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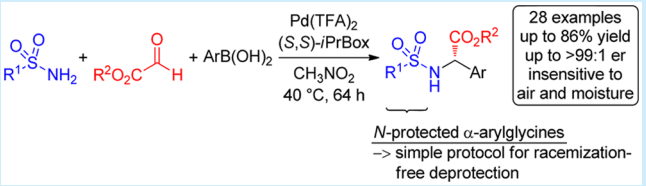
Palladium-Catalyzed Enantioselective Three-Component Synthesis of α-Arylglycines

Tamara Beisel, Andreas M. Diehl, and Georg Manolikakes*

Department of Organic Chemistry and Chemical Biology, Goethe-University Frankfurt am Main, Max-von-Laue-Strasse 7, 60438 Frankfurt am Main, Germany

Supporting Information

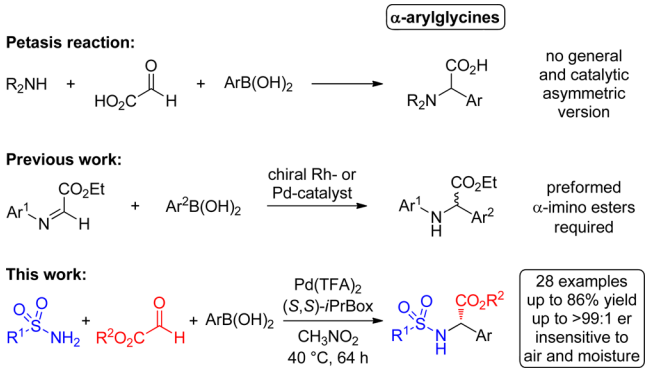
ABSTRACT: A general Pd-catalyzed, enantioselective three-component synthesis of α-arylglycines starting from sulfonamides, glyoxylic acid derivatives, and boronic acids was developed. This operationally straightforward procedure enables the preparation of a wide variety of α-arylglycines in high yields and excellent levels of enantioselectivity from a simple set of readily available starting materials. Incorporation of Pbf-amides gives a racemization-free access to N-unprotected α-arylglycines.



α-Arylglycines are an important class of unnatural or non-proteinogenic α-amino acids.[1] The α-arylglycine fragment can be found in many natural products and drugs, including peptide or glycopeptide antibiotics, such as vancomycin[2] or feglymycin,[3] β-lactam antibiotics (e.g., amoxicllin[4] or cefprozil),[5] or in the antiplatelet agent clopidogrel.[6] Optically active α-arylglycines have been widely used as privileged chiral building blocks in the preparation of biological active molecules, auxiliaries, or ligands.[7] Consequently, the asymmetric synthesis of α-arylglycines has received much attention. A variety of methods for the preparation of this important compound class have been developed.[1,8] Among them, addition of arylboronic acids to α-imino acids, the Petasis or borono-Mannich reaction, has emerged as an attractive strategy due to the widespread commercial availability of a large number of structural diverse boronic acids.[9] However, only electron-rich (hetero)aryl- or vinylboronic acids are efficient coupling partners, and to the best of our knowledge, no general catalytic asymmetric version of the Petasis reaction for the synthesis of arylglycines has been reported so far.[10] The transition-metal-catalyzed addition of boronic acids to preformed or in situ generated imines offers an attractive alternative since it allows the utilization of less reactive arylboronic acids.[11] Whereas the Rh-, Pd-, and Ru-catalyzed asymmetric addition of arylboronic acids to aryl- and aldimines has been well-established,[12] there are only few examples of stereoselective, transition-metal-catalyzed reactions with α-imino acids or esters.[13] Ellman, Batey, Lu, and Xu reported Rh- and Pd-catalyzed diastereoselective addition reactions of arylboronic acids to *N-tert*-butanesulfinylimino esters.[14] Catalytic asymmetric arylations of preformed α-imino esters with arylboronic acids were developed by Lu, Miyaura, and Zeng.[15] In general, the additional step for the preparation of the α-imino esters, the difficult purification, and the instability of these highly electrophilic compounds[16] severely restrict the practicability of these methods. A transition-metal-catalyzed, asymmetric multicomponent reaction,[17] based on the in situ formation of the α-imino ester, would provide an attractive, more practical alternative for the preparation of α-arylglycines.

