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Experimental and Theoretical Investigation of the Coarctate Cyclization of (2-Ethynylphenyl)phenyldiazenes‡

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Received June 11, 2004

A new route to substituted 2-phenyl-2*H*-indazoles through the cyclization of (2-ethynylphenyl)-phenyldiazenes is presented. A coarctate reaction pathway forms the isoindazole carbene under neutral conditions, at moderate temperatures, and without the requirement of a carbene stabilizer. A wide variety of previously unknown diazene precursors was synthesized and cyclized. Trapping of the carbene with a silyl alcohol followed by deprotection affords the 3-hydroxymethyl-2-phenyl-2*H*-indazoles in good overall yield. The free carbene could also be trapped as a [2 + 1] cycloadduct with 2,3-dimethyl-2-butene.

Introduction

Heterocyclic compounds are important in organic synthesis due to their prevalence in biologically active compounds, such as inhibitors and antitumor agents.[1] The indazole moiety constitutes the key subunit in many drug substances with a broad range of pharmacological activities including antitumor,[2] anti-HIV,[3] and antiinflammatory properties.[4] Functionalized cinnolines also have a broad range of pharmacological activities,[5] and 2-alkylisoindazoles are currently being investigated in part of a drug discovery program.[6] Because of this, it is desirable to synthesize these types of compounds in an efficient and high-yielding manner, while tolerating a wide variety of functional groups.

Synthesis of the nitrogen-containing heterocycles mentioned above often involves formation of diazonium salts. These must be generated by strong acids in polar solvents to form a diazonium species susceptible to nucleophilic attack by an activated *o*-carbon nucleophile.[7] This in turn limits the functional group tolerance of these types of reactions. Other recent syntheses of nitrogen-containing heterocycles often utilize a transition metal-mediated route involving an external 1,2-disubstituted alkyne and a substituted iodoarene or an alkynylarene and an alkyl- or arylhalide.[8] A recently reported synthesis of 2-aryl-2*H*-indazoles utilizing a Pd catalyst suffers from moderate cyclization yields and has limited functional group tolerance due to the requirement of excess base for the reaction to proceed.[9] Pd-catalyzed intramolecular aminations have also been utilized in heterocyclic synthesis.[10]

Recently, our group reported a new reaction pathway that allows for the formation of both isoindazoles and cinnolines from a single synthetic precursor, (2-ethynylphenyl)triazenes (**1**), under neutral conditions (Scheme 1).[11] The yields of the two different cyclization products were very good to excellent for all functional groups attempted. Through a combination of computational and experimental data we were able to determine the separate mechanisms of the two cyclizations. Cu-mediated

‡ Dedicated to Professor W. E. Billups on occasion of his 65th birthday.

† To whom inquiries regarding the X-ray data should be directed.

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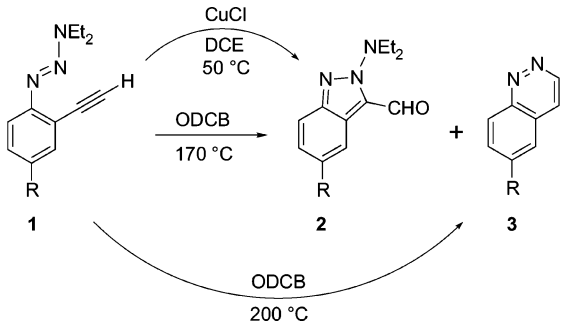
10.1021/jo049011r CCC: $27.50
Published on Web 09/17/2004

SCHEME 1



cyclization in 1,2-dichloroethane (DCE) to the five-membered isoindazole (**2**) proceeds through a pseudocoarctate[11a,12] pathway affording a carbene that can then be trapped by molecular oxygen or an alkene. Cyclization to the six-membered cinnoline (**3**), achieved by heating to 200 °C in *o*-dichlorobenzene (ODCB), proceeds through a cinnolinium zwitterionic intermediate that is then trapped as the cinnoline by loss of *N*-ethylethanimine.[11a] Density Functional Theory (DFT) calculations[13] computed at the B3LYP/6-31G* level of theory supported both the carbene and dehydrocinnolinium mechanistic pathways. Predicted by the relative energies, the isoindazole carbene is the kinetic intermediate and the dehydrocinnolinium zwitterion is the thermodynamic intermediate. This was proven experimentally by independently generating the isoindazole carbene and heating in ODCB to yield the cinnoline, thus supporting the viability of DFT calculations to assist in analyzing these cyclization reactions.

