SYNTHESIS OF LARGE HYDROACENES AND RELATED COMPOUNDS USING GOLD(I) CATALYSIS

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UNIVERSITAT ROVIRA i VIRGILI

Synthesis of Large Hydroacenes and Related Compounds Using Gold(I) Catalysis

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DOCTORAL THESIS
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Institut Català d´Investigació Química (ICIQ)

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I STATE that the present Doctoral Thesis, entitled "Synthesis of Large Hydroacenes and Related Compounds Using Gold(I) Catalysis", presented by Otilia Violeta Stoica for the award of the degree of Doctor in Chemistry, has been carried out under my supervision at the Institut Català d´Investigació Química (ICIQ).

Tarragona, March 25th, 2021

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren Pablos

A mis padres y a mis abuelos

"Lo que no cure el tiempo, lo curará la ciencia."

-Universidad Europea de Canarias

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I want to thank Dr. Szymon Godlewski (Centre for Nanometer-Scale Science and Advanced Materials, NANOSAM), our collaborator from Krakow, Poland, for the STM and ncAFM analyses of our acene precursors.

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At the time of writing this manuscript, part of the results described in this Doctoral Thesis gave rise to the following publications:

1. **On-Surface Synthesis and Intermolecular Cycloadditions of Indacenoditetracenes, Antiaromatic Analogues of Undecacene**
   Zuzak, R.; Stoica, O.; Blieck, R., Echavarren, A. M.; Godlewski, S. *ACS Nano* **2021**, *15*, 1548–1554.

2. **Rh-Catalyzed *Ortho* C–H Alkynylation of Aromatic Aldehydes**
   Tan, E.; Nannini, L.; Stoica, O.; Echavarren, A. M. *Org. Lett.* **2021**, *23*, 1263–1268.

Table of Contents

Prologue

This Doctoral Thesis manuscript has been divided into four main parts, a general introduction on gold(I) catalysis and three research chapters, preceded by the abstract and general objectives, and followed by the overall conclusions. Each chapter contains five sections including a specific introduction on the research topic, the objectives of the project described in the chapter, the discussion of the obtained results, the conclusions reached and, lastly, the experimental section. The references and compounds are numbered independently in each chapter.

The **General Introduction** presents the fundamentals of homogeneous gold(I) catalysis, including the cycloisomerization of enynes, and focuses on the gold-catalyzed synthesis of polyarenes.

Chapter I, '*Gold(I)-Catalyzed Synthesis of Higher Linear Hydroacenes'*, discloses the development of a novel iterative strategy for the preparation of partially saturated higher acenes. An introduction describing the properties and synthesis of acene derivatives has been provided before presenting the results. The new approach for the synthesis of hydroacenes is based on the gold(I)-catalyzed formal [4+2] cycloaddition of aryl-tethered 1,7-enynes previously developed by Dr. Ruth Dorel and Dr. Paul McGonigal, which is described in the introduction of the chapter. Relying on the formation of new multiple 1,7-enynes, the iterative synthesis enabled the acquisition of higher members of the acene series, starting from tridecacene-H8. The former hydroacene was already employed in a surface-assisted dehydrogenative aromatization reaction and afforded the parent tridecacene, the longest acene known up to date. The experiments related to the iterative synthesis were carried out in collaboration with Dr. Rémi Blieck. The STM studies to acquire the tridecacene molecules were performed in the group of Dr. Szymon Godlewski, our collaborator in Krakow, Poland.

Chapter II, '*New Applications of 1,7-Enynes on the Gold(I)-Catalyzed Synthesis of Hydroacene Derivatives'* summarizes the results obtained by employing the gold(I)-catalyzed formal [4+2] cycloaddition in the synthesis of precursors of acene derivatives, such as indacenes and cyclobutadiene-containing acenes. The investigation presented in this chapter was conducted in collaboration with Dr. Rémi Blieck. The STM and nc-AFM studies to acquire the indacene molecules were also performed in the group of Dr. Szymon Godlewski. A part of these results was recently published in *ACS Nano* **2021**, *15*, 1548–1554.

Chapter III, *'Rh-Catalyzed Ortho C–H Alkynylation of Aromatic Aldehydes'*, describes the design of a strategy for the Rh(III)-catalyzed *ortho*-alkynylation of benzaldehydes, enabled by the transient formation of an imine as directing group. A broad scope of substrates was obtained under mild reaction conditions, granting access to mono- and di-alkynylated products. The acquired

alkynylated aldehydes were then used as building blocks in modular syntheses of dibenzopentalenes, isoquinolines, indoles, and indolines. This work was performed in collaboration with Dr. Eric Tan and Dr. Leonardo Nannini, who optimized the conditions of the reaction, studied its scope and carried out the synthesis of dibenzopentalenes. For coherence, their results have been included. The synthesis of ioquinolines was done in collaboration with Dr. Leonardo Nannini. The results obtained in this project were recently published in *Org. Lett.* **2021**, *23*, 1263–1268.

List of Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations of "Guidelines of Authors" of the Journal of Organic Chemistry.

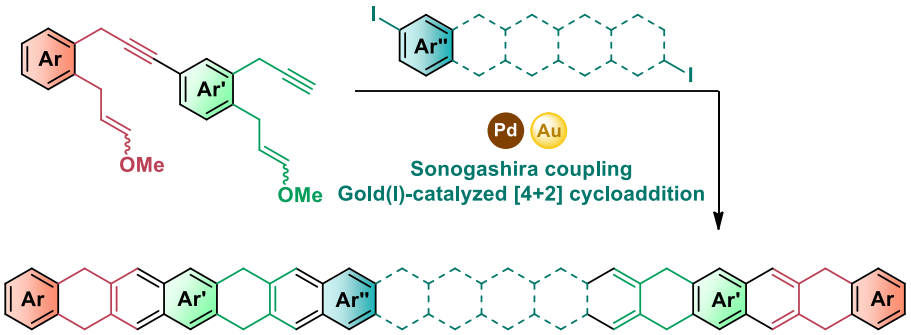
Additional abbreviations and acronyms used in this manuscript are listed below:

APCI	atmospheric pressure chemical ionization
CBD	cyclobutadiene
DIPEA	diisopropyl ethyl amine
DMP	Dess-Martin periodinane
eV	electron volt
ESI	electrosprayionization
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
IF	indenofluorene
L	ligand
LDI	laser desorption ionization
MALDI	matrix assisted laser desorption ionization
MS	mass spectrometry
MW	microwave irradiation
nc-AFM	non-contact force atomic microscopy
NTf_2^-	bis(trifluoromethyl)imidiate
OFET	organic field-effect transistor
OLED	organic light-emitting diode
*o*QDM	*ortho*-quinodimethane
OTf^-	triflate
PAH	polycyclic aromatic hydrocarbon
*p*QDM	*para*-quinodimethane
PHA	polycyclic heteroaromatic hydrocarbon
UHV	ultra high vacuum
STM	scanning tunneling microscopy
STS	scanning tunneling spectroscopy
TDG	transient directing group

Abstract

For the past two decades, our research group has been actively engaged in the synthesis of polycyclic aromatic hydrocarbons (PAHs), such as acenes and their analogues, through gold(I)-catalyzed transformations. Acenes are a category of linear PAHs with promising applications as semiconductors. However, their instability and insolubility, which enhance with their size, hamper their application in molecular electronics. In this regard, an efficient method to synthesize more stable, partially saturated acene precursors was previously developed in our group, based on the gold(I)-catalyzed formal [4+2] cycloaddition of aryl-tethered 1,7-enynes. This approach gave rise to the precursors of higher acenes up to undecacene. Consequently, the main goal of this PhD Thesis was the design of new synthetic methodologies for the preparation of new polyarenes, such as higher members of the acene series and related compounds.

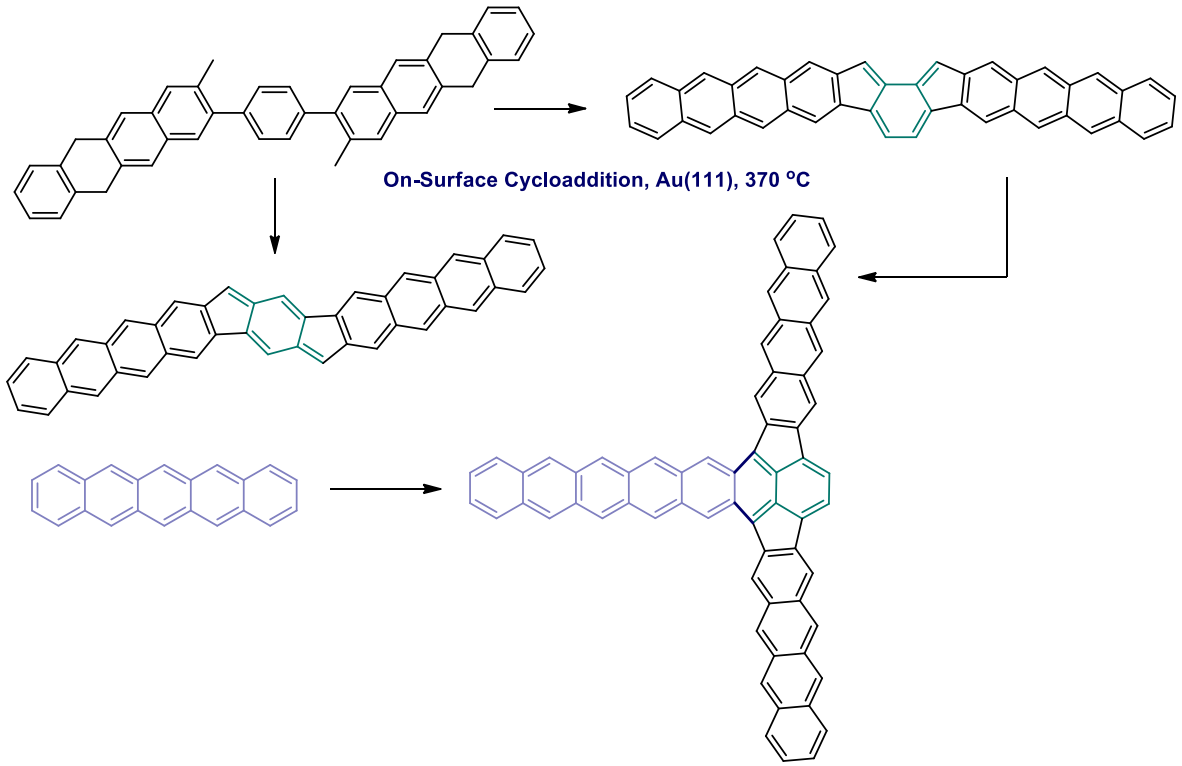
In this context, we first focused on the synthesis of higher hydrogenated acene precursors, starting with tridecacene-H8. Thus, a new iterative synthesis was developed to obtain these hydroacenes, based on successive Sonogashira couplings between 1,7-enynes and diiodinated arenes, as well as multiple gold(I)-catalyzed [4+2] cycloadditions (Scheme 1). This method enabled the formation of unprecedented hydroacenes, such as tridecacene-H8 and higher analogues. Furthermore, the parent tridecacene that remained elusive until now, was prepared by surface-assisted dehydrogenation of its hydroacene precursor, its formation being confirmed by STM studies.



Scheme 1. General synthesis of higher hydroacenes, starting from tridecacene-H8

The synthesis of other classes of acene derivatives with good predicted electronic properties was then explored by surface-assisted manipulation of their precursors, obtained by applying the gold(I)-catalyzed [4+2] cycloaddition. The targeted categories were indacenes and cyclobutadiene-incorporating acenes. In case of the former category, we focused on the formation of *s*-indaceno[1,2-*b*:5,6-*b*']ditetracene and *as*-indaceno[2,3-*b*:6,7-*b*']ditetracene, which are antiaromatic analogues of undecacene incorporating indenofluorene cores. These two products were achieved from a bis-dihydrotetracene precursor, through dehydrogenative surface-assisted cyclization on Au(111) surface and confirmed by scanning tunneling microscopy (STM) and non-contact atomic force microscopy

(nc-AFM). The *as*-indacene was found to be involved in an outstanding intermolecular cycloaddition, unparalleled in solution chemistry, to give T-shaped molecules (Scheme 2). The same outcome was achieved from the reaction of *as*-indaceno[2,3-*b*:6,7-*b*']ditetracene with pentacene and octacene, proving the potential of this method for the generation of fully conjugated extended acenes.

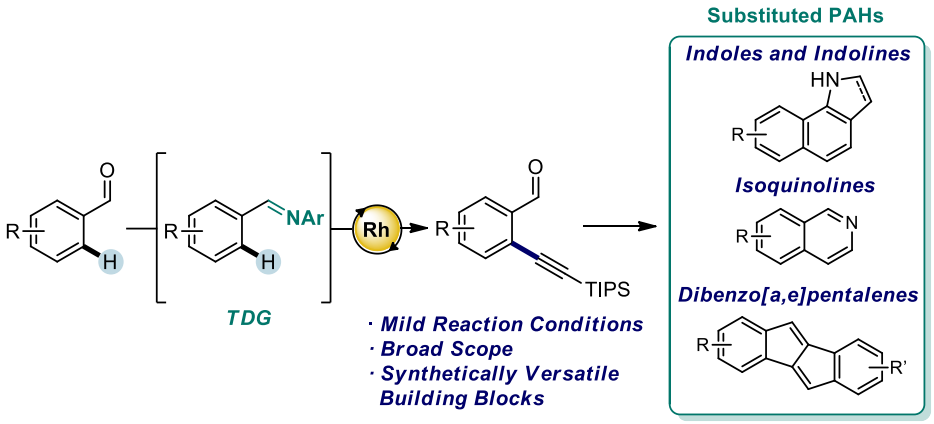


Scheme 2. On-surface synthesis and intermolecular cycloadditions of indacenoditetracenes

The preparation of precursors for cyclobutadiene-containing acenes was next carried out. The synthesis of these derivatives is a good strategy to overcome the instability of acenes in order to exploit them as semiconductors. Thus, the integration of four-membered rings in the acene core increases their number of aromatic sextets and enhances their stability while keeping their linear shape. Thus, using our methodology, 3,3'-dibromo-6,6',11,11'-tetrahydro-2,2'-bitetracene was envisioned as a precursor for 5,10,15,20-tetrahydrocyclobuta[1,2-*b*:3,4-*b*']ditetracene, whose surface-assisted acquisition is already ongoing. Additionally, a doubly substituted 1,7-enyne synthon has been prepared and gave rise to a new precursor of heptacene through a double gold(I)-catalyzed [4+2] cycloaddition. This compound will also be employed in the preparation of heptacenes-H4 tetrasubstituted with halide moieties at the terminal rings, which are envisioned as precursors for heptacene-cyclobutadiene hybrid ribbons by cycloaddition on a Au(111) surface.

Finally, the Rh(III)-catalyzed *ortho* C–H alkynylation of aromatic aldehydes was investigated with a view to acquire new 2-alkynylaryl aldehydes, which would be used as building blocks to form new polyarenes. The transformation was enabled by the formation of an imine as transient directing group (TDG) and proceeded under mild reaction conditions, granting access to a broad range of

mono- and di-alkynylated products (Scheme 3). These readily available building blocks allowed the development of modular syntheses of dibenzopentalenes, isoquinolines, indoles and indolines.



Scheme 3. Rh(III)-catalyzed *ortho* C–H alkynylation of aromatic aldehydes

General Objectives

The main objective of this Doctoral Thesis was the development of new synthetic methodologies for the preparation of new polycyclic aromatic hydrocarbons (PAHs), starting with large linear hydroacenes. In this sense, the following aims were envisioned:

- To improve our previously developed strategy for the synthesis of partially saturated acenes based on an intramolecular gold(I)-catalyzed [4+2] cycloaddition by preparing new 1,7-enyne synthons that would allow the preparation of even higher acene precursors.
- To apply the same methodology to the synthesis of other categories of PAHs, such as indacenes and biphenylene-containing acenes.
- To explore the *ortho*-alkynylation of aromatic aldehydes and its applications on the synthesis of PAHs.

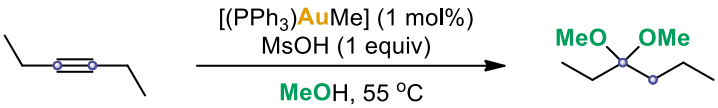
Each chapter of this manuscript contains a more detailed description of the corresponding objectives.

General Introduction

Gold(I) Catalysis: Origin and General Aspects

Gold is one of the first precious metals discovered by mankind and has been associated with beauty, power and wealth ever since. Being one of the least reactive, most ductile and malleable metals, it has been used extensively in jewellery and coinage throughout history.[1]

However, because of its inertness, the catalytic potential of gold has been disregarded until the 70's, when its activity in heterogeneous catalysis was discovered.[2] In this sense, it is worth mentioning that the group of Hutchings engaged metallic gold in the hydrochlorination of acetylene to synthesize vinyl chloride.[3] However, it was not until 1998 that the breakthrough in homogeneous gold catalysis took place when Teles *et al*. described the first gold(I)-catalyzed reaction of alkynes – the formation of acetals by addition of alcohols (Scheme 1).[4] Later on, the hydration of alkynes was also reported by the group of Tanaka by employing the same catalytic system.[5]



Scheme 1. First gold(I)-catalyzed transformation of alkynes under homogeneous conditions

Since then, gold(I) catalysis has emerged as a versatile and powerful synthetic tool for the construction of carbon-carbon and carbon-heteroatom bonds and the assembly of complex molecules through a diverse array of reactions. This is mainly due to the ability of gold complexes to perform electrophilic activation of π-bonds under homogeneous conditions.[6] Thus, unsaturated bonds of complex scaffolds are selectively activated by gold, whose π-acidity has been attributed to relativistic effects.[7]

Relativistic effects take place due to the high velocity of the electrons as they orbit close to a heavy nucleus. Furthermore, these effects increase proportionally with the atomic number. Thus, as the atomic number becomes greater, the electrons situated closest to the nucleus accelerate and in consequence to that, their mass increases as well. This results in the contraction of *s* and *p* orbitals, while the electrons that occupy the *d* and *f* orbitals undergo a weaker nuclear attraction. This contraction/expansion effect is particularly significant for heavy metals that have their 4f and 5*d*

1 Ogden, J. *Interdiscipl. Sci. Rev.* **1992**, *17*, 261–270.
2 (a) Bond, G. C.; Sermon, P. A.; Webb, G.; Buchanan, D. A.; Wells, P. B. *J. Chem. Soc., Chem. Commun.* **1973**, 444–445. (b) Haruta, M.; Kobayashi, T.; Sano, H.; Yamada N. *Chem. Lett.* **1987**, 405–408.
3 Hutchings, G. J. *J. Catal.* **1985**, *96*, 292–295.
4 Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.
5 Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565.
6 Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028–9072.
7 (a) Pyykkö, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3573–3578. (b) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412–4456. (c) Schwartz, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4442–4454.

orbitals filled, – for example Pt, Au and Hg – and reaches a maximum in gold,[8] as the contraction of the 6*s* orbital causes a considerable expansion of the 5*d* orbital, leading to a decreased electron-electron repulsion. As a result, the interactions between the filled 5*d* orbital of gold and the filled *p* orbitals of unsaturated bonds are favoured, attracting the electrons towards gold and depriving the π-bonds of a part of electron density, thus making them more electrophilic and prone to nucleophilic attack.

The contraction of the *s* and *p* orbitals accounts also for the unique properties of gold, such as the resistance to oxidation, the high electronegativity (2.54) and Lewis acidity, as well as for the aurophilic interactions present in gold complexes aggregates. Additionally, it leads to effective *s*/*p* or *s*/*d* hybridizations that justify the preference of gold(I) complexes to adopt a linear di-coordinated geometry.[9] Consequently, the elementary organometallic steps, such as oxidative addition or *β*-hydride elimination are impeded, the interaction of *β*-C–H bonds with gold being obstructed by the filled 5*d* orbital.[10] By contrast, gold(III)-complexes or salts adopt square planar geometries and are able to promote such transformations.[11] Nevertheless, the resistance of gold(I) to oxidation allows the reactions to be carried out under air, without the need for an inert atmosphere.

The relativistic effects are also responsible for the contraction and strengthening of the gold-ligand bond. Thus, the properties and the reactivity of gold complexes can be easily modulated depending on the steric and electronic properties of the ligands employed.[12] Therefore, various gold(I) catalysts used in the activation of unsaturated substrates under homogeneous conditions have been disclosed over the last decade. These complexes can bear a large variety of ligands, from highly donating *N*-heterocyclic carbenes (NHC), giving complexes with limited electrophilicity, to less donating phosphite ligands, leading to formation of highly electrophilic catalysts (Figure 1). In general, the most effective gold(I) catalysts are the complexes with donating ligands that are sterically hindered. By contrast, gold(III) catalysis is still essentially limited to the use of inorganic salts.[13]

8 Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

9 Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511–522.

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13 Schmidbaur, H.; Chier, A. *Arab. J. Sci. Eng.* **2012**, *37*, 1187–1225.

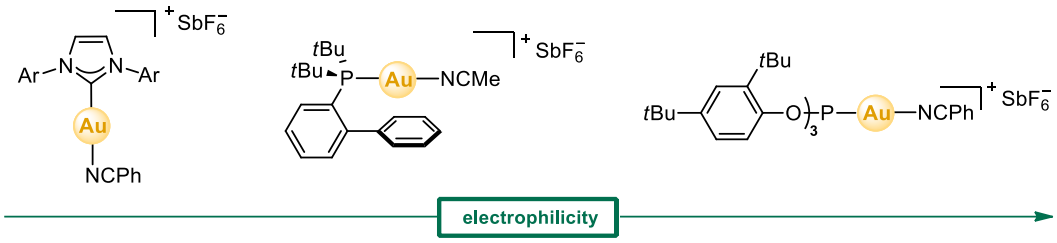

Figure 1. Increase in electrophilicity of cationic gold(I) complexes by tuning of the ligand

In comparison with the gold(I) complexes mentioned above, the readily available neutral gold(I) chloride complexes [LAuCl] are less reactive and used as precatalysts, despite the fact that they can catalyze many transformations. Hence, to enter the catalytic cycle, these complexes need to be activated through chloride abstraction, which allows the substrate to coordinate to the gold(I) atom *via* an associative ligand exchange mechanism.[14] In this sense, *in situ* chloride abstraction can be carried out using silver[15] or copper[16] salts, which are chloride scavengers (Scheme 2). Silver salts are more commonly used to render more reactive species after formation of insoluble AgCl, but their drawbacks include the side reactions or the inactive chloride-bridged digold(I) species that can be formed because of the silver effect.[17] Thus, a preferred alternative for *in situ* chloride abstraction is the preparation of either neutral complexes in which X^- is a weakly coordinating anion (e. g. OTf^-, NTf_2^-), or cationic complexes in which the gold atom is bound to a weakly coordinating ligand, such as acetonitrile or benzonitrile and X^- is a weakly coordinating counterion (e. g. SbF_6^-, BF_4^-).[18] These cationic complexes are favoured as they can readily enter the catalytic cycle, inhibiting the formation of chloride-bridged species and they also induce increased reactivity and selectivity.

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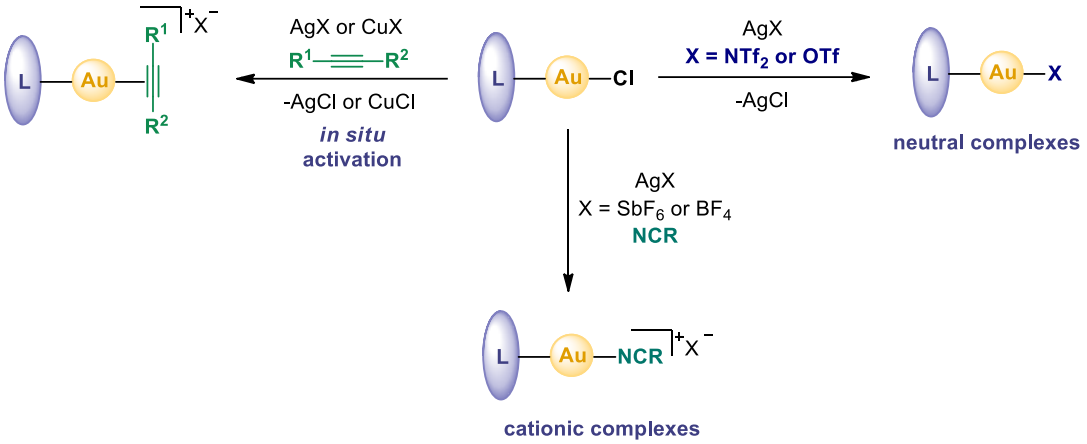
16 (a) Partyka, D. V.; Robilotto, T. J.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2008**, *27*, 28–32. (b) Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324–5332. (c) Hashmi, A. S. K.; Hengst, T.; Lothschütz, C.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 1315–1337. (d) Fortman, G. C.; Nolan, S. P. *Organometallics* **2010**, *29*, 4579–4583. (e) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151–5169.

17 (a) Zhu, Y.; Day, C. S.; Zhang, L.; Hauser, K. J.; Jones, A. C. *Chem –Eur. J.* **2013**, *19*, 12264–12271. (b) Homs, A.; Escofet, I.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 5782–5785.

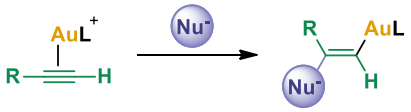
18 Ranieri, B.; Escofet, I.; Echavarren, A. M. *Org. Biomol. Chem.* **2015**, *13*, 7103–7118.



Scheme 2. Activation modes of gold(I) chloride complexes [LAuCl]

Cycloisomerizations of 1,*n*-Enynes

Gold(I) complexes selectively activate alkynes in the presence of other coordinating moieties, which results in the formation of (η^2-alkyne)-gold(I) species prone to undergo nucleophilic attack.[19] The reaction with nucleophilic counterparts generally takes place following a Markovnikov regioselectivity, affording the product of the *anti* addition, the *trans*-alkenyl-gold complex (Scheme 3). Among the carbo- and heteronucleophiles that have been used in either intra- and intermolecular gold(I)-catalyzed reactions are *O*-nucleophiles,[20] *N*-nucleophiles,[21] arenes,[22] and heteroarenes.[23] Specifically, when arenes are used as nucleophiles, alkynes undergo gold(I)-catalyzed Friedel-Crafts-type reactions to hydroarylated products, such as hydroacenes.[24]



Scheme 3. *anti*-Nucleophilic attack to (η^2-alkyne)gold(I) complexes

The electrophilic activation of the alkynes by gold(I) can be explained with the aid of the Dewar-Chatt-Duncanson model,[25] the chemical bonding being regarded as a donor-acceptor

19 (a) Nevado, C.; Echavarren, A. M. *Chem. Soc. Rev*. **2004**, *33*, 431–436. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal*. **2006**, *348*, 2271-2296. (c) Hashmi, A. S. K. *Chem. Rev*. **2007**, *107*, 3180-3211. (d) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed*. **2007**, *46*, 3410–3449. (e) Fürstner, A. *Chem. Soc. Rev*. **2009**, *38*, 3208–3221. (f) Fensterbank, L.; Malacria, M. *Acc. Chem. Res*. **2014**, *47*, 953–965.

20 (a) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed*. **2002**, *41*, 4563–4565. (b) Krauter, C. M.; Hashmi, A. S. K.; Pernpointner, M. *ChemCatChem* **2010**, *2*, 1226–1230. (c) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc*. **2009**, *131*, 448–449.

21 (a) Istrate, F. M.; Gagosz, F. *Org. Lett*. **2007**, *9*, 3181–3184. (b) Quian, J.; Liu, Y.; Cui, J.; Xu, Z. *J. Org. Chem*. **2012**, *77*, 4484–4490.

22 (a) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem*. **2003**, 3485–3496. (b) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182.

23 (a) Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Rivas Nass, A.; Frey, W. *Chem. Eur. J*. **2006**, *12*, 5376–5382. (b) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2006,** *45*, 1105–1109.

24 Dorel, R.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2016**, *55*, 11120–11123.

25 Salvi, N.; Belpassi, L.; Tarantelli, F. *Chem. Eur. J*. **2010**, *16*, 7231–7240.

interaction. Specifically, it is a combination of σ-donation of electron density from the alkyne to an empty *d* orbital of the metal and a π-back-donation from a filled *d* orbital of the metal into the empty antibonding π* orbital of the alkyne. Since there is more electron density lost through σ-donation than gained through π-back- donation, the π-system is rendered electrophilic. Nevertheless, the amount of back-donation is dependent on the ligand, the metal-substrate distance and the substrate rigidity.

The cycloisomerization of 1,*n*-enynes has become one of the most powerful gold(I)-catalyzed carbon−carbon bond forming reactions. Its utility stems from the fact that it gives access to complex molecular frameworks from readily available starting materials through fully intramolecular processes.[26] Additionally, the reactions are atom economic and they can be performed under mild conditions.

With regard to 1,6-enynes, the (η^2-alkyne)-gold(I) complex **I** reacts intramolecularly as an electrophile with the alkene moiety to render the corresponding cyclopropyl gold carbenes **II** and **III** through addition processes, either by 5-*exo*-dig or 6-*endo*-dig pathways (Scheme 4).[27] The evolution of the carbenes is dependent on its substitution pattern, and also on the gold(I) complex and the conditions of the reaction.[27,28]

Thus, in the absence of internal or external nucleophiles, the carbene can undergo different skeletal rearrangements. By contrast, if a nucleophile is present, the cyclopropyl gold(I)-carbene intermediates are opened by attack on the cyclopropane ring. Consequently, if only the alkene moiety of intermediate **II** undergoes carbon−carbon bond cleavage through 1,3-migration of the alkene distal carbon to the distal alkyne carbon, 1,3-dienes of type **1** are formed by single-cleavage rearrangement. Alternatively, a similar *endo*-type process renders products **5** that contain a six-membered ring *via* migration of the proximal alkene carbon to the distal alkyne carbon. However, if **II** suffers a double-

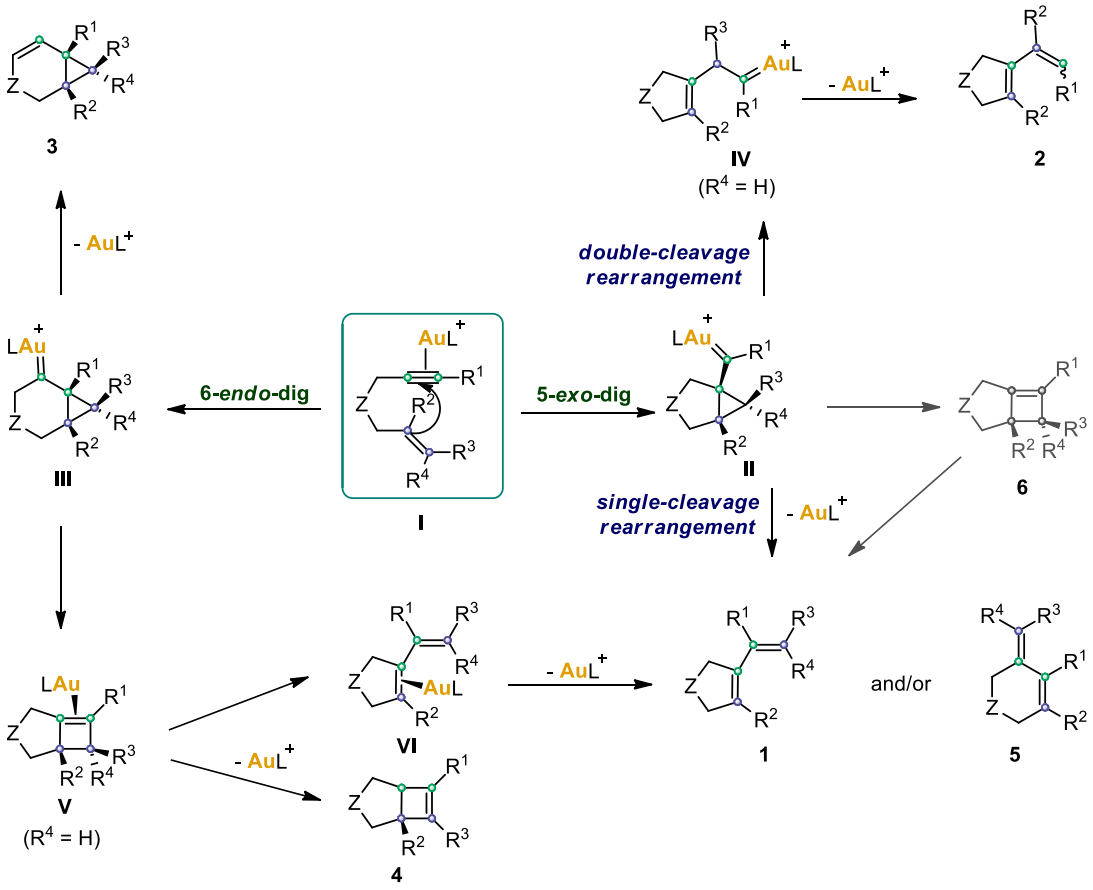
26 (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (b) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. (c) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902–912. (d) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953–965. (e) Obradors, C.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 16–28. (f) Dorel, R.; Echavarren, A. M. *J. Org. Chem.* **2015**, *80*, 7321–7332.

27 (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148. (c) Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero- Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105–6111. (d) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306–6316. (e) Soriano, E.; Marco-Contelles, J. *Acc. Chem. Res.* **2009**, *42*, 1026–1036. (f) For a recent review on gold-catalyzed cycloisomerization reactions: Marín-Luna, M.; Nieto Faza, O.; Silva López, C. *Front. Chem.* **2019**, *7*, 296.

28 (a) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677– 1693; Corrigendum: *Chem. Eur. J.* **2008**, *14*, 5096. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1694–1702. (c) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero- Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279. (d) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916– 5923. (e) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 9366–9372.

cleavage rearrangement in which the terminal carbon of the alkene is inserted into the alkyne carbons, this process results in the formation of gold(I)-carbenes **IV** that go through 1,2-*H* shift and protodeauration to give substituted diene **2**. Further studies revealed that the substituents on the alkyne influence the outcome of the reaction, as 1,6-enynes with electron-donating groups tend to suffer single-cleavage rearrangement, while electron-withdrawing substituents promote double cleavage rearrangement.

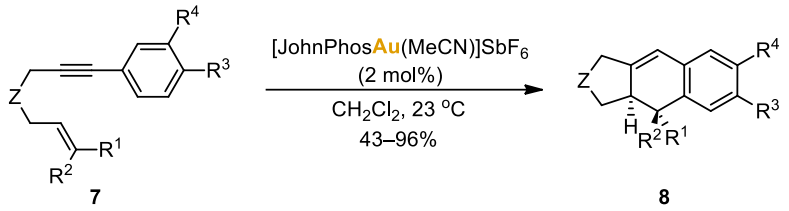
Furthermore, intermediate **III**, the product of the 6-*endo*-dig cyclization, can evolve into bicyclo[4.1.0]hept-2-ene derivatives **3** after 1,2-*H* shift and demetalation. Instead, if **III** undergoes a ring expansion process, (η^2-cyclobutene)-gold(I) complexes of type **V** are generated and they eventually isomerize to cyclobutenes **4**.[27c,28c] By contrast, cyclobutenes **6** have only been rarely observed from the cycloisomerization of 1,6-enynes.[14b, 27c] Nevertheless, intermediates **V** are also able to open up and yield (η^2-alkene)-gold(I) complexes **VI**, being converted ultimately into 1,3-dienes **1**.



Scheme 4. Gold(I)-catalyzed cycloisomerization of 1,6-enynes: main pathways

The cycloisomerization of 1,6-enynes has been successfully applied in the synthesis of arene derivatives. In this sense, particular utility has been exhibited by 1,6-enynes **7** bearing an aryl substituent at the alkyne terminus, as they can undergo Friedel-Crafts-type reactions after formal [4+2] cycloadditions to afford tricyclic scaffolds **8** (Scheme 5).[28c] The mechanism involves the

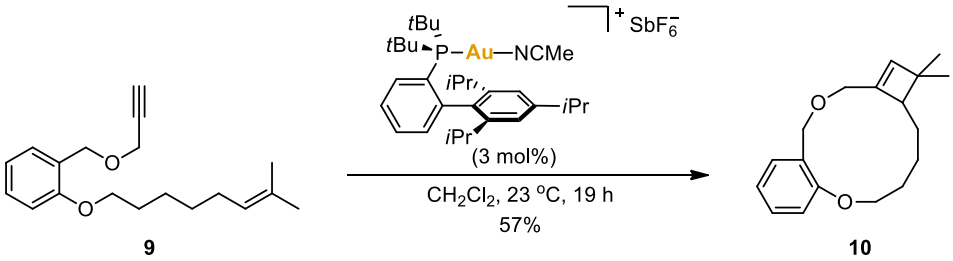
formation of a cyclopropyl gold(I) carbene through a 5-*exo*-dig process and its opening by Friedel-Crafts nucleophilic attack of the aryl ring. The final dihydronaphthalene product is then provided after aromatization and protodeauration.



7 **8**

Scheme 5. Synthesis of dihydronaphthalenes **8** by gold(I)-catalyzed cycloisomerization of 1,6-enynes

1,5-,[29] 1,7-[14b,30] and higher enynes[31] follow similar transformation pathways in reaction with gold(I) complexes. Furthermore, larger 1,*n*-enynes (n = 10–16) give rise to 9- to 15-membered-ring macrocycles incorporating cyclobutenes *via* gold(I)-catalyzed [2+2]-cycloaddition (Scheme 6).[32]



9 **10**

Scheme 6. Gold(I)-catalyzed macrocyclization of 1,14-enyne **9**

29 (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807. (b) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710. (c) López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. *Chem. Eur. J.* **2011**, *17*, 10972–10978.

30 Cabello, N.; Rodríguez, C.; Echavarren, A. M. *Synlett* **2007**, 1753–1758.

31 (a) Böhringer, S.; Gagosz, F. *Adv. Synth. Catal.* **2008**, *350*, 2617–2630. (b) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379–386. (c) Iwai, T.; Okochi, H.; Ito, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4239–4242. (d) Comer, E.; Rohan, E.; Deng, L.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 2123–2126.

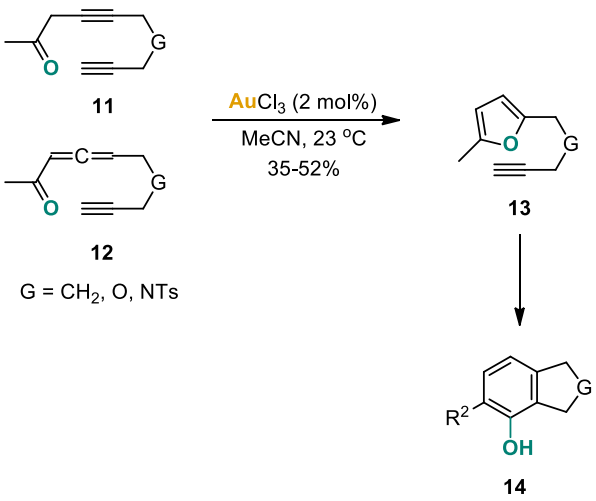
32 Obradors, C.; Leboeuf, D.; Aydin, J.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 1576–1579.

Gold-Catalyzed Synthesis of Arenes

Polycyclic aromatic hydrocarbons (PAHs) have attracted increased attention due to their interesting electronic properties and applications in the manufacture of pharmaceuticals, dyes, pigments or pesticides. In search for new methods to obtain PAH derivatives, gold has been disclosed as an efficient catalyst in the development of new synthetic strategies. Thus, in addition to the example described in Scheme 5, the gold(I)-catalyzed transformations of alkynes and 1,*n*-enynes have been found to offer reliable procedures for the synthesis of arenes, such as benzene derivatives, as well as substituted naphthalenes and anthracenes, which are the first members of the acene series.

Synthesis of Benzene Derivatives

A pioneering example in the field of gold-catalyzed synthesis of arenes was published in 2000 by Hashmi and his co-workers. Their work described the formation of substituted phenols **14** from the cyclization of both propargyl (**11**) and allenyl ketones (**12**), which involves a furan-yne intermediate **13** (Scheme 7).[33] Subsequent reports showed that apart from gold(III), Au(I)[34] could also catalyze this transformation, as well as other d^8 systems, including Pd(II), Pt(II), Rh(I) and Ir(I).[35]



Scheme 7. Gold(III)-catalyzed synthesis of phenols from propargyl and allenyl ketones

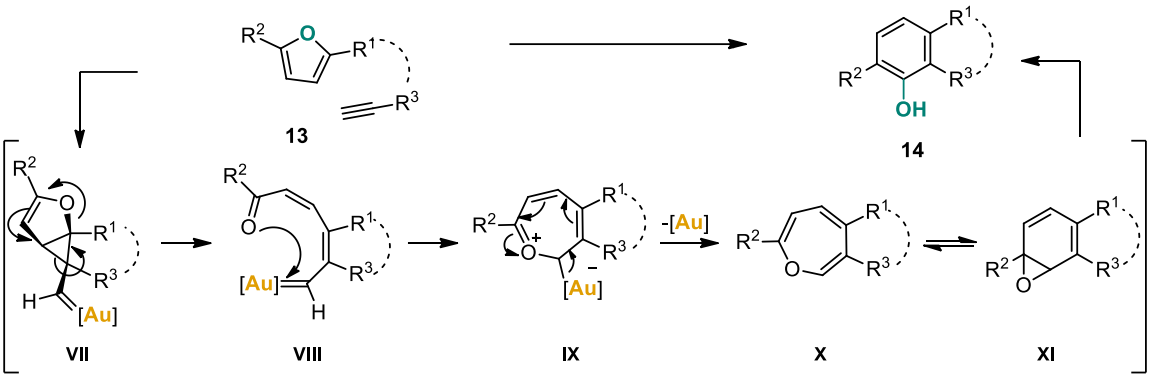
Mechanistic investigations showed its similarity to the cycloisomerization of 1,6-enynes. Thus, the alkynes, previously activated by gold(III), undergo nucleophilic attack by the furan moieties that act as electron-rich alkenes and this results in the formation of cyclopropyl gold

33 Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.

34 (a) Hashmi, A. S. K.; Blanco, M. C.; Kurpejović, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709–713. (b) Chen, Y.; Yan, W.; Akhmedov, N. G.; Shi, X. *Org. Lett.* **2010**, *12*, 344–347. (c) Blanco Jaimes, M. C.; Rominger, F.; Pereira, M. M.; Carrilho, R.M. B.; Carabineiro, S. A. C.; Hashmi, A. S. K. *Chem. Commun.* **2014**, *50*, 4937–4940.

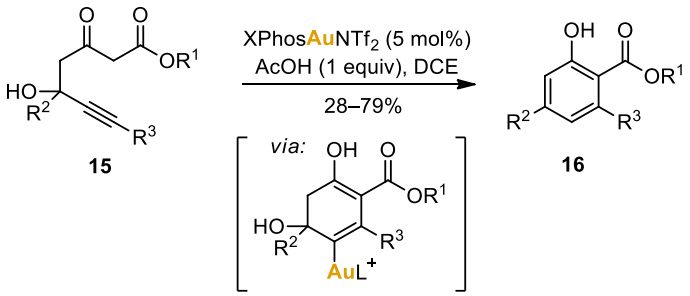
35 (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769–3771. (b) Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4754–4757. (c) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.

carbenes **VII** (Scheme 8). These intermediates then go through a ring-opening, affording conjugated carbenes **VIII**, which collapse to oxepins **X**. The oxepin intermediates are in equilibrium with arene oxides **XI** which undergo regioselective ring-opening to generate the phenol products **14**.[36] Additionally, later on, this reaction was also carried out intermolecularly with the aid of Au(I)-NHC complexes in both Hashmi's[34a,37] and our research group.[38]



Scheme 8. Mechanism of the gold(III)-catalyzed intramolecular furan-yne cyclization

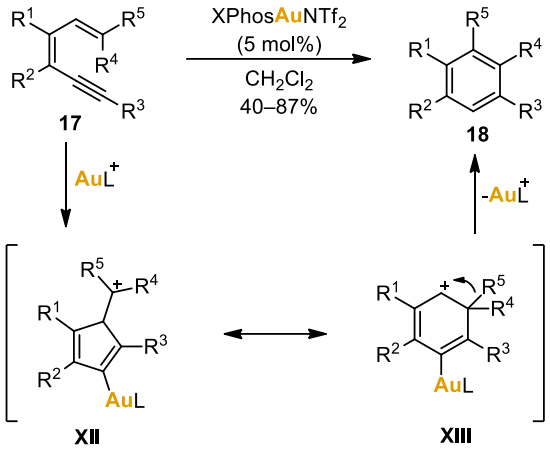
The *o*-phenolic esters **16** are another class of compounds that were accessed by similar procedures. These compounds were prepared through gold(I)-catalyzed cyclization of 5-hydroxy-3-oxoalk-6-ynoate esters **15** (Scheme 9).[39]



Scheme 9. Gold(I)-catalyzed synthesis of *o*-phenolic esters **16**

On the other hand, the preparation of highly substituted benzene derivatives **18** could also be achieved regioselectively using gold(I) catalysis. In this regard, the 5-*endo*-dig cyclization of 1,3-dien-5-ynes **17**, followed by the selective migration of R^5 in **XIII** in a Wagner-Meerwein rearrangement yielded compounds of type **18** (Scheme 10).[40]

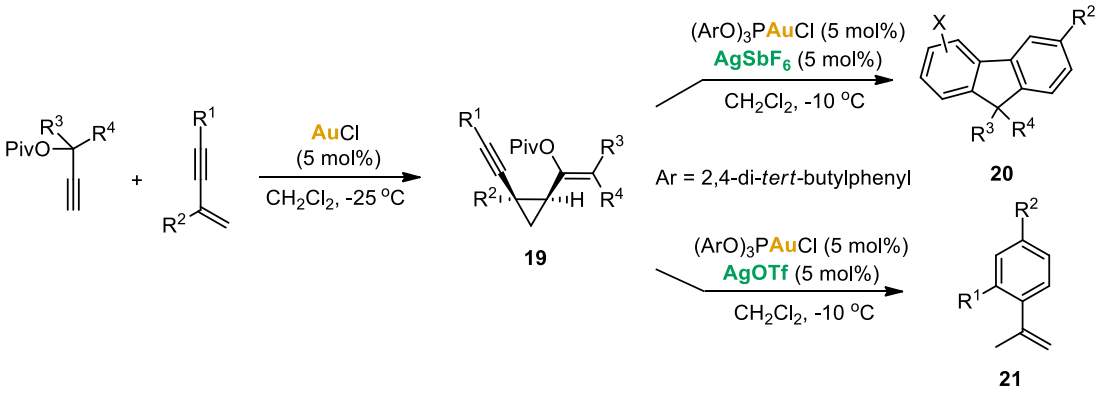
36 Hashmi, A. S. K.; Rudolph, M.; Sielhl, H.-U.; Tanaka, M.; Bats, J. W.; Frey, W. *Chem. Eur. J.* **2008**, *14*, 3703–3708.
37 Zeiler, A.; Ziegler, M. J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2015**, *357*, 1507–1514
38 Huguet, N.; Leboeuf, D.; Echavarren, A. M. *Chem. Eur. J.* **2013**, *19*, 6581–6585.
39 Teo, W. T.; Rao, W.; Ng, C. J. H.; Koh, S. W. Y.; Chan, P. W. H. *Org. Lett.* **2014**, *16*, 1248–1251.
40 García-García, P.; Martínez, A.; Sanjuán, A. M.; Fernández-Rodríguez, M. A.; Sanz, R. *Org. Lett.* **2011**, *13*, 4970–4973.



Scheme 10. Gold(I)-catalyzed cyclization of 1,3-dien-5-ynes **19** to benzene derivatives

Synthesis of Fluorene Derivatives

The first fluorene derivatives synthesized through gold(I)-catalysis were reported by Toste and co-workers in 2008 (Scheme 11).[41] Products **20** were obtained in a diastereoselective manner through gold(I)-promoted 5-*endo*-dig cyclization of cyclopropyl-tethered 1,5-enynes of type **19**. In turn, these enynes were prepared as the *cis* isomers *via* intermolecular reaction between 1,3-enynes and propargyl esters. Depending on the non-coordinating counteranion used as the chloride scavenger, styrenes **21** were also selectively provided.

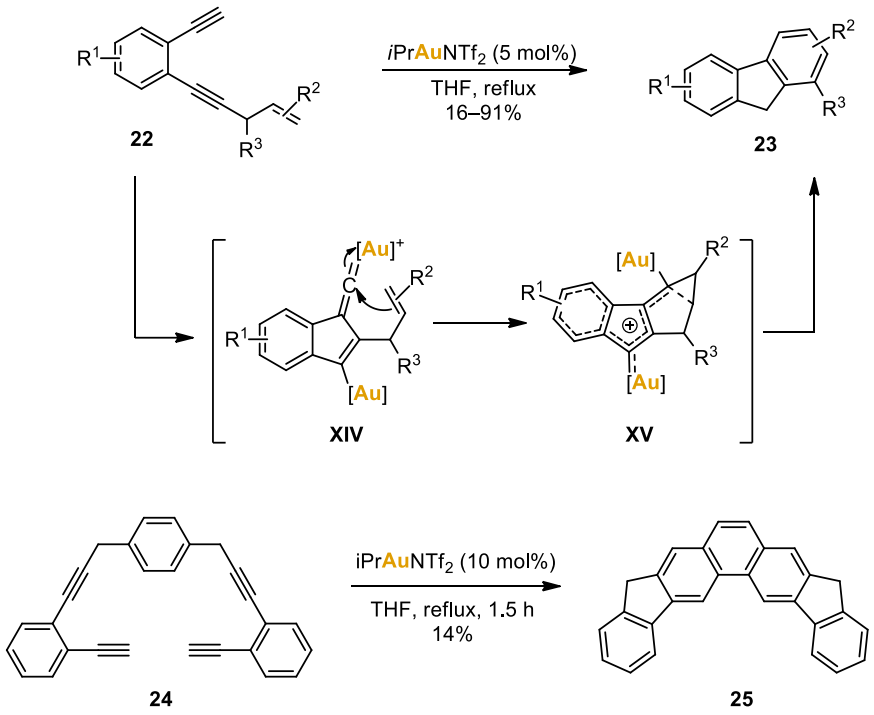


Scheme 11. Gold(I)-catalyzed divergent synthesis of fluorenes **20** and styrenes **21** from cyclopropyl-tethered 1,5-enynes **19**

In 2017, Hashmi *et al.* reported another representative synthesis of fluorenes, which is based on the concept of dual activation of diynes in homogeneous gold catalysis.[42] In this process, the diyne systems are activated by two gold centers that act synergistically: a σ-coordinated gold acetylide that increases the nucleophilic character of the terminal alkyne unit and a π-coordinated second gold catalyst that enhances the electrophilicity of the other triple bond. In this case, 1,5-diynes **22**, which

41 Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736–3737.
42 Bucher, J.; Wurm, T.; Taschinski, S.; Sachs, E.; Ascough, D.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2017**, *359*, 225–233.

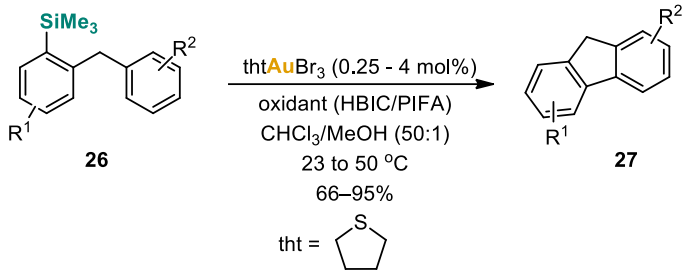
bear a terminal allyl- or benzyl-substituted alkene attached to an aromatic backbone were transformed into the fluorene analogues **23** through a dehydrogenative dual gold(I)-catalyzed activation (Scheme 12). The reaction was proposed to involve the generation of the dually activated gold vinylidene **XIV**, which reacts intermolecularly with the alkene to form the resonance-stabilized homoallyl cation **XV**. This method has also been applied to the preparation of larger annulated ring system **25** by performing the two-fold cyclization of the tetrayne substrate **24**.



Scheme 12. Preparation of fluorene derivatives **23** through dual gold catalysis and application to the synthesis of polyaromatic system **25**

In the same year, Lloyd-Jones and his co-workers reported the synthesis of a range of fluorenes through gold-catalyzed intramolecular arylation of arenes with aryl-trimethylsilanes (Scheme 13). In comparison with its intermolecular version,[43] the cyclization permitted the arylation of neutral and highly electron-defficient arenes, while avoiding the arylsilane homocoupling side-reaction. Thus, the reaction exhibited high tolerance of various electron-donating and electron-withdrawing substituents, including *p*-OMe or *m*-CF_3 and provided fluorenes **27** from easily prepared starting materials **26**, at mild temperatures.[44]

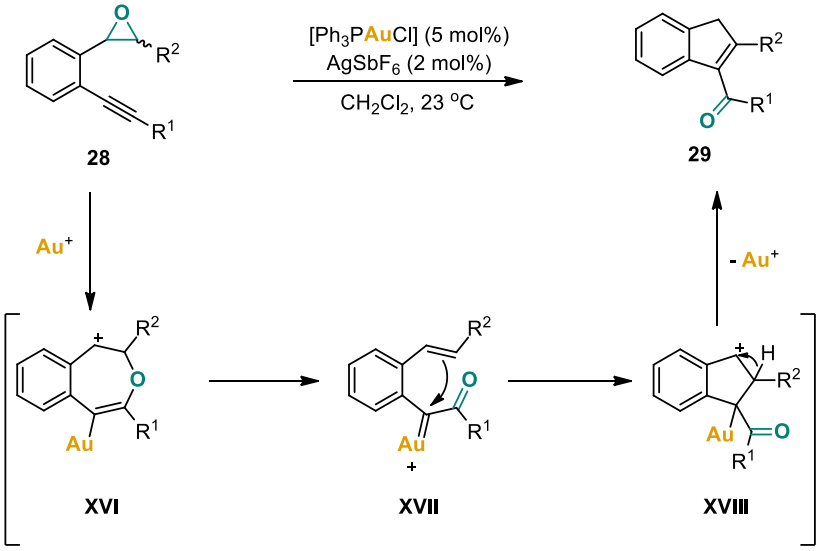
43 Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Science* **2012**, *337*, 1644–1648.
44 Corrie, T. J. A.; Ball, L. T.; Russell, C. A.Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 245–254.



Scheme 13. Synthesis of substituted fluorenes **27** *via* gold-catalyzed intramolecular biaryl coupling

Synthesis of Indene Derivatives

The gold-catalyzed synthesis of indene derivatives has been investigated at the same time by the groups of both Liu[45] and Hashmi.[46] They reported the preparation of indenyl-ketones **29** from alkynyl epoxides **28**, which takes place *via* oxygen-atom transfer from epoxides to alkynes (Scheme 14). Mechanistic studies revealed that the initial 7-*endo* attack of the oxygen on the alkyne renders a highly stable benzylic carbocation **XVI**, which leads to the formation of the gold carbene **XVII**. The nucleophilic attack of the alkene on **XVII** gives the five-membered ring intermediate **XVIII**, which undergoes a 1,2-hydride shift and subsequent protodeauration to afford the final product **29**. The driving force that allows the nucleophilic attack of the oxygen atom is the release of the epoxide ring strain.

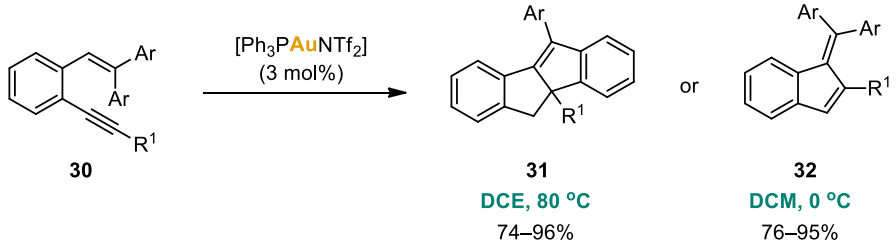


Scheme 14. Gold-catalyzed synthesis of indenyl-ketones **29** from alkynyl epoxides **28**

Dihydroindeno[2,1-*a*]indenes and benzofulvenes have also been achieved through gold(I)-catalyzed processes. Thus, Sanz *et al.* described the preparation of dihydroindeno[2,1-*a*]indenes **31**

45 Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059–5062.
46 Hashmi, A. S. K.; Bürle, M.; Salathé, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059–2064.

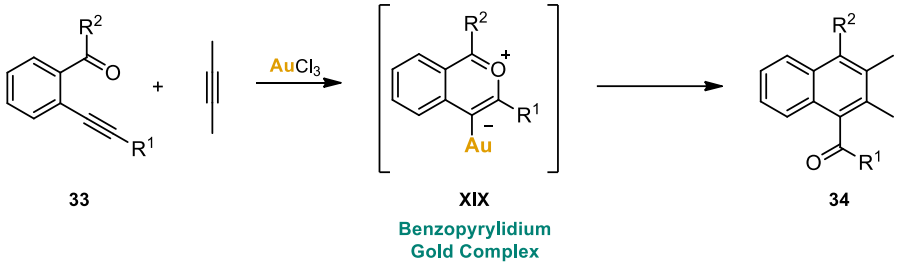
from *β*,*β*-diaryl-*o*-(alkynyl)-styrenes **30** (Scheme 15).[47] This transformation occurs at 80 ºC and involves a formal (4+1)-cycloaddition that takes place through a cascade 5-*endo*-cyclization – diene activation – *iso*-Nazarov cyclization. By contrast, if the reaction is performed at 0 ºC, benzofulvenes **32** are selectively obtained.



Scheme 15. Gold-catalyzed synthesis of dihydroindeno[2,1-*a*]indenes **31** and benzofulvenes **32**

Synthesis of Naphthalene Derivatives

Among the first efficient gold-catalyzed processes to synthesize naphthalene derivatives, it is worth mentioning the [4+2] benzannulation between *o*-alkynyl(oxo)benzenes **33** and alkynes promoted by gold(III) salts, developed by Asao and Yamamoto in 2002 (Scheme 16).[48] This reaction yielded substituted α-naphthyl ketones **34** in good to high yields and its mechanism is thought to involve the zwitterionic benzopyrylium-gold complex **XIX** as the key intermediate, followed by a [4+2] cycloaddition reaction. Moreover, a similar intramolecular reaction has also been performed and yielded the equivalent polycyclic ketones.[49] Additionally, naphtyl ketones have also been reported by Toste *et al.* through gold(I)-catalyzed tandem [3,3]-sigmatropic rearrangement/Myers-Saito cyclization of propargyl esters.[50]



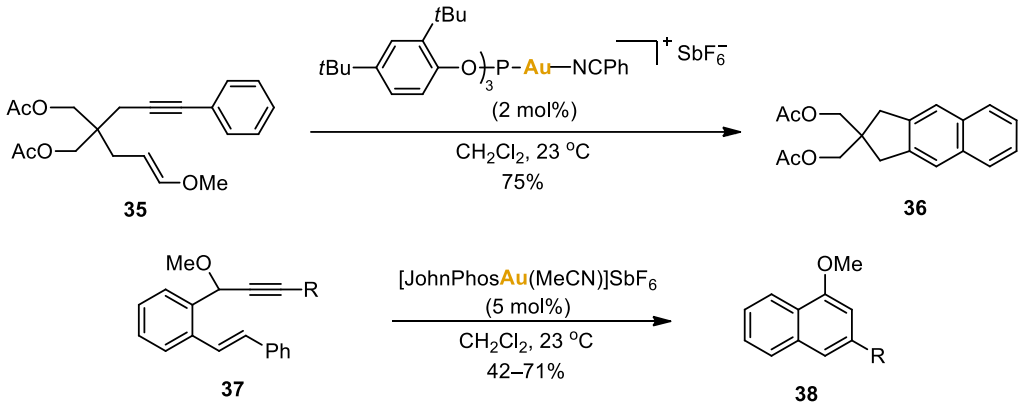
Scheme 16. Synthesis of α-naphthyl ketones *via* formal [4+2] benzannulation

As stated before, the gold(I)-catalyzed cyclization of 1,6-enynes has been extensively employed in the synthesis of substituted naphthalene analogues in recent years. Similarly to the example in Scheme 5, the enyne **35** in which the alkene is part of an enol ether moiety also underwent

47 Sanjuán, A. M.; Virumbrales, C.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. *Org. Lett.* **2016**, *18*, 1072–1075.
48 Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650–12651.
49 Asao, N.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682–3685.
50 Zhao, J.; Hughes, C. O.; Toste, D. F.; *J. Am. Chem. Soc.* **2006**, *128*, 7436–7437.

gold(I)-promoted 5-*exo*-cyclization. Interestingly, in this case, after formation of the cyclopropyl gold(I) carbene, its opening by the Friedel-Crafts-type attack of the phenyl unit and aromatization, elimination of a molecule of methanol takes place, giving rise to naphthalene derivative **36** (Scheme 17).[28c]

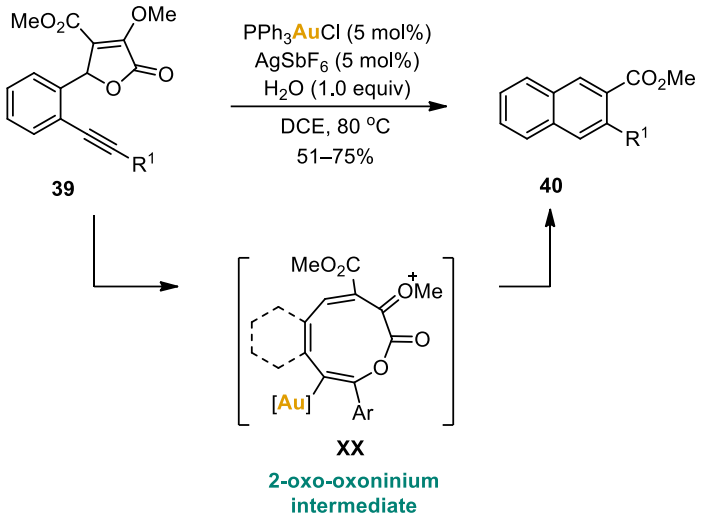
Furthermore, 3-aryl-1-methoxynaphthalenes, such as **38** have also been reported by our research group through rearrangement of the 1,6-enynes **37** bearing methoxy substituents at the propargylic position. The mechanism of the reaction is believed to involve an initial 6-*endo*-dig gold(I)-promoted cyclization and a 1,2-hydride shift that forms an alkenylgold(I)-complex, the last step being a retro-cyclopropanation that renders the substituted naphthalenes, presumably by formation of free gold(I)-carbenes.[51]



Scheme 17. Gold(I)-catalyzed formal [4+2] cycloaddition of 1,6-enynes

Additionally, more recently, Zhu *et al.* reported the synthesis of naphthalene derivatives **40** *via* the gold-catalyzed ring-expansion reaction of 1,6-enyne lactones **39** (Scheme 18). This transformation proceeds through a 2-oxo-oxoninium intermediate (**XX**), which undergoes 6π-electrocyclization and aromatization to afford products **40**.[52]

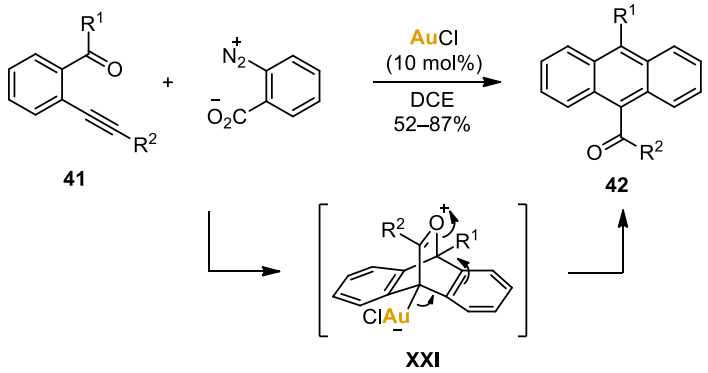
51 Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881–11883.
52 Luo, K.; Cao, T.; Jiang, H.; Chen, L.; Zhu, S. *Org. Lett.* **2017**, *19*, 5856–5859.



