Large-Scale Flow Photochemical Synthesis of Functionalized trans-Cyclooctenes Using Sulfonated Silica Gel

**Ampofo Darko**[b,†,*], **Samantha J. Boyd**[a,†], **Joseph M. Fox**[a,*]

[a]Department of Chemistry and Biochemistry, University of Delaware, Newark DE 19716

[b]Department of Chemistry, University of Tennessee, Knoxville, TN, 37996

Abstract

Functionalized *trans*-cyclooctenes are useful bioorthogonal reagents that are typically prepared using a flow photoisomerization method where the product is captured by $AgNO_3$ on silica gel. While this method is effective, the leaching of silver can be problematic when scaling up syntheses. It is shown here that Ag(I) immobilized on tosic silica gel can be used to capture *trans*-cyclooctene products at higher loadings without leaching. It is demonstrated that the sulfonated silica gel can be regenerated and reused with similar yields over multiple runs. Nine different *trans*-cyclooctenes were synthesized, including those commonly utilized in bioorthogonal chemistry as well as new amine and carboxylic acid derivatives.

Graphical Abstract
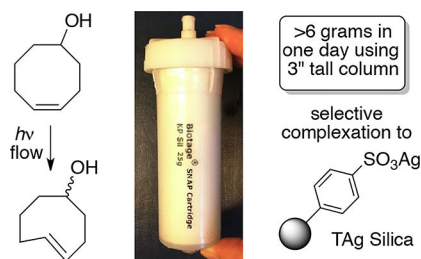
Keywords

flow; photochemistry; *trans*-cyclooctene; large scale; bioorthogonal

Advances in the field of bioorthogonal chemistry have been accompanied by a renaissance in the chemistry of strained molecules including cyclooctynes, cyclopropenes and trans-cyclooctenes.[1–11] Derivatives of *trans*-cyclooctene have emerged as highly reactive coupling partners for bioorthogonal inverse electron demand Diels-Alder reactions[12–17] with rates as fast as 3.3×10^6 $M^{-1}s^{-1}$.[18] A number of multistep routes for the preparation of *trans*-cyclooctenes from *cis*-cyclooctenes had been described,[19–22] but relatively few methods that

have been applied to the synthesis of functionalized *trans*-cyclooctene derivatives.[23–26] Several approaches have been described to produce *trans*-cycloalkenes that contain heteroatoms in the backbone.[27–29] Woerpel has demonstrated that oxasila-*trans*-cycloalkenes can be prepared via silylene additions to vinylepoxides,[30–34] and Tomooka has synthesized and studied the properties of a range of planar chiral heterocycles.[35–38] Bicyclic *trans*-cycloalkenes have been prepared via a sequence of enantioselective cyclopropanation and skeletal rearrangment.[39] Hsung,[40,41] and Takasu[42] have shown that torquoselective opening of bicyclic cyclobutenes can be used to transiently produce *trans*-cycloalkenes.

The singlet sensitized photoisomerization of *cis*-cyclooctene, pioneered by Inoue,[43] is a direct method for the synthesis of *trans*-cyclooctene. To improve the practicality of photoisomerization, we designed a closed-loop flow reactor that perturbs the equilibrium through selective metal complexation of the *trans*-isomer.[44,45] A schematic of the apparatus for preparing *trans*-cyclooctenes is shown in Scheme 1. At completion (usually 6 h), the silica is removed and stirred with ligand (typically NH_4OH) to liberate the *trans*-cyclooctene, which is then recovered by extraction.

Our first generation system ($AgNO_3$ adsorbed on SiO_2- referred to as $AgNO_3/SiO_2$) has been used successfully for a range of *trans*-cyclooctene preparations.[44] A modification of this flow system utilizes a quartz tube in conjunction with a UV light,[46] and a microflow system for cyclooctene photoisomerization has been described.[47] Recently, we described a flow photoisomerization system with in-line cooling that can be used to synthesize *trans*-cycloheptenes.[48] Several groups have also described procedures where the flow photoisomerization protocol is mimicked by periodically stopping irradiation, capturing the *trans*-cyclooctene by filtering through $AgNO_3$ on silica, and resubjecting the filtrate to photoisomerization.[49,50] Tomooka has prepared (*E*)-4-[7]orthocyclophene without flow chemistry by directly adding $AgNO_3/SiO_2$ to a photoisomerization reaction in pentane.[37]

While flow photoisomerization using $AgNO_3/SiO_2$ is a reliable method for producing gram quantities of *trans*-cyclooctenes, leaching of silver (plausibly as the *trans*-alkene•$AgNO_3$ complex) from the column can be problematic when scaling up syntheses of *trans*-cyclooctenes, especially for *trans*-cyclooctenes of high polarity. Herein, we describe a modification for flow photoisomerization that utilizes immobilized Ag(I) on commerical tosic acid silica gel. Throughput is enabled by higher Ag-loadings that can be achieved because the metal is covalently bound to the solid support. The silica gel can be regenerated and reused multiple times without significant change in yield.

Commercially available Dowex ion exchange resins in acid (H+) and sodium salt (Na+) form were evaluated for their ability to prevent silver leaching from $AgNO_3/SiO_2$ (Scheme 2). Here, Dowex was used as a 'catch' resin that was layered beneath the $AgNO_3/SiO_2$. The acidic form of Dowex gave a moderate result (92% conversion, 45% yield, entry 1) whereas the sodium salt was ineffective (entry 2). Similarly, the use of thiolfunctionalized silica as a catch resin gave only traces of product (entry 3). Attempts to directly exchange Ag ions onto Dowex were also ineffective, leading to only 22% of TCO product with acidic Dowex, and trace product with the sodium salt form (entries 4 and 5). More successful was the use of silver-ion exchanged propylsulfonic acid silica (entry 6) or tosic acid silica gel (entry 7).

Both types resulted in good conversions and yields of the *trans*-cyclooctene. The silver exchanged toluenesulfonic acid cartridge provided the highest yield of TCO and was used for further studies.

Silver nitrate adsorbed onto silica gel has long served as a tool for improving chromatography,[51] and sulfonated silica gel that has been subjected to ion exchange with silver (I) has been utilized as a stationary phase for separations of lipids and other fatty acids.[52–56] We subjected commercially available tosic acid silica gel (Silicycle, catalog R60530B) to Ag-ion exchange by eluting with 0.5 M $AgNO_3$ in 9:1 acetonitrile:water until it was no longer acidic. The Ag-ion exchanged tosic acid silica gel (TAg silica) was washed sequentially with methanol, acetone, and hexanes, after which it was dried under a stream of compressed air. As shown in Scheme 2, entry 7, TAg silica functioned efficiently as a solid support for the flow-photoisomerization, providing a 70% isolated yield of isomers of 5-hydroxy-*trans*-cyclooctene **1**. As shown in Scheme 2, entry 6, similarly prepared Ag-ion exchanged propylsulfonic acid silica gel was less effective than tosic acid silica.

For routine photoisomerizations, 13 grams of TAg silica was loaded into a small ('10 gram') Biotage Snap Cartridge that was subsequently wrapped with aluminum foil. Using this cartridge with the experimental setup described in Scheme 1, a 13 mM solution of 5-hydroxy-*cis*-cyclooctene (1 gram) in 9:1 Et_2O:hexanes was continually cycled through this column while irradiated by a Rayonet light source (254 nm). Liberation of the *trans*-cyclooctene by treatment with NH_3-saturated methanol and extractive workup gave 5-hydroxy-*trans*-cyclooctene in 73% isolated yield and 1.5:1 d.r. (Scheme 3, run 1). No leaching was observed with TAg silica. By contrast, much more stationary phase is required with $AgNO_3$ on silica gel, and leaching is occasionally problematic despite inclusion of a large bed of unmodified silica at the bottom of the cartridge.[44]

We demonstrated the ability to reuse the tosic silica gel, which is moderately expensive.[57] As shown in Scheme 3, a SNAP cartridge containing 13 grams of tosic silica gel could be recycled without a significant change in yield ($68 \pm 5\%$) in four consecutive reactions that each began with 1 gram of 5-hydroxy-*cis*-cyclooctene. Between each photoreaction, the sulfonated silica gel was eluted with NH_3-saturated methanol to release the 5-hydroxy-*trans*-cyclooctene. The sulfonated silica gel, which remained in the cartridge, was then neutralized, and Ag-ion exchange was carried out as previously described. Lower yields were observed with TAg silica gel that already been used 4 times, with a 63% isolated yield on run 5 and a 53% yield on run 6.

