DigiChemTree enables programmable light-induced carbene generation for on demand chemical synthesis

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Abhilash Rana[1,2,4], Ruchi Chauhan[1,2,4], Amirreza Mottafegh[3], Dong Pyo Kim [3] & Ajay K. Singh [1,2] ✉

The reproducibility of chemical reactions, when obtaining protocols from literature or databases, is highly challenging for academicians, industry professionals and even now for the machine learning process. To synthesize the organic molecule under the photochemical condition, several years for the reaction optimization, highly skilled manpower, long reaction time etc. are needed, resulting in non-affordability and slow down the research and development. Herein, we have introduced the DigiChemTree backed with the artificial intelligence to auto-optimize the photochemical reaction parameter and synthesizing the on demand library of the molecules in fast manner. Newly, auto-generated digital code was further tested for the late stage functionalization of the various active pharmaceutical ingredient.

Light-induced reactions of diazo compound become crucial in organic synthesis and drug discovery[1–4], facilitating fresh transformations and opening up unexplored chemical space for the biologically active molecule[5]. Highly reactive diazo compounds can undergo various chemical transformations, including C–H[6], O–H[7], Si–H[8,9], N–H[10,11], S–H bonds insertion[12,13], Wolff rearranged product formation[14], cyclopropanation[15,16], cyclopropenation[17], cycloaddition reaction[17,18], etc. In the early phases of research, thermal-assisted conditions were commonly used to generate carbenes[14]. However, these conditions often resulted in low reactivity and selectivity, which hindered process development. Furthermore, the introduction of transition metal carbene has transformed the scenario due to their tunable electronic properties[19] and stability (Scheme 1b)[20–22] Moreover, strong coordination with expensive metal carbenoid[23] and additional impurity generation limits the process for the molecule generation.

Photochemical studies with diazo compounds have a rich legacy in organic synthesis[24], primarily flourishing within academic research sectors[1,25–28], with relatively limited application in industrial settings until recent times[29,30]. Light-induced carbene chemistry faces several challenges, including the need for high-energy UV irradiation[31], costly monochromator filters, susceptibility to numerous side reactions, harsh reaction conditions, low quantum efficiency, and the requirement for specialized batch or flow reactors[32] with significant spacing, thereby restricting the synthetic utility of these methods. On the other hand, many academic researchers, engineers, and professors tend to focus on intuition-driven time-consuming batch process experimentation, such as reaction discovery and exploring substrate
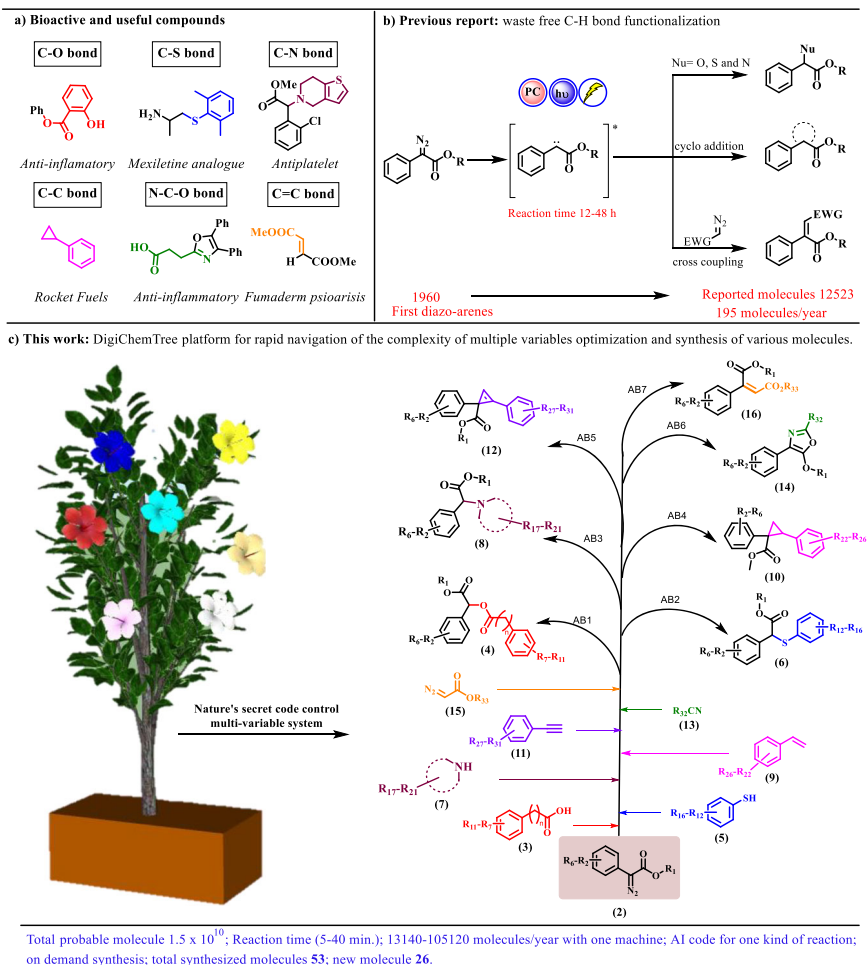
scopes (12,523 molecules in last 60 years, specially in diazo acetate, see the supplementary data table S3).

