Access to Cyclic *N*-Trifluoromethyl Ureas through Photocatalytic Activation of Carbamoyl Azides

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Supporting Information Placeholder

ABSTRACT: We report the mild activation of carbamoyl azides to the corresponding nitrenes by a blue light/[Ir] catalyzed strategy, which enables the stereospecific access to *N*-trifluoromethyl imidazolidinones and benzimidazolones. These novel structural motifs proved to be highly robust, allowing their downstream diversification. On the basis of our combined computational and experimental studies we propose that an electron rebound with the excited metal catalyst is undergone, involving a reduction-triggered nitrogen loss, followed by oxidation to the corresponding carbamoyl nitrene and subsequent C-H functionalization.

Access to new structural space with altered properties is imperative to meet the ever-growing demands for the discovery of new function.[1] In this context, fluorination takes up a prominent role for its potential to modify the physical properties of organic molecules.[2] Given the widespread abundance of nitrogen in functional materials, pharmaceuticals and agrochemicals,[3] its modification *via* trifluoromethylation is of interest, but has been limited by a lack of general and efficient synthetic methodology to access these motifs.[4] While the development of suitable methodology to access trifluoromethylated amines (R_2NCF_3),[5] hydrazines ($R(CF_3)N\text{-}NR_2$),[6] indoles[6a,7] and the *N*-CF_3 carbonyl motif[8] has progressed in recent years, to date, there is no efficient synthetic strategy to access cyclic *N*-CF_3 carbonyl compounds.[9] Especially cyclic ureas are potent pharmaceuticals and find applications as, for example, anti-hypertensive,[10] anti-tumor,[11] anti-viral[12] or anti-bacterial drugs[13] (see Figure 1) and modification to the *N*-CF_3 analogues would be expected to impact their lipophilicity and bioavailability features, among other properties.[2] The current synthetic repertoire is limited to making linear/acyclic *N*-CF_3 ureas however (Figure 1).[8a,14]

Building on our group's previous report of the synthesis of acyclic *N*-CF_3 carbamoyl azides (Figure 1),[8a] we questioned whether we could potentially convert these species to *N*-CF_3 carbamoyl nitrenes and enable their subsequent C_{sp2}-H or C_{sp3}-H insertion to form the desired aromatic as well as aliphatic cyclic *N*-CF_3 ureas. While Lwowski established in 1965 that azides can be activated under UV irradiation,[15] for carbamoyl azides[16] the transformation is associated with low yields and selectivities as well as a limited scope. A milder approach would be beneficial, also to access building blocks that are amenable to diversification. For example, UV irradiation does not tolerate C-halogen bonds, which are key for downstream functionalizations. In this context, Yoon, Xiao, König and others showed the viability of azide photosensitization,[17] which allows access to a nitrene intermediate under relatively mild conditions and analogously for related azidoformates.[18] However, carbamoyl nitrenes have not yet been accessed from the corresponding carbamoyl azide precursors under such conditions, which is potentially due to their high triplet energy and low efficiency in the energy transfer.[19] Carbamoyl nitrenes could recently be unlocked from suitably engineered *N*-oxyureas precursors,[20] which are ultimately synthetically derived from the *N*-hydroxy carbamates (before substitution with an amine, see Figure 1). Since secondary *N*-CF_3 amines, *i.e.* R(H)*N*-CF_3, are so far only accessible for a narrow range of aromatic compounds[5e] and/or are of low stability[21] the corresponding *N*-CF_3 oxyurea is currently synthetically inaccessible and this chemistry therefore not currently transferable to access *N*-CF_3 carbamoyl nitrenes.

