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Automated One-Pot Library Synthesis with Aldehydes as Radical Precursors

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The increased demand for the synthesis of Csp^3 enriched motifs and the urgency of discovering new drugs requires the development of more efficient technologies and synthetic tools to accelerate drug discovery processes. Herein, we report a fully automated strategy for the addition of Csp^3 enriched building blocks onto olefins via Giese addition to forge Csp^3–Csp^3 bonds. The developed fully automated protocol allowed the *in-situ* conversion of aldehydes (non-redox-active species) to electroactive imidazolidines and their use as precursors of C-centered radicals under photoredox catalyzed conditions for the synthesis of building blocks and bioactive compound libraries by synthesizing sp^3-enriched compounds.

Introduction

Active pharmaceutical ingredients (APIs) typically interact with specific biological targets, necessitating a three-dimensional character in bioactive molecules.[1] In the last decades, various 3D descriptors have been extensively studied and correlated with the likelihood of a drug candidate becoming a marketed drug.[2] Among these, Fsp^3 has gained prominence for describing the "flatness" or "3D character" of compounds. Fsp^3 is determined by the ratio of hybridized Csp^3 atoms to the total number of carbon atoms in a molecule; hence, a higher Fsp^3 value indicates a greater 3D character. This factor is directly proportional to improved drug-like properties, such as solubility in aqueous media and CYP450 inhibition.[3–7]

Enhancing the "drug-likeness" of candidates by introducing Csp^3 enriched moieties is crucial. The urgent need to discover new therapeutic agents and explore new chemical spaces has driven chemists to develop innovative methodologies and to expand the chemical toolbox for the forging of Csp^3–Csp^3 bonds.[8,12] High-throughput experimentation and the automation of laboratory processes enable medicinal chemists to accelerate drug discovery projects, significantly increasing the efficacy, productivity and chemical space.[13,16]

Photochemistry has gained reputation as an alternative for Csp^3–Csp^3 bond formation, being more attractive than classical synthetic methodologies.[17–23] Photoredox catalysis involves the interaction of a photocatalyst (PC) with a radical precursor, which is either reduced or oxidized by the excited PC to generate an alkyl radical. The process has expanded the chemical space due to the wide range of available starting materials that can serve as radical sources (e.g. alcohols, carboxylic acids, aldehydes, etc.).[28–32] Transforming functional groups into redox-active species, including Katritzky salts,[25] redox-active esters,[26–27] alkyl tetrafluoroborates,[28] alkyl carboxylates,[28] oxazolidines[29] and Barton esters[30] has further enhanced the versatility of the approach.

Recently, we developed new uncharged carbon-centered radical precursors (e.g. imidazolidines)[31] for the generation of alkyl radicals under both batch and flow conditions. Such conditions were effectively used to generate (un)stabilized α-amino, α-oxy, benzyl, silyl, tertiary and secondary radicals for the functionalization of electron-poor olefins and vinyl (hetero)arenes, as well as bioactive compounds. For example, Vitamin K3 (Menadione) a nutraceutical, was successfully *tert*-butylated, showcasing the potential of imidazolidines in late-stage functionalization (Scheme 1a). Additionally, a methylated derivative of L-benzylsuccinic acid (3-methylbenzylsuccinic ester, a potent inhibitor of carboxypeptidase A)[32–33] was synthesized using this method (Scheme 1b).[31] The alkylated derivatives, prepared with high purity even under flow conditions (Scheme 1c), can be used directly as obtained, making the protocol attractive for automated processes.

