

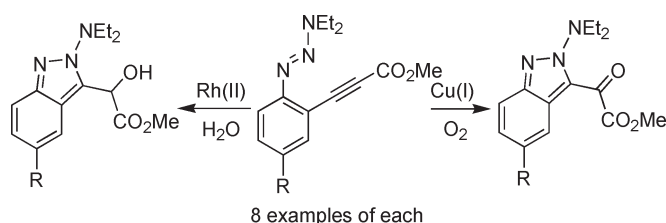
Synthesis of α -Ketoester- and α -Hydroxyester-Substituted Isoindazoles via the Thermodynamic Coarctate Cyclization of Ester-Terminated Azo-Ene-Yne Systems

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The synthesis of isoindazoles bearing α -ketoester and α -hydroxyester groups via the coarctate cyclization of ester-terminated azo-ene-yne precursors is described. Whereas previous studies on isoindazole formation have shown the reaction to proceed through a kinetic coarctate pathway, functionalization of the terminal acetylene with a methyl ester sufficiently stabilizes the carbene intermediate to make the coarctate cyclization the thermodynamic pathway. Density functional theory (DFT) computations reveal ca. 8–9 kcal mol⁻¹ lower energy transition states for the coarctate pathway compared to the parent system.

Introduction

Recently there has been considerable interest in the cyclization reactions of “ene-ene-yne” systems (compounds

that possess alternating double-single-double-single-triple bonds) to prepare a variety of 5-membered aromatic heterocycles.¹ Such heterocyclic compounds have found uses as diverse as incorporation into organic light emitting devices to utilization as pharmacophores in medicinal applications.^{2–4} Our laboratory has been studying a subset of “ene-ene-yne” reactions, namely, the coarctate cyclization of azo-ene-yne^{5–8} and azo-ene-nitrile⁹ systems. Our interest began with the discovery that *o*-ethynylphenyltriazenes (**1**) could undergo two different cyclization pathways by simple modification of the reaction conditions (Figure 1).⁵ Treatment of **1** with

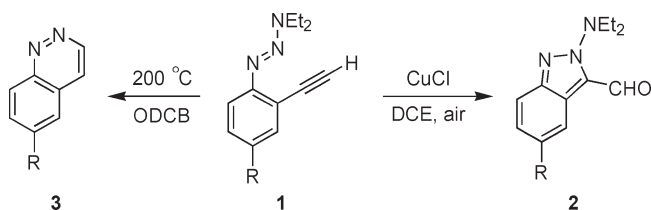


FIGURE 1. Dual cyclization pathways of azo-ene-yne **1**.

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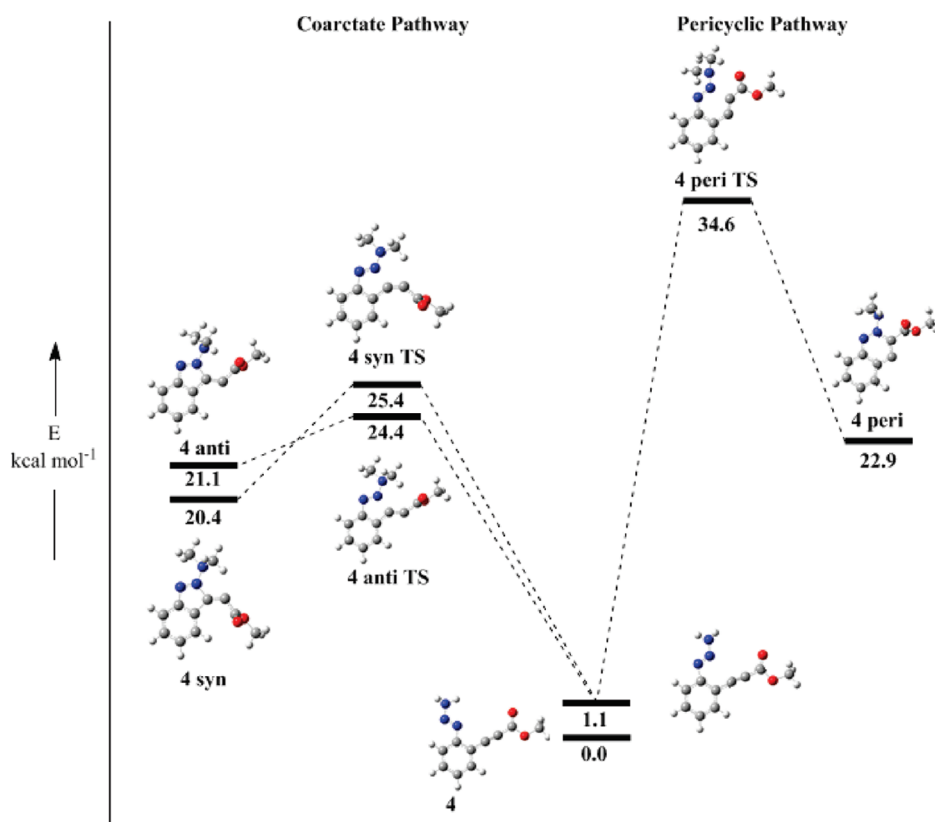


