

PAPER

[View Article Online](#)
[View Journal](#) | [View Issue](#)Cite this: *Org. Biomol. Chem.*, 2022, **20**, 6245Received 18th March 2022,
Accepted 19th May 2022

DOI: 10.1039/d2ob00524g

rsc.li/obcOn-resin C α -functionalization of *N*-arylglycyl peptides with boronic acids†

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A late-stage α -C–H functionalization reaction of resin-bound, electron-rich *N*-aryl peptides with boronic acid nucleophiles under mild conditions is reported. We explore the impact of the *N*-arylglycyl peptide structure on reactivity, and present a scope of the optimized reaction where both the peptide sequence and nature of boronic acid derivatives are varied.

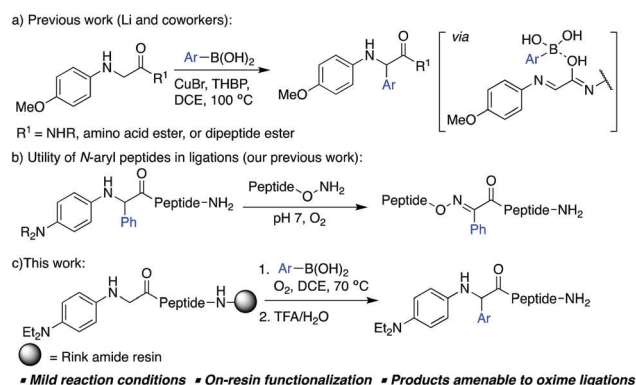
Introduction

The chemoselective C α -functionalization of glycine derivatives enables the rapid elaboration of unnatural amino acids that can be used to expand, probe, and improve the structure and function of peptides for various applications.¹ For example, alkylation² and arylation³ of glycine Schiff bases *via* chemoselective enolate formation have been employed to install natural and unnatural side chains at the α -carbon, which can be performed either in solution or on solid phase.⁴ Site-selective oxidative and cross-dehydrogenative couplings to *N*-aryl glycine-containing substrates have also been reported,⁵ including examples of α -C(sp³)–H functionalization with boronic acid nucleophiles (*e.g.* Scheme 1a).^{5b} The rapid synthesis of phenylglycine derivatives has therapeutic relevance, as these units can be found in many important classes of antibiotics.⁶ While most C α -functionalization reactions ultimately seek to deprotect the amino acid nitrogen for further peptide elongation, our research program exploits the reactivity of C α -substituted *N*-aryl peptide substrates for catalyst-free ketoxime peptide ligations (Scheme 1b).⁷ In that context, methods for the late-stage installation of aryl rings onto the α -carbon of *N*-arylglycyl peptides would be valuable to ultimately control *E/Z* ratios in ketoxime peptides through steric and/or electronic effects, while at the same time introducing side chain diversity at the site of ligation for structure–activity relationship (SAR) studies.

Here, we report reaction conditions for the coupling of boronic acids to resin-bound electron-rich *N*-arylglycyl peptides without the addition of chemical oxidants or metal salts (Scheme 1c). To the best of our knowledge, this constitutes the

first example of an *N*-arylglycyl peptide C α -functionalization on solid phase, with sequences possessing one or several protected amino acids side chains. Given the utility of arylglycine derivatives in peptide ligations and their widespread applications in medicinal chemistry, such methods to introduce unnatural amino acid side chains on-resin at a late-stage should find broad applications.

Guided by our previous work,⁷ we envisioned that electron-rich *N*-arylglycyl peptides could undergo two sequential aerobic oxidative couplings in a controlled manner, where (1) the first reaction would couple a boronic acid derivative in organic solvent, and (2) the second oxidative coupling with an α -nucleophile would only occur when the *N*-aryl peptide was dissolved in buffer (pH 7, see Scheme 1b). Successful implementation of this approach revealed the importance of the electronics of the *N*-arylglycyl peptide to control the reactivity of the boronic acid coupling, and the impact of a neighbouring glycine residue to improve reaction yields.



