

Palladium Catalysis | *Reviews Showcase* Late-Stage Diversification of Tryptophan-Derived BiomoleculesHendrik Gruß and Norbert Sewald*^[a]

Abstract: Pd-mediated reactions have emerged as a powerful tool for the site-selective and bioorthogonal late-stage diversification of amino acids, peptides and related compounds. Indole moieties of tryptophan derivatives are susceptible to C²H-activation, whereas halogenated aromatic amino acids such as halophenylalanines or halotryptophans provide a broad spectrum of different functionalisations. The compatibility of transition-metal-catalysed cross-couplings with functional groups in peptides, other biologically active compounds and even proteins has been demonstrated. This

Review primarily compiles the application of different cross-coupling reactions to modify halotryptophans, halotryptophan containing peptides or halogenated, biologically active compounds derived from tryptophan. Modern approaches use regio- and stereoselective biocatalytic strategies to generate halotryptophans and derivatives on a preparative scale. The combination of bio- and chemocatalysis in cascade reactions is given by the biocompatibility and bioorthogonality of Pd-mediated reactions.

1. Introduction

Late-stage diversifications of biomolecules such as amino acids, peptides or pharmaceutically active compounds comprise powerful tools for the generation of functionalised derivatives with modified properties or biological effects. In particular, improvement of the biological efficacy leads to optimised active substances or drugs showing, for instance, enhanced selectivity or stability. Compared to early-stage modifications, late-stage approaches have several benefits. Firstly, the preparation of a compound library is simplified because one precursor molecule can result in several modified derivatives. Selective reactions make the use of protecting groups in many cases obsolete; hence, reaction as well as work-up and purification steps are saved leading to more efficient and sustainable processes. In addition, late-stage reactions have a great potential for the application as bioorthogonal modification tools for biological macromolecules even in lysates or the presence of living cells. However, these obvious advantages imply several challenges to be overcome. As there are many functional groups present in biomolecules, side reactions might occur or some functional groups may be incompatible with

the reaction conditions and for example, might inhibit the reaction. Application in bioorthogonal chemistry is even more challenging. Additionally, biomolecules often contain stereogenic centres, which is why late-stage diversification reactions need to be performed under mild conditions to avoid epimerisation.


Pd-mediated reactions have been proven useful for the selective modification of biomolecules, which underscores the versatility of this transition metal.^[1–6] The indole moiety of tryptophan constitutes an interesting target to be addressed by such approaches. Tryptophan plays a unique role in peptides and proteins. Considering the low abundance in proteins, it represents at the same time the most abundant amino acid in protein–protein interactions.^[7] Moreover, the spectrophotometric properties of tryptophan render it an interesting probe to study protein dynamics.^[8] Hence, modulation of the spectrophotometric properties of tryptophan is of great interest. Apart from that, tryptophan scaffolds are widely present in bioactive natural products featuring both halogenated and non-halogenated indoles.^[9] Modification of those indoles may lead to novel pharmaceutically active compounds. This minireview deals with late-stage diversification of indoles and indole-based biomolecules beginning with a brief overview on Pd-mediated C²–H activation strategies. Complementary to C²–H activation, the regioselective, enzymatic synthesis of different halotryptophans at various positions at the indole ring provides a handle for diversification. Accordingly, the main focus will be on addressing haloindoles describing and discussing different Pd-mediated cross-coupling strategies.


2. Pd-Catalysed C²–H Activation of Tryptophans


The C² position of indoles and tryptophans can be selectively addressed by transition-metal-catalysed C(sp²)–H activa-

[a] H. Gruß, Prof. Dr. N. Sewald

Organische und Bioorganische Chemie, Fakultät für Chemie
Universität Bielefeld, Universitätsstraße 25, 33615 Bielefeld (Germany)
E-mail: norbert.sewald@uni-bielefeld.de

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