The Hexadehydro-Diels–Alder (HDDA) Benzynes with Nitrogen-Nucleophiles (Diaziridines, *N*–Hetaryls, and C,*N*–Diarylimines); and the Kobayashi Benzynes as HDDA-Diynophiles

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Abstract

Nitrogen heterocycles (*N*-heterocycles) are among the most significant structural components of today's pharmaceuticals. According to a perspective article in *Journal of Medicinal Chemistry*,[57] 84% of the drugs available in the current market have at least one nitrogen atom present in them. More significantly, 59% of the total FDA-approved drugs contain at least one nitrogen heterocycle. These data are compelling and motivate a chemist to creatively develop numerous synthetic strategies that can be used for (i) construction of new *N*-heterocycles from simple starting materials and (ii) functionalization (i.e. modification) of known *N*-heterocycles.

A major portion of my thesis research (Chapter **2**, **3**, and **4**) is guided by these two ideas. In my quest to achieve these goals, I have used a reaction as a tool, which is called the hexadehydro-Diels–Alder (HDDA) reaction. This reaction is a valuable new variant of the Diels–Alder reaction, which is found in every introductory organic chemistry textbook. The HDDA reaction operates in a purely thermal (and therefore milder) environment to generate benzynes, which are one of the most reactive intermediates in organic chemistry. I have reacted the benzynes that were generated via the HDDA reaction with (i) diaziridines (**chapter 2**), (ii) six-membered *N*-hetaryls (**chapter 3**), and (ii) C,*N*-diarylimies (**chapter 4**). In many instances, these thermally generated benzynes allow for the formation of the nitrogen-containing trapping products in a much cleaner and unique manner. In the later section (**chapter 5**) of the thesis, I will demonstrate the utility of classically generated benzynes as a diynophilic partner in the HDDA reaction. This reaction requires only mildly basic and ambient temperature conditions and allows for rapid construction of various naphthalenic products.

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List of Abbreviations

°C	Degree Celcius
18-c-6	18-Crown-6
ar	Atropisomeric ratio
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
^{t}Bu	*tert*-Butyl
$CHCl_3$	Chloroform
CsF	Cesium fluoride
CuCl	Cuprous chloride
DA	Diels–Alder reaction
DABCO	4-diazabicyclo[2.2.2]octane
***o*-DCB**	*ortho*-Dichlorobenzene
DCM	Dichloromethane
DFT	Density functional theory
DMAD	Dimethyl acetylenedicarboxylate
DMAP	*N,N*-4-Dimethylaminopyridine
dr	Diastereomeric ratio
EtOAc	Ethyl acetate
EtOH	Ethanol
GC-MS	Gas chromatography-mass spectrometry
HDDA	Hexadehydro-Diels–Alder reaction

H_2O	Water
IR	Infrared
K_2CO_3	Potassium carbonate
LUMO	Lowest unoccupied molecular orbital
MeCN	Acetonitrile
MeMgBr	Methyl magnesium grignard
MnO_2	Manganese dioxide
mp	Melting point
Ms	Methanesulfonyl
NBS	*N*-Bromo succinimide
***n*-BuLi**	*n*-butyllithium
***n*-Pr**	*n*-Propyl
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser enhancement
PAC	Polyaromatic compound
$Pb(OAc)_4$	Lead tetraacetate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium (0)
PhCl	Chlorobenzene
PhH	Benzene
rr	Regioisomeric ratio
SMD	Solvation model density
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl

TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TBS	*tert*-Butyldimethylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl
TS	Transition state
$ZnCl_2$	Zinc chloride

Chapter 1. Introduction to *o*-benzyne and the HDDA reaction

1.1 *History of o-benzyne and elucidation of its structure*.

Reactive intermediates have always attracted tremendous interest from the organic chemistry community. Although their short lifetime and instability make them very difficult to isolate and, hence, characterize, their fast reactivity can often drive their inherent selectivity towards a unique reaction pathway or a stable product. This particular feature makes them very interesting because studying these short-lived, high-energy molecules allows a chemist to uncover new modes of chemical reactivity. Some of the carbon-containing reactive intermediates known in the literature are radicals, carbenes, carbocations, carbanions, and arynes.

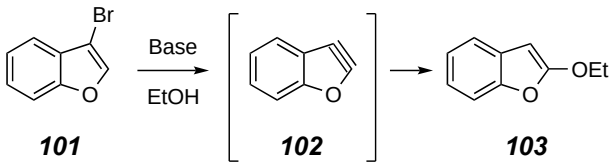
Arynes, which can be formally defined as aromatic systems having a carbon–carbon triple bond, are one of the most well studied and versatile reactive intermediates in organic chemistry. Over more than 100 years, synthetic organic chemists have recognized the potential and value of these highly reactive intermediates (and their variants) towards synthesis of important benzenoids, especially in the field of total synthesis and functional organic materials.[1] The first ever report suggesting the existence of an aryne intermediate was published in 1902 by Stoermer and Kahlert, who observed the formation of 2-ethoxybenzofuran (**103**) after treating 3-bromobenzofuran (**101**) with a base in ethanol (Scheme **1.1**). They proposed that the reaction proceeded through an aryne intermediate, 2,3-didehydrobenzofuran (**102**).[2]

---

[1] (a) Chen, Y.; Larock, R. C. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; pp 401–473. (b) Tadross, P. M.; Stoltz, B. M. A Comprehensive History of Arynes in Natural Product Total Synthesis. *Chem. Rev.* **2012**, *112*, 3550–3577. (c) Gampe, C. M.; Carreira, E. M. Arynes and Cyclohexyne in Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766–3778. (d) Takikawa, H.; Nishii, A.; Sakai, T.; Suzuki, K. Aryne-Based Strategy in the Total Synthesis of Naturally Occurring Polycyclic Compounds. *Chem. Soc. Rev.* **2018**, *47*, 8030–8056. (e) Perez, D.; Pena, D.; Guitian, E. Aryne Cycloaddition Reactions in the Synthesis of Large Polycyclic Aromatic Compounds. *Eur. J. Org. Chem.* **2013**, *2013*, 5981–6013.

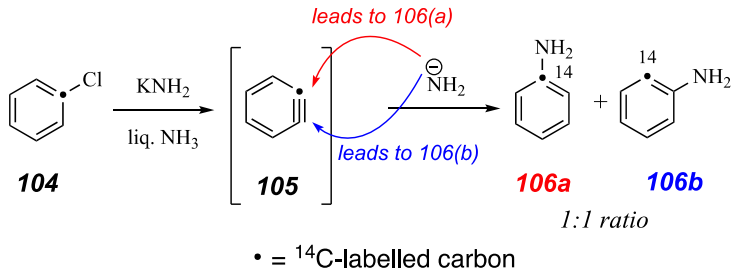
[2] Stoermer, R.; Kahlert, B., Ueber Das 1- und 2-Brom-Cumaron. *Ber. Dtsch. Chem. Ges* **1902,** *35*, 1633–1640.

Scheme 1.1 | First report suggesting the existence of an aryne



Although the initial postulation of an aryne species was reported in 1902, it was not until 1927 that "*ortho*-benzyne" (cf. **107b**, Scheme **1.3**) was suggested as a reactive intermediate.[3] Moreover, the first compelling mechanistic evidence to confirm the intermediacy of an *ortho*-benzyne (*o*-benzyne) was published several decades later (in 1953) after its first postulation.[4] This report came from Roberts group, which detailed a key reaction of isotopically labeled chlorobenzene (**104**) with potassium amide in liquid ammonia. After the reaction, two isotopomers, aniline-1-^{14}C (**106a**) and aniline-2-^{14}C (**106b**), were generated in nearly equal amounts (Scheme **1.2**), which strongly supported the intermediacy of the benzyne species **105**.

Scheme 1.2 | ^{14}C-labeling experiment to demonstrate the structure of *o*-benzyne



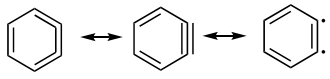
In the following years, the scientific community began to develop an interest in benzyne chemistry, and many researchers studied this intriguing intermediate in more depth. Three resonance structures can be drawn for benzyne (Scheme **1.3**), and therefore, many of these reports focused on determining the major resonance contributor to this molecule. In 1973, Chapman et al. reported the first direct IR spectroscopic detection of

[3] Bachmanand, W. E.; Clark, H. T. The Mechanism of the Wurtz-Fittig Reaction. *J. Am. Chem. Soc.* **1927**, *115*, 2089–2098

[4] Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. Rearrangement in the Reaction of Chlorobenzene-1-C^{14} With Potassium Amide 1. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291.

matrix isolated *o*-benzyne, suggesting **107b** was present as the dominant resonance contributor.[5] In 1992, Radziszewski assigned the triple bond stretch in *o*-benzyne to have a vibration at 1846 cm^{-1}, which was found at a lower wavenumber than that in unstrained alkynes (~ 2150 cm^{-1}).[6]

Scheme 1.3 | Three resonance structures of *o*-benzyne



107a ***107b*** ***107c***

1.2 *Reactivity of o-benzyne.*

The early years spent investigating the structure and intrinsic reactivity of *o*-benzyne paved the way for the development of numerous organic reactions aiming to synthesize natural products and organic materials. There was, however, one important question that still needed to be addressed – why are these strained alkynes very electrophilic and, hence, reactive? Hoffman carried out molecular orbital (MO) calculations by using extended Hückel theory and found that benzyne has a significantly lowered LUMO,[7] which is caused by poor overlap and the strained nature of the benzyne triple bond. The unhybridized p-orbitals of carbon atoms comprising the triple bond are distorted and no longer parallel to each other as in normal alkynes, which makes *o*-benzyne highly electrophilic. Therefore, these short-lived reactive intermediates can take part in myriad reactions, which can generally be placed into one of three categories:

1) Pericyclic reactions:

Scheme **1.4** represents predominant modes of pericyclic reactions shown by *o*-benzynes. Benzyne **107b** reacts with furan (**108**) via [4+2] cycloaddition to generate

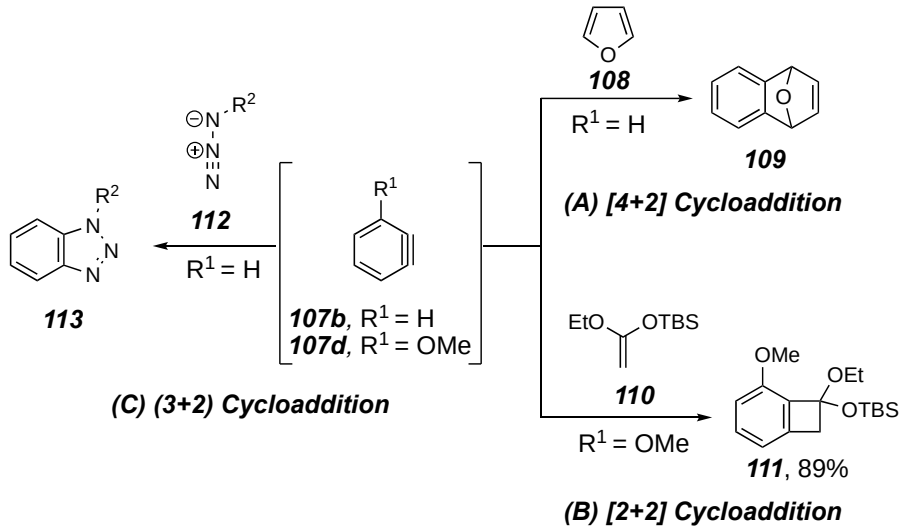
[5] Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky; J.; Calder, J. V.; Orr, G. Photochemical Transformations. LII. Benzyne. *J. Am. Chem. Soc.* **1973**, *95*, 6134–6135.

[6] Orendt, A. M.; Facelli, J. C.; Radziszewski, J. G.; Horton, W. J.; Grant, D. M.; Michl, J. ^{13}C Dipolar NMR Spectrum of Matrix-Isolated *o*-Benzyne-*1,2*-$^{13}C_2$. *J. Am. Chem. Soc.* **1996**, *118*, 846–852.

[7] Jordan, K. D. Perspective on "Benzynes, Dehydroconjugated Molecules, and the Interaction of Orbitals Separated by a Number of Intervening σ Bonds." *Theor. Chem. Acc.* **2000**, *103*, 0286–0288.

norbornene epoxide **109** as the product (Panel **A**).[8] Reactions of benzynes with symmetrical and unsymmetrical olefins lead to the formation of benzocyclobutane derivatives, which are useful synthetic intermediates.[9] For example, Suzuki and co-workers reported the regioselective [2+2] cycloaddition of α-alkoxybenzyne **107d** with silyl ketene acetal **110** (Panel **B**).[10] The methoxy group on the benzyne provided significant electronic perturbation in guiding the regioselectivity towards cyclic product **111** in 89% yield. Benzynes are also known to react with 1,3-dipoles via (3+2) cycloaddition to generate benzofused five-membered heterocyclic systems. For example, an efficient and general method for the synthesis of *N*-substituted triazoles **113** through 1,3-dipolar cycloaddition of arynes with azide derivatives **112** has been reported by Larock and co-workers (Panel **C**).[11]

Scheme 1.4 | Different modes of cycloaddition of benzynes



2) Nucleophilic reactions:

[8] The lack of yield is due to the omission of such information by the original authors.

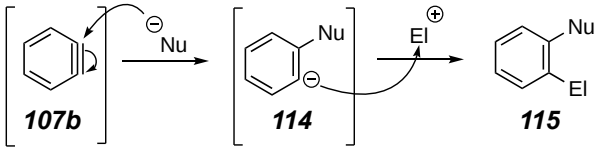
[9] Mehta, G.; Kotha, S. Recent Chemistry of Benzocyclobutenes. *Tetrahedron* **2001**, *57*, 625–659.

[10] Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. Facile Access to Versatile Polyaromatic Building Blocks: Selectively Protected Benzocyclobutenedione Derivatives via Regioselective [2 + 2] Cycloaddition of α-Alkoxybenzyne and Ketene Silyl Acetal. *Helv. Chim. Acta* **2002**, *85*, 3589–3604.

[11] Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. Synthesis of Indazoles by the [3+2] Cycloaddition of Diazo Compounds with Arynes and Subsequent Acyl Migration. *J. Org. Chem.* **2008**, *73*, 219–226.

Because of its highly accessible LUMO, benzyne has been extensively studied for its prominent reactivity with various nucleophiles. Attack of an external nucleophile on benzyne leads to the formation of aryl anion **114**, which in a subsequent trapping event reacts with an electrophile to generate 1,2-disubstituted product **115** (Scheme **1.5**). If the nucleophile and electrophile arise from different species, the overall trimolecular process falls under the category of multicomponent reactions (MCRs), which will be discussed extensively in the later sections (Chapter **3**) of this dossier.

Scheme 1.5 | Nucleophilic addition to the arynes



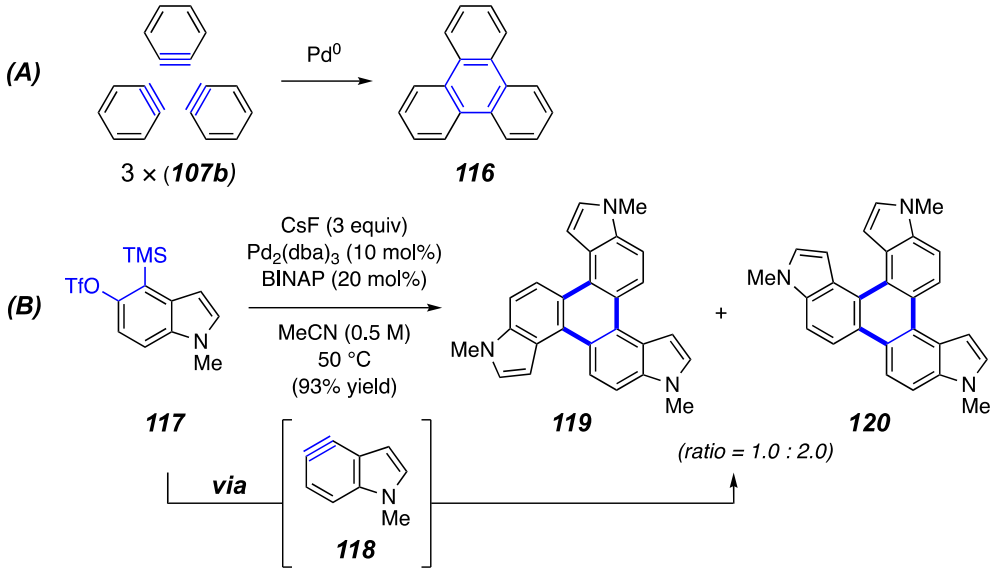
3) Transition metal-mediated reactions:

Another mode by which a benzyne can participate in different bond-formation reactions is through the intermediacy of an aryne-metal complex. Among this body of work, perhaps the most well studied reactions are the cyclotrimerizations of benzynes to form annulated benzenoids. This method of "multiplying the complexity" has opened up new avenues in the synthesis of polycyclic aromatic compounds. Initially, Peña and coworkers reported that the cyclotrimerization of benzyne to triphenylene (**116**) is efficiently catalyzed by palladium (0) complexes [Panel **A**, Scheme **1.6**].[12] Recently, Garg and Houk also validated the feasibility of this process and reported that the indolyne precursor **117** can undergo cyclotrimerization via the intermediacy of hetaryne **118** in the presence of CsF, $Pd_2(dba)_3$, and BINAP to afford isomers **119** and **120** in a ratio of 1:2 [Panel **B**, Scheme **1.6**].[13]

[12] (a) Peña, D.; Escudero, S.; Peréz, D.; Guitián, E.; Castedo, L. Efficient Palladium-Catalyzed Cyclotrimerization of Arynes: Synthesis of Triphenylenes. *Angew. Chem. Int. Ed.* **1998**, *37*, 2659−2661. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. Palladium-Catalyzed Cocyclization of Arynes with Alkynes: Selective Synthesis of Phenanthrenes and Naphthalenes. *J. Am. Chem. Soc.* **1999**, *121*, 5827–5828.

[13] Lin, J. B.; Shah, T. K.; Goetz, A. E.; Garg, N. K.; Houk, K. N. Conjugated Trimeric Scaffolds Accessible from Indolyne Cyclotrimerizations: Synthesis, Structures, and Electronic Properties. *J. Am. Chem. Soc.* **2017**, *139*, 10447–10455.

Scheme 1.6 | Arynes undergoing cyclotrimerization reactions



1.3 *Regioselectivity in benzyne-trapping reactions.*

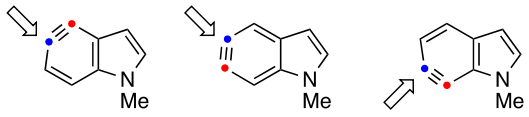
Another concept that is of relevance in conjunction with the reactivity of a benzyne is the formation of regioisomers in the benzyne-trapping reactions. Unlike the prototypical case (cf. **107b**, Scheme **1.3**), an aryne species that is fused and has one or more substituents attached is more often used for practical purposes. In those cases, the C≡C bond in the benzyne is not symmetric and, hence, is the reason for the formation of regioisomers for the respective trapping reactions. Although one can explain (and sometimes even predict) the regioisomeric outcome of benzyne trapping reactions from steric and inductive factors arising from the substitution pattern, having an accurate and quantitative basis for understanding this phenomenon would be of great importance. In this regard, Cramer and Garr,[14] as well as Houk and Garg,[15] have reported a "distortion model" to predict the regioselectivity arising from aryne-trapping reactions. In the unsymmetrical benzyne intermediate, there is a deviation in the internal bond angle from 120°, which leads to one carbon having a more acute angle and the other having a more

[14] Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; Vandervelde, D. Experimental and Theoretical Investigations into the Unusual Regioselectivity of 4,5-, 5,6-, and 6,7-Indole Aryne Cycloadditions. *Org. Lett.* **2010**, *12*, 96–99.

[15] Cheong, P. H. Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. Indolyne and Aryne Distortions and Nucleophilic Regioselectivities. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269.

obtuse angle. The carbon atom with a more acute angle has a greater amount of s-character and a slightly negative partial charge because of the highly electronegative nature of s-electrons. Similarly, the carbon atom having the more obtuse angle has a greater p-character, which makes it more electrophilic, and therefore, a nucleophile prefers to attack at that center. Hence, it seemed evident that the greater the difference between the two angles, the more regioselective the nucleophilic trapping will be. For example, among the three indolyne derivatives in Scheme **1.7**, the 6,7-indolyne **122** (with the difference of the distortion

Scheme 1.7 | Aryne distortion: site of nucleophilic attack at the blue-shaded carbon



118 ***121*** ***122***

118, ∠• = 129°, ∠• = 125°
121, ∠• = 130°, ∠• = 127°
122, ∠• = 135°, ∠• = 117°

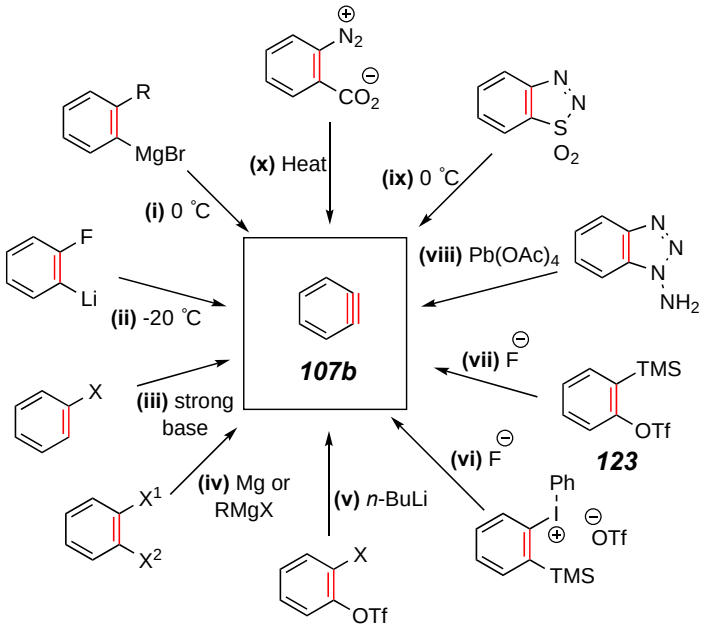
angles of 18º) gives only one regioisomer when trapped with nucleophiles, while **118** and **121** give regioisomeric mixtures. In the modern era, where the majority of synthetic chemists have access to the DFT computations, performing this simple calculation can guide them to predict the regiosiomeric outcome of aryne trapping reactions before they carry out the actual experiment. The author of this thesis, along with several other members of the Hoye research group, have taken the advantage of this strategy for their research activities.

1.4 *Methods of benzyne formation.*

The high reactivity and lack of stability of benzynes requires their in situ generation during a chemical reaction. This reactivity, however, is dependent on the manner by which the aryne is being introduced for the subsequent trapping process. Scheme **1.8** shows the predominant methods of synthesis of 1,2-didehydrobenzene

(**107b**).[16] All of these methods require the precursor arene to be "pre-functionalized", which means that the loss of two adjacent substituents are needed by way of *ortho*-elimination to generate the benzyne intermediate. Most of these methods [from **(i)** to **(v)**] involve very strong basic conditions, e.g. *n*-BuLi and Grignard reagents. Quite intuitively, using these strong basic conditions can significantly limit the scope of trapping agents that can be used to

Scheme 1.8 | Traditional methods of benzyne generation



functionalize the aryne species. In contrast to these, researchers have also developed methods that take advantage of elimination of highly stabilized byproducts to arrive at **107b** [from **(viii)** to **(x)**]. These methods are also scarcely used for most-practical purposes, because of (a) tedious precursor synthesis, (b) usage of stochiometric lead reagents [for method (**viii**)], and (c) shock sensitivity [for method (**x**)]. The most widely used method of benzyne generation is fluoride-induced 1,2-elimination of 2-(trimethylsilyl)phenyl triflate (**123**), which was developed by Kobayashi in 1983.[17] This benzyne precursor **123**, in the presence of a fluoride source (often CsF or TABF), allows

[16] Figure adapted from reference 1(a).

[17] Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-Induced 1,2-Elimination of *o*-Trimethylsilylphenyl Triflate to Benzyne under Mild Conditions. *Chem. Lett.* **1983**, 8, 1211–1214.

for the formation of benzyne in relatively milder conditions. The "Kobayashi method" is largely responsible for the tremendous interest that benzyne chemistry has seen until today. One of the main drawbacks of this protocol is that the synthesis of substituted (or "decorated") precursor arenes can often be very challenging in contrast to the simple precursor **123**.

Another crucial factor that is common in all of these "classic" methods is that byproducts are always formed simply for introducing the benzyne for a subsequent trapping reaction. This is not only disfavored from an atom economy point of view; these byproducts can also interfere with the subsequent trapping chemistry and prevent a synthetic chemist from studying these reactions in an isolated (and, thus, cleaner) environment. Hence, discovery of newer and complementary aryne generation methods that bypass these limitations would be of great importance. The hexadehydro-Diels–Alder (HDDA) reaction, which is an in situ method to produce an aryne species, addresses these limitations up to a significant extent and will be the primary focus of this thesis.

1.5 *The hexadehydro-Diels–Alder (HDDA) reaction.*

1.5.1 *Diels–Alder (DA) reaction and its oxidized variants.*

Few people in the chemical community will disagree with the statement that the Diels–Alder reaction is one of the most important and well studied transformations in organic chemistry.[18,19] Development of this reaction is clearly one of the defining moments in organic chemistry, as recognized by the award of Noble Prize in chemistry in 1950. Panel (**A**) in Scheme

1.9 represents a prototypical Diels–Alder reaction, which can be found in every introductory organic chemistry textbook. In a prototypical event, 1,3-butadiene (**124**, the diene) reacts with ethylene (**125**, the dienophile) to give cyclohexene (**126**) as the

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[18] Diels, O.; Alder, K. Syntheses in the Hydroaromatic Series [in German]. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122.

[19] (a) Onishchenko, A. S. Diene Synthesis (Israel Program for Scientific Translations, 1964). (b) Nicolaou, K. C., Snyder, S. A., Montagnon, T.; Vassilikogiannakis, G. The Diels–Alder Reaction in Total Synthesis. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.

product. During the course of this reaction, two new C–C σ–bonds are formed at the expense of disappearance of two C–C π–bonds. This is responsible for the exothermicity of this reaction because of the greater stability of σ–bonds as compared to π–bonds [-40.1 Kcal•mol^{-1}, Panel (**A**), Scheme **1.9**].[20] The mechanism of the Diels–Alder reaction has always been in debate, although there is much more experimental and theoretical evidence that is consistent with a concerted mechanism rather than a stepwise one.[21]

Prototypes of the oxidized variants of the Diels–Alder reactions are also shown in the Scheme **1.9**. These dehydro-Diels–Alder (DDA) variants can be formally categorized by the amount of desaturation relative to the parent DA reaction or, in simple words, by counting the number of hydrogens that have been removed from both reacting partners. This means that if diene-yne (**124**, **127**) or enyne-ene (**129**, **125**) react with each other, then the [4+2] cyclization is named as the didehydro-Diels–Alder (DDA) reaction [Panel (**B)**, Scheme **1.9**]. Logically, the next-most highly oxidized version is the tetradehydro-Diels–Alder (TDDA) cyclization [Panel (**C**), Scheme **1.9**]. In this category, one prototypical example is the cyclization of vinyl acetylene (**129**) with acetylene (**127**) to generate a strained allene **131**.

The first report on this specific category of DDA reaction came in 1895 by Michael and Bücher,[22] which dates, surprisingly, even before the initial report on the Diels–Alder reaction. Another example of a TDDA reaction is the cycloaddition between 1,3-butadiyne (**133**) and ethylene (**125**) to give the cyclic cumulene **134**. Unlike the parent DA reaction, which has been used for myriad purposes, DDA reactions have met with limited utilization in organic chemistry. This can be attributed to the fact that the

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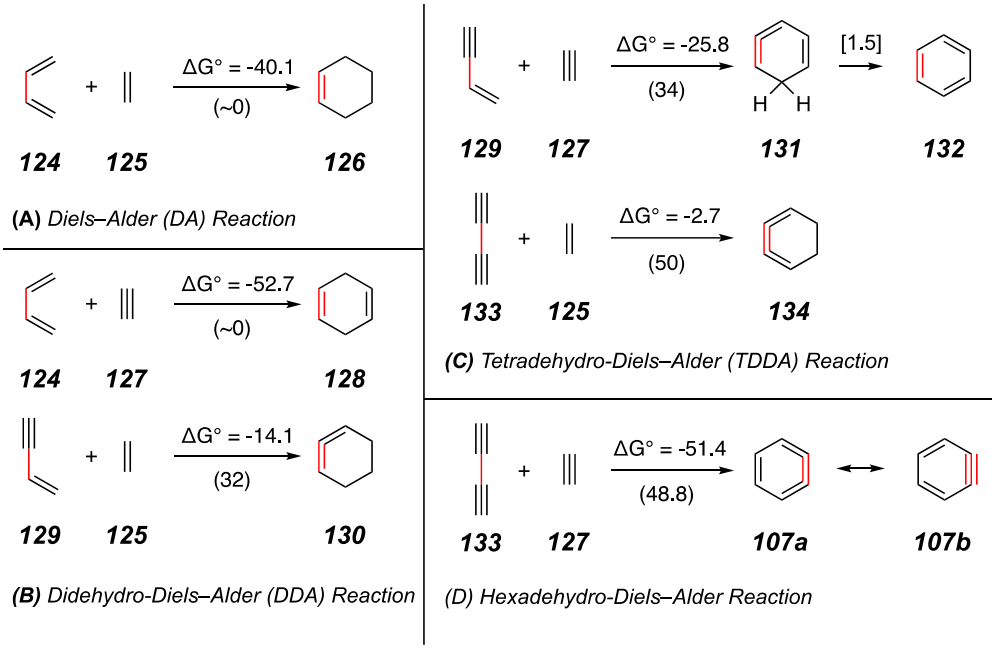
[20] Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P., Concerted vs Stepwise Mechanisms in Dehydro-Diels-Alder Reactions. *J. Org. Chem.* **2011**, *76*, 9320–9328.

[21] (a) Is, D.; Synchronous, N. JyCN / cyE. **1987**, *5546*, 5545–5546. (b) Houk, K. N.; Gonzalez, J.; Li, Y. Pericyclic Reaction Transition States: Passions and Punctilios, 1935-1995. *Acc. Chem. Res.* **1995**, *28*, 81–90. (c) Oldstein, E.; Beno, B.; Houk, K. N. Density Functional Theory Prediction of the Relative Energies and Isotope Effects for the Concerted and Stepwise Mechanisms of the Diels-Alder Reaction of Butadiene and Ethylene. *J. Am. Chem. Soc.* **1996**, *118*, 6036–6043. (d) Houk, K. N.; Lin, Y. T.; Brown, F. K. Evidence for the Concerted Mechanism of the Diels-Alder Reaction of Butadiene with Ethylene. *J. Am. Chem. Soc.* **1986**, *108*, 554–556.

[22] Michael, A.; Bucher, J. E., Ueber die Einwirkung von Essigsäureanhydrid auf Säuren der Acetylenreihe. *Ber. Dtsch. Chem. Ges* **1895**, *28*, 2511–2512.

products formed via these reactions have considerable ring strain (cf. the numbers below the arrows in Scheme **1.8**), and therefore, are not even stable under standard conditions. This inherent ring strain is also the reason that the DDA reactions are less exothermic as compared to the original DA reaction.

Scheme 1.9 | The internal energy of each reaction (above the reaction arrows) and the ring strain of each cyclic product (below the reaction arrows) for Diels–Alder reaction [Panel (**A**)] and of the variations of dehydro-Diels–Alder reaction [Panel (**B**), (**C**), and (**D**)] in kcal•mol^{-1}.[20]



This finally brings us to the most-highly oxidized version of the DA reaction, in which we have 1,3-butadiyne (**133,** the diyne) reacting with acetylene (**127**, the diynophile) to give a strained cumulene **107a** (Panel **D**, Scheme **1.9**). Just to reiterate, since we have removed total of six hydrogens from the two reacting partners when compared to the parent DA reaction, this reaction has been named the hexadehydro-Diels–Alder (HDDA) reaction.[23] The product of this reaction is a cyclic cumulene **107a** that is nothing but the Kekule descriptor of the reactive intermediate benzyne – a main

[23] Hoye, T. R.; Baire, B. B.; Niu, D.; Willoughby, P. H.; Woods, B. P., The Hexadehydro-Diels–Alder Reaction. *Nature* **2012,** *490*, 208.

focus of this thesis. The thermodynamic parameters of the HDDA reaction are very interesting – this reaction is thermodynamically downhill by -51.4 kcal•mol^{-1}, which is even more exergonic than a prototypical DA reaction! This is remarkable and can be easily explained by the aromaticity of the benzyne product leading to a thermodynamic sink towards product formation. However, there is one more factor that contributes to this stabilization – the inherent potential energy of alkynes. During the HDDA reaction, two C≡C bonds are formally converted to two C=C bonds, resulting in the massive stabilization from the thermodynamic point of view.

1.5.2 *Early reports of the HDDA reaction*

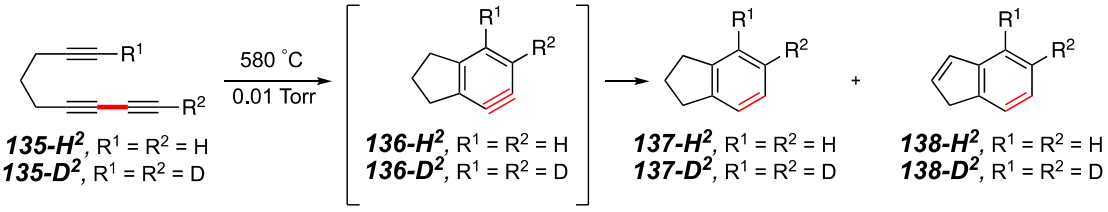
Even though the HDDA reaction is thermodynamically driven and produces a valuable reactive intermediate, it is very surprising that this reaction was not explored at all for almost 100 years since the first reported example of a Diels–Alder cycloaddition. There could be two reasons behind this: (i) to produce (or "trace") a product formed through the HDDA reaction, there needs to be a suitably placed trapping agent in the reaction, which could serve as a hurdle in the reaction discovery and (ii) benzynes are most commonly depicted as **107b** (cf. Scheme **1.3**), and retrosynthetically, it is challenging to envision a [4+2] reaction starting from a 1,3-butadiyne and an alkyne as reacting partners.

The first report on the HDDA reaction came in 1997 from Johnson et al., who reported an intramolecular cyclization of isotopically labelled triynes **135** (Scheme **1.10**).[24] In this experiment, 1,3,8-nonatriyne (**135-H^2**) was heated to 580 °C at 0.01 Torr using flash vaccum pyrolysis (FVP) to form a mixture of indane **137-H^2** and indene **138-H^2**. To confirm the intermediacy of the aryne, deuterated analogue **135-D^2** was also prepared and subsequently treated under the same reaction conditions to give a mixture of **137-D^2** and **138-D^2**. This validated the formation of the aryne intermediates (**136-H^2** and **136-D^2**) in both of the experiments, thereby eliminating another plausible mechanism that

[24] Bradley, A. Z.; Johnson, R. P., Thermolysis of 1,3,8-Nonatriyne: Evidence for Intramolecular [2 + 4] Cycloaromatization to a Benzyne Intermediate. *J. Am. Chem. Soc.* **1997,** *119*, 9917–9918.

involved Bergman cycloaromatization.[25] To delineate the source of formation of **138-H²**, they also subjected **137-H²** to FVP, which gave them **138-H²** as the observed product. This outcome gave evidence that the initial cycloisomerization of triyne leads to **137-H²** (or **137-D²**) through an aryne intermediate, and the indene **138-H²** (or **138-D²**) is just a secondary product obtained after dehydrogenation of the indane core. It is worth mentioning that the "hexadehydro-Diels–Alder" reaction was not referred to as such in their report.

Scheme 1.10 | Flash vacuum pyrolysis of 1,3,8-nonatriyne and its deuterated analogue (**135-H²** and **135-D²**, respectively) to give a mixture of indane (**137-H²/137-D²**) and indene (**138-H²/138-D²**).



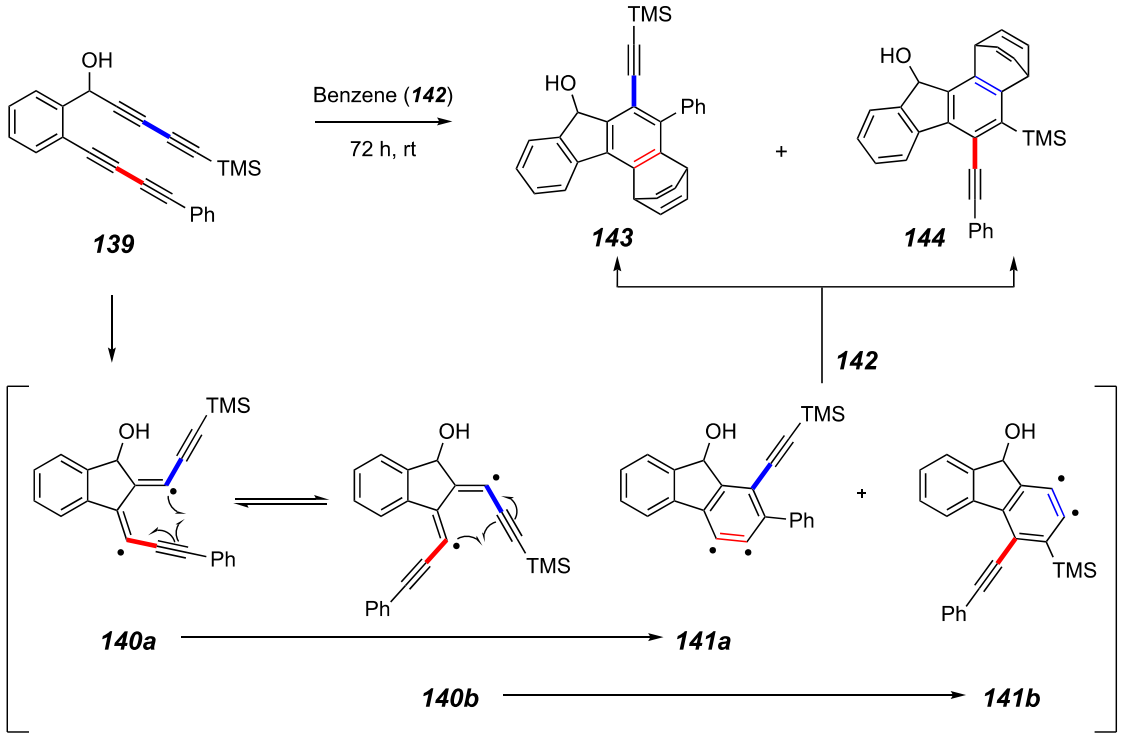
The following years would see several reports from Ueda and co-workers describing cycloaromatization of the tetrayne precursors to benzenoid products.[26] In one example, they demonstrated that tetrayne precursor **139** undergoes cyclization at room temperature to form an equilibrating mixture of structural isomers **143** and **144** (Scheme **1.11**). Their mechanistic rationale, through which they propose the formation of diradical intermediates, is also shown in Scheme **1.11**.Tetrayne **139** was treated with excess

[25] (a) Jones, R. R.; Bergman, R. G., *p*-Benzyne. Generation as an Intermediate in a Thermal Isomerization Reaction and Trapping Evidence for the 1,4-Benzenediyl Structure. *J. Am. Chem. Soc.* **1972,** *94*, 660-661. (b) Bergman, R. G., Reactive 1,4-dehydroaromatics. *Acc. Chem. Res.* **1973,** *6*, 25–31. (c) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D., The Chemistry of Enediynes, Enyne Allenes and Related Compounds. *Tetrahedron* **1996,** *52*, 6453–6518.

[26] (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I., Cycloaromatization of a Non-conjugated Polyenyne System: Synthesis of 5H-Benzo[d]fluoreno[3,2-b]pyrans *via* Diradicals Generated from 1-[2-{4-(2-Alkoxymethylphenyl)butan-1,3-diynyl}]phenylpentan-2,4-diyn-1-ols and Trapping Evidence for the 1,2-Didehydroben. *Tetrahedron Lett.* **1997,** *38*, 3943–3946. (b) Miyawaki, K.; Kawano, T.; Ueda, I., Multiple Cycloaromatization of Novel Aromatic Enediynes Bearing a Triggering Device on the Terminal Acetylene Carbon. *Tetrahedron Lett.* **1998,** *39*, 6923–6926. (c) Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M., An Unprecedented Arylcarbene Formation in Thermal Reaction of Non-conjugated Aromatic Enetetraynes and DNA Strand Cleavage. *Tetrahedron Lett.* **1999,** *40*, 319–322. (d) Miyawaki, K.; Kawano, T.; Ueda, I., Domino Thermal Radical Cycloaromatization of Non-conjugated Aromatic Hexa- and Heptaynes: Synthesis of Fluoranthene and Benzo[a]rubicene Skeletons. *Tetrahedron Lett.* **2000,** *41*, 1447–1451.

benzene (**142**) at room temperature over 72 hours. They proposed that the cycloaromatization proceeds through two isomeric diradical intermediates **140a** and **140b**, both of which subsequently cyclize to give aryne intermediates **141a** and **141b** respectively (notice the diradical depiction of the arynes). These aryne intermediates underwent [4+2]-cycloaddition with benzene to afford benzenoid products **143** and **144**, respectively. Even after having such promising results at that time, the HDDA chemistry did not attract the scientific community in the coming years. As Ueda and co-workers used this strategy to synthesize only polycyclic aromatic hydrocarbons, this reaction seemed to have a very limited substrate scope. Also, depiction of the aryne intermediates as diradical species (cf. **107c**, Scheme **1.3**) could also have played a role against the broader recognition of this foundational work, presumably because arynes are much more commonly depicted as strained alkynes in synthetic organic literature.

Scheme 1.11 | Ueda and co-workers describing cycloaromatization of the tetrayne precursor **139** to benzenoid products **143** and **144**

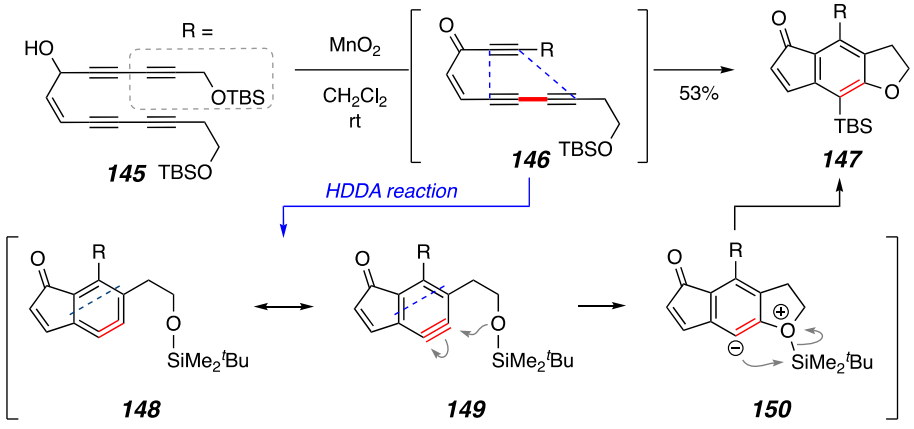


1.5.3 *Serendipitous rediscovery of the HDDA reaction.*

In 2012, with a desire to prepare a biosynthetic precursor that can non-enzymatically lead to nine-membered ene-diyne natural products, postdoctoral researcher Dr. Beeraiah Baire from Hoye lab attempted to synthesize tetrayne **146** via MnO_2 oxidation of the allylic alcohol **145** (Scheme **1.12**).[23] To their surprise, they did not observe the formation of expected enone **146**. A major product was obtained in 53% yield, which, after extensive spectroscopic analysis, was identified as benzenoid **147**. After the confirmation of the product, it was evident that the product had been formed through a benzyne intermediate (**148** and **149**). The silyl ether moiety that is five atoms away from the newly formed benzyne acted as the nucleophile to attack the benzyne, leading to the zwitterion intermediate **150**. This is followed by the retro-Brook rearrangement,[27] which involves silyl migration from the oxonium ion to the aryl carbanion to generate tricyclic benzenoid **147**.

Hoye and coworkers were very fortunate to have placed a two-atom spacer TBS ether in the starting triyne. This functional group served as an "intramolecular trapping agent" for the in situ generated aryne and was very crucial in understanding the reaction pathway of this remarkable transformation. However, one must not assign sole credit to

Scheme 1.12 | Attempted oxidation of alochol **145** and (re)discovery of the HDDA reaction

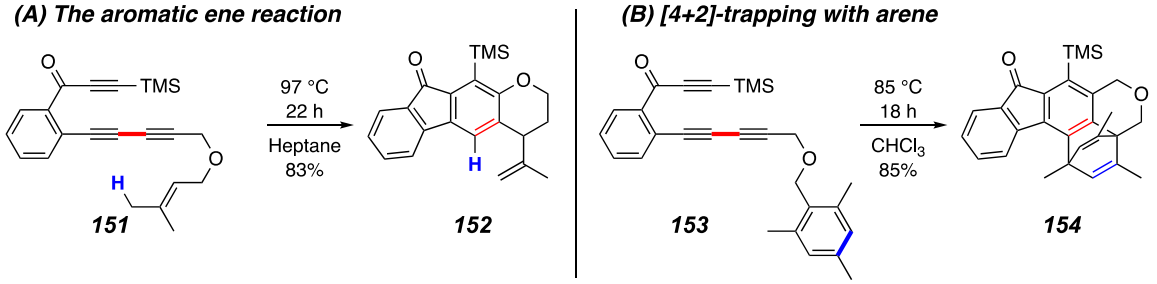


[27] Bailey, W. F. Stereochemistry of the Cyclization of 4-(T-Butyldimethyl)siloxy-5-Hexenyllithium: Cis-Selelective Ring-Closure Accompanied by Retro-[1,4]-Brook Rearrangement. *Arkivoc* **2005**, *2005*, 25–32.

"team benzyne"[28] for rediscovering this reaction as it was, in fact, sheer luck – this outcome served as a reminder that one can always find fruitful opportunities from a "failed" experiment by being diligent in fishing out and characterizing "side products".

This was a moment of realization that "the game is on",[29] and researchers in the Hoye lab quickly realized the potential of this powerful transformation. Even the first reaction that showed the feasibility of the HDDA reaction (from **145** to **147**, Scheme **1.12**) was the first example where silyl ethers were used to trap an aryne. Other successful intramolecular trapping reactions that validated the novelty of this cascade reaction included: (a) the aromatic-ene reaction[30] (from **151** to **152**, Scheme **1.13**), and (b) [4+2]-cyclization by a tethered arene[31] (from **153** to **154**, Scheme **1.13**).

Scheme 1.13 | (**A**) The aromatic ene reaction[30] and (**B**) Intramolecular [4+2]-cyclization by a tethered arene[31]



The synthetic potential of the HDDA reaction was not only limited to intramolecular trapping agents. Scheme **1.14** represents the initial examples of intermolecular HDDA chemistry using the acetate **155**. Benzene and norbornene reacted in a [4+2] and [2+2] manner to give the benzo-fused products **158** and **159**, respectively. Nitrogen-containing nucleophiles like *N*-phenylacetamide trapped in an efficient and highly regioselective manner to produce, for example **160**. Acetic acid and phenol can trap the benzyne via hydroxy proton transfer in a concerted fashion giving rise to **161** and **162**,

[28] The team of Hoye group researchers that were authors on the initial report on the HDDA reaction[23] – Beeru Baire, Dawen Niu, and Patrick Willoughby, and Brian Woods.

[29] T. R. Hoye, July 6, 2011

[30] Niu, D; Hoye, T. R. The Aromatic Ene Reaction. *Nature Chem.* **2014**, *6*, 34–40.

[31] Pogula, V. D.; Wang, T.; Hoye, T. R., Intramolecular [4 + 2] Trapping of a Hexadehydro-Diels–Alder (HDDA) Benzyne by Tethered Arenes. *Org. Lett.* **2015,** *17*, 856–859.

respectively. This unique mode of phenol addition[32] to benzyne is complementary to the previously observed reactions with traditionally generated (Kobayashi's method) benzynes.[33, 34] Finally, HBr addition was achieved across the benzyne using $Br(CH_2CH_3)_2NH_2$•HBr in THF/H_2O (20:1). As shown in Scheme **1.14**, a high level of regioselectivity was achieved in almost all of the cases, which was consistent with the DFT calculated bond angles at the two alkynyl carbons.[14,15]

Overall, rediscovery of this reaction was a significant landmark in benzyne chemistry. Compared to the classical methods of benzyne generation, this protocol: (a) doesn't need the arene to be pre-functionalized and can give an access to relatively structurally complex aryne species, (b) doesn't involve external reagents and byproducts that could interfere with the reaction, and (c) is 100% atom economical. However, most importantly, rediscovery of this reaction has allowed the chemist to uncover inherent aryne reactivity in a pristine, thermal environment, thereby providing an orthogonal platform compared to existing methods (performed in basic environments).

1.5.4 *Applications of the HDDA reaction*

After the initial disclosure of this reaction by Hoye and coworkers, remarkable synthetic utility was demonstrated in the following reports. There have already been publications that review recent developments in this field,[35] and therefore, only reports that involve (i) synthesis and functionalization of heterocycles, and (ii) methods to synthesize naphthynes will be discussed in this section. In 2016, Chen and Palani reported that sulfides can serve as a suitable intermolecular trap for the arynes under

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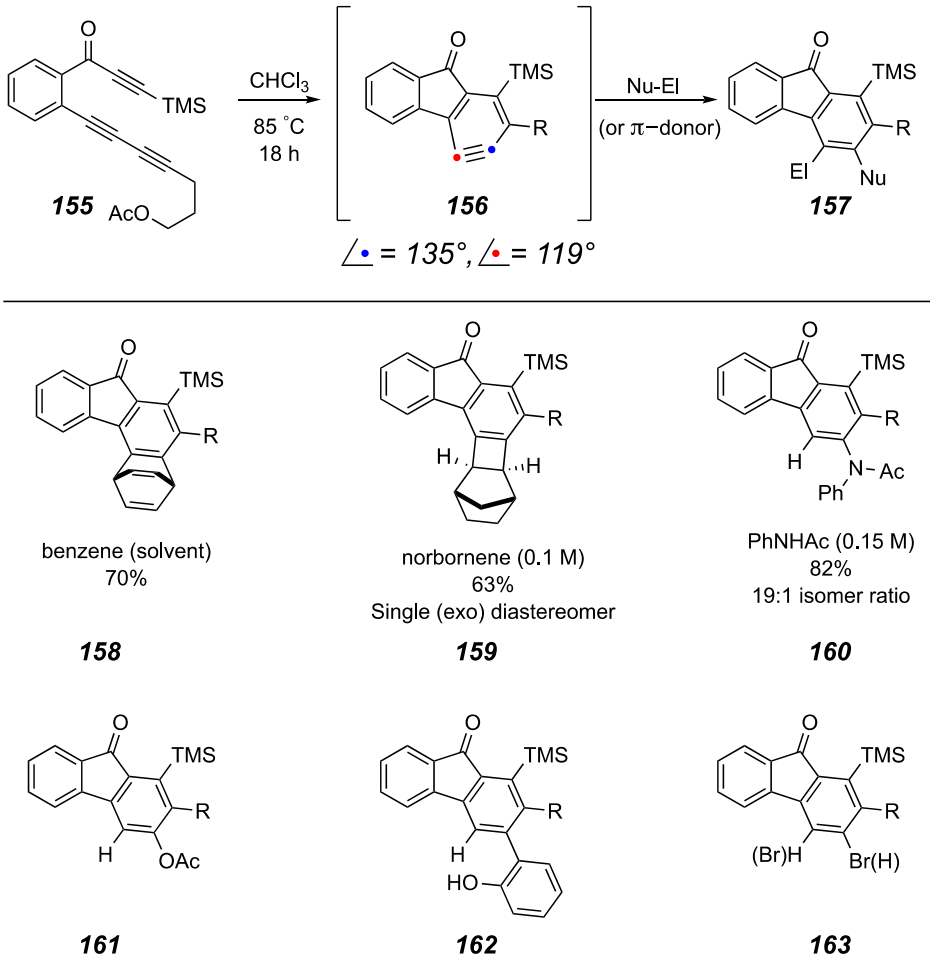
[32] Zhang, J.; Niu, D.; Brinker, V. A.; Hoye, T. R., The Phenol–Ene Reaction: Biaryl Synthesis via Trapping Reactions between HDDA-Generated Benzynes and Phenolics. *Org. Lett.* **2016,** *18*, 5596–5599.

[33] Liu, Z.; Larock, R. C. Facile *O*-Arylation of Phenols and Carboxylic Acids. *Org. Lett.* **2004**, *6*, 99–102.

[34] Cheong, P. H. Y.; Paton, R. S.; Bronner, S. M.; Im, G. Y. J.; Garg, N. K.; Houk, K. N. Indolyne and Aryne Distortions and Nucleophilic Regioselectivites. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269.

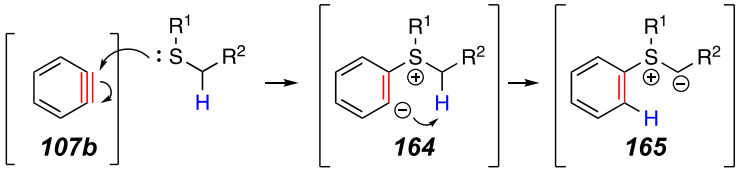
[35] (a) Diamond, O. J.; Marder, T. B., Methodology and Applications of the Hexadehydro-Diels–Alder (HDDA) Reaction. *Org. Chem. Front.* **2017,** *4*, 891–910. (b) Holden , C.; Greaney, M. F., The Hexadehydro-Diels–Alder Reaction: A New Chapter in Aryne Chemistry. *Angew. Chem. Int. Ed.* **2014,** *53*, 5746–5749.

Scheme 1.14 | Intermolecular trapping examples of HDDA-generated benzynes



thermal conditions.[36] Simplistically, trapping of *o*-benzyne that was generated via thermal conditions with alkyl sulfide produces ylide **164**, which was followed by an intramolecular [1,4]-proton shift, to produce the *S*-aryl ylide **165** (Scheme **1.15**).

Scheme 1.15 | Trapping of benzyne **107b** by sulfide in thermal conditions



[36] Chen, J.; Vignesh, P.; Hoye, T. R. Reactions of HDDA-Derived Benzynes with Sulfides: Mechanism, Modes, and Three-Component Reactions. *J. Am. Chem. Soc.* **2016,** *138*, 4318–4321.

Chen and Palani demonstrated the applicability of this work by elegantly choosing trapping agents that could reveal several new modes of reactivity. For example, the sulfur diene **168** reacted with the aryne species **167** that was generated from the tetrayne **166** to finally produce a *S*-aryl ylide **169** (Panel **A**, Scheme **1.16**). This intermediate underwent a [2,3]-sigmatropic rearrangement to give the unsymmetrical diene **170** in a 52% yield. When the same aryne species **167** was treated with dibenzyl sulfide (**171**), the corresponding sulfonium ylide **172** was produced. Ylide **172**, however, underwent a Stevens rearrangement[37] to finally produce an S-arylated product **178** in 25% yield (Panel **B**, Scheme **1.16**).

They also showed that several three-component reactions can be achieved with HDDA-benzynes, cyclic sulfides, and protic nucleophiles. One example includes the reaction of a thermally generated fluorenone aryne **174** with thietane (**175**) and methyl 2-cyanoacetate (**176**) to form the ion pair **177**, which subsequently ring opens to give product **178** in 67% yield, containing components of all three starting materials (Panel **C**, Scheme **1.16**). Interestingly, the skeletons synthesized through this strategy are also being studied in a drug discovery program to study new drug candidates.[38]

In 2018, Ross developed a method to access complex heterocycles from simple starting materials.[39] He reported a broadly applicable, three-component coupling reaction to construct multifunctional heterocyclic motifs from tertiary cyclic amines. Specifically, HDDA-benzyne precursor **179** was treated with DABCO (**180**, the nucleophilic partner) and indole-5-ol (**181**, the electrophilic partner) to give a three-component product **183** (Panel **A**, Scheme **1.17**). This reaction proceeds through a mechanism[40] by which the nucleophilic attack of **180** onto the in situ aryne generated by tetrayne **179** produces an aryl anion (not shown here) that abstracts the acidic proton from the protic nucleophile **181** to finally produce an ion pair **182**. Ross also developed a two-step variant of this

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[37] Bhakat, S. The Controversial Reaction Mechanism of Stevens Rearrangement: A review. *J. Chem. Pharm. Res.* **2011**, *3*, 115−121

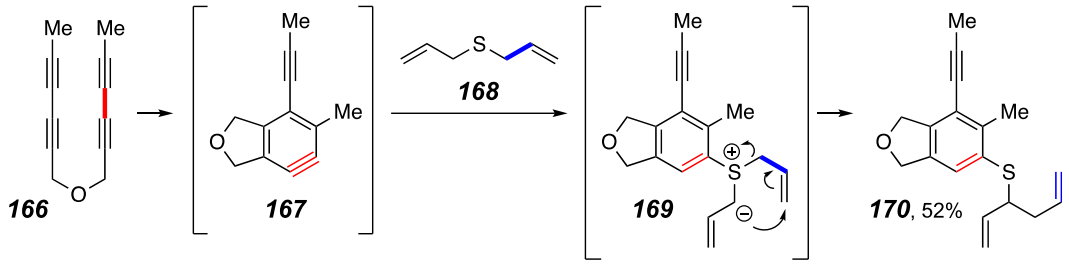
[38] Grand, B. L.; Pignier, C.; Létienne, R.; Cuisiat, F.; Rolland, F.; Mas, A.; and Vacher, F. Sodium Late Current Blockers in Ischemia Reperfusion: Is the Bullet Magic? *J. Med. Chem.*, **2008**, *51*, 3856–3866.

[39] Ross, S. P.; Hoye, T. R., Multiheterocyclic Motifs via Three-Component Reactions of Benzynes, Cyclic Amines, and Protic Nucleophiles. *Org. Lett.* **2018,** *20*, 100–103.

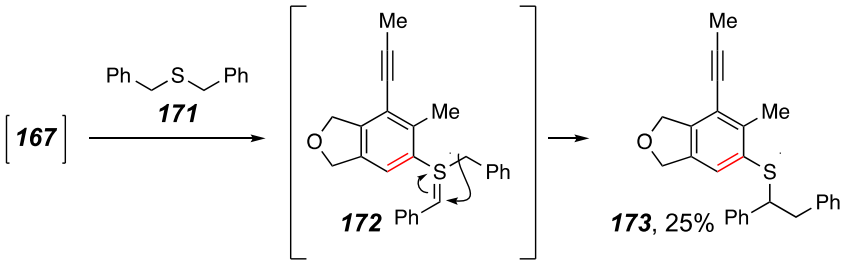
[40] Ross, S. P.; Baire, B.; Hoye, T. R., Mechanistic Duality in Tertiary Amine Additions to Thermally Generated Hexadehydro-Diels–Alder Benzynes. *Org. Lett.* **2017,** *19*, 5705–5708.

Scheme 1.16 | Various novel reactivity was uncovered by trapping thermally-geanerated benzynes with sulfides (and protic nucleophiles)

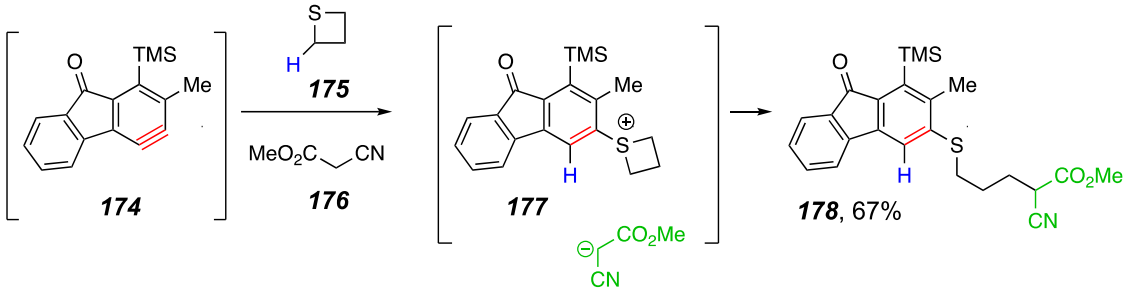
(A) [2,3]-Sigmatropic rearrangements



(B) Stevens rearrangement

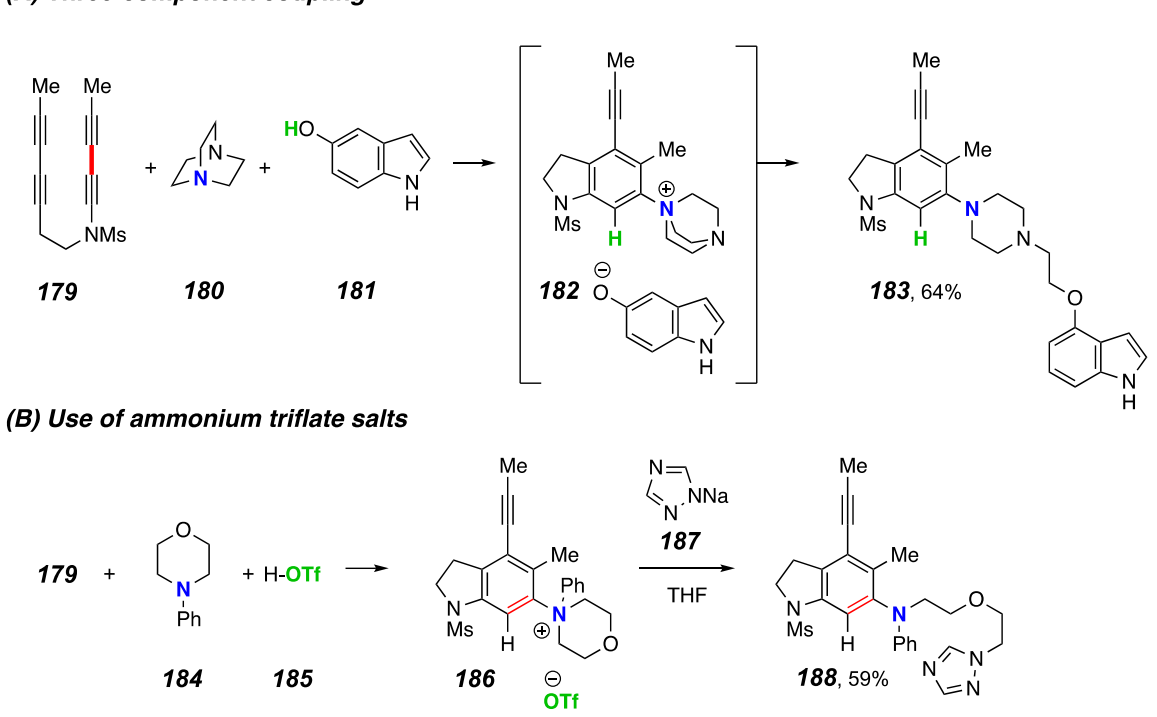


(C) Three-component coupling



reaction to get a better handle on the intermediate ion pair. For example, when a benzyne was generated from **179** in a solution containing *N*–phenylmorpholine (**184**) and its ammonium triflate, the triflate salt **186** was efficiently produced. (Panel **B**, Scheme **1.17**). This triflate salt **186** was subsequently exposed to the sodium amide salt **187** to synthesize complex **188** via a three-component, but a two-pot process.

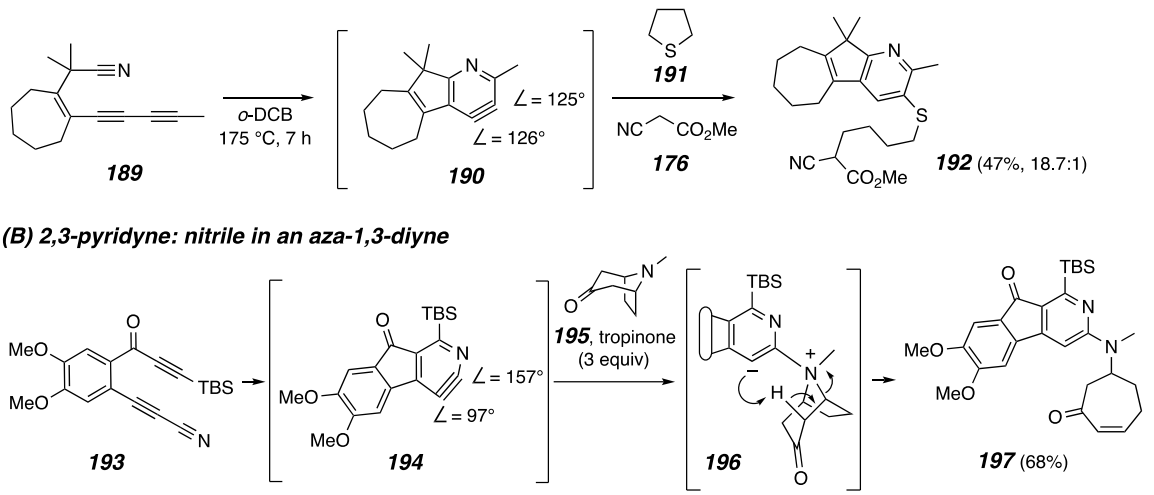
Scheme 1.17 | (A) Three-component (**A**) one pot, and (**B**) two-pot couplings



Last year, Thompson demonstrated the nitrile participation in the HDDA manifold.[41] In this report he uncovered that, in general, two different types of nitrile substrates could thermally cyclize in the HDDA reaction. In the first case (Panel **A**, Scheme **1.18**), cycloheptene precursor **189** that has nitrile group as a diynophile underwent cycloaromatization reaction to give a 3,4-pyridyne **190**. Subsequently, the intermediate **190** engages with tetrahydrothiophene (**191**) and 2-cyanoacetate (**176**) in a three-component reaction to afford **192** in 47% yield with an impressive regioisomeric ratio of 18.7:1 – in spite of the absence of significant distortion in the pyridyne intermediate (cf. **190**, Scheme **1.18**). In the second case (Panel **B**, Scheme **1.18**), the aza-fluorenone precursor **193**, having nitrile as a part of the aza-1,3-diyne unit, undergoes cyclization to give a highly distorted 2,3-pyridyne **194**. This intermediate was efficiently

[41] Thompson, S. K.; Hoye, T. R. The Aza-Hexadehydro-Diels–Alder (aza-HDDA) Reaction *J. Am. Chem. Soc.* **2019**, *141*, 19575–19580.

Scheme 1.18 | The class I (Panel **A**) and class II (Panel **B**) aza-HDDA reactions



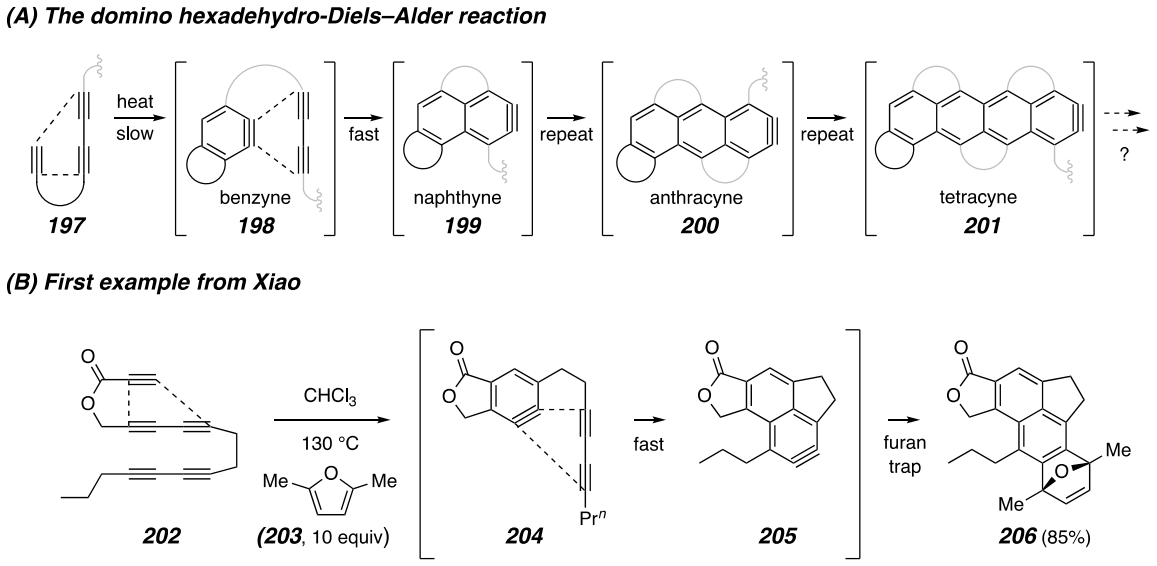
trapped with tropinone (**195**) to give the amino pyridine product **197** in 68% yield.[42] This transformation occurs through initial trapping of the pyridyne **194** with the tertiary amine group present in tropinone to form betaine **196**,[43] which underwent an intramolecular Hofmann-type fragmentation (arrows drawn in Scheme **1.18**) to afford **197.** In 2018, Xiao demonstrated that it is possible to use the HDDA reaction in a sequential manner to synthesize polyacenes from properly designed multiyne precursors via a reaction that has been termed as the domino HDDA reaction.[44] In a very simplistic fashion, an intramolecular cyclization of tethered multiyne precursor **197** produces the isomeric benzyne species **198** in a rate-limiting step (Scheme **1.19**). If we design the starting multiyne precursor in such a way that a suitably placed 1,3-butadiyne unit acts as an arynophile, then, in principle, the second HDDA reaction (from **198** to **199**) would produce naphthyne **199**. This naphthyne, upon formation, could again serve as a

[42] Ross, S. P.; Hoye, T. R., Reactions of Hexadehydro-Diels–Alder Benzynes with Structurally Complex Multifunctional Natural Products. *Nat. Chem.* **2017,** *9*, 523-530.

[43] **196** has been shown in a truncated version for better visualization.

[44] Xiao, X.; Hoye, T. R., The domino hexadehydro-Diels–Alder reaction transforms polyynes to benzynes to naphthynes to anthracynes to tetracynes (and beyond?). *Nat. Chem.* **2018,** *10*, 838–844**.**

Scheme 1.19 | (**A**) A general domino-HDDA reaction and (**B**) First example from Hoye group



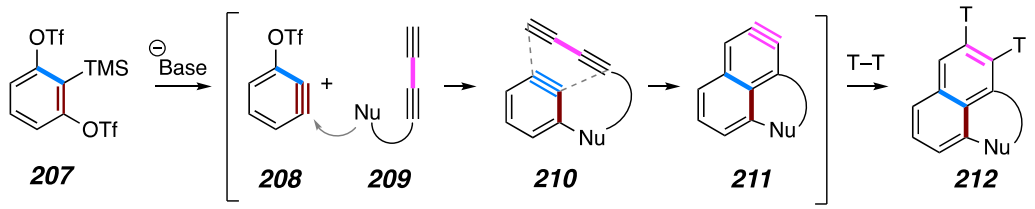
diynophile for the subsequent HDDA reaction with another 1,3-butadiyne unit. This process can potentially continue (via anthracyne **200** and, then, tetracyne **201**) until the terminal aryne species is trapped by an external trapping agent, to generate a polycyclic aromatic compound (PAC). For example, pentayne precursor **202** was designed in such a manner that it would initiate cyclization only in one sense (dashed arrows drawn in Scheme **1.19**) to produce benzyne **204**. The subsequent cyclization to form naphthyne **205** was followed by an external trapping agent **203** to finally achieve epoxy norbornadiene **206** in 85% yield.

Later on, Xiao also developed a strategy that capitalizes on both the Kobayashi protocol and the HDDA reaction to conveniently generate naphthynes from relatively simple building blocks.[45] It was hypothesized that a bis-benzyne equivalent **207** could generate a benzyne **208** upon treatment with a carbonate base or a fluoride source (Scheme **1.20**). The triflate group in intermediate **208** was strategically placed to have

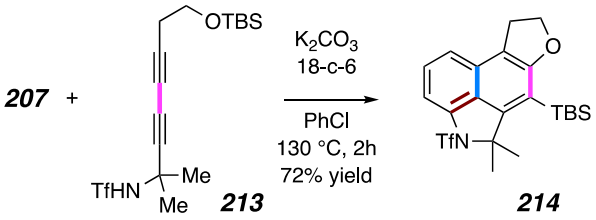
[45] Xiao, X.; Hoye, T. R. One-Pot, Three-Aryne Cascade Strategy for Naphthalene Formation from 1,3-Diynes and 1,2-Benzdiyne Equivalents *J. Am. Chem. Soc.* **2019**, *141*, 9813–9818.

Scheme 1.20 | (**A**) Marrying of classical and HDDA benzyne generation and (**B**) an example that shows utilization of this methodology

(A) Marrying of classical and HDDA benzyne generation



(B) Formation of naphalene derivative



two roles: (i) it directs the nucleophile **209**, bearing a pendant 1,3-diyne moiety, at the *meta*-position; and (ii) it also acts as a leaving group upon addition of the nucleophile to regenerate the benzyne as shown in **210**. At this stage, **210** was set to undergo a HDDA reaction to produce the naphthyne equivalent **211**, which was subsequently trapped with external arynophiles to finally produce arenes **212** in a cascade reaction involving three distinct reactive benzyne species. In one of the examples, naphthalene **214** was synthesized from sulfonamide **213** and bis-benzyne precursor **207** in the presence of K_2CO_3 and 18-crown-6.

1.5.5 *Mechanism of the HDDA reaction.*

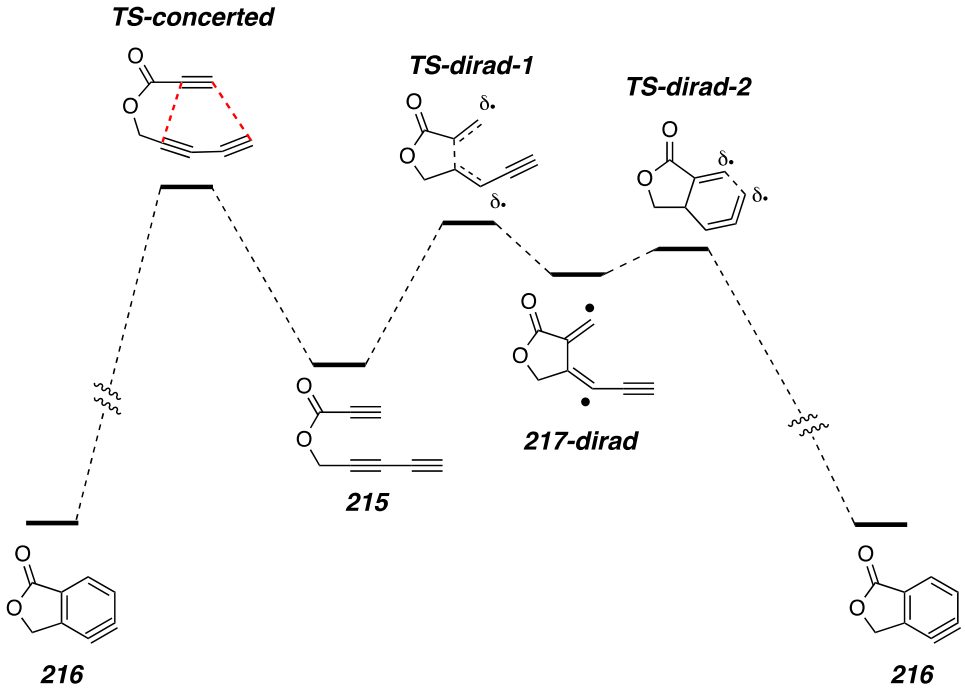
The debate involving the mechanism of the HDDA reaction was settled on the basis of experimental[46] and computational[47] support that suggest that the HDDA reaction more

[46] Wang, T.; Niu, D.; Hoye, T. R., The Hexadehydro-Diels–Alder Cycloisomerization Reaction Proceeds by a Stepwise Mechanism. *J. Am. Chem. Soc.* **2016,** *138*, 7832-7835.

[47] (a) Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C. J.; Hoye, T. R.; Kuwata, K. T., Mechanism of the Intramolecular Hexadehydro-Diels–Alder Reaction. *J. Org. Chem.* **2015,** *80*, 11744-11754. (b) Liang, Y.; Hong, X.; Yu, P.; Houk, K. N., Why Alkynyl Substituents Dramatically Accelerate Hexadehydro-Diels–Alder (HDDA) Reactions: Stepwise Mechanisms of HDDA

likely proceeds through a stepwise mechanism rather than a concerted process. A generic mechanism of this reaction has been shown for an ester-linked triyne **215** in Scheme **1.21**. The triyne **215** could produce the aryne **216** via two pathways: (a) a concerted [4+2] cycloaddition *via* a transition state **TS-concerted**, or (b) a stepwise cyclization via a diradical intermediate **217-dirad** and two transition states **TS-dirad-1** and **TS-dirad-2** for each bond formation. In order for the reaction to proceed in a concerted fashion, the diyne and the diynophile (and, thus, the lactone moiety) have to be extremely distorted (as shown in the red arrows, Scheme **1.21**), to allow for a six-membered transition state. These restrictions can be avoided, at least partially, if the reaction proceeded via a stepwise transition state **TS-dirad-1** to form a diradical intermediate **217-dirad**. This step is the rate-limiting step, as the ring closure of the **217-dirad** to the benzyne **216** is rapid process, favored because of a low-barrier and significant thermodynamic stability.

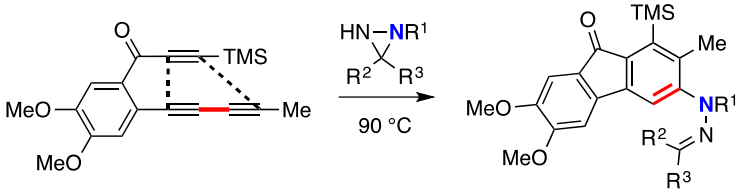
Scheme 1.21 | A generic mechanism of the HDDA reaction



Cycloadditions. *Org. Lett.* **2014,** *16*, 5702-5705. (c) Yu, P.; Yang, Z.; Liang, Y.; Hong, X.; Li, Y.; Houk, K. N., Distortion-Controlled Reactivity and Molecular Dynamics of Dehydro-Diels–Alder Reactions. *J. Am. Chem. Soc.* **2016,** *138*, 8247-8252. (d) Chen, M.; He, C. Q.; Houk, K. N., Mechanism and Regioselectivity of an Unsymmetrical Hexadehydro-Diels–Alder (HDDA) Reaction. *J. Org. Chem.* **2019,** *84*, 1959-1963.

Chapter 2. Reactions of Diaziridines with Benzynes Give *N*-Arylhydrazones

The studies presented in this Section have been disclosed in and largely adapted from a published article.[48] *The Compound Numbers in this Section are directly adapted from reference* ***48****. New numbers (start with* ***201****) only apply to compounds that have NOT been reported in the published manuscript.*



Summary: Reactions of thermally generated benzynes with diaziridines are reported. These trapping reactions follow the same pathway as reported earlier by Heine and coworkers with electron-deficient alkynes. The resulting *N*-aryl hydrazones were obtained efficiently in a single step. The preference for the mode of addition of the nucleophilic diaziridine nitrogen atom to the more electrophilic benzyne carbon was consistent with what is predicted on the basis of distortion analysis. The feasibility of converting the hydrazone into a Fisher-indole adduct was demonstrated.

2.1 *Background and hypothesis of this work.*

Forty-five years ago, Heine and coworkers reported on the reactions of nucleophilic diaziridines with electrophilic alkynes (e.g., **1** + **2** to **5** in Figure **2.1**).[49] This report was from a series of publications from the Heine laboratory dealing with various reactions of diaziridines.[50] Largely as a result of a ^{15}N-labeling experiment (red atoms), the

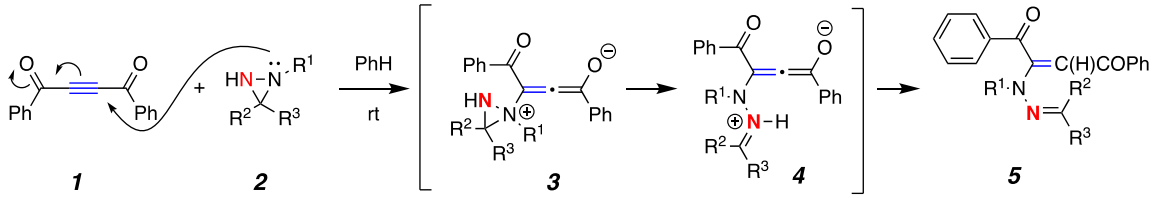
[48] Arora, S.; Palani, V.; Hoye, T. R. Reactions of Diaziridines with Benzynes Give *N*–Arylhydrazones *Org. Lett.* **2018**, *20*, 8082–8085.

[49] Heine, H. W.; Hoye, T. R.; Williard, P. G.; Hoye, R. C. Diaziridines II. The Addition of Diaziridines to Electrophilic Acetylenes. *J. Org. Chem.* **1973**, *38*, 2984–2988.

[50] (a) Heine, H. W.; Williard, P. G.; Hoye, T. R. The Synthesis and Reactions of Some 1-(Nitroaryl)diaziridines. *J. Org. Chem.* **1972**, *37*, 2980–2983. (b) Heine, H. W.; Henrie, R.; Heitz, L; Kovvali, S. R. Diaziridines III. Reaction of Some 1-Alkyl- and 1,1-Dialkyl-1H-diazirino[1,2-b]pthalazine-3,8-diones. *J. Org. Chem.* **1974**, *39*, 3187–3191. (c) Heine, H. W.; Heitz, L. Diaziridines IV. Reaction of

mechanism of the reaction was deemed to involve initial addition of the alkylated (R^1) nitrogen atom to provide the intermediate zwitterion **3**. Ring-opening was then invoked to give the iminium ion **4**, within which proton transfer would then lead to the adduct **5**.

Figure 2.1 | Reaction of nucleophilic diaziridines with electrophilic alkynes[49]



As discussed in Chapter **1** already, arynes owe their high reactivity and, hence, electrophilicity[51] to their highly strained formal triple bond. Inspired by the transformation from Heine and co-workers,[49] I envisioned that the arynes, which are another class of "electrophilic acetylenes", would also react with diaziridines in a similar fashion. Moreover, reports that detail the trapping of cyclic amines with benzynes are also known – studies from the groups of Hoye,[39,40] Larionov[52(a)], and Biju[52(b)-(d)] have suggested that this reaction, generically, proceeds via nucleophilic trapping of the tertiary amine **202** on to the benzyne **201** to form the zwitterion **203** (Figure **2.2**). This zwitterion could react with the protic nucleophile present in the reaction mixture, in a stepwise manner to produce ring opened species **205** – finally via dual activation of the aziridine

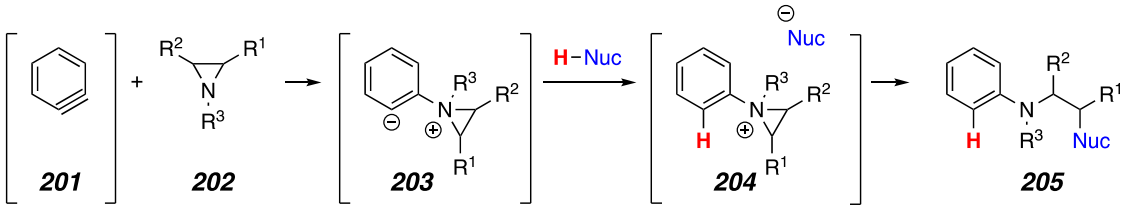
Some 1-Alkyl- and 1,1-Dialkyl-1H-diazirino[1,2-b]pthalazine-3,8-diones with Nitrones. *J. Org. Chem.* **1974**, *39*, 3192–3194. (d) Heine, H. W.; Baclawski, L, M; Bonser, S. M; Wachob, G. D. Diaziridines 5. Reaction of Some 1-Aroyl- and 1,2-Diacyldiaziridines. *J. Org. Chem.* **1976**, *41*, 3229–3232.

[51] Hoffman, R. W. Dehydrobenzene and Cycloalkynes; Academic: New York, 1967.

[52] (a) Stephens, D.; Zhang, Y.; Cormier, M.; Chavez, G.; Arman, H.; Larionov, O. V. Three-Component Reaction of Small-Ring Cyclic Amines with Arynes and Acetonitrile *Chem. Commun.* **2013**, *49*, 6558−6560, (b) Roy, T.; Baviskar, D. R.; Biju, A. T. Synthesis of *N*-Aryl β-Amino Alcohols by Trifluoroacetic Acid Promoted Multicomponent Coupling of Aziridines, Arynes, and Water *J. Org. Chem.* **2015**, *80*, 11131−11137, (c) Roy, T.; Thangaraj, M.; Gonnade, R. G.; Biju, A. T. Synthesis of Functionalized Amino Epoxides by a Three-Component Coupling Involving Aziridines, Arynes and Aldehydes. *Chem. Commun.* **2016**, *52*, 9044−9047, and (d) Roy, T.; Bhojgude, S. S.; Kaicharla, T.; Thangaraj, M.; Garai, B.; Biju, A. T. Employing Carboxylic Acids in Aryne Multicomponent Coupling Triggered by Aziridines/Azetidines *Org. Chem. Front.* **2016**, *3*, 71−76.

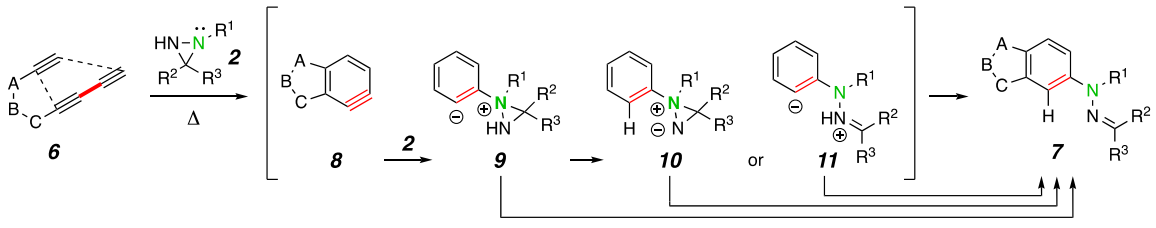
ring. All of this literature precedence on cyclic amine activation via electron deficient alkynes seemed convincing to test out our desired hypothesis.

Figure 2.2 | General mechanistic proposal for the dual activation of aziridines and protic nucleophiles by arynes[52(a)]



Gratifyingly, trapping of diaziridines with thermally generated benzynes follow the same reaction course as uncovered by Heine in 1973. Namely (and as generically shown in Figure **2.3**), when a substrate **6** is heated in the presence of a diaziridine **2**, a hydrazone **7** is formed efficiently. We suggest that this is best rationalized, again, by initial attack of the *N*-alkylated nitrogen in **2** to the benzyne **8** to produce the zwitterion **9**. Secondary amines readily add to electron poor alkynes, so the preferential attack by the more substituted and hindered (albeit also more electron rich) nitrogen atom in **2** to either of the "acetylenes" **1** or **8** may be attainable because of the highly unhindered nature of the electrophilic alkynes, all the more so because of the bent geometry of the sp-carbons in **8**. Also, the trapping of an aryne by a nucleophile (here, the diaziridine nitrogen) is often significantly exothermic. Accordingly, the transition state should be reached early on the reaction coordinate and have a relatively long distance between the nitrogen and

Figure 2.3 | Reaction of a generic HDDA-generated benzyne and a monoalkylated diaziridine (this work)



benzyne carbon atoms. This would further reduce the importance of steric interactions in the initial adduct formation. Further transformation of **9** to **7** requires both a proton transfer and ring-opening event of the strained ring. This could conceivably be a concerted process or occur in either order via intermediate 1,2- or 1,4-zwitterions **10** or **11**, respectively.

2.2 *Experimental results.*

We first examined the reaction[53] of triyne **6a** with seven different diaziridines (**2a–g**, entries **1-7**, Table **2.1**). These trapping agents differed in the nature of alkyl/aryl substitution at the 3–position of the diaziridine ring. All bear one *N*-alkyl group (benzyl), which differentiates the nucleophilicity of the two nitrogen atoms. The products[54] from these seven experiments (**7aa-7ag**) indicated that the benzyne trapping reactions with diaziridines had followed the same course of reaction as precedented (Figure **2.1**) and projected on mechanistic grounds (Figure **2.3**). They all can be rationalized as resulting from attack by the hindered, *N*1 nitrogen atom at the more electrophilic sp-hybridized carbon atom in the distorted benzyne intermediate **8a** (Figure **2.4**).

We proceeded to explore the reactions of other HDDA benzyne substrates, namely **6b–f** (entries **8–17**). These reacted in similar fashion, demonstrating generality within the benzyne component, leading to various *N*-arylated hydrazone products. The matching of which two reactants were used in the examples in entries **8–17** of Table **2.1** (i.e., which benzyne precursor **6** with which diaziridine **2**) was arbitrarily chosen. Nonetheless, this representative subset demonstrates the generality of the reaction.

