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LETTERS

N-Acyl imine and enamide intermediates in the palladium-catalyzed amidocarbonylation reaction

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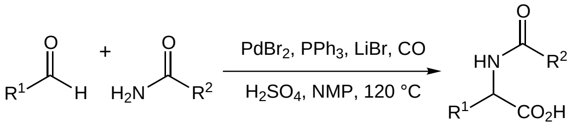
Abstract—*N*-Acyl imines and enamides have been synthesized and subjected to the reaction conditions for palladium-catalyzed amidocarbonylation of aldehydes. These compounds were competent substrates resulting in the formation of *N*-acyl amino acids; however, the presence of water was found to be necessary. Direct study of the same amidocarbonylation reaction revealed that enamides could be detected during the course of the reaction. A slight enhancement in the yield of the amidocarbonylation is observed in the presence of radical inhibitors ruling out a meaningful radical pathway. The results are most consistent with a mechanism involving complex equilibration of the starting materials to a number of intermediates which can converge to a haloamidal that subsequently undergoes a palladium insertion. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of amino acids is important in many fields of chemistry. Currently, there are few general routes to α-amino acids. Strecker cyanation, homologation of glycine derivatives, amination of enolates, and the hydrogenation of dehydroamino acids are among the more versatile of the known methods.[1] While the Strecker synthesis is certainly the simplest, the potential of introducing carbonyl equivalents other than cyanide, such as CO and CO_2, to form amino acids remains attractive.

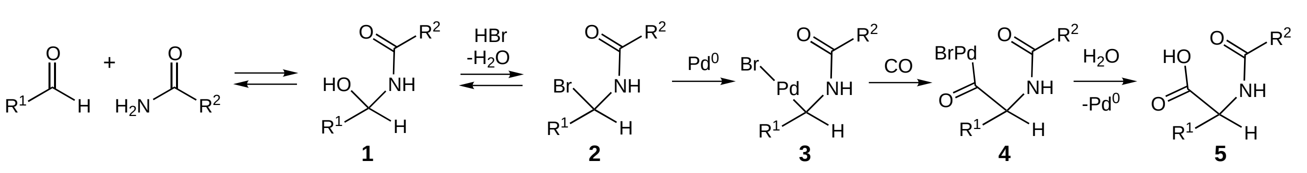
The use of carbon monoxide to achieve such a goal utilizing a cobalt catalyst was first described by Wakamatsu in 1970.[2,3] Recently, Beller et al. showed that the amidocarbonylation reaction proceeds with palladium catalysts against a wider variety of substrates (Eq. (1)).[4] This paper outlines mechanistic studies of several aspects of the palladium-catalyzed amidocarbonylation reaction.

Beller et al. have proposed the following mechanism (Scheme 1) for the palladium-catalyzed reaction mechanism.[4] In this mechanism, oxidative addition of the haloamidal intermediate (**2**) to palladium is followed by CO insertion and hydrolysis to yield the *N*-acyl amino acid **5**.

Other pathways can also be considered for this reaction such as elimination of the halide from the haloamidal to form iminium ion **6**, to which a palladium species might add (Scheme 2). Isomerization of this iminium ion would lead to enamide (**7**), to which a H–Pd might add in a regioselective manner.[5] The role of enamide intermediates in the palladium-catalyzed reaction also has implications for the use of α-substituted aldehydes. In order to probe these possibilities, *N*-acyl imines and enamides have been synthesized and subjected to the conditions of the palladium-catalyzed amidocarbonylation reaction.



(1)



Scheme 1.

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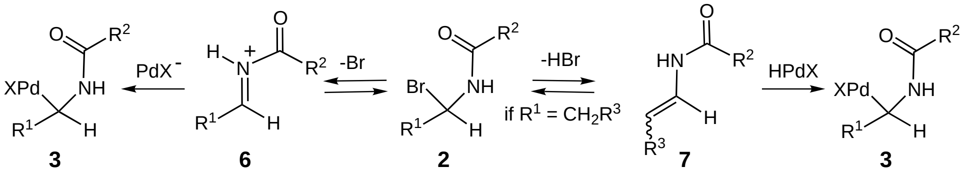


Scheme 2.

