VIP Asymmetric Catalysis

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Enantioselective C–C Bond Activation of Allenyl Cyclobutanes: Access to Cyclohexenones with Quaternary Stereogenic Centers**

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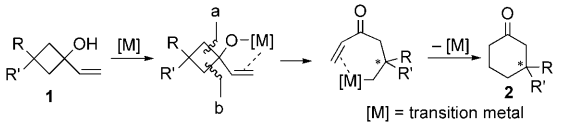
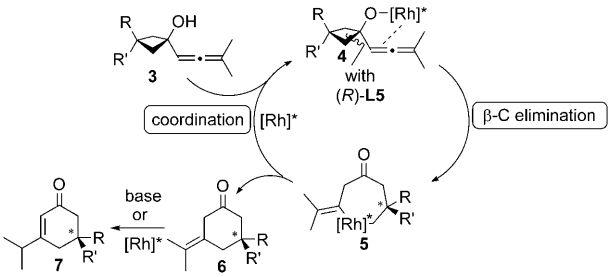
Dedicated to Professor Duilio Arigoni on the occasion of his 80th birthday

The transition-metal-catalyzed activation of carbon–carbon σ bonds has the potential to change organic synthesis fundamentally.[1,2] However, the practical implementation of this concept is still a major challenge; in particular, there are few examples of enantioselective C–C activation.[3] Small strained rings occupy a privileged position in C–C activation reactions because of the energy released by strain reduction in ring-opening reactions.[4] This inherent strain and their convenient accessibility make symmetric cyclobutane derivatives a promising substrate class.[5] The desymmetrization of such symmetric molecules is an excellent approach for the construction of sterically demanding quaternary stereogenic centers, as the chemical transformation does not take place directly at a hindered, asymmetrically substituted carbon atom.[6] The studies of Murakami and co-workers,[3d,e] who used a highly enantioselective rhodium-catalyzed transformation to construct benzocyclopentanones and dihydrocoumarines from cyclobutanones, and Uemura and co-workers,[3a,b] who reported an asymmetric palladium-catalyzed ring-opening arylation of aryl *tert*-cyclobutanols, demonstrate the largely underexplored potential of this concept. For example, the selective insertion of a suitable metal catalyst into one of the two enantiotopic C–C bonds (a or b) of a suitably substituted symmetrical *tert*-cyclobutanol **1** could result in an organometallic species, which might subsequently undergo a cyclization reaction to give the corresponding ring-expanded cyclohexanone **2** [Eq. (1)].[7]



(1)

We report herein a rhodium(I)-catalyzed desymmetrization of allenyl *tert*-cyclobutanols. The transformation leads to highly substituted cyclohexenones with excellent enantioselectivity. We hypothesized that the potential chelating ability of an allenyl *tert*-cyclobutyl alcohol **3**[8] would favor the formation of a well-defined adduct **4** with a chiral rhodium complex, which would ensure efficient transfer of the chiral information of the ligand to the substrate in the enantiodiscriminating step. As depicted in Scheme 1, simultaneous



Scheme 1. Mechanistic proposal for the formation of **6** and **7**.

coordination of the Rh^I center to both the hydroxy group and the proximal double bond of the allene should be favored. An enantioselective insertion into the C–C σ bond of the cyclobutane leads to the seven-membered metallacycle **5**, and reductive elimination results in the formation of the methylene cyclohexanone **6** as the primary product. A metal- or base-catalyzed isomerization of the exocyclic double bond of **6** can lead in a subsequent step to enone **7**.

