HHS Public Access

Author manuscript

Nat Chem. Author manuscript; available in PMC 2017 June 26.

Published in final edited form as:

Nat Chem. 2017 May ; 9(5): 453–456. doi:10.1038/nchem.2690.

Photoredox activation of carbon dioxide for amino acid synthesis in continuous flow

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Abstract

Although carbon dioxide (CO_2) is highly abundant, its low reactivity has limited its use in chemical synthesis. In particular, methods for carbon–carbon bond formation generally rely on two-electron mechanisms for CO_2 activation and require highly activated reaction partners. Alternatively, radical pathways accessed via photoredox catalysis could provide new reactivity under milder conditions. Here we demonstrate the direct coupling of CO_2 and amines via the single-electron reduction of CO_2 for the photoredox-catalyzed, continuous flow synthesis of α-amino acids. By leveraging advantages for utilizing gases and photochemistry in flow, a commercially available organic photoredox catalyst effects the selective α-carboxylation of amines bearing various functional groups and heterocycles. Preliminary mechanistic studies support CO_2 activation and carbon–carbon bond formation via single-electron pathways, and we expect that this strategy will inspire new perspectives on using this feedstock chemical in organic synthesis.

Atmospheric carbon dioxide (CO_2) is an attractive one-carbon building block in chemical synthesis due to its abundance, availability, and sustainability[1–3]. To date, most examples of carbon–carbon bond formation with CO_2 have relied on two-electron mechanisms[4]. The low reactivity and high stability of CO_2 generally limits these transformations to couplings with activated partners such as extended π systems or organometallic reagents (Fig. 1a)[5,6], including work from our group[7]. Herein we apply the single-electron reduction of CO_2 for the synthesis of α-amino acids via the direct, photoredox-catalyzed α-carboxylation of amines in continuous flow (Fig. 1b). Relying on advantages for utilizing gases and photochemistry in flow, this protocol provides a procedure for accessing α-amino acids[8] by combining an amine and CO_2 in the presence of light and a commercially available organic

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Supplementary Information: is available in the online version of the paper.

Author Contributions: H.S. and M.H.K. performed the experiments: M.H.K. and T.F.J. conceived the idea: H.S., M.H.K. and T.F.J. designed the research and wrote the manuscript: All authors commented on the final draft of the manuscript and contributed to the analysis and interpretation of the data.

The authors declare competing financial interests: details accompany the full-text HTML version of the paper.

Readers are welcome to comment on the online version of the paper.

Competing financial interests: T.F.J. is a cofounder of Snapdragon Chemistry, Inc., and a scientific adviser for Zaiput Flow Technologies, Continuus Pharmaceuticals, Paraza Pharmaceuticals, and Asymchem.

photoredox catalyst. Furthermore, this work demonstrates that single-electron reduction of CO_2 is a productive strategy for carbon–carbon bond formation with this stable feedstock chemical.

Although the single-electron reduction of CO_2 has been demonstrated electrochemically and photochemically, the CO_2 radical anion has not shown broad utility as a reactive intermediate in organic synthesis[9,10]. Under the operationally mild conditions of photoredox catalysis[11-16], we envisioned that the productive coupling of this radical anion with another radical would provide the mechanistic framework for novel transformations. The main challenge for this mode of CO_2 activation is the high reduction potential [E^0 = −2.21 V versus saturated calomel electrode (SCE) in *N*,*N*-dimethylformamide (DMF)], which is commonly supplemented by an overpotential of 0.1 to 0.6 V[17,18]. The necessary reduction potential is therefore outside the photoreducing capabilities of the ruthenium and iridium catalysts that are commonly used in visible light photoredox catalysis (the highest reduction potential available for this class of catalysts is for tris[2-phenylpyridinato-C^2, *N*]iridium(III), or Ir(ppy)$_3$, $E_{1/2}^{red}$ = –2.19 V vs SCE in acetonitrile)[12]. Although oligophenylenes have not been widely applied as photoredox catalysts in organic synthesis, we expected that *para*-terphenyl (E^0 = –2.63 V vs SCE in DMF) could overcome this limitation since this organic photoredox catalyst has been studied by Yanagida and co-workers for the reduction of CO_2 to formic acid under UV light[19].

