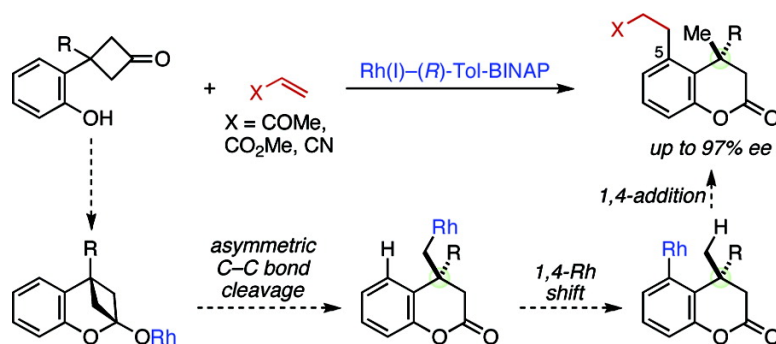Communication

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Asymmetric Synthesis of 3,4-Dihydrocoumarins by Rhodium-Catalyzed Reaction of 3-(2-Hydroxyphenyl)cyclobutanones

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Significant advances have been made over the past decade in the field of activation of carbon−carbon single bonds by means of transition metal catalysis.[1] Now a variety of catalytic processes are available for organic transformations including cross-coupling and ring-expansion reactions.[2] We recently developed the rhodium-catalyzed reaction of boron-substituted cyclobutanones forming 1-indanones. Enantioselectivities up to 95% ee were observed during the sequence of intramolecular addition/ring-opening reactions when stereogenic quaternary carbon centers arose at the benzylic position.[3] It was also found that rhodium catalysts promote the ring-opening reaction of cyclobutanones with phenols to form ester linkages via inter-[4] and intramolecular pathways.[5] In this paper, we describe an asymmetric synthesis of 3,4-dihydrocoumarins by way of a highly enantioselective carbon−carbon bond cleavage.[6] Deuterium-labeling experiments led to the development of a new cascade reaction involving 1,4-rhodium shift and intermolecular conjugate addition.
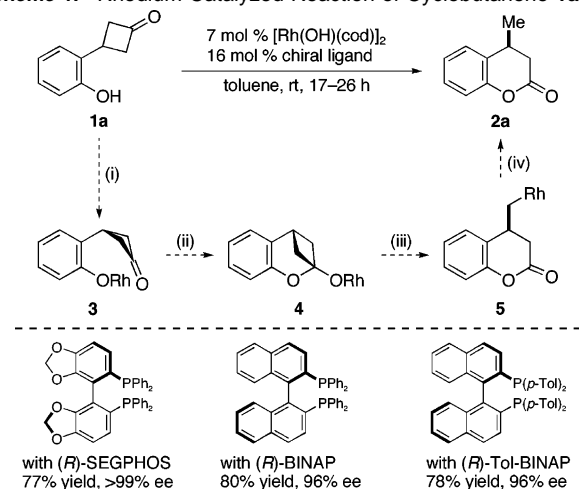
When 3-(2-hydroxyphenyl)cyclobutanone (**1a**)[7] was treated with a catalytic amount of a rhodium(I) catalyst, prepared in situ from [Rh(OH)(cod)]₂ (7 mol %) and (*R*)-SEGPHOS (16 mol %), in toluene at room temperature for 19 h, 4-methyl-3,4-dihydrocoumarin (**2a**) was produced in 77% isolated yield (Scheme 1).[8] Only one enantiomer was observed by chiral HPLC analysis. The absolute configuration was assigned to be *S* by comparison with the reported optical rotation.[9] BINAP and Tol-BINAP were also effective as the chiral ligands, both giving 96% ee. We propose a possible mechanism which consists of (i) generation of rhodium aryloxide **3**, (ii) addition to the carbonyl group forming rhodium cyclobutanolate **4**,[10] (iii) ring opening of the cyclobutane skeleton by β-carbon elimination[11] generating **5**, which is the enantiodifferentiating step, and (iv) protonolysis affording the dihydrocoumarin **2a**, as we proposed recently.[4]

When the reaction of **1a** was carried out in THF−D₂O (4:1), deuterium was incorporated at the 3-position (88% D; 61:39 dr) (Scheme 2). This result indicates that protonolysis occurs not directly from the intermediate **5** but via enolate **6**. From intermediate **5**, in which rhodium is located γ to the carbonyl group, **6** is generated via a series of β-hydride elimination and re-additions.[12] The excellent enantioselectivity observed with **2a** is explained by assuming that rhodium faithfully remains on the same enantioface during the repetitive elimination/re-addition processes.

