Preparation of *d,l*-Phenylalanine by Amidocarbonylation of Benzyl Chloride

Johannes G. de Vries,* René P. de Boer, Marjo Hogeweg, and Esther E. C. G. Gielens

DSM-Research, Dept. Fine Chemicals/Intermediates, P.O. Box 18, 6160 MD Geleen, The Netherlands

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The preparation of *d,l*-phenylalanine via amidocarbonylation of benzyl chloride with acetamide and CO/H_2 is described. The rate of the reaction is dependent upon the CO pressure below 250 bar, but independent of the hydrogen pressure. A reaction temperature of 100 °C gives optimum yields. A relatively large amount of the catalyst, $Co_2(CO)_8$, is needed for complete conversion because of inhibition caused by hydrogen chloride which is formed during the reaction. Addition of $NaHCO_3$ removes HCl as insoluble NaCl, resulting in improved conversion and selectivity of the reaction. It also allows the use of a stoichiometric amount of acetamide, whereas a 2- to 3-fold excess of acetamide is needed for complete conversion of benzyl chloride without $NaHCO_3$. Amidocarbonylation of benzyl alcohol gave d,l-phenylalanine in only 8% yield.

Introduction

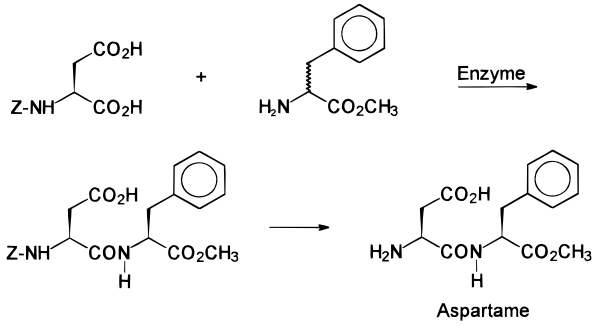
The Holland Sweetener Company's Aspartame process (Scheme 1)[1] hinges on the use of an enzyme for the crucial coupling between the two amino acid components *N*-(benzyloxycarbonyl)aspartic acid (Z-Asp-OH)[2] and phenylalanine methyl ester (H-Phe-OMe). This has a number of advantages, one of which is the ability to use racemic phenylalanine as feedstock as the enzyme will only convert the *S*-enantiomer. As a consequence much effort has been devoted to the development of an economic process for the production of *d,l*-phenylalanine.

A promising procedure for the preparation of amino acids is Wakamatsu's amidocarbonylation reaction[3,4] which allows the preparation of amino acids from aldehydes containing at least one α-proton, CO, and a limited class of amides, in particular acetamide. The necessity of the α-proton is best explained by assuming the intermediacy of the enamide (Scheme 2). This is corroborated by the fact that an enantiopure aldehyde with a chiral carbon atom in the α-position gave rise to a racemic amino acid derivative when submitted to standard amidocarbonylation conditions.[5]

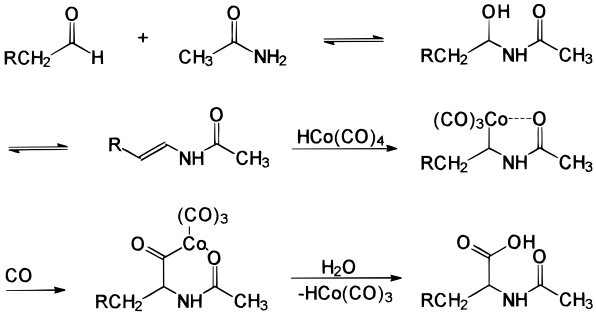
Precursors that will form aldehydes under the conditions of the amidocarbonylation reaction such as olefins,[6,7] epoxides,[8] and allylic alcohols[9] can also be used as substrates. Ojima was able to prepare *N*-acetylphenylalanine (**1**) in excellent yield by amidocarbonylation of styrene oxide in the presence of a titanium cocatalyst to accelerate the rearrangement of the epoxide to the aldehyde.[8] However, styrene oxide is not an attractive feedstock for reasons of cost and toxicity.

