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PHOTOCHEMISTRY AND FLOW TECHNOLOGIES FOR EARLY PHASE DRUG DISCOVERY

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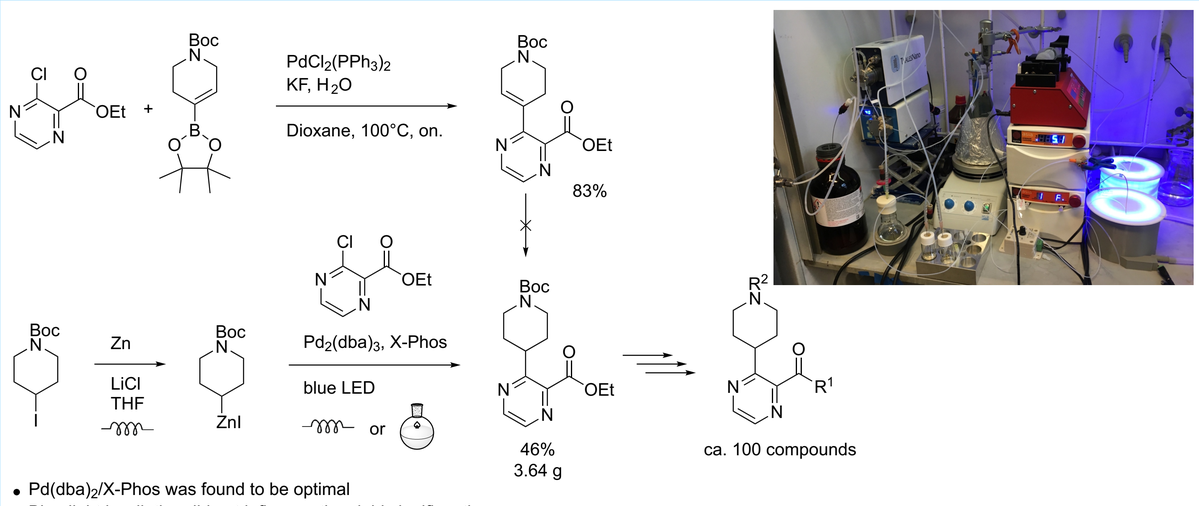
Introduction

Construction of $C(sp^2)$-$C(sp^3)$ bonds is relatively difficult in comparison to $C(sp^2)$-$C(sp^2)$ bonds. Recently, photoredox catalytic and other photochemical methodologies, together with technological achievements expanded the scope of $C(sp^2)$-$C(sp^3)$ bond constructions.[1]
Herein, we show how photochemical and general flow methodologies were employed in the synthesis of novel compounds (screening libraries and DEL building blocks) with high fsp3 content. Furthermore, we demonstrate the application of the Minisci reaction in the preparation of biologically active compounds. In the same project *in situ* generated diazomethane was used for the preparation of amino acid derivatives.

Negishi-Coupling

Alcázar *et al.* developed a continuous flow procedure for the synthesis of organozinc reagents, which were then employed in the Negishi reaction.[2] The same group showed that the efficiency of nickel- and palladium-catalyzed Negishi reactions can be enhanced by irradiation with blue light.[3] Below, we show an example where a Suzuki-coupling-hydrogenation sequence failed to give the desired product using classical methods, while the product was successfully isolated in 46% yield after a two-step one flow Negishi-coupling procedure.

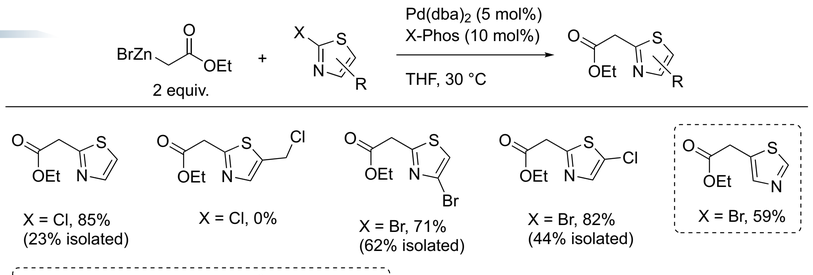


- $Pd(dba)_2$/X-Phos was found to be optimal
- Blue light irradiation did not influence the yield significantly
- 25 min residence time in flow
- 9 h flow process gave 3.64 g product after purification
- Batch and flow yields are similar, but flow is more practical for scale-up

