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CuCl-Induced Formation and Migration of Isoindazolyl Carbenoids

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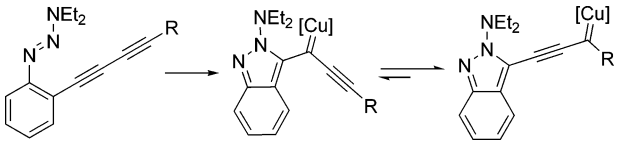

Two azo-ene-butadiyne conjugated systems undergo CuCl-mediated cyclization to afford isoindazolyl carbenoids that could be trapped with 2,3-dimethyl-2-butene as [2 + 1] cycloaddition products. X-ray structure analysis of the resultant cyclopropanes showed that formal migration to the distal carbenoid isomer and subsequent trapping had occurred. The possible CuCl-induced cyclization/migration pathways were explored using density functional theory, which indicated that the reaction most likely occurred via coordination of CuCl to the distal alkyne bond.

Introduction

Aromatic heterocycles continue to play a vital role in chemistry and pharmacology.[1] These compounds possess a breadth of uses that range from biologically active molecules[2] to materials applications.[3] One particular area of interest in heterocyclic methodology is that of tandem or sequential cyclizations. These are desirable because of the complexity of the ring systems that can be formed in one or two synthetic steps. Tandem or sequential cyclizations are well-known in anions,[4] cations,[4,5] radicals,[6] and metal carbenoids.[7] *ortho*-Alkynyl-substituted α-diazoacetophenone derivatives have been shown to produce propargyl carbenoids which, based upon product formation, are theorized to migrate toward the more stable carbenoid isomer.[8] Through additional experimentation it should be possible to predict the more stable alkynyl carbenoid isomer and utilize that knowledge in designing precursors for potential cyclizations. Since considerably less is known synthetically about cyclization/migration reactions involving alkynyl carbenes/carbenoids, our work in the field of coarctate[9]/pseudocoarctate[10] cyclizations of azo-ene-yne compounds **1a**[11]

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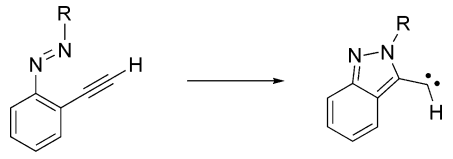
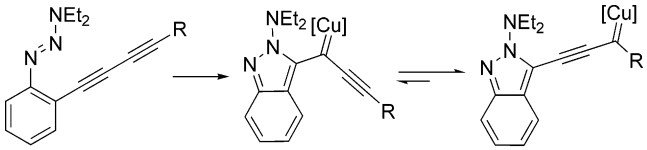
SCHEME 1. Cyclization of Azo-Ene-Yne Moieties To Afford Isoindazoylyl Carbenes/Carbenoids



1a (R=NEt_2)
1b (R=Ph)

2a (R=NEt_2)
2b (R=Ph)

SCHEME 2. CuCl-Induced Cyclization of 3 Affording Carbenoid 4 and Migration Isomer 5



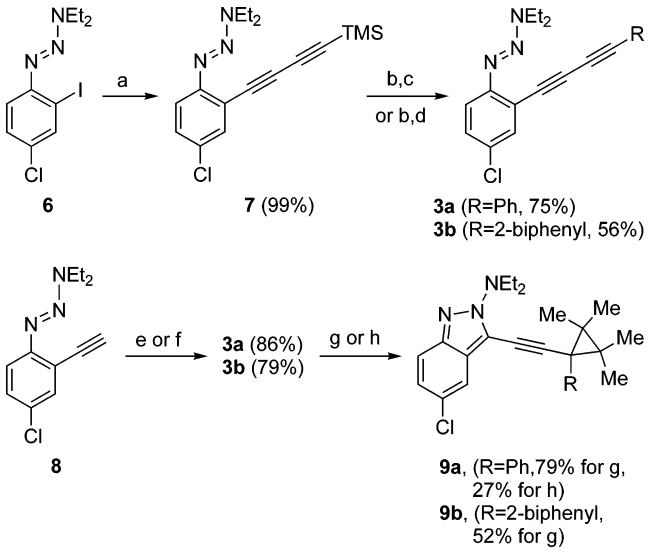
3 **4** **5**

a, R = Ph; **b**, R = 2-biphenyl; **c**, R = TMS

and **1b**[12] afforded us ideal systems for the study of sequential cyclization-carbene/carbenoid migrations (Scheme 1).

We recently elucidated the mechanism(s) of cyclization for symmetric ethyne- and butadiyne-linked triazenes and diazenes,[13] and thus we wanted to utilize similar cyclization-induced carbenoid formation (**3**→**4**) to examine whether or not the carbenoid could migrate along an extended alkyne system (**4**→**5**), i.e., testing the migratory aptitude of the carbenoid (Scheme 2). In many of the previous literature examples of carbene migration, it was not possible to determine whether or not the carbene was truly migrating because of the potential that it does so through a transition metal carbenoid.[7,8,14] Conversely, it could not be determined unequivocally that such a reaction does proceed through a transition metal carbenoid. The rhenium example recently described by Casey et al. is the only example of a true carbenoid migration known to our laboratory where stable intermediates could be isolated.[14] While there has been much discussion in the literature about the mechanism of migration and structure properties of ethynylcarbenes, it is not comprehensive and tends to be contradictory.[15] While the reorganizations of vinylidenes are relatively well-known, synthetic examples of alkynyl carbene migrations in the literature are sparse. In addition, the cyclization products along with the [2 + 1] cycloaddition products resulting from carbene addition to an alkene π-bond are of interest as both cyclopropanes[16] and the isoindazole nucleus[2b,c,17] are medicinally and pharmaceutically relevant synthetic targets. We present herein our experimental and theoretical studies of the CuCl-induced cyclization of **3**.