Building on the previous results obtained by PhotoGreen Lab[29,31] and leveraging Johnson & Johnson's expertise in developing new chemical transformations and efficient processes through cutting-edge chemical technologies (flow chemistry, High-Throughput Experimentation (HTE), parallel and library synthesis and Purification (HTP), automation, etc.),[11,16] we have implemented a fully automated one-pot photoredox process to access libraries of synthetically interesting bioactive compounds. The transformation involves a one-pot photo-induced "formal decarbonylative addition" of aldehydes, which

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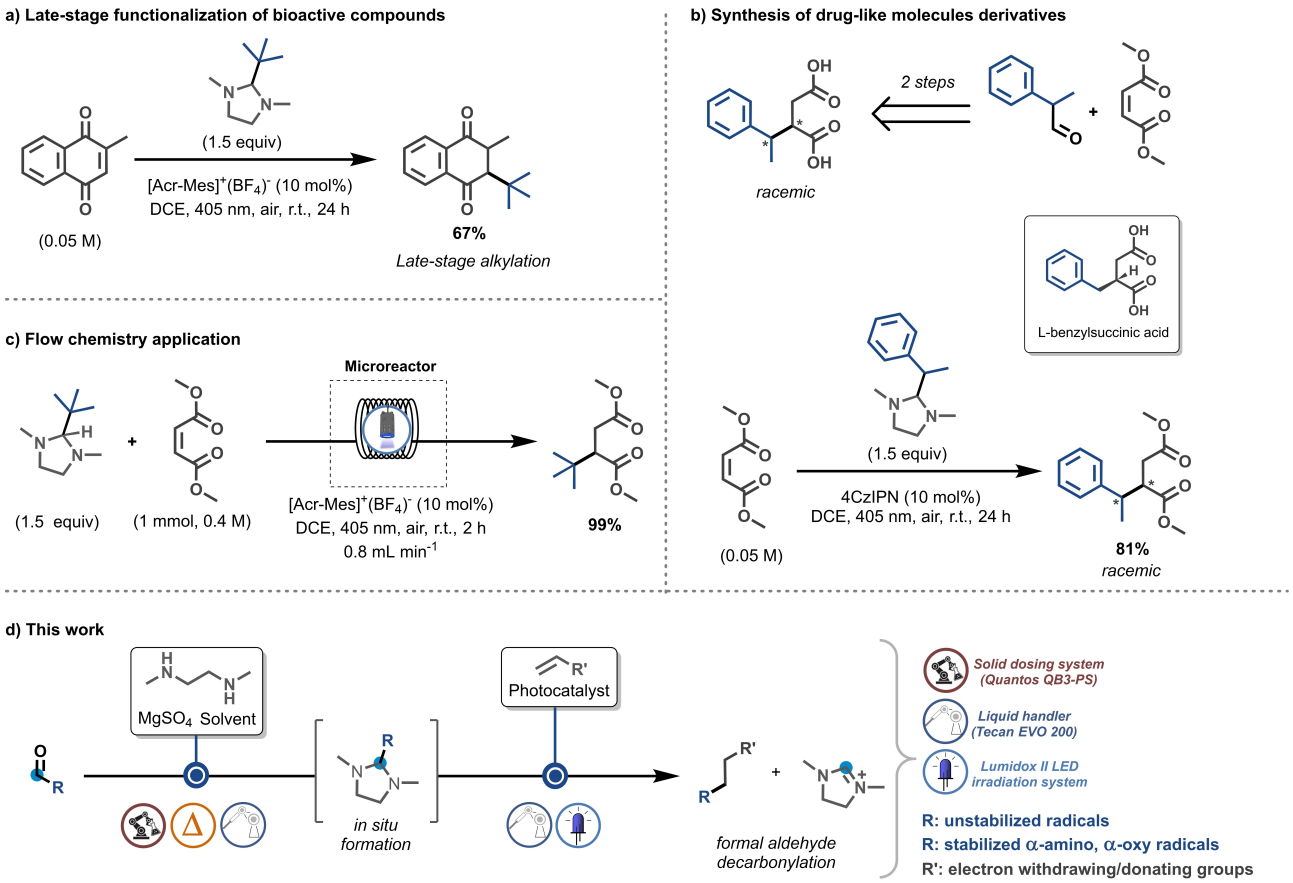