FIGURE 2. DFT (B3LYP/6-31G* + ZPE) calculated relative energies of reactants, transition states, and products for the cyclization of the NMe₂ analogue of ester **4** to isoindazole carbenes and the cinnoline zwitterion.

CuCl led to the formation of the isoindazole ring system (**2**) via a carbene/carbenoid intermediate whereas thermolysis at 200 °C led to the formation of cinnoline derivatives (**3**).

The ability of the one precursor to undergo different cyclizations affording two classes of heterocycles in high yield was very intriguing both synthetically and mechanistically. Whereas the formation of **3** occurs via a pericyclic mechanism, the generation of **2** arises from a coarctate cyclization,⁵ a relatively rare type of concerted reaction mechanism that involves the making and breaking of two bonds at a single atom.¹⁰ Coarctate reactions generally entail the making or breaking of five-membered ring systems along with the formation of an exocyclic carbene/carbenoid intermediate, which can be trapped in a number of ways.^{1,11} Computational analysis of the experimental results confirmed that azo-ene-yne systems do indeed possess dual cyclization pathways, and that the pericyclic pathway is the thermodynamically favored route;^{5–8} however, the pericyclic pathway is often not observed because of additional, high-energy reactions needed to furnish isolable products.^{6–8} On

the basis of the previous works, we theorized that by internally stabilizing the carbene intermediate, it might be possible to make the coarctate cyclization the thermodynamically favored pathway. To that end, incorporation of a methyl ester on the terminus of the azo-ene-yne skeleton should allow for a more facile cyclization reaction and access to functionality not previously available. Herein we present our computational and experimental results which corroborate isoindazole formation via a thermodynamically favored coarctate reaction.

Results and Discussion

Computational Studies. The cyclization of ester **4** was examined by using the Gaussian 03¹² suite of programs at the B3LYP level of theory¹³ and the 6-31G* basis set, which

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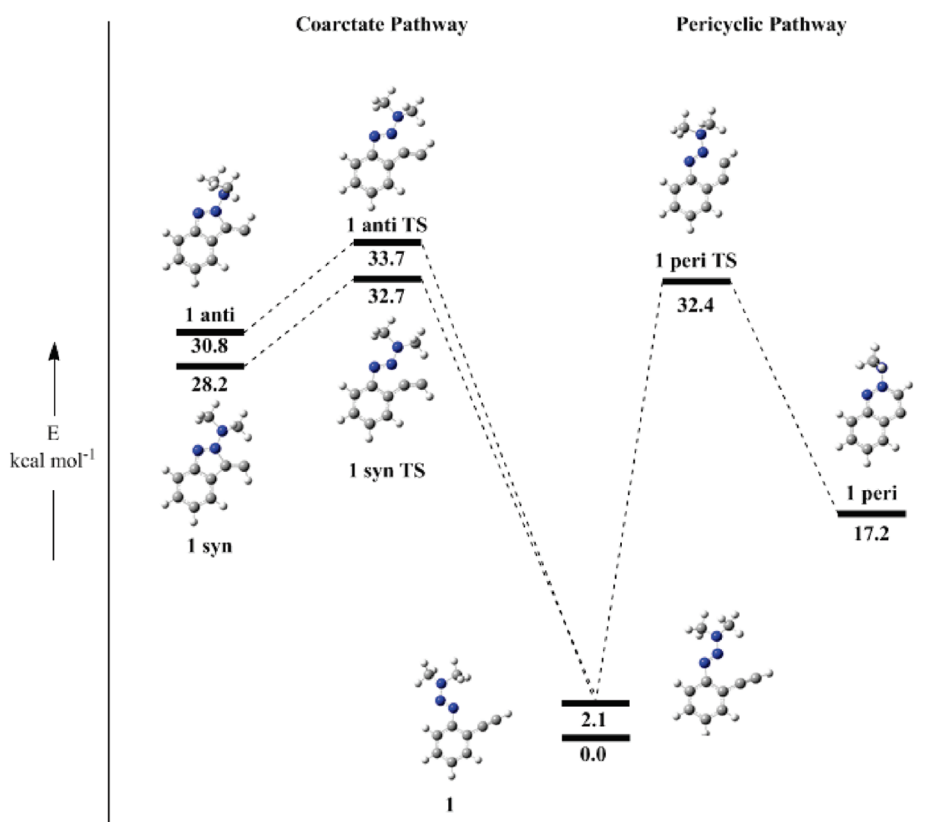


