JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Doubly Coarctate-Stabilized Carbenes: Synthetic and Computational Studies

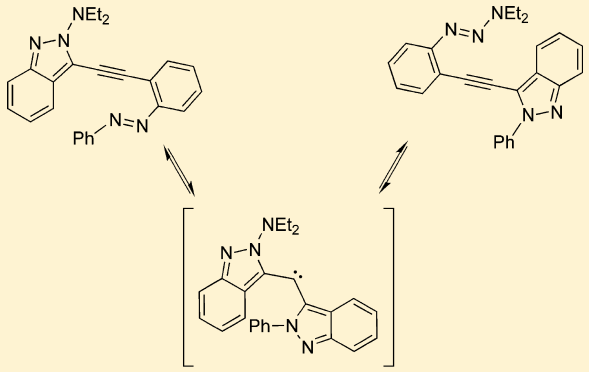
Brian S. Young,[†] Rainer Herges,[‡] and Michael M. Haley*[,†]

[†]Department of Chemistry, University of Oregon, Eugene, Oregon 97403-1253, United States and

[‡]Institut für Organische Chemie, Universität Kiel, 24098 Kiel, Germany

Supporting Information

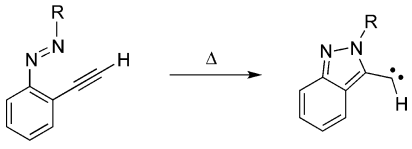
ABSTRACT: Isoindazoles joined by an ethynyl linker to either a phenyltriazene or a phenyldiazene moiety were synthesized, and their subsequent reactivity was examined. Computations suggest that these molecules could rearrange at moderate temperatures via carbene intermediates that are doubly stabilized by coarctate conjugation. The experimental results corroborate the calculations, as the transient carbene can either be trapped with oxygen or undergo ring-opening to afford a rearranged product. Additional calculations illustrate some design principles that might lead to stable carbenes that are the global minimum on the coarctate hypersurface.



INTRODUCTION

Over the past 12 years, we have been investigating the isoindazole-forming cyclizations[1] of hetero-ene−ene−yne systems.[2] Early experiments focused on the cyclization of *o*-ethynylphenyltriazenes (**1a**, Scheme 1), which required the addition of a catalytic metal salt (typically CuCl) to stabilize the carbene/carbenoid intermediate (**2a**).[3] Computational and experimental mechanistic studies indicated that the isoindazole was formed through a concerted mechanism featuring a "coarctate" transition state.[4] A coarctate reaction is defined as one in which two bonds are broken and two bonds are formed in a single step.[5] Interestingly, when the diethyltriazene moiety was replaced with a phenyldiazene (**1b**), the coarctate cyclization proceeded smoothly without the use of a carbene stabilizer.[6] DFT calculations revealed that the energy of activation leading to the carbene intermediate (**2b**) was about 10 kcal mol^{-1} lower for the diazene compared to that of the triazene, results consistent with the more facile cyclization of the diazenes.[6,7]

Scheme 1. Cyclization of Hetero-Ene−Ene−Ynes To Afford Isoindazoyl Carbenes/Carbenoids



1a (R=NEt$_2$)
1b (R=Ph)

2a (R=NEt$_2$)
2b (R=Ph)

Recent calculations showed that pyrazoles and arene-fused pyrazoles (e.g., isoindazoles) strongly stabilize carbenes in the 5-position (e.g., **2**) by as much as 16−17 kcal mol^{-1} over open-chain model systems.[8] We attributed this unusually large stabilization of these heterocyclic singlet carbenes to "coarctate conjugation". The carbene is generated by a coarctate cyclization, and therefore, part of the wave function of the reactant mixes into the carbene wave function. This leads to a significantly shorter bond length between the carbene center and the neighboring carbon atom in the coarctate carbenes compared to the corresponding phenyl and open-chain analogues.[8] By replacing the terminal acetylene proton in the starting material (**1**) with a preformed isoindazole, as in compounds **3** and **4**, it might be possible to induce a cyclization reaction where the resultant carbene **5** could be doubly stabilized by coarctate conjugation (Scheme 2). In addition, depending upon the nature of R^1 and R^2, it might be possible to affect the ratio of **3** to **4** as they interconvert via **5**. Herein we present our computational and experimental results to address both of these issues.[9]

RESULTS AND DISCUSSION

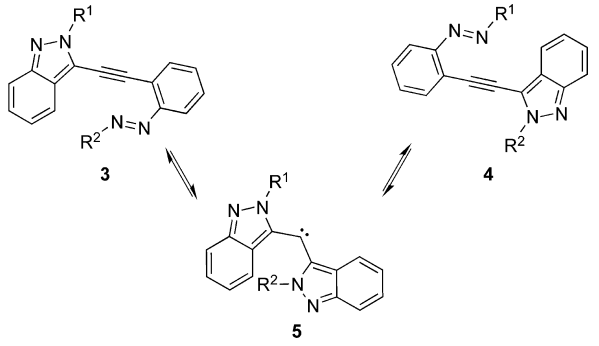
Computational Studies. Before performing any experimental work, model systems **3a** (R^1 = R^2 = NMe$_2$), **3b** (R^1 = R^2 = Ph), and **3c** (R^1 = NMe$_2$, R^2 = Ph) were examined using the Gaussian 03[10] suite of programs to determine the energies required to affect their cyclizations. Density functional theory

Special Issue: Howard Zimmerman Memorial Issue

Received: September 17, 2012
Published: November 5, 2012

   dx.doi.org/10.1021/jo3020374 | J. Org. Chem. 2013, 78, 1977−1983

Scheme 2. Interconversion of 3 and 4 via Doubly Coarctate-Stabilized Carbene 5



(DFT) calculations at the B3LYP level of theory[11] and the 6-31G* basis set once again were utilized as these have proven useful in our previous studies. The calculations showed that the coarctate cyclization of **3a** has a transition-state energy of 33.7 kcal mol^{-1} (Figure 1, left), identical to the energy of activation for the hypothetical NMe_2-analogue of triazene–ene–yne **1a**, and similar energies for carbenes **2a** and **5a**;[9b] therefore, we anticipated that **3a** would cyclize to **5a** under standard isoindazole formation conditions (heating in 1,2-dichloroethane (DCE) to 50 °C in the presence of excess CuCl), which then could be trapped/intercepted by molecular oxygen or an electron-rich alkene.

