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## Two-step continuous flow-driven synthesis of 1,1-cyclopropane aminoketones†

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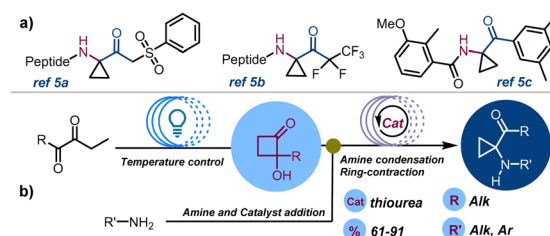
**The continuous flow telescoped synthesis of 1,1-cyclopropane aminoketones was achieved by optimizing the photocyclization of 1,2-diketones to 2-hydroxycyclobutanones (HCBs) and their reaction with aryl- and alkylamines, via tandem condensation C4–C3-ring contraction reaction. With the achieved operational conditions, we were able to obtain a library of cyclopropylamines with good chemical yields, high productivity, and short residence times.**

Aminocyclopropanes have consistently captured the attention of the organic chemistry community due to their crucial roles in the synthesis of biologically active molecules with applications in drug discovery and in total synthesis.<sup>1</sup> In particular, constrained amino derivatives have been proposed as therapeutic agents including MAO inhibitors,<sup>2</sup> opioid antagonists,<sup>3</sup> anticancer,<sup>4</sup> carboxypeptidase,<sup>5a</sup> and protease inhibitors,<sup>5b</sup> and anabolic,<sup>5c</sup> and antidepressant drugs<sup>6</sup> (Scheme 1a). In recent years, interest in nitrogen-decorated strained carbocyclic derivatives has expanded. This is mainly due to the possibility of triggering cyclopropylamine ring-opening reactions through the generation of chemo- or photoinduced radical species (oxidative cleavage) or by nucleophilic ring-opening of cyclopropanes functionalized with EDG-groups (polar reactions). This reactivity is often enhanced in push-pull systems, where donor amine groups and EWG-groups coexist.<sup>7</sup> In particular, research has looked into ring-opening and ring expansion rearrangements,<sup>8</sup> and metal-catalysed and light-induced [3+2]-annulation strategies,<sup>9</sup> for converting three membered ring compounds into synthetically valuable building blocks.<sup>10</sup> Conventional approaches pointing at the construction

of cyclopropylamines have involved Curtius<sup>11a</sup> and Hofmann rearrangement,<sup>11b</sup> Kulinkovich–Szymoniak reaction,<sup>12</sup> and carbene transfer of diazo compounds.<sup>13</sup> More recently Rh,<sup>14</sup> Ru<sup>15</sup> and organo-Zn mediated cyclopropanation,<sup>16</sup> and Cu-catalysed three-component cyclopropane-alkenyl amination<sup>17</sup> have been reported. Furthermore, organocatalytic,<sup>18</sup> electrochemical<sup>19</sup> and metal-free redox-neutral strategies have been unlocked for the preparation of these compounds.<sup>20</sup>

Despite these advancements, 1,1-cyclopropane-aminoketones still represent a relatively underdeveloped class of compounds, hindered by challenging synthetic methods and limited functionalization options.<sup>21</sup> In 2020, a new synthetic batch methodology has been proposed, enabling access to cyclopropyl aminoketones through the condensation of primary and secondary amines to 2-hydroxycyclobutanones (HCBs) followed by  $\alpha$ -iminol rearrangement.<sup>22</sup> However, this method requires extended reaction times (48–72 h) and entails the multi-step preparation of starting materials. Herein, we report our investigations around the development of a continuous-flow cyclopropane aminoketone two-step synthesis.<sup>23</sup> This seamless process combines the swift and secure photocyclization of 1,2-diketones to access HCBs and the addition of aryl- and alkylamines, streamlining and elevating the synthesis of high-value organic compounds (Scheme 1).

We initiated our investigation by optimizing the continuous-flow type II Norrish–Yang (NY II) photocyclization of 1,2-diketones **1** to HCBs **2** by revisiting our previously reported



**Scheme 1** (a) Selected 1,1-cyclopropane aminoketone bioactive compounds; (b) this work: two-step synthesis of 1,1-cyclopropane aminoketones from 1,2-diketones under continuous flow conditions.