Given the success of the triazene cyclizations, we envisaged this type of heterocycle formation being applicable to a wide variety of compounds. Since DFT calculations proved to be a useful tool in determining the energy hypersurface in our initial studies, we utilized DFT to help guide our synthetic strategy. By systematically changing the atoms in the parent triazene, a wide variety of precursors for cyclization was elucidated. DFT calculations were performed on this set of permutations with the most viable precursor synthetically and computationally being the phenyldiazene analogue of the parent triazene. Although diazenes have previously been utilized in transition metal-catalyzed cyclization reactions in combination with external 1,2-disubstituted alkynes,[14] to the best of our knowledge, an intramolecular cyclization of an *o*-alkynylphenyl-substituted diazenes has never been reported. We present here the theoretical and experimental results for the cyclization of a series of (2-ethynylphenyl)phenyldiazenes.

Results and Discussion

Computational Studies. When performing theoretical calculations a compromise between computational cost and accuracy (level of theory, basis set) must be met. The results on the (2-ethynylphenyl)triazenes proved that the B3LYP/6-31G* level of theory is a viable and reliable method.[11a,12,15] The calculated energy diagram of the parent diazene **4** is shown in Figure 1. The energy hypersurface is topologically similar to the parent (ethynylphenyl)triazene.[11a] There are two modes of cyclization: a coarctate[15] 5-ring cyclization yielding a carbene as the primary product and a 6-ring cyclization forming a zwitterionic intermediate. Both reactions exhibit a barrier of activation that is 4−5 kcal mol^{-1} lower than that in the previously investigated triazene derivative. Therefore, the cyclization temperature is expected to be lower than was observed for the triazenes.

The transition structure of the coarctate cyclization with the lowest barrier is shown in Figure 2. As expected for an endothermic reaction the geometry is closer to carbene product than to the reactant. With a length of 1.822 Å the C−N bond being formed during cyclization is quite short. The transition structure is not flat and therefore the question arises whether the cyclization is a pseudocoarctate or a coarctate reaction. An ACID[16] calculation revealed that all C−C and C−N bonds are conjugated (Figure 3). The transition state, therefore, is coarctate.

Following the current density vectors that are plotted onto the ACID isosurface (Figure 3), the bond making and breaking process can be described as a 10-electron ($4n + 2$) process involving the indazole carbene system. The diatropic ring current is constricted at the carbon atom next to the carbene center (hence the name "coarctate" reaction). At the coarctate center two orthogonal p orbitals are involved in a delocalized system of electrons, each contributing two electrons. At the carbene center, the empty p orbital is also included. With 10 electrons the reaction is thermochemically allowed. The phenyl ring with its own diatropic ring current is in conjugation with the delocalized system of electrons of the transition state and probably lowers the barrier of activation further.

Initial Cyclization Studies. The synthesis of silylated (2-alkynylphenyl)diazenes **6**−**8**, our starting materials in the initial cyclization studies, is outlined in Scheme 2. Pd-catalyzed cross-coupling of iododiazene **9**[17] with trimethylsilylacetylene (TMSA) under Sonogashira conditions[18] afforded disappointing yields of **6**, with the best result (50%) achieved with $PdCl_2$(dppf) as catalyst. Diazene **6** visibly degraded upon workup, which we attribute to the lability of the TMS protecting group and instability of the deprotected diazene (vide infra). To circumvent this problem, the more robust triisopropylsilyl and triethylsilyl groups were employed. Utilizing triisopropylsilylacetylene (TIPSA) and triethylsilylacetylene (TESA) under standard conditions furnished the stable diazenes **7** and **8** in 97% and 87% yield, respectively.

