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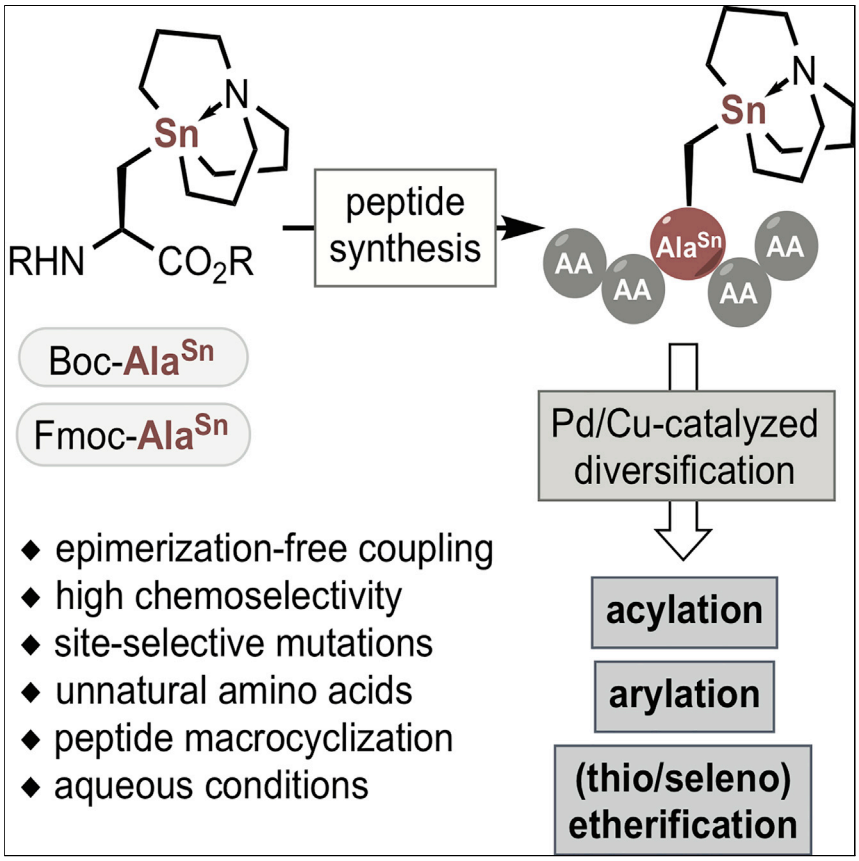
Organometallic Ala^{M} reagents for umpolung peptide diversification



Ala^{M} amino acids with a carbastannatrane group installed at the β position are umpolung reagents that can be engaged in chemoselective Pd- and Cu-catalyzed cross-coupling reactions. Despite their ability to undergo facile transmetalation, they are compatible with common peptide synthesis protocols and operate under aqueous conditions. Ala^{M} building blocks could be incorporated into oligopeptides and produced "mutated" amino acids with aryl, acyl, and thioether functionalities as well as cyclic structures.

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Highlights

Alanine with β-carbastannatrane group are umpolung peptide reagents

Ala^{Sn} reagents undergo chemo- and regioselective C-C, C-S, and C-Se cross-couplings

Inter- and intramolecular reactions produced amino acids with unnatural side chains

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Organometallic Ala^{M} reagents for umpolung peptide diversification

Feng Zhu,[1,2,3] Wyatt C. Powell,[1,3] Ruiheng Jing,[1] and Maciej A. Walczak[1,4,*]

SUMMARY

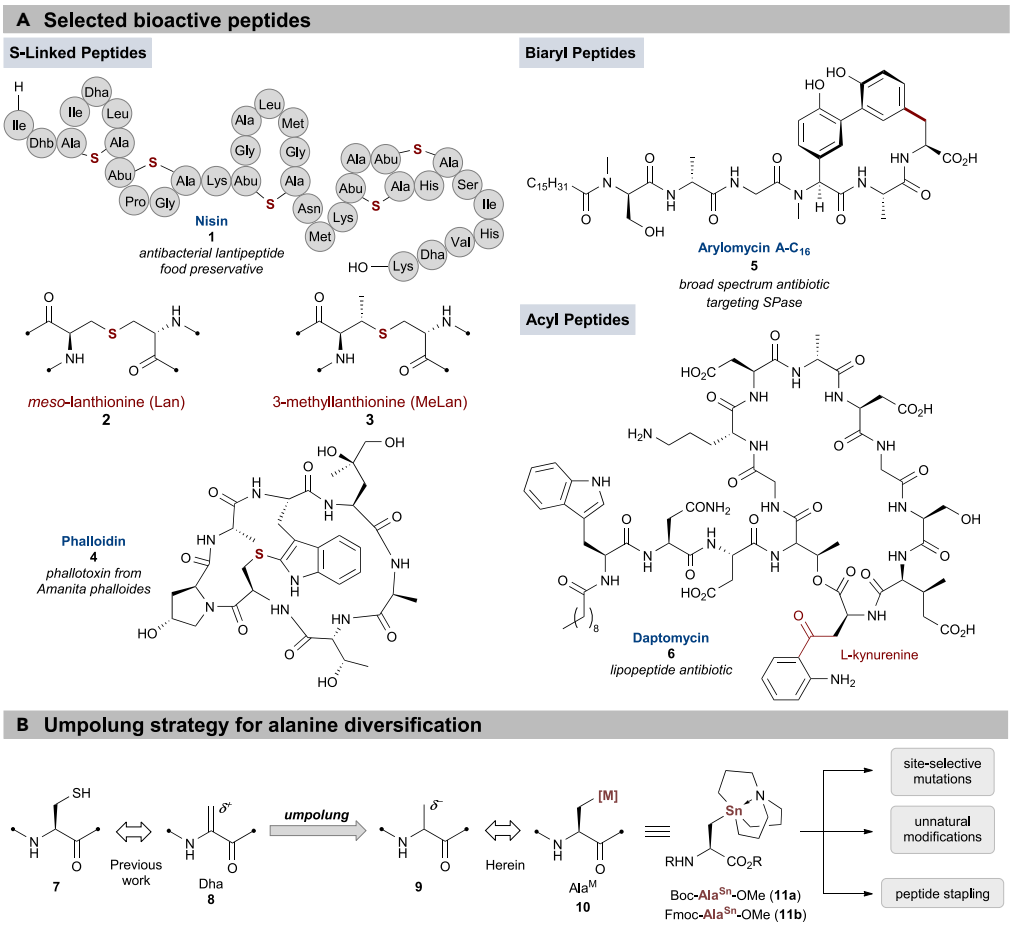
Selective modifications of peptides and proteins have emerged as a promising strategy to develop novel mechanistic probes and prepare compounds with translational potentials. Here, we report alanine carbastannatranes Ala^{Sn} as a universal synthon in various C-C and C-heteroatom bond-forming reactions. These reagents are compatible with peptide manipulation techniques and can undergo chemoselective conjugation in minutes when promoted by Pd(0). Despite their increased nucleophilicity and propensity to transfer the alkyl group, C(sp^3)-C(sp^2) coupling with Ala^{Sn} can be accomplished at room temperature under buffered conditions (pH 6.5–8.5). We also show that Ala^{Sn} can be easily transformed into several canonical L- and D-amino acids in arylation, acylation, and etherification reactions. Furthermore, Ala^{Sn} can partake in macrocyclizations, exemplified by the synthesis of medium-size cyclic peptides with various topologies. Taken together, metalated alanine Ala^{Sn} demonstrates unparalleled scope and represents a new type of umpolung reagent suitable for structure-activity relationship studies and peptide diversification.