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procedure.<sup>24</sup> In that approach, a 0.1 M solution of diketone was pumped into a custom-made flow reactor exposed to blue LEDs, producing a panel of differently substituted HCBs in good yields within a 30 minute residence time ( $t_{\text{res}}$ ). However, to standardize and enhance this synthetic protocol, to more efficient, and commercially available light sources, we substituted the LED light with Kessil lamps, using a thermostatic bath to control the temperature (see ESI,† Section S2). Indeed, earlier observations indicated that the starting diketones **1** and HCBs **2** could undergo degradative processes at high temperatures. Additionally, the photoclosure reaction itself can generate secondary products due to the competition between NY-I (fragmentation)<sup>25</sup> and NY-II (cyclization), leading to reaction yield erosion. To prove our hypotheses, diketone **1a** (0.1 M, ACN) was reacted in a 2 mL custom-made reactor (R1) placed in a thermostatic bath (19–21 °C) and exposed to light (427 nm). The reactor was connected to a syringe pump *via* the inlet and to a collection container *via* the outlet. Using this set-up,  $t_{\text{res}}$  screening indicated that the best reaction conversion could be achieved within 30 minutes, producing the compound **2a** in 81% yield (P: 18.2 mg h<sup>-1</sup>) as reported in Table 1 (entry 1). However, in 15 minutes  $t_{\text{res}}$  **2a** was produced in 79% yield and fairly higher productivity (P: 36.1 mg mL<sup>-1</sup>, entry 3). As a comparison, the same stock solution was pumped into a Vapourtec UV-150 photoreactor (5 mL) setting the temperature at 19 °C. Shorter time reaction ( $t_{\text{res}}$  = 1 min) led to **2a** in 79% yield (flow rate 5 mL min<sup>-1</sup>). This marked a 15-times acceleration compared to our previous continuous flow approach, demonstrating a high level of productivity (entry 7 also refers to the ESI†).

Using the conditions reported in Table 1 (entry 3) we were also able to successfully synthesize other HCB derivatives. The photocyclization of pentane-2,3-dione **1b** allowed us to obtain the corresponding cyclobutanone **2b** in 88% yield. While 5-methylhexane-2,3-dione **1c** afforded **2c** in 90% yield.<sup>26</sup>

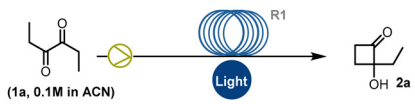
Building on these results, we focused our efforts on the second phase of this investigation concerning the synthesis of

cyclopropane-derivatives **4** under continuous flow conditions. The reaction between the amine **3a** and **1a** was selected as a model transformation to study the  $\alpha$ -iminol C4–C3 ring-contraction reaction<sup>22</sup> (Scheme 1b).

A 2 mL coil reactor (R2) maintained at 22–24 °C was connected *via* a Y-mixer to two pumps dispensing HCB **2a** (0.1 M in ACN) and **3a** (0.1 M in ACN). Using this initial configuration, the target compound **4a** was successfully obtained in a 41% yield (Table 2, entry 1).

However, attempts to increase the yields by simply modifying the reaction times were unsuccessful (see ESI,† Section S2). Subsequently, we tested a panel of acid catalysts to expedite the reaction without altering other parameters. Optimal outcomes were achieved by employing 10 mol% of phenylboronic acid **I** or 2.5 mol% of thiourea **II**, which yielded **4a** in 82% (entry 3) and 80% yield (entry 4), respectively. On the other hand, diphenyl phosphate **III** proved less effective, affording compound **4a** in 77% yield at 20 mol% loading (entry 5). Moreover, extending the residence time ( $t_{\text{res}}$ ) from 15 to 180 minutes allowed us to achieve a 90% yield of **4a** in reactions in the presence of catalysts **I** and **II** (entries 7 and 8). Other reaction conditions were investigated by using a Vapourtec system (see ESI,† Section S3). Reactions conducted at 125 °C and in the absence of catalysts were performed with 5 minute  $t_{\text{res}}$ , affording the compound **4a** in 89% yield (entry 10). To do this, a back pressure regulator system (BPR) was connected at the inlet of R2 to address pressure issues arising from the ACN boiling point (5.2 bar, ESI† Section S3.2). Finally, carrying out these reactions with a stock solution of amine and cat. **II** (2.5 mol%) at 50 °C, the desired cyclopropyl adduct **4a** was obtained in 89% yield (entry 9). Further implementations of the continuous flow setup and the exploration of other reaction conditions (see ESI†) did not show any improvement. Overall, in a cost-

