

PHOTOINDUCED DECARBOXYLATIVE BORYLATION: SCALING VISIBLE LIGHT PHOTOCHEMISTRY



FELIX A. KORTMANN, PETER HERMSEN, ANDRÉ H. M. DE VRIES
InnoSyn B.V., Geleen, The Netherlands

ABSTRACT

Visible light-induced decarboxylative borylation was successfully implemented and scaled-up as key step in a novel route towards vaborbactam. The transformation was carried out in a falling-film photoreactor on a 10 g-scale. Under mild conditions (420 nm blue LEDs, RT, 4 h) the N-hydroxyphthalimide redox active ester was converted to the corresponding pinacolato boronates in 78% isolated yield. Other borylation methodologies, both photochemical as well as organometallic, showed inferior results in comparison experiments.

KEYWORDS: Photochemistry, Borylation, Decarboxylation, Visible light, scale-up, Peer reviewed.

INTRODUCTION

Photochemistry comprises the chemical reactions of atoms or molecules that have been electronically excited by light of an the appropriate wavelength, which can be absorbed by the substrate. Thus, an overlap in wavelengths between the emitted light and those absorbed by the substrate is required. Alternatively, a sensitizer or photocatalyst can be used to absorb radiation and transfer its energy to the substrate (1).

According to the Lambert-Beer law, the intensity of the light decreases logarithmically with the path length traveled through the medium. For practical reasons, most photochemical reactions are done in solution. In industrial photochemistry, high substrate concentrations are preferred. However, for substrates with an assumed molar extinction coefficient of 350, already at a mere 0.5 mol/l concentration of substrate, the incoming light is absorbed within a 0.1 mm thick zone (see Figure 1, left, grey curve). The photo reaction takes place exclusively in this zone and as consequence, most of the reaction medium in traditional immersion type photo reactors (Pfortner reactor, see Figure 1, right) remains "in the dark"/unreacted. Also, at high photon flux, the mass transfer of substrate into this zone and products out of this zone, becomes limiting. Inadequate mass transfer can result in poor selectivity and fouling of the light source due to over-irradiation.

down the inner wall of the cylinder while being irradiated, and the wavy laminar character of the liquid film, ensures sufficient mass transfer to allow for a high photon flux (see Figure 2). The thickness of the liquid film remains the same, irrespective of the dimensions of the reactor. This makes scaling of a falling film reactor, for example in comparison with a photo-flow reactor relatively easy. The reactor geometry is closely related to that of the light source, facilitating an even distribution of the photon flux. Changing the light source is straightforward thanks to its free-hanging mounting. The photon flux can be adjusted by tuning the radiant power of the source to the diameter of the reactor.

LED-TECHNOLOGY

As stated above, the emission spectrum of the light source and the absorption spectrum of the substrate need to overlap, at best 100%. Radiation, that cannot be absorbed by the substrate can cause side-reactions. Thus, ideally a light source is used which emits monochromatic radiation matching the absorption capabilities of the substrate. Traditionally, broadband mercury lamps have been used in combination with filters to eliminate unwanted wavelengths, however this can result in very low efficiencies, with up to only 1-5% of the energy-input being transformed into productive photons.

LEDs lamps, on the other hand, have a narrow emission spectrum of 10-20 nm bandwidth (see Figure 3), hence the LED radiation will in most cases be fully absorbed by the substrate, sensitizer or photocatalyst. Next to this, LEDs provides multiple technical advantages, e.g. higher energy efficiency, thus less heat emission and smaller and flexible housing. With their low voltage and long lifetime, LEDs are expected to be the light sources of the future.

