

Direct access to unnatural cyclobutane α -amino acids through visible light catalyzed [2+2]-cycloaddition

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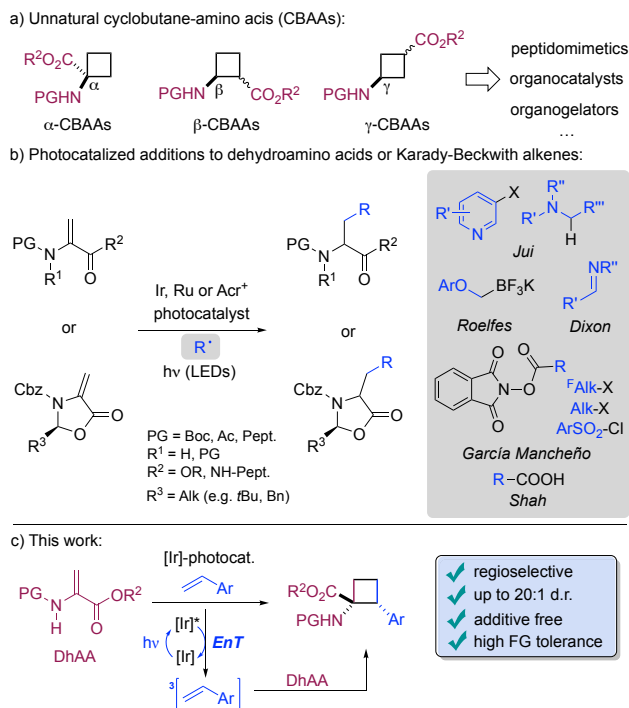
ABSTRACT: In this work, we report the first, selective, photocatalyzed [2+2]-cycloaddition of dehydroamino acids with styrene-type olefins. This simple, mild and scalable approach relies on the use of the triplet energy transfer catalyst [Ir(dFCF₃ppy)₂dtbpy]PF₆ under visible light irradiation and provides fast access to value-added substituted strained cyclobutane α -amino acid derivatives.

INTRODUCTION

Amino acids play an essential role in modern life sciences as they are precursors for chiral auxiliaries,^{1,2} catalysts³ and numerous drugs.⁴ Regarding their biological activity, they present a limitless source for novel structurally diverse target molecules. However, poor physical properties and low metabolic stability amongst others remain considerable challenges in peptide drug design.^{5,6} To overcome these challenges the modification of natural amino acid side chains, as well as the introduction of unnatural amino acids, has proven advantageous.⁷

In this regard, cyclobutane amino acids (CBAAAs)⁸ have evolved as an interesting class of derivatives for the development of new classes of strained, conformational restricted peptide mimetics for medical applications, as well as diverse uses as synthetic building blocks or catalysts.⁹⁻¹² As a result, many efforts have been set to the synthesis of cyclobutane α -,¹³⁻¹⁵ β -,¹⁶⁻¹⁹ and γ -amino acids²⁰⁻²² (Scheme 1a). However, although some derivatives exhibit potent biological activities,²³⁻²⁵ cyclobutane α -amino acids have lately received much less attention, which might be due to a lack of efficient, straightforward approaches for their preparation.²⁶⁻²⁸

In the past few years, visible light photocatalysis²⁹⁻³¹ has emerged as a general, potent and versatile synthetic tool. The mildness of this growing technology has recently also allowed for derivatization of amino acids by selective C-C bond formation reactions.³²⁻³⁷ Recent developments in this field include photoredox catalyzed additions of photooxidative generated radicals into α,β -dehydroamino acids (DhAAs) (Scheme 1b).³⁸⁻⁴³ However, despite its tremendous potential, no photocatalytic [2+2]-cycloaddition^{44,45} with this type of dehydroamino acids that will permit the direct construction of the aimed α -CBAAAs have been reported to date. Indeed, only scarce examples involving formal [2+2]-cycloaddition methodologies have been described, which rely on thermal²⁶ or Al-based Lewis acid promoters.^{27,28}



Scheme 1. a) Cyclobutane amino acids (CBAAAs), b) previous photocatalytic functionalization of dehydroamino acids (DhAAs); and c) this work on visible light mediated photocatalyzed energy transfer [2+2]-cycloaddition towards CBAAAs.

