyst for 1,4-reductions. However, the desired reaction proceeded smoothly upon addition of a mixture of copper *tert*-butoxide (1.2 mol%) and poly(methylhydrosiloxane) (PMHS) as the bulk reductant.[19] The small excess of the DTBM-Segphos ligand present in the reaction mixture is sufficient for a completely selective and catalyst-controlled reduction (Table 5). This attractive feature allows the selective preparation of *both* diastereomers of **3**: Starting with isomer *cis*-**1** leads exclusively to *anti*-**3** products (Table 5, entries 1 and 3). The corresponding *trans*-**1** is transformed in an analogous manner completely selectively to *syn*-**3** (entries 2 and 4).

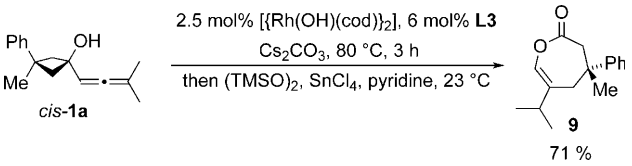
Table 5. One-pot rearrangement/1,4-reduction sequence.[a]



Entry	1	R^1/R^2	3	Yield [%][b]	*ee* [%][c]	*syn*/*anti*[d]
1	*cis*-**1a**	Ph/Me	*anti*-**3a**	74	95 (*R*,*R*)	1:>20
2	*trans*-**1a**	Me/Ph	*syn*-**3a**	65	95 (*S*,*R*)	>20:1
3	*cis*-**1e**	2-Naph/Ph	*anti*-**3e**	51	94 (*R*,*R*)	1:>20
4	*trans*-**1e**	Me/2-Naph	*syn*-**3e**	55	94 (*S*,*R*)	>20:1

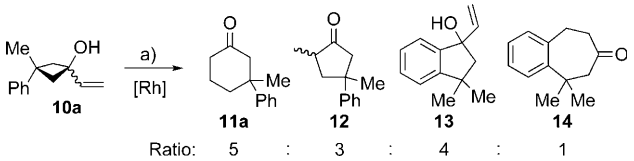
[a] Reaction conditions: 0.1 mmol **1**, 2.5 mol% [{Rh(OH)(cod)}$_2$], 6.0 mol% *ent*-**L5**, 1.5 equiv Cs_2CO_3, toluene (0.25 M), 80 °C, 3 h, then 1.2 mol% CuO*t*Bu and 2.4 equiv PMHS, 5 °C, 48 h. [b] Yield of isolated product **3**. [c] Enantioselectivities were determined on an aliquot of **4** before silane addition by HPLC with a chiral stationary phase. [d] Diastereomeric ratios were determined by proton NMR spectroscopy.

A complementary option for sequential catalysis is the coupling of the rhodium-catalyzed rearrangement to a second step operating under oxidative conditions. Exposure of hexanone **4a** after completion of the rearrangement to a mixture of bis(trimethylsilyl) peroxide, $SnCl_4$, and pyridine promoted a Baeyer–Villiger reaction,[20] and gave ε-enol lactone **9** in good yields as the sole product (Scheme 3). Under these conditions, a selective migration of the vinyl moiety proceeded and no concurrent epoxidation of the olefin was observed, thus opening a door to access linear quaternary stereogenic centers with this technique. Additionally, such enol lactones are synthetically useful building blocks that allow for further elaboration.[21]



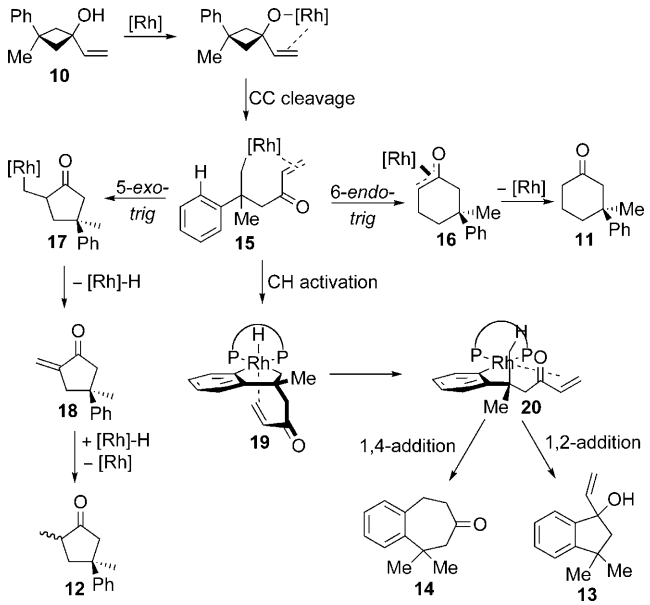
Scheme 3. A Rh^I-catalyzed rearrangement/Baeyer–Villiger combination leads to enol lactone **9**.

