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# Continuous-Flow Synthesis of Cyclobutenes Using LED Technology

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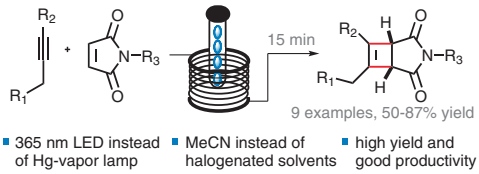


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**Abstract** Cyclobutenes are highly strained ring systems of considerable synthetic interest that can be accessed via cycloaddition reactions between alkenes and alkynes. However, their traditional preparation relies on photochemical [2+2] cycloadditions that exploit low-wavelength UV radiation emitted from inefficient medium-pressure Hg lamps. This paper reports on the development of a modern approach using a high-power LED set-up emitting at the boundary of UV-A and visible light in conjunction with a continuous-flow reactor. The resulting flow process renders a series of cyclobutenes from maleimides and various commercial alkynes. This provides a more energy-efficient approach that is readily scalable to access multigram quantities of cyclobutenes in high chemical yields and short residence times. The value of these products is exemplified by flow-based hydrogenations yielding highly substituted cyclobutanes which represent sought after building blocks in modern medicinal chemistry programs.

**Key words** photochemistry, cycloaddition, cyclobutene, light-emitting diode (LED), flow chemistry

The use of light to drive chemical reactions has gained significant attention in recent years as it unlocks a complementary access to thermal reactions for the synthesis and manipulation of chemical entities.[1] Light is thereby seen as a traceless reagent equivalent whereby variation of the wavelength provides for fine tuning of energy input. Historically, metal vapor lamps (e.g., Hg lamps) were used almost exclusively in photochemical reactions, however, the energy efficiency is poor due to their emission of radiation in the UV, visible, and IR region. This not only leads to undesired side reactions, but also poses safety risks with regards to the harmful UV radiation and the potential of releasing toxic metal vapors in case of accidental lamp breakage.

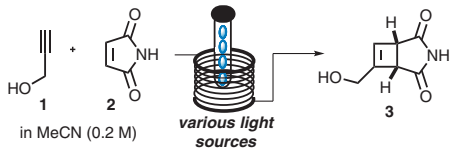
The advent of readily available LEDs as selective and mild light sources for chemical reactions has had a significant impact on revitalizing photochemistry.[2] Modern LEDs possess narrow emission spectra (ca. 10–40 nm) and are available both for visible and UV-A applications at low cost. Their straightforward integration in both batch and continuous-flow photoreactors provides significant value for modern photochemical transformations.

In recent years our group developed several continuous photochemical processes utilizing either benign photocatalysts such as TBADT[3] or the direct irradiation of conjugated substrates[4] to forge new C–C bonds and create druglike entities. Key to this was the use of a tunable high-power (50–100 W) LED emitting light at the boundary between UV-A and visible light (i.e., 360–400 nm with $\lambda_{max}$ = 365 nm). As part of our continuing efforts in this area our attention turned to the photochemical generation of cyclobutenes via [2+2]-cycloaddition reactions between alkynes and alkenes. Cyclobutenes[5] are attractive building blocks characterized by a strained four-membered ring that offers further functionalization of the embedded alkene towards saturated systems.[6] Important contributions by Childs and Johnson,[7] Booker-Milburn,[8] and others[9] have identified the aforementioned photocycloaddition process as the most direct route towards these targets. Commonly, these studies, whether conducted in batch or continuous-flow mode, exploit Hg-vapor lamps in combination with low-pass filters and suitable cooling tools to mitigate the drawbacks of this type of light source. To seek a more energy-efficient and selective approach towards cyclobutenes, the development of a continuous photochemical[10] approach based on the high-power LED as a modern replacement for classical Hg-vapor lamps was studied.