For the coarctate cyclization of diazene–ene–ynes, the calculations for **3b** predicted a transition state energy of 20.5 kcal mol^{-1} (Figure 1, right), which is 2.3–5.3 kcal mol^{-1} lower than the barrier for **1b**; the energy for intermediate **5b** is similarly lowered from **2b**. Given the greater propensity of the diazenes to cyclize,[6,7] we anticipated that **3b** might react readily at ambient temperature and thus only obtain products derived from **5b**.

Asymmetric carbene **5c** presents an interesting possibility. Whereas carbenes **5a** and **5b** must revert back to **3a** and **3b**, respectively, in the equilibrium between the two forms due to symmetry of the intermediates, **5c** can undergo ring-opening to yield *two different* starting ethynylisoindazoles, either **3c** or **4c**. From the energy diagram (Figure 2), a few key observations and conclusions can be made. (1) Isoindazole **3c** is 14 kcal mol^{-1} higher in energy than **4c**; therefore, **3c** should be targeted as its thermally induced rearrangement to more stable **4c** should be possible while the reverse rearrangement should not. (2) The energy barrier for the cyclization of **3c** to its corresponding carbene **5c** is 23.2 kcal mol^{-1}. This value is comparable to diazene **1b**, which has an energy of activation of 22.8 kcal mol^{-1} and required no catalyst to effect cyclization; thus, **3c** is also expected to cyclize without need of a catalyst. (3) The energy barrier from **4c** to **5c** is 31.3 kcal mol^{-1}. This is comparable to the energy predicted to cyclize the *N,N*-dimethyl version of triazene **1** at 33.7 kcal mol^{-1} and indicates that in

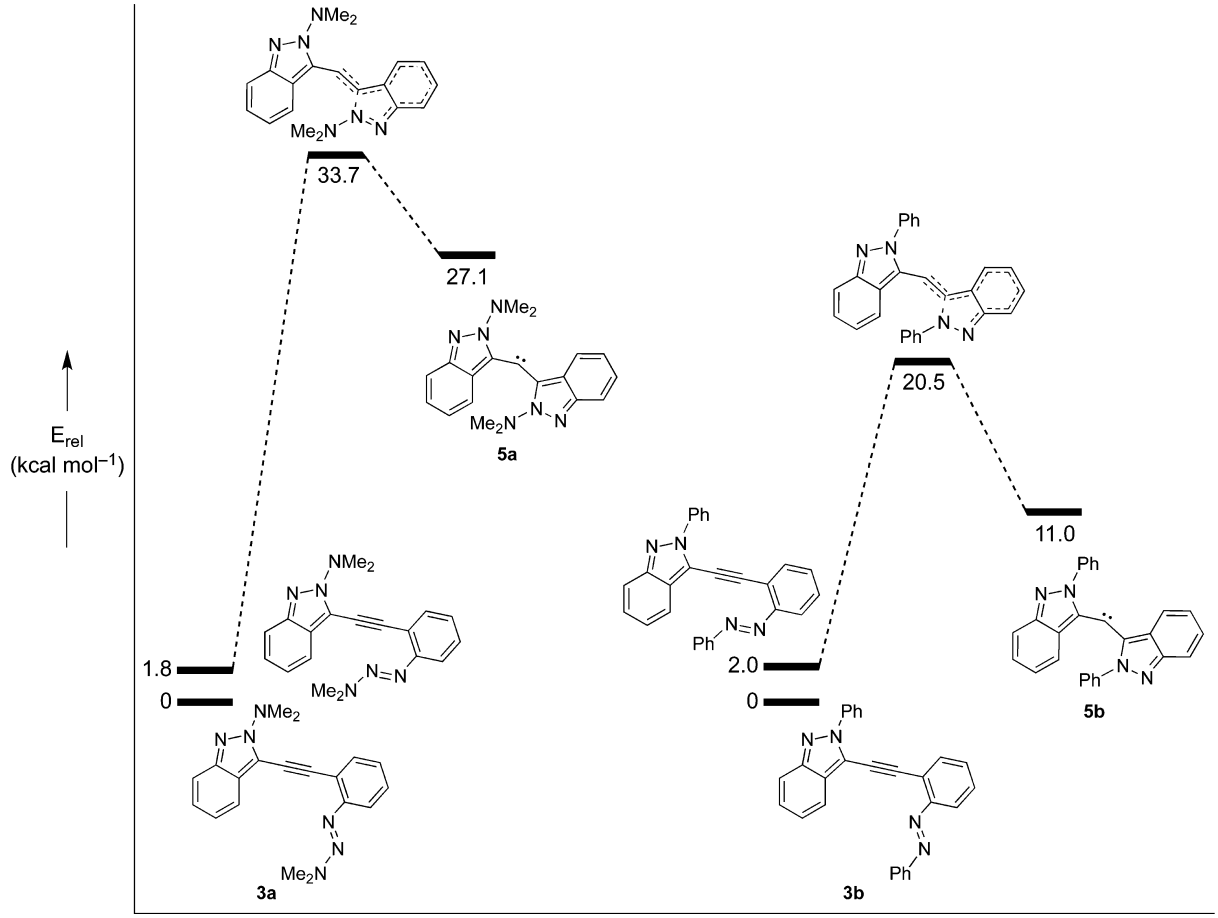


Figure 1. DFT (B3LYP/6-31G* + ZPE)-calculated relative energies of the reactants, transition states, and intermediates involved in the coarctate cyclization of **3a** (left) and **3b** (right).

