

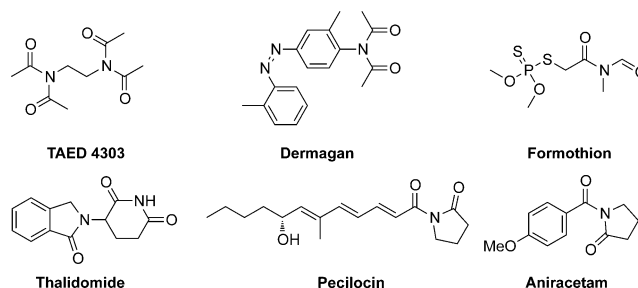
Palladium-Catalyzed Hydroamidocarbonylation of Olefins to Imides**

Haoquan Li, Kaiwu Dong, Helfried Neumann, and Matthias Beller*

Abstract: Carbonylation reactions allow the efficient synthesis of all kinds of carbonyl-containing compounds. Here, we report a straightforward synthesis of various imides from olefins and CO for the first time. The established hydroamidocarbonylation reaction affords imides in good yields (up to 90 %) and with good regioselectivity (up to 99:1) when applying different alkenes and amides. The synthetic potential of the method is highlighted by the synthesis of Aniracetam by intramolecular hydroamidocarbonylation.

Carbonylation reactions using carbon monoxide (CO) as one of the cheapest and most flexible C1 building blocks continues to attract significant interest in organic synthesis and from industrial chemists.^[1] In terms of production scale, carbonylation reactions nowadays constitute the largest industrial applications in the area of homogeneous catalysis.^[2] In addition to the well-known Monsanto^[3] or Cativa process^[4] which produce acetic acid by the carbonylation of methanol, carbonylative transformations of simple alkenes have been shown to be core processes in industry for the production of esters (alkoxycarbonylation)^[5] and aldehydes (hydroformylation).^[6] However, the related synthesis of more value added amides (aminocarbonylations) from simple alkene has been less explored.^[7] In this respect, our research group recently reported a general aminocarbonylation of alkenes by using a palladium catalyst system.^[7b] The aminocarbonylation of various conjugated dienes to synthesize the corresponding β,γ -unsaturated amide was also developed.^[7d] Notably, all these reactions proceed with high atom economy.^[8]

Apart from amides, imides also constitute an important organic moiety in fine chemicals. For example, tetraacetylenediamine (TAED) is used on multi-10 000 ton scale as a peroxide bleach activator in detergents. Moreover, this functional group is used in the synthesis of pharmaceuticals as well as agrochemicals and various bioactive molecules. As shown in Scheme 1, selected examples include Diacetazolol (Dermagan), which stimulates wound epithelization, Formothion, a systemic and contact insecticide, Thalidomide, which



Scheme 1. Selected examples of imide-containing bioactive molecules.

shows antiangiogenic and antineoplastic properties, Pecilocin, with antifungal activity, and the anxiolytic drug Aniracetam (Ampamet).^[9]

Typical syntheses of imides proceed by the nucleophilic substitution of activated carboxylic acid derivatives, for example, acid chlorides or anhydrides, with amides in the presence of base under carefully controlled conditions.^[10] The selective oxidation of amides to imides is also known in a few cases.^[11]