Scheme 18. Gold(I)-catalyzed synthesis of naphthalene derivatives **40** from 1,6-enyne lactones **39**

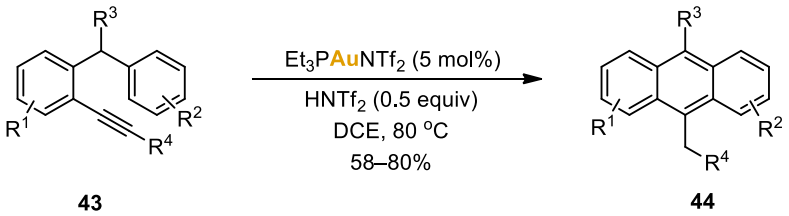
Synthesis of Anthracene and Phenanthrene Derivatives

Substituted anthracene derivatives have also been obtained by gold catalysis. Thus, analogues **42** bearing a ketone functionality at position 9, were obtained by AuCl-catalyzed benzannulation of *o*-alkynylphenyl ketones **41** with benzenediazonium 2-carboxylate as a precursor of benzyne, which proceeds *via* [4+2] cycloaddition (Scheme 19).[53]



Scheme 19. Gold(I)-catalyzed synthesis of functionalized anthracenes **42**

Besides, functionalized anthracene analogues **44** have also been obtained by gold(I)-catalyzed intramolecular hydroarylation of *o*-alkynyldiarylmethanes **43** (Scheme 20).[54]

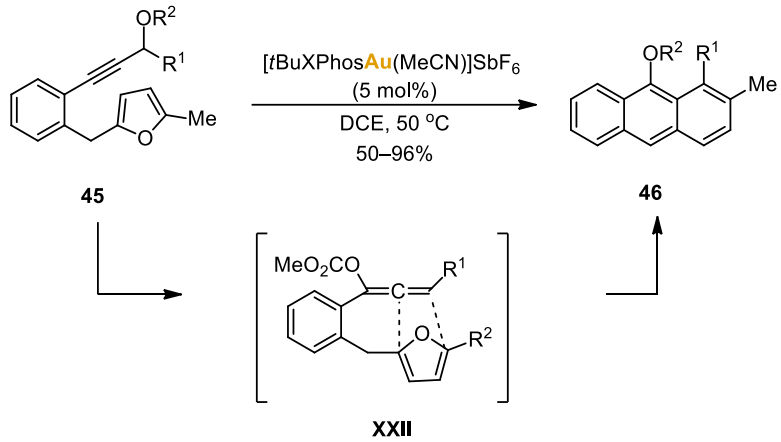


Scheme 20. Gold(I)-catalyzed synthesis of functionalized anthracenes **44**

53 Asao, N.; Sato, K. *Org. Lett.* **2006**, *8*, 5361–5363.

54 Shu, C.; Chen, C.-B.; Chen, W.-X.; Ye, L.-W. *Chem. Eur. J.* **2016**, *22*, 14175–14180.

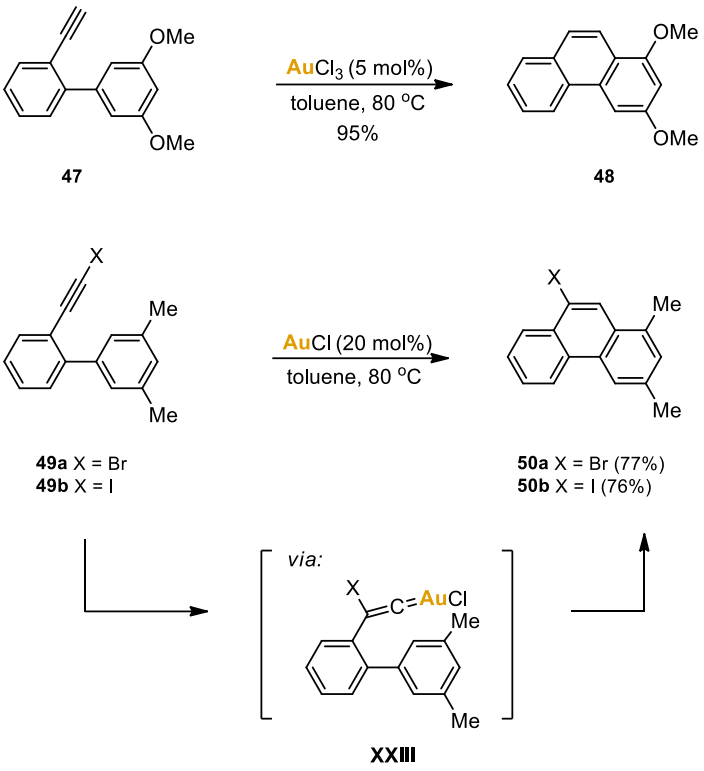
Liu and co-workers have also described the preparation of substituted anthracenes **46** by cyclization of furan-ynes **45** that contain a propargyl carbonate or an ester moiety (Scheme 21). The reaction involves a tandem gold-catalyzed 3,3-rearrangement of the propargyl carboxylate unit, which results in the formation of the allenic intermediate **XXII**, followed by an intramolecular Diels-Alder reaction of the furan and then the opening of the oxa-bridged cycloadduct.[55]



Scheme 21. Gold(I)-catalyzed synthesis of functionalized anthracenes **46** from furan-ynes **45**

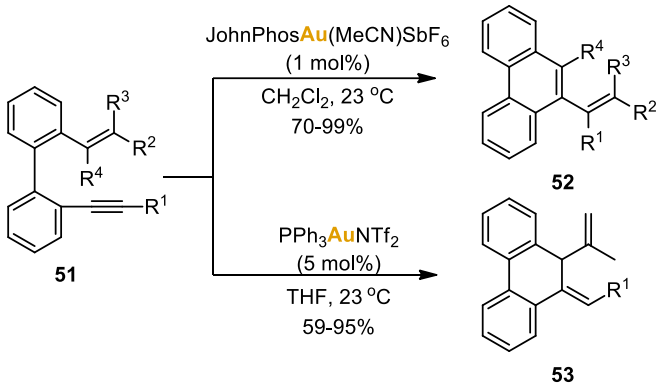
The gold-catalyzed intramolecular hydroarylation of alkynes was also employed in the synthesis of phenanthrenes by Fürstner *et al*.[56] For example, compounds **48** have been reported from the *endo*-cyclization of *o*-alkynylated biphenyl derivatives **47** in a transformation catalyzed by gold(I), as well as gold(III) and other metals. Furthermore, the AuCl-mediated cycloisomerization of haloalkynes **49** yielded phenanthrenes **50**, in which the halide underwent a 1,2-shift (Scheme 22). It was suggested that this reaction occurs through the gold-vinylidene intermediate **XXIII**. By contrast, when $InCl_3$ was used stoichiometrically instead of the gold(I) catalyst, phenanthrenes with halide retention were obtained.

55 Sun, N.; Xie, X.; Chen, H.; Liu, Y. *Chem. Eur. J.* **2016**, *22*, 14175–14180.
56 Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556–4575.



Scheme 22. Synthesis of phenanthrenes by gold(I)-catalyzed intramolecular hydroarylation

Furthermore, Fernández-Rodriguez and co-workers reported recently a solvent-controlled gold-catalyzed synthesis of phenanthrenes **52** and dihydrophenanthrenes **53** through the cycloisomerization of *o*'-alkenyl-*o*-alkynylbiaryls **51**, a particular type of 1,7-enynes (Scheme 23).[57]



Scheme 23. Solvent-controlled gold(I)-catalyzed synthesis of phenantrenes

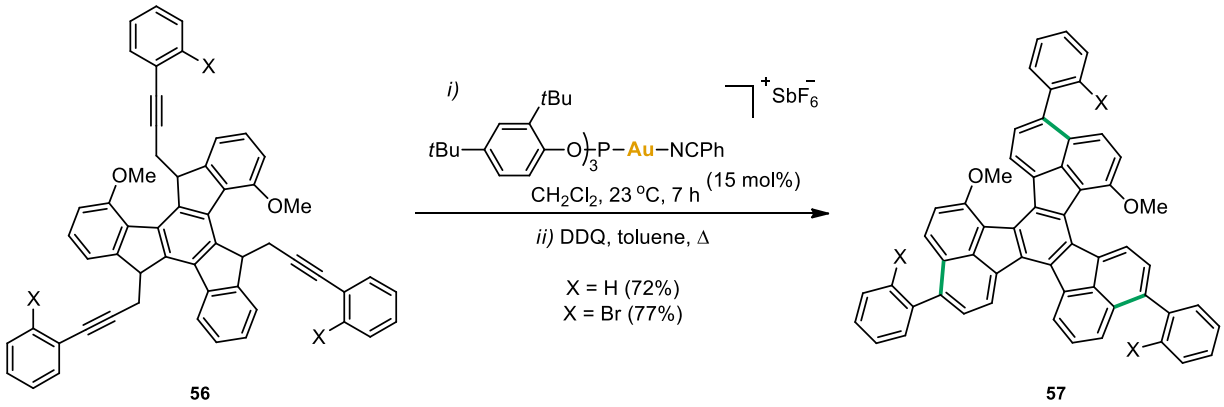
57 Milián, A.; García-García, P.; Pérez-Redondo, A.; Sanz, R.; Vaquero, J. J.; Fernández-Rodríguez, M. A. *Org. Lett.* **2020**, *22*, 8464–8469.

Synthesis of Larger Aromatic Frameworks

A new class of *peri*-halogenated fused aromatics was obtained based on the synthesis of phenanthrenes by AuCl-catalyzed cyclization of *o*-haloalkynebiaryls developed by Fürstner *et al.*[56] Thus, diiodobenzo[*k*]tetraphene **55** was obtained from dialkyne **54** (Scheme 24).[58] It has been suggested that the reaction takes place *via* initial 6-*endo*-dig hydroarylation of the alkyne moiety, followed by a 1,2-*H* shift. Subsequent 1,2-halogen shift of the resulting gold-carbene intermediate yields the rearranged product after deauration.[59]

Scheme 24. Gold(I)-catalyzed synthesis of diiodobenzo[*k*]tetraphene **55**

Furthermore, our group developed a procedure for the gold(I)-catalyzed hydroarylation of alkyne-tethered fluorenes of type **56**. Fluoranthenes and more complex polyarenes such as triarylated decacyclenes **57** were obtained using this method in the presence of a highly electrophilic phosphite gold(I) complex, as depicted in Scheme 25.[60]



Scheme 25. Gold(I)-catalyzed synthesis of triarylated decacyclenes **57**

58 Nakae, T.; Ohnishi, R.; Kitahata, Y.; Soukawa, T.; Sato, H.; Mori, S.; Okijuma, T.; Uno, H.; Sakaguchi, H. *Tetrahedron Lett.* **2012**, *53*, 1617–1619.
59 Huang, G.; Cheng, B.; Xu, L.; Li, Y.; Xia, Y. *Chem. Eur. J.* **2012**, *18*, 5401–5415.
60 Pascual, S.; Bour, C.; de Mendoza, P.; Echavarren, A. M. *Beilstein J. Org. Chem.* **2011**, *7*, 1520–1525.

Chapter I: *Gold(I)-Catalyzed Synthesis of Higher Linear Hydroacenes*

INTRODUCTION

Structure, Reactivity and Properties of Acenes

Acenes are a class of polycylic aromatic hydrocarbons (PAHs) composed of linearly fused benzene rings, with distinctive optoelectronic properties that make them appealing candidates for use in molecular electronics.[1] However, the synthesis of these compounds is very challenging, since they become increasingly insoluble and unstable once the number of annealed ring enhances (Figure 1).

The first two components of this series can be easily isolated from petroleum resources – anthracene is extracted from anthracene oil, a coal tar fraction distilled above 270 °C.[2] However, the larger homologues, starting with tetracene, are not found in nature and require multi-step syntheses in order to overcome their stability and solubility issues. Despite the fact, these compounds have been extensively investigated over the past decades due to their roles as semiconductors in organic light emitting diodes (OLEDs), organic field-effect transistors (OFETs) and photovoltaic devices, besides being constituent parts of nanotubes. Apart from their outstanding applications, the interest in higher acenes has been rekindled in the last decade due to their predicted superior properties, such as a narrower HOMO–LUMO gap and a radical character of the ground state that increases with the size. Consequently, the synthesis of larger analogues would enable the study of the evolution of electronic properties in the acene series, which is crucial for the understanding of electronic transport.

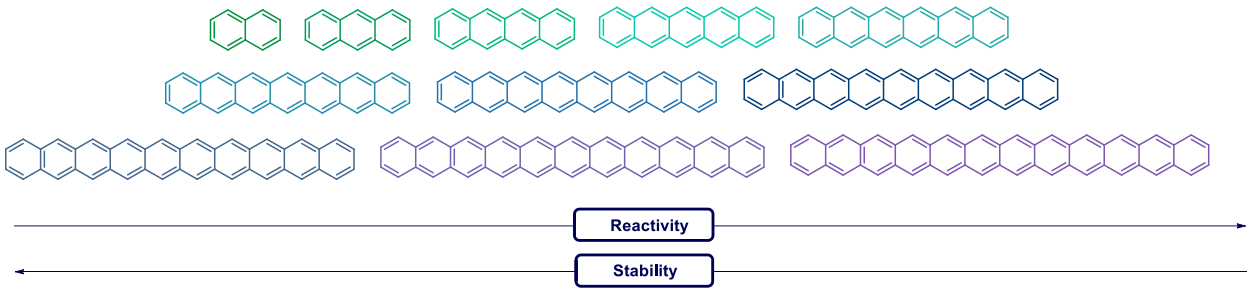


Figure 1. Reactivity and stability trends in n-acenes

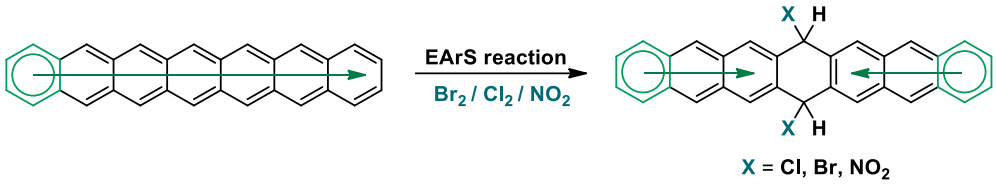
The instability of higher acenes can be explained using Erich Clar's π-aromatic sextet rule, which states that the Kekulé resonance structure with the largest number of disjoint aromatic π-sextets is predominant for the characterization of PAHs.[3] The aromatic π-sextets are benzene-like moieties, defined as six π-electrons localized in a single ring separated from adjacent rings by formal C–C single bonds. According to Clar's rule, the number of these sextets accounts for the stability of PAHs,

1 (a) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891–4946. (b) Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028–5048. (c) Anthony, J. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 452–483. (d) Sun, Z.; Ye, Q.; Chi, C.; Wu, J. *Chem. Soc. Rev.* **2012**, *41*, 7857–7889.

2 Karl, N. *Crystals, Growth, Properties and Applications, Vol. 4* (Ed.: H. C. Freyhardt), Springer, Berlin, 1980.

3 (a) Clar, E. *Polycyclic Hydrocarbons*, Academic Press, London, 1964. (b) Clar, E. *The Aromatic Sextet*, Wiley, London, 1972. (c) Randić, M. *Chem. Rev.* **2003**, *103*, 3449–3606.

which means that the larger the number of such π-sextets, the more stable the PAH. However, despite the number of annealed rings, acenes only possess one aromatic Clar sextet shared over the whole molecule, which makes them highly unstable.[4] Thus, their electronic properties increase rapidly with their size and so does the chemical reactivity. This leads to a fast decrease in the HOMO–LUMO gap as more benzene rings are added and the reactivity at the centermost rings rises considerably, breaking conjugation and forming two smaller acenes of approximately the same size, each of them with its own aromatic sextet (Scheme 1).[5] Therefore, the synthesis of the higher members of the acene family becomes increasingly challenging and different substituents are required for their stabilization.



Scheme 1. Formation of two different Clar sextets after reaction at the centermost ring

The good electronic performance of acenes is influenced by their arrangement in the solid state. Thus, two common packing motifs can be adopted: the 'herringbone', dominated by aromatic edge-to-face interaction, or the coplanar arrangement, in which the molecules stack along their short and long axes with some degree of displacement. Therefore, strong interactions are formed in the π-stacked arrays, permitting the efficient charge transport along the molecules.1[b] Investigations revealed that acenes that crystallize in the classic 'herringbone' motif, such as pentacene, are employed in thin-film devices, while π-stacked materials, like rubrene and other analogues are conventionally used in single-crystal devices.1[b]

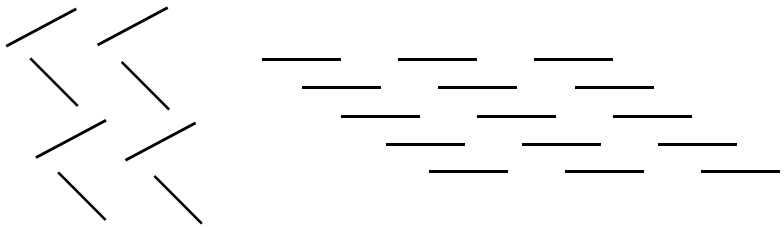


Figure 2. Packing motifs of acenes in the solid state: 'herringbone' (left) and coplanar (right)

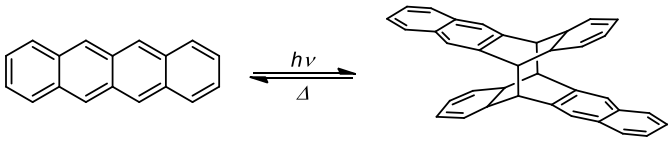
Decomposition Pathways of Acenes

In order to design stabilization strategies for the acenes it is highly important to fully understand the common decomposition pathways that prevent the utilization of this class of compounds as organic semiconductors. In general, acenes tend to decompose through two pathways: 'butterfly' dimerization or oligomerization and oxidation.5 The first processes take place through

4 (a) Suresh, C. H.; Gadre, S. R. *J. Org. Chem.* **1999**, *64*, 2505–2512. (b) Portella, G.; Poater, J.; Bofill, J. M.; Alemany, P.; Solà, M. *J. Org. Chem.* **2005**, *70*, 2509–2521.
5 Thorley, K. J.; Anthony, J. E. *Isr. J. Chem.* **2014**, *54*, 642–649.

Diels-Alder reaction with dienophiles, or [4+4] cycloaddition of the acene backbone. With respect to the oxidation, acenes undergo addition with singlet oxygen and form an endoperoxide that can proceed to further oxidation to quinones.

Computational studies on the dimerization of acenes have showed that the activation barrier of this transformation decreases rapidly with the increase in the number of rings.[6] As a result, tetracene photodimerizes to a colorless, crystalline 'butterfly' dimer, which is quickly reverted to the monomer after heating (Scheme 2).[7] This rapidly reversible dimerization made tetracene one of the first photochromic materials. The 'butterfly' dimer is also formed in the case of pentacene, but the thermal reverse reaction is not as fast as for tetracene.[8] It has been suggested that this reaction leads to the generation of a bipentacene diradical intermediate, which results in larger by-products being formed.[9] To avoid this type of decomposition, the materials need to be isolated in an inert matrix or by growing high-quality crystals in which the edge-to-face arrangement inhibits the dimerization, unlike the face-to-face packing that favours it.[10]



Scheme 2. Reversible 'butterfly'-dimerization of tetracene

With respect to the decomposition by oxidation, acenes with five or more annealed rings react with molecular oxygen in the presence of light and air, giving rise to endoperoxides. Computational studies of this photooxidation by Bendikov *et al.* suggested a diradical mechanism,[11] while other investigations take into account a concerted Diels-Alder-type route.[12] After generation of the endoperoxide, this can either revert to the parent acene[13] or undergo further rearrangement to the quinone.[14] The instability towards both dimerization and photooxidation can be regulated through the attachment of substituents to the conjugated core.[15]

6 Zade, S. S.; Zamoshchik, N.; Reddy, A. R.; Fridman-Marueli, G.; Sheberla, D.; Bendikov, M. *J. Am. Chem. Soc.* **2011**, *133*, 10803–10816.

7 (a) Fritzche, J. *C. R. Hebd. Seances Acad. Sci.* **1867**, *69*, 1035; b) Bouas-Laurent, H.; Dürr, H. *Pure Appl. Chem.* **2001**, *73*, 639.

8 Berg, O.; Chronister, E. L.; Yamashita, T.; Scott, G.W.; Sweet, R. M.; Calabrese, J. *J. Phys. Chem. A* **1999**, *103*, 2451.

9 Roberson, L. B.; Kowalik, J.; Tolbert, L. M.; Kloc, C.; Zeis, R.; Chi, X.; Fleming, R.; Wilkins, C. *J. Am. Chem. Soc.* **2005**, *127*, 3069–3075.

10 Watanabe, M.; Chang, Y. J.; Liu, S.-W.; Chao, T.-H.; Goto, K.; Islam, M. M.; Yuan, C.-H.; Tao, Y.-T.; Shinmyozu, T.; Chow, T. J. *Nat. Chem.* **2012**, *4*, 574–578.

11 Reddy, A. R.; Bendikov, M. *Chem. Commun.* **2006**, 1179–1181.

12 Chien, S.-H.; Cheng, M.-F.; Lau, K.-C.; Li, W.-K. *J. Phys. Chem. A* **2005**, *109*, 7509–7518.

13 Aubry, J.-M.; Pierlot, C.; Rigaudy, J.; Schmidt, R. *Acc. Chem. Res.* **2003**, *36*, 668–675.

14 Kohl, B.; Rominger, F.; Mastalerz, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6051–6056.

15 Kaur, I.; Jia, W.; Kopreski, R. P.; Selvarasah, S.; Dokmeci, M. R.; Pramanik, C.; McGruer, N. E.; Miller, G. P. *J. Am. Chem. Soc.* **2008**, *130*, 16274–16286.

Acenes as Semiconductors

The field of molecular electronics is in a constant need of innovation and creation of new materials. Particularly, the development of new organic semiconductors is required in order to replace the more rigid and expensive inorganic ones. In this sense, acenes and their derivatives are key candidates, since their utilization would bring many advantages, such as reduced manufacturing costs and acquisition of lightweight, flexible devices.[1c,16]

Acenes have exhibited electron-donating characteristics due to the π-conjugation and the high HOMO levels and thus they are employed as p-type semiconductors. These compounds have been mostly exploited as component parts of two main types of organic electronic devices, OLEDs and OFETs, which are core components of flexible displays.1 Moreover, they could also be employed in photovoltaic devices and organic solar cells. The most representative example is pentacene due to its reduced HOMO–LUMO gap and elevated mobility. However, its drawbacks include the low solubility and the tendency for oxidation to pentacene-quinone that limits its applicability and the processability of devices. Furthermore, heterocyclic oligomers like oligothiophenes were also employed as p-semiconductors. By contrast, n-type semiconductors, like perylenediimides, are electron-deficient molecules with low HOMO levels in which radical anions are produced by electron injection. Their applications have not been fully developed yet and their performance in molecular electronics is less satisfactory, new design strategies being required for their improvement.[16d]

Thus, the preparation and characterization of new acene analogues with improved stability is required for their application in effective molecular devices. With a view to obtain high performance semiconductors, the employed acenes must have properties like low reorganization energy,[17] small transport-gap[18] and high charge carrier mobility.[19] In this regard, various functionalization approaches have been examined to stabilize these compounds, most of them relying on the insertion of substituents on their centermost rings to prevent unwanted intermolecular reactions, like dimerization. However, these rings are also the most involved in π-stacking, which is essential for good charge transport, and thus these substituents must be carefully chosen, avoiding disruption of the covalent interactions.

16 (a) Sun, Y.; Liu, Y.; Zhu, D. *J. Mater. Chem.* **2005**, *15***,** 53–65. (b) Murphy, A. R.; Fréchet, J. M. J. *Chem. Rev.* **2007**, *107***,** 1066–1096. (c) Allard, S.; Forster, M.; Souharce, B.; Thiem, H.; Scherf, U. *Angew. Chem., Int. Ed. Engl.* **2008**, *47***,** 4070–4098. (d) Yamashita, Y. *Sci. Technol. Adv. Mater.* **2009**, *10*, 1–9.

17 Deng, W.-Q.; Goddard, W. A., III *J. Phys. Chem. B* **2004**, *108*, 8614–8621.

18 Brocks, G.; van der Brink, J.; Morpurgo, A. F. *Phys. Rev. Lett.* **2004**, *93*, 146405.

19 Cheng, Y. C.; Silbery, R. J.; da Silva Filho, D. A.; Calbert, J. P.; Cornil, J.; Brédas, J. L. *J. Chem. Phys.* **2003**, *118*, 3764–3774.

Functionalization Strategies

Aryl Acenes

The introduction of phenyl rings on the acene core was one of the first methods resulting in increased solubility and stability.[20] Thus, 5,6,11,12-tetraphenyltetracene, also called rubrene, has become a standard compound for single-crystal devices, as it forms high-quality crystals that allow the fabrication of semiconductors directly on their surfaces.[21] The aryl rings give rubrene a strong π-stacking in the solid state, which permits efficient charge transport.[22] Similarly, some diarylpentacenes with different bulky groups on the aryl substituent were also found to be stable and efficient in order to be employed in OLEDs as red emitters.[23]

Ethynyl Acenes

An alternative approach is the insertion of alkyne substituents[24] with bulky trialkysilyl moieties on the centremost rings of the acenes to hinder dimerization.[25] Additionally, the silylethynyl groups shield the molecules from oxidation, shifting the LUMO orbital and hence reducing the ability of the acene to generate singlet oxygen.[26] Apart from that, unlike other substituents, the alkyne directs oxygen addition to the alkyne-substituted ring and promotes the reconversion of possible endoperoxides to the parent acene by heating.[27] Finally, suitable silylalkyne moieties encourage rapid crystallization of the acenes, permitting their isolation from solution.[28]

Electron-Deficient Acenes

Attaching electron-withdrawing groups (EWG) to the acene core has been found as an efficient way of preparing electron deficient acenes, which are good n-type semiconductors.[16d] EWGs lower the LUMO orbitals of the molecules, leading to a narrow HOMO–LUMO gap that offers the acene-based materials good semiconducting properties. Among them, halide units such as chloride or fluoride were directly attached to the acene centermost rings. Consequently, a good example of n-type organic semiconductors used in p-n junctions and complementary circuits is perfluoropentacene.[29] Similarly, due to their low LUMO levels, cyanoacenes demonstrated their performance as good n-type

20 Allen, C. F. H.; Bell, A. *J. Am. Chem. Soc.* **1942**, *64*, 1253–1260.
21 Reese, C.; Bao, Z. *J. Mater. Chem.* **2006**, *16*, 329.
22 Da Silva Filho, D. A.; Kim, E. G.; Brédas, J. L. *Adv. Mater.* **2005**, *17*, 1072.
23 Wolak, M. A.; Jang, B.-B.; Palilis, L. C.; Kafafi, Z. *J. Phys. Chem. B* **2004**, *108*, 5492–5499.
24 (a) Rauhut, M. M.; Roberts, B. G.; Maulding, D. R.; Bergmark, W.; Coleman, R. *J. Org. Chem.* **1975**, *40*, 330–335. (b) Hanhela, P. J.; Paul, D. B. *Aust. J. Chem.* **1981**, *34*, 1701–1717. (c) Maulding, D. R.; Roberts, B. G. *J. Org. Chem.* **1969**, *34*, 1734–1736.
25 Coppo, P.; Yeates, S. G. *Adv. Mater.* **2005**, *17*, 3001–3005.
26 Maliakal, A.; Raghavachari, K.; Katz, H. E.; Chandross, E.; Siegrist, T. *Chem. Mater.* **2004**, *16*, 4980–4986.
27 Fudickar, W.; Linker, T. *J. Am. Chem. Soc.* **2012**, *134*, 15071–15082.
28 Anthony, J. E.; Eaton, D. L.; Parkin, S. R. *Org. Lett.* **2001**, *4*, 15–18.
29 Sakamoto, Y.; Suzuki, T.; Kobayashi, M.; Gao, Y.; Fukai, Y.; Inoue, Y.; Sato, F.; Tokito, S. *J. Am. Chem. Soc.* **2004**, *126*, 8138–8140.

semiconductors.[30] Furtermore, single-crystal devices were fabricated using 5,11-dichlorotetracene due to its good π-stacking in solid state.[31]

Acenes in Molecular Devices

OLEDs are light-emitting diodes made by placing a film of an organic material between two electrodes that emit light when an electric current is applied due to the recombination of holes and electrons. These devices can be applied in TVs, digital cameras or smartphones ensuring high-energy efficiency and pure bright colours. The performance of OLEDs can be determined on account of the charge carrier mobility.[32] In this respect, acenes are convenient in OLEDs as they have showed emission with relatively high quantum efficiencies, the acene core being the chromophore responsible for the emission. Unfortunately, if the acene molecules form aggregates in the solid state or in the devices, this leads to an undesired emission with reduced efficiency and this is a major limitation associated with these compounds. However, this challenge can be overcome by attaching bulky groups to the acene core. As a result, various acene derivatives gave promising results as emissive materials in OLEDs and enabled the low cost fabrication of thin-film devices. Thus, along with pentacene, rubrene is one of the most popular acene derivatives employed in OLEDs.**1**[b] As a result, pentacene derivatives and rubrene are already on the market as high performance red and yellow emitters, respectively.[33] Nevertheless, materials producing blue electroluminescence like anthracene or pyrene-type compounds still represent a challenge in terms of colour purity, low cost of fabrication or high efficiency.[34]

OFETs are a type of transistors that use organic semiconductors in their channel. In OFET devices the current that flows through the semiconductor from the source to the drain can be controlled by applying a voltage to the gate. Since OFETs employ organic polymers or monomers as the semiconductors, they are an alternative to traditional inorganic Si, Ge, and GaAs-based semiconductors.[16d] Thin film transistors based on organic materials are preferred as they are lighter, more flexible, prepared at low temperatures and they provide low-cost, biodegradable products. Since the 1980s pentacene has been the most commonly employed p-type organic conductor in OFETs. The good performance of the OFET devices is based on high mobility and low threshold voltage, as well as high stability under air. Thus, producing new devices based on functionalized acenes with

30 (a) Qu, H.; Cui, W.; Li, J.; Shao, J.; Chi, C. *Org. Lett.* **2011**, *13*, 924–927. (b) Chang, J.; Qu, H.; OOI, Z.-E.; Zhang, J.; Chen, Z.; Wu, J.; Chi, C. *J. Mater. Chem. C* **2013**, *1*, 456–462.

31 Moon, H.; Zeis, R.; Borkent, E.-J.; Besnard, C.; Lovinger, A.-J.; Siegrist, T.; Kloc, C.; Bao, Z. *J. Am. Chem. Soc.* **2004**, *126*, 15322–15323.

32 (a) Patel, N. K.; Cina, S.; Burroughes, J. H. *IEEE J. Sel. Top. Quantum Electron.* **2002**, *8*, 346. (b) Pham, H. D.; Hu, H.; Wong, F.-L.; Lee, C.-S.; Chen, W.-C.; Feron, K.; Manzhos, S.; Wang, H.; Motta, N.; Lam, Y.-M.; Sonar, P. *J. Mater. Chem. C* **2018**, *6*, 9017–9029.

33 Odom, S. A.; Parkin, S. R.; Anthony, J. E. *Org. Lett.* **2003**, *5*, 4245–4248.

34 (a) Kondakov, D. Y.; Sandifer, J. R.; Tang, C. W.; Young, R. H. *J. Appl. Phys.* **2003**, *93*, 1108–1119. (b) Tao, S.; Hong, Z.; Peng, Z.; Ju, W.; Zhang, X.; Wang, P.; Wu, S.; Lee, S. *Chem. Phys. Lett.* **2004**, *397*, 1–4.

increased solubility and stability has been a priority over the past years. Consequently, other organic compounds such as picene, or acenes incorporating thiophene, pyrrole or bulky acetylene units were synthesised and proved their efficiency in OFET devices, their mobilities being comparable to amorphous-silicon-based FETs.

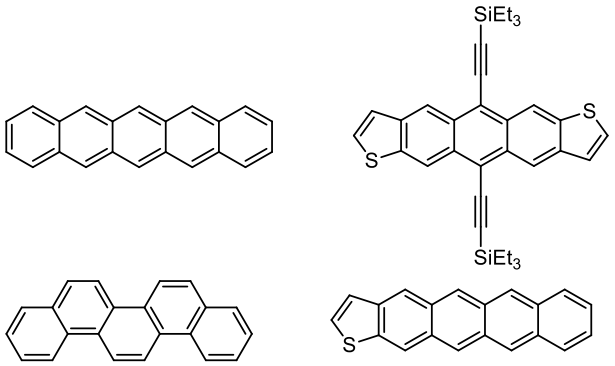


Figure 3. Pentacene derivatives used as semiconductors in OFETs

Acenes have also been employed in photovoltaic and solar cells, even though to a smaller extent. Their properties like low molecular weight, tunable energetics, high charge carrier mobilities and broad absorption spectra make them attractive donor materials.[32b] For instance, a polycrystalline heterojunction using pentacene as the donor and C_{60} as the acceptor yielded solar cells with high photovoltaic efficiency.[35] However, the undesired cycloaddition reactions between the donor and acceptor molecules were considered, as they could impact the device lifetime. Hence, functionalized acene derivatives with improved solubility and stability like rubrene or dibenzo[*b,def*]chrysene have also been investigated as donor materials in organic photovoltaics (OPV) and demonstrated good power conversion efficiency. These derivatives are better alternatives as they do not undergo cycloaddition reactions with the fullerene derivatives, unlike pentacene.[36]

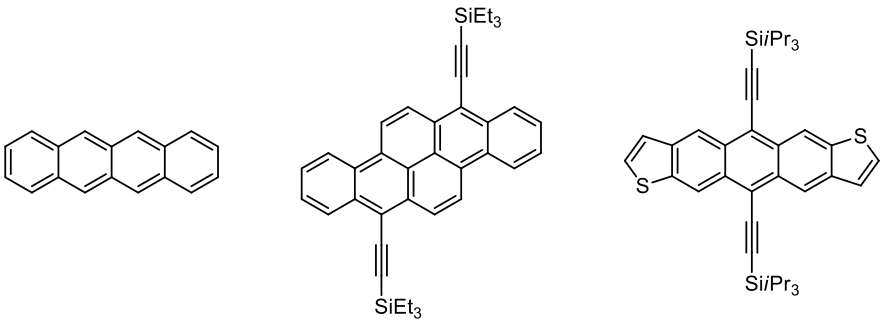


Figure 4. Acene derivatives examined in OPV

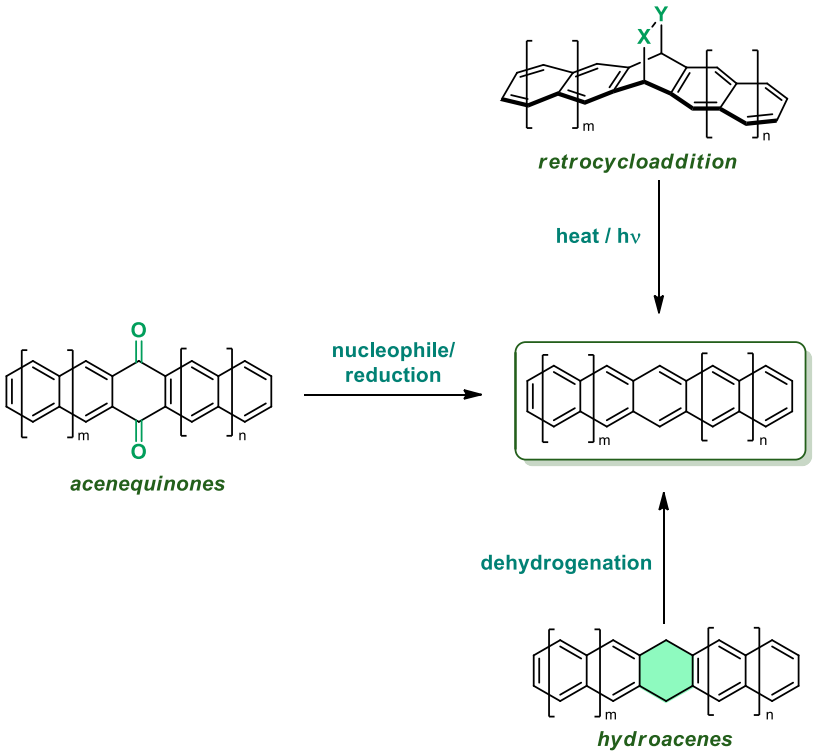
35 (a) Yoo, S.; Domercq, B.; Kippelen, B. *Appl. Phys. Lett.* **2004**, *85*, 5427–5429. (b) Pandey, A. K.; Nunzi, J.-M. *Appl. Phys. Lett.* **2006**, *89*, 213506.

36 Winzenberg, K. N.; Kemppinen, P.; Fanchini, G.; Brow, M.; Collis, G. E.; Forsyth, C. M.; Hegedus, K.; Singh, Th. B.; Watkins, S. E. *Chem. Mater.* **2009**, *21*, 5701–5703.

Strategies for the Preparation of Higher Acenes

As stated before, a large variety of stabilized acenes containing different functional groups have been synthesised lately to improve their applications as semiconductors. However, the preparation of larger unsubstituted homologues is still a challenging task because of their low solubility in organic solvents and their instability in presence of light and oxygen and new methods to obtain them are constantly required. So far, only unsubstituted acenes up to heptacene have been acquired in bulk, the higher members of the series requiring inert matrix isolation under cryogenic conditions (from octacene to undecacene) or being uncovered just by surface-assisted manipulation of suitable precursors, as is the case for dodecacene.

As a result, several approaches have been followed for the acquisition of acenes and investigation of the structure-property relationships,[37] the main ones being depicted in Scheme 3. According to the type of precursor from which the acene core is derived, the compounds were obtained either from intermediates containing solubilising groups through retrocycloadditions, from acenequinones and finally from hydroacenes. Additionally, the surface-assisted synthesis under ultra-high vacuum (UHV) conditions has recently become a powerful tool for the preparation and stabilization of the intrinsically unstable acenes.



Scheme 3. Strategies for the synthesis of acenes

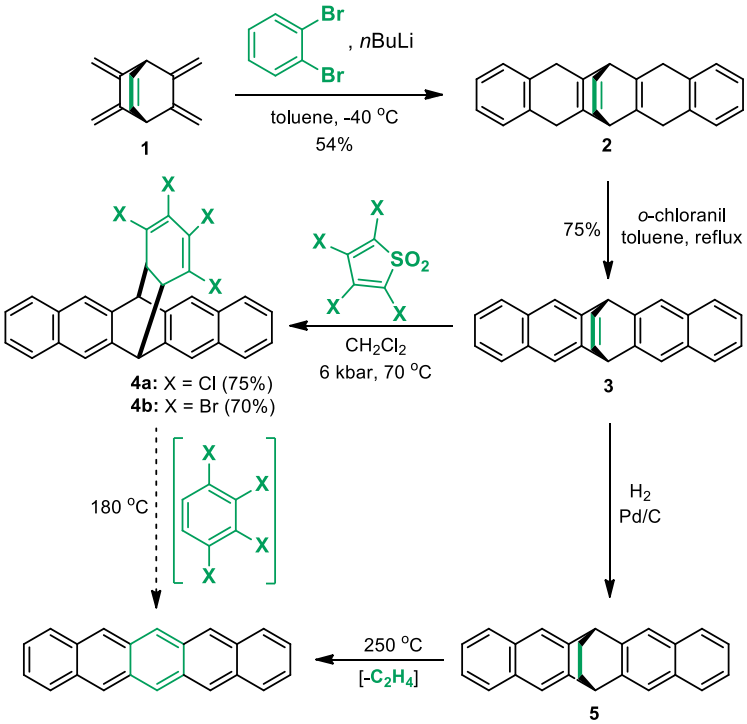
37 (a) Dorel, R.; Echavarren, A. M. *Eur. J. Org. Chem.* **2017**, 14–24. (b) Ye, Q.; Chi, C. *Chem. Mater.* **2014**, *26*, 4046–4056. (c) Müller, M.; Ahrens, L.; Brosius, V.; Freudenberg, J.; Bunz, U. H. F. *J. mater. Chem. C* **2019**, *7*, 14011–14034. (d) Tönshoff, C.; Bettinger, H. F. *Chem. Eur. J.* **2020**, *26*, 1–21.

Acenes by Retrocycloaddition

One of the strategies relies on the thermo- or photoinduced cycloreversion reaction of soluble precursors in the solid state. Unfortunately, the thermal eliminations of small molecules from the pecursors to afford the parent acenes require high temperatures that limit their applicability. Nevertheless, this approach yielded unsubstituted higher acenes up to nonacene, which required inert matrix isolation because of their increased reactivity.[38]

Thermally Induced Eliminations

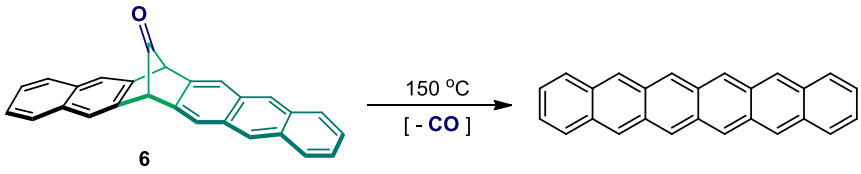
One of the earliest accomplishments in this field was reported in 1996 by Müllen *et al.* who presented the construction of a field-effect transistor that uses pentacene as the active semiconductor. In this case, pentacene was formed in a film *via* thermal elimination of tetrachlorobenzene from precursor **4a**.[39] Both this precursor and its brominated analogue **4b** were prepared through the Diels-Alder cycloaddition of **3** and the corresponding tetrahalothiophene dioxides at high pressure (Scheme 4). Later on, the same group described the preparation of pentacene through thermolysis of **5** after elimination of ethane at 250 °C.[40]



Scheme 4. Synthesis of pentacene through thermally induced retro-Diels-Alder reaction

38 Tönshoff, C.; Bettinger, H. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 4125–4128.
39 Brown, A. R.; Pomp, A.; de Leeuw, D. M.; Klaassen, D. B. M.; Havinga, E. E.; Herwig, P.; Müllen, K. *J. Appl. Phys.* **1996**, *79*, 2136–2138.
40 Herwig, P. T.; Müllen, K. *Adv. Mater.* **1999**, *11*, 480–483.

Hexacene was also prepared in the solid state from the equivalent carbonyl-bridged norbornadienone **6** by extrusion of CO at 180 ºC under a nitrogen atmosphere (Scheme 5). This was the first time that crystalline hexacene was acquired, its structure being unambiguously elucidated through X-ray diffraction analysis of a single crystal grown by physical vapor-transport (PVT). Additionally, the thin films exhibited improved stability in the dark, being stored under ambient conditions for more than one month.[10]

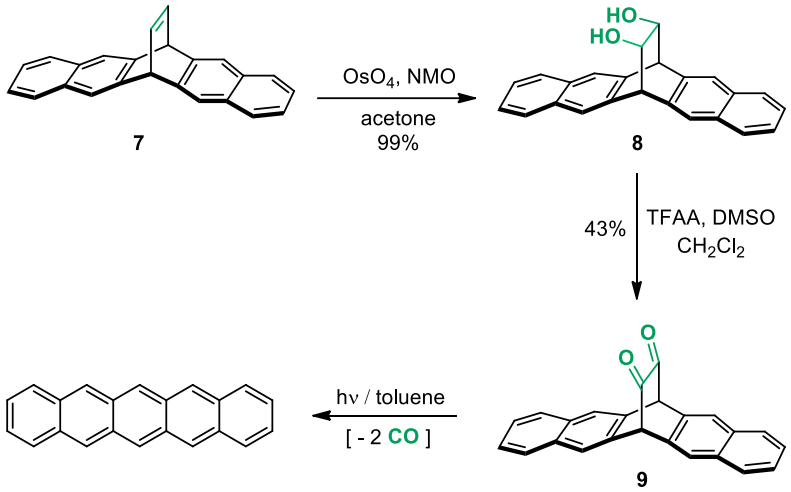


Scheme 5. Synthesis of hexacene through thermal decarbonylation

Photochemically Induced Eliminations

The photochemical synthesis of acenes is a preferred alternative to the thermally induced one, due to its increased safety and the ability to be performed at room temperature. This strategy was first applied to the synthesis of pentacene in 2005 by Watanabe and co-workers and involves a Strating-Zwanenburg reaction of α-diketone precursor **9** bearing a bicyclo[2.2.2]octa-2,3-dione framework.[41] **9** was prepared dihydroxylating the etheno bridge of **7** to acquire diol **8**, which was subjected to a double Swern oxidation (Scheme 6). Pentacene was obtained both in solution and in the solid state through irradiation of **9** in the absence of oxygen to avoid the formation of endoperoxides. The same method was employed by Neckers *et al.* and successfully yielded hexacene.[42] However, the molecule was found to be extremely unstable in solution and prone to dimerization and oxidation. Consequently, they generated the compound in a polymer matrix and it survived for more than 12 hours under ambient conditions. Additionally, hexacenes functionalized at the 6 and 15 positions with phenyl, *p-tert*-butyl and mesityl groups were also obtained, but they also proved to be unstable in solution.

41 Uno, H.; Yamashita, Y.; Kikuchi, M.; Watanabe, H.; Yamada, H.; Okujima, T.; Ogawa, T.; Ono, N. *Tetrahedron Lett.* **2005**, *46*, 1981–1983.
42 Mondal, R.; Adhikari, R. M.; Shah, B. K.; Neckers, D. C. *Org. Lett.* **2007**, *9*, 2505–2508.

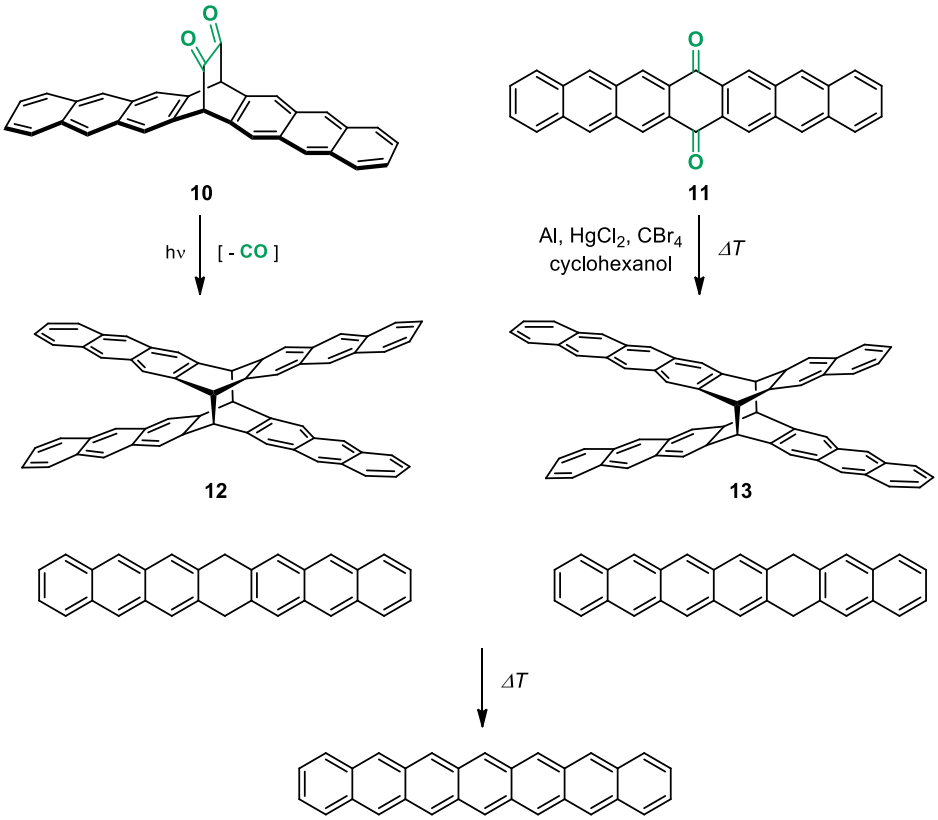


Scheme 6. Synthesis of pentacene through photodecarbonylation of α-diketone precursor **9**

Reports on the synthesis of higher acenes, starting with heptacene, were still ambiguous until recently. Thus, when the same photodegradation of the corresponding quinone was attempted, the higher homologues up to nonacene required isolation in an inert matrix because of their tendency for dimerization or oligomerization. For instance, regardless that the synthesis of heptacene was published by Clar early in the 1940s,[43] its structure could not be elucidated because of its unstable character until 2006, when Neckers *et al.* acquired it in a cryogenic polymer matrix using the same method as in the case of hexacene.[44] In this case the compound underwent a stable charge separation upon photoexcitation, forming the corresponding radical ions, pointing out that heptacene might be a material with promising photoelectronic applications.[45]

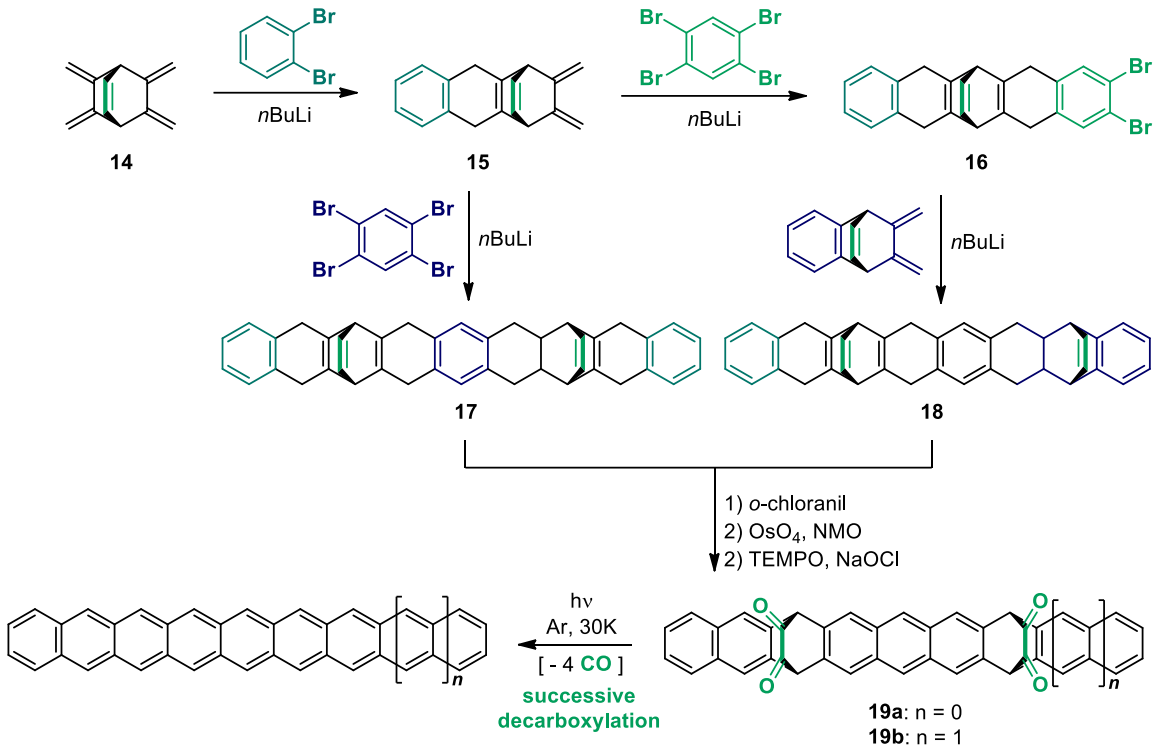
It was not until 2017 that the existence in bulk of heptacene was uncovered by Bettinger *et al.*[46] The synthesis of the acene was accomplished by thermally induced solid state cycloreversion of heptacene butterfly-dimers **12** and **13**, generated by either photochemical double extrusion of CO from dione precursor **10** or Meerwein-Ponndorf-Verley reduction of heptacenequinone **11** (Scheme 7). NMR studies revealed that in thin films heptacene has a half-life of several weeks at room temperature, which permitted the investigation of its properties.

43 Clar, E. *Ber. Dtsch. Chem. Ges.* **1942**, *75B*, 1330–1338.
44 Mondal, R.; Shah, B. K.; Neckers, D. C. *J. Am. Chem. Soc.* **2006**, *128*, 9612–9613.
45 Bettinger, H. F.; Mondal, R.; Neckers, D. C. *Chem. Commun.* **2007**, 5209–5211.
46 Einholz, R.; Fang, T.; Berger, R.; Grüninger, P.; Früh, A.; Chassé, T.; Fink, R. F.; Bettinger, H. F. *J. Am. Chem. Soc.* **2017**, *139*, 4435–4442.



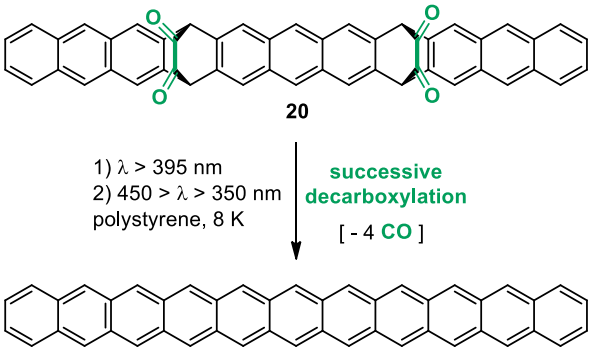
Scheme 7. Synthesis of heptacene from 'butterfly'-dimers **12** and **13**

The photochemical bisdecarbonylation of the corresponding α-diketone precursors **19** at 30 K in an argon matrix was also efficiently employed in the synthesis of both octacene and nonacene by the same group (Scheme 8).[38] To ensure both the stability and solubility of the photoprecursors, no aromatic segment larger than anthracene was introduced. Thus, two *α*-diketone bridges were introduced per molecule and the acene cores were acquired through consecutive Diels-Alder cycloadditions. This led to the partially hydrogenated derivatives **17** and **18** that were converted into aromatic precursors **19** in presence of *o*-chloranil, followed by a dihydroxylation/oxidation sequence previously applied to the synthesis of pentacene precursors.[41] Compounds **19** then underwent successive decarbonylation by irradiation, first with visible light ($\lambda > 360$ nm) to remove the first diketone bridge and then at smaller wavelengths to remove the second one and provide the desired acenes.



Scheme 8. Synthesis of octacene and nonacene

Employing a similar method to the one described above, the Bettinger group also reported the synthesis of undecacene[47] concomitantly with its surface-assisted preparation described by our group. Thus, their synthesis relied on the stepwise photodecarbonylation of tetraketone **20** (Scheme 9). In contrast to the precursor employed in the generation of nonacene, compound **20** decomposed when sublimation was attempted, so an inert-gas matrix isolation was not possible. Consequently, undecacene was formed by conversion of **20** in a polystyrene matrix under cryogenic conditions, which allowed its optical absorption spectrum to be recorded. The decreased HOMO–LUMO gap compared to decacene was in accordance with the predicted progressive closing of the gap with an increase in acene size.



Scheme 9. Synthesis of undecacene by Bettinger *et al.*

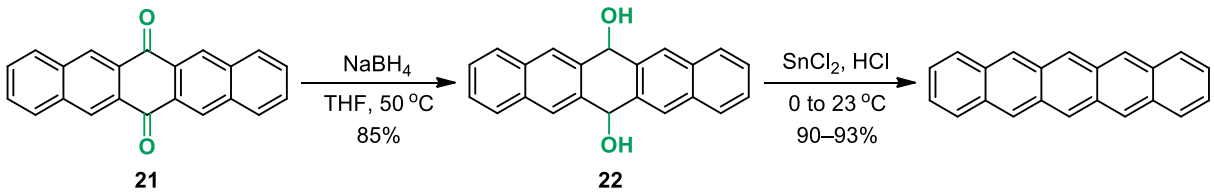
47 Shen, B.; Tatchen, J.; Sanchez-García, E.; Bettinger, H. F. *Angew. Chem. Int. Ed.* **2018**, *57*, 10506–10509.

Acenes from Acenequinones

Acenequinones are one of the main building blocks employed in the synthesis of acenes, as their carbonyl groups enable the functionalization of the acene core through nucleophilic addition of organometallic species and subsequent reductive aromatization. Alternatively, the keto moieties can be cleaved by direct reduction to afford the parent acene.[48] These starting materials have shown enhanced solubility and stability and are generally prepared through aldol condensations[49] or Diels-Alder cycloadditions.[50]

Pentacene Derivatives

The preparation of pentacene has been accomplished through reduction of 6,13-pentacenequinone (**21**). Thus, **21** was reduced in a stepwise manner, *via* the corresponding diol **22** and afforded the parent pentacene under mild conditions (Scheme 10).[48] The same quinone **21** could also be reduced to pentacene in one step using a stronger reducing agent, but the yield suffered considerably.[51]

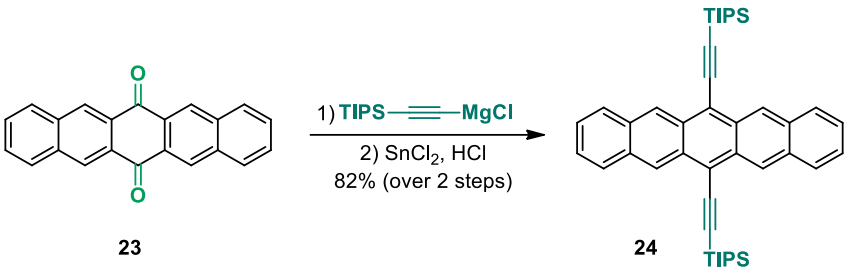


21 **22**

Scheme 10. Synthesis of pentacene through reduction of quinone **21**

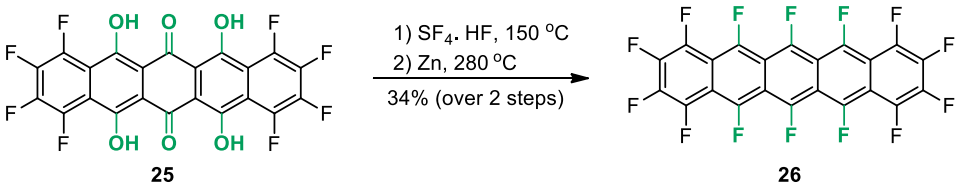
Substituted pentacene derivatives used in molecular electronics were also obtained from acenequinones by silylethynylation, a popular strategy for the stabilization of acenes. In this regard, an important development was made in 2001 when Anthony's group reported the synthesis of 6,13-bis(triisopropylsilylethynyl)pentacene **24** from pentacenequinone **23** by nucleophilic addition of a Grignard reagent, followed by deoxygenation of the addition product by $SnCl_2$ (Scheme 11).[52] The two bulky triisopropylsilylethynyl substituents stabilized the acene framework and resulted in a different arrangement in the solid state, which rendered the new compound with improved conductivity with respect to the parent pentacene. Furthermore, both the solubility and stability of the compound were considerably increased, allowing it to be studied under ambient conditions.

48 Pramanik, C.; Miller, G. P. *Molecules* **2012**, *17*, 4625–4633.
49 (a) Ried, W.; Anthöfer, F. *Angew. Chem.* **1953**, *65*, 601. (b) Sawada, T.; Nakayama, S.; Kawai-Nakamura, A.; Sue, K.; Iwamura, H.; Hiaki, T. *Green Chem.* **2009**, *11*, 1675–1680.
50 (a) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762–3768. (b) Smith, J. G.; Fogg, D. E.; Munday, I. J.; Sandborn, R. E.; Dibble, P. W. *J. Org. Chem.* **1988**, *53*, 2942–2953. (c) Miller, G. P.; Briggs, J. *Tetrahedron Lett.* **2004**, *45*, 477–481.
51 Goodings, E. P.; Mitchard, D. A.; Owen, G. *J. Chem. Soc. Perkin Trans. I* **1972**, 1310–1314.
52 Payne, M. M.; Parkin, S. R.; Anthony, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 8028–8029.



Scheme 11. Synthesis of bis(silylethynyl)pentacene **24**

In the same way, an electron-deficient perfluoropentacene (**26**) was also prepared from quinone **25** by total fluorination with SF_4 followed by defluorination with Zn at 280 ºC (Scheme 12).[29] **25** was employed in the synthesis of transistor devices which showed n-type behaviour with high electron mobilities.

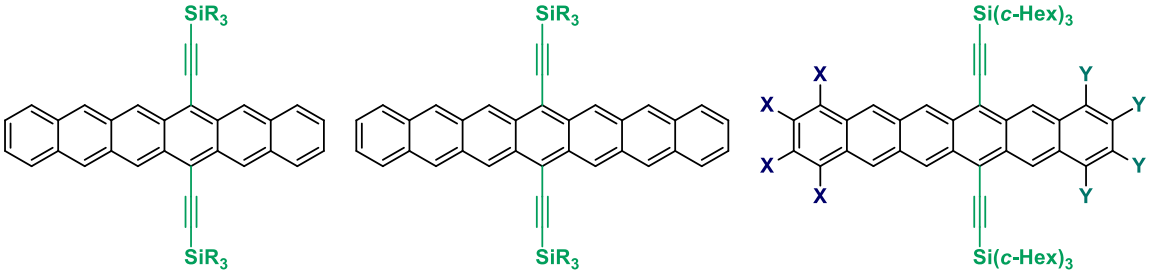


Scheme 12. Synthesis of perfluoropentacene **26**

Hexacene and Heptacene Analogues

Hexacene and heptacene analogues have also been obtained by following the silylethynylation strategy presented earlier. Anthony *et al.* described the synthesis of a series of such derivatives **27** and **28**, which required much bulkier substituents, like tri-*tert*butylsilyl groups or tris(trimethylsilyl)silyl groups, in order to improve their stability and solubility (Figure 5).[52] By contrast, when less bulky silyl moieties were employed, the new compounds, such as **27a**, proved to be more prone to decomposition through dimerization rather than photooxidation. Moreover, the yields were found to be highly dependent on the nature of the substituents, ranging from 89% (**27b**) to 8% (**27c**). The structures of compounds **27** and **28** were unambiguously elucidated by X-ray crystallography, **28c** being the first crystalline heptacene. These results revealed that by varying the substituents at the *meso* positions, the packing motif can be influenced. Thus, a herringbone arrangement was observed for tris(iso-butyl)silyl acetylene-substituted hexacene **27c**, while much bulkier groups resulted in a co-facial packing arrangement for compound **27f**. Similarly to the preparation of **26**, fluorination of the acene backbone was also performed for hexacene and provided further stabilized hexacenes **29** suitable for applications in electronic devices.[53]

53 Purushothaman, B.; Parkin, S. R.; Kendrick, M. J.; David, D.; Ward, J. W.; Yu, L.; Stingelin, N.; Jurchescu, O. D.; Ostroverkhova, O.; Anthony, J. E. *Chem. Commun.* **2012**, *48*, 8261–8263.



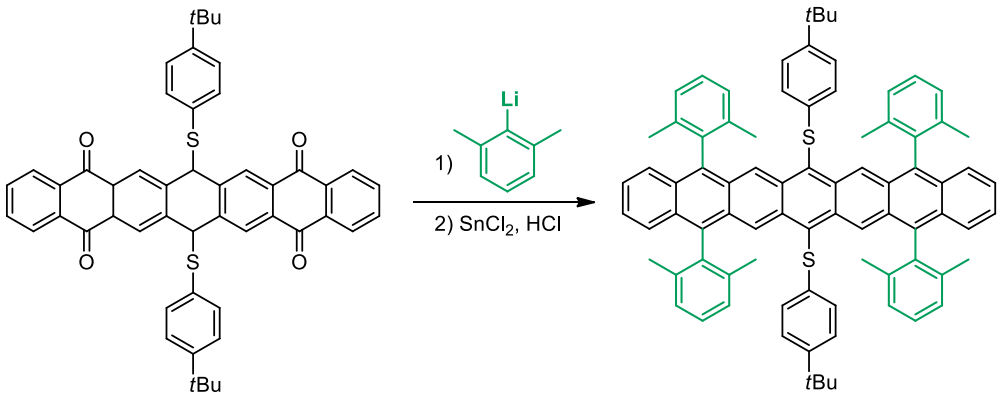
27a: R = *i*Pr
27b: R = *t*Bu
27c: R = *iso*-butyl
27d: R = cyclopentyl
27e: R = cyclohexyl
27f: R = $SiMe_3$

28a: R = *i*Pr
28b: R = *t*Bu
28c: R = $SiMe_3$

29a: X = F, Y = H
29b: X = H, Y = F

Figure 5. Substituted hexacene and heptacene analogues obtained from acenequinones

Another synthesis of a heptacene derivative from bisquinone **30** has been published by Miller's group and relied on a combination of arylthio and *o*-dialkylphenyl substituents to achieve the desired stability (Scheme 13).[54] The aryl substituents attached to the centermost ring prevented the dimerization by inhibiting the effective frontier orbital overlap, while the thioalkyl and thioaryl substituents increased the photo-stability of the molecules. Analogue **31** was found to be stable for weeks in solid state, while in solution it lasted for days in the absence of light and for hours upon exposure to light and air.



