Direct Access to Unnatural Cyclobutane α-Amino Acids through Visible Light Catalyzed [2+2]-Cycloaddition

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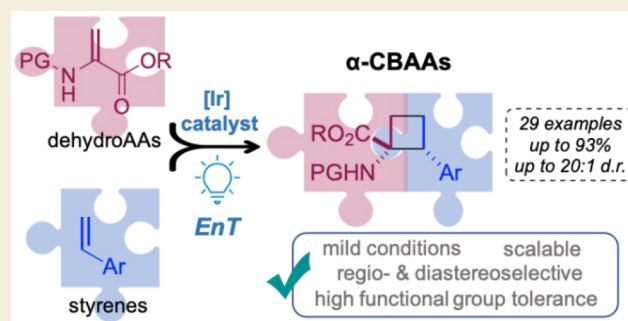
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ABSTRACT: In this work, we report the first selective, photo-catalyzed [2+2]-cycloaddition of dehydroamino acids with styrene-type olefins. This simple, mild, and scalable approach relies on the use of the triplet energy transfer catalyst $[Ir(dFCF_3ppy_2)dtbpy]PF_6$ 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] catalysts,[3] 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 among 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 have proven advantageous.[7]

In this regard, cyclobutane amino acids (CBAAs)[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 acids[20−22] (Scheme 1a). However, although some derivatives exhibit potent biological activities,[23−25] cyclobutane α-amino acids have recently 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 photocatalysis[29−31] 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 desired α-CBAAs has been reported to date. Indeed, only scarce examples involving formal [2+2]-cycloaddition methodologies have been described, which rely on thermal[26] or Al-based Lewis acid promoters.[27,28]

Inspired by earlier works on energy transfer (EnT) photocatalysis[46] and our previous contribution to photo-catalyzed radical additions toward 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).
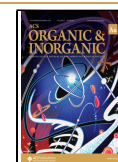
RESULTS AND DISCUSSION

We started our investigation by optimizing the model reaction between methyl 2-acetamidoacrylate (**1a**) and 4-methyl styrene (**2a**) under irradiation with blue LEDs at 20 °C (Table 1; see the Supporting Information (SI) for full

Scheme 1. (a) Cyclobutane Amino Acids (CBAAs), (b) Previous Photocatalytic Functionalization of Dehydroamino Acids (DhAAs), and (c) This Work on Visible Light Mediated Photocatalyzed Energy Transfer [2+2]-Cycloaddition toward CBAAs
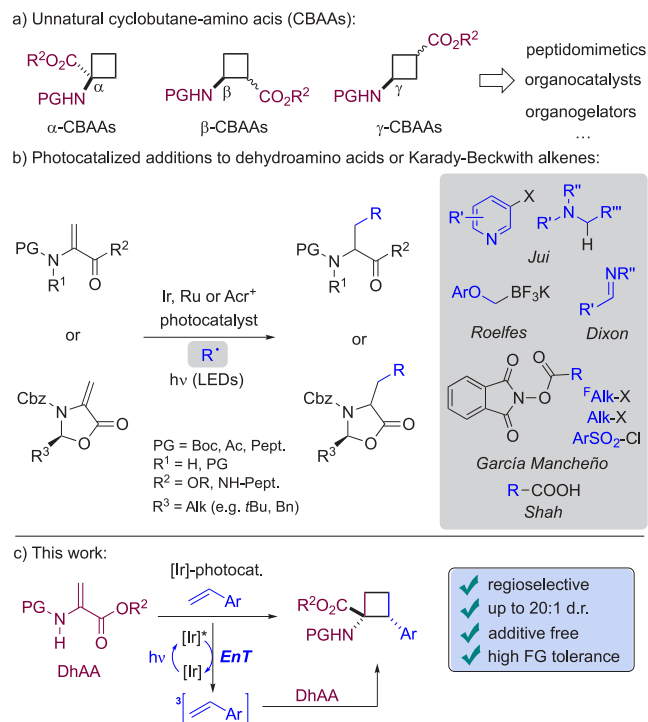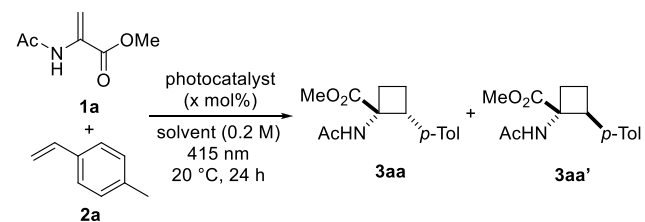
a) Unnatural cyclobutane-amino acis (CBAAs):

b) Photocalized additions to dehydroamino acids or Karady-Beckwith alkenes:

c) This work:

Table 1. Optimization of the Reaction Conditions with 1a[a]

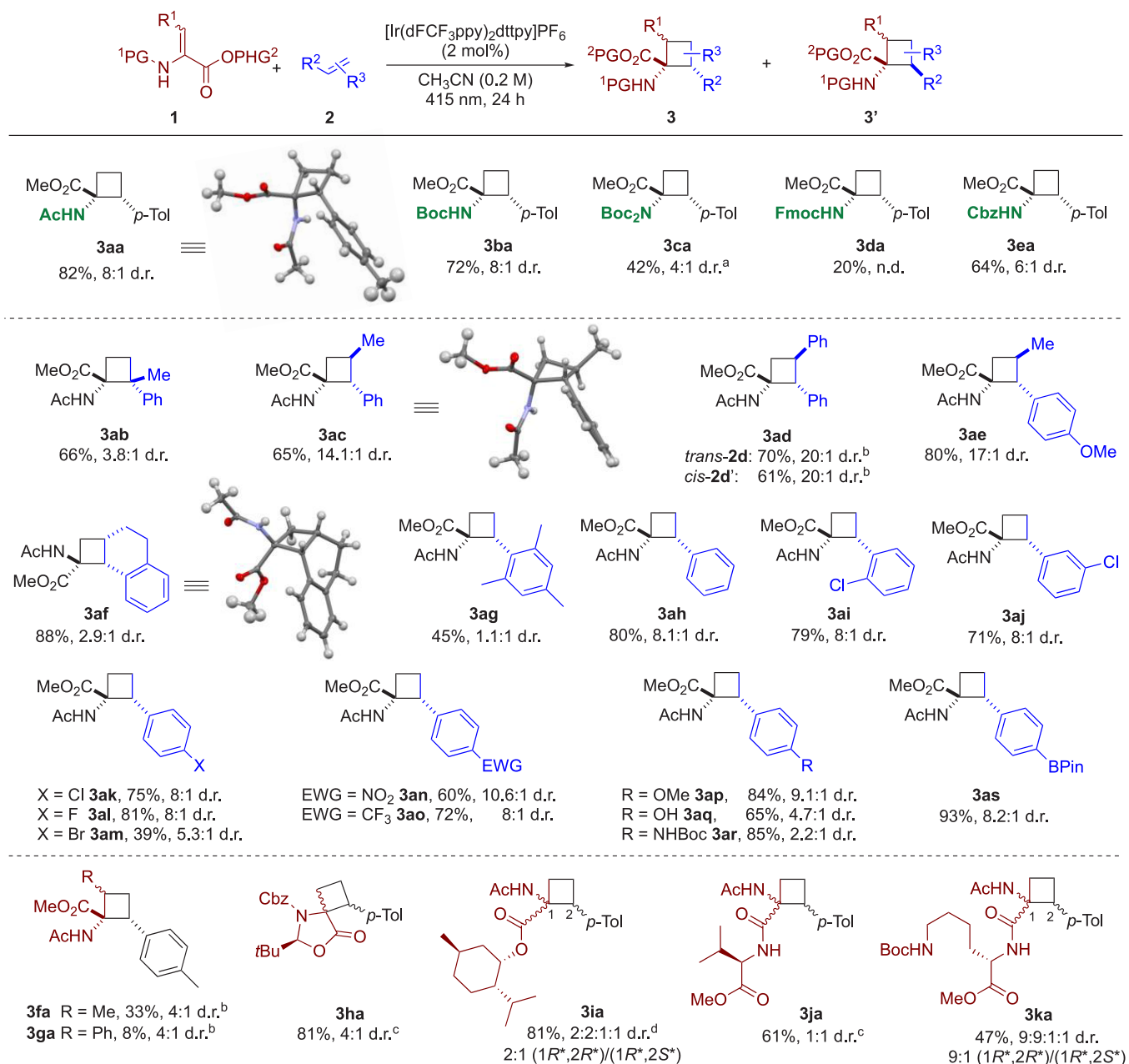| entry	PC (mol %)	solvent	3aa/3aa' d.r.	3 yield (%)[b]
1	no cat. or light	CH$_3$CN		
2	[Ir] (2)	CH$_3$CN	8:1[c]	82
3	[Ir] (4)	CH$_3$CN	8:1[d]	83
4	[Ru] (5)	CH$_3$CN		
5	thioxanthone (10)	CH$_3$CN	3:1[d]	54
6	4Cz-IPN (5)	CH$_3$CN	7:1[d]	70[e]
7	[Ir] (2)	DMF	n.d.	60
8	[Ir] (2)	CDCl$_3$	7:1[d]	75
9	[Ir] (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 photoreactor 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(dFCF$_3$ppy)$_2$dtbpy]PF$_6$; [Ru] = [Ru(bpy)$_3$](PF$_6$)$_2$. n.d. = not determined.