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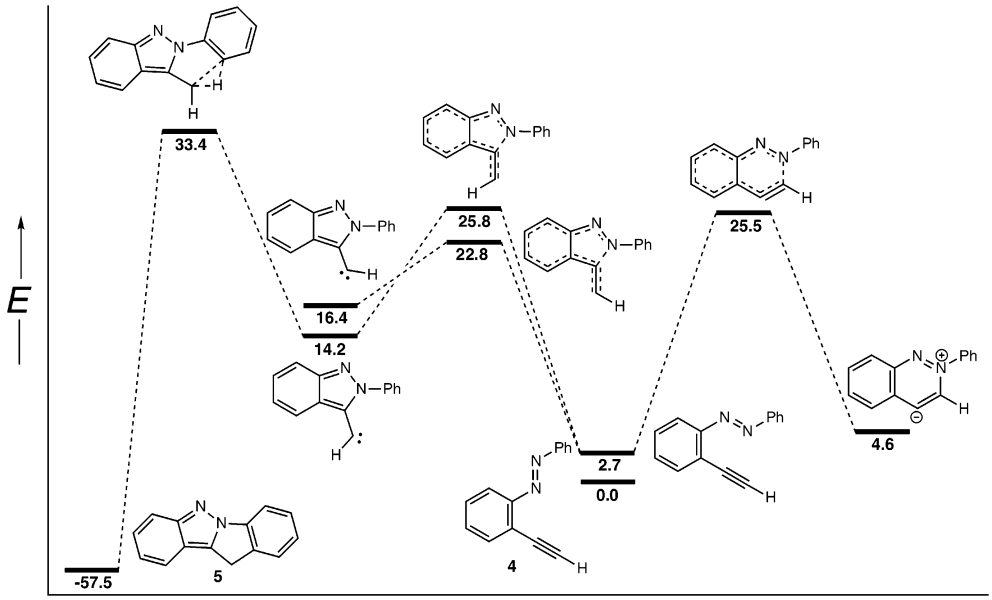


FIGURE 1. DFT (B3LYP/6-31G* + ZPE) calculated relative energies of reactants, transition states, and products.

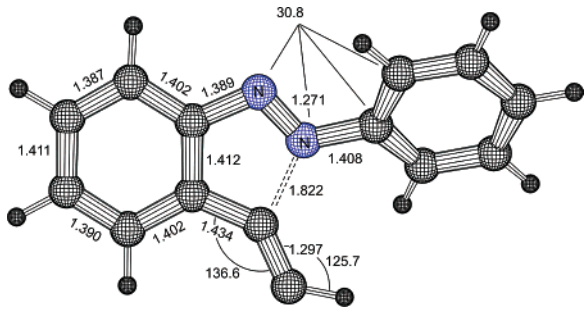


FIGURE 2. B3LYP/6-31G* optimized geometry of the transition state of the coarctate (5-ring) cyclization with the lowest energy of activation (22.8 kcal mol^{-1}).

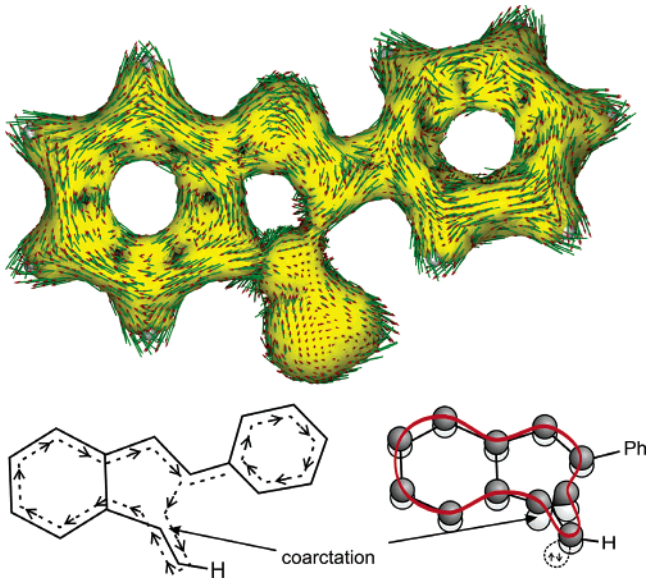


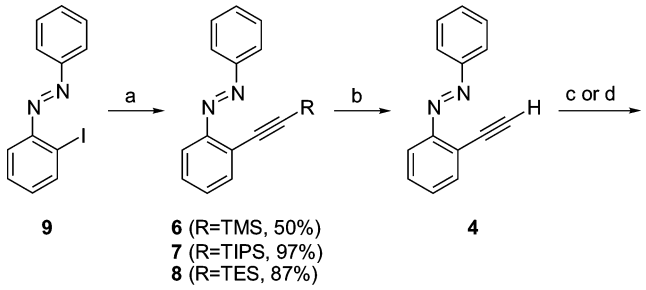
FIGURE 3. ACID plot of the coarctate transition state (see Figure 2). Current density vectors are plotted onto the ACID isosurface (isosurface value 0.045, magnetic field orthogonal to the benzene ring of the indazole system and pointing toward the reader). The "flow of electrons" is schematically depicted in the structural formula (bottom left). The basis orbitals involved in the 10 electron delocalized system are shown in the orbital scheme (bottom right). The red line depicts the topology of the orbital overlap.

