Palladium-Catalyzed Enantioselective Three-Component Synthesis of α-Arylglycine Derivatives from Glyoxylic Acid, Sulfonamides and Aryl Trifluoroborates

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Abstract

A palladium-catalyzed enantioselective three-component reaction of glyoxylic acid, sulfonamides and aryl trifluoroborates is described. This process provides modular access to the important α-arylglycine motif in moderate to good yields and enantioselectivies. The formed α-arylglycine products constitute useful building blocks for the synthesis of peptides or arylglycine-containing natural products.

Keywords

Palladium-catalysis; asymmetric catalysis; amino acids; multicomponent reaction; Petasis reaction; sulfonamides

Introduction

α-Amino acids play a crucial role in every aspect of our human life.[1] They are important synthetic intermediates in the chemical industry and used for the production of drugs, fertilizers, (biodegradable) polymers or nutritional supplements.[2] More importantly, α-amino acids from the backbone of all proteins and enzymes and are therefore essential for almost all biological processes. In the last twenty years non-proteinogenic and chemically synthesized unnatural amino acids received increasing attention due to advances in protein-engineering and the development of protein-based therapeutics.[3,4] Among the different types of non-proteinogenic and unnatural amino acids, α-arylglycines play a particular important role. The arylglycine scaffold can be found in several well-known natural products with interesting biological properties, such as the glycopeptide antibiotics vancomycin and teicoplanin[5] or the

feglymycin[6], a 13mer peptide which contains nine α-arylglycines in its backbone. α-Arylglycines derivatives are used in the production of important drugs, e.g. the antiplatelet drug clopidogrel[7] or the β-lactam antibiotic amoxicillin.[8]