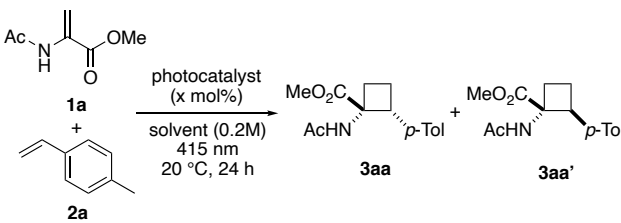
Inspired by earlier works on energy transfer (EnT) photocatalysis⁴⁶ and our previous contribution to photocatalyzed radical additions towards unnatural amino acids,^{42,47} we envisioned an unprecedented method for the functionalization of α,β -dehydroamino acids using a photocatalytic, visible light mediated [2+2]-cycloaddition. Hence, it provides ready access to a variety of cyclobutane 2-substituted α -amino acids, while allowing

for high selectivity and functional group (FG) tolerance (Scheme 1c).

RESULTS AND DISCUSSION

We started our investigation by optimizing the model reaction between methyl 2-acetamidoacrylate (**1a**) and 4-methylstyrene (**2a**) under irradiation with blue LEDs at 20 °C (Table 1; see S.I. for full screening). No product was formed in the control experiments without photocatalyst (PC) and/or light (entry 1). Hence, a screening of a few selected metal and organic photocatalysts such as [Ir(dFCF₃ppy)₂dtbpy]PF₆, [Ru(bpy)₃](PF₆)₂, thioxanthone, and 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4Cz-IPN) in CH₃CN (0.2 M) was conducted (entries 2-6). The Ir-complex was identified as the best catalyst, giving with just 2 mol% loading the desired product **3aa/3aa'** in 82% yield and a good 8:1 diastereoselectivity (entry 2). The

Table 1. Optimization of the reaction conditions with **1a**.^a



Entry	PC (mol%)	Solvent	3aa/3aa' d.r.	3 Yield (%) ^b
1	no cat. or light	CH ₃ CN	--	--
2	[Ir] (2)	CH ₃ CN	8:1 ^c	82
3	[Ir] (4)	CH ₃ CN	8:1 ^d	83
4	[Ru] (5)	CH ₃ CN	--	--
5	thioxanthone (10)	CH ₃ CN	3:1 ^d	54
6	4Cz-IPN (5)	CH ₃ CN	7:1 ^d	70 ^e
7	[Ir] (2)	DMF	n.d.	60
8	[Ir] (2)	CDCl ₃	7:1 ^d	75
9	[Ir] (2)	DMSO	n.d.	73
10	[Ir] (2)	acetone	6:1 ^d	56
11	[Ir] (2)	CH ₃ CN ^f	7:1 ^d	68
12	[Ir] (2)	CH ₃ CN ^g	6:1 ^d	78

