A Biomimetic Approach to Okilactomycin and Chrolactomycin
and
The Hexadehydro-Diels–Alder (HDDA) Reaction

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So many things could have happened differently in the past 27 years and if any of them had, my career would have taken totally different pathways. I am so glad to be where I am today and need to acknowledge many people that made me here.

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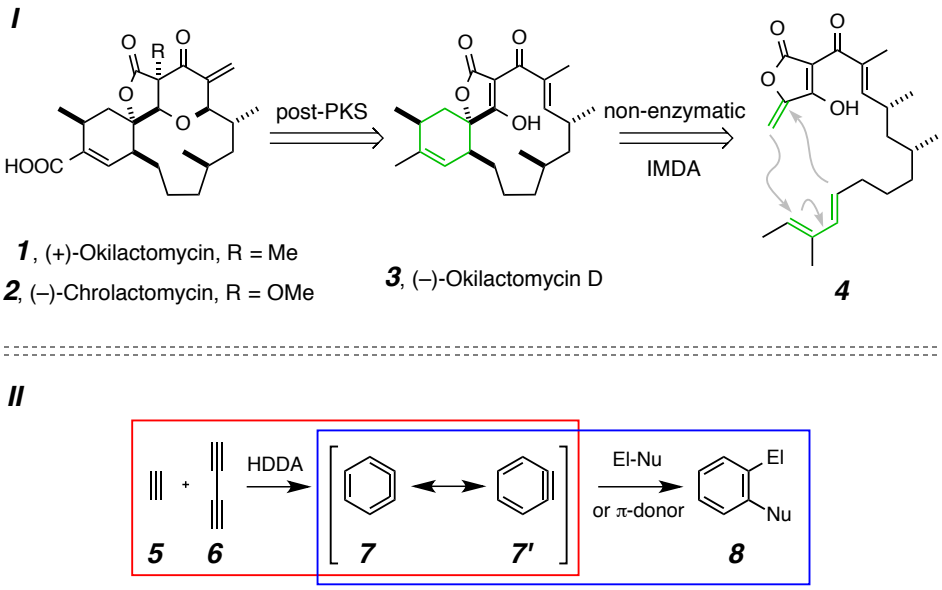
Dedication

This dissertation is dedicated to my family—my spiritual support.

Abstract



We hypothesized that spirotetronate (+)-okilactomycin (**1**) and (–)-chrolactomycin (**2**) are biogenetically derived from a common intermediate, (–)-okilactomycin D (**3**), which in turn arises via an intramolecular Diels-Alder (IMDA) reaction from the linear precursor **4**. Guided by this hypothesis, we have achieved an efficient synthesis of okilactomycin D by a route featuring a substrate-controlled, diastereoselective intramolecular Diels–Alder (IMDA) reaction of an analogue of polyene **4**. The assigned absolute configuration of (−)-**3** was confirmed. Conversion of (−)-**3** toward **1** and **2** has also been explored.

ortho-Benzyne (1,2-didehydrobenzene, **7** or **7'**) is one of the oldest, most interesting, most useful and most well-studied of all reactive intermediates in chemistry. The multifaceted and efficient reactions of benzynes with suitable trapping reagents (**7**→**8**) have long been employed in the service of synthetic chemistry to give products that are

used as pharmaceuticals, agrochemicals, dyes, polymers, and other fine chemicals. An accidental observation made in this laboratory led us to establish an unorthodox yet general aryne-generating strategy—the hexadehydro-Diels–Alder (HDDA) reaction. This enabling transformation, which produces the highly reactive benzyne intermediate from the thermal [4+2] cycloisomerization of a 1,3-diyne (like **6**) with a 'diynophile' (like **5**) in the absence of any metals or reagents, has allowed us to uncover some unprecedented aryne reactivities.

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List of Abbreviations

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
Adm	admantyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
ATA	acyltetronic acid
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre

CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
conc.	concentrated
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutyl aluminum hydride
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dr	diastereomeric ratio
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
El	electrophile
E	trans (entgegen) olefin geometry

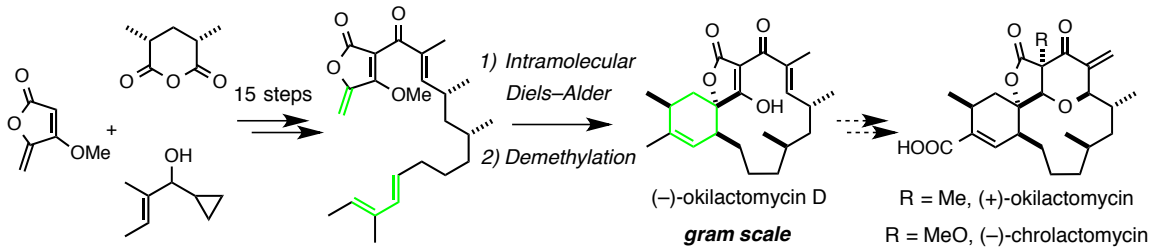
EC_{50}	median effective concentration (50%)
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
g	gram(s)
h	hour(s)
^1H	proton
[H]	reduction
HDDA	hexadehydro-Diels–Alder
HMDS	hexamethyldisilamide or hexamethyldisilazide
*h*ν	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
KHMDS	potassium bis(trimethylsilyl)amide
L	liter or neutral ligand
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide

LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular seives
m/z	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
o	ortho
[O]	oxidation
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl

pH	hydrogen ion concentration in aqueous solution
Piv	pivalate
p*Ka*	acid dissociation constant
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
q	quartet
R	alkyl group
R	rectus
RCM	ring-closing metathesis
s	singlet or seconds
S	sinister
sat.	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TDDA	tetradehydro-Diels–Alder
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography

TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tol	tolyl
Tr	triphenylmethane (trityl)
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry your dissertation

A Biomimetic Approach to (+)-Okilactomycin and (-)-Chrolactomycin

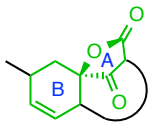


CHAPTER I. INTRODUCTION AND BACKGROUND

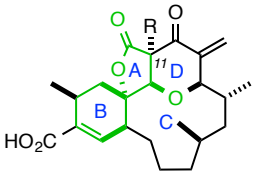
1.1. Historical background of okilactomycins

The spirotetronate polyketides (e.g., chlorothricolides, kijanimicin, and abyssomicins) comprise a class of natural product compounds that are characterized by the presence of a five-membered tetronic acid moiety (ring A) spiro-linked to a cyclohexene ring (ring B, cf. **1001**, Figure 1.1).[1] Their biological activities (which include antitumor,[2] antibacterial,[3] and cholesterol biosynthesis inhibition,[4]) coupled with unusual architectures render them interesting targets for total synthesis studies.

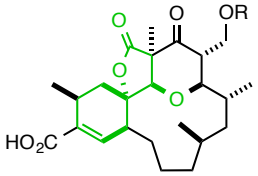
Figure 1.1| Structures of (+)-okilactomycin and (-)-chrolactomycin.



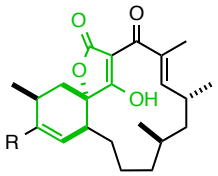
1001 substructure common to many spirotetronates



1002 R = Me, (+)-okilactomycin
1003 R = MeO, (–)-chrolactomycin



1004 R = H, (–)-okilactomycin A
1005 R = 2,3-dihydroxypropyl (–)-okilactomycin B



1006 R = COOH, (–)-okilactomycin C
1007 R = Me, (–)-okilactomycin D

[1] Kelly, W. L. Intramolecular cyclizations of polyketide biosynthesis: mining for a "Diels–Alderase"? *Org. Biomol. Chem.* **2008**, *6*, 4483–4493.

[2] Kang, M; Jones, B. D.; Mandel, A. L.; Hammons, J. C.; DiPasquale, A. G.; Rheingold, A. L.; La Clair, J. J.; Burkart, M. D. Isolation, structure elucidation, and antitumor activity of spirohexenolides A and B. *J. Org. Chem.* **2009**, *74*, 9054–9061.

[3] Igarashi, Y.; Ogura, H.; Furihata, K.; Oku, N.; Indananda, C.; Thanmchaipenet, A. Maklamicin, an antibacterial polyketide from an endophytic *Micromonospora* sp.. *J. Nat. Prod.* **2011**, *74*, 670–674.

[4] Kawashima, A.; Nakamura, Y.; Ohta, Y.; Akama, T.; Yamagishi, M.; Hanada, K. New cholesterol biosynthesis inhibitors MC-031 (O-demethylchlorothricin), -032 (O-demethylhydroxychlorothricin), -033 and -034. *J. Antibiot.* **1992**, *45,* 207–212.

The okilactomycins (**1002-1007**, Figure 1.1), a subclass of spirotetronates, contain either a tri- or tetracyclic skeleton. In 1987, okilactomycin (**1002**) was isolated and structurally characterized by Imai and co-workers from a bioactive filtrate produced by *Streptomyces griseoflavus*, obtained from a soil sample on the island of Zamami, Japan.[5] Its structure (**1002**, Figure 1.1), initially assigned by a combination of spectroscopic methods, contains a unique 13-membered ring (ring C) embedded with a 2,6-*cis*-tetrahydro-γ-pyrone moiety (ring D), a highly functionalized cyclohexene ring (ring B), and a five-membered lactone (ring A). Single-crystal X-ray analysis confirmed its connectivity and relative configuration. The absolute configuration, however, was undefined until Smith's total synthesis of (+)-okilactomycin.[6] In 2001 Yamashita and co-workers described the isolation of the structurally related chrolactomycin (**1003**) from *Streptomyces* sp. 569N-3.[7] Structurally, (–)-chrolactomycin differs from (+)-okilactomycin only by a *C-11* methoxy group versus a methyl group (**1002** vs. **1003**, Figure 1.1). Both of the two compounds have interesting biological activities: **1002** and **1003** showed modest antimicrobial activity against Gram-positive cells; compound **1002** displayed significant cytotoxicity against lymphoid leukemia cells (IC_{50} = 0.037 μM) and leukemia P388 cells (IC_{50} = 0.09 μM); compound **1003** exhibited antiproliferative

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5 a) Imai, H.; K. Suzuki, M.; Morioka, Y.; Numasaki, S.; Kadota, K.; Nagai, T.; Sato, M.; Iwanami, T. Okilactomycin, a novel antibiotic produced by a *Streptomyces* species. I. Taxonomy, fermentation, isolation and characterization. *J. Antibiot.* **1987**, *40*, 1475-1482. b) Imai, H.; H. Kaniwa, T. Tokunaga, S. Fujita, T. Furuya, H. Matsumoto & M. Shimizu: Okilactomycin, a novel antibiotic produced by a *Streptomyces* species. II. Structure determination. *J. Antibiot.* **1987**, *40*, 1483-1489.

6 a) Smith, A. B.; Basu, K.; Bosanac, T. Total synthesis of (–)-okilactomycin. *J. Am. Chem. Soc.* **2007**, *129*, 14872-14874. b) Smith, A. B., Bosanac, T.; Basu, K. Evolution of the total synthesis of (–)-okilactomycin exploiting a tandem oxy-Cope rearrangement/oxidation, a Petasis-Ferrier union/rearrangement, and ring-closing metathesis. *J. Am. Chem. Soc.* **2009**, *131*, 2348–2358.

7 Nakai, R.; Kakita, S.; Asai, A.; Chiba, S.; Akinaga, S.; Mizukami, T.; Yamashita, Y. Chrolactomycin, a novel antitumor antibiotic produced by *Streptomyces* sp.. *J. Antibiot.* **2001**, *54*, 836-839.

activity against several human tumor cell lines with IC_{50} values ranging from 0.45 μM to 1.6 μM.

In 2009 Singh et al.[8] reported four additional members of this class—namely, okilactomycins A, B, C, and D (**1004**–**1007**) [along with okilactomycin (**1002**)] from the bacterium *Streptomyces scabrisporus*. Whereas congeners **1006** and **1007** contain an intact acyltetronic acid (ATA) structural subunit,[9] compounds **1002**, **1004**, and **1005** have a modified tetronate moiety. From the perspectives of bioactivities, **1004-1007** displayed weak to modest antimicrobial activities against Gram-positive bacteria. Interestingly, all of these compounds exhibited preferential inhibition of RNA synthesis over DNA or protein synthesis.

[8] Zhang, C.; Ondeyka, J.; Zink, D.; Basilio, A.; Vicente, F.; Salazar, O.; Genilloud, O.; Dorso, K.; Motyl, M.; Byrne, K.; Singh, S. Discovery of okilactomycin and congeners from *Streptomyces scabrisporus* by antisense differential sensitivity assay targeting ribosomal protein S4. *J. Antibiot.* **2009**, *62*, 55-61.

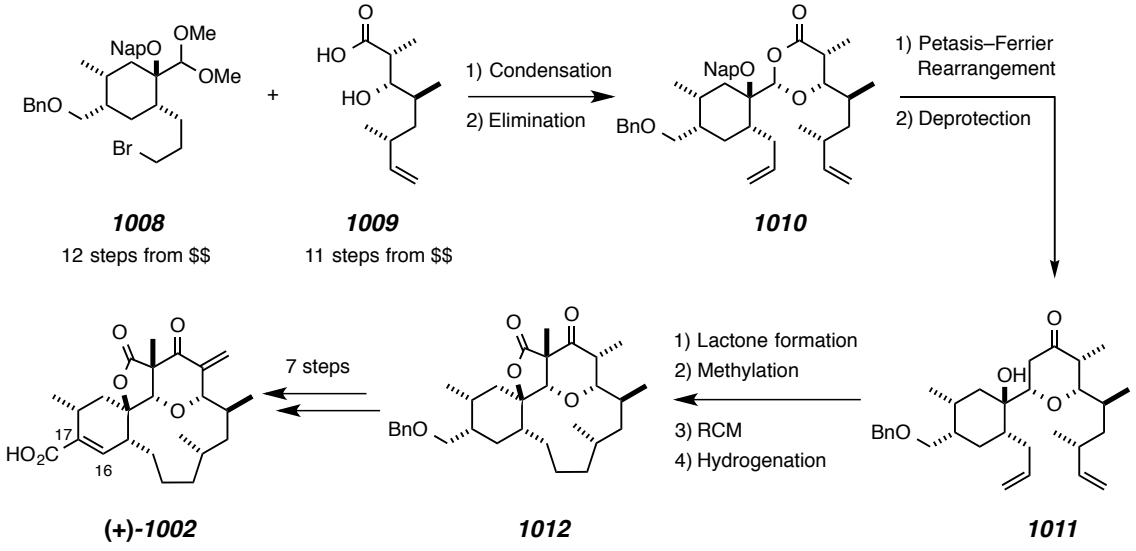
[9] The structure for each of the compounds containing a free acyltetronic acid (ATA) (i.e., **6**, **7**, or **8**) is arbitrarily (and for convenience) portrayed as an endocyclic enol; an internally hydrogen-bonded variant of that endocyclic enol (a rotamer about the C10–C11 bond) or *E*- or *Z*-exocyclic enols are also possible.

1.2 Previous studies directed to the total synthesis of okilactomycins

Since the isolation and structural elucidation of okilactomycin (**1002**) was first reported 26 years ago, several groups have pursued the total synthesis of this natural product with different strategies, culminating in two completed syntheses of okilactomycin and confirmation of its absolute configuration.

In 2009, the Smith[6] group completed the first total synthesis of (+)-okilactomycin [(+)-**1002**], the antipode of the naturally occurring product. Smith's synthesis started from the preparation of functionalized cyclohexane **1008** and β-hydroxy carboxylic acid **1009** (Scheme 1.1). Transacetalyation between **1008** and **1009** furnished dioxanone **1010**, the substrate for the key Petasis[10]–Ferrier[11] union/rearrangement sequence.

Scheme 1.1| Smith's total synthesis of (-)-okilactomycin



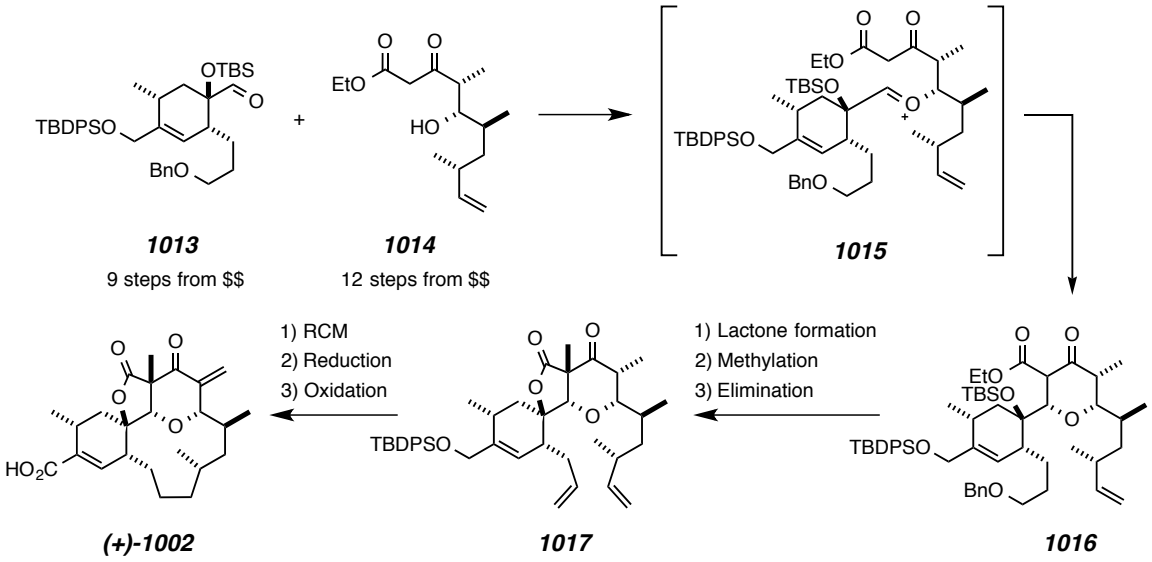
This union/rearrangement process, albeit proceeding in modest yield, gave the tetrahydropyranone intermediate **1011** in a highly diastereoselective fashion. The

[10] Petasis, N. A.; Bzowej, E. I. Titanium-mediated carbonyl olefinations. 1. Methylenations of carbonyl compounds with dimethyltitanocene. *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.

[11] Ferrier, R. J. Unstaturated carbohydrates. Part 21. A carboxylic ring closure of a hex-5-enopyranoside derivative. *J. Chem. Soc.*, *Perkin Trans. 1*, **1979**, 1455-1458.

following carbonylation, methylation, and lactone formation, ring-closing metathesis (RCM), and hydrogenation sequence delivered compound **1012**, which contains all the carbon atoms and stereocenters of compound **1002**. It might be surprising that one pitfall of this synthesis is the conversion of **1012** to **1002**. Due to the difficulty of forming the C16/C17 double bond in **1002**, the authors in the end had to resort to a 7-step, low-yielding sequence to finish their total synthesis of (+)-**1002** from **1012**. This synthesis proceeds with 29 longest linear steps with an overall yield of 0.7%. This synthesis also confirmed the absolute configuration of naturally occurring (–)-okilactomycin.

Scheme 1.2| Scheidt's total synthesis of (-)-okilactomycin



Later in 2011, Scheidt's group[12] reported a different approach to the total synthesis of (–)-okilactomycin. This strategy (Scheme 1.2) capitalized on a Prins union/cyclization cascade between aldehyde **1013** and alcohol **1014**. Pyranone **1016** was formed in a highly diastereoselective fashion via the intermediacy of oxonium **1015**. The following

[12] Tenenbaum, J. M.; Morris, W. J.; Custar, D. W.; Scheidt, K. A. Synthesis of (–)-okilactomycin by a Prins-type fragment-assembly strategy. *Angew. Chem., Int. Ed.* **2011**, *50*, 1-5.

modifications, which included lactone formation, methylation, and elimination, afforded the key intermediate **1017**. Diene **1017** underwent a RCM reaction similar to the one used in Smith's synthesis, giving (–)-**1002** after common functional group manipulations.

Besides the aforementioned efforts, the Paquette[13] and the Rovis group[14] have also pursued studies to the total synthesis of okilactomycin. In fact, the most relevant to my studies described here is the model study reported by Takeda and Yoshii,[15] which will be discussed in more detail in section **2.2**.

[13] a) Paquette, L.A.; Boulet, S.L. Toward a total synthesis of okilactomycin. 1. A direct, enantiocontrolled route to the western sector. *Synthesis*. **2002**, 888-894. b) Paquette, L.A.; Boulet, S.L. Toward a total synthesis of okilactomycin. 2. A metathesis-based approach to the heavily functionalized cyclohexane ring. *Synthesis*. **2002**, 895-900.

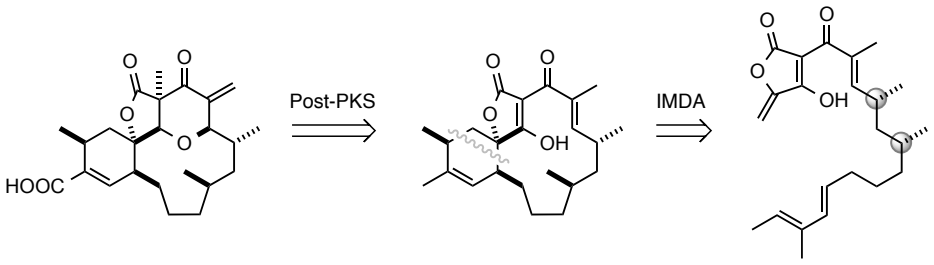
[14] Wheeler, P. A. M. *Catalytically generated acyl triazoliums as versatile acylating reagents and progress toward the total synthesis of okilactomycin.* Ph.D. dissertation, Colorado State University. U.S. ProQuest/UMI. (Publication No. 3565470.)

[15] Takeda, K.; Shimotani, A.; Yoshii, E. A. Lewis acid mediated intramolecular [2+2] cycloaddtion of 3-(9-methylundeca-7,9-dienyl)-9-methylene-2,8-dioxabicyclo [4.3.0]nonane-5,7-dione. *Heterocycles* **1992**, *34*, 2259-2261.

1.3 Biosynthetic hypothesis/synthetic plan of okilactomycins

The unique architecture or the interesting biological activities of okilactomycins alone justify synthetic studies. Nonetheless, what further piqued our interest in this family of natural products is the possible biogenesis of these compounds; how are their unique structural architectures synthesized in Nature? Close scrutiny of the structures of the okilactomycins led us to consider that okilactomycin (**1002**) and other more advanced natural products in this family all biogenetically derive from a common intermediate, okilactomycin D (**1007**), via post polyketide synthase (PKS) modifications (Scheme **1.3**). *We then hypothesized* that the tricyclic topology of okilactomycin D (**1007**) arises in Nature via an intramolecular Diels–Alder reaction[1] (IMDA) from the tetraene **1018**, and that this process is fast enough and stereoselective enough to occur under biologically relevant conditions without the assistance of an enzyme (i.e., a Diels–Alderase).

Scheme 1.3| Biosynthetic hypothesis of okilactomycins



1002 (+)-Okilactomycin ***1007*** (–)-Okilactomycin D ***1018***

The validity of our biosynthetic hypothesis is predicated upon the assumption that the two (highlighted) stereogenic centers in substrate **1018** could control the sense of diastereoselectivity of a Diels–Alder event that is fairly distant. If this hypothesis holds true, the synthesis of the topologically complex okilactomycin D (**1007**) is reduced to the construction of a linear and hence easily accessible tetraene substrate **1018**. A rapid

synthesis of okilactomycin D (**1007**) could in turn pave the road for the production of okilactomycin (**1002**) and other more advanced members in this family.

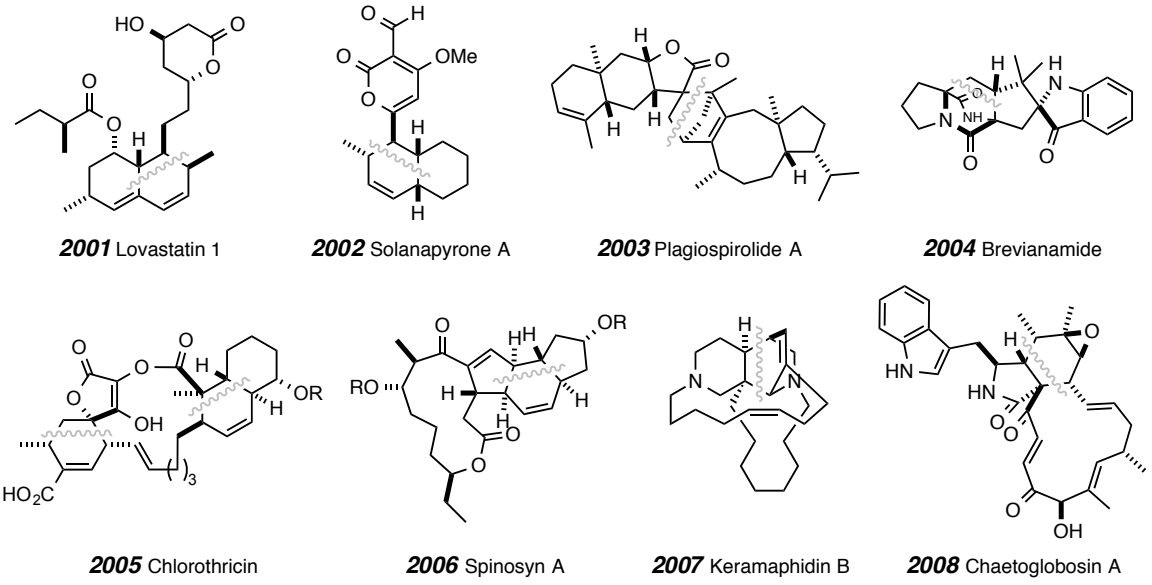
Our studies may not only provide a straightforward syntheses of the okilactomycins, but they also might lend insights into the biogenesis of these structurally intriguing compounds. Along this avenue, we may also see opportunities for the development of some novel synthetic or analytical methods, which may see broader application in the synthetic studies of other natural and unnatural compounds.

CHAPTER 2. INTRAMOLECULAR DIELS–ALDER (IMDA) REACTIONS IN NATURAL PRODUCT SYNTHESES

2.1 Diels–Alder reaction in biosynthesis of natural products

A Diels–Alder (DA) reaction has been suggested as a key step for the biosyntheses of diverse classes of natural products.[1,16,17] Some selected examples are shown in Figure 2.1, with the biosynthetic DA disconnections indicated by the squiggled lines.

Figure 2.1| Examples of natural products for which biosynthetic IMDA reactions have been proposed.



R = glycosyl groups

The compounds shown in Figure 2.1 span from polyketides (**2001, 2002, 2005, 2006**, and **2008**), to alkaloids (**2004** and **2007**), to terpenoids (**2003** and **2004**). Of these, the IMDA reactions in the biosyntheses of **2001**, **2002**, **2004**, and **2006** result in the

[16] Williams, R. M.; Stocking, E. M. Chemistry and biology of biosynthetic Diels–Alder reactions. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115.

[17] Oikawa, H.; Tokiwano, T. Enzymatic catalysis of the Diels–Alder reaction in the biosynthesis of natural products. *Nat. Prod. Rep.*, **2004**, *21*, 321–352.

formation of medium sized (5 or 6 membered) rings, while those involved in the formation of **2005**, **2007**, and **2008** incur the formation of macrocycles. A hetero-Diels–Alder reaction was suggested in the biosynthesis of **2004**. It is also noteworthy that an intermolecular Diels–Alder reaction was proposed to account for the biogenesis of **2003**.

Interestingly, despite the ubiquity of natural products whose biosyntheses apparently involve Diels-Alder reactions, the question whether Diels–Alderases (i.e., enzymes that catalyze biosynthetic Diels–Alder reactions) exist in Nature has been debated for a long time. Above all, a natural Diels–Alderase needs to address the potential product inhibition problem, because the product and transition structure of a Diels–Alder reaction have a high degree of resemblance.

It seems that this dispute was settled recently: five enzymes with the ability to catalyze Diels–Alder reactions have been identified to date.[18,19,20,21,22] In 1995, Oikawa and coworkers reported the identification of a partially purified, cell-free, extract that

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[18] a) Oikawa, H.; Katayama, K.; Suzuki, Y. Ichihara, A. Enzymatic activity catalysing *exo*-selective Diels-Alder reaction in solanapyrone biosynthesis. *J. Chem. Soc. Chem. Comm.,* **1995**, 1321–1322. b) Katayama, K.; Kobayashi, T.; Oikawa, H.; Honma, M.; Ichihara, A. Enzymatic activity and partial purification of solanapyrone synthase: first enzyme catalyzing Diels–Alder reaction. *Biochim. Biophys. Acta,* **1998**, *1384*, 387–395. c) Katayama, K.; Kobayashi, T.; Chijimatsu, M.; Ichihara, A. Oikawa, H. Purification and N-terminal amino acid sequence of solanapyrone synthase, a natural Diels-Alderase from *Alternaria solani*. *Biosci. Biotechnol. Biochem.,* **2008**, *72*, 604–607.

[19] a) Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van den Heever, J. P.; Hutchinson, C. R.; Vederas, J. C. Lovastatin nonaketide synthase catalyzes an intramolecular Diels−Alder reaction of a substrate analogue. *J. Am. Chem. Soc.,* 2000, **122,** 11519-11520. b) Ma, S. M.; Li, J. W.-H.; Choi, J. W.; Zhou, H.; Lee, K. K. M.; Moorthie, V. A.; Xie, X.; Kealey, J. T.; Da Silva, N. A.; Vederas, J. C.; Tang, Y. Complete reconstitution of a highly reducing iterative polyketide synthase. *Science*, **2009**, *326*, 589–592.

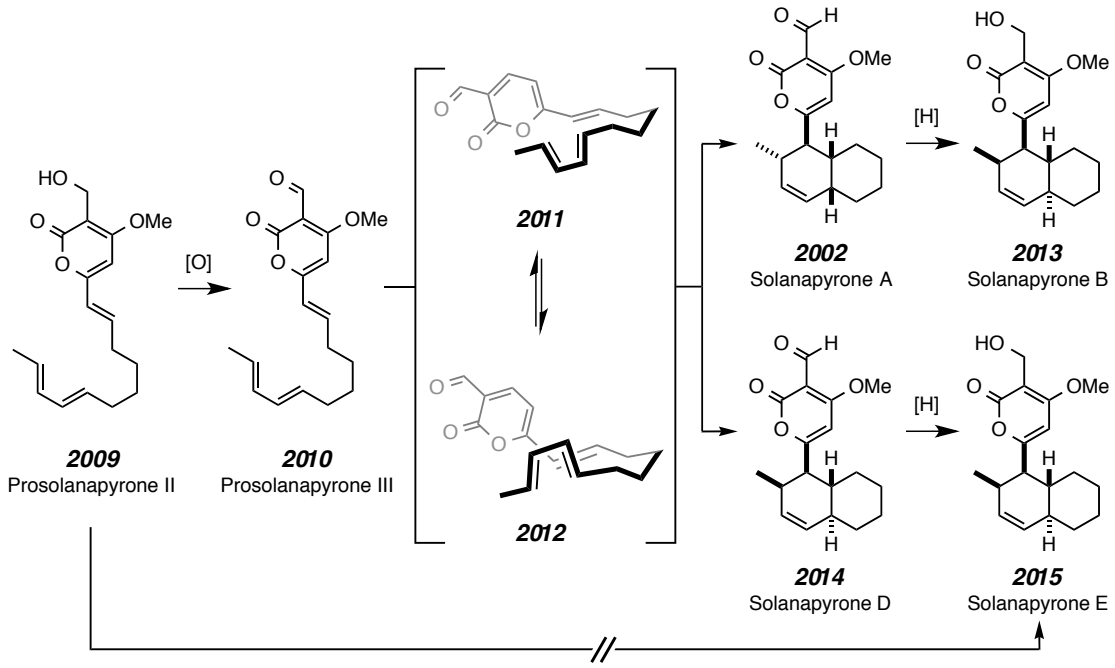
[20] a) Watanabe, K.; Oikawa, H.; Yagi, K.; Ohashi, S.; Mie, T.; Ichihara, A.; Honma, M. Macrophomate synthase: characterization, sequence, and expression in Escherichia coli of the novel enzyme catalyzing unusual multistep transformation of 2-pyrones to benzoates. *J. Biochem.,* **2000**, *127*, 467–473. b) Ose, T.; Watanabe, K.; Mie, T.; Honma, M.; Watanabe, H.; Yao, M.; Oikawa, H.; Tanaka, I. Insight into a natural Diels–Alder reaction from the structure of macrophomate synthase. *Nature*, **2003**, *422*, 185–189.

[21] a) Eberhardt, S. Zingler, N.; Kemter, K.; Richter, G.; Cushman, M.; Bacher, A. Domain structure of riboflavin synthase. *Eur. J. Biochem.* **2001**, *268*, 4315–4323. b) Kim, R.-R.; Illarionov, B.; Joshi, M.; Cushman, M.; Lee, C. Y.; Eisenreich, W.; Fischer, M.; Bacher, A. Mechanistic insights on riboflavin synthase inspired by selective binding of the 6,7-dimethyl-8-ribityllumazine exomethylene anion. *J. Am. Chem. Soc.* **2010**, *132*, 2983–2990.

[22] Kim, H. J.; Ruszczycky, M. W.; Choi, S.-H.; Liu, Y.-N.; Liu, H.-W. Enzyme-catalysed [4+2] cycloaddition is a key step in the biosynthesis of spinosyn A. *Nature*, **2011**, *473*, 109-112.

could catalyze the [4+2] cyclization for the formation of solanapyrones (Scheme 2.1).[18] Subjecting prosolanapyrone II (**2009**) to the extract yielded solanapyrones A, B, D, and E. On the other hand **2009** was found to be inert under identical conditions in the absence of the extract.

Scheme 2.1| Enzymatic IMDA reactions in the biosynthesis of solanapyrones



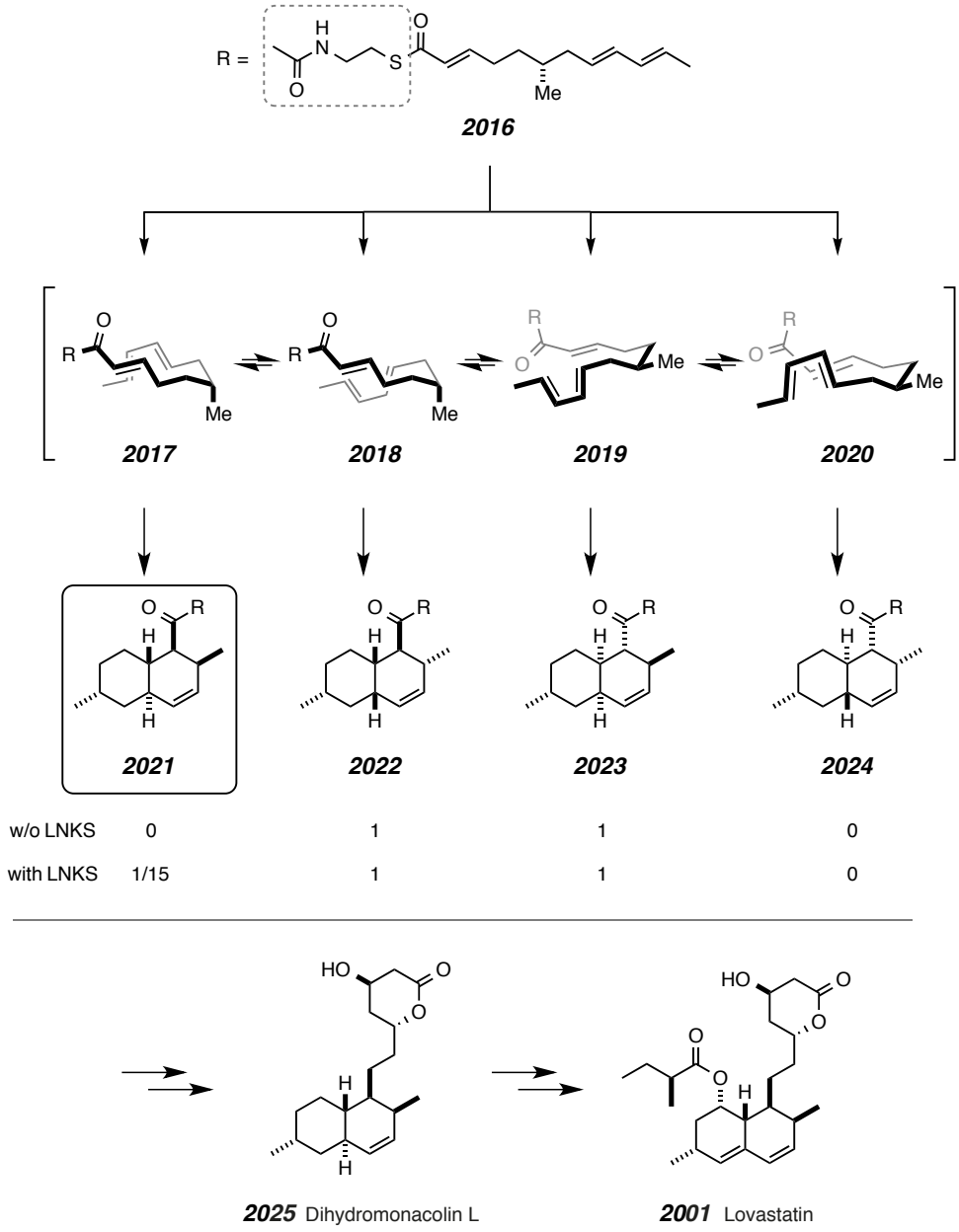
Through careful isotope incorporation studies, the authors concluded that enzymes did not convert **2009** directly to compound **2013** and **2015**, but rather through an oxidation–IMDA–reduction detour, via the intermediacy of **2010** and **2002**/**2014**. The stereochemical-outcome of the IMDA reaction of **2010** is affected by the enzymes present in the extract: cyclization in the presence of the extract gave a mixture of **2002** and **2014** in a 87/13 ratio, favoring the abnormal *exo*-adduct **2002** (cf. **2011**), while nonenzymatic cyclization of **2010** yielded **2002** and **2014** in a 3/97 ratio, favoring the normal *endo*-adduct **2014** (cf. **2012**). In fact, the rate of non-enzymatic cyclization of

2010 is fast in aqueous medium. Therefore, it is believed that Diels–Alderase(s) in solanapyrones biosyntheses works by functioning as a chaperone to guide the stereochemical outcome of the IMDA reactions.

In 2000 Vederas et al.[19] reported the purification of lovastatin nonaketide synthase (LNKS) and demonstrated that this enzyme is capable of catalyzing the IMDA cyclization of triene thioester **2016** (Scheme 2.2). In the absence of LNKS, triene **2016** cyclizes slowly in aqueous media to afford **2022** and **2023** in a 1:1 ratio (via **2018** and **2019**). Formation of decalin **2021** or **2024**, which requires passing through the sterically less favored transition structures (**2017** and **2020**, respectively), was not observed under non-enzymatic conditions. In the presence of LNKS, however, **2021** was formed, albeit as a minor isomer and along with "undesired" **2022** and **2023**. Importantly, the stereochemistry of **2021** is identical to that of dihydromonacolin L (**2025**), the key intermediate in the biosynthesis of lovastatin (**2001**). The authors noted that use of deactivated LNKS does not lead to the formation of **2021**, confirming that LNKS does not function through a non-specific interaction with the substrate. LNKS is the first natural Diels–Alderase isolated to homogeneity.

It is worth mentioning that triene **2016** is not the biosynthetic substrate of LNKS. The real substrate of LNKS should instead be one that is made in situ and covalently linked to the enzyme. The structural deviation might explain the observed low stereoselectivity of LNKS catalyzed IMDA reaction of **2016**.

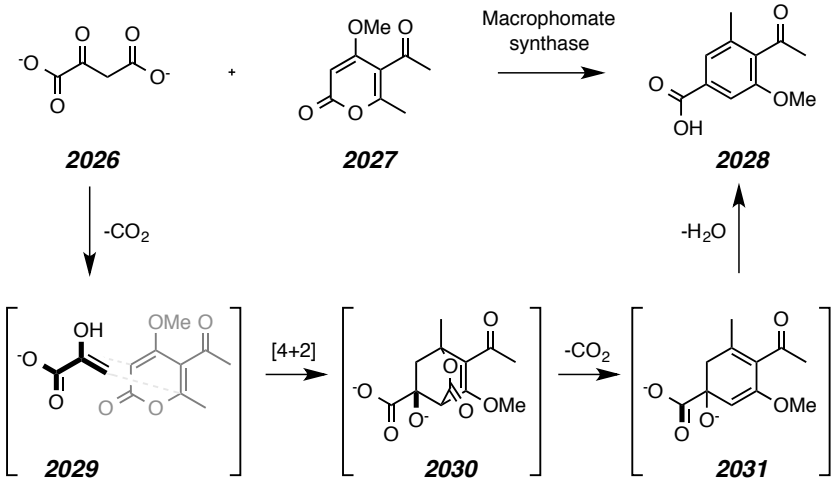
Scheme 2.2| Lovastatin nonaketide synthase (LNKS) as a Diels–Alderase.



Macrophomate synthase (MPS), a Mg^{2+} dependent enzyme, is the first natural Diels–Alderase whose single crystal structure has been resolved.[20] This enzyme catalyzes a complex cascade reaction, converting oxaloacetate **2026** and a 2-pyrone derivative **2027** to the corresponding benzoate **2028** (Scheme 2.3). Oxaloacetate was initially converted through decarboxylation to enol **2029**, which then underwent a net [4+2] addition with pyrone **2027**, providing the bicycle **2030**. Compound **2030** then released a molecule of CO_2 (presumably via a retro-Diels–Alder reaction) and a molecule of H_2O to afford the final benzoate **2028**.

It is still under debate if the [4+2] addition between **2029** and **2027** occurs via a stepwise Michael–aldol addition sequence[23] or a true concerted cyclization mechanism. Nonetheless, this remarkable transformation attests to the power of the enzymatic machinery that Nature has evolved over the years.

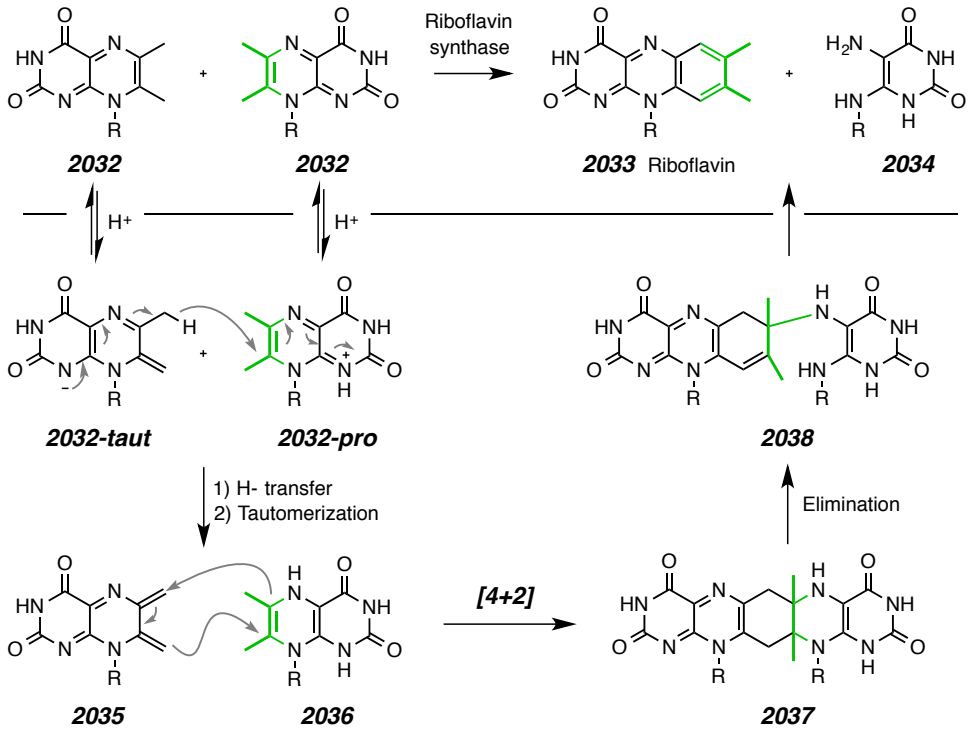
Scheme 2.3| Macrophomate synthase (MPS) as a Diels–Alderase.



[23] Guimares, C. R. W.; Udier-Blagovic, M.; Jørgensen, W. L. Macrophomate synthase: QM/MM simulations address the Diels–Alder versus Michael–aldol reaction mechanism. *J. Am. Chem. Soc.* **2005**, *127*, 3577–3588.

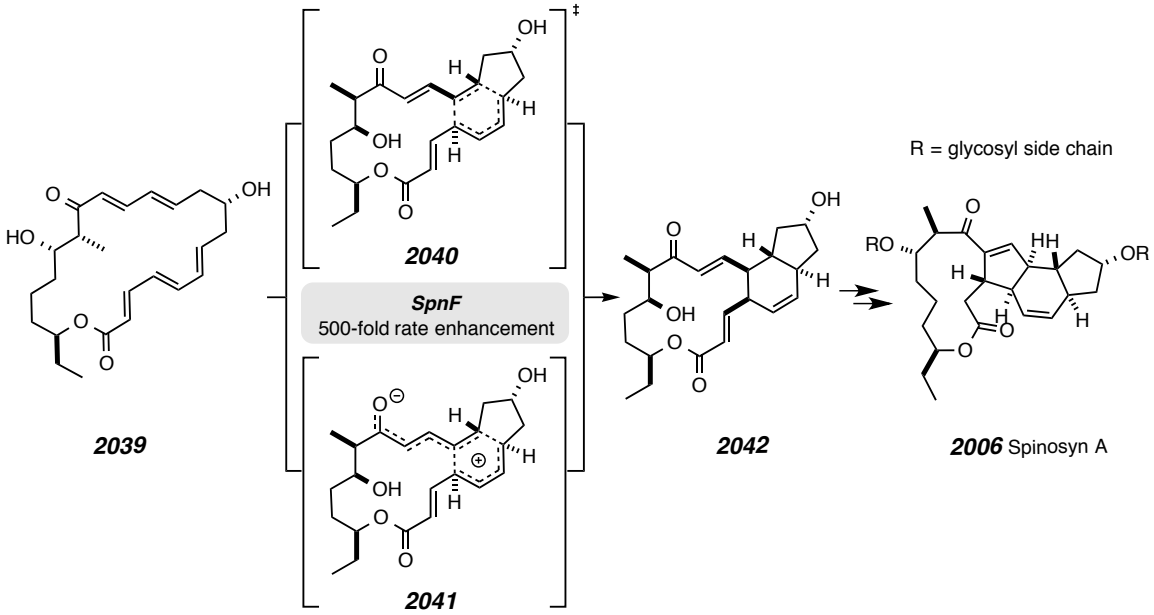
Riboflavin synthase catalyzes the transfer of a four carbon unit (green) between two molecules of **2032**, resulting the formation of riboflavin (**2033**) and a pyrimidinedione byproduct **2034** (Scheme 2.4).[21] Kim et al. hypothesized that this enzyme works by a mechanism that involves a Diels–Alder reaction (Scheme 2.4). Specifically, they proposed this transformation occurs through a sequence that comprises 1) tautomerization and disproportionation of two molecules of **2032** to form **2032-taut** and **2032-pro**, 2) an intermolecular hydride transfer between **2032-taut** and **2032-pro**, giving diene **2035** and dienenophile **2036**, 3) inverse electron demand intermolecular Diels–Alder cyclization between **2035** and **2036**, affording a pentacyclic intermediate **2037**, and 4) stepwise C-N bond cleavage to furnish riboflavin (**2033**) and **2034**, via the intermediacy of **2038**.

Scheme 2.4| A propose catalyzing mechanism of riboflavin synthase.



All of the four enzymes discussed above demonstrated more than one catalytic activity, leaving their specific role in the observed Diels–Alder reactions uncertain. In 2011 Liu's group[22] reported the identification of Spn F, an enzyme whose only identified role is to accelerate the intramolecular [4+2] cycloaddition event in spinosyn A biosynthesis. When subjecting polyene substrate **2039** to Spn F, the authors observed an ca. 500-fold rate enhancement of the transannular [4+2] cyclization responsible for the formation of tricycle **2042**, a key intermediate in the biogenesis of spinosyn A (**2006**, Scheme 2.5). It is still not clear if the reaction catalyzed by Spn F occurs via a concerted transition state (cf. **2040**) or by a stepwise polar addition mechanism (cf. **2041**).

Scheme 2.5| Spn F enhances the transannular [4+2] cycloaddition rate of **2039** by 500-fold.



The number of (putative) Diels–Alderases known to date still pales in comparison with the number of natural products whose biosyntheses apparently incorporate a Diels–Alder reaction. The specific mechanisms by which these enzymes work are still largely

unclear. To the best of my knowledge, no enzyme has been identified to catalyze the IMDA reactions in the biosynthesis of a spirotetronate. In summary, there is a lot more to be learned about natural Diels–Alderases.

2.2. IMDA in chemical synthesis of spirotetronates

Nature has served as an inexhaustible source of inspiration for chemists.[24] Not surprisingly, synthetic organic chemists often employ in their synthetic plans an IMDA reaction that mimics the (proposed) biosynthetic transformation. This biomimetic strategy has enabled many elegant total syntheses of complex natural products. These elegant efforts have been compiled in many recent comprehensive reviews.[16,25,26,27] Only discussed in this section are the reported synthetic studies of spirotetronates where an (biomimetic) IMDA reaction is used.

In their synthesis of chlorothricolide,[28] Yoshii and co-workers attempted an IMDA reaction to form its macrocycle (Scheme 2.6). The pentacyclic skeleton of chlorothricolide was rapidly constructed from the much less complicated precursor **2043**. Unfortunately, the IMDA reaction of polyene **2043** proceeded with only a low level of relative asymmetric induction, to give a mixture of the naturally configured **2044** and three additional diastereomers [dr = **1**:3:2:1]. These differ in the relative configurations at the numbered atoms in structure **2044**. Each of these products had a cis-relationship between the substituents at C18 and C21, implying that all arose from a concerted [4+2] cycloaddition (endo/exo and top/bottom). It is intriguing to wonder how much **2043** is deviating from the real IMDA precursor in the biosynthesis of chlorothricin. Especially

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[24] a) De la Torre, M. C.; Sierra, M. A. Comments on recent achievements in biomimetic organic synthesis. *Angew. Chem., Int. Ed.*, **2004**, *43*, 160–181. b) Bulger, P. G.; Bagal, S. K.; Marquez, R. Recent advances in biomimetic natural product synthesis. *Nat. Prod. Rep.*, **2008**, *25*, 254–297.

[25] 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.

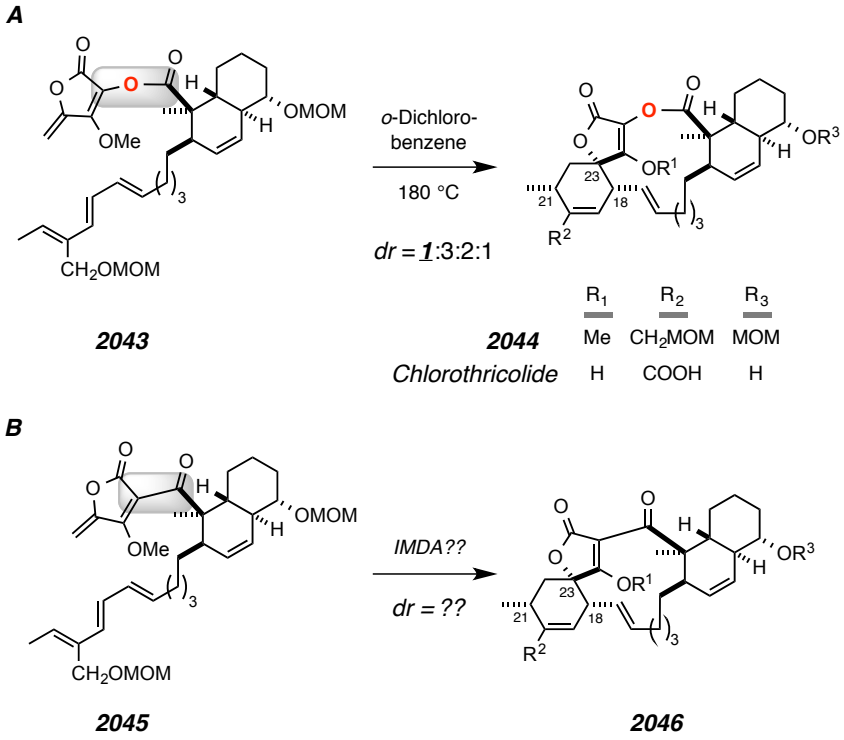
[26] Takao, K.; Munakata, R.; Tadano, K. Recent advances in natural product synthesis by using intramolecular Diels−Alder reactions. *Chem. Rev.* **2005**, *105*, 4779−4807.

[27] Juhl, M.; Tanner, D. Recent applications of intramolecular Diels–Alder reactions to natural product synthesis. *Chem. Soc. Rev.*, **2009**, *38*, 2983–2992.

[28] Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431-3434.

tantalizing is to consider the possibility of preparing pentacycle **2046** using the less oxygenated substrate **2045** (Panel B).

Scheme 2.6| A) IMDA reaction in the total synthesis of chlorothricolide; B) A hypothetical IMDA reaction of a less oxygenated analogue **2046**.



In 1997, Uenishi's group[29] reported the total synthesis of two biosynthetically related natural products, (–)-ircinianin (**2052**) and (+)-wistarin (**2053**, Scheme 2.7). The key step in their synthesis was an IMDA reaction. A Nozaki–Hiyama–Kishi coupling[30] between aldehyde **2047** and vinyl iodide **2048** gave the secondary alcohol **2049** and **2050** smoothly.[31] What was unexpected is the drastic reactivity difference between **2049** and **2050**, which differ from each other only by a C-16 stereocenter. The alcohol adduct **2049**

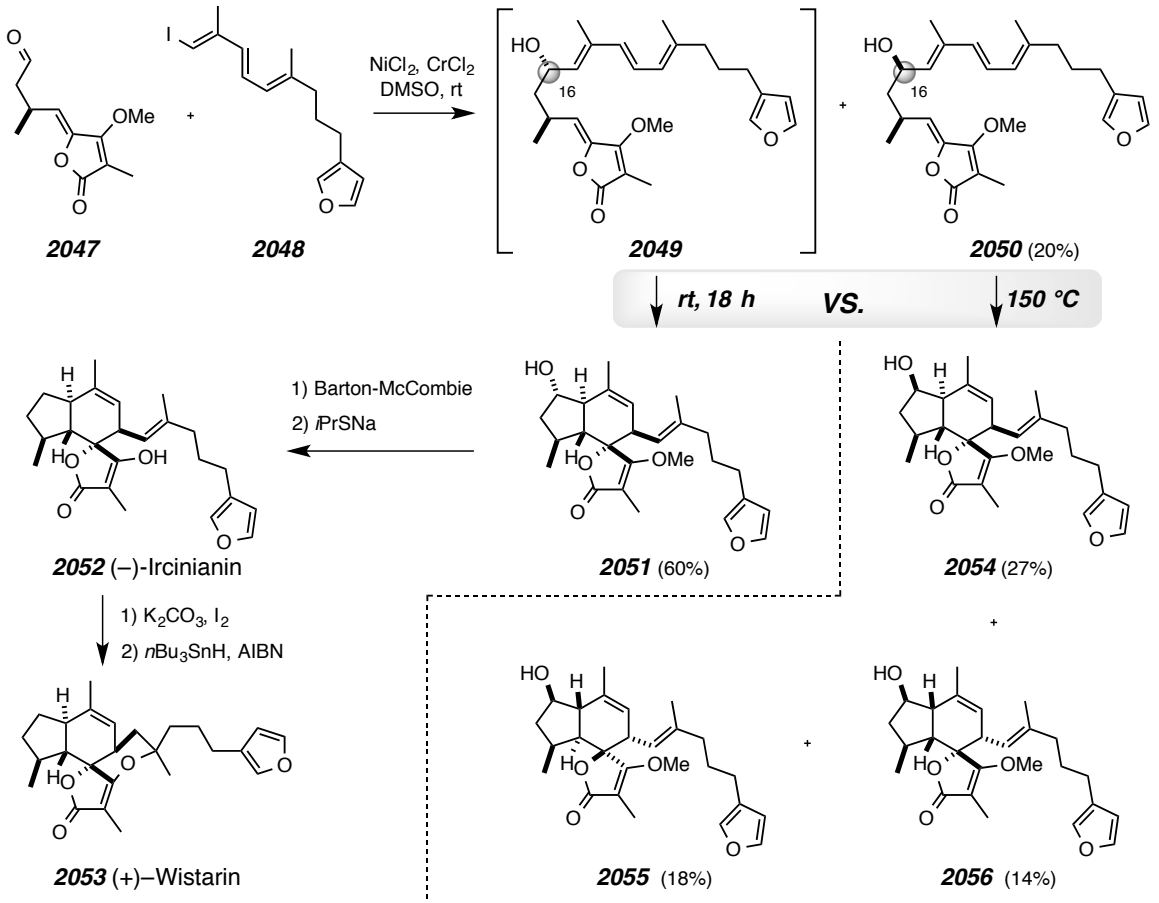
[29] Uenishi, J.; Kawahama, R.; Yonemitsu, O. Total synthesis of (–)-ircinianin and (+)-wistarin. *J. Org. Chem*. **1997**, *62*, 1691–1701.

[30] Fürstner, A. Carbon−Carbon bond formations involving organochromium(III) reagents. *Chem. Rev.*, **1999**, *99*, 991–1046

[31] The ratio of **2049** to **2050** was later estimated to be ca. 3:2.

cyclizes in situ[32] at room temperature, yielding exclusively the spirocycle **2051** that has the same relative configuration as does the natural product; the epimer **2050**, on the other hand, was almost inert under the same reaction conditions, and isomerizes only upon heating to 150 °C in xylene, affording three (out of four possible) diastereoisomers in a nonselective fashion (**2054**:**2055**:**2056** = 27:18:14).

Scheme 2.7| Uenishi's Total synthesis of (–)-ircinianin and (+)-wistarin.

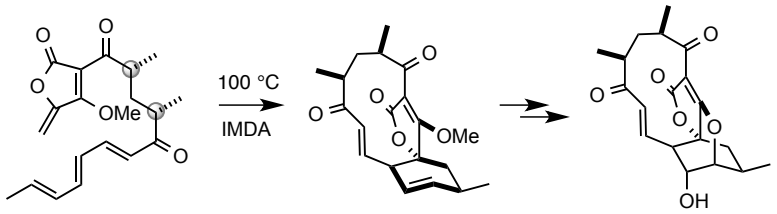


The following functional group manipulations furnished (–)-ircinianin and (+)–wistarin uneventfully. The rapid total synthesis of these two natural products was enabled by the successful execution of the IMDA reaction of **2049**. Additionally, the different

[32] $CrCl_3$ in the reaction mixture presumably functions as a Lewis acid that catalyzes the IMDA reaction of **2049**.

reactivity profiles of **2049** and **2050** emphasize how dramatic influence a seemingly unimportant structure variation can exert on an IMDA reaction.

Scheme 2.8| Total of abyssomicin C by Sorensen, Snider, and Couladouros groups.



2057 ***2058*** (ca. 80%) ***2059*** Abyssomicin C

The Sorensen, Snider, and Couladouros groups have each reported a remarkable total synthesis of abyssomicin C[33] (**2059**) using a biomimetic IMDA strategy (Scheme 2.8).[34] The key step in each synthesis was the diastereoselective IMDA reaction of **2057**, which provided macrocyclic **2058** in ca. 80% yield as a single diastereoisomer. Snider et al.[34b] observed that this conversion occurs at room temperature in chloroform with a measurable rate (40% conversion, 7 days). This extraordinarily successful IMDA reaction allowed a very quick synthesis of abyssomicin C from simple precursors. To the best of my knowledge, this is the only reported example of a diastereoselective IMDA macrocyclization used in the total synthesis of a spirotetronate natural product.

Although the reaction temperature required for **2057**[35] to isomerize at a (bio)synthetically useful rate is well above that of physiologically relevant conditions, the

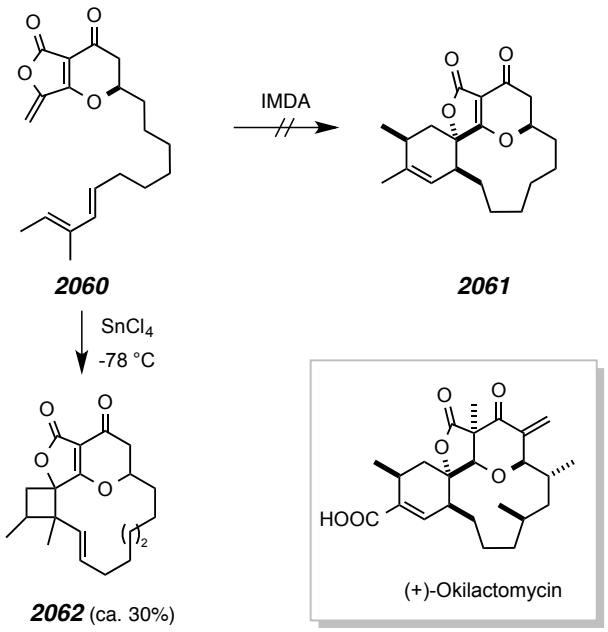
[33] a) Bister, B.; Bischoff, D.; Strobele, M.; Riedlinger, J.; Reicke, A.; Wolter, F.; Bull, A. T.; Zahner, H.; P. Fiedler, H.; Süssmuth, R. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2574–2576; b) Riedlinger, J.; Reicke, A.; Zahner, H.; Krismer, B.; Bull, A. T.; Maldonado, L. A.; Ward, A. C.; Goodfellow, M.; Bister, B.; Bischoff, D.; Süssmuth, R. D.; Fiedler, H. P. *J. Antibiot.* **2004**, *57*, 271–279.

[34] a) Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6533–6537; b) Snider, B. B.; Zou, Y. *Org. Lett*. **2005,** *7*, 4939–4941; c) Couladouros, E. A.; Bouzas, E. A.; Magos, A. D. *Tetrahedron* **2006**, *62*, 5272–5279.

[35] The reactivity of the free tetronate (*O*-demethylated version) of **2.57** was not reported.

exclusive formation of **2058** suggest that an enzyme is not required to control the stereoselectivity this reaction.

Scheme 2.9| Takeda's model study directed to the total synthesis of okilactomycin.



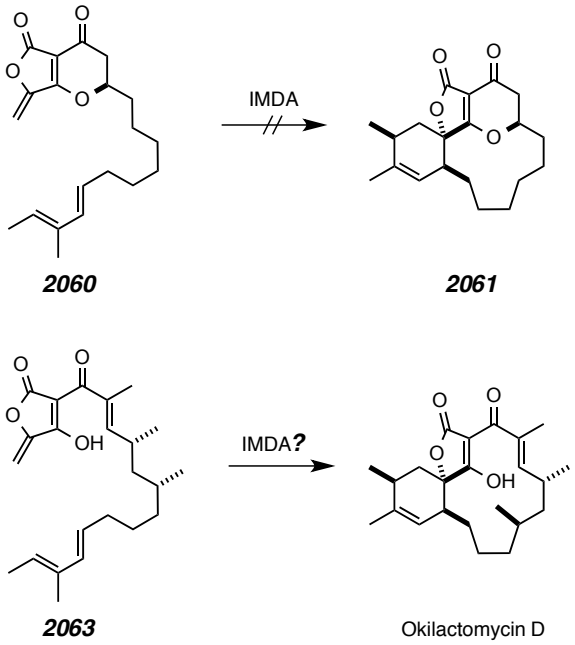
As early as in 1992 Takeda's group conceived using an IMDA strategy to synthesize okilactomycin.[36] They attempted effecting an IMDA reaction of polyene **2060**, expecting to obtain tetracycle **2061**, a tetracyclic compound with the skeleton of (+)-okilactomycin. During this study, they observed that 1) **2060** was thermally unstable, and 2) upon treatment with $SnCl_4$ at -78 °C, **2060** cyclizes in a [2+2] fashion, giving cyclobutanes **2062** in a non-stereoselective fashion.

The track record for IMDA reactions in spirotetronate synthesis is uneven. In particular, the failure in converting **2060** to **2061** seemingly obscured the prospect of synthesizing okilactomycin D from **2063** using an IMDA reaction, due to the high

[36] Takeda, K.; Shimotani, A.; Yoshii, E.; Yamaguchi, K. A Lewis acid mediated intramolecular [2+2] cycloaddition of 3-(9-methylundeca-7,9-dienyl)-9-methylene-2,8-dioxabicyclo[4.3.0]nonane-5,7-dione. *Heterocycles* 1992, *34*, 2259–2261.

structural similarity between **2060** and **2063** (Scheme 2.10). Nonetheless, we still deemed that the efficiency inherent in the preparation and cycloaddition of **2063** to okilactomycin D warranted study. Our confidence in this proposed study was also bolstered by the notion that slight structural difference may have a large impact on substrate reactivity (cf. Scheme 2.7).

Scheme 2.10| Takeda's model study vs. our proposed study.

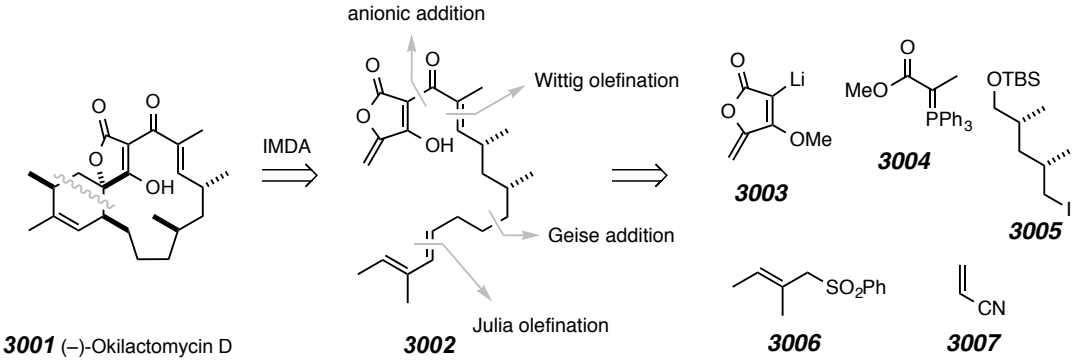


Chapter 3. Total Synthesis of (–)-Okilactomycin D

3.1 First generation synthesis of IMDA substrate

Our synthesis of okilactomycins (e.g., **3001**) commenced with the preparation of the proposed IMDA substrate **3002**. Our first generation strategy to **3002** is shown in Scheme 3.1. The polyene **3002** was dissected by four key carbon-carbon bond forming reactions, which were: 1) an anionic addition by lithiated tetronate **3003**;[37] 2) a Wittig olefination using known ylide **3004**[38] to construct the α,β-unsaturated carbonyl moiety; 3) a Giese type reaction[39] to unite iodide **3005**[13] and acrylonitrile (**3007**); and 4) a Julia–Lythgoe olefination[40] using allyl sulfone **3006** to construct the conjugate diene unit.

Scheme 3.1| First generation synthetic plan of polyene **3002**.



[37] Montgomery, L. J.; Challis, G. L. Concise synthesis of key 3-polyenoyl-5-methylenefuran-2,4-dione putative intermediates in quartromicin biosynthesis. *Synlett* **2008**, 2164–2168.

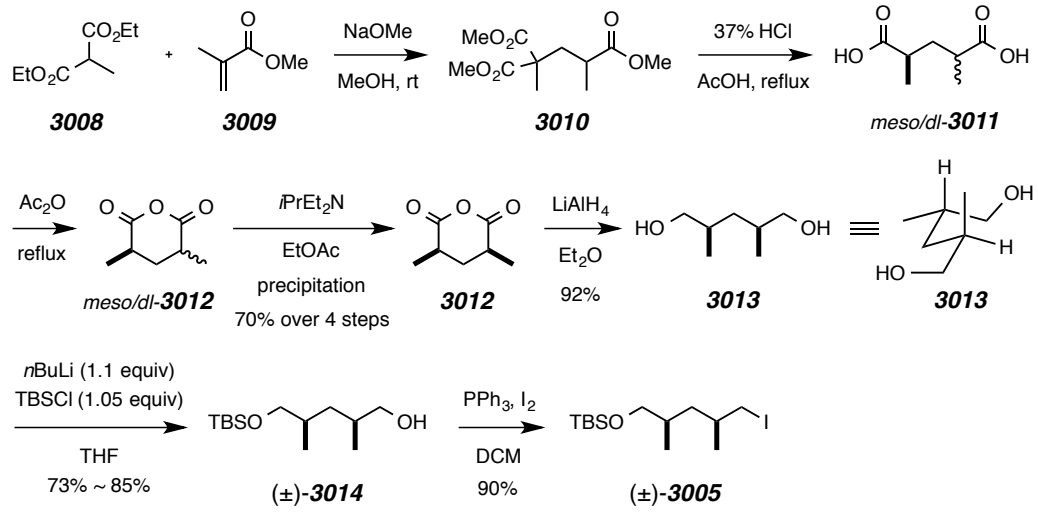
[38] Smonou, I.; Khan, S.; Foote, C. S.; Elemes, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. Reactions of phenyltriazolinedione with alkenes. Stereochemistry of methanol adducts to aziridinium imide intermediates. *J. Am. Chem. Soc.* **1995**, *117*, 7081–7087.

[39] Giese, V. B. Radicals in organic synthesis: Formation of C-C bonds; organic chemistry series, Baldwin, J. E., Series Ed.; Pergamon Press: Oxford, **1986**.

[40] Keck, G. E.; Savin, K. A.; Weglarz, M. A. Use of samarium diiodide as an alternative to sodium/mercury amalgam in the Julia-Lythgoe olefination, *J. Org. Chem.*, **1995**, *60*, 3194–3204, and references therein.

I prepared the iodide **3005** (in racemic form initially) by slight modification of known procedures (Scheme 3.2).[13,41] Base catalyzed Michael addition of diethyl methylmalonate **3008** to methyl methacrylate **3009** (both commercially available) provided triester **3010** quantitatively, albeit with concomitant transesterification. Treating compound **3010** with conc. HCl in acetic acid at reflux for 36 hours effected ester hydrolysis and decarboxylation in one pot, to give a 1:1 diastereomeric mixture of **3011**. Diacid **3011** was then converted to anhydrides *meso/dl*-**3012** through dehydrative cyclization. A solution of *meso/dl*-**3012** in EtOAc was then treated with Hünig's base, which enabled the equilibrium between *dl*-**3012** and *meso*-**3012**. The latter, which is less soluble in EtOAc, precipitated from the solution, thereby driving the equilibrium to the desired direction. Overall, *meso*-**3012** was prepared from compound **3008** and **3009** in 70% yield with over 95% de. Subsequent $LiAlH_4$ reduction of **3012** gave diol **3013** in 92% yield.

Scheme 3.2| Synthesis of (±)-**3005**.

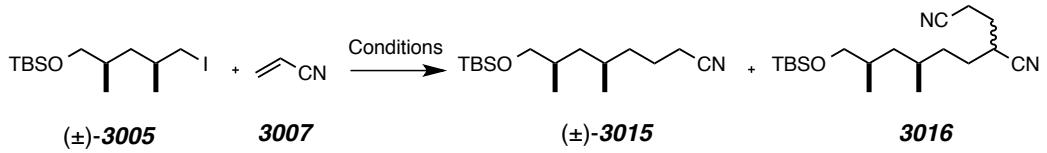


[41] Prusov, E.; Rohm, H.; Maier, M. E. Chemoenzymatic synthesis of the C10-C23 segment of Dictyostation. *Org. Lett.*, **2006**, *8*, 1025–1028.

Treating diol **3.13** with ca. 1 equiv of *n*BuLi followed by addition of ca. 1 equiv of TBSCl resulted in the formation of mono-TBS protected (±)-**3014** in 73-85% yield. This far-above-statistical yield of (±)-**3014** was surprising, considering the long spatial distance between the two hydroxy groups in an energy-minimized conformation of **3013** (and by inference, that of the mono anion of **3013**, see Scheme 3.2). Alcohol (±)-**3014** was then converted to iodide (±)-**3005** under standard conditions. More than 10 grams of (±)-**3005** could be made by this sequence in one batch.

With iodide (±)-**3005** available in large quantities, I investigated its union with acrylonitrile (**3007**) to prepare (±)-**3015** by the use of a radical-based Michael addition reaction (Giese reaction). Encouragingly, the desired nitrile **3015** was obtained in 35% yield by heating a mixture of iodide (±)-**3005** (1 equiv) and **3007** (10 equiv) in benzene with nBu$_3$SnH as the stoichiometric hydride donor and AIBN as the radical initiator. Under this condition, however, dinitrile **3016** was also formed in almost equal amount. To minimize the undesirable formation of dinitrile **3016**, I gradually reduced the amount of acrylonitrile used to 5 equiv, and found that the ratio of **3015** to **3016** as well as the isolated yield of **3015** increased accordingly (entry 1-3). Further lowering the acrylonitrile to 3 equiv didn't increase the yield of **3015**, because the direct deiodination of **3005** became competitive. Lowering the reaction temperature is also beneficial for the formation of **3015** (entry 3 vs. entry 4). The best yield (78%) of **3015** was obtained by using 1.5 equiv of nBu$_3$SnH (entry 5). To my delight, by using the conditions listed in entry 5, nitrile **3015** can be prepared on a gram scale, and byproduct **3016** could be easily separated using column chromatography.

Scheme 3.3| Radical addition of iodide (±)**-3005** to acrylonitrile to give (±)**-3015**.



(±)-***3005*** ***3007*** (±)-***3015*** ***3016***

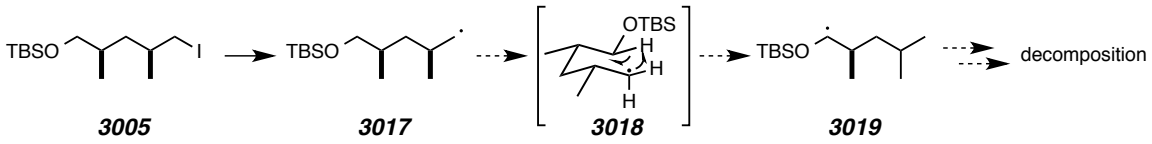
Entry	Conditions[a]	Yield[b] of 3015	Ratio[c] 3015/3016
1	10 equiv **3007**, 1.2 equiv nBu$_3$SnH, 80 °C	35%	1:1.1
2	8 equiv **3007**, 1.2 equiv nBu$_3$SnH, 80 °C	42%	1.5:1
3	5 equiv **3007**, 1.2 equiv nBu$_3$SnH, 80 °C	55%	2.8:1
4	5 equiv **3007**, 1.2 equiv nBu$_3$SnH, 75 °C	68%	3.4:1
5	5 equiv **3007**, 1.5 equiv nBu$_3$SnH, 75 °C	78%	4:1
6	3 equiv **3007**, 1.5 equiv nBu$_3$SnH, 75 °C	57%[d]	N/A

[a] Reactions were conducted as a 0.25 M solution of **3.5** in benzene. AIBN (1% equiv) was used as the radical initiator. Detailed procedures can be found in the experimental section. [b] Isolated yield. [c] Ratios are determined by GC/MS. [d] An appreciable amount of deiodinated product were observed on GC.

It is interesting to recall that I was initially concerned that primary radical **3017** might undergo an intramolecular 1,5-hydrogen atom transfer event[42] to form a hetereoatom stabilized radical **3019** as a decomposition pathway (Scheme 3.4). To my delight, no byproduct resulting from this event was observed throughout this study. In retrospect, this potential decomposing pathway may be prevented by the unfavorable 1,3-dialkyl interaction inherent in the corresponding transition structure **3018**.

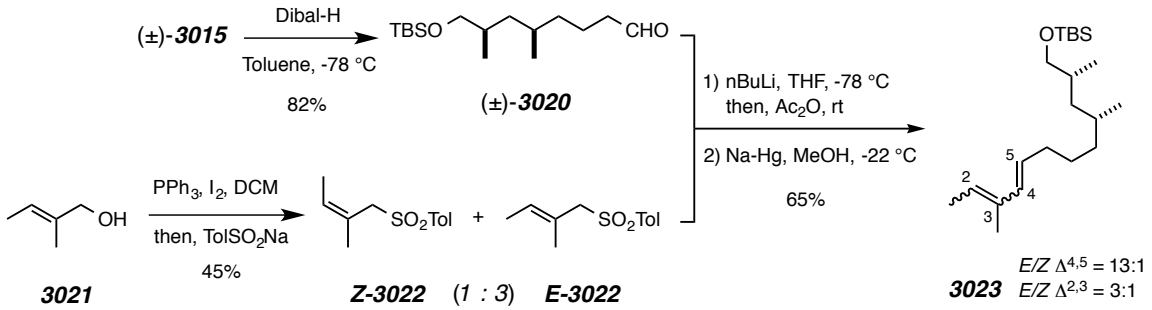
[42] This 1,5-hydrogen shift is ubiquitous in carbohydrates syntheses. For instance, see: Barbaud, C.; Bols, M.; Lundt, I.; Sierks M. R. Synthesis of the first pseudosugar-C-disaccharide. A potential antigen for eliciting glycoside-bond forming antibodies with catalytic groups. *Tetrahedron.* **1995**, *51*, 9063-9078.

Scheme 3.4| A potential 1,5-intramolecular hydrogen atom transfer is not observed presumably because of the unfavorable 1,3-dialkyl interaction present in the transition structure **3018**.



To prepare for the following Julia-Lythgoe olefination, the nitrile (±)-**3015** obtained from the previous step was converted to its corresponding aldehyde (±)-**3020** (Scheme 3.5). The other partner in the olefination step, sulfone **3022**,[43] was made by a two-step sequence from tiglic alcohol **3021** via the intermediacy of an allyl iodide (Scheme 3.5). This iodination-substitution sequence gave sulfone **3022** in a 3:1 isomeric ratio. The desired (*E*)-**3022** could be purified with the assistance of MPLC separation. Because of the volatility and light sensitivity of the allyl iodide intermediate, I found it beneficial to conduct the two reactions in one pot.

Scheme 3.5| Synthesis of diene **3023**.



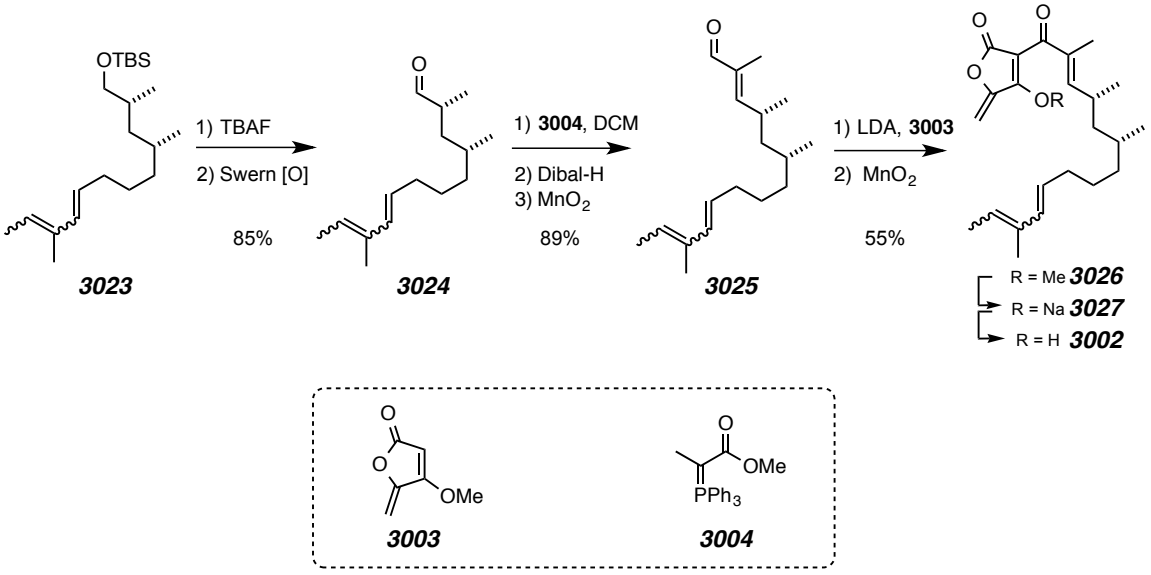
The Julia-Lythgoe olefination[40] between (±)-**3020** and **3022** gave the key diene **3023** in 65% yield over a three step sequence. The newly formed $\Delta^{4,5}$ C=C bond has a high *E*:*Z*

[43] Cox, C. M.; Whiting, D. A. Synthetic studies on electron transport inhibitors. Part 1. Chiral synthesis of a synthon for myxalamide D, piericidin A, and the actinopyrones. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 1901–1905.

ratio. Unfortunately, the stereochemical integrity of the terminal $\Delta^{2,4}$ C=C bond eroded to 3:1 during the reaction.

Nevertheless, this strategy successfully delivered **3023** in the quantity of several hundred milligrams, enough for initial exploratory studies. Pleasingly, the conversion of **3023** to **3002** turned out to be very smooth (Scheme 3.6). Silyl ether **3023** was firstly subjected to TBAF deprotection–Swern oxidation[44] sequence, which gave aldehyde **3024** in 85% yield. Wittig olefination of aldehyde **3024** by the stabilized ylide **3004**[45] and standard processing of the resulting enoate (DIBAL-H reduction and MnO_2 oxidation) provided enal **3025** in 89% yield over 3 steps.

Scheme 3.6| Conversion of **3023** to IMDA precursor **3002**.



[44] Notably, attempted alcohol oxidation using Dess–Martin periodinane appeared to destroy the diene unit present in the substrate, and Parikh–Doering oxidation only gave a low yield of desired aldehyde.

[45] Smonou, I.; Khan, S.; Foote, C. S.; Elemes, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. Reactions of phenyltriazolinedione with alkenes. Stereochemistry of methanol adducts to aziridinium imide intermediates. *J. Am. Chem. Soc.* **1995**, *117*, 7081-7087.

The protocol of Pattenden[46] (as successfully implemented by researchers in the abyssomicin C studies[34]) was used to effect anionic addition of lithiated methyl tetronate **3003**[37] to **3025**. MnO_2 oxidation yielded acyltetronate **3026** in 55% yield[47] over 2 steps. The obtained vinylogous carbonate/ester **3026** was treated with LiCl in d_6-DMSO[48] at 50 °C to cleanly produce (according to ^{1}H NMR analysis) the tetronate, presumably as its lithium salt, which, following a brine wash, was isolated, presumably as the sodium salt **3027**. Neutralization with TFA could be performed at a number of stages to give the neutral acyltetronic acid **3002**.

[46] Clemo, N. G.; Pattenden, G. Vinylic carbanions in synthesis. Novel syntheses of iso-gregatin B, iso-aspertetronin A and related O-methyl tetronic acids. *Tetrahedron Lett.* **1982**, *23*, 585–588.

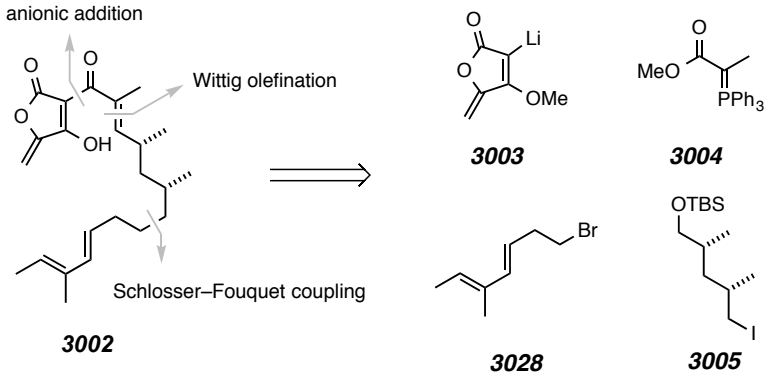
[47] The anionic addition step occurred with >90% yield and 1:1 dr. The less than optimal isolated yield of **3.26** may be caused by product absorption by MnO_2 in the second step.

[48] Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. Total synthesis of tetronolide, the aglycon of tetrocarcins. *Tetrahedron Lett.* **1991**, *32*, 4925–4928.

3.2 Second generation synthesis of IMDA substrate

Although the synthetic strategy in the previous section had provided sufficient amount of polyene **3002** to study its reactivity, the shortcomings of this strategy were also obvious. First, the radical Michael addition (cf. Scheme 3.3) requires the use of stoichiometric amount of toxic nBu$_3$SnH. The stannous byproduct formed during this step also complicated the product purification process. Second, Na/Hg amalgam was used in the Julia olefination step, and the disposal of the mercuric waste of this reaction is tedious. In addition, the olefination reaction gave a mixture of non-separable isomers, which compromised the yield of desired diene **3002**, and caused some additional challenges when studying the reactivity of **3002**.

Scheme 3.7| Second generation synthetic plan of **3002**.



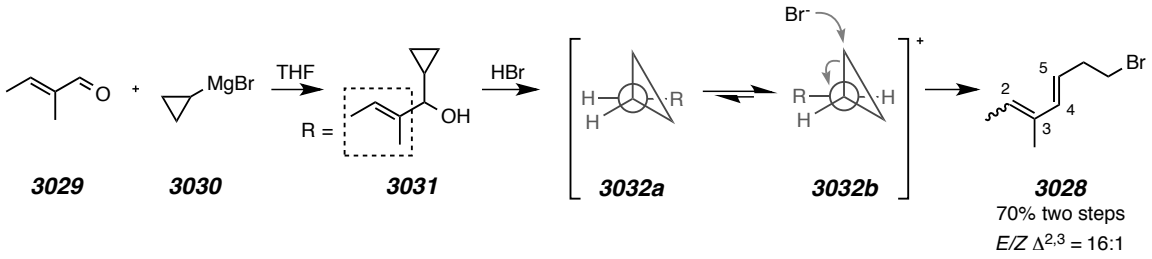
The above shortcomings prompted me to pursue a better strategy to synthesize **3002**. Key steps of our second-generation synthetic plan of **3002** are shown in Scheme 3.7. Two major modifications are made in this new plan: 1) a Schlosser-Fouquet coupling[49] is used to construct the C_{sp3}-C_{sp3} bond, replacing the Giese reaction; 2) the diene unit present in

[49] Fouquet, G.; Schlosser, M. Improved carbon-carbon linking by controlled copper catalysis. *Angew. Chem., Int. Ed.* **1974**, *13,* 82–83.

3002 is carried from compound **3028**, which is prepared prior to the C_{sp3}-C_{sp3} bond formation event.

The synthesis of diene bromide **3028** capitalized on a cyclopropyl ring opening reaction (Scheme 3.8). Addition of Grignard reagent **3030** to tiglic aldehyde (**3029**) gave allyl alcohol **3031**, which upon extractive workup was directly subjected to conc. aqueous HBr[50] to yield the ring opened bromide **3028**. More than 20 grams of diene bromide **3028** could be prepared and isolated in one batch. The **3028** obtained by this method is of very high purity, with only slight erosion of stereochemical integrity at the $\Delta^{2,3}$ double bond. The high *E*:*Z* ratio of the $\Delta^{4,5}$ double bond in the resulting **3028** is presumably a reflection of the relative stability of cationic intermediate **3032a**/**3032b**.

Scheme 3.8| Synthesis of diene bromide **3028**.

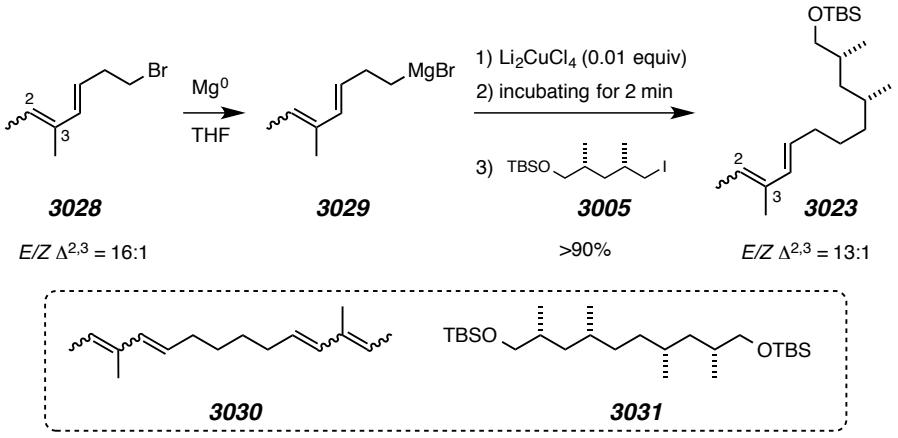


The rapid access of **3028** laid the ground for the next Schlosser-Fouquet coupling (Scheme 3.9). Bromide **3028** was initially converted to the corresponding Grignard reagent **3029**, then incubated with a catalytic amount (0.01 equiv) of Li_2CuCl_4, and finally reacted with iodide **305** (0.25–0.33 equiv). These conditions afforded the key diene **3023** in over 90% yield. Several observations during this reaction are worth mentioning here. First, a superstoichiometric amount of **3029** was used to ensure the full

[50] Jung, M. E.; Miller, S. J. Preparation of *N*-alkadienyl *N*-*E*-2-arylethenylcarbamates *via* sulfoxide elimination in a synthetic approach to lycorine. *Heterocycles* **1990**, *30*, 839-853.

conversion of the more precious **305**. The excess **3029** led to the formation of compounds with the molecular weight of **3030**.[51] Second, it is important to minimize the amount of Li_2CuCl_4 used in the reaction. When 0.1 equiv of Li_2CuCl_4 (with respect to **3029**) was used, compound **3005** were not fully converted, and byproduct **3031** was formed in almost equal amount with **3023** (GC results). Third, some isomerization at $\Delta^{2,3}$ double bond (from 16:1 to 13:1) was noticed during the reaction. I presume this bond isomerization occurred when **3029** was incubated with Li_2CuCl_4: longer incubation with Li_2CuCl_4 (30 vs. <5 minutes, 0 °C) prior to the addition of **3005** led to a greater amount of *E/Z*-isomerization at $\Delta^{2,3}$ double bond, whereas prolonged heating (50-60°C for 2 h) during the preparation of **3029** had little to no effect on the stereochemical integrity of this bond.[52]

Scheme 3.9| Synthesis of **3023** using a Schlosser–Fouquet coupling.



Conversion of **3023** to the IMDA precursor **3002** was completed with the same conversions used in the first generation strategy as described in the previous section. The

[51] Besides the linear products like **3030**, those with varying number of cyclopropyl rings could have also been formed.

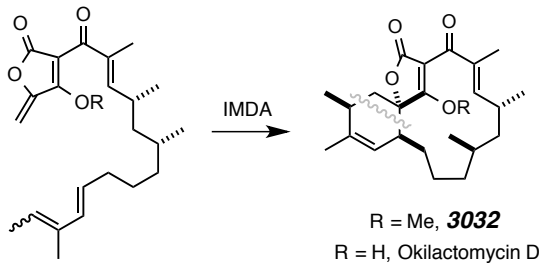
[52] Howden, M. E. H.; Maercker, A.; Burdon, J.; Roberts, J. D. Small-ring compounds. XLV. Influence of vinyl and phenyl substituents on the interconversion of allylcarbinyl-type Grignard reagents. *J. Am. Chem. Soc.*, **1966**, *88*, 1732–1742.

E:*Z* ratio of the double bonds in **3023** was retained throughout these operations. Compared with the first generation synthesis, this new synthetic strategy is more convergent and higher yielding, obviates the use of toxic stannous and mercuric reagents, and provides the desired **3002** in higher purity. Additionally, this new synthetic sequence is very scalable and could be conducted at multi-gram scale at each stage.

3.3. Endgame of (–)-okilactomycin D synthesis

With tetraene **3002** and its close analogues **3026** and **3027** in hand, I next investigated the reactivity profiles of each compound toward an IMDA cyclization. The results are summarized in Table 3.1.

Table 3.1| Summary of reactivity profiles of **3002**, **3026**, and **3027**.



R = Me, ***3032***
R = H, Okilactomycin D

Entry	Substrate	Conditions	Yield[b]
1	**3002**[a] (R = H)	various slovents, rt	Decomp.
2	**3027** (R = Na)	various solvents, rt to 180 °C	Decomp.
3	**3026** (R = Me)	CH_2Cl_2, rt, 30 d	ca. 10%[c]
4	**3026** (R = Me)	Toluene, 110 °C, 96 h	62%
5	**3026** (R = Me)	CH_3OH/H_2O, 90 °C, 6 h	30-55%

[a] free tetronic acids have pKa ≤ 1. [b] isolated yield except for entry 3. [c] ca. 10% conversion

Unfortunately, the free tetronic acid **3002**, our initially proposed biosynthetic precursor to okilactomycin D (cf. Scheme 1.3 and Scheme 2.10), was found to be thermally unstable. It decomposed in various (aqueous or non-aqueous) solvents at ambient temperature before any sign of cyclization could be observed (entry 1). It was informative to learn that acyl tetronic acid moiety like that present in **3002** is rather acidic (pKa ≤ 1).[53] The coexistence of this highly acidic unit and other acid sensitive functional groups (e.g., the diene group and the enol ether group) in **3002** might account for its

[53] Yamaguchi, T.; Saito, K.; Tsujimoto, T.; Yuki, H. NMR spectroscopic studies on the tautomerism in tenuazonic acid analogs. *J. Heterocyclic Chem.* **1976**, *13*, 533-537.

instability.

Because of its strong acidity, compound **3002** should not exist in Nature as a neutral vinylogous acid. We thus modified our original hypothesis, and proposed that the natural biosynthetic precursor to okilactomycin D is a conjugate base of **3002**, like **3027**. We later found that this conjugate base, on the other hand, is rather inert. It stays intact in solution even after being heated to 180 °C for elongated time (entry 2). The surprisingly low reactivity of **3027** might be attributed to the elevated LUMO energy of the anionic dienophile moiety, which raised the activation energy of this normal electron demand biosynthetic IMDA reaction. Meanwhile, *the inertness of **3027** under ambient conditions strongly suggests that the IMDA reaction in the biosynthesis of okilactomycin D is an enzymatic process.* This possibility is currently under investigation in the Challis laboratory.

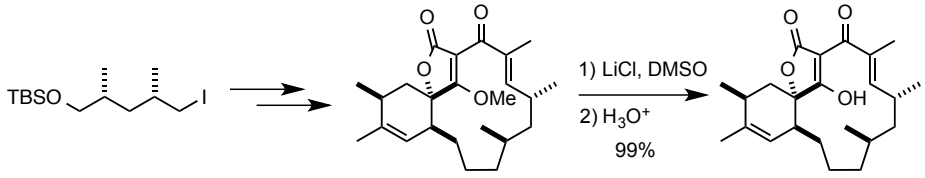
Fortunately, we found that the methyl ester **3026** is a synthetically useful compound endowed with suitably balanced reactivity and stability. Although it has the tendency to polymerize at high concentrations, compound **3026** can be stored as a dilute solution at –20 °C indefinitely. After being heated at 110 °C for 96 h in toluene, **3026** completely isomerized, and yielded **3032**, the tricycle with identical relative configuration to that of okilactomycin D, as the most predominant product (entry 4). Consistent with observations made before, the IMDA reaction of **3026** proceeds at a faster rate in aqueous media,[54] albeit in lower and less reproducible yield (entry 5). In fact, **3026** cyclizes at a measurable rate even at room temperature (entry 3), although the rate is too slow to be biosynthetically viable.

[54] Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. Diels-Alder reactions in aqueous solutions. Enforced hydrophobic interactions between diene and dienophile. *J. Am. Chem. Soc.* **1991**, *113*, 4241–4246.

As in the case of abyssomicin C total synthesis,[34] the (only) two stereocenters in precursor **3026** successfully controlled the sense of diastereoselectivity of the IMDA event. Compared with the IMDA reaction in abyssomicin C total synthesis, the macrocycle formed in this case is of even bigger size (13 membered vs. 11 membered), and the stereo-directing centers are even more distant from the reaction sites (3 C_{sp3} atoms vs. 3 C_{sp2} atoms to diene center and 5 C_{sp2} atoms vs. 3 C_{sp2} atoms to dienophile center).

It is noteworthy that the drastic reactivity difference between **3026** and **2060** (Scheme 2.9 in section 2.2) reinforced the notion that *very small structural variations may exert a huge impact on substrate reactivity.*

Scheme 3.10| Endgame of okilactomycin D synthesis.



(+)-***3005*** (–)-***3032*** ***3001***, (–)-Okilactomycin D

To complete the total synthesis of okilactomycin D (**3001**), the methyl ether **3032** (200 mg) was dissolved in DMSO (15 mL) and LiCl (15 equiv) was added (Scheme 3.10). Once the mixture became homogeneous, the solution was warmed to 55 °C for 48 h. Partitioning between water and ethyl acetate and washing the organic phase with brine resulted in isolation of the conjugate base of okilactomycin D, presumably as its sodium salt. Alternatively, partitioning of the initial reaction mixture between 10% HCl (aq) and ethyl acetate cleanly gave okilactomycin D (**3001**) directly as the neutral acyltetronic acid.

Starting from the nonracemic 5-iodopentane derivative (+)-(2*R*,4*S*)-**3005**,[55] and using the same route, I then synthesized enantiomerically enriched **3001**. The resulting synthetic sample of okilactomycin D gave essentially identical ^{1}H and ^{13}C NMR spectral data (for tabulated differences in chemical shifts between the synthetic and natural sample, see page 174 in Experimental session) and had the same sign of optical rotation as that of the natural sample[56] {$[\alpha]_{D\text{synthetic}} = -32$ (c = 0.3, MeOH); lit.[8] $[\alpha]_{D\text{natural}} = -50$ (c = ca. 0.1, MeOH)}, supporting the assigned absolute configuration of (–)-**3001**.[8]

[55] Takagi, R.; Tsuyumine, S.; Nishitani, H.; Miyanaga, W.; Ohkata, K. Stereoselective synthesis of the hydrophobic side chain of scyphostatin. *Aust. J. Chem.* **2004**, *57*, 439–447. I prepared (+)-(2*R*,4*S*)-**3.5** using slightly modified procedures. These involved enantioselective, lipase-catalyzed (PPL) acetylation of diol **3.13** (the resulting mono-alcohol was measured to have an ca. 9:1 er by Mosher ester analysis), TBS protection, acetate methanolysis, and iodination. The sample of (+)-**3.5** had $[\alpha]_D$ ($CHCl_3$, c = 2.0) = +3.1 [lit. $[\alpha]_D^{22}$ ($CHCl_3$, c = 2.09) = +3.50].

[56] The sample of natural okilactomycin D was isolated after a final purification by HPLC using an eluent doped with trifluoroacetic acid. Thus, its structure is best formulated as **3001**, having the neutral acyltetronic acid. We observed that the ^{1}H NMR spectrum of the sodium salt of **3001** in CD_3OD (or of the analogous cesium salt in CDCl3) contained a resonance for the enone β-proton (H6) that was ca. 0.6 (or 0.2) ppm upfield of that for the sample of neutral **3001**.

3.4 On the diastereoselectivity of the biomimetic IMDA reaction in okilactomycin D synthesis

In fact, the IMDA reaction of polyene **3026** discussed in the previous section (Table 3.1) gave a mixture of four diastereoisomers (**3032**–**3035**, Scheme 3.11). The structures of **3032**, **3033**, and **3034** have all been determined by X-ray crystallographic analysis. Compound **3035** could not be purified to homogeneity, and its structure was assigned with the assumption that this IMDA reaction occurs via a concerted mechanism. In fact, the minor 2*Z*,4*E*-diene isomer (**3026-*Z***)[57] was typically observed in the crude IMDA reaction product mixture, and it was recovered and characterized from a thermal reaction in toluene (entry 2). Thus, the *E*-isomer **3026-*E*** reacts faster than **3026-*Z***, supporting the assumption that this IMDA is a concerted process.[58]

I also attempted using Lewis acids to accelerate the IMDA reaction of **3026** (Scheme 3.11, entry 3-6). During this course of study, I found that 1) while the reagent BF_3•Et_2O (entry 3) or $Cu(OTf)_2$ (entry 4) is not compatible with **3026**,[59] the use of $LiClO_4$ (entry 5) or $MeAlCl_2$ (entry 6) significantly lowered the activation energy of this reaction so that the reaction could be completed within a shorter period of time at ambient temperature or below; and 2) extremely surprisingly, when $LiClO_4$ or $MeAlCl_2$ was used, compounds **3034** and **3035**, the minor products formed under thermal conditions, were produced predominantly (cf. entry 1-2 with 5-6): *the use of these two Lewis acids altered the sense of diastereoselectivity of this biosynthetically relevant IMDA reaction!*

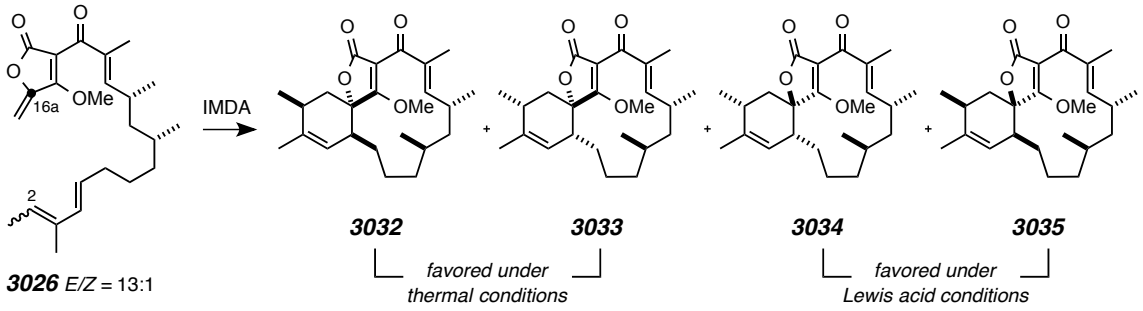
---

[57] This minor isomer was formed as a byproduct in both generations of substrate synthesis (see Scheme 3.5 and 3.9).

[58] It is reasonable to assume that both isomers should react at similar rate if the IMDA reaction occurs via a stepwise mechanism.

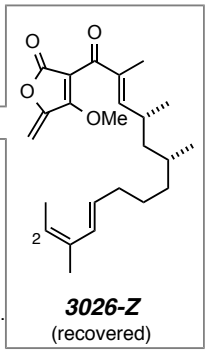
[59] BF_3•Et_2O or $Cu(OTf)_2$ is not tolerated presumably because both reagents would give rise to strong protic acids when reacting with adventitious amount of water.

Scheme 3.11| Diasteroselectivity of the IMDA reaction in okilactomycin D synthesis.



