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An elusive thermal [2+2] cycloaddition driven by visible light photocatalysis: Tapping into strain to access C2-symmetric tricyclic rings

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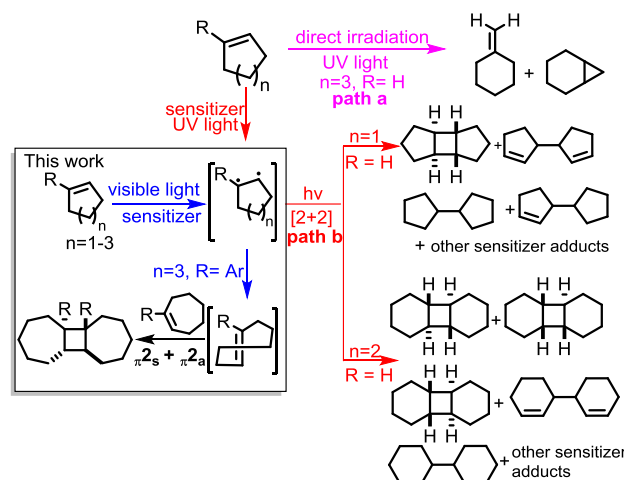
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Kamaljeet Singh, Winston Trinh, and Jimmie D. Weaver III*

A mild and operationally simple methodology is reported for the synthesis of cyclobutane rings imbedded within a C2-symmetric tricyclic framework. The method uses visible light and an iridium-based photocatalyst to drive the oft-stated “forbidden” thermal [2+2] cycloaddition of cycloheptenes and analogs. Importantly, it generates cyclobutane with four new stereocenters with excellent stereoselectivity, and perfect regioselectivity. The reaction is propelled forward when the photocatalyst absorbs a visible light photon, which transfers this energy to the cycloheptene. Key to success is, upon excitation to the triplet via sensitization from the photocatalyst, the double bond isomerizes to give the transient, highly strained, *trans*-cycloheptene. The *trans*-cycloheptene undergoes a strain relieving thermal, intermolecular $[\pi 2_s + \pi 2_a]$ cycloaddition with another *cis*-cycloheptene. X-ray analysis reveals that the major product is the head-to-head, C2-symmetric all *trans*-cyclobutane. Additionally, a dramatic display structural complexity enhancement is observed with the use of chiral cycloheptenols possessing one stereocenter, which result in the formation of cyclobutanes with six contiguous stereocenters with good to excellent diastereocontrol, and can be used to isolate single stereoisomers of stereochemically complex cyclobutanes in good yield.

Introduction

Cyclobutane rings are found in naturally occurring alkaloids and biologically relevant molecules,^{1, 2} and the [2+2] cycloaddition of olefins represents a powerful strategy for the synthesis of such cyclobutane rings. Although thermal [2+2] cycloadditions are energetically favorable ($\Delta G^\circ = -18.0$ kcal/mol for dimerization of ethene),^{3, 4} they are generally considered “forbidden” because the suprafacial approach of pi-orbitals of the alkenes does not give the necessary overlap. While generally kinetically much less feasible because of steric inhibition, the orbital symmetry requirements can be met via an antarafacial / supra-facial approach of the alkenes.⁵ The common exception is the $[\pi 2_s + \pi 2_a]$ of ketenes with alkenes, which is made possible because of the minimal steric hindrance of the ketene partner. Transition metal catalysis offers alternative pathways to promote [2+2] cycloaddition reactions,⁶⁻⁹ with Ti, Mn, Fe, and Ni having been employed.^{10, 11} The presence of d-orbitals in the transition metals allows the [2+2] reaction between alkenes by virtue of low energy pathways to metallacycle intermediates. Another way to overcome the orbital symmetry constraint is to proceed through the photochemical [2+2], in which a higher



Scheme 1. [2+2] cycloaddition of cycloalkenes under thermal and photochemical conditions

energy orbital is utilized and allows the more facile suprafacial approach of both alkenes in the cycloaddition.¹² Unfortunately, the direct irradiation of cycloalkenes with a high energy UV light source often produces a mixture of rearranged products (**path a, Scheme 1**).¹³⁻¹⁵

One alternative to direct irradiation is sensitization. However, again the sensitization of the cycloalkenes, when UV light is used, generally produces a mixture of various cyclobutane stereoisomers (**path b, Scheme 1**), as well as other sensitizer-alkene adducts. These are formed from different mechanisms originating on the excited state alkene surface. Another strategy which has been investigated is the formation