FIGURE 3. DFT (B3LYP/6-31G* + ZPE) calculated relative energies of the reactants, transition states, and products for the cyclization of the NMe₂ analogue of **1** to isindazole carbenes and cinnoline zwitterion.

has been found to be a good balance of computational cost and accuracy in our previous cyclization studies.^{5–8} To reduce the number of conformational degrees of freedom and to save on computational cost, we replaced the NEt₂ group with NMe₂. In previous studies, we computationally examined the cyclizations of NH₂-terminated triazenes; however, with the current system there appeared to be a hydrogen-bonding interaction between the unsubstituted NH₂ group and the carbene. A NMe₂-substituted triazene eliminated this interaction (Figure 2). To compare this system to the parent terminal alkyne, the corresponding cyclization of **1** had to be reevaluated computationally by using a NMe₂-terminated triazene (Figure 3).

As expected, incorporation of the carbomethoxy group leads to a lower energy pathway for the coarctate cyclization versus the pericyclic cyclization by stabilizing the carbene intermediate. The intermediate energies for the syn and anti products (where syn and anti refer to the orientation of the ester to the benzene ring) were lowered by 8.4 and 9.7 kcal mol^{–1}, respectively. A similar change is seen with the transition states (TS) where the syn and anti TS dropped by 7.3 and 9.3 kcal mol^{–1}, respectively. What is interesting, and unexpected, was that the pericyclic cyclization rose in energy, such that both coarctate intermediates are the lowest energy intermediates between the two pathways; thus, incorporation of the methyl ester into the ene-ene-yne scaffold creates a thermodynamic coarctate cyclization. This is achieved in two ways: (1) by stabilizing the carbene intermediate/TS to give the lower energy pathway and (2) by destabilizing the pericyclic pathway. In the case of the pericyclic cyclization,

