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# NEW SYNTHETIC ROUTE TO *N*-ACYL-α-AMINO ACIDS VIA AMIDOCARBONYLATION BY MEANS OF HOMOGENEOUS BINARY CATALYST SYSTEMS *

IWAO OJIMA*,

*Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794 (U.S.A.)*

KENJI HIRAI, MAKOTO FUJITA and TAKAMASA FUCHIKAMI

*Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229 (Japan)*

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## Summary

New catalytic processes which lead to the formation of *N*-acyl-α-amino acids promoted by homogeneous binary systems are described: (a) the isomerization-amidocarbonylation of allyllic alcohols catalyzed by transition metal binary systems, e.g., Co-Rh, Co-Pd, Co-Fe, giving various aliphatic *N*-acyl-α-amino acids; (b) the isomerization-amidocarbonylation of oxiranes catalyzed by cobalt-Lewis acid systems giving *N*-acyl-α-amino acids: The process is extremely effective for the synthesis of *N*-acetylphenylalanine from styrene oxide and (c) the hydroformylation-amidocarbonylation of trifluoropropene catalyzed by cobalt-rhodium binary system giving *N*-acetyltrifluorovaline in excellent regioselectivity and yield. Possible mechanisms for these new processes are discussed.

## Introduction

One of the most challenging problems in catalysis is to create effective multi-catalyst systems which could promote sequential multi-step reactions cooperatively giving useful chemical substances from simple starting materials. As a basic approach to this challenging goal, we have been interested in looking at the efficiency of homogeneous binary systems which can sequentially promote catalytic processes including carbonylation as one of the unit reactions.

Transition metal complex catalyzed carbonylations of olefins, acetylenes, halides, alcohols, amines, nitro compounds, etc., have been extensively studied for a long

* This paper is dedicated to Professor Jack Halpern on the occasion of his 60th birthday and for his outstanding research and teaching in the field of organometallic, inorganic chemistry and catalysis.

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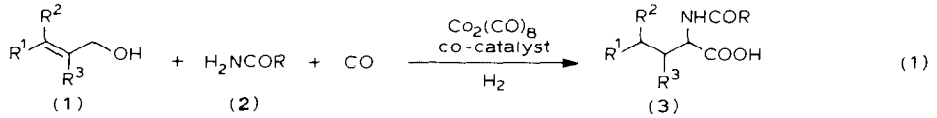
time, and some of these reactions have been established as commercial processes [1,2]. Nevertheless, there are still strong demands for developing efficient catalytic processes for the utilization of carbon monoxide in both industrial and laboratory organic syntheses. Among a variety of catalytic carbonylations, we have focused on the exploitation of the cobalt-catalyzed amidocarbonylation of aldehydes which leads to the formation of *N*-acyl-α-amino acids. This reaction was found in 1971 and developed by Ajinomoto's research group [3], and later reinvestigated precisely by Pino et al. in 1979 with regard to the synthetic potential and the reaction mechanism [4].

On the other hand, the isomerization of allylic alcohols and oxiranes have been shown to be effected by transition metal catalysts, Lewis acids and etc. [5,6]. Accordingly, if the isomerization of allylic alcohols or oxiranes to the corresponding aldehydes were effectively combined with the amidocarbonylation, we could obtain *N*-acyl-α-amino acids, directly from allylic alcohols or oxiranes. Besides the combination of isomerization and amidocarbonylation, that of hydroformylation and amidocarbonylation would also serve as convenient method for the synthesis of *N*-acyl-α-amino acids directly from olefins provided that the hydroformylation of olefins proceeds in highly regioselective manner. We wish to describe here our successful application of homogeneous binary catalyst systems to these isomerization-amidocarbonylation and hydroformylation-amidocarbonylation processes.

## Results and discussion

*Amidocarbonylation of allylic alcohols*

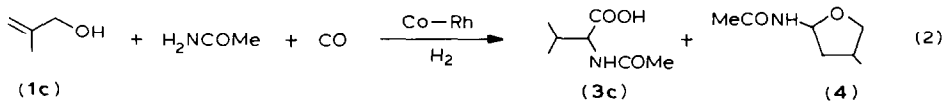
It has been shown that the isomerization of allylic alcohols to the corresponding aldehydes can be effected by various transition metal catalysts such as $Fe(CO)_5$, $RhCl_3 \cdot 3H_2O$, $HRh(CO)(PPh_3)_3$, $HRuCl(PPh_3)_3$, $HRu(OAc)(PPh_3)_3$, $(C_2H_4)$-$Ni[P(o\text{-Tol-}O)_3]_3$, and $[(COD)Ir(PPh_2Me)_2]PF_6$ [5]. We employed $RhCl(PPh_3)_3$, $HRh(CO)(PPh_3)_3$, $RuCl_2(PPh_3)_3$, $HRuCl(CO)(PPh_3)_3$, $Fe_2(CO)_9$ and $PdCl_2(PPh_3)_2$ as the co-catalysts for $Co_2(CO)_8$, and looked at the catalytic activities of these binary systems for the amidocarbonylation of allylic alcohols [7]. Results are summarized in Table 1.




