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Experimental and Computational Exploration of Indolizinyl Carbene Generation. A Route to Biindolizines

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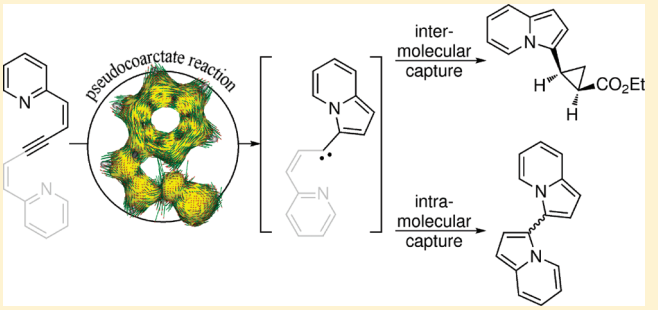
Supporting Information

ABSTRACT: In previous work, (*E*)-2-enynyl pyridines were reported to yield indolizinyl singlet carbenes through base-catalyzed *E*/*Z* isomerization followed by a 5-exo-dig pseudocoarctate cyclization. We report herein that in the presence of ethyl acrylate these carbenes undergo stereoselective cis-cyclopropanation due mainly to electrostatic interactions in the transition state. The scope of this carbene generation scheme has been further explored through the preparation of a symmetric bis(pyridylenyl)alkyne which spontaneously furnished the biindolizine core in a one-pot reaction. Computational characterization of this transformation suggests a highly asynchronous double cyclization.



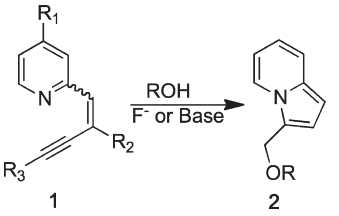
INTRODUCTION

The indolizine nucleus is present in a variety of compounds with relevant biological properties, including antiinflammatory,[1] muscular relaxant,[2] and antioxidant,[3] and as a chromophore it has shown potential usage in dyes and fluorophores.[4] The synthesis of indolizines can be accomplished through a variety of methodologies.[5] Hayford et al. reported the formation of indolyzinyl ethers via treatment of silylated (*Z*)-2-enynyl pyridines with cesium or potassium fluoride in the presence of different alcohols.[6] Later, we reported that (*E*)-2-enynyl pyridines **1** also render the corresponding indolizines **2** (Scheme 1).[7]

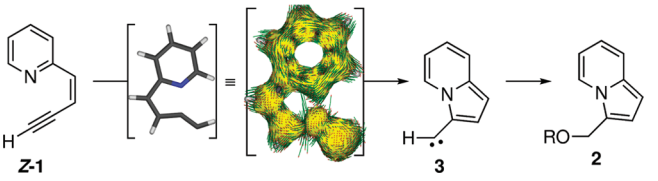
On the basis of B3LYP DFT computations we proposed as the most likely viable mechanism a nucleophile-assisted *E*−*Z* isomerization promoted by the alkoxide species present in the reaction media. The formed (*Z*)-enyne ultimately leads to an intermediate indolizinyl carbene through a 5-exo-dig cyclization step (Scheme 2). As in this last step broken and nascent bonds do not follow a cyclic path (two bonds are made and two broken on the same alkynyl carbon), it can be classified as a coarctate reaction. Similarly to the pericyclic-pseudopericyclic dichotomy, a disconnection, i.e, orthogonal orbitals, in the bonding path makes possible to further differentiate between pseudocoarctate or coarctate reactions.[8] The presence of such a disconnection can be computationally probed by inspecting the isosurfaces of the anisotropy of the current induced density (ACID),[9] a scalar field directly related to the density of the delocalized electrons.[10] ACID analysis of transition structure leading from ***Z*-1** to **2** beautifully showed the pseudocoarctate nature of this cyclization.[7]

In the presence of alcohols, carbene **3** undergoes fast formal insertion onto the OH bond to yield the corresponding ether derivative. Further support for the presence of the transient singlet carbene intermediate was provided when the reaction was

Scheme 1. Base-Catalyzed Formation of Indolizines 2 from (*Z*)- or (*E*)-2-Enynylpyridines 1



Scheme 2. Pseudocoarctate Mechanism for the 5-exo-dig Cyclization of 2-Enynyl Pyridine *Z*-1



carried out in the presence of ethyl acrylate, and a cyclopropyl derivative was obtained. The addition of singlet carbenes to alkenes, a formal $[2\pi + 2\omega]$ cycloaddition, has been the subject of theoretical investigations using different quantum chemistry methodologies.[11] Highly correlated computational methods[11d] indicate that the reaction takes place through a concerted asynchronous process where the second C−C bond is formed