Entry	Solvent[a]	Lewis acid	Temp	Time	Total yield [%]	Ratio[b] (**3032**:**3033**:**3034**:**3035**)
1	H_2O/CH_3OH	None	90 °C	6 h	30–55	43 : 5 : 2 : 3.5
2	Toluene	None	110 °C	96 h	62	41 : 5 : 1 : 1.3[c]
3	CH_2Cl_2	$BF_3{\cdot}Et_2O$	-78 °C to rt	12 h	decomp.	Not available
4	CH_2Cl_2	$Cu(OTf)_2$	-78 °C to rt	12 h	decomp.	Not available
5	Et_2O	$LiClO_4$	rt	24 h	35–45	1.4 : 1 : 7 : 3
6	CH_2Cl_2	$MeAlCl_2$	0 °C	1.5 h	25–35	1.2 : 1 :10: 3

[a] reactions were carried out at 0.01M concentration. [b] product ratios are determined by ^1H NMR analysis.
[c] ***3.26-Z*** is recovered

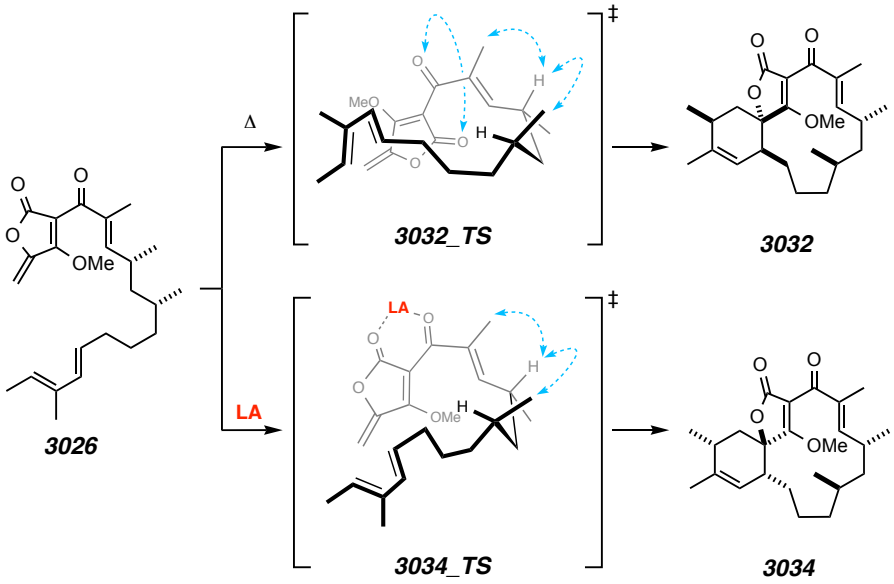


3026-Z (recovered)

This stereochemical dichotomy immediately piqued my interest. Upon a more careful analysis of the structural difference of each product, I noticed that both the most (**3032**) and the second most (**3033**) dominant isomers formed under thermal conditions (entry 1 and 2) arose from the *si*-face attack at C16a of dienophile by the diene, whereas **3034** and **3035**, products preferred under Lewis acid catalyzed conditions result from *re*-face attack at C16a. We attempted to explain this unusual facial selectivity alteration with the two transition structures **3032_TS** and **3034_TS** shown in Scheme 3.11. In the absence of Lewis acids, the IMDA reaction should preferentially pass through the transition structure **3032_TS**, in which 1) the IMDA reaction occurs in an *endo* fashion with respect to the endocyclic double bond; 2) the dipole moment of the two carbonyl groups are

opposed;[60,61] 3) the $A^{1,3}$ interaction is minimized; and 4) the unfavorable 1,3-dialkyl repulsions are avoided. Therefore, tricycle **3032** is produced predominantly. In the presence of Lewis acids (i.e., $LiClO_4$ and $MeAlCl_2$ in these experiments), however, the bis–chelating ability of the metal cations enforced the two carbonyl groups to take the s-*cis* conformation, resulting in the revelation of the opposite face, i.e., *re*-face of C16 to the diene unit, leading to the formation of **3034** as the major product. In short, we presume that the different preferred orientation of the two carbonyl groups under each condition accounts for the observed switch in stereoselectivity.

Scheme 3.12| Rationalization of the difference in facial selectivity under thermal conditions vs. under Lewis acid catalysed conditions.

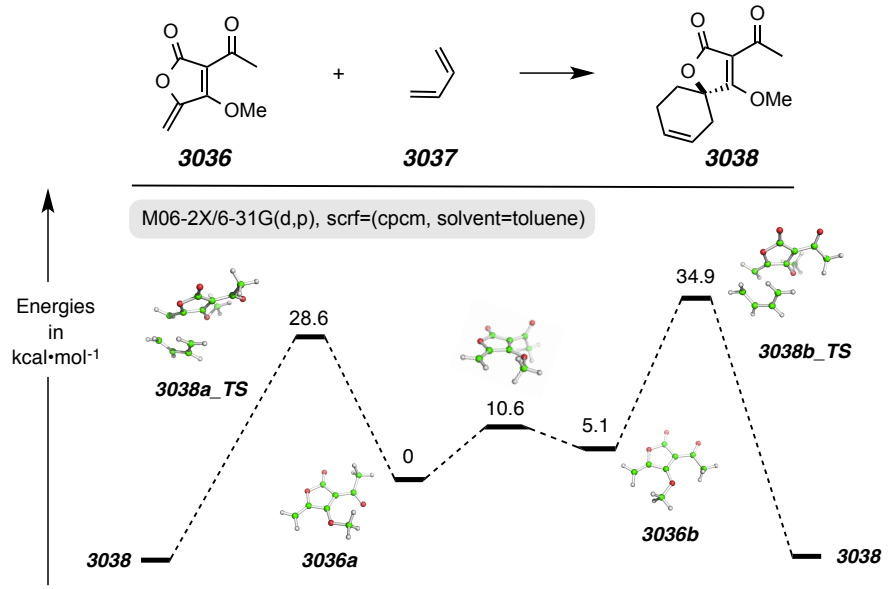


[60] Preference to minimize dipole moment in non-polar solvents has been invoked to explain solvent effects on the reaction rate of certain IMDA reactions. For example, see: Jung, M. E.; Gervay, J. Solvent effects in intramolecular Diels-Alder reactions of 2-furfuryl methyl fumarates: evidence for a polar transition state. *J. Am. Chem. Soc.*, **1989**, *111*, 5469–5470.

[61] This anti-relationship of the two carbonyls was also proposed in the transition structure of the IMDA reaction used in the abyssomycin C synthesis.[34a]

To substantiate the above rationale, I performed a computational study using density functional theory [M062X[62]/6-31+G(d,p), scrf=(cpcm[63], solvent=toluene)]. I have located transition states for a pair of simple model reactions. Namely, the bimolecular cycloaddition between butadiene (**3037**) and the anti vs. syn conformation of the simple enoyltetronate (**3036**) was computed to locate the transition state geometries. That for the anti isomer **3038a-TS** was favored over that for the **3038b-TS** by 6.3 kcal/mol (Scheme 3.13). In fact, this activation energy difference is largely a reflection of the relative stability of the two isomeric starting materials: the s-*cis* isomer **3036b** is less stable than the s-*trans* isomer **3036a** by 5.1 kcal•mol^{-1}, presumably due to the larger dipole moment

Scheme 3.13| Calculated transition structures for [4+2] cycloaddition of butadiene (**3037**) with a truncated model methylene acyltetronate (**3036**).



[62] 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.

[63] Tomasi, J.; Persico, M. Molecular interactions in solution: An overview of methods based on continuous distributions of the solvent. *Chem. Rev.* 1994, *94*, 2027–2094.

of the former (10.6 Debye vs. 4.4 Debye).[64] The computed results of these two model reactions support our assumptions made in Scheme 3.12: under thermal conditions, the two carbonyl groups in **3026** adopt an anti-relationship preferentially, and **3032_TS** is energetically favored over **3034_TS**.

Through studying these aspects of stereoselectivity, we have gained substantial mechanistic insights into this synthetically powerful and biosynthetically significant IMDA reaction. In view of our proposed models (**3032**_TS and **3034**_TS in Scheme 3.12), which are consistent with the observed stereoselectivity switch under different conditions, it is tempting to hypothesize that the anti-relationship of the two carbonyl groups in the acyltetronate subunit is actually adopted by all the transition structures of IMDA reactions that are responsible for the biosynthesis of relevant spirotetronates, and that such an anti-relationship is a key element Nature utilizes to control the diastereoselectivity of these IMDA reactions. It is especially pertinent to mention here that in each of the two "failed" attempts of applying the IMDA reaction in spirotetronate synthesis (see Scheme 2.6[28] and 2.9[36]), the acyltetronate unit had been artificially modified in a way that this anti-relationship became not preferred or not attainable.

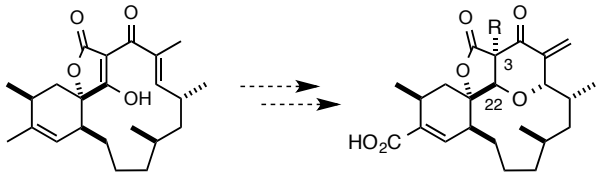
[64] Conformers with larger dipole moments are better stabilized in polar solvents. It is consistent to observe that the facial selectivity is lower in CH_3OH/H_2O than in toluene by a factor of two (compare entry 1 and 2 in Scheme 3.11).

Chapter 4. Progress toward the Total Synthesis of Okilactomycins

4.1. Attempted strategies to convert okilactomycin D to okilactomycin

Having established a robust and scalable synthetic route to okilactomycin D (see Chapter 3), I then made attempts to convert it to other members in the okilactomycin family [e.g., okilactomycin (**4002**) and chrolactomycin (**4003**)]. However, this task turned out to be more complicated than it appeared.

Scheme 4.1| Conversion of okilactomycin D to other okilactomycins



4001 Okilactomycin D

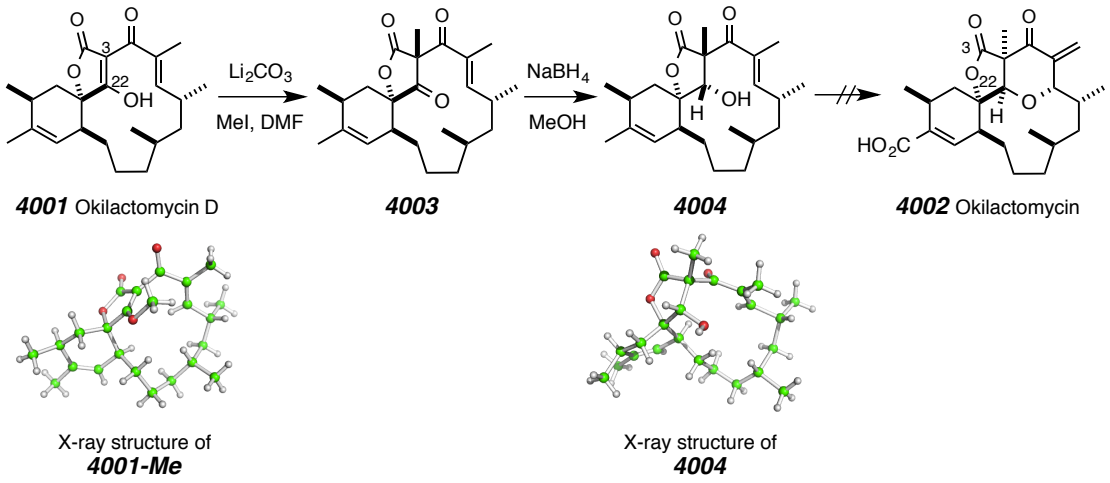
4002 R = Me, Okilactomycin
4003 R = OMe, Chrolactomycin

When comparing okilactomycin (**4002**) with okilactomycin D (**4001**), we noticed that both of the two additional substituents at C3 (a methyl) and C22 (a hydrogen) in the former occupy the α-face (i.e., face beneath the plane). Unfortunately, the α-face of the enolic double bond in okilactomycin D (**4001**) is largely shielded by the macrocyclic chain, as can be inferred from the X-ray crystal structure of *o*-methylated okilactomycin D (**4001-Me**, Scheme 4.2). Indeed, when treating okilactomycin D with C-methylating conditions[65] (Li_2CO_3, MeI, DMF), the triketone **4003**, which bears the incorrect configuration at C3, was formed exclusively. Reduction of **4003** with $NaBH_4$ under carefully controlled conditions yielded the crystalline alcohol **4004**, whose structure was

[65] Wymann, W. E.; Davis, R.; Patterson, J. W.; Pfister, J. R. Selective Alkylations of Certain Phenolic and Enolic Functions with Lithium Carbonate/Alkyl Halide. *Synth. Commun.* **1988**, *18,* 1379–1384.

unambiguously established by X-ray crystallography. Attempts to rectify the incorrect configurations of **4004** at C3 and C22, for example, through the retro-aldol/aldol sequence, were not successful.

Scheme 4.2| First unsuccessful attempt to convert okilactomycin D to okilactomycin.

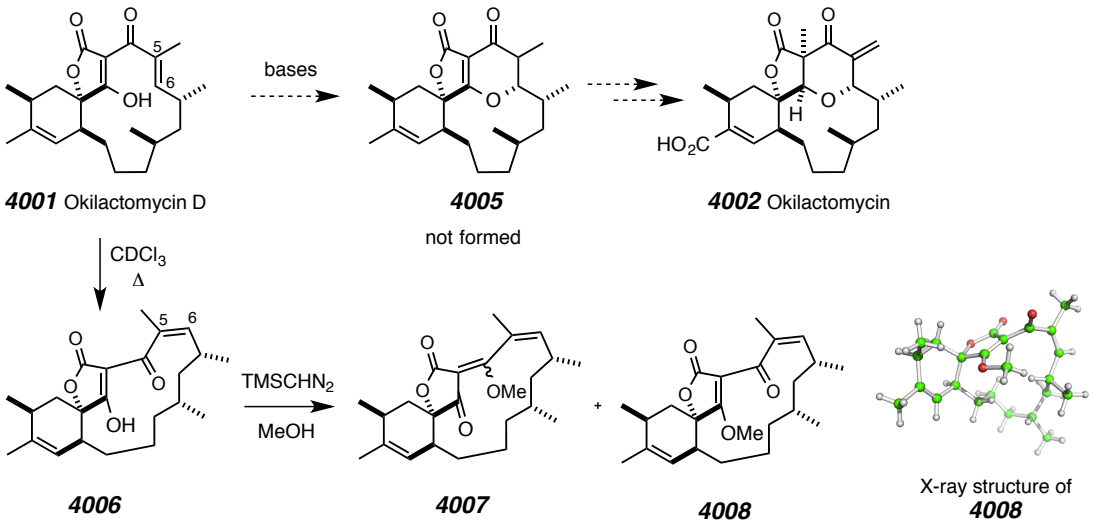


Upon realizing it is hard to override the inherent facial selectivity at C3 and C22 in okilactomycin D (**4001**) imposed by its tricyclic structure, I then decided to convert **4001** to the corresponding pyranone **4005** (Scheme 4.3), anticipating that the resulting tetracyclic structure would take a different posture and reveal the opposite face of its enol ether bond. However, this cyclization could not be realized by any of the basic conditions attempted: the skeleton of **4001** was left intact after treatment with various organic and inorganic bases even at elevated temperatures. The inertness of **4001** under basic conditions might be a result of the low nucleophilicity of acyl tetronic acid moiety.

Interestingly, in our hands a solution of the neutral okilactomycin D (**4001**, pKa ≤ 1[53]) in $CDCl_3$ slowly, but fully, isomerized to the (more stable) C5–C6 *Z*-alkene **4006** (Scheme 3.16, $K_{eq(\mathbf{4006}:\mathbf{4001})} > 50:1$). This transformation was noticeably slower in CD_3OD. Treating this new, previously unreported isomer of okilactomycin D **4006** with

methylating conditions ($TMSCHN_2$, CH_3OH) yielded a ca. 1:1 mixture of two isomeric methyl enol ethers **4007** and **4008**. X-ray analysis of the crystalline compound **4008** unambiguously determined its relative configuration, thereby confirming the structure of **4006**. Interestingly, the natural product itself has not undergone this exergonic *E*-to-*Z* enone isomerization, presumably because acyl tetronic acids exist largely as their conjugate bases in physiological environments.

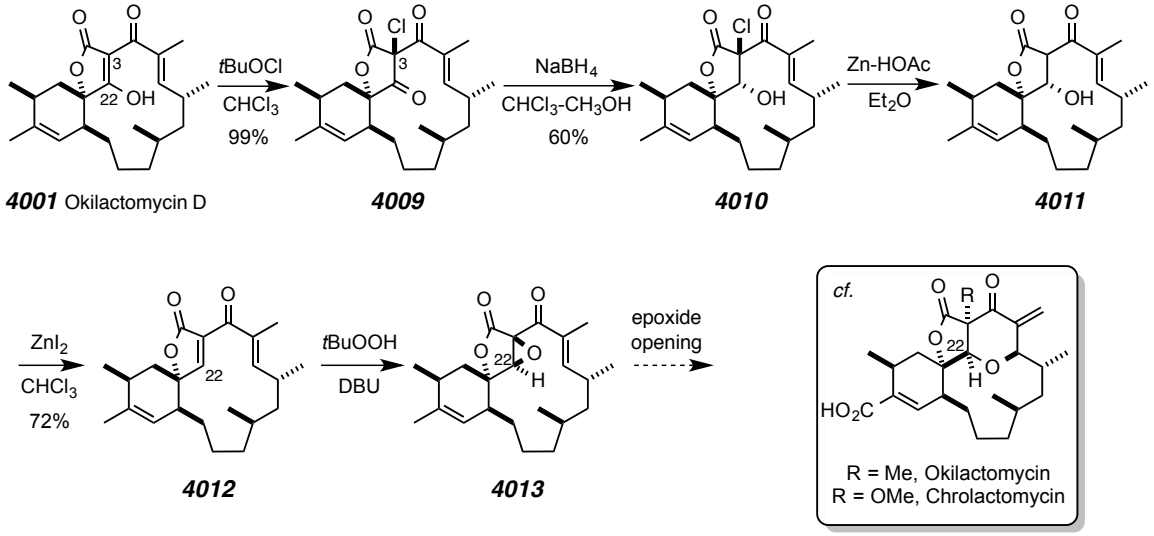
Scheme 4.3| Second unsuccessful attempt to convert okilactomycin D to okilactomycin



Because 1) preparation of tetracycle **4005** from okilactomycin D (**4001**) could not be achieved, and 2) the β-face of C3 in the accidentally obtained isomer **4006** is also blocked (as suggested by the crystal structure of **4008**), I turned to a third strategy, which is shown in Scheme 4.4. In this strategy I initially installed a chlorine atom at C3 of okilactomycin D, forming the tricarbonyl chloride **4009**. This chlorination reaction should also occur at α-face of C3, but the chlorine atom attached could be removed at a late stage. Chemo-, regio-, and stereoselective reduction of **4009** with $NaBH_4$ gave

alcohol **4010** in ca. 60% yield. Dechlorination of **4010** with Zn/HOAc smoothly gave alcohol **4011**, which then underwent dehydration to afford the dienone **4012** under the catalysis of ZnI_2. This 4 step sequence from **4001** to **4012** accomplished a net deoxygenation at C22 of okilactomycin D. Epoxidation of dienone **4012** under basic conditions gave **4013** regioselectively and stereoselectively, which has the correct configuration at C22 and could in principle serve as a common intermediate to both okilactomycin and chrolactomycin. However, methods to open the epoxide ring in **4013** with concomitant introduction of a substituent at C3 have not yet been productive.

Scheme 4.4| Third attempt to convert okilactomycin D to okilactomycin.

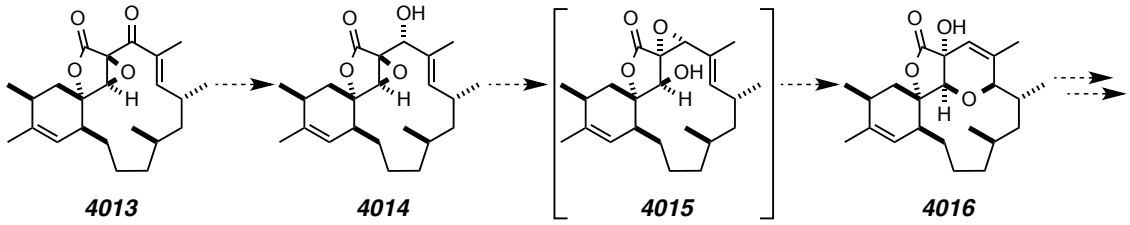


4.2 Future directions

Although a total synthesis of okilactomycin from okilactomycin D has not been achieved yet, additional tactics to solve this problem have been conceived, some of which are discussed in this section.

It is challenging to open the epoxide ring in **4013** (Scheme 4.4) presumably for twofold reasons: 1) the desired reactive center (C3) is quaternized and hence sterically encumbered; in addition, the macrocyclic ring in **4013** blocks the trajectory of an incoming nucleophile; 2) the C3 center is electronically less activated than the C22 center, so a regioselectivity issue must be addressed at the same time.

Scheme 4.5| A Payne rearrangement/cyclization strategy to make tetracyclic skeleton of okilactomycin and chrolactomcyin from **4013**



A potential strategy to overcome both of the above two issues is based upon a Payne rearrangement/pyran ring formation cascade (Scheme 4.5). It is reasonable to assume enone **4013** could be reduced chemo- and stereoselectively to form allyl alcohol **4014**. Allyl alcohol **4014** could then be treated with an appropriate base to undergo a Payne rearrangement,[66] providing the isomeric alcohol **4015**. Alcohols **4014** and **4015** might exist as an equilibrating mixture, but the latter is positioned to undergo an intramolecular

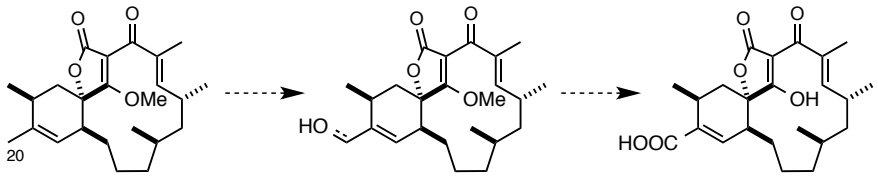
[66] a) Payne, G. B. Epoxide migrations with α,β-epoxy alcohols. *J. Org. Chem.*, **1962**, *27*, 3819–3822. b) Hoye, T. R.; Jeffrey, C. S.; Nelson, D. P. Dynamic kinetic resolution during a vinylogous Payne rearrangement: A concise synthesis of the polar pharmacophoric subunit of (+)-scyphostatin," *Org. Lett.* **2010**, *12*, 52–55.

SN_2' displacement to form the epoxide ring opened tetracycle **4016**, driving the equilibrium to the desired direction. It is noteworthy that tetracycle **4016** has all stereocenters present in chrolactomycin correctly installed.

The total synthesis of okilactomycin C could be investigated in parallel. Studies in this direction is worthwhile for two reasons: 1) a robust strategy to install the oxidation states on C20 in **4001–Me** is a prerequisite to accomplish the synthesis of any other members in okilactomycin family; 2) certain intermediates gleaned along this avenue may have unusual architectures or electronic properties that inspire new strategies to okilactomcyin and chrolactomycin synthesis.

The most straightforward strategy to synthesize okilactomycin C is to directly oxidize the allylic C-H bonds in the C20 methyl group (Scheme 4.6). SeO_2, the reagent conventionally utilized for this purpose has been tried, but with no success. Undesirable oxidation at the two tertiary allyl centers has been observed as the major competing pathways.

Scheme 4.6| Unsuccessful attempt toward total synthesis of okilactomycin C.

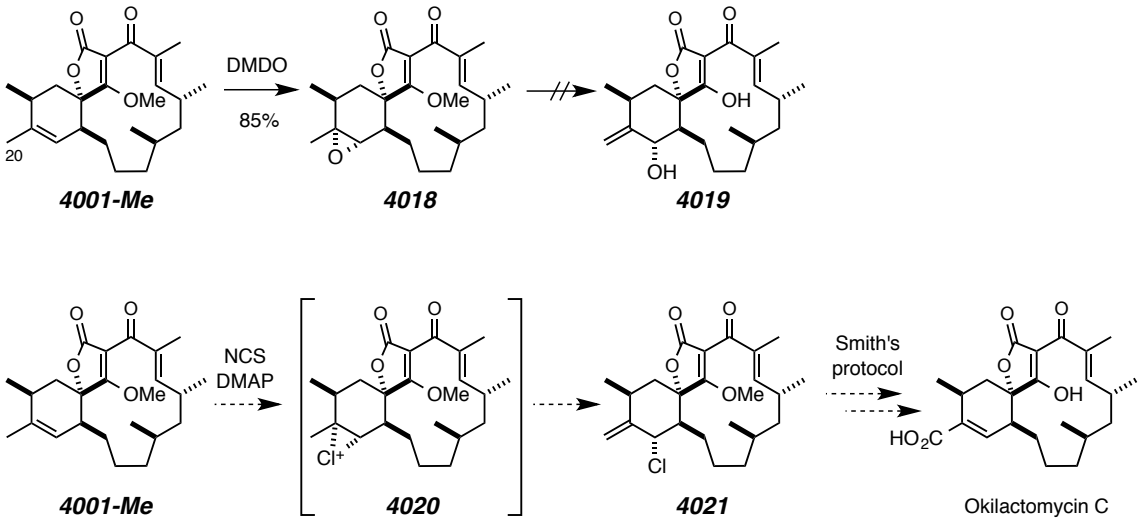


4001-Me ***4017*** Okilactomycin C

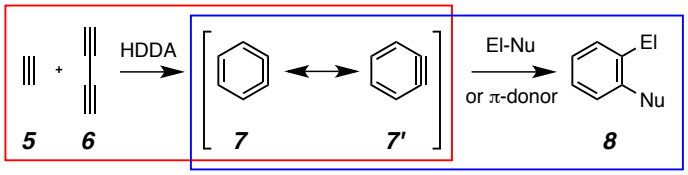
Indirect ways to oxidize the C20 methyl group have also been attempted (Scheme 4.7). Although the oxidation of **4001-Me** to epoxide **4018** could be realized in high yielding by using DMDO, the required ring opening of **4018** to provide **4019** could not be effected by conventional methods. I attribute the difficulty in this conversion to the

relatively low reactivity of an epoxide functional group. However, if a structurally analogous but more reactive chloronium bridge could be formed with *N*-chloro succinimde, an allyl chloride **4020** may be formed directly in the presence of a suitable base. Similar transformations to those used in Smith's total synthesis of okilactomycin could then be adopted to convert allyl chloride **4021** to okilactomycin C.

Scheme 4.7| Strategy toward total synthesis of okilactomycin C.



The Hexadehydro-Diels–Alder (HDDA) Reaction



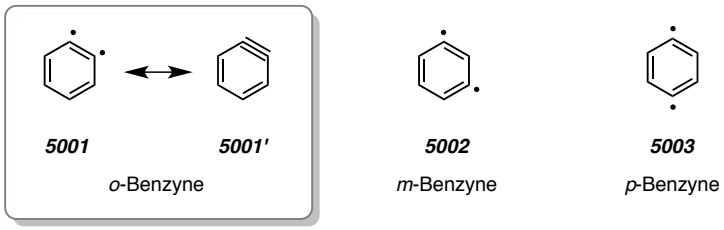
CHAPTER 5. INTRODUCTION TO *O*-BENZYNE

5.1 Historical background of *o*-benzyne

Arynes comprise a class of reactive intermediates that are formally derived from aromatic rings by removal of two substituents (see Figure 5.1 for structures of benzynes). Depending on the relative position of the two substituents that are absent, arynes can be divided into three categories: *ortho*-arynes (cf. **5001**), *meta*-arynes (cf. **5002**), and *para*-arynes (cf. **5003**). These structurally unusual species have been continuously provoking the interests of research groups from all branches of chemistry.

In spite of their identical composition, each class of arynes has its own distinctive physical and chemical properties. For example, the bonding interaction between the two electrons is considerably stronger in **5001** than in **5002** or **5003**, and the structure of *o*-benzyne is most often denoted as **5001'** as a result (vide infra). While more detailed discussion of *m*-arynes and *p*-arynes could be found elsewhere,[67] this chapter will be focused mostly on *o*-arynes.

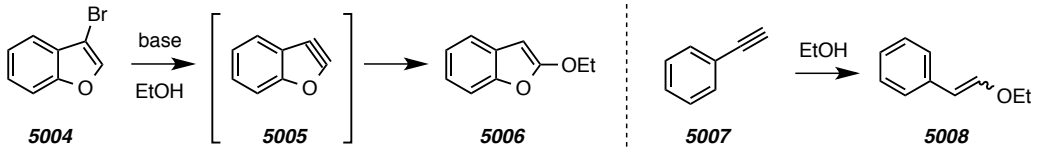
Figure 5.1| Structures of benzynes.



[67] a) Wenthold, P. G. Thermal chemical properties of the benzynes. *Aust. J. Chem.* **2010,** *63,* 1091–1098. b) Wenk, H. H.; Winkler, M.; Sander, W. One century of aryne chemistry. *Angew. Chem. Int. Ed.* **2003**, *42*, 502–528. c) Sander, W. *m*-Benzyne and *p*-benzyne. *Acc. Chem. Res.* **1999**, *32*, 669–676.

o-Aryne (cf. **5001**) is one of the oldest, most well-known, and most extensively studied reactive intermediates in chemistry. The first experimental evidence now interpreted as involving the formation of an aryne intermediate dates back to 1902[68] (Scheme 5.1). When exploring the reactivities of bromobenzofuran derivatives, Stoermer and Kahlert observed the formation of 2-ethoxybenzofuran (**5006**) on treating 3-bromobenzofuran (**5004**) with bases in ethanol. Inspired by the known reaction at the time between phenylacetylene (**5007**) and ethanol that gives enol ether **5008**, the authors bravely postulated the formation of *o*-didehydrobenzofuran (**5005**), a species with a *nonlinear* triple bond, as an intermediate in their reaction (Scheme 5.1).

Scheme 5.1| The first example where an aryne species (**5005**) was explicitly proposed as an intermediate. The proposed mechanism for the formation of **5006** was inspired by the known reaction between phenylacetylene (**5007**) and ethanol to form enol ether **5008**.



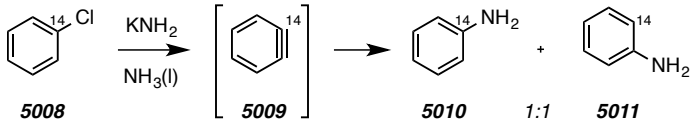
Although the intermediacy of arynes had been speculated occasionally during the following years, definitive evidence for the existence of these unusual species was not obtained until ca. half a century later. In 1953, a classic isotope scrambling reaction reported by Roberts' group[69] for the first time solidified the intermediacy of *o*-benzyne (**5009**, Scheme 5.2). Upon treating the C14-labeled chlorobenzene **5008** with potassium

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

[69] a) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. Rearrangement in the reaction of chlorobenzene-1-C^{14} with potassium amide. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291. b) Roberts, J. D.; Vaughan, C. W.; Carlsmith, L. A.; Semenow, D. A. Orientation in aminations of substituted halobenzenes. *J. Am. Chem. Soc.* **1956**, *78*, 611–614.

amide in liquid NH_3, the authors observed that the isomeric anilines **5010** and **5011** were formed in ca. 1:1 ratio. The formation of almost equal amounts of the two isomeric anilines could only be understood by the formation of a species whose 1- and 2-positions are equivalent, providing compelling evidence for the existence of *o*-benzyne. Almost simultaneous with Roberts' work, Huisgen[70] and Wittig[71] discovered that *o*-benzynes could serve as potent dienophiles and participate in [4+2] cycloadditions with furan. These results provided additional support for the proposed structure of *o*-benzyne.

Scheme 5.2| First definitive evidence for the intermediacy of *o*-benzyne.



Later, *o*-benzyne was observed using physical methods. In 1963, Berry et al.[72] investigated the gas phase decomposition of benzenediazonium carboxylates under photoinitiated conditions and characterized the resulting *o*-benzyne by UV and mass spectrometry. Almost simultaneously, Fisher and Lossing[73] studied the pyrolysis of 1,2-diiodobenzene using mass spectrometry and identified the formation of *o*-benzyne based on the measured ionization potential.

Using negative ion photoelectron spectroscopy, Leopold et al.[74] determined the

[70] Huisgen, R.; Rist, H. Über Umlagerungen bei nucleophilen Substitutionen in der aromatischen Reihe und ihre Deutung. *Naturwissenschaften* **1954**, *41*, 358–359.

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

[72] a) Berry, R. S.; Clardy, J.; Schafer, M. E. Benzyne. *J. Am. Chem. Soc.* **1964**, 86, 2738–2739. b) Berry, R. S.; Spokes, G. N.; Stiles, M. The absorption spectrum of gaseous benzyne. *J. Am. Chem. Soc.* **1962**, *84*, 3570–3577.

[73] Fisher, I. P.; Lossing, F. P. Ionization potential of benzyne. *J. Am. Chem. Soc.* **1963**, *85*, 1018–1019.

[74] Leopold, D. G.; Miller, A. E. S.; Lineberper, W. C. Determination of the singlet-triplet splitting and electron affinity of *o*-benzyne by negative ion photoelectron spectroscopy. *J. Am. Chem. Soc.* **1986**, *108*, 1379–1384.

energy gap between singlet state and triplet state (ΔE_{ST}) of *o*-benzyne to be 37.6 kcal•mol^{-1}. This value was further supported by Wenthold and coworkers[75] using ultraviolet photoelectron spectroscopy. Due to the less effective orbital overlap caused by ring constriction, the bonding interaction of the two electrons at the two adjacent C_{sp} atoms in *o*-benzyne is significantly weaker than those in a typical π-bond (ca. 60 kcal•mol^{-1}). Nonetheless, the bonding interaction is strong enough to render diradical like structure **5001** (Figure 5.1) not a significant resonance contributor for *o*-benzyne.

Infrared (IR) spectroscopy, a technique routinely employed to measure the vibrational frequencies of chemical bonds, provides valuable insights into the strengths of the bonds studied. Not surprisingly, the extremely high reactivity of *o*-benzyne posed significant challenge in its characterization with IR spectroscopy. By using photochemical transformations, Chapman et al.[76] generated *o*-benzyne in an argon matrix at 77 K, and made the first direct IR spectroscopic characterization of *o*-benzyne. However, the vibration frequency of the strained C_{sp}-C_{sp} bond in *o*-benzyne could not be definitively assigned at the time because of the co-occurrence of other species with *o*-benzyne during the reaction. This problem bewildered the community for almost 20 years. In 1992, through a very careful study that combined the use of 1) high-resolution, single-site IR spectra, 2) isotopic shifts, 3) calculated frequencies, 4) experimental symmetries, 5) line shapes, and 6) in part intensities, Radziszewski et al.[77] finally assigned the stretching

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[75] Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. Ultraviolet photoelectron spectroscopy of the *o-, m-,* and *p-benzyne* negative ions. Electron affinities and singlet-triplet splittings for *o-, m-,* and *p-benzyne*. *J. Am. Chem. Soc.* **1998,** *120,* 5279–5290.

[76] a) Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky, J.; Calder, G. V.; Orr, G. Photochemical transformations. LII. Benzyne. *J. Am. Chem. Soc.* **1973**, *95*, 6134–6135. b) Chapman, O. L.; Chang, C. C.; Kolc, J.; Rosenquist, N. R.; Tomioka, H. A photochemical method for the introduction of strained multiple bonds: Benzyne C≡C stretch. *J. Am. Chem. Soc.* **1975**, *97*, 6586–6588.

[77] Radziszewski, J. G.; Hess, B. A. J.; Zahradnik, R. Infrared spectrum of o-benzyne: experiment and theory. *J. Am. Chem. Soc.* **1992**, *114*, 52–57.

frequency of this C_{sp}–C_{sp} bond in *o*-benzyne to an absorption at 1846 cm^{-1}. The measured frequency indicates that the strength of this unusual C_{sp}–C_{sp} bond is closer to a typical C–C triple bond (1974 cm^{-1} in acetylene) than to a typical C–C double bond (1623 cm^{-1} in ethylene).

o-Benzyne has also been characterized by NMR spectroscopy. By using hemicarcerand as a "molecular container", Warmuth[78] reported the isolation and NMR characterization of *o*-benzyne in a THF solution! The obtained NMR data from this work provided a valuable reference for future computational studies on *o*-benzyne. Using dipolar ^{13}C NMR spectrometry, Orendt et al.[79] determined the bond length of the C_{sp}–C_{sp} bond in argon matrix stabilized *o*-benzyne to be 1.24 Å. Again, this value is closer to that of a typical C–C triple bond (1.20 Å pm in acetylene) than that of a C–C double bond (1.34 Å in ethylene).

Not surprisingly, computation has played a critical role in assessing certain properties of *o*-benzyne. For example, using DFT method (B3LYP/6 –311+G**//B3LYP/6–311+G**), De Proft et al.[80] has calculated the aromatic stabilization energy of *o*-benzyne to be 34.9 kcal/mol, suggesting *o*-benzyne has almost as much aromaticity as benzene. Houk, Warmuth, Schleyer, and coworkers[81] estimated the strain energy of the bent bond in *o*-benzyne to be 53.6 kcal•mol^{-1} by comparing the energy difference between a fully

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[78] Warmuth, R. *o*-Benzyne: Strained alkyne or cumulene?—NMR characterization in a molecular container. *Angew. Chem. Int. Ed.* **1997**, *36*, 1347–1350.

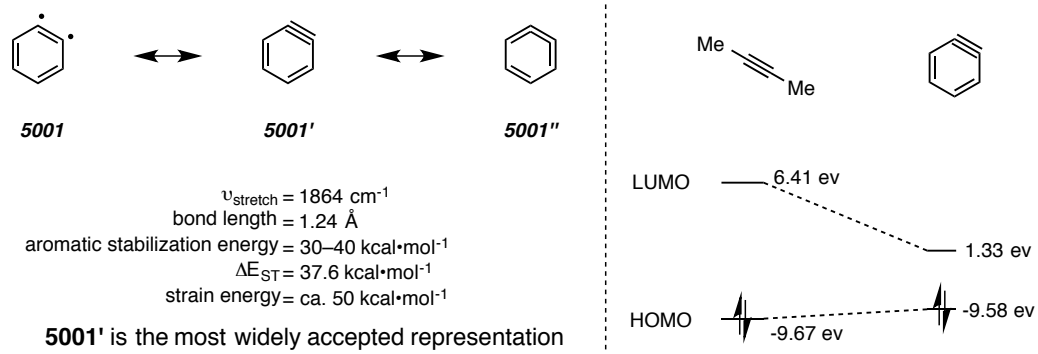
[79] Orendt, A. M.; Facelli, J. C.; Radziszewski, J. G.; Horton, W. J.; Grant, D. M.; Michl, J. ^{13}C dipolar NMR spectrum of matrix-isolated *o*-Benzyne-*1,2*-$^{13}C_2$. *J. Am. Chem. Soc.* **1996**, *118*, 846–852.

[80] De Proft, F.; Schleyer, P. V. R.; Van Lenthe, J. H.; Stahl, F.; Geerlings, P. Magnetic properties and aromaticity of *o*-, *m*-, and *p*-benzyne. *Chem. Eur. J.* **2002**, *8*, 3402–3410.

[81] Jiao, H.; Schleyer, P. V. R.; Beno, B. R.; Houk, K. N.; Warmuth, R. Theoretical studies of the structure, aromaticity, and magnetic properties of *o*-benzyne. *Angew. Chem. Int. Ed.* **1997**, *36*, 2761–2764.

optimized and a partially optimized alkyne. Consistent with this result, Johnson et al.[82] estimated this strain energy to be 50.1 kcal/mol by calculating the ΔH_R of an isodesmic reaction (*o*-benzyne + *Z*-2-butene → benzene + 2-butyne). The large strain energy in *o*-benzyne is a major reason for its kinetic instability. Ab intio calculations revealed that the LUMO energy of *o*-benzyne is significantly lowered compared with that of 2-butyne, while HOMO energies of the two are largely the same. The extremely low LUMO energy explains that *o*-benzyne most frequently serves as the electrophile in the reported transformations.

Figure 5.2| Summary of physical properties of o-benzyne.



To conclude this section, I would like to dabble into a practical issue. At least three resonance structures (**5001**, **5001'** and **5001''** in Figure 5.2) could be drawn for *o*-benzyne. Which one of the three structures reflects most faithfully the inherent properties of *o*-benzyne? From the review above, it became evident that structure **5001'**, one with a strained triple bond, denotes *o*-benzyne most accurately. Indeed, this Lewis structure is the most widely used representation for *o*-benzyne by chemists, although the other two are encountered on certain occasions.

[82] Johnson, R. P.; Daoust, K. J. Interconversions of cyclobutyne, cyclopentyne, cyclohexyne, and their corresponding cycloalkylidenecarbenes. *J. Am. Chem. Soc.* **1995**, *117*, 362–367.

5.2 A brief review of *o*-benzyne trapping methods

o-Arynes have attracted a tremendous amount of attention from the synthetic community because of their synthetic versatility. Because two functional groups can be installed in one operation, synthetic methods involving *o*-aryne intermediates are especially powerful in preparing poly-substituted arenes. In 1950s, seminal work from the groups of Huisgen, Wittig, and Roberts that proved the existence of *o*-benzyne fueled a large amount of in aryne research. By as early as in 1967, hundreds of aryne trapping reactions had already been developed, as elucidated by the manifold results compiled in the monograph by Hoffmann.[83] In 1983, Kobayashi[84] introduced what has become the most widely used aryne-making method. This involved treating 2-(trimethylsilyl)-phenyl triflate (and its derivatives) with fluoride ions. The mild conditions of this method, coupled with its operational ease, sparked a remarkable rebirth of interest in the study of aryne chemistry. This resurgence is exemplified by the plethora of major reviews on benzyne/aryne chemistry that have appeared even over just the past few years.

It is neither practical nor necessary to give an extensive review of all aryne-trapping reactions in this document. Therefore, only several representative transformations that illustrate the most typical reactivities of *o*-arynes will be discussed in this section. For ease of orientation, I arbitrarily divide aryne-trapping reactions into three categories: 1) polar reactions, 2) pericyclic reactions, and 3) transition metal catalyzed reactions. Because arynes are species endowed with high strain energy, the products formed during the initial stage of aryne trapping are often reactive intermediates themselves, and could

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[83] Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes (Organic Chemistry, A Series of Monographs*, vol. 11) (Academic Press, 1967).

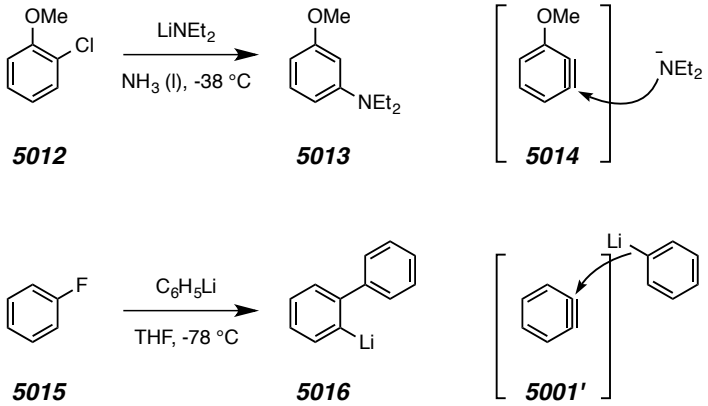
[84] Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-induced 1,2-elimination of *o*-trimethylsilylphenyl triflate to benzyne under mild conditions. *Chem. Lett.* **1983**, *12*, 1211–1214.

isomerize or react with other components to form more stable compounds. In other words, arynes are frequently engaged in multicomponent or cascade reactions, and a certain aryne-trapping transformation may involve, for example, both a polar addition step and a pericyclic reaction step. Some of these reactions are classified into one certain category or the other just for ease of discussion.

1. Polar reactions.

Polar addition is the most commonly encountered aryne reactivity in literature. Although *o*-arynes are electronically neutral species, their extremely low-lying LUMO render these species very potent electrophiles. In fact, the very first reported aryne trapping reaction is a polar addition to aryne by ethanol (Scheme 5.1).

Scheme 5.3| Polar addition to benzyne by anionic species

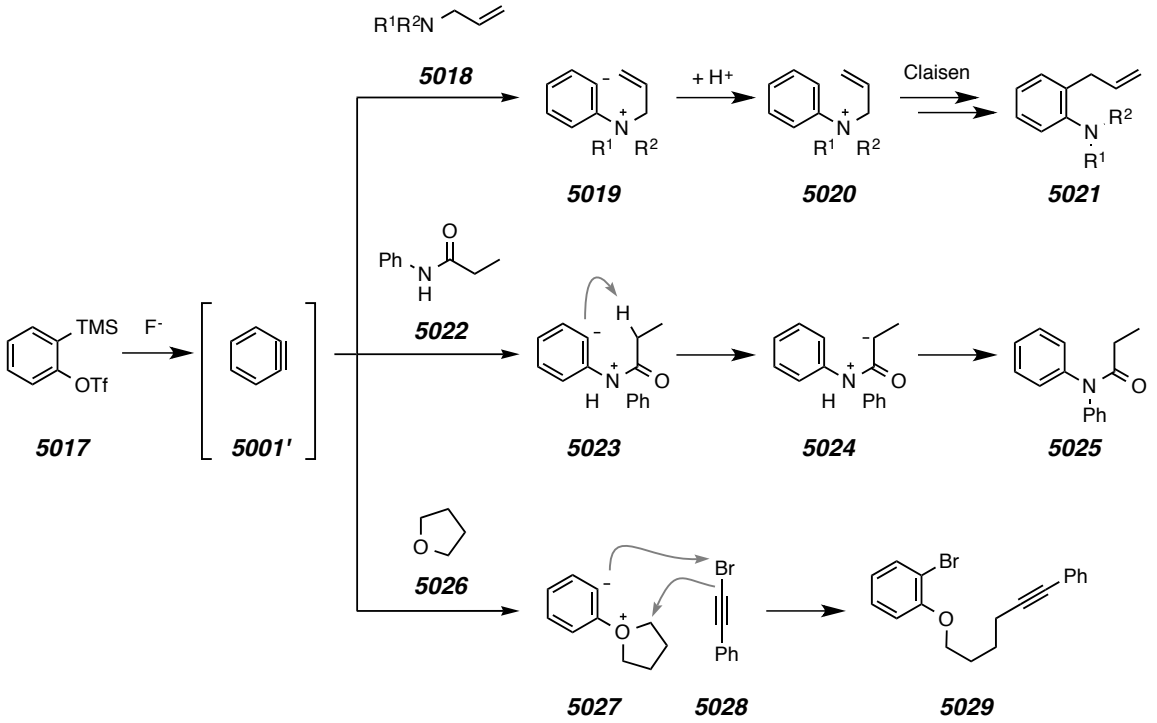


Later in 1940s, Gilman[85] observed an unusual substitution reaction of 2-chloro anisole (**5012**) under basic conditions to give 3-diethylamino anisole (**5013**). In retrospect, this unexpected substitution reaction can be explained by the initial formation of the benzyne derivative **5013**, followed by a regioselective addition to the polarized

[85] Gilman, H.; Avakian, S. Dibenzofuran. XXIII. Rearrangement of halogen compounds in amination by sodamide. *J. Am. Chem. Soc.* **1945**, *67,* 349–351.

triple bond by the external amide anion. Also in the 1940s, Wittig observed that subjecting fluorobenzene (**5015**) to C_6H_5Li yielded the organolithium species **5016**. Apparently, this transformation involved the addition of phenyl anion to *o*-benzyne (**5001'**) generated under the reaction conditions.

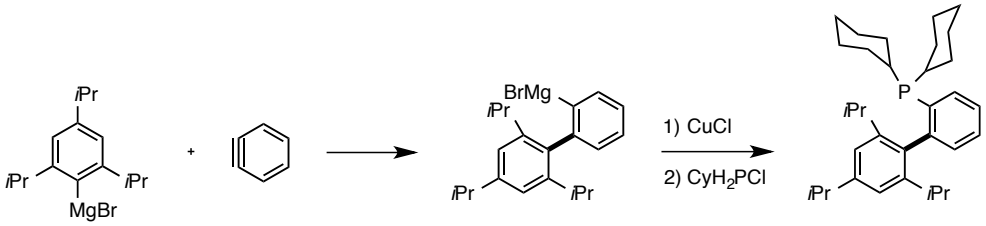
Scheme 5.4| Polar addition to benzyne by neutral species.



Benzyne could also be efficiently trapped by neutral nucleophiles. Because the product resulting from the initial addition step in these transformations is bound to be a zwitterion, a cascade normally ensues. For instance, Greaney reported that benzyne **5001'** (generated from Kobayashi's precursor **5017**) could be trapped by the neutral amine **5018** to furnish **5019** as an intermediate. Zwitterion **5019** is then protonated in situ to give cationic species **5020**, which upon heating undergoes a facile aza-Claisen rearrangement to give aniline derivative **5021** as the final product after tautomerization. The same group

found that benzyne could be attacked by amides, which are deemed to be much less nucleophilic than amines. Reaction between **5001'** and amide **5022** results in the initial formation of **5023**, which is poised to undergo an intramolecular proton transfer to yield the more stable zwitterion **5024**. The following proton transfer events finally afford amide **5025** as the final product. Benzyne could even be intercepted by ethers in a polar addition fashion. Yoshida and coworkers[86] described a multicomponent cascade reaction that was initiated by a polar addition of THF (**5026**) to benzyne **5001'**. They found that the originally formed zwitterion **5027** could react with a bromoalkyne like **5028**, producing bromoarene **5029** as the ultimate product in decent yield.

Scheme 5.5| A polar addition to aryne in the synthesis of XPhos.



5030 ***5001*** ***5031*** ***5032***, XPhos

The high reactivity of benzyne as an electrophile has enabled the formation of otherwise hard-to-construct bonds and finds wide applications in the preparation of many important aromatics. For example, Buchwald's bulky electron-rich phosphine ligands have gained much attention because of their unique ability to effect difficult C-C, C-N, and C-O bond formations. The key step in the syntheses of these ligands [e.g., XPhos

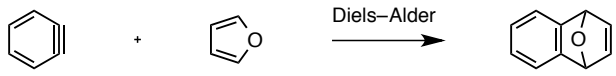
[86] Yoshida, H; Asatsu, Y.; Mimura, Y.; Ito, Y.; Ohshita, J.; Takaki, K. Three-component coupling of arynes and organic bromides. *Angew. Chem. Int. Ed.* **2011**, *50*, 9676–9679.

(**5032**)] involves a polar addition of Grignard reagent **5030** to benzyne **5001'**.[87] The resulting organomagnesium species **5031** is smoothly transformed to phosphine **5032** under the catalysis of Cu(I). The high reactivity of aryne is essential to the efficient construction of the congested aryl–aryl bond in **5032**. This synthesis can be done at substantial scale and tolerates different substitution in either of the reactants, which speaks to the robust nature of this reaction.

2. Pericyclic reactions.

Arynes also function as 2π components in pericyclic reactions. Because of its low-lying LUMO, arynes are also extremely good dienophiles. The first few examples of Diels–Alder reactions involving benzynes were reported by Wittig's group. They found that benzyne could be trapped efficiently by a neutral diene in a [4+2] fashion. Later, Huisgen's group reported that benzynes generated by different methods behave the same in this Diels–Alder reaction.

Scheme 5.6| Diels–Alder reaction between benzyne and furan.



5001' ***5033*** ***5034***

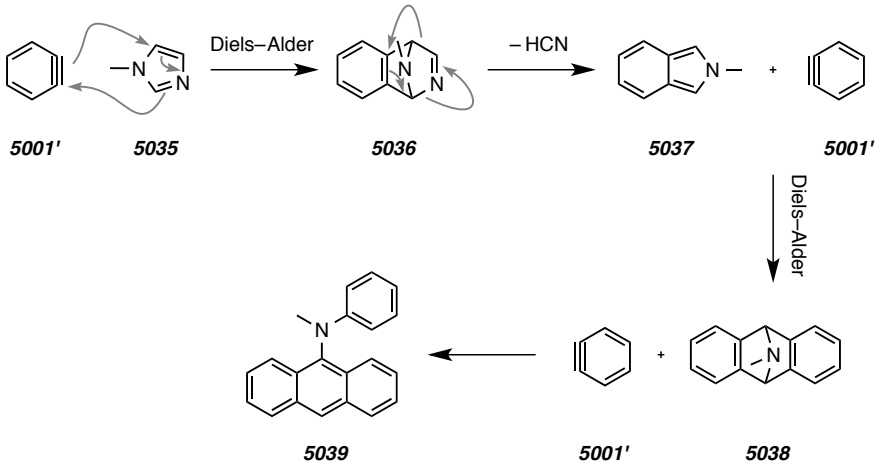
In addition to furan, which is known to be a potent diene in Diels–Alder reactions, benzyne also reacts with other heterocycles traditionally deemed to be sluggish dienes. Zhang and coworkers[88] described a remarkable cascade reaction between benzyne and *N*-substituted imidazoles (Scheme 5.7). The Diels–Alder reaction between o-benzyne with

[87] Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. The use of catalytic amounts of CuCl and other improvements in the benzyne route to biphenyl-based phosphine ligands. *Adv. Synth. Catal.* **2001**, *343*, 789–794.

[88] Xie, C.; Zhang, Y. A new tandem reaction of benzyne: One-pot synthesis of aryl amines containing anthracene. *Org. Lett.* **2007**, *9,* 781–784.

N-methyl imidazole initially gives a tricycle **5036**. The cycloadduct **5036** is not stable under the reaction conditions and undergoes a retro Diels–Alder reaction to eject a molecule of HCN and yields isoindole **5037**. The resulting **5037**, which itself is a potent diene, reacts again in a Diels–Alder fashion with benzyne species that are continuously being generated, to furnish **5038**. The final reaction between amine **5038** and a third molecule of benzyne ultimately provides anthracene **5039**.

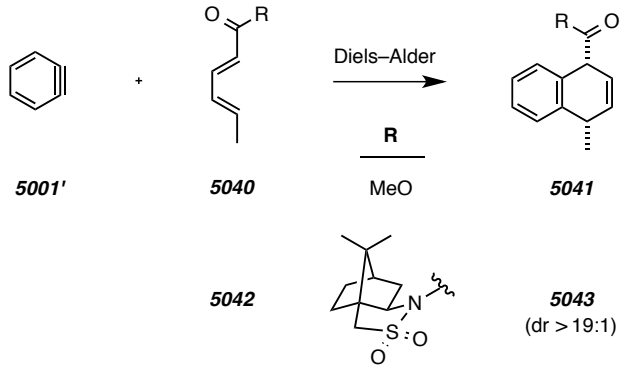
Scheme 5.7| Diels–Alder reaction between benzyne and *N*-methyl imidazole.



Arynes could similarly be trapped by acyclic dienes. Lautens et al.[89] reported that the Diels–Alder reaction between benzyne (generated from Kobayashi's method) and a diene could be used to synthesize functionalized 1,4-dihydronaphthalenes (Scheme 5.8). The high degree of stereoretention observed from diene **5040** to dihydronaphthalene **5041** provides strong support for a concerted reaction mechanism. More impressively, when a diene is endowed with a chiral auxiliary like Oppolzer's sultam (cf. **5041**), the Diels–Alder reaction occurs in a highly diastereoselective fashion, giving **5043** in >19:1 *dr*.

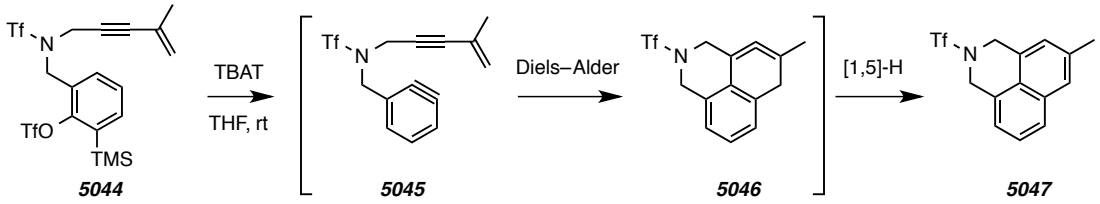
[89] a) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. Synthesis of dihydronaphthalenes via aryne Diels–Alder reactions: scope and diastereoselectivity. *J. Am. Chem. Soc.* **2005**, *127,* 15028–15029. b) Webster, R.; Lautens, M. Conformational effects in diastereoselective aryne Diels–Alder reactions: synthesis of benzo-fused [2.2.1] heterobicycles. *Org. Lett.* **2009**, *11,* 4688–4691.

Scheme 5.8| Diels–Alder reaction between benzyne and acyclic dienes.



Danheiser and coworkers[90] reported that benzyne could engage a conjugated enyne in a Diels–Alder reaction. For instance, a benzyne derivative **5045**, obtained by treating **5044** with a fluoride source (*n*-$Bu_4NSiPh_3F_2$, TBAT), reacts with the intramolecularly tethered enyne subunit to give strained allene **5046** at room temperature, which then rearomatizes smoothly to the more stable naphthalene **5047**. Because high strain is built into the product as well as the corresponding transition structure, Diels–Alder reactions in which enynes function as the 4π component normally require high temperature. The facility under which **5045** cyclizes further attests to the potency of benzynes as dienophiles in Diels–Alder reactions.

Scheme 5.9| Diels–Alder reaction between benzyne and enyne.

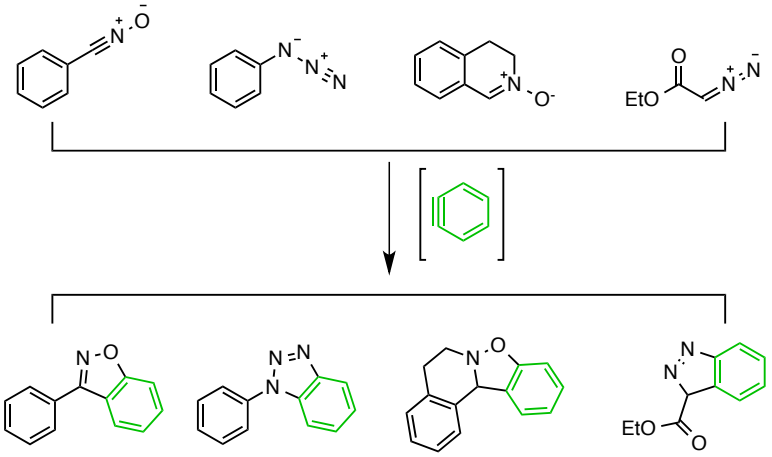


As early as in 1960s, the reactivity of benzynes as potent dipolarophiles had been

[90] Hayes, M. E.; Shinokubo, H. Danheiser, R. L. Intramolecular [4+2] cycloadditions of benzynes with conjugated enynes, arenynes, and dienes. *Org. Lett.* **2005**, *7,* 3917–3920.

explored and established. As summarized in Scheme 5.10, benzyne undergoes efficient [3+2] cycloaddtion reactions with almost all dipoles known to the time.[91,92,93] These reactions represent a useful strategy to prepare benzo-fused heterocycles.

Scheme 5.10| [3+2] cycloaddtion between benzyne and various [1,3]-dipoles

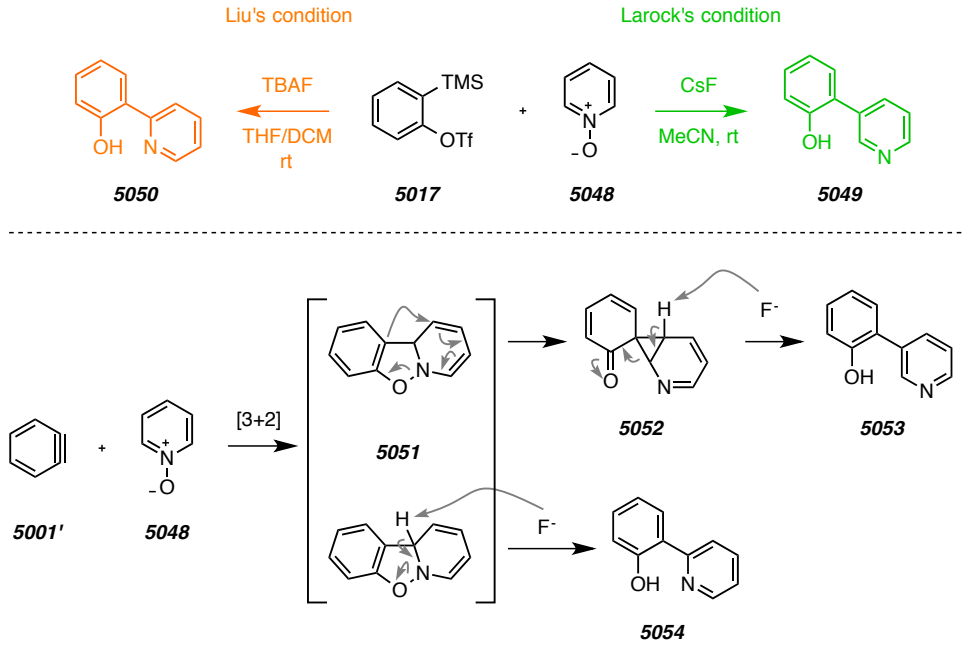


The [3+2] cycloadditions between benzyne and pyridine *N*-oxides are especially interesting (Scheme 5.11). In 2006, Larrock[94] reported that the reaction between **5017** and pyridine *N*-oxide (**5048**) in acetonitrile in the presence of CsF gave 3-substituted pyridine **5049** as the sole product (green). In 2012, Liu[95] noticed that under slightly modified conditions (THF/DCM as solvent, TBAF as fluoride source), the same reactants (**5017** and **5048**) yielded 2-substituted pyridine **5050** as the major product (orange). In fact, the mechanism for the formation of each product involves the same [3+2] cycloaddition

[91] Reaction with nitriloxides: Minisci, F.; Quilico, A. *Chimica e l'Industria* **1964**, *46,* 428.
[92] Reaction with azides: a) Reynolds, G. A. The reaction of organic azides with benzyne. *J. Org. Chem.* 1964, *29,* 3733–3734. b) Wittig, G.; Hoffmann, R. W. Dehydrobenzol aus 1.2.3-Benzothiadiazol-1.1-dioxyd. *Chem. Ber.* **1962,** *95,* 2718–2728.
[93] Reaction with nitrones and diazocompounds: Huisgen, R.; Knorr, R. Benz-in als Dipolarophil. *Naturwissenschaften*, **1961**, *48*, 716–716.
[94] Raminelli, C.; Liu, Z.; Larock, R. C. Regioselective synthesis of 3-(2-hydroxyaryl)pyridines via arynes and pyridine *N*-oxides. *J. Org. Chem.* **2006,** *71,* 4689–4691.
[95] Regioselective synthesis of 2-(2-hydroxyaryl)pyridines from the reactions of benzynes with pyridine *N*-oxides

between benzyne **5001'** and pyridine *N*-oxide **5048**, which gives tricycle **5051** as the initial adduct. Under Larrock's condition, **5051** undergoes an intramolecular bond reorganization that opens the weak N-O bond and affords intermediate **5052**, which contains a three membered ring. In the presence of fluoride ions, intermediate **5052** then rearomatizes to form **5053**. On the other hand, **5051** formed in Liu's condition does not go through the same bond reorganization event as those in Larock's condition, but instead gets rapidly deprotonated in the presence of the high concentration of fluoride ions. Deprotonated **5051** smoothly rearomatizes to deliver the 2-substituted pyridine **5054** directly.

Scheme 5.11| [3+2] cycloadditions between benzyne and pyridine *N*-oxide.



Besides the above-mentioned pericyclic reactions, arynes also undergo Alder-ene reactions with alkenes and alkynes. A more detailed review on this topic is delayed to Section **7.4**.

Benzynes are known to react with alkenes (especially the electron rich alkenes) in [2+2] fashion. However, whether this type of reaction occurs via a stepwise or a concerted mechanism is still under debate.

3. Transition metal catalyzed reactions.

The use of transition metals has enabled the discovery of numerous elegant and powerful transformations with linear alkynes. However, the effect of transition metals on the reactivity of benzynes has not been thoroughly investigated.[96]

It has been known for long that interaction between transition metals and arynes releases a large portion of strain in the triple bonds of arynes and stabilizes these reactive species. In fact, most of the benzyne-transition metal complexes synthesized in the early days were primarily for the purpose of structural studies. On the basis of the work from Erker's group,[97] Buchwald and coworkers[98] developed a protocol that enabled the isolation of a benzyne-zirconocene complex **5055** and its characterization by X-ray crystallography. Further investigation[99] revealed that this zirconocene-benzyne complex **5055** has umpolunged reactivity and behaves like a strong nucleophile. As summarized in Scheme 5.12, this complex reacts efficiently not only with various electrophiles like proton, carbonyls, or nitriles, but also with alkynes or alkenes to give the corresponding metallocycles. None of these types of reactivity is typically observed with free benzynes,

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[96] Guitián, E.; Peréz, D.; Peña, D. Palladium-catalyzed cycloaddition reactions of arynes. *Top. Organomet. Chem.* **2005**, *14*, 109–146.

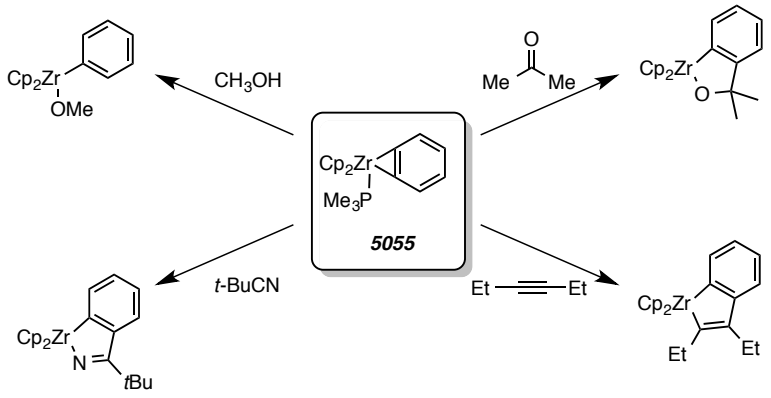
[97] a) Erker, G.; Kropp, K. Equilibrium between metallaindans and aryne olefin-metal complexes. *J. Am. Chem. Soc.* **1979**, *101*, 3659–3660. b) Erker, G. The reaction of intermediate zirconocene-aryne complexes with C–H bonds in the thermolysis of diarylzirconocenes. *J. Organomet. Chem.* **1977**, *134*, 189–202.

[98] Buchwald, S. L.; Watson, B. T.; Huffman, J. C. Trimethylphosphine adduct of the zirconocene-benzyne complex: synthesis, reactions, and x-ray crystal structure. *J. Am. Chem. Soc.* **1986**, *108*, 7411–7413.

[99] a) Buchwald S.L.; Nielsen R. B. Group 4 metal complexes of benzynes, cycloalkynes, acyclic alkynes, and alkenes. *Chem. Rev.* **1988**, *88*,1047–1058. b) Broene, R. D. Buchwald, S. L. Zirconocene complexes of unsaturated organic molecules: New vehicles for organic synthesis. *Science* **1993**, *261*, 1696–1701.

and therefore are results of coordination with zirconium.

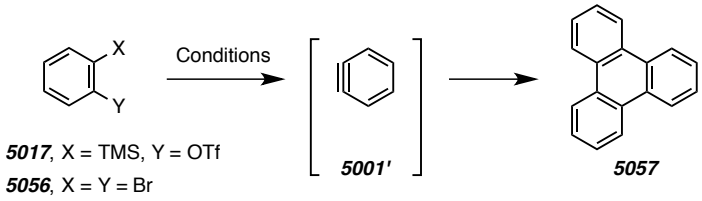
Scheme 5.12| Representative reactivities of benzyne-zirconocene complex.



Almost contemporary with the development of aryne-zirconocene chemistry, the reactivity of arynes complexed with late transition metals was also being explored.[96] These late transition metal containing aryne complexes are even more versatile and show high reactivities toward both nucleophiles and electrophiles.

However, until the late 1990s, the only metal-aryne complexes whose utility in organic synthesis had been explored were limited to a few metal-zirconium complexes. The requirement of using a stoichiometric amount of precious metals along with harsh conditions to generate these complexes significantly hampered serious exploration of their synthetic utilities. The advent of Kobayshi's method,[84] which allowed the generation of benzynes under mild conditions, fueled a rapid growth of transition metal mediated aryne chemistry. Several typical transformations developed since then are listed here to illustrate the power of these reactions.

Scheme 5.13| Pd^0 catalyzed benzyne trimerization.



Entry	Substrate	Reagent	Catalyst	Ligand	Yield
1	**5017**	CsF	$Pd(PPh_3)_4$		83
2	**5017**	CsF	$Pd_2(dba)_3$	dppe	70
3	**5017**	CsF	$Pd_2(dba)_3$	$P(o\text{-tol})_3$	60
4	**5017**	TBAF	$Pd(PPh_3)_4$		71
5	**5056**	*n*BuLi	$Pd(PPh_3)_4$		40

In 1998, Peréz, Guitián and coworkers[100] reported the first metal-*catalyzed* process that involved aryne substrates (Scheme 5.13). They established that when Kobayshi's benzyne precursor[84] **5017** was treated with fluoride sources, the in situ generated benzyne (**5001'**) efficiently trimerized into triphenylene **5057** in the presence of a catalytic amount of Pd^0. Notably, while the nature of the catalysts or ligands employed had only a negligible effect on the efficiency of this reaction, the use of a harsher aryne generating method (entry 5, **5056** + *n*BuLi) dramatically compromised its yield. Under the optimized conditions, more elaborated triphenylenes could be synthesized.

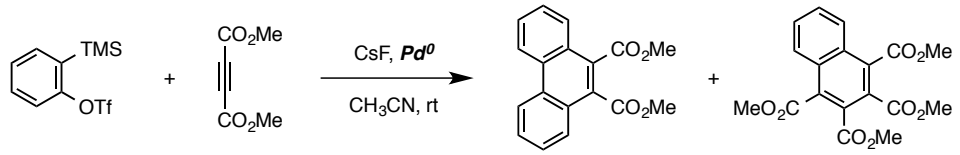
Because of its high reactivity, aryne generated in a reaction flask will not accumulate and its concentration is always low. One very basic law in physical organic chemistry states that "a rate is a rate constant times a concentration[101]". Therefore, in principal, the participation of benzyne in a certain reaction could be outcompeted by other less reactive

[100] Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. Efficient palladium-catalyzed cyclotrimerization of arynes: Synthesis of triphenylenes. *Angew. Chem. Int. Ed.* **1998**, *37*, 2659–2661.

101 Hoye, T. R.; Ryba, T. D. Divergent kinetic control of classical versus ozonolytic lactonization: mechanism-based diastereoselection. *J. Am. Chem. Soc.*, **2005**, *127*, 8256 – 8257.

substrates,[102] if the latter are used at high enough concentrations. For example,[103] when an electron deficient alkyne **5058** (dimethyl acetylene-dicarboxylate, DMAD) was used in the above triphenylene synthesis reactions, phenanthracene **5059** or naphthalene **5060** could be prepared as the major product depending on the catalyst choice. This cotrimerization of aryne and alkynes has demonstrated utility in the synthesis of important polyaromatic hydrocarbons[104] and natural products.[105]

Scheme 5.14| Cotrimerization of benzyne and DMAD.



	5059	5060
$Pd^0 = Pd(PPh_3)_4$	84%	7%
$Pd^0 = Pd_2(dba)_3$	10%	83%

Besides trimerization reactions, transition metal enabled three-component coupling reactions involving an aryne is another type of powerful transformation.[106] A

[102] For the cotrimerization of benzyne and alkenes, see: a) Qintana, I.; Boersma, A. J.; Peña, D.; Pérez, D.; Guitián, E. Metal-catalyzed cotrimerization of arynes and alkenes. *Org. Lett.* **2006**, *8*, 3347–3349. b) Saito, N. Shiotani, K. Kinbara, A.; Sato, Y. Nickel-catalyzed [2+2+2] cycloaddition of arynes and an unactivated alkene: synthesis of 9,10-dihydrophenanthrene derivatives. *Chem. Commun.* **2009**, 4284–4286.

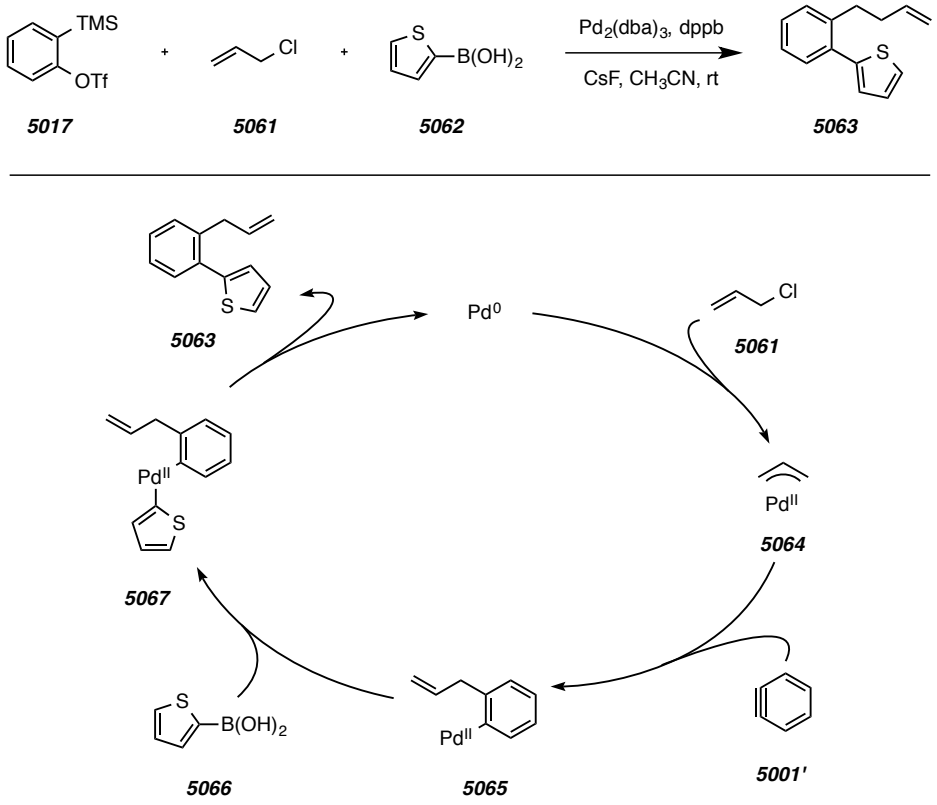
[103] Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. Palladium-catalyzed cocyclization of arynes with alkynes: Selective synthesis of phenanthrenes and naphthalenes. *J. Am. Chem. Soc.* **1999**, *121,* 5827–5828.

[104] Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. Selective Palladium-catalyzed cocyclotrimerization of arynes with dimethyl acetylenedicarboxylate: A versatile method for the synthesis of polycyclic aromatic hydrocarbons. *J. Org. Chem.* **2000**, *65*, 6944–6950.

[105] Sato, Y.; Tamura, T.; Mori, M. Arylnaphthalene lignans through Pd-catalyzed [2+2+2] cocyclization of arynes and diynes: Total synthesis of taiwanins C and E. *Angew. Chem. Int. Ed.*, **2004**, *43*, 2436–2440.

[106] a) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. Three-component coupling of benzyne: Domino intermolecular carbopalladation. *J. Am. Chem. Soc.* **2006**, *128,* 7426–7427. b) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. Highly efficient route to *o*-allylbiaryls via palladium-catalyzed three-component coupling of benzynes, allylic halides, and aryl organometallic reagents. *Org. Lett.* **2005**, *7,* 2921–2924. c) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. A cooperative copper- and palladium-catalyzed three-component coupling of benzynes, allylic epoxides, and terminal Alkynes. *Angew. Chem. Int. Ed.* **2009**, *48,* 391–394. d) Worlikar, S. A.; Larock, R. C. Synthesis of 9-fluorenylidenes and 9,10-phenanthrenes through palladium-catalyzed aryne annulation by *o*-halostyrenes and *o*-halo allylic

Scheme 5.15| Three-component reaction catalyzed by Pd^0.



representative example[106b] of this reaction type is shown in Scheme 5.15. In the presence of proper Pd^0 catalyst and ligand, 1,2-disubstituted arene like **5063** could be made directly from allyl chloride (**5061**), boronic acid **5062**, and benzyne precursor **5017**. The mechanism proposed for this transformation involves four individual steps: 1) oxidative insertion of Pd^0 to allyl chloride to form the π-allyl species **5064**; 2) carbopalladation of the resulting **5064** to the in situ generated benzyne intermediate **5001'** to make the arylpalladium species **5065**; 3) transmetallation between **5065** and **5062** to afford biaryl palladium **5067**; 4) reductive elimination of **5067** to provide the final product **5063** and

benzenes. *J. Org. Chem.* **2009**, *74,* 9132–9139. e) Waldo, J. P.; Zhang, X.; Shi, F.; Larock, R. C. Efficient synthesis of fluoren-9-ones by the palladium-catalyzed annulation of arynes by 2-haloarenecarboxaldehydes. *J. Org. Chem.* **2008**, *73,* 6679–6685.

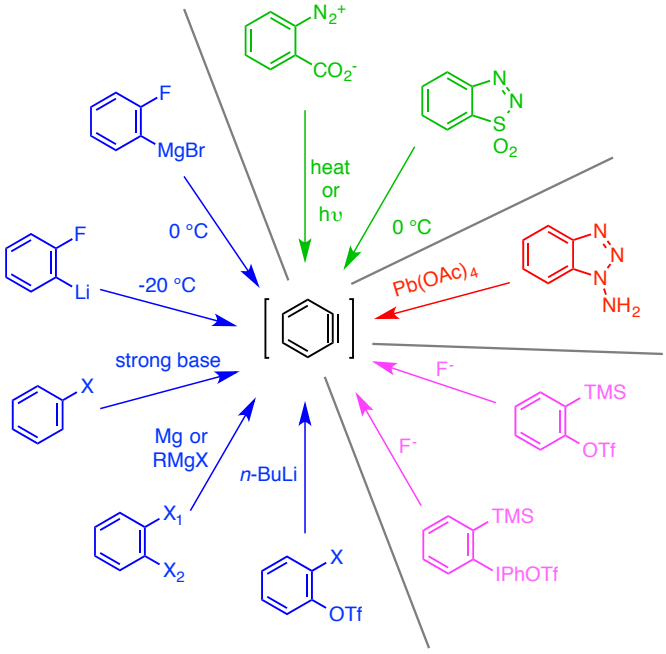
regenerate the Pd^0 catalyst. It is worth pointing out that the second step of this proposed catalytic cycle is a reaction between in situ generated **5064** and in situ generated **5001'**, both of which are present in low concentrations. The success of this transformation can only be explained by the extremely high reactivity of benzyne toward organopalladium species. Given the complexity of this cycle, the functional group tolerance demonstrated by this reaction is very remarkable.

As evident from the above discussion, *o*-arynes have already demonstrated tremendous potential in synthetic chemistry. Nonetheless, many lines of exploration in aryne chemistry are still undeveloped, and new aryne trapping reactions are continuously being discovered. Obviously, the freedom in reagent choice allowed by Kobayashi's aryne generating protocol (see next section for an overview of conventional aryne generating methods) was a key for the recent resurgence of aryne trapping methodologies. It is foreseeable that the emergence of a fundamentally new aryne generating method with greater functional group compatibility will bring even more opportunities into this field.

5.3 A brief review of *o*-benzyne generating methods

In contrast to the myriad benzyne trapping reactions, the methods for its generation are relatively limited. Most of these methods, which I have arbitrarily divided into four categories, are summarized in Figure 5.3.

Figure 5.3| Conventional methods of generating arynes.



The first generation methods discovered for making arynes involved the use of strong base (blue). These were used in, for example, Roberts' study that proved the existence of arynes[69] and Huisgen's investigation on the Diels–Alder reactions between benzyne and furan.[70] The usage of strong bases is obviously a drawback of this series of methods, which causes significant challenges in handling, and more importantly, functional group compatibility issues.

The second category capitalize on the instability of substrates like benzene-diazonium-2-carboxylate and benzo[*d*][1,2,3]thiadiazole 1,1-dioxide (green). Benzyne

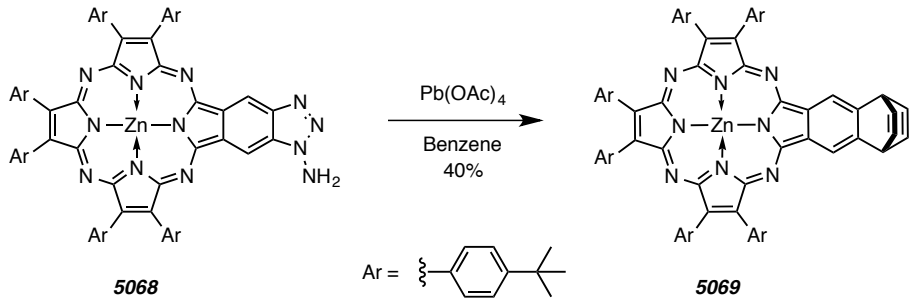
can be generated from these two precursors simply by heating or irradiation in the absence of additional reagents. The light-induced degradation of benzene-diazonium-2-carboxylate enabled low temperature generation of arynes in an argon matrix, which allowed several direct physical characterizations[76,77] of this extremely reactive species. Although the conditions used in these types of methods are the mildest of all, their utility in synthetic chemistry is still limited, presumably for two reasons: 1) the preparation of elaborated aryne precursors of this type is often tedious; 2) the thermal instability of these compounds[107] raises safety concerns.

Third, benzyne can be generated by oxidation of 1-aminobenzotriazole with oxidants like $Pb(OAc)_4$ (red).[108] The power of this method is illustrated by the transformation shown in Scheme 5.16. Treating a benzoporphyrazine derivative **5068** with $Pb(OAc)_4$ initiated the generation of the corresponding benzyne intermediate, which was trapped in situ by benzene solvent to afford the barreleno-fused product **5069** in ca. 40% yield. The complexity of the starting material and product in the reaction are testaments to the mildness of this method. However, the preparation of benzyne precursors of this type is also laborious.

[107] Benzene-diazonium-2-carboxylate is known to be explosive.

[108] a) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. C* **1969**, 742–747. b) Vagin, S. I.; Frickenschmidt, A.; Kammerer, B.; Hanack, M. Reactivity of dehydrometallophthalocyanines and –porphyrazines. *Chem. Eur. J.* **2007**, *13,* 985–991. d) Birkett, M. A.; Knight, D. W.; Little, P. B.; Mitchell, M. B. A new approach to dihydrobenzofurans and dihydrobenzopyrans (chromans) based on the intramolecular trapping by alcohols of benzynes generated from 7-substituted-1-aminobenzotriazoles. *Tetrahedron* **2000**, *56,* 1013–1023. d) Knight, D. W.; Qing, X. A synthesis of α-tocopherol featuring benzyne trapping by an alcohol. *Tetrahedron Lett.* **2009**, *50*, 3534–3537.

Scheme 5.16| Synthesis of zinc barreleno-fused benzoporphyrazine **5069** from 1-aminobenzotriazole derivative **5068**



The most widely used benzyne generation method is the one invented by Kobayashi[84] in 1983 (pink[109]). As alluded to in the previous section, the introduction of this method, which avoided the use of strong bases, has permitted the use of many labile reagents to interrogate the innate reactivities of arynes, and resulted in a recent Renaissance in the study of aryne chemistry. One limitation of this strategy, again, lies in the synthesis of these aryne precursors themselves, which most often requires the use of strong bases.[110]

[109] Kitamura and coworkers introduced the strategically analogous method that uses *o*-silylphenyliodonium salts as the benzyne precursors. For references, see: a) Kitamura, T.; Yamane, M. (Phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate. A new and efficient precursor of benzyne. *J. Chem. Soc. Chem. Commun.* **1995**, 983–984. b) Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. A new and efficient hypervalent iodine−benzyne precursor, (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate: Generation, trapping reaction, and nature of benzyne. *J. Am. Chem. Soc.* 1999, *121,* 11674–11679.

[110] An improved strategy for the syntheses of Kobayashi's benzyne precursors was described by Garg's group. Bronner, S. M.; Garg. N. K. *J. Org. Chem*. **2009**, *74*, 8842–8843.

Chapter 6. The HDDA Reaction: Its Discovery and Initial Explorations on Its Scope

6.1 Discovery of HDDA reaction

In an otherwise "unrelated" course of study, a postdoctoral associate in the laboratory at the time, Baire Beeraiah, was investigating the oxidation of a tetrayne alcohol **6001**, with the purpose of preparing its corresponding ketone (**6003**, Scheme 6.1). To everyone's surprise, however, the product resulting from this reaction was the tricyclic arene **6002**. Two features of this conversion were especially intriguing: 1) an aromatic ring was formed from an acyclic precursor; 2) an O-Si bond, one of the strongest bonds in chemistry (191 kcal•mol^{-1}), was cleaved at room temperate in the absence of any bases!

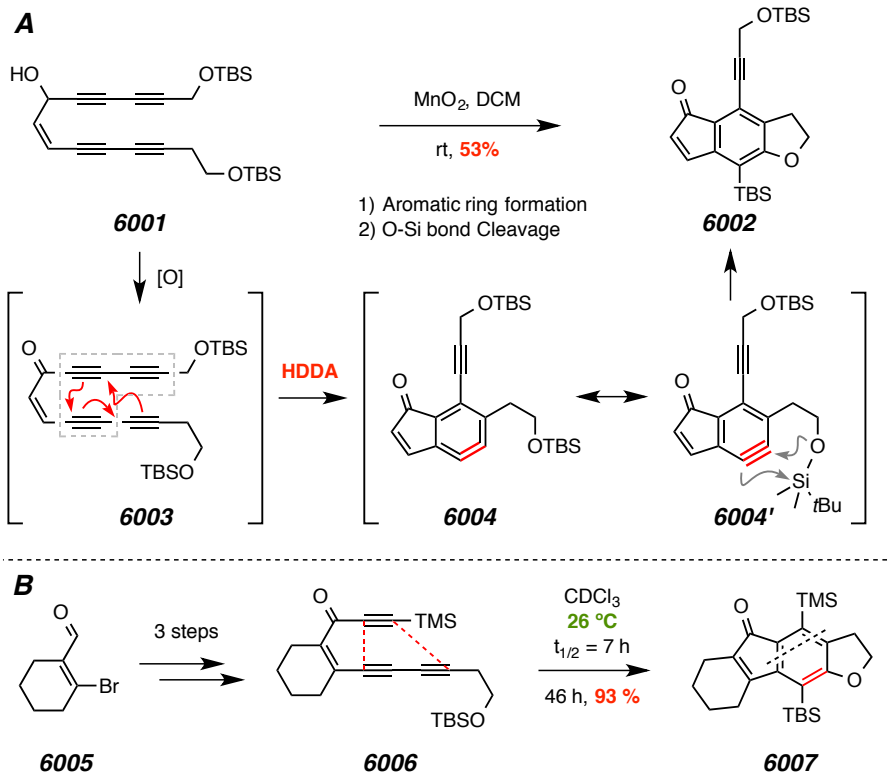
These two distinctive features of this conversion hinted at the mechanism (Scheme 6.1 A). Professor Hoye and Dr. Baire ascribed the facile and unprecedented cleavage of the O-Si bond during the reaction to the high reactivity of benzyne intermediate **6004'** and that the benzyne **6004'** had been in turn, produced from ynone **6003** (the anticipated product from oxidation of alcohol **6001**). We now call this transformation the *hexadehydro-Diels–Alder* (HDDA) reaction.[111]

The modest yield (53%) observed in this reaction was attributed to a competitive, nonproductive [4+2] cyclization mode that is available in structure **6003** as indicated by the gray box. Based on this reasoning, they designed and synthesized a new substrate–the ketotriyne **6006** (3 steps from **6005**, Scheme 6.1 B)–that could only undergo HDDA

[111] Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. The hexadehydro-Diels–Alder reaction. *Nature* **2012**, *490*, 208–212.

reaction with a single regiochemical outcome. Their efforts were rewarded by its smooth transformation at room temperature to the hexasubstituted, tetracyclic indenone derivative **6007** in 93% yield after chromatographic purification.

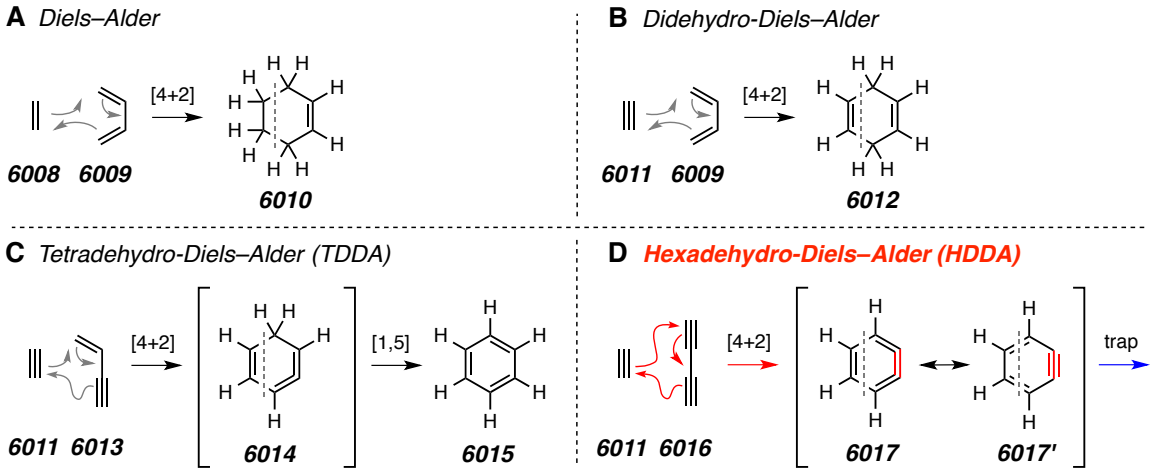
Scheme 6.1| A) Uncovering of hexadehydro-Diels–Alder (HDDA) reaction in the Hoye laboratory; **B**) Rationally designed HDDA substrate **6006** and its efficient conversion to **6007.**



It is proper to diverge at this point and discuss the etymology of "hexadehydro-Diels–Alder". The Diels–Alder [4+2] reaction[112] is arguably the most revered of all chemical reactions[25,113]. The prototypical event, found in every organic chemistry textbook, is the combination of 1,3-butadiene (**6009**) as the 4π-component with ethylene (**6008**) as the dienophile to give cyclohexene (**6010**)–a product at the tetrahydrobenzene oxidation

[112] Diels, O.; Alder, K. Syntheses in the hydroaromatic series [in German]. *J. Liebigs Ann. der Chem.* **1928**, *460*, 98–122.
[113] Onishchenko, A. S. *Diene Synthesis* (Israel Program for Scientific Translations Ltd., 1964).

Scheme 6.2| Etymology of hexadehydro-Diels–Alder reaction.



state. If, instead, an alkyne like ethyne (**6011**) is the dienophile, a 1,4-cyclohexadiene [1,4-dihydrobenzene (**6012**)] results; we suggest this be viewed as a *di*dehydro-Diels–Alder reaction (Scheme 6.2B). Another well-known variant involves engagement of a (yet more highly oxidized) 1,3-enyne (**6013**) as the 4π-component with an alkyne (**6011**, Scheme 6.2C). The intermediate cyclic allene **6014** rapidly rearranges via a [1,5] hydrogen atom shift to benzene (**6015**). This process was known as the dehydro-Diels–Alder (DDA) reaction.[114,115] We suggest amending the moniker for this transformation to *tetra*dehydro-Diels–Alder (TDDA) reaction. The most highly oxidized Diels-Alder variant like the one converting **6005** to **6007** in Baire's study is the cycloaddition between a 1,3-diyne (e.g, **6016**) and an alkyne (e.g., **6011**)–here a di*yn*ophile, which generates *o*-benzyne (cf. **6017**, **6017'**, Scheme 6.2D). This transformation is therefore termed as *hexa*dehydro-Diels–Alder (HDDA) reaction.

The HDDA reaction that converts tetrayne **6003** to benzyne **6004'** was unanticipated

[114] Wessig, P.; Müller, G. The dehydro-Diels–Alder reaction. *Chem. Rev.* **2008**, *108*, 2051–2063.
[115] Michael, A.; Bucher, J. E. Über die Einwirkung von Eissigsäureanhydrid auf Phenylpropiolsäure [in German]. *Chem. Zentrblt.* **1898**, 731–733.

presumably for the following two major reasons. First, as discussed in section 5.1, the most widely accepted (and arguably the most accurate) representation of benzyne is **6017'** (cf. **6004'**). However, it is only through the less commonly encountered, cumulene-like resonance structure **6017** (cf. **6004**) that benzyne can be connected to the alkyne precursors **6011** and **6016** (cf. **6003**) via a Diels–Alder-like reaction arrow pushing. Second, benzyne has left a dogmatic impression on the community as a highly reactive and "unstable" species. In contrast, linear alkynes, because of their easy availability and ubiquity, are usually recognized as "stable" functional groups. It is counterintuitive that conversion of a "stable" alkyne like **6003** to an "unstable" benzyne like **6004'** would be thermodynamically favorable/allowed (see Section 6.4 for more detailed discussion on some thermodynamic features of HDDA reactions). These two reasons might account for the dormancy[116,117,118] of this transformation in the synthetic community until this study.

As exemplified by the transformation from **6001** to **6002**, the HDDA reaction converts poly-yne substrates to highly reactive benzyne intermediates in a metal-, reagent-, and catalyst-free fashion. The mild conditions and operational ease of the HDDA reaction provide obvious advantages over other aryne-generating methods known at the time, and its synthetic potential was immediately apparent to us. Dr. Beeraiah Baire, Patrick H. Willoughby, Brian P. Woods, and I then teamed up and started to explore the possibilities of this aryne-generating strategy.

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[116] 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.

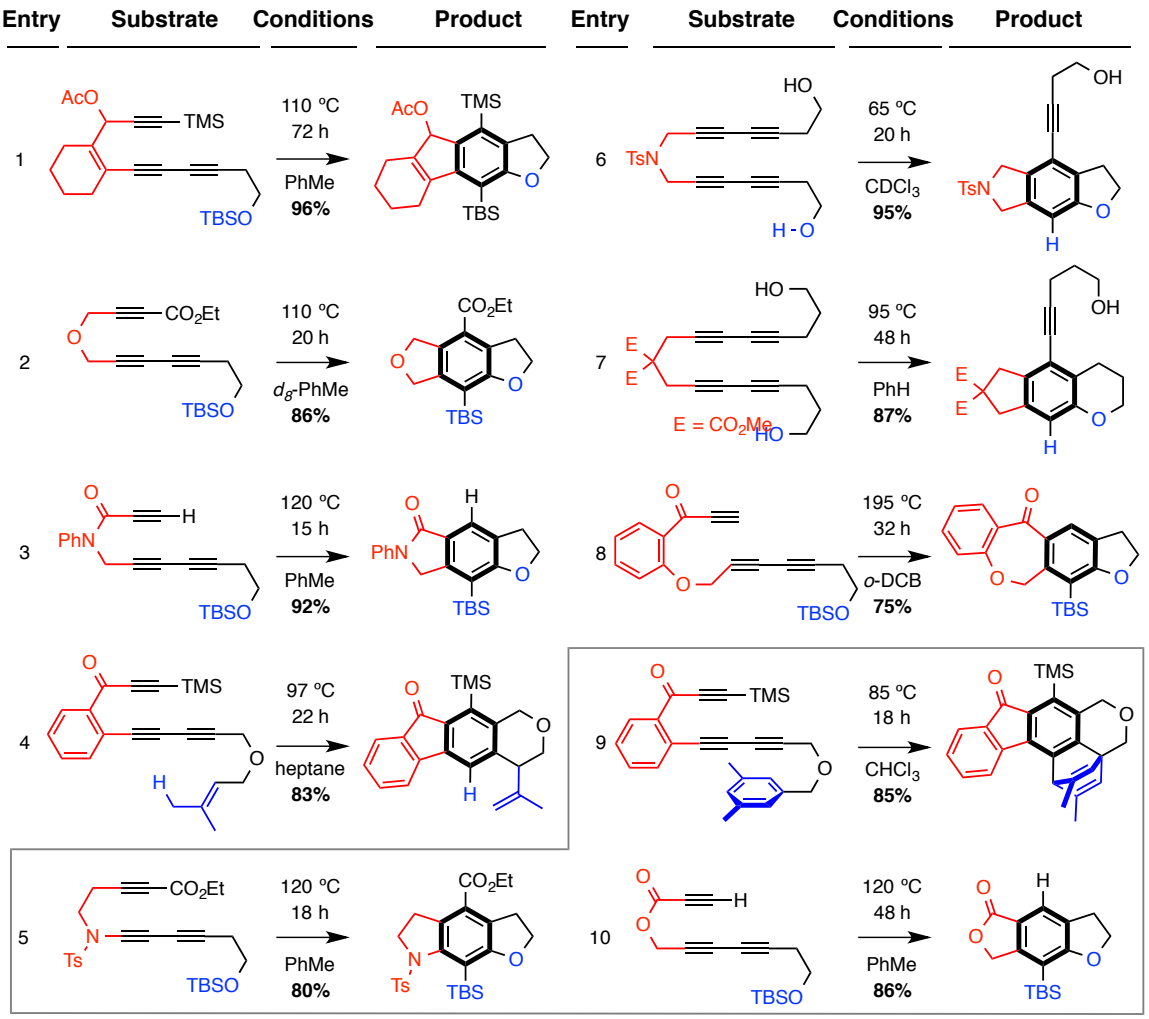
[117] a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. Cycloaromatization of a non-conjugated polyenyne system: Synthesis of 5*H*-benzo[d]fluoreno[3,2-b]pyrans via diradicals generated from 1-[2-{4-(2-alkoxymethylphenyl)butan-1,3-diynyl}]phenylpentan-2,4-diyn-l-ols and trapping evidence for the 1,2-didehydrobenzene diradical. *Tetrahedron Lett*. **1997**, *38*, 3943–3946. b) Kimura, H., Torikai, K., Miyawaki, K.; Ueda, I. Scope of the thermal cyclization of nonconjugated ene-yne-nitrile system: a facile synthesis of cyanofluorenol derivatives. *Chem. Lett.* **2008**, *37*, 662–663 and references therein.

[118] Tsui, J. A.; Sterenberg, B. T. A metal-templated 4 + 2 cycloaddition reaction of an alkyne and a diyne to form a 1,2-aryne. *Organometallics*, **2009**, *28*, 4906–4908.

6.2 Initial explorations on the substrate scope of HDDA reaction

We quickly established that the HDDA reaction is quite general with respect to both substrate scope and the types of intramolecular trapping events (see Scheme 6.3). During this course of study, we found: **i]** the presence of an electron withdrawing substituent on the diynophile enhances substrate reactivity [cf. conditions for **6006** to **6007** (Scheme 6.1 B) vs. entry 1]; similarly, an alkyne substituent on the diynophile also accelerates the

Scheme 6.3| Benzenoid (bold black bonds) synthesis via the HDDA cycloaddition has considerable substrate scope with respect to the nature of i) the poly-yne tether (red) and ii) the intramolecular trapping moiety (blue). My specific contributions to this Scheme are identified by the gray box.

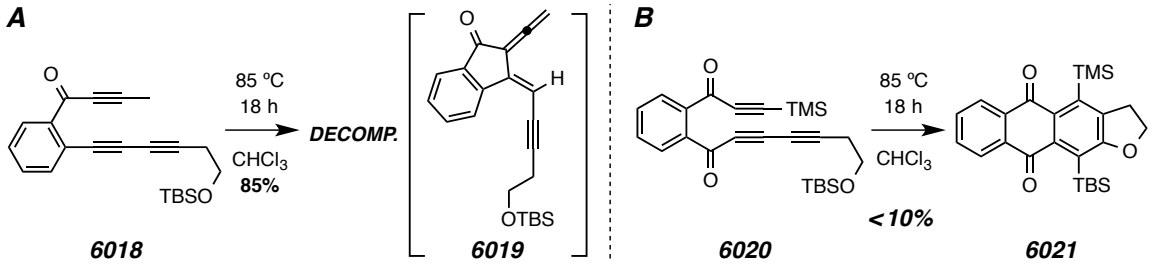


HDDA reactions (entry 6-7); **ii]** the activating carbonyl group can be either a distal (entries 2 and 5) or a tethering substituent (entry 3-4, and 8-10); **iii]** carbonyl activation is not a necessity (entries 1, 6, and 7); **iv]** products having nitrogen-containing heterocycles annulated to the new arene ring can be prepared (entries 3, 5, and 6); **v]** an ester tether (entry 10) cyclizes more slowly than its *N*-phenyl amide analog (entry 3), consistent with the lower concentration[60] of the *s*-cis conformer required for ring closure; **vi]** all of our observations are consistent with the absence of radical character during both the cycloaddition and trapping phases of the process; e.g., reactions performed in chloroform (an excellent hydrogen atom donor) solvent (entries 6 and 9) have shown no evidence of hydrogen atom transfer; **vii]** the previously unknown silyl ether trapping reaction (cf. Scheme 6.1) has considerable generality (entries 1-3, 5, 8, and 10); **viii]** other efficient internal benzyne traps include tethered alcohols (entries 6-7), aryl rings ([4+2] cycloaddition in entry 9), or alkenes (ene reaction in entry 4); **ix]** seven-membered ring formation is feasible (entry 8).

Two limitations of the HDDA reaction we observed during the studies are worth mentioning. First, the terminal position of the diynophile in HDDA reactions does not tolerate primary or secondary alkyl substituents. For example, when substrate **6018** was subjected to the same conditions used for otherwise similar benzyne precursors (cf. entry 4 and 9 in Scheme 6.3), no product resulting from HDDA reaction could be isolated (Scheme 6.4). Based on the study from Danheiser's group,[119] we hypothesize that substrates like **6018** preferentially undergo an intramolecular propargylic ene reaction to form intermediates like **6019**, which ultimately decompose to intractable products.

[119] Robinson, J. M.; Sakai, T.; Okano, K; Kitawaki, T.; Danheiser, R. L. Formal [2+2+2] cycloaddition strategy based on an intramolecular propargylic ene reaction/Diels−Alder cycloaddition cascade. *J. Am. Chem. Soc.* **2010**, *132*, 11039–11041.

Scheme 6.4| Some limitations of HDDA reaction.



The second limitation of HDDA reaction concerns the tether used in the benzyne-forming event. To date, we have only been able to effect *intramolecular* HDDA reactions productively. A tether is required for the cyclization event to 1) lower the activation barrier, and 2) address the selectivity issue (e.g., suppress diyne reacting with diyne). Moreover, unlike in normal Diels–Alder reactions, 4-atom tethers between diyne and diynophile are rather ineffective in promoting HDDA reactions. HDDA reaction of substrates with 4-atom linker either demanded very high temperature (>180 °C) or proceeded in very low yield. For example, cyclization of triynone **6020** gave only trace amount of desired anthraquinone product **6021**. Such unexpected outcome may reflect the difficulty these substrates had in achieving the required parallel arrangement between the diyne and the diynophile moieties for concerted HDDA reactions.