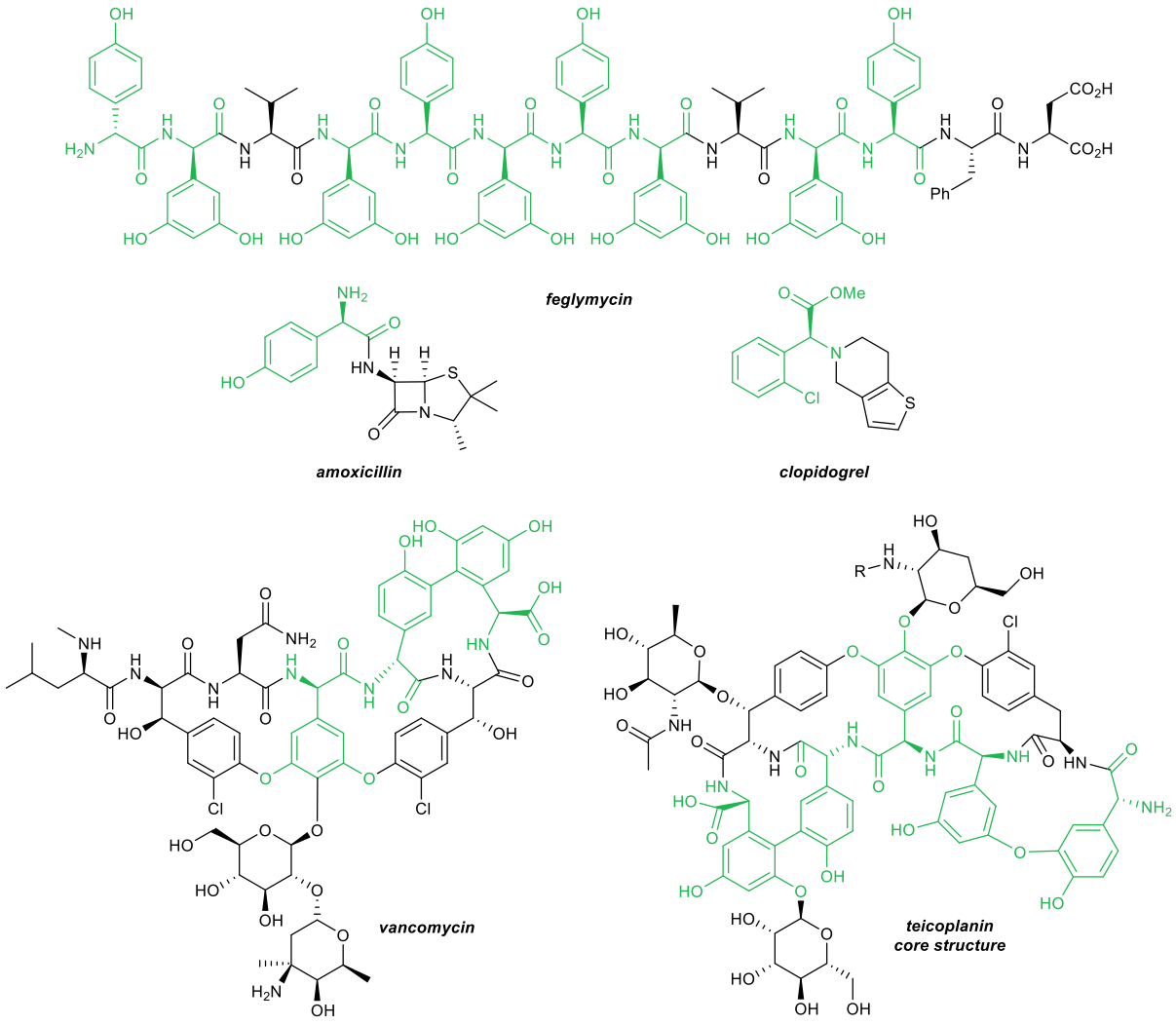


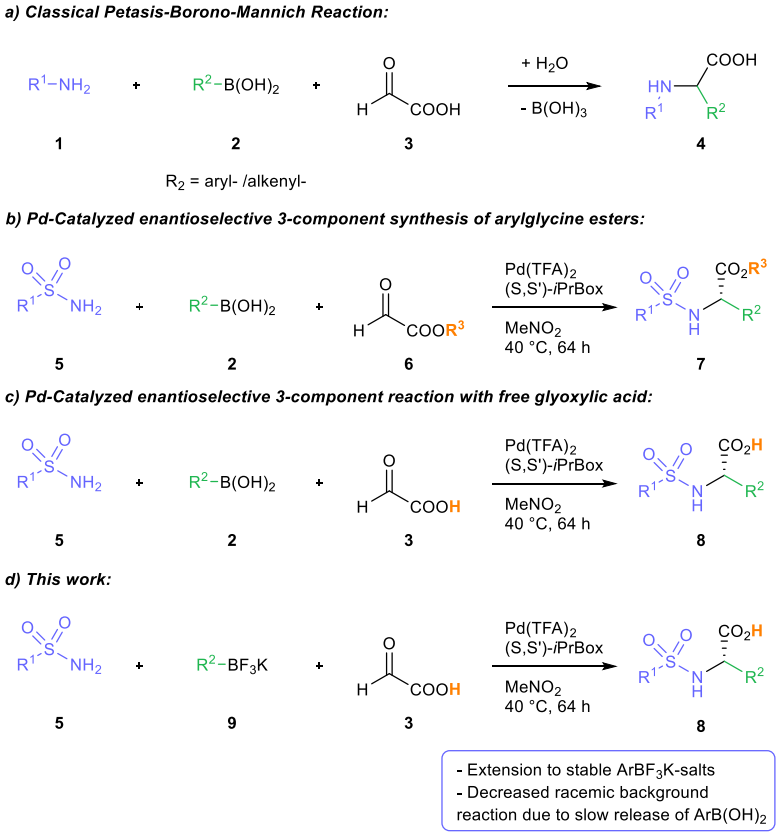
Figure 1: Biologically active molecules containing α-arylglycine motifs (highlighted in green).

Therefore, the chemical synthesis of α-aryglycines has received considerable attention. Among the different methods introduced over time, multicomponent reaction utilizing a in situ generated reactive imine species provide a very flexible approach to the arylglycine scaffold. [2,9] The Petasis-Borono-Mannich reaction constitutes a

prominent example for such an imine-based multicomponent reaction (Scheme 1a). The reaction of glyoxylic acid, an amine component and an aryl boronic acid offers a highly modular access to arylglycines from three readily available building blocks. [10-12] The Petasis-Borono-Mannich reaction usually proceeds in the absence of any external catalyst via zwitterionic intermediate and an intramolecular transfer of the aryl residue form the activated boronate to the electrophilic iminium carbon, leading to the amine product as racemic mixture. Consequently, examples for asymmetric version of the Petasis-Borono-Mannich reaction are rare[13] and usually rely on the utilization of chiral amine components in stoichiometric amounts. [10,11]

As part of our research program utilizing the in situ generation of reactive imine species, we have disclosed iron- and bismuth-catalyzed three-component reactions for the synthesis of α-aryglycines[14-16], in which the aryl boronic acid could be replaced with an electron-rich (hetero)arene as nucleophile. In parallel, we have developed palladium-catalyzed three-component reactions between aryl boronic or carboxylic acids, amides or sulfonamides and different aldehyde components as attractive and broadly applicable alternative to the classical Petasis-Borono-Mannich reaction (Scheme 1b).]17-20] Recently, we were able to extend these transformations to a palladium-catalyzed enantioselective synthesis of α-arylglycine bearing a free carboxylic acid functionality directly from the parent glyoxylic acids (Scheme 1c).[21] We could show, that the desired arylglycine can be synthesized in good to excellent enantioselectivities. However, depending on the nature/substitution pattern of aryl boronic acid, some of the arylglycine products could only be obtained in very low enantioselectivities. This can be attributed to a fast, uncatalyzed racemic background reaction of the boronic acids, in particular for electron-rich or sterically hindered aryl boronic acids.

