Amidocarbonylation of Aldehydes Utilizing Cobalt Oxide-supported Gold Nanoparticles as a Heterogeneous Catalyst

Akiyuki Hamasaki,[1] Xiaohao Liu,[1,2] and Makoto Tokunaga*[1,2]
[1]*Department of Chemistry, Graduate School of Sciences, Kyushu University,*
6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581
[2]*JST (Japan Science and Technology Cooperation) CREST*

(Received September 8, 2008; CL-080855; E-mail: mtok@chem.kyushu-univ.jp)

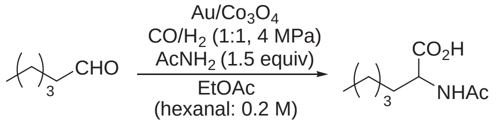
Cobalt oxide-supported gold-nanoparticles-catalyzed transformation of aldehydes and their equivalents to *N*-acyl-α-amino acids was achieved. The desired products were obtained in moderate to excellent yields under milder reaction conditions than previous reports employing octacarbonyldicobalt as a catalyst.

Amidocarbonylation reaction (Wakamatsu reaction) is an efficient method to obtain *N*-acyl-α-amino acid derivatives from aldehydes. It was first reported by Wakamatsu et al.[1] using octacarbonyldicobalt [$Co_2(CO)_8$] as a homogeneous catalyst. In contrast to classical methods of α-amino acid synthesis such as the Strecker reaction, amidocarbonylation can avoid the use of poisonous cyano materials and give the product in a single operation without subsequent hydrolysis. Additionally, from the point of atom-efficiency, this reaction has a superb advantage because H_2O is the only waste formed through the reaction. However, requirement of harsh reaction conditions, especially high pressure of more than 15 MPa, could be a troublesome aspect of $Co_2(CO)_8$-catalyzed amidocarbonylation.[2] One solution of this problem is to use stibine ligands for $Co_2(CO)_8$-catalyzed amidocarbonylation of olefins reported by Gómez et al.[3] Homogeneous palladium[4a,4b] and platinum[5] were found to catalyze the reaction under milder conditions than $Co(CO)_8$. Heterogeneous version of palladium catalyst has also been developed.[4c,4d] However, there are no heterogeneous cobalt-based catalyst for the reaction.

Recently we have explored a novel function of cobalt oxide-supported gold nanoparticles (Au/Co_3O_4) catalyst which effectively catalyzes hydroformylation of olefins.[6] The Co^0 active species is expected to be generated under syngas (CO/H_2) pressure (4 MPa) around 100 °C. As a showcase of the applications of these catalyst systems, amidocarbonylation utilizing Au/Co_3O_4 catalyst are demonstrated in this paper.

Amidocarbonylation of hexanal with acetamide was examined under several conditions (Table 1). When the reactions were conducted in less than 5 h (Entries 1 and 2), the yields were low to moderate even though calculated conversions of hexanal were 77% and 87% respectively, as a result of formation of bisamide product[7] along with the desired product. It was revealed that the by-product disappeared by elongation of reaction time to 20 h and yield of the amino acid was increased (Entry 3). Further longer reaction time (40 h) did not improve the yield any more (Entry 4). Reaction temperature was also a critical factor. The accepted temperature range seemed to be relatively narrow and the optimal one was between 80 to 100 °C (Entries 3 and 5–7).

Table 1. Optimization of reaction conditions



Entry[a]	Temp/°C	Time/h	Yield[b]/%
1	100	2	31
2	100	5	52
3	100	20	68
4	100	40	65
5	60	20	13
6	80	20	86 (64)
7	120	20	17
8[c]	100	20	44
9[d]	100	20	88
10[d]	80	20	84
11[e]	100	20	39[f]
12[g]	100	20	5
13[h]	100	20	0
14[i]	100	20	58

[a]All reactions were carried out in the presence of Au/Co_3O_4 [5 atom % Au/(Au+Co) and 5.7 atom % Co/substrate] except Entry 14. [b]GC yield. Isolated yield in parenthesis. [c]Gas pressure was 2 MPa. [d]CO/H_2 ratio was 3:1. [e]Hexanal/acetamide ratio was 2:1. [f]Based on acetamide. [g]Hexanal concentration was 1 M. [h]In the absence of the catalyst. [i]In the presence of 19 atom % Co/substrate.

Magnus and Slater reported $CO_2(CO)_8$-catalyzed amidocarbonylation of butyraldehyde requires higher temperature around 150 °C and insufficient temperature (90–100 °C) resulted in the exclusive formation of bisamide.[8] This means Au/Co_3O_4-catalyzed amidocarbonylation can be conducted under milder condition with respect to both syngas pressure and temperature than that of $Co_2(CO)_8$-catalyzed reaction. Although the highest yield was achieved at 80 °C, most of the reactions for optimization were carried out at 100 °C to clarify the effect of each factor. Under the same H_2 partial pressure ($P_{H_2} = 1$ MPa), higher CO pressure was preferable (Entries 8 and 9, $P_{CO} = 1$ MPa vs. 3 MPa). This result concurs with the previous report on P_{CO} dependence of reaction rates.[9] Existence of excess aldehyde (Entry 11) or a concentrated condition (Entry 12) lead to the formation of significant amounts of aldol product and resulted in decreasing yield. In the absence of the catalyst, no formation of amino acid, bisamide or aldol product were observed (Entry 13). Increasing the catalyst amount did not improve reaction efficiency (Entry 14).