Commerical tosic silica has an average functionality loading of 0.7 mmol/g,[58] which enables high silver loadings and thereby allows a reduction in the solvent volume and cartridge size required for photoisomerization. In our initial report that used $AgNO_3/SiO_2$, we demonstrated that 5-hydroxy-*cis*-cycloctene could be photoisomerized to produce 3 grams of 5-hydroxy-*trans*-cycloctene in a single run.[44] However, to minimize leaching we used a large, custom column with a bed of unmodified silica gel at the base, which served as a catch resin for leaching silver. With TAg silica, the photoisomerization could be carried out on the same scale with ~90% less stationary phase than is required with $AgNO_3$ on silica. With 40 grams of tosic silica in a 3″ tall Biotage Snap Cartridge, it was possible to produce 6.2

grams of 5-hydroxy *trans*-cyclooctene [Scheme 4.]. In this large scale experiment, **1** was eluted and the column recharged with silver at the 6 h midpoint.

The scope of *trans*-cyclooctenes produced using TAg silica in the flow-photochemical apparatus is shown in Scheme 4. This modification to the closed-loop flow system was used to synthesize *trans*-cyclooctenes with a variety of substitution including: hydroxyl, carboxylic acid, hydroxyethylether, diol, as well as protected amines. Compounds **1–6** are known, and are compounds that have been used broadly for bioorthogonal chemistry.[44,59,60] Additionally, the new amine and carboxylic acid derivatives **7–10** have been synthesized.

In conclusion, a method for photoisomerization of cyclooctenes is reported in which Ag(I) tosic silica gel is used to capture *trans*-cyclooctene products at high loadings without leaching, facilitating large scale synthesis using a minimal amount of solid support. The sulfonated silica gel can be regenerated and reused with similar yields over four runs. A variety of *trans*-cyclooctenes were synthesized, including those commonly utilized in bioorthogonal chemistry as well as new amine and carboxylic acid derivatives.

General Considerations:

All reactions were conducted under N_2 in flame-dried glassware. Tetrahydrofuran was distilled under nitrogen from a mixture of sodium and benzophenone. Unstabilized OmniSolv diethyl ether was purchased from MilliporeSigma and dried by passing through a column of activated molecular sieves. Solutions of NH_3-saturated methanol were prepared by sparging methanol with gaseous ammonia at 0 °C. Reagents were purchased from Aldrich or Alfa Aesar and used as received. Compounds were chromatographed via silica gel (ICN SiliTech 32–62D, 60Å). High resolution mass spectra were obtained using a Thermo Q-Exactive Orbitrap high resolution mass spectrometer using a heated electrospray (HESI) source, or a Waters GCT Premier using a liquid injection field desorption ionization (LIFDI) source. An APT pulse sequence was used for ^{13}C NMR spectra, where methylene and quaternary carbons appear 'up' (u), and methine and methyl carbons appear 'down' (dn).

Photoisomerizations were carried out using a Southern New England Ultraviolet Company Rayonet® reactor model RPR-100 or RPR-200, equipped with 8 low-pressure mercury lamps (2537 Å). Photoisomerizations were carried out in a quartz flask (Southern New England Ultraviolet Company). Biotage® SNAP cartridges (Biotage part No. FSK0–1107) were used to house the $AgNO_3$-exchanged sulfonated silica gel. The bottom of the column was interfaced to PTFE tubing (1/8″ OD × 0.063″ ID, flanged with a thermoelectric flanging tool), equipped with flangeless nylon fittings (1/4–28 thread, IDEX part no. P-582), using a female luer (1/4–28 thread, IDEX part no. P-628). The top of the column was interfaced using a male luer (1/4–28 thread, IDEX part no. P-675). The pump used for recirculating solvents through the photolysis apparatus was purchased from Fluid Metering, Inc. (FMI pump model RP-D equipped with pump head FMI R405). Adapters for interfacing the FMI pump to the PTFE tubing were purchased from IDEX (part no. U-510).

Procedures

Ag-ion exchanged tosic acid silica gel (TAg silica)

Sulfonic acid modified silica gel was purchased from Silicycle (0.57 – 0.89 mmol/g, SKU R60530B, particle size: 40–63 μm/ 230–400 mesh, 60 Å, endcapped). Silica gel (100 g) was transferred to a 100 g Biotage SNAP cartridge (Biotage #FSK0–1107) wrapped in aluminum foil. A solution of $AgNO_3$ (0.5M in 9:1 acetonitrile:water) was passed through the column by gravity until pH neutral. The column was washed with 2×100 mL volumes each of methanol, acetone, and hexanes, respectively. The silica gel was dried under a stream of air, transferred to an amber bottle wrapped in aluminum foil, and stored for further use.

(Z)-N-(Clclooct-4-en-1-yl)-2,2,2-trifluoroacetamide

To a solution of (Z)-cyclooct-4-en-1-amine[61] (1.20 g, 9.58 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added triethylamine (4.0 mL, 29 mmol) and trifluoroacetic anhydride (1.47 mL, 10.5 mmol) dropwise. The solution was allowed to stir overnight at rt, after which TLC analysis showed complete conversion of starting material. The solution was poured into water (20 mL) and extracted twice with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered, and concentrated to give an amber solid. Silica gel chromatography (25% ether/ hexanes) provided the compound as a white solid (1.49 g, 6.74 mmol, 70% yield). m.p. 73– 76 °C. ^{1}H NMR (400 MHz, C_6D_6) δ: 5.87 (s, 1H), 5.56 – 5.37 (m, 2H), 3.85 – 3.71 (m, 1H), 1.97 – 1.66 (m, 4H), 1.45 – 1.14 (m, 5H), 0.93 – 0.84 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ: 155.7 (q, J_{CF} = 36.2 Hz, u), 130.7 (dn), 129.4 (dn), 116.7 (q, J_{CF} = 288.4 Hz, u), 50.3 (dn), 34.1 (u), 34.1 (u), 26.1 (u), 25.9 (u), 23.1 (u). ^{19}F NMR (565 MHz, C_6D_6) δ: 75.8. v_{max} (CH_2CL_2/cm^{-1}: 3300, 3093, 3024, 2931, 2854, 1696, 1554, 1207, 1181, 878, 720. HRMS (LIFDI-TOF) [M$^+$] m/z: calcd for $C_{10}H_{14}F_3NO$: 221.1027; found: 221.1042.

(1R,8S,9S,Z)-Bicyclo[6.1.0]non-4-ene-9-carboxylic acid

Sodium hydroxide (7.21 g, 0.18 mol) was dissolved in water (90 mL) and added to a stirring solution of ethyl (1R,8S,9S,Z)-bicyclo[6.1.0]non-4-ene-9-carboxylate[62] (3.50 g, 0.018 mol) in ethanol (78 mL). The mixture was stirred for 48 h at rt. The mixture was then diluted with CHCl3 and washed with 1M HCl. The organic layer was separated dried over Na_2SO_4, filtered, and concentrated into a white solid that was used without further purification (2.48 g, 0.015 mol, 83% yield). Spectral properties matched those from the literature.[63] ^{1}H NMR (400 MHz, CDCl$_3$) δ: 10.54 (s, 1H), 5.73 – 5.57 (m, 2H), 2.60 – 2.47 (m, 2H), 2.33 – 2.19 (m, 2H), 2.17 – 2.03 (m, 2H), 1.96 – 1.84 (m, 2H), 1.78 (t, J = 8.7 Hz, 1H), 1.59 – 1.46 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 178.7 (u), 129.5 (dn), 27.0 (u), 25.4 (dn), 22.6 (u), 21.1 (dn).

