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Direct α -alkylation of primary aliphatic amines enabled by CO₂ and electrostatics

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Abstract

Primary aliphatic amines are important building blocks in organic synthesis due to the presence of a synthetically versatile NH₂ group. While *N*-functionalization of primary amines is well-established, selective *C*-functionalization of unprotected primary amines remains challenging. Here we report the use of CO₂ 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 CO₂ 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 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.

Graphical abstract

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Author Contributions

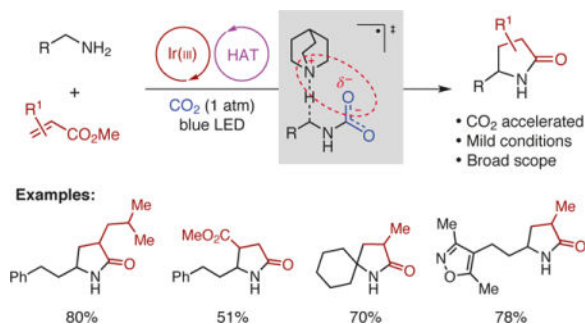
T.R. and J.Y. conceived the concept. T.R. directed the investigation. J.Y. performed the experiments and analysed the data. I.K. and F.S. carried out computational studies. J.Y., T.R., I.K. and F.S. collated the data, discussed the implications and prepared the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Competing financial interests

The authors declare no competing financial interests.



Selective functionalization of aliphatic C–H bonds remains a considerable challenge¹. 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, carbon-hydrogen bonds adjacent to alcohols, ethers and amides have been demonstrated to be susceptible to HAT chemistry with electrophilic agents such as thiyl radical^{2,3} and quinuclidinium radical cation^{4–6}. These processes are selective because of a polarity match² – 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 potential¹⁴ and propensity for overoxidation 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 CO₂ to form carbamates¹⁸. 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 NH₂ motif (Fig. 1b)²¹, thereby providing opportunities for functionalization of less reactive C(sp³)–H bonds. A central advantage of this strategy is that the free NH₂ group would be restored via facile CO₂ 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 quinuclidinium radical cation, we could rely on an electrostatic attraction²⁷ with the carbamate oxygen to potentially facilitate the transformation (Fig. 1b).

Results and discussion

Our proposed mechanistic cycle for a CO₂-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 ($E_{1/2}^{\text{red}}$ [*Ir^{III}/Ir^{II}] = +1.21 V vs saturated calomel electrode (SCE) in CH₃CN)²⁸ capable of

oxidizing a HAT catalyst such as quinuclidine ($E_{1/2}^{\text{ox}} = +1.1$ V vs SCE in CH_3CN)²⁹ to form radical cation **4** and Ir(II) **2**. Meanwhile, primary alkyl amine reacts readily with CO_2 to form alkylammonium carbamate **6** (ref. 18). Facilitated by electrostatic attraction²⁷, the electrophilic quinuclidinium radical **4** should selectively abstract α -C-H bond of the *in situ* generated alkylammonium carbamate **6** to produce carbon-centered radical **7**, which adds to an electron-deficient acrylate to furnish alkyl radical **8**. Single-electron reduction of the radical **8** by the Ir(II) species **2** followed by protonation^{4,19}, CO_2 dissociation, and intramolecular cyclization then affords the final γ -lactam product³⁰.

We began our investigation by using 3-phenyl-1-propylamine **9** and methyl methacrylate **10** as the model substrates and found that α -alkylation/lactamization product **11** could be isolated in 80% yield using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ [dF(CF₃)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 LEDs (Fig. 2b). Control experiments revealed that 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 synthesized³¹ and subjected to the optimal reaction conditions in the absence of CO_2 ; in the event, product **11** was isolated in 75% yield (Fig. 2c), lending further support to our proposal.

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 stereocenter 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**), 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 scale. Alkene- or alkyne-containing amines (**53**, **54**), mono-Boc protected diamines (**55**, **56**), and 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 occurs 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 reaction between primary 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 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 on the mechanistic aspects of this transformation and the origins of selectivity (Fig. 4c). 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 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** versus CO_2 -incorporated analogues, *i.e.* alkylammonium carbamate **60** or carbamic acid **61** (Fig. 4c). Moreover, for carbamate **60**, BDEs predict the benzylic C–H site (γ) to be weakest, 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. Firstly, abstraction of the hydrogen atom at the benzylic C–H site (γ) has a $G^\ddagger = +8.2$ kcal/mol 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 (*e.g.* the starting materials of **45**, **49**, **51** and **52**, see Supplementary Fig. 8). Secondly, the carbamate **60** is predicted to be more reactive relative to the free amine **9** ($G^\ddagger = +4.4$ kcal/mol), 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-control³², and steric factors³³. 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 center 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 *vs* carbon), rendering the benzylic C–H site (γ) more reactive in these cases (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 CO₂ to form the carbamate functionality *in situ* which accelerates the 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 hydricity.