From the outset, we recognized that this transformation would operate ideally in continuous flow, a field which has recently emerged as an important design tool for organic synthesis[20,21]. Figure 1c illustrates our continuous flow setup, in which a liquid solution containing the amine substrate and catalyst are mixed with CO_2 gas in line. Irradiation of this segmented flow mixture with a UV lamp provides the amino acid product. Importantly, our setup allows for control of the amount and pressure of gas, and gas-liquid mixing is generally superior in flow than in batch[22]. The short path length of light also provides enhancements for photochemistry, and flow reactors remove scale limitations encountered with batch photoreactors[23].

We began our investigations using *N*-benzylpiperidine (**1a**) as a model substrate (Table 1). The presence of a benzylic C–H bond was expected to enhance both the reactivity and regioselectivity of the carboxylation reaction. Under conditions similar to those utilized by Yanagida and co-workers[19], *p*-terphenyl catalyzed the formation of α-amino acids **2a** and **3a** in 21% combined yield with 6.6:1 regioselectivity in favor of carboxylation at the benzylic position (entry 1). As in other recent reports of photoredox-catalyzed radical-radical couplings[24], we hypothesized that the inclusion of an exogenous base would increase the yield by promoting deprotonation of an amine radical cation to produce the α-amino radical. Although our choice of base was somewhat limited by the constraint of a homogeneous reaction mixture for our continuous flow setup (see Supplementary Table 1), potassium trifluoroacetate ($KOCOCF_3$) provided the highest yield, with a concomitant increase in regioselectivity, of the organic and inorganic bases investigated (entry 2). Further optimization by increasing the amount of $KOCOCF_3$ from one to three equivalents, decreasing the pressure from 0.69 MPa to 0.34 MPa, and using a 4-minute residence time provided the maximum yield (78%) without a UV filter (entry 3). Operating at this pressure

limited side reactions such as the formation of carbamate salts[25], but further pressure reductions were detrimental to yield (see Supplementary Table 2).

In further optimizing this transformation, we reasoned that short wavelength UV light could lead to other unproductive reactions. We therefore investigated filters for UV light and found that the system recently reported by Beeler and co-workers was ideal for easily testing an array of commercial filters (see Supplementary Fig. 2)[26]. Using a long-pass filter with a 280 nm cut-on wavelength (*p*-terphenyl excitation λ_{max} = 283 nm), the desired product was obtained in 92% yield with almost exclusive regioselectivity in favor of **2a** (entry 4). In comparison, the batch reaction conducted with continuously bubbling CO_2 provided **2a** in poor yield (30%), even after prolonged reaction time (see Supplementary Table 4). These results highlight the advantages of reaction development in continuous flow, as it provides the opportunity to vary parameters that are difficult to adjust in traditional batch optimizations.

Our optimized conditions were applicable to the synthesis of a variety of α-amino acids (Table 2). In all cases, >20:1 regioselectivity in favor of carboxylation at the benzylic position was observed. Initially, we investigated reactions of tertiary *N*-benzylpiperidines bearing a range of electron-neutral and electron-rich arenes. Substrates bearing arenes with ortho-, meta-, and para-alkyl substituents provided the desired amino acids in high yield (**2b**–**2e**). Although *para*-methoxybenzylamines can be deprotected by single electron oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[27], our conditions provided **2f** in 90% yield without C–N bond cleavage. As demonstrated by the synthesis of **2g**, protic functional groups such as N–H bonds are also tolerated by these conditions. Substrates containing ortho-, meta-, and para-chloroarenes provide good to excellent yields of **2h**, **2i**, and **2j** with handles for further elaboration via cross-coupling. *N*-Benzylamines with electron-poor arenes are not suitable substrates for α-carboxylation under these conditions.

