C–C Activation

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Highly Enantioselective Rhodium(I)-Catalyzed Activation of Enantiotopic Cyclobutanone C–C Bonds **

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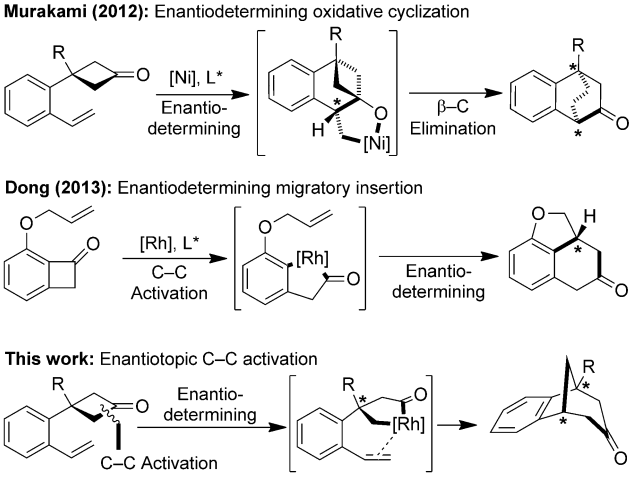
Abstract: *The selective functionalization of carbon–carbon σ bonds is a synthetic strategy that offers uncommon retrosynthetic disconnections. Despite progress in C–C activation and its great importance, the development of asymmetric reactions lags behind. Rhodium(I)-catalyzed selective oxidative additions into enantiotopic C–C bonds in cyclobutanones are reported. Even operating at a reaction temperature of 130 °C, the process is characterized by outstanding enantioselectivity with the e.r. generally greater than 99.5:0.5. The intermediate rhodacycle is shown to react with a wide variety of tethered olefins to deliver complex bicyclic ketones in high yields.*

The selective functionalization of carbon–carbon (C–C) σ bonds by transition-metal catalysts is a prime challenge for organometallic chemistry and represents a complementary synthetic strategy that enables uncommon retrosynthetic disconnections.[1] Important progress has been made over the past decade in the field of C–C activation. However, despite their recognized importance, the development of asymmetric reactions lags behind.[2,3] For instance, most enantioselective variants have been reported for the β-carbon elimination mechanism that allows C–C bond cleavages adjacent to tertiary alcohols.[2c,3,4] For reactions involving C–C cleavage through oxidative addition at transition metals,[5] strained ketones have proven highly versatile.[3d–e,6–8] Two asymmetric reactions of this type, in which the C–C cleavage step is not enantiodetermining, have recently been reported. Murakami and co-workers showed asymmetric nickel-catalyzed reactions of cyclobutanones (Scheme 1).[9] In this case, the enantiodetermining step of the sequence consists of an asymmetric initial oxidative cyclization, which is then followed by a diastereoselective β-carbon elimination. Dong and co-workers reported an asymmetric rhodium-catalyzed transformation involving the C–C activation of benzocyclobutanones.[10] After the achiral initial C–C activation, the enantiodetermining step occurred through facially selective addition across the appended alkene moiety. To our knowledge, processes in which the insertion into the C–C bond is the enantiodetermining step of the reaction are elusive. Oxidative additions with chiral transition-metal complexes able to selectively target one of two enantiotopic C–C bonds are highly intriguing from a mechanistic point of view. Moreover, the maintenance of high levels of chiral induction under the forcing reaction temperatures of such activations is extremely challenging.



Scheme 1. Asymmetric reactions involving a C–C bond cleavage step.

Herein, we report an enantiotopic C–C bond activation that proceeds with exceptionally high enantioselectivity (Scheme 1). We selected cyclobutanone substrates **1**, for which Murakami, Itahashi, and Ito demonstrated the potential for C–C bond activation by using the achiral and cationic [Rh(nbd)dppp]PF_6 complex.[11] Limited modifications to the aryl part and monosubstituted cyclobutanones (R = H) led to symmetric products with hydrogen atoms at both bridgeheads. In our study, the key enantiotopic C–C activation of **1** (R ≠ H) leads to the formation of a quaternary stereogenic center (Scheme 2). The tethered olefin of the substrate **1** should not only provide an intramolecular acceptor but should coordinate to Rh^I to give complex **2**. Such coordination should favor a highly ordered transition state, thus enabling good enantiodiscrimination for the C–C cleavage step to give **3**. Subsequent migratory insertion forms acyl rhodium species **4**, which in turn undergoes reductive elimination to give bicyclic ketone **5**. Depending on the degree of substitution at the double bond, further stereogenic centers can then be created.