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(dFCF$_3$ppy$_2$)dtbpy]PF$_6$, [Ru(bpy)$_3$](PF$_6$)$_2$, thioxanthone, and 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4Cz-IPN) in CH$_3$CN (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 increase of the Ir-catalyst loading to 4 mol % (entry 3), employing other solvents rather than CH$_3$CN (entry 7–10), or varying the concentration (entry 11–12) did not further improve the yield.

With the optimized conditions in hand, 2 mol % [Ir(dFCF$_3$ppy$_2$)dtbpy]PF$_6$ as catalyst in CH$_3$CN (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-methylstyrene 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 with respect to the ester group compared to the one obtained with acyclic olefins was observed for the major product, which was confirmed by X-ray structure analysis of representative products **3** (see the SI 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 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

Scheme 2. Scope of the [2+2]-Cycloaddition by Visible Light Photocatalysis

Reaction scheme: ^{1}PG–NH substrate **1** with R^1 and $OPHG^2$ ester, plus alkene **2** (R^2, R^3), under $[Ir(dFCF_3ppy)_2dttpy]PF_6$ (2 mol%), CH_3CN (0.2 M), 415 nm, 24 h → cyclobutane products **3** and **3'**.

3aa — AcHN, MeO$_2$C, *p*-Tol — 82%, 8:1 d.r.

3ba — BocHN, MeO$_2$C, *p*-Tol — 72%, 8:1 d.r.

3ca — Boc$_2$N, MeO$_2$C, *p*-Tol — 42%, 4:1 d.r.[a]

3da — FmocHN, MeO$_2$C, *p*-Tol — 20%, n.d.

3ea — CbzHN, MeO$_2$C, *p*-Tol — 64%, 6:1 d.r.

3ab — MeO$_2$C, AcHN, Me, Ph — 66%, 3.8:1 d.r.

3ac — MeO$_2$C, AcHN, Me, Ph — 65%, 14.1:1 d.r.

3ad — MeO$_2$C, AcHN, Ph, Ph — *trans*-**2d**: 70%, 20:1 d.r.[b]; *cis*-**2d'**: 61%, 20:1 d.r.[b]

3ae — MeO$_2$C, AcHN, Me, (aryl-OMe) — 80%, 17:1 d.r.

3af — AcHN, MeO$_2$C — 88%, 2.9:1 d.r.

3ag — MeO$_2$C, AcHN, mesityl — 45%, 1.1:1 d.r.

3ah — MeO$_2$C, AcHN, Ph — 80%, 8.1:1 d.r.

3ai — MeO$_2$C, AcHN, (2-Cl-phenyl) — 79%, 8:1 d.r.

3aj — MeO$_2$C, AcHN, (3-Cl-phenyl) — 71%, 8:1 d.r.

3ak/3al/3am — MeO$_2$C, AcHN, (4-X-phenyl): X = Cl **3ak**, 75%, 8:1 d.r.; X = F **3al**, 81%, 8:1 d.r.; X = Br **3am**, 39%, 5.3:1 d.r.

3an/3ao — MeO$_2$C, AcHN, (4-EWG-phenyl): EWG = NO$_2$ **3an**, 60%, 10.6:1 d.r.; EWG = CF$_3$ **3ao**, 72%, 8:1 d.r.

3ap/3aq/3ar — MeO$_2$C, AcHN, (4-R-phenyl): R = OMe **3ap**, 84%, 9.1:1 d.r.; R = OH **3aq**, 65%, 4.7:1 d.r.; R = NHBoc **3ar**, 85%, 2.2:1 d.r.

3as — MeO$_2$C, AcHN, (4-BPin-phenyl) — 93%, 8.2:1 d.r.

