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# Visible light mediated generation of *trans*-arylcyclohexenes and their utilization in the synthesis of cyclic bridged ethers

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**ABSTRACT:** While accessible via UV-irradiation of *cis*-cyclohexene, *trans*-cyclohexene has thus far been an investigation driven by curiosity, and due primarily to its short lifespan, has until recently not been employed for productive synthesis. Herein, we present straightforward conditions that provide access to a class of *trans*-arylcyclohexenes and demonstrate their utility in the formation of oxabicyclic ethers, which are otherwise inaccessible from the corresponding *cis*-cyclohexene. A key challenge to utilizing the incredible *ca*. 52 kcal/mol strain energy of *trans*-cyclohexene to drive synthesis was overcoming its short lifetime. Herein, we show that pre-organization via hydrogen bonding between the substrate and the reaction partner prior to isomerization is a viable strategy to overcome the inherently short lifetime of *trans*-cyclohexene.

### INTRODUCTION

The release of strain energy to facilitate chemical synthesis includes standouts such as Danishefsky's work with cyclobutenone and cyclopentadiene [4+2] cycloadducts, that of Garg with cycloarynes,<sup>2</sup> or that of Fox in which trans cyclooctenes react with tetrazines,<sup>3</sup> though there are many others.<sup>4</sup> The release of this built in or chemically triggered strain can make otherwise challenging transformations possible. In contrast to a one-time event, an attractive alternative approach to building in triggers or integral molecular strain is to capture energy from visible light, as this could alleviate the difficulty associated with performing chemistry on prestrained molecules, or the difficulty associated with the installation of functional groups that serve as the trigger. With this in mind, we were drawn to E.J. Corey's communication from 1965 reporting the formation of trans-2-cycloheptenone,<sup>5</sup> in which the ciscycloheptenone was photoexcited with UV light in situ with cyclopentadiene, which yielded only a [4+2] type product that appeared to be generated through a pericyclic reaction with the *trans*-isomer, elegantly demonstrating the potential of even transient strain to promote synthesis.

In our previous work,<sup>6</sup> we used visible light and Ir-based photocatalysts to dynamically isomerize styrenoids, and generate a photostationary state of alkenes highly enriched in the Z-configuration (Scheme 1A). While works have demonstrated the diverse utility of these and transformations, such as the Noël group's trifluoromethylation, hydrotrifluoromethylation, and difluoromethylation,<sup>7</sup> the Qing group's stereoselective trifluoromethylation of styrenes,<sup>8</sup> the Gilmour group's work with riboflavin mediated isomerizations<sup>9</sup> and corresponding synthetic routes to coumarins,<sup>10</sup> the Rueping<sup>11</sup> and Reiser<sup>12</sup> groups' works toward applications in process, we sought to further build on this foundation, suspecting that it would be possible to use visible light photocatalysis to generate a strained and therefore

reactive *trans*-cycloalkene in a controlled manner. For this, we were drawn to *trans*-cyclohexenes.

Scheme 1. : UV and visible light mediated double bond isomerizations

A.Visible Light Mediated Styrenyl Isomerization



**B.UV-light Mediated Isomerization & Methanol Trapping** 



Larger, less strained *trans*-cycloalkenes can be generated by UV photolysis, and are isolable,<sup>13</sup> or at least readily observable.<sup>14</sup> Evidence for *trans*-cyclohexene was less forthcoming, however, presumably due to its high strain (*ca.* 52 kcal/mol), and correspondingly short lifetime. During pulsed photolysis experiments, Joussot-Dubien<sup>15</sup> and Dauben<sup>15-16</sup> reported having observed a transient species with a 9  $\mu$ s lifetime at room temperature and a *ca.* 7.5 kcal/mol barrier to isomerization back to the starting material. While irradiation with UV light led to multiple products, it has also been shown that if excited in acidic methanol, the *trans*-phenylcyclohexene underwent methanolysis of the olefin<sup>14b, 17</sup> (Scheme 1B). Additionally, Schuster<sup>18</sup> proposed a similar intermediate for the rearrangement of cyclohexenones. Further studies from the McClelland group with UV flash photolysis have demonstrated the presence of a transient cationic intermediate, which in some cases could be intercepted with a solvent.<sup>19</sup> Importantly, these precedents demonstrated the differential reactivity between the *cis*- and *trans*-cyclohexenes, and the potential for productive syntheses.