INTRODUCTION

Site- and chemoselective modification of proteins and peptides is becoming recognized as an important tool for probing structure-function relationships and accessing new therapeutic leads.[1–4] Significant advances have been made over the past decade to modify peptides using heteroatom conjugation with cysteine/selenocysteine,[5–8] serine,[9] lysine,[10] or methionine,[11] site-specific C-H functionalization of aromatic rings in tryptophan, histidine, or phenylalanine,[12–14] radical functionalization,[15,16] and decarboxylative couplings of C-terminal amino acids or side-chain functionalities in aspartic and glutamic acids.[17–21] In addition to these chemical diversification strategies,[22] natural peptides with posttranslational modifications are gaining increasing importance due to their translational potential.[23–27] Among peptides of ribosomal origin,[28] lantipeptides (exemplified by nisin **1**, Scheme 1) form a subset of polycyclic natural products featuring a thioether linkage in the form of *meso*-lanthionine (Lan, **2**) and 3-methyllanthionine (MeLan, **3**).[29] In the same category, tryptothionine crosslinked toxic peptides, such as actin-binding phalloidin **4**[30,31] and RNA polymerase II inhibitor α-amanitin[32,33] from the *Amanita phalloides* mushroom constitute another class of thioether modifications. Furthermore, variations at the aryl groups resulting from oxidative dimerization of tyrosine and hydroxyphenylglycine, such as arylomycins (**5**)[34–39] or oxidative cleavage of the indole ring in tryptophan (L-kynurenine in lipopeptide daptomycin **6**),[40] give rise to agents with promising antibacterial activities. The unique structural modifications contribute to the diversity of peptides but also represent a unique synthetic challenge. One strategy that has attracted considerable attention are conjugate

The bigger picture

Over the last few years, various strategies have emerged to functionalize peptides and proteins by site-selective modifications. While most of these approaches capitalize on inherent nucleophilicity of heteroatoms or conjugate additions to dehydroalanine, reversal of polarity has not been studied extensively. Our work introduces Ala^{M} umpolung reagents in the form of carbastannatrane amino acids that can be engaged in several C-C, C-S, and C-Se bond-forming reactions. To demonstrate this powerful approach, we optimized inter- and intramolecular cross-couplings and applied these protocols to oligopeptide substrates. We also highlight the fact that Ala^{M} reagents are compatible with aqueous conditions and operate at room temperature without compromising chemoselectivity and yield. This article describes a conceptual departure from known strategies in peptide functionalization and sets the stage for future work to access peptide-based structures with novel topologies.



Scheme 1. Peptide posttranslational modifications and chemical methods for their installation

additions to dehydroalanine (Dha) **8** readily generated from cysteine **7** (Scheme 1B).[41–44] Due to its polarization, the β carbon in Dha can accept both radical and anionic reactants offering a broad scope of peptide modifications, and an array of radical and nucleophiles were used to prepare protein conjugates achieving divergent late-stage modifications.[41,45,46] However, the stereochemistry at the resulting α carbon is difficult to control,[47,48] and only a handful of examples, such as nucleophilic addition of dehydroalanine within a complex environment of proteins,[42,43] Rh-catalyzed tandem 1,4-addition/stereoselective protonation,[49–52] and Friedel-Crafts conjugate addition,[53] are known. Complementary to C-C bond-forming processes, enantioselective organocatalytic addition of aryl or benzyl thiols to α-aminoacrylates proceeded in moderate to good enantioselectivities.[54,55]

To address the above limitations, we envisioned that reversal of polarity at the amino acid β carbon represents a promising yet unexplored approach (Scheme 1B). This strategy calls for generation of metalated alanine **Ala^{M} 10** that could be engaged in reactions with electrophilic partners. In addition to addressing the concerns of epimerization, **Ala^{M} 10** constitutes a universal synthon as 15 of out 20 canonical amino acids can be directly derived from this building block through C-C, C-O, or C-S cross-coupling reactions. Furthermore, a broad selection of coupling partners can vastly increase amino acid diversity and provide access to topologically unique structures, such as lantipeptides.

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In designing a new method based on Ala^{M}, two critical considerations need to be addressed: (1) formation and stability of Ala^{M} and (2) efficiency of the potential transmetalation step that can control (and ultimately limit) the compatibility of the protocol with complex systems. These two aspects reduce the reaction discovery process to identification of a suitable metal in Ala^{M} while maintaining the amine and carboxylate groups intact for broad synthetic utility. Catalytic metalation of the methyl group in alanine has been achieved through directed C-H activation,[56–58] but these conditions (high temperatures, pure organic solvents, and specialized directing groups) may be incompatible with complex peptides, proteins, and even some functional groups found in common amino acids. Alternatively, Ala^{M} can be used stoichiometrically as a stable reagent, and previous attempts to realize this strategy utilized organolithium,[59] organozinc,[60–66] organonickel,[67,68] organogermanium,[69–71] and organoboron[58,59,68,72–86] reagents. Although some of these compounds could be successfully engaged in downstream applications, only single amino acid derivatives were used and their instability under aqueous conditions render them suboptimal for a widespread use.

