

Photochemical Strain-Release Driven Cyclobutylation of C(sp³)-Centered Radicals

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Our manuscript describes a photoredox-catalyzed decarboxylative radical addition approach to functionalized cyclobutanes. The reaction involves an unprecedented formal Giese-type addition of C(sp³)-centered radicals to highly strained bicyclo[1.1.0]butanes. The mild photoredox conditions, which make use of a readily available and bench stable phenyl sulfonyl bicyclo[1.1.0]butane, proved to be amenable to a diverse range of α -amino and α -oxy carboxylic acids, providing a concise access to 1,3-disubstituted cyclobutanes. Furthermore, kinetic studies and DFT calculations unveiled mechanistic details on bicyclo[1.1.0]butane reactivity relative to the corresponding olefin system.

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Photochemical Strain-Release Driven Cyclobutylation of C(*sp*³)-centered radicals

Guillaume Ernouf^{*,+}, Egor Chirkin⁺, Lydia Rhyman, Ponnadurai Ramasami, and Jean-Christophe Cintrat^{*}

Abstract: We report a photoredox-catalyzed decarboxylative radical addition approach to functionalized cyclobutanes. The reaction involves an unprecedented formal Giese-type addition of C(*sp*³)-centered radicals to highly strained bicyclo[1.1.0]butanes. The mild photoredox conditions, which make use of a readily available and bench stable phenyl sulfonyl bicyclo[1.1.0]butane, proved to be amenable to a diverse range of α -amino and α -oxy carboxylic acids, providing a concise access to 1,3-disubstituted cyclobutanes. Furthermore, kinetic studies and DFT calculations unveiled mechanistic details on bicyclo[1.1.0]butane reactivity relative to the corresponding olefin system.

Introduction

In recent years, the development of synthetic methods toward functionalized cyclobutanes has attracted substantial attention¹ due to their role of rigid carbon scaffolds² and C(*sp*³)-rich complexity-generating building blocks.³ Several drugs such as the serotonin reuptake inhibitor sibutramine,⁴ the HCV-protease-inhibitor boceprevir,⁵ the analgesic nalbuphine⁶ and the drug candidate IGF-1R-inhibitor linsitinib,⁷ contain the four-membered ring (Figure 1A).⁸ Nonetheless, compared to the high prevalence of common carbocycles such as cyclohexanes and cyclopropanes in marketed drugs, the occurrence of cyclobutanes is scarce.⁹ In this regard, a direct and prompt access to alkylated cyclobutanes would significantly enlarge the chemical space explored in drug discovery programs. To provide a novel synthetic toolkit toward functionalized cyclobutanes, we aimed to exploit the peculiar reactivity of the bicyclo[1.1.0]butane (BCB) framework. BCBs display a remarkable ring strain energy¹⁰ of 64 kcal.mol⁻¹ and a high π -character of the central C–C bond which can serve as a surrogate for the corresponding olefin.¹¹ The recent surge of interest in strain-release strategies led to the preparation of unusual strained bioisosteres, such as bicyclo[1.1.0]pentanes, azetidines and cyclobutanes, through nucleophilic additions¹² or transition metal catalysis.¹³ However, radical additions to the central bond of BCBs have so far been confined to a few sporadic examples.¹⁴ The aforementioned studies and pioneering work of