General Photoisomerization Procedure

A '10 g' Biotage SNAP cartridge wrapped in aluminum foil was used to house the modified silica gel (13.2 g). The (Z)-cyclooctene derivative (0.012–0.024 M in solvent) and methyl benzoate (2.0 equiv.) were dissolved in the indicated solvent in a quartz flask. After sparging the contents with N_2 for 15 minutes, the flask was placed in a Rayonet® reactor and connected via PTFE tubing to a column (Biotage® SNAP) and an FMI pump. The column

was then packed with silver nitrate exchanged sulfonated silica gel. Any remaining space between the silica and the cartridge cap was filled with cotton. The column was flushed with the reaction solvent, followed by equilibration via circulation with the FMI pump (~100 mL per minute). The solution in the quartz flask was then irradiated at 254 nm under continuous flow for the indicated time. Th SNAP cartridge was washed with additional solvent, and then dried by a stream of compressed air. A solution of NH_3-saturated methanol was allowed to pass through the column and the effluent was collected until no more *trans*-cyclooctene product was detected by TLC. The collected solution was then concentrated by rotary evaporation and the residue was purified by flash silica gel chromatography to obtain pure *trans*-cyclooctenes.

rel-(1*R*, 4*E*, p*R*)-Cyclooct-4-en-1-ol (eq-1) and *rel*-(1*R*, 4*E*, p*S*)-Cyclooct-4-en-1-ol (ax-1)

With recycling of TAg Silica.—The general photoisomerization procedure was followed using (*Z*)-cyclooct-4-en-1-ol (840 mg, 6.65 mmol) in 9:1 ether:hexanes (500 mL) and methyl benzoate (2.06 g, 15.1 mmol), in a 500 mL quartz tube. Dodecane (1.28 g, 7.51 mmol) was added as an internal reference for GC analysis. A 25 g Biotage® SNAP cartridge was filled with TAg silica gel (12.8 g, 11.4 mmol). Irradiation was carried out until no change in conversion could be observed by GC analysis. The tubing was disconnected and the column flushed with ether, then dried by a stream of compressed air. NH_3-saturated methanol (100 mL) was passed through the column until no more *trans*-cyclooctene product could be detected by TLC. Methanol (100 mL) was passed through and the column was dried under a stream of air pressure. The crude residue was purified through a short pad of flash silica gel (100% ether) to provide 616 mg (73%) of a 1.6:1 mixture of **eq-1:ax-1** as a pale yellow oil. The diastereomers were separated by silica gel column chromatography (5–20% Et$_2$O/hexanes). Additional column chromatography completely separated the diastereomers. ^{1}H and ^{13}C NMR spectra agreed with previously reported data.[44] **ax-1**: ^{1}H NMR (400 MHz, C$_6$D$_6$) δ 5.37 (m, 1H),5.19 (m, 1H), 3.14 (m, 1H), 2.18–2.04 (m, 3H), 1.80–1.62 (m, 5H), 1.35–1.25 (m, 2H), 0.85 (s, 1H); ^{13}C NMR (100 MHz, C$_6$D$_6$) δ 135.3 (dn), 132.7 (dn), 77.3 (dn), 44.9 (u), 41.3 (u), 34.7 (u), 33.0 (u), 31.6 (u); **eq-1**: ^{1}H NMR (400 MHz, C$_6$D$_6$) δ 5.62 (m, 1H), 5.40 (m, 1H), 3.71 (m, 1H), 2.40 (m, 1H), 2.18 (m, 1H), 2.02–1.67 (m, 5H), 1.67–1.50 (m, 1H), 1.31 (m, 1H), 0,98 (m, 1H), 0.71 (s, 1H); ^{13}C NMR (100 MHz, C$_6$D$_6$) δ 134.9 (dn), 132.4 (dn), 66.9 (dn), 43.3 (u), 34.7 (u), 34.1 (u), 29.7 (u), 27.8 (u).

The sulfonated silica in the column was reused by washing the column sequentially with methanol, water, and then eluting with 1M HNO_3 until the effluent was pH 2. Water was passed through the column to remove excess acid, and then the column was eluted with a 0.5 M solution of silver nitrate (9:1 CH$_3$CN:H$_2$O) until the effluent was no longer acidic. The silica in the column was washed sequentially with methanol, acetone, and hexanes, and then equilibrated to the reaction solvent conditions, and reused for flow-isomerization.

Large Scale Preparation—The general photoisomerization procedure was followed using (*Z*)-cyclooct-4-en-1-ol (9.96 g, 0.078 mol) in ether (500 mL) and methyl benzoate (21.2 g, 0.155 mol), in a 500 mL quartz tube. Dodecane (13.23 g, 0.078 mol) was added as an internal reference for GC analysis. A 25 g Biotage® SNAP cartridge was filled with TAg

silica gel (40.9 g, 0.023 mol). Irradiation was carried out until no change in conversion could be observed by GC analysis (6 h, 30% conversion). The *trans*-cyclooctene product was isolated and the sulfonated silica was reloaded with silver ions following the procedures described above. The column was reconnected to the flow apparatus and irradiation carried out with the same batch for a second time, until no change in conversion could be observed by GC analysis (12 h, 98% conversion). More *trans*-cyclooctene product was isolated and combined with the first batch. Column chromatography provided the products as a 1.4:1 mixture of diastereomers (6.20 g, 0.048 mol, 62% yield). ^{1}H and ^{13}C NMR spectra agreed with previously reported data.[44]

rel-(1*R*,2*S*,*E*)-cyclooct-5-ene-1,2-diol (2)

The general photoisomerization procedure was followed using *rel*-(1*R*,2*S*,*Z*)-cyclooct-5-ene-1,2-diol (566 mg, 3.98 mmol) in 5% IPA:Et_2O (350 mL) and methyl benzoate (1.08 g, 7.96 mmol) in a 500 mL quartz tube. A 10 g Biotage® SNAP cartridge was filled with Ag(I) tosic silica gel (9.15 g, 5.22 mmol, based on 0.57 mmol/g silica). Irradiation was carried out for 16.5 hours. The tubing was disconnected and the column flushed with 10% IPA: Et2O, then dried by a stream of compressed air. A solution of methanolic ammonia (100 mL) was passed through the column by gravity and the solution was concentrated via rotary evaporation. The crude product was purified by silica gel column chromatography (EtOAc) to afford 370 mg (65% yield) of the title compound as a white solid. ^{1}H and ^{13}C NMR spectra agreed with previously reported data.[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77 – 5.64 (m, 1H), 5.50 – 5.37 (m, 1H), 3.97 (s, 1H), 3.69 (m, 1H), 2.44 – 1.96 (m, 6H), 1.82 – 1.61 (m, 3H), 1.56 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ: 135.2, 129.1, 78.6, 76.8, 37.8, 36.0, 31.9, 27.6.

rel-((1*R*, 8*S*, 9*R*, 4*E*)-bicyclo[6.1.0]non-4-en-9-yl)m ethanol (3)

