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Stereospecific Synthesis of Substituted Aziridines by a Crystal-to-Crystal Photodenitrogenation of Δ^2-1,2,3-Triazolines

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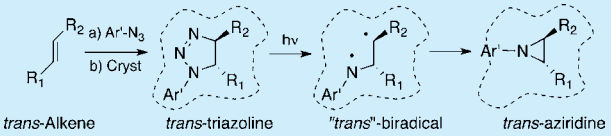
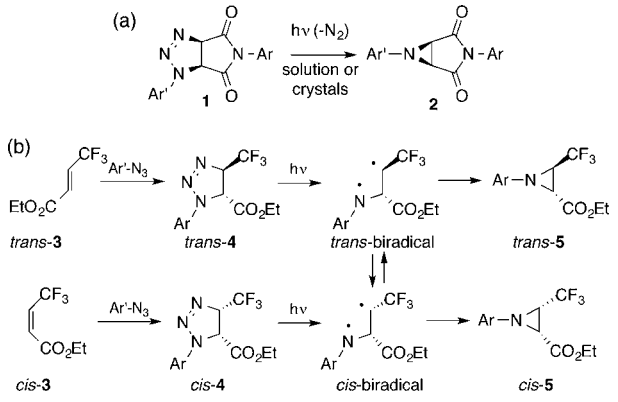
Supporting Information

ABSTRACT: Crystalline *cis*- or *trans*-Δ^2-1,2,3-triazolines prepared by highly stereospecific and regioselective hydrogen bonding-catalyzed dipolar cycloaddition of activated *cis*- or *trans*-alkenes with aryl azides undergo a highly stereospecific photodenitrogenation to form the corresponding *cis*- or *trans*- azidirines in high chemical yields. While examples involving disubstituted and trisubstituted triazolines highlight steric challenges encountered in the dipolar cycloaddition reaction, the stereochemical control exerted by the crystalline lattice is enhanced by bulky substituents in the triazoline precursors to generate aziridines photochemically.



Aziridines are highly strained, nitrogen-containing, saturated, three-membered heterocycles with excellent synthetic potential and valuable biological properties.[1,2] For this reason, there have been numerous recent efforts to synthesize aziridines in a highly stereoselective manner.[3−5] Having recently shown that crystalline bicyclic Δ^2-1,2,3-triazolines derived from *N*-aryl maleimides (**1**, Scheme 1a) can undergo an efficient solid-state photodenitrogenation to form bicyclic aziridines (**2**) in quantitative chemical yields,[6] we set out to explore the potential of a two-step strategy to prepare ring-substituted aziridines in a sterospecific manner. As indicated in Scheme 1b, this approach intends to take advantage of a stereospecific 1,3-dipolar cycloaddition between suitable azides and *cis*- or *trans*-activated alkenes to form the corresponding *cis*- or *trans*-Δ^2-1,2,3-triazoline precursors. Subsequent crystallization and exposure of the resulting solid to UV light is expected to result in cleavage of C−N and N−N bonds to release N_2, with the formation of a 1,3-alkyl-aminyl biradical intermediate confined in the rigid environment of its crystalline precursor.[7] Photochemistry performed in this rigid environment should provide minimal rotational freedom to conserve stereospecificity in forming aziridines.[8,9]

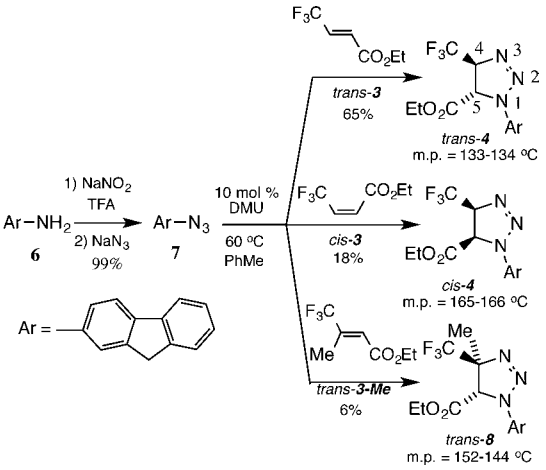
Scheme 1



To test the synthetic hypothesis illustrated in Scheme 1b, we prepared and crystallized samples of diastereomerically pure 1-aryl- Δ^2-1,2,3-triazolines *cis*-**4** and *trans*-**4**, shown in Scheme 1b, and we determined the stereospecificity of their photodenitrogentation reaction in solution and in the solid state. As illustrated in the scheme, one may expect that the 1,3-biradical in solution may be able to explore conformations leading to the loss of stereochemical information in a measure that will depend on its lifetime. Singlet biradicals should display greater stereochemical memory than those generated by sensitization in the triplet state.

