Enantioselective Construction of Indanones from Cyclobutanols Using a Rhodium-Catalyzed C–C/C–H/C–C Bond Activation Process

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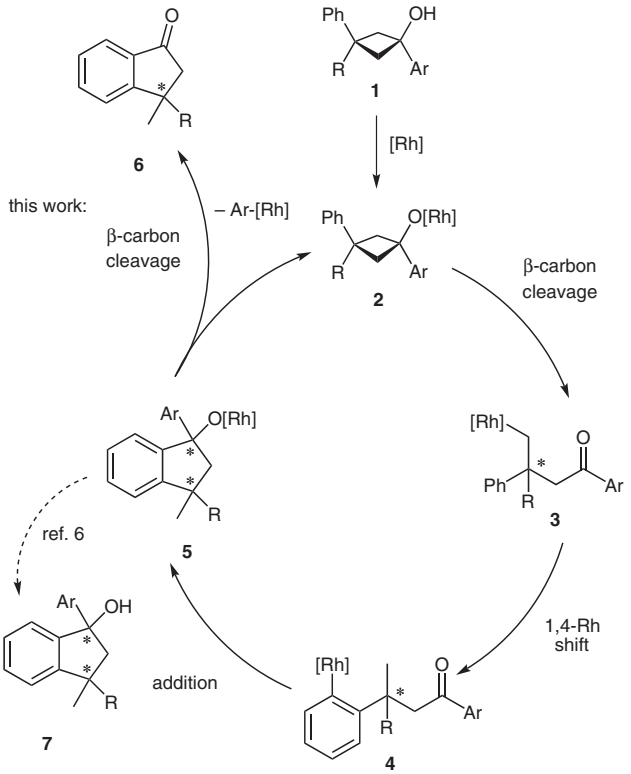
Abstract: Enantioselective rhodium(I)-catalyzed reactions of *tert*-cyclobutanols lead via consecutive C–C/C–H/C–C bond activations to indanones with quaternary stereogenic centers.

Key words: rhodium, ring opening, quaternary stereogenic center, C–C activation, C–H activation

The selective and catalytic functionalization of C–C single bonds mediated by transition-metal complexes is a fundamental challenge in organometallic chemistry. The lack of prefunctionalized reactants makes this area compelling and has broad implications for organic synthesis.[1] However, unfavorable kinetics and thermodynamics for the metal insertion and competing C–H activations make such processes challenging, resulting in reactivity and selectivity issues. Especially efficient enantioselective variants are scarce and mainly focus on strained substrates.[2] The enantioselective activation of C–C σ bonds of symmetrically substituted cyclobutanols via β-carbon cleavage recently came into our focus as attractive tool to access quaternary stereogenic centers.[3] In addition to the formed quaternary stereocenter, this process generates an alkyl-rhodium(I) intermediate that enjoys exceptional high reactivity and participates in a host of synthetically useful and mechanistically intriguing downstream reactions.[4,5] We[6] and Murakami and coworkers[7] recently reported a process involving a 1,4-rhodium shift of such intermediates, providing aryl-rhodium species **4** that adds across the formed ketone to give rise to highly functionalized indanols **7** (Scheme 1). To expand the utility of this reaction, we envisioned a further C–C activation of rhodium alkoxide **5** prior to protonation. A β-aryl cleavage of **5** would lead to indanones **6** bearing quaternary stereogenic centers. This process would represent an appealing example of a C–C/C–H/C–C activation sequence. Such metal-promoted β-aryl cleavages from tertiary alcohols have been reported,[8] and Hartwig and coworkers showed that electron-rich aromatics are cleaved preferentially from differentially substituted triarylmethanols.[9]

Towards this goal, we examined the reactivity of different aromatic groups on prototype cyclobutanols **1** for the β-aryl cleavage (Table 1). Substrates **1** with a phenyl substituent or a more electron-rich *p*-methoxyphenyl group were completely inert towards this second β-carbon elimination and gave exclusively the expected indanols **7** (entries 1 and 2). A furyl substituent allowed for the proposed pathway leading to **6**, although the major product was still indanol **7** (entry 3). When the ligand was switched to Josiphos (**L4**, Figure 1), indanone **6** became the dominant product (entry 4). We observed that the selectivity of this process could be additionally altered by the addition of inorganic bases. For example, addition of cesium carbonate enhanced the reactivity of the aryl β-carbon cleavage, and with these conditions indanone **6** was formed predominantly with Binap (**L1**, entry 5). Further screening of electron-rich aromatic substituents such as a 2,4,6-trimethoxyphenyl, 2-*N*-methylindolyl, and 2-thienyl group confirmed the trend of a higher cleavage propensity with increasing donating character of the aromatic substituent (entries 6–8). Especially the 2-thienyl substituent resulted in a clean and high-yielding reaction and was therefore the substituent of choice.