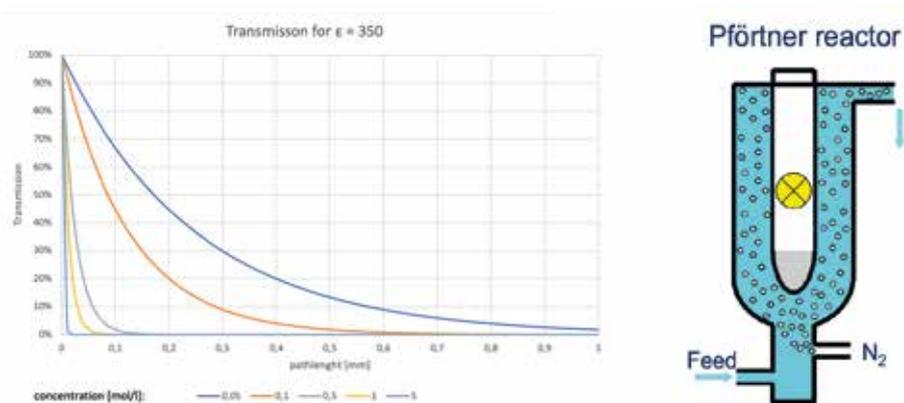


Figure 1. Penetration depth of light at different concentrations (left); Schematic drawing of Pfortner type photoreactor with immersed light source (right).

FALLING FILM TECHNOLOGY

To overcome the latter, a photo reactor must be designed in such way that the entire reaction medium is irradiated and that mass transfer is enhanced in the reaction zone, to balance the high photon flux. The falling film photo reactor, available at InnoSyn, meets these requirements. In this set-up the substrate solution flows

Falling film reactor

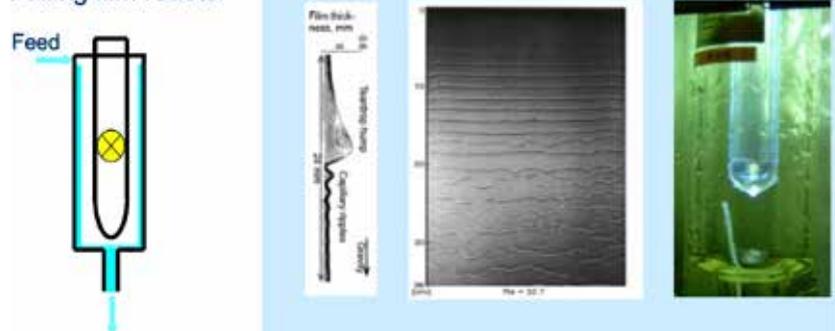


Figure 2. Schematic drawing of falling film reactor (far left), wavy character of falling film schematically (middle left), and a photograph thereof (middle right), typical lab set-up (far right).

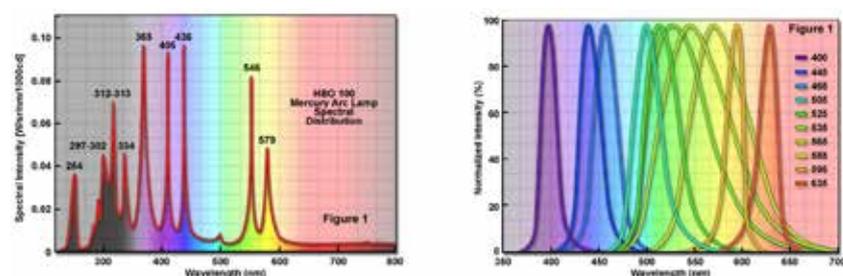


Figure 3. Emission spectrum of a mercury arc lamp (left) and a LED (right), taken from (2).

The recent developments and commercial availability of high power LEDs led to booming applications in photoredox transformations over the last 10 years. Thus, photochemistry has evolved to a powerful and versatile synthetic tool (3-6).

VABORBACTAM – DECARBOXYLATIVE BORYLATION

Vaborbactam (see Figure 4) is a cyclic boronic acid β -lactamase inhibitor, which in combination with meropenem, has been approved for the treatment of complicated urinary tract infections and pyelonephritis (Melinta Therapeutics) (7). The chemical process to manufacture Vaborbactam contains a diastereoselective chain elongation of intermediate 7 using deprotonated dichloromethane at cryogenic conditions (Matteson reaction), for which a continuous flow process was developed (8). The currently used production process towards the crystalline intermediate 6 (registered starting material) is rather long and involves an enzymatic resolution to obtain the required enantiomer (route not shown). At the request of the owner of Vaborbactam, InnoSyn was asked to investigate a more concise, asymmetric synthetic route using a decarboxylative borylation as key step.