2.3 *Aryne distortion from the DFT studies.*

Each of the benzyne species **8a-f** derived from the set of poly-yne substrates **6a-f** is shown in Figure **2.4**. Their reactions with diaziridines were observed to proceed with exclusive regioselectivity for the cases of **8a**, **8e**, and **8f**; mixtures of constitutional

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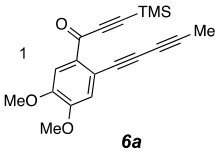
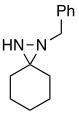
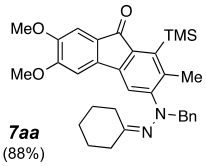
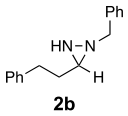
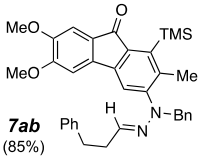
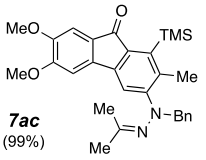
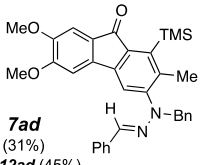
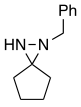
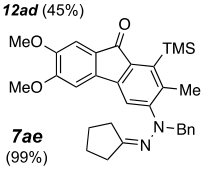
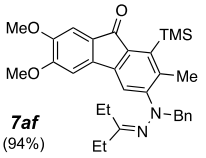
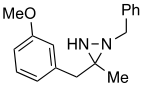
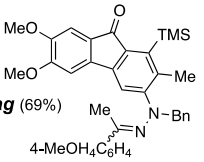
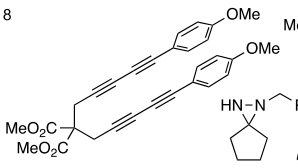
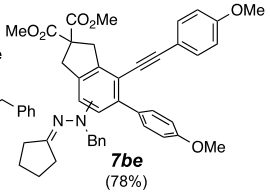
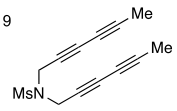
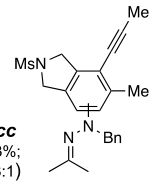
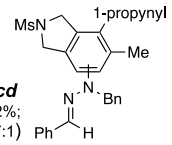
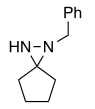
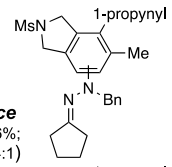
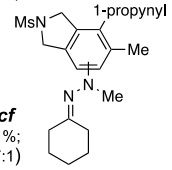
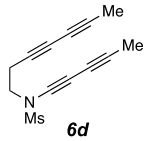
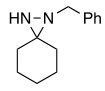
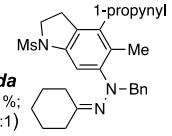
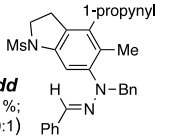
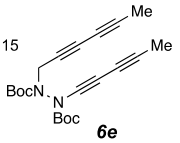
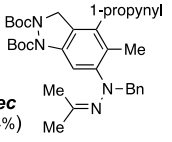
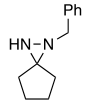
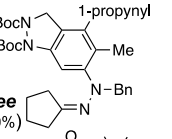
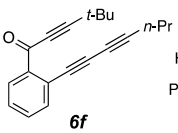
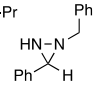
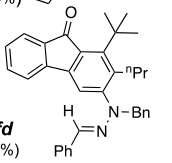
[53] The structure number of each product contains two letters, the first indicating the poly-yne **6** and the second the diaziridine **2** of origin.

[54] All reactions were performed in benzene having an initial [**6**] = 0.02 M and [2] = 0.04 M. Solutions were heated at 85–90 °C (external bath T) for 18-19 h, except for the case of the less reactive **6e**, where the reaction time was 48 h.

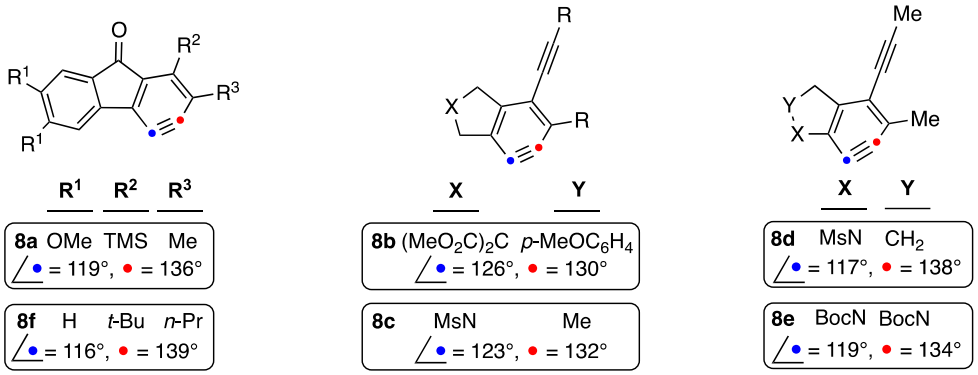
Table 2.1. Products **7a** from reactions between benzyne precursors **6a-f** and diaziridines **2a-h**.

entry	poly-yne substrate	diaziridine	product (yield)
1	 **6a**	 **2a**	 **7aa** (88%)
2	**6a**	 **2b**	 **7ab** (85%)
3	**6a**	 **2c**	 **7ac** (99%)
4	**6a**	 **2d**	 **7ad** (31%) with **12ad** (45%)
5	**6a**	 **2e**	 **7ae** (99%)
6	**6a**	 **2f**	 **7af** (94%)
7	**6a**	 **2g**	 **7ag** (69%) 4-MeOH$_4$C$_6$H$_4$
8	 **6b**	**2e**	 **7be** (78%)

entry	poly-yne substrate	diaziridine	product (yield; maj:min)
9	 **6c**	 **2c**	 **7cc** (93%; 1.8:1)
10	**6c**	 **2d**	 **7cd** (52%; 3.7:1)
11	**6c**	 **2e**	 **7ce** (96%; 2.4:1)
12	**6c**	 **2f**	 **7cf** (91%; 2.7:1)
13	 **6d**	 **2a**	 **7da** (71%; 14:1)
14	**6d**	 **2d**	 **7dd** (31%; 5.0:1)
15	 **6e**	 **2c**	 **7ec** (64%)
16	**6e**	 **2e**	 **7ee** (60%)
17	 **6f**	 **2d**	 **7fd** (38%)

isomers were formed in each of the cases of 8b-d. These selectivities for nucleophilic addition to these benzynes are consistent with those expected either from (i) reported reactions with nucleophiles or (ii) the extent and direction of the computed distortion [DFT, Figure **2.4**: **8a-c** and **8f**, **8d**,[32] and **8e**[36]]. As discussed in Chapter **1**, distortion analysis has been used quite successfully to account for the strong preference for addition by a nucleophile at the more electrophilic, obtuse sp-center, which has a greater proportion of p-character.[14,15] As the magnitude of the difference in the two internal angles diminishes, subtle differences in steric effects for the two potential modes of addition begin to playa more important role (cf. differences in the isomer ratios among entries **9**–**12** or of **13** vs. **14**).

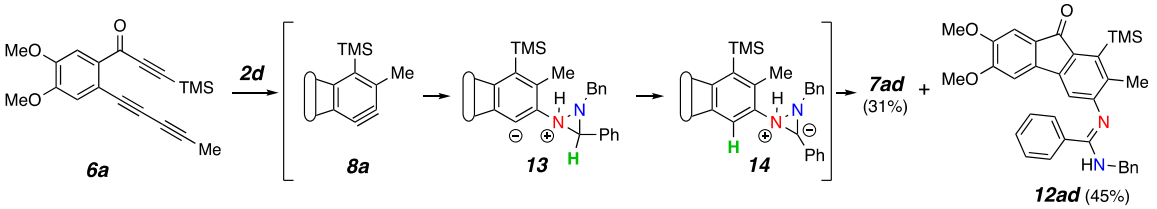
Figure 2.4 | Internal bond angles (∠) at the two benzyne carbons, reflecting the computed ring distortion of the benzynes **8a-f** derived from each of the poly-ynes **6a-f** {DFT: [SMD(benzene)//M06-2X/6-311+G(d,p)}.



2.4 *Unexpected amidine adduct.*

The reactions using the 3-phenyl-substitued diaziridine **2d** gave less efficient formation of the hydrazone products (entries **4**, **10**, **14**, and **17**). In one instance (entry **4**), we separated and identified the product of the major competing pathway – namely, the (polar and chromatographically poorly behaved) amidine **12ad** (Figure **2.5**). Presumably, in this reaction the benzyne **8a** undergoes initial attack by the NH rather than the NBn nitrogen atom of the diaziridine leading to the zwitterion **13**. This species, now containing a benzylic C–H proton, can undergo internal proton transfer to produce **14** followed by a ring-opening event to give the amidine **12ad**.

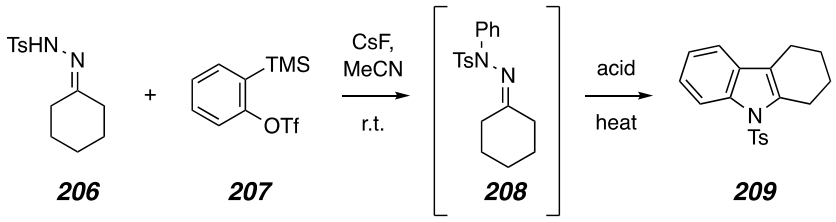
Figure 2.5 | Rationale for formation of amidine **12ad** via initial attack of the secondary amine in **2d** to the benzyne **8a**.



2.5 *Fischer indole adducts derived from hydrazones.*

Finally, we have also demonstrated two examples in which these hydrazone products can be converted into fused indole derivatives. Specifically, we were inspired by the report of Greaney et al. in which benzyne-derived hydrazones underwent Fischer indole cyclization using Lewis acid catalysis to produce indole adducts.[55] For example, the addition of a *N*-Tosyl hydrazone **206** to arynes, generated through a "classic"[17] fluoride activation of 2-(trimethylsilyl)phenyl triflate precursor **207**, led to a *N*-arylated product **208**. Addition of a Lewis acid to the same reaction pot then afforded *N*-tosylindole **209** via Fischer cyclization (Figure **2.6**).

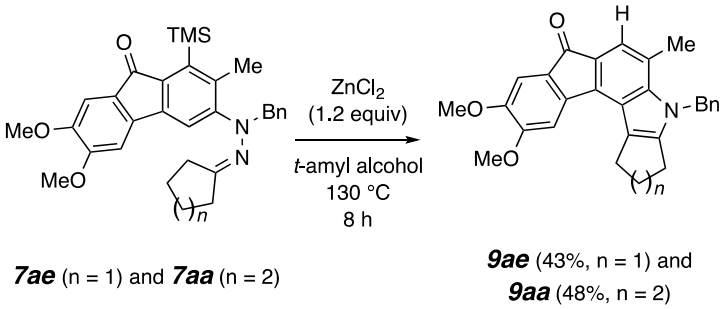
Figure 2.6 | *N*-Arylation and Fischer cyclization of *N*-tosylhydrazones with benzyne



Gratifyingly, hydrazones **7ae** and **7aa** that were generated through the HDDA reaction underwent Fischer indole cyclization in the presence of $ZnCl_2$ at elevated temperature to produce **9ae** and **9aa**, respectively (Figure **2.7**). In both cases Lewis acid mediated desilylation was observed under the reaction conditions.

[55] McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. The Benzyne Fischer-Indole Reaction. *Org. Lett.* **2011**, *13*, 3667–3669.

Figure 2.7 | Fischer indole adducts, **9ae** and **9aa** derived from hydrazones, **7ae** and **7aa**, respectively

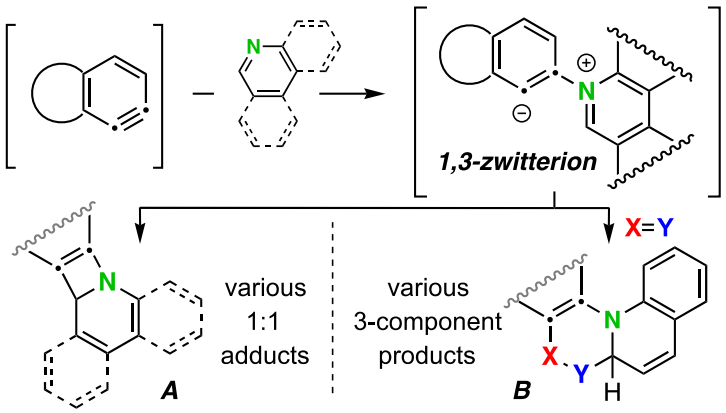


2.6 *Conclusions.*

In conclusion, the results presented here demonstrate the generality of trapping thermally generated, polycyclic benzyne species with heteroatom-rich diaziridines. These trapping reactions lead to *N*-arylated hydrazones in a single step. In some instances, these products can be converted to fused-ring indole derivatives. The mechanism of this trapping reaction with benzynes is consistent with one established earlier with electron deficient acetylenes. The preferred mode of addition was consistent with that suggested by DFT-derived structures of the intermediate benzynes.

Chapter 3. Reactions of thermally generated benzynes with six-membered *N*–heteroaromatics: pathway and product diversity

The studies presented in this Section have been disclosed in and largely adapted from a published article.[56] *The Compound Numbers in this Section are directly adapted from reference 56. New numbers (start with* ***301****) only apply to compounds that have NOT been reported in the published manuscript.*



Summary: We report here various pathways by which six-membered *N*–heteroaromatic compounds react with benzynes that are generated by the HDDA reaction. The initially formed 1,3-zwitterionic species a) can collapse intramolecularly to give novel 1:1 adducts of the heterocycle and benzyne; b) can react with an externally added, electrophilic third-component to give functionalized heterocyclic products; or c) can react with an external protic nucleophile to produce, following collapse of the ion pair resulting from protonation of the zwitterion, a variety of three-component assemblies. Mechanisms for formation of some of the 1:1 adducts are supported by DFT methods. The scope of the protic nucleophilic coupling was also expanded to a two-pot operation by using triflic acid as a protic "non-nucleophile", followed by the addition of a suitably reactive nucleophile. This heteroaromatic trapping of arynes provides the groundwork and

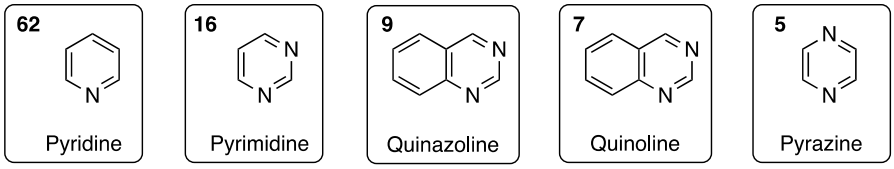
[56] Arora, S.; Zhang, J.; Pogula, V.; Hoye, T. R., Reactions of Thermally Generated Benzynes with Six-Membered *N*–Heteroaromatics: Pathway and Product Diversity. *Chem. Sci.* **2019,** *10*, 9069.

inspiration for Chapter **4** where C,*N*–diarylimines were reacted with thermally generated benzynes to form 1,4-dihydroacridines.

3.1 *Background and motivation.*

Nitrogen heterocycles (*N*–heterocycles) are key components of natural products and pharmaceuticals. According to a perspective article on *N*-heterocycles by Njardarson et al.,[57] 84% of the drugs available in market have at least one nitrogen atom present in them. More significantly, 59% of the total FDA-approved drugs contain at least one nitrogen heterocycle. Six-membered *N*–heterocyclic arenes have also found significant place in this list of active pharmacological agents, accounting for 9% of the total drugs among U.S. FDA approved pharmaceuticals. Among these six-membered heteroaromatics, pyridine clearly stands out – it is present in 62 FDA approved drugs (left, Figure **3.1**). In fact, pyridine is second-most heterocycle found in the pharmaceutical chemical space. The top five of the most commonly used six-membered aromatic nitrogen heterocycles are shown in Figure **3.1**.

Figure 3.1 | The top five of the most commonly used six-membered aromatic nitrogen heterocycles. The number of drugs in which the each heterocycle appears is listed in bold on the top left in each box. (Figure reproduced from Njardarson et.[57])



These data are compelling and motivate a chemist to creatively develop numerous synthetic strategies that can be used for either (i) construction of new heterocycles from simple starting materials, or (ii) functionalization of known heterocycles. Since the discovery of the HDDA reaction, Hoye group has been working on employing the aryne reactivity to meet both of the above-mentioned goals. In 2019, Dr. Severin Thompson

[57] Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the S tructural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014,** *57*, 10257-10274.

reported a *de novo* method of generation of pyridynes from diyne nitriles.[41] These pyridynes were subsequently reacted with variety of intra- and inter-molecular trapping agents to synthesize structurally complex pyridine moieties. On the other hand, modification of a known heterocyclic core to result in a functionalized product is also of great importance. These late stage functionalizations are typically carried out in order to decrease unwanted side effects or toxicity issues of a naturally secondary metabolite. In 2017, Dr. Sean Ross from Hoye group reported an elegant method to functionalize multifunctional natural products with arynes that were generated via the HDDA reaction.[42] A natural extension was to investigate whether *N*-heterocyclic arene compounds ("N-hetaryls", *N*-HARs) would engage with benzynes generated through thermal methods.

It has been already established in the previous chapters of this thesis that the HDDA-benzynes provide an opportunity to reveal new modes of reactivity for reagents already known to engage classical arynes.[23,32,58] Although there are various examples in which six-membered *N*-heterocyclic arenes (prototypically, pyridine, quinoline, and isoquinoline) have engaged classically generated arynes, nearly all have been performed in the presence of an external, third component to give tractable outcomes.[59] In those studies, aliphatic nitriles, terminal alkynes, and various carbonyl compounds have been used as third components. This reaction is presumed to be initiated by attack of the nucleophilic nitrogen atom in the heterocycle onto the electrophilic aryne, producing a 1,3-zwitterion (cf. III, Figure **3.2**[60]). However, to our knowledge, formation of 1:1

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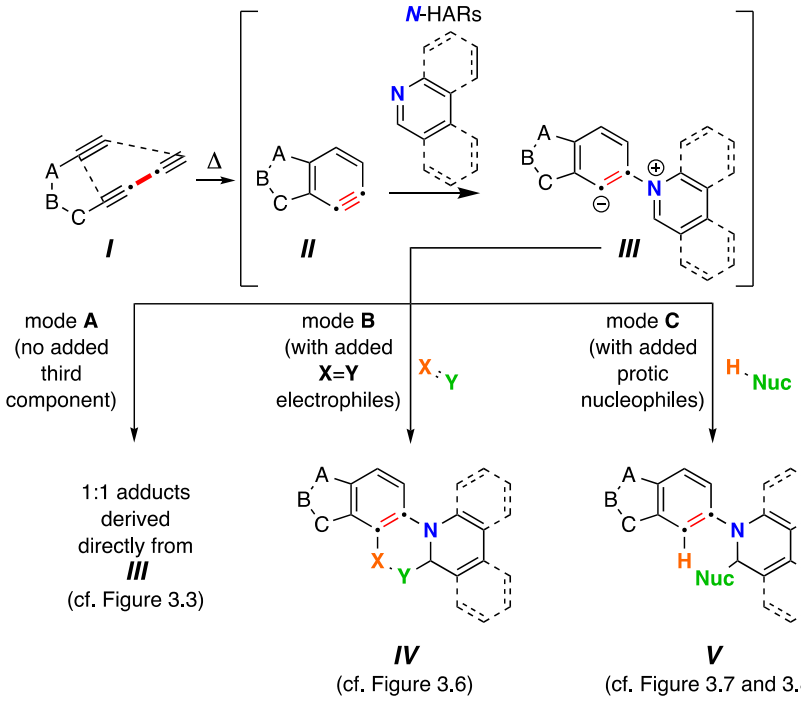
[58] Zhang., J. and Hoye, T. R. Divergent Reactivity during the Trapping of Benzynes by Glycidol Analogs: Ring Cleavage *via* Pinacol-Like Rearrangements vs Oxirane Fragmentations *Org. Lett.*, **2019**, *21*, 2615–2619; (b) Niu, D. and Hoye, T. R. The Aromatic Ene Reaction *Nat. Chem.*, **2014**, *6*, 34–40.

[59] (a) Jeganmohan, M.; Cheng, C. H. Reaction of Arynes, *N*-heteroaromatics and Nitriles. *Chem. Commun.*, **2006**, 2454–2456; (b) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C. H. Synthesis of *N*-Arylated 1,2-Dihydroheteroaromatics Through the Three-Component Reaction of Arynes with *N*-heteroaromatics and Terminal Alkynes or Ketones *Chem. Asian. J.*, **2010**, *5*, 153–159; (c) Bhunia, A; Roy, T; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. Transition-Metal-Free Multicomponent Reactions Involving Arynes, *N*-Heterocycles, and Isatins *Angew. Chem. Int. Ed.*, **2013**, *52*, 10040–10043; (d) Bhunia, A; Porwal, D.; Gonnade, R. G.; Biju, A. T. Multicomponent Reactions Involving Arynes, Quinolines, and Aldehydes *Org. Lett.*, **2013**, *15*, 4620–4623.

[60] Throughout this chapter I have used Roman numerals to label generic or non-isolated structures and intermediates and Arabic numbering for structures of isolated compounds.

adducts between benzynes and *N*-heterocyclic arene compounds ("N-hetaryls", *N*-HARs) has never been definitively demonstrated. Fields and Meyerson (1966) speculated on the intermediacy of [2+2]-addition products from arynes and pyridine on the basis of gas chromatographic and mass spectrometric analyses of the complex product mixtures formed when, for example, phthalic anhydride, a benzyne precursor, was pyrolyzed in the presence of pyridine, but discrete products were not isolated.[61]

Figure 3.2 | Trapping of HDDA-generated benzynes II with *N*–hetaryls (*N*-HARs) of the pyridine family (pyridine, quinoline, isoquinoline, and phenanthridine, etc.) via diverse reaction pathways (Modes A–C).

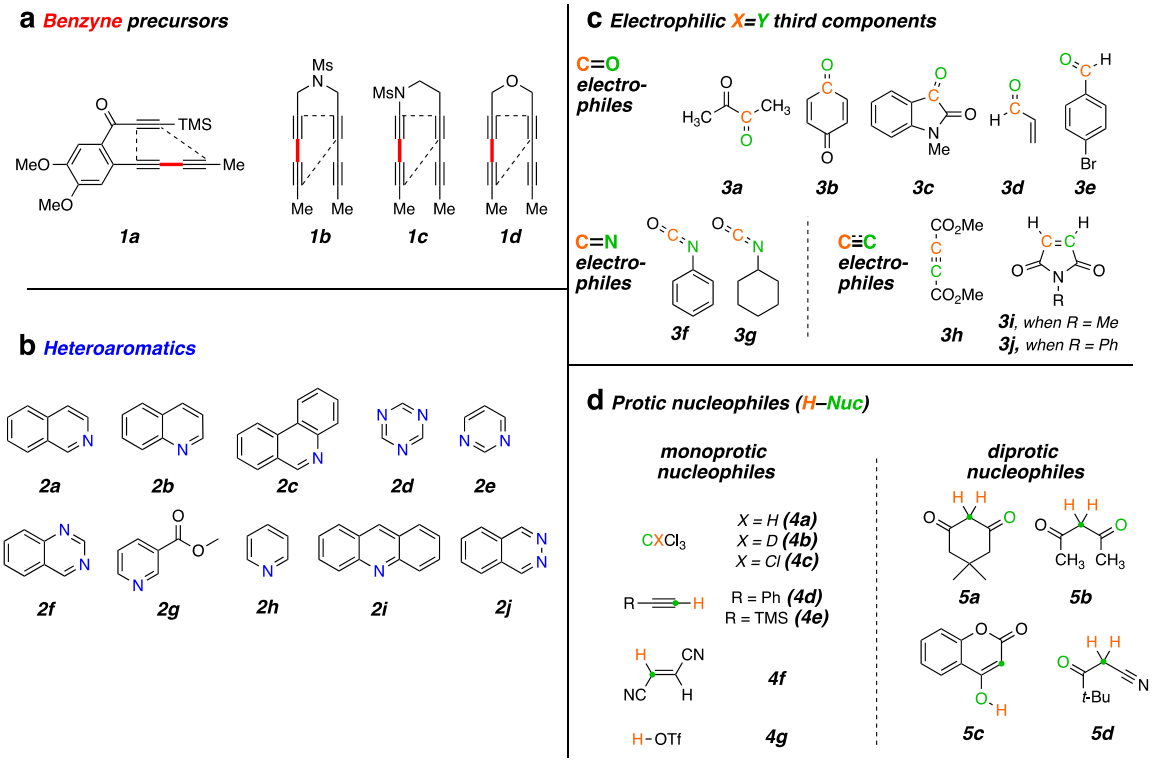


The investigations reported in this chapter had two aims from the start: (a) the possibility of identifying reactions leading to 1:1 adducts of *N*-HARs and benzynes; and (b) the opportunity to uncover new types of three-component reactions of benzynes with *N*-HARs. We herein report that upon formation of **III**, a variety of reaction pathways can ensue. The reactions that we have observed for zwitterions such as **III** can be categorized

[61] Fields, E. K.; Meyerson, S. Arynes by Pyrolysis of Acid Anhydrides *J. Org. Chem.*, **1966**, *31*, 3307–3309.

into three modes. Mode A leads to products that are 1:1 adducts between **II** and the *N*-HAR. In mode B, in situ bimolecular reaction of zwitterion **III** with an electrophile of type **X**=**Y** as a third component forms a new 6-membered ring in products **IV**. In mode C, protonation of **III** by a Brønsted acid [i.e., an in situ protic nucleophile (H–Nuc), the third component] and collapse of the nascent Nuc⁻/iminium⁺ ion pair produces adducts **V**. The full roster of reactants used in the studies we report here are compiled in Chart **3.1**.

Chart 3.1 | List of all reactants used in this study: (**a**) benzyne polyyne precursors; (**b**) *N*-heteroaromatics (*N*-HARs); (**c**) activated electrophiles; and (**d**) protic–nucleophiles.



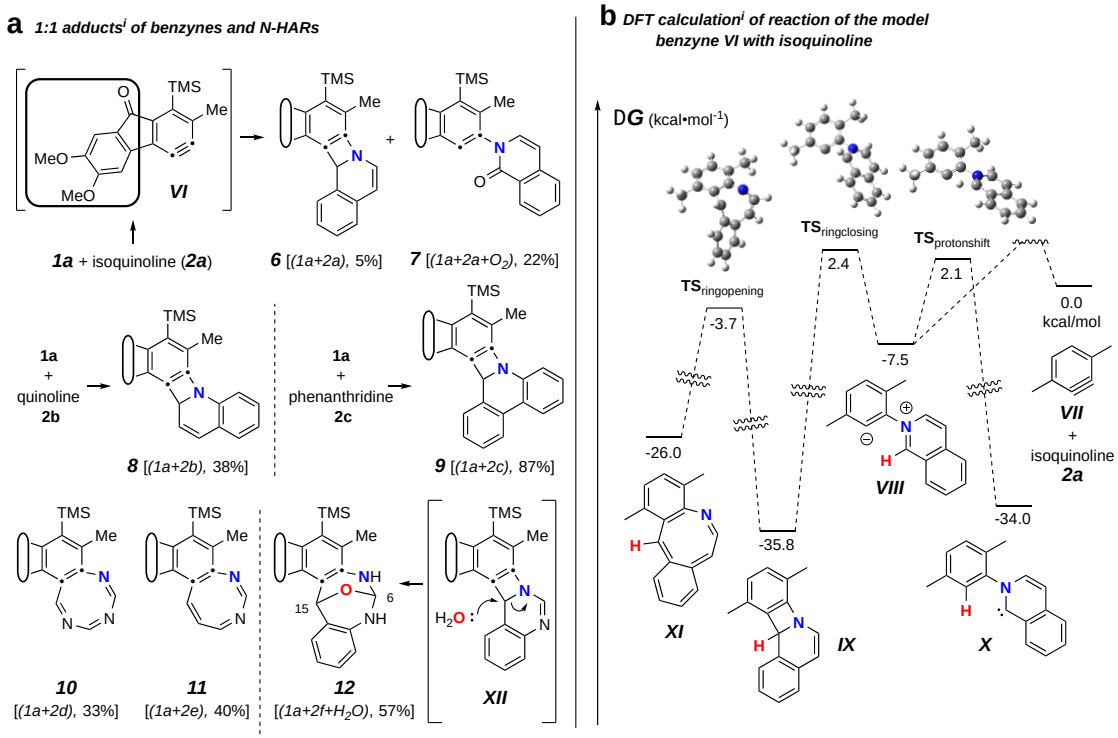
3.2 *Mode A (formation of a 1:1 adduct between an aryne and a N-HAR).*

We first examined reactions of the triyne substrate **1a** with several *N*-HARs in the absence of any added, potential third component. For example, when a benzene solution of **1a** was heated to 85 °C in the presence of isoquinoline (**2a**), the four-membered

benzoazetidine 6[62] and 2-isoquinolone 7[62] were formed (Figure **3.3a**) by in situ trapping of **VI** by **2a**. Probably because of the oxidative

Figure 3.3 | (**a**) Trapping of the benzyne **VI** (from **1a**, Chart **3.1**) with *N*-hetaryls of the pyridine family (i.e., pyridine, quinoline, isoquinoline, phenanthridine, pyrimidine, 1,3,5-triazine, and quinazoline) follow different reaction pathways. (**b**) DFT[i] for **VII** + **2a** showing competitive formation of **IX** and **VIII** and a high barrier for ring opening of **IX** to the azocine **X**.

[i] [SMD(benzene)//M06-2X/6-311+G(d,p)].

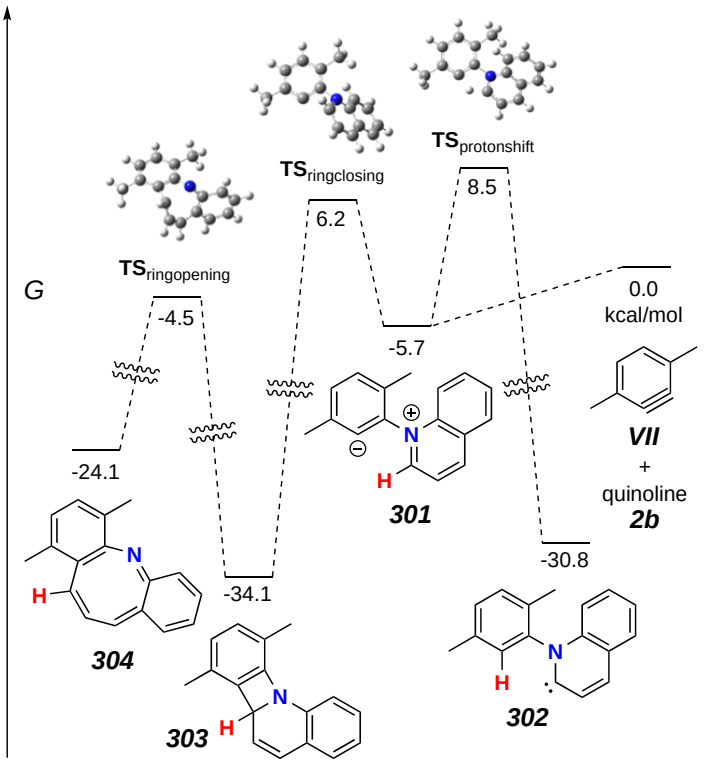


lability of product **6**, it was found to be unstable under ambient conditions and needed to be characterized immediately after isolation. The pathways leading to each of these products were then studied using DFT calculations of the reaction between a simplified aryne [3,6-dimethylbenzyne (VII)] and isoquinoline (2a) (Figure 3.3b). The formation of

[62] The structures of isolated products bear a unique Arabic number. That number is followed (in brackets) by a listing of the reactants that have been incorporated into the compound (cf. Chart **3.1**): polyyne **1** is the benzyne precursor, **2** the *N*-HAR, **3** an electrophilic third component, **4** a monoprotic-nucleophile, and/or **5** a diprotic nucleophile.

6 can be explained by a net [2+2]- addition of **2a** to the benzyne, a process involving simple cyclization of the initial zwitterion (cf. **VIII** to **IX**). Formation of **7**, on the other hand, can be rationalized by an intramolecular proton-transfer within the initially formed 1,3-zwitterion **VIII** and subsequent oxidation of the resulting carbene **X** by oxygen.[63] This type of reactivity was earlier reported by Biju and coworkers.[59(c)] It is notable that the energies of the DFT transition structures for these two competing pathways (i.e., $TS_{ringclosing}$ vs. $TS_{protonshift}$) are quite similar. The computations also suggest that electrocyclic ring-opening of the benzoazetine **IX** to the 8-membered benzoazocine derivative **XI** is both endergonic as well as a high-barrier process, the latter reflecting, at least in part, the loss of benzenoid aromaticity that is fully revealed in structure **XI**.

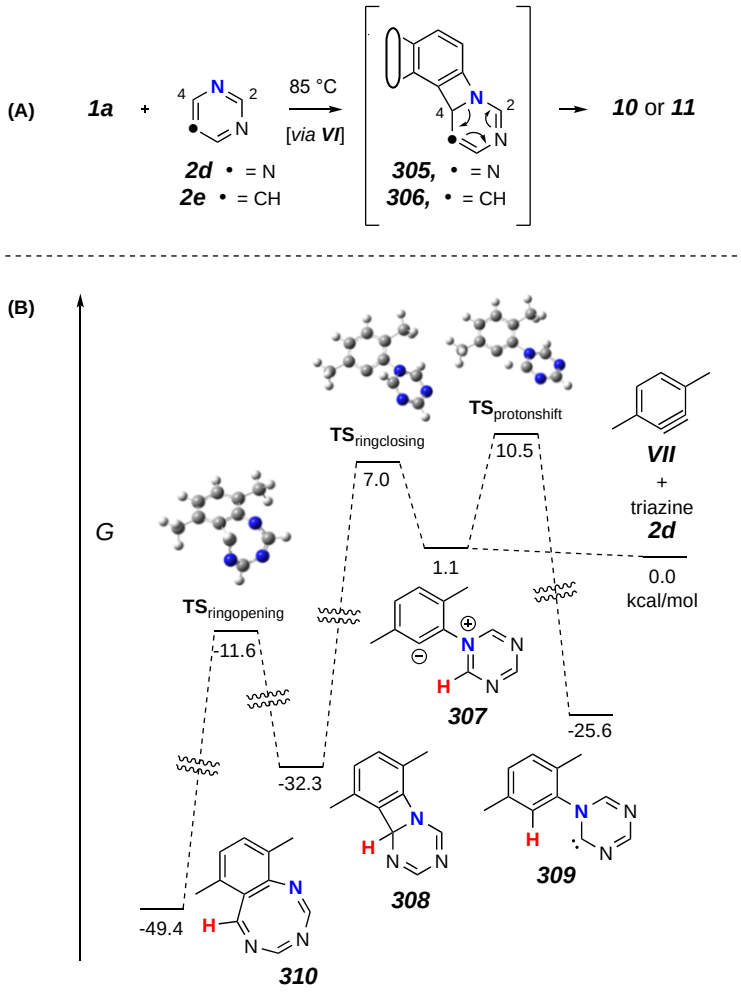
Figure 3.4 | DFT computed PES for reaction of quinoline (**2b**) and model benzyne **VII**.



[63] (a) Kirmse, V. W.; Horner, L.; Hoffmann, H. Über Lichtreaktionen IX. Umsetzungen Photochemisch Erzeugter Carbene. *Justus Liebigs Ann. Chem.* **1958**, *614*, 19–30; (b) Wanzlick, H. W.; Schikora, E. Ein Nucleophiles Carben. *Chem. Ber.* **1961**, *94*, 2389–2393; and (c) Ishiguro, K.; Nojima, T.; Sawaki, Y. Novel Aspects of Carbonyl Oxide Chemistry. *J. Phys. Org. Chem.*, **1997**, *10*, 787–796.

Trapping of the benzyne **VI** with quinoline (**2b**) led to the isolation of only the four-membered species **8**. This compound also was seen to degrade upon storage for extended periods of time. An analogous set of computations using quinoline **2b** showed a lower barrier (by 2.3 kcal•mol^{-1}) favoring formation of azetidine relative to carbene (cf. transition states leading to **302** and **303**, Figure **3.4**). Accordingly, a 2-quinolone product was not observed to accompany **8**. When phenanthridine (**2c**) was used as the *N*-HAR, the yield of the analogous trapping product **9** was significantly higher (87%) than that of **6** or **8**.

Figure 3.5 | (**a**) The initial azetidine derivatives **305** and **306** can arise from closure of an initially formed 1,3-zwitterion. Electrocyclic opening would then account for the formation of **10** and **11** (**b**) DFT computed PES for reaction of triazine (**2d**) and model benzyne **VII**.



Reactions with monocyclic *N*-HARs containing two or more nitrogen atoms proved interesting. 1,3,5-Triazine (**2d**) gave rise to the 1,3,5-triazocine derivative **10**;[64] we can locate only a handful of examples of this (fully unsaturated) heterocycle, and they all bear an amino substituent on the carbon atom between two nitrogen atoms (i.e., guanidines).[65] Compound **10** presumably arises from ring opening of an initially formed, four-membered, [2+2]-adduct analogous to **IX** (cf. **305**, Panel **A**, figure **3.5**). In this case, that strain-relieving event is not accompanied by loss of aromaticity, as would be the case for the opening of any of **6**, **8**, or **9**. DFT calculations (Panel **B**, Figure **3.5**) done on a model benzyne **VII** suggest that the electrocyclic ring-opening of 4-membered **308** has both an accessible activation barrier ($\Delta G^{\ddagger}$ = 20.7 kcal•mol^{-1}) as well as a favorable exergonicity ($\Delta G°$ = –17.1 kcal•mol^{-1}), in contrast to the conversion of **IX** to **XI** ($\Delta G°$ = +9.8 kcal•mol^{-1}).

Pyrimidine (**2e**) reacted by a similar pathway to produce **11**, preferring to close to C4 rather than C2 to give **306** (Panel **B**, Figure **3.5**). The closure of **306** at C4 maintains some of the N1-C2-N3 growing amidine character and stabilization throughout the reaction coordinate, which would be lost if cyclization were to take place at C2. Again, the diazocine **11** represents a relatively rare class of heterocycle, examples appearing in only four reports.[65(c)]

Finally, quinazoline (**2f**) gave rise to the unusual adduct **12**, incorporating a molecule of adventitious water. We suggest that in this instance, ring-opening of the initial benzoazetidine **XII** is assisted by water, the C–N bond being weakened by virtue of the amidine character of **XII** that is absent in the benzoazetidines from quinoline (**2b**) or isoquinoline (**2a**, cf. **IX**). The structure assignment of 12 was secured by the clear

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[64] The structure of each of these novel 8-membered heterocycles (**10** and **11**) were supported by two-dimensional NMR spectroscopic correlations. They were further validated by comparison of the experimental ^{1}H and ^{13}C chemical shifts with those computed (DFT) for several related model structures.

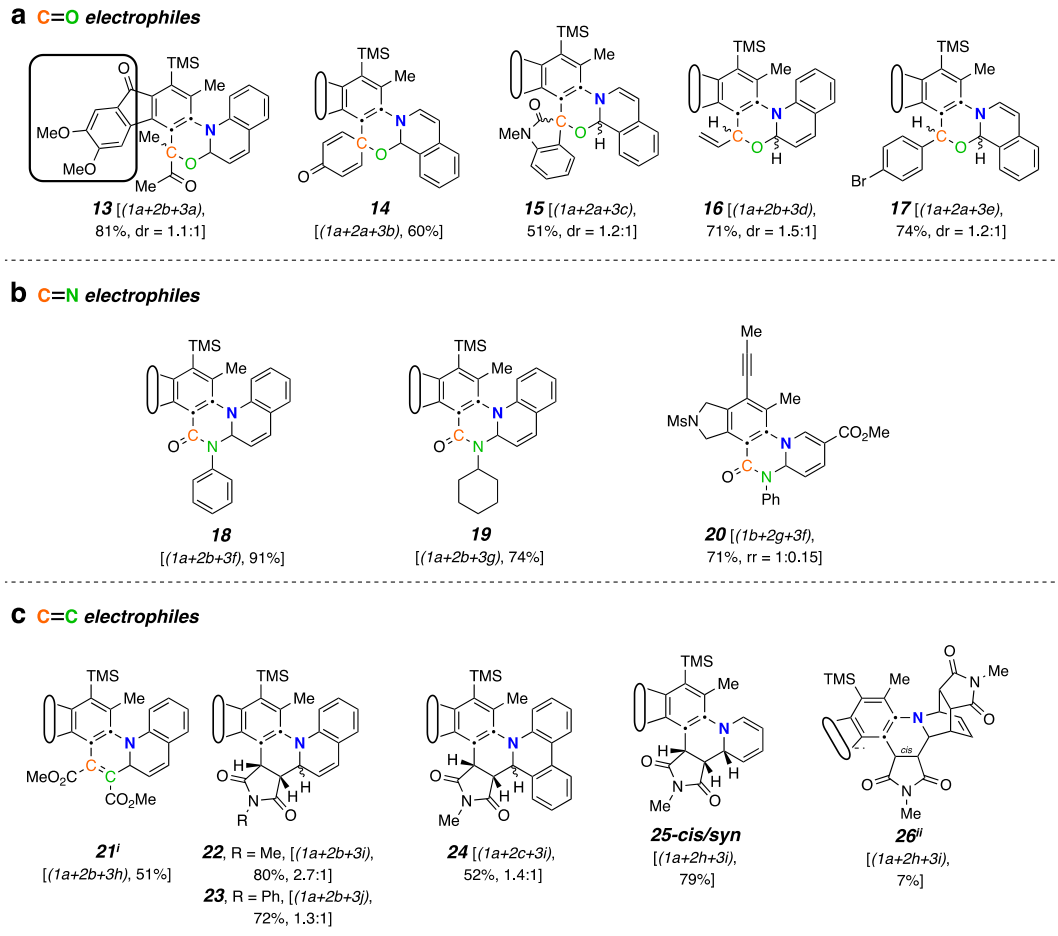
[65] (a) Furukawa, M.; Kojima, Y.; Hayashi, S. Reaction of biguanides and related compounds. IV. Reaction of Arylbiguanide with Benzoylacetone in the Presence of a Small Amount of the Arylbiguanide Hydrochloride. *Chem. Pharm. Bull.*, **1972**, *20*, 927–930. (b) Saied, T.; Jelaiel, N.; Efrit, M. L.; Fort, Y.; Comoy, C. Convenient Synthesis of Substituted Benzo[*e*][1,2,4]- or [d][1,2,6] Oxadiazepines, Benzo [*f*][1,3,5]triazocines from *N*-Aryliminoesters *Tetrahedron*, **2017**, *73*, 1489–1494. (c) Perlmutter, H. D. 1,2-Diazocines, 1,3-Diazocines, Triazocines, and Tetrazocines. *Adv. Heterocycl. Chem.*, **1990**, *50*, 1-83.

HMBCs observed for both H6 (δ 6.18 ppm) to C15 (δ 66.8) and H15 (δ 6.67) to C6 (δ 82.1) as well as the chemical shifts of those four nuclei.

3.3 *Three-component reactions.*

Modes B and C offer the potential to produce structurally complex, polycyclic structures in a single, one-pot, thermal operation. As mentioned, the former (mode B) is precedented[59] for the case of certain carbonyl compounds but not for other types of

Figure 3.6 | Products from mode **B** three-component reactions. Trapping of zwitterions (cf. **III**) by **a)** carbonyl electrophiles, **b)** isocyanates, and **c)** electron-deficient alkenes or alkynes. [i]A byproduct comprising two molecules of dimethyl acetylenedicarboxylate and one of quinoline was isolated [**316**, see SI for Chapter **3**]. [ii]Relative configuration not assigned.



electrophilic species. The latter (mode C) has been reported only for classical benzyne trapping with *N*-HARs in the presence of various terminal alkynes, carbonyl compounds and aliphatic nitriles, as the protic nucleophiles.[59(b)]

3.3.1 *Mode B (TCR with N-HAR + X=Y electrophile).*

A successful mode B TCR (cf. Figure **3.2**) would likely need to meet the following criteria: (i) neither the *N*–HAR nor the **X**=**Y** electrophile should react with the HDDA polyyne precursor faster than its rate of cyclization to the benzyne intermediate (the rate-limiting event); (ii) the *N*–HAR should engage the benzyne faster than it reacts with (at least irreversibly) the electrophile (**X**=**Y**); (iii) the electrophile should be sufficiently reactive to trap the 1,3-zwitterionic species (cf. **III**) to give products like **IV** before the former undergoes a ring-expansion process such as those discussed above in the mode A results.

We screened different electrophiles that might meet these requirements. Reactions were performed in benzene (or in a cosolvent of benzene and acetonitrile, depending on the solubility of the reactants) using an initial concentration of aryne precursor **1** of 0.02 M. Given the ready availability of all of the trapping components explored, we opted to use a stoichiometric ratio of the three reactants of, typically, 1:3:5 (benzyne precursor **1** : *N*-HAR **2** : electrophile **3**); this choice was not further optimized.

Aliphatic aldehydes and ketones (e.g., butyraldehyde and methyl vinyl ketone) did not perform well as a TCR third component. These coupling partners may not be sufficiently electrophilic. Upon switching to biacetyl (**3a**), we observed efficient formation of **13** (Figure **3.6a**) as a mixture of diastereomers in 81% yield. In this reaction triyne **1a**, quinoline (**2b**), and **3a** were heated at 85 °C for 16 h. Other reactive carbonyl compounds could also serve as a third component, as demonstrated by products **14**, **15**, **16**, and **17**, which arise from incorporation of p-benzoquinone also show that both isoquinoline (**2a**) and quinoline (**2b**) can participate in these TCRs. We did not extensively investigate all combinations of the three reactive components. In some instances, both **2a** and **2b** reacted in qualitatively similar fashion to provide the analogous

type of adduct; we believe that the reaction pathways we have identified would be generally applicable to many sets of three reaction partners.

After exploring carbonyls as third components, we proceeded to identify other effective classes of **X**=**Y** electrophiles. Phenyl and cyclohexyl isocyanate (C=N electrophiles **3f** and **3g** (**3b**), *N*-methylisatin (**3c**), acrolein (**3d**), or p-bromobenzaldehyde (**3e**),[66] respectively. These results respectively, Chart **1c**) participated in the coupling process to furnish the quinazolinone derivatives **18**, **19** and **20** (Figure **3.6b**). The last involved the incorporation of a pyridine derivative, specifically methyl nicotinate (**2g**). When pyridine (**2h**) itself was used along with phenyl isocyanate (**3f**), the ^{1}H NMR spectrum of the crude reaction product was fairly clean, suggesting an efficient initial transformation. However, the product proved difficult to isolate, perhaps a reflection of the lability of the 1,2-dihydropyridine that was initially formed. In contrast, the vinylogous carbamate character in **20** rendered that adduct readily tractable.

The final class of mode B TCRs involved trapping the initial 1,3-zwitterion with various electron-deficient alkenes or alkynes (Figure **3.6c**). Classic Diels–Alder dienophiles meet that definition. Dimethyl acetylenedicarboxylate (**3h**) as well as the *N*–substituted maleimides **3i** and **3j** all performed well, giving rise to adducts containing the new six-membered tetrahydropyridine ring present in each of **21**–**25** (Figure **3.6c**). In the case of formation of **24** (52%) from phenanthridine (**2c**) and N-methylmaleimide (**3i**), the 1:1 adduct **9** (cf. Figure **3.3a**) was formed competitively (34%). This suggests a shorter lifetime for the initially formed 1,3-zwitterion. This is expected because its cyclization to

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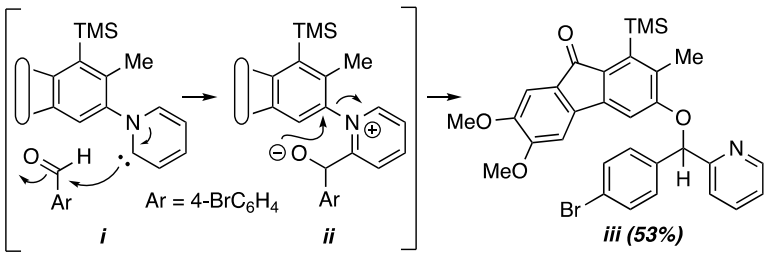
[66] In contrast the reaction of **1a** in the presence of 4-bromobenzaldehyde (**3e**) with pyridine (**2h**) as the *N*-hetaryl instead of isoquinoline produced compound **III** (53%, see SI for chapter **3**), presumably by way of intermediates like **i** (cf. **X**, Figure **3.3b**) and **ii**, a pathway involving final ipso attack as observed and suggested for pyridine by Biju and coworkers.[59(c)]



the azetidine **9** is not accompanied by as large of a loss in aromatic resonance stabilization as is the case for, say, quinoline or isoquinoline. Finally, when pyridine was the *N*-HAR component, **25** was produced efficiently (accompanied by a small amount of the cis-anti diastereomer, see SI for Chapter **3**). This product was also accompanied by one diastereomer of the Diels–Alder adduct **26**, again reflecting a lability of the 1,2-dihydropyridine moiety.

3.3.2 *Mode C (TCR with a monoprotic nucleophile).*

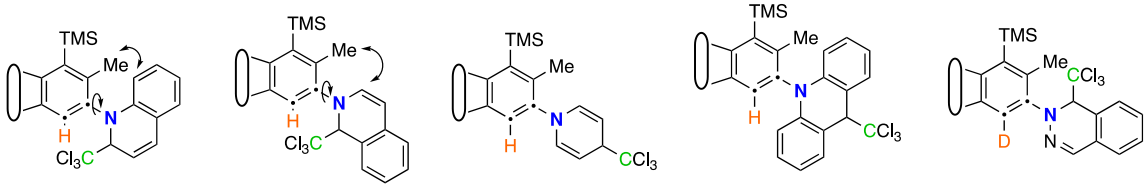
We next studied the outcome of heterocyclic trapping of the benzynes in the presence of various protic nucleophiles (mode **C**, Figure **3.7**). We began by heating the triyne substrate **1a** with quinoline (**2b**) in chloroform (**4a**, 0.02 M). The zwitterionic intermediate abstracted a proton from $CHCl_3$, and the resulting ion pair collapsed to give the trichloromethylated adduct **27** (Figure **3.7a**). This molecule, as well as the other quinoline-derived biaryls, gave evidence of two atropisomers in its ^{1}H and ^{13}C NMR spectra. The analogous reaction with isoquinoline cleanly produced **28**; the NMR spectra for this isomeric compound showed a single set, albeit of broadened, resonances, reflecting the expected lower barrier for biaryl rotation compared to that in **27**.

Because of the relatively high efficiency of the trapping by $CHCl_3$, we examined a wider array of *N*-HARs as well as other benzyne precursors for this class of TCR (Figure **3.7a**). In the case where pyridine (**2h**) was used as the *N*-HAR, the 4-subsituted product **29** was formed. Use of acridine (**2i**) also led to the formation of its para-functionalized product, **30**, because the adduct arising from trapping by Cl_3C^- at an ortho-carbon would significantly interrupt aromaticity. The remote nature of the Cl_3C-bearing carbon in **30** results in a only subtly different pair of atropisomers, a fact revealed in the NMR data for this adduct (see SI for Chapter **3**). The fact that chloroform was the source of the proton in these reactions was validated when $CDCl_3$ was used as the third component; **31** was formed in 95% yield. This result also demonstrated that phthalazine (**2j**) was a participant in this TCR. We then examined several other aryne precursors for this transformation. Each of **33**, **34**, and **35** was produced in a very good yield, starting with **1b**, **1c**, and **1d**,

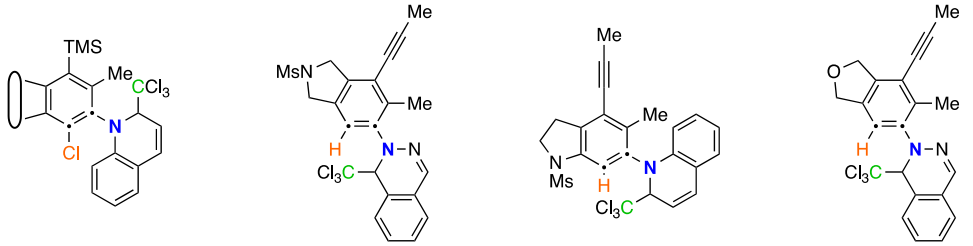
respectively. Finally, when carbon tetrachloride (**4c**) was used as solvent instead of $CHCl_3$, chlorination of the 1,3-zwitterion from quinoline led to the formation of **32**.[67]

Figure 3.7 | Products from mode C three-component reactions using monoprotic nucleophiles. Trapping of zwitterions (cf. **III**) by **a)** CCl_3-containing electrophiles and **b)** carbon-acids (terminal alkynes or fumaronitrile). ^{i}ar = atropisomeric ratio (observed by ^{1}H NMR spectroscopy, see SI for Chapter **3**).

a **HCCl$_3$** ***protic nucleophiles***

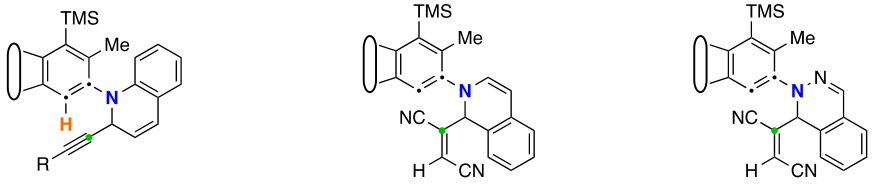


27 [*(1a+2b+4a)*, 93%, ar^{i} = 6.3:1.0] ***28*** [*(1a+2a+4a)*, 88%] ***29*** [*(1a+2h+4a)*, 84%] ***30*** [*(1a+2i+4a)*, 82%, ar = 2:1] ***31*** [*(1a+2j+4b)*, 95%]



32 [*(1a^{+2}b^{+4}c)*, 56%, ar = 2:1] ***33*** [*(1b+2j+4a)*, 77%, rr = 6.3:1] ***34*** [*(1c+2b+4a)*, 92%, ar = 6:1] ***35*** [*(1d+2j+4a)*, 89%, rr = 5:1]

b **H–C$_{sp}$ or H–C$_{sp2}$** ***protic nucleophiles***



36, R = Ph, [*(1a+2b+4d)*, 54%, ar = 5:1] ***37***, R = TMS, [*(1a+2b+4e)*, 84%, ar = 3.7:1] ***38*** [*(1a+2a+4f)*, 85%] ***39*** [*(1a+2j+4f)*, 35%]

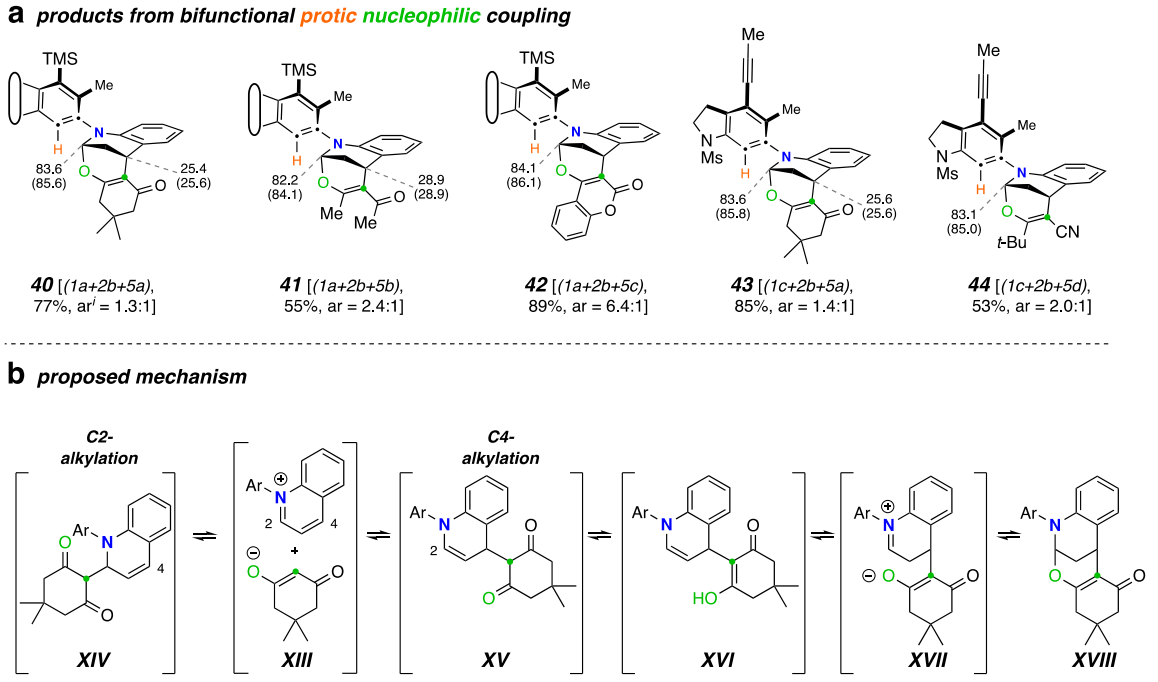
[67] S. J. Li, Y. Wang, J. K. Xu, D. Xie, S. K. Tian and Z. X. Yu, *Org. Lett.*, 2018, **20**, 4545–4548.

TCRs using carbon acids were also shown to be effective. Specifically, we found that terminal alkynes (**4d** and **4e**) were shown to have a sufficiently acidic proton to engage in a TCR to provide the alkynyl derivatives **36** and **37** (Figure **3.7b**). Surprisingly, fumaronitrile (**4f**), which we initially expected to capture the zwitterion in a net [4+2] manner (i.e., via mode B), had a different outcome. Protonation and capture by the conjugate base of **4f** gave product **38** or **39** when isoquinoline (**2a**) or phthalazine (**2j**) was used as the *N*-HAR.

3.3.3 *Mode C (TCR with a diprotic nucleophile).*

We then studied the behavior of several β-dicarbonyl protic nucleophiles (**5a-d**, Chart **3.1d**) and encountered a new type of net bicyclization reaction (Figure **3.8a**). For example, heating the substrate **1a** with quinoline (**2b**) and dimedone (**5a**) resulted in the

Figure 3.8 | Products from mode C three-component reactions using diprotic nucleophiles. **a)** Product structures [ratios of major and minor (separable) atropisomers]. **b**) Mechanistic rationale consistent with the formation of the hemiaminal-containing skeletons in products **40**–**44**.



formation of the bridged benzoxazine **40** (77%) by sequential engagement of benzyne **VI** by **2b** and, then, **5a**. Thus, the third component here was serving as a "doubly protic" nucleophile. In this case the more crowded atropisomers interconverted sufficiently slowly that they now could be chromatographically separated. As the additional examples in Figure **3.8a** demonstrate, acetylacetone (**5b**), 4-hydroxycoumarin (**5c**), and α-cyanopinacolone (**5d**) all participated in this type of transformation. The structures of these novel products (**40**–**44**) were established on the basis of (i) the contiguous four-spin vicinal coupling array among the bridging methylene and bridgehead methine protons and, especially, (ii) the ^{13}C NMR chemical shifts of the bridgehead aminal carbon (82-86 ppm). These spectroscopic signatures were consistently seen in all five of these adducts. HSQC and HMBC experiments were also consistent with these assignments.

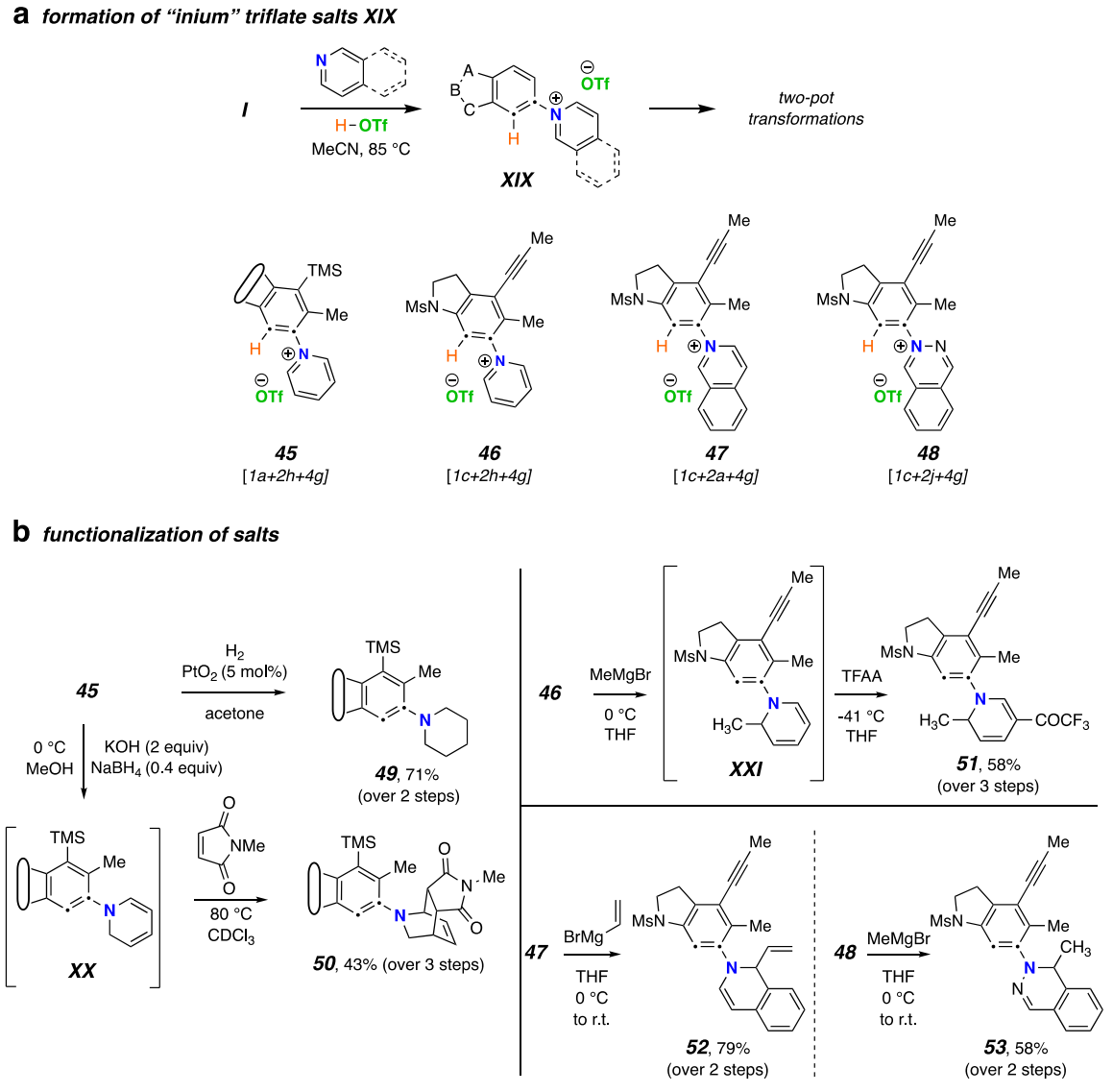
A mechanistic rationale for this interesting transformation is suggested in Figure **3.8b**. Nucleophilic addition of quinoline (**2b**) to the HDDA-benzyne and proton transfer from, for example, dimedone (**5a**) produces the enolate-quinolinium ion pair **XIII**. This can undergo collapse by attack at either C2 (to **XIV**) or C4 (to **XV**). Since C2-attack is the main event in the earlier TCRs, we suggest that **XIII**–**XV** are sufficiently close in energy to be in dynamic equilibrium with one another. Keto-enol tautomerization, while possible for either **XIV** or **XV**, can proceed further from the latter because of its embedded enamine moiety. Specifically, internal protonation within enol **XVI** gives zwitterion **XVII**, the collapse of which would generate **XVIII** (cf. **40**/**43**).

3.3.4 *Two-pot variant of the TCR.*

Finally, we devised a two-pot variant that allows for the use of a wider variety of nucleophiles in these types of reactions. Namely, generation of the benzyne from the polyyne precursor in the presence of the *N*-HAR and "non-nucleophilic" triflic acid (**4g**), typically in a molar ratio of 1:3:2 to ensure the presence of the free-base form of the *N*-HAR, gave rise to isolable salts **XIX** (Figure **3.9a**). Specifically, the N-arylated "inium" triflate salts **45**-**48** were efficiently generated. These reactions were seen to be most efficient using acetonitrile as the reaction solvent. Crude samples of the salts could be

isolated by solvent removal and were characterized by ^{1}H NMR and HRMS analyses. These samples still retained the excess *N*-HAR•H^{+}TfO^{-} salts, but that did not seriously

Figure 3.9 | Use of the "non-nucleophile" triflic acid (**4g**) allows for the incorporation of a broader range of nucleophiles. **a**) TCRs were performed using 3 equiv of the *N*-HAR and 2 equiv of triflic acid in acetonitrile (MeCN), which led to the formation of salts **45–48**. **b**) Examples demonstrating the subsequent diversification of some of these salts to give products **49–53**.



hamper their subsequent reactions with nucleophiles. These inium ions could then be redissolved (or suspended) in various solvents and further transformed to products that

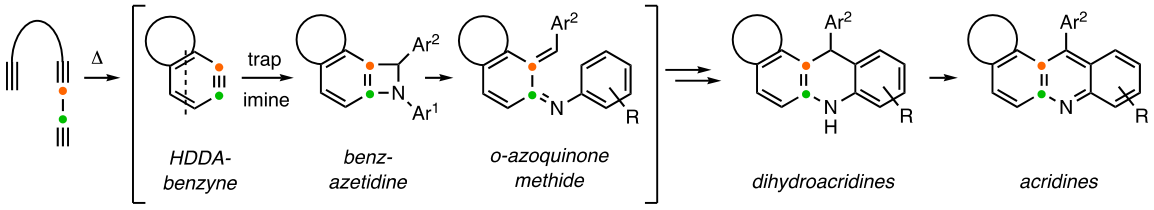
were either complementary to or not compatible with the one-pot TCRs. For example (Figure **3.9b**), the *N*–aryl pyridinium triflate **45** cleanly underwent hydrogenation in the presence of Adams catalyst, producing the piperidine derivative **49** in 71% yield at room temperature. In another reduction **46** was converted to the 1,2-dihydropyridine **XX** using sodium borohydride. As was the case with 1,2- dihydropyridines mentioned earlier, **XX** was also found to be unstable upon attempted silica gel chromatographic purification. However, the crude product could be further treated with *N*–methyl maleimide to furnish the Diels-Alder adduct **50** in 43% overall yield (from **1a**). The triflate salts were also found to react readily with (excess) Grignard reagents. For example, the **1c**-derived pyridinium salt **46** was reacted with MeMgBr in THF to produce **XXI**. This dihydropyridine was transformed directly into **51** using trifluoroacetic anhydride (58% overall yield from **1c**). Grignard reagents were used to convert other heterocyclic derived salts, namely **47** and **48**, into their corresponding alkylated products **52** and **53** in a clean manner.

3.4 *Conclusions.*

We have demonstrated that various modes (A–C) of reaction can be realized by reacting six-membered N-heteroaromatic compounds with benzynes generated by thermal HDDA cycloisomerization of triyne (or tetrayne) precursors. All reactions can be rationalized as passing through an initially formed 1,3-zwitterion arising from attack on the benzyne by the nitrogen atom of the heterocycle. In mode A and in unprecedented fashion, 1:1 adducts emanating from this zwitterion are produced. For the most part, these products belong to either of the benzoazetidine or benzoazocine family. In mode B, the first of two types of three-component reaction, an intermediate electrophile is used to capture the 1,3-zwitterion. Mode B electrophiles can be suitably reactive carbonyl compounds, isocyanates, or electron-poor alkenes or alkynes. In mode C, the third component is a protic acid that quenches the anionic center in the zwitterion to give an ion pair that collapses to product. Diprotic nucleophiles (e.g., β-dicarbonyl compounds) can be used to give novel bridged polycyclic products. Finally, the triflic acid produces isolable *N*-arylinium triflates that subsequently can be subjected to nucleophilic addition to further widen the strategic scope of the process.

Chapter 4. Reactions of HDDA Benzynes with *C,N*-Diarylimines

The studies presented in this Section have been disclosed in and largely adapted from a published article.[68] This work is a result of collaborative and equal efforts from Mr. Dorian Sneddon and the author of this Thesis. The Compound Numbers in this Section are directly adapted from reference 68. New numbers (start with 401) only apply to compounds that have NOT been reported in the published manuscript.



Summary: *o*-Benzynes can be utilized to construct heterocyclic motifs using various nucleophilic and cycloaddition trapping reactions. Acridines have been synthesized by capture of *C,N*-diarylimines with benzynes generated by classical methods (i.e., from *ortho*-elimination of precursor arene compounds), although in poor yields. We report here that these imines can be trapped by benzynes generated by the hexadehydro-Diels–Alder (HDDA) reaction in an efficient manner to produce 1,4-dihydroacridine products. These dihydroacridines were subsequently aromatized using MnO_2 to provide structurally complex acridines.

4.1 Applications of acridine molecules in various industries.

Compounds containing acridine core are an important class of heterocycles because of their numerous pharmaceutical and material applications.[69] The practice of

[68] Arora, S.; Sneddon, D. S.; Hoye, T. R. Reactions of HDDA Benzynes with *C,N*-Diarylimines (ArCH=NAr′). *Eur. J. Org. Chem.* **2020**, *16*, 2379-2383.

[69] Kowalewska, M. G.; Cholewinski, G; Dzierzbicka, K. Recent Developments in the Synthesis and Biological Activity of Acridine/Acridone Analogues. *RSC Adv.*, **2017**, *7*, 15776–15804.

acridine derivatives as pigments and dyes have been known for more than a century.[70] Apart from their usage as dyes, these molecules have also provided numerous applications as a way of fluorescent materials for visualization of a biomolecule.[71] In pharmaceutical industry, acridine molecules have shown several bioactivities such as anti-inflammatory,[72] anticancer,[73] antimalarial,[74] antiviral,[75] and fungicides activities.[76] The applications of acridines in pharmaceutical and material industry can be attributed to the planer structure of these heterocycles. It is also well-known that the acridine and acridone moieties, again, because of their planar structures, can act as a DNA intercalators.[77] Because of their ability to bind to the DNA, synthetic chemists have always taken an appreciable interest in synthesizing acridine-containing molecules to evaluate their antitumor activities. For examples, a couple of *m*-AMSA derivatives – AHMA (**401**) and D3CLP (**402**) have been developed for anticancer properties and removal of many harmful side effects (Figure **4.1**).[78]

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[70] Geddes, C. D. Optical Thin Film Polymeric Sensors for the Determination of Aqueous Chloride, Bromide and Iodide Ions at High pH, Based on the Quenching of Fluorescence of two Acridinium Dyes. *Dyes Pigm.*, **2000**, *45*, 243.

[71] Niknam, K; Damya, M. 1-Butyl-3-methylimidazolium Hydrogen Sulfate [bmim]HSO_4: An Efficient Reusable Acidic Ionic Liquid for the Synthesis of 1,8-Dioxo-octahydroxanthenes. *J. Chin. Chem. Soc.*, **2009**, *56*, 659.

[72] Chen, Y. L.; Lu, C. M.; Chen, I. L.; Tsao, L. T.; Wang, J. P. Synthesis and Antiinflammatory Evaluation of 9-Anilinoacridine and 9-Phenoxyacridine Derivatives. *J. Med. Chem.*, **2002**, *45*, 4689–4694

[73] Gamega, S. A.; Spicer, J. A., Atwell, G. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. Structure–Activity Relationships for Substituted Bis (Acridine-4-carboxamides): A New Class of Anticancer Agents. *J. Med. Chem.*, **1999**, *42*, 2383–2393.

[74] (a) Kumar, A.; Srivastava, K.; Kumar, S. R.; Puri, S. K.; Chauhan, M. S. Synthesis of 9-Anilinoacridine Triazines as New Class of Hybrid Antimalarial Agents. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 6996; (b) Tomar, V.; Bhattacharjee, G.; Kamaluddin; Rajakumar, S.; Srivastava, K.; Puri, S. K. Synthesis of New Chalcone Derivatives Containing Acridinyl Moiety with Potential Antimalarial Activity. *Eur. J. Med. Chem.*, **2010**, *45*, 745–751 and (c) Yu, X. M.; Ramiandrasoa, F.; Guetzoyan, L.; Pradines, B.; Quintino, E.; Gadelle, D.; Forterre, P.; Cresteil, T.; Mahy, J. P.; Pethe, S. Synthesis and Biological Evaluation of Acridine Derivatives as Antimalarial agents. *Chem. Med. Chem.*, **2012**, *7*, 587–605.

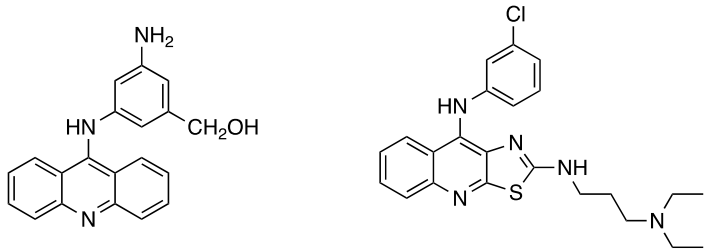
[75] Gupta, H. C.; Jaiswal, V. Synthesis and Antiviral Activity of Some Acridin-9-yl Aryldithiocarbamates. *Indian J. Heterocycl. Chem.*, **2010**, *19*, 409–410.

[76] Srivastava, A.; Nizamuddin, A. Synthesis and Fungicidal Activity of Some Acridine Derivatives. *Indian J. Heterocycl. Chem.*, **2004**, *13*, 261–264.

[77] Baguley, B. C.; Wakelin, L. P. G.; Jacintho, J. D.; Kovacic, P. Mechanisms of Action of DNA Intercalating Acridine-Based Drugs: How Important are Contributions from Electron Transfer and Oxidative Stress? *Curr. Med. Chem.*, **2003**, *10*, 2643–2649.

[78] Lang, X.; Li, L.; Chen, Y.; Sun, Q.; Wu, Q; Liu, F.; Tan, C.; Liu, H.; Gao, C.; Jiang, Y. Novel Synthetic Acridine Derivatives as Potent DNA-Binding and Apoptosis-Inducing Antitumor Agents. *Bioorg. Med. Chem.*, **2013**, *21*, 4170.

Figure 4.1 | Examples of acridine-containing anticancer drugs



m-AMSA
401

D3CLP
402

4.2 Reactions of classical benzynes with C,N-diarylimines.

o-Benzynes and related arynes have been used as versatile intermediates for construction of various aromatic heterocycles.[79] In a few instances, six-membered nitrogen-containing heterocycles of the acridine family have been produced, at least to small extents, by trapping of a classically generated[1(a)] aryne by an imine. The previously observed reaction pathways may be roughly placed into two categories: a) a net [2+2] process by way of an initial, transient zwitterion (Figure **4.2a**); b) initial [4+2] cycloaddition between the benzyne (acting as a dienophile) and the *N*-aryl imine moiety (acting as the diene, Figure **4.2b**).

The initial reports of reactivity between *o*-benzynes and *C,N*-diaryl imines came from the laboratories of M. Yoshida[80](1975)and Storr[81](1984), which independently reported the reaction of *N*-benzylideneaniline [**2**, R^1 =R^2 = Ph (=**2a**)] with *o*-benzyne (**1**) generated from benzenediazonium-2-carboxylate. In both studies the dihydrophenanthridine **7a** was isolated (8% or 6% yield) and in the latter the dihydroacridine **4b** (5%) was also obtained. These were rationalized as arising from competitive [2+2]- vs. [4+2]-cycloaddition of *o*-benzyne with **2a** via intermediates **3b**

[79] a) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. Use of Benzynes for the Synthesis of Heterocycles. *Org. Biomol. Chem.* **2013**, *11*, 191–218 and b) Peña, D.; Pérez, D.; Guitián, E. Aryne-Mediated Synthesis of Heterocycles. *Heterocycles* **2007**, *74*, 89–100.

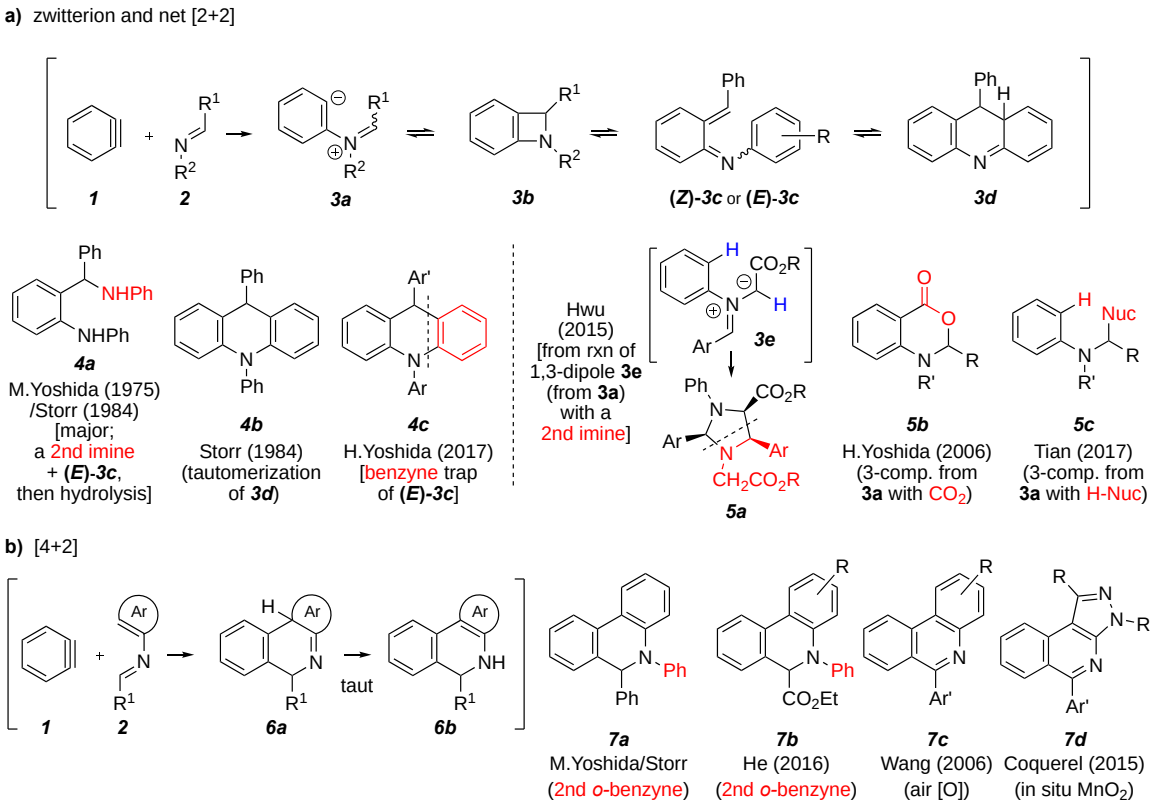
[80] Nakayama, J.; Midorikawa, H.; Yoshida, M. Reaction of Benzyne with *N*-benzilideneaniline. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1063–1064.

[81] Fishwick, C. W. G.; Gupta, R. C.; Storr, R. C. The Reaction of Benzyne with Imines. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2827–2829.

(through **3d**) or **6a** and **6b**, respectively. The major isolated product in both of these original studies (18% and 16%, respectively) was the diamine **4a**.

More recently, additional modes of reactivity between *o*-benzynes and imines have been studied. Some have focused on trapping of the presumed 1,3-zwitterion **3a**, which arises via imine nitrogen attack on the electrophilic benzyne. In 2006 H. Yoshida and co-workers[82] demonstrated the ability to access benzoxazinones **5b** via trapping of the 1,3-zwitterion by carbon dioxide using imines in which the carbon-bound group is an alkyl moiety. In 2015 Hwu et al.[83] showed the

Figure 4.2 | Previous studies of reactions of benzynes with imines in either (**a**) a net [2+2] pathway or (**b**) a [4+2] pathway.



[82] Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. CO_2 Incorporation Reaction Using Arynes: Straightforward Access to Benzoxazinone.*J. Am. Chem. Soc.* **2006**, *128*, 11040–11041.

[83] Swain, S. P.; Shih, Y.; Tsay, S.; Jacob, J.; Lin, C.; Hwang, K. C.; Horng, J.; Hwu, J. R. Aryne-Induced Novel Tandem 1,2-addition/(3+ 2) Cycloaddition to Generate Imidazolidines and Pyrrolidines. *Angew. Chem. Int. Ed.* **2015**, *54*, 9926–9930.

diastereoselective formation of imidazolidines **5a** and other *N*-heterocycles via trapping of the intermediate 1,3-dipole **3e**, formed via intramolecular proton transfer within **3a**. Finally, in 2017 researchers in the Tian laboratory[84] showed that **3a** may be trapped by protic carbon nucleophiles in a three-component fashion to form products of the type **5c**.

In 2017 H. Yoshida and co-workers[85] showed that trapping of the aza-*ortho*-quinone methide intermediate **3c** to form 2:1 imine:benzyne adducts **4c** was possible when benzyne was used in molar excess. This mode of reactivity prevails when the aryl moieties are more highly substituted, presumably slowing the electrocyclization of **3c** to **3d**.

Finally, in addition to M. Yoshida and Storr's initial isolation of phenanthridine adducts, other groups have sought to exploit the [4+2] pathway to access this class of product more efficiently. In 2006 Wang et al.[86] showed that benzyne could be used in a 3-component process to access phenanthridines **7c** with high efficiency using an electron-poor benzaldehyde and an electron-rich aniline. Similarly, in 2016 researchers in the He group[87] were able to isolate **7b** in a three-component process using Kobayashi[17] arynes, an aldehyde ester, and an aniline. In 2015 Coquerel and co-workers[88] reported the formation of isoquinolines **7d** derived from an imine containing a nitrogen-bound pyrazole moiety, and, through a computational study, suggested that an electron-rich aromatic group bound to the imine nitrogen favors [4+2] cycloaddition over a [2+2] pathway.

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[84] Xu, J.; Li, S.; Wang, H.; Xu, W.; Tian, S. Three-Component Carboarylation of Unactivated Imines with Arynes and Carbon Nucleophiles. *Chem. Commun.* **2017**, *53*, 1708– 1711.

[85] Yoshida, H.; Kuriki, H.; Fuji, S.; Ito, Y.; Osaka, I.; Takaki, K. Aryne-Imine-Aryne Coupling Reaction *via* [4+2] Cycloaddition Between Aza-*o*-quinone Methides and Arynes. *Asian J. Org. Chem.* **2017**, *6*, 973-976.

[86] Shou, W.; Yang, Y.; Wang, Y. Cascade Approach to Substituted 6-Aryl-Phenanthridines from Aromatic Aldehydes, Anilines, and Benzenediazonium-2-Carboxylate. *J. Org. Chem.* **2006**, *71*, 9241–9243.

[87] Reddy, R. S.; Lagishetti, C.; Chen, S.; Kiran, I. N. C.; He, Y. Synthesis of Dihydrophenanthridines and Oxoimidazolidines from Anilines and Ethylglyoxylate *via* Aza Diels-Alder Reaction of Arynes and KF-Induced Annulation. *Org. Lett.* **2016**, *18*, 4546–4549.

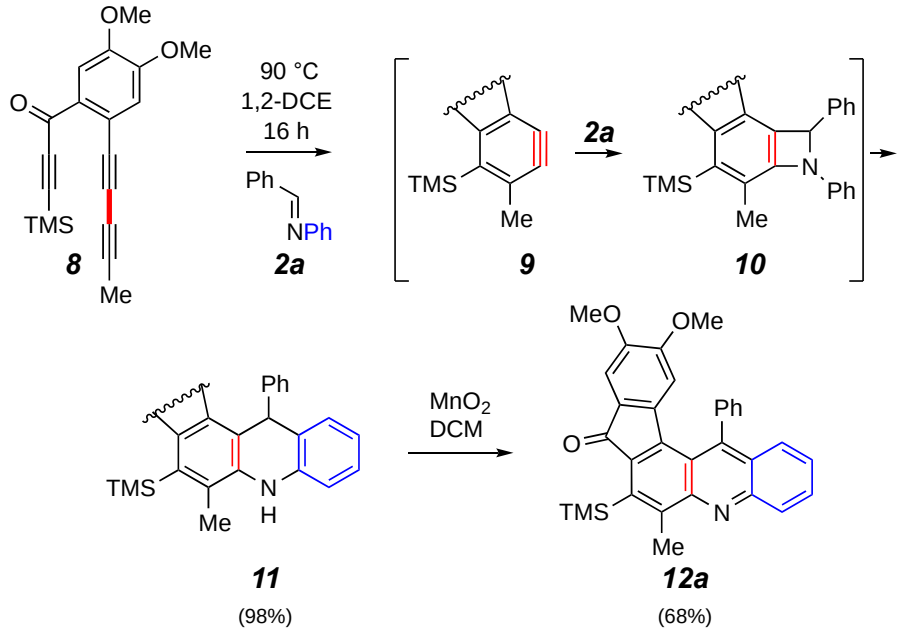
[88] Castillo, J.; Quiroga, J.; Abonia, R.; Rodriguez, J.; Coquerel, Y. The Aryne Aza-Diels–Alder Reaction: Flexible Syntheses of Isoquinolines. *Org. Lett.* **2015**, *17*, 3374–337

To summarize, reported examples of benzynes reacting with imines to give acridine-like products have shown low selectivity and efficiency. Given the interest in acridine compounds more broadly[69–78] as well as the fact that hexadehydro-Diels–Alder (HDDA)-derived benzynes often lead to outcomes complementary to those from classical benzynes,[23,32,58] we have explored the reactions of several polyyne substrates with various imine trapping agents and report the results of those studies here.

4.3 Reactions of fluorenone benzyne 9 with C,N-diarylimines.

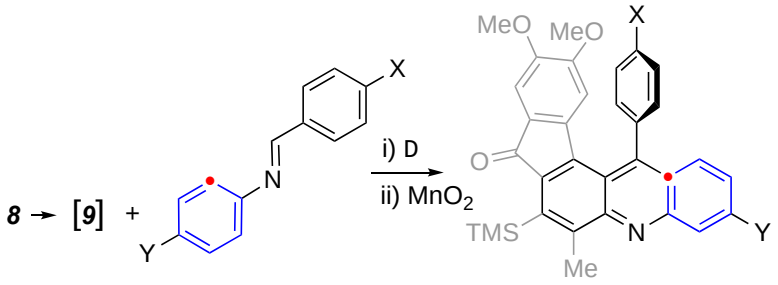
We first examined (Figure **4.3**) the reaction between the fluorenone benzyne **9**, generated by warming triyne **8**, with *N*-benzylidene-aniline (**2a**). This resulted in formation of the dihydroacridine **11** in a remarkably clean reaction, which contrasts significantly with the lower efficiencies of previous reactions giving rise to dihydroacridines (cf. Figure **4.2a**). Compound **11** was subsequently oxidized with MnO_2 to afford the acridine derivative **12a** in 68% yield.

Figure 4.3 | Reaction of the HDDA-generated benzyne **9** proceeds nearly exclusively to the 1,4-dihydroacridine **11**, presumably via the [2+2]-benzazetidine **10**. Compound **11** was subsequently oxidized to acridine **12a**.



To demonstrate generality of this reaction with different types of electronically modified aryl substituents in the imines, we explored the reactions between benzyne **9** and imines **2b**–**2g** (Table **4.1**). For each entry, only the acridine product that results from subsequent MnO_2 oxidation of the intermediate dihydroacridine is shown (see Supporting Information of Chapter **4** for characterization of the dihydro-intermediates **403**–**408**). The reaction showed relatively broad tolerance of electronic perturbation of the aryl substituent on both the carbon and nitrogen atoms composing the imine. That is, imines **2b**–**g** all provided the corresponding dihydroacridines, and then, the acridines **12b**–**g** (Table **4.1**). Only in the instance of the most electron-poor imine **2f**, was the yield of the initial dihydroacridine low. This is consistent with the view that the initial event in the engagement of benzyne with imine is nucleophilic attack by the nitrogen atom to generate the zwitterion **3a** (Figure **4.2a**).

Table 4.1 | Reactions of triyne **8** with several C,N-diaryl imines.

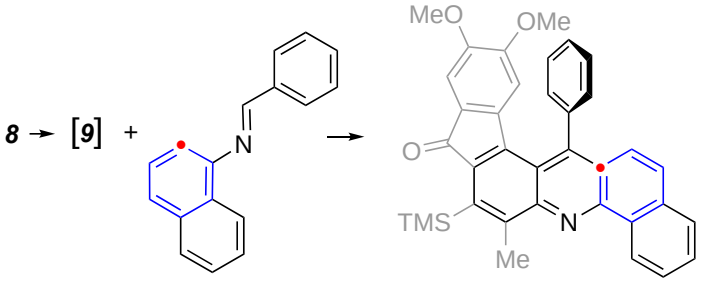


entry	*imine*	*product* [step i[a]: yield%, step ii[b]: yield%]
1	***2a***, X = H, Y = H	***12a*** [step i[a]: 98%, step ii[b]: 68%]
2	***2b***, X = NO_2, Y = H	***12b*** [step i[a]: 68%, step ii[b]: 90%]
3	***2c***, X = OMe, Y = H	***12c*** [step i[a]: 78%, step ii[b]: 86%]
4	***2d***, X = H, Y = NO_2	***12d*** [step i[a]: 62%, step ii[b]: 82%]
5	***2e***, X = H, Y = OMe	***12e*** [step i[a]: 100%, step ii[b]: 97%]
6	***2f***, X = NO_2, Y = NO_2	***12f*** [step i[a]: 19%, step ii[b]: 56%]
7	***2g***, X = OMe, Y = OMe	***12g*** [step i[a]: 88%, step ii[b]: 89%]

As a final example, this with a different type of imine, the 1-naphthyl derivative **13** gave the more highly annulated benzoacridine derivative **14** (Figure **4.4**). This

suggests that additional analogs with yet more extended conjugation can also be accessed.

Figure 4.4 | Reaction of triyne **8** with imine **13**. [a]yield of the 1,4-dihydroacridine from the HDDA reaction. [b]yield of the acridine adduct following MnO_2 treatment.