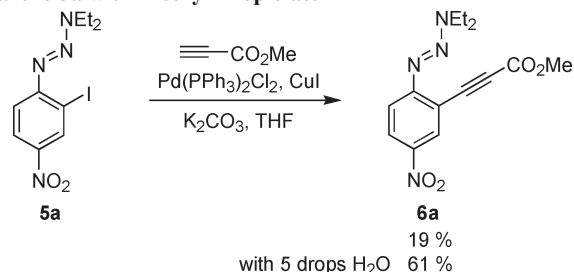
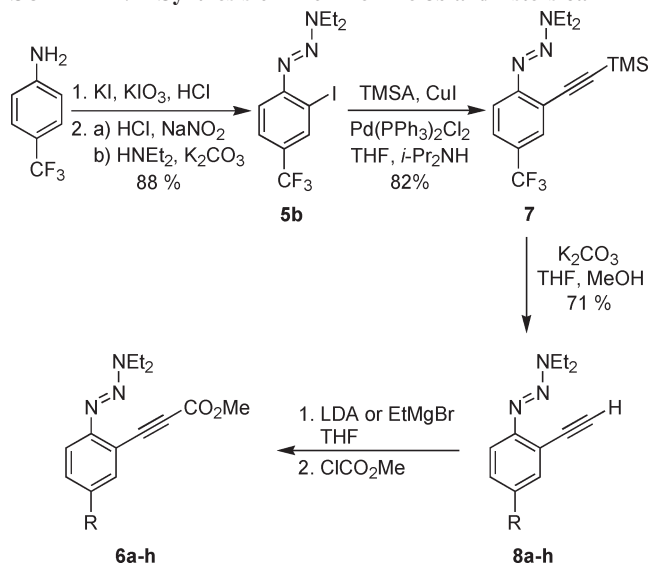
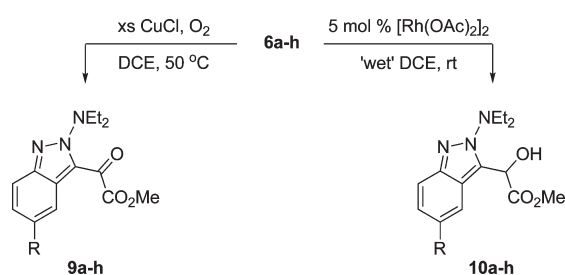
the relative intermediate energy raises by 5.7 kcal mol^{–1} while the TS raises slightly by only 2.2 kcal mol^{–1}. This indicates that we can precisely manipulate the energetics of the cyclization to favor the coarctate pathway, while at the same time disfavoring the pericyclic cyclization. Transition state analysis indicates that the systems are reacting via “true” coarctate and pericyclic mechanisms (see the Supporting Information).

Experimental Studies. The initially envisioned route for the cyclization precursors was a modified Sonogashira cross-coupling between known iodotriazene **5a**^{5c} and methyl propiolate (Scheme 1); however, this “straightforward” method proved problematic. K₂CO₃ was used as the base to minimize deleterious 1,4-additions to the alkyne, according to the procedure of Eckert and Ipaktschi.¹⁴ Unfortunately, we obtained only low (<20%) yields of the desired product **6a**. The addition of a few drops of water to solubilize the base did lead to higher but considerably variable yields; thus, an alternative route was pursued.

The preferential synthesis of the cyclization precursors is illustrated in Scheme 2, using commercially available *p*-trifluoromethylaniline. Iodination¹⁵ followed by triazene formation furnished arene **5b**. Sonogashira cross-coupling with TMSA gave **7**, and subsequent protidesilylation afforded azo-ene-yne **8b** in 52% overall yield for the four steps. Analogues **8a,c–h** were prepared in a similar manner as

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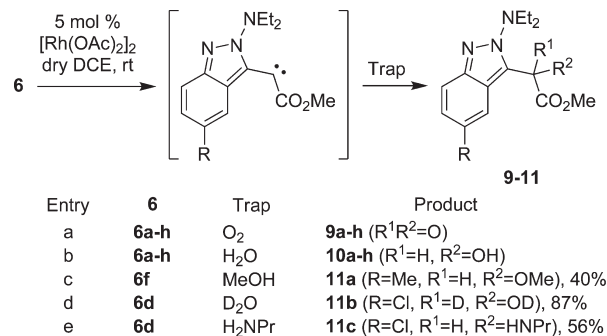
SCHEME 1. Modified Sonogashira Cross-Coupling of Iodo-triazene 5a with Methyl Propiolate

SCHEME 2. Synthesis of Azo-Ene-Yne 8b and Esters 6a–h

SCHEME 3. Cyclization of 6 Affording Isoindazoles 9 or 10


previously described.^{5a,c} Deprotonation with either LDA (**8a,c**) or EtMgBr (**8b,d–h**) in THF followed by addition of methyl chloroformate gave esters **6a–h** in 65–85% yields (Table 1).