Despite these compelling early results, while larger *trans*-cycloalkenes have been deployed in synthesis,<sup>20</sup> the application of trans-cyclohexene in synthesis is still almost non-existent, with the exception of the recent report from the Larionov group<sup>21</sup> of an elegant exploitation of UV light mediated carboborative ring contraction. This sparsity is likely due, in part, to the use of UV light and historically strongly acidic conditions (i.e. H<sub>2</sub>SO<sub>4</sub>),<sup>17b</sup> which limit the functional group tolerance. A more challenging aspect in performing synthesis, however, is contending with the small energetic barrier to isomerization (ca. 7.5 kcal/mol). In order to accomplish this, we reasoned that precoordination of the reactive partner would be the key to overcoming the difficulties of the short lifetime of the trans-alkene, because it would allow the entropic penalty to be paid before the transition state, thus bringing down the energy barrier.

We postulated that an alcohol group could hydrogen bond with an acid prior to isomerization (Scheme 1C), preparing ahead of time for the short lived, high-energy trans-cyclohexene, ultimately facilitating the protonation of the alkene by pre-positioning the acid near the alkene. The generated carbenium ion and the internal alcohol could then undergo ring closure to form the ether product. In addition, use of a tertiary benzylic alcohol, prone to acid catalyzed elimination, would demonstrate the increased reactivity of the trans-cyclohexene. The expected reactivity of transcyclohexene in relation to its cis-isomer would be orthogonal because it would circumvent the expected elimination of the tertiary alcohol and allow reaction to take place only when stimulated by light. Further, we reasoned that the use of a photocatalyst would allow us to generate the requisite trans-cyclohexene indirectly with visible light, preventing side reactions that typically accompany UV photolysis.

## EXPERIMENTAL

To begin our investigation, we subjected cyclohexenol **1a** to catalytic amounts of **PC1** ( $Ir(ppy)_3$ ), formic acid which we anticipated would not induce elimination, due to its weak acidity, and blue LEDs (Table 1, entry 1). We were pleased to observe the formation of the desired bicyclic ether in good conversion (78%). Control reactions established the necessity of all three components (entry 2).

Attempts to use a stronger Brønsted acid, such as HCl, simply led to elimination of water (entry 3).

Next, we evaluated the effect of the photocatalyst on the reaction (entries 4-6). We found, as previously demonstrated,<sup>6a</sup> that both the steric volume and the emissive energy of the catalyst affect the rate of the reaction. Sterically larger photocatalysts such as PC 2 with its much larger molecular radius effectively suppressed reactivity (entry 4 vs. 5), despite very similar emissive energy to PC 1 (54.5 vs. 55.2 kcal/mol), indicating the likelihood of an energy transfer pathway. The most effective catalysts were relatively smaller (entries 5 and 6). The optimal catalyst was found to be **PC 4.** whose emissive energy is 58.6 kcal/mol. but is only slightly larger than standard PC 1. PC 4 was used for further optimization. Evaluation of several carboxylic acids (entries 7-10), revealed that a 90% solution of formic acid was optimal, where both weaker and stronger acids were detrimental to the reaction.



 $^{\rm a}A$  stock solution of catalyst was used. The concentration of 1a was 0.05 M.  $^{\rm b}Determined$  by  $^{19}F$  NMR. The dehydrated product was detected by GCMS.

Analysis of the optimal temperature revealed maximal reaction rate at 45 °C (entry 15). Curiously, examination at early timepoints revealed a bifurcation of the rate constant, which increased with temperatures both higher and lower than 0 °C (entries 11-16). This unusual result is consistent with a highly reactive intermediate, in which lower temperatures extend the lifetime of the reactive species by reducing the free energy available for thermal reversion to the

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*cis*-cyclohexene species. Conversely, we expected that increased temperatures increase the rate either by increasing the probability of the *cis*-cyclohexene encountering an excited photocatalyst to generate the reactive *trans*-cyclohexene, or alternatively, could populate higher energy conformations, which would be more capable of energy transfer. We explore these possibilities below.