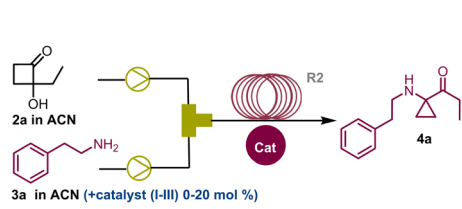
Table 1 Optimization of the continuous flow synthesis of **2a**



Entry	$t_{\text{res}}$ (min)	Yield <sup>a</sup> <b>2a</b> (%)	Productivity (mg h <sup>-1</sup> )
1	30	81 <sup>b</sup>	18.5
2	20	80 <sup>b</sup>	27.4
3	15	79 <sup>b</sup>	36.1
4	10	69 <sup>b</sup>	47.2
5	5	51 <sup>b</sup>	69.8
6	5	85 <sup>c</sup>	116.4
7	1	79 <sup>c</sup>	541.0

<sup>a</sup> Yields were determined by qNMR using 1,2,4,5-tetrachloro-3-nitrobenzene (TCN) as an internal standard. <sup>b</sup> Reaction conditions: hexane-2,3-dione (**1a**, 0.1 M in ACN), FEP tube ( $\phi$  i.d.: 0.8 mm, 2 mL vol.) at 19–21 °C, syringe pump, Kessil PR 427 nm. <sup>c</sup> Reaction conditions: Vapourtec UV-150 photoflow reactor ( $\phi$  i.d.: 0.8 mm, 5 mL volume), 440 nm, 60 W.

Table 2 Optimization of the continuous flow synthesis of **4a**



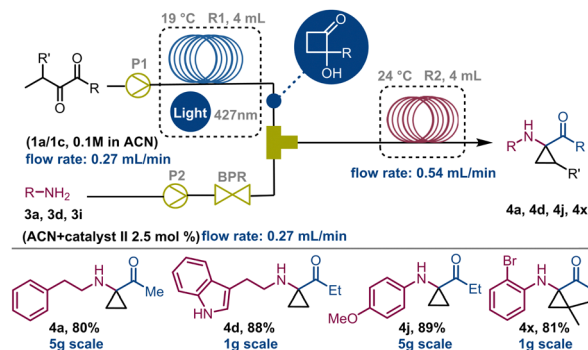
Entry	$t_{\text{res}}$ (min)	Cat. (mol%)	Temp. (°C)	Yield of <b>2a</b> <sup>a</sup> (%)
1	15	—	24	41
2	30	—	24	83
3	15	<b>I</b> (10)	24	82
4	15	<b>II</b> (2.5)	24	80
5	15	<b>III</b> (20)	24	77
6	30	<b>II</b> (2.5)	24	89
7	180	<b>I</b> (10)	24	90
8	180	<b>II</b> (2.5)	24	90
9	15	<b>II</b> (2.5)	50 <sup>b</sup>	89
10	5	—	125 <sup>b</sup>	89

Reactions were performed in a 2 mL coil reactor at the reported temperatures. <sup>a</sup> Yields were determined by qNMR using TCN as an internal standard. <sup>b</sup> Reactions were carried out on a R-series (R4) Vapourtec module as described in the ESI.



benefit balance, the reaction conditions summarised in entry 5 (Table 2) were deemed as the best compromise between productivity and reproducibility. With these results in hand, the scope and the limitations of this synthetic strategy were explored. Reactions carried out with both aliphatic and aromatic amines **3a–z** and HCBs **1a–c** (also including the active pharmaceutical ingredients tyramine **3b**, tryptamine **3c**, and procaine **3v**) delivered the corresponding reaction products in good to high yields (61–91%), showing high functional group tolerance and good degree of purity. However, the synthesis of compounds **4u** and **4v** required modifications to the flow conditions. Enamine **3u** was reacted with **1a** and **1b** in toluene (1.0 M) at 80 °C, yielding the corresponding compounds in 25% and 27% yield, respectively (see ESI,<sup>†</sup> Section S5.1).