As shown in Scheme 2, samples of Δ^2-1,2,3-triazolines *trans*-**4**, *cis*-**4** and *trans*-**8** were obtained by a 1,3-dipolar cycloaddition of aryl azide **7** with dipolarophiles *trans*-**3** and *cis*-**3** and the

Scheme 2



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methyl substituted derivative *trans*-**3-Me**, catalyzed by *N*,*N*-dimethylurea (DMU). While *trans*-**3** and *trans*-**3-Me** are commercially available, *cis*-**4** was obtained by photoisomerizaton of *trans*-**3** using wavelengths $\lambda \geq 220$ nm, which yielded a photostationary state with a ratio *trans*-**3**/*cis*-**3** = 76:24. A sample of fluorenyl amine **6** was converted to the corresponding azide **7** in quantitative yield, using standard protocols.[10] We selected the fluorenyl group as a model system with expectations that it would lead to the formation of high melting solids.

The desired role of the fluorenyl substituent was confirmed as the three triazolines were shown to be crystalline solids with melting points ranging from 133 to 165 °C, which should be suitable for the exploration of solid-to-solid reactions. The stereochemical identity of isomeric triazolines *cis*-**4** and *trans*-**4** could be determined by ^{1}H NMR experiments and was subsequently confirmed by single crystal X-ray diffraction in the case of *trans*-**4** and *trans*-**8**. Briefly, the identity of the heterocyle H4 signal (for numbering see *trans*-**4** in Scheme 2) was established by its vicinal coupling to the CF_3 group ($J_{4,CF3} \approx 8$ Hz) and the *cis*- or *trans*-relation with H5 was established by their vicinal coupling constants ($J_{cis} \approx 13$ Hz and $J_{trans} \approx 8$ Hz) and presence (*cis*) or absence (*trans*) of a 2D NOESY correlations. The regiochemistry of the triazolines was also determined by a 2D NOESY between H5 and the fluorenyl *ortho*-hydrogens. These assignments were all consistent with the X-ray structure shown in Figure 1, which displays the

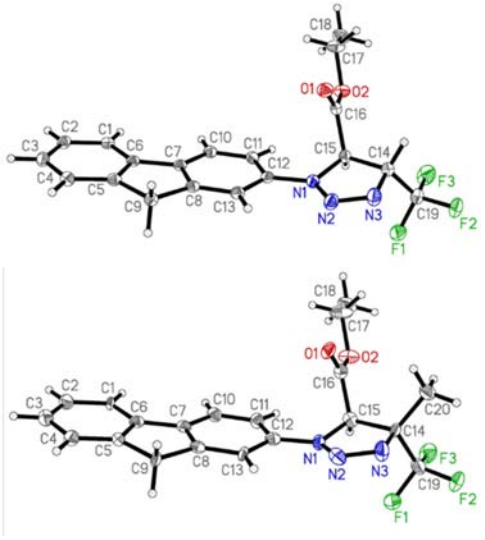

Figure 1. X-ray determined molecular structures of triazolines *trans*-**4** (top) and *trans*-**8** (bottom) with 30% probability ellipsoids, illustrating the trans relationship between the ester and trifluoromethyl groups.

trifluoromethyl and ethoxycarbonyl groups of *trans*-**4** (Figure 1, top) to be on opposite faces of the heterocycle, with the ester being adjacent to the *N*-aryl fragment. Similar features were observed in the case of *trans*-**8** (Figure 1, bottom), which included a conformation with the planes of fluorenyl and triazoline rings nearly coplanar and the corresponding carbonyl oxygens pointing in the direction of the *N*-aryl nitrogen.

