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Amidocarbonylation of alkenes at very low pressures with a $Co_2(CO)_8/SbR_3$ system: two easy routes to reach *N*-acetyl-α-aminoacids

Armando Cabrera [a,*], Pankaj Sharma [a], José Luis Arias [b], José Luis Velasco [a], Javier Pérez-Flores [a], Rosa María Gómez [a,1]

[a] *Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán, 04510 México D.F., Mexico*
[b] *Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, Cuautitlán Izcalli, C.P. 54700, Estado de México, Mexico*

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Abstract

The reaction of Wakamatsu was applied for the preparation of α-acetyl-aminoacids from several unsaturated substrates in very mild conditions in the presence of a cobalt–stibine-modified system in comparison to some classical cobalt–phosphine precursors. The stibine and phosphine ligands used were: triphenylstibine (TPS), *o*- and *p*-tritolylstibine (*o*-TTS, *p*-TTS), phenyl(phenylethynyl)mesitylstibine (PPEMS), phenylthienylmesitylstibine (PTMS), *p*-fluorophenylstibine (*p*-TFPS), triphenylphosphine (TPP), *o*- and -*p*-tritolylphosphine (*o*-TTP, *p*-TTP).

Keywords: Wakamatsu reaction; Amidocarbonylation; Homogeneous catalysis; *N*-acetyl-α-aminoacid; Cobalt–stibine catalyst

1. Introduction

Amidocarbonylation reaction, originally discovered by Wakamatsu et al. in 1971 constitutes a good method for the synthesis of aminoacids using olefins [1], aldehydes [2], allylic alcohols [3], oxiranes [4] and acetals [5] as substrates. Cobalt catalysed amidocarbonylation, is generally carried out in several non-protic solvents using synthesis gas pressures of 50–200 bar and 2.5 mol percent of catalyst precursor. Although in the past Beller et al. have described advances in the named reaction using palladium compounds as catalysts [6] and Törös et al. [7] reported the use of a binary rhodium–cobalt system to promote the hydroformylation-amidocarbonylation of some steroids. The search for alternative modified cobalt systems and efficient ligands remain important and additionally it is known that with the use of phosphine ligands, the amidocarbonylation reaction can be carried out at lower pressures with regio and moderate stereocontrol. Recently, modified stibine rhodium and cobalt system have been reported, for the hydroformylation of alkenes and it have been found that the use of antimony compounds increase extraordinarily the yields of aldehydes with an appreciable *n*/*iso* ratio [8].

In this paper we wish to report the results obtained in the amidocarbonylation of different alkenes using a cobalt–stibine-modified precursor. Two synthetic routes were used for the process (Scheme 1), the behaviour of seven tertiary stibines with some analogues phosphines, as ligands in the routes, at very low syn-gas pressure were studied and the work shows the applicability of this system for the synthesis of α-aminoacids.

2. Experimental

The THF (solvent) was purified, dried and deoxygenated prior to use, $Co_2(CO)_8$ was purchased from Strem Chemical Co., cyclohexene, cyclooctene, 1-pentene, 1-hexene, 2-methylbutene and 2-propen-1-ol, the phosphinic ligands *o*- and *p*-tritolylphosphine (*o*-TTP, *p*-TTP), triphenyl phosphine (TTP) and triphenyl stibine (TPS) were obtained from Aldrich. CO, H_2 were obtained from Matheson and Aga-Gas Inc., respectively, and used without further purification. Two new ligands phenylthienylmesitylstibine (PTMS) and phenyl(phenylethynyl)mesitylstibine

* Corresponding author.
[1] Co-corresponding author

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Pathway (A)

$$\text{Olefin} + H_2 + CO + H_2NCOCH_3 \xrightarrow[R_3Sb]{[Co]} \text{N-acylaminoacid}$$

Pathway (B)

$$\text{Olefin} + H_2 + CO \xrightarrow[R_3Sb]{[Co]} [\text{aldehyde}] \xrightarrow[H_2/CO]{H_2NCOCH_3} \text{N-acylaminoacid}$$

$$HCo(CO)_3SbR_3 \rightleftharpoons HCo(CO)_2SbR_3 + CO \quad (1)$$

Scheme 1.

(PPEMS) were prepared along with some earlier reported stibines [9] *o*- and *p*-tritolylstibine (*o*-TTS, *p*-TTS) and *p*-trifluorophenylstibine (*p*-TFPS) [10,11].