Studies commenced by trialing the reaction between maleimide and propargyl alcohol to generate cyclobutene **3** (Scheme 1). A standardized Vapourtec E-series flow module with its UV150 photoreactor was chosen for all experiments as it allows flexible exchange of light sources and temperature control of the reactor chamber. A medium-

pressure Hg lamp (combined with a low-pass filter), a high-power LED emitting at 365 nm and a medium-power blue LED emitting at 420 nm were used in initial reactions. A standardized reactor coil (10 mL, PFA) was used in all flow experiments and its temperature was regulated to ca. 25 °C.




**Scheme 1** Flow set-up for [2+2] photocycloadditions

These experiments demonstrated that both the Hg lamp (set to 75 W input power) and the LED emitting at 365 nm (set to 75 W input power) generated the desired cyclobutene product (Table 1, entries 1 and 2). However, the UV-A LED provided for a cleaner and higher-yielding process, whereas the formation of a white insoluble precipitate was noted using the Hg lamp that would lead to reactor fouling over time.[11] The blue LED (420 nm, 55 W input power) was also used, but in this case no cyclobutene product was formed and unreacted maleimide was recovered quantitatively (entry 3). As expected, no reaction was observed in the absence of light even at elevated temperatures (entries 4 and 5).

**Table 1** Initial Studies with Various Light Sources ($t_{Res}$ = 20 min)

| Entry | Light source | Details | $^1$H NMR yield of **3a** (%) |
|---|---|---|---|
| 1 | Hg lamp (+ filter) | 75 W | 65 |
| 2 | UV-A LED (365 nm) | 75 W | 81 |
| 3 | blue LED (420 nm) | 55 W | 0 |
| 4 | no light | 25 °C | 0 |
| 5 | no light | 55 °C | 0 |

Having established that the high-power LED lamp emitting at 360–400 nm ($\lambda_{max}$ = 365 nm, see the Supporting Information for more details) was superior to both the medium-pressure Hg lamp and the blue LED, the best conditions were evaluated for a set of different alkynes as well as maleimides. Due to the limited solubility of maleimide in most organic solvents, acetonitrile was identified as the preferred solvent and concentrations of 200 mM were maintained throughout this study. Evaluation of the necessary residence time showed that a more efficient process can be realized using 15 min whereas further reduction of the residence time to 10 min rendered significant amounts of unreacted substrates (ca. 40%). Thus, the conditions highlighted in Scheme 1 were deemed suitable for further explorations with regards to varying both the alkyne and alkene component. It is worth noting that this screen has not only identified the 365 nm LED as a more attractive light source compared to previous reports, but the use of acetonitrile was also attractive as a replacement of chlorinated solvents such as dichloromethane and hexafluoroisopropanol that were used in previous studies towards cyclobutenes.[9b]

The initially established conditions were suitable to generate cyclobutenes derived from maleimide and various alkyne partners such as propargyl alcohol, 1-hexyne, and 3-hexyne (Figure 1, 3a–c) in high chemical yields. Equally, when using a *N*-substituted maleimide (e.g., *N*-cyclopentylmaleimide) the corresponding products **3d–f** were obtained in high efficiency. Using cyclopropyl alkyne as cycloaddition partner did give the desired product **3g** in high yield despite the photolabile cyclopropyl ring. The use of an *N*-arylated maleimide gave no product under the original conditions suggesting competitive light absorption by the aryl chromophore, however, in accordance with reports by Kokotos[9b] addition of a photosensitiser such as thioxanthone (20 mol%) rendered the desired product **3h** in high yield. Lastly, electron-deficient alkynes such as ethyl propiolate were found less effective giving the desired cycloadduct **3i** in a modest yield of 50% under the standard conditions.