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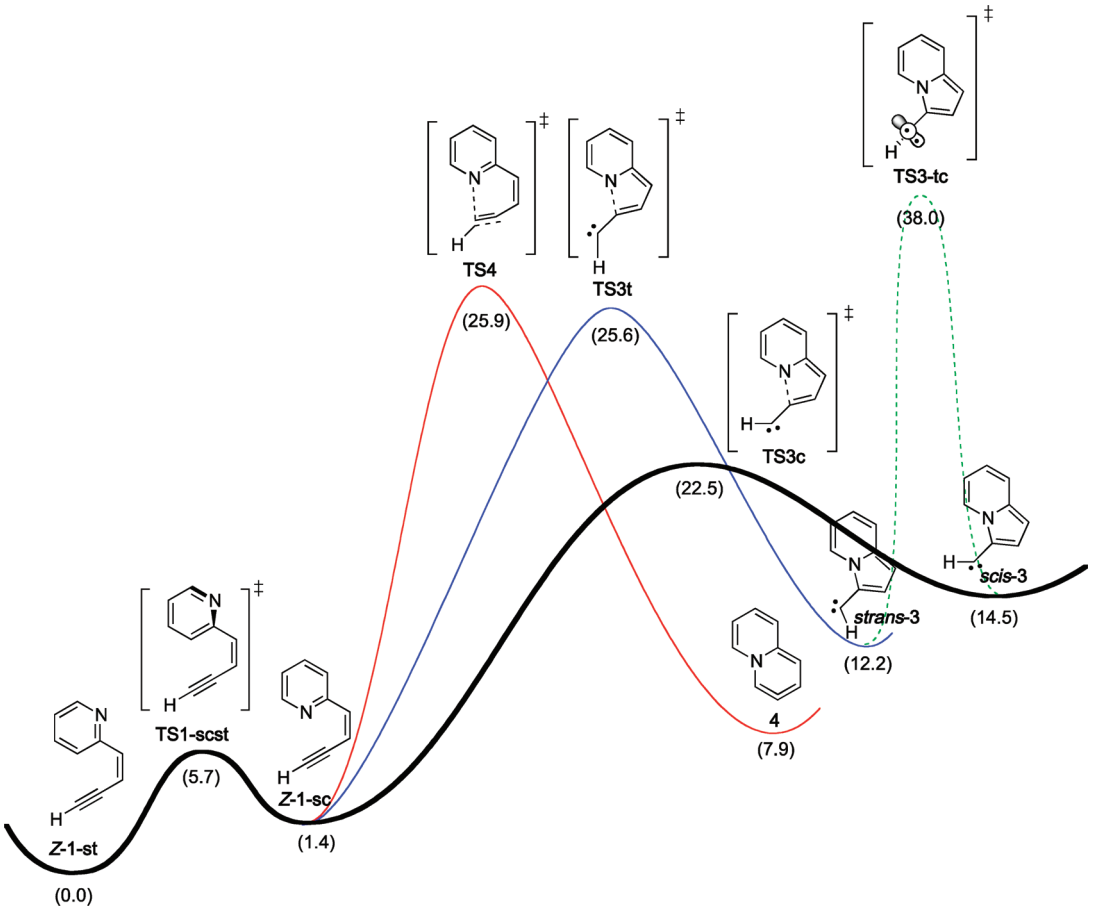

Figure 1. Potential energy surfaces for thermal cyclizations of enynylpyridine **Z-1** (Gibbs free energies ($\Delta G_{298.15K}$) relative to **Z-1-st**). The most favorable pathway is indicated by a bold line and the s-cis/s-trans isomerization by a dashed line.

late in the reaction coordinate, where the alkene approaches the empty p orbital of the carbene center.

Here we present a comprehensive experimental and computational study of the generation, structure, and reactivity of indolizinyl singlet carbenes from 2-enynyl pyridines and their potential in organic synthesis. Thus, we will show how *cis*-indolizinylcarbethoxy cyclopropane can be obtained by intermolecular trapping of a singlet carbene and how the bipyridinylenyne system affords the biindolizine skeleton via an intramolecular pseudocoarctate tandem biscyclization reaction.

COMPUTATIONAL METHODOLOGY

All computations were performed with the Gaussian09 package.[12] Structures were optimized at the DFT level of theory using the hybrid meta-GGA M06 functional,[13] as it provides general performance superior to that of standard hybrid-GGAs,[14] along with the 6-31+G** basis set in its Cartesian (6d) expression and the polarized continuum model using the integral equation formalism (IEFPCM)[15] in its Gaussian09[16] implementation with chloroform parameters. The nature of stationary points and thermochemical corrections, at 298.15 K and 1 atm, were obtained by analytical computation of harmonic vibrational frequencies. Intrinsic reaction coordinate (IRC) computations were performed using the default algorithm in Gaussian09. All relative energies are reported as Gibbs free energies at 298.15 K and 1 atm. ^{1}H NMR chemical shielding tensors were obtained by GIAO[17] DFT computations using the M06L functional[18] and Jensen's pcS-1 basis set.[19] Computed ^{1}H shieldings were transformed into chemical shifts by computation of TMS shieldings at the same level of theory. Bader's AIM analysis[20] was done on particular structures by using the AIM2000[21] program on the M06 densities. An ultrafine pruned (99,590) grid was used for all computations reported here.

RESULTS AND DISCUSSION

Generation and Structure of Singlet Indolizinyl Carbenes: Thermal Cyclization of (*Z*)-Enynyl Pyridines. M06/6-31+G** computations for the cyclization of enynyl pyridine **Z-1**, which has been experimentally prepared as an unstable intermediate from the corresponding trimethylsilylated derivative,[7] indicated that this compound prefers the s-trans conformation **Z-1-st** with the pyridyl nitrogen lying away from the reactive alkyne. **Z-1-st** has to surmount a small barrier of 5.7 kcal/mol through transition structure **TS1-scst** in order to reach the active s-cis conformation **Z-1-sc**, which lies 1.4 kcal/mol over the s-trans form (Figure 1).

