Up-scale pseudo-telescopic photo-induced Arndt-Eistert α-amino acids homologation in flow reactors cascade

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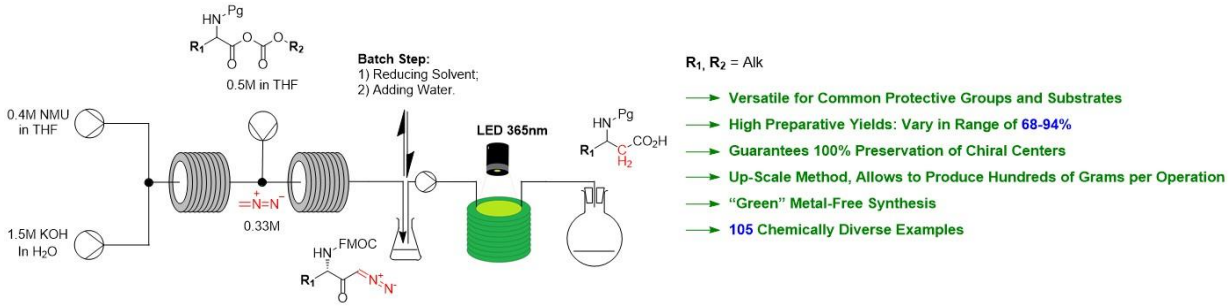


Key words: *diazoketones, diazomethane, flow reactor, photochemistry, Arndt-Eistert homologation, α-protected amino acids, β-amino acids.*

Abstract

We present an efficient, pseudo-telescopic synthesis of β-amino acids via the Arndt Eistert homologation of α-amino acids using flow reactors cascade. Our system utilizes flow generation of diazomethane, diazoketone preparation, and subsequent photo-flow Wolff rearrangement without intermediate isolation. This innovative method enhances safety, improves scalability, and allows access to substrates previously unavailable in the thermal/catalytic Wolff rearrangement. Notably, the reaction conditions are mild, which leads to high yields and excellent purity, thereby expanding the synthetic utility of the Wolff rearrangement. This work unveils a versatile and scalable approach in β-amino acid synthesis, opening new avenues in synthetic and medicinal chemistry.

Introduction

Synthetic organic chemistry has continually advanced, aiming to create safer, more efficient, and scalable procedures for the synthesis of MedChem-relevant compounds. Unnatural amino acids can be viewed as the key precursors in modern peptide[1-3] and macrocycle[4-8] synthesis and proteomics[9-10], which leads to ever-growing interest to them in the perspective of synthetic[11-14], bioorganic[10, 15], and medicinal chemistry[16-17]. However, the synthesis of structurally diverse unnatural amino acids presents certain challenges, particularly with regard to scalability and complexity, emphasizing the need for the development of more efficient synthetic strategies[12-13, 18-20]. Unnatural β-amino acids (β-AAs) stand out from other compounds of this diverse family because they often times exhibit biological activity as "stand alone" compounds[21-23], or become the pharmacophores responsible for such an activity in peptide moieties[24-27]. The notable feature of β-AAs is their improved flexibility introduced by α-methylene, which heavily influences the β-peptides structure, as well as activity and degradation rates[28]. Considering the above, the value of β-amino acids cannot be overstated: β-AAs are the convenient starting material for a broad scope of essential building blocks (**Fig. 1 A**)[29], peptide and polyketide macrocycles (**Fig. 1 B**)[30-31], modified peptides with improved cell permeability and/or antimicrobial properties (**Fig. 1 C**)[32], peptide-based receptor ligands for broad scope of important molecular targets (**Fig. 1 D**)[32].

Homologation of natural amino acids is a long-standing method for the synthesis of unnatural β-AAs[33-36]. The Arndt-Eistert synthesis[37-38] implies a homologation of α-amino acids via Wolff rearrangement[39] of the corresponding diazoketones. This approach allows achieving high yields and more important preservation of the substrate stereochemistry. However, Arndt-Eister process suffers from issues related to safety, efficiency, and substrate scope[28]. On the first step for preparing diazoketones the reaction employs diazomethane, which is an extremely hazardous chemical[40-42]. On the diazoketone rearrangement step using either high temperature[43-44] or metal catalysis[44-51] is necessary, which leads to some structural limitations for the substrates[28]. Sterically hindered compounds, or those with sensitive functional groups, may not be amenable to the thermal conditions or silver salts commonly used in the catalytic Wolff rearrangement[52-53]. Tracing back to the early 20th century with the foundational work of Wolff[39], the rearrangement that bears his name has experienced numerous adaptations and enhancements[45-46, 48, 52-63], including the added later-on photo-induced variant[53, 55, 57, 64-69]. The analysis of these publications shows that recent advances in the realm of organic synthesis, in the context of the photolytic Wolff rearrangement has garnered significant attention over its thermal and catalytic counterparts. The principal advantages lie in its ability to be conducted under milder conditions (no metal catalysts, no heat), leading to reduced byproduct formation and enhanced selectivity. Furthermore, photolytic activation provides a distinctive control mechanism through the precision of light wavelength and intensity, which can be meticulously tuned for optimal yields. With the evolution of modern synthetic techniques, the photolytic Wolff rearrangement has proven to be well-suited for integration into continuous flow conditions[28, 56, 64, 67, 70-73]. This offers the dual benefits of improved reaction efficiency and scalability, underscoring its potential for industrial applications.

