Organometallic Ala^{M} Reagents for Umpolung Peptide Diversification

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ABSTRACT

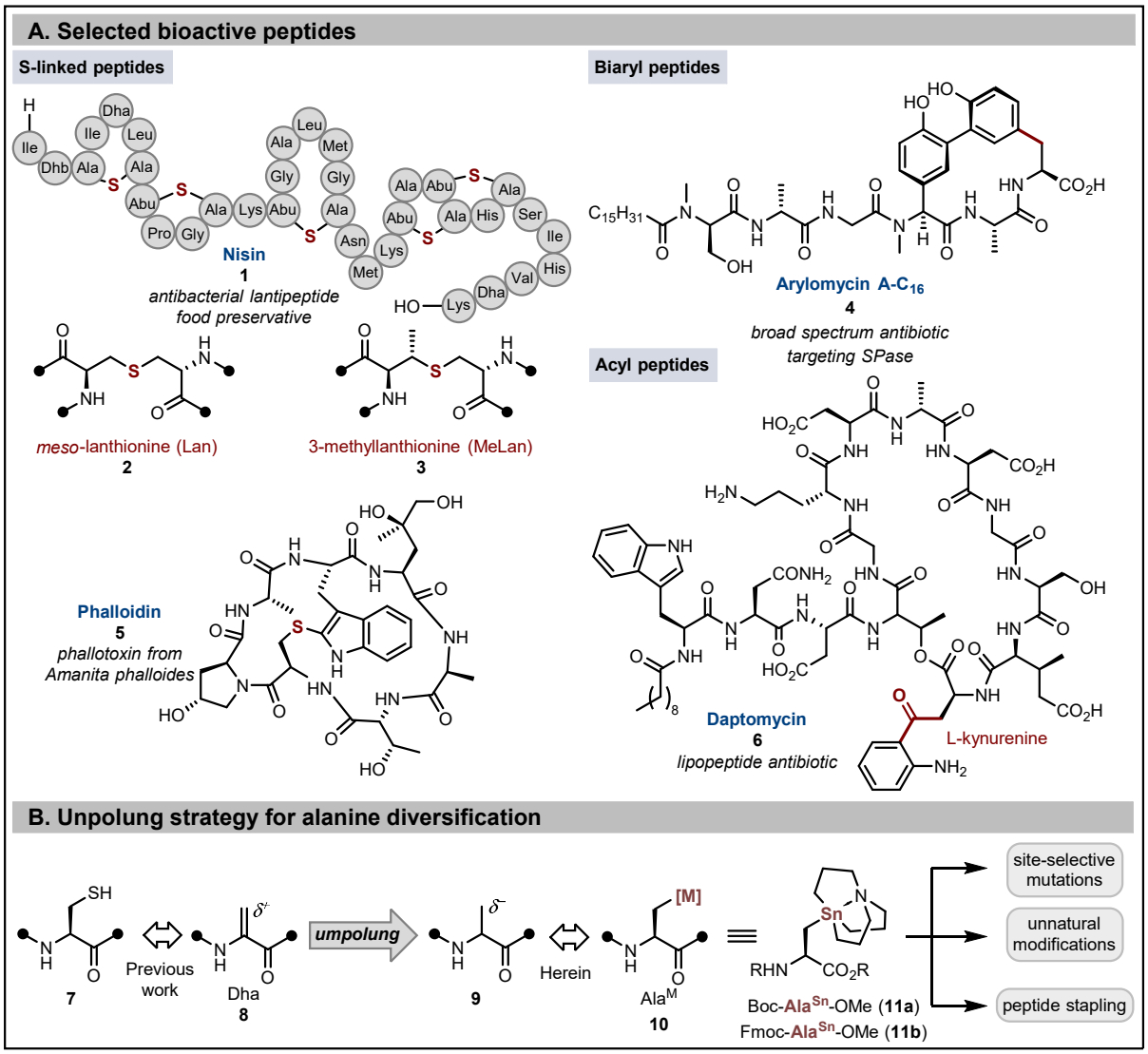
Selective modification of peptides and proteins is emerging as a promising strategy to develop novel mechanistic probes and prepare compounds with translational potential. While many methods to perform direct bioconjugation rely on reactions with dehydroalanine, an alternative strategy capitalizing on polarity reversal at the β carbon in amino acids can open access to a new type of diversification reactions characterized by absolute control of regio- and stereoselectivity. Here, we report that alanine carbastannatranes Ala^{Sn} can serve as a universal synthon in various C-C and C-heteroatom bond-forming reactions demonstrated in over 50 diverse examples. These reagents are compatible with peptide and protein manipulation techniques and undergo chemoselective conjugation in minutes when promoted by Pd(0). Despite their increased nucleophilicity and propensity to transfer the alkyl group, Ala^{Sn} operate 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 (7-13 membered macrocycles). Taken together, metalated alanine Ala^{Sn} demonstrate unparalleled scope and represent a new type of umpolung reagents 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 relationship and accessing new therapeutic leads.[1-4] Significant advances have been made over the past decade to modify peptides using heteroatom conjugation with cysteine or lysine,[5-10] site specific C-H functionalization of aromatic rings in tryptophan, histidine, or phenylalanine,[11-13] radical functionalization,[14, 15] and decarboxylative couplings of C-terminal amino acids or side chains functionalities in aspartic and glutamic acids.[16-20] In addition to the diversification strategies,[21] natural peptides with posttranslational modifications are gaining increasing importance due to their translational potential.[22-26] Among the peptides of ribosomal origin,[27] 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**).[28] In the same category, tryptothionine cross-linked toxic peptides such as actin-binding phalloidin **4**[29, 30] and RNA polymerase II inhibitor α-amanitin[31, 32] from the *Amanita phalloides* mushroom constitute another class of thioether modifications. Furthermore, variations at the aryl groups resulting from oxidative dimerization of tryptophan such as arylomycins (**5**) or oxidative cleavage of the indole ring in tryptophan (L-kynurenine in lipopeptide daptomycin **6**)[33] give rise to agents with promising antibacterial activities. The unique structural modifications contribute to the diversity of peptides but also represent a synthetic challenge. One strategy that has attracted considerable attention are conjugate additions to dehydroalanine (Dha) **8** readily generated from cysteine (Scheme 1B). 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 generate protein conjugates achieving divergent late-stage modifications. However, the stereochemistry at the resulting α-carbon is difficult to control,[34, 35] and only a handful of examples such as nucleophilic addition of dehydroalanine within a complex environment of natural products and proteins,[36, 37] Rh-catalyzed tandem 1,4-addition/stereoselective protonation,[38-41] and Friedel–Crafts conjugate addition[42] 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.[43, 44]

