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Visible-light-mediated late-stage N-functionalization of unprotected peptides: introducing the aza-Zimmerman–O'Connell–Griffin reaction†

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Amides represent a crucial class of compounds in organic chemistry, forming key structural components of biologically significant molecules such as amino acids and peptides. There is a growing need for sustainable methods to synthesize amides that do not rely on coupling reagents or extensive derivatization of carbonyl compounds. In this context, we present an alternative approach for amide synthesis and α-amino acid and peptide functionalization, utilizing the ketene intermediate generated through the photomediated Zimmerman–O'Connell–Griffin (ZOG) rearrangement. This method offers a more sustainable route for late-stage functionalization of peptides, with potential applications in medicinal chemistry, providing a greener alternative to conventional synthetic strategies.

Green foundation

1. The present reaction is one of the few examples of amide coupling that proceeds through photogenerated ketenes. We hope this chemistry will inspire chemists to develop new photochemical transformations that utilize photonic energy rather than chemical energy to generate activated carbonyl reagents for amide couplings and related reactions.
2. In our developed reaction, we can convert a broad plethora of amines into amides and N-functionalized peptides. The reaction generally proceeds in high yields. Purification typically requires no column chromatography, which saves solvent. The reaction does not require any reagents—only light is needed.
3. The reaction could become even greener if we manage to make it solvent-free and reduce the reaction time. We are currently working on expanding the scope of the reaction, which could naturally lead to new transformations and contribute to the growing repertoire of green chemical processes.

1 Introduction

Amides are a cornerstone in organic chemistry, playing pivotal roles in biochemistry, pharmaceuticals, and materials science. Their widespread presence in both natural products and synthetic molecules highlights their importance, with amide bond formation recognized as the most frequently employed reaction in medicinal chemistry.[1] The formation of amides typically involves the reaction of a carboxylic acid with an amine, a process often facilitated by coupling reagents (Scheme 1a).[2]

Alternatively, amides can also be synthesized through the reaction of amines with ketenes, a method that offers distinct advantages in terms of reactivity and simplicity. Both approaches are widely recognized for their efficiency and versatility, catering to various synthetic needs.[3]

However, amide coupling reactions are not without drawbacks. A major limitation is their poor sustainability, as many coupling reagents generate stoichiometric amounts of waste. Additionally, some reactions produce corrosive byproducts, such as HCl or HBr, which can degrade sensitive reagents or products or complicate purification and require specialized handling (Scheme 1b). These factors highlight the need for more sustainable and efficient methods in amide synthesis.

From the perspective of green chemistry, the Zimmerman–O'Connell–Griffin (ZOG) reaction represents an underdeveloped yet promising methodology.[4–6] This reaction facilitates

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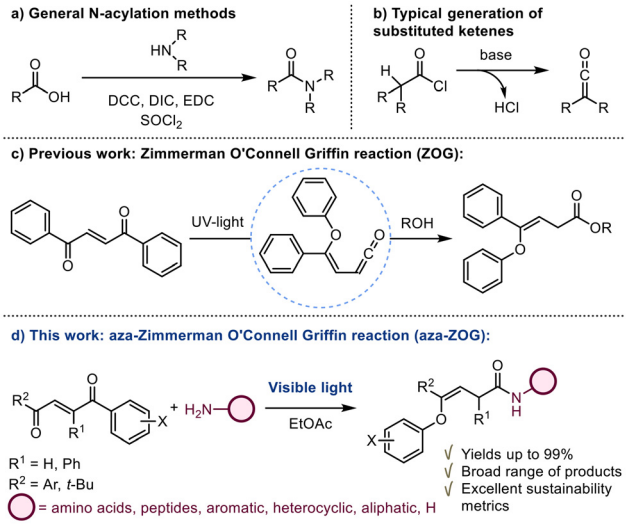
†Electronic supplementary information (ESI) available: Materials and methods, upscaling experiments, green metrics, general synthetic procedure for N-functionalized α-amino acids **3aa–3ar**, general synthetic procedure for amides **5aa–5an**, general synthetic procedure for substrate scope of DBE **3bc–3je**, synthetic procedure for the synthesis of N-functionalized peptides **7aa–7af**, synthesis of **8**, synthesis bifunctional molecule **9**, and characterization by ^{1}H, ^{13}C{^{1}H} NMR, HRMS, IR, melting point and physical description of all molecules synthesized. See DOI: https://doi.org/10.1039/d5gc02108a



