CONTINUOUS FLOW PHOTOCATALYTIC MINISCI REACTION USING *N*-(ACYLOXY)PHTHALIMIDE ESTERS

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Introduction

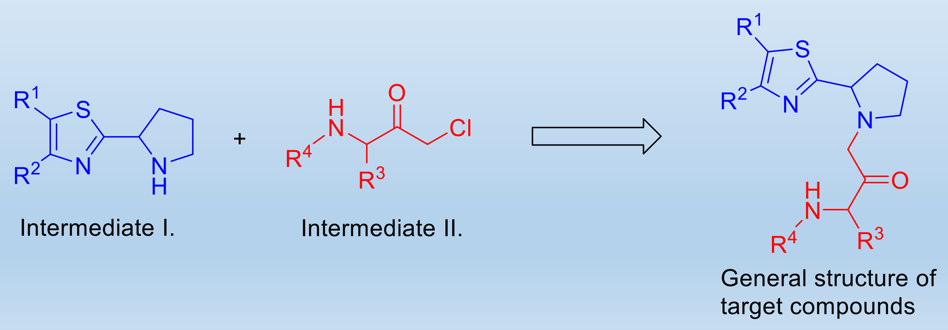
ComInnex is a discovery chemistry CRO. Our core services include the synthesis of proprietary screening libraries and the preparation of building blocks for DNA-encoded libraries. In order to expand our compound portfolio we are continously working on implementing novel methodologies.

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 the photocatalytic Minisci reaction was employed in the synthesis of biologically active compounds to target the treatment of high mortality tumor diseases. Furthermore, we describe our efforts towards the development of a continuous flow Minisci procedure. A novel, multiwavelength batch and flow photoreactor, the PhotoCube™ Pro - codeveloped by ComInnex and ThalesNano - was applied during some of these studies.

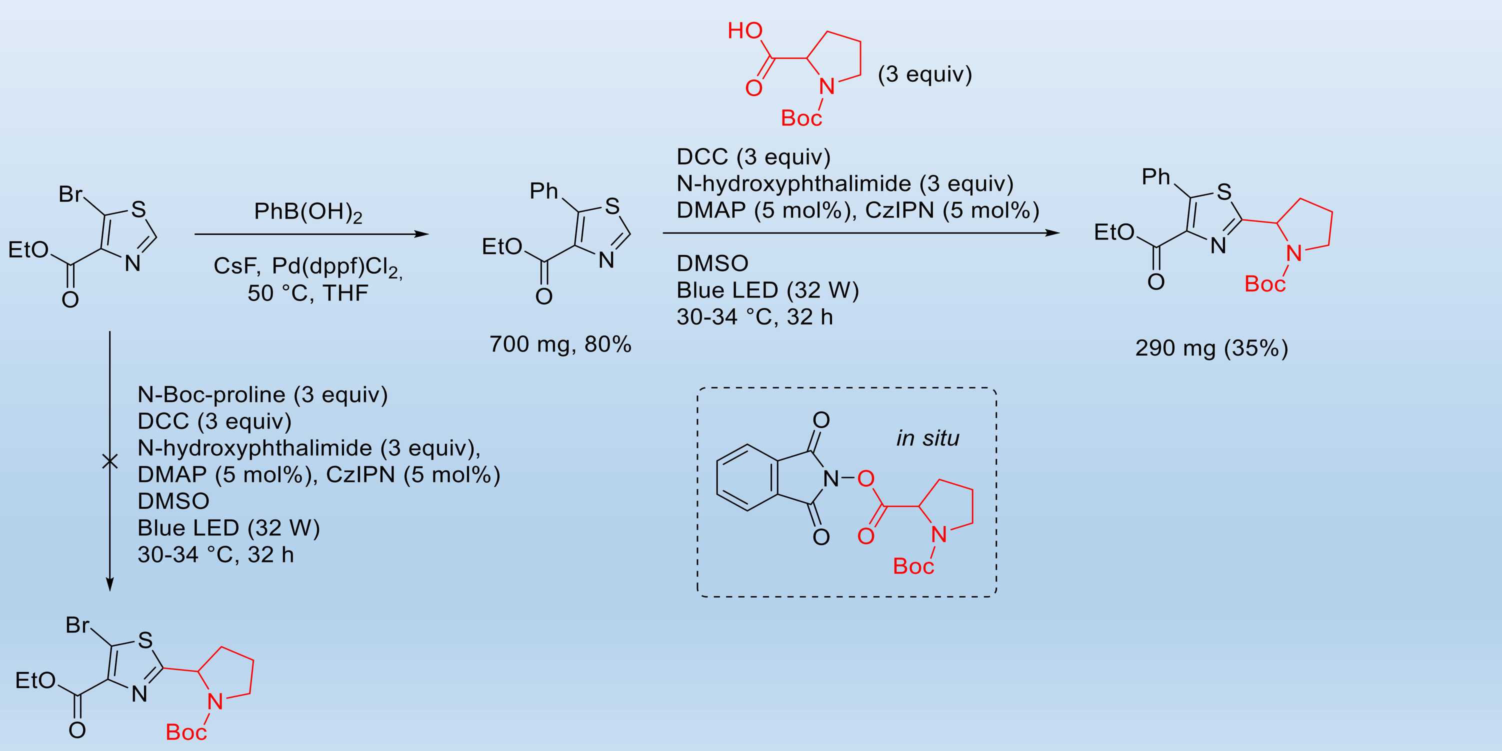
Photo- and flow chemistry in the synthesis of potentially active new compounds to target the treatment of high mortality tumor diseases[2]