However, numerous numerical parameters, such as light intensity, temperature, pressure, reaction time, quantum efficiency, molar concentration of substrate, catalyst loading, and reagent equivalents, as well as categorical parameters like additives, solvents, light sources, and reactor types, are essential for developing methodologies favorable for reproducible industrial applications[33]. But in a conventional laboratory an organic chemist can access only a limited subset of these parameters due to constrain of time and availability of material. In response to the challenge of rapidly optimizing reaction conditions[34], we sought to develop a machine-based platform that facilitates self-optimization, intensification, and on-demand of chemical transformation (Scheme 1c)[35]. Recently, the reaction auto-optimization platform opens the new era for academia and industry to optimize the multivariable reaction condition at a time for a reaction[36,37].

To resolve the above-mentioned industrial favorable methodology issues, we thought to employ the integration of continuous flow reactions[38–40] backed with artificial intelligence (AI) technology[41–49]. We report DigiChemTree for the automated optimization of light-induced carbene generation and its coupling with various nucleophiles (O-H, S-H, N-H), cycloaddition with alkenes, alkynes, C≡N, and cross-coupling with ethyl diazoester. The platform is also extended for late-stage functionalization and accelerated synthesis of innovative biologically active molecules[50].

[1]Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, India. [2]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002 Uttar Pradesh, India. [3]Center for Intelligent Microprocess of Pharmaceutical Synthesis, Department of Chemical Engineering, Pohang University of Science and Technology (POSTECH), Pohang, 37673, Republic of Korea. [4]These authors contributed equally: Abhilash Rana, Ruchi Chauhan. ✉e-mail: ajaysingh015@gmail.com; ajaysingh015@iict.res.in

Scheme 1 | DigiChemTree: automated reaction optimization for accelerating the late-stage functionalization of biologically active molecules. 1a Biologically active compound, **1b** Previously reported protocols for carbene generation, **1c** Proposal of DigiChemTree.

a) Bioactive and useful compounds

b) **Previous report:** waste free C–H bond functionalization

c) **This work:** DigiChemTree platform for rapid navigation of the complexity of multiple variables optimization and synthesis of various molecules.

Nature's secret code control multi-variable system

Total probable molecule 1.5 x 10^10; Reaction time (5-40 min.); 13140-105120 molecules/year with one machine; AI code for one kind of reaction; on demand synthesis; total synthesized molecules **53**; new molecule **26**.