30 **31**

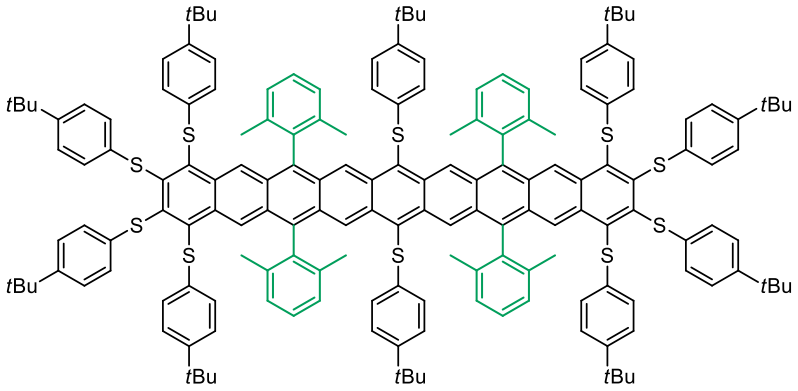
Scheme 13. Synthesis of functionalized heptacene **31**

Nonacene Derivatives

Miller *et al.* also applied the previously mentioned approach based on acenequinones and aryl and thioaryl groups as the stabilizing agents on the preparation of the first nonacene derivative depicted in Figure 6.[55] Thus, compound **32** also known as 'persistent nonacene' was synthesised through nucleophilic addition of an aryllithium reagent to the corresponding bisquinone. The

54 Kaur, I.; Stein, N. N.; Kopreski, R. P.; Miller, G. P. *J. Am. Chem. Soc.* **2009**, *131*, 3424–3425.
55 Kaur, I.; Jazdzyk, M.; Stein, N.; Prusecich, P.; Miller, G. P. *J. Am. Chem. Soc.* **2010**, *132*, 1261–1263.

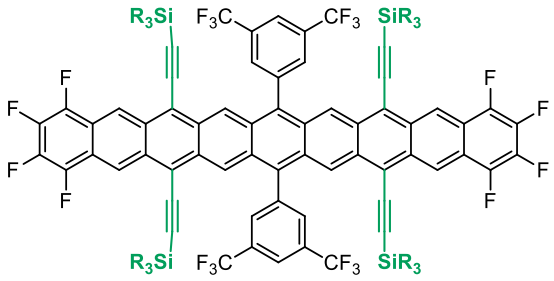
nonacene analogue could be characterized by a set of solution-phase techniques such as ^{1}H and ^{13}C NMR, UV-vis-NIR, and fluorescence spectroscopies. However, it was not clear if derivative **32** was obtained, as the spectroscopic data appeared later to be more consistent with an endoperoxide decomposition product.[56]



32

Figure 6. 'Persistent' nonacene **32** synthesized by Miller *et al.*

Later on, new stable derivatives of nonacene (**33**) were synthesized from bisquinone starting materials, employing both electron-withdrawing and bulky trialkylsilylethynyl functional groups as the stabilizing agents (Figure 7).[56] Consequently, the unambiguous assignment of their structure and the characterization of its optoelectronic properties were allowed by X-ray crystallography and UV-vis spectroscopy. However, when solutions of **33** were exposed to light and air, the compounds were completely decomposed within hours and the corresponding endoperoxides were formed. The spectroscopic data obtained was in accordance with the reports for product **32**.[55]



33a: R = *i*Pr
33b: R = *t*Bu
33c: R = cyclopentyl

Figure 7. Crystalline nonacene derivatives **33** synthesized by Anthony *et al.*

56 Purushothaman, B.; Bruzek, M.; Parkin, S. R.; Miller, A.-F.; Anthony, J. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 7013–7017.

Acenes from Hydroacenes

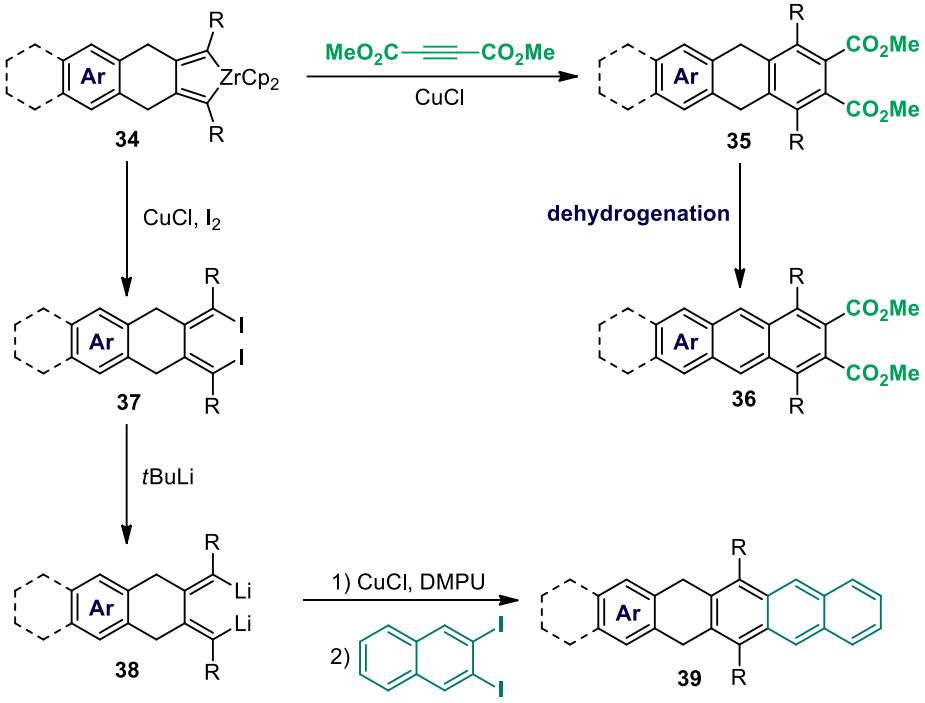
In order to overcome the instability of acenes, an efficient approach is the use of protecting groups, which decrease their reactivity, offer enhanced solubility and permit long-term storage before deprotection of the parent acene. In this regard, hydrogen is considered the simplest protecting group, leading to the formation of hydroacenes, which are partially saturated acenes that bring many advantages. For instance, due to the presence of more aromatic Clar sextets, hydroacenes exhibit remarkably improved solubility and stability in solution in comparison to their acene and acenequinone counterparts, which allows them to be stored for long periods of time without decomposing. Furthermore, hydroacenes can also be prepared by direct reduction of acenequinones, which means that the prior preparation of the parent acene is not required. On the contrary, their deprotection by dehydrogenation with reagents such as DDQ or chloranil affords the desired parent conjugated acenes.

Miller *et al*. reported the first systematic study of hydroacene analogues through the direct reduction of either acenes or acenequinones with HI in refluxing acetic acid.[57] The methodology led to the regioselective hydrogenation of unsubstituted and phenyl-substituted acenes and acene quinones with up to four rings, which took place at the most reactive centermost ring.4 Unfortunately, the method was not successful in case of unsubstituted higher acenes and acenequinones with five or more rings, regioisomeric mixtures of partially reduced products being obtained from their reduction. In case of pentacene, the lack of regioselectivity owes to the reduced difference in reactivity between the centermost ring and the penultimate internal rings. By contrast, the hydrogenation of phenyl-substituted compounds, such as 6,13-diphenylpentacene, 5,7,12,14-tetraphenylpentacene-6,13-dione or 6,8,15,17-tetraphenylheptacene-7,16-dione gave single products in which the terphenyl units remained intact, suggesting that these are the most stable compounds with the greatest resonance delocalization energy. In addition to Miller's study, small hydroacenes were also obtained from anthracene derivatives, tetracene or tetraphene by hydrogenation promoted by the frustrated Lewis pair (FLP) catalyst $B(C_6F_5)_3/Ph_2PC_6F_5$.[58] Unfortunately, this is not a general approach for the synthesis of larger hydroacenes, as the parent acenes must be employed as starting materials. Consequently, the synthesis of larger unsubstituted hydroacenes still remains elusive and more general methods are required.

However, for the preparation of larger hydroacene homologues, zirconacyclopentadienes **34** proved to be a better alternative due to their versatility. These compounds are provided by reaction of diynes with the Negishi reagent (Cp_2ZrBu_2). Therefore, functionalized dihydroacenes of type **35** were acquired by cycloaddition of **34** with electron-deficient alkynes or alkenes (Scheme 14). Compounds

57 Athans, A. J.; Briggs, J. B.; Jia, W.; Miller, G. P. *J. Mater. Chem.* **2007**, *17*, 2636–2641.
58 Segawa, Y.; Stephan, D. W. *Chem. Commun.* **2012**, *48*, 11963–11965.

35 were either dehydrogenated to provide the corresponding substituted acenes **36** or subjected to an iterative sequence that provided larger hydroacene derivatives.[59] Furthermore, **33** also enabled the formation of dihydroacenes **39** by iodination/lithiation, followed by copper(I)-catalyzed coupling with diiodoarenes of the resulting 1,4-dilithiobutadienes **38**.[60]



Scheme 14. Synthesis of hydroacenes from zirconacyclopentadienes **34**

Dehydrogenation of Hydroacenes

Over the last decades, the aromatization of hydroacenes has been one of the most commonly investigated strategies for the acquisition of the desired acene derivatives. Thus, pentacene was synthesized for the first time by Clar in 1929-1930 by subjecting 6,13-dihydropentacene to oxidation.[61] Later on, pentacene was also obtained from 5,14-dihydropentacene by dehydrogenation over Pd/C in quantitative yield.[62]

Higher acenes have also been provided by dehydrogenation of hydroacenes. Thus, the first synthesis of hexacene was accomplished by aromatization of the polyhydrogenated hexacene **42**,

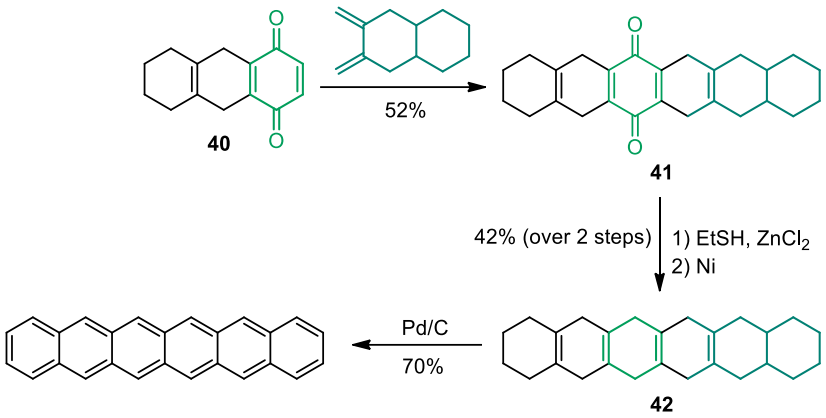
59 (a) Takahashi, T.; Kitamura, M.; Shen, B.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 12876–12877. (b) Takahashi, T.; Li, S.; Huang, W.; Kong, F.; Nakajima, K.; Shen, B.; Ohe, T.; Kanno, K.-i. *J. Org. Chem.* **2006**, *71*, 7967–7977. (c) Takahashi, T.; Li, Y.; Hu, J.; Kong, F.; Nakajima, K.; Zhou, L.; Kanno, K.-i. *Tetrahedron Lett.* **2007**, 6726–6730. (d) Li, S.; Zhou, L.; Song, Z.; Bao, F.; Kanno, K.-i.; Takahashi, T. *Heterocycles* **2007**, *73*, 519–536. (e) Li, S.; Li, Z.; Nakajima, K.; Kanno, K.-i.; Takahashi, T. *Chem. Asian J.* **2009**, *4*, 294–301. (f) Stone, M. T.; Anderson, H. L. *J. Org. Chem.* **2007**, *72*, 9776–9778.

60 (a) Zhou, L.; Nakajima, K.; Kanno, K.-i.; Takahashi, T. *Tetrahedron Lett.* **2009**, *50*, 2722–2726. (b) Jia, Z.; Li, S.; Nakajima, K.; Kanno, K.-i.; Takahashi, T. *J. Org. Chem.* **2011**, *76*, 293–296.

61 (a) Clar, E.; John, F. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 3021–3029. (b) Clar, E.; John, F. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 2967–2977.

62 Luo, J.; Hart, H. *J. Org. Chem.* **1987**, *52*, 4833–4836.

prepared by Diels-Alder reaction of diene **40** (Scheme 15).[63] Furthemore, the synthesis of hexacene was also achieved by dehydrogenation of dihydrohexacene at high temperature over CuO and its structure was assigned on account of spectral analyses.[64] However, the acquisition of hexacene following this method was questioned later on because of its reported instability.[10,65]



Scheme 15. First synthesis of hexacene by dehydrogenation of **42**

On the other hand, heptacene analogues were obtained from hexahydrotetraphenylheptacene through dehydrogenation with DDQ and trapping with C_{60} fullerene by means of [4+2] cycloadditions.[66]

Surface-Assisted Synthesis of Acenes

The development of metal surface-assisted synthesis constitutes a reliable alternative to solution chemistry, providing new means to prepare and stabilize inherently unstable compounds by deposition of stable derivatives on a crystalline substrate followed by transformation into the target products. Combining scanning tunneling and atomic force microscopy (STM/AFM) and the ultrahigh vacuum (UHV) techniques, this approach enables the study of the electronic properties of compounds and allows detailed imaging of both the reactants and products on molecular scale with remarkable resolution and precision, as well as the investigation of various types of reactions and their mechanisms in an ideal clean model system.[67] Pioneered in 2000 by the group of Hla with the

63 (a) Bailey, W. J.; Liao, C.-W. *J. Am. Chem. Soc.* **1955**, *77*, 992–993. (b) Marschalk, C. *Bull. Soc. Chim. Fr.* **1939**, *6*, 1112–1121. (c) Clar, E. *Ber. Dtsch. Chem. Ges. B* **1939**, *72*, 1817–1821.

64 Satchell, M. P.; Stacey, B. E. *J. Chem. Soc. C* **1971**, 468–469.

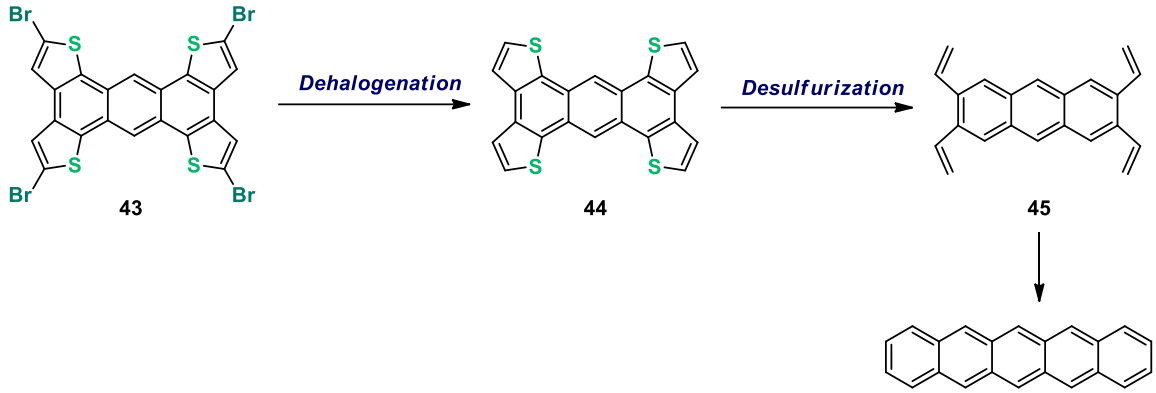
65 Mondal, R.; Adhikari, E. M.; Shah, B. K.; Neckers, D. C. *Org. Lett.* **2007**, *9*, 2505–2508.

66 Miller, G. P.; Briggs, J. *Org. Lett.* **2003**, *5*, 4203–4206.

67 (a) Zwaneveld, N. A. A.; Pawlak, R.; Abel, M.; Catalin, D.; Gigmes, D.; Bertin, D.; Porte, L. *J. Am. Chem. Soc.* **2008**, *130*, 6678−6679. (b) Franc, G.; Gourdon, A. *Phys. Chem. Chem. Phys.* **2011**, *13*, 14283−14292. (c) Grill, L.; Dyer, M.; Lafferentz, L.; Persson, M.; Peters, M. V.; Hecht, S. *Nat. Nanotechnol.* **2007**, *2*, 687–691; (d) Kolmer, M.; Zebari, A. A. A.; Prauzner-Bechcicki, J. S.; Piskorz, W.; Zasada, F.; Godlewski, S.; Such, B.; Sojka, Z.; Szymonski, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10300–10303; *Angew. Chem.* **2013**, *125*, 10490–10493; (e) Abel, M.; Clair, S.; Ourdjini, O.; Mossoyan, M.; Porte, L. *J. Am. Chem. Soc.* **2011**, *133*, 1203−1205. (f) Cai, J.; Ruffieux, P.; Jaafar, R.; Bieri, M.; Braun, T.; Blankenburg, S.; Muoth, M.; Seitsonen, A. P.; Saleh, M.; Feng, X.; Mgllen, K.; Fasel, R. *Nature* **2010**, *466*, 470–473.

formation of biphenyl from iodobenzene,[68] this method was employed in the study of reactions involving the scission of hydrogen atoms, such as C−H-,[69] N−H-[70] and O−H[71] activations, which revealed new impressive molecules that remained elusive before.

Surface-assisted synthesis has also been applied for the preparation of acenes. The first example was reported by Dinca *et al.* for the synthesis of pentacene from tetrathienoanthracene **43** on a Ni(111) surface, presented in Scheme 16.[72] In this case, the target compound was obtained through an unprecedented transformation involving sulfur abstraction from thiophene followed by cyclization.



Scheme 16. Synthesis of pentacene from tetrathienoanthracene **43** on a Ni(111) surface

Later on, in 2017, heptacene was also synthesized by Bettinger and co-workers on a Ag(111) surface from the didecarbonylation of α-diketone precursor **46** (Scheme 17).[73] In a similar manner to the precursors of pentacene,[41] **46** was prepared through photochemically induced Diels-Alder.

68 Hla, S.-W.; Bartels, L.; Meyer, G.; Rieder, K.-H. *Phys. Rev. Lett.* **2000**, *85*, 2777–2780.

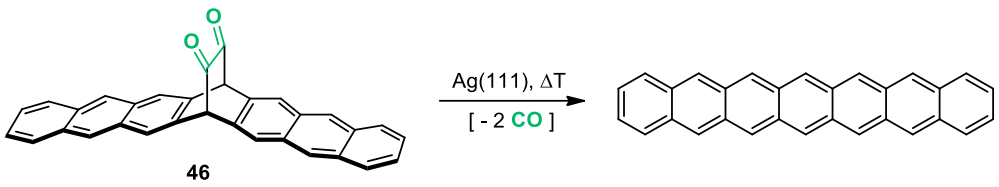
69 Selected examples: (a) In't Veld, M.; Iavicoli, P.; Haq, S.; Amabilino, D. B.; Raval, R. *Chem. Commun.* **2008**, 1536−1538. (b) Treier, M.; Pignedoli, C. A.; Laino, T.; Rieger, R.; Mullen, K.; Passerone, D.; Fasel, R. *Nat. Chem.* **2011**, *3*, 61−67. (c) Zhang, Y. Q.; Kepcija, N.; Kleinschrodt, M.; Diller, K.; Fischer, S.; Papageorgiou, A. C.; Allegretti, F.; Björk, J.; Klyatskaya, S.; Klappenberger, F.; Ruben, M.; Barth, J. V. *Nat. Commun.* **2012**, *3*, 1286. (d) Eichhorn, J.; Heckl, W. M.; Lackinger, M. *Chem. Commun.* **2013**, *49*, 2900−2902. (e) Zhou, H.; Liu, J. Z.; Du, S. X.; Zhang, L. Z.; Li, G.; Zhang, Y.; Tang, B. Z.; Gao, H. J. *J. Am. Chem. Soc.* **2014**, *136*, 5567−5570. (f) Zhang, J. J.; Chang, C. R.; Yang, B.; Cao, N.; Peng, C. C.; Zhang, H. M.; Tang, D. T. D.; Glorius, F.; Erker, G.; Fuchs, H.; Li, Q.; Chi, L. F. *Chem. Eur. J.* **2017**, *23*, 6185−6189.

70 (a) Matena, M.; Björk, J.; Wahl, M.; Lee, T. L.; Zegenhagen, J.; Gade, L. H.; Jung, T. A.; Persson, M.; Stohr, M. *Phys. Rev. B: Condens. Matter Mater. Phys.* **2014**, *90*, 125408. (b) Knor, M.; Gao, H. Y.; Amirjalayer, S.; Studer, A.; Gao, H. J.; Du, S. X.; Fuchs, H. *Chem. Commun.* **2015**, *51*, 10854−10857.

71 (a) Li, Q.; Yang, B.; Lin, H. P.; Aghdassi, N.; Miao, K. J.; Zhang, J. J.; Zhang, H. M.; Li, Y. Y.; Duhm, S.; Fan, J.; Chi, L. F. *J. Am. Chem. Soc.* **2016**, *138*, 2809−2814. (b) Fischer, S.; Papageorgiou, A. C.; Lloyd, J. A.; Oh, S. C.; Diller, K.; Allegretti, F.; Klappenberger, F.; Seitsonen, A. P.; Reichert, J.; Barth, J. V. *ACS Nano* **2014**, *8*, 207−215. (c) Giovanelli, L.; Ourdjini, O.; Abel, M.; Pawlak, R.; Fujii, J.; Porte, L.; Themlin, J. M.; Clair, *S. J. Phys. Chem. C* **2014**, *118*, 14899−14904. (d) Bebensee, F.; Svane, K.; Bombis, C.; Masini, F.; Klyatskaya, S.; Besenbacher, F.; Ruben, M.; Hammer, B.; Linderoth, T. *Chem. Commun.* **2013**, *49*, 9308−9310. (e) Bebensee, F.; Svane, K.; Bombis, C.; Masini, F.; Klyatskaya, S.; Besenbacher, F.; Ruben, M.; Hammer, B.; Linderoth, T. R. *Angew. Chem. Int. Ed.* **2014**, *53*, 12955−12959.

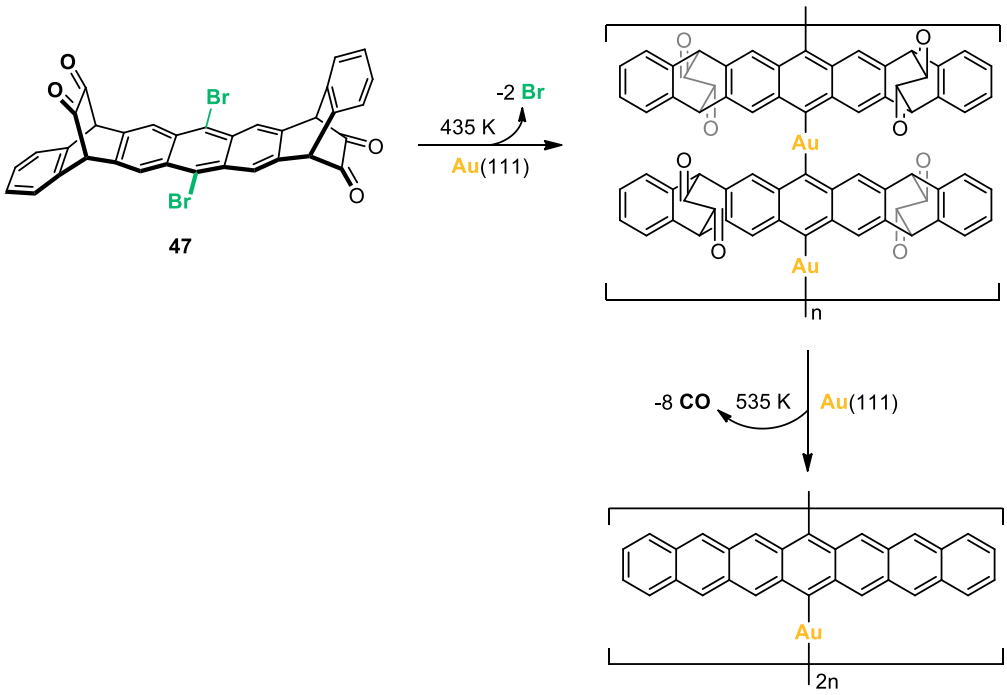
72 Dinca, L. E.; Fu, C.; MacLeod, J. M.; Lipton-Duffin, J.; Brusso, J. L.; Szalacs, C. E.; Ma, D.; Perepichka, D. F.; Rosei, F. *ACS Nano* **2013**, *7*, 1652–1657.

73 Zugermeier, M.; Gruber, M.; Schmid, M.; Klein, B. P.; Ruppenthal, L.; Mgller, P.; Einholz, R.; Hieringer, W.; Berndt, R.; Bettinger, H. F.; Gottfried, J. M. *Nanoscale* **2017**, *9*, 12461−12469.



Scheme 17. Synthesis of heptacene from α-diketone **46** on a Ag(111) surface

Furthermore, the surface-confined formation of heptacene organometallic complexes was also reported by Fasel *et al.* on Au(111) through the selective activation of the dibrominated *α*-diketone precursor **47**.[74] To acquire the desired complexes, two thermal annealing steps were performed (Scheme 18). The first of them involves debromination and generation of the gold-organometallic complexes, while the second one triggered the bisdecarbonylation of the bridging of the *α*-diketone units.



Scheme 18. Surface-assisted synthesis of heptacene organometallic complexes

In addition to that, the preparation of acenes has also been described on Cu(111) and Au(111) surface from epoxyacenes. Thus, Peña and co-workers reported the synthesis of tetracene on Cu(111)[75] and hexacene,[76] decacene[77] and even dodecacene[78] on Au(111) *via* deoxygenation of the

74 Urgel, J.; Hayashi, H.; Di Giovannantonio, M.; Pignedoli, C. A.; Mishra, S.; Deniz, O.; Yamashita, M.; Dienel, T.; Ruffieux, P.; Yamada, H.; Fasel, R. *J. Am. Chem. Soc.* **2017**, *139*, 11658–11661.

75 Krüger, J.; Pavliček, N.; Alonso, J. M.; Pérez, D.; Guitián, E.; Lehmann, T.; Cuniberti, G.; Groudon, A.; Meyer, G.; Gross, L.; Moresco, F.; Peña, D. *ACS Nano* **2016**, *10*, 4538–4542.

76 Krüger, J.; Eisenhut, F.; Alonso, J. M.; Lehmann, T.; Guitián, E.; Pérez, D.; Skidin, D.; Gamaleja, F.; Ryndyk, D. A.; Joachim, C.; Peña, D.; Moresco, F.; Cuniberti, G. *Chem. Commun.* **2017**, *53*, 1583–1586.

77 Krüger, J.; García, F.; Eisenhut, F.; Skidin, D.; Alonso, J. M.; Guitián, E.; Pérez, D.; Cuniberti, G.; Moresco, F.; Peña, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 11945–11948; *Angew. Chem.* **2017**, *129*, 12107–12110.

corresponding epoxy acenes, the latter being the longest acene reported up to date. These precursors were obtained by solution-based sequential aryne additions to isobenzofuran analogues, as illustrated for pentaepoxy dodecacene **54** in Scheme 19. After deposition of the precursors under UHV conditions, the deoxygenation of **54** took place either through annealing at high temperatures of 220 ^{o}C, or with the aid of microscopy techniques, by manipulation of individual molecules, to afford the parent acene.[78] During the Au(111) surface-assisted reaction some partially deoxygenated intemediates **55** with two remaining epoxy groups were observed.

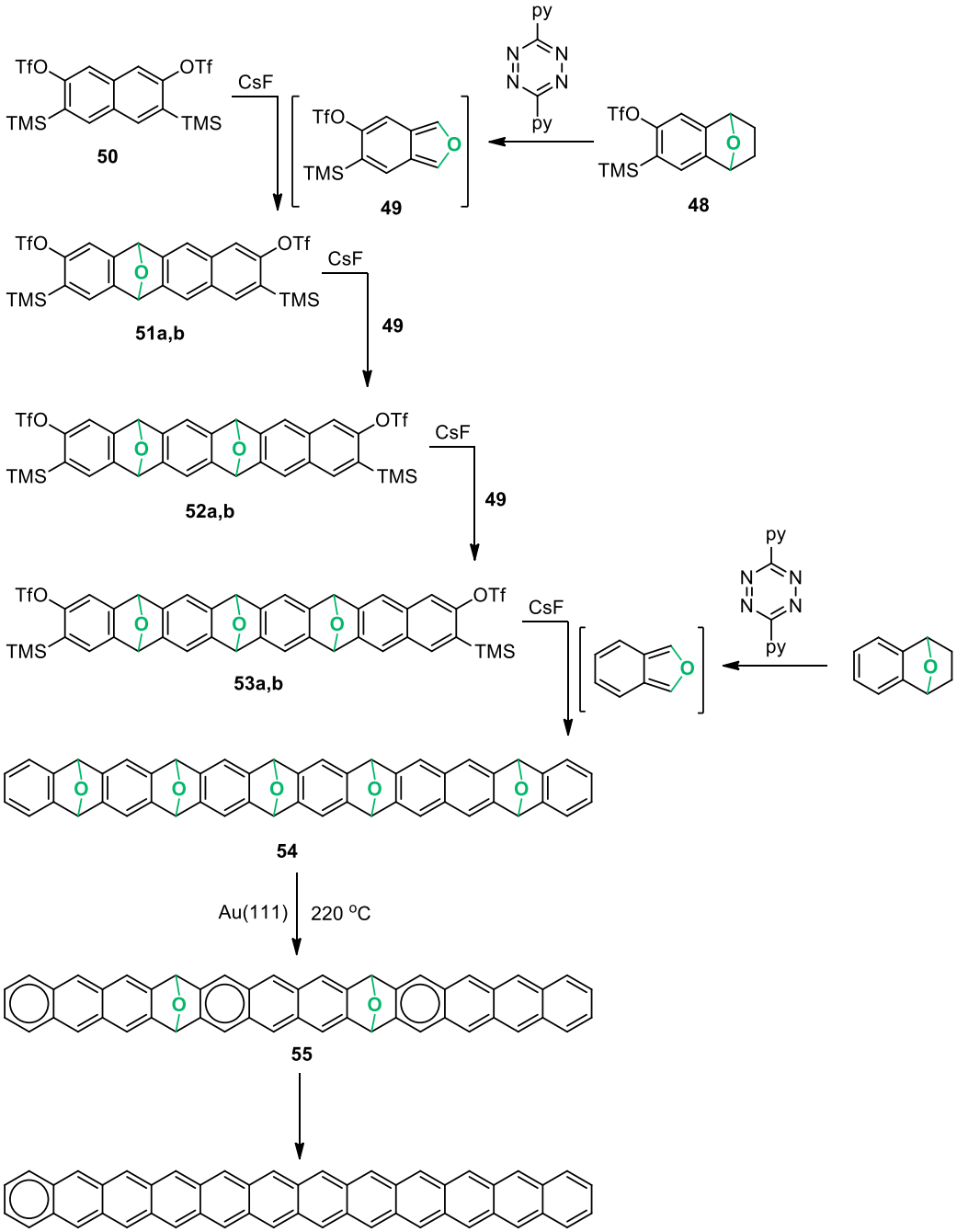
Earlier studies of the acene series predicted that the band gap and reorganization energies diminish as the number of annealed rings increases.**1**[a,c,d,37a,79] Experimental results confirmed that the HOMO−LUMO gap decreases from 2.2 eV in pentacene[80] to approximately 1.1−1.2 eV for decacene[77] and undecacene.[81] However, the characterization of dodecacene showed that the energy gap increases up to 1.4 eV, as a possible result of its higher polyradical character, breaking the established trend. This result indicates that further experiments are needed to fully understand the electronic structures of oligoacenes and explains our motivation to synthesise larger unsubstituted homologues, the first of them being tridecacene.

78 Eisenhut, F.; Kühne, T.; García, F.; Fernández, S.; Guitián, E.; Pérez, D.; Trinquier, G.; Cuniberti, G.; Joachim, C.; Peña, D.; Moresco, F. *ACS Nano* **2020**, *14*, 1011–1017

79 Houk, K. N.; Lee, P. L.; Nendel, M. *J. Org. Chem.* **2001**, 66, 5517–5521.

80 Soe, W.-H.; Manzano, C.; De Sarkar, A.; Chandrasekhar, N.; Joachim, C. *Phys. Rev. Lett.* **2009**, *102*, 176102.

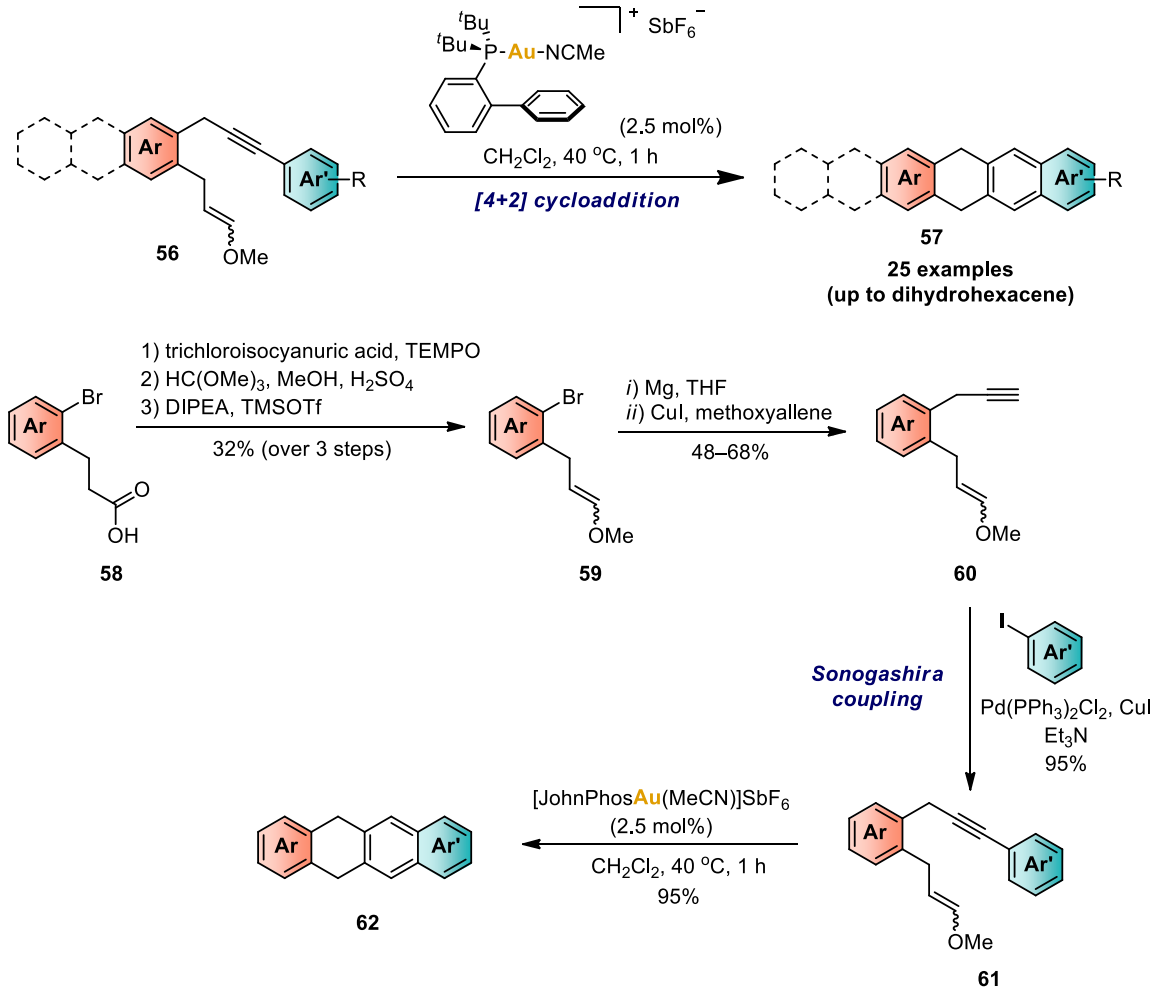
81 Zuzak, R.; Dorel, R.; Kolmer, M.; Szymonski, M.; Godlewski, S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2018**, *57*, 10500–10505.



Scheme 19. Synthesis of dodecacene from pentaepoxy dodecacene **54**

Hydroacenes by Gold(I) Catalysis

The promising results obtained in our group in the gold(I)-catalyzed cyclization of 1,6-enyne **36** *(General Introduction)*, inspired the application of the same method to analogous 1,7-enynes in which the alkene moiety belongs to an enol ether to generate six-membered rings. As a result, in 2016 our group reported the first general synthesis of stable functionalized hydroacenes through gold(I) catalysis (Scheme 20).[82] This highly modular synthesis is based on robust transformations, such as the Sonogashira coupling of commercially available aryl iodides with readily prepared 1,7-enyne synthons, as well as the gold(I)-catalysed intramolecular [4+2] cycloaddition, which is tolerant of several functionalities, proceeds under very mild conditions and uses the commercially available cationic complex [JohnPhosAu(MeCN)]SbF_6 as the catalyst of the key step.



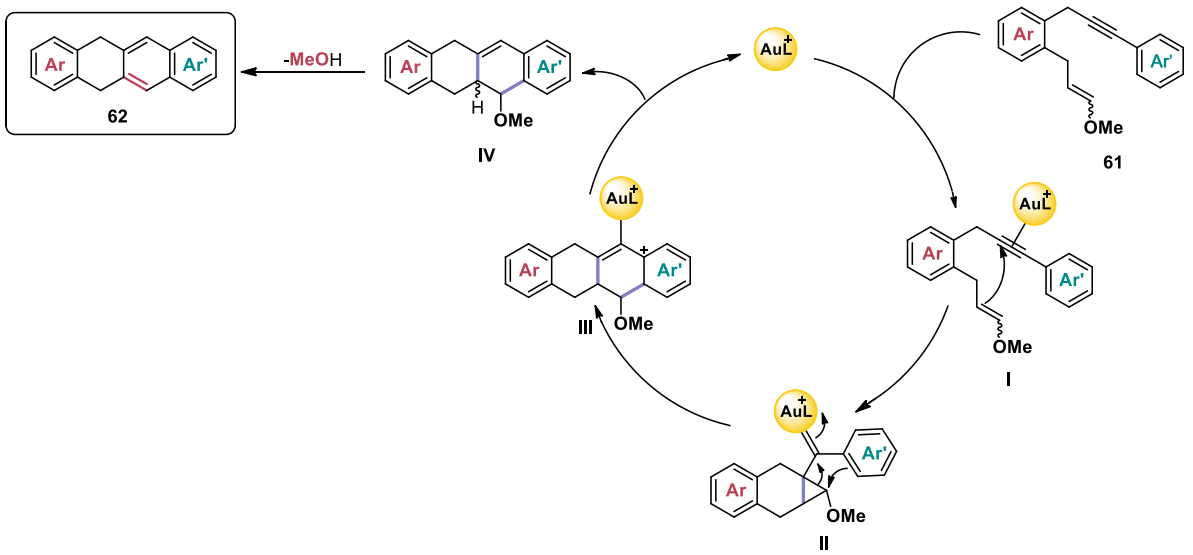
Scheme 20. Gold(I)-catalyzed synthesis of hydroacenes **57** and synthesis of 1,7-enyne **60**

As illustrated in Scheme 20, in its simplest version, this methodology allows the formation of dihydrotetracene **62** from enyne **61**, which is prepared through Sonogashira coupling from iodobenzene and the 1,7-enyne key synthon **60**. This compound is provided from the commercially

82 Dorel, R.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 11120–11123.

available carboxylic acid **58**, which is converted to enol ether **59** after reduction to the equivalent alcohol, oxidation, acetal protection of the resulting aldehyde and TMSOTf-promoted methoxy elimination. Enol ether **59** is then submitted to Grignard reaction, transmetallation with CuI, and subsequent addition to methoxyallene to provide enyne synthon **60**. Finally, Sonogashira cross coupling with iodobenzene under standard conditions yields coupled 1,7-enyne **61**. Thus, when enyne synthon **60** was employed, a wide range of coupled enynes were synthesized and the desired functionalized dihydrotetracenes were successfully obtained *via* Au(I)-catalysed [4+2]-cycloaddition in good to excellent yields. Additionally, by synthesising naphthalenyl- and anthracenyl-1,7-enyne analogous synthons, 6,13-dihydropentacene and 6,15-dihydrohexacene were also successfully rendered.

With respect to the mechanism of the reaction (Scheme 21),[82] the 6-*exo*-dig cyclization starts with activation of the alkyne moiety of the enyne **61** by coordination to gold(I). The nucleophilic attack of the alkene results in the formation of cyclopropyl gold(I) carbene **II**, which is then opened through the Friedel-Crafts-type attack of the aromatic ring, generating intermediate **III** through a formal [4+2] cycloaddition. Aromatization and protodeauration of **III** regenerates the gold(I) complex and yields **IV**, which undergoes aromatization-driven elimination of a molecule of methanol to finally afford the desired hydroacene **62**.

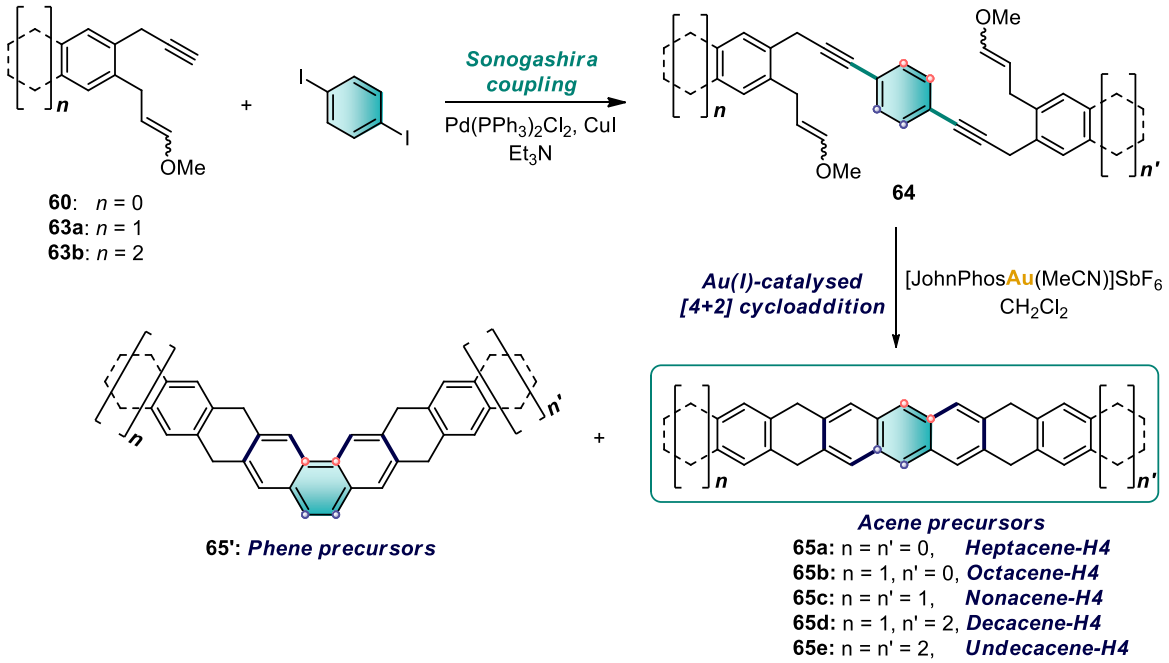


Scheme 21. Mechanism of the gold(I)-catalyzed [4+2] cycloaddition of enyne **61** to dihydrotetracene **62**

The potential of this methodology was further demonstrated through the synthesis of non-functionalized higher hydroacenes *via* double intramolecular [4+2] cycloadditions of enynes **60** and **63** (Scheme 22).[81] For instance, tetrahydroheptacene (**65a**) and tetrahydrononacene (**65c**) were obtained from the cyclization reactions of the 1,7-enynes generated from synthon **60** and its

naphthalene analogue (**63a**), respectively. Later on, when the preparation of an anthracenyl-1,7-enyne (**63b**) was accomplished, the double Au(I)-catalyzed cyclizations of dienynes **64** efficiently provided tetrahydrooctacene (**65b**), tetrahydrodecacene (**65d**) and even tetrahydroundecacene (**65e**), the precursor of undecacene. The corresponding enynes **64** were acquired by Sonogashira coupling of alternating 1,7-enyne synthons.

The desired compounds were obtained from the tested 1,7-enynes together with their hydrophene isomers **65'**, since the Au(I)-cycloisomerisation of the starting materials can take place in two different modes. The final products are air stable and easily purified compounds that can be stored indefinitely under ordinary conditions. The hydrophenes were formed only as minor isomers in case of tetrahydroheptacene, tetrahydrooctacene and tetrahydrononacene and could be easily separated from the hydroacenes due to their much higher solubilities. However, tetrahydrodecacene and tetrahydroundecacene showed similar solubilities to their hydrophene counterparts and could not be fully separated. Finally, the acquired hydroacenes or the mixtures with hydrophenes were successfully aromatized through dehydrogenation on Au(111) surface to afford the parent acenes and phenes.[81,83]

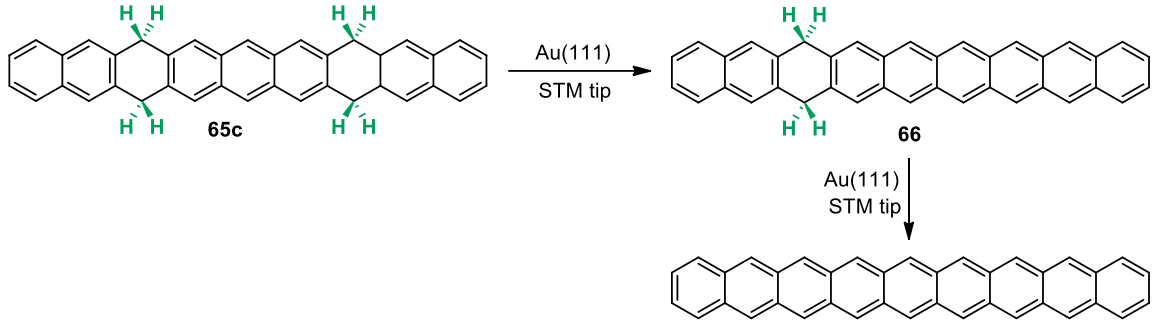


Scheme 22. Au(I)-catalyzed synthesis of hydroacenes **65a−e** *via* double [4+2] cycloaddition

The hydroacenes obtained through double gold(I)-catalyzed cycloaddition of enynes **64** were then employed as stabilized precursors in the Au(111) surface-assisted of the parent acenes. The investigation of the aromatization process started with nonacene-H4 (**65c**), which was deposited on the metal surface and its two non-aromatic rings underwent sequential dehydrogenation by

83 Dorel, R.; Echavarren, A. M. *Acc. Chem. Res.* **2019**, *52*, 1812−1823.

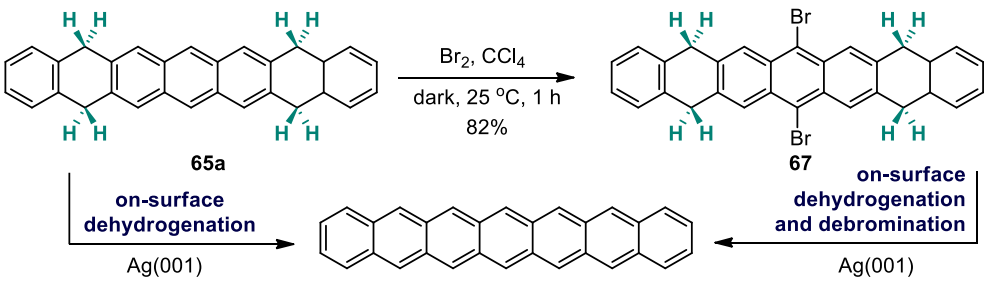
manipulation with the tip of an STM microscopy instrument (Scheme 23).[81] The detailed structure of the nonacene product was confirmed by nc-AFM and the electronic features were studied by means of STS that revealed a transport gap of 1.19 eV. The dehydrogenation of **65c** was also achieved by annealing of the precursors at 210 ºC, after sublimation by deposition under UHV conditions.



Scheme 23. Tip-induced sequential dehydrogenation of **65c** into nonacene on Au(111)

The procedure employed in the dehydrogenative aromatization of nonacene was then converted into a general method to acquire the other members of the acene series. Thus, the dehydrogenation of precursors **65** and **65'** furnished acene molecules up to undecacene, as well as the phene isomers, through both manipulation with a microscope tip and annealing of the samples. The new acenes were confirmed by nc-AFM and the evolution of their electronic band gap was investigated by STS. Complementing other reports,**1**[a,c,d,37a,79] these studies indicated that the band gap undergoes progressive lowering and the open-shell character is significantly more prominent as the number of fused rings increases.

Concurrently, heptacene was also formed from tetrahydroheptacene **65a** and its brominated analogue, 7,16-dibromotetrahydroheptacene (**67**) on a Ag(001) surface,[84] where **67** was acquired by direct bromination of **65a** (Scheme 24). Intriguingly, both precursors generated heptacene, after dehydrogenation processes by annealing the samples at 270 ºC. Compound **67** suffered an unexpected spontaneous hydrogenation at the radical sites generated at the central ring after dehalogenation, even under UHV conditions.



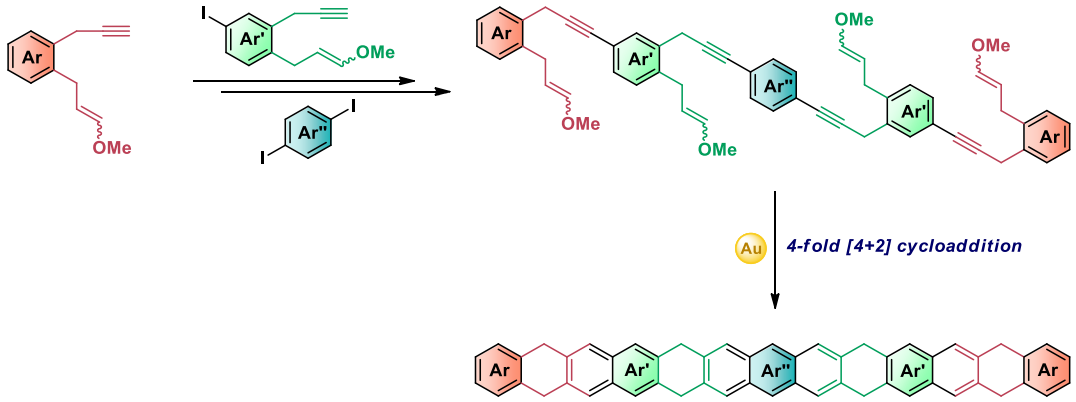
Scheme 24. Synthesis of heptacene from **65a** and **67**

84 Colazzo, L.; Mohammed, M. S. G.; Dorel, R.; Nita, P.; García-Fernández, C.; Abufager, P.; Lorente, N.; Echavarren, A. M.; de Oteyza, D. G. *Chem. Commun.* **2018**, *54*, 10260−10263.

OBJECTIVES

Taking into account the advances in the synthesis of higher hydroacenes and their surface-assisted aromatization, the objective of this work was to broaden the scope of our methodology and prepare even larger unsubstituted linearly fused partially saturated aromatic systems, starting with octahydrotridecacene, to study their electronic properties, in particular their transport gap.

The new molecules would be obtained *via* the gold(I)-catalyzed formal [4+2] cycloaddition reaction developed in our group. To accomplish our goal, our first focus was the design of new 1,7-enyne synthons that would be involved in the Sonogashira reaction and subsequently in the gold(I)-catalyzed key step. Consequently, our intention was to synthesize a tetracenyl-1,7-enyne that would lead to the formation of octahydrotridecacene by means of a double cycloaddition. As an alternative, we proposed an iterative synthesis of the desired higher hydroacenes, based on successive couplings of 1,7-enynes, while the key 4-fold Au(I)-catalyzed [4+2] cycloaddition would be performed at the end of the synthetic route (Scheme 25). Furthermore, another goal was to optimize the preparation of our most common 1,7-enyne synthon **60**, which was previously obtained in six steps.



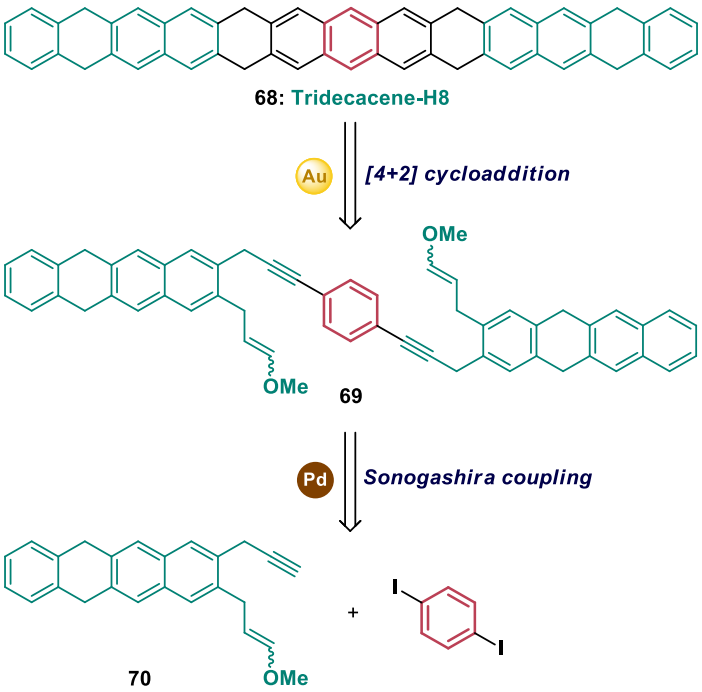
Scheme 25. Proposed synthesis of octahydrotridecacene **68**

We also explored the synthesis of hydroacenes larger than octahydrotridecacene. A final objective was to perform the on-surface dehydrogenative aromatization of the acquired hydroacenes to provide the parent acenes.

RESULTS AND DISCUSSION

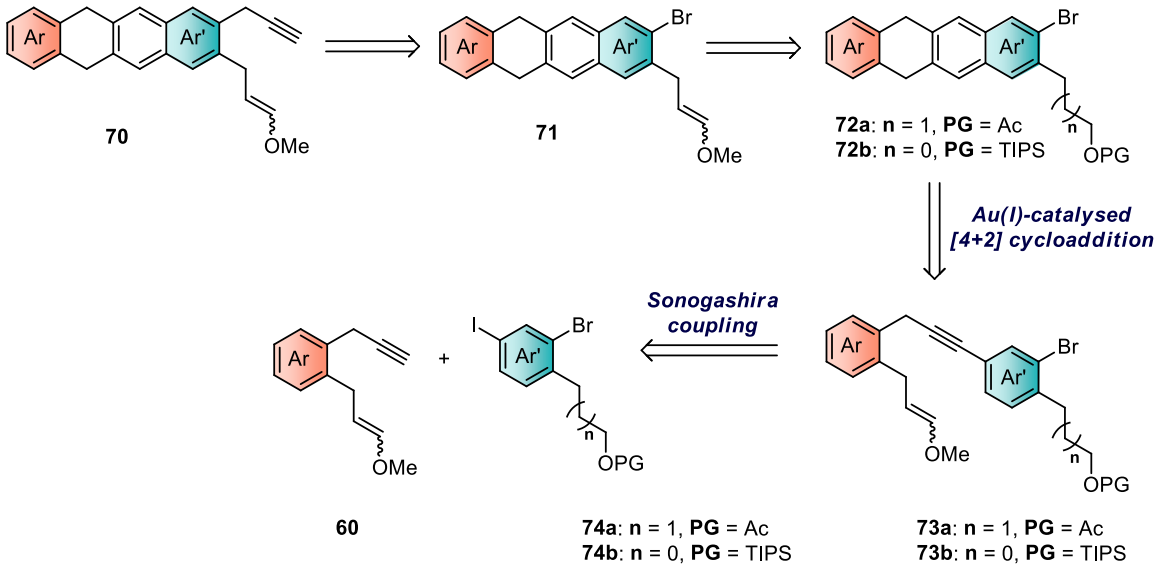
First Approach for the Synthesis of Tridecacene-H8

Due to the good results obtained with the second generation anthracenyl-1,7-enyne synthon in the preparation of large acenes up to undecacene-H4,[81] we envisioned that a third generation tetracenyl synthon **70** prepared following the same route could be engaged to acquire the precursor of the next unknown member of the acene series, tridecacene. Thus, hydroacene **68** would be achieved by double Sonogashira coupling of **70** with 1,4-diiodobenzene and subsequent 2-fold Au(I)-catalyzed [4+2] cycloaddition of double enyne **69** (Scheme 26).



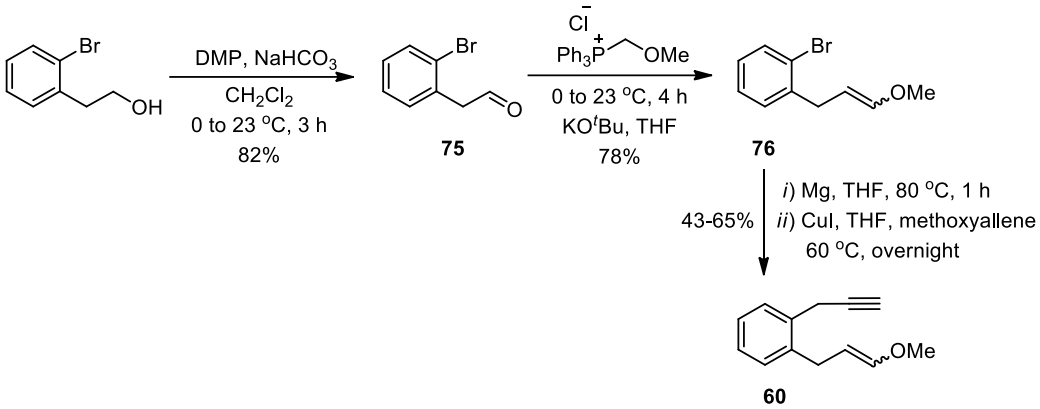
Scheme 26. Initial retrosynthetic analysis of octahydrotridecacene **68**

The synthesis of the tetracenyl-1,7-enyne required the coupling of our first generation synthon **60** with the protected alcohol substrate **74** through Sonogashira reaction, followed by the Au(I)-catalyzed [4+2] cycloaddition to afford compound **72** and then modification of the side chains to introduce the enol ether and alkyne moieties (Scheme 27).



Scheme 27. Retrosynthesis of enyne **70**

First, we focused on the optimization of our simplest 1,7-enyne synthon **60**. In our improved route (Scheme 28), this compound was obtained in only three steps, from the commercially available 2-bromophenethyl alcohol, which underwent oxidation with DMP to the corresponding aldehyde **75**, followed by Wittig olefination with the required triphenylphosphine salt. Subsequent Grignard reaction of enol ether **76** and copper(I)-catalyzed addition to methoxyallene readily provided the desired enyne **60**.

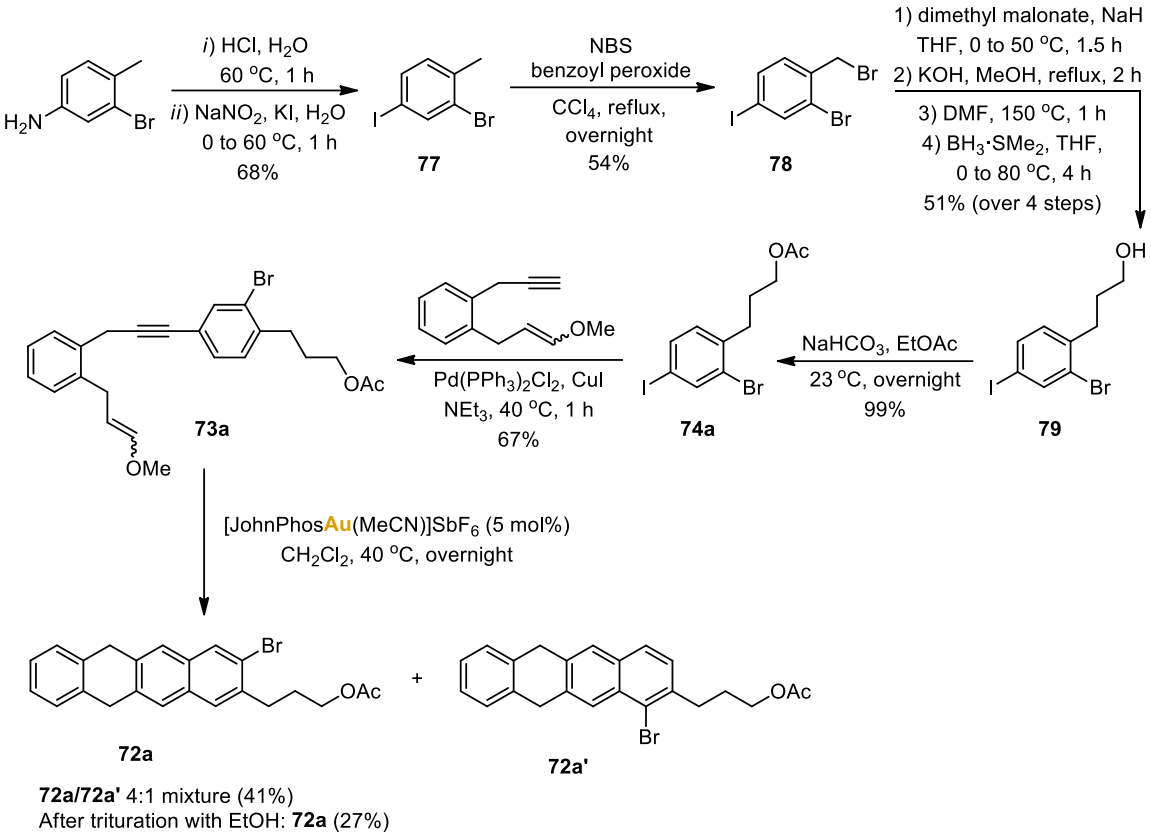


Scheme 28. Improved synthesis of 1,7-enyne **60**

The next step was the preparation of tetracenyl enyne **70**. We planned initially to obtain **70** with the aid of protected alcohol **74a** (Scheme 27), for which an acetate was chosen as the protecting group.

Hence, the synthesis of 1,7-enyne **70** began with the formation of acetate **74a** (Scheme 29). This compound was obtained starting from 3-bromo-4-methylaniline, which was subjected to a Sandmeyer reaction to afford the corresponding iodide **77** in a 68% yield. Subsequent benzylic bromination provided benzyl bromide **78** and after esterification with dimethyl malonate,

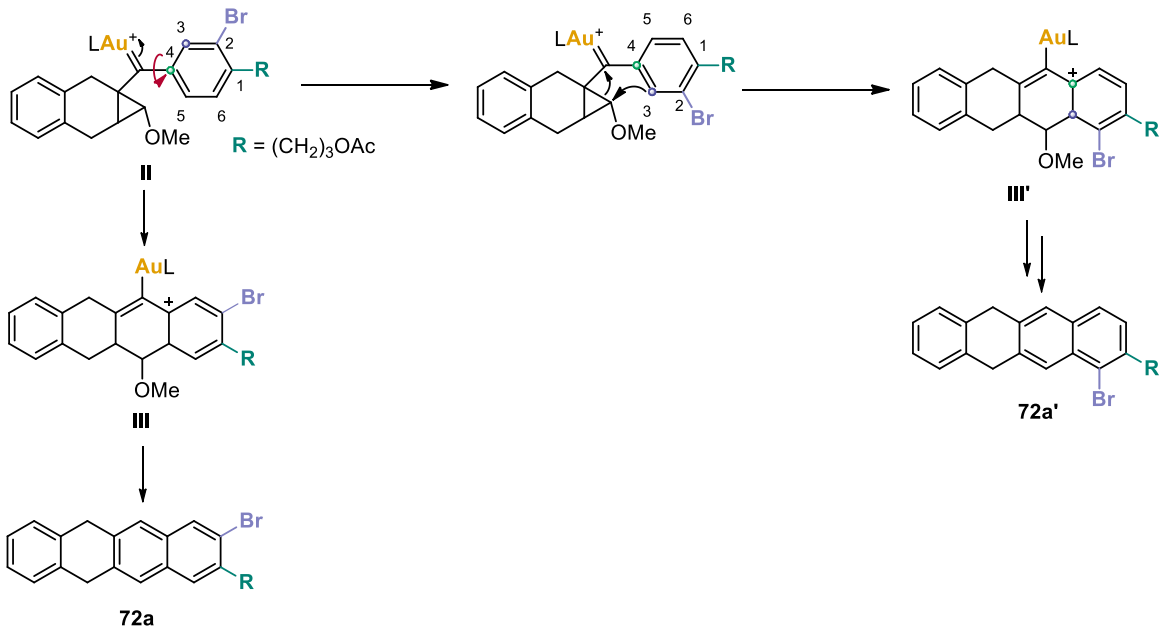
saponification, decarboxylation and reduction with BH_3·DMS, the desired alcohol **79** was obtained. After protection of the alcohol as an acetate, **74a** was subjected to the Sonogashira coupling with **60** and the resulting enyne **73a** underwent the Au(I)-catalzyed [4+2] cycloaddition under the previously optimized conditions.