The results of the Rh(I)−(*R*)-SEGPHOS-catalyzed reaction of other 3-monosubstituted cyclobutanones **1** are shown in Chart 1. Methoxy- and chloro-substituted cyclobutanones gave the corresponding 3,4-dihydrocoumarins, **2b** and **2c**, in good yields and high levels of enantiomeric excess. The reaction of naphthalene derivative produced tricyclic lactone **2d** in 91% yield and 98% ee.

We also tried to synthesize seven-membered ring lactones by the rhodium-catalyzed reaction of 3-monosubstituted cyclobutanones with their tethers extended by one carbon. The reaction of cyclobutanone **7** possessing a benzylic alcohol moiety required heating at 135 °C, and seven-membered lactone **8** was produced in 76% yield and 34% ee (eq 1). Cyclobutanone **9** reacted at 110 °C to give benzolactone **10** in 61% yield with 28% ee (eq 2). The more compact and less flexible 2-oxabicyclo[3.1.1]heptane

Scheme 1. Rhodium-Catalyzed Reaction of Cyclobutanone **1a**

with (*R*)-SEGPHOS
77% yield, >99% ee

with (*R*)-BINAP
80% yield, 96% ee

with (*R*)-Tol-BINAP
78% yield, 96% ee

Scheme 2. Deuterium-Labeling Experiment with **1a**
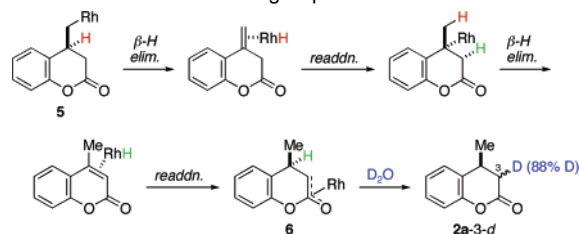
Chart 1. Asymmetric Synthesis of 4-Monosubstituted 3,4-Dihydrocoumarins **2b**−**d**[a]

2b
79% yield, 99% ee

2c
85% yield, 98% ee

2d
91% yield, 98% ee
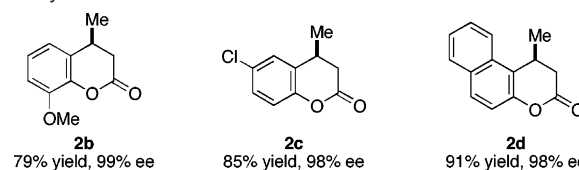
[a] 3.5 mol % of [Rh(OH)(cod)]₂ and 8 mol % of (*R*)-SEGPHOS in toluene for **2b** or in toluene−THF (4:1) for **2c** and **2d** at rt for 12−14 h.

skeleton of **4** is likely preferable for the enantiodifferentiating carbon−carbon bond cleavage step to occur with high selectivity.
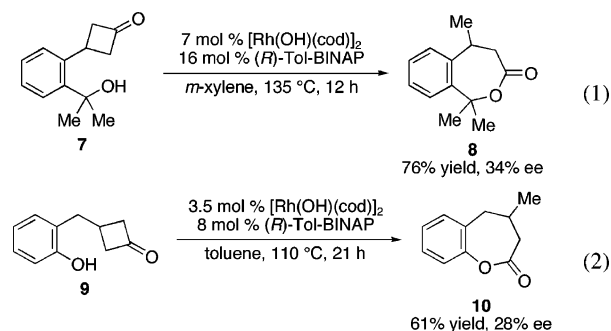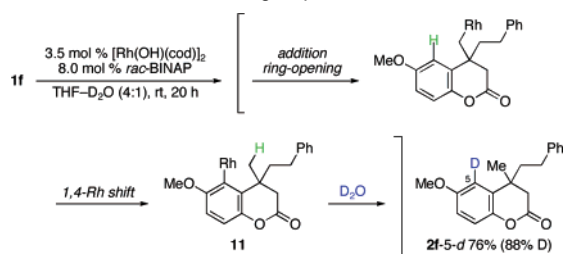

(1)

8
76% yield, 34% ee

(2)