The general photoisomerization procedure was followed using ((1*R*,8*S*,9*r*,*Z*)-bicyclo[6.1.0]non-4-en-9-yl)methanol[64–66] (1.00 g, 6.57 mmol) in 1:1 ether/hexanes (500 mL) and methyl benzoate (1.79 g, 13.1 mmol), in a 500 mL quartz tube. Dodecane (1.12 g, 6.57 mmol) was added as an internal standard. A '10 g' Biotage® SNAP cartridge was filled with silver nitrate exchanged sulfonated silica gel (14.49 g, 9.85 mmol) and irradiation carried out for 4 h, after which GC analysis complete conversion. The tubing was disconnected and the column was flushed with additional solvent (1:1 ether/hexanes), dried by a stream of compressed air, followed by treatment with NH_3-saturated methanol (150 mL). After concentration of the solution, the residue was purified by flash column chromatography using silica gel (10–40% ether/hexanes as eluent) to afford the product as an oil (0.805g, 5.29 mmol, 81% yield). ^{1}H and ^{13}C NMR spectra agreed with previously reported data.[67] ^{1}H NMR (600 MHz, CD_3OD) δ: 5.93 – 5.85 (m, 1H), 5.15 (ddd, *J* = 15.7, 10.5, 3.9 Hz, 1H), 3.50 – 3.41 (m, 2H), 2.44 – 2.36 (m, 1H), 2.34 – 2.17 (m, 3H), 1.98 – 1.90 (m, 2H), 0.98 – 0.87 (m, 1H), 0.70 – 0.59 (m, 1H), 0.55 – 0.46 (m, 1H), 0.42 – 0.32 (m, 2H). v_{max} (film)/cm^{-1}: 3330, 2024, 2854, 1638, 1445, 1059.

rel-((1*R*, 8*S*, 9*S*, 4*E*)-bicyclo[6.1.0]non-4-en-9-yl)methanol (4)

The general photoisomerization procedure was followed using ((1R,8S,9s,Z)-bicyclo[6.1.0]non-4-en-9-yl)methanol (1.00 g, 6.57 mmol) in 1:1 ether/hexanes (500 mL)

and methyl benzoate (1.79 g, 13.1 mmol), in a 500 mL quartz tube. Dodecane (1.12 g, 6.57 mmol) was added as an internal standard. A '10 g' Biotage® SNAP cartridge was filled with silver nitrate exchanged sulfonated silica gel (14.49 g, 9.85 mmol) and irradiation carried out for 8 h, after which GC analysis showed complete conversion. The tubing was disconnected and the column was flushed with additional solvent (1:1 ether/hexanes), dried by a stream of compressed air, followed by treatment with ammonium hydroxide (30% aqueous). The aqueous solution was extracted with twice with CH_2Cl_2. The combined organics were washed with water, dried over Na_2SO_4, filtered, and concentrated to afford the crude product as a pale yellow oil (0.820 g, 5.38 mmol, 82% yield). ^{1}H and ^{13}C NMR spectra agreed with previously reported data.[60] ^{1}H NMR (400 MHz, MeOD) δ 5.94 – 5.81 (m, 1H), 5.23 – 5.10 (m, 1H), 3.50 (d, J = 7.7 Hz, 2H), 2.36 – 2.05 (m, 4H), 2.00 – 1.82 (m, 2H), 1.27 – 1.00 (m, 2H), 0.90 – 0.67 (m, 2H), 0.66 – 0.53 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 138.5 (dn), 131.4 (dn), 59.4 (u), 34.5 (u), 34.2 (u), 27.78 (u), 27.76 (u), 21.5 (dn), 19.4 (dn), 18.3 (dn).

rel-(1*R*, 4*E*, p*R*) –2-(Cyclooct-4-en-1-yloxy)ethan-1-ol (eq-5) and *rel*-(1*R*, 4*E*, p*S*)-2-(Cyclooct-4-en-1-yloxy)ethan-1-ol (ax-5)

The general photoisomerization procedure was followed using (*Z*)-2-(cyclooct-4-en-1-yloxy)ethan-1-ol[59] (1.08 g, 6.33 mmol) in 7:3 ether:hexanes (500 mL) and methyl benzoate (1.73 g, 12.7 mmol) in a 500 mL quartz tube. Dodecane (1.08 g, 6.36 mmol) was added as an internal standard. A '10 g' Biotage® SNAP cartridge was filled with silver nitrate exchanged sulfonated silica gel (16.7 g, 9.51 mmol). Irradiation was carried out for 7 h, after which GC analysis showed 85% conversion. The tubing was disconnected and the column flushed with ether, then dried by a stream of compressed air. The silica gel was poured into a flask and stirred with 30% ammonium hydroxide (100 mL) for approximately 15 minutes. CH_2G_2 (100 mL) was added and the solution was stirred an additional 10 minutes. The solution was filtered and the filtrate was extracted with $3 \times CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude oil was purified by flash silica gel chromatography (15% ether in hexanes) to provide a 1.4:1 mixture of **eq-5:ax-5** as a pale yellow oil (0.662 g, 3.89 mmol, 61% yield). Additional column chromatography completely separated the diastereomers. ^{1}H and ^{13}C NMR spectra agreed with previously reported data.[59]

Ax-5: ^{1}H NMR (400 MHz, C_6D_6) δ: 5.44 – 5.32 (m, 1H), 5.24 – 5.12 (m, 1H), 3.62 – 3.48 (m, 2H), 3.31 – 3.16 (m, 1H), 3.16 – 3.06 (m, 1H), 2.80 (dd, J = 10.6, 5.2 Hz, 1H), 2.38 – 2.25 (m, 1H), 2.25 – 2.12 (m, 2H), 2.12 – 1.97 (m, 2H), 1.88 – 1.61 (m, 4H), 1.41 – 1.15 (m, 2H).). ^{13}C NMR (100 MHz, C_6D_6) δ: 135.5 (dn), 132.3 (dn), 86.1 (dn), 69.7 (u), 62.2 (u), 41.2 (u), 38.0 (u), 34.8 (u), 33.3 (u), 31.9 (u).

Eq-5: ^{1}H NMR (400 MHz, C_6D_6) δ: 5.78 – 5.64 (m, 1H), 5.47 – 5.34 (m, 1H), 3.58 – 3.46 (m, 2H), 3.25 (m, 1H), 3.21 – 3.11 (m, 1H), 3.11 – 3.01 (m, 1H), 2.35 (m, 1H), 2.26 – 2.18 (m, 1H), 2.11 – 2.01 (m, 1H), 1.97 – 1.85 (m, 2H), 1.85 – 1.71 (m, 3H), 1.63 – 1.53 (m, 1H), 1.23 – 1.12 (m, 1H), 0.97 – 0.87 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ: 136.0 (dn), 131.4 (dn), 75.0 (dn), 70.2 (u), 62.1 (u), 40.3 (u), 34.9 (u), 33.2 (u), 30.2 (u), 27.9 (u).

