LATE-STAGE FUNCTIONALIZATION OF PEPTIDES AND CYCLOPEPTIDES USING ORGANOZINC REAGENTS

M. Leroux, T. Vorherr, I. Lewis, M. Schaefer, G. Koch, K. Karaghiosoff and P. Knochel

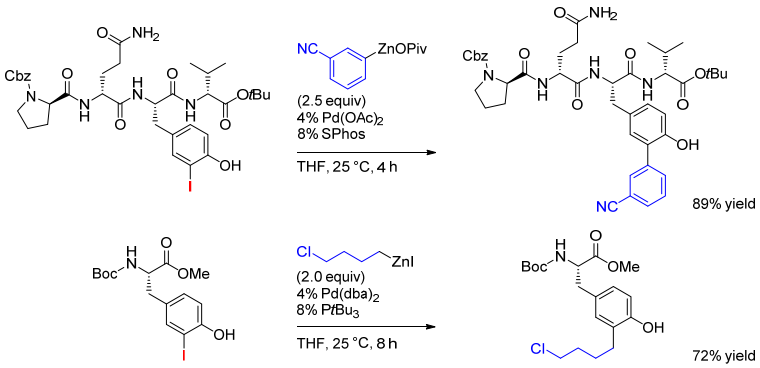
Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 Munich

Late-stage functionalization of peptides and cyclopeptides is an important method to adjust biophysical properties during the drug discovery process. By attaching various moieties e.g. aryl or heteroaryl groups to the peptide side chain, biophysical relevant properties can be altered and further optimized. C-H activations or Suzuki-Miyaura cross-coupling reactions have already been described for the late-stage modification of peptides.

We present a new palladium-catalyzed cross-coupling protocol, using readily available iodotyrosine or iodophenylalanine containing peptides with aryl- and heteroarylzinc pivalates. Various functionalized aryl and heteroaryl groups have been attached to the peptide backbone. This method has been extended to alkylzinc reagents allowing the synthesis of alkylated peptides. Furthermore, bioactive cyclopeptides can be modified by introducing different pyridyl-residues on the side chain. Physico-chemical measurements of solubility and membrane permeability of the modified cyclopeptides and comparison with molecular dynamics calculations haven been performed. They show that the solubility of cyclopeptides can be increased by introduction of pyridyl moiety whereby a high cell-membrane permeability was retained.

Therefore, tyrosine containing peptides can easily be converted into iodotyrosine derivatives:

Following Negishi cross-coupling reactions provide a range of modified peptides in good yields:



Additionally, cyclic hexamer peptides containing a iodophenylalanine side-chain have been treated with pyridylzinc pivalates to obtain modified cyclopeptides.