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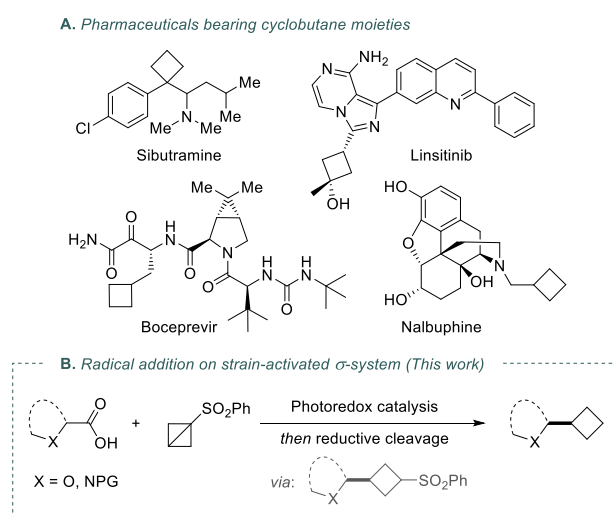
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MacMillan¹⁵ inspired us to ponder whether BCBs could be functionalized with SOMO-activated fragments (Scheme 1A). Thus, we aimed to explore the addition of visible-light-mediated decarboxylative radicals to the C–C central σ -bond of BCB for straightforward incorporation of cyclobutane moiety. Moreover, the use of aryl sulfone as traceless BCB-activating group would therefore enable access to late-stage “cyclobutylated” products after sequential reductive cleavage (Scheme 1B).



Scheme 1. Decarboxylative conjugate radical addition

Results and discussion

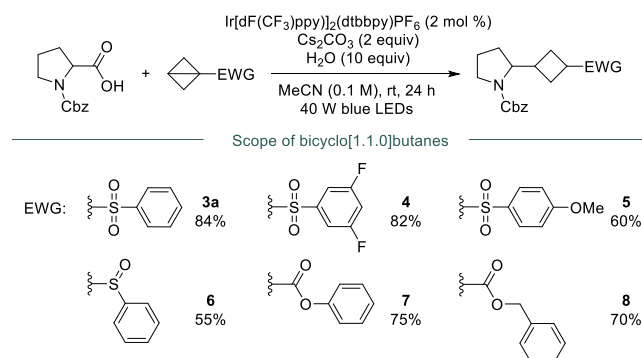
To investigate our proposed reaction, initial studies focused on the decarboxylative reaction between *N*-Cbz-protected proline **1** and the bench stable BCB **2a** (Table 1).¹⁶ After screening of bases (entries 2–4) and solvent systems (entries 5 and 6), we were delighted to discover that the cesium salt, formed by deprotonation of **1** with Cs₂CO₃, led to the CO₂-extrusion/conjugate addition to BCB **2a** upon irradiation with a 40 W blue LED lamp in the presence of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ in MeCN to afford the “cyclobutylated” product **3a** in 84% yield (entry 1). Consistent with previous reports on such systems, almost no diastereoselectivity was observed.¹² Remarkably, only 0.5 mol % of the photocatalyst was sufficient to promote the reaction with high efficiency on a 1 mmol scale (entry 7). During the optimization, we noticed that the addition of water (10 equiv) was crucial for the overall efficiency of this protocol, while the use of anhydrous conditions dropped the yield to 68% (entry 8). Presumably, water both assists in solubilizing the cesium carboxylate and provides a proton source to quench the intermediate anion after radical addition and reduction.¹⁷ It is worth noting that cyanobenzene-based organic photocatalyst 4CzIPN (entry 9) and biocatalytic cofactor riboflavin tetrabutryrate (entry 10) could promote the conjugate addition, although with limited efficacy. Finally, control experiments confirmed that both photocatalyst and visible light were essential for the desired transformation to occur (entries 11 and 12).

Table 1. Optimization studies.

Entry	Deviation from above	Yield 3a ^[a]
1	none	84 (16) ^[b]
2	K ₂ CO ₃	40 (N.D.)
3	CsF	23 (36)
4	TMG	53 (24)
5	DMSO	58 (13)
6	DMF	47 (30)
7	0.5 mol %	80 (N.D.) ^[c]
8	w/o H ₂ O	68 (28)
9	4CzIPN	19 (24)
10	riboflavin tetrabutyrates	34 (48)
11	w/o photocatalyst	0 (91)
12	w/o light	0 (N.D.)

