A Metal-Free Cyclobutadiene Reagent for Intermolecular [4+2] Cycloadditions

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ABSTRACT: Cyclobutadiene is a highly reactive antiaromatic hydrocarbon that has fascinated chemists for over 60 years. However, its preparation and uses in chemical synthesis are sparing, in part due to its lengthy synthesis that generates hazardous byproducts including excess heavy metals. Herein, we report a scalable, metal-free cyclobutadiene reagent, diethyldiazabicyclohexene dicarboxylate, and explore its intermolecular [4+2] cycloaddition with various electron-deficient alkenes. We also demonstrate its utility in a three-step synthesis of dipiperamide G and a diverse array of product derivatizations including bromocyclobutadiene.

Cram has described cyclobutadiene as "the Mona Lisa of organic chemistry in its ability to elicit wonder, stimulate the imagination, and challenge interpretive instincts."[1a] Indeed there has perhaps been no other molecule which has cultivated and sustained such an interest from chemists as cyclobutadiene (**1**, Figure 1A).[1] Despite being the subject of study for over 60 years,[2] its deceptively simple structure remains essential in discussions of aromaticity and highly reactive intermediates. From a synthetic standpoint, cyclobutadiene is a useful building block especially for the construction of strained hydrocarbons. While metal-stabilized adducts of cyclobutadiene have been prepared with palladium,[3] nickel,[4] and cobalt,[5] the flagship complex is cyclobutadieneiron tricarbonyl (**2**, Figure 1A).[6a] Upon oxidation, **2** releases cyclobutadiene that homodimerizes essentially at the diffusion limit to produce *syn*-[3]-ladderdiene **3**.[7] However, it has been engaged in both intra-[8] and intermolecular[1c] [4+2] cycloadditions to produce bicyclohexenes (**4** and **5**, Figure 1A). Although Snapper and coworkers have shown that intramolecular [4+2] cycloadditions can outcompete homodimerization with dienophiles[8a,8b] and even dienes[8c,8d], intermolecular cycloadditions have necessitated the use of electron-poor dienophiles.[1d,9]

Despite the ubiquity and breadth of iron-cyclobutadiene complexes, they suffer from several disadvantages as practical reagents for chemical synthesis. Namely, the most commonly reproduced synthesis requires four steps to access from cyclooctatetraene and chlorine gas, and are prepared from either $Fe_2(CO)_9$, a toxic and water-sensitive solid, or $Fe(CO)_5$, a toxic and volatile liquid.[6b] A shorter synthesis of **2** from $Fe(CO)_5$ was reported by Rosenblum and coworkers, albeit in low yield.[6c] In addition, the release of cyclobutadiene from these complexes uses superstoichiometric quantities of heavy metal oxidants, such as ceric ammonium nitrate or lead tetraacetate. While alternative *N*-oxides have been reported as alternative oxidants,[8] their use has been limited due to the need for longer reaction times and higher reaction temperatures. Nevertheless, these complexes have demonstrated cyclobutadiene's utility in the synthesis of natural products,[10] cubanes,[11] and other highly strained hydrocarbons.[12] We have recently developed other synthetic approaches to prepare ladderene hydrocarbons[13] and