Next, other variations to the amine structure were investigated. 4- and 2-methylpiperidine derivatives provided the corresponding amino acids **2k** and **2l** in good yields. Non-activated benzylic C–H bonds, such as those found in **1m**, are not carboxylated under these conditions. Although unprotected alcohols and ketones are not tolerated, silyl ether **2n** and ketal **2o** are produced in 72% and 88% yield, respectively, and can serve as masked versions of these functional groups. Amino acids containing a number of other heterocycles, including piperazine (**2p**), morpholine (**2q**), thiomorpholine (**2r**), and silapiperidine (**2s**) derivatives, can also be synthesized. Fused rings and different ring sizes, as exemplified by tetrahydroisoquinoline **2t** and azepane **2u**, are accommodated by this protocol. Importantly, amino acids bearing acyclic amines (**2v** and **2w**) can be produced in good yields.

We next sought to expand the scope of this methodology to other substrate classes (Fig. 2a). Ticlopidine (**4**), a marketed antiplatelet agent, was regioselectively derivatized to provide **5** as a single isomer despite the presence of two activated sites. This result points to potential applications of this method for late stage C–H functionalization of complex structures. We also expected that this reactivity would apply to non-benzylic amines with less activated alkyl C–H bonds adjacent to nitrogen. Accordingly, *N*-cyclohexylpiperidine (**6**) underwent regioselective carboxylation of a secondary, rather than tertiary, C–H bond to produce amino

acid **7**. Despite the moderate yield (43%), we are encouraged that substrates beyond *N*-benzylamines undergo photoredox-catalyzed carboxylation and that considerations other than electronic effects can influence regioselectivity. Without applying a UV filter, the product yields in Table 2 and Figure 2a were significantly lower; this comparison highlights the importance of this modification to realize broad substrate scope.

Lastly, we recognized that the synthesis of a free amino acid via the combination of an amine and CO_2 would provide access to this important motif (Fig. 2b). Primary amines were not suitable as substrates, but a screen of amine bis-protecting groups identified 4-piperidone analogues (e.g., **1o**) as optimal for our α-carboxylation conditions. Cleavage of the 4-piperidone protecting group was accomplished under neutral conditions using a polymer-supported amine scavenger to afford free amino acid **8**[28]. Although the current protocol provides a racemic mixture, chiral resolution of such amino acids has been commonly utilized to isolate single enantiomers[29,30].

In view of expanding the scope of this method and investigating further applications of this reactivity, preliminary studies were performed to understand the reaction mechanism. Our proposed catalytic cycle (Fig. 3) combines features of the mechanisms proposed by Yanagida[19] and MacMillan[24] for CO_2 reduction and photoredox-catalyzed radical-radical couplings, respectively. Irradiation of organic photoredox catalyst *p*-terphenyl (**9**) with UV light produces the excited singlet state of *p*-terphenyl (**10**), which undergoes single-electron transfer (SET) with a tertiary amine (**11**) to provide the strongly reducing *p*-terphenyl radical anion (**12**) and the corresponding amine radical cation (**13**). In support of this step, Stern-Volmer plots illustrate that the luminescence of the excited state of *p*-terphenyl (**9**) is quenched by *N*-benzylpiperidine but not CO_2 (see Supplementary Fig. 4). Strong reductant **12** then donates an electron to CO_2 to form the CO_2 radical anion (**14**). Concurrently, deprotonation of amine radical cation **13** affords neutral α-amino radical **15**. The key bond-forming step occurs by radical-radical coupling of **14** and **15** to produce the desired α-amino acid (**16**). Although the fluorescence quenching experiments indicate that base does not appear to be directly involved in the photoredox catalytic cycle (see Supplementary Fig. 4 and 5), the nature of the exogenous base may limit product decomposition by stabilization as a salt. Results from control reactions and radical quenching experiments also agree with this preliminary mechanistic proposal (see Supplementary Table 5 and 6).