In spite of the above listed limitations, the HDDA reaction have many desirable features which include: **i**] each substrate shown in Scheme 6.3 is readily accessible (2-7 steps) by a convergent coupling strategy; **ii**] both the substrates and products of HDDA reaction are otherwise robust at temperatures required for HDDA cyclization; **iii**] stringent exclusion of air or water is not necessary for conducting HDDA reactions; **iv**] arynes generated under these conditions are free of any reagents or by-products, and could be considered “pristine”. These features granted significant scalability and

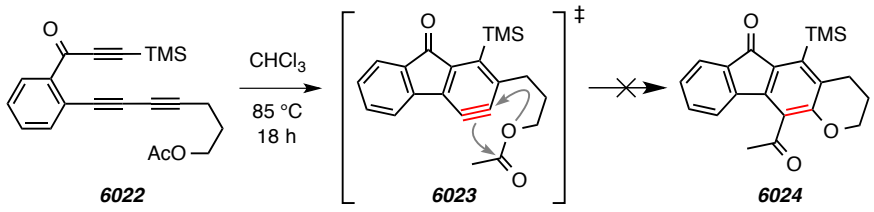
operational ease to this aryne-making method, and enabled us to uncover many unprecedented modes of aryne trapping reaction in a short period of time.

6.3 Initial explorations on the intermolecular trapping reactions of HDDA-born arynes

We were eager to validate the feasibility of *intermolecular* trapping of these thermally generated benzynes. Clearly, this would add considerable versatility and power to a HDDA-initiated transformation.

Anecdotally, my investigation on intermolecular trapping of HDDA-born benzyne was initiated by an "unsuccessful" experiment (Scheme 6.5). Having recognized the power of HDDA reaction, I designed substrate **6022**, which has a properly positioned acetoxy group, to study if this moiety could also efficiently trap the in situ generated benzyne **6023**. Importantly, the reaction of esters with benzynes had not been studied before, probably because of the lability of ester groups to the conventional, basic aryne-generating conditions. Treating **6022** with conditions that successfully promoted HDDA cyclization of very similar substrates (cf. entry 4 and 9 in Scheme 6.3), however, yielded no isolable product. This result suggested that an acetoxy group is too non-nucleophilic to trap benzyne **6023**. Fortunately, however, it also meant that the ca. one gram of **6022** that I prepared could be instead used for exploring the bimolecular trapping reactions of HDDA-born benzynes.

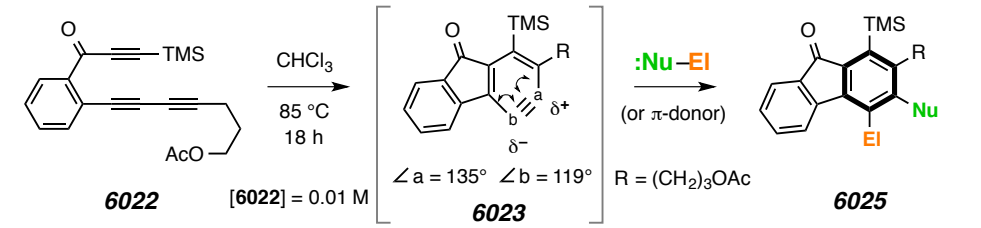
Scheme 6.5| Design of substrate **6022** and its "unsuccessful" intramolecular trapping reaction.



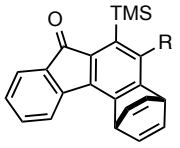
6022 *6023* *6024*

The efforts on intermolecular trapping study turned out to be very fruitful. I quickly established that benzyne **6023** could be captured by a variety of external reagents to give adducts like **6025** (Scheme 6.6). Highlights include: **i]** benzene as solvent forms the Diels–Alder adduct **25a**; although a precedented process,[120] because of the low reactivity of simple aromatics, rarely have they been trapped by benzynes in high yield; this result also indicates that many *intra*molecular trapping events are faster than capture by the aromatic solvents used in earlier examples (entries 1-3, 5, 7-8 and 10 of Scheme 6.3);

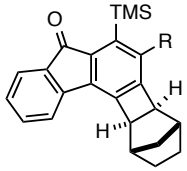
Scheme 6.6| Bimolecular trapping reactions of benzyne **6023** to give adducts **25a-f**.



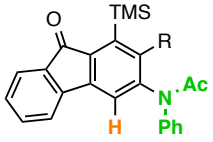
6022 ***6023*** ***6025***



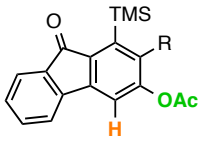
6025a
[PhH (solvent, 14 h); 70%]



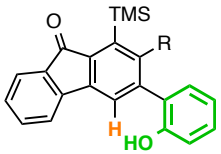
6025b
[norbornene (0.1 M); 63%]
single (exo) diastereomer



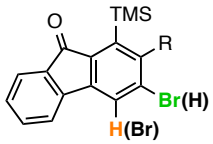
6025c
[PhNHAc (0.15 M); 82%]
19:1 ratio of regioisomers



6025d
[acetic acid (0.8 M); 89%]
single regioisomer



6025e
[phenol (0.1 M); 85%]
single regioisomer



6025f
[$BrCH_2CH_2NH_3^+Br^-$ (0.1 M); 72%]
6:1 ratio of regioisomers
solvent = THF:H_2O (20:1)

[120] Stiles, M.; Miller, R. G.; Burckhardt, U. Reactions of benzyne intermediates in non-basic media. *J. Am. Chem. Soc.* **1963**, *85*, 1792–1797.

Hoffman and Suzuki[121] commented that the abnormally high yield of **6025a** could be ascribed to the higher reactivity of arynes generated by HDDA reaction than those made conventionally; **ii]** the [2+2] cycloaddition of norbornene gives **6025b**; this reaction also occur in higher yield than has been observed for trapping of arynes formed by conventional methods;[83] **iii]** *N*-phenylacetamide gives **6025c**, demonstrating that a nitrogenous substituent can be conveniently installed; **iv]** acetic acid and phenol each traps **6023** to cleanly provide adducts **6025d** and **6025e**, respectively, in processes that may share the mechanistic feature of transfer of a hydroxyl proton coincident with nucleophilic attack (i.e., concerted oxa-ene reaction mechanism, see Section **7.2** for further discussion); **v]** this mode of reaction with acetic acid or phenol is unique and complementary to that seen with benzynes generated by non-reagent-free methods;[122,123,124] **vi]** the first efficient trapping of aryne by halogen ions was achieved using $Br(CH_2)_2NH_2$•HBr in THF/H_2O (20:1) as an HBr source to give **6025f** (6:1 mixture of regioisomers).

The high degree of regioselectivity observed for formation of products **6025c-f** is worth special attention. In fact, the synthetic utility of arynes trapping reactions has in many cases been complicated by their low degree of regioselectivities. In 2010, Buszek

[121] Hoffman, R. W.; Suzuku, K. A "hot, energized" benzyne. *Angew. Chem. Int. Ed.* **2013**, 52, 2655–2656.
[122] Liu, Z.; Larock, R. C. Facile *O*-arylation of phenols and carboxylic acids. *Org. Lett.* **2004**, *6*, 99–102.
[123] a) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G. J.; Garg, N. K.; Houk, K. N. Indolyne and aryne distortions and nucleophilic regioselectivities. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269. b) Im G. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Garg, N. K.; Houk, K. N. Indolyne experimental and computational studies: synthetic applications and origins of selectivities of nucleophilic additions. *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944.
[124] After our initial study was published, Daugulis group reported an efficient phenol-ene reaction with benzynes generated under non-reagent free conditions under the catalysis of Ag^+. Truong, T.; Daugulis, O. Divergent reaction pathways for phenol arylation by arynes: Synthesis of helicenes and 2-arylphenols. *Chem. Sci.* **2013**, *4*, 531-535.

and Cramer[125] and Houk and Garg[123,126] have independently developed computational approaches to predict the regioselectivity of reactions that involve the aryne intermediates. All these studies correlated the relative magnitude of the computed internal bond angles of an unsymmetrical (distorted) arynes with the site of nucleophilic attack. Namely, the more obtuse angle corresponds to the more electron deficient (δ^+) of the two benzyne carbon atoms. We computed the geometry for **6023** [R = CH_3; M06-2X[62]/6-31+G(d,p)] to have internal angles of 135º and 119º at atoms "a" and "b", respectively. Therefore, it is consistent with the established models that the more electrophilic site observed experimentally is also atom "a".

[125] Buszek, K. R.; Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; 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.

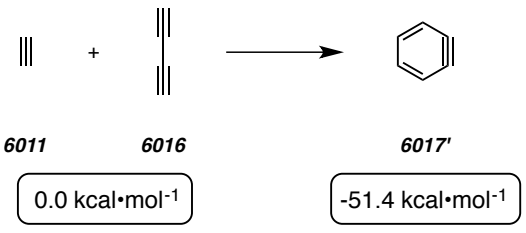
[126] Goetz, A. E.; Bronner, S. M.; Cisneros, J. D.; Melamed, J. M.; Paton, R. S.; Houk, K. N.; Garg, N. K. An efficient computational model to predict the synthetic utility of heterocyclic arynes. *Angew. Chem. Int. Ed.* **2012**, *51*, 2758–2762.

6.4. Thermodynamics of HDDA reaction

As was mentioned in Section 6.1, the thermodynamic feasibility of HDDA reactions that convert "stable alkynes" to "unstable" arynes is very counterintuitive, and therefore warrants a more detailed discussion.

In fact, Johnson and coworkers[127] have recently investigated the HDDA reaction between 1,3-butadiyne (**6016**) and acetylene (**6011**) to generate benzyne (**6017'**) with computational tools. Their calculation suggested this hypothetical reaction is exothermic by 51.4 kcal•mol^{-1}! In other words, in spite of its high strain (which, coincidentally, is also ca. 50 kcal•mol^{-1}), *o*-benzyne is *thermodynamically more stable* than its alkyne precursors by ca. 50 kcal•mol^{-1}. This computational outcome, although surprising, can be rationalized by 1) the aromatic stabilizing energy of benzyne (ca. 30 kcal•mol^{-1}, see section 5.1), and 2) the higher stability of σ-bonds (ca. 81 kcal•mol^{-1}) in product compared with alkynyl π-bonds (ca. 53 kcal•mol^{-1}) in starting materials. This result once again emphasize that thermodynamic stability and kinetic stability are not necessarily correlated.

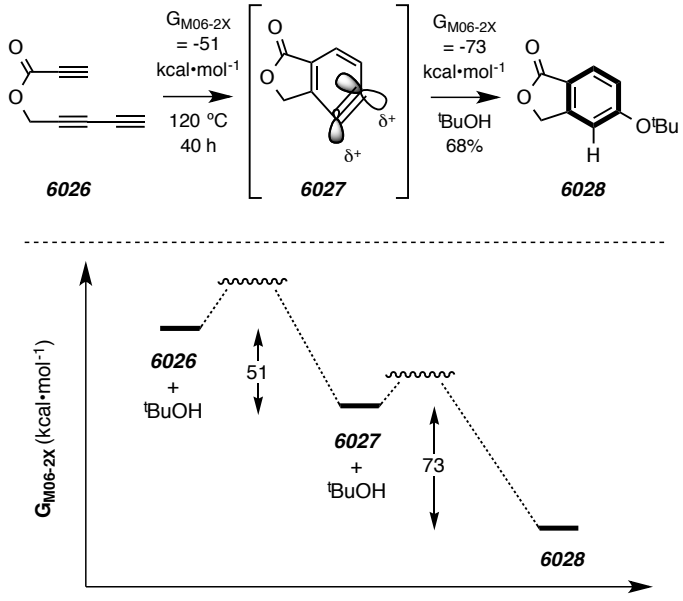
Scheme 6.7| Computed energetics of hypothetical transformation from butadiyne and acetylene to *o*-benzyne.



[127] 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.

In order to gain additional understanding of some of the key thermodynamic features associated with the HDDA reactions, I prepared ester **6026** and studied its HDDA reaction: this simple triyne was cycloisomerized, and the resulting aryne **6027** trapped in *t*-butanol (120 °C, closed tube) to produce 5-*t*-butoxyphthalide (**6028**) in 68% yield. Using DFT methodology, we have computed the free energy of reaction for the conversion of triyne **6026** to the aryne **6027** and found it to be −51 kcal mol^{-1}. These very favorable reaction energetics corroborate the conclusions of Johnson,[127] and reflect the large amount of potential energy inherent in the alkyne functional group. Additionally, the free energy of reaction for the trapping by *t*-butanol of the strained alkyne in **6027** was computed to be −73 kcal mol^{-1}. Thus, the overall transformation of **6026** to **6028** is exothermic by >120 kcal mol^{-1}.

Scheme 6.8| Computed free energy changes for a representative (real) HDDA-initiated cascade.



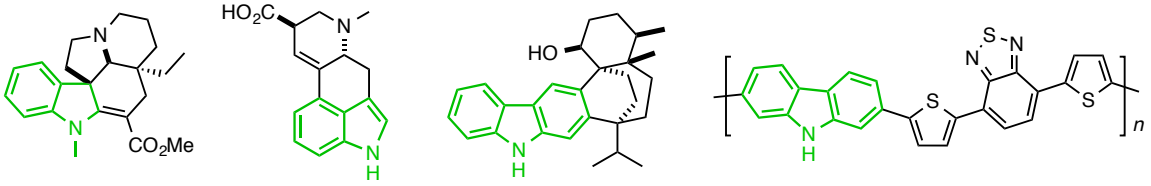
To summarize this chapter, an accidental and serendipitous discovery made by Dr. Baire led us to identify and establish the scope of the previously unexploited HDDA reaction, a powerful method for making benzynes under purely thermal conditions. This HDDA reaction demonstrated an unparalleled level of functional group tolerance. Benzynes generated using this method are on average much more sophisticated than those made conventionally. The subsequent aryne trapping events, which could occur either intra- or intermolecularly, add considerable complexity to the ultimate products. This powerful HDDA/aryne trapping cascade comprises a fundamentally new, arguably revolutionary, way to synthesize benzenoid compounds–especially those highly substituted ones. Equally importantly, because HDDA-derived benzynes are born in the absence of byproducts and external reagents, this reaction constitutes an excellent platform to explore the intrinsic and inherent reactivities of benzynes. Myriad additional unprecedented reactivities have manifested since then and some will be discussed in the next chapter.

CHAPTER 7. SOME ADDITIONAL REACTIONS OF BENZYNES GENERATED BY HDDA REACTIONS

7.1 A HDDA approach to prepare substituted indolines and carbazoles

Nitrogen-containing benzofused heterocycles[128,129,130] like indolines, indoles, and carbazoles are very important moieties present in many biologically active natural products, pharmaceutical agents, and modern functional materials (see Figure 7.1 for some representative examples). Not surprisingly, synthesis of these heterocycles has attracted tremendous amount of interest from synthetic communities. Numerous methods toward these hetereocycles have been developed to date, and new strategies continue to emerge.

Figure 7.1| Some selected examples of natural products and functional materials that contain indole, indoline, or carbazole units.



Minovine Lysergic acid Tubingensin B PCPDTBT

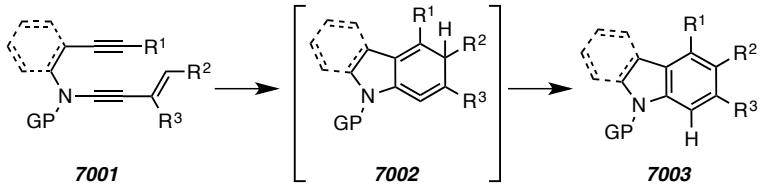
[128] a) Joule, J. A. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2000; Vol. 10, 361−652. b) Sundberg, R. J. *Indoles*; Academic Press: London, 1996.

[129] a) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. Occurrence, biogenesis, and synthesis of biologically active carbazole alkaloids. *Chem. Rev.* **2012**, *112*, 3193−3328. b) Knölker, H.-J.; Reddy, K. R. In The Alkaloids; Cordell, G. A., Ed.; Academic Press: Amsterdam, 2008; Vol. 65, p 1.

[130] Lemasson, F. A.; Strunk, T.; Gerstel, P.; Hennrich, F.; Lebedkin, S.; Barner-Kowollik, C.; Wenzel, W.; Kappes, M. M.; Mayor, M. Selective dispersion of single-walled carbon nanotubes with specific chiral indices by poly(N-decyl-2,7-carbazole). *J. Am. Chem. Soc.* **2011**, *133*, 652−655. b) Li, P.-P.; Chen, Y.; Zhu, J.; Feng, M.; Zhuang, X.; Lin, Y.; Zhan, H. Charm-bracelet-type poly(*N*-vinylcarbazole) functionalized with reduced graphene oxide for broadband optical limiting. *Chem. Eur. J.* **2011**, *17*, 780−785. c) Li, J.; Grimsdale, A. C. Carbazole-based polymers for organic photovoltaic devices. *Chem. Soc. Rev.* **2010**, *39*, 2399−2410.

Nowadays, most strategies[128] developed for preparing indoles and indolines focus on the construction of the 5-membered heterocyclic ring, with the benzenoid ring inherited from the corresponding benzene containing starting materials. One limitation of these methods is that the substitution patterns on the benzenoid ring of these heterocycles are limited by those available in the starting materials. One exception is a tetradehydro-Diels–Alder (TDDA) reaction based approach developed by the Danheiser's group[131] (Scheme 7.1). In this reaction, the intramolecular [4+2] cycloaddition between an alkyne unit and an enyne unit within **7001** initially generates strained isoaromatic cyclic allene **7002**, which under the reaction conditions rearranges via a [1,5] proton or hydrogen atom transfer to afford indoline **7002** as the final product. Later, Saá et al.[132] established that this TDDA reaction could also be applied to the synthesis of carbazoles. This strategy is distinctive from the other established ones in that it has enabled the synthesis of those heterocycles that are heavily substituted on (one of) the benzenoid ring(s).

Scheme 7.1| Tetradehydro-Diels–Alder (TDDA) approach to make indolines and carbazoles.

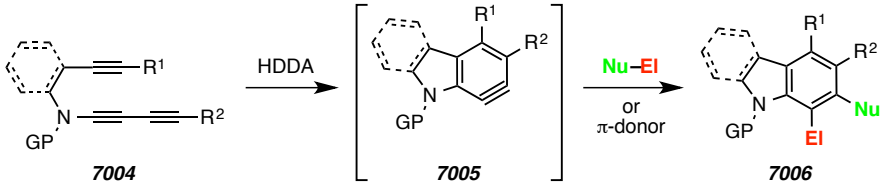


[131] Dunetz, J. R.; Danheiser, R. L. Synthesis of highly substituted indolines and indoles via intramolecular [4+2] cycloaddition of ynamides and conjugated enynes. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777.

[132] a) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. Coupling and cycloaddition of ynamides: homo- and Negishi coupling of tosylynamides and intramolecular [4+2] cycloaddition of *N*-(o-ethynyl)phenyl ynamides and arylynamides. *Tetrahedron*, **2006**, *62*, 3843–3855. b) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. Synthesis of carbazoles by dehydro Diels–Alder reactions of ynamides. *Tetrahedron*, **2008**, *64*, 3674–3686.

Here a HDDA approach to prepare substituted indoline and carbazoles will be described. As generalized in Scheme 7.2, this strategy is to use HDDA reaction of ynamide like **7004** to make intermediate aryne **7005**, which could be trapped in situ to give heterocycle **7006**. As can be inferred from the general structure of **7006**, this method should also be capable of preparing indolines or carbazoles with highly decorated benzenoid rings. Compared with Danheiser's strategy, which is in essence an isomerization reaction, this method has two additional advantages: 1) it enables the construction of those fused benzenoid rings that are fully substituted; 2) it permits the use of external aryne trapping agents, amounting to a two-component or sometimes, even multi-component reaction, thereby adding tremendous flexibility into the choice of functional groups that can be incorporated.

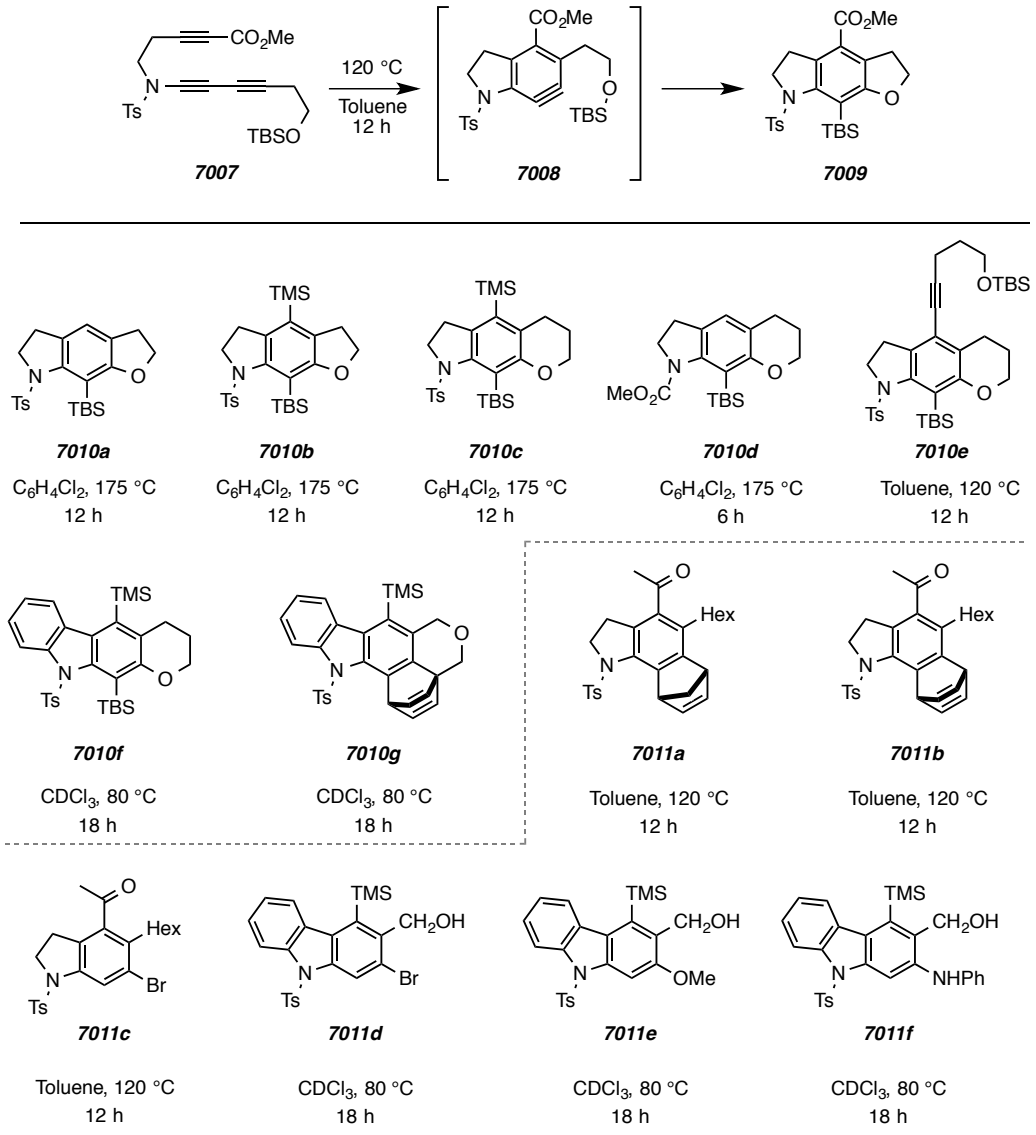
Scheme 7.2| HDDA approach to make indolines and carbazoles



As mentioned in the previous Chapter, I have already had one successful example of such reaction: the conversion of **7007** was converted to **7009** after being heated in toluene for 12 h at 120 °C. We later found that, 1) the ester group on the diynophile accelerates the HDDA event. For example, the formation of **7010a** requires heating at a much higher temperature to achieve a comparable rate. 2) Although a TMS group is sterically more congested than a hydrogen atom, it does not slow down the HDDA reaction dramatically. (cf. **7010a** and **7010b**). 3) The intramolecular trapping event could also lead to the formation of pyran ring (**7010c**). 4) Protecting group on nitrogen atom could be a more

easily removable methoxycarbonyl group[131] (**7010d**), and this new protecting group had little effect on the rate of cyclization. 5) An alkynyl group on diynophile speed up HDDA event significantly (**7010e**). 6) The regioselectivity in the formation of **7010e** is notable.

Scheme 7.3| Preparation of indolines and carbazoles using HDDA reaction.

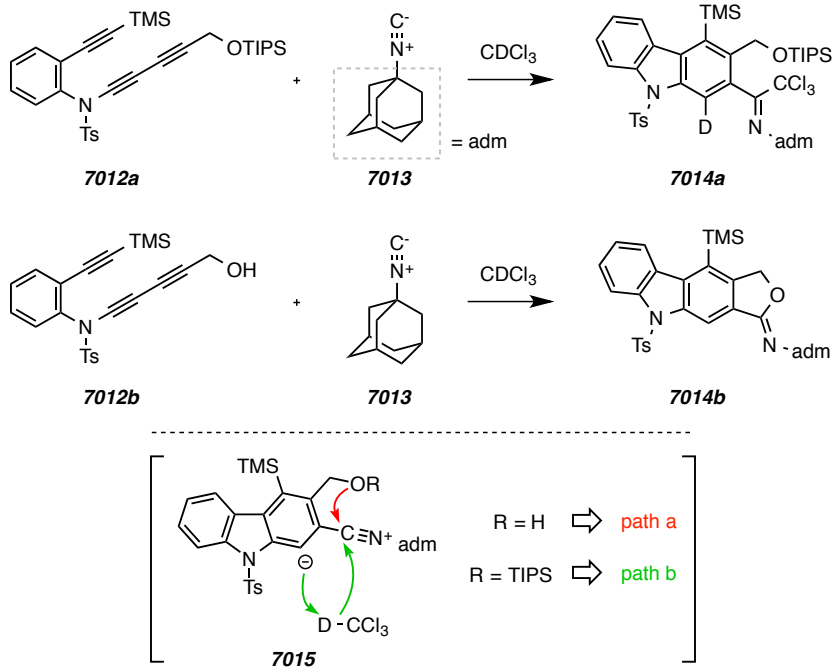


Comparatively, HDDA reactions that generate "carbazolyne" occur at a much faster rate (**7010f-g** vs. **7010e**). The observed higher rates could be attributed to: 1) the buttressing effect of benzoid containing tether between diynophile and diyne; and 2)

electronic activation of the diynophile by the benzene ring.

More importantly, aryne intermediates can react with external trapping agents.[111] The reagent-free nature of HDDA reaction has allowed the use of a wide variety of trapping agents and the discovery of many previously unknown trapping modes of arynes. This feature lends tremendous potential of using HDDA strategy in this setting. As shown in Scheme 7.3, a series of indolines and carbazoles (**7011a-f**) have been efficiently made with this method. Highlights include: i) cycloaddition with cyclopentadiene or benzene are efficient; ii) halogen atoms can be attached to the fleeting benzyne, providing handles for further manipulations; iii) heteroatoms such as O and N can be introduced.

Scheme 7.4| Reaction of arynes with isocyanide.



The reaction of between carbazolyne and isocyanide[133] warrants some special attention (Scheme 7.4). When a solution of triyne **7012a** in $CDCl_3$ was heated in the presence of admantyl isocyanide (**7013**), carbazole **7014a**, which incorporated a molecule of $CDCl_3$, was made in >80% yield. I propose that zwitterion **7015** is capable of deprotonating $CDCl_3$ to generate carbanion CCl_3^-, which then quenches the nitrilium group to give **7014a** (path b). In contrast, when the analogous triyne **7012b**, which bears a free hydroxyl group, was subjected to the same conditions, the tetracycle **7014b** was formed instead. Presumably, tetracycle **7014b** arises from direct trapping of the nascent nitrilium in **7105** with its free hydroxy group (path a).

The question whether HDDA reaction occurs in a concerted or a stepwise mechanism is still not answered. Johnson's group[127] have computed the energetics of each mechanism on the parent butadiyne+acetylene system and found the computed barrier for each pathway to be different only by 0.5 kcal/mol (36.5 kcal/mol for concerted vs. 37 kcal/mol for stepwise mechanism respectively). The authors are inclined toward a stepwise mechanism for this reaction. However, the experimental observations we made are more consistent with a concerted reaction mechanism. For example, we found BHT and hydroquinone, which are deemed to be excellent radical scavengers, can be used in HDDA reactions either as an additive or as an external trapping agent; chloroform is routinely used as solvents; the HDDA reactions showed no sensitivity to oxygen. During the course of indoline synthesis project, Tao Wang and I gained some additional evidence supporting the concerted reaction mechanism.

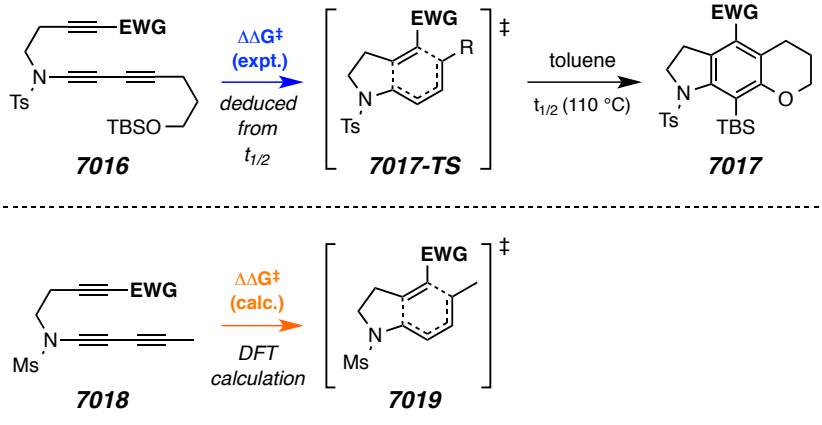
As shown in Scheme 7.5, we have prepared a series of triyne precursors that differ

[133] a) Rigby, J. H.; Laurent, S. Addition of alkyl and aryl isocyanides to benzyne. *J. Org. Chem.* **1998**, *63*, 6742–6744. b) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. Benzannulated bicycles by three-component aryne reactions. *Angew. Chem. Int. Ed.* **2011**, *50*, 4488–4491.

only by the electron-withdrawing groups on the diynophile part, and obtained the half-lives of each substrate under identical conditions. We found that the rate of the HDDA reaction of substrate **7016** increases as the substituent on the diynophile becomes more electron-withdrawing. The observed difference in half-lives was converted into the activation energy difference [$\Delta\Delta G^{\ddagger}_{(exp)}$] among each reaction using Arrhenius equation.

We next investigated the hypothetical HDDA reactions of **7018**, model substrates that resemble **7016**, using DFT methods. The calculated activation energy difference [$\Delta\Delta G^{\ddagger}_{(calc.)}$] of these reactions based on a concerted mechanism (cf. **7019**) agrees well with the experimental ones associated with substrates **7016**. Such agreement provides additional support for a concerted reaction pathway.

Scheme 7.5| Electron withdrawing groups on diynophiles accelerate HDDA reaction: experimental observation and computational prediction.



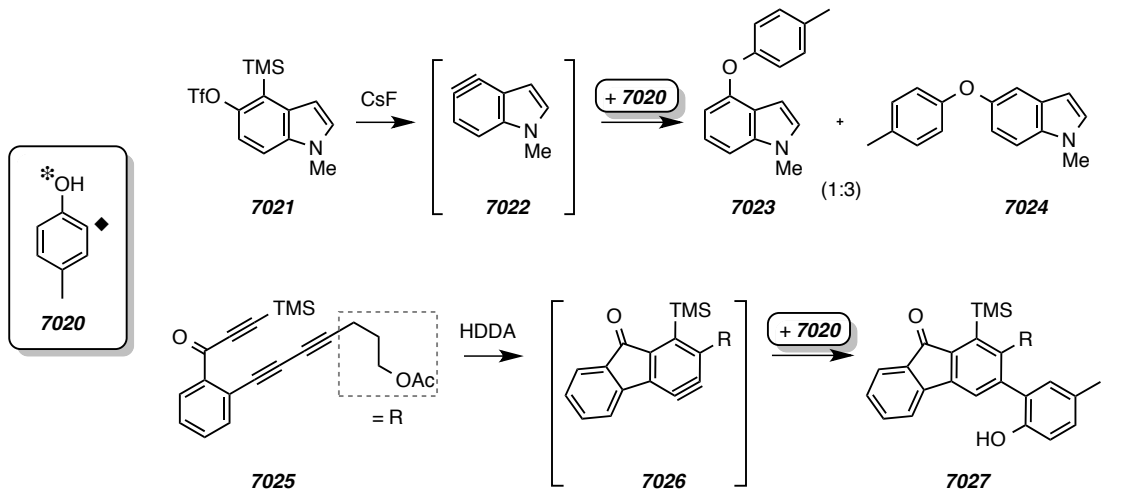
EWG	$t_{1/2}$ (110 °C)	ΔΔG‡ (expt.)	ΔΔG‡ (calc.)
H	>10 days	NA	5.5
$CONEt_2$	75 h	3.6	2.6
CO_2Me	12 h	2.2	1.6
COMe	2.8 h	1.1	1.0
CHO	0.7 h	0	0

In conclusion, we have demonstrated a general strategy that is based on the HDDA reaction to prepare indolines and carbazoles. Complementary to most available ones toward these moieties, this strategy constructs the benzenoid ring de novo. Compared with the TDDA based method developed by Danheiser, this strategy, in which aryne is generated as the primary intermediate, allows more flexibility to introduce functional groups on the newly formed benzene ring, and therefore, is more suitable for library synthesis. Finally, an investigation that combines computational study with kinetic study provides evidence for a concerted mechanism in these HDDA reactions.

7.2 The ene reaction between phenols[124] and HDDA-born benzynes

Phenols, like *p*-cresol (**7020**), are known to be ambiphilic nucleophiles (Scheme 7.6). Their reactions with arynes made under conventional conditions normally occur at the *O*-site. For instance, the aryne **7022** generated by treating **7021** with CsF reacts with *p*-cresol to give two regioisomeric aryl ethers **7023** and **7024** in 1:3 ratio.[123] However, we found that the reaction between *p*-cresol and aryne **7026**, which is derived from **7025** via HDDA reaction, yields biaryl **7027**, the product arising from phenol *C*-site attack to the exclusion of any observable aryl ether products.

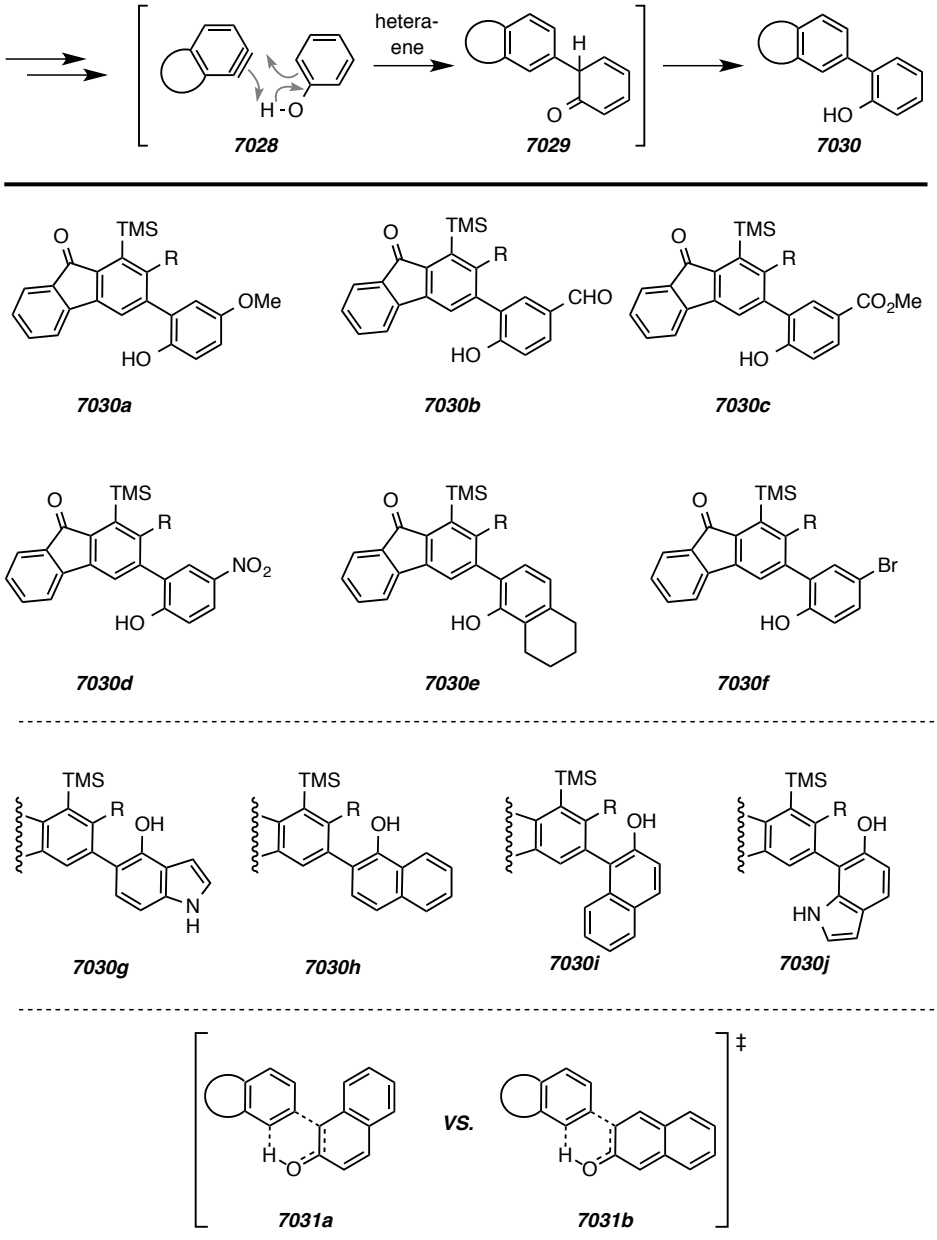
Scheme 7.6| Reactions between *p*-cresol and arynes that are generated in different ways.



The reaction between HDDA-born aryne and phenol, because of its unusual reaction mechanism and the utility of the resulting (biaryl) products, warrants a more detailed investigation. We propose product **7027** arises from a hetera-ene reaction between phenol and aryne (cf. **7028** to **7030** via **7029** in Scheme 7.7). To my delight, this reaction tolerates phenols bearing many different functional groups. For example, electron-rich, electron-neutral, and electron-deficient phenols are all suitable trapping agents of aryne

7026 (cf. **7027** and **7030a-d**), although their trapping efficiency decreases as phenols become more electron-deficient, consistent with the notion that aryne functions as the electrophile in these reactions. Besides, the synthetically versatile aldehyde group (cf. **7030b**) and halogen atoms (cf. **7030f**) are also tolerated.

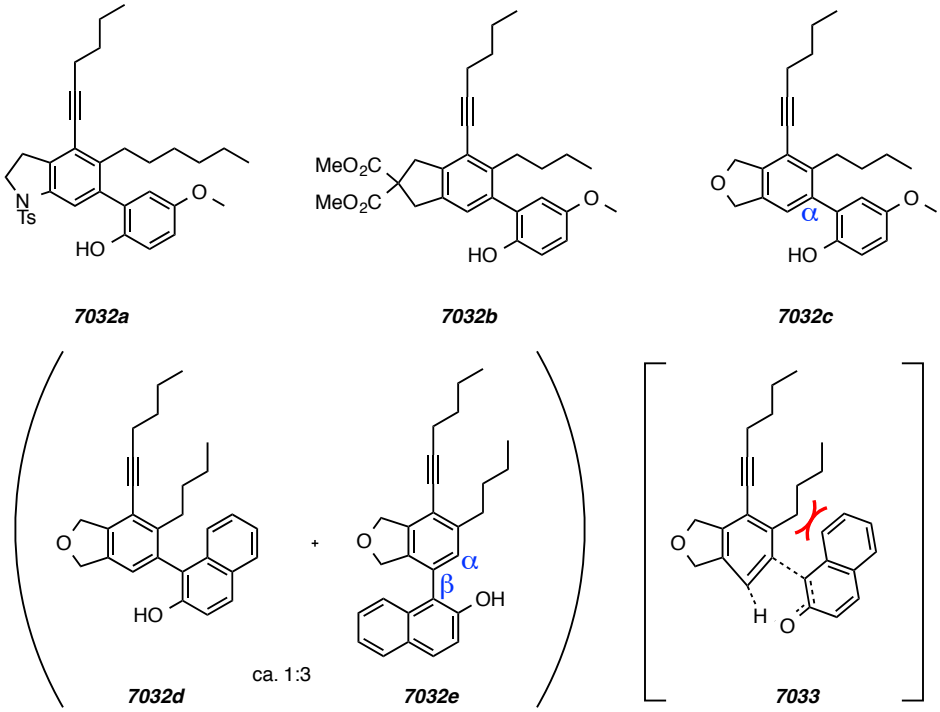
Scheme 7.7| Hetera-ene reaction between aryne and phenol: Scope of phenols and rationale for regioselectivity.



Phenols with a fused arene origin were found to be considerably better ene donors (cf. **7030g-h**). The enhanced reactivity of these substrates is most likely a result of intrinsic lower aromatic stabilizing energy in each ring of these systems. For these phenols with two potential *C*-attacking sites, the high degree of regioselectivity observed (cf. **7030i-j**) is notable. The formation of these regioisomers could be best explained by the minimized breakage of aromaticity in the corresponding transition structures. That is, transition structure like **7031a** is more stable than **7031b** because the aromaticity of one ring is still fully retained in the former. Regardless, the chemoselectivity for reaction between aryne and 5-hydroxy indole is remarkable, and serves as another testament to the mildness of HDDA reactions.

Not surprisingly, this ene reaction tolerates arynes with various substitution patterns and electronic properties. Besides triyne **7025** (Scheme 7.6), tetraynes are also viable aryne precursors, as represented by the decent yields for the formation of **7032a-c**. In all these cases, it is the regioisomer arising from attack at α-*C* position (cf. **7032c**) was formed predominantly, consistent with the notion that the carbon atom with the more obtuse angle is more electrophilic. One exception to this rule was noticed when 2-naphthol was used as the ene donor. In this case, the major product was **7032e**, the compound resulting from phenol attack at β-*C* position. Product **7032d** was formed only as a minor component presumably due to the highly unfavorable steric repulsion between the aryl ring and the butyl group present in transition structure **7033**.

Scheme 7.8| Hetera-ene reaction between aryne and phenol: Scope of arynes and unexpected regioselectivity.

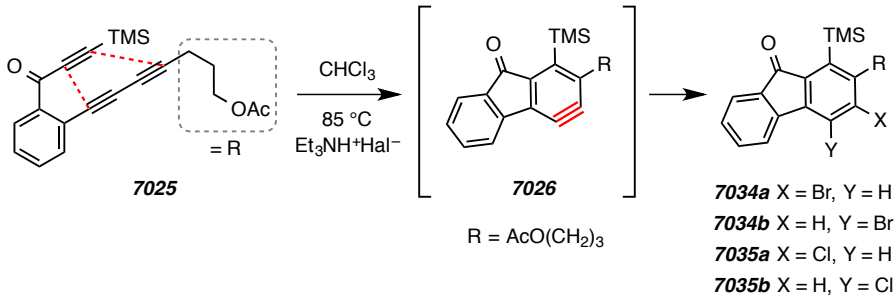


ortho-Arylated phenols are important moieties that are frequently encountered in organo-catalysts, functional materials, and biologically active agents. Direct *ortho*-arylation of unprotected phenols represents the most straightforward method toward these compounds. The hetera-ene reaction between HDDA-born aryne and substituted phenols is one such method. In this section of study, I have investigated the scope and limitations of this reaction. This reaction displays good functional group compatibility with respect to both the aryne and the phenol partner, and represents a general method to prepare these compounds.

7.3. Dichlorination of arynes

Aryl chlorides are commonly encountered in, for example, agrochemicals, pharmaceuticals, natural products, and photonic materials. Aryl chlorides have also grown in importance as synthetic intermediates in light of improved methodologies capable of activating the relatively inert C_{sp2}-Cl bonds.[134] Classically, monochlorobenzenes are made from Sandmeyer reaction or electrophilic aromatic halogenation. We have reported that HDDA-born aryne could be efficiently trapped by a suitable HBr source[111] to produce the monobromoarenes **7034a** and **7034b** (Scheme 7.9). Since then, we have observed that treatment with various ammonium chlorides gives a similar outcome, namely the formation of chlorides **7035a** and **7035b**.

Scheme 7.9| Monohalo arene formation (**7034** or **7035**; 70-80% yield) through hydrogen halide addition to the benzyne **7026** formed via the thermal 4+2 cycloisomerization of the triyne **7025**.

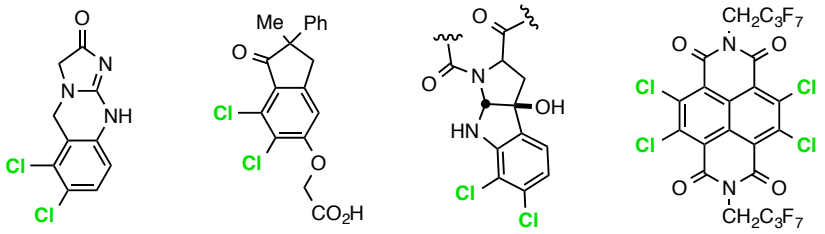


1,2-Dichlorobenzene derivatives, the principal subject of this section, are seen in target compounds of interest, as represented by the structures **7034a-d** (Scheme 7.10). The preparation of *ortho*-dichlorinated arenes is more challenging than that of monochloroarenes. There are only a few reports of direct 1,2-dihalogenation of arynes.

[134] Noyori, S.; Nishihara, Y. *Recent advances in cross–coupling reactions with aryl chloride, tosylates, and mesylates. In Applied Cross Coupling Reactions.* (Springer, 2013).

These are limited to (i) diiodination[135,136] (with I_2) or dibromination[135a](with Br_2), in which the reactions tend to proceed less effectively for arynes more elaborate than those of benzyne itself (from anthranilic acid or *ortho*-TMSPhOTf)[135c] and (ii) vicinal, mixed fluorohalogenation via silver(I)-promoted, net addition of FCl, FBr, or FI to HDDA-generated benzynes.[137] We are not aware of any examples of aryne dichlorination prior to this study. Here we describe a strategy to make 1,2-dichlorinated arenes from triynes via the intermediate benzynes.

Scheme 7.10| Examples of 1,2-dichlorinated target compounds (**7036a**, Agrylin®, platelet reducing agent for treatment of thrombocytosis; **7036b**, indacrinone, diuretic developed for treatment of gout and hypertension; **7036c**, kutznerides, antimicrobial cyclic peptides; and **7036d**, for organoelectronic applications).



7036a Agrylin | ***7036b*** indacrinone | ***7036c*** kutznerides | ***7036d*** organoelectronics

We initially explored the possibility of trapping the HDDA-generated benzyne **7026** with either I_2 or Br_2. We were not surprised that this experiment did not produce observable amounts of the desired dihalobenzenes (i.e., **7034**/**7035** where X = Y = I or Br). In general, one practical feature of HDDA chemistry is that the alkynes in the triyne

[135] a) Friedman, L.; Logullo, F. M. Synthesis of *o*-Dihalogenobenzenes from Benzenediazonium-2-carboxylate. *Angew. Chem., Int. Ed.* **1965**, *4*, 239–240. b) Birkett, M. A.; Knight, D. W.; Little, P. B.; Mitchell, M. B. *Tetrahedron* **2000**, *56*, 1013. c) Perry, R. J.; Turner, S. R. *J. Org. Chem.* **1991**, *56*, 6573. d) Rodríguez-Lojo, D.; Cobas, A.; Peña, D.; Pérez, D.; Guitián, E. Aryne Insertion into I–I σ-Bonds. *Org. Lett.* **2012**, *14*, 1363–1365.

[136] Buchwald, S. L.; Lucas, E. A.; Davis, W. M. *J. Am. Chem. Soc.* **1989**, *111*, 397.

[137] Wang, K.-P., Yun, S. Y., Mamidipalli, P. & Lee, D. Unified approaches for fluorination, trifluoromethylation, and trifluoromethylthiolation of arynes. *Chem. Sci.* **2013**, *4*, 3205–3211.

reactant need to be compatible with the agents intended to trap the intermediate benzynes under the conditions required to generate the benzyne. For example, addition of Cl_2 (and Br_2) to alkynes is relatively fast and is not expected to be compatible with most HDDA substrates. However, various metal halides are known to act as milder dihalogen surrogates for some dihalogen addition reactions.[138] We have learned that dilithium tetrachlorocuprate (Li_2CuCl_4) functions as an effective dichlorinating agent of HDDA-generated benzynes and report those observations here.

We used the symmetrical tetrayne **6** for our initial explorations; it is both quite easy to prepare and has relatively high reactivity as a HDDA substrate. When a solution of **6** in CH_3CN was heated in the presence of either $FeCl_3$, no desired dichlorination product **7** was formed, as judged by GC or TLC analysis (entry 1, Scheme 7.11a). The first indication of a successful outcome was seen with the use of $CuCl_2$ in acetonitrile. Addition of **6** and warming the resulting solution to 68 °C led to the formation of **7** in 67% yield following purification. Using Li_2CuCl_4 in acetonitrile gave similar results. The efficiency of the reaction was increased when the solvent was changed to THF; **7** was isolated in 85% yield. Under these conditions, no noticeable amount of dihydrogenation (by THF, see section **7.5**) or HCl addition products derived from competitive trapping of the intermediate benzyne was observed. Notably, dioxane was an ineffective solvent for this transformation, presumably due to the low solubility of Li_2CuCl_4, which stands in contrast to its high solubility in THF.

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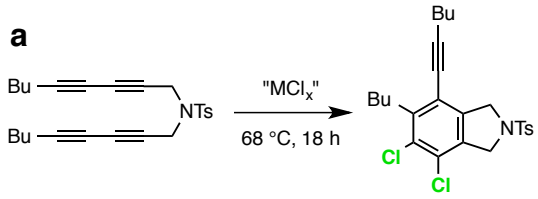
[138] a) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B.; Snyder, J. P. Bromination of alkenyl glycosides with copper(II) bromide and lithium bromide: Synthesis, mechanism, and DFT calculations. *J. Org. Chem.* **1999**, *64*, 1758–1761. b) Uemura, S.; Sasaki, O.; Okano, M. Selective *cis*-chlorination of olefins by antimony(V) chloride. *J. Chem. Soc. D*, **1971**, 1064–1065. c) Kovacic, P.; Brace, N. O. Chlorination of aromatic compounds with metal chlorides. *J. Am. Chem. Soc.* **1954**, *76*, 5491–5494. d) Uemura, S.; Onoe, A.; Okano, M. The chlorination of olefins with antimony(V) chloride. *Bull. Chem. Soc. Jap.* **1974**, *47*, 692–697. e) Yang, L.; Lu, Z.; Stahl, S. S. Regioselective copper-catalyzed chlorination and bromination of arenes with O_2 as the oxidant. *Chem. Commun.* **2009**, 6460–6462.

Scheme 7.11| a. Identification of Li_2CuCl_4 as an effective reagent for *vic*-dichlorination of the benzyne derived from tetrayne **6**. **b.** ^{1}H NMR spectrum of the *crude product mixture* arising from the entry 4 experiment.

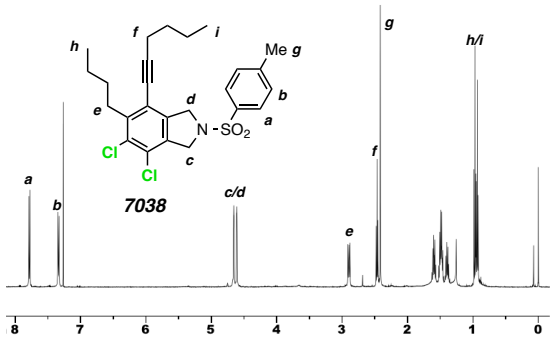
a



7037 ***7038***

Entry	MCl_x	Solvent	Yield
1	$FeCl_3$	CH_3CN	0%*
2	$CuCl_2$	CH_3CN	67%
3	Li_2CuCl_4	CH_3CN	67%
4	**Li_2CuCl_4**	**THF**	**85%**
5	Li_2CuCl_4	dioxane	trace

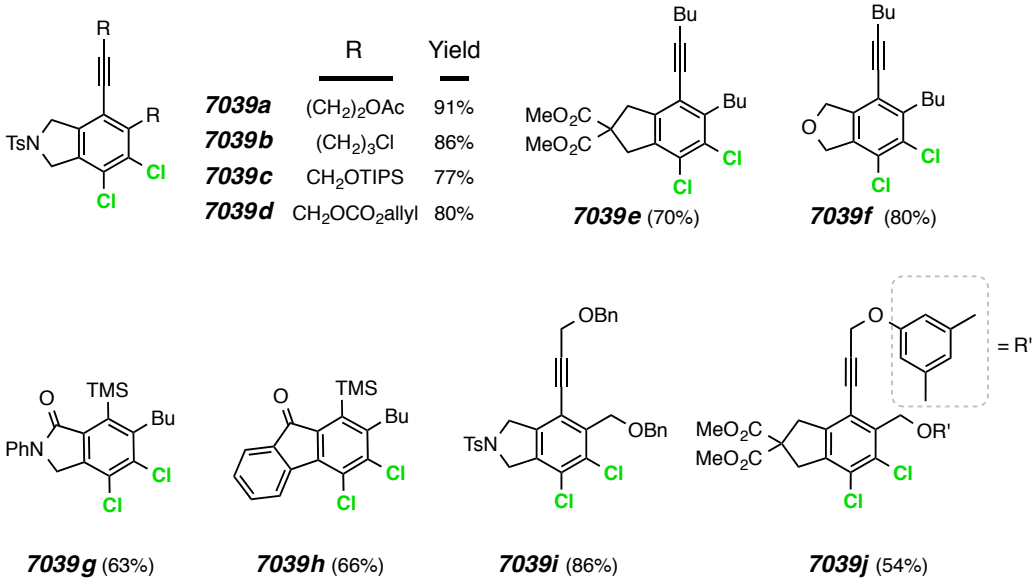
b



We next probed some of the scope of this Li_2CuCl_4-mediated dichlorination reaction. Products **7039a-j** (Scheme 7.12) encompass dichlorinated isoindoline, isoindolone, isobenzofuran, indane, and fluorenone skeletons. These results show that a variety of functional groups, present in the triyne precursors and/or the benzenoid products, are tolerated. They include toluenesulfonamide, ketone, ester, amide, carbonate, alkyl or aryl chloride, silyl ether, silyl alkyne, alkene, and (electron rich) aromatic ring. However, we have observed that triyne substrates containing a free alcohol or terminal alkyne are not compatible.

Notably, each of the benzyne precursors to **7039i-j** bears an intramolecular trap. In the absence of an external trapping agent, efficient aromatic Diels-Alder[111] or aromatic ene (see Section **7.4**) reaction within the intermediate benzyne occurs. However, in the presence of Li_2CuCl_4 these intramolecular trapping modes were largely if not completely superseded by chlorination to instead produce **7039i-j**.

Scheme 7.12| Products (**7039a-j**) of dichlorination (10 equiv of Li_2CuCl_4, $[substrate]_0$ = 0.03 M in THF) of various HDDA-derived benzynes [55-89% isolated yields].

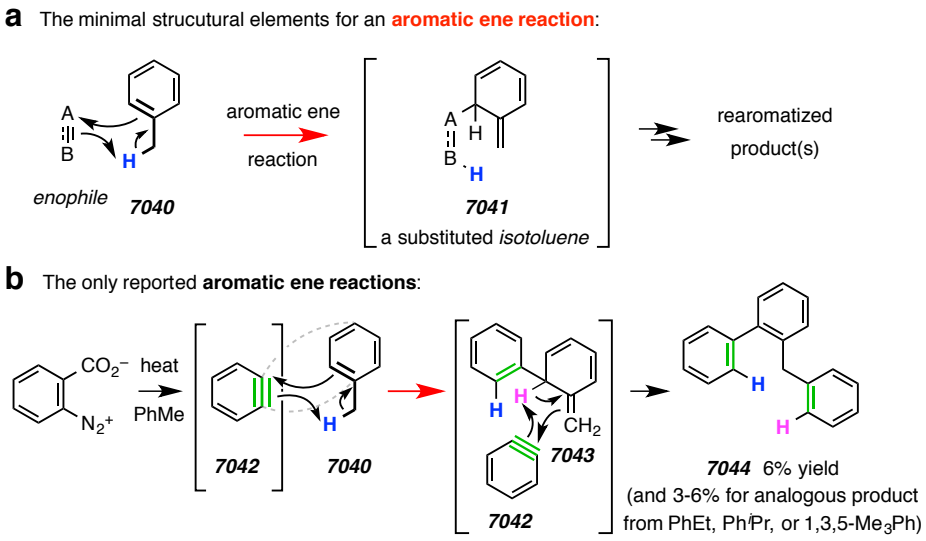


In conclusion, we have developed a new and efficient benzyne dichlorination reaction using the mild oxidizing agent, dilithium tetrachlorocuprate. We have shown that various types of 1,2-dichlorinated products can be accessed. The conditions are compatible with a considerable variety of functional groups in the benzyne precursor and resultant benzenoid product.

7.4 The aromatic ene reaction

Ene reactions,[139] which involve the attack of an alkene (the ene donor) by an unsaturated enophile (A=B or A≡B), are well known in organic chemistry.[140] In the process an allylic hydrogen atom is transferred to the enophile and the alkene π-bond is transposed (i.e., $C^1=C^2–C^3–H$ + A=B to H–B–A–C^1–C^2=C^3).

Scheme 7.13| a) Structural delineation of an aromatic ene reaction. **b)** Previous examples of aromatic ene reaction.



Aromatic ene reactions–those in which an arene bearing a benzylic C–H bond serves as the ene donor (cf. **7040** to **7041**, Scheme 7.13)–are extremely rare. The only (four) reported examples involve *o*-benzyne (**7042**) itself as the enophile. Each proceeds in low yield (≤6%) and is presumed to follow the pathway shown in Fig. 1b (**7042** to **7044** via

[139] Alder, K.; Pascher, F.; Schmitz, A. Über die Anlagerung von Maleinsäure-anhydrid und Azodicarbonsäure-ester an einfach ungesättigte Koh an einfach ungesättigte Kohlenwasserstoffe. Zur Kenntnis von Substitutionsvorgängen in der Allyl-Stellung. *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 27.

[140] Hoffman, H. M. R. The ene reaction. *Angew. Chem. Int. Ed.* **1969**, *8*, 556–577.

7043);[141] the competing formation of bimolecular [4+2] Diels–Alder reaction products between *o*-benzyne (**7042**, now acting as a dienophile) and toluene (the diene) perhaps has contributed to the fact that this fundamentally intriguing and rare type of ene reaction has since remained unexplored and unexploited.

Arynes are known to function as enophiles.[83] The earliest examples of this were sporadic and isolated in their nature, but recent studies have established synthetically useful ene reaction protocols involving arynes as the enophile (Scheme 7.14). Lautens et al. has reported the wide scope of intramolecular ene reactions of (classically generated) benzyne derivatives like **7046** (from **7045**) in which pendant alkenes cyclize efficiently to provide annelated products like **7047**.[142] We recently described the intramolecular ene reaction of the aryne **7049** to give **7050**.[111] Cheng and coworkers have demonstrated the generality of a bimolecular propargylic ene reaction between *o*-benzyne (**7042**, generated from **7051** by the method of Kobayashi[84]) and an alkyne (cf. **7052**) to give an allene (cf. **7053**).[143] Lee et al. have recently described the considerable scope of reactions like **7048** to **7050** as well as an intramolecular propargylic ene reaction (**7054** to **7056** via **7055**).[144] Arynes are also known to participate in hetera-ene reactions with a phenol[111,124] (see Section 7.2) or aniline[145] derivative serving as the ene donor.

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[141] a) Brinkley, Y. J.; Friedman, L. Novel ene and insertion reactions of benzyne and alkylbenzenes. *Tetrahedron Lett.* **1972**, *13*, 4141–4142. b) Tabushi, I.; Yamada, H.; Yoshida, Z.; Oda, R. Reactions of benzyne with substituted benzenes. *Bull. Chem. Soc. Jpn. 1977*, **50**, 285–290.

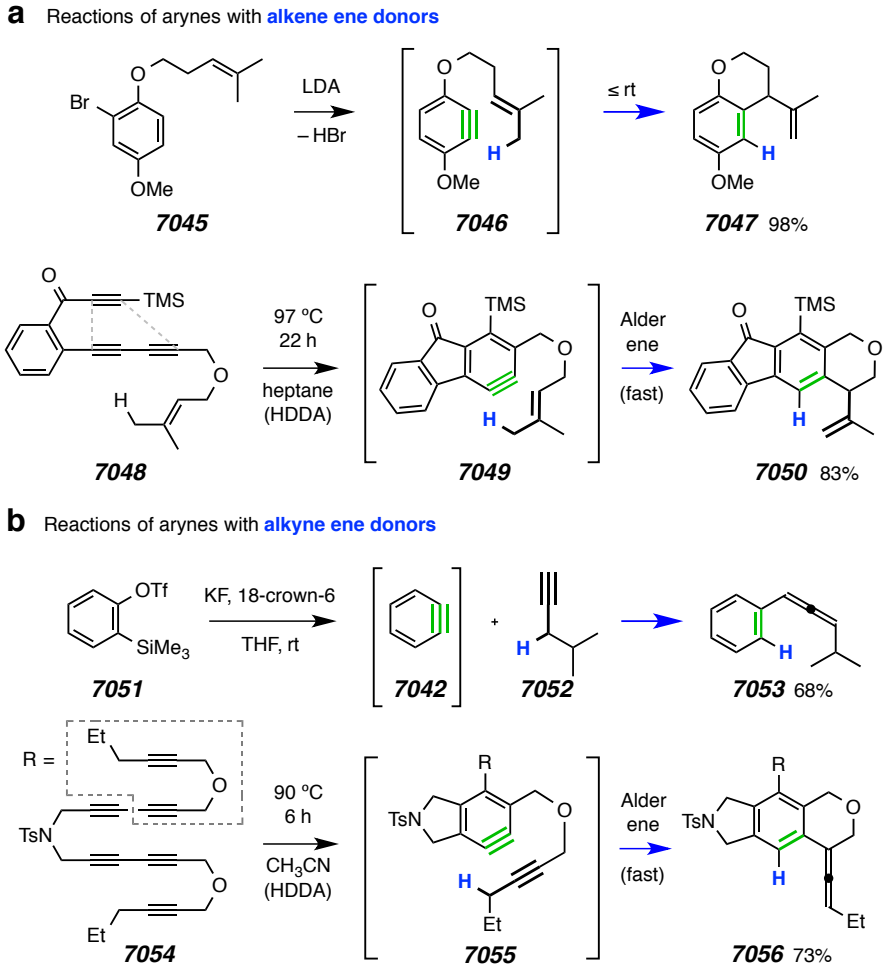
[142] a) Candito, D. A.; Panteleev, J.; Lautens, M. Intramolecular aryne–ene reaction: synthetic and mechanistic studies. *J. Am. Chem. Soc.* **2011**, *133*, 14200–14203. b) Candito, D. A.; Dobrovolsky, D.; Lautens, M. Development of an intramolecular aryne ene reaction and application to the formal synthesis of (±)-crinine. *J. Am. Chem. Soc.* **2012**, *134*, 15572–15580.

[143] Jayanth, T. T.; Jeganmohan, M.; Cheng, M.; Chu, S.; Cheng, C. Ene reaction of arynes with alkynes. *J. Am. Chem. Soc.* **2006**, *128*, 2232–2233.

[144] Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. Alder-ene reactions of arynes. *Org. Lett.* **2013**, *15*, 1938–1941.

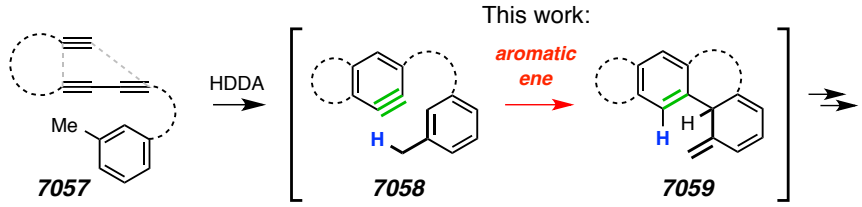
[145] Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. Transition-metal-free direct arylation of anilines. *Angew. Chem. Int. Ed.* **2012**, *51*, 1006–1009.

Scheme 7.14| **Arynes** as enophiles reacting with **a**, an alkene, **b**, an alkyne donor bearing an allylic or propargylic **hydrogen atom**, respectively.



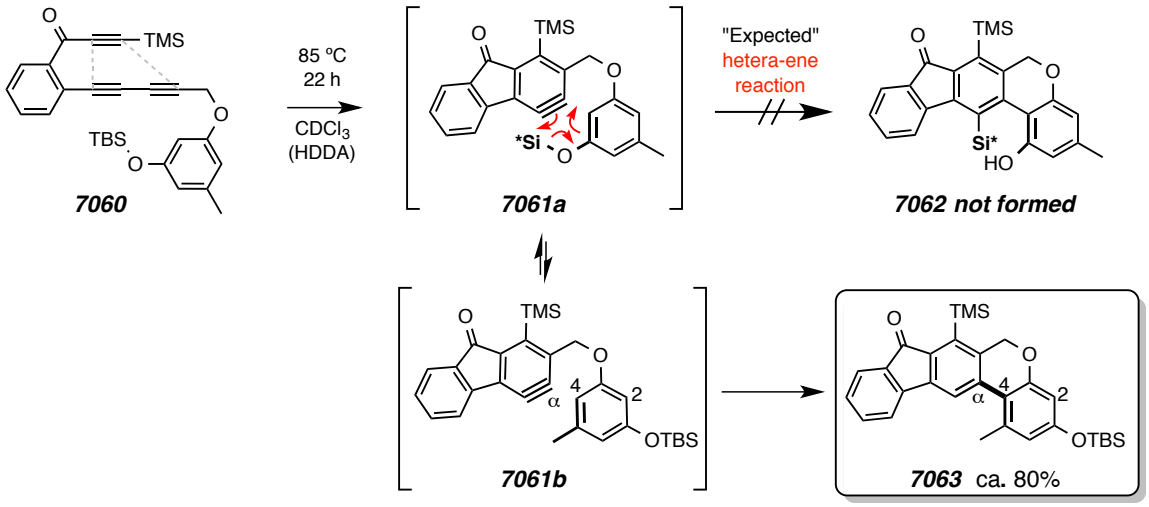
Here we show the first examples of efficient aromatic ene reactions. They were developed in the context of arynes like **7058** (Scheme 7.15), which bear suitably disposed aromatic substituents, and pass through isotoluene species like **7059**, reactive intermediates in their own right for which we also report here some unprecedented transformations.

Scheme 7.15| This work: **aryne** as enophile reacting with arene bearing a benzylic **hydrogen atom**.

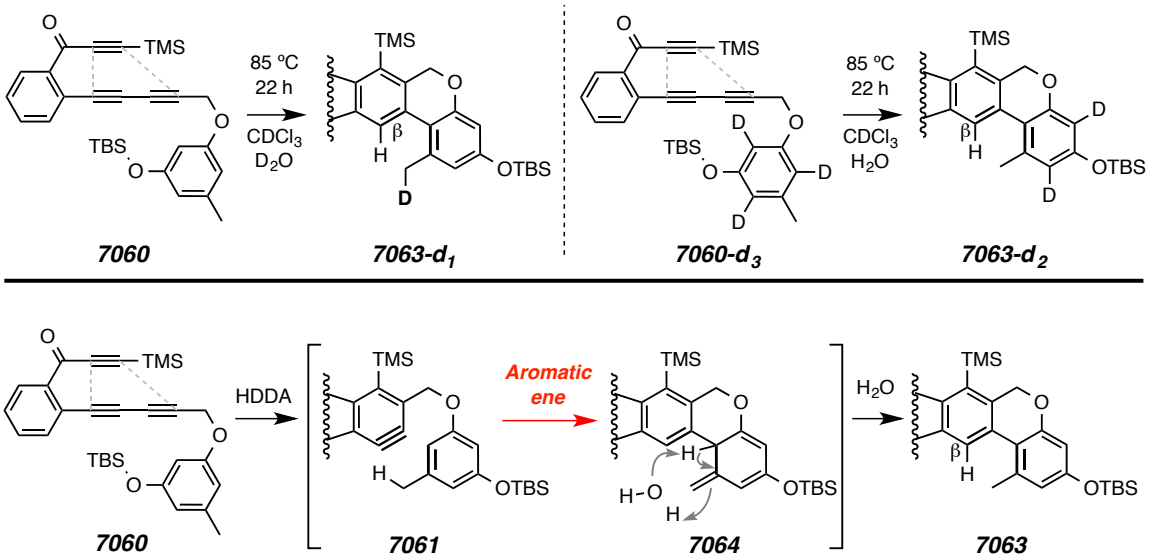


In fact, the "discovery" of aromatic ene reaction in this lab was an accident (Scheme 7.16). Having recognized the ability of aryne to cleave Si-O bonds,[111] I designed and synthesized triyne **7060**, to explore the possibility of a hetera-ene like reaction between aryne and the tethered silyl phenol ether moiety within intermediate **7061a**, expecting the formation of pentacyclic compound **7062**. In reality, however, the isomerization of **7060** gave **7063** as the only isolated product. Not the expected pathway, the conversion from **7060** to **7063** was puzzling and interesting.

Scheme 7.16| Serendipitous discovery of aromatic ene reaction.



Scheme 7.17| Deuterium-labeling experiments to probe the mechanism for the conversion of **7060** to **7063**.



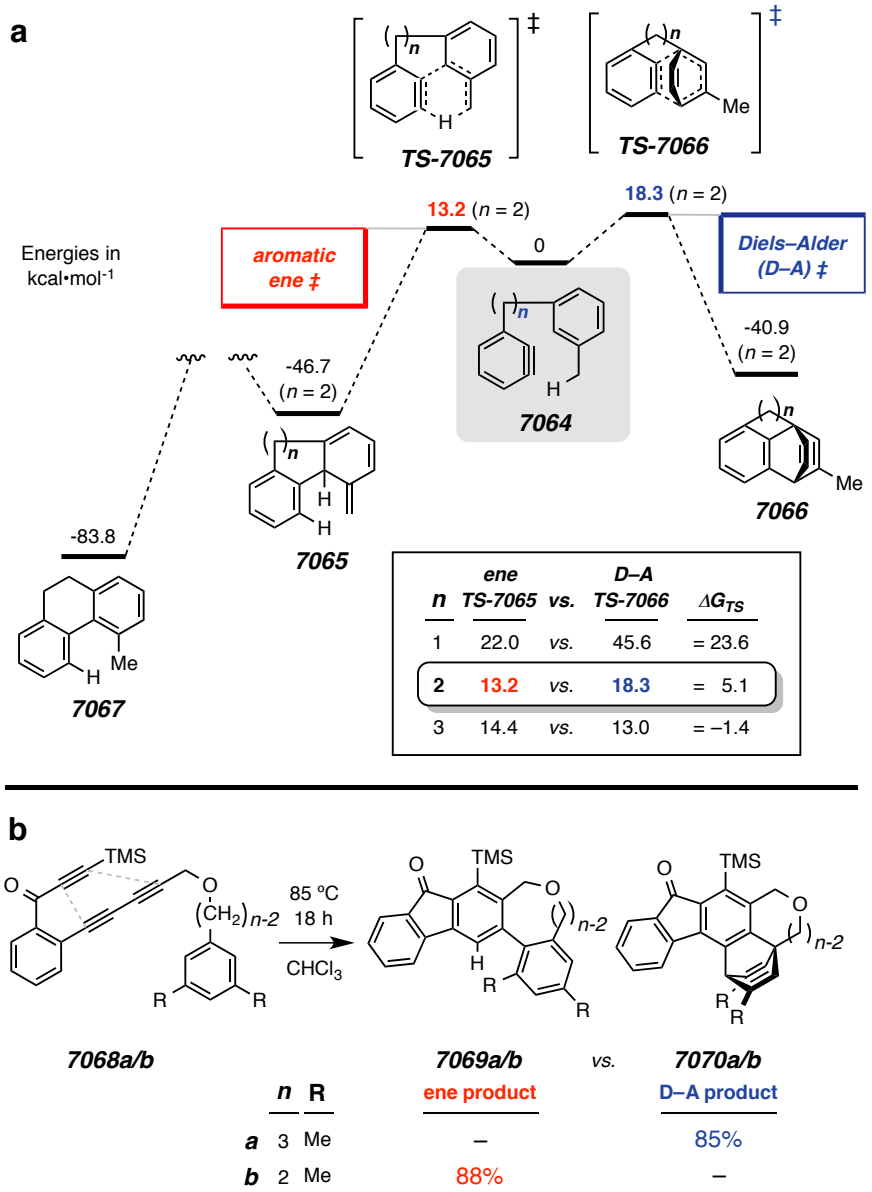
I then performed studies to probe the mechanism of this transformation. The exclusive formation of Cα-C4 bond over Cβ-C2 bond speaks against a Friedel–Crafts type of mechanism. In order to gain additional mechanistic insights, I then conducted two complementary deuterium-labeling experiments. In the first, triyne **7060** was heated in the presence of D_2O (specifically, D_2O-saturated chloroform). The dominant product, **7062-d$_1$** (Scheme 7.17), was monodeuterated (ca. 93% deuterium incorporation, ^{1}H NMR analysis). In the second, trideuterated substrate **7060-d$_3$** was heated, this time in the presence of H_2O. In this case, the dominant product was **7062e-d$_2$**, in which one of the three aromatic deuterium atoms in **7060-d$_3$** had been lost. The results of these two experiments suggested: 1) a benzylic C-H was cleaved under the reaction conditions; 2) the hydrogen atom on Cβ of **7063** originates from the broken benzylic C-H bond. With this information, we propose the conversion of **7060** to **7063** comprises a three-step sequence: 1) the HDDA cyclization to make benzyne **7061**; 2) the aromatic ene reaction

to make isotoluene **7064**; and 3) the rearomatization of **7064** assisted by external H_2O. This transformation represents the first efficient aromatic ene reaction.

In retrospect, the "discovery" of the aromatic ene reaction was a fortunate outcome. Realization of the aromatic ene reaction has heretofore been elusive for at least two fundamental reasons. First, the energetics of dearomatization associated with the primary ene event (cf. **7061** to **7064** in Scheme 7.17) require that the enophile be of inherently high reactivity. Second, *o*-benzyne, the only known enophile capable of overcoming this barrier, displays competitive [4+2] (Diels–Alder) reactivity toward the dienic character that is necessarily present in the requisite aromatic ring of the ene donor.[141] These two issues were fortuitously addressed at the same time by using triyne **7060** that had been designed for a different purpose: 1) the reagent- and byproduct-free nature of the HDDA reaction (of **7060**) in effect rendered the resulting benzyne longer lifetime, and therefore allowed the efficient trapping of benzyne with the tethered tolyl substituent, a process with relatively high activation energy; 2) the skeletal feature of **7060** played a critical role in biasing the reaction outcome against intramolecular Diels–Alder event and toward aromatic ene event. This latter point had not been evident until computational investigation on this reaction was performed.

We used density functional theory [DFT, M062X[62]/6-31G(d)] to study three benzyne derivatives **7064** (*n* = 1, 2, and 3), each differing only in the length of the methylene chain joining the tolyl to benzyne moieties (Scheme 7.18). The computed relative TS energies for **7064** (n = 3) in fact favor the intramolecular Diels–Alder pathway. This result is consistent with an experimental outcome we observed before: reaction of substrate **7068a** gave **7070a** to the exclusion of any observable amount of ene product

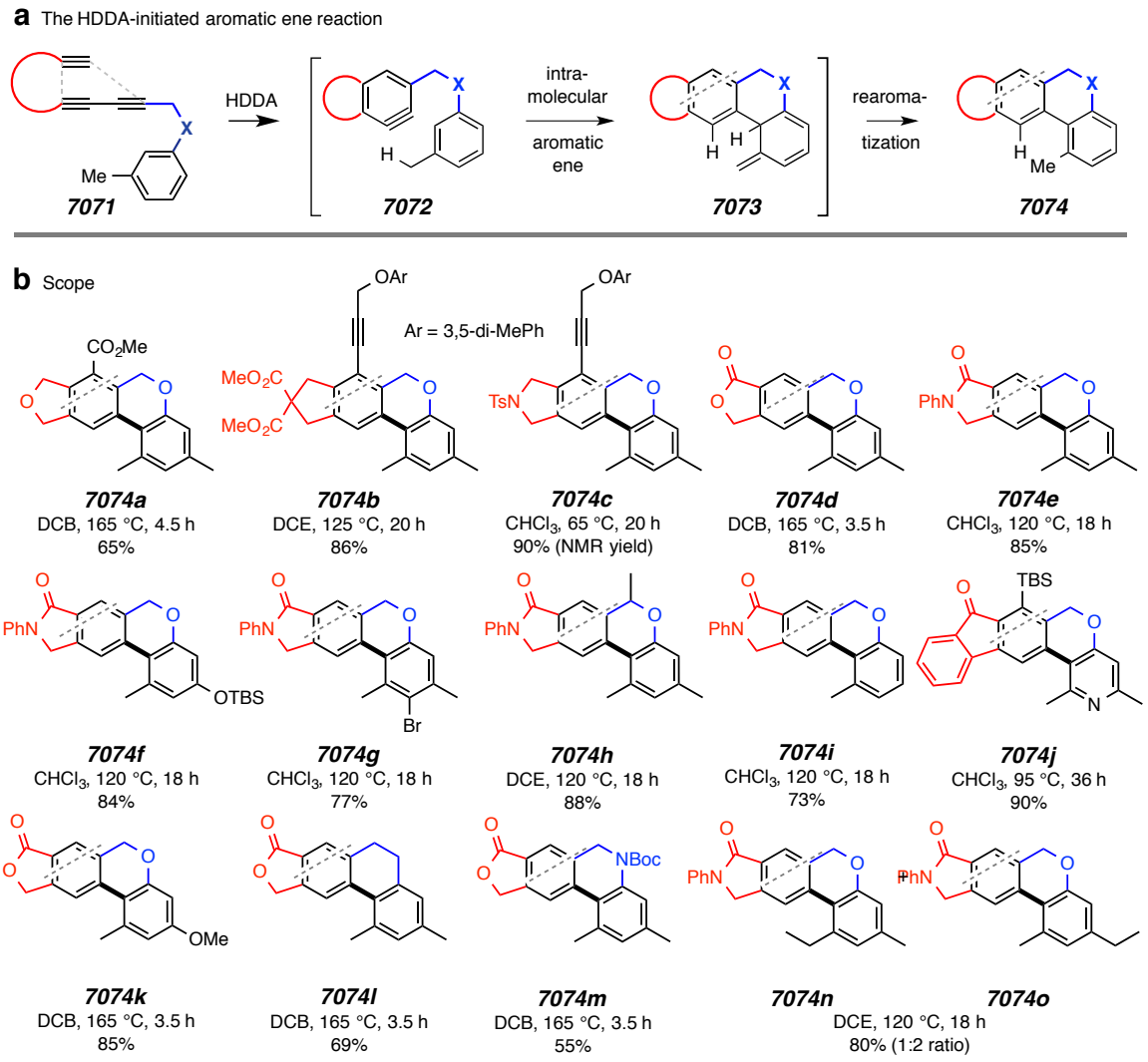
Scheme 7.18| Competition between aromatic ene and aromatic Diels-Alder pathways (*n* is the total number of atoms that link the aryne to the trapping aryl component for each structure in this scheme).



7069a[111] (Scheme 7.18). Computation of either of the other substrates **7064** (*n* = 1 or 2) showed a decided preference for the ene rather than the Diels–Alder event. But the computed activation barrier for the aromatic ene reaction was considerably higher for the case where *n* = 1 than for *n* = 2. Accordingly, the isomerization of compound **7068b**, a

substrate having the similar two-atom link as those in **7060** and **7064** (n = 2), produced only the aromatic ene-type product **7069b** (88% yield). Substrates with one-atom link between the aryne and the tolyl moiety as in **7064** (n = 1) failed to give any isolable product (vide infra). The two-atom linker between the aryne and trapping arene rings therefore is a key structural element that permitted an efficient aromatic ene reaction.

Scheme 7.19| The HDDA-initiated aromatic ene reaction. **a**, the generic transformation, in which three new rings are generated. **b**, scope, demonstrating functional group tolerance and variations in the polycyclic skeletons of the products.

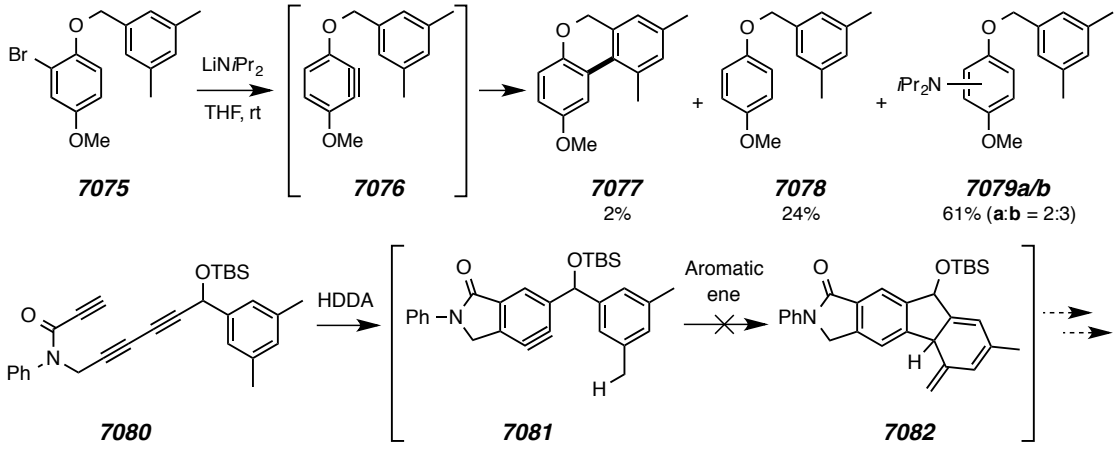


To recapitulate, this unique HDDA//aromatic ene process (Scheme 7.19) converts a triyne substrate like **7071** [bearing a (*meta*-alkyl)aryl substituent, connected through a two atom linker] via an aryne like **7072** to an isotoluene intermediate like **7073**, which aromatizes to a final tricyclic product like **7074**. As with all HDDA-initiated reactions, this transformation is simply thermally induced, can be performed in a variety of non-participating solvents, and does not require particularly stringent reaction conditions (e.g., oxygen- or water-free). The broad scope of the process is demonstrated by the results summarized in Scheme 7.19b. Highlights include: (i) Arynes having a variety of different electronic properties, as governed by the functional groups within the triyne tether (red), are effective enophiles (cf. **7063**, **7070b** and **7074a-e** and **j**); (ii) the linker (blue) between the aryne enophile and arene ene donor can incorporate carbon, nitrogen, or oxygen atoms and can bear substitution (**7074h**); (iii) substituents on the arene donor [e.g., alkoxy (**7074k**), silyloxy (**7063** and **7074f**), or halide (**7074g**)] are well-tolerated; (iv) on the other hand, minimally substituted arenes are also effective (cf. **7074i**); (v) the arene donor is not restricted to benzenoid derivatives; efficient formation of the pyridine-containing product **7074j** bodes well for the potential ene trapping by other heteroaromatics; (vi) secondary benzylic C–H bonds will participate in the ene transfer event, although at a slightly slower rate than that of a primary (cf. 1:2 ratio of products **7074n**:**7074o**).

Some limitations of this reaction are worth mentioning here (Scheme 7.20). The ability to generate the reactive aryne intermediate in the absence of other reagents (i.e., by thermal activation only) was essential for realizing an efficient aromatic ene reaction. This point was illustrated by the outcome of our attempt to use the Lautens strategy (cf.

7045 to **7047** in Scheme 7.14) to effect the aromatic ene trapping of the aryne **7076** generated by base-induced elimination of HBr from bromoarene **7075** (Scheme 7.20). The biaryl **7077** was formed, but in only ca. 2% yield. Products resulting from amine trapping (**7079**) and reduction (**7078**)[146] of the intermediate aryne were formed predominantly. Additionally, high yielding aromatic ene reactions were observed only with substrates that have two atom linker between aryne and tolyl substituent: those with three atom linker gave Diels–Alder adduct predominantly; those with one atom linker like **7081** (from **7080**) failed to give **7082** presumably because of the high activation energy for the process as predicted by computational study.

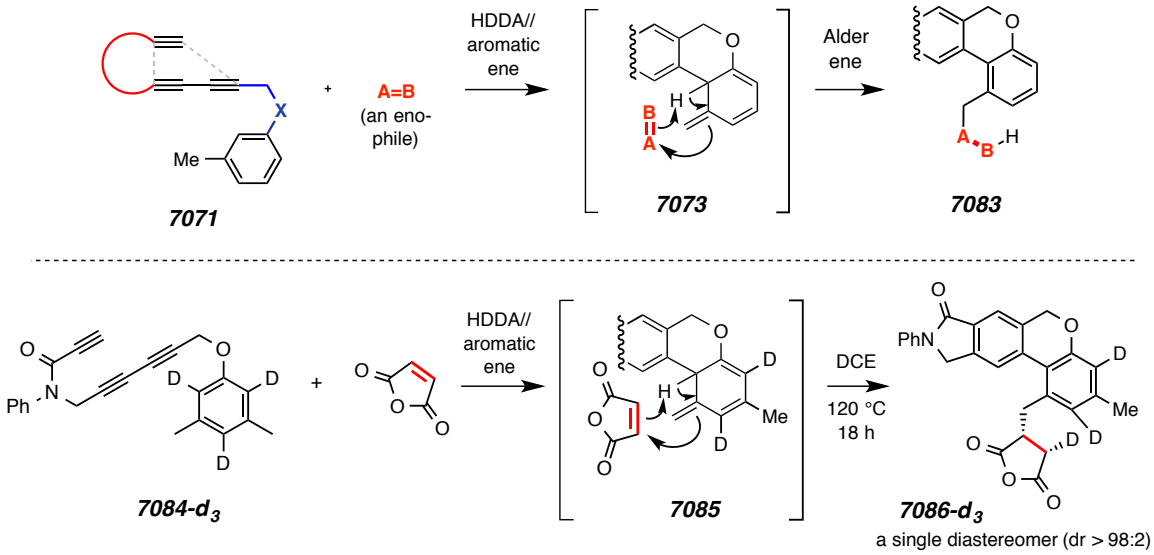
Scheme 7.20| Some limitations of aromatic ene reaction.



Despite these limitations, we still deem the aromatic ene reaction a useful transformation. We further reasoned that because the isotoluene intermediate **7073** formed via the initial aromatic ene reaction was sufficiently long-lived to encounter water, it might be possible to trap this species in an even more productive manner by an added external enophile (cf. A=B, **7073** to **7083** in Scheme 7.21). Indeed, when a 1,2-

[146] Niu, D; Willoughby, P. H.; Woods, B. P.; Baire, B.; Hoye, T. R. Alkane desaturation by concerted double hydrogen atom transfer to benzyne. *Nature* **2013**, *501*, 531–534.

Scheme 7.21| HDDA//aromatic ene//Alder ene cascade.

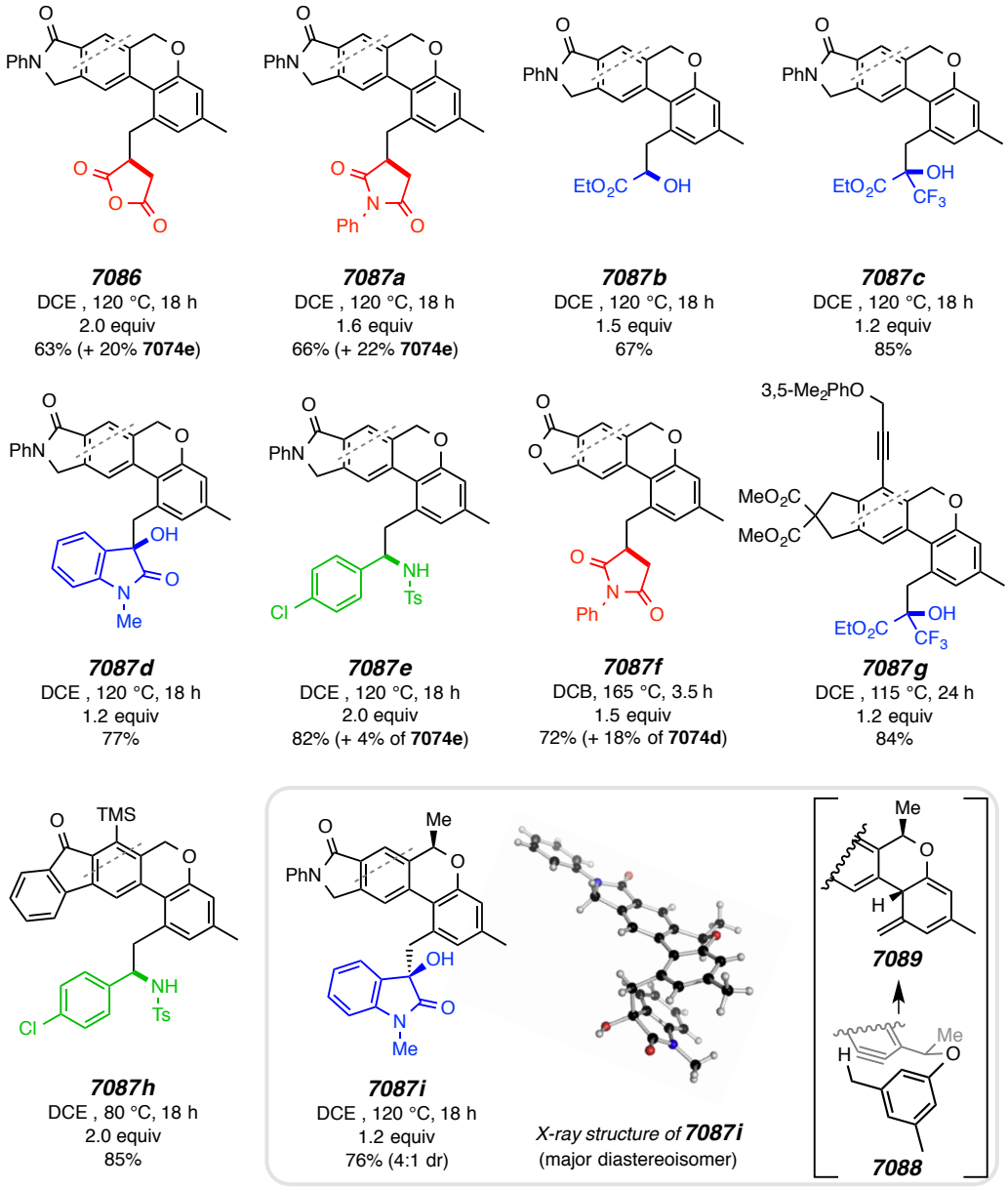


dichloroethane solution of the trideuterated substrate **7084-d$_3$** was heated in the presence of maleic anhydride[147] (Scheme 7.21), the adduct **7086-d$_3$** was formed. The observed net *cis*-addition of carbon and deuterium across the enophile π-bond was stereospecific (coupling constant and chemical shift analysis of the ^{1}H NMR spectrum), providing evidence for a concerted ene reaction between maleic anhydride and **7084-d$_3$**.

This successful transformation of **7084-d$_3$** to **7086-d$_3$** via **7085** showed that it was possible to unite an additional (bimolecular) ene trapping reaction with the initial (unimolecular) aromatic ene reaction. This amounts to a HDDA//aromatic ene//Alder ene cascade. The sequence is enabled because the isotoluene intermediate **7085** is still endowed with a considerable portion of the potential energy embodied by the three alkyne units in the initial HDDA substrate **7084-d$_3$**. The scope of this three-stage cascade process can be seen from the examples shown in Scheme 7.22. Highlights include:

[147] Alder, V. K.; Schmitz-Josten, R. Über die Addition von Maleinsäure-anhydrid an Styrol. *Liebigs Ann. Chem.* **1955**, *595*, 1–37.

Scheme 7.22| Scope of HDDA//aromatic ene//Alder ene cascade.



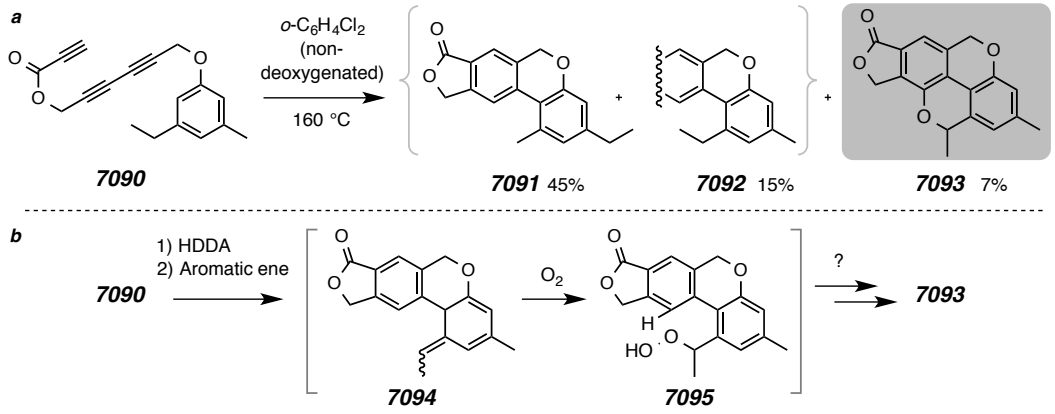
(i) a variety of types of external enophiles can be used to trap the isotoluene intermediate; these include electron-deficient alkenes (maleic anhydride and maleimides), α-dicarbonyl compounds (pyruvates, glyoxalate, and *N*-methylisatin), and an *N*-sulfonylimine; (ii) the overall cascade process is tolerant of a large number of inherently reactive functional groups including imide, anhydride, ketone, ester, halogen, alcohol, aldehyde, and

sulfonamide that are present in the trapping enophiles and the newly formed products, demonstrating a considerable degree of chemoselectivity; (iii) the process is also compatible with a broad array of functionality in the aryne precursor–derivatives of isoindolone, phthalide, fluorenone, and indane can all be produced in high yields; (iv) the reaction can be conducted at relatively high substrate (triyne) concentration (0.2 to 0.3 M), which speaks to the inherently fast nature of the aromatic ene trapping step; (v) only 1.2 to 2 equivalents of external trapping enophiles were used, which suggests that the isotoluene intermediate has a relatively long lifetime and bodes well for application to convergent coupling synthesis strategies using complex triyne substrates *and* complex trapping enophiles; (vi) various steps in the cascade are stereoselective, as indicated by the production of a 4:1 ratio of diastereomers **7087i** and its epimer from the corresponding (chiral) triyne. Although we do not yet know the exact origin of this selectivity, relative asymmetric induction in this case can occur at either (or both) of two stages. The aromatic ene substrate **7088** has diastereotopic re and si faces at its (two equivalent) *ortho*-carbon atoms, as does the isotoluene intermediate **7089** at its *exo*-methylene carbon atom.

Isotoluene intermediate from aromatic ene reaction could also be trapped by other reagents. For example, when aryne precursor **7090** was heated in *o*-dichlorobenzene, a significant byproduct **7093** was formed, along with conventional HDDA//aromatic ene//aromatization products **7091** and **7092** (Scheme 7.23a). Notably, **7093** has a higher oxidation state than **7091** or **7092**, suggesting the participation of some oxidants in the process of its formation. Presumably, oxygen dissolved in the reaction solvent and present in the head space of the reaction flask is responsible for the production of **7093**. A

mechanism shown in Scheme 7.23b was proposed, the key step of which involves the oxidation of isotoluene intermediate **7094** by O_2 to give peroxide intermediate **7095**. However, dehydration of **7095** to form **7093** represents another unprecedented transformation,[148] and its mechanism is still unclear.

Scheme 7.23| a) Formation of **7093** was observed as a byproduct in the reaction with substrate **7090**. b) Proposed mechanism for the formation of **7093** from **7090**.



In conclusion, the transformations shown in this section revealed the generality of a heretofore rare and elusive type of ene reaction in which an arene bearing a benzylic C–H bond functions as the ene donor. I have shown that the isotoluenes generated by this HDDA-enabled "aromatic ene" reaction can rearomatize either by net rearrangement or through interception by an external enophiles. Thus, two complementary processes have emerged. In the first, the isotoluene rearomatizes to provide polycyclic products like **7074a-o** (Scheme 7.19) in a process explained by water-mediated proton shuttling. In the second, the reactive isotoluene is further engaged by an external enophile to give products of yet greater structural complexity (cf. **7087a-i**, Scheme 7.22). This ene-upon-

[148] For precedented metal-free C_{sp2}-H bond activation by peroxides, see: Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. Metal-free oxidation of aromatic carbon-hydrogen bonds through a reverse-rebound mechanism. *Nature*, **2013**, *499*, 192–196.

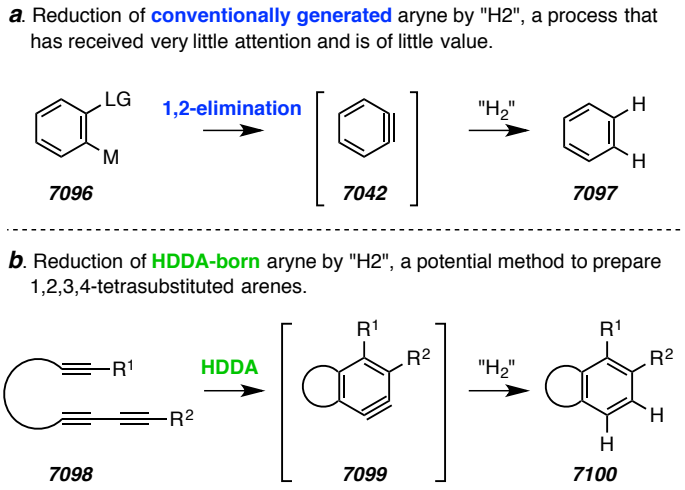
ene cascade reaction involves the overall formation of four carbon-carbon bonds and three rings, requires no external reagents, and generates no byproducts. The discovery of this efficient aromatic ene reaction further attests to the importance of a key feature of the HDDA cycloisomerization—namely, its ability to deliver aryne intermediates in the absence of the potentially interfering reagents that typically accompany aryne formation by classical methods.[149]

[149] Kitamura, T. Synthetic methods for the generation and preparative application of benzyne. *Aust. J. Chem.* **2010**, *63*, 987–1001.

7.5. Double hydrogen transfer between saturated alkanes and benzynes

As can be seen from the discussion in the previous sections, chemists have developed numerous ways to introduce substituents into aryne intermediates, thereby making decorated benzenoid rings. In contrast, the reduction of aryne, i.e., introducing two hydrogen atoms to the strained bond of aryne (Scheme 7.24a) received very little attention from the synthetic community. Two reasons may account for this situation: 1) *o*-aryne like **7042** is highly prone to nucleophilic attack, which may have obscured its ability to react with potential H2 donors; 2) this reduction method is of little preparative value if aryne is produced by a conventional 1,2-elimination method, since the starting material (**7096**) will be more difficult to access than the product (**7097**).

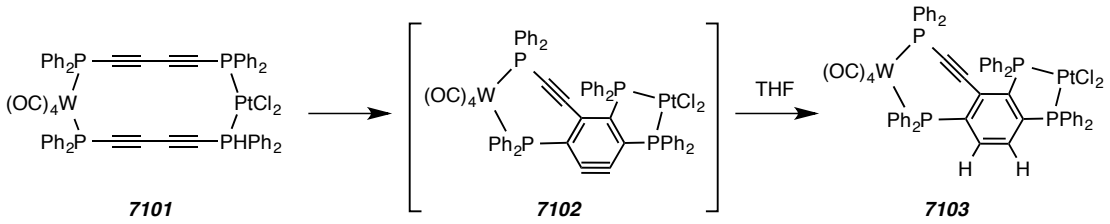
Scheme 7.24| Reduction of aryne by "H2".



On the other hand, the dihydrogenation of aryne like **7099** that is originated from HDDA reaction is of significant synthetic interest because this method would provide direct access to 1,2,3,4-tetrasubstituted arenes like **7100** from suitable triynes like **7098**. The focus of this section will be such a transformation and some additional discoveries made during the course of study.

Initial attempts of effecting dihydrogenation of HDDA-born arynes using conventional hydrogen atom donors like Et_3SiH, Bu_3SnH, or 1,4-cyclohexadiene were not successful. An extensive survey into literature revealed an intriguing observation made by Sterenberg and coworkers: when attempting to recrystallize the bis-diyne-bridged, dinuclear metal complex **7101** from THF, they isolated the reduced arene **7103** in >90%[150] (Scheme 7.25). They later confirmed that the solvent (THF) was the source of the hydrogen (and, in the case of THF-d_8, deuterium) atoms that appeared in the reduced benzenoid product. To gain some further insights into this unusual reduction of **7101**, the authors incubated **7101** with furan, and observed the clean formation of a product apparently arising from the Diels–Alder reaction between aryne **7102** and furan, thereby confirming that in these reactions, tetrayne **7101** initially isomerizes to aryne **7102**. Therefore, they proposed that the formation of arene **7103** is the result of aryne (**7102**) reduction by THF.

Scheme 7.25| Sterenberg's observation: HDDA-born benzyne **7102** could be dihydrogenated by THF.

