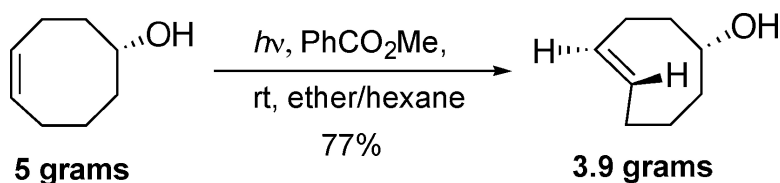


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A Photochemical Synthesis of Functionalized *trans*-Cyclooctenes Driven by Metal Complexation

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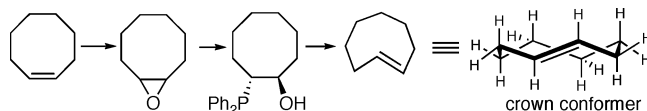
The unusual reactivity and well-defined chiral structure of *trans*-cyclooctene make it an attractive framework for stereocontrolled synthesis. *trans*-Cyclooctene has a chiral plane and a high barrier to racemization (35.6 kcal/mol),^{1a} and the most stable "crown"^{1b,c} conformer of *trans*-cyclooctene has an alternating sequence of equatorial and axial hydrogens (Scheme 1) that is akin to chair cyclohexane. The double bond of *trans*-cyclooctene is twisted severely in the crown conformation,² and as a consequence the HOMO of *trans*-cyclooctene is relatively high in energy.³ As a result, *trans*-cyclooctene displays unusual reactivity in HOMO-alkene controlled cycloaddition reactions with dienes,⁴ 1,3-dipoles,³ and ketenes.⁵ *trans*-Cyclooctene derivatives also serve as excellent ligands for transition metals,⁶ and they are useful monomers for polymerization in the presence of radical initiators or metathesis catalysts.⁷

Although there are many routes to the parent *trans*-cyclooctene, there are few methods for preparing functionalized derivatives.^{3,8} *trans*-Cyclooctene was first prepared as a mixture with *cis*-cyclooctene via Hoffman elimination of trimethylcyclooctyl ammonium iodide.⁹ Several elegant and stereospecific methods for preparing *trans*-cyclooctene from *cis*-cyclooctene have also been described,¹⁰ as exemplified by the sequence of epoxidation/LiPPh₂ addition/elimination shown in Scheme 1.^{10e} However, a limitation of such protocols is that multistep synthesis is required to invert the alkene stereochemistry. A direct method for olefin inversion would facilitate the synthesis and application of functionalized derivatives of *trans*-cyclooctenes.

The photochemical isomerization of *cis*-cyclooctene represents a direct method for the synthesis of *trans*-cyclooctene. Elegant studies by Inoue have greatly expanded the scope and understanding of the photoisomerization, which is typically run under singlet sensitized conditions.¹¹ While the photochemical procedures are effective for the preparation of the parent hydrocarbon, the photochemical synthesis of functionalized *trans*-cyclooctenes has been limited by low *trans/cis* ratios under preparatively useful conditions and by the photodegradation of the *trans*-cyclooctene. For example, we observed that 18-h photolysis of 500 mL of a 0.016 M solution of (*Z*)-cyclooct-4-enol (9:1 Et₂O/hexane, 1 equiv of PhCO₂Me) gave <5% (*E*)-cyclooct-4-enol along with uncharacterized photodegradation products and 24% recovered (*Z*)-cyclooct-4-enol.

To improve the practicality of the photochemical protocol, we devised a strategy that would drive the photoisomerization through selective metal complexation of the *trans*-isomer. Our experiments were based on the earlier observation that *trans*-cyclooctene forms a water soluble complex with AgNO₃, whereas *cis*-cyclooctene binds only weakly to AgNO₃.^{9b,12} Our strategy was also grounded in classic studies on the photoprotonation reactions of cyclic alkenes, which had shown that the *cis/trans* equilibria could be driven by selective addition reactions of *trans*-cycloalkenes.¹³ However, such

Scheme 1. Multistep Synthesis of *trans*- from *cis*-Cyclooctene



reactions do not provide direct access to the *trans*-cycloalkenes themselves.¹⁴

The apparatus for preparing *trans*-cyclooctenes is illustrated schematically in Figure 1. A quartz reaction flask containing methyl benzoate (a singlet sensitizer) and a 0.018 M solution of a *cis*-cyclooctene derivative is photoirradiated at 254 nm. During photoirradiation, the reaction mixture is continuously pumped through a bed of a AgNO₃-impregnated silica gel on column of silica gel. The *trans*-cyclooctene derivative is selectively retained by the AgNO₃ impregnated silica, but the *cis*-isomer elutes back to the reaction flask, where it is photoisomerized and recirculated through the column. After complete consumption of the *cis*-cyclooctene, the silica is removed and stirred with NH₄OH, which liberates the *trans*-cyclooctene from the AgNO₃. The *trans*-cyclooctene derivative is then recovered by extraction.

A Rayonet RPR 200 reactor is a convenient light source for the apparatus illustrated by Figure 1, although a 450-W Hanovia mercury arc lamp is also effective. The apparatus was constructed using a common metering pump, an inexpensive plastic column, and standard LC tubing and fittings. No "homemade" parts are required for the apparatus for preparations on a gram scale.