Crucial steps towards modern-type continuous flow photochemical setups were documented in early 2000-th[74-75]. This made a basis for the seminal work by Hook *et al.* in 2005[76], where flow photochemical reactor was for the first time used to conduct synthesis on a large scale. Notably, this pioneering work has been cited 325 times since then. We have carefully analyzed the publications related to flow photochemistry (112 papers in specialized journals, 281 publications in other peer-reviewed chemical periodic, and 7 book chapters, a total of 400 records), and it is safe to say that such works started to show up in 2004-th systemically. We have separated the 2004-2023 period to even 4-years segments (**Figure 1 E**, chart in green) aiming to better understand the technology maturation timeline for our case. We used the technology evaluation approach proposed earlier by Everett Rogers in his "Diffusion of Innovations" theory[77]. Thus, we can see that over the initial eight years, the field of flow photochemistry witnessed a modest growth in publications, emblematic of its nascent phase dominated by innovators and early adopters. However, the subsequent abrupt surge to over a hundred consistent publications for the following three 4-year segments, which make a total of over a decade, denotes its transition to a mature stage, capturing the attention of the late majority and possibly the laggards. This steady plateau suggests that flow photochemistry has become an integral, foundational component within its domain. Moving forward, the technology is poised for incremental innovations and potential multidisciplinary integrations, underlining its established prominence and persistent relevance. Similar investigation of the patent literature showed a sum of 500 records (according to SciFinder search). Although there are 150 patents related to flow photochemistry in the period from 1981 to 2004 (which does not line up with the journal articles analysis), these documents mostly feature high tonnage chemical processes[78-82] and polymers and films production[83-86] or wastewater treatment[87-90]. In order to properly fit this data with the journal paper analysis we did the same cut as before and found that the trend and numbers for the patents (**Figure 1 E**, chart in blue) are similar to the trends and numbers for papers.