Scheme 1 (a) Previous methods to synthesize *N*-aryl phenylglycine amino acids and peptides from *N*-aryl glycine derivatives. (b) Utility of *N*-aryl peptides in ligations. (c) On-resin C α -functionalization of *N*-arylglycyl peptides with boronic acids under mild conditions (this work).

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†Electronic supplementary information (ESI) available: Experimental details; characterization data for peptides; NMR spectra and LC-MS chromatograms. See DOI: <https://doi.org/10.1039/d2ob00524g>

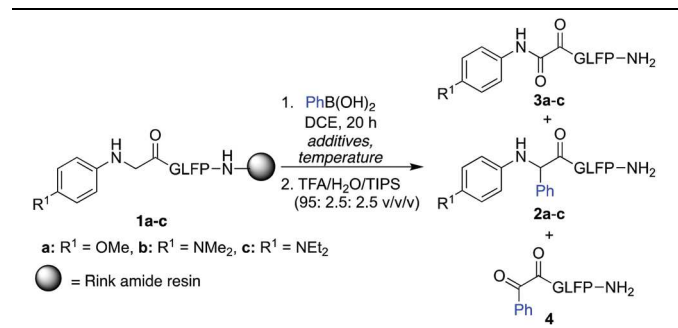
Results and discussion

Reaction optimization

In previously reported oxidative couplings of boronic acid derivatives to *N*-(*p*-MeO-Ph(PMP))glycine amides, tautomerization of the *C*-terminal amide was hypothesized to assist in the complexation/activation of the boronic acid to the boronate adduct (Scheme 1a),^{5b} which is typically required in Petasis-type reactions.⁸ With these *N*-PMP-glycine amide substrates, copper bromide, *tert*-butyl hydroperoxide (TBHP) and high temperatures were necessary for the reaction to proceed in dichloroethane (DCE).^{5b} While serving as a promising starting point, the reaction yields appeared highly contingent on the solvent and reagent equivalents, leading us to wonder if it could be readily adapted to solid support and performed on more diverse peptide sequences. To provide useful substrates for ketoxime peptide ligations,⁷ we also needed to explore and control the reactivity of more electron rich *N*-(*p*-R₂N-Ph)glycyl peptides. At the outset, we thus decided to compare the reactivity of resin-bound *N*-(*p*-MeO-Ph)-glycine-GLFP (**1a**) and *N*-(*p*-Me₂N-Ph)glycine-GLFP (**1b**) with phenyl boronic acid, using GLFP as a simple model peptide. We first subjected peptide **1a** to previously reported conditions with TBHP and CuBr (Table 1, entry 1), recognizing that performing the reaction on solid support would likely impact reactivity, in part due to slower reagent diffusion.⁹ We conducted our optimization using 20 mg of Rink amide resin (loading = 0.69 mmol g⁻¹) in sealed microwave vials, with gentle stirring using a magnetic stir bar set to the lowest stir speed (50 rpm, see ESI†).

Under these conditions, using PhB(OH)₂ as the limiting reagent, undesired oxalic acid derivative **3a** was detected as the major product by LCMS analysis (entry 1). Omitting TBHP from the reaction gave a mixture of desired product **2a**, along with appearance of a new side product, α-ketoamide **4** (entry 2). Considering our previous reports,^{7b} we were initially surprised to see that oxidation of Cα-substituted *N*-aryl peptides (**2**) were readily possible in the absence of buffer; however, we had never evaluated their reactivity in organic solvent at high temperature, and had mainly studied Cα-substituted *N*-aryl peptides with aliphatic side chains. Further studies revealed that all α-arylated peptides (**2a–c**) could indeed undergo oxidation to give **4** in the absence of buffer at high temperature, with only **2a** oxidizing to completion at room temperature (see ESI, Table S2,† for a comprehensive comparative study). When the reaction was run without copper bromide or TBHP (entry 3), an increase in crude purity to the desired product **2a** was observed, primarily due to slower oxidation to **4**. Notably, Cα-functionalizations of *N*-(*p*-MeO-Ph)-glycine amides under O₂ atmosphere, while not reported for boronic acid derivatives in the original publication,^{5b} was later found to be possible with indole nucleophiles.^{5g} Increasing the equivalents of phenyl boronic acid eliminated all traces of **3a** and increased in the production of **2a** (entry 4). Conversely, while lowering the temperature still resulted in complete consumption of starting material, under these conditions we generally