Scheme 1 (a) *N*-Acylation by using coupling reagents on carboxylic acids. (b) Typical generation strategy of substituted ketenes. (c) Previous work: ZOG reaction generating ketenes solely by UV irradiation. (d) This work: development of the visible-light-driven aza-ZOG reaction.

the photogeneration of ketenes from 1,2-dibenzoylethylenes (DBE) under mild reaction conditions, without the need for additional reagents (Scheme 1c). Originally, the reaction was conducted under UV light, but it suffered from low yields, limiting its synthetic utility. In 2023, our group reported a significant advancement in this area, demonstrating a visible light promoted synthesis of substituted β-lactams and β-lactones *via* a regioselective, version of the ZOG reaction, wherein the ketene intermediate was intercepted in a [2 + 2] cycloaddition by imines or aldehydes, respectively.[7] Building on this work, we hypothesized that the ketene generated through the ZOG rearrangement could be intercepted by amine nucleophiles, offering a sustainable and efficient strategy for amide synthesis (Scheme 1d). Herein, we present a visible-light-driven, reagent-free, and chemoselective amidation reaction, termed the aza-Zimmerman–O'Connell–Griffin (aza-ZOG) reaction, which exhibits a broad substrate scope, including unprotected amino acids and peptides. This methodology highlights the potential of the ZOG reaction as a green and versatile tool for organic synthesis, particularly in the context of late-stage functionalization and peptide chemistry.

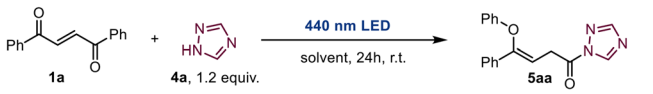
2 Results and discussion

2.1 Optimization

Our study of the aza-ZOG reaction commenced by performing an optimization by reacting (*E*)-1,4-diphenylbut-2-ene-1,4-dione (*E*-DBE) **1a** with 1*H*-1,2,4-triazole **4a**.

Initial optimisation established our standard conditions with ethyl acetate as an excellent reaction solvent giving **5aa** in 95% yield. Other solvents were also employed to evaluate the influence of the solvent in the reaction. Firstly, less polar aprotic solvents were investigated, namely toluene and hexane (Table 1, entries 2 and 3). The reaction proceeded efficiently in dry toluene, affording **5aa** in a 97% yield (Table 1, entry 2). However, when *n*-hexane was used as the reaction medium, no formation of product **5aa** was observed, and all *Z*-DBE remained unreacted, likely due to the low solubility of the starting materials in this solvent (Table 1, entry 3).

Table 1 Optimization of the aza-ZOG reaction



Entry	Deviation from standard conditions	Yield % of **5aa**[a]
1	None	95[b]
2	Toluene as solvent	97
3	*n*-Hexane as solvent	n.r.
4	Acetonitrile as solvent	67
5	Dichloromethane as solvent	85
6	Tetrahydrofuran as solvent	98
7	Diethyl ether as solvent	91

[a] Yields measured by NMR quantification against standard dimethylsulfone. [b] Isolated yield.

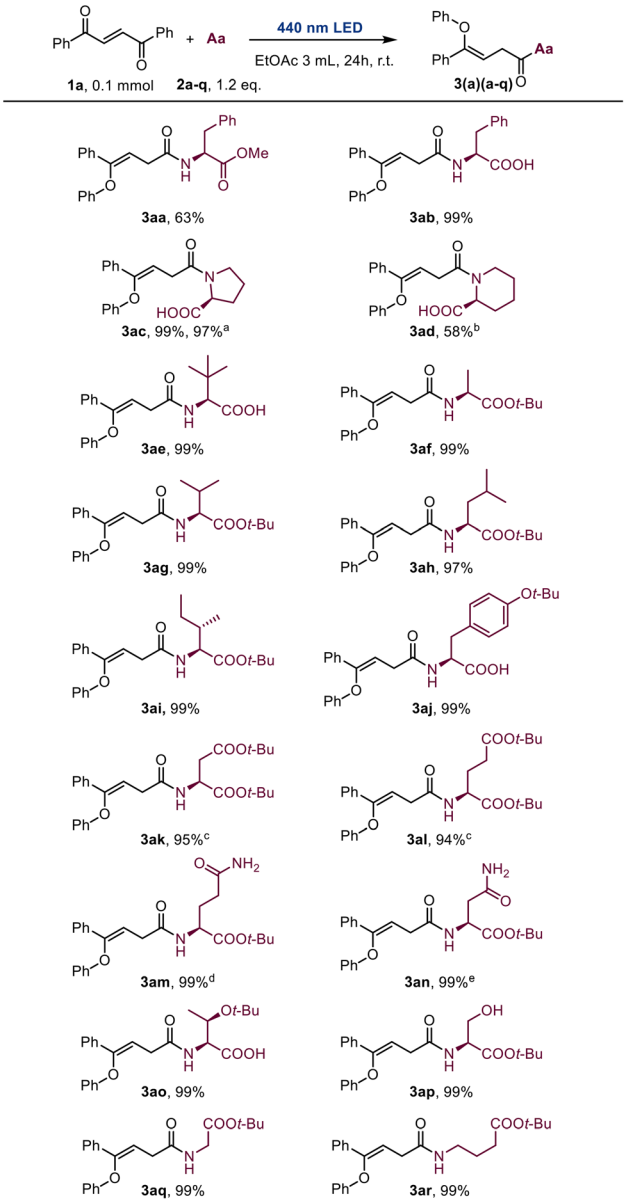
Dry polar aprotic solvents were well tolerated, yielding moderate to excellent conversions of **5aa**, with yields reaching up to 98% with THF as the reaction solvent (Table 1, entry 6). Despite these results, ethyl acetate was selected as reaction solvent for further investigations due to its low toxicity, biodegradability, low environmental impact, pharmaceutical compatibility and favorable performance under standard conditions (Table 1, entry 1). Consequently, these conditions were employed in the exploration of the substrate scope of the aza-ZOG.