Results

Assembly of DigiChemTree and reaction auto-optimization

Our DigiChemTree platform is assembled with 9 liquid delivery pumps, PFA micro-flow tubular reactor, circular blue LED photo-light, controlled light power supply, affordable com port connectivity, 3D printer converted solution collector, and an in-line IR system. It uses a closed-loop BO approach to systematically explore the impact of light intensity and residence time on enhancing the efficiency of high-throughput flow reaction analysis[51]. Before conducting experiments, we conducted an In-line IR background analysis of each compound and further fed the data regarding the signature peak of the product moiety (details in supplementary methods).

We identified a distinctive alignment within the range of 1756 to 1775 cm^{-1} associated with compound **4a** (C=O peak), designated as the signature peak for our analysis (details in supplementary data). We prepared a 0.1 M stock solution of compound **2a** and a 0.2 M stock solution of reagent 3a, loaded into separate syringes connected to the syringe pump. After ensuring communication ports with attached instruments were operational, we set boundaries for the reaction mixture flow rate, power supply voltage, and current, and ran our accessible platform Python code (ab1, code in supplementary software 1). The experimental setup involved mixing the two solutions at a T-junction with the flow rate controlled by a Bayesian optimizer (BO). The resulting solution passed through the PFA tubular reactor in a stoichiometric ratio of 1:2 (compound **2a**: reagent **3a**), exposed to blue LED light at varied wattages. The closed-loop BO systematically explored these varying reaction conditions to maximize the yield percentage. Each optimization cycle comprised 62 experiments in a single day, with results tabulated in the optimization table (supplementary data Table S4). The

initial phase involved three experiments, serving as a preliminary exploration (random search) of the reaction space. Subsequently, the BO algorithm suggested one new experimental condition at a time, aiming to maximize the yield percentage. We observed that at a flow rate of 50 μL min^{-1} each, a residence time of 10 min, and 68 ± 2 W under 3 bar pressure, we achieved a maximum conversion of 99% with a space-time yield of 0.0909 g mL^{-1} h^{-1} (Fig. 1a). Typically, the conventional batch process utilizes either metal catalyst[52], or blue light[24], with longer reaction time with a lower space-time yield 0.0007 g mL^{-1} h^{-1}, which makes process unsuitable for the industrial applications. Given the broader scope of the carbene insertion reaction of diazo compounds in API synthesis (e.g., anti-tumor and anti-inflammatory agents) and chiral-enriched molecules, we are keen to leverage this platform to explore various substituted aromatic benzoic acids (**3a-3o**) and late-stage functionalization of bio-active molecules (**3g-3j**), resulting (**4a-4p**) in excellent yields 82-99%. Furthermore, a comprehensive literature survey revealed that an impressive 15 out of the 16 synthesized photo carboxylation products (**4b-4p**) are entirely recent additions compounds.