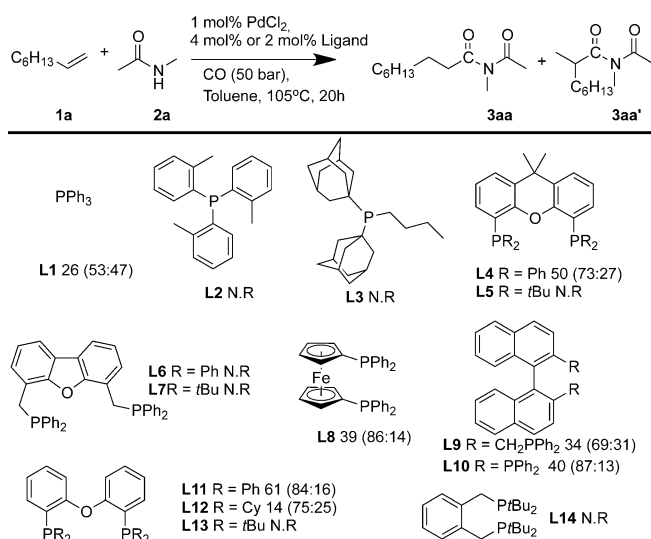
Compared to the existing methods, the direct carbonylation of easily available olefins to imides would be advantageous with respect to waste formation and step economy (100 % atom efficiency). Based on our continued interest and experience in carbonylation reactions, we envisioned and started to explore the synthesis of imides from alkenes and amides.^[12] Herein, we report a novel palladium-catalyzed hydroamidocarbonylation of alkenes for the synthesis of various synthetically interesting imides.

At the beginning of our study, 1-octene and *N*-methylacetamide were chosen as model substrates. A variety of ligands were tested (in the case of monodentate ligands 4 mol %, in the case of bidentate ligands 2 mol %) in the presence of 1 mol % PdCl₂ in toluene at 105 °C under a CO atmosphere (50 bar). With PPh₃ (**L1**) as ligand, a mixture of the desired linear product (*n*-) **3aa** (53 %) and the corresponding branched product (iso-) **3aa'** (47 %) was obtained in a yield of only a 26 % (Scheme 2). No desired product was observed at all with tri(*o*-tolyl)phosphine (**L2**) and di(1-adamantyl)-*n*-butylphosphine (**L3**). However, to our delight, the use of bidentate ligands gave much better results. In fact, a 50 % yield of the desired product with 73 % selectivity was obtained when Xantphos **L4** was tested. Surprisingly, the use of sterically hindered *t*Bu analogues of Xantphos (**L5**) gave no desired product. A similar result was also observed with the DBFphos series (**L6** and **L7**). On the other hand, a 39 % yield with 86 % linear selectivity was obtained when dppe (1,1'-bis(diphenylphosphino)ferrocene) (**L8**) was used. Binap backbone bidentate ligands **L9** and **L10** were also active (34 % yield, 69 % selectivity and 40 % yield, 87 % selectivity,

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Scheme 2. Hydroamidocarbonylation of 1-octene. Reaction conditions: Ligand variation. **2a** (1.0 mmol), **1a** (1.0 mmol), PdCl_2 (1 mol%), monodentate ligand (4 mol%) or bidentate ligand (2 mol%), toluene (2 mL), CO (50 bar) heating at 105°C for 20 h. Yield (%) of the mixture of **3aa** and **3aa'** determined by GC using isooctane as an internal standard, the number in parenthesis indicates the **3/3'** selectivity determined by GC. N.R. indicates no observable product by GC.

respectively). Notably, the best result (61% yield, 84% selectivity) was observed using DPEPhos [(oxydi-2,1-phenylene)bis(diphenylphosphine)] (**L11**). Thus, **L11** was chosen for further studies. Similar to the Xantphos ligand, the sterically hindered cyclohexyl and *tert*-butyl analogues of DPEPhos (**L12** and **L13**) were shown to be less reactive (14% yield, 75% selectivity and no conversion, respectively). Interestingly, the so-called d'bpx ligand α,α' -bis(di-*tert*-butylphosphino)-*o*-xylene (**L14**), which is known to be highly active for palladium-catalyzed carbonylation reactions of alkenes and for the aminocarbonylation of butadiene was shown to be completely inactive in this case.^[13,7c]

In contrast to most of the recently developed palladium-catalyzed carbonylation reactions of olefins, the presented imide formation takes place under “acid-free” conditions. Under such conditions, slow isomerization of 1-octene leads to an accumulation of internal octenes, which are not in fast equilibrium with the terminal olefin. Hence, the use of an increased amount of olefin (2 equiv) resulted in the yield of the desired terminal imide increasing to 85% with similar *n*-iso selectivity (84%). It is noteworthy that carbonylation products derived from internal olefins are not observed under the “acid-free” conditions, which shows that the reaction rates of the terminal alkenes are much faster than the internal ones.