Table 1 Optimization of the boronic acid coupling reaction with *N*-arylglycyl peptides **1a–c**^a



Entry	R ¹	PhB(OH) ₂ (equiv.)	T (°C)	1 ^b (%)	2 ^b (%)	3 ^b (%)	4 ^b (%)
1 ^c	OMe	0.67	100	<5	12 ± 3	49 ± 9	<5
2 ^d	OMe	0.67	100	<5	15 ± 5	<5 ^e	61 ± 9 ^e
3	OMe	0.67	100	<5	41 ± 12	<5 ^e	23 ± 8 ^e
4	OMe	1.5	100	<5	64 ± 5	<5	17 ± 3
5 ^f	OMe	1.5	70	<5	29 ± 24	<5	34 ± 16
6	NMe ₂	0.67	100	16 ± 4	26 ± 7	7 ± 5	21 ± 8
7	NMe ₂	1.5	100	9 ± 1	44 ± 11	<5	24 ± 13
8	NMe ₂	1.5	70	15 ± 3	56 ± 7	6 ± 2	14 ± 1
9	NEt ₂	0.67	100	41 ± 8	27 ± 12	5 ± 2	<5
10	NEt ₂	1.5	100	17 ± 10	59 ± 9	<5	<5
11	NEt ₂	1.5	70	14 ± 2	67 ± 1	<5	<5

^a Unless otherwise noted, the reaction solution was performed on 20 mg (13.8 μmol) of resin (loading = 0.69 mmol g⁻¹) using 0.5 mL DCE sparged with oxygen for 30 seconds, before being left under an oxygen balloon in a microwave vial heated in an oil bath. ^b The % crude purities were determined by LCMS analysis at 214 nm and are averages of three trials. ^c CuBr (0.1 equiv.), TBHP (0.67 equiv.) were added. The reaction was run under air. ^d CuBr (0.1 equiv.) was added. ^e The mass of **3a** (minor) was detected in the same peak as **4** (major), but they could not be separated using different LCMS gradients. ^f Due to the high variability, the averages were calculated from six different trials instead of three. One of the trials was performed on a 50 mg scale.

observed a decrease in product yield and greater variability between trials, for reasons that are poorly understood (entry 5). Given that in all cases undesired oxidation of **2a** to **4** was detected, we conclude that selectivity towards the desired product might be difficult to achieve with **1a** as substrate under the conditions we screened. While these results are intriguing, we were ultimately seeking to optimize and apply this chemistry to more electron-rich substrates like **1b** and **1c**, in view of later utilizing the products in ketoxime peptide ligations at neutral pH.^{7b,c} Resin-bound *N*-(*p*-Me₂N-Ph)glycine-GLFP (**1b**) was thus heated to 100 °C in DCE with varying amounts of phenyl boronic acid (entries 6 and 7), affording the desired product (**2b**) along with mixtures of both unreacted starting material (**1b**) and oxidized product (**4**). In this case, decreasing the temperature to 70 °C lead to a slight increase in crude purity for **2b** with a decrease in **4** (entry 8). Interestingly, a subtle structural modification of the *N*-arylglycyl peptide, where the dimethyl-amino substituent was substituted for a diethylamino group to give **1c**, resulted in improved selectivity (entries 9–11) where

side product **4** could no longer be detected in significant amounts. We thus decided to use substrate **1c** instead of **1b** in our future scope exploration. A representative example of a liquid chromatography (LC) trace of peptide product **2c**, obtained under optimized reaction conditions (entry 11) using 100 mg of resin (70 μ mol), can be found below (Fig. 1).