dx.doi.org/10.1021/jo3020374 | *J. Org. Chem.* 2013, 78, 1977–1983

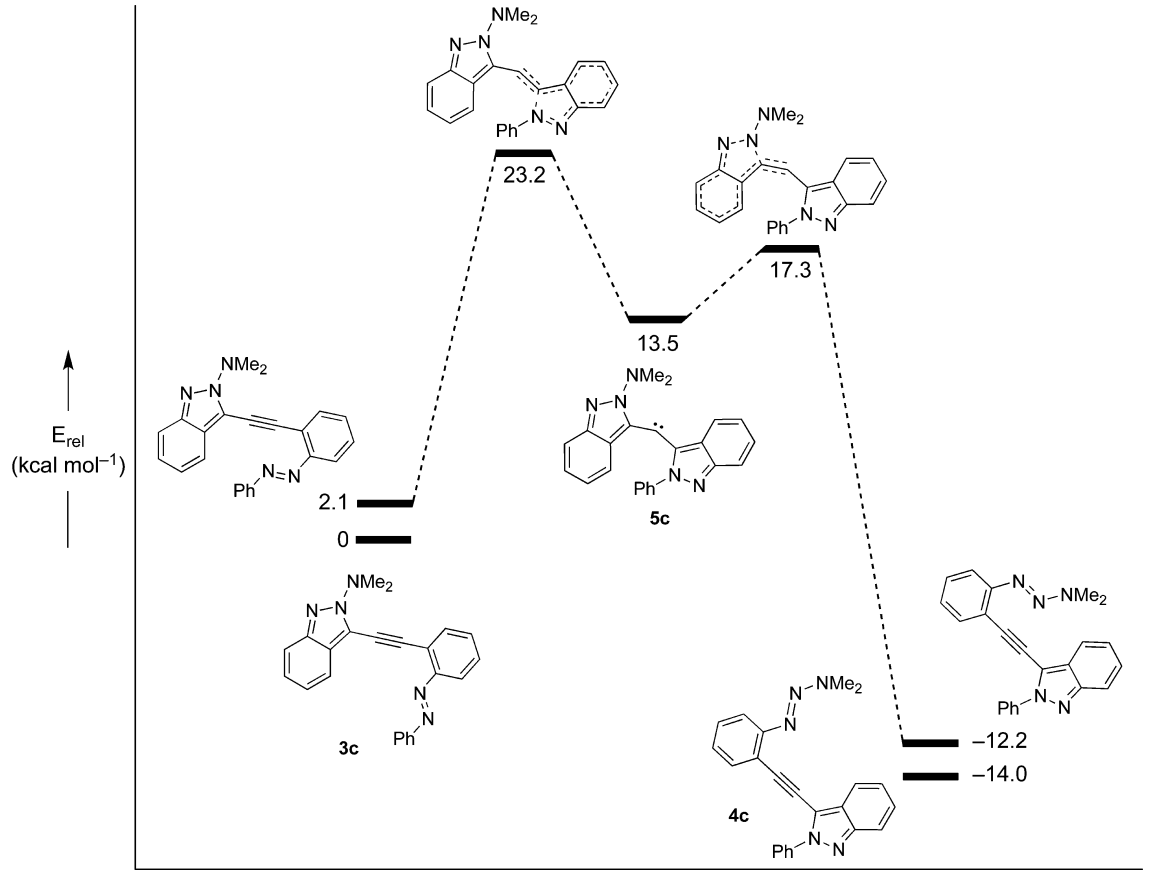
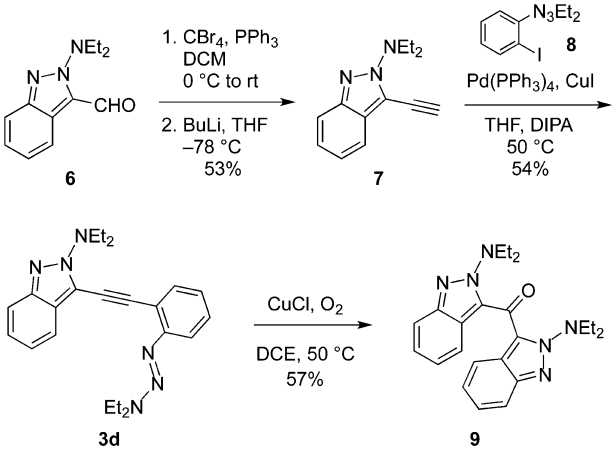


Figure 2. DFT (B3LYP/6-31G* + ZPE)-calculated relative energies of the reactants, transition states, intermediates, and products involved in the proposed conversion of **3c** to **4c** via carbene **5c**.

addition to being more thermodynamically stable than **3c**, **4c** would also be more kinetically stable.

Experimental Studies. Synthesis of **3d** ($R^1 = R^2 = NEt_2$) began with a Corey–Fuchs reaction[12] on known aldehyde **6**[3a] to generate ethynylisoindazole **7** (Scheme 3). Sonogashira cross-coupling with (2-iodophenyl)triazene **8**[13] afforded target molecule **3d**. Based on the calculated activation energy for the coarctate cyclization of **3a**, we expected to be able to trap the resulting carbene using 2,3-dimethyl-2-butene (DMB) as we have previously shown; however, all attempts resulted in only recovered starting material. Gratifyingly, repeating the cyclization reaction in oxygen-saturated DCE gave ketone **9** in 57% yield. These results indicate that while the coarctate reaction of **3d** was energetically favorable, the [2 + 1] cycloaddition with DMB did not occur, likely due to the sterically hindered nature of the carbene center; however, molecular oxygen was small enough to intercept successfully the reactive intermediate.