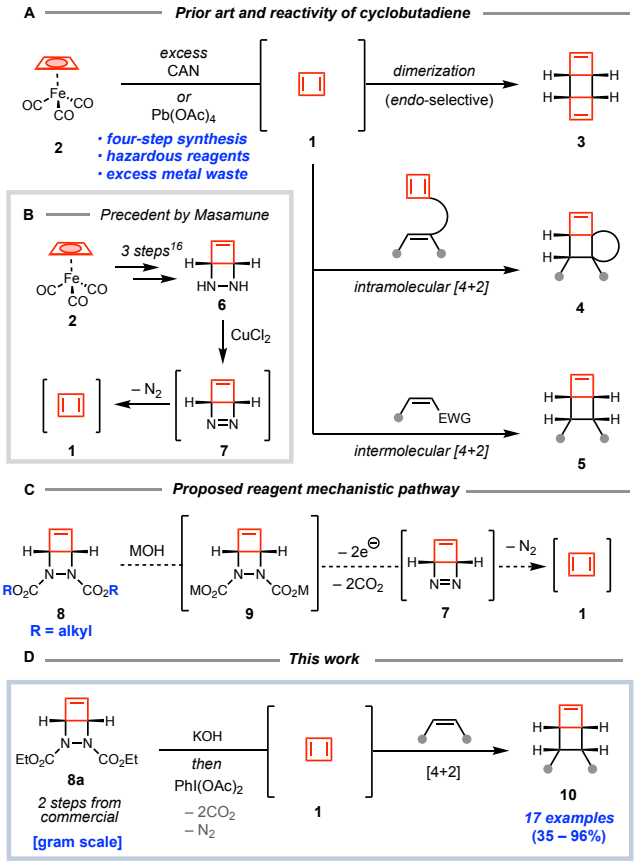
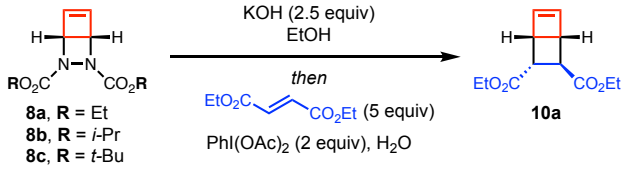


Figure 1. (A) Generating cyclobutadiene from iron-complex 2 yields ladderdiene 3 or bicyclohexenes 4 or 5. (B) Precedent for the generation of 1 from 6. (C) Proposed reagent, 8, and a mechanistic pathway for its generation of 1. (D) Summary of the work reported here.

ladderene polymers,[14] and realized the potential of cyclobutadiene for preparing such scaffolds.

We sought to develop an alternative reagent that would be easily prepared on multigram scale and that would release cyclobutadiene under mild conditions. Surveying the literature of known cyclobutadiene precursors, we noted that although many examples have been reported,[15] they suffer from practical limitations including low yielding preparation and thermal instability or are relegated to gas-phase reactions. Diazabicyclohexene **6**, first reported by Masamune and coworkers[16] (Figure 1B) and later studied by Carpenter and coworkers,[15c] seemed particularly attractive. Those authors observed that **6**, prepared in three steps from iron-cyclobutadiene **2**, could regenerate **1** upon oxidation with copper(II) chloride and proposed that the reaction proceeds via an unobserved intermediate, diaza-Dewar benzene **7**. However, since their synthesis of **6** began from iron-cyclobutadiene **2**, it originally appeared to be an impractical cyclobutadiene precursor. Inspired by this report, we pursued an accessible diazabicyclohexene derivative that could generate cyclobutadiene. We hypothesized that a dialkyl diazabicyclohexene dicarboxylate (**8**, Figure 1C) could be hydrolyzed to produce redox-active salt **9**. Subsequent two-electron oxidation and double decarboxylation should then intercept diaza-Dewar benzene **7**, from which loss of nitrogen would produce cyclobutadiene **1**. Herein we report a practical and scalable preparation of diazabicyclohexene **8a** and its operationally simple use as a metal-free cyclobutadiene precursor (Figure 1D).

Table 1. Reaction optimization.[a]

