

Selective Catalysis

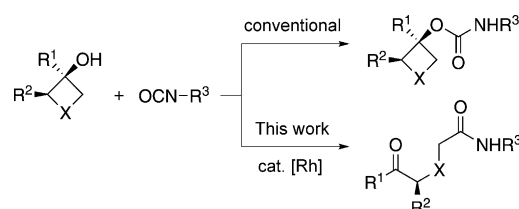
Reactivity Change of Cyclobutanols towards Isocyanates: Rhodium Favors C-Carbamoylation over O-Carbamoylation**

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Dedicated to Professor Scott E. Denmark on the occasion of his 60th birthday

Transition-metal catalysis potentially brings forth unique reactivities that are different from those available under conventional reaction conditions. For example, transition-metal catalysts make it possible to cleave C–C σ -bonds, which are kinetically inert in general and therefore difficult to transform.^[1] Their use can even lead to a drastic change in reaction pathways.^[2]

As shown in Scheme 1, alcohols directly react with isocyanates to afford carbamates. For example, heating a cyclobutanol and an isocyanate at 85 °C in toluene furnishes the cyclobutyl carbamate through nucleophilic addition of the hydroxy group onto the highly electrophilic sp carbon atom of the isocyanate.^[3] The *O*-carbamoylation reaction of alcohols with isocyanates is accelerated by bases, acids, and metallic compounds.^[4] On the other hand, it has been reported that transition-metal-catalyzed reactions of acyclic alcohols can cause the cleavage of C–C bonds.^[5,6] A carbonyl moiety is released to produce an organometallic intermediate, which is employed for subsequent carbon–carbon bond-forming reactions. In the case of cyclobutanols, the cyclobutane ring is opened to generate a δ -oxoalkyl metal species, which may subsequently undergo a variety of reactions, including β -hydride elimination,^[7] arylation,^[8] 1,3-proton abstraction,^[9] intramolecular conjugate addition,^[10] 1,4-metal migration,^[11] and so on.^[12,13] Unlike in the case of acyclic alcohols, the carbonyl unit is retained in the products. These studies led us to propose that cyclobutanols, non-organometallic compounds, may serve as masked carbon-nucleophile equivalents to a δ -oxoalkyl anion; they may add to isocyanates through their carbon atoms rather than through their oxygen atoms. Herein, we report the rhodium-catalyzed addition reaction of cyclobutanols to isocyanates.^[14] In contrast to reactions under conventional conditions, a rhodium catalyst directs the reaction pathway to a sequence of carbon–carbon bond cleavage/formation reactions rather than a simple *O*-carbamoylation reaction (Scheme 1).



Scheme 1. Contrasting pathways for the reaction of cyclobutanols and isocyanates.

The reaction of cyclobutanol **1a** with isocyanate **2a** was examined under various reaction conditions (Table 1). When a mesitylene solution containing only **1a** and **2a** was simply heated at 100 °C, cyclobutyl carbamate **3a** was obtained in quantitative yield (entry 1). Exclusive *O*-carbamoylation even occurred at room temperature when a catalytic amount (5 mol %) of $[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ was present (entry 2). In striking contrast, the addition of 1,1'-bis(diphenylphosphino)ferrocene (DPPF) as a rhodium ligand (Rh/DPPF = 1:1) completely changed the outcome of the reaction to produce the ring-opened amide **4a**, which was isolated in 81 % yield, in preference to carbamate **3a** (10 %; entry 3). The greatest yield (89 %) of **4a** was obtained when a mesitylene solution containing **1a** and **2a** was added dropwise at 70 °C to a mesitylene solution containing the Rh/DPPF catalyst, which was prepared in situ (entry 4).^[15] The product selectivity (**3a**/**4a**) was significantly affected by the choice of phosphine ligands. For example, the use of 2,2'-bis(diphenylphosphino)-

Table 1: Product selectivity in the reaction of **1a** and **2a**.^[a]

Entry	Catalyst (mol %)	Temp. [°C]	Yield ^[b] [%]	
			3a	4a
1	–	100	99	0
2	$[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ (5)	RT	99	0
3	$[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ (5), DPPF (10)	70	10	81
4 ^[c]	$[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ (5), DPPF (10)	70	< 5	89
5	$[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ (5), <i>rac</i> -BINAP (10)	70	73	17

[a] Cyclobutanol **1a** (0.10 mmol) and isocyanate **2a** (0.10 mmol) were reacted in mesitylene (1.8 mL), 12 h. [b] Yields of isolated products. [c] Dropwise addition of **1a** and **2a**. BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, COD = 1,5-cyclooctadiene, DPPF = 1,1'-bis(diphenylphosphino)ferrocene.

