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A Combined Experimental and Density Functional Theory Study on the Pd-Mediated Cycloisomerization of *o*-Alkynylnitrobenzenes – Synthesis of Isatogens and Their Evaluation as Modulators of ROS-Mediated Cell Death

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Highly selective cycloisomerization of *o*-alkynylnitrobenzenes, leading to isatogens, has been achieved by employment of a Pd^{II} complex. This reaction is very general and functional-group-tolerant. The possible mechanism of this reaction was investigated with the help of DFT calculations. Three possible pathways – namely, the addition of the nitro group either in (i) 5-*exo*-dig or (ii) 6-*endo*-dig mode and (iii) halopalladation – and subsequent intramolecular events have been considered and studied in detail. These investigations revealed that pathway (i) is the favored route to isatogen formation. A preliminary screening of the available isatogens reveals the 2-alkylisatogens to be novel ROS scavengers capable of inhibiting cellular necroptosis.

Introduction

Bayer's 1881 inaugural report on the cycloisomerization of *o*-nitrophenylpropiolates documented the first synthesis of isatogens, which are unnatural.[1] To solve the problem of the initially employed harsh reaction conditions, several approaches to facilitate the nitro–alkyne cycloisomerization have been put forward.[2–8] Amongst these, the base-mediated cycloisomerization of *o*-alkynylnitrobenzene derivatives (trivially known as *o*-nitrotolans) under thermal or photochemical conditions has conventionally been employed for isatogen synthesis.[4] It has been reported recently that the nitro–alkyne cycloisomerization can also be effected under mild conditions in the presence of gold(III) bromide or an iridium hydride complex. The outcome of the cyclization, however, is dictated by the nature of the alkyne substituent:[6] *o*-(arylalkynyl)nitrobenzenes, for instance, were seen to give mixtures of isatogens **1** and anthranils **2** (Figure 1) in the presence of catalytic amounts of gold bromide,[6] whereas anthranils were formed exclusively from *o*-(alkylalkynyl)nitrobenzenes in the presence either of gold bromide[6] or of an iridium hydride[7] complex.

Our attention was drawn to the synthesis of isatogens as part of a program directed towards the development of potent and well-tolerated ROS (reactive oxygen species) scavengers. This is because the generation of ROS is a key downstream execution event in necroptotic cell death.[9] The isatogen nucleus was identified on consideration of its ability to trap hydroxy and superoxide radicals.[10] Because of their proximity to the reactive center, the electronic and steric influence of the substituents at the C(2)-position are critical for the modulation of the reactivity of the *N*-oxides.[4b] However, the functional units at the C(2)-positions of reported isatogens are limited mainly to aryl groups, with even reports dealing with C(2)-alkyl groups being scarce.[3d,4b] Because the available catalytic transition metal protocols have limitations for 2-alkyl substituents, the development of a versatile catalyst that promotes the nitro–alkyne cycloisomerization to isatogens is warranted. Here we report a palladium(II)-mediated nitro–alkyne cycloisomerization process[5] that complements the gold- and iridium-mediated cyclizations and provides an efficient and general synthesis of isatogens.

Results and Discussion

Our working hypothesis [Equations (3) and (4), Scheme 1] was based on Crabtree's[7] mechanism [Equation (2), Scheme 1] given for anthranil formation and the mechanism given by Huisgen[11] [Equation (1), Scheme 1] for pyridine-mediated nitro–alkyne cycloisomerization[4b] leading exclusively to isatogens. The given mechanism for anthranil formation involves the initial nucleophilic attack

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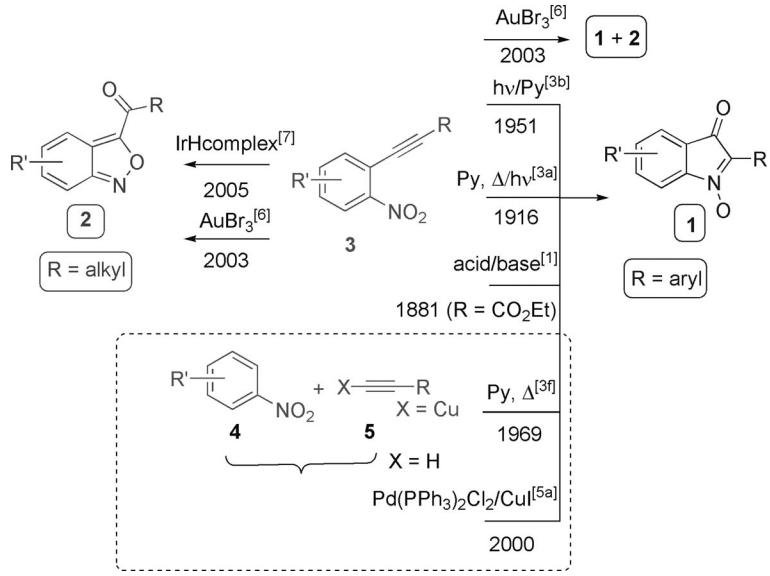
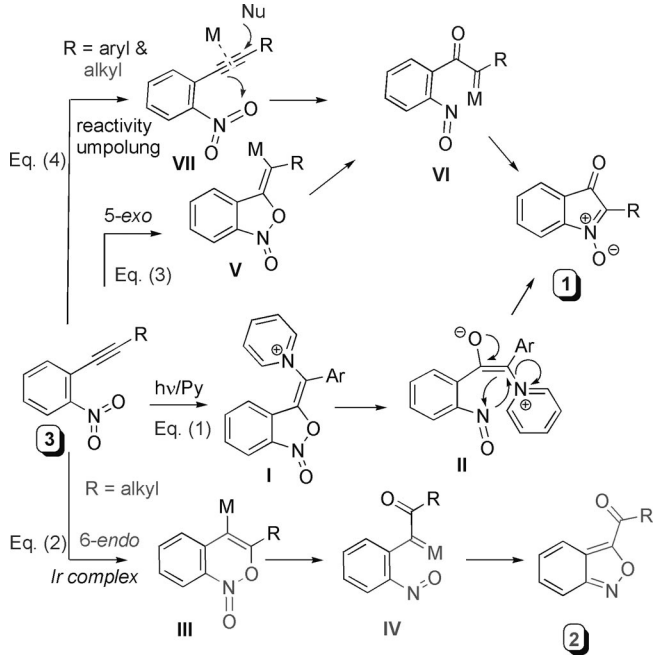


Figure 1. General methods for nitro–alkyne cycloisomerizations leading to isatogens.

of one of the oxygen atoms of the $–NO_2$ group on the metal-coordinated triple bond in a 6-*endo* fashion, which subsequently leads to a (carbene)metal intermediate **IV**. We envisaged that a reactivity umpolung at the nitro group, leading to the isomeric (carbene)metal **VI** [Equation (4)], similarly to the case of pyridine, might provide substituent-independent isatogen synthesis. We postulated the halopalladation of the alkyne unit for such a reactivity umpolung with the chloride being the transient nucleophile-cum-leaving group,[12] albeit not ruling out such a possibility through the addition of nitro oxygen in a 5-*exo*-dig fashion [Equation (3)]. However, earlier investigations from our own group and others had revealed that the NO_2 group remains as a spectator group when another internal nucleophile is present and facilitates the addition of the nucleophile on the β-carbon atom of the alkyne.[13]

With 1-nitro-2-(hept-1-ynyl)benzene (**3aa**)[14] as a model substrate, the feasibility of the nitro–alkyne cycloisomerization was examined with various Pd^{II} complexes as catalysts. The cyclization was facile with $PdCl_2$ and $PdBr_2$ and with their acetonitrile and benzonitrile complexes. Of these complexes, $Pd(CH_3CN)_2Cl_2$ gave better yields of the 2-pentylisatogen **1aa**. The reactions were clean in acetonitrile, whereas use of protic solvents resulted in several other by-products. $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$ were found to be inefficient for this nitro–alkyne cycloisomerization. As a control, when **3aa** was exposed to $AuBr_3$ under similar conditions, the anthranil **2aa** was obtained as the main product (Scheme 2).[6]

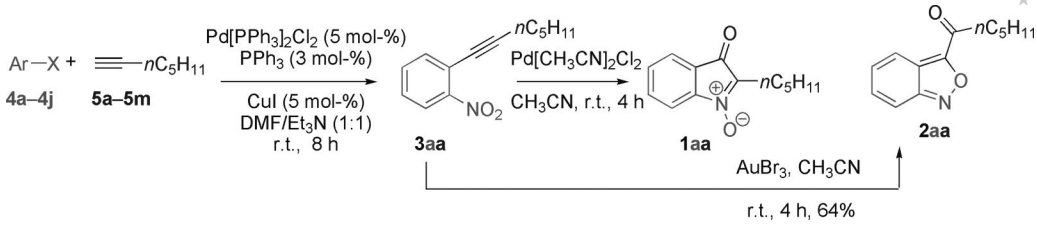
Next, various *o*-alkynylnitrobenzenes were prepared through Sonogashira couplings[15] of the selected aryl iodides **4** and alkynes **5**[16] in order to examine the scope of the palladium-mediated nitro–alkyne cycloisomerization reactions. These cyclizations showed excellent selectivities independent of alkyne substituents (Table 1). The conditions employed were tolerant towards commonly employed protecting groups such as TBS, isopropylidene, and benzyl



Scheme 1. Huisgen mechanism for isatogen formation [Equation (1)] and mechanism for the formation of anthranils [Equation (2)], together with the proposal for general isatogen synthesis either through 5-*exo* addition [Equation (3)] or through halopalladation [Equation (4)].

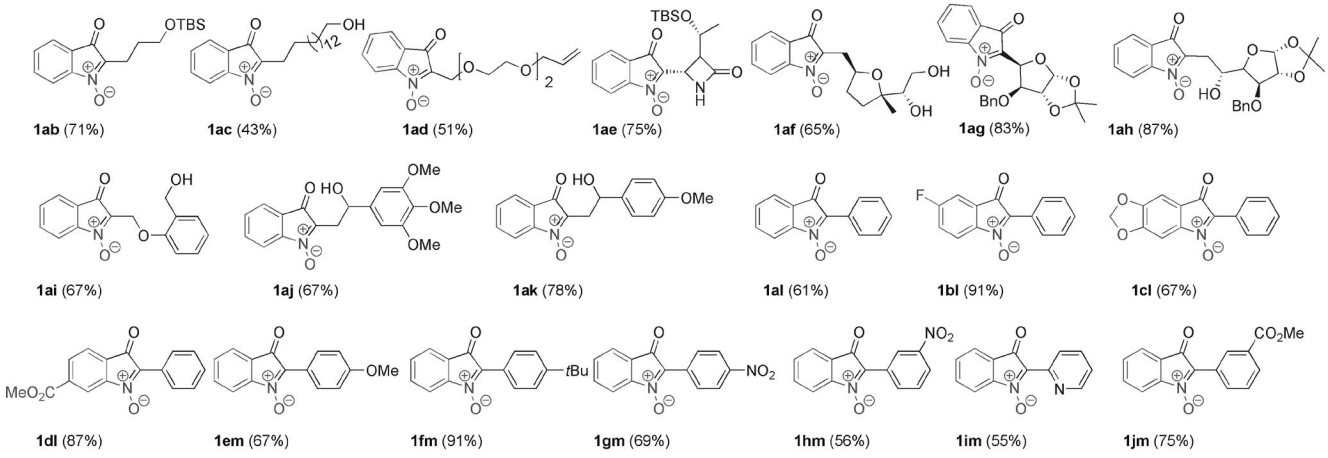
ethers, and also accommodated substituent functionality including free alcohols, β-lactams, heterocycles, and olefins.