We initiated our exploration of the scope of the reaction by varying the substituent attached at the carbinol carbon. The reaction was remarkably tolerant to various substitution at this position, giving the cyclized product in very good yields for electron poor arenes (**2a-2d**), electron neutral arenes (**2e** and **2f**), alkynyl (**2g**), and alkyl substituents (**2h**). The propensity of some of the carbinols to ionize under acidic conditions (i.e. tertiary benzylic<sup>22</sup> or propargylic alcohols<sup>23</sup>), highlights the importance of using a weak acid, and demonstrates the enhanced basicity of *trans*cyclohexene. We next explored the vinyl arene substituent (**2a** vs. **2i-2n**). The arene is an essential component of the substrate as it makes the triplet state of the alkene energetically accessible through visible light photocatalysis.<sup>32</sup>

Because the conjugation is an important facet to triplet stabilization,<sup>24</sup> it is unlikely that the reaction would proceed with ortho substituents which dramatically disrupt the conjugation both in the ground state and the vertically excited triplet. Within this limitation, the arene was quite amenable to substitution with electron rich (2a), neutral (2i), and moderately electron poor (2j and 2k) arenes. However, strongly electron deficient arenes (2l) failed to give any cyclized product. This failure may result from very sluggish protonation of the *trans*-alkene, which instead undergoes thermal reversion to the relaxed *cis*- starting material, although electronic modulation of the HOMO–LUMO gap is possible as well, and may prevent excitation by the pho-

tocatalyst.

At this point in the investigation, several key assumptions about the reaction had been made. It was assumed that, as established previously in related transformations,<sup>6</sup>, photochemical energy from a photon in the visible light region is absorbed by a photosensitizer, which after photoexcitation to a singlet, ultimately leads to a long-lived triplet excited state.<sup>25</sup> Because the catalyst is in a triplet state, and photocatalyst radii dependency is observed (Table 1, entry 4), then the energy transfer most likely occurs via a Dexter<sup>26</sup> mechanism, exciting the substrate to a triplet biradical. This triplet biradical is capable of bond rotation about the former double bond. The triplet biradical rotates to an orthogonal position because not only do the formerly  $\pi$  electrons now repel each other, but rotation also serves to relieve 1,2-eclipsing interactions. Upon returning to the ground state from the triplet landscape via a non-radiative intersystem crossing event (ISC; conical intersection) at, or very near the transition state for rotation about the double bond, the former alkene can then further rotate and relax to form either the trans-cyclohexene which can engage in subsequent reactivity, or unproductively reform the *cis*alkene, evolving its energy as heat.

There were, however, several mechanistic quandaries, such as what purpose does the acid serve? Does the acid serve only as a proton source, or does it actually precoordinate as we have supposed? These questions ultimately culminate in the penultimate question: what does the transition state look like? We therefore sought to probe these questions, beginning by investigating the geometry of the transient reactive species.

## **MECHANISTIC INVESTIGATION**

To gain further insight to the reaction, and determine if



Isolated Yields. ND = not detected. <sup>a</sup>Amounts of formic acid vary from one substrate to the next; see SI for details.

Table 2. Scope of the Photocatalytic Cyclization.

the geometries we were envisioning were feasible, we set out to perform conformational analyses computationally. Since triplet state energies would be of interest here, we settled on using Møller-Plesset (MP2)<sup>27</sup> theory, ultimately with large, correlation consistent basis sets.<sup>28</sup> First, we minimized the starting alcohol and performed two dihedral drivers at the freely rotatable C-C bonds connecting the three rings (Figure 1A). The carbinol phenyl ( $C^1$ ) preferred to rotate 90° from the adjacent ring, presumably to avoid allylic strain. Looking at the styrenyl phenyl revealed a more complex landscape, in which the lowest energy conformer has the two rings 28° out of planarity. We subjected the 90° cross section to an increased number of scan points for rotational angles (Figure 1B). Next, we subjected select structures to a higher level of computational theory, in order to provide insight into the relationship between the thermal and the excited state landscapes.