More interesting is the patent disclosure of Wakamatsu et al. claiming the amidocarbonylation of benzyl halides and alcohols.[10] Presumably, this proceeds via phenylacetaldehyde which is formed from benzyl chloride or alcohol by hydroformylation. The hydroformylation of benzyl chloride with $Co_2(CO)_8$ in the presence of a base has been described by others and gives phenylacetaldehyde in good yield.[11] The hydroformylation of benzyl

Scheme 1. The Holland Sweetener Company's Aspartame Process



Scheme 2. Mechanism of the Amidocarbonylation Reaction



[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1996.

(1) Oyama, K. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley & Sons: New York, 1992, p 237.

(2) The following abbreviations were used: Z-Asp-OH = *N*-(Benzyloxycarbonyl)aspartic acid, H-Phe-OH = phenylalanine, H-Phe-OMe = Phenylalanine methyl ester, Ac-Phe-OH = *N*-acetylphenylalanine, DMF = dimethylformamide, MIBK = methyl isobutyl ketone, EtOAc = ethyl acetate, BzCl = benzyl chloride, HOAc = acetic acid.

(3) Wakamatsu, H.; Uda, J. and Yamakami, N. *J. Chem. Soc., Chem. Commun.* **1971**, 1540.

(4) Lin, J.-J.; Knifton, J. F. In *Homogeneous Transition Metal Catalyzed Reactions, Advances In Chemistry Series 230,* Moser, W. R., Slocum, D. W., Eds.; American Chemical Society: Washington, D.C., 1992, p 235.

(5) Parnaud, J.-J.; Campari, G.; Pino, P. *J. Mol. Catal.* **1979**, *6*, 341.

(6) Stern, R.; Hirschauer, A.; Commereuc, D.; Chauvin, Y.; US Patent 4,264,515 (to Institute Français du Petrol), 1981.

(7) Ojima, I.; Okabe, M.; Kato, K.; Boong Kwon, H.; Horváth, I. T. *J. Am. Chem. Soc.* **1988**, *110*, 150.

(8) Ojima, I.; Hirai, K.; Fujita, M.; Fuchikami, T. *J. Organomet. Chem.* **1985**, *279*, 203.

(9) Hirai, K.; Takahashi, Y.; dand Ojima, I. *Tetrahedron Lett.* **1982**, *23*, 2491.

(10) Yukata, T.; Yamakani, N.; Honma, M.; Komachiya, Y.; Wakamatsu, H. US Patent 3,996,228 (to Ajinomoto Co. Inc.), 1976.

(11) (a) Takano, T.; Suzukamo, G.; Ishino, M.; Ikimi, K. European Patent, 34430 (to Sumitomo Chemical Co. Ltd.), 1981. (b) Ayabe, M.; Hirano, H.; Kibayashi, I.; Shimizui, T.; Kosai, Y. European Patent 109679 (to Denki Kagaku Kogyo K. K.), 1984.

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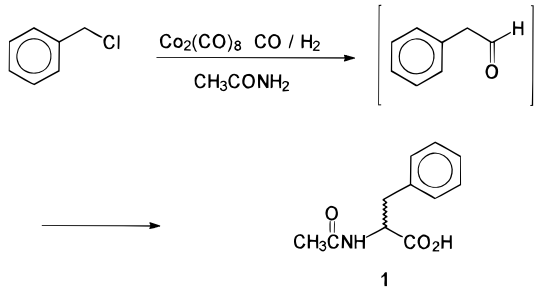
Scheme 3. Amidocarbonylation of Benzyl Chloride



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alcohol was not described before; the expected product is phenylacetic acid. It seems that in both cases the acetamide catalyzes the hydroformylation reaction in some way. The effect seems general for amides. It was found that in the presence of a stoichiometric amount of DMF rather than acetamide, aldehydes were indeed formed, both from benzyl halides and alcohols under conditions of the amidocarbonylation reaction.[10] The origins of this amide effect are unknown, but the effect could be caused by the amide functioning as ligand to the cobalt catalyst.