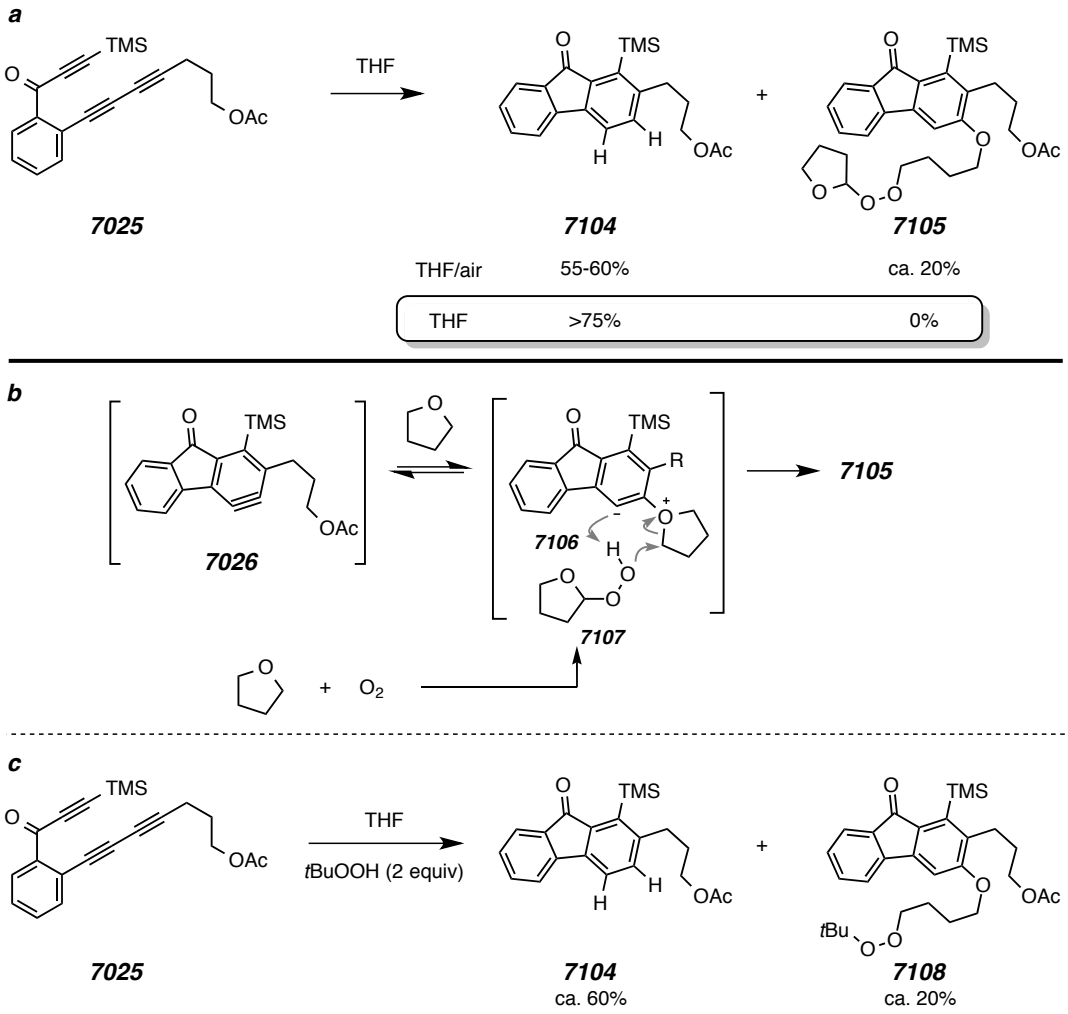


Inspired and encouraged by Sterenberg's observation, I heated substrate **7025** in THF-h_8, to see if the corresponding aryne intermediate could be reduced under such conditions. To my delight, arene **7104** was isolated as the major product (55-60%) when

[150] Tsui, J. A.; Sterenberg, B. T. A metal-templated 4 + 2 cycloaddition reaction of an alkyne and a diyne to form a 1,2-aryne. *Organometallics* **2009**, *28*, 4906–4908.

the reaction was completed. This result verified that THF is indeed an effective reductant for aryne. However, peroxide **7105** was also isolated from the reaction mixture and characterized by ^{1}H NMR and HR ESI-MS, albeit as a minor component (ca. 20%). To rationalize the formation of this peroxide, I proposed the mechanism shown in Scheme

Scheme 7.26| Reaction of aryne with THF: formation of reduced arene and peroxide byproduct.



7.26b, which involves: 1) (reversible) nucleophilic attack of THF to aryne **7026**, generating zwitterion **7106**; and 2) zwitterion quenching by peroxide **7107** originated from THF auto-oxidation. To validate this mechanism, **7025** was heated in air-free THF

in the presence of intentionally added *t*BuOOH. Under these conditions, peroxide **7108** was isolated as the minor product instead. Having established the source of the byproduct **7105**, I then conducted the reduction **7025** using carefully deoxygenated THF. Under these new conditions, the formation of peroxide was almost completely suppressed, and the yield for the desired reduced arene was improved to >75%.

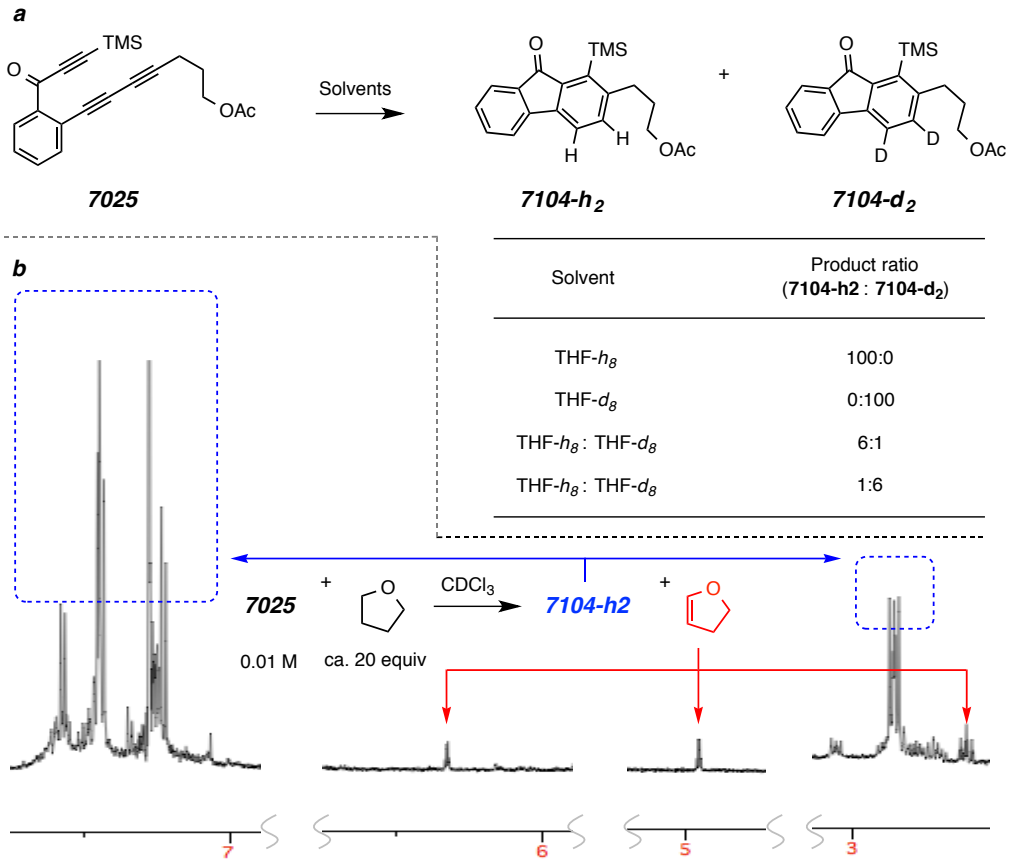
Although a condition for aryne reduction was identified, the mechanism for this transformation was still unclear. In fact, it was very surprising to see THF be an efficient reducing agent for arynes for two reasons. First, THF was one of the most frequently used solvents for reactions involving arynes, yet the only report that documented its ability to reduce aryne was the one from Sterenberg's group. Second, the reported reactions between THF and aryne in most cases occur in a polar addition pathway[86,151] (cf. **7026** to **7106** in Scheme 7.26b).

To gain additional mechanistic insights into this reaction, I repeated the generation and trapping of aryne **7026**, this time in the presence of an equimolar mixture of THF-h_8 and THF-d_8 (Scheme 7.27a). Intriguingly, only the diprotio- and dideuterio-benzenoid products **7104-h$_2$** and **7104-d$_2$** were produced; none of the mono-H/mono-D analog (**7104-hd**) was detected. The observed **7104-h$_2$**:**7104-d$_2$** product ratio was 6:1, indicating a significant H/D kinetic isotope effect for the 2H-transfer. The complementary experiment of using a 1:6 molar ratio of THF-h_8:THF-d_8 resulted in a nearly 1:1 ratio of products **7104-h$_2$**:**7104-d$_2$**. The lack of an observable level of monodeuterated product in any of these experiments is evidence that both of the two added hydrogen atoms in **7104** originate from a single molecule of THF. Moreover, when the reduction of **7025** was

[151] Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babash, E. S. C.; Hsung, R. P. Enamide-benzyne-[2+2] cycloaddition: stereoselective tandem [2+2]-pericyclic ring-opening-intramolecular *N*-tethered [4+2] cycloadditions. *Org. Lett.* **2009**, *11*, 3666–3669.

performed in $CDCl_3$ using 20 equiv of THF, I was able to observe the formation of 2,3-dihydrofuran as a byproduct (Scheme 7.27b). This outcome further suggests that the two transferred hydrogen atoms derive from the vicinal C-H bonds in THF.

Scheme 7.27| a) Deuterium-labeling experiments for the reduction of aryne by THF. **b)** A crude ^1H NMR spectrum for reduction of **7025** (0.01 M) in $CDCl_3$ using ca. 20 equiv THF.

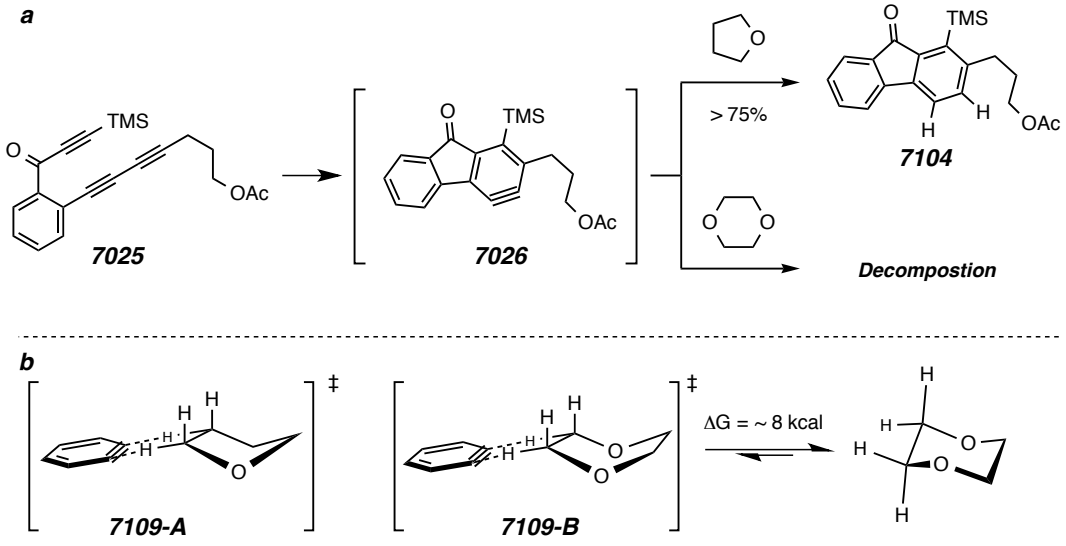


Solvent	Product ratio (**7104-h2** : **7104-d$_2$**)
THF-h_8	100:0
THF-d_8	0:100
THF-h_8 : THF-d_8	6:1
THF-h_8 : THF-d_8	1:6

Additional insights were gained from the reaction between aryne and 1,4-dioxane. It was initially astounding to see that 1,4-dioxane, a molecule structurally very close to THF, is totally ineffective to reduce aryne **7026** (Scheme 7.28a). To rationalize this dichotomy and the observations discussed in the previous paragraph, I proposed that this double hydrogen transfer process occurs in a concerted fashion, the transition structure of

which contains 6 coplanar atoms, as depicted by structure **7109-A** and **7109-B** in Scheme 7.28b.

Scheme 7.28| a. Drastic reactivity difference between THF and 1,4-dioxane in reducing arynes. **b.** Proposed mechanism for double hydrogen transfer between aryne and THF/1,4-dioxane.



Although such a description might seem unusual, the generally accepted mechanism for (i) the reduction of alkenes by diimide (HN=NH)[152] and (ii) type II dyotropic reactions[153] involves a similar simultaneous, co-planar double hydrogen atom transfer. Importantly, this mechanism explains the reactivity difference between THF and 1,4-dioxane in reducing arynes: the reactive conformer of THF is envelop-shaped, low-lying in energy, and therefore highly populated; whereas the reactive conformer of 1,4-dioxane is boat-shaped, ca. 8 kcal•mol^{-1} less stable than the chair conformer, and therefore only present in solution at low concentration.

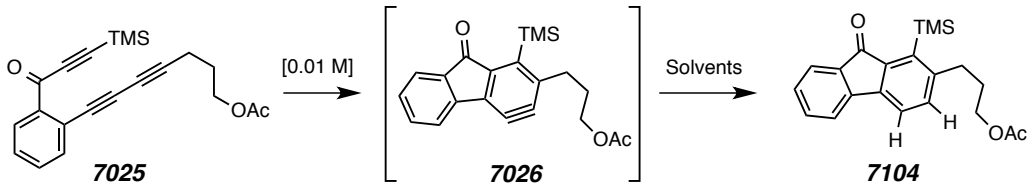
[152] a) Hünig, S.; Müller, H.; Thier, W. Reduktionen mit diimid. *Tetrahedron Lett.* **1961**, *2*, 353–357. b) Corey, E. J.; Pasto, D. J.; Mock, W. L. Chemistry of diimide. II. Stereochemistry of hydrogen transfer to carbon-carbon multiple bonds. *J. Am. Chem. Soc.* **1961**, *83*, 2957–2958.

[153] a) Fernández, I.; Cossío, F. P.; Sierra, M. A. Dyotropic reactions: Mechanisms and synthetic applications. *Chem. Rev.* **2009**, *109*, 6687–6711. b) Fernández, I.; Sierra, M. A.; Cossío, F. P. In-plane aromaticity in double-group transfer reactions. *J. Org. Chem.* **2007**, *72*, 1488–1491.

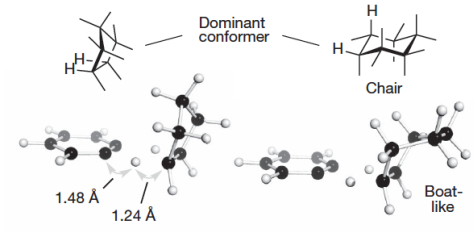
Somewhat satisfied with the above mechanism, I became curious if the propensity to attain conformers with eclipsing vicinal C-H bonds is the most important factor that dictates the ability of a certain molecule to simultaneously transfer two hydrogen atoms to aryne. If so, one should predict aryne to be efficiently reduced by cyclopentane but not by cyclohexane. This prediction initially sounded rather absurd, but turned out to have merit. Reduction of **7025** in cyclopentane afforded the reduced arene **7104** in ca. 80%

Scheme 7.29| a. Relative efficiency of various cyclic alkanes in reducing aryne. **b.** Computed transition structures of double hydrogen transfer process between benzyne and cyclopentane/cyclohexane. **c.** A crude ^{1}H NMR spectrum for reduction of **7025** (0.01 M) in $CDCl_3$ using ca. 20 equiv cyclooctane.

a



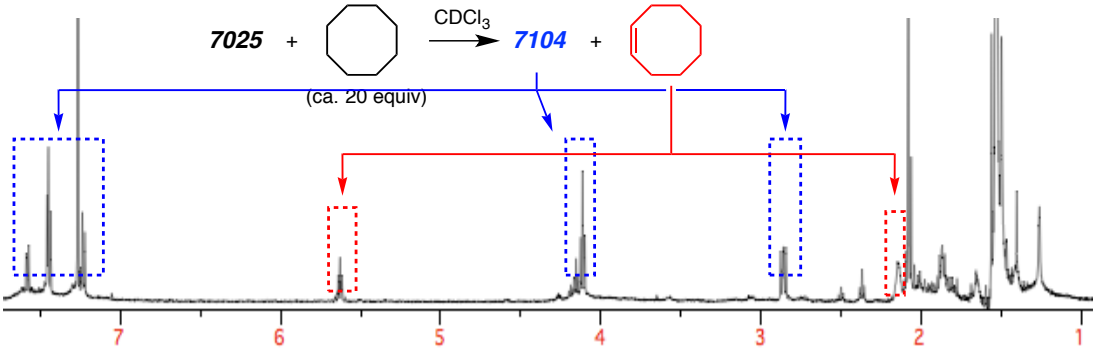
b



$\Delta G^{\ddagger}$ = 18.7 kcal•mol^{-1} $\Delta G^{\ddagger}$ = 24.1 kcal•mol^{-1}

Entry	Solvent	Yield
1	Cyclopentane	ca. 80%
2	Cyclohexane	< 10%
3	Cycloheptane	ca. 80%
4	Cyclooctane	ca. 90%
5	THF	ca. 75%
6	1,4-dioxane	0%

c



yield. On the other hand, the reduction attempted in cyclohexane produced only trace amount of **7104** (Scheme 7.29a, entry 1 and 2). As predicted, cyclopentane is a much more effective 2H-donor than is cyclohexane. In fact, all cyclic alkanes with ring sizes between five and eight (entry 1-4 in the tablet inset of Scheme 7.29a) except cyclohexane are potent 2H-donors. The potency of cyclooctane, for example, can be illustrated by the fairly clean crude ^{1}H NMR spectrum (Scheme 7.29c) of a reaction mixture obtained by heating a $CDCl_3$ solution of **7025** (0.01 M) in the presence of only 20 equiv of cyclooctane.

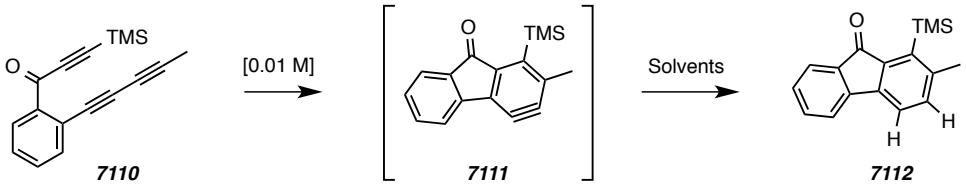
Using computational tools, Dr. Willoughby located the transition structures for the reactions between benzyne and cyclopentane vs. cyclohexane. He found the activation energy ($\Delta G^{\ddagger}$) for the reaction with cyclohexane is ca. 5.4 kcal•mol^{-1} higher than that for cyclopentane. Not coincidentally, the energetic penalty for cyclohexane to adopt the boat (reactive) conformation is ca. 6 kcal•mol^{-1}. All these observations are consistent with the hypothesis that there is a preference for an eclipsed geometry for the relevant $HC_{sp3}C_{sp3}H$ subunit within the 2H-donor molecule. Cyclohexane, dominated by its chair conformation, is least disposed toward transfer of two of its hydrogen atoms, whereas the other hydrocarbons all have low-lying conformers with $HC_{sp3}C_{sp3}H$ dihedral angles much smaller than 60°. That is, those cyclic hydrocarbons populated to a significant extent by conformers having less highly staggered vicinal C–H bonds are the more reactive 2H-donors.

Dr. Willoughby then performed a systematic study that relates to the kinetics of this reaction. With the assistance of No-D NMR[154] and qNMR,[155] He first quantified the

[154] a) Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. No-D NMR (No-deuterium proton NMR) spectroscopy: a simple yet powerful method for analyzing reaction and reagent solutions. *Org.*

relative rate (k_{rel}) of each hydrocarbon in reducing a structurally related aryne **7111** (generated from triyne **7110**) by measuring the ratio of the alkene resonances formed (Scheme 7.30). He noticed that cyclohexane is ca. 100 times less potent than cyclopentane as a 2H-donor. On the contrary, norbornane, having a boat-like cyclohexane embedded in its framework (and an associated $HC_{sp3}C_{sp3}H$ moiety with a 0° dihedral angle) is a kinetically competent donor (entry 4 in Scheme 7.30) even though the product norbornene comprises a strained alkene. He then computed the activation energy for the reaction between the parent o-benzyne with each hydrocarbon. He found there is a remarkably good correlation between the computed $\Delta G^{‡}$ values and the observed k_{rel} values. These observations provide additional support for the idea of substantial dependence on dihedral angle for the process, which can only be true if the double hydrogen atom transfer event is concerted.

Scheme 7.30| Relative efficiency of various cyclic alkanes in reducing aryne.



7110 *7111* *7112*

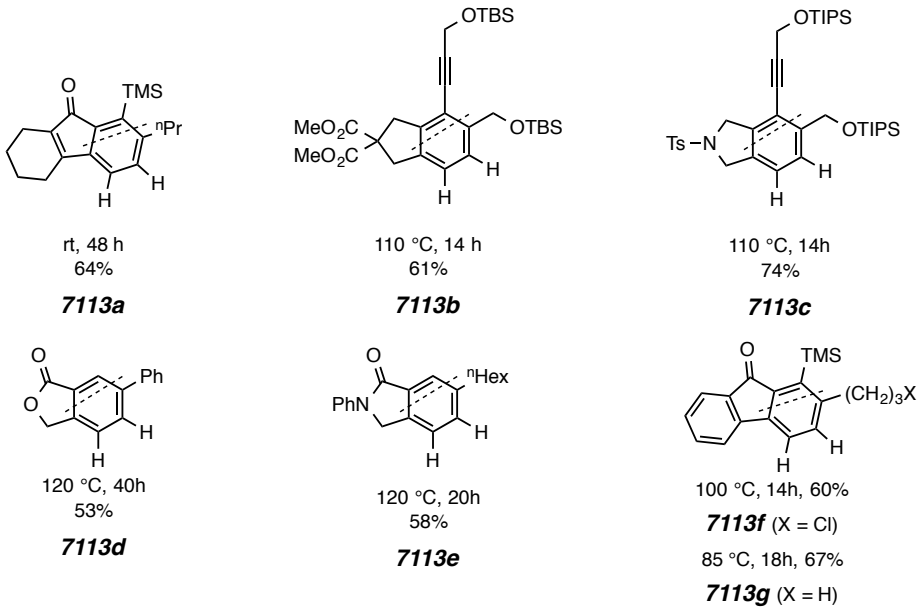
Entry	Solvent	Yield	k_{rel}	$\Delta G^{‡}$
1	Cyclooctane	97%	2.6	17.6
2	Cycloheptane	94%	2.3	17.7
3	Cyclopentane	84%	1.0	18.7
4	Norbornane	66%	0.6	18.5
5	Cyclohexane	20%	0.01	24.1
6	THF	60%	0.4	19.2
7	1,4-dioxane	0%	–	27.1

Lett. **2004**, *6*, 953–956. b) Hoye, T. R.; Eklov, B. M.; Voloshin, M. No-D NMR spectroscopy as a convenient method for titering organolithium (RLi), RMgX, and LDA solutions. *Org. Lett.* **2004**, *6*, 2567–2570.

[155] Pauli, G. F.; Jaki, B. U.; Lankin D. A., Routine experimental protocol for qHNMR illustrated with taxol. *J. Nat. Prod.* **2007**, *70***,** 589–595.

It is relevant to emphasize here that the alkane-to-alkene conversion almost always involves one or more chemical intermediates in a multistep reaction pathway; these may be either isolable species (such as alcohols or alkyl halides) or reactive intermediates (such as carbocations, alkyl radicals, or σ-alkyl-metal species). The one step desaturation of simple, unactivated alkanes by aryne described here is, therefore, mechanistically unique.

Scheme 7.31| Reduced benzenoid products **7113a–g** generated by heating the triyne precursor in cyclooctane under the indicated conditions (starting substrate concentration 10 mM).



Following these mechanistic investigations, we also probed the scope of this aryne reducing methodology. We prepared products **7113a-g** (Scheme 7.31) by incubating the corresponding triyne precursor [inferred from the dashed line in each structure] in cyclooctane under the indicated conditions. Notable features include: (i) a variety of functional groups, present in both the triyne precursor and benzenoid product, are readily tolerant of these benign reducing conditions; (ii) benzynes representing a breadth of

electronic activation and/or perturbation engage in the reaction; (iii) most of the products **7113** have a 1,2,3,4-tetrasubstituted motif, a substitution pattern that can be challenging to access by classical aromatic synthesis strategies; (iv) the double hydrogen atom transfer process occurs readily even at ambient temperature (cf. **7113a**); and (v) the reaction is not limited by scale (cf. **7113g**).

Finally, an ancillary but important practical consideration is worth mentioning. The most common method for generating simple benzyne derivatives, including the parent *o*-benzyne, is that of Kobayashi[84] in which 2-trimethylsilylphenyl triflate [1,2-TMS(OTf)C_6H_4] is exposed to a fluoride ion source (commonly CsF) in, most often, THF as the solvent. We speculated that some known trapping reactions of benzynes generated in THF are compromised in their efficiency due to competitive reduction by that solvent. Indeed, when we exposed *o*-TMSPhOTf to CsF in THF-d_8 in the absence of any other trapping agent, we observed the production of benzene ($C_6H_4D_2$, by ^{1}H NMR analysis). Similarly, benzene (and cyclopentene) was seen when CsF and *o*-TMSPhOTf were reacted in CD_3CN that contained cyclopentane (ca. 25 equiv). We suggest that all traditional benzyne generation methods performed in the presence of a potential 2H-donor (most typically, THF) are at risk to the unwanted, benzyne-depleting, 2H-transfer process, especially when the benzyne trapping event is inherently slow. Indeed, we can infer that this has already been encountered. For example, recent reports show THF to be an inferior medium (vs. 1,4-dioxane[156] or diethyl ether[157]) for some benzyne trapping reactions. This is consistent with (i) the relative efficiency of THF vs. 1,4-dioxane as a

[156] Ma, Z.-X.; Feltenberger, J. B.; Hsung, R. P. Total syntheses of chelidonine and norchelidonine via an enamide–benzyne–[2+2] cycloaddition cascade. *Org. Lett*. **2012**, *14*, 2742–2745.
[157] Sumida, Y.; Kato, T.; Hosoya, T. Generation of arynes via ate complexes of arylboronic esters with an *ortho*-leaving group. *Org. Lett.* **2013**, *15*, 2806–2809.

2H-donor and (ii) our arguments for angle-dependency during the 2H-transfer.

In summary, described in this section is the discovery of an unprecedented bimolecular double hydrogen atom transfer process. The reaction is important from the perspective of both reactants: the saturated alkane donor and the benzyne acceptor. Both (vicinal) hydrogen atoms come from the same donor molecule. There is substantial dihedral angle dependence because donors having a greater degree of eclipsing among their low-energy conformers are more reactive. This finding is reinforced by the geometry of computed transition structures, which show near planarity of the six reacting atoms. Our observations support a pathway in which both hydrogen atoms are transferred simultaneously from the saturated alkane to the benzyne carbon atoms—a process that could be viewed as a metal-free, double C–H activation event.

Chapter 8. A Protocol to Investigate Kinetics of Benzyne-Trapping Reactions

8.1 Mathematical background

Hundreds of aryne trapping reactions have been developed since the initial discovery of this fascinating synthetic intermediate. The myriad trapping modes attest to the synthetic versatility of arynes. Last year, we disclosed hexadehydro-Diels–Alder (HDDA) reaction as a general method to prepare arynes. This method, which converts a triyne substrate to aryne intermediate in a reagent- and byproduct-free fashion, enabled us and others to explore aspects of intrinsic aryne reactivity, including the discovery of some entirely new modes of trapping reactions.[111,146,158,159] However, despite the numerous (and multifaceted) aryne trapping reactions that have been developed to date, rarely has it been possible to probe kinetic aspects of these powerful transformations. This is not a trivial problem because the benzyne forming reaction rather than its subsequent trapping is nearly always the rate-limiting event. Certainly there is no report of a general strategy for studying the kinetics of aryne trapping [e.g., for deducing the kinetic order of the trapping reactant(s)].

When investigating the scope of aryne dichlorination methodology (cf. Section 7.3), I found the trapping of aryne **8002** (generated from **8001**, Scheme 8.1) with Li_2CuCl_4 to be interesting: the production of dichlorinated arene **8003** is accompanied by benzobarrelene **8004** under conventional conditions. However, formation of **8004** was suppressed when a

[158] Niu, D.; Hoye, T. R. The aromatic ene reaction. *Nat. Chem.* **2014**, *6*, 34–40.
[159] a) Yun, S. Y.; Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. Alkane C–H activation by aryne intermediates with a silver catalyst. *J. Am. Chem. Soc.* **2013**, *135*, 4668–4671. b) Wang, K.-P.; Yun, S. Y.; Mamidipalli, P.; Lee, D. Unified approaches for fluorination, trifluoromethylation, and trifluoromethylthiolation of arynes. *Chem. Sci.* **2013**, *4*, 3205–3211.

more concentrated solution of Li_2CuCl_4 was used. The observation that the ratio of **8003** to **8004** is dependent on the concentration of Li_2CuCl_4 used has inspired me to consider whether substrate like **8002**, which has an intramolecular trapping group, could be used as a probe for studying kinetics of intermolecular aryne trapping events.

This thinking is supported by mathematical considerations. Assuming 1) the rate constant for the formation of **8003** is k_1, and 2) the formation of **8003** has n^{th} order of dependence on the concentration of Li_2CuCl_4, then the rate law for the formation of **8003** can be expressed in the following equation:

$$d[\mathbf{8003}] = k_2 \cdot [\mathbf{8002}]^1 \cdot [Li_2CuCl_4]^n \cdot dt \qquad \text{(eq 1)}$$

Benzobarrelene **8004** arises via an intramolecular process, and consequently, the rate of its formation can be expressed by equation 2

$$d[\mathbf{8004}] = k_1 \cdot [\mathbf{8002}]^1 \cdot dt \qquad \text{(eq 2)}$$

The relative rate for the formation of **8003** and **8004** can be expressed as shown in eq 3 and transformed to eq 3'.

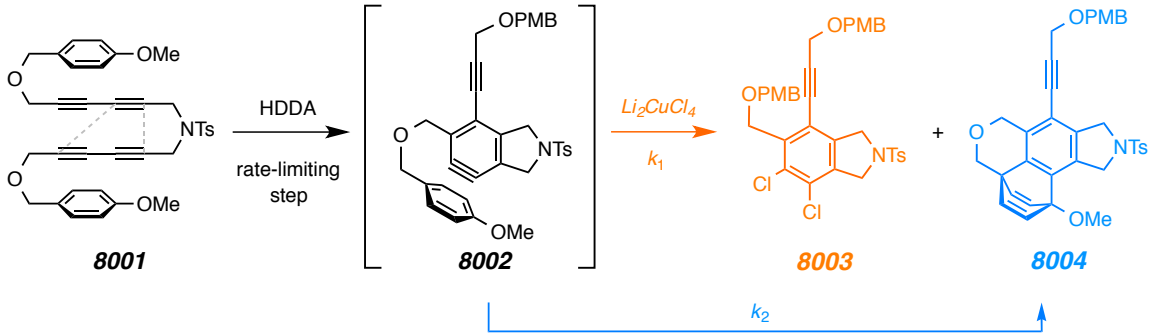
$$\frac{d[\mathbf{8003}]}{d[\mathbf{8004}]} = \frac{k_2 \cdot [\mathbf{8002}]^1 \cdot [Li_2CuCl_4]^n \cdot dt}{k_1 \cdot [\mathbf{8002}]^1 \cdot dt} \Rightarrow \frac{[\mathbf{8003}]}{[\mathbf{8004}]} = \frac{\int k_2 \cdot [\mathbf{8002}]^1 \cdot [Li_2CuCl_4]^n \cdot dt}{\int k_1 \cdot [\mathbf{8002}]^1 \cdot dt} \qquad \text{(eq 3, 3')}$$

When a large excess of Li_2CuCl_4 is used, equation 3' can be approximated as eq 4, which can also be expressed in logarithmic form as eq 4'.

$$\frac{[\mathbf{8003}]}{[\mathbf{8004}]} \approx \frac{k_2}{k_1} \cdot [Li_2CuCl_4]^n \Rightarrow \ln \frac{[\mathbf{8003}]}{[\mathbf{8004}]} \approx n \cdot \ln [Li_2CuCl_4] + \ln \frac{k_2}{k_1} \qquad \text{(eq 4, 4')}$$

According to these equations, the order of dependence on a certain external trapping reagent (in this case, Li_2CuCl_4) can be deduced by plotting its concentration against the ratio of the products arising from intramolecular trapping (like **8004**) and intermolecular trapping (like **8003**).

Scheme 8.1| The competitive formation of dichlorobenzene derivative **8003** and benzobarrelene **8004** under conventional benzyne dichlorination conditions.



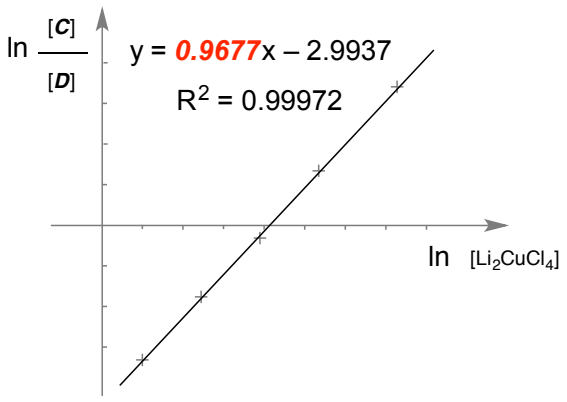
$$d[\mathbf{8003}] = k_2 \cdot [\mathbf{8002}]^1 \cdot [Li_2CuCl_4]^n \cdot dt$$

$$d[\mathbf{8004}] = k_1 \cdot [\mathbf{8002}]^1 \cdot dt$$

$$\frac{[\mathbf{8003}]}{[\mathbf{8004}]} = \frac{\int k_2 \cdot [\mathbf{8002}]^1 \cdot [Li_2CuCl_4]^n \cdot dt}{\int k_1 \cdot [\mathbf{8002}]^1 \cdot dt}$$

$$\frac{[\mathbf{8003}]}{[\mathbf{8004}]} \approx \frac{k_2}{k_1} \cdot [Li_2CuCl_4]^n$$

$$\ln \frac{[\mathbf{8003}]}{[\mathbf{8004}]} \approx n \cdot \ln [Li_2CuCl_4] + \ln \frac{k_2}{k_1}$$

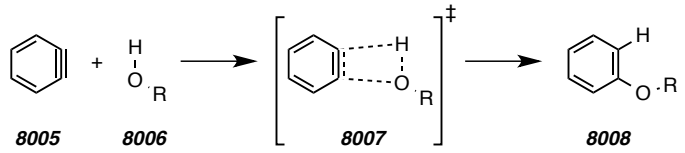


In practice, the product ratio of **8003** to **8004** was measured at a series of concentrations of Li_2CuCl_4 and the results are given in Scheme 8.1. From the slope of the plot of ln[**8003**]/[**8004**] vs. ln[Li_2CuCl_4], we determined that formation of **8003** showed a first-order dependence on [Li_2CuCl_4]. Since aryne precursors with various intramolecular trapping groups can be easily prepared, this protocol should be applicable for studying the molecularity of many intermolecular aryne trapping reactions.

8.2. Kinetics of aryne trapping by alcohols

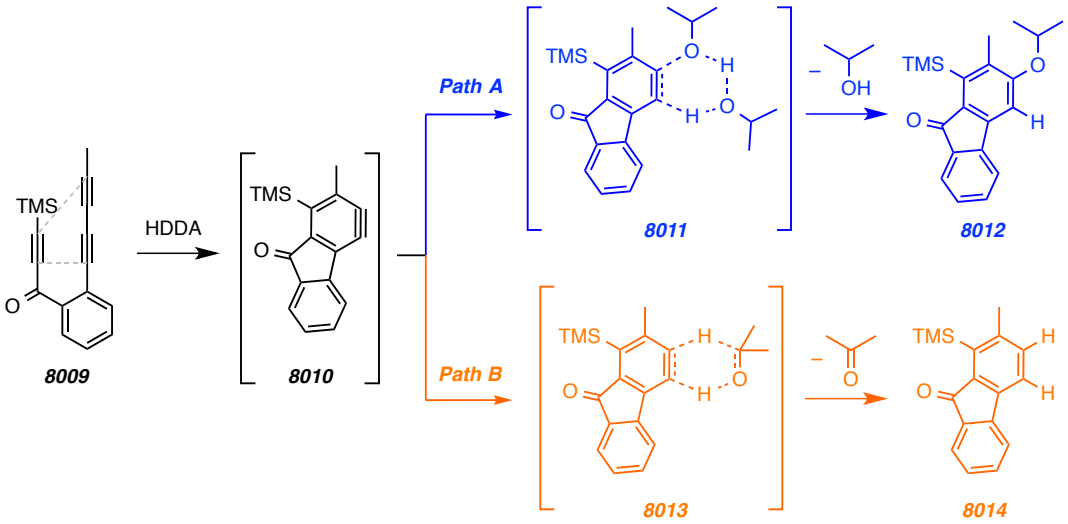
The reaction between aryne like **8005** and alcohol like **8006** has been known for over 100 years. To the best of our knowledge, all the reactions between arynes and alcohols reported resulted in the formation of aryl ethers like **8008**. It is usually proposed[123] that these reactions occur via transition structures like **8007**, which implies a direct insertion into OH bond of alcohol by aryne.

Scheme 8.2| A typical reaction between aryne and alcohol and the widely accepted mechanism of this reaction.



Dr. Willoughby noticed, however, the reaction outcome between HDDA-born aryne like **8010** and alcohol (e.g., isopropanol) is dependent on the concentration of alcohol used: at high concentrations of *i*PrOH, the ethereal product **8012** was formed predominantly (Scheme 8.2, Path A); at low concentrations of *i*PrOH, on the other hand, reduced arene **8014** was produced as the major product (Path B). Following a series of deuterium-labeling experiments and computational study, he hypothesized the hydrogen transfer from alcohol to aryne **8010** occur via a Cannizzaro type of mechanism as indicated by the transition structure **8013**. At the same time, he challenged the generally accepted mechanism for the addition reaction between aryne and alcohol (cf. Scheme **8.2**), and proposed a pathway that involves the participation of alcohol dimer in the transition structure (**8011**).

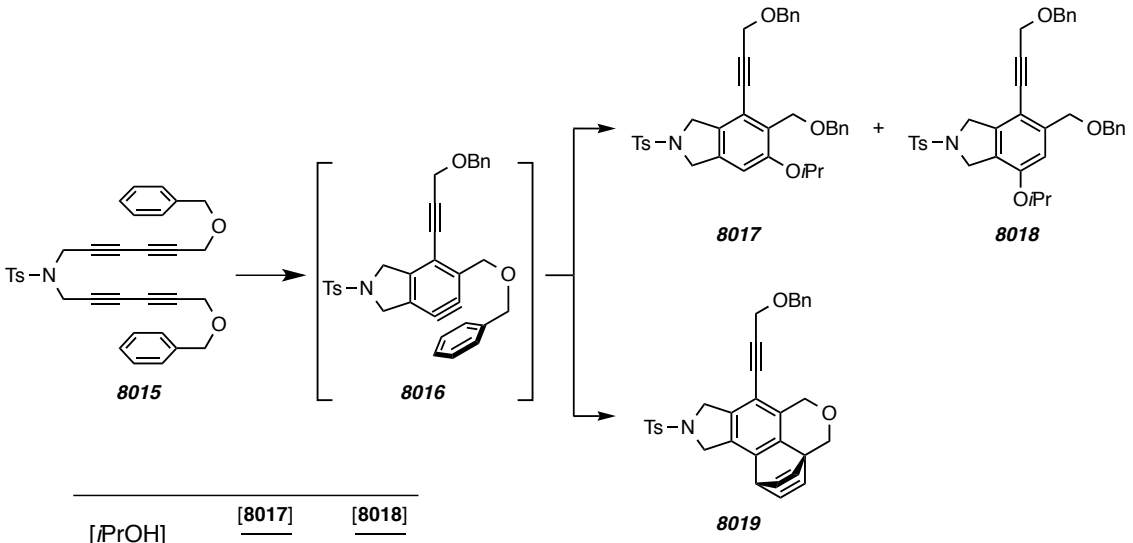
Scheme 8.3| The preferred reaction pathway of HDDA-born aryne with alcohol is dependent on the concentration of alcohol used.



Undoubtedly, knowledge about the kinetic order of alcohol in each trapping mode is valuable to verify Dr. Willoughby's hypotheses. To my fortune, I just developed a protocol that can be used for tapping such information (see Section 8.1).

In order to accurately measure the ratio of products arising from intermolecular trapping to those from intramolecular trapping, the reaction rate for each process should be close. In other words, to probe the kinetic orders of different external trapping agents, aryne precursors with different intramolecular trapping groups may be required. For example, when studying the reaction between aryne and Li_2CuCl_4, aryne **8002** (Scheme 8.1), which bears a 4-methoxybenzyl group, was employed. Since alcohols are less competent trapping reagents for arynes than Li_2CuCl_4, I found the use of aryne **8016**, which has a correspondingly less potent benzyl trapping group, to be most appropriate for this purpose.

Scheme 8.4| Kinetic study for the reactions between aryne **8016** and isopropanol.



[*i*PrOH]	$\frac{[8017]}{[8019]}$	$\frac{[8018]}{[8019]}$
4.37	19.8	3.3
1.87	9.72	0.804
1.31	6.7	0.386
0.66	3.2	0.114
0.44	1.82	N/A
0.33	1.32	N/A

$$\frac{[8017]}{[8019]} = 4.6963 \times [\text{iPrOH}]^{1.0836},\ R^2 = 0.99457$$

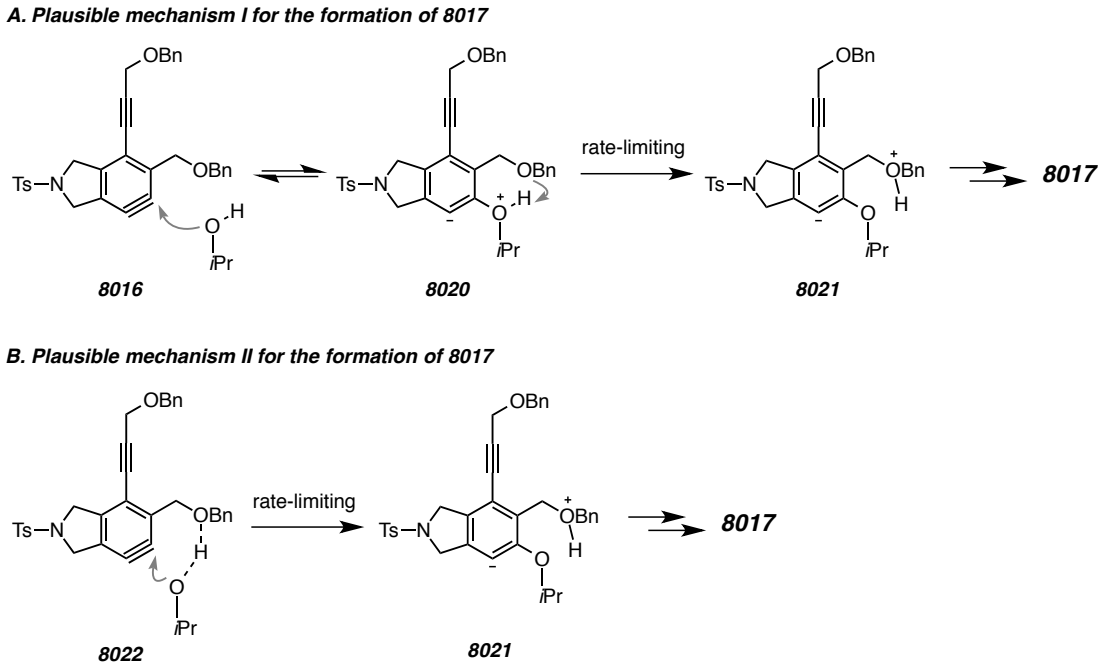
$$\frac{[8018]}{[8019]} = 0.2388 \times [\text{iPrOH}]^{1.8336},\ R^2 = 0.99904$$

To my surprise, no product arising from aryne hydrogenation was formed even when very low concentration of *i*PrOH was used: the reaction between aryne **8016** and isopropanol gave only aryl ether **8017**/**8018** and benzobarrelene product **8019**. Moreover, the isomeric **8017** and **8018** were formed by different mechanisms! This was first seen from the changing regioselectivity of alcohol addition at different alcohol concentrations: the ratio of **8017** to **8018** ranges from 30:1 to 6:1. Later, the product ratio of each ether adduct (**8017** or **8018**) to **8019** was measured at a series of concentrations of isopropanol (results are given in Scheme 8.3). From the regression equations derived from these data, it can be concluded that formation of **8018** has a second-order but formation of **8017** has a first-order dependence on [isopropanol]. No reduction of **8015** was observed even at

low concentrations of isopropanol because the formation of **8017** has a much larger rate constant.

I attributed the "abnormal" mechanism for the formation of **8017** to the presence of a heteroatom (oxygen atom) with the side chain of **8015**, which may assist the rate-limiting proton transfer event as depicted in Scheme 8.5a, or function as a directing group as indicated in Scheme 8.5b.

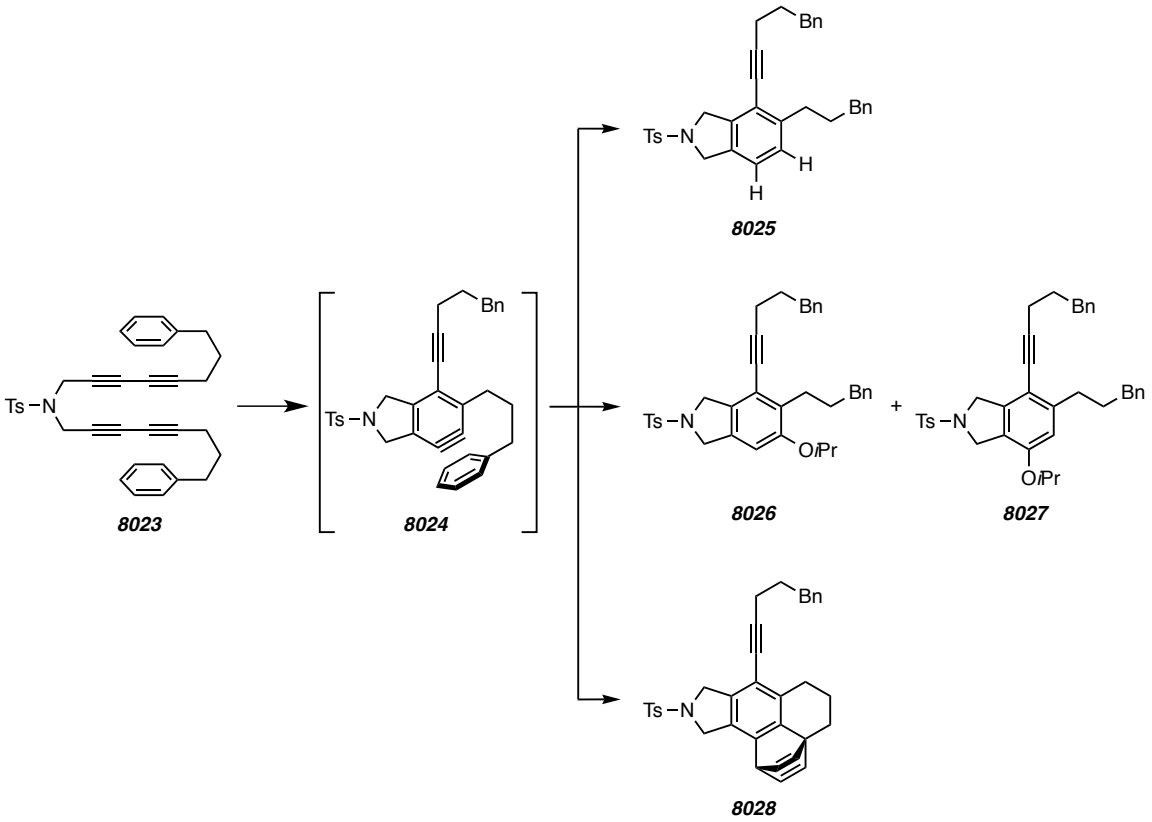
Scheme 8.5| Plausible mechanisms for the formation of **8017**.



Based on the above rationale, I designed and synthesized substrate **8023**, an analogue of **8015** that is devoid of heteroatoms on the side chains (Scheme 8.6), to study the aryne reduction mechanism. Gratifyingly, heating **8023** in the presence of isopropanol indeed gave the reduced arene **8025** as a byproduct. Additionally, the ratio of two isomeric alcohol adducts (**8026** and **8027**) was not affected by the different concentrations of isopropanol used. Finally, plotting the ratio of each product to benzobarrelene **8028**

against [isopropanol] revealed that indeed, the formation of reduced arene **8025** and alcohol adduct **8026** has a first-order and second-order dependence on [isopropanol], respectively.

Scheme 8.6| Kinetic study for the reactions between aryne **8024** and isopropanol conducted in $CDCl_3$.



[*i*PrOH]	$\frac{[8025]}{[8028]}$	$\frac{[8026]}{[8028]}$
1.31	0.457	1.212
0.66	0.256	0.370
0.44	0.167	0.189
0.33	0.123	0.128

$$\frac{[8025]}{[8028]} = 0.3868 \times [iPrOH]^{1.004},\ R^2 = 0.99913$$

$$\frac{[8026]}{[8028]} = 0.7476 \times [iPrOH]^{1.846},\ R^2 = 0.99929$$

In conclusion, by using a protocol that we established for probing kinetic aspects of aryne trapping events, I gained some insights into the mechanisms of reactions between HDDA-born aryne and alcohols. I found that: 1) the previously unprecedented double

hydrogen atom transfer event between alcohol and aryne demonstrated a first-order dependence on the concentration of alcohol, supporting a Cannizzaro type of pathway for this transformation; and 2) as opposed to what was implied by the conventionally proposed mechanism, the alcohol addition to aryne actually showed a second-order dependence on the concentration of alcohol, suggesting the involvement of two alcohol molecules in the rate-limiting step of this transformation. The information obtained in this section of study further attest to the utility of substrates like **8023** in studying mechanism of aryne trapping reactions.

Experimental Section

General Experimental Protocols

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 500 (500 MHz) and Varian Inova 300 (300 MHz) spectrometers. Chemical shifts for proton spectra are referenced to TMS (δ 0.00 ppm) for spectra recorded in $CDCl_3$; to CD_3SOCHD_2 (δ 2.50 ppm) for DMSO-*d*$_6$; and to CHD_2OD (δ 3.31 ppm) for MeOH-*d*$_4$. Non-first order multiplets are identified as "nfom". Chemical shifts for carbon spectra are referenced to $CHCl_3$ (δ 77.23 ppm) for spectra recorded in $CDCl_3$; to $(CD_3)_2SO$ (δ 39.50 ppm) for DMSO-*d*$_6$; and to CD_3OD (δ 49.00 ppm) for MeOH-*d*$_4$. TMS is present in some of the ^{13}C NMR samples (δ ca. 0.0 ppm). HSQC refers to heteronuclear single quantum correlation. The following format was used to report resonances: chemical shift in ppm (multiplicity, coupling constant(s) in Hz, integral value, and assignment). Coupling constant analysis was guided by methods we have described elsewhere.[160] Some complex structures are numbered in order to simplify identification of the proton assignment.

Infrared (IR) spectra were recorded on a Prospect MIDAC FT-IR spectrometer using a NaCl plate (thin film) or ZnSe plate (ATR). Absorptions are reported in cm^{-1}.

MPLC refers to medium pressure liquid chromatography (25-200 psi) using hand-packed columns of silica gel (18-32 μm, 60 Å pore size), a Waters HPLC pump, and a Waters R401 differential refractive index detector. Flash chromatography was performed using E. Merck silica gel (40-63 μm).

GCMS data were recorded on an Agilent 5975 MSD at 70 eV. The methods used are noted parenthetically: e.g., 5025015 refers to 2 min initial hold time at 50 °C, a ramp to 250 °C at a rate of 20 °C min^{-1}, and a final hold time of 3 min (for a total run time of 15 min). The column was 30 m HP-5 × 0.32 mm × 0.25 μm film thickness.

Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in flame or oven dried glassware. Reported (external) reaction temperatures are the temperature of the heating bath. HDDA initiated cascade reactions, including those that were carried out at temperatures above the boiling point of the solvent, were typically carried out in a screw-capped vial or culture tube fitted with an inert, Teflon®-lined cap. Those carried out in deuterated solvents were typically

[160] a) T. R. Hoye, P. R. Hanson, J. R. Vyvyan, *J. Org. Chem.* **1994**, *59*, 4096-4103. b) T. R. Hoye, H. Zhao, *J. Org. Chem.* **2002**, *67*, 4014-4016.

performed in a capped NMR sample tube (5 mm diameter). Anhydrous THF, diethyl ether, toluene, and methylene chloride were tapped immediately prior to use after being passed through a column of activated alumina. Triethylamine and pyridine were distilled from KOH. Diisopropylamine was distilled from CaH_2. DMF and DMSO were stored over 4Å molecular sieves.

General Procedures A-C.

A. General Procedure A: Terminal Alkyne Bromination

Solid $AgNO_3$ (0.1 equiv) was added to a solution of *N*-bromosuccinimide (NBS, 1.05–1.1 equiv) and the terminal alkyne substrate (1.0 equiv) and in acetone (0.1 M) at rt. The resulting slurry was stirred for one hour and then either i) partitioned between water and Et_2O, and washed with brine, dried (Na_2SO_4) or ii) filtered (Celite® using acetone eluent) and then concentrated. The crude material was used either directly or after being purified by flash chromatography.

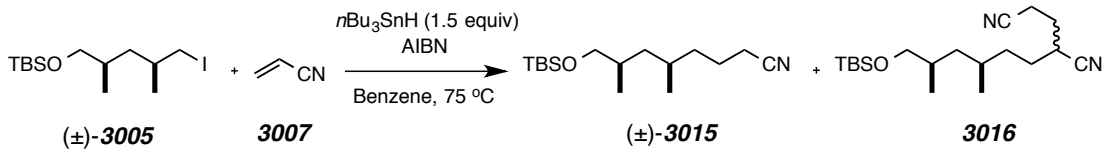
B. General Procedure B: Alkyne Cross-Coupling using Cadiot–Chodkiewicz in piperidine

A solution of a terminal alkyne (1.0 equiv) and a 1-bromoalkyne (1.2–1.5 equiv) in piperidine (0.3-0.8 M) was deoxygenated (three freeze-pump-thaw cycles). The solution was cooled to 0 °C and CuCl was added. After 1 h saturated aqueous NH_4Cl was added and the resulting mixture was extracted with EtOAc or Et_2O. The combined extracts were washed (brine), dried (Na_2SO_4), and concentrated. The crude material was then purified using flash chromatography.

C. General Procedure C: Alkyne Cross-Coupling using Cadiot–Chodkiewicz in Et_2O/*n*-$BuNH_2$/water.

To a solution of CuCl (0.05 equiv) in 30:70 (v:v) *n*-$BuNH_2$:H_2O (0.01 M) in a capped reaction vessel was added an excess of NH_2OH•HCl (typically a few crystals on a reaction scale ≤1 mmol). The color of the solution turned from deep blue to colorless within seconds, indicating full consumption of Cu(II). The resulting solution was then cooled at 0 °C. A solution of the terminal alkyne (1.0 equiv) and the 1-bromoalkyne (1.2–1.5 equiv) in Et_2O (0.25 M) was added dropwise. The reaction mixture was stirred for 1 h, during which time a few crystals of NH_2OH•HCl were periodically added whenever the solution became blue. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc or Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was typically purified by flash chromatography.

(±)–(*5R,7R*)-8-((tert-Butyldimethylsilyl)oxy)-5,7-dimethyloctanenitrile (3015):



(±)-***3005*** ***3007*** (±)-***3015*** ***3016***

To a solution of iodide (±)-**3005** (406 mg, 1.14 mmol, 1 equiv), acrylonitrile (301 mg, 5.69 mmol, 5 equiv), AIBN (5 mg, 28.5 μmol, 2.5% equiv) in benzene (6 mL) heated at 75 °C was added a benzene (3 mL) solution of nBu$_3$SnH (487.2 mg, 1.68 mmol, 1.5 equiv) and AIBN (5 mg, 28.5 μmol, 2.5% equiv) via syringe pump over 30 min. The reaction mixture was maintained at 75 °C for an additional 20 min. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo. The residue was subjected directly to flash chromatography (silica gel, Hexane/EtOAc, 10:1) to give, in elution order, (±)-**3015** (254 mg, 78%) and (±)-**3016**.

Characterization data for (±)-**3015:**

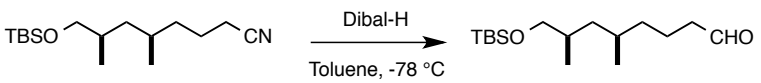
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.42 (dd, J = 9.7, 5.5 *Hz*, 1H, CH_aH$_b$OSi) 3.51 (dd, J = 9.7, 6.3 Hz, 1H, CH$_a$$H_b$OSi), 2.32 (app t, J = 7.2 Hz, 2H, CH_2CN), 1.74-1.54 (m, 3H, CH$_3$CHCH$_2$OSi and CH_2CH$_2$CN), 1.47-1.42 (m, 1H, CH$_3$CH(CH$_2$)CH$_2$CH$_2$CH$_2$), 1.38-1.32 (m, 2H), 1.26-1.16 (m, 2H), 0.91 (d, J = 7 Hz, 3H, CH_3CH), 0.90 (s, 9H, (CH_3)$_3$C), 0.88 (d, J = 5.6 Hz, 3H, CH_3CH), and 0.03 (s, 6H, (CH$_3$)$_2$Si).

^{13}C NMR (500 MHz, $CDCl_3$): δ = 68.1, 40.7, 36.7, 33.1, 29.6, 26.0, 22.9, 20.2, 17.6, 17.5, and -5.4.

IR (neat): 2955, 2927, 2871, 2855, 2244, 1471, 1463, 1255, 1251, 1094, and 837.

HR ESI-MS calcd for $C_{16}H_{33}NOSi$ $[M + Na]^+$ 309.2226, found 309.2275.

(±)–(*5R,7R*)-8-((tert-Butyldimethylsilyl)oxy)-5,7-dimethyloctanal (3020):



(±)-***3015*** 82% (±)-***3020***

To a solution containing nitrile (±)-**3015** (27 mg, 0.096 mmol, 1 equiv) in toluene (1 mL) at -78 °C was added Dibal-H (0.1 mL, 1.5 M in toluene, 0.15 mmol, 1.5 equiv)

dropwise. After addition, the reaction mixture was stirred at the same temperature for 3 h. A 0.5 mL portion of a solution containing acetic acid (2.5 g, 41.7 mmol, 2.4 mL), sodium acetate (2.4 g, 29.1 mmol), and THF (9.5 mL) in water (40 mL) was added dropwise at -78 ^{o}C. The flask was warmed to room temperature and kept for 20 min, at which time Celite was added and stirring was continued for an additional 5 min. The slurry was filtered through a Celite bed. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, Hexane/EtOAc, 19:1) to give (±)-**3020** (22 mg, 82%) as a colorless oil.

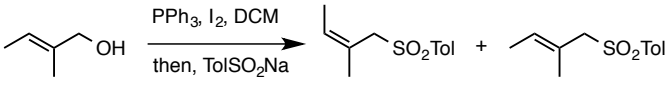
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 2 Hz, 1H, C*H*O), 3.44 (dd, *J* = 10 Hz, 5.5 Hz, 1H, C*Ha*HOSi), 3.32 (dd, *J* = 10 Hz, 6.5 Hz, 1H, CH*H$_b$*OSi), 2.41 (dddd, *J* = 17.8 Hz, 7.7 Hz, 6.9 Hz, 1.9 Hz, 1H, C*H*HCHO, overlapping with *CHHCHO*), 2.41 (dddd, *J* = 18 Hz, 7.9 Hz, 6.9 Hz, 1.8 Hz, 1H, CH*H*CHO, overlapping with C*H*HCHO), 1.69-1.64 (m, 2H), 1.62-1.52 (m, 3H), 1.35-1.26 (m, 3H), 1.08-1.03 (m, 1H), 0.90 (s, 9H, (C*H*$_3$)$_3$C), 0.89 (d, *J* = 7Hz, 3H, C*H*a3CH), 0.87 (d, *J* = 6.5Hz, 3H, C*H*b$_3$CH), 0.03 (s, 6H, (C*H*$_3$)$_2$Si).

^{13}C NMR (500 MHz, $CDCl_3$): δ = 202.8, 68.2, 44.2, 40.9, 36.2, 33.1, 30.0, 29.1, 26.0, 20.2, 19.4, 17.6, and -5.3.

IR (neat): 2927, 2857, 2711, 1735, 1462, 1256, *1251*, 1097, and 837.

HR ESI-MS calcd for $C_{16}H_{34}O_2Si$ $[M + Na]^+$ 306.*2220*, found 306.2183.

(*E*)-1-Methyl-4-((2-methylbut-2-en-1-yl)sulfonyl)benzene (3022):



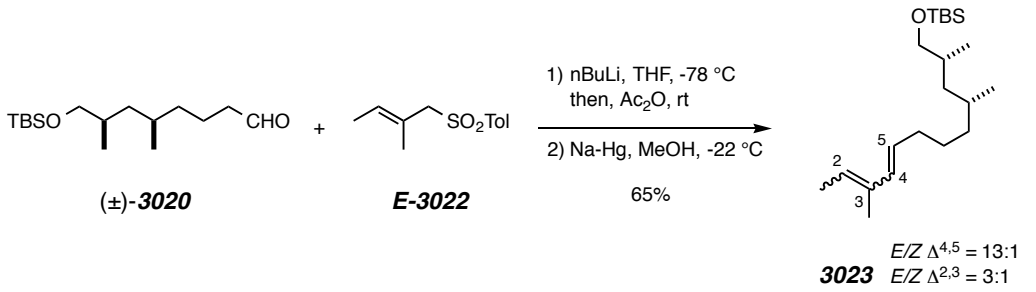
3021 ***Z-3022*** (*1 : 3*) ***E-3022***

To a solution of tiglic alcohol (**3021**, 0.5 g, 5.8 mmol) in dichloromethane (30 mL) cooled at 0 °C was added PPh_3 (1.52 g, 5.8 mmol), imidazole (0.69 g, 10.2 mmol), and I_2 (1.47 g, 5.8 mmol) in sequence. The resulting solution was stirred at this temperature for an additional 2 h, at which time $TolSO_2Na$ (2.68 g, 15 mmol) was added. The reaction was warmed up to rt overnight with stirring in the absence of light. The resulting mixture was partitioned between dichloromethane and water. The aqueous layer was washed with

additional portions of dichloromethane. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to MPLC (silica gel, Hexane/EtOAc, 3:1) to give (*E*)-**3022** (0.6 g, 2.7 mmol, 45%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.2 Hz, 2H, Ar*Ho*SO_2), 7.30 (d, *J* = 8.1 Hz, 2H, Ar*Hm*SO_2), 5.18 (br q, *J* = 6.8 Hz, 1H, C=C*H*), 3.68 (s, 2H, $ArSO_2CH_2$), 2.43 (s, 3H, $ArCH_3$), 1.72 [s, 3H, CH_3CH=C(CH_3)-], and 1.53 (d, *J* = 6.8 Hz, 3H, CH_3CH=C).

(±)–*tert*-Butyldimethyl(((2*R*,4*R*)-2,4,10-trimethyldodeca-8,10-dien-1-yl)oxy)silane (3023)



To a solution of ***E*-3022** (185 mg, 0.83 mmol) in THF (6 mL) cooled at -78 °C was added *n*BuLi (2.5 M, 0.33 mL, 0.83 mmol). The resulting solution was kept at this temperature for 0.5 h, at which time (±)-**3020** (182 mg, 0.64 mmol) in THF (7 mL) was added. The reaction was allowed to proceed for 1 h, when excess Ac_2O was added. The mixture was warmed up to room temperature overnight. The reaction solution was partitioned between EtOAc and water. The aqueous layer was washed with additional portions of dichloromethane. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, Hexane/EtOAc, 8:1) to give intermediate acetate as a mixture of diastereoisomers and epimers (280 mg).

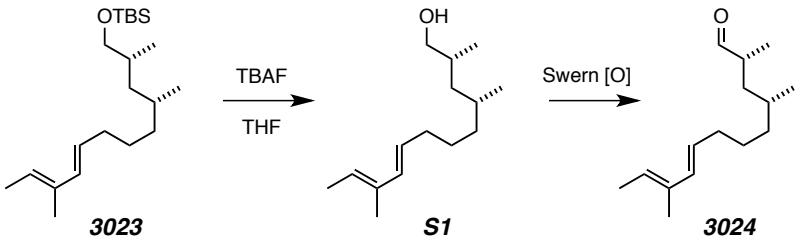
To a solution of the acetate obtained from the previous step in a mixture solvent of THF (18 mL) and MeOH (6 mL) was cooled at -24 °C was added Na-Hg (280 mg, 0.5 mmol). The reaction was stirred at this temperature for 14 h. The resulting organic layer was concentrated and subjected to flash chromatography (silica gel, Hexane/EtOAc,

20:1) to yield **3023** as a mixture of diastereoisomers and epimers (120 mg, 65% overall).

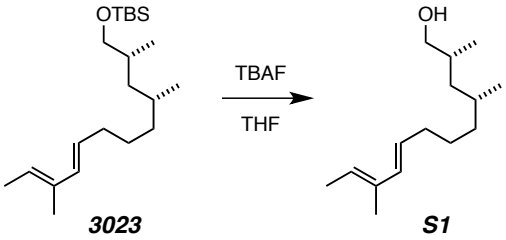
Characterization data of the major epimer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (d, *J* = 16.0 Hz, 1H, C*H*=CHCH$_2$), 5.55 (dt, *J* = 16.0 and 7.0 Hz, 1H, CH=C*H*CH$_2$), 5.44 (q, *J* = 7.0 Hz, 1H, CH$_3$C*H*=), 3.45 (dd, *J* = 5.3, 9.7 Hz, 1H, C*H*$_a$H$_b$OH), 3.31 (dd, *J* = 6.8, 9.8 Hz, 1H, CH$_a$*H*$_b$OH), 2.06 (m, 1H, CH=CHC*H*$_a$H$_b$-), 1.72 (br s, 3H, C*H*$_3$C=CH), 1.71 (d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=), 1.69 (m, 1H, HOCH$_2$C*H*-), 1.5-1.2 (m, 5H), 1.06 (m, 1H), 0.94 (m, 1H), 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], 0.87 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(C*H*$_3$)-], and 0.87 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(CH$_3$)CH$_2$CH(C*H*$_3$)-], and 0.04 [s, 6H, Si(C*H*$_3$)$_2$].

(±)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-Trimethyldodeca-8,10-dienal (3024)



(±)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-Trimethyldodeca-8,10-dien-1-ol (S1)



A solution of **3023** (ca. 120 mg, 0.4 mmol) was dissolved in THF (2 mL) and cooled to 0 ^{o}C. TBAF (1.0 M in THF, 0.6 mL) was added dropwise over 10 min. The resulting solution was stirred overnight. The reaction mixture was quenched by addition of saturated NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (silica gel, hexanes:EtOAc = 8:1) gave purified **S1** (90 mg, 0.4 mmol, quantitative) as a colorless oil.

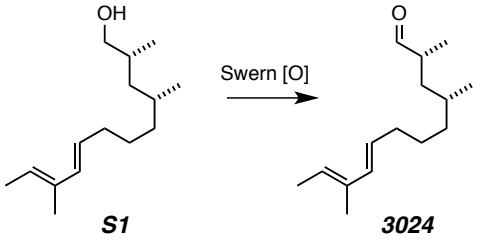
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.04 (d, *J* = 16.0 Hz, 1H, C*H*=CHCH$_2$), 5.53 (dt, *J* = 16.5 and 7.0 Hz, 1H, CH=C*H*CH$_2$), 5.43 (q, *J* = 7.0 Hz, 1H, CH$_3$C*H*=), 3.50 (dd, *J* = 5.0 and 10.0 Hz, 1H, C*H*$_a$H$_b$OH), 3.36 (dd, *J* = 7.5 and 10.0 Hz, 1H, CH$_a$*H*$_b$OH), 2.08 (ddt, *J* = 14.0, 7.0 and 7.0 Hz, 1H, CH=CHC*H*$_a$H$_b$-), 2.03 (ddt, *J* = 14.0, 7.0, and 7.0 Hz, 1H, CH=CHCH$_a$*H*$_b$-), 1.71 (br s, 3H, C*H*$_3$C=CH), 1.69 (d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=), 1.69 (m, 1H, HOCH$_2$C*H*-), 1.46-1.55 [m, 1H, HOCH$_2$CH(CH$_3$)CH$_2$C*H*(CH$_3$)-], 1.38-1.46 (m, 1H), 1.27-1.38 (m, 3H), 1.06 (m, 1H), 0.94 (m, 1H), 0.91 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(C*H*$_3$)-], and 0.88 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(CH$_3$)CH$_2$CH(C*H*$_3$)-].

^{13}C NMR ($CDCl_3$, 125 MHz): 134.6, 134.4, 127.2, 124.4, 68.3, 41.0, 36.2, 33.2, 33.1, 29.9, 27.0, 20.3, 17.3, 13.7, and 12.1 ppm.

IR (neat): 3338, 2924, 2871, 2858, 1652, *1628*, 1459, 1377, 1036, and 962 cm^{-1}.

GC-LRMS: t_R = 9.07 min. *m/z*: 224 (M^+), 209 (M^+-Me), 193 (M^+-CH_2OH), 151 (M^+-C_4H_8OH), 123, 109, 99, 95, 93, 81, 67, and 55 ($C_4H_7^+$).

(±)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-Trimethyldodeca-8,10-dienal (3024)



To a stirred solution of oxalyl chloride (2.02 mL, 23.2 mmol) in CH_2Cl_2 (55 mL) cooled at -78 °C was added dropwise a solution of DMSO (3.08 mL, 46.4 mmol) in CH_2Cl_2 (8 mL). The resulting mixture was stirred at this temperature for 3 min, when a solution of diene alcohol **S1** (2.6 g, 12 mmol) in CH_2Cl_2 (35 mL) was added. The resulting solution was stirred at this temperature for an additional 20 min, and triethylamine (9.7 mL, 69.6 mmol) was added. The resulting mixture was allowed to warm to 0 °C over 1 h with stirring. The mixture was quenched by addition of water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resulting crude

aldehyde was subjected to flash chromatography (silica gel, hexanes:EtOAc = 15:1) to give purified aldehyde **3024** (2.2 g, 85%) as a colorless oil.

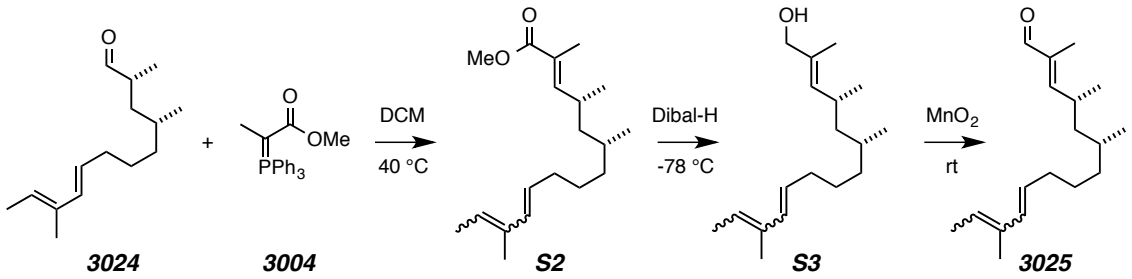
^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.58 (d, *J* = 2.5 Hz, 1H, -C*H*O), 6.05 (d, *J* = 15.5 Hz, 1H, CH_3CH=C(CH_3)C*H*=), 5.53 (dt, *J* = 15.0 and 7.0 Hz, 1H, CH_3CH=C(CH_3)CH=C*H*-), 5.43 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 2.43 (dqd, *J* = 14.0, 7.0 and 2.6 Hz, 1H, -C*H*CHO), 2.07 (ddt, *J* = 14.0, 6.5, and 6.5 Hz, 1H, -CH=CH-C*Ha*Hb-), 2.05 (ddt, *J* = 14.0, 6.5, and 6.5 Hz, 1H, -CH=CH-*CHaHb*-), 1.73 (m, 1H, CHOCH(CH_3)C*Ha*Hb-), 1.72 (br s, 3H, CH_3CH=C(C*H*$_3$)-), 1.70 (d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=), 1.50 [m, 1H, CHOCH(CH_3)CH_2C*H*(CH_3)-], 1.28-1.49 [m, 4H, CHOCH(CH_3)CH_2CH(CH_3)C*H*$_2$C*H*$_2$-], 1.10-1.16 [m, 1H, CHOCH(CH_3)CHa*Hb*-], 1.08 [d, *J* = 7.0 Hz, 3H, CHOCH(C*H*$_3$)-], and 0.90 [d, *J* = 7.5 Hz, 3H, CHOCH(CH_3)CH_2CH(C*H*$_3$)-].

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.5, *134*.9, 134.4, 127.0, 124.5, 44.2, 38.2, 36.3, 33.0, 30.3, 26.9, 19.8, 14.2, 13.7, and 12.1 ppm.

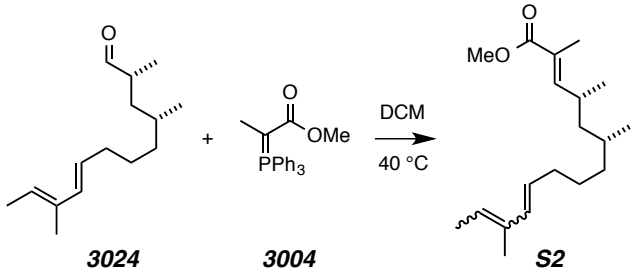
IR (neat): 2961, 2928, 2837, 2857, 2706, 1727, 1458, 1378, 1239, and 963 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{15}H_{26}NaO)^+$: 245.1876. Found: 245.1876.

(±)-(2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-Tetramethyltetradeca-2,10,12-trienal (3025)



(±)-(2*E*,4*R*,6*R*,10*E*,12*E*)-Methyl 2,4,6,12-Tetramethyltetradeca-2,10,12-trienoate (S2)



To a solution of aldehyde **3024** (2.2 g, 9.9 mmol) in CH_2Cl_2 (82.5 mL) was added carbomethoxyethylidene triphenylphosphorane (**3004**, 13.7 g, 39.6 mmol). The resulting solution was heated at 55 °C for 48 h in two capped culture tubes, at which time GC analysis showed full consumption of starting material. The resulting solution was concentrated in vacuo. The resulting yellow solid was triturated with hexanes and filtered. The solid cake was washed with additional hexanes (100 mL x 2). The combined filtrates were then concentrated and purified by flash chromatography (silica gel, hexanes:EtOAc = 15:1) to give triene ester **S2** (2.9 g, 99%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.50 (dq, *J* = 10.0 and 1.5 Hz, 1H, $MeO_2CC(CH_3)$=C*H*-), 6.04 (d, *J* = 15.5 Hz, 1H, CH_3CH=$CH(CH_3)$C*H*=), 5.53 (dt, *J* = 15.0 and 7.0 Hz, 1H, CH_3CH=$CH(CH_3)CH$=C*H*-), 5.43 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 3.73 (s, 3H, -COOC*H*$_3$), 2.60 (m, 1H, $MeO_2CC(CH_3)$=CHC*H*$(CH_3)CH_2$-), 2.04 (dt, *J* = 7.0 and 7.0 Hz, 2H, -CH=CH-C*H*$_2$-), 1.84 (d, *J* = 1.5 Hz, 3H, $MeO_2CC(CH_3)$=CHCH(C*H*$_3$)CH_2-), 1.72 (br s, 3H, CH_3CH=C(C*H*$_3$)CH=), 1.70 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH=), 1.22-1.45 (m, 5H), 1.05-1.18 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H,

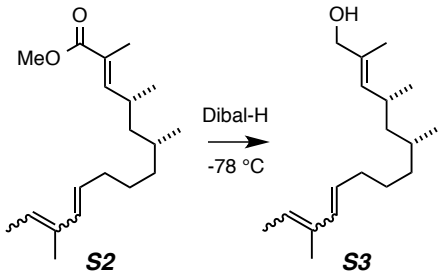
$MeO_2CC(CH_3)$=CHCH(C*H*$_3$)CH_2-), and 0.82 [d, *J* = 6.0 Hz, 3H, $MeO_2CC(CH_3)$=CHCH(CH_3)CH_2CH(C*H*$_3$)-].

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.9, 148.5, 134.7, 134.4, 127.2, 125.9, 124.4, 51.7, 44.5, 37.2, 33.1, 30.9, 30.7, 27.0, 20.6, 19.5, 13.7, 12.5, and 12.1 ppm.

IR (neat): 2954, 2926, 2869, 1717, 1649, 1454, 1435, 1377, 1312, 1274, 1225, 1191, 1155, 1098, 963, and 760 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{19}H_{32}NaO_2)^+$ 315.2295. Found: 315.2292.

(±)-(2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-Tetramethyltetradeca-2,10,12-trien-1-ol (S3)



To a solution of triene ester **S2** (2.9 g, 9.9 mmol) in toluene (100 mL) cooled at -78 ^oC was added dropwise a Dibal-H solution (20 mL, 1.5 M in toluene, 3.1 equiv). The reaction mixture was stirred at this temperature for 2 h, at which time TLC showed full consumption of starting material. The mixture was quenched at -78 °C by slow addition of a solution containing AcOH (2.5 g, 41.7 mmol), NaOAc (2.4 g, 29.1 mmol), THF (9.5 mL), and water (40 mL). The mixture was allowed to warm to room temperature, Celite was added, and stirring was continued for 30 min. The mixture was filtered through a Celite bed. The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resulting crude mixture was purified with flash chromatography (silica gel, hexanes:EtOAc = 10:1) to give triene alcohol **S3** (2.46 g, 9.4 mmol, 94%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.04 [d, *J* = 15.5 Hz, 1H, CH_3CH=CH(CH_3)C*H*=], 5.53 (dt, *J* = 15.0 and 7.0 Hz, 1H, =C*H*CH_2), 5.44 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 5.10 [dtq, *J* = 10.0, 1.5, and 1.5 Hz, 1H, -C*H*=C(CH_3)CH_2OH], 3.98 (br s, 2H, -C*H*$_2$OH), 2.48

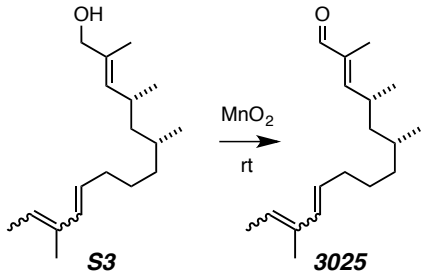
[m, 1H, -C*H*(CH_3)CH=], 2.04 (dt, *J* = 7.5 Hz, 7.5 Hz, 2H, =CH-C*H*$_2$-), 1.72 [dt, *J* = 1.5 and 1.5 Hz, 3H, -CH=C(C*H*$_3$)CH_2OH], 1.70 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH=), 1.67 [d, *J* = 1.5 Hz, 3H, CH_3CH=C(C*H*$_3$)=], 1.30-1.42 (m, 3H), 1.21-1.30 (m, 2H), 1.02-1.15 (m, 2H), 0.91 [d, *J* = 6.5 Hz, 3H, =CHCH(C*H*$_3$)-], and 0.82 [d, *J* = 6.5 Hz, 3H, =CHCH(CH_3)CH_2CH(C*H*$_3$)-].

^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.6, 134.4, 133.1, 133.0, 127.3, 124.4, 69.1, 45.1, 37.2, 33.2, 30.4, 29.6, 27.1, 21.6, 19.6, 13.8, 13.7, and 12.1 ppm.

IR (neat): 3200-3600, 2953, 2924, 2866, 1651, 1628, 1455, 1377, 1069, 1009, 962, 848, and 798 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{18}H_{32}NaO)^+$ 287.2346. Found: 287.2345.

(±)-(2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-Tetramethyltetradeca-2,10,12-trienal (3025)



To a solution of triene alcohol **S3** (2.46 g, 9.4 mmol) in CH_2Cl_2 (250 mL) was added activated MnO_2 (16.3 g, 188 mmol, <5 mm) in three batches at 1 hour intervals at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was filtered through a pad of silica gel and Celite, and the filter pad was thoroughly washed with additional CH_2Cl_2 (100 mL x 2). The combined filtrate was concentrated in vacuo. The crude aldehyde was purified by flash chromatography (silica gel, hexanes:EtOAc = 20:1) to give aldehyde **3025** (2.34 g, 9.0 mmol, 96%) as a clear colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.38 (s, 1H, -C*H*O), 6.21 [dq, *J* = 10.0 and 1.5 Hz, 1H, OHCC(CH_3)=C*H*-], 6.03 [d, *J* = 15.5 Hz, 1H, CH=CH(CH_3)C*H*=], 5.51 [dt, *J* = 15.0, and 7.0 Hz, 1H, CH_3CH=CH(CH_3)CH=C*H*-], 5.43 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 2.80 [m, 1H, OHCC(CH_3)=CHC*H*(CH_3)CH_2-], 2.04 (dt, *J* = 7.5 and 7.5 Hz, 2H, -

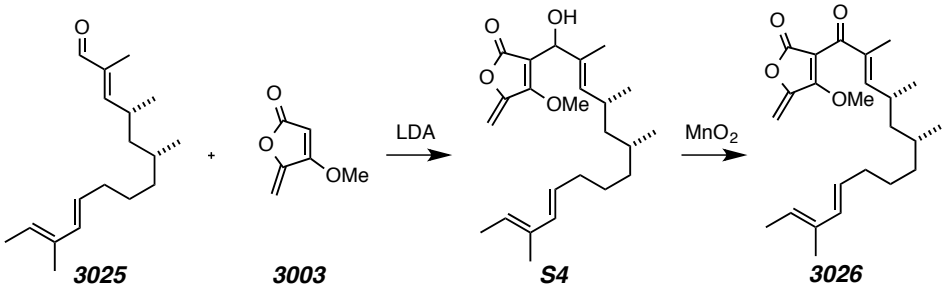
CH=CH-C*H*$_2$-), 1.75 [d, *J* = 1.0 Hz, 3H, OHCC(C*H*$_3$)=CH-], 1.71 [dd, *J* = 1.5 and 1.5 Hz, 3H, CH$_3$CH=C(C*H*$_3$)CH=], 1.69 (d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=), 1.33-1.44 (m, 2H), 1.17-1.32 (m, 4H), 1.10-1.17 (m, 1H), 1.03 [d, *J* = 6.5 Hz, 3H, OHCC(CH$_3$)=CHCH(C*H*$_3$)CH$_2$-], 0.83 [d, *J* = 6.0 Hz, 3H, CH$_2$CH(C*H*$_3$)CH$_2$].

^{13}C NMR ($CDCl_3$, 125 MHz): δ 195.6, 160.8, 137.9, 134.8, 134.4, 127.0, 124.5, 44.4, 37.1, 33.1, 31.2, 30.8, 27.0, 20.4, 19.5, 13.7, 12.1, and 9.4.

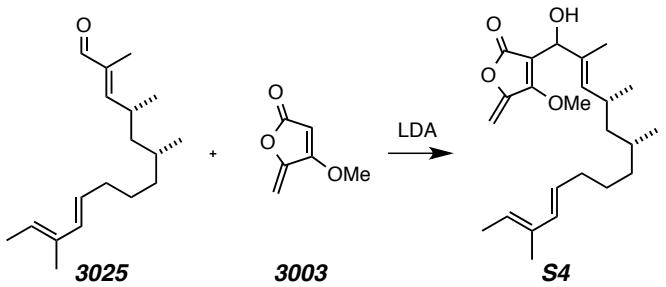
IR (neat): 2960, 2926, 2870, 2857, 2706, 1690, 1644, 1456, 1378, 1312, 1013, and 963 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{18}H_{30}NaO)^+$ 285.2189. Found: 285.2194.

(±)-4-Methoxy-5-methylene-3-((2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-tetramethyltetradeca-2,10,12-trienoyl)furan-2(5*H*)-one (3026)



(±)-3-((2*E*,4*R*,6*R*,10*E*,12*E*)-1-Hydroxy-2,4,6,12-tetramethyltetradeca-2,10,12-trien-1-yl)-4-methoxy-5-methylenefuran-2(5*H*)-one (S4)



Diisopropylamine (2.78 mL, 19.8 mmol) was dissolved in toluene (120 mL) in a 500 mL round bottom flask cooled at -78 °C. To this solution was added *n*BuLi (7.8 mL, 2.5 M in hexanes, 19.5 mmol) dropwise over 10 min. The resulting mixture was stirred at this temperature for 1 h. A solution of the methyl tetronate **3003** (2.26 g, 18 mmol) in a mixture of toluene (21 mL) and THF (18 mL) was added dropwise to the LDA solution over 10 min. The reaction mixture was stirred for an additional 5 min, during which the color of the reaction turned to dark brown. Aldehyde **3025** (2.34 g, 9.0 mmol) was dissolved in toluene (35 mL) and added dropwise to the flask over 15 min, and the resulting solution was stirred for 1.5 h. When TLC showed full conversion of starting material, the saturated NH_4Cl (50 mL) was added, and the resulting mixture was warmed to room temperature. Water (50 mL) was added to dissolve all inorganic salts. The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude mixture was subjected to flash chromatography (silica gel, hexanes:EtOAc = 12:1 then 4:1) to give, in order of elution, an epimeric mixture of the alcohols **S4** (3.15 g, 8.12 mmol, 91%, ca. 1:1 dr as determined by ^{1}H NMR) as a pale yellow oil and unreacted **3003** (1.05 g) as white solid.

^{1}H NMR ($CDCl_3$, 500 MHz, for the mixture of diastereomers): δ 6.03$^+$ (d, *J* = 15.5 Hz, 0.5H, CH_3CH=CH(CH_3)C*H*=), 6.03$^-$ (d, *J* = 15.5 Hz, 0.5H, CH_3CH=CH(CH_3)C*H*=), 5.52 (dt, *J* = 15.5 and 7.0 Hz, 0.5H, CH_3CH=CH(CH_3)CH=C*H*-), 5.51 (dt, *J* = 15.5 and 7.0 Hz, 0.5H, CH_3CH=CH(CH_3)CH=C*H*-), 5.43 (q, *J* = 6.5 Hz, 1H, CH_3CH=), 5.20 (d, *J* = 8.5 Hz, 2H, -O*H*), 5.13 (br d, *J* = 9.5 Hz, 2H, -C*H*=C(CH_3)CHOH-), 5.06 (m, 2H, CH_2=), 4.11 (s, 1.5H, MeO-), 4.10 (s, 1.5H, MeO-), 3.63 (d, *J* = 8.5 Hz,

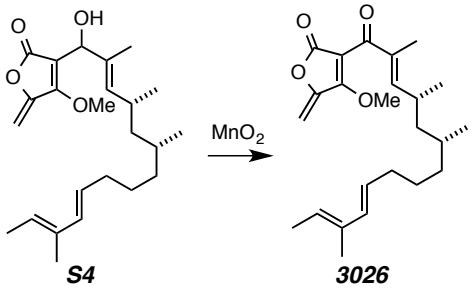
0.5H, HOC*H*=), 3.61 (d, *J* = 8.5 Hz, 0.5H, HOC*H*=), 2.50 (m, 1H, -C*H*(CH_3)CH=C(CH_3)CHOH-), 2.02 (m, 2H, CH_3CH=C(CH_3)CH=CH-CH_2-), 1.70 (m, 3H, -CH=C(CH_3)CH_2OH), 1.69 (m, 6H, CH_3CH=CCH_3), 1.17-1.42 (m, 5H), 1.00-1.15 (m, 2H), 0.90 (d, *J* = 6.5 Hz, 1.5H, -HOCHC(CH_3)=CHCH(CH_3)-), 0.88 (d, *J* = 7.0 Hz, 1.5H, -HOCHC(CH_3)=CHCH(CH_3)-), 0.81 (d, *J* = 6.5 Hz, 1.5H, -HOCHC(CH_3)=CHCH(CH_3)CH_2CH(CH_3)-), and 0.80 (d, *J* = 6.5 Hz, 1.5H, -HOCHC(CH_3)=CHCH(CH_3)CH_2CH(CH_3)-).

^{13}C NMR ($CDCl_3$, 500 MHz, for the mixture of diastereomers): δ 169.95, 169.90, 162.27, 162.20, 149.41, 149.36, 134.69, 134.66, 134.45, 134.42, 134.08, 134.03, 133.14^+, 133.14^-, 127.27, 127.21, 124.36, 124.32, 105.17, 105.05, 99.22, 99.21, 69.91, 69.88, 60.71, 60.56, 45.00, 44.97, 37.17, 37.13, 33.12, 33.10, 30.54, 30.49, 29.79, 29.77, 27.14, 27.12, 21.35, 21.28, 19.66, 19.63, 13.71, 13.68^+, 13.68^-, 13.58, 12.09^+, and 12.09^- ppm.

IR (neat): 3150-3650, 2955, 2925, 2866, 1748, 1667, 1621, 1615, 1462, 1455, 1354, 1277, 1142, 1084, 1031, 978, 866, and 781 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{36}NaO_4)^+$ 411.2506. Found: 411.2511.

(±)-4-Methoxy-5-methylene-3-((2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-tetramethyltetradeca-2,10,12-trienoyl)furan-2(5*H*)-one (3026)



S4 ***3026***

To a solution of alcohol **S4** (3.15 g, 8.12 mmol) dissolved in CH_2Cl_2 (400 mL) was added activated MnO_2 (13.9 g, 160 mmol, <5 mm) in three batches at 1 hour intervals at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was then filtered through a pad of silica gel and Celite, and the pad was thoroughly washed with additional CH_2Cl_2 (100 mL x 3). The combined filtrates were

concentrated in vacuo. The crude mixture was purified by flash chromatography (silica gel, hexanes:EtOAc = 12:1) to give, in order of elution, ketone **3026** (1.88 g, 4.88 mmol, 60%; 66% borsm) as a clear colorless oil and unreacted **S4** (0.29 g, 0.7 mmol).

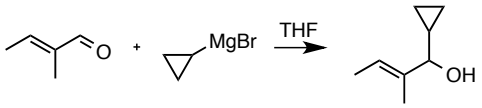
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.31 [dq, *J* = 10.5 and 0.5 Hz, 1H, -COC(CH_3)C*H*-], 6.04 [d, *J* = 15.5 Hz, 1H, =C(CH_3)C*H*=CH-], 5.52 [dt, *J* = 14.5 and 6.5 Hz, 1H, =C(CH_3)CH=C*H*CH_2], 5.44 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 5.17 (d, *J* = 2.5 Hz, 1H, C$H_a$$H_b$=C), 5.15 (d, *J* = 2.5 Hz, 1H, $CH_a$$H_b$=C), 3.91 (s, 3H, C$H_3$O-), 2.77 [m, 1H, =CHC*H*(CH_3)-], 2.05 (dt, *J* = 7.0 and 7.0 Hz, 2H, =CH-CH_2), 1.90 [d, *J* = 0.5 Hz, 3H, -COC(CH_3)=], 1.72 [br s, 3H, CH_3CH=C(CH_3)-], 1.70 (d, *J* = ca. 7 Hz, 3H, CH_3CH=), 1.24-1.41 (m, 5H), 1.08-1.24 (m, 2H), 1.02 [d, *J* = 7.0 Hz, 3H, =CHCH(CH_3)-], and 0.85 [d, *J* = 6.0 Hz, 3H, -CH_2CH(CH_3)CH_2].

^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 166.0, 165.3, 157.1, 148.9, 136.6, 134.8, 134.4, 127.1, 124.4, 104.8, 94.1, 60.9, 44.2, 37.0, 33.0, 31.8, 30.7, 27.0, 20.1, 19.7, 13.7, 12.1, and 11.3 ppm.

IR (neat): 3029, 2959, 2928, 2870, 1939, 1780, 1660, 1461, 1388, 1289, 1257, 1206, 1150, 992, and 876 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2349.

(±)-(*E*)-1-Cyclopropyl-2-methylbut-2-en-1-ol (3031)



3029 ***3030*** ***3031***

A solution of cyclopropyl bromide (**3030**, 18 g, 150 mmol) in THF (60 mL) was added dropwise to magnesium (3.6 g, 150 mmol) in THF (15 mL) under a nitrogen atmosphere at a rate to maintain a gentle reflux. The resulting mixture was stirred at room temperature for an additional 30 min and then cooled in an ice bath. Tiglic aldehyde (11.2 g, 133 mmol) in THF (25 mL) was then added over 15 min. The mixture was stirred at this temperature for 1 hour before saturated aqueous NH_4Cl was added. This mixture was extracted with diethyl ether (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give 18 g of crude alcohol. A portion of this crude alcohol was purified by flash chromatography (silica gel, hexanes:ether = 5:1) to give compound **3031** as a colorless oil.

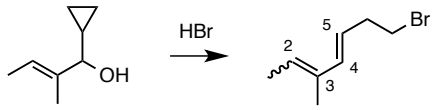
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.47 (qq, *J* = 6.7 and 1.2 Hz, 1H, CH_3CH=), 3.21 (d, *J* = 8.6 Hz, 1H, C*H*OH), 1.71 (dq, *J* = 1.2 and 1.2 Hz, 3H, CH_3C=), 1.62 (qd, *J* = 6.7 and 1.2 Hz, 3H, CH_3CH=), 1.04 (ddddd, *J* = 8.6, 8.3, 8.3, 4.8 and 4.8 Hz, 1H, C*H*CHOH), 0.56 (dddd, *J* = 4.8, 4.8, 8.8, and 8.8 Hz, 1H), 0.50 (dddd, *J* = 4.8, 4.8, 8.8, and 8.8 Hz, 1H), 0.35 (dddd, *J* = 4.8, 4.8, 4.8, and 8.8 Hz, 1H), and 0.19 (dddd, *J* = 4.8, 4.8, 4.8, and 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.8, 120.6, 82.8, 16.4, 13.3, 11.9, 3.7, and 3.0 ppm.

IR (neat): 3400, 3080, 3005, 2919, 2862, 1671, 1433, 1380, 1022, and 1004 cm^{-1}.

GC-LRMS: t_R = 4.33 min; *m/z*: 126 (M+), 111 (M^+ -Me), 98 (M^+ -CH_2=CH_2), 91, 83, 69, and 55 ($C_4H_7^+$).

(2*E*,4*E*)-7-Bromo-3-methylhepta-2,4-diene (3028)



3031 ***3028***

70% two steps

E/Z $\Delta^{2,3}$ = 16:1

A neat sample of the crude alcohol **3031** was cooled to 0 °C in an ice bath. Concentrated aqueous hydrobromic acid (48%, 22 mL) was added dropwise with vigorous stirring over 5 min. The mixture was stirred for an additional 8 min, at which time TLC showed full conversion. The resulting mixture was diluted with water and extracted with diethyl ether (50 mL x 3). The combined organic layers were washed sequentially with saturated $NaHCO_3$ (50 mL x 3) and brine (50 mL), dried over Na_2SO_4, and concentrated to give crude bromide **3028**, which was vacuum distilled from CaH_2 to give **3028** as a colorless liquid (18 g, 95 mmol, 71% overall). bp ca. 56 ^oC/2 mm Hg.

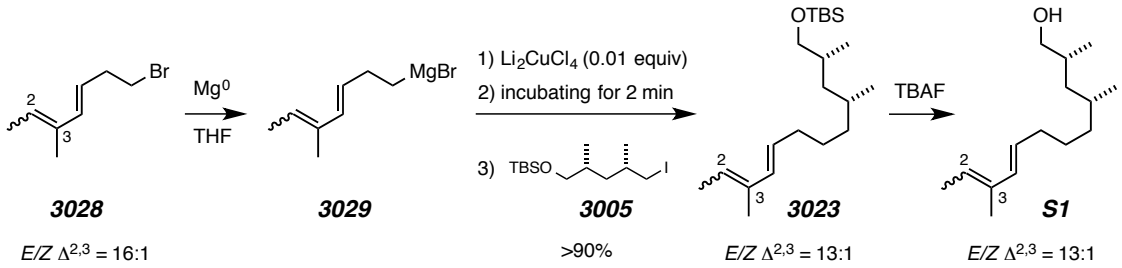
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.15 (dq, *J* = 16.0 and 1.1 Hz, 1H, =CC*H*=CH), 5.52 (qq, *J* = 7.0 and 1.1 Hz, 1H, CH_3CH=), 5.48 (dt, *J* = 16.0 and 7.0 Hz, 1H, CH=C*H*-CH_2), 3.40 (t, *J* = 7.0 Hz, 2H, C*H*$_2$Br), 2.65 (dt, *J* = 7.0 and 7.0 Hz, 2H, C*H*$_2$$CH_2$Br), 1.74 (dd, *J* = 1.0 and 1.0 Hz, 3H, C*H*3C), and 1.72 (br d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.6, 134.0, 126.4, 122.8, 36.2, 32.8, 13.8, and 12.0 ppm.

IR (neat): 3032, 2962, 2918, 2858, 1650, 1445, 1379, 1260, 1206, 1034, 963, and 794 cm^{-1}.

GC-LRMS: t_R = 5.72 min. *m/z*: 190 (M^+), 188 (M^+), 109 (M^+ -Br), 95 (M^+ -CH_2Br), 81 (M^+ -CH_2CH_2Br), 67, and 55 ($C_4H_7^+$).

(±)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-Trimethyldodeca-8,10-dien-1-ol (S1)



A solution of bromodiene **3028** (9.45 g, 50 mmol) in THF (27 mL) was added to crushed magnesium turnings (1.32 g, 55 mL) in THF (6 mL) under a nitrogen atmosphere at a rate to maintain a gentle reflux over 20 min. The Grignard reagent prepared was then transferred into a 100 mL round bottom flask cooled to 0 °C in an ice bath, to which a solution of Li_2CuCl_4 (5 mL, 0.1 M; made from a 2:1 mole ratio of anhydrous LiCl and $CuCl_2$) in THF was then added. The mixture was stirred at this temperature for 10 min, by which time the color of the solution had turned purple. Alkyl iodide **3005**[161] (4.5 g, 12.6 mmol) in THF (12 mL) was added. The resulting mixture was stirred at 0 °C for 2 h, at which time the solution had become grayish red. Aqueous saturated NH_4Cl (30 mL) was added. The aqueous layer was extracted with diethyl ether (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give crude diene silyl ether **3023** (along with hydrocarbon by-products). Without further purification, this crude sample of **3023** was dissolved in THF (75 mL) and cooled to 0 ^oC. TBAF (1.0 M in THF, 18 mL) was added dropwise over 10 min. The resulting solution was stirred overnight. The reaction mixture was quenched by addition of saturated NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (silica gel, hexanes:EtOAc = 8:1) gave purified **S1** (2.6 g, 12 mmol, 92% overall) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.04 (d, *J* = 16.0 Hz, 1H, C*H*=CHCH$_2$), 5.53 (dt, *J* = 16.5 and 7.0 Hz, 1H, CH=C*H*CH$_2$), 5.43 (q, *J* = 7.0 Hz, 1H, CH$_3$C*H*=), 3.50 (dd, *J* = 5.0 and 10.0 Hz, 1H, C*H*$_a$H$_b$OH), 3.36 (dd, *J* = 7.5 and 10.0 Hz, 1H, CH$_a$*H*$_b$OH), 2.08 (ddt, *J* = 14.0, 7.0 and 7.0 Hz, 1H, CH=CHC*H*$_a$H$_b$-), 2.03 (ddt, *J* = 14.0, 7.0, and 7.0

[161] Hoffmann, R. W.; Schopfer, U.; Mueller, G.; Brandl, T. *Helv. Chim. Acta* **2002**, *85*, 4424-4441.

Hz, 1H, CH=CHCH$_a$*H*$_b$-), 1.71 (br s, 3H, C*H*$_3$C=CH), 1.69 (d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=), 1.69 (m, 1H, HOCH$_2$C*H*-), 1.46-1.55 [m, 1H, HOCH$_2$CH(CH$_3$)CH$_2$C*H*(CH$_3$)-], 1.38-1.46 (m, 1H), 1.27-1.38 (m, 3H), 1.06 (m, 1H), 0.94 (m, 1H), 0.91 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(C*H*$_3$)-], and 0.88 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(CH$_3$)CH$_2$CH(C*H*$_3$)-].

^{13}C NMR ($CDCl_3$, 125 MHz): 134.6, 134.4, 127.2, 124.4, 68.3, 41.0, 36.2, 33.2, 33.1, 29.9, 27.0, 20.3, 17.3, 13.7, and 12.1 ppm.

IR (neat): 3338, 2924, 2871, 2858, 1652, 1628, 1459, 1377, 1036, and 962 cm^{-1}.

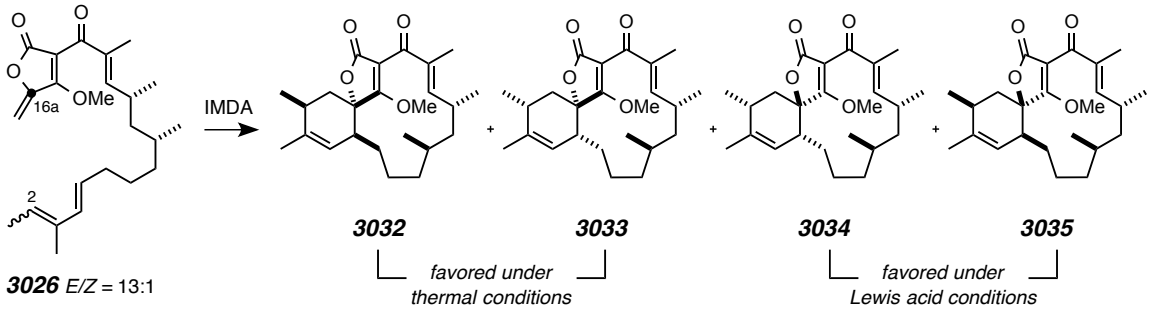
GC-LRMS: t_R = 9.07 min. *m/z*: 224 (M^+), 209 (M^+-Me), 193 (M^+-CH_2OH), 151 (M^+-C_4H_8OH), 123, 109, 99, 95, 93, 81, 67, and 55 ($C_4H_7^+$).

(±)-4-Methoxy-5-methylene-3-((2*E*,4*R*,6*R*,10*E*,12*Z*)-2,4,6,12-tetramethyltetradeca-2,10,12-trienoyl)furan-2(5*H*)-one (3026-*Z*);

(±)-(5*E*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-methoxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione [(±)-*O*-Methyl Okilactomycin D (3022)];

(±)-(5*E*,7*R*,9*R*,12a*R*,15*R*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-methoxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione [(±)-*O*-Methyl 12a,15-bisepi-Okilactomycin D (3033)];

(±)-(5*E*,7*R*,9*R*,12a*R*,15*R*,16a*R*)-8,9,10,11,12,12a,15,16-Octahydro-17-methoxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione [(±)-*O*-Methyl 12a, 15,16a-trisepi-Okilactomycin D (3034)



Ketone **3026** (1.75 g, 4.53 mmol), which contained ca. 8% of the C2-*Z* isomer (**3026-*Z***), and hydroquinone (50 mg, 0.453 mmol) were dissolved in toluene (450 mL), and the resulting solution was heated in an oil bath at 110 ^{o}C in a pressure vessel sealed with a threaded cap for 4 d, at which time ^{1}H NMR analysis showed full consumption of **3026-*E***. The solution was concentrated in vacuo, and the resulting mixture was subjected to flash chromatography (silica gel, hexanes:EtOAc = 12:1 then 5:1). The fractions containing mixtures were further purified using MPLC to yield, in order of elution, unreacted **3026-*Z*** as pale yellow oil (110 mg), co-eluting **3033-3035** as foamy solid (123 mg, 7% as a mixture), and **3032 (**0.98 g, 61%**)** as a white solid. Recrystallization (EtOAc) gave a sample of **3032** suitable for single crystal x-ray analysis. Compound **3033** could be selectively crystallized from the mixture of **3033-3035** using a vial-in-a-vial vapor diffusion crystallization. The mixture was dissolved in EtOAc in an open inner vial and cyclohexane was placed in the outer vial, which was then capped. After standing

overnight at room temperature, **3033** was obtained as colorless crystals, suitable for single crystal x-ray analysis.