Herein we report an improved version of this palladium-catalyzed enantioselective three-component reactions using aryl trifluoroborates are replacement of the aryl boronic acid building block (Scheme 1d). The broader scope of this 2nd generation protocol is exploiting a slow release of the boronic acid from the aryl trifluoroborates and enables to enantioselective synthesis of a broader variety of arylglycines, including a common building block for several biologically active compounds.

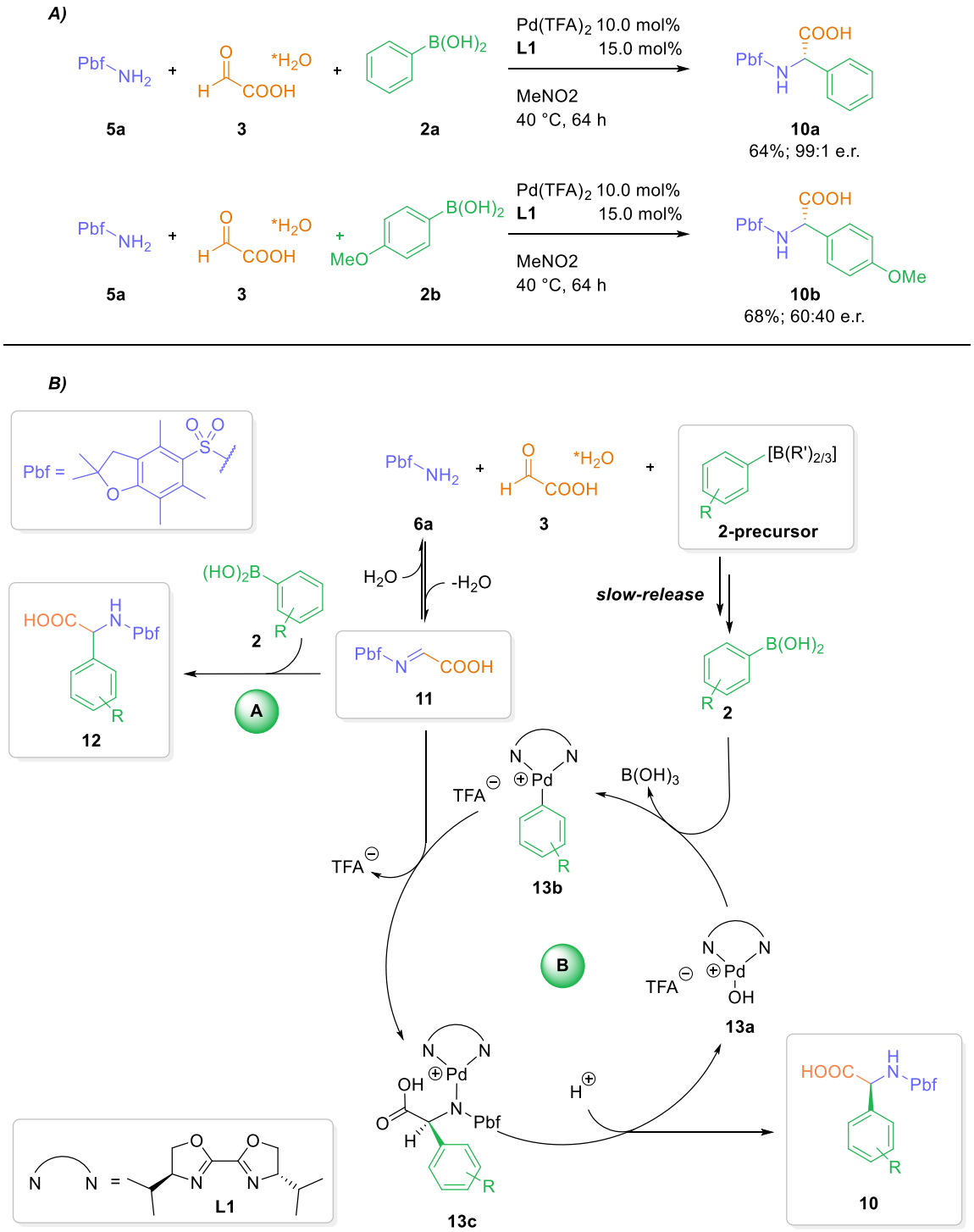


Scheme 1. The Petasis Reaction – Fundamental reactivities and Recent developments

Results and Discussion

During our previous studies, we observed, that the enantioselectivity of the three-component coupling of glyoxylic acid (employed as its solid, easy-to-handle monohydrate) with 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonylamide and an aryl boronic acid was significantly affected by the nature of the boronic acid.