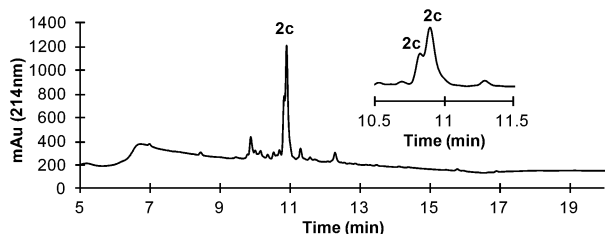
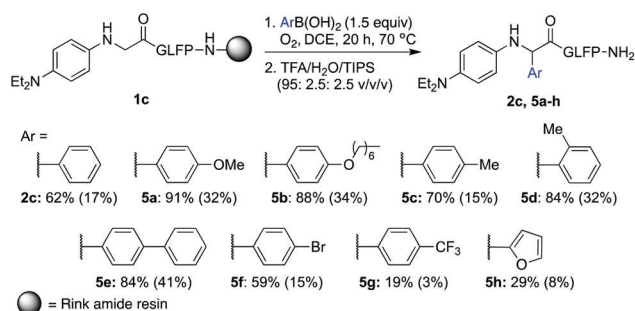


Fig. 1 Representative partial LC trace of peptide **2c** monitored at 214 nm, using a 5 μ M, 150 \times 4.6 mm C18 Luna column with a flow rate of 0.5 mL min⁻¹ and a 5–95% linear gradient of MeCN (0.1% TFA) in water (0.1% TFA). The insert shows the two closely eluting peaks with identical masses.

The site-selectivity of this reaction was confirmed by comparing the ¹H NMR spectra and LCMS retention times of peptide **2c** synthesized using this α -C–H functionalization approach and an alternative submonomer procedure,^{7b,10} entailing acylation with racemic 2-bromo-2-phenylacetic acid and displacement with 4-(diethylamino)aniline (see ESI†). We note that modest diastereomeric excess of peptides are likely obtained during this boronic coupling reaction, as suggested by the presence of two non-equivalent, closely eluting peaks with identical masses (see Fig. 1 and ESI†).

Boronic acid and peptide scope exploration

Using starting peptide **1c**, an evaluation of different boronic acids was then pursued to introduce different aryl rings at the α -carbon (Scheme 2). Consistent with literature precedents^{5b,11} and the expected reaction mechanism, oxidative couplings



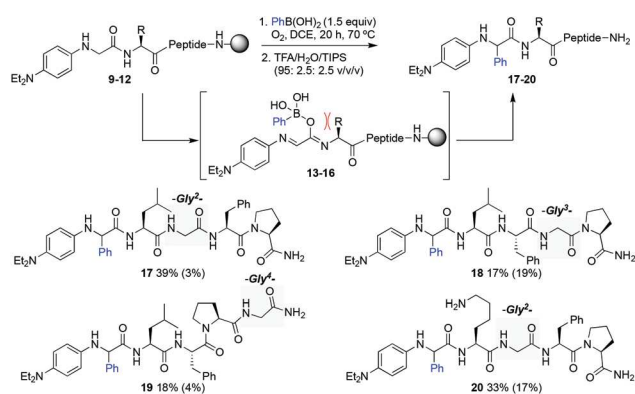
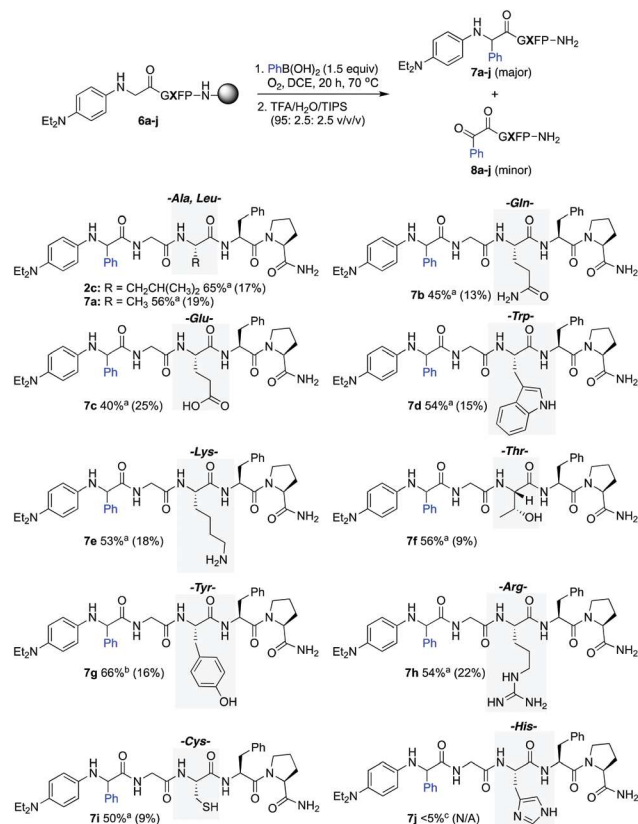
Scheme 2 % crude purities and isolated yields (in parentheses) of the α -arylated products using a variety of boronic acid derivatives. The crude purities were determined by LCMS analysis at 214 nm. The isolated yields after purification by RP-HPLC are based on resin loading (0.69 mmol g⁻¹). These reactions were performed on both 20 mg (14 μ mol) and 50 mg (35 μ mol) of resin; the yields are calculated from the reactions run on 50 mg of resin.