(1)

As Table 1 shows, the reaction proceeds to some extent without a co-catalyst since $HCo(CO)_4$, which should be generated under the reaction conditions, can act as an isomerization catalyst as well as the catalyst for amidocarbonylation. However, it is apparent that the addition of $HRh(CO)(PPh_3)_3$, $Fe_2(CO)_9$ or $PdCl_2(PPh_3)_2$ significantly promote the reaction. Other co-catalysts such as $RuCl_2(PPh_3)_3$ and $HRuCl(PPh_3)_3$ did not bring about good results. As for the solvent, dioxane turned out to be the best as far as we examined. The present process seems to be sensitive to the bulkiness of the aldehyde generated in situ. Thus, the reaction of methallyl alcohol with acetamide in dioxane gave *N*-acetylvaline (**3c**) in rather low yield (25–49%) together with 2-acetamido-4-methyltetrahydrofuran (**4**).

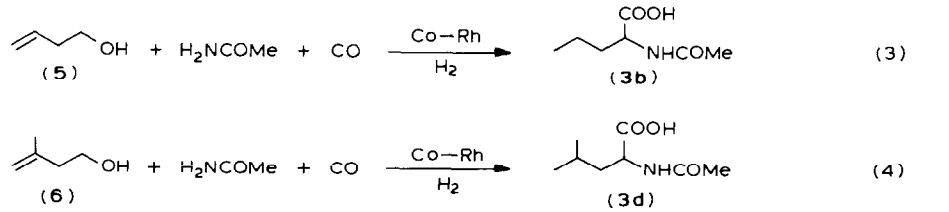
It is noteworthy that 3-methyl-2-buten-1-ol, which is known to be very difficult to



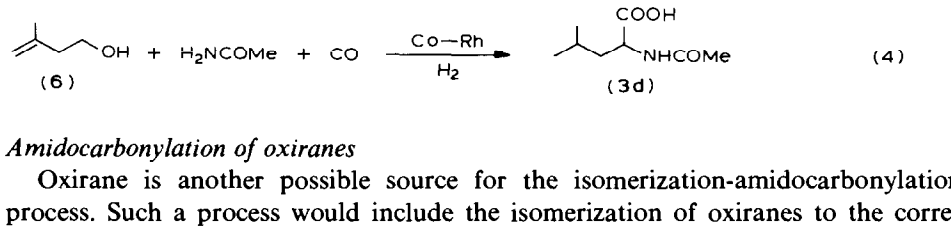

(1c) (3c) (4) (2)

isomerize to 3-methylbutanal [5g], reacts nicely to give *N*-acetylleucine (**3d**) in good yield. The result clearly indicates that the aldehyde supposed to be generated in situ by the isomerization of the allylic alcohol is immediately involved into the successive fast amidocarbonylation to give the *N*-acyl-α-amino acid.

It has also turned out that not only allylic alcohols but also homoallylic alcohols can be employed as substrates. For example, when 3-buten-1-ol and 3-methyl-3-buten-1-ol were used as substrates under similar conditions, *N*-acetylnorvaline (**3b**) and *N*-acetylleucine (**3d**) were obtained in 55 and 34% yields, respectively.




(5) (3b) (3)

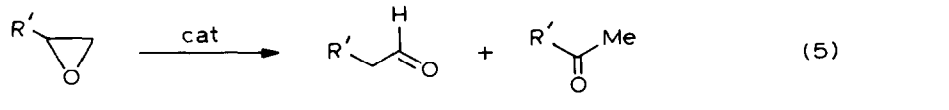



(6) (3d) (4)

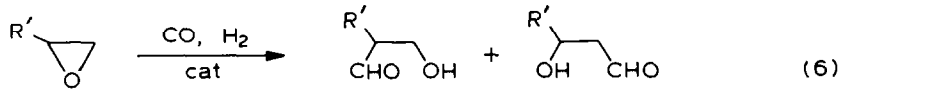
*Amidocarbonylation of oxiranes*

Oxirane is another possible source for the isomerization-amidocarbonylation process. Such a process would include the isomerization of oxiranes to the corresponding aldehydes, which should be immediately incorporated to the subsequent amidocarbonylation. One of the possible side reactions in the isomerization process is conversion of oxiranes to the corresponding ketones (eq. 5). Another possible side reaction is the hydroformylation of oxiranes catalyzed by cobalt carbonyl, which is known to give β-hydroxyaldehydes [8] (eq. 6).

Oligomerizations of oxiranes and the generated aldehydes are also possible. Accordingly, it does not seem to be an easy task to combine and promote the desired process effectively.




(5)




(6)

In fact, when oxiranes such as propene oxide, 1-butene oxide, phenylglycidyl ether and styrene oxide were submitted to amidocarbonylation with acetamide catalyzed only by dicobalt octacarbonyl, $Co_2(CO)_8$, the desired *N*-acyl-α-amino acids were found to be produced in very low yields except *N*-acetylphenylalanine (**3e**), which was obtained in 39% from styrene oxide. Therefore, we searched for good co-catalysts for $Co_2(CO)_8$, which could promote the desired process. Eventually, it was found that (i) transition metal complexes such as $RhCl(PPh_3)_3$, $RuCl_2(PPh_3)_3$ and $Fe_2(CO)_9$ were ineffective although some of these complexes were shown to be quite effective for the amidocarbonylation of allylic alcohols (vide supra), and (ii)