Scheme 1. a) Application of imidazolidines in late-stage functionalization of Vitamin K3 (Menadione). b) Synthesis of a methylated drug-like derivative of L-benzylsuccinic acid. c) Application of imidazolidines in flow chemistry. d) Scheme of automated photoinduced one-pot Giese addition.

are transformed *in situ* into redox-active imidazolidines. These imidazolidines are oxidized by the excited photocatalyst, and after further fragmentation of the corresponding radical cations, generate the desired carbon-centered radicals. These radicals then undergo Giese addition onto suitable olefins, leading to alkylated products (Scheme 1d).

Results and Discussion

Building on our previous achievements and on our background on synthetic photochemistry, we applied the alkylation method to modify various common building blocks present on bioactive drug-like compounds and in late-stage modification of drug-like molecules, aiming for a more efficient and streamlined process. We envisioned a fully automated approach by combining the automated preparation of imidazolidines and the subsequent synthesis of libraries. Solid dosing is performed by a Quantos QS3-PS dosing system and liquid handling by a TECAN EVO200 liquid handler system. Purification was performed in a High-Throughput Purification approach by means of a mass-triggered 1290 Infinity II Agilent reverse phase preparative system. Additionally, a R2–R4 automated Vapourtec system, equipped with a liquid handler injector/collector (Figures S1–S2) and a photoreactor (450 nm) was used to successfully optimize the reaction conditions by High-Throughput Experimentation in flow.

Initially, we optimized the batch preparation of 1,3-dimethyl-2-(1-phenylethyl)imidazolidine **I** starting from 2-phenylpropanal and *N,N'*-dimethylethylenediamine in the presence of $MgSO_4$ (see more information in Table S2). Low boiling point solvents such as DCM and Et_2O, and those that are not solubilizing the photoreaction mixture (THF, Et_2O) were discarded, avoiding liquid handling and clogging issues, facilitating the appropriate automated handling operations. Further optimization was performed in the automated platform by using a more elaborated aldehyde, viz. benzyl 2-formyl-1-piperidinecarboxylate (**A**) screening the performance of DMF and DCE as the media. We discovered that after 3 h at 80 °C, the corresponding imidazolidine **II** was obtained in high purity with a yield over 90 % when DMF was used as the solvent (Figure 1). To ensure reproducibility, we conducted 24 parallel reactions in plate format. We used a QS3-PS Quantos solid dosing system to add $MgSO_4$ to the vials containing pre-dosed aldehyde. The automated liquid handler platform, Tecan EVO200, prepared the reaction mixtures by dispensing a stock solution of *N,N*-dimethylethylendiamine in DMF into the vials.

The results for the automated synthesis of **II** are depicted in the heat map in Figure 1. The plate was successfully obtained with an average yield exceeding 80 %. We tested the formation

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Entry	Deviation from standard condition	II (¹H-NMR % Yield)
1	DCE, 1 h	53
2	DCE, 3 h	33
3	DCE, 17 h	10
4	DCE, 17 h	12
5	DMF, 1 h	64
6	None	91
7	DMF, 17 h	70
8	DMF, 17 h	71