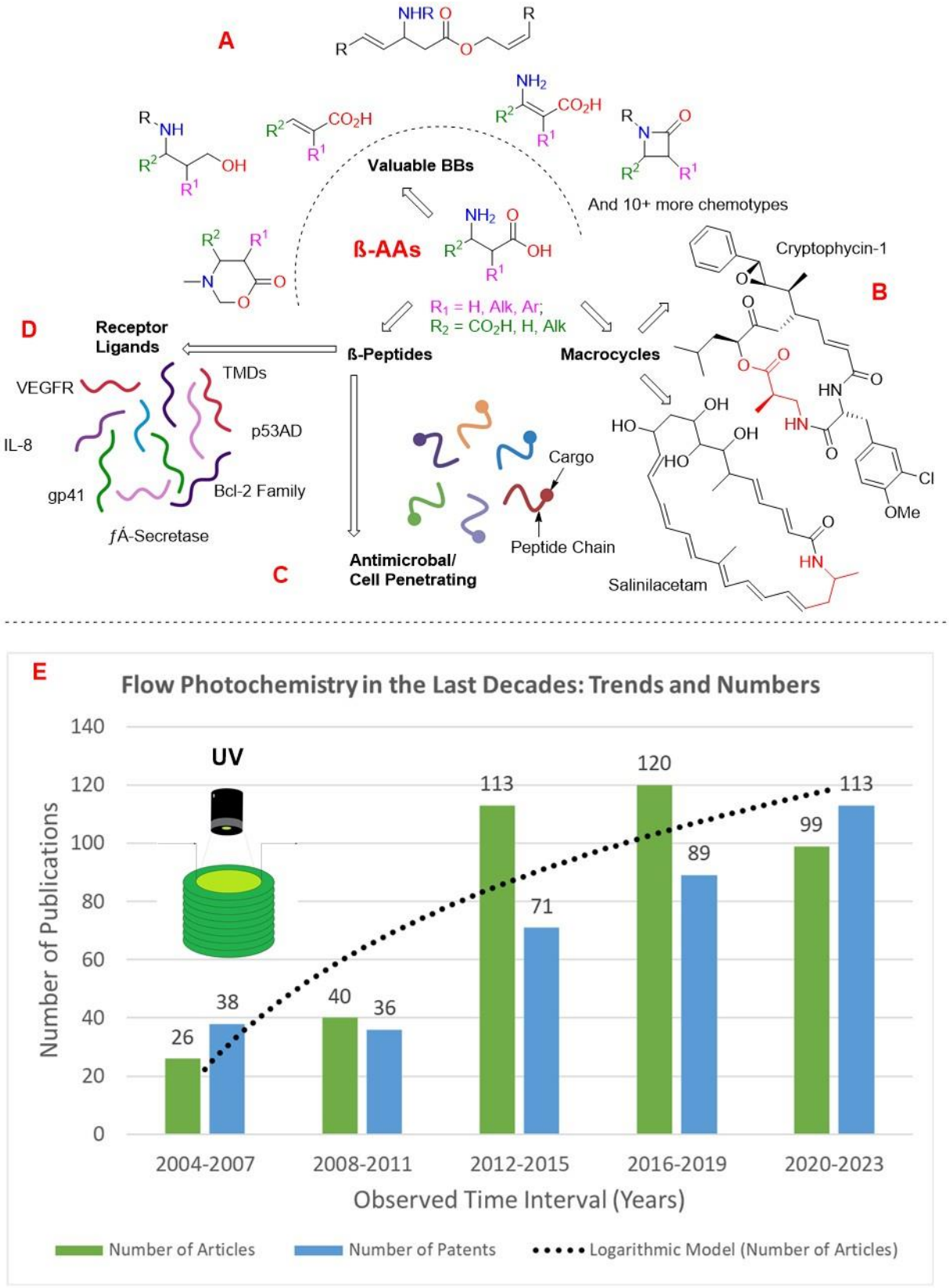


Figure 1. The utility of β-amino acids: versatile precursors to many small molecules chemotypes (**A**); BBs for macrocycles (**B**); BBs for functional peptides (**C**); BBs for receptor ligand peptides (**D**); The statistical analysis number of publications (journal articles and book chapters) related to continuous flow photochemical reaction setups and the general trend in the field (logarithmic model for "number of articles" chart) (**E**).

Herein, we present an innovative, pseudo-telescopic synthesis of *N*-protected β-amino acids from corresponding protected α-amino acids via the Wolff rearrangement using a flow reactors cascade. Although the real telescopic setup was described by Kappe and colleagues previously[28], we were able to scale both diazomethane preparation/addition steps[91] and the following photochemical Wolff rearrangement to the overall impressive 0.12 mol/hour, in addition vastly expanding the scope of α-amino acid substrates viable for such transformations. Based on the collected data, we managed to discover some empiric patterns in the starting α-amino acids derivatives reactivity. Our method leverages the power of flow chemistry[92-98], which improves the transformation safety profile by mitigating the risks associated with the generation and handling of diazomethane, and enables the preparation of diazoketones on a larger scale[91]. Furthermore, the use of a flow reactor facilitates the implementation of photochemical processes[99-101]. Although photo-Wolff rearrangement considered mild compared to thermal and catalytic modifications, our photo-flow process provides even milder reaction conditions at 365 nm LED light versus previously employed 254 nm irradiation[28], which allows accommodating a wider range of substrates.

In our system, the starting *N*-protected α-amino acids mixed anhydrides, prepared previously in batch, are sequentially transformed into diazoketones and then into the homologous acids without the need to isolate or purify the intermediates in the assembly of flow reactors. This strategy significantly streamlines the overall process and enhances the efficiency of the synthesis. The improved scalability and safety features of our reactor system, combined with its ability to generate high yields of pure products under mild conditions, make this method a versatile synthetic routine. Moreover, our approach broadens the substrate scope, enabling access to amino acids that were previously unavailable with the traditional thermal/catalytic Wolff rearrangement[43, 52-53, 57, 102].

This work paves the way for new developments in the synthesis of complex *N*-protected β-amino acids, as well as flow and photochemical process engineering, promising to unlock exciting opportunities in synthetic and medicinal chemistry.

Results and discussion

Considering the above, we started off with testing the previously synthesized[91] diazoketone substrates in the lab-scale flow photochemical device (Uoslab test flow photoreactor with 60W power, 365 nm wavelength LED panel and maximal flow rate up to 3 ml/min, see the SI for details). The photoreactor is versatile for executing diverse photochemical reactions. Its design allows for the effortless substitution of the LED light unit with another emitting a different irradiation wavelength. We were aiming to pre-optimize the reaction conditions (i.e., flow rates, temperature parameters and UV light wavelength and power level) on the model substrates in order to scale it further to the pilot-scale telescopic setup and make the actual optimization easier and less resource-wasteful. Transitioning from a lab/test to a full-scale pilot photochemical reactor required a wide range of experimentations to select the optimal conditions for the photolytic Wolff rearrangement. Since we followed the goal to develop and run the telescopic process, the main criteria, which indicated the efficiency of the setup, were the completion of the diazoketone conversion, control over side products formation and the productivity of the cooling loop. A high diazoketone conversion in the flow mode, in the perfect world scenario, would allow the complete transition to the telescopic process without the need to cycle the reaction mixture in the photochemical module. The effective temperature control within the set boundaries would enable the safe switching from test to large-scale loads without reducing the conversion while maintaining the side products at minimum. The series of tests were performed on the Uoslab test flow photoreactor (see the detailed description in the SI and principal scheme on **Figures 2** and **S1**) using 0.1M diazoketone solution derived from L-phenylalanine **1A** (see the scheme in **Table 1**) in THF, supplemented with 10 equivalents of water. These experiments showed that the conversion of **1A** was over 90% with low side products content in the broad range of parameters: within 1-2.5 ml/min flow rate, and the temperature of the reaction mixture maintained in -5 - +40 °C, range. Notably, screening different LED wavelengths demonstrated that 365 nm UV light was optimal for our type of reactions.