*(Continued on p. 208)*

TABLE 1

SYNTHESIS OF *N*-ACYL-α-AMINO ACIDS BY THE AMIDOCARBONYLATION OF ALLYLIC ALCOHOLS [a]

| Entry | *N*-Acyl-α-amino acid | | | | | $Co_2(CO)_8$ (mol%) | Co-catalyst | (mol%) | **1**/**2** | Solvent | Time (h) | Isolated yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^1$ | $R^2$ | $R^3$ | R | | | | | | | |
| 1 | **3a** | H | H | H | Me | 2.0 | $HRh(CO)(PPh_3)_3$ | 0.10 | 0.5 | Dioxane | 12 | 63 |
| 2 | | | | | | 5.0 | $Fe_2(CO)_9$ | 5.00 | 1.0 | Dioxane | 24 | 58 |
| 3 | | | | | | 3.3 | $RuCl_2(PPh_3)_3$ | 0.33 | 1.0 | Dioxane | 12 | 44 |
| 4 | **3a'** | H | H | H | Ph | 3.3 | $RhCl(PPh_3)_3$ | 0.33 | 1.0 | Dioxane | 12 | 60 |
| 5 | **3b** | Me | H | H | Me | 3.3 | $Fe_2(CO)_9$ | 6.60 | 1.0 | Dioxane | 18 | 75 |
| 6 | | | | | | 1.7 | $HRh(CO)(PPh_3)_3$ | 0.17 | 1.0 | Dioxane | 18 | 70 |
| 7 | | | | | | 1.7 | $HRh(CO)(PPh_3)_3$ | 0.17 | 1.0 | AcOEt | 18 | 49 |
| 8 | | | | | | 1.7 | $HRh(CO)(PPh_3)_3$ | 0.17 | 1.0 | Benzene | 18 | 34 |
| 9 | | | | | | 1.7 | $HRh(CO)(PPh_3)_3$ | 0.17 | 1.0 | THF | 18 | 48 |
| 10 | | | | | | 1.7 | $HRh(CO)(PPh_3)_3$ | 0.17 | 1.0 | Acetone | 18 | 34 |
| 11 | | | | | | 3.3 | $PdCl_2(PPh_3)_2$ | 0.33 | 1.0 | Dioxane | 18 | 77 |
| 12 | | | | | | 3.3 | $HRuCl(CO)(PPh_3)_3$ | 0.33 | 1.0 | Dioxane | 18 | 41 |
| 13 | | | | | | 3.3 | – | | | Dioxane | 18 | 46 |
| 14 | **3b'** | Me | H | H | Ph | 1.7 | $HRh(CO)(PPh_3)_3$ | 0.17 | 0.5 | Dioxane | 18 | 36 |
| 15 | **3c** | H | H | Me | Me | 1.6 | $HRh(CO)(PPh_3)_3$ | 0.10 | 0.5 | Dioxane | 17 | 49 |
| 16 | **3d** | Me | Me | H | Me | 1.7 | $HRh(CO)(PPh_3)_3$ | 0.20 | 1.0 | Dioxane | 12 | 62 |
| 17 | **3d'** | Me | Me | H | Ph | 2.0 | $HRh(CO)(PPh_3)_3$ | 0.20 | 0.5 | Dioxane | 12 | 66 |

[a] All reactions were run with 30–50 mmol of allylic alcohol (**1**) and 30–100 mmol of amide (**2**) in 50–100 ml of solvent at 100 °C and 50 atm of carbon monoxide and 50 atm of hydrogen (initial pressures at 25 °C).

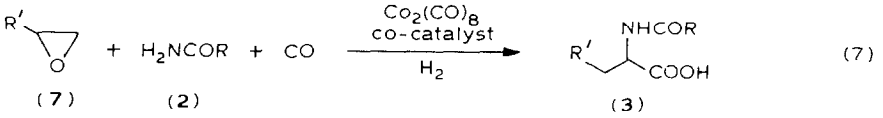
TABLE 2

SYNTHESIS OF *N*-ACYL-α-AMINO ACIDS BY AMIDOCARBONYLATION OF OXIRANES [a]

| Entry | *N*-Acyl-α-amino acid | | | $Co_2(CO)_8$ (mol%) | Lewis acid | (mol%) | 7/2 | $CO/H_2$ [b] (atm) | Temp. (°C) | Time (h) | Isolated yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | R′ | R | | | | | | | | |
| 1 | **3e** | Ph | Me | 3.3 | $Ti(O^iPr)_4$ | 3.3 | 1.0 | 80/20 | 110 | 16 | 92 |
| 2 | | | | 5.0 | $TI(O^iPr)_4$ | 5.0 | 1.5 | 80/50 | 120 | 16 | 95 [c] |
| 3 | | | | 3.3 | $Ti(O^iPr)_4$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 72 [d] |
| 4 | | | | 3.3 | $Al(O^iPr)_3$ | 3.3 | 1.5 | 50/50 | 110 | 12 | 72 [c] |
| 5 | | | | 3.3 | $Al(acac)_3$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 20 |
| 6 | | | | 3.3 | $ZnCl_2$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 72 |
| 7 | | | | 3.3 | $ZnI_2$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 40 |
| 8 | | | | 3.3 | $Zn(acac)_2$ | 3.3 | 1.0 | 50/50 | 110 | 17 | 0 |
| 9 | | | | 3.3 | $SnCl_2$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 0 |
| 10 | | | | 20.0 | $Ti(O^iPr)_4$ | 20.0 | 1.0 | 100/50 | 120 | 2 | 63 |
| 11 | | | | 20.0 | – | | 1.0 | 100/50 | 120 | 2 | 39 |
| 12 | | | | 3.3 | $Ti(O^iPr)_4$ | 3.3 | 1.0 | 100/20 | 120 | 2 | 89 [e] |
| 13 | **3e′** | Ph | Ph | 3.3 | $Ti(O^iPr)_4$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 67 |
| 14 | **3a** | Me | Me | 3.3 | $Ti(O^iPr)_4$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 18 |
| 15 | **3b** | Et | Me | 3.3 | $Ti(O^iPr)_4$ | 3.3 | 1.0 | 50/50 | 110 | 12 | 27 |
| 16 | **3f** | $PhOCH_2$ | Me | 5.0 | $Ti(O^iPr)_4$ | 5.0 | 1.0 | 50/50 | 120 | 16 | 36 [c,f] |