The amidocarbonylation of benzyl chloride to give *d,l*-*N*-acetylphenylalanine (**1**) (Scheme 3) is also described in this patent.[10] In view of the fact that benzyl chloride is a cheap and readily available commodity we decided to further develop this reaction to make it amenable to large scale production. The process as described in the patent has several drawbacks that need to be overcome before scale-up can be attempted. Very high pressures, i.e. between 250 and 300 bar, are needed for good yields of acylated amino acid. Relatively large amounts of the catalyst, $Co_2(CO)_8$, are used which would require an efficient recycle process to be viable. Good yields of product (up to 79%) are obtained only if a two- to three-fold excess of acetamide is used, but this might hamper the purification procedure. Also, the selectivity with respect to acetamide is rather poor. This is even more concerning as acetamide is the most expensive feedstock in the process.

The results of our attempts to address these problems are described in this report.

Results and Discussion

The amidocarbonylation of benzyl chloride with acetamide (Scheme 3) was explored. A standard experiment was devised based on the best results of Wakamatsu et al[10] (See footnote a in Table 1). All reaction parameters were varied, one at the time, and the effects on rate, selectivity, and catalyst stability were recorded. From a screening of six different industrially relevant solvents[12] methyl isobutyl ketone (MIBK) emerged as the solvent of choice, giving the highest yield of **1**.

Reaction Time and Temperature. The results of the standard experiment (Table 1, entry 1) raise the question whether the yield of **1** could further be increased by extending the reaction time, or by raising the temperature, as all starting materials had not yet been converted. This was verified and the results are compiled in Figures 1 and 2. From Figure 1 it is clear that after 85 min the optimum yield of **1** has indeed been reached.

(12) MIBK, acetone, EtOAc, dioxane, DMF, and toluene where tested.

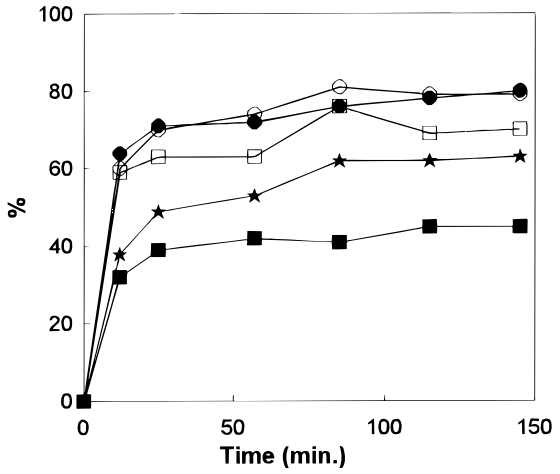


Figure 1. Time dependence of conversion and selectivity in the standard experiment. (●), Conversion benzyl chloride; (○) selectivity benzyl chloride; (■) conversion acetamide; (□) selectivity acetamide; (★) yield of **1**.

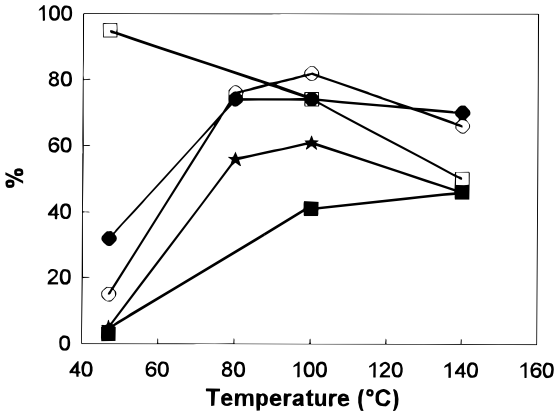


Figure 2. Influence of temperature on conversion and selectivity. (●) Conversion benzyl chloride; (○) selectivity benzyl chloride; (■) conversion acetamide; (□) selectivity acetamide; (★) yield of **1**.