The detailed mechanism of the above reaction was studied with the aid of density functional theory (DFT). The ab initio calculations were carried out with the software Turbomole 5.10[17] with use of the TZVP[18] basis set and the BP-86[19] functional. The mechanism by halopalladation that we propose is outlined in Figures 2 and 3. The values provided here are the ΔE values, calculated after the incorporation of solvent effects, with acetonitrile ($\varepsilon = 37.5$) taken



Scheme 2. Pd^{II}-catalyzed general synthesis of isatogens.

Table 1. Palladium-catalyzed cycloisomerization of *o*-alkynylnitrobenzenes.



as the solvent. To begin with, the substrate **3aa** reacts with one molecule each of $Pd(CH_3CN)_2Cl_2$ and $PdCl_2$ to produce the alkene-coordinated complex **A** and releases one molecule of CH_3CN. This reaction is exothermic by 36.7 kcal mol^{-1} (see Figure 2). Subsequent to this step, the system goes through a transition state **TS1**, in which a leaving palladium species donates a chlorine atom to the β-carbon atom of the alkyl chain and extracts a chlorine atom from the palladium atom that remains coordinated to the original substrate complex. The barrier for the reaction is 14.9 kcal mol^{-1}. The subsequent dissociation reaction to yield $PdCl_2(CH_3CN)$ and the *cis*-chloropalladated species **B** (see Figure 2)[20] is downhill in energy with respect to the transition state **TS1** by 6.4 kcal mol^{-1}, and the overall reaction converting **A** into **B** and the $PdCl_2(CH_3CN)$ complex is slightly endothermic, by 8.5 kcal mol^{-1}. The intermediate **B** is converted into the oxirane **C** via the transition state **TS2**. The earlier reports by Andrews and Chen on the epoxidation of cycloalkenes in the presence of stoichiometric or catalytic amounts of $Pd(CH_3CN)_2NO_2Cl$ complexes at ambient temperatures supports the intermediacy of **C** in our mechanistic route.[21] The conversion taking place here is the transfer of an oxygen atom from the nitro group to the α-carbon atom of the alkyl chain connected at the *ortho* position of the phenyl ring. The transition state for this has the oxygen atom coordinating to the palladium atom and also beginning to form a bond with the α-carbon atom. The barrier for this reaction is 30.5 kcal mol^{-1}, which is the highest barrier in the entire catalytic cycle described. This step is therefore the slowest step – the rate-determining step – in the reaction cycle.[22] The next step in the reaction cycle is the conversion of the oxirane **C** into **D**, in which the palladium atom has shifted its bond from the α- to the β-carbon atom of the alkyl chain. The barrier for this step is 19.7 kcal mol^{-1}. This conversion is exothermic by 10.5 kcal mol^{-1}.

Figure 3 shows the continuation of the reaction cycle, from species **D** to **F**. For this conversion, there is need of an extra molecular species, $Pd(CH_3CN)_2Cl_2$, which essentially acts as a catalyst to transfer a chlorine atom from the β-carbon atom of the alkyl chain to the palladium atom. The way it does so is by acting as a "chlorine shuttle" – forming a five-membered transition state complex **TS4** by coordinating to species **E** (see Figure 3) – and then proceeding to extract a chlorine atom from the β-carbon atom of the alkyl chain, while simultaneously giving its own chlorine atom to the palladium atom, ultimately to yield intermediate **F**. As shown in Figure 3, this reaction is quite facile: the formation of **E** from **D** and $Pd(CH_3CN)_2Cl_2$ is only marginally uphill by 4.8 kcal mol^{-1}, and the barrier of the conversion of **TS4** to **E** is only 12.6 kcal mol^{-1} (see Figure 3). It is interesting to note that an acetonitrile solvent molecule, originally coordinated to the chlorine-shuttling $Pd(CH_3CN)_2Cl_2$ species, is dissociated from the palladium center in the intermediate species **E**. This is the bond that the palladium sacrifices in order to coordinate to the species **D**. However, in the transition state **TS4**, this acetonitrile molecule recoordinates to the palladium center. This is be-

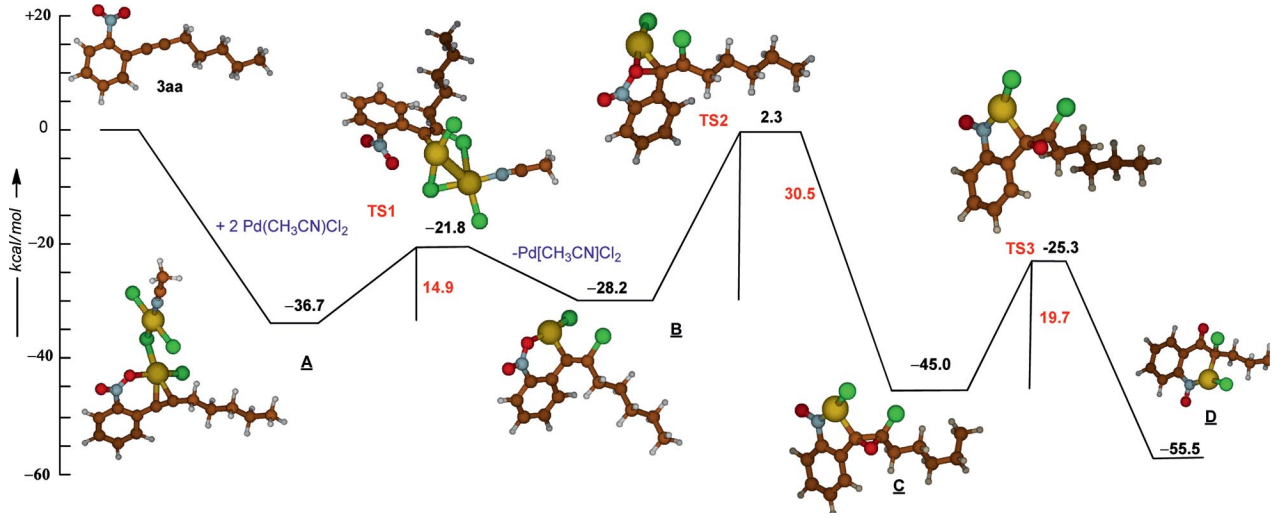


Figure 2. Energy profile for the first steps of the catalysis; that is, the conversion of the substrate **3aa** to **B**, with the aid of two palladium chloride molecules, and the subsequent conversion of the species **B** to **D** through two transition states that shift an oxygen atom from the nitrogen atom (in **B**) to the carbon atom (in **D**) with the help of an interacting palladium species. All the reported energies were calculated with DFT.

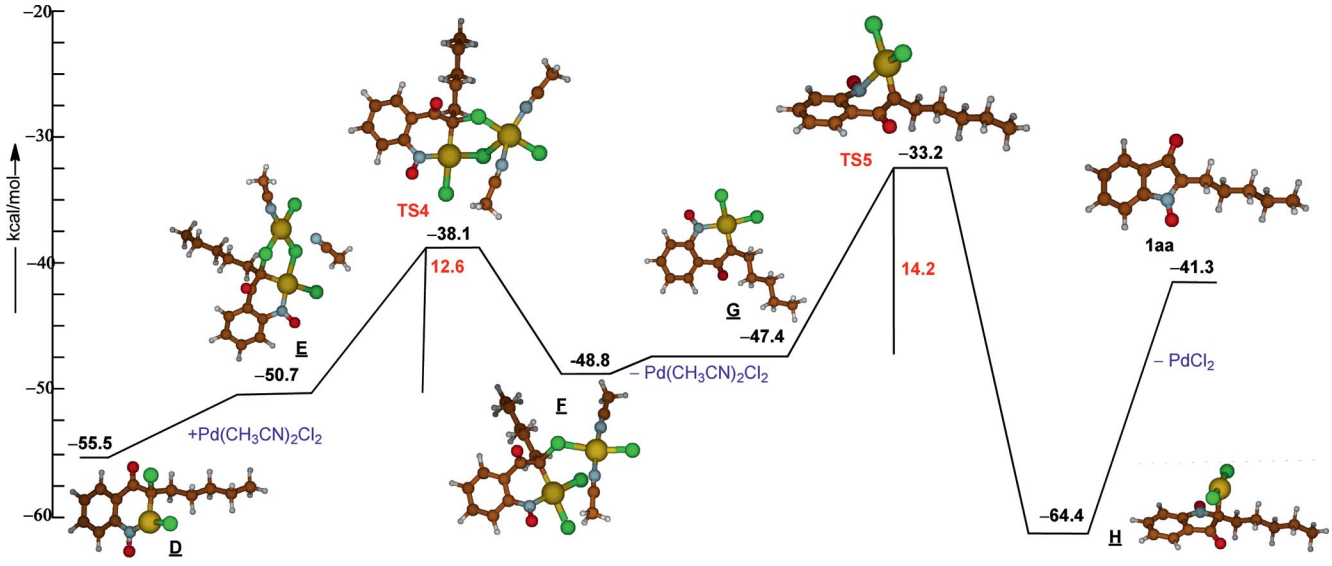


Figure 3. Energy profile for the continuing steps during the catalysis; that is, the conversion of species **D** into **G** with the help of a "chlorine-shuttling" $Pd(CH_3CN)_2Cl_2$ species followed by the conversion of **G** into the final product **1aa**, occurring through the elimination of the $PdCl_2$ species.

cause at the transition state, the two palladium–chlorine bonds in $Pd(CH_3CN)_2Cl_2$ have been weakened due to the exchange of chlorine atoms – one being given to the palladium atom and one taken from the β-carbon atom of the alkyl chain in the original species **D**. This recoordination of the solvent molecule is significant, because it serves to reduce the barrier to only 12.6 kcal mol^{-1}, by providing stability to the palladium center, in which bonding to the transferred chlorine atom is reduced at the transition state. Again here, the dissociation and recoordination of the labile acetonitrile species serves the crucial purpose of reducing the reaction barrier, and thus once again has a significant influence on the reaction cycle in our proposed mechanism.