[a] All reactions were run in a stainless steel autoclave and tetrahydrofuran (15 ml/10 mmol oxirane) was used as solvent unless otherwise noted. [b] Initial pressure at ambient temperature. [c] Based on acetamide used. [d] 1,4-Dioxane was used as solvent. [e] Catalysts were added to the mixture at 120 °C. [f] A small amount of β-hydroxy-γ-phenoxybutanoic acid was formed as by-product in this case.

some Lewis acids promoted the desired process remarkably as shown in Table 2. Titanium tetraisopropoxide, $Ti(O^iPr)_4$, turned out to be the best co-catalyst that we examined. Other Lewis acids such as $Al(O^iPr)_3$ and $ZnCl_2$ were also effective, but $Al(acac)_3$ and $ZnI_2$ suppressed the desired process, and the process was completely inhibited by the addition of $Zn(acac)_2$ or $SnCl_2$.




(7) (2) (3) (7)

The addition of the binary catalyst to the preheated mixture of oxirane and amide in a solvent was also found to accelerate considerably the reaction (Table 2, entry 12). The procedure may exclude the hydroformylation of oxirane which could take place at lower temperatures [8].

From a synthetic point of view, the present cobalt-Lewis acid binary system is particularly effective for the synthesis of *N*-acetylphenylalanine (**3e**) from styrene oxide, but for other oxiranes considerable improvement is necessary. The lower yields in the syntheses of other *N*-acyl-α-amino acids would be ascribed to the undesired isomerization of oxiranes to ketones. Accordingly, it is challenging to find excellent catalyst systems which can promote the selective isomerization of oxiranes to the corresponding aldehydes without disturbing the subsequent amidocarbonylation.

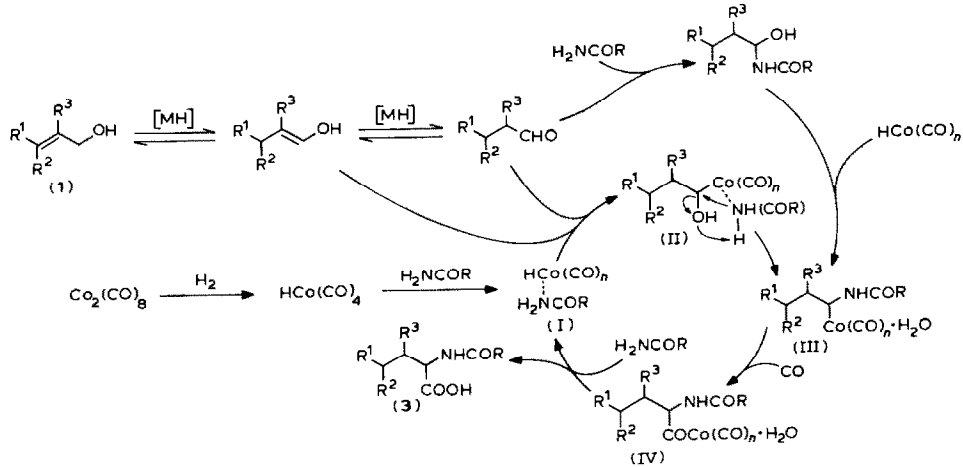
*On the mechanism of the amidocarbonylation of allylic alcohols and oxiranes*

Possible mechanisms which can accomodate the observed results in the amidocarbonylation of allylic alcohol are depicted in Scheme 1.

Since the present reaction is carried out in the presence of both carbon monoxide and hydrogen, side reactions such as hydrogenation and hydroformylation can take place together with amidocarbonylation. Nevertheless, the yields of the obtained *N*-acylamino acids are good by the proper choice of co-catalysts as shown in Table 1. This means that the "aldehyde" generated in situ is effectively incorporated to the subsequent amidocarbonylation as expected. Since it is quite reasonable to assume that the isomerization of allylic alcohol includes addition-elimination of transition metal hydride, there should be two steps to generate the corresponding aldehyde. According to the proposed mechanisms of Wakamatsu's [9] and Pino's [4] groups, the first step of the amidocarbonylation of aldehyde is the formation of hemiamidal from the aldehyde and amide, which further reacts with $HCo(CO)_4$ which is supposed to be the active catalyst to give α-amidoalkylcobalt intermediate (III). Besides this, we can also take into account the possible coordination of amide to cobalt carbonyl and the possible addition of hydridocobalt species such as $HCo(CO)_n(H_2NCOR)$ (I) to aldehyde to form α-hydroxyalkylcobalt intermediate (II), which would be converted to the α-amidoalkylcobalt intermediate (III) by a nucleophilic substitution of α-hydroxy group by the amide group. Moreover, in the present reaction, the second step of the isomerization, i.e., the conversion of vinylic alcohol to aldehyde, could be effected by the hydridocobalt species (I), which should generate the α-hydroxyalkylcobalt intermediate (II) directly without the intermediacy of aldehyde. As mentioned above, the attempted isomerization of 3-methyl-2-buten-1-ol gave the desired 3-methylbutanal only in 16% yield even by using an