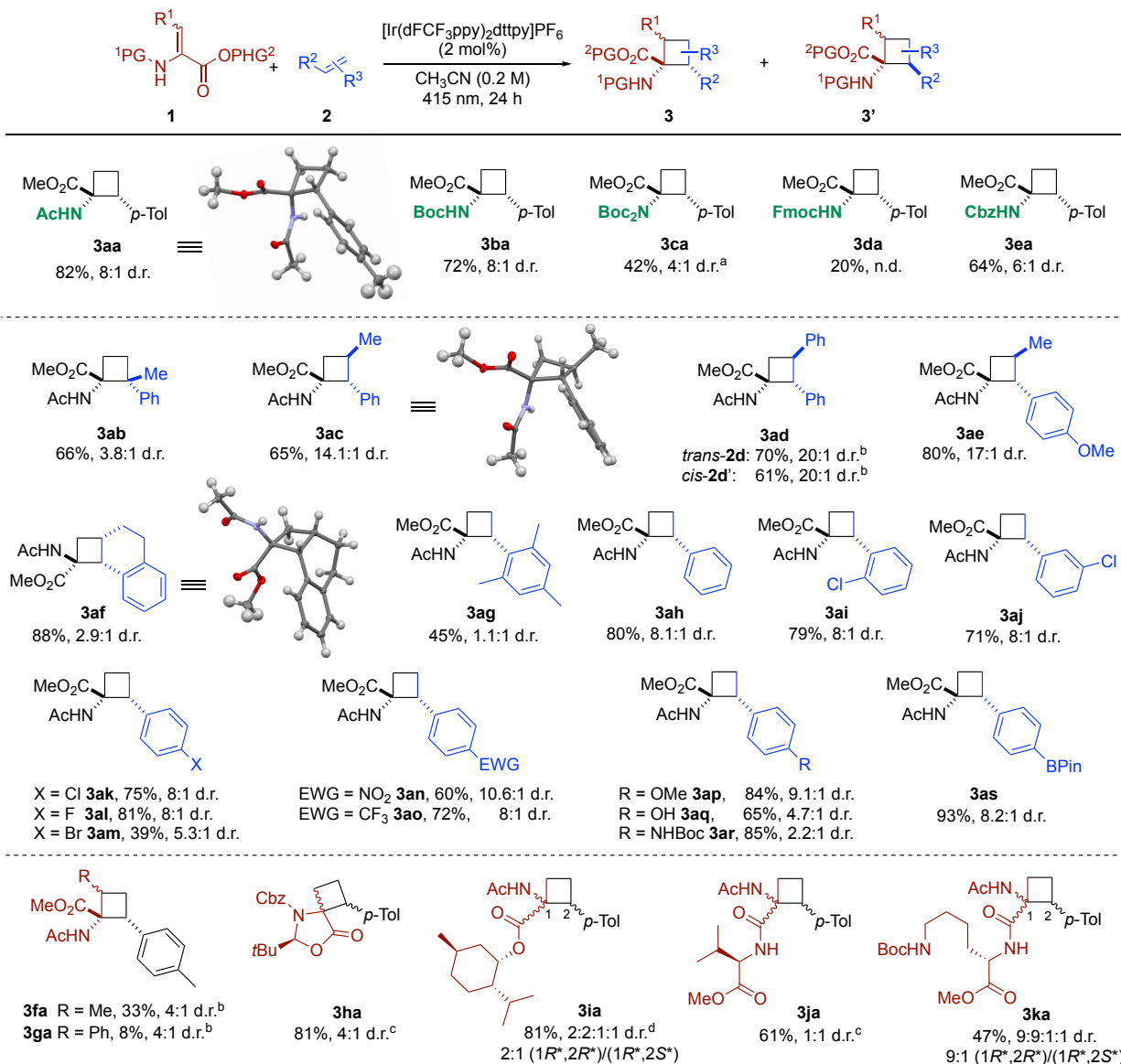
^a Conditions: catalyst (x mol%), **1a** (0.2 mmol, 1.0 equiv.) and **2a** (1.5 equiv.) in degassed solvent [0.2 M] were irradiated in a photo-reactor with a blue LED [λ_{max} 415 nm]. ^b Isolated yield. ^c Determined by crude NMR. ^d Determined from the isolated products. ^e 72 h reaction time. ^f Use of 0.1 M concentration. ^g Use of 0.4 M concentration. [Ir] = [Ir(dFCF₃ppy)₂dtbpy]PF₆; [Ru] = [Ru(bpy)₃](PF₆)₂. n.d. = not determined.

increase of the Ir-catalyst loading to 4 mol% (entry 3), employing other solvents rather than CH₃CN (entry 7-10) or varying

the concentration (entry 11-12) did not further improve the yield.

With the optimized conditions in hand, 2 mol% of [Ir(dFCF₃ppy)₂dtbpy]PF₆ as catalyst in CH₃CN (0.2 M) at 20 °C for 24 h, we next explored the scope and limitations of the reaction (Scheme 2). The influence of other *N*-protecting groups such as Boc, Fmoc and Cbz was first addressed. Although the *N*-acyl group proved the most efficient, Boc and Cbz derivatives were also well tolerated, affording the products **3ba** and **3ea** in moderate to good yields and diastereoselectivities (72%, 8:1 d.r. and 64%, 6:1 d.r., respectively). Notably, the introduction of a second Boc unit (**3ca**) or utilizing the Fmoc protecting group (**3da**) led to diminished reactivity and diastereoselectivity.