Herein, we report the first general Pd-catalyzed asymmetric three-component synthesis of α-arylglycine derivatives starting from sulfonamides, arylboronic acids, and glyoxylic acid derivatives (Scheme 1). The obtained *N*-sulfonyl α-arylglycine products are versatile building blocks for subsequent transformations.

Scheme 1. α-Arylglycine Syntheses by Addition of Boronic Acids to α-Imino Acid Derivatives



Recently, we could develop a Pd-catalyzed enantioselective three-component synthesis of α-arylamines using sulfonamides, arylboronic acids, and either aryl or alkyl aldehydes.[18] To our delight, the same catalyst system, a combination of 10 mol % of $Pd(TFA)_2$ and 15 mol % of the readily available chiral bisoxazoline (*S,S*)-*i*PrBox,[19] could catalyze the three-component reaction between phenylboronic acid, *p*-toluenesulfonamide, and ethyl glyoxalate as the aldehyde component, furnishing the

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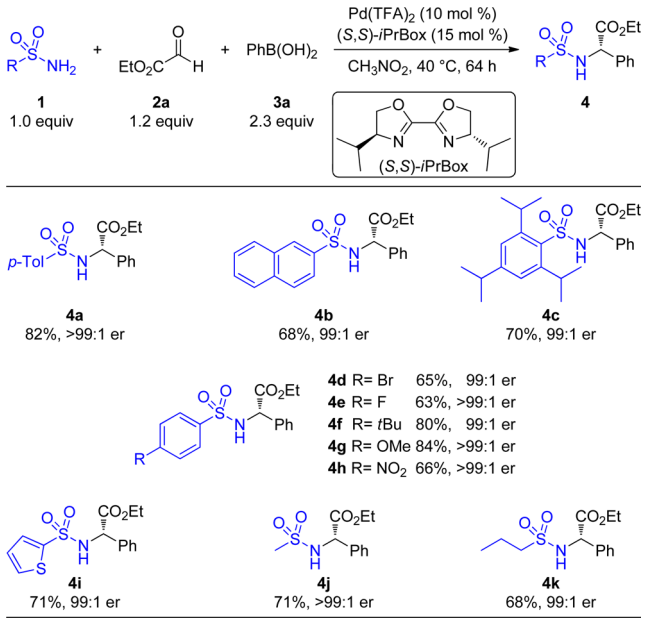
desired α-arylglycine **4a** in 82% yield and >99:1 er (Scheme 2). This reaction exhibits several features, which lead to an

Scheme 2. Variation of Sulfonamides[a]



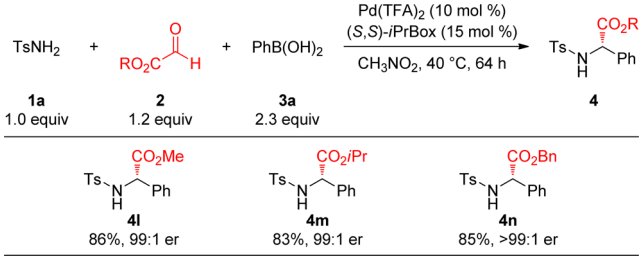
[a]Yields of the isolated products. Enantiomeric ratios determined by chiral HPLC analysis. TFA = trifluoroacetic acetate. *t*Bu = *tert*-butyl. Box = 4,4′,5,5′-tetrahydro-2,2′-bioxazole. *p*-Tol = *para*-tolyl.

