Green, scalable and automated photochemistry in flow

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Summary

The research presented in this thesis focuses on how to utilize continuous-flow technology to empower photochemistry, achieving a green, scalable, and automated photochemical platform.

The work described in this dissertation can be divided into three main research lines. Firstly, heterogeneous photochemical reactions in flow were discussed. Considering the inherent sustainability of heterogeneous photocatalysis and the multiple merits of flow chemistry technology, two examples of performing heterogeneous photocatalysis in flow were presented.

In **Chapter 2**, a robust and efficient ultrasound-intensified milli-reactor with a reactor volume of 12.88 mL was presented. The reactor is composed of five parts: a Langevin-type transducer, a sonotrode, an irradiating cylinder, a coiled glass capillary, and an LED illuminating box. A COMSOL simulation was performed to confirm that the standing waves were formed in both the longitudinal direction inside the sonotrode and the radial direction inside the cylinder, efficiently directing the ultrasound energy to the glass capillary. The efficiency of the ultrasonic reactor was showcased in the TiO_2-catalytic aerobic oxidation of 4-(trifluoromethyl)benzyl alcohol. Ultrasonic irradiation generates cavitation bubbles and causes a vigorous oscillation of both cavitation bubbles and the Taylor bubbles, which improves the liquid mixing, the gas-liquid mass transfer, and ensures resuspension of the settled particles in 2 s. Ultrasound enabled recirculation of the suspended TiO_2 nanoparticles and break-up of the agglomerates. These effects enhance the photon absorption by the semiconductor catalyst, improving the reaction conversion with a factor of 3.6 (from 24 % to 87 %).

In **Chapter 3**, a practical protocol for the photocatalytic C–H azolation of

arenes using heterogeneous mesoporous carbon nitride (mpg-CN_x) was described. Both early- and late-stage functionalization of aryl C(sp^2)–H bonds were amenable to obtaining corresponding products. Due to the heterogeneous nature and high photocatalytic stability of mpg-CN_x, the catalyst was recycled several times without a noticeable reduction in photocatalytic activity. Furthermore, a packed bed reactor was developed to carry out the scale-up experiment, largely enhancing the reaction rate and also avoiding the need for catalyst recovery/recycling strategies.

In the second part of the thesis, a parallel research line focused on the scale-up of photocatalysis. Since the scale-up of photocatalysis in batch is hampered by the non-uniform light irradiation, a combination of high-intensity light source and continuous-flow technology should enable the high productivity required for the scale-up of pharmaceuticals and agrochemicals.

In **Chapter 4**, a continuous oscillatory milli-structured photoreactor was utilized to perform the optimization of decatungstate-catalyzed photocatalytic C(sp^3)–H alkylation. The conversion, yield, and productivity of the reaction were investigated by changing various reaction parameters, including residence time, light intensity, reactant concentrations, and catalyst loading. Productivity of 36.7 mmol/h was reached with optimized conditions and full conversion was obtained within 7.5 min residence time, which illustrated the efficiency of the HANU reactor and its potential use for the scale-up of photochemistry.

Carbon-Nitrogen bonds are ubiquitous in natural products, pharmaceuticals, and materials, prompting the synthetic community to develop new amination methodologies. In **Chapter 5**, aiming to develop a fast and scalable C(sp^3)–H amination protocol, a new continuous-flow photoreactor equipped with a 144 W optical power light source was

constructed in collaboration with Signify. Using this powerful photoreactor, an efficient and scalable decatungstate-catalyzed C(sp^3)–H amination protocol was described, which can convert both activated and nonactivated C(sp^3)–H bonds. Telescoped processes for the synthesis of (protected) hydrazines, pyrazoles, phthalazinones, and amines were carried out to further illustrate the modularity of this protocol. Requiring only a minimal re-optimization of the reaction conditions, this single photoreactor is capable to provide the quantities needed on both the laboratory (i.e., ~2 mmol) and process scale (>2 kg/day). The results presented herein can inspire others to combine synthetic methodology development and chemical engineering principles to obtain a rapid transition from initial discoveries to applications on a process scale.