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Beginning from the minimized geometry with the methoxyphenyl ring canted 28° from planarity with the ciscyclohexene ring, a vertical excitation from the singlet to the triplet state was calculated using the cc-PVTZ basis set.<sup>28b</sup> The energy difference for this excitation was found to be in excess of the emissive energy of the photocatalyst. This is because the minimized geometry favors deconjugation of the methoxyphenyl dihedral angle at C<sup>4</sup> of the *cis*cyclohexene, and therefore puts the singlet to triplet excitation energy out of reach of the photocatalyst. At ca. 1 kcal/mol higher energy, rotation of the methoxyphenyl ring into planarity with the *cis*-cyclohexene double bond is easily thermally accessible at a reaction temperature of 45 °C. Based on a Boltzmann distribution population analysis, increasing reaction temperature from 0 °C to 45 °C increases the frequency of observing a molecule in the fully conjugated conformer by ca. 30%, based on the relative energies of these conformers. This provides some insight to support our prior supposition as to the bifurcation of reaction rate in relation to reaction temperature (Table 2, entries 13-16).

Vertical excitations from the singlet to the triplet state were calculated at minima and maxima of this landscape, as well as 0°. In lieu of performing an exhaustive and correspondingly computationally expensive ring conformer search on the cyclohexene ring, dihedral angles for rotation about the C<sup>4</sup>-methoxyphenyl ring were frozen, and a simple geometry optimization was performed on the ground state singlet, in the gas phase. While absolute energy differences for singlet to triplet excitation are greater than expected, the trend of the gap demonstrates the importance of conjugation. Conjugation of the alkene with the methoxyphenyl  $\pi$  cloud brings the calculated excitation energy to a minimum, which is known experimentally to be within the range of the emission energy of the photocatalyst (58.6 kcal/mol).<sup>30</sup>



1B. Singlet state energies as a function of c4 dihedral angle and vertical excitations to triplet state energies. <sup>a</sup>Excitation values scaled to the experimentally determined maximum value for excitation at 0 ° – 58.6 kcal/mol, the emission energy of the photocatalyst; other triplet state energies relative to this. Energies along ordinate axis are relative to the lowest energy point in the singlet landscape. Singlet curve developed at MP2/STO3G; energies scaled to values determined at MP2/cc-PVTZ.<sup>[29]</sup>

Next, we considered the strained *trans*-cyclohexene species. Importantly, upon ISC, the formation of the *trans*-cyclohexene generates four potential diastereomers, of which only two could lead to ring closure (axial-OH). We have termed these the *syn*-boat and the *anti*-chair (Figure 2). Calculations of the ground state energies of these species indicated that the *anti*-chair would be lower in energy by *ca.* 5.5 kcal/mol, which is consistent with the work of Johnson.<sup>31</sup> This energy difference cannot be used to anticipate the reactive conformer, however, since both are lower

**Figure 1:** Accesibility of the Biradical as a Function of Alkene Conjugation

than the triplet state energy and thus accessible therefrom. In order to discern the reaction pathway, we would need stereochemical evidence. Since the upper limit for the energy to excite the *cis*-cyclohexane is the emission energy of the photocatalyst, then the maximum height conical intersection on the singlet state landscape must also be bounded by this restriction. It is of note that the difference between the ground state energy of the photocatalyst is approximately the same as not only the value that Dauben found for reversion of *trans*-phenylcyclohexene to the *cis*- starting material, but also the computationally determined value determined by Johnson for simple cyclohexene.