With the desired precursors in hand, we examined several different metal salts to mediate the cyclization, and found that, similar to our previous studies, CuCl proved optimal for the cyclization of **6** to isoindazole-substituted α -ketoesters **9** in 60–90% yield (Scheme 3, Table 1). As the calculations suggested, we observed a remarkable decrease in the reaction time indicative of a lower energy pathway: whereas **1** required heating to 50 °C for 16 h with excess CuCl,⁵ ester **6** needed only 4 h at 50 °C to cyclize completely to **9**. The reaction could also be carried out overnight (14 h) at room temperature. All other copper-mediated conditions (e.g., 5%

TABLE 1. Yields (%) for Ester 6 and Isoindazoles 9 and 10

| entry | R | 6 | 9 | 10 |
|-------|-----------------|----|----|----|
| a | NO ₂ | 66 | 85 | 95 |
| b | CF ₃ | 68 | 85 | 99 |
| c | CN | 85 | 92 | 92 |
| d | Cl | 82 | 60 | 95 |
| e | H | 75 | 75 | 95 |
| f | Me | 68 | 88 | 90 |
| g | <i>t</i> -Bu | 65 | 88 | 95 |
| h | OMe | 65 | 69 | 88 |

SCHEME 4. Cyclization of 6 and Trapping of the Carbene Intermediate


CuCl, excess CuI, excess Cu(OAc)₂, excess CuCl₂) failed to give any appreciable amount of **9**.

Interestingly, when using [Rh(OAc)₂]₂ as a catalyst, we did not obtain α -ketoester **9**. The ¹H NMR spectrum of the new material showed two doublets (δ 5.95 and 4.14 ppm for **10a**, J = 6.1 Hz) and asymmetric methylene signals of the diethylamino group, the latter result not observed in any of our prior studies. A strong band in the IR spectrum typical of an O–H stretch suggested the presence of an alcohol group. This was corroborated by shaking the NMR sample (in CDCl₃) with D₂O, which resulted in collapse of the doublet at 5.95 ppm to a singlet and the loss of the signal at 4.15 ppm. Taken as a whole, the data suggested that the carbene/carbenoid had been trapped with a molecule of water via an O–H insertion to afford α -hydroxyester **10a**, a result confirmed by X-ray diffraction (see the Supporting Information). While carbenes are known to undergo O–H insertion reactions, this product was unexpected as water was not intentionally added to the reaction. With vigorous attempts to exclude water (flame-dried glassware, distilled solvents, etc.), the formation of **10** could be suppressed and instead **9** was obtained after several days. Whereas the CuCl-mediated cyclization required excess salt, the [Rh(OAc)₂]₂ cyclizations occurred with as little as 5 mol % of catalyst. These reaction conditions were amenable to a range of substituents, from electron withdrawing to electron donating, all with very good yields. Overall the yields tended to be higher with the Rh-catalyzed reaction than in the Cu-mediated cyclization. Both reactions were very clean, requiring only filtration through a pad of silica to afford pure compounds.

The fact that we could induce cyclization with known carbene/carbenoid stabilizers to afford isoindazoles possessing functionality archetypical of reactions involving carbenes again suggested the presence of such reactive intermediates. In addition to **9** and **10**, we successfully

trapped the carbene/carbenoid (Scheme 4) via O–H insertion (methanol, **11a**), O–D insertion (deuterated water, **11b**), and N–H insertion (propylamine, **11c**). Attempts to demonstrate carbene/carbenoid intermediacy via a [2 + 1] cycloaddition with tetramethylethylene, as done in our prior studies, were unsuccessful. This is likely due to the inability of the sterically crowded carbene to approach the tetrasubstituted alkene, as can be inferred from the crystal structure of **10a** (see the Supporting Information).

Conclusion

In summary, functionalization of **1** with a terminal methyl ester moiety results in stabilization of the carbene intermediate and thus leads to a thermodynamic coarctate cyclization. Computations indicate ca. 8–9 kcal mol^{−1} lower TS barrier and experimental evidence corroborates the lower energy pathway. By using ether CuCl or [Rh(OAc)₂]₂ to induce cyclizations, we were able to trap the isoindazole carbene with molecular oxygen to give α -ketoesters **9a–h** or water to afford α -hydroxyesters **10a–h** in good to excellent yields. Work on transforming **9** into non-natural amino acids is ongoing.

Experimental Section

General Methods. These have been described previously in ref 5.

