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Oscillatory flow reactor facilitates fast photochemical Wolff rearrangement toward synthesis of α-substituted amides in flow

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ABSTRACT

A visible light-promoted fast photochemical Wolff rearrangement was developed toward synthesis of α-substituted amides in continuous flow with the use of a photochemical oscillatory flow reactor (POFR). The control experiment indicates that a fast process of the Wolff rearrangement (<40 s) is involved. Notably, this protocol does not require excess use of any reactants, and the resulting α-substituted amides could be isolated by recrystallization in good to excellent yields.

Amide functional groups are significant structural motifs that are highly prevalent in biologically active compounds and pharmaceuticals [1–5]. One of the most important properties of amides is that the C=O and N–H groups allow to form hydrogen bonding interaction, such as with proteins, to increase the binding specificity [6]. On the other hand, when alkyl or aryl groups are introduced at the α-position of acetamide, these hydrophobic groups are likely crucial elements in determining the binding affinity [5]. Some approved α-alkyl or α-aryl amide drugs are representatively shown in Scheme 1, such as zofenopril [7], levomilnacipran [8], netupitant [9], disopyramide [10], which contain α-alkyl or α-aryl amide groups as a part of pharmacophoric or auxophoric molecular fragments (Scheme 1). Besides these approved drugs, there are still emerging numerous α-substituted amides in drug discovery. Although amide synthesis is well-developed in the past decades and becomes one of the most frequently utilized organic reactions in the pharmaceutical sector [11–14], yet the amide formation avoiding poor atom economy reagents was voted as the top challenge for green chemistry by the American Chemical Society Green Chemistry Institute (ACSGCI) in 2007 (Scheme 2A) [15]. Therefore, given the significance of the α-substituted amide structure, developing facile, highly effective (to bring the product with both high yield and purity), and scalable approaches with high atom economies and less waste generation toward synthesis of α-alkyl or α-substituted amides on demand is synthetically useful and desired [16,17].

Wolff rearrangement has been developed for over a century during which it has triggered an avalanche of applications, and it is still one of the most important transformations hitherto in organic synthesis [18–24]. α-Diazoketones involved Wolff rearrangement are featured with 1,2-shift of an alkyl or an aryl group to generate disubstituted ketenes. Due to their electrophilic nature, they are highly reactive acylating reagents to undergo addition reactions with a wide range of nucleophiles, including amines, to give α-substituted amides or other carboxylic acid derivatives [25]. Furthermore, with the use of asymmetrically substituted diazoketones, a chiral center is able to be created in the α-substituted carboxylic acid derivative products *via* the nucleophilic substitution to the prochiral ketenes [26,27].

Typically, Wolff rearrangements are conducted under thermal [28–33], metal-catalyzed [34–41], or photochemical conditions [42–51]. The photochemical Wolff rearrangement, which can be carried out at ambient temperatures without any other additives, thus is relatively milder, greener, less costly and more

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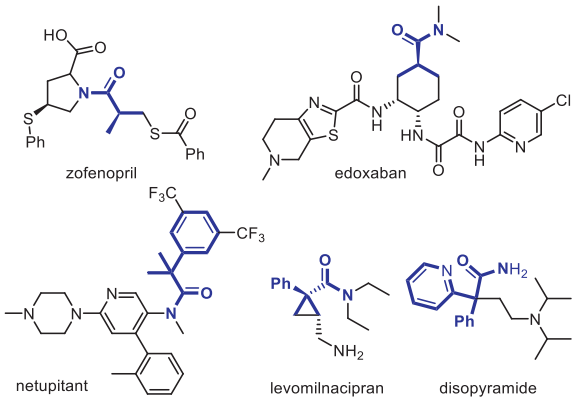
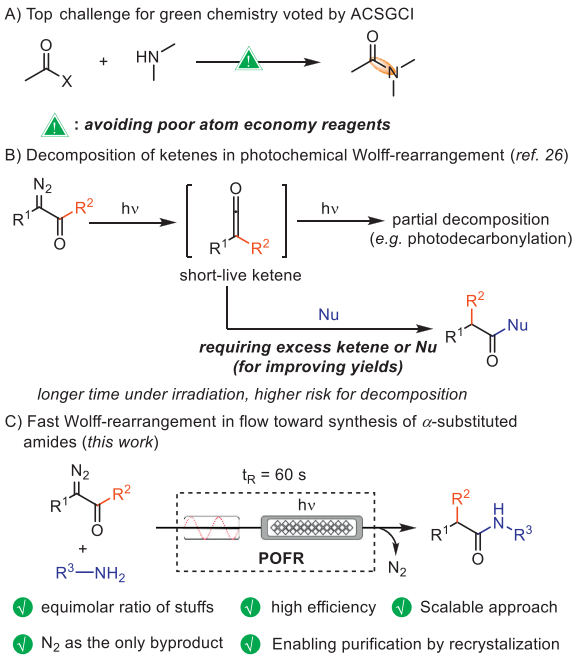