In summary, we have developed a novel photoredox catalytic system for the α-carboxylation of amines with CO_2 in continuous flow. In this high-yielding protocol, carbon–carbon bond formation occurs via a single-electron pathway for the conversion of two stable, unactivated reactants to α-amino acids. We anticipate that the single-electron activation of CO_2 via the system described herein will result in the development of additional transformations with other reaction partners that provide new avenues for utilizing this abundant single carbon synthon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the Novartis-MIT Center for Continuous Manufacturing for financial support and several Novartis colleagues for suggestions, in particular, Berthold Schenkel, Benjamin Martin, Jörg Sedelmeier, Gerhard Penn, Francesco Venturoni, and Julien Haber. H.S. is grateful for a graduate fellowship from the Korean Government Scholarship Program for Study Overseas, and M.H.K. was supported by a postdoctoral fellowship from the NIGMS (F32GM108181). The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank Prof. A. B. Beeler for guidance in setting up the flow photochemistry system, Prof. T. M. Swager for use of a spectrophotometer and L. Li for mass spectral data (conducted on an instrument purchased with the assistance of NSF Grant CHE-0234877).

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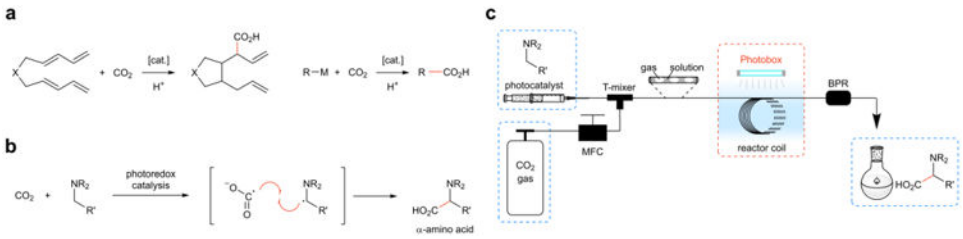


Figure 1. Design plan for α-carboxylation of amines with CO_2

a, Carbon–carbon bond formation with CO_2 has generally relied on two-electron reaction pathways with an extended π system or a strong nucleophile. cat., catalyst. **b**, Single-electron reduction of carbon dioxide and its reaction with an α-amino radical to provide α-amino acid. **c**, Continuous flow setup for the photoredox-catalyzed synthesis of α-amino acids. The reactants were introduced via a gas-tight syringe containing a solution of the amine substrate, base, and catalyst. CO_2 gas was metered into the system by a MFC. These two streams were joined by a T-mixer before irradiation under a UV lamp. The pressure of CO_2 is controlled by a BPR. MFC, mass flow controller; BPR, back pressure regulator.