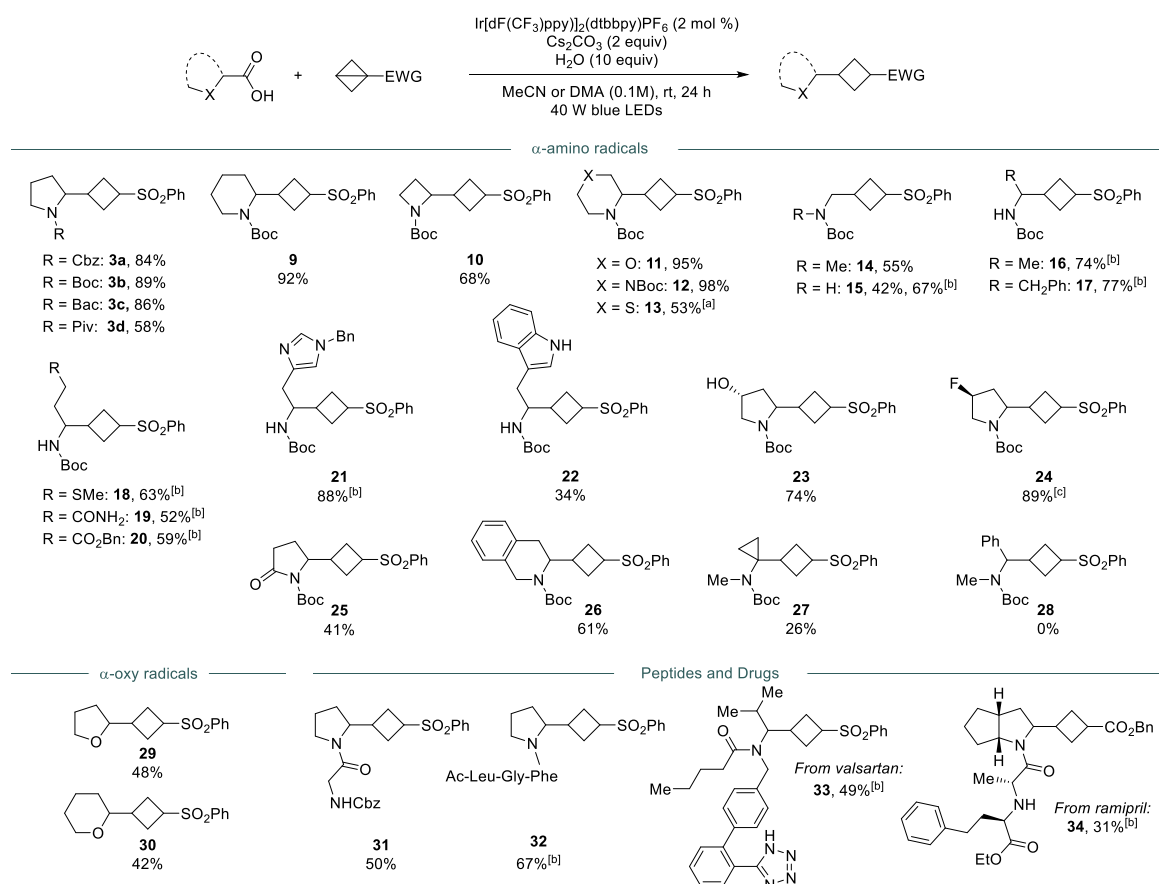
[a] Isolated yield on 0.1 mmol scale. Recovered starting material in parentheses. [b] Average of three runs. [c] 1 mmol scale. 4CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyano-benzene, DMSO = dimethylsulfoxide, DMF = *N,N*-dimethylformamide, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl, ppy = 2-phenylpyridine, TMG = 1,1,3,3-tetramethylguanidine.

With optimal reaction conditions in hand, the scope of this transformation with respect to the BCB partner was assessed (Table 2). The reaction was found to be compatible with BCBs bearing electron-withdrawing (**4**) and electron-donating (**5**) aryl substituents with a slight drop in yield for the latter. The efficiency of the reaction also decreased when less electron-withdrawing aryl sulfoxide **6** (55%) was used instead of the corresponding aryl sulfone **3a** (84%). Finally, BCB carboxylate derivatives reacted efficiently to give the corresponding addition products in high yields (**7**, **8**).