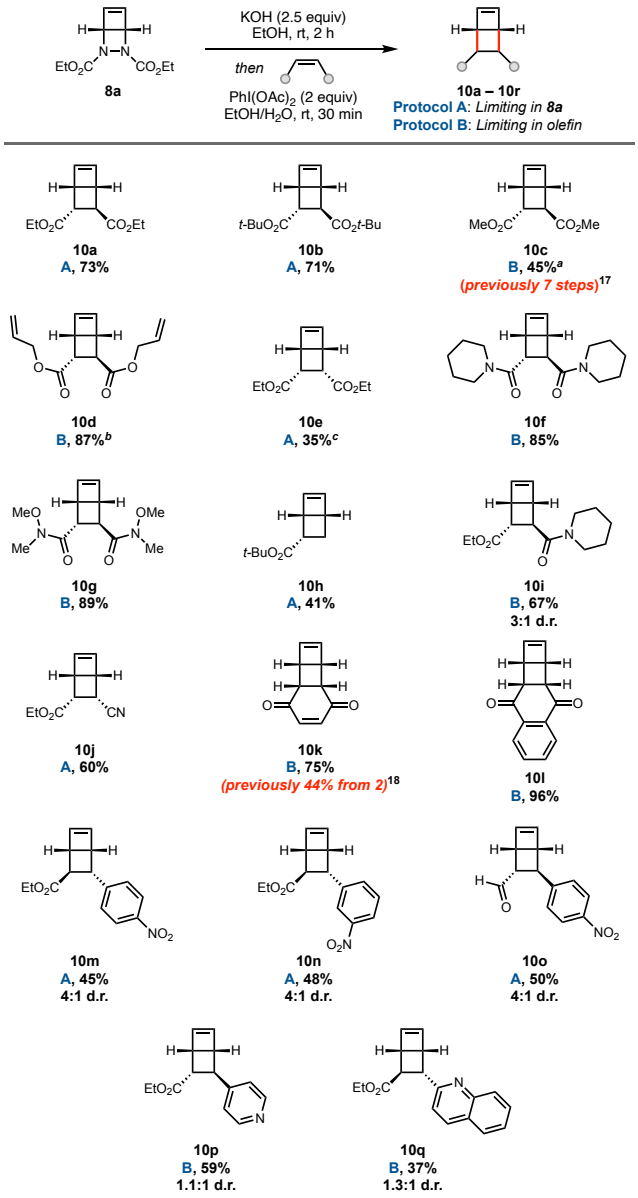


entry	reagent	change from standard conditions	yield (%)[b]
1	**8a**	none	92 (73[c])
2	**8b**	hydrolysis at 40 °C, 30 min	65
3	**8c**	none	6
4	**8a**	$PhI(TFA)_2$	80
5	**8a**	PhIO	72
6	**8a**	no KOH	0
7	**8a**	hydrolysis and oxidation at 0 °C	89
8	**8a**	N_2 atmosphere	84
9	**8a**	no light	88

[a]Reactions were performed open to air at room temperature; hydrolysis run for 2 hours. [b]Yield determined by ^1H NMR using internal standard. [c]Yield of isolated **10a** performed on gram scale.

We began our experimental studies by investigating the liberation of cyclobutadiene from dialkyldiazabicyclohexenes **8a–8c** and the subsequent intermolecular [4+2] cycloaddition with diethyl fumarate (Table 1). After optimizing the hydrolysis and subsequent oxidation, we arrived at optimal conditions for transforming **8a** into bicyclohexene **10a** using potassium hydroxide and (diacetoxyiodo)benzene in 73% isolated yield on gram scale (entry 1). Notably, these conditions are highly convenient since the reaction occurs at room temperature, is tolerant to water, and is performed open to air without the need for an inert atmosphere. Other diazabicyclohexene precursors such as di-*iso*-propyl carbamate **8b** (entry 2) were less readily hydrolyzed and thus performed worse, and di-*tert*-butylcarbamate **8c** gave little product under either basic (entry 3) or acidic conditions (see Supporting information). Other common hypervalent iodine oxidants were also successful at producing **10a** (entry 4–5), albeit in lower yield. When **8a** was subjected directly to oxidation without hydrolysis (entry 6) no product was observed. Changes to the reaction concentration had little effect on the yield, given that the intermolecular reaction of cyclobutadiene outcompeted homodimerization (see Supporting information). Finally, the reaction performed no better when run at 0 °C, under a nitrogen atmosphere, or in the absence of light (entries 7–9).

Table 2. Substrate scope of intermolecular [4+2] with electron-deficient alkenes.

