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Direct α-alkylation of primary aliphatic amines enabled by CO_2 and electrostatics

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Primary aliphatic amines are important building blocks in organic synthesis due to the presence of a synthetically versatile NH_2 group. *N*-functionalization of primary amines is well established, but selective *C*-functionalization of unprotected primary amines remains challenging. Here, we report the use of CO_2 as an activator for the direct transformation of abundant primary aliphatic amines into valuable γ-lactams under photoredox and hydrogen atom transfer (HAT) catalysis. Experimental and computational studies suggest that CO_2 not only inhibits undesired *N*-alkylation of primary amines, but also promotes selective intermolecular HAT by an electrostatically accelerated interaction between the in situ-generated negatively charged carbamate and the positively charged quinuclidinium radical. This electrostatic attraction overwhelms the inherent bond dissociation energies which suggest that HAT should occur unselectively. We anticipate that our findings will open up new avenues for amine functionalizations as well as selectivity control in HAT reactions.

Selective functionalization of aliphatic C–H bonds remains a considerable challenge[1]. Positions adjacent to functional groups tend to be activated towards functionalization, whether by classical deprotonation strategies or by emerging radical abstraction approaches. Among the latter, C–H bonds adjacent to alcohols, ethers and amides have been demonstrated to be susceptible to hydrogen atom transfer (HAT) chemistry with electrophilic agents such as the thiyl radical[2,3] and quinuclidinium radical cation[4–6]. These processes are selective because of a polarity match[2]—a nucleophilic or hydridic hydrogen atom source is required. Amine activation is also an area of intense interest, dominated by tertiary amines which may be oxidized to the radical cation with subsequent proton loss to deliver an α-amino alkyl radical (Fig. 1a)[7–10]. Efficient α-functionalization of simple primary aliphatic amines is exceedingly rare, regardless of mechanism[11–13]. Indeed, primary aliphatic amines pose a significant challenge not just because of their much higher oxidation potential[14] and propensity for over-oxidation to the imine or nitrile (Fig. 1a)[15], but also because of their pronounced nucleophilicity and basicity[16,17].

It has long been recognized that primary alkyl amines react readily and reversibly with CO_2 to form carbamates[18]. In the context of our recent effort in the area of selective amine functionalization[19,20], we speculated that this equilibrium might be utilized to modulate the reactivity of primary alkyl amines, as the formation of alkylammonium carbamate would dramatically diminish the nucleophilicity of the NH_2 motif (Fig. 1b)[21], thereby providing opportunities for functionalization of less reactive C(sp^3)–H bonds. A central advantage of this strategy is that the free NH_2 group would be restored via facile CO_2 dissociation, making further synthetic manipulations possible without the need for protection and deprotection steps[22–24]. However, the installation of an electron-withdrawing group on nitrogen would also render the α-C–H bond less hydridic[25,26], and would thus decelerate functionalization reactions using electrophilic reagents. We speculated, however, that if we used an electrophilic HAT catalyst that was cationic, such as the quinuclidinium radical cation, we could rely on an electrostatic attraction[27] with the carbamate oxygen to potentially facilitate the transformation (Fig. 1b).

Results and discussion

Our proposed mechanistic cycle for a CO_2-promoted α-alkylation/lactamization of primary aliphatic amines is outlined in Fig. 2a. Irradiation of Ir(III) photocatalyst **PC1** with visible light generates the long-lived excited state *Ir(III) **1**, which is a strong oxidant ($E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +1.21 V versus saturated calomel electrode (SCE) in CH_3CN)[28] capable of oxidizing a HAT catalyst such as quinuclidine ($E_{1/2}^{ox}$ = +1.1 V versus SCE in CH_3CN)[29] to form radical cation **4** and Ir(II) **2**. Meanwhile, the primary alkyl amine reacts readily with CO_2 to form alkylammonium carbamate **6** (ref. [18]). Facilitated by electrostatic attraction[27], the electrophilic quinuclidinium radical **4** should selectively abstract the α-C–H bond of the in situ generated alkylammonium carbamate **6** to produce carbon-centred radical **7**, which adds to an electron-deficient acrylate to furnish alkyl radical **8**. Single-electron reduction of radical **8** by Ir(II) species **2**, followed by protonation[4,19], CO_2 dissociation and intramolecular cyclization, then affords the final γ-lactam product[30].