Synthetic strategy



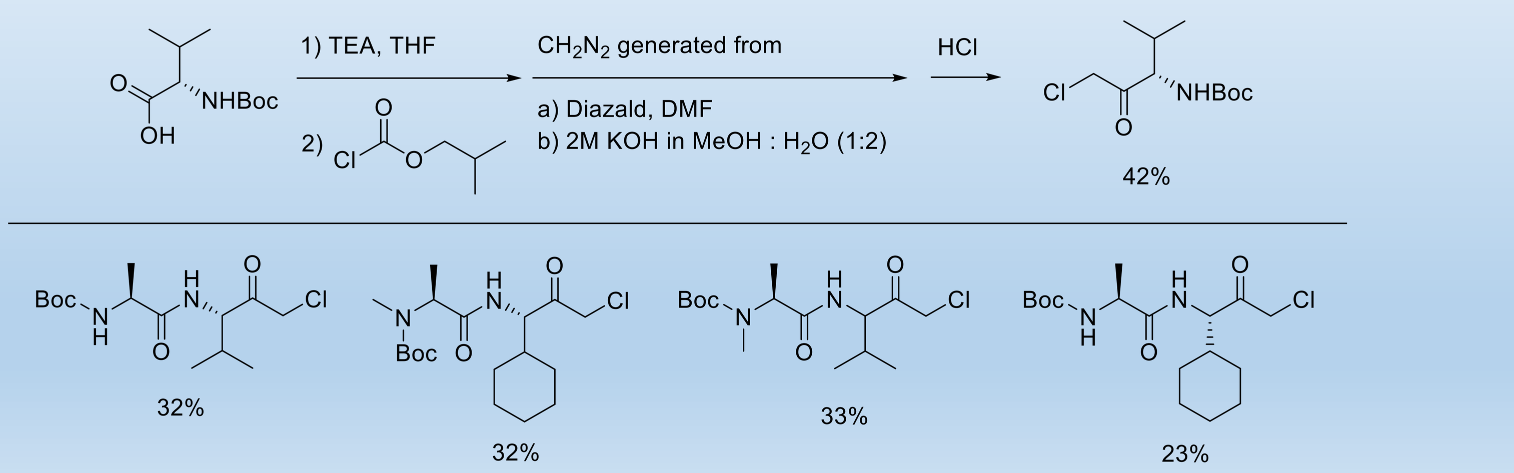
Minisci reaction - key intermediate I.

The Minisci reaction allows the introduction of an alkyl group into nitrogen heterocycles without the need for prefunctionalization.[3] 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.[4]



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.[5] We adapted Kappe's procedure for the synthesis of dipeptides derived α-halo ketones.