As shown in Figure 1, **Z-1-sc** can render carbene **3** in its s-cis (***scis*-3**) or s-trans (***strans*-3**) conformation by a [1,5]-cyclization via transition state **TS3c** or **TS3t**, respectively, the former being 3.1 kcal/mol more stable.

The transition structure **TS3c** has an associated energy of 22.5 kcal/mol and presents a relatively late character with a forming C−N bond length of 1.91 Å and an H−C═C bond angle of 124°. Its isomerization to the most stable s-trans form could in principle be accomplished through inversion of the carbene lone pair. However, as the corresponding C−C−H

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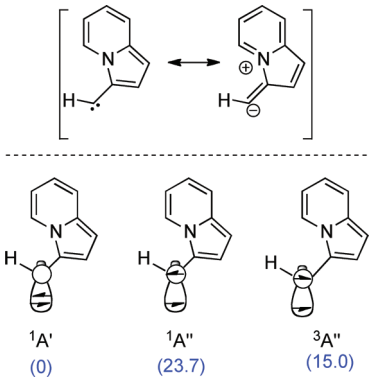


Figure 2. Main resonance structures (top) and adiabatic $\Delta G_{298.15K}$ relative free energy differences (bottom) for the different electronic states of carbene **3**.

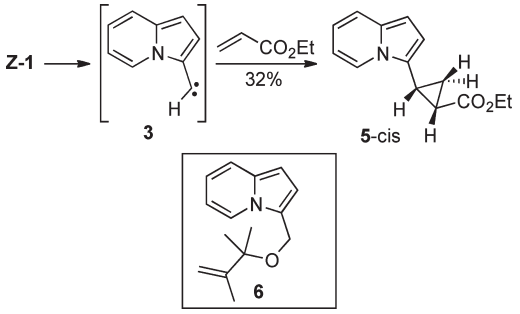
angle progressively opens, ***scis*-3** reverts to the initial enyne ***Z*-1-sc**, likely due to destabilization of the carbene center as its p character increases. An alternative mechanism for the formation of ***strans*-3** is the C−C single-bond rotation passing through a nonplanar structure where the carbene lone pair would point out of the molecular plane. However, this transition structure **TS3-ct** has open-shell character, because a closed-shell structure would imply antiaromatic destabilization of the indolizine 10-electron system.[22] As a consequence **TS3-ct** lies very high in energy (38.0 kcal/mol). It is therefore likely that carbene **3** reacts from the initially formed ***scis*-3** form before having time to isomerize to its more stable ***strans*-3** form.

We have also explored an alternative [1,6]-cyclization mode, which would lead to the cyclic aza-allene **4**. According to our computations, allene **4**, in analogy to its parent 1-aza-2,3,5-cyclohexatriene, has a planar structure, since the nitrogen electronic donation causes the cyclic allene to adopt a singlet zwitterionic electronic state.[23] Although the formation of this allene is less endergonic than the formation of ***scis*-3** or ***strans*-3** (7.9 vs 14.5 or 12.2 kcal/mol), this cyclization mode is kinetically disfavored as the corresponding transition structure **TS4** lies more than 3 kcal/mol over the transition structure **TS3c**. Note, however, that this gap leaves room for structural modifications, which could make the [1,6]-cyclization competitive with the [1,5]-mode.

In order to get a deeper knowledge of the nature of carbene **3**, computations were carried out on the three possible electronic states available to this structure. These calculations have shown that indolizinyl carbenes, in either a cis or trans conformation, prefer a singlet state of $^1A'$ symmetry due to the strongly electron donating character of the indolizine nucleus. The $^3A''$ and $^1A''$ states are quite far away from the basal closed-shell state. The basal $^1A'$ state of **3** presents an important charge transfer from nitrogen to the carbene carbon, and computed dipolar moment values were as high as 8.46 and 6.64 D for ***scis*-3** and ***strans*-3**, respectively. The computed dipolar moments of the $^1A''$ and $^3A''$ excited states of **strans-3** were 1.69 and 0.95 D respectively indicating a much smaller degree of nitrogen−carbon charge transfer. Therefore, in their basal state, indolizinyl carbenes can be better represented as a resonance hybrid between the forms depicted in Figure 2.

Reactivity of Indolizinyl Singlet Carbenes. *(a). Intermolecular Carbene Trapping: Stereoselective Formation of Indolizinyl Cyclopropanes.* In order to explore the reactivity of the indolizinyl carbene **3** and to be able to classify it as either nucleophilic or

Scheme 3. Intermolecular trapping of indolizinyl carbene 3



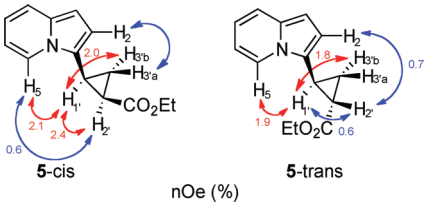


Figure 3. Observed NOE increments for the cis and trans forms of cylopropylindolizine **5**.

electrophilic, cyclopropanation reactions with rich and poor alkenes were pursued. On one part, when the 2-enynyl pyridine **Z-1** was heated in neat dimethylbutene, an electron-rich alkene, at 75 °C for 21 h, the expected cyclopropyl derivative was not obtained; instead, ether **6** was identified as a product (Scheme 3). A plausible explanation for this result is the formal insertion of carbene **3** into the O−H bond of 2,3-dimethyl-3-butenol, which is a dimethylbutene oxidation subproduct.[24]