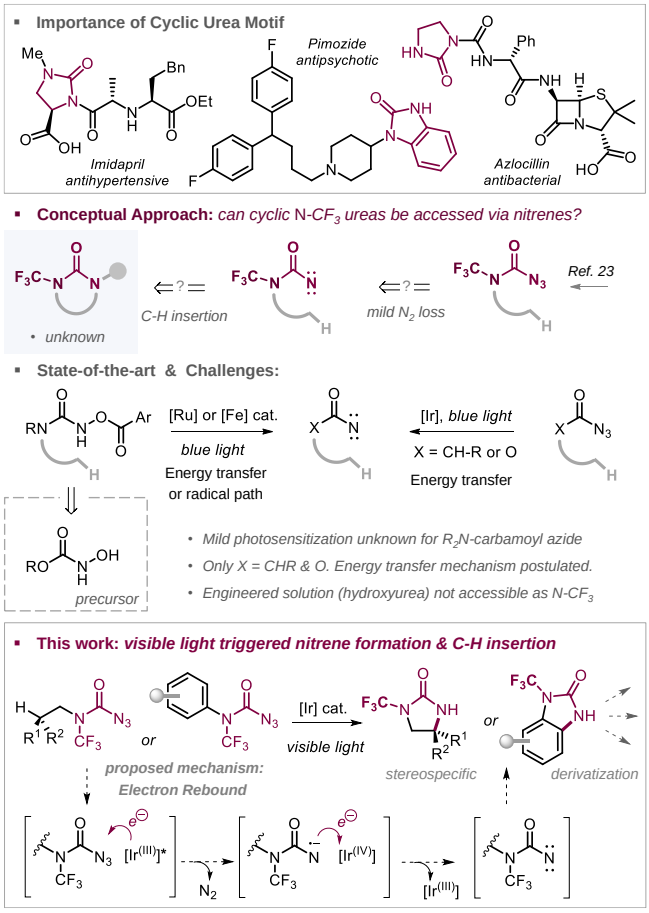
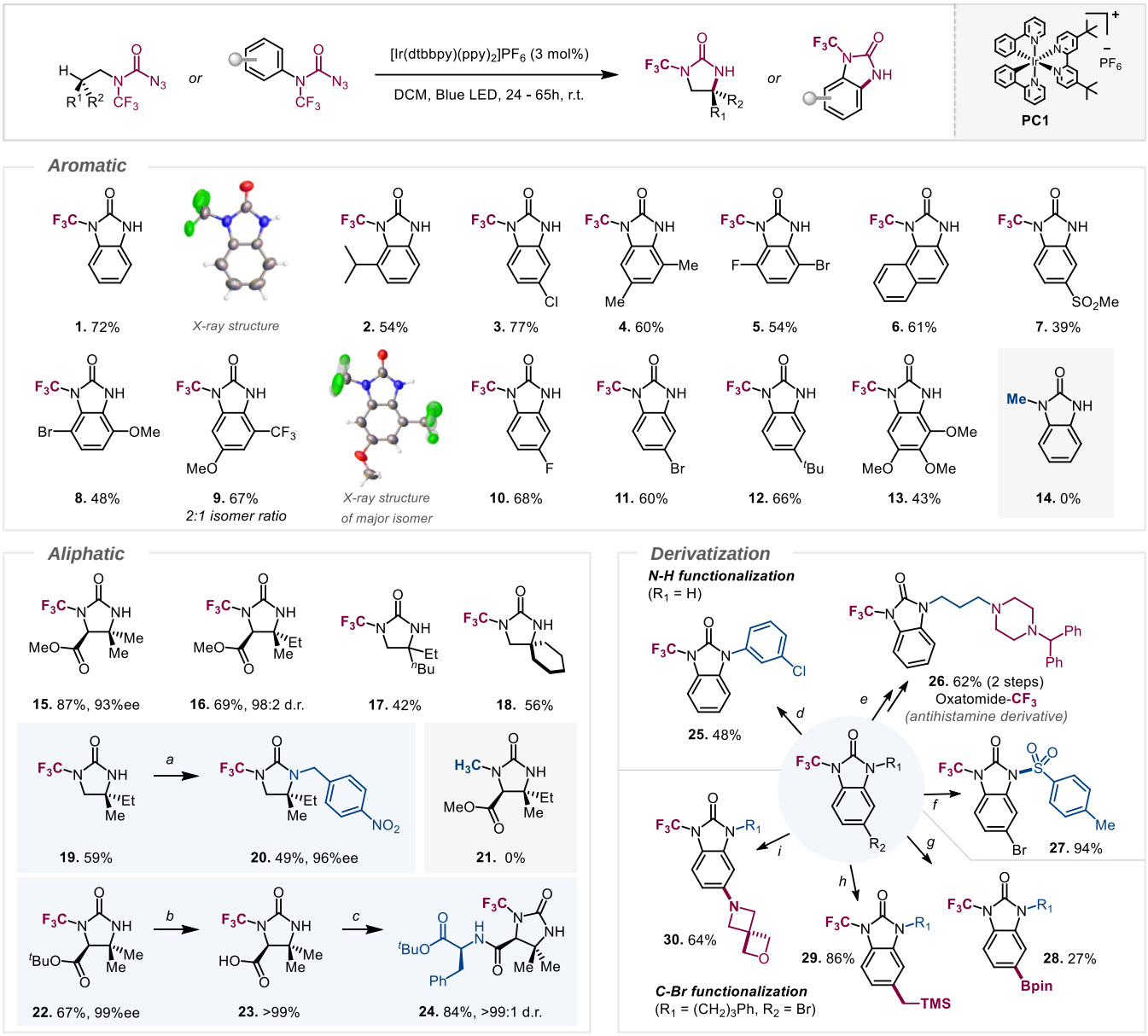


Figure 1. Importance of cyclic ureas, challenges and this work.