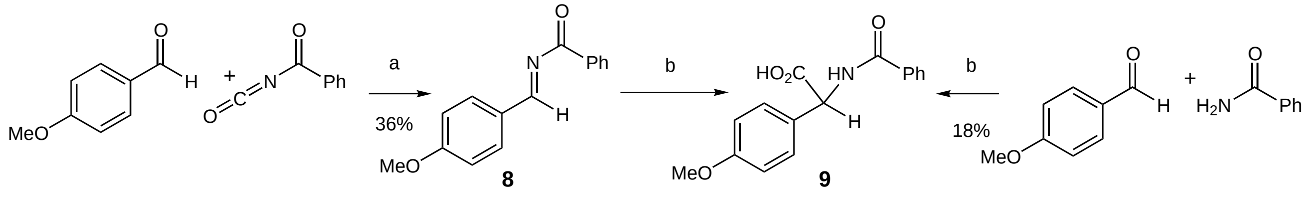
N-Acyl imine **8** was selected for study since it is relatively stable, unlike most *N*-acyl imines, and can be conveniently generated (Scheme 3).[6] When this imine was subjected to the amidocarbonylation conditions in the presence of water, the amidocarbonylation product **9** was produced in ~10% conversion as determined by gas chromatography. The corresponding amidocarbonylation reaction from *p*-methoxybenzaldehyde and benzamide proceeded with a similar conversion (18%) under the same conditions.[7] Thus, imine **8** appears to be a substrate for the amidocarbonylation.

Next, enamide substrates were examined and the readily synthesized *trans*-enamide **11**[8] was subjected to a series of carbonylation conditions (Table 1). Entry 1 shows the results from the corresponding amidocarbonylation reaction between phenylacetaldehyde and acetamide and entry 2 shows the results for the enamide under the identical reaction conditions.[9] The amidocarbonylation product **9** is generated in similar yield from both substrates.

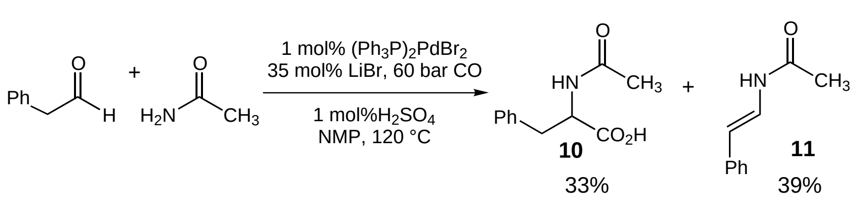
The above result does not distinguish between formation of bromoamidal **2** (Scheme 1) from the enamide by addition of bromide present in the reaction mixture or addition of a Pd–H species to the enamide; however, it does indicate that enamides are competent substrates for the amidocarbonylation reaction. As such, α-substituted aldehyde substrates would be epimerized in the amidocarbonylation via enamide formation. Since this issue is only relevant if enamides form under the reaction conditions, phenylacetaldehyde and acetamide were subjected to the amidocarbonylation conditions and the reaction was halted prior to completion (Eq. (2)). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy against an internal standard indicated the presence of phenylacetaldehyde (5%), *N*-acyl amino acid **10** (33%), *and enamide* ***11*** (39%). In a further experiment, phenylacetaldehyde and acetamide were also found to produce the enamide **11** in 30% conversion when subjected to the amidocarbonylation conditions without the palladium catalyst.