The putative mechanism of the rhodium-catalyzed rearrangement does not per se exclude olefin-substituted cyclobutanols as substrates and suggests that the initial β-carbon elimination step should in principle proceed irrespective of the 1-substituent on the cyclobutanol. However, the chelating environment offered by the allene facilitates the reaction and to explore the limitations, we replaced it with a terminal olefin. Exposure of vinyl cyclobutanol **10a** to the standard reaction conditions, led to the complete consumption of the starting material within 3 h, which indicated that the β-carbon cleavage of **10a** occurred at a comparable rate to that observed with the allene substrates **1** (Scheme 4). The main product of the reaction mixture obtained from the rearrangement of **10a** using *rac*-BINAP as the ligand is the expected cyclohexanone **11a**, which is however only formed in a moderate yield.



Scheme 4. Product mixture formed from olefin *cis*-/*trans*-**10a**: a) [{Rh(OH)(cod)}$_2$] (2.5 mol%), *rac*-BINAP (6 mol%), toluene, 110 °C, 3 h.

Three additional products (**12**–**14**) were identified that account for the remaining mass balance. The cyclization of alkyl-rhodium species **15** occurs at a much lower rate than that of the corresponding allene intermediate, which results in a longer life span of **15** (Scheme 5). This species can now participate in additional reaction pathways leading to the observed product distribution. Apart from the expected conjugate addition forming enolate **16** and ultimately the desired hexanone **11a**, intermediate **15** adds in a 5-*exo*-*trig*, counter-electronic fashion across the olefin to give **17**. β-Hydride elimination and re-addition then forms cyclopentanone **12** as a mixture of diastereomers. A third pathway involves a 1,4-rhodium shift reaction[22] that presumably operates by means of a C–H activation pathway involving Rh^{III} intermediate **19** leading to aryl-rhodium species **20**. Com-



Scheme 5. Mechanistic manifold for the observed product distribution.

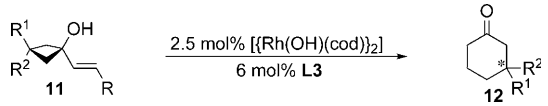
pound **20**, in turn, adds either in a 1,2-fashion to the carbonyl group to yield indanol **13**,[23] or participates in a conjugate addition forming benzocycloheptanone **14**.

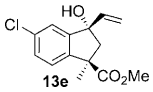
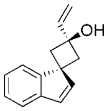
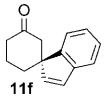
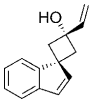
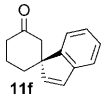
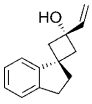
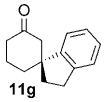
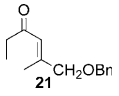
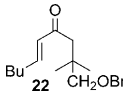
We finally explored the reactivity and selectivity pattern by modulating the steric and electronic properties of several vinyl-substituted cyclobutanols (Table 6). The bulky ligand **L3** improves the selectivity for the cyclohexanones, and aryl-substituted substrates furnish **11** in moderate yields and good to excellent enantioselectivity (entries 1 and 2). Spirocyclic substrates react cleanly to cyclohexanones **11** (entries 7–9), whereas for substrate **10e** that has an electron-poor aromatic substituent, the C–H activation pathway becomes dominant and indanol **13e** is exclusively formed (entry 6). Cyclobutanols lacking aromatic substituents are almost exclusively converted to cyclohexanones **11** and only a trace amount of cyclopentanone is formed (entries 3–5). The drastically slower cyclization rate of the olefins relative to the allenes also becomes apparent when the reaction is performed with cyclobutanol **10h**, which has only one single substituent in the 3-position (entry 10). In contrast to allene **1q**, this substrate does not cyclize anymore and yields instead enone **21**, which arises from a series of β-hydride eliminations and re-additions. A substrate with a 1,2-disubstituted olefin (**10i**) is also reluctant to cyclize and stalls at the ring-opened protonated product **22** (entry 11).

