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Faculty of Chemistry - Organic and Bioorganic Chemistry - OCIII

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C-Glycosylation of Aromatic Amino Acids by Pd-Catalyzed Cross-Coupling

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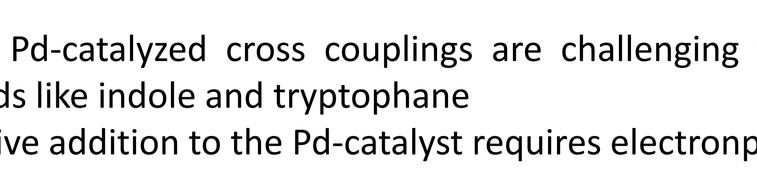
Glycopeptides and their features

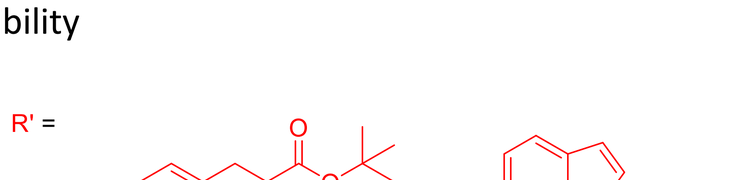
- Glycoproteins play important roles in many biological processes, among them cell adhesion, cell differentiation or regulation of cell growth[1,2]
- Glycosylation in proteins modifies conformation, hydrophilicity and stability of peptides[3]
- Especially in peptide based drugs the introduction of glycosyl residues may lead to a higher membrane permeability (e.g. BBB)[4]
- *C*-Glycosides bear a higher stability towards hydrolysis in comparison to *N*- and *O*-Glycosides[5]
- Pd-catalyzed cross-coupling reactions offer a high potential to generate *C*-Glycosides[6, 7]
- Orthogonal protecting groups are used to imply their use as building blocks in peptide-based chemistry as SPPS

Generation of Boronates

- Generation of glycal boronic acids takes place through deprotonation by ^{t}BuLi followed by transmetallation with $B(OMe)_3$ and hydrolysation
- Boronic acids should be used short after its synthesis



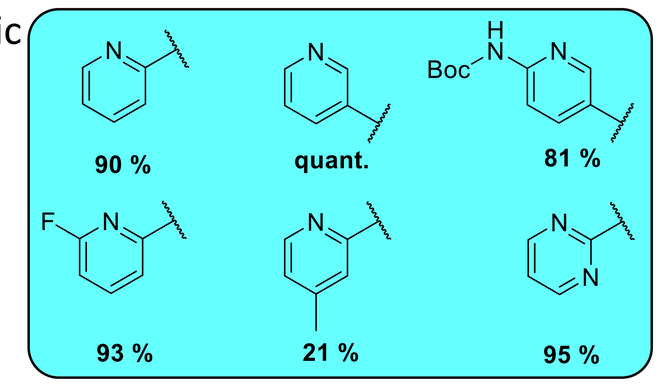
- Boronic acid esters can also be implemented in Suzuki cross coupling reactions
- Advantage of them being less prone to hydrolysis while storage

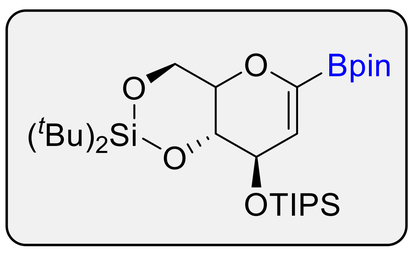


Heteroaromatic glucal library

Library of **16** new heteroaromatic glucals in very good yields

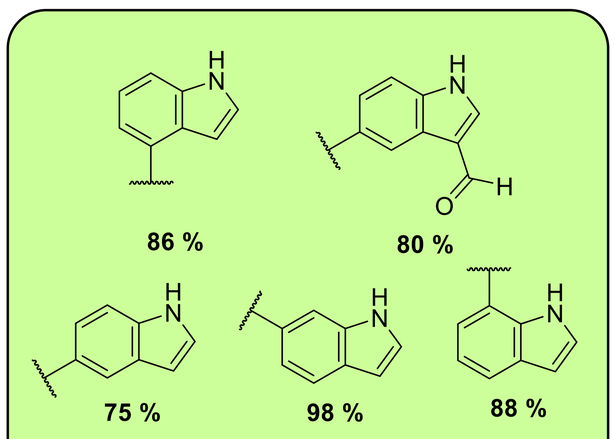
(Un)substituted and aminofunctionalised pyridines and pyrimidines were employed