SCHEME 3. Syntheses of Diyne 3 and Cyclopropane 9[a]



6 **7** (99%) **3a** (R=Ph, 75%) **3b** (R=2-biphenyl, 56%)

3a (86%) **3b** (79%)

8 **9a**, (R=Ph,79% for g, 27% for h) **9b**, (R=2-biphenyl, 52% for g)

[a] Reagents and conditions: (a) TMSC≡CC≡CH, $Pd(PPh_3)_4$, CuI, THF, DIPA, 50 °C; (b) TBAF, THF, MeOH, rt; (c) PhI, $Pd(PPh_3)_4$, CuI, THF, DIPA, 50 °C; (d) 2-iodobiphenyl, $Pd(PPh_3)_4$, CuI, THF, DIPA, 50 °C; (e) CuCl, 1-bromo-2-phenylethyne, H_2O, THF, DIPA; (f) CuCl, 1-bromo-2-phenylethyne, H_2O, THF, DIPA; (g) CuCl, 2,3-dimethyl-2-butene, DCE; (h) $Rh_2(OAc)_4$, 2,3-dimethyl-2-butene, DCE.

Results and Discussion

Synthesis. The system chosen for migration studies, **3a**, arose from iodide **6** which was cross-coupled to trimethylsilylbutadiyne under Sonogashira[18] conditions to afford **7a** in excellent yield (Scheme 3). The silyl group was removed with TBAF and immediately coupled to iodobenzene, affording butadiyne **3a** in 75% yield. Alternatively, diyne **3a** could be synthesized via Cadiot−Chodkiewicz[19] cross-coupling of ter-

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minal alkyne **8**[10c] and 1-bromo-2-phenylethyne.[20] Although the coupling reaction required several days for completion, it proceeded cleanly at room temperature in a respectable 86% yield. Initial attempts to induce cyclization were unsuccessful; heating **3a** to 200 °C in the presence of 2,3-dimethyl-2-butene (DMB) for 50 h resulted in complete recovery of starting material. Temperatures beyond 200 °C led to a decrease in recovered triazene with an increase in polymeric degradation material.

Since Cu and Rh salts are well-known to facilitate the formation of and stabilize high-energy carbene species, experiments incorporating these salts were undertaken. Cyclization of **3a** with CuCl and DMB yielded 79% of a single product, whereas $Rh_2(OAc)_4$-induced cyclization afforded 27% of the same material as its major and only isolable product (Scheme 3). Slow evaporation of a MeCN solution afforded material suitable for single-crystal X-ray analysis. Subsequent determination of structure (see Supporting Information) revealed that the carbenoid had indeed migrated along the alkyne chain to afford the more stable carbenoid, which then underwent [2 + 1] cycloaddition to form cyclopropane **9a**. No product was formed that would have arisen from the nonmigrated carbenoid. The most likely explanation is that the equilibrium between the two carbenoids lies in favor of the isomer where the carbenoid is adjacent to the Ph group (**5**) followed by facile alkene cycloaddition (vide infra). Products corresponding to carbenoid dimerization, a known side reaction,[11c] were not encountered. In addition, protic solvents were employed as carbenoid traps under the optimized conditions. Even though the starting material was consumed (decomposed), O−H insertion products unfortunately were not isolated. Stabilization of the carbenoid via extended conjugation throughout the entire molecule could suppress effectively intermolecular O−H insertion by the unactivated alcohol, allowing for alternative degradation pathways.

Additional attempts to trap the carbenoid were made. By replacing the Ph group in **3a** with a 2-biphenyl moiety (e.g., **3b**), cyclization/migration and subsequent insertion into a C−H bond of the biphenyl should afford a fluorene derivative. This method has been successfully used by Saito et al. to trap the carbene from a structurally related 1,2-diketone-ene-yne system.[21] We too have utilized this C−H insertion reaction to intercept carbenes similar to **2a**.[11b,d] Synthesis of **3b** was achieved by deprotecting **7** with fluoride ion and then immediately cross-coupling the terminal alkyne to commercially available 2-iodobiphenyl, affording **3b** in 56% isolated yield for the two steps (Scheme 3). Analogous to diyne **3a**, **3b** could also be synthesized via Cadiot−Chodkeiwicz coupling of terminal alkyne **8** to 2-(bromoethynyl)biphenyl in 79% yield.

As with **3a**, simply heating **3b** in aprotic solvents was either ineffective at inducing cyclization (200 °C) or resulted in decomposition with formation of only polymeric materials (250 °C). After several synthetic attempts, heating **3b** in the presence of DMB and CuCl in DCE at 80 °C afforded the highest yield (52%) of a stable, isolable product. Although absolute structural determination proved to be a challenge, one thing was clear—the lack of a characteristic sharp singlet around 5.5−6.0 ppm (the fluorene methine proton) in the ^{1}H NMR spectrum strongly suggested that fluorene formation had not occurred. Successful crystallization was achieved via slow evaporation of a solution of **9b** in MeCN that afforded material suitable for X-ray diffraction. On the basis of the synthetic results and NMR data, the unmigrated product was expected; however, the crystal structure (see Supporting Information) revealed surprisingly that the migrated [2 + 1] cycloadduct **9b** had effectively formed (Scheme 3). In the absence of DMB, the isoindazole carbenoid degraded through other reaction pathways. Formation of **9b** was unexpected as there was no obvious explanation as to why the carbenoid migrated yet was incapable of inserting into the C−H bond. It is possible that the rate of alkene addition is higher than the rate of C−H insertion or that C−H insertion is sufficiently slow as to favor other degradation pathways. It is also possible that the more stable Cu-carbenoid exists in an orientation that is not favorable for C−H insertion. Analysis of the product in the solid states lends some validity to this assumption as the biphenyl moiety is oriented in such a fashion as to not be available for C−H insertion. Unfortunately, all other variations upon reaction conditions (time, temperature, excess catalyst) also failed to afford fluorene derivatives.