Conclusion

In summary, we have demonstrated a highly enantioselective rhodium-catalyzed carbon–carbon bond activation of symmetrically substituted cyclobutanols. The alkyl-rhodium species generated thereby subsequently add intramolecularly across a concomitantly formed allenone or enone to provide cyclohexane derivatives in excellent yields and selectivities. The reactivity as well as the selectivity of the activation is largely independent of the substitution pattern, tolerates a broad range of functional groups, and can be conducted with catalyst loadings as low as 0.1 mol% rhodium. We further showed its flexibility and synthetic potential by convert-

Table 6. Rhodium-catalyzed rearrangement of allylic *tert*-cyclobutanols.[a]



Entry	**10**	R^1/R^2	R	**11**	Yield [%][b]	*ee* [%][c]
1[d]	**10a**	Ph/Me	H	**11a**	63	88 (*S*)
2[d]	**10b**	Me/2-Naph	H	**11b**	63	98 (*R*)
3[d]	**10c**	*t*Bu/Me	H	**11c**	71	95 (*S*)
4[d]	**10d**	CH_2OBn/Me	H	**11d**	99	96 (*S*)
5	**10d**	Me/CH_2OBn	H	**11d**	93	95 (*R*)
6[e]	**10e**	*p*-Cl-Ph/CO_2Me	H	 **13e**	82	98 (1*R*,3*S*) 8:1 d.r.
7	*trans*-**10f**			 **11f**	75	94 (*S*)
8[d]	*cis*-**10f**			 **11f**	74	88 (*S*)
9	**10g**			 **11g**	93	92 (*S*)
10	**10h**	H/CH_2OBn	H	 **21**	99	–
11	**10i**	CH_2OBn/Me	Bu	 **22**	99	–

[a] Reaction conditions: 0.1 mmol **10**, 2.5 mol% [{Rh(OH)(cod)}$_2$], 6.0 mol% **L3**, toluene (0.25 M), 110 °C, 12 h. [b] Yield of isolated products. [c] Enantioselectivities were determined by HPLC with a chiral stationary phase. [d] 6.0 mol% *ent*-**L3** was used. [e] 6.0 mol% of (*S*)-Difluorphos was used as ligand.

ing the same substrate under different sets of reaction conditions and additives into structurally diverse sets of products. These are often difficult to efficiently prepare by common synthetic methods. Additionally, this study highlights the potential of combining new catalytic activation modes with traditional reactivity patterns in coupled cascade processes to maximize the increase in molecular complexity. Further exploitation of related cascade processes are ongoing and will be reported in due course.

Experimental Section

Representative procedure for the synthesis of enones 4: Compound *trans*-**1a** (22.8 mg, 0.100 mmol), cesium carbonate (49.0 mg, 0.150 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 μmol), and **L3** (6.90 mg, 6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (80 °C) for 3 h. After TLC analysis showed the complete conversion, the reaction mixture was cooled to 23 °C and directly purified on silica gel (CH_2Cl_2, R_f = 0.29) giving cyclohexenone (*S*)-**4a** (21.7 mg, 95 %, 96 % *ee*) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.11 (m, 5H), 5.82 (q, J = 1.1 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H), 2.72 (d, J = 17.7 Hz, 1H), 2.50 (dd, J = 0.8, 16.2 Hz, 1H), 2.48 (d, J = 17.7 Hz, 1H), 2.33 (sept, J = 5.0 Hz, 1H), 1.30 (s, 3H), 1.01 (d, J = 5.0 Hz, 3H), 0.99 ppm (d, J = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 168.8, 146.9, 128.5, 126.4, 125.2, 123.3, 49.8, 41.5, 40.5, 35.7, 28.9, 20.4, 20.3 ppm; IR (ATR): $\tilde{\nu}$ = 2965, 1664, 1626, 1498, 1445, 1364, 1284, 1249, 1067, 1031, 905 cm^{-1}; HRMS (EI): *m*/*z* calcd for $[C_{16}H_{20}O]^+$: 228.1509; found: 228.1508; $[\alpha]_D^{20}$ = −52.1 (c = 0.88 in $CHCl_3$); HPLC separation (Chiralcel OD, 4.6×250 mm; 1 % *i*PrOH/hexane, 1.0 mL min^{-1}, 254 nm): t_R (minor) = 15.94 min, t_R (major) = 17.00 min.