We began our investigation by using 3-phenyl-1-propylamine **9** and methyl methacrylate **10** as model substrates and found that α-alkylation/lactamization product **11** could be isolated in 80% yield using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ [$dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine] (**PC1**) as the photocatalyst and quinuclidine (**3**) as the HAT catalyst under an atmospheric pressure of CO_2 with illumination by blue light-emitting diodes (LEDs) (Fig. 2b). Control experiments revealed that the photocatalyst, visible light, quinuclidine and CO_2 were all necessary components for achieving high efficiency of this reaction (Supplementary Table 1). To verify if alkylammonium carbamate is involved in the reaction as proposed, carbamate **12** was synthesized[31] and subjected to the optimal reaction conditions in the absence of CO_2; product **11** was isolated in 75% yield (Fig. 2c), lending further support to our proposal.

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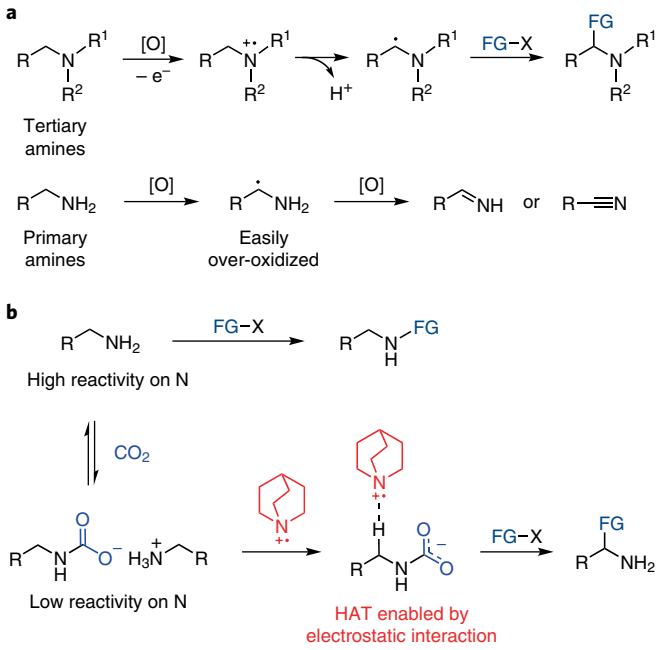

Fig. 1 | Strategies for α-functionalization of aliphatic amines. a, Generation (and the reactivity) of the α-amino radical from tertiary amines is well established, but synthetic studies on the α-amino radical of primary amines are rare, as they can easily be over-oxidized to imines or nitriles. **b**, Our hypothesis using CO_2 as an activator for the α-functionalization of simple primary aliphatic amines relies on an electrostatic attraction between the in situ-formed carbamate and quinuclidinium radical cation. CO_2 also serves as a temporary protecting group to decrease the nucleophilicity of the NH_2 group (counterion omitted for clarity). R, R^1, R^2 and X denote a general organic group. FG, functional group.