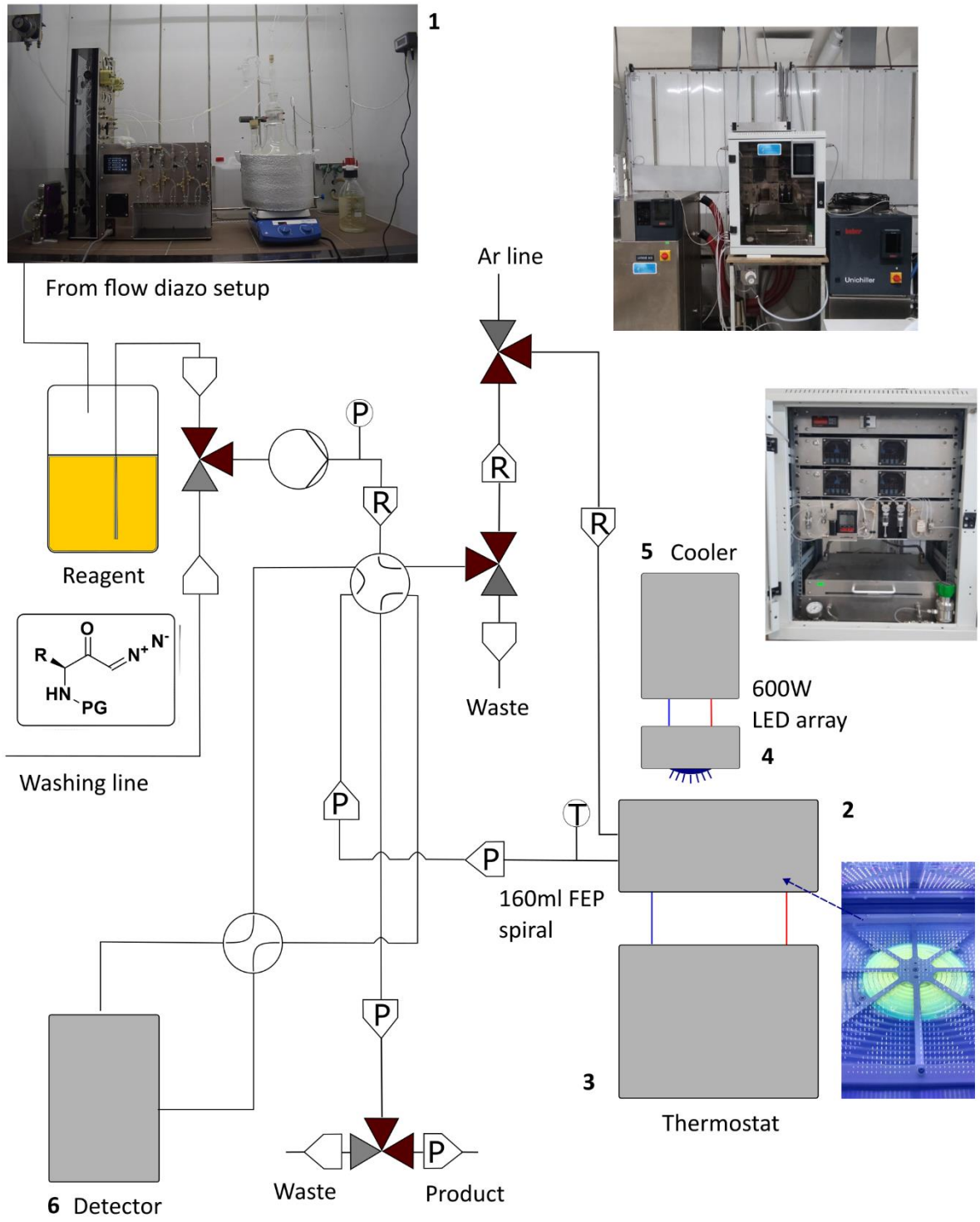


Figure 2. The principal scheme of the photoreactor (**2**, **3**, **4**) equipped with the external cooler (**5**) and fed from the diazomethane-generating reactor (**1**).

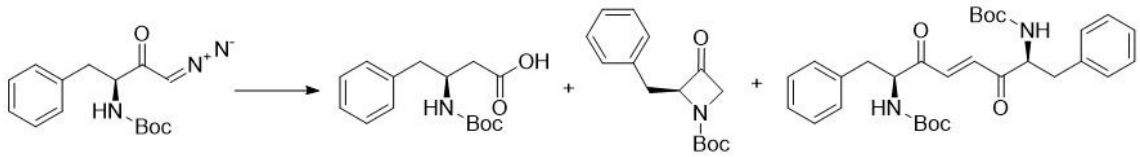
With this preliminary data in hand, we started the optimization of the process on the UOSlab® FlowReactor UF365/450 pilot-scale reactor (hereafter referred to as a photoreactor, **Figure 2**) representing the most up-to-date equipment for conducting photochemical reactions and safe product development in multi-gram quantities. It consisted of a photochemical block with a pump block and control components, and an external thermostat that controlled the temperature inside the reaction coil. One distinct benefit of this design compared to others was that the intense LED illumination targets just a minimal portion of the solution shortly

as it traveled through the device's transparent tubes. This guaranteed optimal conversion, enhanced safety, and a consistent process fluency, crucial for pilot-scale photochemical operations. Moreover, it offered precise and user-friendly temperature regulation, adaptable processing speed, and overall system efficiency.

