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Mechanical Force Induces Ylide-Free Cycloaddition of Nonscissible Aziridines

Sangmin Jung, and Hyo Jae Yoon*

Abstract: Reported herein is that aziridines can be a nonvulnerable mechanophore. Upon exposure to a mechanical force, stereochemically pure nonactivated aziridines incorporated into the backbone of macromolecule do not undergo *cis-trans* isomerization, suggesting the retention of ring structure by the force. Nonetheless, aziridines react with a dipolarophile and seem not to obey conventional reaction pathways that involve C-C or C-N bond cleavage prior to the event of cycloaddition. Our work demonstrates that a nonvulnerable chemical structure can be a mechanophore.

In mechanochemically responsive polymers[1], strong pulling or shearing forces along the backbone of macromolecules transduced by a mechanical force trigger chemical reactions over mechanophores embedded on the backbone. These polymers have found several applications, including structure engineering,[2] catalysis,[3] sensors,[2a] patterning,[4] recycling of resources,[5] materials transfer,[6] and gating to regulate other reactions.[7] Such systems can activate covalent and coordination bonds,[2a-f, 3, 5, 6b, 7-8] and change electrical and optical properties.[2a, 4, 9] The activation of mechanophores also allows one to steer chemical reactions into the routes that are inaccessible under traditional thermal and photochemical conditions.[2c-f, 10] The common approach for mechanochemical studies is to harness vulnerable chemical structures, as mechanophores, that have weak bond energies[3, 11] or high strains.[2e, 2f, 5, 7a] Thus, most of mechanophores usually exhibit irreversible bond scission upon exposure to mechanical forces.[9, 12] A limited number of mechanophores often undergoes isomerization (see Figure 1a for exemplary cases).[2c, 2f]

Highly strained ring structures, much like *gem*-dihalocyclopropanes[13] and epoxides,[14] are attractive mechanophores. Aziridine is the smallest saturated heterocycle containing a nitrogen atom, and its reactivity largely differs from those of *gem*-dihalocyclopropanes and epoxides.[14-15] Depending on the electronic structure of *N*-substituent, the reactivity of aziridine can be tunable.[15f, 16] For example, incorporation of electron-donating moiety into the *N*-substituent yields highly robust non-activated aziridines whereas electron-withdrawing *N*-substituent leads to activated aziridines whose ring structure can be easily opened under mild conditions.

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Cycloaddition reactions of aziridines under thermal and photochemical conditions usually depend on the formation of reactive species before the event of addition reaction, such as i) azomethine ylides resulting from the cleavage of C-C bond in the aziridine ring,[17] ii) zwitterionic 1,3-dipoles from the cleavage of C-N bond,[18] iii) aziridinium ions from the reaction on the nitrogen,[19] and iv) metalla-azetidines from the oxidative addition of metal (Figure S1 in the Supporting Information).[20] For the first two cases, the formation of reactive species necessitates a reversible bond cleavage in the ring structure, which is evidenced by *cis-trans* isomerization of aziridine, often inducing undesirable side-reactions.[21]

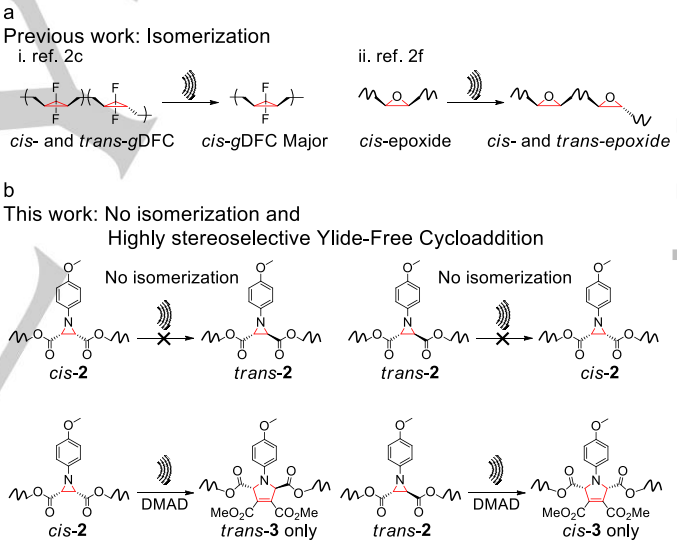

Figure 1. a) Exemplary cases of mechanochemical isomerization of *gem*-difluorocyclopropane (*g*DFC) and epoxide. b) No isomerization of aziridines (*cis*-**2** and *trans*-**2**) under a mechanochemical condition, thereby leading to highly stereoselective cycloaddition reactions with dipolarophile (dimethyl acetylenedicarboxylate, denoted as DMAD).