Experiments performed in 0.15 M

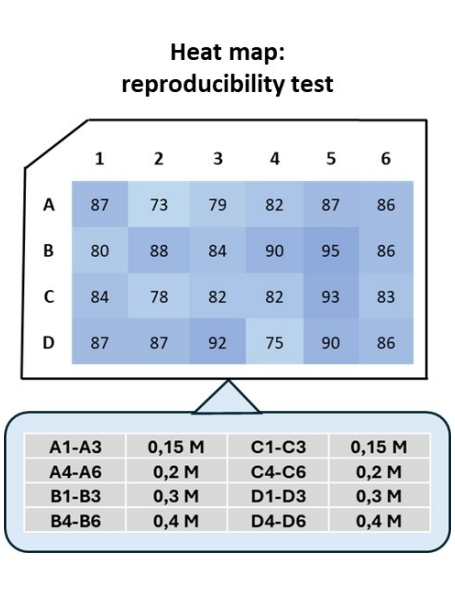
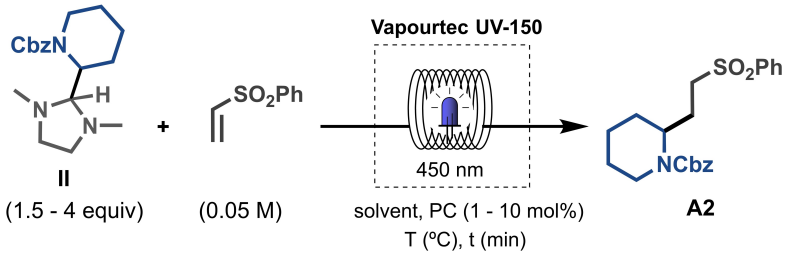


Figure 1. Solvent selection and reproducibility tests for the formation of imidazolidine **II** under batch conditions.

of **II** at different concentrations, from 0.15 M to 0.4 M solutions. As indicated in Figure 1, increasing the concentration is not detrimental for the reaction outcome.

In parallel, we investigated the photochemical alkylation of phenyl vinyl sulfone. For this purpose, we decided to proceed in a HTE approach under flow conditions (see Figures S1–S4). Using rapid automated HTE protocols in flow we could obtain a comprehensive data set of reaction conditions by running several experiments, in a combinatorial manner, screening multiple variables (solvent, solvent mixtures, PC, PC equiv., **II** equiv., temperature, irradiation time, etc.) faster than in batch; therefore, speeding up the optimization of the photochemical alkylation of phenyl vinyl sulfone by **II** as the reaction model to give sulfone **A2** (Table 1). The best conditions found in the HTE

Table 1. Representative HTE results for the reaction optimization of the synthesis of **A2**.



Entry	II (equiv.)	Solvent	PC (mol %)	T (°C)	t (min)	A2 (% yield)
1	1.5	DMF	$[Acr\text{-}Mes]^+BF_4^-$ (10)	40	20	0
2	1.5	DCM	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (10)	40	20	9
3	1.5	DCE	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (10)	40	20	44
4	1.5	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (10)	40	20	70
5	1.5	DCE	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (10)	60	20	72
6	1.5	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (10)	60	10	71
7	1.5	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (5)	60	20	38
8	2	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (5)	60	20	58
9	3	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (5)	60	20	49
10	4	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (1)	60	20	31
11	4	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (2.5)	60	20	51
12	4	DMF	$(Ir[dF(CF_3)ppy]_2(dtbpy))\ PF_6$ (5)	60	20	66

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protocol in flow were: imidazolidine (4 equiv.), (Ir[dF-(CF_3)ppy]$_2$(dtbpy))PF_6 (5 mol%), olefin (1 equiv., 0.05 M) in DMF, 450 nm blue LED irradiation, 60 °C, for 20 min (Table 1, entry 12). DMF was the selected solvent during the formation of imidazolidines and, additionally, it enhances the solubility of drug-like molecules that can be used in the library synthesis. Selected results of the HTE process are depicted in Table 1 (more details in Table S1).[34]