Scheme 29. Synthesis of acetate-containing dihydrotetracenes **72a**

The [4+2] cycloaddition yielded the desired compound **72a** as a 4:1 mixture of two isomers in 41% yield. Previous examples in which the substrate had one substituent (a methoxy, or a methyl group)[85] led also to the formation of two regioisomers as a result of the Friedel-Crafts-type attack of the aromatic ring through either C5 or C3 in intermediate **II**, which leads to **III** and **III'**, respectively. Column chromatography of the mixture did not afford the pure desired compound **72a**, which was obtained after trituration with ethanol in only 27% yield.

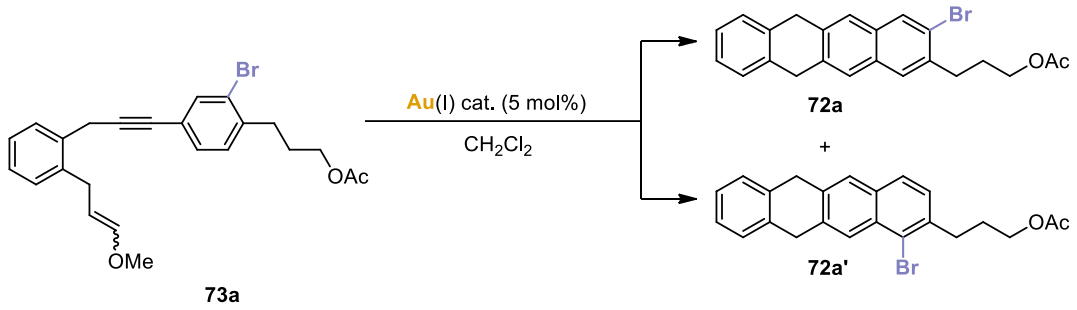
85 Dr. Ruth Dorel, unpublished results, ICIQ, **2015**.



Scheme 30. Formation of regioisomers **72a** and **72a'** in the Au(I)-catalyzed [4+2] cycloaddition

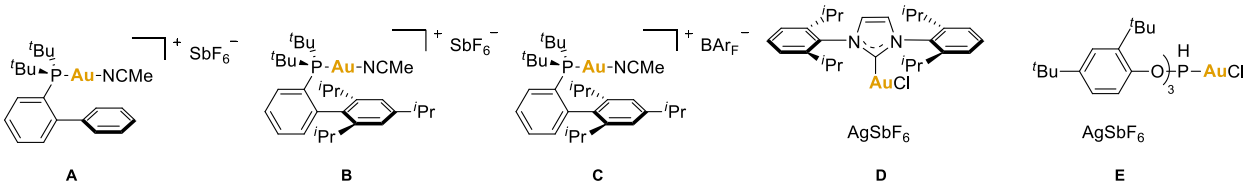
Since the yield of the discussed [4+2] cycloaddition reaction was low, attempts were made to optimize this transformation. We have determined earlier that JohnPhos-Au(I) catalyst **A** had the best performance in this type of reaction at 40 ºC. However, we decided to study how a decrease in temperature or the use of a different catalyst would impact the ratio of the isomers **72a** and **72a'** or the yield. Five complexes **A**–**E** were examined at 23 and 40 ºC (Table 1). When the reaction was performed under the standard conditions but on a smaller scale (Table 1, entry 1), the yield was reasonably improved although the ratio of the isomers remained the same. Lowering the temperature to 23 ºC (Table 1, entry 2) or using catalyst **B** (Table 1, entries 3 and 4) had the same outcome. Catalyst **C** only yielded the desired products at 40 ºC (Table 1, entry 5). By contrast, complex **D** had a better performance at 23 ºC (Table 1, entry 8), only providing the desired linear isomer, although in only 24% yield. Similarly, when the more electrophilic complex **E** was used at 23 ºC (Table 1, entry 10) only traces of isomer **72a'** were observed, but the yield of **72a** was still low. Thus, the formerly optimized conditions using catalyst **A** (Table 1, entry 1) proved to be the most adequate and they were chosen to reproduce the reaction in larger quantities.

Table 1. Optimization of the gold(I)-catalyzed [4+2] cycloaddition of enyne **73a**

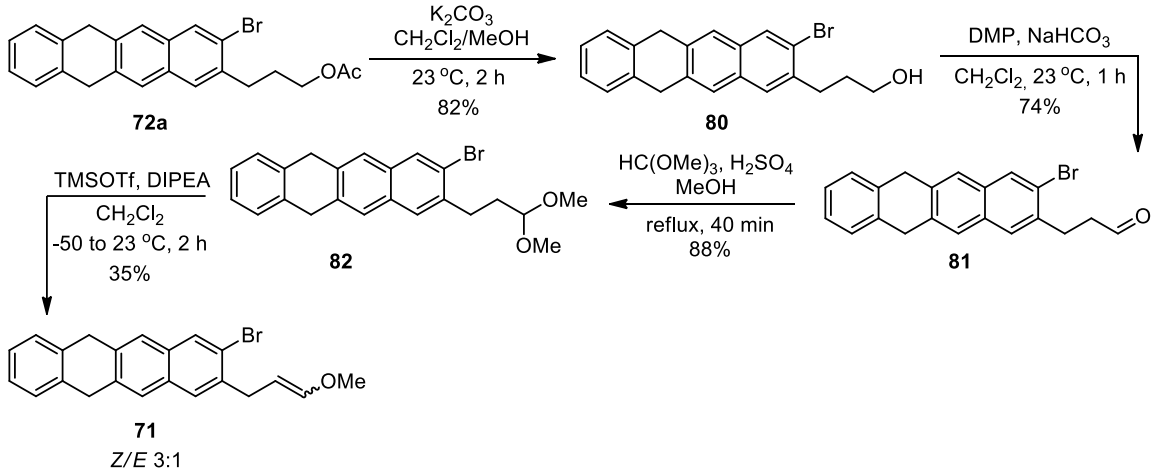


Entry[a]	$[Au]_{cat}$ (mol%)	$AgSbF_6$ (mol%)	T (ºC)	t (h)	Yield 72a (%)[b]	Yield 72a' (%)[b]
1	**A** (5)	-	40	16	56	14
2	**A** (5)	-	23	16	52	20
3	**B** (5)	-	40	16	41	12
4	**B** (5)	-	23	16	45	24
5	**C** (5)	-	40	16	37	9
6	**C** (5)	-	23	16	-	-
7	**D** (5)	5	40	16	10	traces
8	**D** (5)	5	23	16	24	-
9	**E** (5)	5	40	16	39	9
10	**E** (5)	5	23	16	39	traces

[a]Reactions performed on 0.05 mmol scale.
[b]Yields determined by ^{1}H NMR using mesitylene as internal standard.



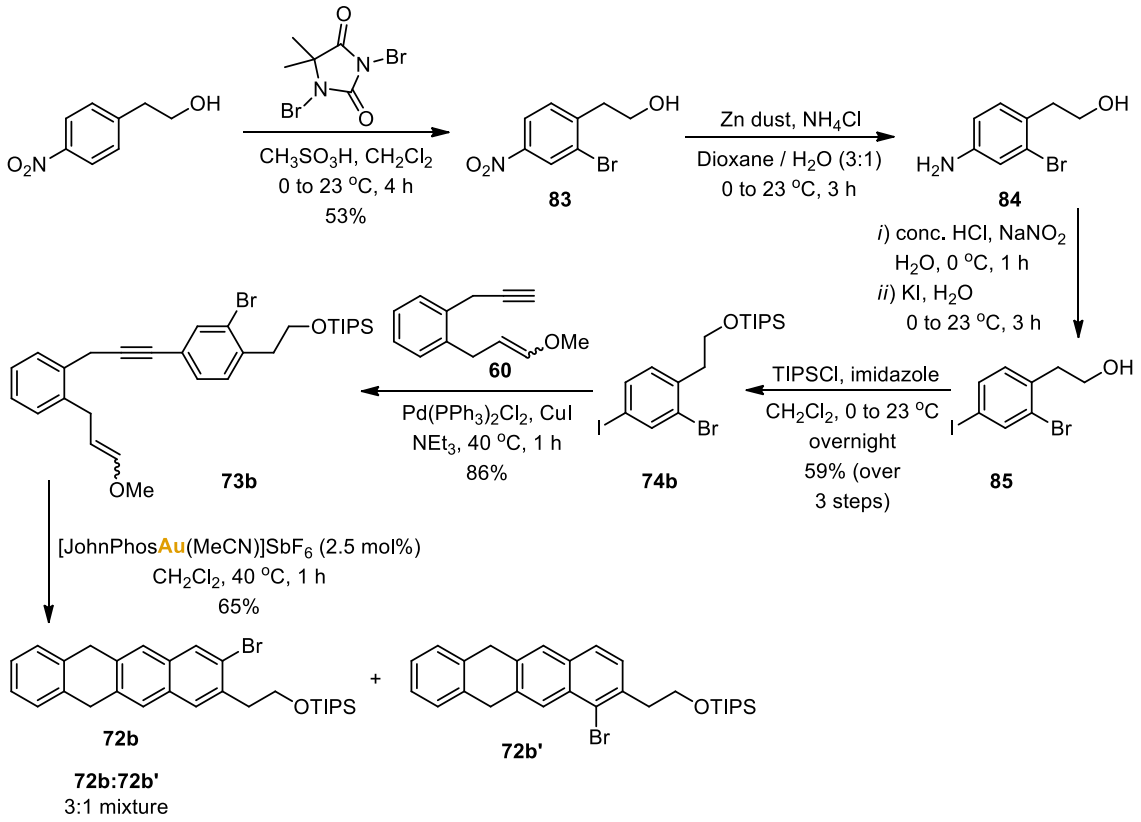
With the acetate **72a** in hand, the introduction of the enyne moiety was next explored (Scheme 31). In a similar manner to our previous approach, the acetate was cleaved by methanolysis and the resulting alcohol **80** was oxidized with Dess-Martin periodinane (DMP) to give aldehyde **81**. This compound was subjected to acetalization to form **82** and then the TMSOTf-promoted elimination of **82** afforded enol ether **71** in modest yield of 35%. Unfortunately, this last reaction had reproducibility issues and **71** could not be synthesised again in reasonable yields by this method.



Scheme 31. Synthesis of enol ether **71**

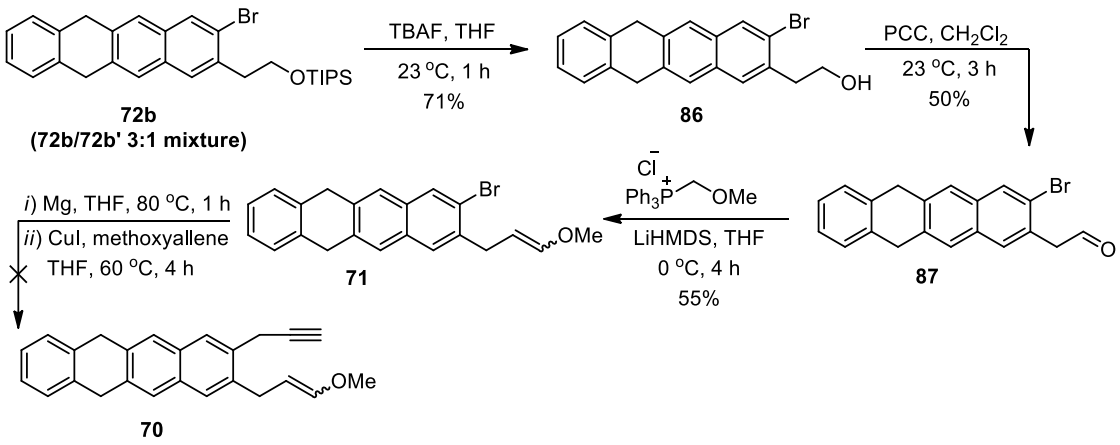
At this stage, we decided to follow a different procedure, in which the enol ether unit would be introduced through Wittig olefination of an aryl acetaldehyde (**87**). In this regard, compound **74b** was selected as the new coupling partner in the Sonogashira reaction and this time the alcohol unit was protected as a silyl ether, as the gold(I)-catalyzed [4+2] cycloaddition with the equivalent acetate gave only 21% yield.

The preparation of **74b** (Scheme 32) started from the commercially available 4-nitrophenethyl alcohol, which was brominated to yield compound **83**. Reduction of the nitro group of **83** to the aniline **84** followed by Sandmeyer reaction and TIPS protection of **85** provided silyl ether **74b**. Sonogashira coupling of iodide **74b** with enyne **60** gave enyne **73b**, which underwent the [4+2] cycloaddition under the standard conditions. The reaction yielded the desired compound as a mixture of two isomers, **72b** and **72b'** in a 3:1 ratio with an improved yield of 65%. The two isomers were inseparable by means of chromatography or crystallization, so the mixture was taken on to the next step.



Scheme 32. Synthesis of silyl ether-containing dihydrotetracene **72b**

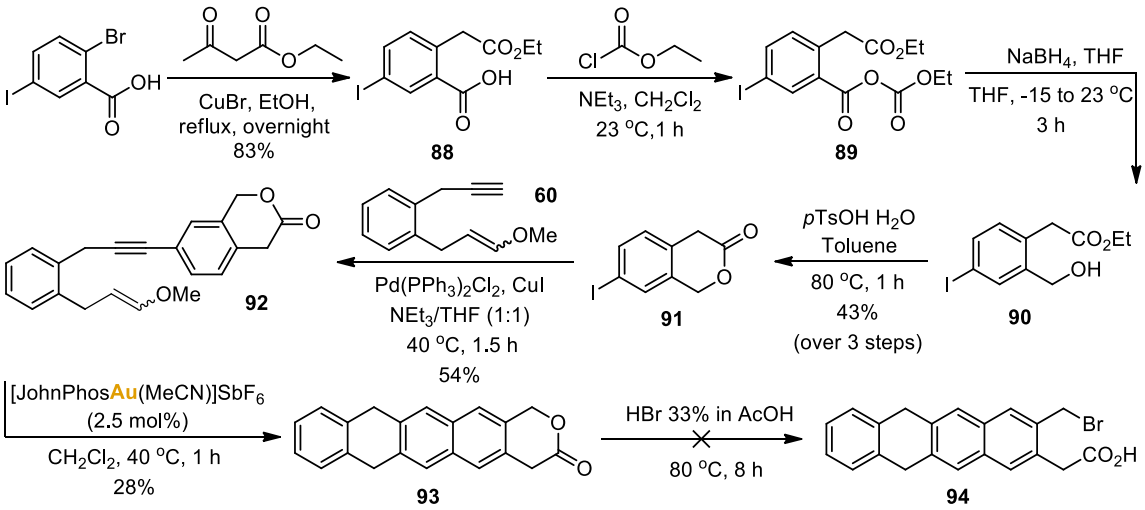
The mixture of silyl alcohols **72b/72b'** was deprotected to afford primary alcohols **86**, which were oxidized to aldehydes **87** (Scheme 33). Then the Wittig reaction was performed and provided enol ether **71** as a 3:1 mixture of regioisomers (2:1 *E*/*Z* mixture for each regioisomer) in a 55% yield. Then, the last step of the synthesis of this enyne precursor was performed to introduce the alkyne moiety *via* reaction with methoxyallene. However, under the previously optimized conditions, the reaction was not successful. Consequently, the copper catalyst, the number of equivalents of methoxyallene and the duration of the reaction were changed with a view to find the optimal reaction conditions, but the desired compound **70** was never observed.



Scheme 33. Attempted synthesis of 1,7-enyne **70**

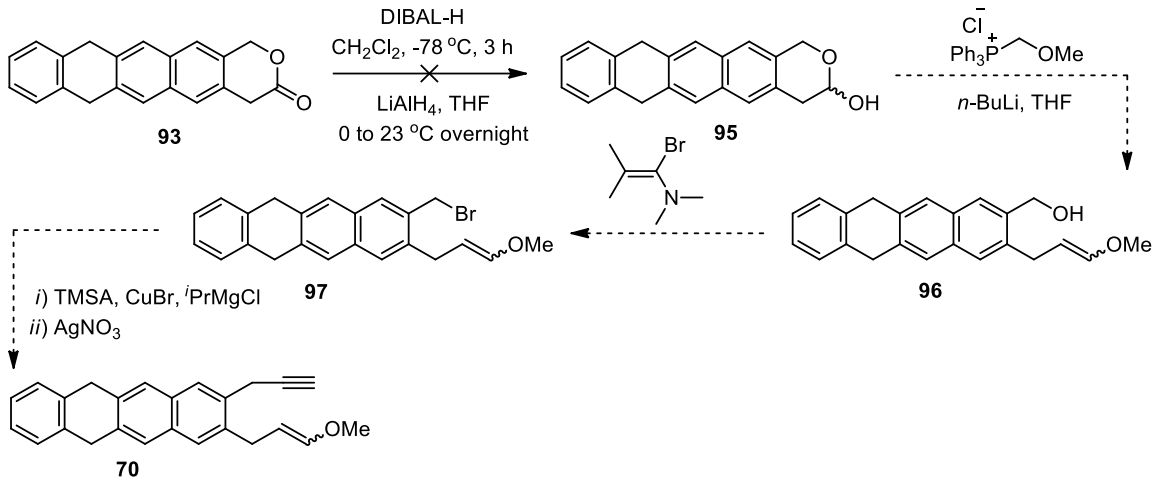
On the basis of these results, the approach towards the targeted enyne **70** was modified again by replacing the substrate that would be coupled with 1,7-enyne **60**, this time with 7-iodoisochroman-3-one (**91**). This compound would simplify the introduction of the alkyne unit, since the alkynylation would take place at a benzyl bromide moiety, rather than a bromo arene as in the previous route. This transformation would occur after Sonogashira coupling of **91**, Au(I)-catalysed [4+2] cycloaddition and opening of the lactone with hydrobromic acid (HBr) (Scheme 34).

The preparation of the desired iodo-substituted isochromanone **91** commenced from 2-bromo-5-iodobenzoic acid, whose bromide moiety was converted into an ester by copper catalyzed nucleophilic aromatic substitution/deacylation (Scheme 34). The carboxylic acid group of **88** was converted into anhydride **89**, which was reduced with $NaBH_4$ to alcohol **90**. Acid-catalyzed lactonization of **90** gave the desired key intermediate **91** in 43% yield. Sonogashira reaction of **91** with **60** led to enyne **92** which underwent the Au(I)-[4+2] cycloaddition under the standard conditions to provide the lactone-containing dihydrotetracene **93** in modest yield. However, the opening of the lactone with HBr 33% in acetic acid failed to give benzyl bromide **94**, presumably because of the low solubility of **93** in acetic acid even at high temperatures.



Scheme 34. Synthesis of lactone-containing dihydrotetracene **93** and its attempted opening with HBr

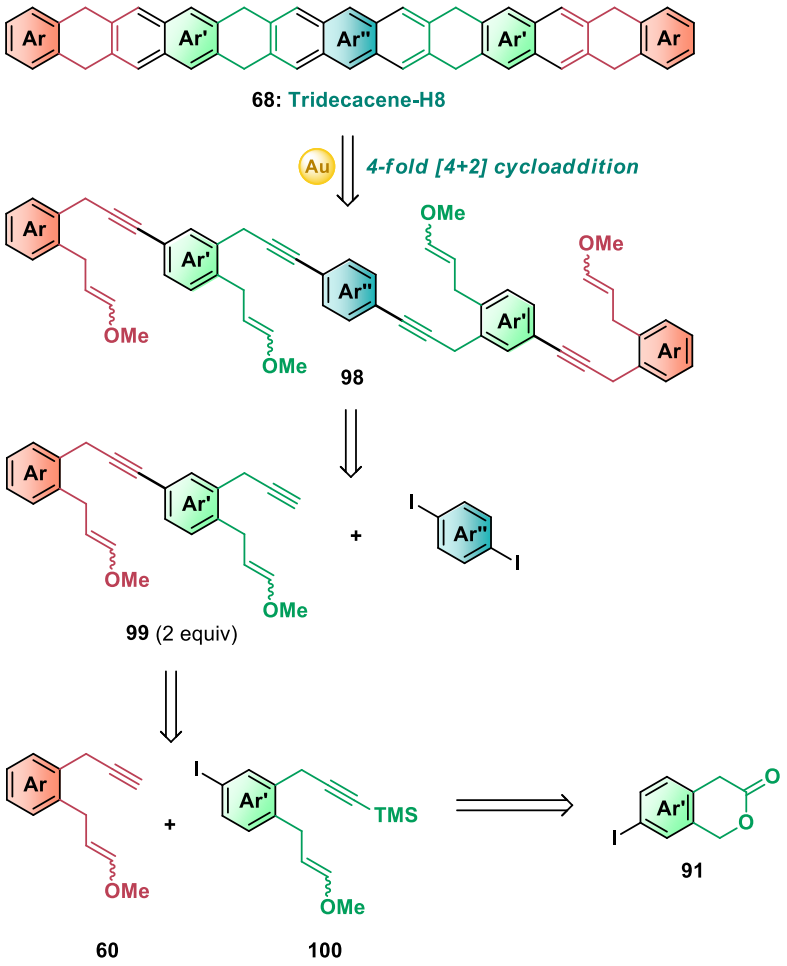
The reduction of lactone **93** to lactol **95** was also attempted (Scheme 35). However, lactol **95** could not be obtained using DIBAL-H or $LiAlH_4$ under different conditions.



Scheme 35. Approach towards enyne **70** by reduction of lactone **93**

Iterative Synthesis of Higher Hydroacenes

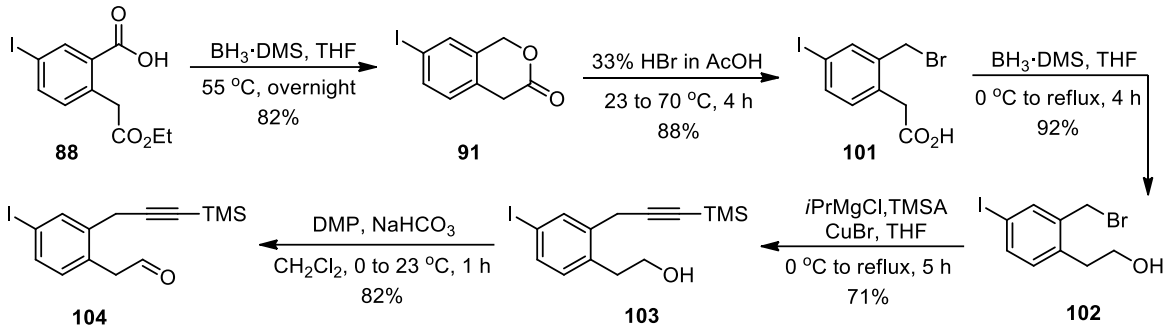
Despite extensive efforts, we could not obtain enyne **70**. All the unsuccessful attempts prompted us to devise a new strategy for the synthesis of octahydrotridecacene (**68**) performing the gold(I)-catalyzed [4+2] cycloaddition key step at the end of the synthesis. Thus, we propose an iterative synthesis based on successive Sonogashira couplings of aryl-tethered 1,7-enynes and diiodinated arenes that would give rise to tetraenynes (Scheme 36). This route involves the Sonogashira coupling of our previously developed 1,7-enyne synthon **60**, as the terminal fragment of the tetraenyne, with a new iodide-substituted 1,7-enyne **100**, which is the internal fragment. Synthon **100** is protected at the alkyne unit with a TMS group, allowing the reaction to take place selectively at its iodide moiety. In turn, this new enyne would be formed from 7-iodoisochroman-3-one (**91**). The acquired dienyne would then be deprotected and subjected to a double cross coupling with 1,4-diiodobenzene, the central fragment, to furnish tetraenyne **98**. Finally, the 4-fold gold(I)-catalyzed [4+2] cycloaddition key step of the synthesis would furnish the desired octahydrotridecacene **68**.



Scheme 36. Second retrosynthesis of octahydrotridecacene **68**

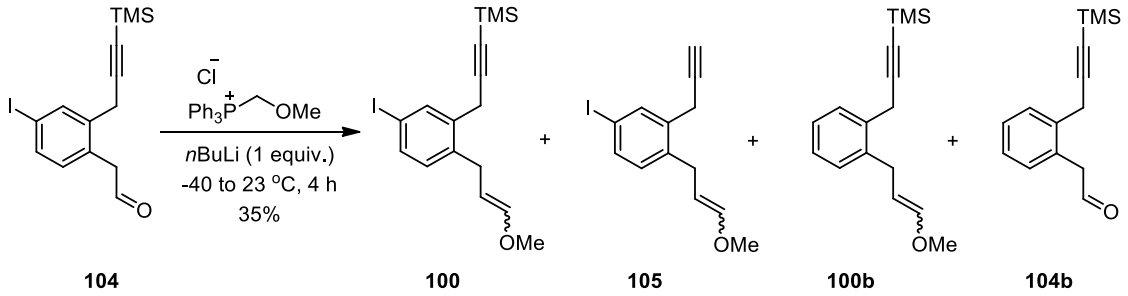
The advantage of this method is its flexibility, enabling the formation of higher hydroacenes of different sizes by changing the size of the central iodinated arene. Furthermore, even though the 4-fold gold(I)-cyclization does not proceed in a completely regioselective manner, we expected that the linear compounds would be the major ones. It is important to remind that the main purpose of this study was not to develop a preparative method for the large-scale synthesis of the final compounds, but rather to furnish enough material for the on surface-assisted dehydrogenation and the study of their electronic properties.

The synthesis of the iodide-substituted enyne **100** began with the improved preparation of lactone **91**, which was now obtained from ester **88** in just one step, after reduction with BH_3·DMS followed by lactonization under the conditions of the acidic work-up (Scheme 37). Then, the lactone moiety of isochromanone **91** was opened with HBr and the carboxylic acid moiety of the resulting benzyl bromide **101** was reduced to the corresponding alcohol **102**. Alkynylation of benzyl bromide **102** gave **103**, which was oxidized with DMP to provide aldehyde **104**.



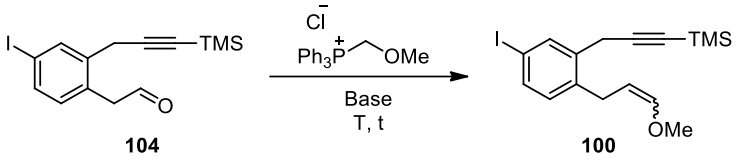
Scheme 37. Synthesis of aldehyde **104**

The Wittig olefination of **104** to introduce the enol ether unit was first attempted under the standard conditions, using KO*t*Bu as the base, but the desired product **100** was not formed as planned, the alkyne being deprotected during the course of the reaction (Scheme 38). Since the Wittig reaction did not render the desired product in presence of KO*t*Bu, the olefination of the aldehyde substrate **104** was studied under different conditions (Table 2). Thus, when *n*-BuLi was employed as the base and the reaction was carried out at -40 to 23 °C (Table 2, entry 2), the desired enol ether **100** was obtained in 35% yield. Again, partial deprotection of the TMS group was observed. In addition, apart from unreacted starting material, the deiodinated enyne **100b** and aldehyde **104b** were also formed as by-products (Scheme 38).



Scheme 38. Attempted Wittig olefination of aldehyde **100** using *n*-BuLi as the base

Performing the reaction at -78 °C only resulted in complete decomposition of the aldehyde (Table 2, entry 3). Additionally, the number of equivalents of salt and base was reduced and the reaction was performed at either -40 or 0 °C (Table 2, entries 4 and 5), but no improvement was observed. The best result was achieved by changing the base to LiHMDS, which completely inhibited the TMS deprotection or dehalogenation. Finally, the reaction was driven to completion by forming the ylide and adding the aldehyde at -40 °C and then allowing the mixture to react at 23 °C for 24 h, leading to the desired enyne **100** in 65% yield (Table 2, entry 6).



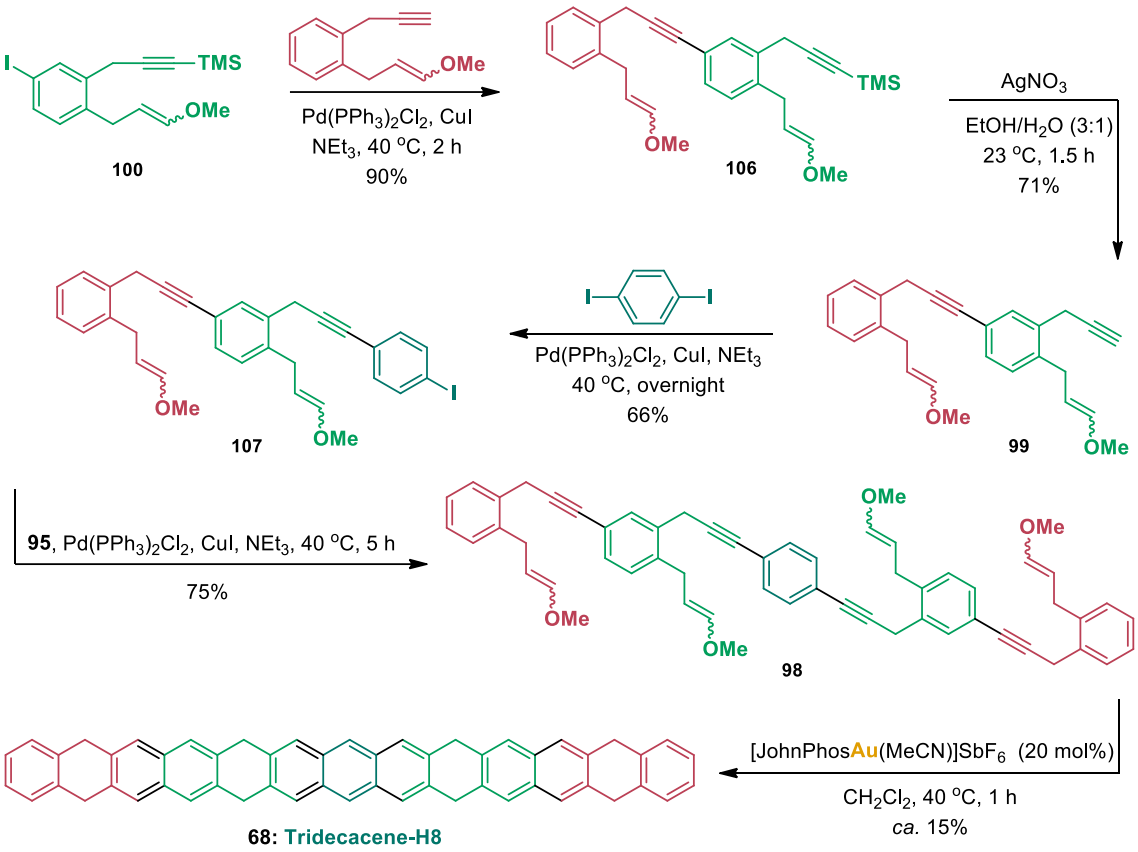
104 100

Table 2. Optimisation of the Wittig olefination of aldehyde **104**

Entry	Base (equiv)	T (ºC)		t (h)		Yield 100 (%)[a]
		Ylide	Aldehyde	Ylide	Aldehyde	
1	KO*t*Bu (1)	0	23	0.5	3	traces
2	*n*-BuLi (2)	-40	23	0.5	3	35
3	*n*-BuLi (2)	-78	-78	0.5	6	decomposition
4	*n*-BuLi (1)	-40	-40	0.5	10	23
5	*n*-BuLi (1)	0	0	0.5	6	33
6	**LiHMDS (1)**	**-40**	**-40 to 23**	**0.5**	**24**	**65**

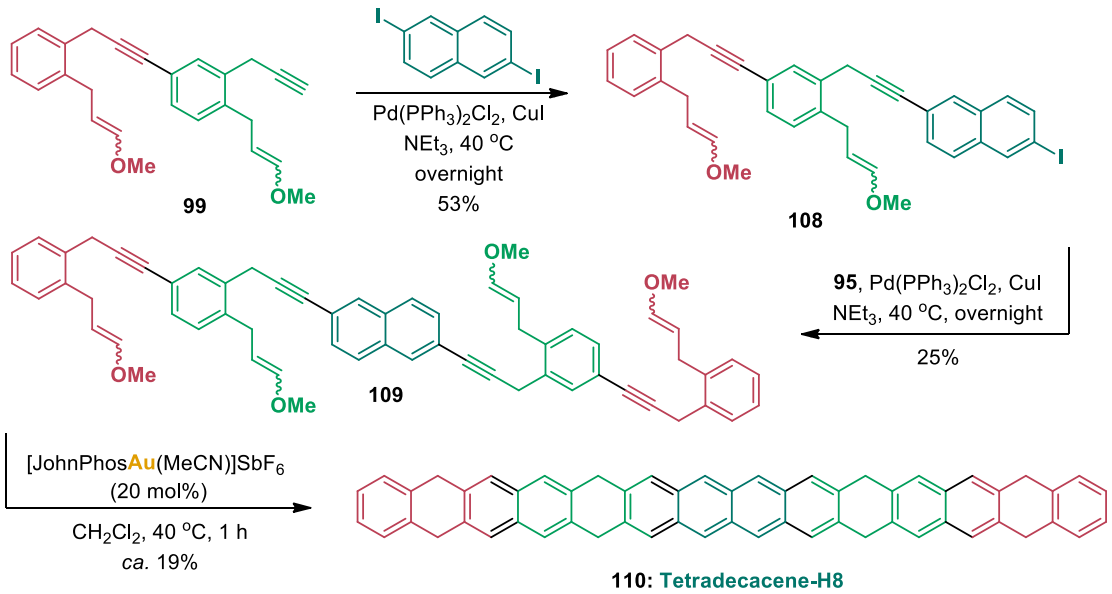
[a]The yields refer to isolated compounds.

The Sonogashira coupling of **100** with synthon **60** successfully provided protected dienyne **106**, whose TMS group was cleaved with $AgNO_3$, to give compound **99** (Scheme 39). Using other nucleophilic reagents, such as potassium carbonate or TBAF, instead of $AgNO_3$ led to isomerisation of the terminally unsubstituted alkyne to the allene. Bisdienyne **99** was subjected to two consecutive Sonogashira couplings, first with 1,4-diiodobenzene and then with another equivalent of bisdienyne **99** to furnish tetraenyne **94**. A direct double Sonogashira coupling, which could have led to the direct formation of **98** from **99**, was also tested. However, it was less selective and led to the formation of a mixture of mono- and doubly coupled enynes, including undesired dehalogenated secondary products. Finally, the 4-fold gold(I)-catalyzed [4+2] cycloaddition yielded the targeted octahydrotridecacene **68**. The structure of the target compound was confirmed by MALDI-MS.



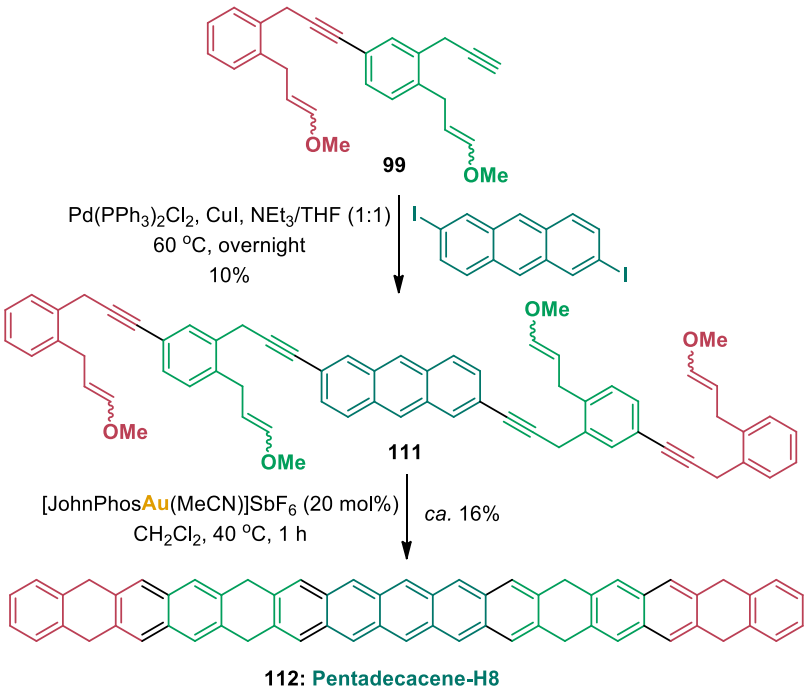
Scheme 39. Synthesis of octahydrotridecacene **68**

Similar syntheses were then performed using bisdienyne **99** in order to obtain tetrahydrotetradecacene and tetrahydropentadecacene. For the synthesis of tetrahydrotetradecacene, 2,6-diiodonaphthalene was used as the central coupling partner to form tetraenyne **109**. After the 4-fold Au(I)-catalyzed [4+2] cycloaddition, tetrahydrotetradecacene **110** was obtained in a yield of *ca.* 19% (Scheme 37).



Scheme 40. Synthesis of octahydrotetradecacene **110**

Likewise, for the precursor of the next analogue, 2,6-diiodoanthracene was used as the central core (Scheme 41). The double Sonogashira reaction occurred preferentially and gave tetraenyne **111**, albeit in low yield even using excess of enyne **99**. Subsequent 4-fold cyclization afforded the desired tetrahydropentadecacene **112**.

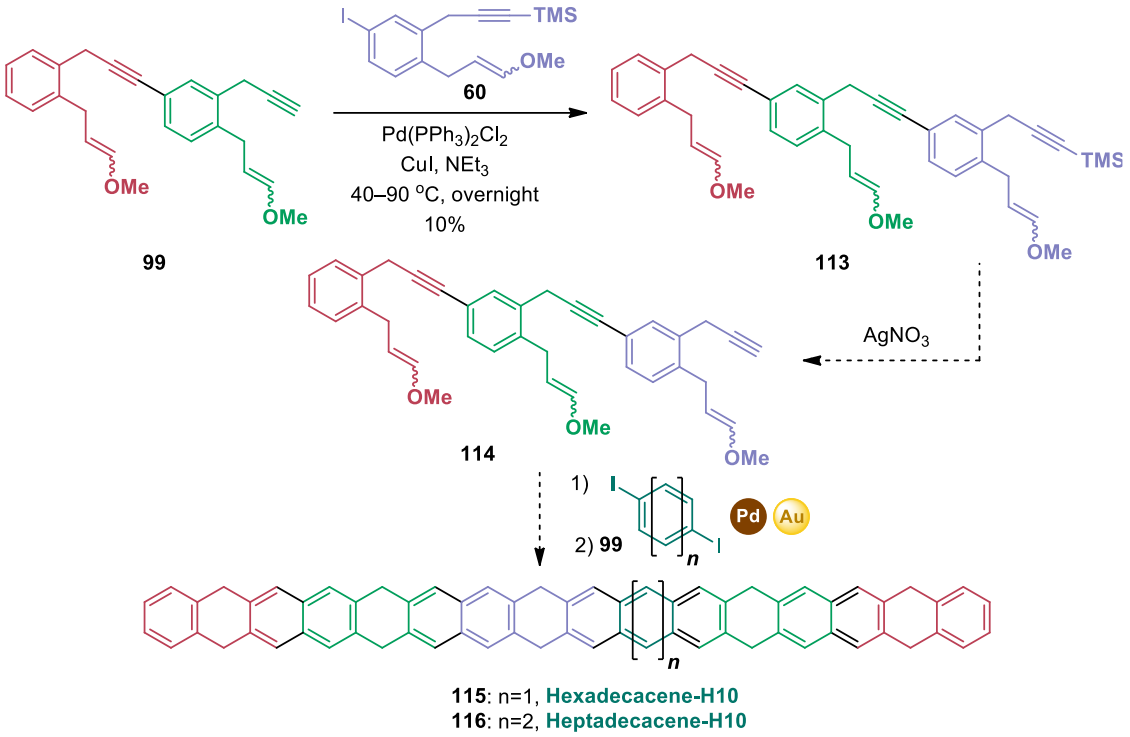


Scheme 41. Synthesis of octahydropentadecacene **112**

All three hydroacenes, **68**, **110** and **112** were isolated by precipitation with a mixture of CH_2Cl_2/Et_2O, followed by filtration. It is worth mentioning that these compounds were obtained as mixtures of several isomers, as each of the Au(I)-cyclizations occurred with moderate regioselectivity. Because of the low solubility of the resulting solids, purification by column chromatography could not be performed. Thus, the solids have been directly submitted to MS analysis. Pleasingly, the analysis of compound **68** showed a single peak with the expected mass of octahydrotridecacene, indicating that only the mixture of isomers was present in the solid (see *Experimental Section*). By contrast, examination of the solids obtained from the cycloadditions of enynes **109** and **111** showed multiple peaks, possibly because of fragmentation. Nevertheless, the masses of compounds **110** and **112** could be successfully detected.

With three new acene precursors in hand, the synthesis of even larger analogues was then investigated, by performing another iterative sequence. Thus, the preparation of trienyne **114** was also intended by Sonogashira coupling of bisdienyne **99** with **100** and subsequent TMS deprotection of **113** (Scheme 42). Enyne **114** would have then been employed in the synthesis of the precursors of hexadecacene and heptadecacene, **115** and **116**. However, the Sonogashira coupling only provided the enyne **113** in only 10% yield, despite testing several temperatures, NEt_3/THF solvent concentrations

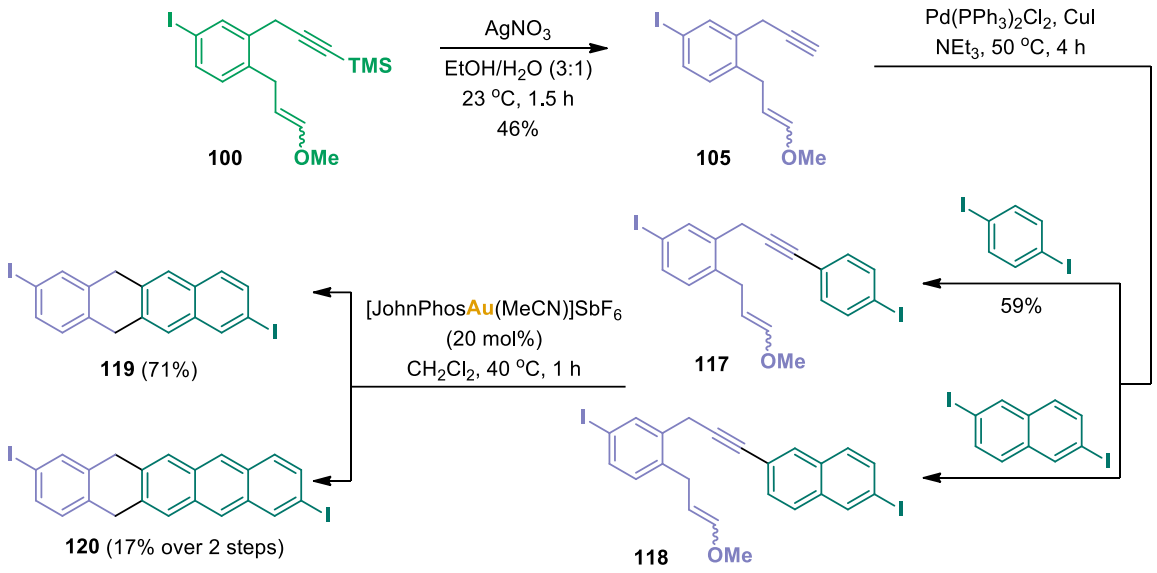
and amounts of catalyst loading. Unfortunately, the obtained quantity of **113** was not sufficient in order to examine its deprotection.



Scheme 42. Attempted synthesis of trienyne **114** and proposed preparation of hydroacenes **115** and **116**

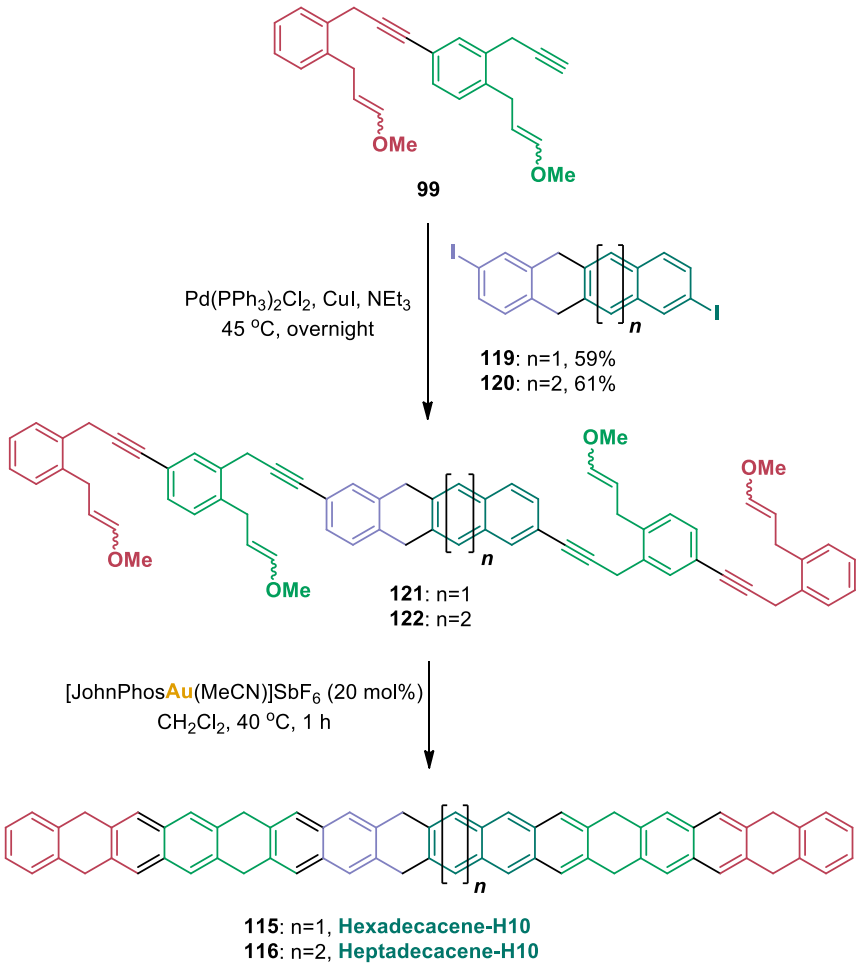
Since our efforts towards obtaining enyne **114** were not successful, we envisaged that instead of employing this compound in the synthesis of the higher hydroacene derivatives, the best alternative was to increase the size of the central coupling partner. Therefore, dienyne **99** would be coupled with larger diiodinated polyarenes (**119** and **120**) with 4 and 5 rings to afford hydroacenes **115** and **116.**

These diiodinated compounds **119** and **120** were also obtained by taking advantage of our gold(I)-catalyzed [4+2] cycloaddition (Scheme 43). Their synthesis started by deprotecting enyne **100** to afford compound **105**. This free enyne was then subjected to Sonogashira coupling with either 1,4-diiodobenzene or 2,6-diiodonaphthalene to provide enynes **117** and **118**, respectively. Subsequent Au(I)-catalyzed cyclization of these enynes afforded the desired diiodide-substituted dihydrotetracene **119** and dihydropentacene **120**.



Scheme 43. Synthesis of diiodide-substituted hydroacenes **119** and **120**

With compounds **119** and **120** in hand, the attention was moved to the synthesis of hydroacenes **115** and **116** (Scheme 44). By employing this synthetic sequence, the acene precursors would have improved stability, containing more non-aromatic rings, whereas the longest aromatic segment is made of 3 rings in case of **115** and 4 rings for **116**, to make them less prone to oxidation or dimerization. Hence, the double Sonogashira coupling of the diiodinated hydroacenes with enyne **99** successfully afforded tetraenynes **121** and **122** and their 4-fold gold(I)-catalyzed [4+2] cycloaddition was next attempted. The reactions gave rise to solid products, which were isolated following the same method employed for the smaller analogues, precipitation and vacuum filtration, and were then submitted to MS analysis. Unfortunately, the desired products could not be identified by examination with the MALDI or LDI-MS techniques, as their mass could not be detected. Furthermore, the small amount and their reduced solubility prevented the NMR analysis from being performed. Since we could not demonstrate that hydroacenes **115** and **116** were obtained, the solids have already been submitted to investigation by means of microscopy to obtain the images that would confirm their structures. Moreover, their dehydrogenation will be explored in the foreseeable future to obtain hexadecacene and heptadecacene, both unprecedented acenes.



Scheme 44. Synthesis of decahydroacenes **115** and **116**

STM Investigation of the Surface-Assisted Synthesis of Tridecacene

After the successful synthesis of undecacene, we envisioned that the new hydroacene molecules, starting with octahydrotridecacene **68**, could also be used as stable direct precursors for the on-surface synthesis of the parent acenes.

In this sense, the molecules of **68** were deposited on a Au(111) surface by sublimation under UHV conditions and successfully provided the unprecedented octahydrotridecacene by dehydrogenative aromatization (Figure 8). Preliminary investigation by STM showed that the dehydrogenation took place sequentially after annealing the precursors at high temperature.[86] This work is currently ongoing and further experiments will be performed to fully characterize the electronic properties of tridecacene. The internal structure of the final product will be uncovered with the aid of high-resolution noncontact atomic force microscopy (nc-AFM). Furthermore, the electronic characteristics of the generated new molecules will also be studied with the assistance of scanning tunneling spectroscopy (STS) measurements and high resolution differential conductance (dI/dV) mapping to determine the transport gap value and observe the frontier HOMO–LUMO molecular orbitals.

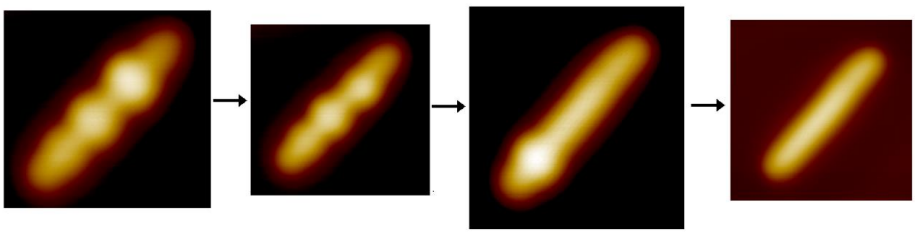
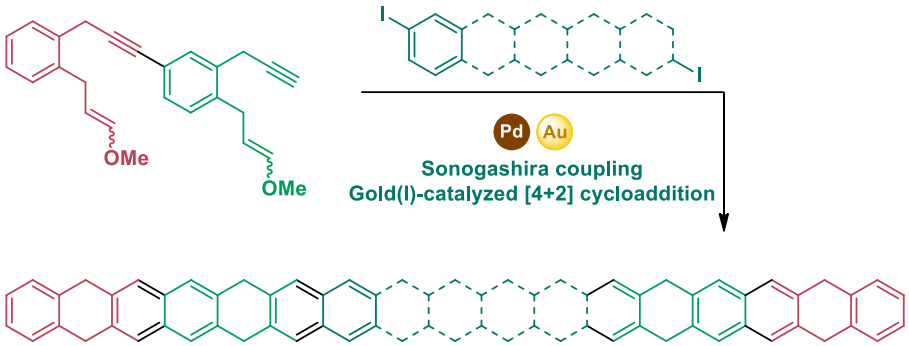


Figure 8. STM images of the sequential dehydrogenation of **68** to tridecacene

86 Preliminary studies by Prof. Szymon Godlewski at *Centre for Nanometer-Scale Science and Advanced Materials* (NANOSAM) in Krakow, Poland.

CONCLUSIONS AND OUTLOOK

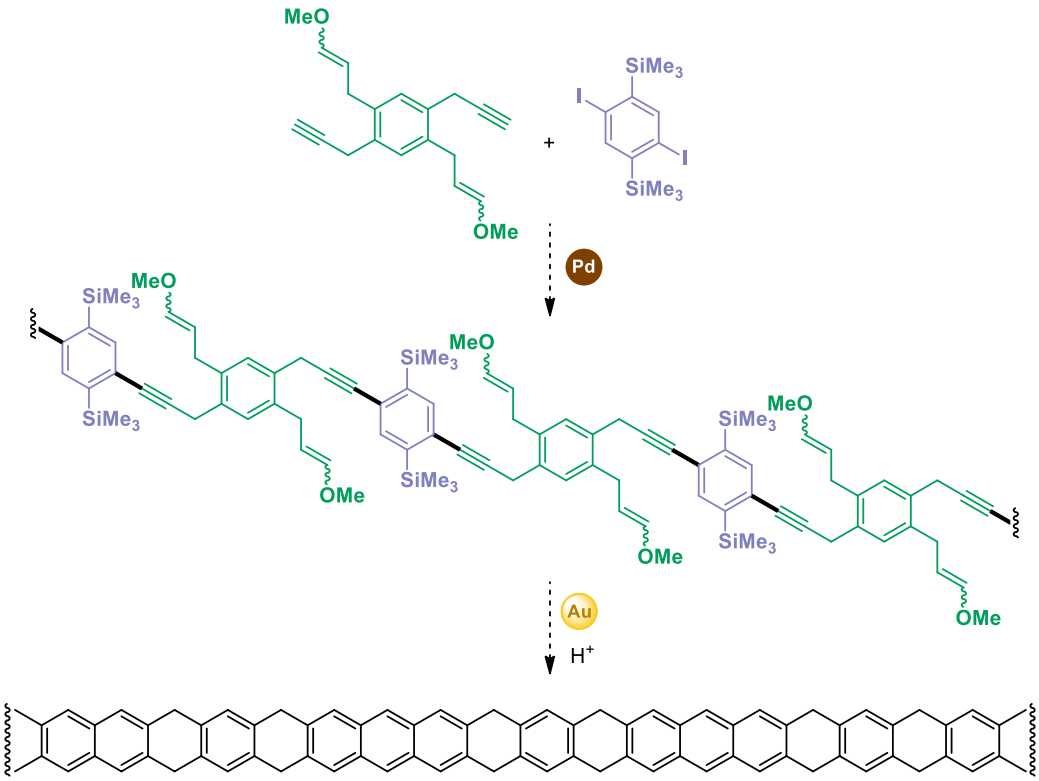
To sum up the results presented in this chapter, a new iterative strategy has been devised for the synthesis of partially hydrogenated higher analogues of the acene series and provided the desired derivatives, starting with tridecacene-H8. This method is based on successive Sonogashira couplings between 1,7-enynes and diiodinated arenes, as well as multiple Au(I)-catalyzed [4+2] cycloadditions, which are robust transformations that proceed under mild conditions. Additionally, by following our novel synthetic routes, the 1,7-enynes are easily accessed in just a few days, through common procedures.



Scheme 45. General synthesis of higher hydroacenes

The Au(111) surface-assisted dehydrogenative aromatization of tridecacene-H8 has already been investigated and successfully led to the unprecedented tridecacene, the longest acene obtained up to date, demonstrating that this method can also be applied to the synthesis of higher acene analogues. Efforts are currently being made to study and fully characterize the electronic properties of tridecacene and the following members of the series by high-resolution scanning probe techniques.

Our 1,7-enynes could also be suitable precursors for the first polymeric acene. This compound could be achieved by Sonogashira coupling of a double 1,7-enyne synthon with an adequate diiodinated partner, followed by a multiple Au(I)-catalyzed [4+2] cycloaddition of the resulting polyenyne and concomitant protodesilylation.



Scheme 46. Proposed synthesis of the first polymeric acene

EXPERIMENTAL SECTION

General Methods

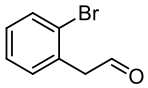
Reactions under argon atmosphere were carried out in solvents dried by passing through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA). Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck GF_{234}) using UV light as the visualizing agent and a solution of vanillin, potassium permanganate, dinitrophenylhydrazine or ninhydrin as stain. Reactions were followed using a GC–MS apparatus or by TLC. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) or an automated flash chromatographer CombiFlash Companion. Preparative TLC was performed on 20 cm × 20 cm silica gel plates (2.0 mm or 1.0 mm thick, Analtech). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. All reagents were used as purchased without further purification, unless otherwise stated.

NMR spectra were recorded in deuterated solvents at 25 ºC on a Bruker Avance 300, 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus, or at 120 ºC on a Bruker Avance 500 Ultrashield apparatus. Chemical shifts (d) are reported in parts per million (ppm) and referenced to residual solvent or tetramethylsilane. Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on a Waters LCT Premier Spectrometer (ESI and APCI) or on an Autoflex Broker Daltonics (MALDI and LDI). Melting points were determined using a Büchi melting point apparatus.

Synthetic Procedures and Analytical Data

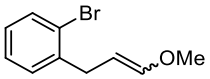
Synthesis of Enyne Precursors

*Improved Synthesis of the 1,7-Enyne **60***



2-(2-Bromophenyl)acetaldehyde (75). To a solution of 2-(2-bromophenyl)ethan-1-ol (1 equiv, 10.0 g, 50.24 mmol) in HPLC grade CH_2Cl_2 (350 mL) were sequentially added DMP (1.2 equiv, 25.62 g, 60.29 mmol) and $NaHCO_3$ (2 equiv, 8.44 g, 100.52 mmol). The resulting pale yellow mixture was stirred at 23 ºC for 1 h and then a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated and washed with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The yellow residue was purified through column chromatography (cyclohexane/EtOAc 95:5) to yield the product as a pale yellow oil (8.19 g, 41.20 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.7 Hz, 1H), 7.91 (td, *J* = 8.0 Hz, 1H), 7.34 (td, *J* = 7.5 Hz, 1H), 7.26 (dd, *J* = 7.7 Hz, 1H), 7.21 (td, *J* = 7.8 Hz, 1H), 3.89 (d, *J* = 1.7 Hz, 2H).
^{13}C NMR (500 MHz, $CDCl_3$) δ 198.3, 133.0, 132.6, 131.8, 129.3, 127.9, 125.0, 50.5.
Spectral data are in accordance with the ones previously reported.[87]



1-Bromo-2-(3,3-dimethoxypropyl)benzene (76). A solution of potassium tert-butoxide (1.16 equiv, 4.20 g, 36.71 mmol) in THF (43 mL) was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (1.1 equiv, 11.93 g, 34.91 mmol) in THF (37 mL) at 0 ºC. The color of the mixture turned from dark orange to red. After stirring for 40 min at 0 ºC the reaction was allowed to warm up to room temperature. Then a solution of **75** (1 equiv, 6.30 g, 31.65 mmol) in THF (20 mL) was added dropwise at 0 ºC and the mixture was then stirred at 23 ºC for 4 h. The reaction was then quenched by addition of sat. aq. NH_4Cl solution (20 mL) and the product was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated. Chromatographic purification (cyclohexane to cyclohexane/CH_2Cl_2 9:1) of the crude material yielded the title compound as a yellow oil (2.5:1 *E*/*Z* ratio, 5.57 g, 24.53 mmol, 78% yield).

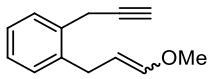
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 1.4H), 7.30 (dd, *J* = 11.0, 4.8 Hz, 0.4H), 7.23 (dd, *J* = 8.8, 4.3 Hz, 1.4H), 7.10 – 7.03 (m, 1.4H), 6.49 – 6.37 (m, 1H, *E*), 6.04 (dd, *J* = 6.1, 0.9 Hz, 0.4H, *Z*),

87 Chang, C.-F.; Huang, C.-Y.; Huang, Y.-C.; Lin, K,-Y.; Lee, Y.-J.; Wang, C.-J. *Syth. Commun.* **2010**, *40*, 3452 – 3466.

4.89 (dt, *J* = 12.7, 7.3 Hz, 1H, *E*), 4.57 (ddd, *J* = 7.4, 6.8, 5.8 Hz, 0.4H, *Z*), 3.64 (d, *J* = 0.8 Hz, 1.2H, *Z*), 3.58 – 3.48 (m, 3.8H), 3.37 (dd, *J* = 7.4, 1.2 Hz, 2H, *E*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.5, 141.0, 133.1, 132.8, 132.7, 130.7, 130.2, 128.3, 127.8, 127.6, 127.6, 127.6, 124.6, 103.7, 100.2, 59.8, 56.2, 43.8, 34.4.

Spectral data are in accordance with the ones previously reported.[88]



1-(3-Methoxyallyl)-2-(prop-2-yn-1-yl)benzene (60).[82] A large MW tube containing Mg turnings (214 mg, 3.52 mmol) was flame dried under an Ar stream, cooled, and charged with 3 mL of anhydrous THF followed by 65 µL of 1,2-dibromoethane. After 2 min stirring at 60 ºC (turbidity, mixture started bubbling), a solution of **76** (1 equiv, 1.50 g, 6.60 mmol) in anhydrous THF (4 mL) was added dropwise. After heating at 80 ºC for 1 h, the reaction was cooled down to room temperature and added over a mixture of CuI (2 mol%, 26 mg, 0.13 mmol) and methoxyallene (1 equiv, 0.56 mL, 6.60 mmol) in anhydrous THF (2 mL). The resulting mixture was heated at 60 ºC for 4 h and then cooled down to room temperature, diluted with EtOAc (10 mL) and quenched by the addition of a saturated solution of $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (cyclohexane to cyclohexane/CH_2Cl_2 19:1) gave the title compound as a colorless oil (2.5:1 *E*/*Z* ratio, 632 mg, 3.40 mmol, 52% yield).

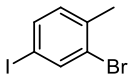
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 9.5, 5.3, 1.9 Hz, 1.8H), 7.28 – 7.22 (m, 4.2H), 6.38 (dt, *J* = 12.6, 1.3 Hz, 1H, *E*), 6.03 (dt, *J* = 6.1, 1.5 Hz, 0.4H, *Z*), 4.90 (dt, *J* = 12.7, 7.0 Hz, 1H, *E*), 4.50 (td, *J* = 7.4, 6.2 Hz, 0.4H, *Z*), 3.69 (s, 1.2H, *Z*), 3.65 (d, *J* = 2.7 Hz, 0.7H, *Z*), 3.64 (d, *J* = 2.6 Hz, 2H, *E*), 3.56 (s, 3H, *E*), 3.46 (dd, *J* = 7.4, 1.5 Hz, 0.7H, *Z*), 3.35 (dd, *J* = 7.0, 1.2 Hz, 2H, E), 2.22 (t, *J* = 2.7 Hz, 1.4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.45, 146.85, 139.23, 139.06, 134.31, 134.22, 129.30, 129.19, 128.82, 128.56, 127.33, 127.20, 126.74, 126.52, 104.51, 100.91, 82.25, 81.99, 70.84, 70.73, 59.82, 56.11, 31.14, 27.72, 22.53, 22.28.

Spectral data are in accordance with the ones previously reported.[82]

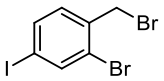
88 Jiménez-Nuñez, E.; Răducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152 – 6155.

*Attempted synthesis of tetracenyl-1,7-enyne **70***



2-Bromo-4-iodo-1-methylbenzene (77). A solution of the amine hydrochloride was prepared by adding with vigorous stirring 34 mL of deionized water to 3-bromo-4-methyl aniline (1.0 equiv, 25.02 g, 134.31 mmol) followed by 34 mL of concentrated HCl. The solution was heated to 60 °C and stirred for 30 min to improve the solubility and reduce the particle size and then it was cooled to 0 °C. A solution of $NaNO_2$ (1.1 equiv, 9.87 g, 143.22 mmol) in 22 mL H_2O was added dropwise to the amine hydrochloride solution maintaining the temperature at 0–5 °C. Then a solution of KI (1.1 equiv, 23.63 g, 24.00 mmol) in 24 mL H_2O was added dropwise with vigorous stirring maintaining the temperature at 0–5 °C. After most of the N_2 evolved, the reaction mixture was heated to 60 °C and stirred for 1 hour, cooled to 23 ºC and diluted with EtOAc. The organic layer was washed with $Na_2S_2O_3$ (3 × 150 mL) and brine (3 × 150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography (cyclohexane) provided the title compound as a transparent liquid (27.12 g, 91.33 mmol, 68% yield).