On the other hand, when **Z-1** was heated in ethyl acrylate, the cyclopropyl derivative **5**-cis was obtained as a single diastereoisomer in 32% yield. It is worth noting that upon standing on $CDCl_3$ the addition product gradually converted to a new isomeric compound, in which the originally observed complex multiplet at 3.76 ppm arising from strong couplings of the diastereotopic CH_2 protons of the carbethoxy group transforms into a 1:3:3:1 quartet at 4.25 ppm, suggesting that the original product should correspond to the **5**-cis form, in which the indolizine moiety is closer to the CH_2 group. Consequently, the newly formed compound should be the trans isomer, **5**-trans (Figure 3), with the indolizine ring lying away from the diastereotopic methylene protons, which become nearly chemically equivalent. This transformation likely proceeds through enol formation catalyzed by traces of hydrochloric acid in the $CDCl_3$ solvent. Indeed, **5**-cis is much more stable in deuterated benzene and, when using activated alumina treated $CDCl_3$, isomerization rates were appreciably lowered. Computations have shown that the **5**-trans product is more stable than **5**-cis by 2.3 kcal/mol, in agreement with the NMR observations.

Verification of this stereochemical assignment was based on the observed NOE enhancement pattern obtained in DPFGSE 1D NOESY experiments, using a mixing time of 500 ms. The spin system of both isomers was characterized on the basis of HSQC and HMBC experiments. Irradiation of $H_{2'}$ leads to an NOE enhancement of 2.4% in $H_{1'}$, in the original product, that falls to 0.6% in the second product (Figure 2). In addition, a long-range NOE (0.6%) is observed for the indolizinyl proton H_5 upon $H_{2'}$ irradiation in **5**-cis. Irradiation of $H_{1'}$ led to the observation of 2.0

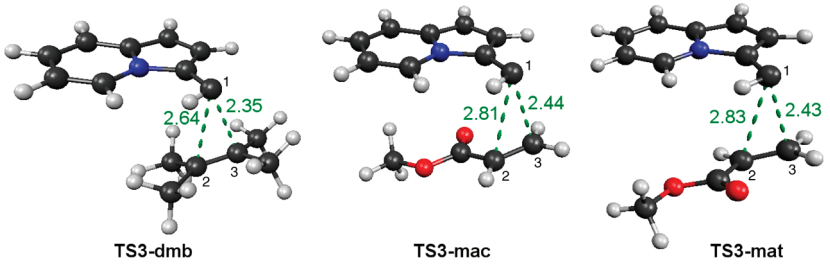


Figure 4. Transition structures for addition of singlet carbene ***scis*-3** to dimethylbutene and *s-cis*-methyl acrylate.

and 1.8% NOE's, in **5**-cis and **5**-trans, respectively, with one of the methylenic protons which was, accordingly, assigned as $H_{3'b}$. The stereochemical outcome of this reaction is similar to that reported by Baceiredo et al., where addition of phosphinosilyl carbenes to acrylate resulted in the stereoselective formation of the cis product.[25]

Remarkably, we noted that the H_1 proton of indolizine **5**-trans slightly broadens until the signal completely vanishes when the $CDCl_3$ solution was allowed to stand for a while. We attribute this behavior to progressive deuteration of the C_1 position of the indolizine nucleus due to the presence of DCl in the $CDCl_3$ solution.[26] In fact, after filtering the indolizine $CDCl_3$ solution was filtered through dry $CaCO_3$, a sharp doublet was observed again for the C_1 proton.

In light of these results, a computational investigation of the transition states associated to the addition of carbene **3** to dimethylbutene and methyl acrylate in its syn and anti approximations has been carried out and the corresponding transition states (**TS3-dmb**, **TS3-mac**, and **TS3-mat**) are depicted in Figure 4. The addition to the symmetric 2,3-dimethylbutene presents an asynchronous transition structure, **TS3-dmb** with forming bond lengths of 2.35 and 2.64 Å and a C1−C3═C2 angle of 113°. The alkene and indolizinyl systems approach nearly face to face with an angle between planes of ca. 160°. The reaction has an activation energy of 10.9 kcal/mol. Note, however, that even with such a moderate barrier the O−H formal insertion reaction seems extraordinarily competitive. This reaction with the OH group likely involves formation of a cationic intermediate[27] due to the nucleophilic nature of the indolizine carbene.

Addition of ***scis*-3** to methyl acrylate proceeds with a similar geometry but with a transition structure **TS3-mac** of earlier character, as denoted by C−C bond lengths of 2.44 and 2.81 Å. This higher asynchronicity, as compared to **TS3-dmb**, is likely caused by an improved nucleophile−electrophile matching between the reacting moieties. The corresponding transition structure for the trans-like approach, **TS3-mat,** also presents a very similar geometry. Associated activation energies for the cis-like **TS3-mac** and trans-like **TS3-mat** transition structures are 8.3 and 9.7 kcal/mol, respectively.

