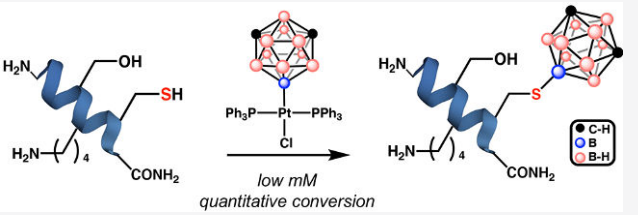
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An Organometallic Strategy for Cysteine Borylation

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ABSTRACT: Synthetic bioconjugation at cysteine (Cys) residues in peptides and proteins has emerged as a powerful tool in chemistry. Soft nucleophilicity of the sulfur in Cys renders an exquisite chemoselectivity with which various functional groups can be placed onto this residue under benign conditions. While a variety of reactions have been successful at producing Cys-based bioconjugates, the majority of these feature sulfur−carbon bonds. We report Cys-borylation, wherein a benchtop stable Pt(II)-based organometallic reagent can be used to transfer a boron-rich cluster onto a sulfur moiety in unprotected peptides forging a boron−sulfur bond. Cys-borylation proceeds at room temperature and tolerates a variety of functional groups present in complex polypeptides. Further, the bioconjugation strategy can be applied to a model protein modification of Cys-containing DARPin (designed ankyrin repeat protein). The resultant bioconjugates show no additional toxicity compared to their Cys alkyl-based congeners. Finally, we demonstrate how the developed Cys-borylation can enhance the proteolytic stability of the resultant peptide bioconjugates while maintaining the binding affinity to a protein target.



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INTRODUCTION

Synthetic bioconjugation has emerged as a powerful tool toward the understanding and alteration of biomolecular interactions. With the mimicking of post-translational modifications ubiquitous to natural biological systems, a variety of C−S, C−O, C−N, and C−C bond forming reactions have been previously reported.[1,2] These synthetic tools have been used to install handles on biomolecules for applications ranging from imaging[3,4] to the enhancement of therapeutic efficacy.[5,6]

Cysteine (Cys) residues in proteins and peptides represent historically attractive sites for synthetic bioconjugation development owing to their soft nucleophilicity and low natural abundance which contribute to their capacity to undergo site-directed mutagenesis and subsequent selective modification.[7] These chemoselective Cys conjugations can be achieved through both metal-free and recently developed metal-mediated routes (Figure 1A). Conjugate addition to Michael acceptors (e.g., maleimides and vinyl sulfones[1,2,8,9]) as well as S_N2 reactions with alkyl electrophilic centers[1,2] represent the most common metal-free transformations; however, a number of other noteworthy alkylation and arylation strategies have been reported.[1,7,10−16] Recently, transition metal-mediated C−S bond forming reactions have attracted considerable attention due to the rapid kinetics, mild reaction conditions, and high functional group tolerance often associated with these metal-based transformations (Figure 1A).[1,17] For example, Buchwald, Pentelute, and co-workers demonstrated a unique approach toward chemoselective Cys modification via arylation using well-defined and benchtop-stable Pd-based organometallic reagents.[17] The reaction conditions were amenable to the covalent linkage of fluorescent and affinity tags, drug molecules, and handles for further conjugation. This concept was also demonstrated using a stochiometric Au(I/III) platform[18,19] as well as several notable catalytic strategies.[15,24]

While a large range of chemoselective C−S bond forming bioconjugations has been reported, analogous transformations resulting in the formation of boron−sulfur bonds (B−S) are conspicuously absent. While substrates containing free thiols have been borylated through metal-mediated and metal-free routes (Figure 1B), these methods generally lack selectivity for thiols over other competing nucleophilic centers which is a key prerequisite for successful bioconjugation reactions. These include thiol borylation reactions using pinacol, 9-BBN, or catechol borane and either aluminum-[20] or ruthenium-based[21] catalysts, where alcohols and amines can also be competent substrates for borylation under similar catalytic conditions (Figure 1B). Similar selectivity issues arise in uncatalyzed borylation of thiols as evidenced by the work of Bertrand and co-workers.[22] In their recent, elegant work, Fontaine et al.[23] used frustrated Lewis pairs to improve the selectivity of the sulfur borylation of aromatic and aliphatic thiol substrates; however, the use of relatively high temperatures and nonpolar