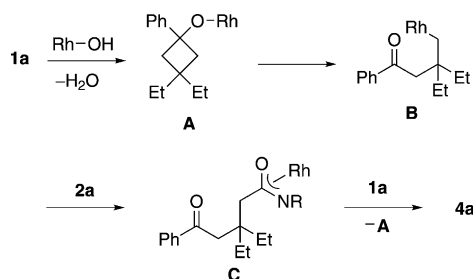
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1,1'-binaphthyl (BINAP) led to reverse selectivity (**3a/4a** ca. 4:1; entry 5), whereas the use of monodentate ligands such as PPh₃ and P(*t*Bu)₃ afforded **3a** exclusively.

The mechanistic scenario for the synthesis of **4a** is depicted in Scheme 2. Initially, cyclobutanol **1a** is deprotonated by a rhodium hydroxide to afford rhodium cyclobutanolate **A**. Subsequent β -carbon elimination cleaves a C–C bond of the cyclobutane ring, thus relieving ring strain. In this way, alkylrhodium intermediate **B** is generated, which subsequently adds to isocyanate **2a**.^[14] The resulting rhodium amide **C** is protonated by another equivalent of **1a**, to give the ring-opened amide **4a**, along with regeneration of the rhodium cyclobutanolate **A**. When $[\{\text{Rh}(\text{OH})(\text{cod})\}_2]/\text{DPPF}$ is used, β -carbon elimination takes place in preference to direct nucleophilic addition to **2a** through the hydroxy group, although the reason is unclear.^[16]



Scheme 2. Proposed mechanism for the formation of **4a** from **1a**.

Various cyclobutanols add to isocyanates through a ring-opening step under the optimized reaction conditions (Table 2). For 1-aryl-3,3-dialkylcyclobutanols **1b–d**, the ring-opened products **4b–d** were isolated by column chromatography on silica gel in yields of 89–82 % (entries 1–3). Less than 5 % of the corresponding cyclobutyl carbamates **3** were detected in the crude reaction mixture. In the case of cyclobutanols with an aryl group at the 3-position, however, skeletal rearrangement through a 1,4-rhodium shift^[11] preceded addition to the isocyanate **2a**, and gave indanols in high yield. 1-Alkyl- and 1-alkenyl-substituted cyclobutanols (**1e** and **1f**) produced the amides **4** (70–71 %) in preference to the carbamates **3**. With bicyclic cyclobutanol **1g**, the sterically less-hindered C–C bond was site-selectively cleaved by β -carbon elimination to furnish **4g** in 85 % yield (entry 6). In addition to cyclobutanols, oxetanols **1h** and **1i** were also selectively converted into the ring-opened amides **4h** and **4i** (entries 7 and 8). The stereochemical integrity of the enantiopure **1i** was completely retained in the resulting amide **4i**.

The functional-group compatibility of the present reaction was examined using various isocyanates (Table 3). Although 4-trifluoromethylphenyl isocyanate (**2b**) is so electrophilic that it spontaneously reacts with alcohols, the ring-opened amide **4j** was successfully obtained by adding separate mesitylene solutions of cyclobutanol **1a** and **2b** dropwise to the mesitylene solution containing the rhodium catalyst (entry 1). Ethoxycarbonyl (**2c**), and bromo (**2d**) substituents on the aryl ring were retained in the product (entries 2 and 3). Alkyl isocyanate **2e** was also amenable to

Table 2: Reactions of **1** and **2a**.^[a]

$\begin{array}{c} \text{R}^1 \\ \\ \text{R}^2 - \text{C} - \text{C} - \text{OH} \\ \quad \\ \text{X} \end{array} + \text{2a} \xrightarrow[\text{mesitylene, 85 } ^\circ\text{C, 12 h}]{[\{\text{Rh}(\text{OH})(\text{cod})\}_2] (5 \text{ mol}\%), \text{DPPF} (10 \text{ mol}\%)} \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2 - \text{C} - \text{C} - \text{X} \\ \quad \\ \text{O} \quad \text{NHR} \end{array}$ $\text{R} = 4\text{-MeOC}_6\text{H}_4$		
Entry	1	4 ^[b]
1		 4b 89%
2		 4c 87%
3		 4d 82%
4 ^[c]		 4e 70%
5 ^[d]		 4f 71%
6		 4g 85%
7		 4h 83%
8		 4i

[a] A mesitylene solution (0.8 mL) containing **1** (0.050 mmol) and **2a** (0.060 mmol) was added dropwise to a mesitylene solution (1.0 mL) containing $[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ (5 mol %) and DPPF (10 mol %) at 85 °C.

[b] Yields of isolated products. [c] **3e** (26 %) was also obtained. [d] **3f** (21 %) was also obtained.

the rhodium-catalyzed ring-opening addition reaction (entry 4).