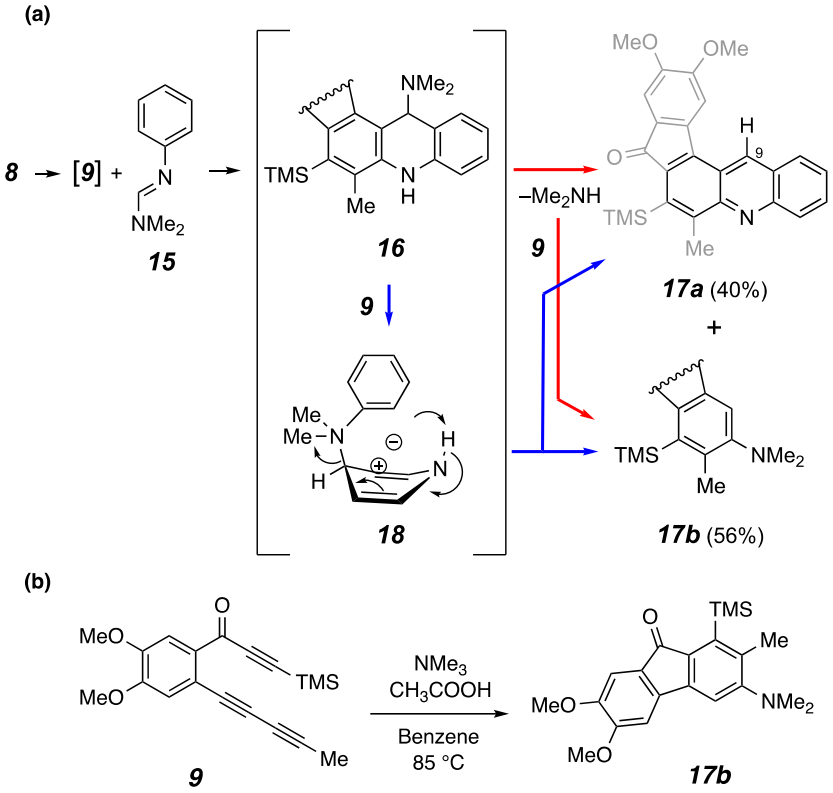
13 ***14*** [step i[a]: 98%, step ii[b]: 69%]

4.4 Reactions HDDA-benzynes with amidines.

Amidines are amino-substituted analogs of imines. *N*,*N*-Dimethyl-*N′*-phenylamidine (**15**) efficiently engaged the benzyne **9** (Figure **4.5a**). It gave rise directly to the acridine derivative **17a**, which has no substituent at C9 of the acridine. However, this reaction was accompanied by the formation of a similar amount of the dimethylamine-trapped benzyne product **17b**. Presumably the dihydroacridine **16**, arising from a [2+2] pathway directly analogous to that depicted for **8** to **11** (Figure **4.2**), underwent an elimination event under the reaction conditions to produce **17a**. That process can be envisioned to proceed by a direct (and possibly unimolecular) loss of dimethylamine, which, once released, then competitively trapped benzyne **9** (red arrows). Alternatively, a second copy of **9** could engage the tertiary aliphatic amine in intermediate **16** to give the 1,3-zwitterion[40,48] **18** (shown in a truncated form for simplicity), which could then collapse directly to one molecule each of **17a** and **17b**. Although of limited preparative value, this trapping reaction with an amidine provides interesting mechanistic insights. This reaction produced **17a** and **17b** as a coeluting mixture of compounds; to confirm the identity of

17a, an authentic sample of the amine-trapped product **17b** was also prepared using a three-component coupling reaction of trimethylamine and acetic acid (Figure **4.5b**).

Figure 4.5 | (a) Reaction of triyne **8** with amidine **15** to give rise to coeluting **17a** and **17b**; (b) synthesis of an authentic sample of the amine-trapped product **17b** using three-component coupling approach

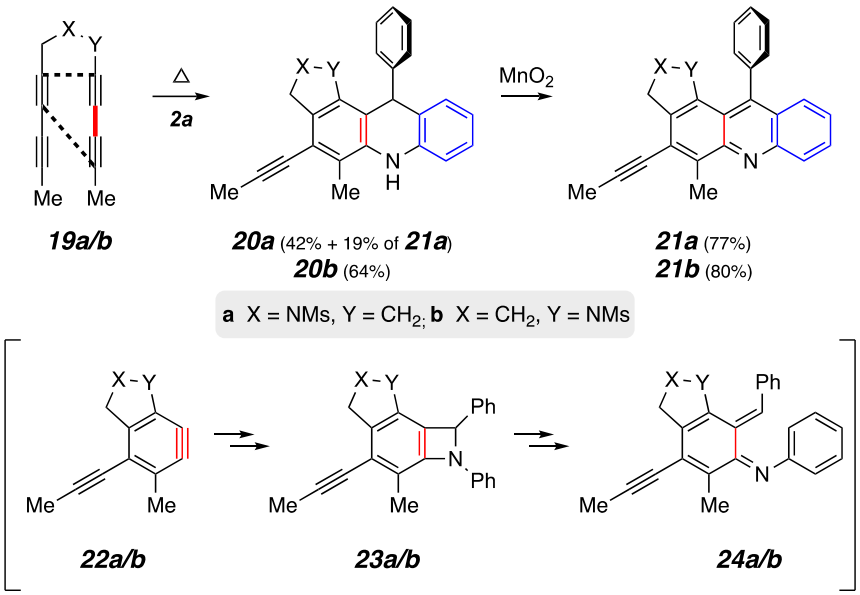


4.5 Reactions of other benzyne precursors with imines.

To establish that the reaction is not limited to benzyne **9**, we have trapped the HDDA benzynes derived from the precursor tetraynes **19a** and **19b** with *N*-benzylideneaniline (**2a**) (Figure **4.6**). The symmetrical tetrayne, which previously has been shown to react with various nucleophiles to give a pair of constitutional isomers with relatively little preference, produced only the single regioisomeric isoindoline derivative **20a** in 42% yield along with the oxidized acridine **21a** (19%), presumably from air oxidation.

Reaction of **19b** and **2a** produced the expected indolinoquinoline **21b** in 51% yield over two steps. The formation of a single benzyne (i.e., **22b**; see dashed lines in **19b**) from this unsymmetrical tetrayne precursor was first observed[89] by Lee and co-workers (and on many subsequent occasions) and is consistent with a computational study[90] that addressed exactly that point. To summarize, the reactions of both **19a/b** with **2a** proceeded via the corresponding benzazetidine **23a/b** and azo-quinonemethide species **24a/b** en route to the 1,4-dihydroacridines **20a/b**.

Figure 4.6 | Reactions of tetraynes **19a/b** with imine **2a** to give acridines **21a/b**.



4.6 Formation of 2:1 adducts.

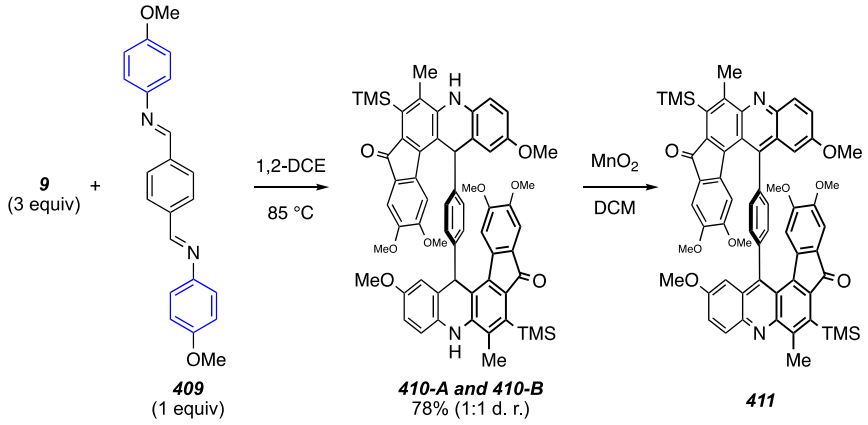
Finally, we were also able to extend this methodology to produce 2:1 adducts of imines and benzynes. Specifically, when three equivalents of triyne precursor **9** were reacted with one equivalent of dimine **409**, a coeluting pair of diastereomers **410-A** and **410-B** were isolated (Figure **4.7**). Furthermore, upon aromatization using MnO_2, both of

[89] Yun, S. Y.; Wang, K. P.; Lee, N. K.; Lee, P. M. D. Alkane C–H Insertion by Aryne Intermediates with a Silver Catalyst. *J. Am. Chem. Soc.* **2013**, *135*, 4668–4671.

[90] Chen, M.; He, C. Q.; Houk, K. N. Mechanism and Regioselectivity of an Unsymmetrical Hexadehydro-Diels–Alder (HDDA) Reaction. *J. Org. Chem.* **2019**, *84*, 1959–1963

the diastereomers converged into a single annulated bis-acridine **411**. This result, again, demonstrated the ease at which highly annulated and extended molecules can be assembled in relatively fewer steps by using HDDA reaction.

Figure 4.7 | Formation of 2:1 adducts of imines and benzynes: HDDA reaction of **9** with **409** resulted in diastereomeric isomers **410-A** and **410-B**, which were subsequently oxidized to **411**.



4.7 Conclusions.

In summary, these results establish that trapping of thermally generated, polycyclic benzyne derivatives with *C,N*-diaryl imines leads to dihydroacridine derivatives, which can be further and readily oxidized to their acridine analogs. These reactions proceed considerably more efficiently than those reported earlier for imine trapping of benzyne itself (from benzenediazonium-2-carboxylate thermolysis). In no case have we observed products arising from initial [4+2] cycloaddition, as has been seen in previous studies.[80,81,86,87,88] This work represents another instance in which the arynes generated through the HDDA-cycloisomerization reaction, which are produced in a purely thermal environment, has allowed for the formation of the trapping products in a much cleaner,[30] if not unique,[42,91] manner.

[91] Shen, H.; Xiao, X.; Haj, M. K.; Willoughby, P. H. and Hoye, T. R. BF_3-Promoted, Carbene-Like, C–H Insertion Reactions of Benzynes. *J. Am. Chem. Soc.* **2018**, *140*, 15616–15620.

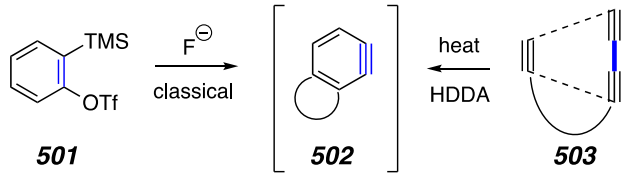
Chapter 5. Kobayashi Benzynes as HDDA-Diynophiles

A portion of the work presented in this Chapter is largely adopted from a manuscript in preparation.

5.1 Introduction.

The continuous interest in the benzyne research within the synthetic community, as well as the general value and tremendous potential of these building blocks in organic synthesis,[1] has been a major driving force for the development of newer methods of aryne generation.[1(a)] As discussed in the previous chapters, the Kobayashi method,[17] which uses a fluoride ion to induce an elimination event in trimethylsilyl phenyl triflate **501** to produce a benzyne intermediate **502**, is perhaps the most widely used method for aryne generation to date (Figure **5.1**). In contrast to that, the hexa-dehydro-Diels–Alder (HDDA) reaction of a tethered triyne (or a tetrayne) precursor to thermally generate an aryne species, has been a powerful and interesting advancement in the field of aryne chemistry in the last decade (**503** to **502**, Figure **5.1**). This method of generation of benzynes that relies on thermal activation of precursors is complementary to the pre-existing methods. This chapter focuses on "marrying" the two complementary methods by the way of using Kobayashi arynes as HDDA-diynophiles and also highlights the synthetic value of resultant naphthyne intermediates as useful building blocks.

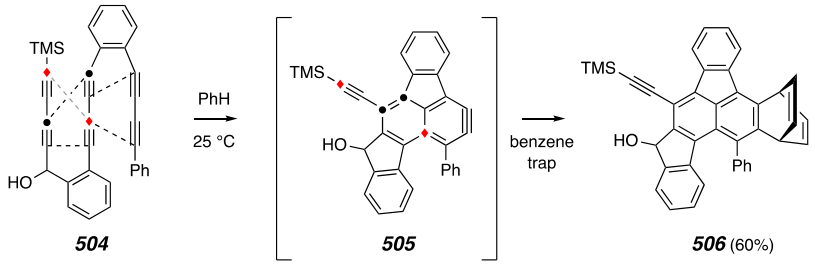
Figure 5.1 | Two complementary methods to generate the aryne intermediate **502**



The idea of using arynes as diynophilic partners in the HDDA reaction has been investigated by a couple of research groups. The earliest report suggesting the

engagement of an aryne with a 1,3-diyne came from the labs of Fields and Meyerson (1967), who suggested the intermediacy of a benzyne in acetylene pyrolysis study.[92] Ueda and coworkers, through a series of publications,[93,94,95] also explored the idea of using benzynes as a diynophilic partner in [4+2]-cycloadditions. For example, hexayne **504** underwent cyclization at room temperature to generate an aryne (not shown here), which served as a diynohile for the subsequent cyclization to afford a naphthyne intermediate **505**. **505** was then trapped by benzene to give naphthalene derivative **506** in 60% yield (Figure **5.2**). The yields of these cyclizations, however, were not ideal (ranging from 10 to 63%) and this presumably can be attributed to the formation of a non-productive benzyne, which was formed by initial ring-closure of the two carbon atoms labelled as ♦ (cf. **504**). Xiao was able to capitalize on this concept by designing polyyne substrates that undergo cyclization in only one sense, in a reaction that was termed as the domino-HDDA reaction (cf. Scheme **1.18**, Chapter **1**).[44] Through this remarkable study,

Figure 5.2 | Benzyne to naphthyne: Ueda et al.[93,94,95]



504 ***505*** ***506*** (60%)

he was able to establish that the domino-HDDA is not only an efficient process that

[92] Fields, E. K. and Meyerson, S. A New Mechanism for Acetylene Pyrolysis to Aromatic Hydrocarbons. *Tetrahedron Lett.* **1967**, *8*, 571–575.

[93] Miyawaki, K.; Kawano, T.; Ueda, I. Multiple Cycloaromatization of Novel Aromatic Enediynes Bearing a Triggering Device on the Terminal Acetylene Carbon. *Tetrahedron Lett.* **1998**, *39*, 6923–6926.

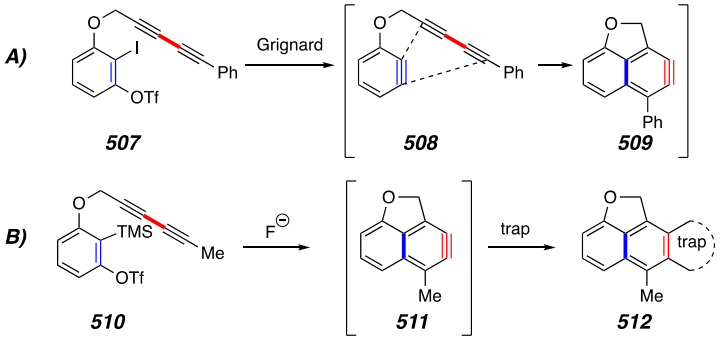
[94] Miyawaki, K.; Kawano, T.; Ueda, I. Domino Thermal Radical Cycloaromatization of Non-Conjugated Aromatic Hexa- and Heptaynes: Synthesis of Fluoranthene and Benzo[a]Rubicene Skeletons. *Tetrahedron Lett.* **2000**, *41*, 1447–1451.

[95] Miyawaki, K., Kawano, T.; Ueda, I. Synthesis and Properties of Functionalized [6]Helicenes by the Thermal Domino Radical Cycloaromatization of Acyclic Polyynes. *Polycycl. Aromat. Compd.* **2000**, *19*, 133–154.

proceeds with a great deal of generality, but can also be utilized for "bottom-up" synthesis of higher-ordered acene derivatives.

The use of aryne derivatives as the diynophilic partner in a HDDA reaction is not only limited to thermally produced benzynes; classically generated benzynes have also been explored for this purpose. Yoshida and coworkers have described the potential of a benzyne **508** that was generated through reductive elimination of an *ortho*-iodotriflate **507** in a subsequent intramolecular cyclization to afford a naphthyne **509** (Panel **A**, Figure **5.3**).[96] This creative method, however, uses a Grignard reagent as a way of introducing the benzyne in the reaction mixture. It is quite intuitive that utility of this method is limited owing to the strong basicity of a Grignard reagent, which perhaps was the reason behind the limited number of examples (three overall) reported by Yoshida and coworkers. I was interested in exploring the possibility of using the relatively tolerant and much more widely used Kobayashi method for the initial aryne formation (from **510** to **511**, Panel **B**, Figure **5.3**), which can possibly tolerate a wider range of intra- and inter-molecular trapping agents (in products **512**).

Figure 5.3 | A) Naphthyne intermediate reported by Yoshida and coworkers[96] and (B) our approach



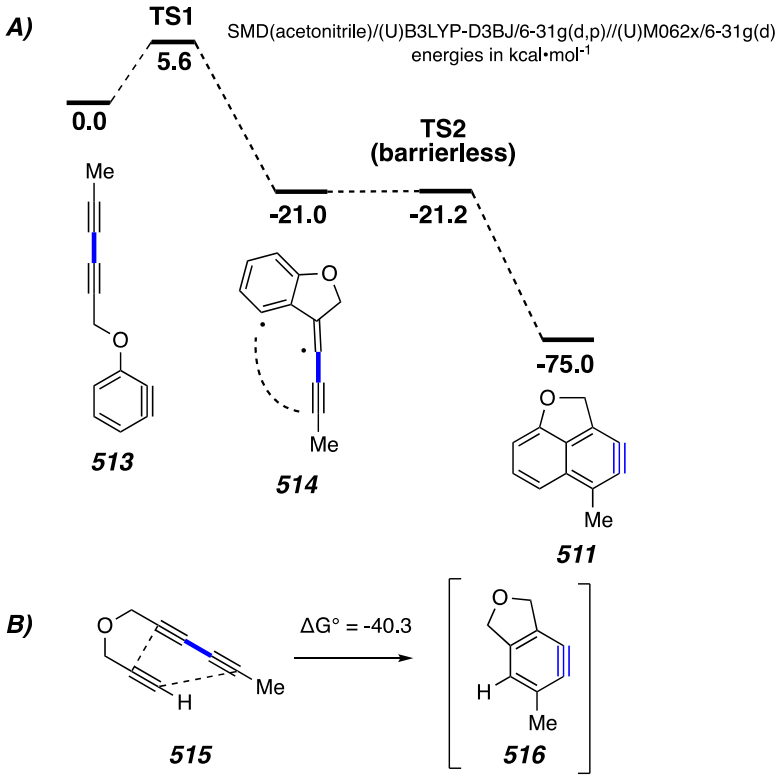
[96] Yoshida, S. et al. Construction of Condensed Polycyclic Aromatic Frameworks Through Intramolecular Cycloaddition Reactions Involving Arynes Bearing an Internal Alkyne Moiety. *Chem. Eur. J.* **2017**, *23*, 15332–15335.

5.2 Initial Computational Studies.

The initial DFT computation calculations on the desired transformation were quite interesting and matched well with the literature precedence.[97] I presumed that the trapping of the initially formed aryne by an intramolecular 1,3-diyne moiety resembles a mechanism analogous to the parent HDDA reaction (cf. Scheme **1.21**), that is, a stepwise cycloaddition involving a diradical intermediate **514** (Figure **5.4**). The initial bond formation had a low-barrier of 5.6 kcal/mol, which is critical for the intramolecular 1,3-diyne trapping in an order to outcompete the intermolecular trapping event (as demonstrated later in sections **5.4** and **5.5**). Subsequently, the resulting diradical **514** collapses to a six-membered naphthyne intermediate **511** via a barrierless process. This is consistent with the fact that the rate-limiting step of this overall transformation is the initial formation of the diradical intermediate **514**. The computed free energy of the reaction was also quite interesting – the conversion of benzyne **513** to the naphthyne **511** was found to be exothermic by 75.0 kcal•mol^{-1}. To compare this value to a standard HDDA reaction, I also computed the free energy change for the cyclization reaction involving analogues triyne substrate **515** to a benzyne **516**, which was found to be exothermic by 40.3 Kcal•mol^{-1}. This remarkable difference between the two free energy changes (**513** to **511** vs. **515** to **516**) can be attributed to the fact that more conjugated, and thus, more stable naphthyne core **511** (compared to benzyne **516**) is formed in the first case.

[97] Xiao, Xiao. PhD Thesis (**2019**). The Hexadehydro-Diels–Alder (HDDA) Reaction-Enabled Bottom-up Synthesis of Elaborated Polycyclic Aromatics. Retrieved from the University of Minnesota Digital Conservancy.

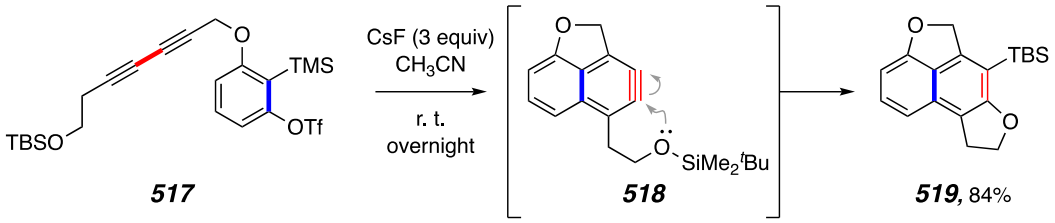
Figure 5.4 | Energy profile for (**A**) the desired reaction and (**B**) model HDDA reaction



5.3 Intramolecular trapping examples.

In order to experimentally probe the potential synthetic value of the naphthyne intermediates, I chose to initially synthesize and test an analogue that contained an intramolecular tethered TBS ether trap (**517**, Figure **5.5**, see SI for Chapter **5** for the synthesis). When an acetonitrile solution of **517** was treated with additional equivalents of CsF, anticipated naphthalene **519** was efficiently formed (84% yield). This is, again, rationalized by the initial formation of the naphthyne intermediate **518**, which undergoes a retro-brook rearrangement to finally afford **519**. The yield and overall cleanliness of this reaction was very encouraging– both GC-MS and ^{1}H NMR spectroscopic analysis of the crude material indicated that the desired cyclization was, by far, the major product in the mixture.

Figure 5.5 | First example demonstrating the potential of naphthynes generated by the combination of Kobayashi and HDDA protocol



After the initial success, a few additional classes of intramolecular trapping agents potentially capable of capturing the naphthyne intermediate were explored (Figure **5.6**). A dibenzofuran moiety **522** was achieved by using an *ortho*-methoxyphenyl substituent as a trapping agent in the precursor diyne **520** via the formation of naphthyne **521**.[45] When a phenyl substituent was placed two carbon atoms away from the in situ generated naphthyne **524**, an intramolecular Diels–Alder (IMDA) trapped adduct **526** was synthesized in 45% yield (starting from the diyne **523**).[31,98] The yield of the IMDA reaction was significantly improved when the trapping-diene was placed three atoms away in the precursor 1,3-diyne **526**. The internal furan trap, now placed more appropriately, is presumably able to engage the naphthyne **527** better than the previous case (cf. **524**), thus allowing for the formation of newly fused six-membered ring **528** in 85% yield.[99] Aromatic ene precursor **529** gave rise to the pyran ring formation in **531** in 64% yield via the formation of the isotoluene intermediate **530**.[30]

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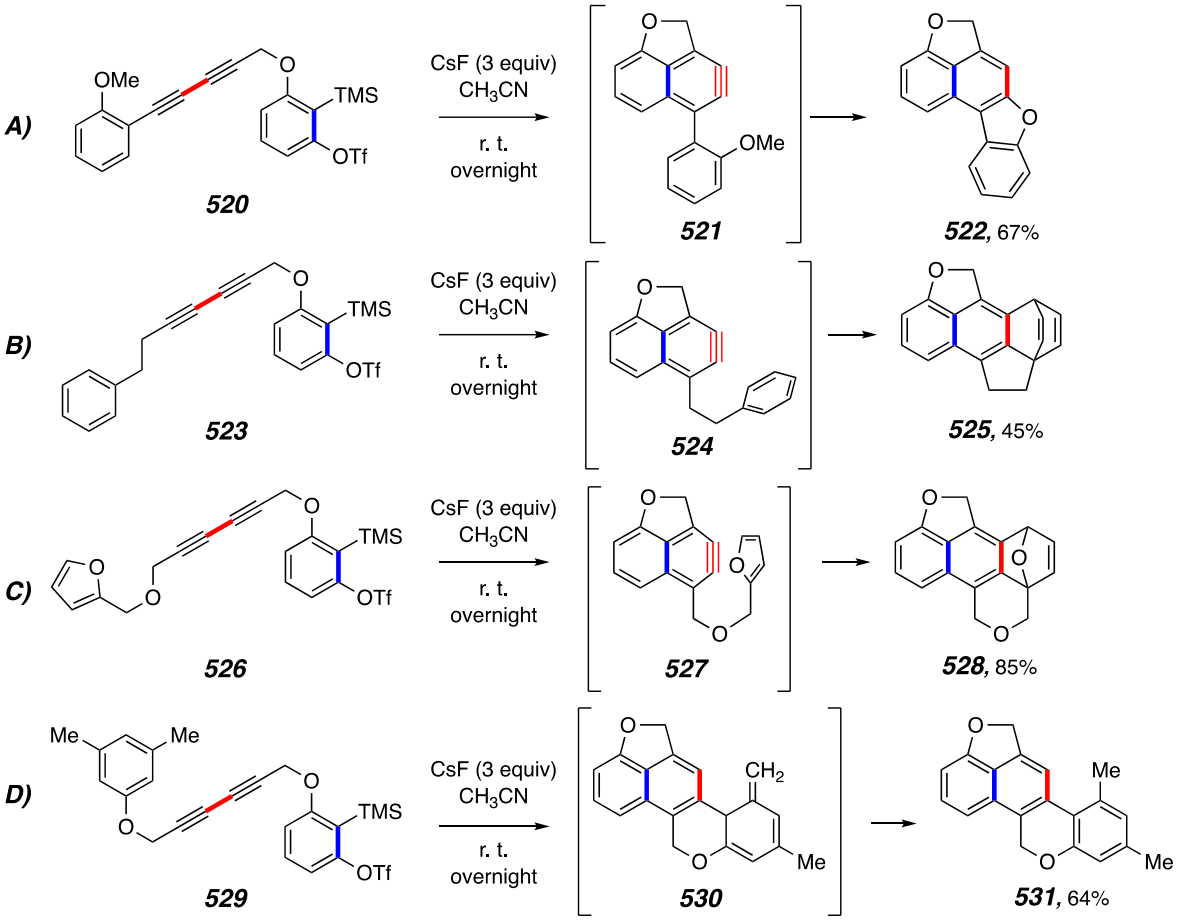
[98] (a) Miller, R. G.; Stiles, M. Reaction of Benzyne with Benzene and Naphthalene. *J. Am. Chem. Soc.* **1963**, *85*, 1798−1800. (b) Tabushi, I.; Yamada, H.; Yoshida, Z.; Oda, R. Reactions of Benzyne with Substituted Benzenes. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 285−290.

[99] Wang, Yuanxian and Hoye, T. R. Intramolecular Capture of HDDA-Derived Benzynes: (i) 6- to 12-Membered Ring Formation, (ii) Internally (vis-à-vis Remotely) Tethered Traps, and (iii) Role of the Rate of Trapping by the Benzynophile. *Org. Lett.* **2018**, *20*, 88–91.

Figure 5.6 | (**A**) *ortho*-methoxyphenyl trap; (**B**) IMDA with benzene; (**C**) IMDA with furan and (**D**) Aromatic ene reaction



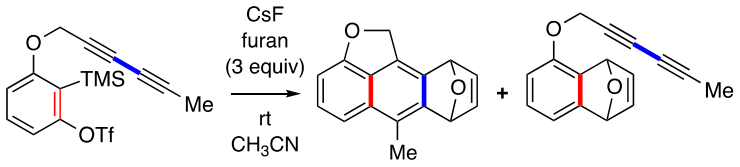
5.4 Intermolecular-trapping examples.

Naturally, the next step was to trap the reactive naphthyne intermediate with trapping agents in a bimolecular (i.e. intermolecular) fashion. In order to investigate the viability of the intermolecular naphthyne-trapping reactions, diyne **510** was synthesized (see SI for Chapter **5** for the synthesis). Furan, a well-established and efficient aryne trapping diene, was present (3 equiv; 0.06 M) in the acetonitrile reaction solution prior to the addition of CsF.[100] When the initial concentration of diyne **510** was 0.02 M, the

[100] Wittig, G.; Pohmer, L. Intermediäre Bildung von Dehydrobenzol (Cyclohexadienin). *Angew. Chem.* **1955**, *67*, 348–348.

products **532** and **533** were obtained in equal amounts [Figure **5.7**, entry **i**)]. Clearly bimolecular benzyne reaction with furan was intercepting the initial aryne **511** (cf. Figure 5.4) with a rate quite competitive with that of its unimolecular cyclization to naphthyne **513** (cf. Figure 5.4). To validate that interpretation experimentally, the process was repeated starting with an initial [**513**]$_0$ = 0.002 M, keeping the furan again at 3 equiv (i.e., 0.006 M).

Figure 5.7 | Competition between naphthyne adduct **532** and benzyne adduct **533**



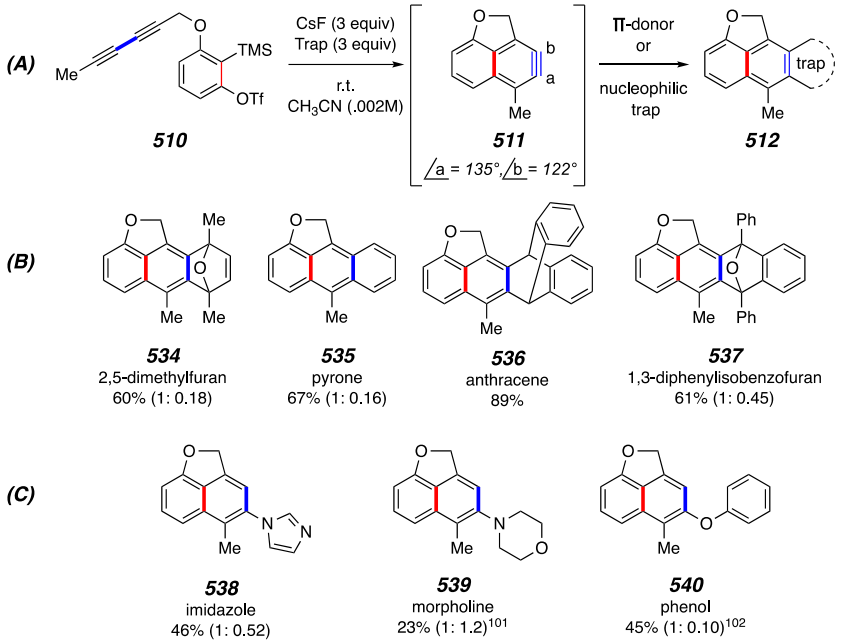
	[furan]$_0$	ratio **532**:**533** (NMR)	isolated yields	
i)	0.06 M	1.0:1.0	48%	50%
ii)	0.006 M	1.0:0.09	78%	8%

Accordingly, with a reduced amount of trapping agent present, the intramolecular closure to **513** outcompeted the intermolecular furan trapping [1.0:0.09 crude NMR ratio, Figure **5.7**, entry **ii**)]. This allowed isolation of the naphthyne adduct **532** in 78% yield.

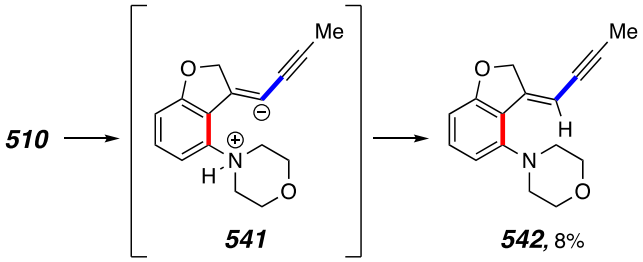
Next, I set out to explore the scope of the reaction with different arynophiles at 0.002M concentration of the diyne **510**. Adducts **534**−**537** arise from trapping by 2,5-dimethylfuran, pyrone (following spontaneous loss of CO_2), anthracene, and 2,5-diphenylfuran, respectively (Panel **B**, Figure **5.8**). ^{1}H NMR spectroscopic analysis of the crude material was used to determine the ratio of naphthyne adduct vs. the prematurely formed benzyne adduct (ratio indicated for each in parenthesis, Figure **5.8**). Among these bimolecular agents, only anthracene gave exclusive naphthyne adduct **538** in a very efficient manner (85% yield). The ratio of the benzyne adduct was even more prominent with the nucleophilic traps, and therefore, adducts **538**−**540** were produced with modest

yields (Panel **C**, Figure **5.8**). The internal bond angles at carbons a and b were computed [DFT, SMD(benzene)/M062X/6-31+G(d,p)] to be 135° and 122°, respectively; the

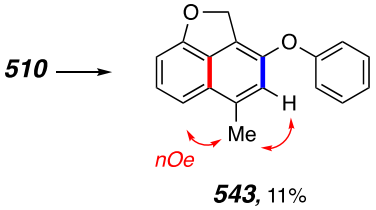
Figure 5.8 | (**A**) Generic reaction of the diyne **510**; (**B**) Adducts from trapping naphthyne **511** through cycloaddition reactions and (**C**) Adducts from trapping with nucleophilic agents.[101,102]



[101] When morpholine was used as a trapping agent, along with the two expected naphthyne and benzyne adducts, enyne **542** was also isolated, presumably by way of intermediate **541**.



[102] Naphthyne and benzyne adducts were accompanied with the minor naphthyne **543** in 11% yield. The minor benzyne was adduct not observed.

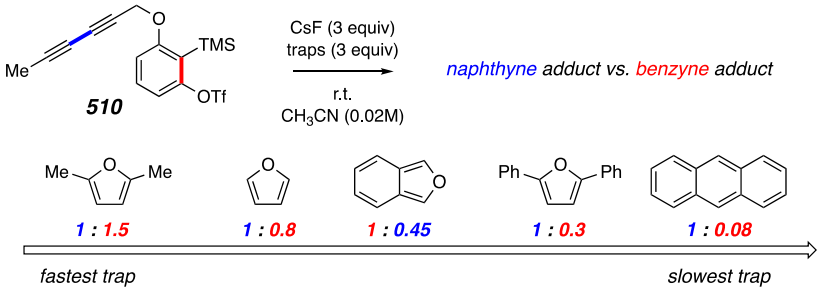


Adduct having attachment of the nucleophile at carbon atom a (C_a) was favored in the three cases. Only in the case of the phenol addition we were able to observe the minor regioisomer at carbon atom b (C_b) in 11% yield.[102]

5.5 Trapping efficiency of different trapping agents.

The premature trapping of the initial aryne by intermolecular trapping agents was frustrating for practical purposes, but it allowed us to quantitatively measure the trapping efficiency of various arynophiles. For this study, 0.02M concentration of the starting diyne **510** was chosen and three equivalents of a trapping agent were used. The trend observed from this study correlated reasonably well with the expected substituent effects (Figure **5.9)**. The greater the steric bulk on the arynophile, higher was the ratio of the naphthyne adduct to the benzyne adduct.

Figure 5.9 | Trapping efficiency of different arynophiles

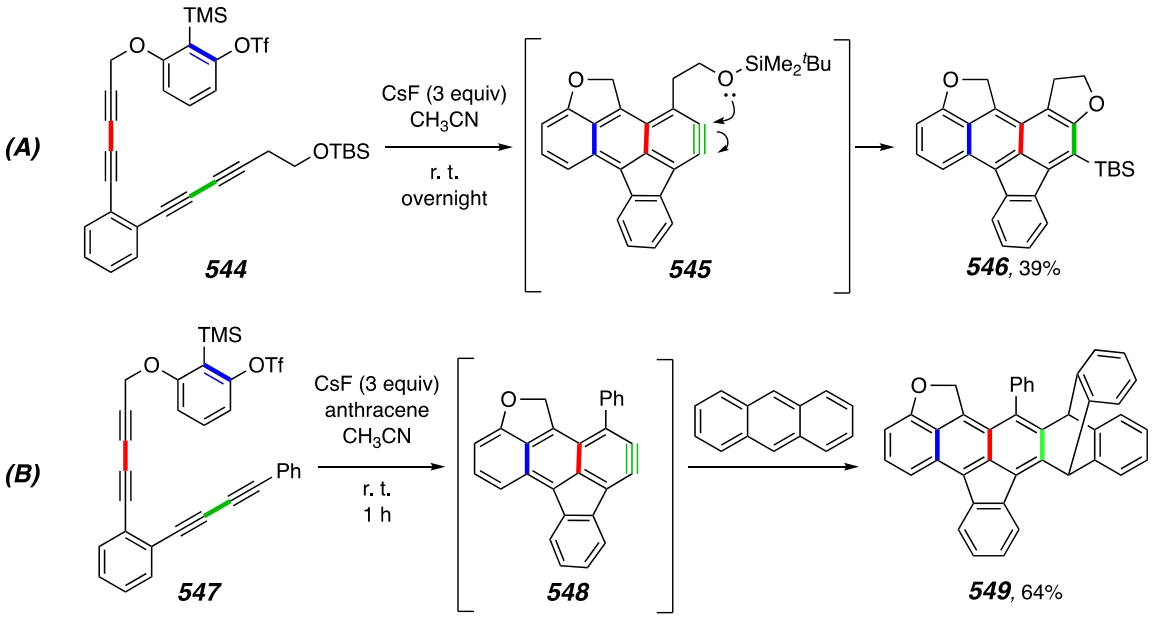


5.6 Anthracyne formation.

I also wanted to explore the extension of the subsequent cycloisomerization process by installing more than one 1,3-diyne unit in the precursors. This extension, in principle, could expand the versatility of this reaction via the formation of the polycyclic anthracyne intermediates. Figure **5.10** represents two examples (one for each intramolecular- and intermolecular- trapping agent) in this category. In the first example, tetrayne **544**, upon treatement with CsF, led to the formation of an anthracyne intermediate **545** by a second HDDA reaction of the naphthyne (not shown here). This

was eventually trapped by the silyl ether to give anthracene derivative **546**. In the second example, anthracyne **548**, which was prepared from the tetrayne **547**, was reacted with anthracene in an intermolecular [4+2]-manner to give rise to a highly fused triptycene derivative **549**. **549**, however, was found to be unstable under ambient conditions and needed to be characterized immediately after isolation. Nonetheless, both of these examples indicate the ease with which highly fused polyacenes derivatives can be synthesized using this method under relatively mild reaction conditions.

Figure 5.10 | (**A**) Intramolecular- and (**B**) intermolecular-trapping of the anthracyne intermediates



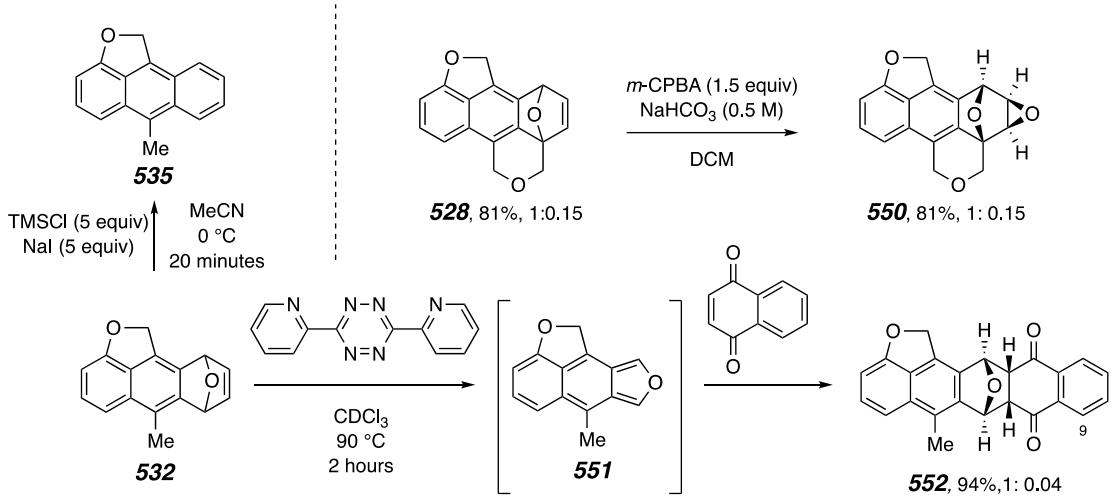
5.7 Derivatization of the benzoxanorbornadiene core.

The benzoxanorbornadiene core synthesized via intermolecular- and intramolecular-trapping of the naphthyne was subjected to further functionalizations. First, **532** was readily converted to the corresponding naphthalene derivative **535** by reductive deoxyaromatization with TMSI (Figure **5.11**).[103] Next, reaction of a suspension

[103] Jung, K. and Koreeda, M. Synthesis of 1,4-, 2,4-, and 3,4- Dimethylphenanthrenes: A Novel Deoxygenation of Arene 1,4-Endoxides with Trimethylsilyl Iodide. *J. Org. Chem.* **1989**, *54*, 5667–5675.

of **532** with 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine in $CDCl_3$ solution at elevated temperatures produced isobenzofuran derivative **551** (concomitant with N_2 elimination), which was directly treated with dienophilic 1,4-naphthoquinone to give predominately *endo* adduct **552.** Oxanorbornadiene **528**, which was formed via intramolecular trapping of the diyne **526** (cf. Figure **5.6**), was subjected to epoxidation using *m*-CPBA to give epoxide **550** as a mixture of diastereomers in 85% yield.

Figure 5.11 | Derivatization of the benzoxanorbornadiene core



5.8 Conclusions.

In summary, we have developed a cascade strategy for naphthyne formation by using Kobayashi benzynes as diynophiles in the HDDA reaction. This transformation only requires mildly basic conditions and allows for rapid construction of various naphthalene products at room temperature (Figures **5.6** and **5.8**). Even though the intermolecular trapping was perturbed by the premature benzyne reactivity (Figure **5.8**), this method allows us to determine the trapping efficiency of various arynophiles (Figure **5.9**). Moreover, we have demonstrated the potential application of this process in the synthesis of large polycyclic arenes (Figure **5.10**).

SUPPLEMENTARY INFORMATION FOR CHAPTER 2

I. General Experimental Protocols

^{13}C and ^{1}H NMR spectra were recorded on an HD-500 or AV-500 (500 MHz) spectrometer. ^{1}H chemical shifts are referenced to TMS (δ 0.00 ppm) in $CDCl_3$ and to the residual CHD_5 resonances (δ 7.15 ppm) in benzene-d_6. Where encountered, a non-first order multiplet in a ^{1}H NMR spectrum is designated as 'nfom'. Data are reported in the following format: chemical shift (ppm) [multiplicity, coupling constant(s) (in Hz), integral (to the nearest whole integer), and assignment of the substructural unit within the overall structure]. This is indicated by, e.g., R^{1}C*Ha*Hb for diastereotopic geminal protons; arbitrarily, the more downfield resonance is labeled as H_a. Coupling constants have been analyzed using protocols previously described.[104,105] The ^{13}C NMR shifts are deciphered from the "1D" spectra.

Infrared spectra were recorded using a Midac Corporation (Prospect 4000) FT-IR spectrometer. Neat or thin films of samples were deposited on a NaCl plate.

High-resolution **mass spectrometry** (HRMS) measurements were made on either a Bruker BioTOF II (ESI-TOF) or Thermo Orbitrap Velos (mass accuracy < 3 ppm) instrument, both in the electrospray ionization mode (ESI). On the Bruker instrument poly(ethylene glycol) (PEG) or poly(propylene glycol) (PPG) was added to the sample as the standard/calibrant. Samples were infused as methanol solutions. HRMS data were collected as approximately 6–7 separate data sets and then averaged to obtain the reported "found" value. On the Velos instrument samples were introduced as a dilute solution in acetonitrile; an external standard/calibrant was used (Pierce™ LTQ).

Medium pressure liquid chromatography (MPLC) was performed on hand-packed columns of silica gel (20-40 μm, 60 Å pore size, Teledyne RediSep Rf Gold® normal-phase) operated at 25-200 psi. The device comprised a Waters HPLC pump (M6000), a Waters (R401) differential refractive index detector, and a Gilson (112 UV) detector. Agela silica gel (230-400 mesh) was used to pack flash chromatography columns. Thin layer chromatography (TLC) was performed on silica gel glass- or plastic-backed plates. These were visualized initially by UV then by dipping into a solution of potassium permanganate or ceric ammonium molybdate (CAM) and heating.

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[104] Hoye, T. R., Hanson, P. R. & Vyvyan, J. R. A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy. *J. Org. Chem*. **59**, 4096-4103 (1994).

[105] Hoye, T. R. & Zhao, H. A Method for Easily Determining Coupling Constant Values: An Addendum to "A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy". *J. Org. Chem*. **67**, 4014–4016 (2002).

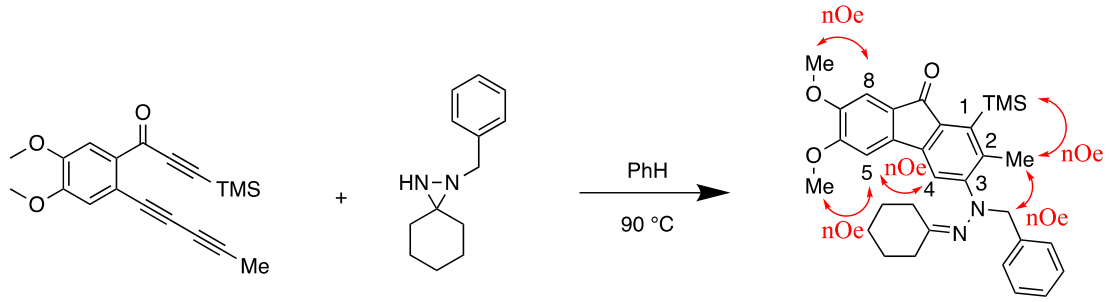
Some compounds were purified by HPLC to achieve mg quantities of samples of high purity, from which the full characterization data set were then collected. This was done in a 10 mm diameter x 250 mm long column of silica gel (Alltech, Econosil, 10 μm).

Unless otherwise noted, reactions performed under anhydrous conditions were carried out in oven-dried glassware under an atmosphere of nitrogen. Anhydrous THF was dried by passage through a column of activated alumina before use. The indicated reaction temperature refers to the temperature of the external cooling or heating bath. HDDA reactions, including those carried out at temperatures higher than the boiling point of the reaction solvent, were performed in a screw-capped vial or culture tube that was fitted with an inert, Teflon®-lined screw cap.

For an experiment performed on a 1 mmol scale of limiting reactant, see page 85 to give products **7ce1** and **7ce2**.

Preparation and Characterization Data for Hydrazones

3-(1-Benzyl-2-cyclohexylidenehydrazinyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (7aa):



6a ***2a*** ***7aa, 88%***

Triynone **6a** (40 mg, 0.123 mmol) and 1-benzyl-1,2-diazaspiro[2.5]octane (**2a**, 50 mg, 0.246 mmol, 2 equiv) were combined in a culture tube, dissolved in benzene (8 mL, 0.02 M), and sealed with a Teflon-lined cap. The solution was heated overnight (18–19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (2:1 Hex:EtOAc) to give **7aa** (0.108 mmol, 88%) as a bright orange oil.

The assignment of the structure of **7aa** was based upon the indicated nOe interactions. The preference for formation of this isomer is consistent with what is predicted on the basis of distortion analysis[10,14,15] of the computed (DFT) geometry.

Data for 7aa:

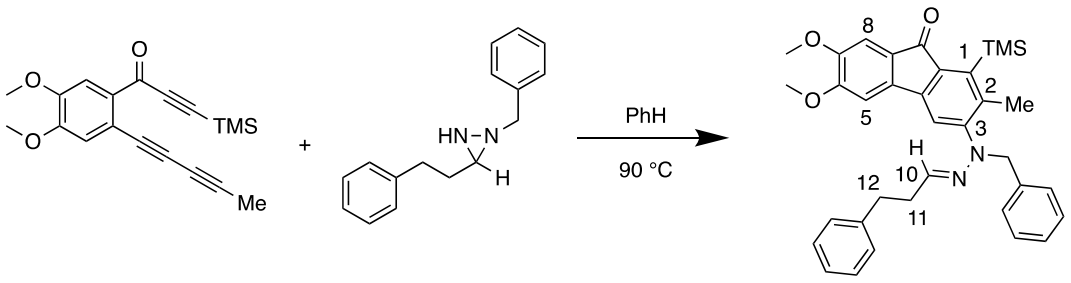
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.4 Hz, 2H, Ar*H*$_o$), 7.34 (s, 1H, Ar*H4*), 7.33 (dd, *J* = 7.4, 7.4 Hz , 2H, Ar*H*$_m$), 7.25 (d, *J* = 7 Hz, 1H, Ar*H*$_p$), 7.11 (s, 1H, Ar*H8*), 6.90 (s, 1H, Ar*H5*), 4.32 (s, 2H, benzylic C*H*$_2$), 3.97 (s, 3H, OC6*H*$_3$), 3.90 (s, 3H, OC7*H*$_3$), 2.55 (s, 3H, $ArCH_3$), 2.34 (t, *J* = 6.7 Hz, 2H, N=CC*H*$_2$), 2.21 (t, *J* = 6.7 Hz, 2H, N=CC*H*$_2$), 1.62 (quin, *J* = 6.6 Hz, 2H, *CH*$_2$), 1.49 (quin, *J* = 6.2 Hz, 2H, *CH*$_2$), 1.33 (quin, *J* = 6.2 Hz, 2H, *CH*$_2$), and 0.44 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 174.3, 157.3, 154.1, 149.4, 143.62, 143.57, 138.7, 135.8, 135.7, 128.9, 128.6, 128.2, 127.2, 127.0, 113.2, 106.7, 102.7, 62.9, 56.4, 56.2, 42.0, 35.7, 30.3, 27.2, 27.0, 25.8, 25.7, 20.1, and 2.8.

IR (CH_2Cl_2): 2939, 2857, 1703, 1588, 1464, 1380, 1352, 1245, 1216, 1092, 1019, 993, and 863 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{32}H_{39}N_2O_3Si^+$ [$M+H^+$] requires 527.2724; found 527.2714

1-Benzyl-2-(3-phenylpropylidene)hydrazinyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (7ab)



6a ***2b*** ***7ab, 85.4%***

Triynone **6a** (25 mg, 0.077 mmol) and 1-benzyl-3-phenethyldiaziridine (**2b**, 37 mg, 0.246 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.02 M). The tube was sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (3:1 Hex:EtOAc) to give **7ab** (0.066 mmol, 85%) as a bright orange oil. This sample was then separately repurified by HPLC (3:1 Hex:EtOAc) to give a sample of **7ab** of higher purity that was used for collection of spectral data.

Data for 7ab:

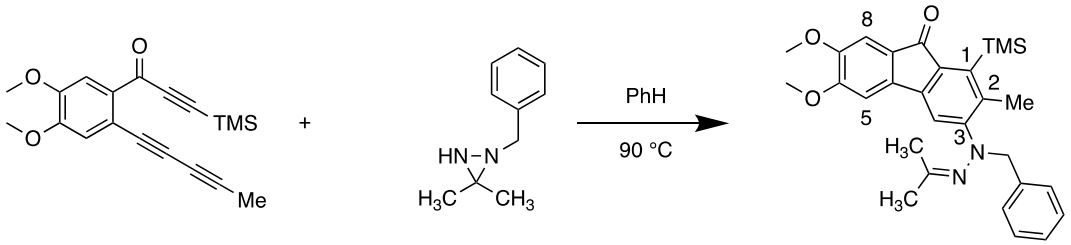
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.26 (m, 5H, Ph*H*), 7.23 (dd, *J* = 7.3, 7.3 Hz, 1H, NCH_2ArH_m), 7.16 (br t, *J* = 7 Hz, 1H, NCH_2ArH_p), 7.12 (s, 1H, Ar*H8*), 7.10 (s, 1H, Ar*H5*), 7.09 (d, *J* = 7 Hz, 2H, NCH_2ArH_o), 6.86 (s, 1H, Ar*H4*), 6.58 (t, *J* = 5.8 Hz, 1H, *H*C=N), 4.70 (s, 2H, ArNCH_2), 4.00 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.76 (t, *J* = 7.7 Hz, 2H, C*12*H_2), 2.57 (td, *J* = 7.7, 5.8 Hz, 2H, C*11*H_2), 2.23 (s, 3H, $ArCH_3$), and 0.40 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 154.2, 151.9, 149.5, 143.9, 143.5, 141.2, 139.1, 138.6, 138.5, 137.5, 137.2, 128.5, 128.5, 128.3, 127.4, 127.1, 127.1, 125.9, 116.2, 106.7, 102.8, 58.0, 56.4, 56.2, 34.6, 33.8, 20.7, and 2.7.

IR (CH_2Cl_2): 3061, 3027, 2939, 2838, 1703, 1588, 1551, 1495, 1454, 1417, 1383, 1316, 1245, 1217, 1150, 1090, 1076, 1045, 1019, 996, 976, 862, 798, 736, and 700 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{35}H_{39}N_2O_3Si^+$ [$M+H^+$] requires 563.2724; found 563.2719.

3-(1-Benzyl-2-(propan-2-ylidene)hydrazinyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (7ac)



6a ***2c*** ***7ac, 99%***

Triynone **6a** (25 mg, 0.077 mmol) and 1-benzyl-3,3-dimethyldiaziridine **2c** (25 mg, 0.154 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.02 M). The tube was sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (1:1 Hex:EtOAc) to give **7ac** (0.076 mmol, 99 %) as a bright orange oil.

Data for 7ac:

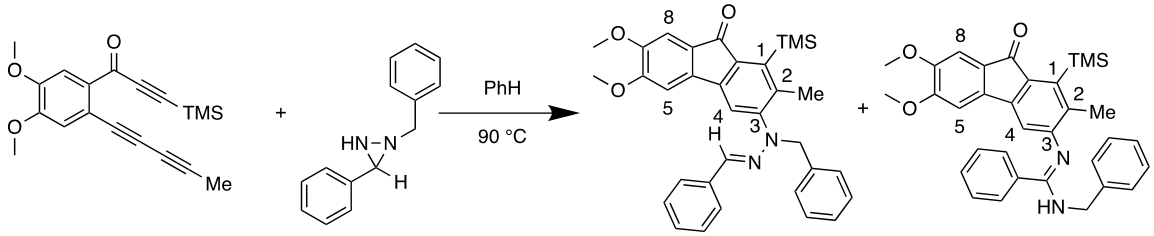
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.24 (m, 6H, Ph*H* and *H4*), 7.12 (s, 1H, Ar*H8*), 6.90 (s, 1H, *H5*), 4.32 (s, 2H, ArNCH_2), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.55 (s, 3H, ArCH_3), 2.01 (s, 3H, CH_3–C=N), 1.70 (s, 3H, CH_3–C=N), and 0.44 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 168.4, 156.7, 154.1, 149.4, 143.6, 143.6, 138.7, 138.6, 136.5, 136.1, 128.5, 128.2, 127.1, 127.0, 113.4, 106.7, 102.8, 63.3, 56.4, 56.2, 25.3, 20.3, 19.8, and 2.8.

HRMS (ESI-TOF): Calcd for $C_{29}H_{35}N_2O_3Si^+$ [M+H$^+$] requires 487.2411; found 487.2409.

IR (CH_2Cl_2): 2951, 2839, 1702, 1636, 1587, 1495, 1315, 1244, 1216, 1091, 1077, 1019, 862, and 797 cm^{-1}.

3-(1-Benzyl-2-benzylidenehydrazinyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (7ad) and *N*-benzyl-*N*'-(6,7-dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)benzimidamide (12ad):



6a ***2d*** ***7ad, 31%*** ***12ad, 45%***

Triynone **6a** (25 mg, 0.077 mmol) and 1-benzyl-3-phenyldiaziridine (**2d**, 25 mg, 0.154 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.02 M). The tube was sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (3:1 Hex:EtOAc) to give, in order of elution, the tertiary amine-trapped adduct **7ad** (11.0 mg, 31%) as a yellow oil and the secondary amine-trapped product **10ad** (16.0 mg, 45%) also as a yellow oil. A small portion of **10ad** was repurified by normal-phase HPLC (3:1 Hex:EtOAc + 1% NEt_3) to give as a yellow oil, which was used for collection of spectral data.

Data for faster eluting tertiary amine-trapped, hydrazone 7ad:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.5 Hz, 2H, Ph*H*), 7.36 (s, 1H, Ar*H4*), 7.25 (s, 1H, Ar*H8*), 7.38–7.22 (m, 8H, PhH_m and PhH_p), 7.19 (s, 1H, Ar*H5*), 7.13 (d, *J* = 7.1 Hz, 1H, PhH_o), 7.12 (s, 1H, Ar*H5*), 6.84 (s, 1H, *H*C=N), 4.89 (s, 2H, ArNCH_2), 3.96 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.30 (s, 3H, ArCH_3), and 0.43 [s, 9H, Si$(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.6, 155.2, 151.2, 150.4, 144.7, 144.2, 140.2, 139.2, 139.0, 137.8, 137.1, 135.9, 129.4, 129.3, 128.7, 128.6, 128.1, 127.8, 126.7, 118.2, 107.5, 103.6, 59.5, 57.2, 57.0, 21.3, and 3.5.

IR (CH_2Cl_2): 2840, 2685, 1704, 1588, 1495, 1455, 1383, 1317, 1217, 1150, 1098, 1048, 1075, 1019, 997, and 860 cm^{-1}

HRMS (ESI-TOF): Calcd for $C_{33}H_{35}N_2O_3Si^+$ [M+H$^+$] requires 535.2411, found 535.2400.

Data for slower eluting secondary amine-trapped, amidine 12ad:

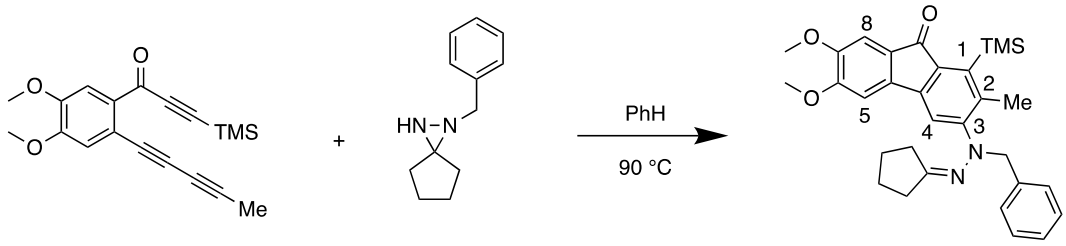
^{1}H NMR (500 MHz, $CDCl_3$): 7.42–7.31 (m, 10H, PhH), 7.06 (s, 1H, Ar*H8*), 6.69 (s, 1H, Ar*H5*), 6.47 (br s, 1H, Ar*H4*), 4.99 [br t, *J* = 5.3 Hz, 1H, (C=N)N*H*)], 4.67 [br d, *J* = 4.6 Hz, 2H, Ar(CH_2)N], 3.92 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 2.24 (s, 3H, ArCH_3), and 0.37 [s, 9H, Si$(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 193.9, 156.2 (br, HMBC from CH_2N), 153.6, 149.2, 143.4, 142.2, 138.9, 138.5, 135.0, 134.7, 134.2, 129.9, 128.7, 128.6, 127.8 (2x), 127.6, 127.5, 114.1, 106.5, 102.5, 56.3, 56.2, 46.4 (br, HSQC from CH_2N), 19.4, and 2.7 (one aromatic carbon was not observed).

HRMS (ESI-TOF): Calcd for $C_{33}H_{35}N_2O_3Si^+$ [M+H$^+$] requires 535.2411, found 535.2421.

IR (CH_2Cl_2): 3380, 2948, 1695, 1627, 1576, 1493, 1469, 1423, 1382, 1311, 1243, 1216, 1185, 1156, 1134, 1090, 1076, 1052, 1019, 873 848, 749, and 699 cm^{-1}.

3-(1-Benzyl-2-cyclopentylidenehydrazinyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (7ae):



6a ***2e*** ***7ae, 99%***

Triynone **6a** (20 mg, 0.062 mmol) and 1-benzyl-1,2-diazaspiro[2.4]heptane **2e** (25 mg, 0.129 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath held at 90 °C and then allowed to cool to room temperature. The residue was purified by MPLC (1:1 Hex:EtOAc) to give **7ae** (31 mg, 0.061 mmol, 99%) as a bright orange oil.

Data for 7ae:

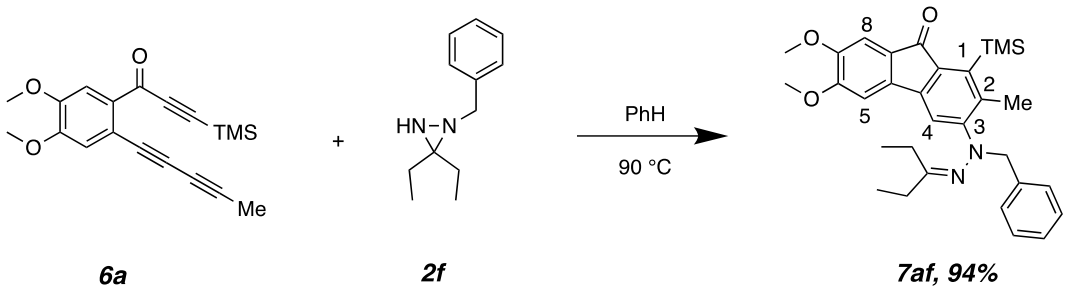
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 6H, Ph*H* and *H4*), 7.12 (s, 1H, Ar*H8*), 6.91 (s, 1H, Ar*H5*), 4.31 (s, 2H, benzylic CH_2), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.52 (s, 3H, ArCH_3), 2.41 [t, *J* = 7.6 Hz, 2H, N=C(*CH*$_2$)'], 2.05 [t, *J* = 7.6 Hz, 2H, N=C(*CH*$_2$)], 1.65 (m, 4H, N=C(CH_2)$_2$*(CH*$_2$*)*$_2$, and 0.43 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 180.2, 156.5, 154.2, 149.4, 143.6, 143.5, 138.7, 137.2, 136.3, 128.6, 128.5 (from HMBC), 128.2, 127.1, 127.0, 113.9, 106.7, 102.8, 63.5, 56.4, 56.2, 33.6, 31.2, 24.6, 24.5, 19.6, and 2.6.

HRMS (ESI-TOF): Calcd for $C_{31}H_{37}N_2O_3Si^+$ [M+H$^+$] requires 513.2568; found 513.2566.

IR (CH_2Cl_2): 2956, 1703, 1644, 1587, 1494, 1454, 1379, 1316, 1245, 1216, 1147, 1091, 1020, 993, 862, 797, 733, and 669 cm^{-1}.

3-(1-Benzyl-2-(pentan-3-ylidene)hydrazinyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (7af):



6a ***2f*** ***7af, 94%***

Triynone **6a** (25 mg, 0.077 mmol) and 1-benzyl-3,3-diethyldiaziridine **2f** (30 mg, 0.154 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath held at 95 °C and then cooled to room temperature. The residue was purified by MPLC (3:1 Hex:EtOAc) to give **7af** (0.072 mmol, 94%) as a bright orange oil.

Data for 7af:

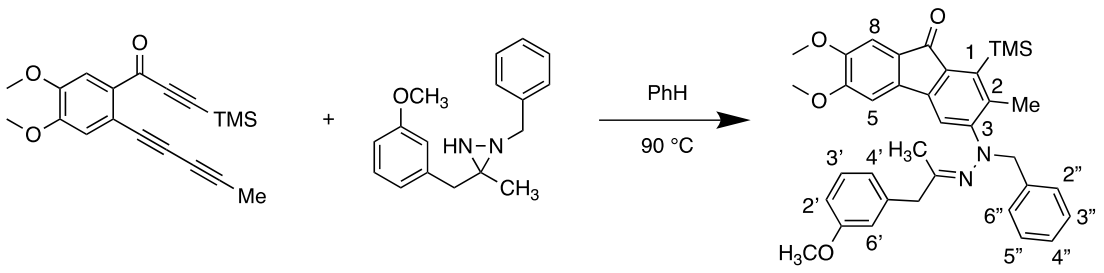
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.24 (m, 6H, Ph*H* and *H4*), 7.11 (s, 1H, Ar*H8*), 6.88 (s, 1H, Ar*H5*), 4.28 (s, 2H, benzylic CH_2), 3.97 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.58 (s, 3H, ArCH_3), 2.30 [q, *J* = 7.6 Hz, 2H, (N=C)CH_2CH_2], 2.12 [q, *J* = 7.6 Hz, 2H, (N=C)CH_2CH_2], 1.07 [t, *J* = 7.6 Hz, 2H, (N=C)CH_2CH_2], 0.77 [t, *J* = 7.6 Hz, 2H, (N=C)CH_2CH_2], and 0.45 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 193.9, 177.3, 157.5, 154.1, 149.4, 143.5, 138.7, 138.5, 136.1, 135.8, 129.0, 128.6, 128.1, 127.2, 127.0, 113.3, 106.7, 102.6, 63.3, 56.3, 56.2, 28.9, 24.7, 19.9, 11.5, 9.9, and 2.8.

IR (CH_2Cl_2): 3061, 2928, 2851, 1702, 1588, 1495, 1464, 1420, 1383, 1354, 1216, 1245, 1216, 1150, 1092, 1077, 1048, 1019, 997, 861, 793, and 737 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{31}H_{39}N_2O_3Si^+$ [M+H^+] requires 515.2724; found 515.2724.

3-(1-Benzyl-2-(1-(3-methoxyphenyl)propan-2-ylidene)hydrazinyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (7ag):



6a ***2g*** ***7ag, 69%***

Triynone **6a** (40 mg, 0.123 mmol) and 1-benzyl-3-(3-methoxybenzyl)-3-methyldiaziridine **2g** (66 mg, 0.246 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath held at 90 °C and then cooled to room temperature. The residue was purified by MPLC (3:1 Hex:EtOAc) to give **7ag** (0.084 mmol, 68% yield) as a yellow oil.

Data for 7ag [the sample contains ca. 6% of what was judged to be the isomeric (and co-eluting) *Z*-hydrazone]:

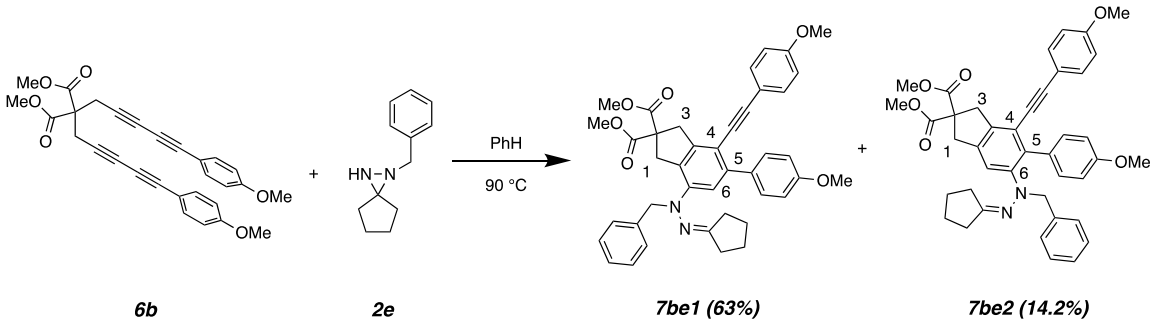
^{1}H NMR (500 MHz, $CDCl_3$): 7.40 (d, *J* = 7.2 Hz, 2H, *H2"* and *H6"*), 7.34 (t, *J* = 7.4 Hz, 2H, *H5"* and *H3'"*), 7.31 (s, 1H, *H4*), 7.28 (t, *J* = 7.3 Hz, 1H, *H4'"*), 7.12 (s, 1H, *H8*), 7.10 (dd, 1H, *J* = 7.7, 7.7 Hz, *H3'*), 6.88 (s, 1H, *H5*), 6.71 (dd, *J* = 8.2, 2.5 Hz, 1H, *H2'*), 6.65 (s, 1H, *H6'*), 6.60 (d, *J* = 7.6 Hz, 1H, *H4'*), 4.40 (s, 2H, NCH_2Ph), 4.00 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.56 [s, 2H, CH_2(C=N)CH_3], 2.54 (s, 3H, NArCH_3), 1.61 [s, 3H, CH_2(C=N)CH_3], and 0.43 [s, 9H, Si(CH_3)$_3$]. [Minor resonances consistent with the presence of the *Z*-hydrazone were observed at 1.86 (s, CH_3C=N), 2.62 (ArCH_3), 3.54 (CH_2C=N), and 4.35 (NCH_2Ph).]

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 168.8, 159.7, 156.4, 154.2, 149.5, 143.7, 143.6, 138.8, 138.5, 136.6, 136.2, 129.5, 128.5, 128.3, 127.1, 127.0, 121.3, 114.9, 113.6, 111.8, 106.7, 102.8, 63.3, 56.4, 56.2, 55.1, 45.5, 19.7, 18.6, and 2.8. (resonance for one aromatic carbon atom not observed).

HRMS (ESI-TOF): Calcd for $C_{36}H_{41}N_2O_4Si^+$ [M+H$^+$] requires 593.2830; found 593.2820.

IR (CH_2Cl_2): 2838, 2685, 2410, 1702, 1640, 1600, 1495, 1422, 1315, 1216, 1149, 1091, and 862 cm^{-1}.

Dimethyl 7-(1-benzyl-2-cyclopentylidenehydrazineyl)-5-(4-methoxyphenyl)-4-((4-methoxyphenyl)ethynyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (7be1) and dimethyl 6-(1-benzyl-2-cyclopentylidenehydrazineyl)-5-(4-methoxyphenyl)-4-((4-methoxyphenyl)ethynyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (7be2)



6b ***2e*** ***7be1 (63%)*** ***7be2 (14.2%)***

Tetrayne **6b** (20 mg, 0.043 mmol) and 1-benzyl-1,2-diazaspiro[2.4]heptane **2e** (16 mg, 0.085 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.01 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18–19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (2:1 Hex:EtOAc) to give, in order of elution, **7be1** (63.4%) and **7be2** (14.2%), each as a transparent oil. The assignment of the structure of each of these was based upon observed (difference) nOe interactions between the aromatic proton and the adjacent aromatic proton (PhH_m to OMe group) or methylene protons, respectively.

Data for faster eluting, major isomer 7be1:

^{1}H NMR (500 MHz, $CDCl_3$): 7.52 [d, *J* = 8.4 Hz, 2H, ArH_m (to OMe)], 7.36 (d, 2H, *J* = 7.5 Hz, 2H, PhH_o), 7.33–7.24 [m, 5H, Ar'H_m (to OMe), PhH_m and PhH_p], 7.01 (s, 1H, Ar*H6*), 6.94 [d, *J* = 7.6 Hz, 2H, Ar'H_o (to OMe)], 6.83 [d, *J* = 7.9 Hz, 2H, Ar'H_o (to OMe)], 4.48 (s, 2H, NCH_2Ph), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.81 (s, 2H, C1H_2 or C3H_2), 3.77 (s, 6H, CO_2CH_3), 3.57 (s, 2H, C1H_2 or C3H_2), 2.39 [t, *J* = 7.1 Hz, 2H, N=C*(CH$_2$)*(CH_2)], 2.01 [t, *J* = 7.1 Hz, 2H, N=C*(C'H$_2$)*(CH_2)], and 1.61 [m, 4H, N=C(CH_2)$_2$*(CH$_2$)$_2$*].

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4, 172.1, 159.4, 159.0, 148.2, 144.6, 143.2, 138.9, 132.9, 132.7, 131.6, 130.4, 128.5, 128.2, 126.9, 121.0, 115.9, 113.9, 113.2, 113.1, 95.2, 86.2, 62.9, 59.8, 55.3, 53.0 (2x), 41.2, 39.8, 33.5, 31.0, 24.8, and 24.4.

HRMS (ESI-TOF): Calcd for $C_{41}H_{41}N_2O_6^+$ [M+H$^+$] requires 657.2959; found 657.2947.

IR (CH_2Cl_2): 2957, 2859, 2350, 1733, 1644, 1607, 1511, 1664, 1436, 1248, 1203, 1176, 1107, 1032, 960, and 834 cm^{-1}.

Data for slower eluting, minor isomer 7be2:

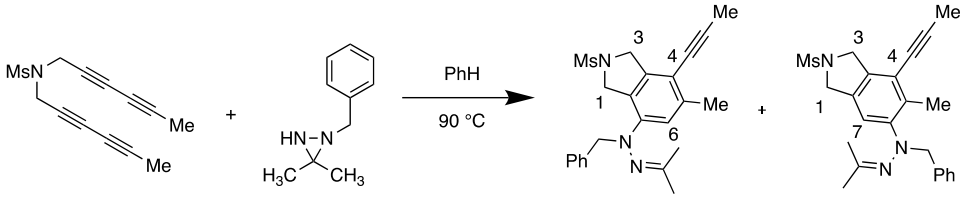
^{1}H NMR (500 MHz, $CDCl_3$): 7.40 [d, *J* = 8.1 Hz, 2H, ArH_m (to OMe)], 7.21 (s, 1H, Ar*H7*), 7.14 [d, *J* = 8.4 Hz, 2H, Ar'H_m (to OMe)], 7.12–7.09 (m, 3H, Ph*H*), 7.00 [d, *J* = 8.2 Hz, 2H, ArH_o (to OMe)], 6.78 [d, *J* = 8.3 Hz, 2H, Ar'H_o (to OMe)], 6.76 (nfom, 2H, Ph*H*), 4.09 (s, 2H, N-CH_2-Ph), 3.87 (s, 3H, OCH_3), 3.78 (s, 9H, OCH_3), 3.75 (s, 2H, C1H_2 or C3H_2), 3.62 (s, 2H, C1H_2 or C3H_2), 2.32 [t, *J* = 7.0 Hz, 2H, N=C*(CH$_2$)*(CH_2)], 1.98 [t, *J* = 7.4 Hz, 2H, N=C*(C'H$_2$)*(CH_2)], and 1.62–1.50 [m, 4H, N=C(CH_2)$_2$*(CH$_2$)$_2$*].

^{13}C NMR (125 MHz, $CDCl_3$): 179.7, 172.2, 159.5, 158.7, 150.8, 139.4, 138.9, 137.4, 136.5, 132.9, 131.9, 131.6, 129.0, 127.6, 126.6, 121.0, 116.6, 115.6, 113.8, 113.4, 96.3, 86.1, 63.6, 59.6, 55.5, 55.3, 53.1, 41.1, 40.7, 33.4, 31.5, 24.7, and 24.3.

HRMS (ESI-TOF): Calcd for $C_{41}H_{41}N_2O_6^+$ [M+H$^+$] requires 657.2959; found 657.2945.

IR (CH_2Cl_2): 2955, 2837, 2360, 2206, 1735, 1606, 1511, 1436, 1247, 1200, 1173, 1106, 1071, 1031, and 833 cm^{-1}.

7-(1-Benzyl-2-(propan-2-ylidene)hydrazinyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7cc1) and 6-(1-benzyl-2-(propan-2-ylidene)hydrazinyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7cc2):



6c ***2c*** ***7cc1*** ***7cc2***

93%** overall **(7cc1: 7cc2= 1: 1.8)

Tetrayne **6c** (50 mg, 0.202 mmol) and 1-benzyl-3,3-dimethyldiaziridine (**2c**, 65.6 mg, 0.404 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (10 mL, 0.02 M). The tube was sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (1:1 Hex:EtOAc) to give, in order of elution, **7cc1** as a yellow oil and **7cc2** also as a yellow oil, which solidified upon storage at -10 °C (93% combined yield, 0.158 mmol). The assignment of the structure of each of these was based upon observed nOe interactions between the aromatic proton and the adjacent benzylic methyl or methylene protons, respectively.

Data for faster eluting, minor isomer 7cc1:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H, PhH), 6.85 (s, 1H, Ar*H6*), 4.66 (s, 2H, ArNC*H*$_2$), 4.53 (s, 2H, MsNC1*H*$_2$ or MsNC3*H*$_2$), 4.37 [s, 2H, N(Ms)C1*H*$_2$ or N(Ms)C3*H*$_2$], 2.80 (s, 3H, C*H*$_3$SO$_2$N), 2.33 (s, 3H, NArC*H*$_3$), 2.09 (s, 3H, C≡CC*H*$_3$), 1.99 (s, 3H, [(C*H*$_3$)$_2$C=N], and 1.70 (s, 3H, [(C*H*$_3$)$_2$C=N].

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 146.4, 141.1, 140.4, 137.9, 128.5, 128.3, 127.2, 125.3, 120.1, 113.2, 93.3, 75.4, 62.0, 54.3, 54.1, 34.5, 25.0, 20.4, 19.7, and 4.6.

IR (CH_2Cl_2): 2919, 2854, 2685, 2231, 1606, 1496, 1422, 1339, 1157, 1080, and 960 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{28}N_3O_2S^+$ [$M+H^+$] requires 410.1897; found 410.1893

Data for slower eluting, major isomer 7cc2::

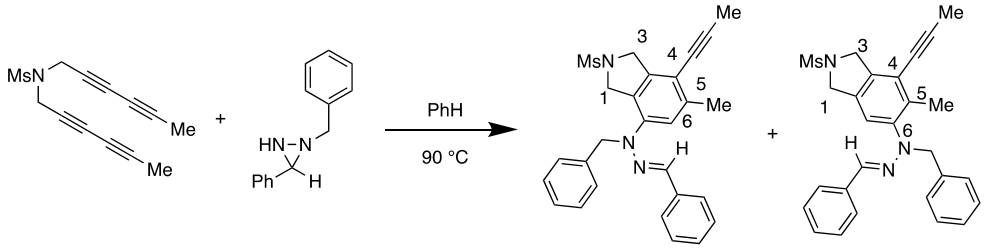
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34- 7.06 (m, 5H, PhH), 7.06 (s, 1H, Ar*H7*), 4.68 (s, 2H, N-C*H*$_2$-Ph), 4.62 [s, 2H, N(Ms)C1*H*$_2$], 4.22 [s, 2H, N(Ms)C3*H*$_2$], 2.86 (s, 3H, C*H*$_3$SO$_2$N), 2.50 (s, 3H, NArC*H*$_3$), 2.12 (s, 3H, C≡CC*H*$_3$), 1.93 (s, 3H, [(C*H*$_3$)$_2$C=N], and 1.63 (s, 3H, [(C*H*$_3$)$_2$C=N].

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 152.5, 138.9, 134.4, 133.8, 133.8, 128.5, 128.1, 126.9, 120.1, 115.6, 94.8, 75.7, 63.5, 54.3, 54.2, 34.7, 25.2, 19.9, 16.0, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{23}H_{28}N_3O_2S^+$ [$M+H^+$] requires 410.1897; found 410.1892.

IR (CH_2Cl_2): 2986, 2920, 2855, 2685, 2232, 1590, 1496, 1455, 1422, 1339, 1156, 1078, 960, and 824 cm^{-1}.

7-(1-Benzyl-2-benzylidenehydrazinyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7cd1) and 6-(1-benzyl-2-benzylidenehydrazinyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7cd2):



6c ***2d*** ***7cd1 (14%)*** ***7cd2 (38%)***

Tetrayne **6c** (60 mg, 0.243 mmol) and 1-benzyl-3-phenyldiaziridine (**2d**, 102 mg, 0.486 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (12 mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath held at 90 °C and then allowed to cool to room temperature. The residue was purified by MPLC (3:1 Hex:EtOAc) to give, in order of elution, **7cd1** (14%, 0.033 mmol) as a flaky white powder and **7cd2** (38%, 0.092 mmol) as a transparent oil, which solidified to a white material upon storage at -10 °C. A small portion of **7cd1** was repurified by normal-phase HPLC (3:1 Hex:EtOAc) to give **7cd1** as a white amorphous powder, which was used for collection of spectral data. The assignment of the structure of each of these was based upon observed nOe interactions (difference nOe) between the aromatic proton and the adjacent benzylic methyl or methylene protons, respectively, for **7cd1** or **7cd2**.

Data for faster eluting minor isomer 7cd1:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.3 Hz, 2H, PhH_o), 7.38–7.30 (m, 7H, PhH_m, PhH_p, Ph'H_m, Ph'H_p, and Ph*H*C=N), 7.22 (d, *J* = 7.2 Hz, 2H, Ph'H_o), 6.60 (s, 1H, *H6*), 5.21 (s, 2H, N(Ms)$C1H_2$ or N(Ms)$C3H_2$), 5.18 (s, 2H, N(Ms)$C1H_2$ or N(Ms)$C3H_2$), 4.74 (s, 2H, N-CH_2-Ph), 2.89 (s, 3H, CH_3SO_2N), 2.33 (s, 3H, NArCH_3), and 2.11 (s, 3H, NArC≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): 142.4, 141.4, 141.0, 135.7, 134.8, 134.5, 129.2, 128.8, 128.3, 127.5, 126.3, 125.9, 121.2, 114.7, 111.5, 93.1, 75.4, 57.2, 54.1, 51.3, 34.4, 20.5, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{27}H_{28}N_3O_2S^+$ [M+H$^+$] requires 458.1897; found 458.1892.

IR (CH_2Cl_2): 2916, 2849, 1606, 1588, 1564, 1496, 1465, 1415, 1327, 1183, 1152, 1123, 1071, 962, and 825 cm^{-1} (alkyne stretching frequency was not observed).

Data for slower eluting major isomer 7cd2:

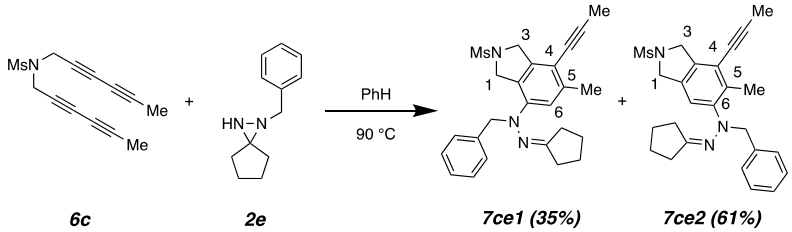
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.4 Hz, 2H, PhH_o), 7.32–7.26 (m, 7H, PhH), 7.21 (br t, *J* = 7.4 Hz, 1H, PhH_p), 6.95 (s, 1H, Ph-C*H*=N), 6.88 (s, 1H, Ar*H7*), 4.84 (s, 2H, N-CH_2-Ph), 4.72 (s, 2H, N(Ms)C3H_2), 4.63 (s, 2H, N(Ms)$C1H_2$), 2.88 (s, 3H, CH_3SO_2N), 2.28 (s, 3H, NArCH_3), and 2.12 (s, 3H, NArC≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 137.4, 137.3, 137.2, 136.3, 134.2, 134.0, 128.5, 128.5, 128.0, 127.7, 127.3, 125.8, 120.6, 119.9, 95.5, 75.4, 59.8, 54.2 (2x), 34.9, 16.4, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{27}H_{28}N_3O_2S^+$ [M+H$^+$] requires 458.1897; found 458.1892.

IR (CH_2Cl_2): 2920, 2854, 2231, 1641, 1588, 1562, 1495, 1454, 1422, 1340, 1156, 1075, 1001, 960, and 825 cm^{-1}.

7-(1-Benzyl-2-cyclopentylidenehydrazinyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7ce1) and 6-(1-benzyl-2-cyclopentylidenehydrazinyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7ce2):



Tetrayne **6c** (40 mg, 0.162 mmol) and 1-benzyl-1,2-diazaspiro[2.4]heptane (**2e**, 60.9 mg, 0.323 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (8 mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18–19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (2:1 Hex:EtOAc) to give, in order of elution, **7ce1** (35%) and **7ce2** (61%), each as a transparent oil. The assignment of the structure of each of these was based upon observed nOe interactions (difference nOe) between the aromatic proton and the adjacent benzylic methyl or methylene protons, respectively.

This reaction was also performed on a 1 mmol scale. Namely, a mixture of tetrayne **6c** (247 mg, 1 mmol, 1 equiv) and 1-benzyl-1,2-diazaspiro[2.4]heptane (**2e**, 377 mg, 2 mmol, 2 equiv) was dissolved in benzene in a 55 mL threaded culture tube, sealed with a Teflon-lined screw-cap, and heated overnight at 90 °C. The products **7ce1** (159 mg, 0.37 mmol, 37%) and **7ce2** (225 mg, 0.50 mmol, 50%) were isolated using the purification conditions described above.

Data for faster eluting, minor isomer 7ce1:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.24 (m, 5H, Ar*H*), 6.89 (s, 1H, NAr*H*), 4.65 (s, 2H, NC*H*$_2$Ph), 4.47 (s, 2H, N(Ms)C1*H*$_2$ or N(Ms)C3*H*$_2$), 4.41 (s, 2H, N(Ms)*C1H*$_2$ or N(Ms)*C3H*$_2$), 2.78 (s, 3H, C*H*$_3$SO$_2$N), 2.41 [t, *J* = 7.7 Hz, 2H, N=C*(CH*$_2$*)*(CH$_2$)], 2.33 (s, 3H, ArC*H*$_3$), 2.09 (s, 3H, ≡CC*H*$_3$), 2.00 [t, *J* = 7.7 Hz, 2H, N=C*(C'H*$_2$*)*(CH$_2$)] and 1.71-1.60 (m, 4H, N=C(CH$_2$)$_2$*(CH*$_2$*)*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 179.0, 146.3, 141.1, 140.2, 138.0, 128.5, 128.3, 127.2, 126.0, 120.8, 113.5, 93.5, 75.3, 62.6, 54.3, 54.1, 34.5, 33.6, 31.0, 24.7, 24.4, 20.4, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{25}H_{30}N_3O_2S^+$ [M+H$^+$] requires 436.2053; found 436.2047.

IR (CH_2Cl_2): 2966, 2685, 1604, 1495, 1479, 1453, 1422, 1139, 1157, 1081, and 960 cm^{-1}.

Data for slower eluting, major isomer 7ce2:

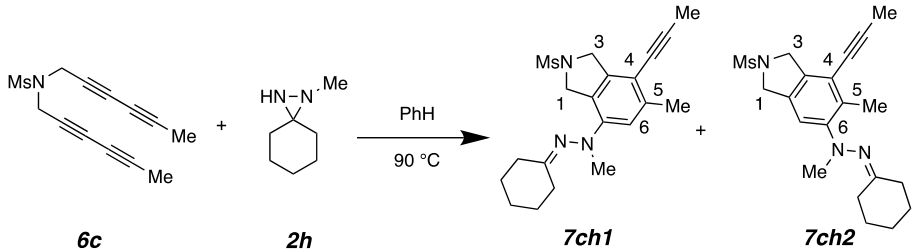
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.22 (m, 5H, Ar*H*), 7.09 (s, 1H, NAr*H*), 4.68 (s, 2H, NC*H*$_2$Ph), 4.63 (s, 2H, N(Ms)C1*H*$_2$ or N(Ms)C3*H*$_2$), 4.24 (s, 2H, N(Ms)*C1H*$_2$ or N(Ms)*C3H*$_2$), 2.88 (s, 3H, C*H*$_3$SO$_2$N), 2.46 [t, *J* = 7.7 Hz, 2H, N=C*(CH*$_2$*)*(CH$_2$)], 2.34 (s, 3H, ArC*H*$_3$), 2.12 (s, 3H, C≡C*H*$_3$), 1.91 [t, *J* = 7.7 Hz, 2H, N=C*(C'H*$_2$*)*(CH$_2$)]. and 1.61 (m, 4H, N=C(CH$_2$)$_2$*(CH*$_2$*)*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 152.3, 138.9, 134.7, 134.5, 133.9, 128.5, 128.1, 126.9, 120.0, 116.3, 94.8, 75.7, 63.8, 54.3, 54.2, 34.9, 33.5, 30.9, 24.7, 24.4, 15.8, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{25}H_{30}N_3O_2S^+$ [$M+H^+$] requires 436.2053; found 436.2044.

IR (CH_2Cl_2): 2967, 1603, 1495, 1480, 1453, 1422, 1338, 1207, 1157, 1080 and 960 cm^{-1}.

7-(2-Cyclohexylidene-1-methylhydrazineyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7ch1) and 6-(2-cyclohexylidene-1-methylhydrazineyl)-5-methyl-2-(methylsulfonyl)-4-(prop-1-yn-1-yl)isoindoline (7ch2):



***91%** (overall)*
regiomeric ratio 7ch1: 7ch2= 1:2.7 (NMR)

Tetrayne **6c** (50 mg, 0.202 mmol) and 1-methyl-1,2-diazaspiro[2.5]octane (**2h**, 65.6 mg, 0.404 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (10 mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18–19 h) in an oil bath held at 90 °C and allowed to cool to room temperature. The residue was purified by MPLC (1:1 Hex:EtOAc) to give a mixture of coeluting regioisomers in ratio of 1:2.7 (NMR) ratio (91% combined yield, 0.166 mmol). A small portion of this mixture was further separated using HPLC (1:1 Hex:EtOAc) to give, in order of elution, **7ch1** as a transparent oil and **7ch2** also as a transparent oil, corresponding to the minor and major isomers, respectively. Both of the products solidified upon storage at -10 °C. The assignment of the structure of each of these was based upon observed (difference) nOe interactions between the aromatic proton and the adjacent benzylic methyl or methylene protons, respectively.

Data for faster eluting, minor isomer 7ch1:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (s, 1H, Ar*H6*), 4.65 (s, 2H, MsNC1H_2 or MsNC3H_2), 4.61 [s, 2H, N(Ms)C1H_2 or N(Ms)C3H_2], 2.87 (s, 3H, NCH_3), 2.82 (s, 3H, CH_3SO_2N), 2.52 (t, J = 6.2 Hz, 2H, N=CCH_2), 2.38 (t, J = 6.2 Hz, 2H, N=CC'H_2), 2.38 (s, 3H, NArCH_3), 2.09 (s, 3H, C≡CCH_3), 1.79 (quin, J = 7.0 Hz, 2H, NCH_2CH_2], and 1.69–1.64 [m, 4H, $NC'H_2(CH_2)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 146.5, 140.9, 140.5, 123.4, 115.8, 111.5, 92.6, 75.6, 55.0, 54.2, 41.9, 35.5, 34.2, 29.3, 27.2, 26.1, 25.7, 20.5, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{20}H_{28}N_3O_2S^+$ [M+H$^+$] requires 374.1902; found 374.1894.

IR (CH_2Cl_2): 2927, 2856, 1705, 1604, 1445, 1332, 1225, 1151, 1077, 1034, 962, 826, 755, 734, 702, and 621 cm^{-1}.