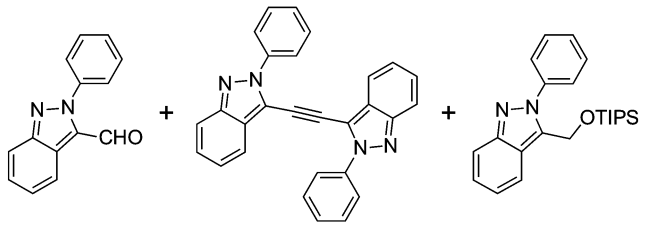
Protiodesilylation of compound **7** was attempted with Bu_4NF (TBAF) in THF/MeOH. After aqueous workup and subsequent solvent removal by heating under reduced pressure, the solution of **4** changed from bright orange-red to dark brown. No unreacted free alkyne was observable by TLC and multiple unidentified degradation products were present. Workup without heat, but employing filtration over a short pad of silica also led to product degradation. Exposure of **4** to air for an extended period of time (ca. 20−25 min) also promoted degradation. None of these problems were encountered in the analogous studies of the parent (2-ethynylphenyl)triazenes, which were stable under ambient conditions for several months. It is possible that the degradation products result from facile formation of the cyclized carbene due to extended conjugation, but other degradation pathways are also possible.

Following conditions for the successful cyclization of **1** to **2**, desilylation of **7** and immediate heating of crude **4** in DCE at 50 °C with 5.0 equiv of CuCl led to rapid discoloration and formation of multiple compounds as evident by TLC. Cooling **4** to 0 °C in DCE followed by subsequent addition of 2.0 equiv of CuCl, however, afforded the expected aldehyde **10** plus two other major unidentified (and unanticipated) products in roughly equal yields (ca. 10% each, Scheme 2). Use of $CuCl_2$ under the same conditions furnished **10** in 39% yield and substantially less of the other products; $Cu(OAc)_2$ gave very poor yields of all three compounds. Yields with several other Cu as well as Rh salts as catalysts were equally discouraging.

Recrystallization of the first unknown from $CHCl_3$ afforded material suitable for X-ray diffraction (see Supporting Information), which identified the compound as alkyne dimer **11** (Scheme 2). This curious molecule arises from the homodimerization of **4** followed by cy-

SCHEME 2 [a]





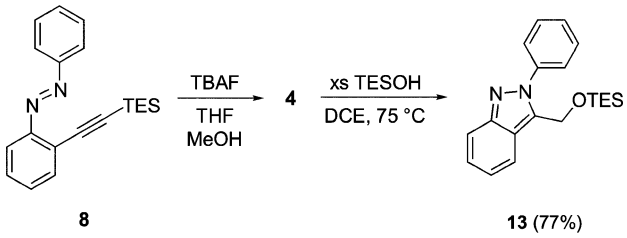
CuCl	10%	11%	9%
$CuCl_2$	39%	4%	3%
$Cu(OAc)_2$	5%	5%	3%
No Cu salt	0%	0%	61%

[a] Reagents and conditions: (a) trialkylsilylacetylene, $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf), CuI, TEA, 30−50 °C; (b) TBAF, MeOH, THF; (c) "Cu" salt, DCE, 0 °C; (d) DCE, 75 °C.

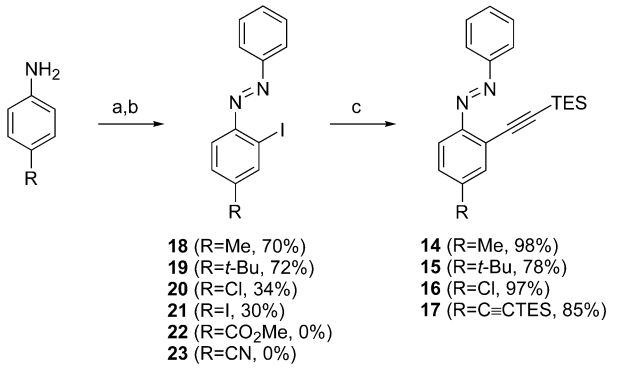
clization of the resultant bis-diazenediyne. Similar research in our laboratory has shown that homodimerization of **1** and subsequent mild heating induces a double cyclization to yield a bis-isoindazole dimer, with the inclusion of CuCl not required for cyclization to occur.[19] Definitive synthesis of **11** was carried out following the method of Mori et al.[20] Homodimerization of organosilane **6** in the presence of CuCl in the polar solvent DMSO at 30 °C furnished **11** in 45% yield; none of the uncyclized homodimer was detected.