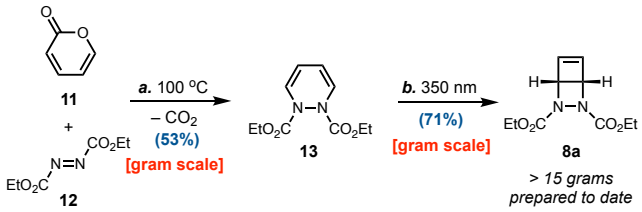


[a]Oxidation performed in methanol. [b]Oxidation performed in allyl alcohol. [c]Yield determined by internal standard.

Having established optimal reaction conditions, our attention then turned to exploring the dienophile scope in intermolecular [4+2] cycloadditions (Table 2). We developed two protocols for performing this reaction: either limiting in **8a**

(protocol A) or limiting in the alkene (protocol B). We began by exploring fumarate esters, and the reaction performed well with diethyl, di-*tert*-butyl, dimethyl and diallyl fumarate, which displayed complete alkene selectivity (**10a**–**10d**). For dimethyl- and diallyl fumarate adducts **10c** and **10d**, conducting the reaction in ethanol solvent resulted in transesterification to form **10a** (see Supporting Information), and thus required methanol and allyl alcohol as solvents, respectively. It is worth noting that **10c** had been prepared previously in seven steps[17] and is now prepared in a single step using our reagent. Diethyl maleate proceeded less efficiently than the corresponding fumarate, and produced **10e** in moderate yield with no detectable formation of adduct **10a**. Fumaramide adducts **10f** and **10g** were produced in high yield, wherein the Weinreb amides in **10g** allow for access to substituted diketobicyclohexenes. Reaction with *tert*-butyl acrylate **10h** proceeded as well, albeit in moderate yield. Mixed fumarate adduct **10i** was formed in 67% yield and 3:1 d.r. (*exo*/*endo*). Nitriles were also tolerated and served as an electron activating substituent, as *syn*-cyanoacrylate adduct **10j** was formed in 60% yield. Furthermore, benzoquinone adduct **10k** and naphthoquinone adduct **10l** were formed in 75% and 96% yield. Notably, the reported yield of **10k** using 1.3 equivalents of cyclobutadieneiron tricarbonyl **2** was 44%,[18] while using the same equivalents of **8a** in our system improved this to 67%. Increasing the amount of **8a** to 2.0 equivalents gave the improved yield of 75%. Turning to electron-deficient cinnamates, *para*-nitrophenyl **10m** and *meta*-nitrophenyl **10n** were formed in 45% yield, 4:1 d.r., and 48% yield, 4:1 d.r., respectively. Reaction with *para*-nitro cinnamaldehyde yielded **10o** in 50% yield and 4:1 d.r., while pyridyl and quinolyl substituted acrylates gave **10p** and **10q** in 59% yield and 1.1:1 d.r., and 37% yield and 1.3:1 d.r., respectively. Electron-neutral and electron-rich dienophiles were also investigated, but competitive homodimerization to *syn*-[3]-ladderdiene **3** was the major or only product (See Supporting Information).

Scheme 1. A scalable two-step synthesis of reagent 8a.[a]

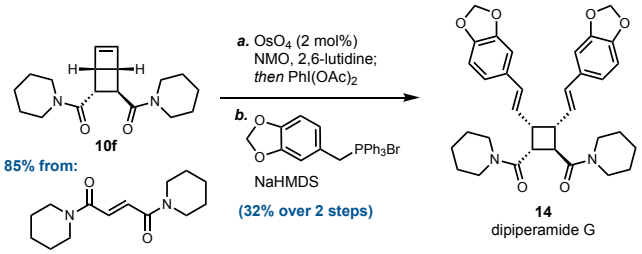


[a]Reagents and conditions: (a) 2-pyrone **11** (3 equiv), diethylazodicarboxylate **12** (1 equiv), PhMe, 100 °C; (b) 350 nm light, PhMe, rt.