Longer reaction times gave somewhat higher conversions but this was offset by a decrease in selectivity. The reaction is initially very rapid, but after about 10 min a much slower phase sets in. This can be explained by inhibition of the catalyst, presumably caused by one of the products of the reaction. The lower selectivities after shorter reaction times point to incomplete conversion of intermediates such as phenylacetaldehyde.

The temperature profile (Figure 2) also indicates that the initially chosen standard temperature of 100 °C is indeed an optimum. At 47 °C condensation between phenylacetaldehyde and acetamide hardly occurs, judging by the low conversion of acetamide. Surprisingly, only a small amount of phenylacetaldehyde was found. This is partially explained by the poorer selectivity of the hydroformylation of benzyl chloride. The hydrogenation product toluene is formed with 12% selectivity against 4% at 110 °C, but most of the products are unknown. At 140 °C selectivities are clearly deteriorating.

Pressure and CO/H_2 Ratio. Figure 3 shows the effect of the total reaction pressure on the yield of **1**. *N*-Ac-Phe-OH is only formed at pressures in excess of 100 bar; above 280 bar the maximum yield seems to have been achieved. The results in Table 1 show that the hydrogen pressure is not the rate-limiting factor, which means that hydrogenation of the cobalt acyl intermediate,

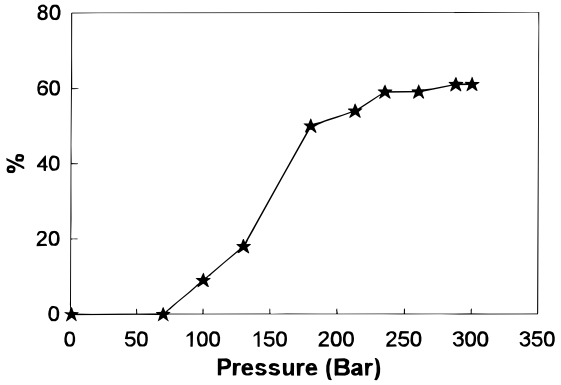


Figure 3. Relation between yield of **1** and total pressure. (★) Yield of **1**.

Table 1. CO/H_2 Ratio[a]

exp	pressure (bar)	CO/H_2 ratio	conv[b] BzCl	conv CH_3CONH_2	sel[c] BzCl	sel CH_3CONH_2	% yield of **1**
1	288	1:1	74	43	82	71	61
2	265	3:1	81	37	79	85	63
3	275	23:1	81	43	78	73	63

[a] Conditions: Benzyl chloride (40 mmol), acetamide (80 mmol), $Co_2(CO)_8$ (5 mmol), solvent (40 mL), CO/H_2 (1:1, 275 bar), 100 °C, 85 min. All conversions, selectivities, and yields are percentages. [b] Conversion is defined as Moles of converted starting material/ Moles of starting material initially present × 100. [c] Selectivity is defined as: Yield of **1** in moles/converted starting material in moles × 100.

the presumed final step in the hydroformylation of benzyl chloride, is not the rate-determining step.

Pino *et al.* showed that the amidocarbonylation of butyraldehyde is dependent upon the CO pressure at 70 °C between 10 and 60 bar; above 110 bar the rate shows a slightly negative dependence upon the CO pressure.[5] The amidocarbonylation of phenylacetaldehyde proceeds rapidly at 140 bar 1:1 CO/H_2.[13] This seems to indicate that the CO pressure dependence below 250 bar is related to the first step, the hydroformylation of benzyl chloride (See Scheme 3).

Amount of Catalyst. Separation and recycle of the catalyst is often one of the most expensive steps of a process that uses homogeneous catalysis. The cobalt catalyst can be recycled by oxidation with air in the presence of HOAc[14,15] or oxalic acid.[16] This results in the formation of Co(II) salts which can be extracted with water. Treatment of the aqueous $Co(OAc)_2$ solution with CO/H_2 at high pressure will regenerate $HCo(CO)_4$, the presumed active species. Obviously, the size of this recycle stream will have a large impact on investment and operating costs. In the standard experiment as much as 12.5 mol % of catalyst is used; reduction of this amount is highly desirable.