Representative procedure for the synthesis of exocyclic double-bond isomers 5: Compound *trans*-**1a** (22.8 mg, 0.100 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 μmol), and *ent*-**L3** (6.90 mg, 6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (100 °C) for 4 h. After TLC analysis showed the complete conversion, the reaction mixture was cooled to 23 °C and directly purified on silica gel (degassed solvent, 0.2 mM in Kishi's radical inhibitor, pentane to pentane/EtOAc 14:1, R_f = 0.30 pentane/EtOAc 15:1) giving cyclohexanone (*R*)-**5a** (21.0 mg, 92 %, 95 % *ee*) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 4H), 7.24–7.18 (m, 1H), 3.27 (d, J = 16.4 Hz, 1H), 2.97 (d, J = 16.5 Hz, 1H), 2.88 (d, J = 14.7 Hz, 1H), 2.74 (s, 2H), 2.54–2.48 (m, 1H), 1.66 (dd, J = 7.9, 0.8 Hz, 6H), 1.26 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.5, 147.7, 128.4, 127.4, 126.2, 125.3, 123.2, 53.6, 46.0, 41.8, 40.7, 27.6, 20.7, 20.2 ppm; IR (ATR): $\tilde{\nu}$ = 3305, 3058, 2962, 2924, 2870, 1712, 1666, 1601, 1498, 1445, 1416, 1378, 1358, 1236, 1156, 1071, 1031, 908, 762, 700 cm^{-1}; HRMS (EI): *m*/*z* calcd for $[C_{16}H_{20}O]^+$: 228.1509; found: 228.1510; $[\alpha]_D^{20}$ = −15 (c = 0.45 in $CHCl_3$); HPLC separations were carried out after DBU-promoted isomerization of **5a** to **4a** using the above conditions.

Hydroperoxide 6: Compound *trans*-**1a** (22.8 mg, 0.100 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 μmol), and *ent*-**L3** (6.90 mg, 6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (100 °C) for 4 h. After TLC analysis showed the complete conversion, the reaction mixture was cooled to 23 °C. Silica gel was added and the mixture was stirred for 2 min under air. Purification on silica gel (pentane/Et_2O 1:1, R_f = 0.13 pentane/Et_2O 2:1) yielded hydroperoxide **6** (26.0 mg, 99 %) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 4H), 7.24–7.20 (m, 1H), 7.05 (s, 1H), 6.03 (s, 1H), 3.02–2.94 (m, 2H), 2.72–2.66 (m, 1H), 2.61–2.56 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.31 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 163.8, 146.8, 128.6, 126.6, 125.4, 125.3, 83.6, 49.5, 40.7, 39.1, 29.5, 23.3, 22.9 ppm; IR (ATR): $\tilde{\nu}$ = 3286, 2966, 2873, 1812, 1723, 1650, 1601, 1498, 1445, 1412, 1379, 1359, 1302, 1287, 1235, 1201, 1152, 1117, 1072, 1031, 1002, 894, 852, 755, 699 cm^{-1}; HRMS (EI): *m*/*z* calcd for $[C_{16}H_{19}O]^+$: 227.1430; found: 227.1432; $[\alpha]_D^{20}$ = −43 (c = 0.88 in $CHCl_3$).

Alcohol 7: Compound *trans*-**1a** (22.8 mg, 0.100 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 μmol), and *ent*-**L3** (6.90 mg, 6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (100 °C) for 4 h. After TLC analysis showed the complete conversion, the reaction mixture was cooled to 23 °C. The reaction was stirred under an atmosphere of oxygen and subsequently triethyl phosphite (35 μL, 0.200 mmol) was added and the mixture was stirred for another 2 h at 23 °C. Direct purification of the reaction mixture on silica gel (Et_2O, R_f = 0.45) yielded alcohol **7** (19.6 mg, 80 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 4H), 7.24–7.18 (m, 1H), 6.20–6.05 (m, 1H), 2.93 (d, J = 17.1 Hz, 2H), 2.66–2.54 (m, 2H), 1.39 (s, 3H), 1.36 (s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 167.3, 146.5, 128.5, 126.5, 125.3, 122.3, 72.6, 49.6, 40.7, 39.5, 29.1, 28.2, 28.2 ppm; IR (ATR): $\tilde{\nu}$ = 3393, 2973, 2931, 1877, 1658, 1498, 1446, 1359, 1311, 1289, 1230, 1177, 1072, 1031, 965, 907, 764, 700 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $[C_{16}H_{20}O_2+H]^+$: 245.1536; found: 245.1535; $[\alpha]_D^{20}$ = −68 (c = 0.26 in $CHCl_3$).

