Carbonylation

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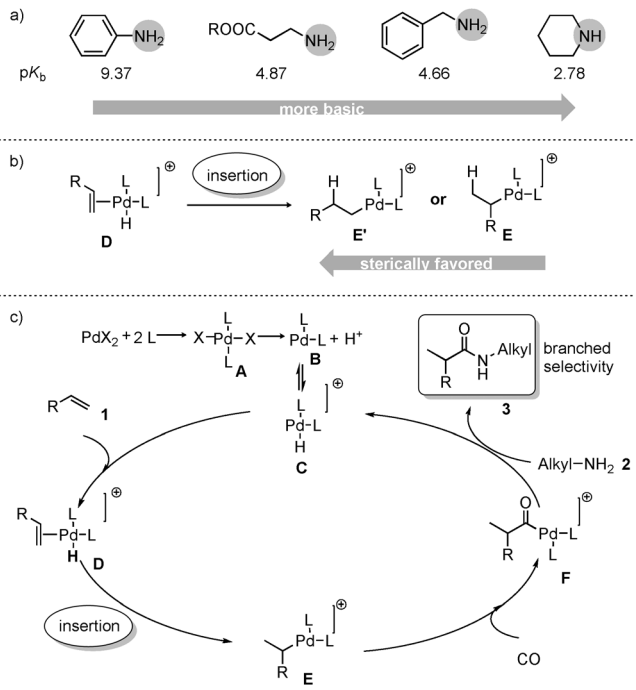
# Selective Palladium-Catalyzed Aminocarbonylation of Olefins to Branched Amides

*Jie Liu, Haoquan Li, Anke Spannenberg, Robert Franke, Ralf Jackstell, and Matthias Beller**

***Abstract:*** *A general and efficient protocol for iso-selective aminocarbonylation of olefins with aliphatic amines has been developed for the first time. Key to the success for this process is the use of a specific 2-phosphino-substituted pyrrole ligand in the presence of $PdX_2$ (X = halide) as a pre-catalyst. Bulk industrial and functionalized olefins react with various aliphatic amines, including amino-acid derivatives, to give the corresponding branched amides generally in good yields (up to 99 %) and regioselectivities (b/l up to 99:1).*

Carbonylation reactions are widely used for the industrial production of fine and bulk chemicals, especially to produce valuable monomers for polymers.[1] Because of the versatility of the carbonyl group and the possibility to easily expand carbon chains, they also find increasing applications in organic synthesis.[2] Within this class of reactions, transition metal catalyzed aminocarbonylations, also called hydroamidations, represent a straightforward method for the conversion of available olefins, CO, and amines into the corresponding amides, which represent important intermediates, building blocks, and functional molecules in organic synthesis, the chemical industry, as well as biological systems.[3]

Since the original work of Reppe and co-workers in the 1950s,[4] numerous catalytic systems based on cobalt,[5] nickel,[6] iron,[7] and ruthenium[8] complexes have been developed, and allow aminocarbonylation of olefins with amines. However, the severe reaction conditions (high temperature and CO pressure), unavoidable byproducts (formamide), and limited substrate scope impeded further applications of these processes. Recently, palladium-based catalysts for aminocarbonylation of olefins were reported independently by the groups of Cole-Hamilton,[9] Liu,[10] and Alper,[11] as well as our group.[12] Despite the significant progress in this area, all these methods are limited to aromatic amines as substrates, and carbonylations with aliphatic amines failed. This behavior is simply explained by the stronger basicity of aliphatic amines: For example, alanine ester ($pK_b = 4.87$), benzylamine ($pK_b = 4.66$), and piperidine ($pK_b = 2.78$) are much more basic than aniline ($pK_b = 9.37$; Scheme 1 a).[13] Hence, aliphatic amines retard the generation of the active palladium hydride species **C**, which are crucial for catalysis (Scheme 1 c). To overcome this problem, Huang and co-workers developed an elegant strategy to utilize aminals as surrogates of aliphatic amines.[14] Alternatively, our group applied a rhodium catalyst as the solution to this problem.[15] Notably, both catalyst systems favor the formation of the linear amides from olefins and aliphatic amines. In contrast, the formation of the branched amides from carbonylation reactions is more challenging because of the increase in steric effects for the olefin insertion into the palladium–hydride bond to form the secondary carbon palladium intermediates **E** (Scheme 1 b).[16] Although a few examples of branched-selective functionalization of olefins, such as hydroformylation,[17] hydroamination,[18] hydroacylation,[19] and hydrocyanation,[20] etc.,[16b] have been developed in recent years, such carbonylations of aliphatic amines with olefins, especially for industrially available bulk olefins such as propene, hexene, octene, etc., are basically unknown and




***Scheme 1.*** a) The $pK_b$ of various amines. b) Two pathways for olefin insertion into the Pd–H bond. c) Catalytic cycle for palladium-catalyzed branched-selective carbonylation of olefins with aliphatic amines.