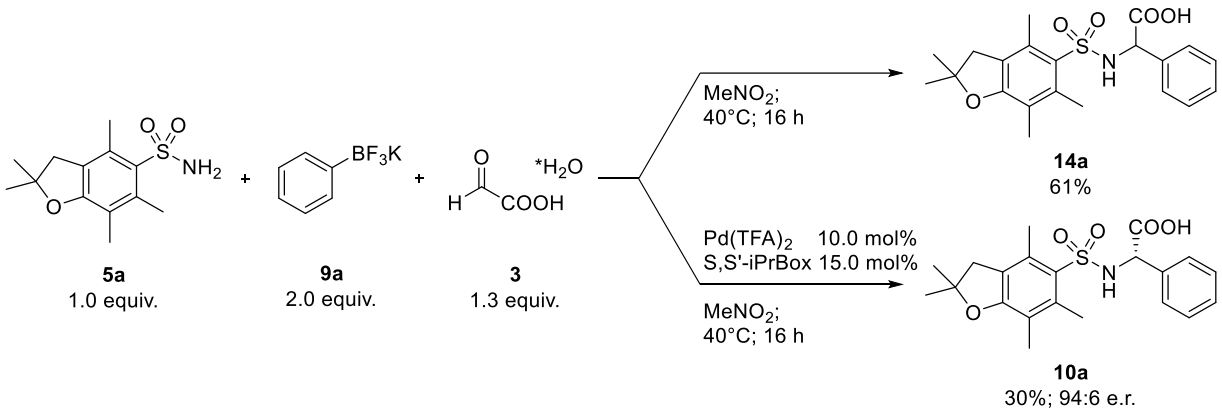
Whereas the reaction with phenyl boronic acid afforded the Pbf-protected[22] phenylglycine derivative **10a** in high yield and enantioselectivity, an almost racemic mixture of **10b** was obtained from the corresponding para-methoxybenzene boronic acid **2b** (Scheme 2a). This decrease in enantioselectivity can be attributed to a faster racemic background reaction (A) of the electron-rich, more nucleophilic para-methoxybenzene boronic acid **2b**, which outcompetes the palladium-catalyzed pathway (B) (Scheme 2b). In turn, suppression or at least a significant deceleration of the uncatalyzed background reaction should lead to an increase in enantioselectivity. Decreasing the aryl boronic acid-to-active catalyst-ratio could be one possible opportunity to decrease the rate of the background reaction. We envisioned, that this could be achieved by slowly generation small amounts of the boronic acid from a suitable precursor. Among different boronic acid derivatives, we identified aryl trifluoroborates as most promising candidates for the slow generation of the corresponding aryl boronic acids under our slightly acid reaction conditions.[23}



Scheme 2. Observations from previous studies and mechanistic rationale.

Therefore, we performed two initial control experiments, the reaction of potassium phenyltrifluoroborate with 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonylamide and glyoxylic acid in nitromethane at 40 °C in the presence and absence

of our previously established Pd(TFA)$_2$-*S*,*S*-IPrBox catalyst system (Scheme 3). To our delight, the palladium-catalyzed transformation afforded the desired α-arlyglycine in 30% yield and an enantiomeric ratio of 94:6. In the absence of a catalyst, the racemic product was formed in 61% yield. Comparison with the uncatalyzed reaction with the free phenylboronic acid showed, that the reaction of the phenyltrifluoroborate is considerably slower (61% yield after 16 h vs. 89% after 2h with PhB(OH)$_2$). These preliminary studies confirmed our initial hypothesis, that aryl trifluoroborates can be utilized as precursors for a slow release of the free boronic acid in our palladium-catalyzed three component reaction.

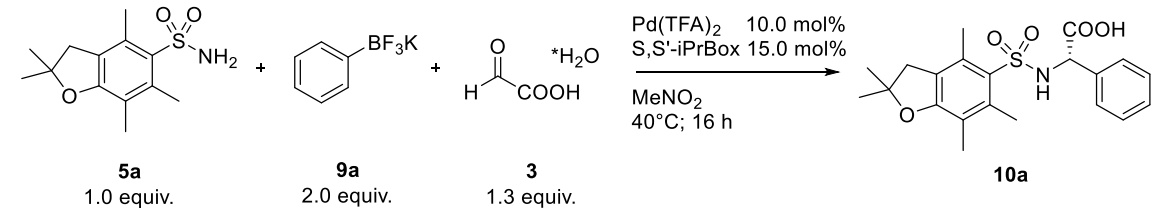


Scheme 3. Initial experiments

Therefore, we started to optimize the reaction conditions for the use of potassium trifluoroborate salts (Table 1). A quick survey of different solvents showed, that the reaction proceeds efficiently only in nitromethane (entry 1). Reactions in other common solvents, such as ethyl acetate, acetonitrile, tetrahydrofuran or dichloromethane led to the formation the arylgylcine in trace amounts (entries 2-5). Contrary to our previous report with arylboronic acids, the presence of air is highly detrimental to the reaction outcome (entry 6). Therefore, inert conditions were employed throughout all subsequent studies. Increasing the reaction temperature to 60 °C and 80 °C furnished the desired product in increased yields of 54-55% together with a slight erosion of