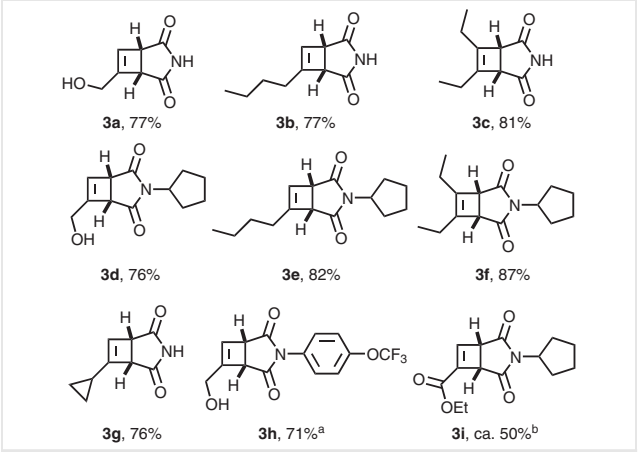


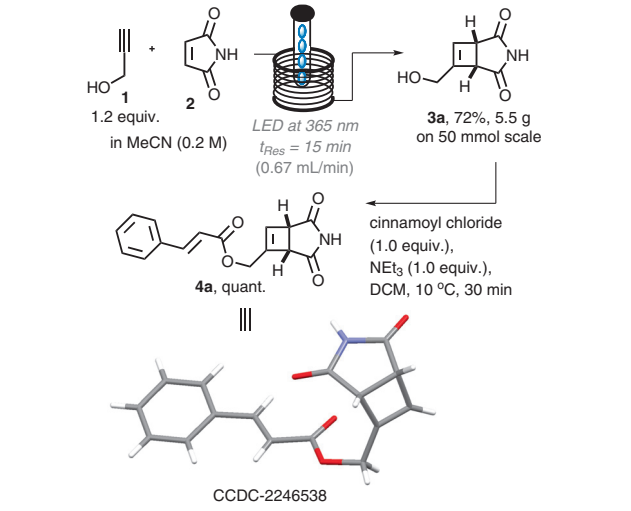

**Figure 1** Substrate scope for continuous cyclobutene synthesis; [a] 20 mol% of thioxanthone used; [b] unstable towards silica.

To establish the robustness of this flow process towards accessing selected cyclobutenes on gram scale, a scale-up to the target product **3a** was trialled. Execution of the original conditions thereby allowed processing of 50 mmol of maleimide in a matter of hours producing the target in a yield of 72% (5.5 g) which parallels the results observed on small scale.

The isolation of this polar product was adjusted by derivatization with cinnamoyl chloride which rendered the related cinnamate product **4a** as a crystalline product. As depicted in Scheme 2 this allowed for securing a single-crystal structure of **4a** which also confirms the expected cyclobutene substructure.[12] Interestingly, it was found that the cy-

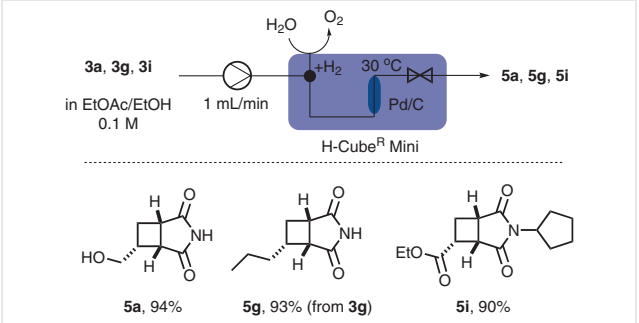
clobutene ring in **4a** is not susceptible towards intramolecular [2+2] cycloaddition in the absence of a photocatalyst. Experimental data showed that partial alkene isomerization occurs on the cinnamate fragment instead.