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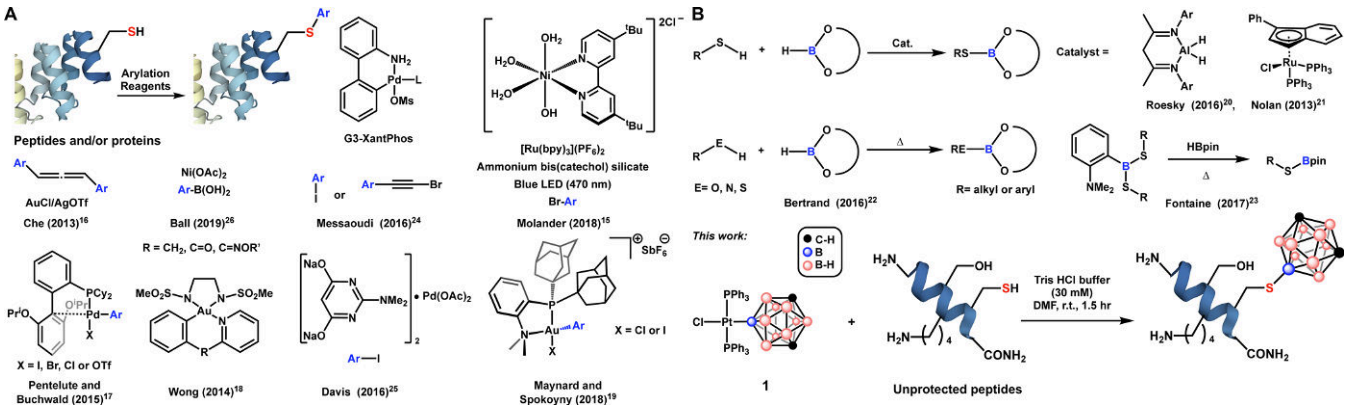


Figure 1. (A) Summary of selective C−S bond forming reactions for bioconjugation of unprotected peptides and proteins. Metal-mediated strategies result in thiol arylation with the transferred group highlighted in blue. (B) Summary of selective S−B bond forming reactions.

solvents precludes the application of this chemistry toward Cys containing biomolecules.

Similar to recently reported transition metal-mediated arylation strategies which augmented the bioconjugation landscape by producing Cys-Ar hybrid systems (Figure 1A) with fundamentally new properties,[16−19,24−26] we envisioned how analogous borylation reactions might further expand the biomolecular toolbox. As there are no existing methods that are effective toward peptide and protein borylation with tricoordinate boron substrates, we hypothesized that these limitations could be overcome by using a different source of boron-based fragment. Icosahedral boranes represent a promising platform to probe this hypothesis, given their three-dimensional delocalized aromaticity[27−33] analogous to the carbon-based aromatic molecules that were previously employed for bioconjugation. Here, we show that a Pt(II) complex[34] supported by a boron-bound carboranyl cluster (**1**) is capable of chemoselective Cys borylation across multiple unprotected peptide substrates to generate the first B−S bond linkages postsynthetically, which was a previously inaccessible modality in bioconjugation. Importantly, the borylated peptides were stable toward excess base, acid, and external thiol and did not display any appreciable toxicity up to 50 μM in cell culture. In addition to providing a new chemical connectivity, the developed Cys borylation offers new opportunities in areas of multivalent binding and the tuning of ligand−receptor interactions in biomolecular targeting.