operational simple process and are worth mentioning. A simple catalyst system is sufficient for this efficient and highly enantioselective transformation. No exogenous base, desiccant, or additives such as silver salts have to be added. The reaction can be performed without the exclusion of air and moisture because imine hydrolysis is not an issue in the three-component reaction. All starting materials are commercially available and can be employed without further purification. Indeed, the purity of the phenylboronic acid has been reported to be crucial for the success in other transformations.[12a,20] Most strikingly, commercially available, technical ethyl glyoxalate, a solution of the polymeric form in toluene, can be used directly.[21] Various other sulfonamides are suitable amide components for this reaction. High yields and excellent enantioselectivities were obtained with aromatic, heteroaromatic, or aliphatic sulfonamides. Steric or electronic effects did not significantly affect yield or enantioselectivities. Indeed, no influence of the sulfonamide structure on the stereoselectivity was observed, and all products (**4a**−**4k**) were formed with an enantiomeric ratio of 99:1 or better.

Moreover, several glyoxylic ester derivatives can be used as aldehyde component (Scheme 3). Reactions of the methyl, isopropyl, and benzylic esters furnished the desired α-arylglycine derivatives **4l**−**4n** in 83−86% yields and excellent enantioselectivities (99:1 er or better).

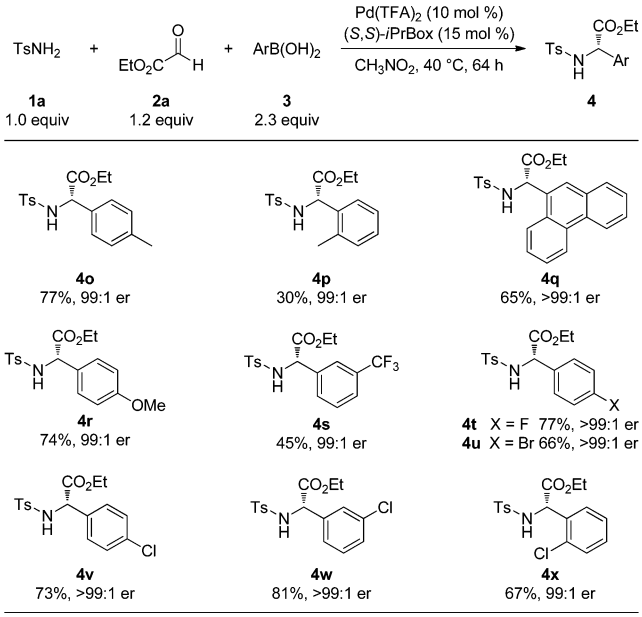
Next, we explored the scope in terms of the boronic acid component (Scheme 4). Various arylboronic acids were found to be efficient starting materials and furnished the corresponding *N*-sulfonyl α-arylglycines **4o**−**4x** in high yields and excellent enantioselectivities (er ≥99:1). Only the sterically hindered *o*-tolyl and the electron-poor *m*-CF_3-phenylboronic acid afforded the products in lower yields, albeit with excellent stereoselectivity. Unfortunately, aryl boronic acids bearing stronger electron-withdrawing substituents, such as −CN or $-CO_2Et$, did

Scheme 3. Variation of Glyoxalates[a]



[a]Yields of the isolated products. Enantiomeric ratios determined by chiral HPLC analysis. TFA = trifluoroacetic acetate. *i*Pr = isopropyl. Box = 4,4′,5,5′-tetrahydro-2,2′-bioxazole. Ts = *para*-tosyl. Bn = benzyl.

Scheme 4. Variation of Boronic Acids[a]



[a]Yields of the isolated products. Enantiomeric ratios determined by chiral HPLC analysis. TFA = trifluoroacetic acetate. *i*Pr = isopropyl. Box = 4,4′,5,5′-tetrahydro-2,2′-bioxazole.

not react at all. Again, no substituent effects on the enantioselectivity of the reaction were observed, and α-arylglycines were isolated almost enantiopure.