Not surprisingly, there was a clear relationship between catalyst concentration and benzyl chloride conversion (Table 2). At the conditions of the standard experiment 25 mol % of catalyst was needed for complete conversion. The question remains whether a large amount of catalyst is really needed when the reaction is allowed to proceed longer or at higher temperatures.

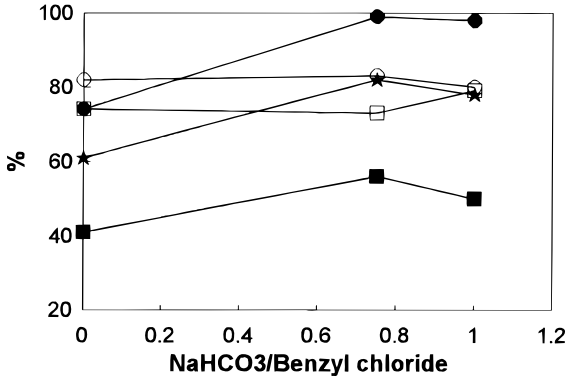


Figure 4. Effect of $NaHCO_3$ on conversion and selectivity of amidocarbonylation. (●) Conversion benzyl chloride; (○) selectivity benzyl chloride; (■) conversion acetamide; (□) selectivity acetamide; (★) yield of **1**.

Table 2. Amount of Catalyst[a]

exp	mol% cat[b]	conv BzCl	conv CH_3CONH_2	sel BzCl	sel CH_3CONH_2	% yield of **1**
1	3.25	41	43	41	20	17
2	3.25[c]	32	22	17	12	3
3	3.25[d]	49	35	42	30	21
4	7.5	58	43	35	23	20
5	12.75	74	41	82	74	61
6	25.75	100	51	83	81	83
7	38.5	100	58	80	69	80

[a] For conditions see footnote a in Table 1. [b] 1 mol % catalyst = 2 mol% Co. [c] T = 140 °C. [d] *t* = 160 min.

Prolongation of the experiment with 3.25 mol % catalyst to 160 min (exp 3) showed that both benzyl chloride conversion and *N*-Ac-Phe-OH yield had only marginally increased. Using the same amount of catalyst at 140 °C (exp 2) led to breakdown of conversion and selectivity as observed before.

The need for a large amount of catalyst can only be satisfactorily explained by catalyst deactivation.

Catalyst Deactivation. An obvious reason for the occurrence of catalyst deactivation is the formation of stoichiometric amounts of HCl in the reaction; chloride is a well known catalyst poison for cobalt catalysts in CO chemistry.[14] In addition, HCl catalyzes the hydrolysis of acetamide. Addition of $NaHCO_3$ should circumvent all these problems by neutralizing the reaction mixture and removing chloride as insoluble NaCl.

Figure 4 shows the effect of the addition of varying amounts of $NaHCO_3$ on conversion and selectivity of the reaction. There clearly is a beneficial effect on the conversion of both benzyl chloride and acetamide. This effect is optimal with slightly less than stoichiometrical amounts of $NaHCO_3$. Apparently, some measure of acidity is necessary to catalyze the condensation of acetamide with phenylacetaldehyde.