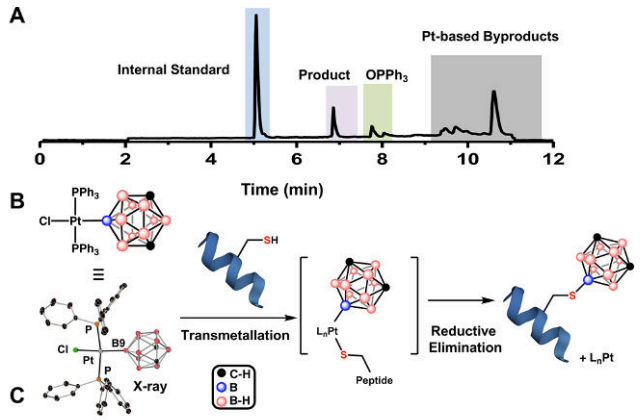
RESULTS/DISCUSSION

To test whether one can use boron-cluster supported organometallic reagents for successful Cys borylation, we subjected model peptide H_2N-VKGALGVCG-$CONH_2$ (**2a**) with **1** under various conditions. Nearly quantitative conversion to a peptide containing a mass consistent with a Cys-borylated peptide was observed within 1.5 h when **2a** (5 mM) was treated with 1.2 equiv of **1** at 25 °C in the presence of Tris·HCl buffer (30 mM) in dimethylformamide (DMF) as assessed by LC-MS analysis of the crude reaction mixture (Figure 2A). In order to verify that the reaction conditions were selective for Cys over other nucleophiles within the model peptide substrate, tandem MS/MS of Cys-borylated peptide **2b** was conducted. Fragmentation patterns support exclusive Cys borylation (Figure S20). Analogous to arylation bioconjugation involving Pd-based reagents,[17] we propose this chemoselectivity arises from the transmetalation of the soft nucleophilic Cys sulfur residue that has a high propensity toward binding a Pt(II) metal center (Figure 2B).[35,36] A subsequent reductive elimination process affords Cys-borylated peptide and Pt-based byproducts (Figure 2B). Importantly, this process proceeds efficiently despite the carboranyl group being significantly more sterically encumbering than the previously demonstrated aryl-based species,[27] ultimately highlighting the advantages of the organometallic approach used.

To ensure generality of this method, we then applied the reaction conditions used to generate **2b** toward other peptide sequences (Figure 2C). Across all peptide substrates tested (entries **2**−**9**), we observed nearly quantitative conversion toward the corresponding borylated product with isolated yields ranging from 22 to 59% after HPLC purification (Figure 2C). Furthermore, the borylation reaction conditions were tolerant to the common labeling dye, fluorescein isothiocyanate (FITC), attached to the N-terminus of the peptide chain despite the presence of a thiourea linkage which could also serve as a chelating ligand toward the metal center (entry **4**). Even though carboranyl ligands are sterically bulky, diborylation of a peptide containing two Cys residues is possible; nearly quantitative conversion of **5a** to **5b** was observed under the optimized reaction conditions (entry **5**). Importantly, only monoborylation was observed when **6a**, which contains identical residues as **5a** except one Cys is mutated to a serine (SER) residue, was subjected to identical treatment (Figures S12 and S13). Overall, the borylation selectivity toward Cys thiols in unprotected peptides using **1** as a transfer reagent mirrors the selectivity of both Pd(II) and Au(III) organometallic Cys arylation reagents.[17,19]

After assuring Cys-borylation was successful across multiple thiol containing peptides, we decided to perform an additional robustness screen for additional reagents that are often used in bioconjugation reactions on peptides. Dilution of the DMF reaction mixture with water did not diminish conversion up to 25% water when model peptide H_2N-VKGALGVCG-$CONH_2$ (**2a**) was treated with **1**. Reaction mixtures exceeding 25% water resulted in a significant reduction in conversion, likely due to the poor solubility of **1** in water (Figure S17). Further, the bioconjugation was compatible with a common denaturing agent guanidine·HCl (3 M, Figure S18A), suggesting the organometallic complex **1** is stable under highly ionic conditions on the time scale of the reaction. Further, addition of Tris(2-carboxyethyl)phosphine hydrochloride (TCEP HCl), a common reducing agent for disulfide moieties in biomolecules, does not significantly alter the conversion

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Entry	Sequence	Isolated Yield (%)	Conversion (%)
2	(a) NH_2-VKGALGVCG-$CONH_2$ (b)	51	>99
3	(a) NH_2-DRKCAT-$CONH_2$ (b)	43	>99
4	(a) FITC-β-ACGGA-$CONH_2$ (b)	22	>99
5	(a) NH_2-GCGEVKEGCG-$CONH_2$ (b)	59	>99
6	(a) NH_2-GSGEVKEGCG-$CONH_2$ (b)	39	>99
7	(a) NH_2-γ-ECG-COOH (b)	38	>99
8	(a) NH_2-SCQPQPLIYP-$CONH_2$ (b)	62	>99
9	(a) NH_2-GCAWNHA-$CONH_2$ (b)	48	>99