Data for slower eluting, major isomer 7ch2:

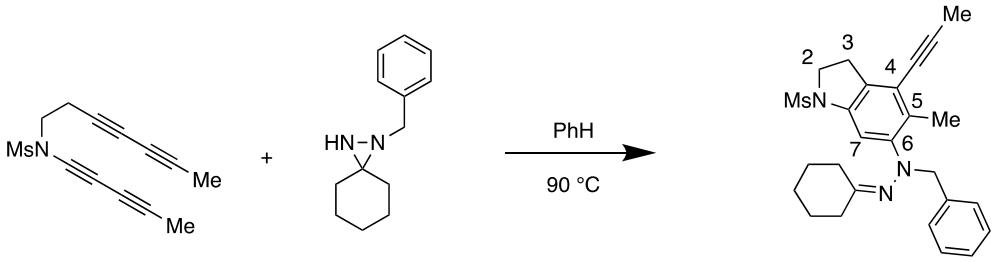
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 1H, Ar*H7*), 4.67 (s, 2H, MsNC3H_2), 4.64 (s, 2H, MsNC1H_2), 2.85 (s, 3H, CH_3SO_2N), 2.83 (s, 3H, NCH_3), 2.39 (s, 3H, NArCH_3), 2.32 (t, J = 6.3 Hz, 2H, N=CCH_2), 2.12 (s, 3H, C≡CCH_3), 1.71 (quin, J = 6.3 Hz, 2H, NCH_2CH_2], 1.57 (quin, J = 5.3 Hz, 2H, $NC'H_2CH_2$), and 1.51 (quin, J = 5.3 Hz, 2H, $NCH_2CH_2CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 153.8, 134.0, 133.697, 133.688, 120.1, 114.3, 94.5, 75.8, 54.4, 54.2, 46.1, 35.6, 34.6, 29.6, 27.2, 25.8, 25.7, 16.1, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{20}H_{28}N_3O_2S^+$ [M+H$^+$] requires 374.1902; found 374.1890.

IR (CH_2Cl_2): 2929, 2856, 1705, 1632, 1591, 1448, 1333, 1296, 1269, 1151, 1076, 1029, 960, 878, and 824.

6-(1-Benzyl-2-cyclohexylidenehydrazinyl)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (7da)



6d ***2a*** ***7da, 71%***

Tetrayne **6d** (30 mg, 0.121 mmol) and 1-benzyl-1,2-diazaspiro[2.5]octane (**2a,** 50 mg, 0.242 mmol, 2 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.02 M), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (2:1 Hex:EtOAc) to give **7da** (0.158 mmol, 72%) as a faint yellow oil.

Data for 7da (has 6% of the other regioisomer as well, inseparable through MPLC):

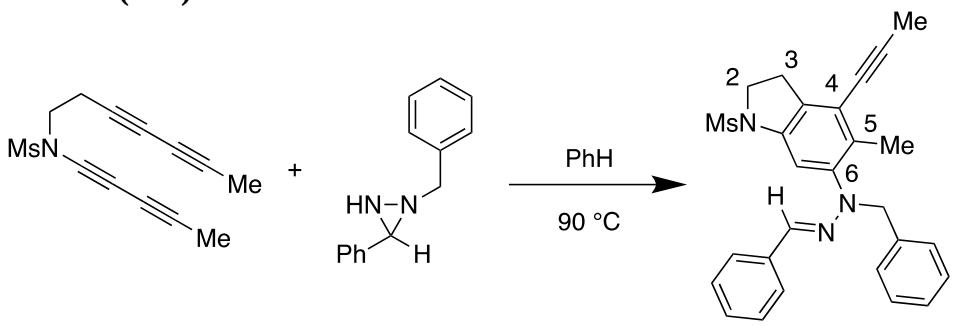
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.5 Hz, 2H, ArH_o), 7.29-7.26 (dd, *J* = 7.2, 7.2 Hz, 2H, ArH_m), 7.20 (d, *J* = 7.3 Hz, 1H ArH_p), 7.18 (s, 1H, *H7*), 3.91 (t, *J* = 8.3 Hz, 2H, MsNCH_2), 3.10 (t, *J* = 8.3 Hz, 2H, MsNCH$_2$CH_2), 2.70 (s, 3H, CH_3SO$_2$N), 2.42 (s, 3H, NArCH_3), 2.27 (t, *J* = 6.7 Hz, 2H, N=CCH_2), 2.13 (s, 3H, NArC≡CH_3), 2.13 (t, *J* = 6.7 Hz, 2H, N=CCH_2), 1.63 (quin, *J* = 6.6 Hz, 2H, CH_2), 1.48 (quin, *J* = 6.2 Hz, 2H, CH_2), and 1.33 (quin, *J* = 6.2 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 152.3, 139.9, 139.0, 129.1, 128.8, 128.6, 128.0, 126.7, 122.0, 107.6, 94.0, 76.3, 62.4, 50.4, 35.6, 34.2, 30.1, 28.0, 27.1, 25.7, 25.6, 16.0, and 4.6.

IR (CH_2Cl_2): 2929, 2856, 2230, 1633, 1591, 1495, 1452, 1348, 1266, 1161, 1102, 967, 736, and 699 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{32}N_3O_2S^+$ [M+H$^+$] requires 450.2210; found 450.2203.

6-(1-Benzyl-2-benzylidenehydrazinyl)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (7dd):



6d ***2d*** ***7dd, 31% (regiomeric ratio= 5:1)***

Tetrayne **6d** (22 mg, 0.089 mmol) and 1-benzyl-3-phenyldiaziridine **2d** (25 mg, 0.116 mmol, 1.3 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18–19 h) in an oil bath at 90 °C and cooled to room temperature. The residue was purified by MPLC (3:1 Hex:EtOAc) to give **7dd** [0.228 mmol, 31% yield, corrected for the presence of the other regioisomer (~20%)] as a yellow oil.

Data for 7dd [contains co-eluting other regioisomer (~20%)]:

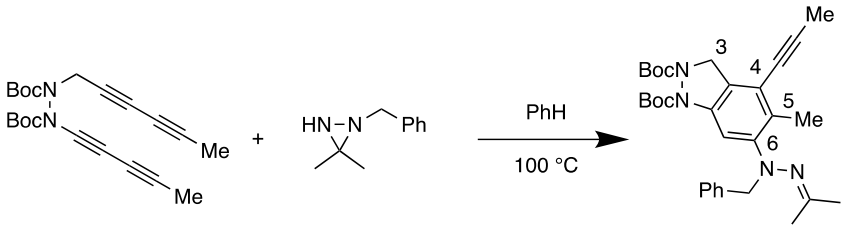
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.4 Hz, 2H, Ph*H*$_o$), 7.34 (d, *J* = 7.8 Hz, 2H, Ph'*H*$_o$), 7.30–7.25 (m, 4H, Ph*H*$_m$ and Ph'*H*$_m$), 7.24–7.18 (m, 2H, Ph*H*$_o$ and Ph'*H*$_o$), 7.04 [s, 1H, *H7* or *H*(C=N)Ph], 6.93 [s, 1H, *H7* or *H*(C=N)Ph], 4.87 (s, 2H, N–C*H*$_2$Ph), 3.95 (t, *J* = 8.3 Hz, 2H, MsNC*H*$_2$), 3.16 (t, *J* = 8.3 Hz, 2H, MsNCH$_2$C*H*$_2$), 2.65 (s, 3H, C*H*$_3$SO$_2$N), 2.21 (s, 3H, NArC*H*$_3$), and 2.12 (s, 3H, NArC≡C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4, 140.3, 137.7, 136.4, 133.8, 133.4, 132.6, 128.44, 128.43, 128.39, 127.6, 127.2, 122.5, 125.8, 111.6, 94.8, 75.9, 60.1, 50.4, 34.1, 28.1, 16.0, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{27}H_{28}N_3O_2S^+$ [M+H$^+$] requires 458.1897; found 458.1891.

IR (CH_2Cl_2): 2921, 2851, 2685, 1641, 1589, 1454, 1422, 1350, 1162, 1070, and 738 cm^{-1}.

di-*tert*-Butyl 6-(1-benzyl-2-(propan-2-ylidene)hydrazinyl)-5-methyl-4-(prop-1-yn-1-yl)-1*H*-indazole-1,2(3*H*)-dicarboxylate (7ec):



6e ***2c*** ***7ec, 60%***

Tetrayne **6e** (20 mg, 0.054 mmol) and 1-benzyl-3,3-dimethyldiaziridine (**2c**, 17.52 mg, 0.108 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.01 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated for 48 h in an oil bath held at 100 °C and then cooled to room temperature. The residue was purified by MPLC (6:1 Hex:EtOAc) to give **7ec** as a transparent oil (64% yield, 0.035 mmol).

Data for 7ec:

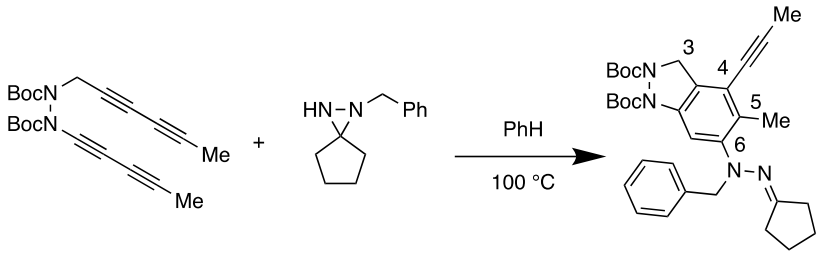
^{1}H NMR (500 MHz, $CDCl_3$): 7.36 (m, 3H, Ar*H7* and PhH_o), 7.32 (dd, *J* = 7.3, 6.7 Hz, 2H, PhH_m), 7.25 (tt, *J* = 7.2, 1.5 Hz, 1H, Ph*Hp*), 5.07 [br d, *J* = 14.6 Hz, 1H, ArCH_aH$_b$N(C=O)], 4.62 (br d, *J* = 14.6 Hz, 1H, ArCH$_a$$H_b$N(C=O), 4.27 (s, 2H, ArNCH_2), 2.46 (s, 3H, NArCH_3), 2.15 (s, 3H, C≡CCH_3), 1.94 (s, 3H, [(CH_3)$_2$C=N], 1.65 (s, 3H, [(CH_3)$_2$C=N], 1.57 (s, 9H, (CH$_3$)$_3$CO(C=O)NAr), and 1.54 (s, 9H, (CH$_3$)$_3$CO(C=O)NAr).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.9, 156.2, 152.5, 152.1, 139.2, 138.4, 129.9, 128.5, 128.1, 126.7, 126.4, 119.0, 110.3, 94.2, 82.5, 82.0, 75.6, 63.6, 51.8, 28.24, 28.19, 25.3, 19.9, 15.7, and 4.6.

HRMS (ESI-TOF): Calcd for $C_{31}H_{41}N_4O_4^+$ [M+H$^+$] requires 533.3122; found 533.3116.

IR (CH_2Cl_2): 2982, 2920, 2874, 2230, 1708, 1640, 1597, 1496, 1454, 1369, 1212, 1149, 1077, 1043, 1027, 1004, 978, 942, 896, and 858 cm^{-1}.

di-*tert*-Butyl 6-(2-cyclopentylidene-1-methylhydrazinyl)-5-methyl-4-(prop-1-yn-1-yl)-1*H*-indazole-1,2(3*H*)-dicarboxylate (7ee):



6e ***2e*** ***7ee, 59.7%***

Tetrayne **6e** (20 mg, 0.054 mmol) and 1-benzyl-1,2-diazaspiro[2.4]heptane **2e** (20.3 mg, 0.108 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (4 mL, 0.01 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated for 48 h in an oil bath held at 100 °C and allowed to cool to room temperature. The residue was purified by MPLC (6:1 Hex:EtOAc) to give **7ee** as a transparent oil (59.7% yield, 0.032 mmol).

Data for 7ee:

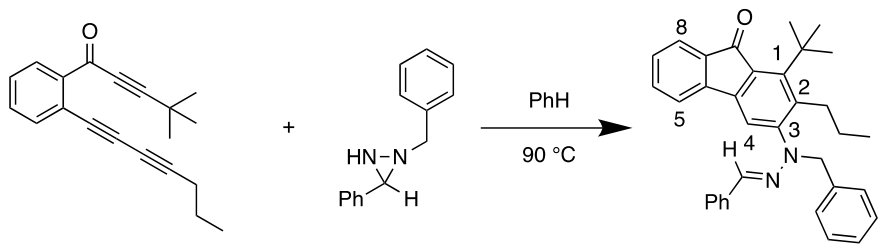
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (s, 1H, NArH), 7.33 (dd, *J* = 7, 1 Hz, 2H, Ph*H*$_o$), 7.29 (dd, *J* = 7.2, 7.2 Hz, 2H, Ph*H*$_m$), 7.22 (tt, *J* = 7.1, 1.5 Hz, 1H, Ph*Hp*), 5.04 (br d, *J* = 14.6 Hz, 1H, ArC*H*$_a$H$_b$N(C=O), 4.60 (br d, *J* = 14.6 Hz, 1H, ArCH$_a$*H*$_b$N(C=O), 4.29 (d, *J* = 13.4 Hz, 1H, PhNC*H*$_a$H$_b$), 4.28 (d, *J* = 13.2 Hz, 1H, PhNCH$_a$*H*$_b$), 2.38 (s, 3H, ArC*H*$_3$), 2.34 [t, *J* = 6.4 Hz, 2H, N=C*(CH*$_2$*)*(CH$_2$)], 2.12 (s, 3H, C≡CC*H*$_3$), 1.91 2.34 [t, *J* = 6.5 Hz, 2H, N=C*(C'H*$_2$*)*(CH$_2$)], 1.64–1.59 (m, 4H, N=C(CH$_2$)$_2$(C*H*$_2$)$_2$), 1.54 (s, 9H, (CH$_3$)$_3$CO(C=O)NAr), and 1.52 (s, 9H, (CH$_3$)$_3$CO(C=O)NAr).

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.3, 152.5, 151.7, 139.1, 138.4, 130.9, 128.4, 128.1, 126.8, 126.7, 118.9, 111.1, 94.2, 82.5, 82.0, 75.6, 63.9, 51.8, 33.6, 30.9, 28.3, 28.2, 24.8, 24.5, 15.6, and 4.6. (one carbon atom not observed)

HRMS (ESI-TOF): Calcd for $C_{33}H_{43}N_4O_4^+$ [M+H$^+$] requires 559.3279; found 559.3268.

IR (CH_2Cl_2): 2982, 2874, 1708, 1598, 1495, 1454, 1423, 1393, 1369, 1211, 1150, 1027, and 857 cm^{-1}.

(1-Benzyl-2-benzylidenehydrazineyl)-1-(*tert*-butyl)-2-propyl-9*H*-fluoren-9-one (7fd):



6f ***2d*** ***7fd, 38%***

Triynone **6f** (30 mg, 0.108 mmol) and 1-benzyl-3-phenyldiaziridine **2d** (46 mg, 0.216 mmol, 2 equiv) were combined in a culture tube and dissolved in benzene (6 mL, 0.02 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath held at 90 °C and then cooled to room temperature. The residue was purified by MPLC (19:1 Hex:EtOAc) to give **7fd** (0.041 mmol, 38%) as a bright yellow oil, which turned into a flaky amorphous solid after being subjected to high vacuum. A small portion of this product was repurified by HPLC to give a pure sample of **7fd**, that was used for collection of spectral data.

Data for 7fd: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.3 Hz, 1H, *H8*), 7.54 (br d, *J* = 7 Hz, 2H, PhH_o), 7.39–7.29 (m, 8H, Ar*H*), 7.25–7.21 (m, 3H, Ar*H*), 7.15 (s, 1H, Ar*H4* or PhC(*H*)=N), 7.04 (s, 1H, Ar*H4* or PhC(*H*)=N), 4.88 (s, 2H, ArNCH_2), 2.91 (br t, *J* = 8.1 Hz, 2H, ArCH_2), 1.62 [(s, 9H, $(CH_3)_3$], 1.41 (br sextet, *J* = 7.5 Hz, 2H, $ArCH_2CH_2CH_2CH_2$), and 0.82 (t, *J* = 7.4 Hz, 3H, $ArCH_2CH_2CH_2CH_3$).

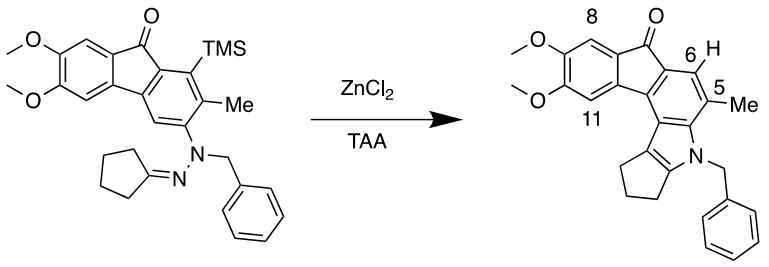
^{13}C NMR (125 MHz, $CDCl_3$): δ 194.2, 156.1, 152.1, 144.9, 142.5, 141.2, 137.2, 136.3, 135.2, 134.2, 134.1, 132.6, 128.8, 128.5, 128.5, 128.1, 127.9, 127.4, 126.0, 123.9, 119.0, 115.9, 60.2, 38.8, 32.8, 32.5, 25.7, and 14.2.

IR (CH_2Cl_2): 3028, 2957, 2869, 1705, 1606, 1589, 1564, 1542, 1495, 1472, 1453, 1398, 1364, 1348, 1297, 1264, 1202, 1180, 1124, 1088, 1072, 1049, 1028, 972, 924, and 886 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{34}H_{35}N_2O^+$ [$M+H^+$] requires 487.2744; found 487.2741.

III. Preparation and Characterization Data for Fischer Indole Products

4-Benzyl-9,10-dimethoxy-5-methyl-1,2,3,4-tetrahydro-7*H*-cyclopenta[*b*]indeno[1,2-*e*]indol-7-one (9ae):



7ae ***9ae, 43 %***

Hydrazone **7ae** (30 mg, 0.059 mmol) and $ZnCl_2$ (10 mg, 0.071 mmol) were combined in a culture tube and dissolved in tertiary amyl alcohol (2 mL, 0.03 M). The tube was sealed with a Teflon-lined screw cap. The solution was heated in an oil bath at 130 °C until the reaction was judged to be complete by crude mass spectrometric analysis of an aliquot (~ 8h). The reaction mixture was cooled to room temperature, filtered through a plug of silica gel (EtOAc), and concentrated. The residue was purified by MPLC (2:1 Hex:EtOAc) to give **9ae** (0.025 mmol, 43%) as an amorphous red powder.

Data for 9ae:

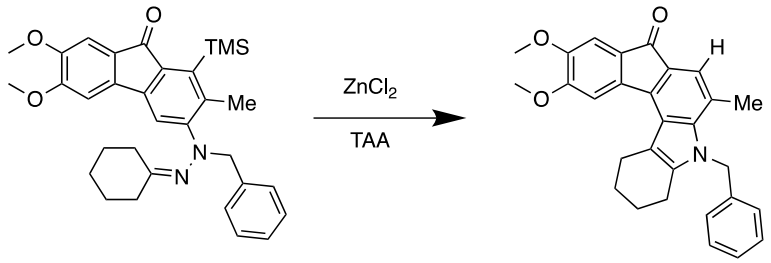
^{1}H NMR (500 MHz, $CDCl_3$): 7.33–7.23 (m, 3H, Ph*H$_m$* and Ph*H$_p$*), 7.28 (s, 1H, *H11*) 7.14 (s, 1H, *H6* or *H8*), 7.04 (s, 1H, *H6* or *H8*), 6.90 (d, *J* = 7.5 Hz, 2H, Ph*H$_o$*), 5.43 (s, 2H, NC*H$_2$*), 3.98 (s, 3H, OC*H$_3$*), 3.92 (s, 3H, OC*H$_3$*), 3.25 (t, *J* =7.0 Hz, 2H, NC=CC*H$_2$*), 2.76 (t, *J* =7.0 Hz, 2H, NC=CC*H$_2$*), 2.57 (pent, 2H, *J* =7.7 Hz, NC=CCH$_2$*CH$_2$*), and 2.42 (s, 3H, $ArCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 153.4, 151.1, 148.4, 145.3, 140.0, 138.9, 135.2, 129.0, 127.9, 127.4, 126.7, 125.1, 120.1, 119.94, 119.88, 117.0, 107.2, 105.5, 56.2, 56.2, 50.3, 28.5, 27.8, 25.1, and 19.4.

HRMS (ESI-TOF): Calcd for $C_{28}H_{26}NO_3^+$ [M+H$^+$] requires 424.1907; found 424.1907.

IR (CH_2Cl_2): 3052, 2927, 2846, 1696, 1601, 1581, 1496, 1475, 1440, 1386, 1366, 1302, 1279, 1265, 1213, 1199, 1154, 1093, 1022, 874, 843, and 802 cm^{-1}.

5-Benzyl-10,11-dimethoxy-6-methyl-2,3,4,5-tetrahydroindeno[2,1-*c*]carbazol-8(1*H*)-one (9aa):



7aa ***9aa, 48 %***

Hydrazone, **S1** (30 mg, 0.057 mmol) and $ZnCl_2$ (9 mg, 0.063 mmol) were combined in a culture tube and dissolved in tertiary amyl alcohol (1 mL, 0.06 M), and the tube was sealed with a Teflon-lined cap. The solution was heated in an oil bath at 130 °C until the reaction was judged to be complete by thin layer chromatography (~ 8h). The reaction mixture was cooled to room temperature, filtered through a plug of silica gel (EtOAc), and concentrated. The residue was purified by MPLC (2:1 Hex:EtOAc) to give **9aa** (0.027 mmol, 48%) as a bright orange amorphous powder.

Data for 9aa:

^{1}H NMR (500 MHz, $CDCl_3$): 7.53 (s, 1H, 7*H*), 7.30-7.22 (m, 3H, PhH_m and PhH_p), 7.17 (s, 1H, 9*H*), 7.11 (s, 1H, 12*H*), 6.86 (d, 1H, PhH_o), 5.48 (s, 2H, NCH_2), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.23 (brs, 2H, NC=CCH_2), 2.58 (brs, 2H, NC(CH_2)=C, 2.47 (s, 3H, ArCH_3), and 1.90 [m, 4H, NC=C$(CH_2)_2$*$(CH_2)_2$*].

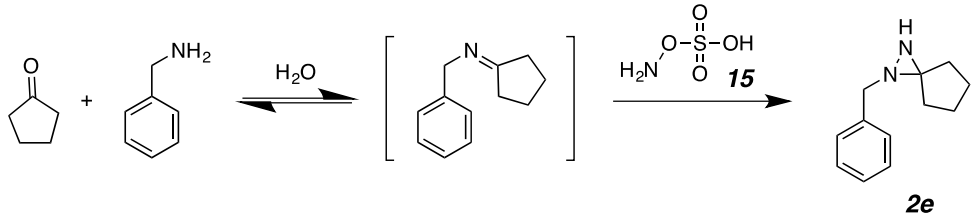
^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 153.1, 148.3, 141.2, 139.9, 138.9, 136.4, 129.0, 128.4, 127.3, 127.2, 124.9, 123.9, 120.7, 119.3, 109.9, 107.7, 107.3, 56.3, 56.2, 47.8, 26.3, 23.8, 22.6, 22.2, and 20.1 (one aromatic carbon resonance not observed).

IR (CH_2Cl_2): 3026, 2930, 2838, 1689, 1597, 1582, 1496, 1474, 1460, 1420, 1408, 1394, 1378, 1363, 1305, 1282, 1213, 1195, 1153, 1177, 1106, 1074, 1044, 1013, 997, 909, 889, 869 and 850 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{29}H_{28}NO_3$ [M+H$^+$] requires 438.2064; found 438.2057.

Preparation and Characterization Data for New Diaziridines

1-Benzyl-1,2-diazaspiro[2.4]heptane (2e):



In a round-bottomed flask at 0 °C, cyclopentanone (0.44 mL, 5.0 mmol, 1.0 equiv) and benzylamine (1.64 mL, 15 mmol, 3.0 equiv) were dissolved in 5 mL of H_2O. This reaction mixture was stirred for two hours. Hydroxylamine-*O*-sulfonic acid (**15**, 0.556 g, 5 mmol, 1 equiv) was added portion wise to this reaction mixture at 0 °C, and the mixture was allowed to warm to room temperature until complete conversion had occurred as judged by ^{1}H NMR analysis of an aliquot (~ 4 h). This mixture was diluted with H_2O (20 mL) and extracted with diethyl ether (3 × 20 mL). The organic layers were dried with $MgSO_4$, filtered, and concentrated by rotary evaporation. This crude product was passed through a plug of silica gel (3:1, Hex:EtOAc), and the resulting residue was purified by MPLC (6:1 Hex:EtOAc) to give **2e** (3.4 mmol, 68% yield) as a yellow oil, which solidified to a yellow solid upon storage at -10 °C. This product returned to an oily state upon being allowed to warm to ambient temperature.

Data for 2e:

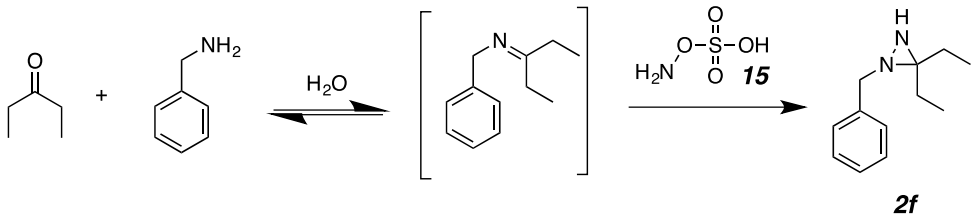
^{1}H NMR (500 MHz, $CDCl_3$): 7.39 (d, *J* =7.3 Hz, 2H, PhH_o), 7.34 (dd, *J* =7.2, 7.2 Hz, 2H, PhH_m), 7.26 (t, *J* = 7 Hz, 1H, PhH_p), 3.67 (d, *J* = 13.7 Hz, 1H, PhCH_aCH$_b$), 3.52 (d, *J* = 13.7 Hz, 1H, PhCH$_a$CH_b), 2.11 (br s, 1H, *NH*), and 2.08–1.65 [m, 8H, C(CH_2)$_4$].

^{13}C NMR (125 MHz, $CDCl_3$): 138.7, 128.4, 128.2, 127.0, 69.2, 59.5, 36.7, 27.3, 25.6, and 24.5.

HRMS (ESI-TOF): Calcd for $C_{12}H_{17}N_2^+$ [M+H$^+$] requires 189.1386; found 189.1381.

IR (neat): 3390, 3204, 3087, 3062, 3029, 2959, 2870, 1496, 1453, 1437, 1377, 1323, 1270, 1209, 1164, 1029, 954, 734, and 698 cm^{-1}.

1-Benzyl-3,3-diethyldiaziridine (2f):



In a round-bottomed flask at 0 °C, pentan-3-one (0.53 mL, 5.0 mmol, 1.0 equiv) and benzylamine (1.64 mL, 15 mmol, 3.0 equiv) were dissolved in 5 mL of H_2O. This reaction mixture was stirred for two hours. Hydroxylamine-*O*-sulfonic acid (**15**, 0.556 g, 4.9 mmol, 1 equiv) was added portion wise to this reaction mixture at 0 °C, and this mixture was allowed to warm to room temperature until complete conversion had occurred, as judged by ^{1}H NMR spectroscopy of an aliquot (~ 4 h). This mixture was diluted with H_2O (20 mL) and extracted with diethyl ether (3 × 20 mL). Organic layers were dried with $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude product. This material was passed through a plug of silica gel (3:1, Hex:EtOAc), and the residue was purified by MPLC (6:1 Hex:EtOAc) to give **2f** (2.64 mmol, 53% yield) as a transparent oil.

Data for 2f:

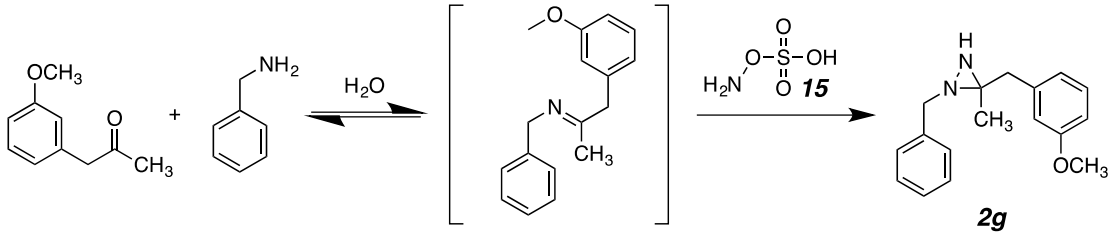
^{1}H NMR (500 MHz, $CDCl_3$): 7.39 (d, *J* =7.7 Hz, 2H, PhH_o), 7.33 (dd, *J* =7.5, 7.5 Hz, 2H, PhH_m), 7.27–7.24 (t, *J* = 7.3 Hz, 1H, PhH_p), 3.78 (d, *J* = 13.7 Hz, 1H, PhCH_aCH$_b$), 3.70 (d, *J* = 13.7 Hz, 1H, PhCH$_a$CH_b), 2.02 (br s, 1H, *NH*), 1.81–1.67 [m, 3H, CH_2CH$_3$ and CH$_a$$H_bCH_3$), 1.53 (dq, *J* = 14.3, 7.4 Hz, 1H, CH_aH$_b$CH$_3$'), 1.06 (t, *J* =7.5 Hz, 3H, CH_3), and 0.93 (t, *J* =7.5 Hz, 3H, CH_3').

^{13}C NMR (125 MHz, $CDCl_3$): 139.1, 128.4, 128.3, 127.0, 64.1, 56.8, 30.4, 21.2, 9.9, and 8.9.

HRMS (ESI-TOF): Calcd for $C_{12}H_{19}N_2^+$ [M+H$^+$] requires 191.1543; found 191.1535.

IR (neat): 3387, 3313, 2969, 3063, 3030, 2937, 2979, 1496, 1455, 1379, 1350, 1300, 1235, 1211, 1096, 1060, 982, 935, 732, and 698 cm^{-1}.

1-Benzyl-3-(3-methoxybenzyl)-3-methyldiaziridine (2g):



In a round-bottomed flask at 0 °C, 1-(3-methoxyphenyl)propan-2-one (0.43 mL, 5.0 mmol, 1.0 equiv) and benzylamine (1.64 mL, 15 mmol, 3.0 equiv) were dissolved in 5 mL of H_2O. This reaction mixture was stirred for two hours. Hydroxylamine-*O*-sulfonic acid (**15**, 0.556 g, 5.0 mmol, 1.0 equiv) was added portion wise at 0 °C. The mixture was allowed to warm to room temperature until complete conversion had occurred as judged by ^{1}H NMR analysis of an aliquot (~ 6 h). This mixture was diluted with H_2O (20 mL) and extracted with diethyl ether (3 × 20 mL). The organic layers were dried with $MgSO_4$, filtered, and concentrated by rotary evaporation. This crude product was passed through a plug of silica gel (1:1, Hex:EtOAc), and the residue was purified by MPLC (6:1 Hex:EtOAc + 1% NEt_3) to give **2g** (2.5 mmol, 50% yield) as a transparent oil.

Data for 2g [an ca. 9:1 mixture of interconverting *N*-invertomers[106]]:

^{1}H NMR (500 MHz, $CDCl_3$): 7.38 (d, *J* = 7.7 Hz, 2H, PhH_o), 7.33 (dd, *J* = 7.4, 7.4 Hz, 2H, PhH_m), 7.27 (t, *J* = 7.4 Hz, 1H, PhH_p), 7.19 [dd, *J* = 7.6, 7.6 Hz, 1H, *meta* to OMe], 6.79–6.77 [m, 3H, *ortho* and *para* to OMe], 3.75 (s, 3H, OMe), 3.72 [d, *J* = 13.4 Hz, 1H, Ph$CH_a$$CH_b$)], 3.67 [d, *J* = 13.6 Hz, Ph$CH_a$$CH_b$)], 2.93 [d, *J* = 13.8 Hz, 1H, Ar$CH_a$$CH_b$)], 2.76 [d, *J* = 13.8 Hz, 1H, ArCH_aCH_b)], 2.15 (s, 1H, *NH*), and 1.38 [s, 3H, CH_2(C)CH_3].

^{13}C NMR (125 MHz, $CDCl_3$): major isomer: 159.5, 138.8, 138.2, 129.3, 128.5, 128.4, 127.1, 122.0, 115.3, 112.3, 60.2, 57.5, 55.1, 47.7, and 15.7. [minor isomer includes: 139.4, 139.0, 129.4, 128.5, 128.3, 127.1, 122.0, 115.3, 60.6, and 16.2.]

HRMS (ESI-TOF): Calcd for $C_{17}H_{20}N_2ONa^+$ [M+Na^+] requires 291.1468; found 291.1468.

IR (CH_2Cl_2): 3423, 3004, 2938, 2836, 1601, 1584, 1490, 1466, 1454, 1436, 1392, 1190, 1153, 1074, 1050, and 781 cm^{-1}.

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[106] a) Mannschreck, A; Radeglia, R; Grundemann, E; Ohme, R. Der Diaziridine-Ring als Asymmetriezentrum. *Chem. Ber.* **1967**, *100*, 1778-1785. b) Mintas M.; Mannschreck A; Klasinc, L. Preparation Separations and Racemization of Enantiomeric Diaziridines. *Tetrahedron* **1980**, *37*, 867-871.

Discussion of Computational Results

DFT computations were performed with the Gaussian 09 software package.[107] The geometries were optimized with the M06-2X functional;[108] the basis set was double-ζ split-valence 6- 311+G(d, p). The SMD continuum solvation model[109] with benzene as solvent was applied during geometry optimization. Harmonic vibrational frequency calculations were performed at 298 K and used for the thermal correction of enthalpies. The value for the "Sum of electronic and thermal Free Energies=" was used as the free energy (G) of the reactants and products.

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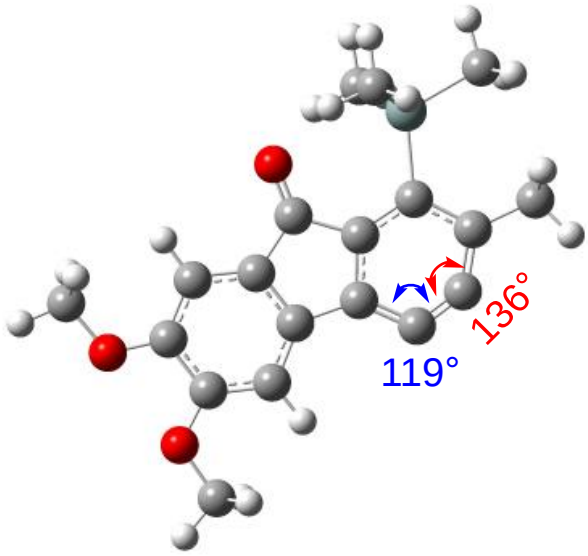
[107] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox. Gaussian 09, revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.

[108] Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

[109] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B,* **2009**, *113,* 6378–6396.

Optimized Geometry of Benzyne 8a [Note the angle difference between two carbons (red vs blue)]:

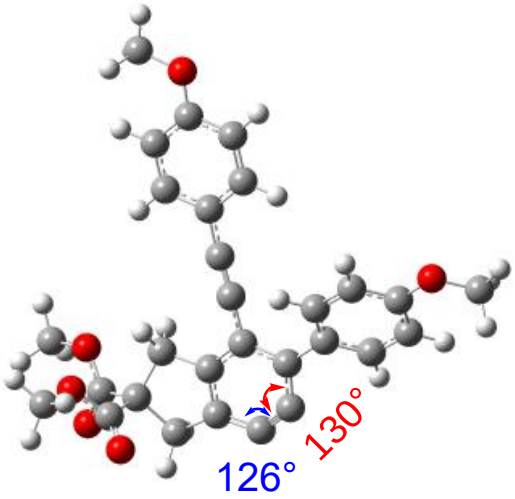


Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.028192	1.409079	-0.009421
2	6	0	0.564696	2.680886	-0.015190
3	6	0	1.810209	2.808598	-0.029424
4	6	0	2.893301	1.961494	-0.041855
5	6	0	2.408676	0.603440	-0.024423
6	6	0	1.016849	0.380198	-0.017238
7	6	0	0.242696	-0.922052	-0.038428
8	6	0	-1.326248	0.826417	-0.005122
9	6	0	-1.202441	-0.556574	-0.022272
10	6	0	-2.314451	-1.394224	-0.024846
11	6	0	-2.578188	1.431694	0.012383
12	6	0	-3.576689	-0.808343	-0.006823
13	6	0	-3.707027	0.609106	0.012542
14	8	0	0.688675	-2.051426	-0.073444
15	8	0	-4.745649	-1.490299	-0.005086
16	8	0	-4.977318	1.061424	0.030081
17	6	0	-4.670201	-2.904899	-0.032597
18	1	0	-4.162018	-3.252942	-0.939011
19	1	0	-4.148012	-3.287292	0.851745
20	1	0	-5.699760	-3.259086	-0.031159
21	6	0	-5.179436	2.464562	0.060326

22	1	0	-6.258463	2.608632	0.075053
23	1	0	-4.736749	2.904505	0.960704
24	1	0	-4.756578	2.940604	-0.831120
25	14	0	3.596243	-0.920706	0.030160
26	6	0	5.434993	-0.492002	0.121404
27	1	0	5.820244	0.011930	-0.768258
28	1	0	5.711016	0.087835	1.005583
29	1	0	5.949645	-1.458405	0.195204
30	6	0	3.267257	-1.875290	1.617687
31	1	0	2.224003	-2.169058	1.733697
32	1	0	3.881904	-2.782594	1.625186
33	1	0	3.564145	-1.266062	2.478219
34	6	0	3.412870	-1.912350	-1.556588
35	1	0	2.392171	-2.257746	-1.722631
36	1	0	3.727629	-1.304145	-2.411445
37	1	0	4.071156	-2.787363	-1.510545
38	6	0	4.326875	2.414453	-0.078049
39	1	0	4.862285	2.127445	0.829796
40	1	0	4.858245	1.988165	-0.931268
41	1	0	4.362363	3.501052	-0.163087
42	1	0	-2.180812	-2.469924	-0.039650
43	1	0	-2.667072	2.511583	0.025938

Optimized Geometry of Benzyne 8b [Note the angle difference between two carbons (red vs blue)]:

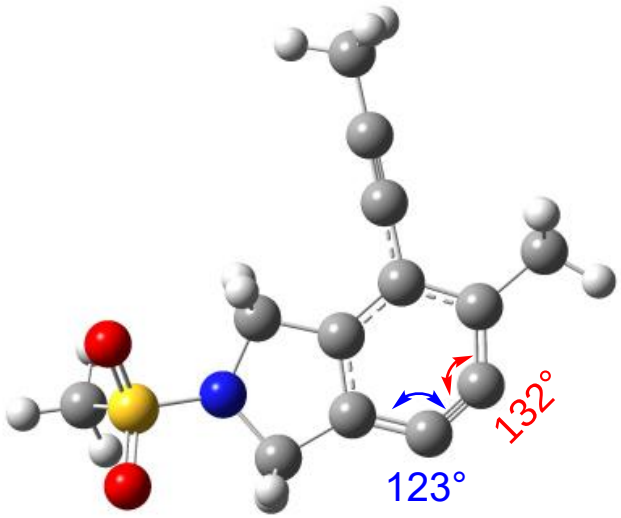


Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.218597	-2.558096	-0.495104
2	6	0	-1.355656	-3.638023	-0.465494
3	6	0	-0.119594	-3.582350	-0.337168
4	6	0	0.707966	-2.478848	-0.178286
5	6	0	-0.096457	-1.291701	-0.223416
6	6	0	-1.502914	-1.357204	-0.365559
7	6	0	2.173130	-2.536310	-0.029635
8	6	0	2.908181	-1.609689	0.727204
9	6	0	2.866415	-3.588109	-0.633105
10	6	0	4.282049	-1.725686	0.848527
11	1	0	2.397015	-0.804723	1.242718
12	6	0	4.247603	-3.714423	-0.524816
13	1	0	2.309119	-4.322365	-1.209334
14	6	0	4.964194	-2.772967	0.217104
15	1	0	4.855417	-1.021200	1.442416
16	1	0	4.746202	-4.540326	-1.017638
17	6	0	0.494626	0.008893	-0.177212
18	6	0	0.960899	1.128451	-0.160785
19	6	0	1.577649	2.416851	-0.127769
20	6	0	0.812081	3.586966	-0.119990
21	6	0	2.980167	2.526012	-0.099132
22	6	0	1.415368	4.840171	-0.083292
23	1	0	-0.270649	3.512568	-0.143019

24	6	0	3.586943	3.766526	-0.061985
25	1	0	3.581802	1.622008	-0.109311
26	6	0	2.809161	4.932822	-0.053163
27	1	0	0.794396	5.727925	-0.078727
28	1	0	4.666900	3.867083	-0.039831
29	6	0	2.756660	7.302083	0.000341
30	1	0	3.489725	8.107365	0.035682
31	1	0	2.146518	7.402408	-0.904684
32	1	0	2.110067	7.357258	0.883617
33	8	0	3.498842	6.098228	-0.014706
34	8	0	6.309062	-2.793846	0.390606
35	6	0	7.030862	-3.848928	-0.213287
36	1	0	6.918926	-3.832864	-1.303634
37	1	0	8.076575	-3.686416	0.046190
38	1	0	6.705536	-4.822591	0.170861
39	6	0	-2.452349	-0.187327	-0.448155
40	1	0	-2.243279	0.601894	0.279201
41	1	0	-2.412799	0.275470	-1.440840
42	6	0	-3.693393	-2.325967	-0.654979
43	1	0	-3.999998	-2.447530	-1.700251
44	6	0	-3.842453	-0.850145	-0.217159
45	1	0	-4.305056	-2.989875	-0.042498
46	6	0	-4.146636	-0.805875	1.285220
47	6	0	-5.005977	-0.169154	-0.922027
48	8	0	-4.103640	-1.749220	2.031897
49	8	0	-6.060980	-0.718321	-1.130706
50	8	0	-4.744243	1.095384	-1.257189
51	8	0	-4.448599	0.439796	1.671636
52	6	0	-4.724179	0.592924	3.068053
53	1	0	-4.947270	1.648557	3.210028
54	1	0	-5.578066	-0.024606	3.352424
55	1	0	-3.853524	0.299360	3.657249
56	6	0	-5.834004	1.798760	-1.861109
57	1	0	-6.686727	1.824020	-1.179922
58	1	0	-5.464319	2.803666	-2.055390
59	1	0	-6.130524	1.308805	-2.790544

Optimized Geometry of Benzyne 8c [Note the angle difference between two carbons (red vs blue)]:

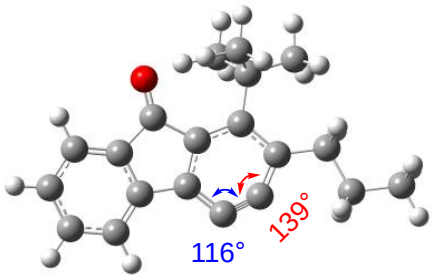


Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.121153	-1.760666	-0.040651
2	6	0	1.078365	-2.758246	-0.029091
3	6	0	2.304144	-2.532204	-0.018936
4	6	0	3.017868	-1.350970	-0.010453
5	6	0	2.090861	-0.264086	-0.019284
6	6	0	0.698711	-0.484812	-0.034871
7	6	0	-0.373750	0.569207	-0.028138
8	1	0	-0.382644	1.144296	0.904681
9	1	0	-0.268755	1.274512	-0.861188
10	6	0	-1.378776	-1.697608	-0.037233
11	1	0	-1.825489	-2.243078	-0.875400
12	1	0	-1.808237	-2.085133	0.892622
13	6	0	2.588121	1.080018	-0.012052
14	6	0	3.005298	2.215557	-0.003786
15	6	0	3.509432	3.587699	0.010468
16	1	0	2.698842	4.299941	-0.165557
17	1	0	3.965059	3.822777	0.976734
18	1	0	4.265820	3.731648	-0.766166
19	6	0	4.502335	-1.144587	0.004203
20	1	0	4.823393	-0.592313	-0.884749
21	1	0	4.799742	-0.554019	0.876281

22	1	0	5.024085	-2.101757	0.031502
23	7	0	-1.597086	-0.244605	-0.175965
24	16	0	-3.068749	0.405997	0.178983
25	6	0	-3.730782	0.855113	-1.413853
26	1	0	-4.713486	1.300856	-1.250644
27	1	0	-3.055463	1.576358	-1.876166
28	1	0	-3.812337	-0.048602	-2.018759
29	8	0	-2.855615	1.638390	0.927522
30	8	0	-3.897987	-0.662854	0.720840

Optimized Geometry of Benzyne 8f [Note the angle difference between two carbons (red vs blue)]:



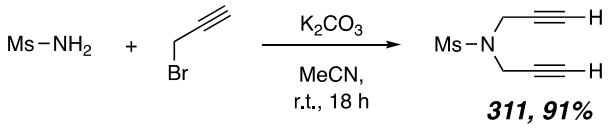
Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.172525	-1.785959	-0.177442
2	6	0	1.907714	-0.628713	-0.088981
3	6	0	0.986957	0.484695	-0.074618
4	6	0	-0.415904	0.206532	-0.058709
5	6	0	-0.956643	-1.112345	-0.130278
6	6	0	-0.024265	-2.131915	-0.207781
7	6	0	-1.637438	1.108140	0.111521
8	6	0	-2.838756	0.215249	0.073635
9	6	0	-4.173778	0.560986	0.171198
10	6	0	-5.116866	-0.470495	0.114509
11	6	0	-4.708836	-1.797090	-0.030966
12	6	0	-3.353765	-2.135499	-0.124122
13	6	0	-2.427465	-1.107482	-0.070585
14	1	0	-4.468264	1.599761	0.287124
15	1	0	-6.175137	-0.240489	0.184830
16	1	0	-5.457643	-2.582339	-0.072492
17	1	0	-3.038390	-3.168788	-0.234430
18	8	0	-1.714573	2.305581	0.285678
19	6	0	1.472419	1.958749	-0.082667
20	6	0	2.980851	2.165861	-0.301460
21	1	0	3.153359	3.245007	-0.366562
22	1	0	3.594193	1.795959	0.520824
23	1	0	3.327056	1.727148	-1.241097
24	6	0	1.142102	2.607626	1.273801
25	1	0	1.447025	3.660227	1.256464
26	1	0	0.080816	2.568054	1.510681
27	1	0	1.703233	2.106366	2.070445
28	6	0	0.817332	2.699455	-1.267863
29	1	0	1.165927	2.264311	-2.210866
30	1	0	-0.267715	2.679049	-1.251456
31	1	0	1.129839	3.749392	-1.246588
32	6	0	3.415918	-0.698987	0.049127
33	1	0	3.918172	-0.192560	-0.778991
34	1	0	3.728839	-0.186144	0.964840
35	6	0	3.906580	-2.146861	0.107645
36	1	0	3.594789	-2.669706	-0.805457
37	1	0	3.418379	-2.661152	0.944636
38	6	0	5.422092	-2.226287	0.260806
39	1	0	5.761792	-3.264593	0.302723
40	1	0	5.927265	-1.740245	-0.580361
41	1	0	5.748411	-1.727858	1.179677

SUPPLEMENTARY INFORMATION FOR CHAPTER 3

(a) Poly-yne substrates and their precursors

N,*N*-Di(prop-2-yn-1-yl)methanesulfonamide (311)



311, 91%

Methanesulfonamide (10.0 g, 105.1 mmol) and potassium carbonate (32.0 g, 231.2 mmol, 2.2 equiv) were placed in a 1 L round-bottom flask equipped with a stir bar. Acetonitrile (263 mL, 0.4 M) was added and the contents were protected from light by wrapping the flask in aluminum foil. Propargyl bromide (80 % w/w in toluene, 24.9 mL, 131.4 mmol, 2.2 equiv) was added, and the resulting suspension was allowed to stir overnight. The mixture was filtered through Celite®, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexane: EtOAc) to give **311** (16.4 g, 90.9 mmol, 91%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.20 (d, 2.5 Hz, 4H NC*H*$_2$), 2.99 (s, 3H, NSO_2C*H*$_3$), and 2.40 (t, 2.5 Hz, 2H, C≡C*H*).

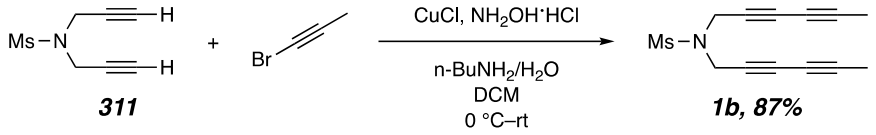
^{13}C NMR (125 MHz, $CDCl_3$): 76.6, 74.6, 38.6, and 36.5.

IR (neat): 3284, 2120, 1434, 1343, 1327, 1152, 1081, 951, 891, and 784 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_7H_9NNaO_2S^+$ [M+Na^+] requires 194.0246; found 194.0249.

mp: 54.5–56.5 °C.

***N,N*-Di(hexa-2,4-diyn-1-yl) methanesulfonamide (1b)**



Copper (I) chloride (199 mg, 2.01 mmol) and hydroxylamine hydrochloride (698 mg, 10 mmol) were added to a 250 mL 3-neck round-bottom flask equipped with a magnetic stir bar and two addition funnels. The reaction vessel was placed under a nitrogen atmosphere and 40/60 (v/v) H_2O/*n*-$BuNH_2$ was added, and the mixture was cooled to 0 °C. *N,N*-Dipropargyl methanesulfonamide (**311**, 3.44 g, 20.1 mmol) in DCM (100 mL) was placed into one addition funnel and bromopropyne in hexane (29.9%, 48.9 mL, 80.4 mmol) into the other. Approximately 10% of the volume of the solution of diyne (~10 mL) was added dropwise, at which time bromopropyne addition was begun. The two solutions were then simultaneously added at approximately the same rate until addition of both reactants was complete. The mixture was allowed to warm to room temperature. After 2 hours, the reaction was judged to be complete by TLC. Note: allowing this coupling reaction to proceed too long makes it susceptible to the possibility of a subsequent (and undesired) pentadehydro-Diels-Alder reaction.[110] The mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and extracted with DCM (100 mL). The combined organic layers were washed with brine (50 mL, 1x), dried with $MgSO_4$, and concentrated to give crude (**1b)** as a pale yellow solid. The crude product was purified by column chromatography (3:1 Hex:EtOAc to 2:1 Hex:EtOAc) to yield **1b** as a white crystalline solid (4.1 g, 16.6 mmol, 87%). The data for this compound matched those previously described.[36,42]

^{1}H-NMR (500 MHz, $CDCl_3$): 4.21 [s, 4H, MsN(CH_2)$_2$], 2.97 (s, 3H, NSO_2CH_3), and 1.94 (s, 6H, C≡CCH_3).

^{13}C-NMR (125 MHz, $CDCl_3$): 77.2, 71.5, 67.7, 63.5, 38.7, 37.5, and 4.3.

IR (neat): 2260, 1430, 1345, 1329, 1154, 1073, 965, 948, 893, and 781 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{13}H_{13}NNaO_2S^+$ [M+Na^+] requires 270.0559; found 270.0553.

mp: 99-101 °C (lit. mp[36,39] = 99-101 °C)

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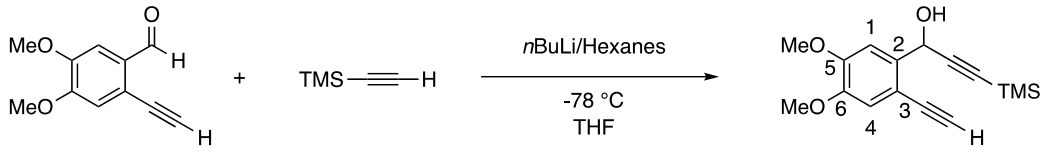
[110] Wang, T.; Naredla, R.; Thompson, S. K. and Hoye, T. R. The Pentadehydro-Diels–Alder Reaction. *Nature*, 2016, **532**, 484–488.

1-(2-Ethynyl-4,5-dimethoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (313)



312 ***313, 82%***

TMS-acetylene (4.49 mL, 31.6 mmol, 1.25 equiv) was added to a 250 mL round-bottom flask, dissolved in THF (70 mL), and cooled to 0 °C. To this solution *n*-BuLi (2.5 M in hexanes, 12.1 mL, 1.2 equiv) was added dropwise and the solution was stirred at 0 °C for 40 min, at which time the solution was cooled to -78 °C. Aldehyde **312**[111] (4.8 g, 25.4 mmol) was added to a 250 mL round bottom flask equipped with an internal thermometer, dissolved in THF (50 mL), placed under N_2, and cooled to -78 °C (internal temperature). To this solution, the -78 °C solution of the lithium acetylide was added via cannula dropwise so that the internal temperature of the receiving solution did not rise above -70 °C. After the addition was complete (~30 min), the solution was stirred for an additional 1 h at which time TLC (3:1 Hex/EtOAc) of an aliquot indicated complete consumption of the starting aldehyde. The reaction mixture was quenched by the addition of a mixture of HOAc (2.5 mL) and THF (2.5 mL) at 0 ºC. The mixture was then warmed to room temperature and concentrated. The resulting residue was diluted with Et_2O (100 mL) and washed successively with sat. NH_4Cl (50 mL), $NaHCO_3$ (70 mL), water (100 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a sticky crude product. This crude product was purified by column chromatography (3:1 Hex:EtOAc) to give the desired alcohol **313** (5.9 g, 82.4 %) as a thick tan oil that turned into an amorphous solid, after being kept in the freezer (-10 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (s, 1H, Ar*H*1), 6.97 (s, 1H, Ar*H*4), 5.85 (s, 1H, ArC*H*OH), 3.93 (s, 3H, C*H*$_3$OC6), 3.88 (s, 3H, C*H*$_3$OC5), 3.29 (s, 1H, C≡C*H*), and 0.20 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.0, 148.6, 136.4, 115.0, 112.6, 110.0, 104.6, 91.6, 81.2, 81.1, 63.1, 56.1, 55.9, and -0.1.

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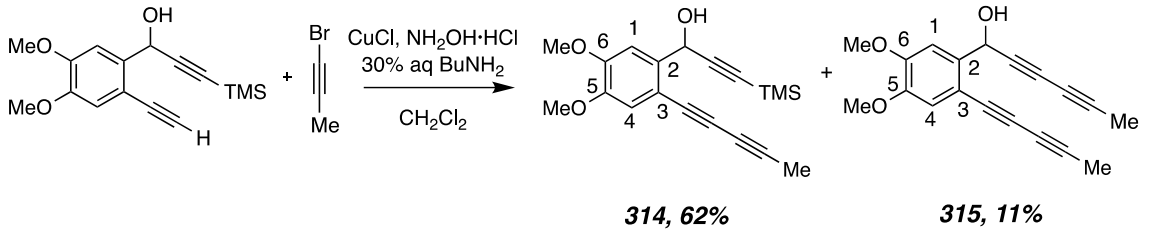
[111] Cikotiene, I.; Buksnaitiene, R. and Sazinas, R. Rapid Access to Benzo-Annelated Heterocycles, Naphthalenes, and Polysubstituted Benzenes Through a Novel Benzannulation Reaction. *Tetrahedron*, 2011, **67**, 706–717.

IR (neat): 3281, 3001, 2959, 2907, 2850, 2172, 2102, 1604, 1510, 1251, 1210, 1095, 1036, and 846 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{16}H_{20}NaO_3Si^+$ [M+Na^+] requires 311.1074; found 311.1072.

1-(4,5-Dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (314) and 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)hexa-2,4-diyn-1-ol (315)



314, 62% ***315, 11%***

Copper (I) chloride (410 mg, 4.12 mmol) and hydroxylamine hydrochloride (714 mg, 21.6 mmol) were added to a 250 mL 3-neck round-bottom flask equipped with a magnetic stir bar and two addition funnels. The reaction vessel was placed under a nitrogen atmosphere, 70/30 (v/v) H_2O/*n*-$BuNH_2$ was added, and the mixture was cooled to 0 °C. 1-(2-Ethynyl-4,5-dimethoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (5.82 g, 20.6 mmol) in DCM (60 mL) was placed into one addition funnel and bromopropyne in hexane (24.9%, 13.8 g, 28.8 mmol) into the other. Approximately 10% of the volume of the solution of diyne (~6 mL) was added dropwise, at which time bromopropyne addition was begun. The two solutions were then simultaneously added at approximately the same rate until addition of both reactants was complete. The mixture was allowed to warm to room temperature. After 1 hour, the reaction was judged to be complete by TLC. The mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and extracted with DCM (50 mL). The combined organic layers were washed with brine (50 mL, 1x), dried with $MgSO_4$, and concentrated to give crude product as a pale yellow solid. The crude product was purified by column chromatography (3:1 Hex:EtOAc) to yield, in order of elution, **314** as an orange-yellow oil (4.2 g, 0.013 mmol, 62%), which solidified upon storage at -10 °C to give an amorphous yellow powder and **315** as a pale yellow amorphous solid (642 mg, 11%).

Data for 314 (Faster eluting product):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 1H, Ar*H1*), 6.94 (s, 1H, Ar*H4*), 5.87 (d, *J* = 3.3 Hz, 1H, ArC*H*OH), 3.92 (s, 3H, C*H*$_3$OC6), 3.87 (s, 3H, C*H*$_3$OC5), 2.41 (s, 1H, O*H*), 2.03 (s, 3H, *H*$_3$C–C≡), and 0.20 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$)**:** δ 150.2, 148.7, 137.3, 115.4, 112.7, 110.1, 104.6, 91.8, 81.6, 78.3, 71.5, 64.4, 63.3, 56.2, 56.0, 4.8, and -0.1.

IR (thin film): 3490, 2959, 2912, 2856, 2836, 2171, 1602, 1509, 1463, 1444, 1405, 1345, 1246, 1207, 1152, 1073, 1035, 1002, 966, 840, 758, 700, 641, 596, and 479 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{21}O_2Si^+$ [M+H$^+$–H_2O] 309.1305, found 309.1302. (most intense ion); Calculated for $C_{19}H_{23}O_3Si^+$ [M+H$^+$] 327.1411, found 327.1374. (minor ion)

Data for 315 (Slower eluting product):

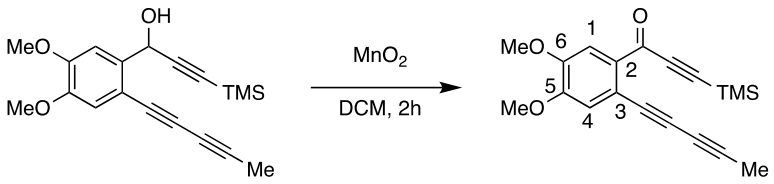
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 1H, Ar*H1*), 6.95 (s, 1H, Ar*H4*), 5.87 (d, *J* = 4.9 Hz, 1H, ArC*H*OH), 3.93 (s, 3H, C*H*$_3$OC6), 3.86 (s, 3H, C*H*$_3$OC5), 2.41 (br s, 1H O*H*), 2.04 (s, 3H, *H*$_3$C–C≡), and 1.95 (s, 3H, *H*$_3$C–C≡).

^{13}C NMR (125 MHz, $CDCl_3$)**:** δ 150.3, 148.7, 136.7, 115.2, 112.3, 109.6, 81.6, 78.22 (2x), 73.8, 71.5, 71.2, 64.2, 63.7, 63.0, 56.065, 56.060, 4.7, and 4.4.

IR (thin film): 3438, 3003, 2961, 2937, 2913, 2836, 2255, 1601, 1509, 1463, 1404, 1373, 1345, 1246, 1206, 1149, 1071, 992, 939, 862, 757, 735, 595, 535, 470, and 419 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{15}O_2^+$ [M+H$^+$–H_2O] 275.1067, found 275.1064 (most intense ion); Calculated for $C_{19}H_{17}O_3^+$ [M+H$^+$] 293.1172, found 293.1183 (minor ion).

1-(4,5-Dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (1a)



314 ***1a, 81%***

MnO_2 (4.98 g, 55.4 mmol) was added to a solution of triyne **314** (3.61 g, 11.1 mmol) in CH_2Cl_2 (24 mL), and the resulting suspension was stirred at room temperature overnight. The reaction mixture was filtered through Celite®, the filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (hexanes:EtOAc = 9:1) to afford the ketotriyne **1a** as a yellow crystalline powder (2.91 g, 81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (s, 1H, Ar*H1*, nOe CH_3OC6), 7.03 (s, 1H, Ar*H4*, nOe CH_3OC5), 3.94 (s, 3H, C*H*$_3$OC6), 3.93 (s, 3H, C*H*$_3$OC5), 2.04 (s, 3H, *H*$_3$C–C≡), and 0.31 [s, 9H, Si(C*H*$_3$)$_3$].

A difference nOe experiment showed enhancement of the C6-methoxy and C5-methoxy protons upon irradiation of ArH1 and ArH4, respectively, allowing the assignment of the proton chemical shifts given above for **1a.**

^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 152.4, 149.1, 132.6, 117.1, 116.3, 113.4, 101.8, 101.3, 82.4, 80.0, 72.4, 65.0, 56.3, 56.0, 4.76, and -0.66.

IR (neat): 3007, 2961, 2913, 2849, 2238, 2154, 1686, 1659, 1642, 1587, 1556, 1463, 1441, 1397, 1353, 1255, 1202, 1170, 1096, 1029, 967, 846, and 760 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{20}NaO_3Si^+$ [M+Na^+] 347.1074, found 347.1080.

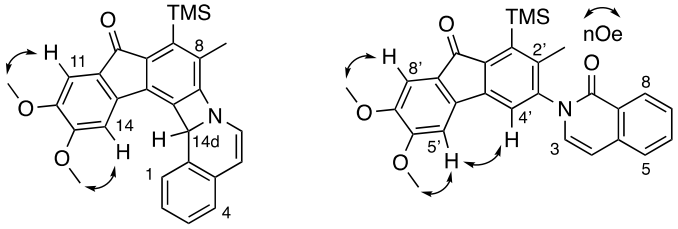
mp: 130-132 °C

TLC: R_f 0.4 (9:1 Hex/EtOAc).

(b) Products obtained from mode a: 1:1 adducts of *N*–heterocycles and arynes

12,13-Dimethoxy-8-methyl-9-(trimethylsilyl)fluoreno[4',3':3,4]azeto[2,1-*a*]isoquinolin-10(14d*H*)-one (6) and

2-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)isoquinolin-1(2*H*)-one (7)



6 (5%) ***7*** (22%)

A solution of ketone **1a** (50.0 mg, 0.154 mmol) and isoquinoline (**2a**, 36.2 μL, 0.308 mmol) in benzene (10 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give the azetidine **6** (3.6 mg, 5%) and isoquinolone **7** (15.5 mg, 22%), each as an orange, foamy solid.

Compound 6 (azetidine)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.31 (nfom, 1H, Ar*H1*), 7.19 (s, 1H, Ar*H11*), 7.17–7.14 (m, 2H, Ar*H2* and Ar*H3*), 7.14 (s, 1H, Ar*H14*), 6.99–6.96 (nfom, 1H, Ar*H4*), 6.68 (s, 1H, *H14d*), 6.59 (d, *J* = 7.2 Hz, 1H, Ar*H6*), 5.73(d, *J* = 7.2 Hz, 1H, Ar*H5*), 4.06 (s, 3H, C13OCH_3), 3.93 (s, 3H, C12OCH_3), 2.27 (s, 3H, ArCH_3), and 0.40 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.7, 161.3, 153.4, 149.9, 145.1, 135.7, 135.5, 131.8, 131.6, 129.4, 128.6, 128.3, 127.6, 126.4, 126.0, 125.6, 125.1, 122.3, 110.5, 106.9, 104.6, 69.2, 56.4, 56.2, 17.5, and 2.7. (Some ^{13}C chemical shift values were obtained from the HSQC and HMBC data)

IR (neat): 2942, 2902, 2844, 1701, 1644, 1592, 1494, 1456, 1417, 1366, 1313, 1270, 1243, 1214, 1122, 1083, 1059, 1018, and 909 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{28}H_{28}NO_3Si^+$ [M+H$^+$] 454.1833, found 454.1832.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

Compound 7 (isoquinolone)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (dddd, *J* = 8.1, 1.2, 0.5, 0.5 Hz, 1H, Ar*H8*), 7.72 (ddd, *J* = 8.0, 7.1, 1.4 Hz, 1H, Ar*H7*), 7.60 (br d, *J* = 8.0 Hz, 1H, Ar*H5*), 7.56 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, Ar*H6*), 7.29 (d, *J* = 0.5 Hz, 1H, *H4'*), 7.16 (s, 1H, Ar*H8'*), 7.02 (d, *J* = 7.4 Hz, 1H, Ar*H3*), 6.90 (s, 1H, Ar*H5'*), 6.63 (dd, *J* = 7.5, 0.5 Hz, 1H, Ar*H4*), 3.94 (s, 3H, C6'OCH_3), 3.92 (s, 3H, C7'OCH_3), 2.20 (s, 3H, ArCH_3), and 0.45 [s, 9H, Si(CH_3)$_3$].

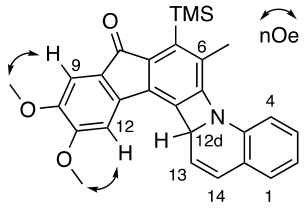
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 161.8, 154.6, 149.8, 144.1, 143.8, 143.4, 141.0, 140.8, 138.2, 137.2, 132.8, 131.6, 128.3, 127.4, 126.7, 126.5, 126.1, 119.7, 106.9, 106.7, 102.9, 56.3, 56.2, 19.2, and 2.8.

IR (neat): 3000, 2990, 2933, 2900, 2836, 1704, 1652, 1625, 1591, 1557, 1494, 1455, 1417, 1381, 1359, 1316, 1266, 1244, 1212, 1152, 1117, 1093, 1056, 1017, 1005, and 983 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{28}H_{28}NO_4Si^+$ [M+H^+] 470.1782, found 470.1773.

TLC: R_f 0.1 (3:1 hexanes:EtOAc).

10,11-Dimethoxy-6-methyl-7-(trimethylsilyl)fluoreno[4',3':3,4]azeto[1,2-*a*]quinolin-8(12d*H*)-one (4e)



***8** (38%)*

A solution of ketone (**1a**, 50.0 mg, 0.154 mmol) and quinoline (**2b**, 36.2 μL, 0.308 mmol) in benzene (10 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give ketone **8** (27.2 mg, 38%) as an orange, foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (br d, *J* = 7.9 Hz, 1H, Ar*H4*), 7.18 (ddd, *J* = 7.9, 6.9, 2.2 Hz, 1H, Ar*H3*), 7.16 (s, 1H, Ar*H9*), 7.01 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, Ar*H2*), 6.99 (br dd, *J* = 7.5, 2.2 Hz, 1H, Ar*H1*), 6.71 (s, 1H, Ar*H12*), 6.34 (dd, *J* = 10.0, 2.2 Hz, 1H, *H13* or *H14*, 6.17 (dd, *J* = 2.3, 2.3 Hz, 1H, *H12d*), 6.07 (dd, *J* = 10.0, 2.2 Hz, 1H, *H13* or *H14*), 4.00 (s, 3H, C11OCH_3), 3.92 (s, 3H, C10OCH_3), 2.36 (s, 3H, ArCH_3), and 0.39 [s, 9H, Si(CH_3)$_3$].

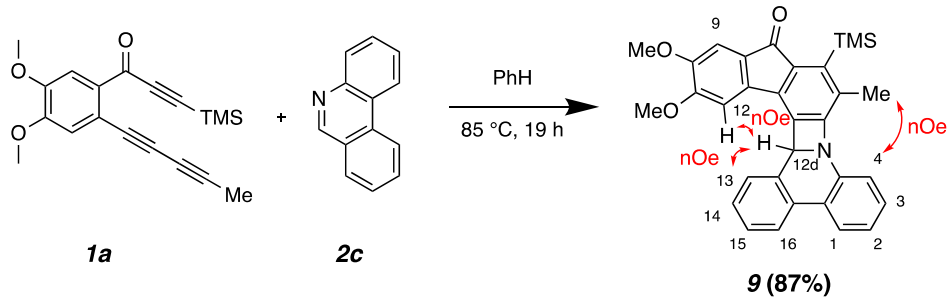
^{13}C NMR (125 MHz, $CDCl_3$): δ 192.7 (C8), 162.4 (C5a), 153.7, 149.8, 145.8, 139.4, 135.7, 134.4, 133.2, 132.7, 129.0 (C3), 128.8, 128.0 (C1), 127.1, 126.1 (C13 or C14), 124.8 (C2), 123.7, 123.4 (C13 or C14), 123.3 (C4), 106.9, 104.2, 68.9 (C12d), 56.4, 56.2, 17.8, and 2.8.

IR (neat): 2945, 2904, 2841, 1703, 1638, 1590, 1496, 1456, 1419, 1363, 1323, 1273, 1241, 1214, 1119, 1080, 1059, 1018, and 989 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{28}H_{28}NO_3Si^+$ [M+H$^+$] 454.1833, found 454.1830.

TLC: R_f 0.4 (2:1 hexanes:EtOAc).

10,11-Dimethoxy-6-methyl-7-(trimethylsilyl)fluoreno[4',3':3,4]azeto[1,2-f]phenanthridin-8(12dH)-one (9)



1a *2c* ***9*** **(87%)**

Triynone **1a** (25 mg, 0.077 mmol) and phenanthridine (**2c**, 41 mg, 0.231 mmol, 3 equiv) were added to a culture tube, dissolved in benzene (6 mL), and sealed with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc elution). The residue was purified by MPLC (1:1 Hex:EtOAc) to give **9** (34 mg, 87%) as a yellow oil.

Data for 9:

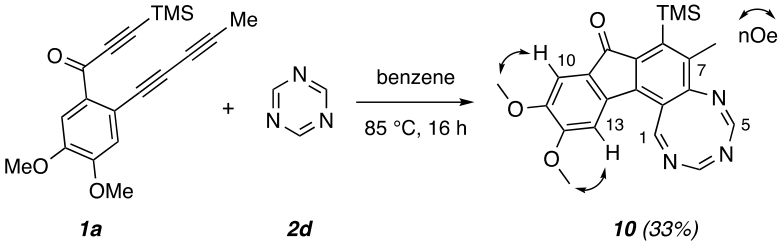
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H16*), 7.81 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H1*), 7.53 (ddd, *J* = 7.6, 1.3, 1.3 Hz, 1H, Ar*H13*), 7.42 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar*H4*), 7.34 (dddd, *J* = 8.0, 8.0, 1.5, 0.9 Hz, 1H, Ar*H15*), 7.30 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H, Ar*H14*), 7.28 (dd, *J* = 7.5, 7.5, 1.3 Hz, 1H, Ar*H3*), 7.20 (s, 1H, Ar*H9*), 7.19 (s, 1H, Ar*H12*), 7.16 (ddd, *J* = 7.9, 7.3, 1.3 Hz, 1H, Ar*H2*), 6.50 (dd, *J* = 1.1, 0.8 Hz, 1H, Ar*H12d*), 4.07 (s, 3H, C11OC*H*$_3$), 3.94 (s, 3H, C10OC*H*$_3$), 2.36 (s, 3H, $ArCH_3$), and 0.38 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (126 MHz, $CDCl_3$): 192.4 (C8), 160.4 (C5a), 153.7 (C11), 150.0 (C10), 146.3 (C7), 138.7 (C4a), 135.5, 135.2 (C8a or C12a), 133.2 (C12e), 132.9, 131.0 (C16a), 129.7 (C8a or C12a), 129.6 (C12c), 129.1 (C14), 128.54 (C3), 128.47 (C15), 127.5 (C16b), 126.2 (C13), 124.6 (C2), 124.5 (C1), 124.3 (C16), 123.9 (C4), 121.2 (C6), 107.1 (C9), 104.7 (C12), 68.8 (C12d), 56.7 (O*Me*), 56.4 (O*Me*), 17.8 (Ar*Me*), and 3.0 (*TMS*). The assignments of carbon resonances were deduced using HSQC, HMBC, and differential nOe interactions (red arrows).

HRMS (APCI-Orbitrap): Calculated for $C_{32}H_{30}NO_3Si^+$ [$M+H^+$]: 504.1989, found 504.1935.

IR ($CDCl_3$): 3071, 3007, 2940, 2900, 2837, 2253, 1698, 1650, 1593, 1493, 1440, 1365, 1311, 1245, 1103, 1079, 1019, 906, 842, 726, 647, 602, 541, 450, and 420 cm^{-1}.

(1*Z*,3*Z*,5*Z*)-11,12-Dimethoxy-7-methyl-8-(trimethylsilyl)-9*H*-fluoreno[3,4-*f*][1,3,5]triazocin-9-one (4d)



1a ***2d*** ***10** (33%)*

A solution of ketone **1a** (50.0 mg, 0.154 mmol) and 1,3,5-triazine (**2d**, 25.0 mg, 0.308 mmol) in benzene (10 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give ketone **10** (20.8 mg, 33%) as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 0.8 Hz, 1H, Ar*H1*), 8.04 (s, 1H, Ar*H5*), 7.97 (d, *J* = 0.8 Hz, 1H, Ar*H3*), 7.18 (s, 1H, Ar*H10*), 6.80 (s, 1H, Ar*H13*), 3.99 (s, 3H, C12OCH_3), 3.93 (s, 3H, C11OCH_3), 2.29 (s, 3H, ArCH_3), and 0.42 [s, 9H, Si(CH_3)$_3$].

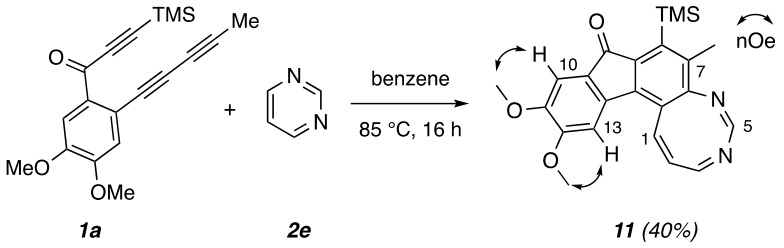
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.1 (C9), 163.8 (C1), 159.7 (C3), 156.0 (C5), 154.0, 150.0, 148.7, 145.4, 139.9, 137.2, 137.1, 136.6, 127.5, 121.8, 107.1 (C10), 105.8 (C13), 56.5, 56.2, 19.8 (ArMe), and 2.6 (TMS). (indicated carbon assignments from HSQC and/or HMBC)

IR (neat): 2999, 2942, 2897, 2836, 1702, 1633, 1588, 1565, 1531, 1492, 1457, 1420, 1361, 1312, 1294, 1240, 1212, 1149, 1081, 1048, 1017, and 949 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{22}H_{24}N_3O_3Si^+$ [M+H$^+$] 406.1581, found 406.1579.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

(1*Z*,3*Z*,5*Z*)-11,12-Dimethoxy-7-methyl-8-(trimethylsilyl)-9*H*-fluoreno[3,4-*d*][1,3]diazocin-9-one (4c)



1a ***2e*** ***11*** *(40%)*

A solution of ketone **1a** (30.0 mg, 0.0924 mmol) and pyrimidine (**2e**, 14.8 μL, 0.185 mmol) in benzene (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (1:1 hexanes:EtOAc) to give ketone **11** (14.8 mg, 40%) as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 0.9, 0.9 Hz, 1H, Ar*H5*), 7.86 (dd, *J* = 1.1, 1.1 Hz, 1H, Ar*H3*), 7.16 (s, 1H, Ar*H10*), 6.99 (d, *J* = 11.7 Hz, 1H, Ar*H1*), 6.95 (s, 1H, Ar*H13*), 6.50 (ddd, *J* = 11.7, 1.2, 0.9 Hz, 1H, Ar*H2*), 3.98 (s, 3H, C12OCH_3), 3.91 (s, 3H, C11OCH_3), 2.33 (s, 3H, ArCH_3), and 0.42 [s, 9H, Si(CH_3)$_3$].

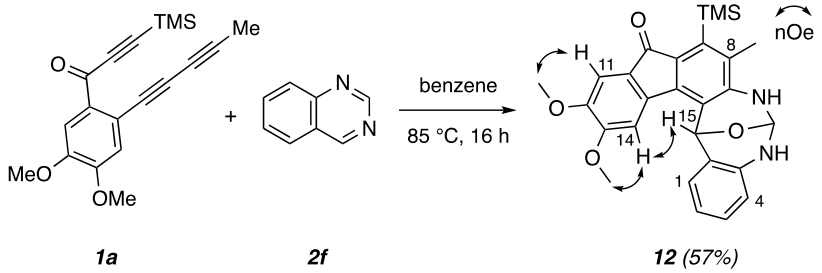
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 164.0, 157.3, 153.5, 149.7, 149.4, 142.5, 140.6, 138.1, 136.9, 136.2, 134.6, 130.7, 127.6, 123.0, 106.9, 106.7, 56.3, 56.2, 20.2, and 2.7.

IR (neat): 2998, 2941, 2899, 2835, 1702, 1637, 1590, 1560, 1525, 1492, 1465, 1416, 1367, 1312, 1246, 1213, 1182, 1149, 1081, 1039, 1019, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{23}H_{25}N_2O_3Si^+$ [M+H$^+$] 405.1629, found 405.1619.

TLC: R_f 0.1 (1:1 hexanes:EtOAc).

12,13-Dimethoxy-8-methyl-9-(trimethylsilyl)-5,6,7,15-tetrahydro-10*H*-6,15-epoxybenzo[*d*]fluoreno[4,3-*g*][1,3]diazocin-10-one (4h)



1a ***2f*** ***12*** *(57%)*

A solution of ketone **1a** (30.0 mg, 0.0924 mmol) and quinazoline (**2f**, 24.0 mg, 0.185 mmol) in benzene (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give ketone **12** (24.7 mg, 57%) as an orange, foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (s, 1H, Ar*H14*), 7.32 (dd, *J* = 7.8, 1.0 Hz, 1H, Ar*H1*), 7.19 (s, 1H, Ar*H11*), 7.14 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H, Ar*H3*), 6.82 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, Ar*H2*), 6.80 (dd, *J* = 7.8, 1.0 Hz, 1H, Ar*H4*), 6.67 (s, 1H, Ar*H15*), 6.18 (d, *J* = 2.7 Hz, 1H, *H6*), 5.06 (d, *J* = 2.7 Hz, 1H, N*H*), 4.84 (br s, 1H, N*H*), 4.03 (s, 3H, C13OCH_3), 3.94 (s, 3H, C12OCH_3), 2.16 (s, 3H, ArCH_3), and 0.38 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.3 156.0, 152.9, 149.3, 142.0, 137.6, 137.0, 130.3, 129.4, 128.4, 125.2, 124.3, 124.1, 121.0, 119.0, 118.2, 106.9, 106.0, 102.9, 82.1 (C6), 66.8 (C15), 56.5, 56.2, 17.4 (ArMe), and 2.9 (TMS). (indicated carbon assignments from HSQC and/or HMBC)

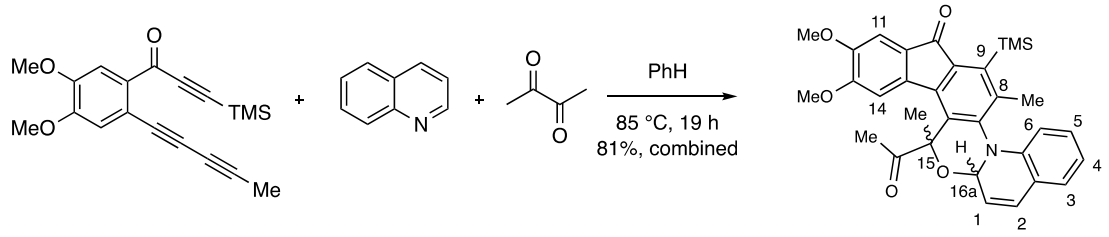
IR (neat): 3433, 3336, 2993, 2944, 2905, 2835, 1681, 1607, 1579, 1547, 1496, 1461, 1419, 1381, 1362, 1341, 1296, 1247, 1209, 1179, 1095, 1049, 1036, 1018, and 989 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{27}H_{29}N_2O_4Si^+$ [M+H$^+$] 473.1891, found 473.1882.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

Products obtained from mode b: electrophilic three-component reactions

15-Acetyl-12,13-dimethoxy-8,15-dimethyl-9-(trimethylsilyl)-16aH-fluoreno[3',4':4,5][1,3]oxazino[3,2-a]quinolin-10(15H)-one (13-A and 13-B)



1a ***2b*** ***3a***

13-A *(38%) and* ***13-B*** *(43%): separable pair of diastereomers,* ***13-A*** *is faster eluting*

Triynone **1a** (20 mg, 0.062 mmol), quinoline (**2b**, 15 μL, 0.124 mmol, 2 equiv) and diacetyl (**3a**, 27 mg, 0.310 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (4 mL, 0.02 M), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc). The residue was purified by MPLC (1:1 Hex:EtOAc) to give, in order of elution, **13-A** (0.024 mmol, 38%) as a yellow oil and **13-B** (0.028 mmol, 43%) also as a yellow oil, which solidified upon storage at -10 °C to give as pale yellow flakes. This product returned to an oily state upon being allowed to warm to ambient temperature.

Data for 13-A (Faster eluting isomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.5, 1.7 Hz, 1H, Ar*H*3), 7.19 (1H, ddd, *J* = 7.4, 7.4, 1.5 Hz, 1H, Ar*H5*), 7.17 (s, 1H, Ar*H11*), 7.10 (s, 1H, Ar*H14*), 6.96 (br d, *J* = 9.8 Hz, 1H, C=C*H2*), 6.93 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, Ar*H4*) , 6.49 (br d, *J* = 8.5 Hz, 1H, Ar*H*6), 6.03 (dd, *J* =9.2, 5.2 Hz, 1H, *H1*C=C), 5.51 (br d, *J* = 5.1 Hz, 1H, C*H*16a), 3.99 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 2.27 (s, 3H, $ArCH_3$ or $O{=}CCH_3$), 1.89 (s, 3H, $ArCH_3$ or $O{=}CCH_3$ or $C15CH_3$), 1.80 (s, 3H, $ArCH_3$ or $O{=}CCH_3$ or $C15CH_3$), and 0.48 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 193.5, 153.9, 149.1, 142.1, 142.0, 140.9, 140.5, 139.7, 138.4, 137.2, 130.3, 129.7, 129.3, 128.4, 127.2, 121.7, 120.3, 117.8, 114.8, 109.7, 106.4, 82.8, 76.1, 56.7, 56.1, 25.9, 21.4, 20.0, and 3.1.

HRMS (APCI-Orbitrap): Calculated for $C_{32}H_{34}NO_5Si^+$ [M+H$^+$]: 540.2201, found 540.2204.

IR (thin film): 3004, 2924, 2852, 1718, 1704, 1644, 1601, 1588, 1526, 1499, 1488, 1456, 1419, 1350, 1311, 1291, 1243, 1221, 1118, 1092, 1074, 1044, 1024, 994, 970, 938, 909, 893, 846, 805, 772, 733, 681, 640, 608, 586, 546, 516, 495, 472, and 411 cm^{-1}.

Data for 13-B (Slower eluting isomer)

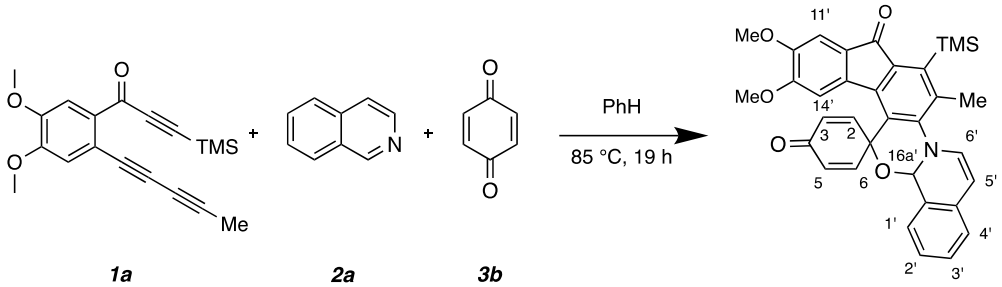
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar*H*3), 7.20 (1H, ddd, *J* = 7.4, 7.4, 1.5 Hz, 1H, Ar*H5*), 7.19 (s, 1H, Ar*H11*), 6.95 (br d, *J* = 8.7 Hz, 1H, C=C*H2*), 6.94 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, Ar*H4*), 6.65 (s, 1H, Ar*H14*), 6.47 (br d, *J* = 8.2 Hz, 1H, Ar*H*6), 6.00 (dd, *J* =9.5, 5.3 Hz, 1H, *H1*C=C), 5.50 (d, *J* = 5.2 Hz, 1H, C*H*16a), 3.919 (s, 3H, OCH_3), 3.921 (s, 3H, OCH_3), 2.37 (s, 3H, $ArCH_3$ or O=CCH_3 or C15CH_3), 2.22 (s, 3H, $ArCH_3$ or O=CCH_3 or C15CH_3), 1.70 (s, 3H, $ArCH_3$ or O=CCH_3 or C15CH_3) and 0.47 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1, 193.4, 153.5, 149.2, 142.7, 141.9, 140.7, 140.3, 139.6, 138.6, 137.0, 130.2, 130.0, 129.3, 128.2, 127.5, 121.6, 120.3, 117.9, 114.5, 108.6, 106.7, 81.2, 78.3, 56.5, 56.1, 25.8, 23.6, 19.6, and 3.0.

IR (thin film): 3055, 2979, 2927, 2853, 1705, 1642, 1601, 1588, 1531, 1488, 1456, 1419, 1354, 1312, 1293, 1262, 1245, 1219, 1204, 1167, 1101, 1075, 1044, 1023, 994, 968, 941, 878, 843, 804, 772, 733, 701, 678, 629, 607, 575, 547, 514, 486, 453, and 414 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{32}H_{34}NO_5Si^+$ [$M+H^+$]: 540.2201, found 540.2201.

12',13'-Dimethoxy-8'-methyl-9'-(trimethylsilyl)-10'H,16a'H-spiro[cyclohexane-1,15'-fluoreno[3',4':4,5][1,3]oxazino[2,3-a]isoquinoline]-2,5-diene-4,10'-dione (14)



Triynone **1a** (25 mg, 0.077 mmol, 1 equiv), isoquinoline (**2a**, 30 μL, 0.231 mmol, 3 equiv), and benzoquinone (**3b**, 42 mg, 0.385 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (10 mL), and sealed with a Teflon-lined screw-cap. The tube was heated overnight (18-19 h) in an oil bath at 85 °C and cooled. The contents were passed through a plug of silica (1:1, Hex:EtOAc eluant). The eluate was concentrated and the residue was purified by MPLC (2:1 Hex:EtOAc) to give **14** (26 mg, 0.0463 mmol, 60%) as a yellow oil, which changed into a flaky, amorphous solid after being subjected to high vacuum.

Data for 101afb (contains a trace (<1%) of benzoquinone as an impurity):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 10.0, 2.7 Hz, 1H, *H2* or *H6*), 7.37 (nfom, 1H, Ar*H1'*), 7.26 (m, 2H, Ar*H2'* and Ar*H3'*), 7.19 (d, *J* = 7.4 Hz, 1H, Ar*H4'*), 7,19 (s, 1H, Ar*H14'* or Ar*H11'*), 7.15 (s, 1H, Ar*H11'* or Ar*H14'*), 6.94 (dd, J = 9.8, 2.8 Hz, 1H, *H2* or *H6*), 6.51 (dd, *J* = 10.1, 1.8 Hz, 1H, *H3* or *H5*), 6.44 (dd, *J* = 9.8, 1.8 Hz, 1H, *H3* or *H5*), 6.37 (dd, *J* = 7.7, 1.5 Hz, Ar*H6'*), 6.10 (d, *J* = 1.5 Hz, 1H, *H16a'*), 5.93 (d, *J* = 7.6 Hz, 1H, *H5'*), 3.89 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 2.45 (s, 3H, ArCH_3), and 0.46 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 185.4, 153.7, 149.4, 148.8, 147.6, 145.2, 145.1, 140.6, 139.1, 137.4, 136.4, 132.2, 131.2, 131.0, 130.2, 129.8, 128.7, 127.6, 126.5, 126.0, 125.2, 124.8, 110.5, 106.6, 102.7, 80.8, 71.7 (quaternary aliphatic carbon), 56.8 (OCH_3), 56.3 (OCH_3), 21.7 (ArCH_3), and 3.0 (TMS).

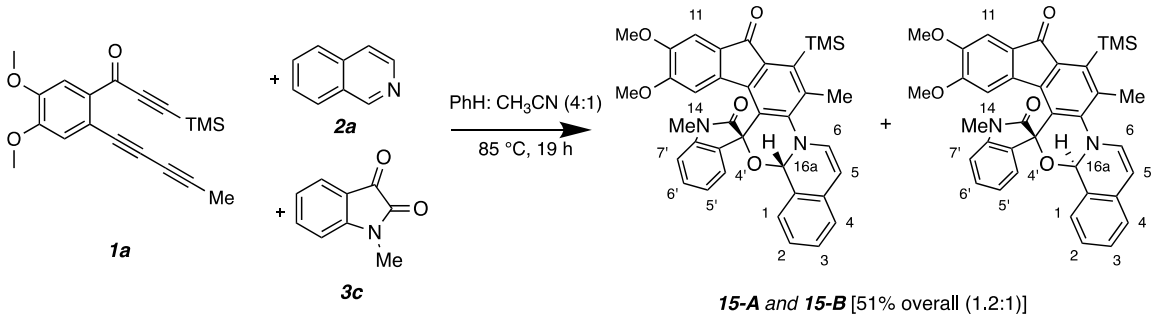
IR ($CDCl_3$): 3073, 3006, 2939, 2900, 2837, 2253, 1702, 1665, 1631, 1605, 1587, 1520, 1492, 1458, 1423, 1366, 1351, 1310, 1288, 1255, 1235, 1209, 1166, 1120, 1096, 1048, 1024, 975, 909, 884, 871, 849, 802, 772, 728, 679, 642, 603, 552, 482, and 408 cm-^{1}.

HRMS (APCI-Orbitrap): Calculated for $C_{34}H_{32}NO_5Si^+$ [$M+H^+$]: 562.2044, found 562.2037.