After identifying and navigated the complexity of optimal conditions for photochemical reactions with carboxylate nucleophiles, we were interested check the feasibility with slightly weak thiophenol (**5a**) nucleophile as a coupling partner. Slight modification of the reaction condition system navigated the optimal condition (ab2 code condition: residence time 5.3 min., exposure light 68 ± 2, yield 98%, corresponding 0.148 g.mL^{-1} h^{-1} STY within 84 cycles of an experiment for C–S bond formation reaction. Further cross-verified the long-term suitability of the optimized condition, we have run the set-up for the 5 h of the reaction time for synthesis of compound **6a** in gram scale. In contrast, a classical batch reaction required 24–48 h and the addition of a metal catalyst, resulting in a suboptimal to
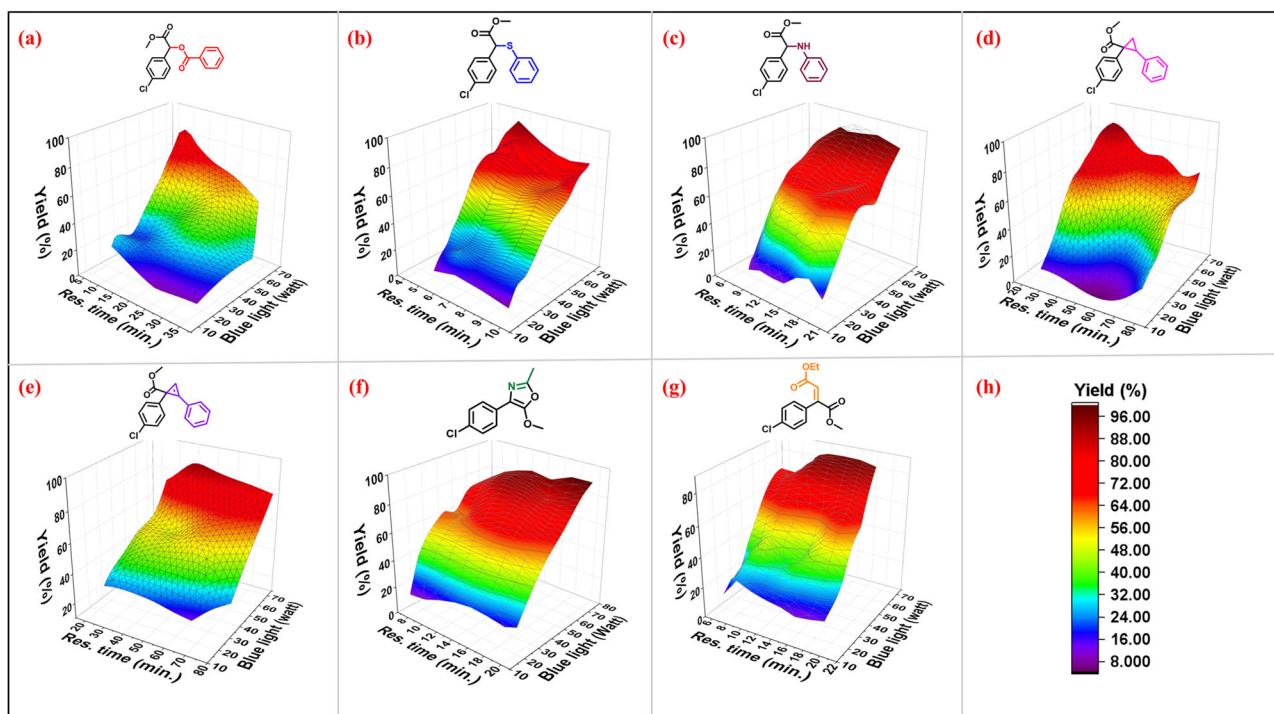
Fig. 1 | Auto-optimization of various parameters for the carbene insertion reaction (code ab1–ab7). a–c Stock solution 0.1: 0.2, 0.2 & 0.2 M of compound **2a**: **3a**, **5a**, and **7a** in EtOAc, respectively; exposure time (10.02, 5.7, & 11 min.) 1 mL reactor volume; **d, e** stock solution 0.1: 0.2, & 0.2 M of compound **2a**: **9a** & **11a**, in DCE, respectively; exposure time (32 & 40 min) 4 mL reactor volume; **f, g** 0.1: 0.2, &

0.2 M of compound **2a**, **13**, & **15** in DCE; exposure time (16.6 & 12.3 min.); **h** represent the yield, 1 mL reactor volume; yields are based on standard IR analysis and cross-verified with crude NMR with ±1% error is acceptable; yield standard bar unit is same for all.

moderate yield of 35–89% for the same thiol derivative **6a** (supplementary data Table S7)[53]. Next, the substrate scope of thiol and aryldiazoester were examined in the photo-flow coupling reaction. Surprisingly, all substrates yielded the corresponding products (**6a-6h**) in excellent yields, ranging from 75-98%. However, based on the literature survey, out of 8 synthesized photo α-thiocarbonyl products, 6 products (**6b-6d**, **6f-6h**) were identified as recent additions.