((2*s*,3a*R*,9a*S*,*E*)-3a,4,5,8,9,9a-Hexahydrocycloocta[*d*][1,3]dioxol-2-yl)m ethanol (6)

The general photoisomerization procedure was followed using ((2*s*,3a*R*,9a*S*,*Z*)-3a,4,5,8,9,9a-hexahydrocycloocta[*d*][1,3]dioxol-2-yl)methanol[18] (*syn/anti =* 1.1:1) (1.11 g, 6.02 mmol) in 1:1 ether/hexanes (450 mL) and methyl benzoate (1.64 g, 12.1 mmol), in a 500 mL quartz tube. A '10 g' Biotage® SNAP cartridge was filled with silver nitrate exchanged sulfonated silica gel (13.29 g, 9.04 mmol) and irradiation carried out for 12 h. The tubing was disconnected and the column was flushed with ether, dried by a stream of compressed air, followed by treatment with NH_3-saturated methanol (100 mL). After concentration of the solution, the residue was purified by passing through a short pad of flash silica gel (50% ether/hexanes as eluent). The fractions were collected and concentrated to afford the product as a white solid (0.571 g, 3.10 mmol, 51% yield). ^{1}H and ^{13}C NMR spectra agreed with previously reported data.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.70 – 5.45 (m, 4H), 5.12 (t, *J* = 3.6 Hz, 1H), 4.86 (t, *J* =3.0 Hz, 1H), 4.15 – 3.89 (m, 4H), 3.72 – 3.62 (m, 2H), 3.61 – 3.52 (m, 2H), 2.48 – 2.07 (m, 8H), 1.96 – 1.48 (m, 10H). ^{13}C NMR (C_6D_6, 100 MHz) δ: 136.3 (dn), 136.1 (dn), 131.3 (dn), 131.1 (dn), 101.5 (dn), 83.6 (dn), 82.8 (dn), 80.7 (dn), 79.2 (dn), 64.2 (u), 63.7(u), 39.6 (u), 39.0 (u), 34.0 (u), 32.3 (u), 31.9 (u), 31.5 (u), 25.8 (u), 25.0 (u).

rel-(1*R*, 4*E*, p*R*) -cyclooct-4-ene-1-carboxylic acid (eq-7) and *rel*-(1*R*, 4*E*, p*S*) -cyclooct-4-ene-1-carboxylic acid (ax-7)

The general photoisomerization procedure was followed using (*Z*)-cyclooct-4-ene-1-carboxylic acid[68] (999.0 mg, 6.403 mmol) in ether (500 mL) and methyl benzoate (1.750 g, 12.85 mmol), in a 500 mL quartz tube. A 25 g Biotage® SNAP cartridge was filled with silver nitrate exchanged sulfonated silica gel (17.17 g, 9.787 mmol). Irradiation was carried out for 4.5 h, after which the tubing was disconnected and the column flushed with ether, then dried by a stream of compressed air. The silica was placed in a flask and stirred with brine (100 mL) and CH_2G_2 (100 mL) for approximately 15 minutes. The solution was filtered and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (0–20% ether in hexanes) to provide a 1.5:1 mixture of **eq-7:ax-7** (536 mg, 3.43 mmol, 54% yield). Analytically pure samples were obtained by additional chromatography.

Axial diastereomer: m.p. 68–70 °C. ^{1}H NMR (400 MHz, C_6D_6) δ: 12.53 (bs, 0.1H), 5.71 – 5.50 (m, 1H), 5.50 – 5.32 (m, 1H), 2.90 (qd, *J* = 11.8, 4.7 Hz, 1H), 2.60 – 2.41 (m, 1H), 2.23 – 1.91 (m, 5H), 1.82 – 1.63 (m, 2H), 1.33 – 1.11 (m, 1H), 0.95 – 0.74 (m, 1H). ^{13}C NMR (151 MHz, C_6D_6) δ: 182.3 (u), 134.48 (dn), 134.43 (dn), 41.2 (dn), 38.4 (u), 34.5 (u), 31.6 (u), 31.1 (u), 30.8 (u). v_{max} (CH_2CL_2/cm^{-1}: 2926, 2860, 1699, 1441, 1237, 1219, 988. HRMS (LIFDI-TOF) [M$^+$] *m/z*: calcd for $C_9H_{14}O_2$: 154.0994; found: 154.0967.

Equatorial diastereomer : m.p. 81–84 °C. ^{1}H NMR(400 MHz, C_6D_6) δ: 12.00 (bs, 0.44H), 5.31 – 5.11 (m, 2H) 2.21 – 2.04 (m, 4H), 1.95 – 1.51 (m, 5H), 1.33 – 1.17 (m, 1H), 1.01 – 0.87 (m, 1H). ^{13}C NMR(101 MHz, C_6D_6) δ: 185.7 (u), 133.97 (dn), 133.95 (dn), 41.2 (dn), 38.4 (u), 34.5 (u), 31.6 (u), 31.1 (u), 30.8 (u). . v_{max} (CH_2Cl_2)/cm^{-1}: 2928, 2855, 1701, 1225, 1215, 1191, 991. HRMS (LIFDI-TOF) [M$^+$] *m/z*: calcd for $C_9H_{14}O_2$: 154.0994; found: 154.0968.

rel-(1*R*, 8*S*, 9*S*, 4*E*)-bicyclo[6.1.0]non-4-ene-9-carboxylic acid (8)

The general photoisomerization procedure was followed using (1R,8S,9s,Z)-bicyclo[6.1.0]non-4-ene-9-carboxylic acid (1.01 g, 6.09 mmol) in 50% ether:hexanes (500 mL) and methyl benzoate (1.66 g, 12.2 mmol), in a 500 mL quartz tube. A 25 g Biotage® SNAP cartridge was filled with silver nitrate exchanged sulfonated silica gel (13.78 g,12.26 mmol). Irradiation was carried out for 15 h, after which GC analysis showed complete conversion. The tubing was disconnected and the column was flushed with ether and dried by a stream of compressed air. The silica was placed in a flask and stirred with brine (100 mL) and CH_2Cl_2 (100 mL) for approximately 15 minutes. The solution was filtered and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (5% ether in hexanes) to provide the product as a white solid (0.634 g, 3.81 mmol, 63% yield). m.p. (°C): 124–127. ^{1}H NMR (400 MHz, C_6D_6) δ: 12.57 (bs, 1H), 5.55 (ddd, J = 15.8, 9.2, 6.0 Hz, 1H), 5.16 – 5.05 (m, 1H), 2.23 – 2.12 (m, 2H), 1.80 – 1.70 (m, 4H), 1.70 – 1.59 (m, 2H), 1.57 – 1.44 (m, 1H), 0.66 – 0.55 (m, 1H), 0.55 – 0.44 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ: 179.8 (u), 137.5 (dn), 132.3 (dn), 33.7 (u), 33.0 (u), 27.1 (u), 25.87 (dn), 25.85 (u), 24.8 (dn), 21.0 (dn). v_{max} (CH_2CL_2/cm^{-1}: 3344, 3002, 2922, 2856, 1688, 1443, 1234, 1200, 1181. HRMS (LIFDI-TOF) [M$^+$] *m/z*: calcd for $C_{10}H_{14}O_2$: 166.0994; found: 166.0983.

rel-(1*R*, 4*E*, p*R*)-*N*-(Cyclooct-4-en-1-yl)-2,2,2-trifluoroacetamide (eq-9) and *rel*-(1*R*, 4*E*, p*S*)-*N*-(Cyclooct-4-en-1-yl)-2,2,2-trifluoroacetam ide (ax-9)

The general photoisomerization procedure was followed using (*Z*)-N-(cyclooct-4-en-1-yl)-2,2,2-trifluoroacetamide (1.01 g, 4.57 mmol) in 4:1 ether/hexanes (400 mL) and methyl benzoate (1.24 g, 9.13 mmol), in a 500 mL quartz tube. A 25 g Biotage® SNAP cartridge was filled with silver nitrate exchanged sulfonated silica gel (24.13 g, 13.75 mmol) and irradiation carried out for 8.5 h, after which GC analysis showed 82% conversion. The tubing was disconnected and the column was flushed with additional ether, dried by a stream of compressed air, followed by treatment with NH_3-saturated methanol (100 mL). After concentration of the solution, the residue was purified by flash column chromatography using C_2-silica gel[69] (15% ether/hexanes) to afford a white solid as a 3:1 mixture of **eq-9:ax-9** (0.514 g, 2.32 mmol, 51%). Analytically pure samples were obtained by additional chromatography.