In a first experiment, the model substrate *trans*-1-(3,3-dimethylallenyl)-3-methyl-3-phenylcyclobutanol (**3a**) was heated to 80 °C in toluene in the presence of [{Rh(OH)(cod)}$_2$] (2.5 mol %) and (*R*)-binap (**L1**; 6 mol %; binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl). Under these conditions, cyclohexanone **6** with an exocyclic double bond was formed in 79 % yield with 76 % *ee* (Table 1, entry 1). However, during the course of the reaction, **6** isomerized slowly to enone **7a**, and a variable amount also decomposed to unidentifiable products. The presence of auxiliary bases, such as cesium carbonate or potassium phosphate, accelerated the isomerization of the double bond and completely suppressed decomposition pathways, so that the conjugated product **7a** was isolated in virtually quantitative yield without loss of selectivity (Table 1, entries 5 and 7). Dioxane was also tested as a solvent, but the use of dry, nonpolar aromatic solvents (toluene or xylene) resulted in shorter reaction times

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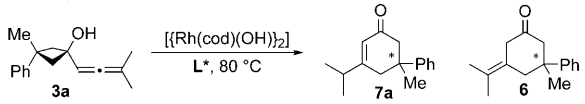
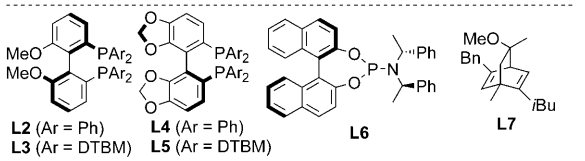
Table 1: Optimization of the reaction conditions.[a]

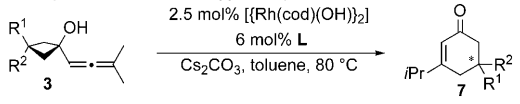


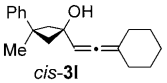
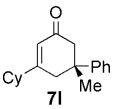
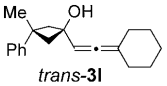
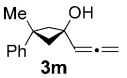
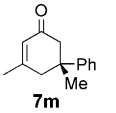
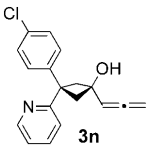
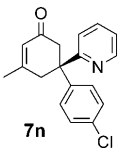


Entry	L*	Base	Solvent	Yield [%][b]	*ee* [%][c]
1[d]	**L1**	–	toluene	79 (**6**)	76 (*S*)
2[d]	**L1**	–	dioxane	< 5	–
3	**L1**	Cs_2CO_3	dioxane, 5 % H_2O	28	73 (*S*)
4	**L1**	Cs_2CO_3	dioxane	90	73 (*S*)
5	**L1**	Cs_2CO_3	toluene	99	80 (*S*)
6	**L1**	NEt_3	toluene	71 (**6**)	79 (*S*)
7	**L1**	K_3PO_4	toluene	79	79 (*S*)
8[d,e]	**L6**	Cs_2CO_3	toluene	83	77 (*S*)
9[d,f]	**L7**	Cs_2CO_3	toluene	58	43 (*R*)
10	**L2**	Cs_2CO_3	toluene	99	83 (*S*)
11	*ent*-**L4**	Cs_2CO_3	toluene	92	85 (*S*)
12	**L3**	Cs_2CO_3	toluene	95	96 (*S*)
13	**L5**	Cs_2CO_3	toluene	92	95 (*R*)
14[d,g]	**L5**	Cs_2CO_3	toluene	99	90 (*R*)

[a] Reaction conditions: **3a** (0.1 mmol), base (1.5 equiv), [{Rh(OH)(cod)}$_2$] (2.5 mol%), **L*** (6.0 mol%), 0.25 M, 80°C, 3–24 h. Bn = benzyl, cod = 1,5-cyclooctadiene, DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl. [b] Yield of the isolated product **7a**. [c] Enantioselectivities were determined by HPLC on a chiral stationary phase. [d] The reaction was carried out at 100°C. [e] **L6**: 12 mol%. [f] The reaction was carried out with [{Rh(OAc)(C$_2$H$_4$)$_2$}$_2$] (2.5 mol%). [g] [{Rh(OH)(cod)}$_2$]: 0.05 mol%, **L5**: 0.12 mol%.