After successful optimization of the acid and thiol, next we were interested to make the automated for the amines. Amines are key fragments in many natural products[54,55], pharmaceuticals[56,57], and agrochemicals[58,59]. For the long-term goal, we were working to synthesize the various amines in a fast manner but identified the long reaction time (80 min.) under the controlled white light photo-flow condition[60]. To further reduce the reaction time, we have introduced the AI system to identify the suitable reaction condition. Over a 24 h period, 44 experiments were systematically conducted under the selected boundary (watt 15–70, residence time 0.1–22.0 min). Remarkably, we observed that at a flow rate of 46 µL min⁻¹ each, a residence time of 11 min, with 68 ± 2 W under 3 bar pressure, yielded a maximum 92% of **8a** product with space-time yield of 0.058 g.mL⁻¹h⁻¹. Having optimized photochemical C-N bond formation reaction python code (ab3), we explored various substituted aromatic amines (**7a-7g**) and aliphatic amines (**7h-7j**), resulting (**8a-8j**) in excellent yields ranging from 79–92%.

After validating the automated platform for single-objective optimization in carbene insertion reactions, the next goal is to explore its capacity for optimizing diverse photo-induced, highly stained ring formations. These strained cycloalkane or alkene rings, characterized by angle, torsional, and steric strains, release substantial energy upon combustion, making them valuable for high-energy materials[61,62]. The synthesis of highly stained molecules is challenging due to the high cost and significant waste associated with organometalloid complexes. Key optimization parameters include the concentration of compounds **2a** and **9a**, voltage, current, and residence time (see Table S10 in supplementary data). After conducting the series of experiments finally, we observed that at a flow rate of 62 µL min⁻¹. each,

residence time of 32 min. with 68 ± 2 W, under 3 bar pressure, yielded a maximum conversion of 95% with space-time yield of 0.025 g.mL⁻¹h⁻¹. These optimal conditions were then utilized for upscaling the transformation on a 0.01 mol scale within a 5 h timeframe. Notably, it's worth to mention here that the conventional batch process for the identical reaction, even under excess use of metal catalyst and long reaction time (10–48 h)[63,64], at higher temperatures (supplementary data Table S11). Various cyclopropanated products were obtained with excellent yields over 74–92% (Fig. 2, **10a–10i**) in 32 min. of residence time by the fully automated photo-flow system with ab4 code and out of the 9 compounds, 3 (**10b, 10c, & 10h**) products were identified as recent additions.

We next investigated phenyl acetylene nucleophile as a coupling partner but failed to get any desired product through the ab4 code. To access the cyclopropenated product, we have further developed the latest optimal condition through the same set-up by just slightly modifying the reaction time as shown in (Fig. 1e) and within 48 h period of the condition was optimized (supplementary data Table S12). We observed that a flow rate of 50 µL min⁻¹ each, residence time of 40 min. with 68 ± 2 W, under 3 bar pressure, provided an excellent 96% yield with a space-time yield of 0.020 g.mL⁻¹ h⁻¹. The optimized condition with python code (ab5), various substituted aromatic phenyl acetylenes (**11a-11h**) were examined, which gave good to excellent yield (**12a-12h**) (75–96%) and out of 8 compounds 3 are latest (**12g, 12f, & 12h**). Further, the result was compared with previously reported literature, and it worth to mention here that convention batch process needs a longer reaction time with additional catalyst[17,65,66].

