Rhodium-catalyzed Reactions of Cyclobutanones with Alcohols and Amines Forming Esters and Amides

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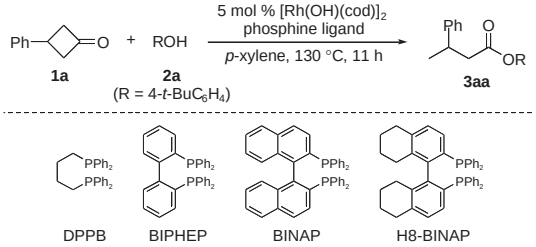
Cyclobutanones react with alcohols in the presence of rhodium(I)–phosphine catalysts to give esters in good yields through an addition/ring-opening process. Amides are formed by a similar reaction with amines.

Transition metal-catalyzed cleavage of carbon–carbon single bonds has gained much interest.[1] We have developed various transformations of cyclobutanones, in which the four-membered carbocyclic rings are opened by the catalysis of transition metals like rhodium[2] and nickels.[3,4] In this paper, we describe a rhodium-catalyzed reaction of cyclobutanones with phenols and alcohols forming ring-opened esters. Amides are also produced by an analogous reaction with amines.

The reaction of 3-phenylcyclobutanone (**1a**) with 4-*tert*-butylphenol (**2a**) was taken as the model to examine the effect of several phosphine ligands in combination with [Rh(OH)(cod)]$_2$ (10 mol % Rh, cod = cycloocta-1,5-diene) (Table 1). Ester **3aa** was obtained in 12% yield with PPh_3 (Entry 1). Whereas no reaction occurred with DPPB (Entry 2), diphosphines having a biaryl backbone were suitable ligands (Entries 3–5). In particular, (*R*)-H8-BINAP gave **3aa** in the best yield of 66%.[5] Use of 10 mol % of the diphosphine (Rh:P = 1:2) decreased the yield (Entry 6). The ester **3aa** was obtained in 47% yield with the use of 2 equiv. of **2a** (Entry 7).

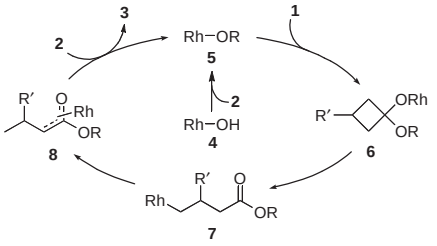
No ester formation was observed in the absence of a rhodium catalyst. Although analogous reactions forming esters from cyclobutanones are known to be promoted by simple acids or bases, the substrates are limited to 2,2-dihalocyclobutanones,[6a]

Table 1. Screening for various phosphine ligands for reaction of **1** and **2**

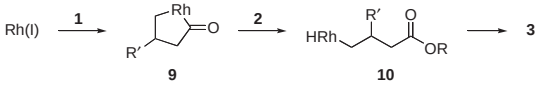


Entry	Ligand (mol %)	Equiv. of **2a**	**3aa** (yield[a])
1	PPh_3 (40)	3.0	12%
2	DPPB (20)	3.0	0%
3	BIPHEP (20)	3.0	53%
4	*rac*-BINAP (20)	3.0	49%
5	(*R*)-H8-BINAP (20)	3.0	66%
6	(*R*)-H8-BINAP (10)	3.0	56%
7	(*R*)-H8-BINAP (20)	2.0	47%

[a]Isolated yield by preparative TLC.



Scheme 1. Mechanism A.



Scheme 2. Mechanism B.

2,2-diphenylcyclobutanones,[6b,6c] and cyclobutanones having a substituent at the 2-position which electronically facilitates the ring-opening, like an acyl group.[6d,6e] In fact, when **1a** was allowed to react with methanol in the presence of *t*-BuOK in Et_2O at room temperature, no ester was formed, and **1a** was converted to polymeric compounds.

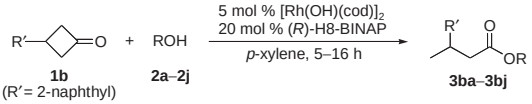
There are two mechanisms A and B conceivable for the formation of ester **3** from cyclobutanone **1** and alcohol **2**. In mechanism A (Scheme 1), rhodium alkoxide **5** is initially generated from the hydroxorhodium **4** and **2**. Addition of the rhodium alkoxide **5** to the carbonyl group of **1** affords rhodium cyclobutanolate **6**, which undergoes ring-opening by β-carbon elimination. The resulting alkylrhodium **7** species isomerizes to rhodium enolate **8** via repetitive β-hydride elimination/readdition process.[2e,7] Finally, protonolysis of **8** with **2** gives product **3** with **5** regenerated.

Alternatively, mechanism B also explains the formation of **3** (Scheme 2). Rhodium(I) initially inserts between the C(carbonyl)–C(α) bond of **1** to afford five-membered acylrhodium intermediate **9**. The hydroxy group of **2** then reacts with the acylrhodium to form an ester linkage. The resultant alkylrhodium(III) hydride **10** undergoes reductive elimination to produce ester **3**.

Hartwig and Krug recently reported that rhodium(I) alkoxides react with aldehydes to give esters, which demonstrated that rhodium(I) alkoxides are reactive enough to add to an aldehydic carbonyl group and that formation of an ester linkage by β-elimination is a viable process.[8] On the basis of this result, we favor mechanism A over mechanism B.