2.2 Substrate scope of amino acids

After establishing the optimal conditions for the aza-ZOG reaction, the investigation was extended to explore the reactivity of various *N*-nucleophiles with *E*-DBE, including amino acids (Scheme 2).

Initially, **1a** was reacted with the methyl ester of L-phenylalanine, yielding product **3aa** in 63% after purification *via* column chromatography. Subsequently, the reaction was performed using unprotected L-phenylalanine as a nucleophile, where a simple filtration through a syringe filter was sufficient to obtain the pure product **3ab** in quantitative yield.

Similarly, L-proline underwent the reaction under the same conditions, affording **3ac** in quantitative yield. Remarkably, we were able to scale this reaction up to 3 mmol without detriment in performance while avoiding chromatographic purification, rendering 97% yield of **3ac** (see ESI for scaling up protocols†). The reaction of **1a** with pipecolic acid (**2d**) rendered the targeted product **3ad** as a mixture of rotamers in 58% yield. However, when unprotected alanine was employed as a nucleophile, the yield decreased significantly to a 15%, necessitating purification *via* column chromatography (not included



Scheme 2 Substrate scope of amino acids run under optimal conditions of Table 1. [a]Yield from the upscaling experiment. [b]Reaction performed at 0.125 mmol scale. [c]1.05 equivalents of nucleophile. [d]2 equivalents of nucleophile. [e]4 equivalents of nucleophile.

in Table 1). A potential explanation could be that alanine forms an electron-donor–acceptor (EDA) complex with *E*-DBE (**1a**). This observation is in line with previous studies from our research group on EDA chemistry that have demonstrated that DBE can act as an acceptor in EDA mediated reactions, forming EDA complexes with electron-rich, sterically unhindered amines.[8–10] To mitigate this effect, the bulkier L-*tert*-butyl leucine was tested as a nucleophile for the aza-ZOG, resulting in a clean and quantitative reaction, yielding 99% of **3ae**.

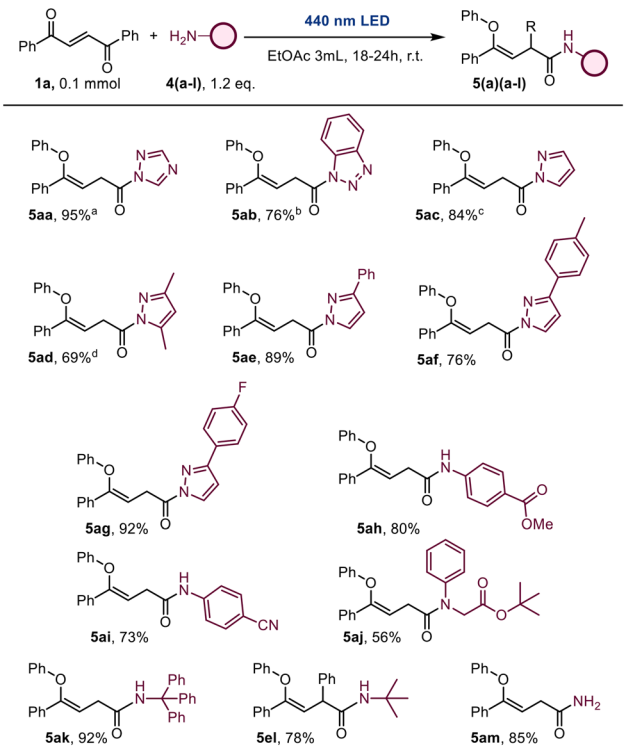
Following this trend, sterically hindered amino acids containing a *tert*-butyl ester were evaluated to suppress side reactivity. *tert*-Butyl L-alaninate afforded product **3af** in quantitative yield, a trend that was consistently observed for **3ag**, **3ah**, **3ai**, **3aq**, and **3ar**. To functionalize L-tyrosine *via* the aza-ZOG reaction, the substrate *O*-*tert*-buty-L-tyrosine was employed to prevent undesired reactivity from the phenolic –OH group, affording the desired product **3aj** in 99% yield.

