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Peptide modification and cyclization via transition-metal catalysis

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Transition-metal catalysis has unlocked new paradigms for the late-stage modification and cyclization of peptides by harnessing the innate reactivity of proteinogenic amino acids. The field is rapidly evolving, with recent advances encompassing three fundamental areas — heteroatom couplings, decarboxylative cross-couplings, and C–H functionalizations — which have markedly extended the scope of conventional peptide modification and bioconjugation strategies. The advances outlined herein facilitate access to high-value peptide targets with promising applications in materials science and drug discovery.

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Introduction

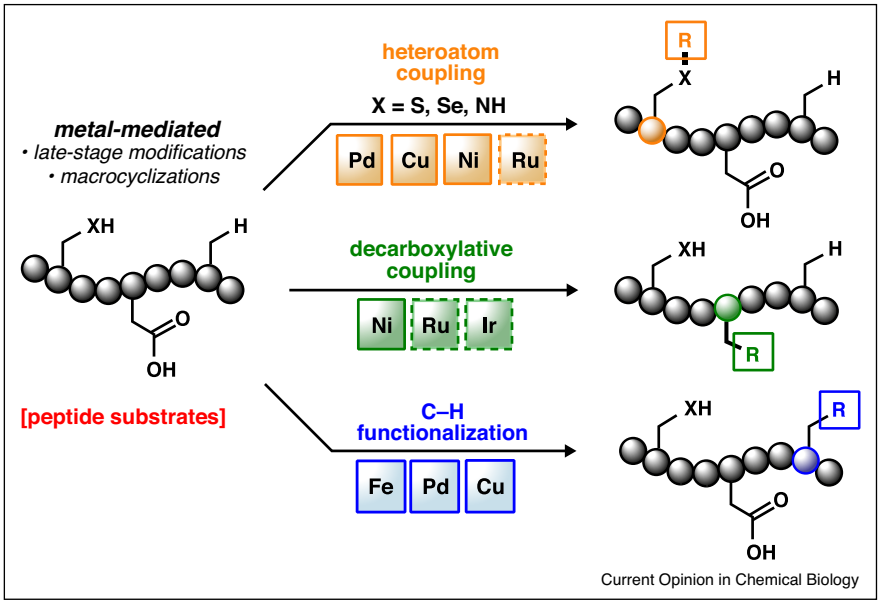
Unnatural amino acids are powerful building blocks for peptide-based materials and therapeutics, enabling chemists to explore beyond the structural and functional limitations imposed by the finite set of canonical amino acids. The ability to surgically tailor single amino acids within the context of a complex peptide represents an ideal approach for direct access to modified peptides, abrogating the need to prepare an orthogonally protected, unnatural amino acid variant — an endeavor which typically requires specialist skills in organic synthesis and laborious, multi-step processes. Indeed, the advantages of late-stage modifications have prompted the recent development of several cutting-edge technologies which utilize native peptides or leverage the incorporation of select unnatural motifs to access a broad range of functionalized peptide products [1].

This opinion article will highlight a handful of transformative strategies for peptide modification and cyclization — focusing primarily on the last two years — which exploit the unique power of *transition-metals* as mediators [2–4] for covalent bond-formation or photoinduced electron transfer (PET) processes. Historically, only a small handful of amino acids have been utilized as handles for peptide functionalization [1,5,6]. However, through the strategic application of transition-metal mediators, the technologies discussed herein take advantage of discrete, often underutilized, amino acid functionalities within the context of more complex peptide and protein scaffolds. Strategies discussed fall into three main categories: heteroatom couplings (at sulfur, selenium, and nitrogen); decarboxylative couplings (at α-COOH, Asp, and Glu); and C–H functionalizations (Figure 1). Emphasis will be placed on the critical role of the metal center as a reaction mediator as well as the utility of accessible peptide products. An overview of the scope and limitations of these emerging strategies is presented.