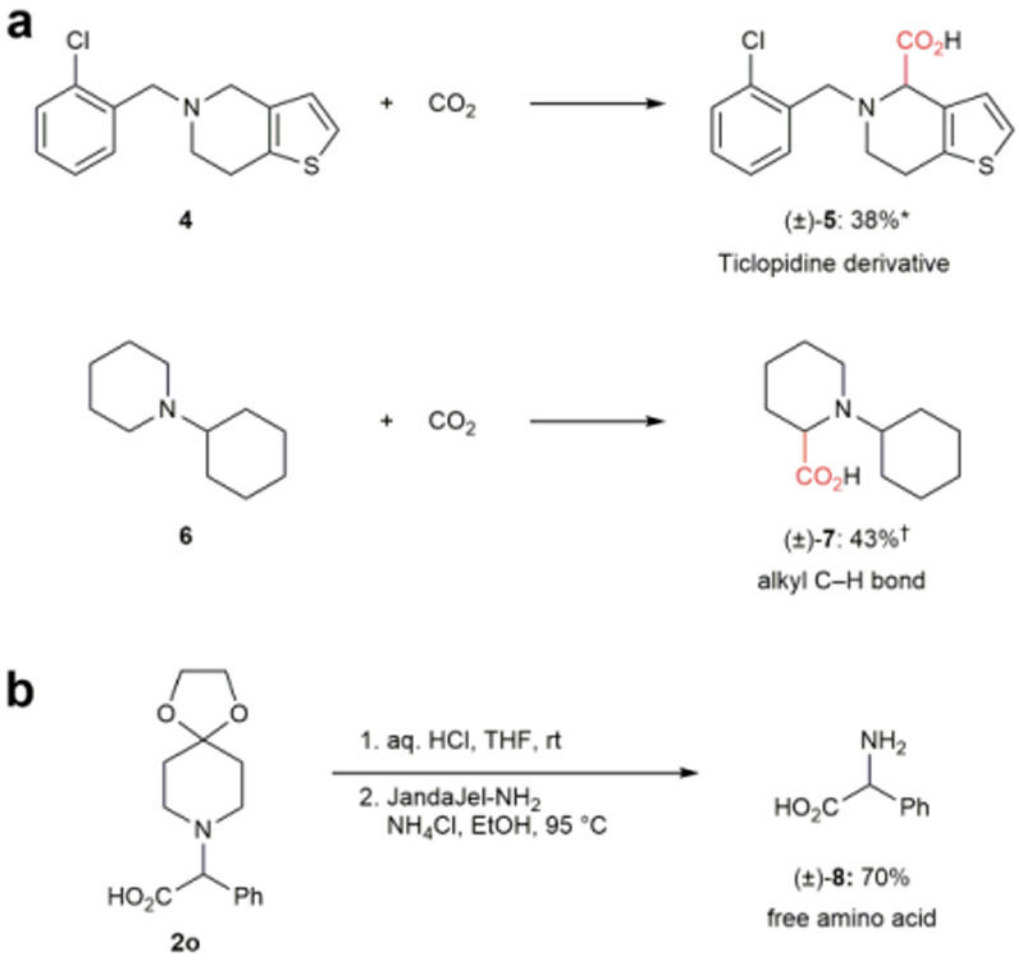


Figure 2. Expanding the scope of the α-carboxylation protocol

a, The carboxylation protocol can be applied to ticlopidine (an active pharmaceutical ingredient containing a heterocycle) and a substrate without a benzylic C–H bond. *Under standard conditions (see Table 2) †Under standard conditions, with atmospheric pressure of CO_2 and t_R = 6 min. **b**, Synthesis of a free amino acid can be achieved via deprotection of a piperidone derivative. THF, tetrahydrofuran.

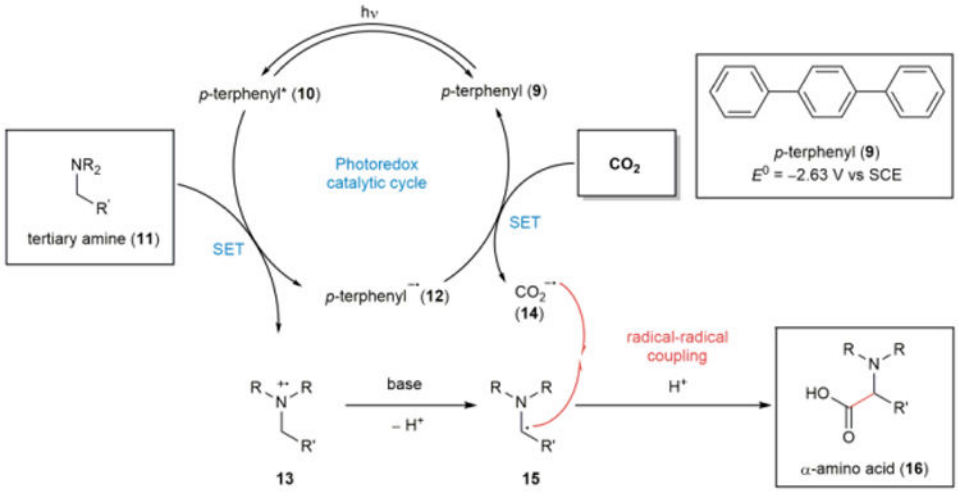
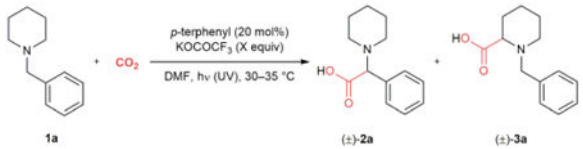


Figure 3. Proposed mechanism for photoredox catalytic α-carboxylation of amines with CO_2

The excited singlet state of the photoredox catalyst *p*-terphenyl (**10**) is quenched by tertiary amine **11**, and the radical anion of *p*-terphenyl (**12**) reduces CO_2 to its radical anion (**14**). After the deprotonation of amine radical cation **13** to afford α-amino radical **15**, radical-radical coupling of **14** and **15** provides α-amino acid **16**.

