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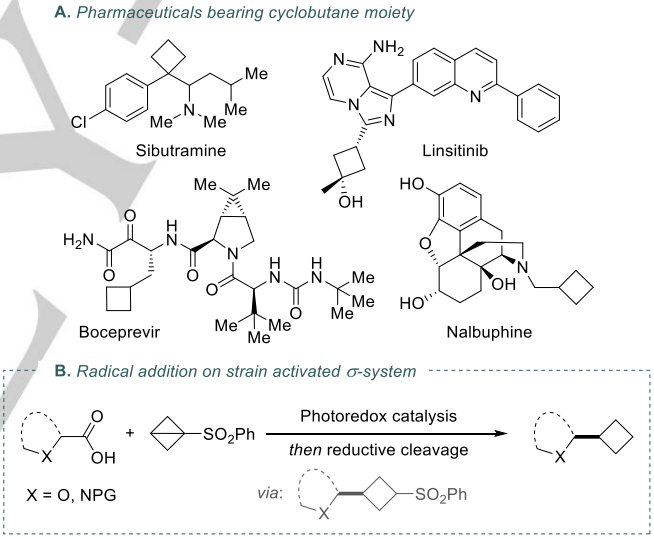
Photochemical Strain-Release-Driven Cyclobutylation of C(sp^3)-centered Radicals

Guillaume Ernouf,*[a]+ Egor Chirkin,[a]+ Lydia Rhyman,[b] Ponnadurai Ramasami,[b] and Jean-Christophe Cintrat*[a]

Abstract: A new photoredox-catalyzed decarboxylative radical addition approach to functionalized cyclobutanes is described. 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 route 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.

In recent years, the development of synthetic methods toward functionalized cyclobutanes has attracted substantial attention[1] because they can act as conformationally restricted scaffolds [2] 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 nalbuphine[6] and the drug candidate IGF-1R-inhibitor linsitinib,[7] contain the four-membered ring (Scheme 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 envisaged to exploit the peculiar reactivity of the bicyclo[1.1.0]butane (BCB) framework. BCBs display a remarkable ring strain energy[10] of 64 kcal.mol^{-1} and 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 bioisosters, such as bicyclo[1.1.0]pentanes, azetidines and cyclobutanes, through nucleophilic additions[12] or transition metal catalysis.[13] By contrast, radical additions to the central bond of BCBs had been confined for a long time to a few sporadic examples.[14] During the course of our investigation, Aggarwal *et al.* reported the addition of electron-deficient radicals to BCB-boronate complexes.[14b] Despite the wide substrate scope and the absence of photocatalyst, the BCB-boronate complex has to be prepared *in situ* using *t*-BuLi and consecutive 1,2-metallate rearrangement needs to operate at –78 °C to afford satisfying diastereoselectivity.

Acting in a complementary way, our approach relies on the addition of highly nucleophilic radicals to the C–C central σ-bond of BCBs for straightforward incorporation of the cyclobutane moiety. While those radicals would be generated from the abundant feedstock of α-amino acids by visible-light-mediated decarboxylation,[15] the use of phenylsulfone as traceless BCB-activating group would enable access to late-stage "cyclobutylated" products after sequential reductive cleavage (Scheme 1B).



Scheme 1. Cyclobutanes in medicinal chemistry (A) and decarboxylative conjugate radical addition (B).

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 a screening of bases (entries 2–4) and solvent systems (entries 5, 6), we were delighted to discover that the cesium salt, formed by deprotonation of **1** with Cs_2CO_3, led to the CO_2-extrusion/conjugate addition on BCB **2a** upon irradiation with a 40 W blue LED lamp in the presence of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ in MeCN to afford the "cyclobutylated" product **3a** in 84% yield (entry 1). In line with previous reports on nucleophilic addition of "turbo amides" 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

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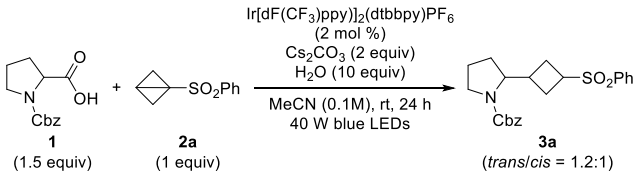
crucial for the overall efficiency of this protocol, while the use of anhydrous conditions dropped the yield to 68% (entry 8). Presumably, water both assists in solubilizing the cesium carboxylate and provides a proton source to quench the intermediate anion after radical addition and reduction.[17] It is worth noting that cyanobenzene-based organic photocatalyst 4CzIPN (entry 9) and biocatalytic cofactor riboflavin tetrabutyrate (entry 10) could promote the conjugate addition, although with limited efficacy. Finally, control experiments confirmed that both the photocatalyst and visible light were essential for the desired transformation to occur (entries 11, 12).