enantioselectivity (entries 7 and 8). Prolonging the reaction time to 64 h increased the yield to 45% without affecting the enantioselectivity (entry 9). Increasing the amount of glyoxylic acid monohydrate to 2.6 equivalents furnished the arylglycine product in an improved yield of 64% and comparable enantioselectivity (entry 10). During our experiments, we often observed partial clouding of the used glass vessel, most likely due to slow release of hydrofluoric acid, an effect which has been observed before with trifluoroborate salts.[24] Since the release of hydrofluoric acid could lead to complications with acid-labile substrates (e.g. the Pbf-protected product **10a**) and safety issues, we decided to investigate the influence of various fluoride scavengers as additives in our three-component process.[24-25] An extensive study (not shown), revealed, that most common scavengers either led to a decreased yield, a decreased stereoselectivity or a combination of both. Yet a combination of $CaCO_3$, tartaric acid and molecular sieves 4Å, each already employed a HF scavenger by itself, did afford the desired arylglycine in high yields and enantioselectivities (entry 11). Although, the use of this scavenger combination did lead to a slightly decreased enantioselectivity (96:4 vs. 97:3), we decided to rely on these conditions in order to avoid potential troubles arising from HF release.

Table 1. Reaction optimization



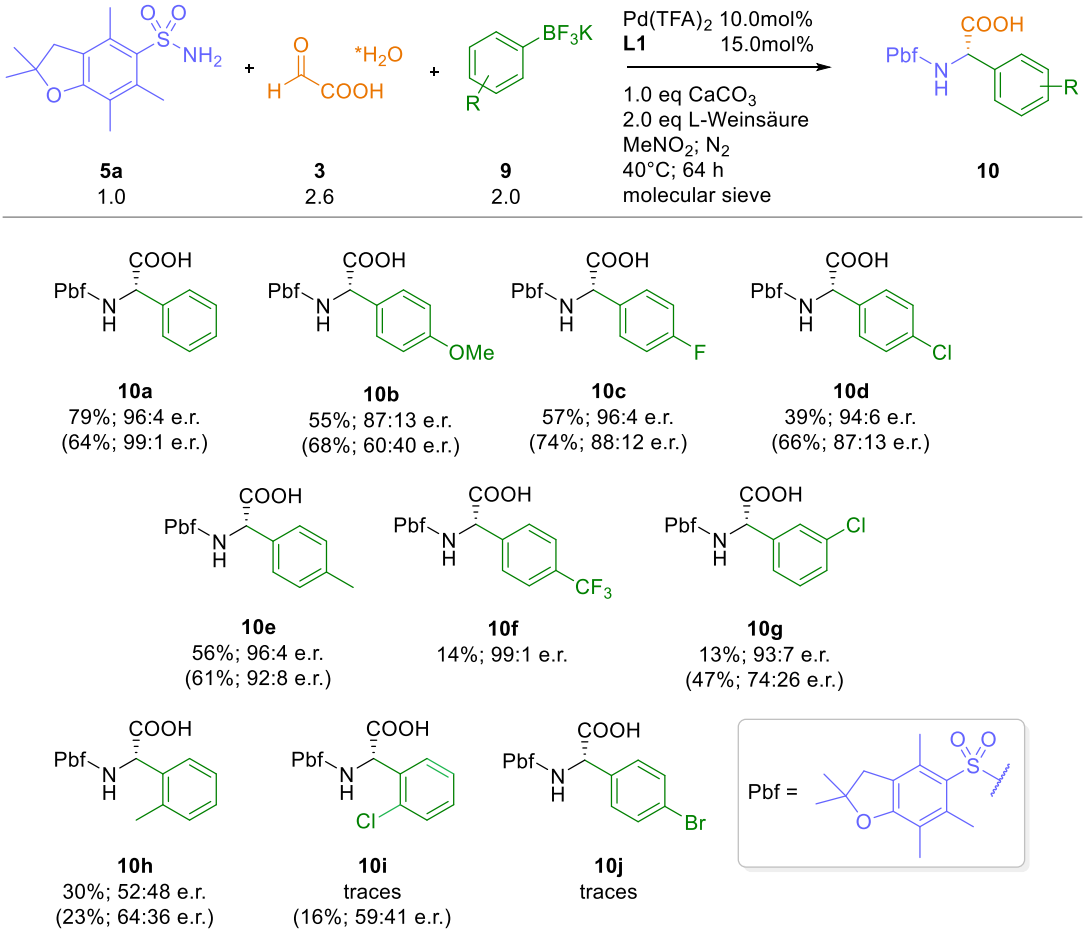
5a 1.0 equiv. **9a** 2.0 equiv. **3** 1.3 equiv. **10a**

