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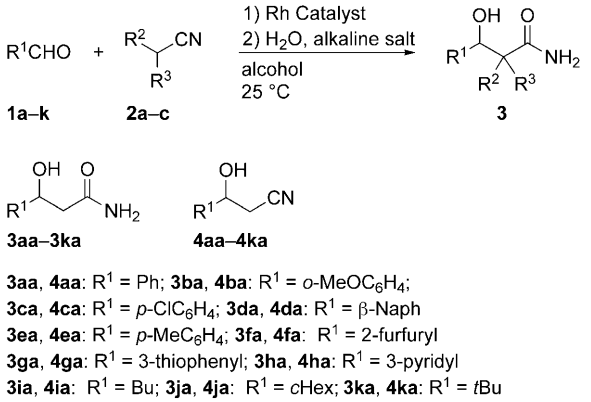
One-Pot Nitrile Aldolization/Hydration Operation Giving β-Hydroxy Carboxamides

Akihiro Goto,[a] Hiroshi Naka,[b] Ryoji Noyori,[a, b, c] and Susumu Saito*[a, c]

On the occasion of the 150th anniversary of the Department of Chemistry, The University of Tokyo

Carboxamide functionalities ($CONH_2$) are versatile synthetic intermediates or building blocks, and have been widely used in the Hofmann rearrangement,[1] N-arylation,[2] N-allylation,[3] and N-alkylation[4] reactions. In addition, $CONH_2$ is a useful protected form of carboxylic acid[5] and a potent pharmacophore in many drug candidates.[6] Therefore, a catalytic chemical transformation incorporating the $-CR_2CONH_2$ moiety (R = H or alkyl) into a molecular framework through a carboxamide enolate, thus effecting a carbon–carbon bond-forming reaction would be of considerable practical importance. However, such a reaction has thus far remained elusive, primarily due to the considerably low acidity of the α-proton of carboxamide in comparison to $CONH_2$ ($pK_a = \sim 25$ in dimethyl sulfoxide).[7] The pK_a value of carboxamides in dimethyl sulfoxide is approximately 35,[7] the highest value out of those reported for aldehydes and ketones ($pK_a = \sim 27$ in dimethyl sulfoxide),[7] or for esters ($pK_a = \sim 31$ in dimethyl sulfoxide).[7]

Herein, we report an alternative pathway to break out of this problem (Scheme 1). The formal aldol products of carboxamides were obtainable by the $Rh^{I}OR$-catalyzed aldol-type reaction (R = H, Me) of nitriles[8] ($pK_a = \sim 31$ in dimethyl sulfoxide),[7] followed by in situ hydration of the nitrile functionality.[9,10] This consecutive process was accommodated in a one-pot operation that minimized the amount and different varieties of salt wastes.



3aa, **4aa**: R^1 = Ph; **3ba**, **4ba**: R^1 = *o*-$MeOC_6H_4$;
3ca, **4ca**: R^1 = *p*-ClC_6H_4; **3da**, **4da**: R^1 = β-Naph
3ea, **4ea**: R^1 = *p*-MeC_6H_4; **3fa**, **4fa**: R^1 = 2-furfuryl
3ga, **4ga**: R^1 = 3-thiophenyl; **3ha**, **4ha**: R^1 = 3-pyridyl
3ia, **4ia**: R^1 = Bu; **3ja**, **4ja**: R^1 = *c*Hex; **3ka**, **4ka**: R^1 = *t*Bu

Scheme 1. General scheme of the nitrile aldolization/hydration sequence.

First, the rhodium(I) catalyst was prepared by treatment of $[Rh(OMe)(cod)]_2$ (cod = cycloocta-l,5-diene) with Cy_3P (1:2; Cy = cyclohexyl) in anhydrous tetrahydrofuran at 25 °C for 15 minutes under argon. After removal of tetrahydrofuran and residual cycloocta-l,5-diene in vacuo, argon-filled *tert*-butanol was added to yield a solution of rhodium catalyst. Nitrile aldolization was carried out by using PhCHO (**1a**) and acetonitrile (**2a**) with the rhodium(I) catalyst at 25 °C (Rh: 1.0×10^{-2} M). Subsequent removal of any volatile components including excess acetonitrile gave a bright red/orange slurry containing β-hydroxy nitrile **4aa**. Addition of argon-filled isopropanol, followed by treatment with Na_2CO_3 and H_2O at 25 °C, gave β-hydroxy carboxamide **3aa** in 96% yield.[11] Likely dehydration products, such as α,β-unsaturated carboxamide and nitrile, were not detected.