The initial evaluation of the reaction conditions was conducted with model cyclobutanone **1a**. Heating **1a** in dioxane at 130 °C in the presence of Binap (**L1**) and [{Rh-

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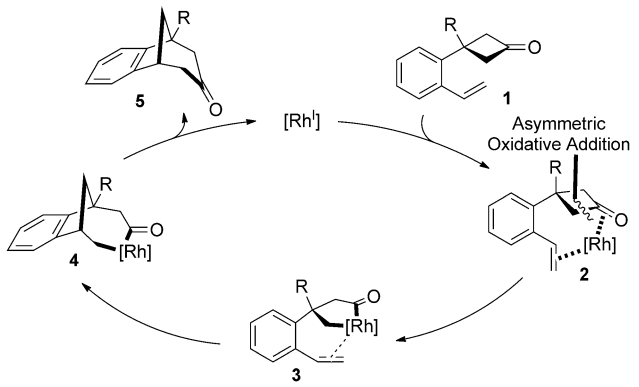
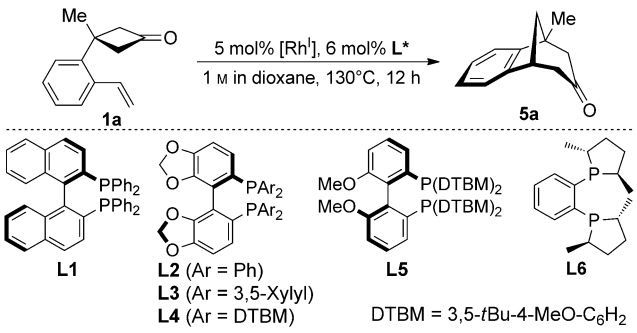


Scheme 2. Mechanistic model for the rhodium(I)-catalyzed asymmetric C–C bond activation.

(COD)Cl}$_2$] as the Rh^I source gave the desired product bicyclic ketone **5a** with an excellent enantiomeric ratio of 98.5:1.5 (Table 1, Entry 1; COD = 1,5-cyclooctadiene). However, moderate conversion restricted the yield to 50%. Further evaluation of ligands of the Segphos family (**L2–4**) further increased the enantioselectivity (Table 1, Entries 2–4). Notably, the bulky congener DTBM-Segphos (**L4**) resulted in the most active catalyst (Table 1, Entry 4). Under these conditions, product **5a** was obtained in 94% yield with an exceptionally high enantiomeric ratio of 99.7:0.3 (Table 1, Entry 4).[12] The related DTBM-MeOBiphep **L5** is less reactive and the reaction stalled at slightly more than half conversion (Table 1, Entry 5). Me-Duphos (**L6**) was not well suited for this transformation (Table 1, Entry 6). Alternative Rh^I precursors such [{Rh(COD)(OH)}$_2$] or cationic [Rh(COD)$_2$]BF$_4$ were both detrimental to the yield and enantioselectivity (Table 1, Entries 7 and 8), thus indicating that the chloride counterion is important. Replacing the dioxane by toluene also decreased the reactivity (Table 1, Entry 9). On the other hand, lowering the temperature to 110°C in dioxane provided full conversion (Table 1, Entry 10). Finally, the reaction works well with 2.5 mol% catalyst loading and 24 h reaction time (Table 1, Entry 11). The fact that the reaction had reached 63% conversion after 12 h indicates that the catalyst maintains activity over prolonged reaction times.