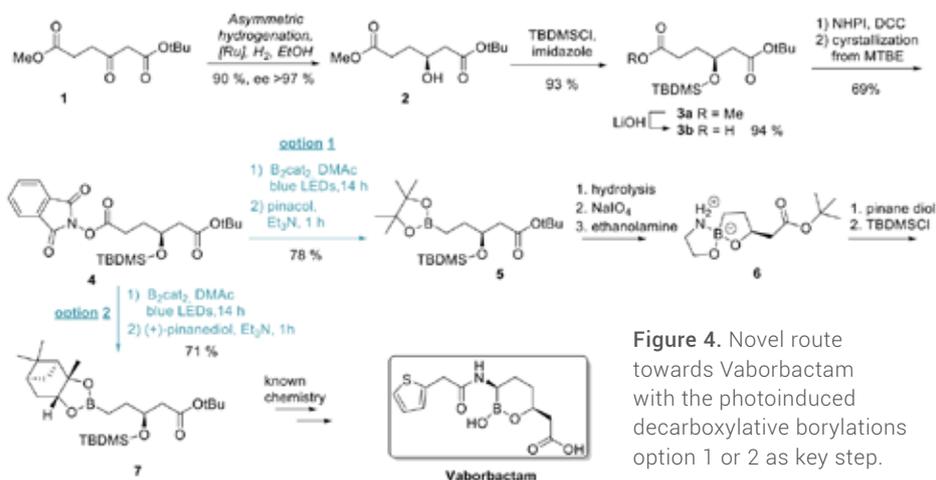


Figure 4. Novel route towards Vaborbactam with the photoinduced decarboxylative borylations option 1 or 2 as key step.

N-hydroxyphthalimide esters, like compound (4), are redox active esters (RAE), which can undergo a single-electron transfer reduction (SET) followed by a rapid decarboxylative fragmentation to an alkyl radical. If the latter is performed in the presence of a diboron reagent, a carbon-boron bond is formed and the net result is a decarboxylative borylation of the redox active ester (see Figure 5). The single-electron transfer reduction can be initiated in the presence of certain transition-metal species, e.g. Ni(9), or upon photoexcitation (10-12).

RESULTS

Intermediate **3b** was obtained relatively straightforward by a Ru-catalyzed asymmetric hydrogenation (e.e. >97%) of the corresponding β -ketoester **1**, and subsequent TBDMS-protection and methyl ester hydrolysis, all on about 50 g scale. The redox active ester **4** was obtained through a DCC-mediated coupling of **3b** and *N*-hydroxyphthalimide followed by crystallization from MTBE on 15 g scale. Next, the decarboxylative borylation of the latter was studied photochemically starting with bis-(catecholato)diboron (B_2cat_2) as reagent, as used by Aggarwal et al.(12)

Initial 1 g-scale photoreactions using blue LED (420 nm) and bis-(catecholato)diboron (B_2cat_2), followed by transesterification with pinacol, resulted in an assay yield of 78% of **5** (option 1, see Figure 5), confirming a successful decarboxylative borylation and a facile transesterification to the corresponding pinacol. To get a better understanding of the reaction kinetics of the decarboxylative borylation, the reaction was repeated while sampling reaction mixture at regular intervals. To these samples was added a solution of pinacol in triethylamine resulting in **5**, which was quantified by HPLC analysis (see Figure 6). After 3 hours, the conversion reached a plateau at approx. 70% assay yield. Further irradiation only led to marginal improvement (< 5%) in yield.

Alternative photochemical decarboxylative borylation approaches applying B_2pin_2 as described by Li et al. (13) and Glorius et al. (14) were investigated, however, none of them resulted in any detectable amount of **5**.

Complementary to the photochemical decarboxylative borylation methodologies, also a Ni-catalyzed protocol for the conversion of carboxylic acids to the corresponding pinacol boronates has been described (9).

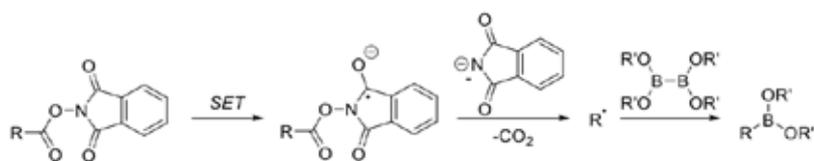


Figure 5. Decarboxylative borylation of N-hydroxyphthalimide esters using a diboron reagent.