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



Entry	L*	3	R^1/R^2	7	Yield [%][b]	*ee* [%][c]
1	**L3**	*cis*-**3a**	Ph/Me	**7a**	97	96 (*R*)
2	**L3**	*cis*-**3b**	Ph/Et	**7b**	99	97 (*R*)
3	**L5**	*trans*-**3b**	Et/Ph	**7b**	99	96 (*R*)
4	**L3**	**3c**	4-ClC_6H_4/Me	**7c**	88	95 (*R*)
5	**L5**	**3d**	Me/4-MeC_6H_4	**7d**	99	95 (*R*)
6	**L5**	**3e**	Me/2-naphthyl	**7e**	97	94 (*R*)
7	**L3**	*cis*-**3f**	*i*Pr/Me	**7f**	80	94 (*R*)
8	**L5**	*trans*-**3f**	Me/*i*Pr	**7f**	91	97 (*R*)
9	**L3**	*cis*-**3g**	*t*Bu/Me	**7g**	81	96 (*R*)
10	**L5**	*trans*-**3g**	Me/*t*Bu	**7g**	80	99 (*R*)
11[d]	**L3**	*trans*-**3h**	Ph/CH_2OBn	**7h**	89	97 (*S*)
12	**L5**	*cis*-**3h**	CH_2OBn/Ph	**7h**	99	94 (*S*)
13[d]	**L3**	*cis*-**3i**	Ph/vinyl	**7i**	85	90 (*R*)
14[d]	**L5**	*trans*-**3i**	vinyl/Ph	**7i**	74	90 (*R*)
15[d]	**L5**	**3j**	Ph/2-pyridyl	**7j**	65	91 (*R*)
16	**L5**	**3k**	Ph/H	**7k**	94	85 (*S*)
17[d]	**L3**	 *cis*-**3l**		 **7l**	91	93 (*R*)
18	**L5**	 *trans*-**3l**			93	92 (*R*)
19[d]	**L5**	 **3m**		 **7m**	93	93 (*R*)
20[d]	**L3**	 **3n**		 **7n**	57	89 (*S*)

[a] Reaction conditions: **3** (0.1 mmol), Cs_2CO_3 (1.5 equiv), [{Rh(cod)(OH)}$_2$] (2.5 mol%), (*R*)-**L3** or (*S*)-**L5** (6.0 mol%), 0.4 mL toluene, 80°C, 3 h. [b] Yield of the isolated product **7**. [c] Enantioselectivities were determined by HPLC on a chiral stationary phase. [d] The reaction was carried out at 100°C for 16 h. Cy = cyclohexyl.

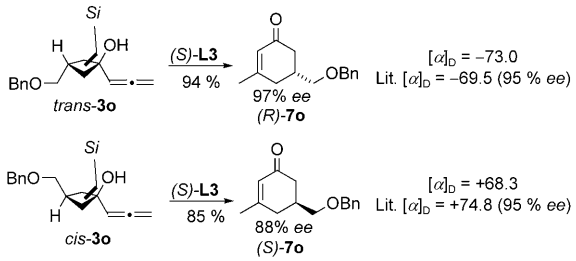
and higher enantioselectivities (Table 1, entries 2–5). We screened a range of chiral ligands and observed complete conversion and moderate to good yields with the phosphoramidite ligand (*R*,*R*,*R*)-**L6**[9] and (−)-dolefine[10] (**L7**; Table 1, entries 8 and 9). However, **7a** was formed with lower enantioselectivity (77% *ee* with **L6** and 43% *ee* with **L7**) than that observed with (*R*)-binap in the best case (80% *ee*; Table 1, entry 5). The use of biaryl phosphines with a narrower dihedral angle[11] than that in binap led to an increase in enantioselectivity. Thus, enone **7a** was formed with 83% *ee* with (*R*)-MeObiphep (**L2**) and 85% *ee* with (*R*)-segphos (**L4**; Table 1, entries 10 and 11). A further significant improvement in selectivity was observed with the sterically demanding homologues (*R*)-DTBM-MeObiphep (**L3**) and (*S*)-DTBM-segphos (**L5**; DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl), which afforded **7a** with 96 (**L3**) and 95% *ee* (**L5**; Table 1, entries 12 and 13). Remarkably, the required catalyst amount – starting with 2.5 mol% [{Rh(OH)(cod)}$_2$] – could be reduced to 0.1 mol% rhodium without any loss in yield and only a minor decrease in enantioselectivity (90 instead of 95% *ee*, Table 1, entry 14).