Axial diastereomer: m.p. 65–66 °C ^{1}H NMR (400 MHz, C_6D_6) δ: 5.92 (br s, 1H), 5.17 – 5.10 (m, 1H), 5.03 – 4.95 (m, 1H), 4.04 (m, 1H), 1.89 – 1.82 (m, 2H), 1.76 – 1.66 (m, 2H), 1.66 – 1.38 (m, 3H), 1.19 – 0.99 (m, 2H), 0.68 – 0.61 (m, 1H). ^{13}C NMR. (101 MHz, C_6D_6) δ: 155.9 (q, J_{CF} = 36.1 Hz), 133.9 (dn), 133.4 (dn), 116.8 (J_{CF} = 288.8 Hz), 45.8 (dn), 40.2 (u), 34.0 (u), 31.3 (u), 29.8 (u), 29.1 (u). ^{19}F NMR (565 MHz, C_6D_6) δ: 75.7. v_{max} (CH_2Cl_2)/cm^{-1} 3344, 2947, 2919, 1711, 1689, 1200, 1181, 1157. HRMS (LIFDI-TOF) [M$^+$] *m/z* calcd for $C_{10}H_{14}F_3NO$: 221.1027; found: 221.1028.

Equatorial diastereomer: m.p. 80–81 °C. ^{1}H NMR (400 MHz, C_6D_6) δ: 5.51 (br s, 1H), 5.29 – 5.14 (m, 2H), 3.21 (s, 1H), 2.17 – 2.09 (m, 1H), 2.05 – 1.86 (m, 2H), 1.75 – 1.42 (m, 3H), 1.35 – 1.14 (m, 2H), 1.10 – 0.91 (m, 2H). ^{13}C NMR. (101 MHz, C_6D_6) δ: 155.4 (q, J_{CF} = 36.0 Hz), 134.0 (dn), 133.7 (dn), 116.7 (q, J_{CF} = 288.3 Hz), 54.5 (dn), 41.2 (u), 39.0 (u),

34.7 (u), 33.4 (u), 32.2 (u). ^{19}F NMR (565 MHz, C_6D_6) δ: 75.7. ν_{max} (CH_2Cl_2)/cm^{-1} 3284, 2937, 1718, 1695, 1209, 1184, 991 HRMS (LIFDI-TOF) [M$^+$] *m/z* calcd for $C_{10}H_{14}F_3NO$: 221.1027; found 221.1045.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

(1). Sletten EM; Bertozzi CR Angew. Chem. Int. Ed 2009, 48, 6974.

(2). Patterson DM; Nazarova LA; Prescher JA ACS Chem. Biol 2014, 9, 592. [PubMed: 24437719]

(3). Lang K; Chin JW ACS Chem. Biol 2014, 9, 16. [PubMed: 24432752]

(4). McKay CS; Finn MG Chem. Biol 2014, 21, 1075. [PubMed: 25237856]

(5). Ramil CP; Lin Q Chem. Commun 2013, 49, 11007.

(6). MacKenzie DA; Sherratt AR; Chigrinova M; Cheung LLW; Pezacki JP Curr. Opin. Chem. Biol 2014, 21, 81. [PubMed: 25022431]

(7). Rossin R; Robillard MS Curr. Opin. Chem. Biol 2014, 21, 161. [PubMed: 25159021]

(8). Meyer J-P; Adumeau P; Lewis JS; Zeglis BM Bioconjug. Chem 2016, acs. bioconjchem.6b00561.

(9). Cycloadditions in Bioorthogonal Chemistry; Vrabel M; Carell T, Eds.; 2016.

(10). Niki I; Lemke EA Curr. Opin. Chem. Biol 2015, 28, 164. [PubMed: 26302384]

(11). Lang K; Chin JW Chem. Rev 2014, 114, 4764. [PubMed: 24655057]

(12). Blackman ML; Royzen M; Fox JM J. Am. Chem. Soc 2008, 130, 13518. [PubMed: 18798613]

(13). Devaraj NK; Weissleder R; Hilderbrand SA Bioconjug. Chem 2008, 19, 2297. [PubMed: 19053305]

(14). Devaraj NK; Weissleder R Acc. Chem. Res 2011, 44, 816. [PubMed: 21627112]

(15). Wu H; Devaraj NK Top. Curr. Chem 2015, 374, 3.

(16). Selvaraj R; Fox JM Curr. Opin. Chem. Biol 2013, 17, 753. [PubMed: 23978373]

(17). Knall A-C; Slugovc C Chem. Soc. Rev 2013, 42, 5131. [PubMed: 23563107]

(18). Darko A; Wallace S; Dmitrenko O; Machovina M; Mehl R; Chin JW; Fox J Chem. Sci 2014, 0, 1.

(19). Cope AC J. Am. Chem. Soc 1962, 84, 3191.

(20). Hines JN; Peagram MJ; Thomas EJ; Whitham GH J. Chem. Soc. Perkin Trans 1 1973, 2332.

(21). Vedejs E; Snoble KAJ; Fuchs PL J. Org. Chem 1973,38, 1178.

(22). Corey EJ; Shulman JI Tetrahedron Lett 1968, 33, 3655.

(23). Reese A, C. B. S J. Am. Chem. Soc 1970, 92, 2566.

(24). Braddock DC; Cansell G; Hermitage SA; White AJP Tetrahedron-Asymmetry 2004, 15, 3123.

(25). Whitham GH; Wright MJ Chem. Soc 1971, 886.

(26). Shea KJ; Kim JS J. Am. Chem. Soc 1992, 114, 4846.

(27). Jendralla H Chem. Ber 1982, 115, 201.

(28). Jendralla H Tetrahedron 1983, 39, 1359.

(29). Kozma E; Niki I; Varga BR; Aramburu IV; Kang JH; Fackler OT; Lemke EA; Kele P ChemBioChem 2016, 17, 1518. [PubMed: 27223658]

(30). Prévost M; Woerpel KA J. Am. Chem. Soc 2009, 131, 14182. [PubMed: 19769355]

(31). Prévost M; Ziller JW; Woerpel KA Dalt. Trans 2010, 39, 9275.

(32). Hurlocker B; Hu C; Woerpel KA Angew. Chem. Int. Ed 2015, 54, 4295.

(33). Santucci J; Sanzone JR; Woerpel KA Eur. J. Org. Chem 2016, 2016, 2933.

(34). Sanzone JR; Woerpel KA Angew. Chem. Int. Ed 2016, 55, 790.

(35). Tomooka K; Uehara K; Nishikawa R; Suzuki M; Igawa KJ Am. Chem. Soc 2010, 132, 9232.

(36). Igawa K; Ichikawa N; Ano Y; Katanoda K; Ito M; Akiyama T; Tomooka KJ Am. Chem. Soc 2015, 137, 7294.

(37). Igawa K; Machida K; Noguchi K; Uehara K; Tomooka KJ Org. Chem 2016, 81, 11587.

(38). Tomooka K; Komine N; Fujiki D; Nakai T; Yanagitsuru SJ Am. Chem. Soc 2005, 127, 12182.

(39). Miura T; Nakamuro T; Liang C-J; Murakami MJ Am. Chem. Soc 2014, 136, 15905.

(40). Wang X-N; Krenske EH; Johnston RC; Houk KN; Hsung RP J. Am. Chem. Soc 2015, 137, 5596. [PubMed: 25895058]

(41). Wang X-N; Krenske EH; Johnston RC; Houk KN; Hsung RP J. Am. Chem. Soc 2014, 136, 9802. [PubMed: 24992255]

(42). Arichi N; Yamada K-I; Yamaoka Y; Takasu KJ Am. Chem. Soc 2015, 137, 9579.

(43). Inoue Y; Mori T In CRC Handbook of Organic Photochemistry and Photobiology; Lenci F; Horspool W, Eds.; Boca Raton, Fl, 2003; pp. 1–16.