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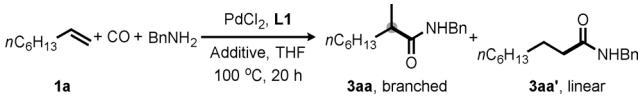
continue to be a challenging goal in homogeneous catalysis. Herein, we report for the first time the development of a general and efficient palladium catalyst for the aminocarbonylation of olefins with aliphatic amines giving selectively branched products.

To prevent the deactivation of the palladium hydride catalyst by the strongly basic aliphatic amine, we investigated the reaction of benzylamine with 1-octene (**1a**) in the presence of different acidic additives including, Brønsted acids and Lewis acids. Based on our recent work on the alkoxylcarbonylation of olefins,[21] we used a combination of $PdCl_2$ and CataCXium® POMeCy (2-(dicyclohexylphosphino)-1-(2-methoxyphenyl)-1*H*-pyrrole; **L1**)[22] under 40 bar of CO in THF at 100 °C. As shown in Table 1, when

***Table 1:*** Selective aminocarbonylation of 1-octene (**1a**) and benzylamine: Effect of additives.[a]




| Entry | Additive | Yield [%] | *b*/*l* |
|---|---|---|---|
| 1 | none | 0 | – |
| 2 | $NEt_3$·HCl (1.0 equiv) | 0 | – |
| 3 | HOAc (1.0 equiv) | 0 | – |
| 4 | HCl (10 mol%) | 0 | – |
| 5 | $Zn(OTf)_2$ (5 mol%) | 0 | – |
| 6 | $Sc(OTf)_3$ (5 mol%) | 0 | – |
| 7 | $Yb(OTf)_3$ (5 mol%) | 0 | – |
| 8 | $BnNH_2$·HCl instead of $BnNH_2$ | 48 | 85:15 |

[a] Reaction conditions: **1a** (2.0 mmol), $BnNH_2$ (1.0 mmol), $PdCl_2$ (1.0 mol%), ligand **1** (2.0 mol%), additive, CO (40 bar), THF (2.0 mL), 100 °C, 20 h. Yields (**3aa** + **3aa′**) and regioselectivities were determined by GC analysis using isooctane as the internal standard. Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

$BnNH_2$ was used without any additives, no desired product was observed at all (entry 1). Similarly, attempts to adjust the pH of the reaction solution by adding hydrochloride salts, like $NEt_3$·HCl, did not give any product in this reaction (entry 2). Other acidic additives, like Brønsted acids (entries 3 and 4) and Lewis acids (entries 5–7), all turned out to be ineffective. However, when applying $BnNH_2$·HCl instead of $BnNH_2$, the branched amide (**3aa**) was formed with high selectivity (85:15) albeit in moderate yield (48%) was achieved (entry 8).

It should be noted that the observed regioselectivity is unexpected, and it intrigued us to further investigate this reaction. Hence, we examined the benchmark reaction in the presence of a series of phosphines (Figure 1). When $PPh_3$ was used as ligand, good yield (69%) was obtained while moderate regioselectivity was observed (*b*/*l* = 68:32). To elaborate the influence of the ligand structure on the catalyst reactivity, more (hetero)arylphosphine ligands were employed (**L2** to **L6**). To our delight, when applying **L2** [2-(diphenylphosphino)-1-(2-methoxyphenyl)-1*H*-pyrrole] the yield of **3aa** increased to 61% with a good branched selectivity (*b*/*l* = 88:12).[23] Notably, **L3**, bearing the *t*Bu group on phosphorus, suppressed this reaction. The modification of