Table 1

Optimization of α-carboxylation of *N*-benzylpiperidine in continuous flow.



Entry*	Equiv $KOCOCF_3$	Pressure† (MPa)	t_R (min)	UV filter	Yield 2a+3a (%)‡	Regioselectivity (2a/3a)‡
1	0	0.69	5	none	21	6.6:1
2	1	0.69	5	none	45	33:1
3	3	0.34	4	none	78	30:1
4	**3**	**0.34**	**10**	**> 280 nm**	**92**	**52:1**

*Reactions were carried out using the original photochemistry system (entry 1–3) or using Beeler's photochemistry system (entry 4). See Supplementary Fig. 1 and 2 for details of the setup.

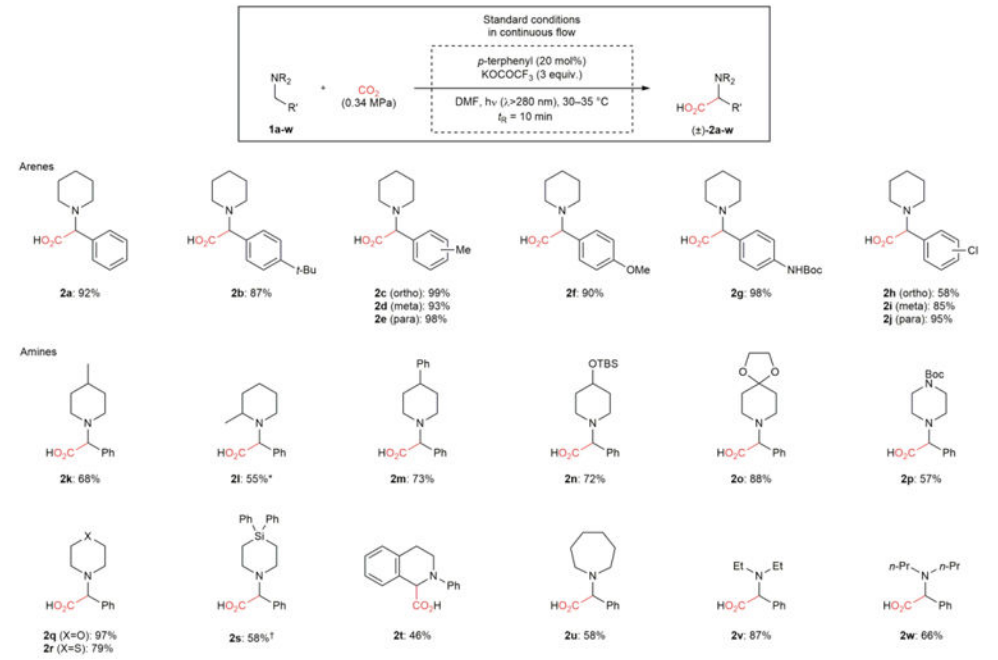
†Pressure of BPR. 0.69 MPa is equivalent to 7.3 equiv of CO_2 and 0.34 MPa to 3.6 equiv.

‡Calculated by gas chromatography (GC) after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard.

DMF, *N*,*N*-dimethylformamide; t_R, residence time.

Table 2

Substrate scope for the α-carboxylation of amines with CO_2.



Various amino acids are synthesized in high yields and excellent regioselectivities (>20:1) with a short residence time. This protocol utilizes readily available starting materials and a commercially available, inexpensive organic catalyst. Products were isolated as trifluoroacetate salts on 0.7 mmol scale. (**2s** and **2t** were isolated as free amines)

*1.3:1 diastereomeric ratio was observed by GC analysis.

†Reaction was carried out under atmospheric pressure of CO_2 (1.1 equiv CO_2) with t_R = 5 min. Boc, *tert*-butyloxycarbonyl; TBS, *tert*-butyldimethylsilyl.