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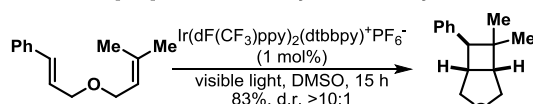
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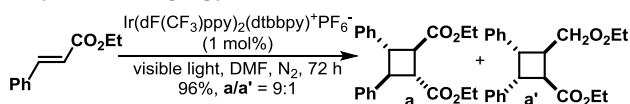
and subsequent trapping of the ground state *trans*-cycloheptene, which can result upon relaxation from the excited state.^{16, 17} One such attempt employed is the use of copper triflate (4 mol%) under UV light irradiation. In this method, Cu⁺ redshifts the absorption and coordinates to the strained, ground state *trans*-cycloheptene sterically restricting the number of available approaches to the *cis*-cycloheptene, thereby minimizing the number of diastereomers formed. In a direct comparison, the acetone sensitized UV irradiation of cyclohexene produced the *trans-anti-trans* dimer in 1%, whereas when catalytic Cu and UV light^{18–21} were employed, the *trans-anti-trans* dimer was formed in 49% yield.^{17, 22–24} While Cu⁺ enhanced the stereoselectivity, the reaction still produced multiple stereoisomers and products. Similarly, Corey and Eaton²⁵ have demonstrated the ability to generate *trans*-cycloheptenones via direct UV irradiation, and Bunce²⁶ and Margaretha²⁷ have studied their dimerization as cyclobutanes. Consequently, despite promising results, essentially no scope was demonstrated.²⁸ While there are some clear shortcomings, this strategy becomes much more attractive if visible light can be used for excitation, because of the lower energy irradiation.²⁹

In this context, Yoon has showcased elegant examples of visible light mediated [2+2] cycloaddition reactions of styrenyl

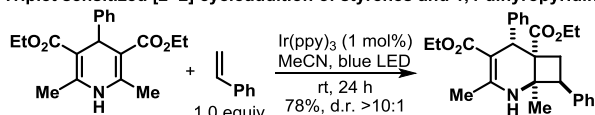
A. Photosensitized [2+2] intramolecular cyclization of styrenes³³



B. Triplet sensitized [2+2] photodimerization of cinnamate derivatives³⁵



C. Triplet sensitized [2+2] cycloaddition of styrenes and 1,4-dihydropyridines³⁶



Scheme 2. Triplet sensitized [2+2] cycloadditions of styrenes using visible light derivatives either by electron transfer^{30–33} or energy transfer mechanisms^{34, 35} initiating from the excited state of photocatalyst (Scheme 2A). Reiser has recently shown the [2+2] dimerization of chalcones, cinnamates, and styrene motifs to access substituted cyclobutanes in moderate to good diastereoselectivities.³⁶ Recently, Lu has also shown the synthesis of cyclobutane rings by [2+2] cycloaddition reactions between 1,4-dihydropyridines and styrenes via energy transfer.³⁷ Common to each of these reactions was the use of a visible light photocatalyst, which interacts with the alkene to directly excite a ground state alkene to its triplet. The triplet then reacts with a ground state singlet alkene via $[\pi 2_s + \pi 2_s]$ mechanisms (i.e. photochemical [2+2]), yielding substituted cyclobutanes in moderate to good diastereoselectivities.

A conceptually different approach to synthesizing cyclobutanes is to initially capture the energy in the form of ring strain. Owing to the immense ring strain (*ca.* 27–36 kcal/mol for *trans*-cycloheptene),^{16, 24, 38, 39} subsequent energy barriers are

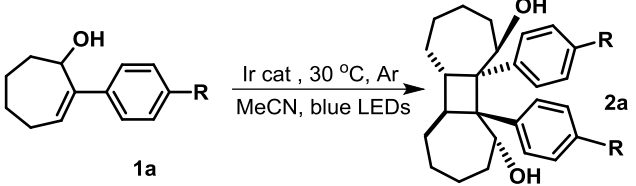
expected to be relatively diminished. The decreased relative energy barriers of the transition states might make it possible for otherwise difficult thermal $[\pi 2_s + \pi 2_a]$ cycloadditions to take place for ground state alkenes. For cyclic alkenes, isomerization leads to *trans*-cycloalkenes, which are known to increase in strain energy with decreasing ring size.⁴⁰ Key to success, would be controlling the concentration of both the excited alkene, and strained *trans*-cycloalkene. Based on our previous work,^{38, 41, 42} we anticipated that the use of visible light photocatalysis would allow us to carefully control the concentration of transient, highly strained, *trans*-phenylcycloheptene, which we anticipated would either undergo the desired thermal $[\pi 2_s + \pi 2_a]$ reaction with the more abundant *cis*-phenylcycloheptene, or alternatively simply revert back to the relaxed isomer with the evolution of heat. Moving out of the UV and into the visible spectrum would ensure that competitive photochemical [2+2] does not occur, and might make it possible to selectively perform a thermal $[\pi 2_s + \pi 2_a]$ cycloaddition.