With the optimal conditions in hand, we investigated the scope of the reaction and found that a diverse array of primary amines and acrylates are viable in this transformation, providing γ-lactams **13**–**57** in moderate to good yields and with diastereomeric ratios, where applicable, ranging from 1:1 to 2.3:1 (Fig. 3). Acrylates with or without an α or β substituent are tolerated, providing the desired products in reasonable to good yields (**13**–**18**, 41–81% yield). In addition to acrylate, methacrylonitrile may be coupled to give cyclic amidine with moderate efficiency (**19**, 54% yield). With respect to primary aliphatic amines, a broad range of simple amines with a linear or branched alkyl chain are successfully alkylated and cyclized to afford γ-lactams **20**–**28** in 50–75% yields. Amines with an α-substituent and cyclic primary amines are well tolerated, furnishing γ-lactams with a tetrasubstituted stereocentre in moderate to good yields (**29**–**37**, 43–70% yield). Sterically demanding primary amines are converted into the desired products **38** and **39** in 52% and 66% yields, respectively. Notably, primary alkyl amines with additional functionalities are also compatible with this protocol. For example, fluorinated amines (**40**, **41**), *tert*-butyldimethylsilyl (TBS)-protected alkanolamine (**42**, **43**), β-alanine ethyl ester (**44**), amines bearing a bisbenzylic hydrogen (**45**, **46**) or an acetal functionality (**47**, **48**) all underwent the reaction smoothly to afford the desired products in 45–75% yield. Moreover, heteroaryl groups commonly found in pharmaceuticals, such as pyridinyl (**49**), imidazolyl (**50**), isoxazolyl (**51**) and thiazolyl (**52**), could be incorporated into the γ-lactam products with equally high efficiency (62–80% yield). Comparable yields of **50** and **52** could be obtained with lower photocatalyst loading when the reactions were carried out on 1 or 3 mmol scales. Alkene- or alkyne-containing amines (**53**, **54**), mono-Boc (Boc, *tert*-butoxycarbonyl) protected diamines (**55**, **56**) and the L-lysine derivative (**57**) are also effective substrates. Of particular note is that when *N*-Boc-1,3-propanediamine was subjected to the standard reaction conditions, alkylation occurred selectively at the α position of the free NH_2 group to give γ-lactam **55** in 64% yield, demonstrating that even subtle difference between *N*-Boc carbamate and the in situ generated alkylammonium carbamate can be differentiated under the reaction conditions. It is also noteworthy that the α-amino radical derived from the anionic carbamate is more nucleophilic than that derived from the *N*-Boc carbamate, leading to a faster alkylation.

A series of mechanistic studies were performed to better understand the mechanism of the reaction. Stern–Volmer luminescence quenching experiments revealed that quinuclidine efficiently quenches the excited state of photocatalyst **PC1** while primary amine **9** and the corresponding carbamate **12** do not (Supplementary Section 6). Careful monitoring of the reaction between primary