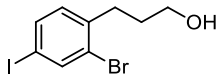
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.96 (dd, *J* = 8.0, 0.6 Hz, 1H), 2.34 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 137.8, 136.4, 132.4, 125.9, 90.6, 22.7.
The spectroscopic data were consistent with those previously reported.[89]



2-Bromo-1-(bromomethyl)-4-iodobenzene (78). NBS (1.5 equiv, 27.6 g, 0.103 mol) and benzoyl peroxide (0.022 equiv, 540 mg, 2.23 mmol) were sequentially added to a solution of **77** (1.0 equiv, 30.73 g, 103.13 mmol) in $CHCl_3$ (1.3 M, 80 mL). The resulting mixture was refluxed overnight, then cooled down to 23 ºC and the volatiles were removed under reduced pressure. Purification by column chromatography (cyclohexane) gave the title compound as a transparent oil (20.93 g, 55.69 mmol, 54% yield).[90]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.7 Hz, 1H), 7.63 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 4.53 (s, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 137.1, 136.8, 132.5, 125.2, 94.6, 32.6.

89 Shultz, D. A.; Hollomon, M. G. *Chem. Mater.* **2000**, *12*, 580–585.
90 Procedure adapted from *reference 82*.



3-(2-Bromo-4-iodophenyl)propan-1-ol (79). Sodium hydride (1.8 equiv, 1.48 g, 61.72 mmol, 60% in mineral oil) was suspended in THF (0.11 M, 306 mL) and cooled to 0 ºC. Dimethyl malonate (1.05 equiv, 4.1 mL, 35.51 mmol) was added dropwise over a 30 minute period and the reaction was stirred for an additional 30 min at 0 ºC. A solution of **78** (1.0 equiv, 12.74 g, 33.68 mmol) in THF (20 mL) was then added in a single portion causing the immediate formation of a white precipitate and the mixture was heated at 50 ºC for 1 h. After cooling down to 23 ºC, the cloudy white suspension was diluted with EtOAc (300 mL) and washed with H_2O (300 mL). The aqueous layer was extracted with EtOAc (300 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure.

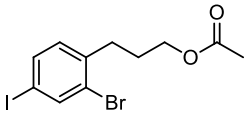
The crude diester was dissolved in MeOH (0.23 M, 150 mL) and solid KOH (5.0 equiv, 9.45 g, 168.49 mmol) was added at 23 ºC. The resulting mixture was refluxed for 2 h, then cooled down to 23 ºC and the volatiles removed under reduced pressure. The solid was dissolved in H_2O (250 mL) and the aqueous mixture was washed with EtOAc (300 mL) and then acidified by the slow addition of concentrated HCl to pH < 1. The product was extracted with EtOAc (3 × 200 mL) and the combined organic layers were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to obtain pure diacid as a white solid.

The diacid was directly dissolved in DMF (1 M, 35 mL) and heated at 150 ºC for 1 h. After cooling down to 23 ºC the pH was adjusted to 14 by the addition of 2.0 M solution of KOH. The aqueous phase was washed with Et_2O (2 × 200 mL) and then acidified by the slow addition of concentrated HCl to pH < 1. The product was extracted with EtOAc (3 × 200 mL) and the combined organic layers were washed with brine (300 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to obtain the crude carboxylic acid as an orange solid, which was taken on to the next step without further purification.

$BH_3{\cdot}SMe_2$ (2.2 equiv, 7.03 mL, 74.09 mmol) was added dropwise to a solution of the crude carboxylic acid in anhydrous THF (0.15 M, 225 mL) at 0 ºC. Once the addition was completed the ice bath was removed, the resulting mixture was allowed to warm to 23 ºC and then heated gradually to reflux. After refluxing at that temperature for 2 h, the mixture was cooled to 0 ºC and quenched by slow addition of 1 M solution of HCl (250 mL). The product was extracted with Et_2O (3 × 200 mL) and the combined organic layers washed with brine (350 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 4:1) afforded the title compound as a colourless oil (5.86 g, 17.19 mmol, 51% yield over 4 steps).[90]

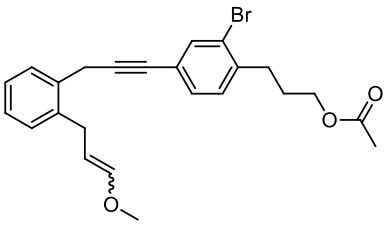
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 2.80 – 2.75 (m, 2H), 1.89 – 1.81 (m, 2H), 1.50 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 140.7, 136.6, 132.0, 125.4, 91.1, 61.8, 32.6, 32.1.



3-(2-Bromo-4-iodophenyl)propyl acetate (74a). A mixture of **79** (1.0 equiv, 7.20 g, 20.08 mmol), Ac_2O (5.0 equiv, 10 mL, 105.5 mmol) and $NaHCO_3$ (2.0 equiv, 3.55 g, 42.19 mmol) in EtOAc (0.17 M, 125 mL) was stirred at 23 ºC for the 24 h. After completion of the reaction, the mixture was filtered and the filtrate was concentrated. To the residue was added dichloromethane (200 mL) and water (75 mL) and the phases separated. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 95:5) afforded the title compound as a pale yellow oil (7.61 g, 19.88 mmol, 99% yield).[91]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 2.74 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.04 (s, 3H), 1.95 – 1.88 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 140.7, 140.3, 136.6, 131.8, 125.3, 91.4, 63.6, 32.3, 28.5, 20.9.

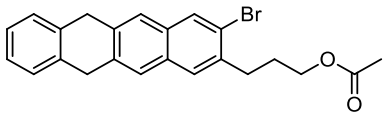


3-(2-Bromo-4-(3-(2-(3-methoxyallyl)phenyl)prop-yn-1-yl)phenyl)propyl acetate (73a). $PdCl_2(PPh_3)_2$ (149 mg, 212 μmol, 5 mol%) and CuI (72 mg, 377 μmol, 10 mol%) were suspended in Et_3N (19 mL) and the mixture was bubbled with Ar for 10 min. A solution of **74a** (1.0 equiv, 1.44 g, 3.76 mmol) and **60** (1.0 equiv, 700 mg, 3.76 mmol) in degassed NEt_3 (19 mL) were subsequently added and the reaction was stirred at 40 ºC for 1 h. Then the mixture was diluted with EtOAc (30 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/NEt_3 99:1) afforded the title compound as an yellow oil (2:1 *E*/*Z* ratio 1.05 g, 2.52 mmol, 67% yield).[90]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 1.7, 0.5H, *Z*), 7.64 (d, *J* = 1.7, 1H, *E*) 7.54 – 7.51 (m, 0.5H, *Z*), 7.51 – 7.47 (m, 1.5H), 7.34 – 7.30 (m, 1.5H), 7.28 – 7.21 (m, 4.5 H), 7.16 (d, *J* = 7.9, 1.5H), 6.39 (dt, *J* = 12.7, 1.4 Hz, 1H, *E*), 6.04 (dt, *J* = 6.2, 1.5 Hz, 0.5H, *Z*), 4.91 (dt, *J* = 12.8, 7.0 Hz, 1H, *E*), 4.52 (td, *J* = 7.3, 6.1 Hz, 0.5H, *Z*), 4.13 (t, *J* = 6.5 Hz, 3H), 3.84 (s, 1H, *Z*), 3.83 (s, 2H, *E*), 3.69 (s, 1.5H, *Z*), 3.55 (s, 3H, *E*), 3.50 (dd, *J* = 7.4, 1.3 Hz, 1H, *Z*), 3.38 (dd, *J* = 7.0, 1.0 Hz, 2H, *E*), 2.85 – 2.80 (m, 3H), 2.09 (s, 4.5H), 2.01 – 1.94 (m, 2H).

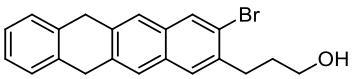
91 Procedure adapted from: Lugemwa, F. N.; Shaikh, K.; Hochstedt, E. *Catalysts*, **2013**, *3*, 954–965.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 148.4, 146.9, 140.8, 140.5, 140.4, 139.3, 139.1, 136.7, 135.8, 135.8, 134.6, 134.5, 130.7, 130.7, 130.1, 130.0, 129.4, 129.2, 128.9, 128.7, 127.3, 127.2, 126.7, 126.5, 124.1, 124.0, 123.7, 123.5, 104.5, 100.9, 89.0, 88.7, 81.4, 81.3, 63.7, 63.6, 59.8, 56.1, 32.6, 31.2, 28.7, 27.7, 23.5, 23.3, 21.1 (2 peaks missing due to overlapping).



3-(3-Bromo-6,11-dihydrotetracen-2-yl)propyl acetate (72a). To a solution of **73a** (1.0 equiv, 1.66 g, 3.97 mmol) in HPLC grade CH_2Cl_2 (0.1 M, 40 mL) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (155 mg, 196 μmol, 5 mol%) and the mixture was stirred at reflux overnight. After cooling to 23 ºC, NEt_3 (2 mL) was added and then the solvents were evaporated under reduced pressure. Purification by column chromatography (cyclohexane/CH_2Cl_2 4:1) afforded the title compound as a mixture of two isomers (4:1 **72a**/**72a'**, 671 mg, 1.63 mmol, 41% yield). Trituration of the solid mixture with EtOH afforded the desired isomer **72a** as a white solid (439 mg, 1.07 mmol, 27% yield).[90]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.66 (s, 1H), 7.62 (s, 1H), 7.61 (s, 1H), 7.33 (dt, *J* = 7.1, 3.5 Hz, 2H), 7.24 – 7.19 (m, 2H), 4.16 (t, *J* = 6.5 Hz, 2H), 4.06 (d, *J* = 4.8 Hz, 4H), 2.98 – 2.91 (m, 2H), 2.10 – 2.02 (m, 5H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 137.2, 137.0, 136.9, 136.6, 136.5, 132.3, 131.6, 130.8, 128.0, 127.4, 127.4, 126.5, 124.7, 124.0, 122.3, 64.0, 37.0, 36.9, 32.8, 29.0, 21.2 (1 peak missing due to overlapping).

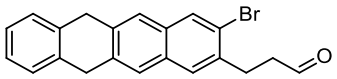


3-(3-Bromo-6,11-dihydrotetracen-2-yl)propan-1-ol (80). To a solution of **72a** (1.0 equiv, 650 mg, 1.59 mmol) in CH_2Cl_2 (0.33 M, 4.8 mL) and MeOH (0.08 M, 19 mL) was added potassium carbonate (5.4 equiv, 8.62 mmol, 1.19 g) and the mixture was stirred at 23 ºC for 1 h. Then, the reaction was quenched by addition of water (20 mL) and diluted with CH_2Cl_2 (20 mL). The organic layer was separated and washed with more water (3 × 20 mL) and brine (3 × 20 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Filtration of the crude through a short pad of silica (cyclohexane/EtOAc 4:1) afforded the title compound as a white solid (480 mg, 1.32 mmol, 82% yield).[92]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.66 (s, 1H), 7.63 (d, *J* = 3.9 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.24 – 7.19 (m, 2H), 4.06 (d, *J* = 5.0 Hz, 4H), 3.74 (dd, *J* = 11.6, 6.1 Hz, 2H), 3.01 – 2.94 (m, 2H), 2.02 – 1.94 (m, 2H).

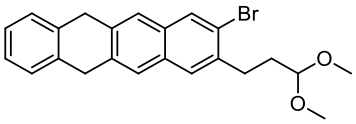
92 Procedure adapted from: Jung, M. E.; Chamberlain, B. T.; Koch, P.; Niazi, K. R. *Org. Lett.* **2015**, *17*, 3608–3611.

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 136.97, 136.9, 136.6, 136.4, 132.2, 131.6, 130.8, 128.0, 127.4, 127.4, 126.5, 124.7, 124.0, 122.4, 62.4, 37.0, 36.9, 33.1, 32.6 (one peak missing due to overlapping).



3-(3-Bromo-6,11-dihydrotetracen-2-yl)propanal (81). To a solution of **80** (1.0, 490.0 mg, 1.334 mmol) in CH_2Cl_2 (0.05 M, 27 mL), DMP (1.2 equiv, 680 mg, 1.601 mmol) and $NaHCO_3$ (2.0 equiv, 224 mg, 2.668 mmol) were sequentially added. The resulting mixture was stirred at 23 ºC for 1 h, then a saturated solution of $NaHCO_3$ (20 mL) was added. The organic layer was separated and washed with $Na_2S_2O_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude by column chromatography (cyclohexane/EtOAc 95:5) afforded the title compound as a yellow solid (360 mg, 0.98 mmol, 74% yield).[90]

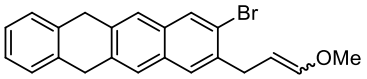
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (t, *J* = 1.2 Hz, 1H), 8.02 (s, 1H), 7.68 (s, 1H), 7.64 (s, 2H), 7.39 – 7.31 (m, 2H), 7.27 – 7.20 (m, 2H), 4.07 (s, 4H), 3.22 (t, *J* = 7.4 Hz, 2H), 2.90 (t, *J* = 7.4 Hz, 2 H).[93]



8-Bromo-9-(3,3-dimethoxypropyl)-5,12-dihydrotetracene (82). To a solution of **81** (1.0 equiv, 355 mg, 967 μmol) in MeOH (0.5 M, 2 mL), $HC(OMe)_3$ (2.0 equiv, 212 μL, 1.94 mmol) was added, followed by 2 drops of H_2SO_4. The reaction was refluxed for 1.5 h and then cooled down to 23 ºC. Na_2CO_3 (3.0 equiv, 308 mg, 2.90 mmol) was added and the mixture stirred at 23 ºC for 20 min, then filtered and concentrated under reduced pressure. Purification through column chromatography (cyclohexane/CH_2Cl_2/Et_3N 80:20:1 to 50:50:1) afforded the title compound as an orange oil (350 mg, 851 μmol, 88% yield).[90]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.66 (s, 1H), 7.62 (s, 2H), 7.33 (dt, *J* = 7.0, 3.5 Hz, 2H), 7.24 – 7.18 (m, 2H), 4.44 (s, 1H), 4.06 (d, *J* = 3.7 Hz, 4H), 3.49 (s, 3H), 3.36 (s, 6H), 2.96 – 2.89 (m, 2H), 2.02 (ddd, *J* = 10.3, 8.0, 5.8 Hz, 2H).[94]

First synthesis of enol ether **71**



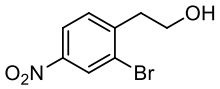
8-Bromo-9-(3-methoxyallyl)-5,12-dihydrotetracene (71).[90] To a solution of **82** (1 equiv, 30 mg, 73 μmol) in CH_2Cl_2 (2.5 mL, 0.03 M) at -50 ºC was added diisopropylethylamine (1.7 equiv, 22 μL, 124

93 This compound was found to be highly unstable, and hence a clean ^{13}C NMR spectrum could not be recorded. It was directly submitted to the acetal protection.

94 This compound was found to quickly decompose to the aldehyde, and hence a clean ^{13}C NMR spectrum could not be recorded. It was directly submitted to the formation of the enol ether.

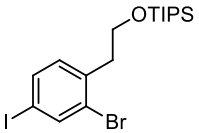
μmol) and then TMSOTf (1.5 equiv, 20 μL, 110 μmol) dropwise over 10 min. The resulting mixture was allowed to warm to 23 ºC over 2 h and then stirred for 3 h at this temperature. The reaction was then quenched by the addition of saturated aqueous solution of $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (pentane:CH_2Cl_2:NEt_3 94:5:1) afforded the title compound as a pale yellow oil that turned into a solid upon being placed in the freezer (1:2 *E*/*Z* ratio, 9.7 mg, 26 μmol, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 0.5H, *E*), 7.99 (s, 1H, *Z*), 7.68 (s, 0.5H, *E*), 7.66 (s, 2H, *Z*), 7.63 (s, 1H, *E*), 7.63 (s, 1H, *Z*), 7.34 (dd, *J* = 5.1, 3.5 Hz, 3H), 7.24 – 7.19 (m, 3H), 6.46 (dt, *J* = 12.6, 1.1 Hz, 0.5H), 6.10 (dt, *J* = 6.2, 1.4 Hz, 1H), 4.99 (dt, *J* = 12.7, 7.3 Hz, 0.5H), 4.67 (td, *J* = 7.3, 6.2 Hz, 1H), 4.05 (d, *J* = 5.5 Hz, 6H), 3.67 – 3.63 (m, 5H), 3.58 (s, 1.5H), 3.50 (d, *J* = 7.3 Hz, 1H).



2-(2-Bromo-4-nitrophenyl)ethanol (83).[95] *N*,*N*-dibromodimethylhydantoin (0.7 equiv, 5.98 g, 20.94 mmol) was added portionwise at 0 ºC to a solution of 2-(4-nitrophenyl)ethanol (1.0 equiv, 5.00 g, 29.90 mmol) and methanesulfonic acid (5.0 equiv, 9.6 mL, 148.00 mmol) in CH_2Cl_2 (91 mL, 0.3 M). The ice bath was then removed and the mixture was stirred at 23 ºC for 4 h. After this time, the mixture was poured into water (150 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the orange oil residue by column chromatography (cyclohexane to cyclohexane/EtOAc 3:2) afforded the title compound as a pale yellow oil (3.86 g, 15.71 mmol, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.3 Hz, 1H), 8.11 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H), 1.66 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 146.0, 131.7, 128.0, 124.9, 122.3, 77.5, 77.2, 76.8, 61.4, 39.3.



(2-Bromo-4-iodophenethoxy)triisopropylsilane (74b). To a solution of **83** (1 equiv, 3.50 g, 14.22 mmol) in a 3:1 mixture (0.1 M) of dioxane (107 mL) and water (36 mL) was added NH_4Cl (7.5 equiv, 5.71 g, 106.5 mmol) and Zn dust (7.5 equiv, 6.98 g, 106.50 mmol) at 0 ºC. The reaction mixture was stirred for 3 h at this temperature and then it was filtered through a celite pad. The filtrate was partitioned between water (100 mL) and EtOAc (100 mL) and the pH was adjusted to 14 by addition of 4 M KOH. The product was extracted with more EtAOc (3 × 100 mL), the organic layer was

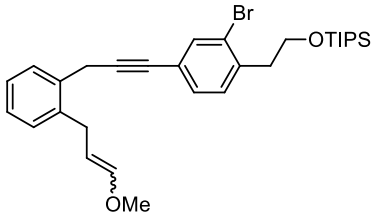
95 Procedure from: Sun, X.; Lv, M.; Yang, F.; Tong, C. Peop. Rep. China Patent 104250257A, **2013**.

separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude amine **84** that was taken on to the next step without further purification.

To a solution of amine **84** in concentrated hydrochloric acid (26 mL, 0.5 M), a solution of sodium nitrite (1.1 equiv, 1.07 g, 15.60 mmol) in water (47 mL) was added dropwise at 0 ºC and the mixture was allowed to stir at this temperature for 1 h. After that it was filtered and the filtrate was added dropwise at 0 ºC to a solution of potassium iodide (1.1 equiv, 21.5 g, 129.6 mmol) with rapid stirring. The ice bath was then removed and the stirring was continued for 3 h at 23 ºC. The mixture was then filtered and the compound was extracted from the filtrate with CH_2Cl_2 (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the crude iodide **85**, which was taken on to the next step without further purification.

To a solution of alcohol **85** in CH_2Cl_2 (36 mL, 0.4 M) were added imidazole (2.5 equiv, 2.42 g, 35.49 mmol) and triisopropylsilyl chloride (1.5 equiv, 4.6 mL, 21.30 mmol) at 0 ºC. The resulting mixture was stirred overnight at 23 ºC and then quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 19:1) to afford the title compound as a pale yellow liquid (4.05 g, 8.38 mmol, 59% yield over 3 steps).[96]

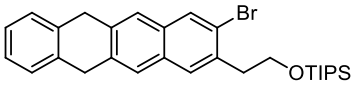
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.3 Hz, 1H), 8.08 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 1.04 – 0.96 (m, 21H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 146.7, 132.3, 127.8, 124.7, 122.0, 62.0, 39.8, 18.0, 12.0.



(2-Bromo-4-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenethoxy)triisopropylsilane (73b). $PdCl_2(PPh_3)_2$ (48 mg, 68 μmol, 5 mol%) and CuI (24 mg, 126 μmol, 10 mol%) were suspended in Et_3N (6.5 mL) and the mixture was bubbled with Ar for 10 min. A solution of **60** (1.0 equiv, 232 mg, 1.24 mmol) and **74b** (1.0 equiv, 600 mg, 1.24 mmol) in degassed NEt_3 (6.5 mL) were subsequently added and the reaction was stirred at 40 ºC for 1 h. Then the mixture was diluted with EtOAc (15 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/NEt_3 99:1) afforded the title compound as an orange oil (3:1 *E*/*Z* ratio, 580 mg, 1.07 mmol, 86% yield).

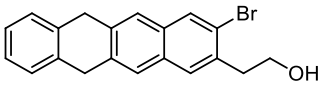
96 Procedure adapted from: Tsuji, H.; Yamagata, K.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Int. Ed.* **2007**, *46*, 8060 – 8062.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 3.8, 1.6 Hz, 1.3H), 7.53 – 7.45 (m, 1.3H), 7.25 – 7.18 (m, 6.5H), 6.37 (dt, *J* = 12.6, 1.4 Hz, 1H, *E*), 6.01 (dt, *J* = 6.1, 1.5 Hz, 0.3H, *Z*), 4.88 (dt, *J* = 12.7, 7.0 Hz, 1H, *E*), 4.49 (dd, *J* = 13.5, 7.3 Hz, 0.3H, *Z*), 3.88 (t, *J* = 6.9 Hz, 2.6H), 3.81 (s, 2H, *E*), 3.80 (s, 0.7H, *Z*), 3.66 (s, 1H, *Z*), 3.52 (s, 3H, *E*), 3.47 (dd, *J* = 7.4, 1.4 Hz, 0.7H, *Z*), 3.35 (dd, *J* = 7.0, 1.1 Hz, 2H, *E*), 2.98 (t, *J* = 6.9 Hz, 2.7H), 1.07 – 0.99 (m, 28H).



(2-(3-Bromo-6,11-dihydrotetracen-2-yl)ethoxy)triisopropylsilane (72b). To a solution of **72b** (1.0 equiv, 990 mg, 1.83 mmol) in HPLC grade CH_2Cl_2 (0.1 M, 19 mL) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (36 mg, 46 μmol, 2.5 mol%) and the mixture was stirred at reflux for 2 h. After cooling to 23 ºC, NEt_3 (1 mL) was added and then the solvents were evaporated under reduced pressure. Purification by column chromatography (cyclohexane/CH_2Cl_2 9:1) afforded the title compound as a mixture of two isomers (3:1 **72b**/**72b'**), with a dark red oil appearance (605 mg, 1.19 mmol, 65% yield).

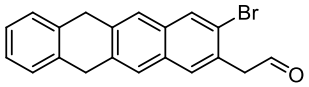
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 0.3H), 7.99 (s, 1H), 7.71 (s, 0.3H), 7.69 (s, 1H), 7.67 (s, 0.3H), 7.65 (s, 1H), 7.61 (s, 1H), 7.37 – 7.32 (m, 2.6H), 7.25 – 7.19 (m, 2.6H), 4.15 (s, 0.6H), 4.09 (s, 0.6H), 4.06 (d, *J* = 4.2 Hz, 4H), 3.98 (td, *J* = 7.0, 3.3 Hz, 2.7H), 3.24 (t, *J* = 7.1 Hz, 0.6H), 3.14 (t, *J* = 7.0 Hz, 2H), 1.15 – 1.01 (m, 28H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 137.1, 137.0, 137.0, 136.9, 136.4, 136.3, 136.2, 135.9, 135.1, 132.4, 132.4, 131.6, 131.5, 130.5, 129.5, 128.8, 127.5, 127.4, 126.7, 126.5, 125.5, 124.9, 124.8, 124.0, 123.5, 122.5, 63.2, 63.1, 53.6, 41.1, 40.0, 37.2, 37.0, 36.9, 36.5, 18.2, 12.1.



2-(3-Bromo-6,11-dihydrotetracen-2-yl)ethanol (86). TBAF (1 M in THF, 2.0 equiv, 2.6 mL, 2.62 mmol) was added to a solution of **72b** (1 equiv, 670 mg, 1.31 mmol) in THF (13 ml, 0.1 M) at 0 ºC. The ice bath was removed and the mixture was stirred for 1 h at 23 ºC. Afterwards it was partitioned between EtOAc (30 ml) and water (20 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Filtration through a short pad of silica (cyclohexane/EtOAc 95:5) afforded the title compound as a mixture of two isomers, with an orange oil appearance (329 mg, 930 μmol, 71% yield). The mixture was taken on to the next step without further purification.[97]

97 Procedure adapted from: Yin, X.; Zuccarello, G.; García-Morales, C.; Echavarren, A. M. *Chem. Eur. J.* **2019**, *25*, 9485–9490.

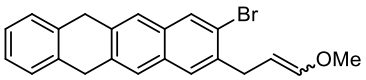
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 0.3H), 8.02 (s, 1H), 7.72 (d, *J* = 4.0 Hz, 0.3H), 7.68 (s, 2H), 7.64 (s, 1H), 7.36 – 7.30 (m, 2.6H), 7.24 – 7.19 (m, 2.6H), 4.15 (s, 0.6H), 4.09 (s, 0.6H), 4.07 (d, *J* = 4.4 Hz, 4H), 3.96 (dd, *J* = 11.5, 6.3 Hz, 2.7H), 3.27 (t, *J* = 6.8 Hz, 0.7H), 3.17 (t, *J* = 6.6 Hz, 2H).



2-(3-Bromo-6,11-dihydrotetracen-2-yl)acetaldehyde (87). A solution of **86** (1 equiv, 261 mg, 739 μmol) in CH_2Cl_2 (10 ml) was added to a suspension of pyridinium chlorochromate (1.5 equiv, 239 mg, 1.11 mmol) in CH_2Cl_2 (5 mL, 0.15 M) while stirring. The resulting mixture was left to react at 23 ºC for 2 h and was then diluted with more CH_2Cl_2 (15 mL). The resulting suspension was filtered through a pad of Celite and washed with copious amounts of CH_2Cl_2. The solvents were removed under reduced pressure and the remaining residue was purified by column chromatography (cyclohexane/EtOAc 95:5) to yield the title compound, as a mixture of two isomers, with a yellow oil appearance (129 mg, 370 μmol, 50% yield).[98]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (t, *J* = 1.8 Hz, 1H), 9.81 (t, *J* = 1.9 Hz, 0.3H), 8.23 (s, 0.3H), 8.06 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 0.7H), 7.68 (s, 1.3H), 7.65 (s, 2.6H), 7.35 (dd, *J* = 9.0, 4.4 Hz, 2.7H), 7.25 – 7.21 (m, 2.7H), 4.15 (s, 0.7H), 4.10 (s, 0.7H), 4.07 (d, 4H), 3.99 (d, *J* = 1.8 Hz, 2.7H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 198.7, 138.2, 137.4, 137.1, 137.0, 136.8, 136.7, 136.6, 132.9, 132.9, 131.6, 131.5, 131.1, 130.2, 130.0, 129.4, 128.0, 127.7, 127.5, 127.4, 127.4, 126.6, 125.7, 125.0, 124.9, 124.1, 121.8, 53.6, 51.9, 50.7, 37.2, 37.0, 36.9, 36.6 (peaks missing due to overlapping).

Second Synthesis of Enol Ether **71**

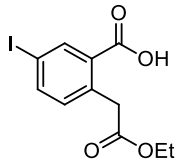


8-Bromo-9-(3-methoxyallyl)-5,12-dihydrotetracene (71). A solution of LiHMDS (2.1 equiv, 512 mg, 1.50 mmol) in THF (3 mL) was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (2.1 equiv, 251 mg, 1.50 mmol) in THF (1 mL) at 0 ºC. The color of the mixture turned from dark orange to red. After stirring for 40 min at 0 ºC the reaction was allowed to warm up to 23 ºC. Then a solution of **87** (1.0 equiv, 250 mg, 712 μmol) in THF (1 mL) was added dropwise at 0 ºC and the mixture was then stirred overnight at 23 ºC. The reaction was quenched by addition of sat. aq. NH_4Cl (5 mL) and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated. Chromatographic purification (cyclohexane to cyclohexane/CH_2Cl_2 9:1) of the crude

98 Procedure adapted from: Hartman, G. D.; Phillips, B. T.; Halczenko, W. *J. Org. Chem.* **1985**, *50*, 2423–2427.

material yielded the title compound (3:1 mixture of isomers) as a yellow oil that turns into a solid upon being placed in the fridge (2:1 *E*/*Z* ratio for each regioisomer, 149 mg, 392 μmol, 55% yield).[99]

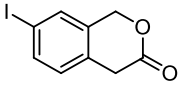
^{1}H NMR (500 MHz, $CDCl_3$) 8.00 (s, 1H, *E*), 7.99 (s, 0.5H, *Z*), 7.72 – 7.65 (m, 2.6H), 7.64 – 7.60 (m, 3.3H), 7.38 – 7.28 (m, 3.6H), 7.25 – 7.19 (m, 3.6H), 6.46 (dt, *J* = 12.7, 1.1 Hz, 1H, *E*), 6.09 (dt, *J* = 6.1, 1.4 Hz, 0.5H, *Z*), 4.98 (dt, *J* = 12.7, 7.3 Hz, 1H, *E*), 4.66 (td, *J* = 7.3, 6.2 Hz, 0.5H, *Z*), 4.15 (s, 0.3H, **71b**), 4.09 (s, 0.3H, **71b'**), 4.06 (s, 6H), 3.65 (s, 1.5 H, *Z*), 3.62 (d, *J* = 5.4 Hz, 1H, *Z*), 3.58 (s, 3H, *E*), 3.50 (d, *J* = 7.3 Hz, 2H, *E*).



2-(2-Ethoxy-2-oxoethyl)-5-iodobenzoic acid (88). Sodium (2.1 equiv, 739 mg, 32.11 mmol) was added to abs. EtOH HPLC graded (0.12 M, 125 mL) under Ar atmosphere at 0 ºC. After warming up to 23 ºC, the mixture was left to stir for 1 h. Ethyl acetoacetate (1.2 equiv, 2.3 mL, 18.39 mmol) was then added and the mixture was stirred at 23 ºC for 10 min. Then, CuBr (1 equiv, 2.19 g, 15.30 mmol) and 2-bromo-5-iodobenzoic acid (1 equiv, 5.00 g, 15.30 mmol) were added and the reaction mixture was refluxed for 16 h. After completion, the dark green reaction mixture was concentrated *in vacuo*, acidified with 1M HCl (200 mL) and diluted with CH_2Cl_2 (200 mL). The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting dark orange solid residue was triturated with cyclohexane (100 mL) to afford the title compound as a pale orange solid (4.23 g, 15.30 mmol, 82% yield), which was taken on to the next step without further purification.[100]

Melting point = 149–151 ºC.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 2.0 Hz, 1H), 7.87 (dd, *J* = 2.0 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (500 MHz, $CDCl_3$) δ 171.0, 170.8, 142.1, 140.5, 136.4, 134.1, 130.5, 92.3, 61.0, 40.4, 14.2.
HRMS (ESI-) m/z calc. for $C_{11}H_{10}IO_4$ $[M-H]^-$: 332.9634. Found: 332.9629.

First synthesis of Isochromanone **91**



7-Iodoisochroman-3-one (91). Ethyl chloroformate (1.1 equiv, 3.8 mL, 39.49 mmol) was added at 0 °C to an orange solution of **88** (1 equiv, 12.0 g, 35.90 mmol) and NEt_3 (1.1 equiv, 5.50 mL, 35.90 mmol) in dry CH_2Cl_2 (72 mL). After stirring for 2 h at 23 ºC, the orange mixture was quenched by

99 Procedure adapted from *reference 88.*
100 Procedure adapted from: Tang, S.-Q.; Bricard, J.; Schmitt, M.; Bihel, F. *Org. Lett.* **2019**, *21*, 844–848.

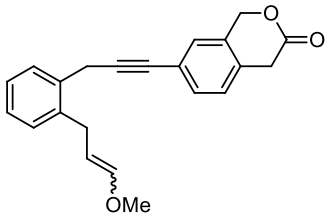
addition of 1 M HCl (100 mL) and diluted with more CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The crude anhydride **89** (orange oil that turns into a solid when placed in the fridge) was dissolved in dry THF (105 mL) and the orange solution was added to $NaBH_4$ (~2 equiv, 3.00 g, 71.80 mmol) at -15 °C. After stirring at -15 °C for 1 h and at 23 °C for 2 h, the yellow mixture was quenched by addition of 1M HCl (100 mL) and extracted with AcOEt (3 × 200 mL). The organic layers were washed with sat. aq. $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. *p*-TsOH·H_2O (~0.05 equiv, 342 mg, 1.80 mmol) was added to a solution of the crude alcohol **90** (pale yellow oil) in toluene (90 mL) and the mixture was heated at 80 °C for 1 h. After cooling to 23 °C, the bright orange mixture was concentrated, diluted with AcOEt (150 mL) and washed with sat. aq. $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated to give an orange residue. The residue was triturated with EtOH to afford the title compound as a white solid (4.22 g, 15.30 mmol, 43% yield after 3 steps).[101]

Melting point = 154–156 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 8.0 Hz, 1H), 7.58 (s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 5.23 (s, 2H), 3.64 (s, 2H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 170.2, 138.8, 134.1, 134.0, 131.0, 129.2, 92.6, 69.4, 35.6.

HRMS (ESI+) m/z calc. for $C_9H_7INaO_2$ $[M+Na]^+$: 296.9383. Found: 296.9381.



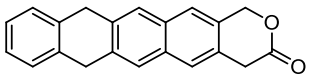
7-(3-(2-(3-Methoxyallyl)phenyl)prop-1-yn-1-yl)isochroman-3-one (92). $PdCl_2(PPh_3)_2$ (270 mg, 385 μmol, 5 mol%) and CuI (134 mg, 702 μmol, 10 mol%) were suspended in Et_3N (35 mL) and the mixture was bubbled with Ar for 10 min. A solution of **91** (1.0 equiv, 1.92 g, 6.99 mmol) and **58** (1.0 equiv, 1.30 g, 6.99 mmol) in degassed THF (35 mL) were subsequently added and the reaction was stirred at 40 °C for 1.5 h. Then the mixture was diluted with EtOAc (50 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 99:1) afforded the title compound as an yellow oil (2:1 *E*/*Z* ratio, 1.25 g, 3.78 mmol, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 1.5H), 7.43 – 7.39 (m, 1.5H), 7.33 (s, 0.5H, *Z*), 7.32 (s, 1H, *E*), 7.25 – 7.20 (m, 4.5H), 7.15 (d, *J* = 7.8 Hz, 1.5H), 6.36 (dt, *J* = 12.7, 1.3 Hz, 1H, *E*), 6.01 (dt, *J* = 6.1, 1.5 Hz, 0.5H, *Z*), 5.27 (s, 3H), 4.89 (dt, *J* = 12.7, 7.0 Hz, 1H, *E*), 4.49 (td, *J* = 7.4, 6.2 Hz,

101 Procedure adapted from: Velcicky, J.; Bodendorf, U.; Rigollier, P.; Epple, R.; Beisner, D. R; Guerini, D.; Smith, P.; Liu, B.; Feifel, R.; Wipfli, P.; Aichholz, R.; Couttet, P.; Dix, I; Widmer, T.; Wen, B.; Brandl, T. *J. Med. Chem.* **2018**, *61*, 865–880.

0.5H, *Z*), 3.82 (s, 1H, *Z*), 3.81 (s, 2H, *E*), 3.70 (s, 3H), 3.66 (s, 1.5H, *Z*), 3.52 (s, 3H, *E*), 3.48 (dd, *J* = 7.4, 1.5 Hz, 1H, *Z*), 3.36 (dd, *J* = 7.0, 1.2 Hz, 2H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 148.4, 148.4, 146.9, 146.2, 139.3, 139.2, 134.6, 134.5, 133.2, 132.6, 132.1, 131.7, 131.7, 130.6, 130.5, 129.4, 129.2, 128.9, 127.9, 127.3, 127.2, 126.7, 123.3, 123.2, 106.1, 104.5, 100.9, 97.4, 88.9, 88.6, 82.0, 81.9, 69.8, 57.1, 56.1, 53.6, 36.2, 31.2, 27.7, 23.5 (2 peaks missing due to overlapping).

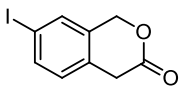


7,12-Dihydro-1*H*-anthra[2,3-*g*]isochromen-3(4*H*)-one (93). To a solution of **92** (1.0 equiv, 1.00 g, 3.33 mmol) in HPLC grade CH_2Cl_2 (33 mL, 0.1 M) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (66 mg, 83 μmol, 2.5 mol%) and the mixture was stirred at reflux for 1 h. After cooling to 23 °C, NEt_3 (1 mL) was added. The title compound precipitated upon cooling the solution to 23 °C and it was isolated by filtration as a white solid (280 mg, 932 μmol, 28% yield).

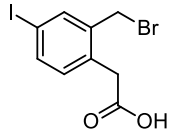
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 4.8 Hz, 2H), 7.67 (s, 1H), 7.63 (s, 1H), 7.35 (dd, *J* = 5.1, 3.6 Hz, 2H), 7.22 (dd, *J* = 5.6, 3.3 Hz, 2H), 5.44 (s, 2H), 4.09 (s, 4H), 3.88 (s, 2H).[102]

*Synthesis of Iodide-Substituted 1,7-Enyne **96***

Second Synthesis of **91**



7-Iodoisochroman-3-one (91). To a stirred solution of **88** (1.0 equiv, 7.80 g, 23.40 mmol) in THF (0.33 M, 71 mL) was added $BH_3{\cdot}Me_2S$ (1.1 equiv, 2.5 mL, 25.71 mmol) at 0 °C. The mixture was then slowly heated to 55 °C and stirred at this temperature for 18 h. After cooling to 23 °C, 4.0 M HCl (300 mL) was added to the thus formed alcohol to quench the reaction and allow lactonization to take place. The mixture was extracted with diethyl ether (200 mL × 3) and washed with brine (300 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to provide the title compound as a white solid (5.24 g, 23.42 mmol, 82% yield), which was taken on to the next step without further purification.[103]



2-(2-(Bromomethyl)-4-iodophenyl)acetic acid (101). An orange solution of **91** (1.0 equiv, 6.00 g, 21.89 mmol) in 33% HBr in acetic acid (13.0 equiv, 1.4 M, 30.0 mL) was stirred at 23 °C under Ar for

102 Because of the low solubility in most deuterated solvents a ^{13}C NMR was not recorded.

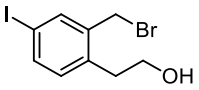
103 Procedure adapted from: Zhu, J.; Li, R.; Su, Y.; Gu, P. *J. Org. Chem.* **2019**, *84*, 5813–5820.

2 h and then at 70 °C for 1 h. After cooling down to 23 ºC, the mixture was poured into ice-water. Filtration of the white precipitate afforded the desired benzyl bromide as a white solid which was taken on to the next step without further purification (6.84 g, 19.27 mmol, 88% yield).[104]

Melting point = 132–134 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.8 Hz, 1H), 7.60 (dd, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 4.43 (s, 2H), 3.76 (s, 2H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 176.5, 139.7, 138.9, 138.6, 133.4, 132.5, 93.6, 37.9, 30.9.[105]

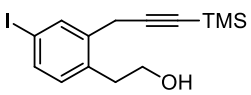


2-(2-(Bromomethyl)-4-iodophenyl)ethan-1-ol (102). $BH_3{\cdot}SMe_2$ (2.0 equiv, 1.30 mL, 13.72 mmol) was added dropwise to a solution of the crude **101** (1.0 equiv, 2.43 g, 6.85 mmol) in anhydrous THF (0.14 M, 50 mL) at 0 ºC. Once the addition was completed, the ice bath was removed, the resulting mixture was allowed to warm to 23 ºC and then heated gradually to 80 ºC. After refluxing at that temperature for 2 h, the mixture was cooled to 0 ºC and quenched by slow addition of 1 M solution of HCl (80 mL). The product was extracted with Et_2O (3 × 70 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the yellow oil residue by column chromatography (cyclohexane/EtOAc 95:5 to 4:1) afforded the product as a pale yellow oil (2.15 g, 6.30 mmol, 92% yield).[90]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.9 Hz, 1H), 7.59 (dd, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 4.48 (s, 2H), 3.90 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 139.4, 138.7, 138.1, 137.5, 132.4, 91.8, 62.8, 35.1, 30.4.

HRMS (APCI+) m/z calc. for $C_9H_{10}IO$ $[M\text{-}Br]^+$: 260.9771. Found: 260.9767; (APCI+) m/z calc. for C_9H_9BrI $[M\text{-}OH]^+$: 322.8927. Found: 322.8923.



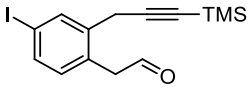
2-(4-Iodo-2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)ethan-1-ol (103). To a solution of ethynyltrimethylsilane (4.0 equiv, 2.43 mL, 17.59 mmol) in THF (15 mL), was added *i*-PrMgCl (4.0 equiv, 8.78 mL, 2 M in THF, 17.59 mmol) dropwise at 0 ºC. After stirring for 30 min at 0 ºC and 30 min at 23 ºC, CuBr (0.6 equiv, 378 mg, 2.63 mmol) was added in one portion. The pale blue reaction mixture was stirred for 30 min at 23 ºC before adding **102** (1.0 equiv, 1.50 g, 4.39 mmol) as a solution

104 Procedure adapted from: Albrecht, S.; Defoin, A.; Salomon, E.; Tarnus, C.; Wetterholm, A.; Haeggström, J. Z. *Bioorg. Med. Chem.* **2006**, *14*, 7241–7257.

105 The mass of the compound could not be detected by MS because of fragmentation taking place.

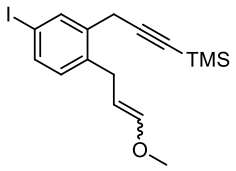
in THF (5 mL). The pale yellow mixture was then refluxed for 16 h. After being cooled to 23 ºC, the bright yellow solution was poured into a saturated aqueous solution of NH_4Cl (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The crude material was purified by column chromatography (cyclohexane/EtOAc 95:5 to 9:1) to afford the title compound as a pale yellow oil (1.12 g, 3.12 mmol, 71% yield).[106]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.9 Hz, 1H), 7.57 (dd, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 3.87 (t, *J* = 6.7 Hz, 2H), 3.61 (s, 2H), 2.88 (t, *J* = 6.7 Hz, 2H).
^{13}C NMR (500 MHz, $CDCl_3$) δ 138.0, 137.4, 136.2, 136.1, 131.7, 103.4, 92.1, 88.1, 62.7, 35.3, 23.9. 0.0.
HRMS (ESI+) m/z calc. for $C_{14}H_{19}INaOSi$ $[M+Na]^+$: 381.0142. Found: 381.0145.



2-(4-Iodo-2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)acetaldehyde (104). To a solution of **103** (1.0 equiv, 2.78 g, 7.75 mmol) in HPLC grade CH_2Cl_2 (0.23 M, 33 mL) were sequentially added DMP (1.2 equiv, 3.94 g, 9.30 mmol) and $NaHCO_3$ (2 equiv, 1.30 g, 15.50 mmol). The resulting pale yellow mixture was stirred at 23 ºC for 1 h and then a saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The organic layer was separated and washed with sat. aq. $NaHCO_3$ (100 mL) and sat. aq. $Na_2S_2O_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The yellow residue was purified through column chromatography (cyclohexane/EtOAc 19:1) to yield the title compound as a pale yellow oil (2.25 g, 6.33 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, J = 1.8 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.62 (dd, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 3.77 (d, J = 1.8 Hz, 2H), 3.51 (s, 2H), 0.19 (s, 9H).
^{13}C NMR (500 MHz, $CDCl_3$) δ 198.1, 138.5, 137.9, 136.6, 132.7, 130.3, 102.5, 93.5, 88.6, 47.4, 24.4, 0.08.
HRMS (ESI+) m/z calc. for $C_{14}H_{17}INaOSi$ $[M+Na]^+$: 378.9986. Found: 378.9970.



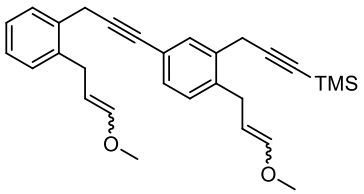
(3-(5-Iodo-2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)trimethylsilane (100). A suspension of (methoxylmethyl)triphenylphosphonium chloride (1.1 equiv, 1.06 g, 3.09 mmol) in dry THF (20 mL) was cooled to -40 ºC, then a solution of lithium bis(trimethylsilyl)amide (1.1 equiv, 517 mg,

106 Procedure adapted from: Huang, X.; Bugarin, A. *Chem. Eur. J.* **2016**, *22*, 12696–12700.

3.09 mmol) in dry THF (15 mL) was added dropwise. After stirring the mixture for 30 min at -40 ºC, a solution of **104** (1.0 equiv, 1.00 g, 2.81 mmol) was added dropwise. The reaction mixture was stirred for an additional 30 min at -40 ºC, then slowly warmed to 23 ºC and stirred overnight. A saturated aqueous solution of NH_4Cl (30 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The brown residue was purified through column chromatography on silica gel (cyclohexane to cyclohexane/Et_2O 97:3) to give the title compound as an orange oil (2:1 *E*/*Z*, 693 mg, 1.81 mmol, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 1H), 7.55 – 7.48 (m, 1H), 6.96 – 6.90 (m, 1H), 6.32 (dt, *J* = 12.6, 1.4 Hz, 0.7H, *E*), 5.99 (dt, *J* = 6.1, 1.5 Hz, 0.35H, *Z*), 4.79 (dt, *J* = 12.6, 7.0 Hz, 0.7H, *E*), 4.40 (td, *J* = 7.4, 6.1 Hz, 0.35H, *Z*), 3.64 (s, 1.2H, *E*), 3.57 (s, 0.65H, *Z*), 3.56 (s, 1.2H, *Z*), 3.52 (s, 2.15H, *E*), 3.33 (dd, *J* = 7.3, 1.5 Hz, 0.7H, *Z*), 3.22 (dd, *J* = 7.0, 1.4 Hz, 1.4H, *E*), 0.23 – 0.15 (m, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 147.2, 139.1, 138.9, 137.7, 137.4, 137.0, 136.9, 136.2, 136.0, 131.1, 131.0, 103.7, 103.3, 100.2, 91.8, 91.5, 88.3, 59.8, 56.1, 30.7, 27.3, 23.6, 23.4, 0.2, 0.2.
HRMS (ESI+) m/z calc. for $C_{16}H_{21}INaOSi$ $[M+Na]^+$: 407.0299. Found: 407.0292.

Synthesis of Multi-Enyne Containing Compounds:

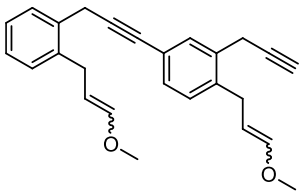


(3-(2-(3-Methoxyallyl)-5-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenyl)prop-1-yn-1-yl)trimethylsilane (106). $PdCl_2(PPh_3)_2$ (54.8 mg, 78.1 µmol, 5 mol%) and copper(I) iodide (29.7 mg, 156 µmol, 10 mol%) were suspended in previously degassed Et_3N (9 mL). A solution of **60** (1.2 equiv, 349 mg, 1.87 mmol) and **100** (1.0 equiv, 600 mg, 1.56 mmol) in degassed NEt_3 (9 mL) were subsequently added and the reaction was stirred at 40 ºC for 2 h. Then the mixture was diluted with EtOAc (30 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc 99:1 to 98:2) afforded the title compound as a pale yellow oil (620 mg, 1.40 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.50 (m, 2H), 7.32 – 7.25 (m, 1H), 7.25 – 7.19 (m, 4H), 7.16 – 7.11 (m, 1H), 6.41 – 6.30 (m, 1.4H), 6.04 – 5.96 (m, 0.7H), 4.94 – 4.78 (m, 1.4H), 4.53 – 4.41 (m, 0.6H), 3.85 – 3.81 (m, 1H), 3.68 – 3.63 (m, 2H), 3.59 (d, *J* = 1.9 Hz, 2H), 3.54 – 3.51 (m, 4H), 3.48 (d, *J* = 7.4 Hz, 0.8H), 3.40 (d, *J* = 7.5 Hz, 0.6H), 3.38 – 3.35 (m, 1.5H), 3.28 (dd, *J* = 6.9, 1.5 Hz, 1.4H), 0.21 – 0.17 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.59, 148.57, 148.43, 147.08, 146.84, 139.15, 139.12, 134.91, 134.55, 132.15, 132.12, 131.86, 130.33, 130.31, 130.21, 129.27, 129.25, 129.19, 129.13, 129.04, 128.91, 128.65, 127.18, 127.15, 127.05, 126.69, 126.48, 122.07, 121.93, 104.63, 104.08, 103.80, 101.02, 100.60, 100.56, 87.65, 87.61, 87.41, 87.12, 83.20, 83.03, 59.81, 56.13, 56.09, 31.22, 30.98, 27.77, 27.52, 23.92, 23.71, 23.57, 23.30, 0.21.

HRMS (ESI+) m/z calc. for $C_{29}H_{34}NaO_2Si$ $[M+Na]^+$: 465.2220. Found: 465.2207.

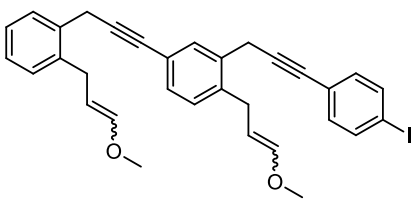


1-(3-Methoxyallyl)-4-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)-2-(prop-2-yn-1-yl)benzene (99). To a solution of **106** (1.0 equiv, 620 mg, 1.40 mmol) in abs. EtOH (13 mL) was added a solution of silver nitrate (3.0 equiv, 714 mg, 4.20 mmol) in dist. water (0.5 mL), which led to the instant formation of a white precipitate. The solution was stirred at 23 °C, with appearance of an insoluble brown oil in the reaction mixture. After 1 h, the reaction was quenched by addition of aqueous $Na_2S_2O_3$ and diluted with 5 mL of CH_2Cl_2. The suspension was filtered through a pad of celite, rinsed with CH_2Cl_2 and the volatiles were eliminated under vacuum. The remaining solution was extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 94:5:1) afforded the title compound as a yellow oil (317 mg, 1.00 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (ddd, *J* = 9.0, 7.9, 4.1 Hz, 3H), 7.34 – 7.28 (m, 1.5H), 7.24 (dd, *J* = 8.1, 3.0 Hz, 4.8H), 7.16 (dd, *J* = 7.8, 2.8 Hz, 1.4H), 6.43 – 6.29 (m, 2H), 6.01 (tt, *J* = 7.5, 1.2 Hz, 0.8H), 4.95 – 4.81 (m, 2H), 4.54 – 4.42 (m, 0.8H), 3.87 – 3.81 (m, 2.8H), 3.66 (dd, *J* = 9.4, 5.2 Hz, 2.8H), 3.57 (dd, *J* = 9.6, 2.5 Hz, 2.8H), 3.54 – 3.48 (m, 7.5H), 3.36 (ddd, *J* = 38.5, 25.2, 7.2 Hz, 6.2H), 2.26 – 2.18 (m, 1.2H).

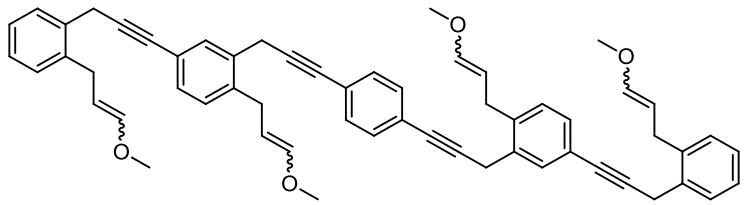
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 148.6, 148.4, 147.1, 146.8, 139.2, 139.0, 134.8, 134.3, 131.9, 131.9, 131.7, 130.5, 130.4, 130.3, 129.2, 129.2, 129.2, 129.2, 129.1, 129.1, 129.1, 128.9, 128.7, 127.2, 127.1, 127.0, 126.6, 126.6, 126.4, 122.0, 104.6, 103.9, 101.0, 100.5, 100.4, 87.5, 87.2, 87.0, 83.0, 82.9, 82.8, 81.7, 81.5, 81.4, 71.2, 71.2, 71.1, 59.8, 56.1, 56.0, 31.2, 31.0, 27.7, 27.5, 23.5, 23.3, 22.3, 22.1.

HRMS (ESI+) m/z calc. for $C_{26}H_{26}NaO_2$ $[M+Na]^+$: 393.1825. Found: 393.1823.



2-(3-(4-Iodophenyl)prop-2-yn-1-yl)-1-(3-methoxyallyl)-4-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)benzene (107). $PdCl_2(PPh_3)_2$ (5.3 mg, 7.5 µmol, 5 mol%) and copper(I) iodide (2.9 mg, 15.0 µmol, 10 mol%) were suspended in previously degassed Et_3N (0.6 mL) and the mixture was bubbled with Ar for 10 min. A solution of **99** (1.0 equiv, 56.0 mg, 150 µmol) and 1,4-diiodobenzene (1.2 equiv, 59.0 mg, 180 mmol) in degassed NEt_3 (1.2 mL) were subsequently added and the reaction was stirred at 40 ºC overnight. Then the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 94.5:4.5:1 to 89.5:9.5:1) afforded the title compound as an orange oil (56.3 mg, 97.8 µmol, 66% yield).

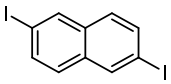
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.59 – 7.50 (m, 3H), 7.31 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.25 – 7.18 (m, 5H), 7.18 – 7.14 (m, 3H), 6.35 (t, *J* = 12.5 Hz, 2H), 6.00 (t, *J* = 6.1 Hz, 1H), 4.94 – 4.80 (m, 3H), 4.52 – 4.43 (m, 1H), 3.84 – 3.81 (m, 2.4H), 3.76 (d, *J* = 6.1 Hz, 1.6H), 3.65 (d, *J* = 1.3 Hz, 4H), 3.51 (s, 6H), 3.47 (ddd, *J* = 14.8, 7.4, 1.6 Hz, 1.6H), 3.35 (ddd, *J* = 15.6, 7.0, 1.4 Hz, 4H).
HRMS (ESI+) m/z calc. for $C_{32}H_{29}INaO_2$ $[M+Na]^+$: 595.1104. Found: 595.1094.



1,4-bis(3-(2-(3-Methoxyallyl)-5-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenyl)prop-1-yn-1-yl)benzene (98). $PdCl_2(PPh_3)_2$ (3.10 mg, 4.45 µmol, 5 mol%) and copper(I) iodide (1.70 mg, 8.91 µmol, 10 mol%) were suspended in previously degassed Et_3N (0.6 mL). A solution of **99** (1.0 equiv, 33.0 mg, 89.1 µmol) in degassed NEt_3 (1.5 mL) and another solution of **107** (1.1 equiv, 56.1 mg, 98.0 µmol) in degassed NEt_3 (1.2 mL) were subsequently added and the reaction was stirred at 40 ºC for 5 h. Then the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 94.5:4.5:1 to 89.5:9.5:1) afforded the title compound as an orange oil (54.6 mg, 89.1 µmol, 75% yield).[107]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 5.4H), 7.39 – 7.33 (m, 5.4H), 7.32 – 7.27 (m, 2.6H), 7.25 – 7.19 (m, 8.2H), 7.16 (dd, *J* = 7.8, 3.5 Hz, 2.7H), 6.35 (dd, *J* = 12.6, 7.3 Hz, 4H), 6.04 – 5.95 (m, 1.4H), 4.87 (qd, *J* = 14.5, 4.4 Hz, 4H), 4.54 – 4.42 (m, 1.4H), 3.80 (dd, *J* = 19.4, 5.4 Hz, 11H), 3.66 – 3.62 (m, 4.3H), 3.52 – 3.49 (m, 12H), 3.46 (t, *J* = 8.4 Hz, 2.9H), 3.35 (t, *J* = 7.6 Hz, 8H).
HRMS (APCI+) m/z calc. for $C_{58}H_{55}O_4$ $[M+H]^+$: 815.4095. Found: 815.4093.

107 Due to the instability of the tetraenynes and some of the dienynes, their ^{13}C NMR spectra could not be recorded.



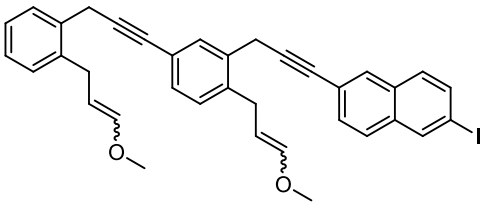
2,6-Diiodonapthalene (S1). A solution of 2.5 M of *n*-BuLi in cyclohexane (4 equiv, 5.6 mL, 13.99 mmol) was added dropwise to a solution of 2,6-dibromonaphthalene (1 equiv, 1.00 g, 3.50 mmol) in dry THF (16 mL, 0.22 M) at -78 ºC, under an Ar atmosphere, while maintaining a good stirring. After stirring for 1 h, a solution of iodine (4.0 equiv, 3.53 g, 14.0 mmol) in THF (30 ml) was added dropwise. The reaction mixture was warmed to 23 ºC and stirred at this temperature for 1 h. The reaction mixture was poured into water and extracted with dichloromethane (3 × 50 mL). The combined organic layer was washed with $NaHSO_3$ (70 mL) and the solvent was removed under vacuo, without previously drying with $MgSO_4$ since some solid product was present. Trituration of the crude with cyclohexane (50 mL) afforded the title compound as a white solid (879 mg, 2.31 mmol, 66% yield).

Melting point = 205–207 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 135.4, 133.7, 128.4, 92.2.

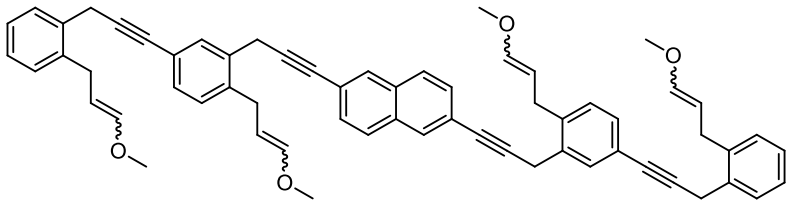
HRMS (APCI+) m/z calc. for $C_{10}H_6I_2$ $[M]^+$: 379.8553. Found: 379.8558.



2-iodo-6-(3-(2-(3-Methoxyallyl)-5-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenyl)prop-1-yn-1-yl)naphthalene (108). $PdCl_2(PPh_3)_2$ (7.0 mg, 10.0 µmol, 5 mol%) and copper(I) iodide (3.80 mg, 20.0 µmol, 10 mol%) were suspended in previously degassed Et_3N (0.5 mL) and the mixture was bubbled with Ar for 10 min. 2,6-Diiodonaphthalene (**S1**) (1.1 equiv, 84.0 mg, 220 µmol) and a solution of **99** (1.0 equiv, 74.0 mg, 200 µmol) in degassed THF (2 mL) were subsequently added and the reaction was stirred at 40 ºC. Since the 2,6-diiodonaphthalene was not completely dissolved, THF (3 mL) was added again after 15 min and the reaction was left at 40 ºC for 2.5 h. Since after this time there was still a large quantity of 2,6-diiodonapthalene remaining, another solution of **99** (1.0 equiv, 74.0 mg, 200 µmol) in degassed THF (2 mL) was added and the mixture was left to stir at 40 ºC overnight. After that, the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification

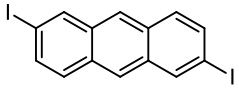
by column chromatography (cyclohexane/CH_2Cl_2/NEt_3 94.5:4.5:1) afforded the title compound as an orange oil (66.3 mg, 106 µmol, 53% yield).[108]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.68 (m, 1H), 7.64 – 7.37 (m, 5H), 7.32 (dd, *J* = 6.5, 4.9 Hz, 2H), 7.25 – 7.07 (m, 7H), 6.42 – 6.30 (m, 2H), 6.01 (ddd, *J* = 6.0, 3.7, 2.2 Hz, 0.7H), 4.87 (ddt, *J* = 13.9, 13.0, 7.0 Hz, 2H), 4.55 – 4.41 (m, 0.7H), 3.83 (d, *J* = 3.7 Hz, 3H), 3.66 (d, *J* = 4.1 Hz, 3H), 3.58 – 3.49 (m, 8.4H), 3.44 – 3.25 (m, 5.5H).



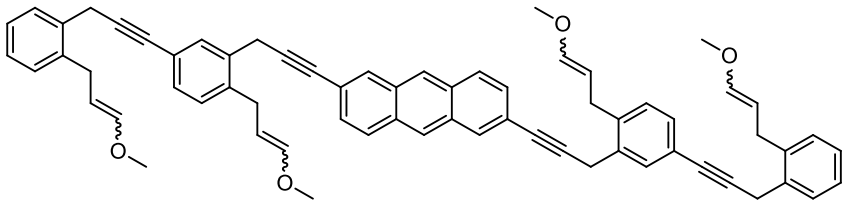
2,6-Bis(3-(2-(3-methoxyallyl)-5-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenyl)prop-1-yn-1-yl)naphthalene (109). $PdCl_2(PPh_3)_2$ (3.41 mg, 4.86 µmol, 5 mol%) and copper(I) iodide (1.85 mg, 9.72 µmol, 10 mol%) were suspended in previously degassed Et_3N (0.6 mL) and the mixture was bubbled with Ar for 10 min. A solution of **108** (1.1 equiv, 66.5 mg, 107 µmol) in degassed THF (1 mL) and another solution of **99** (1.0 equiv, 36.0 mg, 97.2 µmol) in degassed THF (1 mL) were subsequently added and the reaction was stirred at 40 ºC. Since the 2,6-diiodonaphthalene was not completely dissolved, THF (3 mL) was added again after 15 min and the reaction was left to stir at 40 ºC overnight. After that, the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 94.5:4.5:1 to 91.5:7.5:1 to 89.5:9.5:1) afforded the title compound as an orange oil (20.8 mg, 24.0 µmol, 25% yield).[109]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.72 – 7.47 (m, 11H), 7.36 – 7.29 (m, 2H), 7.26 – 7.18 (m, 11H), 6.47 – 6.32 (m, 4H), 6.08 – 5.95 (m, 1.5H), 4.98 – 4.84 (m, 4H), 4.58 – 4.46 (m, 1.5H), 3.84 (s, 10H), 3.69 – 3.63 (m, 5H), 3.56 – 3.50 (m, 13H), 3.39 (dt, *J* = 5.1, 2.3 Hz, 9H).



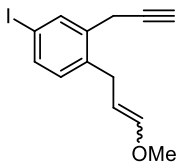
2,6-Diiodoanthracene (**S2**) was prepared following a reported procedure.[110]

108 The mass of the compound could not be detected by HRMS analysis.
109 The mass of the compound could not be detected by HRMS analysis.
110 Stone, M. T.; Anderson, H. L. *Chem. Commun.* **2007**, 2387–2389.



2,6-Bis(3-(2-(3-methoxyallyl)-5-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenyl)prop-1-yn-1-yl)anthracene (111). $PdCl_2(PPh_3)_2$ (4.08 mg, 5.81 µmol, 5 mol%) and copper(I) iodide (2.20 mg, 11.6 µmol, 10 mol%) were suspended in previously degassed Et_3N (0.5 mL) and the mixture was bubbled with Ar for 10 min. 2,6-Diiodoanthracene (**S3**) (1.0 equiv, 50.0 mg, 116 µmol) and a solution of **99** (2.5 equiv, 108 mg, 291 µmol) in degassed THF (5 mL) were subsequently added and the reaction was stirred overnight at 60 ºC. After that, the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 94.5:4.5:1 to 89.5:9.5:1) afforded the title compound as a brown oil (11 mg, 12.0 µmol, 10% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.09 (s, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.71 – 7.61 (m, 1H), 7.59 – 7.37 (m, 6H), 7.37 – 7.28 (m, 2H), 7.25 – 7.03 (m, 14H), 6.43 – 6.27 (m, 4H), 6.03 – 5.94 (m, 1.5H), 4.87 (ddd, *J* = 15.5, 11.3, 7.7 Hz, 4H), 4.48 (dt, *J* = 15.0, 6.3 Hz, 1.5H), 3.83 (dd, *J* = 12.1, 3.5 Hz, 7H), 3.68 – 3.60 (m, 7H), 3.55 – 3.44 (m, 13H), 3.42 – 3.25 (m, 10H).
HRMS (APCI+) m/z calc. for $C_{66}H_{59}O_4$ $[M+H]^+$: 915.4408. Found: 915.4407.