Table 1. Optimization studies.



1 (1.5 equiv) + **2a** (1 equiv) → **3a** (*trans*/*cis* = 1.2:1)

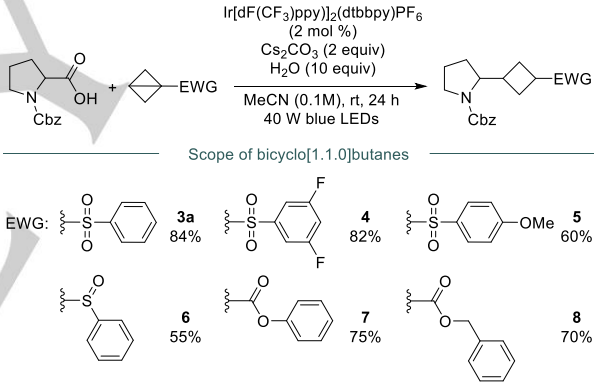
Entry	Deviation from above	Yield **3a**[a]
1	none	84 (16)[b]
2	K_2CO_3	40 (N.D.)
3	CsF	23 (36)
4	TMG	53 (24)
5	DMSO	58 (13)
6	DMF	47 (30)
7	0.5 mol %	80 (N.D.)[c]
8	w/o H_2O	68 (28)
9	4CzIPN	19 (24)
10	riboflavin tetrabutyrate	34 (48)
11	w/o photocatalyst	0 (91)
12	w/o light	0 (N.D.)

[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, Cbz = carboxybenzyl, DMSO = dimethylsulfoxide, DMF = *N,N*-dimethylformamide, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl, N.D. = not determined, 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. Use of less electron-withdrawing aryl sulfoxide instead of the corresponding aryl sulfone afforded **6** in 55% yield. Finally, BCB carboxylate derivatives reacted efficiently to give the corresponding addition products in high yields (**7**, **8**).

To expand the generality of the reaction, we next investigated the scope of carboxylic acid component (Table 3). First, other α-carbamyl 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%). By contrast, the unproductive attempts to react cyclohexyl radical with BCB **2a**, highlighted the crucial role of the α-substituent for the success of the reaction.[18] Because of 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 our survey, the reaction was found to be quite sensitive to the nature of the α-aminoalkyl radical. Thus, our initial attempts to expand the scope of this transformation to substrates bearing free NH group was met with limited success. In MeCN, 1,3-disubstituted cyclobutane **15** derived from glycine was only isolated in 42% yield with a significant amount of unconverted starting material, whereas *N*-methylated acyclic amino acids, *e.g.* sarcosine (**14**), performed with good efficiency (Table S2).[16] The choice of solvent was of essential importance for the inclusion of NH amino acids as the yield of adduct **15** eventually rose to 67% when DMA was used.

Table 2. Scope of bicyclo[1.1.0]butanes.



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 viable substrates, affording **20** (59%) and **21** (88%), respectively. 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 fluorine, hydroxyl and carbonyl substituents (**23**–**25**) and was compatible with the tetrahydroisoquinoline moiety (**26**). Use of tertiary α-amino cyclopropyl radical met with moderate success (**27**). The surprising reluctance of *N*-Boc-*N*-methyl phenylglycine may arise from the loss of the high-lying SOMO-character of the radical due to the presence of phenyl ring (**28**).[16] α-Oxy radicals were also suitable partners, yielding tetrahydrofuran **29** and tetrahydropyran **30** in 48% and 42% yield, respectively. In each instance, the reaction proceeds with negligible diastereoselectivity.