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.

In designing a new method based on **Ala^{M}**, two critical considerations need to be addressed: (a) formation and stability of **Ala^{M}** and (b) 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,[45-47] but these conditions (high temperatures, pure organic solvents, and specialized directing groups) may be incompatible with complex peptides,



Scheme 1. Peptide post-translational modifications and chemical methods for their installation.

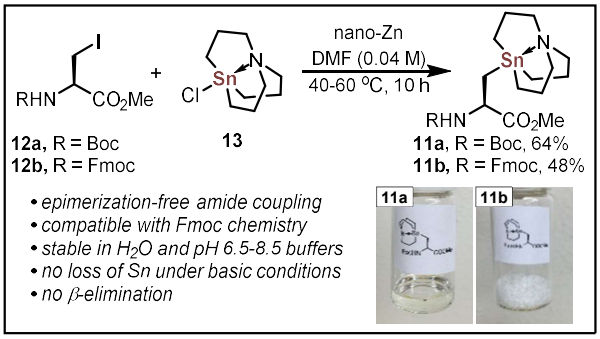
proteins, and even some functional groups found in common amino acids. Alternatively, **Ala^{M}** can be used stoichiometrically as a stable reagent, and previous attempts to realize this strategy utilized organolithium,[48] organozinc,[49-55] organonickel,[56, 57] and organoboron[58-60] reagents derived from protected L-alaninol or L-alanine. 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,[61-65] 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[66, 67] 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 "normal" stannanes[68] and are compatible with aqueous and buffered conditions. Coordination of the nitrogen atom improves their reactivity and determines a selective transfer of one alkyl group. Herein, we reported a novel strategy for the late-stage modification of peptides and proteins with **Ala^{Sn}** carbastannatrane amino acid synthons. This protocol exhibits high chemoselectivity compared to 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 diversification of peptides or proteins.