The regioselectivity of the 1,3-dipolar cycloaddition could be explained from theoretical calculations using the M06-2X[11] density functional theory. The methyl ester analogue of *trans*-**3** is activated by DMU and phenyl azide is a model 1,3-dipole. The lowest energy transition structures **TS1** and **TS2** lead to the two possible regioisomeric cycloadducts (Figure 2). **TS2** is 3.8 kcal mol^{-1} lower in free energy than **TS1**, corresponding to the observed regioisomer.[12]

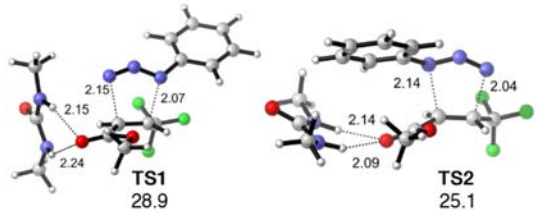

Figure 2. Transition structures for the DMU-catalyzed (3 + 2) cycloaddition of PhN_3 and *trans*-**3**. Bond lengths are reported in Å and energies in kcal mol^{-1}.

Analysis of the reactant and reaction energetics showed that DMU-complexed *trans*-**3** has a LUMO energy (−2.21 eV) that is 0.44 eV lower than that of the noncomplexed dipolarophile (−1.87 eV), which accounts for the increased reactivity in the presence of the catalyst.[13] We found that the frontier orbital coefficients of the two carbon atoms in the dipolarophile are essentially identical, with or without the catalyst, suggesting that the reaction regioselectivity is determined by factors affecting the energies of the two transition states, as expected by the distortion/interaction model,[14] rather than by the intrinsic properties of the reactants. Thus, the computed activation free energies ($\Delta E^{\ddagger}$) of **TS1** and **TS2** are 14.1 and 9.6 kcal mol^{-1}, respectively, and agree with the observed regioselectivity. The distortion energies ($\Delta E_d^{\ddagger}$) for the competing transition states are 30.0 and 33.3 kcal mol^{-1}, for **TS1** and **TS2**, respectively, indicating that the reactants must distort further to reach the geometry of **TS2**. However, the corresponding interaction energies ($\Delta E_i^{\ddagger}$), − 15.9 and −23.7 kcal mol^{-1}, respectively, reveal a stronger stabilizing effect for **TS2** as compared to **TS1**. In fact, the interaction energy difference favoring **TS2**, $\Delta\Delta E_i^{\ddagger}$, is much greater than the distortion energy difference favoring **TS1**, $\Delta\Delta E_d^{\ddagger}$ (7.8 vs 3.3 kcal mol^{-1}, respectively). The large $\Delta\Delta E_i^{\ddagger}$ value in favor of **TS2** is likely due to a combination of favorable $\pi-\pi$ dispersive interactions between the phenyl group and the ester−DMU complex (Figure 2) and the binding mode of DMU to the alkene in the transition structure. **TS2** shows DMU coordinated to both in-plane carbonyl lone pair orbitals, which further improves the FMO interaction in **TS2**. In fact, azide **7** with a more extensive fluorenyl π-system may contribute to the larger preference for **TS2** beyond that predicted by DFT computations for a phenyl group.

The solution photochemistry of triazolines *trans*-**4** and *cis*-**4** was analyzed with samples of ca. 5−8 mg dissolved in MeCN-d_3 in an NMR tube, and degassed with Argon for approximately 15 min. After exposure to the output of a medium pressure 400 W Hanovia Hg arc lamp equipped with a Pyrex filter (cutoff of $\lambda \leq 290$ nm), the reactions were analyzed by ^{1}H NMR to determine conversion to product and the relative amounts of the *cis*- and *trans*-aziridines. The two aziridines were purified and characterized by spectroscopic methods with their identity easily established from the coupling constants of the aziridine hydrogens, with values $J_{trans} \approx 2.3$ Hz and $J_{cis} \approx 6.5$ Hz.[15]

As shown in Table 1, photochemical reactions in solution yielded aziridines **5** and **9** as the only product with significant stereochemical retention. While reaction of *trans*-**4** resulted in preferential formation of *trans*-**5** in 76% yield in MeCN-d_3, *cis*-**4** preferentially yielded *cis*-**5** in 68%. Similarly, methyl triazoline

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Table 1. Ratio of *cis*- and *trans*-Aziridines from Photoreactions in Solution and in the Solid-State[a]

triazoline	MeCN-d_3	Me_2CO-d_6	crystals
	trans-**5**/*cis*-**5**	*trans*-**5**/*cis*-**5**	*trans*-**5**/*cis*-**5**
trans-**4**	76:24	99:1	83:17
cis-**4**	32:68	99:1	10:90
trans-**8**	86:14[b]	99:1[b]	99:1[b]

[a]Ratios were determined by ^{1}H NMR. [b]These entries pertain to product ratios from aziridine **9**.

trans-**8** yielded aziridine *trans*-**9** in 86% yield in MeCN-d_3. Recognizing that high stereochemical retention values are indicative of a short-lived 1,3-biradical singlet biradical where bond formation must be competitive with conformational relaxation, we also carried out experiments using acetone-d_6 as solvent and triplet sensitizer. In all three cases, the triplet sensitized reaction resulted in the exclusive formation of the less sterically encumbered *trans*-aziridine, suggesting that a longer-lived triplet 1,3-biradical has an opportunity to relax and give thermodynamically more stable product.