Recent work by Popp et al.[23] shows that labile monodentate ligands can readily associate with and dissociate from palladium centers and have a significant influence on the mechanisms of palladium-mediated catalysis reactions. The labile ligand in the palladium catalyst system reported by Popp et al. was pyridine; in our system[23f] the labile ligand is the acetonitrile solvent molecule. The intermediate species **F** then undergoes a marginally uphill (by 0.6 kcal mol^{-1}) conversion into the species **G**, in which the palladium complexes preferentially with the nitrogen atom of NO.[24] The involvement of such stable Pd^{II}–carbene species and subsequent electrocyclizations is well documented.[25] The calculations revealed that the conversion of the

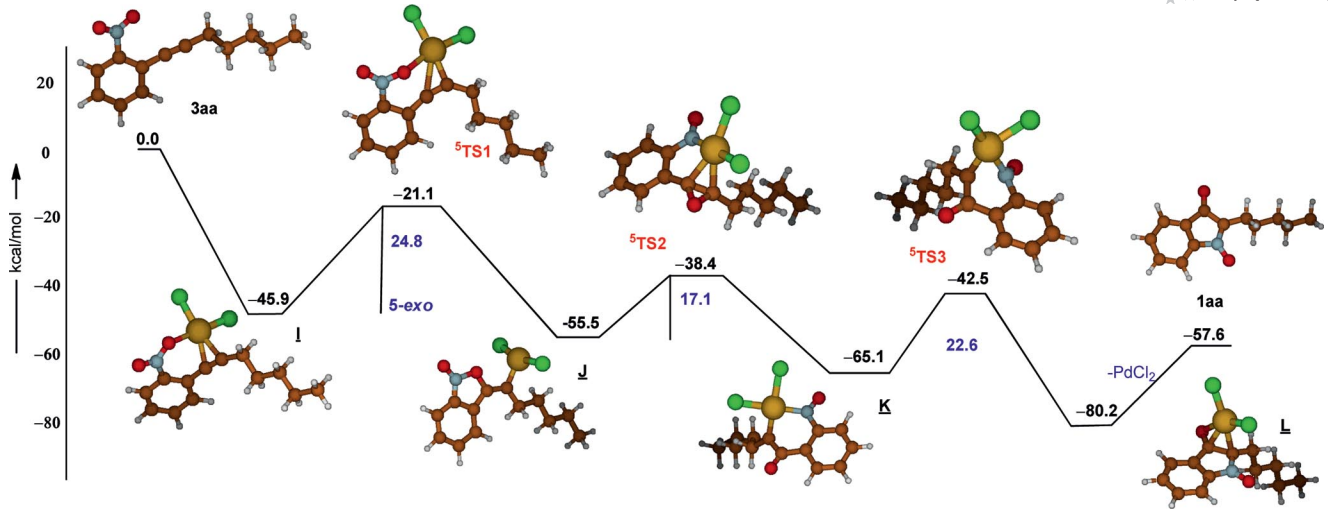


Figure 4. Energy profile for the Pd-mediated 5-*exo*-dig addition of the nitro-group oxygen atom and the subsequent steps.

species **G** into **H** goes through the transition state **TS5**. This conversion involves the bonding of the nitrogen atom, attached in structure **G** to the palladium atom, to the β-carbon atom of the alkyl chain – leading to structure **H** with the palladium atom coordinated to the β-carbon atom and two chlorine atoms (having relinquished its bonding to the nitrogen atom). This reaction is exothermic by 17.0 kcal mol^{-1} and has a barrier of only 14.2 kcal mol^{-1}, suggesting that it is quite feasible. Once **H** has been formed, it can dissociate to give the desired product **1aa** and the $PdCl_2$ catalyst. On the potential energy surface, this reaction is endothermic by 23.1 kcal mol^{-1}, but because the reaction is favorable entropically, yielding two species (**1aa** and $PdCl_2$) from one (**H**), such a dissociation is likely to occur at room temperature.

The mechanism discussed above relates to the $PdCl_2$-catalyzed halopalladation route to form isatogen. Although halopalladation had been envisaged by us in deciding the use of palladium as the catalyst for isatogen synthesis, a perusal of the mechanism makes it clear that it suffers from several problems: (i) it is very circuitous and complicated, (ii) it is likely to be entropically disfavored because two $PdCl_2$ and one CH_3CN solvent molecule have to be invoked in order to catalyze the reaction, and (iii) the barrier for the rate-determining step – 30.5 kcal mol^{-1} – is on the higher side for a reaction taking place at room temperature. These considerations prompted us to consider the possibility that the transformation might be taking place through an alternative pathway – the 5-*exo*-dig route discussed earlier in the introduction and elucidated in Scheme 1. Calculations were carried out to determine the feasibility of this route, and the potential energy surface for the entire mechanistic route is shown in Figure 4. The addition of a $PdCl_2$ molecule to the substrate **3aa** leads to the formation of the complex **A**, which lies 45.9 kcal mol^{-1} below the reactant on the potential energy surface. This complex has the $PdCl_2$ group bound to the two alkyne carbon atoms as well as to one of the oxygen atoms of the NO_2 group (sees Figure 4). The high exothermicity of this reaction makes it quite feasible.

From here, the next step involves the transformation into the intermediate species **B**, which has the oxygen atom of the nitro group coordinated to the α-carbon atom of the alkyne, while the palladium atom has lost its coordination to the α-carbon atom as well as the oxygen atom and is now bound to the β-alkyne carbon atom. This species lies 5.6 kcal mol^{-1} below species **I**, and is therefore 55.5 kcal mol^{-1} below the original reactant species (see Figure 4). The transition state that connects the two species **I** and **J** – **^{5}TS1** – lies 24.8 kcal mol^{-1} above **I**, and features a lengthening of the N–O bond as well as of the Pd–α-carbon bond, while the palladium atom is seen to come closer to the β-carbon atom of the alkyne. Subsequent to the formation of species **J**, the system undergoes further transformation into species **K**, in which the palladium atom is bound to the nitrogen atom as well as to the β-carbon atom of the alkyne. This occurs via the transition state **^{5}TS2**, in which the oxygen atom has lost its coordination to the nitrogen atom and is now bound in an epoxy fashion to the two alkyne carbon atoms, while the palladium atom, approaching the nitrogen atom, is bound to both of the alkyne carbon atoms (see Figure 4). This transition state lies 17.1 kcal mol^{-1} above species **J**, whereas the formed intermediate **K** is more stable than **J**, and lies 65.1 kcal mol^{-1} below the reactants on the potential energy surface. From this point, intermediate **K** is converted into species **L**, which has the nitrogen atom bound to the β-alkyne carbon atom, while the palladium atom has bonds to both of the atoms. This structure is formed via the transition state **^{5}TS3**, which features a shortening of the bond between the nitrogen and β-alkyne carbon atoms, and has a barrier of 22.6 kcal mol^{-1}. Species **L** is in essence the isatogen with a coordinating $PdCl_2$ species, the loss of which gives the final desired product **1aa**, at an energy cost of 22.6 kcal mol^{-1}.

This 5-*exo*-dig route to isatogen formation has significant advantages over the halopalladation. To begin with, it is considerably simpler, involving three transition states as opposed to five for the halopalladation, and also requiring only the presence of one $PdCl_2$ molecule as the catalyst

rather than two $PdCl_2$ molecules and a CH_3CN solvent molecule as required for the halopalladation process. Moreover, the rate-determining step has a barrier of 24.8 kcal mol^{-1}, which is 5.7 kcal mol^{-1} lower than the rate-determining barrier in the halopalladation case (for the oxygen transfer). Indeed, because the reaction takes place at room temperature, the necessity of the barrier for the reaction to be less than 25.0 kcal mol^{-1} strongly suggests the favorability of the 5-*exo*-dig route. Finally, it is interesting to note that every successive step in the reaction pathway for the 5-*exo*-dig route to isatogen formation features an intermediate that is lower in energy than the previous intermediate species (see Figure 4). This suggests that each successive step would be thermodynamically favored in this route, which makes this mechanism highly feasible.

It is also noted here that we have also considered the possibility that (alkyne)palladium complex **I** might proceed in a 6-*endo*-dig fashion to produce the regiomeric carbene **K**, which was postulated by Crabtree and co-workers as a possible intermediate when iridium was used as the catalyst. As shown in Figure 5, this pathway is significantly disfavored, with ^{6}**TS1** lying 43.6 kcal mol^{-1} higher in energy than **I** on the potential energy surface. As also shown in Figure 5, the palladium complex **I** has the energetically much more favorable choice of passing through the transition state ^{5}**TS1** (barrier 24.8 kcal mol^{-1}) to give the 5-*exo*-dig intermediate **J**, which makes the 6-*endo*-dig pathway unlikely and helps explain why the isatogen is formed exclusively, whereas the carbene **M**, resulting from the 6-*endo*-dig pathway leading to the anthranil **2aa**, is not formed. The reason for the high barrier for this route is the steric strain involved – the transition state ^{6}**TS1** has a strained nitro group in which both oxygen atoms have bonds to two atoms, thereby giving rise to two different rings. Therefore, when $PdCl_2$ is used as the catalyst, the results from the DFT calculations indicate that the route to isatogen formation exclusively involves the formation of the 5-*exo*-dig species. Future work in this regard would involve the determination of the barrier heights for the analogous reactions when using iridium and gold catalysts in place of palladium (work in progress).

After having established a general synthesis of isatogens and a plausible mechanism through DFT calculations, we next proceeded to evaluate the efficiency of isatogens in in-

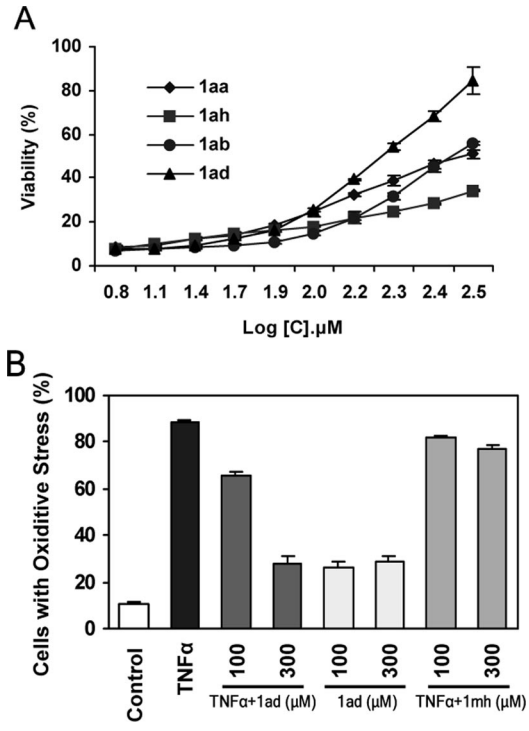


Figure 6. Inhibition of necroptosis (A) and oxidative stress (B) in L929 cells by isatogens. L929 cells were treated with mouse TNFα (Cell Sciences, Canton, MA; 10 ng mL^{-1}) in the presence of the indicated concentrations of the compounds for 24 h. Cell viability was measured by Cell Titer-Glo assay (Promega, Madison, WI). ROS levels were determined by measuring the fluorescence of the cells stained with Mito Sox reagent (BD Biosciences, Eugene, OR; 10 μM) by FACS analysis.