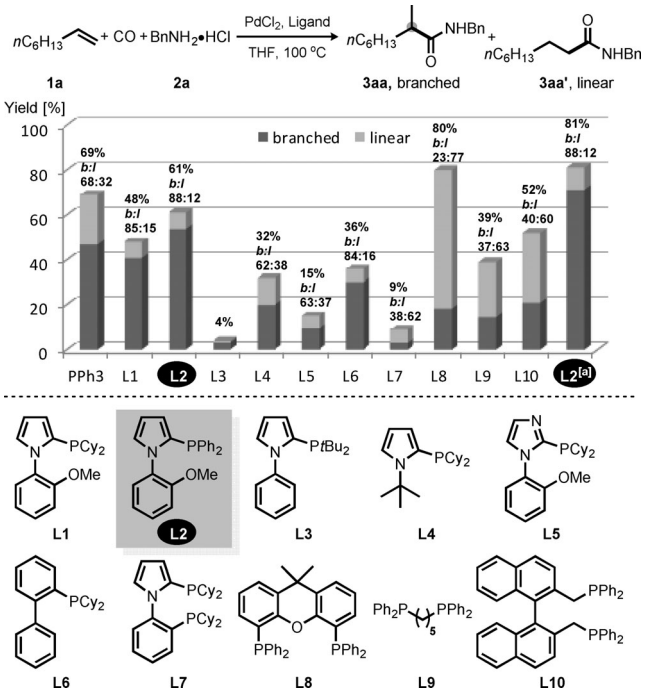



***Figure 1.*** Ligand effect for branched selective aminocarbonylation of **1a** with **2a**. Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), $PdCl_2$ (1.0 mol%), monodentate ligand (2.0 mol%), or bidentate ligand (1.0 mol%), CO (40 bar), THF (2.0 mL), 100 °C, 20 h. Yields and regioselectivities were determined by GC analysis using isooctane as the internal standard. [a] 1.5 mol% $PdCl_2$, 3.0 mol% **L2** was added, 125 °C, 24 h.

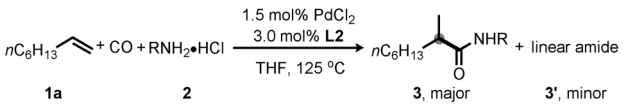
substitution, at N on the pyrrole, from an aryl to alkyl group (**L4**), did not present any improvement in this reaction. Notably, changing the pyrrole moiety to imidazolyl and phenyl (**L5** and **L6**), the catalytic performance of the corresponding catalysts declined. Interestingly, bidentate ligands such as **L7**–**L10** gave the linear amide as the major product.[16a] Finally, using 1.5 mol% palladium catalyst at 125 °C led to the desired product in 81% yield and good regioselectivity (*b*/*l* = 88:12)[24] (for detailed optimization of the reaction conditions, see the Supporting Information; Table S1–S6.)

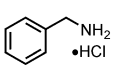
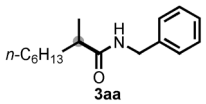
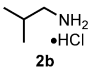
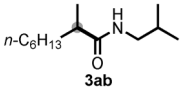
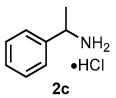
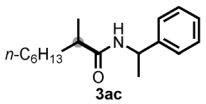
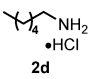
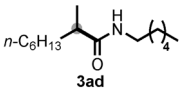
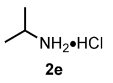
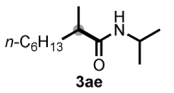
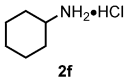
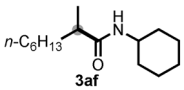
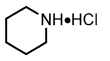
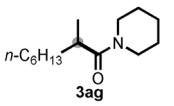
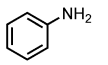
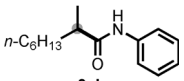
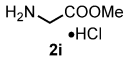
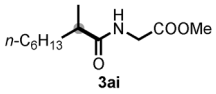
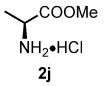
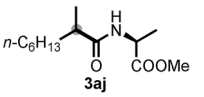
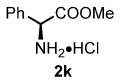
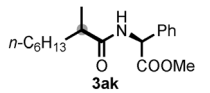
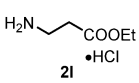
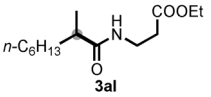
With the optimized reaction conditions in hand, we explored the substrate scope. At first, the reactions of various aliphatic amine hydrochlorides (**2**) with 1-octene (**1a**) were studied (Table 2). With primary amines such as benzylamine (**2a**), isobutylamine (**2b**), α-methylbenzylamine (**2c**), and hexylamine (**2d**) as starting materials, good yields (72–80%) and regioselectivities (*b* selectivity up to 88%) were achieved (entries 1–4). More bulky substituted amines, such as isopropylamine (**2e**) and cyclohexylamine (**2f**), also underwent this transformation smoothly in moderate to good yields (entries 5 and 6). The reaction of piperidine (**2g**), as an example of a secondary amine, provided the corresponding product in moderate yield (entry 7).