Thiazoles and Pyrazoles

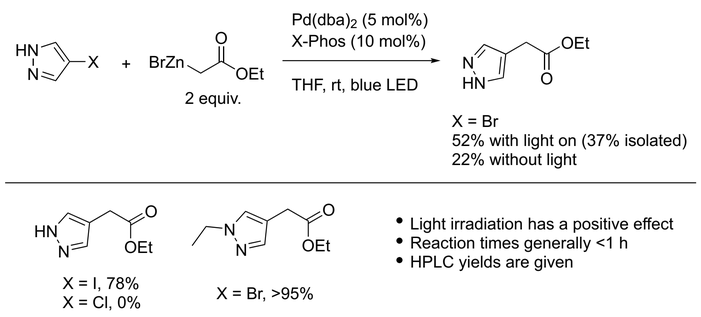
Thiazoles and pyrazoles are among the most frequently utilized ring systems in small molecule drugs.[4] Nevertheless, these structures have been scarcely utilized in Negishi-couplings. We have started a systematic investigation in this area to access building blocks for DNA-encoded libraries. The obtained α-heteroaryl acetates provide opportunity for derivatization both on the heteroaryl ring or at the acetate motif.

Thiazoles



- Organozinc reagents were prepared in flow
- Negishi couplings were performed in batch
- Catalyst: $Pd(dba)_2$/X-Phos or $Pd(dppf)Cl_2$
- Blue light irradiation did not influence the reaction
- Reactions times generally <1 h
- HPLC yields are given

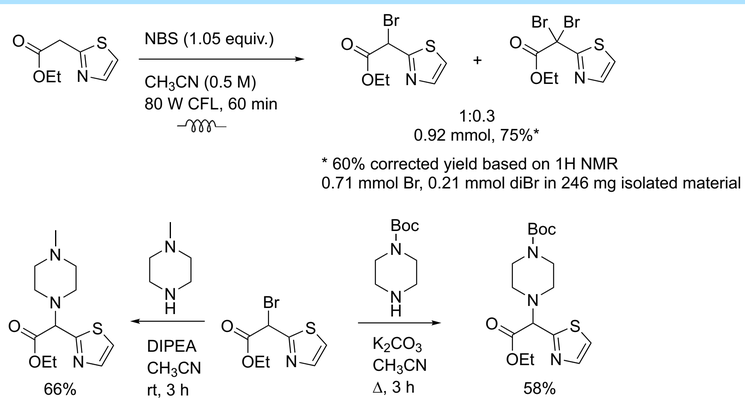
Pyrazoles – where light matters



- Light irradiation has a positive effect
- Reaction times generally <1 h
- HPLC yields are given

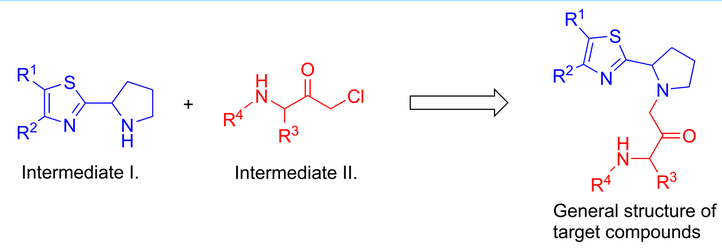
Towards Amino Acid Analogues

A flow photochemical benzylic bromination was described by Kappe *et al*[5] The method is good yielding, scalable and the reaction proceeds in CH_3CN without the need for radical initiators. We surmised that similar treatment of α-heteroaryl acetates would provide α-bromo-α-heteroaryl acetates, and those would lead us to the synthesis of novel unnatural amino acids.



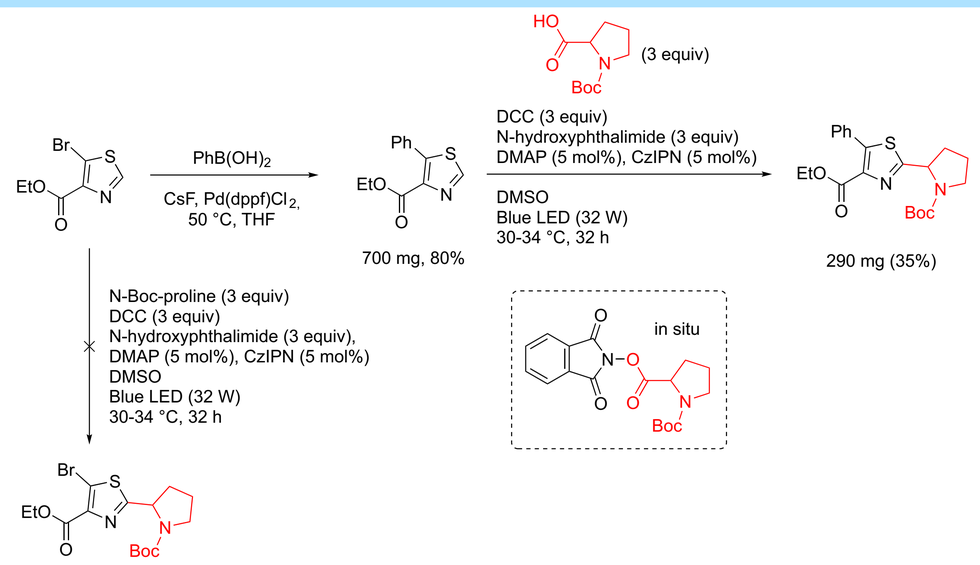
Synthesis of Biologically Active Compounds