Figure 2: Only the *syn-* and *anti-* diastereomers of the *trans-*cyclohexane can lead to oxabicyclic etherification



 $^{a}\Delta G_{rel} = 51.7$  kcal/mol relative to product - Scheme 2D

It was envisioned that a deuterium label could provide stereochemical evidence of the geometry of the bond which undergoes hydro-alkoxylation, as the face of incorporation and the number of sites deuterated would provide mechanistic insight with regard to the reversibility of the protonation step. Submitting **1a** to reaction conditions in which a large excess of  $D_2O$  was added resulted in deuterium incorporation only on the face of the cyclohexene ring opposite that of the forming ether, so that the deuterated product shows signal attenuation equivalent to the incorporation of 1 hydrogen only in the axial position of the product (Figure 3A). This was affirmed by correlation with computational NMR simulation (Figure 3B).<sup>29, 32</sup>





The presence of isotopic scrambling only on the formerly vinyl carbon indicated that the protonation/deuteration was essentially irreversible, and could have occurred in two ways. Exo protonation of the syn-boat can be ruled out, since it would lead to incorporation of the deuteron on the same side of the ring as the forming ether, not the experimentally observed product. Similarly, endo protonation of the anti-chair conformer should be ruled out because it too leads to the incorrect deuterated regioisomer. It is possible that the protonation/deuteration could have occurred from the endo face of the svn-boat trans-cyclohexene ring. However, because the endo face is the more sterically congested, it seemed unlikely to be the face of protonation. Conceivably, the C<sup>1</sup> hydroxyl could have been serving to protonate the endo face of the syn-boat conformer. Assessment of this scenario reveals that the proton or deuteron would subsequently have to travel through the van der Waals cloud of the cyclohexane ring, likely requiring a tunneling event to arrive at the proper orbital to generate the experimentally observed product. If this did occur, one could expect a very large kinetic isotope effect (KIE),  $(k_H/k_D >$ 40),<sup>33</sup> but it was not observed (vide infra). The simplest explanation is that the deuteration event happens from the exo face of the anti-chair. Although the exo protonation of the anti-chair conformer seemed the most likely, the question still to be answered was how that exo protonation occurred

In order to probe this, we next began investigating the kinetics of the reaction. Initial rates experiments indicate that the reaction is first order with respect to catalyst. With the substrate, the reaction appeared to have zero order kinetics.<sup>29</sup> With formic acid, at low loadings there was a line-

ar response to concentration, while at higher loadings it fell out of the rate expression.<sup>29</sup> This led us to suspect that the acid may be undergoing a pre-rate determining step equilibrium, i.e. a precoordination event. Further support for the latter idea was observed in <sup>1</sup>H NMR via titration of the tertiary alcohol starting material (**1f**) with formic acid under anhydrous conditions, which resulted in a slight deshielding of the hydroxyl signal in the reaction solvent, acetonitrile.<sup>29</sup> This is consistent with hydrogen bonding of the proton with an H-bond acceptor, such as an oxygen in formic acid. It is remarkable that this interaction can be observed at all, given that acetonitrile can compete with other hydrogen bond acceptors, and overshadow many nonbonding or partially bonding interactions.<sup>34</sup>

This precoordination of the substrate and acid serve to reduce the entropy of the transition state. Importantly, we anticipate such precoordination provides a proximal proton to the trans-alkene upon its genesis, and that this is essential to harnessing the strain energy. Similarly, while not discussed in Larionov's<sup>21</sup> recent carboborative ring contraction, we suspect that the absence of dimerization products or products of other reaction pathways is due to the precoordination of a Lewis acidic trialkyl borane with the alkene, which serves a similar role to immediate protonation. We conducted tandem rate experiments with phenylcyclohexene, which is devoid of a hydroxyl group, and 1f<sup>29</sup> under the standard reaction conditions in order to investigate the relative effect of the precoordination. These experiments revealed much faster reactivity with the substrate capable of precoordination (1f) than the phenylcyclohexene could achieve without a hydrogen bond to the formic acid, supportive of the assumption that the precoordination aids the reactivity.