With the reaction conditions established, we next explored the generality of the C–C activation process. First, we evaluated different substituents of the cyclobutanone moiety. Aliphatic and aromatic groups, as well as esters, nitriles, and protected ethers are well tolerated and provide products with a variety of functionalized bridgeheads (Table 2, entries 1–6). The yield and selectivity are consistently excellent. Electronic modification of the aryl tether has no influence on the reaction outcome (Table 2, Entries 6–8).[13] Notably, the reaction is not limited to terminal olefins. For instance, 1,1-disubstituted alkenes deliver bicyclic ketones **5j** and **5k** with two different quaternary stereogenic centers at the two

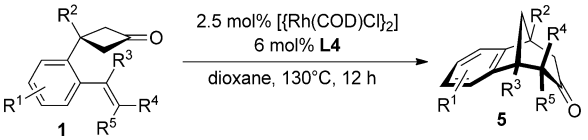
Table 1: Optimization of the enantioselective C–C activation of **1a**.[a]



Entry	[Rh^I]	L*	Changes	[%] Yield[b]	e.r.[c]
1	[{Rh(COD)Cl}$_2$]	**L1**	–	50	98.5:1.5
2	[{Rh(COD)Cl}$_2$]	**L2**	–	44	99:1
3	[{Rh(COD)Cl}$_2$]	**L3**	–	72	99.5:0.5
4	[{Rh(COD)Cl}$_2$]	**L4**	–	94	99.7:0.3
5	[{Rh(COD)Cl}$_2$]	**L5**	–	53	99.5:0.5
6	[{Rh(COD)Cl}$_2$]	**L6**	–	15	93.5:6.5
7	[{Rh(COD)(OH)}$_2$]	**L4**	–	64	91:9
8	[Rh(COD)$_2$]BF$_4$	**L4**	–	70	85:15
9	[{Rh(COD)Cl}$_2$]	**L4**	in toluene	78	99:1
10	[{Rh(COD)Cl}$_2$]	**L4**	at 110°C	97	99.7:0.3
11	[{Rh(COD)Cl}$_2$]	**L4**	2.5 mol%, 24 h	85	99.6:0.4

[a] Reaction conditions: **1a** (0.05 mmol), [Rh^I] (2.50 μmol), **L*** (3.00 μmol), 1.0 M in dioxane at 130°C for 12 h; [b] Yield of isolated product; [c] Determined by HPLC with a chiral stationary phase.

Table 2: Scope of the enantioselective C–C activation of cyclobutanones **1**.[a]



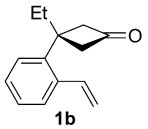
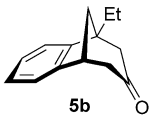
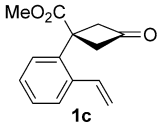
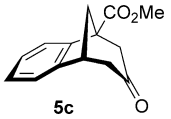
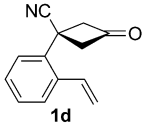
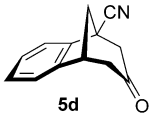
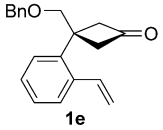
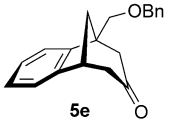
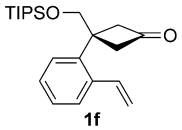
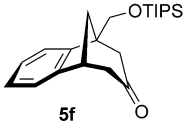
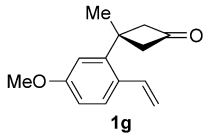
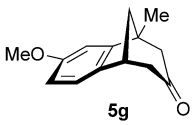
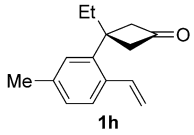
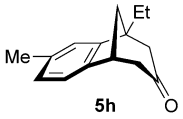
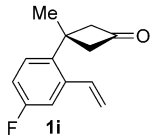
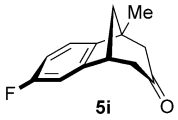
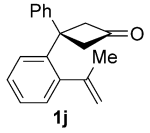
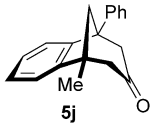
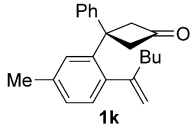
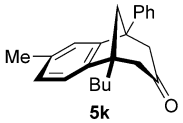
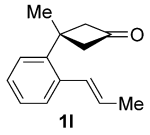
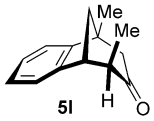
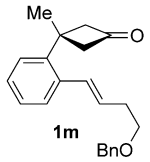
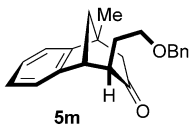
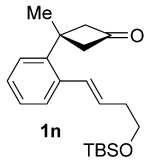
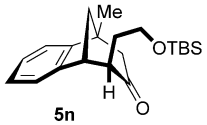
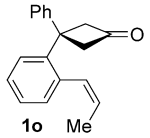
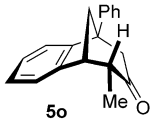
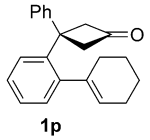
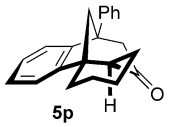
Entry	Cyclobutanone **1**	Ketone **5**	[%] Yield[b]	e.r.[c]
1[d]	 **1b**	 **5b**	91	99.6:0.4
2[d]	 **1c**	 **5c**	78	99.8:0.2
3	 **1d**	 **5d**	95	99.6:0.4
4[d]	 **1e**	 **5e**	96	99.6:0.4
5	 **1f**	 **5f**	89	99.6:0.4