Scheme 1. Scope of the reaction and derivatization of synthesized cyclic *N*-CF_3 ureas.



Reaction conditions for derivatizations: [a]NaH (2 equiv.), THF, r.t., 1 h; then alkyl bromide (3 equiv.), 60 °C, 24 h. [b]TFA:DCM (20% v/v), r.t., 4h. [c]H-Phe-O^{t}Bu (1.1 equiv.), HBTU (1.2 equiv.), DIEA (4 equiv.), DCM, r.t., 13 h. [d]Aryl iodide (2.4 equiv), Cs_2CO_3 (1.8 equiv.), CuI (1 equiv.), phenanthroline (1 equiv.), DMF, 100 °C, 4 h (R_1=R_2=H). [e]1. 1,3-dibromopropane (5 equiv.), K_2CO_3 (1 equiv.), TBAB (5 mol%), H_2O, μw, 60 °C, 2 h; 2. 1-benzhydrylpiperazine (2 equiv.), K_2CO_3 (1 equiv.), DMF, r.t., 18 h (R_1=R_2=H). [f]TsCl (1.1 equiv), DMAP (10 mol%), Et_3N (1 equiv.) DCM, r.t., 3 h. (R_1=H, R_2=Br). [g]B_2pin_2 (1.1 equiv.), KOAc (3 equiv.), $PdCl_2(MeCN)_2$ (3 mol%), dppf (3 mol%), DMF, 110 °C, 18 h [R_1=$(CH_2)_3$Ph, R_2=Br]. [h]$TMSCH_2MgCl$ (1.5 equiv), Pd(I) (2.5 mol%), PhMe, r.t., 20 mins [R_1=$(CH_2)_3$Ph, R_2=Br]. [i]Amine (1.5 equiv.), $Pd(OAc)_2$ (20 mol%), P^tBu_3 (20 mol%), Cs_2CO_3 (1.5 equiv.) PhMe, 110 °C, 18 h [R_1=$(CH_2)_3$Ph, R_2=Br].

We herein report the realization of a photosensitized conversion of aromatic and aliphatic *N*-CF_3 carbamoyl azides to the corresponding cyclic *N*-CF_3 ureas and showcase the robustness of the new motif in numerous follow up derivatizations.

To our delight, when we exposed a phenyl *N*-CF_3 carbamoyl azide to the widely used Ir photocatalyst, $[Ir(dtbbpy)(ppy)_2]PF_6$ (**PC1**), under blue light irradiation in DCM, we observed the formation of the cyclic *N*-CF_3 urea **1** at room temperature (in 72% yield), see Scheme 1. By contrast, when we attempted to synthesize the corresponding *N*-Me analogue (**14**), no reaction was seen and unreacted azide was exclusively recovered. The structure of the cyclic *N*-CF_3 urea **1** was unambiguously confirmed by X-ray crystallography (illustrated in Scheme 1, for details see SI). Closer inspection of the structure of **1** as compared to its *N*-Me counterpart (CCDC 967012[22]) revealed that the N_{CF3}-C(=O) bond is slightly elongated (1.42 Å) compared to N_{CH3}-C(=O) (1.38 Å), paralleling our previous observations with other *N*-CF_3 compounds.[6a,23]

We subsequently explored the wider scope of this transformation and observed that electron-donating (trimethoxy **13** or alkyl **2**, **4**) and withdrawing groups, such as CF_3 (**9**) or C-halogen (**3**, **5**, **8**, **10**, **11**) or sulfone (**7**), could be tolerated. The tolerance of C-Br and C-Cl is testimony of the mildness of the process. A UV-light triggered transformation would not tolerate such groups,[24] which in turn are useful linchpins for follow-up derivatizations. Moreover, the polyaromatic **6** was exclusively formed from 1,5-cyclization; the 1,6-process did not take place. For the non-symmetric case **9** we

obtained a mixture of the two possible isomers in a 2:1 ratio. A suitable crystal of the major isomer was grown and analyzed by X-ray crystallography (for details see SI). The cyclic *N*-CF_3 urea motif proved to be robust towards purification. For example, the products could be isolated using acid/base extraction. Direct purification by column chromatography was similarly effective.