We herein show that nonactivated aziridines can act as a mechanophore and likely obeys an ylide-free reaction pathway. Upon application of mechanical force *via* ultrasound sonication, stereochemically pure aziridines do not undergo *cis-trans* isomerization (Figure 1b). Intuitively, enough mechanochemical reactivity would not be anticipated in such robust molecular structures. However, the aziridines unexpectedly allow access to force-induced cycloaddition reactions with a dipolarophile (dimethyl acetylenedicarboxylate, DMAD; Figure 1b). This is counterintuitive considering that the typical cycloaddition of

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aziridines follows reaction pathways involving C-C or C-N bond cleavages before the event of addition (as described above).

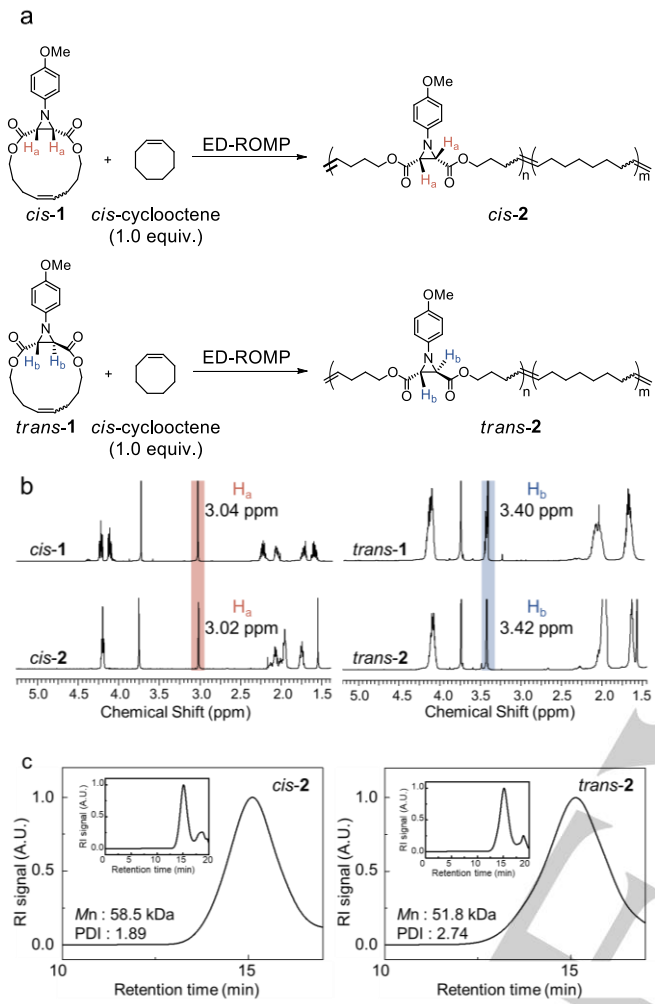

Figure 2. a) Synthesis of *N*-(4-methoxyphenyl) *cis*- and *trans*-aziridine copolymers (denoted as *cis*-**2** and *trans*-**2**) from the macrocyclic monomers (*cis*-**1** and *trans*-**1**) *via* entropically-driven ring opening metathesis copolymerization (ED-ROMP). b) Comparison of ^{1}H NMR spectra for the monomers and polymers. c) Size exclusion chromatography (SEC) traces of *cis*-**2** and *trans*-**2**. Insets show the full SEC plots.