Figure 2. (A) Representative LC trace collected after **1** (1.2 equiv) and H_2N-VKGALGVCG-$CONH_2$ (5 mM) were allowed to react for 1.5 h at 25 °C in the presence of Tris·HCl buffer (30 mM) in dimethylformamide (DMF). Internal standard was produced through alkylation of H_2N-VKGALGVCG-$CONH_2$ (see SI section I). (B) Proposed reaction scheme between **1** and cysteine-containing peptide. (C) Peptide substrate scope with isolated yields (%) and conversion (%).

efficiency of the reaction (Figure S18B) indicating excess phosphine does not shut down the reactivity of **1** on the time scale of the reaction.

In order to probe the local environment of the carboranyl cluster on the purified Cys-borylated peptides using ^{11}B NMR spectroscopy, we decided to apply the borylation reaction to a peptide substrate with a low molecular weight to increase the signal-to-noise outcome of this experiment. Commercially available L-glutathione (**7a**) was thus chosen for these studies. Successfully Cys-borylated glutathione (**7b**) was subjected to a routine HPLC purification followed by ^{11}B NMR spectroscopic analysis. A distinct singlet resonance was observed at 2 ppm along with multiple broad doublets in an integral ratio of 1:9 consistent with the splitting pattern of a B(9)-substituted, intact *m*-carboranyl cluster (Figure S21A). Importantly, the $^{11}B\{^1H\}$ NMR spectrum of the same sample indicates that the doublets that were observed stem from the $^{11}B-^1H$ coupling, and the resonance at 2 ppm is consistent with a ^{11}B atom that is not bound to a ^1H nucleus (Figure S21B). On the basis of these observations and previously reported NMR spectroscopy data collected on B_9 substituted carboranethiols and thioether species,[34] the resonance at 2 ppm was assigned to the $^{11}B(9)$-S nucleus on the intact *m*-carborane cluster attached to the peptide. Finally, IR spectroscopy was used to further corroborate structural elements of **7b**. A diagnostic stretching band ascribed to the B−H bond vibrations on the cluster (2532−2681 cm^{-1}) was observed in samples of **7b** and was absent in **7a** when both samples were analyzed as powders by ATR IR spectroscopy (Figure S22). Additional evidence that Cys thiol conjugation had proceeded is provided by the disappearance of a free S−H stretch (2454−2545 cm^{-1}) in the spectrum of **7b** compared to the spectrum of **7a** (Figure S22). The spectroscopic results outlined above unequivocally confirm successful B−S bond formation using **1** and unprotected peptides containing Cys residues.

We then extended the bioconjugation to a more complex substrate, DARPin (designed ankyrin repeat protein), which has been previously shown to successfully undergo Cys arylation with various organometallic reagents.[17,19] After treatment of DARPin with excess **1** for 6.5 h, a deconvoluted mass consistent with complete DARPin borylation was observed by LCMS (Figure S23). The capacity to fully conjugate a protein target further highlights the potential of this Pt-mediated route to transfer carboranyl clusters directly to large biomacromolecules at micromolar concentrations.

Next, we evaluated the stability of the B−S bond using **7b** as a model Cys-borylated peptide. Specifically, we assessed the fidelity of **7b** toward an acidic environment with a pH of 2.3, as this value falls within the normal pH range for stomach acid (pH = 1 to 3).[37] A sample of **7b** (0.05 mM) was incubated in the presence of hydrochloric acid (5 mM) at 25 and 37 °C for 72 h (Figure 3A). No fragmentation was observed by LC-MS analysis of the mixture, indicating that the S−B bond within **7b** stays intact at pH 2.3 under the time frame of the experiment. Further, stability toward highly acidic environments suggests that Cys-boryl conjugates could be compatible with harsh reagents normally used to cleave synthesized peptides from solid supports.[2i] To probe this hypothesis, we treated a model peptide bound to Rink amide resin with excess **1** under buffered conditions for 1.5 h (SI Figure S24). Resin was then isolated and peptide was globally cleaved using a standard solution of trifluoroactetic acid, water and triisopropyl silane (90%, 5%, 5% v/v) (SI Section VIII). Full conversion of Cys-