The reaction products were analysed on a JEOL JMS-AX505H-A GC-MS equipment with a 25 m × 0.25 mm glass column packed with 5% phenylsilicone. The ^{1}H and ^{13}C NMR spectra were obtained on a JEOL 300 MHz spectrometer using TMS as an internal reference in $CDCl_3$ as solvent at 25 °C. The IR spectra were obtained on a Nicolet FTIR Magna 750 spectrometer. The isolation of the main products of the reaction (*N*-acylaminoacids) was performed as follows.

1. Cyclohexene derivative: the final solution was concentrated under vacuum and then treated with acetone to obtain the crystalline product of amidocarbonylation.
2. 1-Pentene, 1-hexene, 2-methylbutene, cyclooctene, and 2-propen-1-ol derivatives: The reaction solution was concentrated under vacuum and passed through a chromatographic column (silica gel 60–230 mesh) and eluted with hexane/ethylacetate 60/40 in order to isolate the products.

2.1. General catalytic procedure

2.1.1. Pathway (A)

A solution of 3.46 mmol of the unsaturated compound, 5.20 mmol of acetamide 0.12 mmol of $Co_2(CO)_8$ and 0.12 mmol of ligand in 10 ml of dry THF (in a Schlenk tube) was transferred to a 45 ml stainless steel autoclave (PARR) magnetically stirred, purged with N_2. After this, the reaction was taken until the desired pressure (28 bar, CO/H_2; 3/1) warmed in an oil bath at 120 °C for 20 h, at the end of this time, the reactor was cooled, the gases were liberated. The solution was worked up in order to yield the products of the reaction. The named solution was also analysed by GC and GC–MS to quantify the remanent substrate and also the secondary products (aldehydes and alcohols).

2.1.2. Pathway (B)

A solution of 3.46 mmol of the olefin, 0.12 mmol of $Co_2(CO)_8$ and 0.12 mmol of ligand in 10 ml of dry THF (in a Schlenk tube) was transferred to a 45 ml stainless steel autoclave (PARR) magnetically stirred, purged with N_2, taken until the desired pressure (28 bar, CO/H_2; 3/1) and warmed in an oil bath at 120 °C for 10 h, at the end of this time, the reactor was cooled, and 5.20 mmol of acetamide were added, the reactor was recharged with 28 bar, CO/H_2 3/1 and warmed at 120 °C for 10 h, at the end the solution was analysed and worked up to give the reaction products.

2.2. Characterisation of the N-acyl aminoacids entries 15 and 19–23

(±)-*N*-Acetyl-α-cyclohexylglycine (15): mp 183 °C; ^{1}H NMR (CD_3OD) δ: 1.03–1.73 (bs 11H), 1.93 (s, 3H), 4.25 (t, 1H), 7.8 (d, 1H), 12.03 (bs, 1H); ^{13}C (CD_3OD) δ: 22.16, 25.49, 27.88, 29.03, 56.57, 39.94, 169.51, 172.92; FTIR ν (cm^{-1}): 3340, 2930–2855, 1701, 1615; ME–EI *m*/*z* 199 (M 5%), 43 (100%).

(±)-*N*-Acetyl-α-*n*-pentylglycine (19): mp 86 °C; ^{1}H NMR (CD_3OD) δ: 0.87 (t, 3H), 1.22–1.70 (m, 4H), 2.04 (s, 3H), 4.57 (q, 1H), 6.36 (d, 1H), 9.22 (bs, 1H); ^{13}C (CD_3OD) δ: 13.99, 22.45, 22.78, 24.89, 31.39, 32.04, 52.59, 171.43; FTIR ν (cm^{-1}): 3345, 2957–2928, 1717, 1597; MS–EI *m*/*z* 187 (M 5%) 100 (100%).

(±)-*N*-Acetyl-α-*n*-hexylglycine (20): mp 91 °C; ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, 3H), 1.23–1.97 (m, 4H), 2.04 (s, 3H), 4.54 (q, 1H), 6.40 (d, 1H), 9.33 (bs, 1H); ^{13}C (CD_3OD) δ: 13.73, 22.58, 22.98, 31.62, 32.17, 35.63, 52.34, 171.21, 175.61; FTIR ν (cm^{-1}): 3345, 2958–2929, 1718, 1596; MS–EI *m*/*z* 201 (M 4%), 114 (100%).