Previous chapters have shown the potential of the homogeneous photocatalyst tetrabutylammonium decatungstate (TBADT) for the functionalization of C(sp^3)–H bonds. However, to translate these studies into large-scale industrial processes, careful considerations of catalyst consumption, cost, and removal are required. An inline TBADT recovery as the answer to the concerns around the scale-up of decatungstate-catalyzed photocatalytic HAT reactions was presented in **Chapter 6**, which offers a solution to minimize the catalyst consumption and cost. A suitable organic solvent nanofiltration (OSN) membrane was identified, the experimental setup was designed, and the operating conditions were optimized to achieve suitable catalyst and product recovery. Continuous photocatalytic C(sp^3)–H alkylation reactions were carried out with in-line TBADT recovery via two OSN steps. Notably, the product yields of the reactions performed with in-line catalyst recycling are comparable to those of reactions carried out with pristine TBADT, therefore highlighting that not only catalyst recovery (>99%, TON >6500) is technically feasible, but it also does not compromise reaction performance.

Finally, in the third part of the thesis, research focused on expanding the

potential of continuous-flow photochemistry with automation and was presented in **Chapter 7**. Automated processes can reduce time and expensive labor, enable to accelerate chemical discovery, and can increase reaction accuracy and reproducibility. In this chapter, a user-friendly and algorithm-driven automated continuous-flow photochemical platform was established. A real-time updated graphical user interface (GUI) was created with the open-source python module, Streamlit, to obviate the usage of proprietary software and to lower the barrier of the automated system to chemists. The reaction conditions, including continuous (e.g., residence time) and discrete variables (e.g., base), were optimized by a Bayesian Optimization (BO) algorithm, which employs a Gaussian process surrogate model to mathematically fit the black-box functions. The experimental conditions proposed by the BO algorithm were performed on an automated continuous-flow platform equipped with a liquid handler, a powerful photoreactor, and an inline NMR, which enables analyzing the results and getting the feedback in time to obtain closed-loop experimentation. The first proof of concept result was obtained using photocatalytic hydrogen-atom transfer as a benchmark to validate the practicality of the algorithm-driven automated platform for photochemistry.

In conclusion, the synergistic combination of continuous-flow technology and photochemistry resulted in the development of green, scalable, and automated processes. Nowadays, chemists both from academic and fine chemical companies have embraced those technologies in their procedures. Despite this interest, further efforts to lower the barriers of the automated system towards the non-experts are still necessary. For example, promoting the usage of open-source programming tools, automating more standardized devices, and building a user-friendly GUI might increase the popularity of automation and boost chemistry discovery.

Samenvatting

Het onderzoek dat in dit proefschrift werd gepresenteerd richt zich op het gebruik van continue-stromingstechnologie om fotochemie mogelijk te maken, en om zo een groen, schaalbaar en geautomatiseerd fotochemisch systeem te realiseren.

Het werk beschreven in dit proefschrift kan worden onderverdeeld in drie hoofdonderzoekslijnen. Ten eerste werden heterogene fotochemische reacties in flow besproken. Rekening houdend met de inherente duurzaamheid van heterogene fotokatalyse en de meerdere verdiensten van flow chemie technologie, werden twee voorbeelden gepresenteerd van het uitvoeren van heterogene fotokatalyse in stroom.

In **Hoofdstuk 2** werd een robuuste en efficiënte ultrageluid-geïntensiveerde millireactor met een reactorvolume van 12.88 ml gepresenteerd. Deze reactor bestaat uit vijf delen: een Langevin-type transducer, een sonotrode, een bestralingscilinder, een opgerold glazen capillair en een LED-verlichtingsbak. Er werd een COMSOL-simulatie uitgevoerd om te bevestigen dat de staande golven werden gevormd in zowel de longitudinale richting binnen de sonotrode als de radiale richting binnen de cilinder, waardoor de ultrasone energie efficiënt naar het glazen capillair kon worden geleid. De efficiëntie van de ultrasone reactor werd gedemonstreerd met de TiO_2-katalytische aerobe oxidatie van 4-(trifluormethyl)benzylalcohol. Ultrasone bestraling genereert cavitatiebellen en veroorzaakt een krachtige oscillatie van zowel cavitatiebellen als Taylor-bellen, wat zowel de vloeistofmenging als de gas-vloeistofmassaoverdracht verbetert en zorgt voor resuspensie van de bezonken deeltjes in 2 s. Echografie maakte recirculatie van de gesuspendeerde TiO_2-nanodeeltjes en het uiteenvallen van de agglomeraten mogelijk. Deze effecten verhoogden de fotonenabsorptie

van de halfgeleiderkatalysator, waardoor de reactieconversie met een factor 3,6 verbetert (van 24% naar 87%).