To establish the conditions required for a solid state photochemical reaction, we determined the thermal stability of the three triazoline crystals using differential scanning calorimetric (DSC) and thermogravimetric analysis (TGA). The DSC results showed a relatively sharp endothermic transition which correlated with the melting temperature determined visually at 133−134 °C for *trans*-**4**, and 165−166 °C for *cis*-**4** (DSC for *trans*-**8** does not show sharp endothermic transition but only shows denitrogenation). In all three cases, a melting endotherm was followed by a broad exothermic transition corresponding to the thermal denitrogenation of the corresponding triazoline (see SI section). The loss of mass corresponding to N_2 was also documented by TGA. After noting that the purified aziridines were crystalline, and with melting points in the range of 84−125 °C, we recognized that the triazoline reactant-to-aziridine product mixture could be a good candidate for a solid-to-solid reaction at room temperature. This was confirmed with solid-state photochemical experiments carried out with ca. 5−10 mg of triazoline crystals ground between two microscope slides and subsequently exposed to Pyrex-filtered UV light. We also note that the bulk powder triazolines used for solid-state photochemistry were shown to be different polymorphs than those used for single crystal X-ray diffractions. We were not able to replicate the same polymorphic triazolines after numerous crystallization attempts and we were not able to get good quality single crystals of the new forms.

The solid-state photochemistry shown in the last column of Table 1 was fully reacted to the aziridine product with quantitative conversions. As expected, reactions in the solid-state were more stereoselective than reactions in solution (Table 1), suggesting a decrease in conformational relaxation for the postulated 1,3-biradical. Samples of *trans*-**4** and *cis*-**4** yielded *trans*-**5** and *cis*-**5** in 83% and 90% yield, respectively. The highest level of retention was observed upon reaction of the trisubstituted triazoline, *trans*-**8**, where the added methyl group further hinders rotation of the 1,3-biradical intermediate. The *trans*-aziridine was obtained in quantitative yield. A small loss of stereochemical retention in the case of *trans*-**4** and *cis*-**4** indicates that a fraction of the 1,3-biradical is able to change the configuration of the carbon bearing the CF_3 group within the rigid crystalline lattice.

In conclusion, the synthesis of substituted aziridines by a stereospecific dipolar cycloaddition of activated alkenes and azides followed by the photodenitrogenation of the resulting triazolines in the crystalline phase presents some promise and also some challenges. Although we confirmed a remarkably high regioselectivity and stereospecificity for the hydrogen-bond DMU-catalyzed dipolar cycloaddition of CF_3-activated acrylates, reaction yields are moderate to low. DFT calculations suggest that dispersive $\pi-\pi$ stacking interactions are responsible for the regioselectivity of the (3 + 2) dipolar cycloaddition and suggest that more active catalysts would be needed. By contrast, we showed that solution photochemistry of Δ^2-1,2,3-triazolines gives good to excellent results. Direct photochemical excitation generates the singlet 1,3-biradicals, which afford the kinetically controlled *trans*- or *cis*-aziridine products with good to excellent stereospecificities, as previously reported by Scheiner with different Δ^2-1,2,3-triazolines.[16] We also found that reactions carried out using acetone as a triplet sensitizer proceed through the longer-lived triplet 1,3-birdical and give the thermodynamically favored *trans*-product regardless of the nature of the precursor. Finally, photochemical solid-to-solid reactions occur with the highest stereochemical retention values and in quantitative yields, suggesting that the reaction has synthetic potential.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02290.

Synthetic, photochemical procedures; IR, ^{1}H and ^{13}C NMR; X-ray diffraction spectra (PDF)
Crystallographic data for *trans*-**8** (CIF)
Crystallographic data for *trans*-**4** (CIF)

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Notes

The authors declare no competing financial interest.

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