Computational Methods. The energy diagrams for the cyclization of **10a**−**d** were calculated using the Gaussian03[22] suite of programs at the B3LYP[23] level of theory and the 6-31G* basis set. This level of theory has proven to be a reasonable compromise between accuracy and computational cost in a number of very similar cyclization reactions.[11b,d,12,13] All stationary points were confirmed by harmonic frequency analysis. The $-NEt_2$ groups were replaced by $-NH_2$ to reduce the conformational degrees of freedom and to cut computational costs. Solvent dependence was considered using the polarizable continuum model (PCM) as implemented in Gaussian03.[24] To include the coordination of solvent chlorine atoms to the copper, we calculated the reaction energy hypersurface with explicit methyl chloride as well. Because there are many examples of dinuclear complexes of alkynes with Cu, we also explored the reaction with two CuCl molecules, either coordinated to both π systems of a single alkyne or each bound to a separate alkyne.

There are two conformations for the reactant (Figures 1 and 2), with the triazene unit in an unfavorable position for cyclization (**10**) and with the attacking nitrogen atom pointing toward the proximate sp carbon (**11**). Conformations **10a**−**d** (unfavorable for the cyclization) are about 1−2 kcal mol^{-1} more stable than conformations **11a**−**d**. CuCl was assumed to coordinate to the proximate (next to the triazene, Figure 1) or

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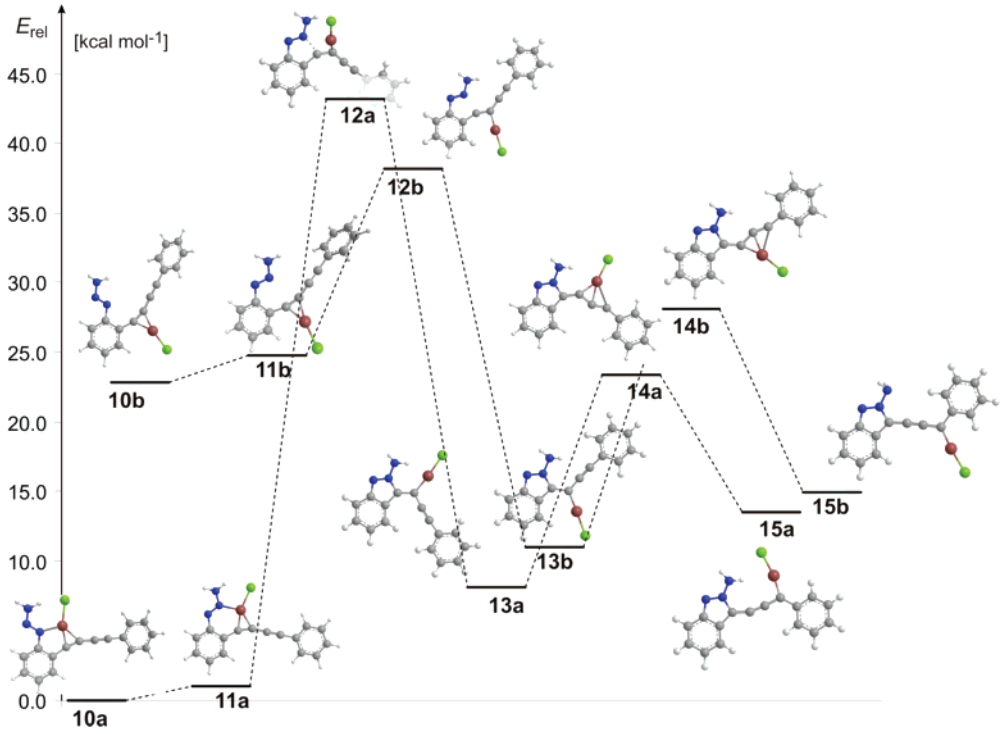

FIGURE 1. DFT (B3LYP/6-31G*) calculated relative energies [kcal mol^{-1}] of educts, transitions states, intermediates, and products of the title reaction (ring closure and carbene shift). CuCl was assumed to coordinate to the proximate (relative to the triazine unit) acetylenic π bond and to the carbenoid centers.

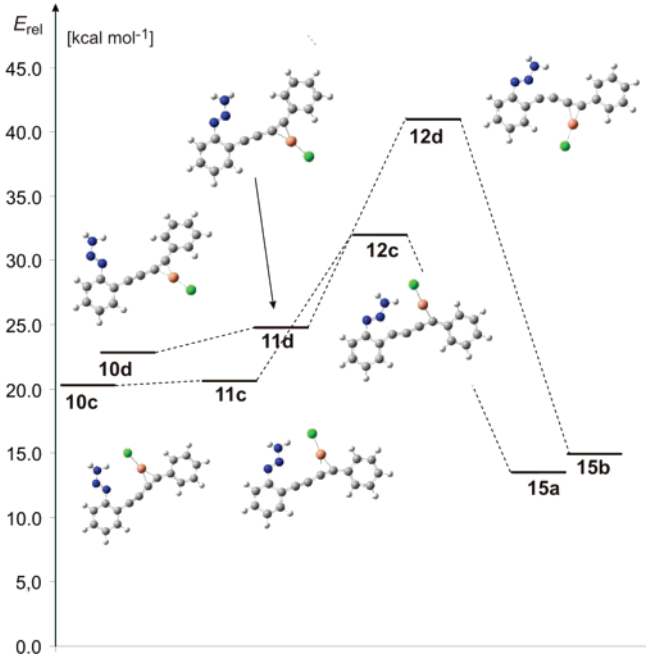

FIGURE 2. DFT (B3LYP/6-31G*) calculated relative energies [kcal mol^{-1}] of educts, transitions states, intermediates, and products of the title reaction (ring closure and carbene shift). CuCl was assumed to coordinate to the remote (relative to the triazine unit) acetylenic π bond and to the carbenoid centers. Compound **12c** is the lowest transition state located in the CuCl-catalyzed coarctate cyclization.