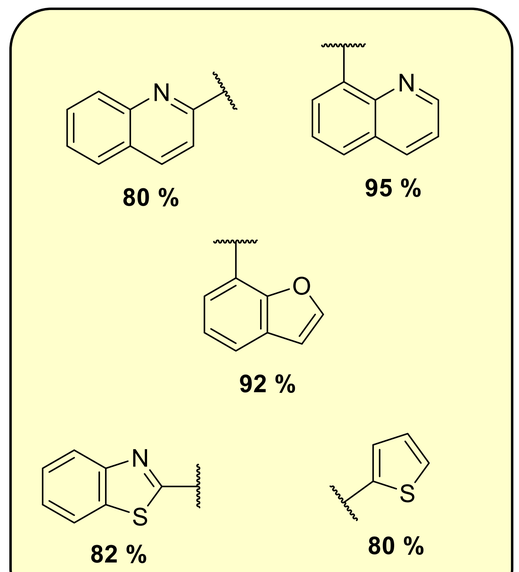


\+ HetAr-**Br**

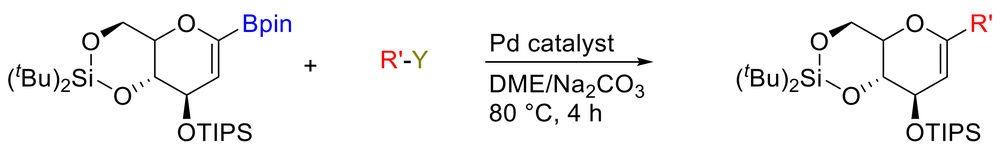
4-, 5-, 6- and 7-bromoindoles and 3-carbaldehyde-5-bromoindole have been implemented



Chinolines, benzofuranes, benzothiazoles and thiophenes were cross coupled

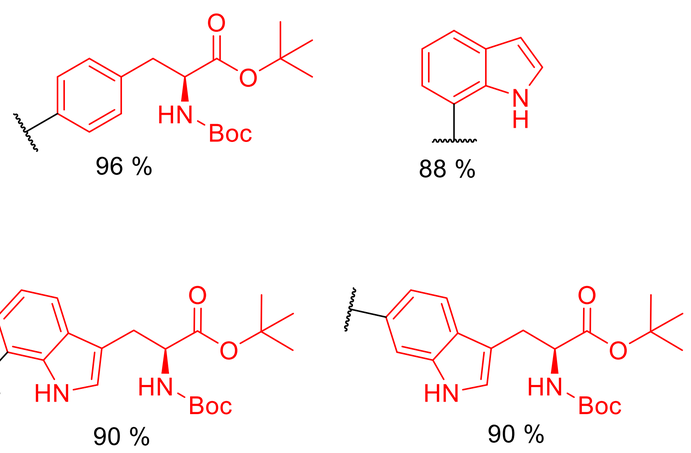


SUZUKI cross coupling

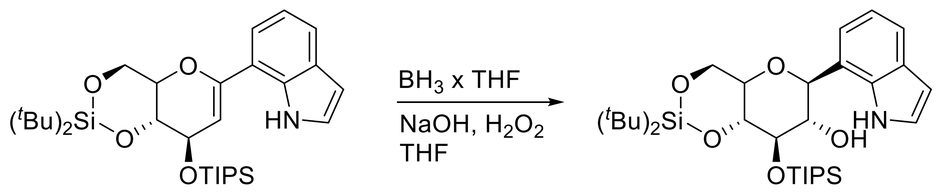


- SUZUKI cross-coupling has been established for D-Glucal
- Generally Pd-catalyzed cross couplings are challenging for electronrich compounds like indole and tryptophane
  - Oxidative addition to the Pd-catalyst requires electronpoor aryl halides
- Enhancement of reaction conditions to obtain good yields and to ensure reproducibility

R' =

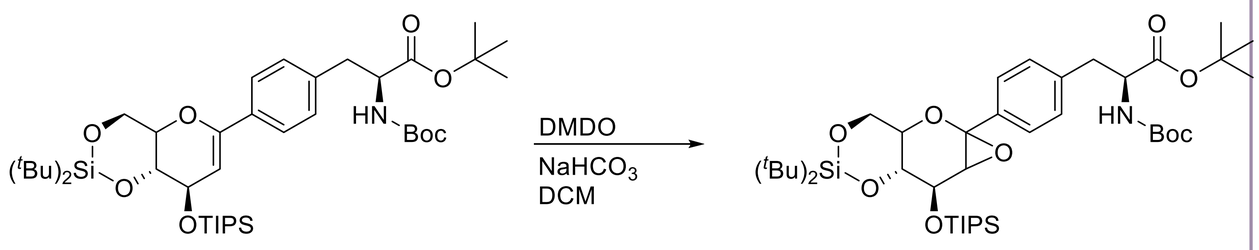


Glucal oxidation



Hydroboration-Oxidation

- Anti-Markownikow addition of borane to alkene → **syn-addition**
- Stereoselective reaction to yield **β-anomer**



Epoxidation

- Epoxidation followed by reduction of oxirane
- Stereoselective reaction is supposed to yield **α-anomer**
- not suitable for indoles

References

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