Very interestingly, derivatives **4y** and **4z**, observed by <sup>1</sup>H NMR analysis of the corresponding crude mixtures, spontaneously transformed into crystalline imines **5y** and **5z** upon isolation from the reaction medium, as confirmed by XRD analysis (Scheme 2; see also ESI,<sup>†</sup> Section S8). Subsequently, it was observed that this behaviour is common to all the aliphatic cyclopropylamines having a geminal dimethylamino-system on the carbocyclic unit that we tested (ESI<sup>†</sup>). Beyond this

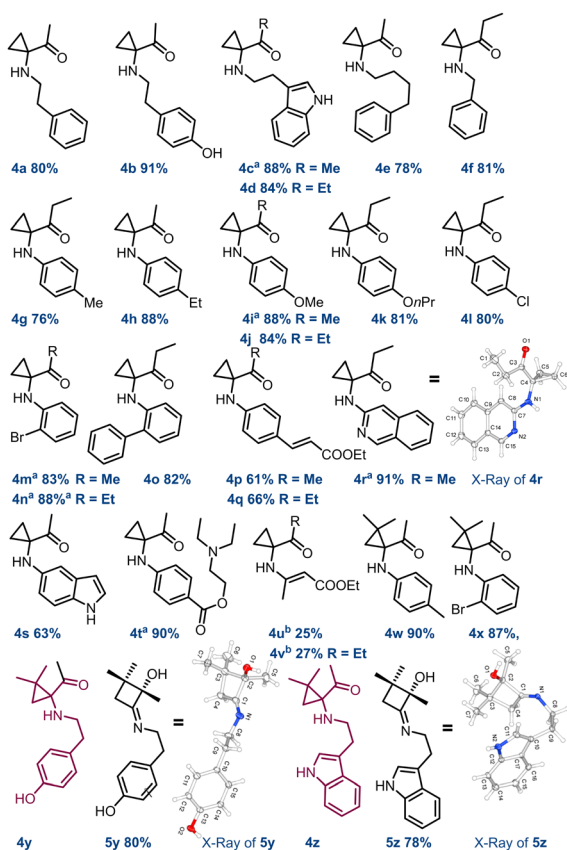


**Scheme 3** Telescoped synthesis of 1,1-cyclopropane aminoketones under continuous flow conditions.

observation, this represents the first example of crystalline structures of 2-hydroxycyclobutyl imine to date. At this point, following the systematic optimization of each reaction step, the focus was on merging the two flow reaction processes to achieve a telescoped continuous-flow, two-step synthesis of 1,1-cyclopropane aminoketones **4** from compound **1** (Scheme 3). To perform this, a 4 mL FEP coil reactor (R1), maintained at 19 °C and exposed to blue light (427 nm), was connected to a syringe pump feeding a 0.1 M stock solution of **1a** in ACN (flow rate: 0.27 mL min<sup>−1</sup>). The reactor outlet was connected *via* a Y-mixer with a stream of amine **3a** (0.1 M in ACN) containing 2.5 mol% of thiourea using a second syringe pump and a back pressure regulator (BPR, pressure = 5.2 bar). The nucleophilic addition of **3a** to HCB **1a** occurred in a second 4 mL tubing reactor (R2) maintained at 22–24 °C and connected directly to a collection container (flow rate: 0.54 mL min<sup>−1</sup>). Experiments carried out with this configuration enabled compound **4a** to be obtained in 80% yield over two-steps (overall *t*<sub>res</sub> over two-steps: 30 min; P: 208 mg h<sup>−1</sup>).