The experiment in which only 3.25 mol % of catalyst was used was also repeated with addition of 1 equiv of $NaHCO_3$. The outcome was rather disappointing; even after 160 min less than 1% of **1** had been formed. Most revealing was the fact that in this case there was an excellent conversion (86%) of benzyl chloride, mostly to phenylacetaldehyde, whereas acetamide remained largely unconverted (3%). Lack of acid catalyst for the condensation step is one possible explanation for the inhibition of the amidocarbonylation of phenylacetaldehyde. Indeed, no reaction occurred when amidocarbonylation of phenylacetaldehyde was attempted in the presence of 1

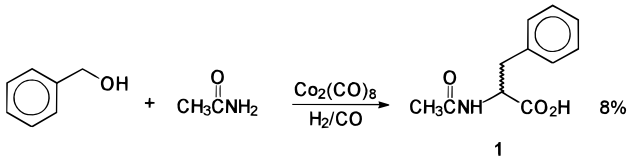
(13) Lin, J.-J.; Knifton, J. *J. Organomet. Chem.* **1991**, *147*, 99.
(14) Falbe, J. *Synthesen mit Kohlenmonoxid*; Springer Verlag, New York, 1967, p 19.
(15) Falbe, J. *New Syntheses with Carbon Monoxide*; Springer Verlag, New York, 1980; p 80.
(16) El-Chahawi, M.; Meyer, G. German Patent 3345411 (to Hüls Troisdorf AG), 1985.

Table 3. Acetamide/Benzyl Chloride Ratio and Effect of $NaHCO_3$[a]

exp	CH_3CONH_2/ BzCl	additives and changes	conv BzCl	conv CH_3CONH_2	sel BzCl	sel CH_3CONH_2	% yield of **1**
1	1	–	60	59	79	80	47
2	1	140 °C	63	59	56	60	35
3	1	160 min	62	64	75	35	46
4	1.5	–	67	42	81	86	54
5	2	–	74	41	82	74	61
6	3	–	92	ND[b]	65	–	60
7	1	$NaHCO_3$ (20)	90	85	85	90	76
8	1	$NaHCO_3$ (30)	96	90	87	91	82
9	1	$NaHCO_3$ (40)	98	89	77	85	76
10	1	$NaHCO_3$ (40)[c]	99	89	79	89	79
11	2	*d*	86	47	63	57	54
12	1	$NaHCO_3$(40)[d]	99	89	81	90	80
13	1	$NaHCO_3$(40)[e]	100	ND	41	ND	41
14	1	$NaHCO_3$(50)	87	79	84	90	71
15	2	$NaHCO_3$(30)	99	56	83	73	82
16	2	$NaHCO_3$(40)	98	50	80	79	78

[a] For conditions see footnote a in Table 1. [b] Not determined. [c] t = 160 min. [d] 20 mL of MIBK. [e] No solvent.

Scheme 4. Amidocarbonylation of Benzyl Alcohol



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equiv of $NaHCO_3$. Fine tuning the amount of $NaHCO_3$ seems an obvious way to make more progress in this area.

Addition of 1 equiv amount of pyridine resulted in full conversion of benzyl chloride, but neither **1** nor phenylacetaldehyde was formed. Quaternization of pyridine with benzyl chloride seems a likely explanation for this result.

A more radical way to solve the chloride problem would be to use benzyl alcohol as starting material. Amidocarbonylation of benzyl alcohol (Scheme 4) does indeed occur under the standard conditions but conversion and selectivity were much lower than with benzyl chloride.[17]

Acetamide/Benzyl Chloride Ratio. All of the above experiments were carried out with an acetamide/benzyl chloride ratio of two. Figure 5 clearly shows the "linear" relationship between acetamide/benzyl chloride ratio and conversion of benzyl chloride. It is not clear at this point what the origins are of this effect. It might mean that the condensation of acetamide with phenylacetaldehyde is rate determining, but it is also possible that acetamide is a catalyst for the hydroformylation step, depending on which step is rate determining. Another explanation could be that acetamide plays a role in the prevention of catalyst inhibition.

If the reaction with 1 equiv of acetamide was allowed to proceed during 160 min, conversion and yield did not increase. This clearly points to an earlier onset of catalyst inhibition. Increasing the temperature to 140 °C gave lower selectivities leading to a lower yield of **1**.