We synthesized 14-membered macrocyclic monomers that contained *cis*- and *trans*-*N*-(4-methoxyphenyl) aziridines (*cis*-**1** and *trans*-**1** in Figure 2a) from *cis*- or *trans*-diethyl 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylates in two steps. The desired structures and stereochemistry of monomers were confirmed by ^{1}H and ^{13}C NMR spectroscopies and high-resolution mass spectrometry (HR-MS) (see the Supporting Information for details on synthetic procedures and characterization of the monomers). The protons of aziridine carbons in *cis*-**1** and *trans*-**1** showed the resonances at δ = 3.04 and 3.40 ppm, respectively, confirming the formation of aziridine ring structures (Figure 2b).

Aziridine-containing polymers (*cis*-**2** and *trans*-**2**) were synthesized by entropically-driven ring opening metathesis copolymerization with 1:1 molar ratio of *cis*-cyclooctene and the monomer (*cis*-**1** or *trans*-**1**) in the presence of Grubbs 2nd generation catalyst (Figure 2a). ^{1}H NMR analysis confirmed that the 1:1 molar ratio was straightforwardly translated into the monomer ratio in the polymer chain. The copolymers *cis*-**2** and *trans*-**2** exhibited the proton resonances at δ = 3.02 ppm and 3.42 ppm, respectively (Figure 2b). These proton resonances were consistent with those of the aziridine in the monomers. This confirms the intact ring structure and the retention of stereochemistry after the completion of polymerization. Figure 2c shows size exclusion chromatography (SEC) traces for the polymers. From the traces, we estimated the number average molecular weight (M_n) and polydispersity index (PDI): 58.5 kDa and 1.89 for *cis*-**2** and 51.8 kDa and 2.74 for *trans*-**2**.

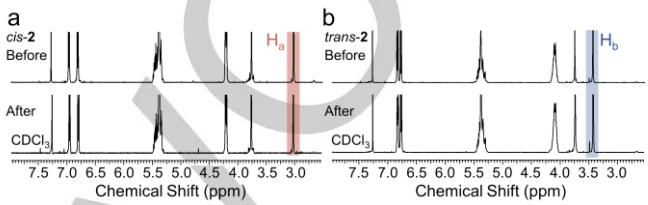

Figure 3. a, b) ^{1}H NMR spectra of *cis*-**2** and *trans*-**2** before and after 2 h of sonication at 30% amplitude.

Our aziridines did not undergo *cis*-*trans* isomerization. Each solution of *cis*-**2** and *trans*-**2** in THF (1 mg/mL) was sonicated at 4 - 8 °C with a high intensity probe (20 kHz, 30% amplitude; pulse sequence: 1 sec on and 1 sec off) under N_2 atmosphere. After 2 h ultrasound sonication, we observed no changes in ^{1}H NMR spectra for *cis*-**2** and *trans*-**2** (Figure 3a, b). This finding evidenced no significant isomerization of aziridine under mechanochemical condition.

Intuitively, we hypothesized that non-isomerizable robust aziridines may not be a good mechanophore. To test this hypothesis, each of *cis*-**2** and *trans*-**2** was reacted with 0.2 M DMAD under the identical mechanochemical condition used for the isomerization experiment. After 2 h sonication, apparent changes in ^{1}H NMR spectra were unexpectedly observed. For the reaction of *cis*-**2**, new proton resonances at *δ* = 6.61, 5.52, 4.07, 3.83, and 3.72 ppm appeared (a-e in Figure 4a); similarly, ^{1}H NMR spectra for the reaction of *trans*-**2** showed new proton resonances at δ = 6.71 and 5.28 ppm (a, b in Figure 4b). The integration ratio of the new proton resonances was a:b:c:d:e = 1.5:1:1:2:3 and a:b = 1:1 for *cis*-**2** and *trans*-**2**, respectively (Figure S2 in the Supporting Information). The ^{1}H NMR spectra of copolymers were compared with those of [3+2] cycloaddition products (pyrrolines), analogous polymers separately synthesized with *cis*-**2** and *trans*-**2** under thermal condition (denoted as *trans*-**3**-heat and *cis*-**3**-heat; see the Supporting Information for details about synthesis and characterization of these polymers). The comparison indicated that the newly formed proton resonances in the mechanochemical products (denoted as *trans*-**3** and *cis*-**3**) corresponded to pyrrolines. Note that *cis*-**2** and *trans*-**2** were converted into *trans*-**3** and *cis*-**3**, respectively. Interestingly, no mixture of *cis*- and *trans*-products was observed for both reactions (Figure 4), indicating that our mechanochemical reactions were highly stereoselective. In conjunction with the observation of no *cis*-*trans* isomerization, our result surprisingly implies that force induces the cycloaddition of nonactivated aziridines, probably, without the formation of azomethine ylides[17] that result from C-C

