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Photomechanochemical control over stereoselectivity in the [2 + 2] photodimerization of acenaphthylene†

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Tuning solubility and mechanical activation alters the stereoselectivity of the [2 + 2] photochemical cycloaddition of acenaphthylene. Photomechanochemical conditions produce the *syn* cyclobutane, whereas the solid-state reaction in the absence of mechanical activation provides the *anti*. When the photochemical dimerization occurs in a solubilizing organic solvent, there is no selectivity. Dimerization in H₂O, in which acenaphthylene is insoluble, provides the *anti* product. DFT calculations reveal that insoluble and solid-state reactions proceed via a covalently bonded excimer, which drives *anti* selectivity. Alternatively, the noncovalently bound *syn* conformer is more mechanosusceptible than the *anti*, meaning it experiences greater destabilization, thereby producing the *syn* product under photomechanochemical conditions. Cyclobutanes are important components of biologically active natural products and organic materials, and we demonstrate stereoselective methods for obtaining *syn* or *anti* cyclobutanes under mild conditions and without organic solvents. With this work,

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we validate photomechanocchemistry as a viable new direction for the preparation of complex organic scaffolds.

Introduction

Mechanochemistry involves^{1–3} the use of force/strain/curvature to make or break chemical bonds, and such methods are attractive because they satisfy all twelve principles of green chemistry.⁴ In addition to the minimal environmental impact, the benefits of mechanochemical reactions can include faster reaction kinetics,⁵ improved stereoselectivities and yields, or access to stereo- and regioisomers, or other chemical products,⁶ that are not accessible by solvothermal methods. Recognizing the advantages of mechanochemistry and the growing suite of tools for performing and studying reactions under force, the diversity of reactions that have been performed mechanochemically is rapidly expanding, and includes the formation of metal–organic frameworks,⁷ synthetic polymers,⁸ and small molecules.^{1,9} Amongst the reactions that have been most thoroughly studied under mechanochemical activation is the thermally allowed $[4 + 2]$ Diels–Alder^{3,10,11} reaction, and it is now known that this reaction can be driven forward with force because of its negative volume of activation.^{12–14} The Diels–Alder reaction is an example of a broader class of reactions, the pericyclic cycloadditions,¹⁵ that also have negative activation volumes, and many of these have been carried out mechanochemically as well.^{10,16,17} A class of pericyclic reactions which should also possess negative activation volumes, and thus should be accelerated by the application of force, are symmetry-allowed $[4n]$ photochemical cycloadditions, which are widely exploited in organic synthesis to prepare complex molecular scaffolds.^{14,18,19} The potential benefits of performing photochemical cycloadditions mechanochemically include improved yields and stereochemical control, the latter of which is particularly important as a mixture of stereoisomers is often obtained.²⁰ Despite these potential advantages, $[4n]$ cycloadditions have not yet been investigated under photomechanocchemical conditions – where both illumination and force are applied to the reactants simultaneously – because of challenges associated with developing instrumentation that is capable of illuminating the reactants during compression. To this end, here we implement a new reactor to drive a $[2 + 2]$ cycloaddition reaction under compression, and, in doing-so, show that such conditions are highly stereoselective as a result of a unique photomechanocchemical reaction pathway.

The symmetry-allowed $[2 + 2]$ photochemical cycloadditions of alkenes to form cyclobutanes²⁰ are frequently used to form primary and secondary metabolites^{21,22} with attractive antimicrobial,^{23,24} antibacterial,²⁴ and analgesic properties,²⁴ and cyclobutanes are being increasingly explored as a responsive component of functional materials.^{25–27} As a consequence, developing methods for their construction remains a focus of the synthetic community.²³ One challenge that still remains, however, is controlling the stereoselectivity of these photoreactions because an undesired mixture of cyclobutane stereoisomers is often produced.^{20,28–30} For example, the dimerization of acenaphthylene is considered a model reaction for understanding how experimental conditions affect the yields and stereochemical outcomes of $[2 + 2]$ photocycloadditions.^{31–36} In organic solvents, a mixture of *syn* and *anti* isomers of the acenaphthylene dimer is