Under Lewis acidic conditions, cycloadduct **3034** and **3035** were formed predominantly. A pure sample of **3034** was obtained using the following method:

Ketone **3026** (60 mg, 0.16 mmol), which contained ca. 8% of the C2-*Z* isomer (**3026-Z**), was dissolved in a solution of $LiClO_4$ in Et_2O (5M, 10 mL). The resulting solution was kept at room temperature under a nitrogen atmosphere for 24 h. The resulting mixture was partitioned between Et_2O and water. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was subjected to MPLC to give a co-eluting mixture of **3033-3035** as foamy solid (21 mg, 0.054 mmol, 39% as a mixture), followed by **3032** (ca. 3 mg). Compound **3034**, the major component in the mixture produced in this experiment, could be selectively crystallized using a vial-in-a-vial vapor diffusion crystallization method. The mixture of **3033-3035** was dissolved in EtOAc (ca. 0.5 mL) in an open inner vial and cyclohexane (ca. 2 mL) was placed in the outer vial, which was then capped. After standing 2 days at room temperature, **3034** was obtained as colorless crystals, suitable for single crystal x-ray analysis.

Compound 3026-Z

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.44 [d, *J* = 15.5 Hz, 1H, =C(CH_3)C*H*=CH], 6.31 [dq, *J* = 10.0 Hz, 1.5 Hz, 1H, -COC(CH_3)C*H*-], 5.65 [dt, *J* = 15.5 Hz, 7.5 Hz, 1H, =C(CH_3)CH=C*H*CH_2], 5.32 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 5.17 (d, *J* = 2.5 Hz, 1H, C$H_a$$H_b$=C), 5.15 (d, *J* = 2.5 Hz, 1H, C$H_a$$H_b$=C), 3.91 (s, 3H, C$H_3$O-), 2.79 [m, 1H, =CHC*H*(CH_3)-], 2.11 (dt, *J* = 7.0 and 7.0 Hz, 2H, =CH-CH_2), 1.92 (d, *J* = 1.0 Hz, 3H, -COC(CH_3)=), 1.78 [br s, 3H, CH_3CH=C(CH_3)-], 1.71 (app d, *J* = 6.0 Hz, 3H, CH_3CH=), 1.24-1.45 (m, 5H), 1.08-1.24 (m, 2H), 1.03 [d, *J* = 6.5 Hz, 3H, =CHCH(CH_3)-], and 0.86 [d, *J* = 6.5 Hz, 3H, -CH_2CH(CH_3)CH_2].

^{13}C NMR ($CDCl_3$, 125 MHz, DEPT): 157.1 (CH), 130.3 (CH), 126.9 (CH), 122.6 (CH), 94.1 (CH_2), 60.9 (CH_3), 44.2 (CH_2), 37.0 (CH_2), 33.5 (CH_2), 31.8 (CH), 30.7 (CH), 27.0 (CH_2), 20.6 (CH_3), 20.1 (CH_3), 19.7 (CH_3), 13.0 (CH_3), and 11.2 (CH_3) ppm.

IR (neat): 2957, 2926, 2870, 1773, 1636, 1454, 1388, 1287, 1257, 990, 973, and 874 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2354.

Compound 3032

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.44 [dq, *J* = 7.7 and 1.4 Hz, 1H, -COC(CH_3)=C*H*], 5.45 (ddq, *J* = 4.5, 1.6, and 1.6 Hz, 1H, CH_3C=C*H*-), 3.82 (s, 3H, CH_3O), 2.61 [ddqd, *J* = 10.9, 7.2, 7.2, and 3.8 Hz, 1H, -COC(CH_3)=CHC*H*], 2.43 [ddqddq, *J* = 10.5, 6.5, 6.5, 1.5, 1.5, and 1.5 Hz, 1H, CH_3C*H*(CH_2-)C=], 2.11 [dddq, *J* = 10, 4.5, 3.2, and 1.6 Hz, 1H, CH_3C(CH-)=CHC*H*-], 1.87 [d, *J* = 1.3 Hz, 3H, O=CC(CH_3)=], 1.88-1.82 [m, 2H, CH_3C(CHC$H_a$$H_b$)=CH and CH_3C(CH-)=CHCHC$H_a$$H_b$], 1.70 [ddd, *J* = 1.4, 1.4, and 1.4 Hz, 3H, CH_3C(CH-)=CH], 1.67-1.58 (m, 1H), 1.64 [dd, *J* = 13.5, and 10.5 Hz, 1H, CH_3C(CHC$H_a$$H_b$)=CH], 1.44 (ddddd, *J* = 14.5, 7.4, 7.4, 7.4, and 4.8 Hz, 1H, CH_2C$H_a$$H_b$$CH_2$),1.42-1.35 (m, 1H), 1.35-1.19 (m, 4H), 1.14 [dddd, *J* = 14.0, 10.0, 6.5, and 6.5 Hz, 1H, CH_3C(CH-)=CHCHC$H_a$$H_b$], 1.07 [d, *J* = 7.0 Hz, 3H, CH_3CH(CH_3)CH_2C], 1.02 (d, *J* = 7.0 Hz, 3H, CH_3CHCH=C), and 0.89 (d, *J* = 6.0 Hz, 3H, CH_2CH_3CHCH_2).

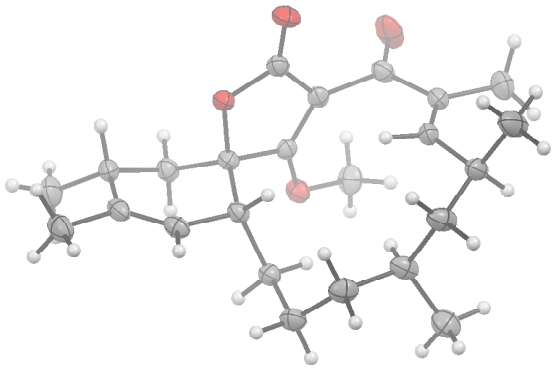
^{13}C NMR ($CDCl_3$, 75 MHz): 192.2, 179.8, 168.4, 157.2, 140.7, 136.4, 122.3, 103.2, 86.0, 59.7, 46.2, 45.0, 35.2, 34.0, 32.0, 30.6, 28.6, 28.4, 23.1, 20.9, 19.8, 19.5, 18.7, and 10.9 ppm.

IR (neat): 2963, 2922, 2860, 1745, 1644, 1635, 1455, 1371, 1355, 1260, 1002, and 945 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2358.

mp: 215-216 °C.

ORTEP rendering for 3032:



Compound 3033

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.65 (dq, *J* = 8.0 and 1.1 Hz, 1H, -COC(CH_3)=C*H*), 5.24 [br q, *J* = 1.7 Hz, 1H, HC(CH_3)C=C*H*-], 3.79 (s, 3H, C*H*$_3$O), 2.61 [ddqd, *J* = 12, 8, 7, and 2.5 Hz, 1H, -COC(CH_3)=CHC*H*], 2.44 (ddddd, *J* = 8.6, 2.2, 2.2, 2.2, and 2.2 Hz, 1H, CH_2C*H*CH=C), 2.27 (dqdq, *J* = 7, 7, 1.5 and 1.5 Hz), 2.20 (dd, *J* = 13.9 and 7.1 Hz, 1H, CH_3CH(C=)CH_aH$_b$), 1.86 (d, *J* = 1.2 Hz, 3H, O=CC(C*H*$_3$)=), 1.74 [dd, *J* = 1.8 and 1.8 Hz, 3H, C*H*$_3$C(CH-)=CH], 1.69 (d, *J* = 13.8 Hz, 1H, CH_3CH(C=)CH_a*H*$_b$), 1.63-1.70 (m, 1H), 1.50-1.38 (m, 4H), 1.26-1.34 (nfom, 1H), 1.20 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CHCH_2CO), 1.12-1.19 (m, 3H), 1.05 [d, *J* = 6.9 Hz, 3H, C*H*$_3$CHCH=C(CH_3)C=O], and 0.88 [br d, *J* = 5.9 Hz, 3H, C*H*$_3$CHCH_2CH(CH_3)C=].

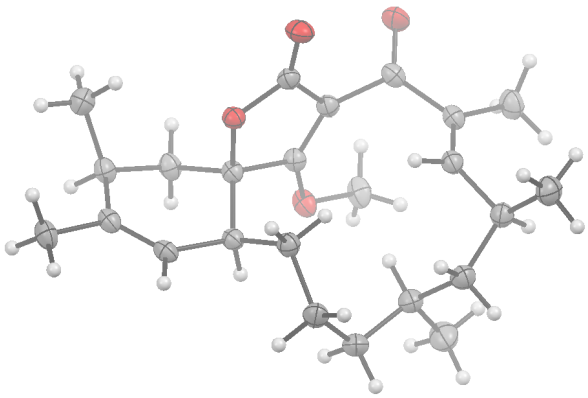
^{13}C NMR ($CDCl_3$, 75 MHz): 194.1, 178.8, 169.7, 158.9, 139.7, 137.1, 120.7, 106.0, 84.9, 60.3, 43.6, 38.0, 37.1, 34.6, 32.3, 32.1, 29.9, 26.8, 23.1, 22.1, 21.6, 20.2, 19.5, and 11.3 ppm.

IR (neat): 2957, 2923, 2868, 1754, 1638, 1448, 1350, 1260, 1230, 1096, 998, and 958 cm^{-1}.

HRMS: Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2352.

mp: 171-172 °C.

ORTEP rendering for 3033:



Compound 3034

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.73 [dq, *J* = 6.7 and 1.4 Hz, 1H, -COC(CH_3)=C*H*], 5.27 (ddq, *J* = 1.5, 1.5, and 1.5 Hz, 1H, CH_3C=C*H*-), 3.86 (s, 3H, C*H*$_3$O), 2.60 [ddqdq, *J* = 10.3, 6.9, 6.9, 3.3, and 0.8 Hz, 1H, -COC(CH_3)=CHC*H*], 2.41-2.47 (m, 2H, -C*H*C=CHC*H*-), 2.12 [dd, *J* = 13.9 and 7.5 Hz, 1H, CH_3C(CHCH_aH$_b$)=CH], 1.91 [dd, *J* = 1.0 and 1.0 Hz, 3H, O=CC(C*H*$_3$)=], 1.79-1.70 (m, 1H, O-CCHCH_aH$_b$), 1.72 [dd, *J* = 14.0 and 6.9 Hz, 1H, CH_3C(CHCH_a*H*$_b$)=CH], 1.71 [br s, 3H, C*H*$_3$C(CH)=CHCH], 1.55-1.38 (m, 6H), 1.29 (ddd, *J* = 14.3, 7.8, and 3.3 Hz), 1.25-1.17 (m, 1H), 1.11 [d, *J* = 7.0 Hz, 3H, C*H*$_3$CH(CH=CC=O)CH_2-], 1.08 [d, *J* = 7.2 Hz, 3H, C*H*$_3$CHC(CH_3)=], and 0.89 [d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH_2CH(CH_3)CH_2-].

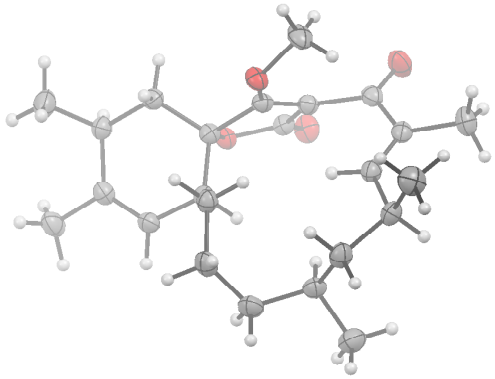
^{13}C NMR (DEPT) ($CDCl_3$, 75 MHz): 156.0 (CH), 122.7 (CH), 60.3 (CH_3), 44.4 (CH_2), 43.9 (CH), 37.2 (CH_2), 35.4 (CH_2), 32.7 (CH), 32.0 (CH), 31.7 (CH), 31.6 (CH_2), 24.2 (CH_2), 22.5 (CH_3), 21.2 (CH_3), 20.1 (CH_3), 19.2 (CH_3), and 11.3 (CH_3).

IR (neat): 2953, 2922, 2868, 1755, 1644, 1450, 1344, 1255, 1050, and 957 cm^{-1}.

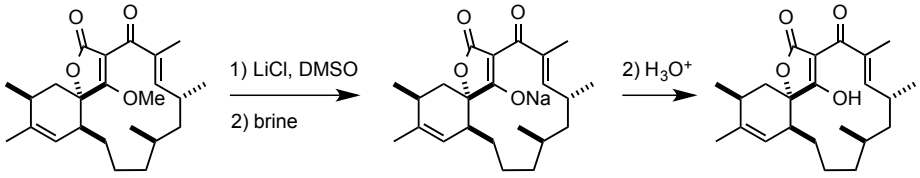
HRMS (ESI-TOF): Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2356.

mp: 152-153 °C.

ORTEP rendering for 3034:



(±)-(5*E*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-hydroxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione [(±)-Okilactomycin D (3001)] and its Sodium Salt S5



(–)-***3032*** ***S5*** ***3001***, (–)-Okilactomycin D

For S5: Compound **3032** (300 mg, 0.78 mmol) and LiCl (495 mg, 11.6 mmol) were dissolved in DMSO (30 mL). The solution was heated at 55 °C for 48 h. The reaction solution was partitioned between EtOAc and half-saturated aqueous NaCl solution. The organic layer was washed with half-saturated NaCl three more times, dried over Na_2SO_4, and concentrated to give **S5** as a white amorphous solid (292 mg, 0.77 mmol, 95%). The NMR spectrum of this sample shows no evidence of anything other than **S5**.

For 3001: Compound **3032** (500 mg, 1.30 mmol) and LiCl (780 mg, 18.4 mmol) were dissolved in DMSO (75 mL).The reaction solution was cooled to room temperature and partitioned between EtOAc and 10% aqueous HCl solution. The organic layer was dried (Na_2SO_4) and carefully concentrated to provide okilactomcyin D (**3001**) (465 mg and 96%) as a white amorphous solid. The NMR spectrum of this sample indicates a purity level of ca. 95%. The material was passed through a bed of SiO_2 using 90:9.9:0.1 (DCM:EtOAc:TFA) as the eluant. This resulted in ca. 120% mass recovery of a slightly yellow solid, presumably due to retention of a portion of TFA. The purity level (^{1}H NMR) was virtually the same as prior to this treatment.

Compound S5

^{1}H NMR (CD_3OD, 500 MHz): δ 5.86 [br d, *J* = 7.9 Hz, 1H, -COC(CH_3)=C*H*], 5.51 (ddq, *J* = 5.2, 1.8, and 1.8 Hz, 1H, CH_3C=C*H*-), 2.54-2.45 (m, 1H, O=CC=CHC*H*), 2.39-2.28 (m, 2H, $CH_3CHCH_aH_bC$-O), 1.83 [br s, 3H, O=CC(C*H*$_3$)=], 1.83 (m, 1H, CH_3C=CHC*H*), 1.68 (ddd, *J* = 1.2, 1.2, and 1.2 Hz, 3H, C*H*$_3$C=CHCH), 1.71-1.56 (m, 4H), 1.30-1.14 (m, 3H), 1.10 (ddd, *J* = 13.5, 8.0, and 2.8 Hz, 1H, $CH_3CHCH_aH_bCHCH_3$), 1.04 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCH2C-O), 1.05-0.97 (m, 2H), 0.92 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCH=CC=O), and 0.86 [d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH$_2$CH(CH_3)C=].

^{13}C NMR (CD_3OD, 75 MHz): 200.2, 199.5, 177.1, 145.4, 139.7, 136.1, 126.4, 97.1, 86.8, 47.7, 46.8, 37.6, 36.0, 32.8, 32.2, 30.6, 30.2, 27.3, 22.2, 21.4, 21.1, 19.7, and 12.8 ppm.

HRMS: Calcd for $(C_{23}H_{31}O_4)^-$ 371.2227. Found: 371.2221.

***Okilactomycin D* (7)**

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.94 [br d, *J* = 7.7 Hz, 1H, -COC(CH_3)=C*H*], 5.51 (ddq, *J* = 5.5, 1.5, and 1.5 Hz, 1H, CH_3C=C*H*-), 2.49 (dddq, *J* = 7.0, 7.0, 7.0 and 7.0 Hz, 1H, O=CC=CHC*H*), 2.43-2.32 (m, 1H), 1.99 [br s, 3H, O=CC(C*H*$_3$)=], 1.92-1.66 (m, 4H), 1.61 (dddd, *J* = 13.4, 7.8, 2.6 and 2.6 Hz, 1H), 1.69 (ddd, *J* = 1.4, 1.4, and 1.4 Hz, 3H, C*H*$_3$C=CHCH), 1.42-1.12 (m, 7H), 1.04 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCH_2C-O), 0.92 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCH=CC=O), and 0.86 [d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH_2CH(CH_3).

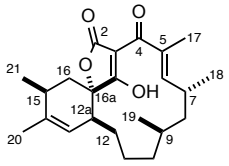
^{1}H NMR (CD_3OD, 500 MHz): See table in next page.

^{13}C NMR (CD_3OD, 75 MHz): See table in next page.

IR (neat): 2954, 2920, 2870, 1698, 1621, 1558, 1455, 1360, 1307, 1259, 1082, 968, 886, and 846 cm^{-1}.

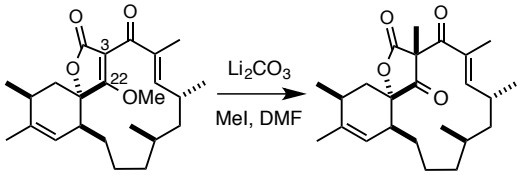
mp: 132-134 °C.

Comparison of the ^{1}H and ^{13}C NMR spectral data of natural (CD_3OD, 500 and 125 MHz) and synthetic (CD_3OD, 500 and 75 MHz, this work) okilactomycin D (3001).



Position	Natural 7 d (multiplicity; *J* in Hz)	Synthetic 7 d (multiplicity; *J* in Hz)	Dd	Natural 7 (d)	Synthetic 7 (d)	Dd
2	–	–	–	172.1	171.8	-0.3
3	–	–	–	101.2	102.9	1.7
4	–	–	–	194.3	194.0	-0.3
5	–	–	–	140.1	140.3	0.2
6	6.38 (dd; 7.5, 1.2)	6.42 (dq; 7.5, 1.4)	0.04	154.3	155.0	0.7
7	2.64 (m)	2.65 (ddqd; 10.2, 7.1, 7.1, 3.3)	0.01	33.1	33.3	0.2
8	1.22 (m) 1.38 (m)	1.22 (ddd; 13.6, 8.5, 3.3)	0.00	46.4	46.5	0.1
9	1.45 (m)	1.68-1.76 (m; 1H) 1.33-1.48 (m; 4H) 1.08-1.23 (m; 2H)	N/A	29.8	29.9	0.1
10	1.18 (m) 1.36 (m)			36.8	37.0	0.2
11	1.37 (m) 1.73 (m)			25.6	25.7	0.1
12	1.12 (m) 2.21 (m)	2.20 (dddd; 14.0, 8.6, 6.0, 2.8)	-0.01	30.0	30.1	0.1
12a	2.02 (m)	2.02-2.06 (m)	0.02	47.3	47.8	0.5
13	5.57 (dt; 5.0, 1.5)	5.58 (ddq; 5.0, 1.8, 1.8)	0.01	125.0	124.9	-0.1
14	–	–	–	136.9	137.1	0.2
15	2.38 (dq; 10.7, 6.7)	2.38 (br dqd; 10.8, 7.1, 5.9)	0.00	32.1	32.3	0.2
16	1.73 (dd; 14.2, 10.4) 1.80 (ddd; 13.8, 5.9, 1.6)	1.73 (dd; 13.9, 10.9) 1.82 (ddd; 13.8, 5.9, 1.6)	0.00 0.02	35.3	35.4	0.1
16a	–	–	–	87.3	87.4	0.1
17	1.86 (d; 1.1)	1.86 (d; 1.1)	0.00	11.8	11.8	0.0
18	1.01 (d; 7.0)	1.01 (d; 7.0)	0.00	20.2	20.3	0.1
19	0.89 (d; 6.8)	0.89 (d; 6.5)	0.00	20.9	21.0	0.1
20	1.72 (d; 1.2)	1.72 (ddd; 1.4, 1.4, 1.4)	0.00	21.2	21.4	0.2
21	1.10 (d; 7.0)	1.10 (d; 7.0)	0.00	19.4	19.5	0.1
22	–	–	–	187.3	186.3	-1.0

C3-Methylated Okilactomycin D (4003)

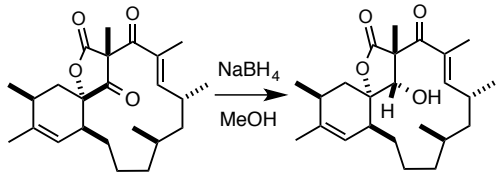


O-Methyl okilactomycin D **4003**

A solution of *O*-methyl okilactomycin D, Li_2CO_3, and MeI in DMF was heated at 70 °C for 72 h. The resulting mixture was partitioned between EtOAc and H2O, with the aqueous layer being washed with additional portions of EtOAc. The combined organic layers were washed with brine, dried, and concentrated. The residue was subjected to flash chromatography (SiO_2, Hexanes:EtOAc = 12:1) to give triketone **4003** as a colorless oil.

^{1}H NMR: δ 5.91 (dq, *J* = 9.7, 1.4 Hz, 1H, *H6*), 5.51 (ddq, *J* = 5.1, 1.6, 1.6 Hz, *H13*), 2.72-2.62 (m, 1H), 2.45-2.40 (m, 1H), 2.28-2.23 (m, 1H), 1.90 (d, *J* = 1.2 Hz, 3H, *H17*), 1.90-1.85 (m, 1H), 1.80 (dd, *J* = 14.0, 11.0 Hz, 1H), 1.73 (ddd, *J* = 1.4, 1.4, and 1.4 Hz, 3H, *H20*), 1.72 (s, 3H, C3C*H*$_3$), 1.08 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), and 0.86 (d, *J* = 6.4 Hz, 3H).

Diketonol 4004



4003 **4004**

A solution of **4003** in MeOH and $CHCl_3$ was cooled at -42 °C. $NaBH_4$ was added to the solution in one portion. The resulting mixture was left at this temperature for 40 seconds, and then quenched by addition of 1M HCl. The resulting mixture was partitioned between EtOAc and H_2O, with the aqueous layer being washed with additional portions of EtOAc. The combined organic layers were washed with brine,

dried, and concentrated. The residue was subjected to flash chromatography (SiO_2, Hexanes:EtOAc = 12:1, then 3:1) to give **4004** as a colorless solid following recovered **4003**.

^{1}H NMR: δ 6.42 (br d, *J* = 9.4 Hz, 1H, *H6*), 5.28 (br s, 1H, *H13*), 4.39 (d, *J* = 4.5 Hz, 1H, C*H*OH), 2.77 (d, *J* = 4.5 Hz, 1H, CHO*H*), 2.56-2.40 (m, 1H), 2.42-2.38 (m, 1H), 2.17 (dd, *J* = 13.7, 8.2 Hz, 1H), 1.86 (br s, 3H, *H17*), 1.72 (dd, *J* = 13.7, 3.5 Hz, 1H), 1.68 (br s, 3H, *H20*), 1.66 (s, 3H, C3C*H*$_3$), 1.50–1.40 (m, 3H), 1.35–1.25 (m, 1H), 1.18 (d, *J* = 7.5 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), and 0.91 (d, *J* = 6.5 Hz, 3H).

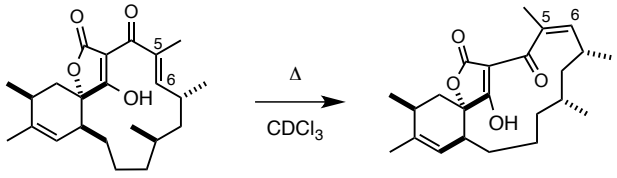
^{13}C NMR: δ 198.2, 177.5, 150.6, 137.1, 137.0, 125.4, 89.2, 84.1, 60.1, 44.4, 43.5, 42.8, 36.5, 33.5, 33.4, 31.1, 28.7, 26.0, 24.8, 22.8, 21.2, 21.0, 20.8, and 13.8.

Mp: 214-216 °C.

IR: 3380, 2954, 2917, 2869, 2845, 1760, 1661, 1611, 1453, 1266, 1185, 1007, 974, and 959.

HRMS (ESI-TOF): Calcd for $C_{24}H_{36}NaO_4^+$ $[M+Na]^+$ requires 411.2506; found 411.2531.

(±)-(5*Z*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-hydroxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione (4006)



Okilactomycin D ***4006***

In an NMR tube, a sample of okilactomycin D obtained by acidification of the sodium salt (see above; 20 mg, 0.054 mmol) was dissolved in $CDCl_3$ (0.7 mL) and heated to 60 °C for 20 min. The resulting solution was concentrated to give compound **4006** as a colorless oil. Approximately 7% of **7** remained in this equilibrated mixture.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.43 [dq, *J* = 11.0 and 1.6 Hz, 1H, -COC(CH_3)=C*H*], 5.06 [ddq, *J* = 1.5, 1.5 and 1.5 Hz, 1H, CH_3C(CH-)=C*H*-], 2.65 [ddddq, *J* = 12.2, 2.3,

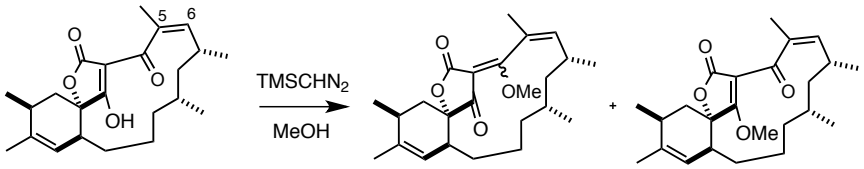
2.3, 2.3 and 2.3 Hz, 1H, $CH_3C(CH\text{-})=CHCH$], 2.43-2.37 [overlapping ms, 2H, $CH_3CH(CH_aH_b\text{-})C=$], 2.00 (d, J = 1.6 Hz, 3H, $CH_3CC=O$), 1.88 [ddqd, J = 11.0, 11.0, 6.5, and 2.0 Hz, 1H, $CH_3C(CO)=CHCH$], 1.83 [d, J = 12.1 Hz, 1H, $CH_3CH(CH_aH_b\text{-})C=$], 1.76 [ddd, J = 2.5, 1.5 and 0.5 Hz, 3H, $CH_3C(CH\text{-})=CH$], 1.75-1.69 (m, 1H, $CH_3CHCH_aH_bCHCH_3$), 1.53 (dddd, J = 14, 14, 4, and 2.5 Hz, 1H, $CH_3C=CHCHCH_aH_b$), 1.32-1.11 (m, 5H), 1.22 [d, J = 7.3 Hz, 3H, $CH_3CHC(CH_3)=$], 1.06-0.97 (m, 1H), 1.00 (ddd, J = 14.0, 11.7, and 4.4 Hz, 1H, $CH_3CHCH_aH_bCHCH_3$), 0.91 (d, J = 6.4 Hz, 3H, $O=CCCHCHCH_3$), and 0.83 [d, J = 6.9 Hz, 3H, $CH_3CHCH_2CH(CH_3)CH=$].

^{13}C NMR ($CDCl_3$, 75 MHz): 202.8, 193.4, 166.6, 138.3, 137.9, 127.6, 123.9, 103.4, 88.2, 42.5, 40.1, 39.5, 35.4, 33.4, 32.6, 32.4, 27.8, 21.5, 20.8, 20.5, 19.7, 19.2, and 18.8 ppm.

IR (neat): 2957, 2926, 2870, 1773, 1636, 1454, 1388, 1287, 1257, 990, and 874 cm^{-1}.

HRMS: Calcd for $(C_{23}H_{31}O_4)^-$ 371.2227. Found: 371.2222.

(±)-(5*Z*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-methoxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione (4007) and its regioisomer 4008.



4006 ***4007*** ***4008***

Compound **4006** (20 mg) was dissolved in a mixed solvent of $CHCl_3$ (1 mL) and CH_3OH (1 mL), and a solution of $TMSCHN_2$ [*CAUTION*: this reagent is potentially hazardous and should always be handled in a properly functioning fume hood] (0.25 mL, 2.0 M in Et_2O) was added at room temperature. The solution was kept at this temperature for an additional 30 min and then concentrated. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc = 8:1 then 4:1) to give **4007** as a white solid (ca. 10 mg, 50%). A similar portion of a more slowly eluting isomer was tentatively assigned

to have the structure **4008** on the basis of analysis of its ^{1}H NMR spectrum. The sample of **4007** was recrystallized by the technique described above for **3033** and **3034** to provide colorless crystals suitable for single crystal x-ray analysis.

Compound 4007

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.51 [dq, *J* = 11.5 and 1.4 Hz, 1H, -COC(CH_3)=C*H*], 5.05 (ddq, *J* = 1.8, 1.8, and 1.8 Hz, 1H, CH_3C=C*H*-), 4.04 (s, 3H, C*H*$_3$O), 2.64 [ddddq, *J* = 12.2, 2.5, 2.5, 2.5, and 2.5 Hz, 1H, -CHC(CH_3)=CHC*H*CH_2], 2.51 [ddqd, *J* = 11.6, 11.6, 6.5, and 2.7 Hz, 1H, -COC(CH_3)=CHC*H*-], 2.41-2.35 (m, 1H, CH_3C*H*CH_2C-O), 2.32 [dd, *J* = 13.9 and 7.2 Hz, 1H, CH_3CH(C=)CH_aH$_b$], 1.97 [d, *J* = 1.5 Hz, 3H, O=CC(C*H*$_3$)=], 1.72 [ddd, *J* = 2.5, 1.3, and 1.3 Hz, 3H, C*H*$_3$C(CH-)=CH], 1.68 [dd, *J* = 13.9 and 3.0 Hz, 1H, CH_3CH(C=)CH_a*H*$_b$], ca. 1.67 (m, 1H), 1.58-1.50 (m, 1H), 1.40 (ddd, *J* = 13.4, 10.4, and 2.7 Hz, 1H, CH_3CHCH_aH$_b$CHCH$_3$), 1.37-1.15 (m, 5H, CH_a*H*$_b$C*H*$_2$C*H*$_2$CH), 1.10 (d, *J* = 7.3 Hz, 3H, C*H*$_3$CHCH$_2$CO), 1.01 (ddd, *J* = 14.0, 11.6, and 4.3 Hz, 1H, CH_3CHCH_a*H*$_b$CHCH$_3$), 0.89 [d, *J* = 6.5 Hz, 3H, C*H*$_3$CHCH=C(CH_3)C=O], and 0.87 [d, *J* = 6.9 Hz, 3H, C*H*$_3$CHCH_2CH(CH_3)C=].

^{13}C NMR ($CDCl_3$, 75 MHz): 195.1, 183.8, 169.1, 139.5, 138.2, 134.3, 124.7, 108.2, 86.0, 62.8, 42.0, 41.8, 40.3, 35.2, 34.4, 32.7, 32.3, 27.9, 21.8, 21.6, 21.4, 21.2, 19.13, and 19.09 ppm.

IR (neat): 2951, 2927, 2862, 1752, 1650, 1607, 1450, 1373, 1329, 1307, 1227, 1095, 1055, 1021, and 946 cm^{-1}.

HRMS: Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2352.

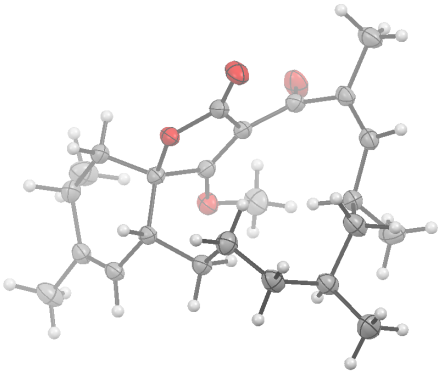
mp: 176-177 °C.

Compound 4008

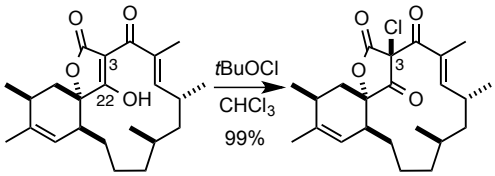
^{1}H NMR ($CDCl_3$, 500 MHz): d 5.59 [dq, *J* = 11.2 and 1.4 Hz, 1H, COC(CH_3)=C*H*], 5.03 [ddq, *J* = 1.8, 1.8, and 1.8 Hz, 1H, CH_3C(CH)=C*H*], 4.03 (s, 3H, OC*H*$_3$), 2.52 [ddddq, *J* = 11.6, 2.4, 2.4, 2.4, and 2.4 Hz, 1H, -CHCH_3C(CH)=CHC*H*CH_2], 2.40-2.33 [m, 1H, CH_3C*H*CH_2C-O], 2.22 [dd, *J* = 14.0 and 7.5 Hz, 1H, CH_3CH(C=)CH_aH$_b$], 2.01 [d, *J* = 1.6 Hz, 3H, COC(C*H*$_3$)=CH], 1.91 [ddqd, *J* = 11.6, 11.6, 6.3, and 1.9 Hz, 1H, COC(CH_3)=CHC*H*], 1.78 [dd, *J* = 14.1 and 2.6 Hz, 1H, CH_3CH(C=)CH_a*H*$_b$], 1.73

[ddd, J = 2.3, 1.1, and 1.1 Hz, 3H, CH_3CH(C=)CH$_a$H$_b$], 1.81-1.65 (m, 2H), 1.47 (ddd, J = 13.8, 9.3, and 2.5 Hz, 1H, CH$_3$CHCH_aH$_b$CHCH$_3$), 1.3-1.1 (m, 5H), 1.19 (d, J =7.5 Hz, 3H, CH_3CHCH$_2$CO), 0.99 (ddd, J = 13.9, 11.5, and 3.8 Hz, 1H, CH$_3$CHCH$_a$$H_b$CHCH$_3$), 0.92 [d, J = 6.4 Hz, 3H, CH_3CHCH=C(CH$_3$)C=O], and 0.84 [d, J = 6.9 Hz, 3H, CH_3CHCH$_2$CH(CH$_3$)C=].

ORTEP rendering for 4008:



Synthesis of chloroketone 4009.



Okilactomycin D ***4009***

To a solution of neutral okilactomycin D (14 mg, 0.04 mmol) in $CHCl_3$ (1.2 mL) was added *t*BuOCl (4.7 mg, 0.044 mmol, 1.1 equiv). The reaction was kept at room temperature for 30 min, and concentrated. Purification by flash chromatography (SiO2, hexanes:EtOAc = 4:1) gave **4009** as a yellow solid.

^{1}H NMR: δ 6.21 (dq, J = 10.4, 1.3 Hz, 1H, *H6*), 5.44 (ddq, J = 5.0, 1.6, 1.6 Hz, *H13*), 2.65-2.56 (m, 1H), 2.45-2.38 (m, 1H), 2.10-2.06 (m, 1H), 2.06 (d, J = 1.3 Hz, 3H, *H17*), 2.00 (ddd, J = 14.1, 6.1, 2.1 Hz, 1H), 1.85 (dd, J = 14.2, 10.9 Hz, 1H), 1.71 (ddd, J = 1.4, 1.4, and 1.4 Hz, 3H, *H20*), 1.65–1.56 (m, 1H), 1.54–1.47 (m, 1H), 1.35–1.10 (m, 5H), 1.08 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), and 0.80 (d, J = 6.4 Hz, 3H).

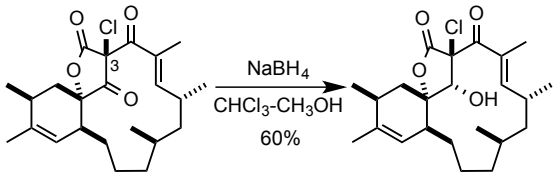
^{13}C NMR: δ 199.4, 184.1, 164.5, 154.2, 137.7, 134.0, 120.3, 93.3, 68.2, 44.3, 43.4, 35.8, 35.6, 33.6, 30.5, 30.0, 28.3, 22.4, 22.0, 21.3, 20.6, 18.8, and 13.8.

IR: 2957, 2919, 2869, 1817, 1764, 1689, 1604, 1456, 1223, 1182, 1032, and 989.

HRMS (ESI-TOF): Calcd for $C_{24}H_{35}ClNaO_5^+$ $[M+CH_3OH+Na]^+$ requires 461.2065; found 461.2059.

Mp: 152-155 °C.

Synthesis of chloroalcohol 4010.



4009 ***4010***

A solution of **4009** (116 mg, 0.28 mmol) in MeOH (4.5 mL) and $CHCl_3$ (6 mL) was cooled at -42 °C. $NaBH_4$ (10 mg, 0.28 mmol) was added to the solution in one portion. The resulting mixture was left at this temperature for 120 seconds, and then quenched by addition of 1M HCl. The resulting mixture was partitioned between EtOAc and H_2O, with the aqueous layer being washed with additional portions of EtOAc. The combined organic layers were washed with brine, dried, and concentrated. The residue was subjected to flash chromatography (SiO_2, Hexanes:EtOAc = 12:1, then 3:1) to give **4010** as a colorless solid (70 mg) following recovered **4009**.

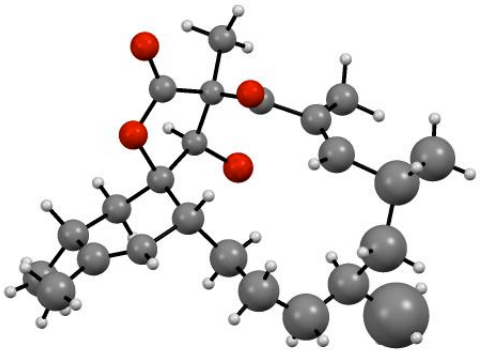
^{1}H NMR: δ 6.33 (br d, *J* = 10.3 Hz, 1H, *H6*), 5.34 (br d, *J* = 4.5 Hz, 1H, *H13*), 4.69 (d, *J* = 3.0 Hz, 1H, C*H*OH), 3.61 (br d, *J* = 4.0 Hz, 1H, CHO*H*), 2.59-2.42 (m, 3H), 2.14 (s, 3H), 1.99 (dd, *J* = 13.9, 8.3 Hz, 1H), 1.99 (dd, *J* = 13.8, 7.1 Hz, 1H), 1.67 (br s, 3H, *H17*), 1.58–1.48 (m, 1H), 1.40–1.35 (m, 1H), 1.30–1.22 (m, 5H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), and 0.94 (d, *J* = 5.8 Hz, 3H).

^{13}C NMR: δ 192.6, 169.1, 152.9, 136.6, 135.7, 123.7, 88.5, 86.4, 72.8, 44.2, 43.3, 40.3, 36.7, 33.9, 32.5, 31.1, 29.1, 24.4, 23.5, 21.1, 20.8, 19.8, and 14.9.

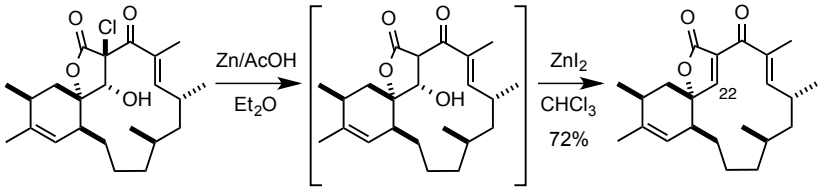
IR: 3433, 2956, 2924, 2869, 1796, 1772, 1667, 1605, 1456, 1439, 1247, 1208, 1185, 1091, and 968.

HRMS (ESI-TOF): Calcd for $C_{23}H_{33}ClNaO_4^+$ $[M+Na]^+$ requires 431.1960; found 431.1973.

ORTEP rendering for 4010:



Synthesis of dienone 4012.



4010 *4011* *4012*

To a solution of **4010** (25 mg, 0.07 mmol) in Et_2O (0.7 mL) was added Zn dust (75 mg, 1.15 mmol) and AcOH (0.6 mL). The resulting slurry was vigorously stirred for 2 h, and filtered through celite. Two procedures could be used to generate **4012**.

1) The filtrate (mostly **4011**) is concentrated and the residue redissolved in $CHCl_3$. The solution was heated at 60 °C to yield **4012** at a rate with $t_{1/2}$ = 40 min.

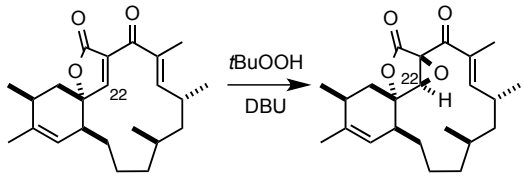
2) The filtrate was washed with satd. $NaHCO_3$, brine, dried, and concentrated. The residue was purified by flash chromatography to give **4011**. ZnI_2 (7 mg, 0.02 mmol) was added to a solution of **4011** (40 mg, 0.12 mmol) in $CHCl_3$ (4 mL) heated at 60 °C. The reaction was stirred at this temperature for 30 min, and concentrated. Purification by flash chromatography (SiO_2, hexanes:EtOAc = 3:1) gave **4012** as a colorless solid (ca. 35 mg).

^{1}H NMR: δ 7.61 (s, 1H, C22*H*), 6.32 (dq, *J* = 10.3, 1.3 Hz, 1H, *H6*), 5.40 (ddq, *J* = 4.5, 1.5, 1.5 Hz, 1H, *H13*), 2.49 (dddq, *J* = 7.3, 7.3, 7.3 and 7.3 Hz, 1H, O=CC=CHC*H*), 2.47-2.40 (m, 1H), 2.16-2.11 (m, 1H), 1.88 [d, *J* = 1.2 H, 3H, O=CC(CH_3)=], 1.60 (dd, *J* = 13.6, 9.4 Hz, 1H), 1.45-1.25 (m, 6H), 1.25-1.15 (m, 1H), 1.06 (d, *J* = 7.2 Hz, 3H, CH_3CHCH$_2$C-O), 1.01 (d, *J* = 6.9 Hz, 3H, CH_3CHCH=CC=O), and 0.91 [d, *J* = 6.5 Hz, 3H, CH_3CHCH$_2$CH(CH$_3$).

^{13}C NMR: δ 191.7, 168.3, 161.7, 156.6, 138.9, 136.8, 133.1, 123.7, 88.7, 45.9, 45.3, 36.9, 36.3, 33.2, 32.8, 31.4, 31.0, 25.8, 21.6, 21.3, 19.9, 19.3, and 11.6.

IR: 2955, 2925, 2870, 1763, 1659, 1635, 1455, 1336, 1217, 1090, and 1072.

HRMS (ESI-TOF): Calcd for $C_{23}H_{32}NaO_3^+$ [M+Na]$^+$ requires 379.2244; found 379.2270.



4012 ***4013***

To a solution of **4012** (32 mg, 0.1 mmol) in DCM (2.4 mL) cooled at 0 °C was added tBuOOH (3.96 M in toluene, 0.033 mL, 0.13 mmol, 1.3 equiv) and DBU (13 mg, 0.1 mmol, 1 equiv). The reaction was kept at this temperature for 1 h and concentrated. Purification by flash chromatography (SiO_2, hexanes:EtOAc = 3:1) gave **4013** as a colorless solid (30 mg).

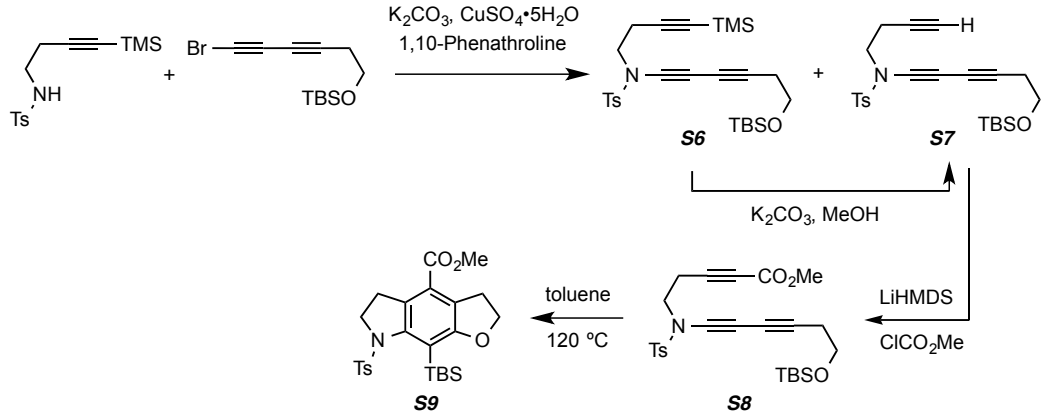
^{1}H NMR: δ 6.49 (dq, *J* = 9.0, 1.2 Hz, 1H, *H6*), 5.27 (m, 1H, *H13*), 4.04 (s, 1H, C22*H*), 2.73-2.63 (m, 1H), 2.36-2.29 (m, 2H), 2.10 (dd, *J* = 13.4, 6.7 Hz, 1H), 1.86 [br s, *J* = 1.2 H, 3H, O=CC(CH_3)=], 1.80 (dd, *J* = 13.5, 5.3 Hz, 1H), 1.72 (br s, 3H, C20CH_3), 1.65-1.50 (m, 2H), 1.40-1.30 (m, 3H), 1.25-1.20 (m, 2H), 1.15 (d, *J* = 7.3 Hz, 3H, CH_3CHCH$_2$C-O), 1.08 (d, *J* = 6.8 Hz, 3H, CH_3CHCH=CC=O), and 0.89 [d, *J* = 5.8 Hz, 3H, CH_3CHCH$_2$CH(CH$_3$).

^{13}C NMR: δ 187.0, 168.9, 155.9, 138.6, 136.2, 121.2, 87.0, 65.2, 63.3, 43.5, 42.7, 35.6, 35.1, 33.1, 32.7, 28.5, 28.2, 23.2, 21.5, 21.2, 20.0, 19.8, and 11.7.

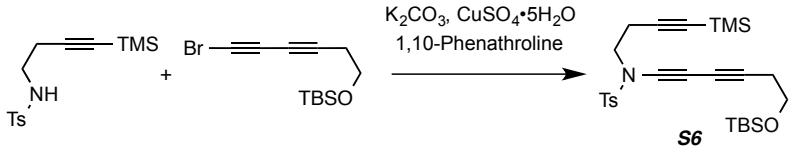
IR: 2948, 2919, 1762, 1683, and 1270.

HRMS (ESI-TOF): Calcd for $C_{23}H_{32}NaO_4^+$ [M+Na]$^+$ requires 395.2193; found 395.2204.

Synthesis of indoline S6 (Scheme 6.3**, entry** 5**)**



***N*-(6-((*tert*-Butyldimethylsilyl)oxy)hexa-1,3-diyn-1-yl)-4-methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide (S6)**



A solution of 4-methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide[162] (200 mg, 0.680 mmol), ((6-bromohexa-3,5-diyn-1-yl)oxy)(tert-butyl)dimethylsilane (230 mg, 0.8 mmol), K_2CO_3 (190 mg, 1.4 mmol), $CuSO_4{\cdot}5H_2O$ (17 mg, 0.068 mmol), and 1,10-phenanthroline (22 mg, 0.14 mmol) in anhydrous toluene (1 mL) was heated to 65 ºC. After 16 h the reaction mixture was directly subjected to gradient flash chromatography (hexanes:EtOAc 12:1 to 5:1) to yield, in order of elution, the triynes **S6** (210 mg, 0.420 mmol, 62%) and **S7** (19 mg, 6%, 0.0378), each as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H, SO_2ArH_o), 7.36 (d, J = 8.2 Hz, 2H, SO_2ArH_m), 3.74 (t, J = 7.1 Hz, 2H, OCH_2), 3.49 (d, J = 7.7 Hz, 2H, NCH_2), 2.54 (t, J = 7.9 Hz, 2H, NCH_2CH_2), 2.52 (t, J = 7.1 Hz, 2H, OCH_2CH_2), 2.46 (s, 3H, $ArCH_3$), 0.90 [s, 9H, $SiC(CH_3)_3$], 0.13 [s, 9H, $Si(CH_3)_3$], and 0.08 [s, 6H, $Si(CH_3)_2C$].

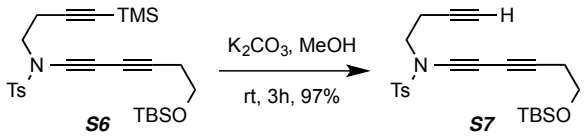
[162] Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. A regioselective Ru-catalyzed alkene−alkyne coupling. *Org. Lett.* **2000**, *2*, 1761–1764.

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 134.8, 130.1, 127.7, 101.7, 87.6, 81.4, 67.2, 65.6, 61.6, 59.0, 50.4, 26.0, 24.1, 21.8, 20.0, 18.5, 0.1, and -5.2.

IR (neat): 2955, 2930, 2857, 2253, 2228, 2179, 1598, 1469, 1376, 1252, 1172, 1105, and 842 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{39}NNaO_3SSi_2^+$ [M+Na^+] requires 524.2081; found 524.2088.

_N_-(But-3-yn-1-yl)-_N_-(6-((_tert_-butyldimethylsilyl)oxy)hexa-1,3-diyn-1-yl)-4-methylbenzenesulfonamide (S7)



K_2CO_3 (62 mg, 0.44 mmol) was added to a stirred solution of **S6** (112 mg, 0.22 mmol) in MeOH (8 mL) at room temperature. After 3 h the reaction mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 5:1) to yield **S7** (90 mg, 97%) as pale yellow oil.

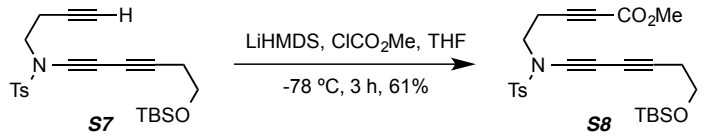
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H_o}$), 7.36 (d, J = 8.1 Hz, 2H, $SO_2Ar\mathit{H_m}$), 3.74 (t, J = 7.1 Hz, 2H, $OC\mathit{H_2}$), 3.50 (t, J = 7.5 Hz, 2H, $NC\mathit{H_2}$), 2.52 (t, J = 7.0 Hz, 2H, $OCH_2C\mathit{H_2}$), 2.51 (td, J = 7.4, 2.7 Hz, 2H, $NCH_2C\mathit{H_2}$), 2.46 (s, 3H, $ArC\mathit{H_3}$), 1.97 (t, J = 2.6 Hz, 1H, C≡CH), 0.90 [s, 9H, $SiC(C\mathit{H_3})_3$], and 0.08 [s, 6H, $Si(C\mathit{H_3})_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 134.6, 130.1, 127.8, 81.5, 79.5, 70.9, 66.9, 65.5, 61.6, 59.2, 50.2, 26.0, 24.1, 21.8, 18.54, 18.47, and -5.1.

IR (neat): 3297, 2953, 2930, 2857, 2360, 2340, 2254, 2166, 1597, 1468, 1373, 1255, 1171, 1092, 903, and 839 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{31}NNaO_3SSi^+$ [M+Na^+] requires 452.1686; found 452.1687.

Methyl 5-(_N_-(6-((_tert_-Butyldimethylsilyl)oxy)hexa-1,3-diyn-1-yl)-4-methylphenylsulfonamido)pent-2-ynoate (S8)



LiHMDS [0.15 mL, ca. 1.0 M in THF, 0.15 mmol, prepared by addition of *n*-BuLi (2.0 mL, 2.5 M in hexanes, 5.0 mmol) to a stirred solution of HMDS (1.0 mL, 4.8 mmol) in THF (2 mL) at -78 ºC] was added to a stirred solution of **S7** (43 mg, 0.10 mmol) in THF (1 mL) at -78 ºC. After 1 h methyl chloroformate was added at the same temperature. After an additional 2 h the reaction mixture was quenched with satd. aq. NH_4Cl, diluted with H_2O, and washed with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexanes:EtOAc 5:1) gave the ynoate **S8** (30 mg, 61%) as a pale yellow oil and recovered starting material **S7** (11 mg, 26%).

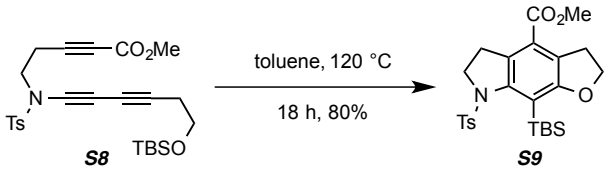
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H_o}$), 7.37 (d, J = 8.1 Hz, 2H, $SO_2Ar\mathit{H_m}$), 3.76 (s, 3H, $CO_2\mathit{Me}$), 3.74 (t, J = 7.1 Hz, 2H, $OC\mathit{H_2}$), 3.55 (t, J = 7.5 Hz, 2H, $NC\mathit{H_2}$), 2.67 (t, J = 7.9 Hz, 2H, $NCH_2C\mathit{H_2}$), 2.53 (t, J = 7.0 Hz, 2H, $OCH_2C\mathit{H_2}$), 2.46 (s, 3H, $Ar\mathit{CH_3}$), 0.90 [s, 9H, $SiC(C\mathit{H_3})_3$], and 0.08 [s, 6H, $Si(C\mathit{H_3})_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 145.5, 134.4, 130.2, 127.8, 84.1, 81.8, 74.7, 66.5, 65.4, 61.6, 59.6, 52.9, 49.2, 26.0, 24.1, 21.9, 18.8, 18.5, and -5.1.

IR (neat): 2953, 2930, 2857, 2247, 2166, 1717, 1597, 1463, 1435, 1373, 1256, 1171, 1090, and 839 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{33}NNaO_5SSi^+$ [$M+Na^+$] requires 510.1741; found 510.1779.

Methyl 8-(*tert*-Butyldimethylsilyl)-7-toluenesulfonyl -3,5,6,7-tetrahydro-2*H*-furo[3,2-f]indole-4-carboxylate (S9, entry 5, Scheme 6.3)



S8 ***S9***

A solution of **S8** (15 mg, 0.031 mmol) in toluene (3 mL) in a sealed vial was heated to 120 ºC (external bath temperature) in a sealed tube. After 18 h the reaction mixture was cooled and concentrated. Purification by flash chromatography (hexanes:EtOAc 5:1) gave the tricycle **S9** (12 mg, 0.025, 80%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.12 (d, J = 8.6 Hz, 2H, $SO_2Ar\mathit{H}_m$), 4.64 (ddd, J = 8.9, 8.9, 7.9 Hz, 1H, $OC\mathit{H}_aH_b$), 4.53 (ddd, J = 9.7, 8.7, 8.7 Hz, 1H, $OCH_a\mathit{H}_b$), 4.02 (ddd, J = 13.1, 8.0, 1.1 Hz, 1H, $NC\mathit{H}_aH_b$), 3.77 (s, 3H, $CO_2\mathit{Me}$), 3.71 (ddd, J = 13.2, 11.8, 8.5 Hz, 1H, $NCH_a\mathit{H}_b$), 3.46 (br t, J = 9 Hz, 2H, $OCH_2C\mathit{H}_2$), 2.60 (ddd, J = 16.9, 8.5, 1.0 Hz, 1H, $NCH_2C\mathit{H}_aH_b$), 2.37 (s, 3H, Ar*Me*), 1.74 (ddd, J = 16.9, 11.8, 8.0 Hz, 1H, $NCH_2CH_a\mathit{H}_b$), 0.95 [s, 9H, $SiC(C\mathit{H}_3)_3$], 0.54 (s, 3H, $SiC\mathit{H}_3$), and 0.41 (s, 3H, $SiC\mathit{H}_3$).

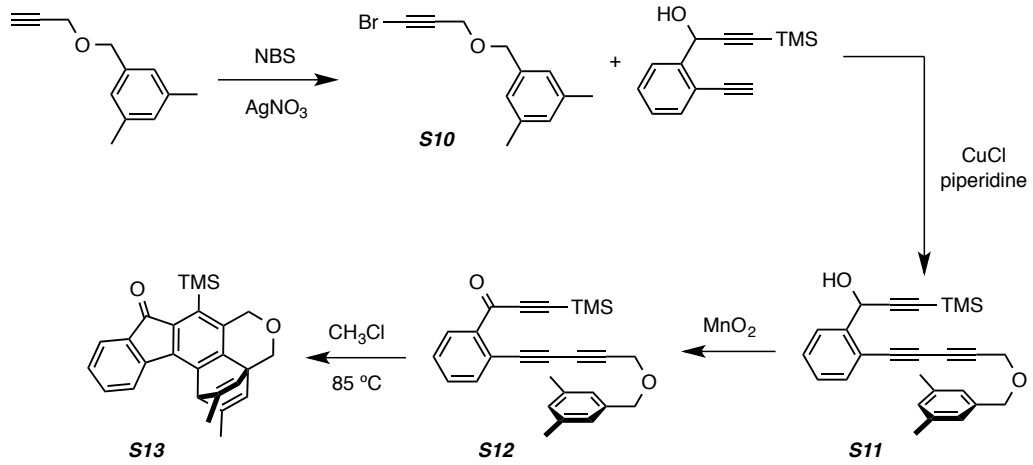
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 166.1, 148.8, 144.1, 134.1, 131.0, 129.4, 128.2, 126.5, 123.0, 120.5, 70.9, 51.8, 51.7, 31.3, 29.1, 28.6, 21.7, 18.1, -0.9, and -1.9.

IR (neat): 2952, 2928, 2896, 2854, 1718, 1597, 1564, 1456, 1385, 1252, 1163, 1089, 1065, 1049, 1011, and 739 cm^{-1}.

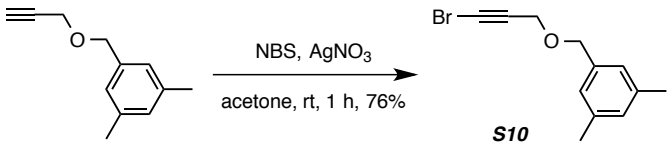
HRMS (ESI-TOF): Calcd for $C_{25}H_{33}NO_5SSi^+$ [$M+H^+$] requires 488.1921; found 488.1953.

mp: 144-147 ºC.

Synthesis of fluorenone (Scheme 6.3, entry 9)



1-(((3-Bromoprop-2-yn-1-yl)oxy)methyl)-3,5-dimethylbenzene (S10)



Bromoalkyne **S10** was prepared by treating 1,3-dimethyl-5-((prop-2-yn-1-yloxy)methyl)benzene (150 mg, 0.86 mmol) with *N*-bromosuccinimide (NBS, 170 mg, 0.96 mmol) and $AgNO_3$ (17 mg, 0.10 mmol) in acetone (10 mL). Purification by flash chromatography (hexanes:EtOAc 12:1) gave bromoalkyne **S29** (166 mg, 0.66 mmol, 76%) as a pale yellow oil.

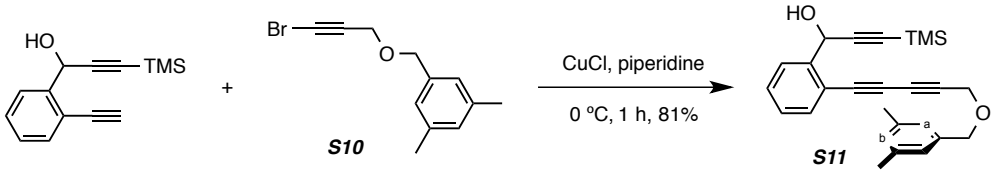
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (br s, 2H, Ar*H2,H6*), 6.94 (br s, 1H, Ar*H4*), 4.52 (s, 2H, OCH_2C≡C), 4.19 (t, J = 0.8 Hz, 2H, ArCH_2), and 2.31 [br s, 6H, Ar(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 137.2, 129.7, 126.1, 76.5, 72.0, 58.2, 46.1, and 21.4.

IR (neat): 3015, 2918, 2854, 2213, 1608, 1463, 1380, 1351, 1160, 1088, 1036, and 844 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{12}H_{13}NaOBr^+$ [M+Na^+] requires 275.0042; found 275.0066.

1-(2-(5-((3,5-Dimethylbenzyl)oxy)penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (S11)



Triyne **S11** was prepared by stirring 1-(2-ethynylphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol[163] (82 mg, 0.36 mmol), bromoalkyne **S10** (95 mg, 0.38 mmol), and CuCl (4 mg, 0.04 mmol) in dearated piperidine (1 mL) for 1 hour at 0 °C. Purification by gradient flash chromatography (hexanes:EtOAc 12:1 to 8:1) gave the triyne **S11** (117 mg, 0.29 mmol, 81%) as a clear yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 7.8, 1.5 Hz, 1H, *H3*), 7.53 (dd, *J* = 7.7, 1.5 Hz, 1H, *H6*), 7.42 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H, *H5*), 7.30 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, *H4*), 6.99 (br s, 2H, ArH_a), 6.95 (br s, 1H, ArH_b), 5.83 (d, *J* = 5.7 Hz, 1H, ArC*H*), 4.57 (br s, 2H, OCH_2C≡C), 4.33 (br s, 2H, ArCH_2), 2.42 (d, *J* = 5.7 Hz, 1H, O*H*), 2.33 [br s, 6H, Ar(CH_3)$_2$], and 0.20 (s, 9H, SiCH_3).

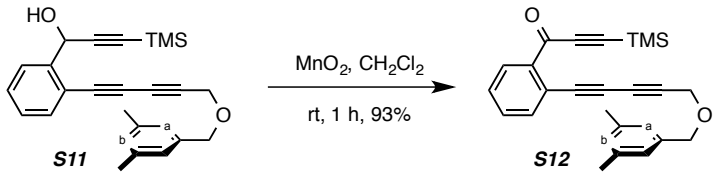
^{13}C NMR (125 MHz, $CDCl_3$): δ143.7, 138.2, 137.1, 133.9, 130.0, 129.8, 128.5, 127.1, 126.2, 120.2, 104.1, 92.1, 80.6, 78.7, 75.3, 72.1, 71.0, 63.5, 57.9, 21.4, and 0.04.

IR (neat): 3417, 3017, 2957, 2920, 2856, 2237, 2173, 1607, 1450, 1351, 1250, 1085, 1056, 1040, 984, and 845 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{28}NaO_2Si^+$ [M+Na^+] requires 423.1751; found 423.1744.

[163] Suffert, J.; Abraham, E.; Raeppel, S.; Brückner, R. Synthesis of 5-/10-membered ring analogues of the dienediyne core of neocarzinostatine chromophore by palladium(0)-mediated ring-closure reaction. *Liebigs Ann.* **1996**, *1996*, 447–456.

1-(2-(5-((3,5-Dimethylbenzyl)oxy)penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (S12)



MnO_2 (380 mg, 4.37 mmol) was added to a stirred solution of alcohol **S11** (117 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) at room temperature. After 1 h the reaction mixture was filtered through a plug of Celite® (CH_2Cl_2) and concentrated to give the triyne **S12** (108 mg, 0.27 mmol, 93%) as a pale yellow oil.

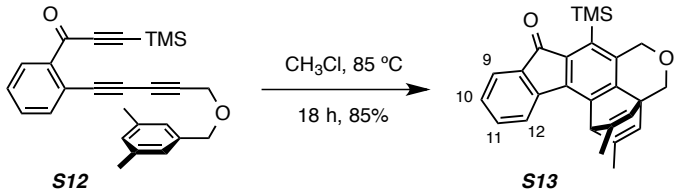
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.6, 1.7 Hz, 1H, *H6*), 7.64 (dd, *J* = 7.7, 1.4 Hz, 1H, *H3*), 7.52 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, *H4*), 7.48 (ddd, *J* = 7.6, 7.6,1.4 Hz, 1H, *H5*), 6.99 (br s, 2H, ArH_a), 6.94 (br s, 1H, ArH_b), 4.56 (br s, 2H, OCH_2C≡C), 4.33 (br s, 2H, ArCH_2O), 2.32 [br s, 6H, Ar(CH_3)$_2$], and 0.31 (s, 9H, SiCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 176.5, 139.2, 138.2, 137.1, 135.9, 132.7, 132.1, 129.8, 129.0, 126.2, 121.5, 101.6, 101.4, 81.2, 79.4, 76.2, 72.1, 71.5, 57.9, 21.4, and 0.6.

IR (neat): 2959, 2918, 2852, 2238, 2152, 1706, 1647, 1607, 1590, 1561, 1480, 1467, 1351, 1236, 1096, 1076, 1014, and 848 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{26}NaO_2Si^+$ [M+Na^+] requires 421.1594; found 421.1599.

(1*r*,3a*r*)-2,14-Dimethyl-7-(trimethylsilyl)-4,6-dihydro-1,3a-ethenobenzo[*de*]indeno[1,2-*g*]isochromen-8(1*H*)-one (S13, Scheme 6.3, entry 9)



A solution of ketone **S12** (20 mg, 0.050 mmol) in $CHCl_3$ (4 mL) was heated to 85 ºC (external bath temperature) in a sealed tube. After 16 h the reaction mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 12:1) to give the

polycyclic ketone **S13** (17 mg, 0.043, 85%) as a bright yellow oil.

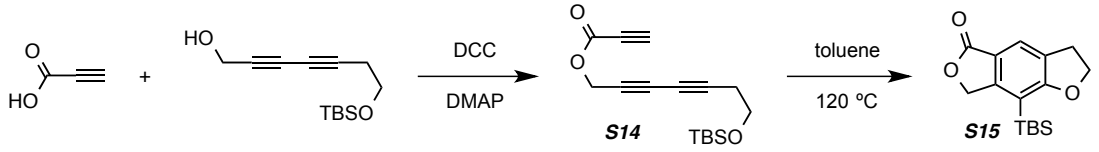
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.5 Hz, 1H, *H9*), 7.63 (d, *J* = 7.0 Hz, 1H, *H12*), 7.51 (dd, *J* = 7.5, 7.5 Hz, 1H, *H11*), 7.28 (dd, *J* = 7.5, 7.5 Hz, 1H, *H10*), 6.16 (br s, 2H, MeC=C*H*), 4.96 (s, 1H, *H*CR_3), 4.79 (br s, 2H, OCH_2C_{Ar}), 4.39 (br s, 2H, OCH_2CR_3), 1.99 (br s, 6H, CCH_3), and 0.36 (s, 9H, SiCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.3, 149.8, 148.8, 144.6, 142.4, 136.3, 136.0, 135.5, 135.1, 135.0, 134.4, 133.7, 128.3, 124.2, 121.8, 71.2, 70.4, 56.2, 51.2, 20.0, and 2.3.

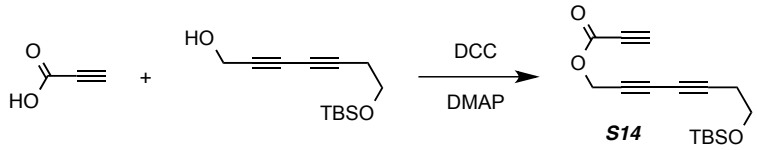
IR (neat): 2950, 2903, 2849, 1705, 1606, 1560, 1466, 1375, 1353, 1205, 1189, 1174, 1122, 1097, 995, and 942 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{26}NaO_2Si^+$ [M+Na^+] requires 421.1594; found 421.1559.

Synthesis of benzodifuranone (Scheme 6.3, entry 10)



7-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl Propiolate (S14)



DCC (110 mg, 0.55 mmol) was added to a stirred solution of propiolic acid (39 mg, 0.55 mmol), alcohol **S14** (119 mg, 0.50 mmol), and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) at 0 ºC. After 2 h the mixture was passed through a plug of Celite® (EtOAc eluent) and concentrated. Purification by flash chromatography (hexanes:EtOAc 12:1) gave the ester **S15** (71 mg, 0.24 mmol, 48%) as a pale yellow oil.

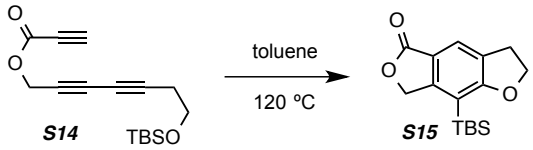
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83 (t, *J* = 1.1 Hz, 2H, CO_2CH_2), 3.74 (t, *J* = 6.9 Hz, 2H, OCH_2), 2.94 (s, 1H, C≡C*H*), 2.50 (tt, *J* = 1.1, 6.9 Hz, 2H, OCH_2CH_2), 0.90 [s, 9H, $SiC(CH_3)_3$] and 0.07 [s, 6H, $Si(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9, 79.9, 76.1, 74.0, 72.7, 68.1, 65.3, 61.3, 54.2, 26.0, 23.9, 18.4, and -5.2.

IR (neat): 3289, 2953, 2931, 2836, 2857, 2262, 2123, 1724, 1470, 1367, 1257, 1206, 1105, and 839cm^{-1}.

HRMS (CIMS): Calcd for $C_{16}H_{22}NaO_3Si^+$ [M+Na$^+$] requires 313.1230; found 313.1252.

8-(*tert*-Butyldimethylsilyl)-2,3-dihydrobenzo[1,2-b:4,5-c']difuran-5(7*H*)-one (S15, entry 10, Scheme 6.3)



A solution of triyne **S14** (29 mg, 0.10 mmol) in toluene (4 mL) was heated to 120 ºC (external bath temperature) in a sealed tube. After 48 h the reaction mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 4:1) gave the tricycle **S15** (25 mg, 0.086, 86%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (t, *J* = 1.4 Hz, 1H, Ar*H*), 5.20 (s, 2H, ArCH_2O), 4.64 (t, *J* = 8.7 Hz, 2H, ArCH$_2$CH_2), 3.25 (dt, *J* = 8.7, 1.2 Hz, 2H, ArCH_2CH$_2$), 0.89 [s, 9H, SiC(CH_3)$_3$], and 0.33 [s, 6H, Si(CH_3)$_2$].

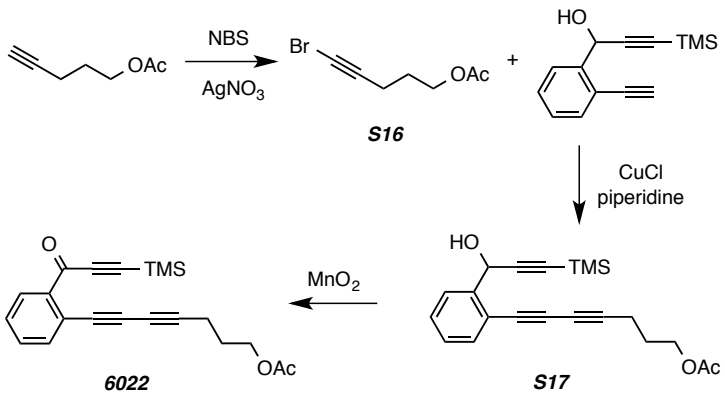
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 171.4, 155.3, 128.7, 123.2, 117.9, 111.4, 71.9, 71.2, 28.7, 26.7, 18.6, and 3.8.

IR (neat): 2949, 2927, 2902, 2855, 1747, 1589, 1459, 1400, 1360, 1325, 1259, 1099, 1023, 1013, 881, and 839 cm^{-1}.

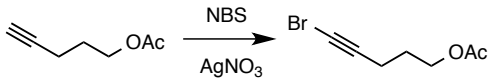
HRMS (CIMS): Calcd for $C_{16}H_{22}NaO_3Si^+$ [M+Na$^+$] requires 313.1230; found 313.1237.

mp: 167–169 ºC.

Synthesis of triyne 6022



5-Bromopent-4-yn-1-yl Acetate (S16)



S16

5-Bromopent-4-yn-1-yl acetate was prepared by treating pent-4-yn-1-yl acetate[164] (780 mg, 6.19 mmol) with *N*-bromosuccinimide (NBS, 1.24 g, 6.97 mmol) and $AgNO_3$ (108 mg, 0.64 mmol) in acetone (40 mL) at rt for 2 hours. Purification by flash chromatography (hexanes:EtOAc 12:1) gave the bromoalkyne (1.30 g, 6.34 mmol, 91%) **S16** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.15 (t, J = 6.3 Hz, 2H, AcOCH_2), 2.32 (t, J = 7.0 Hz, 2H, C≡CCH_2), 2.06 (s, 3H, CH_3CO), and 1.85 (tt, J = 7.0, 6.3 Hz, 2H, CH_2CH$_2$O).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 79.0, 63.1, 38.8, 27.5, 21.0, and 16.7.

IR (neat): 2961, 2340, 1738, 1434, 1367, 1240, and 1044 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_7H_9AgBrO_2^+$ [M+Ag$^+$] requires 310.8831; found 310.8811.

7-(2-(1-Hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)hepta-4,6-diyn-1-yl Acetate (S17)

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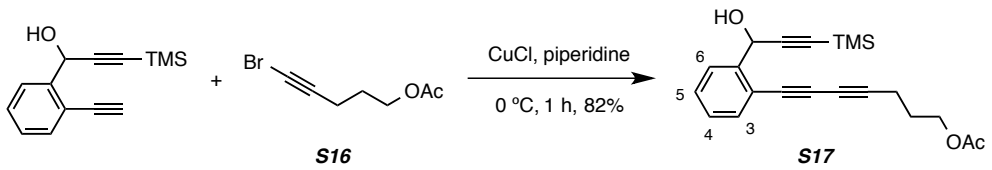
[164] White, J. D.; Kim, T.-S.; Nambu, M. Absolute configuration and total synthesis of (+)-curacin A, an antiproliferative agent from the cyanobacterium *Lyngbya majuscule*. *J. Am. Chem. Soc.* **1997**, *119*, 103–111.



S16 ***S17***

Triyne **S17** was prepared by stirring 1-(2-ethynylphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol[163] (200 mg, 0.88 mmol), bromoalkyne **S16** (200 mg, 0.98 mmol), and CuCl (8 mg, 0.08 mmol), in dearated piperidine (2.5 mL) at 0 °C for 1 hour. Purification by flash chromatography (hexanes:EtOAc 5:1) gave the triyne **S17** (255 mg, 0.72 mmol, 82%) as a pale yellow oil. This compound is contaminated with ca. 15% bromoalkyne **S16** (^{1}H NMR), which can be removed chromatographically in the subsequent step.

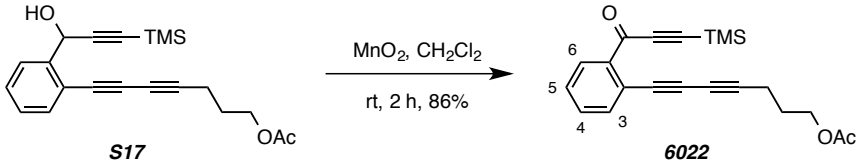
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar*H6*), 7.50 (dd, *J* = 7.7, 1.0 Hz, 1H, Ar*H3*), 7.40 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H, Ar*H4/H5*), 7.29 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, Ar*H4/H5*), 5.82 (d, *J* = 5.7 Hz, 1H, ArC*H*), 4.19 (t, *J* = 6.2 Hz, 2H, AcOCH_2), 2.51 (d, *J* = 5.8 Hz, 1H, O*H*), 2.49 (t, *J* = 7.3 Hz, 2H, C≡CCH_2), 2.08 (s, 3H, CH_3CO), 1.92 (tt, *J* = 7.0, 6.2 Hz, 2H, AcOCH$_2$CH_2), and 0.20 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 143.5, 133.7, 129.6, 128.5, 127.1, 120.7, 104.2, 91.9, 84.6, 79.4, 72.3, 65.8, 63.5, 63.0, 27.4, 21.0, 16.7, and 0.05.

IR (neat): 3450, 2960, 2899, 2362, 2239, 2172, 1738, 1480, 1448, 1425, 1390, 1367, 1247, 1041, 984, 955, and 848 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{21}H_{24}NaO_3Si^+$ [M+Na$^+$] requires 375.1392; found 375.1389.

7-(2-(3-(Trimethylsilyl)propioloyl)phenyl)hepta-4,6-diyn-1-yl Acetate (6022)



S17 ***6022***

MnO_2 (400 mg, 4.60 mmol) was added to a stirred solution of triyne **S17** (105 mg, 0.298 mmol) in CH_2Cl_2 (3 mL) at room temperature. After 2 h the reaction mixture was filtered through a plug of Celite® (CH_2Cl_2 eluent) and concentrated. Purification by flash chromatography (hexanes:EtOAc 12:1) gave the ketone **6022** (90 mg, 0.26 mmol, 86%)

as a clear amber oil.

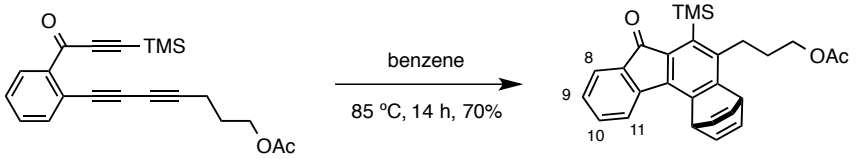
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.7 Hz, 1H, *H6*), 7.60 (d, *J* = 7.6 Hz, 1H, *H3*), 7.50 (dd, *J* = 7.5, 7.5 Hz, *H4*), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1H, *H5*), 4.18 (t, *J* = 6.2 Hz, 2H, AcOCH_2), 2.49 (t, *J* = 7.0 Hz, 2H, ArCH_2), 2.07 (s, 3H, CH_3CO), 1.91 (tt, *J* = 6.6, 6.6 Hz, 2H, $ArCH_2CH_2$), and 0.30 (s, 9H, SiCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 171.1, 139.1, 135.8, 132.6, 132.0, 128.6, 122.0, 101.5, 101.4, 85.4, 80.4, 73.3, 66.4, 63.1, 27.5, 21.1, 16.8, and 0.6.

IR (neat): 2961, 2900, 2240, 2152, 1739, 1648, 1589, 1560, 1479, 1366, 1235, 1044, 1015, 955, and 850 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{21}H_{22}NaO_3Si^+$ [$M+Na^+$] requires 373.1230; found 373.1206.

3-(7-Oxo-6-(trimethylsilyl)-4,7-dihydro-1*H*-1,4-ethenobenzo[*c*]fluoren-5-yl)propyl Acetate (6025a)



6022 ***6025a***

A solution of triyne **6022** (20 mg, 0.057 mmol) in benzene (5.5 mL) was heated at 85 ºC (external bath temperature) in a sealed tube. After 14 h the reaction mixture was concentrated and purified by flash chromatography (12:1) to give fluorenone **6025a** (17 mg, 0.040 mmol, 70%) as a bright yellow oil.

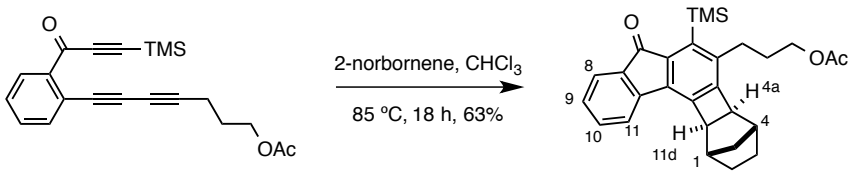
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (ddd, *J* = 7.7, 0.9, 0.9 Hz, 1H, *H8*), 7.60 (ddd, *J* = 7.3, 1.3, 0.7 Hz, 1H, *H11*), 7.49 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, *H10*), 7.25 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H, *H9*), 6.94 (ddd, *J* = 6.5, 6.5, 1.6 Hz, 2H, CH_a=CH_b), 6.88 (ddd, *J* = 6.0, 6.0, 1.6 Hz, 2H, CH_a=CH_b), 5.71 (dddd, *J* = 5.9, 5.9, 1.7, 1.7 Hz, 1H, C^{sp3}*H*CH=CHC^{sp3}H), 5.24 (dddd, *J* = 5.9, 5.9, 1.6, 1.6 Hz, 1H, C^{sp3}HCH=CHC^{sp3}*H*), 4.16 (t, *J* = 6.5 Hz, 2H, AcOCH_2), 3.05-3.01 (br t, *J* = 8.2 Hz, 2H, ArCH_2), 2.12 (s, 3H, CH_3CO), 1.83-1.76 (br tt, Σ_{Js} = 29 Hz, 2H, $ArCH_2CH_2$), and 0.41 (s, 9H, SiCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.5, 171.3, 152.1, 144.3, 143.0, 140.7, 139.1, 138.9, 138.4, 136.8, 135.3, 135.1, 134.2, 128.2, 124.1, 122.3, 64.0, 46.0, 45.2, 32.0, 28.4, 21.2, and 3.2.

IR (neat): 3065, 2951, 2897, 1738, 1705, 1607, 1586, 1550, 1467, 1387, 1365, 1326, 1301, 1244, 1043, and 857 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{28}NaO_3Si^+$ [M+Na^+] requires 451.1700; found 451.1724.

3-((1*R,4*S**,4aR*,11dS*)-7-Oxo-6-(trimethylsilyl)-2,3,4,4a,7,11d-hexahydro-1*H*-1,4-methanobenzo[3,4]cyclobuta[1,2-c]fluoren-5-yl)propyl Acetate (6025b)**



6022 ***6025b***

A solution of triyne **6022** (20 mg, 0.057 mmol) and 2-norbornene (83 mg, 0.88 mmol) in ethanol-free $CHCl_3$ (5 mL) was heated at 85 ºC (external bath temperature) in a sealed tube. After 18 h the reaction mixture was concentrated and purified by flash chromatography (12:1) to give fluorenone **6025b** (16 mg, 0.036 mmol, 63%) as a bright yellow oil, which is assigned as the endo adduct on the basis of comparative spectral data for the known exo and endo adducts of *o*-benzyne and norbornene.[165] No evidence was seen for the formation of a second diastereomer.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H8*), 7.41 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, *H10*), 7.32 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, *H11*), 7.22 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, *H9*), 4.122 (dt, *J* = 11.0, 6.5 Hz, 1H, C*H*$_a$H$_b$OAc), 4.116 (dt, *J* = 11.0, 6.6 Hz, 1H, CH$_a$*H*$_b$OAc) 3.31 [dd, *J* = 4.0, 1.0 Hz, 1H, *H4a* (or H11d)], 3.29 [dd, *J* = 4.0, 1.0 Hz, 1H, *H11d* (or H4a)], 2.71 (br t, *J* = 8.0 Hz, 2H, ArC*H*$_2$), 2.47 (br s, 1H, *H1*), 2.37 (br s, 1H, *H4*), 2.08 (s, 3H, CC*H*$_3$), 1.88-1.72 (m, 2H, AcOCH$_2$C*H*$_2$), 1.72-1.62 (m, 2H), 1.31-1.22 (m, 2H), 1.10 (br s, 2H), and 0.42 (s, 9H, SiC*H*$_3$).

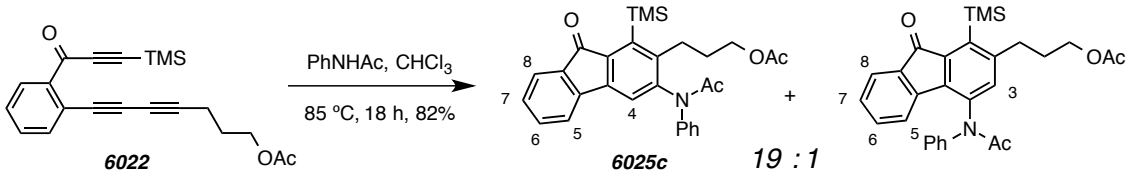
[165] Simmons, H. E. A cycloaddition reaction of benzyne. *J. Am. Chem. Soc.* **1961**, *83*, 1657–1662.

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 171.2, 152.4, 143.1, 142.0, 140.7, 140.4, 140.3, 137.5, 134.6, 134.3, 128.6, 124.0, 121.5, 64.2, 52.1, 48.6, 36.5, 35.9, 32.7, 32.0, 28.0, 27.8, 27.7, 21.1, and 2.7.

IR (neat): 2948, 2872, 1740, 1708, 1605, 1571, 1464, 1386, 1364, 1293, 1237, 1182, 1173, 1079, 1042, 997, 998, 950, and 917 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{28}H_{32}NaO_3Si^+$ [M+Na^+] requires 467.2013; found 467.2027.

3-(9-Oxo-3-(*N*-phenylacetamido)-1-(trimethylsilyl)-9*H*-fluoren-2-yl)propyl Acetate (6025c)



A solution of triyne **6022** (20 mg, 0.057 mmol) and *N*-phenylacetamide (72 mg, 0.53 mmol) in $CHCl_3$ (5 mL) was heated at 85 ºC (external bath temperature) in a sealed tube. After 18 h the reaction mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 5:1) to give the fluorenone **6025c** (23 mg, 0.047 mmol, 82%) as a bright yellow oil. This sample contains ca. 5% of a second component to which we have tentatively assigned as the regioisomer based on resonances in the ^{1}H NMR spectrum of the sample. The regioselectivity was substantiated by nOe analysis of the purified product mixture.

Characterization data for 6025c

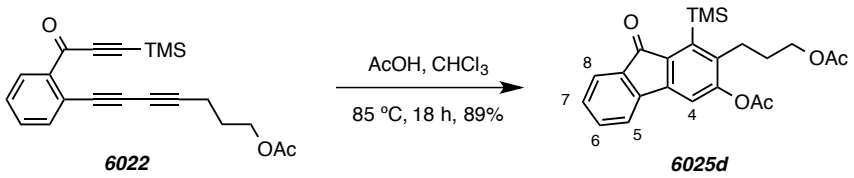
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (ddd, J = 7.3, 1.2, 1.2 Hz, 1H, *H8*), 7.47–7.41 (m, 2H, *H5* and *H6*), 7.35 (s, 1H, *H4*), 7.31–7.21 (m, 3H, PhH_m and *H7*), 7.05 (tt, J = 7.5, 1.3 Hz, 1H, PhH_p), 6.75 (dd, J = 8.4, 1.3 Hz, 2H, PhH_o), 4.17 (t, J = 6.4 Hz, 2H, OCH_2C), 2.86 (br t, J = 8.2 Hz, 2H, ArCH_2), 2.13 (s, 3H, CH_3CON), 2.08 (s, 3H, C$H_3$$CO_2$), 1.96–1.85 (m, Σ$J$s = 29.2 Hz, 2H, $ArCH_2CH_2$), and 0.46 (s, 9H, SiCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 171.2, 161.1, 155.5, 148.1, 145.0, 144.1, 143.4, 140.4, 137.3, 134.5, 134.3, 129.2, 129.1, 123.9, 123.7, 120.8, 119.8, 116.6, 64.5, 31.1, 26.5, 21.2, 16.1, and 2.8.

IR (neat): 2950, 1738, 1711, 1685, 1591, 1487, 1467, 1368, 1295, 1224, 1164, 1120, 1039, and 858 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{29}H_{31}NNaO_4Si^+$ [M+Na^+] requires 508.1915; found 508.1882.

3-(3-Acetoxy-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-2-yl)propyl Acetate (6025d)



6022 ***6025d***

A solution of triyne **6022** (22 mg, 0.062 mmol) and acetic acid (0.2 mL, 3.5 mmol) in $CHCl_3$ (5 mL) was heated at 85 ºC (external bath temperature) in a sealed tube. After 18 h the reaction mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 5:1) to give fluorenone **6025d** (23 mg, 0.056 mmol 89%) as a bright yellow oil. The regioselectivity was substantiated by nOe analysis of the purified product mixture.

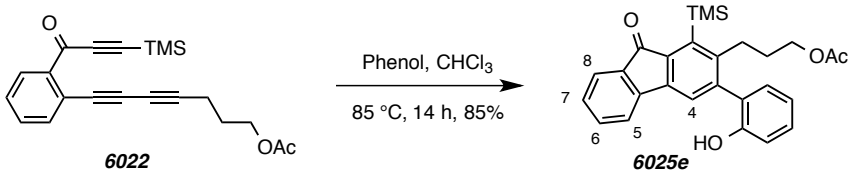
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (ddd, *J* = 7.2, 1.0, 1.0 Hz, 1H, *H8*), 7.46 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, *H6*), 7.41 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, *H5*), 7.28 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, *H7*), 7.22 (s, 1H, *H4*), 4.11 (t, *J* = 6.4 Hz, 2H), 2.78 (m, 2H, ArCH_2), 2.39 (s, 3H, CH_3CO_2Ar), 2.08 (s, 3H, $CH_3CO_2CH_2$), 1.82-1.75 (br tt, ΣJ_s = 29 Hz, 2H, $ArCH_2CH_2$), and 0.46 (s, 9H, $SiCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.3, 171.2, 169.4, 153.2, 145.2, 142.4, 143.1, 140.0, 137.8, 134.7, 134.1, 129.3, 124.1, 119.9, 115.9, 64.2, 31.0, 26.3, 21.18, 21.12, and 2.7.

IR (neat): 2949, 1759, 1739, 1713, 1605, 1591, 1467, 1387, 1366, 1295, 1243, 1201, 1159, 1118, 1039, 995, and 854 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{26}NaO_5Si^+$ [M+Na^+] requires 433.1441; found 433,1436.

3-(3-(2-Hydroxyphenyl)-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-2-yl)propyl Acetate (6025e)



A solution of triyne **6022** (21 mg, 0.06 mmol) and phenol (70 mg, 0.74 mmol) in $CHCl_3$ (5 mL) was heated at 85 ºC (external bath temperature) in a sealed tube. After 14 h the reaction mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 5:1) to give fluorenone **6025e** (23 mg, 0.052, 86%) as a bright yellow oil. The regioselectivity was substantiated by nOe analysis of the purified product mixture.

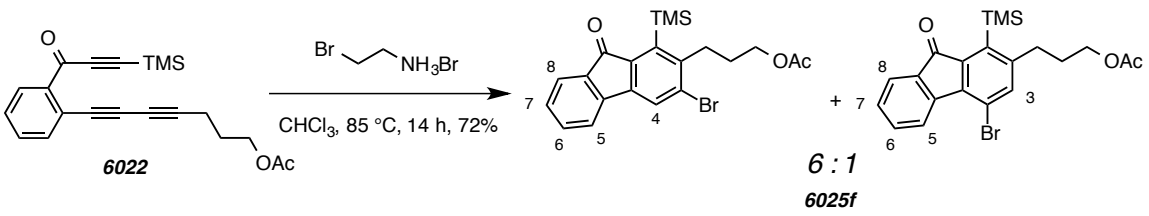
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, *H8*), 7.46 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, *H6*), 7.41 (ddd, *J* = 7.5, 1.0, 1.0 Hz, 1H, *H5*), 7.40 (s, 1H, *H4*), 7.32 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H, *H4'*), 7.28 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H, *H7*), 7.15 (dd, 7.5, 1.7 Hz, 1H, *H6'*), 7.03 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H, *H5'*), 7.01 (dd, *J* = 7.0, 1.3 Hz, 1H, *H3'*), 4.84 (s, 1H, O*H*), 3.83 (dt, *J* = 6.1, 11.0 Hz, 1H, AcOC*H*$_a$Hb), 3.82 (dt, *J* = 6.0, 10.9 Hz, 1H, AcOCH$_a$*Hb*), 2.87 (ddd, *J* = 13.7, 11.1, 5.4 Hz, 1H, ArC*Ha*Hb), 2.65 (ddd, *J* = 13.7, 11.0, 5.5 Hz, 1H, ArCHa*Hb*), 1.87 (s, 3H, C*H*$_3$CO$_2$), 1.70-1.54 (m, 2H, ArCH$_2$C*H*$_2$), and 0.49 (s, 9H, SiC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 171.1, 152.2, 148.5, 143.60, 143.59, 143.4, 142.0, 140.7, 134.8, 134.0, 130.2, 129.7, 129.2, 128.4, 124.2, 123.9, 121.0, 119.8, 115.9, 63.8, 32.1, 29.4, 21.0, and 2.9.

IR (neat): 3440, 2951, 1736, 1710, 1606, 1590, 1541, 1464, 1448, 1386, 1363, 1247, 1185, 1040, and 979 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{28}NaO_4Si^+$ [M+Na$^+$] requires 467.1649; found 467.1647.

3-(3-Bromo-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate and 3-(4-Bromo-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate (6025f)



A solution of triyne **6022** (18 mg, 0.051 mmol) and 2-bromoethylamine hydrobromide (the HBr source, 110 mg, 0.537 mmol) in THF:H_2O (5 mL, 19:1) was heated at 85 ºC (external bath temperature) in a sealed vial. After 18 h the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic extracts were concentrated and purified by flash chromatography (hexanes: EtOAc 12:1) to give a mixture (6:1) of coeluting, regioisomeric fluorenones **6025f** (16 mg, 0.037 mmol, 72%) as a bright yellow oil. These were spectroscopically characterized as a mixture.

Characterization data of major component in 6025f

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H, *H4*), 7.60 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, *H8*), 7.48 (dd, *J* = 7.4, 7.4, 1.1 Hz, 1H, *H6*), 7.44 (d, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H5*), 7.30 (ddd, *J* = 7.3, 7.3, 7.3, 1.1 Hz, *H7*), 4.17 (t, *J* = 6.5 Hz, 2H, AcOCH_2), 3.09 (br t, *J* = 8.3 Hz, 2H, ArCH_2), 2.08 (s, 3H, CH_3CO_2), 1.90-1.80 (m, 2H, $ArCH_2CH_2$), and 0.46 (s, 9H, SiCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 171.19, 147.0, 144.6, 144.2, 142.8, 139.5, 134.8, 134.0, 132.6, 129.5, 126.3, 124.3, 119.9, 64.1, 32.6, 30.6, 21.11, and 3.0

Characterization data of minor component in 6025f

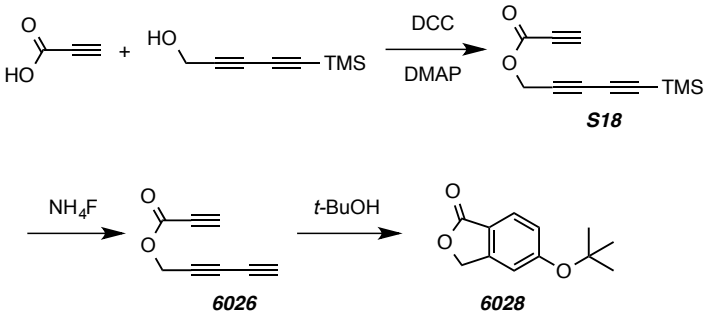
^{1}H NMR of S40 (500 MHz, $CDCl_3$): δ 8.32 (ddd, *J* = 7.7, 0.9, 0.9 Hz, 1H, *H5*), 7.63 (d, *J* = 7.3, 1.2, 0.8 Hz, 1H, *H8*), 7.51 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, *H6*), 7.39 (s, 1H, *H3*), 7.32 (ddd, *J* = 7.5, 7.5, 0.8 Hz, 1H, *H7*), 4.12 (t, *J* = 6.4 Hz, 2H, AcOCH_2), 2.83 (br t, *J* = 8.2 Hz, 2H, ArCH_2), 2.08 (s, 3H, CH_3CO_2), 1.90-1.80 (m, 2H, $ArCH_2CH_2$), and 0.43 (s, 9H, SiCH_3).

^{13}C NMR of S40 (125 MHz, $CDCl_3$): δ 194.2, 171.15, 150.5, 143.4, 143.3, 141.4, 140.3, 134.7, 133.9, 129.2, 124.2, 123.2, 118.8, 63.7, 32.9, 32.1, 21.08, and 2.7 (one aromatic resonance is not detectable).

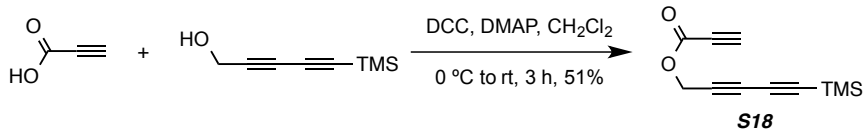
IR (neat): 2951, 1739, 1715, 1606, 1575, 1466, 1386, 1365, 1235, 1187, 1043, 974, 850, and 745 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{21}H_{23}BrNaO_3Si^+$ [M+Na^+] requires 453.0492; found 453.0512.

Synthesis of phthalide 6028



5-(Trimethylsilyl)penta-2,4-diyn-1-yl Propiolate (S18)



The following agents were added in sequence to CH_2Cl_2 (1.5 mL) at 0 ºC: 5-trimethylsilyl-2,4-pentadiyn-1-ol[166] (750 mg, 4.92 mmol), propiolic acid (420 mg, 6.00 mmol), DCC (1.2 g, 5.8 mmol), and DMAP (60 mg, 0.49 mmol). The resulting homogeneous solution quickly became cloudy. After 3 h the resulting slurry was passed through a pad of Celite® (CH_2Cl_2) and concentrated. Purification by flash chromatography (hexanes:EtOAc 12:1) gave the ester **S18** (513 mg, 2.51 mmol, 51%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.84 (s, 2H, CH_2O), 2.95 (s, 1H, *H*C≡C), and 0.20 (s, 9H, CH_3Si).

^{13}C NMR (125 MHz, $CDCl_3$): δ 151.8, 89.2, 86.8, 76.2, 73.9, 72.6, 70.0, 54.0, and –0.4.

IR (neat): 3289, 2961, 2902, 2122, 1723, 1430, 1364, 1252, 1208, 966, 859, and 847 cm^{-1}.

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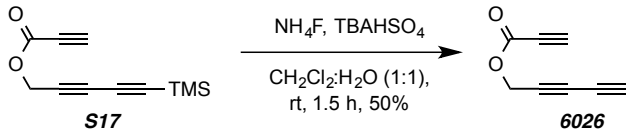
[166] Hoheisel, T. N.; Frauenrath, H. A convenient Negishi protocol for the synthesis of glycosylated oligo(ethynylene)s. *Org. Lett.* **2008**, *10*, 4525–4528.

HRMS (CIMS): Calcd for $C_{11}H_{16}NO_2Si^+$ [M+NH_4^+] requires 222.0945; found 222.0968.

Penta-2,4-diyn-1-yl Propiolate (6026)



Tetra-*n*-butylammonium bisulfate ($TBAHSO_4$, 10 mg, 0.03 mmol) was added to a vigorously stirring solution of silyl alkyne **S17** (220 mg, 1.08 mmol) and NH_4F (2.5 mL, 45 wt. % in water, 30 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 1.5 h the organic phase was separated from the biphasic reaction mixture and concentrated. Purification by flash chromatography (hexanes:EtOAc 12:1) gave the ester 60**26** (72 mg, 0.55 mmol, 50%) as a pale yellow oil.

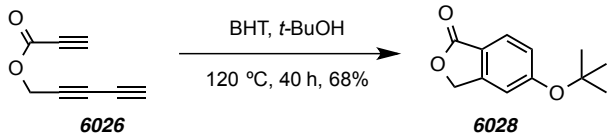
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.84 (d, *J* = 1.0 Hz, 2H, C*H*$_2$O), 2.97 (s, 1H, *H*C≡CC=O), and 2.24 (t, *J* = 1.0 Hz, 1H, *H*C≡CC≡C).

^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7, 76.4, 73.8, 71.9, 69.5, 68.8, 67.1, and 53.7.

IR (neat): 3289, 2123, 1720, 1432, 1367, 1209, and 966 cm^{-1}.

HRMS (CIMS): Calcd for $C_8H_8NO_2^+$ [M+NH_4^+] requires 150.0550; found 150.0564.

5-(*tert*-Butoxy)isobenzofuran-1(3*H*)-one (6028)



A solution of ester **6026** (15 mg, 0.11 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene, BHT, 2 mg, 0.009 mmol) in *t*-BuOH (9 mL) was heated to 120 ºC (external bath temperature) in a sealed tube. After 40 h the resulting solution was concentrated and purified by gradient flash chromatography (hexanes:EtOAc 12:1 to 5:1) to give the ester **6028** (16 mg, 0.078 mmol, 68%) as a clear colorless oil.

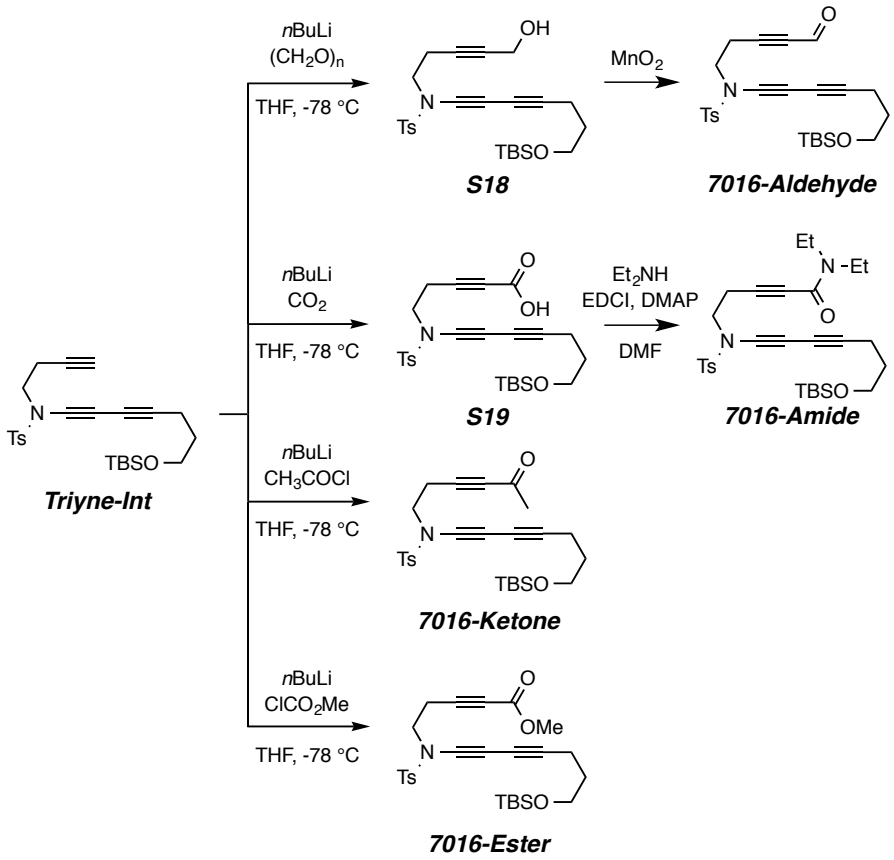
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 0.4, 8.4 Hz, 1H, *H7*), 7.11 (ddt, *J* = 8.4, 2.0, 0.9 Hz, 1H, *H6*), 7.04 (ddt, *J* = 2.0, 0.9, 0.9 Hz, 2H, *H4*), 5.26 (dd, *J* = 0.8, 0.8 Hz, 2H, C*H*$_2$O), and 1.45 [s, 9H, C(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 161.7, 148.6, 126.8, 124.1, 120.0, 115.2, 80.4, 69.2, and 29.0.

