Selective Catalysis

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

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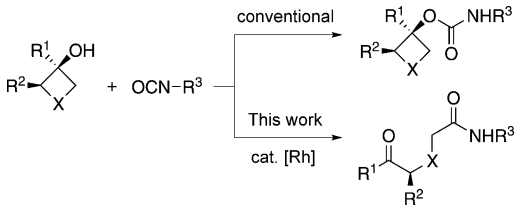
Dedicated to Professor Scott E. Denmark on the occasion of his 60th birthday

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]

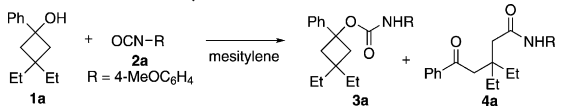
As shown in Scheme 1, alcohols directly react with isocyanates to afford carbamates. For example, heating a cyclobutanol and an isocyanate at 85 °C in toluene furnishes the cyclobutyl carbamate through nucleophilic addition of the hydroxy group onto the highly electrophilic sp carbon atom of the isocyanate.[3] 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 [{Rh(OH)(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	[{Rh(OH)(cod)}$_2$] (5)	RT	99	0
3	[{Rh(OH)(cod)}$_2$] (5), DPPF (10)	70	10	81
4[c]	[{Rh(OH)(cod)}$_2$] (5), DPPF (10)	70	< 5	89
5	[{Rh(OH)(cod)}$_2$] (5), *rac*-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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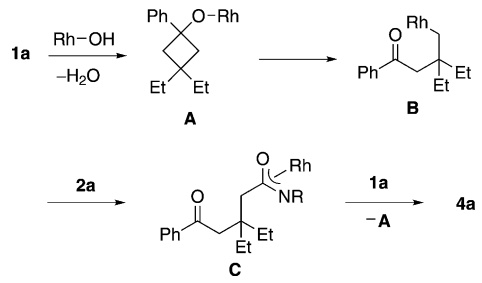
1,1′-binaphthyl (BINAP) led to reverse selectivity (**3a**/**4a** ca. 4:1; entry 5), whereas the use of monodentate ligands such as PPh_3 and $P(tBu)_3$ afforded **3a** exclusively.

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 amidate **C** is protonated by another equivalent of **1a**, to give the ring-opened amide **4a**, along with regeneration of the rhodium cyclobutanolate **A**. When [{Rh(OH)(cod)}$_2$]/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]

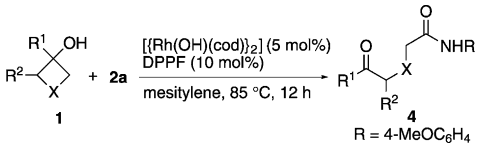


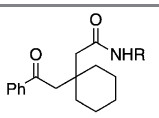
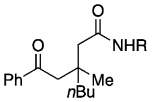
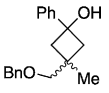
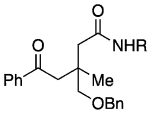
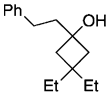
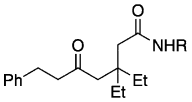
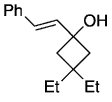
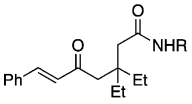
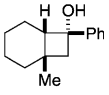
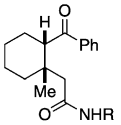
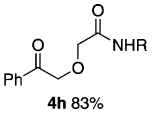
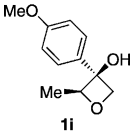
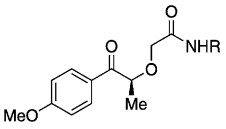
Scheme 2. Proposed mechanism for the formation of **4a** from **1a**.

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

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



Entry	**1**	**4**[b]
1	 **1b**	 **4b** 89%
2	 **1c** (56:44)	 **4c** 87%
3	 **1d** (75:25)	 **4d** 82%
4[c]	 **1e**	 **4e** 70%
5[d]	 **1f**	 **4f** 71%
6	 **1g**	 **4g** 85%
7	 **1h**	 **4h** 83%
8	 **1i** e.r.> 99:1 d.r.> 20:1	 **4i** 91%, e.r.> 99:1

[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 [{Rh(OH)(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.

When isolated *trans*-**1c** was treated with a catalytic amount of [{Rh(OH)(cod)}$_2$]/(*S*)-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

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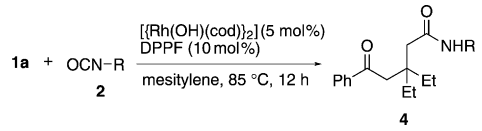
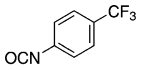
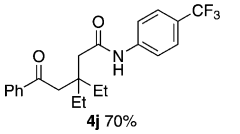
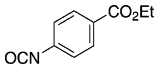
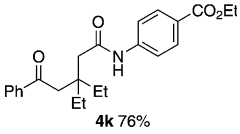
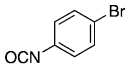
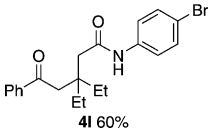
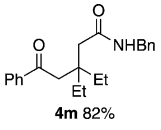
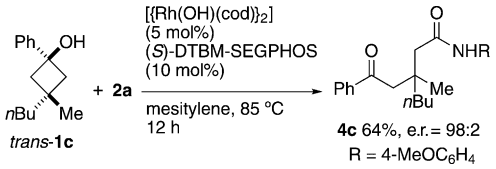
Table 3: Reactions of **1a** and **2**.[a]



Entry	2	4[b]
1[c]	 **2b**	 **4j** 70%
2[d]	 **2c**	 **4k** 76%
3	 **2d**	 **4l** 60%
4	OCN–Bn **2e**	 **4m** 82%

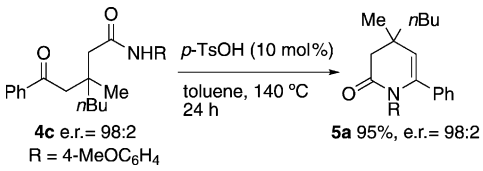
[a] A mesitylene solution (0.8 mL) containing **1a** (0.050 mmol) and **2** (0.060 mmol) was added dropwise to a mesitylene solution (1.0 mL) containing [{Rh(OH)(cod)}$_2$] (5 mol%) and DPPF (10 mol%) at 85 °C. [b] Yields of isolated products. [c] **3j** (26%) was also obtained; two separate solutions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

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

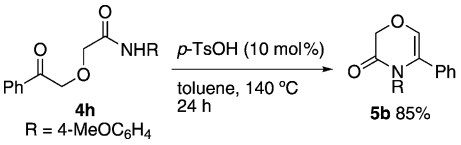


(1)

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**.



(2)



(3)

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 [{Rh(OH)(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}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (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, $CDCl_3$): $\delta = 7.6$, 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 $C_{22}H_{28}NO_3$ $[M+H]^+$ 354.2064, found 354.2061.

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Keywords: C–C activation · homogeneous catalysis · isocyanates · rhodium · strained molecules

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