obtained,³⁷ and, generally, the former is the major product.³⁴ Strategies to alter the reaction outcome so that the primary product is *anti* include the use of heavy atom solvents,³⁴ photosensitizers,³⁴ or a combination of a photosensitizer and a molecular cage,³⁸ but such conditions often require undesirable solvents, use expensive catalysts, or continue to produce a mixture of isomers. As such, further efforts are needed to understand the drivers of stereoselectivity, which could result in design rules that could be deployed to develop simple, scalable, and widely accessible methods for the stereochemical control of [2 + 2] photochemical cycloadditions that minimize the use of organic solvents and complex and expensive reagents.

Results and discussion

Here we study the [2 + 2] photodimerization of acenaphthylene under four different conditions, (i) illumination of the solid-state acenaphthylene under ball milling, (ii) illumination of the solid-state crystal in the absence of ball milling, (iii) illumination in organic solvents (soluble phase), and (iv) illumination in H₂O (insoluble phase). For (i), we find that primarily the *syn* dimer is selectively formed, whereas (ii) and (iv) selectively form the *anti* dimer. Interestingly, we do not observe any noticeable selectivity for (iii). First-principles Density Functional Theory (DFT) calculations reveal that the extent of solubility changes the cycloaddition pathway: for insoluble and solid-state conditions (b and d), the cycloaddition proceeds *via* the formation of a covalently bonded excimer, which is geometrically and energetically closer to the *anti* transition state, thereby explaining the *anti* selectivity observed in (ii) and (iv). Additionally, we reveal that the noncovalently bound *syn* dimer is more mechanosusceptible, as it experiences more destabilization upon mechanical compression, which underpins the formation of the *syn* product under ball milling (i). Therefore, in addition to providing mild conditions for the selective production of both *syn* and *anti* cyclobutanes that avoid the use of organic solvents, this work lays the foundation for understanding photomechanochemical stereoselectivity, which in turn, could lead to environmentally benign methods for the production of important chemical reagents.

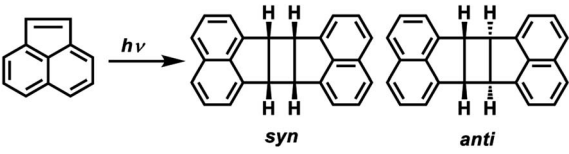
Solid-state [2 + 2] photocycloaddition of acenaphthylene

We first investigated whether the [2 + 2] dimerization of acenaphthylene can be driven photomechanochemically and how these conditions affect reaction yield and stereoselectivity. To do so, a ball-mill reactor (SPEXSamplePrep, 8000M) was modified (Fig. S1†) with a blue LED (HepatoChem, DX Series light 30 W, $\lambda_{\text{max}} = 450$ nm), and the reaction was run in a glass vial (20 mL) with two methacrylate balls (SPEXSamplePrep, 8006A, 9.5 mm diameter, 350 mg) so that light could reach the reagents during milling. In addition, we found it necessary to fluorinate the vial³⁹ and add silica gel (SILICYCLE, SilicaFlash® GE60, 70–230 mesh) to the reaction to prevent the reagents from adhering to the side walls. Acenaphthylene (1.2 g) and silica gel (1.2 g) were added to the vial under an inert Ar atmosphere, unless otherwise noted, and milled for 20 h at a frequency of 17.7 Hz. Upon completion of the milling, yields and *anti* : *syn* ratios were determined by ¹H NMR spectroscopy by dissolving a portion of the crude mixture in CDCl₃ followed by