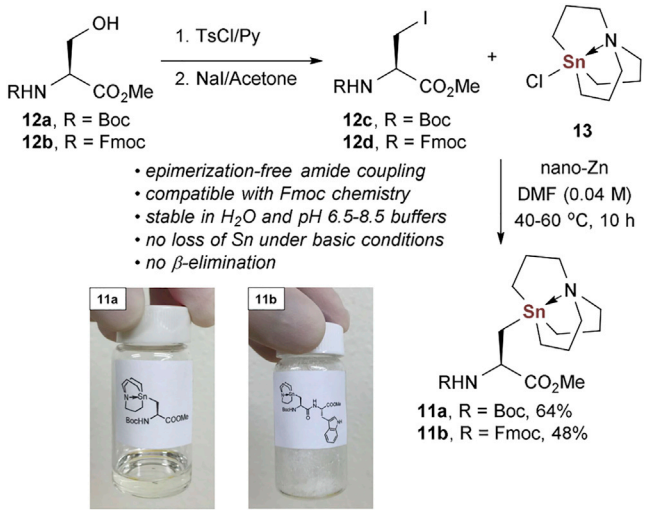
In line with our interest in glycoconjugate synthesis via cross-coupling with anomeric nucleophiles,[87–91] we hypothesized that a stable stannane could be installed at the β carbon in alanine. Tetraalkylstannanes are generally considered poorly nucleophilic, but selective transfer of alkyl groups can be achieved using carbastannatranes[92–96] leading us to propose amino acids with the general formula Ala^{Sn} **11** as competent reagents for umpolung functionalization. Carbastannatranes are significantly less toxic than tetraalkyl stannanes[97] and compatible with aqueous and buffered conditions (see below). By-products of reactions with carbastannatranes are in general polar and poorly soluble in organic solvents, thus simple flash purification is sufficient to obtain products in high purity. Coordination of the nitrogen atom improves their reactivity and determines a selective transfer of one alkyl group. Here, we reported a novel strategy for the late-stage modification of peptides with Ala^{Sn} carbastannatrane amino acid synthons. This protocol exhibits high chemoselectivity compared with other heteroatom-based nucleophiles and conjugation with a variety of electrophiles was achieved through C-C, C-S, C-Se bond-forming processes. All of these protocols are operational under mild "biological" conditions (aqueous buffers, high dilution, and room temperatures) and can be applied to complex substrates.

RESULTS AND DISCUSSION

C(sp^3)-C(sp^2) arylation

At the outset of our studies we investigated protocols for the synthesis of Ala^{M} amino acids (Scheme 2). Ala^{Sn} derivatives **11a** and **11b** were prepared in a reaction of β-iodoalanine **12c** and **12d** with zinc followed by quenching with 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane **13** (48%–64%). Methyl esters **11** were easily synthesized on a multigram scale and could be converted into acids via saponification (NaOH, LiOH, Me_3SnOH, or TMSOK). The Fmoc group in **11b** can be removed under standard deprotection conditions (piperidine, DBU, Et_2NH) without loss of the carbastannatrane group. Free amines and carboxylic acids of **11** can be also engaged in amide couplings without epimerization in either component, and these reagents are stable in water and various buffered solutions (pH 6.5–8.5) for at least 24 h at room temperature. We also note that *S*-phenylthioester of Boc-Ala^{Sn} can participate in native chemical ligation with L-cysteine, therefore free thiols remain compatible with activated carbastannatranes.

Having access to the key building blocks, we next prepared model dipeptide **14a** and used it in optimization studies geared toward C(sp^3)-C(sp^2) cross-coupling

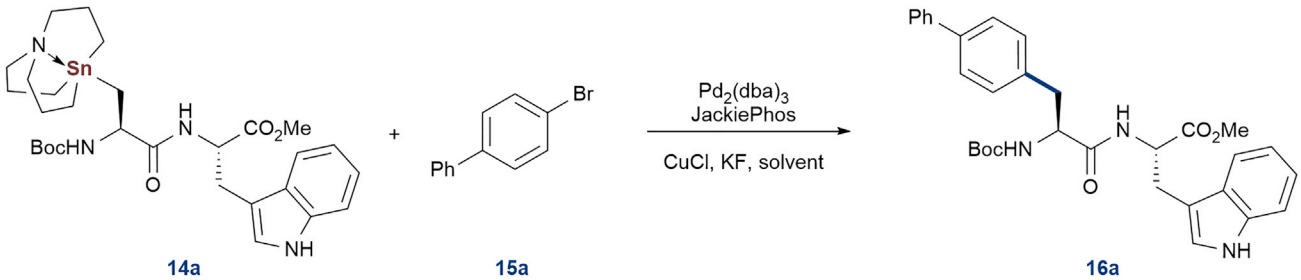


Scheme 2. Synthesis of Ala^{Sn} reagents

(Table 1). The initial evaluations using $Pd_2(dba)_3$ (5 mol %) and JackiePhos (20 mol %)[98,99] as the catalytic system with CuCl (1.5 equiv), KF (2.0 equiv), and 4-phenylbromobenzene **15a** (1.5 equiv) in 1,4-dioxane proved to be quite effective and afforded biphenyl peptide **16a** in 88% yield (entry 1). We note that no C-N cross-coupling by-products of tryptophan and 4-bromodiphenyl were observed. Several control experiments established that the Pd catalyst and CuCl were indispensable for the success of this reaction, but absence of KF had no significant effect on the reaction yield (entries 2–4). When 1,4-dioxane was replaced with DMF or MeCN as alternative solvents, the yields of the desired product **16a** were reduced to 46% and 70%, respectively. Moreover, our attempts to use other mono- and bidentate phosphines, such as PPh_3, dppf, AdBrettPhos, or *t*BuBrettPhos, proved ineffective and the yields were consistently lower than for JackiePhos (for details, see Table S1). Further reduction of the amount of CuCl to 50 mol % led to little improvement (entries 7 and 8). To develop mild bioconjugation conditions, we ultimately found that the C-C cross-coupling worked well at 23°C (entries 9–11). Furthermore, to our delight, we established that dipeptide **14a** was compatible with co-solvent systems of MeCN or *t*-BuOH and water, with 70% isolated yield of **16a** obtained by tuning the amount of the nucleophile (entries 12–14). To further demonstrate the mildness of the new protocol, we employed phosphate buffers with near-neutral pH that are relevant to bioconjugation of peptides and proteins.[100] The desired peptide was also obtained in good yield (66%–70%) when phosphate buffers within the range of pH 6.5–8.5 were used. Of note is the fact that the cross-coupling reactions can be completed in 15 min (0.005 M) with 83% isolated yield of **16a** (for details, see Schemes S1 and S2). The high chemoselectivity and mild conditions (room temperature, aqueous buffers, and short reaction times) make this method suitable for the late-stage modification of complex oligopeptides.