**Scheme 2** Reaction scale-up and formation of crystalline cinnamate adduct **4a**

Lastly, evaluation of the value of the cyclobutene scaffolds towards generating related cyclobutanes by simple hydrogenation protocols was investigated. A straightforward flow process utilizing an H-Cube® Mini reactor combined with suitable catalyst cartridges (10% Pd/C) was devised and exploited to render a small set of saturated derivatives as shown in Scheme 3. Substrate solutions were prepared in EtOAc/EtOH (0.1 M, 50/50 by volume) and pumped through the catalyst cartridge (heated to 30 °C) with a flow rate of 1 mL/min. Analysis of the products (**5a**, **5g**, **5i**) by $^1$H NMR spectroscopy confirmed that these conditions allowed for clean hydrogenation of the cyclobutene ring system. Additionally, all products were obtained as single diastereomers whereby NOESY experiments confirmed the addition of hydrogen from the more accessible convex site. Interestingly, this protocol yielded clean conversion of the cyclopropane-bearing system **3g** which was accompanied by hydrogenolysis of the three-membered ring,[13] as well as the unstable ester containing cyclobutene **3i** to the corresponding cyclobutanes with high efficiency.

In summary, the development of a continuous-flow process generating sets of bicyclic cyclobutenes through the [2+2] photocycloaddition of alkynes and maleimides is reported.[14] Crucially, the process can be operated using an adjustable high-power LED emitting at 365 nm thus allowing the replacement of classical medium-pressure Hg lamps. In addition to realizing a more energy-efficient process, it was found that the desired cyclobutene targets can be accessed in short residence times of 15 min in a scalable manner as




**Scheme 3** Flow-based hydrogenation of selected cyclobutenes

demonstrated by performing multigram-scale experiments. Overall, the cyclobutenes were isolated in high chemical yields that allow for straightforward derivatization, e.g., by flow-based hydrogenations to render related cyclobutanes as single diastereoisomers. Overall, this continuous-flow approach showcases the effective generation of strained 4-membered ring systems exploiting modern LED-based transformations that do not require expensive transition-metal catalysts and thus provide an improved entry to these structures of industrial interest.

## Conflict of Interest

The authors declare no conflict of interest.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2086-0630.

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(14) **Synthesis of Substrates 2a and 2b**

To a solution of maleic anhydride (1 equiv.) in chloroform (1 M) and acetic acid (10 equiv.) was added either cyclopentyl amine (1.5 equiv.) or 4-trifluoromethoxyaniline (1.5 equiv.). The resulting mixture was then heated at reflux for ca. 10 h when sampling by $^1$H NMR indicated near-quantitative formation of the desired maleimide product. The pure products were isolated by column chromatography (10–30% EtOAc in cyclohexane) after neutralization with $K_2CO_3$ and aqueous extraction.

**1-Cyclopentyl-1*H*-pyrrole-2,5-dione (2a)**

Yield 76% (7.6 mmol, 1.25 g), colorless solid, melting range 68–71 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.61 (s, 2 H), 4.39 (p, *J* = 8.3 Hz, 1 H), 2.03–1.75 (m, 6 H), 1.63–1.51 (m, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.9 (2 C), 134.0 (2 CH), 50.9 (CH), 29.4 (2 $CH_2$), 24.8 (2 $CH_2$). IR: ν = 3443 (w), 3092 (w), 2967 (m), 2874 (w), 1691 (s), 1373 (s), 1208 (m), 1128 (m), 837 (s), 689 (s), 432 (s). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_9H_{12}NO_2$: 165.0790; found: 165.0786.

**1-[4-(Trifluoromethoxy)phenyl]-1*H*-pyrrole-2,5-dione (2b)**

Yield 70% (1.8 mmol, 460 mg), off-white powder, melting range 75–77 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 9.2 Hz, 2 H), 7.29 (d, *J* = 9.2 Hz, 2 H), 6.84 (s, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.1 (2 C), 148.2 (q, *J* = 4 Hz, C), 134.3 (2 CH), 129.7 (C), 127.2 (2 CH), 121.6 (2 CH), 119.7 (q, *J* = 258 Hz, $CF_3$). $^{19}$F NMR (376 MHz, $CDCl_3$): δ = –58.0 (s). IR: ν = 3072 (w), 1720 (s), 1703 (s), 1514 (m), 1265 (s), 1214 (m), 1160 (s), 819 (m), 691 (m). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{11}H_7F_3NO_3$: 258.0373; found: 258.0374.