filtration to remove silica from the CDCl_3 solution. We found (Table 1, entries 1–2) that, photomechanochemically, the dimerization reaction proceeded with yields of up to 96% with 6 : 94 *anti* : *syn* selectivity. Stereochemical assignments were confirmed by ^1H NMR spectroscopy and microcrystal electron diffraction^{40,41} on the crystallites isolated from the reactions (Fig. S26 and Table S2†). This *syn* selectivity and yield were retained in the ambient atmosphere. In the absence of the illumination, no product was observed. To put this result in context, in organic solvents, this reaction favors the *syn* product but with poor selectivity, and high *syn* selectivity has only been obtained using expensive and complex reagents or undesirable organic solvents.^{42–45} For example, Kaanumalle *et al.*⁴⁶ reported 99% *syn* product (99% yield) in borate buffer using an organometallic molecular cage, while Cowan *et al.*³⁴ obtained 98% *syn* (39% yield) selectivity in O_2 -saturated benzene. Thus, we find that photomechanochemical conditions provide the mildest route towards the *syn* product of the acenaphthylene dimer yet reported.

From these experiments it was unclear whether the *syn* selectivity was the result of carrying out the reaction in the solid state or whether force played an active role in dictating stereoselectivity. To determine whether force has a role in stereoselectivity, the reaction was carried out on acenaphthylene crystals by illuminating them in the absence of force. The acenaphthylene crystals (100 mg) were ground with a mortar and pestle, sealed in a Petri dish under either an inert or ambient atmosphere, and the crystals were then irradiated with the same blue LED for 20 h (Table 1, entries 3–4). Under Ar, we found that the reaction favored the *anti* isomer (70 : 30 *anti* : *syn*), while the ambient atmosphere provided a mixture with a 46 : 54 *anti* : *syn* ratio. So, in the absence of O_2 , more *anti* product forms, but as O_2 is introduced, such selectivity is diminished. This was also observed by Haga *et al.*,³⁶ who noted that the presence of a triplet quencher (here O_2) reduces the *anti*-selectivity. These results show that the absence of force provides substantially different products than when the products were milled

Table 1 Solid-state [2 + 2] photocycloaddition of acenaphthylene^a



Entry	Atm.	Total product yield (%)	<i>Anti</i> : <i>Syn</i>
1 ^b	Ar	95	6 : 94
2 ^b	Air	87	8 : 92
3 ^c	Ar	65	70 : 30
4 ^c	Air	99	46 : 54

^a All reactions were performed at 20 °C. Acenaphthylene samples were irradiated with a blue LED (HepatoChem, DX Series light 30 W, $\lambda_{\text{max}} = 450 \text{ nm}$) for 20 h. Yields and selectivities were obtained from ^1H NMR in CDCl_3 . ^b Ball-milling reactions were performed in the presence of silica as an additive to prevent the reagents from adhering to the side walls of the reaction vessel. ^c Reactions were performed in a Petri dish with ground acenaphthylene crystals and no milling during illumination.

during illumination. Therefore, we find that running the $[2 + 2]$ photodimerization of acenaphthylene under Ar while milling results in the opposite stereoselectivity than when the reaction is carried out without milling. These observations confirm that a unique photomechanicochemical reaction pathway exists for the dimerization of acenaphthylene that is distinct from the pathway followed during irradiation in the absence of force.

$[2 + 2]$ photocycloaddition of acenaphthylene in solution-state

We then studied the photodimerization of acenaphthylene in different organic solvents with variable H_2O : organic solvent ratios at room temperature. Here we have examined the photodimerization with 5 different organic solvents that are miscible with H_2O – DMSO, EtOH, MeOH, DMF, and MeCN – along with H_2O itself, under blue light illumination. As acenaphthylene is insoluble in H_2O , these experiments provide insight into the role of solubility in the stereoselectivity. To maximize solvent/acenaphthylene interaction (especially for the solvent mixture where acenaphthylene is poorly soluble), a 5 M solution of acenaphthylene was prepared in DMSO, and 4 μL of this stock solution was then added to 1 mL of the desired solvent system to prepare 20 mM solutions of acenaphthylene. The solution was then sonicated for 1 min. A summary of the stereoselectivity observed in these experiments is given in Fig. 1C and Table S1.[†] Although we find that the absolute value of the *anti* : *syn* ratio varies depending on the nature of the organic solvent, we observe the conspicuous trend that the *anti* selectivity increases with the amount of H_2O , where using just H_2O selectively provides the *anti* product. Because of the insolubility of the acenaphthylene in H_2O , the