Methods

General procedure for the 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(CF₃)ppy)₂(dtbbpy)]PF₆ (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, v/v). The reaction tube was sealed, frozen by liquid nitrogen for 10 minutes, and evacuated under vacuum and backfilled with CO₂ (balloon) three times through a three-way stopcock. Liquid nitrogen and the CO₂ balloon were then removed. The reaction tube was sealed and allowed to stand at room temperature for 10 minutes, at which time the plug of the tube was slowly opened to release the excess of CO₂ 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 the indicated period of time. 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 4 gram column on a Teledyne ISCO CombiFlash[®] 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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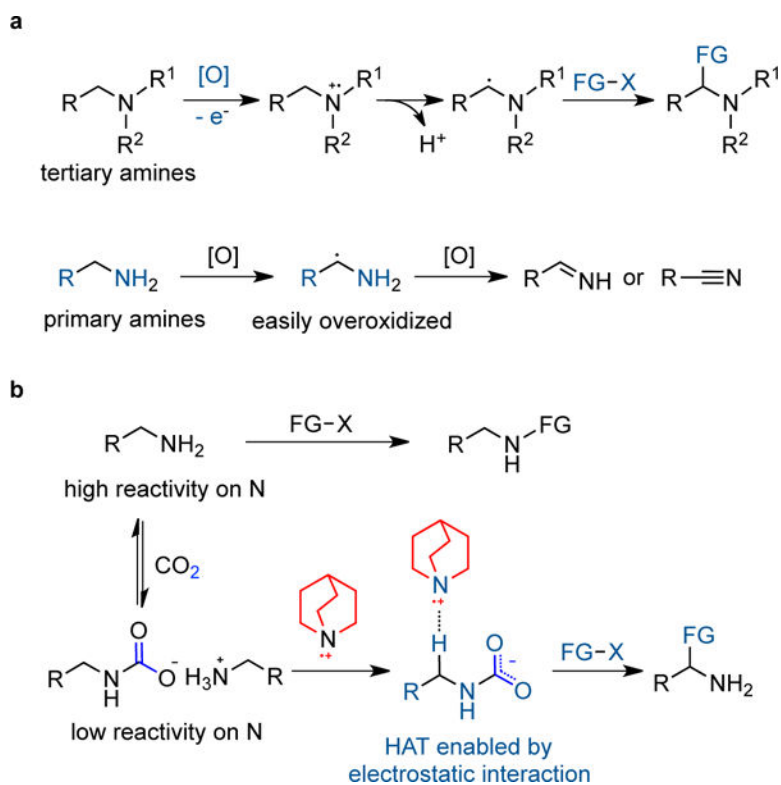


Figure 1. Strategies for α -functionalization of aliphatic amines

a. Generation and reactivity of α -amino radical from tertiary amines have been well established but synthetic studies on α -amino radical of primary amines are rare as they can be easily overoxidized 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. HAT, hydrogen atom transfer.