Entry	Deviations from optimized conditions	Yield (%)[a]	e.r.
1	$MeNO_2$	30	94:6
2	ethyl acetate	traces	-
3	MeCN	traces	-

4	THF	traces	-
5	CH_2Cl_2	traces	-
6	N_2 atmosphere	40	98:2
7	60 °C	54	96:4
8	80 °C	55	94:6
9	64 h	45	98:2
10	2.6 equiv. glyoxylic acid **x**	65	97:3
11	1.0 equiv. $CaCO_3$; 2.0 equiv. tartaric acid; MS 4Å	**79**	**96:4**

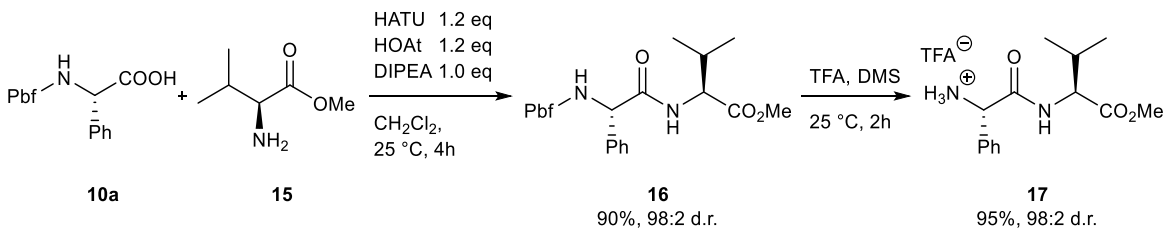
[a] Isolated yield of analytically pure product.

With the optimized conditions, we studied the reaction of glyoxylic acid monohydrate and 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonylamide with different aryl trifluoroborate salts. To our delight, these three-component reactions afforded the desired arylglycines in consistently high levels of enantioselectivity, even for electron-rich aryl trifluoroborates (Scheme 4). This can be highlighted by the synthesis of the methoxy-substituted arylglycine **10b**, which was obtained in 55% yield and an enantiomeric ratio of 87:13 (compared to 68% and an enantiomeric ratio of 60:40 with the boronic acid). As in the case of arylboronic acids, reactions with a sterically hindered ortho-substituted trifluoroborate, furnished the arylglycine product in almost racemic form. Unfortunately, reactions with aryl trifluoroborates did not proceed as efficiently as with the free boronic acid and the arylglycine products **10c**-**10j** were obtained decreased yields (compared to our previous reactions with $ArB(OH)_2$).



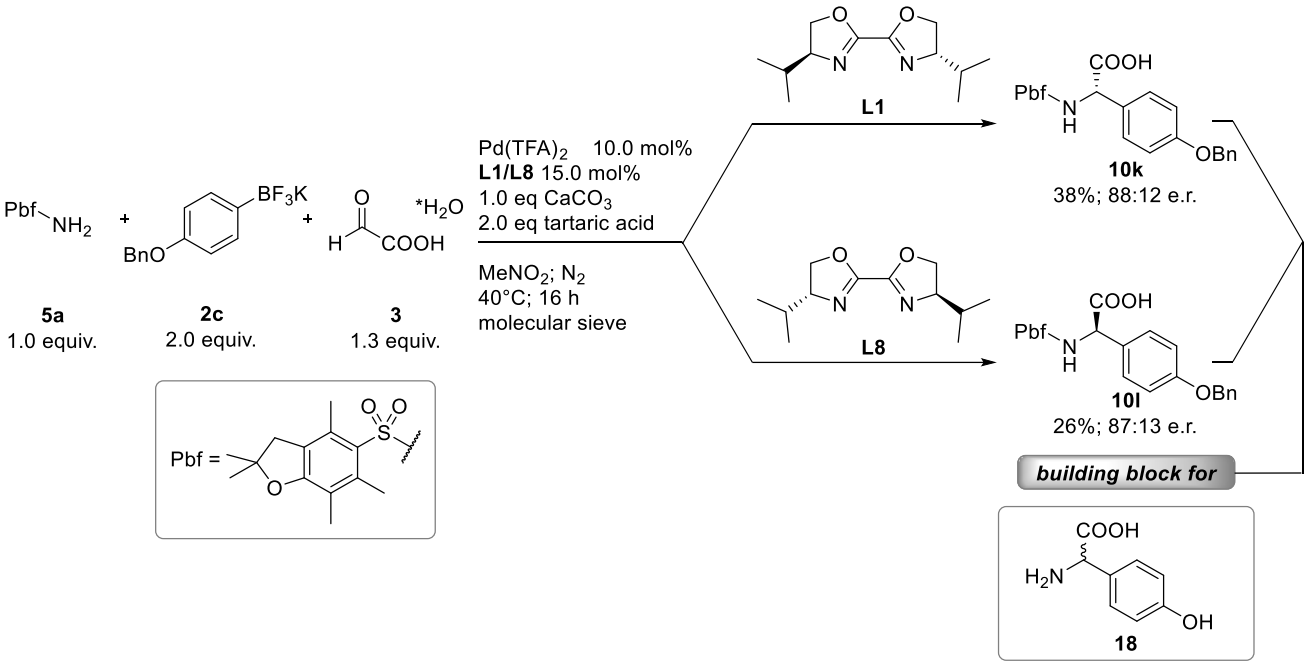
Scheme 3. Reaction Scope – Aryl Trifluoroborates (Yields and e.r in parentheses refer to our previous study with the corresponding boronic acids[21])