Results and discussion

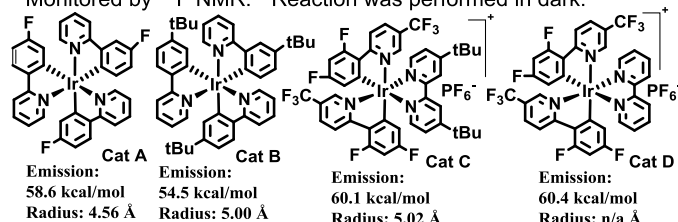
Starting with similar conditions to our previous work,⁴³ we performed a reaction with Ir catalyst **A** (0.3 mol%) in MeCN, at 30 °C, under an atmosphere of argon, with 0.05 M concentration of **1a**, using blue LEDs. We were pleased to see 80% conversion to the desired product **2a** after 24 h of irradiation, as observed by ¹⁹F NMR (entry 1, **Table 1**). Screening revealed that the reaction progressed in a number of solvents, which is consistent with a reaction that does not generate polar intermediates. However, the solvent dimethylformamide (DMF) provided full conversion within 24 h of irradiation (entry 3). Next, we examined the role of the catalyst structure in the reaction. For these experiments, lower catalyst loadings (0.08 mol%) were used to slow the reactions, and exaggerate the differences in reactivity, making it easier to discern the effects on the rates of the reactions.

We anticipated that the catalyst structure would be important, having previously observed that the catalyst volume, in addition to its emissive energy, played a significant role in the rate of isomerization of styrene derivatives; rates slowed as the photocatalyst became larger.⁴⁴ Indeed, we found that **Cat A**,⁴⁵ which is significantly smaller⁴⁶ than the other catalysts, gave higher conversion in the same time period than sterically larger **Cat B**, **Cat C**, and **Cat D** (entries 6–9). The emissive energies of **Cat C** and **Cat D** are substantially higher than that of catalyst **Cat B**, confirming that the exergonicity of the sensitization is not the only important feature. Thus, we used **Cat A** for further optimization. Next, the effect of catalyst loading was evaluated. With higher catalyst loadings, greater conversion to the product **2a** was observed within the same time period (entries 10–12). The photocatalyst is an 18-electron complex that is coordinatively saturated with three chelating ligands, making it very robust. This is evidenced by the high catalyst turnover number (1563 in entry 10), and likely represents a minimum since this was suboptimal conditions, and that the reaction had not yet reached completion.

Given that the lifetime of the strained *trans*-cycloheptene was anticipated to decrease with increasing temperature, we

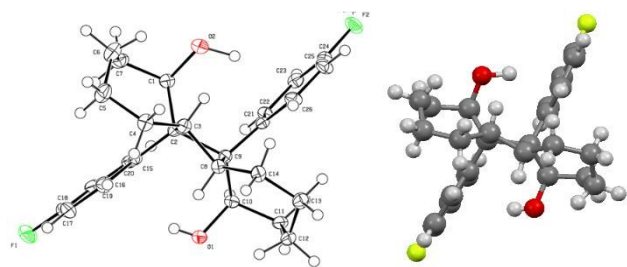
Table 1. Optimization of reaction conditions


entry	R	solvent	temp (°C)	Ir cat	cat. loading (mol%)	%conv- -ersion ^a	time (h)	initial [1a] (M)
1	F	MeCN	30	A	0.300	80	24	0.05
2	F	CH ₂ Cl ₂	30	A	0.300	72	24	0.05
3	F	DMF	30	A	0.300	100	24	0.05
4	F	THF	30	A	0.300	83	24	0.05
5	F	Et ₂ O	30	A	0.300	47	24	0.05
6	H	DMF	30	A	0.0800	55	37	0.05
7	H	DMF	30	B	0.0800	48	37	0.05
8	H	DMF	30	C	0.0800	36	37	0.05
9	H	DMF	30	D	0.0800	23	37	0.05
10	H	DMF	30	A	0.0320	50	22	0.5
11	H	DMF	30	A	0.0640	88	22	0.5
12	H	DMF	30	A	0.125	95	22	0.5
13	H	DMF	-30	A	0.125	80	18	0.5
14	H	DMF	0	A	0.125	79	18	0.5
15	H	DMF	15	A	0.125	76	18	0.5
16	H	DMF	30	A	0.125	95	18	0.5
17	F	DMF	30	-	-	0	18	0.5
18 ^b	F	DMF	30	A	0.125	0	18	0.5

^a Monitored by ¹⁹F NMR. ^b Reaction was performed in dark.