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or C-N bond cleavage. It is noteworthy that cycloaddition of intact aziridine has not been reported before.

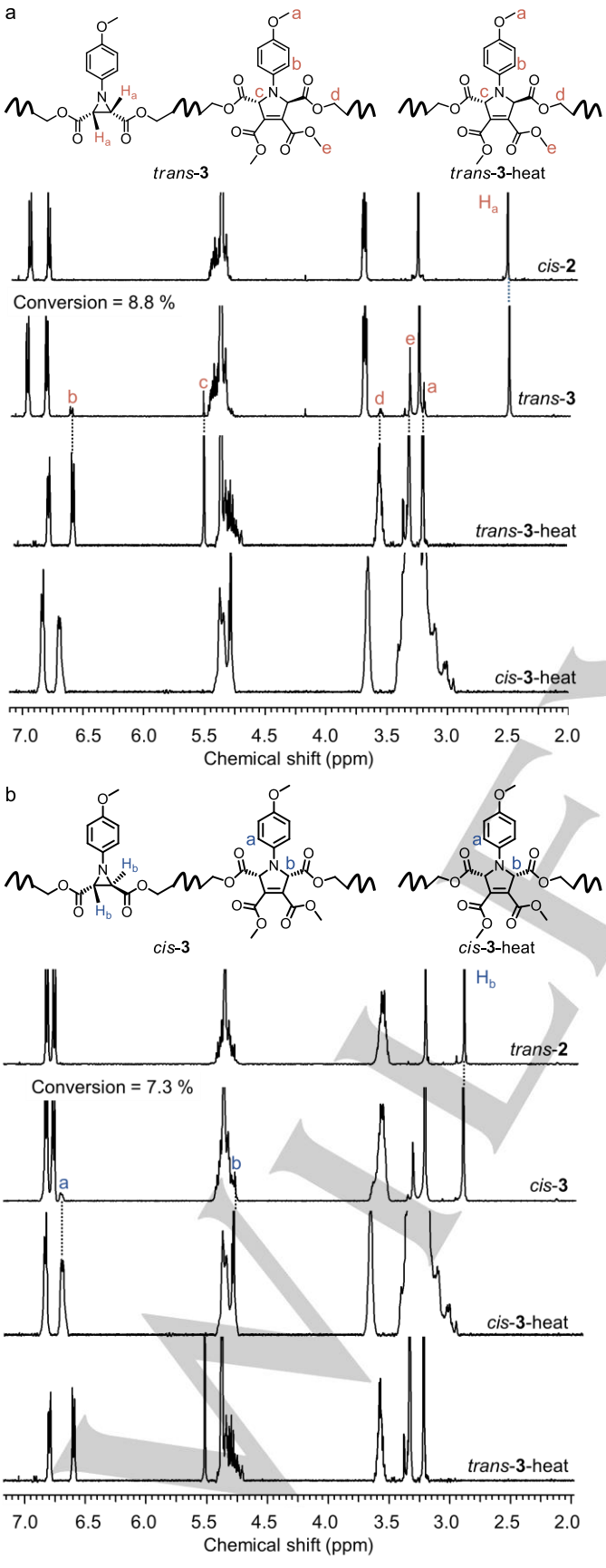

Figure 4. a, b) The molecular structures of mechanochemical products formed from *cis*-**2** and *trans*-**2** reactants (denoted as *trans*-**3** and *cis*-**3**), and the corresponding thermal products (*trans*-**3**-heat and *cis*-**3**-heat). Comparison of ^{1}H NMR spectra between these.