In **Hoofdstuk 3** werd een praktisch protocol voor de fotokatalytische C-H azolering van arenen met behulp van heterogeen mesoporeus koolstofnitride (mpg-CN_x) beschreven. Zowel vroeg- als laat-stadium functionalisering van aryl C(sp^2)-H bindingen was toepasbaar voor het verkrijgen van de overeenkomstige producten. Vanwege het heterogene karakter en de hoge fotokatalytische stabiliteit van mpg-CN_x, werd de katalysator meerdere keren gerecycled zonder een merkbare vermindering van de fotokatalytische activiteit. Verder werd een gepakt bedreactor ontwikkeld om het opschalingsexperiment uit te voeren, waardoor de reactiesnelheid grotendeels werd verhoogd en ook de noodzaak van strategieën voor het terugwinnen/recyclen van katalysatoren werd vermeden.

In het tweede deel van het proefschrift werd een parallelle onderzoekslijn gepresenteerd, gericht op de opschaling van fotokatalyse. Aangezien de opschaling van traditionele fotokatalyse in het batchsysteem werd belemmerd door de niet-uniforme lichtinstraling, moet een combinatie van een lichtbron met hoge intensiteit en continue-flowtechnologie de hoge productiviteit creëren die nodig is voor de opschaling in de farmacie.

In **Hoofdstuk 4** werd een continue oscillerende milligestructureerde fotoreactor gebruikt om de optimalisatie van decatungstate-gekatalyseerde fotokatalytische C(sp^3)-H alkylering uit te voeren. De omzetting, opbrengst en productiviteit van de reactie werden onderzocht door verschillende reactieparameters te veranderen, waaronder verblijftijd, lichtintensiteit, reactantconcentraties en katalysatordosering. Ender geoptimaliseerde omstandigheden werd een productiviteit van 36.7 mmol/u bereikt en volledige conversie werd

verkregen binnen 7.5 min verblijftijd, wat de efficiëntie van de HANU-reactor en het potentiële gebruik ervan voor de opschaling van fotochemie illustreerde.

Koolstof-stikstofbindingen zijn aanwezig in natuurlijke en farmaceutische stoffen en materialen, wat de synthetische gemeenschap ertoe aanzet nieuwe amineringsmethodologieën te ontwikkelen. In **Hoofdstuk 5**, met als doel een snel en schaalbaar C(sp^3)–H-amineringsprotocol te ontwikkelen, werd een nieuwe continue-flowfotoreactor ontwikkeld, uitgerust met een 144 W optische lichtbron. Met behulp van deze krachtige fotoreactor werd een efficiënt en schaalbaar decatungstate-gekatalyseerd C(sp^3)-H-amineringsprotocol beschreven, dat zowel geactiveerde als niet-geactiveerde C(sp^3)-H-bindingen kan omzetten. Telescopische processen voor de synthese van (beschermde) hydrazinen, pyrazolen, ftalazinonen en aminen werden uitgevoerd om de modulariteit van dit protocol verder te illustreren. Deze enkele fotoreactor vereist slechts een minimale heroptimalisatie van de reactieomstandigheden en is in staat om de hoeveelheden te leveren van zowel laboratoriumschaal (d.w.z. ~2 mmol) als processchaal (>2 kg/dag). De hierin gepresenteerde resultaten kunnen anderen inspireren om de ontwikkeling van synthetische methodologie en chemische technologieprincipes te combineren om zo een snelle overgang van initiële ontdekkingen naar toepassingen op processchaal te verkrijgen.

Eerdere hoofdstukken hebben het potentieel van de homogene fotokatalysator tetrabutylammoniumdecatungstate (TBADT) voor de functionalisering van C(sp^3)–H-bindingen aangetoond. Om deze studies echter te vertalen naar grootschalige industriële processen, is een zorgvuldige afweging van het katalysatorverbruik, de kosten en de verwijdering vereist. In **Hoofdstuk 6** werd dan ook, als antwoord op de

zorgen rond de opschaling van decatungstate-gekatalyseerde fotokatalytische HAT-reacties, een in-line TBADT-terugwinning gepresenteerd. Dit zal niet alleen een oplossing bieden voor het katalysatorverbruik, maar ook voor de minimalisatie van de kosten. Een geschikt organisch oplosmiddel nanofiltratie (OSN) membraan werd geïdentificeerd, de experimentele opstelling werd ontworpen en de gebruiksomstandigheden werden geoptimaliseerd om een geschikte katalysator en productterugwinning te bereiken. Continue fotokatalytische C(sp^3)-H-alkyleringsreacties werden uitgevoerd met in-line TBADT-terugwinning via twee OSN-stappen. De productopbrengsten van de reacties die worden uitgevoerd met in-line katalysatorrecycling zijn vergelijkbaar met die van reacties uitgevoerd met ongerepte TBADT, wat erop wijst dat niet alleen katalysatorterugwinning (>99%, TON>6500) technisch haalbaar is, maar ook de reactieprestaties niet in gevaar brengt.