**Synthesis of Cyclobutenes 3a–i**

A stock solution of the maleimide (1.0 equiv.) and alkyne (1.2 equiv.) was prepared in MeCN (0.2 M) and pumped through the reactor coil (10 mL, PFA, 15 min residence time) of a Vapourtec flow reactor combined with its UV150 unit. As light source an adjustable high-intensity LED emitting at 365 nm was used with a set input power of 75 W. After collection of the product solution, the volatiles were removed by evaporation and the pure product was isolated after silica column chromatography (eluent 10–20% EtOAc/cyclohexane).

**(*rac*)-(1*S*,5*S*)-6-(Hydroxymethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3a)**

Yield 77% (3.9 mmol, 590 mg), pale yellow wax. $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 6.33 (d, *J* = 1.8 Hz, 1 H), 4.27 (s, 2 H), 3.86 (br s, 1 H), 3.74 (br s, 1 H), 1.99 (s, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 174.6 (C), 174.3 (C), 151.1 (C), 130.4 (CH), 59.5 ($CH_2$), 48.7 (CH), 45.6 (CH). IR: δ = 3435 (m), 3218 (m), 3078 (m), 2985 (w), 1763 (m), 1691 (s), 1338 (m), 1248 (m), 1171 (s), 1036 (m), 973 (m), 791 (m), 630 (m). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_7H_8NO_3$: 154.0499; found: 154.0500.

**(*rac*)-(1*S*,5*S*)-6-Butyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3b)**

Yield 77% (3.1 mmol, 550 mg), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.42 (br s, 1 H), 6.05 (d, *J* = 1.5 Hz, 1 H), 3.66 (dd, *J* = 3.0, 1.4 Hz, 1 H), 3.64–3.56 (m, 1 H), 2.15 (dddd, *J* = 8.2, 6.4, 3.8,

 

2.0 Hz, 2 H), 1.56–1.42 (m, 2 H), 1.31 (dt, *J* = 14.8, 7.3 Hz, 2 H), 0.87 (t, *J* = 7.3 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.3 (C), 175.3 (C), 154.0 (C), 129.0 (CH), 49.9 (CH), 45.3 (CH), 29.6 ($CH_2$), 28.0 ($CH_2$), 22.2 ($CH_2$), 13.7 ($CH_3$). IR: ν = 3221 (br m), 2958 (m), 2930 (m), 1764 (m), 1694 (s), 1337 (m), 1247 (m), 1170 (m), 957 (m), 781 (m), 676 (m), 625 (m). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{10}H_{14}NO_2$: 180.1019; found: 180.1020.

**(*rac*)-(1*R*,5*S*)-6,7-Diethyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3c)**

Yield 81% (2.7 mmol, 480 mg), white solid, melting range 72–75 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.55 (br s, 1 H), 3.52 (s, 2 H), 2.24–2.05 (m, 4 H), 1.03 (t, *J* = 7.6 Hz, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.6 (2 C), 144.3 (2 C), 46.4 (2 CH), 21.1 (2 $CH_2$), 11.7 (2 $CH_3$). IR: ν = 3280 (br), 2971 (m), 2914 (w), 1758 (w), 1703 (s), 1460 (w), 1334 (m), 1247 (m), 1181 (m), 1145 (m), 754 (m), 700 (w). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{10}H_{14}NO_2$: 180.1019; found: 180.1020.