the remote triple bond (Figure 2) in a fashion known from X-ray structures of a number of Cu−alkyne complexes.[25] Both orientations, CuCl *syn* to the triazene side (**10a**, **11a**, **10c**, **11c**) and *anti* to the triazene (**10b**, **11b**, **10d**, **11d**), were considered. All four reaction hypersurfaces, proximate/*syn* (**a**), proximate/*anti* (**b**), remote/*syn* (**c**), and remote/*anti* (**d**), were investigated, and minima and transition states were located (Figures 1 and 2).

The energy difference between the two different coordination modes **10a** vs **10b** and **11a** vs **11b** is quite large. In **10a** and **11a** the Cu center is additionally coordinated to the middle nitrogen of the triazene unit, which lowers the energy by more than 20 kcal mol^{-1} with respect to **10b** and **11b**. However, the more stable coordination in **11a** disfavors the cyclization. During the ring closure the Cu atom has to leave both coordination sites, between which the new C−N bond is formed (the sp carbon and the attacking nitrogen in the triazene unit). Moreover, the nucleophilicity of the attacking nitrogen is reduced in the early stage of the reaction path. Coordination of Cu opposite to the triazene unit favors the nucleophilic attack by withdrawing electrons from the reacting sp carbon. Selected NBO[26] charges are given in Figure 3.

The coarctate nature of the uncatalyzed reaction, thus, is shifted toward a more polar reaction mechanism and an earlier transition state by Cu(I) catalysis. Cu complexation reverses the natural charges of the two proximate alkyne carbon atoms (next to the triazene substituted phenyl group). This might explain why we never detected 6-membered ring products by attack to the second sp carbon (natural charge: −0.43) in CuCl-catalyzed coarctate cyclizations, whereas this is the main reaction path in the uncatalyzed ring closure of the parent (2-ethynylphenyl)triazene.[11] The relative barrier for cyclization, starting from **11b** via transition state **12b** is lowered to only

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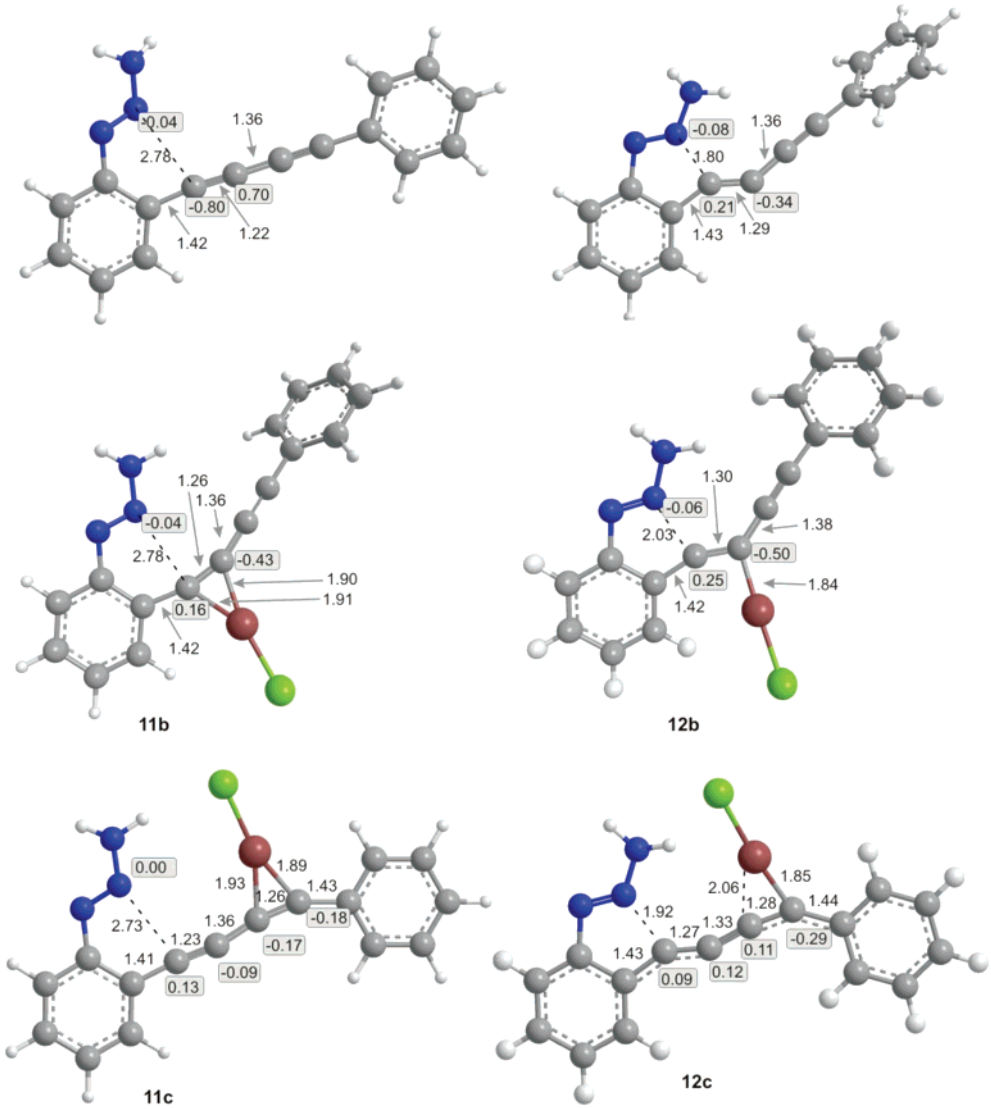