The observed stereoselectivity can be simply explained in terms of electrostatic effects. The computed dipole moments for the **TS3-mac** and **TS3-mat** transition structures are 6.55 and 8.70 D, respectively. In fact, switching the conformation of methyl acrylate from s-cis to s-trans in the **TS3-mac** structure, which should appreciably affect secondary orbital interactions, barely changes the activation energy of the process (8.3 vs 8.5 kcal/mol). The computed free energy of reaction for the addition of ***scis*-3** to s-cis acrylate to give the initial cyclopropane **5**-cis is largely negative ($\Delta G_{298.15K}$ = −52.5 kcal/mol).[28]

AIM (atoms in molecules) analysis[20] of the transition structure **TS3-mac** (Figure 5) showed that only a bond critical point

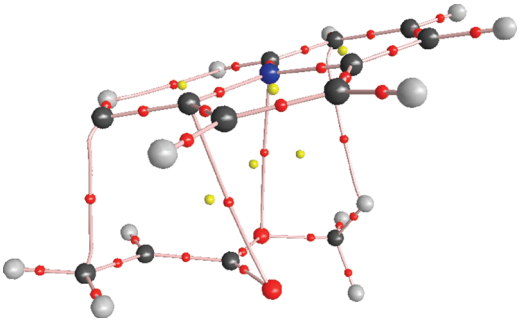
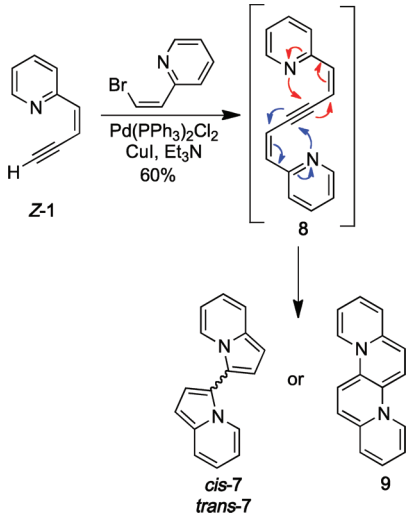


Figure 5. AIM critical points and bond paths for the transition structure **TS3-mac**: (red) bond points; (yellow) ring points.

Scheme 4. Two Tandem Pseudocoarctate Reactions: Synthesis of Biindolizine 7



for the C−C3 bond exists, thus resembling a Michael-type addition, whereas the C−C2 bond is only formed late in the reaction coordinate, accounting for the high asynchronicity of the reaction. By exploring the topology of the electron density along the reaction coordinate, we were able to confirm that the second C−C2 critical point arises later in the reaction profile (see the Supporting Information). The molecular graph shows the presence of three other weak "bonding" interactions between the acrylate and indolizinyl moieties that might contribute to stabilize the syn approximation and favor **TS3-mac**.

(b). Intramolecular Carbene Trapping: Synthesis of Biindolizines. Bis(pyridylenyl)yne **8** was prepared from the 2-enynyl pyridine ***Z*-1** and 2-bromovinylpyridine under palladium-catalyzed

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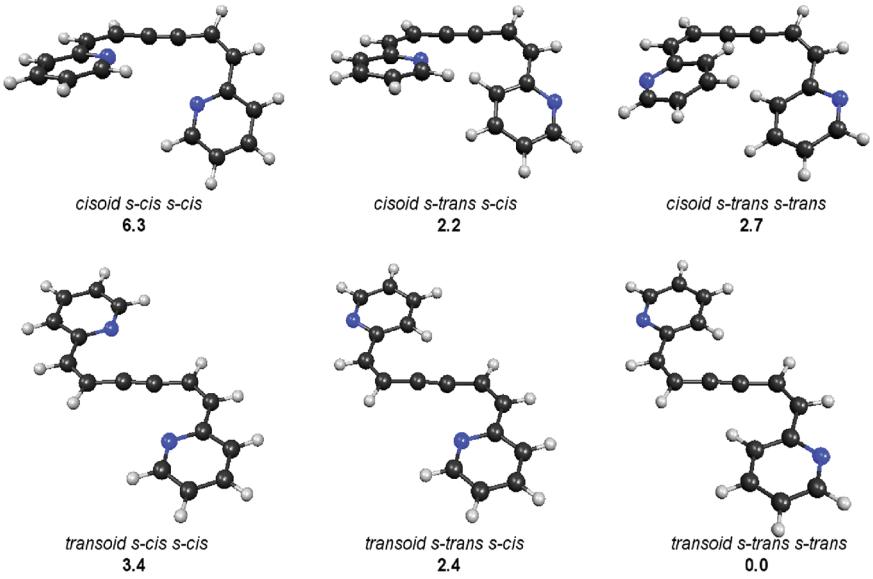

Figure 6. Relative energies for all conformations of bispyridine **8**.

Sonogashira cross-coupling conditions. Surprisingly, compound **8** suffered a spontaneous reaction that led to a single product in 60% yield (Scheme 4). The spectral data were consistent with the biindolizine structure **7**, whose ^{13}C chemical shifts were nearly identical with those already reported.[29] According to M06/6-31+G** computations, structure **7** presents two possible conformations of C_2 symmetry, s-cis and s-trans, with N−C−C−N dihedral angles of 64 and 134°, respectively, the trans form being slightly higher in energy (0.7 kcal/mol) than the cis. Note that the alternative structure diazachrysene **9**, product of a double [6,6]-cyclization, although also consistent with the 2D NMR correlations, can be easily discarded, since the ^1H resonances would be strongly shielded due to its antiaromatic character. M06L/pcS-1//M06/6-31+G** computations predict that all proton shifts of **9** would be in the 1.8−4.2 ppm range. This until now unreported 20-electron antiaromatic structure **9** is predicted to have a closed-shell nonplanar C_2 structure according to computations.