excellent isomerization catalyst, $[Ir(COD)(PPh_2Me_2)]PF_6$ [5g], while the amidocarbonylation of the same alcohol with benzamide catalyzed by $HRh(CO)(PPh_3)_3$-$Co_2(CO)_8$ system gave *N*-benzoylleucine (**3d'**) in 66% yield. The result strongly indicates the extremely well-organized incorporation of the allylic alcohol moiety into the amidocarbonylation. Accordingly, it is possible to assume that the first isomerization of allylic alcohol to vinylic alcohol is effectively promoted by the co-catalysts such as $HRh(CO)(PPh_3)_3$, $RhCl(PPh_3)_3$, $Fe_2(CO)_9$ and $PdCl_2(PPh_3)_2$ and the vinylic alcohol thus generated is immediately incorporated into the cobalt-catalyzed amidocarbonylation via the intermediates, II and III, as shown in Scheme 1.

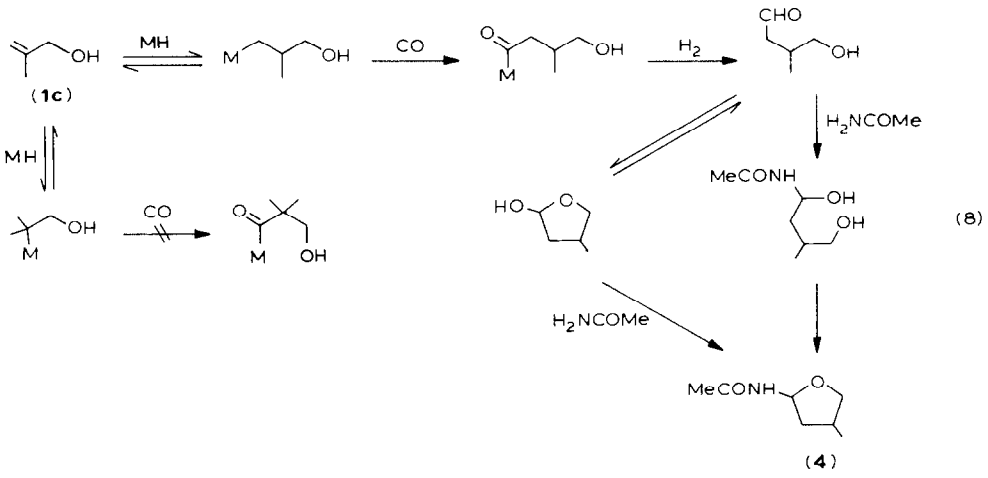
SCHEME 1. Possible mechanism for the amidocarbonylation of allylic alcohols.



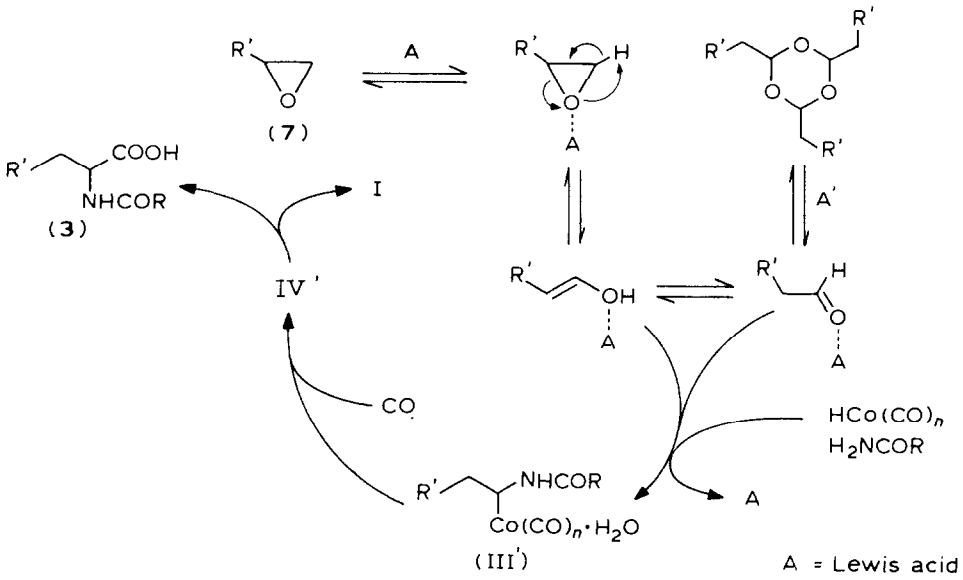

When methallyl alcohol was employed as substrate, 2-acetamido-4-methyltetrahydrofuran (**4**) was isolated as side reaction product besides *N*-acetylvaline (**3c**) (vide supra). The formation of 2-acetamido-4-methyltetrahydrofuran (**4**) is best explained by considering the hydroformylation of methallyl alcohol giving 4-hydroxy-3-methylbutanal, which can proceed through the carbon monoxide insertion into the $\alpha$-hydroxyalkylmetal intermediate which is the common intermediate for isomerization. The possible formation of 3-hydroxy-2,2-dimethylpropanal would be hampered by severe steric hindrance in the carbon monoxide insertion step. 4-Hydroxy-3-methylbutanal thus formed can be converted to 4-methyl-2-acetamidotetrahydrofuran (**4**) either through lactonization and amidation or through hemiamidal formation and cyclization (eq. 8).