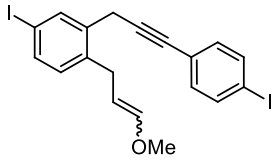
4-Iodo-1-(3-methoxyallyl)-2-(prop-2-yn-1-yl)benzene (105). To a solution of **100** (1.0 equiv, 221 mg, 575 µmol) in abs. EtOH (5.5 mL, 0.1 M) was added a solution of silver nitrate (3.0 equiv, 293 mg, 1.73 mmol) in dist. water (1 mL), which led to the instant formation of a white precipitate. The mixture was stirred at 23 ºC for 1.5 h and then the reaction was quenched by addition of aqueous $Na_2S_2O_3$ (3 mL) and diluted with EtOAc (20 mL). The suspension was filtered and the product was extracted from the filtrate with more EtOAc (3 × 10 mL), washed with more $Na_2S_2O_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc 19:1) afforded the title compound as a bright yellow oil (83 mg, 270 µmol, 46% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.80 (dd, *J* = 4.5, 1.8 Hz, 1.5H), 7.57 – 7.50 (m, 1.5H), 6.97 (d, *J* = 8.1 Hz, 1.5H), 6.34 (dt, *J* = 12.7, 1.3 Hz, 1H, *E*), 6.02 (dt, *J* = 6.1, 1.5 Hz, 0.5H, *Z*), 4.81 (dt, *J* = 12.7, 7.0 Hz, 1H, *E*), 4.41 (td, *J* = 7.4, 6.1 Hz, 0.5H, *Z*), 3.63 (s, 1.5H, *Z*), 3.55 (d, *J* = 2.6 Hz, 3H), 3.50 (s,

3H, *E*), 3.33 (dd, *J* = 7.4, 1.3 Hz, 1H, *Z*), 3.23 (dd, *J* = 7.0, 0.8 Hz, 2H, *E*), 2.27 (td, *J* = 2.7, 2.0 Hz, 1.5H).

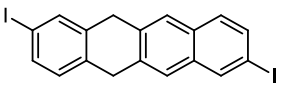
^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.2, 147.8, 139.7, 139.6, 137.8, 137.6, 137.4, 137.3, 136.7, 136.6, 131.6, 131.6, 103.7, 100.5, 91.9, 91.7, 81.7, 81.5, 71.8, 71.7, 60.2, 56.5, 31.1, 27.6, 22.5, 22.3.

HRMS (APCI+) m/z calc. for $C_{13}H_{14}IO$ $[M+H]^+$: 313.0084. Found: 313.0081.



4-Iodo-2-(3-(4-iodophenyl)prop-2-yn-1-yl)-1-(3-methoxyallyl)benzene (117). $PdCl_2(PPh_3)_2$ (6.30 mg, 9.0 µmol, 10 mol%) and copper(I) iodide (3.4 mg, 18.0 µmol, 20 mol%) were suspended in previously degassed Et_3N (0.8 mL) and the mixture was bubbled with Ar for 10 min. A solution of **105** (1.0 equiv, 28.0 mg, 90 µmol) and 1,4-diiodobenzene (1.2 equiv, 36.0 mg, 110 µmol) in degassed THF (2 mL) were subsequently added and the reaction was stirred at 50 ºC for 4 h. Then the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc 98:2) afforded the title compound as an yellow oil (*E*/*Z* 3:1, 25.8 mg, 50.2 µmol, 59% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 1.8 Hz, 0.3H, *Z*), 7.78 (d, *J* = 1.8 Hz, 1H, *E*), 7.68 – 7.60 (m, 2.7H), 7.53 (td, *J* = 8.0, 1.8 Hz, 1.3H), 7.20 – 7.12 (m, 2.7H), 6.96 (dd, *J* = 8.1, 2.3 Hz, 1.3H), 6.34 (d, *J* = 12.6, 1.3 Hz, 1H, *E*), 6.01 (dt, *J* = 6.1, 1.4 Hz, 0.3H, *Z*), 4.82 (dt, *J* = 12.7, 7.0 Hz, 1H, *E*), 4.43 (td, *J* = 7.4, 6.2 Hz, 0.3H, *Z*), 3.74 (s, 0.7 H, *Z*) 3.73 (s, 2H, *E*), 3.64 (s, 1H, *Z*), 3.51 (s, 3H, *E*), 3.39 (dd, *J* = 7.3, 1.2 Hz, 0.7H, *Z*), 3.28 (d, *J* = 6.9 Hz, 2H, *E*).

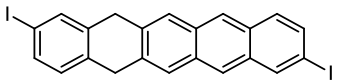


2,8-Diiodo-5,12-dihydrotetracene (119). To a MW vial containing a solution of **117** (1.0 equiv, 12.0 mg, 23.3 µmol) in HPLC grade CH_2Cl_2 (2 mL, 0.01 M) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (3.6 mg, 4.67 µmol, 20 mol%). The vial was sealed and the reaction mixture was stirred at 40 ºC for 1 h. After cooling to 23 ºC, NEt_3 (1 drop) was added and the solvent was removed under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 19:1 to 9:1) afforded the title compound as a white solid (8.0 mg, 17 µmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.68 (s, 2H), 7.65 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.61 (s, 1H), 7.55 – 7.50 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 1H), 4.00 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 136.6, 136.2, 136.1, 136.1, 135.7, 135.5, 134.1, 131.2, 129.3, 129.0, 125.5, 124.3, 91.4, 91.1, 36.5, 36.4.

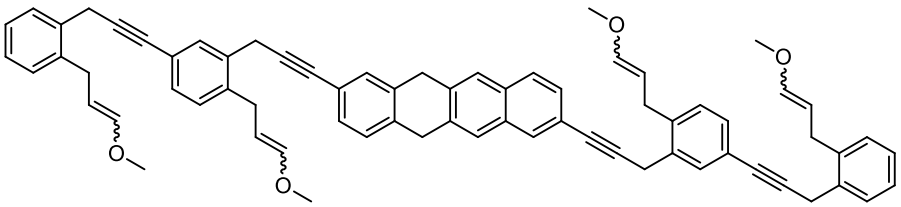
HRMS (APCI+) m/z calc. for $C_{18}H_{13}I_2$ $[M+H]^+$: 482.9101. Found: 482.9100.



2,9-Diiodo-5,14-dihydropentacene (120). $PdCl_2(PPh_3)_2$ (0.3 equiv, 34 mg, 9.0 µmol) and copper(I) iodide (0.6 equiv, 27 mg, 18.0 µmol) were suspended in previously degassed Et_3N (2 mL) and the mixture was bubbled with Ar for 10 min. A solution of **105** (1.0 equiv, 50 mg, 88.6 µmol) and 1,4-diiodobenzene (1.2 equiv, 73 mg, 190 µmol) in degassed THF (2 mL) were subsequently added and the reaction was stirred at 40 ºC for 4 h. Then the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc 98:2) was attempted, but the enyne **118** was not afforded with complete purity. Thus, the resulting yellow oil was taken on to the cycloisomerization step.

To a MW vial containing a solution of **118** (~44.0 µmol) in HPLC grade CH_2Cl_2 (2 mL, 0.01 M) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (6.8 mg, 8.9 µmol, 20 mol%). The vial was sealed and the reaction mixture was stirred at 50 ºC for 1 h. After cooling to 23 ºC, NEt_3 (1 drop) was added and the solvent was removed under reduced pressure. Purification by column chromatography (cyclohexane/CH_2Cl_2 95:5) afforded the title compound as a yellow solid (8.1 mg, 15 µmol, 17% yield over 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 1.8 Hz, 1H), 7.89 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.78 (s, 1H), 7.73 – 7.69 (m, 2H), 7.59 – 7.53 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 1H), 4.10 (d, *J* = 17.0 Hz, 4H).[111]
HRMS (APCI+) m/z calc. for $C_{22}H_{15}I_2$ $[M+H]^+$: 532.9258. Found: 532.9269.

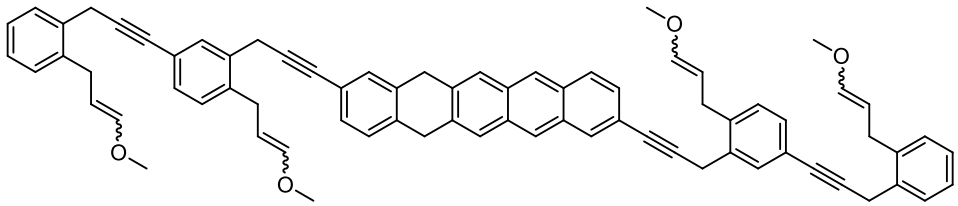


2,8-Bis(3-(2-(3-methoxyallyl)-5-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenyl)prop-1-yn-1-yl)-5,12-dihydrotetracene (121). $PdCl_2(PPh_3)_2$ (3.1 mg, 4.4 µmol, 30 mol%) and copper(I) iodide (0.5 mg, 2.2 µmol, 15 mol%) were suspended in previously degassed Et_3N (0.5 mL) and the mixture was bubbled with Ar for 10 min. A solution of **119** (1.0 equiv, 7.0 mg, 15.0 µmol) and a solution of **99** (4 equiv, 22.0 mg, 58.0 µmol) in degassed THF (2 mL) were subsequently added and the reaction was stirred overnight at 45 ºC. After that, the mixture was diluted with EtOAc (10 mL), filtered

111 Because of the decreased solubility of the compound in common organic solvents, a ^{13}C NMR spectrum could not be recorded.

through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 94.5:4.5:1 to 89.5:9.5:1) afforded the title compound as a brown oil (8.3 mg, 8.6 µmol, 59% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 7H), 7.54 – 7.39 (m, 15H), 7.20 (ddd, *J* = 4.4, 3.9, 2.0 Hz, 11H), 6.34 (dddd, *J* = 10.1, 6.6, 5.0, 4.2 Hz, 4H), 6.02 – 5.94 (m, 1.5H), 4.93 – 4.80 (m, 4H), 4.50 – 4.41 (m, 1.5H), 3.71 – 3.59 (m, 11H), 3.51 (d, *J* = 2.3 Hz, 11H), 3.42 – 3.24 (m, 7H).

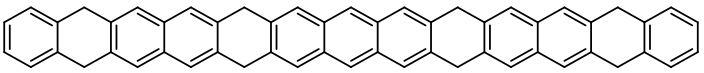


2,9-Bis(3-(2-(3-methoxyallyl)-5-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)phenyl)prop-1-yn-1-yl)-5,14-dihydropentacene (122). $PdCl_2(PPh_3)_2$ (5.5 mg, 7.9 µmol, 30 mol%) and copper(I) iodide (1 mg, 4.0 µmol, 15 mol%) were suspended in previously degassed Et_3N (1 mL) and the mixture was bubbled with Ar for 10 min. A solution of **120** (1.0 equiv, 14.0 mg, 26.3 µmol) and a solution of **102** (4 equiv, 39.0 mg, 105 µmol) in degassed THF (4 mL) were subsequently added and the reaction was stirred overnight at 45 ºC. After that, the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 (99:1) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 94.5:4.5:1 to 89.5:9.5:1) afforded the title compound as a brown oil (9.2 mg, 9.2 µmol, 61% yield).

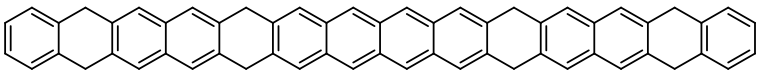
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.63 (m, 2H), 7.59 – 7.36 (m, 7H), 7.29 (d, *J* = 1.5 Hz, 1H), 7.18 (ddd, *J* = 22.4, 10.9, 5.4 Hz, 12H), 6.40 – 6.29 (m, 4H), 5.99 (t, *J* = 6.5 Hz, 1.5H), 4.87 (ddd, *J* = 21.0, 13.9, 7.0 Hz, 4H), 4.52 – 4.39 (m, 1.5H), 3.82 (d, *J* = 2.9 Hz, 2H), 3.65 (dt, *J* = 10.9, 5.5 Hz, 9H), 3.51 (d, *J* = 2.6 Hz, 10H), 3.41 – 3.24 (m, 9H).

General Procedure for the Synthesis of Higher Hydroacenes:

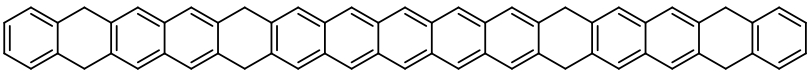
A MW vial containing a solution of the corresponding tetraenyne (1 equiv) in anhydrous CH_2Cl_2 (0.1 M) was taken inside a glovebox filled with Ar and cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (20 mol%) was subsequently added. The MW vial was sealed and the reaction was heated to 40 ºC for 1 h. Then it was cooled to 23 ºC and quenched by the addition of one drop of degassed NEt_3. After removing the volatiles under vacuum, the mixture of hydroacenes was dissolved in CH_2Cl_2, precipitated by addition of Et_2O and isolated by vacuum filtration under Ar.
All the acquired hydroacenes were kept under Ar all the time due to their instability in the presence of oxygen.



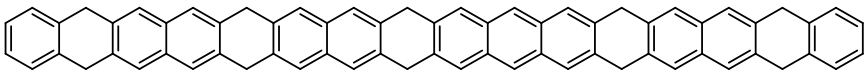
5,8,12,15,20,23,27,30-Octahydrotridecacene (Tridecacene-H8 (68)). The title compound was obtained as an off-white solid (mixture of isomers, 5 mg, 10 µmol, *ca.* 15% yield) following the general procedure from tetraenyne **94** (54 mg, 66 µmol).



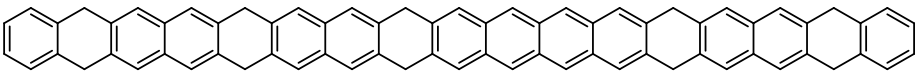
5,8,13,16,21,24,29,32-Octahydrotetradecacene (Tetradecacene-H8 (110)). The title compound was obtained as a yellow solid (mixture of isomers, 3.0 mg, 4 µmol, *ca.* 19% yield) following the general procedure from tetraenyne **105** (18 mg, 21 µmol).



5,8,14,17,22,25,31,34-Octahydropentadecacene (Pentadecacene-H8 (112)). The title compound was obtained as an off-white solid (mixture of isomers, 2.0 mg, 2.5 µmol, *ca.* 16% yield) following the general procedure from tetraenyne **107** (15 mg, 16 µmol).

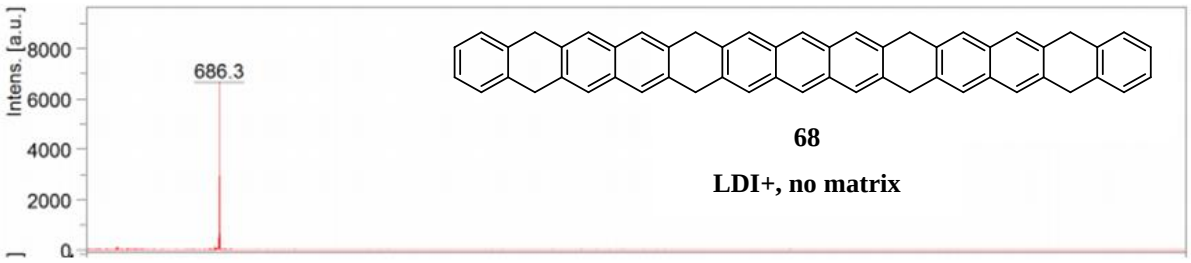


5,8,11,15,18,23,26,30,33,36-Decahydrobenzo[*b*]pentadecacene (Hexadecacene-H10 (115)). The title compound was obtained as a pale orange solid (mixture of isomers, 2.0 mg) following the general procedure from tetraenyne **117** (9 mg, 9 µmol).

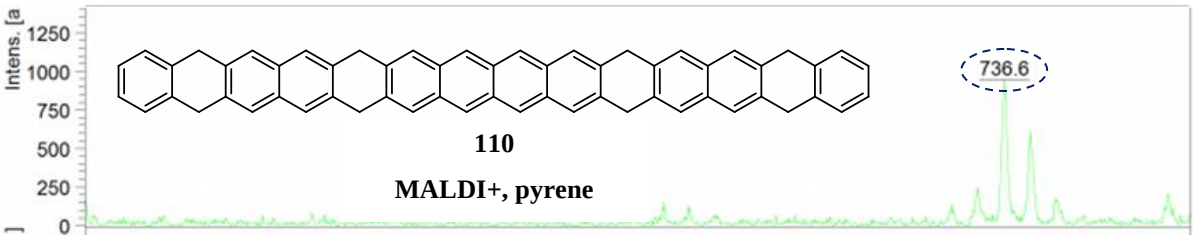


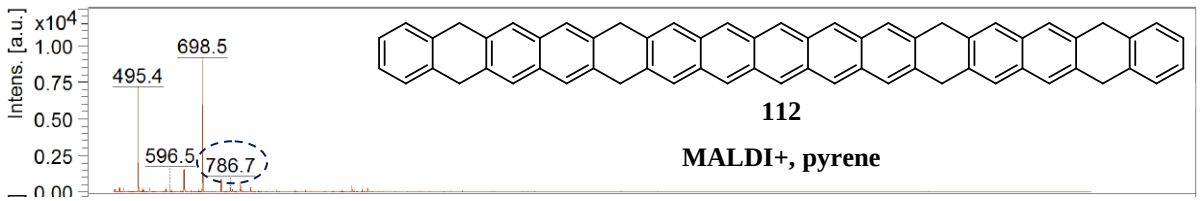
5,8,11,16,19,24,27,32,35,38-decahydronaphtho[2,3-*b*]pentadecacene (Heptadecacene-H10 (116)). The title compound was obtained as a pale brown solid (mixture of isomers, 1.5 mg) following the general procedure from tetraenyne **117** (11.2 mg, 11 µmol). This product was isolated by vacuum filtration under Ar after dissolving in CH_2Cl_2 and precipitating with MeOH.

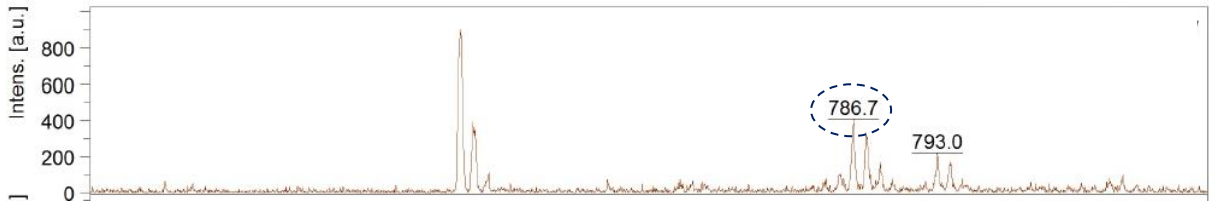
Mass Spectra of Polyhydroacenes



The masses of compounds **110** and **112** were detected in the crude solid obtained after vacuum filtration.







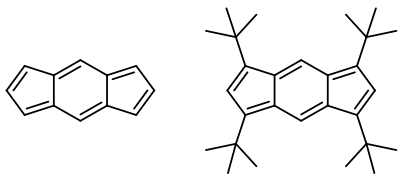
Chapter II: *New Applications of 1,7-Enynes on the Gold(I)-Catalyzed Synthesis of Hydroacene Derivatives*

INTRODUCTION

Indacene Derivatives

Indacenes are conjugated cyclic hydrocarbons, with antiaromatic character, containing destabilized 4n π-electrons,[1] while aromatic compounds have (4n + 2) π-electrons. Consequently, these molecules are inherently destabilized and have a small energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).[2] Furthermore, in comparison to aromatic molecules, their HOMO and LUMO energy levels are low-lying and their bonds have alternated lengths.[3]

The tricyclic *s*-indacene (**1**), illustrated in Figure 1 has been synthesized by Hafner *et al*. early in the 1960's, but could not be isolated because of its extreme thermal instability and susceptibility to autoxidation.[4] In order to permit its characterization, the compound was subjected later on to tetrasubstitution with four bulky *tert*-butyl groups. The new analogue **2** was found to be kinetically stable and was isolated as a crystalline solid.[5]



1 **2**

Figure 1. Structures of indacene and 1,3,5,7-tetra-*tert*-butyl-*s*-indacene

To overcome the issues related to their instability, indacenes have been integrated within larger conjugated systems, such as indenofluorenes[3,6] or naphthoindacenes.[7] As a result, these compounds and their derivatives have been investigated in the field of semiconducting materials.[8] Thus, preliminary studies indicated mobilities as high as 0.44 $cm^2/(V\ s)$ for indacenodibenzothiophenes.[6] Furthermore, the reduced aromaticity that stems from the replacement

1 Rudebusch, G. E.; Haley, M. M. In *Polycyclic Arenes and Heteroarenes*; Miao, Q.; Wiley-VCH Verlag: Weinheim, Germany, **2015**.
2 Minsky, A.; Meyer, A. Y.; Rabinovitz, M. *Tetrahedron* **1985**, *41*, 785−791.
3 Frederickson, C. K.; Rose, B. D.; Haley, M. M. *Acc. Chem. Res.* **2017**, *50*, 977−987.
4 Hafner, K.; Häfner, K. H.; König, C.; Kreuder, M.; Ploss, G.; Schulz, G.; Sturm, E.; Vöpel, K. H. *Angew. Int. Ed.* **1963**, *3*, 123−134.
5 Hafner, K.; Stowasser, B.; Krimmer, H.-P.; Fischer, S.; Böhm, M. C.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 630−632.
6 Marshall, J. L.; Uchida, K.; Frederickson, C. K.; Schütt, C.; Zeidell, A. M.; Goetz, K. P.; Finn, T. W.; Jarolimek, K.; Zakharov, L. N.; Risko, C.; Herges, R.; Jurchescu, O. D.; Haley, M. M.; *Chem. Sci.* **2016**, *7*, 5547−5558.
7 Zeidell, A. M.; Jennings, L.; Frederickson, C. K.; Ai, Q.; Dressler, J. J.; Zakharov, L. N.; Risko, C.; Haley, M. M.; Jurchescu, O. *Chem. Mater.* **2019**, *31*, *17*, 6962−6970.
8 Chase, D. T.; Fix, A. G.; Kang, S. J.; Rose, B. D.; Weber, C. D.; Zhong, Y.; Zakharov, L. N.; Lonergan, M. C.; Nuckolls, C.; Haley, M. M. *J. Am. Chem. Soc.* **2012**, *134*, 10349−10352.

of two six-membered rings with five-membered rings in acenes enhances their stability and enables efficient charge transport, as it has already been demonstrated for heteroacenes, such as dithiophenes[9] and dibenzothienothiophenes.[10]

Among the extended *s*-indacene derivatives, indenofluorenes (IFs) are very interesting compounds due to their formal antiaromaticity, open-shell biradical character and narrow band gaps. Thus, compared to pentacene, their linear aromatic counterpart, IFs contain a 6-5-6-5-6 fused ring system and a formally antiaromatic 20 π-electron system.3 The family of indenofluorenes contains 5 isomers (Figure 2). However, this discussion will focus on indeno[1,2-*b*]fluorene (**4**) and indeno[2,1-*a*]fluorene (**5**).

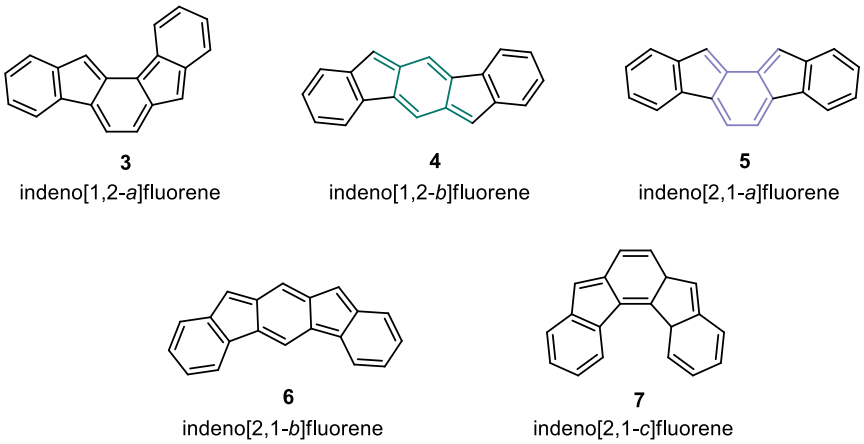


Figure 2. The IF family of compounds

IF **4** contains a central eight π-electron *para*-quinodimethane (*para*-xylylene, blue bonds) core, a well-known reactive intermediate with an open shell configuration that readily undergoes dimerization or polymerization.[11] By contrast, IF **4** has a closed-shell configuration with two Clar sextets, which might be converted into the major resonance form **I**, with an open-shell diradical configuration and three sextets after aromatization (Scheme 1).[12] The parent member of this family, compound **4**, was expected to be highly reactive and, indeed, its synthesis has only been reported very recently.[13]

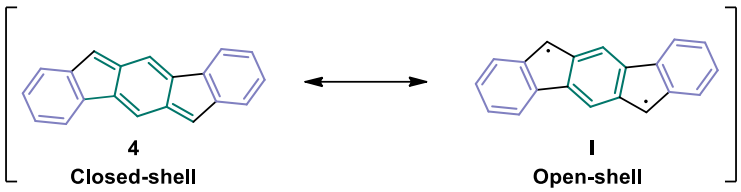
9 (a) Goetz, K. P.; Li, Z.; Ward, J. W.; Bougher, C.; Rivnay, J.; Smith, J.; Conrad, B. R.; Parkin, S. R.; Anthopoulos, T. D.; Salleo, A.; Anthony, J. E.; Jurchescu, O. D. *Adv. Mater.* **2011**, *23*, 3698−3703. (b) Subramanian, S.; Park, S. K.; Parkin, S. R.; Podzorov, V.; Jackson, T. N.; Anthony, J. E. *J. Am. Chem. Soc.* **2008**, *130*, 2706−2707.

10 Niimi, K.; Kang, M. J.; Miyazaki, E.; Osaka, I.; Takimiya, K. *Org. Lett.* **2011**, *13*, 3430−3433.

11 Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, Germany, **2000**.

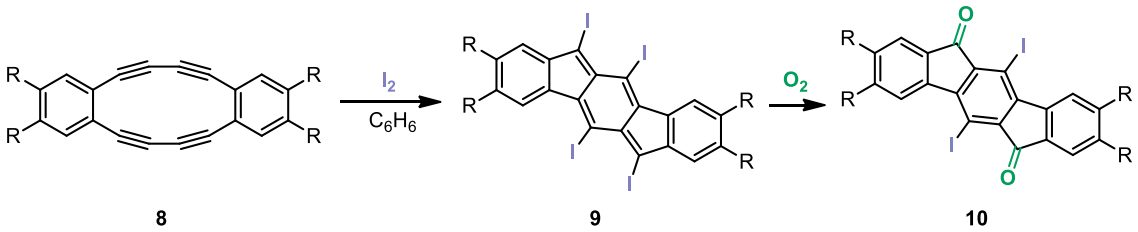
12 (a) Kubo, T. *Chem. Lett.* ***2015***, *44*, 111–112. (b) Fukuda, K.; Nagami, T.; Fujiyoshi, J.; Nakano, M. *J. Phys. Chem. A* **2015**, *119*, 10620–10627.

13 Majzik, Z.; Pavlicek, N.; Vilas-Varela, M.; Pérez, D.; Moll, N.; Guitián, E.; Meyer, G.; Peña, D.; Gross, L. *Nat. Commun.* **2018**, *9*, 1198–1204.



Scheme 1. Resonance structures of IF **4**

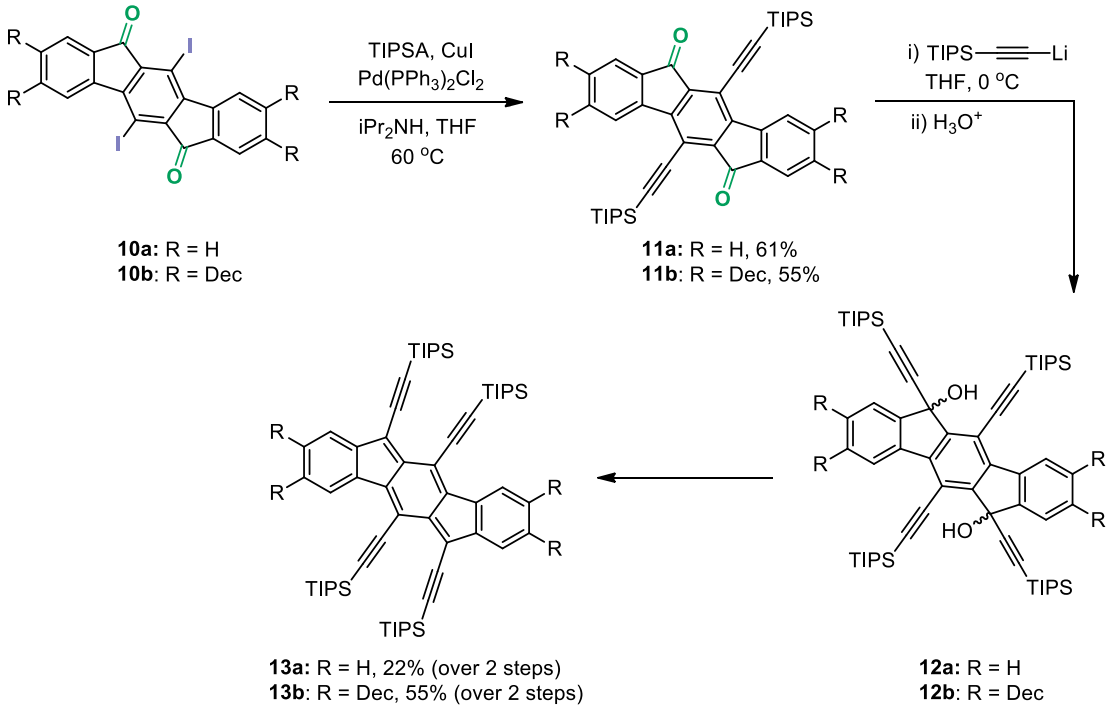
Since *s*-indacene **4** can be stabilized by functionalization, extensive efforts were made to generate substituted derivatives that are stable enough to allow isolation and characterization. The pioneering strategy for the synthesis of derivatives of **4** was developed by Swager *et al.*,[14] who prepared and characterized iodide-substituted indenofluorenes **9** from the treatment of octadehydrodibenz[12]annulene **8** with iodine *via* transannular cyclization (Scheme 2). However, after exposure to air, compounds **9** were quickly oxidized to form diones **10**.



Scheme 2. First synthetic route to IF **4** derivatives

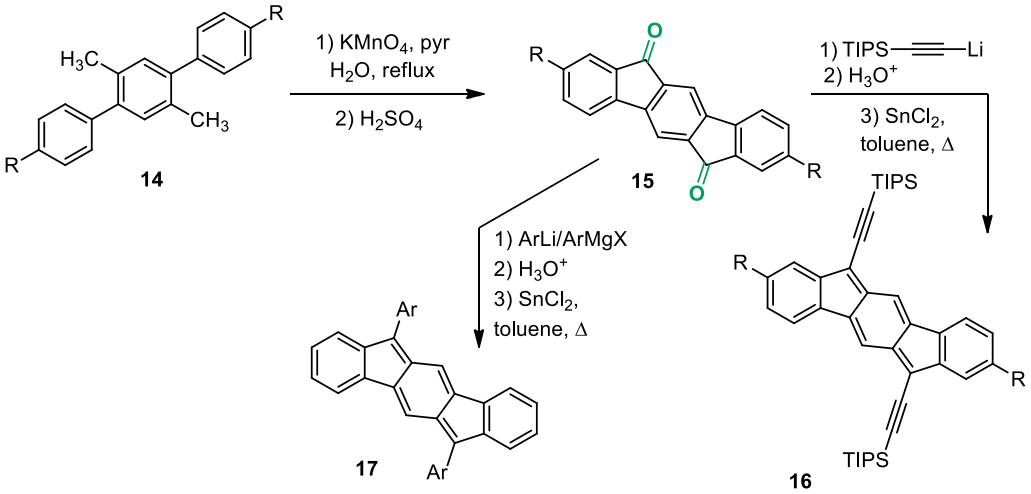
Inspired by this strategy, Haley and co-workers described the synthesis of silylethynylated indenofluorenes **13**,[15] which were obtained from diiododiones **10** after Sonogashira cross-coupling, addition of the required lithiated acetylide to the ketone groups of **11** and subsequent reduction of diols **12** (Scheme 3). The structures of the compounds were confirmed by X-ray diffraction, which showed the clear presence of the *p*-xylylene core. Additionally, investigation of the optoelectronic properties of the new molecules revealed that they are comparable to those of pentacene, while showing higher stability.

14 Zhou, Q.; Carroll, P. J.; Swager, T. M. *J. Org. Chem.* **1994**, *59*, 1294–1301.
15 Chase, D. T.; Rose, B. D.; McClintock, S. P.; Zakharov, L. N.; Haley, M. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 1127–1130.



Scheme 3. Synthesis of indenofluorenes **13**

Subsequently, the same group reported the preparation of new substituted analogues by improving the previous methodology.[16] Compounds **16** were obtained from terphenyls **14** *via* intramolecular Friedel-Crafts acylation (Scheme 4). The method gave rise to new derivatives substituted at 2,8-positions, but showed little variation in their electronic properties, as these carbons have minimal HOMO/LUMO density. Since DFT calculations revealed that substitution at 6,12-positions would be more significant, aryl-functionalized compounds **17** were also obtained.8 The analogues containing bulkier functionalities such as mesitylene proved to be more stable, with a half-life of several weeks in solution.



Scheme 4. Synthesis of indenofluorenes **13**

16 Chase, D. T.; Fix, A. G.; Rose, B. D.; Weber, C. D.; Nobusue, S.; Stockwell, C. E.; Zakharov, L. N.; Lonergan, M. C.; Haley, M. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11103−11106.

On the other hand, employing the sequence of reactions presented above, other derivatives were obtained by modifying the ring system fused to the indacene core. Thus, different Sonogashira coupling partners were engaged and afforded new compounds incorporating heterocycles, such as indacenodithiophene **18**[17] and indacenodibenzothiophenes **21**.6 Additionally, other arenes were introduced to provide dinaphthoindacene regioisomers **19** and **20** and diphenanthroindacenes **22**.[18]

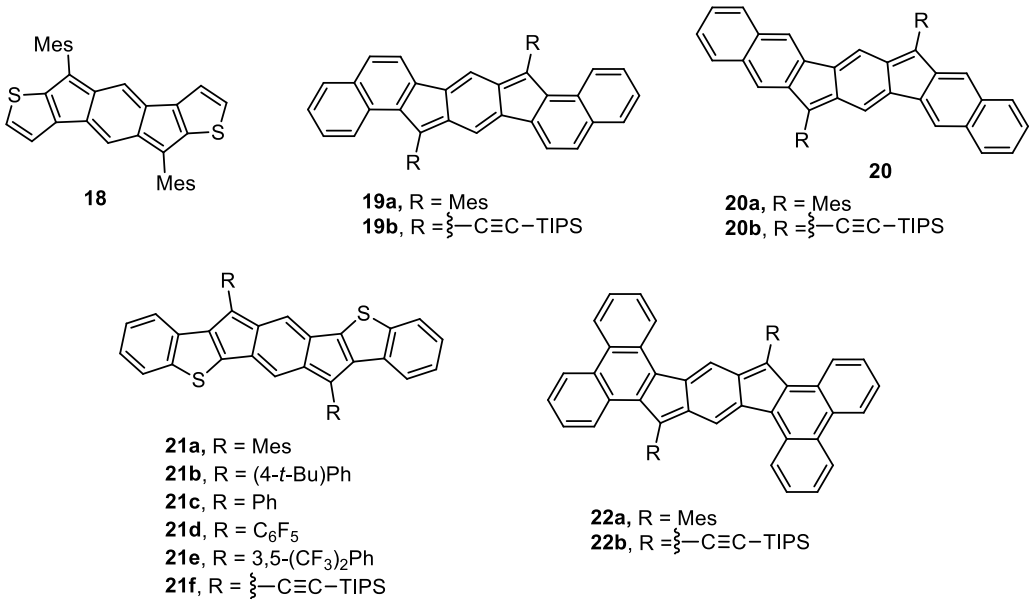
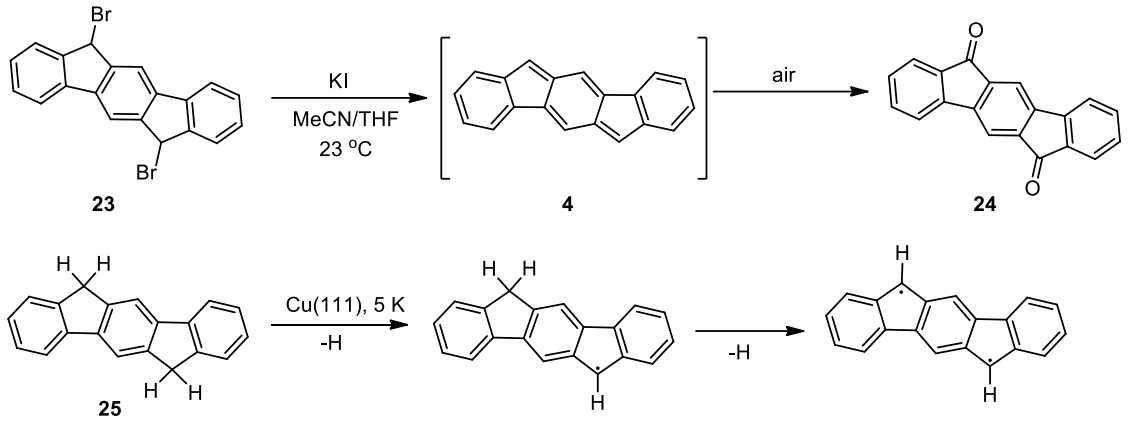


Figure 3. Indenofluorene derivatives prepared by Haley *et al.*

Unsubstituted **4** was obtained by Peña *et al.* both in solution and on-surface (Scheme 5).[13] Thus, **4** was formed in solution by iodide-promoted debromination of compound **23** and survived for a few minutes under ambient conditions before decomposing to form dione **24**. The reaction was monitored by UV spectroscopy and **4** was identified by the appearance of a group of signals between 460 and 520 nm, characteristic for the indenofluorene chromophore. On the other hand, the surface-assisted synthesis took place by tip-induced dehydrogenation of **25** on both Cu(111) and bilayer NaCl at low temperatures. On Cu(111), the two hydrogens were removed sequentially, whereas on NaCl bilayer, the dehydrogenation was concerted, giving rise to **4** without the generation of a stable intermediate. The electronic properties of **4** were investigated by STM and nc-AFM with CO-functionalized tips. The analysis revealed that on the NaCl film the molecule preserves its predicted antiaromatic, closed shell configuration. By contrast, on Cu(111) significant bond-order reorganization was encountered, with deviations from the closed-shell configuration, indicating that the π-electron distribution is highly influenced by the molecule-surface interactions.

17 Young, B. S.; Chase, D. T.; Marshall, J. L.; Vonnegut, C. L.; Zakharov, L. N.; Haley, M. M. *Chem. Sci.* **2014**, *5*, 1008−1014.

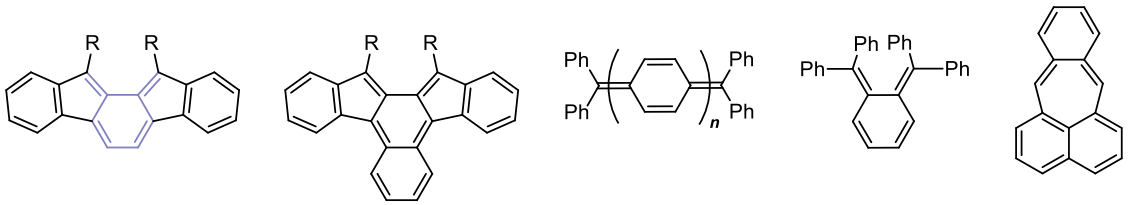
18 Frederickson, C. K.; Zakharov, L. N.; Haley, M. M. *J. Am. Chem. Soc.* **2016**, *138*, 16827−16838.



Scheme 5. Synthesis of indenofluorene **4** (a) in solution and (b) on Cu(111) surface

In contrast to indenofluorene **4**, the studies performed for IF **5a** and other *ortho*-quinodimethane-containing derivatives are scarce. The reason for that is the highly reactive *ortho*-quinodimethane core (Figure 4, purple bonds), which has an enhanced reactivity due to the presence of the s-*cis* diene unit. Furthermore, since *o*QDMs[19] have smaller HOMO–LUMO gap than *p*QDMs,[20] the compounds incorporating *o*QDMs would have smaller gaps than the *p*QDMs derivatives discussed before, which makes them attractive candidates in optoelectronics.

The parent indenofluorene **5a** (Figure 4) has attracted attention due to its structure containing a benzo bridge to the *o*QDM moiety that extends the π-conjugated system and inhibits the cyclization suffered by *o*QDMs to form benzocyclobutenes.[21] Furthermore, since **5a** contains a *cis*-diene unit, it could be engaged in Diels-Alder cycloadditions with proper dienophiles.[22] Figure 4 also depicts some known members from the family of *o*QDMs. Among them, tetraphenyl-*o*QDM[23] (**29**) and pleiadene[24] (**30**) were too reactive and could only be generated in rigid glass matrices.



5a: R= H
5b: R = Ph
5c: R = Mes

26a: R= H
26b: R = Ph
26c: R = Mes

27: ***n*** = 1
28: ***n*** = 2

29

30

Figure 4. Known compounds of the *o*QDM family

19 (a) Szwarc, M. *Discuss. Faraday Soc.* **1947**, *2*, 46–49. (b) Pearson, J. M.; Six, H. A.; Williams, D. J.; Levy, M. *J. Am. Chem. Soc.* **1971**, *93*, 5034–5036.

20 (a) Errede, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 949–954. (b) Migirdicyan, E.; Baudet, J. *J. Am. Chem. Soc.* **1975**, *97*, 7400–7404.

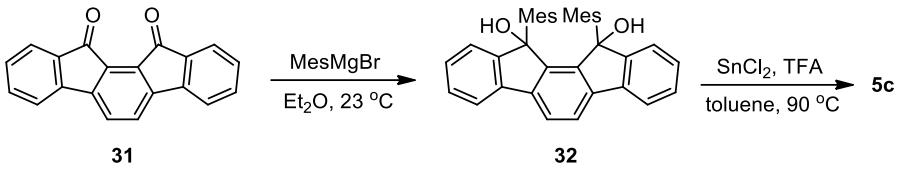
21 Shimizu, A.; Tobe, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 6906–6910.

22 Segura, J. L.; Martín, N. *Chem. Rev.* **1999**, *99*, 3199–3246.

23 (a) Quinkert, G.; Wiersdorff, W.-W.; Finke, M.; Opitz, K. *Tetrahedron Lett.* **1966**, *7*, 2193–2200. (b) Quinkert, G.; Wiersdorf, W.-W.; Finke, M.; Opitz, K.; von der Haar, F.-G. *Chem. Ber.* **1968**, *101*, 2302–2325.

24 (a) Kolc, J.; Michl, J. *J. Am. Chem. Soc.* **1970**, *92*, 4147–4148. (b) Kolc, J.; Michl, J. *J. Am. Chem. Soc.* **1973**, *95*, 7391–7401.

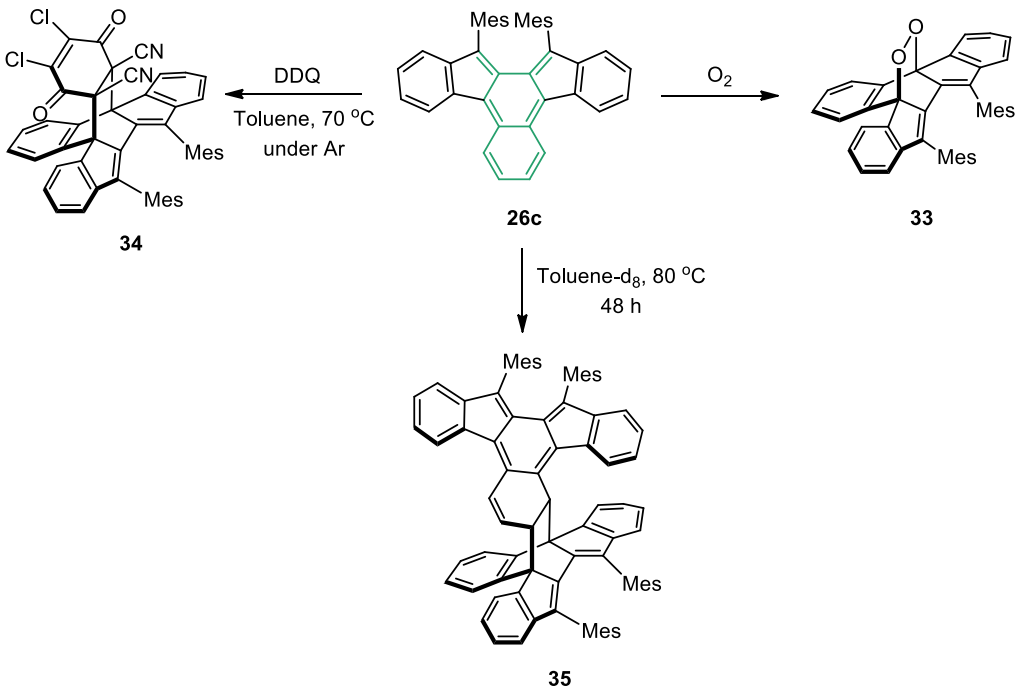
One of the first derivatives of **5a**, the 11,12-diphenyl analogue **5b** was prepared by Le Berre *et al.*,[25] but its molecular and electronic structures could not be investigated because of its high instability in presence of oxygen.[26] By contrast, the group of Tobe described the air-stable compound **5c**, substituted with mesityl groups at positions 11,12 to ensure steric protection.[21] This analogue was obtained from diketone **31**, after addition of the required Grignard reagent and dehydroxylation of the resulting diol **32** (Scheme 6). IF **5c** was found to be stable in solution under ambient conditions for one week and resistant to reaction with maleic anhydride even at 100 °C. Furthermore, the mesityl groups allowed the confirmation of its structure by X-ray crystallography and examination of the bond lengths indicated the presence of the *o*QDM moiety.



Scheme 6. Preparation of IF **5c**

Inspired by the stability of derivative **5c**, the same group also reported the synthesis of compound **26c** employing the same method.[27] This derivative incorporates the highly reactive naphthoquinodimethane core (Figure 4). Analogue **26c** was found to be more reactive in comparison to its indenofluorene counterpart **5c** due to its enhanced singlet biradical character demonstrated by X-ray crystallography and spectroscopic studies. The compound was found to be stable under argon in both solid state and in solution, but it decomposed under air to the endoperoxide **33**, which was generated by addition of oxygen at the inner naphthalene carbons (Scheme 7). Interestingly, the addition did not take place at the most reactive *exo*-methylene positions due to the steric protection of the mesityl groups, which inhibit the approach of oxygen or dienophiles. Thus, the reaction of **26c** with DDQ led to **34** by Diels-Alder cycloaddition at the internal positions. Furthermore, **26c** also underwent a [4+2] self-cyclodimerization to render dimer **35**, in which the inner naphthalene acted like the 4π component, while the outer double bond of the naphthalene played the role of the 2π reactant.

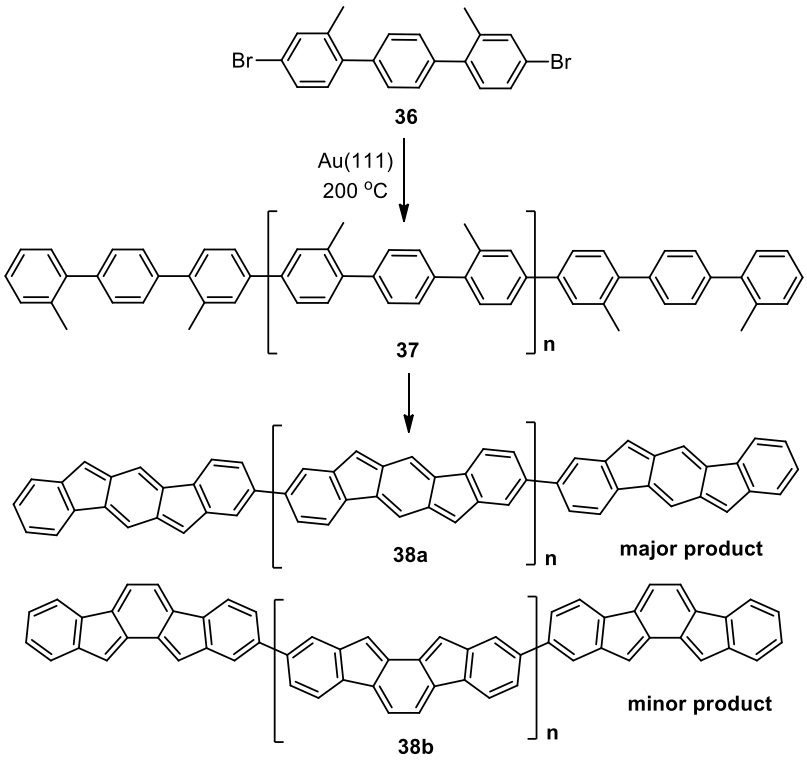
25 (a) Etienne, A.; Le Berre, A. C. R. *Hebd. Seances Acad. Sci.* **1956**, *242*, 1493–1496.
26 Le Berre, A. *Ann. Chim.* **1957**, *13*, 371–379.
27 Miyoshi, H.; Nobusue, S.; Shimizu, A.; Hisaki, I.; Miyata, M.; Tobe, Y. *Chem. Sci.* **2014**, *5*, 163–168.



Scheme 7. [4+2] Cycloadditions of IF **26c**

Surface-assisted synthesis has become an interesting alternative for the synthesis of molecules with embedded indenofluorene units that remained elusive previously. Thus, in addition to the synthesis of IF **4** reported by Peña *et al.*, another strategy was published by Müllen and Fasel for the formation of one-dimensional conjugated polymers **38** composed of indenofluorene moieties (Scheme 8).[28] Their method employs a poly(*para*-phenylene) backbone containing *ortho*-methyl groups and relies on the surface-assisted oxidative ring closure between a methyl unit and the neighboring aryl moiety to generate the five-membered rings at the desired positions. The polymeric backbone was formed on a flat Au(111) surface, under UHV conditions from terphenyl precursor **36** after debromination by annealing at 200 ºC. Further annealing at 350 ºC induces the formation of polymers with basic constituents **4** and **5a**. The synthetic steps were investigated by STM and the structure of the polymers was elucidated by nc-AFM, with the aid of a CO-functionalized tip. Hence, it was revealed that indeno[1,2-*b*]fluorene polymers **38a** are mainly observed on the surface, while the indeno[2,1-*a*]fluorene products **38b** are minor. The preferential formation of **38a** was rationalized by taking into account that **38a** requires the rotation of the *ortho*-methylphenylene subunits, whereas the generation of **38b** would involve the bending of the entire chain, which is less likely. Finally, the study of the electronic properties disclosed that the polymer has a band gap of 2.3 eV and a closed-shell electron configuration.

28 Di Giovannantonio, M.; Urgel, J. I.; Beser, U.; Yakutovich, A. V., Wilhelm, J. Pignedoli, C. A.; Ruffieux, P. Narita, A. Müllen, K., Fasel, R. *J. Am. Chem. Soc.* **2018**, *140*, 3532−3536.

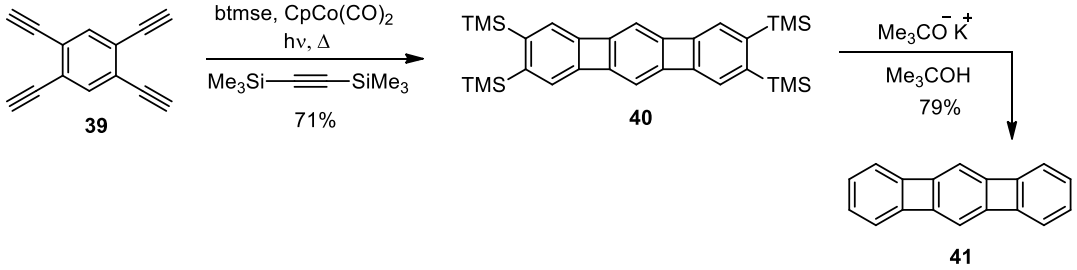


Scheme 8. On-surface synthesis of indenofluorene polymers **38**

Cyclobutadiene-Containing Acenes

The instability of acenes is an obstacle to the development of higher analogues of the series for use as semiconductors in molecular devices. An effective strategy to overcome this issue is the integration of four-membered rings in the acene core, as they increase their number of aromatic sextets and enhance their stability while keeping their linear shape.[29] The most frequent example is the introduction of cyclobutadiene (CBD), characterized by its highly antiaromatic character. The direct juxtaposition of cyclobutadiene and benzene rings gives rise to [*N*]phenylenes, the smallest member being biphenylene. [*N*]phenylenes have conjugated ladder structures, with alternating aromatic 6π-electron benzenoid and 4π-electron antiaromatic cyclobutadienoid rings, which contribute to their dearomatization, as it can be observed from the significant bond alternation.[30] Thus, due to their interesting electronic properties and distinctive chemical behavior, phenylenes are also promising semiconducting materials, whose band gaps have also been predicted to decrease rapidly with an increase in the number of ring components. Additionally, they present the advantage of being more stable to Diels-Alder reactions than acenes, as the products would be disfavoured, containing strained double bonds or benzocyclobutadienoid structures.

The classical syntheses of phenylenes were designed by Vollhardt and co-workers and rely on the cobalt-catalyzed [2+2+2] cycloaddition of *o*-diethynylbenzenes **39** with substituted alkynes under photolysis (Scheme 9).[31] Most of the [*N*]phenylenes reported up to date are prepared following this strategy,[32] although the synthesis of the ethynylated aromatic rings requires many steps and the targeted compounds are obtained in moderate yields.



Scheme 9. Vollhardt's synthesis of [*N*]phenylenes

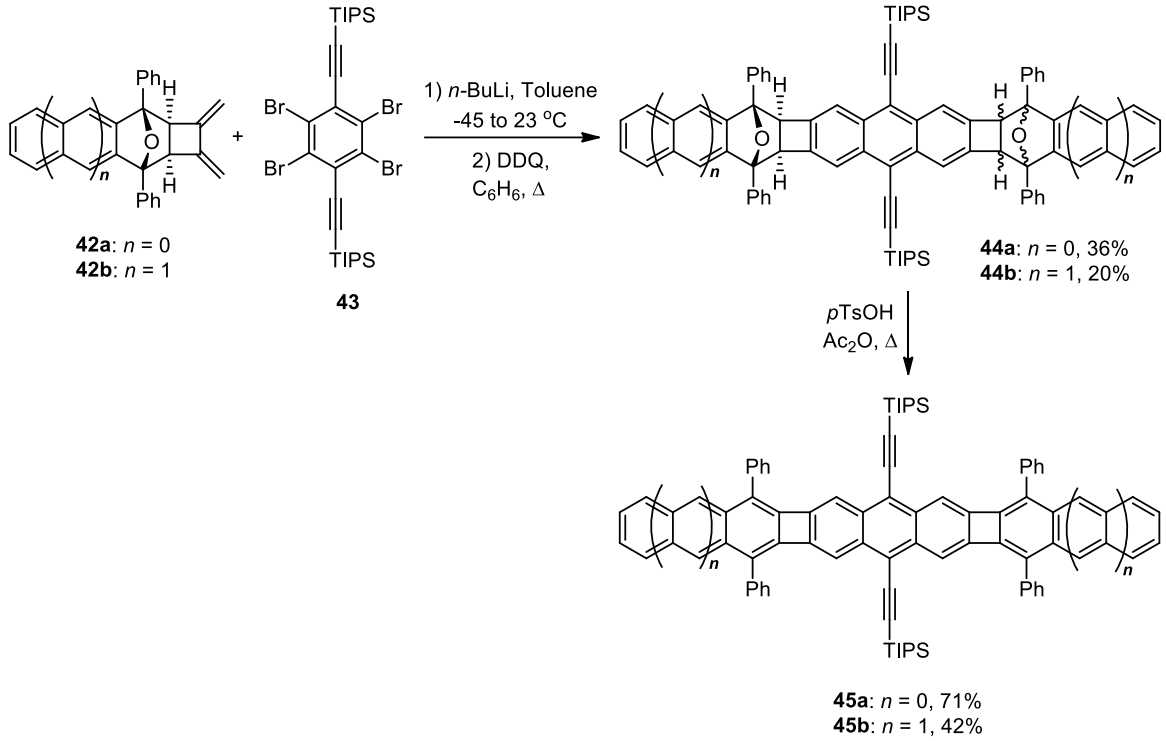
29 Biegger, P.; Schaffroth, M.; Patze, C.; Tverskoy, O.; Rominger, F.; Bunz, U. H. F. *Chem. Eur. J.* **2015**, *21*, 7048–7052.

30 Miljanic, O. S.; Vollhardt, K. P. C.; Haley, M. M.; Tykwinski, R. R. *Carbon-Rich Compounds: From Molecules to Materials*, Wiley-VCH: Weinheim, **2006**.

31 (a) Berris, B. C.; Hovakeemian, G. H.; Lai, Y. H.; Mestdagh, H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 5670−5687.

32 (a) Hirthammer, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2481−2482. (b) Schmidt-Radde, R. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1992**, *114*, 9713−9715. (c) Eickmeier, C.; Holmes, D.; Junga, H.; Matzger, A. J.; Scherhag, F.; Shim, M.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 800−804. (d) Han, S.; Bond, A. D.; Disch, R. L.; Holmes, D.; Schulman, J. M.; Teat, S. J.; Vollhardt, K. P. C.; Whitener, G. D. *Angew. Chem. Int. Ed.* **2002**, *41*, 3223−3227.

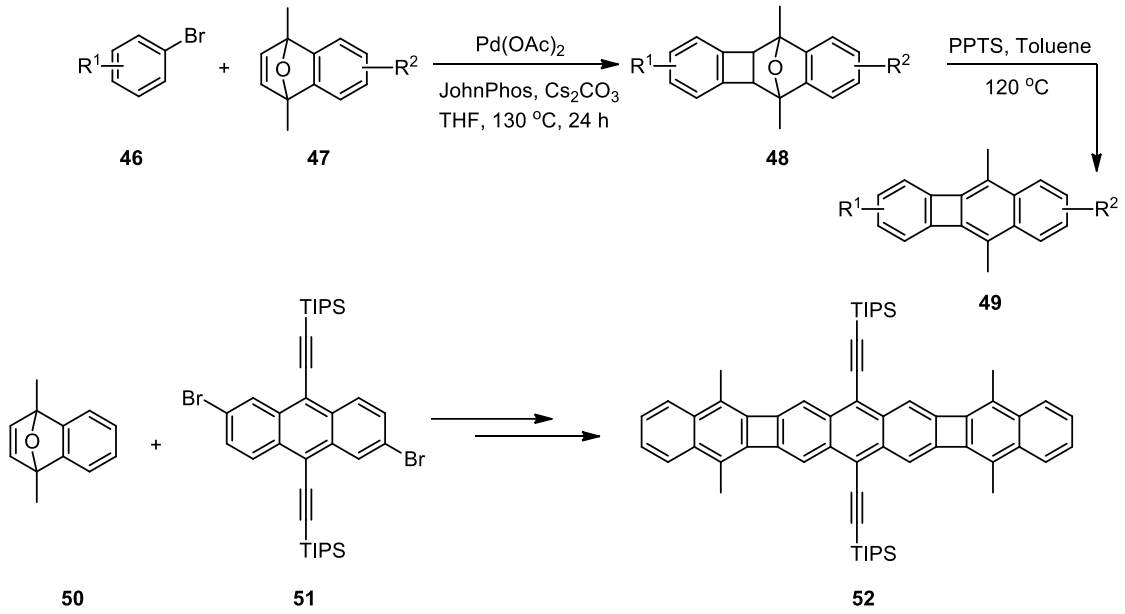
Swager extended the [*N*]phenylenes and described the synthesis of a new class of similar molecules, phenylene-containing oligoacenes (POAs) **45** (Scheme 10).[33] These compounds were obtained by consecutive Diels-Alder reactions, starting from 3,4-bis(methylene)cyclobutene as the building block. Nevertheless, this compound is unstable to air, requiring preparation by flash vacuum pyrolysis. Hence, diene **42**, afforded *via* Diels-Alder reaction between 1,3-diphenylisonaphthofuran and 3,4-bis(methylene)cyclobutene, underwent another Diels-Alder reaction with the bisaryne resulting from **43** and provided compound **44** after aromatization with DDQ. Finally, dehydration in presence of *p*TsOH successfully rendered POAs **45**, which demonstrated to be highly stable chromophores, with decreasing band gaps as their length increases.



Scheme 10. Synthesis of POAs **45**

A modular and high-yielding synthesis of acenes containing CBD rings was published by Xia and co-workers based on efficient palladium-catalyzed C−H activated annulation (CANAL) of aryl bromides **46** with readily prepared oxanorbornenes (oNBE) **47** and subsequent aromatization under acidic conditions (Scheme 11).[34] Compounds **48** are stable under ambient conditions. The same methodology was applied to prepare the acene-like compound **51**, incorporating two CBD rings, from silylethynylated anthracene **49** and oNBE **50**. The C−H activation and annulations took place regioselectively at positions 3 and 7 of the anthracene core. The crystal packing of **51** shows a face-to-face π-stacking, optimal for charge-carrier transport and applications in transistor devices.

33 Parkhurst, R. R.; Swager, T. M. *J. Am. Chem. Soc.* **2012**, *134*, 15351−15356.
34 Jin, Z.; Teo, Y. C.; Zulaybar, N. G., Smith, M. D.; Xia, Y. *J. Am. Chem. Soc.* **2017**, *139*, 1806−1809.



Scheme 11. Synthesis of CBD-containing acenes **49** and **52**

For all the previously described syntheses, crystal structures and DFT calculations revealed that the π-bonds are localized within the benzene ring, exocyclic to the CBD rings, reducing the antiaromatic character. Thus, following a similar synthetic sequence, the group of Xia described the synthesis of dinaphthobenzo[1,2:4,5]dicyclobutadienes **53**, compounds with a highly dearomatized benzenoid core embedded between two antiaromatic CBD rings (Figure 5).[35] The benzo[1,2:4,5]dicyclobutadiene core was reported by Vollhardt to have strong paratropicity, but in this structure it is stabilized by the neighbouring naphthalene moieties. Furthermore, the silylethynyl substituents on the central ring inhibit the degradation of the molecules and modulate the crystal packing required for OFET applications, depending on the chosen group. Thus, using TIPS as the protecting group of the alkynes, compounds **53** showed a two-dimensional bricklayer packing that determined an excellent behavior as semiconductor in OFETs. Following Xia's strategy, the group of Miao synthesized new derivatives of bisnaphtho-[2,3:3,4]cyclobut[1,2-*b*:1,2-*i*]anthracene **54**.[36] The compounds demonstrated that the π-π stacking of the molecules in a single crystal can be optimized by backbone functionalization with alkyl groups of different lengths. Thus, the tetrahexyl-substituted analogue **54c** exhibited π-π stacking with a particular zig-zag arrangement and high field-effect mobility, confirming the potential of biphenylene-containing analogues of acenes as effective p-type semiconductors.

35 Jin, Z.; Yao, Z.-F.; Barker, K. P.; Pei, X.; Xia, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 2034–2039.
36 Wang, J.; Chu, M.; Fan, J.-X.; Lau, T. K.; Ren, A.-M.; Lu, X.; Miao, Q. *J. Am. Chem. Soc.* **2019**, *141*, 3589−3596.