IR (neat): 2977, 2937, 2877, 1759, 1612, 1484, 1454, 1369, 1354, 1264, 1168, 1141, 1099, 1045, 1006, and 948 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{12}H_{14}NaO_3$ [$M+Na^+$] requires 229.0835; found 229.0859.

Synthesis of indoline precursors 7016



Indoline precursors that bear different electron-withdrawing groups were synthesized from the common intermediate **Triyne-Int**.

For **7016-Aldehyde**:

*n*BuLi (0.07 mL, 0.175 mmol, 1.5 equiv) was added to a stirred solution of **Triyne-Int** (50 mg, 0.11 mmol) in THF (1 mL) at -78 ºC. After 1 h excess paraformaldehyde was added as solid in one portion at the same temperature. The reaction mixture was warmed up to room temperature overnight, then quenched with satd. aq. NH_4Cl, diluted with H_2O, and washed with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexanes:EtOAc 1:1) gave the ynol **S18** (30 mg, 61%) as a pale yellow oil and recovered starting material **Triyne-Int** (11 mg, 26%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 2H, ArH_oSO$_2$), 7.37 (d, J = 8.1 Hz, 2H, ArH_mSO$_2$), 4.20 (dt, J = 6.0, 2.0 Hz, 2H, CH_2OH), 3.68 (t, J = 5.9 Hz, 2H,

CH_2OTBS), 3.50 (t, J = 7.3 Hz, 2H, NCH_2), 2.56 (tt, J = 7.4, 2.1 Hz, 2H, NCH$_2$CH_2), 2.46 (s, 3H, ArCH_3), 2.40 (t, J = 7.1 Hz, 2H, CCCH_2), 1.73 (tt, J = 7.0, 6.0 Hz, 2H, CH$_2$CH_2CH$_2$), 1.26 (t, J = 7.2 Hz, 1H, OH), 0.90 [s, 9H, C(CH_3)$_3$], and 0.06 [s, 6H, Si(CH_3)$_2$].

To a solution of **S18** (11 mg) in DCM at room temperature was added MnO_2 (70 mg). The mixture was stirred for 3 h, filtered and concentrated. Flash chromatography (SiO_2, hexanes:EtOAc = 5:1) gave **7016-Aldehyde** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 (s, 1H, CHO), 7.80 (d, J = 8.4 Hz, 2H, ArH_oSO$_2$), 7.38 (d, J = 8.0 Hz, 2H, ArH_mSO$_2$), 3.68 (t, J = 5.9 Hz, 2H, CH_2OTBS), 3.58 (t, J = 7.2 Hz, 2H, NCH_2), 2.77 (t, J = 7.4 Hz, 2H, NCH$_2$CH_2), 2.47 (s, 3H, ArCH_3), 2.41 (t, J = 7.1 Hz, 2H, CCCH_2), 1.74 (tt, J = 7.0, 6.1 Hz, 2H, CH$_2$CH_2CH$_2$), 0.90 [s, 9H, C(CH_3)$_3$], and 0.06 [s, 6H, Si(CH_3)$_2$].

For **7016-Amide**:

*n*BuLi (0.07 mL, 0.175 mmol, 1.5 equiv) was added to a stirred solution of **Triyne-Int** (50 mg, 0.11 mmol) in THF (1 mL) at -78 ºC. After 1 h excess CO_2 (gas) was bubbled through the reaction solution at the same temperature. Without further purification, the reaction mixture was concentrated to give the carboxylate.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.2 Hz, 2H, ArH_oSO$_2$), 7.33 (d, J = 8.3 Hz, 2H, ArH_mSO$_2$), 3.64 (t, J = 5.9 Hz, 2H, CH_2OTBS), 3.46 (br t, J = 5 Hz, 2H, NCH_2), 2.51 (br t, J = 5 Hz, 2H, NCH$_2$CH_2), 2.41 (s, 3H, ArCH_3), 2.36 (t, J = 7.1 Hz, 2H, CCCH_2), 1.69 (tt, J = 6.7, 6.7 Hz, 2H, CH$_2$CH_2CH$_2$), 0.88 [s, 9H, C(CH_3)$_3$], and 0.04 [s, 6H, Si(CH_3)$_2$].

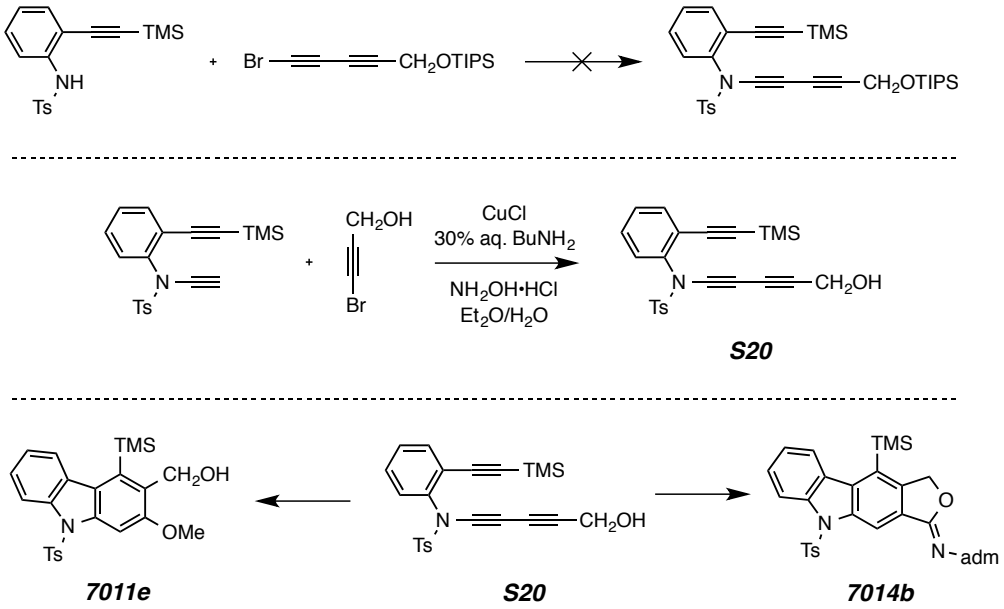
EDCI and DMAP were added to a DMF solution of Et_2NH (1.1 equiv) and **S19** obtained from the previous step. The reaction was worked up as usual. Flash chromatography (SiO_2, hexanes:EtOAc = 5:1) gave **7016-Amide** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H, ArH_oSO$_2$), 7.37 (d, J = 8.5 Hz, 2H, ArH_mSO$_2$), 3.68 (t, J = 5.9 Hz, 2H, CH_2OTBS), 3.57 (q, J = 7.2 Hz, 2H, NCH_{2a}CH$_{3a}$), 3.52 (t, J = 7.4 Hz, 2H), 3.40 (q, J = 7.2 Hz, 2H, NCH_{2b}CH$_{3b}$), 2.72 (t, J = 7.4 Hz, 2H), 2.46 (s, 3H, ArCH_3), 2.40 (t, J = 7.1 Hz, 2H, CCCH_2), 1.73 (tt, J = 7.1,

6.1 Hz, 2H, $CH_2CH_2CH_2$), 1.21 (q, J = 7.1 Hz, 3H, $NCH_{2a}CH_{3a}$), 1.13 (q, J = 7.1 Hz, 3H, $NCH_{2b}CH_{3b}$), 0.89 [s, 9H, $C(CH_3)_3$], and 0.06 [s, 6H, $Si(CH_3)_2$].

7016-Ketone and **7016-Ester** were prepared using protocols similar to that used in the synthesis of **S8**, from acetyl chloride and methyl chloroformate, respectively.

Synthesis of carbazoles using HDDA reaction



Hsung's ynamide synthesis method was successful in prepare indoline precursors, but not effective in making carbazole precursors like **S20**. Instead, **S20** was prepared following General Procedure C from the known *N*-ethynyl-4-methyl-*N*-(2-((trimethylsilyl)ethynyl)phenyl)benzenesulfonamide (160 mg, 0.44 mmol), bromopropargyl alcohol (1.5 equiv, 0.66 mmol), 30% aq. $BuNH_2$ (2 mL), CuCl (10 mg), and Et_2O (2 mL). **S20** was obtained following flash chromatography as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.3 Hz, 2H, ArH_oSO_2), 7.48-7.45 (m, 1H, Ar*H*), 7.35-7.28 (m, 5H, ArH_mSO_2 and Ar*H*), 4.35 (s, 2H, CH_2OH), 2.45 (s, 3H, $ArCH_3$), and 0.16 [s, 9H, $Si(CH_3)_3$].

A solution of **S20** and MeOH or admantyl isocyanide in $CDCl_3$ was heated at 80 °C for 18 h. The resulting solution was concentrated and purified with flash chromatography to give **7011e** or **7014b** as light yellow oil.

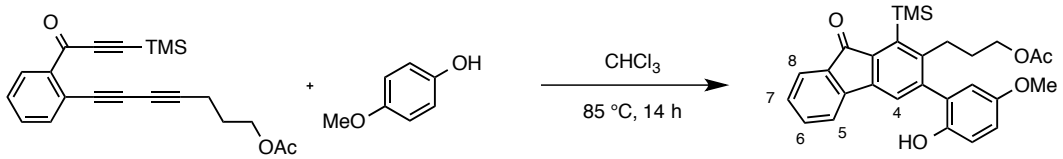
Chracterization data for **7011e**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.3 Hz, 1H), 8.03 (s, 1H, Ar*H*), 7.95 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H, Ar$H_o$$SO_2$), 7.38 (ddd, *J* = 8.4, 7.3, 1.1 Hz, 1H), 7.33-7.28 (m overlapping with **S20**), 7.12 (d, *J* = 8.4 Hz, 2H, Ar$H_m$$SO_2$), 4.85 (s, 2H, C$H_2$O), 4.04 (s, 3H, C$H_3$O), 2.29 (s, 3H, ArC$H_3$), and 0.54 [s, 9H, Si(C$H_3$)$_3$].

Chracterization data for **7014d**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, <1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H, Ar$H_o$$SO_2$), 7.51 (ddd, *J* = 8.4, 7.3, 1.1 Hz, 1H), 7.35 (ddd, *J* = 8.2, 7.3, 1.0 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H, Ar$H_m$$SO_2$), 5.45 (s, 2H, C$H_2$O), 2.28 (s, 3H, ArC$H_3$), 2.10-1.66 (overlapping m), and 0.52 [s, 9H, Si(CH_3)$_3$].

3-(3-(2-hydroxy-5-methoxyphenyl)-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate



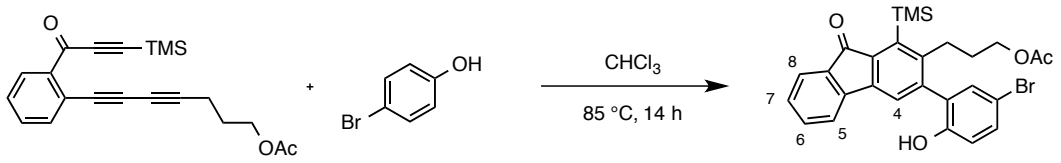
7030a

A solution of triyne (21 mg, 0.06 mmol) and *p*-cresol (70 mg, 0.74 mmol) in $CHCl_3$ (5 mL) was heated at 85 ºC (external bath temperature) in a sealed tube. After 14 h the reaction mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 5:1) to give fluorenone **7030a** (23 mg, 0.052, 86%) as a bright yellow oil.

H NMR (500 MHz, $CDCl_3$): δ 7.61 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H5*), 7.46 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, *H6*), 7.42 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, *H8*), 7.40 (s, 1H, *H4*), 7.30 (ddd, *J* = 7.3, 7.3, 1.1 Hz, 1H, *H7*), 6.93 (d, *J* = 8.9 Hz, 1H, *H3'*), 6.88 (dd, *J* =8.9, 3.0 Hz, 1H, *H4'*), 6.70 (d, *J* = 3.0 Hz, 1H, *H6'*), 4.56 (s, 1H, O*H*), 3.86 (dt, *J* = 11.0, 6.0 Hz, 1H, AcOC*Ha*Hb), 3.83 (dt, *J* = 11.1, 6.0 Hz, 1H, AcOCHa*Hb*), 3.80 (s, 3H, CH_3O), 2.88 (ddd, *J* = 13.7, 10.9, 5.6 Hz, 1H, ArC*Ha*CHb), 2.69 (ddd, *J* = 13.7, 10.9, 5.7 Hz, 1H, ArCHaC*Hb*), 1.89 (s, 3H, CH_3C=O), 1.72-1.57 (m, 2H, CH_2C$H_2$$CH_2$), and 0.49 [s, 9H, Si(C$H_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.2, 171.3, 153.7, 148.3, 146.2, 143.7, 143.6, 143.4, 142.3, 140.7, 134.9, 134.0, 129.2, 129.1, 124.2, 123.9, 119.9, 116.8, 115.2, 115.1, 64.0, 56.0, 32.1, 29.5, 21.0, and 3.0 ppm.

3-(3-(2-hydroxy-5-bromophenyl)-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate (7030f)



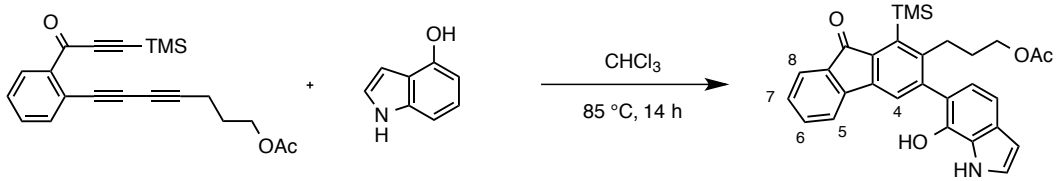
7030f

Compound **7030f** was made following the same procedure used in the synthesis of **7030a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H5*), 7.47 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, *H6*), 7.423 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, *H8*), 7.416 (dd, *J* =8.3, 2.4 Hz, 1H, *H4'*), 7.37 (s, 1H, *H4*), 7.30 (d, *J* = 2.5 Hz, 1H, *H6'*), 7.29 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, *H7*), 6.91 (d, *J* = 8.7 Hz, 1H, *H3'*), 5.08 (s, 1H, O*H*), 3.86 (t, *J* = 6.1 Hz, 2H, AcOCH_2), 2.85 (ddd, *J* = 13.7, 11.0, 5.4 Hz, 1H, ArC*Ha*CHb), 2.67 (ddd, *J* = 13.8, 11.0, 5.5 Hz, 1H, ArCHaC*Hb*), 1.90 (s, 3H, CH_3C=O), 1.71-1.54 (m, 2H, $CH_2CH_2CH_2$), and 0.48 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.0, 171.3, 151.7, 148.3, 143.7, 143.5, 141.1, 140.6, 135.0, 133.9, 132.7, 132.5, 130.5, 129.4, 124.3, 123.7, 119.9, 117.9, 112.9, 63.8, 21.1, 29.5, 21.0, and 2.9 ppm (one carbon missing).

3-(3-(7-hydroxy-*1H*-indol-6-yl)-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate (7030g)



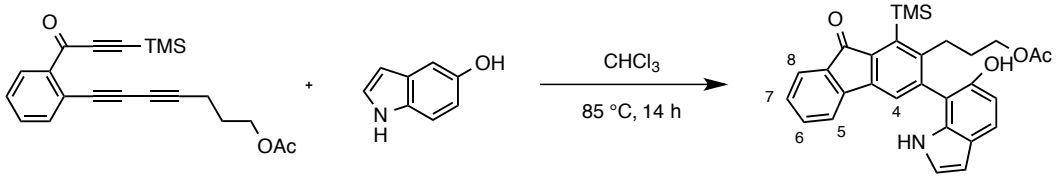
7030g

Compound **7030g** was made following the same procedure used in the synthesis of **7030a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H, N*H*), 7.61 (d, *J* = 7.4, 1.1, 0.7 Hz, 1H), 7.47 (s, 1H, *H4*), 7.44 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 7.39 (ddd, *J* = 7.5, 1.2, 0.8 Hz, 1H), 7.27 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 7.21 (dd, *J* = 3.3, 2.3 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.70 (ddd, *J* = 3.2, 2.1, 1.0 Hz, 1H), 5.16 (s, 1H, O*H*), 3.78 (dt, *J* = 11.4, 6.4 Hz, 1H), 3.76 (dt, *J* = 11.4, 6.4 Hz, 1H), 2.90 (ddd, *J* = 13.7, 9.8, 6.6 Hz, 1H, ArC*Ha*Hb), 2.74 (ddd, *J* = 13.6, 9.6, 6.6 Hz, 1H, ArCHa*Hb*), 1.66 (s, 3H, C*H*$_3$C=O), 1.65-1.57 (m, 2H, $CH_2CH_2CH_2$), and 0.50 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (HSQC, 125 MHz, $CDCl_3$): δ 134.5 (CH), 128.9 (CH), 124.7 (CH), 124.2 (CH), 123.9 (CH), 123.4 (CH), 119.5 (CH), 104.1 (CH), 99.9 (CH), 63.8 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 20.5 (CH_3), and 3.0 (CH_3) ppm.

3-(3-(6-hydroxy-*1H*-indol-7-yl)-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate (7030j)



7030j

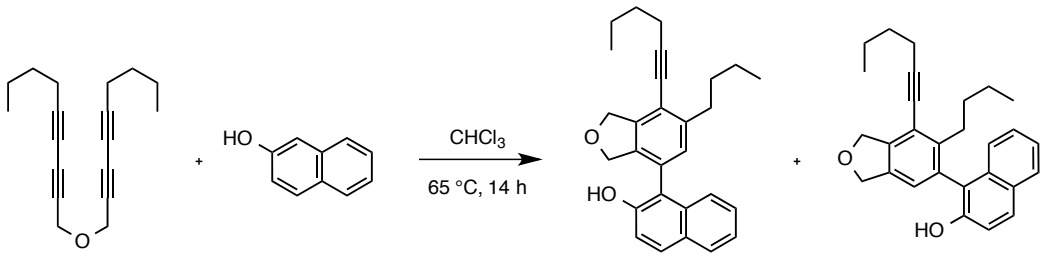
Compound **7030j** was made following the same procedure used in the synthesis of **7030a**

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (s, 1H, N*H*), 7.61 (d, *J* = 7.3, 1.0, 1.0 Hz, 1H), 7.50 (s, 1H, *H4*), 7.43 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.38 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H), 7.33 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.27 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H), 7.19 (dd, *J* = 3.1, 2.5, 0.5 Hz, 1H), 6.9 (dd, *J* = 8.7, 0.5 Hz, 1H), 6.11 (ddd, *J* = 3.1, 2.1, 0.9 Hz, 1H), 4.68 (s, 1H, O*H*), 3.70 (t, *J* = 6.3 Hz, 1H), 2.90 (ddd, *J* = 13.7, 9.8, 6.6 Hz, 1H, ArC*Ha*Hb), 2.77 (nfom, *2*H, $ArCH_2$), 1.78 (s, 3H, C*H*$_3$C=O), 1.67-1.51 (m, 2H, $CH_2CH_2CH_2$), and 0.50 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.0 (CH), 129.6 (CH), 125.9 (CH), 124.7 (CH), 124.4 (CH), 120.2 (CH), 112.5 (CH), 112.2 (CH), 101.9 (CH), 64.4 (CH_2), 32.4 (CH_2), 30.0 (CH_2), 21.2 (CH_3), and 3.3 (CH_3) ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{19}NNaO^+$ $[M+Na]^+$ requires 312.1359; found 312.1371.

1-(6-butyl-7-(hex-1-yn-1-yl)-1,3-dihydroisobenzofuran-4-yl)naphthalen-2-ol (7032e)

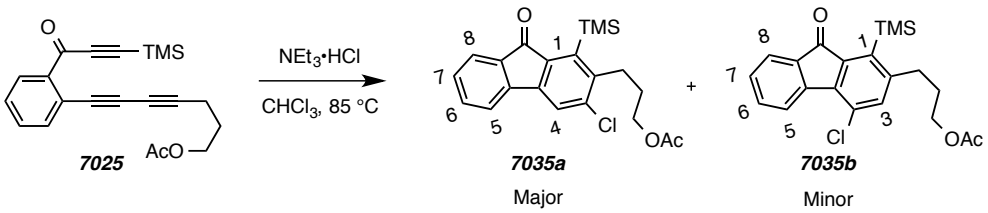


7032e ***7032d***

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H, *H4*), 7.36 (ddd, *J* = 6.9, 6.9, 1.7 Hz, 1H), 7.33 (ddd, *J* = 6.8, 6.8, 1.9 Hz, 1H), 7.30 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 1H, *H3*), 7.12 (s, 1H, *H5'*), 5.26 (dt, *J* = 13.4, 1.8 Hz, C*Ha*HbO), 5.23 (dt, *J* = 13.2, 2.2 Hz, CHa*Hb*O), 5.05 (s, 1H, O*H*), 4.81 (dt, *J* = 12.8, 2.0 Hz, 1H, C*Ha'*Hb'O), 4.75 (dt, *J* = 12.7, 2.2 Hz, 1H, CHa'*Hb'*O), 2.83 (br t, *J* = 7.9 Hz, 2H, ArCH_2), 2.52 (t, *J* = 7.0 Hz, 2H, CCCH_2), 1.69-1.61 (m, 4H, CH_2), 1.54 (dt, *J* = 7.8, 7.8 Hz, 2H, CH_2CH_3), 1.40 (dt, *J* = 7.5, 7.5 Hz, 2H, CH_2CH_3), 0.99 (t, *J* = 7.4 Hz, 3H, CH_3), and 0.94 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (HSQC, 125 MHz, $CDCl_3$): δ 130.5 (CH), 130.0 (CH), 128.5 (CH), 127.0 (CH), 124.3 (CH), 123.6 (CH), 117.5 (CH), 74.7 (CH_2), 74.2 (CH_2), 34.0 (CH_2), 33.1 (CH_2), 31.0 (CH_2), 22.8 (CH_2), 22.1 (CH_2), 19.5 (CH_2), 14.1 (CH_3), and 13.8 (CH_3) ppm.

Synthesis of monochlorinated fluorenones 7035a and 7035b (Scheme 7.9)



7025 ***7035a*** Major ***7035b*** Minor

3-(3-Chloro-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate (7035a)

and **3-(4-Chloro-9-oxo-1-(trimethylsilyl)-9H-fluoren-2-yl)propyl acetate (7035b)**

A solution of known triyne acetate **1** (27 mg, 0.077 mmol, 1 equiv) and Et_3N•HCl (53 mg, 0.385 mmol, 5 equiv) in $CHCl_3$ was heated at 85 °C for 18 h. The resulting solution was concentrated and subjected to flash chromatography (SiO_2, Hexanes:EtOAc = 5:1) to give a co-eluting mixture (6:1 ratio by ^{1}H NMR analysis, 23 mg, 77%) of **7035a** and **7035b** from which the following spectral data were deduced.

Characteristic peaks for **7035a:**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H8*), 7.54 (s, 1H, *H4*), 7.47 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H, *H6*), 7.44 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H5*), 7.29 (ddd, *J* = 7.3, 7.3, 1.3 Hz, 1H, *H7*), 4.16 (t, *J* = 6.4 Hz, AcOCH_2), 3.05 (br t, *J* = 8.3 Hz, 2H, ArCH_2), 2.08 (s, 3H, CH_3C=O), 1.88-1.82 (m, 2H, $CH_2CH_2CH_2$), and 0.47 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.3, 171.3, 145.6, 144.7, 144.2, 142.9, 140.9, 138.8, 134.8, 134.1, 129.5, 124.3, 122.8, 119.9, 64.2, 30.4, 29.8, 21.2, and 3.0 ppm.

Characteristic peaks for **7035b:**

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (ddd, *J* = 7.6, 0.9, 0.9 Hz, 1H, *H5*), 7.62 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H8*), 7.50 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, *H6*), 7.31 (ddd, *J* = 7.3, 7.3, 1.0 Hz, 1H, *H7*), 7.20 (s, 1H, *H3*), 4.12 (t, *J* = 6.5 Hz, AcOCH_2), 2.84 (br t, *J* = 8.0 Hz, 2H, ArCH_2), 1.90-1.83 (m, 2H, $CH_2CH_2CH_2$), and 0.43 [s, 9H, Si(CH_3)$_3$].

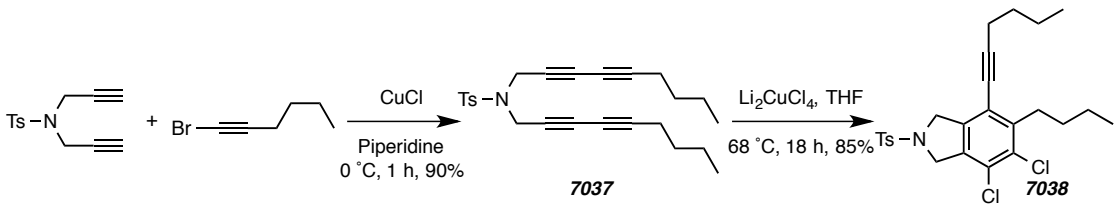
^{13}C NMR (125 MHz, $CDCl_3$, not all resonances were discernable for the minor isomer): δ 136.3, 135.0, 129.2, 124.2, 123.8, 63.8, 33.0, 32.2, and 2.7 ppm.

IR (neat): 2951, 2896, 1740, 1714, 1606, 1582, 1469, 1386, 1365, 1247, 1233, and 851cm^{-1}.

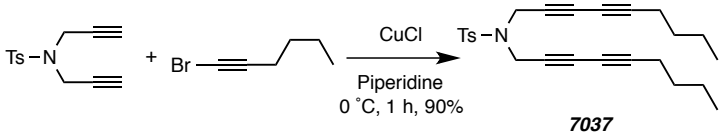
HRMS (ESI-TOF): Calcd for $C_{21}H_{23}ClNaO_3Si^+$ $[M+Na]^+$ requires 409.0997; found 409.1050.

mp: 57–64 °C.

Synthesis of isoindoline 7038 (Scheme 7.11)



4-Methyl-*N*,*N*-di(nona-2,4-diyn-1-yl)benzenesulfonamide (7037)



Tetrayne **7037** was prepared following General Procedure B from 4-methyl-*N,N*-di(prop-2-yn-1-yl)benzenesulfonamide[167] (500 mg, 2.0 mmol), 1-bromohex-1-yne[168] (ca. 3 g, 40 wt% in pentane, 1.2 g, 7.5 mmol), CuCl (60 mg, 0.6 mmol), and piperidine (5 mL). Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the tetrayne **7037** (733 mg, 1.8 mmol, 90%) as a clear yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3 Hz, 2H, SO_2Ar*Ho*), 7.32 (d, J = 8.2 Hz, 2H, SO_2Ar*Hm*), 4.18 (s, 4H, NCH_2), 2.43 (s, 3H, ArCH_3), 2.24 (t, J = 6.9 Hz, 4H, C≡CCH_2), 1.53-1.45 (m, 4H, C≡CCH$_2$CH_2), 1.44-1.35 [m, 4H, CH_2CH$_3$], and 0.91 (t, J s= 7.2 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 134.9, 129.9, 128.1, 81.1, 71.2, 68.1, 64.4, 37.5, 30.3, 22.1, 21.8, 19.1 and 13.7.

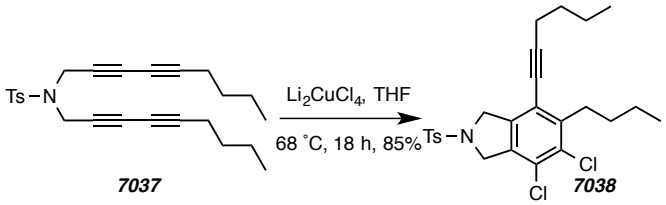
IR: 2958, 2932, 2872, 2257, 1465, 1426, 1354, 1164, 1093, and 894 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{29}NNaO_2S^+$ $[M+Na]^+$ requires 430.1811; found 430.1813.

5-Butyl-6,7-dichloro-4-(hex-1-yn-1-yl)-2-tosylisoindoline (7038)

[167] Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. Palladium-catalysed intramolecular cyclisations of olefinic propargylic carbonates and application to the diastereoselective synthesis of enantiomerically pure (−)-α-thujone. *Helv. Chim. Acta.* **1997**, 80, 623–639.

[168] Niggemann, M.; Jelonek, A.; Biber, N.; Wuchrer, M.; Plietker, B. A General, Iterative, and Modular Approach toward Carbohydrate Libraries Based on Ruthenium-Catalyzed Oxidative Cyclizations. *J. Org. Chem.* **2008**, *73*, 7028–7036.



Dichloride **7** was prepared by heating tetrayne **7037** (28 mg, 0.07 mmol) and Li_2CuCl_4 (0.7 mL, 1M in THF, 0.7 mmol) in THF (1.4 mL) at 68 °C for 18 hours. Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the dichloride **7038** (28 mg, 0.059 mmol, 85%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 2H, $SO_2Ar\mathit{H_o}$), 7.34 (d, J = 8.0 Hz, 2H, $SO_2Ar\mathit{H_m}$), 4.66 (s, 2H, $NC\mathit{H_2}$), 4.61 (s, 2H, $NC'\mathit{H_2}$), 2.89 (nfom, 2H, $ArC\mathit{H_2}$), 2.47 (t, 2H, J = 6.9 Hz, $C{\equiv}CC\mathit{H_2}$), 2.42 (s, 3H, $ArC\mathit{H_3}$), 1.60 (m, 2H,$C\mathit{H_2}CH_2CH_3$), 1.49 (m, 4H, $C\mathit{H_2}CH_3$ and $C'\mathit{H_2}C'H_2C'H_3$), 1.39 (tq, J = 7.3, 7.3 Hz, 2H, $C\mathit{H_2}CH_3$), 0.97 (t, J = 7.3 Hz, 3H, $CH_2C\mathit{H_3}$), and 0.93 (t, J =7.3 Hz, 3H, $C'H_2C'\mathit{H_3}$).

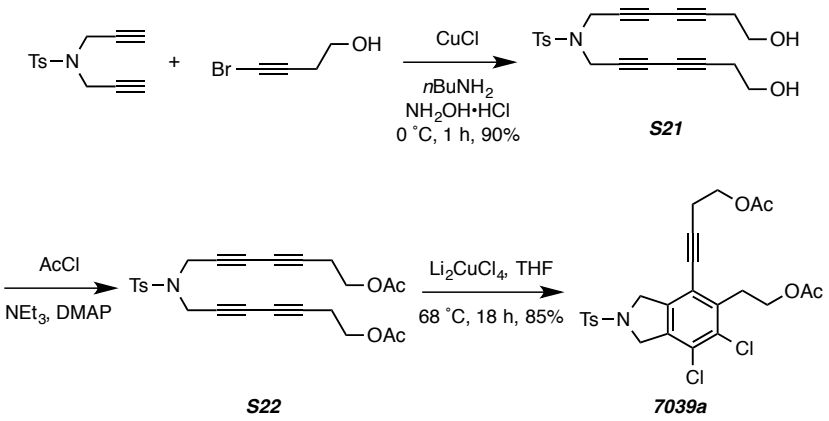
^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 144.1, 138.3, 133.8, 133.7, 131.7, 130.2, 127.7, 126.8, 118.6, 100.3, 75.5, 55.1, 54.6, 33.1, 31.2, 30.9, 23.0, 22.2, 21.7, 19.5, 14.1, and 13.8.

IR (neat): 2955, 2933, 2861, 2226, 1346, 1153, 1098, 764, and 751 cm^{-1}.

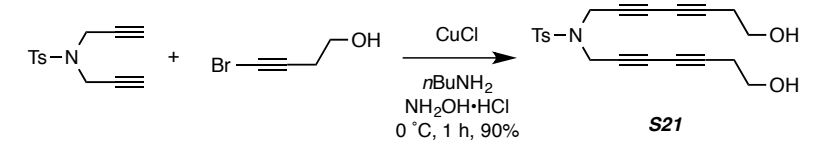
HRMS (ESI-TOF): Calcd for $C_{23}H_{25}Cl_2NNaO_2S^+$ [$M+Na^+$] requires 500.1188; found 500.1204.

mp: 132–134 °C.

Synthesis of isoindoline 7039a



***N*,*N*-Bis(7-hydroxyhepta-2,4-diyn-1-yl)-4-methylbenzenesulfonamide (S21)**



Diol **S21** was prepared by General Procedure C form 4-methyl-*N,N*-di(prop-2-yn-1-yl)benzenesulfonamide (412 mg, 1.67 mmol), 4-bromobut-3-yn-1-ol (740 mg, 5 mmol), CuCl (33 mg, 0.33 mmol), 30% aq. nBuNH$_2$ (4 mL), and CH_2Cl_2 (4 mL). Purification by flash chromatography (hexanes:EtOAc = 1:1) gave the diol **S21** (575 mg, 1.5 mmol, 90%) as a light yellow oil.

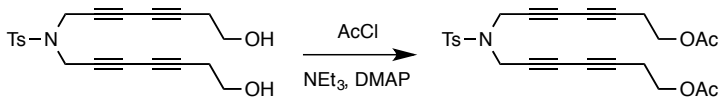
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.33 (d, J = 8.2 Hz, 2H, $SO_2Ar\mathit{H}_m$), 4.18 (s, 4H, $NC\mathit{H}_2$), 3.73 (br dt, J = 5.3, 5.3 Hz, 4H, $OC\mathit{H}_2$), 2.52 (t, J = 6.3 Hz, 4H, $C{\equiv}CC\mathit{H}_2$), 2.44 (s, 3H, $ArC\mathit{H}_3$), and 2.17 (t, J = 5.7 Hz, 2H, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.5, 134.7, 129.9, 128.0, 77.7, 70.9, 68.8, 66.0, 60.7, 37.5, 23.7, and 21.8 ppm.

IR (neat): 3374, 2943, 2888, 2258, 1597, 1420, 1348, 1329, 1160, 1092, 1045, and 750 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{21}H_{21}NNaO_4S^+$ $[M+Na]^+$ requires 406.1083; found 406.1072.

***N*,*N*-Bis(7-acetoxyhepta-2,4-diyn-1-yl)-4-methylbenzenesulfonamide (S22)**



S21 ***S22***

To a solution of diol **S21** (80 mg, 0.21 mmol) in DCM (1 mL) cooled at 0 °C was sequentially added NEt_3 (80 mg, 0.8 mmol), DMAP (a few crystals), and AcCl (47 mg, 0.6 mmol). The reaction mixture was allowed to stir at this temperature for an additional 2 h. The resulting solution was partitioned between water and EtOAc. The organic layer was washed (satd. NH_4Cl and brine), dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by flash chromatography (hexanes:EtOAc = 1:1) to give the diacetate **S22** (70 mg, 0.15 mmol, 71%) as a light yellow oil.

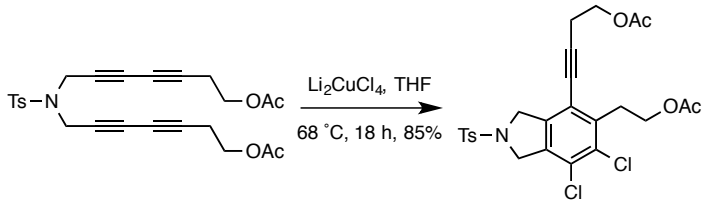
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H_o}$), 7.33 (d, J = 8.1 Hz, 2H, $SO_2Ar\mathit{H_m}$), 4.18 (s, 4H, $NC\mathit{H_2}$), 4.14 (t, J = 6.7 Hz, 4H, $OC\mathit{H_2}$), 2.60 (t, J = 6.7 Hz, 4H, $C{\equiv}CC\mathit{H_2}$), 2.44 (s, 3H, $ArC\mathit{H_3}$), and 2.08 (s, 6H, $C\mathit{H_3}C{=}O$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 144.4, 134.8, 129.9, 128.0, 76.3, 70.8, 69.0, 65.9, 61.7, 37.4, 21.8, 21.1, and 19.9 ppm.

IR (neat): 2966, 2918, 2261, 1739, 1598, 1494, 1452, 1353, 1232, 1163, 1093, 1043, and 903 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{25}NNaO_6S^+$ $[M+Na]^+$ requires 490.1295; found 490.1311.

2-[4-(4-Acetoxybut-1-yn-1-yl)-6,7-dichloro-2-tosylisoindolin-5-yl]ethyl acetate (7039a)



S22 ***7039a***

Dichloride **7039a** was prepared by heating tetrayne **S22** (21 mg, 0.045 mmol) and Li_2CuCl_4 (0.45 mL, 1M in THF, 0.45 mmol) in THF (1 mL) at 68 °C for 18 hours. Purification by flash chromatography (hexanes:EtOAc 5:1 to 2:1) gave the dichloride **7039a** (22 mg, 0.041 mmol, 91%) as a colorless oil.

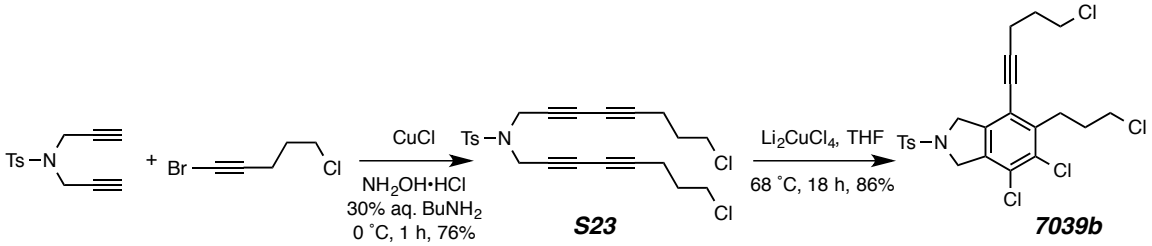
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.35 (d, J = 8.0 Hz, 2H, $SO_2Ar\mathit{H}_m$), 4.67 (br s, 2H), 4.63 (br s, 2H), 4.27 (t, J = 6.6 Hz, 2H, $AcOC\mathit{H}_2$), 4.25 (t, J = 6.6 Hz, 2H, $AcOC'\mathit{H}_2$), 3.28 (t, J = 6.9 Hz, 2H, $ArC\mathit{H}_2CH_2$), 2.82 (t, J = 6.5 Hz, 2H, $\equiv CC\mathit{H}_2CH_2$), 2.43 (s, 3H, $ArC\mathit{H}_3$), 2.13 (s, 3H, $C\mathit{H}_3C{=}O$), and 2.01 (s, 3H, $C'\mathit{H}_3C{=}O$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.01, 171.00, 144.3, 139.3, 138.7, 135.1, 133.8, 132.5, 130.2, 127.74, 127.72, 118.7, 96.2, 76.4, 62.3, 62.1, 55.0, 54.6, 32.5, 21.8, 21.2, 21.0, and 20.4 ppm.

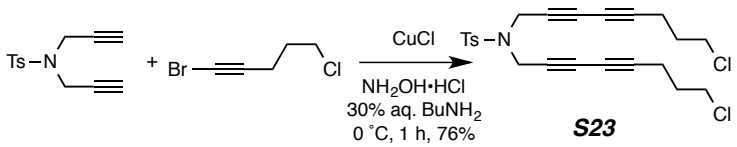
IR (neat): 2960, 2925, 2856, 1739, 1351, 1234, 1165, 1098, 1042, and 816 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{25}Cl_2NNaO_6S^+$ $[M+Na]^+$ requires 560.0672; found 560.0677.

Synthesis of isoindoline 7039b



***N,N*-Bis(8-chloroocta-2,4-diyn-1-yl)-4-methylbenzenesulfonamide (S20)**



Tetrayne **S23** was prepared following General Procedure C from 4-methyl-*N,N*-di(prop-2-yn-1-yl)benzenesulfonamide (124 mg, 0.5 mmol), 1-bromo-5-chloropent-1-yne[169] (305 mg, 1.69 mmol), CuCl (15 mg, 0.15 mmol), NH_2OH•HCl (a few crystals), CH_2Cl_2 (2 mL), and 30 wt% aqueous $BuNH_2$ (1.5 mL). Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the tetrayne **S3** (170 mg, 0.38 mmol, 76%) as a clear yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.33 (d, J = 8.5 Hz, 2H, $SO_2Ar\mathit{H}_m$), 4.18 (s, 4H, $C\mathit{H}_2N$), 3.62 (t, J = 6.3 Hz, 4H, CH_2Cl), 2.46 (t, J = 6.8 Hz, 4H, ≡CCH_2), 2.44 (s, 3H, $C\mathit{H}_3$), and 1.97 (tt, J = 6.8, 6.8 Hz, 4H, $CH_2C\mathit{H}_2CH_2$).

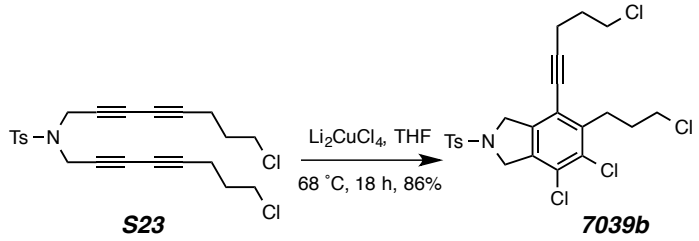
^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 134.8, 129.9, 128.0, 78.9, 70.9, 68.6, 65.4, 43.5, 37.4, 30.9, 21.8, and 16.8 ppm.

IR (neat): 2961, 2258, 1597, 1494, 1440, 1351, 1162, 1092, 891, and 815 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}Cl_2NNaO_2S^+$ $[M+Na]^+$ requires 470.0719; found 470.0751.

[169] Nicolai, S.; Sedigh-Zadeh, R.; Waser, J. Pd(0)-catalyzed alkene oxy- and aminoalkynylation with aliphatic bromoacetylenes. *J. Org. Chem.* **2013**, *78*, 3783–3801.

4,5-Dichloro-7-(5-chloropent-1-yn-1-yl)-6-(3-chloropropyl)-2-tosylisoindoline (7039b)



S23 ***7039b***

Dichloride **7039b** was prepared by heating tetrayne **S23** (50 mg, 0.12 mmol) and Li_2CuCl_4 (1.2 mL, 1M in THF, 1.2 mmol) in THF (2.8 mL) at 68 °C for 18 hours. Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the dichloride **7039b** (50 mg, 0.097 mmol, 86%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.35 (d, J = 8.0 Hz, 2H, $SO_2Ar\mathit{H}_m$), 4.66 (s, 2H, $NC\mathit{H}_2$), 4.62 (s, 2H, $NC'\mathit{H}_2$), 3.69 (t, 2H, J = 6.2 Hz, $C\mathit{H}_2Cl$), 3.59 (t, 2H, J = 6.3 Hz, $C'\mathit{H}_2Cl$), 3.07 (nfom, 2H, $ArC\mathit{H}_2$), 2.70 (t, J = 6.9 Hz, 2H, $C{\equiv}CC\mathit{H}_2$), 2.42 (s, 3H, $ArC\mathit{H}_3$), 2.09 (tt, J = 6.5, 6.5 Hz, 2H, $C{\equiv}CCH_2C\mathit{H}_2$), and 1.99 (nfom, 2H, $ArCH_2C\mathit{H}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 142.5, 138.5, 134.5, 133.7, 131.9, 130.2, 127.7, 127.4, 118.3, 98.7, 76.0, 55.0, 54.6, 44., 43.8, 31.7, 31.2, 30.9, 21.7, and 17.3.

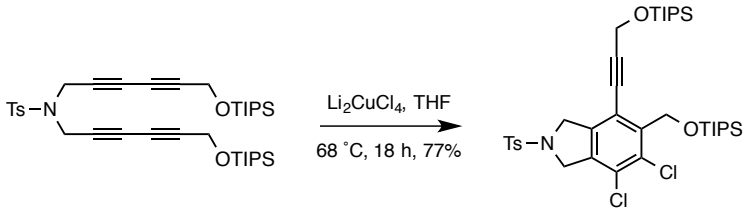
IR (neat): 2960, 2861, 2230, 1349, 1164, 1098, 1069, 764, and 751 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}Cl_4NNaO_2S^+$ [$M+Na^+$] requires 540.0096; found 540.0087.

mp: 138–144 °C.

Synthesis of isoindoline 7039c

4,5-Dichloro-2-tosyl-6-{[(triisopropylsilyl)oxy]methyl}-7-{3-[(triisopropylsilyl)oxy]prop-1-yn-1-yl}isoindoline (7039c)



7039c

Dichloride **7039c** was prepared following General Procedure C from known tetrayne[170] (20 mg, 0.03 mmol), Li_2CuCl_4 (0.3 mL, 1M in THF, 0.3 mmol), and THF (0.7 mL). Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the dichloride **7039c** (17 mg, 0.023 mmol, 77%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.0 Hz, 2H, SO_2ArH_o), 7.33 (d, J = 8.0 Hz, 2H, SO_2ArH_M), 4.97 (s, 2H, CH_2), 4.68 (s, 2H, CH_2), 4.65 (s, 2H, CH_2), 4.61 (s, 2H, CH_2), 2.42 (s, 3H, $ArCH_3$), 1.20-1.08 (m, 2H, $SiCH(CH_3)_2$], 1.12 [d, J = 5.9 Hz, 6H, $SiCH(CH_3)_2$], and 1.07 [d, J = 6.5 Hz, 6H, $SiCH(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 141.3, 138.9, 136.0, 133.7, 133.5, 130.2, 128.2, 127.8, 118.2, 97.6, 78.8, 62.5, 55.1, 54.7, 52.7, 21.8, 18.2, 12.3, and 12.2.

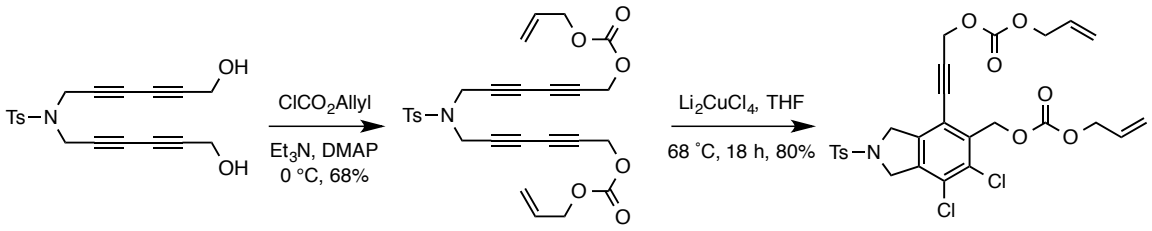
IR (neat): 2944, 2891, 2863, 2362, 2343, 1463, 1356, 1167, 1100, 1068, 883, and 813 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{37}H_{57}Cl_2NNaO_4SSi_2^+$ [M+Na^+] requires 760.2816; found 760.2839.

mp: 122–126 °C.

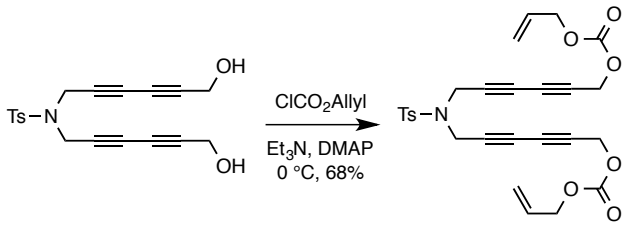
[170] Chen, J.; Baire, B.; Hoye, T. R. Cycloaddition reaction of azide, furan, and pyrrole units with benzynes generated by the hexadehydro-Diels–Alder (HDDA) reaction. *Heterocycles* **2014**, *88*, 1191–1200.

Synthesis of isoindoline 7039d



S24 ***7039d***

Diallyl [(tosylazanediyl)bis(hexa-2,4-diyne-6,1-diyl)] bis(carbonate) (S24)



S24

To a solution of *N*,*N*-bis(6-hydroxyhexa-2,4-diyn-1-yl)-4-methylbenzenesulfonamide[170] (90 mg, 0.25 mmol) in CH_2Cl_2 cooled at 0 °C was sequentially added allyl chloroformate (90 mg, 0.75 mmol), NEt_3 (100 mg, 1 mmol), and DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred at this temperature for 2 h. The resulting solution was partitioned between EtOAc and aq. NH_4Cl. The aqueous layer was washed with EtOAc two times. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting oil was subjected to flash chromatography (SiO_2, hexanes:EtOAc = 12:1 to 5:1) to give carbonate **S24** (90 mg, 0.17 mmol, 68%) as a clear yellow oil.

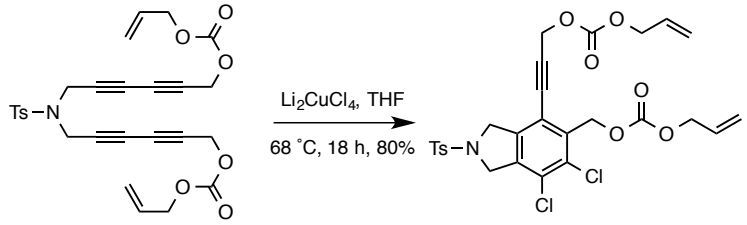
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.33 (d, J = 8.0 Hz, 2H, $SO_2Ar\mathit{H}_m$), 5.94 (ddt, J = 17.1, 10.5, 5.8 Hz, 2H, $CH_2C\mathit{H}$=C), 5.38 (ddt, J = 17.2, 1.4, 1.4 Hz, 2H, CH=CH_ZH$_E$), 5.30 (ddt, J = 10.4, 1.2, 1.2 Hz, 2H, CH=CH$_Z\mathit{H}_E$), 4.77 (s, 4H, OCH_2), 4.66 (ddd, J = 5.8, 1.3, 1.3 Hz, 4H, CH_2C=), 4.20 (s, 4H, NCH_2), and 2.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 144.8, 134.4, 131.2, 130.0, 127.9, 119.5, 72.8, 72.1, 71.1, 69.9, 69.2, 55.6, 37.5, and 21.7 ppm.

IR: 3005, 2989, 2918, 2261, 1752, 1649, 1597, 1449, 1382, 1353, 1274, 1164, 1092, 968, and 893 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{25}NNaO_8S^+$ $[M+Na]^+$ requires 546.1193; found 546.1201.

Allyl {[4-(3-(((allyloxy)carbonyl)oxy)prop-1-yn-1-yl)-6,7-dichloro-2-tosylisoindolin-5-yl]methyl} carbonate (7039d)



S24 ***7039d***

Dichloride **7039d** was prepared by heating tetrayne **S24** (23 mg, 0.04 mmol) and Li_2CuCl_4 (0.4 mL, 1M in THF, 0.4 mmol) in THF (1.2 mL) at 68 °C for 18 hours. Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the dichloride **7039d** (20 mg, 0.034 mmol, 80%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.35 (d, J = 8.1 Hz, 2H, $SO_2Ar\mathit{H}_m$), 5.97 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H, CH_2=CH), 5.92 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H, C'H_2=C'H), 5.41 (ddt, J = 17.2, 1.4, 1.4 Hz, 1H, CH_ZH$_E$=CH), 5.41 (s, 2H, ArCH_2O), 5.35 (ddt, J = 17.2, 1.4, 1.4 Hz, 1H, C'H_ZH$_E$=C'H), 5.32 (ddt, J = 10.5, 1.2, 1.2 Hz, 1H, CH$_Z\mathit{H}_E$=CH), 5.26 (ddt, J = 10.4, 1.2, 1.2 Hz, 1H, C'H$_Z\mathit{H}_E$=C'H), 4.98 (s, 2H, OCH_2C≡), 4.71 (ddd, J = 5.8, 1.3, 1.3 Hz, 2H, $CO_2C\mathit{H}_2$), 4.69 (nfom, 2H, CH_2N), 4.65 (nfom, 2H, C'H_2N), 4.64 (ddd, J = 5.8, 1.3, 1.3 Hz, 2H, C'O$_2$C'H_2), and 2.43 (s, 3H, ArCH_3).

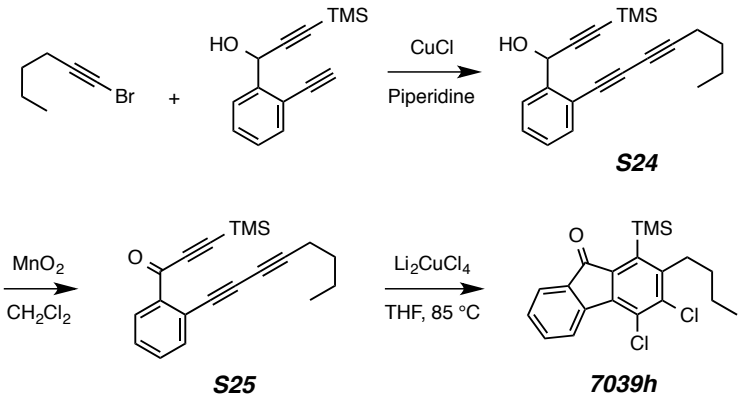
^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 154.5, 144.4, 139.3, 137.8, 136.0, 134.1, 133.5, 131.6, 131.4, 130.3, 129.1, 127.7, 119.7, 119.2, 118.4, 93.1, 80.4, 69.4, 69.0, 65.6, 55.8, 54.8, 54.7, and 21.8 ppm

IR (neat): 2954, 2853, 1750, 1438, 1383, 1353, 1256, 1165, 1098, and 958 cm^{-1}.

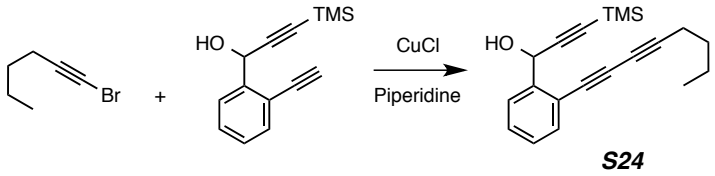
HRMS (ESI-TOF): Calcd for $C_{27}H_{25}Cl_2NNaO_8S^+$ $[M+Na]^+$ requires 616.0570; found 616.0589.

mp: 112–116 °C.

Synthesis of fluorenone 7039h



1-(2-(Octa-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (S24)



Triyne **S24** was prepared following General Procedure B from 1-(2-ethynylphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (160 mg, 0.7 mmol), 1-bromohex-1-yne (500 mg, ca. 40 wt% in pentane, 1.25 mmol), CuCl (7 mg, 0.07 mmol), and piperidine (2 mL). Purification by MPLC (hexanes:EtOAc 7:1) gave the diyne **S24** (153 mg, 0.5 mmol, 71%) as a yellow oil. This sample contained ca. 10 mol% of the starting diyne, with which it coeluted.

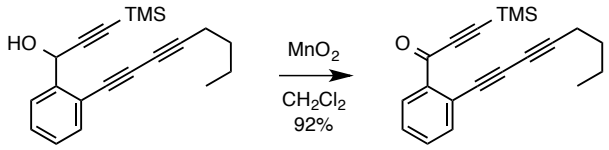
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 1H, H3), 7.50 (d, *J* = 7.5 Hz, 1H, H6), 7.38 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.28 (dd, *J* = 8.0, 8.0 Hz, 1H), 5.83 (d, *J* = 5.5 Hz, 1H, C*H*OH), 2.38 (t, *J* = 7.0 Hz, 2H, C≡CC*H*$_2$), 1.57 (tt, *J* = 7, 7 Hz, 2H, C≡CCH$_2$C*H*$_2$), 1.46 (tq, *J* = 7, 7 Hz, 2H, CH$_2$C*H*$_2$CH$_3$), and 0.94 (t, *J* = 7.0 Hz, 3H, C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 133.8, 129.5, 128.5, 127.1, 121.0, 104.3, 92.0, 86.7, 80.0, 71.9, 65.1, 63.7, 30.4, 22.2, 19.5, 13.7, and 0.02.

IR: 3364, 2959, 2934, 2872, 2238, 2174, 1482, 1466, 1449, 1249, 1037, 983, and 845 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{20}H_{24}NaOSi^+$ $[M+Na]^+$ requires 331.1489; found 331.1496.

1-(2-(Octa-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (S25)



S24 ***S25***

Activated MnO_2 (300 mg, 3.44 mmol) was added to a solution of triyne **S24** (150 mg, 0.49 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt until full conversion (within 2 h) was indicated by TLC analysis. The mixture was then filtered through Celite® and the filter cake was washed with a copious amount of CH_2Cl_2. The filtrate was concentrated and the residue subjected to column chromatography (hexanes:EtOAc = 12:1) to yield ketone **S25** as a pale yellow oil (138 mg, 0.45 mmol, 92%).

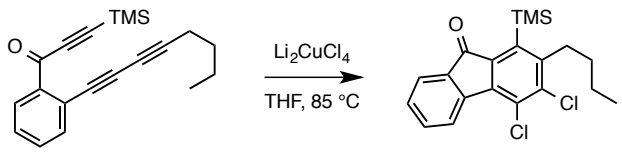
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H6*), 7.61 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar*H3*), 7.50 (ddd, *J* = 7.5, 7.5, and 1.5 Hz, 1H, Ar*H4*), 7.40 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, Ar*H5*), 2.39 (t, *J* = 7.0 Hz, 2H, CCCH_2), 1.56 (app p, *J* = 7.0 Hz, 2H, $CH_2CH_2CH_2$), 1.45 (app sextet, *J* = 7.5 Hz, 2H, $CH_2CH_2CH_3$), and 0.93 (t, *J* = 7.5 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8, 139.1, 135.8, 132.7, 131.9, 128.5, 122.3, 101.62, 101.58, 87.5, 80.9, 72.8, 65.7, 30.4, 22.2, 19.6, 13.8, and -0.5 ppm

IR: 2959, 2933, 2873, 2239, 2153, 1649, 1589, 1561, 1480, 1274, 1251, 1234, 1014, 848, and 755 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{20}H_{22}NaOSi^+$ $[M+Na]^+$ requires 329.1332; found 329.1329.

2-Butyl-3,4-dichloro-1-(trimethylsilyl)-9H-fluoren-9-one (7039h)



S25 ***7039h***

Dichloride **7039h** was prepared by heating triyne **S25** (15 mg, 0.049 mmol) and Li_2CuCl_4 (0.2 mmol) in THF (2 mL) at 85 °C for 18 hours. Purification by MPLC (hexanes:EtOAc = 5:1) gave the dichloride **7039h** (12 mg, 0.032 mmol, 65%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (ddd, *J* = 7.7, 0.9, 0.9 Hz, 1H, *H5*), 7.64 (ddd, *J* = 7.3, 0.9, and 0.9 Hz, 1H, *H8*), 7.52 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, *H6*), 7.34 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, *H7*), 3.02 (br t, *J* = 8.0 Hz, 2H, ArCH_2), 1.52-1.40 (m, 4H, CH_2CH_2CH_3), 0.97 (t, *J* = 7.2 Hz, 3H, CH_3), and 0.45 [s, 9H, Si(CH_3)$_3$].

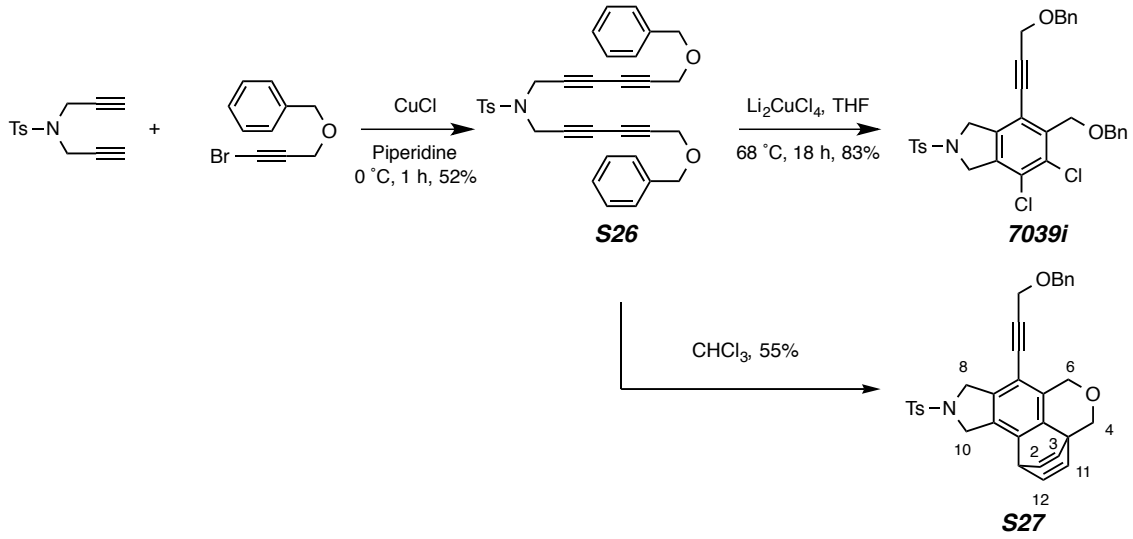
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 149.4, 142.7, 141.6, 141.0, 139.8, 139.5, 134.9, 134.1, 129.9, 129.5, 124.2, 124.1, 34.4, 33.6, 22.9, 14.2, and 3.2 ppm.

IR: 2958, 2931, 2871, 1719, 1601, 1466, 1249, 1093, and 849 cm^{-1}.

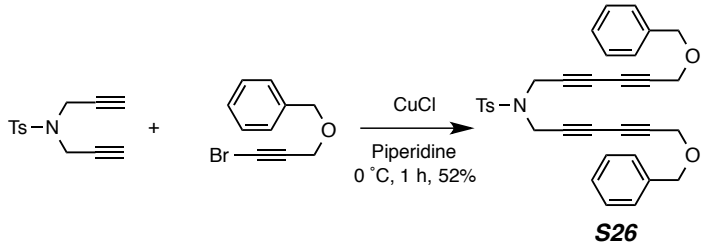
HRMS (ESI-TOF): Calcd for $C_{20}H_{24}Cl_2NaOSi^+$ $[M+Na]^+$ requires 399.0709; found 399.0713.

mp: 110–111 °C.

Synthesis of isoindolines 7039i



***N,N*-Bis[6-(benzyloxy)hexa-2,4-diyn-1-yl]-4-methylbenzenesulfonamide (S26)**



Tetrayne **S26** was prepared following General Procedure B from 4-methyl-*N,N*-di(prop-2-yn-1-yl)benzenesulfonamide (198 mg, 0.8 mmol), {[(3-bromoprop-2-yn-1-yl)oxy]methyl}benzene[171] (540 mg, 2.4 mmol), CuCl (24 mg, 0.24 mmol), and piperidine (2.5 mL). Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the tetrayne **S26** (223 mg, 0.41 mmol, 52%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 2H, SO_2ArHo), 7.38-7.29 (m, 12H, Ar*H*), 4.57 (s, 4H, OCH_2Ar), 4.23 (s, 4H, $OCH_2C{\equiv}C$), 4.19 (s, 4H, NCH_2), and 2.39 (s, 3H, $ArCH_3$).

[171] Yang, X.; Zhu, Li.; Zhou, Y.; Li, Z.; Zhai, H. Efficient synthesis of monosubstituted 3-alkynylfurans via Suzuki coupling. *Synthesis* **2008**, 1729–1732.

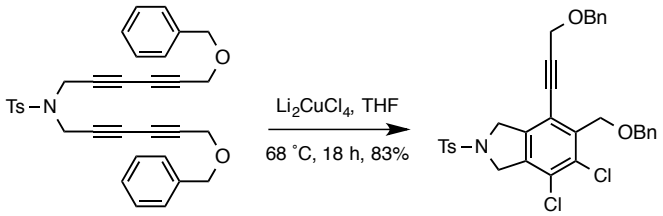
^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 137.1, 134.7, 130.0, 128.7, 128.30, 128.27, 128.0, 75.4, 72.0, 71.7, 70.4, 70.3, 57.6, 37.5, and 21.8 ppm.

IR: 3031, 2865, 2255, 1597, 1495, 1454, 1351, 1164, 1091, 1073, 1027, 945, and 892 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{29}NNaO_4S^+$ $[M+Na]^+$ requires 558.1710; found 558.1713.

mp: 64–66 °C.

5-((Benzyloxy)methyl)-4-(3-(benzyloxy)prop-1-yn-1-yl)-6,7-dichloro-2-tosylisoindoline (7039i)



S26 ***7039i***

Dichloride **7039i** was prepared following General Procedure C from tetrayne **S26** (50 mg, 0.093 mmol) and Li_2CuCl_4 (0.9 mL, 1M in THF, 0.9 mmol) in THF (2.1 mL). Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the dichloride **7039i** (48 mg, 0.079 mmol, 83%) as a colorless solid.

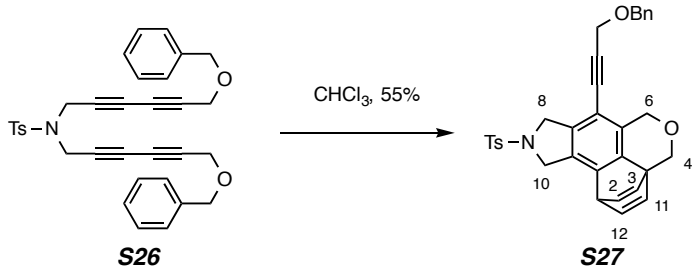
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 2H, $SO_2Ar\mathit{H_O}$), 7.31 (m, 12H), 4.77 (s, 2H, $ArCH_2OBn$), 4.71 (br s, 2H, CH_2N), 4.65 (br s, 2H, $C'H_2N$), 4.63 (s, 2H, $PhCH_2O$), 4.57 (s, 2H, $PhCH_2O$), 4.38 (s, 2H, $\equiv CCH_2OBn$), and 2.41 (s, 3H, $ArCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 138.82, 138.80, 138.0, 137.2, 136.7, 133.9, 133.5, 130.3, 128.8, 128.53, 128.51, 128.34, 128.31, 128.00, 127.95, 127.7, 118.7, 95.2, 80.4, 73.2, 72.1, 68.4, 57.9, 55.0, 54.7, and 21.8.

IR (neat): 3064, 3033, 2855, 1454, 1351, 1166, 1096, 1071, 857, 827, and 817 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{29}Cl_2NNaO_4S^+$ $[M+Na^+]$ requires 628.1087; found 628.1204.

7-[3-(Benzyloxy)prop-1-yn-1-yl]-9-tosyl-6,8,9,10-tetrahydro-1*H*,4*H*-1,3a-ethenoisochromeno[5,4-ef]isoindole (S27)



S26 ***S27***

A solution of tetrayne **S26** (22 mg, 0.041 mmol) in $CHCl_3$ (2 mL) was heated at 68 °C for 18 h. The resulting solution was concentrated and subjected to flash chromatography (SiO_2, hexanes:EtOAc = 5:1) to give isoindoline **S27** (12 mg, 0.022 mmol, 55%) as a colorless solid.

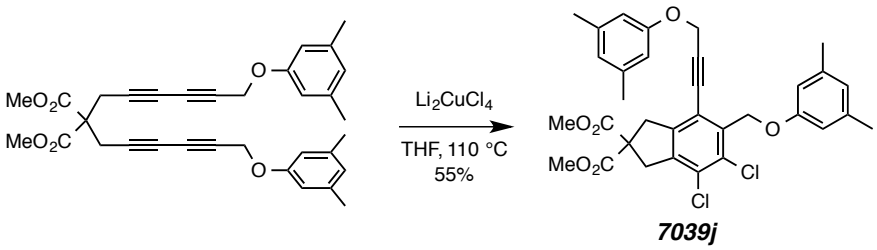
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H, $SO_2Ar\mathit{H_o}$), 7.40-7.32 (m, 5H, $C_6\mathit{H_5}$), 7.31 (d, *J* = 8.0 Hz, 2H, $SO_2Ar\mathit{H_m}$), 6.85 (dd, *J* = 6.4, 5.8 Hz, 2H, *H*2 and *H*12), 6.68 (d, *J* = 6.5, 1.5 Hz, 2H, *H*3 and *H*11), 4.81 (tt, *J* = 5.8, 1.5 Hz, 1H, *H1*), 4.73 (br s, 2H, $C\mathit{H_2}$), 4.66 (br s, 2H, $C\mathit{H_2}$), 4.63 (br s, 2H, $C\mathit{H_2}$), 4.58 (br s, 2H, $C\mathit{H_2}$), 4.53 (br s, 2H, $C\mathit{H_2}$), 4.40 (br s, 2H, $C\mathit{H_2}$), and 2.40 (s, 3H, $ArC\mathit{H_3}$).

^{13}C NMR (125 MHz, CD_3CN): δ 145.1, 144.0, 143.8, 142.9, 141.1, 138.9, 135.3, 134.3, 132.7, 130.8, 129.3, 129.0, 128.8, 128.7, 128.5, 108.5, 93.8, 80.8, 72.1, 71.5, 66.5, 58.5, 54.5, 53.3, 51.8, 46.8, and 21.4.

IR (neat): 3062, 2945, 2918, 1597, 1495, 1454, 1348, 1163, 1096, 1073, 920, and 816 cm^{-1}.

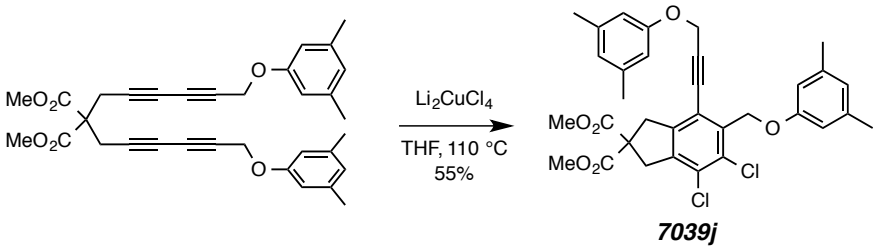
HRMS (ESI-TOF): Calcd for $C_{33}H_{29}NNaO_4S^+$ $[M+Na]^+$ requires 558.1710; found 558.1695.

Synthesis of indane 7039j



7039j

Dimethyl 4,5-dichloro-6-[(3,5-dimethylphenoxy)methyl]-7-[3-(3,5-dimethylphenoxy)prop-1-yn-1-yl]-1,3-dihydro-2H-indene-2,2-dicarboxylate (7039j)



7039j

Dichloride **7039j** was prepared by heating the dimethyl tetraynylmalonate (14 mg, 0.027 mmol) and Li_2CuCl_4 (4 mL, 0.1 M in THF) at 110 °C for 24 h. Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the dichloride **7039j** (9 mg, 0.015 mmol, 55%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (t of sextet, J = 0.7, 0.7 Hz, 1H, OAr_p), 6.61 (overlapping br s, 3H), 6.59 (dq, J = 0.7, 0.7 Hz, 2H, OAr_o), 5.18 (s, 2H, $ArCH_2O$), 4.85 (s, 2H, $\equiv CCH_2O$), 3.77 (s, 6H, CO_2CH_3), 3.69 (s, 2H, CH_2CCH_2), 3.66 (s, 2H, CH_2CCH_2), 2.29 (ddd, J = 0.7, 0.7, 0.7 Hz, 6H, $ArCH_3$), and 2.25 (ddd, J = 0.7, 0.7, 0.7 Hz, 6H, $ArCH_3$).

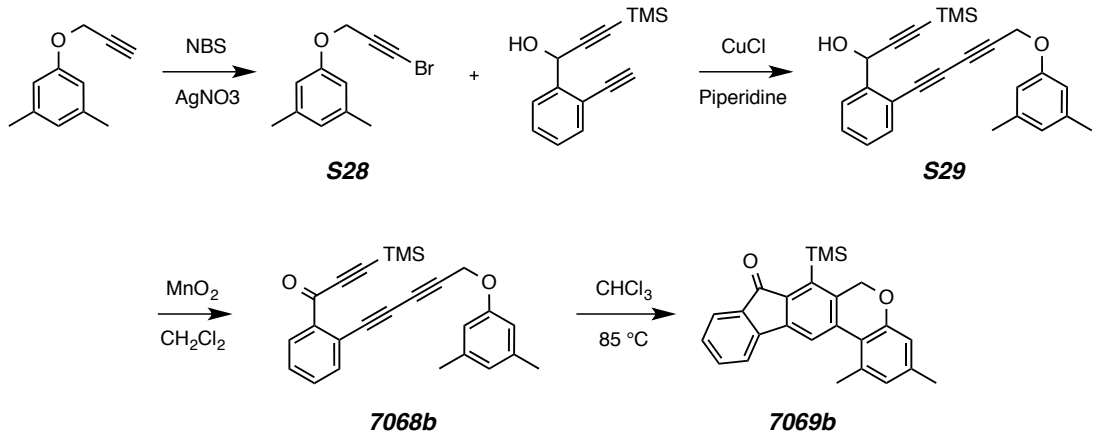
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 159.2, 157.7, 143.0, 140.7, 139.44, 139.37, 136.8, 133.2, 130.3, 123.6, 123.2, 119.7, 112.9, 112.8, 93.6, 81.9, 66.8, 58.9, 56.4, 53.5, 41.53, 41.50, 21.7, and 21.6 ppm.

IR: 2954, 2920, 1738, 1593, 1434, 1293, 1256, 1167, 1153, and 1061cm^{-1}.

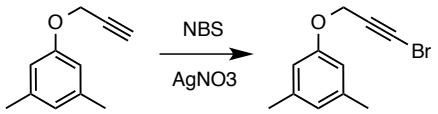
HRMS (ESI-TOF): Calcd for $C_{33}H_{32}Cl_2NaO_6^+$ $[M+Na]^+$ requires 617.1468; found 617.1487.

mp: 140–143 °C.

Synthesis of fluorenone 7069b



1-((3-Bromoprop-2-yn-1-yl)oxy)-3,5-dimethylbenzene (S28)



Bromoalkyne **S28** was prepared following General Procedure A from 1,3-dimethyl-5-(prop-2-yn-1-yloxy)benzene[172] (400 mg, 2.5 mmol), *N*-bromosuccinimide (NBS, 460 mg, 2.6 mmol), $AgNO_3$ (34 mg, 0.2 mmol), and acetone (25 mL). Purification by flash chromatography (hexanes:EtOAc 19:1) gave the bromoalkyne **S28** (500 mg, 2.1 mmol, 84%) as a clear yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (s, 1H, Ar*H4*), 6.58 (s, 2H, Ar*H2H6*), 4.67 (s, 2H, CH_2O), and 2.30 [s, 6H, Ar(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 139.5, 123.6, 112.7, 75.5, 56.8, 47.5, and 21.7.

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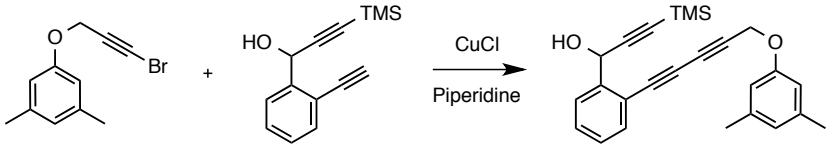
[172] Wang, Y., Ji, K., Lan, S. & Zhang, L. Rapid access to chroman-3-ones through gold-catalyzed oxidation of propargyl aryl ethers. *Angew. Chem. Int. Ed.* **2012**, *51*, 1915–1918.

IR: 2919, 2862, 2219, 1615, 1594, 1470, 1451, 1373, 1318, 1293, 1168, 1151, 1070, and 829 cm^{-1}.

GC-LRMS: t_R = 7.37 min. *m/z*: 240 (M+, 50), 238 (M+, 50), 225 (M+-CH_3, 25), 223 (M+-CH_3, 25), 159 (M+-Br, 70), 131 (70), 116 (70), 91 (C_7H_7+, 100), and 77 (C_6H_5+, 50).

1-(2-(5-(3,5-Dimethylphenoxy)penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (S29)



S28 ***S29***

Triyne **S29** was prepared following General Procedure B from 1-(2-ethynylphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (160 mg, 0.7 mmol), **S28** (237 mg, 1 mmol), CuCl (7 mg, 0.07 mmol), and piperidine (2 mL). Purification by MPLC (hexanes:EtOAc 5:1) gave the diyne **S29** (90 mg, 0.23 mmol, 33%) as a yellow oil.

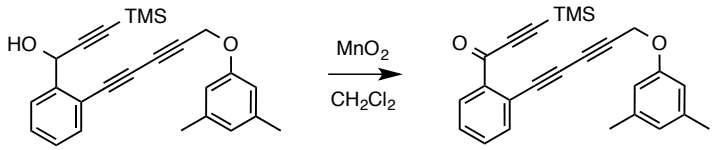
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.8 Hz, 1H, *H6*), 7.49 (d, *J* = 7.7 Hz, 1H, *H3*), 7.40 (dd, *J* = 7.7, 7.7 Hz, 1H, *H4*), 7.27 (dd, *J* = 7.6, 7.6 Hz, 1H, *H5*), 6.65 (br s, 1H, *H4'*), 6.60 (br s, 2H, *H2'H6'*), 5.78 (br s, 1H, C*H*OH), 4.79 (s, 2H, CH_2O), 2.52 (br s, 1H, CHO*H*), 2.30 [br s, 6H, Ar(CH_3)$_2$], and 0.19 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 143.7, 139.5, 133.9, 130.1, 128.5, 127.1, 123.7, 120.0, 112.7, 104.2, 92.0, 79.2, 78.5, 75.9, 71.5, 63.4, 56.4, 21.6, and 0.0.

IR: 3420, 2959, 2240, 2174, 1614, 1594, 1473, 1449, 1372, 1318, 1291, 1250, 1169, 1150, 1059, and 985 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{26}NaO_2Si^+$ $[M+Na]^+$ requires 409.1594; found 409.1633.

1-(2-(5-(3,5-Dimethylphenoxy)penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (7068b)



S29 ***7068b***

Activated MnO_2 (300 mg, 3.44 mmol) was added to a solution of triyne **S29** (90 mg, 0.23 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt until full conversion (within 2 h) was indicated by TLC analysis. The mixture was then filtered through Celite® and the filter cake was washed with copious amount of CH_2Cl_2. The filtrate was concentrated and the residue subjected to column chromatography (hexanes:EtOAc = 12:1) to yield ketone **7068b** as a pale yellow oil (83 mg, 0.22 mmol, 93%).

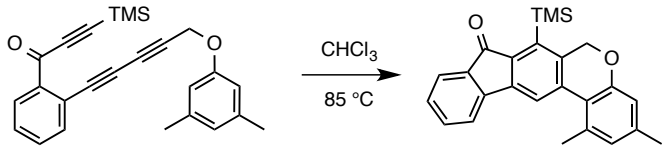
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 7.7, 1.4 Hz, 1H, *H3*), 7.61 (dd, *J* = 7.5, 1.4 Hz, 1H, *H6*), 7.51 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, *H5*), 7.47 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, *H4*), 6.65 (t of septets, *J* = 0.7, 0.7 Hz, 1H, *H4'*), 6.65 (dq, *J* = 0.7, 0.7 Hz, 2H, *H2'H6'*), 4.81 (s, 2H, C*H*$_2$O), 2.30 [dt, *J* = 0.6, 0.6 Hz, 6H, Ar(C*H*$_3$)$_2$], and 0.29 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 176.5, 157.8, 139.5, 139.2, 136.0, 132.8, 132.1, 129.1, 123.7, 121.4, 112.8, 101.8, 101.4, 79.9, 79.3, 76.8, 72.0, 56.5, 21.7, and -0.5.

IR: 2960, 2922, 2153, 1648, 1614, 1592, 1562, 1481, 1373, 1319, 1291, 1251, 1237, 1150, 1060, 1015, and 847 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{24}NaO_2Si^+$ $[M+Na]^+$ requires 407.1438; found 407.1437.

1,3-Dimethyl-7-(trimethylsilyl)fluoreno[2,3-c]chromen-8(6H)-one (7069b)



7068b ***7069b***

A solution of **7068b** (16 mg, 0.042 mmol) in $CHCl_3$ (1.4 mL) was heated at 85 °C for 18 h. The resulting mixture was directly subjected to MPLC (SiO_2, hexanes:EtOAc = 9:1) to yield **7069b** as a golden oil (14 mg, 0.036 mmol, 88%).

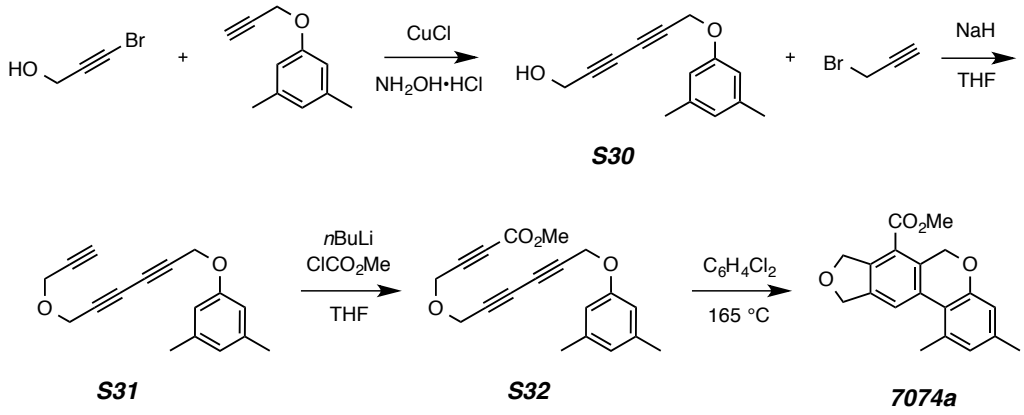
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H, *H13*), 7.61 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H9*), 7.50 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H12*), 7.47 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H, *H11*), 7.29 (ddd, *J* = 7.2, 7.2, 1.4 Hz, 1H, *H10*), 6.82 (d, *J* = 1.7 Hz, 1H, *H2*), 6.73 (d, *J* = 1.8 Hz, 1H, *H4*), 5.05 (s, 2H, C*H*$_2$O), 2.69 (s, 3H, C1-C*H*$_3$), 2.34 (s, 3H, C3-C*H*$_3$), and 0.46 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.8, 157.1, 144.2, 144.0, 141.6, 140.2, 139.0, 137.9, 136.0, 135.7, 134.6, 134.5, 129.2, 127.1, 124.1, 121.3, 119.7, 119.1, 115.2, 70.0, 22.4, 21.6, and 2.3.

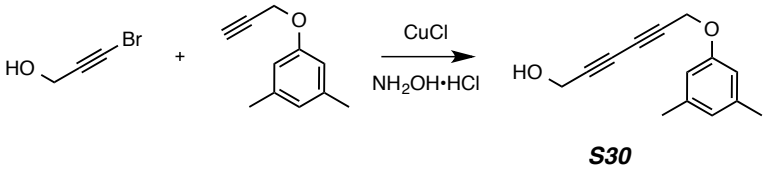
IR: 2949, 2921, 2855, 1709, 1606, 1588, 1463, 1300, 1294, 1248, 1181, 1135, 1071, 974, 961, 867, and 846 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{24}NaO_2Si^+$ $[M+Na]^+$ requires 407.1438; found 407.1435.

Synthesis of isobenzofuran 7074a



6-(3,5-Dimethylphenoxy)hexa-2,4-diyn-1-ol (S30)



Diynol **S30** was prepared following General Procedure C from 3-bromoprop-2-yn-1-ol[173] (520 mg, 3.9 mmol, 1.3 equiv), 1,3-dimethyl-5-(prop-2-yn-1-yloxy)benzene (480 mg, 3 mmol, 1 equiv), CuCl (30 mg, 0.3 mmol, 0.1 equiv), 30% aqueous $BuNH_2$ (12 mL), and Et_2O (12 mL). Diynol **S30** was obtained as a yellow oil (350 mg, 1.64 mmol, 55%) following purification by flash chromatography (hexanes:EtOAc = 5:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (s, 1H, Ar*H*4), 6.57 (s, 2H, Ar*H*2*H*6), 4.71 (br s, 2H), 4.32 (br s, 2H), and 2.29 (s, 6H, ArC*H*$_3$).

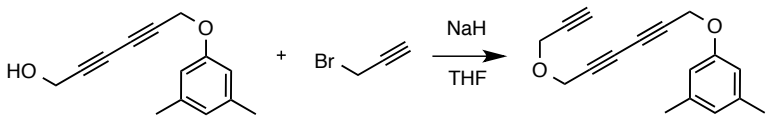
^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 139.5, 123.7, 112.8, 77.9, 74.8, 71.1, 70.0, 56.3, 51.6, and 21.6.

IR: 3600-3100, 2919, 2860, 2258, 2185, 1614, 1594, 1472, 1447, 1372, 1318, 1293, 1168, 1150, 1062, 1022, and 829 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{14}H_{14}NaO_2^+$ $[M+Na]^+$ requires 237.0886; found 237.0884.

[173] Ouyang, X., Fowler, F. W. & Lauher, J. W. Single-Crystal-to-Single-Crystal topochemical polymerizations of a terminal diacetylene: two remarkable transformations give the same conjugated polymer. *J. Am. Chem. Soc.* **2003**, *125*, 12400–12401.

3,5-Dimethyl-1-((6-(prop-2-yn-1-yloxy)hexa-2,4-diyn-1-yl)oxy)benzene (S31)



S30 ***S31***

A solution of diynol **S30** (214 mg, 1 mmol) in THF (2 mL) was added to a stirred suspension of NaH (80 mg, 60% suspension in mineral oil, 2 mmol) in THF (10 mL) at 0 ºC. The reaction mixture was allowed to warm to rt over 1 h and propargyl bromide (0.24 mL, 80 wt. % in toluene, 2.2 mmol) was added. After 18 h the mixture was cooled to 0 ºC, water was added, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexanes:EtOAc = 20:1) gave the triyne **S31** (110 mg, 0.44 mmol, 44%) as a colorless oil.

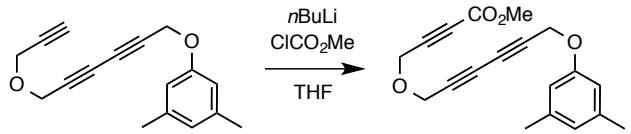
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (tqq, *J* = 0.7, 0.7, 0.7 Hz, 1H, Ar*H4*), 6.57 (dq, *J* = 0.7, 0.7 Hz, 2H, Ar*H2H6*), 4.73 (t, *J* = 0.9 Hz, 2H), 4.33 (t, *J* = 0.9 Hz, 2H), 4.25 (d, *J* = 2.4 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 1H, *H*C≡), and 2.30 [dt, *J* = 0.7, 0.7 Hz, 6H, Ar(C*H*$_3$)$_2$]

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 139.6, 123.8, 112.8, 78.7, 75.6, 75.1, 74.7, 71.11, 71.06, 57.1, 56.9, 56.3, and 21.7.

IR: 3295, 2965, 2918, 2855, 2119, 1614, 1594, 1472, 1443, 1344, 1318, 1293, 1168, 1150, 1081, 1065, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{17}H_{16}AgO_2^+$ $[M+Ag]^+$ requires 359.0196; found 359.0204 [the sample solution in MeOH was doped with $AgNO_3$ (ca. 10-100 μM) prior to introduction into the ionizing chamber].

Methyl 4-((6-(3,5-Dimethylphenoxy)hexa-2,4-diyn-1-yl)oxy)but-2-ynoate (S32)



S31 ***S32***

n-BuLi (0.072 mL, 2.5 M in hexanes, 0.18 mmol) was added to a stirred solution of triyne **S31** (40 mg, 0.16 mmol) in THF (1 mL) at -78 ºC. The reaction mixture turned dark green immediately. After 20 min methyl chloroformate (0.17 mL, 1.8 mmol) was added. After 30 min saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexanes:EtOAc = 20:1) yielded, in order of elution, recovered **S31** (15 mg, 0.06 mmol, 37%) and the triyne **S32** (20 mg, 0.064 mmol, 40%) as a clear amber oil.

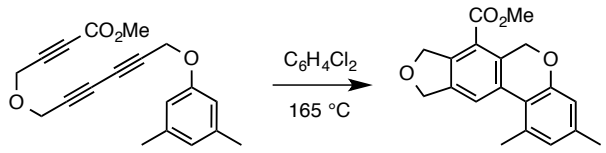
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (tqq, *J* = 0.7, 0.7, 0.7 Hz, 1H, Ar*H4*), 6.57 (dq, *J* = 0.7, 0.7 Hz, 2H, Ar*H2H6*), 4.73 (t, *J* = 0.9 Hz, 2H), 4.38 (s, 2H, OCH_2CCCO$_2$Me), 4.34 (t, *J* = 0.9 Hz, 2H), 3.79 (s, 3H, O*Me*), and 2.30 [dt, *J* = 0.7, 0.7 Hz, 6H, Ar(CH_3)$_2$]

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 153.6, 139.6, 123.8, 112.8, 82.5, 78.7, 75.0, 74.4, 71.7, 70.9, 57.6, 56.5, 56.3, 53.1, and 21.7.

IR: 2954, 2919, 2853, 2239, 1718, 1614, 1594, 1535, 1345, 1318, 1293, 1255, 1169, 1151, 1089, 1062, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{19}H_{18}NaO_4^+$ $[M+Na]^+$ requires 333.1097; found 333.1055.

Methyl 1,3-Dimethyl-8,10-dihydro-6*H*-isobenzofuro[5,6-*c*]chromene-7-carboxylate (7074a)



S32 ***7074a***

A solution of triyne **S32** (17 mg, 0.055 mmol) in dichlorobenzene (1.8 mL) was heated at 165 °C for 4.5 h. The resulting solution was cooled to rt and directly subjected to MPLC (hexanes:EtOAc = 5:1) to yield **7074a** as a pale yellow oil (11 mg, 0.035 mmol, 65%), which solidified upon standing.

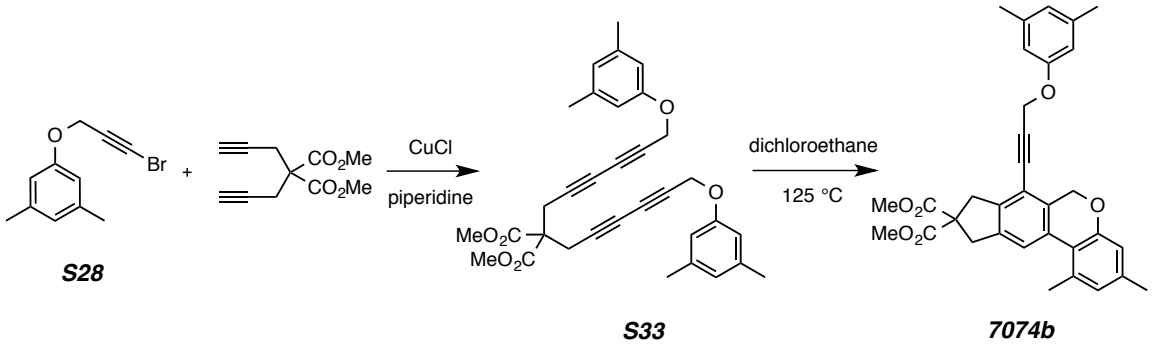
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (t, *J* = 1.0 Hz, 1H, Ar*H11*), 6.79 (s, 1H, Ar*H*), 6.76 (s, 1H, Ar*H*), 5.34 (t, *J* = 2.0 Hz, 2H), 5.31 (s, 2H), 5.18 (td, *J* = 2.0, 1.0 Hz), 3.93 (s, 3H, OCH_3), 2.59 (s, 3H, C1-CH_3), and 2.33 (s, 3H, C3-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 156.7, 139.8, 139.37, 139.36, 136.2, 135.0, 132.0, 127.0, 122.4, 122.0, 120.4, 115.4, 75.3, 73.6, 66.9, 52.4, 22.6, and 21.4.

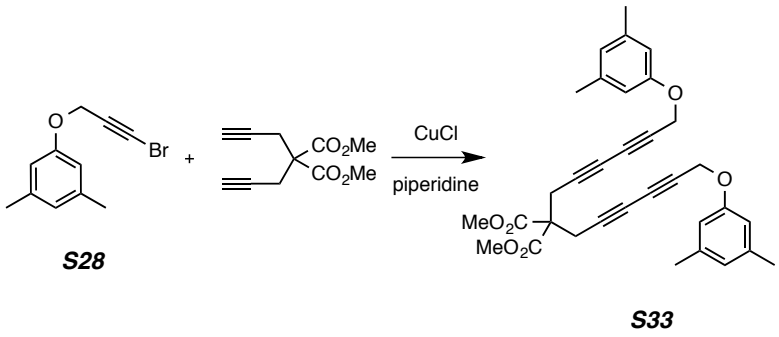
IR: 2951, 2920, 2854, 1717, 1616, 1563, 1462, 1434, 1362, 1321, 1294, 1260, 1240, 1222, 1195, 1177, 1114, 1057, 1025, 994, 911, and 846 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{19}H_{18}NaO_4^+$ $[M+Na]^+$ requires 333.1097; found 333.1131.
mp: 115-119 °C.

Synthesis of isobenzofuran 7074b



Dimethyl 2,2-Bis(6-(3,5-dimethylphenoxy)hexa-2,4-diyn-1-yl)malonate (S33)



Compound **S33** was prepared following General Procedure B from dimethyl 2,2-di(prop-2-yn-1-yl)malonate (176 mg, 0.85 mmol, 1 equiv), **S28** (480 mg, 2.01 mmol, 2.4 equiv), piperidine (2 mL), and CuCl (17 mg, 0.2 equiv). Tetrayne **S33** was isolated as a colorless solid (250 mg, 56%) following flash chromatography (hexanes:EtOAc = 6:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (s, 2H, Ar*H4*), 6.56 (s, 4H, Ar*H2H6*), 4.69 (s, 4H, OCH_2), 3.76 (s, 6H, OCH_3), 3.07 (s, 4H, CCH_2C), and 2.29 [s, 12H, Ar(CH_3)$_2$].

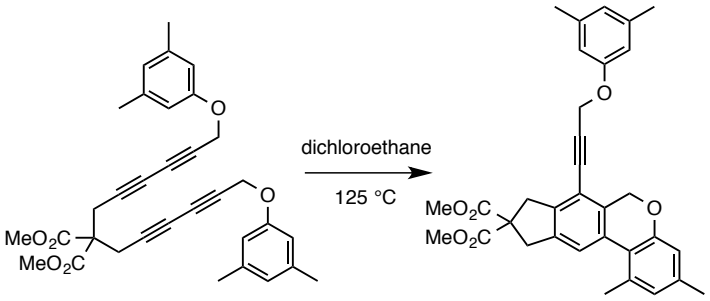
^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 157.7, 139.5, 123.7, 112.7, 75.0, 72.3, 71.5, 68.0, 56.7, 56.3, 53.6, 24.1, and 21.7.

IR: 2954, 2920, 2861, 2260, 1742, 1614, 1594, 1470, 1436, 1373, 1318, 1293, 1255, 1212, 1169, 1151, 1062, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{32}NaO_6^+$ $[M+Na]^+$ requires 547.2091; found 547.2097.

mp: 148-150 °C.

Dimethyl 7-(3-(3,5-Dimethylphenoxy)prop-1-yn-1-yl)-1,3-dimethyl-8,10-dihydroindeno[5,6-*c*]chromene-9,9(6*H*)-dicarboxylate (7074b)



S33 ***7074b***

A solution of tetrayne **S33** (26 mg, 0.05 mmol) in dichloroethane (1.7 mL) was heated at 125 °C for 20 h. The resulting solution was concentrated and purified by MPLC (hexanes:EtOAc = 5:1) to yield **7074b** as a colorless oil (22 mg, 0.042 mmol, 84%).

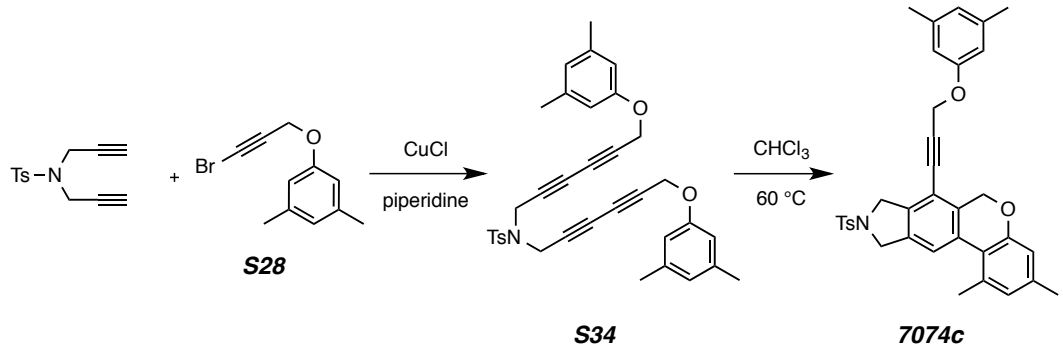
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (s, 1H, Ar*H11*), 6.73 (s, 1H, Ar*H*), 6.71 (s, 1H, Ar*H*), 6.68 (s, 1H, Ar*H*), 6.66 (s, 2H, Ar*H*), 5.00 (s, 2H, OCH_2), 4.96 (s, 2H, OCH_2), 3.76 (s, 6H, OCH_3), 3.65 (s, 2H, CCH_2Ar), 3.64 (s, 2H, CCH_2Ar), 2.58 (s, 3H, C1-CH_3), 2.32 [s, 6H, Ar(CH_3)$_2$], and 2.30 (s, 3H, C3-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 157.8, 156.5, 141.3, 139.4, 139.2, 138.9, 135.2, 134.7, 130.1, 126.8, 123.6, 122.2, 120.5, 115.6, 115.3, 113.1, 92.4, 82.4, 67.2, 59.8, 56.6, 53.3, 41.2, 40.6, 22.8, 21.7, and 21.4.

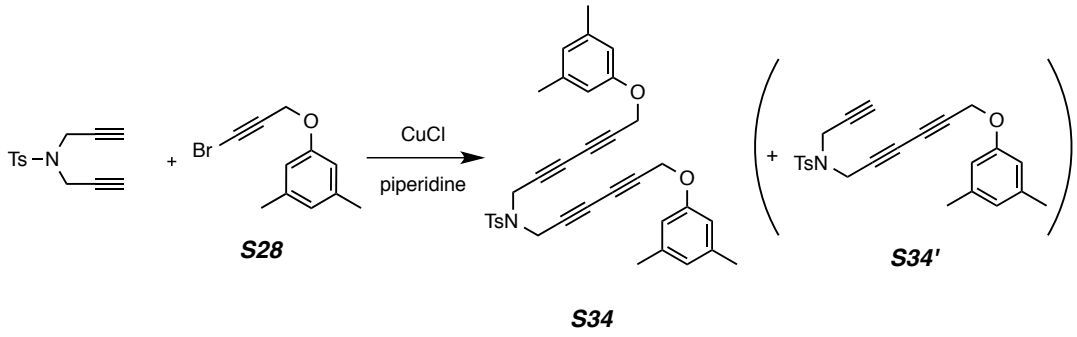
IR: 3005, 2988, 2953, 2854, 2260, 1737, 1615, 1594, 1455, 1435, 1318, 1291, 1277, 1260, 1246, 1199, 1166, and 764 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{32}NaO_6^+$ $[M+Na]^+$ requires 547.2091; found 547.2123.

Synthesis of isoindoline 7074c



***N,N*-Bis(6-(3,5-dimethylphenoxy)hexa-2,4-diyn-1-yl)-4-methylbenzenesulfonamide (S34)**



Compound **S34** was prepared following General Procedure B from *N,N*-di(prop-2-yn-1-yl) toluenesulfonamide[167] (176 mg, 0.71 mmol, 1 equiv), bromoalkyne **S28** (370 mg, 1.78 mmol, 2.5 equiv), piperidine (1.5 mL), and CuCl (14 mg, 0.2 equiv). Tetrayne **S34** and triyne **S34'** were isolated by flash chromatography (5:1 hexanes:EtOAc) as a coeluting mixture [pale yellow oil, 220 mg, **S34** (ca. 40%) and **S34'** (ca. 20%)]. Data for **S34** are taken from spectra of the mixture in which it was the major component.

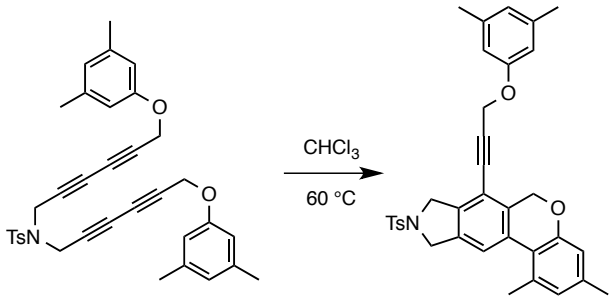
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 8.3, 2H, *o*-SO_2Ar*H*), 7.26 (d, J = 7.9 Hz, 2H, *m*-SO_2Ar*H*), 6.65 (s, 2H, Ar*H*p), 6.54 (s, 4H, Ar*H*o), 4.66 (s, 4H, CH_2O), 4.18 (s, 4H, CH_2N), 2.35 (s, 3H, SO_2ArCH_3), and 2.29 [s, 12H, Ar(CH_3)$_2$].

^{13}C NMR (125 MHz, HMQC, $CDCl_3$): δ 129.8, 127.7, 123.6, 112.5, 56.0, 37.4, 21.5, 21.5 (CH-containing carbons only, from the HMQC spectrum).

IR: 2919, 2855, 2258, 1614, 1594, 1471, 1447, 1353, 1319, 1293, 1164, 1152, 1093, 1064, and 892 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{32}H_{33}NNaO_4S^+$ $[M+Na]^+$ requires 586.2023; found 586.1998.

7-(3-(3,5-Dimethylphenoxy)prop-1-yn-1-yl)-1,3-dimethyl-9-tosyl-6,8,9,10-tetrahydrochromeno[3,4-*f*]isoindole (7074c)



S34 ***7074c***

A solution of **S34** (50 mg, containing ca. 50 mol% of **S34'**, ca. 0.065 mmol) in $CHCl_3$ (2 mL) was heated at 65 °C for 20 h. The reaction mixture was concentrated to dryness. The resulting oil was initially triturated with ethanol, and the resulting slurry was dissolved in additional dichloromethane. The resulting solution was allowed to evaporate slowly. Compound **7074c** precipitated as a light yellow solid. The yield of **7974c** was determined by ^{1}H NMR analysis of the crude oil (using **S34'** as the internal standard) to be (≥ 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H, *o*-SO_2Ar*H*), 7.43 (s, 1H, Ar*H11*), 7.30 (d, *J* = 8.4 Hz, 2H, *m*-SO_2Ar*H*), 6.74 (s, 1H, Ar*H*), 6.71 (s, 1H, Ar*H*), 6.70 (s, 1H, Ar*H*), 6.66 (s, 2H, Ar*Ho*), 4.96 (s, 2H, CH_2O), 4.95 (s, 2H, CH_2O), 4.66 (s, 2H, CH_2N), 4.62 (s, 2H, CH_2N), 2.54 (s, 3H, ArCH_3), 2.40 (s, 3H, ArCH_3), 2.35 [s, 6H, Ar(CH_3)$_2$], and 2.29 (s, 3H, ArCH_3).