Reactions employing various aldehydes and amides were performed to reveal the scope of the reaction (Table 2). The reactivities of aldehyde materials seemed to be quite affected by

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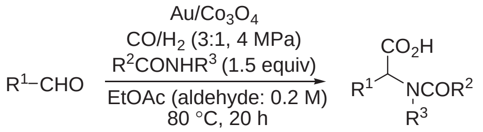
Table 2. Amidocarbonylation reactions of various aldehydes and amides

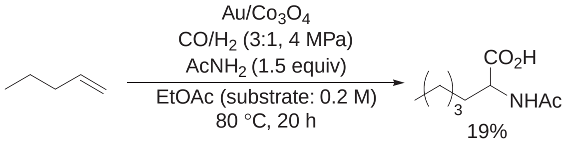


Entry	R^1	R^2	R^3	Yield[b]/%
1	Et	CH_3	H	53
2	*i*-Pr	CH_3	H	64
3	Heptyl	CH_3	H	81 (68)
4	Nonyl	CH_3	H	quant. (65)
5	*c*-Hexyl	CH_3	H	79 (51)
6	Pentyl	Ph	H	28 (16)
7[c]	Pentyl	CH_3	Et	32 (18)
8[d]	Ph	CH_3	H	0[e]

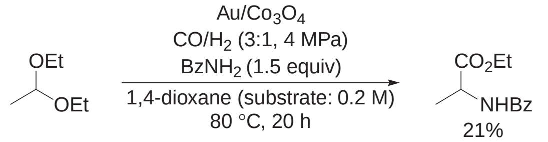
[a]All reactions were carried out in the presence of Au/Co_3O_4 (5 atom % Au/(Au+Co) and 5.7 atom % Co/substrate. [b]GC yield. Isolated yield in parenthesis. [c]3 equiv of amide was used. [d]CO/H_2 ratio was 1:1 and temperature was 100 °C. [e]65% of *N*-benzylacetamide was found.

alkyl chain lengths, generally higher aldehydes gave better yields (Entries 1–4). Low reactivity of isobutyraldehyde was not considered owing to steric hindrance of branched chain since cyclohexane carboaldehyde gave acceptable yield (Entry 5). Benzamide shows poor reactivity for this reaction (Entry 6). Increasing syngas pressure to 6 MPa did not improve the yield (25%). Secondary amide can be used for the reaction though the efficiency was slightly unsatisfactory (Entry 7). According to previous reports, aldehyde substrates lacking α-hydrogen are not suitable for $Co_2(CO)_8$-catalyzed amidocarbonylation.[8] It should be noted that treatment of benzaldehyde with acetamide in the presence of Au/Co_3O_4 catalyst gave *N*-benzylacetamide in 65% yield instead of desired α-amino acid (Entry 11). This result indicated that reductive amidation took precedence over amidocarbonylation and resembled the case of $Co_2(CO)_8$-catalyzed reaction.

Several compounds such as olefins and acetals are known to give aldehyde functionality under amidocarbonylation conditions and formed aldehydes are spontaneously transformed into α-amino acids.[9] Treatment of 1-pentene with 1.5 equiv of acetamide under Au/Co_3O_4-catalyzed amidocarbonylation conditions (CO/H_2 = 3:1, 4 MPa, 80 °C, 20 h) produced 2-acetamidoheptanoic acid in 19% yield along with a small amount of 2-acetamido-3-methylhexanoic acid (eq 1). Similarly, treatment of acetal or phenylacetaldehyde dimethylacetal with benzamide gave 21% *N*-benzoylalanine ethyl ester (eq 2) or 27% *N*-benzoylphenylalanine methyl ester respectively. Although some modifications of the reaction conditions are required to improve reaction efficiency, Au/Co_3O_4 also catalyzed one-pot transformation of aldehydes equivalents.



(1)



(2)

Recycle use of Au/Co_3O_4 catalyst was examined by simple decantation. While good recyclability was observed in the case of hydroformylation,[6] the catalyst activity was completely lost in the first recycle run. Izawa assumed the real active species of $Co_2(CO)_8$-catalyzed hydroformylation and amidocarbonylation were $HCo(CO)_3$ and strong acidic $HCo(CO)_4$, respectively.[9] Au/Co_3O_4-catalyzed amidocarbonylation in the presence of 1.5 equiv of pyridine under optimized conditions gave only 19% yield (cf. Table 1, Entry 6). This result indicates base-sensitive active species are also involved in the case of Au/Co_3O_4-catalyzed amidocarbonylation, and even weak basicity of amides could affect the recycle of Au/Co_3O_4.

TEM images of the catalyst before being used for amidocarbonylation are shown in Supporting Information.[10] It was clearly observed gold nanoparticles (ca. 2–4 nm diameter) were deposited on cobalt oxide surface.

In this paper, application of Au/Co_3O_4 catalyst for amidocarbonylation reactions was described. This catalyst system effectively provides the product under milder reaction conditions with respect to pressure and temperature than that of classical $Co_2(CO)_8$-catalyzed reactions. Studies on detailed reaction mechanisms are underway.

This work is supported by Grant-in-Aid for Global-COE program, “Science for Future Molecular Systems” from the MEXT (Japan). We appreciate Professor Katsuki and his group for permission to use NMR equipment.

Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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10 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) December 5, 2008; doi:10.1246/cl.2008.1292