Reducing the equivalents of di-*tert*-butyl esters of L-aspartic acid and L-glutamic acid from 1.2 to 1.05 equivalents was necessary to obtain clean products **3ak** and **3al** after filtration in 95% and 94% yields respectively. The reason for this reduction of equivalents was that the di-*tert*-butyl esters exhibited higher solubility in ethyl acetate than other *tert*-butyl esters of amino acids. In the case of product **3am**, in which an amide group is also present, increasing the equivalents of *tert*-butyl L-glutaminate from 1.2 to 2 equivalents resulted in complete selectivity towards the amine. A similar scenario was observed for **3an**, where 4 equivalents of *tert*-butyl L-asparaginate were used to suppress the formation of byproducts. As no chromatography was required, the excess material could be recovered.

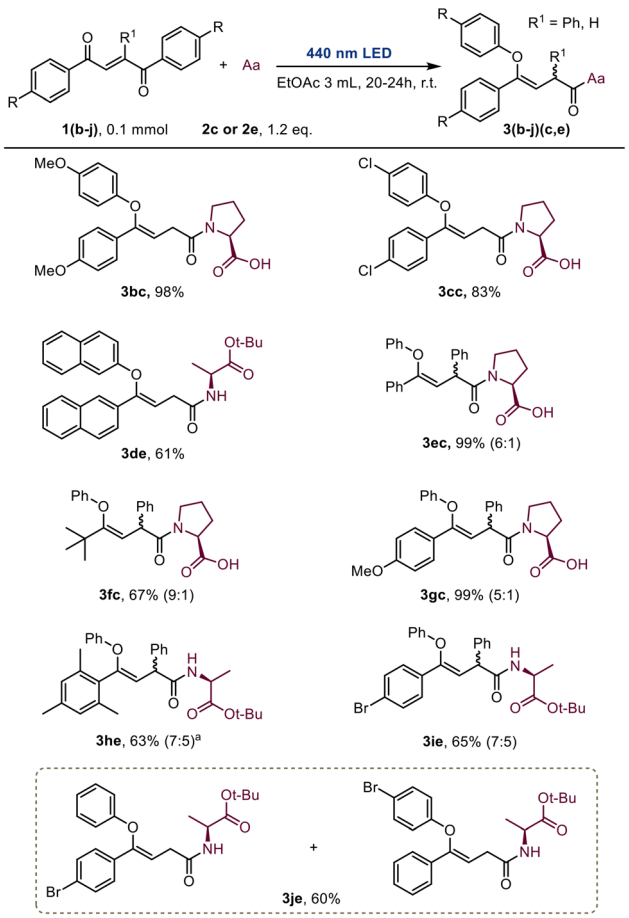
It was anticipated that employing a *tert*-butyl protecting group on the secondary alcohol of *O*-(*tert*-butyl)-L-threonine would prevent the side reaction in which the hydroxyl group acts as a nucleophile, successfully resulting in a quantitative yield of **3ao**. Interestingly, when *E*-DBE was reacted with *tert*-butyl L-serinate, containing an unprotected primary alcohol, complete selectivity for amine functionalization was observed, yielding **3ap** in 99%.