Scheme 3. Synthesis and Coarctate Cyclization of 3d

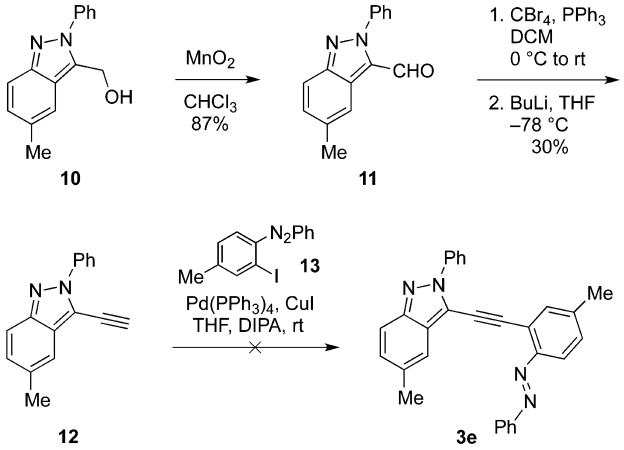


For the synthesis of **3e** and **3f**, we elected to include methyl groups in the starting materials. These provided the dual benefits of reducing the complexity of the aromatic region of the ^{1}H NMR spectra due to the added *N*-phenyl groups while at the same time giving clear spectroscopic handles in the alkyl region to ascertain purity. MnO_2-mediated oxidation of known alcohol **10**[6] gave aldehyde **11** (Scheme 4). Subjecting this aldehyde to Corey–Fuchs conditions led to alkyne **12**. Unfortunately, Sonogashira cross-coupling of **12** to iodide **13**[6] failed to provide the desired isomer **3e**. While all starting material was consumed, no identifiable products were recovered. A plausible explanation is that the desired product **3e** did form but that it readily rearranged to generate carbene **5e** that subsequently reacted to generate several unidentifiable products. This is consistent with our previous work involving (2-ethynylphenyl)phenyldiazenes[6] in which these molecules would undergo coarctate cyclization under ambient conditions, resulting in a number of unidentifiable products. All attempts to intercept **5e** or any reactive intermediates in this reaction were unsuccessful.

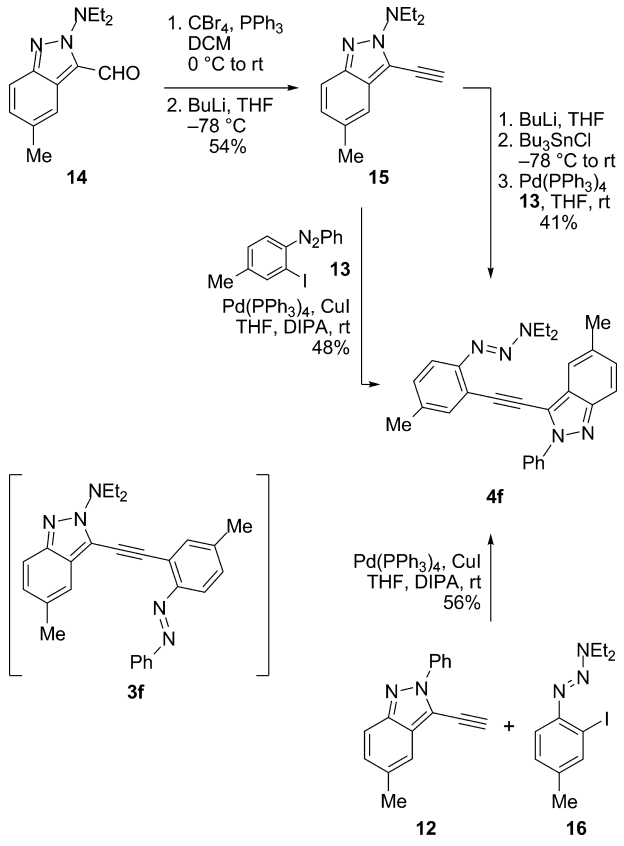
We next focused on the asymmetrical structure **3f** and the potential rearranged product **4f**. Isoindazole aldehyde **14**[3a] was subjected to a Corey–Fuchs sequence to form alkyne **15** (Scheme 5), which was subsequently cross-coupled under

dx.doi.org/10.1021/jo3020374 | J. Org. Chem. 2013, 78, 1977–1983

Scheme 4. Attempted Synthesis of 3e



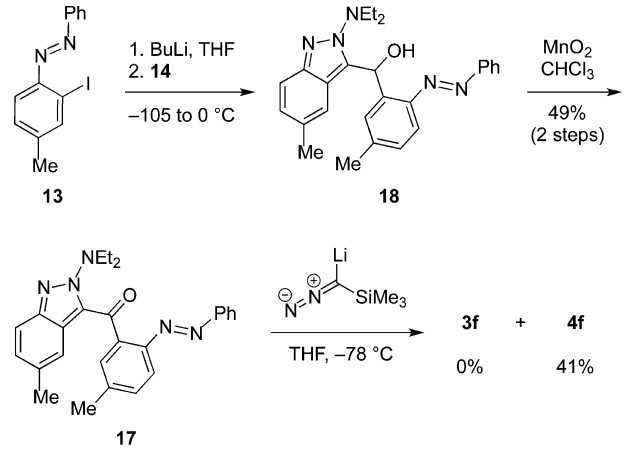
Scheme 5. Synthesis of 4f through Sonogashira and Stille Cross-Coupling Reactions



Sonogashira conditions with iodide **13**. Surprisingly, the proton NMR spectra of the resultant material strongly suggested that the only characterizable product was **4f**! Intentionally synthesizing **4f** afforded definitive proof: cross-coupling alkyne **12** to iodide **16**[3a] furnished a compound whose NMR data were identical to those of the material formed in the previous reaction. It appears that while **3f** was formed in situ, it immediately rearranged under the reaction conditions to form **4f**.