Control experiments were also conducted over small molecule systems. Large extensional shear forces are generated by pulsed ultrasound[1], and this is usually facilitated by a polymer backbone. Under the same sonication conditions as those of polymeric systems, *cis*- and *trans*-*N*-(4-methoxyphenyl) aziridine small molecules (denoted as *cis*-aziridine and *trans*-aziridine) did not react with DMAD, evidenced by no detectable change in ^{1}H NMR spectra (Figure 5a, b). This result confirms that the cycloaddition reactions by pulsed ultrasound of the aziridine copolymers were caused by the extensional shear force along the polymer backbone, not by high-pressure energy and elevated temperature generated by ultrasonic waves.

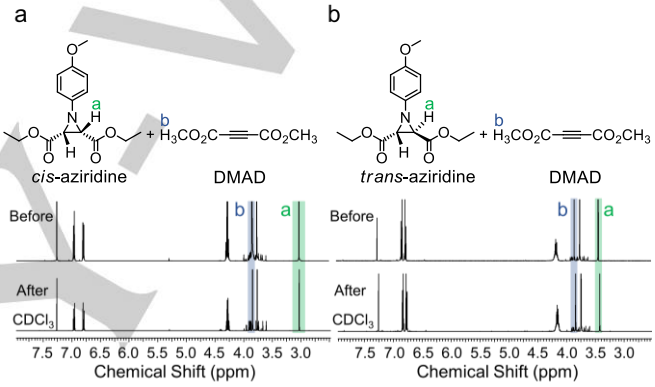

Figure 5. a, b) ^{1}H NMR spectra of *cis*- and *trans*-aziridine model compounds (the corresponding small molecules without the macromolecular backbone) before and after 2 h of sonication under the same condition.

To explain the mechanism of our mechanochemical reactions, we conducted CoGEF (Constrained Geometries for simulating External Force) calculations using density functional theory (DFT) at B3LYP/6-31G*.[22] To simulate force induced structural changes, the straight-line distance between the methoxy substituents (*d*, Å) increased gradually as shown in Figure 6a. The increased Δ*d* (the change in *d* relative to intact aziridine) led to i) increased relative energy of aziridines (Figure 6b), ii) elongated C-C bond in aziridines (Figure 6c), iii) reduced negative charge character on carbon atoms of aziridine (Figure 6d), and iv) increased negative charge character on nitrogen atom (Figure 6e). At the end of calculation, *cis*- and *trans*-aziridines underwent C-C bond cleavage at Δ*d* = 1.70 and 1.65 Å, respectively.

The stereoselective feature in our mechanochemical reactions is an unexpected observation. Unraveling detailed mechanisms of mechanochemical reactions is a significant chemical challenge. Indeed, despite the CoGEF calculation, our current understanding is insufficient to fully explain the mechanism of our reactions. Recently, a stimulating study by Martinez and Xia *et al*.[23] has shown that a newly developed ab initio steered molecular dynamics can be useful for investigating mechanistic hypotheses of mechanochemical reactions. Further study using this new simulation method may be needed to explain the mechanism of our reactions.