Along with searching for optimal conditions for cyclization to the 2*H*-indazolecarbaldehydes (**10**), conditions favorable for cyclization and subsequent insertion of the carbene into the phenyl C−H bond to furnish **5** were also underway. To promote this insertion, we needed to heat **4** in an environment devoid of other molecules which could function as carbene traps. Diazene **7** was deprotected with TBAF, subjected to aqueous workup, and concentrated without heat. The red oil was taken up in DCE and subjected to 4 freeze/pump/thaw cycles to remove oxygen from the system. Heating **4** at 75 °C overnight and subsequent workup afforded what was at first thought to be the tetracyclic product **5**, contaminated with triisopropylsilanol (TIPSOH). The spectral data, however, were consistent with the second of the previous unknowns produced by the Cu-mediated cyclization. As before, determination of the X-ray crystal structure (see Supporting Information) provided another surprising

SCHEME 3



SCHEME 4 [a]



[a] Reagents and conditions: (a) $BnNEt_3ICl_2$, $CaCO_3$, MeOH, CH_2Cl_2; (b) PhNO, AcOH, 85 °C; (c) TESA, $PdCl_2(PPh_3)_2$, CuI, TEA, 50 °C.

result: instead of inserting into the phenyl C−H bond, the carbene had indeed been trapped by inserting into the O−H bond of residual TIPSOH, affording **12** in 61% yield (Scheme 2). Although TIPSF is produced by the desilylation reaction, the molecule is readily hydrolyzed in the aqueous workup, giving TIPSOH. The low volatility and polarity of this latter material makes it difficult to remove by normal vacuum or chromatographic means. Unfortunately, tetracycle **5** was never observed in any of our synthetic trials.

The formation of **12** in moderate yield suggested that trapping the carbene with a silanol might be a viable alternative to Cu-induced cyclization, which at best had provided **10** in modest yield. For these experiments we chose TESOH because of its greater volatility than TIPSOH, consequently aiding in removal of the excess silanol upon workup. Silylated precursor **8** was deprotected following the stringent conditions previously determined, taken up in DCE, and immediately degassed. An excess of TESOH (2.7 equiv) was added and the reaction was allowed to stir at 75 °C for 3 h. After workup of the reaction, the trapped isoindazole **13** was obtained in a gratifying 77% yield (Scheme 3).

Diazene Syntheses. With the success of the TESOH-trapped isoindazole, we moved our attention to the synthesis of a wide variety of substituted phenyl 2-(triethylsilylethynyl)phenyl diazene precursors. Compounds **14**−**17** were prepared in moderate to very good overall yields for the three steps from the corresponding 4-substituted anilines (Scheme 4). Iodination of the anilines with $BnNEt_3ICl_2$ and $CaCO_3$ in $MeOH/CH_2Cl_2$ followed by condensation with nitrosobenzene in AcOH at 85 °C furnished iododiazenes **18**−**21**.[17,21] Synthesis of the more electron-deficient diazenes **22** and **23**, however, was not possible via this route as the amine functionality was

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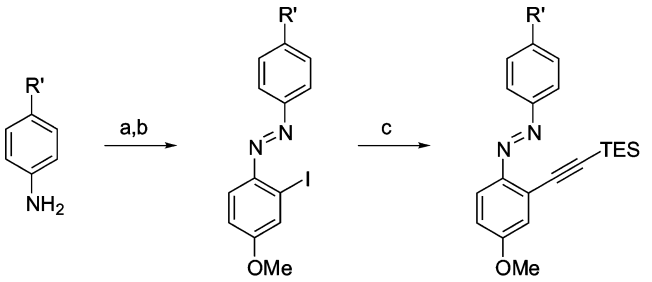
SCHEME 5 [a]



24 (R=H, 77%)
25 (R=Br, 45%)
26 (R=F, 66%)
27 (R=CO_2Me, 69%)
28 (R=CN, 53%)
29 (R=NO_2, 53%)