**(*rac*)-(1*S*,5*S*)-3-Cyclopentyl-6-(hydroxymethyl)-3-azabicyclo-[3.2.0]hept-6-ene-2,4-dione (3d)**

Yield 76% (2.9 mmol, 639 mg), waxy solid. $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.27 (d, *J* = 1.4 Hz, 1 H), 4.40 (p, *J* = 8.6 Hz, 1 H), 4.21 (d, *J* = 5.1 Hz, 2 H), 3.72 (d, *J* = 3.1 Hz, 1 H), 3.63–3.54 (m, 1 H), 2.62 (t, *J* = 5.8 Hz, 1 H), 1.99–1.84 (m, 4 H), 1.83–1.70 (m, 2 H), 1.61–1.47 (m, 2 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 175.2 (C), 175.0 (C), 151.7 (C), 130.5 (CH), 59.4 ($CH_2$), 51.4 (CH), 46.7 (CH), 43.7 (CH), 28.5 ($CH_2$), 28.4 ($CH_2$), 25.3 (2 $CH_2$). IR: ν = 3438 (br), 2956 (w), 2870 (w), 1762 (w), 1687 (s), 1395 (m), 1250 (w), 1218 (m), 1039 (w), 668 (w). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{12}H_{16}NO_3$: 222.1125; found: 222.1124.

**(*rac*)-(1*S*,5*S*)-6-Butyl-3-cyclopentyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3e)**

Yield 82% (2.5 mmol, 620 mg), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.05 (d, *J* = 1.5 Hz, 1 H), 4.40 (p, *J* = 8.4 Hz, 1 H), 3.57 (d, *J* = 3.4 Hz, 1 H), 3.49 (dd, *J* = 2.7, 1.1 Hz, 1 H), 2.17–2.11 (m, 2 H), 1.98–1.82 (m, 4 H), 1.77 (qt, *J* = 8.2, 2.3 Hz, 2 H), 1.58–1.52 (m, 2 H), 1.49–1.40 (m, 2 H), 1.29 (dq, *J* = 14.7, 7.3 Hz, 2 H), 0.88 (t, *J* = 7.3 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.0 (C), 175.1 (C), 154.4 (C), 129.4 (CH), 51.2 (CH), 48.1 (CH), 43.4 (CH), 29.6 ($CH_2$), 28.4 (2 $CH_2$), 28.1 ($CH_2$), 25.3 (2 $CH_2$), 22.2 ($CH_2$), 13.7 ($CH_3$). IR: ν = 2956 (m), 2932 (w), 2871 (w), 1764 (w), 1697 (s), 1365 (m), 1217 (w), 1154 (m). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{15}H_{22}NO_2$: 248.1645; found: 248.1646.

**(*rac*)-(1*R*,5*S*)-3-Cyclopentyl-6,7-diethyl-3-azabicyclo[3.2.0]-hept-6-ene-2,4-dione (3f)**

Yield 87% (4.1 mmol, 1.0 g), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 4.38 (p, *J* = 8.5 Hz, 1 H), 3.41 (s, 2 H), 2.14 (qd, *J* = 7.6, 5.1 Hz, 4 H), 1.97–1.80 (m, 4 H), 1.79–1.71 (m, 2 H), 1.56–1.47 (m, 2 H), 1.03 (t, *J* = 7.6 Hz, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.1 (2 C), 144.7 (2 C), 51.0 (CH), 44.6 (2 CH), 28.4 (2 $CH_2$), 25.3 (2 $CH_2$), 21.1 (2 $CH_2$), 12.0 (2 $CH_3$). IR: ν = 2966 (m), 2874 (w), 1762 (w), 1693 (s), 1460 (w), 1394 (w), 1366 (m), 1215 (m), 1156 (m), 1139 (m). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{15}H_{22}NO_2$: 248.1645; found: 248.1648.