Encouraged by the pronounced stability of the aromatic cyclic *N*-CF_3 ureas, we subsequently set out to extend our studies to non-aromatic examples, *i.e.* *N*-CF_3 imidazolidin-2-ones (see Scheme 1, bottom left). The same conditions proved to be effective for non-aromatic *N*-CF_3 carbamoyl azides and we successfully generated the corresponding imidazolidinones. The transformation was successful for these fully aliphatic molecules and tolerated substituents α to the *N*-CF_3 (**15, 16, 22**) and also at the C-N bond forming carbon center.

Most notably, the ring formation and formal nitrene C-H insertion was found to be fully stereospecific. For example, the isoleucine derived *N*-CF_3 carbamoyl azide gave rise to **16** in high yield as a single diastereomer (d.r. 98:2). Also, in the absence of the ester substituent the ring formation was found to be fully stereospecific: **20** was isolated in high enantiomeric purity (following *N*-H arylation of the stereospecifically formed imidazolidinone **19**, which was necessary to induce sufficient UV absorption for HPLC analysis).

With the methodology to construct cyclic *N*-CF_3 ureas established, we subsequently examined the robustness of the motif in follow-up derivatizations to explore its wider potential as a building block. The deprotection of the *tert*-butyl ester of **22** with 20 mol% TFA in DCM was readily achieved and gave **23** in quantitative yield (Scheme 1). The structure was confirmed by crystallographic analysis (for details see SI). The subsequent coupling with an amino acid under typical peptide coupling conditions gave **24** in good yield and with a diastereomeric ratio of >99:1. Moreover, *N*-arylation under Ullman conditions (Cu, 100 °C, 16 h) to **25** was feasible as well as *N*-alkylation to ultimately prepare the *N*-CF_3 analogue of Oxatomide, an antihistaminic drug **26**. Sulfonylation to the tosyl urea, prevalent in antidiabetic drugs,[25] was also possible to furnish **27**, of which the structure was also confirmed by crystallographic analysis (for details see SI). The *N*-CF_3 benzimidazolone core was also amenable to traditional cross coupling with the bromide moiety undergoing borylation (**28**), alkylation (**29**) and amination (**30**). These examples illustrate the stability of the *N*-CF_3 core in follow-up synthetic manipulations and therefore its promising potential as a building block in novel compounds of relevance to materials, agrochemicals or the pharmaceutical arenas.

Intrigued by the observed reactivity, we set out to gain further insight on the distinct effect of *N*-CF_3. When we applied the same conditions to an analogous *N*-Me carbamoyl azide (instead of *N*-CF_3 in analogy to the aromatic case **14** but now en-route to **21**), no marked reaction occurred and instead unreacted carbamoyl azide was recovered. This observation is in line with the literature and current lack of precedent of photosensitized carbamoyl nitrene activation.

In the absence of photocatalyst and/or light we observed no reaction of the *N*-CF_3 carbamoyl azide. For alternative azidoformates and hydroxamates, an energy transfer mechanism was previously suggested to be operative and that triplet nitrene intermediates would be formed.[19] Despite the invoked triplet nature of the nitrene, Chang observed (for one substrate) stereoretention in the corresponding C_{sp3}-H insertion step to form a cyclic amides.[19] By contrast, Beauchemin saw loss of stereochemical integrity in photosensitized C-H amination with *N*-oxyureas, albeit with a structurally different example.[20a] On the basis of these precedents, both a singlet or triplet nitrene could in principle be involved in our system.

However, interestingly our calculation[26] of the triplet energy gap for energy transfer to the azide at the SMD (MeCN) MN15/def2-TZVPP//SMD (MeCN) ωB97XD/6-31+G(d,p) level of theory[27] indicated 57.9 kcal/mol for the *N*-CF_3 carbamoyl azide precursor of **15** (**I**), but virtually the same 56.4 kcal/mol for the corresponding *N*-Me analogue (**II**, see Figure 2). Similarly, we obtained analogous activation barriers and exergonicities for the subsequent N_2-loss to either *N*-Me or *N*-CF_3 carbamoyl nitrene. Yet, only the *N*-CF_3 system is reactive with **PC1** which has a calculated emission energy (emission λ_{max}) of E' = 57.7 kcal/mol.[28] Surprisingly, our tests with the fluorinated photocatalyst analogue **PC2** that displays a marginally greater calculated emission energy of E' = 60.8 kcal/mol neither converted the *N*-CF_3 (**I**) nor the *N*-Me (**II**) substrate. Evidently, the catalyst's emission energy does not correlate with the observed reactivity, suggesting that an energy transfer mechanism[29,30] might not be operative. To this end, we additionally performed frontier molecular orbital analyses of the substrates and catalysts as well as UV-vis measurements to examine whether there are possibly different interactions of the *N*-CF_3 *vs.* *N*-Me substrates with the catalysts, which in turn could potentially affect the kinetics of energy transfer despite analogous thermodynamics.[31] However, our UV-data indicated no marked interactions, and the orbital analyses also revealed no correlation (see supporting information for details), further underscoring that an energy transfer mechanism appears unlikely.