As for the amidocarbonylation of oxiranes, we can depict a mechanism similar to that for allylic alcohols, viz., oxiranes would be isomerized to aldehyde or ketone and only the aldehyde is incorporated into the amidocarbonylation to give *N*-acylamino acid through the intermediates III' and IV' where substituents are the only difference from III and IV in Scheme 1. For the role of the Lewis acid, especially $Ti(O^iPr)_4$, it would promote the isomerization of oxirane to aldehyde as well as contribute to the suppression or inhibition of the oligomerization of either oxiranes or aldehydes in situ generated. A proposed mechanism is shown in Scheme 2.

Although it is reasonable to assume that the Lewis acid and the cobalt catalyst




SCHEME 2. Possible mechanism for the amidocarbonylation of oxiranes.



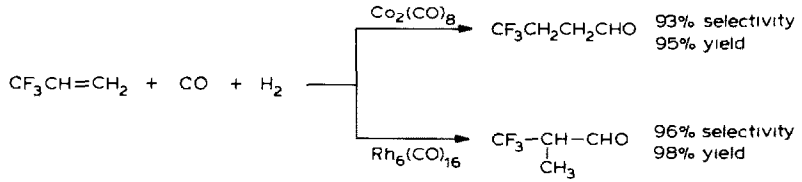

promote the reaction cooperatively but in independent steps, a possible formation of an active catalyst consisting of cobalt carbonyl and the Lewis acid cannot be excluded at this stage since the catalytic activities of the binary systems vary dramatically as exemplified in Table 2. Detailed understanding must wait further investigation.

*Hydroformylation-amidocarbonylation of trifluoropropene (TFP)*

Although the possible synthesis of *N*-acyl-α-amino acids via cobalt-catalyzed amidocarbonylation of olefins was already suggested by Wakamatsu in his review in 1974 [9], it was only recent that the process was actually examined by French researchers and appeared as patent [10]. In the patent, Stern et al. described that the

process was useful for the production of C(9)–C(31) straight chain *N*-acyl-α-amino acids although the process gave a mixture of straight chain and branched isomers. It was also indicated that straight chain selectivity was considerably higher than that observed in the simple hydroformylation of the same olefins.

We recently found [11] that unusually high regioselectivities were achieved for producing both straight chain and branched aldehydes in the hydroformylation of trifluoropropene (TFP) by using cobalt carbonyl and rhodium carbonyl as catalysts, respectively, in sharp contrast to the hydroformylation of normal olefins (eq. 9).




(9)

Accordingly, if these processes were successfully combined with the cobalt-catalyzed amidocarbonylation, both straight chain and branched *N*-acyl-α-amino acids could be obtained with excellent regioselectivity directly from TFP. In fact, we have succeeded in the highly regioselective synthesis of *N*-acetyltrifluorovaline (**10**) and *N*-acetyltrifluoronorvaline (**11**) in high yields by using $Co_2(CO)_8$-$Rh_6(CO)_{16}$ and $Co_2(CO)_8$ as catalysts, respectively, for the hydroformylation-amidocarbonylation of TFP (eq. 10).


(10)

| Catalyst | Total yield (%) | Product ratio (%) | |
|---|---|---|---|
| | | **10** | **11** |
| $Co_2(CO)_8$ (5 mol%) | 83 | 4 | 96 |
| $Co_2(CO)_8$ (5 mol%) + $Rh_6(CO)_{16}$ (0.1 mol%) | 87 | 94 | 6 |

As for the mechanism of the process catalyzed by Co-Rh binary system, the rhodium-catalyzed hydroformylation of TFP takes place exclusively in the first step to give the branched aldehyde highly selectively, which is incorporated to the subsequent cobalt-catalyzed amidocarbonylation as expected.

As the rhodium-catalyzed hydroformylation of TFP was found to proceed with the substrate/rhodium (metal) ratio of 10,000-50,000 [12], the amount of $Rh_6(CO)_{16}$ which is necessary to promote the desired process could be reduced to 1/500–1/100 of $Co_2(CO)_8$ used.

In conclusion, it is demonstrated that homogeneous binary catalyst systems are effective for the isomerization-amidocarbonylation and hydroformylation-amidocarbonylation processes, which give various *N*-acyl-α-amino acids directly from allylic alcohols, oxiranes and a fluorolefin, and some of the processes are quite efficient and practical. The present approach can be applicable to a variety of multi-step catalytic processes and may open a new aspect of homogeneous catalysis.

## Experimental

Melting points are uncorrected. $^1H$ NMR spectra were recorded on Varian

EM-360, EM-390, XL-100-15A or Nicolet NT-300 spectrometer, with tetramethylsilane as the internal standard. $^{19}F$ NMR spectra were measured with Hitachi R-20B or Varian XL-100-15A spectrometer, with fluorotrichloromethane as the internal standard. Chemical shifts ($\delta$), in ppm from the internal standard, are given as positive values for downfield shifts in all cases. IR spectra were recorded on a Jasco A-202 spectrometer by using samples as neat liquids or in KBr disks.