Table 2. Scope of bicyclo[1.1.0]butanes.

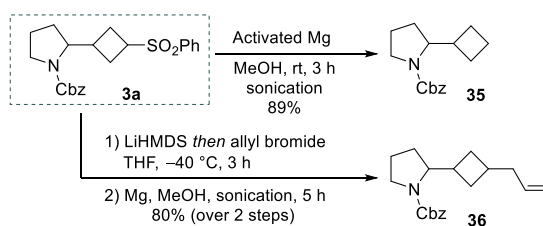
Next, we investigated the nature of the carboxylic acid partner to expand the generality of the reaction (Table 3). First, other α -carbonyl radicals derived from protected proline were explored. *N*-Boc and *N*-Bac protecting groups (**3b**, **3c**) were shown to perform similarly, delivering the desired “cyclobutylated” products in excellent yields. Under the same conditions, *N*-pivaloyl-protected proline furnished adduct **3d**, albeit in a slightly lower yield (58%). Given the importance of nitrogen-containing saturated heterocycles in medicinal chemistry, we were delighted to find that *N*-Boc-protected piperidine, azetidine, morpholine and piperazine-based substrates readily participated in this transformation providing products **9–12** in high yields (68–98%). Due to the poor solubility of the starting material, switching solvent from MeCN to DMSO was necessary to generate *N*-Boc thiomorpholine adduct **13** in good yield (53%). During the course of our investigation, the reaction was found to be quite sensitive to the nature of the α -aminoalkyl radical involved. Thus, our initial attempts to extend the scope of this transformation to substrates bearing free NH group met with limited success. In acetonitrile, 1,3-disubstituted cyclobutane **15** derived from glycine was only isolated in 42% yield together with a significant amount of unconverted starting material, whereas *N*-methylated acyclic amino acids, like sarcosine (**14**), performed with good efficiency (Table S2).¹⁴ Eventually, the choice of solvent was of essential importance for the inclusion of NH amino acids and we found that the yield of adduct **15** rose to 67% when DMA was used as the solvent.

Further exploration of amino acid inventory showed that these slightly modified reaction conditions were compatible with a wide range of *N*-Boc protected secondary amino acids, including alanine, phenylalanine, cysteine and glutamine (**16–19**). Likewise, *N*-Boc-glutamic acid 5-benzyl ester and benzyl-protected histidine were efficient in this transformation affording respectively, product **20** (59%) and **21** (88%). Remarkably, the unprotected indole moiety of *N*-Boc-tryptophan was rather well tolerated, giving adduct **22** in a moderate 34% yield. The reaction also worked well in the presence of pharmaceutically relevant fluoro, hydroxy and ketone functionalities (**23–25**) and was compatible with the tetrahydroisoquinoline moiety (**26**). Use of tertiary α -amino cyclopropyl radical provided **27** with a moderate yield. Surprisingly, *N*-Boc *N*-methyl phenylglycine failed to provide the desired product, probably arising from the loss of the high-lying SOMO character of the radical due to presence of the phenyl ring (**28**).¹⁸ α -Oxy radicals were also suitable partners, yielding tetrahydrofuran **29** and tetrahydropyran **30** in 48% and 42% yields, respectively. To demonstrate the potential of our methodology for late-stage functionalization, we turned our attention to more complex radical precursors. A simple dipeptide Z-Gly-Pro-OH was a proficient substrate (**31**) along with more challenging tetrapeptide (**32**). Furthermore, the mild reaction conditions were compatible with densely functionalized antihypertensive drugs Valsartan (**33**) and Ramipril (**34**). Upon ester cleavage, the latter compound can furnish a valuable ‘elongated’ carboxylic acid for medicinal studies purposes.

