https://doi.org/10.17952/37EPS.2024.P2013

Faculty of Chemistry - Organic and Bioorganic Chemistry - OCIII

UNIVERSITÄT BIELEFELD

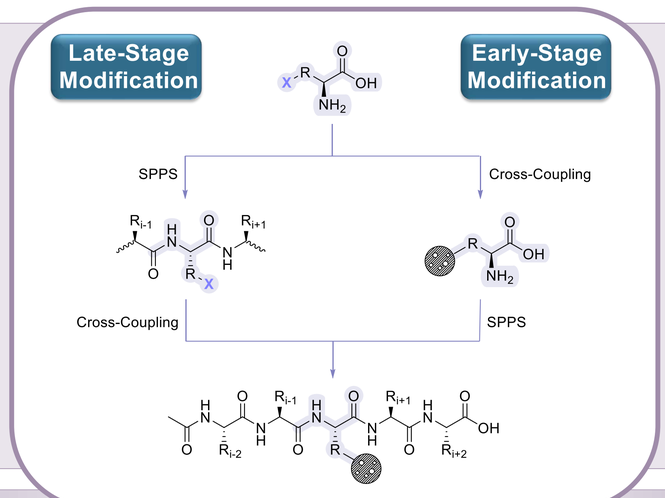
New Opportunities for Side-Chain Functionalization of Halogenated Amino Acids

Laura Cerveson and Norbert Sewald

Organic and Bioorganic Chemistry, Faculty of Chemistry, Bielefeld University, Germany.

laura.cerveson@uni-bielefeld.de

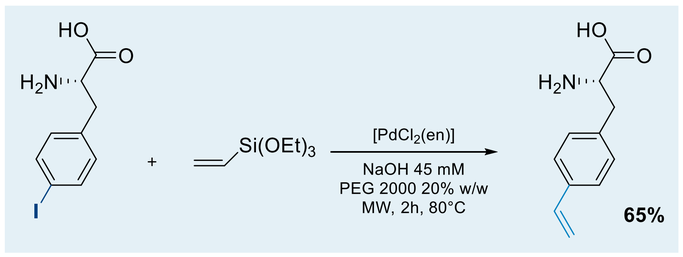
- Chemical modifications of amino acids and peptides embody a vast and significant field of biochemical research because they permit to obtain arrays of functionalised derivatives with modified properties or biological effects.
- One particularly attractive method for diversification is provided by **transition-metal catalysed cross-coupling** reactions. However, the functionalisation of amino acids and peptides is considered **challenging** and not all cross-couplings are suitable.[1]

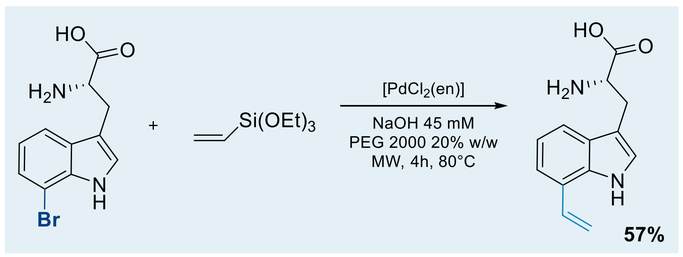


- **Phenylalanine** and **tryptophan** are considered interesting substrates to be used for chemical modification. They show, indeed, noteworthy fluorescence properties and take part in important biological processes. In particular, tryptophan participates in the determination of protein folding and protein-protein interactions.[2]
- Here in we present cross-coupling reactions that can be used for both **early-** and **late-stage modification** of peptides containing **halogenated amino acids** such as 6-bromo-tryptphane and 4-iodo-phenylalanine.