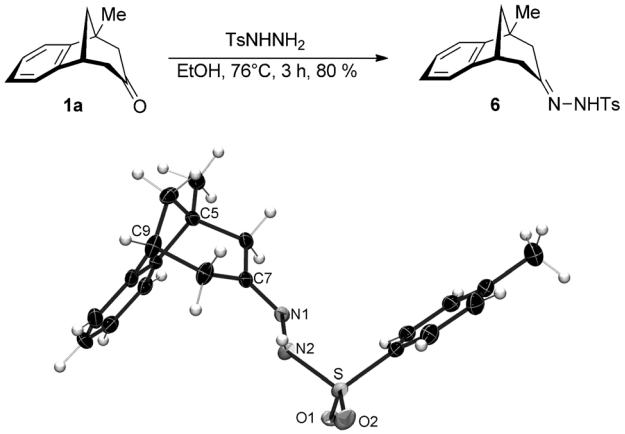
Table 2: (Continued)

Entry	Cyclobutanone **1**	Ketone **5**	[%] Yield[b]	e.r.[c]
6	 **1g**	 **5g**	92	99.7:0.3
7[d]	 **1h**	 **5h**	81	99.6:0.4
8[d]	 **1i**	 **5i**	88	>99.8:0.2
9[d]	 **1j**	 **5j**	95	99.6:0.4
10	 **1k**	 **5k**	89	99.4:0.6
11[d]	 **1l**	 **5l**	90	97.7:2.3 d.r. > 20:1
12	 **1m**	 **5m**	85	99.8:0.2 d.r. > 20:1
13	 **1n**	 **5n**	82	99.7:0.3 d.r. > 20:1
14	 **1o**	 **5o**	0	–
15	 **1p**	 **5p**	73	98.3:1.7

[a] **1** (0.10 mmol), [{Rh(COD)Cl}$_2$] (2.50 μmol), **L4** (6.00 μmol), 1.0 M in dioxane at 130 °C for 12 h; [b] Yield of isolated product; [c] Determined by HPLC with a chiral stationary phase. [d] [{Rh(COD)Cl}$_2$] (5.00 μmol), **L4** (12.0 μmol), 0.2 M in dioxane at 130 °C for 24 h.