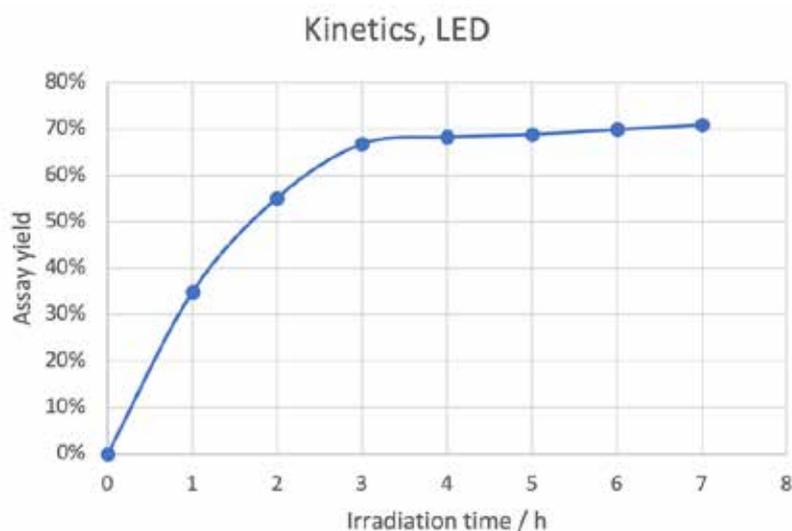


Figure 6. Assay yield of 5 as function of time.

Application of the reported experimental procedure (using 3.3 eq. of B_2pin_2) provided 5 in a rewarding 78% assay yield (at full conversion). To make this synthetic approach economically feasible, the excess of B_2pin_2 needed to be reduced significantly. Hence this Ni-induced decarboxylative borylation towards compound 5 was attempted using 2.7, 2 and 1.3 equivalents of B_2pin_2 , respectively, at ambient temperature. Unfortunately, observed assay yields of compound 5 dropped linearly with a decreasing excess of B_2pin_2 , to even below 10%.

Based on yield and consumption of the diboron reagent, the use of B_2cat_2 in the photoinduced decarboxylative borylation was in our eyes the most attractive option for scale up, also comparing with a later described Cu-catalyzed version (15).

In addition, it is also the most flexible one, as it allows the synthesis of other boronates, e.g. towards compound 7. The latter opens the way to an even more concise synthesis of Vaborbactam.

SCALE-UP

The decarboxylative borylation of 1 was scaled up to 10 g of starting material (0.05 M), using a

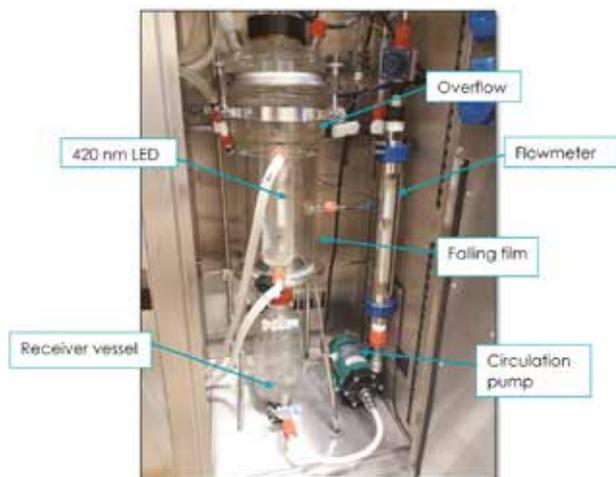


Figure 7. Falling film photoreactor used for the scaleup of photoinduced decarboxylative reactions.

falling film photoreactor equipped with a 420 nm blue LED (100 W) as light source. (see Figure 7). Due to the low penetration of light in Pförtner type photoreactors (vide supra), the 10 g scale reaction was only studied using this falling film set-up (16).

The receiver vessel was filled with the reaction mixture, which was circulated to the overflow. From there, the solution flowed along the cooled (20°C) reactor wall, back to the receiver bottle, creating a liquid film of approximately 1–2 mm thickness. The mixture was kept under N_2 -atmosphere and irradiated for 4h. Subsequently, a solution of pinacol in triethyl amine was added. The circulation was continued for another hour without irradiation. After aqueous work up, compound 5 was obtained in 71 % overall yield (corrected for assay).

The ease of transesterification of the catechol intermediate with pinacol to compound 5, prompted us to investigate whether pinacol could be replaced by pinane diol to yield compound 7 directly, thus omitting two additional synthetic steps. Indeed, using the same falling film reactor set-up, and the same photochemical procedure, a gratifying 71% isolated yield of compound 7 was obtained.