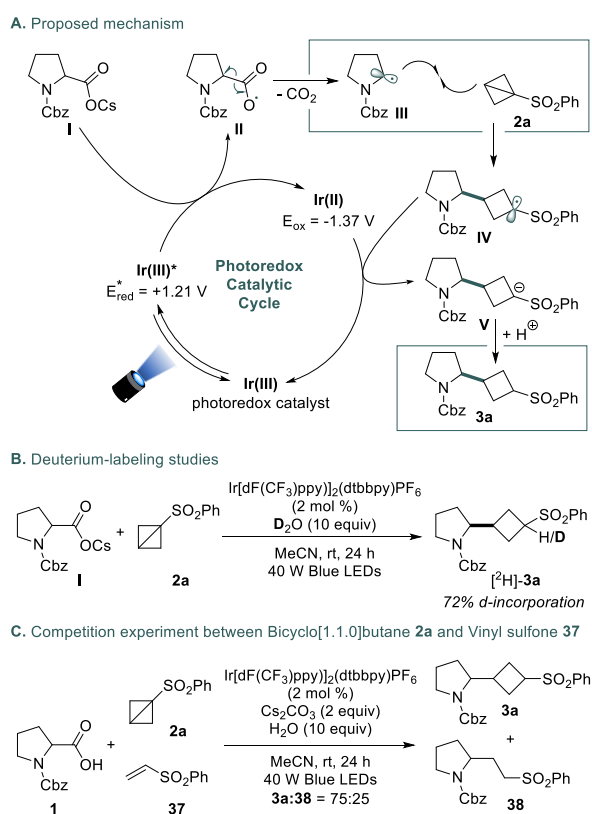
Table 3. Scope of the carboxylic acids.

All yields are isolated yields. [a] In DMSO. [b] In DMA. [c] dr = 2.8 : 1, as determined by ¹⁹F NMR based on the desulfonylated product. Bac = *tert*-butylaminocarbonyl, Boc = *tert*-butoxycarbonyl, Bn = benzyl, DMA = *N,N*-dimethylacetamide, Piv = pivaloyl.

We then showcased the synthetic usefulness of aryl sulfone moiety through diverse transformations (Table 4). A traceless cyclobutylation could easily be achieved through phenyl sulfone cleavage under mild reductive conditions (Mg, MeOH) in an excellent 89% yield (**35**). The exalted acidity of the proton adjacent to the phenyl sulfonyl group enabled the deprotonation/alkylation sequence giving rise to allyl cyclobutane **36** after reductive desulfonylation. Interestingly, direct arylation of the sulfone could be envisaged through iron-catalyzed cross-coupling, albeit with limited success.¹⁹

Table 4. Product functionalization.

The mechanistic details on our photoredox decarboxylative conjugate addition are outlined in Scheme 2A. Initial single-electron transfer (SET) between the photoexcited Ir(III) catalyst and the *in situ* formed cesium carboxylate **I** generates α -carboxyl radical **II** that undergoes CO₂-extrusion to form the carbon-centered radical **III**. Upon Giese radical addition²⁰ of the highly nucleophilic species **III** to BCB **2a**, strain release-driven breakage of the central σ -bond generates the α -sulfonyl radical **IV**. Completion of the photocatalytic cycle would then be accomplished *via* reduction of the radical intermediate **IV** with the strongly reducing Ir(II) photocatalyst followed by protonation of the resultant α -sulfonyl anion **V** to furnish the α -amino “cyclobutylated” sulfone **3a**. The proposed single-electron reduction of **IV** to the corresponding anion **V** was then supported by deuterium-labelling studies. When the reaction was carried out with the preformed cesium salt in the presence of deuterium oxide, the desired product [²H]-**3a** was formed with 72% *d*-incorporation α to the phenylsulfonyl group, thus confirming the formation of the transient α -sulfonyl anion **V** (Scheme 2B). Interestingly, despite numerous reports on BCB polymerization processes,^{14,21} and the recent report on electron deficient radical addition to the central strained bond of BCB-boronate complexes,^{13b} cyclobutyl radical intermediate **IV** did not undergo telomerization, showing that reduction/protonation are faster processes.