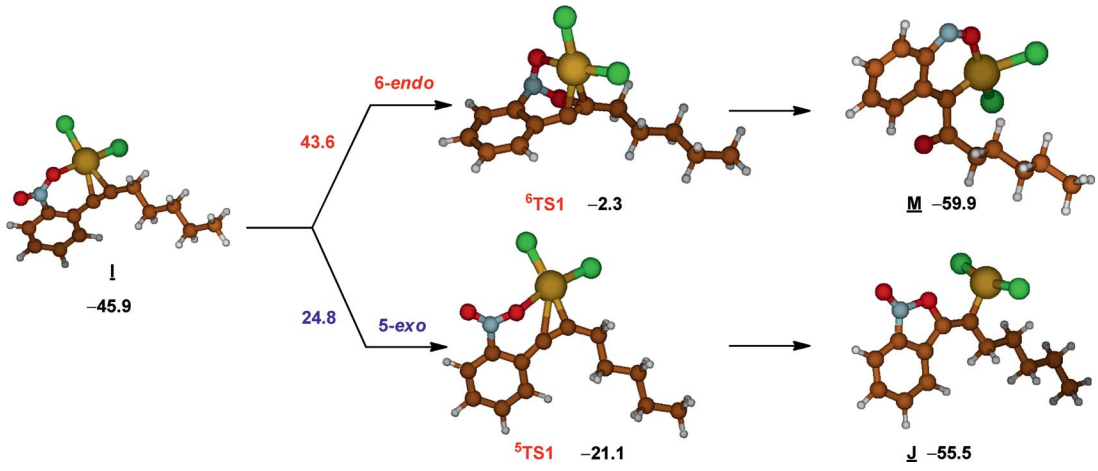


Figure 5. Difference in the activation energies for the addition of the nitro-group oxygen atom in 5-*exo* or 6-*endo*-dig modes.

hibiting ROS-mediated necroptotic cell death. These experiments employed mouse fibrosarcoma L929 cells treated with TNFα. As shown in Figure 6A, isatogens indeed displayed significant protection from necroptosis. The EC_{50} values of some of the active compounds are shown in Table 2. Compound **1ad** displayed the highest activity (EC_{50} = 188 μM). Other molecules were found to lack activity. To confirm that inhibition of cell death was related to the suppression of ROS, we directly measured the production of mitochondrial superoxide in necroptotic L929 cells. As shown in Figure 6B, **1ad** indeed efficiently suppressed TNF α-induced ROS, in contrast to the related inactive analogue. The inhibition of necroptosis selectively by 2-alkylisatogens and not by 2-arylisatogens can be explained by considering the superior spin trapping abilities and also the longer half-life times of the corresponding spin adducts of the former. Overall, these data confirm that isatogens represent a new family of ROS scavengers capable of inhibiting cellular necroptosis.

Table 2. EC_{50} values of selected compounds.

Compound:	**1aa**	**1ah**	**1ab**	**1ad**
EC_{50} [μM]	327.34	879.02	299.92	188.36

Conclusions

Cycloisomerization of *o*-alkynylnitroaryl systems mediated by an electrophilic palladium(II) complex has been explored, and its mechanism has been proposed on the basis of DFT calculations. We identified the 2-alkylisatogens as new candidates for inhibiting necroptosis-mediated cell death through the efficient trapping of the reactive oxygen species. The reaction conditions employed are catalytic in nature and mild, accommodate both aryl and alkyl substituents, and are tolerant towards commonly employed protecting groups/functional units. Given the fact that the field of transition-metal-catalyzed cycloisomerization of nitro–alkynes is still in its infancy, as well as the remarkable reactivity differences noticed with different metal salts/complexes, we believe that the results described in this paper will provide a fresh impetus for the development of new reactions.

Experimental Section

General: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an argon atmosphere in oven-dried glassware. All anhydrous solvents were distilled prior to use: CH_3CN and DMF from CaH_2; Et_3N from KOH. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (100-200 mesh). Optical rotations were determined with a Jasco DIP-370 digital polarimeter at 25 °C. ^1H and ^{13}C NMR spectroscopy measurements were carried out with a Bruker AC 200 MHz or Bruker DRX 400 MHz spectrometer, and TMS was used as internal standard. The ^1H and ^{13}C NMR chemical shifts are reported in parts per million downfield from tetramethylsilane. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. The multiplicities of the ^{13}C NMR signals were assigned with the help of DEPT spectra and the terms s = singlet, d = doublet, t = triplet, and q = quartet represent C (quaternary), CH, CH_2, and CH_3, respectively. Mass spectroscopy was carried out with a API QStar Pulsar (Hybrid Quadrupole-TOF LC–MS–MS) spectrometer. Elemental analysis data were obtained with a Thermo Finnigan Flash EA 1112 Series CHNS Analyzer.

General Procedure for the Sonogashira Coupling: Triphenylphosphane (TPP; 0.1 mmol) and $Pd(PPh_3)_2Cl_2$ (0.1 mmol) were added to a solution of an alkyne **5** (1 mmol) and an aryl iodide **4** (1.2 mmol) in Et_3N (16 mL) and DMF (8 mL), and the mixture was deaerated with argon for 30 min. CuI (0.1 mmol) was added, and the mixture was deaerated with argon for 10 min and stirred at room temp. for 6 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated, and the residue obtained was purified by column chromatography (ethyl acetate in petroleum ether) to afford a compound **3**.

Compound 3aa:[14b] Yellow liquid, 70% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.2 Hz, 3 H), 1.28–1.37 (m, 2 H), 1.38–1.45 (m, 2 H), 1.56–1.63 (m, 2 H), 2.42 (t, J = 7.2 Hz, 2 H), 7.33 (br. ddd, J = 1.6, 7.3, 8.2 Hz, 1 H), 7.46 (dt, J = 1.2, 7.7 Hz, 1 H), 7.51 (dd, J = 1.6, 7.8 Hz, 1 H), 7.90 (dd, J = 8.3, 1.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (q), 19.7 (t), 22.1 (t), 27.9 (t), 30.9 (t), 75.9 (s), 99.2 (s), 119.3 (s), 124.2 (d), 127.7 (d), 132.3 (d), 134.6 (d), 150.0 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3022, 2958, 2922, 2860, 2233, 1608, 1568, 1527, 1480, 1466, 1345, 1216, 851, 757, 668 cm^{-1}. $C_{13}H_{15}NO_2$ (217.27): calcd. C 71.87, H 6.96, N 6.45; found C 71.76, H 6.91, N 6.40.

Compound 3ab:[14a] Yellow liquid, 72% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.88 (s, 9 H), 1.82 (quint, J = 6.6 Hz, 2 H), 2.55 (d, J = 7.1 Hz, 2 H), 3.76 (t, J = 6.0 Hz, 2 H), 7.37 (br. ddd, J = 2.2, 6.8, 8.2 Hz, 1 H), 7.50 (dt, J = 1.2, 7.7 Hz, 1 H), 7.55 (dd, J = 2.2, 8.2 Hz, 1 H), 7.94 (br. d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.5 (q, 2 C), 16.1 (t), 18.2 (s), 25.8 (q, 3 C), 31.2 (t), 61.3 (t), 75.9 (s), 98.7 (s), 119.1 (s), 124.2 (d), 127.8 (d), 132.4 (d), 134.6 (d), 149.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3032, 2954, 2885, 1684, 1634, 1557, 1520, 1471, 1465, 1445, 1345, 1276, 1255, 1180, 1143, 1101, 1006, 980, 836, 776 cm^{-1}. $C_{17}H_{25}NO_3Si$ (319.48): calcd. C 63.91, H 7.89, N 4.38; found C 63.81, H 7.72, N 4.32.

Compound 3ac: Yellow liquid, 68% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (br. s, 22 H), 1.52–1.68 (m, 5 H), 2.46 (t, J = 6.8 Hz, 2 H), 3.62 (t, J = 6.6 Hz, 2 H), 7.37 (br. ddd, J = 2.1, 7.1, 8.2 Hz, 1 H), 7.51 (dt, J = 1.2, 7.7 Hz, 1 H), 7.57 (dd, J = 2.1, 8.7 Hz, 1 H), 7.96 (dd, J = 1.2, 8.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.8 (t), 25.7 (t), 28.3 (t), 28.8 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.5 (t, 3 C), 29.6 (t, 3 C), 32.7 (t), 62.9 (t), 75.9 (s), 99.4 (s), 119.3 (s), 124.3 (d), 127.8 (d), 132.5 (d), 134.7 (d), 150.0 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3367, 2922, 2852, 2400, 1608, 1528, 1464, 1320, 1056, 755 cm^{-1}. $C_{23}H_{35}NO_3$ (373.53): calcd. C 73.96, H 9.44, N 3.75; found C 73.88, H 9.34, N 3.71.

Compound 3ad: Yellow liquid, 62% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.60–3.65 (m, 2 H), 3.67–3.76 (m, 4 H), 3.81–3.86 (m, 2 H), 4.03 (dt, J = 5.7, 1.4 Hz, 2 H), 4.50 (s, 2 H), 5.18 (ddd, J = 10.4, 3.1, 1.3 Hz, 1 H), 5.27 (ddd, J = 17.2, 3.1, 1.3 Hz, 1 H), 5.92 (ddt, J = 17.2, 10.4, 5.7 Hz, 1 H), 7.37 (br. ddd, J = 1.8, 7.1, 8.0 Hz, 1 H), 7.50 (dt, J = 1.4, 7.7 Hz, 1 H), 7.55 (dd, J = 2.0, 7.7 Hz, 1 H), 7.94 (d, J = 1.4, 8.0 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 59.0 (t), 69.2 (t), 69.3 (t), 70.4 (t), 70.6 (t), 72.1 (t), 81.5 (s), 93.4

(s), 116.9 (s), 117.9 (t), 124.5 (d), 128.8 (d), 132.7 (d), 134.7 (d), 134.8 (d), 149.7 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2915, 2403, 1683, 1613, 1559, 1505, 1469, 1401, 1265, 1097, 1034, 933, 765 cm^{-1}. ESI-MS: *m/z* (%) = 328.4 (100) $[M + Na]^+$. $C_{16}H_{19}NO_5$ (305.33): calcd. C 62.94, H 6.27, N 4.59; found C 62.82, H 6.21, N 4.49.