A benefit of using enamides as substrates is that the role of water in the amidocarbonylation mechanism can be delineated.[10,11] The *N*-acyl amino acid **5** observed in these reactions could arise from the reductive elimination of palladium to the acyl bromide followed by hydrolysis (path ***a***, Scheme 4), from the direct hydrolysis of the acylpalladium species (path ***b***), or from hydrolysis of an oxazolone intermediate arising from intramolecular displacement of the palladium (path ***c***). In all cases, hydrolysis would be accomplished by the water released from the aldehyde upon formation of the bromoamidal **2**. With enamides, this water is not present and it may be possible to trap the intermediate leading to the final product with other nucleophiles. To this end, the enamide reaction was performed in the presence of MeOH (entry 3, Table 1) which resulted in a very high conversion (78%). Surprisingly, only 21% was the methyl ester and the remaining 57% was the acid. In an identical reaction performed under rigorously anhydrous conditions (entry 4), the conversion dropped substantially to 9% of the acid and 1% of the methyl ester. Apparently the trace amount of water introduced during assembly of the high pressure apparatus is necessary to allow formation of the *N*-acyl amino acid. The successful simulation of the aldehyde reaction conditions (entry 1) by the addition of one equivalent of water to the enamide reaction (entry 6), provided further evidence that water is not detrimental.

The lack of product formation under anhydrous conditions[10] in the presence of methanol suggests that there is quite a difference in the hydrolysis versus methanolysis rate of the true intermediate.[12] This points away from paths ***a*** and ***c*** since methanolysis of the respective acyl bromide (**12**) and oxazolone (**13**) inter-

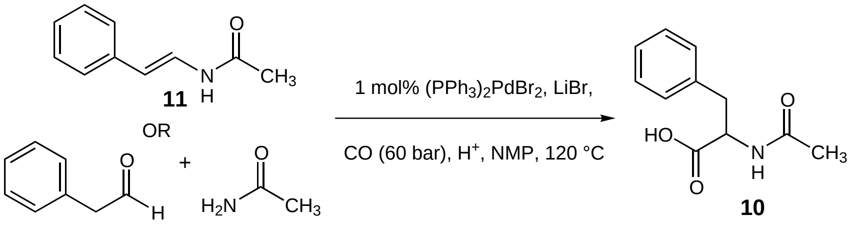


Scheme 3. (a) Ether, reflux; (b) 1 mol% $(PPh_3)_2PdBr_2$, 35 mol% LiBr, 1 mol% H_2SO_4, CO, NMP, 120°C.



(2)

Table 1. Amidocarbonylation of enamide substrates (Eq. (3))[a]



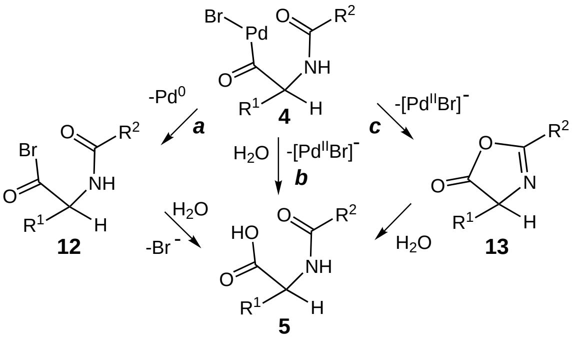
(3)

Entry	Substrate	LiBr (mol%)	H^+ (mol%)	Additive (mol%)	Conv. (%)[b]
1	**Aldehyde/amide**	35	1 H_2SO_4	–	33
2	Enamide (**11**)	35	1 H_2SO_4	–	36
3	Enamide (**11**)	35	1 H_2SO_4	**100 MeOH**	78 (21 ester)
4	Enamide (**11**)	35	1 H_2SO_4	**100 MeOH**, anhyd.[c]	10 (<1 ester)
5	Enamide (**11**)	35	1 H_2SO_4	**1000 MeOH**	0
6	Enamide (**11**)	35	1 H_2SO_4	**100 H_2O**	26
7	Enamide (**11**)	**0**	1 H_2SO_4	–	8
8	Enamide (**11**)	**100**	1 H_2SO_4	–	32
9	Enamide (**11**)	35	**100 H_2SO_4**	–	27
10	Enamide (**11**)	35	**10 $BF_3{\cdot}OEt_2$**	–	39

[a] Performed using anhydrous solvents and reagents in a dried glass liner.