To facilitate our studies, we developed a scalable synthesis of **8a** (Scheme 1). Although **8a** had been prepared previously,[19] we aimed to shorten its synthesis. Thermal cycloaddition of 2-pyrone **11** (commercially available or readily prepared from the pyrolysis of coumalic acid[20]) and diethylazodicarboxylate **12** yielded dihydropyridazine **13** on multi-gram scale**.** This reaction required careful optimization of temperature and duration to achieve high yields due to competitive product decomposition (see Supporting Information). Irradiation of **13** with 350 nm light resulted in 4π electrocyclic closure to **8a** in 71% yield according to the report by Altman[21] and Coote[19c]. We performed this two-step sequence routinely on multigram scale. No decomposition of **8a** was observed by ^{1}H NMR after several days on the bench, and we observed no decomposition after several weeks when stored at –20 °C. Due to the inherent ring-strain of **8a**, we carried out an initial safety assessment using differential scanning calorimetry (DSC, see the Supporting Information). The DSC data for **8a** exhibited a minor, broad exotherm starting at around 115 °C, followed by a larger, broad exotherm with an onset temperature of 211 °C. From this result, we concluded that our scale-up, storage, and reaction conditions did not pose a significant safety risk.

Seeking to demonstrate the utility of **8a** in total synthesis, we targeted dipiperamide G (**14**, Scheme 2). Isolated from the fruits of *Piper retrofractum* from southeast Asia,[22] **14** is a diamide natural product that has demonstrated modest cytotoxicity against 5178Y mouse lymphoma cells. We approached **14** by intercepting dipiperamide **10f** which was formed in 85% yield from di(piperidyl)fumarate. Oxidative cleavage of the cyclobutene with the Nicolaou modification of the Johnson-Lemieux oxidation[23] produced a silica-sensitive dialdehyde, which was used immediately in a double Wittig olefination to produce **14** in two steps and 32% yield from **10f**.

Scheme 2. Total synthesis of dipiperamide G.[a]



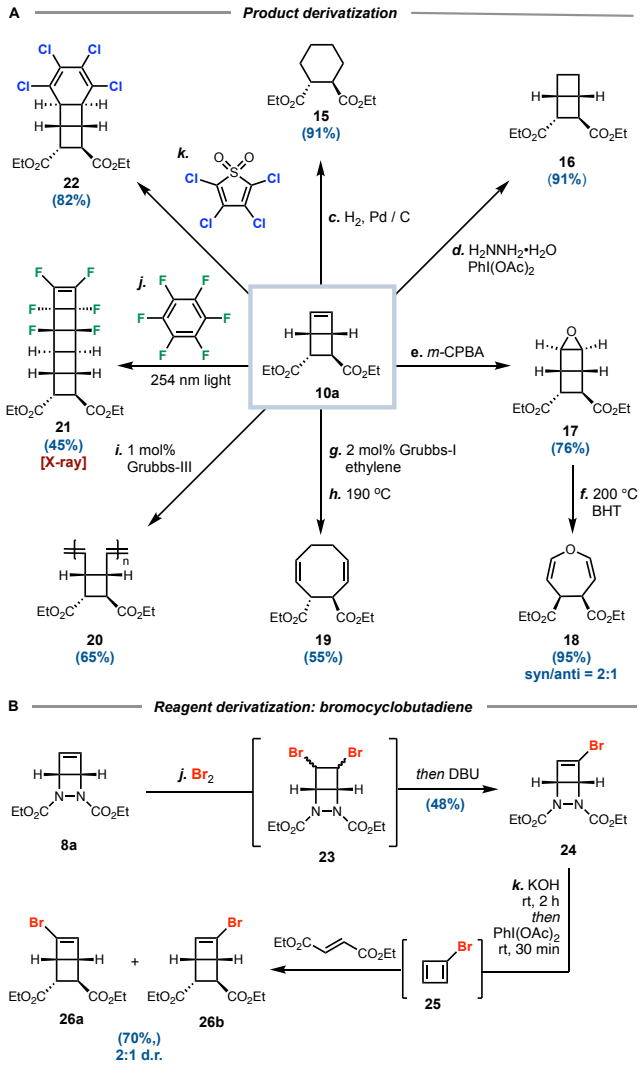
[a]Reagents and conditions: (a) OsO_4 (2 mol%), NMO (1.5 equiv), 2,6-lutidine (3 equiv), then $PhI(OAc)_2$ (1.5 equiv), H_2O/acetone, rt; (b) (piperonyl)triphenylphosphonium bromide (10 equiv), NaHMDS (9.9 equiv), THF, 0 °C.