With the optimized conditions in hand, we next evaluated the generality of C(sp^3)-C(sp^2) cross-coupling method (Scheme 3). A wide range of electrophiles with different functional groups could be successfully transformed into arylalanine derivatives (Scheme 3A). In addition of aryl halides (PhCl, PhBr, and PhI), oxygen-based partners, such as PhOTf, are also viable under the standard conditions, resulting in the preparation of L-phenylalanine **16b** (L-Ala^{M} → L-Phe mutation). Notably, substituents such as ester (**16c**), cyano (**16d**), trifluoromethyl (**16e**), pyridyl (**16f**), furyl

Table 1. Reaction development of Ala^{M} Aryl cross-coupling



Entry	CuCl (equiv)	KF (equiv)	Solvent	Temperature (°C)	Yield (%)
1	1.50	2	dioxane	100	88
2	1.50	–	dioxane	100	84
3	–	2	dioxane	100	N/D
4[a]	1.50	2	dioxane	100	N/D
5	1.50	2	DMF	100	46
6	1.50	2	MeCN	100	70
7	0.50	2	dioxane	100	95
8	0.50	–	dioxane	100	92
9	0.50	–	dioxane	60	97
10	0.50	–	dioxane	40	95
11	0.50	–	dioxane	23	90
12	0.50	–	MeCN:H_2O (3:1)	23	54
13[b]	0.50	–	MeCN:H_2O (3:1)	23	70
14[b]	0.50	–	*t*-BuOH:H_2O (3:1)	23	70

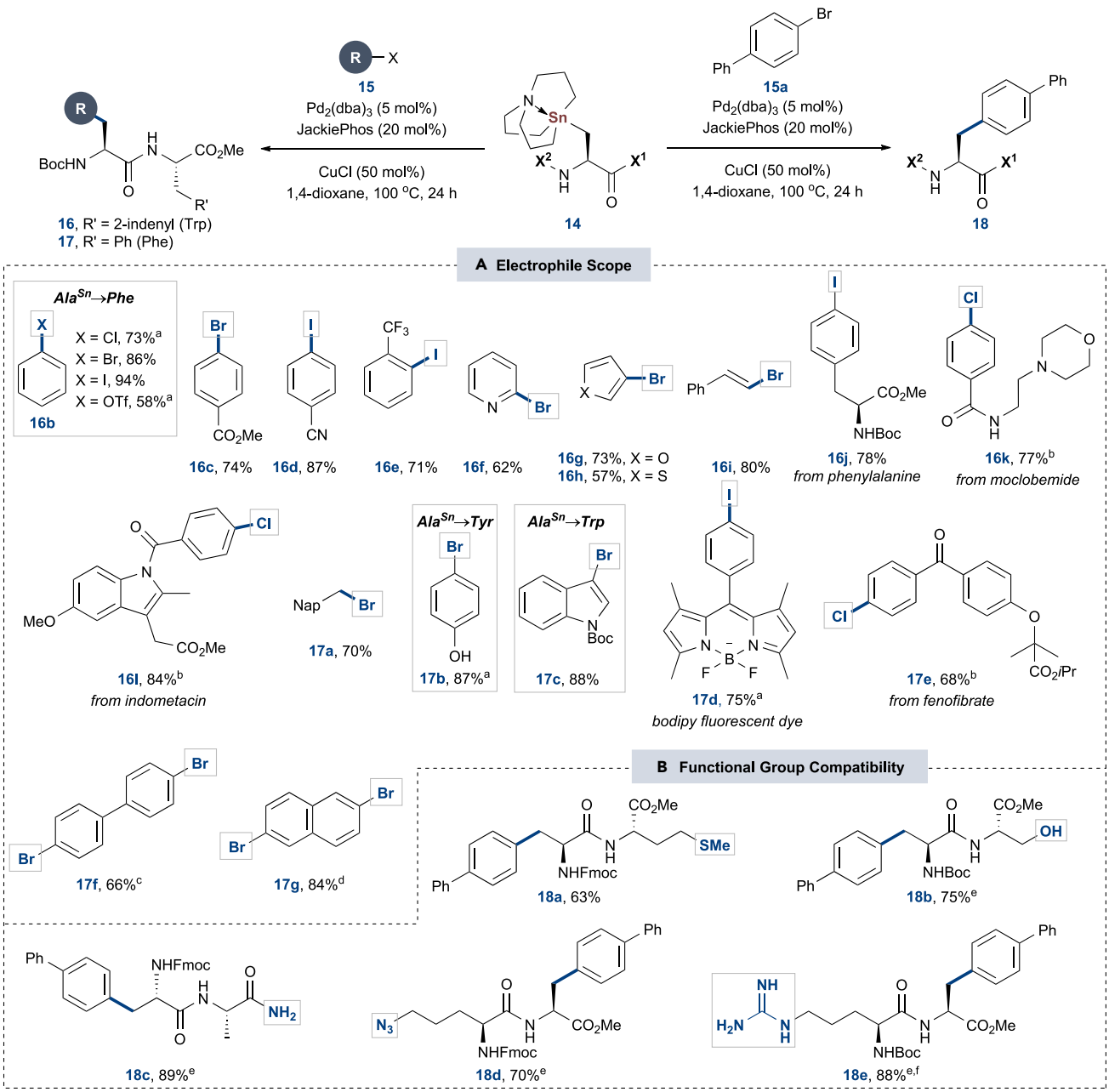
14a (0.100 mmol, 1 equiv), 4-bromodiphenyl (1.50 equiv), $Pd_2(dba)_3$ (2.5–5.0 mol %), JackiePhos (10–20 mol %), CuCl (0.50–1.50 equiv), KF (2.00 equiv), solvent (2.00 mL), 100°C, 24 h, isolated yields.