Because Cu(I) salts effect coarctate cyclizations, we hypothesized that the small amount of CuI used for the Sonogashira reaction could have promoted the unwanted rearrangement. To perform a Cu-free reaction, the corresponding tributylstannane of alkyne **15** was formed and cross-coupled to iodide **13** under Stille conditions; again, the only product isolated was **4f**. While it appeared that **3f** was simply not stable and spontaneously rearranged to **4f**, there still existed the possibility that the Pd catalyst was facilitating the rearrangement. While Cu(I) is usually utilized to perform our coarctate cyclizations, other transition metals such as Rh(II) have been used as well. To rule out Pd as the cause for the rearrangement, a transition-metal-free strategy to form **3f** was required. We envisioned that a Colvin rearrangement[14] of the appropriate ketone **17** could be a viable way of producing **3f** without the use of transition metals (Scheme 6).[13] Lithium–halogen

Scheme 6. Transition-Metal-Free Attempt To Synthesize 3f



exchange on **13** followed by nucleophilic attack on aldehyde **14** gave crude alcohol **18**, which was smoothly oxidized to the corresponding ketone **17** using MnO_2. Finally, treatment of **17** with the Li salt of trimethylsilyldiazomethane induced a Colvin rearrangement. Unfortunately, this also resulted in formation of **4f** rather than **3f**. Rearrangement inevitably occurs at room temperature or lower even in the complete absence of transition metals that could act as carbene stabilizers.

Computational Studies Revisited. In title systems **3** and **4** coarctate cyclization is coupled to coarctate ring-opening proceeding via carbenes **5** (Scheme 2). Even though the carbenes are stabilized by coarctate conjugation, they are short-lived intermediates that cannot be isolated but only trapped with oxygen. A straightforward way to stabilize the carbene, and to make it the global minimum on the three-minimum reaction hypersurface (ring closure, carbene, ring-opening) would be to include the triple bond of the ene–ene–yne as part of a ring system. Use of a medium-sized ring will enforce more strain upon the overall system and thus destabilize the alkyne. The molecule should then readily cyclize to the carbene form, which is naturally bent and thus will relieve ring strain. To check this hypothesis, we performed calculations on the hypothetical cyclooctyne **19a** and the corresponding carbene **20a**, as well as the phenyl substituted systems **19b** and **20b** (Figure 3). As expected, upon bridging the isoindazole rings with ethyne and methylene units forming an 8-membered ring, carbene **20a** becomes 25.6 kcal mol^{-1} more stable than ene–ene–yne **19a**. For the phenyl-substituted systems, carbene **20b** is calculated to be 11.9 kcal mol^{-1} more stable than cyclooctyne **19b**. Both carbenes are singlet ground states. It therefore appears that coarctate stabilization in combination with ring strain could provide a way to design stable carbenes that differ structurally

dx.doi.org/10.1021/jo3020374 | J. Org. Chem. 2013, 78, 1977–1983

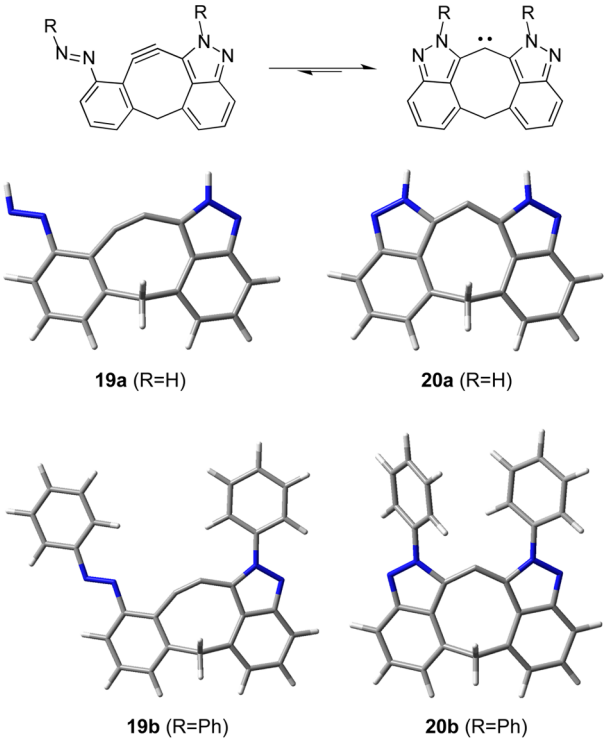


Figure 3. Bridged systems **19a,b** that are calculated to be more stable in the carbene forms **20a,b**.

from the more commonly utilized imidazole-based N-heterocyclic carbenes.[15]