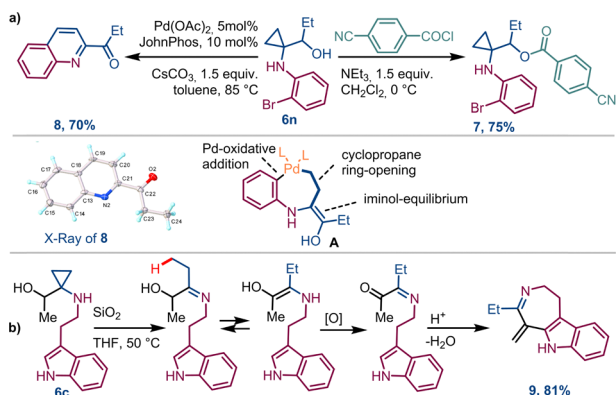
This process was also evaluated in the telescoped synthesis of derivatives **4d** (88%), **4j** (89%) and **4x** (81%). Nevertheless, performing these processes on a multigram scale we were able to obtain approximately 5g of compounds **4a** and **4j** over 12 hours, and 1g of **4d** and **4x** after about 2 hours (see ESI,<sup>†</sup> Section S3). These values are aligned with those obtained for the individual transformations (steps 1 and 2) confirming the efficiency of the entire designed process. To demonstrate the synthetic utility of these derivatives, compound **4n**, once reduced to **6n** with NaBH<sub>4</sub> before purification, was submitted to selective acylation to produce derivative **7** in 75% yield. Also, the Pd-induced tandem ring-opening-intramolecular cyclization reaction of **6n** allowed access to quinoline **8** in 70% yield, probably *via* adduct **A** (Scheme 4a). On the other hand, stirring **6c** in THF at 50 °C in the presence of SiO<sub>2</sub>, compound **9** was produced in 81% yield. As in the previous case, it is proposed that cyclopropane ring-opening triggers an iminium-like equilibrium, leading to the formation of an α-imino-ketone adduct. Once protonated, this adduct can be susceptible of nucleophilic attack by the indole moiety, leading to the tricyclic compound **9** (Scheme 4b).

In summary, we have developed and optimized two continuous flow processes, involving (a) the photocyclization of



**Scheme 2** Continuous flow synthesis of 1,1-cyclopropane aminoketone substrate scope. Yields of compounds **4c**, **4i**, **4m–n**, **4r**, and **4t** were determined by qNMR using 1,3,5-trimethoxybenzene as an internal standard. <sup>a</sup>Compounds **4c**, **4i**, **4m–n**, **4r**, and **4t** were purified after reduction with NaBH<sub>4</sub> in THF at 0 °C; <sup>b</sup>reaction carried out in toluene (1.0 M) at 80 °C. **4r** CCDC 2373555, **5y** CCDC 2373554, **5z** CCDC 2373556.<sup>†</sup>





**Scheme 4** Post functionalization of 1,1-cyclopropane aminoketones **4n** and **4c** via alcohols **6n** (a) and **6c** (b). CCDC deposition number of **8**: 2387960.

1,2-diketones to access HCBs and (b) the reaction between a panel of amines and HCBs to obtain cyclopropane aminoketones. The two established protocols were subsequently merged to design a telescoped 2-step continuous-flow process, enabling the direct transformation of diketones into the corresponding cyclopropylamines in good yields, eliminating intermediate purifications, shortening the reaction times (30 minutes vs. 48 hours for batch reactions), and maximizing the process productivity. Studies dedicated to understanding the reaction mechanism leading to the formation of compounds **8** and **9** are currently underway in our laboratories.

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## Data availability

The data supporting this article have been included in the ESI.<sup>†</sup> Crystallographic data for **4r**, **5y**, **5z** and **8** has been deposited at the CCDC [CCDC numbers: 2373554, 2373555, 2373556, 2387960] and can be obtained from [[https://www.ccdc.cam.ac.uk/structures/?gad\\_source=1&gclid=Cj0KCQjwn9y1BhC2ARIsAG5IY4ff70AulkNmVdTV06QberBmhXhiavEOu9tw1Vlb87\\_36Wo\\_5ULGsaAu4IEALw\\_wcB](https://www.ccdc.cam.ac.uk/structures/?gad_source=1&gclid=Cj0KCQjwn9y1BhC2ARIsAG5IY4ff70AulkNmVdTV06QberBmhXhiavEOu9tw1Vlb87_36Wo_5ULGsaAu4IEALw_wcB)].

## Conflicts of interest

There are no conflicts to declare.

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