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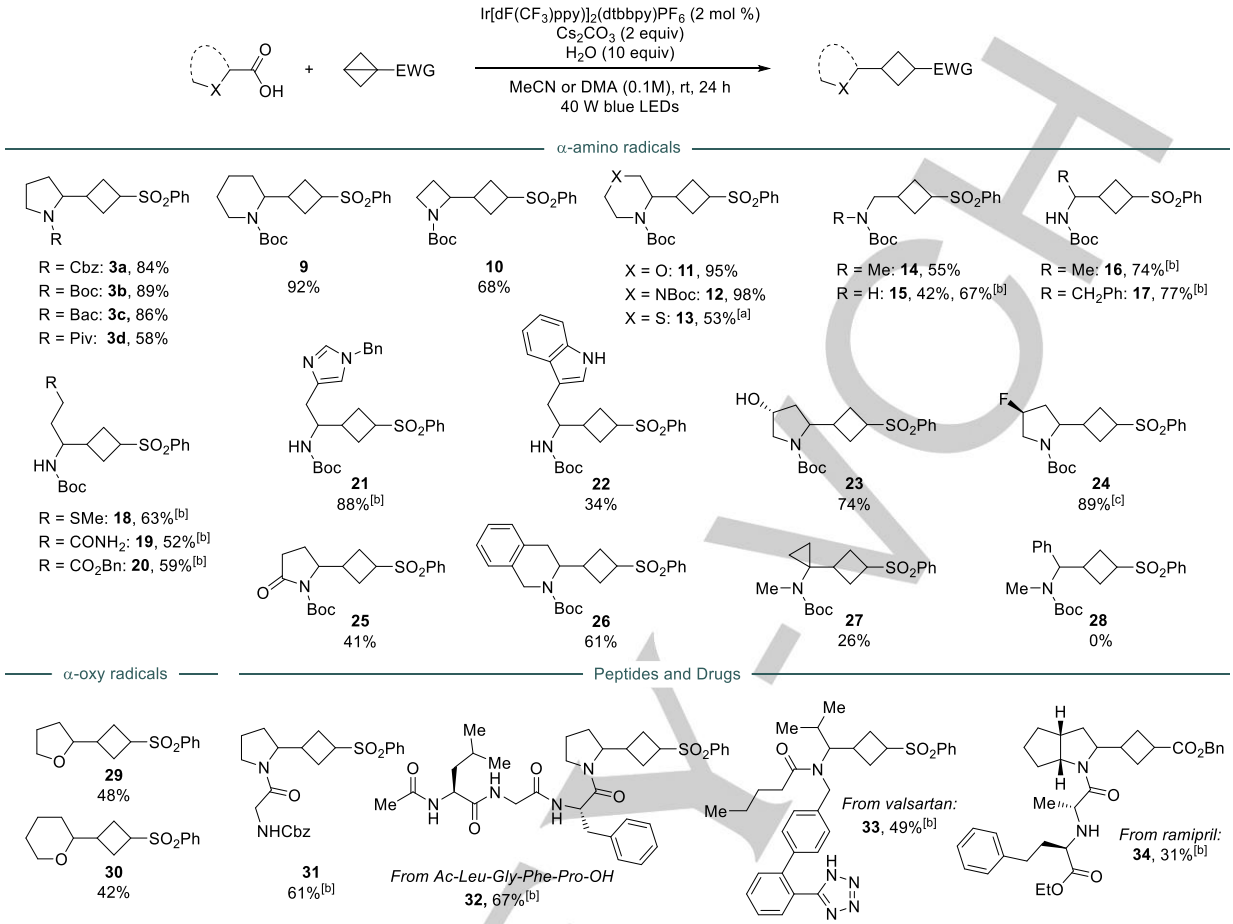
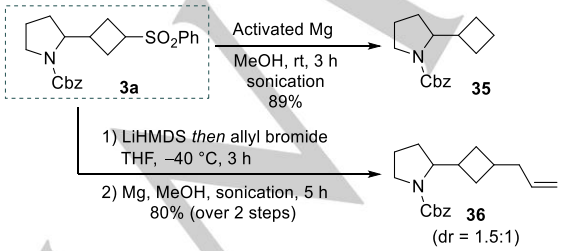
Table 3. Scope of carboxylic acids.



All yields are isolated yields. Ratios of diastereomers determined by mass-directed RP-HPLC analysis of the crude reaction mixture lie between 1:1 and 3.5:1 (see SI). [a] In DMSO. [b] In DMA. [c] dr = 4:1, as determined by ^{19}F NMR based on the desulfonylated product. Bac = *tert*-butylaminocarbonyl, Boc = *tert*-butoxycarbonyl, Bn = benzyl, DMA = *N,N*-dimethylacetamide, Piv = pivaloyl.

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 along with more challenging tetrapeptide were proficient substrates (**31**, **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 afford an "elongated" carboxylic acid valuable for medicinal chemistry studies.



Scheme 2. Product functionalization

We then showcased the synthetic usefulness of aryl sulfone moiety through diverse transformations (Scheme 2). A traceless cyclobutylation could easily be achieved through phenyl sulfone cleavage under mild reductive conditions (Mg, MeOH) in excellent 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 was envisaged through iron-catalyzed cross-coupling, albeit with limited success.[19]

The mechanistic details on our photoredox decarboxylative conjugate addition are outlined in Scheme 3A. 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 CO_2-extrusion to form the carbon-centered radical **III**. Upon Giese radical addition of the highly nucleophilic species **III** to BCB **2a**, strain-release driven rupture of the central σ-bond generates the α-sulfonyl radical **IV**. Completion of the photocatalytic cycle would then be achieved *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