FIGURE 3. Selected bond lengths (Å) and NBO charges (in frames) of reactants **11b** and **11c** and the transition states for ring closure **12b** and **12c** compared with the corresponding stationary points of the uncatalyzed reaction.

13.3 kcal mol^{-1} following this push−pull mechanism (compared to 43 kcal mol^{-1} for **11a→12a**). The overall activation barrier, starting from the much more stable Cu complex **10a**, however, is still quite high (38.1 kcal mol^{-1}), because **10a** is 22.9 kcal mol^{-1} more stable than **11b** (Figure 1).

A similar charge displacement effect but to a somewhat lesser extent is observed if the CuCl unit is coordinated to the remote triple bond (**11c**/**12c**, Figure 3). The activation barrier (transition structure **12c**, Figure 2) is considerably lower (33.1 kcal mol^{-1}) than the corresponding barrier (transition structure **12b**) with the CuCl coordinated to the proximate triple bond (38.1 kcal mol^{-1}). Interestingly, the "remote catalysis" is more efficient if the Cu is bound in *syn* position with respect to the triazene unit (**12c** (*syn*): 33.1, **12d** (*anti*): 41.7 kcal mol^{-1}). Our findings are in agreement with the stereochemistry in nucleophilic substitution reactions. S_N2 reactions prefer the *anti* mechanism and S_N2' reactions frequently follow a *syn* reaction. The most favorable pathway of the CuCl-catalyzed cyclization reaction therefore resembles a S_N2'-type mechanism.

Further coordination or solvation should largely level out the energy difference of the two types of reactant complexes (**10b**−**d** and **11b**−**d** with CuCl η^2-bound to an acetylene vs **10a**, **10e**, **10g**, **11a**, **11e**, and **11g** in which the Cu additionally coordinates to a nitrogen atom of the triazine unit) and thus lowers the barrier. Consideration of the reaction solvent (1,2-dichloroethane) using the simple PCM continuum model[24] using the dielectric constant of DCE lowers the energy difference of both complexes by about 0.5 kcal mol^{-1} and the barrier for ring closure to 36.4 kcal mol^{-1}. Explicit consideration of the coordination properties of the solvent was attempted by optimizing the stationary points with a methyl chloride molecule attached to the Cu atom. The energetic preference of the more stable N-coordinated reactants **10a** and **11a** vs **10b** and **11b** is thus lowered by 3 kcal mol^{-1}; however, the barrier for ring closure remains at 38.0 kcal mol^{-1}. In the experimental system most probably CuCl is further coordinated intermolecularly to the nitrogen atoms of the reactant and product molecules, which would lead to a further decrease of the activation enthalpy for ring closure.

Alkynes are known to form dinuclear Cu complexes.[27,28] To model the influence of multiple coordination we optimized the stationary points with an additional CuCl molecule coordinated