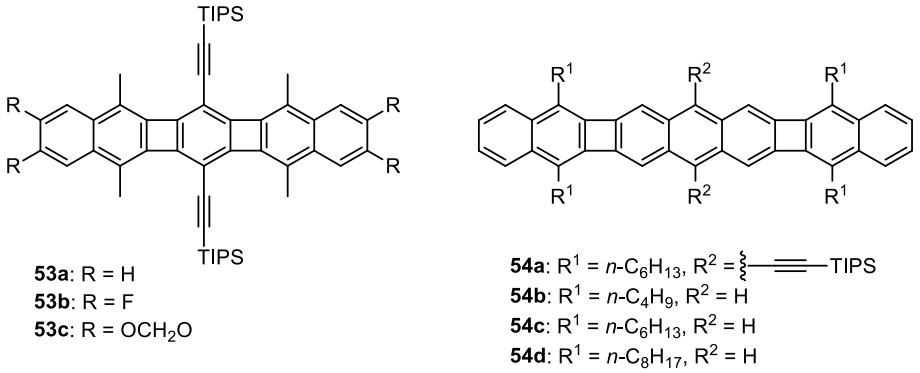
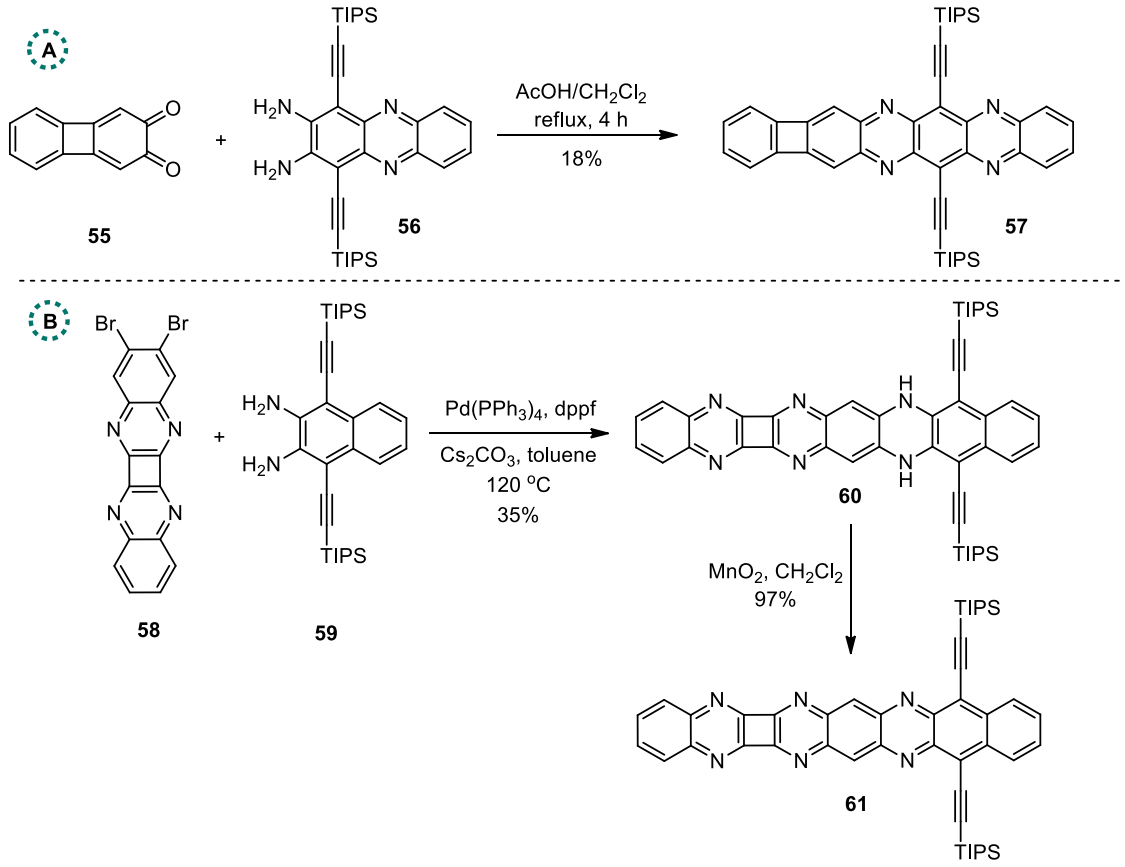


Figure 5. CBD-containing acenes designed by Xia's and Miao's groups

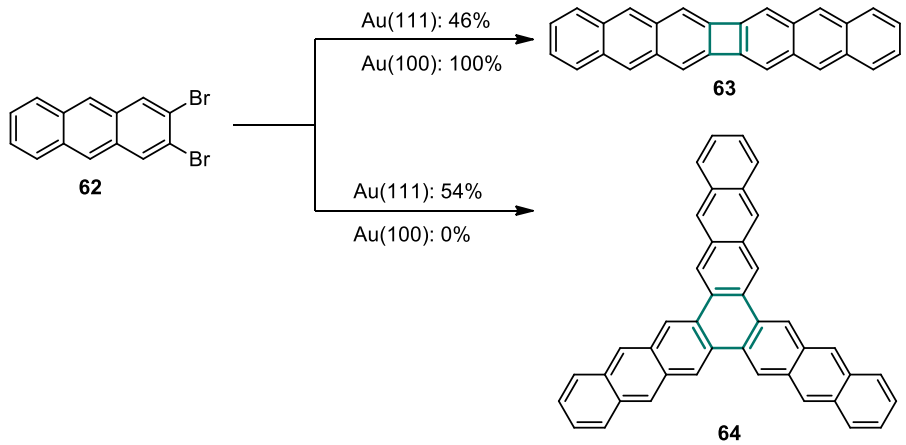
Azaphenylenes have also been described by the groups of Bunz[37] and Miao.[38] Bunz *et al.* obtained compound **57** *via* condensation of substituted *ortho*-diamine **56** with the stable biphenylene-2,3-dione **55** (Scheme 12a). The final compound was stable for a long period of time and showed good solubility. On the other hand, the azaphenylene **60**, described by Miao, was obtained by Pd-catalyzed coupling of 2,3-dibromo-cyclobuta[1,2-*b*:3,4-*b*']diquinoxaline **58** with phenylenediamine **59**, followed by MnO_2 oxidation of **60** (Scheme 12b). Compound **61** was found to be a good n-type semiconductor, demonstrating that the CBD ring is a good linker for the extension of *N*-heteroacenes.



Scheme 12. Syntheses of azaphenylenes reported by Bunz and Miao

37 Biegger, P.; Schaffroth, M.; Tsverkoy, O.; Rominger, F.; Bunz, U. H. F. *Chem. Eur. J.* **2016**, *22*, 15896–15901.
38 Yang, S.; Shan, B.; Xu, X.; Miao, Q. *Chem. Eur. J.* **2016**, *22*, 6637–6642.

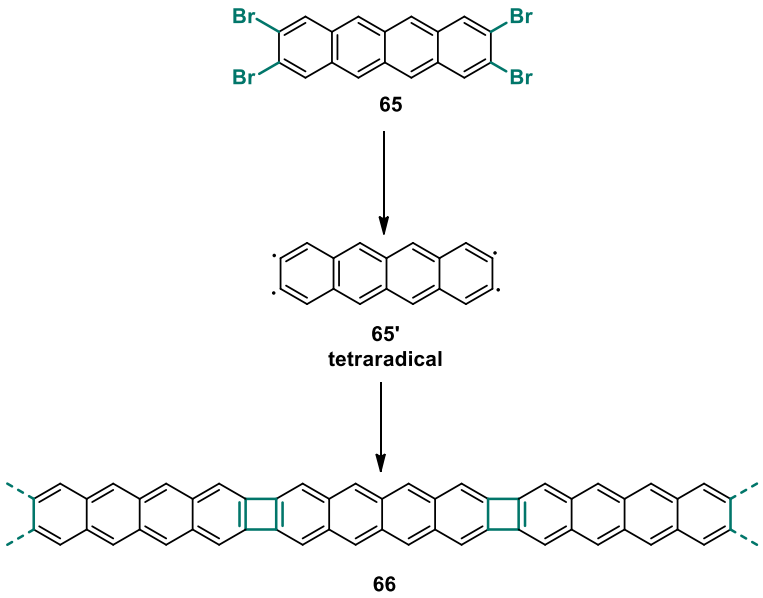
Surface-assisted synthesis has also demonstrated its potential in the synthesis of biphenylene-containing acenes. Hence, Grill and co-workers described the on-surface transformations of 2,3-dibromoanthracene (**62**) on both Au(100) and Au(111) (Scheme 13).[39] Heating the sample at 250 ºC resulted in removal of the bromine atoms and different oligomerizations of the anthracene moieties. Thus, the molecules of **62** were converted either into the linear dimers **63** by [2+2] cycloaddition or into the star-shaped trimers **64** through [2+2+2] cycloaddition. Both dimeric and trimeric structures were observed on Au(111), whereas on Au(100) only the formation of dimers is favoured. The high selectivity for the linear dimer is believed to stem from the ridged Au(100) that induces the parallel alignment of the precursors, an ideal arrangement for dimerization. Concomitantly, Fasel *et al.* reported similar reactions from 2,3-dibromotetracene.[40]



Scheme 13. Surface-assisted syntheses of dimers **63** and trimers **64** from **62**

Furthermore, Müllen, Fasel *et al.* reported the Ag(111) surface-assisted generation of hybrid cyclobutadiene-tetracene ribbons from thermally activated molecules of 2,3,8,9-tetrabromotetracene (**65**) (Scheme 14).[41] After deposition of the precursors, the nanoribbons are formed in two steps, the first of them being monomer activation by dehalogenation at room temperature, which gives rise to metal-coordinated nanostructures. Subsequent covalent coupling by formal [2+2] cycloaddition at 475 K led to polymers **66**. The transformations were investigated by high-resolution scanning tunneling microscopy (HRSTM) and nc-AFM with CO-functionalized tips, which unambiguously confirmed the presence of the CBD rings.

39 Koch, M.; Gille, M.; Hecht, S.; Grill, L. *Surface Science* **2018**, *678*,194–200.
40 Sánchez-Sánchez, C.; Nicolai, A.; Rossel, F.; Cai, J.; Liu, J.; Feng, X.; Müllen, K.; Ruffieux, P. Fase, R.; Meunier, V. *J. Am. Chem. Soc.* **2017**, *139*, 17617−17623.
41 Sánchez-Sánchez, C.; Dienel, T.; Nicolai, A.; Kharche, N.; Liang, L.; Daniels, C.; Meunier, V.; Liu, J.; Feng, X.; Müllen, K.; Sánchez-Valencia, J. R.; Gröning, O.; Ruffieux, P.; Fasel, R. *Chem. Eur. J.* **2019**, *25*, 12074–12082.



Scheme 14. Surface-assisted syntheses of tetracene nanoribbons **66**

OBJECTIVES

Given the versatility of our previously developed gold(I)-catalyzed [4+2] cycloadditions, our objective was to apply this cycloaddition on the synthesis of precursors of various acene derivatives, such as indacenes, cyclobutadiene-incorporating acenes and heteroacenes. Thus, we envisioned that the surface-assisted cyclization of 3,3'-dibromo-6,6',11,11'-tetrahydro-2,2'-bitetracene would give rise to *s*-indaceno[1,2-*b*:5,6-*b*']ditetracene, an analogue of undecacene with antiaromatic character and interesting electronic properties due to the presence of the indenofluorene core.

We also targeted the formation of 5,10,15,20-tetrahydrocyclobuta[1,2-*b*:3,4-*b*']ditetracene, a linear derivative of nonacene containing a cyclobutadiene ring, from 3,3'-dibromo-6,6',11,11'-tetrahydro-2,2'-bitetracene and the study of its electronic properties after cyclization on Au(111) surface. Finally, the formation of heptacene-cyclobutadiene hybrid ribbons was envisioned from heptacenes-H4 tetrasubstituted with halide moieties at the terminal rings. The tetrahydroheptacenes would be obtained using a new doubly substituted 1,7-enyne precursor, by double gold(I)-catalyzed [4+2] cycloadditions.

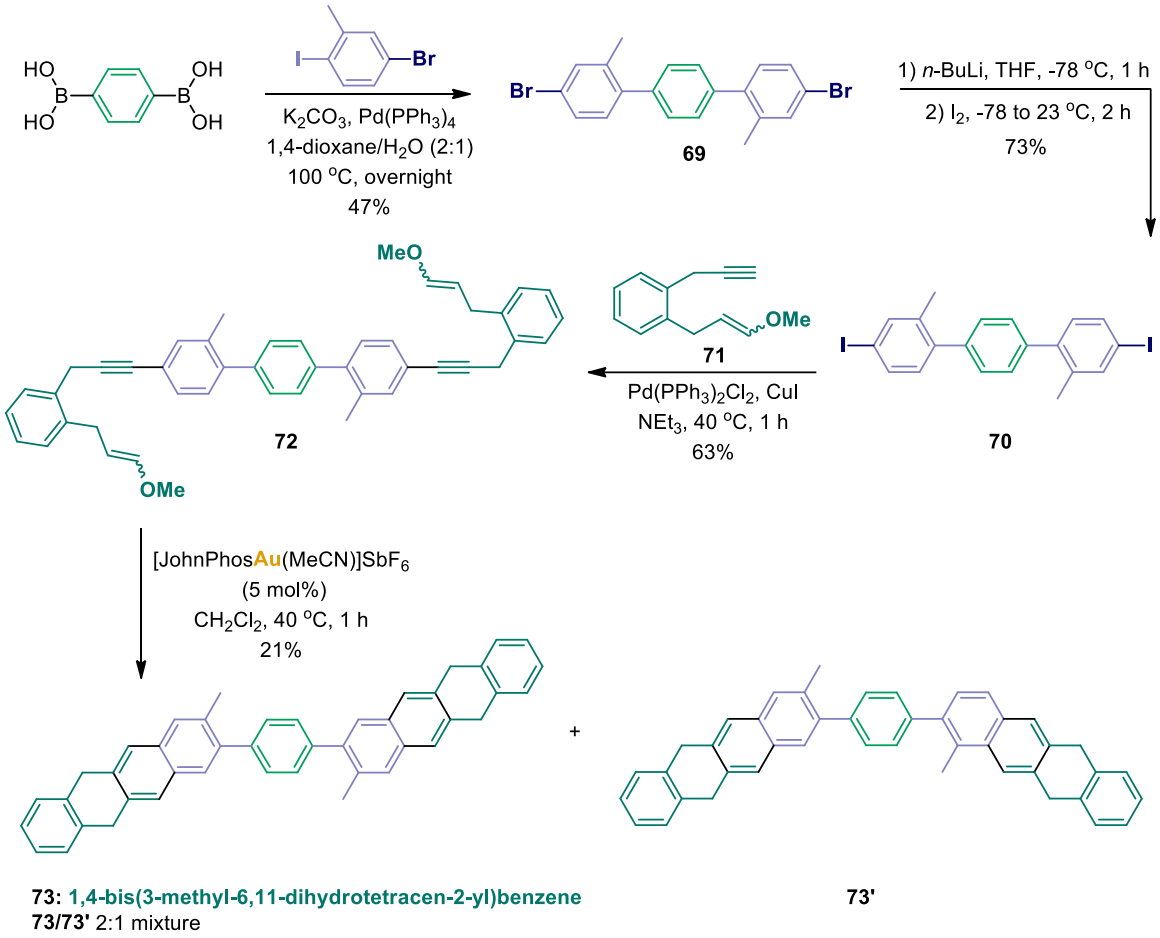
RESULTS AND DISCUSSION

Indacenes

Synthesis of *s*-Indaceno[1,2-*b*:5,6-*b*']ditetracene (67)

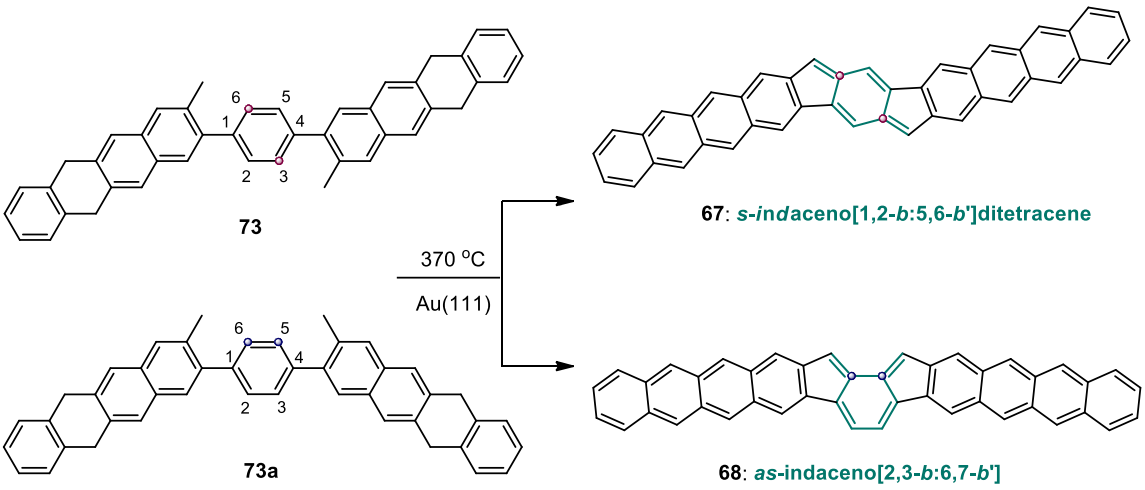
The methodology developed in our group, based on a gold(I)-catalyzed [4+2] cycloaddition, could also be applied to the preparation of extended PAHs and one relevant example is the synthesis of *s*-indacene derivatives. As a result, we propose the surface-assisted synthesis of *s*-indaceno[1,2-*b*:5,6-*b*']ditetracene (**67**) and *as*-indaceno[2,3-*b*:6,7-*b*']ditetracene (**68**), which are antiaromatic analogues of undecacene incorporating two five-membered rings. These molecules are interesting targets, since they contain indeno[1,2-*b*]fluorene (**4**) and indeno-[2,1-*a*]fluorene (**5a**) substructures, which have been reported to have partial diradicaloid character. Furthermore, as stated previously, their extended terminal acene components result in a decreased paratropicity.

Encouraged by the results obtained by Müllen and Fasel in the synthesis of conjugated polymers **38** that contain indenofluorene moieties,[28] we envisaged that compounds **67** and **68** could be acquired from the bis-dihydrotetracene precursor **73** by Au(111) surface-assisted oxidative ring closure. The key intermediate **73** was prepared from terphenyl **70**, which was in turn obtained through a double Suzuki reaction between 4-bromo-1-iodo-2-methylbenzene and 1,4-phenylenediboronic acid, followed by halide exchange of **69**. After double Sonogashira coupling of **70** with 1,7-enyne **71** and 2-fold Au(I)-catalysed [4+2] cycloaddition of enyne **72**, the target bishydroacene **73** was obtained together with a non-symmetric isomer **73'** (Scheme 15).



Scheme 15. Synthesis of hydroacenes **73**

The mixture of precursors **73** was then successfully deposited on Au(111) at 23 ºC and the desired dehydrogenation and cyclization took place after annealing at 370 ºC (Scheme 16). Since compound **73** exists as a mixture of rotamers, together with **73a**, the on-surface cyclization could occur both in a 1,4-fashion (at 2,5-positions of the central ring, major pathway) and in a 1,2-fashion (at 2,3-positions of the central ring, minor pathway). Consequently, the target product has been obtained as a mixture of two isomers, **67** and **68**, the second one as the minor regioisomer.



Scheme 16. Surface-assisted synthesis of indacenes **67** and **68**

Surface-Assisted Studies of 67 and 68

The molecules generated after deposition on Au(111) and annealing are illustrated in Figure 6. Visualization of the sample with the aid of STM clearly allowed the differentiation between the molecules of **67** (marked with a green rectangle) and **68** (highlighted by a yellow rectangle). Furthermore, apart from these structures, larger and differently shaped molecules were also detected, suggesting that intermolecular reactions had taken place. Among them, it is worth mentioning the structures distinguished with white circles due to their characteristic tuning fork shape, resulting from two molecules of **67**, cross-coupled along the tetracene moieties. Additionally, other covalently bound molecular structures resulting from the coupling of three units of **67** or **68** were also observed and are marked by yellow dashed circles. Besides, a V-shaped product originating from the 1,4-cyclization of the non-symmetrical precursor **73'** was found (white dashed rectangle). Nevertheless, the most remarkable structures encountered are the T-shaped molecules highlighted with a white triangle, undoubtedly derived from the perpendicular connection of two precursor molecules.

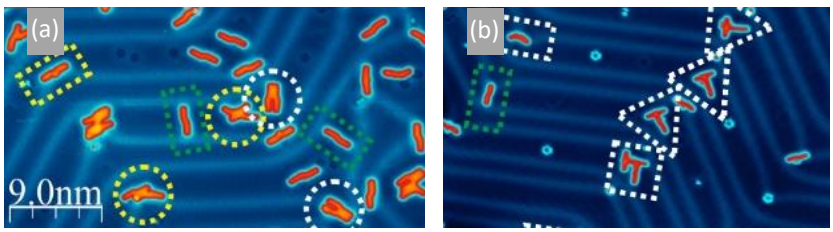


Figure 6. High-resolution STM images of the molecules after deposition on Au(111) and annealing at 370 °C (*a*: +0.5 V, 15 pA; *b*: -1.0 V, 100 pA)

As depicted in Figure 7 (a and b), the generation of the described molecular nanoarchitectures was validated by complementing the STM measurements with nc-AFM imaging with CO functionalized tips, an ideal tool for single molecule structural analysis by bond resolved images. Figure 7c and d provide identification of the first structure as indacene **67**, confirming the successful

cyclodehydrogenation of **73**. In order to obtain more information about **67** on Au(111), scanning tunneling spectroscopy measurements (STS) were carried out. Thus, an energy gap of approximately 2 eV was calculated, in good agreement with previously reported gas phase calculations for **67** that indicated the gap value of 1.87 eV.[18]

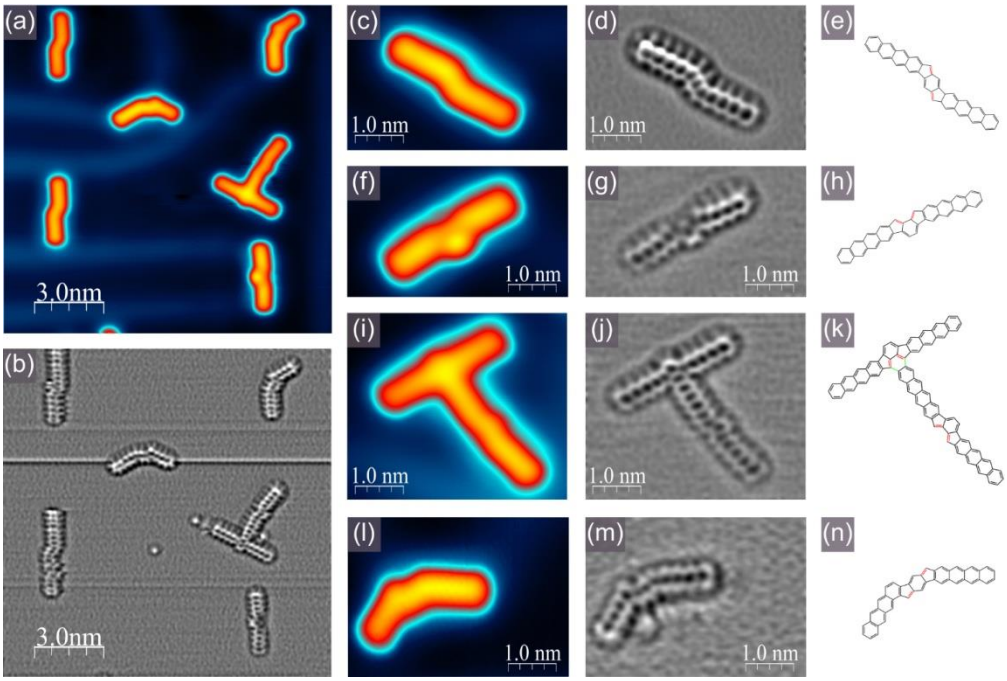
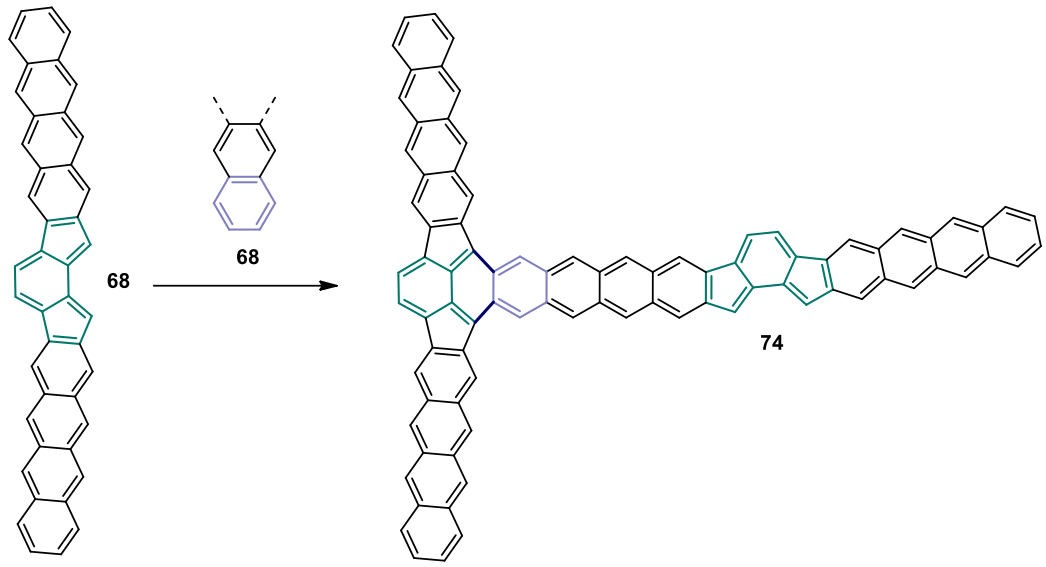


Figure 7. Assigned structures of the molecules **67**, **68**, **74** and **75** based on complementary STM (+0.5 V, 15 pA) and nc-AFM studies

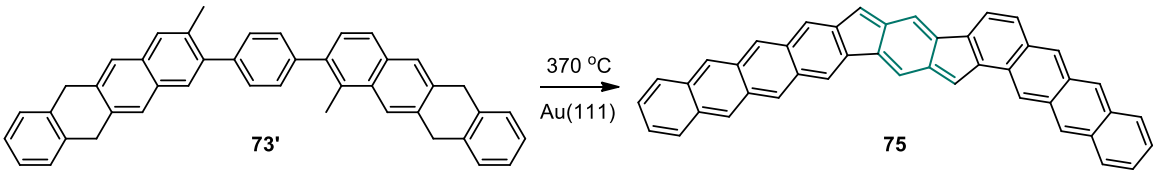
Furthermore, the STM studies allowed the identification of the almost straight feature with an additional bump in Figure 7f as **68**. The bond-resolved nc-AFM image (Figure 7g) points to the inclination of the central part of the molecule with the phenyl ring protruding from the surface and the two pentagonal rings rotated toward the surface within the surface pattern corner. Such a conformation could be rationalized by the high reactivity of both the specific surface areas as well as the 1,3-diene moiety located in the central part of the molecule **68**.

The T-shaped structure depicted in Figures 7i and 7j has been assigned as **74**. This kind of molecules made of two perpendicularly connected precursors **68** are clearly generated through a noteworthy cycloaddition reaction of **68** through its central *o*-quinodimethane moiety with the terminal aryl ring of another molecule (Scheme 17). Close inspection of the T-leg by STM indicated an almost identical appearance as for **68** (Figure 7f). Additionally, its bond-resolved nc-AFM image demonstrated its formation from **68**. Hence, the appearance of the T-molecular unit confirms the unprecedented on-surface cycloaddition-type reaction between two indacenoditetracene units **68** to form **74** (Figure 7k). This cycloaddition might proceed stepwise by a radical mechanism and not in the concerted manner of standard Diels-Alder reactions.



Scheme 17. Formal cycloaddition of **68** to form T-shaped molecule **74**

Additionally, the high-resolution STM and nc-AFM images in Figure 7l−m solve the structure of molecules with a V-type appearance, which correspond to structure **75** (Figure 7n). This molecule depicted in Scheme 18 originates from surface-assisted cyclization of the minor regioisomer **73'** formed in the gold(I)-catalyzed [4+2] cycloaddition of double enyne **72**.



Scheme 18. Surface-assisted generation of structure **75** from **73'**

Finally, the molecule bearing a tuning fork shape comprising two covalently merged precursors was assigned as **78** (Figure 12). Among other possible pathways, compound **78** could arise by dimerization of two molecules of 9,21-dihydro-*s*-indaceno-[1,2-*b*:5,6-*b*′]ditetracene (**76**), an intermediate in the formation of **67** from **73**, to give **77**, followed by the stepwise formation of the four additional C−C bonds (Scheme 19).

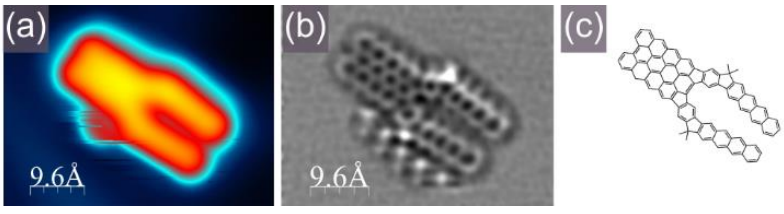
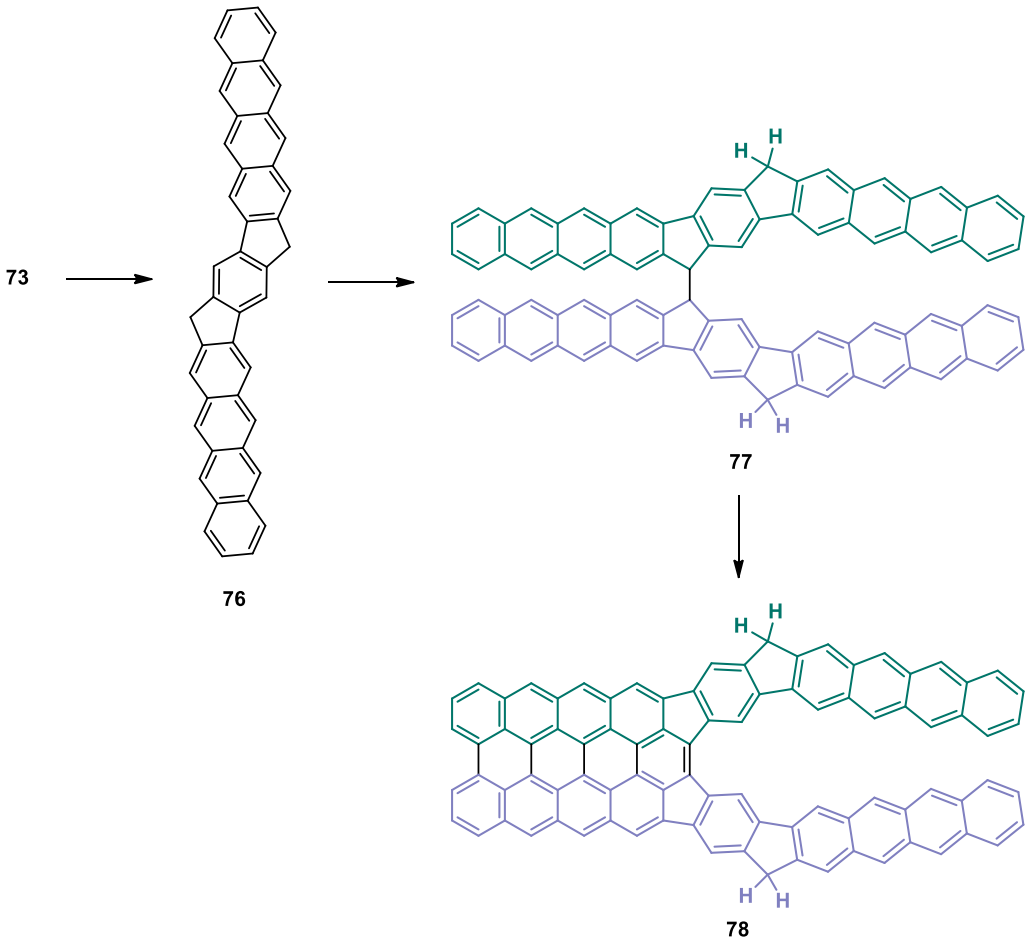


Figure 8. Assigned structures of the tuning-fork-shaped molecule **78** (c) by STM (a) (+0.5 V, 15 pA) and nc-AFM studies (b)

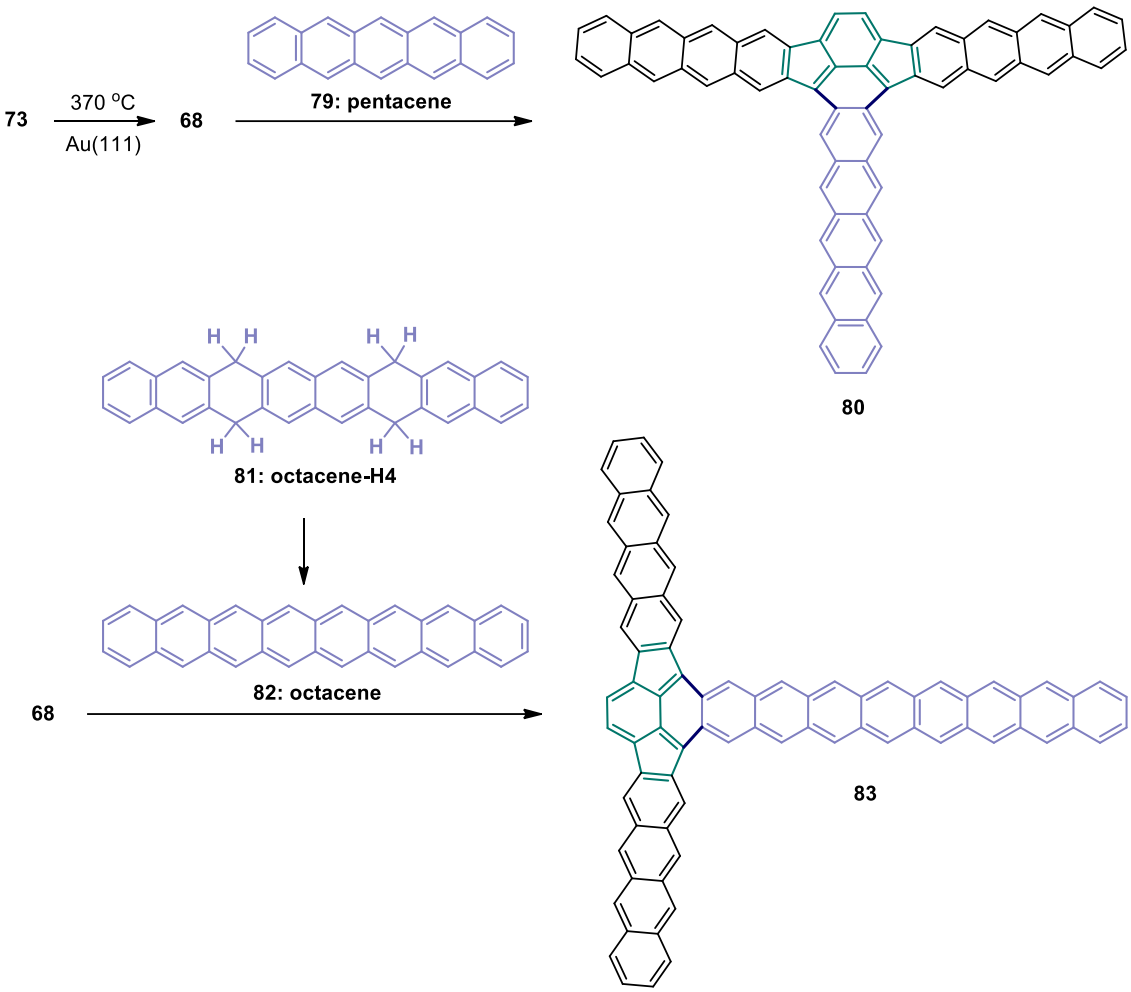


Scheme 19. Molecular pitchfork **78** generated from covalent coupling of two precursors **76**

Surface-Assisted Cycloadditions

The unexpected formation of the T-shaped molecules **74** by on-surface cycloaddition of two molecules of **68** suggested the possibility to perform heteromolecular cycloadditions with two different molecules and generate other types of T-shaped molecular structures. Thus, the reaction was tested with both pentacene and octacene (Scheme 20). In the second case, octacene was generated on the Au(111) surface from tetrahydrooctacene (octacene-H4), according to our original procedure.[42] The precursors **73** were sublimed onto Au(111) and transformed into indacenoditetracene **68** by annealing at 370 °C following the method described above. Pentacene (**79**) or octacene-H4 (**81**) have been deposited subsequently on the same sample followed by annealing at 370 °C in order to initiate the heteromolecular cycloadditions.

42 Zuzak, R.; Dorel, R.; Kolmer, M.; Szymonski, M.; Godlewski, S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2018**, *57*, 10500–10505.



Scheme 20. Intermolecular fusion between *as*-indacene **68** and acenes **79** and **82**

The successful formation of the T-nanostructures **80** and **83** by cycloaddition of pentacene and octacene with **68** was demonstrated by high-resolution STM and bond-resolved nc-AFM. Thus, Figures 9a and b show the molecules generated through on-surface fusion of **68** and pentacene, with an additional pentacene molecule in the bottom right-hand corner. The magnified image of **80** can be observed in Figure 9c. Furthermore, the high-resolution STM images of the T-shaped nanostructure **83** are displayed in Figures 9d and 9e. These results demonstrate the potential of this remarkable reaction, which could be used to generate fully conjugated extended acenes.

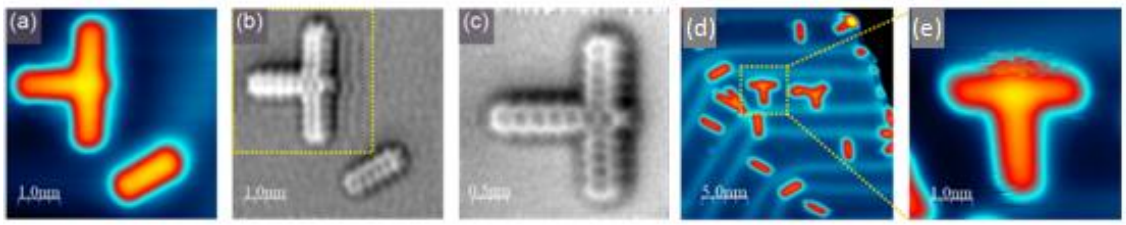


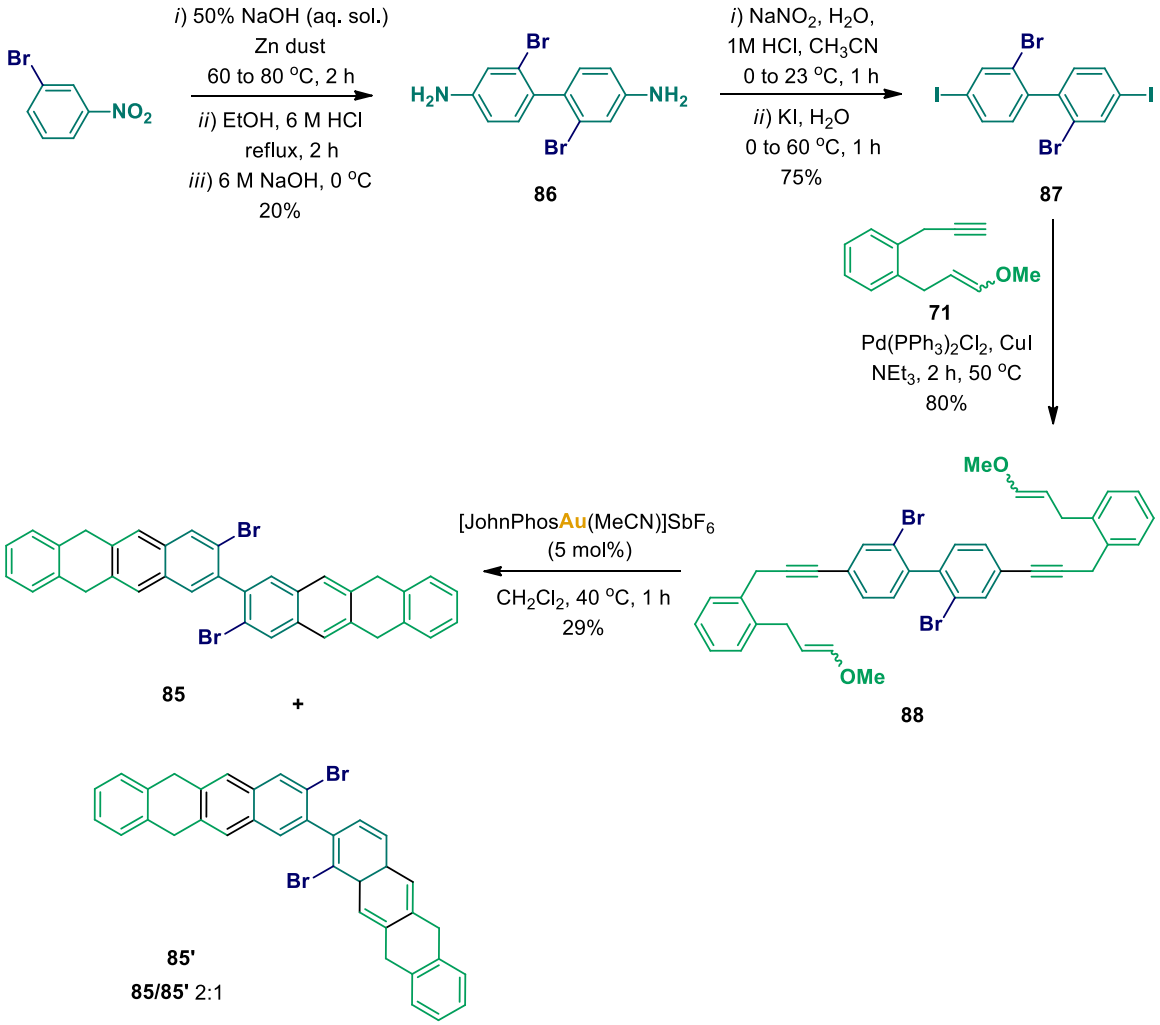
Figure 9. Study of the T-shaped nanoarchitectures **80** and **83** by STM (a: +0.5 V, 25 pA; b: 0.5 V, 15 pA) and nc-AFM

Cyclobutadiene-Containing Acenes

Synthesis of 5,10,15,20-Tetrahydrocyclobuta[1,2-*b*:3,4-*b*']ditetracene (84)

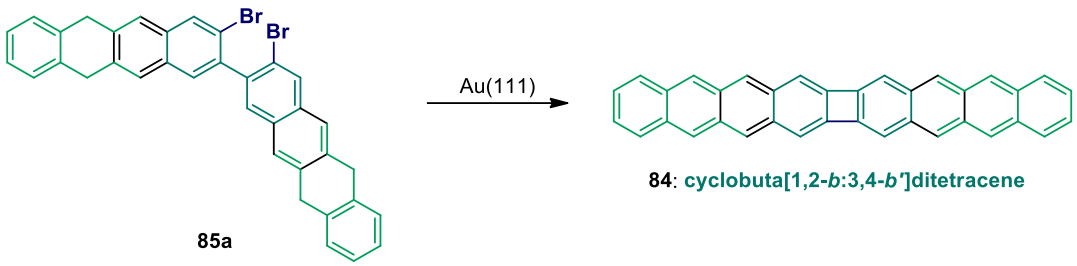
Our methodology has also been investigated in the synthesis of cyclobutadiene-containing acenes, such as 5,10,15,20-tetrahydrocyclobuta[1,2-*b*:3,4-*b'*]ditetracene (**84**). This compound could be obtained through on-surface manipulation of bis-dihydrotetracene precursor **85** (Scheme 21).

Precursor **85** was provided as a mixture of two regioisomers by double Sonogashira coupling of 1,7-enyne **71** with biphenyl **87** and subsequent 2-fold Au(I)-catalyzed [4+2] cycloaddition. In turn, compound **87** was synthesized *via* formation of benzidine **86** from 1-bromo-3-nitrobenzene, followed by double Sandmeyer reaction (Scheme 21).



Scheme 21. Synthesis of hydroacenes **85**

The synthesis of **84** was then tested on a Au(111) surface by deposition of the mixture of regioisomers **85** by sublimation under UHV conditions (Scheme 22).



Scheme 22. Synthesis of hydroacene **84**

Preliminary STM studies (Figure 10) suggested that the desired acene **84** was indeed formed from the rotamer **85a** of compound **85**, but the investigation of the cyclization and aromatization reactions is currently under study.[43] Thus, further experiments are currently performed to visualize the new molecule by high resolution nc-AFM and to characterize its electronic properties.

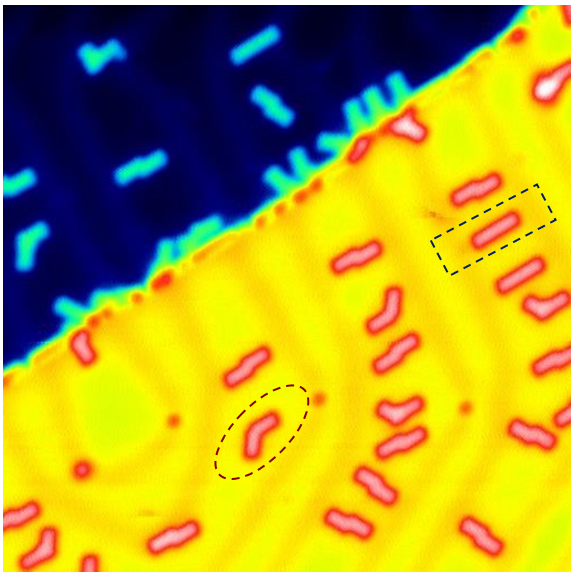
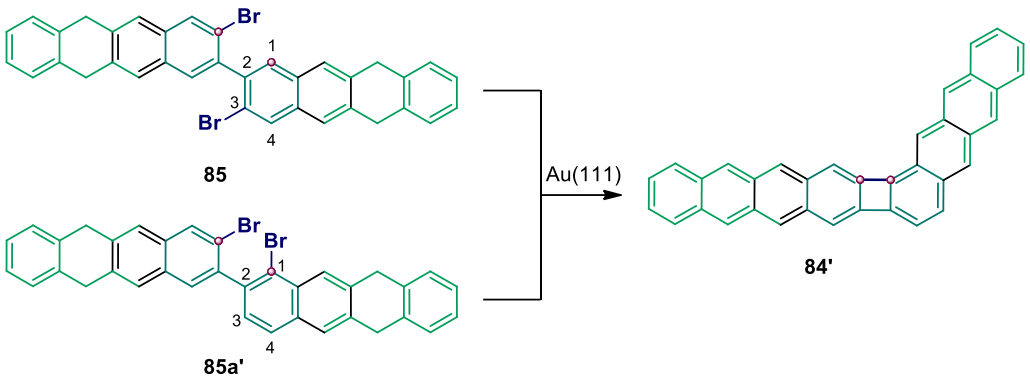


Figure 10. STM image of the molecules of **84** (black dashed rectangle) and **84'** (brown dashed circle) after deposition on Au(111)

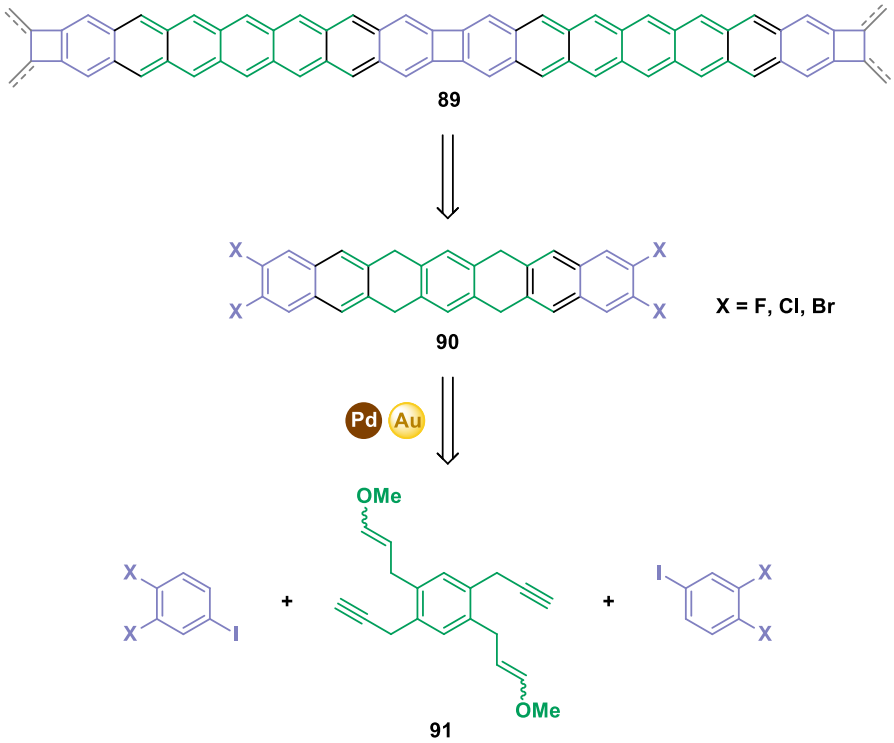
The STM image of the molecules generated from precursors **85** suggests that in addition to the targeted linear acene **84**, another V-shaped compound **84'** has also been formed. We propose that this structure can be derived either from hydroacene **85** or from the rotamer **85a'** of regioisomer **85'** (Scheme 23). In case of the former pathway, **84'** could be generated by cyclization at position 1, after formation of the corresponding radicals by loss of the two bromide moieties. Alternatively, rotamer **85'** would lead to the same compound through a similar mechanism that also occurs at its position 1. However, both mechanisms require further investigation.

43 Preliminary studies by Prof. Szymon Godlewski at *Centre for Nanometer-Scale Science and Advanced Materials* (NANOSAM) in Krakow, Poland.



Scheme 23. Synthesis of hydroacene **84'**

The synthesis of hybrid tetracene nanoribbons accomplished by Fasel *et al.*[41] led us to consider the formation of ribbons incorporating cyclobutadiene units and even larger acene components by applying our methodology. Consequently, we envision that the new ribbons **89** could be prepared from tetrahydroheptacene precursors **90**, tetrasubstituted at the terminal rings (Scheme 24). In order to achieve these precursors, the synthesis of a new double 1,7-enyne precursor (**91**) was intended. **91** would then be coupled with the appropriate halogenated arenes through double Sonogashira coupling and the resulting enynes would be subjected to double gold(I)-catalyzed [4+2] cycloaddition.

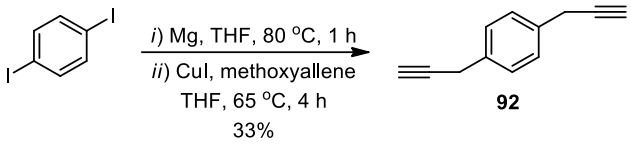


Scheme 24. Retrosynthetic analysis of hybrid nanoribbons **89**

Synthesis of the Doubly-Functionalized 1,7-Enyne Precursor

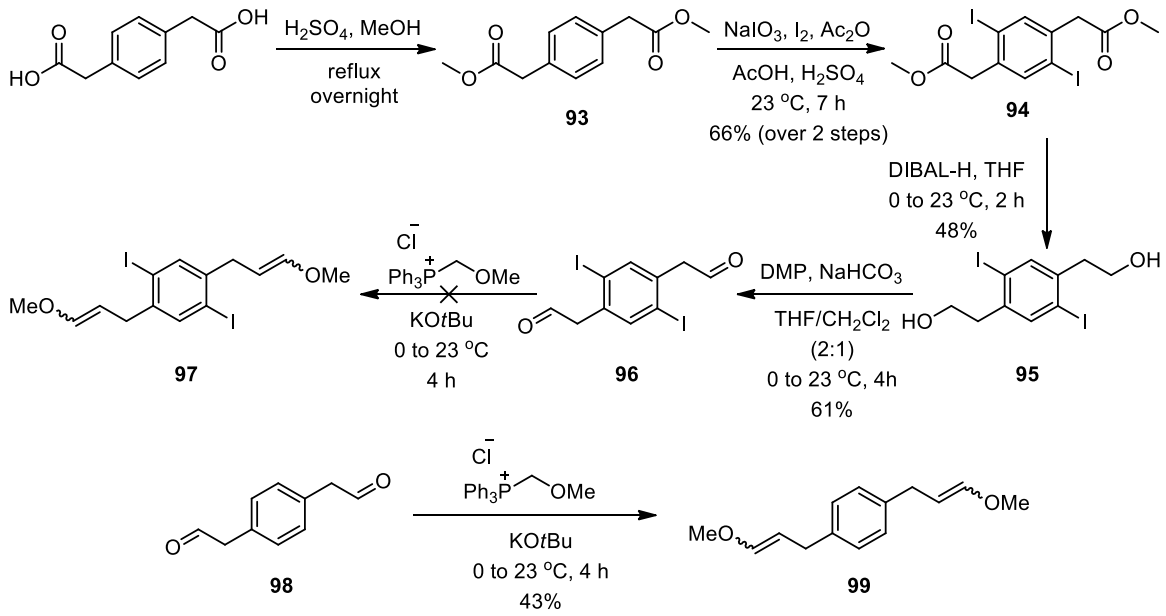
In this regard, our investigation commenced with the preparation of the doubly-functionalized 1,7-enyne **91**. The interest in this compound is derived from its ability to react with two equivalents of various electrophiles *via* the Sonogashira reaction, thus facilitating the synthesis of even larger or substituted hydroacenes.

At the outset, the synthesis of compound **91** was envisioned by following a sequence similar to our shorter and improved synthesis for our first generation 1,7-enyne discussed in *Chapter I*. The bromide units required for the introduction of the alkynes through Grignard reaction were replaced with the corresponding iodides after examining both 1,4-dibromobenzene and 1,4-diiodobenzene as model substrates. Thus, 1,4-diiodobenzene provided the desired double alkyne **92**, although in only 33% yield (Scheme 25).



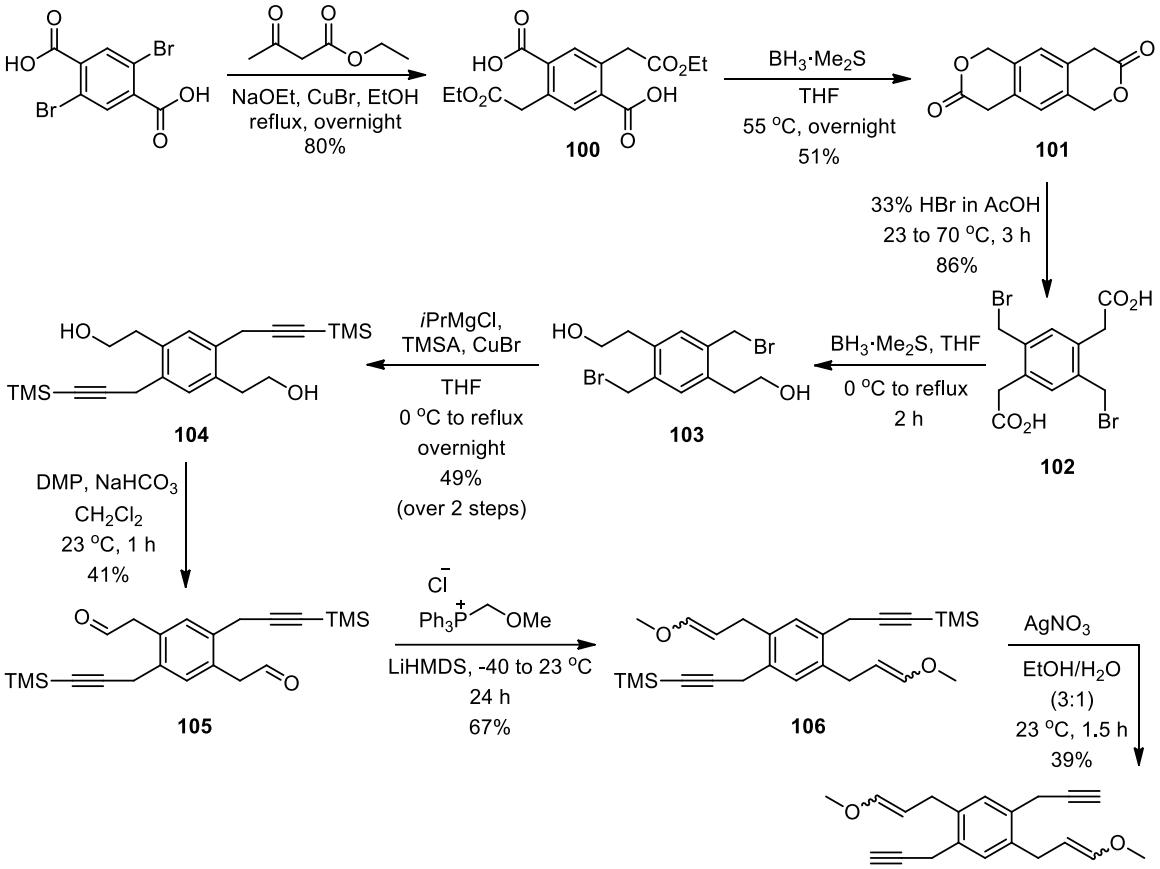
Scheme 25. Preparation of diyne **92**

The preparation of enyne **91** started from 1,4-phenylenediacetic acid, which was subjected to esterification (Scheme 26). Then, double ester **93** underwent an iodination reaction to provide compound **94**, whose ester moieties were reduced with DIBAL-H to form diol **95**. Subsequent Dess-Martin oxidation of **95** afforded the double aldehyde **96** required for the 2-fold Wittig olefination. However, all the attempts to introduce the enol ether side chains failed usingeither *n*-BuLi or KO*t*Bu as the bases. Because of the very low solubility of **96** in solvents like THF or Et_2O, the reaction had to be performed at a very low concentration (0.01 M), which proved to be detrimental. By contrast, when the same reaction was performed with double aldehyde **98**, the double enol ether **99** was obtained in 43% yield using KO*t*Bu as the base. This last transformation succeeded due to the improved solubility of **98** in THF, which allowed the reaction to be carried out at a higher concentration (0.5 M).



Scheme 26. Attempted synthesis of double 1,7-enyne **91**

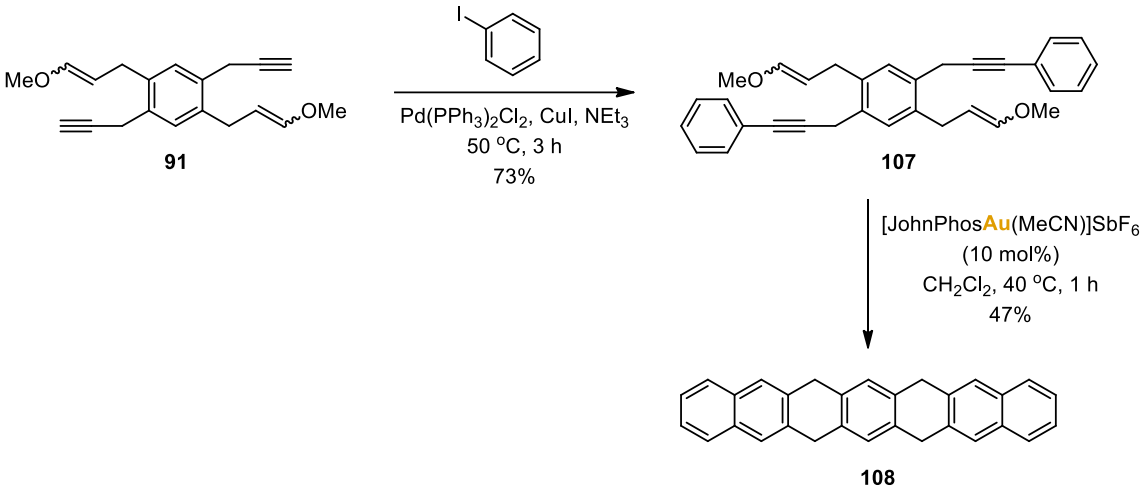
Since the first attempt to prepare enyne **91** was not successful, we opted for testing the synthetic route developed for the generation of a new iodinated enyne, which has been described in *Chapter I*. Analogously, the sequence started from a similar starting material, 2,5-dibromoterephthalic acid, which also underwent a double copper catalyzed nucleophilic aromatic substitution/deacylation to afford double ester **100** (Scheme 27). Lactonization by reduction with $BH_3 \cdot Me_2S$ followed by acidic work-up provided compound **101** in 51% yield. The double lactone was opened with HBr and the corresponding carboxylic acid units underwent reduction providing diol **103**. The 2-fold alkynylation was then carried out and alcohol **104** was oxidized to aldehyde **105**. Finally, double Wittig olefination, followed by TMS deprotection afforded the desired double 1,7-enyne **91**.



Scheme 27. Accomplished synthesis of double 1,7-enyne **91**

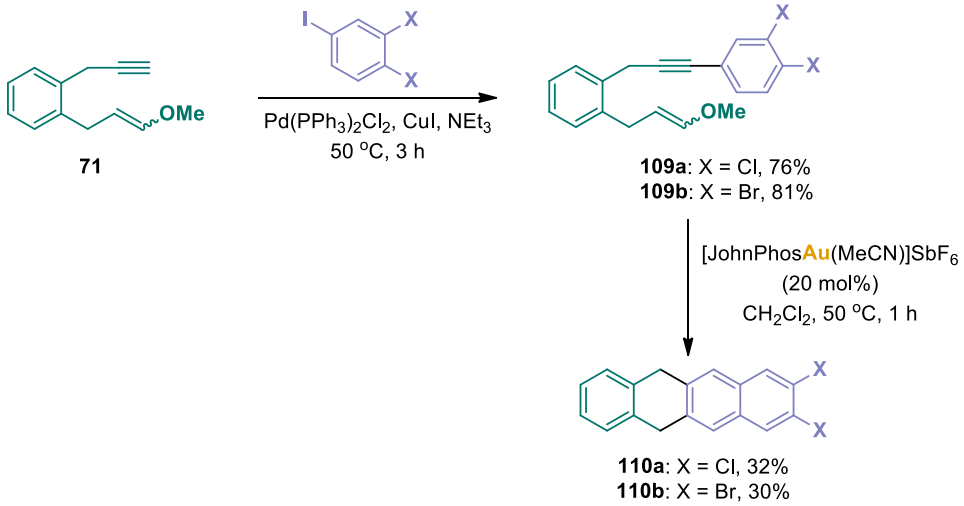
After accomplishing the synthesis of the new 1,7-enyne **91**, the formation of a new tetrahydroheptacene compound by double cycloisomerization was next explored. Double synthon **91** was engaged in a double Sonogashira coupling with iodobenzene followed by Au(I)-catalyzed [4+2] cycloaddition, which afforded 6,8,15,17-tetrahydroheptacene (**108**) in 43% yield (Scheme 28). The structure of **108** could be confirmed by ^{1}H and ^{13}C NMR experiments at 393 K, as well as MALDI-MS. This compound is a new precursor of heptacene, different from the one synthesized previously in our group,[44] with improved solubility and stability. The largest aromatic segment in **108** is naphthalene, in contrast with our previous precursor that contained an anthracene.

44 Dorel, R.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 11120–11123.



Scheme 28. Synthesis of 6,8,15,17-tetrahydroheptacene **108**

After proving that enyne **91** is a suitable precursor for hydroacenes of type **108**, we focused on the gold(I)-catalyzed cycloaddition with 1,7-enynes functionalized with halide groups, as they are weakly deactivating. The investigation was carried out using our first generation 1,7-enyne precursor (**71**) and started with coupled enyne **109a**, which contains two chloride units, since no example has been reported previously (Scheme 29). Enyne **109a** was prepared by Sonogashira coupling of **122** with 1,2-dichloro-4-iodobenzene. The cyclization of enyne **109a** was tested with a catalyst loading of 5 mol% and did not yield the desired product, all the starting material being recovered. By contrast, increasing the catalyst loading up to 20 mol%, dihydrotetracene **110a** was successfully provided. A similar synthetic sequence was also explored with 1,2-dibromo-4-iodobenzene and afforded **110b**, the analogue incorporating two bromide substituents.