Compound 3ae: Light gray solid, 67% yield. M.p. 119 °C. $[\alpha]_D^{25}$ = +42.6 (*c* = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.87 (s, 9 H), 1.28 (d, *J* = 6.3 Hz, 3 H), 3.41–3.44 (m, 1 H), 4.23–4.34 (m, 1 H), 4.61 (d, *J* = 2.5 Hz, 1 H), 6.32 (br. s, 1 H), 7.42–7.52 (m, 1 H), 7.56–7.59 (m, 2 H), 8.04 (dd, *J* = 1.1, 7.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.2 (q), –4.4 (q), 17.8 (s), 22.2 (q), 25.6 (q, 3 C), 39.3 (d), 64.4 (d), 67.8 (d), 79.9 (s), 95.1 (s), 117.6 (s), 124.5 (d), 128.9 (d), 132.7 (d), 134.6 (d), 149.8 (s), 167.7 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3019, 2956, 2930, 2885, 2400, 1770, 1672, 1609, 1570, 1529, 1472, 1377, 1346, 1215, 1144, 1065, 959, 756 cm^{-1}. ESI-MS: *m/z* (%) = 397.6 (100), $[M + Na]^+$. $C_{19}H_{26}N_2O_4Si$ (374.51): calcd. C 60.93, H 7.0, N 7.48; found C 60.81, H 7.2, N 7.34.

Compound 3af: Yellow liquid, 57% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.58–1.66 (m, 1 H), 1.88–1.96 (m, 1 H), 2.04–2.16 (m, 2 H), 2.71 (t, *J* = 5.7 Hz, 2 H), 3.05 (br. s, 1 H), 3.31 (br. s, 1 H), 3.47–3.53 (m, 1 H), 3.62–3.71 (m, 2 H), 4.11–4.19 (m, 1 H), 7.33–7.41 (m, 1 H), 7.45–7.56 (m, 2 H), 7.93 (d, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.7 (q), 26.8 (t), 30.9 (t), 32.7 (t), 63.1 (t), 76.7 (d), 77.3 (s), 78.0 (d), 85.0 (s), 95.2 (s), 118.7 (s), 124.3 (d), 128.1 (d), 132.6 (d), 134.7 (d), 149.8 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3390, 2975, 2742, 2235, 1608, 1595, 1527, 1476, 1380, 1280, 1069, 755 cm^{-1}. $C_{16}H_{19}NO_5$ (305.33): calcd. C 62.94, H 6.27, N 4.59; found C 62.79, H 6.38, N 4.48.

Compound 3ag: Yellow liquid, 73% yield. $[\alpha]_D^{25}$ = +88.8 (*c* = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.50 (s, 3 H), 4.14 (d, *J* = 3.0 Hz, 1 H), 4.63 (d, *J* = 3.8 Hz, 1 H), 4.80 (d, *J* = 12.2 Hz, 1 H), 4.89 (d, *J* = 12.2 Hz, 1 H), 5.14 (d, *J* = 3.0 Hz, 1 H), 6.03 (d, *J* = 3.8 Hz, 1 H), 7.26–7.39 (m, 5 H), 7.52–7.61 (m, 2 H), 7.67 (dd, *J* = 7.6, 1.8 Hz, 1 H), 8.06 (dd, *J* = 7.9, 1.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.1 (q), 26.8 (q), 71.5 (d), 72.8 (t), 82.7 (d), 82.9 (d), 83.0 (s), 91.0 (s), 104.7 (d), 112.1 (s), 117.7 (s), 124.5 (d), 127.7 (d, 2 C), 127.8 (d), 128.4 (d, 2 C), 129.1 (d), 132.8 (d), 135.2 (d), 137.3 (s), 149.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2960, 2400, 1608, 1575, 1530, 1481, 1437, 1385, 1347, 1215, 1163, 1075, 928, 758 cm^{-1}. $C_{22}H_{21}NO_6$ (395.41): calcd. C 66.83, H 5.35, N 3.54; found C 66.85, H 5.45, N 3.47.

Compound 3ah: Yellow liquid, 75% yield. $[\alpha]_D^{25}$ = –42.2 (*c* = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.48 (s, 3 H), 2.69 (br. s, 1 H), 2.85 (d, *J* = 5.6 Hz, 1 H), 2.89 (t, *J* = 2.0 Hz, 1 H), 4.14–4.29 (m, 3 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 3.7 Hz, 1 H), 4.75 (d, *J* = 11.7 Hz, 1 H), 5.95 (d, *J* = 3.7 Hz, 1 H), 7.33–7.39 (m, 5 H), 7.46–7.51 (m, 1 H), 7.51–7.62 (m, 2 H), 8.03 (dd, *J* = 8.0, 0.9 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.1 (t), 26.3 (q), 26.7 (q), 67.1 (d), 72.3 (t), 78.6 (s), 81.4 (d), 81.7 (d), 82.4 (d), 94.8 (s), 105.1 (d), 111.8 (s), 118.7 (s), 124.5 (d), 127.8 (d, 2 C), 128.1 (d), 128.2 (d), 128.6 (d, 2 C), 132.8 (d), 134.7 (d), 137.3 (s), 149.8 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3678, 3020, 2950, 2934, 2400, 1676, 1612, 1569, 1528, 1454, 1375, 1345, 1215, 1120, 1076, 1025, 758 cm^{-1}. $C_{24}H_{25}NO_7$ (439.46): calcd. C 65.59, H 5.73, N 3.19; found C 65.41, H 5.69, N 3.14.

Compound 3ai: Yellow liquid, 68% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 1 H), 4.74 (s, 2 H), 5.03 (s, 2 H), 6.97–7.12 (m, 2 H), 7.26–7.36 (m, 2 H), 7.42–7.52 (m, 1 H), 7.55–7.61 (m, 2 H), 8.03 (dd, *J* = 7.7, 1.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.65 (t), 61.46 (t), 82.40 (s), 91.58 (s), 111.97 (d), 117.38 (s), 121.58 (d), 124.53 (d), 128.77 (d), 128.81 (d), 129.15 (d), 129.70 (s), 132.82 (d), 134.91 (d), 149.55 (s), 155.29 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3372, 3019, 2953, 2400, 1656, 1616, 1587, 1531, 1487, 1456, 1291, 1230, 1119, 753 cm^{-1}. $C_{16}H_{13}NO_4$ (283.28): calcd. C 67.84, H 4.63, N 4.94; found C 67.79, H 4.69, N 4.83.

Compound 3aj: Gray spongy mass, 62% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.83 (d, *J* = 6.2 Hz, 2 H), 3.19 (s, 1 H), 3.72 (s, 3 H), 3.74 (s, 6 H), 4.84 (t, *J* = 6.2 Hz, 1 H), 6.58 (s, 2 H), 7.27–7.36 (m, 1 H), 7.38–7.49 (m, 2 H), 7.89 (d, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.8 (t), 55.7 (q, 2 C), 60.5 (q), 72.1 (d), 78.2 (s), 94.9 (s), 102.3 (d, 2 C), 118.3 (s), 124.3 (d), 128.1 (d), 132.6 (d), 134.5 (d), 136.7 (s), 138.4 (s), 149.4 (s), 152.8 (s, 2 C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3352, 3010, 2939, 2400, 1694, 1593, 1505, 1463, 1328, 1236, 1126, 1004, 754 cm^{-1}. $C_{19}H_{19}NO_6$ (357.36): calcd. C 63.86, H 5.36, N 3.92; found C 63.79, H 5.31, N 3.88.

Compound 3ak: Dark yellow liquid, 61% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.75 (br. s, 1 H), 2.89 (d, *J* = 6.3 Hz, 2 H), 3.79 (s, 3 H), 4.95 (t, *J* = 6.0 Hz, 1 H), 6.89 (dt, *J* = 8.7, 2.3 Hz, 2 H), 7.34–7.45 (m, 3 H), 7.51–7.56 (m, 2 H), 8.01 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.8 (t), 55.1 (q), 71.8 (d), 78.3 (s), 95.2 (s), 113.7 (d, 2 C), 113.8 (s), 118.6 (s), 124.4 (d), 126.9 (d, 2 C), 128.2 (d), 128.5 (s), 132.7 (d), 134.6 (d), 149.7 (s), 159.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 3019, 2936, 2834, 2400, 2223, 1611, 1527, 1514, 1465, 1441, 1345, 1250, 1215, 1111, 1035, 757 cm^{-1}. $C_{17}H_{15}NO_4$ (297.31): calcd. C 68.68, H 5.09, N 4.71; found C 68.79, H 5.23, N 4.65.

Compound 3al:[14c] Orange spongy mass, 67% yield (*the sample also contains small amounts of isatogen*). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.40 (m, 3 H), 7.44–7.50 (m, 1 H), 7.56–7.62 (m, 3 H), 7.66–7.72 (m, 1 H), 8.07 (d, *J* = 1.2, 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.8 (s), 97.1 (s), 113.9 (s), 122.3 (s), 124.5 (d), 128.3 (d, 2 C), 128.3 (d), 129.1 (d), 131.9 (d, 2 C), 132.6 (d), 134.4 (d), 149.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2410, 1605, 1567, 1514, 1465, 1345 cm^{-1}. $C_{14}H_9NO_2$ (223.23): calcd. C 75.33, H 4.06, N 6.27; found C 75.53, H 4.16, N 6.13.

Compound 3bl: Dark orange solid, 75% yield. M.p. 45 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.14 (ddd, *J* = 9.1, 6.4, 2.7 Hz, 1 H), 7.36–7.43 (m, 4 H), 7.57–7.63 (m, 2 H), 8.15 (dd, *J* = 9.2, 5.1 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 83.9 (s), 98.5 (s), 116.0 (d, $J_{C\beta,F}$ = 24.1 Hz), 121.1 (d, $J_{C\beta,F}$ = 24.1 Hz), 121.4 (s, $J_{C\gamma,F}$ = 10.7 Hz), 121.7 (s), 127.4 (d, $J_{C\gamma,F}$ = 10.7 Hz), 128.4 (d, 2 C), 129.5 (d), 132.0 (d, 2 C), 145.6 (s, $J_{C\delta,F}$ = 3.3 Hz), 164.3 (s, $J_{C\alpha,F}$ = 257.2 Hz) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3054, 2936, 1652, 1610, 1578, 1520, 1477, 1447, 1385, 1357, 1260, 895, 780, 756, 688, 603 cm^{-1}. $C_{14}H_8FNO_2$ (241.22): calcd. C 69.71, H 3.34, F 7.88, N 5.8; found C 69.63, H 3.41, F 7.72, N 5.78.