RESULTS AND DISCUSSION

A. 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 **12** 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 two model dipeptides **14** and used them in optimization studies geared toward C(sp^3)-C(sp^2) cross-coupling (Scheme 3A). Initial evaluations using $Pd_2(dba)_3$ (5 mol%) and



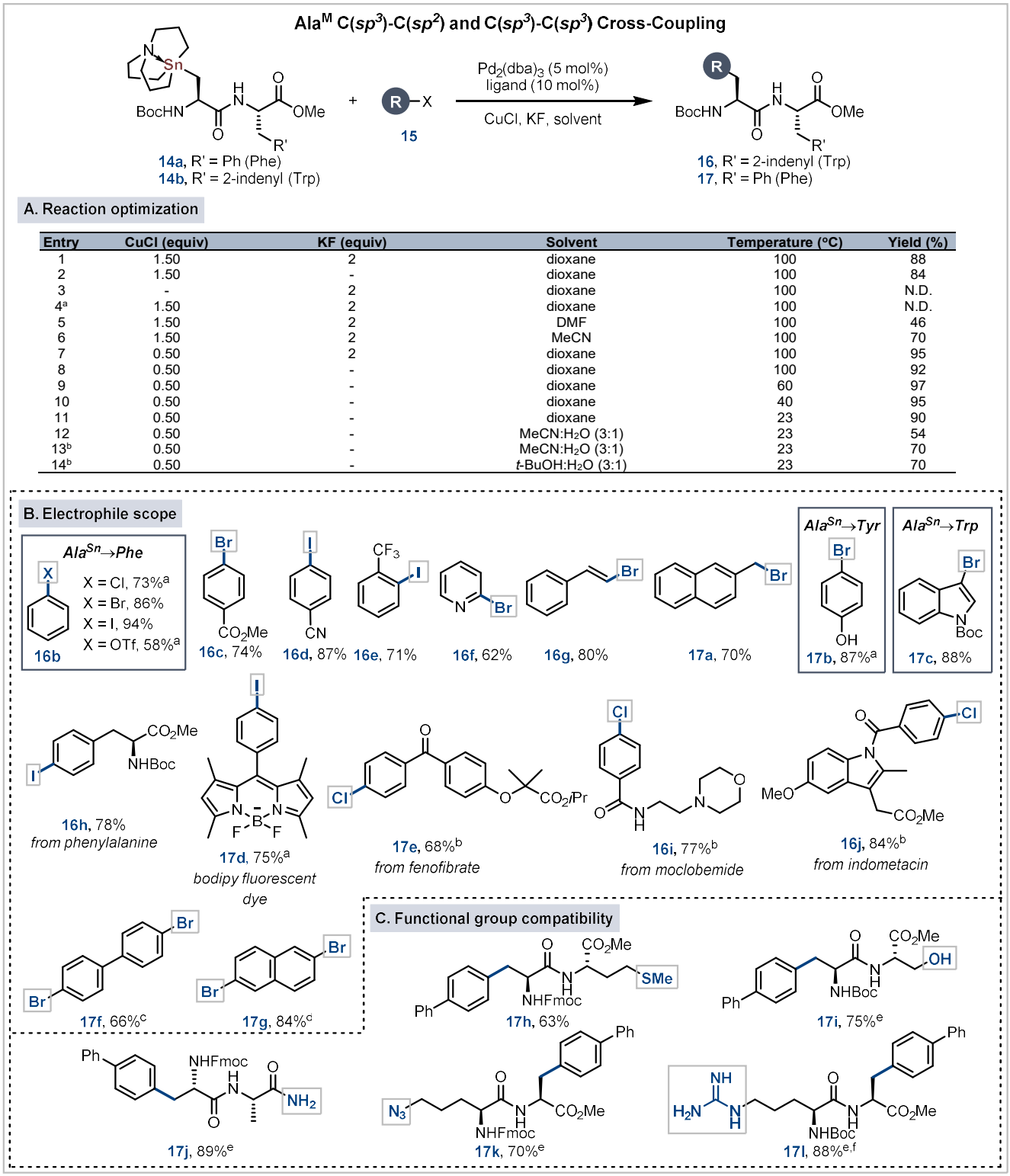
Scheme 2. Synthesis of Ala^{Sn} reagents.