CONCLUSIONS

Molecules that can undergo coarctate cyclization to form carbene intermediates, specifically, isoindazoles fused via an ethynyl linker to either phenyldiazenes or diethyltriazenes, were studied computationally and experimentally. DFT calculations suggested that the isoindazoles fused to phenyldiazenes would rearrange via carbenes at lower temperatures when compared to their diethyltriazene counterparts; this was confirmed experimentally. Both **3d** and **4f** are stable at room temperature, with activation energies of coarctate cyclization of 33.4 and 33.7 kcal mol^{-1}, respectively. It was shown that **3d** can rearrange to a carbene and be trapped by molecular oxygen in the presence of CuCl, much like our previously observed triazene systems. While **3e** unfortunately degraded into multiple products, **3f** was presumably formed in situ and rearranged to **4f** in modest yield. Additional calculations indicate that modification of the molecular framework by including the alkyne portion of these molecules into a medium-sized ring would result in carbenes that are the global minimum on the coarctate hypersurface. Coarctate stabilization along with ring strain, then, could lead to the development of novel stable carbenes that could be interesting ligands of transition-metal compounds.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a 300 (^1H: 299.93 MHz, ^{13}C: 75.42 MHz), 500 (^1H: 500.11 MHz, ^{13}C: 125.75 MHz), or 600 MHz (^1H: 599.90 MHz, ^{13}C: 150.88 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm relative to the residual chloroform (^1H: 7.26 ppm, ^{13}C: 77.16 ppm) reference. High-resolution mass spectra were recorded on instruments using either an electric/magnetic sector or a TOF analyzer. Dry THF was distilled from Na and benzophenone under N_2. All purchased reagents were used as received unless otherwise indicated.

Alkyne 7. PPh_3 (0.893 g, 3.4 mmol) was added to a stirred solution of CBr_4 (0.565 g, 1.7 mmol) in DCM (10 mL) at 0 °C. To this was added dropwise a solution of aldehyde **6**[3a] (0.185 g, 0.85 mmol) in DCM (10 mL). The reaction mixture was warmed to rt and stirred overnight. The mixture was filtered through a pad of silica with DCM, and the solvent removed under reduced pressure to give the crude dibromoalkene (0.274 g, 85%) as a waxy yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (dt, J = 8.7, 0.9 Hz, 1H), 7.77 (s, 1H), 7.70 (dt, J = 8.7, 0.9 Hz, 1H), 7.36–7.29 (m, 1H), 7.20–7.14 (m, 1H), 3.28 (br s, 4H), 0.83 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.6, 131.3, 127.7, 126.4, 122.4, 122.3, 118.1, 116.9, 92.5, 52.7, 12.1.

To a stirred solution of dibromoalkene (0.274 g, 0.7 mmol) in dry THF (25 mL) at −95 °C was added BuLi (1.4 mL, 2.5 M, 3.5 mmol) dropwise. After 40 min, the reaction was quenched with satd aq NH_4Cl solution and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the crude product was purified by preparative TLC (1:2 EtOAc/hexanes) to give alkyne **7** (0.097 g, 62%) as a pale yellow solid: mp 93–94 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.71 (m, 1H), 7.70–7.68 (m, 1H), 7.36–7.33 (m, 1H), 7.20–7.15 (m, 1H), 3.81 (s, 1H), 3.33 (q, J = 7.2 Hz, 4H), 0.88 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.3, 126.9, 123.1, 122.4, 120.2, 118.2, 117.9, 87.6, 72.1, 53.0, 12.1; HRMS (EI+) for $C_{13}H_{15}N_3$ calcd 213.1266, found 213.1264.

Triazene 3d. A stirred mixture of iodide **8**[13] (0.152 g, 0.5 mmol), $Pd(PPh_3)_4$ (0.008 g, 0.007 mmol), CuI (0.003 g, 0.013 mmol), THF (10 mL), and DIPA (20 mL) was purged with Ar for 45 min. A solution of alkyne **7** (0.072 g, 0.34 mmol) in Ar-purged THF (10 mL) was added via cannula, and the mixture was stirred overnight at 50 °C. After cooling, the crude mixture was filtered through a pad of silica (acetone), concentrated, and purified by preparative TLC (1:3 EtOAc/hexanes) to give **3d** (0.070 g, 54%) as a pale yellow solid: mp 109–110 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.37–7.28 (m, 2H), 7.18–7.08 (m, 2H), 3.91–3.78 (m, 4H), 3.34 (q, J = 7.2 Hz, 4H), 1.30 (br s, 6H), 0.93 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 146.3, 133.4, 129.6, 126.7, 124.8, 122.2, 122.0, 121.5, 120.7, 117.9, 117.8, 117.2, 98.5, 81.1, 52.7, 47.9, 19.3, 12.3; HRMS (ESI+) for $C_{23}H_{28}N_6$ $(M + H)^+$ calcd 389.2454, found 389.2439.

Ketone 9. A solution of **3d** (0.02 g, 0.05 mmol) in DCM (20 mL) was sparged with O_2 for 30 min, CuCl (0.051 g, 0.5 mmol) was added, and the mixture was stirred overnight at 50 °C. After cooling, the crude mixture was filtered through a pad of silica (1:3 EtOAc/hexanes), concentrated, and purified by preparative TLC (1:19 EtOAc/DCM) to give ketone **9** (0.012 g, 57%) as a yellow solid: mp 145–146 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 9.0 Hz, 2H), 7.36–7.29 (m, 2H), 7.07–7.00 (m, 2H), 6.98–6.93 (m, 2H), 3.33 (q, J = 7.2 Hz, 8H), 0.89 (t, J = 7.2 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 145.7, 133.7, 126.7, 124.7, 120.4, 120.3, 118.2, 52.4, 12.1; HRMS (ESI+) for $C_{23}H_{28}N_6O$ $(M + H)^+$ calcd 405.2403, found 405.2386.

Aldehyde 11. Isoindazole alcohol **10**[6] (0.83 g, 3.5 mmol) was dissolved in $CHCl_3$ (50 mL), MnO_2 (6.05 g, 70 mmol) was added, and the reaction was stirred for 16 h. The crude reaction mixture was filtered through Celite, and the solvent was removed under reduced pressure to yield **11** (0.712 g, 87%) as an orange solid: mp 101–102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.06 (s, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.66–7.53 (m, 5H), 7.30 (dd, J = 9.0, 1.2 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.1, 147.5, 138.9, 137.6, 131.6, 130.7, 130.0, 129.6, 126.5, 124.0, 119.5, 118.4, 22.2; HRMS (EI+) for $C_{15}H_{12}N_2O$ calcd 236.0950, found 236.0956.