2.3 Substrate scope of various *N*-nucleophiles

Furthermore, the reactivity of this rearrangement was investigated using a variety of amines (Scheme 3). Unsubstituted heterocyclic amines, including 1*H*-1,2,4-triazole, 1*H*-benzo[*d*][1,2,3]triazole, and 1*H*-pyrazole, successfully participated in the reaction, affording the corresponding products **5aa**, **5ab**, and **5ac** in 95%, 76%, and 84% yield, respectively. Substituted heterocyclic amines containing electron-donating groups, such as 3,5-dimethy-L-1*H*-pyrazole, 3-phenyl-1*H*-pyrazole, and 3-(*p*-tolyl)-1*H*-pyrazole, demonstrated good nucleophilicity, yielding products **5ad**, **5ae**, and **5af** in 69%, 89%, and 76% yield, respectively. Additionally, the heterocyclic amine 3-(4-fluorophenyl)-1*H*-pyrazole, bearing an electron-withdrawing *p*-fluorophenyl group, exhibited excellent reactivity, producing **5ag** in 92% yield. Electron-deficient anilines methyl 4-aminobenzoate and 4-aminobenzonitrile were effective nucleophiles, providing the corresponding products **5ah** and **5ai** in good yields of 80% and 73%, respectively. *tert*-Butyl phenylglycinate also worked well in the transformation delivering the **5aj** in 56% yield. Of note, is that the *N*-phenyl glycine is a competent donor in EDA reactions together with unsaturated carbonyl compounds.[11] Further strengthening the hypothesis that bulky amines divert the reactivity from EDA chemistry to the ZOG reactivity. In line with this observation, bulky amines, such as triphenylmethanamine, also proved to be effective nucleophiles in this transformation, affording the desired product **5ak** in 92% yield. Similarly, the aliphatic amine *tert*-butyl



Scheme 3 Substrate scope with amines as nucleophiles run under the optimal conditions of Table 1. [a]The reaction was performed using 0.2 mmol of **1a** and 1.07 equivalents of 1*H*-1,2,4-triazole. [b]The reaction was performed using 0.2 mmol of **1a** and 4.2 equivalents of 1*H*-benzo[*d*][1,2,3]triazole. [c]The reaction was performed using 0.11 mmol of **1a** and 6.6 equivalents of 1*H*-pyrazole. [d]1.4 equivalents of nucleophile.



Scheme 4 Substrate scope of *E*-DBE run under the optimal conditions of Table 1. [a]Irradiated for 48 hours.

amine demonstrated good reactivity, yielding **5el** in 78% after isolation. Finally, the reaction of *E*-DBE with ammonium acetate was explored, wherein ammonium acetate functioned as a nucleophile, leading to the formation of the primary amide **5am** in 85% yield.

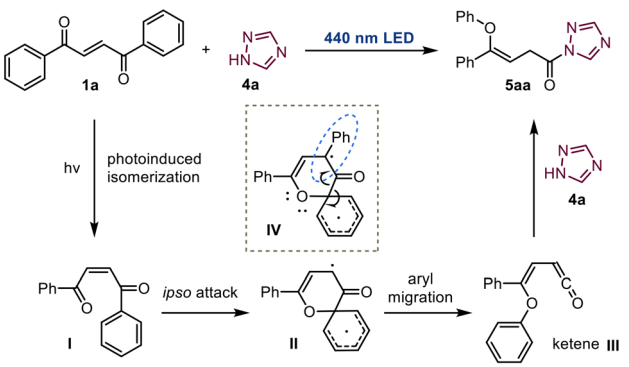
2.4 Substrate scope of *E*-DBE

The reactivity of various *E*-DBE derivatives possessing different steric and electronic properties was also investigated (Scheme 4). The di-*p*-methoxy-substituted DBE (**1b**) exhibited good compatibility with the ZOG rearrangement when reacted with L-proline, affording product **3bc** in 98% yield. Similarly, the di-*p*-chloro-substituted *E*-DBE underwent the reaction efficiently, yielding **3cc** in high yield when coupled with L-proline.

For more sterically hindered *E*-DBE derivatives, such as the substrate bearing two naphthyl groups (**1d**), the reaction proceeded with a yield of 61% for **3de** when employing the *tert*-butyl ester of L-alanine as the nucleophile. When *E*-DBE **1e**, incorporating an additional phenyl group, was subjected to the reaction with L-proline, the formation of a new stereogenic centre was observed post-rearrangement, resulting in **3ec** with a 99% yield and a diastereomeric ratio of 6 : 1.

Additionally, a *E*-DBE derivative in which one of the phenyl substituents was replaced by a *tert*-butyl group was evaluated, demonstrating that the rearrangement still proceeded successfully, yielding **3fc** in 67%. However, a prolonged irradiation time of 48 hours was required for complete consumption of the starting material.