JackiePhos (20 mol%)[69, 70] as the catalytic system with CuCl (1.5 equiv), KF (2.0 equiv), and 4-phenylbromobenzene (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 has 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 products **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 detail, see the SI). 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 dipeptides **14** were compatible with co-solvent systems of MeCN or *t*-BuOH with water and 70% isolated yield of **16** was obtained by tuning the amount of 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 complex peptides and proteins.[71] The desired peptide **16a** 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 minutes (0.005 M) with 83% isolated yield of **16a**. The high chemoselectivity and mild conditions (room temperature, aqueous buffers, and short reaction time) make this method suitable for the late-stage modification of complex peptides and proteins.

With the optimized conditions in hand, we next evaluated the generality of C(sp^3)-C(sp^2) cross-coupling method (Scheme 3B and 3C). A wide range of electrophiles with different functional groups could be successfully transformed into arylalanine derivatives (Scheme 3B). 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**), and pyridyl (**16f**) groups were tolerated without significant variation in yield (62-87%) 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-allylalanine **16g** (80%) and L-homoalanine **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**, 89%).

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.[72] Several complex substrates including commercially available pharmaceuticals and other biologically active molecules (**16h**-**16j**, **17d** and **17e**) shown in Scheme 3B demonstrate that late-stage functionalization can be advantageous for the preparation of new scaffolds derived from