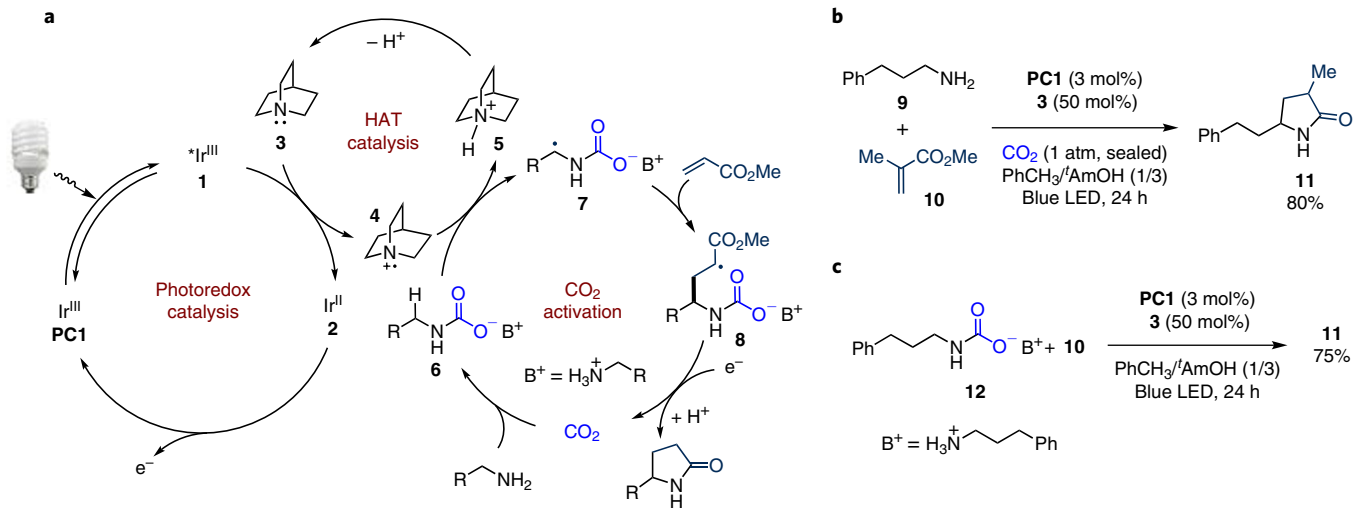

Fig. 2 | Reaction development. a, Proposed mechanism for CO_2-promoted α-alkylation/lactamization of primary aliphatic amines. One-electron oxidation of quinuclidine **3** by excited photocatalyst **1** furnishes quinuclidinium radical cation **4**, which undergoes selective HAT with in situ-formed alkylammonium carbamate **6** to afford radical **7**. Addition into acrylate provides adduct **8**, which is reduced by reduced photocatalyst **2** and protonated to give the final γ-lactam product after CO_2 dissociation. **b**, Photocatalyst **PC1** and quinuclidine are identified as the optimal catalyst combination in the model reaction using a mixture of toluene and ^{t}AmOH as the solvent. **c**, Reaction using preformed alkylammonium carbamate **12** in the absence of CO_2 provides the desired product in 75% yield, which supports our proposal. Isolated yields are shown. ^{t}AmOH, *tert*-amyl alcohol.