Scheme 1 Proposed mechanism for the formation of indanone **6** by a β-carbon cleavage, 1,4-Rh shift, 1,2-addition, and β-aryl cleavage

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With (*R*)-Binap (**L1**), we obtained indanone **6a** with an ee value of 79% (entry 8). While the Josiphos ligand (**L4**) exhibited the highest reactivity for the β-aryl cleavage, its selectivity for the crucial enantiodetermining first β-carbon cleavage was very poor (<5% ee, entry 9). (*R*)-Segphos (**L2**) gave an improved enantioselectivity and yielded **6a** with 88% ee (entry 10). While (*R*)-Difluorphos (**L3**) induced the same enantioselectivity, its higher reactivity allowed isolating indanone **6a** in a virtually quantitative yield (entry 11). Therefore **L3** was chosen as the standard ligand for this process.

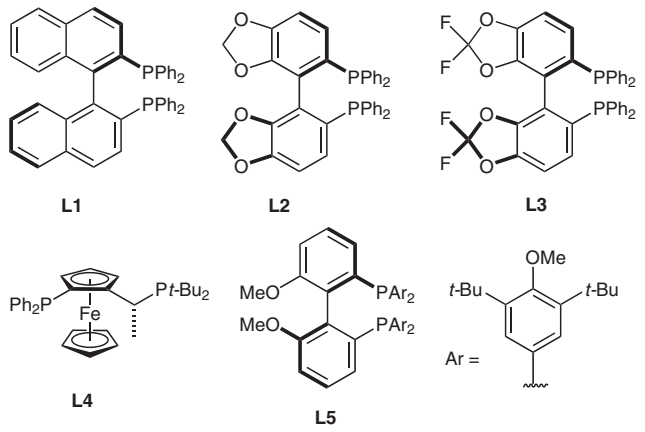
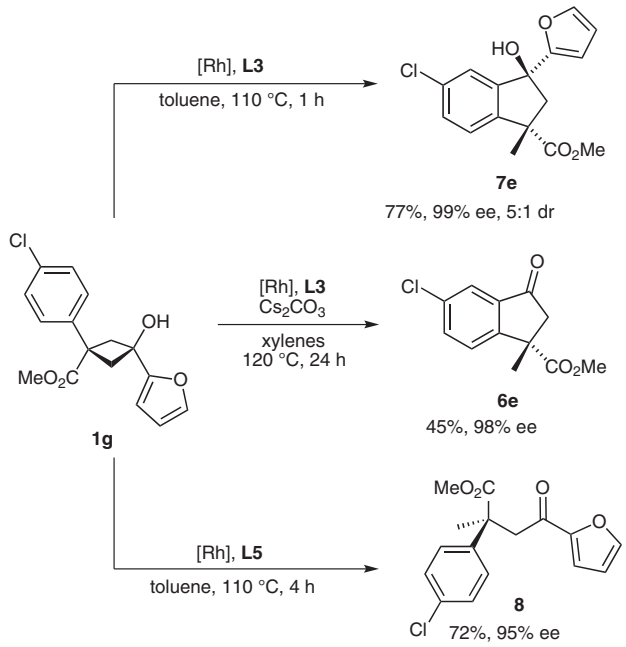


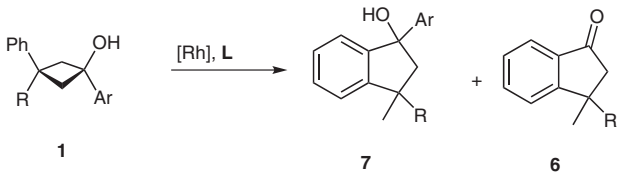
Figure 1 Ligands employed in this study

With these optimized conditions, we explored the scope of the process.[10] The reactivity as well as the selectivity is maintained throughout a range of different substituted cyclobutanols **1** (Table 2).[11] Silyl groups, ester functionalities as well as aryl chlorides are well tolerated (entries 3–8). Coordinating heterocycles like pyridine do not inhibit the reaction. Noteworthy, the electron-poor pyridine core participates preferentially over a phenyl group in the 1,4-rhodium shift, thus leading to the formation of azaindanone **6f** in excellent enantioselectivity (entry 9).