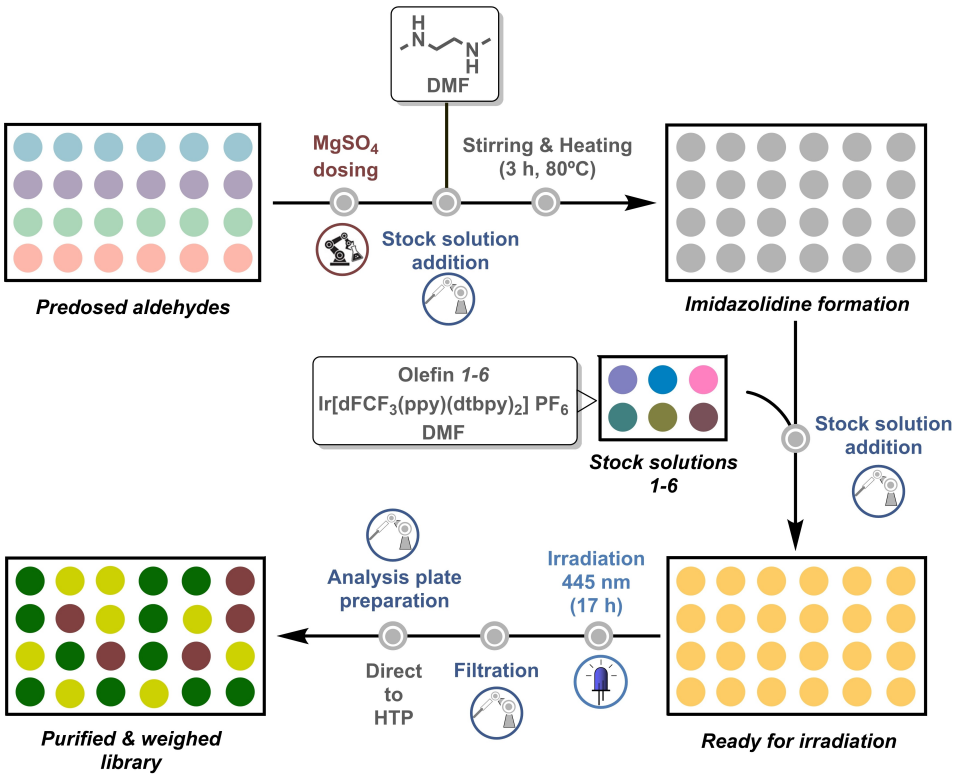
After a rapid optimization we could easily translate the process into a one-pot protocol in batch (Scheme 2).

Gratifyingly, the previously optimized conditions for the photoinduced alkylation of phenyl vinyl sulfone (Table 1, entry 12) rapidly found in the HTE experiments in flow perfectly worked in batch when the *N*-Boc protected piperidine analogue was used as the aldehyde, and the reaction time was prolonged for 17 h at room temperature, yielding the Giese product in 64% yield (more details in Table S3). The adopted conditions detected by HTE resulted to be better than those previously reported in literature by our group for the alkylation of vinyl sulfones (Entry 5, Table 2). Additionally, as one-pot protocol, no $MgSO_4$ filtration was needed between the imidazolidine formation and the photoredox reaction, confirming that the presence of $MgSO_4$ in the reaction mixture is not interfering in the light absorption process by the PC, nor the reaction performance (Entry 1, Table 2).

In this one-pot process, the *in situ* prepared imidazolidine **III** (DMF, 3 h, 80 °C) was irradiated under blue light (456 nm, Kessil lamp, 50 W, 17 h, r.t.) in the presence of 5 mol% of photocatalyst. The corresponding alkyl radical (via a "formal decarbonylation" of the aldehyde) was thus formed, which, upon addition to the olefin, yielded the alkylated product (for set up information see Figure S5). Furthermore, we tested different Michael acceptors to evaluate reaction performance before translating the manual process into an automated one, obtaining compounds **IV–VII** in moderate to excellent yields (Table 2).

Finally, we combined a set of automated platforms, including the QS3-PS Quantos for solid dosing, Tecan EVO200 as liquid handler, Lumidox 24 GII LED array irradiation system, 1290 Infinity II Perperative system from Agilent Technologies for purification, and a Tecan weighing station. Inspired by the recent work at Janssen, where various parameters affecting the performance of commercial photoreactors were studied, we chose the Lumidox 24 GII for its ability to provide homogeneous irradiation over the plate.[34] This system can be integrated with the Tecan EVO200 for library synthesis, as shown in Scheme 2 (details in Figures S6).