Next, the effect of the counterion was investigated by testing different palladium sources (see Table S1 in the Supporting Information). $[\text{Pd}(\text{cod})\text{Cl}_2]$ and $[\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2]$ resulted in similar linear selectivity, however with slightly decreased yields (Table S1, entries 3 and 4). Surprisingly, almost quantitative yields and an increased linear selectivity of the reactions were observed with both PdBr_2 and PdI_2 as the palladium source (85% and 88%, respectively; Table S1,

entries 5 and 6). However, with $\text{Pd}(\text{OAc})_2$ and $[\text{Pd}(\text{acac})_2]$, only traces of product could be observed, with low conversion of **1a** (Table S1, entries 7 and 8). By using PdI_2 as the palladium source, the reaction even proceeded at 80°C, although giving a lower yield (Table S1, entry 9). In general, the catalyst system was shown to be robust and almost the same yield and selectivity (92%, 89%; Table S1, entry 11) was achieved at a lower catalyst loading (0.25 mol%). To our surprise, the addition of 0.75 mol% *p*-toluenesulfonic acid led to a significant decrease in the yield of the product (64% yield; Table S1, entry 13). Monitoring the gas consumption showed that the reaction reached over 90% conversion after 10 h (see the Supporting Information for details).

With the optimized conditions in hand, a range of easily available and structurally diverse olefins were tested (Table 1). Primarily, 1-decene (**1b**) gave a very similar result to 1-octene (**1a**, Table 1, entries 1 and 2; 87% and 88% yield of isolated **3**, 89% *n*-selectivity). To our delight, different cyclic olefins (1 equiv) also reacted smoothly. For example, the reactions with cyclopentene (**1c**) and cyclohexene (**1d**) resulted in complete conversion and good yields of the isolated products (Table 1, entries 3 and 4; 83% and 90% yield, respectively). With norbornene (**1e**) as substrate, the reaction was shown to be completely *exo*-selective, with the imide moiety in the equatorial position (58% yield; Table 1, entry 5). Interestingly, the basic industrial feedstock ethylene (**1f**) gave **3fa** in 91% yield (Table 1, entry 6). Excellent linear selectivities were observed in the case of sterically hindered 1-alkenes. For example, 4-methyl-1-pentene (**1g**) and allylcyclohexane (**1h**) led to yields of 85% and 86% of isolated product with an *n*-selectivity of 89% for **3ga** and **3ha** (Table 1, entries 7 and 8). With 4-vinylcyclohexene (**1i**) as substrate, 97% linear selectivity was obtained with a 90% yield of the isolated product (Table 1, entry 9). It is noteworthy that in this case the internal C=C bond remained intact after reaction, thus showing that the terminal alkene is much more reactive in this reaction than the cyclic internal alkene. Natural oil derived substrate citronellene (**1j**) gave a 76% yield of **3ja** with an *n*-selectivity of more than 99%. The trisubstituted internal double bond also stayed intact in this case (Table 1, entry 10). To our delight, the optimized conditions are also compatible with more bulky substrates, such as **1k** and **1l**, which resulted in 55% and 60% yields, respectively, with complete linear selectivity (Table 1, entries 11 and 12). The electronic effect of substituted allylbenzenes was also studied. The reaction between allylbenzene and *N*-methylacetamide went to complete conversion at a slightly elevated temperature (120°C), and the corresponding linear imide **3ma** was isolated in 88% yield with an *n*-selectivity of 90% (Table 1, entry 13). With 1-allyl-4-fluorobenzene (**1n**) as the substrate, the reaction was complete at 105°C and afforded **3na** in 85% yield and 88% selectivity (Table 1, entry 14). Finally, styrene was successfully employed as an example of an aromatic olefin (Table 1, entry 15; 63% yield and 70% *n*-selectivity). This system was further demonstrated to tolerate Br and Cl substituents on styrene derivatives. Under the optimized reaction conditions, low conversions were observed (28% and 31% yield of isolated product for **3pa** and **3qa**, respectively). By increasing

Table 1: Palladium-catalyzed hydroamidocarbonylation of different alkenes.