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

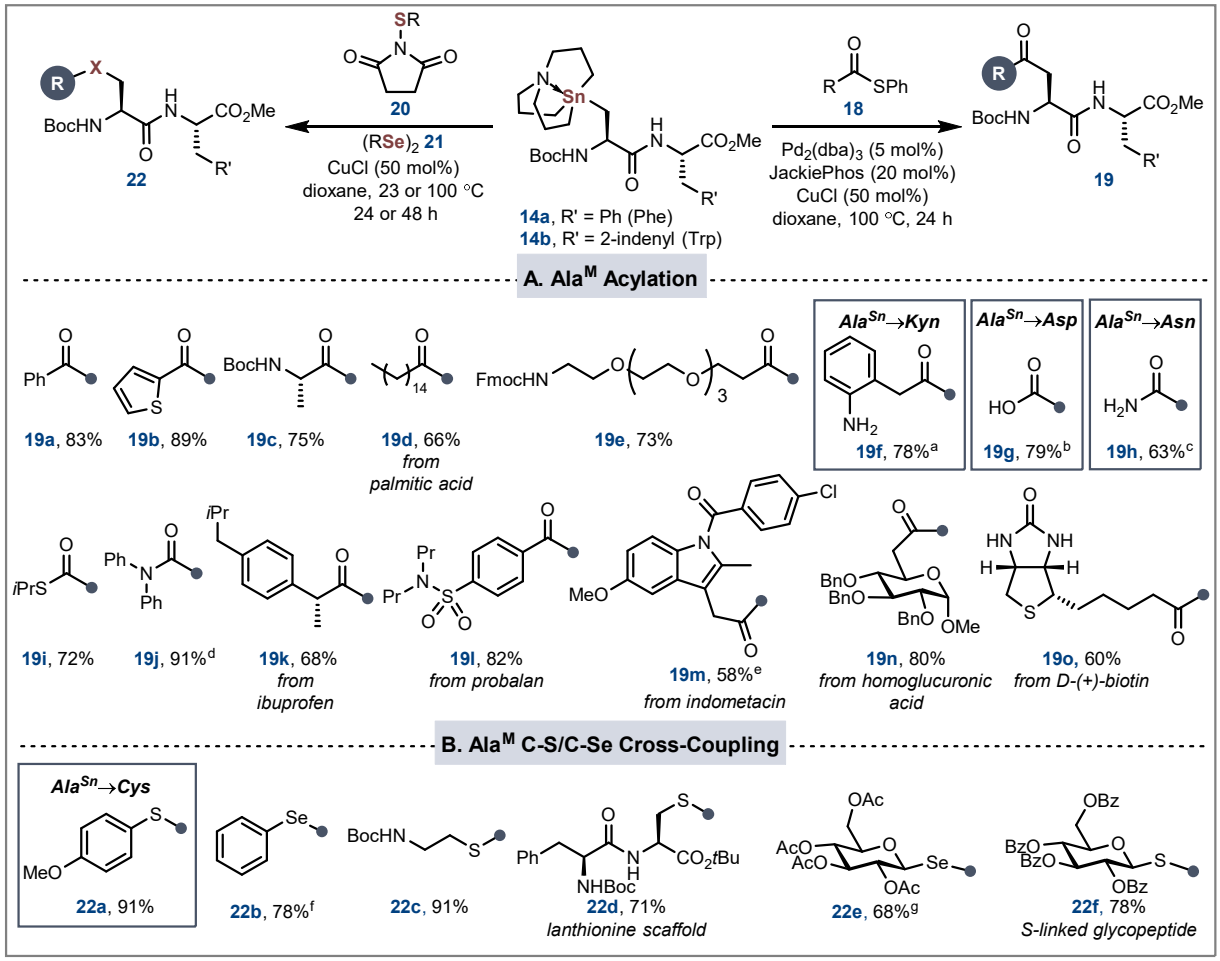
Scheme 3. *General reaction conditions*: **14a** or **14b** (0.100 mmol, 1.0 equiv), electrophile reagent (1.5 equiv), $Pd_2(dba)_3$ (5.0 mol%), JackiePhos (20 mol%), CuCl (50 mol%), 1,4-dioxane (2 mL), 100 °C, 24 h, isolated yields. [a]$Pd_2(dba)_3$ was not used. [b]**14b** (0.150 mmol, 1.5 equiv) was used. [d]**14a** (0.150 mmol, 1.5 equiv) was used. [e]CuCl (1.5 equiv), KF (2 equiv), and 36 h were used. [f]**14b** (2.50 equiv), CuCl (1 equiv), 37 °C, and 48 h were used. [g]**14b** (2.5 equiv), CuCl (1 equiv), 90 °C, and 48 h was used. [h]23 °C, 48 h was used. [i]10% Pd/C in MeOH/EtOAc (1:1), H_2 (1 atm). dba = dibenzylideneacetone.

phenylalanine (**16h**), BODIPY dye (**17d**), lipid-lowering drug fenofibrate (**17e**), antidepressant moclobemide (**16i**), and anti-inflammatory drug indomethacin (**16j**) all achieved by coupling with dipeptide stannanes **14**. The installation of a fluorescence imaging probe such as BODIPY (**17d**) is of particular significance[73] because it complements nucleophilic cysteine arylation methods previously described to attached BODIPY to peptides[74] and avoids the use nitrogen protecting

groups required to direct CH activation in the earlier attempts to install fluorescent dyes.[75, 76] High chemoselectivity was also observed in the reactions with aromatic chlorides (**17e**, **16i**). 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 presents in peptides and proteins. 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 3C, potentially detrimental functionalities such as thioesters (**17h**), primary alcohols (**17i**) and amides (**17j**), azides (**17k**), and guanidine in arginine (**17l**) were compatible with Pd(0) and JackiePhos.

B. 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.[77, 78] The synthesis of amino ketones from α-amino acid derivatives either with organometallic reagents[79-81] or via Friedel−Crafts acylation[82] were 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.[83] Enantioselective synthesis of side chain amino ketone derivatives by an NHC-Catalyzed intermolecular Stetter reaction of aromatic aldehydes and methyl 2-acetamidoacrylate were developed, but electron-rich alkyl aldehydes were not compatible with these conditions.[84] Collectively, the lack of general methods for side chain



