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Palladium-Catalyzed Decarboxylative Three-Component Synthesis of α-Arylglycines: Replacing Boronic with Carboxylic Acids in the Petasis Reaction

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In memory of Prof. *Rolf Huisgen*

A palladium-catalyzed three-component synthesis of α-arylglycines from benzoic acids, sulfonamides and glyoxylic acid is reported. This novel reaction offers straightforward access to the important arylglycine motif in good yields and high structural diversity. By replacing boronic with carboxylic acids as nucleophilic component, this method can be considered as a more sustainable version of the classical Petasis reaction for synthesis of arylglycines.

α-Amino acids are ubiquitous in every aspect of our daily life. As backbone of all peptides and proteins they play a central role in almost all biological processes.[1] In addition, many α-amino acids have important, nonprotein-related functions. α-Amino acids are key building blocks for the production of agrochemicals, drugs, fertilizers, biodegradable plastics or nutritional supplements.[1,2] Due to the tremendous advances in the development of protein-based drugs[3] and protein-engineering,[4] non-proteinogenic (or unnatural) amino acids have attracted considerable attention.

Among the different classes of non-proteinogenic α-amino acids, α-arylglycines are of outstanding importance. The α-arylglycine motif can be found in various natural products with unique biological activities, such as vancomycin[5] or feglymycin.[6] α-Arylglycines are versatile building blocks in organic synthesis and have been successfully employed in the construction of several active pharmaceutical ingredients, e.g. the β-lactam antibiotic amoxicillin[7] or the antiplatelet agent clopidogrel.[8]

Therefore, the need to synthesize the α-arylglycine scaffold in an efficient and sustainable manner is constantly increasing. Indeed, various approaches for the construction of these class of α-amino acids have been developed over the years.[9] The most common procedures for the synthesis of α-arylglycines include reactions based on the addition of a nucleophilic component to a reactive imine species, such as the Strecker reaction,[10] aza-Friedel-Crafts-type reactions[11] or the Petasis-(Borono)-Mannich reaction.[12] The latter one represents a very attractive strategy for the rapid assembly of α-arylglycines (Figure 1a). This three-component reaction between aryl boronic acids, a glyoxylic acid derivative and an amine component gives access to the arylglycine scaffold in great structural diversity.[12,13] However, from an ecological as well as an economical point of view, the stoichiometric use of organoboron reagents, usually prepared in several steps involving reactive organometallic intermediates, is highly problematic.

In the last two decades, the use of aryl carboxylic acids instead of preformed organometallic reagents has become a powerful new tool for a more sustainable construction of carbon-carbon as well as carbon-heteroatom bonds.[14] Aromatic carboxylic acids are bench stable and readily available in a huge variety. Their use as aryl donors in metal-catalyzed decarboxylative transformations generates a minimum amount of waste, viz. one equivalent of carbon dioxide. Especially decarboxylative cross-coupling reactions of benzoic acids with aryl halides have been studied extensively.[15]

Considering the synthetic utility of the Petasis reaction, it would be of great interest to replace the organoboron component in this transformation in a similar manner with aryl carboxylic acids. However, the use of benzoic acids as aryl nucleophiles in Petasis-type reactions has, to the best of our knowledge, not been reported so far.[16]

Herein, we describe the development of a palladium-catalyzed, three-component synthesis of α-arylglycines from

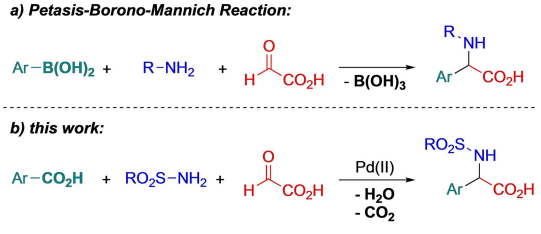

Figure 1. Synthesis of arylglycines from aryl boronic or aryl carboxylic acids.