Representative procedure for the rearrangement/1,2-reduction sequence: Compound *trans*-**1a** (22.8 mg, 0.100 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 μmol), and **L3** (6.90 mg, 6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (100 °C) for 4 h. After TLC analysis showed the complete conversion, the reaction mixture was cooled to 23 °C and dimethylphenylsilane (46.7 μL, 0.300 mmol) was added to the reaction mixture. The reaction mixture was stirred for 13 h at 30 °C and evaporated in vacuo. Purification on silica gel (pentane to pentane/EtOAc 50:1, R_f = 0.29) yielded silyl ether (*S*)-**8a** (36.4 mg, 99 %) as a colorless oil; d.r. (*syn*/*anti*) = 1.2:1. ^{1}H NMR (400 MHz, $CDCl_3$; * denotes the signals of the minor isomer): δ = 7.67–7.03 (m, 10H, 10H*), 3.80 (tt, J = 11.0, 4.5 Hz, 1H), 3.53–3.40 (m, 1H*), 3.09 (dt, J = 14.2, 1.9 Hz, 1H*), 2.94–2.81 (m, 1H), 2.77–2.60 (m, 1H, 1H*), 2.37 (ddt, J = 13.1, 4.0, 2.1 Hz, 1H*), 2.07–1.90 (m, 2H), 1.84–1.72 (m, 1H, 3H*), 1.68 (t, J = 3.4 Hz, 3H*), 1.66 (s, 3H), 1.63 (s, 3H), 1.57 (dd, J = 13.1, 10.8 Hz, 1H), 1.52–1.49 (m, 1H*), 1.19 (s, 3H*), 1.08 (s, 3H), 0.42 (s, 6H), 0.36 (s, 3H*), 0.36 ppm (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; signals of both diastereomers): δ = 152.0, 148.6, 139.5, 139.4, 134.7, 134.6, 130.7, 130.6, 129.3, 129.1, 128.9 (2C), 127.9, 127.7, 127.1, 126.8, 126.7, 126.3, 126.3, 125.3, 70.4, 69.4, 49.2, 48.4, 42.5, 41.7, 41.7, 41.4, 41.0, 40.6, 35.5, 25.7, 21.7, 21.6, 21.3, 21.3, −0.0, −0.1, −0.2, −0.4 ppm; IR (ATR): $\tilde{\nu}$ = 3059, 3021, 2960, 2927, 2902, 2862, 1497, 1444, 1428, 1374, 1252, 1117, 1080, 1058, 829, 786, 699 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $[C_{24}H_{32}OSi+NH_4]^+$: 382.2561; found: 382.2564.

Representative procedure for the synthesis of ketones 3: Compound *cis*-**1a** (22.8 mg, 0.100 mmol), cesium carbonate (49.0 mg, 0.150 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 μmol), and *ent*-**L5** (7.1 mg, 6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (80 °C) for 3 h. A solution of copper *tert*-butoxide and PHMS in toluene (10 mM in Cu and 2.0 M in PHMS, 0.12 mL, prepared according to ref. [19]) was added and the reaction was