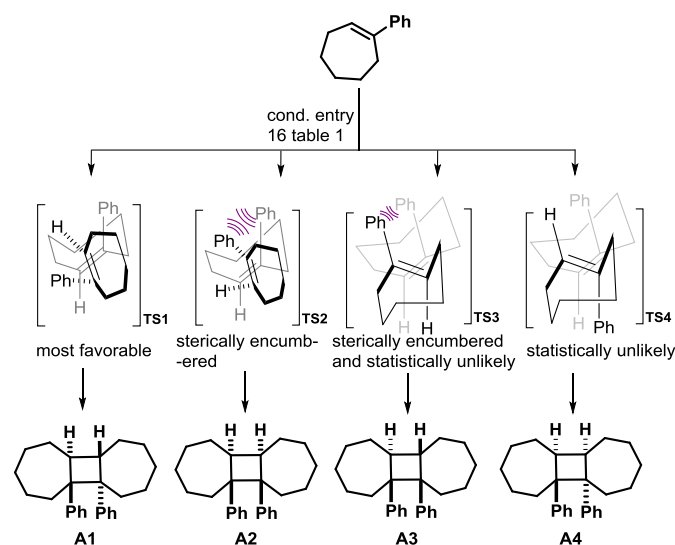
evaluated the effect of temperature on the reaction outcome. To our surprise, the rate of reaction was found to be relatively impervious across a range of temperatures (-30 to 15 °C) (entries 13-16), however, upon increase to 30 °C an increase in the reaction rate was observed.⁴⁷ Finally, control experiments revealed that both light and photocatalyst are necessary components for the desired [$\pi 2_s + \pi 2_a$] cycloaddition reaction.

Having determined optimal conditions, we next assessed the stereochemical outcome of the reaction. When allylic alcohol **1a** was dimerized, X-ray analysis revealed that the major diastereomer was the C2-symmetric cyclobutandiol, **2a**.

**Fig. 1** X-ray crystal structure of major diastereomer **2a**

Specifically, it showed that the dimerization resulted in the formation of the head-to-head regioisomer, and that both 7-membered rings were *trans*-fused onto the cyclobutane and *trans* to the other 7-membered ring. Both rings adopted a chair conformation (**Fig. 1**).

This stereochemical outcome is best explained by the involvement of the ground state *trans*-cycloheptene and a *cis*-cycloheptene, operating under orbital symmetry conservation restrictions, which dictates that the olefins approach one another orthogonally.¹² Within this restriction, there are several potential ways in which such an orthogonal approach could occur. At the outset, the involvement of two *cis*-phenylcycloheptenes can be ruled out, because these do not dimerize on their own.⁴⁸ Likewise, other unobserved stereochemical possibilities **A3** and **A4** could stem from the cycloaddition of two *trans*-phenyl cycloheptenes. This scenario is both statistically unlikely, due to the short half-life of the strained cycloalkene, and furthermore, is expected to be higher in energy because of severe interactions between the phenyl rings, as well as the methylene bridges of the cycloheptene rings. A more likely scenario involves one isomerized *trans*-phenylcycloheptene and one *cis*-phenylcycloheptene,²² of which there are two possible approaches (**Fig. 2**).

**Fig. 2** Rationale for the relative stereochemistry of the major diastereomer observed, **A1**, during [$\pi 2_s + \pi 2_a$] cycloaddition

The major isomer, **A1** (as confirmed by x-ray analysis of **2a**), most probably results from the orthogonal approach of the *cis*- and *trans*-phenylcycloheptenes. This approach occurs in such a way that both the phenyl groups point away from one another (**TS1**, **Fig. 2**) in order to minimize the steric interaction. Alternatively, if the phenyl groups approach on the same side (**TS2**), this leads to cyclobutane **A2**, in which both the phenyl groups will be *cis* to each other. It was anticipated that there would be considerable steric interactions between the phenyl groups in this transition state, which also lead to a higher energy product (*vide infra*). Thus, while up to 128 regio- and stereoisomers are possible, the reaction takes place

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predominantly through **TS1**, and gives primarily a cyclobutane of type **A1**.

The possibility of a stepwise mechanism involving the excited state biradical can be ruled out for several reasons. First, when the reaction was run in presence of TEMPO (a radical scavenger), no TEMPO adduct was formed, nor was the rate or yield reduced. TEMPO and other radical traps have been shown to inhibit stepwise radical additions.³⁷ Further, we did not observe any dicycloheptanes arising from failure to complete the cyclization which is often seen when such step-wise additions occur¹⁸ (see path b, Scheme 1). Finally, we found that the electronics of the phenyl ring did not substantially impact the rate of the reaction which would be expected to affect both the rate and selectivity of the reaction.^{36, 49}

As we were capturing a portion of the photochemical energy in the form of strain energy (i.e. ca 36 kcal/mol)³⁸ this raised the possibility that we could be formally performing uphill catalysis, by driving the reaction in the contra thermodynamic

direction. Thus, we became curious to learn more about the energetics of the reaction. When we looked into the literature, we found that although the dimerization of ethylene to cyclobutane was exergonic in nature, that the dimerization of more substituted alkenes became progressively more endergonic. In fact, Burford has calculated that the reaction is expected to be slightly endergonic with 1,2-mesityl substitution and when the methyl groups of mesitylenes were replaced with ^tPr groups, the dimerization became endergonic by 5-16 kcal/mol. In general, the endergonicity of the dimerization reaction increases further with increase in the steric bulk around the cyclobutane.⁵⁰ This sensitivity to the sterics is expected. First, substitution of alkenes stabilizes the starting material, ethylene being the least substituted and stable. Additionally, the cyclobutane ring dramatically exaggerates steric interactions when compared to their cyclohexane magnitudes. To probe this question, we performed the computational analysis of the thermodynamics of several [2+2]