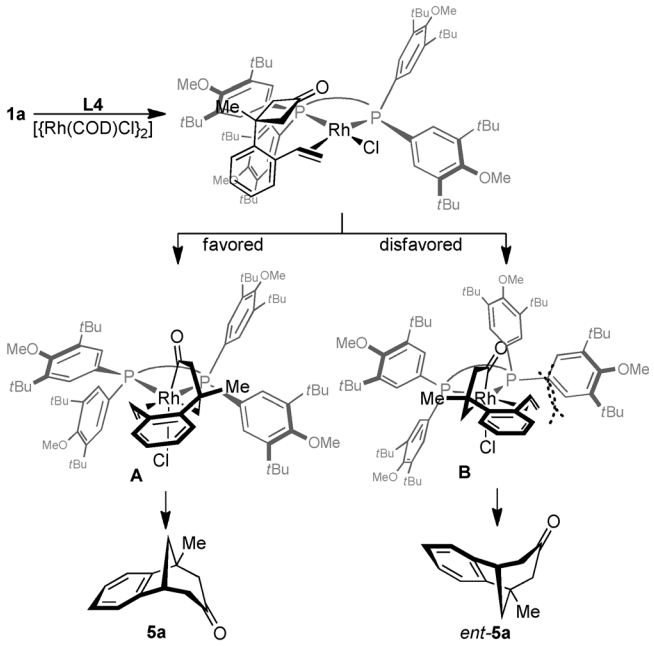
bridgehead positions (Table 2, Entries 9 and 10). In addition, 1,2-disubstituted alkenes react well and fully maintain their stereochemical information. The *trans* starting materials deliver ketones **5l–n** (Table 2, Entries 11–13). Importantly, no epimerization of the stereogenic center at the α position of the carbonyl group was detected under the reaction conditions and the products were obtained with d.r. > 20:1 and excellent enantioselectivity. Notably, the obtained product is the thermodynamically less stable diastereomer and can be isomerized by base to the more stable one.[14] Attempts to obtain this isomer directly through C–C activation failed. The corresponding isomeric substrate **1o**, which has a *cis* double bond, does not give the rearranged product and only degrades slowly under the reaction conditions (Table 2, x 14). By contrast, a tri-substituted olefin is well tolerated and reacts smoothly under the described conditions to provide a rapid and convenient entry to highly complex ketone **5p** (Table 2, Entry 15).

The absolute configuration of the bicyclic ketone **1a** was unambiguously established by X-ray crystallographic analysis of the *p*-tosyl hydrazone derivative **6** (Scheme 3).[15]



Scheme 3. Synthesis of *p*-tosyl hydrazone derivative **6** and its ORTEP representation.

The absolute configuration can be rationalized by the speculative stereochemical pathway illustrated in Scheme 4. Initially, substrate **1** coordinates to the catalyst to give the square-planar Rh^{I} complex. Subsequent oxidative addition would provide the octahedral Rh^{III} intermediates **A** or **B**. Intermediate **A** is preferred over **B** because it avoids the very unfavorable interaction between the olefin portion of the substrate and a DTBM residue of ligand **L4**. This arrangement also accounts for the broad tolerance of substitution of the arene and cyclobutyl rings because both are pointing away from the ligand bulk in intermediates **A** and **B**.



Scheme 4. Speculative stereochemical pathway for the activation.

In summary, we report an asymmetric rhodium(I)-catalyzed C–C activation of cyclobutanones that gives efficient access to the valuable bicycloheptanone scaffold with exceptionally high enantioselectivity. This demonstrates the feasibility of selective oxidative additions of enantiotopic C–C bonds at high reaction temperatures. The method shown allows rapid access to complex cyclic structure and serves as a blueprint for the design of further asymmetric C–C bond activations.

Experimental Section

Cyclobutanone **1a** (18.6 mg, 0.100 mmol), [{Rh(COD)Cl}$_2$] (1.14 mg, 2.50 μmol), and (*R*)-DTBM-Segphos (6.00 μmol) were weighed into an oven-dried vial equipped with a magnetic stir bar. The vial was then capped with a septum and purged with nitrogen. Dry dioxane (0.1 mL) was added and the mixture was degassed with three freeze–pump–thaw cycles. The mixture was stirred for 20 min at 23 °C and subsequently heated at 130 °C. After 12 h, the reaction mixture was cooled to 23 °C and purified by silica gel column chromatography by eluting with pentane/ethyl acetate (20:1). Ketone **5a** was isolated as a colorless oil in 94 % yield (17.5 mg) and e.r. = 99.7:0.3.

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[13] Although not studied yet in detail, the reactivity is enhanced by conformational restriction of the benzene tether. Addressing this potential limitation will be the subject of future investigations.

[14] Exposure of **5l** to *t*BuOK at ambient temperature led to epimerization of the stereogenic center α to the carbonyl group to give the thermodynamically more stable diastereomer **5l′** in a 5:1 ratio.

[15] Crystallographic data for **6**: CCDC 977682 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.