The principal scheme of the photoreactor and the general view of its main components and assemblies is given on the scheme in **Figure 2** (see SI for more details). The design of the reactor provides mode switching between substrate solution input and the flushing mode, using digital valve **V1**. To fully unload the coil, a switch between the gas and liquid lines **V2** is used. The diazoketone solution is fed from the vessel, marked as "**Reagent**" on the scheme through pump **SP** to a temperature-regulated coil illuminated by a set of LEDs, the blank THF for cleaning purpose is fed from the "**Washing line**". The LED block is equipped with a system for cooling the LEDs and controlling the temperature of the reaction solution. The control system, in turn, allows an emergency shutdown of LEDs in case of overheating or overcooling, which is also dangerous, primarily due to the appearance of unwanted condensate on the electronic boards of the LED block. There is also a viewing window provided for visual control of the process. For safety reasons, when the lid of the photoreaction module is opened, the LED panels automatically switch off. The coil's temperature is maintained by an external thermostat, and the LED array is also cooled by an external cooler. A digital pressure gauge **P1** is used to monitor the incoming flow, which, through the pump block controller, halts supply when the pressure threshold is exceeded, preventing emergency situations in case of reactor blockage. The system's overall pressure is adjusted using a 3 atm back-pressure regulator (**BPR**) with an analog pressure gauge **P2**. Temperature of the reaction mixture is measured at the coil's outlet with an immersion thermocouple **T1**. The system's final valve **V3** switches the flow between the receiver and waste. The build allows for flow connections to external in-line detectors (UV, IR, or other types if needed).

Transitioning to the pilot-scale setup we started the optimization with the same diazoketone **1A** (0.1 M, THF plus 10 equiv. of water), with scaling the reactor technological parameters ten times higher compared to pre-optimization step. The mixture was passed through the photoreactor and irradiated with LED light at 365 nm wavelength at different flow rates and temperatures of the cooling circuit. The product solution was collected, and the composition of the mixture was analyzed using NMR spectroscopy. We were able to identify three products of the rearrangement: the desired β-amino acids (**Table 1**, **2A**), azetidinone **3A**, and the coupling product **4A**. The experimental data are collected in **Table 1**.

Table 1. Optimization of Wolff rearrangement conditions in flow mode using diazoketone derived from L-phenylalanine as a model substrate.



1A **2A** **3A** **4A**

Flow rate, ml/min	Cooler temperature, °C	Reaction mixture temperature, °C	Conversion, %	Side products formation (NMR), %	
				3A	4A
15	**-20**	**-5**	**100**	**4**	**2**
15	-10	9	100	3	3
15	0	23	100	3	2
15	10	38	100	4	2
20	-20	-3	97	3	3
20	-10	12	100	4	2
20	0	28	100	3	3
20	10	40	100	3	3

25	-20	0	88	4	2
25	-10	14	95	2	3
25	0	32	100	3	4
25	10	45	100	4	2

Given the results of optimizing the reaction conditions, a flow rate of 20 ml/min at the cooler temperature set for -10 °C was chosen as an optimal pick for the further preparative synthesis of the series of β-amino acids (**Table 1**, highlighted in green). Under these conditions, despite a fairly high flow rate, the substrate has sufficient time to absorb enough light for the complete conversion. At the same time, the temperature of the reaction medium remains within a technologically convenient temperature range. It should be noted that despite the fact that we could technically fit our photo-flow reactor to the flow setup for diazoketone synthesis[91] (optimal flow rates are of the same magnitude, and it is enough to cycle the reaction mixture through the photoreactor coil only once), we were unable to actually assemble this into a true telescopic setup as it was described previously by Kappe and colleagues at the small scale[28]. This comes up to two main issues: first, we cannot prepare the homogeneous diazoketone solution on the water addition step in case we use the diazoketone/THF/CH_2Cl_2 reaction mixture from the diazomethane reactor[91], and second, we need some residence time for the mixed anhydride to fully convert to diazoketone in case we use this class of compounds instead of chloroanhydride (which is often the case) as the starting material[91]. This leads us to necessity of having a batch step, where we allow the reaction to complete, remove the excess diazomethane by quenching it with formic acid and reducer the CH_2Cl_2 content via evaporation. Then we dilute the mixture with necessary amount of fresh THF to reach the 0.1 M concentration of diazoketone, which we found to be optimal, and dilute with 10 equivalents of water, making the solution ready to use in the photoreactor. Summarizing these observations, it is fair to assert that the true telescopic photo-Arndt-Eister can work out on the nano-scale setup, however it is not translatable to pilot-scale synthesis.