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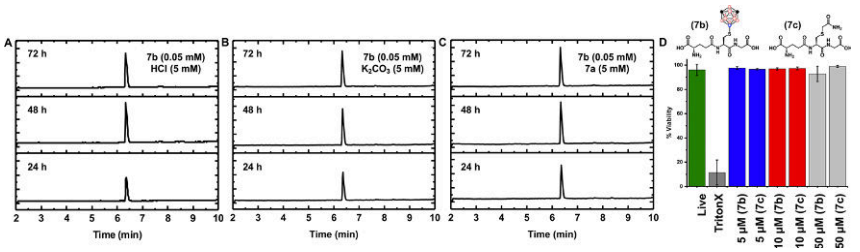


Figure 3. LC-MS traces of **7b** incubated with 100 excess (A) hydrochloric acid (B) potassium carbonate and (C) **7a** after 24 h at r.t. followed by 48 and 72 h at 37 °C (see SI Section VII for full details). (D) The % cell viability assessed after 4 h incubation of **7b** and **7c** with Chinese Hamster Ovarian (CHO) cells at 5 μM, 10 μM, and 50 μM concentration of analyte (see SI Section IX for full details).

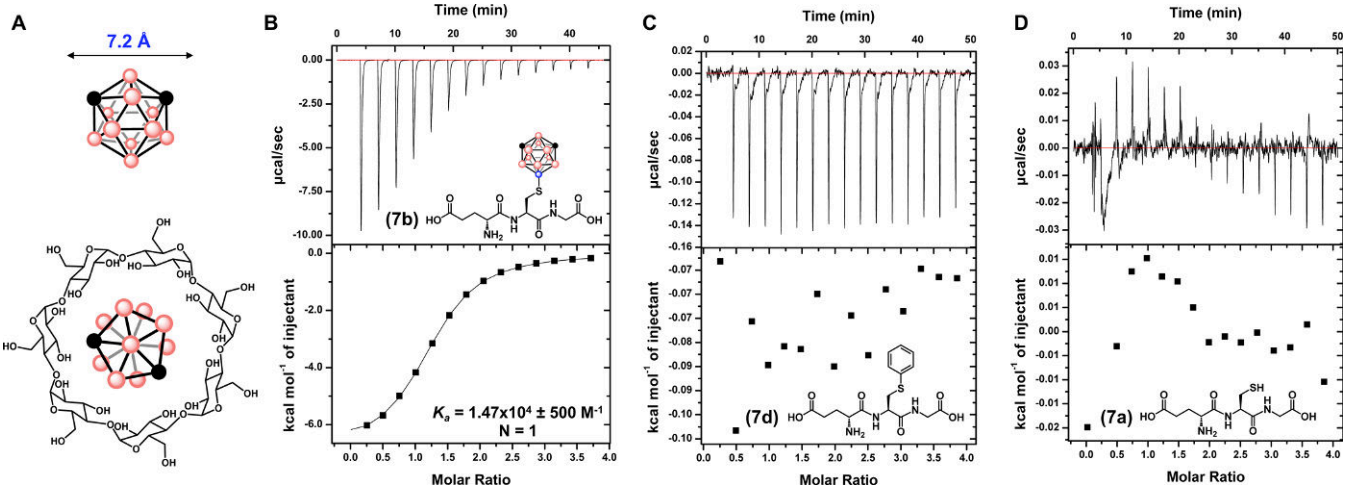


Figure 4. (A) Representation of the inclusion complex formed between *m*-carborane and β-cyclodextrin.[53,54] (B) ITC binding plot for carboranylated glutathione and β-cyclodextrin to yield an association constant (K_a = 1.47 × 10^4 ± 500 M^{-1}) and binding stoichiometry (N = 1). (C) ITC binding plot for phenyl-glutathione and β-cyclodextrin. (D) ITC binding plot for unmodified glutathione and β-cyclodextrin.