Scheme 1. α-Alkyl and α-aryl amide drugs.

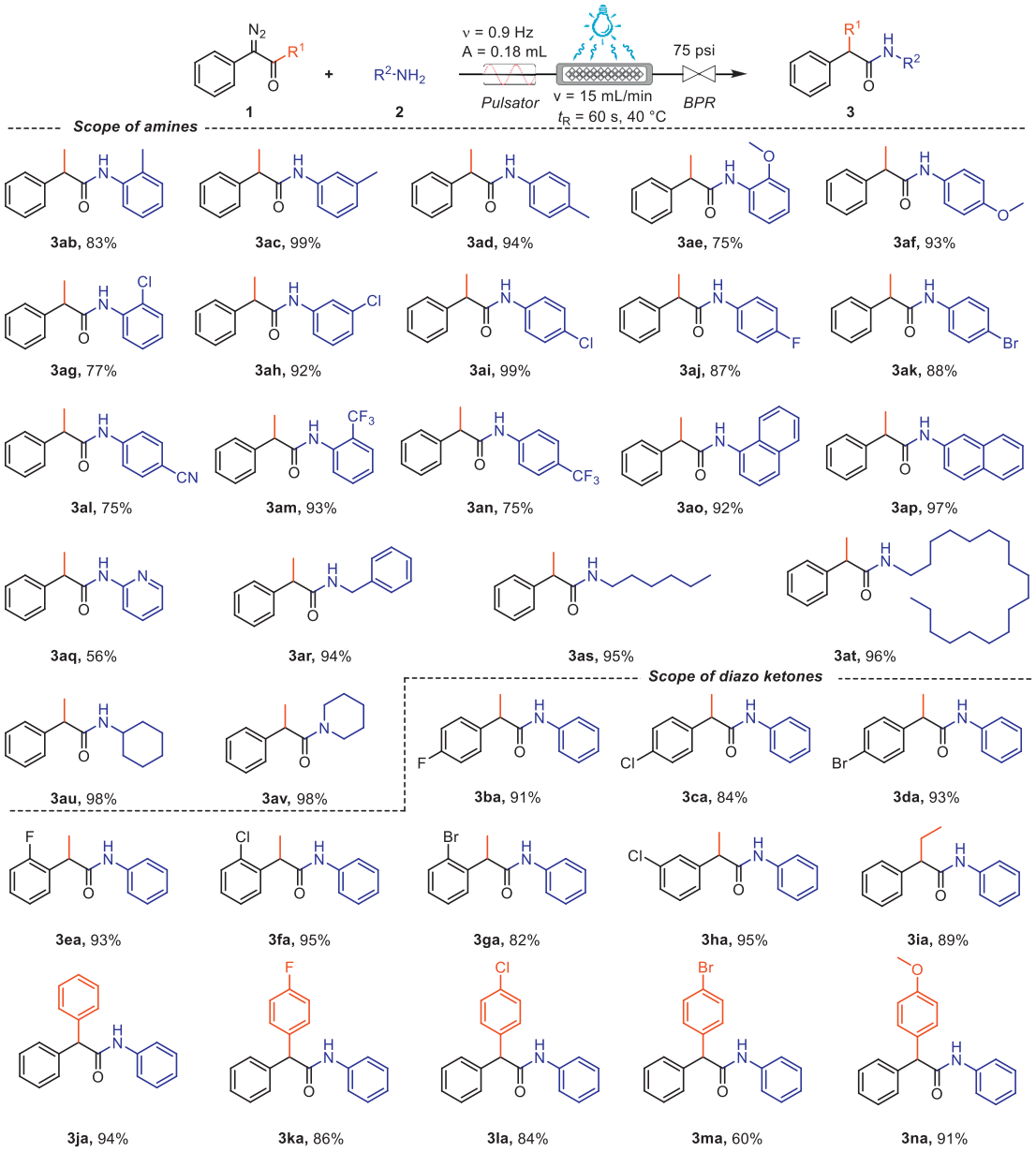


Scheme 2. (A) Top challenge for green chemistry voted by ACSGCI. (B) Decomposition of ketene under irradiation. (C) Fast Wolff-rearrangement in flow toward synthesis of α-substituted amides.