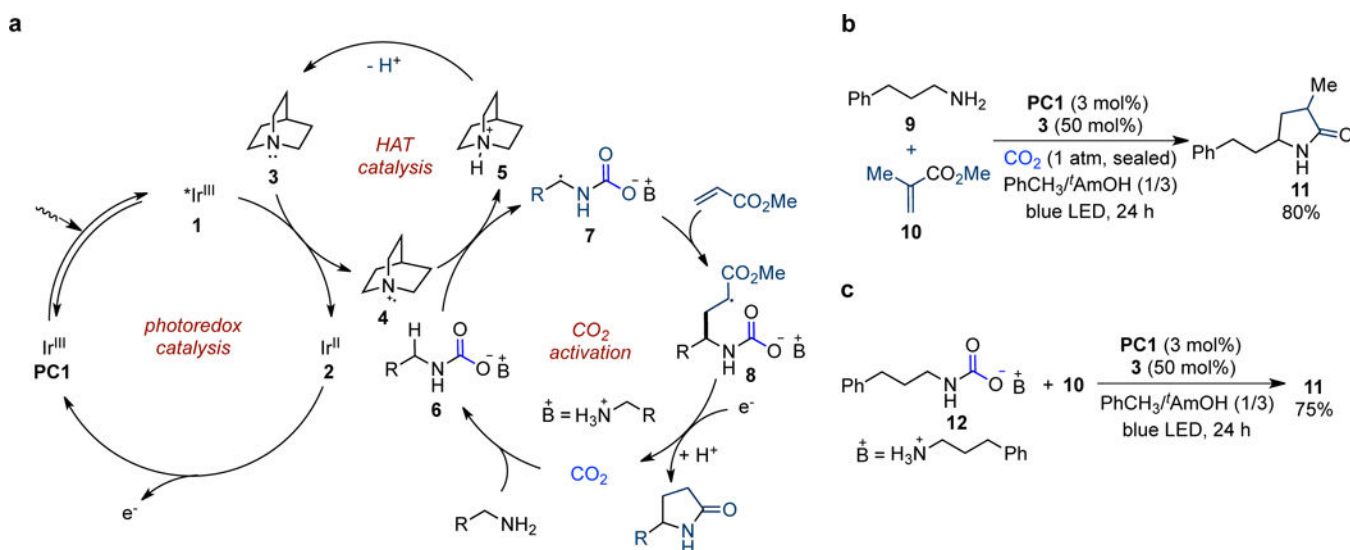


Figure 2. Reaction development

a, Proposed mechanism for the CO_2 -promoted α -alkylation/lactamization of primary aliphatic amines. One-electron oxidation of quinuclidine **3** by the excited photocatalyst **1** furnishes quinuclidinium radical cation **4**, which undergoes selective HAT with the *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.