From a synthetic point of view *N*-sulfonyl-protected α-arylglycines can be problematic. Removal of common sulfonyl protecting groups, such as the tosyl or the nosyl group, is achieved under basic or reducing conditions.[22] However, α-arylglycines are prone to base-catalyzed racemization of the α-stereocenter.[1] Therefore, the incorporation of a sulfonamide, which allows facile removal of the sulfonyl group under acidic conditions, ideally with full compatibility to standard peptide synthesis, would be highly desirable. Based on these requirements, we identified the 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl (Pbf) group as most promising candidate. The Pbf group, originally introduced for the side chain protection of arginine, can be cleaved with acid, similar to the conditions applied for Boc deprotection.[23] It is compatible with solid-phase peptide synthesis, and the corresponding sulfonamide **1b** is readily available.[24] The reaction of **1b** with ethyl glyoxalate and phenylboronic acid using our standard protocol furnished the *N*-Pbf-protected α-arylglycine **4y** in 82% yield and

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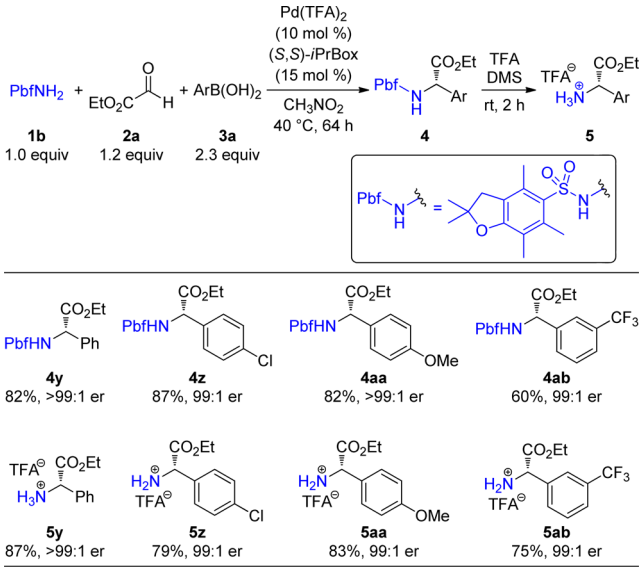
>99:1 er (Scheme 5). Removal of the Pbf group with TFA and DMS can be achieved with complete retention of configuration.

Scheme 5. Examples with Pbf-Sulfonamide and Their Deprotection[a]



[a]Yields of the isolated products. Enantiomeric ratios determined by chiral HPLC analysis. TFA = trifluoroacetic acetate. *i*Pr = isopropyl. Box = 4,4′,5,5′-tetrahydro-2,2′-bioxazole. Pbf = 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl. DMS = dimethylsulfide.

The free amine (**5y**), isolated as more stable TFA salt, was obtained in 71% overall yield. The applicability of the Pbf strategy was demonstrated in the synthesis of three more unprotected α-arylglycines. The desired α-amino acid derivatives **5z**–**5ab** could be prepared in 45–69% overall yields almost enantiopure.

In summary, an efficient and highly enantioselective Pd-catalyzed three-component synthesis of α-arylglycines from sulfonamides, glyoxylic acid derivatives, and arylboronic acids has been developed. A wide variety of commercially available starting materials can be utilized directly in this operationally very simple transformation. Common problems, such as imine hydrolysis, purification of the glyoxalate component, or boroxine contamination, were fully overcome by the three-component approach. The desired α-arylglycines, important compounds for biological studies and the synthesis of drugs and natural products, are obtained in high yields and excellent enantioselectivities. Introduction of the Pbf-protecting group allows a racemization-free removal of the sulfonyl group and gives simple access to the free amines. Studies toward the application of this method for the synthesis of biologically active molecules and α-arylglycine-rich natural products as well as investigations of the reaction mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02045.

Full experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: g.manolikakes@chemie.uni-frankfurt.de.

Notes

The authors declare no competing financial interest.

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(24) 2,2,4,6,7-Pentamethyl-2,3-dihydrobenzofuran-5-sulfonamide (**1b**) is commercially available or can be synthesized in one step from the corresponding sulfonyl chloride, which is cheaper and available from a larger number of different providers.

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