One of our medicinal chemistry project focuses on the synthesis of biologically active compounds to target the treatment of high mortality tumor diseases. As depicted on the scheme our synthetic strategy relied on two key intermediates which were prepared through photoredox Minisci reaction and by homologation of amino acids, respectively.



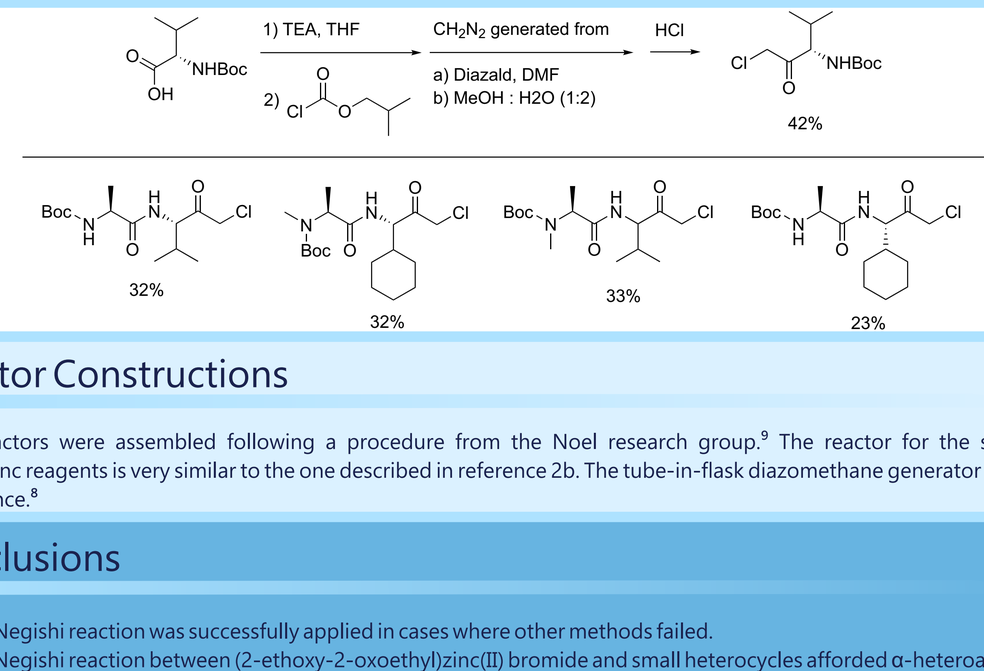
Minisci Reaction - Key Intermediate I.

The Minisci reaction allows the introduction of an alkyl group into nitrogen heterocycles without the need for prefunctionalization.[6] Traditional procedures require harsh reaction conditions and often provide low yields, however, photoredox Minisci reactions can be performed under mild conditions with good selectivity and improved yields.[7]



The Synthesis of α-halo Ketones - Key Intermediate II.

Diazomethane is an explosive and toxic gas, and at the same time a useful methylating agent. The Kappe group described a tube-in-flask reactor in which safe handling of anhydrous diazomethane was realized, and a method for the synthesis of α-halo ketones was developed.[8] We adapted Kappe's procedure for the synthesis of dipeptides derived α-halo ketones.



Reactor Constructions

Photoreactors were assembled following a procedure from the Noel research group.[9] The reactor for the synthesis of organozinc reagents is very similar to the one described in reference 2b. The tube-in-flask diazomethane generator is described in reference.[8]

Conclusions

- The Negishi reaction was successfully applied in cases where other methods failed.
- The Negishi reaction between (2-ethoxy-2-oxoethyl)zinc(II) bromide and small heterocycles afforded α-heteroaryl acetates. These compounds provide an easy entry to further derivatization.
- Key intermediates of novel biologically active compounds were accessed through photoredox Minisci reaction and through homologation of dipeptides with diazomethane.

Acknowledgement

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