atom-economic than that under any other conditions. Nevertheless, photochemical reactions commonly suffer from a limited penetration depth in batch photochemical reactions. Therefore, photochemical Wolff rearrangement in batch usually shows unsatisfied efficiency, especially for scaling up reactions. To settle these issues, microreactors featured with large surface-to-volume ratio extremely enhance the mass and heat transfer properties, as well as improve the light penetration, thus is considered ideal for photochemical transformations [52–59]. Konopelski *et al.* reported the generation of ketenes by photochemical Wolff rearrangement in continuous flow for the first time in 2010, allowing the synthesis of β-lactams from α-dizao-β-ketoamides [60]. Thereafter, there are only isolated examples to date for the generation of ketenes *via* photochemical Wolff rearrangement in flow to take part in transformations, including cycloaddition, nucleophilic addition or Arndt–Eistert homologation [61–66]. However, a relatively long retention time (usually in minutes or even longer) is usually required for intermolecular reactions, which increases the risk of photodecomposition of ketenes [26,63], accompanying the generation of byproducts at the same time (Scheme 2B). Therefore, an excess amount of one of the reactants is required to improve the yields, and a procedure of column chromatography for product purification become necessary. Recently, Yoshida *et al.* developed a concept of flash chemistry, which allowed the reaction to proceed extremely fast (typically within a reaction time in the range from milliseconds to seconds), avoiding the decomposition of the active intermediate, so that realized some challenging reactions in micro reactors instead of flasks [67,68]. Enlighten by the concept of flash chemistry, we envisioned that fast photochemical Wolff rearrangement followed by fast nucleophilic addition, which occurs very rapidly, may avoid the photochemical decomposition of the short-live ketene intermediate and concurrently improve the utilization of the reactants. Therefore, an equimolar ratio or near equimolar ratio of reactants is possibly enough for such an efficient transformation so that the resulting product is produced with enough purity and can be easily separated from the mixture without the tedious chromatography procedure (Scheme 2C). To reach this goal, herein we showcase a fast photochemical Wolff rearrangement toward synthesis of a series of α-substituted amides.

At the outset, 1-diazo-1-phenylpropan-2-one (**1a**) and aniline (**2a**, 2 equiv.) were used as the model substrates in batch reactions to investigate the preliminary reaction conditions. Dichloromethane (DCM) was found to be better than any other tested solvents, including 1,2-dichloroethane, acetonitrile, toluene, tetrahydrofuran, *tert*–butyl methyl ether, and 1,4-dioxane (Table S1 in Supporting information), affording the desired product *N*,2-diphenyl-propanamide (**3aa**) in 94% yield. With the batch conditions in hand, next an initial flow experiment was conducted with a homemade micro-tubing photochemical reactor, but showed reaction efficiencies far behind our expectations. After careful investigation of the micro-structured reactors, a commercially available HANU^{TM} flow photochemical reactor (from Creaflow, for detail see Supporting information), which had a visualized internal flow channel equipped with a series of cubic static mixing elements and could be used in combination with an extra auxiliary oscillatory diaphragm pulsator to vibrate the flowing reaction mixtures for enhancing the split-and-recombine mixing [69–71], was found to be effective to promote the transformation under the irradiation of blue LEDs. When a solution of **1a** (0.04 mol/L) and **2a** (0.1 mol/L) in dichloromethane was pumped into the photochemical oscillatory flow reactor (POFR) at a flow rate of 1.5 mL/min (t_R = 600 s), the desired product, *N*,2-diphenyl-propanamide (**3aa**) was furnished in 96% yield with 50% maximum light intensity (LI) of the blue LEDs (Table 1, entry 1). Increasing the flow rate to 15 mL/min (t_R = 60 s) made an adverse effect on the yield albeit under the irradiation with maximum light intensity (entries 2 and 3). Nevertheless, embedding a back pressure regulator (BPR) (75 psi) into the downstream system to ensure a steady flow rate and to prevent cavitation facilitated the conversion of the reaction within a residence time of 60 s (entry 4), whilst no further improvement was observed by increasing the back pressure (entry 5). With the help of the back pressure regulator, the solution was allowed to be superheated and resulted in a better yield at 40 °C than that at either an elevated temperature or an ambient temperature (entries 6 and 7). Notably, the flow protocol was found to be robust even when the reactants were fed into the POFR in an equimolar ratio, yet without compromising the yield through the dilution of the reaction (entries 8–10). At this point, without much superfluous reactants remaining in the crude mixture after reaction, the product was easily purified from the mixture by recrystallization to give **3aa** in 96% yield under the optimal conditions (entry 10). Further shortening the residence time to 50 s brought a deleterious impact on the yield (entry 11).