We then focused our attention on the effect of the substitution at the alkene reagent. The use of α -methyl styrene provided the product **3ab** in a moderate yield and diastereoselectivity (66%, 3.8:1 d.r.). To our delight, switching to a 1,2-substitution pattern afforded the corresponding products **3ac-3ae** in good yields (up to 80%) and excellent diastereoselectivities (up to 20:1 d.r.). It is worthy to note that the same diastereoselectivity (20:1 d.r.) was obtained for **3ad** using either the *trans*- (**2d**) or *cis*-stilbene (**2d'**), suggesting a stepwise process. Additionally, it was possible to construct a fused ring system **3af** with a good 88% yield and moderate diastereoselectivity (2.9:1 d.r.). Interestingly, the opposite relative alignment in respect to the ester group compared to the obtained with acyclic olefins was observed for the major product, which was confirmed by x-ray structure analysis of representative products **3** (see S.I. for details).⁴⁸ Pleasingly, different substitution on the styrene aromatic ring was allowed, leading to the desired products **3ag-3as** in moderate to high yields (45-93%). While a significant drop in both yield and diastereoselectivity (45%, 1.1:1 d.r.) was observed by introducing the bulky mesitylene-group (**3ag**), halide-containing styrenes afforded the products **3ai-3am** in good yield (71%-81%) and diastereoselectivity (8:1 d.r.). Only in the case of the bromide derivative **3am**, a less efficient reaction was monitored (39%, 5.3:1 d.r.). Moreover, both electron withdrawing and donating groups were well tolerated, providing the products **3an-3ar** in good yields (60-85%) and moderate to high diastereoselectivities up to 10.6:1 d.r.. Remarkably, a boronic ester derivative was converted into **3as** in an excellent 93% yield and 8.2:1 d.r., opening up the possibility for further derivatization. The substitution at the double bond of the dehydroalanine core required however longer reaction times (72 h) and gave the products **3fa** and **3ga** in significantly lower yields (33% and 8%), while the Karady-Beckwith alkene was converted to **3ha** in good 81% yield and moderate diastereoselectivity (4:1 d.r.). Finally, the reaction with more complex, nature derived products was carried out. Thus, the menthol ester derivative gave rise to **3ia** in high yield (81%) as a mixture of diastereoisomers (2:2:1:1 d.r.) with a 2:1 ratio of *cis*- (**3ia**) and *trans*- (**3ia'**) NHAc/*p*Tol arrangement in the cyclobutane, respectively (see S.I. for details).^{48,49} Furthermore, more challenging dipeptide-containing dehydroamino acids were subjected to the reaction and gave the corresponding products **3ja** (α -

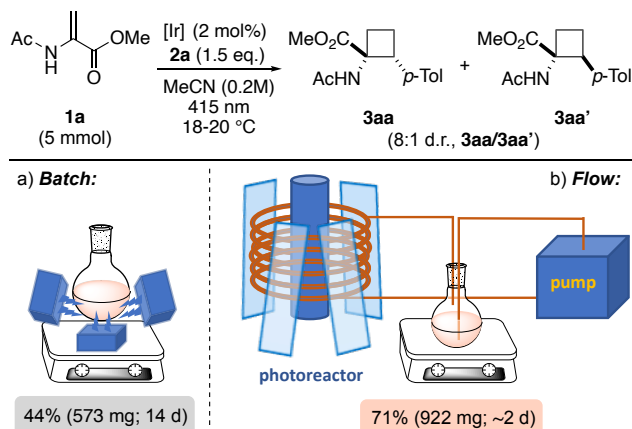


Scheme 2. Scope of the [2+2]-cycloaddition by visible light photocatalysis. ^a 7 days reaction time. ^b 72 h reaction time. ^c Only two isomers could be detected in the crude NMR. ^d Each isolated fraction **3ia** (major) and **3ia'** (minor) contains a ~1:1 mixture of diastereoisomers. Ellipsoid contours given at the 30% probability level for **3aa** and **3fa**, and 40% for **3ac**.

CBAAL-Val) and **3ka** (α -CBAAL-Lys) in 61% and 47% yield, respectively.

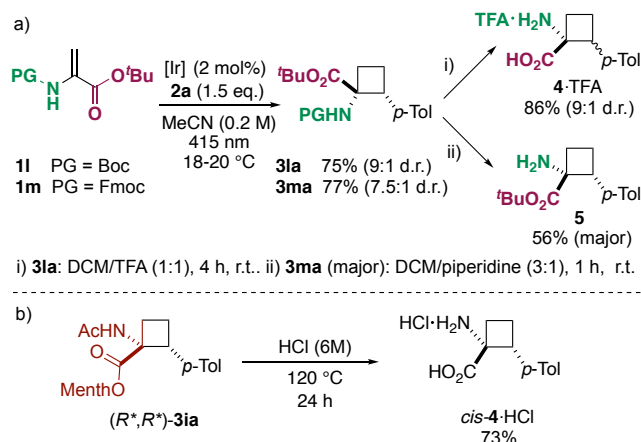
To demonstrate the robustness and synthetic utility of the method, a 25-fold upscaling of the reaction was performed in batch without adjusting the conditions using side irradiation with three single blue LEDs (3 W, 415 nm) (Scheme 3a), providing **3aa/3aa'** with unchanged selectivity of 8:1 d.r. and in a moderate 44% yield after a prolonged reaction time. This result could be significantly improved by conducting the reaction in continuous flow in a custom-built photoreactor (30x3 W LED, 415 nm, 6 ml/min flow rate and 18 °C; see S.I. for more details). Hence, the desired product was obtained in 71% yield and the same selectivity after 52 h (> 900 mg) (Scheme 3b).