Addition of a catalytic amount of Na_2CO_3 was critical for this one-pot operation. In the absence of Na_2CO_3, little hy-

[a] Dr. A. Goto, Dr. R. Noyori, Dr. S. Saito
Department of Chemistry
Graduate School of Science
Nagoya University
Chikusa, Nagoya 464-8602 (Japan)
Fax: (+81) 52-789-5945
E-mail: saito.susumu@f.mbox.nagoya-u.ac.jp

[b] Dr. H. Naka, Dr. R. Noyori
Research Center for Materials Science
Nagoya University
Chikusa, Nagoya 464-8602 (Japan)

[c] Dr. R. Noyori, Dr. S. Saito
Institute for Advanced Research
Nagoya University
Chikusa, Nagoya 464-8601 (Japan)

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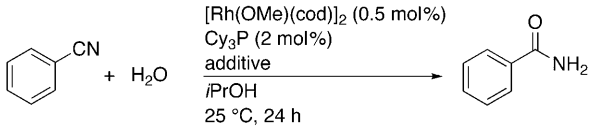
dration took place (**3aa**: <15%) even in the presence of 40–110 molar amounts of water in isopropanol (Rh: 1.0×10^{-2}–2.9×10^{-2} M). The requirement of a weak base is presumably related to the marginal but detrimental formation of benzoic acid from **1a**. In fact, a tiny amount of the acid was detected by GC-MS after the aldolization or hydration step. Benzoic acid was probably formed by side reactions, such as the Cannizzaro and/or Tishchenko reaction during the aldolization followed by hydrolysis. Indeed, the hydration was completely or partially suppressed when the rhodium(I)-promoted hydrations were performed separately using benzonitrile as a standard model[10q] in the presence of a small amount of benzoic acid or its ester (Table 1, entries 2–4). In sharp contrast, addition of a catalytic amount of Na_2CO_3 promoted the hydration reaction (entry 5).

Table 1. Detrimental effects of carboxylic acid and ester on nitrile hydration.[a]

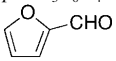
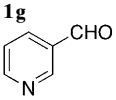


Entry	Additive(s) [mol %]	Benzamide [%][b]
1	None	99
2	Benzyl benzoate (5%)	72
3	Benzoic acid (5%)	<1
4	Benzoic acid (1%)	<1
5	Benzoic acid (1%)/Na_2CO_3 (2.5%)	99
6	Benzyl alcohol (5%)	98

[a] Rh:Cy_3P:nitrile:H_2O = 1:2:100:2000; [Rh] = 7.4×10^{-3} M. [b] Yield of isolated purified product.

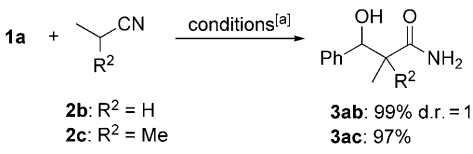
Other examples of this transformation are listed in Table 2, which illustrate the broad applicability of the reaction (see the footnote [a] of Table 2) with a range of aldehydes. There are several characteristic features in each of the reaction steps: (1) The use of a polar solvent, such as dimethyl sulfoxide, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, or 1,3-dimethyl-2-imidazolidinone (DMI), in place of *tert*-butanol gave a faster reaction rate of aldolization;[8h] however, the second hydration step was barely detectable when isopropanol and water (**1a**:H_2O = 1:40) were added to the initial solvent (e.g., dimethyl sulfoxide), whereby a mixed solvent system (Rh: 5.8×10^{-3} M) was prepared for the second step. (2) Of the alcoholic solvents tested in this study, the first and second steps of the reaction were best performed in *tert*-butanol and isopropanol, respectively. In fact, if the general reaction conditions were followed with the exception of *tert*-butanol or isopropanol being used in the second step or in the first step, respectively, yields of **3aa** decreased. (3) Na_2CO_3 was the most effective alkaline metal carbonate (amongst Li_2CO_3, K_2CO_3, and Cs_2CO_3) for the hydration step, to obtain maximum conversion. (4) When $[Rh(OMe)(cod)]_2$ was replaced by $[Rh(OH)(cod)]_2$, K_2CO_3 was the additive of choice for the aldolization (entry 2). However, apart from entry 9, none of the reaction conditions using $[Rh(OH)(cod)]_2$ gave as good an overall yield as the general reaction conditions using $[Rh(OMe)(cod)]_2$. (5) Aliphatic aldehydes were well suited for the catalysis, because significant self-condensation was not observed (entries 11 and 13). Indeed, the aldolization step in the absence of an alkaline carbonate, performed under more neutral pH, gave a better result for the valeraldehyde transformation (entry 11 vs 12). A retro-aldol reaction was nonobservable or negligible in all runs (Table 2). The $CONH_2$ groups, having rather acidic hydrogen atoms, did not prevent the hydration from taking place. These observations suggest that more neutral pH conditions are advantageous for generating the desired products.