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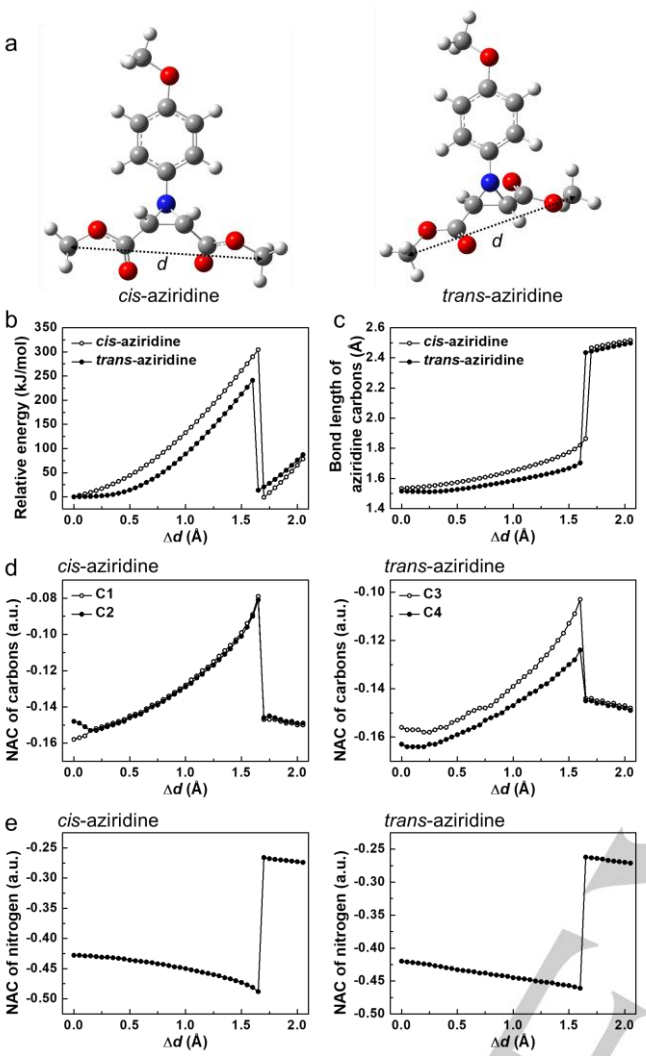

Figure 6. a) Simulation of tensile stress induced structural changes in *cis*- and *trans*-aziridines. The beeline distance between methoxy groups (*d*, Å) increased from 0.0 to 2.05 Å. b) Plots of relative energy between as a function of the change in *d* relative to intact aziridine (Δ*d*). c) Plots of bond lengths between aziridine carbons as a function of Δ*d*. d) Plots of natural atomic charge (NAC) of aziridine's carbon atoms as a function of Δ*d* (C1-C2 and C3-C4 for *cis*- and *trans*-aziridines, respectively). e) Plots of NAC of aziridine's nitrogen atom as a function of Δ*d*.

We believe, however, that the following possibilities in the reaction mechanism could be eliminated because the stereochemical information in products is not consistent with the experimentally observed one. i) If the activated aziridines obey concerted [3+2] cycloaddition reaction routes, *cis*- and *trans*-aziridines would be converted into *cis*- and *trans*-pyrrolines, respectively, as summarized in Figure S4a in the Supporting Information. ii) If the aziridines are converted into ylides under the mechanochemical condition (this seems not true according to our experiment), disrotatory and conrotatory ring opening of *cis*- and *trans*-aziridines yields the same *W*-shaped azomethine ylide, [3+2] cycloaddition of this ylide with DMAD affords only *cis*-pyrroline (Figure S4b in the Supporting Information). iii) If the electron-rich nitrogen atom resulting from the increased C-N dipole pushes a pair of electrons into the carbon atom and subsequently the C-C σ bond attacks DMAD in a transition state, dipolar intermediates with the same stereochemistry for *cis*- and *trans*-aziridines are formed, obeying Baldwin's rules, (Figure S4c in the Supporting Information). Intramolecular cyclization of these intermediates affords only *cis*-pyrroline for both *cis*- and *trans*-aziridine.

In summary, we have demonstrated that the robust ring structure of aziridines surprisingly reacts with a dipolarophile under a mechanochemical condition. This unprecedented finding suggests that a nonvulnerable chemical structure can be considered as a mechanophore for not only solving the problems in mechanochemical reactions with vulnerable mechanophores but also exploring unconventional reaction routes that are inaccessible under traditional reaction conditions. The trivalent nitrogen atom in aziridine makes it possible to control the chemical and electronic structure of *N*-substituent, which promises to modulate the mechanochemical reactivity of aziridine mechanophore.

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Keywords: Mechanochemistry • Nonvulnerable mechanophore • Nonscissible aziridine • Highly stereoselective cycloaddition • Ylide-free

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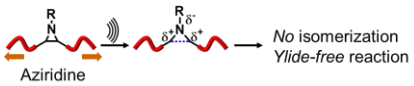

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Mechanical force-induced cycloaddition of intact aziridines with a dipolarophile does not obey reaction pathways that occur in traditional thermal and photochemical conditions. Our results demonstrate that nonvulnerable chemical structure can be an attractive mechanophore.