Bispyridine **8** may present several conformations due to rotation around the two pyridyl−alkene bonds, which we noted as s-trans or s-cis, and also by rotation around C−C═C bond which will result in transoid or cisoid conformations (the transoid s-cis/s-cis conformer is shown in Scheme 4). According to M06 computations the most stable form of *transoid*-**8** is the s-trans/s-trans form where the nitrogen lone pair points away from the alkyne moiety, the s-trans/s-cis and s-cis/s-cis forms being 2.4 and 3.4 kcal/mol higher in energy, respectively.

The conformational energy profile changes when we consider the cisoid conformations; s-trans/s-trans and s-cis/s-cis conformations are appreciably higher in energy, 2.7 and 6.3 kcal/mol, over the basal transoid s-trans/s-trans forms, respectively, whereas the s-trans/s-cis form is slightly most stable than its transoid counterpart, 2.4 vs 2.2 kcal/mol, respectively (Figure 6).

We attribute this change in the conformational preference to the presence of a favorable contact between the nitrogen lone pair and the proton at the 6-position of the other pyridine ring. The existence of this weak hydrogen bond has been probed by AIM analysis of the M06 density, which showed a critical bond point between those centers (Figure 7).

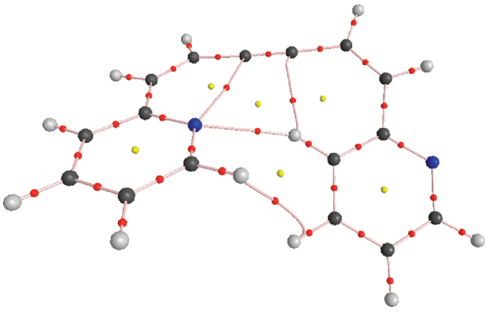

Figure 7. Critical points and bond paths fort the s-trans/s-cis conformation of bispyridine **8**: (red) bond points; (yellow) ring points.

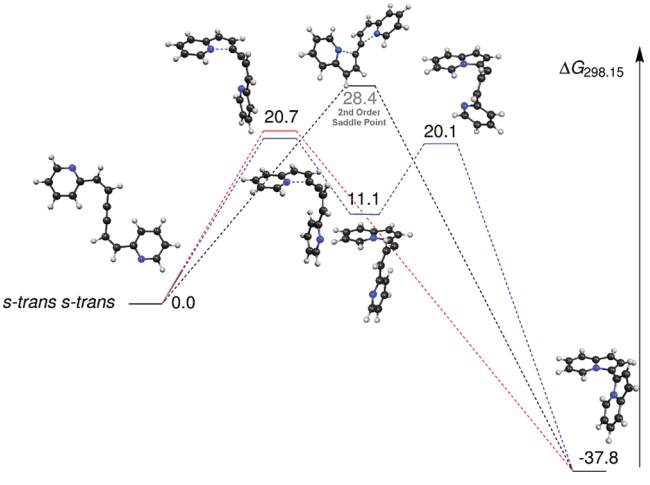

Figure 8. Potential free energy surface for biscyclization of bispyridine **8**.

The cyclization reaction of the dipyridylene-yne here presented has to proceed either from the transoid (cisoid) s-trans/s-cis or s-cis/s-cis conformers. Interestingly, both conformers undergo cyclization through nearly isoenergetic transition structures

(20.7 kcal/mol, $\Delta G_{298.15K}$).[30] In the case of the s-cis/s-cis transition structure IRC computations indicate that the product directly evolves to the final product **7**, with no intermediate transition state for the formation of the second C−N bond (Figure 8). However reaction from the s-cis/s-trans isomer proceeds through formation of an intermediate carbene, which further evolves to **7** through rotation of the pyridyl group and subsequent barrierless carbene collapse. This rotation process has an associated activation barrier from the basal state of 20.1 kcal/mol. The overall process is highly exergonic and therefore fundamentally irreversible ($\Delta G_{298.15K}$ = −37.8 kcal/mol). A C_2-symmetric structure of formal coarctate nature, corresponding to synchronous formation of the two C−N bonds, is a second-order saddle point higher in energy ($\Delta G_{298.15K}$ = 28.4 kcal/mol) than the asynchronous transition state and therefore is not relevant in the reaction pathway.

CONCLUSIONS

We have shown that enynyl pyridines undergo a stereoselective addition to ethyl acrylate through the formation of a transient nucleophilic singlet carbene to give cis-cyclopropyl indolizines. DFT computations show that the stereoselectivity of these reactions has a kinetic origin and is due to the strongly dipolar moment of the indolizine nucleus. Biindolizine was obtained in good yield when the singlet carbene was trapped intramolecularly, in a one-pot reaction in which three bonds are sequentially formed (Scheme 4). A computational analysis showed that this reaction could proceed by two pathways, one through a very asynchronous single transition structure and the other via a second carbene intermediate, although both reaction paths are almost energetically degenerate.

EXPERIMENTAL SECTION

(*Z*)-2-(But-1′-en-3′-ynyl)pyridine (*Z*-1). A solution of (*Z*)-2-(2′-bromovinyl)pyridine (300 mg, 1.64 mmol) in dry triethylamine (6.5 mL) was sparged with argon. $Pd(PPh_3)_2Cl_2$ (23 mg, 32 μmol) and CuI (18 mg, 94 μmol) were sequentially added with further sparging with argon after each addition. Then ethynyltrimethylsilane (464 μL, 3.28 mmol) was added and the mixture was stirred for 40 h at 25 °C. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 85:15), giving 241 mg (72%) of (*Z*)-2-(4′-(trimethylsilyl)-but-1′-en-3′-ynyl)pyridine (***Z*-1-TMS**)[6] and 50 mg (13%) of a compound identified as the 3,3′-biindolizine (**7**).