When the aqueous environment of the reaction was replaced with D<sub>2</sub>O, we observed a solvent KIE  $k_{\rm H}/k_{\rm D}$  of 1.5. This is unusual because it is outside the ranges for what would be expected for either a primary (greater than 2) or a secondary normal KIE (1 to 1.4).<sup>33</sup> Furthermore, in the case of a rehybridization from an sp<sup>2</sup> to sp<sup>3</sup> carbon in the rate determining step, one would expect to observe an inverse KIE (0.8 to 1). Further obfuscating the interpretation of the observed KIE is that there are multiple sites for deuterium exchange, not only at the site observed in the final product, but also in the hydroxyl, and in formic acid itself. Additionally, if the proton/deuteron being transferred is from a formic acid coordinated to the hydroxyl group, then a non-linear transition state is expected, and thus a diminished KIE would be expected as well. What could be said at this

point was that it further suggests that the protonation of the alkene is not occurring from the endo face of the *syn*-boat conformer. If it was, it would have to travel through the van der Waals cloud of the cyclohexene ring and would therefore likely have tunneling characteristics.<sup>33</sup>

We then sought to combine the evidence of hydrogen bonding between the hydroxyl proton and formic acid with our conformational analysis of the trans-cyclohexene. Since exo protonation of the anti-chair trans-cyclohexene is most likely, we sought to model a hydrogen bonded formic acid molecule with the anti-chair geometry to see if a potential transition state would be geometrically feasible. Optimization of the aforementioned geometries with a transition state minimization at low basis set and theory level (HF/3-21G) resulted in the geometry in Figure 4. This model clearly demonstrates the possibility of such a transition state in which a formic acid bridges the gap and allows the exo-protonation. While we are hesitant to assign the identity of the transition state due to the inherent difficulties therein,<sup>35</sup> this geometry explains a nonlinear transition state and a corresponding smaller KIE.

#### Figure 4. Geometry of Presumptive Transition State



Geometry identified at HF/3-21G. Proton transfer pathways indicated with dashed lines

### DISCUSSION



Combining all of these ideas into a cohesive, tentative mechanistic proposal (Scheme 2), we believe key features include the precoordination of a formic acid with the hydroxyl proton (Scheme 2A). Upon excitation from the ground state photocatalyst (G) an excited triplet state photocatalyst (H) intercepts a cis-cyclohexene substrate, which is in the proper conjugated conformer with an accessible triplet state energy (F). The triplet state photocatalyst and the singlet ground state substrate undergo Dexter energy transfer to produce the excited triplet state *cis*-cyclohexene biradical (I) and regenerate the ground state singlet photocatalyst (G). The excited triplet state substrate biradical (I) is then no longer bonding and undergoes rotation about the remaining C–C  $\sigma$  bond so that the singly occupied orbitals rotate orthogonal to each other (structures in Scheme 2B). The substrate biradical is then close in both geometry and energy to the thermal transition state for rotation, and undergoes an intersystem crossing event. Upon crossing from the triplet back into the singlet energy landscape, it can either relax to the *cis*-cyclohexene starting material (F) or continue to rotate to the trans-cyclohexene anti-chair conformer (J), which is still coordinated with the formic acid through a hydrogen bond (C). The protonation of the alkene

through an apparent *exo*-protonation of the *anti*-chair diastereomer of the *trans*-cyclohexene likely transfers more than one hydrogen in the rate-determining step via a nonlinear transition state (Figure 4). Protonation of the alkene generates a carbenium ion, which is rapidly attacked by the alcohol oxygen to produce the oxabicyclic ether (D).

# CONCLUSIONS

In conclusion, we have exploited the ability to dynamically capture energy from visible light, and we have developed a strategy to exploit this energy to synthesize new organic molecules. We have highlighted some of the intricacies that should be considered when thinking about energy transfer photocatalysis, such as appropriate choice of photocatalyst not only energetically, but also geometrically, and in addition have highlighted the importance of the accessibility of the triplet state as a function of conformer conjugation. A key hydrogen bonded precoordination event makes possible the singular reactivity, and results in a product that is not otherwise accessible. Its short lifetime is a general and persistent issue that for many years has resulted in *trans*-cyclohexene's recalcitrance with regard to synthesis. We have demonstrated how precoordination with the reactive partner (an acid) can be used to overcome this obstinacy without resorting to the use of UV light, and provided a methodology that will hopefully make synthesis involving *trans*-cyclohexene more tractable.

## ASSOCIATED CONTENT

Experimental details and product characterization. This material is available free of charge via the Internet at <a href="http://pubs.acs.org">http://pubs.acs.org</a>

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