As already demonstrated in our previous work, the Pbf-protected arylglycine products can be directly used as building blocks for peptide synthesis.[21] This is exemplified in the preparation of the dipeptide **17** via a standard peptide coupling of arylglycine **10a** with L-valine methyl ester hydrochloride, followed by TFA-mediated removal of the Pbf-protecting group.



Scheme 3. Synthesis of dipeptide **17** from arylglycine **10a**.[21]

Finally, we utilized our method for the preparation of a protected version of para-hydroxphenylglycine, a common structural motif in vancomycin, teicoplanin, feglymycin and amoxicillin. Therefore the OBn-protected aryl trifluoroborate was subjected to our standard reaction conditions, affording the desired N,O-protected (*S*)-arylglycine-derivative **10k** in 38% yield and enantiomeric ratio of 88:12. By employing the corresponding *R*,*R*-iPrBox-ligand the second enantiomer, (*R*)-arylglycine **10l**, could be prepared with a similar yield and enantioselectivity.



Scheme 4. Synthesis of both enantiomers of arylglycine building block **18.**

Conclusion

In summary, we have reported a palladium-catalyzed enantioselective three-component reaction of aryl trifluoroborates, sulfonamides and glyoxylic acid. This method is an improved extension of our pervious protocol with arylboronic acids and provides access to enantioenriched α-arylglycines with an improved substrate

diversity. It can be used for the direct synthesis of peptide-like building blocks, which can find direct application in the total synthesis of arylglycine-containing natural products. Currently, we are performing a detailed mechanistic study in order to overcome still existing limitations of our method and provide a truly general approach to arylglycines with uniformly high yields and enantioselectivities.

Experimental

Experimental

Thin layer chromatography (TLC) was performed on precoated aluminum sheets (TLC silica gel 60 F_{254}). The spots were visualized by ultraviolet light, iodine or cerium(IV) ammonium molybdate. Flash column chromatography was performed using a puriflash XS 420+ Flash purifier machine from Interchim with prepacked flash columns (puriFlash_Silica HP_15 µm_F0040, puriFlash PF C18HP 30 µm F0012) and the respectively solvent mixture. All yields refer to the isolated yields of compounds estimated to be > 95% pure as determined by ^{1}H NMR.

Materials

Unless noted, all starting material were purchased from different commercial sources and used without further purification. Sulfonamide **5a** and ligand **L1** were synthesized according to known literature procedures.[22,26] Racemic products for chiral HPLC analysis were prepared according to the same typical procedures reported for the enantioselective 3-component reactions by utilizing the corresponding sulfonamide (0.5 mmol), glyoxylic acid (0.65 mmol) and arylboronic acids (1.0 mmol) in nitromethane (2.0 mL) at 60 °C for 24h.[27]

Analytical Data and Instrumentation

NMR spectroscopy - Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon spectra (^{13}C NMR) were recorded at a frequency of 400 MHz (^{1}H) and 101 MHz (^{13}C), respectively. Chemical shifts are expressed as parts of million downfield shift on the δ scale and are referenced to the solvent peak (Chloroform-d_1: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C; DMSO-d_6: δ = 2.50 ppm for ^{1}H, δ = 39.52 ppm for ^{13}C). ^{19}F NMR spectra were recorded proton decoupled at a frequency of 282 MHz. Chemical shifts are quoted in parts per million and are not referenced. Coupling constants (*J*) are quoted in Hz and the observed signal multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ***Mass spectrometry*** - Mass spectra (MS) were measured using ESI (electrospray ionization) techniques. High resolution mass spectra (HRMS) were acquired on a Waters GCT Premium using electron ionization mass spectroscopy (EI-MS-TOF). ***Infrared spectroscopy*** - Infrared spectra (IR) were recorded on a FT-IR (Fourier transform infrared spectroscopy) spectrometer including a diamond universal ATR sampling technique (attenuated total reflectance) from 4000-400 cm^{-1}. The absorption bands were reported in wave numbers (cm^{-1}). ***Optical rotations*** - Rotation values (α) were measured using with an analog type *243B polarimeter* from *PerkinElmer*, equipped with a sodium lamp source (589 nm), at 20 °C in 10 cm cell and the indicated solvent. The specific rotation values are reported as $[\alpha]_{\lambda}^{T}$ (mass concentration (*c*) in g*100 mL^{-1}, solvent) and are quoted in deg*mL*dm^{-1}*g^{-1}. ***Analytical chiral HPLC*** – Enantiomeric ratios (e.r.) and accordingly enantiomeric excesses (e.e.) were determined by normal phase high performance liquid chromatographic (HPLC) analysis with a *Hewlett Packard*™ system (G1322A degasser, G1311 quadruple pump, G1316A diode array detector with visualization at 254 nm) and the use of a Chiralpak® IA, Chiralcel® OD-H or OJ-H as chiral column (4.6 mm x 25 cm) obtained from *Daicel Chemical Industries, Ltd*. Elution conditions for