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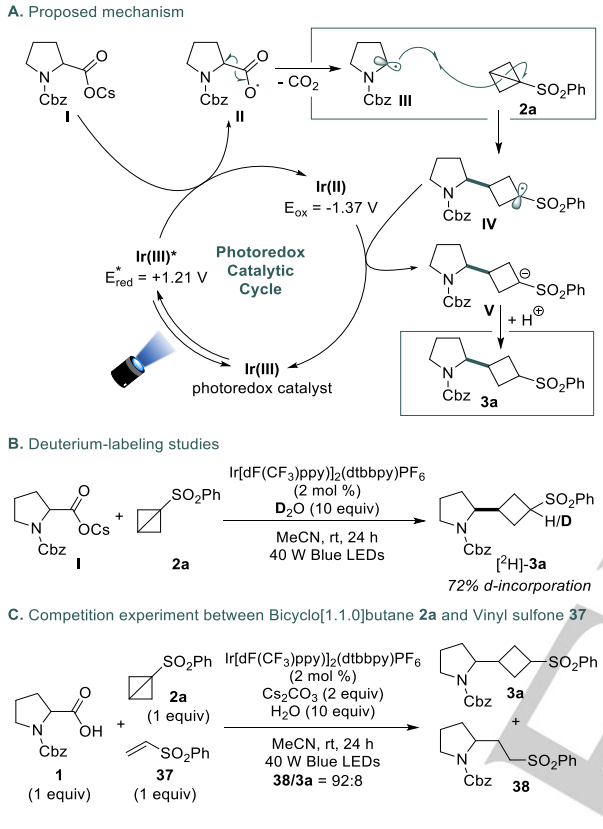
anion **V** was further supported by deuterium-labelling experiment. When the reaction was carried out with the preformed cesium salt in the presence of deuterium oxide, the desired product [^{2}H]-**3a** was formed with 72% *d*-incorporation α to the phenyl sulfonyl group, thus confirming the formation of the transient α-sulfonyl anion **V** (Scheme 3B). Interestingly, despite numerous reports on BCB polymerization processes,[14,20] cyclobutyl radical intermediate **IV** did not undergo telomerization, showing that reduction/protonation are faster processes.



Scheme 3. 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 phenyl vinyl sulfone **37**. In the competition experiment, the olefin **37** proved to be more reactive than BCB **2a** leading predominantly to adduct **38** in a 92:8 ratio (Scheme 3C). 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.[16] This finding was in agreement 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. End-on addition of pyrrolidine radical **III** to BCB **2a** proceeded smoothly with an 18.4 kcal.mol^{-1} free energy of activation. Comparatively, phenyl vinyl sulfone acted as an excellent radical acceptor with a free energy of activation 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 *vs*. 22.1 kcal.mol^{-1} for **IV**. These calculations turned out to be in good accordance with the experimental observations and comprehensively explained why the radical addition to the BCB is less favored than to the corresponding olefin.

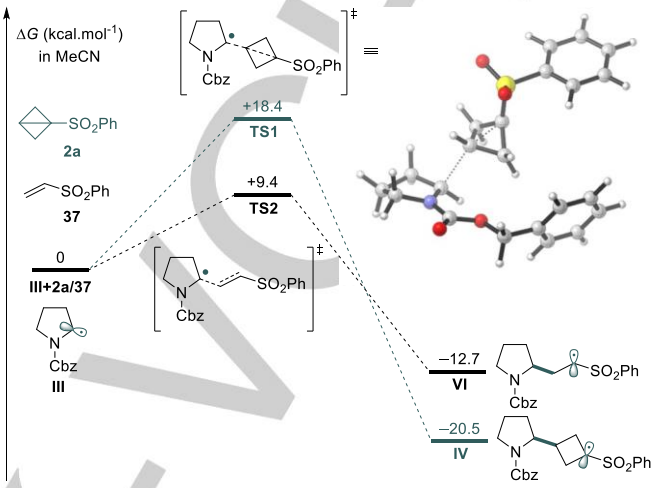


Figure 1. Relative energies for radical addition to BCB **2a** and vinyl sulfone **37.**

In summary, we have demonstrated the utility of bicyclo[1.1.0]butanes as radical acceptors for the direct and mild C(sp^3)–C(sp^3) 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 range of diverse 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.

Acknowledgements

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Keywords: bicyclo[1.1.0]butanes • cyclobutanes • late-stage functionalization • photocatalysis • strained molecules

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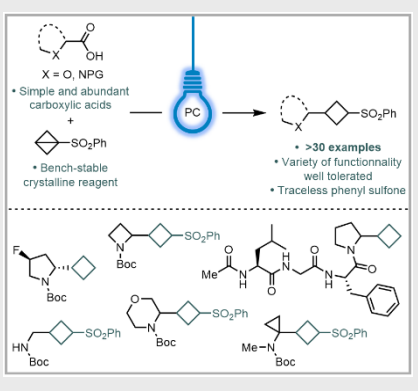
High-lying SOMO radicals, generated *in situ* under visible-light photoredox conditions, undergo an efficient addition to highly strained bicyclo[1.1.0]butanes, providing a straightforward access to valuable alkylated cyclobutanes.



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