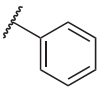
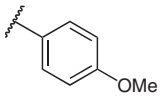
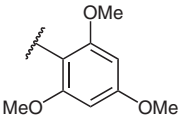
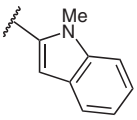


Scheme 2 Ligands and conditions adjustments steer the chemoselectivity of the reaction {[Rh] = 2.5 mol% [Rh(OH)(cod)]$_2$, 6 mol% **L***}

Table 1 Optimization of the Second β-Carbon Cleavage Step[a]



1 7 6

Entry	L	R	Ar	6/7[b]	Yield of 6 (%)[c]
1	**L1**	Me		<1:20	n.d.
2	**L1**	Me		<1:20	n.d.
3	**L1**	Me		1:9	n.d.
4	**L4**	Me		6:1	42
5[e]	**L1**	Me		9:1	80
6[e]	**L1**	Et		1:2	31
7[e]	**L1**	Et		3:1	55
8[e]	**L1**	Et		>20:1	99 (79% ee)[d]
9[e]	**L4**	Et		>20:1	48 (<5% ee)[d]
10[e]	**L2**	Et		>20:1	74 (88% ee)[d]
11[e]	**L3**	Et		>20:1	99 (88% ee)[d]

[a] Reaction conditions: 0.1 mmol **1**, 2.5 mol% [Rh(OH)(cod)]$_2$, 6.0 mol% **L**, 0.25 M in xylenes, 120 °C, 12 h.
[b] Ratios were determined by ^{1}H NMR.
[c] Isolated yields.
[d] The ee values were determined by HPLC with a chiral stationary phase.
[e] With 1.5 equiv Cs_2CO_3.

The importance of the ligand and the employed conditions for the reaction outcome is demonstrated for the furyl-substituted cyclobutanol **1g**, allowing to selectively address the formation of three different products (Scheme 2). Difluorphos (**L3**), short reaction times, and base-free conditions promote the selective formation of indanol **7e**. The reaction leading to indanone **6e** can be triggered by the addition of cesium carbonate in combination with prolonged reaction times. Sterically demanding ligands like DTBM-MeOBiphep (**L5**) promote the cyclobutanol cleavage in excellent selectivity, but stop at the stage of intermediate **3** or **4**. The organorhodium species undergoes instead protodemetalation giving ketone **8** with an acyclic methyl quaternary stereocenter.[4e]

In summary, we reported a C–C/C–H/C–C activation sequence of *tert*-cyclobutanols providing access to indanones with quaternary stereogenic centers in excellent enantioselectivities. This triple activation process extends the range of accessible and synthetically useful building blocks from catalytic enantioselective C–C bond activations.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 2 Scope of the C–C/C–H/C–C Activation Reaction[a]