To further illustrate the utility of the bicyclohexene motif produced in these reactions, we then prepared several derivatives of **10a** (Scheme 2B). We were conscious that the highly strained, fused bicyclic structure can be exploited in strain-release reactions. Hydrogenation with palladium on carbon yielded cyclohexane **15** in 91% yield, while hydrogenation with diimide[24] selectively reduced the cyclobutene to produce bicyclohexane **16** in 91% yield. Oxidation of **10a** with *meta*-chloroperoxybenzoic acid provided epoxide **17** as a single diastereomer in 76% yield. Thermolysis of **17** then gave oxepine **18** in 95% yield and as a 2:1 mixture of diastereomers. A similar epimerization to that of **18** was reported by Leyhane and coworkers.[25] **10a** was also engaged in ring-opening cross metathesis with ethylene followed by a thermal Cope rearrangement to form cyclooctadiene **19** in 55% yield. Ring-opening metathesis polymerization of **10a** at 0 °C with Grubbs third-generation catalyst yielded polymer **20** with a 65% recovery. The photochemical cycloaddition/electrocyclic closure cascade reaction of **10a** with hexafluorobenzene led to **21** as a single diastereomer.[14d,26] The structure of **21** was confirmed by single crystal X-ray crystallography (see Supporting Information). Product **10a** was also engaged in an inverse electron-demand Diels–Alder cycloaddition with tetrachlorothiophene dioxide,[27] which, after subsequent cheletropic extrusion of sulfur dioxide, yielded **22** in 82%.

We then turned our attention to preparing a substituted cyclobutadiene. After consulting the literature, we noted that the synthesis of bromocyclobutadiene was underexplored,[28] yet

we anticipated rapid access from **8a**. Therefore, **8a** was dibrominated to yield **23** as an inconsequential mixture of isomers, which was eliminated with DBU to yield **24** in 48% yield over this sequence (Scheme 3B). When **24** was subjected to our standard conditions in the presence of diethyl fumarate, a 2:1 mixture of brominated adducts **26a** and **26b** were formed in 70% yield. We propose that this reaction proceeds *via* unobserved bromocyclobutadiene **25**.

Scheme 3. Derivatizations. (A) Derivatizations of 10a. (B) Derivatization of 8a to bromocyclobutadiene.[a]



[a]Reagents and conditions: (a) H_2 (1 atm), Pd/C (10%), hexanes, rt; (b) hydrazine monohydrate (4 equiv), $PhI(OAc)_2$ (2 equiv), CH_2Cl_2, rt; (c) *m*-CPBA (2 equiv), CH_2Cl_2, rt; (d) BHT (5 mol%), PhMe, 200 °C; (e) ethylene (1 atm), Grubbs-I (2 mol%), PhH, rt; (f) PhMe, 190 °C; (g) Grubbs-III (1 mol%), $CHCl_3$, 0 °C; (h) 254 nm light, hexafluorobenzene (1 equiv), pentane, rt; (i) tetrachlorothiophene dioxide (1.2 equiv), $CHCl_3$, 50 °C; (j) Br_2 (3 equiv), CH_2Cl_2, 0 °C, *then* DBU (1.3 equiv), THF. (k) KOH (2.5 equiv), ethanol, rt, *then* $PhI(OAc)_2$ (2 equiv), diethyl fumarate (3 equiv), ethanol/water, rt.

In summary, we have developed an easily accessible metal-free reagent for producing cyclobutadiene under mild conditions and have explored its reaction with intermolecular [4+2] reactions with electron-deficient alkenes. Products from this method have been derivatized to a variety of small molecules including the natural product dipiperamide G. Further explorations into the application of this reagent are currently ongoing.

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