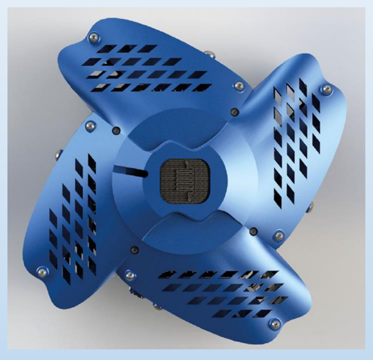


Instrumentation

Photocatalytic experiments were carried out in photoreactors either developed in-house or in instruments assembled following a procedure from the Noel research group.[6] The tube-in-flask diazomethane generator is described in reference 5. NAP intermediate formation was carried out in a ThalesNano's Phoenix Flow Reactor™ equipped with a 4 or 16 mL stainless steal loop. Pumping of the solutions was either done using Syrris Asia or an Aladdin2000 syringe pumps.

PhotoCube™ Pro prototype

ThalesNano's PhotoCube™ Pro is a multifunctional batch and flow photoreactor with 8 simoultaneously available wavelength was develepod in-house.

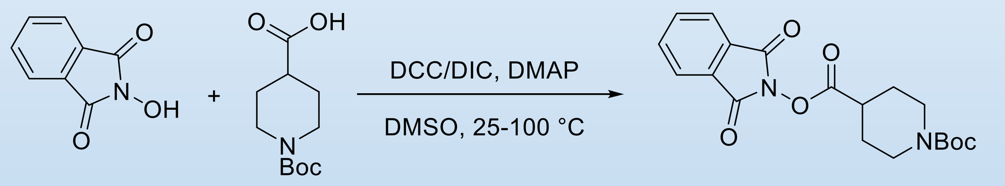


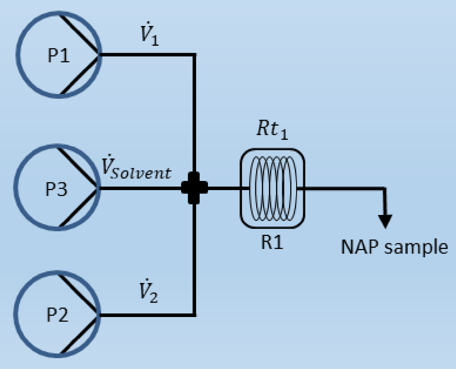
Technical specification
Available wavelengths: 365, 395, 457, 500, 523, 595, 623 nm and white
Available batch reactor volumes: 4 mL and 20 mL glass vials
Available FEP or PFA loop volumes: 2-19 mL
Temperature range: 20 to 60 °C
Maximum LED input power/wavelength: 128 W (365 nm), 84 W (457 nm)
Maximum LED input power: 300 W

Development of a continuous flow photocatalytic Minisci reaction

Why go flow? The batch procedure is oftentimes low yielding and time consuming (27-48 hours).