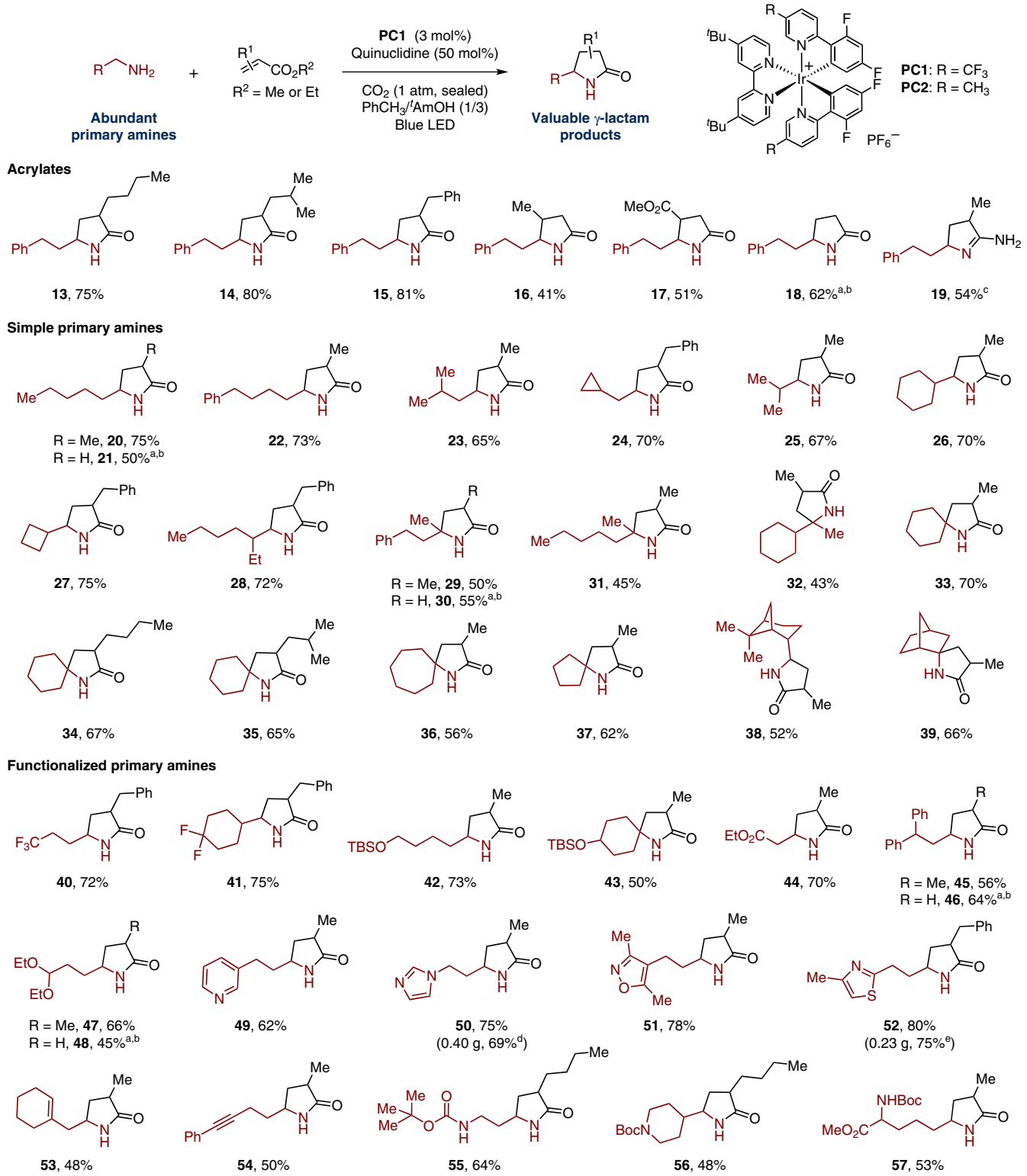

Fig. 3 | Exploration of substrate scope. The scope of the reaction was found to be very broad, with a wide variety of primary amines and acrylates applicable in this reaction. Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale irradiated with a 34 W Kessil blue LED. Isolated yields are reported. All products are formed as racemates and the diastereomeric ratios (d.r.), where applicable, are between 1:1 and 2.3:1; see Supplementary Section 5 for details. TBS, *tert*-butyldimethylsilyl; Boc, *tert*-butoxycarbonyl. [a]Reaction was performed using **PC2** as the photocatalyst and toluene as the solvent. [b]The primary amine solution was stirred for 30 min under CO_2 before adding the other reagents. [c]Methacrylonitrile was used in place of acrylate. [d]Reaction performed on 3 mmol scale with 1 mol% of **PC1**. [e]Reaction performed on 1 mmol scale with 2 mol% of **PC1**.

amine **9** and acrylate **58** in the presence and absence of CO_2 revealed that acrylate consumption and product formation are much faster in the presence of CO_2 (Fig. 4a). If the sole role of CO_2 is to insulate the amine from undergoing *N*-alkylation via reversible formation of alkylammonium carbamate, the acrylate should be consumed faster in the absence of CO_2. The fact that the reverse is true suggests that