$Co_2(CO)_8$, $Rh_6(CO)_{16}$ and $Fe_2(CO)_9$ were purchased form Strem Chemicals, Inc. $Ti(O^iPr)_4$, $Al(O^iPr)_3$, $Al(acac)_3$, $Zn(acac)_2$, $ZnCl_2$, $ZnI_2$ and $SnCl_2$ were commercially available from Aldrich Chemical Co. and used as purchased. $RhCl(PPh_3)_3$ [13], $HRh(CO)(PPh_3)_3$ [14], $PdCl_2(PPh_3)_2$ [15], $RuCl_2(PPh_3)_3$ [16], $HRuCl(CO)(PPh_3)_3$ [17] were prepared by literature methods. 3,3,3-Trifluoropropene was commercially available from Japan Halon Co. and PCR Research Chemicals, Inc.

*Amidocarbonylation of allylic alcohols*

Typical procedure is described for the reaction of crotyl alcohol with acetamide and carbon monoxide catalyzed by $Co_2(CO)_8$ and $HRh(CO)(PPh_3)_3$.

In a 100 ml stainless steel autoclave was placed a mixture of crotyl alcohol (50 mmol) and acetamide (100 mmol) in dioxane (50 ml), and to this mixture were added $Co_2(CO)_8$ (1.7 mmol) and $HRh(CO)(PPh_3)_3$ (0.17 mmol). Then, a 1/1 mixture of carbon monoxide and hydrogen was introduced to the autoclave (initial pressure: 100 atm at 25 °C). The autoclave was heated up to 110 °C, at which temperature the pressure was 100 atm, and the mixture was stirred for 17 h at this temperature (usually the pressure decreased to 80 atm). The autoclave was then cooled to ambient temperature and carbon monoxide and hydrogen were carefully purged out. After the solvent was removed under reduced pressure, the reaction mixture was treated with 10% aqueous sodium carbonate and extracted with ethyl acetate to remove unreacted acetamide and other side product(s). The aqueous solution was then acidified with phosphoric acid and extracted with ethyl acetate. Removal of solvent in vacuo from the extract gave 5.60 g of *N*-acetylnorvaline (**3b**) as a colorless solid (70% based on crotyl alcohol).

**3b**: m.p. 109–111 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 0.93 (t, *J* 7 Hz, 3H), 1.20–1.80 (m, 4H), 2.05 (s, 3H), 4.38 (m, 1H), 6.77 (d, *J* 8 Hz, 1H) and 8.91 (bs, 1H). IR(KBr disk): 3350 ($\nu$(NH)), 1720, 1600 ($\nu$(C=O)) and 1540 ($\delta$(NH)) $cm^{-1}$.

In a similar manner, *N*-acetylhomoalanine (**3a**), *N*-acetylvaline (**3c**), *N*-acetylleucine (**3d**), *N*-benzoylhomoalanine (**3a'**), *N*-benzoylnorvaline (**3b'**) and *N*-benzoylleucine (**3d'**) were obtained (see Table 1). The structures of these *N*-acyl-$\alpha$-amino acids were confirmed based on the comparison of their NMR and IR spectral data and melting points with literature values.

In the reaction of methallyl alcohol with acetamide and carbon monoxide, 2-acetamido-4-methyltetrahydrofuran (**4**) was isolated from reaction mixture by column chromatography on silica gel as a side product in 0–30% yield: The yield depended on co-catalyst and reaction conditions, e.g., the slower heating up increased the yield of **4**.

**4**: Colorless liquid. $^1H$ NMR ($CDCl_3$): $\delta$ 1.08 (d, *J* 7 Hz, 3H), 1.97 (s, 3H), 1.67–2.63 (m, 3H), 3.33 (m, 1H), 3.98 (m, 1H), 5.70 (m, 1H) and 6.80 (bs, 1H). IR (neat): 3300 ($\nu$(NH)), 1665 ($\nu$(C=O)) and 1565 ($\delta$(NH)) $cm^{-1}$. (Found: C, 54.50; H, 9.15; N, 8.97. $C_7H_{13}NO_2 \cdot 3/5H_2O$ calcd.: C, 54.60; H, 8.90; N, 9.10%).

*Amidocarbonylation of oxiranes*

The reaction of styrene oxide with acetamide and carbon monoxide catalyzed by $Co_2(CO)_8$ and $Ti(O^iPr)_4$ is described as a typical example.

A mixture of styrene oxide (2.40 g, 20 mmol), acetamide (1.18 g, 20 mmol), $Co_2(CO)_8$ (227 mg, 0.67 mmol) and $Ti(O^iPr)_4$ (186 mg, 0.67 mmol) in 30 ml of tetrahydrofuran was transferred into a 50 ml stainless steel autoclave. The autoclave was pressurized with carbon monoxide (80 atm) and hydrogen (20 atm), and then heated to 110 °C for 16 h with stirring. After cooling the autoclave to ambient temperature, the gasses were released carefully from the autoclave, and the reaction mixture was concentrated under reduced pressure. To the residue was added 5% aqueous sodium carbonate (100 ml) and the mixture was extracted with ethyl acetate to remove the unreacted starting materials and organic by-products. Then, the aqueous layer was acidified (ca. pH 1) with phosphoric acid (ca. 30 ml), extracted with ethyl acetate, dried over anhydrous magnesium sulfate and concentrated in vacuo to give *N*-acetylphenylalanine (**3e**) as colorless crystals (3.80 g, 92% yield).