with electron-rich phenyl boronic acids (*e.g.*, **5a–d**) proceeded more efficiently compared to electron-poor derivatives (*e.g.*, **5g**). The use of 4-bromophenyl boronic acid as the nucleophile provided **5f** in 59% crude purity, potentially providing an entry for further modification by Pd-catalyzed cross-coupling reactions in the future.¹² In terms of steric effects, the presence of a methyl group at the *para* (**5c**) vs *ortho* (**5d**) position was not found to impact the reaction yield significantly. The coupling of 2-furyl boronic acid provided the desired product in ~30% crude purity.

To diversify the peptide sequence and assess the generality of our optimized reaction conditions, we next substituted the internal Leu residue in GLFP for a variety of side-chain protected amino acids (Scheme 3). In almost all cases evaluated, the desired product (**7a–j**) was the major detected product by LCMS, obtained in crude purity either similar or slightly decreased compared to substrate **1c**. Interestingly, the sequence containing histidine was the only peptide that did not form any detectable C α -arylated product, affording starting material and a variety of unidentified side products instead. Attempts at optimizing the reaction by increasing the equivalents of phenyl boronic acid resulted in an increase of **8j** without detection of **7j**.‡

Notably, all *N*-terminal *N*-aryl amino acids contained an adjacent glycine residue in our peptide scope (Scheme 3). In addition, the vast majority of *N*-aryl di- and tri-peptide substrates studied in various oxidative coupling reactions in the literature also possess neighbouring glycine residue(s),⁵ presumably to showcase the site-selectivity and/or due to the incompatibility of other neighbouring residues in the transformations. To gain a deeper understanding of this reaction and its limitations, we wanted to probe if a proximal glycine was required for this transformation to be high-yielding. Thus, the position of the glycine residue within the GLFP tetrapeptide was systematically varied to afford three additional peptides: LGFP (**9**), LFPG (**10**), and LFPG (**11**) (Scheme 4). Comparative analyses revealed that the position of the glycine did have a significant impact on reactivity, with a progressive decrease in reaction conversions as the glycine residue was moved closer to the *C*-terminus. Specifically, moving the Gly one residue away from the *N*-terminus caused a ~25% decrease in crude purity (*e.g.* **17** vs. **2c**), and moving it to the third and fourth position was even more detrimental (*e.g.* **18** and **19**). To confirm this trend, we synthesized one additional peptide, *N*-(*p*-Et₂N-Ph)G-KGFP, and compared its reactivity to *N*-(*p*-Et₂N-Ph)G-GKFP. The crude purity was found to again decrease from 53% to 33% for **7e** and **20**, respectively. We hypothesized that this may be due to steric hindrance disfavoring amide tautomerization and subsequent boronic acid com-

‡The LCMS trace was much cleaner when using 3.0 instead of 1.5 equiv. of phenyl boronic acid (see ESI†); however, further optimization would be necessary to inhibit oxidation of the product under these conditions. Using a substrate with a Boc-protected instead of Trt-protected imidazole ring did not improve reactivity.



plexation to the iminol, when the neighbouring residue is something other than glycine (see Scheme 4).