**(*rac*)-(1*S*,5*S*)-6-Cyclopropyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3g)**

Yield 76% (7.2 mmol, 1.17 g), waxy solid. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.59 (br s, 1 H), 5.99 (s, 1 H), 3.57–3.48 (m, 2 H), 1.55–1.39 (m, 1 H), 0.92–0.70 (m, 3 H), 0.66–0.54 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.2 (C), 175.4 (C), 154.5 (C), 126.3 ($CH_2$), 48.4 (CH), 44.5 (CH), 11.3 (CH), 6.5 ($CH_2$), 6.1 ($CH_2$). IR: ν = 3221 (br), 3078 (w), 3009 (w), 1765 (w), 1703 (s), 1338 (w), 1250 (w), 1184 (w), 792 (w). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_9H_{10}NO_2$: 164.0706; found: 164.0708.

**(*rac*)-(1*S*,5*S*)-6-(Hydroxymethyl)-3-[4-(trifluoromethoxy)phenyl]-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3h)**

Yield 71% (2.0 mmol, 625 mg), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 4 H), 6.39 (app q, *J* = 1.7 Hz, 1 H), 4.30 (d, *J* = 5.2 Hz, 2 H), 3.97 (d, *J* = 3.1 Hz, 1 H), 3.87–3.82 (m, 1 H), 1.89 (t, *J* = 5.9 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 173.5 (C), 173.3 (C), 151.5 (C), 148.8 (C), 130.6 (CH), 130.1 (C), 128.0 (2 CH), 121.6 (2 CH), 120.3 (q, *J* = 252 Hz, $CF_3$), 59.5 ($CH_2$), 47.1 (CH), 44.1 (CH). $^{19}$F NMR (376 MHz, $CDCl_3$): δ = –57.9 (s). IR: ν = 3467 (br), 2923 (w), 1773 (w), 1707 (s), 1510 (m), 1379 (w), 1259 (s), 1214 (s), 1170 (s), 1021 (w). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{14}H_{11}NF_3NO_4$: 314.0635; found: 314.0634.

**(*rac*)-{(1*S*,5*S*)-2,4-Dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl}methyl Cinnamate (4a)**

Quantitative yield, white solid, melting range 145–148 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.29 (br s, 1 H), 7.73 (d, *J* = 15.9 Hz, 1 H), 7.65–7.50 (m, 2 H), 7.40–7.33 (m, 3 H), 6.43 (d, *J* = 15.9 Hz, 1 H), 6.35 (s, 1 H), 4.77 (d, *J* = 2.5 Hz, 2 H), 3.84 (d, *J* = 3.1 Hz, 1 H), 3.72 (d, *J* = 2.7 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.6 (C), 173.7 (C), 166.3 (C), 146.7 (C), 146.0 (CH), 134.1 (C), 132.8 (CH), 130.6 (CH), 128.9 (2 CH), 128.2 (2 CH), 116.9 (CH), 60.0 ($CH_2$), 49.0 (CH), 46.0 (CH). IR: ν = 3188 (br), 3061 (w), 2960 (w), 1770 (w), 1696 (s), 1633 (s), 1337 (m), 1312 (m), 1161 (s), 963 (m), 821 (s), 768 (s), 689 s), 630 (s), 414 (s). X-ray data: *P*1 (2), *a* = 5.6738(3) Å, *b* = 10.4380(4) Å, *c* = 11.8262(2) Å, *α* = 104.359(3), *β* = 101.334(4), *γ* = 96.871(4). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{16}H_{14}NO_4$: 284.0917; found: 284.0913.

**Synthesis of Cyclobutanes 5a, 5g, and 5i**

A solution of the desired cyclobutene (**3a**, **3g**, **3i**) was prepared (0.1 M in EtOAc/EtOH, 50/50 by volume) and pumped into an H-Cube® Mini reactor equipped with a catalyst cartridge (10% Pd/C, 30 °C) using a flow rate of 1 mL/min. The reaction solution was collected, evaporated under reduced pressure, and subjected to purification via silica gel chromatography (10–25% EtOAc/cyclohexane) to obtain the pure products prior to analysis and characterization.

