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

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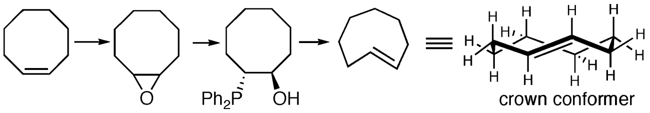
The unusual reactivity and well-defined chiral structure of *trans*-cyclooctene make it an attractive framework for stereocontrolled synthesis. *trans*-Cyclooctene has a chiral plane and a high barrier to racemization (35.6 kcal/mol),[1a] and the most stable "crown" [1b,c] conformer of *trans*-cyclooctene 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/$LiPPh_2$ 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 Et_2O/hexane, 1 equiv of $PhCO_2Me$) 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 $AgNO_3$, whereas *cis*-cyclooctene binds only weakly to $AgNO_3$.[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 reactions do not provide direct access to the *trans*-cycloalkenes themselves.[14]

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



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 $AgNO_3$-impregnated silica gel on column of silica gel. The *trans*-cyclooctene derivative is selectively retained by the $AgNO_3$ 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 NH_4OH, which liberates the *trans*-cyclooctene from the $AgNO_3$. 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]

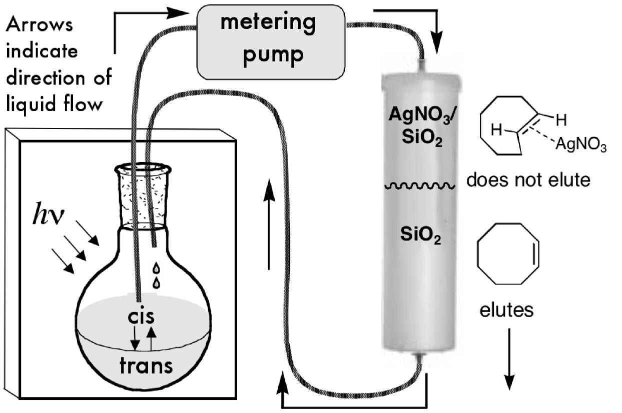
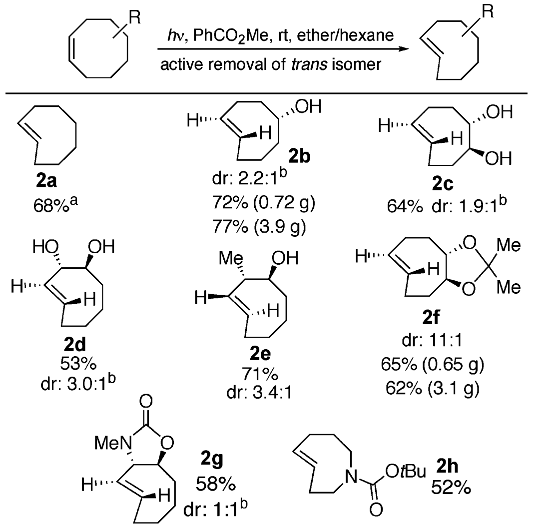


Figure 1. Schematic of apparatus for *trans*-cyclooctene synthesis.

10.1021/ja8001919 CCC: $40.75

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.

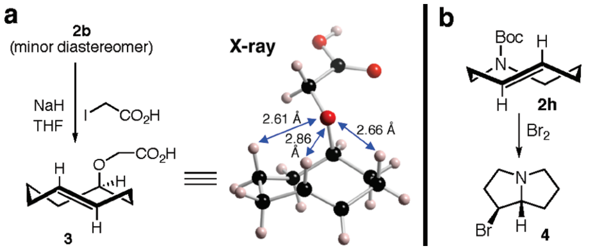


Figure 2. (a) Preparation and X-ray structure of a *trans*-cyclooctene with an axial substituent. 1,3-Diaxial interactions are highlighted. (b) Stereospecific, transannular cyclization.

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 ^{1}H NMR analysis). Alkene stereochemistry controls the diasteoselectivity, as 4-aza-*cis*-cyclooctene leads to the opposite diastereomer of **4**.[18]

In summary, selective complexation to $AgNO_3$/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 hexahydropyrrolizine 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, ^{1}H and ^{13}C 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 $AgNO_3$-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 oxazolidionone) 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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JA8001919