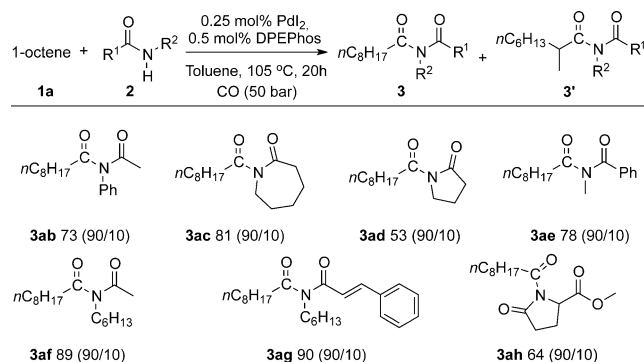
		$\text{R-CH=CH}_2 + \text{CH}_3\text{CONH-R} \xrightarrow[\text{CO (50 bar)}]{\text{0.25 mol\% PdI}_2, \text{0.5 mol\% DPEPhos, Toluene, 105 }^\circ\text{C, 20h}}$		
Entry ^[a]	1	3	Yield [%] (<i>n</i> / <i>iso</i>) ^[b]	
1			87 (89/11) 88 (89/11) ^[f]	
2			88 (89/11)	
3 ^[c]			83	
4 ^[c]			90	
5 ^[c]			58 (+/-)	
6 ^[d]			91	
7			85 (89/11)	
8			86 (89/11)	
9			90 (97/3)	
10			76 (>99/1)	
11			55 (>99/1)	
12			60 (>99/1)	
13 ^[e]			88 (90/10)	
14			85 (88/12)	
15			63 (70/30)	
16 ^[g]			60 (75/25)	
17 ^[g]			67 (75/25)	

[a] **1** (1.5 mmol), **2** (1 mmol), PdI₂ (0.0025 mmol, 0.25 mol %), DPEPhos (0.005 mmol, 0.5 mol %), CO (50 bar), toluene, 105 °C, 20 h. [b] Yield of isolated **3**, the number in parenthesis indicates *n*/*iso* selectivity determined by gas chromatography. [c] **1** (1 mmol). [d] Reaction carried out on a 4 mmol scale with 0.5 g ethylene (ca. 4.5 equiv) in a 25 mL autoclave. [e] 120 °C. [f] Reaction carried out on a 10 mmol scale. [g] PdI₂ (0.01 mmol, 1 mol %), DPEPhos (0.02 mmol, 2 mol %).

the catalyst loading (1 mol % PdI₂, 2 mol % DPEPhos), the corresponding products **3pa** and **3qa** were isolated in 60 %

and 67 % yield, respectively, with 75 % *n*-selectivity (Table 1, entries 16 and 17).

To reveal the generality of this method, different amides were tested (Scheme 3). By using acetanilide (**2b**) under the standard conditions, **3ab** was obtained in 73 % yield with 90 % *n*-selectivity. Industrially important aliphatic lactams, which

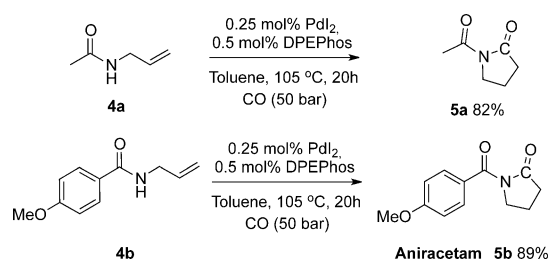


Scheme 3. Hydroamidocarbonylation with different amides as nucleophile. Reaction conditions: **1** (1.5 mmol), **2** (1 mmol), PdI₂ (0.0025 mmol), DPEPhos (0.005 mmol), CO (50 bar), toluene, 105 °C, 20 h. In each case, the yield (%) of isolated compound **3** is given, and the number in the parenthesis indicates the **3/3'** ratio.