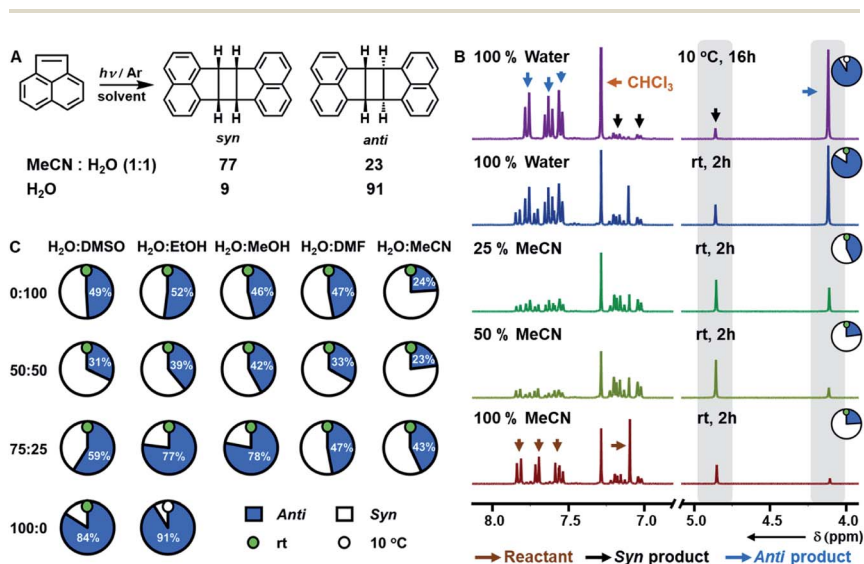


Fig. 1 (A) $[2 + 2]$ photocycloaddition of acenaphthylene, with the most stereoselective conditions for *syn* and *anti* dimers noted. (B) ^1H NMR (300 MHz, CDCl_3) of the products of the $[2 + 2]$ photocycloaddition of acenaphthylene in a binary solvent mixture composed of different ratios of MeCN and H_2O . (C) Change in selectivity with changing solvent composition for the $[2 + 2]$ photocycloaddition of acenaphthylene in binary solvent mixtures.

solution was sonicated to disperse the reactant, which led to a cloudy, opaque solution. Following irradiation, the *anti* isomer was recovered as the major product (84 : 16 *anti* : *syn*) in 84% yield. In other words, the insolubility of acenaphthylene favors the *anti* product. This observation is in good agreement with the solid-phase reactions on the crystal in the absence of milling, which also resulted in *anti* stereoselectivity (*anti* : *syn* 70 : 30). Thus, we conclude that solubility also plays an important role in determining the stereoselectivity. For photocycloadditions, it is known that lowering the reaction temperature can improve regio- and stereoselectivity.⁴⁷ As such, the reaction temperature was then lowered to 10 °C, and running the reaction for 16 h in H₂O resulted in quantitative conversion, with *anti* : *syn* reaching 91 : 9. The *anti* selectivity observed here is similar to those reported by Guo *et al.*³⁸ who used a molecular cage composed of a Ru²⁺ photocatalyst to achieve 89 : 11 *anti* : *syn*. So a major challenge in stereocontrolled photochemical cycloadditions – obtaining the *anti* isomer of acenaphthylene as the major product – was resolved by simply running the reaction in H₂O, which, in addition to providing an otherwise elusive product, is both atom-efficient and environmentally benign.