stirred for 48 h at 5 °C. The reaction was quenched with TBAF (1 M in THF, 0.26 mL, 0.260 mmol) and acetic acid (16 µl, 0.280 mmol) and the mixture was stirred for 10 min. The mixture was poured into saturated NH_4Cl solution and extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated. Purification on silica gel (pentane/EtOAc 15:1, R_f = 0.28) yielded ketone (*R*,*R*)-**3a** (17.0 mg, 74 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 4H), 7.23–7.14 (m, 1H), 3.09–2.98 (m, 1H), 2.39–2.22 (m, 3H), 2.03–1.93 (m, 1H), 1.59 (dd, J = 15.9, 10.0 Hz, 1H), 1.51–1.44 (m, 1H), 1.37 (s, 3H), 1.33–1.27 (m, 1H), 0.83 ppm (dd, J = 9.2, 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 146.3, 128.6, 126.0, 126.0, 52.3, 44.4, 42.3, 42.2, 39.4, 33.9, 32.3, 19.3, 19.1 ppm; IR (ATR): $\tilde{\nu}$ = 2959, 2927, 2873, 1712, 1602, 1499, 1460, 1445, 1388, 1369, 1304, 1265, 1244, 1227, 1031, 765, 701 cm^{-1}; HRMS (EI): m/z calcd for $[C_{16}H_{22}O]^+$: 230.1666; found: 230.1664; $[\alpha]_D^{20}$ = −68 (c = 0.29 in $CHCl_3$); R_f = 0.28 (pentane/EtOAc 15:1).

Enol lactone 9: Compound *cis*-**1a** (22.8 mg, 0.100 mmol), cesium carbonate (49.0 mg, 0.150 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 µmol), and **L3** (6.90 mg, 6.00 µmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (80 °C) for 3 h. The reaction mixture was cooled to 23 °C, filtered over silica gel, and then added as a solution in dichloromethane (0.20 mL) to a 0 °C preformed suspension containing powdered 4 Å molecular sieves (35 mg), pyridine (4.0 µl, 0.05 mmol), tin(IV) chloride (1.0 M in dichloromethane, 0.05 mL, 0.05 mmol), and bis(trimethysilyl) peroxide (0.087 mL, 0.400 mmol) in dichloromethane (0.8 mL). The ice bath was removed and the reaction was stirred for 24 h at 23 °C. Sodium sulfite was added and the suspension was stirred for 1 h at 23 °C. Purification on silica gel (CH_2Cl_2, R_f = 0.38) yielded enol lactone **9** (17.3 mg, 71 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 4H), 7.26–7.20 (m, 1H), 6.42–6.35 (m, 1H), 3.26 (d, J = 11.8 Hz, 1H), 2.65 (dd, J = 11.8, 0.7 Hz, 1H), 2.56 (d, J = 14.3 Hz, 1H), 2.43 (d, J = 14.2 Hz, 1H), 2.12 (septd, J = 6.8, 1.1 Hz, 1H), 1.49 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.85 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 146.9, 136.0, 133.9, 128.6, 126.7, 125.1, 46.6, 43.6, 40.0, 32.1, 30.1, 21.2, 21.1 ppm; IR (ATR): $\tilde{\nu}$ = 2965, 2874, 1755, 1657, 1498, 1464, 1445, 1321, 1186, 1175, 1146, 1093, 1043, 910, 819, 760, 700 cm^{-1}; HRMS (EI): m/z calcd for $[C_{16}H_{20}O_2]^+$: 244.1458; found: 244.1461; $[\alpha]_D^{20}$ = +14 (c = 0.29 in $CHCl_3$).

Representative procedure for the synthesis of cyclohexanones 11: Compound *cis*-**10d** (23.2 mg, 0.100 mmol), [{Rh(cod)(OH)}$_2$] (1.14 mg, 2.50 µmol), and *ent*-**L3** (6.90 mg, 6.00 µmol) were weighed into an oven-dried vial equipped with a magnetic stirrer bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of dry toluene (0.4 mL), the reaction mixture was degassed by three freeze–pump–thaw cycles, stirred for 10 min at 23 °C, and subsequently immersed into a preheated oil bath (110 °C) for 12 h. After TLC analysis showed the complete conversion, the reaction mixture was cooled to 23 °C and directly purified on silica gel (pentane/EtOAc 15:1, R_f = 0.19) yielding cyclohexanone (*S*)-**11** (23.1 mg, 99 %, 96 % *ee*) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5H), 4.51 (s, 2H), 3.23–3.15 (m, 2H), 2.43 (d, J = 13.9 Hz, 1H), 2.31–2.24 (m, 2H), 2.11–2.05 (m, 1H), 1.98–1.82 (m, 3H), 1.56–1.43 (m, 1H), 0.95 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.9, 138.3, 128.2, 127.4, 127.2, 78.3, 73.2, 50.6, 41.0, 40.1, 33.2, 23.2, 22.0 ppm; IR (ATR): $\tilde{\nu}$ = 2951, 2873, 1710, 1497, 1454, 1228, 1100, 1028, 737, 698 cm^{-1}; HRMS (ESI): m/z calcd for $[C_{15}H_{20}O_2+Na]^+$: 255.1356; found: 255.1354; $[\alpha]_D^{20}$ = −3 (c = 1.00 in $CHCl_3$); HPLC separation (Chiralcel OJ, 4.6 × 250 mm; 5 % *i*PrOH/hexane, 1.0 mL min^{-1}, 254 nm): t_R (minor) = 12.93 min, t_R (major) = 15.35 min), 96 % *ee*.