Compound 3cl: Pale brown solid, 72% yield. M.p. 101 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.14 (s, 2 H), 7.04 (s, 1 H), 7.35–7.38 (m, 3 H), 7.55–7.60 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 5.4 (s), 96.1 (s), 103.9 (t), 105.4 (d), 112.4 (d), 114.7 (s), 122.5 (s), 128.4 (d, 2 C), 129.0 (d), 131.9 (d, 2 C), 144.4 (s), 147.8 (s), 151.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3077, 3022, 2400, 1614, 1557, 1522, 1493, 1443, 1341, 1297, 1210, 1073, 959, 754 cm^{-1}. $C_{15}H_9NO_4$ (267.24): calcd. C 67.42, H 3.39, N 5.24; found C 67.37, H 3.42, N 5.20.

Compound 3dl: Orange solid, 65% yield. M.p. 108 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.97 (s, 3 H), 7.35–7.43 (m, 3 H), 7.58 (dd, *J* = 0.9, 3.4 Hz, 1 H), 7.6 (br. dd, *J* = 2.1, 7.7 Hz, 1 H), 7.77 (d, *J* = 8.1 Hz, 1 H), 8.22 (dd, *J* = 1.6, 8.1 Hz, 1 H), 8.70 (d, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.7 (q), 84.5 (s), 100.4 (s), 121.7 (s), 122.7 (s), 125.7 (d), 128.5 (d, 2 C), 129.7 (d), 130.1 (s), 132.1 (d, 2 C), 133.1 (d), 134.6 (d), 149.3 (s), 164.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3022, 2924, 2400, 1728, 1617, 1557, 1532, 1437, 1345,

1286, 1115, 1026, 756 cm^{-1}. $C_{16}H_{11}NO_4$ (281.27): calcd. C 68.32, H 3.94, N 4.98; found C 68.28, H 3.81, N 4.93.

Compound 3em:[14d] Brick-red spongy mass, 78% yield. M.p. 161 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 6.89 (br. dt, J = 9.1, 2.5 Hz, 2 H), 7.42 (ddd, J = 1.6, 7.3, 8.2 Hz, 1 H), 7.50–7.55 (m, 2 H), 7.59 (dd, J = 7.3, 1.5 Hz, 1 H), 7.68 (dd, J = 7.7, 1.5 Hz, 1 H), 8.07 (dd, J = 8.2, 1.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.2 (q), 83.9 (s), 97.7 (s), 114.1 (d, 2 C), 114.4 (s), 119.2 (s), 124.7 (d), 127.9 (d), 132.6 (d), 133.6 (d, 2 C), 134.3 (d), 149.4 (s), 160.4 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2936, 2400, 1720, 1611, 1600, 1567, 1523, 1464, 1439, 1342, 1288, 1251, 1080, 1029, 833, 756 cm^{-1}. $C_{15}H_{11}NO_3$ (253.26): calcd. C 71.14, H 4.38, N 5.53; found C 71.31, H 4.31, N 5.47.

Compound 3fm: Red spongy mass, 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 7.38–7.45 (m, 3 H), 7.48–7.63 (m, 3 H), 7.72 (dd, J = 7.7, 1.6 Hz, 1 H), 8.08 (dd, J = 8.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.1 (q, 3 C), 34.8 (s), 84.2 (s), 97.4 (s), 118.9 (s), 119.3 (s), 124.6 (d), 125.4 (d, 2 C), 128.3 (d), 131.7 (d, 2 C), 132.7 (d), 134.5 (d), 141.8 (s), 152.6 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2960, 2400, 1603, 1568, 1526, 1476, 1346, 1293, 1215, 1105, 1022, 837, 757 cm^{-1}. $C_{18}H_{17}NO_2$ (279.34): calcd. C 77.40, H 6.13, N 5.01; found C 77.29, H 6.24, N 4.92.

Compound 3gm:[14e] Orange spongy mass, 65% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.56 (ddd, J = 1.7, 7.3, 8.0 Hz, 1 H), 7.67 (dt, J = 1.5, 7.7 Hz, 1 H), 7.72–7.79 (m, 3 H), 8.15 (dd, J = 8.1, 1.3 Hz, 1 H), 8.25 (dt, J = 9.0, 2.1 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 89.4 (s), 94.3 (s), 117.5 (s), 123.6 (d, 2 C), 124.9 (d), 128.1 (s), 129.1 (s), 129.6 (d), 132.7 (d, 2 C), 133.1 (d), 134.7 (d), 147.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2985, 2400, 1608, 1596, 1447, 1373, 1276, 1215, 1017, 909, 759 cm^{-1}. $C_{14}H_8N_2O_4$ (268.23): calcd. C 62.69, H 3.01, N 10.44; found C 62.62, H 3.09, N 10.39.

Compound 3hm: Orange spongy mass, 62% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.58 (dt, J = 7.9, 1.4 Hz, 2 H), 7.69 (dd, J = 7.3, 1.4 Hz, 1 H), 7.77 (dd, J = 7.7, 1.4 Hz, 1 H), 7.91 (dt, J = 1.2, 7.7 Hz, 1 H), 8.15 (dd, J = 1.1, 8.2 Hz, 1 H), 8.25 (ddd, J = 1.0, 2.2, 8.3 Hz, 1 H), 8.43 (t, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 86.9 (s), 93.9 (s), 117.6 (s), 123.8 (d), 124.2 (s), 124.9 (d), 126.6 (d), 129.4 (d), 129.5 (d), 133.1 (d), 134.7 (d), 137.7 (d), 148.1 (s), 149.6 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2956, 2400, 1603, 1596, 1524, 1479, 1465, 1373, 1359, 1242, 1097, 1047, 938, 738 cm^{-1}. $C_{14}H_8N_2O_4$ (268.23): calcd. C 62.69, H 3.01, N 10.44; found C 62.60, H 3.11, N 10.36.

Compound 3im: Red solid, 55% yield. M.p. 95 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.32 (m, 1 H), 7.53 (tt, J = 7.8, 1.5 Hz, 1 H), 7.62–7.66 (m, 2 H), 7.73 (tt, J = 7.7, 1.7 Hz, 1 H), 7.80–7.82 (m, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 8.66 (d, J = 4.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.1 (s), 95.5 (s), 117.7 (s), 123.5 (d), 124.7 (d), 127.9 (d), 129.3 (d), 132.9 (d), 134.9 (d), 136.2 (d), 142.6 (s), 149.7 (s), 150.1 (d) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3032, 2958, 2233, 1632, 1608, 1568, 1527, 1480, 1467, 1345, 1216, 1145, 851, 757 cm^{-1}. $C_{13}H_8N_2O_2$ (224.22): calcd. C 69.64, H 3.60, N 12.49; found C 69.69, H 3.72, N 12.41.

Compound 3jm: Orange color solid, 85% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 7.45 (dt, J = 04, 7.8 Hz, 1 H), 7.47 (ddd, J = 1.6, 7.3, 8.1 Hz, 1 H), 7.61 (dt, J = 1.4, 7.7 Hz, 1 H), 7.71 (ddd, J = 0.4, 1.6, 7.3 Hz, 1 H), 7.76 (dd, J = 1.4, 7.7 Hz, 1 H), 8.09 (dd, J = 1.2, 8.1 Hz, 1 H), 8.03 (ddd, J = 1.2, 1.7, 7.8 Hz, 1 H), 8.23 (dt, J = 1.7, 0.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.3 (q), 85.5 (s), 95.7 (s), 118.2 (s), 122.7 (s), 124.7 (d), 128.6 (d), 128.8 (d), 130.1 (d), 130.5 (s), 132.8 (d), 132.9 (d), 134.6 (d), 136.0 (d), 149.4 (s), 166.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3021, 2953, 2400, 1743, 1610, 1527, 1438, 1345, 1296, 1262, 1215, 1152, 1083, 910, 756 cm^{-1}. $C_{16}H_{11}NO_4$ (281.27): calcd. C 68.32, H 3.94, N 4.98; found C 68.27, H 3.84, N 4.91.

General Procedure for the Cycloisomerization: $Pd(CH_3CN)_2Cl_2$ (0.025 mmol, 5 mol-%) was added to a solution of an alkyne **3** (0.5 mmol) in CH_3CN (15 mL), and the mixture was stirred under argon at room temp. for 4 h. The reaction mixture was concentrated, and the residue obtained was purified by column chromatography (ethyl acetate in petroleum ether) to afford a compound **1**.

Compound 1aa: Yellow syrup, 69% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3 H), 1.31–1.40 (m, 4 H), 1.63–1.71 (m, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 7.50–7.56 (m, 2 H), 7.60–7.66 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (q), 21.3 (t), 22.3 (t), 25.1 (t), 31.7 (t), 113.7 (d), 121.3 (d), 123.1 (s), 125.5 (s), 130.9 (d), 134.3 (d), 147.4 (s), 186.8 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2958, 2930, 1711, 1695, 1607, 1588, 1528, 1466, 1353, 1322, 1297, 1216, 1180, 1056, 755 cm^{-1}. $C_{13}H_{15}NO_2$ (217.27): calcd. C 71.87, H 6.96, N 6.45; found C 71.76, H 6.91, N 6.40.

Compound 2aa: $AuBr_3$ (10 mg, 0.023 mmol, 5 mol-%) was added to a solution of the alkyne **3aa** (100 mg. 0.46 mmol) in CH_3CN (15 mL) and the mixture was stirred under argon at room temp. for 4 h. The reaction mixture was concentrated, and the residue obtained was purified by column chromatography (5% → 10% ethyl acetate in petroleum ether) to afford **2aa** (75 mg, 75%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl3): δ = 0.93 (t, J = 6.9 Hz, 3 H), 1.36–1.45 (m, 4 H), 1.76–1.90 (m, 2 H), 3.17 (t, J = 7.4 Hz, 2 H), 7.27 (ddd, J = 1.0, 6.4, 8.7 Hz, 1 H), 7.40 (ddd, J = 1.0, 6.4, 8.9 Hz, 1 H),7.73 (dt, J = 1.0, 8.8 Hz, 1 H), 8.05 (dt, J = 1.0, 8.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (q), 22.4 (t), 23.2 (t), 31.3 (t), 40.1 (t), 115.9 (d), 119.1 (s), 121.2 (d), 128.4 (d), 131.2 (d), 157.5 (s), 159.7 (s), 190.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3022, 2958, 2932, 1732, 1608, 1568, 1527, 1480, 1480, 1345, 1216, 851, 757, 668 cm^{-1}. $C_{13}H_{15}NO_2$ (217.27): calcd. C 71.87, H 6.96, N 6.45; found C 71.61, H 7.08, N 6.40.