(±)-(15*R*,16a*R*)-12,13-Dimethoxy-1',8-dimethyl-9-(trimethylsilyl)-10H,16aH-spiro[fluoreno[3',4':4,5][1,3]oxazino[2,3-a]isoquinoline-15,3'-indoline]-2',10-dione (15-A)

and

(±)-(15*R*,16a*S*)-12,13-Dimethoxy-1',8-dimethyl-9-(trimethylsilyl)-10H,16aH-spiro[fluoreno[3',4':4,5][1,3]oxazino[2,3-a]isoquinoline-15,3'-indoline]-2',10-dione (15-B):



Triynone **1a** (25 mg, 0.077 mmol, 1 equiv), isoquinoline (**2a**, 30 μL, 0.231 mmol, 3 equiv), and *N*–methylisatin (**3c**, 62 mg, 0.385 mmol, 5 equiv) were combined in a culture tube, dissolved in a mixture of benzene and acetonitrile (4:1, overall 10 mL), and sealed with a Teflon-lined screw-cap. The tube was heated overnight (18-19 h) in an oil bath at 85 °C and cooled. The contents were passed through a plug of silica (EtOAc elution). The eluate was concentrated and the residue was purified by MPLC (1:1 Hex:EtOAc) to give **15** (24 mg, 0.039 mmol, 51%), a yellow oil, as a coeluting mixture of diastereomers (1.2:1 ratio). A small portion of this mixture was resolved by normal phase HPLC (2:1, Hex:EtOAc) to give, **15-A** and **15-B**, each as a yellow oil. The assignment of relative configuration of each was not undertaken.

Data for the faster eluting, major diastereomer, 15-A:

^{1}H NMR (500 MHz, $CDCl_3$): δ□□□□□□□□□d, *J* = 7.5, 7.5, 1.5, Hz, 1H, Ar*H3* or Ar*H6'*), 7.29$^+$ (ddd, *J* = 7.8, 7.8, 1.3 Hz, 1H, Ar*H3* or Ar*H6'*), 7.29$^-$ (dd, *J* = 7.8, 1.2 Hz, 1H, Ar*H1* or Ar*H4'*), 7.20 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H, Ar*H2* or Ar*H5'*), 7.13 (dd, *J* = 7.7, 1.2 Hz, 1H, Ar*H4* or Ar*H7'*), 7.11 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar*H1* or Ar*H4'*), 7.08 (s, 1H, Ar*H11*), 6.94 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, Ar*H2* or Ar*H5'*), 6.85 (ddd, *J* = 7.7, 0.8, 0.8 Hz, 1H, Ar*H7'* or Ar*H4*), 6.78 (d, *J* = 1.5 Hz, H*16a*), 6.44 (dd, *J* = 7.6, 1.4 Hz, 1H,

Ar*H6*), 6.13 (s, 1H, Ar*H14*), 5.91 (d, *J* = 7.7 Hz, 1H, Ar*H5*), 3.83 (s, 3H, OC*H*$_3$), 3.54 (s, 3H, OC*H*$_3$), 3.36 (s, 3H, NC*H*$_3$), 2.46 (s, 3H, ArC*H*$_3$) and 0.47 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR (125 MHz, CDCl$_3$): δ 193.4, 174.1, 153.5, 149.5, 147.6, 145.0, 144.8, 141.2, 138.6, 137.8, 137.1, 136.9, 132.5, 131.6, 130.8, 129.9, 129.5, 129.0, 127.9, 126.3, 125.1, 124.5, 124.1, 121.1, 109.2, 107.7, 106.7, 102.7, 80.5, 79.3, 56.8, 56.2, 27.0, 21.6, and 2.9.

IR (CDCl$_3$): 3060, 2937, 2899, 2838, 2252, 1718, 1704, 1632, 1612, 1588, 1525, 1491, 1460, 1433, 1365, 1312, 1290, 1244, 1210, 1167, 1131, 1091, 1054, 1030, 1013, 969, 942, 910, 891, 849, 811, 792, 772, 729, 690, 648, 629, 599, 553, 539, 488, 470, and 410 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{37}H_{35}N_2O_5Si^+$ [M+H$^+$]: 615.2310, found 615.2308.

Data for the slower eluting, minor diastereomer, 15-B:

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.45 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H, Ar*H3* or Ar*H6'*), 7.41 (dd, *J* = 7.3, 1.3 Hz, 1H, Ar*H1* or Ar*H4'*), 7.30 (ddd, *J* = 7.6, 7.6, 1.3 Hz, Ar*H3* or Ar*H6'*), 7.15 (dd, *J* = 7.8, 1.3 Hz, 1H, Ar*H1* or Ar*H4'*), 7.11 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar*H2* or Ar*H5'*), 7.08 (ddd, *J* = 7.3, 7.3, 1.3 Hz, 1H, Ar*H2* or Ar*H5'*), 7.08 (s, 1H, Ar*H11*), 6.95 (d, *J* = 7.8 Hz, 1H, Ar*H7'* or Ar*H4*), 6.78 (dd, *J* = 7.7 Hz, 1.2 Hz, 1H, Ar*H7'* or Ar*H4*), 6.47 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar*H6*), 6.14 (d, *J* = 1.6 Hz, H*16a*), 5.96 (s, 1H, Ar*H14*), 5.92 (d, *J* = 7.7 Hz, 1H, Ar*H5*), 3.83 (s, 3H, OC*H*$_3$), 3.42 (s, 3H, OC*H*$_3$), 3.26 (s, 3H, NC*H*$_3$) 2.49 (s, 3H, ArC*H*$_3$) and 0.46 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR (125 MHz, CDCl$_3$): δ 193.4, 172.9, 153.3, 149.2, 147.1, 144.7, 143.8, 140.9, 138.1, 136.9, 136.1, 133.0, 131.8, 131.6, 130.5, 129.8, 128.5, 127.8, 125.9, 124.7, 124.5, 123.7, 123.2, 119.9, 109.4, 107.3, 106.5, 102.5, 81.2, 80.0, 56.6, 56.0, 27.0, 21.7, and 2.9.

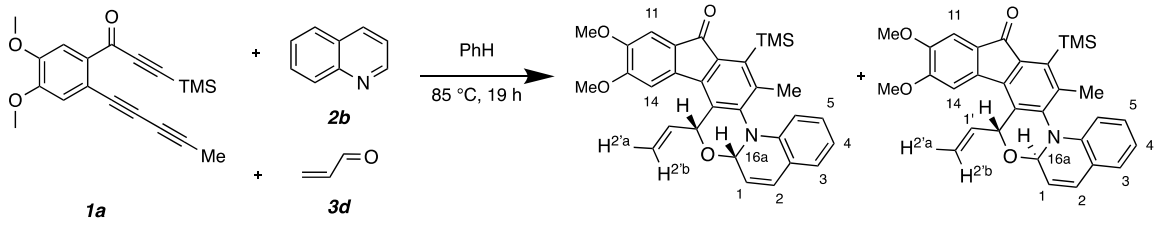
IR (CDCl$_3$): 3057, 3001, 2938, 2902, 2837, 2253, 1737, 1705, 1633, 1609, 1559, 1525, 1492, 1460, 1427, 1365, 1313, 1288, 1247, 1211, 1120, 1095, 1053, 1030, 1012, 966, 944, 913, 881, 847, 797, 772, 754, 730, 693, 648, 629, 598, 540, and 489 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{37}H_{35}N_2O_5Si^+$ [M+H$^+$]: 615.2310, found 615.2302.

(±)-(15*R*,16a*R*)-12,13-Dimethoxy-8-methyl-9-(trimethylsilyl)-15-vinyl-16aH-fluoreno[3',4':4,5][1,3]oxazino [3,2-a]quinolin-10(15H)-one (16-A)

and

(±)-(15*R*,16a*S*)-12,13-Dimethoxy-8-methyl-9-(trimethylsilyl)-15-vinyl-16aH-fluoreno[3',4':4,5][1,3]oxazino [3,2-a]quinolin-10(15H)-one (16-B)



***16-A** and **16-B** (71%, ratio from NMR: 1.5:1)*

Triynone **1a** (25 mg, 0.077 mmol, 1 equiv), quinoline (**2b**, 30 μL, 0.231 mmol, 3 equiv), and acrolein (**3d**, 26 μL, 0.385 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (10 mL), and sealed with a Teflon-lined screw-cap. The tube was heated overnight (18-19 h) in an oil bath at 85 °C and cooled. The contents were passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (2:1 Hex:EtOAc) to **16** (28 mg, 0.0263 mmol, 71%), a yellow oil, as a coeluting mixture of diastereomers (1.5:1 ratio). A small portion of this sample was further resolved by normal phase HPLC (2:1, Hex:EtOAc) to give, as partially overlapping peaks, **16-A** and **16-B**, each as a yellow oil. The assignment of relative configuration of each was not undertaken.

Data for the faster eluting, minor diastereomer, 16-A:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar*H3*), 7.18 (s, 1H, Ar*H11*), 7.15 (ddd, *J* = 8.8, 7.6, 1.8 Hz, 1H, Ar*H5*), 6.91 (d, *J* = 10.0 Hz, 1H, *H2*), 6.90 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, Ar*H4*), 6.78 (s, 1H, Ar*H14*), 6.40 (ddd, *J* = 8.3, 1.0, 1.0 Hz, 1H, *H6*), 6.18 (ddd, *J* = 17.4, 10.6, 3.7 Hz, *H1'*), 6.06 (dd, *J* = 9.5, 5.3 Hz, 1H, *H1*), 5.72 (ddd, *J* = 3.6, 1.7, 1.7 Hz, 1H, *H15*), 5.47 (d, *J* = 5.0 Hz, 1H, *H16a*), 5.41 (ddd, *J* = 10.5, 1.4, 1.4 Hz, *H2'a*), 5.30 (ddd, *J* = 17.2, 1.4, 1.4 Hz, *H2'b*), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.23 (s, 3H, ArCH_3), and 0.48 [s, 9H, Si$(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 194.0, 153.6, 149.3, 142.9, 141.0, 140.3, 139.8, 139.0, 137.8, 137.7, 137.0, 130.0, 129.1, 128.2, 127.7, 127.3, 122.2, 120.4, 119.2, 118.7, 115.7, 108.7, 106.8, 75.9, 73.3, 56.4, 56.3, 20.0, and 3.2.

IR (thin film): 3003, 2925, 2902, 2852, 2253, 1703, 1645, 1591, 1569, 1536, 1488, 1455, 1421, 1365, 1313, 1288, 1243, 1207, 1114, 1081, 1019, 992, 935, 911, 840, 804, 772, 729, 646, 635, 602, 567, 541, 468, and 410 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{31}H_{32}NO_4Si^+$ [$M+H^+$]: 510.2095, found 510.2095.

Data for the slower eluting, major diastereomer, 16-B (contains ~20% of the minor diastereomer, **16-A**):

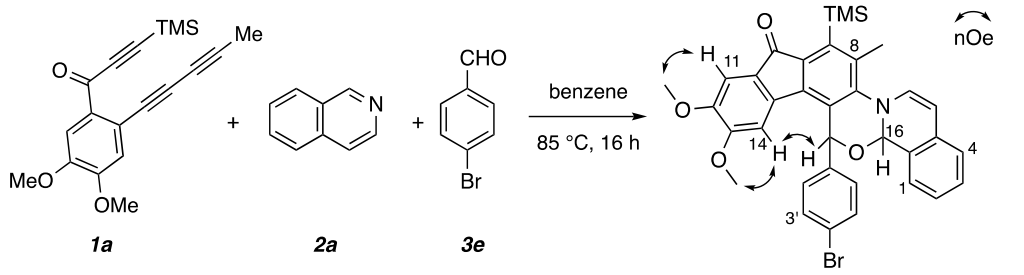
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H3*), 7.20 (s, 1H, Ar*H11*), 7.18 (ddd, *J* = 8.1, 8.1, 1.6 Hz, Ar*H5*), 7.00 (s, 1H, Ar*H14*), 6.92 (br d, *J* = 9.5 Hz, 1H, *H2*) 6.91 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, Ar*H4*), 6.48 (ddd, *J* = 8.3, 1.1, 1.1 Hz, 1H, Ar*H6*), 6.06 (dd, *J* = 9.5, 5.1 Hz, 1H, *H1*), 6.06 (dd, *J* = 5.5, 1.3 Hz, 1H, *H16a*), 5.85 (ddd, *J* = 17.0, 10.3, 5.6 Hz, *H1'*), 5.52 (d, *J* = 5.0 Hz, 1H, *H15*), 5.15 (ddd, *J* = 17.0, 1.3, 1.3 Hz, *H2'b*), 5.02 (ddd, *J* = 10.2, 1.3, 1.3 Hz, *H2'a*), 3.94 (s, 3H, OC*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 2.18 (s, 3H, ArC*H*$_3$) and 0.46 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 193.8, 153.7, 149.4, 143.6, 142.0, 140.0, 139.9, 139.0, 138.7, 137.6, 137.0, 136.3, 129.8, 129.2, 128.2, 127.7, 121.5, 120.0, 118.4, 117.2, 114.8, 107.8, 107.1, 79.6, 74.2, 56.4, 56.3, 19.6, and 2.8.

IR ($CDCl_3$): 3039, 3004, 2956, 2929, 2902, 2853, 2838, 2253, 1703, 1642, 1591, 1570, 1541, 1489, 1456, 1421, 1357, 1313, 1290, 1244, 1206, 1114, 1081, 1015, 907, 840, 803, 772, 727, 647, 606, 543, 459, and 409 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{31}H_{32}NO_4Si^+$ [$M+H^+$]: 510.2095, found 510.2075.

(±)-(15*R,16*R**)- and (±)-(15*R**,16*S**)-15-(4-Bromophenyl)-12,13-dimethoxy-8-methyl-9-(trimethylsilyl)-16a*H*-fluoreno[3',4':4,5][1,3]oxazino[2,3-*a*]isoquinolin-10(15*H*)-one (17-A and 17-B)**



A solution of ketone **1a** (30.0 mg, 0.0924 mmol) isoquinoline (**2a**, 21.7 μL, 0.185 mmol), and *p*-bromobenzaldehyde (**3e**, 85.5 mg, 0.462 mmol) in benzene (5 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (6:1 hexanes:EtOAc) to give the diastereomeric ketones **17-A** (23.9 mg, 41%) and **17-B** (19.4 mg, 33%), each as an orange, foamy, amorphous solid.

17-A (faster eluting, major isomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (br s, 2H, Ar*H3'a* and Ar*H3'b*), 7.32 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, Ar*H3*), 7.32 (br s, 1H, Ar*H2'a*), 7.19–7.10 (m, 3H, Ar*H2*, Ar*H4*, Ar*H2'b*), 7.12 (s, 1H, Ar*H11*), 6.73 (d, *J* = 7.6 Hz, 1H, Ar*H1*), 6.34 (dd, *J* = 7.7, 1.5 Hz, 1H, Ar*H6*), 6.17 (s, 1H, Ar*H14*), 6.14 (s, 1H, *H15*), 5.87 (d, *J* = 7.7 Hz, 1H, Ar*H5*), 5.74 (d, *J* = 1.4 Hz, 1H, *H16*), 3.86 (s, 3H, C12OC*H*$_3$), 3.45 (s, 3H, C13OC*H*$_3$), 2.48 (s, 3H, ArC*H*$_3$), and 0.49 [s, 9H, Si(C*H*$_3$)$_3$]. (rotation about the hindered *p*-BrC_6H_4–C bond was slow enough at ambient temperature to broaden the four ArH resonances on the *p*-BrC_6H_4 ring.)

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 153.3, 149.0, 145.7, 143.4, 140.1, 139.7, 136.7, 136.3, 134.9, 133.1, 131.1, 130.7, 129.7, 128.3, 127.6, 126.1, 125.6, 125.1, 124.3, 122.92, 122.89, 108.3, 106.5, 102.1, 78.3, 75.2, 56.1, 56.0, 21.2, and 3.0.

IR (neat): 2999, 2932, 2903, 2848, 1702, 1633, 1591, 1569, 1535, 1493, 1457, 1431, 1400, 1367, 1314, 1284, 1244, 1211, 1120, 1098, 1057, 1031, 1009, and 958 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{35}H_{33}BrNO_4Si^+$ [M+H$^+$] 638.1357, found 638.1343.

TLC: R_f 0.2 (6:1 hexanes:EtOAc).

17-B (slower eluting, minor isomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (superposition of two doublets: d, *J* = 8.5 Hz, 2H, H3’ and d, *J* ca. 8 Hz, 1H, H4), 7.34 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H, *H2* or *H3*), 7.24 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, *H2* or *H3*), 7.15 (superposition of two doublets: d, *J* = 8.4 Hz, 2H, H2’ and d, *J* ca. 8 Hz, 1H, H1), 7.12 (s, 1H, Ar*H11*), 6.64 (s, 1H, *H15*), 6.58 (s, 1H, Ar*H14*), 6.46 (dd, *J* = 7.5, 1.3 Hz, 1H, Ar*H6*), 6.06 (d, *J* = 1.1 Hz, 1H, *H16*), 5.86 (d, *J* = 7.6 Hz, 1H, Ar*H5*), 3.86 (s, 3H, C13OCH_3), 3.73 (s, 3H, C12OCH_3), 2.42 (s, 3H, ArCH_3), and 0.48 [s, 9H, Si(CH_3)$_3$].

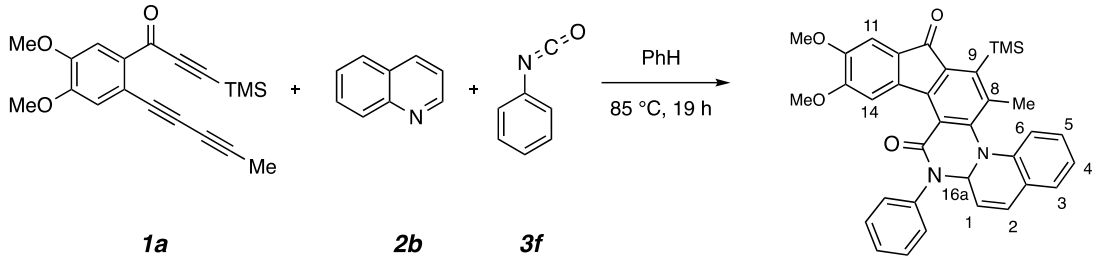
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 153.4, 149.2, 146.2, 143.4, 140.0, 139.3, 137.7, 136.9, 136.1, 132.0, 131.7, 131.3, 129.6, 129.5, 128.3, 127.4, 126.6, 126.0, 125.7, 124.6, 122.6, 108.1, 106.7, 102.0, 83.0, 77.0, 56.3, 56.1, 20.2, and 2.6.

IR (neat): 3006, 2940, 2894, 1702, 1630, 1590, 1566, 1538, 1492, 1458, 1433, 1404, 1360, 1312, 1285, 1241, 1210, 1119, 1098, 1059, 1031, 1009, and 986 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{35}H_{33}{}^{79}BrNO_4Si^+$ [M+H$^+$] 638.1357, found 638.1336.

TLC: R_f 0.1 (6:1 hexanes:EtOAc).

12,13-Dimethoxy-8-methyl-16-phenyl-9-(trimethylsilyl)-16,16a-dihydroindeno[1,2-*f*]quinolino[1,2-*a*]quinazoline-10,15-dione (18)



1a ***2b*** ***3f*** ***18 (91%)***

Triynone **1a** (20 mg, 0.062 mmol), quinoline(**2b**, 15 μl, 0.124 mmol, 2 equiv), and phenyl isocyanate (**3f**, 45.9 μL, 0.310 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (4 mL, 0.02 M), and sealed with a Teflon-lined cap. The vial was heated overnight (18-19 h) in an oil bath at 85 °C and cooled, and the contents were passed through a plug of silica (EtOAc elution). The residue was purified by MPLC (3:1 Hex:EtOAc +1% NEt_3) to give **18** (91%) as a yellow crystalline film.

Data for 18:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H, Ar*H14*), 7.32 (br m, 3H, Ph*Hs*), 7.24 (1H, ddd, *J* = 7.4, 7.4, 1.5 Hz, 1H, Ar*H5*), 7.16 (s, 1H, Ar*H11*), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*3), 6.97 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, Ar*H4*), 6.89 (vbr s, 2H, Ph*Hs*), 6.64 (d, *J* = 9.8 Hz, 1H, C=C*H2*), 6.53 (d, *J* = 8.2 Hz, 1H, Ar*H*6), 6.01 (d, *J* = 5.9 Hz, 1H, C*H*16a), 5.53 (dd, *J* =9.6, 5.8 Hz, 1H, *H1*C=C), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.25 (s, 3H, ArCH_3) and 0.48 [s, 9H, $Si(CH_3)_3$].

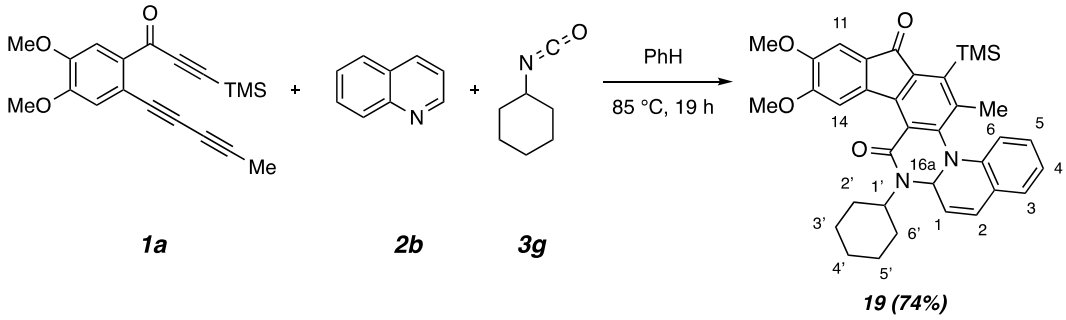
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 162.4, 154.0, 149.9, 146.9, 144.3, 143.8, 140.2, 138.1, 137.9, 137.2, 137.1, 129.61, 129.57, 129.3, 129.0, 128.0, 127.7, 127.5, 123.5, 122.2, 121.2, 117.2, 115.9, 110.5, 105.9, 67.8, 56.5, 56.1, 20.2, and 2.7.

IR (thin film): 2955, 2922, 2853, 1703, 1656, 1593, 1562, 1533, 1488, 1455, 1420, 1397, 1354, 1314, 1292, 1260, 1239, 1220, 1183, 1118, 1074, 1022, 1003, 955, 929, 847, 820, 804, 789, 763, 735, 696, 654, 636, 607, 596, 569, 550, 514, 463, and 433 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{35}H_{33}N_2O_4Si^+$ [$M+H^+$]: 573.2204, found 573.2201.

mp: >230 °C.

16-Cyclohexyl-12,13-dimethoxy-8-methyl-9-(trimethylsilyl)-16,16a-dihydroindeno[1,2-f]quinolino[1,2-a]quinazoline-10,15-dione (19)



Triynone **1a** (25 mg, 0.077 mmol), quinoline (**2b**, 28 μL, 0.231 mmol, 3 equiv), and cyclohexyl isocyanate (**3g**, 49 μL, 0.385 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (10 mL), and sealed with a Teflon-lined screw-cap. The tube was heated overnight (18-19 h) in an oil bath at 85 °C and cooled. The contents were passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (3:1 Hex:EtOAc) to give **19** (74%) as a yellow oil.

Data for 19:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H, Ar*H14*), 7.24 (dd, *J* = 7.5, 1.3 Hz, 1H, Ar*H3*), 7.19 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H, Ar*H5*), 7.14 (s, 1H, Ar*H11*), 6.98 (br d, *J* = 9.6 Hz, 1H, *H2*), 6.94 (ddd, *J* = 8.4, 7.4, 1.0 Hz, 1H, Ar*H4*), 6.45 (d, *J* = 8.0 Hz, 1H, Ar*H6*), 5.96 (dd, *J* = 9.5, 6.1, 1H, *H1*C=C), 5.66 (d, *J* = 6.1 Hz, 1H, C*H*16a), 4.00 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3'), 3.44 (br m, 1H, *H1'*), 2.58 (br m, 1H), 2.04 (dddd, *J* = 12.6, 12.6, 12.6, 3.9 Hz, 1H), 2.16 (s, 3H, ArCH_3), 1.81 (br d, *J* = 12.7 Hz, 1H), 1.67 (br d, *J* = 12.0 Hz, 1H), 1.61 (br d, *J* = 12.9 Hz, 1H), 1.56 (br d, *J* = 12.1 Hz, 1H), 1.21 (ddddd, *J* = 13.0, 13.0, 13.0, 3.2, 3.2 Hz, 1H), 1.16 (ddddd, *J* = 12.8, 12.8, 12.8, 3.3, 3.3 Hz, 1H), and 1.06 (ddddd, *J* = 12.9, 12.9, 12.9, 3.5, 3.5 Hz, 1H), and 0.45 [s, 9H, $Si(CH_3)_3$].

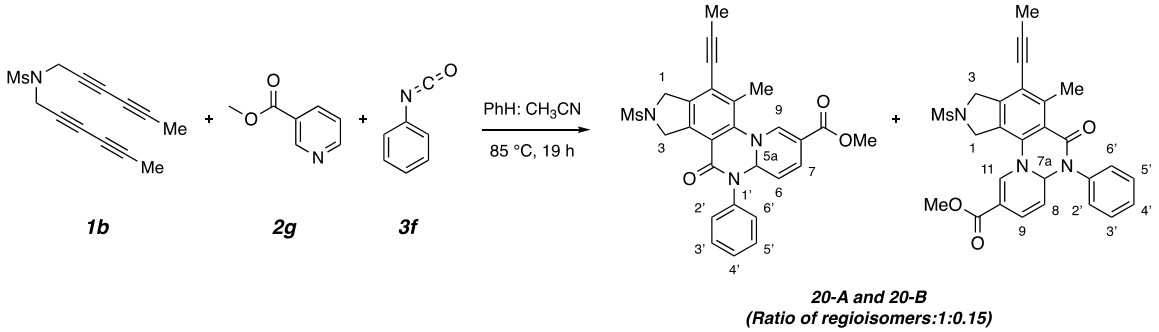
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 162.7, 153.9, 149.8, 146.1, 144.1, 143.1, 139.9, 138.1, 137.5, 137.3, 130.2, 129.7, 127.6, 124.6, 122.3, 121.0, 116.9, 116.3, 110.2, 106.0, 67.4, 56.4, 56.2, 55.7, 30.0, 29.3, 26.9, 26.4, 25.3, 20.2, and 2.8.

IR (thin film): 2930, 2853, 2253, 1703, 1638, 1599, 1567, 1536, 1488, 1455, 1359, 1315, 1289, 1246, 1219, 1114, 1085, 1053, 1022, 1003, 903, 881, 844, 788, 767, 728, 698, 646, 635, 607, 595, 570, 551, 519, 467, and 418 cm^{-1}.

HRMS: (APCI-Orbitrap): Calculated for $C_{35}H_{39}N_2O_4Si^+$ [$M+H^+$]: 579.2674, found 579.2651.

Methyl-11-methyl-2-(methylsulfonyl)-4-oxo-5-phenyl-12-(prop-1-yn-1-yl)-1,2,3,4,5,5a-hexahydropyrido[1,2-a]pyrrolo[3,4-f]quinazoline-8-carboxylate (20-A) and

Methyl-5-methyl-2-(methylsulfonyl)-6-oxo-7-phenyl-4-(prop-1-yn-1-yl)-1,2,3,6,7,7a-hexahydropyrido[1,2-a]pyrrolo[3,4-h]quinazoline-10-carboxylate (20-B):



Tetrayne **1b** (60 mg, 0.242 mmol), methyl nicotinate (**2g**, 100 mg, 0.727 mmol, 3 equiv), and phenyl isocyanate (**3f**, 132 μL, 1.21 mmol, 5 equiv) were combined in a culture tube, dissolved in a mixture of benzene and acetonitrile (14 mL, 3:2 ratio), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (pure EtOAc). The residue was purified by gradient flash chromatography–first by 2:1, Hex:EtOAc and then pure EtOAc to obtain a crude mixture of isomers (ratio: 1:0.15). This product was repurified by MPLC (1:1, EtOAc:Hex+ 1% NEt_3) to give **20** as a pale brown powder, which was obtained as a mixture of coeluting isomers **20-A** and **20-B** (86 mg, 71% yield, ratio: 1:0.15).

Data for the major isomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.36 (m, 4H, Ph*Hm*, Ph*Hp* and *H9*), 7.08 (br d, *J* = 6.5 Hz, 2H, Ph*Ho*), 6.71 (dd, *J* = 10.0, 1.0 Hz, 1H, *H7*), 6.23 (d, *J* = 5.0 Hz, 1H, *H5a*), 5.22 (br d, *J* = 16.1 Hz, 1H, MsNC3*H$_a$*C3H$_b$), 5.02 (dd, *J* = 10.1, 5.0 Hz, 1H, *H6*) 4.99 (dd, *J* = 16.5, 2.7 Hz, 1H, MsNC3H$_a$C3*H$_b$*), 4.80 (br d, *J* = 15.1 Hz, 1H, MsN*C1H$_a$*C1H$_b$), 4.70 (br d, *J* = 15.0 Hz, 1H, MsNC1H$_a$C1*H$_b$*), 3.77 (s, 3H, CO_2*Me*), 2.88 (s, 3H, C*H*$_3$$SO_2$N), 2.51 (s, 3H, NArC*H*$_3$), and 2.19 (s, 3H, C≡CC*H*$_3$).

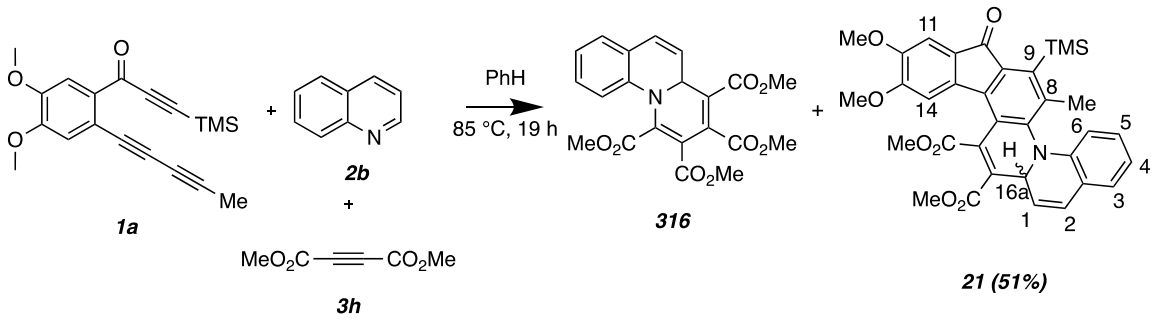
^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 161.7, 141.6, 140.8, 138.8, 138.2, 136.3, 135.7, 134.7, 131.4, 129.4, 128.5, 124.7, 120.2, 110.0, 104.3, 99.4, 75.3, 68.1, 55.6, 53.6, 51.6, 35.3, 16.2, and 5.0.

HRMS (APCI-Orbitrap): Calculated for $C_{23}H_{26}N_3O_5S^+$ [M+H$^+$]: 504.1588, found 504.1587.

IR ($CDCl_3$): 3066, 2952, 2920, 2852, 2253, 2234, 1726, 1698, 1642, 1593, 1531, 1494, 1436, 1406, 1336, 1262, 1191, 1153, 1114, 1075, 1025, 961, 907, 824, 725, 692. 647, 613, 565, and 518 cm^{-1}.

^{1}H NMR identifiable, unique resonances for the minor isomer (500 MHz, $CDCl_3$): 6.64 (s, 1H, *H9*) 6.60 (d, *J* = 7.2 Hz, 1H, *H5a* or *H7*), 5.57 (dd, *J* = 6.7, 6.7 Hz, 1H, *H6*), 5.26 (br d, 1H, MsNC3*H$_a$*C3H$_b$), 4.99 (br d, 1H, MsNC3H$_a$C3*H$_b$*), 3.48 (s, 3H, CO_2*Me*), and 2.45 (s, 3H, NArC*H*$_3$). (the integral values for resonances corresponding to H1, H3, PhH$_m$, PhH$_p$, CH_3SO_2, and $CH_3C{\equiv}C$ suggest that these are overlapping from both major and minor isomers.)

Dimethyl-12,13-Dimethoxy-8-methyl-10-oxo-9-(trimethylsilyl)-10,16a dihydroindeno[1,2*f*]quinolino [1,2-*a*]quinoline-15,16-dicarboxylate (21)



Triynone **1a** (20 mg, 0.062 mmol), quinoline (**2e**, 22 μL, 0.186 mmol, 3 equiv) and dimethyl acetylenedicarboxylate (**3h**, 76 μL, 0.62 mmol, 10 equiv) were combined in a culture tube, dissolved in benzene (4 mL, 0.02 M), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc). The residue was purified by MPLC (3:2 Hex:EtOAc) to give, in order of elution, the known 2:1 adduct of quinoline and **3h** [**316** (25 mg, 0.060 mmol) as a pale yellow solid] followed by the three-component coupling product **21** (19 mg, 51%) as a yellow oil. The latter was further purified by HPLC (3:2 Hex:EtOAc) to give a more pure sample of **21** that was used for collection of spectral data.

Data for 316: Characterization data were in accordance with the reported literature.[112]

Data for 21: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (s, 1H, Ar*H11*), 7.07 (1H, ddd, *J* = 7.8, 7.8, 1.6 Hz, 1H, Ar*H5*), 7.03 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar*H*3), 6.82 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H, Ar*H4*), 6.72 (s, 1H, Ar*H14*), 6.67 (ddd, *J* = 9.7, 0.8, 0.8 Hz, 1H, C=C*H2*), 6.31 (d, *J* = 8.2 Hz, 1H, Ar*H*6), 5.97 (dd, *J* = 9.8, 6.1 Hz, 1H, *H1*C=C), 4.71 (dd, *J* = 6.1, 0.7 Hz, 1H, C*H*16a), 3.92 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.74 (s, 3H, CO_2CH_3), 3.56 (s, 3H, CO_2CH_3), 2.27 (s, 3H, $ArCH_3$), and 0.48 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 166.4, 165.9, 154.2, 149.5, 144.5, 142.6, 141.3, 140.3, 138.6, 138.5, 138.2, 138.1, 129.2, 128.8, 127.6, 127.1, 126.3, 122.3, 121.6, 120.8, 119.5, 115.7, 106.7, 105.9, 56.6, 56.3, 54.9, 52.7, 52.5, 21.0, and 2.8.

IR (thin film): 2956, 2921, 2852, 1736, 1728, 1711, 1659, 1598, 1531, 1486, 1458, 1365, 1302, 1259, 1218, 1136, 1092, 1021, 849, 801, 721, 637, and 608 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{34}H_{32}NO_7Si^+$ [M–H$^-$]: 594.1943, found 594.1940.

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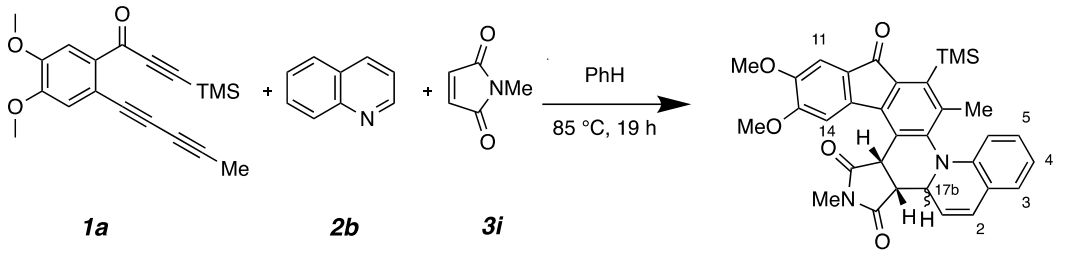
[112] Valizadeh, H.; Shomali, A. and Gholipour, H. A Facile and Efficient Addition Reaction of Nitrogen-Containing Heterocyclic Compounds with DMAD Under Neat Conditions. *J. Heterocyclic Chem.*, 2011, **48**, 1440–1444.

(±)-(14d*R*,17a*S*,17b*R*)- and (±)-(14d*R*,17a*S*,17b*S*)-12,13-Dimethoxy-8,16-dimethyl-9-(trimethylsilyl)-17a,17b-dihydro-10H-indeno[1,2-f]pyrrolo[3,4-c]quinolino[1,2-a]quinoline-10,15,17(14dH,16H)-trione (22-cis/anti) and (22-cis/syn), respectively.



22-cis/anti H_{17b} "down" (58%)
22-cis/syn H_{17b} "up"(22%)
80% (combined)

Triynone **1a** (30 mg, 0.092 mmol), quinoline (**2b**, 22 μL, 0.185 mmol, 2 equiv) and *N*-methylmaleimide (**3i**, 51 mg, 0.460 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.02 M), and sealed with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc). The filtrate was concentrated and the residue was purified by MPLC (1:1 Hex:EtOAc + 1% NEt_3) to give, in order of elution, **22-cis/anti** (30 mg, 58% yield) as a yellow oil and **22-cis/syn** as a yellow amorphous solid (11 mg, 22% yield).

Data for 22-cis/anti:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 1H, Ar*H11*), 7.09 (d, *J* = 7.4 Hz, 1H, Ar*H*3), 7.00 (1H, dd, *J* = 7.9, 7.9, 1H, Ar*H5*), 6.82 (s, 1H, Ar*H14*), 6.82 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar*H4*), 6.71 (d, *J* = 9.9 Hz, 1H, C=C2*H*), 6.04 (d, *J* = 8.4 Hz, 1H, Ar*H*6), 6.01 (dd, *J* = 9.6, 5.8 Hz, 1H, *H*C1=C2), 4.52 (d, *J* = 7.0 Hz, 1H, C*H14d*), 3.97 (dd, *J* =10.4, 6.0 Hz, 1H, *H17b*), 3.93 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.52 (dd, *J* =10.3, 7.0 Hz, 1H, *H17a*), 3.05 (s, 3H, NCH_3), 2.22 (s, 3H, ArCH_3), and 0.44 [s, 9H, Si$(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 174.9, 174.3, 153.6, 149.7, 143.7, 143.5, 142.0, 140.6, 139.9, 139.6, 138.8, 129.4, 127.84, 127.78, 127.77, 123.5, 121.9, 120.7, 120.1, 115.3, 107.9, 106.5, 56.5, 56.3, 56.2, 43.0, 42.9, 25.4, 19.6, and 3.2.

HRMS (APCI-Orbitrap): Calculated for $C_{33}H_{33}N_2O_5Si^+$ [M+H$^+$]: 565.2153, found 565.2151.

IR (thin film): 3056, 2943, 2898, 2836, 2253, 1776, 1699, 1591, 1567, 1534, 1485, 1454, 1431, 1366, 1313, 1274, 1241, 1204, 1113, 1089, 1067, 1029, 993, 963, 928, 911, 838, 810, 797, 772, 728, 701, 680, 647, 622, 605, 573, 555, 515, 445, and 411 cm^{-1}.

Data for 22-cis/syn:

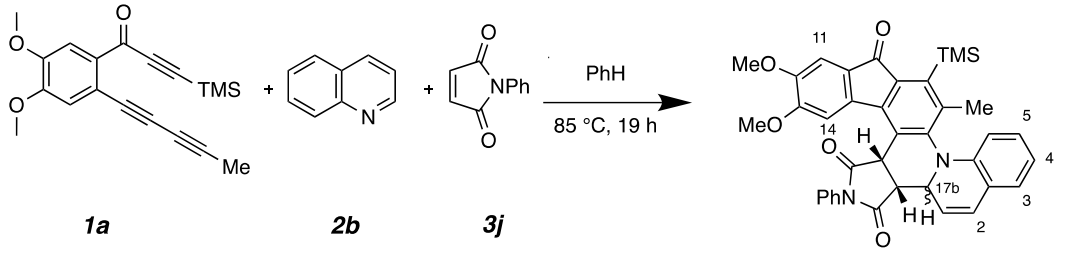
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H, Ar*H11*), 7.15 (s, 1H, Ar*H14*), 7.01 (d, *J* = 7.6 Hz, 1H, Ar*H*3), 6.96 (1H, ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H, Ar*H5*), 6.71 (d, *J* = 10.1 Hz, 1H, C=C2*H*), 6.70 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, Ar*H4*), 6.11 (d, *J* = 8.2 Hz, 1H, Ar*H*6), 6.02 (dd, *J* = 9.9, 5.6 Hz, 1H, *H*C1=C2), 4.69 (d, *J* = 8.6 Hz, 1H, C*H14d*), 4.44 (dd, *J* =5.8, 5.8 Hz, 1H, *H17b*), 3.95 (s, 3H, OC*H*$_3$), 3.94 (s, 3H, OC*H*$_3$), 3.35 (dd, *J* = 8.6, 5.8 Hz, 1H, *H17a*), 2.47 (s, 3H, NC*H*$_3$), 2.13 (s, 3H, $ArCH_3$), and 0.43 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 175.4, 175.1, 153.9, 149.8, 145.5, 143.0, 142.8, 140.0, 139.6, 139.5, 138.5, 129.5, 128.2, 127.9, 127.5, 124.8, 122.4, 121.0, 119.9, 112.4, 107.2, 106.6, 56.9, 56.7, 56.3, 50.9, 41.9, 25.1, 19.3, and 2.9.

IR (thin film): 3053, 2944, 2899, 2837, 1774, 1695, 1573, 1545, 1486, 1455, 1433, 1380, 1359, 1301, 1242, 1219, 1160, 1106, 1047, 1022, 954, 908, 845, 799, 769, 730, 700, 678, 647, 606, 573, 542, 502, 443, and 409 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{33}H_{33}N_2O_5Si^+$ [$M+H^+$]: 565.2153, found 565.2137

(±)-(14d*R*,17a*S*,17b*R*)- and (±)-(14d*R*,17a*S*,17b*S*)-12,13-Dimethoxy-8-methyl-16-phenyl-9-(trimethylsilyl)-17a,17b-dihydro-10*H*-indeno[1,2-*f*]pyrrolo[3,4-*c*]quinolino[1,2-*a*]quinoline-10,15,17(14d*H*,16*H*)-trione: (23-cis/anti) and (23-cis/syn), respectively.



23-cis/anti H_{17b} "down" (32%)
23-cis/syn H_{17b} "up"(40%)
72% (combined)

Triynone **1** (30 mg, 0.092 mmol), quinoline (**2b**, 22 μL, 0.185 mmol, 2 equiv) and *N*-phenylmaleimide (**3j**, 79.7 mg, 0.460 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.02 M), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc). The eluate was concentrated and the residue was purified by MPLC (2:1 Hex:EtOAc) to give, in order of elution **23-cis/anti** (32%) as a yellow oil and **23-cis/syn** (40%), which solidified upon storage at -10 °C to a pale yellow amorphous powder.

Data for faster eluting, minor isomer (23-cis/anti):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (t, *J* = 7.8 Hz, 2H, *ArH*$_m$), 7.39 (t, *J* = 7.4 Hz, 1H, *ArH*$_p$), 7.29 (d, *J* = 7.8 Hz, 2H, *ArH*$_o$), 7.19 (s, 1H, Ar*H11*), 7.11 (d, *J* = 7.3 Hz, 1H, Ar*H3*), 7.03 (dd, *J* = 7.4, 7.4 Hz, 1H, Ar*H5*), 6.88 (s, 1H, Ar*H14*), 6.85 (dd, J = 7.4, 7.4 Hz, 1H, Ar*H4*), 6.72 (d, *J* = 9.8, 1H, C=C2*H*), 6.10 (d, *J* = 8.1 Hz, 1H, Ar*H6*), 6.04 (dd, *J* = 9.6, 5.9 Hz, 1H, *H*C1=C2), 4.70 (d, *J* = 7.0 Hz, 1H, *H14d*), 4.17 (dd, *J* = 10.2, 5.9 Hz, *H17b*), 3.92 (s, 3H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 3.62 (dd, *J* = 10.3, 7.0 Hz, 1H, *H17a*), 2.25 (s, 3H, ArC*H*$_3$), and 0.45 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 173.6, 173.3, 153.6, 149.7, 143.9, 143.4, 142.1, 140.5, 139.9, 139.5, 138.8, 131.6, 129.41, 129.40, 129.0, 128.0, 127.84, 127.83, 126.1, 123.5, 121.7, 120.8, 119.9, 115.4, 107.7, 106.5, 56.4, 56.4, 56.3, 43.1, 43.0, 19.7, and 3.2.

HRMS (APCI-Orbitrap): Calculated for $C_{38}H_{35}N_2O_5Si^+$ [M+H$^+$]: 627.2310, found 627.2304.

IR (thin film): 3066, 2945, 2899, 2836, 1707, 1596, 1536, 1497, 1455, 1376, 1316, 1244, 1207, 1115, 1066, 1023, 852, 808, 772, 743, 690, and 609 cm^{-1}.

Data for slower eluting, major isomer (23-cis/syn):

^{1}H NMR (500 MHz, $CDCl_3$): 7.25–7.23 (m, 3H, Ph*H*), 7.22 (s, 1H, Ar*H14* or Ar*H11*), 7.21 (s, 1H, Ar*H14* or Ar*H11*), 7.02 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H3*), 7.00 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H, Ar*H5*), 6.76 (dd, *J* = 7.6, 7.6, 1.0 Hz, 1H, Ar*H4*), 6.69 (ddd, *J* = 9.9, 1.1, 1.1 Hz, 1H, C=C2*H*), 6.48–6.49 (m, 2H, PhH), 6.21 (d, *J* = 8.0 Hz, 1H, Ar*H6*), 6.04 (dd, *J* = 9.8, 5.5 Hz, 1H, *H*C1=C2), 4.89 (d, *J* = 9.0 Hz, 1H, Ar*H14d*), 4.61 (ddd, *J* = 5.7, 5.7, 1.1 Hz, *H17b*), 3.98 (s, 3H, OC*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 3.54 (dd, *J* = 8.8, 5.8 Hz, 1H, *H17a*), 2.16 (s, 3H, ArC*H*$_3$), and 0.43 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 193.4, 174.2, 174.1, 153.9, 149.9, 145.4, 143.3, 143.0, 140.0, 139.6, 139.4, 138.4, 131.6, 129.8, 128.9, 128.7, 128.3, 127.9, 127.7, 126.3, 124.6, 122.2, 121.0, 119.9, 112.8, 107.2, 106.8, 57.2, 56.8, 56.3, 51.6, 41.9, 19.6, and 2.9.

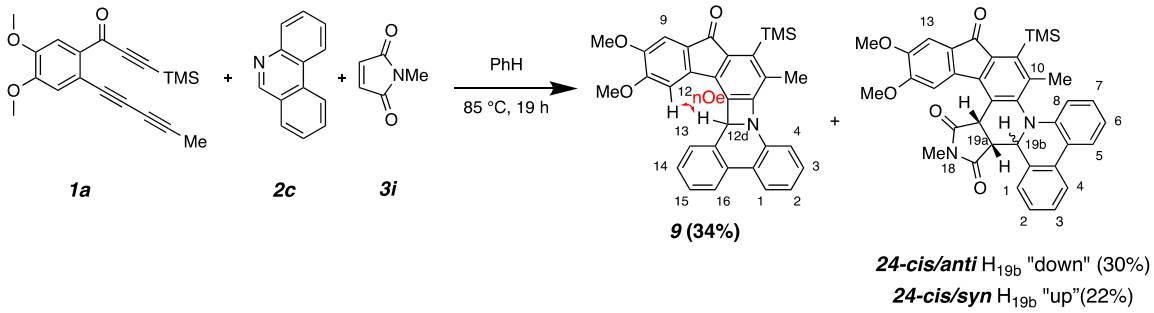
HRMS (APCI-Orbitrap): Calculated for $C_{38}H_{35}N_2O_5Si^+$ [M+H$^+$]: 627.2310, found 627.2304.

IR (thin film): 3055, 2945, 2899, 2837, 1704, 1594, 1487, 1455, 1380, 1301, 1243, 1204, 1108, 1019, 923, 843, 799, 766, 732, 694, 650, 606, 542, 523, and 462 cm^{-1}.

10,11-Dimethoxy-6-methyl-7-(trimethylsilyl)fluoreno[4',3':3,4]azeto[1,2-f]phenanthridin-8(12dH)-one (9),

(±)- (16dS,19aR,19bR)-14,15-dimethoxy-10,18-dimethyl-11-(trimethylsilyl)-19a,19b-dihydro-12H-indeno[1',2':5,6]pyrrolo[3',4':3,4]quinolino[1,2-f]phenanthridine-12,17,19(16dH,18H)-trione (24-cis/anti), and

(±)-(16dS,19aR,19bS)-14,15-Dimethoxy-10,18-dimethyl-11-(trimethylsilyl)-19a,19b-dihydro-12H-indeno[1',2':5,6]pyrrolo[3',4':3,4]quinolino[1,2-f]phenanthridine-12,17,19(16dH,18H)-trione (24-cis/syn):



Triynone **1a** (25 mg, 0.077 mmol), phenanthridine (**2c**, 41 mg, 0.231 mmol, 3 equiv), and N-methyl maleimide (**3i**, 70 mg, 0.615 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (10 mL), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (1:1, Hex:EtOAc) to give, in order of elution, **1a** (13 mg, 0.026 mmol, 34%; characterized on page S14, above) as an orange oil, **24-cis/anti** (14 mg, 0.023 mmol, 30%) as a yellow amorphous solid, and **24-cis/syn** (10 mg, 0.016 mmol, 22%), also as an orange oil.

Data for the faster eluting, three-component isomer 24-cis/anti

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H4*), 7.82 (dd, *J* = 7.8, 1.6 Hz, 1H, Ar*H5*), 7.50 (ddd, *J* = 7.6, 7.6 , 1.4 Hz, 1H, Ar*H3*), 7.33 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, Ar*H2*), 7.22 (s, 1H, Ar*H13*), 7.10 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H, Ar*H7*), 7.00 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, Ar*H6*), 6.87 (dd, *J* = 7.6, 1.3 Hz, 1H, Ar*H1)*, 6.22 (s, 1H, Ar*H16*), 6.15 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar*H8*), 4.53 (d, *J* = 7.0 Hz, 1H, *H19b*), 4.32 (d, *J* = 10.4 Hz, 1H, *H16d*), 3.94 (s, 3H, C14OC*H*$_3$), 3.85 (s, 3H, C15OC*H*$_3$), 3.47 (dd, *J* = 10.4, 6.7 Hz, 1H, *H19a*), 3.11 (s, 3H, N*Me*), 2.23 (s, 3H, $ArCH_3$), and 0.38 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (126 MHz, $CDCl_3$): δ 193.9, 174.7, 174.4, 153.6, 149.7, 144.4, 143.8, 142.1, 141.3, 140.7, 139.5, 139.0, 130.9, 130.5, 129.5, 129.4, 128.3, 127.8, 127.2, 124.6, 123.5, 123.1, 121.5, 120.2, 116.7, 107.8, 106.6, 61.2, 56.4, 56.3, 43.6, 42.5, 25.4, 19.2, and 3.2.

HRMS (APCI-Orbitrap): Calculated for $C_{37}H_{35}N_2O_5Si^+$ [M+H^+]: 615.2310, found 615.2305.

IR ($CDCl_3$): 3069, 3000, 2941, 2899, 2837, 2251, 1777, 1699, 1591, 1568, 1536, 1494, 1457, 1436, 1353, 1314, 1271, 1242, 1208, 1117, 1088, 1067, 1026, 991, 967, 940, 910, 849, 799, 749, 728, 669, 647, 608, 586, 506, and 455 cm^{-1}.

Data for slower eluting, three-component isomer 24-cis/syn:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H4*), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H, Ar*H5*), 7.50 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H, Ar*H3*), 7.40 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H, Ar*H2*), 7.26 (dd, *J* = 7.6, 1.3 Hz, 1H, Ar*H1)*, 7.24 (s, 1H, Ar*H13* or Ar*H16*), 7.18 (s, 1H, Ar*H13* or Ar*H16*), 7.06 (ddd, *J* = 8.7, 7.5, 1.6 Hz, 1H, Ar*H7*), 6.88 (ddd, *J* = 7.6, 1.2 Hz, 1H, Ar*H6*), 6.25 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar*H8*), 4.86 (d, *J* = 6.0 Hz, 1H, *H19b*), 4.75 (d, *J* = 8.9 Hz, 1H, *H16d*), 3.950 (s, 3H, OC*H*$_3$), 3.947 (s, 3H, OC*H*$_3$), 3.51 (dd, *J* = 8.8, 6.0 Hz, 1H, *H19a*), 2.35 (s, 3H, N*Me*), 2.15 (s, 3H, $ArCH_3$), and 0.43 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (126 MHz, $CDCl_3$): δ 193.6, 175.3, 174.9, 154.0, 149.8, 145.8, 143.2, 142.8, 140.6, 140.5, 140.0, 138.5, 132.0, 130.6, 129.5, 129.0, 128.2, 127.9, 126.5, 124.6, 124.3, 123.0, 122.9, 120.7, 113.7, 107.1, 106.8, 59.6, 56.7, 56.3, 49.9, 41.7, 24.9, 18.7, and 3.0.

HRMS (APCI-Orbitrap): Calculated for $C_{37}H_{35}N_2O_5Si^+$ [M+H^+]: 615.2310, found 615.2276.

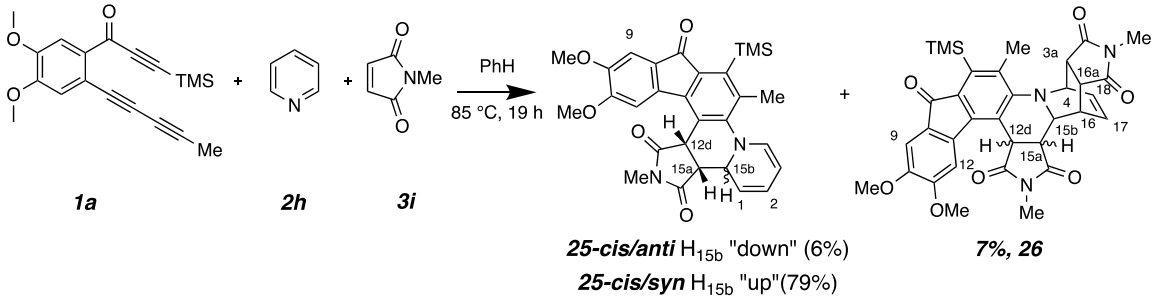
IR ($CDCl_3$): 3069, 2999, 2945, 2904, 2838, 2253, 1775, 1698, 1602, 1546, 1495, 1439, 1382, 1361, 1302, 1285, 1244, 1215, 1113, 1079, 1022, 992, 911, 848, 797, 781, 752, 732, 678, 647, 602, and 526 cm^{-1}.

(±)-(12d*S*,15a*R*,15b*S*)-10,11-Dimethoxy-6,14-dimethyl-7-(trimethylsilyl)-15a,15b-dihydro-8H-indeno[1,2-f]pyrido[1,2-a]pyrrolo[3,4-c]quinoline-8,13,15(12dH,14H)-trione (25-cis/anti)

(±)-(12d*S*,15a*R*,15b*S*)-10,11-Dimethoxy-6,14-dimethyl-7-(trimethylsilyl)-15a,15b-dihydro-8H-indeno[1,2-f]pyrido[1,2-a]pyrrolo[3,4-c]quinoline-8,13,15(12dH,14H)-trione (25-cis/syn)

and

10,11-Dimethoxy-2,6,14-trimethyl-7-(trimethylsilyl)-3a,12d,15a,15b,16,16a-hexahydro-4,16-ethenoindeno[1,2-f]pyrrolo[3,4-c]pyrrolo[3',4':4,5]pyrido[1,2-a]quinoline-1,3,8,13,15(2H,4H,14H)-pentaone (26)



Triynone **1a** (50 mg, 0.123 mmol, 1equiv), pyridine (**2h**, 30 μL, 0.369 mmol, 3 equiv), and N-methyl maleimide (**3i**, 68 mg, 0.615 mmol, 5 equiv) were combined in a culture tube, dissolved in a mixture of benzene (10 mL), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc). The eluate was concentrated and the residue was purified by MPLC (1:1, Hex:EtOAc) to give, in order of elution, **25-cis/anti** (4 mg, 0.008 mmol, 6%) as a yellow oil, **25-cis/syn** (50 mg, 0.115 mmol, 79%) as a dark red oil, and the 2:1 adduct **26** (5 mg, 0.065 mmol, 7%) as a yellow oil. Both of the primary products **25-cis/anti** and **25-cis/syn** showed signs of decomposition upon storage and handling, and therefore were characterized soon after their synthesis.

Data for the faster eluting, minor, primary isomer, 25-cis/anti:

^{1}H NMR (500 MHz, $CDCl_3$): 7.17 (s, 1H, Ar*H9*), 6.82 (s, 1H, Ar*H12*), 6.16 (dd, *J* = 9.5, 5.6 Hz, 1H, *H2*), 5.82 (d, *J* = 7.4 Hz, 1H, *H4*), 5.50 (dd, *J* = 9.6, 5.7 Hz, 1H, *H1*), 5.14 (dd, *J* = 7.3, 5.6 Hz, 1H, *H3*), 4.48 (d, *J* = 6.6 Hz, 1H, *H12d*), 4.03 (dd, *J* = 9.7, 5.6 Hz, *H15b*), 3.92 (s, 3H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 3.69 (dd, *J* = 9.9, 6.9 Hz, 1H, *H15a*), 3.05 (s, 3H, NC*H*$_3$), 2.38 (s, 3H, ArCH$_3$), and 0.43 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR (126 MHz, $CDCl_3$): δ 193.7, 174.7, 174.3, 153.5, 149.7, 146.4, 143.4, 143.1, 138.9, 137.7, 135.4, 135.3, 128.2, 124.8, 118.0, 114.2, 108.0, 106.5, 100.7, 56.5, 56.3, 56.1, 43.0, 41.5, 25.3, 21.0, and 3.2.

HRMS (APCI-Orbitrap): Calculated for $C_{29}H_{31}N_2O_5Si^+$ [M+H^+]: 515.1997, found 515.1984.

IR ($CDCl_3$): 2947, 1776, 1701, 1642, 1590, 1568, 1535, 1494, 1462, 1433, 1369, 1314, 1275, 1242, 1210, 1106, 1023, 995, 919, 846, 796, 768, 731, 698, 628, 602, 562, 536, 505, and 464 cm^{-1}.

Data for the faster eluting, major, primary isomer, 25-cis/syn:

^{1}H NMR (500 MHz, $CDCl_3$): 7.20 (s, 1H, Ar*H9*), 7.17 (s, 1H, Ar*H12*), 6.19 (dd, *J* = 9.9, 5.8 Hz, 1H, *H2*), 5.89 (d, *J* = 7.4 Hz, 1H, *H4*), 5.54 (dd, *J* = 9.9, 5.2 Hz, 1H, *H1*), 4.90 (dd, *J* = 7.1, 5.7 Hz, 1H, *H3*), 4.70 (d, *J* = 8.9 Hz, 1H, *H12d*), 4.56 (dd, *J* = 5.4, 5.4 Hz, *H15b*), 3.96 (s, 3H, OC*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 3.29 (dd, *J* = 8.8, 5.4 Hz, 1H, *H15a*), 3.03 (s, 3H, NC*H*$_3$), 2.31 (s, 3H, ArCH_3), and 0.41 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (126 MHz, $CDCl_3$): 193.3, 175.3, 175.2, 153.8, 149.8, 147.6, 143.9, 142.2, 138.7, 138.4, 136.3, 132.5, 128.4, 124.9, 122.4, 113.9, 107.0, 106.9, 98.1, 56.7, 56.30, 56.28, 51.4, 41.6, 26.0, 20.4, and 2.7.

HRMS (APCI-Orbitrap): Calculated for $C_{29}H_{31}N_2O_5Si^+$ [M+H^+]: 515.1997, found 515.1990.

IR (thin film)**:** 2945, 1774, 1695, 1641, 1566, 1543, 1494, 1461, 1433, 1366, 1285, 1246, 1209, 1104, 1046, 1022, 954, 930, 843, 797, 776, 731, 700, 602, 553, and 508 cm^{-1}.

Data for 26 (post-HDDA adduct):

^{1}H NMR (500 MHz, $CDCl_3$): 7.18 (s, 1H, Ar*H9*), 6.86 (s, 1H, Ar*H12*), 6.40 (ddd, *J* = 7.8, 6.0, 1.5 Hz, 1H, *H17* or *H18*), 5.98 (ddd, *J* = 7.7, 6.1, 1.4 Hz, 1H, *H17* or *H18*), 4.53 (d, *J* = 9.3 Hz, 1H, *H12d*), 4.31 (ddd, *J* = 5.8, 4.1, 1.5 Hz, 1H, *H4*), 4.06 (dddd, 1H, *J* = 6.3, 3.2, 1.9, 1.9 Hz, 1H, *H16*), 3.99 (dd, *J* = 9.0, 1.9 Hz, 1H, *15b*), 3.91 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 3.82 (dd, *J* = 7.9, 4.0 Hz, 1H, *H3a*), 3.55 (dd, *J* = 9.1, 9.1 Hz, 1H, *H15a*), 3.11 (dd, *J* = 7.9, 2.9 Hz, 1H, *H16a*), 3.01 (s, 3H, NC*H*$_3$), 2.90 (s, 3H, NC*H*$_3$), 2.40 (s, 3H, ArCH_3), and 0.43 [s, 9H, Si(CH_3)$_3$].

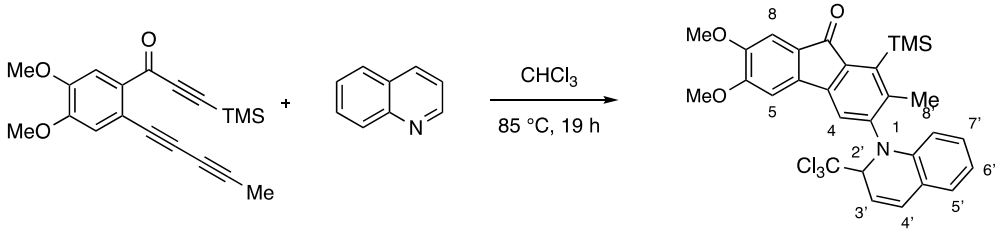
^{13}C NMR (126 MHz, $CDCl_3$): δ 193.1, 177.5, 177.2, 176.0, 175.3, 153.4, 149.7, 148.7, 145.5, 142.7, 138.0, 135.5, 134.8, 133.5, 130.6, 129.0, 118.6, 107.0, 107.0, 56.7, 56.6, 56.3, 52.8, 47.7, 47.5, 41.4, 40.4, 36.3, 25.8, 25.0, 23.7, and 2.6.

HRMS (APCI-Orbitrap): Calculated for $C_{34}H_{36}N_3O_7Si^+$ [M+H^+]: 626.2317, found 626.2315.

IR (thin film): 3057, 2944, 2931, 2855, 1776, 1692, 1570, 1541, 1493, 1433, 1378, 1353, 1311, 1290, 1247, 1210, 1176, 1131, 1104, 1032, 968, 915, 842, 778, 763, 730, 700, 677, 646, 614, 595, 514, and 445 cm^{-1}.

(d) Products obtained from mode c: nucleophilic three-component reactions

6,7-Dimethoxy-2-methyl-3-(2-(trichloromethyl)quinolin-1(2H)-yl)-1-(trimethylsilyl)-9H-fluoren-9-one (27)



Triynone **1a** (25 mg, 0.077 mmol) and quinoline (**2b**, 30 μL, 0.231 mmol, 3 equiv) were combined in a culture tube, dissolved in $CHCl_3$ (6 mL), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (3:1 Hex:EtOAc) to give **27** (41 mg, 93%), as a mixture of atropisomers (1: 0.16 ratio) and yellow oil.

Data for 27 [a mixture of atropisomers in a ratio of 1:0.16]:

^{1}H NMR for the major atropisomer (500 MHz, $CDCl_3$): δ 7.79 (s, 1H, Ar*H4*), 7.17 (s, 1H, Ar*H8*), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H5'*), 7.06 (ddd, *J* = 9.0, 7.2, 1.7 Hz, 1H, Ar*H7'*), 7.01 (s, 1H, Ar*H5*), 6.96 (d, *J* = 9.7 Hz, C*H4'*), 6.80 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, Ar*H6'*), 6.74 (d, *J* = 8.3 Hz, Ar*H8'*), 6.15 (dd, *J* = 9.8, 5.8 Hz, 1H, C*H3'*), 4.89 (d, *J* = 5.8 Hz, 1H, C*H2'*), 4.05 (s, 3H, CH_3OC7), 3.93 (s, 3H, CH_3OC6), 2.93 (s, 3H, ArC*H3*), and 0.41 [s, 9H, Si(CH_3)$_3$].

^{1}H NMR identifiable resonances for the minor atropisomer (500 MHz, $CDCl_3$): 6.37 (d, *J* = 8.4 Hz, 1H, Ar*H8'*), 6.18 (dd, *J* = 9.7, 5.4 Hz, 1H, C*H3'*), 5.42 (d, *J* = 5.5 Hz, 1H, C*H2'*), 3.96 (s, 3H, CH_3OC7), 3.91 (s, 3H, CH_3OC6), 2.58 (s, 3H, ArC*H3*), and 0.48 [s, 9H, Si(CH_3)$_3$].

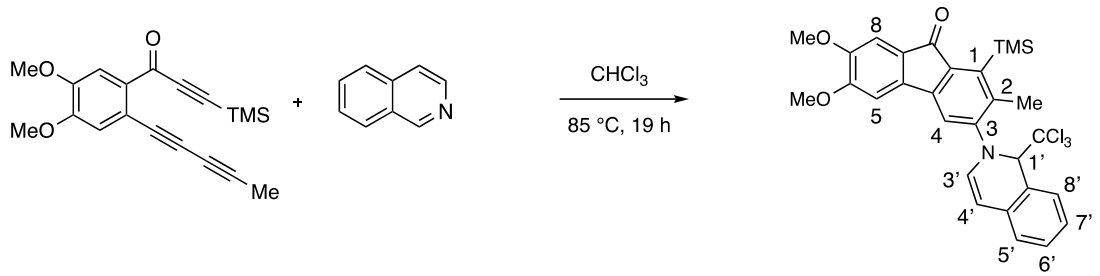
^{13}C NMR for the major atropisomer (126 MHz, $CDCl_3$): δ 193.9, 154.9, 149.9, 149.2, 145.1, 142.5, 141.8, 141.7, 139.9, 138.7, 130.7, 129.3, 128.0, 127.2, 126.9, 121.7, 119.5, 116.3, 115.0, 107.0, 105.5 (CCl_3), 103.1, 74.9, 56.7, 56.4, 19.4, and 2.9.

IR (thin film): 3054, 3002, 2941, 2837, 1703, 1645, 1588, 1487, 1455, 1367, 1315, 1291, 1243, 1213, 1173, 1151, 1106, 1070, 1016, 991, 921, 845, 830, 799, 771, 736, 717, 701, 678, 639, 605, 528, 504, and 426 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{28}H_{28}NO_3Si^+$ $[M–CCl_3^–]^+$: 454.1833, found 454.1817.

Reverse phase liquid chromatography: Only one peak corresponding to **27** was observed, consistent with the assumption that the atropisomers are interconverting sufficiently rapidly to coeluted.

2-Methyl-3-(1-(trichloromethyl)isoquinolin-2(1H)-yl)-1-(trimethylsilyl)-9H-fluoren-9-one (28)



Triynone **1a** (30 mg, 0.093 mmol) and isoquinoline (**2a**, 32.7 μL, 0.277 mmol, 3 equiv) were added to a culture tube, dissolved in $CHCl_3$ (6 mL), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc elution). The residue was purified by MPLC (3:1 Hex:EtOAc) to give **28** (46.6 mg, 88%) as a yellow oil.

^{1}H NMR (500 MHz, C_6D_6, **343K**): δ 7.40 (br s, 1H, Ar*H4*), 7.34 (dd, *J* = 7.5, 0.5 Hz, 1H, Ar*H8'*), 7.18 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, Ar*H6'*), 7.13 (s, 1H, Ar*H8*), 7.08 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, Ar*H7'*), 7.03 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H5'*), 6.66 (s, 1H, Ar*H5*), 6.40 (dd, *J* = 7.5, 1.0 Hz, 1H, C*H3'*), 5.72 (dd, *J* = 7.5, 0.5 Hz, 1H, C*H4'*), 5.63 (br s, 1H, *CH1'*), 3.35 (s, 3H, C6OCH_3), 3.32 (s, 3H, C5OCH_3), 2.31 (s, 3H, ArCH_3), and 0.58 [s, 9H, Si(CH_3)$_3$].

A differential nOe experiment showed enhancement of the *H*5, *H*1', and *H3'* upon irradiation of Ar*H*4, and C6-methoxy and *H*4 upon irradiation of *H5* for allowing the regioisomeric assignment of the shown **28**.

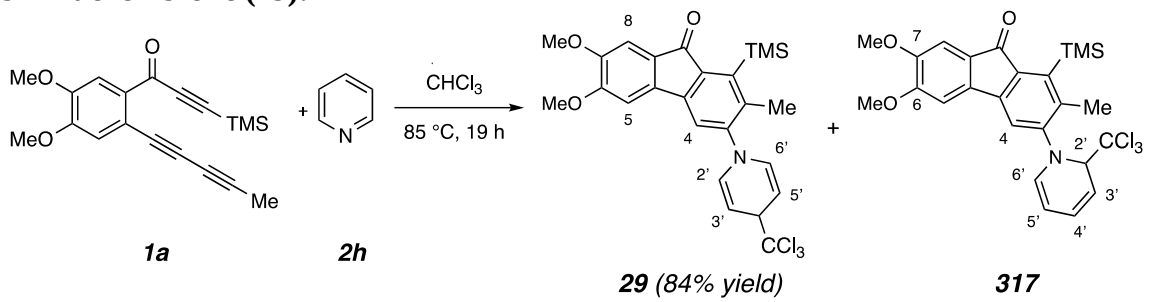
^{13}C NMR (126 MHz, $CDCl_3$): δ 193.6, 154.6, 152.4, 149.9, 145.0, 143.8, 138.27 (br), 138.20, 138.18, 134.1, 133.9, 131.2, 129.6, 127.1, 125.4, 124.2, 121.4, ca. 119 (v br), 106.9, 105.3 (x), 103.3, 103.0, 76.9, 56.6, 56.3, 21.1, and 2.9.

IR (neat): 2950, 1711, 1625, 1420, 1391, 1298, 1274, 1247, 1006, 968, 945, 934, 856, 846, 822, and 768 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{28}H_{28}NO_3Si^+$ $[M–CCl_3^–]^+$ 454.1833, found 454.1849.

TLC: R_f 0.3 (3:1 Hex/EtOAc).

6,7-Dimethoxy-2-methyl-3-(4-(trichloromethyl)pyridin-1(4H)-yl)-1-(trimethylsilyl)-9H-fluoren-9-one (29):



1a ***2h*** ***29*** *(84% yield)* ***317***

Triynone **1a** (40 mg, 0.123 mmol) and pyridine (**2h**, 30 μL, 0.370 mmol, 3 equiv) were combined in a culture tube, dissolved in $CHCl_3$ (10 mL), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (6:1 Hex:EtOAc) to give a 10:1 mixture of isomers (60 mg, 94% combined yield) as a yellow oil. A small portion of the mixture was separately repurified by normal phase HPLC (6:1, Hex:EtOAc) to give, in order of elution, **29** (major isomer) as an orange oil, and the minor isomer **317**, also as a transparent oil. The latter was contaminated with ca. 15% of **29**. The broad resonances observed in the ^{1}H NMR spectrum were an indicator of rotamer issues; not surprisingly, the ^{13}C data were of marginal quality and gave very limited useful information.

Data for the major regioisomer, 29: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (s, 1H, Ar*H8*), 7.09 (s, 1H, Ar*H5* or Ar*H4*), 6.93 (s, 1H, Ar*H5* or Ar*H4*), 6.41 (d, *J* = 7.9 Hz, 2H, NC*H*CH), 5.05 (dd, *J* = 8.1, 4.5 Hz, 2H, NCHC*H*), 4.17 (t, *J* = 4.3 Hz, 1H, Cl_3CCH), 4.01 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O'), 2.32 (s, 3H, ArC*H3*), and 0.43 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR for the major regioisomer, 29 (100 MHz, $CDCl_3$): δ 193.7, 154.7, 150.0, 147.6, 144.9, 143.8, 139.0, 138.6, 138.1, 133.4 (br), 127.1, 116.8 (br), 107.0, 102.9, 97.4 (br), 56.6, 56.4, 55.4 (br), 20.4, and 2.7. (one resonance was not observed)

IR (thin film): 3111, 3065, 3000, 2943, 2900, 2837, 1706, 1673, 1589, 1495, 1456, 1444, 1383, 1359, 1317, 1245, 1213, 1153, 1102, 1046, 1015, 996, 911, 843, 769, 728, 699, 601, 536, 514, 483, and 415 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{25}H_{27}Cl_3NO_3Si^+$ $[M+H^+]^+$: 522.0820, found 522.0781, Calculated for $C_{24}H_{26}NO_3Si^+$ $[M–CCl_3^-]^+$: 404.1676, found 404.1660 (minor ion).

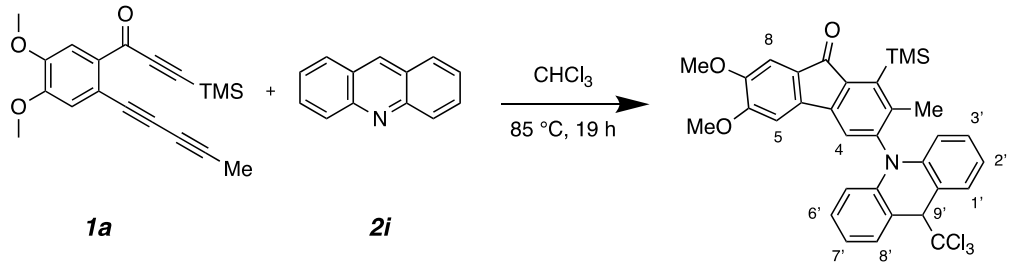
Data for the minor isomer 317 [contains coeluting major regioisomer 29 (15%)]:

^{1}H NMR for the minor regioisomer, 4aak-C2 (500 MHz, $CDCl_3$): δ ca. 7.4–7.0 (v br, ca. 1H, Ar*H4*), 7.13 (s, 1H, Ar*H8*), 6.96 (s, 1H, Ar*H5*), 6.49 (dd, *J* = 9.4, 6.0 Hz, 1H, *H4'*), 6.38 (br s, 1H, *H6'*), 5.73 (br s, 1H, *H3'*), 5.22 (ddd, J = 7.2, 6.0, 1.2 Hz, 1H, *H5'*), 5.5 and 4.9 (v br s, not yet coalesced, 1H, *H2'*), 4.03 (s, 3H, C*H*$_3$O), 3.91 (s, 3H, C*H*$_3$O), 2.44 (br s, 3H, ArC*H3*), and 0.44 [s, 9H, Si(C*H*$_3$)$_3$].

HRMS (APCI-Orbitrap): Calculated for $C_{24}H_{26}NO_3Si^+$ $[M–CCl_3^–]^+$: 404.1676, found 404.1675

IR (CH_2Cl_2): 3061, 2931, 2853, 1705, 1588, 1495, 1463, 1382, 1358, 1316, 1246, 1214, 1153, 1102, 1017, 845, 769, 734, 700, 603, and 415 cm^{-1}.

6,7-Dimethoxy-2-methyl-3-(9-(trichloromethyl)acridin-10(9*H*)-yl)-1-(trimethylsilyl)-9*H*-fluoren-9-one (30):



1a ***2i*** ***30* (82%, ratio: 1:0.5)**

Triynone **1a** (15 mg, 0.046 mmol) and acridine (**2i**, 25 mg, 0.092 mmol, 2 equiv) were dissolved in benzene (4 mL, 0.01M), paced into a threaded vial, and sealed with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (2:1, Hex:EtOAc). The residue was purified by MPLC (3:1, Hex:EtOAc) to give **30** (23 mg) as a yellow oil.

Data for 30 [a mixture of atropisomers in a ratio of 1 :0.38]:

^{1}H NMR for the major atropisomer (500 MHz, $CDCl_3$): 7.65 (dd, *J* = 7.7, 1.0 Hz, 2H, Ar*H1'* and Ar*H8'*), 7.26 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 2H, Ar*H3'* and Ar*H6'*), 7.181 (s, 1H, Ar*H5* or Ar*H8*), 7.177 (s, 1H, Ar*H5* or Ar*H8*), 7.06 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 2H, Ar*H2'* and Ar*H7'*), 6.80 (s, 1H, Ar*H4*), 6.46 (dd, *J* = 8.4, 1.0 Hz, 2H, Ar*H4'* and Ar*H5'*), 5.06 (s, 1H, *H9'*), 3.93 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 1.87 (s, 3H, ArCH_3), and 0.480 [s, 9H, Si$(CH_3)_3$].

^{1}H NMR identifiable resonances for the minor atropisomer (500 MHz, $CDCl_3$): 7.70 (dd, *J* = 7.8, 1.3 Hz, 2H, Ar*H1'* and Ar*H8'*), 7.25 (ddd, *J* = 8, 7.4, 1.5 Hz, 2H, Ar*H3'* and Ar*H6'*), 7.18 (s, 1H, Ar*H5* or Ar*H8*), 7.08 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 2H, Ar*H2'* and Ar*H7'*), 6.91 (s, 1H, Ar*H5* or Ar*H8*), 6.76 (s, 1H, Ar*H4*), 6.49 (dd, *J* = 8.4, 1.0 Hz, 2H, Ar*H4'* and Ar*H5'*), 5.14 (s, 1H, *H9'*), 3.92 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.33 (s, 3H, ArCH_3), and 0.484 [s, 9H, Si$(CH_3)_3$].

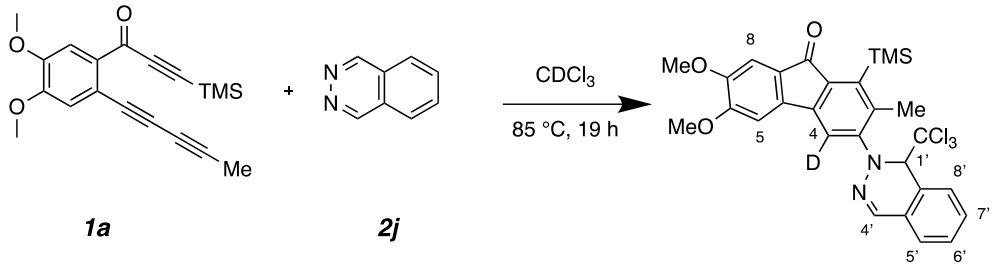
^{13}C NMR for the major atropisomer (126 MHz, $CDCl_3$): δ 194.0, 154.9, 150.1, 145.3, 144.72, 144.2, 142.4, 142.2, 141.0, 138.30, 133.3, 129.6, 126.7, 122.0, 120.5, 115.8, 113.9, 107.01, 105.8 (CCl_3), 103.0, 62.18, 56.6, 56.37, 19.18, and 3.0.

^{13}C NMR for the minor atropisomer (126 MHz, $CDCl_3$): δ 193.9, 154.8, 150.0, 145.1, 144.8, 144.70, 144.0, 141.3, 140.0, 138.31, 133.2, 129.4, 126.8, 122.4, 120.6, 115.7, 114.6, 106.97, 103.1, 62.17, 56.43, 56.39, 19.19, and 2.9. (CCl_3 resonance not observed)

HRMS (APCI-Orbitrap): Calculated for $C_{32}H_{30}NO_3Si^+$ $[M–CCl_3^–]^+$: 504.1989, found 504.1993.

IR (thin film): 3072, 3002, 2928, 2903, 2839, 1708, 1590, 1494, 1476, 1459, 1374, 1359, 1341, 1311, 1264, 1243, 1216, 1169, 1149, 1130, 1079, 1051, 1016, 990, 929, 910, 843, 783, 751, 731, 672, 635, 617, 603, 547, 509, 464, and 422 cm^{-1}.

6,7-Dimethoxy-2-methyl-3-(1-(trichloromethyl)phthalazin-2(1*H*)-yl)-1-(trimethylsilyl)-9*H*-fluoren-9-one-4-*d* (31):



Triynone **1a** (20 mg, 0.062 mmol) and phthalazine (**2j**, 16 mg, 0.124 mmol, 2 equiv) were dissolved in benzene (4 mL, 0.02 M), and sealed with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (2:1, Hex:EtOAc). The residue was purified by MPLC (2:1, Hex:EtOAc) to give **31** (0.059 mmol, 95%) as a yellow oil.

Data for 31:

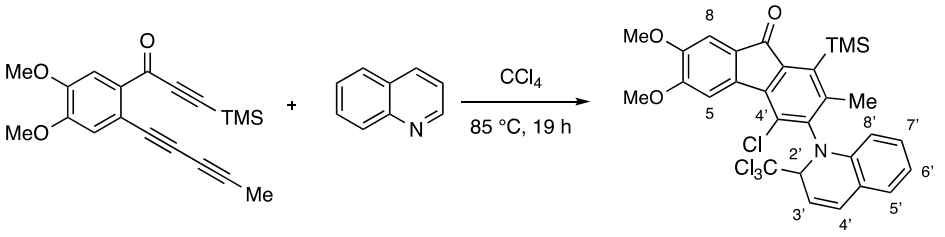
^{1}H NMR (500 MHz, $CDCl_3$): 7.69 (s, 1H, Ar*H4'*), 7.64 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.60 (nfom, 2H, Ar*H6'* and Ar*H7'*), 7.42 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.14 (s, 1H, Ar*H8*), 7.01 (s, 1H, Ar*H5*), 5.76 (s, 1H, Ar*H1'*), 4.02 (s, 3H, OC*H*$_3$), 3.91 (s, 3H, OC*H*$_3$), 2.35 (s, 3H, $ArCH_3$), and 0.44 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 193.8, 154.5, 152.4, 149.8, 144.7, 143.4, 138.5, 138.0, 137.6, 135.5, 130.6, 130.33, 130.30, 127.3, 126.4, 124.9, 123.1, 106.8, 103.6, 103.3, 72.9 (C1'), 56.6, 56.3, 21.3, and 2.9. (one carbon resonance was not identified).

HRMS (ESI-TOF): Calculated for $C_{28}H_{27}DCl_3N_2O_3Si^+$ $[M+H^+]^+$: 574.0992, found 574.0984.

IR (thin film): 3066, 2999, 2936, 2901, 2852, 2837, 1701, 1598, 1578, 1492, 1453, 1406, 1365, 1315, 1266, 1243, 1214, 1128, 1095, 1048, 1014, 963, 922, 847, 829, 780, 754, 734, 701, 674, 647, 635, 612, 600, 584, 536, 470, and 422 cm^{-1}.

4-Chloro-6,7-dimethoxy-2-methyl-3-(2-(trichloromethyl)quinolin-1(2H)-yl)-1-(trimethylsilyl)-9H-fluoren-9-one (32):



1a ***2b*** ***32* (56%)**
Ratio of atropisomers: 1:0.5

Triynone **1a** (20 mg, 0.062 mmol) and quinoline (**2b**, 14.7 μL, 0.124 mmol, 2 equiv) were combined in a culture tube, dissolved in CCl_4 (2 mL), and sealed with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (3:1 Hex:EtOAc) to give **32** (21 mg, 0.035 mmol, 56%) as an orange oil. A small portion of this product was separately repurified by HPLC (1:1, Hex:EtOAc) to give sample of higher purity for characterization purposes. The ^{1}H NMR spectrum indicated that this compound was a 2.3:1 ratio of diastereomeric atropisomers.

Data for 32:

^{1}H NMR for the major atropisomer (500 MHz, $CDCl_3$): δ 7.72 (s, 1H, Ar*H5*), 7.68 (dd, *J* = 7.8, 1.4 Hz, 1H, ArH*5*'), 7.20 (s, 1H, Ar*H8*), 7.20 (1H, ddd, *J* = 8, 7.3, 1.8 Hz, 1H, Ar*H7'*), 7.05 (ddd, *J* =7.8, 7.8, 1.3 Hz, 1H, Ar*H6'*), 6.39 (d, *J* = 8.0 Hz, Ar*H8'*), 6.39 (d, *J* = 8.0 Hz, Ar*H4'*), 5.24 (dd, *J* = 8.0, 5.2 Hz, 1H, *H3'*), 4.68 (d, *J* = 5.1 Hz, 1H, *H2'*), 3.98 (s, 3H, OC*H*$_3$), 3.94 (s, 3H, OC*H*$_3$*'*), 2.04 (s, 3H, ArCH$_3$), and 0.43 [s, 9H, Si(CH$_3$)$_3$].

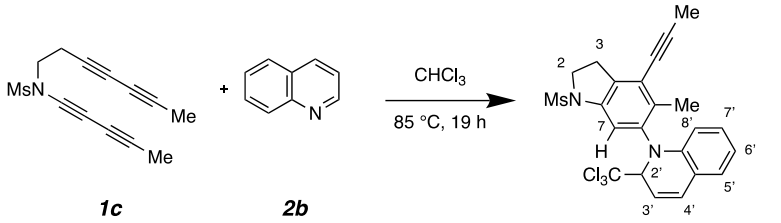
^{1}H NMR identifiable resonances for the minor atropisomer (500 MHz, $CDCl_3$): δ 7.87 (s, 1H, Ar*H5*), 7.21 (s, 1H, Ar*H8*), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H, ArH*5*'), 7.09 (ddd, *J* = 8.8, 7.3, 1.9 Hz, 1H, Ar*H7'*), 6.93 (d, *J* = 9.9 Hz, Ar*H4'*), 6.83 (dd, *J* = 7.4, 7.4, 0.9 Hz, Ar*H6'*), 6.54 (dd, *J* = 8.4, 0.7 Hz, 1H, *H8'*), 6.13 (dd, *J* = 9.8, 5.4 Hz, 1H, *H3'*), 4.98 (dd, *J* = 5.5, 0.9 Hz, 1H, *H2'*), 4.04 (s, 3H, OC*H*$_3$), 3.95 (s, 3H, OC*H*$_3$*'*), 2.22 (s, 3H, ArCH$_3$), and 0.42 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR for the major atropisomer (125 MHz, $CDCl_3$): δ 192.9, 154.5, 150.0, 145.0, 142.6, 142.1, 140.1, 140.0, 137.9, 134.3, 133.0, 130.8, 129.2, 128.1, 127.0, 121.7, 119.8, 113.3, 107.2, 106.9, 106.0, 95.2, 58.4, 56.5, 56.3, 20.3, and 2.9.

HRMS (APCI-Orbitrap): Calculated for $C_{29}H_{28}Cl_4NO_3Si^+$ $[M+H^+]^+$: 606.0587, found 606.0561.

IR (thin film): 3057, 3003, 2928, 2901, 2837, 1707, 1655, 1588, 1489, 1458, 1394, 1359, 1337, 1312, 1246, 1214, 1119, 1106, 1074, 1019, 996, 949, 934, 886, 845, 770, 732, 628, 605, 575, 530 515, 493, 436, and 409 cm^{-1}.

1-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2-(trichloromethyl)-1,2-dihydroquinoline (33):



***33* (92%)**
Ratio of atropisomers: 1:0.33

Tetrayne **1c** (25 mg, 0.101 mmol, 1 equiv) and quinoline (**2b**, 42 μL, 0.303 mmol, 3 equiv) were combined in a culture tube, dissolved in chloroform (6 mL, 0.02M), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (2:1, Hex:EtOAc) to give a mixture of atropisomers **33** (46 mg, 92% overall, 1:0.33 ratio) as a flaky white amorphous solid.

Data for 33 [a mixture of atropisomers in a ratio of 1:0.33]:

^{1}H NMR for the major atropisomer (400 MHz, $CDCl_3$): δ 7.88 (s, 1H, Ar*H7*), 7.10 (dd, *J* = 7.4, 1.7 Hz, 1H, Ar*H5'*), 7.01 (ddd, *J* = 8.5, 7.4, 1.6 Hz, 1H, Ar*H7'*), 6.95 (ddd, *J* = 9.7, 1.0, 1.0 Hz, 1H, Ar*H4'*), 6.77 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, Ar*H6'*), 6.60 (d, *J* = 8.2 Hz, 1H, Ar*H8'*), 6.13 (dd, *J* = 9.7, 5.7 Hz, 1H, *H3'*), 4.87 (dd, *J* = 5.8, 0.9 Hz, 1H, *H2'*), 4.14–4.04 (overlapping m, 1H, $CH_3SO_2NCH_aH_bCH_2$), 4.03–3.91 (overlapping m, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.21 (t, *J* = 8.8 Hz, 2H, $NMsCH_2CH_2$), 2.89 (s, 3H, CH_3SO_2N), 2.10 (s, 3H, $NArCH_3$), and 2.05 (s, 3H, $C{\equiv}CCH_3$).

^{1}H NMR identifiable resonances for the minor atropisomer (400 MHz, $CDCl_3$): δ 6.89 (ddd, *J* = 9.9, 1.0, 1.0 Hz, 1H, Ar*H4'*), 6.27 (d, *J* = 8.3 Hz, 1H, Ar*H8'*), 6.10 (dd, *J* = 9.8, 5.4 Hz, 1H, *H3'*), 5.38 (dd, *J* = 5.4, 1.0 Hz, 1H, *H2'*), 4.14–4.04 (overlapping m, 1H, $CH_3SO_2NCH_aH_bCH_2$), 4.03–3.91 (overlapping m, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.22 (t, *J* = 8.4 Hz, 2H, $NMsCH_2CH_2$), 2.82 (s, 3H, CH_3SO_2N), 2.47 (s, 3H, $NArCH_3$), and 2.17 (s, 3H, $C{\equiv}CCH_3$).

^{13}C NMR for the major atropisomer (126 MHz, $CDCl_3$): δ 145.6, 142.9, 139.3, 134.0, 133.8, 130.6, 129.3, 127.6, 120.7, 119.4, 116.4, 116.0, 114.4, 112.8, 105.4 (CCl_3), 95.2, 75.8, 74.9, 50.6, 34.9, 28.4, 15.4, and 4.7.