[b] Conversions are the average from two trials and were measured by ^{1}H NMR (see Ref. 9).

[c] Performed under rigorously anhydrous conditions, in which the autoclave was heated overnight at 80°C, cooled under vacuum, and assembled inside an inert atmosphere box.



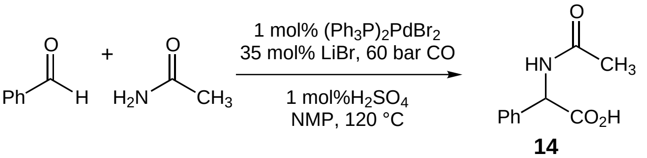
Scheme 4.

mediates should be facile. On the other hand, the direct cleavage of the acylpalladium **4** by a palladium-associated water (path ***b***) would account for this reactivity pattern.[13] Alternatively, water may be necessary in order for the enamide to react; perhaps a water molecule remains in close proximity to the palladium throughout the cycle.[11] Regardless, the enhancement in yield upon addition of MeOH (entry 3) is difficult to explain. The use of further MeOH (10-fold excess, entry 5) results in no conversion which may be due to a solvent effect. Consistent with this, when methanol was used instead of NMP as solvent in the aldehyde amidocarbonylation no reaction was observed.

The results from varying the amounts of LiBr and acid (entries 7–10 of Table 1) with the enamide substrate closely parallel those observed in the reaction of the aldehyde and the amide.[14] For example, removal of LiBr caused a drop in conversion since there is less halide for formation of the bromoamidal intermediate. On the other hand, the addition of a full equivalent of LiBr does not enhance the conversion, which also points away from an acyl bromide product. The use of a full equivalent of protic acid results in a mild decrease in conversion while the use of $BF_3{\cdot}OEt_2$ instead of H_2SO_4 is not detrimental. These similar reaction patterns suggest that the enamide and the aldehyde/amide react via a similar mechanism.

In a further experiment, radical inhibitors (hydroquinone and BHT) were added to the palladium-catalyzed amidocarbonylation reaction to discern if the bromoamidal intermediate **2** underwent radical cleavage over the course of the reaction. With both inhibitors, somewhat higher yields (64–65% versus 55%) of **14** were observed indicating that the formation of radicals leads to deleterious side reactions (Eq. (4)).

In conclusion, *N*-acyl imines and enamides have been shown to lead to the same amidocarbonylation products as produced from aldehydes and amides. Additionally, an enamide byproduct was observed in the amidocarbonylation of phenylacetaldehyde providing evidence that enamide intermediates are relevant to these reactions. Further experiments with enamides have shown that water is critical for the reaction consis-



no inhibitor	55%
10% hydroquinone	65%
10% BHT	64%

(4)

tent with direct hydrolysis of an acylpalladium species to form the carboxylic acid product. Overall the experiments described above indicate that the amidocarbonylation largely proceeds as outlined in Scheme 1.

Acknowledgements

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9. This reaction was not run to completion in order to determine if enamide was formed. With further conversion, isolated yields of 85% have been reported for **10** (Ref. 4a). The same reaction conditions were employed for all entries in Table 1: the substrates (2.5 mmol each of aldehyde and acetamide or 2.5 mmol enamide) were placed in an oven-dried glass liner under N_2 and were combined with distilled NMP (5 mL), $PdBr_2$ (1 mol%), Ph_3P (2 mol%), anhydrous LiBr (35 mol%), and H_2SO_4 (1 mol%). The reaction vessel was placed in a high pressure reactor (Parr No. N4767 or 4712) which was purged with CO, pressurized to 60 bar with CO, and magnetically stirred for 14 h at 120°C (bath temperature). After cooling to rt, the reactor was depressurized and *i*PrOH (5.0 mmol) was added as an internal standard. The amounts of aldehyde, enamide, *N*-acyl amino acid, and *N*-acyl amino ester were determined by integration of the crude reaction mixture ^1H NMR signals ($CDCl_3$).
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