(±)-*N*-Acetyl-α(-2-methylbutyl)glycine (21): mp 107 °C; ^{1}H NMR (CD_3OD) δ: 0.88 (t, 3H), 0.91 (d, 3H), 1.24–1.70 (m, 5H), 2.0 (s, 3H), 4.42 (q, 1H), 6.37 (d, 1H), 8.15 (bs, 1H); ^{13}C (CD_3OD) δ: 11.25, 18.60, 22.54, 27.85, 34.18, 39.25, 52.67, 171.26, 175.59; FTIR ν (cm^{-1}): 3338, 2958–2931, 1703, 1622; MS–EI *m*/*z* 187 (M 5%) 100 (100%).

(±)-*N*-Acetyl-α-cyclooctylglycine (22): mp 126 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ: 1.25–1.68 (m, 4H), 2.02 (s, 3H), 2.11 (m, 1H), 4.49 (dd, 1H), 6.57 (d, 1H); ^{13}C (CD_3OD) δ: 13.73, 18.60, 23.12, 25.34, 34.23, 39.88, 58.09, 170.95,

175.61; FTIR ν (cm^{-1}): 3363, 2929–2856, 1701, 1623; MS–EI *m/z* 227 (M 5%), 117 (100%).

(±)-*N*-Acetyl-α-ethylglycine (23): mp 138 °C; ^{1}H NMR (CD_3OD) δ: 0.97 (t, 3H), 1.79 (m, 2H), 1.98 (s, 3H), 4.28 (q, 1H), 6.03 (d, 1H); ^{13}C (CD_3OD) δ: 10.57, 22.29, 25.85, 55.13, 173.41, 175.39; FTIR ν (cm^{-1}): 3348, 2974–2941, 1716, 1593; MS–EI *m/z* 145 (M 10%), 58 (100%).

3. Results and discussion

The results obtained when the reaction was studied in both pathways (A) and (B) are shown in Tables 1 and 2. Earlier we have reported the incipient results in the amidocarbonylation of cyclohexene and 1-pentene using stibine-modified $Co_2(CO)_8$ [12]. It was observed that good conversions were obtained when tertiary stibines were used as ligands in both the pathways. In the case of route (B) the reaction is nearly quantitative to obtain the *N*-acetyl-α-aminoacid. The equilibria in reaction (1) suggests that the stibinic ligand remains in the coordination sphere of cobalt specie, which may be responsible for the interesting activity shown by the system.

Table 1
Selected experiments in cobalt–stibine catalysed amidocarbonylation of cyclohexene pathway (A)[a]

Entry	*N*-Acylaminoacid isolated yield (%)	Ligands
1	7	TPP
2	23	*p*-TTP
3	39	*o*-TTP
4	48	TPS
5	56	No ligand
6	57	*p*-TTS
7	68	PTMS
8	73	PPEMS
9	77	*o*-TTS
10	78	*p*-TFPS

[a] T = 120 °C; t = 20 h; $Co_2(CO)_8$/L (1/1) 0.12 mmol; acetamide 5.20 mmol (1.5 eq.); cyclohexene 3.46 mmol (1 eq.); syn-gas pressure CO/H_2 (3/1) (28 bar); THF (10 ml).

Table 2
Selected experiments in cobalt–stibine-catalyzed amidocarbonylation of cyclohexene pathway (B)[a]

Entry	*N*-Acylaminoacid isolated yield (%)	Ligands
11	27	*p*-TTP
12	64	TPS
13	69	No ligand
14	89	*p*-TTS
15	97	*o*-TTS
16	97	PTMS
17	98	PPEMS
18	99	*p*-TFPS

[a] T = 120 °C; t = 20 h; $Co_2(CO)_8$/L (1/1) 0.12 mmol; acetamide 5.20 mmol (1.5 eq.) (added after 10 h of reaction); cyclohexene 3.46 mmol (1 eq.); syn-gas pressure CO/H_2 (3/1) (28 bar); THF (10 ml).