are produced as bulk chemicals, were also tested: the use of ϵ -caprolactam (**2c**) and 2-pyrrolidinone (**2d**) as nucleophiles led to the corresponding imides **3ac** and **3ad** in 81 % and 53 % yield, respectively, with 90 % *n*-selectivity. *N*-Methylbenzamide (**2e**) was also shown to be compatible, and afforded **3ae** in 78 % yield and 90 % *n*-selectivity. Moreover, longer aliphatic chain amides also reacted smoothly. When *N*-hexylacetamide (**2f**) was subjected to the optimized conditions, an excellent yield of **3af** was obtained. With *N*-hexylcinnamide (**2g**) as the substrate, **3ag** was obtained in an excellent yield (90 % yield, 90 % *n*-selectivity). More strikingly, amino acid derived methyl pyroglutamate (**2h**) also proved to be a suitable substrate and afforded **3ah** in 64 % yield and 90 % selectivity.

To further demonstrate the applicability of this novel method, an example of an intramolecular hydroamidocarbonylation was also investigated. Gratifyingly, carbonylation of the allylic amide **4a** occurred in a straightforward manner and afforded the expected product in 82 % yield (Scheme 4). This result inspired us to synthesize Aniracetam, which is sold in Europe as a prescription drug and is considered to be more potent than the well-known Piracetam. Simply starting from *N*-allyl-4-methoxybenzamide, carbonylation proceeded at 105 °C and 50 bar of CO to give Aniracetam in 89 % yield of the isolated product.^[14]

Although the detailed mechanism of this reaction remains to be further elucidated, we suggest that the reaction goes through a similar reaction pathway as the well-known alkoxycarbonylation reaction mechanism, with Pd-H as the key intermediate.^[15] Initially, the active Pd-H catalyst is generated from the respective Pd^{II} precursor.^[16] This assumption is also supported by the alkene isomerization observed



Scheme 4. Intramolecular hydroamidocarbonylation. Reaction conditions: **4** (1 mmol), PdI₂ (0.0025 mmol), DPEPhos (**L12**, 0.005 mmol), CO (50 bar), toluene (2 mL), 105 °C, 20 h. The yield of isolated product is given.

after reaction being promoted by the Pd-H species. Notably, the role of the counterion could possibly be rationalized by the Pd-H species being generated more easily with a palladium precursor with a conjugate anion from a strong acid (e.g. Cl[−], Br[−], I[−]). Insertion of the alkene, followed by reaction with CO leads to the corresponding acylpalladium intermediate. Finally, nucleophilic attack of the amide affords the imide as the final product and regenerates the active species Pd-H.^[7d,i] However, we are not able to exclude other mechanistic pathways.

In summary, a novel palladium-catalyzed hydroamidocarbonylation reaction of aliphatic and aromatic alkenes using amides as nucleophile was successfully developed. This method provides an economical and sustainable synthesis of versatile imides. The optimal catalyst system (PdI₂/DPEPhos) is commercially available and is shown to be efficient and robust at relatively low catalyst loading. With respect to applications, it is noteworthy that alkenes with different structural characteristics are tolerated and the corresponding imides are produced highly selectively (89–99% *n*-selectivity). Moreover, various amides were tested and transformed to the corresponding imides in moderate to excellent yields (64–90%). The synthetic utility of the method is showcased by the synthesis of the anxiolytic drug Aniracetam in an atom-economic manner.

Keywords: alkenes · amides · carbonylation · homogeneous catalysis · imides

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- [16] The initial reduction of Pd^{II} to Pd⁰ to form the active palladium hydride species is possible through interaction with the substrate, phosphorus ligand, or carbon monoxide in the presence of traces of H₂O. The effect of the water content was also studied. Similar results were obtained on addition of a small amount of water (2.5 μL mL⁻¹). However, decreased product yields were observed on increasing the water content. This can be explained by decomposition of the catalyst and/or the product in the presence of a higher concentration of water (See Figure S1 in Supporting Information for details).

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