The scope of the photochemical *trans*-cyclooctene synthesis using the described apparatus was investigated as shown in Table 1. The method was successful for the synthesis of *trans*-cyclooctenes that were substituted by alkyl, hydroxyl, acetal, amide, and oxazolidinone functionalities.¹⁵ It was also demonstrated that aza-*trans*-cyclooctene derivative **2h** could be prepared. The yields in Table 1 (63% on average) compare favorably with the overall yields from multistep preparations of *trans*-cyclooctene from *cis*-cyclooctene,^{9,10}

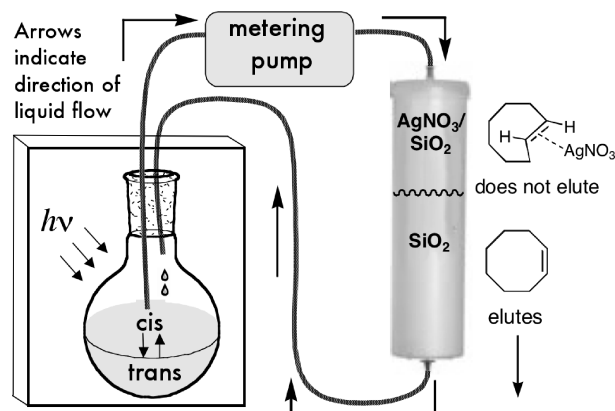
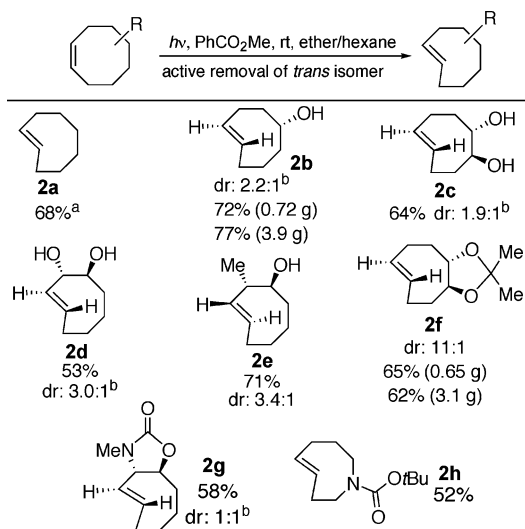


Figure 1. Schematic of apparatus for *trans*-cyclooctene synthesis.

Table 1. Synthesis of *trans*-Cyclooctene Derivatives^c

^a GC yield. ^b Diastereomers were separable on silica gel. ^c Unless noted otherwise, all yields represent isolated yields as the average of two runs.

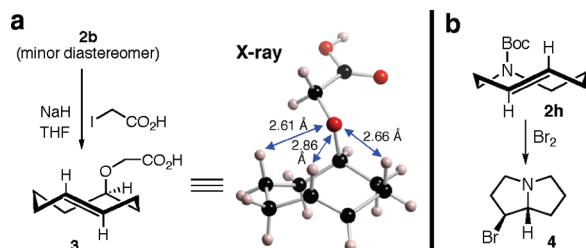


Figure 2. (a) Preparation and X-ray structure of a *trans*-cyclooctene with an axial substituent. 1,3-Diaxial interactions are highlighted. (b) Stereospecific, transannular cyclization.

and all of the preparations in Table 1 were carried out on a useful scale. The preparations of **2a–2g** were carried out with 1 g of the *cis*-cyclooctene in 500 mL of solvent (~0.015 M). Preparations of **2b** and **2f** were also demonstrated on a larger scale: 5.0 g of the *cis*-alkene in 500 mL of solvent gave 3.9 g of **2b** and 3.1 g of **2f**.

In the preparations of **2b–2g**, two diastereomers were formed. The highest diastereoselectivity was observed in the formation of **2f** (dr 11:1). In most cases, the diastereomers were readily separable on silica. X-ray crystallographic analysis was conducted for the major diastereomer of **2c** and for **3**, which was prepared from the minor diastereomer of **2b**. The crown conformation is observed in both structures. For **3**, the crown conformation comes at the expense of three 1,3-diaxial interactions with the α -alkoxyacetic acid substituent (Figure 2a). Observation of a crown conformer with an axial substituent provides evidence that the chair conformer of *trans*-cyclooctene is significantly less stable.^{1b}

The availability of functionalized *trans*-cyclooctenes offers new possibilities for stereospecific, transannular cyclization reactions.¹⁶ As illustration, it was shown that transannular cyclization of 4-*aza-trans*-cyclooctene derivative **2h** provides entry to the pyrrolizidine framework that is common to a range of natural products.¹⁷ Thus, treatment of **2h** with bromine provides pyrrolizidine **4** in >90% isomeric purity (crude ¹H NMR analysis). Alkene stereochemistry controls the diastereoselectivity, as 4-*aza-cis*-cyclooctene leads to the opposite diastereomer of **4**.¹⁸

In summary, selective complexation to AgNO₃/silica was used to facilitate photochemical syntheses of *trans*-cyclooctene derivatives on a useful scale. A derivative adopts a crown conformation despite an axial substituent, and it was shown that alkene stereochemistry is transferred to the hexahydropyrrolizidine framework in the transannular cyclization of 5-*aza-trans*-cyclooctene.

Acknowledgment. This work was supported by NIH Grant GM068640-01.

Supporting Information Available: The photochemical apparatus is described in detail. Provided are experimental and characterization details, ¹H and ¹³C NMR spectra for new compounds, NOE data for **4**, and CIF files for **2c**, **3**, and the desmethyl analogue of **2g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (15) Known limitations of the described method: The photoreaction of 1-methylcyclooctene was unsuccessful because the *trans*-isomer did not bind to AgNO₃-impregnated silica gel. Also, the carbonate of **2d** led only to products of decomposition. Finally, photoreaction of an analogue of **2g** that lacks the *N*-methyl group (i.e., the free oxazolidinone) proceeded only in 35% yield but gave a single diastereomer. We believe that the minor diastereomer decomposes under the reaction conditions, thereby accounting for the low yield and high diastereoselectivity relative to **2g**.
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