[a]$Pd_2(dba)_3$ was not used.

[b]**14a** (0.150 mmol, 1.5 equiv) was used. Dba, dibenzylideneacetone; N/D, not detected.

(**16g**), and thienyl (**16h**) groups were tolerated without significant variation in yield (57%–87%) delivering the targeted products in excellent chemoselectivities. We were pleased to find that alkenyl and benzyl bromides are suitable for the cross-coupling under the general conditions delivering L-phenylallylglycine **16i** (80%) and L-homoalanine derivative **17a** (70%). It is worth pointing out that **Ala^{Sn}** is compatible with free phenols and indole derivatives resulting in a conversion of L-**Ala^{Sn}** into L-tyrosine (**17b**, 87%) and L-tryptophan (**17c**, 88%).

We next applied the **Ala^{M}** cross-coupling protocol to peptide conjugation with small bioactive molecules. These studies were inspired by the previous work on direct attachment of cytotoxic payloads to antibodies as well as modifications of cyclic peptides with low-molecular-weight iron chelators exemplifying only selected strategies to overcome target selectivity and poor cellular permeability by site-selective modifications.[101] Several complex substrates, including commercially available pharmaceuticals and other biologically active molecules (**16j**-**16l**, **17d**, and **17e**) shown in Scheme 3A demonstrate that late-stage functionalization can be advantageous for the preparation of new scaffolds derived from phenylalanine (**16j**), BODIPY dye (**17d**), lipid-lowering drug fenofibrate (**17e**), antidepressant moclobemide (**16k**), and anti-inflammatory drug indomethacin (**16l**), all achieved by coupling with dipeptide stannanes **14**. The installation of a fluorescence imaging probe, such as BODIPY (**17d**), is of particular significance[102] because it complements nucleophilic cysteine arylation methods previously described to attach BODIPY to peptides[103] and avoids the use of nitrogen protecting groups required to direct CH activation in the earlier attempts to install fluorescent