Next, the introduction of other protecting groups that allow for orthogonal cleavage such as O*Bu* esters was conducted (Scheme 4a). Hence, the O*Bu* substituted CBAAL **3la**



Scheme 3. Upscaling reactions in a) batch and b) continuous flow. **3aa** and **3ma** presenting a NBoc and NFmoc group were prepared following the standard cycloaddition reaction in 75% (8:1 d.r.) and 77% (7.5:1 d.r.), respectively. While the double

deprotection in **31m** of the Boc and O'Bu groups under acidic conditions using trifluoroacetic acid (TFA) provided the free amino acid **4** as TFA salt in good 86% yield and 9:1 d.r., the free amino derivative **5** was obtained in 56% yield by selective cleavage of the Fmoc unit using piperidine. Moreover, the possibility of preparing the free α -amino acids from the products bearing the methyl ester and acetamide units was depicted by the hydrolysis of both protecting groups of **3ia** with a 6M HCl solution at 120 °C for 24 h (Scheme 4b). The free CBAs *cis*-**4** was then obtained as its HCl salt in 73% yield.



Scheme 4. a) Orthogonal deprotection reactions of CBAs **3**, and b) synthesis of *cis*-**4** by acetamide-methyl ester hydrolysis.

Finally, to elucidate the underlying mechanism, Stern-Volmer quenching experiments were performed (see S.I.), showing a strong quenching of the excited photocatalyst with 4-methyl styrene (**2a**). Additionally, a notable weaker interaction with **1a** could also be observed. However, the homocoupling control experiments showed no productive pathway from excited **1a** (see S.I., Table S3). Moreover, comparing the excited state oxidation potential of [Ir(dFCF₃ppy)₂dtbpy]PF₆ ($E^*_{ox} = +1.21$ V vs SCE)⁵⁰ with the oxidation potentials of 2-acetamidoacrylate (**1a**) ($E_{1/2} = +2.43$ V vs SCE) and 4-methyl styrene (**2a**) ($E_{1/2} = +1.38$ V vs SCE),⁵¹ this [Ir]-species does not possess an excited state oxidation potential sufficient to generate the radical cations of **1a** or **2a**. Therefore, a single electron transfer oxidation pathway seems improbable. Instead, the catalyst [Ir(dFCF₃ppy)₂dtbpy]PF₆ is known to be a potent triplet sensitizer with an excited state triplet energy (E_T) of 61.8 kcal mol⁻¹, while styrenes generally present E_T of approximately 60 kcal mol⁻¹.⁵¹ This suggests that an energy transfer from the excited photocatalyst to the styrene derivative is most likely to occur. This assumption is consistent with our findings that using [Ru(bpy)₃](PF₆)₂ ($E_T = 49.0$ kcal mol⁻¹),⁵² with an E_T significantly lower than **2a**, did not yield the desired product, while other known energy transfer catalysts (see Table 1, entries 5 and 6) also built the cyclobutanes **3**.

CONCLUSION

In conclusion, we reported herein a photocatalytic approach for the fast construction of unnatural 2-substituted cyclobutane α -amino acids from readily accessible dehydroamino acids and styrenes as reaction partners. An iridium photosensitizer with appropriate excited state triplet energy is used to activate a variety of styrenes by energy transfer, giving rise to the targeted α -CBAs in generally good yields, 1,2-regioselectivity, and diastereoselectivities up to 20:1 d.r.. The applicability and

robustness of the method were also demonstrated by efficiently employing natural product-like derivatives such as menthol ester or dipeptide substrates, as well as by orthogonal deprotections and conducting a gram scale reaction, in which the use of continuous flow provided the best results. Hence, this method provides an unprecedented, selective, simple and direct access to a new series of functionalized α -CBAs under mild photocatalytic conditions.

ASSOCIATED CONTENT

Supporting Information. Complete reaction screening, experimental procedures, characterization data, additional experiments, electrochemical data, X-ray structure analysis of **3aa**, **3ac**, **3af**, **3af'** and **3ia**, and NMR collection (PDF).