The mono-*p*-methoxy-substituted DBE (**1g**) displayed total selectivity for the migration of the unsubstituted phenyl group during the rearrangement, presumably due to stabilization of the radical intermediate **IV** (Scheme 5) by the phenyl substitu-



Scheme 5 Proposed mechanism for aza-ZOG rearrangement.

ent, yielding **3gc** in 99% with a diastereomeric ratio of 5 : 1. This selective migration of the unsubstituted phenyl group was also observed in the formation of **3he** and **3ie**, obtained in 63% and 65% yield, respectively, with diastereomeric ratios of 7 : 5.

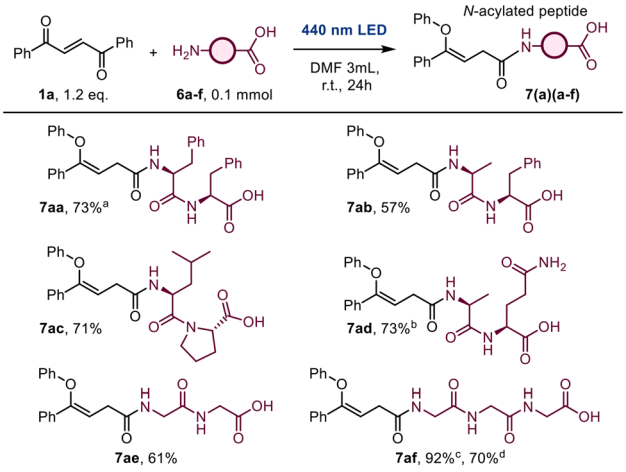
In contrast, when a mono-*p*-bromo-substituted DBE (**3j**) lacking a stabilizing phenyl ring was tested, a near-equimolar (1 : 1) mixture of products was obtained for **3je**, suggesting that both phenyl groups migrated with comparable probability.

2.5 Proposed mechanism for the aza-ZOG reaction

Scheme 5 illustrates the proposed mechanism of the aza-ZOG rearrangement. Upon irradiation, the *E*-DBE undergoes rapid isomerization to the *Z* isomer **I** within 30 minutes. Subsequently, continued irradiation excites the n–π* electrons of one ketene which subsequently perform an *ipso* attack on the phenyl group located on the opposite side of the molecule, forming a new oxygen-carbon bond, resulting in the formation of the intermediate **II**. Following this step, electronic reorganization occurs in which the aryl ring migrates, yielding the ketene intermediate **III**. The highly reactive ketene is then attacked by a nitrogen-containing nucleophile, leading to the formation of the final product (**5aa**).

2.6 Functionalization of peptides with the aza-ZOG reaction

The applicability of the aza-ZOG rearrangement was extended to peptide functionalization (Scheme 6). The initial attempt involved the reaction of L-phenylalanyl-L-phenylalanine (**6a**) under the optimized conditions outlined in Table 1, successfully yielding the functionalized product (**7aa**) in 73% yield.



Scheme 6 Scope of peptides functionalized with the aza-ZOG rearrangement. [a]The reaction solvent was dry ethyl acetate, 1.2 equivalents of diphenylalanine were used respect 0.1 mmol of *E*-DBE and the product was cleaned by cooling down to −20 °C and syringe filtration. [b]Was used 1 equivalent of *E*-DBE and the reaction was irradiated for 48 hours. [c]The reaction was irradiated for 48 hours and was purified by wash of the solids with diethyl ether and centrifugation. [d]Yield from the upscaling experiment.

Subsequently, *E*-DBE was reacted with L-alanyl-L-phenylalanine (**6b**) using ethyl acetate as the solvent; however, no reaction was observed, and both the dipeptide and *Z*-DBE were recovered unreacted. It was suspected that this result was due to a solubility issue, and consequently the solvent was changed to dry DMF, a medium in which peptides exhibit higher solubility. Under these modified conditions, the reaction proceeded successfully, affording the desired product (**7ab**) in 57% yield. Furthermore, L-leucyl-L-proline (**6c**) and glycylglycine (**6e**) were successfully functionalized with *E*-DBE, yielding **7ac** in 71% and **7ae** in 61% under the established peptide functionalization conditions.