Ten slotte, in het derde deel van het proefschrift, werd in **Hoofdstuk 7** onderzoek gepresenteerd dat gericht was op het uitbreiden van het potentieel van continue-flowfotochemie met automatisering. Geautomatiseerde processen kunnen tijd en dure arbeid verminderen, chemische ontdekking versnellen en de nauwkeurigheid en reproduceerbaarheid vergroten. In dit hoofdstuk werd een gebruiksvriendelijk en algoritme-gestuurd geautomatiseerd continue-flow fotochemisch platform opgezet. Een realtime bijgewerkte grafische gebruikersinterface (GUI) is ontworpen met de open-source python-module, Streamlit, om het gebruik van zelf-ontwikkelde software te voorkomen en om de drempel van het geautomatiseerde systeem voor chemici te verlagen. De reactieomstandigheden, waaronder continue (bijv. verblijftijd) en discrete variabelen (bijv. base), werden geoptimaliseerd door een Bayesiaans optimalisatie (BO) -algoritme, dat gebruikmaakt van een Gaussiaans proces-surrogaatmodel om wiskundig

de functies van de black-box te passen. De experimentele omstandigheden die door het BO-algoritme worden voorgesteld werden uitgevoerd op een geautomatiseerd continue-flowplatform uitgerust met een vloeistofhandelaar, een krachtige fotoreactor en een in-line NMR, waarmee de resultaten kunnen worden geanalyseerd en de feedback op tijd kan worden verkregen om zo experimenten in gesloten lus te verkrijgen. Er werden verschillende fotokatalytische waterstofatoom overdrachtsreacties uitgevoerd om de bruikbaarheid van het algoritme gestuurde geautomatiseerde platform voor fotochemie te valideren.

Concluderend heeft de positieve combinatie van continue-flowtechnologie en fotochemie geleid tot de ontwikkeling van groene, schaalbare en geautomatiseerde processen. Tegenwoordig hebben scheikundigen van zowel academische als fijnchemische bedrijven deze technologieën omarmd in hun procedures. Ondanks deze belangstelling zijn verdere inspanningen nodig om de drempels van het geautomatiseerde systeem richting de niet-experts te verlagen. Het promoten van het gebruik van open-source programmeertools, het automatiseren van meer gestandaardiseerde apparaten en het bouwen van een gebruiksvriendelijke GUI kan bijvoorbeeld de populariteit van automatisering vergroten en de ontdekking van chemie stimuleren.

List of publications

Peer-reviewed articles:

1. T. Wan,[+] **Z. Wen**,[+] G. Laudadio, L. Capaldo, R. Lammers, J. A. Rincón, P. G. Losada, C. Mateos, M. O. Frederick, R. Broersmad and T. Noël*. Accelerated and Scalable C(sp^3)-H Amination via Decatungstate Photocatalysis using a Flow Photoreactor equipped with High-Intensity LEDs. *ACS Central Science*. **2022**, *8*, 1, 51–56. ([+]These authors contributed equally.)

2. **Z. Wen**, T. Wan, A. Vijeta, C. Casadevall, L. Buglioni, E. Reisner* and T. Noël*. Photocatalytic C–H Azolation of Arenes using Heterogeneous Carbon Nitride. *ChemSusChem*. **2021**, *14* (23), 5265-5270.

   (Highlighted by OPR&D and Chemistry Europe)

3. Z. Dong, S. D. A. Zondag, M. Schmid, **Z. Wen**, T. Noël*. A meso-scale ultrasonic milli-reactor enables gas-liquid-solid photocatalytic reactions in flow. *Chemical Engineering Journal*. **2022**, *428*, 130968.

4. Z. Dong, **Z. Wen**, F. Zhao, S. Kuhn, T. Noël*. Scale-up of micro- and milli-reactors: An overview of strategies, design principles and applications. *Chemical Engineering Science: X*. **2021**, *10*, 100097.