Next, we attempted the sixth reaction using acetonitrile to form oxazole under previously reported photo-flow conditions (ab1-ab5), but the yield was disappointingly poor. To achieve maximum yield, we have established a fresh reaction condition with acetonitrile as the coupling partner. Notably, the 24 h period is sufficient to optimize the reaction for acetonitrile as the nucleophile within 44 experiments (supplementary data Table S14). We observed that at a flow rate of 31 µL min⁻¹, residence time of 16 min. with
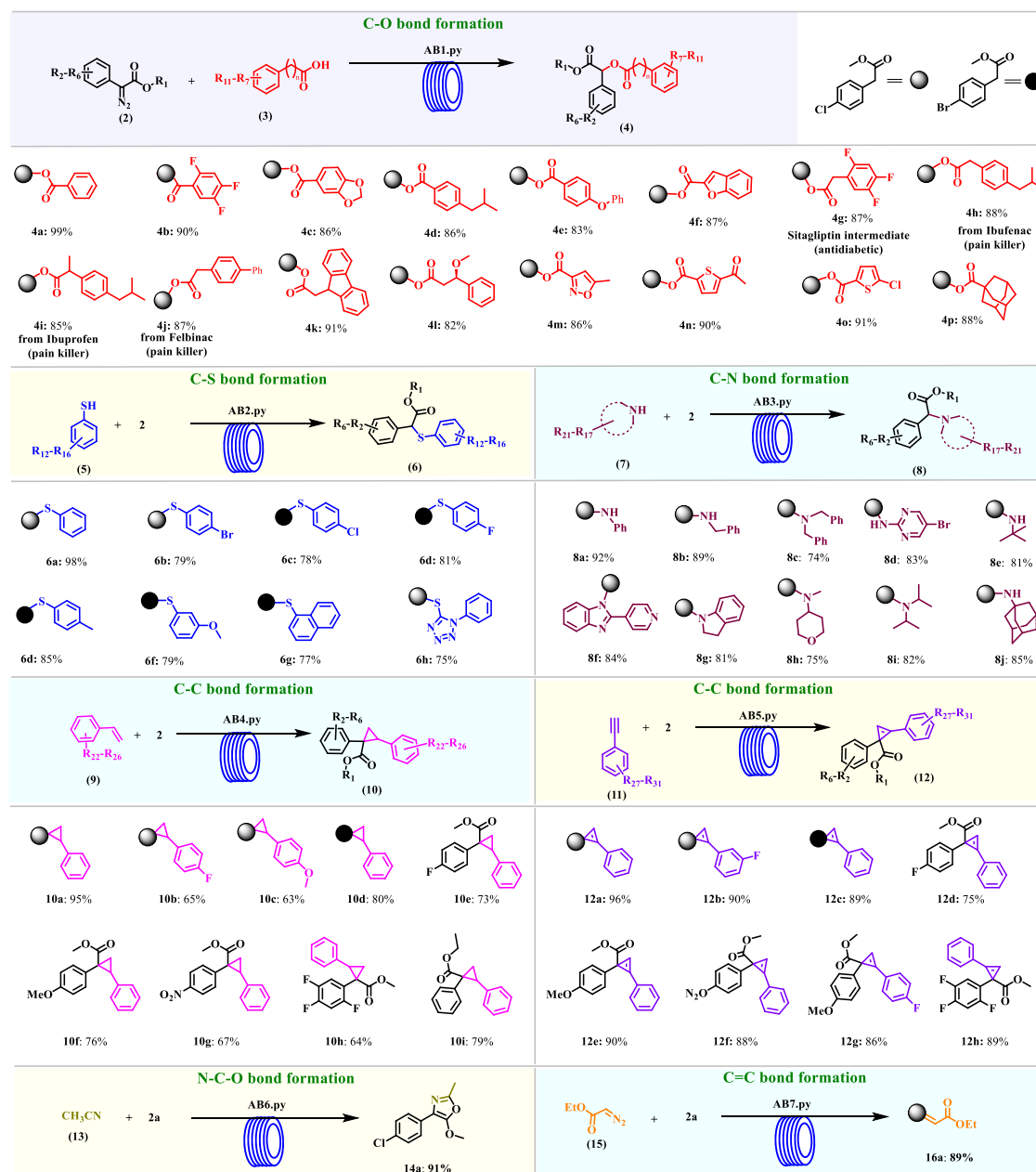
Fig. 2 | One code, one kind reaction. Reaction condition: 69 ± 1 W light intensity; pressure 3 bar, **AB1.py, AB2.py, & AB3.py;** 0.1: 0.2, 0.2 & 0.2 M of compound **2, 3, 5, & 7** in EtOAc; exposure time (10.02, 5.7, & 11 min.); solution collection time & volume (5 h, 30 mL, 53 mL, 28 mL); 1 mL reactor volume; **AB4.py & AB5.py;** 0.1: 0.2, & 0.2 M of compound **2, 9, & 11** in DCE; exposure time (32 & 40 min); solution collection time & volume (5 h, 37 mL, 30 mL); 4 mL reactor volume; **AB6.py & AB7.py;** 0.1: 0.2, & 0.2 M of compound **2a, 13, & 15** in DCE; exposure time (16.6 & 12.3 min.); solution collection time & volume (5 h, 18 mL, 24 mL); 1 mL reactor volume; yields are based on isolated yield.