The isomeric cyclobutanol *cis*-**3a** was transformed into the opposite enantiomer (*R*)-**7a** with excellent enantioselectivity under the standard conditions with (*R*)-**L3** as the ligand (Table 2, entry 1; compare Table 1, entry 12). This result shows that the enantiotopic C–C bond activated is determined by the ligand employed and should therefore be largely independent of the substitution pattern at the 3-position of the cyclobutanol substrate.

We next explored the scope of the rhodium-catalyzed rearrangement under the optimized reaction conditions (Table 2). A variety of aromatic substituents are tolerated (Table 2, entries 1–6), as well as sterically demanding alkyl substituents (Table 2, entries 7–10). Substrates with functionalized substituents (Table 2, entries 11 and 12) also react smoothly with very good selectivities. However, coordinating groups, such as a 2-pyridyl substituent (Table 2, entry 15) or a vinyl group (Table 2, entries 13 and 14), slow the reaction down significantly, so that a higher temperature (100°C) and a longer reaction time (16 h) are required to ensure complete conversion. Remarkably, the cyclobutanol derivative **3k**,

which has just one substituent in the 3-position ($R^2 = H$; Table 2, entry 16), did not undergo potential β-hydride elimination and was converted smoothly into the corresponding cyclohexenone. However, the resulting enone **7k** was formed with slightly lower enantioselectivity (85% *ee*). Allenes *cis*-**3l** and *trans*-**3l**, which have a cyclic substituent in place of the geminal methyl groups in substrates **3a–k**, also underwent ring expansion to give the desired cyclohexenone under these conditions (Table 2, entries 17 and 18). The terminal allenes **3m** and **3n** were converted into the corresponding 3-methylcyclohexenones **7m** and **7n** in comparable yields and selectivities (Table 2, entries 19 and 20).

The absolute configuration of the products was determined by comparison of the optical rotation of the known derivative **7o**.[12] The ring expansion of cyclobutanol *trans*-**3o** gave cyclohexenone (*R*)-**7o** with 97% *ee* with the ligand (*S*)-DTBM-MeObiphep, whereas the treatment of *cis*-**3o** under identical conditions resulted in the formation of (*S*)-**7o** (Scheme 2).



Scheme 2. Reaction conditions: **3o** (0.1 mmol), Cs_2CO_3 (1.5 equiv), [{Rh(cod)(OH)}$_2$] (2.5 mol%), (*S*)-**L3** (6.0 mol%), 0.4 mL toluene, 100°C, 3 h.

In summary, we have demonstrated that allenyl cyclobutyl alcohols can be activated through an enantioselective rhodium(I)-catalyzed insertion into the C–C σ bond. A ring expansion results to provide highly substituted cyclohexenone derivatives with quaternary stereogenic centers. Such compounds are difficult to prepare by common synthetic methods. The reaction tolerates a broad range of substituents and can be conducted with a catalyst loading as low as 0.1 mol% in rhodium. Studies to further increase the scope and application of the transformation are in progress.

Experimental Section

The cyclobutanol *trans*-**3a** (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 (*R*)-DTBM-MeObiphep (**L3**; 6.90 mg, 6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stir bar. The vial was then sealed with a rubber septum and flushed with nitrogen. Dry toluene (0.4 mL) was added, and the reaction mixture was degassed through three freeze–pump–thaw cycles, stirred at 23°C for 10 min, and then heated for 3 h in an oil bath preheated to 80°C. When TLC analysis indicated complete conversion, the reaction mixture was cooled to 23°C and purified directly on silica gel (CH_2Cl_2, $R_f = 0.29$). The cyclohexenone (*S*)-**7a** (21.7 mg, 95%, 96% *ee*) was obtained as a colorless oil.

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