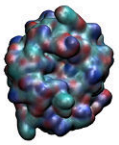
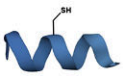
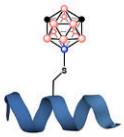
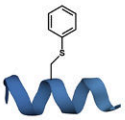
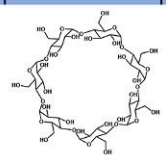
borylated peptide was observed by LC-MS (SI Figure S24) indicating the bioconjugation could be also successfully applied to peptides appended to solid supports. After assessment of stability toward acid, we probed the resistance of **7b** toward basic conditions. While intracellular pH remains close to neutral, published reports suggest alkaline microenvironments could be important in cellular signaling.[38] To rigorously determine the tolerance of Cys-borylated peptides toward base, we incubated **7b** at pH 11, a significantly more alkaline environment than that anticipated for human cells. A sample of **7b** (0.05 mM) was incubated in the presence of potassium carbonate (5 mM) at 25 and 37 °C for 72 h. No fragmentation was observed by the LC-MS analysis of the mixture, indicating stability of the S−B bond within **7b** (Figure 3B). Finally, we evaluated the stability of **7b** toward an external thiol source. Glutathione (**7a**) was selected as it represents the most abundant nonprotein source of thiol in eukaryotic cells with intracellular concentrations ranging from 1 to 10 mM.[39] A sample of **7b** (0.05 mM) was incubated in the presence of **7a** (5 mM) at 25 and 37 °C for 72 h. No fragmentation was observed by the LC-MS analysis of the mixture, indicating the S−B bond within **7b** does not undergo thiol exchange chemistry in the presence of large excess of external thiol (Figure 3C). Importantly, this stability toward external thiol is in contrast to classical Cys-based bioconjugation tools that employ Michael acceptors which often undergo retro-Michael addition when subjected to the presence of other thiol substrates.[1] Altogether, the stability of **7b** demonstrated herein suggests the S−B bond within Cys-borylated peptides can be bioorthogonal toward harsh biological milieu.

After confirming the stability of these constructs, we decided to evaluate the toxicity of the Cys-borylated peptides toward Chinese Hamster Ovarian (CHO) cells using **7b** as a model peptide. As Pt(II) complexes have well-described toxicity,[40] we first assessed the efficiency of the purification method toward removing all metal-based byproducts. The ICP-AES analysis of **7b** purified by reversed-phase HPLC indicated that >99.9% platinum content had been removed (see SI Section II, Figure S1). A 4 h incubation of pure, isolated **7b** with CHO cells resulted in no appreciable toxicity up to 50 μM (Figure 3D). As a control sample, acetamide-glutathione (**7c**) was also incubated under the same conditions and exhibited no appreciable toxicity up to 50 μM (Figure 3D). The similar cell viability profiles for Cys-boryl glutathione and Cys-acetamide glutathione suggest no inherent cytotoxicity is added through forging a B−S bond by appending a boron cluster to unprotected peptides.

Few post-translational modifications are competent toward the chemoselective transfer of bulky substrates containing large cone angles directly to amino acid sites. A rare example was demonstrated independently by both Park[41] and Davis[42] who prepared *tert*-Leu residues via dehydroalanine; however, the bioconjugates formed are racemates. The present strategy offers the first organometallic-based route toward unprotected peptide modification with a highly bulky moiety that does not alter the local stereochemistry, affording unique opportunities to assess the role steric encumbering at amino acid sites has

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Table 1. Reaction Schemes and the Observed Corresponding Degradation of 2a, 2b, and 2c with Proteinase K under Various Conditions

Entry	Proteinase K	Unmodified Peptide (2a)	Borylated Peptide (2b)	Arylated Peptide (2c)	β-cyclodextrin	% Peptide Intact*
						