68 ± 2 W, under 3 bar pressure, yielded a maximum conversion of 91% with a space-time yield of 0.038 g.mL^{-1}h^{-1}.

Similar pattern was applied to track the cross-coupling of aryldiazoacetates with ethyldiazoacetate reaction, using molar solutions of 2a and 15. A total of 44 experiments were conducted within a 24 h timeframe, with outcomes recorded in the optimization table (supplementary data Table S16). We observed that at a flow rate of 40 µL min^{-1}, a residence time of 12 min, with 68 ± 2 W under 3 bar pressure, yielded a maximum conversion of 89% with a space-time yield of 0.058 g.mL^{-1}h^{-1} of compound **16a**. Furthermore, the results for both reactions were compared with previously reported literature, and it is noteworthy that the conventional batch process requires a significantly longer reaction time[67,68].

After successfully developing several optimized individual Python codes (AB1, AB2, AB3, AB4, AB5, AB6, AB7) for the synthesis of various cross-coupling products, we have now developed an integrated platform named "Innovative DigiChemTree." This platform facilitates on-demand customized chemical synthesis, enabling both late-stage functionalization (LSF) and early-stage diversification of molecules. This capability is particularly beneficial for the de novo design and synthesis of drug molecules for structure-activity relationship (SAR) studies, eliminating the need for highly trained personnel[69,70].

The pre-optimized codes (AB1 through AB7) were consolidated into a single Python code (see supplementary software 2), and the system components, such as the flow reactor, pump, in-line analysis, and solution

Fig. 3 | DigiChemTree machine process system for the man-free on-demand carbene inserted product. Reaction condition: **AB1.py**, **AB2.py**, & **AB3.py**; 0.1: 0.2, 0.2 & 0.2 M of compound **2, 3, 5, &** **7** in EtOAc; exposure time (10.02, 5.7, & 11 min.); **AB4.py & AB5.py**; 0.1: 0.2, & 0.2 M of compound **2, 9, & 11** in DCE; exposure time (32 & 40 min); **AB6.py & AB7.py**; 0.1: 0.2, & 0.2 M of compound **2a, 13, & 15** in DCE; exposure time (16.6 & 12.3 min.); yields are based on isolated yield.
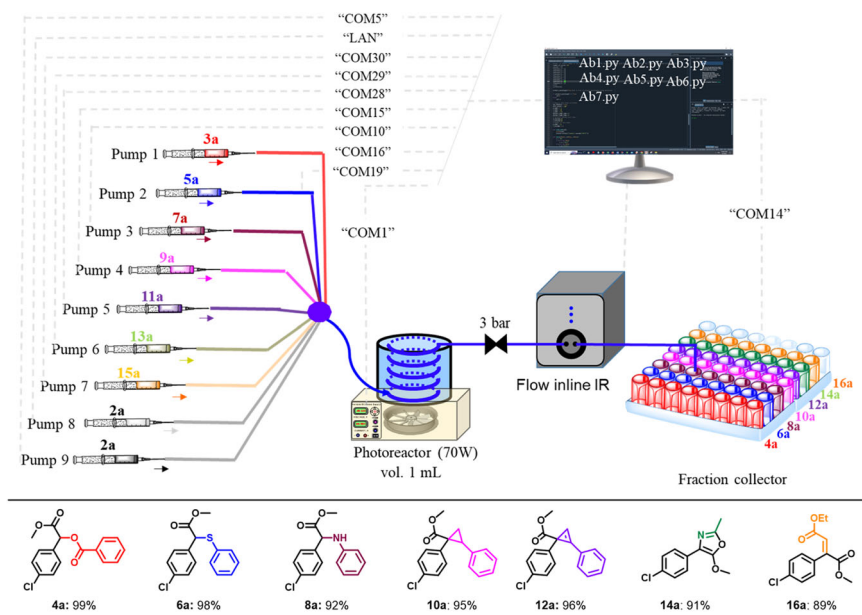
collector, were systematically arranged as depicted in Fig. 3 (further details and video are available in the supplementary data and supplementary video). It is important to highlight that DigiChemTree can synthesize cross-coupling molecules (**4a-16a**) in excellent yields without human intervention.