Compound 1ab: Yellow liquid, 71% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.05 (s, 6 H), 0.80 (s, 9 H), 1.81–1.94 (m, 2 H), 2.71 (t, J = 7.4 Hz, 2 H), 3.65 (t, J = 5.9 Hz, 2 H), 7.44–7.51 (m, 2 H), 7.55–7.60 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.5 (q, 2 C), 18.2 (s), 18.6 (t), 25.8 (q, 3 C), 28.3 (t), 62.8 (t), 113.6 (d), 121.3 (d), 123.2 (s), 125.5 (s), 130.8 (d), 134.2 (d), 147.5 (s), 186.7 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2954, 2929, 2885, 1709, 1684, 1634, 1557, 1520, 1471, 1465, 1445, 1345, 1276, 1255, 1194, 1143, 1101, 1006, 980, 836, 776 cm^{-1}. $C_{17}H_{25}NO_3Si$ (319.48): calcd. C 63.91, H 7.89, N 4.38; found C 63.81, H 7.72, N 4.32.

Compound 1ac: Dark brown gum, 43% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25–1.35 (m, 22 H), 1.50–1.69 (m, 5 H), 2.66 (t, J = 7.5 Hz, 2 H), 3.64 (t, J = 6.6 Hz, 2 H), 7.51–7.66 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4 (t), 25.4 (t), 25.7 (t), 29.2 (t), 29.4 (t, 2 C), 29.6 (t, 6 C), 29.7 (t), 32.8 (t), 63.1 (t), 113.7 (d), 121.3 (d), 123.1 (s), 125.6 (s), 130.9 (d), 134.3 (d), 147.4 (s), 186.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3381, 2920, 2851, 1705, 1607, 1531, 1475, 1385, 1185, 1058, 755 cm^{-1}. $C_{23}H_{35}NO_3$ (373.53): calcd. C 73.96, H 9.44, N 3.75; found C 73.88, H 9.34, N 3.71.

Compound 1ad: Dark brown spongy mass, 51% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.54–3.60 (m, 2 H), 3.63–3.69 (m, 4 H), 3.73–3.78 (m, 2 H), 4.01 (dt, J = 5.7, 1.4 Hz, 2 H), 4.58 (s, 2 H), 5.18 (ddd, J = 10.4, 3.1, 1.3 Hz, 1 H), 5.27 (ddd, J = 17.2, 3.1, 1.3 Hz, 1 H), 5.90 (ddt, J = 17.2, 10.4, 5.7 Hz, 1 H), 7.51–7.63 (m, 2 H), 7.64–7.70 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 58.9 (t), 69.4 (t), 70.3 (t), 70.5 (t), 71.4 (t), 72.2 (t), 112.2 (d), 117.1

(t), 119.0 (s), 123.5 (s), 123.9 (d), 125.8 (d), 134.8 (d), 138.6 (d), 149.1 (s), 182.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3079, 2919, 2856, 1707, 1608, 1568, 1526, 1475, 1459, 1345, 1262, 1180, 1098, 928, 747 cm^{-1}. $C_{16}H_{19}NO_5$ (305.33): calcd. C 62.94, H 6.27, N 4.59; found C 62.82, H 6.21, N 4.49.

Compound 1ae: Yellow solid, 75% yield. M.p. 103 °C. $[a]_D^{25}$ = +22.4 (c = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.11 (d, J = 1.3 Hz, 6 H), 0.89 (s, 9 H), 1.27 (d, J = 6.3 Hz, 3 H), 3.87–3.90 (m, 1 H), 4.31–4.42 (m, 1 H), 4.90 (d, J = 2.5 Hz, 1 H), 6.16 (s, 1 H), 7.57–7.69 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.0 (q), –4.2 (q), 18.0 (s), 22.6 (q), 25.8 (q, 3 C), 41.8 (d), 62.8 (d), 64.5 (d), 114.1 (d), 121.9 (d), 123.1 (s), 131.9 (d), 134.6 (d), 146.8 (s), 167.7 (s), 185.2 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3019, 2956, 2930, 2885, 1770, 1712, 1672, 1609, 1570, 1529, 1472, 1377, 1346, 1215, 1180, 1144, 1065, 959, 756 cm^{-1}. $C_{19}H_{26}N_2O_4Si$ (374.51): calcd. C 60.93, H 7.0, N 7.48, Si 7.50; found C 60.81, H 7.2, N 7.34, Si 7.13.

Compound 1af: Orange oil. 65% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.57–1.84 (m, 3 H), 2.01–2.16 (m, 2 H), 2.69 (br. s, 1 H), 2.82 (dd, J = 5.8, 14.4 Hz, 1 H), 2.98 (dd, J = 7.3, 14.4 Hz, 1 H), 3.43–3.53 (m, 1 H), 3.60–3.69 (m, 2 H), 4.39–4.53 (m, 1 H), 7.47–7.76 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.0 (q), 29.7 (t), 32.2 (t), 32.4 (t), 63.1 (t), 76.0 (d), 76.6 (d), 85.0 (s), 113.9 (d), 121.5 (d), 123.0 (s), 127.6 (s), 132.2 (d), 134.4 (d), 147.3 (s), 186.6 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 2971, 2931, 1713, 1608, 1559, 1527, 1463, 1376, 1217, 1174, 1089, 755 cm^{-1}. $C_{16}H_{19}NO_5$ (305.33): calcd. C 62.99, H 6.27, N 4.59; found C 62.79, H 6.38, N 4.48.

Compound 1ag: Brown syrup. 83% yield. $[a]_D^{25}$ = –18.5 (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.53 (s, 3 H), 4.40 (d, J = 4.5 Hz, 1 H), 4.43 (d, J = 13.1 Hz, 1 H), 4.63 (d, J = 12.1 Hz, 1 H), 4.77 (d, J = 3.9 Hz, 1 H), 5.65 (d, J = 4.5 Hz, 1 H), 6.21 (d, J = 3.9 Hz, 1 H), 7.04–7.13 (m, 5 H), 7.54–7.58 (m, 3 H), 7.63 (dd, J = 1.5, 7.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7 (q), 27.3 (q), 72.5 (t), 74.7 (d), 83.2 (d), 83.7 (d), 105.8 (d), 112.7 (s), 113.9 (d), 121.7 (d), 123.4 (s), 127.3 (d, 2 C), 127.7 (d), 128.3 (d, 2 C), 131.5 (d), 134.1 (d), 134.3 (s), 137.0 (s), 146.6 (s), 184.2 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3054, 2987, 2685, 1711, 1606, 1575, 1502, 1421, 1265, 1165, 1061, 896, 739, 705 cm^{-1}. $C_{22}H_{21}NO_6$ (395.41): calcd. C 66.83, H 5.35, N 3.54; found C 66.85, H 5.45, N 3.47.

Compound 1ah: Yellow oil, 87% yield. $[a]_D^{25}$ = –12.8 (c = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.45 (s, 3 H), 2.95 (dd, J = 15.3, 8.8 Hz, 1 H), 3.16 (dd, J = 15.3, 3.6 Hz, 1 H), 3.58 (br. s, 1 H), 4.08 (dd, J = 7.7, 3.2 Hz, 1 H), 4.16 (d, J = 3.2 Hz, 1 H), 4.57–4.75 (m, 3 H), 5.93 (d, J = 6.6 Hz, 1 H), 7.31–7.38 (m, 5 H), 7.51–7.66 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.3 (q), 26.7 (q), 27.7 (t), 66.9 (d), 72.2 (t), 81.6 (d), 82.3 (d), 82.5 (d), 105.1 (d), 111.8 (s), 113.9 (d), 121.7 (d), 123.0 (s), 127.9 (d, 2 C), 128.1 (d), 128.6 (d, 2 C), 131.2 (d), 134.5 (d), 137.1 (s), 137.2 (s), 186.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3370, 3019, 2930, 1712, 1685, 1606, 1555, 1535, 1454, 1438, 1216, 1174, 1076, 1012, 756 cm^{-1}. $C_{24}H_{25}NO_7$ (439.46): calcd. C 65.59, H 5.73, N 3.19; found C 65.41, H 5.69, N 3.14.

Compound 1ai: Yellow liquid, 67% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.68 (br. s, 1 H), 4.66 (s, 2 H), 5.19 (s, 2 H), 6.93–7.06 (m, 2 H), 7.24–7.28 (m, 2 H), 7.56–7.71 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.2 (t), 61.9 (t), 111.5 (d), 114.4 (d), 121.8 (d), 122.0 (d), 122.8 (s), 129.0 (d), 129.5 (d), 130.1 (s), 132.1 (d), 133.5 (s), 134.7 (d), 146.8 (s), 155.6 (s), 185.4 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 2923, 2852, 1705, 1655, 1608, 1588, 1530, 1487, 1458, 1348, 1295, 1231, 1173, 1037, 756 cm^{-1}. $C_{16}H_{13}NO_4$ (283.28): calcd. C 67.84, H 4.63, N 4.94; found C 67.79, H 4.69, N 4.83.

Compound 1aj: Dark brown gum, 67% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.08 (dd, J = 15.0, 4.0 Hz, 1 H), 3.24 (dd, J = 15.0, 8.0 Hz, 1 H), 3.84 (s, 9 H), 5.14 (dd, J = 8.0, 4.0 Hz, 1 H), 5.48 (s, 1 H), 6.63 (s, 2 H), 7.50–7.65 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.8 (t), 56.1 (q, 2 C), 60.8 (q), 71.4 (d), 102.0 (d, 2 C), 114.0 (d), 121.9 (d), 122.8 (s), 131.4 (d), 134.7 (d), 136.8 (s), 137.1 (s), 138.8 (s), 147.2 (s), 153.2 (s, 2 C), 186.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 2929, 2898, 1707, 1603, 1593, 1538, 1506, 1463, 1420, 1327, 1234, 1180, 1126, 769 cm^{-1}. $C_{19}H_{19}NO_6$ (357.36): calcd. C 63.86, H 5.36, N 3.92; found C 63.79, H 5.31, N 3.88.