Moreover, aromatic amines such as aniline were selectively carbonylated to the branch amide in excellent yields and selectivities (Table 2, entry 8). In contrast, this novel methodology allows functionalization of a series of amino-

***Table 2:*** Palladium-catalyzed aminocarbonylation with the aliphatic amine salts **2**.[a]



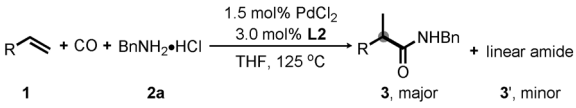

| Entry | Amine·HCl | Major product | Yield [%][b] | *b*/*l*[c] |
|---|---|---|---|---|
| 1 |  **2a** |  **3aa** | 80 | 88:12 |
| 2 |  **2b** |  **3ab** | 74 | 83:17 |
| 3 |  **2c** |  **3ac** | 70 | 83:17 |
| 4 |  **2d** |  **3ad** | 76 | 82:18 |
| 5 |  **2e** |  **3ae** | 72 | 84:16 |
| 6 |  **2f** |  **3af** | 68 | 85:15 |
| 7[d] |  **2g** |  **3ag** | 42 | 82:18 |
| 8[e] |  **2h** |  **3ah** | 99 (99[f]) | 87:13 |
| 9[g] |  **2i** |  **3ai** | 58 | 91:9 |
| 10[g] |  **2j** |  **3aj** | 68 | 88:12 |
| 11[g] |  **2k** |  **3ak** | 73 | 88:12 |
| 12[g] |  **2l** |  **3al** | 62 | 85:15 |

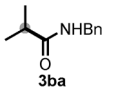
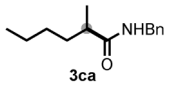
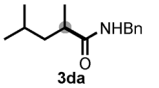
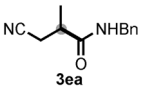
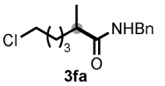
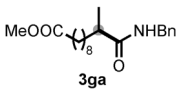
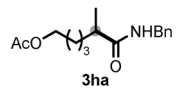
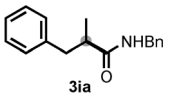
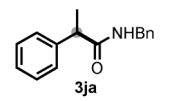
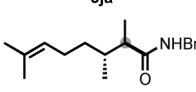
[a] Reaction conditions: **1a** (2.0 mmol), **2** (1.0 mmol), $PdCl_2$ (1.5 mol%), L2 (3.0 mol%), CO (40 bar), THF (2.0 mL), 125 °C, 24 h. [b] Yield of isolated amides as a mixture of branched (major) and linear (minor) products. [c] Regioselectivity was determined by GC analysis. [d] Reaction at 110 °C for 36 h. [e] **1a** (2.0 mmol), aniline (1.0 mmol), $H_2O$ (5 μL), $PdBr_2$ (1.5 mol%), L2 (3.0 mol%), CO (40 bar), THF (2.0 mL), 125 °C, 24 h. [f] With 1.5 mol% $[Pd(\mathbf{L2})_2Br_2]$ pre-catalyst (complex **A**) as catalyst precursor. [g] Reaction at 125 °C for 36 h.

acid derivatives in a straightforward manner. Here, several natural α-amino-acid derivatives, such as glycine methyl ester (**2i**), L-alanine methyl ester (**2j**), and (*S*)-(+)-2-phenylglycine methyl ester hydrochloride (**2k**), participated efficiently in this process without racemization (entries 9–11). Additionally, the β-amino-acid derivative β-alanine ethyl ester hydrochloride (**2l**) also reacted smoothly to give the corresponding amide (**3al**) selectively (entry 12).