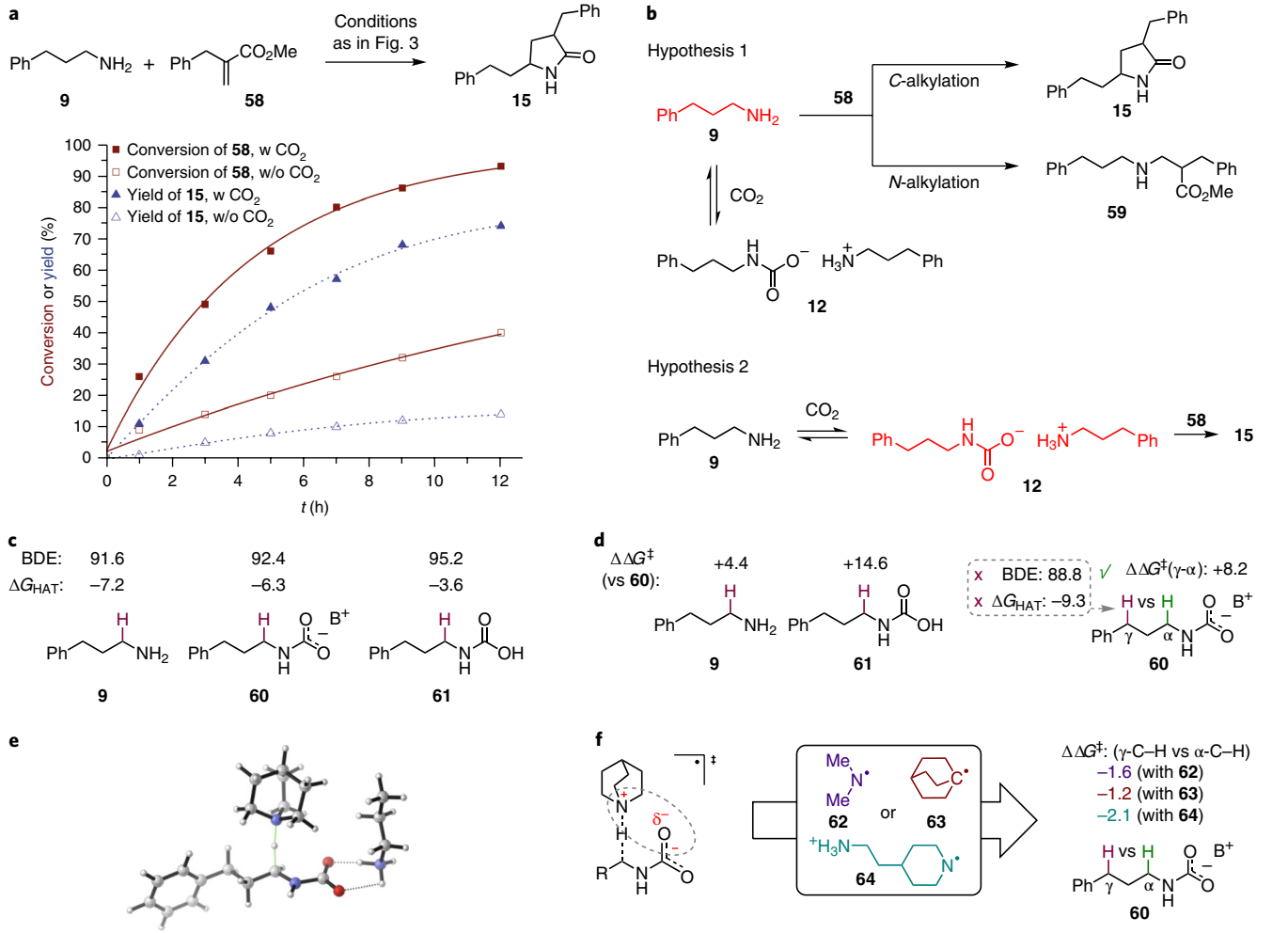

Fig. 4 | Mechanistic and computational studies. a, ^{1}H NMR studies show that both acrylate consumption and product formation are faster in the presence of CO_2. **b**, Two hypotheses for the role of CO_2 in the reaction. In hypothesis 1, where CO_2 is merely a protecting group, acrylate consumption and product formation should be slower in the presence of CO_2 due to the lower concentration of free amine **9**. In hypothesis 2, where CO_2 is an activator, acrylate consumption and product formation should be faster in the presence of CO_2 due to the conversion of free amine into more reactive alkylammonium carbamate **12**. **c**, Computed thermodynamic descriptors are unable to explain the rate acceleration by CO_2 as well as the high α-C–H selectivity. **d**, Selectivity and reactivity enhancement are achieved in the transition state. **e**, Computed HAT transition state. **f**, Computational test for the role of electrostatics—removal or relocation of positive charge in the HAT reagent diminishes site selectivity. Values are energies in kcal mol^{-1}. BDE, bond dissociation energy. $B^+ = n\text{-}C_3H_7NH_3^+$.

the in situ generated carbamate is activated towards productive HAT and subsequent alkylation by acrylate (Fig. 4b).