The effect of the addition of $NaHCO_3$ in these experiments was even more dramatic (Table 3). Addition of 0.75 equiv of $NaHCO_3$ resulted in an 82% yield of **1** (exp 8). A result which could not be improved by the use of 2 equiv of acetamide (exp 15). The selectivities were even better for the lower amount of acetamide.

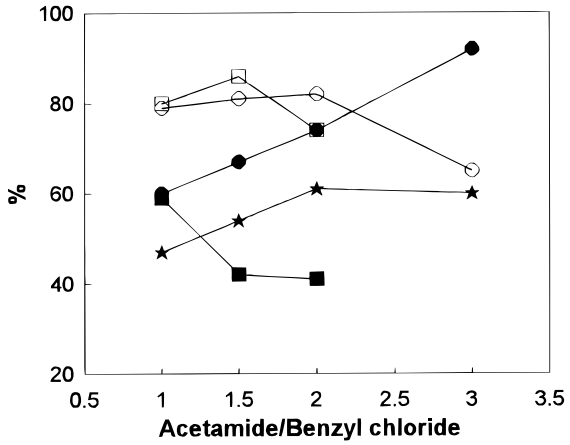


Figure 5. Influence of acetamide benzyl chloride ratio. (●) Conversion benzyl chloride; (○) selectivity benzyl chloride; (■) conversion acetamide; (□) selectivity acetamide; (★) yield of **1**.

Lowering the amount of solvent gave rise to lower selectivities and yields (Table 3, exp 11), but addition of bicarbonate allows the amount of solvent to be halved (Table 3, exp 12). Total omission of solvent was not possible and led to sharply reduced yields.

Side Products. The main side product is toluene (**2**) which is formed in amounts of 4–6 mol % by hydrogenation of benzyl chloride. Smaller amounts of phenylacetaldehyde (**3**) and its hydrogenation product phenylethanol (**4**) are also formed. But even in reactions where the selectivity in benzyl chloride is low the amount of these products never exceeds 2 mol %. In a number of reactions minor amounts of 2-acetamidostyrene (**5**) were formed (both *E* and *Z*). In the GC of all reaction mixtures azalactone (**6**) was observed. Formation of this product is readily explained by internal attack of the amide carbonyl group on the cobalt acyl intermediate (Scheme 5).[18] However, even when pure **1** was injected this peak was observed, suggesting that thermal dehydration of **1** to **6** is possible. This throws doubt on the presence of this compound in the amidocarbonylation mixtures. The formation of azalactone can be induced by addition of molecular sieves to the amidocarbonylation reaction.[19]

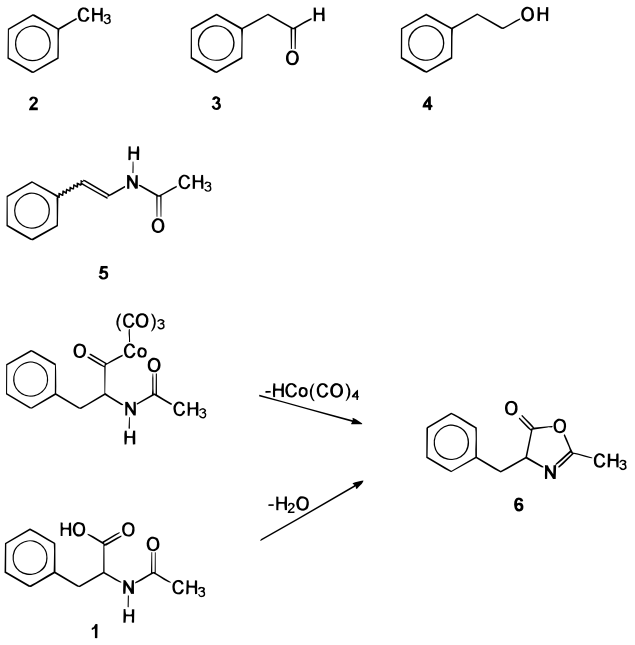
Conclusion

The amidocarbonylation reaction is a very promising way to prepare *d,l*-*N*-acetylphenylalanine. We were able

(17) Results of the amidocarbonylation of benzyl alcohol under conditions of the "Standard Experiment": $PhCH_2OH$: conv 22%, sel 38%; CH_3CONH_2: conv 17%, sel 24%, yield *N*-Ac-Phe-OH: 8%.