The next step was to check the suitability of the chosen model conditions for the wide range of N-protected α-amino acid-based diazoketones. Diazoketones of the diverse chemical nature were chosen to test them for reactivity and functional groups tolerance in the process. Knowing that there are issues with some popular protecting groups, such as Fmoc in thermal/catalytic conditions from our own experience, as well as from the literature[103-112], we used substrates bearing Boc-, Fmoc-, Cbz- *N*-protecting groups as well as their combinations on diamino acids, in order to assure the universality of our approach. The other parameter to be tested was the preservation of the chirality on the broad scope of substrates. We used pairs of enantiomeric compounds, in all cases where it was possible, and compared chromatographical %*ee* of the products to the *ee* of starting materials. The results are summarized in **Figure 3**.

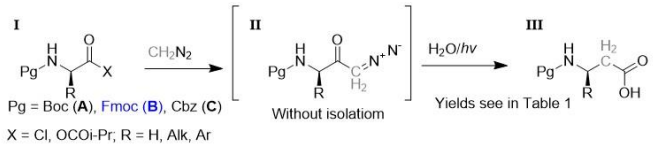
All the reactions were carried out according to the general procedure given in the Experimental section. We started with the series of the most common and popular, as well as the least problematic reactivity-wise *N*-Boc protected α-amino acids (**2A**, **5-24A**, **59AC**, **60AC**, **62AC** and **64AC**, **Fig. 3**). We did not isolate and/or purify the intermediate diazoketones, so the given yields include two steps starting with the *N*-protected anhydrides. The yields varied from good to excellent, and the enantiomeric excess in all cases resembles the *ee* of starting compounds (see SI for details). There are many examples of diazoketones that are either stable towards silver-based catalysis (the most common one for the Wolff rearrangement)[53], or demonstrate low reactivity for other reasons, in any case leading to drastically lower homologation yields. In this connection, it is worth mentioning that the sulfur-containing compounds in our practice were often inactive in the silver oxide-catalyzed Wolff rearrangement, presumably because of the sulfur-induced catalyst deactivation. However, taking these compounds in photo-rearrangement in our reactor allowed to afford the homologated derivatives **17A**, **18A** and **24A** (**Fig. 3**) in good yields. Another group of substrates that regularly show reactivity issues in catalytic/thermal conditions are the *N*-Fmoc-protected α-amino acids-based diazoketones. We could assume that the reasons for such a decreased reactivity might lay in the overall worse solubility of the *N*-Fmoc amino acids compared to Boc-protected analogues, and/or in the realm of steric effects, which could limit the access

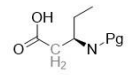
of catalysts to the reaction sites. And though the actual reason for such a behavior of the Fmoc-protected substrates remains unclear, there are many adaptations in the literature, used to overcome this phenomenon via alternative approaches to activating the rearrangement, like wisesonication[103], MW irradiation[108-109, 113], catalyst or reaction environment modification[106, 111-112], etc., and, importantly, UV irradiation[105]. On the first place we used for the photo-rearrangement those *N*-Fmoc amino acids, which we previously failed to react under silver catalysis, and this time we were able to obtain the desired homologation products **24A**, **17-18B**, **51B** (**Fig. 3**) in good yields. We also used some Fmoc-protected analogues of the corresponding *N*-Boc derivatives, already used in the previous step, in order to evaluate the impact of the Fmoc-protecting group on the substrate reactivity in photo-flow conditions. This resulted series of products **5-17B** and **19B**; **21B**, **25-57B**, **61B** and **63B** (**Fig. 3**) with yields comparable with top "parent" *N*-Boc-amino acids **5-17B**, **19B** and **21B** (**Fig. 3**). We found that our conditions tolerate many functional groups like acetylene **21A/B**; olefins **33B** and **34B**; ethers **27B**, **28B**, **55B** and **57B**; and esters **25B, 28B** and **56B**; halogens at sp^3-carbon in **37B** and **38B**, at aromatics in **48B** and **49B**, as well as sulfur(II)-containing molecules **24A**, **17A/B** and **18A** (**Fig. 3**). The doubly *N*-protected diamino acids also gave homologated products **58AC, 59AC, 60AB, 61AB, 62AC, 63AB** and **64AC** with high yields (**Fig. 3**).

Although the yields in all cases were good to excellent (**Fig. 3**), it is safe to say that *N*-Boc diazoketones displayed an overall better reactivity in the photolytic Wolff rearrangement compared to their *N*-Fmoc counterparts. All the synthesized chiral compounds were checked for retention of optical purity (%*ee*) using chiral chromatography. The results showed complete preservation of *ee* inherent to the starting acid (see SI for the details).