specific compounds are reported in the SI. ***Melting points*** - Melting points are uncorrected.

General procedures (GP)

GP1 (Initial experiments) – A 10 mL screw cap glass vial was charged with a magnetic stirring bar, sulfonamide **5a** (134.7 mg, 0.50 mmol, 1.0 equiv), glyoxylic acid (59.8 mg, 0.65 mmol, 1.3 equiv), potassium phenyltrifluoroborate (184.0 mg, 1.00 mmol, 2.0 equiv), $Pd(TFA)_2$ (16.6 mg, 50 µmol, 0.10 equiv), *S,S'-i*PrBox **L1** (16.8 mg, 75.0 µmol, 0.15 equiv) and nitromethane (0.25 M referring to sulfonamide, 2 mL) as solvent. Then the vial was closed with a teflon lined screw cap and the resulting reaction mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with acetone and filtered through a short plug of celite and silica gel. The filter pad was rinsed with additional acetone and the combined filtrates were concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product.

GP2 (Parameter optimization) – A 8 mL glass vial with a ground glass joint was charged with a magnetic stirring bar, sulfonamide **5a** (134.7 mg, 0.50 mmol, 1.0 equiv), glyoxylic acid (59.8 mg, 0.65 mmol, 1.3 equiv), potassium phenyltrifluoroborate (184.0 mg, 1.00 mmol, 2.0 equiv), $Pd(TFA)_2$ (16.6 mg, 50 µmol, 0.10 equiv), *S,S'-i*PrBox **L1** (16.8 mg, 75.0 µmol, 0.15 equiv). The glass vile was closed with a rubber septum, evacuated and filled with nitrogen twice before adding nitromethane (0.25 M referring to sulfonamide, 2 mL) as solvent. The resulting reaction mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with acetone and filtered through a short plug of celite and silica gel. The filter pad was rinsed with additional acetone and the combined filtrates were concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product.

GP3 (BF_3K-salt variation) – A 8 mL glass vial with a ground glass joint was charged with a magnetic stirring bar, sulfonamide **5a** (134.7 mg, 0.50 mmol, 1.0 equiv), glyoxylic acid (119.6 mg, 1.30 mmol, 2.6 equiv), potassium aryl trifluoroborate (1.00 mmol, 2.0 equiv), $Pd(TFA)_2$ (16.6 mg, 50 µmol, 0.10 equiv), *S,S'-i*PrBox **L1** (16.8 mg, 75.0 µmol, 0.15 equiv), $CaCO_3$ (50.1 mg, 0.5 mmol, 1.0 eq), tartaric acid (150.9 mg, 1.0 mmol, 2.0 eq) and molecular sieve 4Å (200 mg). The glass vial was closed with a rubber septum, evacuated and filled with nitrogen twice before adding nitromethane (0.25 M referring to sulfonamide, 2 mL) as solvent. The resulting reaction mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with acetone and filtered through a short plug of celite and silica gel. The filter pad was rinsed with additional acetone and the combined filtrates were concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product.

GP4 (BF_3K-salt synthesis) – A 100 mL round flask was charged with a magnetic stirring bar, boronic acid **2** (8.2 mmol, 1.0 eq) and 40 mL MeCN. Afterwards an aqueous KF-solution (3.3 mL, 10 M, 32.8 mmol, 4.0 eq) was added and stirred at room temperature for 15 minutes. The tartaric acid solution (33.5 mL, 1 M in THF, 33.6 mmol, 2.05 eq) was slowly dropped into the reaction mixture and stirred for additional 30 minutes. The reaction mixture was filtered and washed three times with 15 mL MeCN each. The solvent was concentrated to 20 mL in vacuo and Et2O was added until the product precipitated. The product was filtered again and washed with Et2O and dried in oil pump vacuum.

Funding

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