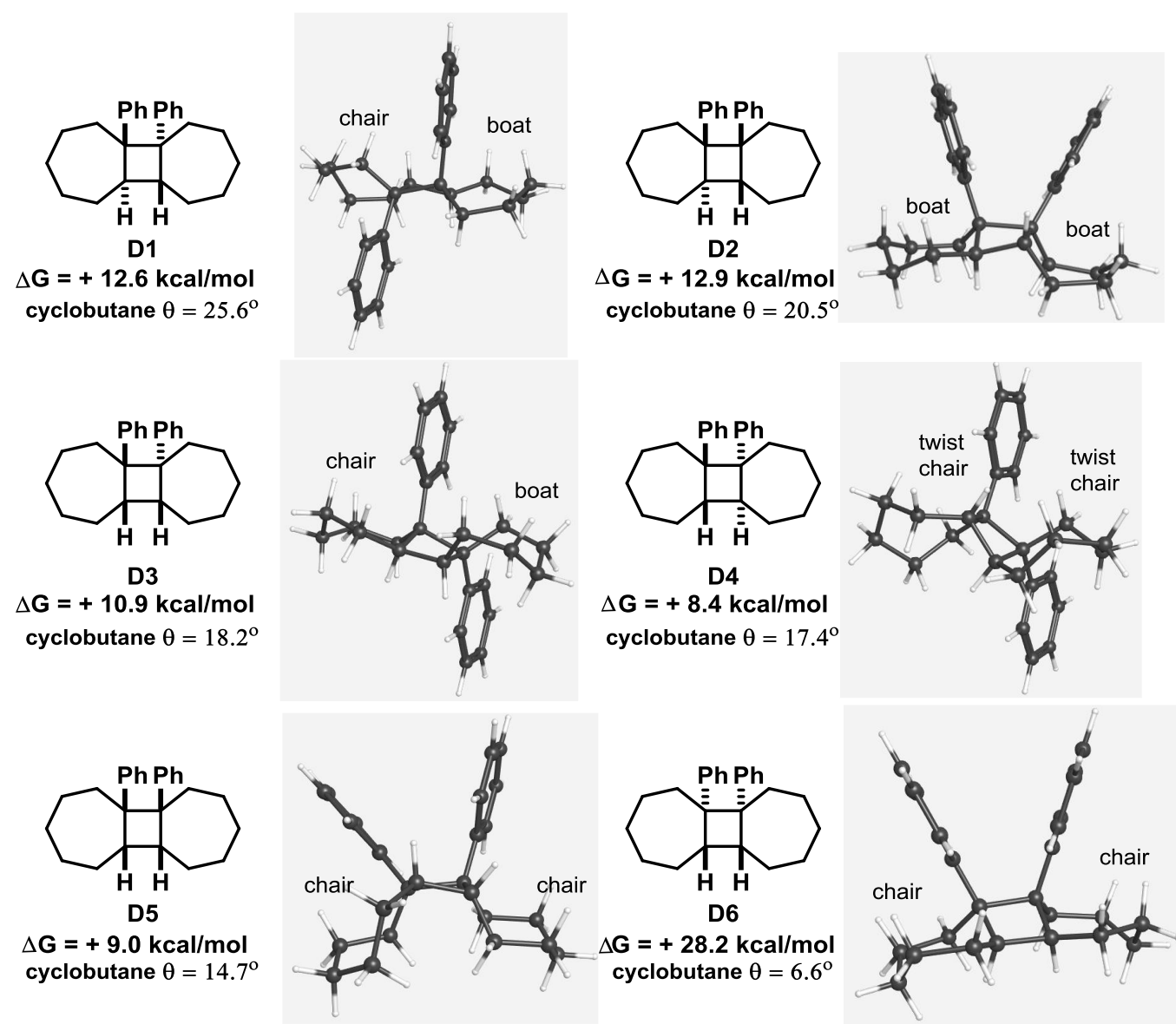


Fig. 3 The energies of the various diastereomers reported are relative to the phenyl cycloheptene as calculated using B3LYP/6-31

cycloadducts. Density functional theory calculations were performed (geometry/energy) on **1a** and **2a**, which indicated that this particular $[\pi 2_s + \pi 2_a]$ cycloaddition reaction is indeed net endothermic in nature. B3LYP/6-31 G(d) calculations of the minimized energy structures of **1a** and **2a** revealed that the $[\pi 2_s + \pi 2_a]$ cycloadduct **2a** is higher in energy as compared to **1a** ($\Delta H = +5.0$ kcal/mol),⁴⁹ highlighting the ability of photocatalysis to facilitate contra-thermodynamic catalysis.⁵¹⁻⁵³