DFT calculations for the [2 + 2] photocycloaddition of acenaphthylene in solution-state

We performed DFT calculations⁴⁸ to understand why liquid and solid phase reactions result in different stereoisomers. In doing so, we explored the potential energy surfaces by considering the photodimerization pathways from three different initial states – *syn* and *anti* conformers, which are noncovalently bound supramolecular dimers, and a state that consists of two separated monomers (Fig. 2). On the other hand, the noncovalently bound *syn* and *anti* conformers correspond to the insoluble solid-state acenaphthylene (and state present in H₂O), when the monomers are close to each other and experience a net stabilizing interaction as compared to separated monomers. We find that the thermal activation barrier for the *anti* product formation (179 kJ mol^{−1}) is lower than that of the *syn* product formation (269 kJ mol^{−1}) (Fig. 2). Such high barriers suggest that

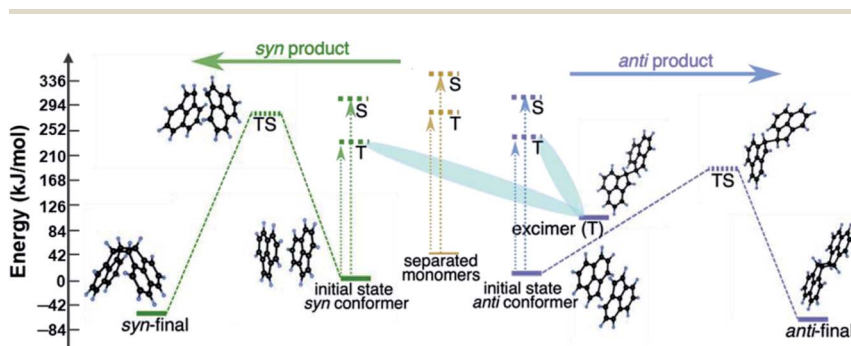


Fig. 2 Potential energy surface obtained using the geometries at the B3LYP-D3/6-31G(d) level of theory showing the pathways for *syn* and *anti* product formation. The abbreviations are as follows: T: triplet; S: singlet; TS: transition state. Dotted arrows represent vertical photoexcitation, and cyan shading illustrates relaxation of the triplet conformer states to the excimer.

the reactions cannot be performed at room temperature without photoexcitation, which we also observe experimentally. In the soluble-phase scenario, we find that the excited triplet (T) and singlet (S) states of the separated monomers (yellow dotted lines in Fig. 2) are above the *syn* and *anti* transition states (TS). Thus, when completely solvated, photoexcitation injects sufficient energy to access both the *anti* and *syn* TS; this in turn leads to both *syn* and *anti* product formation, explaining the loss of selectivity for this reaction in organic solvents. In the solid state or in H₂O, where the poor solubility keeps the acenaphthylene aggregated, the molecules exist as noncovalently bound *syn* and *anti* supramolecular conformers. We find that the spin-flipped T states for both the *syn* and *anti* supramolecular conformers lead to the formation (shaded cyan region in Fig. 2) of a covalently bonded excimer (excimer in Fig. 2). The formation of excimers in photochemical reactions has been reported previously^{49–51} to have a role in determining the selectivity of the products. Therefore, as the photoexcitation occurs in the insoluble phase, the supramolecular dimers form a covalent bond in the excimer, gaining a stabilization of nearly 117 kcal mol^{−1} per dimer compared to the vertically excited T state. We find that the geometry of this bonded excimer resembles more closely the *anti* transition state than the *syn*. Additionally, as the *anti* TS has lower energy than the *syn* TS, energetically it is also easier to access the *anti* TS from the bonded excimer. Thus, the formation of the bonded excimer preferentially leads to the *anti* product. This explains the selective formation of the *anti* product in the insoluble phase, *i.e.* in H₂O and in crystals in the absence of ball milling.