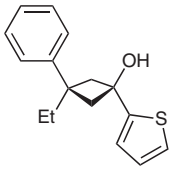
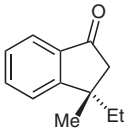
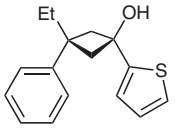
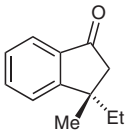
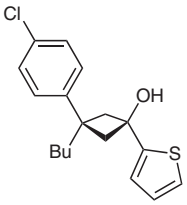
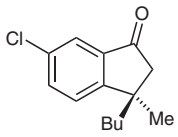
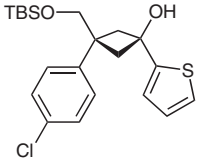
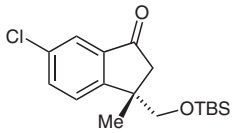
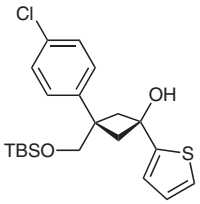
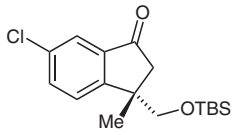
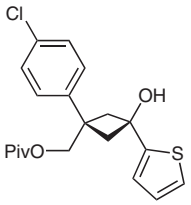
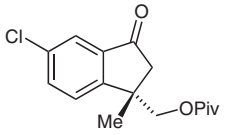
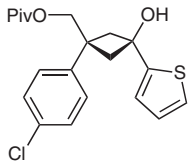
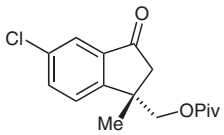
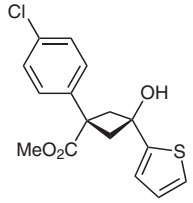
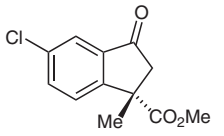
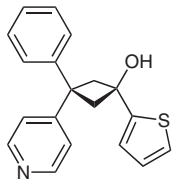
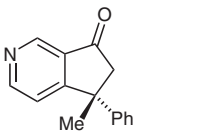
Entry	1		6		Yield (%)[b]	ee (%)[c]
1	*cis*-**1a**			**6a**	99	88
2[d]	*trans*-**1a**			**6a**	98	86
3[d]	*cis*-**1b**			**6b**	97	88
4[d]	*cis*-**1c**			**6c**	99	80
5	*trans*-**1c**			**6c**	99	93
6[e]	*trans*-**1d**			**6d**	73	89

Table 2 Scope of the C–C/C–H/C–C Activation Reaction[a] (continued)

Entry	1		6		Yield (%)[b]	ee (%)[c]
7[d]	*cis*-**1d**			**6d**	94	83
8[e]	*trans*-**1e**			**6e**	60	94
9[d,f]	*trans*-**1f**			**6f**	60	92

[a] Reaction conditions: 0.1 mmol **1**, 2.5 mol% $[Rh(OH)(cod)]_2$, 6.0 mol% **L3**, 1.5 equiv Cs_2CO_3, 0.25 M in xylenes, 120 °C, 12 h.
[b] Isolated yields.
[c] Determined by HPLC with a chiral stationary phase.
[d] With *ent*-**L3**.
[e] After 12 h, 2.5 mol% $[Rh(OH)(cod)]_2$ and 6.0 mol% **L4** were added.
[f] Aza-indanone **6f** was formed preferentially over the indanone (2:1 selectivity).

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References and Notes

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(10) **Typical Procedure for the Preparation of (*S*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-6-chloro-3-methylindan-1-one (6c)**
tert-Cyclobutanol *trans*-**1c** (40.9 mg, 0.100 mmol), $[Rh(cod)(OH)]_2$ (1.14 mg, 2.50 μmol), (*R*)-Difluorphos (**L3**, 4.10 mg, 6.00 μmol), and Cs_2CO_3 (0.150 mmol, 48.9 mg) were weighted into an oven-dried vial equipped with a magnetic stir bar, capped with a septum, and purged with nitrogen. Dry xylenes (0.5 mL) were added, and the mixture was degassed with three freeze-pump-thaw cycles. The mixture was stirred for 10 min at 23 °C and subsequently immersed into a preheated oil bath (120 °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 30:1, R_f = 0.18) giving 32.2 mg (99%, 93% ee) of indanone (*S*)-**6c** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.60 (m, 1 H), 7.54 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.45 (dd, *J* = 8.2, 0.5 Hz, 1 H), 3.62–3.56 (m, 2 H), 2.75 (d, *J* = 18.7 Hz, 1 H), 2.41 (d, *J* = 18.7 Hz, 1 H), 1.40 (s, 3 H), 0.77 (s, 9 H), –0.06 (s, 3 H), –0.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.0, 158.2, 138.5, 134.3, 134.1, 125.7, 122.9, 70.7, 48.5, 44.1, 25.6, 23.4, 18.1,

–5.7, –5.8. HRMS (EI$^+$): *m/z* calcd for $C_{13}H_{16}ClO_2Si$ [M – C_4H_9]$^+$: 267.0603; found: 267.0603. IR (ATR): 2955, 2929, 2885, 2856, 1720, 1602, 1470, 1254, 1236, 1180, 1109, 837, 777 cm^{-1}. $[\alpha]_D^{20}$ –21 (*c* 0.94, $CHCl_3$).

(11) The absolute configuration of compounds **6** were assigned in analogy to the reported cleavage site. See ref. 4c,d, and 6.