We next looked at several diastereomers of the head-to-head dimerization products of phenylcycloheptene, devoid of the OH group. The geometries of the diastereomers were minimized using the aforementioned conditions, and the results are shown in **Fig. 3**. In all cases, the $[2+2]$ cycloaddition reactions were found to be endergonic in nature, but ranged from +8.4 to +28.2 kcal/mol. The major diastereomer formed in this reaction (**D1**) was found to be +12.6 kcal/mol, and closely matched the X-ray structure. This diversity of energies of the diastereomers could be in part due to the different conformations of the cycloheptane rings. Hendrickson has found that the most stable twist chair conformation is around 3 kcal/mol lower in energy than the highest energy boat conformation of cycloheptane.⁵⁴ With two cycloheptane rings in our structures, variation of roughly 6 kcal/mol energy difference could exist within different conformers of each diastereomer. By analysis of the structures, we hoped to be able to provide some guidelines that would allow prediction of the relative stability of such tricyclic systems.

The least stable diastereomer, **D6**, which was subjected to multiple geometry optimization calculations, was found to be substantially higher in energy (+28.2 kcal/mol) than all the other structures (average **D1-D5** +10.8 kcal/mol). Chair, boat, and twist chair cycloheptane conformers were all observed. High energy **D6** displayed two chair conformers, as did the relatively more stable **D5** (+9.0 kcal/mol), indicating that cycloheptane conformer analysis is not a reliable predictor of the overall strain energy. **D6** places both phenyl groups syn and could cause substantial strain, but this is also true with **D5** and **D2** which are not as strained (+9.0 and +12.9 kcal/mol, respectively). **D6** is unique in that it is the least puckered of the cyclobutanes 6.6° dihedral angle,¹⁹ whereas **D1-D5** range from 14.7-25.6° which likely serves to relieve the torsional strain caused by the cyclobutane substituents.

Importantly, while all of these cyclobutanes are expected to be net endergonic, they are exergonic when compared to the *trans*-cycloheptene (+36 kcal/mol)³⁸ and therefore are energetically accessible. Furthermore, while we are using highly strained molecules, the reaction exhibits a significant and synthetically useful difference in transition state energies that lead to each diastereomeric cyclobutane. Cycloheptene dimer product **2a**, whose calculated and crystal structure were well matched, was found to be of lower energy as compared to the dimer **D1** (5.0 vs. 12.1 kcal/mol). This difference is likely due to the H atoms of both the OH groups on the cycloheptane rings point directly towards the π -electron cloud of the phenyl rings which stabilizes **2a** compared to **D1**.⁵⁵

We next explored the scope of the reaction (**Table 2**). A variety of functional groups were tolerated on the phenyl ring

and resulted in good yields of the cyclobutane product (**2a**, **2b**, **2d**, **2f**, and **2h**), as well as good to excellent diastereoselectivities. In most cases, only one major diastereomer was isolated after purification. It is interesting that despite the numerous possible stereoisomers (16 in the case of R = H and 64 if R = OH) only two to four stereoisomers are ever observed in the crude reaction mixture. The $[\pi 2_s + \pi 2_a]$ cycloaddition appears to be the primary reaction pathway and occurs in a highly diastereoselective fashion.

When the alcohol in **1f** was protected with a pivalate group, **2f** was obtained in high yields, and good diastereoselectivity. The reaction also worked very well when there was no alcohol group present in **1**. It was interesting to see that the 4-fluorophenylcycloheptene **1g** produced only one diastereomer **2g** and the reaction completed within 6 hours of irradiation. Substrates **1**, devoid of an OH group, were reacted in MeCN in order to take advantage of the low solubility of the product cyclobutane in MeCN. After the reaction, the cyclobutanes could be easily filtered to obtain the analytically pure product as a colorless solid, making the reaction and isolation extremely simple to carry out. The compound **1h** which contains three fluorine atoms on the phenyl ring was found to be highly diastereoselective, yielding the desired cyclobutane product **2h** in 80% yield with d.r. >99:1. Similarly, **1i** which contained electron withdrawing trifluoromethyl groups, also produced the desired cyclobutane product **2i** in 85% yield, and high

Table 2. Substrate scope^{a, b}

^aSee ESI for experimental details. ^bIsolated yields. ^cDiastereomer confirmed by X-ray analysis.

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diastereoselectivity (>99:1) after isolation. Cycloheptenone **1j** also underwent the dimerization reaction smoothly to yield the desired $[\pi 2_s + \pi 2_a]$ adduct in 70% yield as a single diastereomer after isolation. An optically active chiral allylic alcohol **1k** (96% ee) was synthesized, and exposed to reaction conditions. **2k** was formed with high enantioselectivity (97% ee)⁵⁶ and diastereoselectivity (11.5:1) with 58% isolated yield. Allylic alcohol (**1l**) with the OH group transposed to the tail carbon also produced the $[\pi 2_s + \pi 2_a]$ cycloadduct **2l** in moderate yield and high d.r. (>99:1) after isolation.