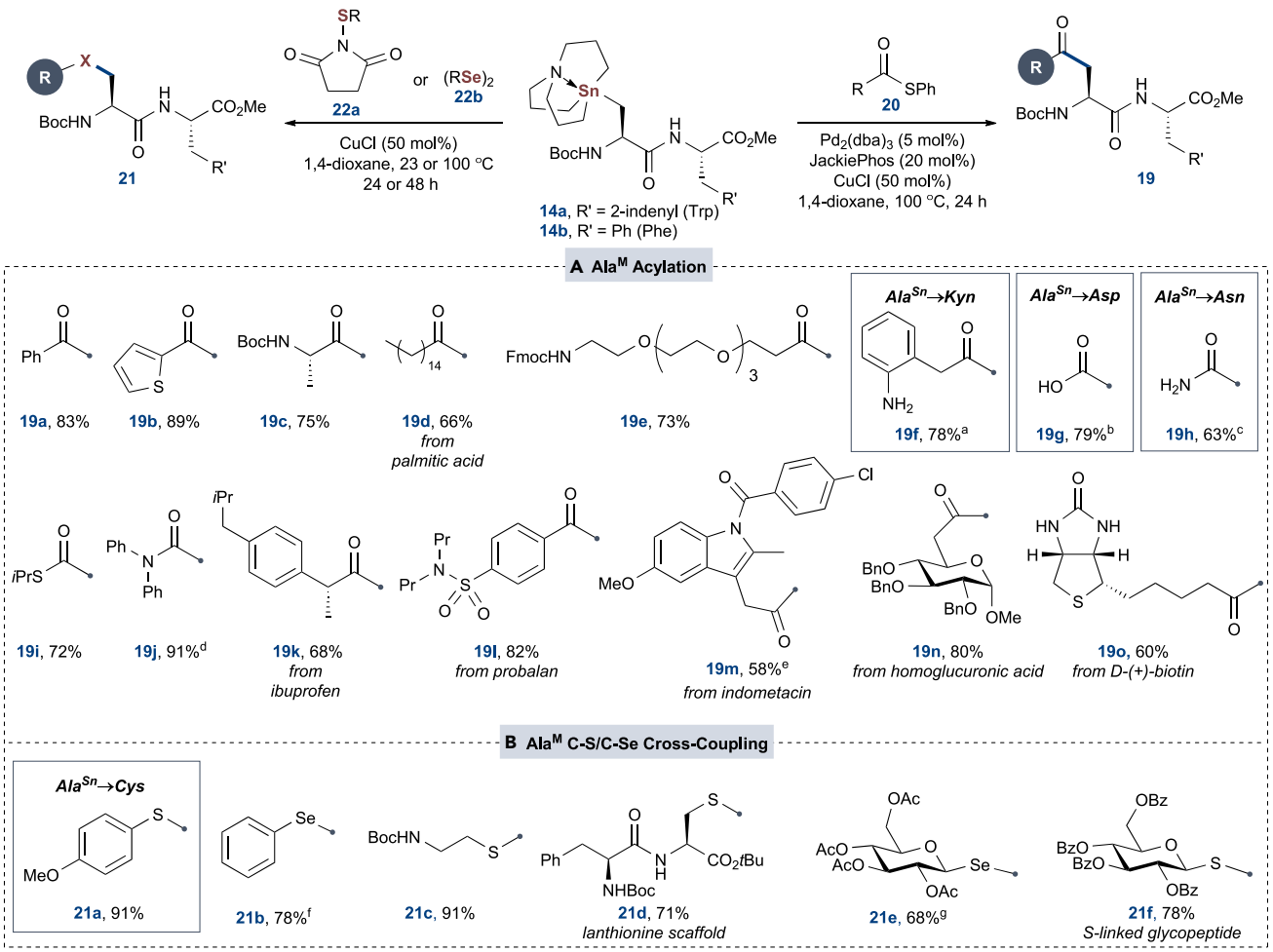


Scheme 3. Scope of Ala^{M} arylation

General reaction conditions: **14** (0.100 mmol, 1.0 equiv), electrophile reagent (1.5 equiv), $Pd_2(dba)_3$ (5.0 mol %), JackiePhos (20 mol %), CuCl (50 mol %), 1,4-dioxane (2.00 mL), 100°C, 24 h, isolated yields. [a]**14a** or **14b** (0.150 mmol, 1.5 equiv) was used. [b]KF (0.200 mmol, 2.0 equiv) was used. [c]**14b** (0.250 mmol, 2.5 equiv), CuCl (1 equiv), 37°C, and 48 h were used. [d]**14b** (2.5 equiv), CuCl (1 equiv), 90°C, and 48 h were used. [e]23°C, 48 h was used; [f]Arg side chain protected with Cbz and removed with 10% Pd/C in MeOH/EtOAc (1:1), H_2 (1 atm). Nap = 2-naphthyl.

dyes.[104,105] High chemoselectivity was also observed in the reactions with aromatic chlorides (**16k**, **16l**, and **17e**). A series of substituents such as methyl, methoxy, chloro, carbonyl, and amido groups were tolerated. We note that the cross-coupling protocol can be easily extended to double coupling (**17f** and **17g**) in excellent yields.

The overall success of Ala^{Sn} cross-coupling relies on the compatibility of the optimized conditions with common functional groups present in peptides and proteins.



Scheme 4. Scope of Ala^{M} acylation and etherification

General reaction conditions for Ala^{M} acylation: **14a** or **14b** (0.100 mmol, 1 equiv), electrophile (1.5 equiv), $Pd_2(dba)_3$ (5.0 mol %), JackiePhos (20 mol %), CuCl (50 mol %), 1,4-dioxane (2.00 mL), 100°C, 24 h, isolated yields, **14a** was used for **19a**–**19d** and **19k**–**19n**; **14b** was used for **19e**–**19j** and **19o**. [a]*tert*-Butyl ester of **14b** and Fmoc-protected anthranilic acid *S*-phenyl ester were used for cross-coupling, then 20% piperidine in CH_2Cl_2 was used for aniline deprotection. [b]*tert*-Butyl ester of **14b** was used for cross-coupling, then $LiOH \cdot H_2O$ was used for hydrolysis. [c]*tert*-Butyl ester of **14b** was used for cross-coupling, then saturated solution of ammonia in methanol was used. [d]$Pd_2(dba)_3$ (10 mol %), dppp (25 mol %), CuCl (3 equiv), 1,4-dioxane (2.00 mL), 110°C, 24 h. [e]36 h reaction time. *General reaction conditions for Ala^{M} C-S/C-Se cross-coupling:* **14a** (0.100 mmol, 1 equiv), electrophile reagents (1.5 equiv), CuCl (50 mol %), 1,4-dioxane (2.00 mL), 23°C, 48 h, isolated yields. [f]100°C, 24 h. [g]**14a** (0.100 mmol, 1 equiv), diselenide glycosyl donor (0.75 equiv), 100°C, 24 h, under air. dppp = 1,3-bis(diphenylphosphino)propane.

Since carbastannatranes are stable under typical amidation conditions (as shown here in the preparation of several Ala^{Sn}-containing peptides), the next task was to evaluate the Pd-catalyzed protocols. As shown in Scheme 3B, potentially detrimental functionalities, such as thioethers (**18a**), primary alcohols (**18b**), amides (**18c**), azides (**18d**), and guanidine in arginine (**18e**), were compatible with Pd(0) and JackiePhos.

Alanine acylation

We next evaluated the generality of our approach in alanine acylations that introduce a carbonyl functionality at the β-methylene position (Scheme 4A). In addition to direct conversion of Ala^{M} into aspartic acid and asparagine, β-amino acid ketones represent an important class of bioactive peptides.[106,107] The synthesis of amino ketones from α-amino acid derivatives either with organometallic reagents[108–110] or via

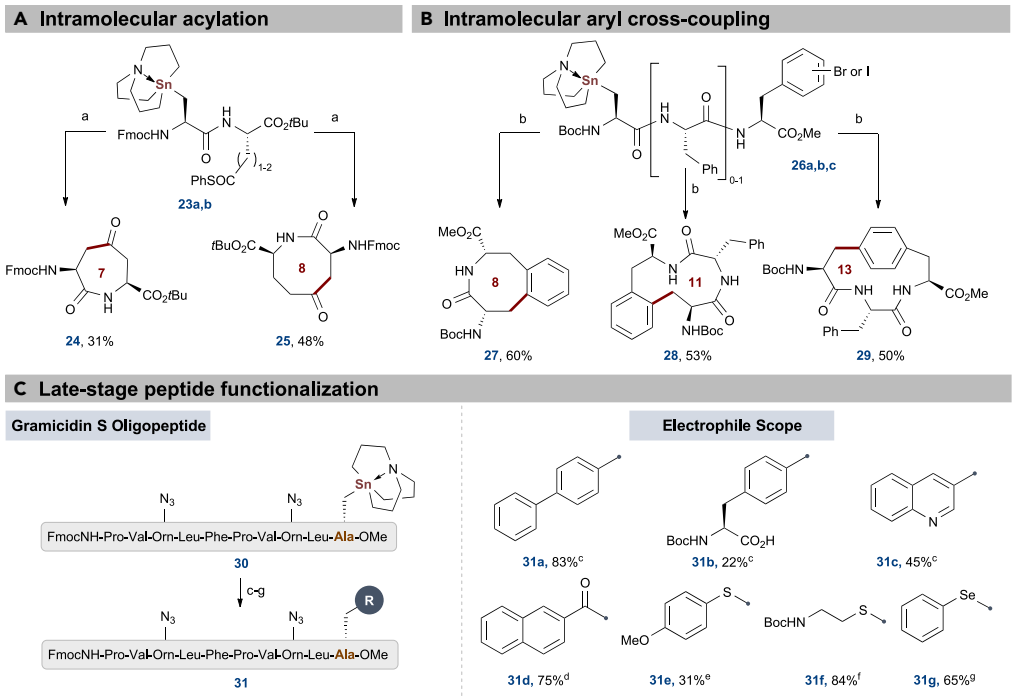
Friedel-Crafts acylation[111] was described, but the catalytic reactions targeting carboxylic acid side groups of amino acids to obtain amino ketones are rare. To the best of our knowledge, only one palladium-catalyzed Suzuki-Miyaura reaction of phenyl esters of aspartic acid with aryl boronic acids was reported.[112] Enantioselective synthesis of side-chain amino ketone derivatives by an NHC-catalyzed intermolecular Stetter reaction of aromatic aldehydes and methyl 2-acetamidoacrylate was developed, but electron-rich alkyl aldehydes were not compatible with these conditions.[113] Collectively, the lack of general methods for the side-chain acylation represents an opportunity to develop new synthetic strategies, and $\mathbf{Ala^M}$ are suitable for this study because a large collection of potential acyl donors is known.