Using this setup, we successfully synthesized a combinatorial library by the combination of four different pre-dosed aldehydes (**A–D**) with six different olefins and (hetero)arenes (**1–6**). This automated protocol significantly enhanced our previously developed methodology,[31] allowing us to isolate and detect compounds from neutral and non-electron poor olefins unexpectedly showing the electronic umpolung of vinyl motifs (**A3–D3**). For instance, the late-stage alkylation of the bioactive (8*S*-9*R*)-quinine (a natural quinolone alkaloid effective against malaria)[35] yielded compound **C6** in 33% yield when an α-oxy radical was added. Additionally, derivatives from vinyl



Scheme 2. Workflow scheme for the fully automated processes (one-pot batch approach).

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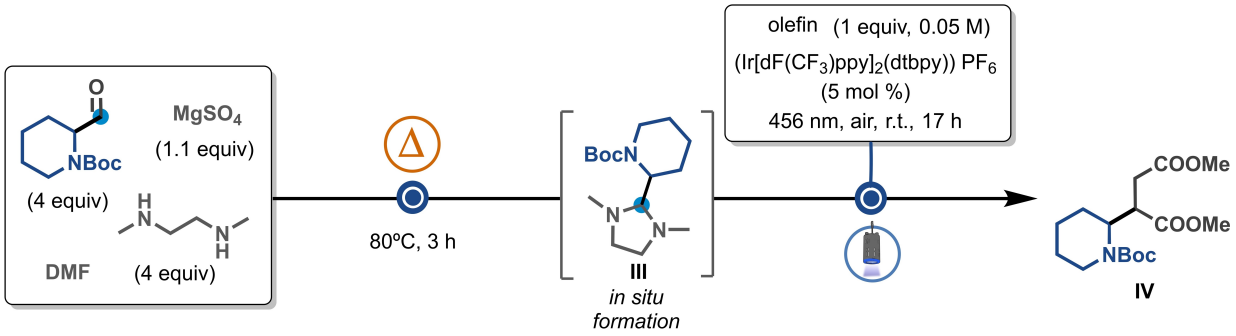
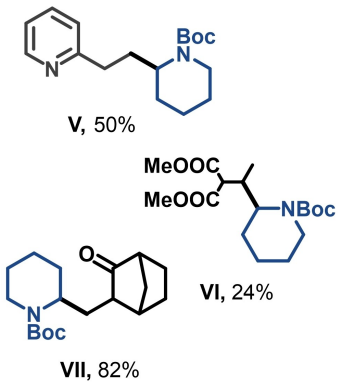
Table 2. Optimization of the photochemical one-pot Giese addition. Modified HTE optimized conditions.



Entry	Deviations from standard conditions	IV (% GC-Yield)
1	None	64
2	(Ir[dF(CF$_3$)ppy]$_2$(dtbpy)) PF$_6$ (3.5 mol %)	50
3	(Ir[dF(CF$_3$)ppy]$_2$(dtbpy)) PF$_6$ (2.5 mol %)	48
4	(Ir[dF(CF$_3$)ppy]$_2$(dtbpy)) PF$_6$ (1 mol %)	35
5	DCE as solvent, [Acr-Mes]$^+$BF$_4^-$ (10 mol %)	13



anisole (an electron-rich vinyl arene) were obtained in low to moderate yields (**A3–D3**, 9%, 19%), with the main challenge being the formation of the corresponding dialkylated dimer, as detected by LC–MS, which hindered the isolation of those derivatives.