Scheme 4. *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 mL), 100 °C, 24 h, isolated yields, **14b** was used for **19a**-**19d** and **19k**-**19n**; **14a** was used for **19e** -**19j** and **19o**. [a]*tert*-Butyl ester of **14a** was used for cross-coupling, then 20% piperidine in CH_2Cl_2 was used for deprotection. [b]*tert*-Butyl ester of **14a** was used for cross-coupling, then $LiOH·H_2O$ was used for hydrolysis. [c]*tert*-Butyl ester of **14a** 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 mL), 110 °C, 24 h. [e]36 h was used. *General reaction conditions for **Ala^{M}** C-S/C-Se cross-coupling:* **14b** (0.100 mmol, 1 equiv), electrophile reagents (1.5 equiv), CuCl (50 mol%), 1,4-dioxane (2 mL), 23 °C, 48 h, isolated yields. [f]100 °C, 24 h. [g]**14b** (0.100 mmol, 1 equiv), diselenide glycosyl donor (0.75 equiv), 100 °C, 24 h, under air. dppp = 1,3-bis(diphenylphosphino)propane.

acylation represents an opportunity to develop new synthetic strategies and **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 thiophenol group is sufficiently activated to serve as a general acyl donor in all reactions described here.

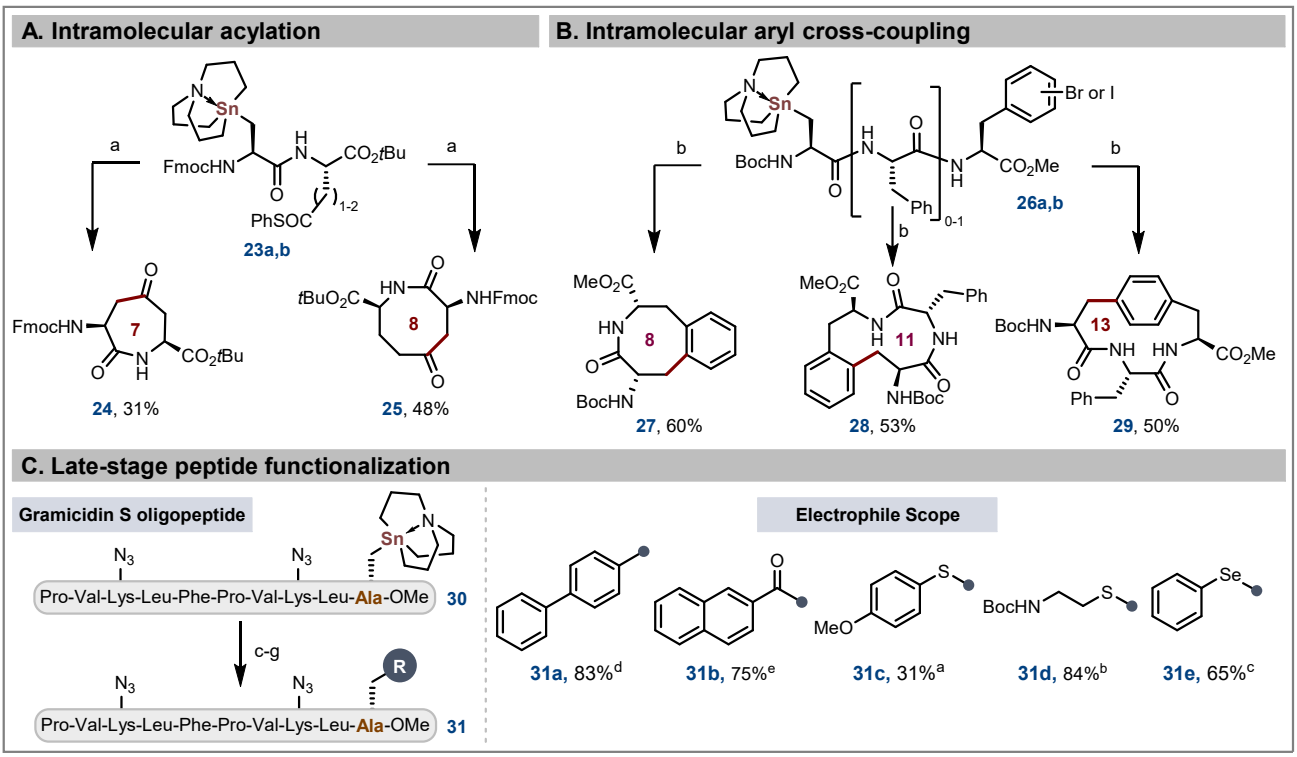
After surveying several palladium pre-catalysts and phosphine ligands, we found that $Pd_2(dba)_3$, JackiePhos, and CuCl are the optimal combination for a broad collection of aryl and alkyl thioesters. Phenyl thioesters **18** were readily converted to the corresponding ketones in moderate to excellent yields, with alkyl thioesters resulting in ~20% lower yields. Aromatic thioesters such as phenyl (**19a**) and thiophenyl (**19b**) performed well despite the potential issues with catalyst deactivation by the resultant thiophenolate. To our delight, alkyl thioesters 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 **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.[85] 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 adjusting the ratio 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 **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.