Conclusion

In summary, we have developed a "one code one kind of reaction Digi-ChemTree" platform for the autonomous optimization and intensification of photochemical processes in a continuous flow manner. This innovative DigiChemTree platform demonstrated its efficacy through automated optimization and a high degree of adaptability for various types of photo-catalytic reactions. Significant enhancements in yield were observed across all reactions, surpassing the performance achieved under-reported model reaction conditions. The rapid reaction auto-optimization and further utility in late-stage functionalization open fresh opportunities for medicinal chemistry to synthesize the on-demand library of the molecule. It's also shorting out the highly trained organic chemist problem to make the innovative complex molecule. Human interface software work is going on in our laboratory, and soon we will report someplace.

Methods
Materials

Most of the reagents and chemicals are bought from Sigma-Aldrich and used as such without any further purification. Common organic chemicals and salts were purchased from AVRA Chemicals, India. The water used for the experiments was deionized water (18.2 mS conductivity). All work-up and purification procedures were carried out with reagent-grade solvents in the air. Analytical thin-layer chromatography (TLC) was performed using analytical chromatography silica gel 60 F254 precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm). PTFE (id = 500 µm) tubing, T-junction, high-purity PFA tubing was purchased from Upchurch IDEX HEALTH &SCIENCE. The photo-batch reactor bought from Lelesil Mumbai, India, was slightly modified for the continuous flow reaction. The visible light (Blue, Red, Green LED) reactor was bought from Smartchemsynth Machine Pvt. Ltd, Hyderabad.

General method

For synthetic details and analytical data of all reaction compounds (**4, 6, 8, 10, 12, 14, 16**) see supplementary data and for NMR spectra see supplementary data 1.

General procedure for DigiChemTree. Before starting the experiments, 0.1 M stock solutions of compound **2a** were prepared in both EtOAc and DCE, alongside 0.2 M solutions of compounds **3a, 5a, 7a, 9a, 11a, 13a**, and **15a**, which were stored in conical flasks and syringes connected to pumps. The integrated continuous flow setup, enhanced by AI, was activated to execute various experiment codes (AB1.py to AB7.py). Each experiment involved different pump configurations to dispense specific solutions at optimized flow rates, with the reaction mixtures traversing through a 1 mL PFA tubular reactor under blue LED illumination and controlled pressure. After each run, the resulting products were collected in individual test tubes for analysis, demonstrating successful outcomes in synthesizing diverse biologically active molecules through various photochemical carbene and coupling reactions (details in supplementary data).

Data availability

The authors declare that all other data supporting the findings of this study are available within the manuscript file and supplementary information files and also are available from the corresponding author upon request (supplementary data, supplementary data 1, supplementary movie, supplementary software 1 and 2). Source data are provided with the publication.

Code availability

The code used for the simulations is available from the authors upon request.

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Author contributions

A.K.S. conceived the project. A.R., R.C. conducted the process experiments. A.K.S., A.R., and R.C. wrote the paper. A.M. and D.P.K. wrote the Python code for running the automated system.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Ajay K. Singh.

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