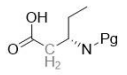
Conclusions

In this comprehensive study, we have delineated the development and optimization of a photoreactor setup to expedite the Wolff rearrangement in diazoketones, aiming for the efficient synthesis of β-amino acids. By initiating our work on a lab-scale setup, we swiftly discerned the importance of reactor parameters, notably the flow rate and cooler temperature. Translating our findings to a pilot-scale system, we achieved optimal conditions at a flow rate of 20 ml/min at cooler temperature of -10 °C, which ensured complete substrate conversion and minimum side products. Importantly, our efforts underscored a limitation: while the nano-scale setup could be integrated into a telescopic system, the same could not be said for its pilot-scale counterpart. The challenges in ensuring homogeneous diazoketone solution preparation, along with the need for a residence time for complete conversion of mixed anhydrides to diazoketones, called for an interim batch step. When probing the adaptability of our model conditions on a diverse array of *N*-protected α-amino acid-based diazoketones, we observed a broad functional group tolerance, attesting to the versatility of our approach. Specifically, compounds often deemed unreactive like sulfur-containing compounds and *N*-Fmoc-protected α-amino acids or potentially unstable like acetylenes, olefines, halogenides and esters, when taken for the traditional catalytic or thermal conditions, yielded promising results in photo-rearrangement, emphasizing the potential of the method. UOSlab® FlowReactor UF365/450 system presents a promising avenue for the photolytic Wolff rearrangement, offering both efficiency and versatility. While challenges persist, the strides made in this study provide a robust foundation for future endeavors in the realm of β-amino acid synthesis and far beyond.

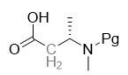




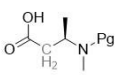
5A, 88% yield, 100/100 *ee*
5B, 76% yield, 99/99 *ee*



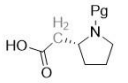
6A, 87% yield, 100/100 *ee*
6B, 76% yield, 99/99 *ee*



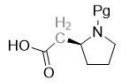
7A, 77% yield, 98/98 *ee*
7B, 68% yield, 96/96 *ee*



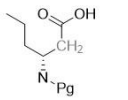
8A, 75% yield, 99/99 *ee*
8B, 70% yield, 96/96 *ee*



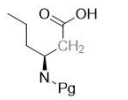
9A, 78% yield, 100/100 *ee*
9B, 65% yield, 99/99 *ee*



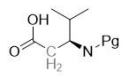
10A, 80% yield, 100/100 *ee*
10B, 66% yield, 99/99 *ee*



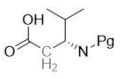
11A, 90% yield, 100/100 *ee*
11B, 86% yield, 99/99 *ee*



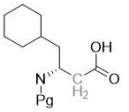
12A, 92% yield, 97/97 *ee*
12B, 85% yield, 99/99 *ee*



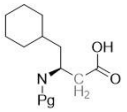
13A, 87% yield, 100/100 *ee*
13B, 85% yield, 99/99 *ee*



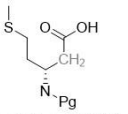
14A, 87% yield, 100/100 *ee*
14B, 83% yield, 99/99 *ee*



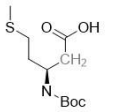
15A, 88% yield, 100/100 *ee*
15B, 84% yield, 99/99 *ee*



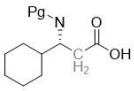
16A, 82% yield, 99/99 *ee*
16B, 82% yield, 99/99 *ee*



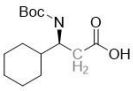
17A, 78% yield, 99/99 *ee*



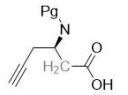
18A, 78% yield, 100/100 *ee*



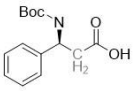
19A, 84% yield, 100/100 *ee*
19B, 78% yield, 100/100 *ee*



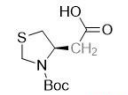
20A, 85% yield, 100/100 *ee*



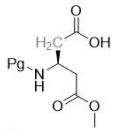
21A, 84% yield, 100/100 *ee*
21B, 80% yield, 100/100 *ee*



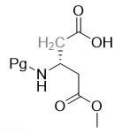
22A, 92% yield, 100/100 *ee*



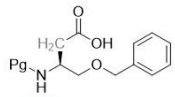
24A, 82% yield, 99/99 *ee*



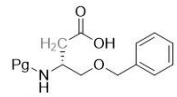
25A, 92% yield, 99/99 *ee*
25B, 86% yield, 99/99 *ee*



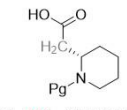
26A, 92% yield, 99/99 *ee*
26B, 84% yield, 99/99 *ee*



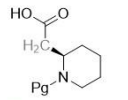
27A, 88% yield, 98/98 *ee*
27B, 83% yield, 98/98 *ee*



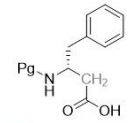
28A, 89% yield, 98/98 *ee*
28B, 83% yield, 98/98 *ee*



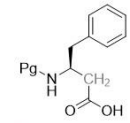
29A, 79% yield, 99/99 *ee*
29B, 75% yield, 99/99 *ee*



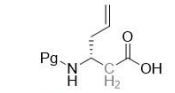
30A, 78% yield, 97/97 *ee*
30B, 74% yield, 97/97 *ee*



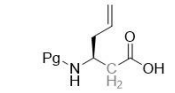
31A, 92% yield, 99/99 *ee*
31B, 85% yield, 99/99 *ee*