On the other hand, the *N*-CF_3 carbamoyl azide is more electron-deficient and likely a better electron acceptor than the *N*-Me analogue. Indeed, our calculations of the reduction potentials indicate $E_{1/2}$ = -1.27 V for *N*-CF_3 **I** and $E_{1/2}$ = -1.68 V for *N*-Me **II**, which were confirmed also experimentally by cyclic voltammetry.[32,33] Our calculations of the excited state potential of **PC1** and **PC2** are -1.40 V and -1.15 V respectively, which are in line with the observed reactivities that only **PC1** is capable of activating the *N*-CF_3 substrate **I**, but no catalyst activates *N*-Me **II.** An electron transfer, rather than energy transfer mechanism, appears to explain the observed reactivity difference of *N*-Me *vs.* *N*-CF_3 (see Figure 2).

Our Born-Oppenheimer molecular dynamics calculations[34] of the putative carbamoyl azide radical anion indicated that out of 20 trajectories that we run, nine spontaneously lost nitrogen within 30-60 fs at room temperature,[35] suggesting that if the carbamoyl azide is reduced, the generated azide radical anion would readily lose nitrogen to the corresponding nitrene radical anion. The calculated potential of the oxidation of the *N*-CF_3 nitrene radical anion to the nitrene ($E_{1/2}$ = +0.56 V) is also in the range of the reduction of the ground state $Ir^{(IV)}$ back to $Ir^{(III)}$ of **PC1**, *i.e.* $E_{1/2}$ = +1.10 V. As such, the reactive nitrene would be formed for subsequent C-H insertion, and the $Ir^{(III)}$ photocatalyst would be reformed. These consecutive SET events may best be described as an 'electron-rebound mechanism', as the electron flow stays within the catalyst-substrate-complex (see Figure 2), which is not necessarily invoked by the established terminology for other SET processes.