The alkylation of electron-poor olefins was demonstrated by functionalizing phenyl vinyl sulfone and vinyl pyridine (Figure 2). Phenyl vinyl sulfone was successfully alkylated by tertiary, secondary, α-oxy, and α-amino radicals achieving yields ranging from moderate to excellent. Surprisingly, the addition of α-amino radicals yielded moderate to excellent results (**D2, A2**, 78%, 28%), despite the same reaction failed in previously reported works.[29, 31] Additionally, we successfully diversified vinyl pyridine (**A1–D1**) with yields ranging from 24% to 73%. Both vinyl sulfone and vinyl pyridine functionalities are prevalent in drug-like molecules, such as Axitinib (an anticancer agent[38]) and Rigosertib (an antitumoral agent).[39] These groups are attractive for late-stage functionalization processes and for introducing different functionalities to discover new pyridine-containing and sulfone-based drug-like analogues.[38–40] Moreover, pyridine is present in about 14% of the marketed drugs, making it the second most common *N*-heterocyclic core after piperidine (30%).[41] We demonstrated the successful introduction of an α-amino radical from Cbz protected piperidine into various olefins from moderate (16%) to excellent yields (78%, **A1–A5**), thereby incorporating a highly demanded core into different structures. The low yields obtained in some cases may be due to the incomplete olefin consumption, the low reactivity of the radical trap or (for vinyl arenes) competitive dimerization of the olefin.

The synthesis of unnatural amino acids (uAA) has been extensively studied due to the significance of some marketed uAA drugs, such as Levodopa for Alzheimer disease, and for creating new drug candidates like peptidomimetics, cyclic polypeptides, and antimicrobial peptides (AMP).[42] The modification of amino acids (AA) or de novo synthesis of uAA remains challenging due to the limited synthetic methodologies, with biocatalytic or biochemical approaches being the primary routes.[42–43] In this work, we demonstrated the facile functionalization of two different AA via photoredox catalysis, generating seven out of eight possible uAA in a 90% success rate, **A4–D4** and **A5–C5**, in moderate to excellent yields (**A5**, 16% and **B4**, 92%).

This methodology is an effective protocol for synthesizing and diversifying uAA, obtaining a wide range of uAA with diverse functionalities as building blocks for further synthetically application. During the experiment, we introduced piperidine rings (**A4–A5**, 35%, 16%), strained cycles such as cyclobutane ring (**D4**, 37%), protected amines (**A4–A5** and **D4**), alkyl moieties like the *tert*-butyl group (**B4–B5**, 92%, 51%), and ethers (**C4–C5**, 55%, 63%), paving the way for introducing protected carbonyl groups, as demonstrated in our previous works by introducing dioxolane moieties.[29,33]