Acknowledgements

We thank G. Cathomen for synthetic assistance and Dr. B. Schweizer for the X-ray crystallographic analysis of compound **6**. We are grateful to the Swiss National Foundation (21-119750.01), Solvias AG for the MeOBiphep ligands, Takasago International Corporation for the Segphos ligands, and Umicore AG & Co. KG for the rhodium salts, as well as Prof. Dr. E. M. Carreira for generous support. The Fonds der Chemischen Industrie is acknowledged for a Liebig-Fellowship (N.C.) and a Kekulé-Fellowship (T.S.).

[1] For reviews on C–H bond functionalization, see: a) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834; b) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211–241; c) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; e) F. Kakiuchi, *Top. Organomet. Chem.* **2008**, *24*, 1–33; f) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025.

[2] For reviews on C–C bond functionalization, see: a) B. Rybtchinski, D. Milstein, *Angew. Chem.* **1999**, *111*, 918–932; *Angew. Chem. Int. Ed.* **1999**, *38*, 870–883; b) M. Murakami, Y. Ito, *Top. Organomet. Chem.* **1999**, *3*, 97–129; c) C.-H. Jun, C. W. Moon, D.-Y. Lee, *Chem. Eur. J.* **2002**, *8*, 2423–2428; d) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759–1792; e) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610–618; f) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2005**, *14*, 1–20.

[3] P. Zhao, J. F. Hartwig, *Organometallics* **2008**, *27*, 4749–4757.

[4] For examples, see: a) T. Kondo, K. Kodoi, E. Nishinaga, T. Okada, Y. Morisaki, Y. Watanabe, T.-A. Mitsudo, *J. Am. Chem. Soc.* **1998**, *120*, 5587–5588; b) Y. Terao, H. Wakui, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2001**, *123*, 10407–10408; c) H. Wakui, S. Kawasaki, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2004**, *126*, 8658–8659; d) D. Necas, M. Tursky, M. Kotora, *J. Am. Chem. Soc.* **2004**, *126*, 10222–10223; e) A. Funayama, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2005**, *127*, 15354–15355; f) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211; g) T. Nishimura, T. Katoh, T. Hayashi, *Angew. Chem.* **2007**, *119*, 5025–5027; *Angew. Chem. Int. Ed.* **2007**, *46*, 4937–4939; h) T. Nishimura, T. Katoh, K. Takatsu, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 14158–14159; i) R. Shintani, K. Takatsu, T. Katoh, T. Nishimura, T. Hayashi, *Angew. Chem.* **2008**, *120*, 1469–1471; *Angew. Chem. Int. Ed.* **2008**, *47*, 1447–1449.

[5] For examples, see: nickel-catalyzed: a) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2006**, *128*, 2166–2167; iridium-catalyzed: b) T. Nishimura, T. Yoshinaka, Y. Nishiguchi, Y. Maeda, S. Uemura, *Org. Lett.* **2005**, *7*, 2425–2427; palladium-catalyzed: c) T. Nishimura, K. Ohe, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 2645–2646; d) T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 11010–11011; e) R. C. Larock, C. K. Reddy, *Org. Lett.* **2000**, *2*, 3325–3327; rhodium-catalyzed: f) M. Hayashi, T. Ohmatsu, Y.-P. Meng, K. Saigo, *Angew. Chem.* **1998**, *110*, 877–879; *Angew. Chem. Int. Ed.* **1998**, *37*, 837–839; g) M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 13976–13977; h) T. Matsuda, M. Makino, M. Murakami, *Angew. Chem.* **2005**, *117*, 4684–4687; *Angew. Chem. Int. Ed.* **2005**, *44*, 4608–4611; i) C. Aissa, A. Fürstner, *J. Am. Chem. Soc.* **2007**, *129*, 14836–14837; ruthenium-catalyzed: j) T. Kondo, A. Nakamura, T. Okada, N. Suzuki, K. Wada, T. Mitsudo, *J. Am. Chem. Soc.* **2000**, *122*, 6319–6320; Iron-catalyzed: k) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004.