General Procedure A: Ester Formation with EtMgBr. Alkyne **8** (1 equiv) was dissolved in freshly distilled THF (0.1 M) under an Ar atmosphere. EtMgBr (0.98 equiv, 1 M in THF) was added dropwise and the reaction was allowed to stir at room temperature until the evolution of ethane ceased (~2 h). The reaction was then cooled to −78 °C and methyl chloroformate (1.5 equiv) was added dropwise. The reaction was allowed to stir at −78 °C for 1 h before slowly warming to room temperature. The reaction was quenched with aq saturated NaHCO₃ solution then diluted with EtOAc and the layers were separated. The organic layer was then washed with water twice and then brine. The organic layer was dried (MgSO₄) and filtered through a short pad of silica. The solvent was removed in vacuo and the residue was purified via column chromatography.

General Procedure B: Ester Formation with LDA. A solution of *i*-Pr₂NH (1.15 equiv) in freshly distilled THF (1 M based on *i*-Pr₂NH) was cooled to −78 °C under an Ar atmosphere. BuLi (1.1 equiv, 2.5 M in hexanes) was added slowly and the mixture was stirred at −78 °C for 1 h. In a second flask, alkyne **8** (1 equiv) was dissolved in freshly distilled THF (0.1 M based on **8**) and cooled to −78 °C under Ar. The LDA solution was transferred via cannula into the solution of **8** and the reaction was stirred at −78 °C for 2 h. With continued cooling at −78 °C, methyl chloroformate (1.5 equiv) was added and the reaction was stirred at −78 °C for 1 h before slowly warming to room temperature. The reaction was quenched with aq saturated NaHCO₃ solution then diluted with EtOAc and the layers were separated. The organic layer was then washed with water twice and then brine. The organic layer was dried (MgSO₄) and filtered through a short pad of silica. The solvent was removed in vacuo and the residue was purified via column chromatography.

General Procedure C: CuCl-Mediated Cyclization. 1,2-Dichloroethane (0.02 M) was bubbled with O₂ for 30 min, after which ester **6** (1 equiv) and CuCl (10 equiv) were added. The sealed flask was heated to 50 °C until TLC indicated the complete consumption of **6** (ca. 4 h). Upon completion, the cooled reaction was filtered through a pad of silica eluting with

1:1 hexanes:EtOAc and the solvent was removed in vacuo to afford pure **9**.

General Procedure D: [Rh(OAc)₂]₂-Catalyzed Cyclization. Ester **6** (1 equiv) and [Rh(OAc)₂]₂ (5 mol %) were dissolved in 1,2-dichloroethane (0.02 M) and the mixture was stirred at room temperature open to the air. Upon completion (TLC), the reaction was filtered through a pad of silica eluting with 1:1 hexanes:EtOAc and the solvent was removed in vacuo to afford pure **10**.

Iodotriazene 5b. 4-(Trifluoromethyl)aniline (3.0 g, 18.8 mmol), KIO₃ (1.40 g, 6.6 mmol), and KI (2.07 g, 12.5 mmol) were dissolved in water (60 mL) and methanol (10 mL). HCl (1M, 20.5 mL, 20.5 mmol) was added dropwise to the stirred solution over a period of 45 min. Upon complete addition of the HCl, the reaction was stirred for 3 h, diluted with water, and extracted three times with CH₂Cl₂. The combined organics were washed with aq NaHSO₃ (2×), water (2×), and brine. The organic layer was dried (MgSO₄) and filtered through a pad of silica then the solvent was removed in vacuo to yield 2-iodo-4-(trifluoromethyl)aniline as a tan solid. The product was immediately dissolved in a minimal amount of MeCN and treated with conc HCl (10 mL, 120 mmol) with stirring. The reaction was cooled to −10 °C and a solution of NaNO₂ (2.5 g, 36.2 mmol) in water (15 mL) and MeCN (5 mL) was added slowly such that the internal temperature stayed below 0 °C. Upon completion the mixture was allowed to stir for 45 min at −10 °C. The diazonium solution was transferred via cannula to a stirred quench solution of HNEt₂ (18.1 mL, 172 mmol) and K₂CO₃ (11.9 g, 86.1 mmol) in water (150 mL) and MeCN (50 mL) cooled to −10 °C. After warming to room temperature overnight, the reaction was extracted three times with ether. The organic layer was dried (MgSO₄) and filtered through a pad of silica then solvent was removed in vacuo to yield **5b** (6.08 g, 88%) as a red oil. ¹H NMR (CDCl₃) δ 8.06 (d, *J* = 1.2 Hz, 1H), 7.51 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 3.83 (q, *J* = 7.4 Hz, 4H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃) δ 136.2, 136.1, 136.0, 125.7, 125.6, 117.0, 95.7, 49.6, 42.6, 14.4, 10.8. IR (NaCl) ν 2977, 2936, 2875, 1317, 1254, 1121, 1074 cm^{−1}. HRMS (EI+) for C₁₁H₁₃N₃F₃: calcd 371.01066, found 371.01190.