With the optimal conditions in hand, we next turned our attention to investigating the substrate scope (Scheme 3). Electron-donating groups (Me, OMe) and electron-withdrawing groups (halides, CN, CF_3) are well tolerated on the phenyl ring of ani-

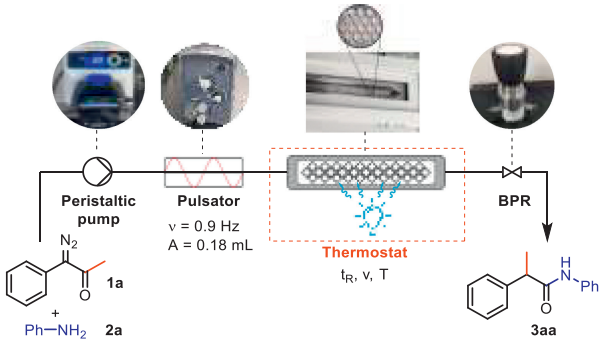


Scheme 3. Substrate scope.

lines (**2b**-**2n**). α- and β-naphthylamines (**2o**, **2p**) were employed and afforded the corresponding amides in 92% and 97% yield, respectively. Pyridin-2-amine (**2q**) was also a suitable substrate in our protocol albeit producing the product **3aq** in a moderate yield. To our delight, the substrate scope could be expanded to aliphatic amines, including benzylamine, and other primary and secondary amines that gave their corresponding amides **3ar**-**3av** in excellent yields. Additionally, a series of 1-diazo-1-phenylpropan-2-ones bearing halides were tested and produced the desired α-disubstituted amides in excellent yields (**3ba**-**3ha**), whilst the introduction of halides in these products offered opportunities for further derivatization. Besides the methyl group, ethyl (**3ia**) and aryl groups (**3ja**-**3na**) also migrated readily in the Wolff rearrangement, but a bromo atom on the phenyl ring had a negative impact on its migratory aptitude (**3ma**). Notably, all the above-mentioned products were isolated and purified by recrystallization.

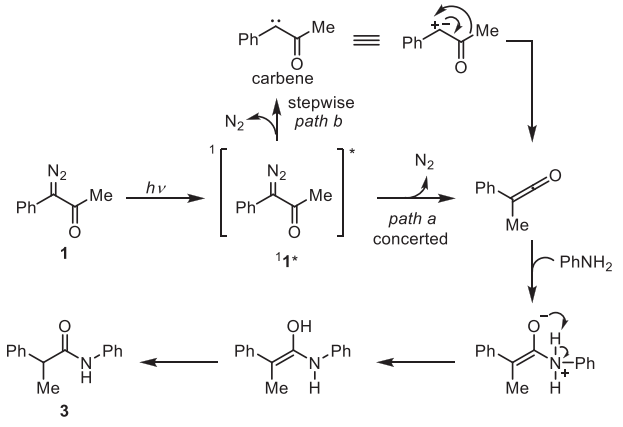
Control experiments were performed to understand the mechanism of the reaction. α-Diazoketone **1a** pumped to the reactor alone under the standard reaction conditions led to complete conversion to phenyl methyl ketene. Notably, the retention time was able to be reduced to less than 40 s without any deleterious effect on the conversion. Then the ketene intermediate was thoroughly converted to **3aa** after that the collected ketene solution was mixed with aniline and once again pumped into the POFR within a retention time of 60 s (Supporting information). It indicates that a fast Wolff rearrangement is involved and the rate of the whole reaction is limited by the rate of nucleophilic addition of amine to the ketene intermediate. Based on the control experiments and previous studies [22], a proposed mechanism is shown in Scheme 4. An excited singlet state of α-diazo ketone (^{1}**1***) resulting from irradiation undergoes decomposition to generate a ketene intermediate *via* two pathways. Ketene is possibly formed by a concerted nitrogen extrusion and 1,2-shift of the methyl group (path a). Another pathway involves a stepwise process in which a singlet state α-oxo-carbene intermediate is produced *via* nitrogen extrusion followed by the methyl group migration (path b). Finally,