Next, to a solution of ***Z*-1-TMS** (68 mg, 0.33 mmol) in THF/MeOH (20/1; 3.5 mL) was added TBAF (1 M solution in THF, 670 μL, 0.67 mmol) at 25 °C. After 15 min at 25 °C, the mixture was partitioned between hexane and a saturated aqueous $NaHCO_3$ solution, the phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, and water, dried over Na_2SO_4, and concentrated in vacuo, giving 24 mg (56%) of (*Z*)-2-(but-1′-en-3′-ynyl)pyridine (***Z*-1**) as an unstable oil.

Data for ***Z*-1-TMS**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.7, 1H, H_6), 8.45 (d, *J* = 8.1, 1H, H_3), 7.66 (dt, *J* = 1.8, 7.9, 1H, H_4), 7.16 (ddd, *J* = 1.9, 4.9, 7.3, 1H, H_5), 6.86 (d, *J* = 12.3, 1H, $H_{1'}$), 5.93 (d, *J* = 12.3, 1H, $H_{2'}$), 0.24 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (C), 149.3 (CH), 140.6 (CH), 135.8 (CH), 122.9 (CH), 122.8 (CH), 110.8 (CH), 103.9 (C), 102.9 (C), −0.30 (CH_3, $Si(CH_3)_3$); MS (EI^+) *m*/*z* (%) 201 ([M^+], 15), 200 (46), 69 (100).

Data for ***Z*-1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 3.8, 1H), 8.34 (d, *J* = 8.0, 1H), 7.69 (t, *J* = 7.7, 1H), 7.21−7.15 (m, 1H), 6.91 (d, *J* = 12.3, 1H), 5.91 (dd, *J* = 2.6, 12.3, 1H), 3.42 (s, 1H).

3,3′-Biindolizine (7). To a solution of ***Z*-1** (24 mg, 0.18 mmol) in Et_3N (0.5 mL) were added a degassed solution of $Pd(PPh_3)_2Cl_2$ (1.3 mg, 1.86 μmol), CuI (1.2 mg, 6.28 μmol), and (*Z*)-bromovinylpyridine (17 mg, 0.09 mmol) in Et_3N (1 mL). The mixture was stirred at 25 °C for 19 h. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 85/15), giving 13 mg (60%) of 3,3′-biindolizine (**7**).

^{1}H NMR (400 MHz, C_6D_6): δ 7.40 (dd, *J* = 1.0, 7.1, 2H, H_5), 7.33 (d, *J* = 9.0, 2H, H_8), 7.02 (d, *J* = 4.0, 2H, H_2), 6.70 (d, *J* = 4.0, 2H, H_1), 6.51 (ddd, *J* = 1.0, 6.5, 9.0, 2H, H_7), 6.10 (dt, *J* = 1.2, 7.2, 2H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.0 (C, C_9), 123.4 (CH, C_5), 119.6 (CH, C_8), 117.6 (CH, C_7), 115.9 (CH, C_2), 115.4 (C, C_3), 110.9 (CH, C_6), 99.5 (CH, C_1). MS (EI^+): *m*/*z* (%) 233 (15), 232 ([M^+], 100), 231 (49), 230 (20), 229 (10), 155 (6), 154 (47), 153(7), 152 (5). HRMS (EI^+): *m*/*z* calcd for $C_{16}H_{12}N_2$ 232.1000, found 232.1003.

3-(3′,3′,4′-Trimethyl-2′-oxapent-4′-en-1′-yl)indolizine (6). To a solution of ***Z*-1**-TMS (150 mg, 0.74 mmol) in THF/MeOH (20/1; 10 mL) was added TBAF (1 M solution in THF, 1.5 mL, 1.5 mmol) at 25 °C. After 15 min at 25 °C, the mixture was partitioned between hexane and a saturated aqueous $NaHCO_3$ solution, the phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, and water, dried over Na_2SO_4, and concentrated in vacuo. The resultant oil ***Z*-1** was washed with benzene, purged under an argon atmosphere (15 min), and redissolved in dimethylbut-2-ene (2 mL) and the solution stirred for 21 h at 75 °C. Then the solvent was removed under reduced pressure, the crude residue was dissolved in AcOEt, and the solution washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on SiO_2 (hexane/ethyl acetate 95/5) gave 42 mg (35%) of **6**, among other uncharacterized products.

^{1}H NMR (400 MHz, C_6D_6): δ 7.98 (d, *J* = 7.0, 1H, H_5), 7.20 (d, *J* = 9.0, 1H, H_8), 6.72 (d, *J* = 3.8, 1H, H_1), 6.46 (d, *J* = 3.8, 1H, H_2), 6.44−6.37 (m, *J* = 6.5, 8.1, 1H, H_7), 6.21 (t, *J* = 6.7, 1H, H_6), 5.00 − 4.84 (m, 2H, $H_{5'}$), 4.38 (s, 2H, $H_{1'}$), 1.69 (d, *J* = 9.0, 3H, $H_{4'}$-Me), 1.23 (s, 6H, $H_{3'}$-$(Me)_2$). ^{13}C NMR (100 MHz, C_6D_6): δ 149.3 (C, $C_{4'}$), 134.4 (C, C_9), 123.9 (CH, C_5), 122.4 (C, C_3), 119.9 (CH, C_8), 117.2 (CH, C_7), 114.5 (CH, C_2), 112.9 (CH_2, $C_{4'}$-CH_2), 110.5 (CH, C_6), 99.2 (CH, C_1), 77.7 (C, $C_{3'}$), 57.5 (CH_2, $C_{1'}$), 26.2 (CH_3, $C_{3'}$-$(Me)_2$), 19.8 (CH_3, $C_{4'}$-Me). MS (EI^+): *m*/*z* (%) 230 (3), 229 ([M^+], 23), 146 (11), 145 (57), 131 (18), 130 (100), 117 (23), 116 (4). HRMS (IE^+): *m*/*z* calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1476.