The scope of the acylation reaction with dipeptide carbastannatranes **14** was tested using various thioesters derived from C(sp^2) and C(sp^3) carboxylic acids (Scheme 4A). Thioesters represent a compromise between reactivity of the acyl donor, stability, and the ease of preparation. Furthermore, their properties can be matched with the reactivity of the nucleophile by changing the electronics of the thiolate leaving group. However, in our studies we found that the thiophenyl group is sufficiently activated to serve as a general acyl donor in all reactions described here.

After surveying several palladium pre-catalysts and phosphine ligands, we found that $Pd_2(dba)_3$, JackiePhos, and CuCl are the optimal combination for a broad collection of aryl and alkyl carboxylic acid thioesters. *S*-Phenyl thioesters **20** were readily converted to the corresponding ketones in moderate to excellent yields, whereas *S*-alkyl thioesters resulted in ~20% lower yields. Aromatic carboxylic acid thioesters, such as *S*-phenyl benzothioate (**19a**) and *S*-phenyl thiophene-2-carbothioate (**19b**), performed well despite the potential issues with catalyst deactivation by the resultant thiophenolate. To our delight, *S*-phenyl thioesters with alkyl side chains were also viable substrates, as demonstrated by a smooth conversion alanine-derived ester (**19c**), fatty acid donor (**19d**), or PEG-derived amino acid (**19e**). Notably, we were unable to detect any loss of stereochemical integrity at the α-position or loss of CO for alkyl and aryl substrates.

The acylation protocol allows for a direct conversion of $\mathbf{Ala^M}$ into naturally occurring amino acids. For example, a reaction of (2-aminophenyl)acetic acid thioester with the model peptide **14b** afforded a metabolite amino acid kynurenine **19f** typically introduced into the peptide via ozonolysis of tryptophan.[114] Similarly, when **14a** was treated with *i*PrSCOSePh as the acyl electrophile followed by basic hydrolysis (LiOH, H_2O), aspartic acid **19g** was obtained in 79%. In this reaction the C-Se bond underwent preferential cleavage, and the potentially problematic second activation of the intermediate thioester was suppressed by maintaining a slight excess of the electrophile (1.5 equiv). Furthermore, treatment of thioester intermediate **19i** with NH_3 in MeOH afforded asparagine **19h**. Thioester **19i** can be isolated if needed (72%) and can serve as a competent acyl donor for downstream functionalizations. Similarly, N-linked asparagine derivatives can be introduced into peptides if *N*,*N*-diaryl thiocarbamates are used (**19j**).

To further demonstrate the practicality of the $\mathbf{Ala^{Sn}}$ acylation as a tool for site-selective conjugation, we converted several bioactive small-molecule carboxylic acids into thioesters and engaged them in C-C couplings. These reactions included derivatives of ibuprofen (**19k**), probalan (**19l**), indometacin (**19m**), D-homoglucuronic acid (**19n**), and D-(+)-biotin (**19o**) used here as examples of functional group compatibility and high chemoselectivity.



Scheme 5. Scope of late-stage functionalization

General reaction conditions for intramolecular acylation and aryl cross-coupling: **23** or **26** (0.100 mmol, 1 equiv), $Pd_2(dba)_3$ (5.0 mol %), JackiePhos (20 mol %), CuCl (1 equiv), 1,4-dioxane (50.0 mL), isolated yields; **a**, 90°C and 48 h were used; **b**, room temperature and 72 h were used. *Reaction conditions for late-stage peptide functionalization:* **c**, **30** (0.010 mmol), aryl bromide (0.100 mmol), $Pd_2(dba)_3$ (0.050 mmol), JackiePhos (0.200 mmol), CuCl (0.100 mmol), MeCN:buffer [pH 7.5] (1:1, 2.00 mL), 37°C, 1 h; **d**, **30** (0.010 mmol), *S*-phenyl naphthalene-2-carbothioate (0.100 mmol), $Pd_2(dba)_3$ (0.05 mmol), JackiePhos (0.200 mmol), CuCl (0.100 mmol), 1,4-dioxane (1.00 mL), 37°C, 4 h; **e**, **30** (0.010 mmol), 1-((4-methoxyphenyl)thio)pyrrolidine-2,5-dione (0.100 mmol), CuCl (0.200 mmol), MeCN:CH_2Cl_2 (1:1, 2.00 mL), 37°C, 2 h; **f**, **31** (0.010 mmol), *tert*-butyl (2-((2,5-dioxopyrrolidin-1-yl)thio)ethyl)carbamate (0.100 mmol), CuCl (0.200 mmol), 1,4-dioxane:CH_2Cl_2 (1:1, 2.00 mL), 37°C, 12 h; **g**, **30** (0.010 mmol), CuCl (0.100 mmol), 1,2-diphenyldiselenide (0.100 mmol), MeCN:buffer [pH 7.5] (1:1, 2.00 mL), 37°C, 1 h.