Alkyne 12. PPh_3 (3.16 g, 12.1 mmol) was added to a stirred solution of CBr_4 (1.99 g, 6.0 mmol) in DCM (20 mL) at 0 °C. To this solution was added dropwise a solution of aldehyde **11** (0.712 g, 3.0 mmol) in DCM (10 mL). The reaction mixture was warmed to rt and stirred overnight. The mixture was filtered through a pad of silica with DCM and the solvent removed under reduced pressure to give the dibromoalkene (0.693 g, 59%) as a waxy yellow solid: ^1H NMR (300

dx.doi.org/10.1021/jo3020374 | J. Org. Chem. 2013, 78, 1977–1983

MHz, $CDCl_3$) δ 7.70 (d, J = 9.0 Hz, 1H), 7.66−7.45 (m, 7H), 7.20 (dd, J = 9.0, 1.2 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.1, 140.0, 132.7, 130.1, 129.5, 129.2, 129.0, 127.8, 125.3, 121.2, 119.7, 118.1, 95.1, 22.2.

To a stirred solution of dibromoalkene (0.693 g, 1.8 mmol) in dry THF (25 mL) at −95 °C was added BuLi (3.5 mL, 2.5 M, 8.75 mmol) dropwise. After 40 min, the reaction was quenched with satd aq NH_4Cl solution and extracted with DCM. The organic layer was dried ($MgSO_4$), and the crude product was concentrated and then purified by preparative TLC (DCM) to give alkyne **12** (0.204 g, 50%) as a purple solid: mp 66−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 9.0 Hz, 1H), 7.58−7.41 (m, 4H), 7.21 (dd, J = 9.0, 1.2 Hz, 1H), 3.80 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 140.2, 133.5, 130.4, 129.1, 128.7, 126.9, 124.5, 118.2, 118.2, 116.2, 88.6, 72.9, 22.0; HRMS (EI+) for $C_{16}H_{12}N_2$ calcd 232.1000, found 232.1005.

Alkyne 15. PPh_3 (1.270 g, 4.8 mmol) was added to a stirred solution of CBr_4 (0.803 g, 2.4 mmol) in DCM (10 mL) at 0 °C. To this solution was added dropwise a solution of aldehyde **14** (0.280 g, 1.2 mmol) in DCM (10 mL). The reaction mixture was warmed to rt and stirred overnight. The mixture was filtered through a pad of silica with DCM and the crude material was concentrated and then purified by preparative TLC(1:3 EtOAc:hexanes) to give the corresponding dibromide (0.396 g, 85%) as a waxy yellow semisolid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H) 7.61 (d, J = 8.7 Hz, 1H), 7.55 (s, 1H), 7.18 (d, J = 8.7 Hz, 1H), 3.27 (s, 4H), 2.46 (s, 3H), 0.82 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4, 131.9, 129.3, 127.8, 120.5, 117.8, 117.1, 92.2, 52.7, 22.2, 12.1.

To a stirred solution of dibromoalkene (0.390 g, 1.0 mmol) in dry THF (25 mL) at −95 °C was added BuLi (2.0 mL, 2.5 M, 5.0 mmol) dropwise. After 40 min, the reaction was quenched with satd aq NH_4Cl solution and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the crude product was purified by preparative TLC (1:3 EtOAc/hexanes) to give **15** (0.146 g, 64%) as a pale yellow solid: mp 95−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.9 Hz, 1H), 7.46 (s, 1H), 7.18 (d, J = 8.9 Hz, 1H), 3.79 (s, 1H), 3.32 (q, J = 7.2 Hz, 4H), 2.44 (s, 3H), 0.87 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.6, 129.3, 126.3, 119.1, 115.2, 114.9, 114.4, 83.9, 68.9, 49.5, 18.5, 8.6; HRMS (EI+) for $C_{14}H_{17}N_3$ calcd 227.1422, found 227.1413.

Triazene 4f via Sonogashira Reaction/Rearrangement. A stirred mixture of iodide **13**[6] (0.085 g, 0.26 mmol), $Pd(PPh_3)_4$ (0.004 g, 0.004 mmol), CuI (0.002 g, 0.009 mmol), THF (10 mL), and DIPA (20 mL) was purged with Ar for 45 min. A solution of alkyne **15** (0.050 g, 0.22 mmol) in Ar-purged THF (10 mL) was added via cannula, and the mixture was stirred overnight at room temperature. The crude mixture was filtered through a pad of silica (acetone), concentrated, and purified by preparative TLC (1:3 EtOAc/hexanes) to give **4f** (0.044 g, 48%) as a pale yellow solid: mp 115−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.5 Hz, 2H), 7.70 (d, J = 7.2 Hz, 1H), 7.59 (s, 1H), 7.55−7.49 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H) 7.28 (s, 1H), 7.2 (dd, J = 9.0, 1.2 Hz, 1H), 7.12 (dd, J = 8.4, 1.5 Hz, 1H), 3.75 (q, J = 7.2 Hz, 4H), 2.46 (s, 3H), 2.33 (s, 3H), 1.25 (br s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.4, 147.9, 140.6, 134.5, 133.0, 132.5, 130.8, 130.3, 129.0, 128.2, 126.2, 124.4, 118.9, 118.3, 118.0, 117.2, 117.1, 99.7, 81.6, 47.1 (br), 21.9, 20.9, 19.5; HRMS (ESI+) for $C_{27}H_{27}N_5$ $(M + H)^+$ calcd 422.2345, found 422.2328.