(1′*RS*,2′*SR*)-Ethyl 2-(Indolizin-3-yl)cyclopropanecarboxylate (5-cis). To a solution of ***Z*-1-TMS** (240 mg, 1,18 mmol) in ethyl acrylate (5 mL) was added CsF (270 mg, 1.77 mmol) and MeOH (38 mg, 1,18 mmol). The mixture was stirred for 4.5 h at 70 °C under argon. Then, ethyl acrylate was removed under reduced pressure and the crude residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on SiO_2 (hexane/ethyl acetate 90/10) gave 76 mg (32%) of ethyl 2-(indolizin-3-yl)cyclopropanecarboxylate and 11 mg (6%) of 3-methoxymethylindolizine, among other indolizines that were not characterized.

When **5**-cis was allowed to stand in $CDCl_3$ for several days, it underwent an isomerization reaction and (1′*RS*,2′*RS*)-ethyl 2-(indolizin-3-yl)-cyclopropanecarboxylate (**5**-trans) was obtained.

Data for **5**-cis: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 0.9, 7.1, 1H, H_5), 7.31 (dt, *J* = 1.2, 8.9, 1H, H_8), 6.65 (3.9, 1H, H_2), 6.61 (ddd, *J* = 0.9, 6.4, 8.9, 1H, H_7), 6.49 (td, *J* = 1.3, 6.9, 1H, H_6), 6.35 (d, *J* = 3.9, 1H, H_1), 3.76 (m, 2H, $-CO_2CH_2CH_3$), 2.46 (q, *J* = 8.0, 1H, $H_{1'}$), 2.18 (dt, *J* = 5.8, 8.0, 1H, $H_{2'}$), 1.77 (ddd, *J* = 4.8, 5.7, 8.0, 1H, $H_{3'b}$), 1.48 (dt, *J* = 4.8, 8.0, 1H, $H_{3'a}$), 0.79 (t, *J* = 7.1, 3H, $-CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, C_6D_6) δ 170.1 (C, $-CO_2Et$), 133.7 (C, C_9), 122.7 (CH, C_5), 120.7 (C, C_3), 119.9 (CH, C_8), 116.4 (CH, C_7), 115.3 (CH, C_1), 110.3

(CH, C_6), 99.2 (CH, C_2), 60.4 (CH_2, $-OCH_2CH_3$), 21.3 (CH, $C_{2'}$), 16.7 (CH, $C_{1'}$), 14.1 (CH_3, $-OCH_2CH_3$), 11.5 (CH_2, $C_{3'}$); MS (EI^+) m/z (%) 230 (6), 229 ([M^+], 35), 228 (4), 157 (16), 156 (100), 154 (81); HRMS (EI^+) m/z calcd for $C_{14}H_{15}NO_2$ 229.1103, found 229.1104.

Data for **5**-trans: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.1, 1H, H_5), 7.34 (dt, J = 1.1, 9.0, 1H, H_8), 6.66 (ddd, J = 1.0, 6.5, 8.9, 1H, H_7), 6.54 (td, J = 1.1, 6.9, 1H, H_6), 6.51 (s, 1H, H_2), 6.33 (s, 1H, H_1), 4.25 (q, J = 7.1, 2H, $-CO_2CH_2CH_3$), 2.52 (ddd, J = 4.2, 6.4, 9.2, 1H, $H_{1'}$), 1.81 (ddd, J = 4.2, 5.0, 8.4, 1H, $H_{2'}$), 1.63 (ddd, J = 4.2, 5.0, 9.2, 1H, $H_{3'b}$), 1.35 (ddd, J = 4.3, 6.4, 8.4, 1H, $H_{3'a}$), 1.30 (t, J = 7.1, 3H, $-CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 173.62 (C, $-CO_2Et$), 133.34 (C, C_9), 122.67 (C, C_3), 122.26 (CH, C_5), 119.51 (CH, C_8), 116.75 (CH, C_7), 111.83 (CH, C_2), 110.64 (CH, C_6), 98.05 (CH, C_1), 61.07 (CH_2, $-OCH_2CH_3$), 21.68 (CH, $C_{2'}$), 17.55 (CH, $C_{1'}$), 14.88 (CH_2, $C_{3'}$), 14.52 (CH_3, $-OCH_2CH_3$); HRMS (EI^+) m/z calcd for $C_{14}H_{15}NO_2$ 229.1103, found 229.1111.

■ ASSOCIATED CONTENT

Supporting Information. Tables and figures giving ^{1}H, ^{13}C, and 2D NMR spectra of compounds ***Z*-1-TMS**, **5**-cis, **5**-trans, **6**, and **7**, ^{1}H NMR spectrum of ***Z*-1**, and Cartesian coordinates and free energy of all computed species, and 2D potential surface scan for addition of 3 to methylacrylate. This material is available free of charge via the Internet at http://pubs.acs.org.

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