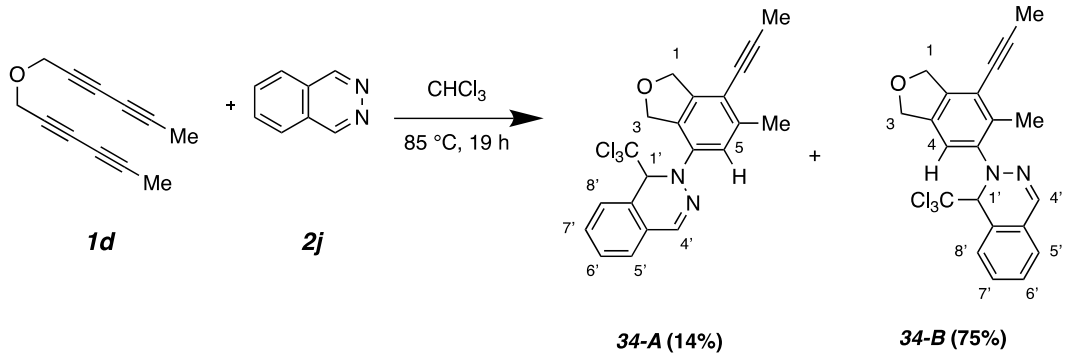
HRMS (APCI-Orbitrap): Calculated for $C_{22}H_{21}N_2O_2S^+$ $[M–CCl_3^–]^+$: 377.1318, found 377.1318.

IR (thin film): 3055, 3024, 2916, 2850, 2232, 1737, 1643, 1593, 1486, 1453, 1346, 1287, 1254, 1154, 1111, 1066, 1000, 968, 893, 829, 801, 774, 751, 717, 663, 629, 607, 568, 545, 514, and 441 cm^{-1}.

Reverse phase liquid chromatography: Only one peak corresponding to **33** was observed, consistent with the assumption that the atropisomers are interconverting sufficiently rapidly to coeluted.

2-(6-Methyl-7-(prop-1-yn-1-yl)-1,3-dihydroisobenzofuran-4-yl)-1-(trichloromethyl)-1,2-dihydrophthalazine (34-A) and

2-(6-Methyl-7-(prop-1-yn-1-yl)-1,3-dihydroisobenzofuran-5-yl)-1-(trichloromethyl)-1,2-dihydrophthalazine (34-B)



Tetrayne **1d** (20 mg, 0.118 mmol) and phthalazine (**2j**, 45.9 mg, 0.353 mmol, 3 equiv) were combined in a culture tube, dissolved in chloroform (4 mL, 0.03M), and sealed in a vial with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (2:1, Hex:EtOAc). The residue was purified by MPLC (6:1, Hex:EtOAc) to give, in order of elution, **34-A** (7 mg, 0.016 mmol, 14%) as a pale yellow oil, and (37 mg, 0.088 mmol, 75%), also as a yellow oil. The assignment of the structure of both isomers was based upon observed nOe interactions (difference nOe) between the aromatic proton with benzylic methyl or methylene protons, respectively.

Data for faster eluting, minor regioisomer, 34-A:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 1H, Ar*H4'*), 7.63 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.55 (m, 2H, Ar*H6'* and Ar*H7'*), 7.37 (nfom, 1H, Ar*H5'* or Ar*H8'*), 6.94 (s, 1H, Ar*H5*), 6.14 (s, 1H, *H1'*), 5.44 (br d, *J* = 12.9 Hz, 1H, O*C3H$_a$*H$_b$), 5.30 (br d, *J* = 12.9 Hz, 1H, OC3H$_a$*H$_b$*), 5.15 (br d, *J* = 13.6 Hz, 1H, C1*H$_a$*H$_b$), 5.11 (br d, *J* = 13.1 Hz, 1H, C1H$_a$*H$_b$*), 2.41 (s, 3H, NArC*H*$_3$), and 2.10 (s, 3H, C≡CC*H*$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 142.1, 140.3, 137.9, 130.32, 130.28, 130.2, 128.0, 126.5, 124.7, 123.4, 116.4, 111.8, 103.3, 92.6, 75.9, 75.6, 74.1, 69.8, 20.5, and 4.7.

HRMS (APCI-Orbitrap): Calculated for $C_{21}H_{18}Cl_3N_2O^+$ [M+H$^+$]: 419.0479, found 419.0477.

IR (thin film): 3068, 3036, 2917, 2852, 2253, 1603, 1490, 1453, 1414, 1373, 1318, 1288, 1247, 1224, 1172, 1130, 1108, 1053, 929, 906, 853, 833, 809, 783, 759, 734, 649, 612, 582, 521, and 419 cm^{-1}.

Data for slower eluting, major regioisomer 34-B:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 1H, Ar*H4'*), 7.58–7.52 [m, 3H, 1H, Ar*H5'* (or Ar*H8'*), Ar*H6',* and Ar*H7'*), 7.37 [nfom, 1H, Ar*H8'* (or Ar*H5'*)], 7.26 (s, 1H, Ar*H4*), 5.80 (s, 1H, *H1'*), 5.12 (br s, 2H, C1H_2), 5.10 (br s, 2H, C3H_2), 2.44 (s, 3H, NArCH_3), and 2.11 (s, 3H, C≡CCH_3).

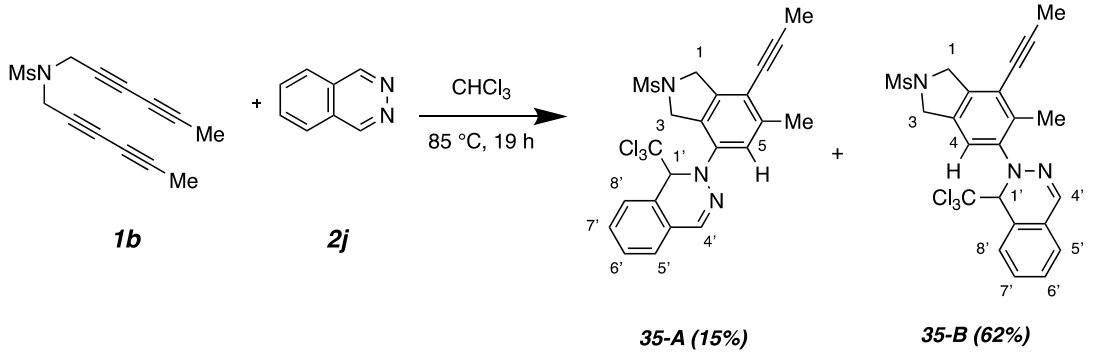
^{13}C NMR (126 MHz, $CDCl_3$): δ 148.0, 139.5, 137.3, 136.4, 133.8, 130.6, 130.1, 130.0, 126.5, 124.6, 122.6, 119.2, 118.8, 103.9, 94.2, 76.1, 74.2, 74.1, 73.3, 17.0, and 4.7.

IR (thin film): 2954, 2922, 2852, 2227, 1681, 1589, 1555, 1453, 1371, 1303, 1254, 1128, 1101, 1054, 961 923, 902, 864, 829, 781, 761, 735, 706, 650, 612, 583, 564, and 424 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{21}H_{18}Cl_3N_2O^+$ $[M+H^+]^+$: 419.0479, found 419.0481.

2-(6-Methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-4-yl)-1-(trichloromethyl)-1,2-dihydrophthalazine (35-A) and

2-(6-Methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-5-yl)-1-(trichloromethyl)-1,2-dihydrophthalazine (35-B):



Tetrayne **1b** (40 mg, 0.162 mmol) and phthalazine (**2j**, 42 mg, 0.323 mmol, 2 equiv) were combined in a culture tube, dissolved in chloroform (6 mL, 0.02M), and sealed in a vial with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (2:1, Hex:EtOAc). The residue was purified by MPLC (2:1, Hex:EtOAc) to give, in order of elution, **35-A** (12 mg, 0.024 mmol, 15%) as a white crystalline solid, and **35-B** (50 mg, 0.101, 62%), as a transparent oil, which turned into a white crystalline solid after being subjected to high vacuum. The assignment of the structure of both isomers was based upon observed nOe interactions (difference nOe) between the aromatic proton with benzylic methyl or methylene protons, respectively.

Data for faster eluting, minor isomer: 35-A:

^{1}H NMR (500 MHz, $CDCl_3$): 7.63 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.63 (s, 1H, Ar*H4'*), 7.57 (m, 2H, Ar*H6'* and Ar*H7'*), 7.38 (nfom, 1H, Ar*H5'* or Ar*H8'*), 6.92 (s, 1H, Ar*H5*), 5.79 (s, 1H, *H1'*), 5.12 (br d, *J* = 14.8 Hz, 1H, MsN*C3H$_a$*C3H$_b$), 4.87 (dd, *J* = 14.8, 2.2 Hz, 1H, MsNC3H$_a$*C3H$_b$*), 4.76 (dd, *J* = 14.4, 2.9 Hz, 1H, MsN*C1H$_a$*C1H$_b$), 4.70 (br d, *J* = 14.4 Hz, 1H, MsNC1H$_a$C1*H$_b$*), 2.88 (s, 3H, C*H*$_3$SO$_2$N), 2.40 (s, 3H, NArC*H*$_3$), and 2.11 (s, 3H, C≡CC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): 143.0, 141.8, 140.9, 137.8, 130.42, 130.39, 130.35, 126.4, 126.2, 124.9, 123.3, 117.6, 113.8, 103.4, 94.0, 75.4, 70.3, 55.6, 54.5, 34.4, 20.6, and 4.7.

HRMS (ESI-TOF): Calculated for $C_{21}H_{20}N_3O_2S^+$ [M–CCl_3^-]$^+$: 378.1271, found 378.1262.

IR (thin film): 3051, 2919, 2853, 2232, 1603, 1489, 1452, 1418, 1375, 1320, 1265, 1222, 1151, 1129, 1107, 1061, 959, 927, 912, 862, 832, 809, 783, 755, 731, 702, 649, 612, 581, 554, 518, 495, 449, and 418 cm^{-1}.

mp: 225–228 °C.

Data for slower eluting, major isomer, 35-B:

^{1}H NMR (500 MHz, $CDCl_3$): 7.61 (s, 1H, Ar*H4'*), 7.59 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.56 (m, 2H, Ar*H6'* and Ar*H7'*), 7.38 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.28 (s, 1H, Ar*H4*), 5.79 (s, 1H, *H1'*), 4.72–4.66 (m, 4H, MsNC3H_2 and MsNC1H_2), 2.87 (s, 3H, CH_3SO_2N), 2.45 (s, 3H, NArCH_3), and 2.13 (s, 3H, C≡CCH_3).

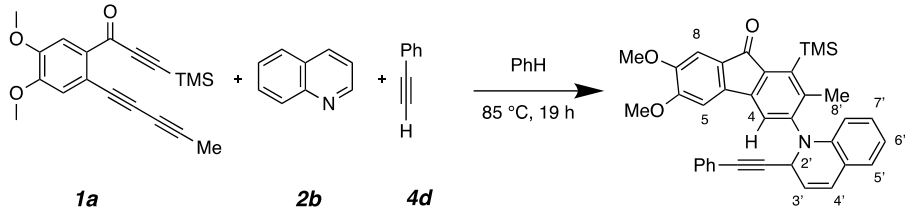
^{13}C NMR (125 MHz, $CDCl_3$): 148.6, 136.8, 136.4, 134.5, 134.1, 130.6, 130.2, 130.2, 126.4, 124.7, 122.6, 121.0, 120.1, 103.8, 95.5, 75.7, 73.1, 54.3, 54.3, 34.9, 17.2, and 4.7.

HRMS (ESI-TOF): Calculated for $C_{22}H_{21}Cl_3N_3O_2S^+$ $[M+H^+]^+$: 496.0415, found 496.0403.

IR (thin film): 3051, 2918, 2853, 2227, 1739, 1602, 1589, 1461, 1372, 1334, 1265, 1150, 1082, 1002, 959, 921, 865, 828, 781, 755, 731, 702, 652, 612, 598, 582, 556, 519, 506, 488, and 422 cm^{-1}.

mp: 171–174 °C.

6,7-Dimethoxy-2-methyl-3-(2-(phenylethynyl)quinolin-1(2*H*)-yl)-1-(trimethylsilyl)-9*H*-fluoren-9-one (36):



Triynone **1a** (30 mg, 0.092 mmol, 1 equiv), quinoline (**2b**, 22 μL, 0.184 mmol, 2 equiv), and ethynylbenzene (**4d**, 48 μL, 0.462 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.02M), and sealed with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (6:1, Hex:EtOAc) to give **36** (28 mg, 54% overall, 1:0.3 ratio) as a yellow oil, which turned into a flaky amorphous solid after being subjected to high vacuum.

Data for 36 [a mixture of atropisomers in a ratio of 1 :0.3]:

^{1}H NMR for the major atropisomer (500 MHz, $CDCl_3$): 7.89 (s, 1H, Ar*H4*), 7.37 (dd, *J* = 7.4, 1.5 Hz, 2H, PhH_o), 7.23 (m, 3H, PhH_m and PhH_p), 7.15 (s, 1H, Ar*H8*), 7.07 (dd, *J* = 7.4, 1.6 Hz, 1H, Ar*H5*'), 7.00 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H, Ar*H7'*), 6.78 (s, 1H, Ar*H5*), 6.74 (ddd, *J* =7.3, 7.3, 0.9 Hz, 1H, Ar*H6'*), 6.58 (d, *J* = 9.6 Hz, 1H, *H4*'), 6.28 (d, *J* = 8.2 Hz, 1H, Ar*H8*'), 5.89 (dd, *J* = 9.5, 5.7 Hz, 1H, *H3'*), 5.21 (dd, *J* = 5.7, 0.8 Hz, 1H, *H2'*), 3.91 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.25 (s, 3H, ArCH_3), and 0.44 [s, 9H, Si$(CH_3)_3$].

^{1}H NMR identifiable resonances for the minor atropisomer (500 MHz, $CDCl_3$): 7.15 (s, 1H, Ar*H8*), 6.96 (1H, ddd, *J* = 8.3, 7.5, 1.5 Hz, 1H, Ar*H7'*), 6.89 (s, 1H, Ar*H5*), 6.68 (ddd, *J* =7.3, 7.3, 1.1 Hz, 1H, Ar*H6'*), 6.51 (dd, *J* = 9.9, 1.6 Hz, 1H, *H*4'), 6.01 (br d, *J* = 8.1 Hz, 1H, *H8*'), 5.67 (dd, *J* = 2.1, 3.3 Hz, 1H, *H2'*), 5.78 (dd, J = 9.7, 3.4, 1H, *H3'*), 3.96 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.47 (s, 3H, ArCH_3), and 0.42 [s, 9H, ArSi$(CH_3)_3$].

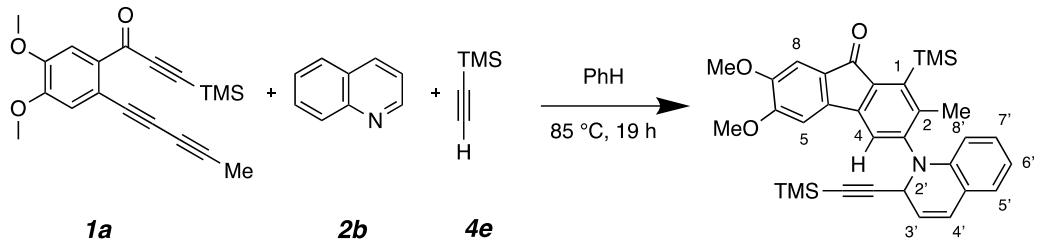
^{13}C NMR for the major atropisomer (126 MHz, $CDCl_3$): δ 194.1, 154.5, 149.7, 146.8, 144.3, 143.5, 142.3, 141.6, 139.2, 138.8, 131.8, 129.2, 128.6, 128.4, 127.8, 127.0, 126.5, 123.0, 121.8, 121.6, 120.7, 118.7, 113.8, 107.0, 102.6, 89.0, 85.1, 56.3, 56.2, 51.4, 19.2, and 2.9.

HRMS (ESI-TOF): Calculated for $C_{36}H_{32}NO_3Si^+$ $[M–H^–]^+$: 554.2146, found 554.2135 and calculated for $C_{28}H_{28}NO_3Si^+$ $[M–C{\equiv}CPh^–]^+$: 454.1833, found 454.1825.

IR (thin film): 3053, 3003, 2939, 2899, 2837, 1703, 1659, 1590, 1487, 1454, 1410, 1381, 1314, 1243, 1214, 1119, 1098, 1065, 1015, 990, 914, 843, 798, 733, 690, 633, 602, 525, 500, 451, and 416 cm^{-1}.

Reverse phase liquid chromatography: Only one peak corresponding to **36** was observed, consistent with the assumption that the atropisomers are interconverting sufficiently rapidly to coeluted.

6,7-Dimethoxy-2-methyl-1-(trimethylsilyl)-3-(2-((trimethylsilyl)ethynyl)quinolin-1(2*H*)-yl)-9*H*-fluoren-9-one (37):



Triynone **1a** (30 mg, 0.092 mmol), quinoline (**2b,** 22 μL, 0.184 mmol, 2 equiv), and ethynyltrimethylsilane (**4e**, 64 μL, 0.462 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.02M), and sealed with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (2:1, Hex:EtOAc eluant). The residue was purified by MPLC (3:1, Hex:EtOAc) to give **37** (43 mg, 84% overall, 1:0.2 ratio) as a yellow oil.

Data for 37 [a mixture of atropisomers in a ratio of 1 :0.2]:

^{1}H NMR for the major atropisomer (500 MHz, $CDCl_3$): 7.76 (s, 1H, Ar*H4*), 7.16 (s, 1H, Ar*H8*), 7.04 (dd, *J* = 7.3, 1.5 Hz, 1H, ArH*5*'), 6.99 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H, Ar*H7'*), 6.90 (s, 1H, Ar*H5*), 6.72 (ddd, *J* =7.5, 7.5, 1.2 Hz, 1H, Ar*H6'*), 6.52 (ddd, *J* = 9.6, 1.0, 1.0 Hz, 1H, *H*4'), 6.24 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 1H, *H8*'), 5.79 (dd, *J* = 9.6, 5.6 Hz, 1H, *H3'*), 5.01 (dd, *J* = 5.6, 0.9 Hz, 1H, *H2'*), 3.957 (s, 3H, OC*H*$_3$), 3.925 (s, 3H, OC*H*$_3$), 2.18 (s, 3H, $ArCH_3$), 0.42 [s, 9H, $ArSi(CH_3)_3$], and 0.14 [s, 9H, C≡C*H*$_3$Si$(CH_3)_3$].

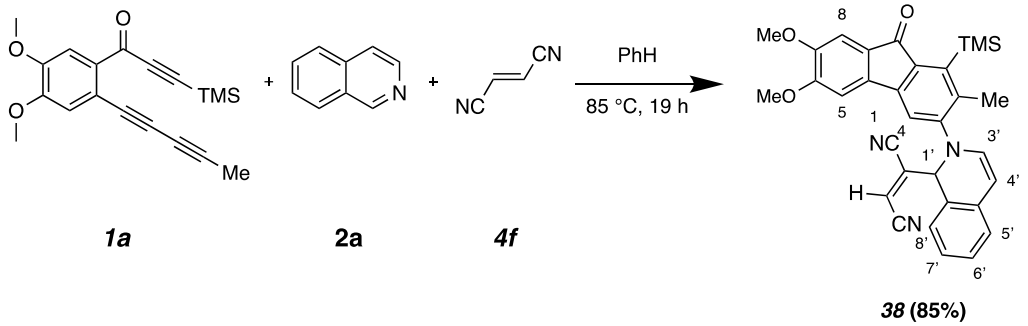
^{1}H NMR identifiable resonances for the minor atropisomer (500 MHz, $CDCl_3$): 7.15 (s, 1H, Ar*H8*), 6.94 (1H, ddd, *J* = 7.4, 7.4, 1.6 Hz, 1H, Ar*H7'*), 6.89 (s, 1H, Ar*H5*), 6.65 (ddd, *J* =7.4, 7.4, 0.9 Hz, 1H, Ar*H6'*), 6.45 (nfom, 1H, *H*4'), 6.01 (br d, *J* = 8.1 Hz, 1H, *H8*'), 5.67 (nfom, 1H, *H3'*), 5.66 (s, 1H, *H2'*), 3.961 (s, 3H, OC*H*$_3$), 3.916 (s, 3H, OC*H*$_3$), 2.41 (s, 3H, $ArCH_3$), 0.45 [s, 9H, $ArSi(CH_3)_3$], and 0.03 [s, 9H, C≡C*H*$_3$Si$(CH_3)_3$].

^{13}C NMR for the major atropisomer (101 MHz, $CDCl_3$): δ 194.1, 154.6, 149.7, 146.9, 144.3, 143.6, 142.2, 141.4, 139.2, 138.8, 129.1, 127.0, 127.7, 126.3, 121.5, 121.6, 120.8, 118.6, 113.7, 107.0, 105.1, 102.8, 89.4 56.4, 56.4, 51.5, 19.3, 2.9, and 0.2.

HRMS (APCI-Orbitrap): Calculated for $C_{33}H_{38}NO_3Si_2^+$ [M+H$^+$]: 552.2385, found 552.2373.

IR (thin film): 3001, 2955, 2927, 2900, 2853, 2161, 1704, 1589, 1487, 1455, 1410, 1381, 1315, 1244, 1214, 1153, 1099, 1066, 1016, 944, 916, 840, 800, 748, 701, 659, 634, 603, 539, 498, 460, and 418 cm^{-1}.

2-(2-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9H-fluoren-3-yl)-1,2-dihydroisoquinolin-1-yl)fumaronitrile (38) :



Triynone **1a** (20 mg, 0.062 mmol), isoquinoline (**2a**, 14.5 μL, 0.124 mmol, 2 equiv) and fumaronitrile (**4f**, 24.2 mg, 0.310 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (4 mL, 0.02 M), and sealed with a Teflon-lined cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc elution). The eluant was concentrated and the residue purified by MPLC (3:1 Hex:EtOAc) to give **38** (0.060 mmol, 85%) as a brick red oil, which was an orange oil after passage through a normal phase high pressure liquid chromatography column (HPLC). The ^{1}H NMR spectra appeared essentially identical before and after the HPLC treatment.

Data for 38:

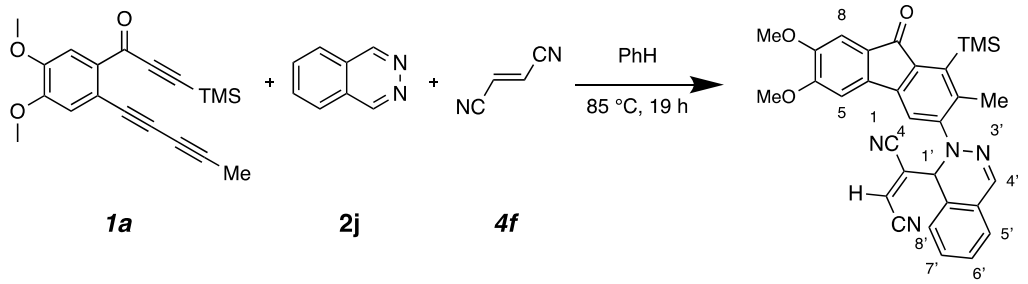
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, Ar*H6'*), 7.31 (s, 1H, Ar*H5* or Ar*H4*), 7.19 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, Ar*H7'*), 7.15 (s, 1H, Ar*H*8), 7.13 (dd, *J* = 7.8, 1.1 Hz, 1H, Ar*H8'*), 7.09 (dd, *J* = 7.7. 1.0 Hz, 1H, Ar*H5*'), 6.99 (s, 1H, Ar*H5* or Ar*H4*), 6.45 (br d, 1H, *J* = 7.8 Hz, C=C*H3'*), 6.18 [br s, 1H, *H*C=C(CN)], 5.62 (d, *J* = 8.0 Hz, 1H, C=C*H4'*), 5.58 (br s, 1H, C*H1'*), 4.03 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.51 (s, 3H, ArCH_3) and 0.44 [s, 9H, Si$(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 154.8, 150.1, 147.6, 145.7, 144.0, 139.1, 138.7, 138.1, 134.2, 133.7, 132.1, 130.2, 127.0, 127.0, 126.8, 125.2, 123.6, 118.3, 115.9, 113.1, 109.0, 107.0, 103.1, 101.7, 63.0, 56.7, 56.4, 20.1, and 2.6.

IR ($CDCl_3$): 2956, 2923, 2853, 2255, 2208, 1704, 1589, 1495, 1463, 1377, 1315, 1244, 1216, 1091, 1045, 1015, 910, 845, 793, 767, 730, 647, 603, and 417 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{28}H_{28}NO_3Si^+$ [M-(CN)C=C(CN)(H)]: 454.1833, found 454.1831 (most intense ion); Calculated for $C_{32}H_{30}N_3O_3Si^+$ [M+H$^+$]: 532.2051, found 532.2009 (minor ion).

2-(2-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9H-fluoren-3-yl)-1,2-dihydrophthalazin-1-yl)fumaronitrile (39):



1a **2j** ***4f*** ***39*** **(35%)**

Triynone **1a** (25 mg, 0.077 mmol, 1 equiv), phthalazine (**2j**, 31 mg, 0.231 mmol, 3 equiv), and fumaronitrile (**4f**, 30 mg, 0.385 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (10 mL), and sealed with a Teflon-lined screw-cap. The tube was heated overnight (18-19 h) in an oil bath at 85 °C and cooled. The contents were passed through a plug of silica (EtOAc elution). The eluate was concentrated and the residue purified by MPLC (1:1 Hex:EtOAc) to give **39** (14 mg, 0.0263 mmol, 35%) as a yellow oil. The absence of a difference nOe between *H1'* and (NC)*H*C=CCN was used as the basis for assigning the *E*-alkene geometry.

Data for 39:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H, Ar*H4'*), 7.64 (s, 1H, Ar*H4 or ArH5*), 7.55 (m, 2H, Ar*H6* and Ar*H7'*), 7.44 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.25 (nfom, 1H, Ar*H5'* or Ar*H8'*), 7.15 (s, 1H, Ar*H8*), 7.05 (s, 1H, Ar*H4 or ArH5*), 6.06 [s, 1H, *H*C=C(CN)], 5.63 (s, 1H, C*H1'*), 4.04 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.54 (s, 3H, ArCH_3), and 0.45 [s, 9H, Si$(CH_3)_3$].

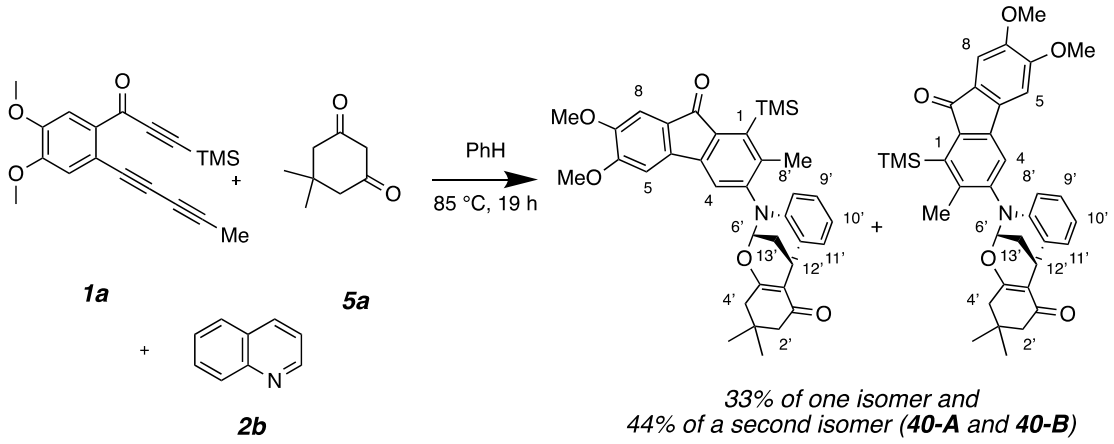
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 154.7, 149.9, 148.8, 145.2, 143.7, 139.2, 138.7, 138.5, 135.7, 133.2, 132.0, 130.9, 127.1, 126.8, 126.6, 126.3, 124.4, 117.7, 115.5, 112.8, 111.2, 106.8, 103.3, 59.4, 56.7, 56.4, 20.0, and 2.6.

IR ($CDCl_3$): 3038, 3007, 2942, 2900, 2839, 2254, 1702, 1588, 1494, 1463, 1455, 1381, 1360, 1315, 1244, 1215, 1150, 1089, 1018, 993, 908, 847, 759, 727, 647, 594, and 564 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{27}H_{27}N_2O_3Si^+$ [M-(CN)C=C(CN)(H)]: 455.1785, found 455.1785 (most intense ion); Calculated for $C_{31}H_{29}N_4O_3Si^+$ [M+H$^+$]: 533.2003, found 533.2004 (minor ion).

7-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9H-fluoren-3-yl)-3,3-dimethyl-2,3,4,6,7,12-hexahydro-1H-6,12-methanodibenzo[d,g][1,3]oxazocin-1-one (40-A) and

7-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9H-fluoren-3-yl)-3,3-dimethyl-2,3,4,6,7,12-hexahydro-1H-6,12-methanodibenzo[d,g][1,3]oxazocin-1-one (40-B)



Triynone **1a** (30 mg, 0.092 mmol), quinoline (**2b,** 22 μL, 0.184 mmol, 2 equiv), and dimedone (**5a**, 64.7 mg, 0.462 mmol, 5 equiv) were combined in a culture tube, dissolved in a mixture of benzene and acetonitrile (8 mL, 0.02M, 3:1 ratio), and sealed in a vial with a Teflon-lined screw cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (2:1, Hex:EtOAc) to give, in order of elution, atropisomeric diastereomers, **40-A** (018 mg, 0.030 mmol, 33%) as yellow oil and **40-B** (24 mg, 0.040, 44%) also as a yellow oil, which solidified upon storage at -10 °C. This product returned to an oily state upon being allowed to warm to ambient temperature.

Data for faster eluting, minor isomer, 40-A:

^{1}H NMR (500 MHz, $CDCl_3$): 7.47 (dd, *J* = 7.6, 1.7 Hz, 1H, ArH*11'*), 7.15 (s, 1H, Ar*H8*), 6.98 (s, 1H, Ar*H4*), 6.96 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H, Ar*H9'*), 6.78 (s, 1H, Ar*H5*), 6.76 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, Ar*H10*'), 6.28 (dd, *J* = 8.2, 1.1 Hz, 1H, Ar*H8*'), 5.55 (nfom, 1H, *H6'*), 4.23 (nfom, 1H, *H12'*), 3.93 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 2.33 (s, 3H, ArCH$_3$), 2.29 (br s, 2H, *H4'*), 2.25 (s, 2H, *H2'*), 2.19 (ddd, *J* = 13.1, 2.6, 2.6 Hz, 1H, *C13'H*$_a$H$_b$), 2.16 (ddd, *J* = 12.8, 3.1, 3.1 Hz, 1H, *C13'*H$_a$*H*$_b$), 1.08 (s, 3H, C3'*CH*$_3$), 1.04 (s, 3H, C3'*CH*$_3$), and 0.47 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR (126 MHz, $CDCl_3$): δ 195.9(C1'), 194.0(C9), 168.0(C4a'), 154.7, 149.9, 146.5, 144.5, 143.8, 142.2, 140.7, 140.0, 138.5, 128.5, 127.6, 127.2, 126.9, 122.1(C4), 119.3, 115.5, 113.5, 107.0(C8), 102.9(C5), 83.6, 56.5, 56.4, 50.6, 42.3, 32.5, 29.5, 27.9, 26.0, 25.4, 19.2, and 2.9.

HRMS (ESI-TOF): Calculated for $C_{36}H_{40}NO_5Si^+$ [M+H$^+$]: 594.2670, found 594.2659.

IR (thin film): 2955, 2897, 2870, 2838, 1706, 1650, 1618, 1591, 1491, 1457, 1375, 1316, 1266, 1245, 1215, 1196, 1181, 1162, 1111, 1074, 1039, 1017, 992, 958, 910, 845, 790, 730, 699, 677, 650, 621, 601, 571, 508, 490, 453, 432, and 412 cm^{-1}.

Data for slower eluting, major isomer, 40-B:

^{1}H NMR (500 MHz, $CDCl_3$): 7.47 (dd, *J* = 7.6, 1.6 Hz, 1H, ArH*11'*), 7.20 (s, 1H, Ar*H4*), 7.17 (s, 1H, Ar*H8*), 6.95 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H, Ar*H9'*), 6.93 (s, 1H, Ar*H5*), 6.76 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, Ar*H10*'), 6.19 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar*H8*'), 5.94 (nfom, *H6'*), 4.23 (dd, *J* = 3.2, 3.2 Hz, 1H, *H12'*), 3.99 (s, 3H, OC*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 2.33 (s, 3H, ArCH$_3$), 2.17–2.29 (m, 4H, C*H2'* and C*H4'*), 2.16 (ddd, *J* =12.5, 3.2, 3.2 Hz, 1H, *C13'H*$_a$H$_b$), 2.12 (ddd, *J* = 12.8, 2.4, 2.4 Hz, 1H, *C13'*H$_a$*H*$_b$), 1.07 (s, 3H, C3'*CH*$_3$), 0.97 (s, 3H, C3'*CH*$_3$) and 0.44 [s, 9H, Si(CH$_3$)$_3$].

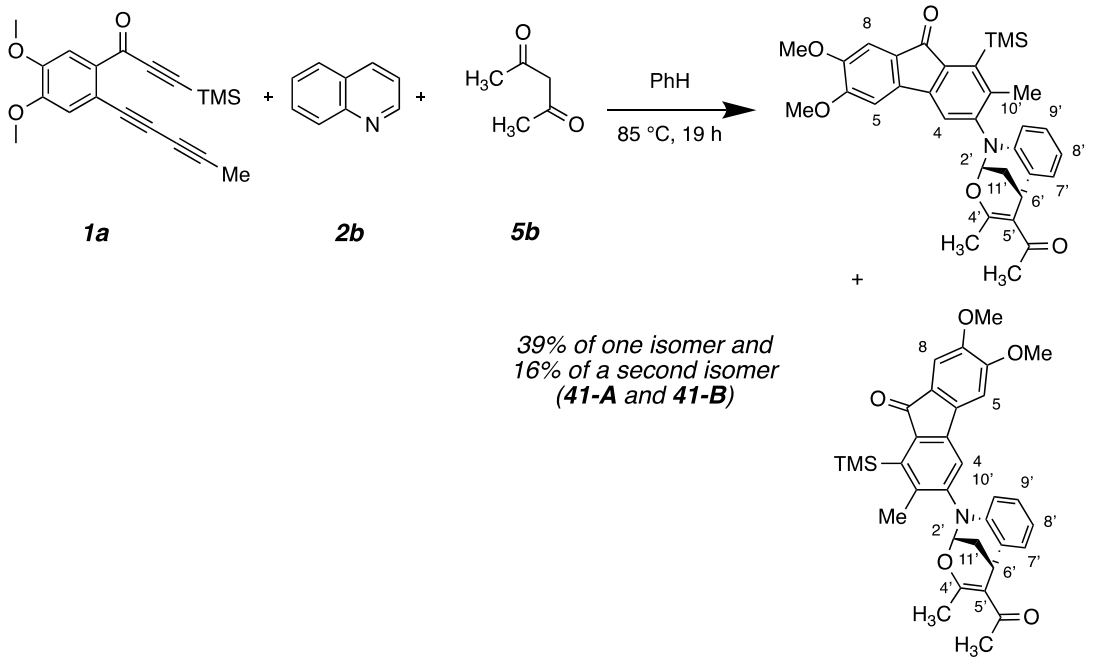
^{13}C NMR (126 MHz, $CDCl_3$): δ 196.2 (C1'), 193.9 (C9), 167.7 (C4a'), 154.7 (C67), 149.9 (C67), 146.9, 144.8, 144.1, 143.6, 139.9 (2x), 138.3, 128.6 (C11'), 127.3 (C8'), 126.9 (C9'), 126.4, 120.9 (C4), 119.2 (C10'), 114.8, 111.9 (C8'), 107.0 (C8), 102.8 (C5), 85.6, 56.5, 56.4, 50.7, 42.1, 32.3, 29.2, 27.9, 26.2, 25.6, 19.7, and 3.0.

HRMS (ESI-TOF): Calculated for $C_{36}H_{40}NO_5Si^+$ [M+H$^+$]: 594.2670, found 594.2658.

IR (thin film): 3036, 2956, 2898, 2871, 1706, 1651, 1618, 1592. 1491, 1459, 1381, 1369, 1317, 1269, 1246, 1215, 1180, 1151, 1111, 1075, 1040, 1018, 994, 959, 910, 861, 840, 792, 751, 731, 700, 677, 648, 622, 603, 573, 512, 490, 454, and 432 cm^{-1}.

3-(5- -4-methyl-2H-2,6-methanobenzo[d][1,3]oxazocin-1(6H)-yl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9H-fluoren-9-one (41-A) and

3-(5-Acetyl-4-methyl-2H-2,6-methanobenzo[d][1,3]oxazocin-1(6H)-yl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9H-fluoren-9-one (41-B):



Triynone **1a** (30 mg, 0.092 mmol), quinoline (**2b**, 22 μl, 0.184 mmol, 2 equiv), and acetylacetone (**5b**, 10 μL, 0.462 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.02M), and sealed in a vial with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (2:1, Hex:EtOAc) to give, in order of elution, impure **41-A** (20 mg, 0.029 mmol, 39% yield, corrected for the presence of residual quinoline from the mixture) as yellow oil and **41-B** (8 mg, 0.015 mmol, 16%) also as a yellow oil. A small portion of each product was later repurified by HPLC (2:1, Hex:EtOAc for **41-A** and 1:1, Hex:EtOAc for **41-B** to give samples of higher purity for characterization purposes.

Data for faster eluting, major isomer, 41-A:

^{1}H NMR (500 MHz, $CDCl_3$): 7.38 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH*7'*), 7.15 (s, 1H, Ar*H8*), 7.07 (s, 1H, Ar*H4*), 6.97 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H, Ar*H9'*), 6.84 (s, 1H, Ar*H5*), 6.75 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, Ar*H8'*), 6.29 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar*H10'*), 5.45 (nfom, 1H, *H2'*), 4.28 (nfom, 1H, *H6'*), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.45 (s, 3H,

C*H*$_3$C=O), 2.30 [s, 3H, ArC*H*$_3$], 2.27 [s, 3H, C4'C*H*$_3$], 2.15 (dd, *J* = 3, 3 Hz, 2H, *C11'H*$_2$), and 0.47 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR (126 MHz, CDCl$_3$): δ 197.1(MeC=O), 193.9(C9), 162.9(C4'), 154.6, 149.7, 146.4, 144.2, 143.8, 142.1, 140.8, 139.9, 138.5, 127.7, 127.4, 127.4, 126.7, 122.2(C4), 118.8, 117.7(C5'), 113.4, 106.8(C8), 102.9(C5), 82.2(C2'), 56.5, 56.2, 31.0, 28.9(C6'), 25.5, 21.2, 19.1, and 2.8.

HRMS (APCI-Orbitrap): Calculated for $C_{33}H_{36}NO_5Si^+$ [M+H$^+$]: 554.2357, found 554.2359.

IR (thin film): 3068, 2926, 2853, 1705, 1666, 1589, 1492, 1458, 1376, 1356, 1317, 1264, 1246, 1216, 1176, 1150, 1120, 1108, 1075, 1049, 1018, 976, 933, 896, 843, 810, 751, 732, 700, 655, 613, 517, and 436 cm^{-1}.

Data for slower eluting, minor isomer, 41-B: ^{1}H NMR (500 MHz, CDCl$_3$): 7.36 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH*7'*), 7.19 (s, 1H, *H4*), 7.17 (s, 1H, Ar*H8*), 6.97 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H, Ar*H9'*), 6.92 (s, 1H, *H5*), 6.75 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, Ar*H8*'), 6.22 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar*H10*'), 5.86 (nfom, 1H, Σ*J* = 6.8 Hz, *H2'*), 4.27 (nfom, Σ*J* = 8.0 Hz, 1H, *H6'*), 3.98 (s, 3H, OC*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 2.39 (s, 3H, C*H*$_3$C=O), 2.21 [s, 3H, C4'C*H*$_3$], 2.15 (ddd, *J* = 12.7, 3.3, 3.3 Hz, 1H, *C11'H*$_a$H$_b$), 2.07 (ddd, *J* = 12.5, 2.6, 2.6 Hz, 1H, *C11'*H$_a$*H*$_b$) 2.01 [s, 3H, Ar*CH*$_3$], and 0.43 [s, 9H, Si(CH$_3$)$_3$].

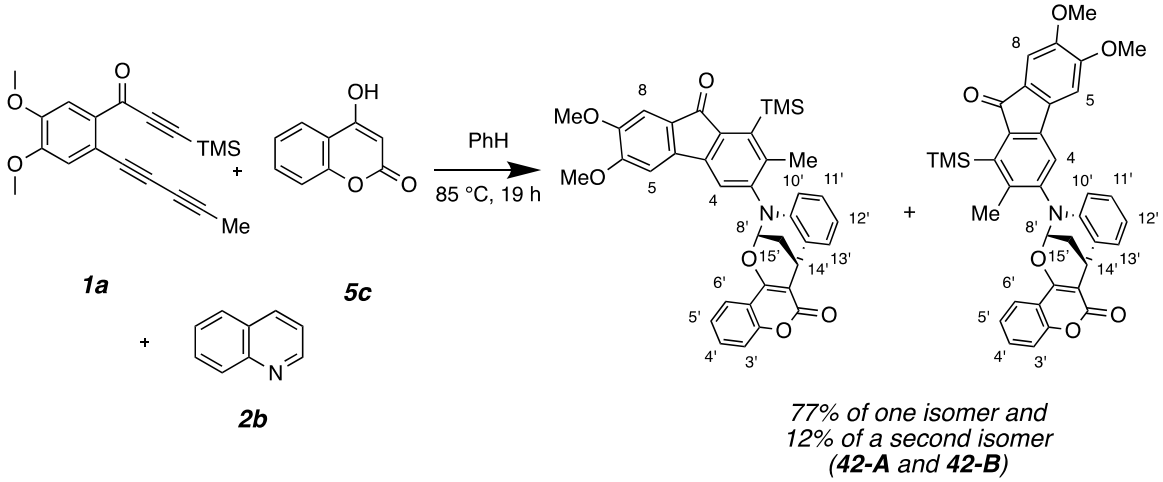
^{13}C NMR (126 MHz, CDCl$_3$): δ 197.4 (MeC=O), 194.0(C9), 162.6(C4'), 154.7, 149.9, 146.8, 144.7, 144.2, 143.7, 140.3, 139.8, 138.4, 127.8, 127.4, 126.9, 126.7, 120.8 (C4), 118.9, 117.0, 112.1, 107.0 (C8), 102.8 (C5), 84.1 (C2'), 56.5, 56.4, 31.3, 28.9 (C6'), 25.9, 21.2, 19.4, and 2.9.

HRMS (APCI-Orbitrap): Calculated for $C_{33}H_{36}NO_5Si^+$ [M+H$^+$]: 554.2357, found 554.2355.

IR (thin film): 3065, 2926, 2853, 1704, 1666, 1589, 1491, 1458, 1379, 1355, 1316, 1264, 1244, 1215, 1177, 1149, 1120, 1107, 1075, 1048, 1008, 976, 932, 896, 839, 730, 700, 648, 620, 602, 575, 517, and 432 cm^{-1}.

9-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9H-fluoren-3-yl)-9,14-dihydro-1H,8H-8,14-methanobenzo[d]chromeno[3,4-g][1,3]oxazocin-1-one (42-A) and

9-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9H-fluoren-3-yl)-9,14-dihydro-1H,8H-8,14-methanobenzo[d]chromeno[3,4-g][1,3]oxazocin-1-one (42-B):



Triynone **1a** (30 mg, 0.092 mmol), quinoline (**2b**, 22 μL, 0.184 mmol, 2 equiv), and 4-hydroxycoumarin (**5c**, 75 mg, 0.462 mmol, 5 equiv) were combined in a culture tube, dissolved in a mixture of benzene and acetonitrile (6 mL, 0.02M, 6:1 ratio), and sealed with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (3:1, Hex:EtOAc). The residue was purified by MPLC (3:1, Hex:EtOAc) to give, in order of elution, **42-A** (43 mg, 0.070 mmol, 77%) as a pale yellow amorphous film and **42-B** (7 mg, 0.011 mmol, 12%) as a yellow amorphous powder. A small portion of each sample was separately repurified by HPLC (3:1, Hex:EtOAc) to give samples of somewhat higher purity for characterization purposes.

Data for faster eluting, major diastereomer: 42-A:

^{1}H NMR (500 MHz, $CDCl_3$): 7.73 (dd, *J* = 7.9, 1.6 Hz, 1H, ArH*6'*), 7.60 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH*13'*), 7.49 (ddd, *J* = 8.4, 7.3, 1.7 Hz, 1H, Ar*H4'*), 7.32 (dd, *J* = 8.3, 1.2 Hz, 1H, Ar*H3'*), 7.19 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H, Ar*H5'*), 7.13 (s, 1H, Ar*H8*), 6.99 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H, Ar*H11'*), 6.87 (s, 1H, Ar*H4*), 6.82 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, Ar*H12'*), 6.45 (s, 1H, Ar*H5*), 6.28 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar*H10'*), 5.82 (nfom, 1H, *H8'*), 4.40 (ddd, *J* = 3.0, 3.0, 1.5 Hz, 1H, *H14'*), 3.90 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.47 (ddd, *J* = 13.1, 3.2, 3.2 Hz, 1H, *C15'*H_aH$_b$), 2.45 (ddd, *J* = 13.0, 2.8, 2.2 Hz, 1H, *C15'*H$_a$$H_b$), 2.40 (s, 3H, $ArCH_3$), and 0.50 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.0, 161.9, 158.9, 154.7, 152.5, 149.9, 145.8, 144.2, 143.9, 142.7, 140.7, 140.4, 138.4, 131.8, 128.6, 127.9, 126.7, 126.2, 123.9, 122.8, 122.6, 119.7, 116.9, 115.9, 113.5, 106.9, 106.6, 102.7, 84.1, 56.36, 56.34, 27.6, 25.9, 18.9, and 3.0.

HRMS (APCI-Orbitrap): Calculated for $C_{37}H_{34}NO_6Si^+$ [M+H$^+$]: 616.2150, found 616.2154.

IR (thin film)**:** 3070, 2945, 2903, 2853, 1708, 1626, 1592, 1492, 1456, 1383, 1317, 1295, 1266, 1246, 1214, 1151, 1114, 1101, 1076, 1038, 1018, 965, 929, 912, 860, 751, 699, 673, 622, 604, 499, and 437 cm^{-1}.

Data for slower eluting, minor isomer, 42-B:

^{1}H NMR (500 MHz, $CDCl_3$): 7.71 (br d, *J* = 7.8 Hz, 1H, ArH*6'*), 7.60 (br d, *J* = 7.6 Hz, 1H, ArH*13*'), 7.50 (br t, *J* = 7.9 Hz, 1H, Ar*H4'*), 7.30 (br d, *J* = 8.0 Hz, 1H, Ar*H3*'), 7.26 (s, 1H, *H4* or *H5*), 7.25 (br t, *J* = 7.5 Hz, 1H, Ar*H5'*), 7.18 (s, 1H, Ar*H8*), 7.00 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 1H, Ar*H11'*), 6.96 (s, 1H, *H4* or *H5*), 6.82 (br dd, *J* =7.4, 7.4 Hz, 1H, Ar*H12'*), 6.22 (br d, *J* = 8.1 Hz, 1H, Ar*H10'*), 6.21 (m, 1H, *H8'*), 4.39 (br s, 1H, *H14'*), 4.00 (s, 3H, OC*H*$_3$), 3.94 (s, 3H, OC*H*$_3$), 2.44 (br d, *J* = 12.8 Hz, 1H, *C15'*H$_a$H$_b$), 2.35 (br d, *J* = 12.8 Hz, 1H, *C15'*H$_a$*H$_b$*), 1.79 (s, 3H, ArCH$_3$), and 0.37 [s, 9H, Si(CH$_3$)$_3$].

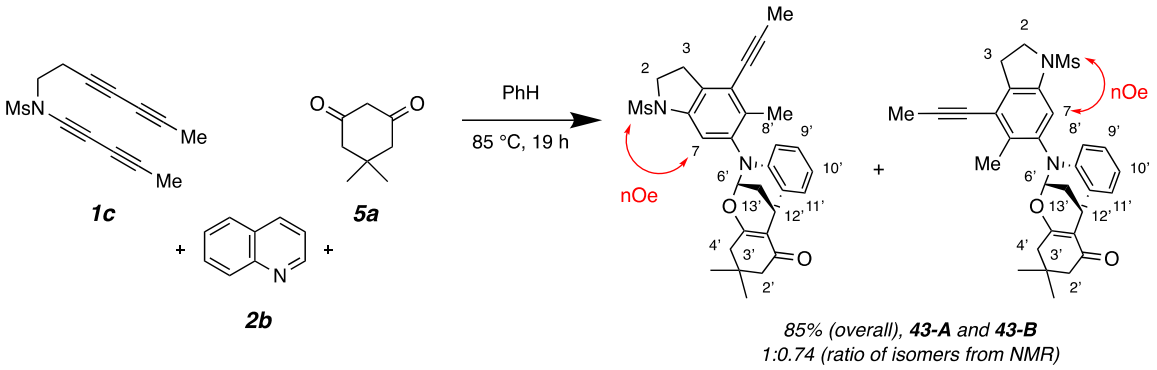
^{13}C NMR (126 MHz, $CDCl_3$): δ 193.9, 162.1, 158.7, 154.8, 152.4, 150.0, 146.4, 144.8, 144.3, 144.1, 140.3, 140.0, 138.3, 131.9, 128.7, 128.0, 126.9, 125.0, 124.1, 122.8, 121.0, 119.6, 116.9, 115.6, 112.2, 107.1, 105.6, 102.9, 86.1, 56.5, 56.4, 27.7, 26.0, 19.5, and 2.8.

HRMS (ESI-TOF): Calculated for $C_{37}H_{33}NNaO_6Si^+$ [M+Na$^+$]: 638.1969, found 638.1957.

IR (thin film)**:** 3056, 2926, 2853, 1702, 1625, 1590, 1491, 1455, 1382, 1370, 1316, 1295, 1265, 1241, 1210, 1146, 1113, 1100, 1075, 1037, 1015, 964, 929, 912, 889, 845, 813, 732, 699, 671, 637, 622, 602, 574, 557, 543, 497, 479, 437, and 411 cm^{-1}.

3,3-Dimethyl-7-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2,3,4,6,7,12-hexahydro-1H-6,12-methanodibenzo[d,g][1,3]oxazocin-1-one (43-A) and

3,3-Dimethyl-7-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-2,3,4,6,7,12-hexahydro-1H-6,12-methanodibenzo[d,g][1,3]oxazocin-1-one (43-B)



Tetrayne **1c** (50 mg, 0.202 mmol), quinoline (**2b**, 71.9 μL, 0.606 mmol, 3 equiv), and dimedone (**5a**, 142 mg, 1.01 mmol, 5 equiv) were combined in a culture tube, dissolved in a mixture of benzene and acetonitrile (14 mL, 3:2 ratio, 0.02M), and sealed in a vial with a Teflon-lined screw-cap. The solution was heated overnight (18–19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (2:1, Hex:EtOAc) to give, as partially overlapping peaks, a mixture of **43-A** and **43-B** (88 mg, 85% yield). These were present in a 1:0.74 ratio (^{1}H NMR spectrum) in the crude product mixture. A small portion of the mixture was separately repurified by normal phase HPLC (2:1, Hex:EtOAc) to give, in order of elution, **43-A** (major isomer) as a transparent oil, and **43-B** (minor isomer) also as a transparent oil. Differential nOe was used to confirm that each isomer had the same constitution (i.e., that the compounds were atropisomers and not regioisomers). The assignment of relative configuration within each atropisomeric is ambiguous. These further-purified samples were used for characterization purposes.

Data for faster eluting isomer, major isomer, 43-A:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H11'*), 7.03 (s, 1H, Ar*H7*), 6.87 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H, Ar*H9'*), 6.70 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar*H10'*), 6.03 (d, *J* = 8.1 Hz, Ar*H8'*), 5.40 (nfom, 1H, *H6'*), 4.19 (nfom, 1H, *H12'*), 4.03 (ddd, *J* = 10.3, 8.5, 8.5 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.99 (ddd, *J* = 10.2, 8.9, 8.9 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.23 (t, J = 8.7 Hz, 2H, $NMsCH_2CH_2$), 2.80 (s, 3H, CH_3SO_2N), 2.70 (d, *J* = 17.2 Hz, 1H, C2'H_aH_b or C4'H_aH_b), 2.26–2.15 (overlapping m, 2H, C4'H_2), 2.25 (s, 3H, $NArCH_3$), 2.21 (d, *J* = 17.2 Hz, 1H, C2'H_aH_b or C4'H_aH_b), 2.17 (ddd, *J* = 12.6, 2.6,

2.6 Hz, 1H, C13'H_aH_b), 2.16 (s, 3H, NArC≡CCH_3), 2.13 (ddd, *J* = 12.7, 3.1, 3.1 Hz, 1H, C13'H_aH_b), 1.05 [s, 3H, (*CH_3*)C3'], and 0.99 [s, 3H, (*CH_3*)C3'].

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.3, 168.3, 141.8, 140.8, 140.8, 134.6, 133.8, 128.3, 127.1, 127.0, 123.1, 118.8, 115.8, 115.5, 112.4, 95.3 (alkyne), 83.6 (*C6'*), 75.9 (alkyne), 50.64 (*C2'* or *C4'*), 50.59 (NMs*CH_2*), 41.9 (*C2'* or *C4'*), 34.4 (Ms), 32.4 (C3'), 29.2 [(*CH_3*)C3'], 28.4 (NMsCH_2*CH_2*), 27.7 [(*CH_3*)C3'], 26.1 (C13'), 25.5 (*C12'*), 15.3 (NAr*CH_3*), and 4.7 (NArC≡CCH_3). The indicated carbon peaks are assigned using HSQC data.

HRMS (APCI-Orbitrap): Calculated for $C_{30}H_{33}N_2O_4S^+$ [M+H^+]: 517.2156, found 517.2162.

IR (thin film): 3055, 2958, 2929, 2890, 2870, 2358, 2234, 1649, 1616, 1490, 1454, 1380, 1348, 1265, 1231, 1182, 1158, 1110, 1075, 1039, 968, 911, 825, 791, 730, 701, 665, 623, 543, 513, 495, and 455 cm^{-1}.

Data for slower eluting, minor isomer, 43-B:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H11'*), 7.20 (s, 1H, Ar*H7*), 6.88 (ddd, *J* = 7.9, 7.9, 1.5 Hz, 1H, Ar*H9'*), 6.72 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, Ar*H10'*), 6.01 (d, *J* = 8.1 Hz, Ar*H8'*), 5.85 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H, *H6'*), 4.18 (nfom, 1H, *H12'*), 4.07 (ddd, *J* = 10.3, 9.2, 9.2 Hz, 1H, CH_3SO_2NC*H_a*$H_b$$CH_2$), 4.00 (ddd, *J* = 10.5, 9.5, 9.5 Hz, 1H, $CH_3SO_2NCH_a$*H_b*CH_2), 3.23 (m, 2H, NMsCH_2*CH_2*), 2.89 (s, 3H, CH_3SO_2N), 2.26–2.11 (m, 4H, *H2'* and *H4'*), 2.13 (s, 3H, NArCH_3), 2.09 (t, *J* = 2.9 Hz, 2H, *H13'*), 1.92 (s, 3H, NArC≡CCH_3), 1.06 [s, 3H, (*CH_3*)C3'], and 0.95 [s, 3H, (*CH_3*)C3'].

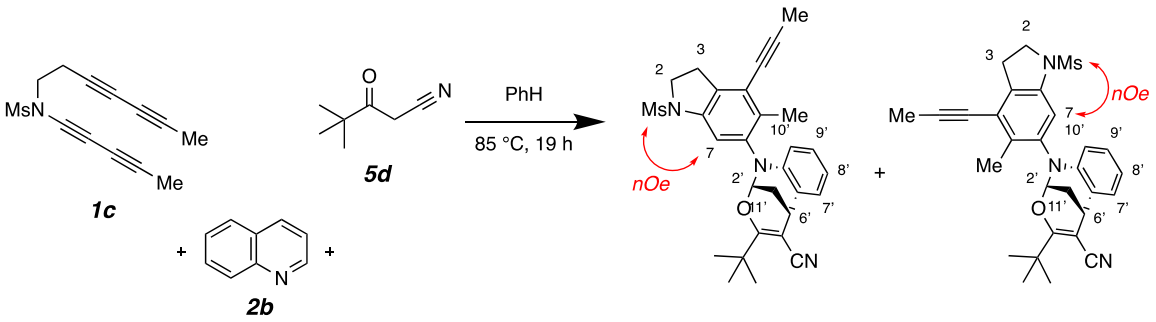
^{13}C NMR (125 MHz, $CDCl_3$): δ 196.2, 167.7, 142.5, 141.3, 140.2, 135.3, 133.4, 128.5, 127.1, 126.3, 123.1, 118.9, 114.8, 114.1, 111.6, 95.3, 85.8, 75.9, 50.7, 50.6, 42.1, 34.6, 32.2, 29.2, 28.4, 28.0, 26.1, 25.6, 16.1, and 4.7.

HRMS (APCI-Orbitrap): Calculated for $C_{30}H_{33}N_2O_4S^+$ [M+H]: 517.2156, found 517.2161.

IR (thin film): 3054, 2959, 2927, 2870, 1649, 1616, 1490, 1455, 1379, 1348, 1265, 1231, 1181, 1158, 1111, 1075, 1039, 992, 968, 911, 826, 792, 730, 701, 657, 622, 564, 542, 513, 495, and 455 cm^{-1}.

4-(Tert-butyl)-1-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-1,6-dihydro-2H-2,6-methanobenzo[d][1,3]oxazocine-5-carbonitrile atropisomer-maj (44-A) and

4-(Tert-butyl)-1-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-1,6-dihydro-2H-2,6-methanobenzo[d][1,3]oxazocine-5-carbonitrile atropisomer-min (44-B)



*53% (overall), **44-A** and **44-B***
1:0.56 (ratio of isomers from NMR)

Tetrayne **1c** (20 mg, 0.081 mmol), quinoline (**2b**, 20 μL, 0.162 mmol, 2 equiv), and pivaloylacetonitrile (**5d**, 50.7 mg, 0.405 mmol, 5 equiv) were combined in a culture tube, dissolved in benzene (6 mL, 0.02M), and sealed in a vial with a Teflon-lined screw-cap. The solution was heated overnight (18-19 h) in an oil bath at 85 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (1:1, Hex:EtOAc) to give a coeluting mixture of isomers, which also contained residual pivaloylacetonitrile (**5d**), as a transparent oil. This mixture was repurified by MPLC (2:1, Hex:EtOAc) to give coeluting mixture of atropisomeric diastereomers, **44-A** and **44-B** (22 mg, 0.044 mmol, 53% overall) as a transparent oil. There was no evidence of shouldering or other peak asymmetry in the MPLC chromatogram. The characterization spectral data were collected using the mixture of **44-A** and **44-B**. Differential nOe was used to confirm that both structures share the same constitution (i.e., represent only a single regioisomer).

^{1}H NMR for the major diastereomer, 44-A (500 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 7.1, 1.9 Hz, 1H, Ar*H9'*), 7.08 (s, 1H, Ar*H7*), 6.96 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H, ArH*7'*), 6.77 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, Ar*H8'*), 6.04 (dd, J = 8.2, 0.9 Hz, Ar*H10'*), 5.46 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H, *H2'*), 4.09-3.95 (m, 2H, MsNCH_2), 3.59 (ddd, *J* = 3, 3, 3 Hz, 1H, *H6'*), 3.26–3.21 (m, 2H, MsNCH$_2$CH_2), 2.80 (s, 3H, CH_3SO_2N), 2.19 (s, 3H, NArCH_3), 2.15 (s, 3H, NArC≡CCH_3), 2.13 (ddd, *J* = includes 2.6, 2.6 Hz, 1H, *H11'$_a$*), 2.09 (ddd, *J* = 12.0, 2.4, 2.4 Hz, 1H, *H11'$_b$*), and 1.29 [s, 9H, $(CH_3)_3$].

^{1}H NMR of the identifiable resonances for the minor diastereomer (500 MHz, $CDCl_3$): 7.27 (dd, *J* = 6.9, 1.9 Hz, 1H, Ar*H9'*), 7.15 (s, 1H, Ar*H7*), 6.97 (ddd, *J* = 7.6, 7.6, 1.7 Hz, 1H, Ar*H7'*), 6.78 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, Ar*H8'*), 6.04 (dd, J = 8, 0.8 Hz, Ar*H10'*), 5.91 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H, *H2'*), 4.09-3.95 (m, 2H, MsNC*H*$_2$), 3.61 (ddd, *J* = 3, 3, 3 Hz, 1H, *H6'*), 3.26–3.21 (m, 2H, $MsNCH_2C\mathit{H}_2$), 2.89 (s, 3H, CH_3SO_2N), ca. 2.2–2.14 (m, 2H, *H11'*$_2$), 2.13 (s, 3H, $NArCH_3$), 1.96 (s, 3H, $NArC{\equiv}CCH_3$), and 1.24 [s, 9H, $(CH_3)_3$].

Because of partial overlap of some of the proton resonances in the NMR spectrum recorded in $CDCl_3$, the spectrum was also taken in C_6D_6.

^{1}H NMR for the major diastereomer, 44-A (500 MHz, C_6D_6): δ 7.37 (s, 1H, Ar*H7*), 7.29 (dd, *J* = 7.4, 1.2 Hz, 1H, Ar*H7'*), 6.82 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H, Ar*H9'*), 6.68 (ddd, *J* = 7.5, 7.5 1.3 Hz, 1H, ArH*8'*), 6.11 (dd, *J* = 8.4, 0.8 Hz, 1H, Ar*H10'*), 4.98 (nfom, 1H, *H2'*), 3.54–3.48 (m, 1H, *H2*$_a$H2$_b$), 3.42–3.33 (m, 1H, H2$_a$*H2*$_b$), 3.24 (ddd, *J* = 3, 3, 3 Hz, 1H, *H6'*), 2.77–2.62 (m, 2H, *H3*), 2.13 (s, 3H, CH_3SO_2N), 2.06 (s, 3H, $NArCH_3$), 1.74 (s, 3H, $NArC{\equiv}CCH_3$), 1.47 (ddd, *J* =12.9, 3.8, 3.8 Hz, 1H, *C11'H*$_a$H$_b$), 1.40 (ddd, *J* = 12.5, 2.5, 2.5 Hz, 1H, *C11'*H$_a$*H*$_b$), and 1.36 [s, 9H, $(CH_3)_3$]

^{1}H NMR of the identifiable resonances for the minor diastereomer, 44-B (500 MHz, C_6D_6): 7.37 (s, 1H, Ar*H7*), 7.23 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar*H7'*), 6.88 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H, Ar*H9'*), 6.70 (ddd, *J* = 8.3, 7.4, 1.1 Hz, 1H, ArH*8'*), 6.17 (dd, *J* = 8.1, 0.8 Hz, 1H, Ar*H10'*), 5.51 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H, *H2'*), 3.54–3.48 (m, 1H, *H2*$_a$H2$_b$), 3.42–3.33 (m, 1H, H2$_a$*H2*$_b$), 3.14 (nfom, 1H, *H6'*), 2.77–2.62 (m, 2H, *H3*), 2.19 (s, 3H, CH_3SO_2N), 2.02 (s, 3H, $NArCH_3$), 1.66 (s, 3H, $NArC{\equiv}CCH_3$), 1.18 [s, 9H, $(CH_3)_3$], 1.27 (ddd, *J* =12.8, 3.5, 3.5 Hz, 1H, *C11'H*$_a$H$_b$), and 1.07 (ddd, *J* = 12.9, 2.4, 2.4 Hz, 1H, *C11'*H$_a$*H*$_b$)

^{13}C NMR for major diastereomer, 44-A (125 MHz, $CDCl_3$): δ 173.8, 141.5, 141.0, 140.4, 134.1, 134.0, 128.1, 127.4, 125.2, 123.4, 120.3, 119.0, 115.4, 112.3, 95.5, 86.3, 83.1, 75.8, 50.5, 38.1, 34.5, 33.5, 28.9, 28.3, 25.1, 15.4, and 4.7.

^{13}C NMR identifiable resonances for minor diastereomer, 44-B (125 MHz, $CDCl_3$): δ 173.6, 142.2, 141.3, 139.8, 134.9, 133.5, 128.1, 127.6, 124.9, 123.1, 120.5, 119.2, 113.5, 112.2, 95.6, 85.6, 85.0, 75.8, 50.6, 37.8, 34.8, 33.3, 28.9, 28.4, 25.3, 16.6, and 4.7.

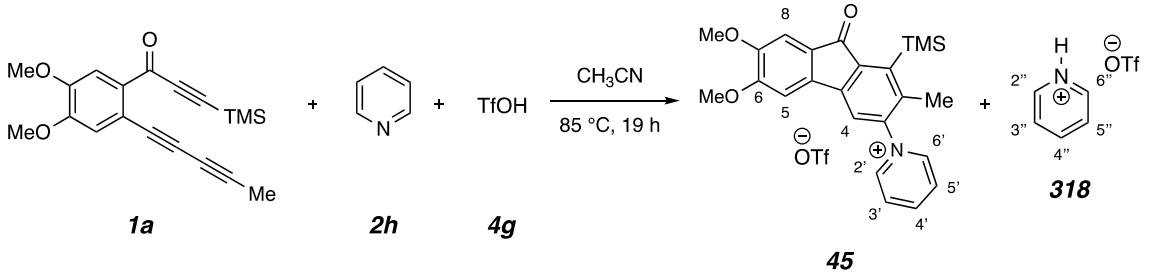
HRMS (APCI-Orbitrap): Calculated for $C_{29}H_{32}N_3O_3S^+$ [M+H$^+$]: 502.2159, found 502.2153.

IR (thin film): 3042, 2971, 2918, 2873, 2200, 1735, 1595, 1491, 1457, 1398, 1349, 1315, 1266, 1241, 1158, 1137, 1111, 1083, 1061, 1024, 967, 911, 876, 844, 812, 733, 702, 654, 613, 584, 566, 543, 514, 500, and 479 cm^{-1}.

Reverse phase liquid chromatography: Only one peak corresponding to **44** was observed, consistent with the assumption that the atropisomers are interconverting sufficiently rapidly to coeluted.

(e) Products obtained from triflate salt formations and their functionalizations

1-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9H-fluoren-3-yl)pyridin-1-ium triflate (45)



Triynone **1a** (100 mg, 0.308 mmol) and pyridine (**2h**, 80 μL, 0.924 mmol, 3 equiv) were combined in a culture tube and dissolved in CH_3CN (20 mL). Triflic acid (**4g**, 54, μL, 0.616 mmol, 2 equiv) was added to this solution, and culture tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (16 h) in an oil bath at 85 °C, cooled, and concentrated to give a brown colored mixture of **45**, **318**, and residual pyridine (**2h**). This mixture was heated under vacuum (~0.1 torr) at 50 °C to provide a mixture of **45** and **318** as a pale brown powder.

Data for 45:

^{1}H NMR (500 MHz, DMSO): δ 9.33 (dd, *J* = 6.6, 1.3 Hz, 2H, Ar*H2'*), 8.89 (tt, *J* = 8.0, 1.7 Hz, 1H, Ar*H4'*), 8.41 (dd, *J* = 7.7, 6.5 Hz, 2H, Ar*H3'*), 7.98 (s, 1H, Ar*H4*), 7.41 (s, 1H, Ar*H5*), 7.21 (s, 1H, Ar*H8*), 3.89 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 2.08 (s, 3H, $ArCH_3$), and 0.43 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, DMSO): δ 192.6, 155.2, 150.2, 147.6, 145.8, 145.7, 145.5, 143.1, 143.1, 141.8, 137.8, 136.9, 125.4, 119.1, 107.2, 104.5, 56.2, 55.9, 18.9, and 2.6.

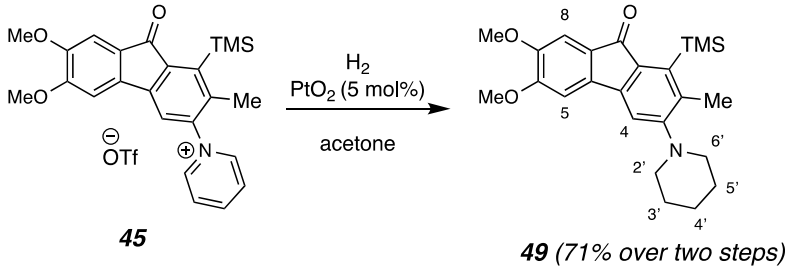
HRMS (ESI-TOF): Calculated for $C_{24}H_{26}NO_3Si^+$ [M]: 404.1676, found 404.1673.

Data for S-8:

^{1}H NMR (500 MHz, DMSO): δ 8.92 (dd, *J* = 6.8, 1.7 Hz, 1H, Ar*H6''*), 8.57 (tt, *J* = 7.9, 1.8 Hz, 1H, Ar*H4''*), and 8.05 (dd, *J* = 7.6, 6.6 Hz, 2H, Ar*H3''*).

^{13}C NMR (125 MHz, DMSO): δ 142.7, 128.6, and 127.0.

6,7-Dimethoxy-2-methyl-3-(piperidin-1-yl)-1-(trimethylsilyl)-9H-fluoren-9-one (49)



45 ***49*** *(71% over two steps)*

An oven dried 20 mL culture tube having a magnetic stir bar was evacuated with vacuum and purged with N_2 gas. Pyridinium triflate salt **45** (25 mg, 0.045 mmol, 1 equiv) was added, and the salt was dissolved in 5 mL of acetone. Adams catalyst (0.5 mg, 5 mol%) was added, and this solution was stirred under one atmosphere of H_2 at room temperature. The reaction progress was monitored by crude mass spectrometric analysis. After the consumption of the starting material (ca. 2 h), the reaction mixture was filtered through Celite® and concentrated under reduced pressure. The crude residue was dissolved in DCM and washed with sat. aq. $NaHCO_3$. The aqueous phase was washed with DCM (3x, ~30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. This residue was passed through a plug of silica gel (100 % EtOAc) to obtain **49** (13 mg, 71% yield) as an orange colored crystalline powder.

Data for 49:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H, Ar*H8*), 7.02 (s, 1H, Ar*H4*), 6.92 (s, 1H, Ar*H5*), 4.01 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 2.95 (br t, *J* = 4.7 Hz, 4H, *H2'* and *H6'*), 2.38 (s, 3H, $ArCH_3$), 1.74 (pent, *J* = 5.9 Hz, 4H, *H3'* and *H5'*), 1.62 (br pent, *J* = 6.8 Hz, 2H, *H4'*), and 0.42 [s, 9H, $Si(CH_3)_3$].

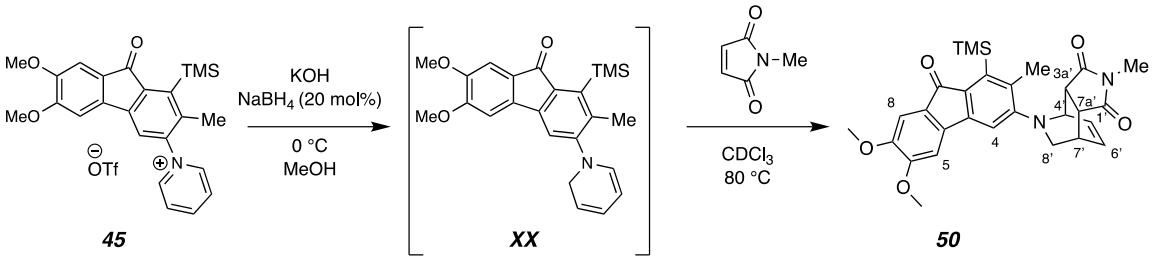
^{13}C NMR (125 MHz, $CDCl_3$): δ 194.1, 157.7, 154.0, 149.4, 144.0, 143.5, 138.7, 137.0, 134.2, 127.5, 110.8, 106.8, 102.6, 56.5, 56.3, 53.3, 26.5, 24.5, 20.3, and 2.8.

HRMS (APCI-Orbitrap): Calculated for $C_{24}H_{32}NO_3Si^+$ [M+H$^+$]: 410.2146, found 410.2143.

IR (thin film): 2973, 2937, 2845, 1692, 1585, 1544, 1495, 1459, 1411, 1385, 1357, 1311, 1242, 1220, 1150, 1135, 1090, 1045, 1017, 1000, 856, 797, 759, 733, 701, 676, 636, 607, 584, 542, 456, and 415 cm^{-1}.

mp: 162-165 °C

9-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione (50):



An oven dried 30 mL culture tube having a magnetic stir bar was evacuated with vacuum and purged with N_2 gas. Pyridinium triflate salt **45** (25 mg, 0.045 mmol, 1 equiv) was added, and the salt was dissolved in 8 mL of methanol. The solution was cooled to 0 °C, and powdered potassium hydroxide (10 mg, 0.181 mmol, 2 equiv) and $NaBH_4$ (0.700 mg, 20 mol%) were added in sequence. The reaction mixture was warmed to room temperature and stirred under a nitrogen atmosphere until the reaction was judged to completed by crude mass spectrometric analysis (ca. 2 h). The solution was concentrated under reduced pressure to obtain a crude material, which was dissolved in EtOAc and washed with sat. aq. $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (3x, ~30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain a crude product (**XX**). This dihydropyridine **50** showed signs of decomposition upon storage and handling and, therefore, was directly used for the next step without chromatographic purification.

The crude product **XX** and *N*-methylmaleimide (**3i**, 25 mg, 0.225 mmol, 5 equiv) were combined in a culture tube, dissolved in $CDCl_3$ (4 mL), and sealed with a Teflon-lined screw cap. The solution was heated overnight (12 h) in an oil bath at 80 °C, cooled, and passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (1:1, Hex:EtOAc) to give **50** (10 mg, 43%, 0.019 mmol) as a yellow oil. A small portion of this material was separately repurified by HPLC (1:1, Hex:EtOAc).

Data for Diels–Alder adduct 50:

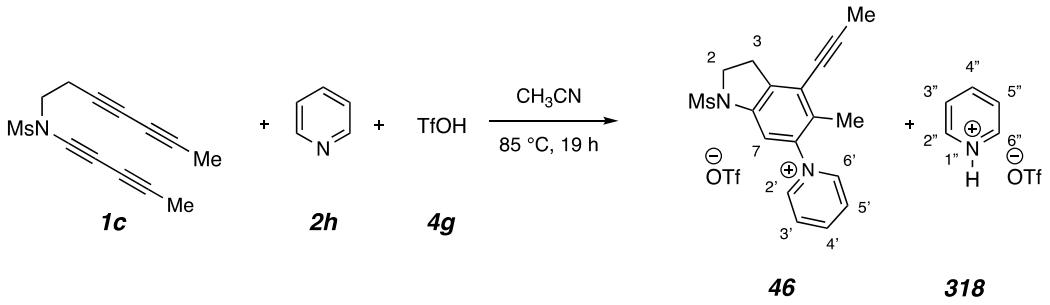
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H, Ar*H8*), 6.90 (s, 1H, Ar*H5* or Ar*H4*), 6.88 (s, 1H, Ar*H5* or Ar*H4*), 6.66 (ddd, *J* = 8.2, 5.3, 1.5 Hz, 1H, *H1'* or *H6'*), 6.40 (ddd, *J* = 8.0, 6.4, 1.4 Hz, 1H, *H1'* or *H6'*), 4.62 (ddd, *J* = 5.4, 4.1, 1.4 Hz, 1H, *H4'*), 4.03 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.62 (dd, *J* = 9.6, 1.8 Hz, 1H, *H8'*), 3.53 (dd, *J* = 8.0, 4.1 Hz, 1H, *H3a'*), 3.39–3.36 (m, Σ□ = 15.8 Hz (which accommodates the following values that should be within this resonance: 6.4, 3.1, 2.6, 1.8, and 1.5 seen in each of five other resonances coupled to this bridgehead proton) 1H, *H7'*), 3.13 (dd, *J* = 8.0, 3.1 Hz, 1H, *H7a'*), 2.60 (dd, *J* = 9.7, 2.6 Hz, 1H, *H8'*), 2.95 (s, 3H, N*CH*$_3$), 2.32 (s, 3H, ArCH$_3$), and 0.41 [s, 9H, Si(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 178.1, 177.0, 155.5, 154.1, 149.7, 144.6, 143.8, 138.2, 135.4, 134.6, 132.6, 132.0, 127.6, 111.0, 106.8, 102.5, 56.6, 56.3, 52.6, 52.2, 46.4, 41.7, 33.7, 25.0, 22.3, and 2.6.

HRMS (APCI-Orbitrap): Calculated for $C_{29}H_{33}N_2O_5Si^+$ [M+H$^+$]: 517.2153, found 517.2147.

IR (thin film): 3057, 2942, 2900, 2873, 1775, 1694, 1585, 1545, 1493, 1465, 1437, 1412, 1383, 1353, 1313, 1269, 1243, 1214, 1151, 1127, 1094, 1018, 1001, 914, 843, 796, 755, 728, 700, 616, 602, 582, 557, 517, and 433 cm^{-1}.

1-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)pyridin-1-ium triflate (46):



In a 20 mL culture tube, pyridine (**2h**, 65 μL, 0.982 mmol, 4 equiv) was dissolved in CH_3CN (8 mL). Triflic acid (**4g**, 27 μL, 0.303 mmol, 1.5 equiv) was added and then tetrayne **1c** (50 mg, 0.202 mmol, 1 equiv) were added to this solution. The culture tube was sealed with a Teflon-lined screw cap. The solution was heated overnight (16 h) in an oil bath at 85 °C, cooled, and concentrated to give a dark brown colored sticky solid. This mixture was heated under vacuum (~0.1 torr) at 50 °C to remove excess pyridine and provide the residual pyridinium triflate salts **46** and **318**.

Data for 46:

^{1}H NMR (500 MHz, CD_3CN): δ 8.79 (dd, *J* = 6.4, 1.4 Hz, 2H, Ar*H2'*), 8.72 (tt, *J* = 7.9, 1.5 Hz, 1H, Ar*H4'*), 8.21 (dd, *J* = 7.7, 6.4 Hz, 2H, Ar*H3'*), 7.37 (s, 1H, Ar*H7*), 4.08 (t, *J* = 8.6 Hz, 2H, *H2*), 3.27 (t, *J* = 8.7 Hz, 2H, *H3*), 2.97 (s, 3H, C*H*$_3$SO$_2$N), 2.14 (s, 3H, NArC*H*$_3$), and 2.06 (s, 3H, C≡CC*H*$_3$).

^{13}C NMR (125 MHz, CD_3CN): δ 148.3, 146.9, 146.8, 143.8, 142.1, 139.1, 130.1, 129.1, 128.1, 98.6, 75.2, 51.2, 35.5, 28.9, 15.4, and 4.5.

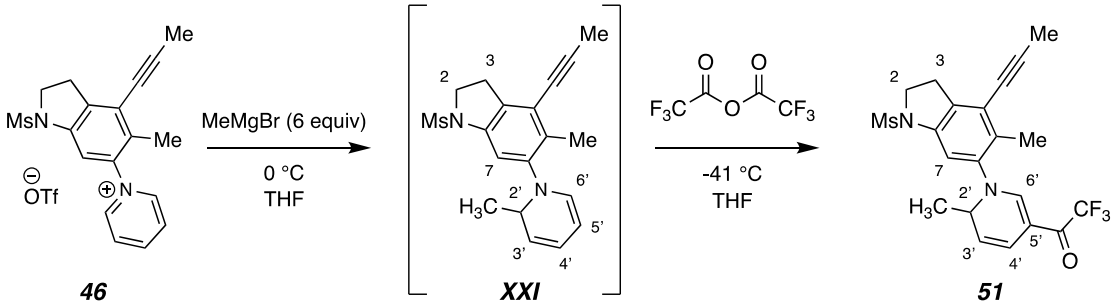
HRMS (ESI-TOF): Calculated for $C_{18}H_{19}N_2O_2S^+$ [M]: 327.1162, found 327.1158.

Data for 318:

^{1}H NMR (500 MHz, CD_3CN): δ 10.42 [s, 1H, (pyr)$^+$-*H*], 8.73 (dd, *J* = 6.4, 1.5 Hz, 1H, Ar*H6''*), 8.49 (tt, *J* = 8.0, 1.6 Hz, 1H, Ar*H4''*), and 7.96 (dd, *J* = 7.7, 6.4 Hz, 2H, Ar*H3''*).

^{13}C NMR (125 MHz, CD_3CN): δ 129.6, 118.4, and 110.8.

2,2,2-Trifluoro-1-(6-methyl-1-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-1,6-dihydropyridin-3-yl)ethan-1-one (51)



46 *XXI* *51*

In a 100 mL round bottom flask, crude salt **46** was added. This salt was dissolved in 15 mL of THF, and then cooled to 0 °C using an ice bath. Methylmagnesium bromide (0.67 mL, 3M solution in THF, 6 equiv, 2.02 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for two hours at 0 °C. Formation of the product was confirmed by TLC and mass spectrometric analysis Satd. aq. $NaHCO_3$ (10 mL) and diethyl ether (10 mL) were added. The aqueous phase was extracted with diethyl ether (3x, ~45 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the crude product mixture containing the dihydropyridine (**XXI**). **XXI** proved to be very sensitive towards silica gel chromatography. This compound was carried into the next reaction without purification.

^{1}H NMR data for the acid sensitive intermediate XXI:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (s, 1H, Ar*H7*), 6.03 (d, *J* = 7.2 Hz, 1H, *H6'*), 5.94 (dd, *J* = 9.3, 5.5 Hz, 1H, *H4'*), 5.17 (dd, *J* = 9.2, 5.3 Hz, 1H, *H3'*), 4.86 (ddd, *J* = 7.0, 5.5, 1.3 Hz, 1H, Ar*H5'*), 4.31 (pent, *J* = 6.3 Hz, 1H, *H2'*), 4.01 (ddd, *J* = 10.3, 10.3, 8.2 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.95 (ddd, *J* = 10.8, 10.8, 8.3 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.15 (t, *J* = 8.4 Hz, 2H, $NMsCH_2CH_2$), 2.85 (s, 3H, CH_3SO_2N), 2.35 (s, 3H, $NArCH_3$), 2.13 (s, 3H, $C{\equiv}CCH_3$), and 1.06 [d, *J* = 6.3 Hz, 3H, $N(CH)CH_3$].

Crude **XXI** was dissolved in THF (15 mL), cooled to -41 °C, and trifluoroacetic anhydride (40 μL, 0.283 mmol, 1.4 equiv) was added. This solution was warmed to room temperature. Saturated Na_2CO_3 (10 mL) was added and the mixture was extracted with DCM (3x, ~45 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the crude trifluoromethyl ketone **51**. This was passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (1:1, Hex:EtOAc) to give impure **51** as a yellow oil. This impure product was repurified

by MPLC (2:1, Hex:EtOAc) to give pure **51** (50 mg, 0.114 mmol, 56% overall yield) as a bright yellow oil.

Data for 51:

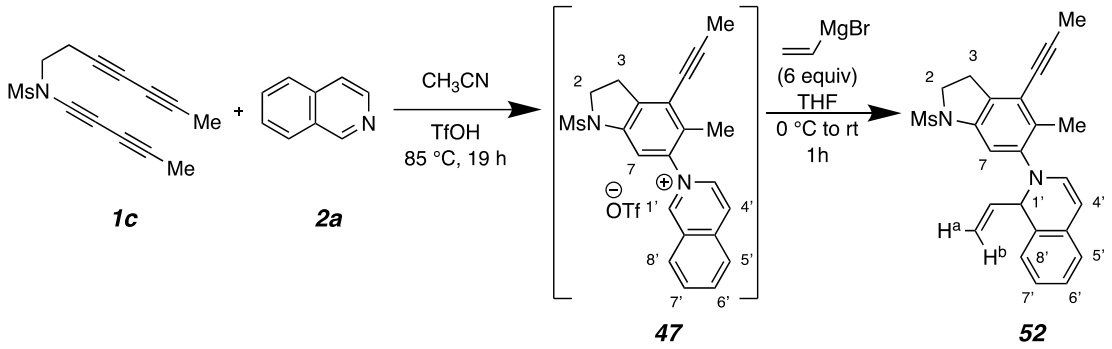
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (br s, 1H, Ar*H6'*), 7.23 (s, 1H, Ar*H7*), 6.58 (br d, *J* = 9.7 Hz, *H4'*), 5.35 (br d, *J* = 9.8 Hz, *H3'*), 4.59 (br s, 1H, *H2'*), 4.10–4.00 (m, 2H, $CH_3SO_3NCH_2$), 3.24 (t, *J* = 8.6 Hz, 2H, $NMsCH_2CH_2$), 2.93 (s, 3H, CH_3SO_2N), 2.35 (s, 3H, $NArCH_3$), 2.17 (s, 3H, $C{\equiv}CCH_3$), and 1.26 [d, *J* = 6.4 Hz, 3H, $N(CH)CH_3$].

^{13}C NMR (126 MHz, $CDCl_3$): δ 151.5 (*C6'*), 142.6, 140.8, 134.7, 131.5, 123.9, 118 (q, CF_3, *J* = 290 Hz), 119.0 (*C4'*), 118.7 (*C3'*, from HSQC), 116.8, 111.0 (*C7*, from HSQC), 96.5, 75.3, 57.3 (C2'), 50.4, 35.2, 28.3, 21.8, 15.7, and 4.7. (resonance for the ketone carbonyl carbon not observed)

HRMS (APCI-Orbitrap): Calculated for $C_{21}H_{22}F_3N_2O_3S^+$ $[M+H^+]$: 439.1295, found 439.1298.

IR (thin film): 3058, 2973, 2924, 2853, 2232, 1633, 1597, 1559, 1534, 1447, 1415, 1347, 1323, 1294, 1219, 1182, 1157, 1127, 1022, 965, 908, 872, 797, 756, 727, 663, 614, 568, 543, 513, and 426 cm^{-1}.

2-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-1-vinyl-1,2-dihydroisoquinoline (52):



In a 20 mL culture tube, isoquinoline (**2a**, 42 μL, 0.363 mmol, 3 equiv) was dissolved in CH_3CN (8 mL). Triflic acid (**4g**, 16 μL, 0.182 mmol, 1.5 equiv) was added to this solution, followed by the addition of tetrayne **1c** (30 mg, 0.121 mmol, 1 equiv). The culture tube was sealed with a Teflon-lined screw cap. This solution was heated overnight (16 h) in an oil bath at 85 °C, cooled, and concentrated to give a red colored sticky solid **47**. The formation of the salt **47** was confirmed by ^{1}H NMR and HRMS analysis.

NMR and HRMS analysis of the intermediate salt, 47:

^{1}H NMR (500 MHz, DMSO): δ 10.22 (s, 1H, Ar*H1'*), 8.87 (d, *J* = 6.8 Hz, 1H, Ar*H3'* or Ar*H4'*), 8.73 (d, *J* = 6.8 Hz, 1H, Ar*H3'* or Ar*H4'*), 8.56 (d, *J* = 8.2 Hz, 1H, Ar*H8'* or Ar*H5'*), 8.46 (d, *J* = 8.2 Hz, 1H, Ar*H8'* or Ar*H5'*), 8.37 (t, *J* = 8.1 Hz, 1H, Ar*H6'*), 8.16 (t, *J* = 7.5 Hz, 1H, Ar*H7'*), 7.55 (s, 1H, Ar*H7*), 4.09 (t, *J* = 8.6 Hz, 2H, *H2*), 3.26 (t, *J* = 8.6 Hz, 2H, *H3*), 3.15 (s, 3H, C*H*$_3$SO$_2$N), 2.19 (s, 3H, NArC*H*$_3$), and 2.12 (s, 3H, C≡CC*H*$_3$).

HRMS (ESI-TOF): Calculated for $C_{22}H_{21}N_2O_2S^+$ [M]: 377.1318, found 377.1317.

In a 100 mL round bottom flask, the triflate salt **47** was dissolved in 15 mL of THF and cooled to 0 °C using an ice bath. Vinylmagnesium bromide (0.73 mL, 1 M solution in THF, 6 equiv, 0.726 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for one hour at 0 °C. Formation of the product was confirmed by TLC and mass spectrometric analysis. Satd. aq. $NaHCO_3$ (10 mL) EtOAc (10 mL) were added. The aqueous phase was washed with EtOAc (3x, ~30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. This crude product mixture was passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (2:1, Hex:EtOAc) to give **52** (39 mg, 79%, 0.096 mmol) as an orange oil, which solidified into an amorphous solid in the freezer (-10 °C).