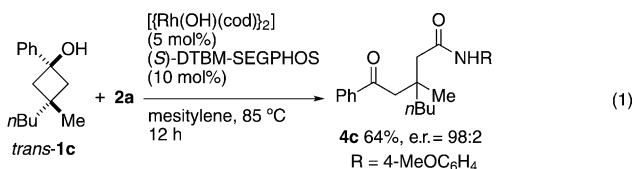
When isolated *trans*-**1c** was treated with a catalytic amount of $[\{\text{Rh}(\text{OH})(\text{cod})\}_2]/(S)\text{-DTBM-SEGPHOS}$ (DTBM-SEGPHOS = 5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole), the symmetric cyclobutane ring was opened in an enantioselective manner, as previously reported [Eq. (1)].^[9b] The amide **4c**, which possesses an all-carbon quaternary stereogenic center at the β -position, was obtained with an enantiomeric ratio of 98:2

Table 3: Reactions of **1a** and **2**.^[a]

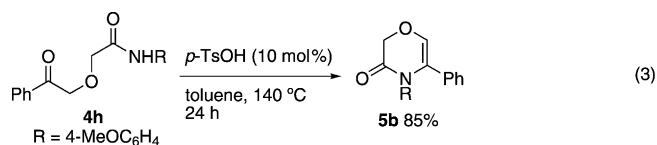
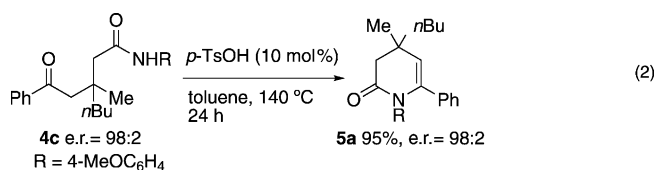
Entry	2	4 ^[b]
1 ^[c]		 4j 70%
2 ^[d]		 4k 76%
3		 4l 60%
4		 4m 82%

[a] A mesitylene solution (0.8 mL) containing **1a** (0.050 mmol) and **2** (0.060 mmol) was added dropwise to a mesitylene solution (1.0 mL) containing $[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ (5 mol %) and DPPF (10 mol %) at 85 °C. [b] Yields of isolated products. [c] **3j** (26%) was also obtained; two separate solutions of **1** and **2** were added simultaneously. [d] **3k** (17%) was also obtained.

(64% yield), along with the corresponding carbamate **3** (15%).



Thus, the present rhodium-catalyzed reaction provides access to various δ -keto amides **4** including optically active derivatives. Further derivatization to N-heterocycles may be achieved by a simple acid-catalyzed dehydrative cyclization, as shown in Equations (2) and (3).^[17] When **4c** was heated in toluene at reflux in the presence of *p*-toluenesulfonic acid (10 mol %), the chiral dihydropyridone **5a** was obtained in 95% yield with retention of enantiopurity. The morpholinone **5b** was obtained in 85% yield by analogous cyclization of **4h**.



In summary, we have reported that a rhodium catalyst can change the reaction pathway of cyclobutanols with isocyanates to form a carbon–carbon bond between the two reactants. This process occurs because ring opening of the cyclobutane ring precedes direct *O*-addition of the hydroxy moiety to the isocyanate. Although cyclobutanols are non-organometallic compounds, they can act as a carbon nucleophiles towards isocyanates without losing the carbonyl unit, with the aid of rhodium catalysis.

Experimental Section

Procedure for the ring-opening reaction of cyclobutanol **1a** and isocyanate **2a**: A mesitylene solution (0.8 mL) containing cyclobutanol **1a** (20.4 mg, 0.10 mmol) and isocyanate **2a** (17.9 mg, 0.12 mmol) was added over 1 h by syringe pump to a mesitylene solution (1.0 mL) heated at 70 °C and containing $[\{\text{Rh}(\text{OH})(\text{cod})\}_2]$ (2.28 mg, 5.0 μmol , 5 mol %) and DPPF (5.65 mg, 10 μmol , 10 mol %). The reaction mixture was stirred at this temperature for further 11 h and then cooled to room temperature. The resulting mixture was diluted with ethyl acetate, passed through a pad of silica gel and concentrated under reduced pressure. The residue was isolated by preparative thin layer chromatography (*n*-hexane/ethyl acetate = 3:1) to afford amide **4a** (31.4 mg, 0.089 mmol, 89%). IR (neat): $\tilde{\nu}$ = 3306, 2963, 1651, 1597, 1508, 1447, 1410, 1242, 1178, 1034, 827, 746, 689 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 0.85 (t, *J* = 7.4 Hz, 6H), 1.49 (q, *J* = 7.4 Hz, 4H), 2.51 (s, 2H), 3.05 (s, 2H), 3.76 (s, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 7.45–7.51 (m, 4H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 9.01 ppm (s, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ = 7.6, 29.0, 41.0, 42.2, 43.7, 55.4, 113.9, 121.0, 128.3, 128.7, 131.6, 133.5, 138.3, 155.9, 169.7, 203.6 ppm; HRMS (ESI⁺) Calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_3$ [*M*+*H*]⁺ 354.2064, found 354.2061.

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