Scheme 2. Mechanistic investigations and competition experiment.

Once the performance of bicyclo[1.1.0]butane **2a** in this decarboxylative Giese-type reaction was established, we compared its reactivity to that of the corresponding vinyl sulfone **37**. In the competition experiment between BCB **2a** and the olefin surrogate **37**, phenyl vinyl sulfone **37** proved to be more

reactive leading to the adduct **38** in a 75:25 ratio (Scheme 2C). Kinetic studies carried out with these electrophiles revealed that the addition of the radical to vinyl sulfone went to completion within 0.5 h, while addition to the BCB required several hours. This finding was in keeping with previously reported higher reaction rates of acrylates as compared to various BCBs in a glutathione (GSH)-based assay.^{12b} Density functional theory (DFT) method (UM06-2X/6-31G(d)) was then employed to corroborate the experimental results and to provide insights into the reasons behind this drastic difference in reactivity. Addition of pyrrolidine radical **III** to BCB **2a** proceeded sluggishly with an activation free energy of 18.4 kcal.mol⁻¹. Comparatively, phenyl vinyl sulfone acts as an excellent radical acceptor with an activation free energy amounting to a mere 9.4 kcal.mol⁻¹. On the other hand, the cleavage of the central bond that led to BCB-radical intermediate **IV**, dissipated a very high stabilization energy of 38.9 kcal.mol⁻¹ resulting from the strain-release (*versus* 22.1 kcal.mol⁻¹ for **VI**). These calculations turned out to be in good accordance with the experimental observation and comprehensively explained why the radical addition to the BCB is less favored than to the corresponding olefin. However, it is worth mentioning that the reduction of radical intermediates **IV** and **VI** to the corresponding anions might also be a critical limiting step in that photoredox process.

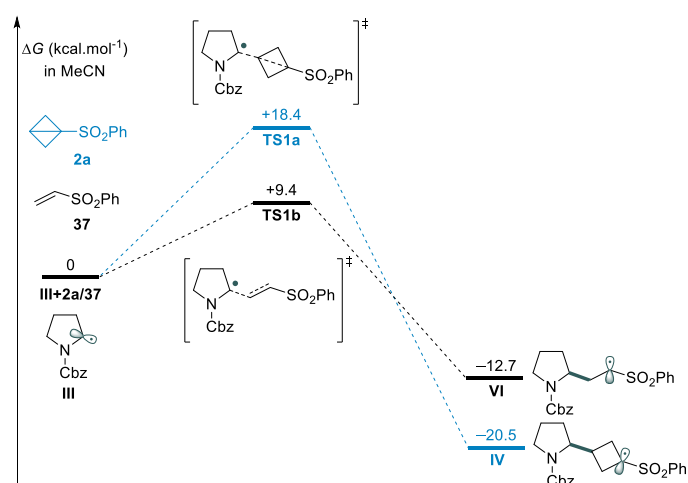


Figure 1. Relative energies for radical addition to BCB **2a** and vinyl sulfone **37**.

Conclusions

In summary, we have demonstrated the utility of bicyclo[1.1.0]butanes as radical acceptors for the direct and mild C(sp³)–C(sp³) bond formation *via* visible light-mediated photoredox catalysis. The protocol provides a concise access to highly valuable alkylated cyclobutanes, thus allowing the introduction of a high degree of structural complexity within one synthetic step. From a synthetic standpoint, the mild reaction conditions together with the tolerance toward a diverse range of functional groups render the devised strategy potentially amenable to late-stage derivatization of complex

molecules. The transition from the batch cyclobutylation to continuous flow conditions is a subject of ongoing research in our laboratory.

Acknowledgments

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