Data for 52:

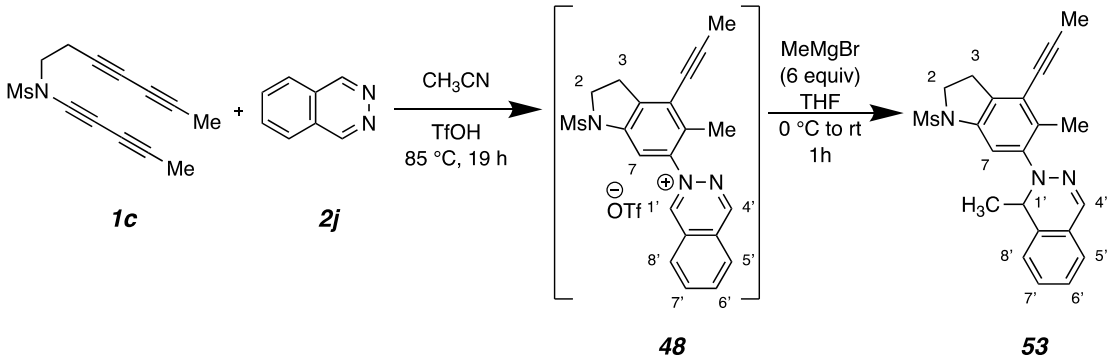
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1H, Ar*H7*), 7.17 (ddd, *J* = 8.8, 7.5, 1.5 Hz, 1H, Ar*H6'*), 7.07 (ddd, *J* = 8.8, 7.5, 1.3 Hz, 1H, Ar*H7'*), 6.99 (br d, *J* = 7.4 Hz, 1H, Ar*H8'*), 6.97 (br d, *J* = 7.3 Hz, 1H, Ar*H5'*), 6.24 (d, *J* = 7.4 Hz, 1H, *H3'*), 6.11 (ddd, *J* = 17.3, 10.3, 7.3 Hz, 1H, =C*H*C1'), 5.52 (d, *J* = 7.4 Hz, 1H, *H4'*), 5.04 (d, *J* = 7.5 Hz, 1H, *H1'*), 4.93 (d, 1H, *J* = 10.1 Hz, H^a), 4.91 (d, 1H, *J* = 17.1 Hz, H^b), 4.00 (ddd, *J* = 10.4, 10.4, 8.5 Hz, 1H, $CH_3SO_2NC\mathit{H}_aH_bCH_2$), 3.98 (ddd, *J* = 10.7, 10.7, 8.8 Hz, 1H, $CH_3SO_2NCH_a\mathit{H}_bCH_2$), 3.16 (t, *J* = 8.5 Hz, 2H, $NMsCH_2\mathit{CH_2}$), 2.83 (s, 3H, CH_3SO_2N), 2.32 (s, 3H, $NArCH_3$), and 2.12 (s, 3H, $C{\equiv}CC\mathit{H_3}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 140.0, 136.3, 134.9, 132.3, 131.3, 131.1, 129.1, 127.8, 126.3, 125.5, 123.4, 122.8, 115.0, 112.3, 99.9, 94.8, 76.1, 65.6, 50.6, 34.4, 28.2, 16.4, and 4.7.

HRMS (APCI-Orbitrap): Calculated for $C_{24}H_{25}N_2O_2S^+$ $[M+H^+]$: 405.1631, found 405.1635.

IR (thin film): 3057, 3008, 2919, 2853, 2233, 1676, 1656, 1626, 1594, 1454, 1344, 1279, 1267, 1234, 1155, 1113, 1061, 966, 906, 790, 731, 697, 659, 569, 544, and 514 cm^{-1}.

1-Methyl-2-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-1,2-dihydrophthalazine (53)



In a 20 mL culture tube, phthalazine (**2j**, 39 mg, 0.303 mmol, 3 equiv) was dissolved in CH_3CN (8 mL). Triflic acid (**4g**, 14 μL, 0.152 mmol, 1.5 equiv) was added followed by the tetrayne **1c** (25 mg, 0.101 mmol, 1 equiv). The culture tube was sealed with a Teflon-lined screw cap. This solution was heated overnight (16 h) in an oil bath at 85 °C, cooled, and concentrated to give a red colored sticky solid. The formation of the salt **48** was confirmed by the ^{1}H NMR spectrum of this crude material and further supported by HRMS analysis.

Data for salt 48:

^{1}H NMR (500 MHz, DMSO): δ 10.89 (s, 1H, Ar*H1'*), 10.20 (s, 1H, Ar*H4'*), 8.70 (d, *J* = 8.1 Hz, 1H, Ar*H8'* or Ar*H5'*), 8.67 (d, *J* = 8.2 Hz, 1H, Ar*H8'* or Ar*H5'*), 8.62 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar*H7'* or Ar*H6'*), 8.49 (dd, *J* = 7.9, 7.9 Hz, 1H, Ar*H7'* or Ar*H6'*), 7.65 (s, 1H, Ar*H7*), 4.09 (t, *J* = 8.5 Hz, 2H, *H2*), 3.27 (t, *J* = 8.5 Hz, 2H, *H3*), 3.12 (s, 3H, C*H*$_3$SO$_2$N), 2.21 (s, 3H, NArCH$_3$), and 2.19 (s, 3H, C≡CC*H*$_3$).

HRMS (ESI-TOF): Calculated for $C_{21}H_{20}N_3O_2S^+$ [M]: 378.1271, found 378.1268.

In a 20 mL culture tube, the crude salt **48** was partially dissolved in THF (10 mL) to give a heterogeneous mixture. This was cooled to 0 °C using an ice bath, and MeMgBr (0.2 mL, 3M solution in ether, 6 equiv, 0.152 mmol) was added dropwise over 10 minutes. After the addition, the reaction mixture became less heterogeneous and turned to a bright red color. The ice bath was removed, and the reaction mixture was stirred for one hour. The formation of the product was confirmed by both thin layer chromatography and crude mass spectrometric analysis. The reaction mixture was washed with satd aq $NaHCO_3$ (10 mL) and diluted with EtOAc (10 mL). The aqueous phase was washed with EtOAc (3x, ~30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated

under vacuum to obtain a crude product **53**. This was passed through a plug of silica (1:1, Hex:EtOAc). The residue was purified by MPLC (1:1, Hex:EtOAc) to give **53** (23 mg, 58%, 0.058 mmol) as an orange oil.

Data for 53:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (s, 1H, Ar*H4'*), 7.52 (s, 1H, Ar*H7*), 7.37 (ddd, *J* = 8.7, 7.4, 1.2 Hz, 1H, Ar*H6'*), 7.33 (ddd, *J* = 8.6, 7.5, 1.4 Hz, 1H, Ar*H7'*), 7.21 (d, *J* = 7.4 Hz, 1H, Ar*H8'*), 7.08 (d, *J* = 7.3 Hz, 1H, Ar*H5'*), 4.65 (q, *J* = 6.5 Hz, 1H, *H1'*), 4.04 (ddd, *J* = 9.9, 9.9, 7.1 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.95 (ddd, *J* = 9.4, 9.4, 7.9 Hz, 1H, $CH_3SO_2NCH_aH_bCH_2$), 3.23–3.12 (m, 2H, $NMsCH_2CH_2$), 2.88 (s, 3H, CH_3SO_2N), 2.36 (s, 3H, $NArCH_3$), 2.13 (s, 3H, $C{\equiv}CCH_3$), and 1.09 [d, *J* = 6.6 Hz, 3H, $N(CH)CH_3$].

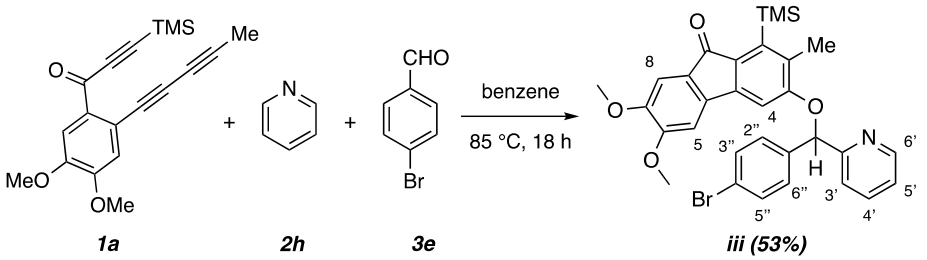
^{13}C NMR (125 MHz, $CDCl_3$): 146.8, 140.1, 137.7, 134.8, 131.0, 130.4, 128.8, 128.0, 124.85, 124.84, 124.4, 122.4, 112.5, 94.4, 76.3, 55.3, 50.7, 34.5, 28.2, 16.01, 15.99, and 4.7.

HRMS (APCI-Orbitrap): Calculated for $C_{22}H_{24}N_3O_2S^+$ [$M+H^+$]: 394.1584, found 394.1580.

IR (thin film): 3056, 2973, 2854, 2229, 1733, 1591, 1450, 1346, 1320, 1265, 1156, 1099, 1070, 1038, 1001, 964, 909, 875, 804, 730, 702, 652, 627, 595, 567, 541, 513, 478, and 411 cm^{-1}.

Product obtained from carbene capture with *p*-bromobenzaldehyde (Endnote #66):

3-((4-Bromophenyl)(pyridin-2-yl)methoxy)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9H-fluoren-9-one (iii)



1a ***2h*** ***3e*** ***iii (53%)***

An oven-dried, 25 mL culture tube having a magnetic stir bar was evacuated and purged with N_2 gas. Triynone **1a** (30 mg, 0.093 mmol, 1 equiv) and *p*-bromobenzaldehyde (**3e**, 86 mg, 0.463 mmol, 5 equiv) were added and the headspace was refilled with N_2. Benzene (8 mL, 0.01M) was added and nitrogen was bubbled through the solution. Pyridine (**2h**, 23 μL, 0.277, 3 equiv) was added and the culture tube was sealed with a Teflon-lined screw cap. The solution was heated for 18 h in an oil bath at 85 °C, cooled, and passed through a plug of silica (EtOAc eluant). The residue was purified by MPLC (1:1, Hex:EtOAc) to give **iii** (29 mg, 0.049 mmol, 53%) as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H, *H6'*), 7.71 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H, *H4'*), 7.51 (nfod, *J* = 8.5 Hz, 2H, *H2''/H6''* or *H3''/H5''*), 7.51 (overlapped d, 1H, *H3'*), 7.45 (nfod, *J* = 8.5 Hz, 2H, *H2''/H6''* or *H3''/H5''*), 7.23 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H, *H5'*), 7.07 (s, 1H, Ar*H8*), 6.84 (s, 1H, Ar*H4*), 6.75 (s, 1H, Ar*H5*), 6.47 (s, 1H, C*H*OAr), 3.97 (s, 3H, C6OC*H*$_3$), 3.88 (s, 3H, C7OC*H*$_3$), 2.47 (s, 3H, ArC*H*$_3$), and 0.43 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 160.3, 159.2, 154.0, 149.7, 149.3, 145.1, 143.5, 139.1, 137.9, 137.8, 133.1, 132.3, 132.0, 128.2, 127.3, 123.3, 122.3, 120.6, 106.8, 105.2, 102.8, 82.0, 56.6, 56.3, 17.4, and 2.8.

IR (neat): 3054, 3002, 2937, 2901, 2841, 1700, 1585, 1558, 1493, 1467, 1391, 1355, 1311, 1230, 1216, 1147, 1087, 1010, 993, 865, 841, 796, 766, 733, 632, 596, and 537 cm^{-1}.

HRMS (APCI-Orbitrap): Calculated for $C_{31}H_{30}{}^{79}BrNNaO_4Si^+$ [M+Na$^+$] 610.1020, found 610.1023.

Discussion of Computational Results

NMR chemical shift calculations were performed following a reported protocol[113] at the following level of theory: SMD(chloroform)/B3LYP/6-311+G(2d,p)//M062X/6-31+G(d,p). The shifts for model benzotriazocine **319** and benzodiazocines **320** and **321** were examined. The chemical shifts for the key proton and carbon resonances within the eight membered ring of each were shown to be a good match between the data for **10** and structure **319** and the data for **11** matched far better (and quite well on an absolute basis) with the structure **310** rather than its regioisomeric analog **311**.

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[113] Willoughby, P. H.; Jansma, M. J. and Hoye, T. R. A Guide to Small Molecule Structure Assignment Through Computation of (^{1}H and ^{13}C) NMR Chemical Shifts. *Nature Protocols*, 2014, **9**, 643–660.

Energies and Geometries of the species in Figures 3.3b, 3.4, and 3.5b.

Figure 3.3b

3,6-dimethylbenzyne (**VII**)

isoquinoline (**2a**)

zwitterion **VIII**

$TS_{protonshift}$

carbene **X**

$TS_{ringclosing}$

azetidine **IX**

$TS_{ringopening}$

benzoazocine **XI**

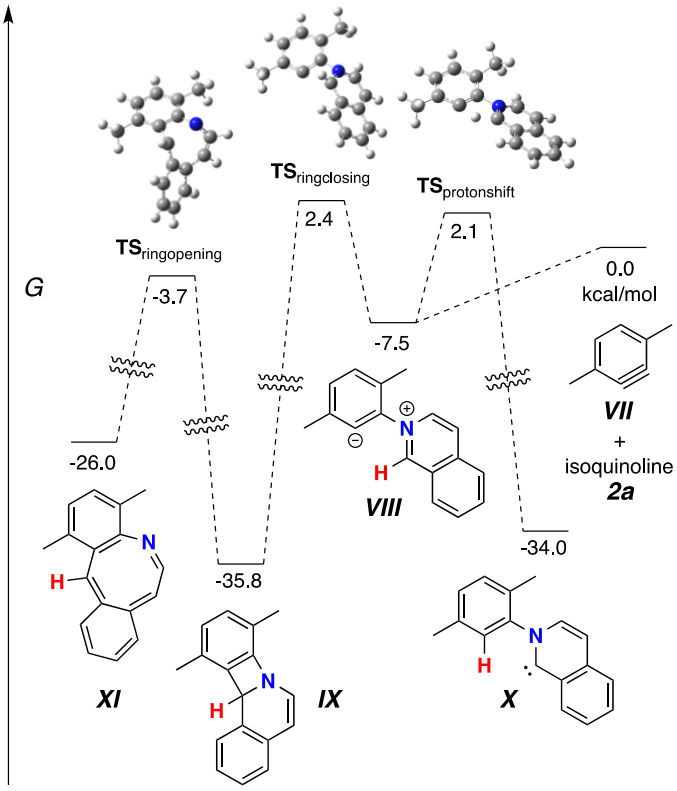


Figure 3.4. DFT computed PES for reaction of quinoline (2b) and model benzyne VII.

3,6-dimethylbenzyne (**VII**)

quinoline (**2b**)

quinoline zwitterion **301**

$TS_{quinolinecarbene}$

quinoline carbene **302**

$TS_{quinolineringclosing}$

quinoline azetidine **303**

$TS_{quinolineringopening}$

quinoline azocine **304**

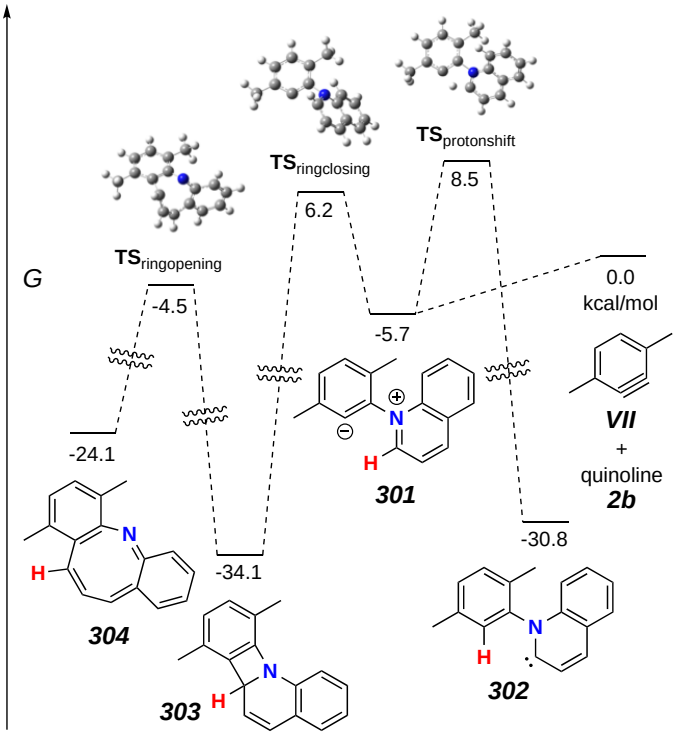


Figure 3.5b. DFT computed PES for reaction of 2,4,6-triazine (2d) and model benzyne VII.

3,6-dimethylbenzyne (**VII**)

triazine (**2d**)

triazine zwitterion **315**

TS$_{triazinecarbene}$

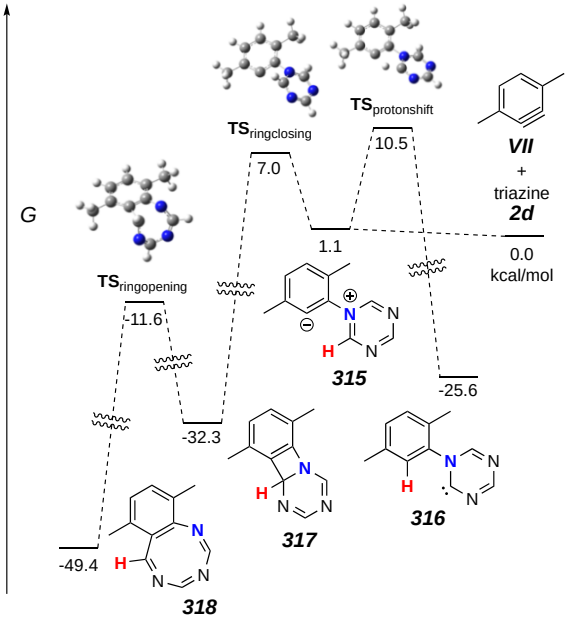
triazine carbene **316**

TS$_{triazineringclosing}$

triazine azetidine **317**

TS$_{triazineringopening}$

triazine azocine **318**



SUPPLEMENTARY INFORMATION FOR CHAPTER 4

A. General Procedure for trapping of HDDA-generated arynes with imines

The polyyne precursor (1 equiv) and the imine (1-3 equiv) were combined in a screw-capped culture tube. 1,2-Dichloroethane was added (0.05 M) and the resulting solution was placed in an oil bath maintained at 90 °C and allowed to react overnight. Subsequently, the solvent was removed under reduced pressure, and the crude material was purified using MPLC with the elution solvent mixture indicated for each compound.

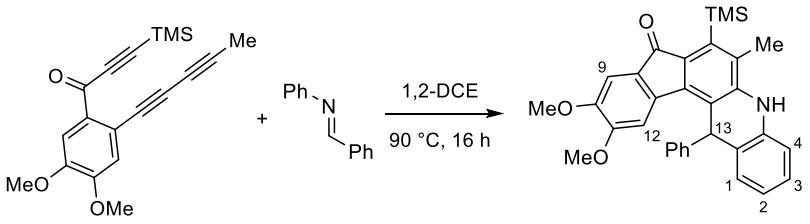
B. General Procedure for oxidation of 1,4-dihydroacridines to their respective acridines

A scintillation vial or a culture tube was charged with a stir bar and the respective 1,4-dihydroacridine (1 equiv). Chloroform or dichloromethane (0.005 M) was added, along with MnO_2 (ca. 10-20 equiv). The resulting slurry was allowed to stir at ambient temperature until the reaction was observed to be complete by TLC analysis. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo.

C. General Procedure for one-pot synthesis of acridines from HDDA-generated benzynes and imines

The HDDA polyyne precursor (1 equiv) and the imine (1-3 equiv) were added to a screw-cap culture tube. 1,2-Dichloroethane was added (0.05 M), and the resulting solution was placed in an oil bath maintained at 90 °C and allowed to react overnight. MnO_2 (ca. 10-20 equiv) and a stir bar were added. The slurry was then stirred at ambient temperature until the reaction was observed to be complete by TLC. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo.

10,11-Dimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (11)



8 *2a* *11*, 98%

N-Benzylideneaniline (**2a**) was prepared according to a reported procedure.[114]

Following general procedure A, 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (**8**, 0.024 g, 0.074 mmol, 1 equiv), (*E*)-*N*,1-diphenylmethanimine (**2a**, 0.015 g, 0.083 mmol, 1.1 equiv), and dichloroethane (2 mL) were used to prepare the 1,4-dihydroacridine **11**. Purification of the crude product by MPLC (2:1 hexanes:EtOAc) yielded **11** (0.038 g, 0.076 mmol, 98%) as an orange crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.8, 1.4 Hz, 1H, *H1*), 7.29 (nfod, J_{app} = 7.5 Hz, 2H, ArH_o), 7.22 (nfodd, J_{app} = 7.7, 7.7 Hz, 2H, PhH_m), 7.126 (ddd, *J* = 7.4, 7.4, 1.5 Hz, 1H, *H3*), 7.125 (tt, *J* = 7.4, 1.5 Hz, 1H, ArH_p), 7.10 (s, 1H, *H9*), 7.09 (s, 1H, *H12*), 6.95 (dd, *J* = 7.4, 7.4, 1.1 Hz, 1H, *H2*), 6.81 (dd, *J* = 7.9, 1.3 Hz, 1H, *H4*), 6.48 (s, 1H, N*H*), 5.77 (s, 1H, *H13*), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.45 (s, 3H, ArCH_3), and 0.46 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): 193.6, 153.0, 149.0, 144.7, 143.1, 142.6, 141.2, 137.6, 137.5, 133.8, 129.1, 128.70, 128.67, 127.8, 127.1, 127.0, 125.3, 123.9, 122.3, 118.8, 115.2, 107.8, 106.7, 56.6, 56.2, 44.7, 18.2, and 3.2.

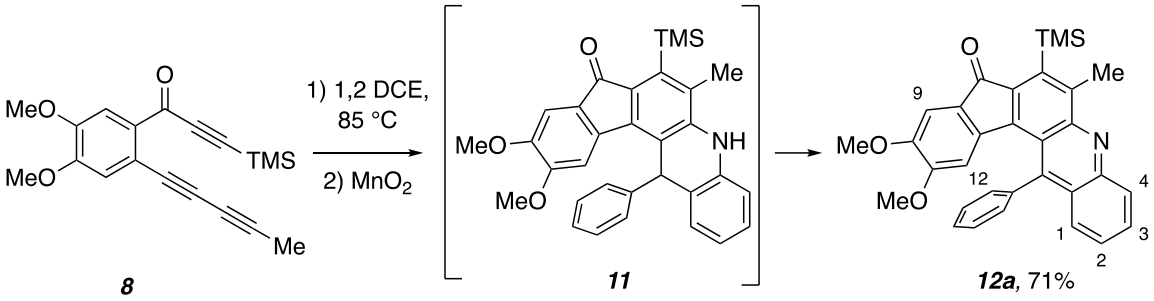
HRMS (ESI-TOF): Calcd for $C_{32}H_{32}NO_3Si^+$ $[M+H^+]^+$ requires 506.2146; found 506.2150.

IR (neat): 3440, 3390, 3059, 3001, 2924, 2853, 2359, 2342, 2069, 2034, 1976, 1961, 1944, 1694, 1605, 1577, 1546, 1489, 1465, 1432, 1416, 1375, 1343, 1324, 1299, 1283, 1259, 1245, 1215, 1173, 1158, 1091, 1045, 1027, 991, 936, 873, 854, 797, 771, 751, 727, 699, 676, 645, 630, 613, 599, 575, 519, 493, 449, and 408 cm^{-1}.

mp: 249-250 °C.

[114] Malig, T. C.; Yu, D.; Hein, J. E. A Revised Mechanism for the Kinugasa Reaction. *J. Am. Chem. Soc.* **2018**, *140*, 9167–9173

10,11-Dimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12a)



8 ***11*** ***12a***, 71%

Following general procedure C, 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (**8**, 0.010 g, 0.030 mmol, 1 equiv), (*E*)-*N*,1-diphenylmethanimine (**2a**, 0.007 g, 0.038 mmol, 1.3 equiv), MnO_2 (xs), and dichloroethane (2 mL) were used to prepare acridine **12a**. Purification of the crude product yielded acridine **12a** (0.011 g, 0.022 mmol, 71%) as a purple crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.6 Hz, 1H, *H4*), 8.14 (d, *J* = 8.9 Hz, 1H, *H1*), 7.78 (nfod, J_{app} = 7.2 Hz, 2H, PhH_o), 7.77 (br dd, *J* = 8.8, 6.8 Hz, 1H, *H3*), 7.56 (nfodd, J_{app} = 7.5, 7.5 Hz, 2H, PhH_m), 7.53 (tt, *J* = 6.9, 1.7 Hz, 1H, PhH_p), 7.48 (br dd, *J* = 8.6, 6.6 Hz, 1H, *H2*), 7.04 (s, 1H, *H9*), 5.64 (s, 1H, *H12*), 3.83 (s, 3H, C10OCH_3), 3.51 (s, 3H, C11OCH_3), 3.06 (s, 1H, ArCH_3), and 0.51 (s, 9H, Si(CH_3)$_3$).

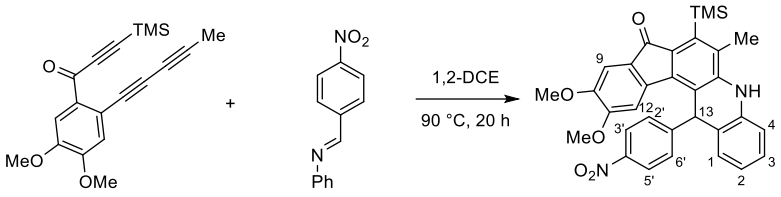
^{13}C NMR (126 MHz, $CDCl_3$): 195.4, 153.0, 150.6, 149.0, 148.0, 146.9, 145.1, 143.0, 140.1, 138.6, 137.3, 136.1, 132.8, 130.9, 130.3, 129.5, 129.0, 126.7, 126.5, 125.2, 125.0, 120.8, 109.3, 106.5, 56.7, 56.1, 20.7, and 2.7.

HRMS (ESI-TOF): Calcd for $C_{32}H_{30}NO_3Si^+$ $[M+H^+]^+$ requires 504.1989; found 504.1983.

IR (neat): 3062, 2956, 2922, 2852, 2357, 2171, 2099, 2041, 2023, 1984, 1758, 1709, 1595, 1579, 1498, 1463, 1442, 1418, 1405, 1376, 1336, 1285, 1250, 1224, 1180, 1144, 1109, 1059, 1026, 1012, 972, 896, 842, 816, 799, 764, 734, 702, 671, 642, 619, 604, 568, 544, 519, 507, and 412 cm^{-1}.

mp: 96-97 °C.

10,11-Dimethoxy-6-methyl-13-(4-nitrophenyl)-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (403):



8 *2b* *SI-1,* 68%

1-(4-Nitrophenyl)-*N*-phenylmethanimine (**2b**) was prepared according to a reported procedure.[115]

Following general procedure A, 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (**8**, 0.009 g, 0.029 mmol, 1 equiv), (*E*)-1-(4-nitrophenyl)-N-phenylmethanimine (**2b**, 0.023 g, 0.093 mmol, 3.2 equiv), and dichloroethane (2 mL) were used to prepare the 1,4-dihydroacridine **403**. Purification of the crude product by MPLC (2:1 hexanes:EtOAc) yielded **403** (0.011 g, 0.020 mmol, 68%) as an orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (nfod, J_{app} = 8.6 Hz, 2H, *H3'* and *H5'*), 7.43 (nfod, J_{app} = 9.0 Hz, 2H, *H2'* and *H6'*), 7.43 (dd, *J* = 7.5, 1.5 Hz, 1H, *H1*), 7.18 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, *H3*), 7.12 (s, 1H, *H9*), 7.02 (s, 1H, *H12*), 6.99 (ddd, *J* = 7.5, 7.5, 1.8 Hz, 1H, *H2*), 6.86 (dd, *J* = 7.6, 1.8 Hz, 1H, *H4*), 6.53 (s, 1H, N*H*), 5.90 (s, 1H, *H13*), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.46 (s, 3H, ArCH_3), and 0.46 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 193.2, 153.1, 151.4, 149.4, 146.9, 142.7, 142.4, 142.1, 137.8, 137.0, 134.0, 128.8, 128.6, 128.5, 127.9, 125.8, 124.4, 122.6, 122.0, 117.3, 115.5, 107.3, 107.0, 56.6, 56.3, 44.6, 18.2, and 3.2.

HRMS (ESI-TOF): Calcd for $C_{32}H_{31}N_2O_5Si^+$ $[M+H^+]^+$ requires 551.1997; found 551.1958 (major ion) and Calcd for $C_{32}H_{29}N_2O_5Si^+$ $[M-2H+H^+]^+$ requires 549.1840; found 549.1817.

IR (neat): 3433, 3103, 3057, 3002, 2943, 2899, 2835, 2452, 2346, 2220, 2122, 1925, 1696, 1604, 1593, 1577, 1546, 1521, 1489, 1465, 1431, 1415, 1374, 1344, 1299, 1282, 1259, 1244, 1214, 1110, 1090, 1044, 1022, 1014, 990, 937, 852, 797, 770, 751, 711, 696, 677, 642, 628, 603, 576, 544, 519, 494, 457, and 433 cm^{-1}.

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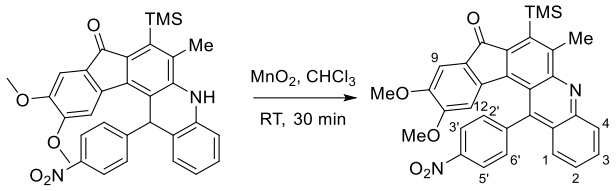
[115] Madhuprasad; Swathi, N.; Manjunatha, J. R.; Das, U. K.; Shetty, A. N.; Trivedi, D. R. Dual Colorimetric Receptor With Logic Gate Operations: Anion Induced Solvatochromism. *New J. Chem.* **2014**, *38*, 1484.

10,11-Dimethoxy-6-methyl-13-(4-nitrophenyl)-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12b):



SI-1 *12b,* 90%

Following General Procedure B, 10,11-dimethoxy-6-methyl-13-(4-nitrophenyl)-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (**403**, 0.009 g, 0.015 mmol, 1 equiv), MnO_2 (xs), and $CHCl_3$ (10 mL) were used to prepare acridine **12b**. Purification of the crude product yielded **12b** (0.008 g, 0.014 mmol, 90%) as a purple amorphous solid.

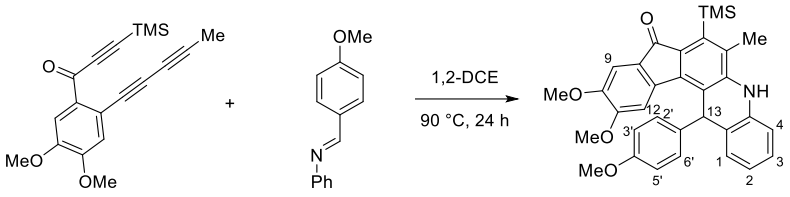
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (nfod, J_{app} = 8.7 Hz, 2H, *H3'* and *H5'*), 8.30 (dd, *J* = 8.3, 1.1 Hz, 1H, *H4*), 7.99 (nfod, J_{app} = 8.7 Hz, 2H, *H2'* and *H6'*), 7.98 (dd, *J* = 8.3, 1.1 Hz, 1H, *H1*), 7.80 (ddd, *J* = 8.8, 6.5, 1.3 Hz, 1H, *H3*), 7.53 (ddd, *J* = 8.8, 6.5, 1.3 Hz, 1H, *H2*), 7.06 (s, 1H, *H9*), 5.60 (s, 1H, *H12*), 3.83 (s, 3H, C10-OCH_3), 3.50 (s, 3H, C11-OCH_3), 3.07 (s, 3H, ArCH_3), and 0.51 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): 194.9, 152.9, 150.3, 148.9, 148.6, 148.1, 147.4, 145.0, 141.8, 141.7, 139.3, 137.9, 136.6, 133.6, 131.3, 130.5, 127.7, 125.4, 125.2, 124.3, 124.0, 120.1, 108.9, 107.1, 56.6, 56.2, 20.6, and 2.6.

HRMS (ESI-TOF): Calcd for $C_{32}H_{29}N_2O_5Si^+$ $[M+H^+]^+$ requires 549.1840; found 549.1827.

IR (neat): 3104, 3074, 2999, 2945, 2900, 2838, 2702, 2456, 2036, 2007, 1974, 1950, 1707, 1598, 1586, 1524, 1493, 1460, 1406, 1379, 1367, 1346, 1295, 1248, 1217, 1182, 1165, 1133, 1099, 1060, 1014, 981, 944, 884, 854, 812, 793, 762, 735, 704, 680, 662, 644, 627, 619, 606, 580, 569, 530, 493, 485, 451, and 414 cm^{-1}.

10,11-Dimethoxy-13-(4-methoxyphenyl)-6-methyl-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (404)



8 *2c* *SI-2*, 78%

1-(4-Methoxyphenyl)-*N*-phenylmethanimine (**2c**) was prepared according to a reported procedure.[116]

Following General Procedure A, 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (**8**, 0.020 g, 0.063 mmol, 1 equiv), (*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine (**2c**, 0.041 g, 0.179 mmol, 2.9 equiv), and dichloroethane (2 mL) were used to prepare the 1,4-dihydroacridine **404**. Purification of the crude product by MPLC (2:1 hexanes:EtOAc) yielded **404** (0.027 g, 0.048 mmol, 78%) as an orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.6, 1.4 Hz, 1H, *H1*), 7.18 (nfod, J_{app} = 8.8 Hz, 2H, *H2'* and *H6'*), 7.12 (ddd, *J* = 7.6, 7.6, 1.5 Hz, 1H, *H3*), 7.098 (s, 1H, *H9* or *H12*), 7.096 (s, 1H, *H9* or *H12*), 6.95 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, *H2*), 6.80 (dd, *J* = 7.9, 1.2 Hz, 1H, *H4*), 6.75 (nfod, J_{app} = 8.8 Hz, 2H, *H3'* and *H5'*), 6.47 (s, 1H, N*H*), 5.71 (s, 1H, *H13*), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.68 (s, 3H, C4'-OCH_3), 2.43 (s, 3H, ArCH_3), and 0.46 (s, 9H, Si(CH_3)$_3$).

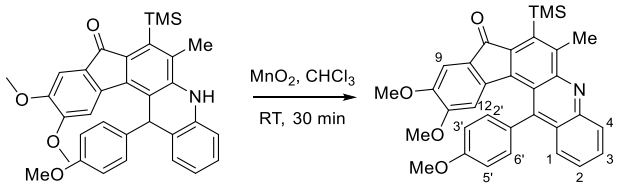
^{13}C NMR (125 MHz, $CDCl_3$): 193.6, 158.5, 153.0, 149.0, 143.0, 142.5, 141.1, 137.6, 137.5, 136.9, 133.7, 128.7, 128.6, 128.1, 127.7, 125.3, 124.2, 122.2, 119.1, 115.1, 114.4, 107.8, 106.6, 56.5, 56.2, 55.3, 18.2, and 3.2.

HRMS (ESI-TOF): Calcd for $C_{33}H_{32}NO_4Si^+$ $[M-2H+H^+]^+$ requires 534.2095; found 534.2078.

IR (neat): 3445, 3388, 3055, 2999, 2948, 2902, 2835, 2358, 2344, 2197, 2174, 2144, 2121, 2068, 2027, 2014, 1981, 1963, 1950, 1926, 1693, 1607, 1577, 1546, 1507, 1489, 1464, 1431, 1415, 1374, 1342, 1324, 1298, 1283, 1246, 1214, 1179, 1110, 1090, 1030, 990, 874, 846, 797, 788, 770, 748, 699, 676, 646, 631, 607, 588, 557, 529, 487, 474, 453, 435, and 417 cm^{-1}.

[116] Lawson, J. R.; Wilkins, L. C. and Melen, R. L. Tris (2, 4, 6-Trifluorophenyl) Borane: An Efficient Hydroboration Catalyst. *Chem. Eur. J.* **2017**, *23*, 10997–11000.

10,11-Dimethoxy-13-(4-methoxyphenyl)-6-methyl-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12c)



SI-2 *12c*, 86%

Following General Procedure B, 10,11-dimethoxy-13-(4-methoxyphenyl)-6-methyl-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (**404**, 0.025 g, 0.045 mmol, 1 equiv), MnO_2 (xs), and $CHCl_3$ (10 mL) were used to prepare acridine **12c**. Purification of the crude product yielded **12c** (0.021 g, 0.039 mmol, 86%) as a purple amorphous solid.

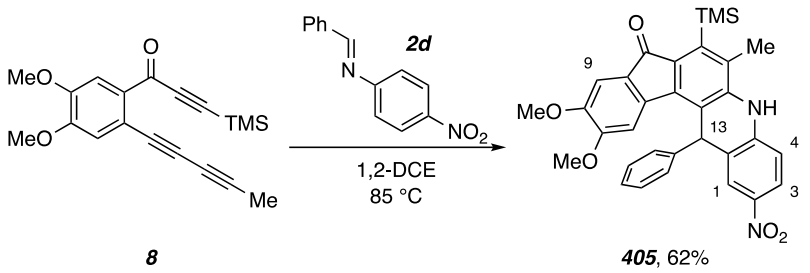
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (dd, *J* = 8.7, 1.2 Hz, 1H, *H4*), 8.16 (dd, *J* = 8.9, 1.2 Hz, 1H, *H1*), 7.75 (ddd, *J* = 8.7, 6.5, 1.3 Hz, 1H, *H3*), 7.69 (nfod, J_{app} = 8.7 Hz, 2H, *H2'* and *H6'*), 7.47 (ddd, *J* = 8.9, 6.5, 1.3 Hz, 1H, *H2*), 7.07 (nfod, J_{app} = 8.8 Hz, 2H, *H3'* and *H5'*), 7.05 (s, 1H, *H9*), 5.67 (s, 1H, *H12*), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.55 (s, 3H, C11-OCH_3), 3.05 (s, 3H, Ar-CH_3), and 0.51 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): 195.4, 160.7, 153.1, 150.7, 149.0, 148.0, 146.8, 145.0, 143.2, 140.1, 137.0, 136.0, 134.0, 131.0, 130.9, 130.2, 126.5, 125.4, 125.3, 121.0, 114.5, 109.6, 106.4, 56.6, 56.1, 55.6, 20.6, and 2.6. (missing one aromatic C; one of the resonances at 134.0, 126.5, and 114.4 ppm is likely two non-resolved resonances)

HRMS (ESI-TOF): Calcd for $C_{33}H_{32}NO_4Si^+$ $[M+H^+]^+$ requires 534.2095; found 534.2081.

IR (neat): 3068, 3000, 2945, 2901, 2838, 2023, 1915, 1703, 1605, 1586, 1539, 1494, 1459, 1406, 1378, 1367, 1329, 1294, 1250, 1217, 1177, 1133, 1112, 1099, 1061, 1029, 1017, 949, 842, 813, 790, 763, 733, 701, 670, 652, 633, 621, 608, 588, 570, 529, 505, 493, 476, 450, 420, and 406 cm^{-1}.

10,11-Dimethoxy-6-methyl-2-nitro-13-phenyl-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (405):



N-(4-Nitrophenyl)-1-phenylmethanimine (**2d**) was prepared according to a reported procedure with the modification that elevated temperature was used to increase the rate of imine formation.[117]

Triynone **8** (20 mg, 0.0616 mmol, 1 equiv) and the imine **2d** (45 mg, 0.185 mmol, 3 equiv) were added to a screw-capped culture tube containing freshly activated 4Å molecular sieves. 1,2-DCE was added (0.05 M) and the resulting solution was placed in an oil bath maintained at 85 °C and kept overnight. The solvent was partially removed under reduced pressure, chloroform was added, and the mixture was directly loaded onto the MPLC column and eluted (2:1 hexanes:EtOAc) to give **405** (21 mg, 62%) as a dark red amorphous solid.

The extremely low solubility of this material, likely due to strong hydrogen bonding in the crystal lattice of this *p*-nitroaniline derivative, precluded obtaining a suitable ^{13}C NMR spectrum.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 2.6 Hz, 1H, *H1*), 8.05 (dd, *J* = 8.8, 2.5 Hz, 1H, *H3*), 7.34–7.30 (m, PhH_o and PhH_m), 7.18 (tt, J = 8.6, 1.5 Hz, PhH_p), 7.11 (s, 1H, *H9* or *H12*), 7.04 (s, 1H, *H9* or *H12*), 6.91 (br s, 1H, N*H*), 6.88 (d, *J* = 8.9 Hz, 1H, *H4*), 5.81 (s, 1H, *H13*), 3.94 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 2.50 (s, 3H, ArCH_3), and 0.47 (s, 9H, Si(CH_3)$_3$).

HRMS (ESI-TOF): Calcd for $C_{32}H_{31}N_2O_5Si^+$ $[M+H^+]^+$ requires 551.1997; found 551.1945 (major ion) and Calcd for $C_{32}H_{29}N_2O_5Si^+$ $[M-2H+H^+]^+$ requires 549.1840; found 549.1817 (minor ion).

IR (neat): 3379, 3084, 2954, 2904, 2852, 2368, 2136, 2074, 2041, 1952, 1700, 1675, 1600, 1576, 1545, 1522, 1490, 1457, 1427, 1408, 1375, 1321, 1298, 1244, 1213, 1191, 1086, 1045, 1023, 990, 967, 950, 864, 841, 797, 780, 769, 741, 675, 657, 639, 617, 607, 577, 550, 520, 495, 450, 420, and 409 cm^{-1}.

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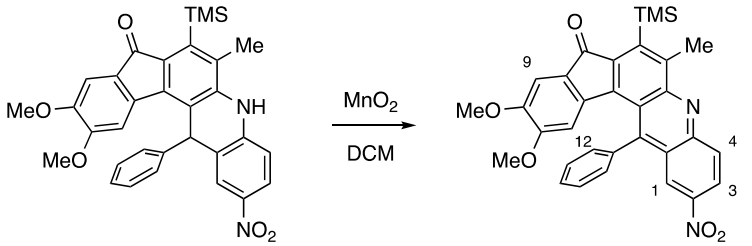
[117] Yang, X.; Zhao, L.; Fox, T.; Wang, Z. X. and Berke, H. Transfer Hydrogenation of Imines with Ammonia-Borane: A Concerted Double-Hydrogen-Transfer Reaction. *Angew. Chem. Int. Ed.* **2010**, *49*, 2058–2062.

10,11-Dimethoxy-6-methyl-2-nitro-13-phenyl-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12d):



405 ***12d***, 86%

The acridine **12d** was synthesized according to General Procedure B: 14 mg of amine **405** (1 equiv) and 22 mg of MnO_2 (10 equiv). The reaction mixture was filtered through Celite® (DCM elution) to afford **12d** (12 mg, 82%) as a purple amorphous solid.

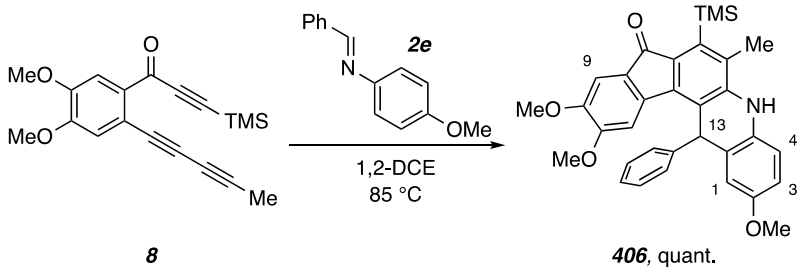
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (d, 2.4 Hz, 1H, *H1*), 8.47 (dd, *J* = 9.5, 2.3 Hz, 1H, *H3*), 8.36 (d, *J* = 9.5 Hz, 1H, *H4*), 7.81–7.77 (nfom, 2H, PhH_o), 7.66–7.62 (m, 3H, PhH_m and PhH_p), 7.06 (s, 1H, *H9*), 5.60 (s, 1H, *H12*), 3.84 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.05 (s, 3H, ArCH_3), and 0.52 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): 194.9, 153.3, 152.2, 149.6, 148.7, 148.5, 147.2, 145.6, 142.9, 139.6, 139.2, 138.3, 137.4, 132.8, 132.7, 130.6, 129.6, 125.0, 124.9, 123.2, 123.1, 121.4, 109.1, 106.7, 56.7, 56.2, 20.6, and 2.6.

HRMS (ESI-TOF): Calcd for $C_{32}H_{29}N_2O_5Si^+$ $[M+H^+]^+$ requires 549.1840; found 549.1827.

IR (neat): 3058, 3001, 2943, 2903, 2851, 2194, 2152, 2069, 2021, 1977, 1707, 1620, 1602, 1585, 1560, 1540, 1518, 1494, 1465, 1456, 1417, 1401, 1370, 1335, 1293, 1246, 1218, 1182, 1159, 1131, 1104, 1086, 1064, 1028, 1014, 971, 928, 909, 867, 839, 814, 803, 788, 767, 738, 707, 679, 664, 642, 623, 586, 565, 542, 520, 494, 458, 433, and 414 cm^{-1}.

2,10,11-Trimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (406)



8 ***406***, quant.

N-(4-Methoxyphenyl)-1-phenylmethanimine (**2e**) was prepared according to a reported procedure.[118]

The dihydroacridine **406** was synthesized according to General Procedure A using the triyne **8** (25 mg) and the imine **2e** (49 mg, 3 equiv). Purification by MPLC (2:1 hexanes:EtOAc) afforded (41 mg, 100%) as a red amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (nfod, J_{app} = 8.2 Hz, 2H, ArH_o), 7.22 (nfodd, J_{app} = 7.5, 7.5 Hz, 2H, PhH_m), 7.12 (tt, *J* = 7.3, 1.4 Hz, 1H, ArH_p), 7.09 (s, 1H, *H9*), 7.08 (s, 1H, *H12*), 6.99 (d, *J* = 2.6 Hz, 1H, *H1*), 6.75 (d, *J* = 8.6 Hz, 1H, *H4*), 6.70 (dd, *J* = 8.6, 2.7 Hz, 1H, *H3*), 6.39 (s, 1H, N*H*), 5.73 (s, 1H, *H13*), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.42 (s, 3H, ArCH_3), and 0.46 (s, 9H, Si(CH_3)$_3$).

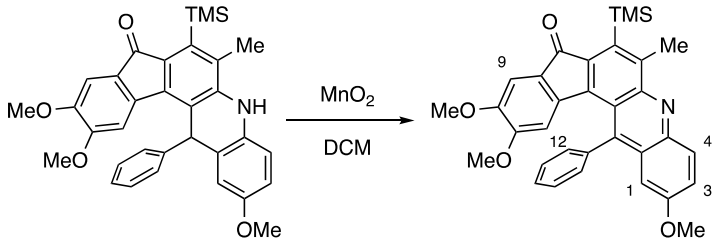
^{13}C NMR (125 MHz, $CDCl_3$): 193.4, 155.2, 152.9, 149.0, 144.6, 143.4, 142.6, 141.1, 137.4, 133.3, 131.5, 129.0, 128.8, 127.1, 127.0, 125.1, 124.8, 118.1, 115.9, 114.0, 113.4, 107.8, 106.6, 56.6, 56.2, 55.9, 45.0, 18.2, and 3.2.

HRMS (ESI-TOF): Calcd for $C_{33}H_{34}NO_4Si^+$ $[M+H^+]^+$ requires 536.2252; found 536.2219 (major ion) and Calcd for $C_{33}H_{32}NO_4Si^+$ $[M-2H+H^+]^+$ requires 534.2095; found 534.2084 (minor ion).

IR (neat): 3440, 3392, 3058, 3020, 2999, 2941, 2900, 2834, 2361, 2339, 2225, 2182, 2153, 2028, 1957, 1692, 1602, 1575, 1546, 1492, 1462, 1442, 1411, 1374, 1343, 1309, 1284, 1259, 1245, 1212, 1173, 1164, 1153, 1131, 1118, 1091, 1043, 1029, 990, 952, 863, 841, 797, 768, 734, 701, 644, 627, 609, 567, 552, 535, 514, 493, 459, 451, 416, and 405 cm^{-1}.

[118] Vayer, M.; Morcillo, S. P.; Dupont, J.; Gandon, V. and Bour, C. Photoinduced Remote Functionalization of Amides and Amines Using Electrophilic Nitrogen Radicals. *Angew. Chem. Int. Ed.* **2018**, *57*, 3228–3232.

2,10,11-Trimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12e):



406 ***12e***, 94%

The acridine **12e** was synthesized according to General Procedure B (36 mg of amine **406**). The reaction mixture was filtered through Celite® (DCM elution) to afford **12e** (36 mg, quant.) as a purple oil. This material was purified by MPLC on silica gel (2:1 hexanes:EtOAc) to give **12e** (34 mg, 94%) as a purple amorphous solid.

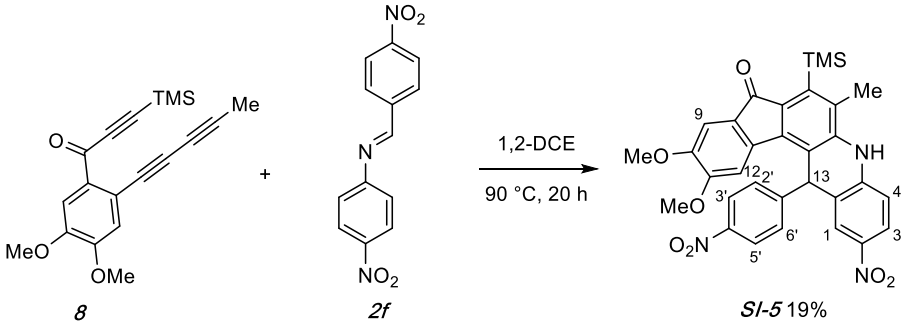
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, 9.4 Hz, 1H, *H4*), 7.78 (nfod, J_{app} = 6.9 Hz, 2H, PhH_o), 7.55 (nfodd, J_{app} = 7.1, 7.1 Hz, 2H, PhH_m), 7.49 (tt, *J* = 7.3, 1.5 Hz, 1H, PhH_p), 7.45 (br dd, *J* = 9.4, 2.7 Hz, 1H, *H3*), 7.37 (d, *J* = 2.6 Hz, 1H, *H1*), 7.03 (s, 1H, *H9*), 5.65 (s, 1H, *H12*), 3.831 (s, 3H, C2- or C10-OCH_3), 3.828 (s, 3H, C2- or C10-OCH_3), 3.52 (s, 3H, C11-OCH_3), 3.04 (s, 1H, ArCH_3), and 0.50 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): 195.5, 158.0, 153.0, 149.2, 147.9, 146.9, 146.2, 142.4, 142.3, 140.3, 139.1, 137.5, 134.9, 132.5, 132.4, 129.3, 129.0, 126.0, 125.3, 125.0, 121.0, 109.2, 106.4, 101.9, 56.6, 56.1, 55.5, 20.6, and 2.7.

HRMS (ESI-TOF): Calcd for $C_{33}H_{32}NO_4Si^+$ $[M+H^+]^+$ requires 534.2095; found 534.2079.

IR (neat): 3120, 3057, 2999, 2947, 2902, 2835, 2356, 2194, 2048, 1970, 1703, 1604, 1586, 1552, 1524, 1512, 1493, 1467, 1442, 1406, 1375, 1369, 1354, 1293, 1261, 1247, 1227, 1210, 1171, 1157, 1120, 1102, 1066, 1028, 1016, 976, 868, 839, 831, 808, 792, 768, 739, 706, 676, 654, 636, 613, 587, 577, 554, 540, 521, 497, 460, 437, 424, and 410 cm^{-1}.

10,11-Dimethoxy-6-methyl-2-nitro-13-(4-nitrophenyl)-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (407)



Following general procedure A, 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (**8**, 0.025 g, 0.078 mmol, 1 equiv), *N*,1-bis(4-nitrophenyl)methanimine (**2f**, 0.063 g, 0.23 mmol, 3.0 equiv), and 1,2-dichloroethane (2 mL) were used to prepare the 1,4-dihydroacridine **407**. Purification of the crude product by MPLC (3:1 hexanes:EtOAc) yielded **407** (0.009 g, 0.015 mmol, 19%) as an orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 2.4 Hz, 1H, Ar*H1*), 8.14 (nfod, J_{app} = 8.8 Hz, 2H, ArH*3'* and Ar*H5'*), 8.10 (dd, *J* = 8.9, 2.5 Hz, 1H, *H3*), 7.47 (nfod, J_{app} = 8.8 Hz, 2H, Ar*H2'* and Ar*H6'*), 7.14 (s, 1H, Ar*H9*), 6.97 (s, 1H, Ar*H12*), 6.95 (br s, 1H, N*H*), 6.92 (d, *J* = 8.9 Hz, 1H, *H4*) 5.95 (s, 1H, *H13*), 3.96 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.51 (s, 3H, ArCH_3), and 0.47 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): 192.6, 153.6, 150.3, 149.8, 147.4, 143.0, 143.0, 142.5, 142.2, 140.3, 136.6, 135.9, 128.5, 127.9, 126.7, 125.2, 124.8, 124.8, 122.3, 116.7, 115.3, 107.2, 107.1, 56.7, 56.3, 44.2, 18.3, and 3.1.

HRMS (ESI-TOF): Calcd for $C_{32}H_{30}N_3O_7Si^+$ $[M+H^+]^+$ requires 596.1848; found 596.1814.

IR (neat): 3628, 3380, 3006, 2946, 2837, 1890, 1700, 1602, 1551, 1523, 1495, 1462, 1409, 1375, 1345, 1327, 1301, 1245, 1213, 1111, 1089, 1046, 1015, 990, 949, 865, 854, 833, 797, 773, 726, 699, 675, 667, 640, 609, 581, 565, 555, 522, 492, 482, 455, 435, and 412 cm^{-1}.

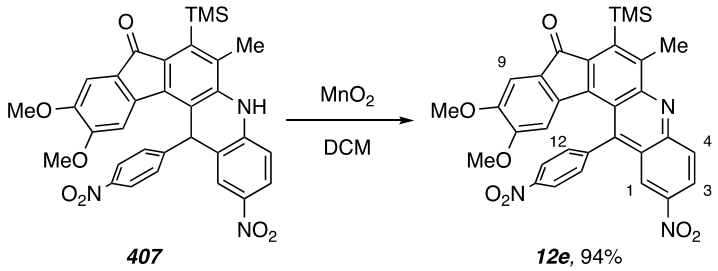
N,1-bis(4-Nitrophenyl)methanimine (**2f**) was prepared according to the following procedure:

p-Nitroaniline (0.30 g, 2.2 mmol, 1 equiv) and *p*-nitrobenzaldehyde (0.33 g, 2.2 mmol, 1 equiv) were added to a 50 mL round-bottom flask and suspended in 20 mL of toluene. The solution was heated to refluxed, during which time it became homogeneous, for 12 hours. The reaction solution was allowed to cool to room temperature. During this time, a yellow solid crystallized from the solution. The crystals were collected via vacuum filtration and washed with cold hexanes. Yellow needles of *N*,1-bis(4-

nitrophenyl)methanimine (**2f**, ca. 0.5 g) were obtained and used without further purification. The ^{1}H NMR spectral data were consistent with previously reported data.[119]

[119] Chen, C. W.; Tseng, M. C.; Hsiao, S. K.; Chen, W. H. and Chu, Y. H. Transimination Reactions in [B-3C-Im][NTf $_2$] Ionic Liquid. *Org. Biomol. Chem.* **2011**, *9*, 4188–4193.

10,11-Dimethoxy-6-methyl-2-nitro-13-(4-nitrophenyl)-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12f):



407 ***12e***, 94%

Following General Procedure B, 10,11-dimethoxy-6-methyl-2-nitro-13-(4-nitrophenyl)-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (**407**, 0.009 g, 0.015 mmol, 1 equiv), MnO_2 (xs), and $CHCl_3$ (10 mL) were used to prepare acridine **12f**. This oxidation reaction was accompanied by formation of a second, bright yellow compound of higher polarity, which required separation by MPLC (3:1 hexanes:EtOAc). This byproduct was not fully identified, but its ^{1}H NMR spectrum suggested that, at least, the aromatic methyl group had been oxidized to an aldehyde. Purification of the crude product yielded **12f** (0.004 g, 0.007 mmol, 56%) as a dark green amorphous solid.

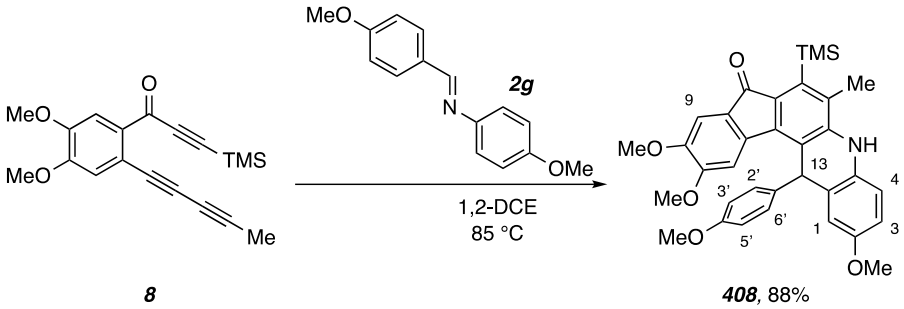
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (d, *J* = 2.4 Hz, 1H, *H1*), 8.52 (dd, *J* = 9.4, 2.4 Hz, 1H, *H3*), 8.50 (nfod, J_{app} = 8.8 Hz, 2H, *H3'* and *H5'*), 8.42 (d, *J* = 9.4 Hz, 1H, *H4*), 8.01 (nfod, J_{app} = 8.7 Hz, 2H, *H2'* and *H6'*), 7.08 (s, 1H, *H9*), 5.56 (s, 1H, *H12*), 3.84 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.07 (s, 1H, ArCH_3), and 0.53 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): 194.4, 153.2, 151.9, 149.4, 149.0, 148.7, 147.8, 146.1, 145.3, 143.5, 141.8, 139.8, 138.9, 138.8, 133.5, 133.3, 125.2, 124.5, 123.4, 123.3, 122.6, 120.9, 108.7, 107.3, 56.6, 56.2, 20.7, and 2.5.

HRMS (ESI-TOF): Calcd for $C_{32}H_{28}N_3O_7Si^+$ $[M+H^+]^+$ requires 594.1691; found 594.1676.

IR (neat): 3103, 3078, 3000, 2944, 2902, 2873, 2854, 2840, 1948, 1707, 1620, 1599, 1586, 1561, 1521, 1494, 1464, 1455, 1416, 1401, 1347, 1336, 1294, 1246, 1217, 1181.3, 1158.4, 1132, 1108, 1086, 1065, 1012, 990, 925, 906, 869, 854, 838, 813, 800, 787, 755, 726, 704, 682, 667, 652, 639, 606, 586, 566, 542, 519, 495, 484, 453, and 416 cm^{-1}.

2,10,11-Trimethoxy-13-(4-methoxyphenyl)-6-methyl-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (408)



N,1-bis(4-Methoxyphenyl)methanimine (**2g**) was prepared according to a reported procedure.[120]

The dihydroacridine **408** was synthesized according to General Procedure A using the triyne **8** (25 mg) and the imine **2g** (56 mg, 3 equiv). Purification by MPLC (2:1 hexanes:EtOAc) afforded (38 mg, 88%) as a red amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (nfod, J_{app} = 8.7 Hz, 2H, Ar*H2'* and Ar*H6'*), 7.099 (s, 1H, Ar*H9* or Ar*H12*), 7.096 (s, 1H, Ar*H9* or Ar*H12*), 6.97 (d, *J* = 2.5 Hz, 1H, *H1*), 6.76 (nfod, J_{app} = 8.8 Hz, 2H, Ar*H3'* and Ar*H5'*), 6.75 (d, *J* = 8.6 Hz, 1H, *H4*), 6.72 (dd, *J* = 8.6, 2.7 Hz, 1H, *H3*), 6.36 (s, 1H, N*H*), 5.68 (s, 1H, *H13*), 3.92 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.42 (s, 3H, ArCH_3), and 0.45 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): 193.5, 158.5, 155.3, 152.9, 149.0, 143.4, 142.6, 141.0, 137.4, 136.8, 133.3, 131.5, 128.8, 128.1, 125.2, 125.0, 118.4, 115.9, 114.4, 114.0, 113.3, 107.8, 106.6, 56.6, 56.2, 55.9, 55.3, 44.1, 18.2, and 3.2.

HRMS (ESI-TOF): Calcd for $C_{34}H_{34}NO_5Si^+$ $[M-2H]^+$ requires 564.2201; found 564.2193 (major ion) and Calcd for $C_{34}H_{36}NO_5Si^+$ $[M+H^+]^+$ requires 566.2357; found 566.2316 (minor ion).

IR (neat): 3440, 3386, 2998, 2948, 2904, 2834, 2337, 2320, 2074, 2009, 1732, 1689, 1604, 1576, 1506, 1492, 1442, 1413, 1374, 1343, 1309, 1285, 1177, 1152, 1131, 1111, 1091, 1032, 990, 952, 862, 839, 792, 739, 687, 642, 629, 607, 567, 544, 480, 447, and 409 cm^{-1}.

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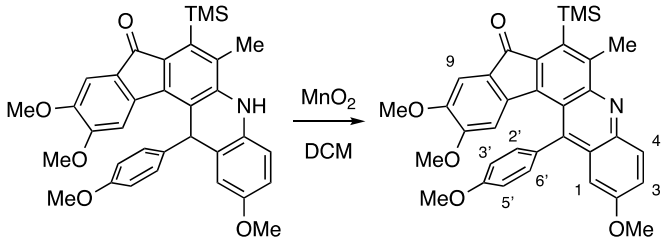
[120] O'Boyle, N. M.; Pollock, J. K.; Carr, M.; Knox, A. J. S.; Nathwani, S. M.; Wang, S.; Caboni, L.; Zisterer, D. M. and Meegan, M. J. β-Lactam Estrogen Receptor Antagonists and a Dual-Targeting Estrogen Receptor/Tubulin Ligand. *J. Med. Chem.* **2014**, *57*, 9370–9382.

2,10,11-Trimethoxy-13-(4-methoxyphenyl)-6-methyl-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12g):



408 ***12g***, 89%

The acridine **12g** was synthesized according to General Procedure B (19 mg of amine **408**). The reaction mixture was filtered through Celite® (DCM elution) to afford crude **12g** as a purple oil. This material was purified by MPLC on silica gel (1:1 hexanes:EtOAc) to give **12g** (17 mg, 89%) as a purple amorphous solid.

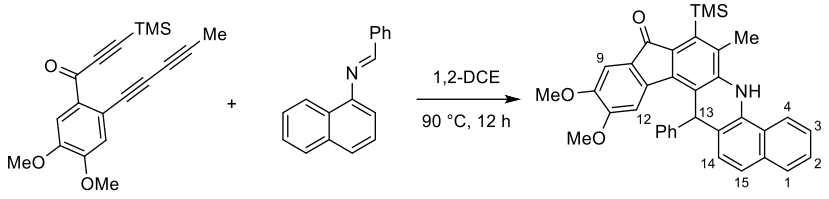
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 9.3 Hz, 1H, *H4*), 7.70 (nfod, J_{app} = 8.7 Hz, 2H, Ar*H2'* and Ar*H6'*), 7.45 (dd, *J* = 9.2, 2.7 Hz, 1H, *H3*), 7.39 (d, *J* = 2.6 Hz, 1H, *H1*), 7.07 (nfod, J_{app} = 8.7 Hz, 2H, Ar*H3'* and Ar*H5'*), 7.05 (s, 1H, *H9*), 5.68 (s, 1H, *H12*), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.04 (s, 1H, ArCH_3), and 0.50 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 195.5, 160.5, 158.0, 153.1, 149.3, 147.9, 146.9, 146.2, 142.6, 142.3, 140.3, 137.3, 134.9, 133.6, 132.5, 131.4, 126.2, 125.4, 124.9, 121.3, 114.5, 109.6, 106.4, 102.0, 56.6, 56.1, 55.6, 55.6, 20.5, and 2.7.

HRMS (ESI-TOF): Calcd for $C_{34}H_{34}NO_5Si^+$ $[M-2H]^+$ requires 564.2201; found 564.2182

IR (neat): 3057, 3000, 2836, 2682, 2544, 2437, 2355, 2254, 2044, 1915, 1701, 1623, 1604, 1585, 1513, 1492, 1464, 1440, 1405, 1291, 1246, 1223, 1207, 1175, 1115, 1099, 1066, 1026, 1014, 868, 807, 766, 646, 612, 489, and 424 cm^{-1}.

10,11-Dimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-5,13-dihydro-8H-benzo[h]indeno[1,2-a]acridin-8-one (409)



8 *13* *SI-7*, 98%

N-(Naphthalen-1-yl)-1-phenylmethanimine (**13**) was prepared according to a reported procedure.[121]

Following general procedure A, triynone **8** (0.010 g, 0.030 mmol, 1 equiv), (*E*)-*N*-(naphthalen-1-yl)-1-phenylmethanimine (**13**, 0.023 g, 0.10 mmol, 3.3 equiv), and dichloroethane (1 mL) were used to prepare the 1,4-dihydroacridine **409**. Purification of the crude product by MPLC (2:1 hexanes:EtOAc) yielded **409** (0.016 g, 0.029 mmol, 98%) as an orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.814 (dd, *J* = 7.9, 0.9 Hz, 1H, *H1* or *H4*), 7.809 (d, *J* = 8.0, 1.6 Hz, 1H, *H1* or *H4*), 7.57 (d, *J* = 8.4 Hz, 1H, *H14*), 7.55 (dd, *J* = 8.4, 6.8, 1.4 Hz, 1H, *H2* or *H3*), 7.47 (dd, *J* = 8.1, 6.8, 1.2 Hz, 1H, *H2* or *H3*), 7.47 (br d, *J* = 8.5 Hz, 1H, *H15*), 7.35 (nfod, J_{app} = 7.3 Hz, 2H, PhH_o), 7.27 (s, 1H, N*H*), 7.22 (nfodd, J_{app} = 7.5, 7.5 Hz, 2H, PhH_m), 7.15 (s, 1H, *H9* or *H12*), 7.11 (s, 1H, *H9* or *H12*), 7.13 (tt, *J* = 7.7, 1.5 Hz, 1H, PhH_p), 5.90 (s, 1H, *H13*), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 2.62 (s, 3H, ArCH_3), and 0.49 (s, 9H, Si(CH_3)$_3$).

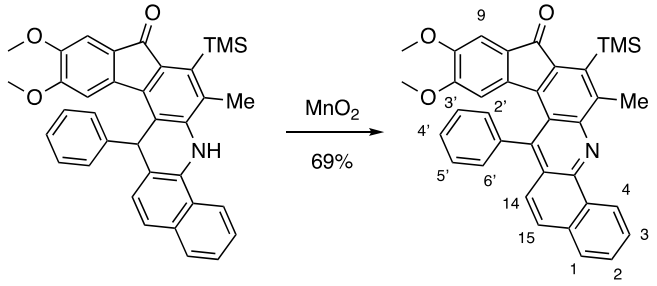
^{13}C NMR (126 MHz, $CDCl_3$): 193.6, 153.1, 149.1, 144.9, 142.7, 142.6, 141.2, 137.5, 134.4, 133.2, 131.8, 129.11, 129.08, 128.6, 127.2, 127.1, 126.8, 126.2, 125.97, 125.95, 122.2, 122.0, 119.0, 118.6, 118.2, 107.8, 106.7, 56.6, 56.2, 45.2, 18.2, and 3.2.

HRMS (ESI-TOF): Calcd for $C_{36}H_{32}NO_3Si^+$ $[M-2H]^+$ requires 554.2146; found 554.2132 (most intense ion) and Calcd for $C_{36}H_{34}NO_3Si^+$ $[M+H^+]^+$ requires 556.2302; found 556.2260 (minor ion).

IR (neat): 3467, 3370, 3290, 3057, 3002, 2935, 2904, 854, 2837, 2359, 2183, 2123, 2048, 2007, 1977, 1949, 1712, 1694, 1614, 1578, 1550, 1516, 1492, 1460, 1406, 1375, 1349, 1310, 1293, 1277, 1251, 1214, 1173, 1130, 1094, 1018, 971, 946, 853, 804, 793, 771, 752, 736, 715, 703, 679, 668, 643, 626, 598, 582, 563, 542, 527, 496, 443, 432, 421, and 409 cm^{-1}.

[121] Chen, N.; Dai, X. J.; Wang, H. and Li, C. J. Umpolung Addition of Aldehydes to Aryl Imines. *Angew. Chem. Int. Ed.* **2017**, *56*, 6260–6263.

10,11-Dimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-8H-benzo[h]indeno[1,2-a]acridin-8-one (14)



409 *14*

Acridine **14** was prepared according to General Procedure B starting with 16 mg of amine **409**. Purification by MPLC (3:1 hexanes:EtOAc) afforded **14** (11 mg, 69%) as a purple amorphous solid.

^{1}H NMR (500 MHz, C_6D_6): 9.47 (dd, *J* = 8.2, 1.2 Hz, 1H, *H4*), 7.79 (d, *J* = 9.4 Hz, 1H, *H14*), 7.63 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, *H3* or *H2*), 7.60 (dd, *J* = 7.9, 1.6 Hz, 1H, *H1*), 7.50 (ddd, *J* = 8.2, 7.0, 1.4 Hz, 1H, *H3* or *H2*), 7.39 (d, *J* = 9.4, 0.9 Hz, 1H, *H15*), 7.32–7.30 (nfom, 2H, *H2'* and *H6'*), 7.12 (s, 1H, *H9*), 7.02–6.97 (m, 3H, *H3', H4'* and *H5'*), 5.57 (s, 1H, *H12*), 3.39 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.20 (s, 1H, ArCH_3), and 0.79 (s, 9H, Si(CH_3)$_3$).

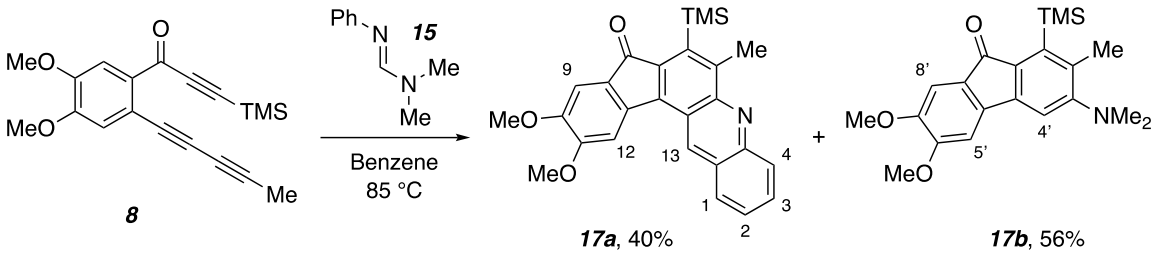
^{13}C NMR (126 MHz, C_6D_6): δ 195.2, 153.9, 149.7, 149.3, 147.8, 147.2, 144.4, 143.1, 140.3, 138.9, 138.2, 136.8, 134.1, 132.9, 132.8, 129.7, 129.0, 128.8, 128.3, 127.9, 126.5, 126.1, 123.9, 123.5, 121.9, 110.4, 107.3, 56.4, 55.3, 21.0, and 3.1. (one aromatic signal wasn't observed, perhaps obscured by the solvent resonances).

^{13}C NMR (126 MHz, $CDCl_3$): 195.4, 153.1, 149.1, 148.1, 147.5, 146.9, 144.0, 142.6, 140.2, 138.7, 137.6, 136.6, 133.7, 132.8, 132.3, 129.5, 129.4, 129.0, 128.4, 127.7, 127.6, 126.0, 125.5, 123.6, 123.2, 121.4, 109.4, 106.4, 56.7, 56.1, 20.6, and 2.8.

HRMS (ESI-TOF): Calcd for $C_{36}H_{32}NO_3Si^+$ $[M+H^+]^+$ requires 554.2146; found 554.2128.

IR (neat): 3121, 3057, 2999, 2947, 2900, 2874, 2851, 2837, 2684, 2315, 2180, 2052, 1949, 1703, 1602, 1584, 1558, 1492, 1464, 1441, 1415, 1395, 1376, 1364, 1352, 1329, 1295, 1247, 1229, 1215, 1184, 1154, 1102, 1080, 1067, 1037, 1021, 1008, 978, 889, 850, 834, 803, 776, 747, 704, 683, 661, 637, 624, 600, 572, 552, 526, 501, 456, and 413 cm^{-1}.

10,11-Dimethoxy-6-methyl-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (17a) and
3-(Dimethylamino)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9H-fluoren-9-one (17b)



Amidine **15** was prepared according to a reported procedure.[122]

Triynone **8** (20 mg, 0.0616 mmol, 1 equiv) and the formamidine **15** (28 mg, 0.185 mmol, 3 equiv) were added to a screw-capped culture tube containing freshly activated 4Å molecular sieves. Benzene was added (0.05 M) and the resulting solution was placed in an oil bath maintained at 85 °C and kept overnight. The solvent was then removed under reduced pressure, and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give a coeluting mixture of **17a** (40% yield) and **17b** (56% yield).

Data for 17a and 17b (a mixture of coeluting products in a ratio of 2:3)

Data for 17a, the acridine adduct, minor product:

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H, *H13*), 8.24 (dd, *J* = 8.9, 1.0 Hz, 1H, *H4*), 8.04 (dd, *J* = 8.6, 1.5 Hz, 1H, *H1*), 7.81 (ddd, *J* = 8.7, 6.6, 1.4 Hz, 1H, *H3*), 7.61 (s, 1H, *H12*), 7.57 (ddd, *J* = 8.1, 6.6, 1.3 Hz, 1H, *H2*), 7.23 (s, 1H, *H9*), 4.15 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.11 (s, 3H, ArCH_3), and 0.52 (s, 9H, Si(CH_3)$_3$).

HRMS (ESI-TOF): Calcd for $C_{26}H_{26}NO_3Si^+$ $[M+H^+]^+$ requires 428.1676; found 428.1674.

^{13}C NMR (126 MHz, $CDCl_3$): 195.2, 153.3, 150.1, 149.3, 146.0, 142.0, 138.7, 137.4, 135.8, 132.6, 131.2, 130.6, 128.4, 126.8, 126.8, 126.6, 122.0, 107.7, 107.3, 102.6, 56.8, 56.3, 20.2, and 3.2.

Data for 17b, the amine-trapped adduct, major product:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H, *H8'*), 7.01 (s, 1H, *H5'*), 6.93 (s, 1H, *H4'*), 4.01 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.11 (s, 3H, ArCH_3), and 0.52 (s, 9H, Si(CH_3)$_3$).

HRMS (ESI-TOF): Calcd for $C_{21}H_{28}NO_3Si^+$ $[M+H^+]^+$ requires 370.1833; found 370.1832.

^{13}C NMR (125 MHz, $CDCl_3$): 193.9, 157.6, 154.0, 149.5, 144.0, 143.9, 138.6, 135.7, 133.8, 127.7, 109.9, 106.8, 102.6, 56.5, 56.3, 43.9, 21.1, and 2.8.

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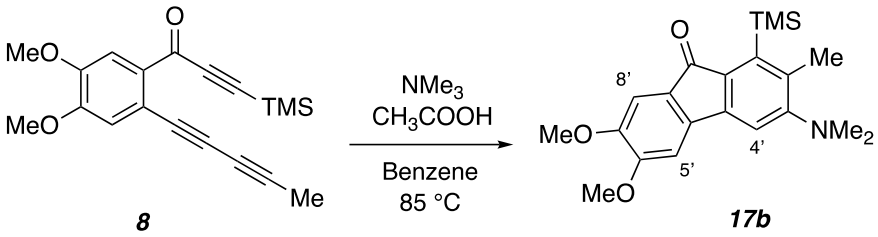
[122] Wu, Y.; Zhou, G.; Meng, Q.; Tang, X.; Liu, G.; Yin, H.; Zhao, J.; Yang, F.; Yu, Z. and Luo, Y. Visible Light-Induced Aerobic Epoxidation of α, β-Unsaturated Ketones Mediated by Amidines. *J. Org. Chem.* **2018**, *83*, 13051–13062.

An authentic sample of the amine-trapped product **17b** was also prepared using the following procedure:



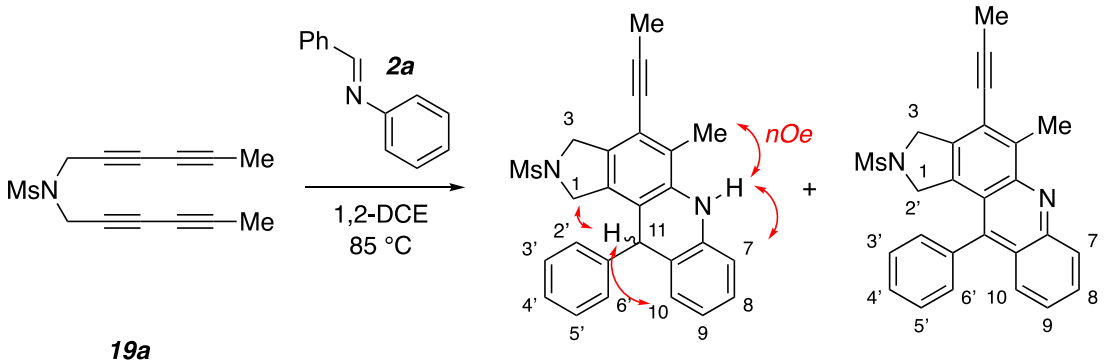
8 ***17b***

Triynone **8** (20 mg, 0.0616 mmol, 1 equiv) and acetic acid (5.42 μL, 0.092 mmol, 1.5 equiv) were added to a screw-capped culture tube. Benzene was added (0.05 M) and trimethylamine gas was bubbled through the mixture. This solution was placed in an oil bath maintained at 85 °C and kept overnight. The solvent was then removed under reduced pressure, and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give **17b** as an orange oil. ^{1}H and ^{13}C spectrum for **17b** from this experiment were used as a reference to aid in the interpretation of the NMR data obtained from the sample of a mixture of the acridine and amine adducts **17a** and **17b** (from the above experiment).

5-Methyl-2-(methylsulfonyl)-11-phenyl-4-(prop-1-yn-1-yl)-2,3-dihydro-1H-pyrrolo[3,4-a]acridine (20a)

and

5-Methyl-2-(methylsulfonyl)-11-phenyl-4-(prop-1-yn-1-yl)-2,3-dihydro-1H-pyrrolo[3,4-a]acridine (21a):



This reaction was performed using general Procedure A: 20 mg of polyyne **19a** (1 equiv) and 55 mg of the imine **2a** (3 equiv). Purification by MPLC (2:1 hexanes:EtOAc) afforded the 1,4-dihydroacridine **20a** (18 mg, 42%) as a pale yellow crystalline solid along with the corresponding acridine **21a** (8 mg, 19%), which presumably arises through air oxidation, also as a yellow crystalline solid.

The assignment of the structure of the dihydroacridine **20a** was based upon observed (difference) nOe interactions between i) the amine proton (*NH*) with the adjacent aryl methyl group and the H7 aromatic proton; and ii) the methine proton (*H11*) with the adjacent methylene (C1*H2*) and H10 aromatic proton.

Data for acridine 21a, the faster eluting minor product:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (ddd, *J* = 8.8, 1.0, 1.0 Hz, 1H, *H7*), 7.75 [(ddd, *J* = 8.3, 6.3, 1.6 Hz, 1H, *H9*], 7.63 (tt, *J* = 7.4, 1.4 Hz, 1H, *H4'*), 7.56 (nfom, 1H, *H3'* and *H5'*), 7.47–7.38 [overlapped m, 2H, *H10* and *H8*], 7.36 (nfod, J_{app} = 6.8 Hz, 2H, *H2'* and *H6'*), 4.79 (br t, *J* = 3.3 Hz, 2H, *C3*H_2), 4.04 (br t, *J* = 3.2 Hz, 2H, *C1*H_2), 3.09 (s, 3H, CH_3SO_2N), 2.72 (s, 3H, NArCH3), and 2.20 (s, 3H, C≡CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 148.2, 147.7, 145.2, 141.4, 137.5, 135.6, 130.3, 130.2, 130.0, 129.4, 128.7, 128.4, 126.7, 126.5, 126.1, 120.6, 119.5, 96.8, 76.5, 55.8, 54.8, 34.9, 16.8, and 5.0.

HRMS (ESI-TOF): Calcd for $C_{26}H_{23}N_2O_2S^+$ $[M+H^+]^+$ requires 427.1475; found 427.1465.

IR (neat): 3404, 3059, 3024, 2915, 2852, 2357, 2227, 2045, 2014, 1960, 1721, 1609, 1584, 1496, 1467, 1445, 1412, 1379, 1333, 1286, 1269, 1255, 1079, 1044, 894, 853, 752, 737, 679, 643, 629, 609, 573, 555, 450, 437, and 418 cm^{-1}.

mp: 262-264 °C (with decomposition).

Data for 1,4-dihydroacridine 20a, the slower eluting major product:

^{1}H NMR (500 MHz, C_6D_6): δ 7.10 (m, 2H, *H2'* and *H6'*), 7.05 (dd, *J* = 7.8, 1.6 Hz, 1H, *H10*), 6.977 (ddd, *J* = 7.5, 7.5, 1.6 Hz, 2H, *H8*), 6.975 (nfodd, J_{app} = 7.4, 7.4 Hz, 2H, *H3'* and *H5'*), 6.89 (tt , *J* = 6.8, 1.3 Hz, 1H, *H4'*), 6.79 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, *H9*), 6.41 (dd, *J* = 8.0, 1.1 Hz, 1H, *H7*), 5.65 (s, 1H, *NH*), 4.85 (dddd, *J* = 13.3, 2.9, 0.9, 0.9 Hz, 1H, MsN*C3H$_a$*C3H$_b$), 4.81 (dd, *J* = 0.6, 0.6 Hz, 1H, *H11*), 4.57 (br dddd, *J* = 13.6, 3.0, 0.9, 0.9 Hz, 1H, MsN*C1H$_a$*C1H$_b$), 4.48 (ddd, *J* = 13.4, 3.1, 1.7 Hz, 1H, MsNC1H$_a$*C1H$_b$*), 4.18 (br d, *J* = 13.5 Hz, 1H, MsNC1H$_a$*C1H$_b$*), 2.14 (s, 3H, CH_3SO_2N), 1.94 (s, 3H, NArCH3), and 1.69 (s, 3H, C≡CCH_3).

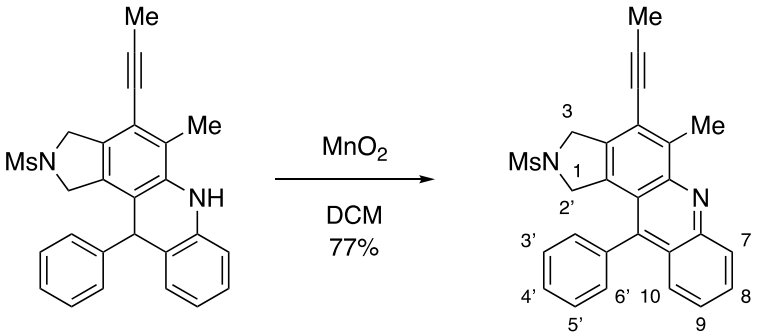
^{13}C NMR (126 MHz, $CDCl_3$): 146.2, 137.8, 137.2, 132.9, 130.7, 129.5, 129.0, 127.7, 127.3, 126.9, 123.1, 122.7, 121.6, 117.8, 117.4, 114.8, 93.9, 75.9, 54.5, 53.5, 45.9, 34.4, 14.8, and 4.7.

HRMS (ESI-TOF): Calcd for $C_{26}H_{25}N_2O_2S^+$ $[M+H^+]^+$ requires 429.1631; found 429.1621 (minor ion) and Calcd for $C_{26}H_{23}N_2O_2S^+$ $[M-2H]^+$ requires 427.1475; found 427.1469 (major ion).

IR (neat): 3052, 3033, 3006, 2924, 2873, 2852, 2241, 2222, 2161, 2019, 1715, 1622, 1601, 1560, 1541, 1526, 1492, 1475, 1452, 1445, 1415, 1379, 1355, 1332, 1308, 1294, 1265, 1192, 1156, 1088, 1032, 994, 976, 923, 911, 862, 841, 824, 790, 762, 749, 712, 674, 646, 611, 571, 563, 518, 496, 460, 423, and 415 cm^{-1}.

mp: 304-306 °C (with decomposition).

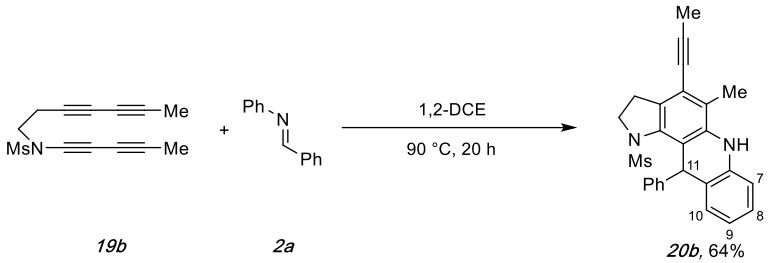
5-Methyl-2-(methylsulfonyl)-11-phenyl-4-(prop-1-yn-1-yl)-2,3-dihydro-1H-pyrrolo[3,4-a]acridine (21a):



20a ***21a***

The acridine **21a** was synthesized according to General Procedure B (40 mg of amine **20a**). Purification by MPLC (2:1 hexanes:EtOAc) afforded **21a** (30 mg, 77%) as a yellow crystalline solid (characterization data given above).

5-Methyl-1-(methylsulfonyl)-11-phenyl-4-(prop-1-yn-1-yl)-2,3,6,11-tetrahydro-1H-pyrrolo[2,3-a]acridine (20b)



19b *2a* *20b,* 64%

Following general procedure A, *N*-(hepta-3,5-diyn-1-yl)-*N*-(penta-1,3-diyn-1-yl)methanesulfonamide (**19b**, 0.020 g, 0.081 mmol, 1 equiv), (*E*)-*N*,1-diphenylmethanimine (**2a**, 0.015 g, 0.088 mmol, 1.1 equiv), and 1,2-dichloroethane (2 mL) were used to prepare the 1,4-dihydroacridine **20b**. Purification of the crude product by MPLC (2:1 hexanes:EtOAc) yielded **20b** (0.023 g, 0.053 mmol, 64%) as a pale yellow amorphous solid.

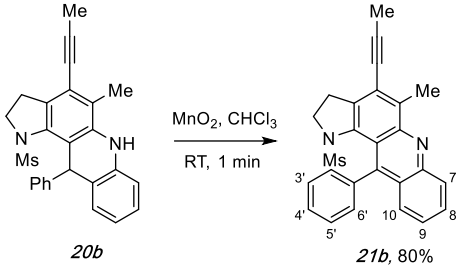
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (br d, *J* = 7.5 Hz, 1H, *H10*), 7.16 (ddd, *J* = 9.0, 7.9, 1.5 Hz, 1H, *H8*), 7.10 (br dd, *J* = 7.6, 7.6 Hz, 2H, PhH_m), 7.05–7.02 (overlapping m's, 3H, PhH_o and PhH_p), 6.95 (ddd, *J* = 9.0, 7.5, 1.2 Hz, 1H, *H9*), 6.87 (br d, *J* = 7.9 Hz, 1H, *H7*), 6.36 (s, 1H, *H11*), 6.22 (br s, 1H, N*H*), 4.29 (dd, *J* = 13.0, 7.8 Hz, 1H, MsNCH_aH$_b$CH$_2$), 3.82 (ddd , *J* = 12.9, 12.9, 8.3 Hz, 1H, MsNCH$_a$$H_bCH_2$), 3.21 (ddd, *J* = 16.2, 12.0, 7.8, 1H, MsNCH$_2$CH_aH$_b$), 2.84 (dd, *J* = 16.2, 8.2 Hz, 1H, MsNCH$_2$CH$_a$$H_b$), 2.72 (s, 3H, C$H_3SO_2$N), 2.40 (s, 3H, ArC$H_3$), and 2.11 (s, 3H, C≡CC$H_3$).

^{13}C NMR (126 MHz, $CDCl_3$): 145.5, 139.0, 138.5, 138.3, 130.8, 129.6, 128.3, 127.4, 127.1, 126.2, 123.7, 122.0, 121.3, 119.4, 117.5, 114.3, 93.1, 76.6, 53.5, 42.6, 36.1, 29.8, 14.9, and 4.7.

HRMS (ESI-TOF): Calcd for $C_{26}H_{25}N_2O_2S^+$ $[M+H^+]^+$ requires 429.1631; found 429.1613.

IR (neat): 3407, 3057, 3024, 3004, 2955, 2915, 2852, 2342, 2235, 2142, 2000, 1609, 1598, 1577, 1494, 1465, 1434, 1381, 1339, 1328, 1295, 1279, 1252, 1241, 1198, 1154, 1121, 1076, 1045, 1031, 1014, 964, 937, 901, 885, 850, 804, 752, 734, 699, 664, 647, 617, 592, 561, 542, 513, 460, 445, 423, and 405 cm^{-1}.

5-Methyl-1-(methylsulfonyl)-11-phenyl-4-(prop-1-yn-1-yl)-2,3-dihydro-1H-pyrrolo[2,3-a]acridine (21b)



20b *21b*, 80%

Following general procedure B, 5-methyl-1-(methylsulfonyl)-11-phenyl-4-(prop-1-yn-1-yl)-2,3,6,11-tetrahydro-1H-pyrrolo[2,3-a]acridine (**20b**, 0.024 g, 0.057 mmol, 1 equiv), MnO_2 (xs) and $CHCl_3$ (10 mL) were used to prepare acridine **21b**. Purification of the crude product yielded acridine **21b** (0.019 g, 0.045 mmol, 80%) as a light green amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 8.7, 0.6 Hz, 1H, *H7*), 7.88 (br d, *J* = 7.6 Hz, 1H, *H2'* or *H6'),* 7.80 (dd, *J* = 8.8, 0.7 Hz, 1H, *H10*), 7.69 (ddd, *J* = 8.5, 6.5, 1.4 Hz, 1H, *H8*), 7.59 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, *H3'* or *H5'*), 7.47 (dddd, *J* = 7.5, 7.5, 1.4, 1.4 Hz, 1H, *H4'*), 7.39 (ddd, *J* = 8.5, 7.7, 0.9 Hz, 1H, *H9*), 7.38 (dd, *J* = 7.6, 7.6, 1.4 Hz, 1H, *H3'* or *H5'*), 7.11 (ddd, *J* = 7.8, 1.4, 1.4 Hz, 1H, *H2'* or *H6'*), 3.99 (dd, *J* = 12.0, 7.0 Hz, 1H, MsNC*H*$_a$H$_b$CH$_2$), 3.70 (ddd, *J* = 11.9, 11.9, 7.9 Hz, 1H, MsNCH$_a$*H*$_b$CH$_2$), 3.57 (ddd, *J* = 16.2, 11.7, 7.0 Hz, 1H, MsNCH$_2$C*H*$_a$H$_b$), 3.09 (s, 3H, C*H*$_3$SO$_2$N), 3.01 (dd, *J* = 16.2, 7.8 Hz, 1H, MsNCH$_2$CH$_a$*H*$_b$), 2.21 (overlapping s, 3H, ArC*H*$_3$), 2.21 (overlapping s, 3H, C≡CC*H*$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): 148.04, 148.00, 144.7, 140.8, 137.8, 137.0, 133.9, 133.1, 132.1, 130.5, 129.5, 127.7, 127.4, 126.6, 126.5, 126.2, 125.6, 120.9, 119.4, 95.8, 77.1, 52.0, 37.8, 32.0, 17.0, and 5.0.