In this article we have presented the successful implementation and scale-up of a visible light-induced decarboxylative borylation as key step in a novel route towards vaborbactam.

REFERENCES AND NOTES

1. D. M. Arias-Rotondo, J. K. McCusker, *Chem. Soc. Rev.* 45, 5803–5820 (2016)
2. "Microscope Light Sources," can be found under <http://zeiss-campus.magnet.fsu.edu/articles/lightsources/> (last checked 04 Mar 2021)
3. C. Stephenson, T. Yoon, D. W. C. MacMillan, *Visible Light Photocatalysis in Organic Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2018.
4. K. Teegardin, J. I. Day, J. Chan, J. Weaver, *Org. Process Res. Dev.* 20, 1156–1163 (2016)
5. M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* 81, 6898–6926 (2016)
6. N. J. Gesmundo, M. H. Shaw, J. Twilton, J. C. Tellis, D. W. C. Macmillan, D. A. Nicewicz, *Sigma Aldrich* 1–60 (2019).
7. "FDA approves new antibacterial drug," can be found under <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573955.htm> (last checked 04 Mar 2021)

8. C. Stueckler, P. Hermsen, B. Ritzen, M. Vasiloiu, P. Poechlauer, S. Steinhofer, A. Pelz, C. Zinganell, U. Felfer, S. Boyer, M. Goldbach, A. de Vries, T. Pabst, G. Winkler, V. LaVopa, S. Hecker, C. Schuster et al., *Org. Process Res. Dev.* 23, 1069–1077 (2019)
9. C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. a Johnson, A. K. Chatterjee, et al., *Science* 356, 7355 (2017)
10. M. C. Fu, R. Shang, B. Zhao, B. Wang, Y. Fu, *Science* 363, 1429–1434 (2019)
11. B. Yadagiri, K. Daipule, S. P. Singh, *Asian J. Org. Chem.* 10, 7–37 (2021)
12. A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers, V. K. Aggarwal, *Science* 357, 283–286 (2017)
13. D. Hu, L. Wang, P. Li, *Org. Lett.* 19, 2770–2773 (2017)
14. L. Candish, M. Teders, F. Glorius, *J. Am. Chem. Soc.* 139, 7440–7443 (2017).
15. A Cu-catalyzed decarboxylative borylation of compound 4 using B2Pin2 has been described (60–64% yield); see J. Wang, M. Shang, H. Lundberg, K.S. Feu, S.J. Hecker, T.Qin, D.G. Blackmond, P.S. Baran, *ACS Catalysis*, 8, 9537–9542 (2018)
16. A similar successful scale up of a photoinduced decarboxylative borylation using B2(cat)2 has been described recently; see M.D. VanHeyst, J. Qi, A.J. Roecker, J.M.E. Hughes, L. Cheng, Z. Zhao, J.Yin, *Org. Lett.* 22, 1648–1654 (2020).

ABOUT THE AUTHORS



André H.M. de Vries received a PhD in organic chemistry in 1996 from the University of Groningen, the Netherlands, under the supervision of Prof. Ben L. Feringa on asymmetric catalysis. After a post-doctoral position at the University of Oxford, he joined DSM in 1998. Since then André has been involved in chemical process developments applying innovative technologies such as catalytic asymmetric hydrogenations, and palladium catalyzed C–C and C–N bond formations. Since 1st of May 2017 the chemical R&D group became InnoSyn B.V., an independent chemical process R&D supplier.



Felix Kortmann received his Ph.D. in organic chemistry from the university of Groningen, NL.

Since 2014, he has been working for DSM Innovative Synthesis/InnoSyn.

His expertise lies in scaling of photochemical processes and development of synthetic organic routes.



Peter Hermsen has been working in the field of process R&D for over 20 years. After obtaining his PhD from the University of Nijmegen, The Netherlands, he joined the development group of DSM Pharma Chemicals, where he was active in the scale-up, implementation and optimization of fine chemical processes. In 2005, he was appointed Senior Scientist at DSM Research, where he was involved in numerous and diverse route scouting projects, for both internal and external customers. As of May 2017, he continues this role within InnoSyn BV.

marketchemica.com



market
chemica

Intelligence
Research
Communications

a new marketing approach in the chemical industry