Triazene 4f via Direct Sonogashira Reaction. A stirred mixture of iodide **16** (0.034 g, 0.10 mmol), $Pd(PPh_3)_4$ (0.003 g, 0.002 mmol), CuI (0.001 g, 0.004 mmol), THF (10 mL), and DIPA (20 mL) was purged with Ar for 45 min. A solution of alkyne **12** (0.025 g, 0.10 mmol) in Ar-purged THF (10 mL) was added via cannula, and the mixture was stirred overnight at room temperature. The crude mixture was filtered through a pad of silica (acetone), concentrated, and purified by preparative TLC (1:3 EtOAc/hexanes) to give **4f** (0.025 g, 56%) as a pale yellow solid. The spectroscopic data of this product matched those described ealier for **4f**.

Ketone 17. To a solution of iodide **13** (0.100 g, 0.3 mmol) in THF (10 mL) cooled to −105 °C was added BuLi (0.13 mL, 2.5 M, 0.325 mmol) dropwise. After the solution was stirred for 5 min, a solution of aldehyde **14** in THF (1 mL) was added dropwise by syringe. The reaction was warmed to 0 °C and stirred for 3 h at that temperature. The reaction was quenched with satd aq $NaHCO_3$ solution and extracted three times with DCM. The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give crude alcohol **18**. Alcohol **18** was redissolved in $CHCl_3$ (10 mL), and excess MnO_2 was added. After the reaction was stirred for 16 h, the mixture was filtered through a pad of Celite and concentrated. Purification by preparative TLC (1:2 EtOAc/hexanes) gave ketone **17** (0.062 g, 49%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.77 (m, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.43−7.38 (m, 2H), 7.28−7.15 (m, 6H), 2.96 (br s, 4H), 2.49 (s, 3H), 2.47 (s, 3H), 0.63 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.7, 152.2, 148.0, 144.8, 141.7, 140.5, 135.3, 133.6, 131.3, 131.1, 129.7, 128.9, 128.8, 123.0, 121.5, 120.0, 117.6, 117.6, 51.3, 22.2, 21.6, 12.0; HRMS (ESI+) for $C_{26}H_{27}N_5O$ $(M + H)^+$ calcd 426.2294, found 426.2300.

Triazene 4f via Colvin Rearrangement. To a solution of (trimethylsilyl)diazomethane (0.07 mL, 2.0 M, 0.14 mmol) in THF (5 mL) cooled to −78 °C was added BuLi (0.05 mL, 2.5 M, 0.13 mmol). The reaction mixture was stirred for 40 min, after which it was transferred by cannula into a stirred, −78 °C solution of ketone **17** (0.042 g, 0.10 mmol) in dry THF (10 mL). After 1 h, the reaction was quenched with satd aq $NaHCO_3$ solution, diluted with Et_2O, and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The product was purified by preparative TLC (1:2 EtOAc/hexanes) to give triazene **4f** (0.012 g, 41%) as a pale yellow solid. The spectroscopic data of this product matched those described above for **4f**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

All computational details including Cartesian coordinates, total energies, and imaginary frequencies for all computed structures as well as transition-state analysis; copies of ^{1}H and ^{13}C NMR spectra for **3d**, **4f**, **7**, **9**, **11**, **12**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: haley@uoregon.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE-1013022) for continued support of this research as well as for support in the form of instrumentation grants (CHE-0923589).

■ REFERENCES

(1) Young, B. S.; Herges, R.; Haley, M. M. *Chem. Commun.* **2012**, *48*, 9441−9455.

(2) Shirtcliff, L. D.; McClintock, S. P.; Haley, M. M. *Chem. Soc. Rev.* **2008**, *37*, 343−364.

(3) (a) Kimball, D. B.; Weakley, T. J. R.; Haley, M. M. *J. Org. Chem.* **2002**, *67*, 6395−6405. (b) Kimball, D. B.; Hayes, A. G.; Haley, M. M. *Org. Lett.* **2000**, *2*, 3825−3827.

(4) (a) Kimball, D. B.; Weakley, T. J. R.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 13463−13473. (b) Kimball, D. B.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 1572−1573.

(5) (a) Herges, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 255−276. (b) Herges, R. *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 91−102.

(6) Shirtcliff, L. D.; Weakley, T. J. R.; Haley, M. M.; Kohler, F.; Herges, R. *J. Org. Chem.* **2004**, *69*, 6979−6985.

(7) Shirtcliff, L. D.; Hayes, A. G.; Haley, M. M; Kohler, F.; Hess, K.; Herges, R. *J. Am. Chem. Soc.* **2006**, *128*, 9711−9721.

(8) Young, B. S.; Koehler, F.; Herges, R.; Haley, M. M. *J. Org. Chem.* **2011**, *76*, 8483−8487.
(9) Additional o-ethynylaryltriazene studies: (a) Shirtcliff, L. D.; Haley, M. M.; Herges, R. *J. Org. Chem.* **2007**, *72*, 2411−2418. (b) McClintock, S. P.; Forster, N.; Herges, R.; Haley, M. M. *J. Org. Chem.* **2009**, *74*, 6631−6636. (c) McClintock, S. P.; Zakharov, L. N.; Herges, R.; Haley, M. M. *Chem.—Eur. J.* **2011**, *17*, 6798−6806. (d) Young, B. S.; Marshall, J. L.; MacDonald, E.; Vonnegut, C. L.; Haley, M. M. *Chem. Commun.* **2012**, *48*, 5166−5168.
(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.04, Gaussian, Inc.: Pittsburgh, PA, 2003.
(11) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(12) Corey, E. J.; Fuchs, P. W. *Tetrahedron Lett.* **1972**, 3769−3772.
(13) Kehoe, J. M.; Kiley, J. H.; English, J. J.; Johnson, C. A.; Petersen, R. C.; Haley, M. M. *Org. Lett.* **2000**, *2*, 969−972.
(14) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869−874.
(15) (a) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940−6952. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309.