Perhaps the good π-acceptor character and trans effect of the antimony species is responsible for the enhancement in the exchange of ligands, giving the appropriate cobalt intermediates needed for the process. The very low CO pressure in the medium also supports the observed behaviour. On the other side, the experiments performed with the use of tertiary phosphines as ligands, show low activities which may be due to its fast dissociation from the coordination sphere, this last will promote the formation of less active species and decrease the reaction rate. 89% of α-acetylaminoacid yield was approx. obtained when *p*-TTS was used, which is three times of the isolated yield, when *p*-TTP was used (entry 14 and 11 respectively). This observation reinforces previously suggested criteria.

$$HCo(CO)_3SbR_3 \rightleftharpoons HCo(CO)_2SbR_3 + CO \quad (1)$$

In spite of some isolated examples previously reported, amidocarbonylation reaction, in general, still unable to resolve the chirality induction in the obtained aminoacid [13–16]. In order to observe chiral induction in the aminoacid synthesis two new chiral stibine ligands (where R_1, R_2 and R_3 are phenyl, thienyl, mesityl or phenyl, phenylethynyl, mesityl, respectively) were used with $Co_2(CO)_8$ (entries 7, 8, 16, 17). A very good conversion of *N*-acetyl-α-cyclohexyl glycine with $[\alpha] \neq 0$ was obtained from the reaction when cyclohexene was used as a substrate. Studies to evaluate the enantiomeric excess with the use of chiral $R_1R_2R_3Sb$–Co-modified system are in progress.

3.1. Evaluation of reaction conditions

In order to explore the best conditions for the amidocarbonylation of cyclohexene, using *o*-TTS as ligand with $Co_2(CO)_8$, the effect of some important variables were studied (Table 3).

When the CO pressure is in excess relative to hydrogen (3:1), good conversions were obtained suggesting the influence of CO partial pressure is very important for the Co–stibine-modified catalysed amidocarbonylation. Increase in concentration of $Co_2(CO)_8$ increases the yield of *N*-acylaminoacid and the best results were found using a 1/29 ($Co_2(CO)_8$/cyclohexene) ratio (Table 4).

Table 3
Effect of the CO/H_2 ratio in amidocarbonylation of cyclohexene pathway (A)[a]

Pressure (bar)	*N*-Acylaminoacid isolated yield (%)	CO/H_2 ratio
28	4	1/1
28	51	2/1
28	77	3/1
28	31	4/1

[a] T = 120 °C; t = 20 h; $Co_2(CO)_8$/*o*-TTS (1/1) 0.12 mmol; acetamide 5.20 mmol (1.5 eq.); cyclohexene 3.46 mmol (1 eq.); THF (10 ml).

Table 4
Effect of $Co_2(CO)_8$ concentration in amidocarbonylation of cyclohexene pathway (A)[a]

Pressure (bar)	*N*-Acylaminoacid isolated yield (%)	$Co_2(CO)_8$ mmol
28	2	0.03
28	40	0.06
28	56	0.09
28	77	0.12
28	18	0.15

[a] $T = 120\,^{\circ}C$; $t = 20$ h; acetamide 5.20 mmol (1.5 eq.); cyclohexene 3.46 mmol (1 eq.); THF (10 ml); syn-gas ratio CO/H_2 (3/1); $Co_2(CO)_8$/*o*-TTS (1/1).

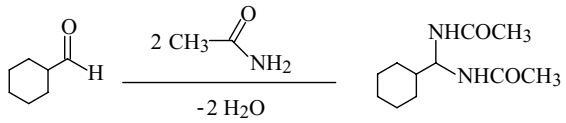
Table 5
Effect of acetamide concentration in amidocarbonylation of cyclohexene pathway (A)[a]

Pressure (bar)	*N*-Acylaminoacid isolated yield (%)	Acetamide equivalents
28	13	1.0
28	77	1.5
28	59	2.5

[a] $T = 120\,^{\circ}C$; $t = 20$ h; cyclohexene 3.46 mmol (1 eq.); THF (10 ml); syn-gas ratio CO/H_2 (3/1); $Co_2(CO)_8$/*o*-TTS (1/1).

3.2. Effect of the acetamide concentration

The results of the influence of the acetamide concentration are shown in Table 5. It is known that the concentration of nucleophile (acetamide) is very important toward attack to aldehyde and the use of 1.5 equivalents gave the best results, an excess of acetamide into the reaction media promotes a second nucleophilic pathway yielding a bis amidal byproduct (Scheme 2), this last specie is not capable to be activated to form amino acid.



Scheme 2.