(44). Royzen M; Yap GPA; Fox JM J. Am. Chem. Soc 2008, 130, 3760. [PubMed: 18321114]

(45). Royzen M; Taylor MT; Deangelis A; Fox JM Chem. Sci 2011, 2, 2162. [PubMed: 23125911]

(46). Svatunek D; Denk C; Rosecker V; Sohr B; Hametner C; Allmaier G; Fröhlich J; Mikula H Monatsh. Chem 2016, 147, 579. [PubMed: 27069284]

(47). Billaud EMF; Shahbazali E; Ahamed M; Cleeren F; Noël T; Koole M; Verbruggen A; Hessel V; Bormans G Chem. Sci 2017, 8, 1251. [PubMed: 28451267]

(48). Fox J; Fang Y; Zhang H; Huang Z; Scinto S; Yang J; Ende C. W. am; Dmitrenko O; Johnson DS Chem. Sci 2018, 7, 1953.

(49). Devaraj NK; Upadhyay R; Haun JB; Hilderbrand SA; Weissleder R Angew. Chem. Int. Ed 2009, 48, 7013.

(50). Schoch J; Staudt M; Samanta A; Wiessler M; Jäschke A Bioconjug. Chem 2012, 23, 1382. [PubMed: 22709568]

(51). Mander LN; Williams CM Tetrahedron 2016, 72, 1133.

(52). Christie WW J. Chromatogr. A 1988, 454, 273.

(53). Christie WW J. Lipid Res 1989, 30, 1471. [PubMed: 2600547]

(54). Christie WW J. Sci. Food Agric 1990, 52, 573.

(55). Christie WW J. High Resolut. Chromatogr. Chromatogr. Commun 1987, 10, 148.

(56). Momchilova S; Nikolova-Damyanova BJ Sep. Sci 2003, 26, 261.

(57). The current cost of SiliaBond® Tosic Acid (SCX) silica gel, R60530B, is $3–5/gram, dependent upon quantity purchased.

(58). For tosic silica gel, the loading of the tosic functional group is lot dependent ranging from 0.57 – 0.89 mmol/g.

(59). Li Z; Cai H; Hassink M; Blackman ML; Brown RCD; Conti PS; Fox JM Chem. Commun 2010, 46, 8043.

(60). Wang M; Svatunek D; Rohlfing K; Liu Y; Wang H; Giglio B; Yuan H; Wu Z; Li Z; Fox JM Theranostics 2016, 6, 887. [PubMed: 27162558]

(61). Oh C; Kim K; Ham W Tetrahedron Lett 1998, 39, 2133.

(62). O'Brien J; Chintala S; Fox JM J. Org. Chem 2018, DOI: 10.1021/acs.joc.7b02329.

(63). Dehmlow EV; Plückebaum OJ Prakt. Chem./Chem.-Zeit 1996, 338, 303.

(64). Anciaux AJ; Hubert AJ; Noels AF; Petiniot N; Teyssie PJ Org. Chem 1980, 45, 695.

(65). Ast W; Rheinwald G; Kerber R Die Makromol. Chemie 1976, 177, 1349.

(66). Dommerholt J; Schmidt S; Temming R; Hendriks LJA; Rutjes FPJT; van Hest JCM; Lefeber DJ; Friedl P; van Delft FL Angew. Chem. Int. Ed. Engl 2010, 49, 9422. [PubMed: 20857472]

(67). Taylor MT; Blackman ML; Dmitrenko O; Fox JM J. Am. Chem. Soc 2011, 133, 9646. [PubMed: 21599005]

(68). Bloodworth AJ; Melvin T; Mitchell JC J. Org. Chem 1988, 53, 1078.

(69). Panne P; Fox JM J. Am. Chem. Soc 2007, 129, 22. [PubMed: 17199269]
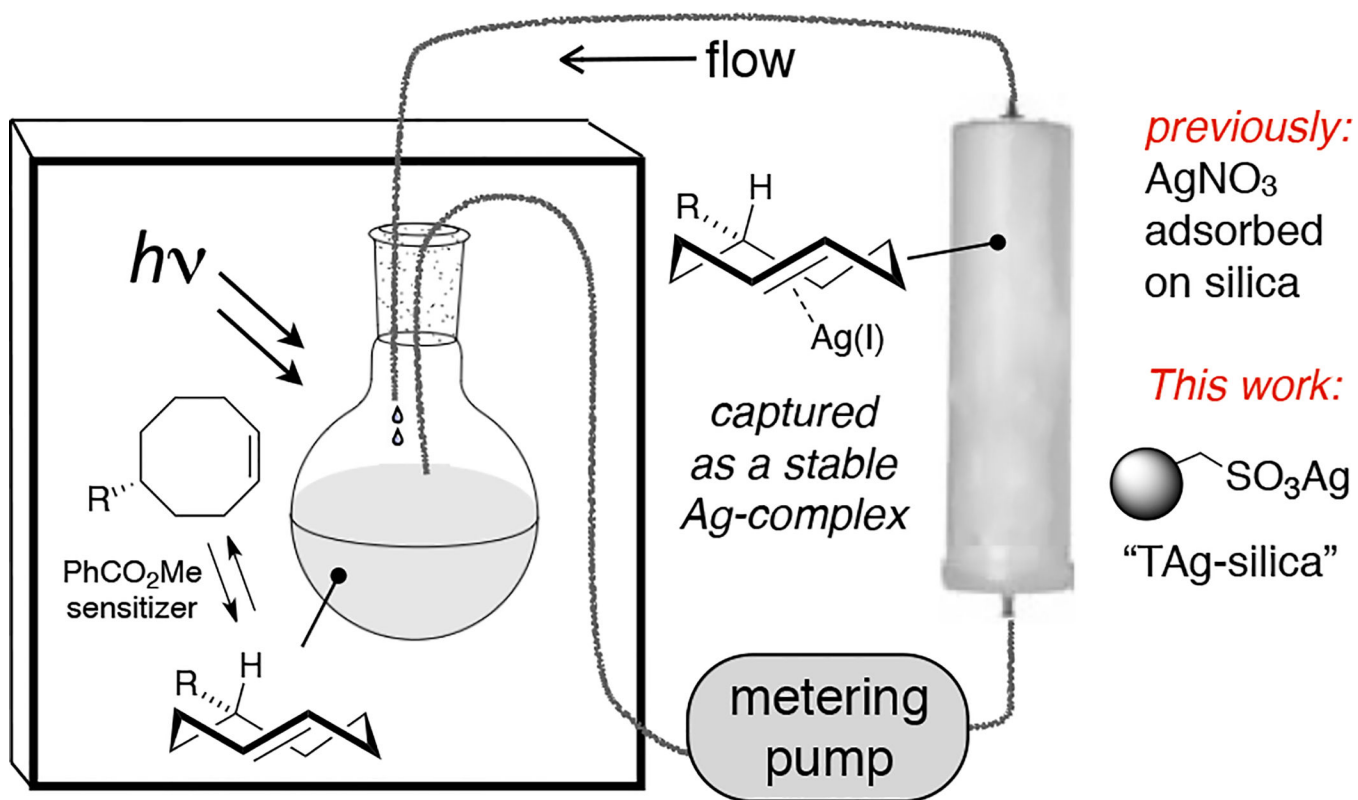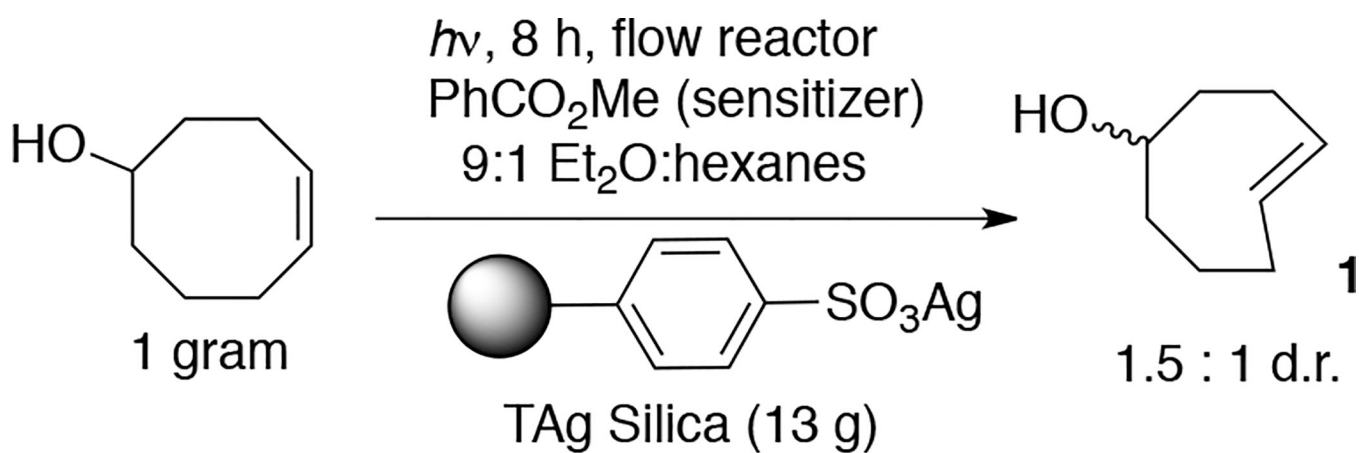
Scheme 1.
Schematic of flow reactor