30 (R=H, 67%)
31 (R=Br, 92%)
32 (R=F, 78%)
33 (R=CO_2Me, 86%)
34 (R=CN, 66%)
35 (R=NO_2, 65%)

[a] Reagents and conditions: (a) HCl, $NaNO_2$, 3-iodophenol, KOH, MeCN, H_2O; (b) MeI, Cs_2CO_3, DMF; (c) TESA, $PdCl_2$(dppf), CuI, DIPA, THF, 50 °C.

effectively deactivated toward attack of the nitroso group. Pd-catalyzed cross-coupling of **18**−**21** with TESA gave precursors **14**−**17**.

An alternative approach to diazene formation involved capture of an arenediazonium electrophile with an activated arene. Our initial attempts at reacting the diazonium salts of the iodinated anilines with a basic solution of aqueous phenol failed to provide the diazenes in satisfactory yield; however, reversing the placement of the iodo substituent proved more successful (Scheme 5). Thus, diazotization of several commercially available 4-substituted anilines and subsequent addition to a basic solution of 3-iodophenol furnished the desired diazenes. The hydroxyl groups were then converted to their methyl ethers by addition of MeI and Cs_2CO_3 in DMF, affording iododiazenes **24**−**29** in 45−77% yield for the two steps. The methoxy functionality was chosen to circumvent foreseeable problems that could be encountered if the hydroxyl group was present during Sonogashira cross-coupling. Also, due to the relatively high insolubility of the polar diazenes, ease of workup and purification was increased upon conversion to the methoxy derivatives. Inclusion of the activating substituent on the iodoarene ring, however, disfavored standard Sonogashira conditions as cross-coupling with TESA and $PdCl_2(PPh_3)_2$ as catalyst suffered from lower than desirable yields. Utilizing the more active catalyst $PdCl_2$(dppf) resulted in yields that were increased typically by 15−20%, affording ethynylated diazenes **30**−**35**.

Optimized Isoindazole Formation. With a variety of synthesized diazenes in hand, we turned our attention toward heterocycle formation. Deprotection, cyclization, and subsequent removal of the silyl group to yield the free −OH was carried out (Scheme 6) and the results are summarized in Table 1. The yields of isoindazoles **36**−**46** were very good for all functional groups attempted except for the formation of **46**, which bears the electron-withdrawing nitro group. In this instance, isoindazole formation was also accompanied by formation of several low-yielding, unidentified side products. Unfortunately,

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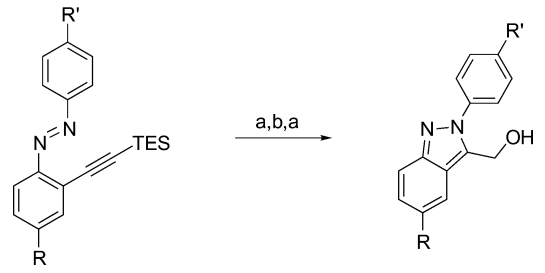
SCHEME 6 [a]



8, **14-17**, **30-35** **36-46**

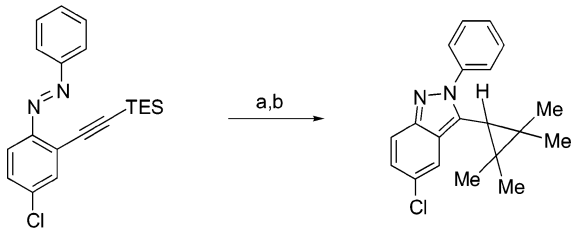
[a] Reagents and conditions: (a) TBAF, THF, MeOH; (b) excess TESOH, DCE, 75 °C.

TABLE 1. Yields of Isoindazoles via Scheme 6

s.m.	R	R′	isoindazole[a]
8	H	H	**36**, 75%
14	Me	H	**37**, 80%
15	*t*-Bu	H	**38**, 79%
16	Cl	H	**39**, 82%
17	C≡CH[b]	H	**40**, 80%
30	OMe	H	**41**, 79%
31	OMe	Br	**42**, 79%
32	OMe	F	**43**, 78%
33	OMe	CO_2Me	**44**, 72%
34	OMe	CN	**45**, 73%
35	OMe	NO_2	**46**, 54%

[a] Overall yield for the three synthetic steps. [b] Both TES groups are removed in step a.