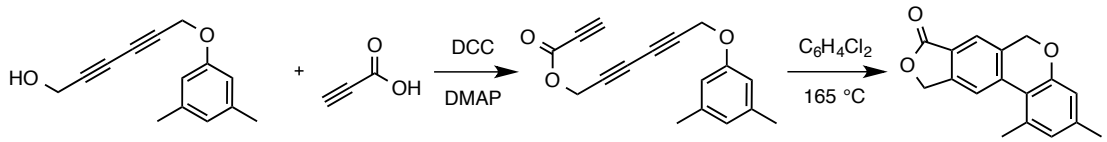
^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 156.6, 144.0, 139.58, 139.55, 137.3, 135.53, 135.48, 135.2, 133.9, 131.5, 130.1, 127.8, 127.0, 123.8, 120.3, 120.0, 115.7, 114.1, 113.0, 93.4, 81.2, 66.9, 56.4, 54.6, 53.9, 22.8, 21.7/21.7 (2 unresolved resonances, as confirmed by HSQC), and 21.4.

IR: 2953, 2919, 2854, 2254, 1615, 1594, 1457, 1349, 1292, 1164, 1098, 1066, and 910 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{32}H_{33}NNaO_4S^+$ $[M+Na]^+$ requires 586.2023; found 586.2019.

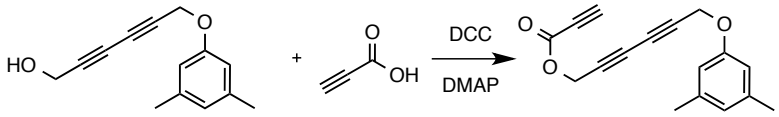
mp: 150-153 °C.

Synthesis of isobenzofuran 7074d



S30 ***S35*** ***7074d***

6-(3,5-Dimethylphenoxy)hexa-2,4-diyn-1-yl Propiolate (S35)



S30 ***S35***

Triyne **S35** was prepared following General Procedure D from **S30** (214 mg, 1 mmol), propiolic acid (84 mg, 1.2 mmol), DCC (227 mg, 1.1 mmol), DMAP (12 mg, 0.1 mmol), and CH_2Cl_2 (10 mL). **S35** was obtained following flash chromatography (hexanes:EtOAc = 12:1) as a light yellow oil (222 mg, 0.76 mmol, 76%).

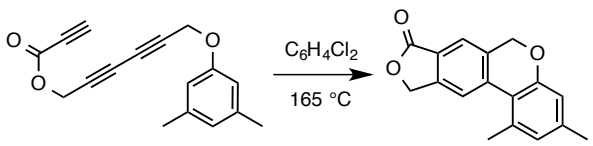
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (s, 1H, Ar*H*4), 6.56 (s, 2H, Ar*H*2*H*6), 4.84 (t, *J* = 1.0 Hz, 2H), 4.73 (t, *J* = 1.0 Hz, 2H), 2.96 (s, 1H, CC*H*), and 2.30 (s, 6H, ArC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 151.8, 139.6, 123.8, 112.7, 76.4, 75.8, 73.9, 72.0, 71.8, 70.7, 56.2, 54.0, and 21.7.

IR: 3280, 2920, 2124, 1723, 1615, 1594, 1472, 1445, 1363, 1318, 1293, 1206, 1169, 1151, 1064, 980, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{17}H_{14}NaO_3^+$ $[M+Na]^+$ requires 289.0835; found 289.0849.

1,3-Dimethyl-6*H*-isobenzofuro[5,6-*c*]chromen-8(10*H*)-one (7074d)



S35 ***7074d***

A solution of **S35** (21 mg, 0.072 mmol) in dichlorobenzene (2.4 mL) was heated at

165 °C for 4 h. The resulting solution was directly subjected to MPLC (hexanes:EtOAc = 3:1) to give isobenzofuran **7074d** as a colorless solid (17 mg, 0.058 mmol, 81%)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 1.0 Hz, 1H), 7.76 (d, *J* = 1.0 Hz, 1H), 6.82 (br s, 1H), 6.80 (br s, 1H), 5.36 (br s, 2H), 4.99 (br s, 2H), 2.66 (br s, 3H, C1-CH_3), and 2.34 (br s, 3H, C3-CH_3).

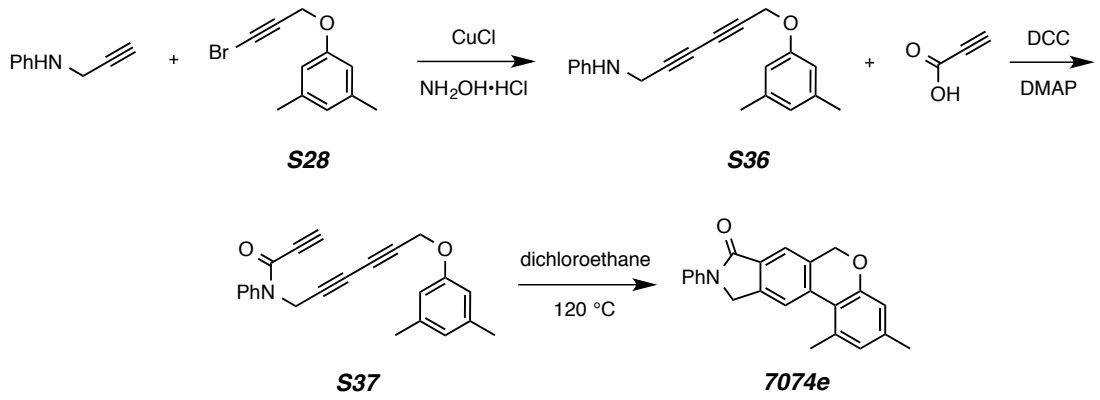
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 157.4, 146.7, 141.0, 137.4, 136.0, 135.1, 127.3, 123.6, 122.0, 119.9, 119.2, 116.0, 70.0, 69.2, 22.9, and 21.5.

IR: 2959, 2917, 2857, 1757, 1615, 1593, 1451, 1355, 1355, 1315, 1287, 1195, 1180, 1154, 1138, 1067, 1046, 1015, 1006, 908, 847, 776, and 755 cm^{-1}.

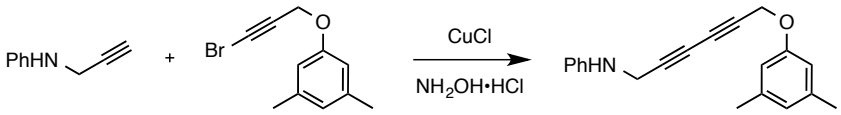
HRMS (ESI-TOF): Calcd for $C_{17}H_{14}NaO_3^+$ $[M+Na]^+$ requires 289.0835; found 289.0849.

mp: 154-156 °C.

Synthesis of isoindolones 7074e



***N*-(6-(3,5-Dimethylphenoxy)hexa-2,4-diyn-1-yl)aniline (S36)**



Diyne **S36** was prepared following General Procedure C from *N*-(prop-2-yn-1-yl)aniline (131 mg, 1 mmol), **S28** (287 mg, 1.2 mmol), CuCl (5 mg, 0.05 mmol), 30% aqueous $BuNH_2$ (4 mL), and Et_2O (4 mL). Compound **S36** was isolated as a clear yellow oil (170 mg, 0.059 mmol, 59%) after purification by flash chromatography (hexanes:EtOAc 12:1 then 5:1).

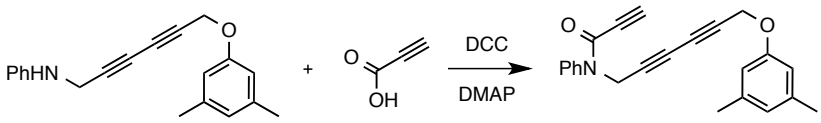
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.6, 7.4 Hz, 2H, NAr*H*m), 6.80 (tt, *J* = 7.4, 1.0 Hz, 1H, NAr*H*p), 6.66 (dd, *J* = 8.6, 1.0 Hz, 1H, NAr*H*o), 6.64 (s, 1H, OAr*H*p), 6.55 (s, 2H, OAr*H*o), 4.68 (s, 2H, CH_2O), 4.01 (s, 2H, CH_2N), 3.86 (s, 1H, N*H*), and 2.28 [s, 6H, Ar(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 146.7, 139.5, 129.5, 123.7, 119.1, 113.8, 112.7, 77.6, 73.2, 71.5, 67.4, 56.3, 34.5, and 21.7

IR: 3052, 3020, 2918, 2860, 2255, 1602, 1596, 1504, 1472, 1439, 1374, 1350, 1316, 1293, 1258, 1168, 1150, 1062, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{20}H_{19}NNaO^+$ $[M+Na]^+$ requires 312.1359; found 312.1371.

***N*-(6-(3,5-Dimethylphenoxy)hexa-2,4-diyn-1-yl)-*N*-phenylpropiolamide (S37)**



S36 ***S37***

To a solution of **S36** (289 mg, 1 mmol) and propiolic acid (84 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) was added DCC (227 mg, 1.1 mmol) and DMAP (12 mg, 0.1 mmol) in one portion. Compound **S37** was isolated using MPLC (hexanes:EtOAc = 3:1) as a clear yellow oil (208 mg, 0.61 mmol, 61%).

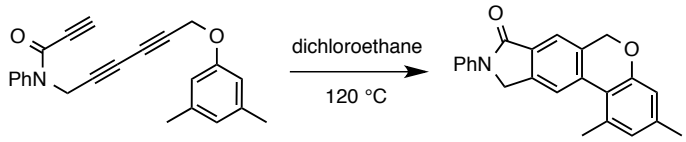
^{1}H NMR (500 MHz, $CDCl_3$, as a 8:1 ratio of two rotamers): Major rotamer δ 7.46-7.40 (m, 3H, NAr*H*m*H*p), 7.35-7.31 (m, 2H, NAr*H*o), 6.65 (s, 1H, OAr*H*p), 6.56 (s, 2H, OAr*H*o), 4.70 (s, 2H, CH_2O), 4.60 (s, 2H, CH_2N), 2.84 (s, 1H, C≡C*H*), and 2.29 [s, 6H, Ar(CH_3)$_2$]. Minor rotamer δ 4.80 (s, 2H, CH_2O), 4.75 (s, 2H, CH_2N), 3.32 (s, 1H, C≡C*H*), and 2.42 [s, 6H, Ar(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 152.8, 140.4, 139.5, 129.7, 129.2, 128.4, 123.7, 112.7, 80.7, 75.8, 74.2, 73.8, 71.2, 68.7, 56.3, 38.8, and 21.7 (only resonances for the major rotamer are reported).

IR: 3287, 2919, 2859, 2111, 1644, 1614, 1594, 1493, 1383, 1318, 1292, 1276, 1220, 1168, 1151, 1063, 831, 765, and 750 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{19}NNaO_2^+$ $[M+Na]^+$ requires 364.1308; found 364.1311.

1,3-Dimethyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7074e)



S37 ***7074e***

A solution of **S37** (20 mg, 0.059 mmol) in dichloroethane (2 mL) was heated at 120 °C for 18 h. The resulting solution was concentrated and subjected to MPLC (hexanes:EtOAc = 3:1) to give **7074e** as a colorless solid (17 mg, 0.05 mmol, 85%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 8.9, 1.3 Hz, 2H, *Ho*), 7.83 (br s, 1H, *H7*), 7.77 (br s, 1H, *H11*), 7.44 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.19 (tt, *J* = 7.4, 1.2 Hz, 1H, *Hp*), 6.82 (d, *J* = 1.6 Hz, 1H, *H2* or *H4*), 6.78 (d, *J* = 1.7 Hz, 1H, *H4* or *H2*), 5.01 (s, 2H, *H6* or *H10*), 4.92 (s, 2H, *H6* or *H10*), 2.69 (s, 3H, C1-CH_3), 2.34 (s, 3H, C3-CH_3).

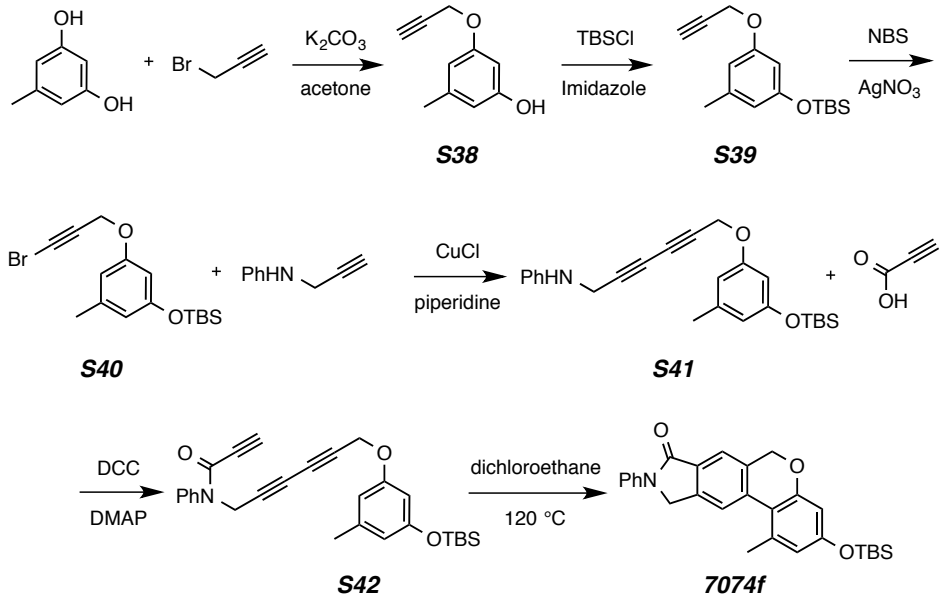
^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 157.2, 140.3, 140.1, 139.8, 135.7, 135.3, 134.3, 131.3, 129.4, 127.2, 124.6, 120.5, 120.3, 120.0, 119.5, 116.0, 69.3, 51.1, 23.0, and 21.4.

IR: 2981, 2916, 2856, 1682, 1616, 1597, 1502, 1448, 1387, 1287, 1180, 1130, 1061, 1011, 891, and 857 cm^{-1}.

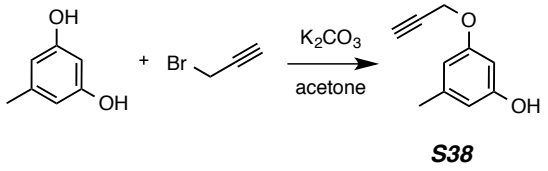
HRMS (ESI-TOF): Calcd for $C_{23}H_{19}NNaO_2^+$ $[M+Na]^+$ requires 364.1308; found 364.1298.

mp: 235-239 °C.

Synthesis of isoindolone 7074f



3-Methyl-5-(prop-2-yn-1-yloxy)phenol (S38)



K_2CO_3 (2.76 g, 20 mmol, 2 equiv) was added to a solution of orcinol (1.24 g, 10 mmol, 1 equiv) and 3-bromoprop-1-yne (1.77 g, 15 mmol, 1.5 equiv) in acetone (50 mL). The resulting mixture was heated at 50 °C with stirring overnight. The resulting slurry was partitioned between EtOAc and H_2O. The aqueous layer was washed with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting oil was subjected to flash chromatography (hexanes:EtOAc = 19:1 then 5:1 then 3:1) to give **S38** as a light yellow oil (550 mg, 3.4 mmol, 34%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 (br dd, *J* = 1.8, 1.8 Hz, 1H), 6.30 (overlapping d, *J* = 1.8 Hz, 2H), 4.65 (s, 1H, O*H*), 4.64 (d, *J* = 2.4 Hz, 2H, CH_2O), 2.52 (t, *J* = 2.4 Hz, 1H, C≡C*H*), and 2.28 (br s, 3H, CH_3).

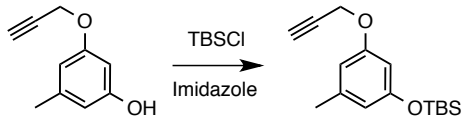
^{13}C NMR (125 MHz, $CDCl_3$):

δ 159.0, 156.6, 140.9, 109.7, 108.4, 99.8, 78.8, 75.7, 56.0, and 21.8.

IR: 3390, 3290, 2923, 2867, 2123, 1596, 1496, 1467, 1372, 1327, 1305, 1146, 1056, 1023, and 832 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{10}H_9O_2^-$ $[M-H]^-$ requires 161.0608; found 161.0606.

***tert*-Butyldimethyl(3-methyl-5-(prop-2-yn-1-yloxy)phenoxy)silane (S39)**



S38 ***S39***

TBSCl (360 mg, 2.4 mmol, 1.2 equiv) and imidazole (272 mg, 4 mmol, 2 equiv) were sequentially added to a solution of **S38** (324 mg, 2 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt. After 3 h the reaction mixture was partitioned between CH_2Cl_2 (20 mL) and saturated aqueous NH_4Cl (20 mL). The aqueous layer was washed with CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc = 19:1) to give **S39** as a clear colorless oil (510 mg, 1.84 mmol, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (s, 1H, Ar*H*), 6.32 (s, 1H, Ar*H*), 6.30 (dd, *J* = 2.1, 2.1 Hz, 1H, Ar*H*), 4.63 (d, *J* = 2.4 Hz, 2H, CH_2O), 2.51 (t, *J* = 2.4 Hz, 1H, C≡C*H*), 2.27 (s, 3H, ArCH_3), 0.98 [s, 9H, C(CH_3)$_3$], and 0.19 [s, 6H, Si(CH_3)$_2$].

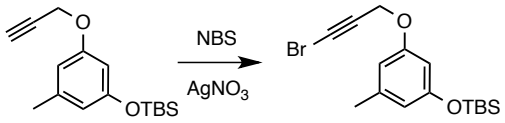
^{13}C NMR (125 MHz, $CDCl_3$):

δ 158.6, 156.7, 140.3, 114.6, 108.9, 104.4, 78.9, 75.6, 56.0, 25.9, 21.9, 18.4 and -4.2.

IR: 3307, 2957, 2930, 2859, 2124, 1590, 1471, 1463, 1370, 1324, 1254, 1154, 1061, 1038, and 839 cm^{-1}.

GC-LRMS: t_R = 8.29 min. *m*/*z*: 276 (M+, 100), 261 (M+-CH_3, 20), 248 (M+-C_2H_4, 20), 219 [M+-C$(CH_3)_3$, 90], 203 (45), 189 (65), and 145 (70).

(3-((3-Bromoprop-2-yn-1-yl)oxy)-5-methylphenoxy)(*tert*-butyl)dimethylsilane (S40)



S39 ***S40***

Bromoalkyne **S40** was prepared following General Procedure A from **S39** (276 mg, 1 mmol, 1 equiv), NBS (186 mg, 1.05 mmol, 1.05 equiv), $AgNO_3$ (16 mg, 0.1 mmol, 0.1 equiv), and acetone (10 mL). The reaction was closely monitored (GC analysis) to minimize over-bromination on the aromatic ring. **S40** was obtained as a clear yellow oil (320 mg, 0.90 mmol, 90%) following flash chromatography (hexanes:EtOAc = 19:1).

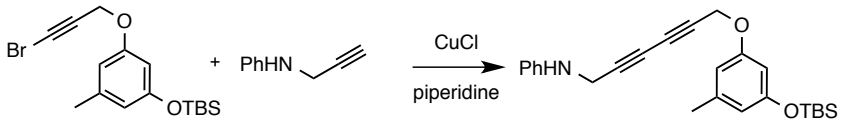
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 (s, 1H, Ar*H*), 6.32 (s, 1H, Ar*H*), 6.28 (dd, *J* = 2.1, 2.1 Hz, 1H, Ar*H*), 4.65 (s, 2H, CH_2O), 2.27 (s, 3H, ArCH_3), 0.98 [s, 9H, C(CH_3)$_3$], and 0.20 [s, 6H, Si(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 156.7, 140.4, 114.7, 109.0, 104.3, 75.4, 56.9, 47.6, 25.9, 21.8, 18.4, and -4.2.

IR: 2956, 2930, 2859, 2219, 1590, 1471, 1463, 1371, 1323, 1300, 1254, 1153, 1067, 1042, and 839 cm^{-1}.

GC-LRMS: t_R = 9.71 min. *m/z*: 356 (M+, 70), 354 (M+, 70), 299 [M+-C$(CH_3)_3$, 20], 297 [M+-C$(CH_3)_3$, 20], 284 (15), 282 (15), 269 (20), 267 (20), 217(50), 203 (100), 189 (40), and 73 (45).

***N*-(6-(3-((*tert*-Butyldimethylsilyl)oxy)-5-methylphenoxy)hexa-2,4-diyn-1-yl)aniline (S41)**



S40 ***S41***

Diyne **S41** was prepared following General Procedure B from **S40** (316 mg, 0.89 mmol, 1.2 equiv), *N*-(prop-2-yn-1-yl)aniline (100 mg, 0.76 mmol, 1 equiv), CuCl (8 mg, 0.08 mmol, 0.1 equiv), and piperidine (2 mL). **S41** was obtained following flash chromatography (hexanes:EtOAc = 5:1) as a clear yellow oil (220 mg, 0.54 mmol, 71%).

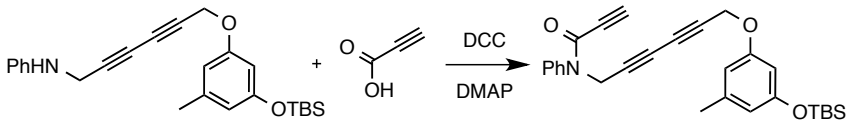
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.6, 7.4 Hz, 2H, Ar*H*m), 6.80 (tt, *J* = 7.3, 1.0 Hz, 1H, Ar*H*p), 6.67 (dd, *J* = 8.6, 1.0 Hz, 2H, Ar*H*o), 6.35 (m, 1H, Ar*H*), 6.31 (m, 1H, Ar*H*), 6.25 (m, 1H, Ar*H*), 4.66 (s, 2H, CH_2O), 4.01 (d, *J* = 6.1 Hz, 2H, NHCH_2), 3.86 (br t, *J* = 5.6 Hz, 1H, N*H*CH_2), 2.26 (s, 3H, ArCH_3), 0.97 [s, 9H, C(CH_3)$_3$], and 0.18 [s, 6H, Si(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 156.7, 146.7, 140.4, 129.5, 119.1, 114.7, 113.8, 108.9, 104.3, 77.7, 73.0, 71.6, 67.3, 56.4, 34.4, 25.9, 21.9, 18.4, and -4.2.

IR: 3400, 2955, 2930, 2886, 2858, 2258, 1603, 1591, 1505, 1471, 1463, 1321, 1254, 1152, 1058, 1035, and 840 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{25}H_{31}NNaO_2Si^+$ $[M+Na]^+$ requires 428.2016; found 428.2011.

_N_-(6-(3-((*tert*-Butyldimethylsilyl)oxy)-5-methylphenoxy)hexa-2,4-diyn-1-yl)-_N_-phenylpropiolamide (S42)



S41 ***S42***

Amide **S42** was prepared following General Procedure D from **S41** (202 mg, 0.5 mmol), propiolic acid (42 mg, 0.6 mmol), DCC (125 mg, 0.6 mmol), DMAP (6 mg, 0.05 mmol), and CH_2Cl_2 (4 mL). Amide **S42** was obtained following flash chromatography (hexanes:EtOAc = 3:1) as a clear yellow oil (119 mg, 0.26 mmol, 52%).

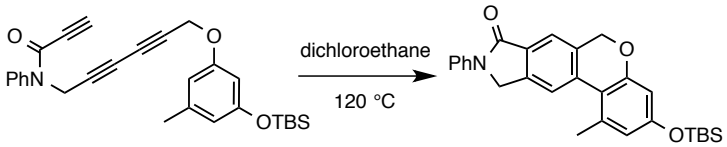
^{1}H NMR (500 MHz, $CDCl_3$, as a 6.5:1 ratio of two rotamers): Major rotamer δ 7.47-7.40 (m, 3H, Ar*H*o*H*p), 7.36-7.31 (m, 2H, Ar*H*m), 6.36 (s, 1H, Ar*H*), 6.32 (s, 1H, Ar*H*), 6.25 (s, 1H, Ar*H*), 4.67 (s, 2H, CH_2), 4.60 (s, 2H, CH_2), 2.83 (s, 1H, C≡C*H*), 2.27 (s, 3H, ArCH_3), 0.97 [s, 9H, C(CH_3)$_3$], and 0.19 [s, 6H, Si(CH_3)$_2$]. Minor rotamer δ 4.78 (s, 2H, CH_2), 4.69 (s, 2H, CH_2), and 3.29 (s, 1H, C≡C*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 156.7, 152.7, 140.4, 140.3, 129.6, 129.2, 128.4, 114.7, 108.8, 104.3, 80.7, 75.8, 74.2, 73.6, 71.3, 68.6, 56.3, 38.8, 25.9, 21.8, 18.4, and -4.2. (only resonances for the major rotamer are reported).

IR: 3286, 2955, 2930, 2858, 2112, 1648, 1644, 1591, 1493, 1469, 1463, 1382, 1323, 1294, 1271, 1253, 1220, 1151, 1058, 1034, and 840 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{28}H_{31}NNaO_3Si^+$ $[M+Na]^+$ requires 480.1965; found 480.1950.

3-((*tert*-Butyldimethylsilyl)oxy)-1-methyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7074f)



S42 ***7074f***

A solution of **S42** (25 mg, 0.055 mmol) in dichloroethane (1.8 mL) was heated to 120 °C for 18 h. The resulting solution was concentrated and subjected to MPLC (hexanes:EtOAc = 3:1) to give **7074f** as a colorless solid (21 mg, 0.046 mmol, 84%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.7, 1.1 Hz, 2H, *Ho*), 7.77 (s, 1H, *H7* or *H11*), 7.74 (s, 1H, *H7* or *H11*), 7.43 (dd, *J* = 8.8, 7.4 Hz, 2H, *Hm*), 7.18 (tt, *J* = 7.4, 1.0 Hz, 1H, *Hp*), 6.50 (d, *J* = 2.5 Hz, 1H, *H2*), 6.44 (d, *J* = 2.5 Hz, 1H, *H4*), 4.99 (s, 2H, *H6* or *H10*), 4.90 (s, 2H, *H6* or *H10*), 2.66 (s, 3H, ArCH_3), 1.00 [s, 9H, $C(CH_3)_3$], and 0.25 [s, 6H, $Si(CH_3)_2$].

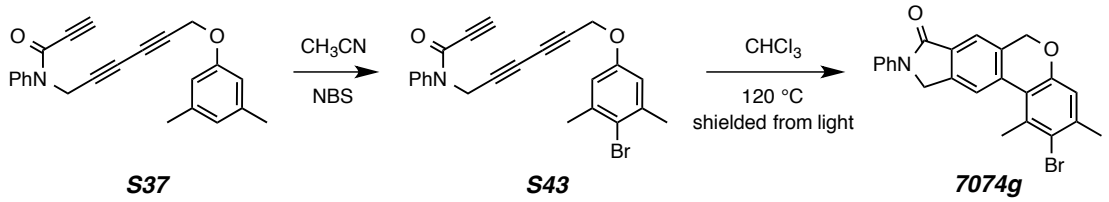
^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 158.3, 156.9, 140.2, 139.8, 137.2, 135.4, 133.6, 130.9, 129.4, 124.6, 120.5, 119.6, 119.5, 118.4, 116.9, 106.8, 69.5, 51.1, 25.9, 23.1, 18.4, and -4.1.

IR: 2956, 2931, 2859, 1700, 1689, 1681, 1608, 1596, 1563, 1501, 1494, 1473, 1456, 1441, 1405, 1380, 1316, 1254, 1175, 1154, 1067, 853, and 836 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{28}H_{31}NNaO_3Si^+$ $[M+Na]^+$ requires 480.1965; found 480.1955.

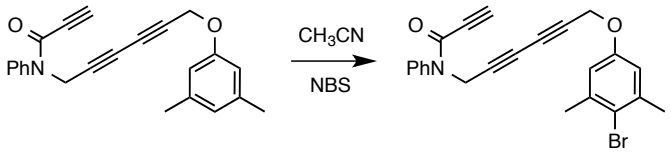
mp: 188-193 °C.

Synthesis of isoindolone 7074g



S37 ***S43*** ***7074g***

***N*-(6-(4-Bromo-3,5-dimethylphenoxy)hexa-2,4-diyn-1-yl)-*N*-phenylpropiolamide (S43)**



S37 ***S43***

NBS (15 mg, 0.085 mmol) was added to a solution of **S37** (28 mg, 0.082 mmol) in CH_3CN (0.27 mL)[174]. The reaction mixture was stirred for 1 h at rt and partitioned between H_2O and EtOAc. The aqueous layer was washed with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc = 3:1) to give **S38** as a clear brown oil (29 mg, 0.069 mmol, 84%).

^{1}H NMR (500 MHz, $CDCl_3$, as a 9:1 ratio of two rotamers): Major rotamer δ 7.46-7.39 (m, 3H, ArH_mH_p), 7.33 (dd, J = 8.0, 2.1 Hz, 2H, ArH_o), 6.67 (br s, 2H, Ar*H2/H6*), 4.68 (t, J = 0.9 Hz, 2H, OCH_2 or NCH_2), 4.59 (t, J = 0.9 Hz, 2H, OCH_2 or NCH_2), 2.84 (s, 1H, C≡C*H*), and 2.39 [br s, 6H, Ar(CH_3)$_2$]. Minor rotamer δ 4.78 (br s, 2H, OCH_2), 4.71 (br s, 2H, NCH_2), and 3.30 (s, 1H, C≡C*H*).

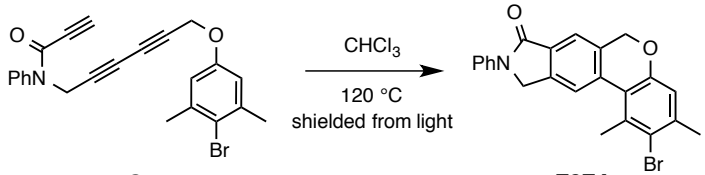
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 152.7, 140.4, 139.5, 129.7, 129.2, 128.4, 119.6, 114.9, 80.8, 75.8, 74.4, 73.3, 71.5, 68.5, 56.5, 38.8, and 24.3. (only resonances for the major rotamer are reported)

[174] Eli, Z-C.; Karla, A.; Siegel, J. S. Synthesis of arylbromides from arenes and *N*-bromosuccinimide (NBS) in acetonitrile—A convenient method for aromatic bromination. *Can. J. Chem.* **2009**, *87*, 440-447.

IR: 2922, 2857, 2111, 1644, 1593, 1585, 1494, 1468, 1384, 1310, 1293, 1276, 1220, 1160, 1067, 1031, and 1017 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{23}H_{18}BrNNaO_2^+$ $[M+Na]^+$ requires 442.0413; found 442.0420.

2-Bromo-1,3-dimethyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7074g)



S43 ***7074g***

A solution of **S43** (15 mg, 0.036 mmol) in $CHCl_3$ (1 mL) was heated to 120 °C for 18 h shielded from light. The resulting solution was concentrated and subjected to MPLC (hexanes:EtOAc = 3:1) to give **7074g** as a colorless solid (11.5 mg, 0.028 mmol, 77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.8, 1.1 Hz, 2H, *Ho*), 7.79 (s, 1H, *H7* or *H11*), 7.73 (s, 1H, *H7* or *H11*), 7.44 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.20 (tt, *J* = 7.4, 1.0 Hz, 1H, *Hp*), 6.90 (br s, 1H, *H4*), 5.00 (s, 2H, OCH_2 or NCH_2), 4.92 (s, 2H, OCH_2 or NCH_2), 2.79 (s, 3H, C1-CH_3), and 2.45 (br s, 3H, C3-CH_3).

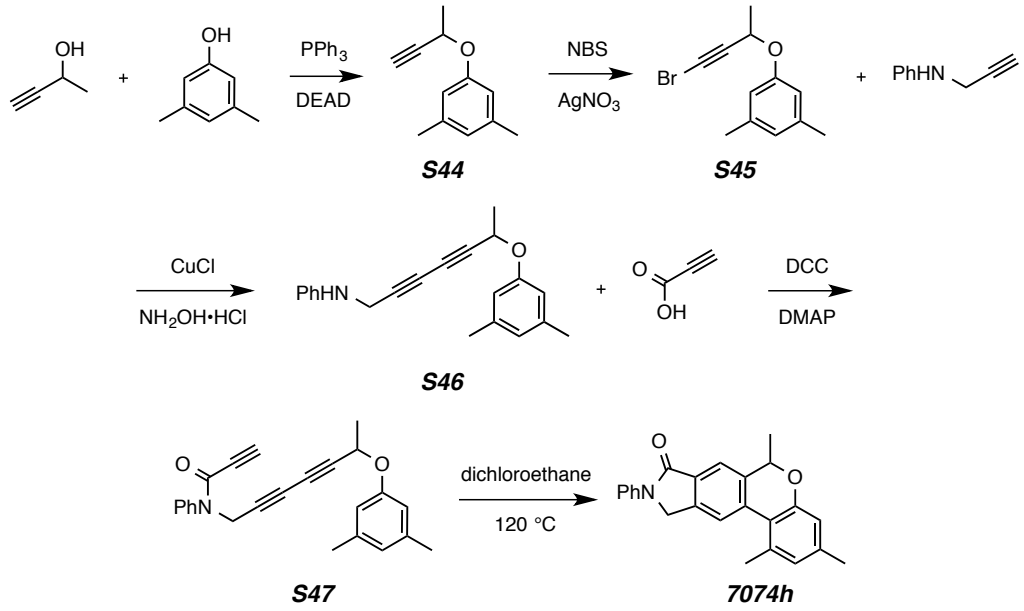
^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 155.7, 140.6, 140.1, 139.7, 135.5, 134.9, 134.3, 131.9, 129.4, 124.8, 123.0, 122.8, 120.9, 120.8, 119.6, 117.2, 69.5, 51.1, 24.7, and 24.1.

IR: 2918, 2854, 1686, 1625, 1596, 1502, 1444, 1377, 1289, 1179, 1169, 1132, 1069, 957, 895, and 857 cm^{-1}.

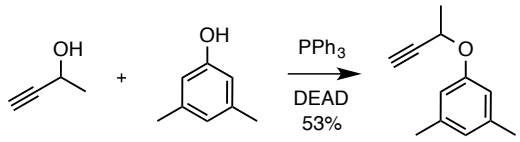
HRMS (ESI-TOF): Calcd for $C_{23}H_{18}BrNNaO_2^+$ $[M+Na]^+$ requires 442.0413; found 442.0434.

mp: 272-274 °C.

Synthesis of isoindolone 7074h



1-(But-3-yn-2-yloxy)-3,5-dimethylbenzene (S44)



To a solution of but-3-yn-2-ol (560 mg, 8 mmol), 3,5-dimethylphenol (976 mg, 8 mmol), and PPh_3 (2.1 g, 8 mmol) in THF cooled at 0 °C was added diisopropyl azodicarboxylate (1.94 g, 9.6 mmol) dropwise. The resulting solution was stirred at this temperature for an additional 3 h. The resulting mixture was partitioned between H_2O and EtOAc. The aqueous layer was washed with EtOAc (20 mL x 2). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting slurry was purified by flash chromatography (hexanes:EtOAc = 25:1) to give **S44** as a light yellow oil (730 mg, 4.2 mmol, 53%), which solidified upon standing.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (overlapping s, 3H, Ar*H*), 4.85 (qd, *J* = 6.5, 2.0 Hz, 1H, C*H*OAr), 2.45 (d, *J* = 2.0 Hz, 1H, C≡C*H*), 2.29 [dt, *J* = 0.7, 0.7 Hz, 6H, Ar(CH_3)$_2$], and 1.64 (d, *J* = 6.5 Hz, 3H, CH_3CH).

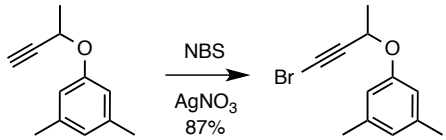
^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 139.3, 123.5, 113.6, 83.4, 73.8, 63.5, 22.4, and 21.7.

IR: 3293, 2990, 2938, 2920, 2115, 1613, 1594, 1470, 1447, 1375, 1317, 1291, 1169, 1154, 1127, 1091, 1054, and 830 cm-1.

GC-LRMS: t_R = 5.59 min. *m/z*: 174 (M+, 70), 159 (M+-CH_3, 95), 122 (M+ -C_4H_4, 100), 107 (M+ -C_5H_7, 80), 91 (C_7H_7+, 30), 77 (C_6H_5+, 28), and 53 (20).

mp: 46-48 °C.

1-((4-Bromobut-3-yn-2-yl)oxy)-3,5-dimethylbenzene (S45)



S44 ***S45***

Bromoalkyne **S45** was prepared following General Procedure A from **S44** (530 mg, 3.05 mmol), NBS (563 mg, 3.20 mmol), $AgNO_3$ (50 mg, 0.3 mmol), and acetone (20 mL). **S45** was obtained as a yellow oil (670 mg, 2.65 mmol, 87%), which solidified upon standing, following flash chromatography (Hexanes:EtOAc = 20:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 1H, Ar*Hp*), 6.61 (s, 2H, Ar*Ho*), 4.84 (q, *J* = 6.6 Hz, 1H, C*H*OAr), 2.29 [s, 6H, Ar(CH_3)$_2$], and 1.62 (d, *J* = 6.6 Hz, 3H, CH_3CH).

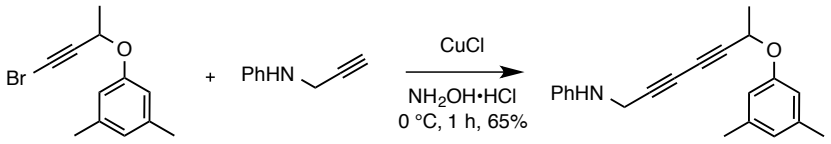
^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 139.4, 123.5, 113.6, 79.8, 64.5, 46.0, 22.4, and 21.7.

IR: 2989, 2936, 2920, 2209, 1613, 1594, 1471, 1450, 1374, 1316, 1291, 1169, 1154, 1131, 1093, 1060, and 829 cm^{-1}.

GC-LRMS: t_R = 7.23 min. *m/z:* 254 (M+, 15), 252 (M+, 15), 239 (M+-CH_3, 10), 237 (M+-CH_3, 10), 173 (M+-Br, 40), 145 (30), 122 (M+-BrC_4H_3, 100), 107 (M+-BrC_4H_3-CH_3, 70), 91 (C_7H_7+, 25), and 77 (C_6H_5+, 25).

mp: 41-51 °C.

***N*-(6-(3,5-Dimethylphenoxy)hepta-2,4-diyn-1-yl)aniline (S46)**



S45 ***S46***

Diyne **S46** was prepared following General Procedure C from **S45** (625 mg, 2.48 mmol, 1.24 equiv), *N*-(prop-2-yn-1-yl)aniline (262 mg, 2 mmol, 1 equiv), CuCl (10 mg, 0.1 mmol, 0.05 equiv), 30% aqueous $BuNH_2$ (8 mL), and Et_2O (8 mL). **S46** was obtained as a clear yellow oil (394 mg, 1.3 mmol, 65%) following flash chromatography (hexanes:EtOAc = 5:1).

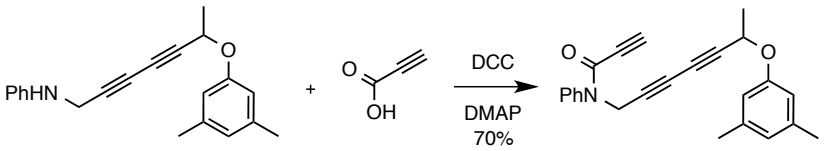
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (t, *J* = 7.5 Hz, 2H, NAr*Hm*), 6.79 (t, *J* = 7.5 Hz, 1H, NAr*Hp*), 6.65 (d, *J* = 7.5 Hz, 2H, NAr*Ho*), 6.63 (s, 1H, OAr*Hp*), 6.58 (s, 1H, OAr*Ho*), 4.84 (q, *J* = 6.6 Hz, 1H, CH_3CH), 3.99 (s, 2H, NCH_2), 3.85 (br s, 1H, N*H*), 2.28 [s, 6H, $Ar(CH_3)_2$], and 1.61 (d, *J* = 6.6 Hz, CH_3CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4, 146.7, 139.4, 129.5, 123.6, 119.0, 113.7, 113.5, 77.6, 77.4, 70.0, 67.3, 63.9, 34.4, 22.3, and 21.7

IR: 3470-3330, 3051, 2988, 2919, 2870, 2250, 2165, 1602, 1594, 1504, 1472, 1439, 1314, 1290, 1260, 1168, 1153, 1081, 1048, 964, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{21}H_{21}NNaO^+$ $[M+Na]^+$ requires 326.1515; found 326.1521.

_N_-(6-(3,5-Dimethylphenoxy)hepta-2,4-diyn-1-yl)-_N_-phenylpropiolamide (S47)



S46 ***S47***

To a solution of **S20** (303 mg, 1 mmol, 1 equiv) and propiolic acid (84 mg, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (8 mL) cooled at 0 °C was added DCC (237 mg, 1.15 mmol, 1.15 equiv) and DMAP (6 mg, 0.05 mmol, 0.05 equiv) in one portion. Amide **S47** was obtained following flash chromatography (hexanes:EtOAc = 3:1) as a clear brown oil (249 mg, 0.7 mmol, 70%).

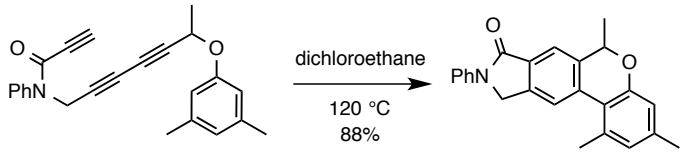
^{1}H NMR (500 MHz, $CDCl_3$, as a 8.5:1 ratio of two rotamers): Major rotamer δ 7.46-7.30 (m, 5H, NAr*H*), 6.64 (s, 1H, OAr*Hp*), 6.58 (s, 1H, OAr*Ho*), 4.86 (q, *J* = 6.6 Hz, 1H, CH_3CH), 4.57 (s, 2H, NCH_2), 2.83 (s, 1H, CC*H*), 2.29 [s, 6H, $Ar(CH_3)_2$], and 1.62 (d, *J* = 6.6 Hz, CH_3CH). Minor rotamer δ 6.59 (s, 1H, OAr*Hp*), 4.59 (s, 2H, NCH_2), 4.88 (q, *J* = 6.6 Hz, 1H, CH_3CH), 4.76 (s, 2H, NCH_2), 3.28 (s, 1H, CC*H*), and 1.64 (d, *J* = 6.7 Hz, CH_3CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4, 152.7, 140.5, 139.4, 129.6, 129.2, 128.4, 123.6, 113.5, 80.7, 78.0, 75.8, 74.1, 69.8, 68.7, 63.9, 38.9, 22.2, and 21.7 (only resonances for the major rotamer are reported).

IR: 3282, 2917, 2849, 2111, 1644, 1613, 1594, 1493, 1383, 1315, 1290, 1278, 1220, 1168, 1153, 1116, 1082, 1052, 1016, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{24}H_{21}NNaO_2^+$ $[M+Na]^+$ requires 378.1465; found 378.1455.

1,3,6-Trimethyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7074h)



S47 ***7074h***

A solution of **S47** (17 mg, 0.048 mmol) in dichloroethane (1.6 mL) was heated to 120

°C for 18 h. The resulting solution was concentrated and subjected to MPLC (hexanes:EtOAc = 3:1) to give **7074h** as a colorless solid (15 mg, 0.042 mmol, 88%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (dd, *J* = 8.8, 1.1 Hz, 2H, *Ho*), 7.80 (br s, 1H, *H7* or *H11*), 7.78 (br s, 1H, *H7* or *H11*), 7.43 (dd, *J* = 8.6, 7.4 Hz, 2H, *Hm*), 7.18 (tt, *J* = 7.4, 1.0 Hz, 1H, *Hp*), 6.79 (br d, *J* = 1.7 Hz, 1H, *H2*), 6.76 (br d, *J* = 1.7 Hz, 1H, *H4*), 5.02 (q, *J* = 6.5 Hz, 1H, C*H*CH_3), 4.91 (d, *J* = 16.1 Hz, 1H, *H10a*), 4.86 (d, *J* = 16.1 Hz, 1H, *H10b*), 2.68 (s, 3H, C1-*CH_3*), 2.33 (s, 3H, C3-*CH_3*), and 1.73 (d, *J* = 6.5 Hz, 3H, CHC*H_3*).

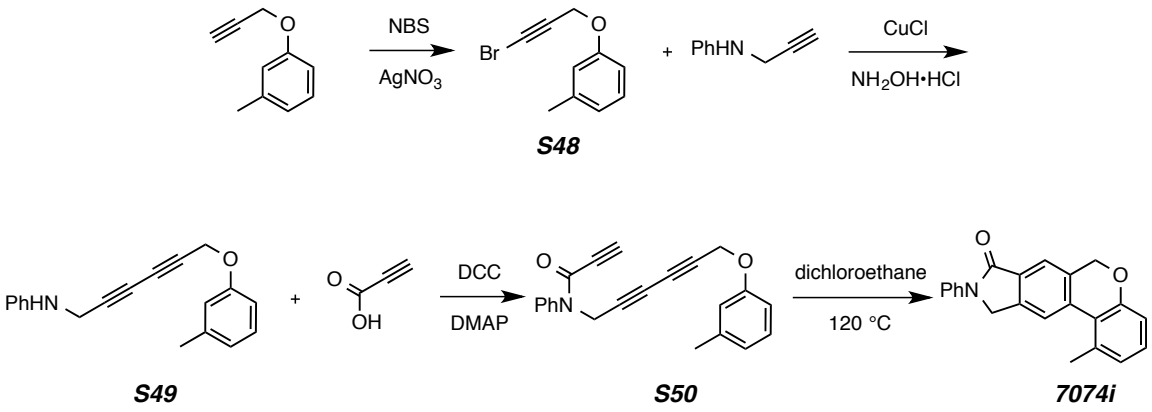
^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 156.2, 140.2, 139.8, 139.6, 138.5, 135.4, 135.1, 131.4, 129.4, 127.0, 124.6, 120.3, 120.1, 119.6, 119.3, 116.2, 73.9, 51.1, 23.0, 21.5, and 18.8.

IR: 2978, 2917, 2849, 1693, 1615, 1598, 1501, 1449, 1379, 1293, 1267, 1179, 1135, 1086, 1059, 898, 846, and 767 cm^{-1}.

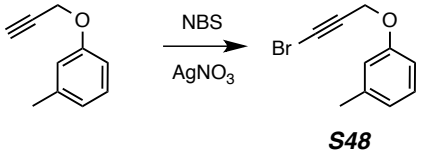
HRMS (ESI-TOF): Calcd for $C_{24}H_{21}NNaO_2^+$ $[M+Na]^+$ requires 378.1465; found 378.1455.

mp: 171-173 °C.

Synthesis of isoindolone 7074i



1-((3-Bromoprop-2-yn-1-yl)oxy)-3-methylbenzene (S48)



Bromoalkyne **S48** was prepared following General Procedure A from 1-methyl-3-(prop-2-yn-1-yloxy)benzene[172] (422 mg, 2.89 mmol, 1 equiv), NBS (553 mg, 3.18 mmol, 1.1 equiv), $AgNO_3$ (49 mg, 0.29 mmol, 0.1 equiv), and acetone (20 mL). **S48** was obtained following flash chromatography (hexanes:EtOAc = 19:1) as a clear yellow oil (540 mg, 2.4 mmol, 83%).

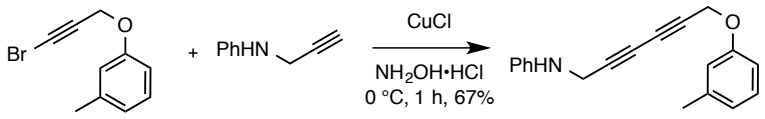
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (br dd, *J* = 7.4, 7.4 Hz, 1H, *H5*), 6.81 (d, *J* = 7.7 Hz, 1H, *H4*), 6.77 (br s, 1H, *H2*), 6.76 (br d, *J* = 7.1 Hz, 1H, *H6*), 4.68 (s, 2H, CH_2O), and 2.34 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 139.8, 129.4, 122.7, 115.9, 111.8, 75.4, 56.8, 47.6, and 21.7.

IR: 2914, 2861, 2218, 1603, 1585, 1489, 1451, 1373, 1291, 1258, 1152, 1056, 1021, 991, and 770 cm^{-1}.

GC-LRMS: t_R = 6.80 min. *m/z:* 226 (M+, 25), 224 (M+, 25), 211 (M+-CH_3, 20), 209 (M+-CH_3, 20), 145 (M+ -Br, 70), 117 (M+-$CH_3C_6H_4O$, 100), 115 (M+-$CH_3C_6H_4O$, 90), 91 (C_7H_7+, 60), and 77 (C_6H_5+, 50).

***N*-(6-(*m*-Tolyloxy)hexa-2,4-diyn-1-yl)aniline (S49)**



S48 ***S49***

Diyne **S49** was prepared following General Procedure C from **S48** (390 mg, 1.73 mmol, 1.4 equiv), *N*-(prop-2-yn-1-yl)aniline (162 mg, 1.24 mmol, 1 equiv), CuCl (6 mg, 0.06 mmol, 0.05 equiv), 30% aqueous $BuNH_2$ (8 mL), and Et_2O (8 mL). **S49** was obtained following flash chromatography (hexanes:EtOAc = 5:1) as a clear yellow oil (230 mg, 0.84 mmol, 67%).

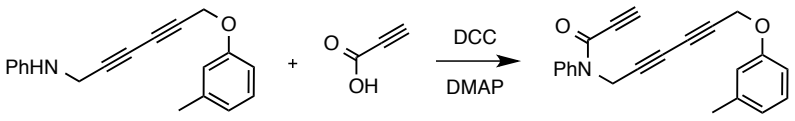
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23-7.15 (m, 3H, Ar*H*), 6.81-6.77 (m, 2H, Ar*H*), 6.74-6.72 (m, 2H, Ar*H*), 6.67-6.64 (m, 2H, Ar*H*), 4.69 (s, 2H, OCH_2), 3.99 (d, *J* = 5.7 Hz, 2H, NCH_2), 3.84 (br t, *J* = 5.7 Hz, 1H, N*H*), and 2.32 (s, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 146.7, 139.8, 129.5, 129.4, 122.7, 119.0, 115.9, 113.7, 111.8, 77.7, 73.0, 71.6, 67.3, 56.3, 34.4, and 21.7.

IR: 3400, 3053, 2917, 2255, 1602, 1585, 1504, 1489, 1438, 1375, 1350, 1313, 1291, 1257, 1152, 1095, 1041, 924, 875, and 771 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{19}H_{17}NNaO^+$ $[M+Na]^+$ requires 298.1202; found 298.1205.

***N*-Phenyl-*N*-(6-(*m*-tolyloxy)hexa-2,4-diyn-1-yl)propiolamide (S50)**



S49 ***S50***

To a solution of **S23** (113 mg, 0.4 mmol, 1 equiv) and propiolic acid (42 mg, 0.6 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) cooled at 0 °C was added DMAP (6 mg, 0.05 mmol, 0.05 equiv) and DCC (124 mg, 0.6 mmol, 1.5 equiv) in one portion. Amide **S50** was

obtained following flash chromatography (hexanes:EtOAc = 3:1) as a clear brown oil (84 mg, 0.26 mmol, 64%).

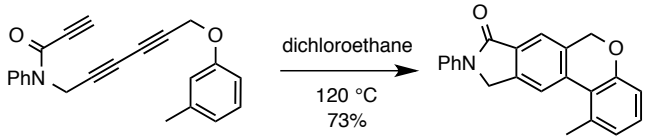
^{1}H NMR (500 MHz, $CDCl_3$, as a 7:1 ratio of two rotamers): Major rotamer δ 7.46-7.38 (m, 3H, Ar*H*), 7.33 (dd, *J* = 8.1, 2.0 Hz, 2H, Ar*Ho*), 7.18 (t, *J* = 7.5 Hz, 1H, Ar*H5*), 6.81 (d, *J* =7.3 Hz, 1H, Ar*H4*), 6.76-6.72 (m, 2H, Ar*H*), 4.71 (s, 2H, OCH_2), 4.59 (d, *J* = 5.7 Hz, 2H, NCH_2), 2.83 (s, 1H, CC*H*), and 2.34 (s, 3H, Ar*Me*). Minor rotamer δ 4.78 (s, 2H), 4.75 (s, 2H), and 3.30 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 152.7, 140.4, 139.9, 129.7, 129.4, 129.2, 128.4, 122.8, 115.9, 111.8, 80.7, 75.8, 74.2, 73.7, 71.3, 68.6, 56.3, 38.8, and 21.7 (only resonances for the major rotamer are reported).

IR: 3280, 2930, 2856, 2111, 1642, 1593, 1587, 1491, 1382, 1290, 1277, 1259, 1244, 1220, 1152, 1035, 1061, 935, and 772 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{22}H_{17}NNaO_2^+$ $[M+Na]^+$ requires 350.1151; found 350.1167.

1-Methyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7074i)



S50 ***7074i***

A solution of **S50** (22 mg, 0.067 mmol) in dichloroethane (2.2 mL) was heated to 120 °C for 18 h. The resulting solution was concentrated and subjected to MPLC (hexanes:EtOAc = 3:1) to give **7074i** as a colorless solid (16 mg, 0.049 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.7, 1.1 Hz, 2H, *Ho*), 7.84 (s, 1H, *H7* or *H11*), 7.77 (s, 1H, *H7* or *H11*), 7.43 (dd, *J* = 8.9, 7.4 Hz, 2H, *Hm*), 7.20 (dd, *J* = 7.9, 7.3 Hz, 1H, *H3*), 7.18 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 6.98 (ddq, *J* = 7.6, 1.4, 0.7 Hz, 1H, *H2*), 6.95 (ddq, *J* = 8.0, 1.3, 0.6 Hz, 1H, *H4*), 5.02 (s, 2H, *H6* or *H10*), 4.90 (s, 2H, *H6* or *H10*), and 2.72 (br s, 3H, ArCH_3).

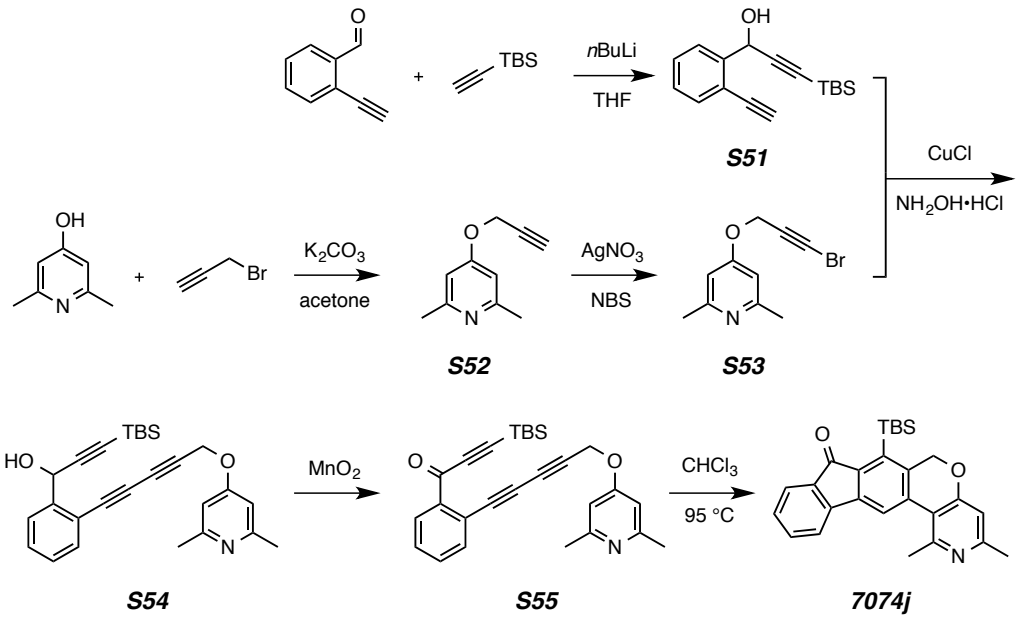
^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 157.2, 140.0, 139.7, 136.0, 135.0, 134.7, 131.7, 129.8, 129.4, 126.1, 124.7, 123.1, 120.6, 120.4, 119.6, 115.5, 69.3, 51.1, and 23.0.

IR: 2917, 2857, 1683, 1596, 1503, 1449, 1417, 1385, 1328, 1293, 1272, 1260, 1241, 1203, 1179, 1158, 1133, 1039, 1009, and 892 cm^{-1}.

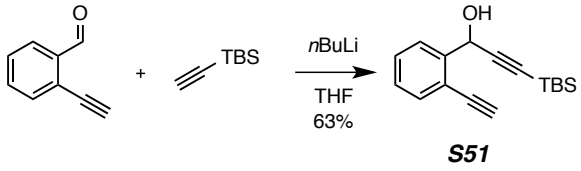
HRMS (ESI-TOF): Calcd for $C_{22}H_{17}NNaO_2^+$ $[M+Na]^+$ requires 350.1151; found 350.1159.

mp: 252-254 °C.

Synthesis of fluorenone 7074j



3-(*tert*-Butyldimethylsilyl)-1-(2-ethynylphenyl)prop-2-yn-1-ol (S52)



*n*BuLi (2.4 mL, 2.5 M solution in hexanes, 6 mmol, 1.2 equiv) was added to a solution of *tert*-butyl(ethynyl)dimethylsilane (6 mmol, 1.2 equiv) in THF (30 mL) cooled at -78 °C. The solution was allowed to stir for 1 h at this temperature. A solution of 2-ethynylbenzaldehyde (650 mg, 5 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. The resulting mixture was stirred for additional 2 h, after which saturated aqueous NH_4Cl was added. The resulting slurry was partitioned between EtOAc and H_2O. The aqueous layer was washed with EtOAc (15 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude oil was subjected to flash chromatography (Hexanes:EtOAc = 5:1) to give **S51** as a light yellow oil (850 mg, 3.15 mmol, 63%).

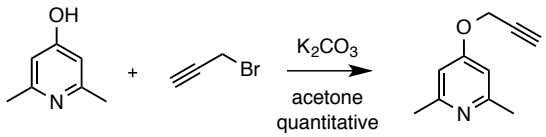
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 7.8, 1.3 Hz, 1H, Ar*H*), 7.51 (dd, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.40 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H, Ar*H*), 7.30 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, Ar*H*), 5.88 (d, *J* = 5.9, 1H, C*H*OH), 3.36 (s, 1H, CC*H*), 2.56 (d, *J* = 5.9 Hz, 1H, O*H*), 0.94 [s, 9H, C(CH_3)$_3$], and 0.13 [s, 6H, Si(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 133.4, 129.6, 128.5, 127.0, 121.0, 105.0, 90.3, 82.8, 81.2, 63.6, 26.3, 16.8, and -4.5.

IR: 3500, 3300, 2954, 2929, 2885, 2857, 2173, 1471, 1463, 1449, 1250, 1037, 980, and 840 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{17}H_{22}NaOSi^+$ $[M+Na]^+$ requires 293.1332; found 293.1337.

2,6-Dimethyl-4-(prop-2-yn-1-yloxy)pyridine (S52)



S52

K_2CO_3 (3.36 g, 24.4 mmol, 2 equiv), 2,6-dimethylpyridin-4-ol (1.5 g, 12.2 mmol, 1 equiv), and 3-bromoprop-1-yne (2.37 g, 15.8 mmol, 1.3 equiv) in acetone (25 mL) were heated with stirring at 50 °C overnight. The resulting slurry was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting dark oil (**S52**, 2.01 g, 102%) was used without further purification for the next step. A small aliquot was passed through a pad of silica gel (EtOAc) for characterization.

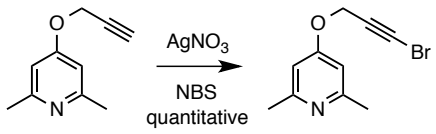
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (s, 2H, Ar*H*), 4.70 (d, *J* = 2.4 Hz, 2H, CH_2), 2.56 (t, *J* = 2.4 Hz, 1H, CH), and 2.49 (s, 6H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 159.6, 107.1, 77.8, 76.4, 55.5, and 24.9.

IR: 3293, 2957, 2922, 2852, 2120, 1599, 1579, 1455, 1329, 1319, 1152, and 1060 cm^{-1}.

GC-LRMS: t_R = 5.67 min. *m/z:* 161 (M+, 100), 146 (M+-CH_3, 40), 132 (50), 118 (55), and 91 (70).

4-((3-Bromoprop-2-yn-1-yl)oxy)-2,6-dimethylpyridine (S53)



S52 ***S53***

Bromide **S53** was prepared following General Procedure A from **S52** (480 mg, 3 mmol, 1 equiv), NBS (580 mg, 3.3 mmol, 1.1 equiv), $AgNO_3$ (51 mg, 0.3 mmol, 1 equiv), and acetone (20 mL). Compound **S53** was obtained and used for the next step without column chromatography. A small aliquot was passed through a pad of silica gel (EtOAc) for characterization.

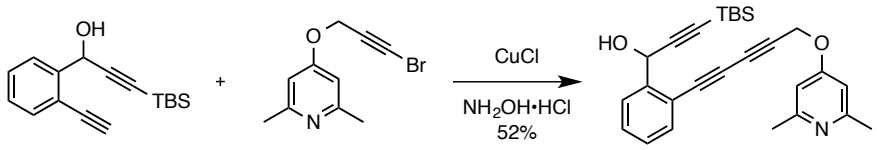
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (s, 2H, Ar*H*), 4.72 (s, 2H, CH_2), and 2.49 (s, 6H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 159.6, 107.0, 74.3, 56.3, 48.8, and 24.9.

IR: 3083, 2962, 2921, 2865, 2225, 1600, 1579, 1465, 1452, 1372, 1327, 1217, 1158, 993, 956, 849, and 823 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{10}H_{11}BrNO^+$ $[M+H]^+$ requires 240.0019; found 240.0027.

3-(*tert*-Butyldimethylsilyl)-1-(2-(5-((2,6-dimethylpyridin-4-yl)oxy)penta-1,3-diyn-1-yl)phenyl)prop-2-yn-1-ol (S54)



S51 ***S53*** ***S54***

Triyne **S54** was prepared following General Procedure C from **S51** (95 mg, 0.35 mmol, 1.2 equiv), **S53** (70 mg, 0.29 mmol, 1.0 equiv), CuCl (3 mg, 0.03 mmol, 0.1 equiv), 30% aqueous $BuNH_2$ (1.5 mL), and Et_2O (1.5 mL). Compound **S54** was obtained following flash chromatography (hexanes:EtOAc = 1:1, then pure EtOAc) as a brown oil (65 mg, 0.15 mmol, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.50 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.42 (dd, *J* = 6.9, 6.9 Hz, 1H, Ar*H*), 7.30 (dd, *J* = 7.6, 7.6 Hz, 1H, Ar*H*), 6.56

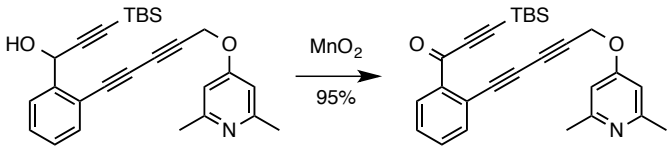
(s, 2H, HetAr*H*), 5.81 (s, 1H, C*H*OH), 4.84 (s, 2H, CH_2O), 2.49 [s, 6H, HetAr(CH_3)$_2$], 0.91 [s, 9H, SiC(CH_3)$_3$], and 0.10 [s, 6H, Si(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 159.6, 144.3, 133.9, 130.2, 128.4, 127.1, 119.8, 107.1, 105.3, 90.0, 77.9, 77.4, 76.8, 72.5, 63.1, 56.1, 26.2, 24.8, 16.7, and -4.5.

IR: 2954, 2928, 2857, 2240, 2172, 1601, 1580, 1469, 1364, 1322, 1275, 1259, 1154, 1056, 988, 909, and 840 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{32}NO_2Si^+$ $[M+H]^+$ requires 430.2197; found 430.2199.

3-(*tert*-Butyldimethylsilyl)-1-(2-(5-((2,6-dimethylpyridin-4-yl)oxy)penta-1,3-diyn-1-yl)phenyl)prop-2-yn-1-one (S55)



S54 ***S55***

A mixture of **S54** (50 mg, 0.12 mmol) and MnO_2 (265 mg, 3.04 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 3 h. The resulting solution was filtered through a pad of Celite® and silica gel and concentrated to give **S55** as a clear yellow oil (48 mg, 0.11 mmol, 95%).

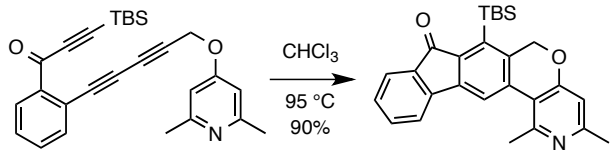
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 7.4, 1.6 Hz, 1H, Ar*H*), 7.62 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar*H*), 7.52 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, Ar*H*), 7.49 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H, Ar*H*), 6.57 (s, 2H, HetAr*H*), 4.86 (s, 2H, CH_2O), 2.50 [s, 6H, HetAr(CH_3)$_2$], 1.00 [s, 9H, SiC(CH_3)$_3$], and 0.23 [s, 6H, Si(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 164.5, 159.6, 139.3, 136.0, 132.8, 132.4, 129.3, 121.1, 107.0, 102.1, 100.5, 78.6, 78.2, 77.6, 72.9, 56.1, 26.3, 24.9, 16.9, and -4.9.

IR: 2997, 2953, 2928, 2857, 2150, 1648, 1596, 1580, 1563, 1470, 1322, 1270, 1265, 1237, 1151, 1055, 1017, and 843 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{30}NO_2Si^+$ $[M+H]^+$ requires 428.2040; found 428.2040.

7-(*tert*-Butyldimethylsilyl)-1,3-dimethylindeno[1',2':6,7]isochromeno[4,3-*c*]pyridin-8(6*H*)-one (7074j)



S55 ***7074j***

A solution of **S55** (20 mg, 0.046 mmol) in $CHCl_3$ (1.4 mL) was heated at 95 °C for 36 h. The resulting solution was concentrated and subjected to flash chromatography (hexanes:EtOAc = 1:1) to give **7074j** as a yellow oil (18 mg, 0.042 mmol, 90%).

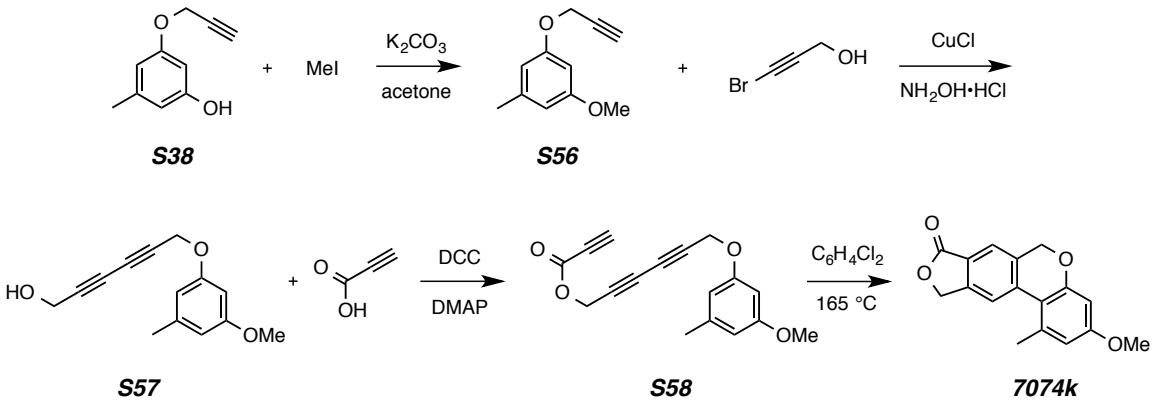
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1H, Ar*H*), 7.62 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.55 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.50 (dd, *J* = 7.4, 7.4 Hz, 1H, Ar*H*), 7.31 (dd, *J* = 7.4, 7.4 Hz, 1H, Ar*H*), 6.69 (s, 1H, HetAr*H*), 5.08 (s, 2H, CH_2O), 2.90 (s, 3H, C1CH_3), 2.53 (s, 3H, C3CH_3), 1.14 [s, 9H, SiC(CH_3)$_3$], and 0.43 [s, 6H, Si(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 163.8, 159.1, 155.6, 145.0, 143.2, 141.1, 139.6, 138.3, 134.7, 134.34, 134.32, 129.5, 124.2, 119.7, 118.7, 117.7, 109.0, 70.9, 28.4, 25.5, 24.8, 19.8, and 0.8.

IR: 2952, 2928, 2855, 1715, 1590, 1567, 1467, 1434, 1383, 1298, 1250, 1181, 1165, 1136, 1072, and 828 cm^{-1}.

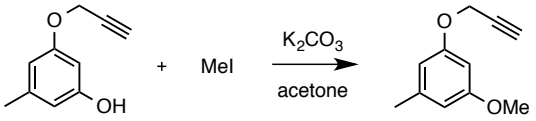
HRMS (ESI-TOF): Calcd for $C_{27}H_{30}NO_2Si^+$ $[M+H]^+$ requires 428.2040; found 428.2068.

Synthesis of isobenzofuranone 7074k



S38 ***S56*** ***S57*** ***S58*** ***7074k***

1-Methoxy-3-methyl-5-(prop-2-yn-1-yloxy)benzene (S56)



S38 ***S56***

K_2CO_3 (828 mg, 6 mmol, 3 equiv), **S38** (324 mg, 2 mmol, 1 equiv), and MeI (568 mg, 4 mmol, 2 equiv) in acetone (10 mL) are heated with stirring at 50 °C overnight. The resulting slurry was partitioned between EtOAc and H_2O. The aqueous layer was washed with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting oil was subjected to flash chromatography (hexanes:EtOAc = 19 :1) to give **S56** as a light yellow oil (338 mg, 1.9 mmol, 95%).

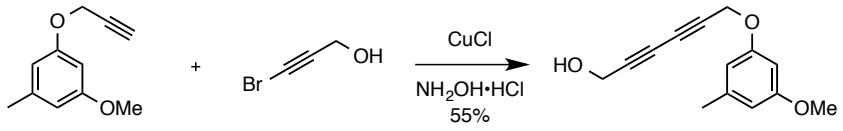
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.39 (br s, 1H, ArH), 6.38 (br s, 1H, ArH), 6.36 (br dd, *J* = 2.3, 2.3 Hz, 1H, ArH), 4.65 (d, *J* = 2.4 Hz, 2H, C*H*$_2$O), 3.77 (s, 3H, C*H*$_3$O), 2.52 (t, *J* = 2.4 Hz, 1H, C≡C*H*), and 2.31 (s, 3H, ArC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 158.8, 140.5, 108.3, 108.0, 98.7, 78.8, 75.6, 56.0, 55.5, and 22.0.

IR: 3286, 3000, 2955, 2922, 2840, 2122, 1596, 1470, 1372, 1337, 1311, 1293, 1196, 1148, 1068, 1054, and 829 cm^{-1}.

GC-LRMS: t_R = 6.52 min *m/z*: 176 (M+, 100), 161 (M+-CH_3, 90), 145 (M+-CH_3O, 25), 133 (40), 105 (30), and 77 (C6H5+, 30).

6-(3-Methoxy-5-methylphenoxy)hexa-2,4-diyn-1-ol (S57)



S56 ***S57***

Diynol **S57** was prepared following General Procedure C from **S56** (150 mg, 0.85 mmol, 1 equiv), 3-bromoprop-2-yn-1-ol (126 mg, 0.94 mmol, 1.1 equiv), CuCl (4 mg, 0.04 mmol, 0.05 equiv), 30% aqueous $BuNH_2$ (4 mL) and Et_2O (4 mL). **S57** was obtained following flash chromatography (hexanes:EtOAc = 3:1) as a clear colorless oil (108 mg, 0.47 mmol, 55%).

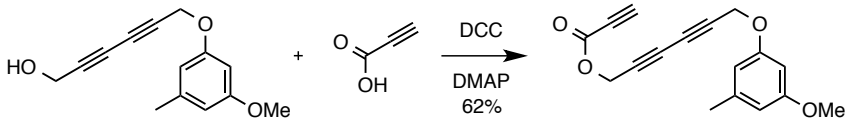
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.39 (br d, *J* = 3.0 Hz, 1H, ArH), 6.37 (br d, *J* = 2.0 Hz, 1H, ArH), 6.33 (dd, *J* = 2.5, 2.5 Hz, 1H, ArH), 4.72 (t, *J* = 1.0 Hz, 2H, C*H*$_2$O), 4.33 (br d, *J* = 4.5 Hz, 2H, C*H*$_2$OH), 3.77 (s, 3H, C*H*$_3$O), 2.31 (br s, 3H, ArC*H*$_3$), and 1.75 (t, *J* = 5.5 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 158.7, 140.6, 108.4, 108.0, 98.7, 77.9, 74.6, 71.2, 70.0, 56.4, 55.5, 51.6, and 22.0.

IR: 3406, 3000, 2920, 2841, 2258, 1595, 1471, 1371, 1336, 1310, 1293, 1195, 1148, 1068, 1048, 1023, and 828 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{14}H_{14}NaO_3^+$ $[M+Na]^+$ requires 253.0835; found 253.0855.

6-(3-Methoxy-5-methylphenoxy)hexa-2,4-diyn-1-yl Propiolate (S58)



S57 ***S58***

Ester **S58** was prepared by treating a solution of **S57** (54 mg, 0.23 mmol, 1.0 equiv) and propiolic acid (18 mg, 0.26 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) with DCC (54 mg, 0.026 mmol, 1.1 equiv) and DMAP (2 mg, 0.016 mmol, 0.07 equiv). **S58** was obtained

following flash chromatography (hexanes:EtOAc = 12:1 then 5:1 then 3:1) as a clear colorless oil (40 mg, 0.14 mmol, 62%).

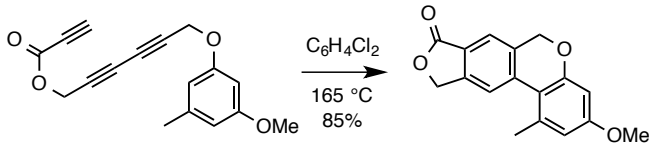
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.39 (s, 1H, ArH), 6.37 (s, 1H, ArH), 6.32 (s, 1H, ArH), 4.83 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 3.77 (s, 3H, CH_3O), 2.96 (s, 1H, CC*H*), and 2.31 (s, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 158.6, 151.8, 140.6, 108.5, 108.0, 98.7, 76.4, 75.6, 73.9, 72.1, 71.7, 70.8, 56.3, 55.5, 53.9, and 22.0.

IR: 3271, 3005, 2990, 2923, 2850, 2123, 1722, 1595, 1471, 1364, 1275, 1262, 1206, 1148, 1069, and 1051 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{17}H_{14}NaO_4^+$ $[M+Na]^+$ requires 305.0784; found 305.0767.

3-Methoxy-1-methyl-6*H*-isobenzofuro[5,6-*c*]chromen-8(10*H*)-one (7074k)



S58 ***7074k***

A solution of **S58** (13 mg, 0.046 mmol) in 1,2-dichlorobenzene (1.5 mL) was heated at 165 °C for 3.5 h. The resulting solution was directly subjected to MPLC (hexanes:EtOAc = 3:1) to yield **7074k** as a clear colorless oil (11 mg, 0.039 mmol, 85%).

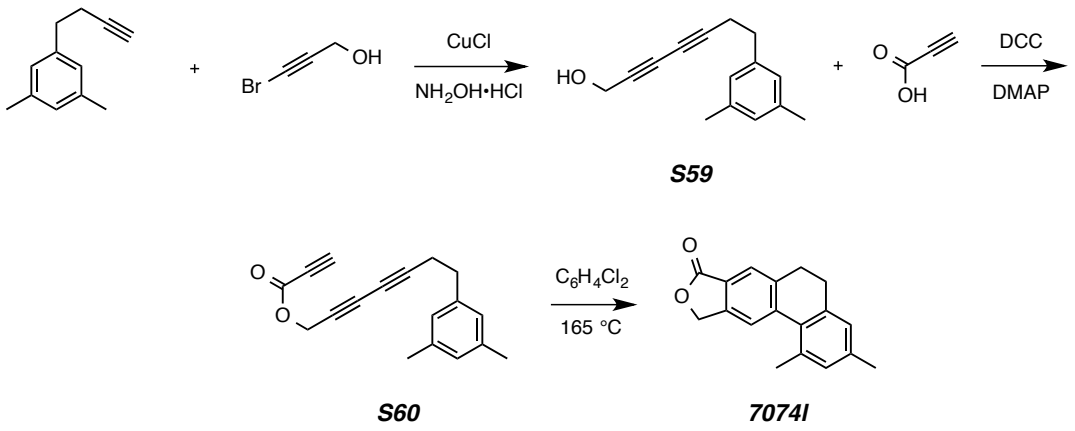
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (br s, 1H, *H7*), 7.72 (br s, 1H, *H11*), 6.56 (dq, *J* = 2.7, 0.7 Hz, 1H, *H2*), 6.50 (d, *J* = 2.7 Hz, 1H, *H4*), 5.35 (s, 2H, H*10*), 4.99 (s, 2H, *H6*), 3.83 (s, 3H, OCH_3), and 2.67 (br s, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 161.1, 158.9, 146.8, 137.7, 137.4, 134.2, 123.0, 121.9, 118.6, 115.7, 113.2, 100.3, 69.9, 69.3, 55.6, and 23.2.

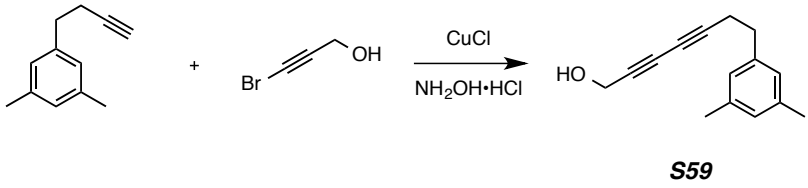
IR: 2958, 2925, 2850, 1756, 1716, 1609, 1592, 1570, 1453, 1412, 1356, 1320, 1295, 1195, 1149, 1142, 1070, 1040, and 1014 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{17}H_{14}NaO_4^+$ $[M+Na]^+$ requires 305.0784; found 305.0810.

Synthesis of isobenzofuranone 7074l



7-(3,5-Dimethylphenyl)hepta-2,4-diyn-1-ol (S59)



Diynol **S59** was prepared following General Procedure C from 1-(but-3-yn-1-yl)-3,5-dimethylbenzene[175] (100 mg, 0.63 mmol, 1 equiv), 3-bromoprop-2-yn-1-ol (101 mg, 0.76 mmol, 1.2 equiv), CuCl (6 mg, 0.06 mmol, 0.1 equiv), 30% aqueous $BuNH_2$ (2.4 mL) and Et_2O (2.4 mL). **S59** was obtained following flash chromatography (hexanes:EtOAc = 3:1) as a clear colorless oil (75 mg, 0.35 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (s, 1H, Ar*H*4), 6.81 (s, 2H, Ar*H*2*H*6), 4.32 (d, *J* = 5.5 Hz, 2H, C*H*$_2$OH), 2.77 (t, *J* = 7.5 Hz, 2H, CH_2CH_2), 2.55 (t, *J* = 7.5 Hz, 2H, CH_2CH_2), 2.29 [s, 6H, Ar(C*H*$_3$)$_2$], and 1.55 (t, *J* = 6.0 Hz, O*H*).

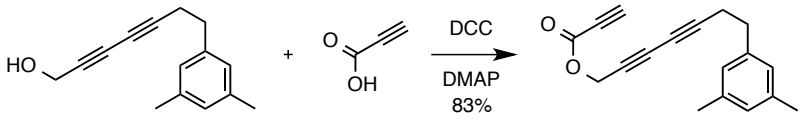
^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1, 138.2, 128.3, 126.4, 81.2, 74.0, 71.1, 65.1, 51.8, 34.6, 21.7, and 21.5.

IR: 3340, 3015, 2944, 2918, 2857, 2257, 1606, 1464, 1447, 1424, 1376, 1350, 1231, 1017, and 846 cm^{-1}.

[175] Zhang, L.; Kozmin, S. A. Brønsted acid-promoted cyclizations of siloxyalkynes with arenes and alkenes. *J. Am. Chem. Soc.* **2004**, *126*, 10204–10205.

HRMS (ESI-TOF): Calcd for $C_{15}H_{16}NaO^+$ $[M+Na]^+$ requires 235.1093; found 235.1092.

7-(3,5-Dimethylphenyl)hepta-2,4-diyn-1-yl Propiolate (S60)



S59 ***S60***

Ester **S60** was prepared by treating a solution of **S33** (32 mg, 0.15 mmol, 1.0 equiv) and propiolic acid (11.5 mg, 0.165 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) cooled at 0 °C with DCC (34 mg, 0.165 mmol, 1.1 equiv) and DMAP (2 mg, 0.016 mmol, 0.1 equiv). **S60** was obtained following flash chromatography (hexanes:EtOAc = 12:1) as a clear colorless oil (33 mg, 0.13 mmol, 83%).

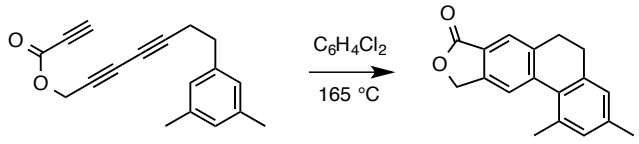
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (s, 1H, Ar*H*4), 6.81 (s, 2H, Ar*H*2*H*6), 4.82 (s, 2H, OCH_2), 2.93 (s, 1H, CC*H*), 2.77 (t, *J* = 7.6 Hz, 2H, CH_2), 2.55 (t, *J* = 7.6 Hz, 2H, CH_2), and 2.29 [s, 6H, Ar(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9, 139.9, 138.2, 128.4, 126.3, 82.1, 76.2, 74.0, 72.9, 68.2, 64.9, 54.3, 34.4, 21.7, and 21.5.

IR: 3283, 3015, 2920, 2861, 2260, 2123, 1722, 1606, 1469, 1443, 1368, 1206, 979, 958, and 843 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{18}H_{16}NaO_2^+$ $[M+Na]^+$ requires 287.1043; found 287.1058.

1,3-Dimethyl-5,6-dihydrophenanthro[2,3-*c*]furan-8(10*H*)-one (7074l)



S60 ***7074l***

A solution of **S60** (18 mg, 0.068 mmol) in 1,2-dichlorobenzene (2.2 mL) was heated at 165 °C for 3.5 h. The resulting solution was directly subjected to MPLC (hexanes:EtOAc = 3:1) to yield **7074l** as a colorless solid (12.5 mg, 0.047 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (br s, 1H, *H7*), 7.67 (br s, 1H, *H11*), 7.05 (br s, 1H, *H4*), 6.99 (br s, 1H, *H2*), 5.34 (s, 2H, OCH_2), 2.83 (dd, *J* = 9.4, 5.7 Hz, 2H, *H5* or *H6*), 2.75 (dd, *J* = 9.4, 5.7 Hz, 2H, *H6* or *H5*), 2.60 (s, 3H, $C1CH_3$), and 2.35 (s, 3H, $C3CH_3$).

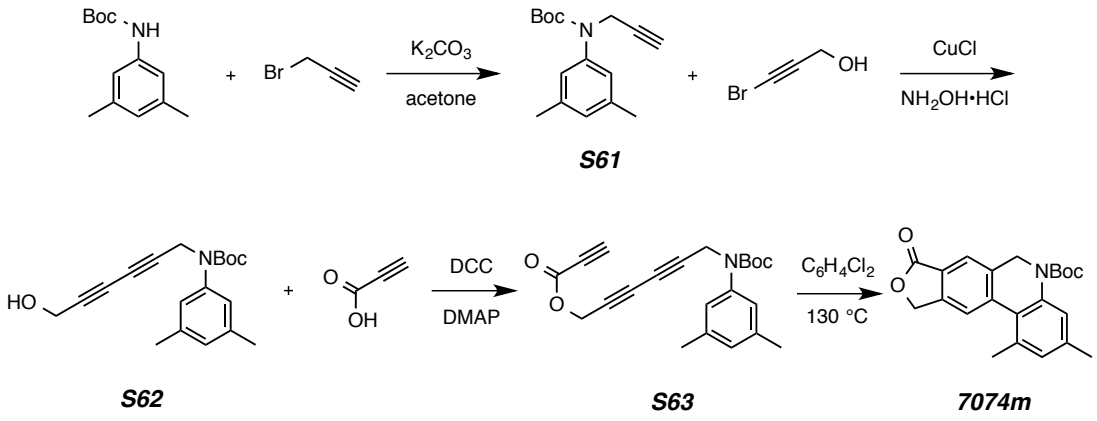
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 144.8, 141.4, 141.3, 140.8, 138.4, 135.2, 131.8, 130.8, 126.8, 124.2, 123.4, 121.1, 69.9, 30.6, 30.4, 23.1, and 21.3.

IR: 2942, 1756, 1622, 1611, 1449, 1353, 1304, 1274, 1132, 1043, and 1009 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{18}H_{16}NaO_2^+$ $[M+Na]^+$ requires 287.1043; found 287.1051.

mp: 129-133 °C.

Synthesis of isobenzofuranone 7074m



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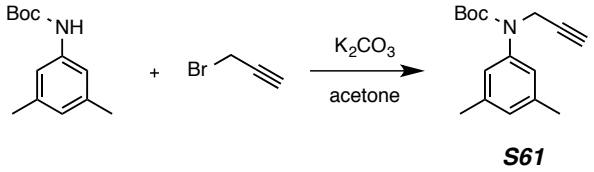
tert-Butyl (3,5-dimethylphenyl)(prop-2-yn-1-yl)carbamate (S61)



A solution of *tert*-butyl (3,5-dimethylphenyl)carbamate[176] (880 mg, 4 mmol, 1 equiv) in 12 mL of a 1:l mixture of DMF/THF was treated with NaH (60% dispersion in mineral oil, 320 mg, 8 mmol, 2 equiv) at 0 °C. This resulting solution was stirred for an additional 30 min at rt. The mixture was allowed to react with 3-bromoprop-1-yne (566 mg, 4.8 mmol, 1.2 equiv) and the mixture was stirred at rt for 8 h. The excess NaH was quenched with saturated aqueous NH_4Cl solution. The mixture was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude oil was subjected to flash chromatography (hexanes:EtOAc = 3:1) to yield **S61** as a yellow oil (930 mg, 3.59 mmol, 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (br s, 2H, Ar*H*2*H*6), 6.85 (br s, 1H, Ar*H*4), 4.32 (d, J = 2.5 Hz, 2H, CH_2), 2.30 [br s, 6H, Ar(CH_3)$_2$], 2.24 (t, J = 2.5 Hz, 1H, CC*H*), and 1.47 [br s, 9H, C(CH_3)$_3$].

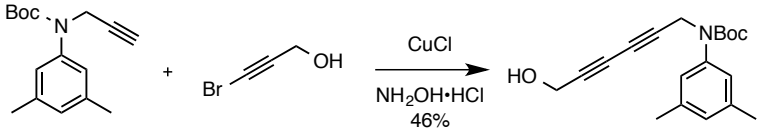
[176] Brucelle, F.; Renaud, P. Synthesis of indolines, indoles, and benzopyrrolizidinones from simple aryl azides. *Org. Lett.* **2012**, *14*, 3048–3051.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 142.2, 138.5, 128.2, 124.1, 81.0, 80.4, 71.7, 40.1 (br), 28.5, and 21.5

IR: 3293, 2976, 2923, 2866, 2121, 1700, 1610, 1598, 1473, 1455, 1433, 1422, 1376, 1367, 1316, 1245, 1168, 1143, 1083, 878, 851, and 769 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{16}H_{21}NNaO_2^+$ $[M+Na]^+$ requires 282.1465; found 282.1453.

***tert*-Butyl (3,5-dimethylphenyl)(6-hydroxyhexa-2,4-diyn-1-yl)carbamate (S62)**



S61 ***S62***

Diynol **S62** was prepared following General Procedure C from **S61** (300 mg, 1.15 mmol, 1 equiv), 3-bromoprop-2-yn-1-ol (190 mg, 1.40 mmol, 1.2 equiv), CuCl (6 mg, 0.06 mmol, 0.05 equiv), 30% aqueous $BuNH_2$ (4 mL), and Et_2O (4 mL). **S62** was obtained following flash chromatography (hexanes:EtOAc = 3:1 then 1:1) as a clear colorless oil (165 mg, 0.53 mmol, 46%).

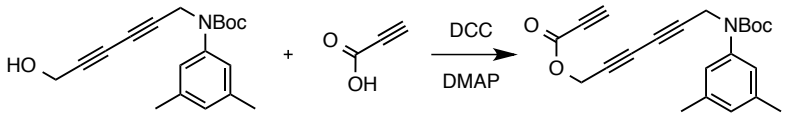
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (br s, 2H, Ar*H*2*H*6), 6.86 (br s, 1H, Ar*H*4), 4.39 (br s, 2H, CH_2), 4.31 (br s, 2H, CH_2), 2.31 [br s, 6H, Ar(CH_3)$_2$], and 1.47 (s, 9H, *t*Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 142.0, 138.6, 128.4, 124.1, 81.4, 76.6, 76.2, 70.5, 67.5, 51.7, 40.9 (br), 28.5, and 21.5.

IR: 3428, 2977, 2923, 2255, 1698, 1683, 1610, 1597, 1472, 1455, 1430, 1390, 1368, 1315, 1248, 1164, 1145, 1081, 1031, and 879 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{19}H_{23}NNaO_3^+$ $[M+Na]^+$ requires 336.1570; found 336.1568.

6-((*tert*-Butoxycarbonyl)(3,5-dimethylphenyl)amino)hexa-2,4-diyn-1-yl Propiolate (S63)



S62 ***S63***

Ester **S63** was prepared by treating a solution of **S36** (80 mg, 0.26 mmol, 1.0 equiv) and propiolic acid (21 mg, 0.3 mmol, 1.15 equiv) in CH_2Cl_2 (2 mL) cooled at 0 °C with DCC (60 mg, 0.29 mmol, 1.1 equiv) and DMAP (2 mg, 0.016 mmol, 0.06 equiv). **S63** was obtained following flash chromatography (hexanes:EtOAc = 12:1 then 5:1) as a clear colorless oil (49 mg, 0.134 mmol, 83%). This material contained ca. 10% of an unidentified impurity, perhaps originating from propiolic acid as judged from analysis of the ^{1}H and ^{13}C NMR data, but was of sufficient quality to be used as the substrate in the subsequent HDDA/ene reaction.

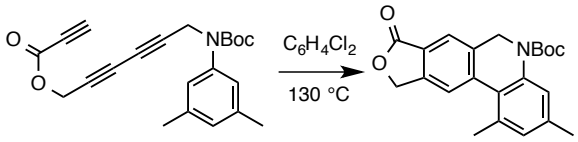
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (br s, 2H, Ar*H*2*H*6), 6.86 (br s, 1H, Ar*H*4), 4.84 (br s, 2H, CH_2OCO), 4.40 (br s, 2H, CH_2N), 2.97 (s, 1H, *H*CC), 2.31 [br s, 6H, Ar(CH_3)$_2$], and 1.47 [s, 9H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 151.9, 141.9, 138.7, 128.5, 124.1, 81.4, 77.6, 76.3, 74.0, 72.3, 70.3, 67.2, 54.1, 40.9 (br), 28.5, and 21.5.

IR: 3221, 2977, 2933, 2857, 2121, 1723, 1698, 1659, 1609, 1598, 1475, 1458, 1429, 1368, 1315, 1243, 1207, 1165, 1144, and 978 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{22}H_{23}NNaO_4^+$ $[M+Na]^+$ requires 388.1519; found 388.1525.

tert-Butyl 1,3-dimethyl-8-oxo-8,10-dihydrofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylate (7074m)



S63 ***7074m***

A solution of **S65** (20 mg, 0.055 mmol) in 1,2-dichlorobenzene (1.8 mL) was heated at 130 °C for 16 h. The resulting solution was directly subjected to MPLC

(hexanes:EtOAc = 3:1) to give **7074m** as a colorless solid (11 mg, 0.03 mmol, 55%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (s, 1H, Ar*H*), 7.77, (s, 1H, Ar*H*), 7.43-7.32 (br s, 1H, Ar*H*), 6.98 (s, 1H, Ar*H*), 5.36 (s, 2H, ArCH_2O), 4.71-4.64 (br s, 2H, ArCH_2N), 2.63 (s, 3H, C1CH_3), 2.38 (s, 3H, C3CH_3), and 1.48 [br s, 9H, C(CH_3)$_3$].

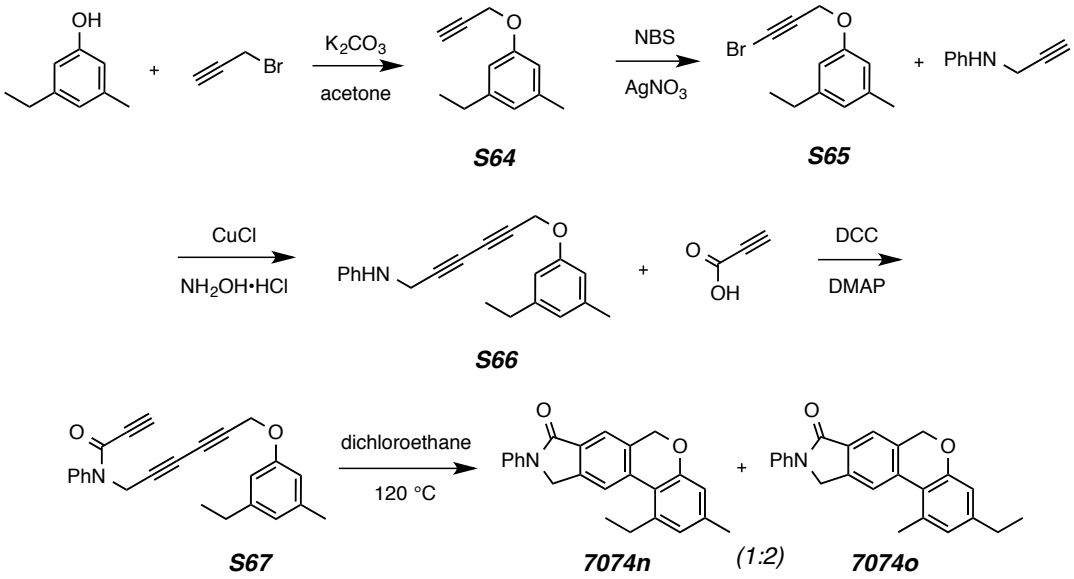
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 152.6, 145.8, 140.2, 139.0 (br), 138.8, 137.7 (br), 135.3, 129.7, 125.1, 123.7, 123.5, 122.3 (br), 120.8, 81.7, 69.9, 48.0 (br), 28.5, 23.0, and 21.6.

IR: 2975, 2919, 1762, 1698, 1613, 1590, 1451, 1412, 1370, 1346, 1284, 1229, 1155, 1132, 1044, 1009, 890, 855, and 761 cm^{-1}.

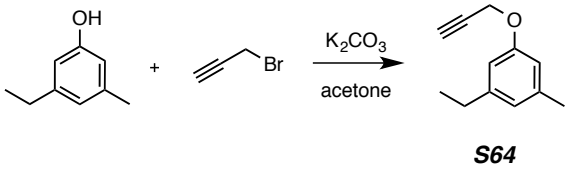
HRMS (ESI-TOF): Calcd for $C_{22}H_{23}NNaO_4^+$ $[M+Na]^+$ requires 388.1519; found 388.1530.

mp: 201-204 °C.

Synthesis of isoindolone 7074n and 7074o



1-Ethyl-3-methyl-5-(prop-2-yn-1-yloxy)benzene (S64)



A mixture of K_2CO_3 (2.76 g, 20 mmol, 2 equiv), 3-ethyl-5-methylphenol (1.36 g, 10 mmol, 1 equiv), and 3-bromoprop-1-yne (1.77 g, 15 mmol, 1.5 equiv) were heated with stirring at 50 °C in acetone (50 mL) overnight. The resulting slurry was partitioned between EtOAc and H_2O. The aqueous layer was washed with EtOAc (30 mL x 3). The combined layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude oil was subjected to flash chromatography (hexanes:EtOAc = 19:1) to give **S64** as a light yellow oil (1.64 g, 9.4 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (br s, 1H), 6.63 (br s, 1H), 6.61 (br s, 1H), 4.66 (d, *J* = 2.4 Hz, 2H, C*H*$_2$O), 2.59 (q, *J* = 7.6 Hz, C*H*$_2$CH$_3$), 2.50 (t, *J* = 2.4 Hz, 1H, *H*C≡C), 2.31 (s, 3H, ArC*H*$_3$), and 1.22 (t, *J* = 7.6 Hz, 3H, CH$_2$C*H*$_3$).

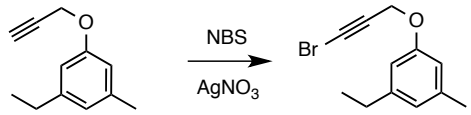
^{13}C NMR (125 MHz, $CDCl_3$):

δ 157.9, 145.9, 139.5, 122.3, 112.9, 111.8, 79.1, 75.4, 55.9, 29.1, 21.7, and 15.7.

IR: 3288, 2965, 2921, 2872, 2122, 1611, 1594, 1457, 1330, 1288, 1168, 1151, 1078, 1049, 1012, 941, and 844 cm^{-1}.

GC-LRMS: t_R = 6.09 min. *m/z:* 174 (M+, 50), 159 (M+-CH_3, 70), 145 (M+ -CH_2CH_3, 100), 131 (M+ -C_3H_7, 40), 91 (C_7H_7+, 70), and 77 (C_6H_5+, 20).

1-((3-Bromoprop-2-yn-1-yl)oxy)-3-ethyl-5-methylbenzene (S65)



S64 ***S65***

Bromoalkyne **S65** was prepared following General Procedure A from **S64** (865 mg, 5 mmol, 1 equiv), NBS (929 mg, 5.25 mmol, 1.05 equiv), $AgNO_3$ (42 mg, 0.25 mmol, 0.05 equiv), and acetone (40 mL). **S65** was isolated following flash chromatography (hexanes:EtOAc = 19:1) as a clear yellow oil (1.10 g, 0.44 mmol, 88%).

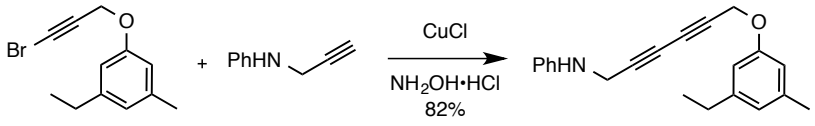
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67 (br s, 1H, *H4*), 6.60 (br s, 1H, *H6*), 6.59 (br s, 1H, *H2*), 4.67 (br s, 2H, C*H*$_2$O), 2.59 (br q, *J* = 7.6 Hz, 2H, C*H*$_2$CH$_3$), 2.31 (br s, 3H, ArC*H*$_3$), and 1.22 (t, *J* = 7.6 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (125 MHz, CDCl3): δ 157.8, 146.0, 139.6, 122.4, 112.8, 111.7, 75.5, 56.8, 47.5, 29.1, 21.7, and 15.7.

IR: 2965, 2931, 2872, 2218, 1611, 1593, 1461, 1453, 1371, 1330, 1287, 1167, 1150, 1079, 1054, and 843 cm^{-1}.

GC-LRMS: t_R = 7.82 min. *m/z:* 254 (M+, 40), 252 (M+, 40), 239 (M+-CH_3, 20), 237 (M+-CH_3, 20), 225 (M+-CH_2CH_3, 30), 223 (M+-CH_2CH_3, 30), 173 (M+-Br, 60), 158 (50), 145 (80), 130 (50), 117 (70), 91 (C_7H_7+, 100), and 77 (C_6H_5+, 25).

***N*-(6-(3-Ethyl-5-methylphenoxy)hexa-2,4-diyn-1-yl)aniline (S66)**



S65 ***S66***

Diyne **S66** was prepared following General Procedure C from **S65** (506 mg, 2 mmol, 1.3 equiv), *N*-(prop-2-yn-1-yl)aniline (201 mg, 1.53 mmol, 1.0 equiv), CuCl (7 mg, 0.07 mmol, 0.05 equiv), 30% aqueous $BuNH_2$ (7 mL), and Et_2O (7 mL). **S66** was obtained following flash chromatography (hexanes:EtOAc = 5:1) as a clear yellow oil (381 mg, 1.26 mmol, 82%).

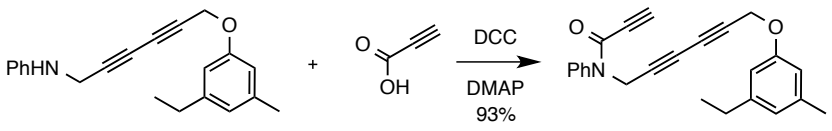
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 8.2, 7.7 Hz, 2H, *Hm*), 6.79 (t, *J* = 7.4 Hz, 1H, *Hp*), 6.66 (d, *J* = 7.9 Hz, 2H, *Ho*), 6.65 (br s, 1H, *H4*), 6.58 (br s, 1H, *H6*), 6.56 (br s, 1H, *H2*), 4.68 (br s, 2H, CH_2O), 4.00 (br s, 2H, NCH_2), 3.85 (br s, 1H, N*H*), 2.57 (br q, *J* = 7.6 Hz, 2H, CH_2CH_3), 2.30 (br s, 3H, $ArCH_3$), and 1.20 (t, *J* = 7.6 Hz, 3H, CH_2CH_3).

^{13}C NMR (125 MHz, CDCl3): δ 157.8, 146.7, 146.0, 139.6, 129.5, 122.4, 119.1, 113.8, 112.8, 111.7, 77.7, 73.2, 71.5, 67.3, 56.3, 34.4, 29.0, 21.7, and 15.7.

IR: 3405, 2965, 2931, 2869, 2255, 1602, 1593, 1505, 1456, 1437, 1314, 1287, 1258, 1167, 1150, 1075, 1046, and 752 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{21}H_{21}NNaO^+$ $[M+Na]^+$ requires 326.1515; found 326.1519.

***N*-(6-(3-Ethyl-5-methylphenoxy)hexa-2,4-diyn-1-yl)-*N*-phenylpropiolamide (S67)**



S66 ***S67***

Amide **S67** was prepared by treating a solution of **S66** (303 mg, 1 mmol, 1.0 equiv) and propiolic acid (91 mg, 1.3 mmol, 1.3 equiv) in CH_2Cl_2 (10 mL) cooled at 0 °C with DCC (236 mg, 1.15 mmol, 1.15 equiv) and DMAP (6 mg, 0.05 mmol, 0.05 equiv). **S67** was obtained following flash chromatography (hexanes:EtOAc = 3:1) as a clear brown oil (355 mg, 0.93 mmol, 93%).