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Author Contributions

All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. α -Amino acids, β -Amino Alcohols and Related compounds as Chiral Auxiliaries, Ligands and Catalysts in the Asymmetric Aldol Reaction. *Curr. Org. Chem.* **2005**, *9*, 219–235.
- (2) Gnas, Y.; Glorius, F. Chiral Auxiliaries – Principles and Recent Applications. *Synthesis*, **2006**, *12*, 1899–1930.
- (3) Hughes, A. B., Amino Acids, Peptides and Proteins in Organic Chemistry: Building Blocks, Catalysis and Coupling Chemistry, Wiley-VCH, Weinheim, 2011.
- (4) Lau, J. L.; Dunn, M. K. Therapeutic Peptides: Historical perspectives, current development trends, and future directions. *Bioorg. Med. Chem.* **2018**, *26*, 2700–2707.
- (5) Otvos, L. Jr.; Wade, J.D. Current challenges in peptide-based drug discovery. *Front. Chem.* **2014**, *2*, 62.
- (6) Srivastava, V. *Peptide-based Drug Discovery: Challenges and New Therapeutics*, The Royal Society of Chemistry, London, 2017.
- (7) Blaskovich, M. A. T. Unusual Amino Acids in Medicinal Chemistry. *J. Med. Chem.*, **2016**, *59*, 10807–10836.
- (8) Avotins, F. M. Aminoacids of the cyclobutane series. *Russ. Chem. Rev.* **1993**, *62*, 897–906.
- (9) Ortuño, R. M.; Moglioni, A. G.; Moltrasio, G. Y. Cyclobutane Biomolecules: Synthetic Approaches to Amino Acids, Peptides and Nucleosides. *Curr. Org. Chem.* **2005**, *9*, 237–259.
- (10) Torres, E.; Puigmartí-Luis, L.; Pérez del Pino, Á.; Ortuño, R. M.; Amabilino, D. B. Use of unnatural β -peptides as a self-assembling component in functional organic fibres. *Org. Biomol. Chem.* **2010**, *8*, 1661–1665.
- (11) Illa, O.; Porcar-Tost, O.; Robledillo, C.; Elvira, C.; Nolis, P.; Reiser, O.; Branchadell, V.; Ortuño, R. M. Stereoselectivity of Proline/Cyclobutane Amino Acid-Containing Peptide Organocatalysts for Asymmetric Aldol Additions: A Rational. *J. Org. Chem.* **2018**, *83*, 350–363.