In order to see whether an intramolecular cycloaddition could outcompete the intermolecular $[\pi 2_s + \pi 2_a]$ cycloaddition, the OH group in **1m** was substituted with an allyl group. In this case, no intramolecular $[\pi 2_s + \pi 2_a]$ occurred, rather only intermolecular $[\pi 2_s + \pi 2_a]$ reaction occurred to yield **2m** in 73% yield, albeit with moderate d.r. of 1.3:1.3:1. Aside from the stereochemistry, the fact that a tethered alkene does not undergo preferential photochemical [2+2] highlights the benefits of moving to the visible region, which allows alkenyl functional groups to survive the reaction which would not likely be possible using UV irradiation.⁵⁷ Interestingly, replacing the allyl with a cinnamyl ether (**1n**) completely halts the intermolecular cycloaddition, and instead gives rise exclusively to the intramolecular cycloaddition product. After isolation, the product **2n** was obtained in moderate yield (58%) as an exclusive diastereomer.⁵⁸ It may be possible that stacking of the phenyl groups preorganizes the molecule, such that even short-lived excited state intermediates are rapidly intercepted, or because the potential for benzyl stabilization is present, a step-wise biradical could be involved.

We next replaced carbon with other heteroatoms in the cycloheptene ring, which we found were also well tolerated. For instance, cycloheptene ring containing an *N*-Ts group (**1o**) was synthesized and exposed to reaction conditions. The desired cycloadduct **2o** was obtained in good yields (78%) as a single diastereomer both before and after purification.

While the reaction requires the presence of an aryl group attached to the cycloheptene ring to make the triplet state energetically accessible, it does not necessarily have to be a phenyl derivative. A substrate containing a pyridine ring instead of phenyl ring was synthesized (**1p**) and was exposed to reaction conditions. The desired $[\pi 2_s + \pi 2_a]$ cyclobutane product was formed in 65% yield with d.r. >99:1. The relative stereochemistry was confirmed via X-ray analysis.⁴⁹

Conclusions

In conclusion, we have developed a method which is very mild and operationally straightforward, and requires only visible light and very low concentrations of the Ir photocatalyst and easy to access alkenes, and results in the formation of valuable cyclobutanes. The use of visible light photocatalysis makes it possible to access the highly strained *trans*-cycloheptene and avoid reaction on the excited state surface. Consequently, this work demonstrates the ability to convert photochemical energy into useable forms, i.e. ring strain, which can be used to drive the synthesis of cyclobutanes and to open up a mechanistic pathway which has heretofore been

energetically inaccessible. We anticipate that this reaction will spur other strategic uses of visible light energy to drive endergonic chemical synthesis.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1-33.
- V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559-1581.
- K. Jug and H.-W. Krüger, *Theor Chim Acta*, 1979, **52**, 19-26.
- K. B. Wiberg, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 312-322.
- R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed.*, 1969, **8**, 781-932.
- A. Nishimura, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2012, **134**, 15692-15695.
- K. Sakai, T. Kochi and F. Kakiuchi, *Org. Lett.*, 2013, **15**, 1024-1027.
- C. M. Rasik and M. K. Brown, *Angew. Chem. Int. Ed.*, 2014, **53**, 14522-14526.
- N. Saito, Y. Tanaka and Y. Sato, *Organometallics*, 2009, **28**, 669-671.
- P. Heimbach, *Angew. Chem. Int. Ed. Engl.*, 1973, **12**, 975-989.
- J. M. Hoyt, V. A. Schmidt, A. M. Tondreau and P. J. Chirik, *Science*, 2015, **349**, 960-963.
- H. Hart and E. Dunkelblum, *J. Org. Chem.*, 1979, **44**, 4752-4757.
- Y. Inoue, S. Takamuku and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 1975, 577-578.
- Y. Unoue, S. Takamuku and H. Sakurai, *J. Chem. Soc., Perkin Trans. 2*, 1977, DOI: 10.1039/P29770001635, 1635-1642.
- I. Yoshihisa, M. Toshio and H. Tadao, *Chem. Lett.*, 1982, **11**, 1045-1048.
- Y. Inoue, T. Ueoka, T. Kuroda and T. Hakushi, *J. Chem. Soc., Perkin Trans. 2*, 1983, DOI: 10.1039/P29830000983, 983-988.
- R. Hoffmann and Y. Inoue, *J. Am. Chem. Soc.*, 1999, **121**, 10702-10710.
- R. G. Salomon and K. Folting, *J. Am. Chem. Soc.*, 1974, **96**, 1145-1152.
- T. Spee, J. T. M. Evers and A. Mackor, *Tetrahedron*, 1982, **38**, 1311-1319.
- P. J. J. A. Timmermans, G. M. J. de Ruiter, A. H. A. Tinnemans and A. Mackor, *Tetrahedron Lett.*, 1983, **24**, 1419-1422.
- T. Bach and A. Spiegel, *Eur. J. Org. Chem.*, 2002, **2002**, 645-654.
- S. Fujita, Y. Hayashi, T. Nômi and H. Nozaki, *Tetrahedron*, 1971, **27**, 1607-1613.
- G. M. Wallraff, R. H. Boyd and J. Michl, *J. Am. Chem. Soc.*, 1983, **105**, 4550-4555.
- M. E. Squillacote, J. DeFellipis and Q. Shu, *J. Am. Chem. Soc.*, 2005, **127**, 15983-15988.
- P. E. Eaton and K. Lin, *J. Am. Chem. Soc.*, 1965, **87**, 2052-2054.