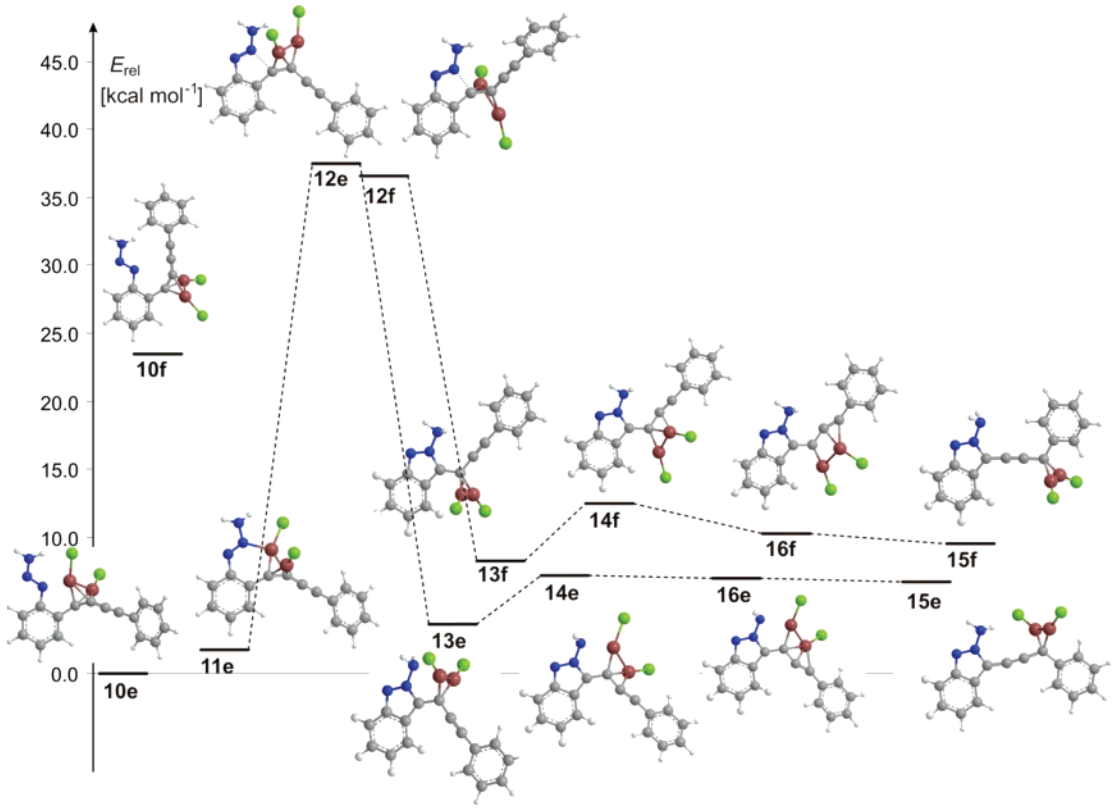

FIGURE 4. DFT (B3LYP/6-31G*) calculated relative energies [kcal mol^{-1}] of educts, transitions states, intermediates, and products of the title reaction (ring closure and carbene shift). Two molecules of CuCl were assumed to coordinate to the sp carbon atoms and the π bonds of the proximate triple bond.

to the second π bond orthogonal to the first CuCl and obtained structures which are similar to published X-ray structures.[27,28] We also considered the mechanism with two CuCl units bound to the proximate and the remote triple bond. With two CuCl molecules both bound to the proximate alkyne (Figure 4), there is only one conformation **11c** (equivalent to **11a**). The barrier for ring closure is 4.4 kcal mol^{-1} higher as compared to the lowest computed barrier with only one CuCl. The stationary points for the reaction with the CuCl units bound to both triple bonds are given in Figure 5. The activation barrier with 41.2 kcal mol^{-1} is too high to represent a plausible pathway.

The energy differences between the two coordination modes, *syn* and *anti* to the triazene (or after ring closure, to the isoindazole unit), are smaller in the carbenoid products **13c**,**d** and **15c**,**d** and the transition state of the carbenoid shift **14c**,**d** as compared to the 1:1 complexes (Table 1). The activation energies for the carbenoid shift do not follow a systematic trend upon including solvation or changing the coordination mode (relative barrier with respect to carbenoid **13a**,**b** and **13c**,**d**: 13.7−17.1 kcal mol^{-1}); however, coordination of a second CuCl drastically lowers the barrier for the carbene shift (~4 kcal mol^{-1}).

In the trapping experiment, exclusively the cyclopropane derived from the remote carbenoid (next to the phenyl substituent) and no product from the proximate carbenoid (α to the isoindazole) was observed. According to our calculations the energetically most favorable S_N2'-type cyclization mechanism does not involve the proximate carbenoid as an intermediate; thus, the remote carbenoid might be trapped before it rearranges to the proximate isomer. Moreover, the proximate carbenoid is sterically shielded by the 2-diethylaminoisoindazole unit, and the trapping reaction, therefore, might be hindered.

TABLE 1. Relative Energies[a] for the Calculated Stationary Points in Figures 1, 2, 4, and 5

one CuCl unit				two CuCl units			
entry	E_{rel}[b]	E_{rel}[c]	E_{rel}[d]	entry	E_{rel}[e]	entry	E_{rel}
10a	0.0	0.0	0.0	**10e**	0.0	**10g**	1.2
10b	22.9	22.2	20.7	**10f**	23.3	–	–
10c	20.2	–	–	–	–	–	–
10d	23.2	–	–	–	–	–	–
11a	0.8	0.7	1.9	**11e**	1.7	**11g**	1.7
11b	24.8	24.4	23.3	–	–	–	–
11c	20.6	-	–	–	–	–	–
11d	25.0	–	–	–	–	–	–
12a	43.0	42.3	42.9	**12e**	37.5	**12g**	41.2
12b	38.1	36.4	38.0	**12f**	36.7	–	–
12c	33.1	–	–	–	–	–	–
12d	41.7	–	–	–	–	–	–
13a	8.2	9.6	8.1	**13e**	3.6	**13g**	7.3
13b	11.0	9.1	11.3	**13f**	8.3	–	–
14a	23.4	22.3	24.3	**14e**	7.3	**14g**	10.8
14b	28.1	25.2	28.7	**14f**	12.5	–	–
15a	13.5	14.5	14.0	**15e**	7.0	**15g**	10.7
15b	14.9	11.9	15.0	**15f**	9.5	–	–
				16e	6.6		
				16f	10.3		

[a] B3LYP/6-31G* calculated optimized geometries. [b] Vacuum. [c] Solvent DCE. [d] Explicit MeCl. [e] Two CuCl at the proximate triple bond. [f] Two CuCl at the remote triple bond.