(18) Magnus, P.; Slater, M. *Tetrahedron Lett.* **1987**, *28*, 2829.
(19) Izawa, K.; Nishi, S.; Asada, S. *J. Mol. Catal.* **1987**, *41*, 135.

Scheme 5. Side Products in the Amidocarbonylation of Benzyl Chloride



to greatly improve the reaction by addition of $NaHCO_3$. This addition obviates the need to use a two-fold excess of acetamide and also allows us to reduce the amount of solvent. Fine tuning the amount of $NaHCO_3$ might permit further reduction of the substrate catalyst ratio which is still unacceptably high.

Experimental Section

Materials and Methods. All chemicals were commercial products that were used as received. Solvents were degassed with nitrogen before use. DMF was freed from dimethylamine and formic acid by storing over molecular sieves (4 Å) for at least 48 h. Acetamide was dried under high vacuum for 24 h. The benzyl chloride used was stabilized with 0.25% propylene oxide. Phenylacetaldehyde was stabilized with 15% 2-phenylethanol. Amidocarbonylation experiments up to 180 bar pressure were carried out in a 50 mL Parr autoclave (Hastelloy C) equipped with a rupture disk, a manometer and a propeller type stirrer which was operated at 700 rpm. Higher pressure experiments were performed in Carius tubes (Hastelloy C) with an empty volume of 220 mL, equipped with a manometer and a rupture disc. The tubes were heated in a stainless steel heating block mounted on a rocker. Toluene, benzyl chloride, 2-phenylethanol, phenylacetaldehyde, and benzyl alcohol were analyzed by GC on a 25 m CP-Sil 5CB column (0.32 mm i.d, 2 μm film thickness). Initial temperature 60 °C, 60−250 °C (10 °C/min). Injection temperature 280 °C, detection temperature 280 °C. Acetamide was analyzed by GC on a 25 m CP-wax 51 column (0.25 mm i.d., 0.2 μm film thickness). Initial temperature 60 °C, 60−250 °C (10 °C/min). Injection temperature 250 °C, detection temperature 250 °C. *N*-Ac-Phe-OH, *N*-For-Phe-OH, and H-Phe-OH were analyzed by HPLC (HP 1090) on a 25 × 0.4 cm Nucleosil 120−5-C18 column using gradient elution (1 mL/min). Solvent A: 50 mM phosphate buffer pH 2.5, solvent B: 20% A/80% acetonitrile. Column temperature 40 °C, injection volume 25 μL. Waters 480 UV detection (257 nm). TLC analyses were performed on Merck silica plates.

Standard Experiment. A Carius tube was flushed with nitrogen for 10 min, filled with benzyl chloride (5.06 g, 40 mmol), acetamide (4.73 g, 80 mmol), ethyl benzene (500 μL, 4 mmol, internal standard), MIBK (40 mL), and $Co_2(CO)_8$ (1.76 g, 5 mmol), and closed. The tube was brought to 275 bar with CO/H_2 (1:1) and placed in a preheated heating block at 100 °C. The tube was shaken at this temperature for 85 min. After this period the tube was removed from the heating block and forcibly cooled to room temperature by immersion in cold water. After 30−60 min the tube was opened and the contents transferred to a volumetric flask (100 mL). The tube was carefully rinsed with DMF to ensure complete removal of the contents. The washings were also added to the volumetric flask, and more DMF was added up to 100 mL. The solution was analyzed by GC (two different columns, see Materials and Methods) and HPLC. In a number of cases GC-MS was performed to characterize unknown components. All amidocarbonylation experiments described in the preceding sections were variations of this standard experiment. The experiments in the Parr autoclave were carried out in a similar manner.

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