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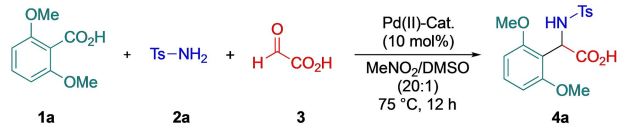
benzoic acids, sulfonamides and glyoxylic acid. This method offers a novel, highly versatile and more sustainable approach to the arylglycine scaffold (Figure 1b).

After an extensive preliminary screening campaign, we were able to obtain a first encouraging result. In the presence of 10 mol% $Pd(OAc)_2$ the reaction between 2,6-dimethoxybenzoic acid (**1a**), *p*-toluenesulfonamide (**2a**) and glyoxylic acid (**3**), employed in its solid and simple-to-handle monohydrate form, in a nitromethane/dimethlysulfoxide solvent mixture (5 vol% DMSO) afforded the desired arylglycine **4a** in 65% yield after 12 hours reaction time at 75 °C (Table 1, entry 1, see the supporting information for more details). An improved yield of 81% was obtained with palladium(II) trifluoroacetate ($Pd(TFA)_2$) as catalyst (entry 2). The addition of DMSO as cosolvent is crucial for an efficient reaction.[17] Decreasing the amount of DMSO to 2.5 vol% or 1.0 vol% led to a minimal reduction of the isolated yield (entry 3). Lower concentration of DMSO had a detrimental effect on the reaction (entry 4). On the other hand, no product formation was observed in the absence of DMSO (entry 5). The addition of silver(I) salts, which often display beneficial effects in Pd-catalyzed decarboxylative reactions, led to reduced yields (entry 6). The reaction proceeds with similar efficiencies in EtOAc or diglyme as solvent (entries 7 and 8). Within the further course of our studies, we observed, that reactions in $MeNO_2$ proceeded in general more efficiently than in EtOAc. Therefore, $MeNO_2$ was used predominantly in this work. Slightly lower amounts of the arylglycine **4a** were obtained in toluene or DMF (entries 9 and 10). Reduced catalyst loadings resulted in diminished yields (entry 11 and 12). Whereas a reduced temperature of 60 °C affords arylglycine **4a** in comparable yields (entry 13), reactions at lower or higher temperatures proved to be more sluggish (entries 14 and 15). Although slightly lower yields were obtained at 60 °C, reactions performed at this temperature provided the desired products with a better impurity profile, which greatly facilitated the final purification. Therefore, most reactions were performed at 60 °C in the further course of this project.

With the optimized conditions in hand, we investigated the scope of this reaction for different sulfonamide components (**2**) (Scheme 1). A broad range of aromatic sulfonamides, bearing electron-donating, electron-withdrawing or halogen substituents performed well in the decarboxylative three-component reactions, affording the desired arylglycines **4a**-**4g** in 50–82% yield. Reactions with a naphthalene- and a thiophen-derived sulfonamide led to the arylglycine derivatives **4i** and **4l** in 85% yield. Even sulfonamide components containing an amide functionality or bulky substituents in the *ortho*-position, were tolerated under the standard conditions, furnishing the desired products **4h** and **4j** in 68% and 58% yield. Reactions with different alkyl sulfonamides led to the formation of arylglycines **4m**–**4o** in 75–83% yield. For a synthetic chemist, *N*-sulfonylated arylglycines have advantages as well disadvantages. These products can be of interest by themselves, due to the sulfonamide scaffold, a privileged motif in medicinal chemistry.[18] On the other hand, further application in the synthesis of arylglycine-containing peptides requires the removal of the sulfonyl group from the amine. However, cleavage of common sulfonyl protecting groups, e.g. the tosyl group, usually requires quite harsh conditions.[19] Therefore, the direct incorporation of readily cleavable *N*-sulfonyl protecting groups in the three- component reaction would be highly desirable.