- (12) Illa, O.; Ospina, J.; Sánchez-Aparicio, J.-E.; Pulido, X.; Abengozar, M.Á.; Gaztelumendi, N.; Carbajo, D.; Nogués, C.; Rivas, L.; Maréchal, J.-D.; Royo, M.; Ortuño, R. M. Hybrid Cyclobutane/Proline-Containing Peptidomimetics: The Conformational Constraint Influences Their Cell-Penetration Ability. *Int. J. Mol. Sci.* **2021**, *22*, 5092.
- (13) Hughes, P.; Clardy, J. Total synthesis of cyclobutane amino acids from Atelia herbert smithii. *J. Org. Chem.* **1988**, *53*, 4793–4796.
- (14) Volk, F.-J.; Wagner, M.; Frahm, A. W. Cyclobutane amino acids (CBAA): asymmetric Strecker synthesis of enantiopure cis- and trans-2,4-methanovalines. *Tetrahedron: Asymmetry*, **2003**, *14*, 497–502.
- (15) Feskov, I. O.; Chernykh, A. V.; Kondratov, I. S.; Klyachina, M.; Daniliuc, C. D.; Haufe, G. Cyclobutyl-Containing Rigid Analogues of Threonine: Synthesis and Physical Chemical Properties. *J. Org. Chem.* **2017**, *82*, 12863–12868.
- (16) Izquierdo, S.; Rúa, F.; Sbai, A.; Parella, T.; Branchadell, V.; Ortuño, R. M. (+)- and (–)-2-Aminocyclobutane-1-carboxylic Acids and Their Incorporation into Highly Rigid β -Peptides: Stereoselective Synthesis and a Structural Study. *J. Org. Chem.* **2005**, *70*, 7963–7971.
- (17) Fernandes, C.; Pereira, E.; Phaure, S.; Aitken, D. J. Expedient Preparation of All Isomers of 2-Aminocyclobutanecarboxylic Acid in Enantiomerically Pure Form. *J. Org. Chem.* **2009**, *74*, 3217–3220.
- (18) Chang, Z.; Boyaud, F.; Guillot, R.; Boddaert, T.; Aitken, D. J. A Photochemical Route to 3- and 4-Hydroxy Derivatives of 2-Aminocyclobutane-1-carboxylic Acid with an all-cis Geometry. *J. Org. Chem.* **2018**, *83*, 527–534.
- (19) Verkh, Y.; Illa, O.; Ortuño, R. M. Synthesis of Chiral Scaffolds Based on Polyfunctional Cyclobutane β -Amino Acids. *Eur. J. Org. Chem.*, **2021**, 6022–6027.
- (20) André, V.; Vidal, A.; Ollivier, J.; Robin, S.; Aitken, D. J. Rapid access to cis-cyclobutane γ -amino acids in enantiomerically pure form. *Tetrahedron Letters*, **2011**, *52*, 1253–1255.
- (21) Aguilera, J.; Cobos, J. A.; Gutierrez-Abad, R.; Acosta, C.; Nolis, P.; Illa, O.; Ortuño, R. M. The Role of the Chiral cis-1,3-Disubstituted 2,2-Dimethylcyclobutane Motif in the Conformational Bias of Several Types of γ -Peptides. *Eur. J. Org. Chem.* **2013**, *17*, 3494–3503.
- (22) Kerres, S.; Plut, E.; Malcherek, S.; Rehbein, J.; Reiser, O. Visible Light-Mediated Synthesis of Enantiopure γ -cyclobutane Amino and 3-(Aminomethyl)-5-phenylpentanoic Acids. *Adv. Synth. Catal.* **2019**, *361*, 1400–1407.
- (23) Allan, R. D.; Hanrahan, J. R.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Mitrovic, A. D. Synthesis and activity of a potent N-methyl-D-aspartic acid agonist, trans-1-aminocyclobutane-1,3-dicarboxylic acid and related phosphonic and carboxylic acids. *J. Med. Chem.*, **1990**, *33*, 2905–2915.
- (24) Gershonov, E.; Granoth, R.; Tzehoval, E.; Gaoni, Y.; Fridkin, M. 1-Aminocyclobutanecarboxylic Acid Derivatives as Novel Structural Elements in Bioactive Peptides: Application to Tuftsin Analogs. *J. Med. Chem.* **1996**, *39*, 4833–4843.
- (25) Odewole, O. A.; Tade, F. I.; Nieh, P. T.; Savir-Baruch, B.; Jani, A. B.; Master, V. A.; Rossi, P. J.; Halkar, R. K.; Osunkoya, A. O.; AkinAkintayo, O.; Zhang, C.; Chen, Z.; Goodman, M. M.; Schuster, D. M. Recurrent prostate cancer detection with anti-3-[(18F)FACBC PET/CT: comparison with CT. *Eur. J. Nucl. Med. Mol. Imaging* **2016**, *43*, 1773–1783.
- (26) Avenoz, A.; Busto, J. H.; Canal, N.; Peregrina, J. M. Synthesis of Cyclobutane Serine Analogues. *J. Org. Chem.* **2005**, *70*, 330–333.
- (27) Avenoz, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Pérez-Fernández, M. Selective Michael-Aldol Reaction by Use of Sterically Hindered Aluminum Aryloxides as Lewis Acids: An Easy Approach to Cyclobutane Amino Acids. *Org. Lett.* **2005**, *7*, 3597–3600.
- (28) Avenoz, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Pérez-Fernández, M.; Rodríguez, F. Cyclobutane Amino Acid Analogues of Furanomycin Obtained by a Formal [2+2] Cycloaddition Strategy Promoted by Methylaluminoxane. *J. Org. Chem.*, **2010**, *75*, 545–552.
- (29) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363.
- (30) Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J. Visible Light Photocatalysis: Applications and New Disconnections in the Synthesis of Pharmaceutical Agents. *Org. Process Res. Dev.* **2016**, *20*, 1134