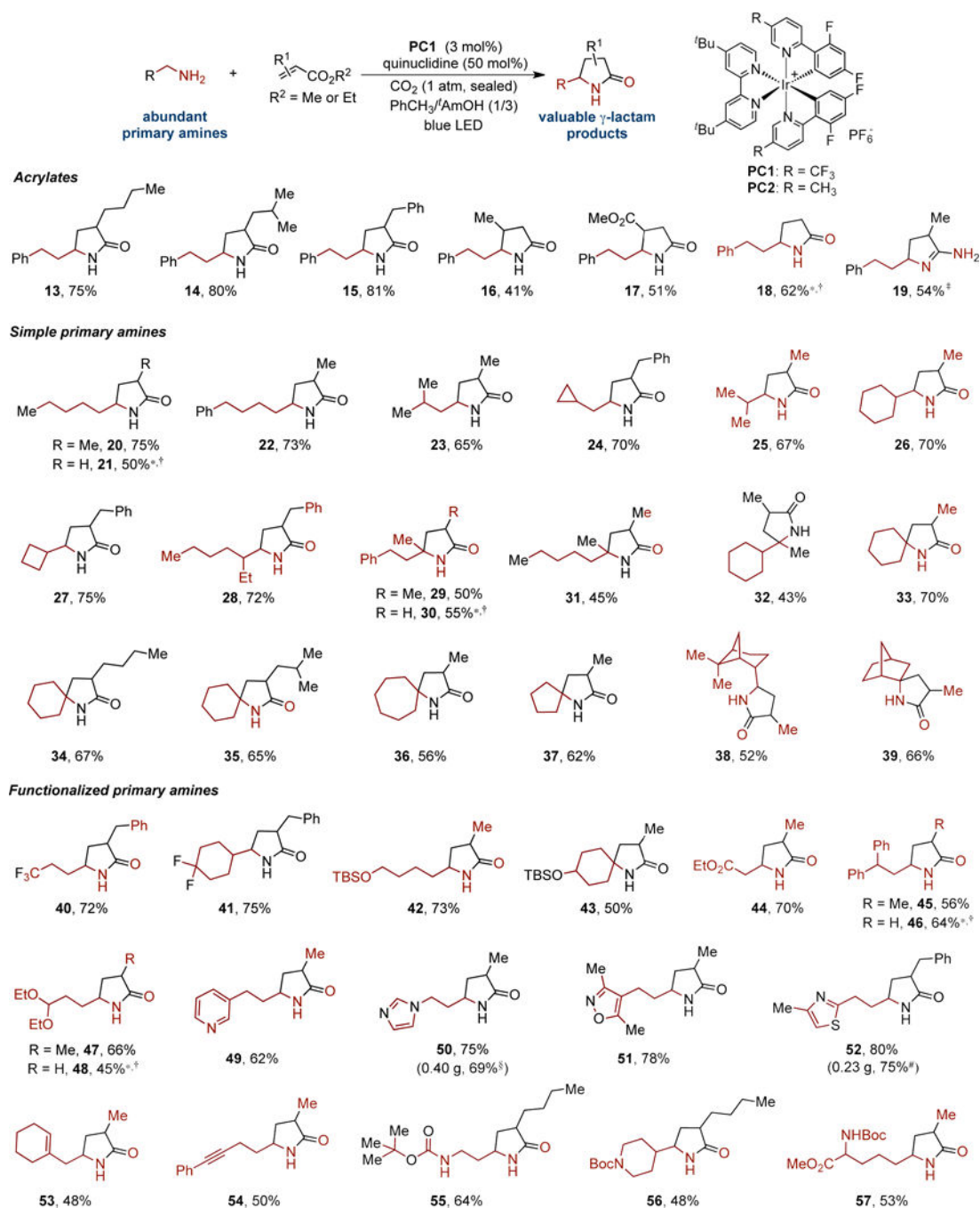


Figure 3. Exploration of substrate scope

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 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 Information for details. TBS, *tert*-butyldimethylsilyl; Boc, *tert*-butoxycarbonyl; *Reaction was performed using **PC2** as the photocatalyst and toluene as the solvent; [†]The primary amine solution was stirred for 30

minutes under CO₂ before adding the other reagents.†methacrylonitrile was used in place of acrylate;§Reaction performed on 3 mmol scale with 1 mol% of **PC1**.#Reaction performed on 1 mmol scale with 2 mol% of **PC1**.

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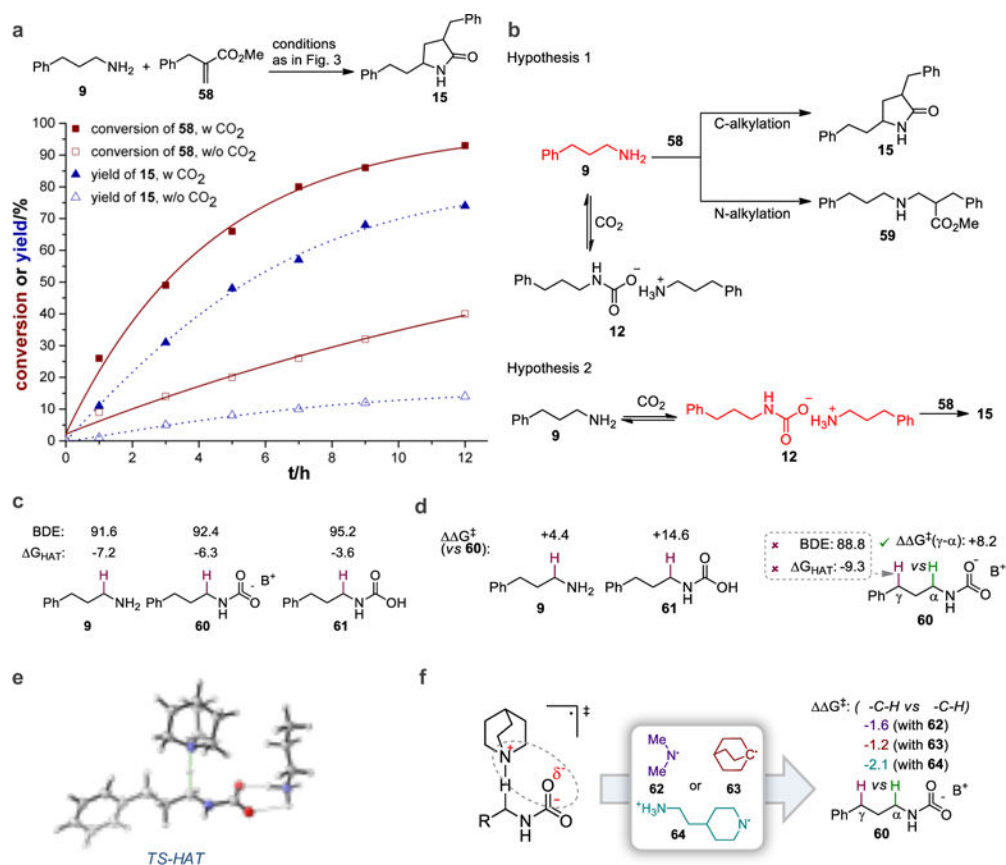


Figure 4. Mechanistic and computational studies

a, ¹H nuclear magnetic resonance (NMR) studies show that both acrylate consumption and product formation are faster in the presence of CO₂. **b**, Two hypotheses for the role of CO₂ in the reaction. In hypothesis 1, where CO₂ is merely a protecting group, acrylate consumption and product formation should be slower in the presence of CO₂ due to the lower concentration of free amine **9**. In hypothesis 2, where CO₂ is an activator, acrylate consumption and product formation should be faster in the presence of CO₂ due to the conversion of free amine into more reactive alkylammonium carbamate **12**. **c**, Computed thermodynamic descriptors are unable to explain rate-acceleration by CO₂ as well as high α -C-H selectivity. **d**, Selectivity and reactivity enhancement are achieved in the transition state (TS). **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. BDE, bond dissociation energy. B⁺ = *n*-C₃H₇NH₃⁺.