Heteroatom coupling

Several strategies for heteroatom arylation have recently been developed that exploit select side-chain functionalities as handles for palladium catalyzed C(sp^2)–X bond formation (X = S, Se, or N) [7]. Such peptide-aryl constructs are attractive given the relative stability of the linkage in comparison with other modes of bioconjugation and the commercial availability of diverse aryl substrates. Following early work employing cyclometalated gold(III) complexes [8], a pivotal study from Pentelute and Buchwald in 2015 [9••] demonstrated the rapid, Cys-selective arylation of unprotected peptides using bench-stable, organopalladium reagents (e.g. **1**, Figure 2), formed through the oxidative addition of an aryl (pseudo)halide. Arylation reactions proceeded under mild, dilute conditions in mixed aqueous/organic media to form diverse peptide products, including Cys-linked drug molecules, affinity tags, and fluorescent dyes (see **2**, Figure 2a), as well as bioconjugates of native proteins and antibodies. Furthermore, the preparation of several bis-palladium species (e.g. **4**, Figure 2b) facilitated peptide macrocyclization through the dual modification of two Cys side-chains (**5**) [10]. Notably, a variety of second generation arylpalladium complexes with distinct ligands have emerged as suitable catalysts for arylation and peptide stapling at Lys residues (**6**) [11•] as well as water-soluble organometallic reagents to facilitate Cys arylation in purely aqueous media [12].

Figure 1



Transition-metal-mediated approaches to peptide modification. Representative transition-metals are highlighted, with dotted lines indicative of metals employed in photoinduced electron transfer (PET) processes.

Extending the scope of protein substrates amenable to targeted arylation, Davis and coworkers reported the use of in situ generated arylpalladium species for the site-selective arylation of a single Cys in mannosyl glycerate synthase (MGS), despite the presence of multiple potentially reactive Cys residues [13•]. The authors cleverly exploit an endogenous metal-binding motif (Asp100-Ala101-Asp102) embedded within the protein to guide the reactive metal complex to a single Cys residue, thereby precisely incorporating a variety of functionalities, including substituted aromatics, bioorthogonal handles, and glycans.

A mechanistically distinct, dual nickel/ruthenium photoredox-catalyzed Cys arylation protocol with aryl bromides was reported by Molander and coworkers in 2018 [14]. The authors utilize an ammonium *bis*(catechol) silicate hydrogen-atom transfer (HAT) reagent, which readily undergoes single electron transfer (SET) to form an alkyl radical in the presence of ruthenium photocatalyst **3** and blue light (Figure 2a). Rapid hydrogen abstraction from the thiol S–H affords a peptide thiyl radical which is relayed into the nickel-catalyzed cross-coupling cycle, ultimately affording a Cys-arylated peptide. Although less tolerant to diverse functional groups and aqueous media than the organopalladium approaches, the scalability and exceptionally low catalyst loadings (5 mol% Ni, 2 mol% Ru) render this a promising mode of Cys modification. The appeal of a radical mechanism which proceeds orthogonally to two-electron processes has also prompted the exploration of alternative, metal-free approaches to Cys arylation [15].

In a rare display of selective backbone amide modification, Ball and coworkers reported a copper-catalyzed, histidine-directed arylation of backbone N–H bonds using aryl and alkenyl boronic acids in 2016 [16•]. Copper binding to internal His residues promotes site-selective backbone arylation at the neighboring *i*-1 position (see **7** to **8**, Figure 2c). Incorporation of diverse N-aryl and N-alkenyl units into peptide substrates, as well as the selective arylation of lysozyme (bearing a single His residue) were readily accomplished. Notably, the copper-mediated oxidative coupling of boronic acids to oxidized selenocysteine residues under mild, aqueous conditions has also been demonstrated — a testament to the suitability of copper-catalyzed arylation manifolds for the diverse modification of peptides [17].

Given the demonstrated versatility of heteroatom couplings, it is envisaged that such techniques will continue to emerge as valuable strategies for peptide modification. Careful tuning of the ligated-metal complex to achieve the desired reactivity without sacrificing selectivity is an important on-going challenge; nevertheless, efforts toward this goal may also deliver new functional group-selective coupling methods, targeting alternative proteinogenic handles (e.g. side-chain alcohols or amides) and building on promising new strategies for the incorporation of diverse appendages (e.g. alkynes [18]).