We subsequently undertook computational studies to gain further insight into the mechanistic aspects of this transformation and the origins of selectivity (Fig. 4c–f). Using a high-level but affordable quantum-chemical approach at the CPCM (toluene) DLPNO-CCSD(T)/def2-TZVPD//CPCM (toluene) M06L/6-31+G(d,p) level of theory (see Supplementary Section 9 for details), we initially assessed the effect of CO_2 incorporation on the bond dissociation energy (BDE) of various C–H sites in the substrate. This analysis revealed that there is no pronounced difference in BDEs of the reactive C–H bonds between the free amine **9** and CO_2-incorporated analogues, that is, alkylammonium carbamate **60** or carbamic acid **61** (Fig. 4c). Moreover, for carbamate **60**, BDEs predict the benzylic C–H site (γ) to be the weakest (BDE = 88.8 kcal mol^{-1}), yet selective functionalization at the α-C–H site was observed experimentally. Thus, although commonly utilized as guidelines to rationalize and predict radical reactivities, thermodynamic descriptors, such as radical stabilities or bond strengths, do not allow rationalization of the observed site selectivity nor reactivity enhancement under CO_2 conditions. By contrast, our calculations of the activation free energy barriers for hydrogen atom abstraction by a quinuclidinium radical cation were fully consistent with experimental observations (Fig. 4d). First, abstraction of the hydrogen atom at the benzylic C–H site (γ) has a $\Delta\Delta G^‡$ of +8.2 kcal mol^{-1} higher activation free energy barrier than abstraction at the α-C–H site, in line with exclusive functionalization at the α site. We observed the same trend also with other substrates containing an activated γ-C–H site (for example, the starting materials of **45**, **49**, **51** and **52**, Supplementary Fig. 8). Second, the carbamate **60** is predicted to be more reactive relative to the free amine **9** ($\Delta\Delta G^‡ = +4.4$ kcal mol^{-1}), consistent with the reactivity enhancement observed (Fig. 4a). Similar observations of counter-thermodynamic reactivity trends in HAT reactions have previously been made, with the underlying causes being ascribed to polarity matching[4,6], entropy control[32] and steric factors[33]. Our data suggest that the origin of the exquisite site selectivity is due primarily to stabilizing electrostatic interactions in the transition state between the reactive centre α to the alkylammonium carbamate and the proximal positive charge of the quinuclidinium, displaying therefore the lowest activation barrier over alternative sites. In line with this, we predict decreased selectivities for HAT reagents for which the charge is absent (**62**, **63**) or is located more distantly (**64**), regardless of the size of the reagent and the central atom (nitrogen versus carbon), rendering the benzylic C–H site (γ) more reactive in these cases (Fig. 4f and Supplementary Fig. 6).

Conclusions

In summary, we have developed a direct alkylation of primary amines using photoredox catalysis. The key finding is the use of CO_2 to form the carbamate functionality in situ, which accelerates C–H bond activation by HAT. We present experimental and computational evidence in support of an electrostatic attraction again highlighting the unique role of the carbamate, which is capable of undergoing accelerated HAT with the quinuclidinium radical cation in spite of its decreased hydridicity.

Methods

General procedure for α-alkylation/lactamization of primary aliphatic amines. To a 25 ml oven-dried Schlenk sealing tube containing a magnetic stir bar were added $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (6.6 mg, 0.006 mmol), quinuclidine (11.1 mg, 0.1 mmol), primary alkyl amine (0.3 mmol), acrylate (0.2 mmol) and 0.5 ml of toluene and ^{t}AmOH mixture (1/3, vol/vol). The reaction tube was sealed, frozen by liquid nitrogen for 10 min, and evacuated under vacuum and backfilled with CO_2 (balloon) three times through a three-way stopcock. Liquid nitrogen and the CO_2 balloon were then removed. The reaction tube was sealed and allowed to stand at room temperature for 10 min, at which time the plug of the tube was slowly opened to release the excess CO_2 gas. The tube was then resealed and placed approximately 3 inches away from a Kessil LED illuminator. The reaction mixture was stirred and irradiated for 24–48 h. The internal temperature was measured to be approximately 40 °C using an infrared thermometer. The crude mixture was then concentrated in vacuo and purified by flash chromatography on silica gel with a 4g column on a Teledyne ISCO Combi*Flash Rf*$^+$ Lumen instrument using the indicated solvent system.

Data availability. All data generated and analysed during this study are included in this Article and its Supplementary Information, and are also available from the corresponding authors upon reasonable request.

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Author contributions

T.R. and J.Y. conceived the concept. T.R. directed the investigation. J.Y. performed the experiments and analysed the data. I.K. and F.S. carried out computational studies. J.Y., T.R., I.K. and F.S. collated the data, discussed the implications and prepared the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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