A	+	+	-	-	-	0
B	+	+	-	-	+	0
C	-	-	-	+	-	100
D	+	-	-	+	-	0
E	+	-	-	+	+	0
F	-	-	+	-	-	100
G	+	-	+	-	-	45 ± 1
H	+	-	+	-	+	70 ± 10

upon downstream peptidic properties. Specifically, we probed the capacity of Cys-boryl peptides to participate in receptor binding by titrating **7b** as a model peptide to *β*-cyclodextrin, a sugar macrocycle which is widely used in catalysis, analytical separation, and solubilization.[43] An isothermal titration calorimetry (ITC) experiment was carried out where peptide **7b** (10 mM) was titrated to *β*-cyclodextrin (0.25 mM) in an aqueous buffered solution at pH 3.4 revealing a binding stoichiometry (N = 1) and an association constant (K_a = 1.47 × 10^4 ± 500 M^{-1}) (Figure 4A,B). The approximated binding stoichiometry of N = 1 is consistent with a 1:1 **7b**⊂*β*-cyclodextrin inclusion complex promoted by the chaotropic properties of the cluster cage insertion into the macrocycle cavity.[44,45] The observed K_a is an order of magnitude higher than that observed between unmodified *m*-carborane and *β*-cyclodextrin when measured by a displacement binding technique,[46] which could be attributed to the enhanced solubility of **7b** over unmodified *m*-carborane in aqueous media. Cys-modified S-phenyl glutathione **7d** (Figure 4C) and **7a** (Figure 4D) were used as controls and did not exhibit any appreciable binding affinity to *β*-cyclodextrin by ITC under the same measurement conditions. These controls highlight the receptor specificity and the capacity of borylation to engender a unique binding profile between **7b** and a macrocyclic sugar.

Finally, we evaluated the stability of Cys-boryl peptides toward a broadly acting serine protease, Proteinase K. Specifically, Cys-boryl peptide **2b** was chosen as a model substrate owing to the many aliphatic amino acid residues in the sequence which are cleavable by Proteinase K.[46] We envisaged **2b** might resist the activity of Proteinase K to a higher degree than **2a** owing to the steric hindrance of the carboranyl group positioned proximally to the peptide backbone thereby blocking access to cleavable residues. To test this hypothesis, **2b** was incubated with Proteinase K for 5 min at 60 °C in the presence of Tris·HCl buffer (50 mM, pH = 8.2) and $CaCl_2$ (5 mM). After treatment, 45 ± 1% **2b** remained intact as assessed by integration of the peak compared to integration of the internal standard (Table 1, entry G). In contrast, no intact peptide remained when **2a** was subjected to the same reaction conditions (Table 1, entry A), indicating Cys-borylation is competent toward inhibiting the action of Proteinase K within this time frame. We then subjected Cys-aryl peptide **2c** to Proteinase K treatment for 5 min at 60 °C in the presence of buffer (50 mM) and $CaCl_2$ (5 mM) (Table 1, entry D). No intact peptide was observed under these conditions, suggesting that inhibition of proteolytic degradation is unique to Cys-boryl conjugates in comparison to aryl-based congeners.

To extend the steric hindrance surrounding the Cys moiety, we next subjected the **2b**⊂*β*-cyclodextrin inclusion complex to Proteinase K treatment (see SI section X for further details on the characterization of **2b**⊂*β*-cyclodextrin). The complex **2b**⊂*β*-cyclodextrin was heated for 5 min at 60 °C in the presence of buffered Proteinase K (Tris·HCl, 50 mM, pH = 8.2) and $CaCl_2$ (5 mM). After this treatment, 70 ± 10% intact **2b** remained (Table 1, entry H). Importantly, incubation of **2a** and **2c** with *β*-cyclodextrin prior to treatment with the same Proteinase K reaction conditions resulted in full degradation (Table 1, entries B and E), indicating the presence of *β*-cyclodextrin alone is insufficient toward inhibiting degradation. Overall, these experiments suggest that Cys-borylation can render peptides more proteolytically stable.