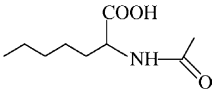
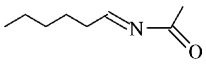
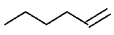
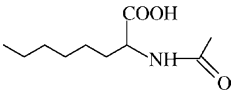
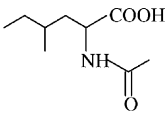
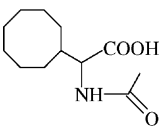
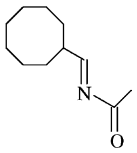
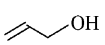
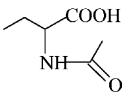
3.3. Synthetic application of the Co–stibine-modified system

In order to show the applicability of the catalytic system different alkenes were tested under the best reaction conditions (pathway B). The results are shown in Table 6. Cobalt–stibine system promotes the process, the first step of the reaction (hydroformylation) is almost quantitative and the second step (amidocarbonylation) gives a good conversion of *N*-acetylaminoacids. The *n*/*iso* ratio in all the studied cases is almost double, in comparison to, when the reaction is carried out without the stibine ligands.

3.4. The active species

In order to investigate the active species involved in this process, IR spectra of the resultant solution containing

Table 6
N-Acylaminoacids via Co–stibine catalysed amidocarbonylation pathway (B)[a]

Entry	Starting compound	*N*-Acylamino acid	Imine intermediate	Yield (%)[b]	*n*/*iso*[c] aminoacids
19			+ 	60/10	2/1
20				59	1.5/1
21				51	–
22			+ 	47/50	–
23				65	–

[a] $T = 120\,^{\circ}C$; $t = 20$ h; $Co_2(CO)_8$/*o*-TTS (1/1) 0.12 mmol; acetamide 5.20 mmol (1.5 eq.) (added after 10 h of reaction); alkene 3.46 mmol (1 eq.); syn-gas pressure CO/H_2 (3/1) (28 bar); THF 10 ml.
[b] Isolated yield.
[c] The *n*/*iso* ratio was determined by ^1H RMN using the signal corresponding to the amide proton.

Table 7
Infrared frequencies in the region 1980–2025 cm^{-1} into the reaction media[a]

Ligand	ν (Co–H) (cm^{-1})	ν (CO) (cm^{-1})
o-TTS	1984.51	2022.3 s
p-TTS	1990.81	2019.0 s
p-TFPS	1995.31	2019.5 s

[a] $T = 120\,^{\circ}C$; $t = 5$ h; $Co_2(CO)_8$/L (1/1) 0.12 mmol; syn-gas pressure CO/H_2 (3/1) (28 bar); THF (10 ml).

$Co_2(CO)_8$, stibines as ligands, under syn-gas pressure and in the absence of substrate in THF, were recorded (Table 7).

The IR study is in agreement with the existence of hydrido-carbonylic species of type $HCo(CO)_3SbR_3$ according with previous reports [17,18]. All these prepared solutions were successfully used as catalytic media in the amidocarbonylation reaction and the good conversions were obtained using these solutions, very similar to those observed in entries (14, 15, 18). When *o*-tritolylstibine (*o*-TTS) was used as ligand, an air sensitive solid was isolated which was studied by FAB–mass spectrometry (positive mode) giving $M + 1$ an important fragment at *m*/*z* 546, this fragment is comparable with its theoretical isotopic distribution.

This last suggests the existence of a $[Co(H_2O)_2(CO)_2(o\text{-TTS})]^-H^+$ species and reinforce the equilibria shown in equilibria (2), and it appears that $[Co(H_2O)_2(CO)_2(R_3Sb)]^-$ is the contributing key specie in the cobalt–stibine-modified catalytic system, here reported. Finally, when the named air sensitive compound was used as a promoter in the amidocarbonylation of cyclohexene the results obtained were in agreement with those reported in entry (15).

$$[Co(CO)_3L]^- \overset{-CO}{\rightleftharpoons} [Co(CO)_2L]^- \overset{+H_2O}{\rightleftharpoons} [Co(CO)_2L(H_2O)]^- \overset{+H_2O}{\rightleftharpoons} [Co(CO)_2L(H_2O)_2]^- \quad (2)$$

4. Conclusions

The classical cobalt catalysed amidocarbonylation of alkenes was modified with the use of R_3Sb ligands and it was found that this system not only enhances the catalytic activity but also increases the selectivity in the reaction at a very low pressure. The inclusion of a stibine ligand in the coordination sphere of cobalt gives special chemo and regioselectivity in the reaction. In some cases the imino intermediate, was also isolated suggesting its participation in the carbonylation step. Two new chiral stibines $R_1R_2R_3Sb$ ligands were also successfully used in this process and enantiomeric excess of the reaction products were obtained. The existence of hydro-stibinic species may be responsible for the substrate activation.

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