Compound 1ak: Pale gray solid, 78% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.69 (s, 1 H), 3.07 (dd, J = 15.0, 4.1 Hz, 1 H), 3.21 (dd, J = 15.0, 8.1 Hz, 1 H), 3.77 (s, 3 H), 5.17 (dd, J = 8.1, 4.1 Hz, 1 H), 6.83–6.90 (m, 2 H), 7.31–7.38 (m, 2 H), 7.53–7.59 (m, 2 H), 7.62–7.67 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.9 (t), 55.2 (q), 70.8 (d), 113.8 (d, 2 C), 114.0 (d), 121.7 (d), 122.8 (s), 126.6 (d, 2 C), 131.2 (d), 134.6 (d), 135.3 (s), 136.8 (s), 147.2 (s), 159.1 (s), 186.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3350, 3019, 2928, 1712, 1664, 1611, 1514, 1494, 1464, 1345, 1215, 1174, 1056, 756 cm^{-1}. $C_{17}H_{15}NO_4$ (297.31): calcd. C 68.68, H 5.09, N 4.71; found C 68.79, H 5.23, N 4.65.

Compound 1al:[4d,26a] Dark orange solid, 61% yield. M.p. 183 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.45–7.50 (m, 3 H), 7.53–7.57 (m, 1 H), 7.61–7.65 (m, 1 H), 7.67–7.70 (m, 2 H), 8.61–8.66 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 114.2 (d), 121.5 (d), 122.9 (s), 125.9 (s), 127.8 (d, 2 C), 127.8 (s), 128.5 (d, 2 C), 130.7 (d), 131.1 (d), 134.7 (d), 147.9 (s), 186.7 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3054, 2986, 1702, 1601, 1569, 1527, 1512, 1496, 1422, 1374, 1265, 1178, 1046, 1029, 739, 705 cm^{-1}. $C_{14}H_9NO_2$ (223.23): calcd. C 75.33, H 4.06, N 6.27; found C 75.53, H 4.16, N 6.13.

Compound 1bl: Orange solid, 91% yield. M.p. 143 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.35 (m, 2 H), 7.48–7.51 (m, 3 H), 7.67 (dd, J = 9.0, 3.9 Hz, 1 H), 8.57–8.62 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 109.66 (d, $J_{C\beta,F}$ = 26.4 Hz), 115.92 (d, $J_{C\gamma,F}$ = 8.6 Hz), 120.6 (d, $J_{C\beta,F}$ = 26.4 Hz), 124.8 (s, $J_{C\gamma,F}$ = 8.6 Hz), 125.6 (s), 127.5 (d, 2 C), 128.5 (d, 2 C), 128.5 (s), 130.8 (d), 143.2 (s, $J_{C\delta,F}$ = 2.0 Hz) 164.3 (s, J = 253.9 Hz), 185.4 (s, $J_{C\delta,F}$ = 1.9 Hz) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3032, 2998, 1704, 1597, 1523, 1481, 1446, 1385, 1283, 1181, 1020, 875, 758, 685 cm^{-1}. $C_{14}H_8FNO_2$ (241.22): calcd. C 69.71, H 3.34, F 7.88, N 5.81; found C 69.63, H 3.41, F 7.72, N 5.78.

Compound 1cl:[4d] Red solid, 67% yield. M.p. 176 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.14 (s, 2 H), 7.02 (s, 1 H), 7.16 (s, 1 H), 7.43–7.51 (m, 3 H), 8.57–7.61 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 97.3 (d), 102.1 (d), 103.1 (t), 116.5 (s), 125.9 (s), 127.4 (d, 2 C), 128.4 (d, 2 C), 128.6 (s), 130.3 (d), 144.6 (s), 149.6 (s), 152.7 (s), 185.8 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3100, 3090, 2917, 1702, 1632, 1587, 1505, 1489, 1445, 1390, 1350, 1277, 1168, 1029, 919, 775 cm^{-1}. $C_{15}H_9NO_4$ (267.24): calcd. C 67.42, H 3.39, N 5.24; found C 67.37, H 3.42, N 5.20.

Compound 1dl: Orange color solid, 87% yield. M.p. 150 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.99 (s, 3 H), 7.48–7.51 (m, 3 H), 7.70 (d, J = 7.4 Hz, 1 H), 8.26 (dd, J = 1.3, 7.6 Hz, 1 H), 8.29 (br. s, 1 H), 8.60–8.64 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.9 (q), 114.9 (d), 121.4 (d), 125.5 (s), 125.9 (s), 127.8 (d, 2 C), 128.6 (d, 2 C), 128.6 (s), 131.0 (d), 133.0 (d), 136.2 (s), 147.6 (s), 164.8 (s), 185.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3084, 3031, 2955, 1746, 1709, 1596, 1577, 1475, 1460, 1379, 1352, 1284, 1185, 1068, 910, 807, 760 cm^{-1}. $C_{16}H_{11}NO_4$ (281.27): calcd. C 68.32, H 3.94, N 4.98; found C 68.28, H 3.81, N 4.93.

Compound 1em:[4d,6,26e,26f] Red solid, 67% yield. M.p. 160 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 7.00 (dt, J = 9.5,

2.3 Hz, 2 H), 7.46–7.51 (m, 1 H), 7.57–7.64 (m, 3 H), 8.70 (dt, J = 9.5, 2.3 Hz, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 55.3 (q), 113.9 (d), 114.1 (d, 2 C), 118.8 (s), 121.5 (d), 122.8 (s), 124.8 (s), 129.7 (d, 2 C), 130.7 (s), 134.8 (d), 148.0 (d), 161.3 (s), 187.3 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3054, 2958, 1709, 1615, 1540, 1520, 1496, 1374, 1270, 1180, 1046, 745 cm^{-1}. $C_{15}H_{11}NO_3$ (253.26): calcd. C 71.14, H 4.38, N 5.53; found C 71.31, H 4.31, N 5.47.

Compound 1fm: Crimson-red solid, 91% yield. M.p. 130 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 7.50–7.57 (m, 3 H), 7.61–7.65 (m, 1 H), 7.67–7.70 (m, 2 H), 8.59 (dt, J = 8.8, 2.1 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.9 (q, 3 C), 34.9 (s), 113.9 (d), 121.4 (d), 122.7 (s), 122.9 (s), 125.3 (s), 125.5 (d, 2 C), 127.6 (d, 2 C), 130.9 (d), 134.7 (d), 147.8 (s), 154.1 (s), 186.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3065, 2951, 1702, 1596, 1529, 1494, 1461, 1377, 1320, 1284, 1184, 1024, 878, 839, 756 cm^{-1}. $C_{18}H_{17}NO_2$ (279.34): calcd. C 77.40, H 6.13, N 5.01; found C 77.29, H 6.24, N 4.92.

Compound 1gm:[4d,26d] Orange solid, 69% yield. M.p. 237 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.58–7.69 (m, 2 H), 7.72–7.76 (m, 2 H), 8.33 (dt, J = 8.3, 2.1 Hz, 2 H), 8.89 (dt, J = 8.3, 2.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 114.6 (d), 122.1 (d), 122.6 (s), 123.7 (d, 2 C), 123.9 (s), 128.2 (d, 2 C), 131.6 (s), 132.2 (d), 135.3 (d), 147.7 (s), 147.9 (s), 186.2 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 3002, 1706, 1655, 1595, 1517, 1484, 1388, 1347, 1215, 1180, 1019, 756 cm^{-1}. $C_{14}H_8N_2O_4$ (268.23): calcd. C 62.69, H 3.01, N 10.44; found C 62.60, H 3.11, N 10.36.

Compound 1hm:[26d] Dark yellow solid, 56% yield. M.p. 240 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.77 (m, 5 H), 8.32 (ddd, J = 0.9, 2.1, 8.3 Hz, 1 H), 9.0 (dd, J = 0.9, 1.5, 7.9 Hz, 1 H), 9.61 (t, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.6 (d), 122.1 (d), 122.3 (d), 122.6 (s), 124.8 (d), 127.3 (s), 128.0 (s), 129.6 (d), 131.9 (d), 132.9 (d), 135.2 (d), 147.6 (s), 148.3 (s), 186.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2927, 1711, 1619, 1595, 1529, 1469, 1317, 1216, 1175, 1093, 754 cm^{-1}. $C_{14}H_8N_2O_4$ (268.23): calcd. C 62.69, H 3.01, N 10.44; found C 62.60, H 3.11, N 10.36.

Compound 1im:[26b,26c] Red solid, 55% yield. M.p. 162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (ddd, J = 0.4, 4.7, 7.5 Hz, 1 H), 7.61 (dt, J = 0.9, 7.3 Hz, 1 H), 7.71 (d, J = 7.1 Hz, 2 H), 7.73–7.76 (m, 1 H), 7.86 (dt, J = 7.8, 1.7 Hz, 1 H), 8.48 (d, J = 8.0 Hz, 1 H), 8.88 (d, J = 4.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 114.6 (d), 121.9 (d), 122.8 (s), 124.3 (d), 124.9 (d), 128.3 (s), 131.9 (d), 134.7 (d), 136.4 (d), 145.6 (s), 147.6 (s), 150.4 (d), 185.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3084, 3031, 1708, 1596, 1519, 1485, 1459, 1376, 1272, 1184, 1091, 871, 751 cm^{-1}. $C_{13}H_8N_2O_2$ (224.22): calcd. C 69.64, H 3.60, N 12.49; found C 69.69, H 3.72, N 12.41.

Compound 1jm: Yellow solid, 75% yield. M.p. 183 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.97 (s, 3 H), 7.55–7.61 (m, 2 H), 7.63–7.65 (m, 1 H), 7.68–7.73 (m, 2 H), 8.14 (ddd, J = 1.1, 1.6, 7.8 Hz, 1 H), 8.82 (ddd, J = 1.1, 1.6, 8.1 Hz, 1 H), 9.30 (dt, J = 1.7, 0.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.3 (q), 114.3 (d), 121.7 (d), 122.6 (s), 126.0 (s), 128.7 (d, 3 C), 130.5 (s), 131.3 (s), 131.4 (d, 2 C), 131.7 (d), 134.9 (d), 147.6 (s), 166.4 (s), 186.5 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3084, 3031, 2955, 1746, 1709, 1596, 1577, 1519, 1485, 1434, 1376, 1298, 1272, 1184, 1091, 871, 751 cm^{-1}. $C_{16}H_{11}NO_4$ (281.27): calcd. C 68.32, H 3.94, N 4.98; found C 68.27, H 3.84, N 4.91.

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[22] We greatly appreciate the reviewers' remarks and their insistence that we study the formation of the isatogen through the mechanistic route involving the addition of nitro oxygen in a 5-*exo*-dig fashion to the α-carbon atom of the alkyne, which seems to be the facile one. One of the reviewers suggested a reductive elimination of **B** involving O–C formation and then oxidative addition of the N–O bond leading to **D**. However, we believe that routes involving halopalladation are less likely due to the involvement of external coordinating species such as solvent and an additional Pd^{II} species, and that the newly studied 5-*exo*-dig mechanism is the more likely pathway. Therefore, we have not explored other possible mechanisms for isatogen formation involving routes subsequent to the halopalladation.

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