^{1}H NMR (500 MHz, $CDCl_3$, as a 7:1 ratio of two amide rotamers): Major isomer δ 7.45-7.40 (m, 3H, *HmHp*), 7.33 (dd, *J* = 7.9, 2.0 Hz, 2H, *Ho*), 6.67 (br s, 1H, *H4*), 6.58 (br s, 1H, *H6*), 6.57 (br s, 1H, *H2*), 4.70 (br s, 2H, CH_2O), 4.59 (br s, 2H, NCH_2), 2.83 (s, 1H, C≡C*H*), 2.59 (br q, *J* = 7.6 Hz, 2H, CH_2CH$_3$), 2.31 (br s, 3H, ArCH_3), and 1.21 (t, *J* = 7.6 Hz, 3H, CH$_2$CH_3). Minor isomer δ 4.77 (br s, 2H, CH_2O), 4.72 (br s, 2H, NCH_2), and 3.29 (s, 1H, CC*H*).

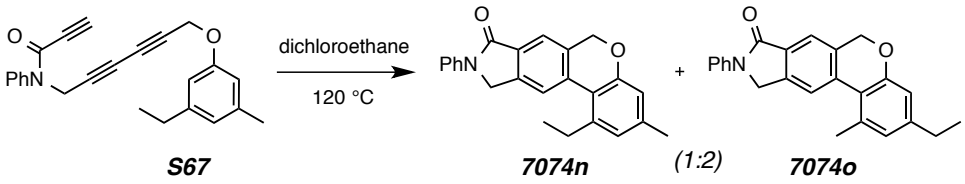
^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 152.7, 146.0, 140.4, 139.6, 129.6, 129.2, 128.4, 122.5, 112.8, 111.7, 80.7, 75.8, 74.2, 73.8, 71.2, 68.7, 56.3, 38.8, 29.0, 21.7, and 15.7 (only resonances for the major rotamer are reported).

IR: 3283, 2965, 2923, 2873, 2111, 1643, 1611, 1593, 1492, 1456, 1414, 1383, 1330, 1287, 1220, 1168, 1150, 1076, 1048, 1015, and 842 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{24}H_{21}NNaO_2^+$ $[M+Na]^+$ requires 378.1465; found 378.1455.

1-Ethyl-3-methyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7074n) and

1-Methyl-3-ethyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7074o)



A solution of **S67** (25 mg, 0.07 mmol) in dichloroethane (2.3 mL) was heated at 120 °C for 18 h. The resulting solution was concentrated and subjected to MPLC (hexanes:EtOAc = 3:1) to yield **7074n** and **7074o** as a coeluting 1:2 mixture (20 mg, 0.056 mmol, 80% combined yield).

Characterization data for 7074n

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.8, 1.0 Hz, 1H, *Ho*), 7.74 (br s, 1H, *H7*), 7.73 (br s, 1H, *H11*), 7.42 (overlapping dd, *J* = 8.5, 7.5 Hz, 2H, *Hm*), 7.17 (overlapping tt, *J* = 7.4, 1.0 Hz, 1H, *Hp*), 6.87 (br d, *J* = 1.8 Hz, 1H, *H2*), 6.77 (br d, *J* = 1.8 Hz, 1H, *H4*), 4.97 (br s, 2H, OCH_2), 4.89 (br s, 2H, NCH_2), 3.02 (q, *J* = 7.6 Hz, 3H, CH_2CH_3), 2.35 (br s, 3H, C3CH_3), and 1.40 (t, *J* = 7.6 Hz, 3H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$, shifts deduced from HSQC): δ 128.8, 124.6, 124.0, 119.5, 119.5, 118.9, 115.1, 68.8, 50.6, 27.1, 21.3, and 15.3 (several of the cross peaks overlapping with major product).

Characterization data for 7074o

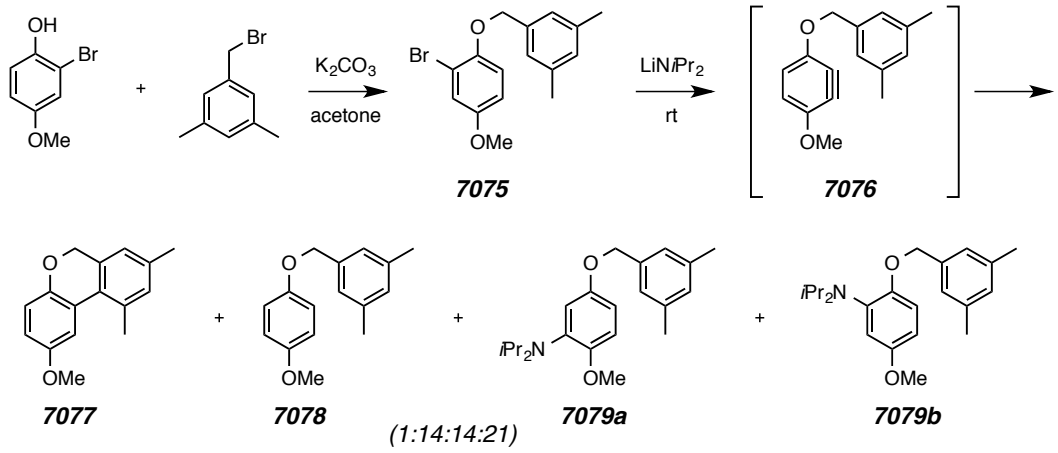
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 8.8, 1.0 Hz, 1H, *Ho*), 7.81 (br s, 1H, *H7*), 7.74 (br s, 1H, *H11*), 7.42 (overlapping dd, *J* = 8.5, 7.5 Hz, 2H, *Hm*), 7.17 (overlapping tt, *J* = 7.4, 1.0 Hz, 1H, *Hp*), 6.83 (br d, *J* = 1.8 Hz, 1H, *H2*), 6.79 (br d, *J* = 1.8 Hz, 1H, *H4*), 5.00 (br s, 2H, OCH_2), 4.88 (br s, 2H, NCH_2), 2.69 (br s, 3H, C1CH_3), 2.63 (q, *J* = 7.6 Hz, 3H, CH_2CH_3), and 1.26 (t, *J* = 7.6 Hz, 3H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$, shifts deduced from HSQC): δ 128.8, 125.4, 124.0, 120.0, 119.5, 118.9, 114.0, 68.9, 50.6, 28.2, 22.8, and 15.0 (several of the cross peaks overlapping with major product).

IR: 2966, 2928, 2863, 1693, 1625, 1614, 1598, 1501, 1459, 1449, 1407, 1380, 1328, 1293, 1270, 1175, 1130, 1077, 1057, 1015, 908, and 859 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{24}H_{21}NNaO_2^+$ $[M+Na]^+$ requires 378.1465; found 378.1439.

Synthesis of 7077, 7078, 7079a, and 7079b.



2-Bromo-1-((3,5-dimethylbenzyl)oxy)-4-methoxybenzene (7075)

K_2CO_3 (924 mg, 6.7 mmol, 2 equiv), 2-bromo-4-methoxyphenol (800 mg, 4 mmol, 1.2 mmol), and 1-(bromomethyl)-3,5-dimethylbenzene (670 mg, 3.35 mmol, 1 equiv) in acetone (5 mL) was stirred at 50 °C overnight. The resulting slurry was partitioned between EtOAc and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude oil was subjected to MPLC (hexanes:EtOAc = 20:1) to give **7075** (612 mg, 57%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 3.0 Hz, 1H, *H3*), 7.07 (br s, 2H, *H2'H6'*), 6.95 (br s, 1H, *H4'*), 6.87 (d, *J* = 9.0 Hz, 1H, *H6*), 6.77 (dd, *J* = 9.0, 3.0 Hz, 1H, *H5*), 5.01 (s, 2H, C*H*$_2$O), 3.76 (s, 3H, C*H*$_3$O), and 2.33 [br s, 6H, Ar(C*H*$_3$)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 149.8, 138.3, 136.9, 129.7, 125.2, 119.0, 115.9, 113.9, 113.4, 72.4, 56.1, and 21.5.

IR: 3005, 2940, 2916, 2834, 1609, 1576, 1492, 1459, 1440, 1297, 1272, 1212, 1040, 844, and 786 cm^{-1}.

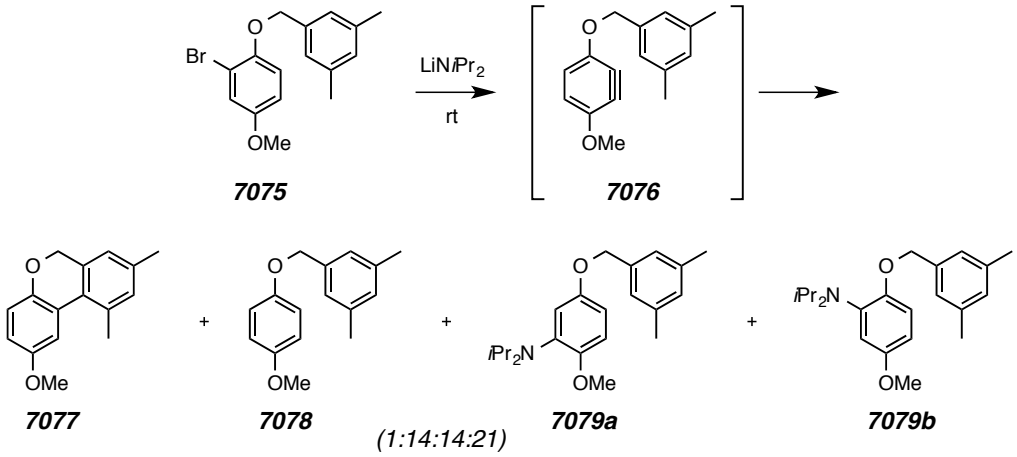
GC-LRMS: t_R = 10.79 min. *m/z*: 322 (M+, 10), 320 (M+, 10), 119 (C_9H_{11}+, 100), 91 (C_7H_7+, 8), and 77 (C_6H_5+, 4).

2-Methoxy-8,10-dimethyl-6*H*-benzo[*c*]chromene (7077)

1-((4-Methoxyphenoxy)methyl)-3,5-dimethylbenzene (7078)

5-((3,5-Dimethylbenzyl)oxy)-*N*,*N*-diisopropyl-2-methoxyaniline (7079a) and

2-((3,5-Dimethylbenzyl)oxy)-*N*,*N*-diisopropyl-5-methoxyaniline (7079b)



A THF solution of LDA was freshly prepared at -10 °C from *n*BuLi (2.5 M solution in hexanes, 0.4 mL, 1 mmol), HN*i*Pr$_2$ (101 mg, 1 mmol), and THF (2 mL). To a solution of **7075** (80 mg, 0.25 mmol) in THF (5 mL) was added the freshly prepared LDA (ca. 0.4 M, 0.7 mL, 0.28 mmol, 1.1 equiv) at rt. The reaction was monitored by TLC and GCMS. An additional amount of LDA (0.8 mL, 0.32 mmol, 1.3 equiv) was added 1 h later to drive the reaction to completion. The resulting solution was stirred for 30 min and quenched by addition of saturated aqueous NH_4Cl solution. The mixture was partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The ratio of products (i.e., 1:14:14:21) was determined by analysis of the ^{1}H NMR spectrum of this crude oil. This ratio was qualitatively consistent with that observed by GC-MS analysis of the sample of crude products. This oil was then subjected to flash chromatography (hexanes:EtOAc = 16:1 then 5:1) to give, in order of elution, **7077** and **7078** as a co-eluting mixture, followed by **7079a** as colorless oil, and finally **7079b** as colorless oil. The overall mass recovery was ca. 85% (70 mg isolated).

Characterization data for 7077 (containing ca. 5 mol% of 7078)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (br s, 2H, *H2H6*), 6.99 (br s, 1H, *H4*), 6.95 (d, *J* = 9.0 Hz, 2H, *H2'H6'*), 6.86 (d, *J* = 9.1 Hz, 2H, *H3'H5'*), 4.96 (s, 2H, C*H*$_2$O), 3.80 (s, 3H, C*H*$_3$O), and 2.36 (br s, 6H, Ar(C*H*$_3$)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 153.3, 138.6, 137.3, 129.8, 125.6, 116.0, 114.8, 71.1, 55.9, and 21.5.

IR: 3002, 2948, 2917, 2865, 2833, 1610, 1592, 1507, 1463, 1442, 1228, 1040, and 825 cm^{-1}.

GC-LRMS: t_R = 9.69 min. *m*/*z*: 242 (M+, 30), 119 (C_9H_{11}+, 100), 91 (C_7H_7+, 10), and 77 (C_6H_5+, 4).

Characteristic ^{1}H NMR peaks of **7078**

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.92 (s, C*H*$_2$O), 3.86 (s, C*H*$_3$O), 2.66 (s, C10C*H*$_3$), and 2.37 (s, C8C*H*$_3$).

GC-LRMS: t_R = 10.40 min. *m*/*z*: 240 (M+, 100), 225 (M+-CH_3, 50), 197 (20), 182 (10), 165 (12), 153 (12), 128 (10), and 115 (8).

Characterization data for 7079a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (br s, 2H, *H2'H6'*), 6.92 (br s, 1H, *H4'*), 6.78 (d, *J* = 8.9 Hz, 1H, *H3*), 6.75 (d, *J* = 3.1 Hz, 1H, *H6*), 6.59 (dd, *J* = 8.9, 3.1 Hz, 1H, *H4*), 4.98 (s, 2H, C*H*$_2$O), 3.75 (s, 3H, C*H*$_3$O), 3.60 {septet, *J* = 6.4 Hz, 2H, N[C*H*(CH_3)$_2$]$_2$}, 2.31 [br s, 6H, Ar(C*H*$_3$)$_2$], and 1.04 {d, *J* = 6.4 Hz, 12H, N[CH(C*H*$_3$)$_2$]$_2$}.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 152.4, 138.31, 138.26, 138.1, 129.2, 125.1, 118.0, 114.8, 109.6, 71.4, 55.8, 49.6, 22.0, and 21.5.

IR: 2967, 2928, 2870, 2832, 1609, 1581, 1494, 1463, 1379, 1208, 1179, 1046, and 845 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{22}H_{32}NO_2^+$ $[M+H]^+$ requires 342.2428; found 342.2448.

Characterization data for 7079b

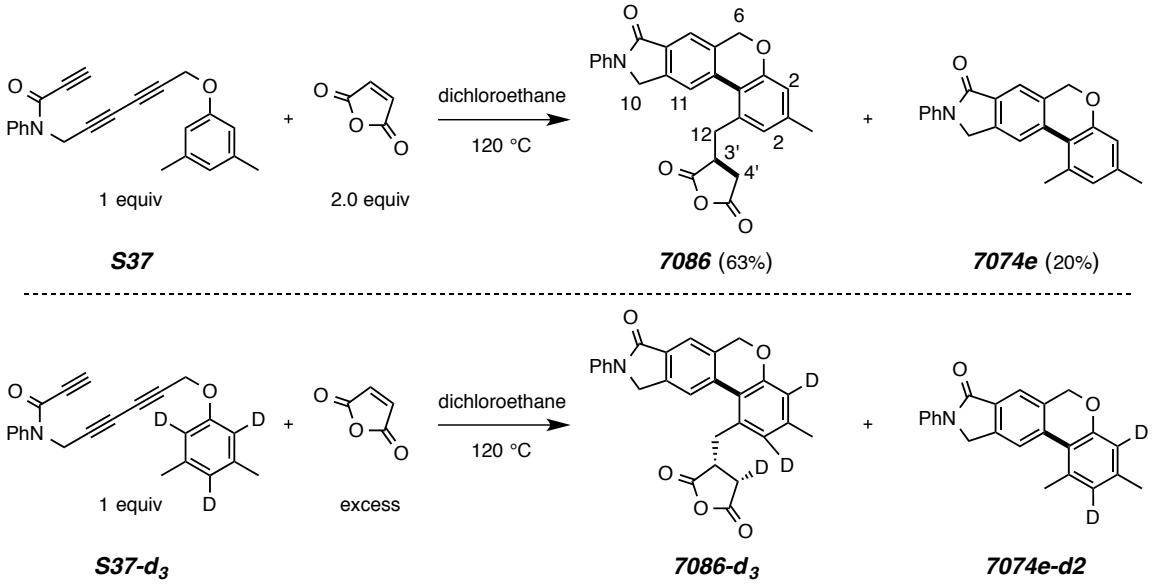
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (br s, 2H, *H2'H6'*), 6.95 (br s, 1H, *H4'*), 6.82 (d, *J* = 3.1 Hz, 1H, *H6*), 6.78 (d, *J* = 8.9 Hz, 1H, *H3*), 6.73 (dd, *J* = 8.9, 3.1 Hz, 1H, *H4*), 4.91 (s, 2H, C*H*$_2$O), 3.76 (s, 3H, C*H*$_3$O), 3.52 {septet, *J* = 6.4 Hz, 2H, N[C*H*$(CH_3)_2]_2$}, 2.32 [br s, 6H, Ar(C*H*$_3)_2$], and 0.99 {d, *J* = 6.4 Hz, 12H, N[CH(C*H*$_3)_2]_2$}.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 152.6, 138.3, 137.5, 137.4, 129.7, 125.8, 118.6, 112.1, 111.1, 71.0, 56.1, 49.7, 21.49, and 21.46.

IR: 2967, 2929, 2869, 2832, 1609, 1580, 1494, 1463, 1378, 1275, 1257, 1224, 1200, 1179, 1038, and 846 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{22}H_{32}NO_2^+$ $[M+H]^+$ requires 342.2428; found 342.2437.

3-((3-Methyl-8-oxo-9-phenyl-6,8,9,10-tetrahydrochromeno[3,4-*f*]isoindol-1-yl)methyl)dihydrofuran-2,5-dione (7086 and 7086-d_3)



Compound **7086** was prepared by heating amide **S37** (22 mg, 0.065 mmol, 1 equiv) and maleic anhydride (13 mg, 0.13 mmol, 2 equiv) in dichloroethane (0.25 mL) at 120 °C for 18 h. Compound **7086** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 3:1 then 1:1) as a light yellow oil (18 mg, 0.04 mmol, 63%). The previously described rearomatized product **7074e** was observed in the ^{1}H NMR spectrum of the crude reaction mixture (ca. 20%). Compound **7086-d_3** was obtained from the corresponding reaction using **S37-d_3**. The relative configuration of **7086-d_3** was determined by coupling constant analysis of the crude ^{1}H NMR spectrum of this reaction.

Characterization data for **7086**

^{1}H NMR (500 MHz, $CDCl_3$): 7.84 (dd, *J* = 8.8, 1.2 Hz, 2H, *Ho*), 7.78 (s, 1H, *H7*), 7.73 (s, 1H, *H11*), 7.42 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.18 (tt, *J* = 7.4, 1.2 Hz, 1H, *Hp*), 6.86 (br d, *J* = 1.8 Hz, 1H, *H2*), 6.76 (br d, *J* = 1.7 Hz, 1H, *H4*), 4.97 (d, *J* = 12.7 Hz, *H6a*), 4.94 (d, *J* = 12.7 Hz, *H6b*), 4.89 (d, *J* = 16.5 Hz, *H10a*), 4.85 (d, *J* = 16.5 Hz, *H10b*), 4.08 (dd, *J* = 15.0, 4.0 Hz, 1H, *H12a*), 3.52 (dddd, *J* = 10.7, 9.8, 6.6, 4.0 Hz, 1H, *H3'*), 3.16 (dd, *J* = 15.0, 11.0 Hz, 1H, *H12b*), 2.88 (dd, *J* = 18.9, 9.8 Hz, 1H, *H4'a*), 2.56 (dd, *J* = 19.0, 6.6 Hz, 1H, *H4'b*), and 2.35 (dd, *J* = 0.6, 0.6 Hz, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 169.5, 166.9, 158.0, 141.3, 140.7, 139.5, 134.44, 134.42, 133.8, 132.1, 129.4, 125.6, 124.8, 121.0, 120.2, 119.7, 119.6, 117.8, 69.3, 51.0, 41.3, 36.0, 34.1, and 21.6.

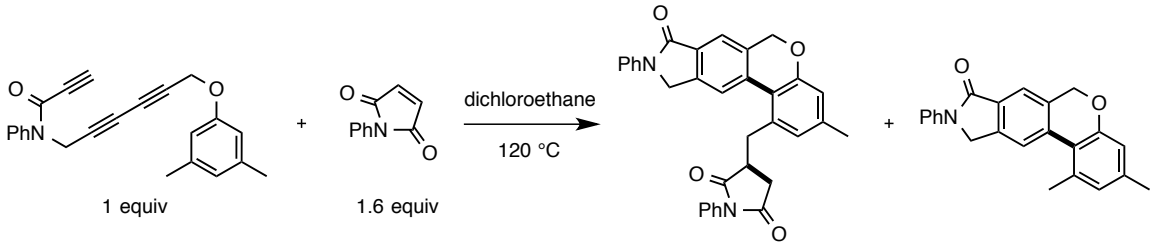
IR: 2919, 2859, 1862, 1780, 1690, 1615, 1598, 1501, 1459, 1448, 1383, 1293, 1268, 1227, 1177, 1129, 1071, 1023, 922, and 760 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{21}NNaO_5^+$ $[M+Na]^+$ requires 462.1312; found 462.1319.

^{1}H NMR data for **7086-d$_3$** (contaminated with excess maleic anhydride and **7074e-d$_2$**)

^{1}H NMR (500 MHz, $CDCl_3$): 7.87 (dd, *J* = 8.8, 1.2 Hz, 2H, *Ho*), 7.83 (s, 1H, *H7*), 7.78 (s, 1H, *H11*), 7.44 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.20 (tt, *J* = 7.4, 1.2 Hz, 1H, *Hp*), 5.01 (d, *J* = 12.7 Hz, *H6a*), 4.98 (d, *J* = 12.7 Hz, *H6b*), 4.97 (d, *J* = 16.5 Hz, *H10a*), 4.92 (d, *J* = 16.5 Hz, *H10b*), 4.09 (dd, *J* = 15.0, 4.0 Hz, 1H, *H12a*), 3.54 (ddd, *J* = 10.7, 9.7, 4.0 Hz, 1H, *H3'*), 3.19 (dd, *J* = 15.0, 10.9 Hz, 1H, *H12b*), 2.88 (br d, *J* = 9.8 Hz, 1H, *H4'a*), and 2.35 (br s, 3H, ArCH_3).

3-((3-Methyl-8-oxo-9-phenyl-6,8,9,10-tetrahydrochromeno[3,4-*f*]isoindol-1-yl)methyl)-1-phenylpyrrolidine-2,5-dione (7087a)



S37 ***7087a*** (66%) ***7074e*** (22%)

Compound **7087a** was prepared by heating amide **38** (25 mg, 0.073 mmol, 1 equiv) and *N*-phenyl maleimide (20 mg, 0.12 mmol, 1.6 equiv) in dichloroethane (0.25 mL) at 120 °C for 18 h. Compound **7087a** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 3:1 then 1:1) as a clear yellow oil (25 mg, 0.049 mmol, 66%). The previously described rearomatized product **7074e** was observed in the ^{1}H NMR spectrum of the crude reaction mixture (ca. 22%).

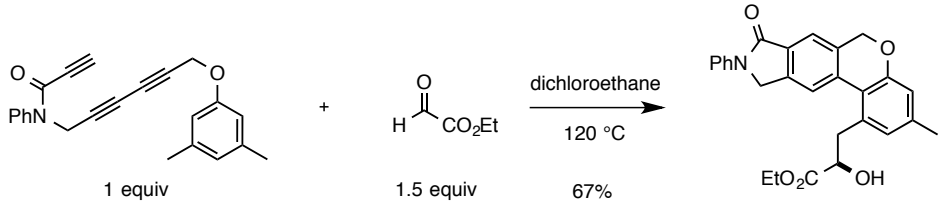
^{1}H NMR (500 MHz, $CDCl_3$): 7.93 (s, 1H, *H7*), 7.86 (dd, *J* = 8.8, 1.1 Hz, 2H, *Ho*), 7.78 (s, 1H, *H11*), 7.46 (dd, *J* = 8.7, 7.3 Hz, 2H, *Hm*), 7.42 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm'*), 7.39 (tt, *J* = 7.4, 1.3 Hz, 1H, *Hp'*), 7.23 (dd, *J* = 8.7, 1.5 Hz, 2H, *Ho'*), 7.18 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 6.87 (br d, *J* = 1.7 Hz, 1H, *H2*), 6.83 (br d, *J* = 1.7 Hz, 1H, *H4*), 5.01 (d, *J* = 12.5 Hz, *H6a*), 4.98 (d, *J* = 13.0 Hz, *H6b*), 4.93 (d, *J* = 16.7 Hz, *H10a*), 4.89 (d, *J* = 16.6 Hz, *H10b*), 4.19 (dd, *J* = 15.0, 3.6 Hz, 1H, *H4'a*), 3.36 (dddd, *J* = 10.5, 8.6, 4.8, 3.6 Hz, 1H, *H3'*), 3.11 (dd, *J* = 14.9, 10.7 Hz, 1H, *H4'b*), 2.80 (dd, *J* = 18.5, 9.2 Hz, 1H, *H12a*), 2.47 (dd, *J* = 18.5, 5.0 Hz, 1H, *H12b*), and 2.36 (dd, *J* = 0.6, 0.6 Hz, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 175.2, 167.1, 157.9, 141.0, 140.7, 139.6, 135.6, 134.5, 134.2, 132.0, 131.9, 129.40, 129.38, 128.9, 126.5, 125.9, 124.8, 120.9, 120.3, 120.1, 119.6, 117.5, 69.4, 51.1, 40.6, 36.6, 34.6, and 21.6.

IR: 2983, 2916, 1709, 1695, 1615, 1598, 1501, 1457, 1449, 1382, 1292, 1268, 1178, 1129, 1062, 909, and 759 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{26}N_2NaO_4^+$ $[M+Na]^+$ requires 537.1785; found 537.1790.

Ethyl 2-Hydroxy-3-(3-methyl-8-oxo-9-phenyl-6,8,9,10-tetrahydrochromeno[3,4-*f*]isoindol-1-yl)propanoate (7087b)



S37 ***7087b***

Compound **7087b** was prepared by heating amide **S37** (22 mg, 0.064 mmol, 1 equiv) and ethyl glyoxalate (20 mg, 50 wt.% in toluene, 0.098 mmol, 1.5 equiv) in dichloroethane (0.3 mL) at 120 °C for 18 h. Compound **7087b** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 1:1) as a colorless solid (19 mg, 0.043 mmol, 67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 1H, *H7'*), 7.86 (dd, *J* = 8.4, 1.0 Hz, 2H, *Ho*), 7.75 (s, 1H, *H11'*), 7.43 (dd, *J* = 8.3, 7.4 Hz, 2H, *Hm*), 7.18 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 6.94 (br d, *J* = 1.8 Hz, 1H, *H2'*), 6.82 (br d, *J* = 1.8 Hz, 1H, *H4'*), 4.97 (d, *J* = 12.5 Hz, 1H, *H6a'*), 4.94 (d, *J* = 12.6 Hz, 1H, *H6b'*), 4.90 (d, *J* = 17.5 Hz, 1H, *H10a'*), 4.86 (d, *J* = 18.0 Hz, 1H, *H10b'*), 4.58 (ddd, *J* = 8.1, 5.5, 4.4 Hz, 1H, *H2*), 4.22 (dq, *J* = 10.8, 7.2 Hz, 1H, CH_3CHa), 4.14 (dq, *J* = 10.8, 7.2 Hz, 1H, CH_3CHb), 3.54 (dd, *J* = 14.7, 4.4 Hz, 1H, *H3a*), 3.43 (dd, *J* = 14.7, 8.2 Hz, 1H, *H3b*), 2.94 [dd, *J* = 8.6 (to H_2O in the NMR sample), 5.6 Hz, 1H, O*H*], 2.34 (br s, 3H, $ArCH_3$), and 1.24 (t, *J* = 7.1 Hz, 3H, CH_3CH_2).

^{1}H NMR (500 MHz, DMSO): δ 8.12 (s, 1H, *H7'*), 7.94 (dd, *J* = 8.8, 1.1 Hz, 2H, *Ho*), 7.80 (s, 1H, *H11'*), 7.45 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.18 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 6.99 (br d, *J* = 1.8 Hz, 1H, *H2'*), 6.80 (br d, *J* = 1.8 Hz, 1H, *H4'*), 5.74 (d, *J* = 5.8 Hz, 1H, O*H*), 5.07 (d, *J* = 17.0 Hz, 1H, *H6a'*), 5.03 (d, *J* = 17.1 Hz, 1H, *H6b'*), 5.01 (d, *J* = 13.0 Hz, 1H, *H10a'*), 4.98 (d, *J* = 13.1 Hz, 1H, *H10b'*), 4.43 (ddd, *J* = 8.4, 5.8, 5.1 Hz, 1H, *H2*), 4.06 (q, *J* = 6.9 Hz, 1H, CH_3CH_2), 3.39 (dd, *J* = 14.6, 5.0

Hz, 1H, *H*3a), 3.32 (dd, *J* = 14.6, 8.4 Hz, 1H, *H*3b), 2.29 (br s, 3H, ArC*H*$_3$), and 1.13 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$).

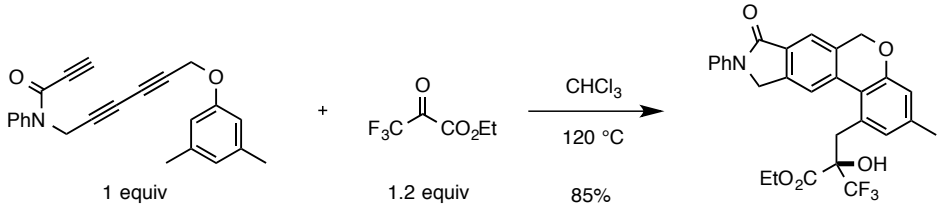
^{13}C NMR (125 MHz, DMSO): δ 173.5, 166.3, 156.6, 140.8, 139.5, 139.4, 135.9, 134.1, 133.8, 130.6, 129.0, 126.0, 124.0, 120.6, 120.5, 120.0, 119.2, 115.7, 70.9, 68.2, 60.2, 50.6, 37.8, 20.9, and 14.0.

IR: 3420, 2980, 2917, 2859, 1736, 1694, 1615, 1598, 1501, 1459, 1448, 1381, 1292, 1269, 1178, 1129, 1096, 1062, 1031, 1017, 897, 852, 774, and 761 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{25}NNaO_5^+$ $[M+Na]^+$ requires 466.1625; found 466.1629.

mp: 180-184 °C.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-((3-methyl-8-oxo-9-phenyl-6,8,9,10-tetrahydrochromeno[3,4-f]isoindol-1-yl)methyl)propanoate (7087c)



S37 ***7087c***

Compound **7087c** was prepared by heating amide **S37** (11 mg, 0.032 mmol, 1 equiv) and ethyl trifluoropyruvate (6.4 mg, 0.038 mmol, 1.2 equiv) in chloroform (0.1 mL) at 120 °C for 18 h. Compound **7087c** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 3:1) as a clear colorless oil (14.2 mg, 0.028 mmol, 85%).

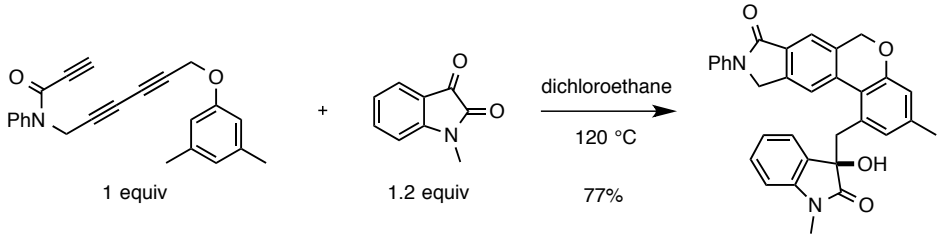
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H, *H7'*), 7.89 (dd, *J* = 8.8, 1.1 Hz, 2H, *Ho*), 7.78 (s, 1H, *H11'*), 7.44 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.19 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 6.85 (br d, *J* = 1.8 Hz, 1H, *H2'*), 6.84 (br d, *J* = 1.8 Hz, 1H, *H4'*), 5.05 (d, *J* = 12.5 Hz, 1H, *H6a'*), 4.94 (d, *J* = 16.5 Hz, 1H, *H10a'*), 4.90 (d, *J* = 16.2 Hz, 1H, *H10b'*), 4.81 (d, *J* = 12.4 Hz, 1H, *H6b'*), 4.27 (dq, *J* = 10.7, 7.1 Hz, 1H, CH_3CHa), 4.04 (dq, *J* = 10.7, 7.2 Hz, 1H, CH_3CHb), 3.96 (s, 1H, O*H*), 3.85 (d, *J* = 14.5 Hz, 1H, ArC*H*a), 3.73 (d, *J* = 14.4 Hz, 1H, ArC*H*b), 2.34 (s, 3H, $ArCH_3$), and 1.19 (t, *J* = 7.1 Hz, 3H, CH_3CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 167.3, 157.6, 140.4, 140.3, 139.7, 134.7, 134.4, 131.7, 130.9, 129.4, 126.4, 124.7, 123.7 (q, $^{1}J_{FC}$ = 286 Hz), 122.0, 120.8, 120.7, 119.6, 117.5, 78.5 (q, $^{2}J_{FC}$ = 28.3 Hz), 69.5, 64.1, 51.0, 34.3, 21.6, and 13.9.

IR: 2983, 2916, 2860, 1744, 1693, 1626, 1615, 1598, 1502, 1460, 1449, 1382, 1309, 1293, 1270, 1233, 1213, 1179, 1125, 1063, 1019, 953, 909, 858, and 758 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{28}H_{24}F_3NNaO_5^+$ $[M+Na]^+$ requires 534.1499; found 534.1503.

1-((3-Hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)-3-methyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6H)-one (7087d)



S37 ***7087d***

Compound **7087d** was prepared by heating amide **S37** (12.5 mg, 0.037 mmol, 1 equiv) and *N*-methyl isatin (6.9 mg, 0.043 mmol, 1.2 equiv) in dichloroethane (0.17 mL) at 120 °C for 18 h. The reaction mixture became a slurry as **7087d** precipitated. The reaction mixture was cooled to -20 °C and filtered while cold. The filter cake (mostly **7087d**) was carefully washed with a 3:1 mixture of hexanes and EtOAc to provide **7087d** as a colorless solid (14 mg, 0.028 mmol, 77%).

^{1}H NMR (500 MHz, DMSO): δ 7.94 (dd, *J* = 8.8, 1.2 Hz, 2H, *Ho*), 7.74 (s, 1H, *H7*), 7.68 (s, 1H, *H11*), 7.46 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.19 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 7.10 (ddd, *J* = 7.8, 6.9, 2.0 Hz, 1H, *H6'*), 6.73 (d, *J* = 1.9 Hz, 1H, *H2*), 6.69 (ddd, *J* = 7.8, 0.8, 0.8 Hz, 1H, *H7'*), 6.63 (d, *J* = 1.8 Hz, 1H, *H4*), 6.54 (ddd, *J* = 7.3, 7.3, 1.0 Hz, 1H, *H5'*), 6.52 (ddd, *J* = 7.3, 2.1, 0.6 Hz, 1H, *H4'*), 6.22 (s, 1H, O*H*), 5.15 (d, *J* = 17.1 Hz, 1H, *H10a*), 4.95 (d, *J* = 17.2 Hz, 1H, *H10b*), 4.90 (d, *J* = 12.5 Hz, 1H, *H6a*), 4.14 (d, *J* = 12.6 Hz, 1H, *H6b*), 4.01 (d, *J* = 13.2 Hz, 1H, ArC*H*aHb), 3.43 (d, *J* = 13.1 Hz, 1H, ArCHa*H*b), 2.85 (s, 3H, NCH_3), and 2.19 (dd, *J* = 0.7, 0.7 Hz, 3H, ArCH_3).

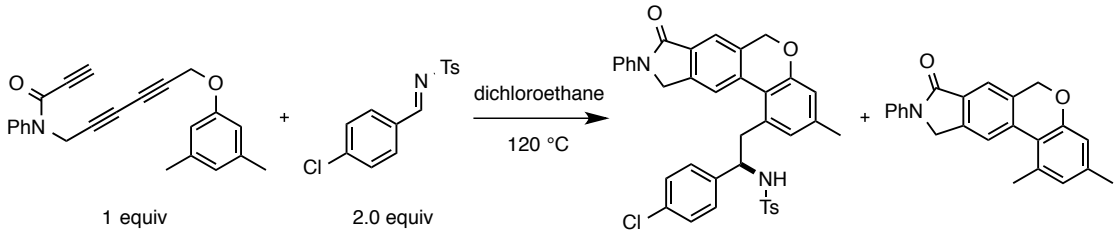
^{13}C NMR (125 MHz, DMSO): δ 177.0, 166.4, 156.0, 142.9, 140.7, 139.6, 138.6, 134.2, 134.0, 132.6, 130.3, 129.9, 129.0, 128.7, 126.5, 124.1, 123.6, 121.5, 121.0, 120.6, 119.8, 119.2, 115.5, 107.6, 77.3, 68.2, 50.5, 40.5, 25.5, and 20.8.

IR: 3390, 2917, 2850, 1716, 1694, 1673, 1613, 1599, 1501, 1494, 1470, 1449, 1380, 1292, 1270, 1175, 1129, 1089, 1057, 1016, 908, and 759 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{32}H_{26}N_2NaO_4^+$ $[M+Na]^+$ requires 525.1785; found 525.1775.

mp: 273-276 °C.

_N_-(1-(4-Chlorophenyl)-2-(3-methyl-8-oxo-9-phenyl-6,8,9,10-tetrahydrochromeno[3,4-*f*]isoindol-1-yl)ethyl)-4-methylbenzenesulfonamide (7087e)



S37 ***7087e*** (82%) ***7074e*** (4%)

Compound **7087e** was prepared by heating amide **38** (35 mg, 0.103 mmol, 1 equiv) and *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide[177] (58 mg, 0.2 mmol, 2 equiv) in dichloroethane (0.35 mL) at 120 °C for 18 h. Compound **7087e** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 1:1) as a colorless solid (53 mg, 0.083 mmol, 82%). The previously described rearomatized product **7074e** was observed in the ^{1}H NMR spectrum of the crude reaction mixture (ca. 4%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 8.8, 1.1 Hz, 2H, *Ho*), 7.73 (s, 1H, *H7*), 7.72 (s, 1H, *H11*), 7.42 (dd, *J* = 8.6, 7.4 Hz, 2H, *Hm*), 7.32 (d, *J* = 8.3 Hz, 2H, ClAr*H*3), 7.19 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 7.03 (d, *J* = 8.6 Hz, 2H, ClAr*H*2), 7.01 (d, *J* = 8.4 Hz, O_2SAr*H*2), 6.77 (d, *J* = 8.4 Hz, O_2SAr*H*3), 6.71 (br d, *J* = 1.8 Hz, 1H, *H*2), 6.53 (d, *J* = 1.8 Hz, 1H, *H*4), 5.08 (d, *J* = 6.4 Hz, 1H, N*H*), 4.89 (d, *J* = 16.4 Hz, *H*10a), 4.83 (d, *J* = 17.0 Hz, *H*10b), 4.82 (d, *J* = 12.2 Hz, *H*6a), 4.72 (d, *J* = 12.4 Hz, *H*6b), 4.51 (ddd, *J* = 7, 7, 7 Hz, 1H, C*H*NH), 3.65 (dd, *J* = 14.3, 7.0 Hz, Ar*H*aHb), 3.43 (dd, *J* = 14.3, 7.0 Hz, ArHa*H*b), 2.33 (br s, 3H, CH_3-$C_6H_4SO_2$), and 2.22 (s, 3H, C3CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 157.5, 143.6, 140.6, 140.5, 139.6, 138.8, 137.2, 134.48, 134.45, 134.2, 133.5, 131.5, 129.5, 129.4, 128.6, 128.2, 127.0, 126.6, 124.7, 120.8, 120.6, 120.0, 119.4, 116.9, 69.2, 58.7, 51.0, 42.4, 21.6, and 21.5.

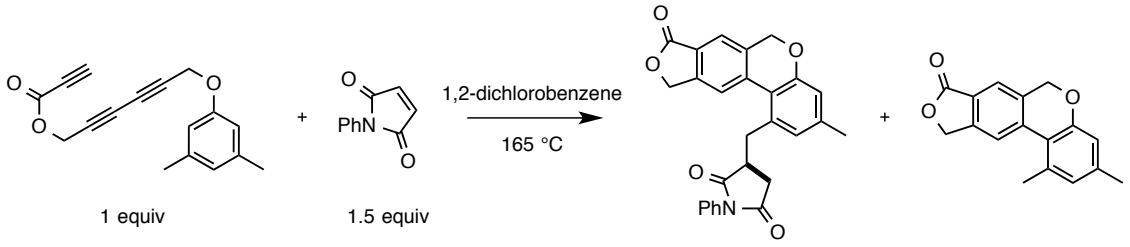
IR: 3250, 2925, 2863, 1679, 1615, 1598, 1501, 1493, 1449, 1384, 1326, 1292, 1269, 1158, 1129, 1092, 1062, 1014, 812, and 760 cm^{-1}.

[177] McNulty, J.; McLeod, D. Amine- and sulfonamide-promoted Wittig olefination reactions in water. *Chem. Eur. J.* **2001**, *17*, 8794–8798.

HRMS (ESI-TOF): Calcd for $C_{37}H_{31}ClNNaO_4SSi^+$ $[M+Na]^+$ requires 657.1585; found 657.1562.

mp: 140-143 °C.

3-((3-Methyl-8-oxo-8,10-dihydro-6*H*-isobenzofuro[5,6-*c*]chromen-1-yl)methyl)-1-phenylpyrrolidine-2,5-dione (7087f)



Compound **7087f** was prepared by heating amide **S35** (30.8 mg, 0.12 mmol, 1 equiv) and *N*-phenyl maleimide (31 mg, 0.18 mmol, 1.5 equiv) in 1,2-dichlorobenzene (0.6 mL). The reaction solution was stirred at 165 °C for 4 h. Compound **7087f** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 1:1) as a clear light yellow oil (36 mg, 0.082 mmol, 71%).

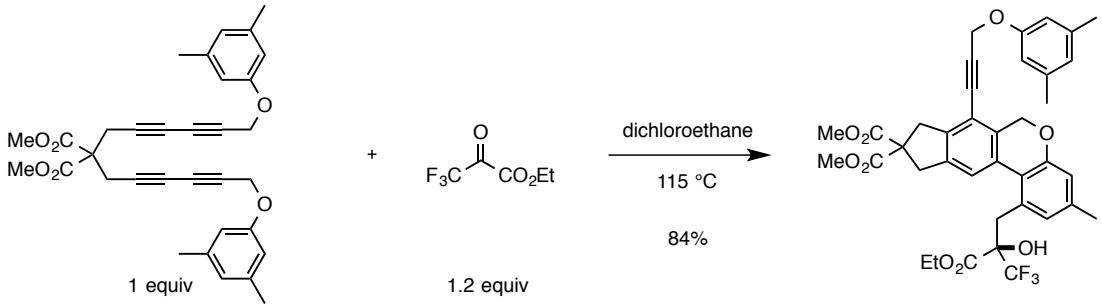
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (s, 1H, *H7*), 7.76 (s, 1H, *H11*), 7.46 (dd, *J* = 8.7, 7.3 Hz, 2H, *Hm*), 7.39 (tt, *J* = 7.4, 1.3 Hz, 1H, *Hp*), 7.22 (dd, *J* = 8.7, 1.5 Hz, 2H, *Ho*), 6.87 (br d, *J* = 1.7 Hz, 1H, *H2*), 6.85 (br d, *J* = 1.7 Hz, 1H, *H4*), 5.36 (d, *J* = 15.5 Hz, *H10a*), 5.32 (d, *J* = 15.7 Hz, *H10b*), 4.97 (s, 2H, *H6*), 4.10 (dd, *J* = 14.7, 3.7 Hz, 1H, *H4'a*), 3.36 (dddd, *J* = 10.5, 8.9, 5.0, 3.8 Hz, 1H, *H3'*), 3.13 (dd, *J* = 14.8, 10.5 Hz, 1H, *H4'b*), 2.81 (dd, *J* = 18.4, 9.2 Hz, 1H, ArC*H*aHb), 2.44 (dd, *J* = 18.5, 5.0 Hz, 1H, ArCHa*H*b), and 2.36 (dd, *J* = 0.6, 0.6 Hz, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): 178.3, 175.1, 170.7, 158.1, 147.1, 141.7, 136.2, 135.9, 135.1, 131.8, 129.4, 128.9, 126.4, 125.8, 124.1, 122.3, 120.0, 119.4, 117.4, 69.9, 69.2, 40.7, 36.2, 34.5, and 21.7.

IR: 2916, 2849, 1757, 1708, 1615, 1594, 1500, 1454, 1384, 1355, 1315, 1294, 1181, 1155, 1138, 1047, 1007, 909, and 759 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{27}H_{21}NNaO_5^+$ $[M+Na]^+$ requires 462.1312; found 462.1343.

Dimethyl 7-(3-(3,5-Dimethylphenoxy)prop-1-yn-1-yl)-1-(2-(ethoxycarbonyl)-3,3,3-trifluoro-2-hydroxypropyl)-3-methyl-8,10-dihydroindeno[5,6-*c*]chromene-9,9(6*H*)-dicarboxylate (7087g)



S34 ***7087g***

Compound **7087g** was prepared following General Procedure E from amide **S34** (30 mg, 0.057 mmol, 1 equiv) and ethyl trifluoropyruvate (11.5 mg, 0.068 mmol, 1.2 equiv) in 1,2-dichlorobenzene (0.2 mL). The reaction solution was stirred at 115 °C for 24 h. Compound **7087g** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 2:1) as a clear colorless oil (33.5 mg, 0.048 mmol, 84%).

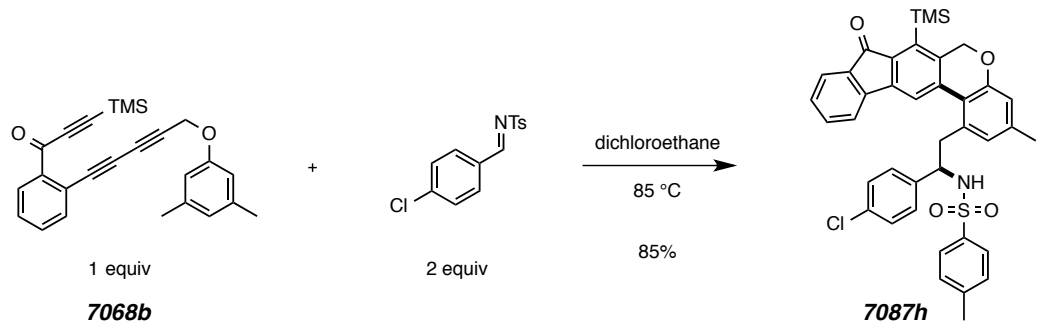
^{1}H NMR (500 MHz, $CDCl_3$): 7.65 (s, 1H, *H11*), 6.80 (br d, *J* = 1.8 Hz, 1H, *H2*), 6.78 (br d, *J* = 1.8 Hz, 1H, *H4*), 6.68 (br s, 2H, *Ho*), 6.66 (br s, 1H, *Hp*), 5.21 (d, *J* = 13.0 Hz, 1H, *H*6a), 4.96 (s, 2H, C≡CCH_2), 4.64 (d, *J* = 13.0 Hz, 1H, *H6b*), 4.19 (dq, *J* = 10.6, 7.1 Hz, 1H, CH_3CHaHb), 3.91 (dq, *J* = 10.6, 7.1 Hz, 1H, CH_3CHaHb), 3.81 (s, 1H, O*H*), 3.79 (d, *J* = 14.7 Hz, 1H, ArC*H*aHb), 3.77 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 3.65 [br s, 4H, $CH_2C(CO_2Me)CH_2$], 3.56 (d, *J* = 14.4 Hz, 1H, ArCHa*H*b), 2.32 [dt, *J* = 0.6, 0.6 Hz, 6H, $Ar(CH_3)_2$], and 2.28 (dd, *J* = 0.6, 0.6 Hz, 3H, $ArCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 171.9, 169.4, 157.7, 156.9, 141.7, 139.8, 139.5, 139.0, 135.0, 130.4, 129.9, 126.1, 123.7 (q, $^1J_{FC}$ = 286 Hz), 123.6, 122.8, 122.1, 117.1, 115.5, 113.1, 92.5, 82.3, 78.5 (q, $^2J_{FC}$ = 28.4 Hz), 67.2, 63.9, 59.8, 56.6, 53.27, 53.26, 41.1, 40.5, 34.2, 21.6, 21.5, and 13.8.

IR: 3474, 2955, 2918, 2849, 1737, 1615, 1594, 1436, 1370, 1315, 1291, 1258, 1239, 1202, 1179, 1168, 1152, 1138, 1121, 1064, 1017, 956, 856, and 832 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{38}H_{37}F_3NaO_9^+$ $[M+Na]^+$ requires 717.2282; found 717.2277.

_N_-(1-(4-Chlorophenyl)-2-(3-methyl-8-oxo-7-(trimethylsilyl)-6,8-dihydrofluoreno[2,3-_c_]chromen-1-yl)ethyl)-4-methylbenzenesulfonamide (7087h)



1 equiv 2 equiv

7068b ***7087h***

Compound **7087h** was prepared by heating ketone **26b** (21 mg, 0.054 mmol, 1 equiv) and *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide[177] (32 mg, 0.109 mmol, 2.0 equiv) in 1,2-dichloroethane (0.2 mL) at 85 °C for 18 h. Compound **7087h** was isolated following flash chromatography (hexanes:EtOAc = 5:1 then 2:1) as a bright yellow oil (32 mg, 0.047 mmol, 85%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.3 Hz, 1H, *H9*), 7.59 (s, 1H, *H13*), 7.47-7.44 (nfom, 2H, *H11* and *H12*), 7.32 (d, *J* = 8.2 Hz, 2H, ClAr*H*3), 7.32-7.28 (nfom, 1H, *H10*), 7.01 (d, *J* = 8.1 Hz, 2H, ClAr*H*2), 6.88 (d, *J* = 8.3 Hz, 2H, O_2SAr*H*2), 6.69 (br s, 1H, *H2*), 6.66 (br s, 1H, *H4*), 6.64 (d, *J* = 8.4 Hz, 2H, O_2SAr*H*3), 4.98 (d, *J* = 6.2 Hz, 1H, N*H*), 4.88 (d, *J* = 12.8 Hz, 1H, *H6a*), 4.44 (d, *J* = 12.8 Hz, 1H, *H6b*), 4.41 (ddd, *J* = 7, 7, 7 Hz, 1H, C*H*NH), 3.55 (dd, *J* = 13.9, 7.8 Hz, 1H, ArC*H*aHb), 3.50 (dd, *J* = 13.9, 7.1 Hz, 1H, ArCHa*H*b), 2.32 (s, 3H, CH_3-$C_6H_4SO_2$), 2.28 (s, 3H, C3CH_3), and 0.46 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): 194.6, 157.4, 144.4, 143.61, 143.55, 141.9, 140.7, 139.5, 138.3, 138.0, 137.1, 135.2, 134.8, 134.4, 134.0, 133.4, 129.5, 129.4, 128.4, 128.2, 127.1, 126.4, 124.1, 122.0, 120.0, 119.0, 116.2, 69.8, 59.2, 41.6, 21.63, 21.60 and 2.2.

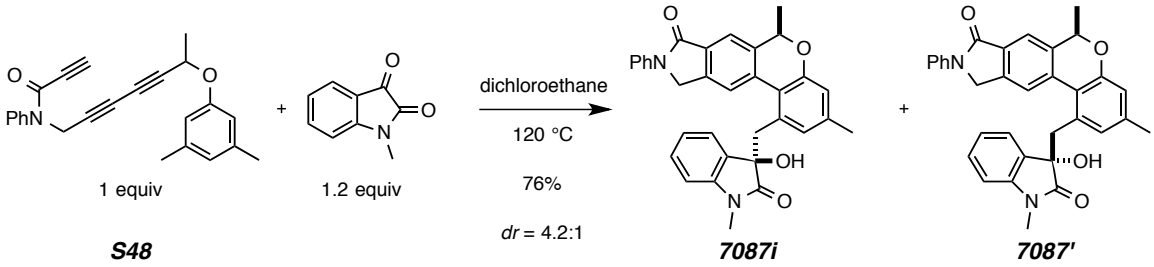
IR: 3258, 3055, 2997, 2948, 2900, 1709, 1606, 1588, 1492, 1463, 1322, 1303, 1248, 1183, 1158, 1091, 1063, 1014, 966, 901, and 859 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{39}H_{36}ClNNaO_4SSi^+$ $[M+Na]^+$ requires 700.1715; found 700.1760.

(±)-(*R*)-1-(((*R*)-3-Hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)-3,6-dimethyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7087i)

and

(±)-(*R*)-1-(((*S*)-3-Hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)-3,6-dimethyl-9-phenyl-9,10-dihydrochromeno[3,4-*f*]isoindol-8(6*H*)-one (7087i')



Compound **7087i** was prepared by heating amide **S48** (19 mg, 0.054 mmol, 1 equiv) and *N*-methyl isatin (10.5 mg, 0.065 mmol, 1.2 equiv) in 1,2-dichloroethane (0.25 mL). The reaction solution was stirred at 120 °C for 18 h. The reaction mixture became a slurry as **7087i** precipitated. The reaction mixture was cooled to -20 °C and filtered while cold. The filter cake (mostly **7087i**) was carefully washed with a 3:1 mixture of hexanes and EtOAc to give compound **7087i** as a colorless solid (16.8 mg, 0.033 mmol, 60%). The filtrate was concentrated, and subjected to column chromatography (hexanes:EtOAc = 3:1 then 1:1) to give a coeluting mixture of the minor epimer **7087i'** as a pale yellow oil (4.6 mg, 0.0089 mmol, 16%, containing ca. 20 mol% of **7087i**, as judged from the ^{1}H NMR data).

Characterization data for **7087i**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 8.8, 1.2 Hz, 2H, *Ho*), 7.75 (s, 1H, *H7*), 7.65 (s, 1H, *H11*), 7.47 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.22 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 7.12 (ddd, *J* = 7.7, 7.2, 1.9 Hz, 1H, *H6'*), 6.85 (d, *J* = 1.7 Hz, 1H, *H2*), 6.64 (dd, *J* = 1.8, 0.8 Hz, 1H, *H4*), 6.58 (ddd, *J* = 7.3, 7.3, 0.9 Hz, 1H, *H5'*), 6.544 (dd, *J* = 7.3, 1.7 Hz, 1H, *H4'*), 6.536 (d, *J* = 7.8 Hz, 1H, *H7'*), 5.02 (d, *J* = 16.2 Hz, 1H, *H10a*), 4.84 (d, *J* = 16.3 Hz, 1H, *H10b*), 4.32 (d, *J* = 13.0 Hz, ArC*H*aHb), 4.02 (q, *J* = 6.5 Hz, 1H,

H6), 3.47 (d, *J* = 13.0 Hz, 1H, ArCHa*H*b), 2.95 (s, 3H, NCH_3), 2.88 (s, 1H, O*H*), 2.27 (br s, 3H, ArCH_3), and 1.70 (d, *J* = 6.5 Hz, 3H, CHCH_3).

^{1}H NMR (500 MHz, DMSO): δ 7.95 (dd, *J* = 8.8, 1.1 Hz, 2H, *Ho*), 7.73 (s, 1H, *H7*), 7.60 (s, 1H, *H11*), 7.47 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.20 (tt, *J* = 7.4, 1.1 Hz, 1H, *Hp*), 7.09 (nfom, 1H, *H6'*), 6.73 (d, *J* = 1.8 Hz, 1H, *H2*), 6.69 (ddd, *J* = 7.8, 0.8, 0.8 Hz, 1H, *H7'*), 6.60 (d, *J* = 1.8 Hz, 1H, *H4*), 6.52-6.48 (nfom, 2H, *H4'H5'*), 6.21 (s, 1H, O*H*), 5.18 (d, *J* = 17.0 Hz, 1H, *H10a*), 4.94 (d, *J* = 17.0 Hz, 1H, *H10b*), 4.09 (d, *J* = 12.9 Hz, 1H, ArC*H*aHb), 4.08 (q, *J* = 6.5 Hz, 1H, C*H*CH$_3$), 3.39 (d, *J* = 13.0 Hz, 1H, ArCHa*H*b), 2.85 (s, 3H, NCH_3), 2.18 (dd, *J* = 0.7, 0.7 Hz, 3H, ArCH_3), and 1.60 (d, *J* = 6.5 Hz, 3H, CHCH_3).

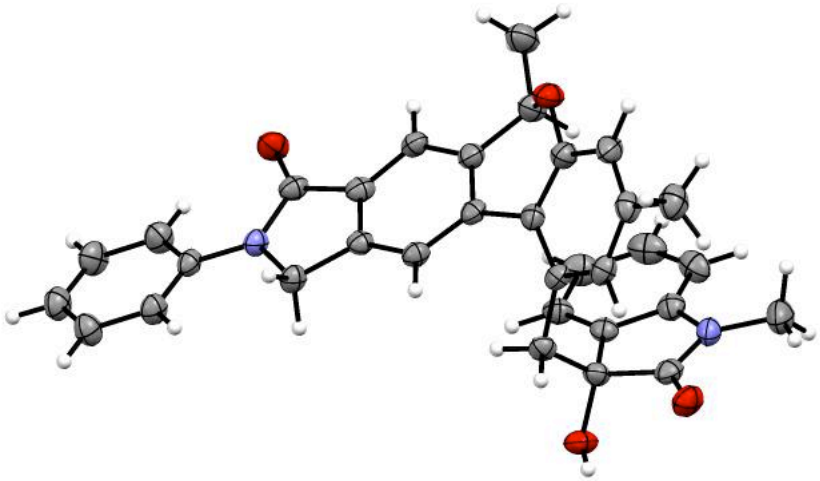
^{13}C NMR (125 MHz, DMSO): δ 176.9, 166.5, 155.5, 142.9, 140.4, 139.6, 138.5, 138.0, 134.4, 132.4, 130.6, 129.9, 129.0, 128.7, 126.1, 124.1, 123.5, 121.5, 121.0, 120.8, 119.2, 117.9, 115.4, 107.7, 77.4, 73.2, 50.5, 40.4, 25.5, 20.8, and 17.3.

IR: 3350, 1697, 1615, 1599, 1561, 1502, 1492, 1380, 1094, and 767 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{33}H_{28}N_2NaO_4^+$ $[M+Na]^+$ requires 539.1941; found 539.1928.

mp: 297-299 °C.

ORTEP rendering for 7087i:

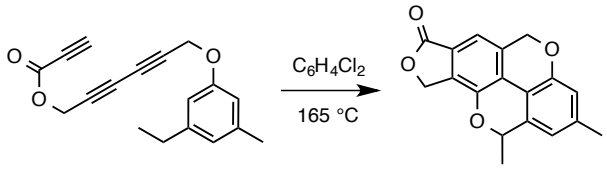


Characterization data for **7087i'**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 8.8, 1.2 Hz, 2H, *Ho*), 7.70 (s, 1H, *H7*), 7.65 (s, 1H, *H11*), 7.44 (dd, *J* = 8.7, 7.4 Hz, 2H, *Hm*), 7.19 (tt, *J* = 7.4, 1.2 Hz, 1H, *Hp*), 7.16 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H, *H6'*), 6.85 (d, *J* = 1.7 Hz, 1H, *H2*), 6.81 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, *H5'*), 6.74 (dd, *J* = 7.4, 1.4 Hz, 1H, *H4'*), 6.72 (br d, *J* = 1.7 Hz, 1H, *H4*), 6.64 (d, *J* = 6.7 Hz, 1H, *H7'*), 4.88 (d, *J* = 16.5 Hz, 1H *H10a*), 4.86 (q, *J* = 6.7 Hz, 1H, *H6*), 4.85 (d, *J* = 16.5 Hz, 1H, *H10b*), 3.87 (d, *J* = 13.0 Hz, ArC*H*aHb), 3.71 (d, *J* = 13.0 Hz, 1H, ArCHa*H*b), 3.00 (s, 3H, NCH_3), 2.85 (s, 1H, O*H*), 2.25 (br s, 3H, ArCH_3), and 1.49 (d, *J* = 6.5 Hz, 3H, CHCH_3).

^{1}C NMR (125 MHz, $CDCl_3$, shifts determined from HSQC data): δ 130.0, 129.3, 127.1, 124.6, 124.6, 122.9, 120.6, 119.6, 119.5, 116.7, 108.3, 74.0, 50.8, 40.9, 26.1, 21.4, and 18.2.

2,11-Dimethyl-5,11-dihydro-7*H*,9*H*-chromeno[5,4,3-*cde*]furo[3,4-*h*]chromen-7-one (7074d)



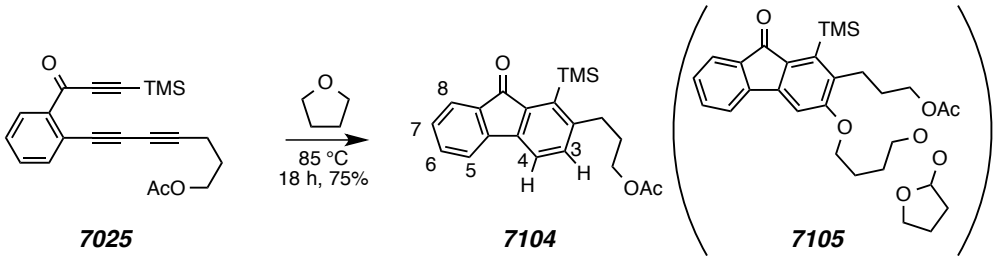
7090 ***7074d***

A solution of **7090** in non-deoxygenated $C_6H_4Cl_2$ was heated at 165 °C for 6 h. Compound **7074d** was formed as a byproduct.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (br s, 1H), 6.89 (br s, 1H), 6.77 (br s, 1H), 5.45 (q, *J* = 6.6 Hz, 2H), 5.29 (d, *J* = 8.8 Hz, 1H, CH_aH$_b$O), 5.27 (d, *J* = 8.5 Hz, 1H, CH$_a$$H_b$O), 4.97 (br s, 2H), 1.69 (d, *J* = 6.6 Hz, 3H, C*H*CH$_3$), and 1.55 (br s, 3H, C3-CH_3).

3-(9-Oxo-1-(trimethylsilyl)-9*H*-fluoren-2-yl)propyl acetate (7104)

and **3-(9-oxo-3-(4-((tetrahydrofuran-2-yl)peroxy)butoxy)-1-(trimethylsilyl)-9*H*-fluoren-2-yl)propyl acetate (7105)**



A solution of known acetate **7014** (20 mg, 0.057 mmol) in THF (6 mL) under N_2 atomsphere was heated to 85 °C for 18 h. The resulting solution was concentrated and purified using flash column chromatography (hexanes:EtOAc 15:1) to yield **7025** (15 mg, 0.043 mmol, 75%) as a golden oil.

If this reaction was performed under 1 atm of air, peroxide **7105** was formed as a byproduct, compromising the yield of **7104**.

Characterization data for **7104**:

^{1}H NMR (500 MHz, CD_3Cl): δ 7.57 (d, *J* = 7.3 Hz, 1H, *H8*), 7.42-7.46 (m, 3H, *H4/H5/H6*), 7.24-7.26 (nfom, 1H, *H7*), 7.22 (d, *J* = 7.6 Hz, 1H, *H3*), 4.11 (t, *J* = 6.5 Hz, 2H, C*H2*O), 2.85 (d, *J* = 8.0 Hz, 2H, ArCH_2), 2.07 (s, 3H, CH_3CO), 1.86 (nfom, 2H, CH_2CH$_2$O), 0.45 [s, 9H, Si(CH_3)$_3$].

^{1}H NMR (500 MHz, CD_3OD): δ 7.59 (ddd, *J* = 7.4, 1.0, 1.0 Hz, 1H, *H8*), 7.58 (d, *J* = 7.6 Hz, 1H, *H4*), 7.53 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H5*), 7.51 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H, *H6*), 7.33 (d, *J* = 7.7 Hz, 1H, *H3*), 7.29 (ddd, *J* = 7.4, 7.4, 1.1 Hz, *H7*), 4.11 (t, *J* = 6.4 Hz, 2H, CH_2O), 2.89 (br t, *J* = 8.0 Hz, 2H, ArCH_2), 2.04 (s, 3H, CH_3CO), 1.87 (nfom that includes *J* = 8.1 and 6.2 Hz, 2H, CH_2CH$_2$O), and 0.43 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.5, 171.3, 149.2, 144.1, 143.6, 141.2, 140.6, 135.4, 134.7, 134.0, 128.9, 124.1, 121.1, 119.7, 63.9, 33.2, 32.5, 21.2, and 2.6 ppm.

IR (neat): 2950, 2848, 1739, 1713, 1606, 1586, 1467, 1438, 1386, 1365, 1245, 1183, 1043, 862, and 847 cm^{-1}.

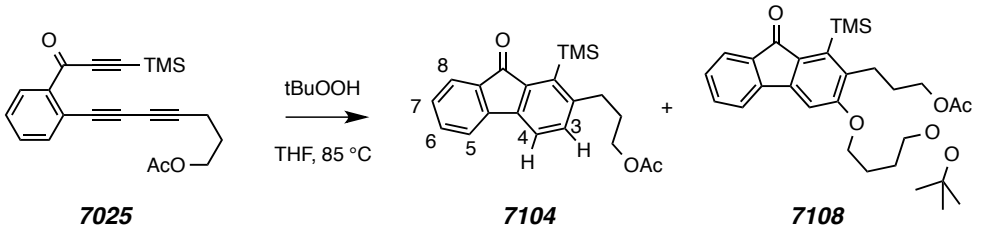
HRMS (ESI-TOF): Calcd for $C_{21}H_{24}NaO_3Si^+$ $[M+Na]^+$ requires 375.1387; found 375.1386.

Characterization data for **7105**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (br d, *J* = 7.3 Hz, 1H, *H8*), 7.44-7.40 (m, 2H), 7.27-7.23 (m, 1H), 7.01 (br s, 1H), 5.67 (dd, *J* = 6.2, 2.3 Hz, 1H), 4.22-4.10 (m, 6H), 3.99-3.92 (m, 2H), 2.87 (br t, *J* = 8.1 Hz, 2H, ArC*H*$_2$), 2.07 (s, 3H, C*H*$_3$CO), 2.10-1.90 (m, 4H), 1.90-1.75 (m, 6H), and 0.45 [s, 9H, Si(C*H*$_3$)$_3$].

HRMS (ESI-TOF): Calcd for $C_{29}H_{38}NaO_7Si^+$ $[M+Na]^+$ requires 549.2279; found 549.2285.

3-(3-(4-(*tert*-Butylperoxy)butoxy)-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-2-yl)propyl acetate (7108)



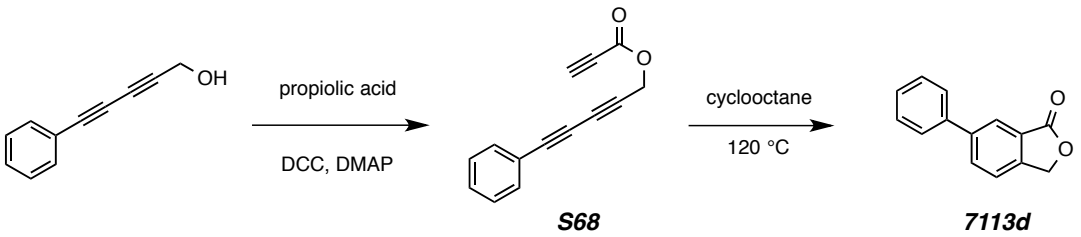
7025 ***7104*** ***7108***

When reduction of **7025** with THF was preformed in the presence of intentionally added tBuOOH (2 equiv) under N_2 atomsphere, peroxide **7108** was formed as a byproduct that coelutes with **7104**.

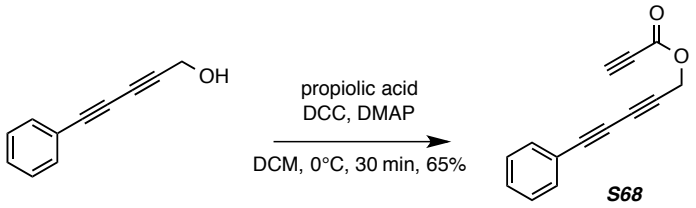
Characterization data for **7108**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H, *H5*), 7.43-7.39 (m, 2H), 7.00 (s, 1H), 4.14 (t, *J* = 6.2 Hz, 2H, C*H*$_2$O), 4.12 (t, *J* = 6.6 Hz, 2H, C*H*$_2$O), 4.04 (t, *J* = 6.2 Hz, 2H, C*H*$_2$O), 2.88 (br t, *J* = 8.0 Hz, 2H, ArC*H*$_2$), 2.07 (s, 3H, C*H*$_3$CO), 2.00-1.93 (m, 2H), 1.88-1.84 (m, 2H), 1.84-1.77 (m, 2H), 1.26 [s, 9H, C(CH$_3$)$_3$], and 0.46 [s, 9H, Si(C*H*$_3$)$_3$].

Synthesis of phthalide 7113d



5-Phenylpenta-2,4-diyn-1-yl propiolate (S68)



To a solution of 5-phenylpenta-2,4-diyn-1-ol[178] (312 mg, 2.0 mmol) and propiolic acid (154 mg, 2.2 mmol) in dichloromethane cooled at 0 °C was added DCC (494 mg, 2.4 mmol) and DMAP (12 mg, 0.1 mmol). The reaction mixture was stirred for an additional 30 min at this temperature. The resulting slurry was filtered through Celite®, concentrated, and purified with column chromatography (hexanes:EtOAc 12:1) to give ester **S68** (270 mg, 1.3 mmol, 65%) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 (br d, J = 7.4 Hz, 2H, ArH_o), 7.38 (tt, J = 7.5, 1.4 Hz, 1H, ArH_p), 7.33 (br dd, J = 7.3, 7.3 Hz, ArH_m), 4.93 (s, 2H, CH_2O), and 2.97 (s, 1H, C≡CH).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.9, 132.9, 129.8, 128.7, 121.2, 79.6, 76.3, 74.7, 74.0, 73.0, 72.5, and 54.3 ppm.

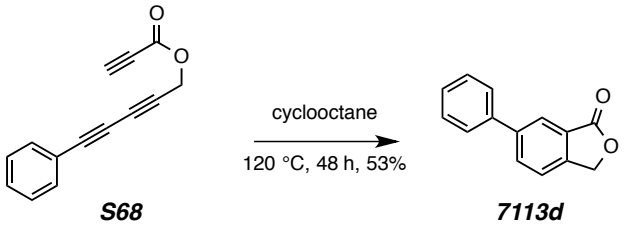
IR: 3283, 2932, 2856, 2250, 2121, 1722, 1649, 1596, 1491, 1441, 1368, 1209, 963, 755, and 689 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{14}H_8AgO_2^+$ [M+Ag^+] requires 314.9570; found 314.9587.

Mp: 51-52 °C.

[178] Meng, X.; Li, C.; Han, B.; Wang, T.; Chen, B. Iron/copper promoted oxidative homo-coupling reaction of terminal alkynes using air as the oxidant. *Tetrahedron* **2010**, *66*, 4029–4031.

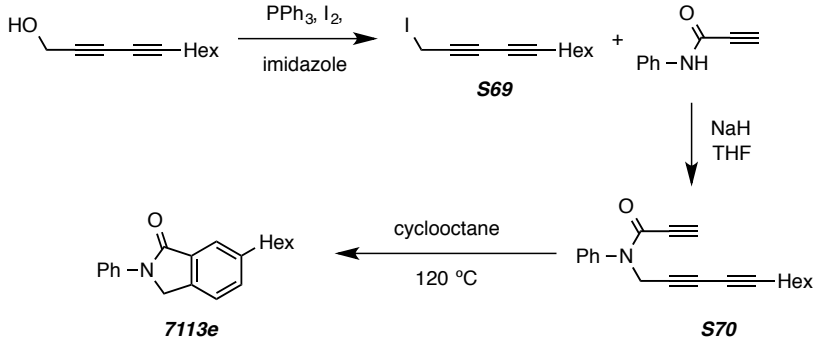
6-Phenylisobenzofuran-1(3*H*)-one (7113d)



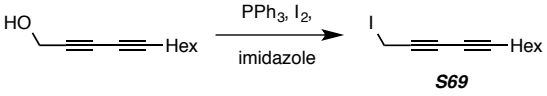
S68 ***7113d***

Phthalide **7113d** was prepared following general procedure C (120 ºC, 48 h) from ester **S68** (21 mg, 0.10 mmol) and cyclooctane (10 mL). The crude material was purified by flash column chromatography (hexanes:EtOAc 3:1) to yield phthalide **7113d** (11 mg, 0.053 mmol, 53%). The ^{1}H NMR spectrum is consistent with the reported data[179].

Synthesis of isoindolinone 7113e



1-Iodoundeca-2,4-diyne (S69)



PPh_3 (1.15 g, 4.4 mmol), I_2 (1.2 g, 4.8 mmol), and imidazole (0.56 g, 8 mmol) were sequentially added to a stirred solution of undeca-2,4-diyn-1-ol[180] (678 mg, 4.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 2 h the reaction mixture was diluted with CH_2Cl_2 and washed with satd. aq. $Na_2S_2O_3$. The organic extract was washed with brine, dried

[179] Novak, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. Synergistic palladium-catalyzed C(sp3)-H activation/C(sp3)-O bond formation: A direct, step-economical route to benzolactones. *Angew. Chem. Int. Ed.* **2011**, *50*, 12236–12239.

[180] Montierth, J. M.; DeMario, D. R.; Kurth, M. J.; Schore, N. E. The polymer-supported Cadiot-Chodkiewicz coupling of acetylenes to produce unsymmetrical diynes. *Tetrahedron* **1998**, *54*, 11741–11748.

(Na_2SO_4), and concentrated. Purification by flash chromatography (hexanes:EtOAc 12:1) gave the iodide **S69** (1.0 g, 3.7 mmol, 90%) as a pale yellow oil. This compound was stored in a refrigerator as a precaution toward decomposition.

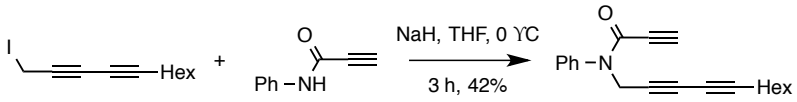
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (t, *J* = 1.2 Hz, 2H, C*H*$_2$I), 2.27 (tt, *J* = 7.0, 1.1 Hz, 2H, C≡CC*H*$_2$CH$_2$), 1.53 (tt, *J* = 7.3, 7.3 Hz, 2H, C≡CCH$_2$C*H*$_2$), 1.41-1.34 (m, 2H), 1.33-1.23 (m, 4H), and 0.89 (t, *J* = 7.2 Hz, 3H, C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 83.2, 72.2, 70.6, 65.0, 31.5, 28.7, 28.3, 22.7, 19.6, 14.3 and -18.1 ppm.

IR (neat): 2953, 2929, 2857, 2248, 1460, 1378, 1255, and 1143 cm^{-1}.

GC-MS: Retention time 8.39 min; electron impact (70 eV), *m/z* (ion, rel int): 274 (M+, 4), 203 (M+-C5H11, 5), 147 (M+-I, 7), 127 (I+, 18), 119 (C_9H_{11}+, 51), 105 (C_8H_9+, 100), 91 (C_7H_7+, 95), and 77 (C_6H_5+, 66).

_N_-Phenyl-_N_-(undeca-2,4-diyn-1-yl)propiolamide (S70)



S69 ***S70***

NaH (60% dispersion in mineral oil, 44 mg, 1.1 mmol) was added to a stirred solution of *N*-phenylpropiolamide[181] (145 mg, 1 mmol) in THF (6 mL) pre-cooled at 0 °C. The resulting mixture was kept at this temperature for 30 min, after which iodide **S69** (345 mg, 1.2 mmol) in THF (1.2 mL) was added dropwise. The reaction mixture was stirred for an additional 3 h and quenched by addition of satd. aq. NH_4Cl. The resulting mixture was separated and the aqueous layer washed with EtOAc. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc 5:1) to give the amide **S70** (122 mg, 0.42 mmol, 42%) as a pale yellow oil.

[181] Yanada, R.; Obika, S.; Kobayashi, Y.; Inokuma, T.; Oyama, M.; Yanada, K.; Takemoto, Y. Stereoselective synthesis of 3-Alkylideneoxindoles using tandem indium-mediated carbomallation and palladium-catalyzed cross-coupling reactions. *Adv. Synth. Catal.* **2005**, *347*, 1632–1642et.

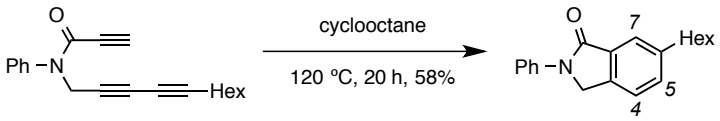
^{1}H NMR (500 MHz, $CDCl_3$, as a 6:1 mixture of rotamers): major rotamer: δ 7.45-7.40 (m, 3H, ArH_mH_p), 7.35 (d, J = 7.5 Hz, 2H, ArH_o), 4.58 (s, 2H, NCH_2), 2.82 (s, 1H, C≡CH), 2.45 (t, J = 7.0 Hz, 2H, C≡CCH_2CH$_2$), 1.51 (tt, J = 7.6, 7.6 Hz, 2H, C≡CCH$_2$CH_2), 1.37 (tt, J = 7.8, 7.8 Hz, 2H, C≡CCH$_2$CH$_2$CH_2), 1.33-1.23 (m, 4H), and 0.89 (t, J = 7.1 Hz, 3H, CH_3). Minor rotamer: δ 4.75 (s, NCH_2), 3.28 (s, C≡CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.7, 140.6, 129.6, 129.1, 128.5, 81.0, 80.5, 76.0, 69.9, 69.8, 64.8, 38.9, 31.4, 28.7, 28.3, 22.7, 19.4, and 14.2 ppm.

IR (neat): 2954, 2930, 2858, 2257, 2110, 1646, 1595, 1494, 1456, 1383, 1275, 1220, and 697 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{20}H_{21}NNaO^+$ $[M+Na]^+$ requires 314.1515; found 314.1509.

6-Hexyl-2-phenylisoindolin-1-one (7113e)



S70 ***7113e***

Isoindolinone **7113e** was prepared by heating amide **S70** (15 mg, 0.052 mmol) in cyclooctane (5 mL) at 120 ºC for 20 h. The crude material was purified by flash column chromatography (hexanes:EtOAc 3:1) to yield the isoindolinone **7113e** (9 mg, 0.03 mmol, 58%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): 7.87 (dd, J = 8.6, 1.0 Hz, 2H, PhH_o), 7.74 (s, 1H, *H7*), 7.42 (dd, J = 8.6, 7.5 Hz, 2H, PhH_m), 7.43-7.39 (m, 2H, *H4H5*), 7.17 (tt, J = 7.4, 1.1 Hz, 1H, PhH_p), 4.82 (s, 2H, CH_2N), 2.72 (br t, J = 7.8 Hz, 2H, ArCH_2CH$_2$), 1.69-1.62 (m, 2H, ArCH$_2$CH_2), 1.36-1.25 (m, 6H), and 0.88 (br t, J = 7.0 Hz, CH_3).

^{1}H NMR (500 MHz, CD_3CN): 7.90 (dd, J = 8.8, 1.1 Hz, 2H, PhH_o), 7.61 (dd, J = 1.6, 0.8 Hz, 1H, *H7*), 7.50 (ddt, J = 7.7, 0.8, 0.8 Hz, 1H, *H4*), 7.48 (dd, J =7.7, 1.6 Hz, 1H, *H5*), 7.44 (dd, J = 8.8, 7.4 Hz, 2H, PhH_m), 7.18 (tt, J = 7.4, 1.8 Hz, 1H, PhH_p), 4.86 (d, J = 0.8 Hz, 2H, NCH_2), 2.73 (br t, J = 7.7 Hz, 2H, ArCH_2), 1.65 (br tt, J = 7.5, 7.5 Hz, 2H, ArCH$_2$CH_2), 1.38-1.26 (m, 6H), and 0.89 (br t, J = 7.0 Hz, CH_3).

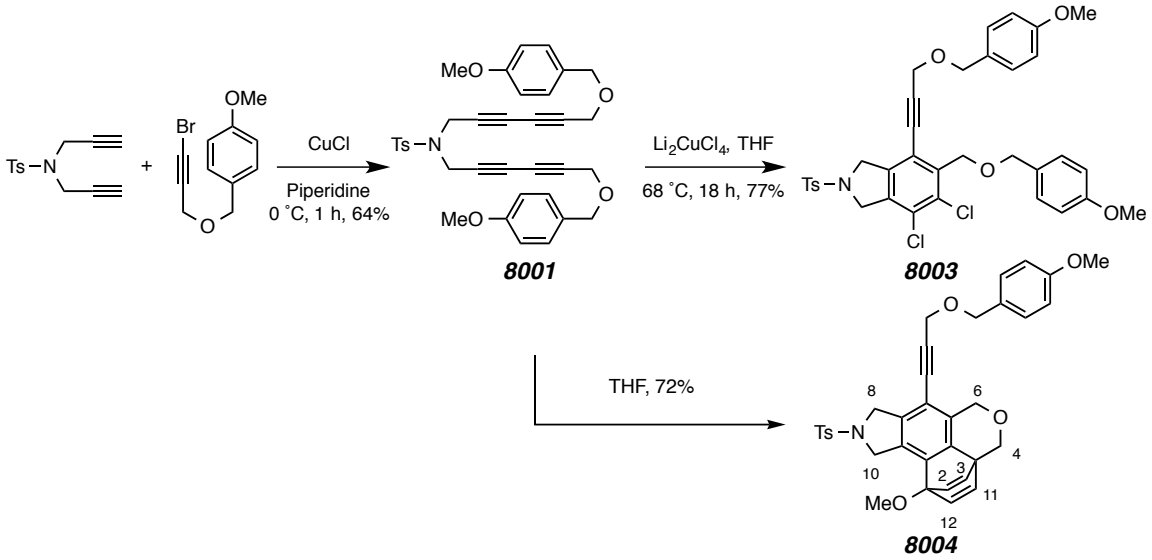
^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 143.8, 139.9, 137.8, 133.5, 132.8, 129.3, 124.6, 123.9, 122.5, 119.7, 50.8, 36.0, 31.9, 31.7, 29.1, 22.8, and 14.3 ppm.

IR (neat): 2954, 2924, 2855, 1682, 1598, 1500, 1463, 1382, 1307, 1171, 1142, and 908 cm^{-1}.

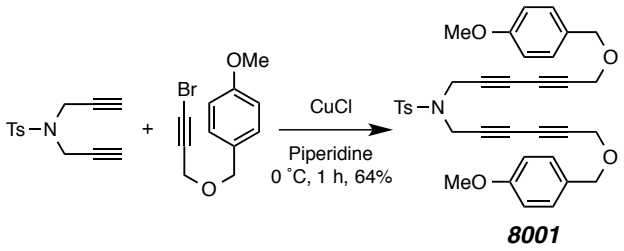
HRMS (ESI-TOF): Calcd for $C_{20}H_{23}NNaO^+$ $[M+Na]^+$ requires 316.1672; found 316.1667.

Mp: 121-123 °C.

Synthesis of isoindoline 8003 and 8004



***N,N*-Bis{6-[(4-methoxybenzyl)oxy]hexa-2,4-diyn-1-yl}-4-methylbenzenesulfonamide (8001)**



Tetrayne **8001** was prepared following General Procedure B from 4-methyl-*N,N*-di(prop-2-yn-1-yl)benzenesulfonamide (150 mg, 0.6 mmol), 1-{[(3-bromoprop-2-yn-1-yl)oxy]methyl}-4-methoxybenzene (512 mg, 2.0 mmol), CuCl (24 mg, 0.24 mmol), and piperidine (2 mL). Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the tetrayne **8001** (230 mg, 0.39 mmol, 64%) as a yellow oil.

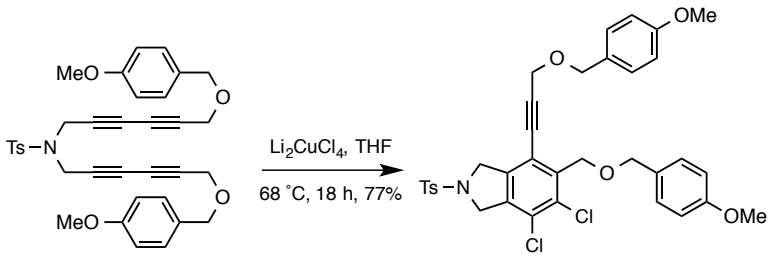
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 2H, SO_2ArHo), 7.32 (d, *J* = 8.4 Hz, 2H, SO_2ArHm), 7.26 (d, *J* = 8.6 Hz, 4H, $MeOArH_m$), 6.88 (d, *J* = 8.8 Hz, 4H, $MeOArH_o$), 4.50 (s, 4H, OCH_2Ar), 4.23 (s, 4H, $OCH_2C{\equiv}C$), 4.15 (s, 4H, NCH_2), 3.80 (s, 6H, OCH_3), and 2.39 (s, 3H, $ArCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 144.6, 134.6, 129.99, 129.94, 129.1, 128.0, 114.0, 75.5, 71.6, 70.3, 70.2, 57.2, 55.4, 37.5, and 21.8 ppm.

IR: 3010, 2838, 2365, 1612, 1586, 1513, 1350, 1303, 1249, 1163, 1071, 1033, 891, and 817 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{35}H_{33}NNaO_6S^+$ $[M+Na]^+$ requires 618.1921; found 618.1978.

4,5-Dichloro-6-{[(3-methoxybenzyl)oxy]methyl}-7-{3-[(4-methoxybenzyl)oxy]prop-1-yn-1-yl}-2-tosylisoindoline (8003)



8001 ***8003***

Dichloride **8003** was prepared by heating tetrayne **8001** (24 mg, 0.04 mmol) and Li_2CuCl_4 (0.4 mL, 1M in THF, 0.4 mmol) in THF (1 mL) at 68 °C for 18h. Purification by flash chromatography (hexanes:EtOAc 12:1 to 5:1) gave the dichloride **8003** (21 mg, 0.032 mmol, 77%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H_o}$), 7.30 (d, J = 8.5 Hz, 2H, $SO_2Ar\mathit{H_m}$), 7.29 (d, J = 8.6 Hz, 2H, MeOAr$\mathit{H_m}$), 6.98 (d, J = 7.0 Hz, 2H, MeOAr'$\mathit{H_m}$), 6.91 (d, J = 8.6 Hz, 2H, MeOAr$\mathit{H_o}$), 6.83 (d, J = 7.0 Hz, 2H, MeOAr'$\mathit{H_o}$), 4.74 (s, 2H), 4.71 (br s, 2H), 4.65 (br s, 2H), 4.56 (s, 2H), 4.51 (s, 2H), 4.35 (s, 2H), 3.82 (s, 3H, OC$\mathit{H_3}$), 3.77 (s, 3H, OC$\mathit{H_3}$), and 2.41 (s, 3H, ArC$\mathit{H_3}$).

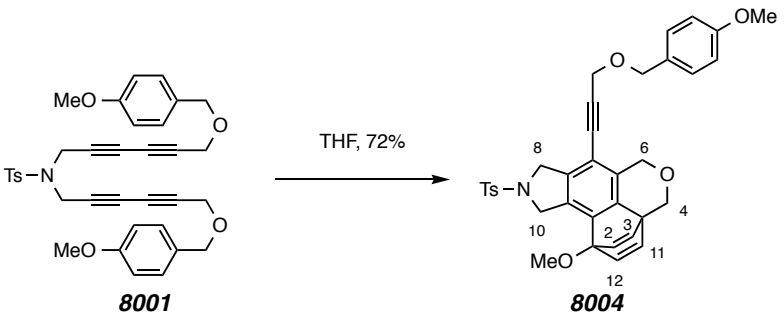
^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 159.5, 144.3, 138.9, 138.8, 136.6, 133.9, 133.6, 130.3, 130.2, 130.0, 129.7, 129.3, 128.5, 127.7, 118.8, 114.2, 113.9, 95.3, 80.4, 73.0, 71.8, 68.2, 57.6, 55.52, 55.46, 55.0, 54.7, and 21.8 ppm.

IR (neat): 2932, 2838, 1612, 1513, 1350, 1249, 1164, 1096, 1071, and 1034cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{35}H_{33}Cl_2NNaO_6S^+$ $[M+Na]^+$ requires 688.1298; found 688.1315.

mp: 132–137 °C.

1-Methoxy-7-{3-[(4-methoxybenzyl)oxy]prop-1-yn-1-yl}-9-tosyl-6,8,9,10-tetrahydro-1*H*,4*H*-1,3a-ethenoisochromeno[5,4-*ef*]isoindole (8004)



8001 ***8004***

A solution of tetrayne **8001** (22 mg, 0.037 mmol) in THF (2 mL) was heated at 68 °C for 18 h. The resulting solution was concentrated and subjected to flash chromatography (SiO_2, hexanes:EtOAc = 5:1) to give isoindoline **8004** (16 mg, 0.027 mmol, 72%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H, SO_2ArH_o), 7.30 (d, *J* = 8.6 Hz, 2H, MeOArH_m), 7.29 (d, *J* = 8.7 Hz, 2H, SO_2ArH_m), 6.98 (d, *J* = 6.9 Hz, 2H, *H*2 and *H*12), 6.91 (d, *J* = 8.7 Hz, 2H, MeOArH_o), 6.63 (d, *J* = 6.9 Hz, 2H, *H*3 and *H*11), 4.83 (br s, 2H, CH_2), 4.71 (br s, 2H, CH_2), 4.56 (br s, 2H, CH_2), 4.52 (br s, 2H, CH_2), 4.48 (br s, 2H, CH_2), 4.35 (br s, 2H, CH_2), 3.82 (s, 3H, ArOCH_3), 3.73 (s, 3H, C1OCH_3), and 2.40 (s, 3H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 143.7, 143.0, 141.5, 141.3, 140.7, 136.0, 134.0, 131.5, 130.1, 130.0, 129.4, 127.8, 127.7, 114.1, 108.8, 93.1, 90.9, 80.4, 71.4, 71.1, 66.5, 57.6, 55.5, 54.6, 53.5, 53.0, 50.2, and 21.7 ppm.

IR: 2946, 2837, 1612, 1513, 1459, 1440, 1344, 1249, 1163, 1097, 1068, 1036, 909, and 817 cm^{-1}.

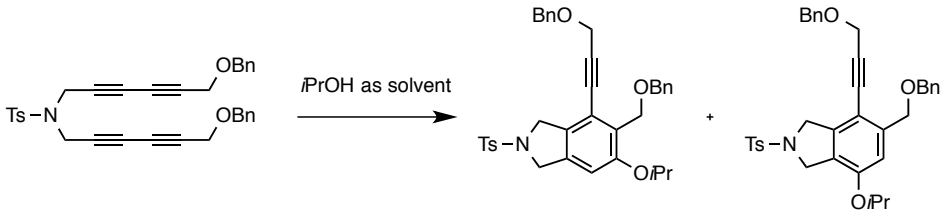
HRMS (ESI-TOF): Calcd for $C_{35}H_{33}NNaO_6S^+$ $[M+Na]^+$ requires 618.1921; found 618.1915.

mp: 185–191 °C.

Synthesis of 5-((Benzyloxy)methyl)-4-(3-(benzyloxy)prop-1-yn-1-yl)-6-isopropoxy-2-tosylisoindoline (8017)

and

5-((Benzyloxy)methyl)-4-(3-(benzyloxy)prop-1-yn-1-yl)-7-isopropoxy-2-tosylisoindoline (8018)



8015 ***8017*** 2.6:1 ***8018***

A solution of **8015** (10 mg) in *i*PrOH (2 mL) was heated at 68 °C for 18 h. The resulting solution was concentrated. Analysis of the crude ^{1}H NMR spectrum of the resulting residue revealed **8017** and **8108** were formed in ca. 2.6:1 ratio.

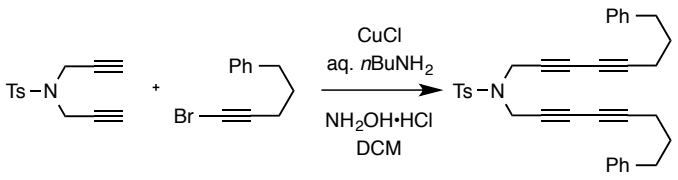
Characteristic peaks of **8017**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.38-7.20 (overlapping m, 12H), 6.68 (s, 1H, *H*7), 4.47 [septet, J = 6.0 Hz, 1H, $CH(CH_3)_2$], 2.40 (s, 3H, $ArCH_3$), and 1.29 [d, J = 6.1 Hz, 6H, $CH(CH_3)_2$].

Characteristic peaks of **8018**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.38-7.20 (overlapping m, 12H), 6.89 (s, 1H, *H*6), 2.41 (s, 3H, $ArCH_3$), and 1.30 [d, J = 5.7 Hz, 6H, $CH(CH_3)_2$].

Synthesis of 4-methyl-*N*,*N*-bis(8-phenylocta-2,4-diyn-1-yl)benzenesulfonamide (8023)



8023

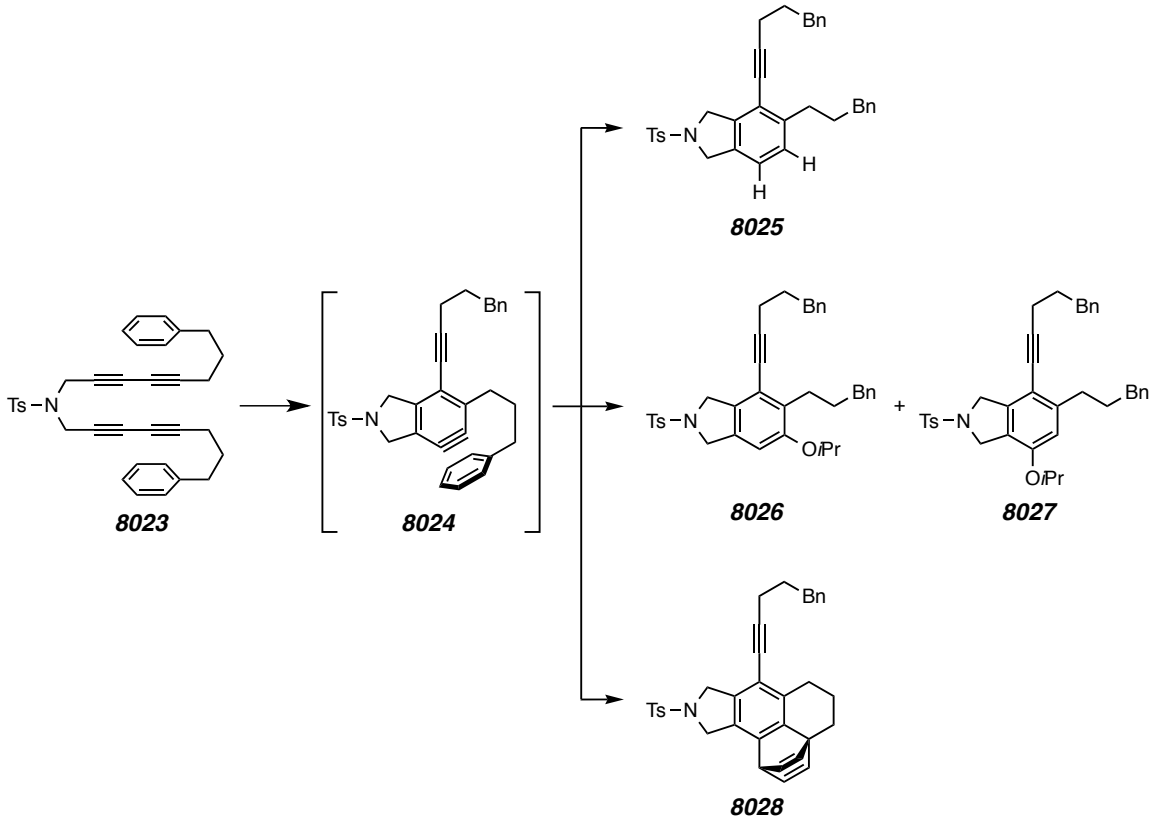
Tetrayne **8023** was prepared following General Procedure C from 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (124 mg, 0.5 mmol), (5-bromopent-4-yn-1-yl)benzene (555 mg, 2.5 mmol), NH_2OH•HCl (a few crystals), CuCl (20 mg, 0.2 mmol), 30% aq. *n*$BuNH_2$ (2 mL), and DCM (2 mL). Compound **8023** was isolated following flash chromatography (SiO_2, hexanes:EtOAc = 5:1) as a yellow oil (250 mg, 0.47 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H, $SO_2Ar\mathit{H}_o$), 7.32 (d, *J* = 8.7 Hz, 2H, $SO_2Ar\mathit{H}_m$), 7.30 (dd, *J* = 7.6 Hz, 4H, $Ar\mathit{H}_m$), 7.21 (t, *J* = 7.4 Hz, 2H, $Ar\mathit{H}_p$), 7.21 (d, *J* = 7.6 Hz, 4H, $Ar\mathit{H}_o$), 4.21 (s, 4H, $TsNC\mathit{H}_2$), 2.70 (t, *J* = 7.4 Hz, 4H, $C\mathit{H}_2CH_2CH_2$), 2.39 (s, 3H, $ArC\mathit{H}_3$), 2.25 (t, *J* = 6.9 Hz, 4H, $CH_2CH_2C\mathit{H}_2$), and 1.83 (tt, *J* = 7.7, 7.7 Hz, 4H, $CH_2C\mathit{H}_2CH_2$).

Synthesis of 4-(5-phenylpent-1-yn-1-yl)-5-(3-phenylpropyl)-2-tosylisoindoline (8025), 6-isopropoxy-4-(5-phenylpent-1-yn-1-yl)-5-(3-phenylpropyl)-2-tosylisoindoline (8026), 7-isopropoxy-4-(5-phenylpent-1-yn-1-yl)-5-(3-phenylpropyl)-2-tosylisoindoline (8027),

and

(1*s*,3a*s*)-7-(5-phenylpent-1-yn-1-yl)-9-tosyl-4,5,6,8,9,10-hexahydro-1*H*-1,3a-ethenonaphtho[1,8-*ef*]isoindole (8028)



Solutions of **8023** and iPrOH in various amount of $CDCl_3$ (0.9 mL to 3.9 mL) were heated at 68 °C for 18 h. The resulting solutions were concentrated. The residues were dissolved in $CDCl_3$. Analysis of the ^1H NMR spectra gave the ratio of each compound to **8028** at different concentrations of iPrOH.

Characteristic peaks of **8025**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (d, *J* = 7.9 Hz, 1H, *H*7), 7.07 (d, *J* = 7.8 Hz, 1H, *H*6).

Characteristic peaks of **8026**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 1H, *H*7), 4.44 [septet, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$], 2.40 (s, 3H, ArC*H*$_3$), and 1.29 [d, *J* = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$].

Characteristic peaks of **8026**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54 (s, 1H, *H*6), 4.52 [septet, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$], 2.40 (s, 3H, ArC*H*$_3$), and 1.31 [d, *J* = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$].

Characterization data for **8028**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H, SO_2Ar*H*$_o$), 7.35-7.20 (m, 12H, Ar*H*), 6.79 (dd, *J* = 6.3, 6.3 Hz, 2H, *H2*), 6.59 (dd, *J* = 6.6, 1.6 Hz, 2H, *H2a*), 4.74 (tt, *J* = 5.8, 1.6 Hz, 1H, *H1*), 4.66 (t, *J* = 1.6 Hz, 2H), 4.57 (t, *J* = 1.8 Hz, 2H), 2.80-2.72 (m, 4H), 2.46-2.42 (m, 4H), 2.39 (s, 3H, ArC*H*$_3$), and 1.93-1.84 (m, 4H).

Notes

1) The structure for each of the compounds containing a free acyltetronic acid (ATA) (i.e., **6**, **7**, or **8**) is arbitrarily (and for convenience) portrayed as an endocyclic enol; an internally hydrogen-bonded variant of that endocyclic enol (a rotamer about the C10–C11 bond) or *E*- or *Z*-exocyclic enols are also possible.

2) The ratio of **2049** to **2050** was later estimated to be ca. 3:2.

3) $CrCl_2$ in the reaction mixture presumably function as a Lewis acid that catalyzes the IMDA reaction of **2049**.

4) The reactivity of the free tetronate (*O*-demethylated version) of **2.57** was not reported.

5) Notably, attempted alcohol oxidation using Dess–Martin periodinane appeared to destroy the diene unit present in the substrate, and Parikh–Doering oxidation only gave a low yield of desired aldehyde.

6) The anionic addition step occurred with >90% yield and 1:1 dr. The less than optimal isolated yield of **3.26** may be caused by product absorption by MnO_2 in the second step.

7) Besides the linear products like **3.30**, those with different number of cyclopropyl rings could have also been formed.

8) Takagi, R.; Tsuyumine, S.; Nishitani, H.; Miyanaga, W.; Ohkata, K. Stereoselective synthesis of the hydrophobic side chain of scyphostatin. *Aust. J. Chem.* **2004**, *57*, 439–447. I prepared (+)-(2*R*,4*S*)-**3.5** using slightly modified procedures. These involved enantioselective, lipase-catalyzed (PPL) acetylation of diol **3.13** (the resulting mono-alcohol was measured to have an ca. 9:1 er by Mosher ester analysis), TBS protection, acetate methanolysis, and iodination. The sample of (+)-**3.5** had $[\alpha]_D$ ($CHCl_3$, c = 2.0) = +3.1 [lit. $[\alpha]_D^{22}$ ($CHCl_3$, c = 2.09) = +3.50].

9) The sample of natural okilactomycin D was isolated after a final purification by HPLC using an eluent doped with trifluoroacetic acid. Thus, its structure is best formulated as **3001**, having the neutral acyltetronic acid. We observed that the ^1H NMR spectrum of the sodium salt of **3001** in CD_3OD (or of the analogous cesium salt in CDCl3) contained a resonance for the enone β-proton (H6) that was ca. 0.6 (or 0.2) ppm upfield of that for the sample of neutral **3001**.

10) This minor isomer was formed as a byproduct in both generations of substrate synthesis (see Scheme 3.5 and 3.9).

11) It is reasonable to assume that both isomers should react at similar rate if the IMDA reaction occurs via a stepwise mechanism.

12) BF_3•Et_2O or $Cu(OTf)_2$ is not tolerated presumably because both reagents would give rise to strong protic acids when reacting with adventitious amount of water.

13) This anti-relationship of the two carbonyls was also proposed in the transition structure of the IMDA reaction used in the abyssomycin C synthesis.[34a]

14) Conformers with larger dipole moments are better stabilized in polar solvents. It is consistent to observe that the facial selectivity is lower in CH_3OH/H_2O than in toluene by a factor of two (compare entry 1 and 2 in Scheme 3.11).

15) Regioselective synthesis of 2-(2-hydroxyaryl)pyridines from the reactions of benzynes with pyridine *N*-oxides

16) Benzene-diazonium-2-carboxylate is known to be explosive.

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