26. R. A. Bunce, V. L. Taylor and E. M. Holt, *J. Photochem. Photobiol. A: Chem.*, 1991, **57**, 317-329.
27. M. R. J. Vallée, I. Inhülsen and P. Margaretha, *Helv. Chim. Acta*, 2010, **93**, 17-24.
28. In 1980, Evers and Mackor observed the trimerization of cycloheptene via direct irradiation in the presence of CuOTf, occurring from the thermal reaction of trans cycloheptene
29. P. Esser, B. Pohlmann and H.-D. Scharf, *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 2009-2023.
30. M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**, 12886-12887.
31. J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2009, **131**, 14604-14605.
32. M. A. Ischay, Z. Lu and T. P. Yoon, *J. Am. Chem. Soc.*, 2010, **132**, 8572-8574.
33. M. A. Ischay, M. S. Ament and T. P. Yoon, *Chem. Sci.*, 2012, **3**, 2807-2811.
34. Z. Lu and T. P. Yoon, *Angew. Chem. Int. Ed.*, 2012, **51**, 10329-10332.
35. A. E. Hurtley, Z. Lu and T. P. Yoon, *Angew. Chem. Int. Ed.*, 2014, **53**, 8991-8994.
36. S. K. Pagire, A. Hossain, L. Traub, S. Kerres and O. Reiser, *Chem. Commun.*, 2017, **53**, 12072-12075.
37. C. Wang and Z. Lu, *Org. Lett.*, 2017, **19**, 5888-5891.
38. K. Singh, C. J. Fennell, E. A. Coutasias, R. Latifi, S. Hartson and J. D. Weaver, *Chem*, 2018, **4**, 124-137.
39. N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, 1972, **94**, 5734-5747.
40. A. D. Strickland and R. A. Caldwell, *J. Phys. Chem.*, 1993, **97**, 13394-13402.
41. K. Singh, S. J. Staig and J. D. Weaver, *J. Am. Chem. Soc.*, 2014, **136**, 5275.
42. A. Singh, C. J. Fennell and J. D. Weaver, *Chem. Sci.*, 2016, **7**, 6796-6802.
43. K. Singh, S. J. Staig and J. D. Weaver, *J. Am. Chem. Soc.*, 2014, **136**, 5275-5278.
44. A. Singh, J. J. Kubik and J. D. Weaver, *Chem. Sci.*, 2015, **6**, 7206-7212.
45. A. Singh, K. Teegardin, M. Kelly, K. S. Prasad, S. Krishnan and J. D. Weaver, *J. Organomet. Chem.*, 2015, **776**, 51-59.
46. The volume of the catalyst is the electrons per Å³ electron density isosurface. These volumes were converted to effective radius and assuming a spherical shape for simplicity
47. Further increase in temperature to 45 and 90 C did not lead to further improvement.
48. Attempt to dimerize analogous phenyl cyclohexene, which is expected to be of similar triplet state energy but a shorter lifetime than the trans-cycloheptene, does not dimerize under these conditions.
49. See ESI for details.
50. N. Burford, J. A. C. Clyburne and M. S. W. Chan, *Inorg. Chem.*, 1997, **36**, 3204-3206.
51. J. B. Metternich and R. Gilmour, *Synlett*, 2016, **27**, 2541-2552.
52. J. B. Metternich and R. Gilmour, *J. Am. Chem. Soc.*, 2015, **137**, 11254-11257.
53. J. J. Molloy, J. B. Metternich, C. G. Daniliuc, A. J. B. Watson and R. Gilmour, *Angew. Chem. Int. Ed.*, 2018, **57**, 3168-3172.
54. J. B. Hendrickson, *J. Am. Chem. Soc.*, 1961, **83**, 4537-4547.
55. J. W. G. Bloom, R. K. Raju and S. E. Wheeler, *J. Chem. Theory Comput.*, 2012, **8**, 3167-3174.
56. The enrichment in the ee is the result of statistical enrichment of the diastereomers.
57. Y. Tamura, Y. Kita, H. Ishibashi and M. Ikeda, *J. Chem. Soc. D*, 1971, 1167.
DOI: 10.1039/C8OB01273C
58. Since the crystals could not be grown, the relative stereochemistry between the two phenyl rings is unassigned.