DFT calculations for the [2 + 2] photocycloaddition of acenaphthylene in solid-state

To understand the origin of *syn* selectivity that occurs under the photo-mechanochemical conditions, we have applied force (*F*) along the C–C bond forming vector of the *syn* and *anti* conformations using the external force explicitly induced (EFEI) method.^{52,53} In this simulation, the intertwined effect of *F* and photoexcitation is not incorporated, rather only the effect of compressive *F* on stability is studied. We envisage that ball milling exerts compression by bringing the monomers in the *syn* and the *anti* supramolecular conformers closer to each other. Thus, applying forces along the C–C bonds in the simulation (as shown in Fig. 3A) can have an effect similar to what occurs in a ball mill. We find that the *syn* conformer undergoes bond formation at lower *F* (between 8 nN and 9 nN), compared to the *anti* dimer (between 12 nN and 13 nN), which is shown by the grey shaded regions in Fig. 3B. To understand why the *syn* supramolecular conformer is more susceptible to *F*, we examined the *F* range of 5–8 nN with more datapoints. The reaction coordinate (RC) in Fig. 3C is defined based on the C–C distance, wherein the bond distances at 5 nN and 8.55 nN correspond to RC of 0 and 1, respectively. We find that the slope of RC *vs.* *F* (black dashed lines in Fig. 3C) is higher for the *syn* supramolecular conformer. This shows that a more significant change in RC is attained for *syn* than *anti* at the same applied *F*. In other words, the results directly confirm that the *syn* supramolecular conformer is more mechanosusceptible, meaning that its RC has a stronger dependence on *F*. In addition, the *syn* supramolecular conformer experiences more destabilization for the same applied *F* than the *anti* (filled markers in Fig. 3C). To analyze these

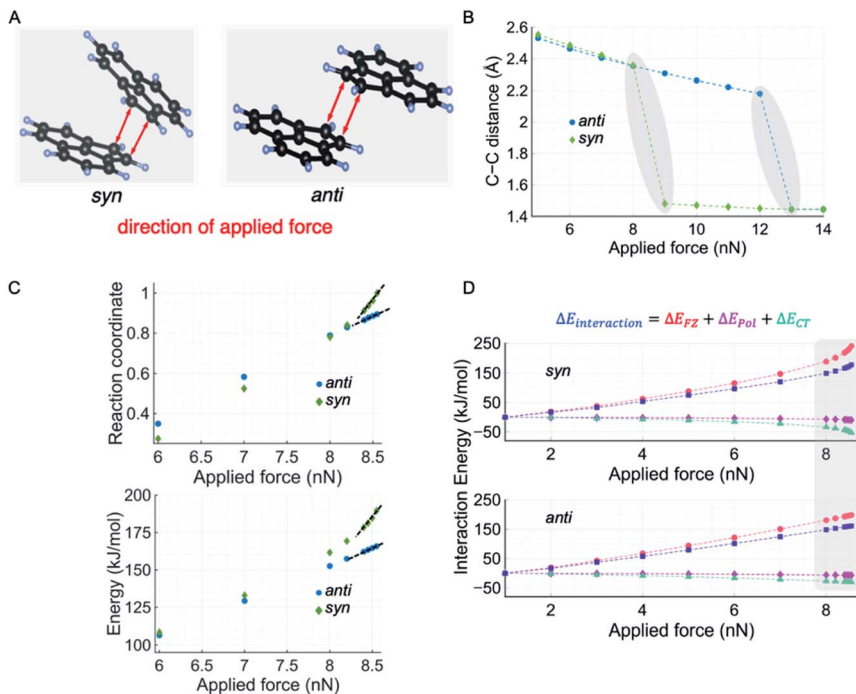


Fig. 3 Effect of force on the dimerization of *syn* and *anti* supramolecular conformers. (A) The directions of the applied forces in simulations using the external force explicitly included (EFEI) method are shown. (B) The effect of applied force on C–C bond formation for *syn* and *anti* conformers. The shaded regions indicate where the *syn* and/or *anti* dimers undergo covalent C–C bond formation from a noncovalent conformer. (C) The change in reaction coordinate (RC) and energy (E) as a function of the applied force. The RC is defined based on the C–C distance, wherein distances at 5 nN and 8.55 nN correspond to RC 0 and 1, respectively. The filled circles/diamonds correspond to the E values, whereas unfilled markers indicate the change in the RC. (D) Energy decomposition analysis showing the effect of force on different interaction terms between the monomers. The abbreviations are: FZ: frozen density, CT: charge transfer, Pol: polarization.