SCHEME 7 [a]



16 **47** (75%)

[a] Reagents and conditions: (a) TBAF, THF, MeOH; (b) excess 2,3-dimethyl-2-butene, 75 °C.

decreasing the cyclization temperature did not remedy this problem. It should be noted that although there are six synthetic steps from the commercially available anilines to form the final isoindazoles, the overall yields averaged around 40%.

Unlike the triazene cyclization reactions, which required inclusion of Cu salts to stabilize the reactive species as the carbenoid, the diazenes underwent cyclization and concomitant formation of the free carbene, which could be intercepted with TESOH by insertion into the O−H bond. To further confirm experimentally formation of the free carbene, diazene **16** was deprotected and cyclized with use of a well-known carbene trap, 2,3-dimethyl-2-butene, as solvent (Scheme 7). From the reaction mixture cyclopropane **47** was obtained in 75% isolated yield, indeed confirming carbene formation.

It is worth noting that in none of the diazene experiments did we ever observe formation of the six-membered-ring cinnoline, unlike what was observed in the triazene

cyclizations. Heating to higher temperatures and allowing for longer reaction times in a variety of solvents failed to provide products derived from six-membered-ring cyclization and generally resulted in complete decomposition. Whereas with a (2-ethynylphenyl)triazene intermolecular deprotonation/elimination of the zwitterionic intermediate afforded an imine and the neutral cinnoline, the analogous reaction pathway for a (2-ethynylphenyl)-phenyldiazene would produce a cinnoline along with benzyne. Clearly, formation of such a high energy species is disfavored, and thus only the coarctate pathway for formation of the isoindazole carbene is observed.

Conclusions

A novel route for the selective synthesis of 2-phenyl-2*H*-indazoles from previously unknown (2-alkynylphenyl)phenyldiazenes has been developed. Unlike earlier methods, these cyclizations are performed under neutral conditions that allow for greater versatility and functional group tolerance. Thus, selective trapping of the isoindazole carbene with TESOH and subsequent desilylation provides the 2-phenyl-2*H*-indazole-3-carbinols in very good overall yield. We are currently working on extending this new methodology to the construction of other heterocyclic compounds.

Computational Methods

All theoretical calculations have been performed with the Gaussian 98 suite of programs[22] at the B3LYP/6-31G* level[23] of DFT. All stationary points were confirmed by harmonic frequency analysis, and the energies of the stationary points were determined, including zero point energies at the same level of theory. ACID scalar fields were computed with our own program.[16] Current density vectors were calculated with the CSGT method of Keith and Bader.[24]

Experimental Section

General. See Supporting Information.

General Iodination Procedure A. The starting aniline (1 equiv), $BnNEt_3ICl_2$ (1.15 equiv), and $CaCO_3$ (1.4 equiv) were dissolved in 5:1 CH_2Cl_2:MeOH (0.1 M) and the solution was stirred at room temperature for 8 h. The resulting mixture was filtered, and the solvent was evaporated. The crude product was redissolved in Et_2O and washed successively with a $NaHSO_3$ solution (10 wt %), brine, and H_2O. The organic layer was dried ($MgSO_4$), filtered over a short pad of silica, and concentrated to afford the desired product in sufficiently pure form for further use.

General Diazene Procedure B. The iodinated aniline (1.0 equiv) was dissolved in AcOH (0.1 M) and to this was added nitrosobenzene (1.7−2.0 equiv). The solution was heated to 85 °C for 40 h. The resulting mixture was cooled to room temperature, diluted with EtOAc, and washed with brine (2×) and H_2O (3×). The organic layer was dried ($MgSO_4$), filtered over Celite, and concentrated in vacuo. The resulting oil was dissolved in a 1:1 mixture of CH_2Cl_2:hexanes and filtered over a short pad of silica. Column chromatography on silica gel gave the desired product.