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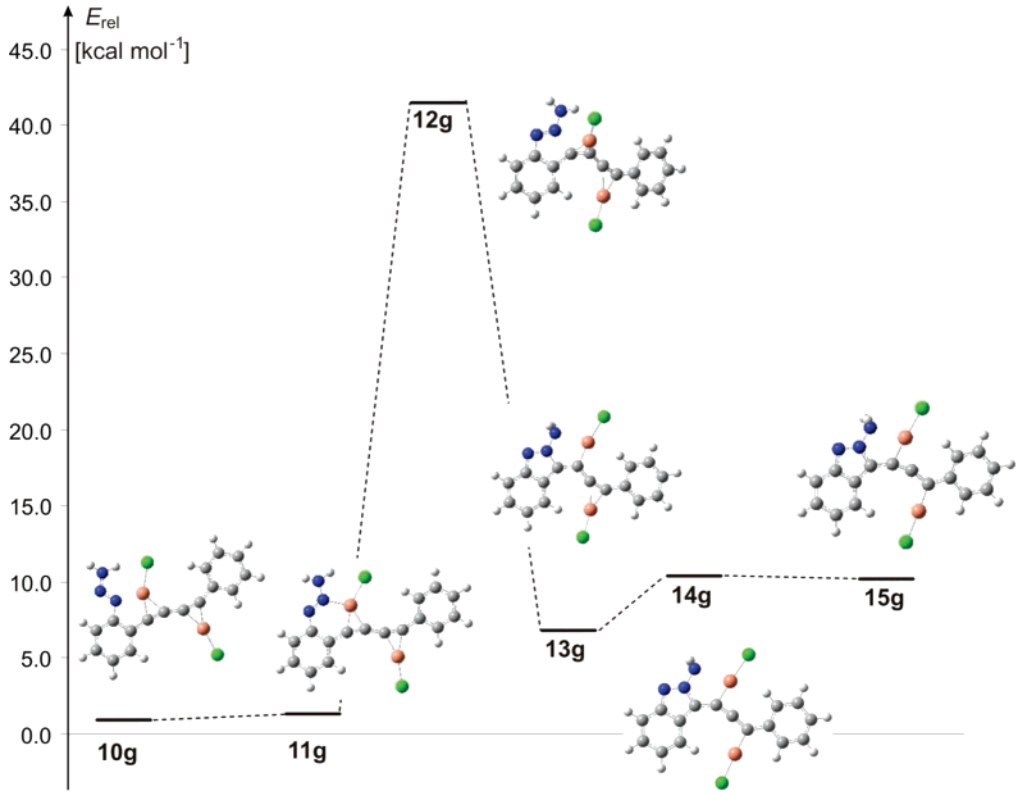

FIGURE 5. DFT (B3LYP/6-31G*) calculated relative energies [kcal mol^{-1}] of educts, transitions states, intermediates, and products of the title reaction (ring closure and carbene shift). Two molecules of CuCl were assumed to coordinate to the sp carbon atoms and the π bonds of the remote triple bond.

Conclusions

In summary, our laboratory has demonstrated the synthetic utility of the coarctate azo-ene-yne cyclization to generate isoindazolyl carbene/carbenoids. As has been demonstrated by our group and others, alkynyl carbenoids undergo formal 1,3-carbene shifts and the rearranged carbenoids can be trapped efficiently with 2,3-dimethyl-2-butene. Calculations indicate that the observed Cu(I) catalysis is based on an electrophilic activation of the remote triple bond by coordination with CuCl. The pathway with the lowest barrier resembles a S_N2' reaction. Further studies of coarctate cyclizations of conjugated hetero-dieneynes to generate heterocycles are in progress.

Experimental Section

General Methods. These are described in reference 13.

TMS-diyne 7. Triazene **6** (1.03 g, 3.05 mmol), $Pd(PPh_3)_4$ (0.185 g, 0.16 mmol), and CuI (60 mg, 0.31 mmol) were dissolved in THF (15 mL) and DIPA (15 mL), and the solution was purged with Ar for 20 min. Trimethylsilylbutadiyne (0.45 g, 3.65 mmol) was added and the reaction mixture stirred under N_2 for 40 h at 50 °C. After cooling, the solution was concentrated. The crude product was redissolved in 4:1 hexanes:CH_2Cl_2, filtered over a short pad of silica, and concentrated in vacuo to afford **7** (1.00 g, 99%) as a tan oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H) 7.21 (dd, J = 8.4, 2.4 Hz, 1H), 3.79 (q, J = 6.9 Hz, 4H), 1.31 (br s, 6H), 0.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.0, 133.0, 130.0, 129.4, 118.3, 117.4, 91.1, 88.1, 78.7, 74.3, 49.3, 42.0, 14.5, 10.7, −0.3; IR (neat) 2963, 2198, 2101, 1465, 846 cm^{-1}; MS (APCI) m/z (%) 332.3 (100, $M^+ + H$), 234.0 (25, $M^+ - C_5H_9Si$), 231.0 (95, $M^+ - C_4H_{10}N_3$).

Phenylbutadiyne 3a. Diyne **7** (0.335 g, 1.0 mmol) was dissolved in THF/MeOH (20:1, 0.1 M), and TBAF (2.0 mL, 1 M THF solution) was added. Upon complete deprotection, as observed by TLC, the mixture was diluted with Et_2O and the organic layer was washed successively with aqueous NH_4Cl (3×) and H_2O (2×), dried ($MgSO_4$), filtered over a short pad of silica, and concentrated in vacuo. The crude alkyne (0.24 g, 0.96 mmol) and iodobenzene (0.11 mL, 0.95 mmol) were dissolved in THF (10 mL) and DIPA (10 mL), and the solution purged with Ar for 20 min. $Pd(PPh_3)_4$ (60 mg, 0.048 mmol) and CuI (12 mg, 0.096 mmol) were added, and the solution was purged for an additional 5 min. The reaction mixture was stirred under N_2 for 40 h at 55 °C. After cooling, the solution was concentrated and purified by chromatography over silica (9:1 hexanes:EtOAc) to afford **3a** (0.245 g, 75%) as a tan solid, mp 58.9−59.7 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.51 (m, 2H), 7.48 (d, J = 2.7 Hz, 1H), 7.38−7.31 (m, 4H), 7.24 (dd, J = 8.7, 2.7 Hz, 1H), 3.31 (q, J = 7.2 Hz, 4H), 1.34 (br s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.7, 132.8, 132.4, 129.8, 129.4, 129.0, 128.4, 122.0, 118.3, 117.8, 82.1, 79.1, 78.4, 74.2, 49.2, 42.0, 14.5, 14.8; IR (neat) 2974, 2208, 2141, 1465 cm^{-1}; MS (APCI) m/z (%) 336.0 (30, $M^+ + H$) 235.0 (80, $M^+ - C_4H_{10}N_3$) 200.2 (60, $M^+ - C_4H_{10}N_3Cl$).