Molecular dynamics (MD) simulations were used to elucidate the possible nature of the stability enhancement toward proteolysis. MD simulations of **2a**, **2b**, and **2c** with Proteinase K demonstrated the stable binding of all peptides to the reported substrate recognition site[47] comprising, Gly100 to Tyr104 and Ser132 to Gly136 (Movies 1−3). A second binding pocket (Figure 5A) formed by Gly134-Gly135-Gly-136 and Gly160-Asn161-Asn162 was identified for the unique capacity to bind the carborane of **2b** as a result of B−H···H−N dihydrogen[48] and C−H···O or C−H···N hydrogen bonding interactions[27] (Figure 5B). This binding might prevent the peptide from approaching the Asp39-His69-Ser224 catalytic

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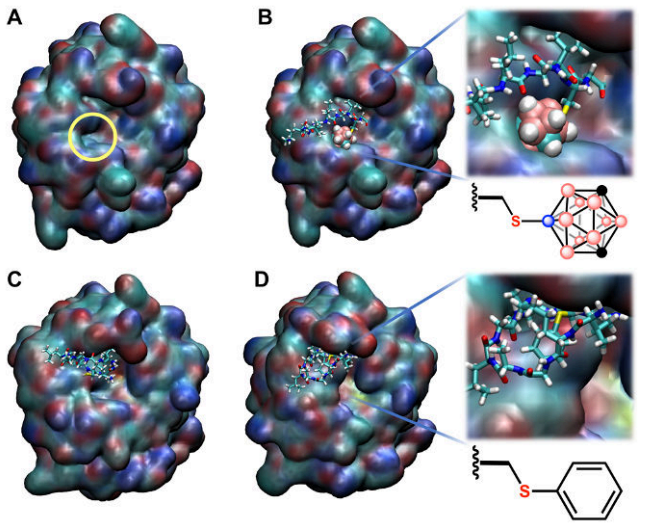


Figure 5. Molecular dynamics simulations of (A) the secondary binding pocket identified as an important docking site, (B) **2b** binding with Proteinase K, (C) **2a** binding with Proteinase K, and (D) **2c** binding with Proteinase K at 120 ns of equilibration. Proteinase K is represented using QuickSurf representation in VMD.

triad, since **2b** was on average 2.12 Å further away from the catalytic triad than **2a** over the entire simulation time frame (Figure 5C). Importantly, **2c** did not exhibit stable binding to the pocket formed by Gly134-Gly135-Gly-136 and Gly160-Asn161-Asn162 (Movie 3, Figure 5D) indicating the proteolytic protection is unique to Cys-borylation and is likely a result of placing a sterically encumbering functional group like carborane in close proximity to the polypeptide chain.

While Cys-borylation can render peptides more resistant toward proteolytic degradation, we wondered whether one can design hybrid agents with preserved binding capabilities to a protein target. To probe protein binding, we designed a model peptide (**8a**) containing a Ile-Tyr-Pro sequence which was previously identified as active toward inhibiting the activity of angiotensin-converting enzyme (ACE),[49] an important protein class implicated in the regulation of blood pressure and, recently, SARS-CoV-2 infection.[50] Specifically, at 5 μM, unmodified **8a** and Cys-borylated **8b** were found to inhibit the activity of ACE by 24 ± 5% and 17 ± 4%, respectively (see SI Section XII). Increasing the concentration of **8a** and **8b** to 50 μM enhanced the inhibition of ACE activity by 54 ± 7% and 52 ± 1%, respectively (see SI Section XII). The observed similarity in rates of inhibition between **8a** and **8b** suggests that Cys-borylation maintains the binding efficacy of the therapeutically relevant peptides while it simultaneously enhances their proteolytic stability.

CONCLUSION

In conclusion, an organometallic strategy for borylating Cys residues within unprotected peptide sequences and a model protein has been demonstrated. This work significantly expands our fundamental ability to construct new bioconjugates via a Cys residue by the introduction of a new room-temperature, boron−sulfur bond forming pathway in unprotected peptides. Importantly, Cys-borylation can engender stable hybrid peptides, featuring unique recognition and binding properties toward a macrocyclic sugar, as well as render the resulting peptides more proteolytically resistant while maintaining their binding affinity toward a protein target. This work further demonstrates the growing importance of organometallic chemistry in the field of bioconjugation,[51−60] where a designer post-translational synthetic modification can enable a chemoselective delivery of a sterically encumbering, abiotic functional group (e.g., carborane) directly to a native amino acid residue in a complex biomolecule.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c02206.

Experimental procedures and characterization for all new compounds (PDF)
(MOV)
(MOV)
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Notes

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