General Diazene/Methoxy Formation Procedure C. The commercially available para-substituted aniline (1.0 equiv) was dissolved in a minimal amount of MeCN. Concentrated HCl (2.0 equiv) was added and a minimal amount of H_2O was added to keep the aniline in solution. The reaction mixture was then cooled to below −5 °C in a brine/ice bath (monitored internally). $NaNO_2$ (1.2 equiv) was dissolved in a minimal amount of MeCN:H_2O (1:1) and slowly added to the reaction mixture at a rate such that the temperature of the forming diazonium solution remained below −2 °C. Upon completion, the reaction was allowed to stir at −10 °C for 30 min. In a separate flask, 3-iodophenol (1.1 equiv) and KOH (2.0 equiv) were dissolved in the minimal amount of MeCN:H_2O (10:1) and cooled to below −5 °C in a brine/ice bath (monitored internally). The cooled diazonium salt solution was then added via cannula into the basic solution. Once addition was complete, the reaction mixture was slowly allowed to warm to room temperature over 3 h and stirring was continued at room temperature for an additional 3 h. The reaction mixture was then diluted with EtOAc and the aqueous layer acidified. The organic layer was washed with 10% HCl solution (2×), brine (2×), and H_2O (1×). The organic layer was dried ($MgSO_4$), filtered over a short pad of silica (EtOAc), and concentrated to give the hydroxydiazene.

The crude hydroxydiazene produced above was dissolved in DMF (0.05 M) and Cs_2CO_3 (2.1 equiv) and MeI (1.2 equiv) were added. The mixture was allowed to stir at ambient temperature for 40 h, diluted with 10% HCl solution, and extracted with EtOAc (3×). The combined organics were washed with H_2O (1×), 0.5 M NaOH solution (2×), and H_2O (2×). The organic layer was dried ($MgSO_4$), filtered over a short pad of silica, and concentrated in vacuo. The solids were then recrystallized from a EtOH/H_2O mixture, filtered, and dried to yield the desired product.

General Acetylene Coupling Procedure D. The (2-iodophenyl)phenyldiazene (1 equiv), Pd(II) catalyst (0.02−0.05 equiv), CuI (0.1 equiv), and either (trimethylsilyl)acetylene, (triisopropylsilyl)acetylene, or (triethylsilyl)acetylene (1.4 equiv) were dissolved in an amine base (0.1 M solution based on diazene). The mixture was immediately degassed by three successive freeze−pump−thaw cycles, and the flask was charged with N_2. The mixture was heated to 50 °C and stirred under N_2 overnight. After cooling, the mixture was filtered over a short pad of silica (CH_2Cl_2) and concentrated in vacuo. Column chromatography on silica gel gave the desired product.

General Deprotection/TESOH Cyclization/Desilylation Procedure E. The (2-triethylsilylethynylphenyl)phenyldiazene was dissolved in a mixture of THF:MeOH (20:1, 0.1 M). TBAF (1 M solution in THF, 2.0 equiv) was added and the reaction was allowed to stir at room temperature for 1−3 min. The solution was diluted with Et_2O, and successively washed with a saturated aqueous NH_4Cl solution (4×), brine (3×), and H_2O (4×). The organic layer was dried ($MgSO_4$), filtered over Celite under a constant stream of N_2, and concentrated in vacuo with no heat. The desilylated product was taken up in DCE (0.05 M) and immediately degassed by two successive freeze−pump−thaw cycles. TESOH (2.7 equiv) was added and the reaction was degassed by two additional freeze−pump−thaw cycles. The flask was placed in a 75 °C preheated sand bath and allowed to stir under vacuum for 3 h. After cooling to room temperature, the crude 2-phenyl-3-triethylsilanyloxymethyl-2*H*-indazole was dissolved in a mixture of THF:MeOH (20:1, 0.1 M). Excess TBAF (1 M solution

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in THF) was added and the reaction was allowed to stir at room temperature until the complete desilylation of isoindazole had taken place (generally 1−5 min). Progress was monitored by TLC. Upon completion, the solution was diluted with Et_2O and washed successively with saturated aqueous NH_4Cl solution (4×), brine (3×), and H_2O (4×). The organic layer was dried ($MgSO_4$), filtered over a short pad of silica (Et_2O), and concentrated in vacuo to afford the product.

Acknowledgment. We thank the National Science Foundation and the Fonds der Chemischen Industrie for financial support. L.D.S. acknowledges the NSF for an IGERT fellowship. We thank Jazmin Rivers for her help in preparing and purifying selected compounds.

Supporting Information Available: Synthetic details and spectral data for **6**−**21** and **24**−**47**; copies of ^1H or ^{13}C NMR spectra for **8**, **10**, **11**, **13**, **14**−**17**, and **30**−**47**; X-ray structures of **11** and **12**, structure refinement details, tables of atomic coordinates, thermal parameters, bond lengths, bond angles, torsion angles, and mean planes, Cartesian coordinates for all optimized structures in Figure 1. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049011R