Vinylation of Halogenated Trp and Phe

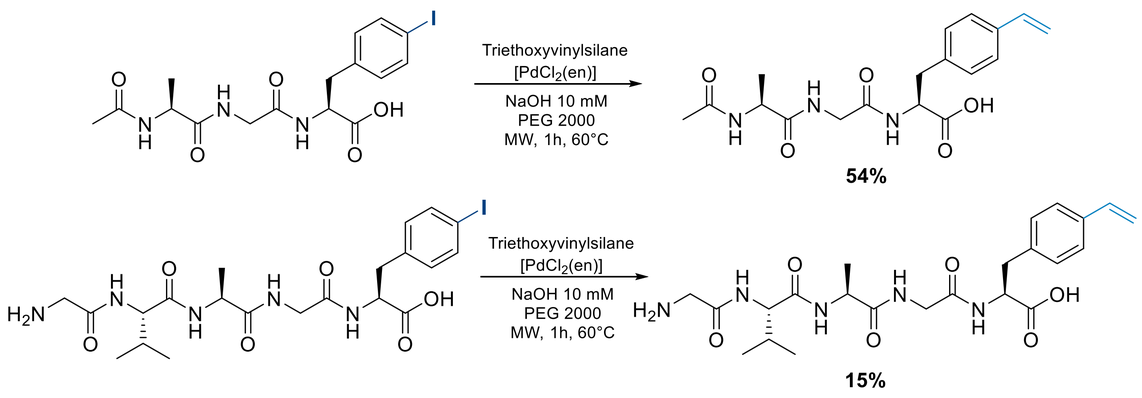
- Halogenated amino acids can be cross-coupled with triethoxyvinylsilane in water to give the corresponding **vinylated** product.[3]
- One advantage of this kind of reaction is that **no protecting groups** are needed since it proved to be compatible with functional groups such as amines and carboxylic acids.
- Even if strong basic conditions are required for the course of the reaction, no perceptible racemization occurred. However, this represents a problem when moving to peptides as it leads to epimerization.





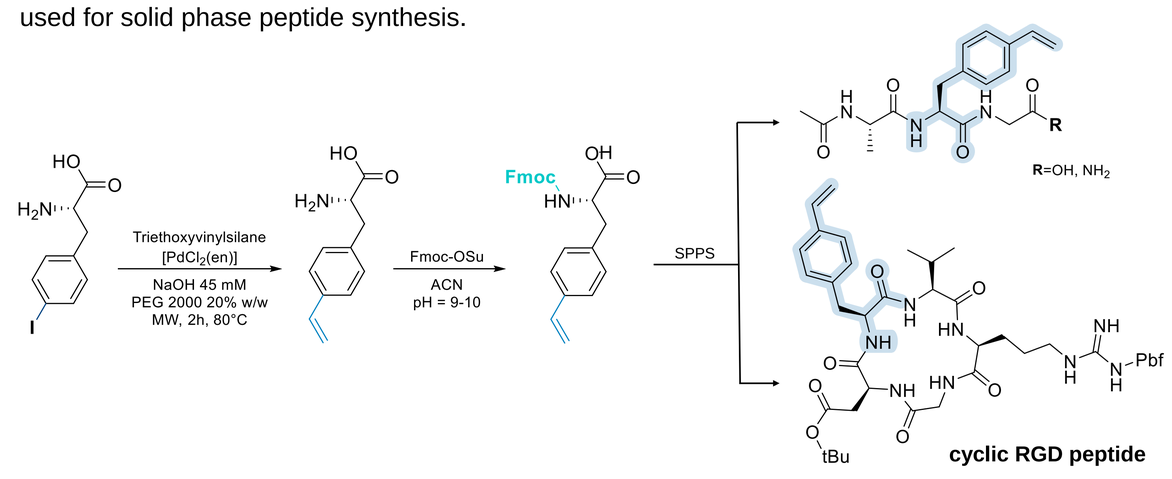
Late-Stage Modification of Peptides

- Late-stage vinylation of iodophenylalanine containing peptides is possible at certain conditions: the reaction must be conducted in diluted conditions but keeping the same equivalents of NaOH and the halogenated amino acid must occupy the **last position** in the peptide sequence.



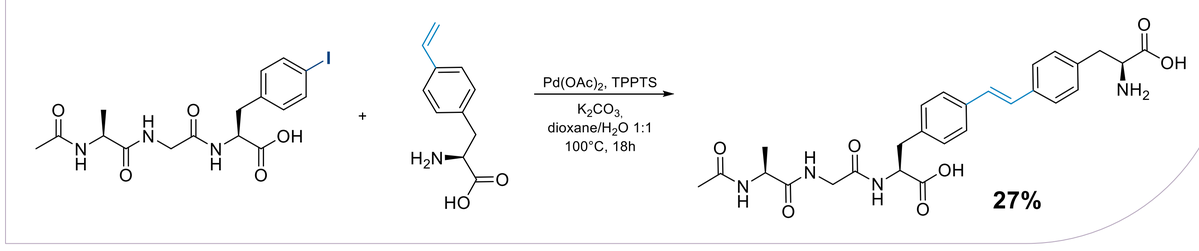
Early-Stage Modification of Peptides

- 4-vinyl-phenylalanine can be directly Fmoc-protected, **without purification** from prior reaction, and used for solid phase peptide synthesis.