hv, flow reactor
PhCO$_2$Me (sensitizer)
9:1 Et$_2$O:hexanes
—— **resin·Ag** ——→ **1**
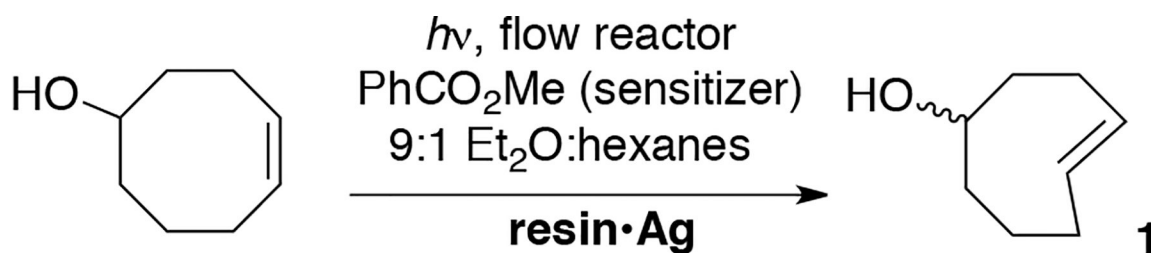
entry	resin·Ag	conversion	yield
1	AgNO$_3$·SiO$_2$ above Dowex resin (H+)	92%	45%
2	AgNO$_3$·SiO$_2$ above Dowex resin (Na+)	45%	<5%
3	AgNO$_3$·SiO$_2$ above siliaMetS (thiol) silica	64%	<5%
4	AgNO$_3$ exchanged Dowex resin (H+)	50%	22%
5	AgNO$_3$ exchanged Dowex resin (Na+)	<5%	<5%
6	AgNO$_3$ exchanged Propylsulfonic Acid Silica	78%	57%
7	AgNO$_3$ exchanged Tosic Acid (TAg) Silica	91%[a]	70%[a]

Scheme 2.
Screening of Resins for Flow-photoisomerization
All resins were packed in a Biotage Snap Cartridge. For entries 1–3, two resins were packed in the same cartridge. Conversions were calculated by adding dodecane to the reaction mixture followed by GC analysis. [a] average of 4 runs. See Scheme 3.

Scheme 3.
Flow photoisomerization requires minimal TAg silica. Reactions run on 1 gram scale were carried out using a '10 gram' cartridge that could be recycled multiple times with similar results.

run	conversion	yield
1	86%	73%
2	93%	67%
3	93%	67%
4	92%	72%
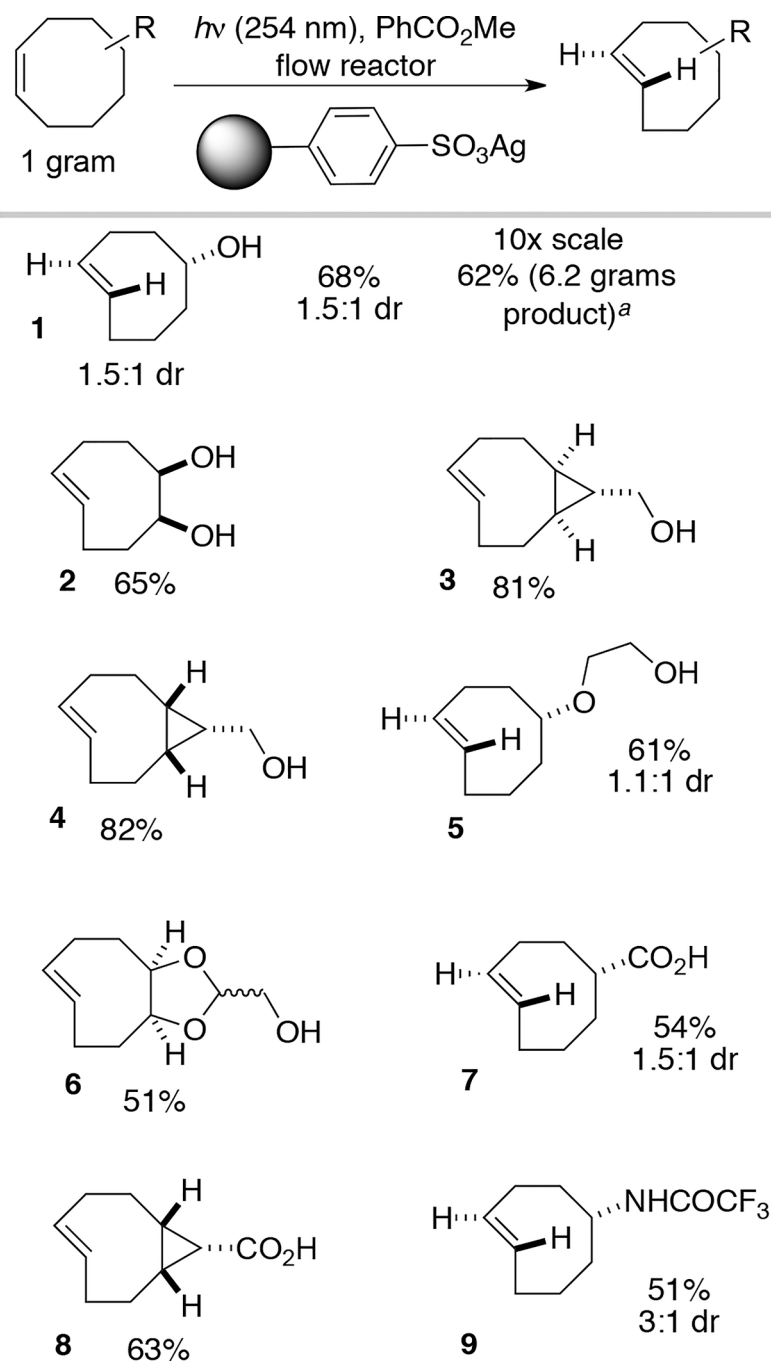
Scheme 4.
Substrate scope for silver ion exchanged sulfonated silica gel used in flow photoisomerization. All reactions were conducted starting with 1 gram of *cis*-cyclooctene starting material using 13 grams of tosic silica gel in a small Biotage SNAP cartridge. Compound **1** was also photoisomerized on larger scale using 40 grams of tosic silica gel in a 3″ tall Biotage SNAP cartridge.