5. **Z. Wen**, A. Maheshwari, C. Sambiagio, Y. Deng, G. Laudadio, K. V. Aken, Y. Sun, H. P. L. Gemoets, T. Noël*. Optimization of a decatungstate-catalyzed C(sp^3)-H alkylation using a continuous oscillatory milli-structured photoreactor. *Organic Process Research & Development.* **2020**, *24*(10), 2356–2361. (Highlighted by *Synfacts*)

Submitted/In Preparation:

6. **Z. Wen**,[+] D. Pintossi,[+] T. Noël*. Membrane-based TBADT recovery: a step towards more sustainable HAT photochemistry. *ChemRxiv.* **2022**, DOI: 10.26434/chemrxiv-2022-fdxzn. ([+]These authors contributed equally.)

7. **Z. Wen**,[+] A. Slattery,[+] P. Tenblad,[+] D. Pintossi, J. Sanjosé-Orduna, T. Noël*. Bayesian-optimization-driven automated platform for continuous-flow photochemistry. Manuscript in preparation. ([+]These authors contributed equally.)

Out of the thesis:

8. **Z. Wen**, M. Yang, C. Yao, S. Zhao, F. Zhou, G. W. Chen*. Kinetics study of heterogeneously continuous-flow nitration of trifluoromethoxybenzene. *Reaction Chemistry & Engineering*. **2018**, *3*, 379-387.

9. **Z. Wen**, F. Jiao, M. Yang, S. Zhao, F. Zhou, G. Chen*. Process development and scale-up of continuous flow nitration of trifluoromethoxybenzene. *Organic Process Research & Development*. **2017**, *21*(11), 1843-1850.

10. S. Zhao, Z. Dong, C. Yao, **Z. Wen**, G. Chen*, Q. Yuan. Liquid-liquid two-phase flow in ultrasonic microreactors: cavitation, emulsification and mass transfer enhancement. *AIChE Journal*. **2018**, *64*(4): 1412-1423.

11. F. Zhou, B. Zhang, H. Liu, **Z. Wen**, K. Wang, G. Chen*. Facile preparation of N-alkyl-2-pyrrolidones in a continuous-flow microreactor. *Organic Process Research & Development*. **2018**, *22*(4), 504-511.

12. F. Zhou, H. Liu, **Z. Wen**, B. Zhang, K. Wang, G. Chen*. Toward the efficient synthesis of pseudoionone from citral in a continuous-flow microreactor. *Industrial & Engineering Chemistry Research*. **2018**, *57*(33), 11288-11298

Conference presentations

Oral

1. **Z. Wen** and T. Noël. Decatungstate-mediated HAT photochemistry and in-line catalyst recovery in flow. *The Netherlands' Catalysis and Chemistry Conference* (*NCCC*), 9th – 11th May 2022, Noordwijkerhout, The Netherlands.

Poster

1. **Z. Wen** and T. Noël. Green and Scalable photochemistry in flow. *First Annual HIMS symposium*, 15th June 2022, Amsterdam, The Netherlands.
2. **Z. Wen** and T. Noël. Photocatalytic C– H Azolation of Arenes Using Heterogeneous Carbon Nitride in Batch and Flow. *#RSCPoster* 2022 (Virtual Conference), 1st March 2022.
3. **Z. Wen,** T. Wan, and T. Noël. Photocatalytic azolation with mpg-CN_x and scale-up in flow. *CHemistry as INnovative Science (CHAINS),* 7th -8th December 2021. (Online conference)

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Regards,

Zhenghui

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About the author

Zhenghui Wen（温正慧）was born in Wenzhou (China) on July 15th, 1993. In 2010, he started his Bachelor of Science studies in Chemical Engineering at Huazhong University of Science and Technology (Wuhan, China), which he completed with honors in 2014. He received his master's degree in chemical engineering from the University of Chinese Academy of Sciences (Beijing, China) and Dalian Institute of Chemical Physics (Dalian, China), under the supervision of Prof. Guangwen Chen. His thesis focused on the kinetic study and scale-up of nitration of trifluoromethoxybenzene in a microreactor. After graduating in November 2017, he worked as a research assistant in the Microchemical Engineering & Technology Group at the Dalian Institute of Chemical Physics.

In September 2018, he moved to the Netherlands and started his PhD project in the Micro Flow Chemistry and Synthetic Methodology at the Eindhoven University of Technology (Netherlands), under the supervision of Prof. Timothy Noël. In 2020, he moved to the University of Amsterdam and joined the Flow chemistry group with Prof. Timothy Noël. His PhD research focuses on green, scalable, and automated photochemistry in continuous flow. The results of the studies are presented in this dissertation.

After completing his PhD in 2022, he plans to stay at Prof. Noel's group as a post-doc, where he will keep working on extending the potential of continuous microflow technology in photochemistry.