Inverse (seleno)cysteine arylation and alkylation

In the course of the method development, we turned to reactions that give rise to (seleno)cysteine-modified peptides (Scheme 4B). Cysteine arylations have received considerable attention as a means to perform site-selective conjugation complementing thiol alkylations or Michael additions.[5,100,115] In these protocols, the nucleophilic cysteine thiol was modified with organopalladium/organogold reagents,[116] boronic acids,[117] or diazonium salts.[118] As a complementary strategy representing an inverse approach, we envisioned that Ala^{Sn} could be used to introduce aryl (seleno)cysteine with redox-neutral electrophiles, such as *N*-sulfenylsuccinimides **22a** or diselenides **22b** (Scheme 4B). We found that the cross-coupling of Ala^{Sn} could be catalyzed by CuCl (50 mol %) with no additional activators since the Ala^{Sn} nucleophiles are sufficiently activated to undergo transmetalation. Other Cu(I) sources, such as CuBr or CuI, were less efficient in promoting this transformation, an observation consistent with our previous work that underscored the importance of the halide counterion. Substrates, such as aryl (**21a**, **21b**) and alkyl *N*-sulfenylsuccinimides (**21c**) were converted into thioethers at room temperature or selenides at 100°C. A direct coupling of cysteine *N*-sulfenylsuccinimide dipeptide generated S-linked lanthionine **21d** in 71% without epimerization at the α-carbonyl. This strategy is complementary to the earlier synthetic studies that relied on nucleophilic substitution of β-haloalanine with free cysteine.[119] This example further demonstrates that oligopeptides can be efficiently coupled without detrimental formation of

Dha, which frequently competes with substitutions of β-haloalanine electrophiles. These results led us then to extend the scope of C-heteroatom cross-couplings with symmetrical D-glucose diselenide (**21e**) and *N*-sulfenylsuccinimidate donors (**21f**), resulting in 68% and 78%, respectively, with retention of anomeric configuration for both examples. This strategy, which represents an umpolung approach to glycodiversification, can be used in the preparation of (seleno)cysteine-modified peptides.[88–90]

Peptide macrocyclization

Complementary to intermolecular transformations, we were intrigued by the possibility of engaging **Ala^{Sn}** in cyclizations with properly functionalized electrophiles (Schemes 5A and 5B). Because cyclic peptides are a promising scaffold for the development of drug candidates due to their ability to bind to a wide range of target molecules and proteolytic stability, research into the synthetic methodology for peptide cyclization focusses on side-chain cyclizations and, more recently, biosynthetic engineering.[120–122] Among these, methods that can selectively connect the aromatic ring in the form of cyclophane-type frameworks can facilitate the discovery of novel bioactive compounds.[13,123,124] The rigid, planar, and hydrophobic aromatic rings that support the cyclic structures can be fully fitted into the main skeleton of the cyclic peptide molecule and are amenable to structural modifications. The non-canonical aryl linkers can stabilize secondary structures and promote hydrogen bonding, which can be beneficial for optimizing membrane permeability and bioavailability. Inspired by these novel functions of cyclic peptides, we wondered whether our methods could be employed to generate similar structures via intramolecular C(sp^3)-C(sp^2) reactions. We pursued two cyclization strategies that were dictated by the availability of the electrophilic components and their ease of introduction into a peptide: (1) reactions at the acyl side chains of Asp (**23a**) and Glu (**23b**) in the form of a thioester that furnished 7- and 8-membered ketones **24** and **25** in 31%–48% yield, and (2) couplings of phenylalanine functionalized with a halogen handle at the *ortho* (**26a**, **26b**) and *para* (**26c**) positions leading the formation for 8-membered (**27**), 11-membered (**28**), and 13-membered (**29**) rings in 53%–60%. The reactions with thioesters represent a rare example of carbonylative cyclization in peptide scaffold **24** and **25** and introduce a novel ketone linker. Similarly, arylation reactions with a phenylalanine electrophile produced a strained *para*-cyclophane structure **29** formed through a unique cyclization strategy.

Oligopeptide functionalization

To further demonstrate the utility of all coupling methods in a relevant peptide example, we assembled, via automated solid-support peptide synthesis, gramicidin S oligopeptide **30** with one position mutated into D-**Ala^{Sn}** (Scheme 5C). This linear peptide was used to compare side-by-side all reactions developed earlier but in a more complex setting. Consistent with the results described earlier, both arylation and acylation reactions provided the C-C coupling products **31a**–**31d** in good yields, and heteroaromatic substrates, such as 3-bromoquinoline (**31c**), can be accomplished in acceptable 45% yield. Notably, low temperature ($\leq$37°C) and close-to-neutral pH buffers were optimal for these reactions. Furthermore, thioetherifications performed in variable yields (**31e** and **31f**, 31%–84%), and introduction of selenocysteine proceeded with a somewhat moderate yield (**31g**, 65%) but in excellent chemoselectivity.

Conclusions

It is becoming abundantly clear that polarity reversal applied to biomolecule functionalization offers an unprecedented opportunity to access new reactivity and

explore novel chemical space. Here, we demonstrated that a stable nucleophile installed at the β carbon in Ala^{M} can serve as an efficient synthon for divergent synthesis of modified peptides. This strategy capitalizes on transmetalation of primary carbastannatranes embedded in a peptide chain that could be coupled with aryl-, acyl-, and chalcogen-based electrophiles, even at ambient conditions and in aqueous solutions. As we showcased these reactions in the synthesis of several high-value structures, late-stage functionalization and cyclization reactions stand out due to their potential to streamline discovery of new biomaterials, therapeutics, and probes. It is also conceivable that the presented collection of methods can be integrated with the emerging technologies in peptide manipulation, such as encoded libraries and direct bioconjugation.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Maciej Walczak (maciej.walczak@colorado.edu).

Materials availability

All unique reagents generated in this study will be made available on request to the lead contact.

Data and code availability

- There is no dataset or code associated with this paper.
- Full experimental procedures are provided in the supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.checat.2021.05.016.

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AUTHOR CONTRIBUTIONS

Conceptualization, F.Z. and M.A.W.; methodology, F.Z., W.C.P., R.J., and M.A.W.; validation, F.Z., W.C.P., and R.J.; formal analysis, F.Z., W.C.P., R.J., and M.A.W.; investigation, F.Z., W.C.P., and R.J.; resources, F.Z., W.C.P., R.J., and M.A.W.; data curation, F.Z., W.C.P., and M.A.W.; writing – original draft, F.Z. and M.A.W.; writing – review & editing, F.Z., W.C.P., and M.A.W.; visualization, F.Z., W.C.P., and M.A.W.; supervision, F.Z. and M.A.W.; project administration, M.A.W.; funding acquisition, M.A.W.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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