**3e**: m.p. 148–152 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 1.92 (s, 3H), 3.10 (m, 2H), 4.81 (m, 1H), 6.28 (d, $J$ 8Hz, 1H), 7.20 (m, 5H) and 9.23 (s, 1H). IR (KBr disk): 3380 ($\nu$(NH)), 1712, 1615 ($\nu$(C=O)) and 1547 ($\delta$(NH)) $cm^{-1}$.

In a similar manner, *N*-benzoylphenylalanine (**3d'**), *N*-acetylhomoalanine (**3a**), *N*-acetylnorvaline (**3b**), *N*-acetyl-O-phenylhomoserine (**3f**) were obtained (see Table 2). The structures of these *N*-acyl-$\alpha$-amino acids were confirmed based on the comparison of their NMR and IR spectra and melting points with literature values.

*Hydroformylation-amidocarbonylation of 3,3,3-trifluoropropene (TFP)*

A 100 ml stainless steel autoclave fitted with a magnetic stirring bar was charged with acetamide (887 mg, 15.0 mmol), $Co_2(CO)_8$ (174 mg, 0.509 mmol), $Rh_6(CO)_{16}$ (11.3 mg, 0.0106 mmol) and dioxane (10 ml). The autoclave was cooled with dry ice-acetone and evacuated. Then, gaseous TFP (960 mg, 10 mmol) was introduced, and the autoclave was pressured with carbon monoxide (80 atm, 25 °C) and hydrogen (50 atm, 25 °C). The autoclave was heated to 120 °C and stirred for 10 h at this temperature. Then, the apparatus was rapidly cooled with ice-water, and the gasses were carefully purged out. To the reaction mixture was added 5% aqueous sodium carbonate and ethyl acetate (50 ml). Water layer was separated and organic layer was extracted with water (20 ml) and the water extract was combined with the water layer. The aqueous solution was acidified with phosphoric acid (5 ml) and extracted with ethyl acetate (40 ml × 4). The extract was dried over anhydrous magnesium sulfate in the presence of a small quantity of Norit, filtered and concentrated in vacuo to give *N*-acetyltrifluorovaline (**10**) (12.85 g, 87% yield) as pale yellow crystals. $^{19}F$ NMR analysis revealed that the obtained **10** contained 6% of *N*-acetyltrifluoronorvaline (**11**), and **10** was a mixture of two diastereomers (65/35). Pure sample of **10** was obtained by recrystallization from n-hexane/chloroform.

**10**: m.p. 75–90 °C (mixture of diastereomers). $^1H$ NMR ($CDCl_3$/DMSO-$d_6$): $\delta$ 1.16 (major) and 1.19 (minor) (d, $J$ 6.9 Hz, 3H), 1.99 (major) and 2.01 (minor) (s, 3H), 2.94 (m, 1H), 4.76 (d,d, $J$ 9.0, 5.0 Hz) (minor) and 4.99 (d,d, $J$ 9.6, 3.2 Hz) (major) (1H), 7.72 (d, $J$ 9.0 Hz) (minor) and 7.90 (d, $J$ 9.6 Hz) (major) (1H) and 9.70 (bs, 1H). $^{19}F$ NMR ($CDCl_3$): $\delta$ −78.8 (d, $J$ 9.6 Hz) (major diastereomer); $\delta$ −68.9 (d, $J$ 9.0 Hz) (minor diastereomer). IR (KBr disk): 3360 ($\nu$(NH)), 1735, 1625 ($\nu$(C=O)) and 1560 ($\delta$(NH)) $cm^{-1}$. (Found: C, 39.15; H, 4.89; N, 6.78. $C_7H_{10}F_3NO_3$

calcd.: C, 39.44; H, 4.73; N, 6.57%).

In a similar manner, *N*-acetyltrifluoronorvaline (**11**) was obtained by using $Co_2(CO)_8$ as sole catalyst. $^{19}F$ NMR analysis revelaed that the obtained **11** contained 4% of **10**. Pure sample of **11** was obtained by recrystallization from n-hexane/chloroform as pale yellow crystals.

**11**: m.p. 110–115 °C. $^1H$ NMR ($CDCl_3$/DMSO-$d_6$): $\delta$ 1.98 (s, 3H), 1.80–2.10 (m, 2H), 2.10–2.40 (m, 2H), 4.46 (d,d,d, *J* 7.8, 4.9, 7.8 Hz, 1H), 7.97 (d, *J* 7.8 Hz, 1H) and 8.10 (bs, 1H). $^{19}F$ NMR ($CDCl_3/CD_3OD$): $\delta$ −67.3 (t, *J* 9.7 Hz). IR (KBr disk): 3365 ($\nu$(NH)), 1726, 1610 ($\nu$(C=O)) and 1550 ($\delta$(NH)) $cm^{-1}$. (Found: C, 39.17; H, 4.82; N, 6.82. $C_7H_{10}F_3NO_3$ calcd.: C, 39.44; H, 4.73; N, 6.57%).

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