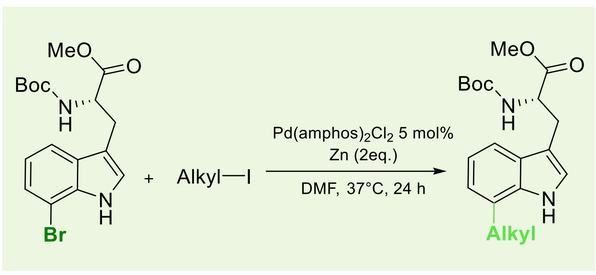
Further Modifications

- Vinylated amino acids or peptides can undergo further reactions, such as **Heck cross-coupling**.[4]



Negishi Cross-Coupling: Alkylation of Trp

- In a previous work, Negishi cross-coupling was used for diversification of protected 7-bromo-tryptophan enabling its **selective alkylation**.[5]
- The reaction is carried out using mild conditions without preformation of the metal organyls.



- Different types of alkyl iodides were employed for a **substrate screening**.

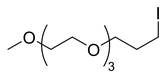
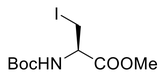
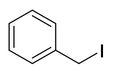
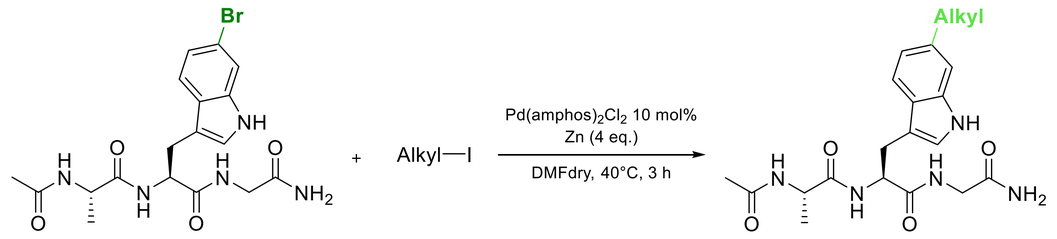
Entry	Alkyl iodide	T [°C]	Yield [%]	Entry	Alkyl iodide	*T* [°C]	Yield [%]
1		20	26	**4**		20	0
		37	83			37	0
2		20	21	**5**		20	n.d.[a]
		37	52			37	73
3		20	37	**6**		20	0
		37	81			37	0

Table 1 – Substrate screening at 20°C and 37°C. [a] not detected due to low conversion

Late-Stage Modification of Tripeptides

- For the late-stage functionalization of 6-bromo-tryptophan containing peptides some **modifications** from the previous procedure were necessary to obtain acceptable yields.



- Different alkyl iodides and pentapeptides are currently being tested in order to prove the validity of this reaction for late-stage alkylation of bromotryptophan containing peptides.

Entry	Alkyl iodide	Yield [%]
1		44
2		45

Conclusion

- We reported here **two strategies** for the early- and late-stage functionalization of halogenated amino acids containing peptides.
- The first one permits to selectively vinylate 6-bromotryptophan and 4-iodophenylalanine and works for both early- and late-stage.
- Vinylated compounds can be used for further modifications, such as Heck cross-coupling. A development of the latter would be its application for the synthesis of **cyclic peptides**.
- Negishi cross-coupling between bromotryptophan and different alkyl iodides provides alkylated derivatives and it's being tested for late-stage modification.

References

1. Gruß, H.; Sewald, *N. Chem. Eur. J.* **2020**, 26, 5328-5340.
2. Rose, G.,D.; Geselowitz, A., R.; Lesser, G., J.; Lee, R., H.; Zehfus, M., H. *Science* **1985**, 229, 834-838.
3. Gordillo, A.; Ortuno, M., A.; Lòpez-Mardomingo, C.; Lledòs, A.; Ujaque, G.; de Jesùs, E. *J. Am. Chem. Soc.* **2013**.
4. Gruß, H.; Belu, C.; Bernhard, L., M.; Merschel, A.; Sewald, *N. Chem. Eur. J.* **2019**, 25, 5880-5883.
5. Dachwitz, S.; Scharkowski, B.; Sewald, N. *Chem. Eur. J.* **2021**, 27, 18043.