N-(Acyloxy)phthalimide ester (NAP) intermediate formation in flow

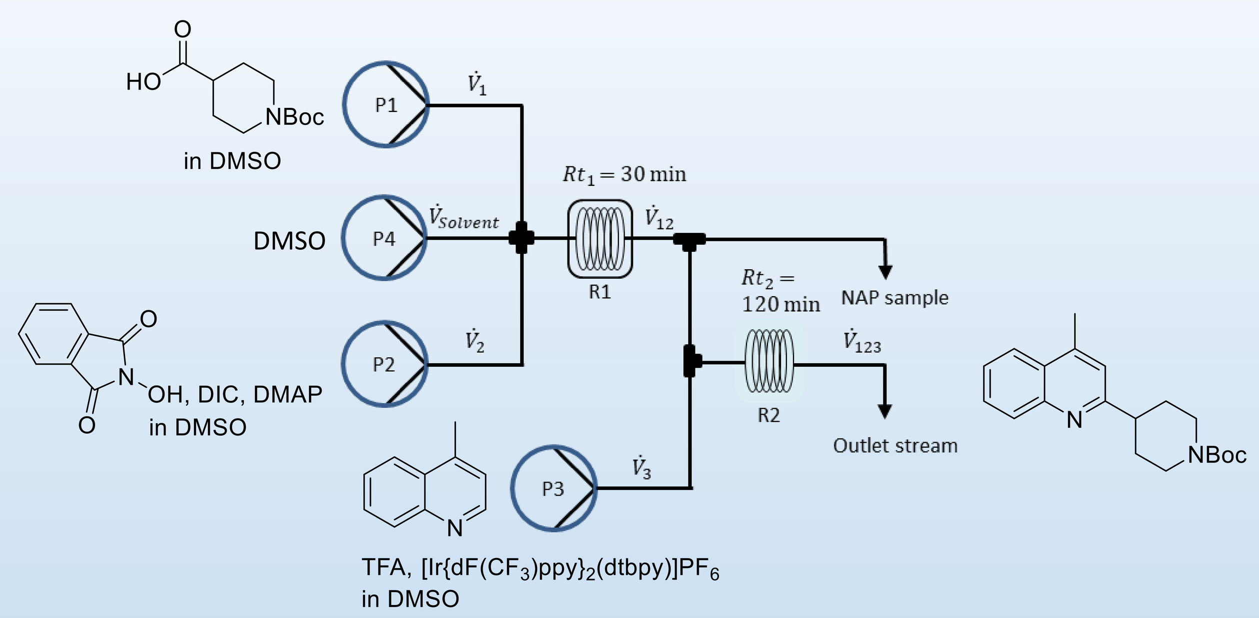




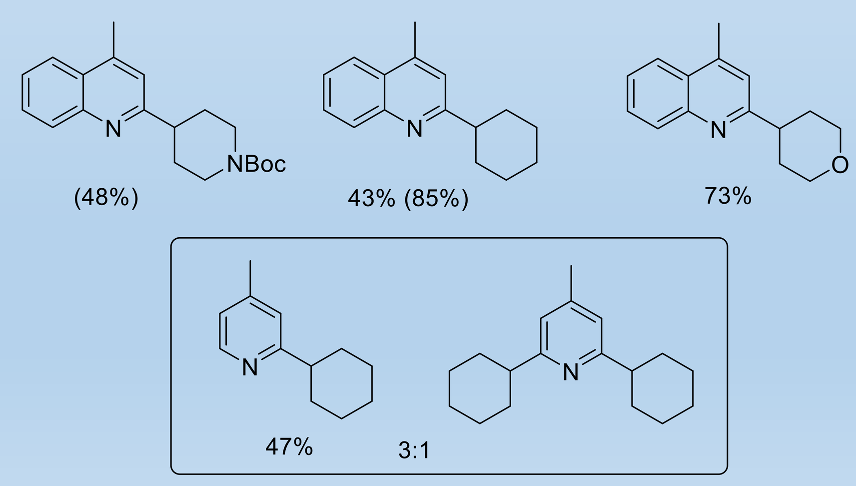
P1	P2	T /°C	t / min	HPLC yield / %
Phth-NOH, RCOOH, DMAP	DIC	25	10	53
Phth-NOH, RCOOH, DMAP	DIC	55	10	59
Phth-NOH, RCOOH, DMAP	DIC	80	10	63
Phth-NOH, RCOOH, DMAP	DIC	100	12	-
RCOOH	**Phth-NOH, DMAP, DIC**	**80**	**30**	**92**
RCOOH, DMAP,DIC	Phth-NOH	80	30	90

All reactions were carried out in DMSO. Phth-NOH = N-hydroxyphthalimide, RCOOH = N-boc-isonipecotic acid, DMAP = 4-(dimethylamino)pyridine, DIC = 1,3-diisopropylcarbodiimide;

Telescoping the NAP intermediate formation and the Minisci reaction



Preliminary flow results



Left: The PhotoCube™ Pro Prototype (indicated as R2 on the flow graph above) in operation during a Minisci reaction. Right: The switch box of the PhotoCube ™ Pro.

Conclusions

- Key intermediates of novel biologically active compounds were accessed through a photoccatalytic Minisci reaction and through homologation of dipeptides with diazomethane.
- NAP intermediate formation was adapted into flow and coupled with a photocatalytic Minisci reaction step using simple photoreactors and ThalesNano's novel PhotoCube™ Pro instrument.
- The not yet optimized telescoping of the NAP-Minisci sequence shows promising results. Notably, in case of the model substrates the overall process time was decreased from 27 hours to 4 hours, however the yields yet to be increased.

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AZ NKFI ALAPBÓL MEGVALÓSULÓ PROJEKT

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