Next, reactions of $BnNH_2$·HCl (**2a**) with bulk industrial, as well as functionalized olefins (**1**), were studied. For example, industrially important propene (**1b**) gave *N*-benzyl isobutyric amide, in the presence of only 0.2 mol% of the catalyst, in excellent yield (Table 3, entry 1). 1-Hexene (**1c**) and 4-methyl-1-pentene (**1d**) also furnished the desired aminocarbonylation products in moderate yields and branched selectivities (entries 2 and 3). Olefins containing

***Table 3:*** Palladium-catalyzed aminocarbonylation with different olefins (**1**).[a]




| Entry | Olefin | Major product | Yield [%][b] | *b*/*l*[c] |
|---|---|---|---|---|
| 1[d] | **1b** |  **3ba** | 98 | 92:8 |
| 2 | **1c** |  **3ca** | 74 | 90:10 |
| 3[e] | **1d** |  **3da** | 65 | 87:13 |
| 4 | **1e** |  **3ea** | 86 | 87:13 |
| 5 | **1f** |  **3fa** | 62 | 89:11 |
| 6 | **1g** |  **3ga** | 68 | 85:15 |
| 7[e] | **1h** |  **3ha** | 41 | 81:19 |
| 8 | **1i** |  **3ia** | 97 | 88:12 |
| 9 | **1j** |  **3ja** | 97 | >99:1 |
| 10[e] | **1k** |  **3ka** | 39 | 62:38 |

[a] Reaction conditions: **1** (2.0 mmol), **2a** (1.0 mmol), $PdCl_2$ (1.5 mol%), L2 (3.0 mol%), CO (40 bar), THF (2.0 mL), 125 °C, 24 h. [b] Yield of isolated amides as a mixture of branched (major) and linear (minor) products. [c] Regioselectivity was determined by GC analysis. [d] **1b** (20 mmol), **2a** (5.0 mmol), $PdCl_2$ (0.2 mol%), L2 (0.8 mol%), CO (40 bar), THF (6.0 mL), 130 °C, 36 h. [e] Reaction time of 36 h.

nitrile (**1e**), halogen (**1f**), and ester groups (**1g** and **1h**) were efficiently converted into the branched amines (41–86%) with good regioselectivities (entries 4–7). Allylbenzene (**1i**) also demonstrated excellent reactivity and high regioselectivity (entry 8). Gratifyingly, aromatic olefins like styrene (**1j**) led to the corresponding amide in high yield with excellent *b* selectivity (>99%; entry 9). When (−)-β-citronellene (**1k**) was used as the substrate, the internal bond remained intact and only the double bond in the terminal position was selectively carbonylated to the branched amide (entry 10).

In summary, we developed the first palladium catalyst system for a general and selective aminocarbonylation of olefins with aliphatic amines. By applying a special pyrrole-type ligand, a wide range of aliphatic amines and olefins are efficiently transformed into the corresponding branched amides in good yields and often with high regioselectivity. Apart from simple aliphatic and aromatic amines, this procedure allows the efficient and selective aminocarbonylation of amino acids derivatives, too. In view of the easy availability of the substrates, the efficiency, and the good regioselectivity, this method is expected to complement the current methods for carbonylations in organic synthesis.

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**Keywords:** amines · carbonylation · olefins · P ligands · synthetic methodology

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[23] The molecular structure of the [Pd(**L2**)$_2$Br$_2$] pre-catalyst (CCDC 1480945) is given in supporting information (Figure S1). CCDC 1480945 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[24] Theoretically, simple 1-octene might form four different regio-isomeric C9-amides because of the olefin isomerization reaction and then followed by carbonylation of different internal olefins. In the presence of our catalyst system, **3aa** and **3aa′** were mainly obtained and only trace amounts of other internal isomeric amides were observed by GC.

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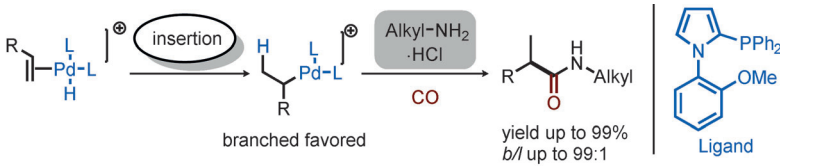
# Communications

**Carbonylation**

J. Liu, H. Li, A. Spannenberg, R. Franke, R. Jackstell, M. Beller* ——— ■■■■–■■■■

Selective Palladium-Catalyzed Aminocarbonylation of Olefins to Branched Amides




**Branch out**: A general protocol for *iso*-selective olefin aminocarbonylation has been developed. Key to success is the use of a specific 2-phosphino-substituted pyrrole ligand in the presence of $PdX_2$. Bulk industrial and functionalized olefins react with various aliphatic amines, including amino acid derivatives, to give the corresponding branched amides in good yields and regioselectivities.