Ester 6a via Modified Sonogashira Cross-Coupling. Iodotriazene **5a** (92 mg, 0.26 mmol), Pd(PPh₃)₂Cl₂ (4 mg, 0.005 mmol, 2 mol %), CuI (2 mg, 0.01 mmol, 4 mol %), and K₂CO₃ (144 mg, 1.04 mmol) were dissolved in freshly distilled THF (2 mL) and water (5 drops) in a screw-top reaction vessel. The solution was purged with Ar for 45 min, then methyl propiolate (0.1 mL, 1.04 mmol) was added. The sealed vessel was heated to 65 °C overnight. Upon cooling, the carbonate was filtered and the solvent was removed in vacuo. The crude material was dissolved in ether and the solution was filtered through a pad of silica and then concentrated. The residue was purified by preparative TLC (CH₂Cl₂) to yield **6a** (50 mg, 61%) as a yellow solid. ¹H NMR (CDCl₃) δ 8.42 (d, *J* = 2.7 Hz, 1H), 8.18 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 3.90 (q, *J* = 7.2 Hz, 4H), 3.84 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃) δ 158.6, 154.2, 143.5, 129.6, 126.2, 117.0, 114.6, 85.1, 83.0, 52.7, 50.2, 43.2, 14.2, 10.6. IR (NaCl) ν 2979, 2225, 1713, 1575, 1516, 1320, 1253, 1083 cm^{−1}. HRMS (EI+) for C₁₄H₁₆N₄O₄: calcd 304.11715, found 304.11908.

Ester 6a via General Procedure B. Triazene **8a** was reacted according to General Procedure B. Purification as above afforded **6a** (0.054 g, 66%) as a yellow solid whose spectral data were identical with those given above.

Triazene 7. A stirred solution of **5b** (6.08 g, 16.4 mmol), CuI (125 mg, 0.6 mmol, 4 mol %), and Pd(PPh₃)₂Cl₂ (220 mg, 0.3 mmol, 2 mol %) in freshly distilled THF (80 mL) and *i*-Pr₂NH (80 mL) was purged with Ar for 45 min. TMSA (9.3 mL, 65.5 mmol) was added and the reaction was stirred at room temperature until TLC indicated completion. The solvent

was then removed in vacuo and the crude solid was dissolved in 9:1 hexanes:CH₂Cl₂. The mixture was filtered through a pad of silica eluting with 4:1 hexanes:CH₂Cl₂ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (9:1 hexanes:CH₂Cl₂) to yield **7** (4.60 g, 82%) as a dark oil. ¹H NMR (CDCl₃) δ 7.73 (d, *J* = 1.8 Hz, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.45 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.82 (q, *J* = 7.5 Hz, 4H), 1.33 (m, 6H), 0.25 (s, 9H). ¹³C NMR (CDCl₃) δ 155.1, 130.4, 126.4, 126.0, 125.6, 122.3, 118.2, 116.9, 102.0, 99.4, 49.5, 42.2, 14.4, 10.9, −0.08. IR (NaCl) ν 2965, 2938, 2901, 2160, 2068, 1607, 1456, 1422, 1190 cm^{−1}. HRMS (EI+) for C₁₆H₂₂N₃F₃Si: calcd 341.15351, found 341.15484.