HRMS (ESI-TOF): Calcd for $C_{26}H_{23}N_2O_2S^+$ $[M+H^+]^+$ requires 427.1475; found 427.1468.
IR (neat): 3055, 3031, 2955, 2917, 2850, 2233, 1730, 1619, 1593, 1548, 1442, 1413, 1353, 1321, 1263, 1150, 1103, 1015, 963, 921, 848, 803, 763, 736, 701, 670, 650, 623, 606, 536, 511, and 470 cm^{-1}.

SUPPLEMENTARY INFORMATION FOR CHAPTER 5

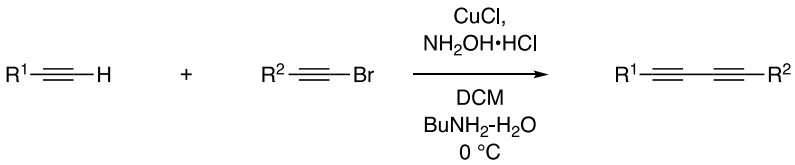
II. Preparation procedures and characterization data for all new compounds

General Procedures:

General Procedure A: General procedure for bromination of a terminal alkyne

To a culture tube of appropriate size was added terminal alkyne (1.0 equiv) and *N*–bromosuccinimide (NBS, 1.1 equiv) in acetone (0.10 M). Powdered $AgNO_3$ (0.10 equiv) was added and the suspension was stirred at room temperature for 1–2 hours (TLC and GC monitoring). This suspension was first passed through a plug of silica gel using the indicated elution solvent (to remove succinimide). The residue was further purified by flash chromatography/MPLC on silica gel using the indicated elution solvent.

General Procedure B: General procedure for the Cadiot–Chodkiewicz cross-coupling reaction:



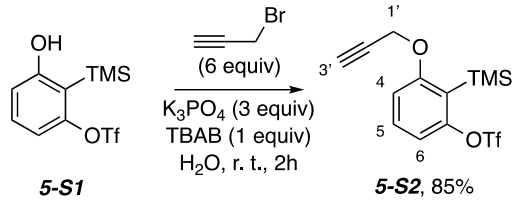
To a round bottom flask of appropriate size under N_2 was added Copper (I) chloride (10 mol%) and hydroxylamine hydrochloride (0.5 equiv). The reaction vessel was backfilled with N_2 using an outlet needle. 30/70 (v/v) H_2O/*n*-$BuNH_2$ was added and the mixture was cooled to 0 °C. Approximately 10% of the volume of the solution of the terminal alkyne (1 equiv) in DCM (ca. 10 mL/mmol) was added dropwise using a syringe, at which time 1-bromoalkyne (ca. 1-1.5 equiv) in CH_2Cl_2 (ca. 10 mL/mmol) addition begun. The two solutions were then simultaneously added at approximately the same rate until addition of both reactants was complete. The mixture was then kept stirring at the indicated temperature (0 ºC or rt). The progress of the reaction mixture was monitored by TLC and/or GC-MS analysis of the crude reaction mixture and/or crude mass spectrometric analysis using Advion CMS. The mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The extracts were dried and concentrated. The crude material was subsequently purified by flash chromatography/MPLC on silica gel.

General Procedure C: General procedure for the cesium fluoride induced HDDA reaction

To a culture tube of appropriate size under N_2 was added CsF (3.0 equiv). The culture tube was backfilled with N_2 with a balloon and an outlet needle. To this culture tube, a solution

of diyne precursor (1.0 equiv) in dry CH_3CN (typically 0.002 M) was added, which was followed by addition of a trapping reagent (for the cases of intermolecular trapping). The culture tube was fitted with an inert, Teflon®-lined cap, firmly sealed, and stirred at room temperature. The progress of the reaction mixture was monitored by TLC and/or GC-MS analysis of the crude reaction mixture. The reaction mixture was concentrated, and the crude product was purified by passage through a small silica plug. The residue was further purified medium pressure liquid chromatography using indicated elution solvent.

3-(Prop-2-yn-1-yloxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (5-S2):



5-S1 ***5-S2***, 85%

3-Hydroxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (7.35 g, 23.4 mmol, 1 equiv) was suspended in water (300 mL). Propargyl bromide (13.8 mL, 140.2 mmol, 6.0 equiv, 80% solution in toluene), tetrabutylammonium bromide (7.54 g, 23.4 mmol, 1.0 equiv), and K_3PO_4 (14.9 g, 70.2 mmol, 3 equiv) were added at room temperature. The completion of reaction was established by GC-MS analysis of an aliquot. After ca. 2 h the suspension was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hex:EtOAc, 19:1) to afford the impure alkyne **5-S2** (7.5 g, 19.9 mmol, 85%) as a colorless oil. This material was repurified by MPLC (pure hexanes) to give a more pure sample for spectral characterization and subsequent reactions.

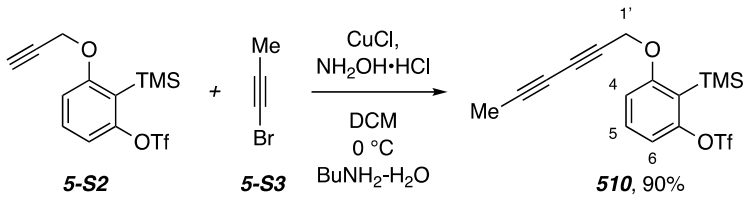
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 8.3, 8.3 Hz, 1H, *H5*), 6.99 (ddq, *J* 4.71 (d, *J* = 2.5 Hz, 2H, *H1'*), 2.52 (t, *J* = 2.4 Hz, 1H, *H3'*), and 0.39 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 162.8, 156.0, 131.6, 121.8, 118.7 (q, $^1J_{C\text{-}F}$ = 320 Hz, OSO_2CF_3), 113.7, 110.9, 77.9, 76.1, 56.2, and 1.0.

HRMS (ESI-TOF): Calcd for $C_{12}H_{12}F_3O_4SSi^+$ $[M+H^+–CH_4]^+$ 337.0172; found 337.0166.

IR (neat): 3303, 2958, 2903, 2126, 1206, and 1035 cm^{-1}.

3-(Hexa-2,4-diyn-1-yloxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (5-S3):



5-S2 ***5-S3*** ***510***, 90%

Following general procedure B, terminal alkyne **5-S2** (200 mg, 0.568 mmol, 1 equiv), bromopropyne in hexanes (25% wt%) (**5-S3**, 0.6 mL, 0.851 mmol, 1.5 equiv), CuCl (6 mg, 0.057 mmol, 10 mol%), NH_2OH•HCl (38 mg, 0.5 equiv), *n*-butylamine/H_2O (v:v, 30:70, 20 mL), and DCM (20 mL) were used to prepare diyne **##**. Purification of the crude material by MPLC (hexanes:EtOAc 19:1) provided diyne **510** (200 mg, 0.512 mmol, 90%) as a colorless oil.

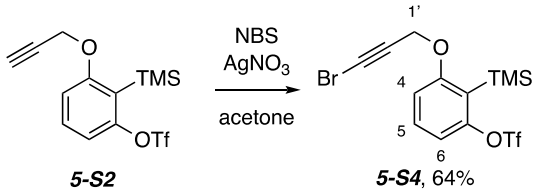
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 8.4, 8.4 Hz, 1H, *H5*), 6.99 (dd, *J* = 8.4, 0.9 Hz, 1H, *H6*), 6.91 (dd, *J* = 8.2, 0.8 Hz, 1H, *H4*), 4.75 (q, *J* = 1.1 Hz, 2H, *H1'*), 1.92 (t, *J* = 1.2 Hz, 3H, *CH*$_3$), and 0.38 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 163.4, 154.8, 131.7, 121.7, 118.7 (q, $^1J_{C\text{-}F}$ = 320.6 Hz, *CF*$_3$), 113.7, 110.9, 78.2, 72.8, 68.8, 63.6, 56.8, 21.1, and 4.4.

HRMS (ESI-TOF): Calcd for $C_{15}H_{14}F_3O_4SSi^+$ $[M+H^+ - CH_4]^+$ 375.0329; found 375.0304.

IR (neat): 2957, 2903, 2261, 1210, and 1162 cm^{-1}.

3-((3-Bromoprop-2-yn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (5-S4):



5-S2 ***5-S4***, 64%

Bromoalkyne **5-S4** was synthesized from terminal alkyne **5-S2** (104 mg, 0.297 mmol), *N*–bromosuccinimide (58 mg, 0.327 mmol), silver nitrate (5 mg, 0.030 mmol), and acetone (3 mL) following general procedure A. The crude product was purified by passage through a small silica gel plug (3:1, Hexanes: EtOAc) followed by further purification by medium pressure liquid chromatography (19:1, Hexanes: EtOAc) to afford bromoalkyne **5-S4** (82 mg, 0.190 mmol, 64%) as a pale-yellow oil.

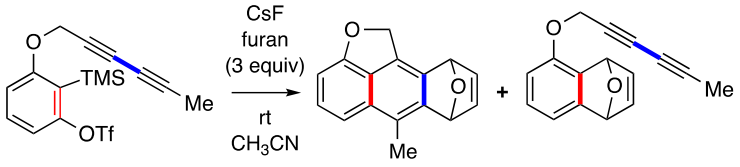
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 8.4, 8.4 Hz, 1H, *H5*), 7.00 (d, *J* = 8.4 Hz, 1H, *H6*), 6.92 (dd, *J* = 8.3, 0.6 Hz, *H4*), 4.73 (s, 2H, *H1'*), and 0.38 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 163.4, 154.8, 131.7, 121.8, 118.8 (q, $^{1}J_{C\text{-}F}$ = 320.6 Hz, CF_3), 113.8, 110.9, 74.5, 57.1, 48.3, and 1.0.

HRMS (ESI-TOF): Calcd for $C_{12}H_{11}BrF_3O_4SSi^+$ $[M+H^+ - CH_4]^+$ 414.9277; found 414.9265.

IR (neat): 2958, 2902, 2220, 1596, 1205, and 1137 cm^{-1}.

6-Methyl-7,10-dihydro-1H-7,10-epoxyanthra[1,9-bc]furan (532) and 5-(Hexa-2,4-diyn-1-yloxy)-1,4-dihydro-1,4-epoxynaphthalene (533)



	[furan]$_0$	ratio **532**:**533** (NMR)	isolated yields	
i)	0.06 M	1.0:1.0	48%	50%
ii)	0.006 M	1.0:0.09	78%	8%

Conditions i, [diyne 510 initial concentration (0.02 M)]: Naphthalene **532** was obtained following general procedure C from diyne **510** (23 mg, 0.0589 mmol, 1 equiv), furan (13μL, 0.177 mmol, 3 equiv), CsF (27 mg, 0.177 mmol, 3 equiv), and acetonitrile (3 mL, 0.02 M). The reaction was judged to be complete at ~3 hours by GCMS analysis of an aliquot of the reaction mixture. Purification by MPLC (hexanes:EtOAc, 3:1) afforded, in order of elution, benzyne adduct **533** (5 mg, 0.021 mmol, 36%) as a yellow oil, and naphthalene **532** (6 mg, 0.025 mmol, 43%) as a white solid.

Conditions ii, [diyne ## initial concentration (0.002 M)]: Naphthalene **532** was obtained following general procedure C from diyne **510** (27 mg, 0.0692 mmol, 1 equiv), furan (15 μL, 0.207 mmol, 3 equiv), CsF (32 mg, 0.207 mmol, 3 equiv), and acetonitrile (35 mL, 0.002 M). The reaction mixture was worked up after 8 hours. Purification by MPLC (hexanes:EtOAc, 3:1) afforded, in order of elution, benzyne adduct **533** (2 mg, 0.008 mmol, 12%) as a yellow oil, and naphthalene **532** (12 mg, 0.051 mmol, 74%) as a white solid.

Data for the slower eluting naphthyne adduct (532):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 8.3, 7.5 Hz, 1H, *H4*), 7.18 (d, *J* = 8.3 Hz, 1H, *H5*), 7.01 (dd, *J* = 5.6, 1.9 Hz, *H8* or *H9*), 6.96 (dd, *J* = 5.6, 1.8 Hz, *H8* or *H9*), 6.73 (d, *J* = 7.4 Hz, *H3*), 5.93 (dd, *J* = 1.9, 0.9 Hz, *H7* or *H10*), 5.76 (dd, *J* = 2.0, 0.9 Hz, *H7* or *H10*), 5.73 (d, *J* = 14.6 Hz, 1H, C*H$_a$*H$_b$), 5.62 (d, *J* = 14.4 Hz, 1H, CH$_a$*H$_b$*), and 2.53 (s, 3H, Ar*CH$_3$*).

^{13}C NMR (105 MHz, $CDCl_3$): 161.9, 145.2, 142.0, 141.3, 133.5, 130.4, 129.5, 127.0, 126.8, 123.2, 113.5, 102.3, 80.8, 80.7, 75.1, and 14.1.

HRMS (ESI-TOF): Calcd for $C_{16}H_{13}O_2^+$ $[M+H^+]^+$ 237.0910; found 237.0882.

IR (neat): 3059, 3024, 3008, 2861, 2730, 1617, 1515, and 1019 cm^{-1}.

Data for the faster eluting benzyne adduct (533):

^{1}H NMR (500 MHz, C_6D_6): δ 6.73 (dd, *J* = 8.2, 7.0 Hz, 1H, *H7*), 6.68 (ddd, *J* = 7, 0.9, 0.9 Hz, 1H, *H8*), 6.67 (dd, *J* = 5.5, 1.9 Hz, *H2* or *H3*), 6.54 (dd, *J* = 5.5, 1.9 Hz, *H2* or *H3*), 6.42 (dd, *J* = 8.2, 1.0 Hz, 1H, *H6*), 5.94 (ddd, *J* =1.8, 0.9, 0.9 Hz, 1H, *H1*), 5.36 (d, *J*

= 1.8, 0.9 Hz, 1H, *H4*), 4.16 (q, *J* = 1.1 Hz, 2H, *H1'*), and 1.22 (t, *J* = 1.1 Hz, 3H, C≡C*CH*$_3$).

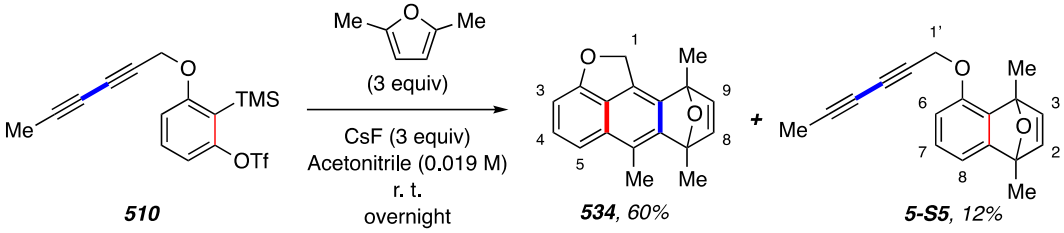
^{13}C NMR (125 MHz, C_6D_6): 152.9, 151.5, 143.3, 143.1, 137.1, 126.9, 114.6, 112.2, 82.8, 80.5, 78.1, 73.1, 70.6, 64.5, 57.0, and 3.5.

^{13}C NMR (100 MHz, $CDCl_3$): 152.3, 150.1, 143.2, 142.9, 135.9, 125.4, 114.3, 111.3, 82.7, 80.3, 78.0, 72.7, 70.5, 63.7, 57.4, and 4.9.

HRMS (ESI-TOF): Calcd for $C_{16}H_{13}O_2^+$ $[M+H^+]^+$ 237.0910; found 237.0893.

IR (neat): 3062, 3010, 2920, 2863, 2258, 1650, and 1022 cm^{-1}.

6,7,10-Trimethyl-7,10-dihydro-1H-7,10-epoxyanthra[1,9-bc]furan (534) and 5-(hexa-2,4-diyn-1-yloxy)-1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalene (5-S5):



*Crude NMR ratio of **534** and **5-S5** = 1:0.18*

Following general procedure C, diyne **510** (62 mg, 0.159 mmol), 2,5-dimethylfuran (##, 52 μL, 0.477 mmol, 3 equiv), CsF (72 mg, 0.477 mmol), and acetonitrile (80 mL) were used to prepare naphthobenzofuran **534**. The reaction was judged to be complete at ~8 h by GCMS analysis of an aliquot of the reaction mixture. Purification by MPLC (hexanes:EtOAc, 9:1) afforded, in order of elution, benzyne adduct **5-S5** (5 mg, 0.019 mmol, 12%) as a yellow oil, and naphthalene **534** (25 mg, 0.095 mmol, 60%) as a white solid.

Data for the slower eluting naphthyne adduct (534):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 8.3, 7.5 Hz, 1H, *H4*), 7.22 (d, *J* = 8.2 Hz, 1H, *H5*), 6.79 (d, *J* = 5.3 Hz, 1H, *H8* or *H9*), 6.73 (d, *J* = 5.4 Hz, 1H, *H8* or *H9*), 6.72 (d, *J* = 7.4 Hz, 1H, *H3*), 5.78 (d, *J* = 14.3 Hz, 1H, CH_aH_b), 5.65 (d, *J* = 14.3 Hz, 1H, CH_aH_b), 2.57 (s, 3H, ArCH_3), 2.11 (s, 3H, C10CH_3 or C7CH_3), and 1.91 (s, 3H, C10CH_3 or C7CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 148.2, 146.1, 145.3, 138.8, 130.9, 129.3, 126.9, 125.7, 123.4, 113.5, 102.2, 90.5, 86.9, 74.6, 19.0, 16.2, and 13.0.

HRMS (ESI-TOF): Calcd for $C_{18}H_{17}O_2^+$ $[M+H^+]^+$ 265.1223; found 265.1212.

IR (neat): 2972, 2933, 2871, 1648, 1380, and 1147 cm^{-1}.

Data for the faster eluting benzyne adduct (5-S5) [also contains 21% of the naphthyne adduct, 534]:

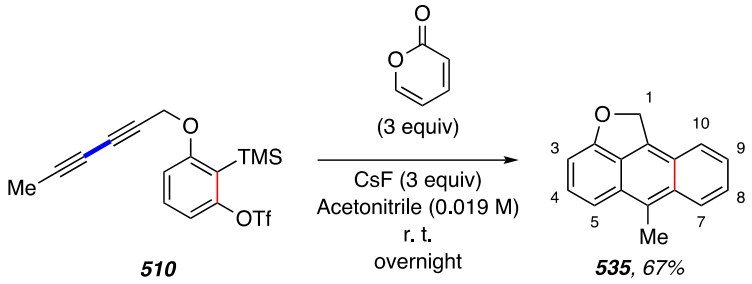
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 8.3, 7.1 Hz, 1H, *H7*), 6.87 (d, *J* = 5.3 Hz, 1H, *H2* or *H3*), 6.83 (dd, *J* = 7.0, 0.7 Hz, 1H, *H8*), 6.75 (d, *J* = 5.3 Hz, 1H, *H2* or *H3*), 6.66 (dd, *J* = 8.4, 0.6 Hz, 1H, *H6*), 4.72 (dq, *J* = 16.5, 1.1 Hz, 1H, H1'a), 4.69 (dq, *J* = 16.5, 1.1 Hz, 1H, H1'b), 2.02 (s, 3H, C1CH_3 or C4CH_3), 1.93 (t, *J* = 1.1 Hz, 3H, C≡CCH_3), and 1.87 (s, 3H, C1CH_3 or C4CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): 156.2, 152.4, 147.5, 146.7, 139.0, 135.4, 127.1, 123.5, 113.0, 112.2, 89.5, 88.7, 77.8, 72.4, 70.0, 63.8, 57.3, 17.3, 15.5, and 4.5.

IR (neat): 3067, 2866, 2259, 1571, 1471, 1381, and 1024 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{18}H_{17}O_2^+$ $[M+H^+]^+$ 265.1223; found 265.1209.

6-Methyl-1H-anthra[1,9-bc]furan (535):

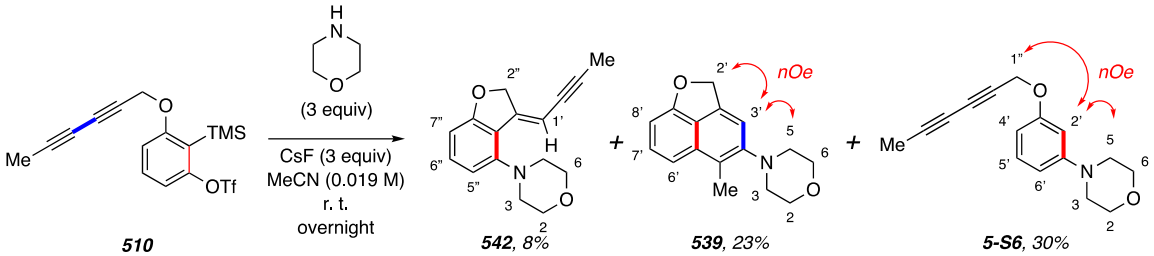


510 ***535**, 67%*

Following general procedure C, diyne **510** (19 mg, 0.048 mmol), pyrone (12 μL, 0.144 mmol, 3 equiv), CsF (22 mg, 0.144 mmol, 3 equiv), and acetonitrile (25 mL) were used to prepare anthracene **535**. The reaction was judged to be complete ab GCMS analysis of an aliquot taken after ~8 hours. The crude reaction mixture was purified by passage through a small silica gel plug (3:1, Hexanes: EtOAc) followed by further purification by medium pressure liquid chromatography (19:1, Hexanes: EtOAc) to afford the anthracene derivative **535** (7 mg, 0.0320 mmol, 67%) as a white solid.

The ^{1}H NMR spectral data for this compound matched closely those for the same compound prepared by reductive deoxygenation of the furan-trapped adduct **532**.

4-(3-(But-2-yn-1-ylidene)-2,3-dihydrobenzofuran-4-yl)morpholine (542), 4-(5-methyl-2H-naphtho[1,8-bc]furan-4-yl)morpholine (539), and 4-(3-(hexa-2,4-diyn-1-yloxy)phenyl)morpholine (5-S6):



510 *542, 8%* *539, 23%* *5-S6, 30%*

Crude NMR ratio of **542**, **539** and **5-S6**: 0.13: 1.00: 1.2

Following general procedure C, diyne **510** (20 mg, 0.051 mmol), morpholine (14 μL, 0.154 mmol, 3 equiv), CsF (23 mg, 0.154 mmol, 3 equiv), and acetonitrile (30 mL) were used to prepare the naphthalene derivative **539**. The reaction was judged to be complete by GCMS analysis of an aliquot taken after ~2 hours. The reaction mixture was purified by passage through a small silica gel plug (1:1, hexanes:EtOAc) followed by further purification by medium pressure liquid chromatography (6:1, hexanes:EtOAc) to afford enyne adduct **542** (1 mg, 0.004 mmol, 10%) as a yellow oil, the morpholine-trapped naphthalene derivative **539** (3 mg, 0.012 mmol, 20%), and morpholine attached benzyne adduct **5-S6** (4 mg, 0.016 mmol, 30%).

Data for the first eluting fraction, enyne adduct 542:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 8.1, 8.1 Hz ,1H, *H6"*), 6.60 (dd, *J* = 8.1, 0.7 Hz, 1H, *H5"* or *H7"*), 6.57 (dd, *J* = 8.1, 0.8 Hz, 1H, *H5"* or *H7"*), 6.00 (qt, *J* = 3.4, 2.5 Hz, 1H, *H1'*), 5.21 (dq, *J* = 3.4, 1 Hz, 2H, *H2"*), 3.85 (br s, 4H, *H2* and *H6*), 3.00 (br s, 4H, *H3* and *H5*), and 2.07 (dt, *J* = 2.5, 1 Hz, 1H, CH_3).

HRMS (ESI-TOF): Calcd for $C_{16}H_{18}NO_2^+$ $[M+H^+]^+$ 256.1332; found 256.1301.

IR: 3056, 2960, 2923, 2854, 2219, 1722, 1601, 1584, 1262, and 733 cm^{-1}.

Data for the second eluting fraction, naphthalene adduct 539:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 8.4, 7.3 Hz , 1H, *H7'*), 7.24 (d, *J* = 8.4 Hz, 1H, *H6'*), 7.14 (t, *J* = 1.7 Hz, 1H, *H3'*), 6.63 (d, *J* = 7.3 Hz, 1H, *H8'*), 5.73 (dq, *J* = 1.3, 1.3 Hz, 2H, *H2'*), 3.91 (nfom, 4H, *H2* and *H6*), 2.97 (nfom, 4H, *H3* and *H5*), and 2.56 (t, *J* = 1.3 Hz, 1H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 151.0, 137.3, 132.6, 129.8, 125.7, 124.8, 113.3, 109.3, 99.8, 76.8, 67.7, 53.1, and 12.8.

A difference nOe experiment showed enhancement of protons H2' and H5 upon irradiation of ArH3', allowing the regioisomeric assignment given in structure **539**.

HRMS (ESI-TOF): Calcd for $C_{16}H_{18}NO_2^+$ $[M+H^+]^+$ 256.1332; found 256.1317.

IR: 3058, 2956, 2922, 1772, 1655, 1386, 1260, and 1114, and 771 cm^{-1}.

Data for the third eluting fraction, benzyne adduct 5-S6:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (ddd, *J* = 8.2, 7.3, 0.6 Hz, 1H, *H5'*), 6.57 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H, *H4'* or *H6'*), 6.50 (ddd, *J* = 2.3, 2.3, 0.5 Hz, 1H, *H2'*), 6.49 (ddd, *J* = 7.8, 2.5, 0.9 Hz, 1H, *H4'* or *H6'*), 4.71 (q, *J* = 1.2 Hz, 2H, *H1"*), 3.85 (nfom, 4H, *H2* and *H6*), 3.15 (nfom, 4H, *H3* and *H5*), and 1.93 (t, *J* = 1.1 Hz, 1H, CH_3).

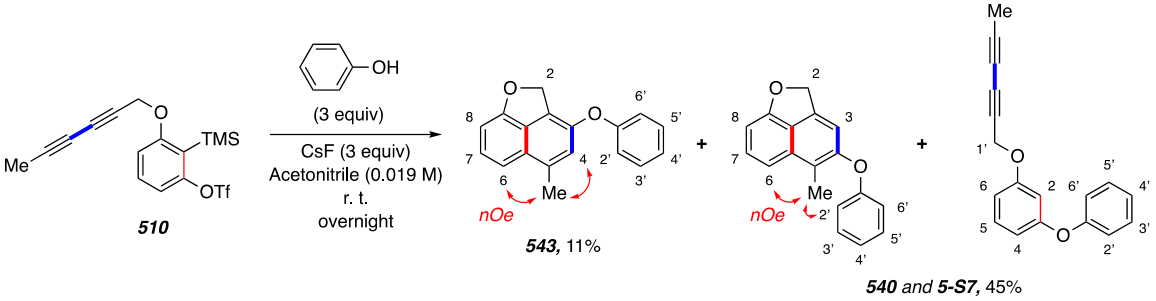
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 152.6, 130.0, 109.4, 105.7, 103.3, 77.7, 72.4, 69.9, 67.0, 63.8, 56.5, 49.3, and 4.5.

A difference nOe experiment showed enhancement of the H1" and H5 protons upon irradiation of ArH2', allowing the regioisomeric assignment as given in **5-S6**.

HRMS (ESI-TOF): Calcd for $C_{16}H_{18}NO_2^+$ $[M+H^+]^+$ 256.1332; found 256.1316.

IR: 3051, 2962, 2913, 2855, 2827, 2259, 1599, 1577, 1493, 1448, 1170, 1119, and 1034 cm^{-1}.

5-Methyl-3-phenoxy-2H-naphtho[1,8-bc]furan (543), 5-methyl-4-phenoxy-2H-naphtho[1,8-bc]furan (540), and 1-(hexa-2,4-diyn-1-yloxy)-3-phenoxybenzene (5-S7):



Crude NMR ratio of **540**, **543**, and **5-S7** = 1: 0.30: 0.10

Following general procedure C, diyne **510** (59 mg, 0.151 mmol), phenol (43 mg, 0.453 mmol, 3 equiv), CsF (69 mg, 0.453 mmol, 3 equiv), and acetonitrile (80 mL) were used to prepare the naphthalene derivatives **540** and **543**. The mixture was stirred overnight, and the completion of the reaction was confirmed by the crude GCMS analysis. The reaction mixture was purified by passage through a small silica gel plug (pure EtOAc) followed by further purification by medium pressure liquid chromatography (pure hexanes) to afford, in an order of elution, *C-3* regioisomer **543** (5 mg, 0.019 mmol, 11%), and a mixture the *C-4* regioisomer **540** and the benzyne adduct **5-S7** (20 mg, 45% combined, 0.076 mmol, 1:0.09 ratio) as a white solid.

Data for the first eluting fraction, C3-regioisomer 543 [which also contains 9% of the C4-regioisomer, 540]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 8.6, 7.4 Hz ,1H, *H7*), 7.37–7.31 (nfodd, J_{app} = 8.5, 7.2 Hz, 2H, *H3'* and *H5'*), 7.27 [d, *J* ~ 9 Hz (overlapped with C*H*Cl_3 peak, 1H, *H6*], 7.13 (tt, *J* = 7.3, 1.1 Hz, 1H, *H4'*), 7.09 (q, *J* = 1.1 Hz, *H4*), 7.02 (nfod, J_{app} = 8.7 Hz, 2H, *H2'* and *H6'*), 6.69 (dd, *J* = 7.3, 0.6 Hz, 1H, *H8*), 5.33 (q, *J* = 1.3 Hz, 2H, *H2*), and 2.60 (dt, *J* = 1.1, 1.1 Hz, 1H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 156.8, 145.6, 135.0, 130.4, 129.9, 128.5, 128.0, 123.6, 122.6, 121.9, 118.6, 113.2, 101.2, 75.4, and 18.0.

A difference nOe experiment showed enhancement of protons *H6* and *H4* upon irradiation of ArCH_3, allowing the regioisomeric assignment given in structure **543**.

HRMS (ESI-TOF): Calcd for $C_{18}H_{15}O_2^+$ $[M+H^+]^+$ 263.1067; found 263.1006 (minor ion), Calcd for $C_{18}H_{13}O_2^+$ $[M–H^-]^+$ 261.0910; found 261.0896 (major ion).

IR (neat): 3063, 3037, 2926, 2867, 1586, 1487, 1214, and 743 cm^{-1}.

^{1}H NMR identifiable, unique resonances for the benzyne adduct (500 MHz, C_6D_6):

δ 7.05 (nfodd, J_{app} = 8.6, 7.3 Hz, 2H, *H3*' and *H5'*), 6.97 (nfod, J_{app} = 8.6 Hz, 2H, *H2'* and *H6'*), 6.92 (dd, *J* = 8.3, 8.3 Hz, 1H, *H5*), 6.73 (dd, *J* = 2.3, 2.3 Hz, 1H, *H2*), 6.61 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H, *H4* or *H6*), 6.58 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H, *H4* or *H6*), 4.08 (q, *J* = 1.1 Hz, 1H, H1'), and 2.39 (t, *J* = 1.2 Hz, 1H, CH_3).

Data for the C4-regioisomer 540:

^{1}H NMR (500 MHz, C_6D_6): δ 7.26 (dd, *J* = 8.3, 7.5 Hz, 1H, *H7*), 7.15 (d, *J* = 8.4 Hz, 1H, *H6*), 7.09 (nfodd, J_{app} = 8.7, 7.3 Hz, 2H, *H3'* and *H5'*), 6.88 (nfod, J_{app} = 8.7 Hz, 2H, *H2'* and *H6'*), 6.86 (tt, *J* = 7.4, 1.2 Hz, 1H, *H4'*), 6.71 (d, *J* = 7.4 Hz, 1H, *H8*), 6.49 (t, *J* = 1.8 Hz, 1H, *H3*), 5.02 (dq, *J* = 1.4, 1.4 Hz, 2H, *H2*), and 2.39 (t, *J* = 1.2 Hz, 3H, Ar*CH*$_3$).

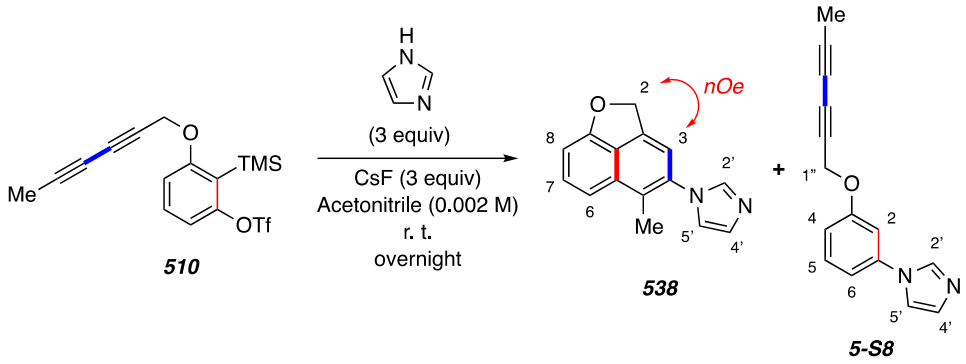
^{13}C NMR (125 MHz, C_6D_6): δ 162.9, 159.3, 153.7, 138.5, 133.1, 130.6, 130.1, 126.3, 122.4, 122.1, 117.2, 113.3, 111.0, 100.8, 76.3, and 10.2.

A difference nOe experiment showed enhancement of protons *H6* and *H2'* (and *H6'*) upon irradiation of Ar*CH*$_3$, allowing the regioisomeric assignment given in structure **540**.

HRMS (ESI-TOF): Calcd for $C_{18}H_{15}O_2^+$ $[M+H^+]^+$ 263.1067; found 263.1052 (minor ion), Calcd for $C_{18}H_{13}O_2^+$ $[M–H^–]^+$ 261.0910; found 261.0897 (major ion).

IR (neat): 3063, 3038, 2931, 2866, 2260, 1624, 1589, 1488, 1382, 1213, and 750 cm^{-1}.

1-(5-Methyl-2H-naphtho[1,8-bc]furan-4-yl)-1H-imidazole (##) and 1-(3-(hexa-2,4-diyn-1-yloxy)phenyl)-1H-imidazole (##):



*Crude NMR ratio of **538** and **5-S8** = 1: 0.52*

Following general procedure C, diyne **510** (60 mg, 0.151 mmol), imidazole (31 mg, 0.453 mmol, 3 equiv), CsF (69 mg, 0.453 mmol, 3 equiv), and acetonitrile (80 mL) were used to prepare the naphthalene derivative **538** and benzyne adduct **5-S8**. The mixture was stirred overnight, and the completion of the reaction was confirmed by the crude GCMS analysis. The reaction mixture was purified by passage through a small silica gel plug (pure EtOAc) followed by further purification by medium pressure liquid chromatography (pure EtOAc) to afford, in an order of elution, benzyne adduct **5-S8** (9 mg, 0.038 mmol, 24%) as a transparent oil, and naphthalene adduct **538** (17 mg, 0.071 mmol, 46%,) as a white solid.

Data for the slower eluting, naphthyne adduct (538):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (br s, 1H, *H2'*), 7.52 (dd, *J* = 8.4, 7.5 Hz, 1H, *H7*), 7.35 (d, *J* = 8.3 Hz, 1H, *H6*), 7.26 (br s, 1H, *H4'*), 7.13 (br s, 1H, *H5'*), 7.09 (t, *J* = 1.6 Hz, 1H, *H3*), 6.82 (d, *J* = 7.4 Hz, 1H, *H8*), 5.78 (br s, 2H, *H2*), and 2.37 (t, *J* = 1.1 Hz, 3H, Ar*CH*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 138.3 (v br), 137.9, 135.8, 131.7, 131.1, 129.7 (br), 128.2, 127.9, 121.2 (br), 114.7, 113.8, 102.3, 76.5, and 13.0.

A difference nOe experiment showed enhancement of protons *H2* upon irradiation of *H3*, allowing the regioisomeric assignment given in structure **538**.

HRMS (ESI-TOF): Calcd for $C_{15}H_{13}N_2O^+$ $[M+H^+]^+$ 237.1022; found 237.1006.

IR: 3111, 3063, 2930, 2867, 1687, 1489, 1386, 941, and 746 cm^{-1}.

Data for the faster eluting, benzyne adduct (5-S8):

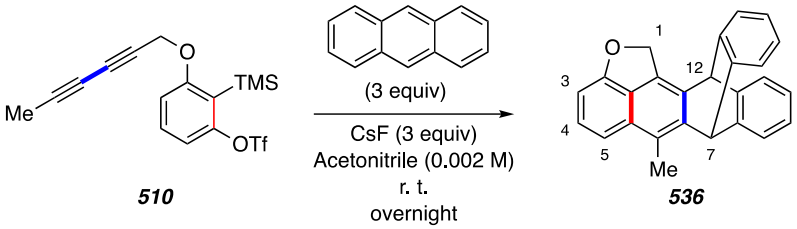
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (br s, 1H, *H2'*), 7.52 (dd, *J* = 8.1, 8.1 Hz, 1H, *H5*), 7.36–7.12 (two br s, 2H, *H5'* and *H4'*), 7.04 (br m, 1H, *H6*), 7.01 (br s, 1H, *H2*), 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H, *H4*), 4.79 (q, J = 1.1 Hz, 2H, *H1''*), and 1.94 (t, J = 1.2 Hz, 3H, C≡C*CH*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 138.6, 136 (br), 131.0, 131 (br), 118 (br), 114.7, 113.7, 109.0, 78.4, 73.1, 68.9, 63.6, 56.8, and 4.5.

HRMS (ESI-TOF): Calcd for $C_{15}H_{13}N_2O^+$ $[M+H^+]^+$ 237.1022; found 237.1008.

IR: 3119, 2961, 1916, 2861, 2259, 1597, 1504, 1202, and 1030 cm^{-1}.

6-Methyl-7,12-dihydro-1H-7,12-[1,2]benzenotetraceno[1,12-bc]furan (536):



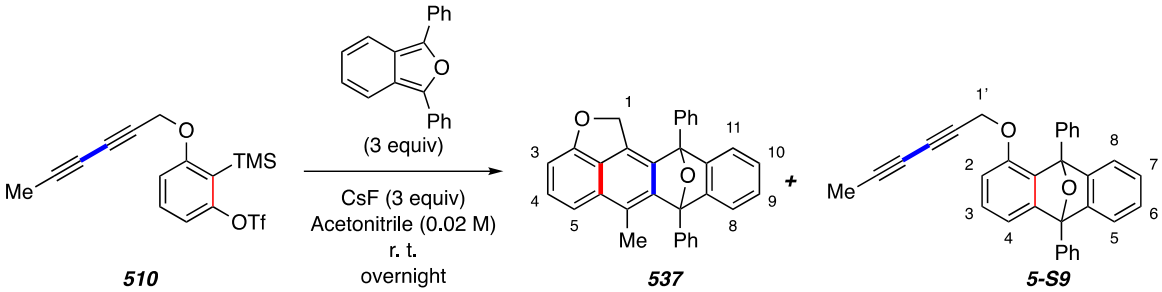
Following general procedure C, diyne **510** (25 mg, 0.065 mmol), anthracene (35 mg, 0.194 mmol, 3 equiv), CsF (30 mg, 0.194 mmol, 3 equiv), and acetonitrile (32 mL) were used to prepare the naphthalene derivative **536**. The mixture was stirred overnight, and the completion of the reaction was confirmed by the crude GCMS analysis. The reaction mixture was purified by passage through a small silica gel plug (pure EtOAc) followed by further purification by medium pressure liquid chromatography (Hex:EtOAc, 19:1) to afford naphthalene adduct **536** (46%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.37 (m, 4H, Ar*H*$_m$), 7.29 (dd, *J* = 8.4, 7.4 Hz, 1H, *H4*), 7.18 (d, *J* = 8.4 Hz, 1H, *H5*), 7.05–7.01 (m, 4H, Ar*H*$_o$), 6.62 (d, *J* = 7.4 Hz, 1H, *H3*), 5.87 (s, 1H, *H7* or *H12*), 5.86 (q, *J* = 1.2 Hz, 2H, *H1*), 5.38 (s, 1H, *H7* or *H12*), and 2.75 (t, *J* = 1.1 Hz, 3H, Ar*CH*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.9, 144.8, 144.4, 142.6, 132.2, 129.9, 129.0, 129.0, 126.4, 125.8, 125.7, 125.0, 124.1, 123.7, 113.4, 100.9, 75.6, 51.4, 50.9, and 13.6.

HRMS (ESI-TOF): Calcd for $C_{26}H_{19}O^+$ $[M+H^+]^+$ 347.1430; found 347.1394.

6-Methyl-7,12-diphenyl-7,12-dihydro-1H-7,12-epoxytetraceno[1,12-bc]furan (##) and 1-(hexa-2,4-diyn-1-yloxy)-9,10-diphenyl-9,10-dihydro-9,10-epoxyanthracene (##):



naphthyne **vs.** *benzyne* **=** *1* **:** *0.45*

Following general procedure C, diyne **510** (25 mg, 0.064 mmol), 1,3-diphenylisobenzofuran (42 mg, 0.192 mmol, 3 equiv), CsF (30 mg, 0.192 mmol, 3 equiv), and acetonitrile (3.2 mL) were used to prepare the naphthyne adduct **537** and benzyne adduct **5-S9**. The mixture was stirred overnight, and the completion of the reaction was confirmed by the crude GCMS analysis. The reaction mixture was purified by passage through a small silica gel plug (pure EtOAc) followed by further purification by medium pressure liquid chromatography (Hex:EtOAc, 9:1) to afford a mixture of naphthyne adduct **537** and benzyne adduct in 61% overall yield. This sample was repurified by MPLC (19:1, Hex:EtOAc) to give pure **537** as the major product and pure **5-S9** as the minor product.

Data for the faster eluting, naphthyne adduct 537:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00–7.97 (nfod, *J* = 8 Hz, 2H, Ph*H*$_o$), 7.91–7.88 (nfod, *J* = 8 Hz, 2H, Ph'*H*$_o$), 7.67 [ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H8* (or *H11*)], 7.58–7.49 [m, 7H, Ar*H*$_m$, Ar*H*$_p$, and *H11* (or *H8*)], 7.29 (dd, *J* = 8.4, 7.4 Hz, 1H, *H4*), 7.18 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H, *H9* or *H10*), 7.17 (d, *J* = 8.4 Hz, 1H, *H5*), 7.12 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, *H9* or *H10*), 6.69 (d, *J* = 7.4 Hz, 1H, *H3*), 5.45 (dq, *J* = 15.2, 1.0 Hz, 1H, C*H*$_a$H$_b$), 5.39 (dq, *J* = 15.2, 1.0 Hz, 1H, CH$_a$*H*$_b$), and 2.16 (t, *J* = 1.0 Hz, 3H, Ar*CH*$_3$).

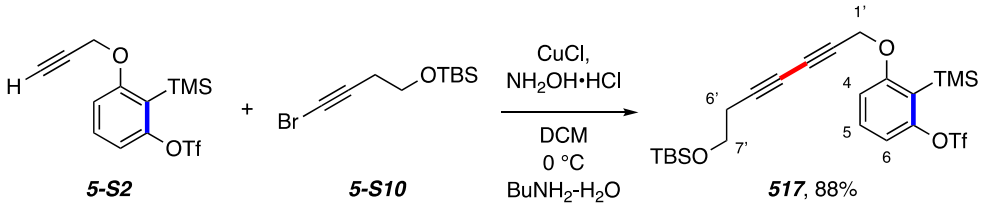
^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 150.6, 148.3, 147.8, 138.4, 135.5, 134.4, 131.4, 129.8, 129.6, 129.4, 129.0, 129.0, 128.9, 127.7, 127.6, 127.3, 126.6, 126.2, 125.2, 122.2, 121.3, 113.2, 102.1, 92.5, 89.4, 75.6, and 15.0.

Data for the slower eluting, benzyne adduct 5-S9:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (nfod, J_{app} = 7.3 Hz, 2H, Ph*H*$_o$), 7.90 (nfod, J_{app} = 7.4 Hz, 2H, Ph'*H*$_o$), 7.57–7.43 [m, 7H, Ar*H*$_m$, Ar*H*$_p$, and *H5* (or *H8*)], 7.36 [dd, *J* = 7.2, 1.4 Hz, 1H, and *H5* (or *H8*)], 7.08 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, *H6* or *H7*), 7.03 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H, *H6* or *H7*), 7.04 (d, *J* = 7.0 Hz, 1H, *H4*),7.02 (dd, *J* = 7.3, 7.3 Hz, 1H, *H3*), 6.73 (dd, *J* = 7.3, 1.8 Hz, 1H, *H2*), 4.49 (q, *J* = 1.3 Hz, 2H, *H1'*), and 1.93 (t, *J* = 1.1 Hz, 3H, C≡C*CH*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): 153.9, 151.8, 151.4, 149.8, 137.5, 135.0, 134.6, 129.4, 128.8, 128.7, 128.4, 128.1, 128.1, 127.1, 126.0, 125.7, 121.4, 120.7, 114.7, 113.4, 91.8, 90.5, 77.8, 72.4, 69.8, 63.8, 57.1, and 4.5.

3-((7-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (517)



5-S2 ***5-S10*** ***517***, 88%

Following general procedure A, the terminal alkyne **5-S2** (50 mg, 0.142 mmol, 1 equiv), ((4-bromobut-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane (**5-S10**, 56 mg, 0.213 mmol, 1.5 equiv), CuCl (2 mg, 0.0142 mmol, 10 mol%), NH_2OH•HCl (3 mg, 0.5 equiv), *n*-butylamine/H_2O (v:v, 30:70, 1.5 mL), and DCM (1.5 mL) were used to prepare the diyne **517**. Purification of the crude material by MPLC (hexanes:EtOAc 9:1) provided **517** (67 mg, 0.125 mmol, 88%) as a colorless oil.

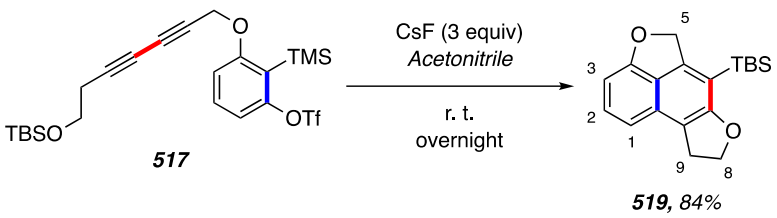
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 8.4, 8.4 Hz, 1H, *H5*), 6.99 (d, *J* = 8.4 Hz, 1H, *H6*), 6.91 (dd, *J* = 8.2, 0.7 Hz, 1H, *H4*), 4.76 (t, *J* = 1.0 Hz, 2H, *H1'*), 3.74 (t, *J* = 6.9 Hz, 2H, *H7'*), 2.49 (tt, *J* = 6.9, 1.1 Hz, 2H, *H6'*), 0.89 [s, 9H, $OSi(CH_3)_2(CH_3)_3$], 0.38 [s, 9H, $Si(CH_3)_3$], and 0.06 [s, 6H, $OSi(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): 164.4, 155.5, 131.7, 118.7 (q, $^1J_{C\text{-}F}$ = 320.6 Hz, CF_3), 113.7 (q, $^5J_{C\text{-}F}$ = 1.6 Hz, *C6*), 110.9, 79.6, 72.2, 69.7, 65.4, 61.3, 56.8, 27.0, 23.3, 17.6, 1.0, -5.2.

HRMS (ESI-TOF): Calcd for $C_{23}H_{34}F_3O_5SSi_2^+$ $[M+H^+]^+$ 535.1612; found 535.1576.

IR (neat): 2956, 2931, 2858, 2261, 1596, 1250, 1213, 1141, 1113, and 838 cm^{-1}.

tert-Butyl(8,9-dihydro-5H-naphtho[2,1-b:5,4-b'c']difuran-6-yl)dimethylsilane (519)



Following general procedure C, the diyne **517** (53 mg, 0.099 mmol), CsF (45 mg, 0.297 mmol), and acetonitrile (50 mL) were used to prepare the naphthalene derivative **519**. Purification of the crude material by MPLC (9:1, Hex:EtOAc) provided impure naphthalene **519** as a pale-yellow solid. This sample was repurified by MPLC (19:1, Hex:EtOAc) to give pure naphthalene **519** (26 mg, 0.068 mmol, 84% yield) as a white crystalline solid.

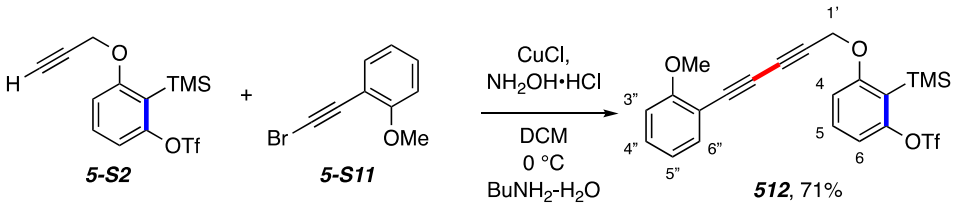
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 8.2, 7.4 Hz, 1H, *H2*), 6.91 (d, *J* = 8.2 Hz, 1H, *H1*), 6.50 (d, *J* = 7.4 Hz, 1H, *H3*), 5.68 (t, *J* = 1.6 Hz, 2H, *H5*), 4.67 (t, *J* = 9.0 Hz, 2H, *H8*), 3.32 (tt, *J* = 9.0. 1.5 Hz, 2H, *H9*), 0.90 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], and 0.34 [s, 6H, $Si(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): 166.2, 162.7, 147.6, 131.2, 130.1, 124.1, 114.7, 111.35, 111.32, 98.2, 78.1, 71.5, 27.8, 26.7, and -4.0.

HRMS (ESI-TOF): Calcd for $C_{19}H_{25}O_2Si^+$ $[M+H^+]^+$ 313.1618; found 313.1596.

Mp: 98-100 ºC**.**

3-((5-(2-Methoxyphenyl)penta-2,4-diyn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (512)



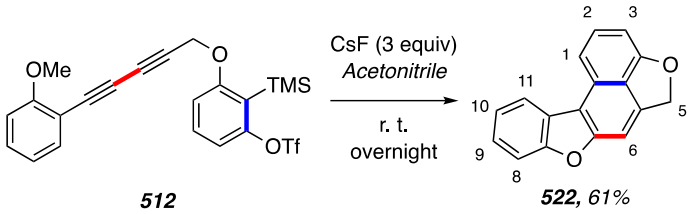
Following general procedure A, the terminal alkyne **5-S2** (36 mg, 0.102 mmol, 1 equiv), 1-(bromoethynyl)-2-methoxybenzene (**5-S11**, 32 mg, 0.153 mmol, 1.5 equiv), CuCl (1 mg, 0.0142 mmol, 10 mol%), NH_2OH•HCl (2 mg, 0.5 equiv), *n*-butylamine/H_2O (v:v, 30:70, 1.5 mL), and DCM (1.5 mL) were used to prepare diyne **512**. Purification of the crude material by MPLC (hexanes:EtOAc 9:1) provided diyne **512** (35 mg, 0.072 mmol, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.6, 1.7 Hz, 1H, *H6"*), 7.39 (dd, *J* = 8.3, 8.3 Hz, 1H, *H5*), 7.34 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H, *H4"*), 7.00 (br d, *J* = 8.4 Hz, 1H, *H6*), 6.97 (dd, *J* = 8.3, 0.6 Hz, 1H, *H4*), 6.90 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 1H, *H5"*), 6.88 (dd, *J* = 8.5, 1.0 Hz, 1H, *H3"*), 4.86 (s, 2H, *H1'*), 3.88 (s, 3H, O*CH*$_3$), and 0.39 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 163.4, 161.8, 154.9, 134.8, 131.7, 131.2, 121.7, 120.7, 118.8 (q, $^1J_{C\text{-}F}$ = 320.6 Hz, OSO_2CF_3), 113.8 (br), 111.0, 110.8, 110.5, 76.9, 76.8, 75.9, 72.6, 57.0, 56.0, and 1.1.

HRMS (ESI-TOF): Calcd for $C_{22}H_{22}F_3O_5SSi^+$ $[M+H^+]^+$ 483.0904; found 483.0898.
IR (neat): 3079, 2956, 2902, 2839, 2242, 1595, 1207, and 1137 cm^{-1}.

4,5-Dihydrobenzo[2,3]benzofuro[6,5,4-cd]benzofuran (522)



512 ***522**, 61%*

Following general procedure C, the diyne **512** (32 mg, 0.066 mmol), CsF (30 mg, 0.199 mmol), and acetonitrile (30 mL) were used to prepare naphthobenzofuran **522**. Purification of the crude material by MPLC (19:1, Hex:EtOAc) provided the pentacyclic benzofuran derivative **522** (11 mg, 0.045 mmol, 67% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (nfom, 1H, *H11*), 7.79 (d, *J* = 8.2 Hz, *H1*), 7.66 (nfom, 1H, *H8*), 7.60 (dd, *J* = 8.2, 7.5 Hz, 1H, *H2*), 7.50–7.43 (m, 3H, *H*9, *H*6, *H*10), 6.82 (d, *J* = 7.5 Hz, 1H, *H3*), and 5.86 (d, *J* = 1.8 Hz, 1H, *H5*).

^{1}H NMR (500 MHz, C_6D_6): 8.06 (ddd, *J* = 7.4, 1.6, 0.8 Hz, 1H, *H11*), 7.68 (dd, *J* = 8.2, 0.5 Hz, 1H, *H1*), 7.51 (ddd, *J* = 8.0, 1.2, 0.7 Hz, *H8*), 7.40 (dd, *J* = 8.2, 7.5 Hz, 1H, *H2*), 7.24 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, *H9*), 7.20 (ddd, *J* = 7.4, 7.4, 1.5 Hz, 1H, *H10*), 6.90 (t, *J* = 1.8 Hz, 1H, *H6*), 6.79 (dd, *J* = 7.6, 0.4 Hz, 1H, *H3*), and 5.86 (d, *J* = 1.9 Hz, 1H, *H5*).

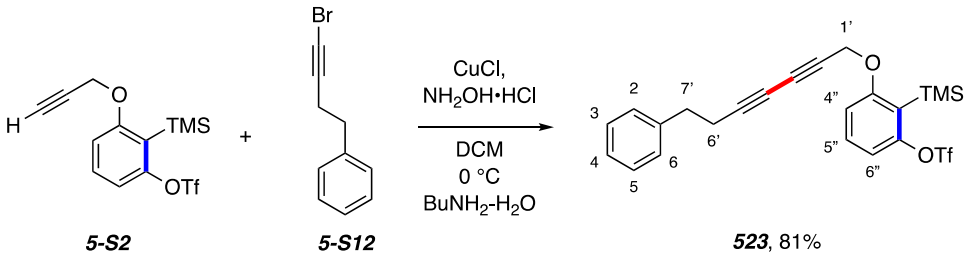
^{13}C NMR (125 MHz, $CDCl_3$): 162.7, 157.4, 156.1, 139.4, 131.5, 127.0, 125.8, 125.4, 124.9, 123.3, 121.7, 115.8, 112.9, 111.8, 102.8, 101.0, and 76.6.

^{13}C NMR (125 MHz, C_6D_6): 163.3, 157.8, 156.5, 139.9, 131.7, 127.3, 126.0, 125.8, 125.3, 123.5, 122.0, 116.0, 113.1, 111.9, 102.8, 101.3, and 76.2.

HMRS (ESI-TOF): Calcd for $C_{17}H_{11}O_2^+$ $[M+H^+]^+$ 247.0754; found 247.0740.

IR (neat): 3067, 2929, 2865, and 1201 cm^{-1}.

3-((7-Phenylhepta-2,4-diyn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (523)



5-S2 ***5-S12*** ***523***, 81%

Following general procedure A, the terminal alkyne **5-S3** (83 mg, 0.24 mmol, 1 equiv), (4-bromobut-3-yn-1-yl)benzene (**5-S12**, 73 mg, 0.35 mmol, 1.5 equiv), CuCl (2.3 mg, 0.024 mmol, 10 mol%), NH_2OH•HCl (4 mg, 0.5 equiv), *n*-butylamine/H_2O (v:v, 30:70, 5 mL), and DCM (5 mL) were used to prepare diyne **523**. Purification of the crude material by MPLC (hexanes:EtOAc 19:1) provided diyne **523** (91 mg, 0.19 mmol, 81%) as a colorless oil.

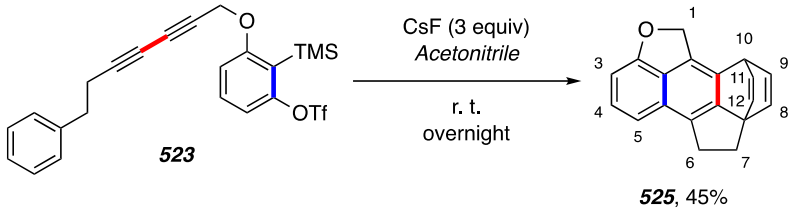
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 8.3, 8.3 Hz, 1H, *H5"*), 7.29 (nfodd, 1H, *J* = 7.5, 7.3 Hz, 2H, *H3* and *H5*), 7.22 (app tt, *J* = 7.4, 1.4 Hz, 1H, *H4*), 7.20–7.18 (nfom, 2H, *H2* and *H6*), 6.99 (dd, *J* = 8.4, 0.8 Hz, 1H, *H6"*), 6.90 (dd, *J* = 8.3, 0.7 Hz, 1H, *H4"*), 4.74 (t, 2H, *J* = 1.0 Hz, *H1"*), 2.84 (t, 2H, *J* = 7.5 Hz, *H7'*), 2.56 (tt, 2H, *J* = 7.6, 1.1 Hz, *H6'*), and 0.38 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 163.4, 154.8, 140.0, 131.7, 128.7, 128.6, 128.5, 126.7, 118.7 (q, $^1J_{C\text{-}F}$ = 320.6 Hz, OSO_2CF_3), 113.7, 110.9, 81.5, 72.7, 69.9, 65.1, 56.8, 34.5, 21.6, and 1.0.

HRMS (ESI-TOF): Calcd for $C_{23}H_{24}F_3O_4SSi^+$ $[M+H^+]^+$ 481.1111; found 481.1106

IR (neat): 3064, 3029, 2954, 2904, 2258, 1416, 1292, 1137, and 824 cm^{-1}.

1,6,7,10-Tetrahydro-7a,10-ethenoaceanthryleno[7,6-bc]furan (525):



Following general procedure C, the diyne **523** (70 mg, 0.146 mmol), CsF (67 mg, 0.437 mmol), and acetonitrile (30 mL) were used to prepare the naphthalene derivative **525**. Purification of the crude material by MPLC (9:1, Hex:EtOAc) provided **525** (17 mg, 0.066 mmol, 45% yield) as a white crystalline solid.

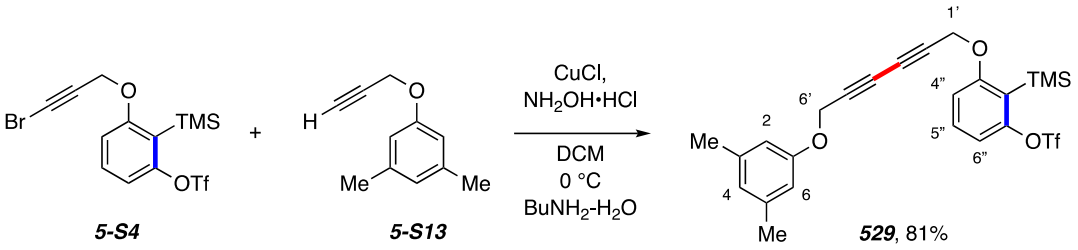
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.2, 7.4 Hz, 1H, *H4*), 7.00 (d, *J* = 8.1 Hz, 1H, *H5*), 6.85 (dd, *J* = 6.5, 1.4 Hz, 2H, *H8* and *H12*), 6.72 (dd, *J* = 6.7, 5.6 Hz, 2H, *H9* and *H11*), 6.63 (d, *J* = 7.5 Hz, 1H, *H3*), 5.72 (t, *J* = 1.6 Hz, 2H, *H1*), 4.94 (tt, *J* = 5.6, 1.3 Hz, 1H, *H10*), 3.41–3.37 (nfom, 2H, H6), and 2.98–2.95 (nfom, 2H, *H7*).

^{13}C NMR (125 MHz, $CDCl_3$): 162.1, 155.3, 146.8, 137.3, 130.8, 129.0, 128.5, 128.1, 127.35, 127.30, 113.1, 100.8, 75.0, 61.2, 46.3, 32.6, and 31.3.

HRMS (ESI-TOF): Calcd for $C_{19}H_{15}O^+$ $[M+H^+]^+$ 259.1117; found 259.1104.

IR (neat): 3053, 2931, 2862, 1611, 1361, and 1235 cm^{-1}.

3-((6-(3,5-Dimethylphenoxy)hexa-2,4-diyn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (529)



Following general procedure A, the terminal alkyne **5-S13** (51 mg, 0.32 mmol, 1 equiv), 3-((3-bromoprop-2-yn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**5-S4**, 150 mg, 0.348 mmol, 1.1 equiv), CuCl (3 mg, 0.032 mmol, 10 mol%), NH_2OH•HCl (6 mg, 0.5 equiv), *n*-butylamine/H_2O (v:v, 30:70, 5 mL), and DCM (5 mL) were used to prepare the diyne **529**. Purification of the crude material by MPLC (hexanes:EtOAc 9:1) provided **529** as a colorless oil.

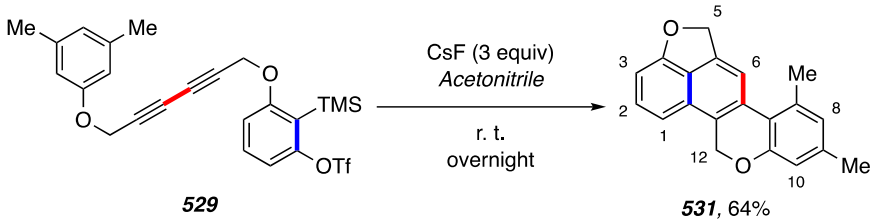
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 8.4, 8.4 Hz, 1H, *H5"*), 7.00 (br d, *J* = 8.4 Hz, 1H, *H6"*), 6.88 (dd, *J* = 8.3, 0.8 Hz, 1H, *H4"*), 6.65 (br s, 1H, *H4*), 6.60 (br s, 2H, *H2* and *H6*), 4.76 (t, 2H, *J* = 1.0 Hz, *H1'*), 4.70 (t, 2H, *J* = 1.0 Hz, *H6'*), 2.29 (br s, 6H, C3*CH*$_3$ and C5*CH*$_3$), and 0.38 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 163.2, 157.6, 154.8, 139.5, 131.7, 123.7, 121.8, 118.7 (q, $^1J_{C\text{-}F}$ = 320.6 Hz, OSO_2CF_3), 113.9, 112.7, 110.8, 75.4, 73.6, 71.7, 70.7, 56.6, 56.2, 21.6, and 1.0.

HRMS (ESI-TOF): Calcd for $C_{24}H_{26}F_3O_5SSi^+$ $[M+H^+]^+$ 511.1217; found 511.1211

IR (neat): 2956, 2920, 2905, 2861, 2157, 1594, 1206, 1138, 1031, and 605 cm^{-1}.

7,9-Dimethyl-5,12-dihydrofuro[4',3',2':4,5]naphtho[1,2-c]chromene (531):



529 ***531***, 64%

Following general procedure C, the diyne **529** (67 mg, 0.13 mmol), CsF (60 mg, 0.39 mmol), and acetonitrile (50 mL) were used to prepare the naphthochromene **531**. Purification of the crude material by MPLC (19:1, Hex:EtOAc) provided **531** (24 mg, 0.083 mmol, 64% yield) as a white solid.

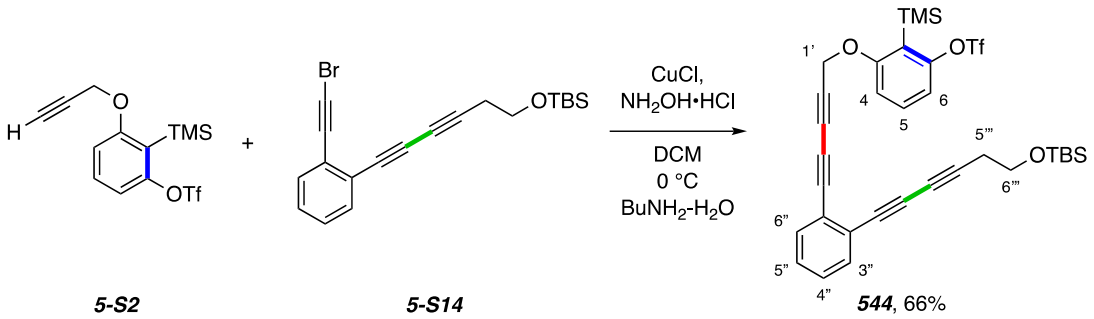
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (t, *J* = 1.7 Hz, 1H, *H6*), 7.42 (dd, *J* = 8.3, 7.5 Hz, 1H, *H2*), 7.23 (d, *J* = 8.3 Hz, 1H, *H1*), 6.79 (br s, 2H, *H8* and *H10*), 6.70 (d, *J* = 7.4 Hz, 1H, *H3*), 5.79 (br s, 2H, *H5*), 5.28 (br s, 2H, *H12*), 2.66 (s, 3H, C7*CH_3*), and 2.33 (s, 3H, C9*CH_3*).

^{13}C NMR (125 MHz, $CDCl_3$): 162.3, 156.5, 139.1, 138.0, 135.0, 131.3, 130.5, 128.1, 127.4, 126.9, 126.1, 122.0, 115.4, 114.0, 111.9, 100.9, 77.3, 65.0, 22.9, and 21.4.

HRMS (ESI-TOF): Calcd for $C_{17}H_{11}O_2^+$ $[M+H^+]^+$ 247.0754; found 247.0740.

IR (neat): 3049, 2974, 2951, 2919, 2862, 2730, 1661, 1465, and 734 cm^{-1}.

3-((5-(2-(6-((*tert*-Butyldimethylsilyl)oxy)hexa-1,3-diyn-1-yl)phenyl)penta-2,4-diyn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (544):



5-S2 ***5-S14*** ***544***, 66%

Following general procedure A, the terminal alkyne **5-S2** (50 mg, 0.14 mmol, 1 equiv), ((6-(2-(bromoethynyl)phenyl)hexa-3,5-diyn-1-yl)oxy)(tert-butyl)dimethylsilane (**5-S14**, 61 mg, 0.16 mmol, 1.1 equiv), CuCl (1.4 mg, 0.014 mmol, 10 mol%), NH_2OH•HCl (3 mg, 0.5 equiv), *n*-butylamine/H_2O (v:v, 30:70, 1 mL), and DCM (1 mL) were used to prepare tetrayne **544**. Purification of the crude material by MPLC (hexanes:EtOAc, 19:1) provided tetrayne **544** (62 mg, 0.10 mmol, 66%) as a colorless oil.

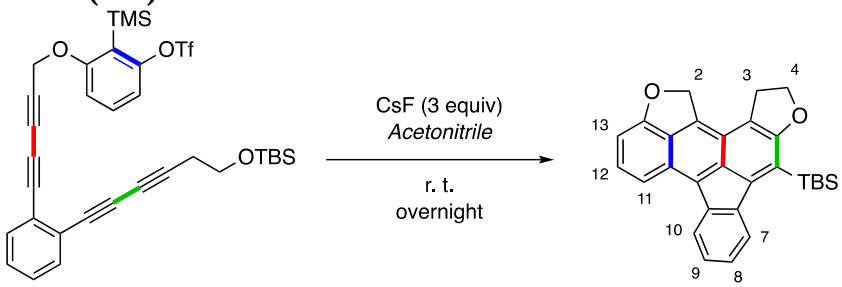
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.48 (nfom, 1H, *H3''* or *H6'*), 7.41 (dd, *J* = 8.4, 8.4 Hz, 1H, *H5*), 7.47–7.46 (nfom, 1H, *H3''* or *H6'*), 7.32–7.26 (m, 2H, *H5''* and *H4''*), 7.01 (d, *J* = 8.4 Hz, 1H, *H6*), 6.98 (dd, *J* = 8.3, 0.7 Hz, 1H, *H4*), 4.88 (s, 2H, *H1'*), 3.80 (t, *J* = 7.0 Hz, 2H, *H6'''*), 2.60 (t, *J* = 7.0 Hz, 2H, *H5'''*), 0.91 [s, 9H, $OSi(CH_3)_2(CH_3)_3$], 0.41 [s, 9H, $Si(CH_3)_3$], and 0.10 [s, 6H, $OSi(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4, 154.9, 133.5 (2x), 131.8, 129.3, 128.7, 125.9, 124.7, 121.8, 119.0 (q, $^1J_{C\text{-}F}$ = 320.6 Hz, OSO_2CF_3), 113.9, 110.9, 83.6, 78.7, 77.7, 77.2, 76.8, 72.8, 72.4, 66.3, 61.5, 57.0, 26.0, 24.3, 18.5, 1.1, and -5.1.

HRMS (ESI-TOF): Calcd for $C_{33}H_{38}F_3O_5SSi_2^+$ $[M+H^+]^+$ 659.1925; found 659.1907.

IR (neat): 3063, 2955, 2900, 2858, 2356, 2239, 1416, 1209, and 735 cm^{-1}.

***tert*-Butyl(3,4-dihydro-2H-benzo[1,2]aceanthryleno[4,5-b:7,6-b'c']difuran-6-yl)dimethylsilane (546):**



544 ***546*, 39%**

Following general procedure C, the tetrayne **544** (40 mg, 0.060 mmol, 1 equiv), CsF (28 mg, 0.180 mmol, 3 equiv), and acetonitrile (32 mL) were used to prepare the anthracene derivative ***##***. Purification of the crude material by MPLC (9:1, Hex:EtOAc) provided anthracene **546** (10 mg, 39% yield, 0.023 mmol) as a brick red solid.

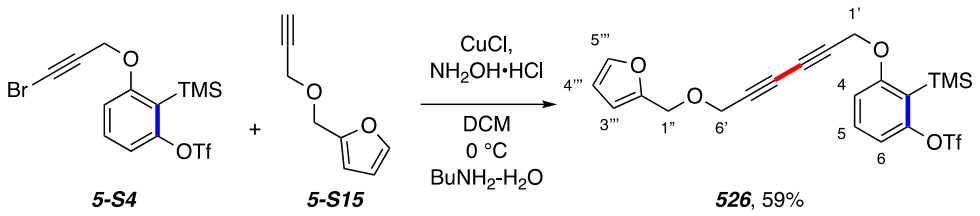
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.192 (dd, *J* = 7.9, 1.2 Hz, 1H, *H7* or *H10*), 8.190 (dd, *J* = 7.9, 1.2 Hz, 1H, *H7* or *H10*), 7.86 (d, *J* = 8.7 Hz, 1H, *H11*), 7.46 (dd, *J* = 8.7, 7.3 Hz, 1H, *H12*), 7.40 (ddd, *J* = 7.5, 7.6, 1.3 Hz, 1H, *H8* or *H9*), 7.29 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, *H8* or *H9*), 6.65 (d, *J* = 7.2 Hz, 1H, *H13*), 6.18 (s, 2H, *H2*), 4.75 (t, *J* = 9.2 Hz, 2H, *H4*), 3.59 (t, *J* = 9.1 Hz, 2H, *H3*), 1.15 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], and 0.58 [s, 6H, $Si(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 164.0, 146.6, 141.2, 139.2, 133.0, 131.6, 130.6, 130.5, 129.2, 127.6, 125.6, 125.2, 124.7, 124.6, 123.0, 119.6, 115.9, 113.7, 98.7, 77.3, 69.3, 29.6, 28.0, 26.0, and 0.43.

HRMS (ESI-TOF): Calcd for $C_{33}H_{38}F_3O_5SSi_2^+$ $[M–H^–]^+$ 435.1775; found 435.1770.

IR (neat): 3051, 2952, 2928, 2894, 2855, 1714, 1461, 1258, and 734 cm^{-1}.

3-((6-(Furan-2-ylmethoxy)hexa-2,4-diyn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (526)



Following general procedure A, the terminal alkyne **5-S15** (22 mg, 0.156 mmol, 1 equiv), 3-((3-bromoprop-2-yn-1-yl)oxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**5-S4**, 74 mg, 0.172 mmol, 1.1 equiv), CuCl (1.5 mg, 0.016 mmol, 10 mol%), NH_2OH•HCl (3 mg, 0.5 equiv), *n*-butylamine/H_2O (v:v, 30:70, 1 mL), and DCM (1 mL) were used to prepare the diyne **526**. Purification of the crude material by MPLC (hexanes:EtOAc, 19:1) provided **526** (45 mg, 0.093 mmol, 59%) as a colorless oil.

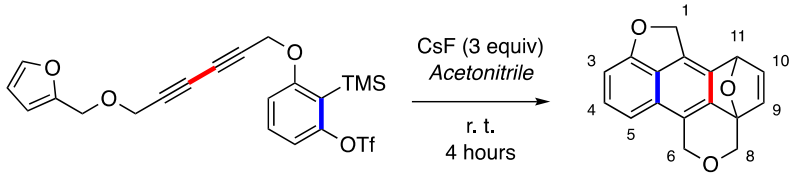
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 1.9, 0.9 Hz, 1H, *H5'''*), 7.42 (dd, *J* = 8.3, 8.3 Hz, 1H, *H5*), 7.03 (br d, *J* = 8.4 Hz, 1H, *H6*), 6.94 (dd, *J* = 8.3, 0.7 Hz, 1H, *H4*), 6.40 (dd, *J* = 3.2, 0.9 Hz, 1H, *H3'''*), 6.37 (dd, *J* = 3.3, 1.9 Hz, 1H, *H4'''*), 4.82 (t, 2H, *J* = 1.0 Hz, *H1'*), 4.56 (s, 2H, *H1''*), 4.25 (t, 2H, *J* = 1.0 Hz, *H6'*), and 0.41 [s, 9H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 154.8, 150.6, 143.4, 131.7, 121.8, 118.7 (q, $^1J_{C\text{-}F}$ = 320.6 Hz, OSO_2CF_3), 113.9, 110.8, 110.6, 110.4, 75.6, 73.2, 71.8, 70.4, 63.6, 57.3, 56.7, and 1.1.

HRMS (ESI-TOF): Calcd for $C_{21}H_{22}F_3O_6SSi^+$ $[M+H^+]^+$ 487.0853; found 487.0849.

IR (neat): 2958, 2904, 1731, 1595, 1416, 1206, 842, and 607 cm^{-1}.

1,11-Dihydro-6H,8H-8a,11-epoxyfuro[4',3',2':4,5]naphtho[1,2,3-de]isochromene (##):



526 ***528***, 85%

Following general procedure C, the diyne **526** (37 mg, 0.076 mmol), CsF (35 mg, 0.228 mmol), and acetonitrile (40 mL) were used to prepare the isochromene derivative **528**. Purification of the crude material by MPLC (3:1, Hex:EtOAc) provided **528** (17 mg, 0.064 mmol, 85% yield) as a pale yellow oil.

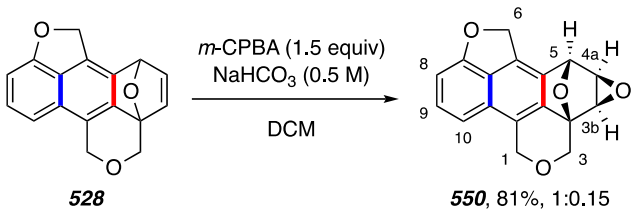
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 8.2, 7.7 Hz, 1H, *H4*), 7.12 (d, *J* = 5.6 Hz, 1H, *H9*), 7.00 (ddd, *J* = 5.6, 2.0, 1.1 Hz, 1H, *H10*), 6.98 (d, *J* = 8.4 Hz, 1H, *H5*), 6.77 (d, *J* = 7.5 Hz, 1H, *H3*), 5.79 (d, *J* = 2.0 Hz, 1H, *H11*), 5.73 (ddd, *J* = 14.9, 1.2, 1.2 Hz, 1H, C1*H*$_a$H$_b$), 5.65 (ddd, *J* = 14.9, 1.2, 1.2 Hz, 1H, C1H$_a$*H*$_b$), 5.12 (ddd, *J* = 15.0, 1.2, 1.2 Hz, 1H, C8*H*$_a$H$_b$), 4.82 (ddd, *J* = 15.1, 1.3, 1.3 Hz, 1H, C8H$_a$*H*$_b$), 4.72 (d, *J* = 11.3 Hz, 1H, C6*H*$_a$H$_b$), and 4.00 (dd, *J* = 11.3, 1.2 Hz, 1H, C6H$_a$*H*$_b$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 143.2, 142.6, 141.1, 132.8, 130.3, 128.8, 127.1, 126.5, 122.9, 112.0, 102.9, 83.4, 80.9, 75.1, 66.7, and 64.7.

HRMS (ESI-TOF): Calcd for $C_{17}H_{13}O_3^+$ $[M+H^+]^+$ 265.0859; found 265.0801 (minor ion), Calcd for $C_{17}H_{11}O_3^+$ $[M–H^-]^+$ 263.0703; found 263.0689 (major ion).

IR (neat): 3064, 2959, 2926, 2853, 1712, 1619, and 1264 cm^{-1}.

Tetrahydro-1H,3H-3a,5-epoxyfuro[4',3',2':4,5]naphtho[1,2,3-de]oxireno[2,3-h]isochromene (550):



To a suspension of the benzoxanorbornadiene derivative **528** (7 mg, 1.0 equiv, 0.0265 mmol) in DCM (1 mL) was added *m*CPBA (7 mg, 1.5 equiv, 0.400 mmol) and sat. $NaHCO_3$ solution (53 μL, 0.5 M). The mixture was stirred overnight, and the completion of the reaction was confirmed by the crude GCMS analysis. The crude product was purified by passage through a small silica gel plug (pure EtOAc) followed by further purification by medium pressure liquid chromatography (2:1, Hexanes: EtOAc) to give **550** (6 mg, 81% overall), a transparent oil, as a coeluting mixture of diastereomers (1:0.15 ratio).

Data for the major isomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 8.2, 7.6 Hz, 1H, *H9*), 7.05 (d, *J* = 8.2 Hz, 1H, *H10*), 6.82 (d, *J* = 7.5 Hz, 1H, *H8*), 5.75 (ddd, *J* = 15.3, 1.4, 1.4 Hz, 1H, C6H_aH$_b$), 5.73 (ddd, *J* = 15.3, 1.3, 1.3 Hz, 1H, C6H$_a$$H_b$), 5.33 (s, 1H, *H5*), 5.15 (ddd, *J* = 15.3, 1.2, 1.2 Hz, 1H, C1H_aH$_b$), 4.81 (ddd, *J* = 15.3, 1.6, 1.6 Hz, 1H, C1H$_a$$H_b$), 4.73 (d, *J* = 11.3 Hz, 1H, C1*Ha*Hb), 3.90 (d, *J* = 11.3 Hz, 1H, C1Ha*Hb*), 3.85 (d, *J* = 3.5 Hz, 1H, *H3b* or *H4a*), and 3.72 (d, *J* = 3.5 Hz, 1H, *H3b* or *H4a*).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 142.2, 131.0, 130.8, 130.3, 128.4, 127.1, 124.7, 111.0, 103.0, 78.1, 75.1, 65.0, 64.4, 60.6, 54.0, and 53.2.

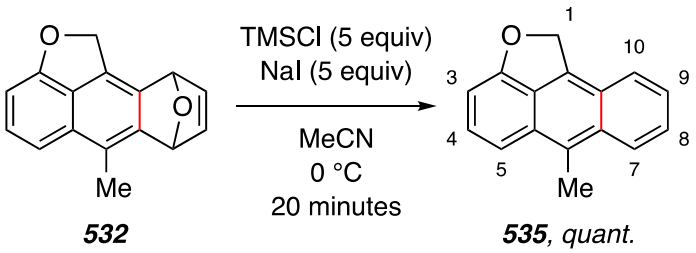
HRMS (ESI-TOF): Calcd for $C_{17}H_{13}O_4^+$ $[M+H^+]^+$ 281.0808; found 281.0797.

^{1}H NMR identifiable, unique resonances attributable to the minor diastereomer (500 MHz, $CDCl_3$):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 7.9, 7.9 Hz, 1H, *H9*), 6.66 (d, *J* = 8.0 Hz, 1H, *H8*), 5.83 (ddd, *J* = 15.9, 1.3, 1.3 Hz, 1H, C6H_aH$_b$), 5.69 (ddd, *J* = 15.2, 1.2, 1.2 Hz, 1H, C6H$_a$$H_b$), 5.30 (s, 1H, *H5*), 4.66 (d, *J* = 11.2 Hz, 1H, C3*Ha*Hb), 3.86 (d, *J* = 3.6 Hz, 1H, *H3b* or *H4a*), and 3.71 (d, *J* = 3.6 Hz, 1H, *H3b* or *H4a*).

IR (neat): 3060, 2958, 2854, 1783, 1722, 1676, 1620, 1261, and 1064 cm^{-1}.

6-Methyl-1H-anthra[1,9-bc]furan (535):



532 ***535**, quant.*

To a suspension of the benzoxanorbornadiene derivative **532** (6 mg, 1.0 equiv, 0.0254 mmol) and NaI (19 mg, 5.0 equiv, 0.127 mmol) in dry MeCN (0.03 M) at 0 ºC was added TMSCl (16 μL, 5.0 equiv, 0.127 mmol) dropwise by wiretrol. The mixture was stirred at 0 ºC and the reaction progress was monitored by GCMS analysis of an aliquot taken after ~30 minutes. The orange-brown suspension was quenched by dropwise addition of an aqueous $Na_2S_2O_3$ solution at 0 ºC. The resulting mixture was extracted three times with EtOAc. The organic extracts were combined, washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by passage through a small silica gel plug (3:1, Hexanes: EtOAc) followed by further purification by medium pressure liquid chromatography (19:1, Hexanes: EtOAc) to afford the anthracene derivative **535** (6 mg, quant.) as a white solid.

Data for anthracene adduct (535):

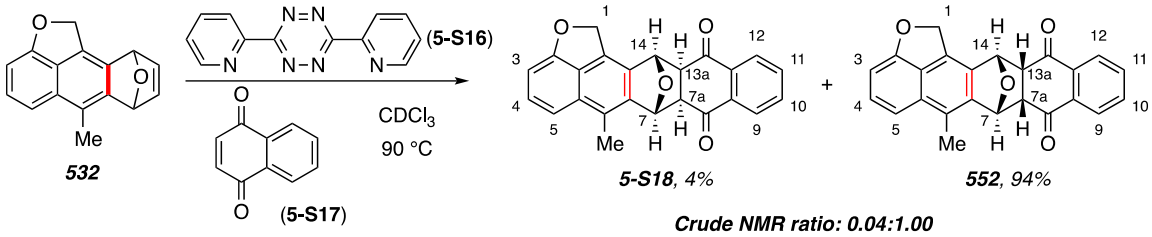
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (ddd, *J* = 8.8, 1.2, 0.9 Hz , 1H, *H10* or *H7*), 7.78 (dd, *J* = 8.3, 1.3, 0.9 Hz, 1H, *H10* or *H7*), 7.55 (ddd, *J* = 8.0, 6.6, 1.5 Hz, 1H, *H8* or *H9*), 7.50 (ddd, *J* = 8.2, 6.6, 1.3 Hz, 1H, *H8* or *H9*), 7.49 (dd, *J* = 8.8, 0.5 Hz, 1H, *H5*), 7.40 (dd, *J* = 8.2, 7.1 Hz, 1H, *H4*), 6.62 (d, *J* = 7.0 Hz, 1H, *H3*), 6.15 (br s, 2H, *H1*), and 2.98 (t, *J* = 1.7 Hz, 3H, Ar*CH*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 132.7, 132.3, 129.1, 129.0, 127.9, 127.7, 126.2, 125.6, 124.9, 124.9, 124.1, 113.5, 97.6, 77.4, and 13.7.

HRMS (ESI-TOF): Calcd for $C_{16}H_{13}O^+$ $[M+H^+]^+$ 221.0961; found 221.0945.

IR (neat): 3059, 3033, 2921, 2858, 1780, 1630, 1391, 740, and 728 cm^{-1}.

(±)-*exo*-(7R,7aR,13aS,14S)-6-Methyl-7,7a,13a,14-tetrahydro-1H-7,14-epoxypentaceno[1,14-bc]furan-8,13-dione (5-S18) and (±)-*endo*-(7R,7aS,13aR,14S)-6-Methyl-7,7a,13a,14-tetrahydro-1H-7,14-epoxypentaceno[1,14-bc]furan-8,13-dione (552)



A solution of the benzoxanorbornadiene derivative **532** (15 mg, 0.0635 mmol, 1 equiv), 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**5-S16**, 23 mg, 0.095 mmol, 1.5 equiv), and naphthalene-1,4-dione (**5-S17**, 15 mg, 0.095 mmol, 1.5 equiv) in $CDCl_3$ (4 mL, 0.016 M) was heated in an 90 ºC bath in a screw-capped culture tube. After 2 hours, the reaction was judged to be complete by TLC. The reaction mixture was then cooled and passed through a plug of silica (1:1, Hex: EtOAc). The residue was purified by MPLC (3:1, Hex:EtOAc) to give, in order of elution, the exo-isomer **5-S18** (1 mg, 0.003 mmol, 4%) and the endo-isomer **552** (22 mg, 0.060 mmol, 94%)

Data for faster eluting, minor diastereomer, 5-S18:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (m, 2H, Ar*H9* and Ar*H12*), 7.81 (m, 2H, Ar*H10* and Ar*H11*), 7.45 (dd, *J* = 8.2, 7.3 Hz, 1H, *H4*), 7.33 (d, *J* = 8.2 Hz, 1H, *H5*), 6.79 (d, *J* = 7.3 Hz, 1H, *H3*), 6.03 (br s, 1H, *H7* or *H14*), 5.88 (br s, 1H, *H7* or *H14*), 5.83 (d, *J* = 15.5 Hz, 1H, C1*Ha*Hb), 5.82 (d, *J* = 15.5 Hz, 1H, C1Ha*Hb*), 3.19 (d, *J* = 8.6 Hz, 1H, *H13a* or *H7a*), 3.17 (d, *J* = 8.7 Hz, 1H, *H13a* or *H7a*), and 2.71 (s, 3H, ArCH_3).

HRMS (ESI-TOF): Calcd for $C_{24}H_{17}O_4^+$ $[M+H^+]^+$ 369.1121; found 369.1110.

Data for slower eluting, major diastereomer, 552:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62–7.57 (two overlapping nfoms, 2H, Ar*H9* and Ar*H12*), 7.30–7.25 (two overlapping nfoms, 2H, Ar*H10* and Ar*H11*), 7.23 (dd, *J* = 8.1, 7.6 Hz, 1H, *H4*), 7.01 (d, *J* = 8.4 Hz, 1H, *H5*), 6.58 (d, *J* = 7.4 Hz, 1H, *H3*), 6.12 (nfom, *H7* or *H14*), 5.94 (nfom, *H7* or *H14*), 5.67 (d, *J* = 15.4 Hz, 1H, C1H_aHb), 5.38 (d, *J* = 15.3 Hz, 1H, C1HaH_b), 3.87 (nfom, 2H, *H7a* and *H13a*), and 2.40 (s, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 193.9, 161.7, 141.0, 134.0, 134.0, 133.8, 133.6, 131.0, 129.6, 129.4, 128.5, 127.7, 125.8, 125.6, 124.1, 113.2, 101.7, 81.8, 81.7, 75.4, 50.4, 50.0, and 14.2.

HRMS (ESI-TOF): Calcd for $C_{24}H_{17}O_4^+$ $[M+H^+]^+$ 369.1121; found 369.1098.

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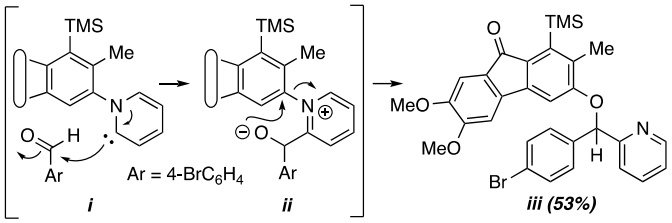
and **ii**, a pathway involving final ipso attack as observed and suggested for pyridine by Biju and coworkers.[57(c)]



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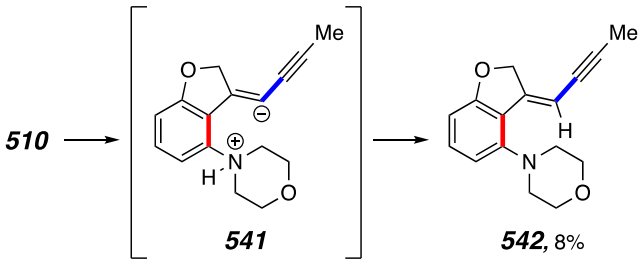
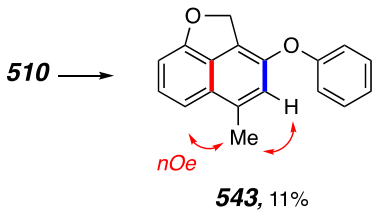
101. When morpholine was used as a trapping agent, along with the two expected naphthyne and benzyne adducts, enyne **542** was also isolated, presumably by way of intermediate **541**.



102. Naphthyne and benzyne adducts were accompanied with the minor naphthyne **543** in 11% yield. The minor benzyne was adduct not observed.



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