10
61% yield, 28% ee

Table 1. Asymmetric Synthesis of 4,4-Disubstituted 3,4-Dihydrocoumarins **2e–j**[a]

	cyclobutanone			dihydrocoumarin		
entry	1	R[1]	R[2]	2	%yield[b]	%ee[c]
1	**1e**	(CH$_2$)$_2$Ph	H	**2e**	81 (79[d])	94 (80[d])
2[e]	**1f**	(CH$_2$)$_2$Ph	OMe	**2f**	92	95
3[f]	**1g**	Et	H	**2g**	80	94
4[f]	**1h**	i-Pr	H	**2h**	87	93
5[g]	**1i**	Ph	H	**2i**	68	92
6[e,f]	**1j**	(CH$_2$)$_3$OH	Me	**2j**	77	77

[a] Unless otherwise noted, cyclobutanone **1** was reacted in the presence of 3.5 mol % of [Rh(OH)(cod)]$_2$ and 8.0 mol % of (R)-Tol-BINAP in toluene at room temperature for 11–24 h. [b] Isolated yield by preparative TLC. [c] Determined by chiral HPLC. [d] Result with (R)-SEGPHOS. [e] Toluene–THF (4:1) was used. [f] 7.0 mol % of [Rh(OH)(cod)]$_2$ and 16 mol % of (R)-Tol-BINAP were used. [g] THF was used.

Scheme 3. Deuterium-Labeling Experiment with **1f**

Next, the reaction of 3,3-disubstituted cyclobutanone **1e** was examined (Table 1). In contrast to the cases of 3-monosubstituted cyclobutanones **1a–d**, Tol-BINAP proved to operate more selectively than SEGPHOS in constructing the chiral quaternary carbon center (entry 1). Enantiomeric excesses ranging from 92 to 95% were generally observed in the reaction of various 3,3-disubstituted cyclobutanones **1f–i**, except for the case of **1j** having a 3-hydroxypropyl side chain (entries 2–6).

A deuterium-labeling experiment was carried out also with the 3,3-disubstituted cyclobutanone **1f**, for which it was impossible to follow the protonolysis pathway shown in Scheme 2 because of the lack of β-hydrogen. In this case, deuterium was incorporated at the 5-position, implying the generation of arylrhodium species **11** via a 1,4-rhodium shift[13] prior to protonolysis (Scheme 3).

These results led us to examine the competency of intermediary arylrhodium **11** in a subsequent 1,4-addition reaction.[14] When the reaction of **1f** was carried out in the presence of acrylonitrile (**12a**), the arylrhodium generated in an enantioenriched form via 1,4-rhodium shift underwent 1,4-addition to **12a**,[15] and the cascade

Table 2. Rhodium-Catalyzed Cascade Reaction of **1** with Electron-Deficient Alkenes **12**[a]

entry	1 (R[1], R[2])	12 (X)	13	%yield[b]	%ee[c]
1	**1f** ((CH$_2$)$_2$Ph, OMe)	**12a** (CN)	**13fa**	93	95
2	**1f**	**12b** (COMe)	**13fb**	65	96
3[d]	**1f**	**12c** (CO$_2$Me)	**13fc**	76	95
4	**1g** (Et, H)	**12b**	**13gb**	75	97
5	**1h** (i-Pr, H)	**12a**	**13ha**	89	91

[a] Cyclobutanone **1** was added dropwise to a THF solution of alkene **12** (10 equiv) over 1 h in the presence of the rhodium catalyst at 50 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was carried out at 60 °C for 17 h.

product **13fa** was obtained in 93% yield with 95% ee (Table 2, entry 1). Other electron-deficient alkenes such as methyl vinyl ketone (**12b**) and methyl acrylate (**12c**) could be employed (entries 2 and 3).[16] Cyclobutanones **1g** and **1h** also underwent the cascade reaction to furnish the corresponding alkylated dihydrocoumarins **13** (entries 4 and 5).

In summary, 3,4-dihydrocoumarins have been synthesized in a highly enantioselective manner through an asymmetric β-carbon elimination step. A new asymmetric cascade reaction consisting of carbonyl addition/ring opening/1,4-addition has been developed by utilization of the intermediary arylrhodium species generated from 3,3-disubstituted cyclobutanones.

Supporting Information Available: Experimental details and selected spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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