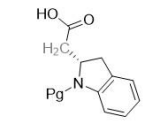
32A, 90% yield, 99/99 *ee*
32B, 86% yield, 99/99 *ee*



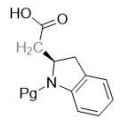
33A, 83% yield, 99/99 *ee*
33B, 76% yield, 99/99 *ee*



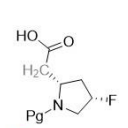
34A, 82% yield, 99/99 *ee*
34B, 77% yield, 99/99 *ee*



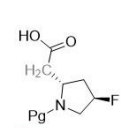
35A, 78% yield, 99/99 *ee*
35B, 70% yield, 99/99 *ee*



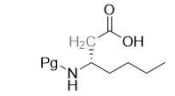
36A, 77% yield, 99/99 *ee*
36B, 69% yield, 99/99 *ee*



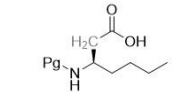
37A, 82% yield, 99/99 *ee*
37B, 75% yield, 99/99 *ee*



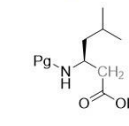
38A, 80% yield, 99/99 *ee*
38B, 77% yield, 99/99 *ee*



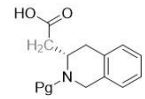
39A, 88% yield, 100/100 *ee*
39B, 73% yield, 100/100 *ee*



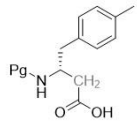
40A, 88% yield, 100/100 *ee*
40B, 75% yield, 100/100 *ee*



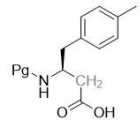
41A, 94% yield, 99/99 *ee*
41B, 84% yield, 99/99 *ee*



42A, 77% yield, 99/99 *ee*
42B, 70% yield, 99/99 *ee*



43A, 92% yield, 99/99 *ee*
43B, 86% yield, 99/99 *ee*



44A, 91% yield, 99/99 *ee*
44C, 87% yield, 99/99 *ee*

45A, 91% yield, 99/99 *ee*
45B, 77% yield, 99/99 *ee*

46A, 90% yield, 99/99 *ee*
46B, 75% yield, 99/99 *ee*

47A, 92% yield, 99/99 *ee*
47B, 84% yield, 99/99 *ee*

48A, 87% yield, 99/99 *ee*
48B, 77% yield, 99/99 *ee*

49A, 87% yield, 99/99 *ee*
49B, 78% yield, 99/99 *ee*

50A, 81% yield, 99/99 *ee*
50B, 75% yield, 99/99 *ee*

51A, 85% yield, 99/99 *ee*
51B, 71% yield, 99/99 *ee*

52A, 81% yield, 99/99 *ee*
52B, 78% yield, 99/99 *ee*

53B, 80% yield, 99/99 *ee*

54A, 92% yield, 99/99 *ee*
54B, 84% yield, 99/99 *ee*

55A, 87% yield, 99/99 *ee*
55B, 76% yield, 99/99 *ee*

56A, 80% yield, 99/99 *ee*
56B, 75% yield, 99/99 *ee*

57A, 76% yield, 99/99 *ee*
57B, 71% yield, 99/99 *ee*

58AC, 90% yield, *ee* N/A

59AC, 92% yield, *ee* N/A

60AB, 85% yield, 99/99 *ee*

61AB, 83% yield, 99/99 *ee*

62AC, 81% yield, 99/99 *ee*

63AB, 84% yield, 99/99 *ee*

64AC, 86% yield, 99/99 *ee*

Figure 3. Scope of the photolytic Wolff rearrangement in UOSlab® FlowReactor UF365/450 on pilot scale using *N*-Boc-Fmoc- and -Cbz-protected α-amino acids diazoketones as substrates. **A** (in black): Pg = Boc; **B** (in blue): Pg = Fmoc; **AB(C)** (in green): a combination of Boc/Fmoc or Boc/Cbz protecting groups.

Experimental section

General:

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on automated melting point system. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for Protons and 126 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for Carbon-13, and 376 MHz for Fluorine-19). Tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) were used as standards. Preparative HPLC analyses were done on an Agilent 1200. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument using atmosphere pressure chemical ionization (APCI).

General procedure for flow photochemical Wolff rearrangement:

For testing preparative conditions, solutions of diazoketones with a volume of 1 L and a concentration of 0.1 M were prepared. Diazoketones were obtained using a diazomethane flow generator and the corresponding mixed anhydrides[92]. Diazoketones were isolated by evaporating the solvent from the reaction mixture and transferred to a THF solution without additional purification. The diazoketone solution (0.1 M, THF), to which 10 equiv. of H_2O was added, was passed at a rate of 20 ml/min through a flow photoreactor with irradiation with LEDs with a wavelength of 365 nm at a cooling contour temperature of -10 °C and a pressure of 3 atm. The reaction solution of the product at the output of the photoreactor was collected in a bottle. THF was evaporated, the residue was treated with water solution of $NaHCO_3$ and washed twice with ethyl acetate. The water phase was acidified with 1M HCl to pH = 4, extracted three times with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The results of the test experiments are given in **Table 1**, and spectral data are provided in the SI.

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