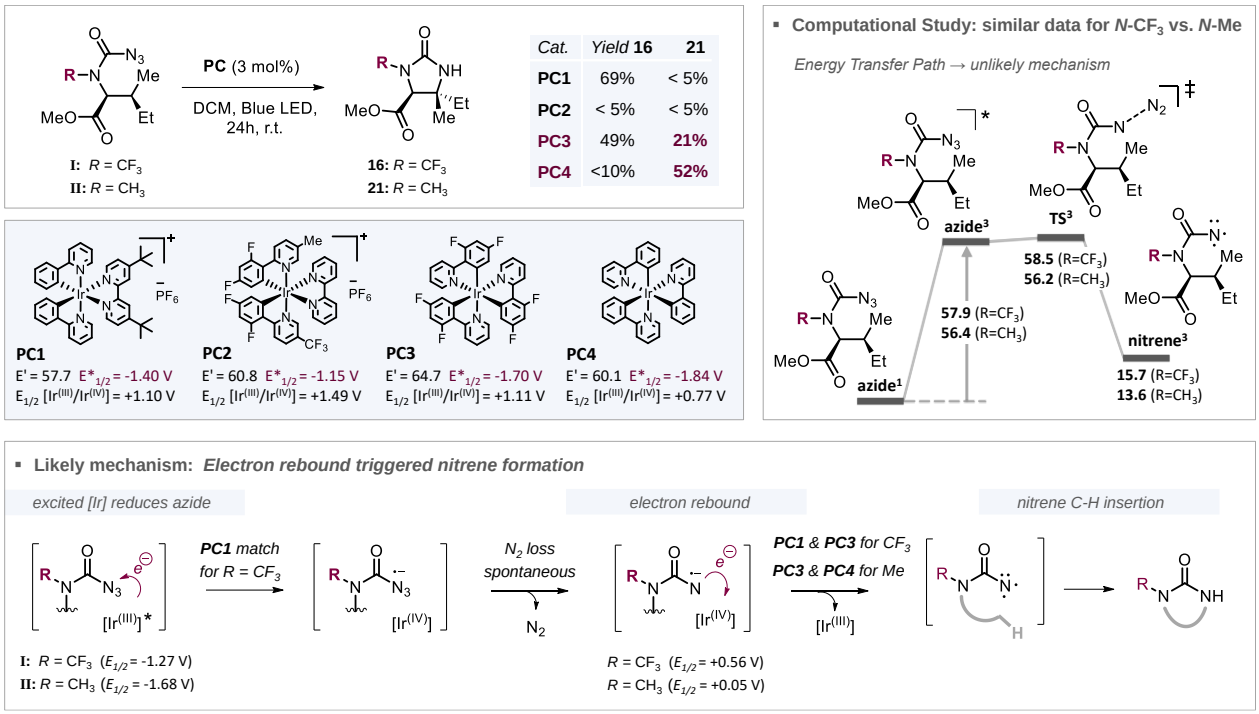


Figure 2. Mechanistic studies and proposed electron rebound mechanism. Calculations were performed at the SMD (MeCN) MN15/def2-TZVPP//SMD (MeCN) ωB97XD/6-31+G(d,p) level of theory.[27]

If this were to be the case, we would expect a stronger donor, *i.e.* a photocatalyst with a higher excited state reduction potential, to then be able to activate the *N*-Me carbamoyl azides. To examine this, we next tested photocatalyst Ir(dFppy)$_3$ (**PC3**), which displays a calculated emission energy of E' = 64.7 kcal/mol) and an excited state reductive potential of $E^*_{1/2}$ = -1.70 V (see Figure 2). When we tested catalyst **PC3**, we now were able to stereospecifically cyclize the *N*-Me carbamoyl azide **II** to **21** in 21% yield. Conversely, *N*-CF$_3$ **I** was also efficiently transformed (to **16** in 49% yield).

Interestingly, **PC4**, which possesses an even stronger excited state reduction potential ($E^*_{1/2}$ = -1.84V) only efficiently transformed the *N*-Me substrate (**21** in 52%, >99:1 d.r.), but not *N*-CF$_3$.

Considering our proposed mechanism, this observation would be consistent with the required oxidation of the nitrene radical anion to the reactive nitrene intermediate, which is calculated to be more facile for the *N*-Me than for the *N*-CF$_3$ substrate (by 0.51 V, see Figure 2). **PC4** possesses a lower Ir$^{(IV)}$ oxidizing power compared to **PC1** and would hence be less effective in oxidizing the *N*-CF$_3$ radical anion (and hence regenerate the catalyst). Given the structural similarities of the substrates and catalysts, an energy transfer mechanism appears inconsistent with these observations.

In conclusion, we demonstrated the first mild photocatalyst/blue light triggered activation of carbamoyl azides to the corresponding nitrene to yield cyclic *N*-CF$_3$ urea compounds upon insertion to aliphatic or aromatic C-H bonds. The method is operationally simple, stereospecific and solely makes use of a catalyst, free of sacrificial reductants/reagents. Our mechanistic data indicate an energy transfer mechanism to be unlikely. Instead, we propose that a reductive rebound between the photocatalyst and carbamoyl azide might be operative, in which SET triggers N$_2$ loss and subsequent re-oxidation generates a nitrene intermediate which undergoes (stereospecific) C-H insertion. The unlocked cyclic *N*-CF$_3$ urea motif proved to be highly robust, which was demonstrated in various downstream derivatizations.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data of compounds, crystallographic data and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interests.

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(32) Our measured potentials lie within 0.1 V, *i.e.* $E_{1/2}$ = -1.4 V for *N*-CF_3 (**I**) and $E_{1/2}$ = -1.7 V for *N*-Me (**II**).

(33) The reduction potential was hardly effected by the electron richness of the *N*-CF_3 substrate. The carbamoyl azide leading to compound **13** was determined to have a potential of $E_{1/2}$ = -1.2 V.

(34) Born-Oppenheimer molecular dynamics trajectories were run at the SMD (MeCN) ωB97XD/6-31+G(d,p) level of theory, using a step size of 0.5 fs and an overall simulation time of 1.5 ps. For further details, please see the Supporting Information.

(35) We performed the BOMD calculations on the enforced radical anion of the azide geometry to best describe the events immediately following electron transfer.

Table of Contents artwork