However, a slight modification of the reaction conditions was necessary to obtain **7ad** in 73% yield, employing 1 equivalent of *E*-DBE to prevent functionalization at the primary amide of the L-glutamine residue. Additionally, an extended reaction time of 48 hours was necessary to ensure complete consumption *Z*-DBE for this same reaction. For the synthesis of the functionalized tripeptide **7af** (92% yield), the reaction was irradiated for 48 hours to maximize the conversion of *Z*-DBE. Due to the insolubility of **7af** in organic solvents, purification was achieved through a simple washing step with diethyl ether and centrifugation to remove any residual unreacted *Z*-DBE. In addition, we were able to scale this reaction up to 2.5 mmol without detriment in performance while avoiding chromatographic purification rendering 70% yield of **7af** (see ESI for scaling up protocols†).

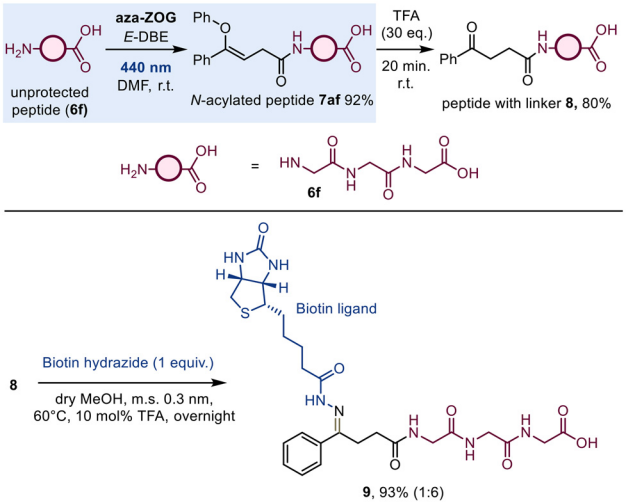
2.7 Application of the protocol installing a linker on peptides

We hypothesized that the (*Z*)-4-phenoxy-4-phenylbut-3-en fragment remaining after N-functionalizing peptides with *E*-DBE under visible light could serve as a linker for late-stage functionalization of unprotected peptides. Our investigation revealed that hydrolysis of the *O*-phenyl enolate could be achieved using trifluoroacetic acid (TFA), yielding the structure **8** in 80% yield as shown in Scheme 7. The structure **8** is a N-functionalized unprotected peptide with a linker that contains a ketene functional group, susceptible of undergoing several chemical transformations. These transformations include the formation of imines, hydrazones or oximes to create bifunctional molecules,[12] keto–enol reactions or reduction to hydroxyl group.

The N-functionalized peptide **8** was then reacted with a stoichiometric amount of biotin hydrazide, resulting in the formation of a hydrazone bond, yielding bifunctional molecule **9** in 93% crude yield with a *Z*/*E* stereoisomer ratio of 1 : 6. Considering the critical role of biotin in chemical biology[13] and its relevance in the development of novel therapeutics,[14] including antibody–drug conjugates, this methodology for late-stage functionalization of unprotected peptides presents promising opportunities for the discovery of new bioactive molecules.

2.8 Sustainability assessment

Encouraged by the excellent results observed, we decided to carry out an unbiased assessment of the environmental



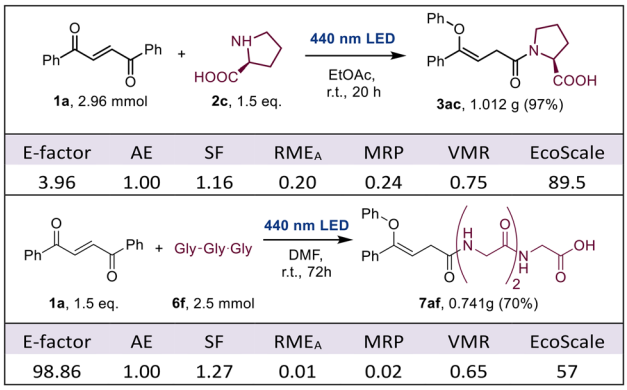
Scheme 7 Application of the aza-ZOG reaction for functionalizing peptides with a ketyl linker by hydrolysis with trifluoroacetic acid and reactivity on the linker.

impact of the aza-ZOG reaction under the conditions described herein. We thus selected the gram scale preparation of **3ac** and **7af** as representative examples of our methodology. Regarding quantitative metrics, we calculated the *E*-factor,[15] stoichiometric factor (SF),[16] atom economy (AE),[17] Andraos' reaction mass efficiency (RME_A)[18] and materials recovery parameter (MRP).[19,20] The four metrics were combined along with yield into a vector magnitude ratio (VMR) to provide a quick view of the overall material efficiency of the protocol. To address qualitative aspects, we determined the EcoScale scores for both synthetic protocols (Table 2).[21]