Table 1
Reaction optimization with the use of POFR in flow.[a]



Entry	ν (mL/min)	t_R (s)	C_{1a} (mol/L)	C_{2a} (mol/L)	Yield (%)[f]
1[b,d]	1.5	600	0.04	0.1	96
2[c,d]	3	300	0.04	0.1	95
3[d]	15	60	0.04	0.1	53
4	15	60	0.04	0.1	75
5[e]	15	60	0.04	0.1	76
6[g]	15	60	0.04	0.1	82
7[h]	15	60	0.04	0.1	80
8[g]	15	60	0.02	0.5	84
9[g]	15	60	0.01	0.025	88
10[g]	15	60	0.01	0.01	96
11[g]	18	50	0.01	0.01	85

[a] Under the irradiation of 596 W blue LEDs (460 nm, light intensity = 100%) at 75 psi back pressure and room temperature.
[b] Light intensity = 50%.
[c] Light intensity = 90%.
[d] Without BPR.
[e] BPR (100 psi) was used.
[f] Isolated yield.
[g] 40 °C.
[h] 60 °C.

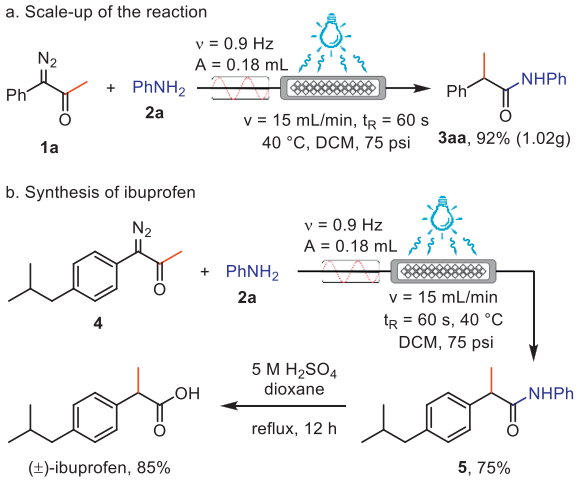


Scheme 4. Proposed mechanism.

the amide **3** is furnished by the addition of aniline to the ketene intermediate.

To demonstrate the synthetic value of this protocol, the reaction was performed on a 5 mmol scale to produce 1.02 g **3aa** with 92% yield after recrystallization (Scheme 5a). Additionally, the present protocol may provide an alternative for the preparation of bioactive α-alkyl-α-arylcarboxylic acid derivatives. For instance, 2-(4-isobutylphenyl)-*N*-phenylpropanamide **5** was readily prepared under the standard conditions from the diazo ketone **4** and aniline, which could be further hydrolyzed into (±)-ibuprofen, a popular anti-inflammatory drug (Scheme 5b).

In conclusion, we have developed a fast photochemical Wolff rearrangement toward synthesis of a range of α-substituted amides with the use of a POFR under visible-light irradiation. Control experiment indicates that a fast process of the Wolff rearrangement (<40 s) is involved. The present protocol is easily scalable, and does not require the excess use of any reactants, and the α-substituted amides could be isolated by recrystallization in good to excellent yields.



Scheme 5. Synthetic application.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Huashan Huang: Investigation. **Jingze Chen:** Investigation. **Luyun Zhang:** Investigation. **Hong Yan:** Writing – review & editing, Writing – original draft. **Siqi Li:** Investigation. **Fen-Er Chen:** Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109992.

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