- (31) Stephenson, C.; Yoon, T.; MacMillan, D. W. C. *Visible Light Photocatalysis in Organic Chemistry*, Wiley-VCH, Weinheim, 2018.
- (32) Sato, S.; Nakamura, H. Ligand-directed selective protein modification based on local single-electron-transfer catalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 8681–8684.
- (33) Jiang, M.; Jin, Y.; Yang, H.; Fu, H. Visible-light photoredox synthesis of unnatural chiral α -amino acids. *Sci. Rep.* **2016**, *6*, 26161.
- (34) Ichiishi, N.; Caldwell, J. P.; Lin, M.; Zhong, W.; Zhu, X.; Streckfuss, E.; Kim, H.-Y.; Parish, C. A.; Krska, S. W. Protecting group free radical C-H trifluoromethylation of peptides. *Chem. Sci.* **2018**, *9*, 4168–4175.
- (35) Yu, Y.; Zhang, L.-K.; Buevich, A. V.; Li, G.; Tang, H.; Vachal, P.; Colletti, S. L.; Shi, Z.-C. Chemoselective peptide modification via photocatalytic tryptophan β -position conjugation. *J. Am. Chem. Soc.* **2018**, *140*, 6797–6800.
- (36) Bottecchia, C.; Noël, T. Photocatalytic Modification of Amino Acids, Peptides, and Proteins. *Chem. Eur. J.* **2019**, *25*, 26–42.
- (37) King, T. A.; Mandrup Kandemir, J.; Walsh, S. J.; Spring, D. R. Photocatalytic methods for amino acid modification. *Chem. Soc. Rev.* **2021**, *50*, 39–57.
- (38) Aycock, R. A.; Vogt, D. B.; Jui, N. T. A practical and scalable system for heteroaryl amino acid synthesis. *Chem. Sci.* **2017**, *8*, 7998–8003.
- (39) Aycock, R. A.; Pratt, C. J.; Jui, N. T. Aminoalkyl radicals as powerful intermediates for the synthesis of unnatural amino acids and peptides. *ACS Catal.* **2018**, *8*, 9115–9119.
- (40) de Bruijn, A. D.; Roelfes, G. Chemical modification of dehydrated amino acids in natural antimicrobial peptides by photoredox catalysis. *Chem. Eur. J.* **2018**, *24*, 11314–11318.
- (41) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic three-component umpolung synthesis of 1,3-diamines. *Org. Lett.* **2018**, *20*, 6794–6798.
- (42) Brandhofer, T.; García Mancheño, O. Versatile Ru-Photoredox-Catalyzed functionalization of Dehydro-Amino Acids and Peptides. *ChemCatChem* **2019**, *11*, 3797–3801.
- (43) Shah, A. A.; Kelly III, J. M.; Perkins, J. J. Access to unnatural α -amino acids via visible-light-mediated decarboxylative conjugate addition to dehydroalanine. *Org. Lett.* **2020**, *22*, 6, 2196–2200.
- (44) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent advances in the synthesis of cyclobutanes by olefin [2+2] photocycloaddition reactions. *Chem. Rev.* **2016**, *116*, 9748–9815.
- (45) Sicignano, M.; Rodríguez, R. I. J. Alemán. Recent Visible Light and Metal Free Strategies in [2+2] and [4+2] Photocycloadditions. *Eur. J. Org. Chem.* **2021**, *22*, 3303–3321.
- (46) Lu, Z.; Yoon, T. P. Visible light photocatalysis of [2+2] styrene cycloadditions by energy transfer. *Angew. Chem. Int. Ed.* **2012**, *51*, 10329–10332.
- (47) Brandhofer, T.; Stinglhamer, M.; Derdau, V.; Méndez, M.; Pöverslein, C.; García Mancheño, O. Easy access to drug building-blocks through benzylic C-H functionalization of phenolic ethers by photoredox catalysis. *Chem. Commun.*, **2021**, *57*, 6756–6759.
- (48) The crystallographic data of CCDC-2174645 (**3aa**), CCDC-2174646 (**3ac**), CCDC-2174647 (**3af**), CCDC-2174648 (**3af'**) and CCDC-2192789 (**3ia**) are provided free of charge by The Cambridge Crystallographic Data Centre. See also the S.I.
- (49) The 1:1 diastereomeric mixture in CBAA *cis*-**3ia** (major) and *trans*-**3ia'** (minor) was determined by x-ray analysis, and by NMR and confirmed by RP-HPLC, respectively. See S.I.
- (50) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A., Jr.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater.* **2005**, *17*, 5712–5719.
- (51) Garrison, J. M.; Ostović, D.; Bruce, T. C. Is a Linear Relationship between the Free Energies of activation and One-Electron Oxidation Potential Evidence for One-Electron Transfer Being Rate Determining? Intermediates in the Epoxidation of a Series of Alkenes by Cytochrome P-450 Models. 4. Epoxidation of a Series of Alkenes by Oxo(meso-tetrakis(2,6-dibromophenyl)porphyrinato)-chromium(V). *J. Am. Chem. Soc.* **1989**, *111*, 4960–4966.

(52) Stieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy transfer catalysis mediated by visible light: principles, applications, directions. *Chem. Soc. Rev.*, **2018**, *47*, 7190–7202.