Table 2. Catalytic aldolization of **2a** with various aldehydes **1** and subsequent hydration of **4** in a one-pot operation.[a]

Entry	Aldehyde		**3** [%][b]	**4** [%][c]
1	PhCHO (**1a**)		96	<1
2[d]	**1a**		92	7
3	*o*-$MeOC_6H_4CHO$ (**1b**)		96	<1
4	*p*-ClC_6H_4CHO (**1c**)		94	<1
5[e]	β-NaphCHO (**1d**)		77	<1
6	*p*-$CH_3C_6H_4CHO$ (**1e**)		70	2
7[e,f]		(**1f**)	84	6
8		(**1g**)	65	3
9[d–f]	**1g**		87	<1
10[e]		(**1h**)	>99	<1
11	$CH_3(CH_2)_3CHO$ (**1i**)		70	13
12[d]	**1i**		38	10
13	*c*HexCHO (**1j**)		94	<1
14[e,f]	*t*BuCHO (**1k**)		91	<1

[a] Unless otherwise specified, a molar ratio of **1**:**2a** = 1:38 was used. The first step: $[Rh(OMe)(cod)]_2$:Cy_3P = 0.02:0.08; *t*BuOH, 25 °C, 24 h (Rh: 6.5×10^{-3}–1.0×10^{-2} M); the second step: H_2O:Na_2CO_3 = 40:0.1, *i*PrOH, 25 °C, 24–48 h (Rh: 2.3×10^{-2} M). [b] Yield of isolated purified **3**. [c] Yield of isolated purified **4**. [d] The first step: $[Rh(OH)(cod)]_2$:Cy_3P:K_2CO_3 = 0.02:0.08:0.1, *t*BuOH, 25 °C, 24 h (Rh: 1.0×10^{-2} M); the second step: H_2O (**1**:H_2O = 1:40), *i*PrOH, 25 °C, 24–48 h (Rh: 2.3×10^{-2} M). [e] Hydration step: **1**:H_2O = 1:80, 48 h. [f] Aldolization step: **1**:**2** = 1:77.

A range of α-substituted nitriles are potentially capable of undergoing the reaction sequence of aldolization/hydration. Indeed, when a similar reaction sequence was applied to nitriles **2b** and **2c**, which have the elongated or branched carbon chain, the corresponding carboxamides **3ab** and **3ac** were obtained almost quantitatively (Scheme 2).



Scheme 2. Nitrile Aldolization/hydration using other nitriles. [a] Reaction conditions were the same as described in footnotes [e] and [f] of Table 2.

In summary, we have developed a straightforward method to provide β-hydroxy carboxamides from aldehydes, nitriles, and water, which is atom-economical and redox neutral. The present reaction is essentially the first example of the catalytic aldol reaction of "unactivated" carboxamides ($CONH_2$), although related reactions of carboxamides activated by auxiliary elements or groups do exist.[12] No protection/activation/deprotection sequence is needed and thus the formation of a stoichiometric amount of salt waste is obviated.

Experimental Section

A 1.0 M toluene solution of Cy_3P (40 μL, 0.04 mmol) at 25 °C was added to a solution of $[Rh(OMe)(cod)]_2$ (4.8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred at this temperature for 15 min. After any volatile compounds were evaporated in vacuo (1–3 Torr), argon-filled *t*BuOH (1 mL) was added to the resulting slurry, followed by sequential addition of nitrile **2** (19–38 mmol) and aldehyde **1** (0.5 mmol). The reaction mixture was stirred at 25 °C for 24 h. After any volatile compounds were evaporated in vacuo (1–3 Torr), argon-filled *i*PrOH (0.5 mL) was added to the resulting slurry, followed by sequential addition of Na_2CO_3 (5.3 mg, 0.05 mmol) and argon-filled H_2O (720 μL, 40 mmol). The resulting mixture was stirred at 25 °C for 24–48 h. The mixture was diluted with MeOH (10–20 mL) to dissolve all the precipitate, filtered through a short pad of silica gel. The filtrate was concentrated under a reduced pressure using an evaporator. The crude product was washed with hexane and then purified by chromatography on silica gel, eluting with EtOAc/MeOH (10:1 – 1:1; v/v), to provide the desired product **3**.

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Keywords: aldol reaction · catalysis · hydration · nitriles · rhodium

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[11] See Table 1, entry 1 and the Supporting Information (SI) for details. When we used a reduced amount of nitrile (e.g., **1a**:**2a** = 1:3 or 1:2), the reaction rate was considerably slower in *t*BuOH and not practically useful. See also Ref. [8h].

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