[6] For a review, see: T. Seiser, N. Cramer, *Org. Biomol. Chem.* **2009**, *7*, 2835–2840.

[7] a) T. Nishimura, S. Matsumura, Y. Maeda, S. Uemura, *Chem. Commun.* **2002**, 50–51; b) S. Matsumura, Y. Maeda, T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 8862–8869.

[8] a) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379–3381; b) T. Matsuda, M. Shigeno, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12086–12087.

[9] a) J. D. Christopher, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; b) B. M. Trost, D. C. Jiang, *Synthesis* **2006**, 369–396; c) *Quaternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.

[10] T. Seiser, N. Cramer, *Angew. Chem.* **2008**, *120*, 9435–9438; *Angew. Chem. Int. Ed.* **2008**, *47*, 9294–9297.

[11] S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, P. Dellis, *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5799–5804.

[12] P. A. Wender, N. M. Deschamps, R. Sun, *Angew. Chem.* **2006**, *118*, 4061–4064; *Angew. Chem. Int. Ed.* **2006**, *45*, 3957–3960.

[13] J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem.* **2008**, *120*, 7768–7771; *Angew. Chem. Int. Ed.* **2008**, *47*, 7656–7658.

[14] a) M. Carda, J. Van der Eycken, M. Vandervalle, *Tetrahedron: Asymmetry* **1990**, *1*, 17–20; b) D. F. Taber, K. Kanai, Q. Jiang, G. Bui, *J. Am. Chem. Soc.* **2000**, *122*, 6807–6808.

[15] Crystallographic data for **6**: $C_{16}H_{20}O_3$; $M_r = 260.33$; orthorhombic; space group $P2_12_12_1$; $a = 8.2125(3)$, $b = 12.0678(5)$, $c = 14.2225(7)$ Å; $V = 1409.5(1)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.227$ Mg m^{-3}; $T = 173$ K; reflections collected: 2492; independent reflections: 2474 ($R_{int} = 0.040$); R(all) = 0.0608, wR(gt) = 0.1373. CCDC-752893 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] a) A. Nickon, W. L. Mendelson, *J. Org. Chem.* **1965**, *30*, 2087–2089; b) A. B. Smith III, J. Kingery-Wood, T. L. Leenay, E. G. Nolen, T. Sunazuka, *J. Am. Chem. Soc.* **1992**, *114*, 1438–1449.

[17] Y. Kishi, M. Aratani, M. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, H. Kakoi, *J. Chem. Soc., Chem. Commun.* **1972**, *64*–65.

[18] H. Nishiyama, K. Itoh in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, pp. 111–143.

[19] a) B. H. Lipshutz, B. A. Frieman, *Angew. Chem.* **2005**, *117*, 6503–6506; *Angew. Chem. Int. Ed.* **2005**, *44*, 6345–6348; b) C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* **2008**, *108*, 2916–2927.

[20] R. Göttlich, K. Yamakoshi, H. Sasai, M. Shibasaki, *Synlett* **1997**, 971–973.

[21] P. A. Aristoff, *J. Org. Chem.* **1985**, *50*, 1765–1766.

[22] Review: a) S. Ma, Z. Gu, *Angew. Chem.* **2005**, *117*, 7680–7685; *Angew. Chem. Int. Ed.* **2005**, *44*, 7512–7517; Recent examples: b) T. Miura, T. Sasaki, H. Nakazawa, M. Murakami, *J. Am. Chem. Soc.* **2005**, *127*, 1390–1391; c) T. Matsuda, M. Shigeno, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12086–12087; d) R. Shintani, K. Takatsu, T. Katoh, T. Nishimura, T. Hayashi, *Angew. Chem.* **2008**, *120*, 1469–1471; *Angew. Chem. Int. Ed.* **2008**, *47*, 1447–1449.

[23] T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438–6441; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320–6323.

Received: November 25, 2009
Published online: February 9, 2010