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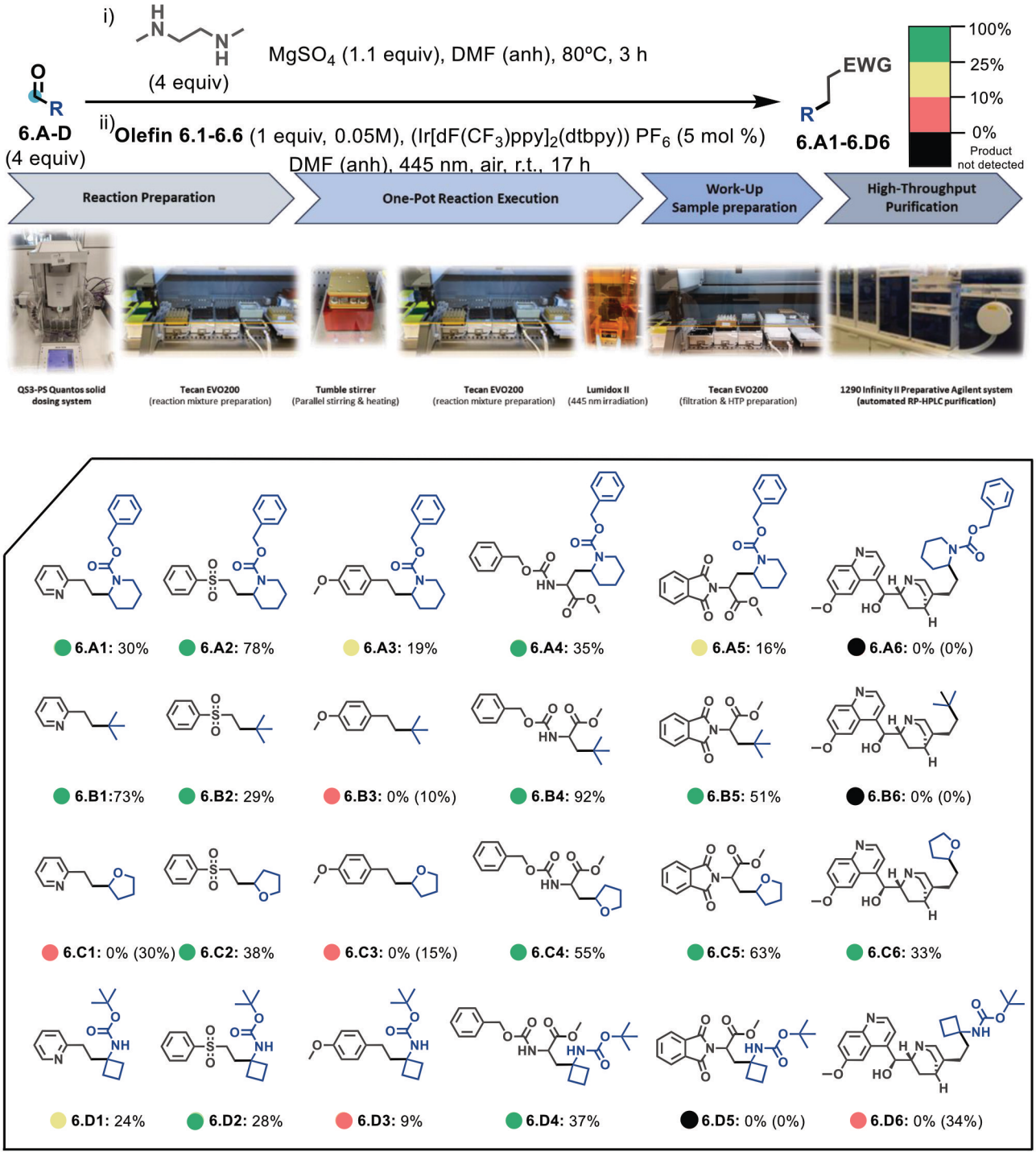

Figure 2. Results and workflow for the synthesized library via fully automated photoinduced one-pot Giese addition. Isolated yields (LC–MS conversion of the starting substrate into desired product).

Conclusions

In this work, we developed a fully automated one-pot photoinduced alkylation process for synthesizing valuable building blocks and drug-like molecules through late-stage functionalization. We demonstrated the potential application of aldehydes as readily available starting material in a one-pot protocol for the photoredox generation of C-centered radicals (tertiary, secondary, α-amino, and α-oxy) for the alkylation of diverse vinyl (hetero)arenes, vinyl amino acids and electron-rich olefins. This protocol effectively synthesizes libraries of unnatural amino acids and facilitates the late-stage functionalization of drug-like molecules.

Moreover, we report this methodology as a tool to enhance the 3D character of the resulting molecules by adding enriched F(sp^3) moieties, exploring diverse chemical space through the formation of C(sp^3)–C(sp^3) bonds, a hot topic in medicinal chemistry. The process is efficient and straightforward, utilizing an automated protocol allowing the preparation of compounds that were unsuitable following the previously reported methods i.e. vinyl anisole and other non-activated alkenes derivatives. It is also worth mentioning that collaborations between academia and industry are becoming increasingly important for innovation in organic chemistry. These partnerships are combining cutting-edge technology with innovative ideas, directly impacting science and society.

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Conflict of Interests

There are no conflicts to declare.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

Keywords: Flow chemistry · High-Throughput Experimentation · Imidazolidines · Late-state functionalization · Photoredox catalysis · Unnatural amino acids

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