C. 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.[71, 86] In these protocols, the nucleophilic cysteine thiol was modified with organopalladium, organogold reagents,[87] boronic acids,[88] or diazonium salts.[89] 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 **20** or diselenides **21** (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 prior work that underscored the importance of the halide counterion. Substrates such as aryl (**22a**, **22b**) and alkyl *N*-sulfenylsuccinimides (**22c**) were converted into thioethers at room temperature (thioethers) or at 100 °C (selenides). A direct coupling of cysteine *N*-sulfenylsuccinimide dipeptide generated *S*-linked lanthionine **22d** 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.[90] This example further demonstrates that oligopeptides can be efficiently coupled without detrimental formation of Dha that 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 (**22e**) and *N*-sulfenylsuccinimidate donors (**22f**), 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.[61, 64, 65]

D. Peptide macrocyclization. Complementary to intermolecular transformations, we were intrigued by the possibility of engaging **Ala^{Sn}** in cyclizations with properly functionalized electrophiles (Scheme 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 in synthetic methodology for peptide cyclization focus on side chain cyclizations and, more recently, biosynthetic engineering.[91-93] Among those, methods that can selectively connect the aromatic ring in the form cyclophane-type frameworks can facilitate the discovery of novel bioactive compounds.[13, 94,95] The rigid, planar, and hydrophobic aromatic rings 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 that 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 availably of the electrophilic components and their ease of introduction into a peptide: (a) reactions at the acyl side chains of Asp and Glu in the form of a thioester that furnished 7- and 8-membered ketones **24** and **25** in 31-48% yield, and (b) couplings of phenylalanine functionalized with a halogen handle at the ortho- (**27**, **29**) and para- (**30**) positions leading the formation for 8-, 11-, and 13- membered rings in 53-62%. The reactions with thioesters represent a



Scheme 5. *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 (100 mol%), 1,4-dioxane (50.0 mL), isolated yield; **a**. 90 °C and 48 h were used; **b**. room temperature and 72 h were used. *Reaction conditions for late-stage peptide functionalization :* **c. 31** (0.010 mmol), 4-bromo-1,1'-biphenyl (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 mL), 37 °C, 1 h; **d. 31** (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 mL), 37 °C, 4 h; **e. 31** (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 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 mL), 37 °C, 12 h; **g. 31** (0.010 mmol), CuCl (0.100 mmol), 1,2-diphenyldiselenide (0.100 mmol), MeCN:Buffer pH 7.5 (1:1, 2 mL), 37 °C, 1 h.

rare example of carbonylative cyclization in peptide scaffold **24** and **25** and introduce a novel ketone linker. Similarly, arylation reactions with alanine electrophiles produce a strained para-cyclophane structure formed through a unique cyclization strategy.

E. 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** and **31b** in uniformly high yields. Notably, low temperature (≤37°C), close to neutral pH buffers were optimal for these reactions. Furthermore, the thioetherifications performed better for alkyl thiols (**31c** and **31d**), whereas introduction of selenocysteine proceeded in a somewhat moderate yield (**31e**) 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 and protein manipulation such as encoded libraries and direct bioconjugation.

ASSOCIATED CONTENT

Full experimental details, copies of NMR spectra (PDF)

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