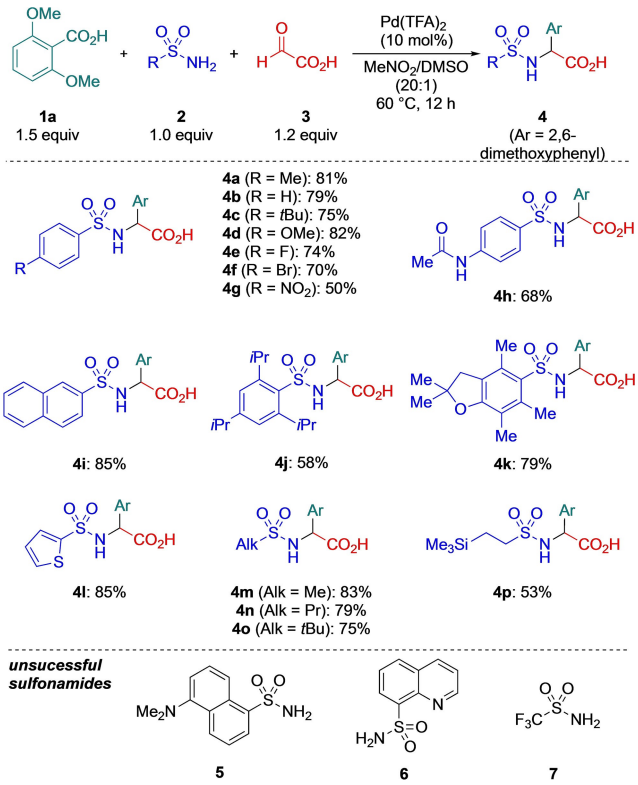
Table 1. Selected examples from the optimization of the reaction.[a]



1a 1.5 equiv | **2a** 1.0 equiv | **3** 1.2 equiv | **4a**

Entry	Variation	Yield [%][b]
1	w/ $Pd(OAc)_2$	65
2	w/ $Pd(TFA)_2$	**81**
3	w/ $Pd(TFA)_2$; 1–2.5 vol% DMSO	77-78
4	w/ $Pd(TFA)_2$; 0.1 vol% DMSO	53
5	w/ $Pd(TFA)_2$; w/o DMSO	-
6	w/ $Pd(TFA)_2$ and Ag_2CO_3 (10 mol%)	66
7	w/ $Pd(TFA)_2$; EtOAc instead of $MeNO_2$	**81**
8	w/ $Pd(TFA)_2$; diglyme instead of $MeNO_2$	75
9	w/ $Pd(TFA)_2$; toluene instead of $MeNO_2$	51
10	w/ $Pd(TFA)_2$; DMF instead of $MeNO_2$	69
11	w/ $Pd(TFA)_2$ (5 mol%)	72
12	w/ $Pd(TFA)_2$ (2.5 mol%)	62
13	w/ $Pd(TFA)_2$; at 60 °C	**75**
14	w/ $Pd(TFA)_2$; at 45 °C	33
15	w/ $Pd(TFA)_2$; at 100 °C	63

[a] All reactions were performed on a 0.5 mmol scale. Reactions were carried out without the exclusion of air or moisture. [b] Yield of isolated product after purification. Ts = *para*-Tosyl. TFA = trifluoroacetate.