Finally, the peptide sequence scope was expanded to include five randomly generated sequences§ (N -(p - $\text{Et}_2\text{N-Ph}$)G-TTFCI, N -(p - $\text{Et}_2\text{N-Ph}$)G-AHLEQ, N -(p - $\text{Et}_2\text{N-Ph}$)G-SEDQA, N -(p - $\text{Et}_2\text{N-Ph}$)G-IWFRF, and N -(p - $\text{Et}_2\text{N-Ph}$)G-RWYPC), in addition to Angiotensin I derivative (N -(p - $\text{Et}_2\text{N-Ph}$)G-DRVYIHPFHL) as an example of a longer bioactive peptide. Since none of these sequences contained a glycine, it is perhaps not surprising that only N -(p - $\text{Et}_2\text{N-Ph}$)G-SEDQA provided appreciable conversions to the desired α -functionalized product (**21**, Fig. 2). In that case, it is possible that the neighbouring serine side chain, albeit protected as a *tert*-butyl ether, can assist with complexation of the boronic acid to some extent. When a glycine was added to the sequence, a slight increase in the reaction conversion and isolated yield was observed to give **22**. Gratifyingly, Angiotensin I derivative N -(p - $\text{Et}_2\text{N-Ph}$)G-GDRVYIHPF was found to recover reactivity when a glycine was added, giving product **23** in 17% crude purity (Fig. 2). However, it should be noted that the addition of a glycine residue was not found to be a general solution to improve reactivity, suggesting that further optimization of the reaction might be required with highly functionalized resin-bound peptides possessing multiple residues with side chains other than alkyl groups.

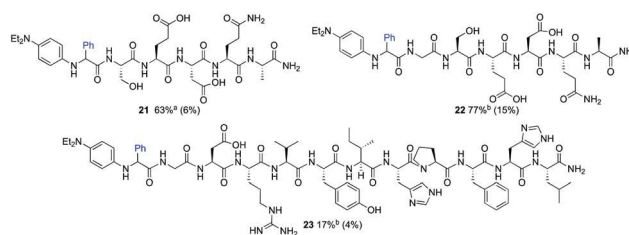


Fig. 2 Crude purities and isolated yields (in parentheses) of the desired α -arylated products for more functionally-dense peptides. The % crude purities were determined by LCMS analysis at 214 nm and the isolated yields after purification by RP-HPLC are based on resin loading (0.69 mmol g^{-1}). ^aA mixture of unidentified side products was also observed. ^bA mixture of unreacted starting material, oxidized product, and unidentified side products was also observed.

Conclusions

In summary, we developed mild conditions that allow for the late-stage functionalization of N -arylglycyl peptides with boronic acid derivatives on solid support, without addition of chemical oxidants or metal catalysts. Minor structural changes to the N -aryl ring allowed for tuning of the reactivity with minimal side product formation. The optimized conditions were compatible with a variety of electron-rich phenyl boronic acids and were readily applied to >15 different peptides. While

§ https://www.bioinformatics.org/sms2/random_protein.html

expanding the sequence scope, we discovered that the presence of an adjacent glycine residue often improved reaction yields, likely due to more facile tautomerization to the iminol resonance form required for boronic acid complexation. Studies towards the use of C α -arylated *N*-aryl peptides in ketoxime peptide ligations are currently ongoing and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Science Foundation (NSF) for the funds to support this project (CHE 2046681). All NMR and high-resolution mass spectrometry experiments were performed in the Molecular Education, Technology, and Research Innovation Center (METRIC) at NC State University, which is supported by the State of North Carolina.

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