Results of the reaction of 3-(2-naphthyl)cyclobutanone (**1b**) with various alcohols **2** are shown in Table 2. Phenols **2a**–**2c** gave the corresponding esters **3ba**–**3bc** in yields ranging from 64 to 90% (Entries 1–3). However, **2d** having a trifluoromethyl group at the para position failed to produce ester (Entry 4). 3,5-

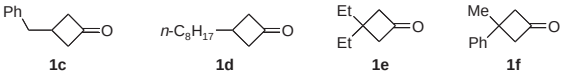
Table 2. Rhodium-catalyzed reaction of cyclobutanone **1b** with alcohols **2a–2j**[a]



1b (R′ = 2-naphthyl) **2a–2j** **3ba–3bj**

Entry	2	R	Temp/°C	3	Yield[b]%
1	**2a**	4-*t*-BuC_6H_4	130	**3ba**	81
2	**2b**	Ph	130	**3bb**	64
3	**2c**	4-MeOC_6H_4	130	**3bc**	90
4	**2d**	4-$CF_3C_6H_4$	130	**3bd**	0
5	**2e**	3,5-$Me_2C_6H_3$	130	**3be**	69
6	**2f**	2-MeC_6H_4	130	**3bf**	58
7	**2g**	2-Naphthyl	130	**3bg**	40
8	**2h**	$PhCH_2$	90	**3bh**	75
9	**2i**	(*R*)-PhMeCH	90	**3bi**	45[c]
10	**2j**	$Ph(CH_2)_3$	90	**3bj**	50

[a]Cyclobutanone **1b** and alcohols **2a–2j** (3.0 equiv. to **1b**) were heated in *p*-xylene for 5–16 h in the presence of $[Rh(OH)(cod)]_2$ (5 mol %) and (*R*)-H8-BINAP (20 mol %). [b]Isolated yield. [c]A 54:46 mixture of diastereomers was obtained.



1c **1d** **1e** **1f**

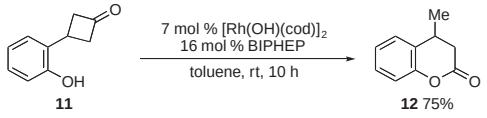
Chart 1.

Xylenol (**2e**) and sterically more demanding *o*-cresol (**2f**) afforded esters **3be** and **3bf** in 69 and 58% yields, respectively (Entries 5 and 6). 2-Naphthyl ester **3bg** was obtained in lower yield (Entry 7). The addition/ring-opening reaction took place also with alkanols like benzyl alcohol (**2h**), (*R*)-1-phenylethanol (**2i**), and 3-phenylpropanol (**2j**) (Entries 8–10). However, diphenylmethanol failed to produce an ester, presumably due to steric reasons.

Other 3-monosubstituted cyclobutanones **1c** and **1d** (Chart 1) reacted with **2a** to give the corresponding esters **3ca** (60%) and **3da** (60%), respectively. On the contrary, 3,3-disubstituted cyclobutanones such as **1e** and **1f** failed to react with **2a**. The inaccessibility of a rhodium enolate from the ring-opened intermediate corresponding to **7** might disfavor the ring-opening process.

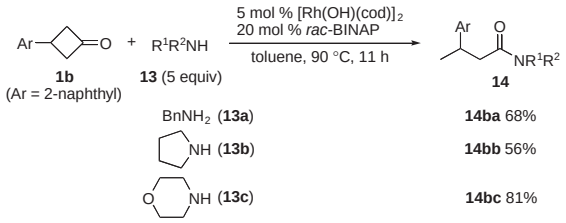
We previously reported the rhodium-catalyzed reaction of phenol-containing cyclobutanones affording lactones; heating cyclobutanone **11** at 140 °C in the presence of a rhodium catalyst generated in situ from $[Rh(cod)_2]BF_4$ and P(*c*-Hex)Ph_2 produced lactone **12** in 57% yield.[2a] A mechanistic pathway similar to mechanism B was proposed therein. Next, the $[Rh(OH)(cod)]_2$–BIPHEP catalyst system was applied to the intramolecular reaction of **11**. Surprisingly, the reaction occurred at room temperature to furnish **12** in 75% yield (Scheme 3). On the basis of the results reported by Hartwig and Krug,[8] we now assume that mechanism A operates also in the intramolecular reaction of **11**.

Our attention was next directed to amide formation by



11 **12** 75%

Scheme 3.



1b (Ar = 2-naphthyl) **13** (5 equiv) **14**

Scheme 4.

the addition of amines to cyclobutanones (Scheme 4).[9] Benzylamine and cyclic secondary amines were good substrates for the reaction. Especially, amide **14bc** was obtained in 81% yield with morpholine (**13c**).[10] However, acyclic secondary amines (*N*-methylaniline, *N*-methylbenzylamine, and diisopropylamine) as well as aniline failed to afford the corresponding amides.

In summary, we have found that the reaction of cyclobutanones with alcohols and amines is catalyzed by rhodium–phosphine complexes to produce esters and amides, respectively.

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10 Heating a toluene solution of **1b** and **13c** at 90 °C in the absence of the rhodium catalyst gave no amide **14bc**.

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