**(rac)-(1*S*,5*R*,6*R*)-6-(Hydroxymethyl)-3-azabicyclo[3.2.0]-heptane-2,4-dione (5a)**

Yield 94% (0.94 mmol, 145 mg), waxy solid. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.62 (br s, 1 H), 3.73 (dd, *J* = 12.1, 4.5 Hz, 1 H), 3.63 (dd, *J* = 11.9, 7.7 Hz, 1 H), 3.43 (dd, *J* = 10.2, 6.6 Hz, 1 H), 3.28–3.23 (m, 1 H), 3.10 (ttd, *J* = 10.1, 7.8, 4.6 Hz, 1 H), 2.68 (dtd, *J* = 13.1, 10.2, 1.3 Hz, 1 H), 2.48 (br s, 1 H), 2.16 (ddd, *J* = 13.4, 8.1, 5.7 Hz, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 179.8 (C), 179.7 (C), 62.7 ($CH_2$), 42.4 (CH), 36.6 (CH), 36.0 (CH), 25.0 ($CH_2$). IR: ν = 3444 (br), 3230 (br), 2950 (w), 1760 (m), 1701 (s), 1349 (w), 1180 (w), 1029 (w), 605 (w). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_7H_9NO_3Na$: 178.0475; found: 178.0474.

**(*rac*)-(1*S*,5*R*,6*R*)-6-Propyl-3-azabicyclo[3.2.0]heptane-2,4-dione (5g)**

Yield 93% (0.93 mmol, 155 mg), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.02 (br s, 1 H), 3.40–3.33 (m, 1 H), 3.18 (dt, *J* = 10.2, 6.2 Hz, 1 H), 2.87–2.70 (m, 2 H), 1.87 (ddd, *J* = 12.5, 6.7, 4.9 Hz, 1 H), 1.67–1.56 (m, 1 H), 1.33–1.20 (m, 3 H), 0.86 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 180.3 (C), 177.8 (C), 43.8 (CH), 36.9 (CH), 35.0 ($CH_2$), 34.1 (CH), 29.7 ($CH_2$), 19.8 ($CH_2$), 13.8 ($CH_3$). IR: ν = 3206 (br), 2958 (m), 2931 (m), 1758 (m), 1706 (s), 1338 (m), 1167 (m), 977 (m), 826 (m), 599 (m).

**(*rac*)-Ethyl (1*S*,5*S*,6*R*)-3-Cyclopentyl-2,4-dioxo-3-azabicyclo-[3.2.0]heptane-6-carboxylate (5i)**

Yield 90% (0.90 mmol, 237 mg), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 4.48 (p, *J* = 8.5 Hz, 1 H), 4.20–4.03 (m, 2 H), 3.58 (td, *J* = 10.0, 7.4 Hz, 1 H), 3.42 (dd, *J* = 10.4, 6.7 Hz, 1 H), 3.15 (ddd, *J* =

 

10.3, 6.8, 5.3 Hz, 1 H), 2.71 (dtd, *J* = 13.3, 9.8, 1.2 Hz, 1 H), 2.48 (ddd, *J* = 12.9, 7.4, 5.2 Hz, 1 H), 2.06–1.95 (m, 2 H), 1.94–1.75 (m, 4 H), 1.59–1.51 (m, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.8 (C), 176.3 (C), 171.2 (C), 61.3 ($CH_2$), 51.9 (CH), 40.2 (CH), 37.4 (CH), 35.1 (CH), 28.6 ($CH_2$), 28.3 ($CH_2$), 25.4 ($CH_2$), 25.3 ($CH_2$), 25.2 ($CH_2$), 14.1 ($CH_3$). IR: ν = 2957 (m), 2872 (w), 1770 (m), 1729 (m), 1697 (s), 1396 (m), 1195 (m), 1146 (m), 855 (w). HRMS (ES-TOF)$^+$: *m/z* calcd for $C_{14}H_{19}NO_4Na$: 288.1206; found: 288.1207.

 