Beginning with the synthesis of **3ac**, the obtained metrics highlight the excellent material efficiency of the aza-ZOG reaction. The *E*-factor is remarkably low, firmly within the desired range for the elaboration of bulk chemicals (1 to 5), greatly benefitting from avoiding chromatography. In addition to near-quantitative yield, the intrinsic mechanism of this transformation implies a perfect 1.00 (*i.e.*, 100%) AE value. The SF deviates from ideality slightly due to the excess **2c** required, although this is mostly negated by the possibility of completely recovering the unreacted material. Indeed, almost complete recovery of both solvent and excess **2c** was achieved, which shows in the outstanding values of RME_A and MRP and plays a huge role in the excellent *E*-factor observed. Overall, the material efficiency of this reaction is excellent, with a VMR of 0.75 (of 1). Regarding the EcoScale, this protocol is only held back slightly due to the flammability of ethyl acetate and the requirement for dry conditions but is otherwise firmly classified as excellent (above 75 points).

The numbers for the preparation of **7af** are significantly lower although they are still very good considering the significantly higher difficulty of the transformation in hand. The *E*-factor is within the desired range for the manufacture of pharmaceuticals (25 to 100). AE is still 1, being the same type

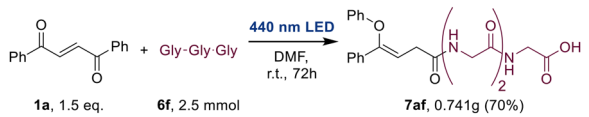
Table 2 Sustainability assessment



E-factor	AE	SF	RME_A	MRP	VMR	EcoScale
3.96	1.00	1.16	0.20	0.24	0.75	89.5

E-factor	AE	SF	RME_A	MRP	VMR	EcoScale
98.86	1.00	1.27	0.01	0.02	0.65	57

E-Factor	AE	SF	RME_A	MRP	VMR	EcoScale
3.96	1.00	1.16	0.20	0.24	0.75	89.5



E-Factor	AE	SF	RME_A	MRP	VMR	EcoScale
98.86	1.00	1.27	0.01	0.02	0.65	57

of reaction and SF is a touch higher than before, due to the lower yield, but still good, nonetheless. RME_A and MRP are both lower due to the lower relative recovery of materials, which is limited to the diethyl ether used to precipitate and wash the material. Still, the material efficiency is very good, with a VMR of 0.65. The EcoScale highlights the effects of the lower yield and the solvents used, although remains an acceptable protocol (50 to 75 points). At this point, it is important to note that the lower numbers observed mostly come from the necessity of using DMF to solubilize **6f**, which will be present in one way or another on most protocols using it as a substrate. Remarkably, we still completely avoid chromatographic purification, which would add 1500 to 2500 points to the *E*-factor and 10 penalty points to the EcoScale. We also dealt with logistic constraints which forced us to rely on azeotropic distillation with toluene to remove the DMF, rather than using a high vacuum apparatus. Avoiding toluene and recovering the solvent would imply an *E*-factor of around 17 and an EcoScale of 62, besides much increased RME_A and MRP scores. In general, the numbers obtained for both protocols highlight the exceptional sustainability of the aza-ZOG reaction.

3. Conclusions

In summary, we have developed a novel transformation by adapting the ZOG rearrangement to accommodate nitrogen nucleophiles, resulting in the aza-ZOG reaction. This methodology demonstrates broad substrate scope, tolerating a wide

range of *N*-nucleophiles including N-heterocycles, aromatic and aliphatic amines, sterically hindered amines, and ammonium salts. The reaction is effective for the direct functionalization of amino acids (up to 99% yield) and unprotected peptides (up to 92% yield), with scalability and minimal purification requirements, eliminating the need for chromatographic separation in many cases. This compares exceptionally well with recent advances in photochemical peptide bond formation.[22,23] Sustainability metrics further highlight the environmental compatibility of this protocol. Importantly, the installation of ketene linkers on peptides enables subsequent derivatization, offering valuable opportunities for late-stage peptide modification and the development of bifunctional biomolecules.

Author contributions

The conceptualization of the project was developed by the authors H. Sundén and S. Bacaicoa. The experimental and analytical work was carried out by S. Bacaicoa, W. Yhlen Graf, M. Martos, A. Runemark, G. Shinde, G. Ghotekar. The sustainability assessment was performed by M. Martos. The manuscript and ESI were written by S. Bacaicoa, H. Sundén and M. Martos.†

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its ESI.†

Acknowledgements

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