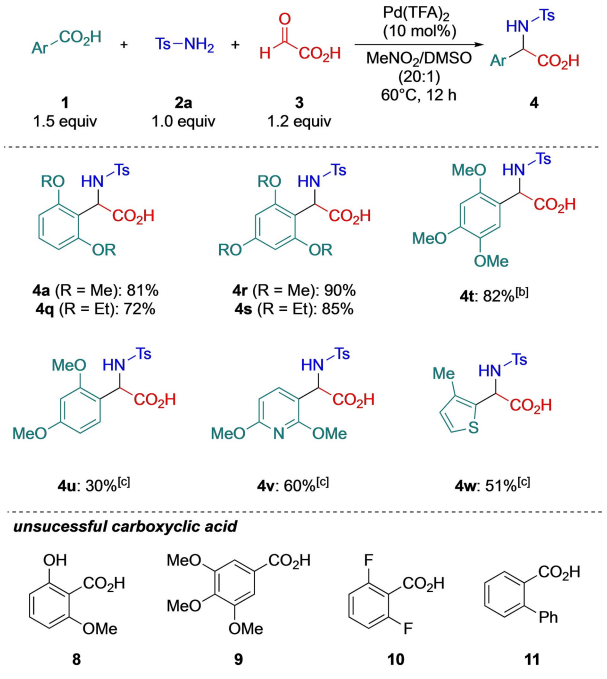


Scheme 1. Reaction scope - sulfonamide component.[a] [a] All reactions were performed on a 0.5 mmol scale. Yields of isolated products after purification.

Gratifyingly, both the reaction with 2-(trimethylsilyl)-ethanesulfonamide (SES-NH_2) and with 2,2,4,6,7-pentamethyl-dihydrobenzofurane-5-sulfon-amide (Pbf-NH_2) furnished the arylglycines **4k** and **4p**, bearing easy-to-remove SES- or Pbf-protecting groups,[20,21] in 79% and 53% yield. Unfortunately, reactions with sulfonamides bearing a basic nitrogen functionality, e.g. **5** and **6**, or the trifluoromethyl derivative **7**, did not afford the desired products.

Next we investigated reactions with different carboxylic acid components (Scheme 2). In general, this decarboxylative three-component reaction is limited to electron-rich benzoic acids containing at least one substituent in *ortho*-position. This kind of reactivity is in agreement with previous studies on Pd-catalyzed decarboxylative reactions by Kozlowski and Larhed.[22] Both 2,6-dimethoxy- and 2,6-diethoxybenzoic acid provided the desired arylglycines **4a** and **4q** in high yields. In case of the corresponding 2,4,6-trialkoxybenzoic acids, the expected products **4r** and **4s** were formed in even higher yields of 85–90%. Reactions with benzoic acids bearing only one methoxy-substituent in *ortho*-position required higher temperatures of 80–100 °C, furnishing the arylglycine derivatives **4t** and **4u** in 82% and 30% yield. To our delight, reactions with 2,6-dimethoxynicotinic acid and 3-methlythiophene-2-carboxylic acid proceeded smoothly, affording the two hetero-arylglycines **4v** and **4w** in good yields. Strikingly, even under more forcing reaction conditions, such as in the synthesis of **4t**, no decarboxylation of the arylglycine products was observed. Unfortunately, several other types of carboxylic acids, such as phenolic acid **8** or 3,4,5-trimethoxybenzoic acid (**9**), bearing no substituent in the *ortho*-position, did not afford the desired products. Also, *ortho*-substituted benzoic acids **10** and **11** lacking an electron-donating group, did not react.

In summary, we have developed a novel, palladium-catalyzed decarboxylative coupling of benzoic acids, sulfonamides and glyoxylic acid. This three-component reaction provides straightforward access to various α-arylglycines in good yields with a high degree of structural diversity. One could consider this process as a modern version of the classical Petasis reaction. By replacing the boronic acid component with a readily available carboxylic acid, it provides a more sustainable access to the arylglycine scaffold. Considering the prevalence of the arylglycine and the sulfonamide motif in biologically active molecules, this three-component reaction can become a highly useful tool not only for drug discovery but also for more sustainable organic synthesis. Studies to identify more active catalyst systems and extend the scope of this method are currently underway in our laboratory.



Scheme 2. Reaction scope – carboxylic acid component.[a] [a] All reactions were performed on a 0.5 mmol scale. Yields of isolated products after purification. [b] Reaction at 100 °C. [c] Reaction at 80 °C.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Synthetic methods · Multicomponent reaction · Sulfonamide · Palladium · Amino acid

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