Biphenylbutadiyne 3b. Diyne **7** (0.57 g, 1.7 mmol) was dissolved in THF/MeOH (20:1, 0.1 M), and TBAF (3.4 mL, 1M THF soln) was added. Upon complete deprotection, as observed by TLC, the mixture was diluted with Et_2O and the organic layer was washed successively with aqueous NH_4Cl (3×) and H_2O (2×), dried ($MgSO_4$), filtered over a short pad of silica, and concentrated in vacuo. The crude alkyne (0.45 g, 1.7 mmol) and 2-iodobiphenyl (0.38 g, 1.38 mmol) were dissolved in THF (10 mL) and DIPA (10 mL), and the solution was purged with Ar for 20 min. $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) and CuI (30 mg, 0.14 mmol) were added, and the solution was purged for an additional 5 min. The reaction mixture was stirred under N_2 for 40 h at 50 °C. After cooling, the mixture was diluted with EtOAc, filtered over a short pad of silica, and concentrated in vacuo. The crude diyne was

chromatographed on silica (4:1 hexanes:CH_2Cl_2) to afford **3b** (0.32 g, 56%) as a tan oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66−7.59 (m, 3H), 7.46−7.37 (m, 5H), 7.34−7.29 (m, 3H), 7.20 (dd, J = 8.7, 2.4 Hz, 1H), 3.76 (q, J = 7.2 Hz, 4H), 1.26 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 144.8, 140.0 134.3, 132.6, 129.8, 129.6, 129.4, 129.2, 129.1, 128.1, 127.6, 127.0, 120.3, 118.3, 117.8, 81.8, 79.3, 78.7, 76.9, 49.26, 42.1, 14.4, 10.69; IR (neat) 2975, 2207, 2137, 1466, 1389 cm^{-1}; MS (APCI) *m*/*z* (%) 412.2 (100, $M^+ + H$), 311.0 (20, $M^+ - C_4H_{10}N_3$), 276.0 (60, $M^+ - C_4H_{10}N_3Cl$).

Phenylcyclopropane 9a. A pressure flask was charged with diyne **3a** (0.22 g, 0.66 mmol), DCE (25 mL), and 2,3-dimethyl-2-butene (5 mL). The resulting solution was purged with Ar for 5 min. CuCl was added (0.124 g, 1.22 mmol), and the sealed flask was heated in a 125 °C sand bath for 15 h. The mixture was cooled to room temperature, filtered over a short pad of silica (eluting with CH_2Cl_2), and concentrated in vacuo to yield **9a** (0.234 g, 79%) as a pale yellow solid, mp 132.4−133.7 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, J = 9.3 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.37−7.24 (m, 5H), 7.18 (dd, J = 9.3, 2.1 Hz, 1H), 3.21 (q, J = 6.9 H, 4H), 1.50 (s, 6H), 1.09 (s, 9H), 0.80 (t, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.2, 138.4, 131.3, 128.3, 127.7, 127.4, 126.6, 121.5, 121.3, 119.3, 119.1, 104.9, 67.9, 52.2, 33.5, 30.8, 20.6, 20.5, 12.0; IR (KBr) 2973, 2220, 1885, 1462 cm^{-1}; MS (APCI) *m*/*z* (%) 420.2 (100, $M^+ + H$), 348.1 (30, $M^+ - C_5H_{12}$), 336.2 ($M^+ - C_6H_{12}$).

Biphenylcyclopropane 9b. A pressure flask was charged with diyne **3b** (0.180 g, 0.44 mmol), DCE (25 mL), and 2,3-dimethyl-2-butene (5 mL). The resulting solution was purged with Ar for 5 min. CuCl (0.17 g, 1.75 mmol) was added, and the sealed flask was heated in an 80 °C sand bath for 30 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2, filtered over a short pad of silica, and concentrated. The resultant crude material was chromatographed over silica (4:1 hexanes:CH_2Cl_2) to afford **9b** (0.11 g, 52%) as a yellow solid, mp 155.5−156.7 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98−7.93 (m, 2H), 7.61−7.68 (m, 2H), 7.46−7.33 (m, 7H), 7.25 (dd, J = 9.0, 1.8 Hz, 1H), 3.25 (q, J = 7.2 Hz, 4H), 1.50 (s, 3H), 1.09 (s, 3H), 0.99 (s, 3H), 0.83 (t, J = 7.2 Hz, 6H), 0.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.4, 142.8, 138.3, 135.9, 124.1, 132.6, 131.2, 130.1, 128.8, 127.8, 127.7, 127.19, 127.16, 126.9, 121.6, 119.3, 119.2, 106.3, 69.5, 52.4, 32.2, 31.3, 29.6, 20.8, 20.5, 19.7, 19.4, 11.9 IR (KBr) 2964, 2207, 1732, 1456 cm^{-1}; MS (APCI) *m*/*z* (%) 495.8 (100, $M^+ + H$), 411.7 (95, $M^+ - C_6H_{12}$) 304.8 (30, $M^+ - C_{10}H_{20}NCl$).

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Supporting Information Available: Experimental details and copies of ^{1}H and ^{13}C NMR spectra for **3a**, **3b**, **7**, **9a**, and **9b**; X-ray structural data for **9a** and **9b** (cif file, structure refinement details, tables of atomic coordinates, thermal parameters, bond lengths, bond angles, etc); Cartesian coordinates for computed structures in Figures 1−5. This material is available free of charge via the Internet at http://pubs.acs.org.

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