effects, we implement energy decomposition analysis (EDA)⁵⁴ to understand the origin of the mechanosusceptibility by quantifying the interaction energy between the acenaphthylene monomers (Fig. 3D). EDA consists of three terms: frozen density (E_{FZ}), charge transfer (E_{CT}), and polarization (E_{Pol}).⁵⁴ We find that the E_{FZ} dominates in the higher F regime, and it increases drastically near 7–8.55 nN for the *syn*, but *anti* does not exhibit such behavior (Fig. 3D). As E_{FZ} captures the interaction between the unrelaxed electron density between the monomers, we conclude that the face-to-face orientation of the π -clouds of the *syn* supramolecular conformer, and the resulting repulsion at smaller distances, make it more mechanosusceptible, whereas for the *anti* supramolecular dimer, π -clouds interact to a lesser extent. Additionally, it is worth noting that the TS for the *syn* product formation corresponds solely to compression along the C–C bonds participating in the [2 + 2] cycloaddition (*syn* TS in Fig. 2). On the other hand, for the *anti* product formation, shear force also plays an important role along with compression as the monomers need to slide to form the *anti* product (*anti* TS in

Fig. 2). We conjecture that as attaining shear and compression simultaneously is statistically less probable under ball milling than just compression, *syn* selectivity is boosted. Thus, these results explain qualitatively the stereoselectivity of solid-state photomechanicochemical conditions.

Conclusion

In conclusion, we have studied the $[2 + 2]$ dimerization of acenaphthylene and explored how light, force, and solvent can be combined to achieve both *syn* and *anti* stereoselective photodimerization. We find that *syn* stereoselectivity is observed under photomechanicochemical conditions because of the greater mechanosusceptibility of the noncovalently bound *syn* supramolecular conformer compared to the *anti* conformer. In studying how solvents and solubility affect yields and stereoselectivity, we have shown that simply running the photodimerization in H₂O provides the *anti* dimer in high yields, and these conditions provide among the highest *anti* stereoselectivity yet observed because of the formation of a bonded excimer in insoluble phases. Thus, we report scalable and mild conditions for obtaining both *syn* and *anti* $[2 + 2]$ cycloaddition products without necessitating organic solvent or complex additional reagents. More importantly, we demonstrate that photomechanicochemical pathways exist that are distinct from solvothermal or solid-state reaction pathways, and we explain stereochemistry based upon mechanosusceptibility, a concept that may be used to predict stereoselectivity for other mechanochemical reactions as well. In doing so, we have shown that photomechanicochemistry and photosolvocchemistry can provide mutually orthogonal stereoselective routes for making complex organic scaffolds. Therefore, photomechanicochemistry merits further investigation as a scalable and environmentally benign approach to stereoselective photochemistry.

Experimental section

Experimental procedures, synthesis, and characterization of all new compounds, NMR spectra, and microcrystalline electron diffraction are provided in the ESI file.†

Author contributions

Sankarsan Biswas (S. B.1.) performed the experiments with guidance from A. B. Sayan Banerjee (S. B.2.) performed the DFT calculations with guidance from A. M. R. S. B.1., S. B.2., A. B., and A. M. R. interpreted the results and wrote the manuscript together. Milan A. Shlain (M. S. A.) helped to modify the photoreactor for performing photomechanicochemistry. Brent L. Nannenga (B. L. N.) and Andrey Alex Bardin (A. A. B.) performed microED experiments for determining the crystal structure of the photo dimers. Rein V. Ulijn (R. V. U.) provided scientific input. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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