Ethynyltriazene 8b. A solution of **7** (1.4 g, 4.2 mmol) and K₂CO₃ (5.8 g, 42.3 mmol) in distilled THF (50 mL) and MeOH (10 mL) was stirred at room temperature for 3 h. The excess carbonate was filtered and the solvent was removed in vacuo. The crude material was dissolved in EtOAc and the organic layer was washed with aq NH₄Cl solution (2×), water (3×), and brine (2×). The organic layer was dried (MgSO₄) and filtered through a pad of silica then the solvent was removed in vacuo to afford **8b** (0.811 g, 72%) as a yellow oil, which was used without further purification. ¹H NMR (CDCl₃) δ 7.74 (s, 1H), 7.49 (m, 2H), 3.83 (q, *J* = 8.1 Hz, 4H), 3.30 (s, 1H), 1.31 (m, 6H). ¹³C NMR (CDCl₃) δ 155.4, 130.6, 126.4, 125.9, 125.8, 122.2, 117.1, 81.9, 80.7, 49.4, 42.1, 14.3, 10.6. IR (NaCl) ν 3309, 2979, 2938, 2876, 2111, 1652, 1327, 1253, 1102 1072 cm^{−1}. HRMS (EI+) for C₁₃H₁₄N₃F₃: calcd 269.11398, found 269.11376.

α-Ketoester 9a. Ester **6a** was cyclized according to General Procedure C to give **9a** (19 mg, 85%) as a yellow solid. ¹H NMR (CDCl₃) δ 9.18 (d, *J* = 2.1 Hz, 1H), 8.27 (dd, *J* = 9.3, 2.1 Hz, 1H), 7.91 (d, *J* = 9.3 Hz, 1H), 4.00 (s, 3H), 3.33 (q, *J* = 7.2 Hz, 4H), 0.96 (t, *J* = 7.2 Hz, 6H). ¹³C NMR (CDCl₃) δ 177.1, 163.7, 147.4, 146.4, 131.7, 121.8, 120.1, 119.8, 119.7, 52.7, 52.3, 11.1. IR (NaCl) ν 3111, 2982, 2926, 2873, 1741, 1663, 1575, 1522, 1456, 1344, 1266, 1038, 1029 cm^{−1}. HRMS (EI+) for C₁₄H₁₆N₄O₅: calcd 320.11206, found 320.11071.

α-Hydroxyester 10a. Ester **6a** was cyclized according to General Procedure D to give **10a** (20 mg, 95%) as a tan solid. ¹H NMR (CDCl₃) δ 8.67 (d, *J* = 2.4 Hz, 1H), 8.14 (dd, *J* = 9.9, 2.4 Hz, 1H), 7.73 (d, *J* = 9.9 Hz, 1H), 5.95 (d, *J* = 6.0 Hz, 1H), 4.14 (d, *J* = 6.0 Hz,

1H), 3.80 (s, 3H), 3.51–3.22 (m, 4H), 0.93 (br t, 6H). ¹³C NMR (CDCl₃) δ 171.8, 147.2, 143.3, 135.9, 120.8, 118.8, 118.7, 116.0, 64.6, 53.5, 52.5, 52.4, 11.8. IR (NaCl) ν 3477 (br), 3103, 2978, 2922, 2852, 1749, 1627, 1569, 1516, 1334, 1216, 1116, 1080 cm^{−1}. HRMS (EI+) for C₁₄H₁₈N₄O₅: calcd 322.12771, found 322.12795.

Computational Methods. All computations were calculated with use of the Gaussian 03¹² suite of programs at the B3LYP/6-31G* level of theory.¹³ All stationary points were confirmed by harmonic frequency analysis and checked for stability for triplet and SCF convergence. The energies of the stationary points were determined, including zero-point energies, at the same level of theory. ACID calculations were performed (see the Supporting Information) by using the previously reported method of Herges et al.¹⁶ with the ACID scalar fields interpreted as the density of delocalized electrons.

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Supporting Information Available: All computational details including Cartesian coordinates, total energies, and imaginary frequencies for all computed structures as well as transition state analysis; experimental details for **9b–h**, **10b–h**, and **11a–c**; copies of ¹H and ¹³C NMR spectra for **5b**, **6a–h**, **7**, **8**, **9a–h**, **10a–h**, **11a–c**; X-ray cif file for **10a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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