3fa R = Me, 33%, 4:1 d.r.[b]; **3ga** R = Ph, 8%, 4:1 d.r.[b] — MeO$_2$C, AcHN, R, (tolyl)

3ha — Cbz-N, ^{t}Bu, O, *p*-Tol — 81%, 4:1 d.r.[c]

3ia — AcHN, *p*-Tol, menthyl ester — 81%, 2:2:1:1 d.r.[d]; 2:1 (1*R**,2*R**)/(1*R**,2*S**)

3ja — AcHN, *p*-Tol, Val (NH, MeO, O) — 61%, 1:1 d.r.[c]

3ka — AcHN, *p*-Tol, Lys (BocHN, NH, MeO, O) — 47%, 9:9:1:1 d.r.; 9:1 (1*R**,2*R**)/(1*R**,2*S**)

[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**.

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 the SI for details).[48,49] Furthermore, more challenging dipeptide-containing dehydroamino acids were subjected to the reaction and gave the corresponding products **3ja** (α-CBAA-Val) and **3ka** (α-CBAA-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 (30 × 3 W LED, 415 nm, 6 mL/min flow rate and 18 °C; see the SI 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^{t}Bu esters was conducted (Scheme 4a). Hence, the O^{t}Bu substituted CBAA **3la** 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 **3lm** of the Boc and O^{t}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

Scheme 3. Upscaling Reactions in (a) Batch and (b) Continuous Flow
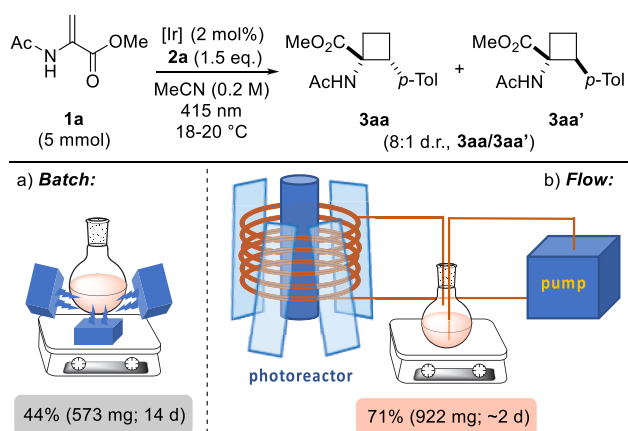
Scheme 4. (a) Orthogonal Deprotection Reactions of CBAAs 3 and (b) Synthesis of *cis*-4 by Acetamide-Methyl Ester Hydrolysis

i) **3la**: DCM/TFA (1:1), 4 h, r.t.. ii) **3ma** (major): DCM/piperidine (3:1), 1 h, r.t.

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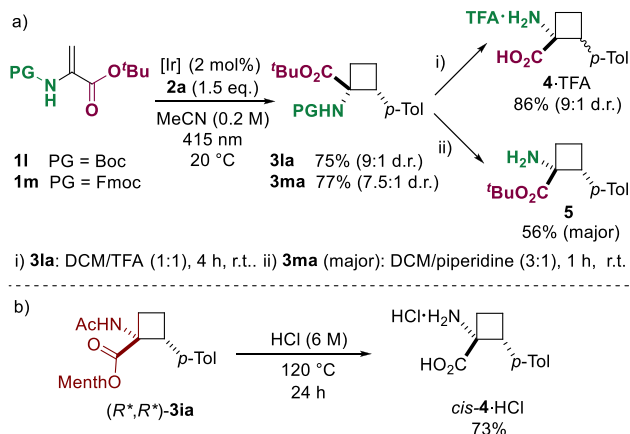
derivative **5** was obtained in 56% yield by selective cleavage of the Fmoc unit using piperidine. Moreover, the possibility of preparing the free α-amino acids from the products bearing the methyl ester and acetamide units was depicted by the hydrolysis of both protecting groups of **3ia** with a 6 M HCl solution at 120 °C for 24 h (Scheme 4b). The free CBAAs *cis*-**4** was then obtained as its HCl salt in 73% yield.

Finally, to elucidate the underlying mechanism, Stern–Volmer quenching experiments were performed (see the SI), showing a strong quenching of the excited photocatalyst with 4-methylstyrene (**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 SI, Table S3). Moreover, comparing the excited state oxidation potential of [Ir-(dFCF$_3$ppy$_2$)dtbpy]PF$_6$ (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-methylstyrene (**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-(dFCF$_3$ppy$_2$)dtbpy]PF$_6$ 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 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)$_3$](PF$_6$)$_2$ (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-CBAAs 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 unprecedented, selective, simple, and direct access to a new series of functionalized α-CBAAs under mild photocatalytic conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.2c00026.

> 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

Notes

The authors declare no competing financial interest.

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