Scheme 29. Synthesis of halogen-substituted dihydrotetracenes **110a**–**b**

On the basis of these results, in the foreseeable future the synthesis of the desired substituted tetrahydroheptacenes will be explored employing double enyne **91** in a double Sonogashira coupling

with either 1,2-dichloro-, 1,2-dibromo- or 1,2-difluoro-4-iodobenzene and subsequent 2-fold Au(I)-catalyzed [4+2] cycloaddition. Hydroacenes **90** would then be employed in the formation of the envisioned hybrid heptacene-cyclobutadiene ribbons.

CONCLUSIONS

We have accomplished the synthesis of novel acene-related compounds by applying our gold(I)-catalyzed [4+2] cycloaddition. For instance, the synthesis of the indacene derivatives *s*-indaceno[1,2-*b*:5,6-*b*']ditetracene and *as*-indaceno[2,3-*b*:6,7-*b*']ditetracene was achieved through dehydrogenative surface-assisted cyclization of 1,4-bis(3-methyl-6,11-dihydrotetracen-2-yl)benzene. Surprisingly, the *as*-indacene was found to be involved in a noteworthy intermolecular cycloaddition to give T-shaped molecules. Furthermore, the cycloaddition of this compound with pentacene and octacene also leads to similar T-shaped molecules.[45]

Furthermore, 3,3'-dibromo-6,6',11,11'-tetrahydro-2,2'-bitetracene was prepared as an envisioned precursor of 5,10,15,20-tetrahydrocyclobuta[1,2-*b*:3,4-*b*']ditetracene. Preliminary STM studies showed that the cyclobutadiene-incorporating compound has already been accomplished and its characterization by nc-AFM is currently ongoing. Moreover, the synthesis of a new doubly substituted 1,7-enyne precursor was accomplished and enabled the preparation of a new precursor of heptacene. This new synthon will be tested as the substrate for heptacenes-H4 tetrasubstituted with halide moieties at the terminal rings through double gold(I)-catalyzed [4+2] cycloadditions. These compounds would then be investigated as precursors for heptacene-cyclobutadiene hybrid ribbons by surface-assisted cycloaddition.

45 Zuzak, R.; Stoica, O.; Blieck, R., Echavarren, A. M.; Godlewski, S. *ACS Nano* **2021**, *15*, 1548–1554.

EXPERIMENTAL SECTION

General Methods

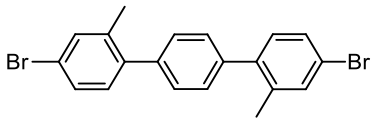
The general information has been provided in the experimental section of *Chapter I*.

In addition to that, all surface-assisted experiments were conducted in the Scienta Omicron STM/nc-AFM microscope in LHe temperature (5 K) with the base pressure in the microscope chamber below 3×10^{-10} mbar. The Au(111) monocrystalline samples were prepared by the standard procedure of simultaneous annealing and ion sputtering (Ar^+ ions). The molecules were evaporated from a Knudsen cell (Kentax GmbH), at the temperatures of T = 210 °C (**73**), 210 °C (octacene-H4), 130 °C (pentacene). The molecular flux was maintained at the approximate rate of 0.1 Hz/min with the application of a quartz microbalance. After deposition, the samples with precursors were annealed at 370 °C by a resistive heater in the preparation chamber (temperature of the sample was monitored by the thermocouple, type K). To obtain high-resolution constant height frequency shift nc-AFM images, the procedure for nc-AFM tip functionalization described by Gross et al. was applied. In all nc-AFM measurements, the resonant frequency of the qPlus cantilever was ~26 kHz, and the oscillation amplitude was kept in the range of 100−150 pm. For image processing, Scanning Probe Image Processor and WSxM software has been applied.

Synthetic Procedures and Analytical Data

Synthesis of precursor 73

1,7-Enyne **71** was prepared according to the procedure reported in *Chapter I*.

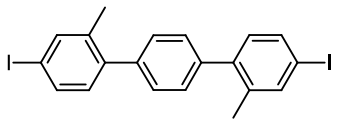


4,4''-Dibromo-2,2''-dimethyl-1,1':4',1''-terphenyl (69). To a degassed suspension of benzene-1,4-diboronic acid (1.0 equiv, 500 mg, 3.017 mmol), 5-bromo-2-iodotoluene (4.0 equiv, 1.800 g, 6.062 mmol), and potassium carbonate (10 equiv, 8.378 g, 60.62 mmol) in a mixture of dioxane (8 mL, 0.4 M) and water (4 mL, 0.75 M), tetrakis(triphenylphosphino)palladium(0) (174 mg, 0.151 mmol, 5 mol%) was added and the reaction mixture was stirred at 100 °C for 14 h under Ar. After cooling to 23 °C, EtOAc (30 mL) was added. The organic phase was separated and the aqueous one was extracted with more EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Purification by silica gel column chromatography (cyclohexane/CH_2Cl_2 9:1) gave the title compound as white solid (585 mg, 1.405 mmol, 47% yield).

^{1}H NMR (400 MHz, $CHCl_3$) δ 7.45 (d, *J* = 1.9, 2H), 7.39 (dd, *J* = 8.1, 2.0 Hz, 2H), 7.33 (s, 4H), 7.15 (d, *J* = 8.1 Hz, 2H), 2.31 (s, 6H);

^{13}C NMR (104 MHz, $CHCl_3$) δ 140.6, 139.7, 137.8, 133.3, 131.5, 129.0, 121.3, 20.6 (two peaks missing due to overlapping).

HRMS (APCI+) m/z calc. for $C_{20}H_{16}Br_2$ $[M]^+$: 413.9613. Found: 413.9615. Spectral data are in agreement with the literature.[28]



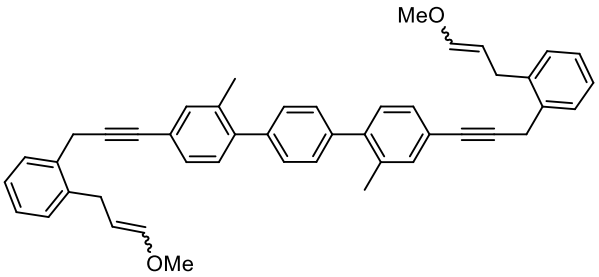
4,4''-Diiodo-2,2''-dimethyl-1,1':4',1''-terphenyl (70). A solution of 2.5 M of *n*-BuLi in cyclohexane (4 equiv, 2.4 mL, 5.925 mmol) was added dropwise to a solution of **69** (1 equiv, 820 mg, 1.975 mmol) in dry THF (10 mL, 0.2 M) at -78 ºC, under an Ar atmosphere, while maintaining a good stirring. After stirring for 1 h, a solution of iodine (5 equiv, 2.498 g, 9.875 mmol) in dry THF (10 ml) was added dropwise. The reaction mixture was warmed to 23 ºC and stirred at this temperature for 1 h. Water (15 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with $NaHSO_3$ (50 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification of the crude through column chromatography (cyclohexane) afforded the title compound as a white solid (733 mg, 1.437 mmol, 73% yield).

Melting point = 202–204 ºC.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*= 1.3 Hz, 2H), 7.59 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.32 (s, 4H), 7.01 (d, *J* = 8.0 Hz, 2H), 2.28 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ141.2, 139.8, 139.2, 138.0, 135.1, 131.7, 129.0, 93.1, 20.4 (one peak missing due to overlapping).

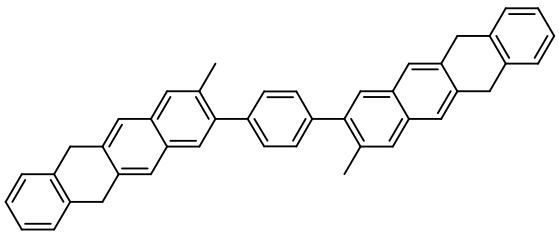
HRMS (APCI+) m/z calc. for $C_{20}H_{16}I_2$ $[M]^+$: 509.9335. Found: 509.9336.



4,4''-Bis(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)-2,2''-dimethyl-1,1':4',1''-terphenyl (72). $PdCl_2(PPh_3)_2$ (106 mg, 0.151 mmol, 10 mol%) and CuI (53 mg, 0.277 mmol, 20 mol%) were suspended in Et_3N (7 mL) and the mixture was bubbled with Ar for 10 min. A solution of **70** (1.0 equiv, 700 mg, 1.372 mmol) and **71** (3.2 equiv, 817 mg, 4.392 mmol) in a mixture of degassed NEt_3 (7 mL) and THF (20 mL) were subsequently added and the reaction was stirred at 40 ºC for 2 h. Then the mixture was diluted with EtOAc (30 mL), filtered through a short pad of silica gel compacted with

EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 98:2) afforded the title compound as a pale yellow oil (542 mg, 0.865 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 3.6H), 7.41 – 7.32 (m, 12.4H), 7.31– 7.21 (m, 10.7H), 6.39 (dt, *J* = 12.6, 1.1 Hz, 2H, *E*), 6.02 (dt, *J* = 6.1, 1.5 Hz, 0.6H, *Z*), 4.92 (dt, *J* = 12.7, 7.0 Hz, 2H, *E*), 4.52 (td, *J* = 7.3, 6.2 Hz, 0.6H, *Z*), 3.86 (s, 1.2H, *Z*), 3.85 (s, 4H, *E*), 3.67 (s, 1.8H, *Z*), 3.56 (s, 6H, *E*), 3.50 (dd, *J* = 7.4, 1.3 Hz, 1.8H, *Z*), 3.39 (dd, *J* = 7.0, 1.1 Hz, 4H, *E*), 2.31 (s, 7.8H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 146.9, 141.3, 141.2, 140.1, 140.1, 140.1, 139.3, 139.2, 135.5, 135.5, 135.0, 1349., 133.7, 129.9, 129.3, 129.2, 129.0, 128.7, 127.2, 127.1, 126.7, 126.5, 122.9, 122.7, 104.6, 101.0, 87.9, 87.6, 83.0, 83.0, 59.8, 56.1, 31.3, 27.8, 27.1, 23.6, 23.4, 20.5. (peaks missing due to overlapping).
HRMS (ESI+) m/z calc. for $C_{46}H_{43}O_2$ $[M+H]^+$: 627.3236. Found: 627.3258.

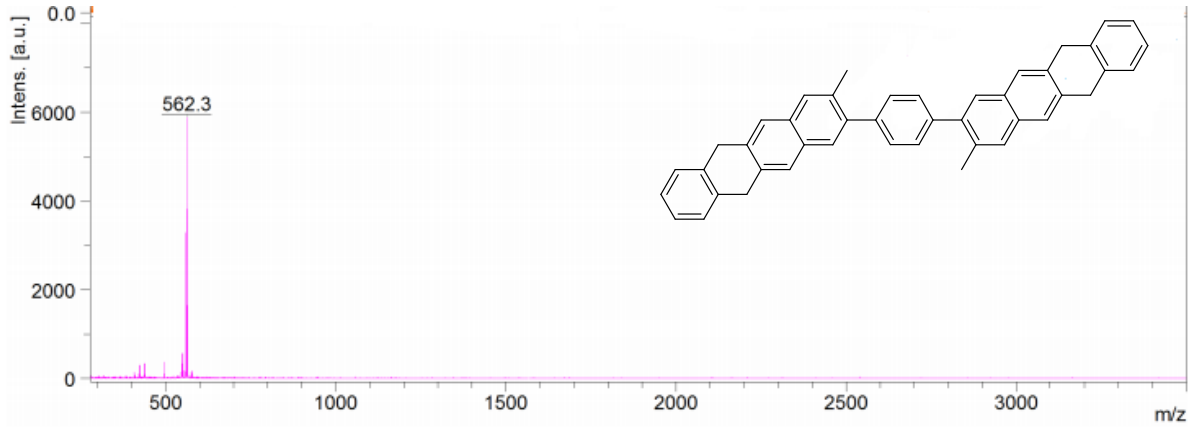


1,4-Bis(3-methyl-6,11-dihydrotetracen-2-yl)benzene (73). To a solution of **72** (1 equiv, 150 mg, 239 μmol) in HPLC grade CH_2Cl_2 (0.1 M, 2.4 mL) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (9.5 mg, 5 mol%) and the mixture was stirred at 40 ºC for 1 hour under air. After cooling to 23 ºC, NEt_3 (0.5 mL) was added and then the solvents were evaporated under reduced pressure. Purification by column chromatography (cyclohexane/CH_2Cl_2 9:1) afforded the title compound as a 2:1 mixture of regioisomers – symmetrical **73** and non-symmetrical **73'**, the major one being **73** (28 mg, 50 μmol, 21% yield).

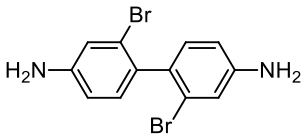
^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 393 K) δ 8.11 (s, 1H), 7.85 (s, 1H), 7.79 – 7.74 (m, 9H), 7.54 – 7.48 (m, 7H), 7.41 – 7.39 (m, 6H), 7.29 – 7.24 (m, 6H), 4.25 (s, 2H), 4.20 (s, 2H), 4.17 (d, *J* = 4.4 Hz, 8H), 2.75 (s, 3H), 2.52 (s, 6H).
HRMS (MALDI+) m/z calc. for $C_{44}H_{34}$ $[M]^+$: 562.2661. Found: 562.2631; m/z calc. for $C_{44}H_{35}$ $[M+H]^+$: 563.2741. Found: 563.2734.

The desired symmetric isomer **73** was then separated by dissolving the mixture in CH_2Cl_2 followed by precipitation with pentane and was obtained as a white solid after vacuum filtration.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 6H), 7.69 (s, 2H), 7.37 – 7.34 (m, 4H), 7.22 (dd, *J*= 5.5, 3.3 Hz, 4H), 4.10 (d, *J* = 4.4 Hz, 8H), 2.48 (s, 6H).

LDI-MS spectrum of hydroacene **124**



Synthesis of Precursor 136

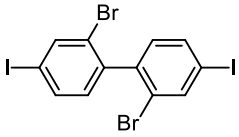


2,2'-Dibromo-[1,1'-biphenyl]-4,4'-diamine (86). To a stirred solution of 1-bromo-3-nitrobenzene (1.0 equiv, 5.50 g, 27.2 mmol) in ethanol (60 mL) and aqueous sodium hydroxide (2.3 equiv, 2.50 g, 62.5 mmol, 15 mL), zinc dust (5.6 equiv, 10 g, 153 mmol) was added portionwise, so that the temperature does not exceed 70 ºC. After stirring at this temperature for 15 min, more zinc (3.4 equiv, 6 g, 92 mmol) was added. The transparent mixture was then left to stir under reflux for 2 h and filtered through a Celite pad after cooling down to 23 ºC. The zinc residue was washed with ethanol (2 × 30 mL). The combined filtrate was diluted with ethyl acetate (200 mL) and water (100 mL). The organic phase was extracted with more ethyl acetate (3 × 100 mL) and then washed with water and brine, dried (MgSO4) and the solvent was evaporated *in vacuo*. The resulting yellow oil was slowly poured onto 20% H_2SO_4 (ca. 150 mL) at 0 ºC and stirred at this temperature for ca. 40 min. This afforded the desired hydrazine as a pale orange solid which was isolated through vacuum filtration (*ca*. 3.500 g).

The crude hydrazine was dissolved in ethanol (60 mL), added to 6 M HCl (60 mL) and stirred at reflux for 2 h. After this time, the dark orange solution was cooled on ice. Thus, some solid benzidine hydrochloride precipitated. Then, a solution of 25% aq. NaOH (120 mL) was added dropwise through a dropping funnel at 0 ºC to make the solution basic to a pH of 11. The brown solution was extracted with diethyl ether (3 × 150 mL) and the extracts were dried ($MgSO_4$), filtered, and evaporated. The crude benzidine was crystallized from a ethanol-water mixture and was obtained as a pale orange solid (1.834 g, 5.362 mmol, 20% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.64 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.74 (s, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 132.2, 132.2, 124.9, 118.4, 113.9. Spectral data are in agreement with the literature.[46]



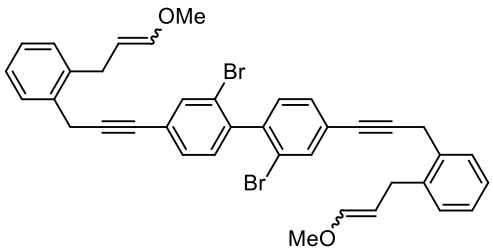
2,2'-Dibromo-4,4'-diiodo-1,1'-biphenyl (87). Benzidine **86** (1.0 equiv, 600 mg, 1.75 mmol) was dissolved in acetonitrile (0.141 M, 20 mL) and 1 M HCl (10 mL) and the resulting slurry was cooled to 0 °C. Then a solution of sodium nitrite (2.4 equiv, 289 mg, 4.19 mmol) in water (5 mL) was slowly added. The reaction mixture was then stirred for 30 min at 0 °C and then added to a second RBF containing a solution of potassium iodide (10 equiv, 2.91 g, 17.5 mmol) in water (10 mL) cooled to 0 °C. After that, the solution was allowed to warm to 23 ºC with stirring for 1 h and was then heated to 60 °C for another hour. The reaction was allowed to cool to 23 ºC and was diluted with water and EtOAc. The product was extracted with EtOAc (3 × 50 mL) and the organic phase was washed with $NaHSO_3$ and brine, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by column chromatography (cyclohexane) gave the title compound as a white solid (738 mg, 1.310 mmol, 75% yield).

Melting point = 78–81 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (d, *J* = 1.7 Hz, 1H), 12.09 (dd, *J* = 8.1, 1.7 Hz, 1H), 11.33 (d, *J* = 8.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 140.8, 136.5, 132.2, 124.3, 94.2.

HRMS (APCI+) m/z calc. for $C_{12}H_6Br_2I_2$ $[M]^+$: 561.6920, found: 561.6918.

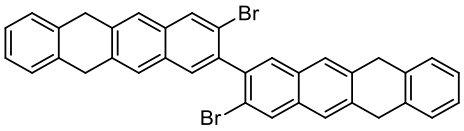


2,2'-Dibromo-4,4'-bis(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)-1,1'-biphenyl (88). $PdCl_2(PPh_3)_2$ (25.0 mg, 36 μmol, 10 mol%) and CuI (13.5 mg, 71 μmol, 20 mol%) were suspended in Et_3N (1.8 mL) and the mixture was bubbled with Ar for 10 min. A solution of **87** (1.0 equiv, 353 μmol, 200 mg) and **71** (3.0 equiv, 198 mg, 1.06 mmol) in a mixture of degassed NEt_3 (1.8 mL) was subsequently added and the reaction was stirred at 40 ºC for 2 h. Then the mixture was diluted with

46 Talipov, M. R.; Hossain, M. M.; Boddeda, A.; Thakur, K.; Rathore, R. *Org. Biomol. Chem.*, **2016**, *14*, 2961–2968.

EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 98:2) afforded the title compound as a pale yellow oil (192 mg, 0.282 mmol, 80% yield).

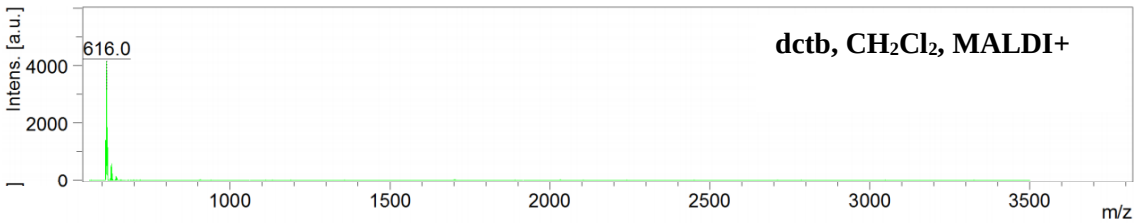
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 6.1, 1.5 Hz, 20H), 7.55 – 7.46 (m, 24H), 7.42 (ddd, *J* = 7.9, 5.0, 1.6 Hz, 22H), 7.25 – 7.21 (m, 62H), 7.14 (dd, *J* = 7.9, 1.7 Hz, 22H), 6.41 – 6.35 (m, 16H), 6.02 (dt, *J* = 6.1, 1.5 Hz, 4H), 4.93 – 4.87 (m, 17H), 3.84 (s, 9H), 3.83 (s, 33H), 3.67 (d, *J* = 2.1 Hz, 13H), 3.53 (s, 50H), 3.49 (dd, *J* = 7.3, 1.5 Hz, 12H), 3.37 (dd, *J* = 7.0, 1.1 Hz, 35H), 3.29 (dt, *J* = 4.6, 2.3 Hz, 6H);
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 146.9, 141.19, 141.15, 139.38, 139.18, 138.16, 135.55, 134.53, 134.42, 130.73, 130.71, 130.42, 130.41, 129.44, 129.27, 128.99, 128.73, 127.48, 127.40, 127.27, 126.79, 126.56, 125.40, 123.15, 104.53, 100.99, 89.72, 89.70, 81.33, 81.25, 59.87, 56.14, 56.12, 53.56, 31.27, 31.22, 27.79, 23.58, 23.36 (peaks missing due to overlapping).
HRMS (APCI+) m/z calc. for $C_{38}H_{33}Br_2O_2$ $[M+H]^+$: 679.0842, found: 679.0844.



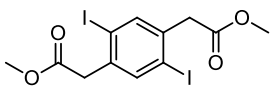
3,3'-Dibromo-6,6',11,11'-tetrahydro-2,2'-bitetracene (85). To a solution of **88** (1 equiv, 65 mg, 0.096 mmol) in HPLC grade CH_2Cl_2 (0.1 M, 1.0 mL) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (3.7 mg, 5 mol%) and the mixture was stirred at 40 ºC for 1 hour under air. After cooling to 23 ºC, NEt_3 (0.1 mL) was added and then the solvents were evaporated under reduced pressure. Purification by column chromatography (cyclohexane/CH_2Cl_2 9:1) afforded the title compound as a 2:1 mixture of isomers – symmetric **85** and non-symmetric **85'**, with **85** being the major one (17 mg, 28 μmol, 29% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.15 (s, 1H), 8.14 (s, 2H), 7.84 (dd, *J* = 10.9, 7.6 Hz, 3H), 7.74 (d, *J* = 2.2 Hz, 10H), 7.41 – 7.30 (m, 11H), 7.23 (dt, *J* = 9.9, 3.6 Hz, 9H), 4.16 (d, *J* = 12.9 Hz, 5H), 4.10 (d, *J* = 14.7 Hz, 14H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 140.1, 139.8, 139.2, 138.1, 138.0, 137.4, 137.4, 137.1, 136.9, 136.9, 136.8, 136.8, 133.0, 133.0, 132.9, 131.2, 131.1, 131.0, 130.5, 130.3, 129.5, 129.3, 127.8, 127.6, 127.5, 127.4, 127.4, 126.9, 126.8, 126.5, 126.5, 125.7, 125.4, 125.4, 125.3, 124.2, 121.4, 120.9.

MALDI-MS spectrum of hydroacene **85**:



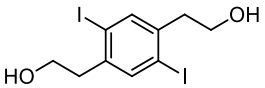
Attempted Synthesis of the Double 1,7-Enyne *91*



Dimethyl 2,2'-(2,5-diiodo-1,4-phenylene)diacetate (94). To a suspension of 2,2'-(1,4-phenylene)diacetic acid (1 equiv, 5.00 g, 25.70 mmol) in MeOH (100 mL, 0.26 M), conc. H_2SO_4 (5 mL) was added dropwise at 0 ºC . The ice-bath was removed and the resulting slurry was heated to reflux to give a clear solution. After stirring at this temperature for 18 h, the reaction mixture was cooled to 23 ºC and the volatiles were removed *in vacuo*. The resulting residue was dissolved in EtOAc (150 mL) and sat. aq. NaHCO3 (30 mL) was slowly added to achieve pH = 8.0 in the aqueous layer. The solution was transferred to a separating funnel, the aqueous layer removed and the organic layer washed with water (3 × 100 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude ester **93** as a pale yellow solid, which was taken on to the next step without further purification.

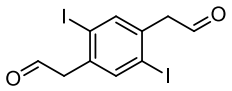
Sodium periodate (0.4 equiv, 2.07 g, 9.68 mmol) and iodine (1.2 equiv, 12.25 g, 48.4 mmol) were stirred into a mixture of glacial acetic acid (15 mL, 0.6 M) and acetic anhydride (32 mL, 1.3 M) at 0–5°C. Concentrated sulfuric acid (10 equiv, 12 mL, 242 mmol) was then added slowly to the stirring suspension. Diester **93** (5.500 g, 24.2 mmol) was added to this solution and stirred continuously for 6 h at 23 ºC. The reaction mixture was then poured into an ice-water mixture (100 mL) containing previously dissolved Na_2SO_3. The precipitate was collected and recrystallized in ethanol to give the title compound as a white solid (8.09 g, 17.1 mmol, 66% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 2H), 3.73 (s, 10H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 140.8, 138.7, 100.8, 52.5, 45.1.



2,2'-(2,5-Diiodo-1,4-phenylene)diethanol (95). To a solution of **94** (1.0 equiv, 4.00 g, 8.44 mmol) in anhydrous THF (77 mL, 0.11 M) at 0 ºC was added DIBAL-H (1.0 M in toluene, 6.1 equiv, 51.5 mL) dropwise. After removing the ice-bath, the mixture was stirred at 23 ºC for 6 h. After that, the reaction was quenched by addition of EtOAc at 0 ºC, followed by water and then HCl 2M. The compound was extracted with EtOAc (3 × 100 mL), washed with brine and dried ($MgSO_4$). The title compound was obtained as a white solid (1.69 g, 4.05 mmol, 48% yield), which was used in the next step without further purification.

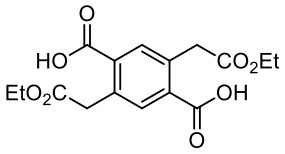
^{1}H NMR (400 MHz, DMSO) δ 7.71 (s, 1H), 4.73 (t, *J* = 5.2 Hz, 1H), 3.54 (dd, *J* = 12.1, 6.8 Hz, 2H), 2.75 (t, *J* = 6.9 Hz, 2H).
^{13}C NMR (101 MHz, DMSO) δ 141.8, 139.8, 100.8, 60.2, 42.2.



2,2'-(2,5-Diiodo-1,4-phenylene)diacetaldehyde (96). To a suspension of **95** (1.0 equiv, 1.525 g, 3.648 mmol) in HPLC grade CH_2Cl_2 (0.1 M, 40 mL) and THF (40 mL) were sequentially added DMP (2.4 equiv, 3.715 g, 8.76 mmol) and $NaHCO_3$ (4 equiv, 1.226 g, 14.6 mmol). The resulting mixture was stirred at 23 ºC for 1 h and then a saturated aqueous solution of $NaHCO_3$ (30 mL) was added. The organic layer was separated and washed with sat. aq. $Na_2S_2O_3$ (60 mL) and brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified through column chromatography (cyclohexane/EtOAc 95:5 to 9:1) to yield the title compound as a white solid (921 mg, 2.225 mmol, 61% yield).

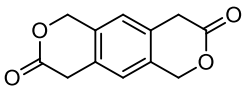
^{1}H NMR (400 MHz, DMSO) δ 9.71 (s, 2H), 7.83 (s, 2H), 3.93 (s, 4H).
^{13}C NMR (101 MHz, DMSO) δ 199.1, 140.8, 138.2, 101.5, 52.7.

Synthesis of the Double 1,7-Enyne *91*



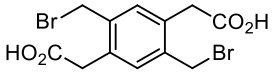
2,5-Bis(2-ethoxy-2-oxoethyl)terephthalic acid (100). Sodium (6 equiv, 2.13 g, 61.70 mmol) was added to abs. EtOH HPLC graded (120 mL, 0.13 M) under Ar atmosphere at 0 ºC. After warming up to 23 ºC, the mixture was left to stir for 1 h. Ethyl acetoacetate (4 equiv, 7.80 mL, 61.7 mmol) was then added and the mixture was stirred at 23 ºC for 10 min. Then, CuBr (2 equiv, 4.43 g, 30.9 mmol) and 2-bromo-5-iodobenzoic acid (1 equiv, 5.00 g, 15.40 mmol) were added and the reaction mixture was refluxed for 16 h. After completion, the dark green reaction mixture was concentrated *in vacuo*, acidified with 1 M HCl (200 mL) and diluted with CH_2Cl_2 (200 mL). The title compound precipitated during extraction as a white solid placed between the two phases. Filtration of both phases and washing with water (300 mL) and CH_2Cl_2 (200 mL) provided the title compound as a white solid (4.18 g, 12.3 mmol, 80% yield), which was taken on to the next step without further purification.

Melting point = 245–247 ºC.
^{1}H NMR (400 MHz, DMSO) δ 7.87 (s, 2H), 4.08–4.03 (s, 8H), 1.17 (s, 6H).
^{13}C NMR (101 MHz, DMSO) δ 170.8, 134.8, 134.4, 133.4, 60.1, 14.1.
HRMS (ESI-) m/z calc. for $C_{16}H_{17}O_8$ $[M-H]^-$: 337.0929. Found: 337.0936.



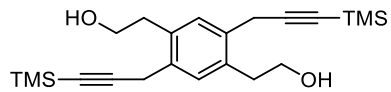
6,9-Dihydropyrano[3,4-*g*]isochromene-3,8(1*H*,4*H*)-dione (101). To a stirred suspension of **100** (1.0 equiv, 7.40 g, 20.20 mmol) in anhydrous THF (0.33 M, 61.0 mL) was added $BH_3 \cdot Me_2S$ (2.2 equiv, 4.20 mL, 44.4 mmol) at 0 ºC. The mixture was then slowly heated to 55 °C and stirred at this temperature for 18 h. After cooling to 23 ºC, 4.0 M HCl (200 mL) was added to the thus formed alcohol to quench the reaction and allow lactonization to take place. Then the compound was allowed to precipitate overnight from the acidic solution. Filtration of both phases and washing with water (200 mL) and CH_2Cl_2 (100 mL) provided the title compound as a white solid (2.25 g, 10.30 mmol, 51% yield), which was taken on to the next step without further purification.

Melting point = 253–255 ºC.
^{1}H NMR (400 MHz, DMSO) δ 7.29 (s, 2H), 5.34 (s, 4H), 3.80 (s, 4H).
^{13}C NMR (101 MHz, DMSO) δ 170.7, 132.5, 130.5, 123.3, 69.1, 35.6.
HRMS (ESI+) m/z calc. for $C_{12}H_{10}NaO_4$ $[M+Na]^+$: 241.0471. Found: 241.0474.



2,2'-(2,5-Bis(bromomethyl)-1,4-phenylene)diacetic acid (102). An orange solution of **101** (1.0 equiv, 2.60 g, 11.9 mmol) in 33% HBr in acetic acid (30.0 mL, 0.40 M) was stirred under Ar at 23 ºC for 2 h and then at 70 °C for 1 h. After cooling down to 23 ºC, the mixture was poured into ice-water (150 mL). Filtration of the white precipitate afforded the title compound as a pure white solid which was taken on to the next step without further purification (3.89 g, 10.23 mmol, 86% yield).

Melting point = 242–244 ºC.
^{1}H NMR (300 MHz, DMSO) δ 7.34 (s, 2H), 4.69 (s, 4H), 3.70 (s, 4H).
^{13}C NMR (101 MHz, DMSO) δ 170.8, 132.6, 130.6, 123.3, 69.2, 35.7.
HRMS (ESI-) m/z calc. for $C_{12}H_{11}Br_2O_4$ $[M-H]^-$: 376.9030. Found: 376.9032.

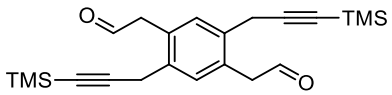


2,2'-(2,5-Bis(3-(trimethylsilyl)prop-2-yn-1-yl)-1,4-phenylene)diethanol (104). $BH_3 \cdot SMe_2$ (3.5 equiv, 1.95 mL, 20.6 mmol) was added dropwise to a solution of **102** (1 equiv, 2.24 g, 5.88 mmol) in anhydrous THF (0.05 M, 118 mL) at 0 ºC. Once the addition was completed, the ice bath was removed and the resulting mixture was allowed to warm to 23 ºC and then heated gradually to 80 ºC. After refluxing at that temperature for 2 h, the mixture was cooled to 0 ºC and quenched by slow addition of 1 M solution of HCl (80 mL). The product was extracted with AcOEt (3 × 100 mL) and the combined organic layers washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated

under reduced pressure. The obtained double alcohol was then taken on to the next step without further purification.

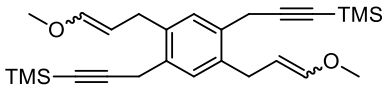
To a solution of ethynyltrimethylsilane (8 equiv, 5.50 mL, 38.6 mmol) in anhydrous THF (30 mL), was added *i*PrMgCl (8 equiv, 19.3 mL, 2 M in THF, 38.6 mmol) dropwise at 0 ºC. After stirring for 30 min at 0 ºC and 30 min at 23 ºC, CuBr (1.2 equiv, 832 mg, 5.79 mmol) was added in one portion. The pale blue reaction mixture was stirred for 30 min at 23 ºC before adding the crude benzyl bromide **103** (1.0 equiv, 1.70 g, 4.83 mmol) as a suspension in anhydrous THF (60 mL). The pale grey mixture was then refluxed for 16 h. After being cooled to 23 ºC, the bright yellow solution was poured into a saturated aqueous solution of NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The crude material was purified by column chromatography (cyclohexane/EtOAc 9:1 to 7:3) to afford the title compound as a white solid (1.11 g, 2.88 mmol, 49% yield over 2 steps).

Melting point = 92–94 ºC.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 2H), 3.88 (s, 4H), 3.61 (s, 4H), 2.90 (s, 4H), 0.17 (s, 18H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0, 133.9, 130.9, 104.6, 87.3, 63.0, 35.5, 24.0, 0.2.
HRMS (ESI+) m/z calc. for $C_{22}H_{34}O_2Si_2$ $[M+Na]^+$: 409.1990. Found: 409.1978.



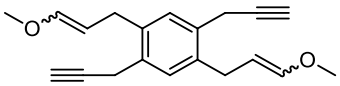
2,2'-(2,5-Bis(3-(trimethylsilyl)prop-2-yn-1-yl)-1,4-phenylene)diacetaldehyde (105). To a solution of the alcohol **104** (1 equiv, 920 mg, 2.380 mmol) in HPLC grade CH_2Cl_2 (0.1 M, 23.8 mL) were sequentially added DMP (2.4 equiv, 2.420 g, 5.710 mmol) and $NaHCO_3$ (4 equiv, 800 mg, 9.520 mmol). The resulting pale yellow mixture was stirred at 23 ºC for 1 h and then a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The organic layer was separated and washed with sat. aq. $Na_2S_2O_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The yellow residue was purified through column chromatography (cyclohexane/EtOAc 95:5 to 9:1) to yield the title compound as a white solid (373 mg, 0.975 mmol, 41% yield).

Melting point = 127–129 ºC.
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.9 Hz, 2H), 7.24 (s, 2H), 3.79 (d, *J* = 1.9 Hz, 4H), 3.53 (s, 4H), 0.15 (s, 18H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 135.0, 132.4, 130.5, 103.3, 88.1, 47.6, 24.5, 0.1.
HRMS (APCI+) m/z calc. for $C_{22}H_{31}O_2Si_2$ $[M+H]^+$: 383.1857. Found: 383.1865.



((2,5-bis(3-methoxyallyl)-1,4-phenylene)bis(prop-1-yne-3,1-diyl))bis(trimethylsilane) (106). A suspension of (methoxylmethyl)triphenylphosphonium chloride (2.2 equiv, 158 mg, 460 μmol) in anhydrous THF (3.1 mL) was cooled to -40 ºC and then a solution of lithium bis(trimethylsilyl)amide (2.2 equiv, 77.0 mg, 460 μmol) in dry THF (2.3 mL) was added dropwise. After stirring the mixture for 30 min at -40 ºC, a solution of **105** (1.0 equiv, 80.0 mg, 0.209 mmol) in dry THF (2.3 mL) was added dropwise. The reaction mixture was stirred for an additional 30 min at -40 ºC, then slowly warmed to 23 ºC and stirred overnight. A saturated aqueous solution of NH_4Cl (5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The orange residue was purified through column chromatography on silica gel (cyclohexane to cyclohexane/EtOAc 99:1 to 97:3) to give the title compound as a pale yellow oil (61.0 mg, 140 μmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.2 Hz, 1H), 7.27 (d, *J* = 4.7 Hz, 2H), 6.37 (d, *J* = 12.6 Hz, 2H), 5.99 (ddt, *J* = 6.1, 3.1, 1.5 Hz, 1H), 4.85 (dtd, *J* = 8.2, 7.1, 1.0 Hz, 2H), 4.48 (td, *J* = 7.4, 6.2 Hz, 1H), 3.64 (d, *J* = 1.9 Hz, 3H), 3.60 (t, *J* = 2.9 Hz, 6H), 3.52 (d, *J* = 2.3 Hz, 6H), 3.39 (dd, *J* = 7.4, 1.4 Hz, 2H), 3.27 (dd, *J* = 7.0, 0.9 Hz, 4H), 0.24 – 0.12 (m, 27H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 148.2, 146.8, 146.7, 137.2, 137.2, 137.0, 136.9, 133.1, 133.0, 132.9, 132.8, 129.7, 129.5, 129.5, 129.2, 104.9, 104.8, 104.7, 104.5, 101.1, 101.0, 87.2, 87.1, 87.1, 87.0, 59.8, 59.8, 56.1, 56.0, 30.8, 30.8, 27.2, 23.7, 23.5, 0.3, 0.2.
HRMS (ESI+) m/z calc. for $C_{26}H_{38}NaO_2Si_2$ $[M+Na]^+$: 461.2303. Found: 461.2299.



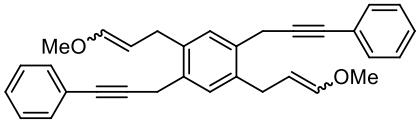
1,4-Bis(3-methoxyallyl)-2,5-di(prop-2-yn-1-yl)benzene (91). Protected alkyne **106** (1.0 equiv, 88.0 mg, 200 μmol) was dissolved in abs. EtOH (0.11 M, 1.9 mL). Then, silver nitrate (6.0 equiv, 200 mg, 1.20 mmol) in solution in deionized water (0.2 mL) was added, leading to the instant formation of a white precipitate. The mixture was stirred at 23 ºC for 1.5 h and then the reaction was quenched by addition of aqueous $Na_2S_2O_3$ (3 mL) and diluted with 10 mL of EtOAc. The suspension was filtered and the remaining biphasic solution was extracted with EtOAc (3 × 10 mL), washed with more $Na_2S_2O_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel (cyclohexane/EtOAc 95:5) afforded the title compound as a white solid (23 mg, 78 μmol, 39% yield).

Melting point = 76–78 ºC.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.26 (s, 2H), 6.36 (d, *J* = 12.6 Hz, 2H), 5.98 (tt, *J* = 4.9, 1.5 Hz, 1H), 4.86 (dt, *J* = 12.8, 7.0 Hz, 2H), 4.46 (dt, *J* = 13.5, 6.8 Hz, 1H), 3.65 (d, *J* = 1.7 Hz, 3H),

3.56 (dt, *J* = 6.8, 3.5 Hz, 6H), 3.53 (d, *J* = 2.8 Hz, 6H), 3.40 (dd, *J* = 7.3, 1.3 Hz, 2H), 3.29 (d, *J* = 7.0 Hz, 4H), 2.19 – 2.14 (m, 2.3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 148.3, 146.8, 146.7, 137.4, 137.3, 137.2, 137.0, 133.1, 133.0, 133.0, 132.9, 129.9, 129.8, 129.7, 129.6, 104.8, 104.7, 101.1, 101.0, 82.5, 82.4, 82.2, 82.1, 70.7, 70.6, 70.6, 70.5, 59.8, 59.8, 56.1, 56.1, 30.9, 30.8, 27.4, 27.3, 22.2, 22.2, 22.0, 22.0.

HRMS (ESI+) m/z calc. for $C_{20}H_{22}NaO_2$ $[M+Na]^+$: 317.1512. Found: 317.1520.

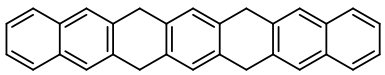


((2,5-Bis(3-methoxyallyl)-1,4-phenylene)bis(prop-1-yne-3,1-diyl))dibenzene (107). $PdCl_2(PPh_3)_2$ (20.0 mg, 6.8 μmol, 10 mol%) and CuI (4.8 mg, 14μmol, 20 mol%) were suspended in Et_3N (0.7 mL) and the mixture was bubbled with Ar for 10 min. A solution of **91** (1.0 equiv, 20 mg, 68 μmol) and iodobenzene (2.5 equiv, 35 mg, 170 μmol) in degassed THF (2 mL) was subsequently added and the reaction was stirred at 50 ºC for 3 h. Then the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 98:2) afforded the title compound as a white solid (22 mg, 68 μmol, 73% yield).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.47 – 7.41 (m, 6H), 7.36 (dd, *J* = 6.5, 2.2 Hz, 3H), 7.31 (dd, *J* = 6.6, 2.7 Hz, 9H), 6.42 (d, *J* = 12.6 Hz, 2H), 6.03 (dtd, *J* = 3.8, 2.6, 1.5 Hz, 1H), 4.91 (dt, *J* = 12.9, 7.1 Hz, 2H), 4.52 (td, *J* = 7.4, 6.3 Hz, 1H), 3.79 (d, *J* = 3.4 Hz, 6H), 3.62 (d, *J* = 2.0 Hz, 3H), 3.47 (d, *J* = 2.4 Hz, 6H), 3.45 (d, *J* = 1.5 Hz, 2H), 3.36 (d, *J* = 7.1 Hz, 4H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 148.9, 148.9, 148.8, 147.4, 147.4, 147.3, 147.3, 138.0, 138.0, 137.8, 137.8, 134.0, 133.9, 133.8, 132.0, 130.2, 130.1, 128.8, 128.8, 128.4, 128.3, 128.3, 124.4, 124.4, 124.3, 124.3, 105.0, 105.0, 104.9, 104.9, 103.0, 103.0, 102.9, 102.9, 101.5, 101.4, 88.6, 88.5, 88.4, 88.3, 83.1, 83.0, 60.1, 60.1, 56.4, 56.4, 31.2, 27.6, 23.6, 23.4.

HRMS (MALDI+) m/z calc. for $C_{30}H_{22}$ $[M+H]^+$: 447.2319. Found: 447.2314.

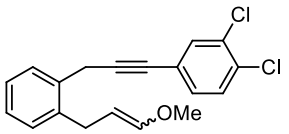


6,8,15,17-Tetrahydroheptacene (108). To a MW vial containing a solution of **107** (1 equiv, 21 mg, 47 μmol) in HPLC grade CH_2Cl_2 (0.1 M, 1.0 mL) was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (3.6 mg, 10 mol%). The vial was sealed and the mixture was stirred at 40 ºC for 1 hour under air. After cooling to 23 ºC, NEt_3 (1 drop) was added and then the solvents were evaporated under reduced pressure. The remaining solid was dissolved in CH_2Cl_2 (0.4 mL) and MeOH (4 mL) was added to precipitate the title compound, which was isolated by vacuum filtration under Ar and afforded as an off-white solid (8.7 mg, 22 μmol, 47% yield).

^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 393 K) δ 7.82 (dd, *J* = 6.2, 3.3 Hz, 4H), 7.79 (s, 4H), 7.45 (dd, *J* = 6.3, 3.2 Hz, 4H), 7.36 (s, 2H), 4.16 (s, 8H).

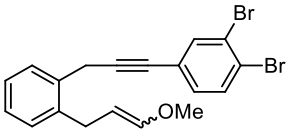
^{13}C NMR (126 MHz, $C_2D_2Cl_4$, 393 K) δ 135.6, 134.8, 132.4, 127.0, 126.0, 125.1, 125.0, 36.2.

HRMS (MALDI+) m/z calc. for $C_{30}H_{22}$ $[M]^+$: 382.1716. Found: 382.1724.



1,2-Dichloro-4-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)benzene (109a). $PdCl_2(PPh_3)_2$ (6.4 mg, 9.2 μmol, 5 mol%) and CuI (3.5 mg, 18 μmol, 10 mol%) were suspended in Et_3N (1.0 mL) and the mixture was bubbled with Ar for 10 min. A solution of **71** (1.2 equiv, 50 mg, 180 μmol) and 1,2-dichloro-4-iodobenzene (1.0 equiv, 41 mg, 220 μmol) in degassed NEt_3 (1.0 mL) was subsequently added and the reaction was stirred at 50 ºC for 3 h. Then the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 98:2) afforded the title compound as a pale yellow oil (3:1 *E*/*Z* ratio, 46 mg, 140 μmol, 76% yield).

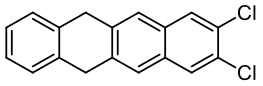
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 3.4, 1.9 Hz, 1.3H), 7.49 – 7.42 (m, 1.3H), 7.36 (d, *J* = 8.3 Hz, 1.3H), 7.22 (ddd, *J* = 7.8, 5.7, 3.2 Hz, 5.2H), 6.36 (d, *J* = 12.6 Hz, 1H), 6.01 (dt, *J* = 6.2, 1.4 Hz, 0.3H), 4.88 (dt, *J* = 12.8, 7.0 Hz, 1H), 4.49 (dd, *J* = 13.5, 7.3 Hz, 0.3H), 3.80 (d, *J* = 2.8 Hz, 2.7H), 3.66 (s, 1H), 3.52 (s, 3H), 3.47 (dd, *J* = 7.4, 1.4 Hz, 0.7H), 3.35 (dd, *J* = 6.9, 0.9 Hz, 2H).



1,2-Dibromo-4-(3-(2-(3-methoxyallyl)phenyl)prop-1-yn-1-yl)benzene (109b). $PdCl_2(PPh_3)_2$ (4.9 mg, 6.9 μmol, 5 mol%) and CuI (2.6 mg, 14 μmol, 10 mol%) were suspended in Et_3N (1.0 mL) and the mixture was bubbled with Ar for 10 min. A solution of **71** (1.2 equiv, 50 mg, 140 μmol) and 1,2-dibromo-4-iodobenzene (1.0 equiv, 31 mg, 170 μmol) in degassed NEt_3 (1.0 mL) was subsequently added and the reaction was stirred at 50 ºC for 3 h. Then the mixture was diluted with EtOAc (10 mL), filtered through a short pad of silica gel compacted with EtOAc/NEt_3 99:1 and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 98:2) afforded the title compound as a pale yellow oil (2:1 *E*/*Z* ratio, 47 mg, 110 μmol, 81% yield).

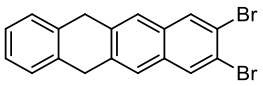
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 4.7, 1.9 Hz, 1.5H), 7.53 (d, *J* = 8.3 Hz, 1.55H), 7.46 (ddd, *J* = 8.2, 5.3, 3.4 Hz, 1.5H), 7.25 – 7.18 (m, 6H), 6.36 (dt, *J* = 12.6, 1.2 Hz, 1H), 6.01 (dt, *J* = 6.1, 1.5 Hz, 0.5H), 4.88 (dt, *J* = 12.7, 7.0 Hz, 1H), 4.49 (td, *J* = 7.3, 6.2 Hz, 0.5H), 3.80 (d, *J* = 4.0 Hz, 3H), 3.66 (s, 1.5H), 3.52 (s, 3H), 3.47 (dd, *J* = 7.4, 1.5 Hz, 1H), 3.35 (dd, *J* = 7.0, 1.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 146.9, 139.4, 139.2, 136.5, 136.5, 134.2, 133.5, 133.5, 131.6, 131.6, 129.5, 129.3, 129.0, 128.7, 127.5, 127.3, 126.8, 126.6, 124.6, 124.5, 104.5, 100.9, 90.6, 90.3, 80.7, 59.9, 56.1, 31.3, 27.8, 23.6, 23.4.



8,9-Dichloro-5,12-dihydrotetracene (110a). To a solution of **109a** (1.0 equiv, 43 mg, 130 μmmol) in HPLC grade CH_2Cl_2 (0.1 M, 1.3 mL), in a sealed MW vial, was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (20 mg, 20 mol%) and the mixture was stirred at 50 ºC for 1 hour under air. After cooling to 23 ºC, NEt_3 (1 drop) was added and then the solvents were evaporated under reduced pressure. The crude solid was dissolved in CH_2Cl_2 (1 mL) and MeOH (4 mL) was added to precipitate the title compound, which was obtained as an off-white solid after vacuum filtration (12.5 mg, 41.8 μmol, 32% yield).

^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 393 K) δ 7.94 (s, 2H), 7.70 (s, 2H), 7.38 (dd, *J* = 5.2, 3.4 Hz, 2H), 7.27 (dd, *J* = 5.5, 3.3 Hz, 2H), 4.13 (s, 4H).
^{13}C NMR (126 MHz, $C_2D_2Cl_4$, 393 K) δ 137.2, 136.1, 131.3, 129.4, 127.9, 127.1, 126.3, 124.0, 36.4.
HRMS (APCI+) m/z calc. for $C_{18}H_{13}Cl_2$ $[M+H]^+$: 299.0389. Found: 299.0382.



8,9-Dibromo-5,12-dihydrotetracene (110b). To a solution of **109b** (1 equiv, 45 mg, 110 μmmol) in HPLC grade CH_2Cl_2 (0.1 M, 1.1 mL), in a sealed MW vial, was added cationic gold catalyst [JohnPhosAu(MeCN)]SbF_6 (17 mg, 20 mol%) and the mixture was stirred at 50 ºC for 1 hour under air. After cooling to 23 ºC, NEt_3 (1 drop) was added and then the solvents were evaporated under reduced pressure. The crude solid was dissolved in CH_2Cl_2 (1 mL) and MeOH (4 mL) was added to precipitate the title compound, which was obtained as an off-white solid after vacuum filtration (12.4 mg, 32.0 μmol, 30% yield).

^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 353 K) δ 8.12 (s, 1H), 7.68 (s, 1H), 7.40 – 7.34 (m, 1H), 7.29 – 7.24 (m, 1H), 4.11 (s, 2H).
^{13}C NMR (126 MHz, $C_2D_2Cl_4$, 353 K) δ 137.4, 136.2, 132.0, 131.4, 127.2, 126.4, 124.0, 121.0, 36.5.
HRMS (APCI+) m/z calc. for $C_{18}H_{12}Br_2$ $[M+H]^+$: 385.9300. Found: 385.9288.

Chapter III: *Rh-Catalyzed Ortho C–H Alkynylation of Aromatic Aldehydes*

INTRODUCTION

Alkynes and their derivatives are among the most useful functional groups in organic chemistry, being key constituent parts of natural products and synthetic pharmaceuticals. For instance, the naturally occurring enediyne antitumour antibiotic uncialamycin[1] is one of the most potent cytotoxic agents known until now (Figure 1). Its impressive biological activity stems from the presence of the enediyne structural motif, which plays a main role in its mechanism of action that involves cleavage of double-strand DNA through a cycloaromatization of Bergmann type. Furthermore, Efavirenz[2] is an antiretroviral and Terbinafine[3] is an antifungal agent.

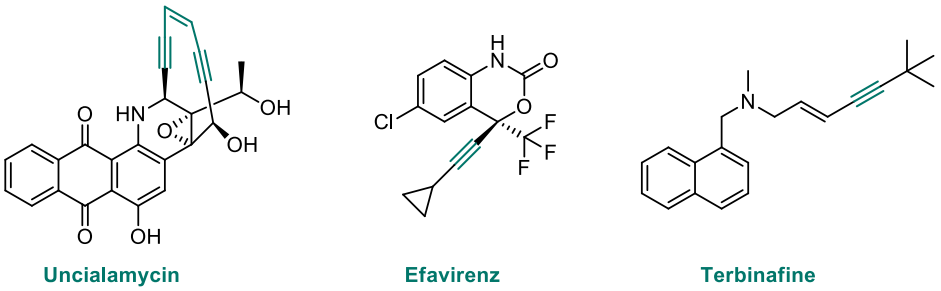
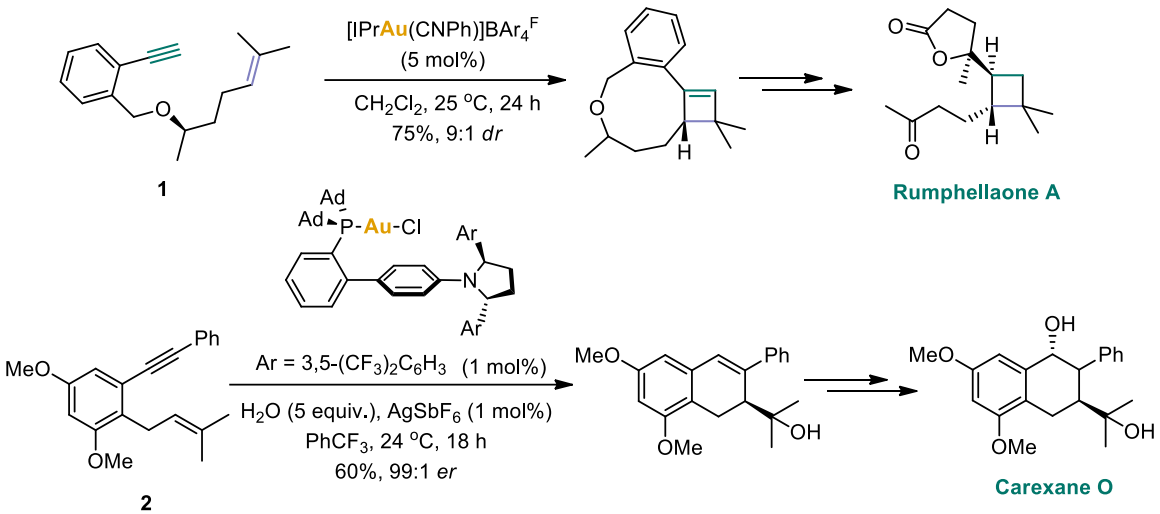


Figure 1. Bioactive compounds containing alkyne units

Carbon–carbon triple bonds are used as relevant precursors for the assembly of several carbocycles and heterocycles and complex molecular architectures, as they can act as electrophiles. For example, our group has exploited the reactivity of alkynes as components of enynes in the synthesis of natural products, like rumphellaones[4] or carexanes[5] (Scheme 1).



Scheme 1. Gold(I)-catalyzed synthesis of rumphellaone A and carexane O from enynes **1** and **2**

1 Davies, J.; Wang, H.; Taylor, T.; Warabi, K.; Huang, X.-H.; Andersen, R. J. *Org. Lett.* **2005**, *7*, 5233–5236.
2 Rakhamanina, N. Y.; van den Anker, J. *Expert Opin Drug Metab Toxicol* **2010**, *6*, 95–103.
3 Newland, J. G.; Abdel-Rahman, S. M. *Clin. Cosmet. Investig. Dermatol.* **2009,** *2*, 49–63
4 Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. *Org. Lett*. **2016**, *18*, 1614–1617.
5 Zuccarello, G.; Mayans, J. G.; Escofet, I.; Scharnagel, D.; Kirillova, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; B oother, J. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863.

In addition, as explained in *Chapter I* and *Chapter II*, alkynes are essential for the construction of materials for the field of optoelectronics. In our group, alkynes are part of the key synthons involved in the synthesis of hydroacenes, stable precursors of acenes. Besides, as stated before, the functionalization of acenes and their derivatives with silyl alkynes is already a general procedure that enhances their stability and modulates their arrangement in the crystal packing, which determines their semiconducting properties. Figure 2 illustrates three silylethynylated linear PAHs which exhibit good charge-carrier mobilities in OFETs.[6]

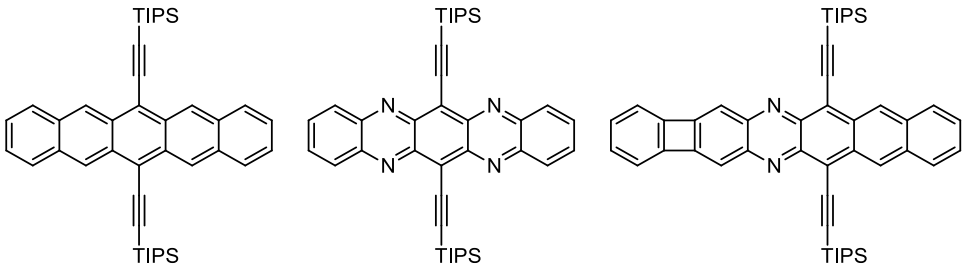
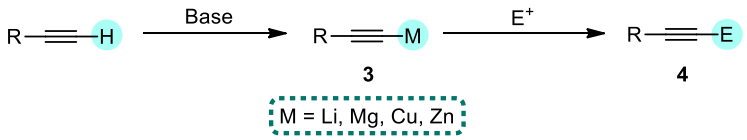


Figure 2. Silyl ethynylated acene derivatives used as semiconductors in OFETs

Synthesis of Alkynes

Acetylene, the simplest alkyne is produced in the industry by hydrolysis of calcium carbide or by combustion of methane during petroleum processing, whereas propyne is generated by thermal cracking of hydrocarbons. For the synthesis of the higher analogues four main approaches are generally followed. For instance, the deprotonation of terminal alkynes can be performed with a strong base due to the relatively low pK_a of the terminal proton (pK_a = 24–26), giving rise to doubly substituted alkynes **4** (Scheme 2). The treatment with strong bases renders metalated alkynes **3**, which can react with electrophiles, such as alkyl halides, ketones or imines, to synthesize a wide range of products.

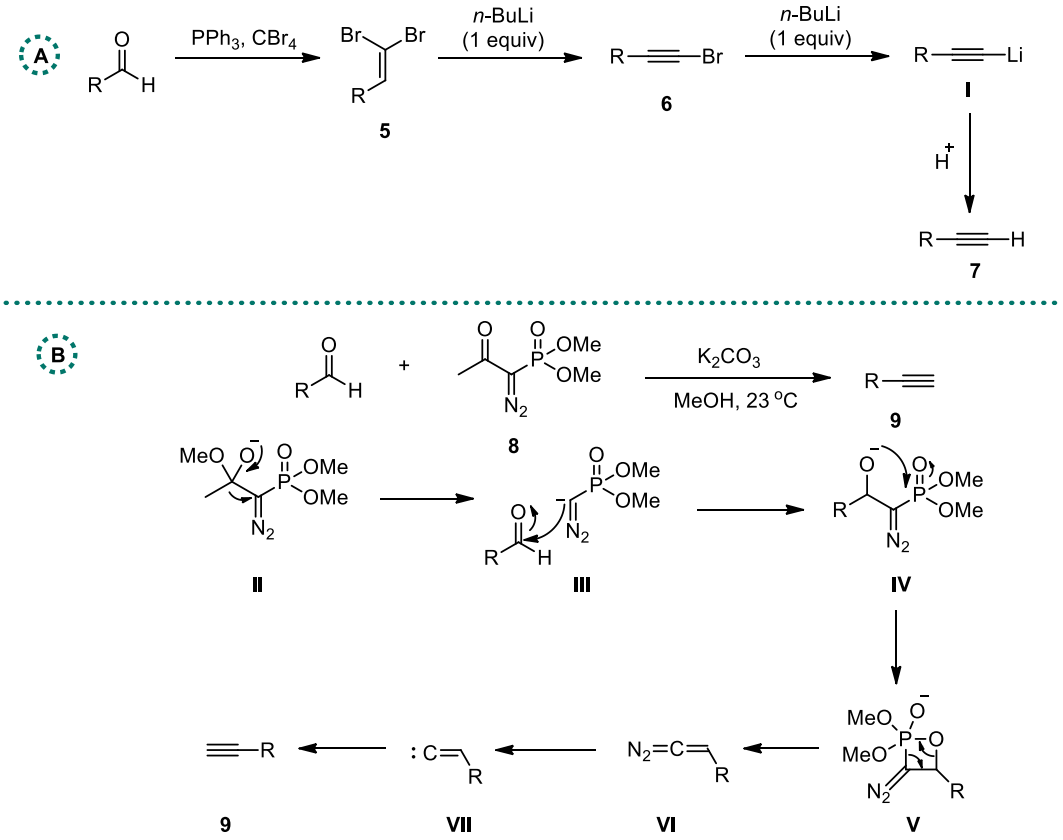


Scheme 2. Synthesis of internal alkynes by deprotonation with a strong base *via* metal acetylides

The second strategy relies on the formation of the triple bonds by one carbon homologation of aldehydes with phosphorous reagents and subsequent elimination. For this strategy, relevant examples

6 (a) Anthony, J. E.; Brooks, J. S.; Eaton, D. L.; Parkin, S. R. *J. Am. Chem. Soc.* **2001**, *123*, 482−483. (b) Miao, S.; Appleton, A. L.; Berger, N.; Barlow, S.; Marder, S. R.; Hardcastle, K. I.; Bunz, U. H. F. *Chem. Eur. J.* **2009**, *15*, 4990–4993. (c) Biegger, P.; Schaffroth, M.; Patze, C.; Tverskoy, O.; Rominger, F.; Bunz, U. H. F. *Chem. Eur. J.* **2015**, *21*, 7048–7052.

are the pioneering Corey-Fuchs reaction (Scheme 3A)[7] and the Ohira-Bestmann[8], which is a modification of the Seyferth-Gilbert homologation (Scheme 3B). The former reaction provides the alkynylated product after alkenylation with a phosphonium ylide, followed by stepwise treatment with *n*-BuLi of vinyl dibromide **5**. One equiv of base generates bromoalkyne **6**, while the second yields alkyne **7** *via* lithium-halogen exchange of intermediate **I**. Likewise, the diazophosphonate Ohira-Bestmann reagent yields the alkyne product by a Wittig-type reaction with an aldehyde. The mechanism involves an oxaphosphetane intermediate **V**, which suffers cycloelimination to generate diazoalkene **VI**. Loss of nitrogen gives vinylidene carbene **VII** that is converted into the alkyne **9** after 1,2-*H* migration. Despite the efficiency of these methods, their drawbacks include the use of a strong base (*n*-BuLi) or potentially explosive diazo reagents in stoichiometric amounts.

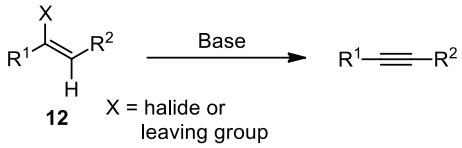


Scheme 3. Synthesis of alkynes by (a) Corey-Fuchs homologation and (b) Ohira-Bestmann homologation

7 Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

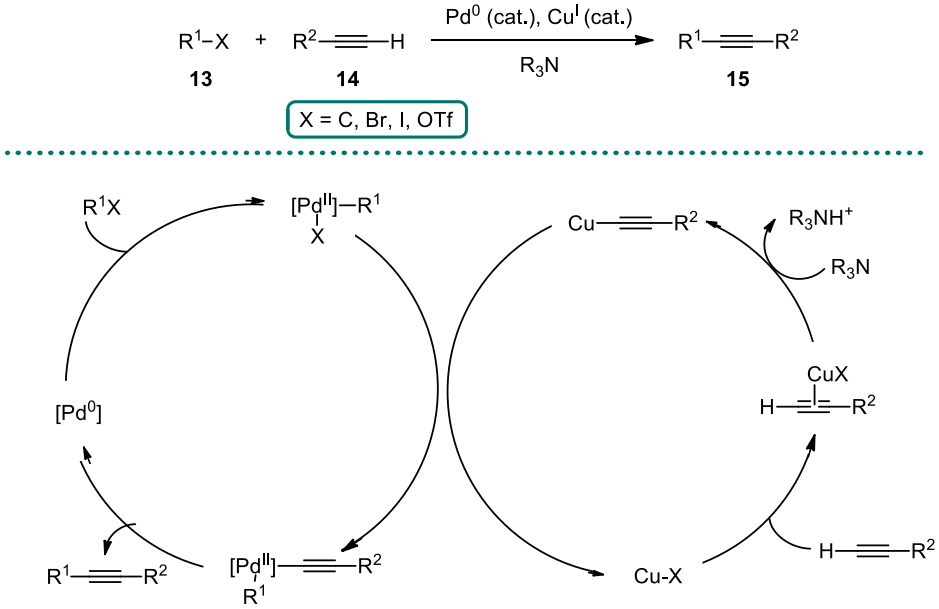
8 (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379–1386 (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.*, **1982**, *47*, 1837–1845. (c) Ohira, S. *Synth. Commun.* **1986**, *19*, 561–564. (d) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J., *Synlett* **1996**, 521–522.

The third strategy towards alkynes involves elimination reactions, such as dehydrohalogenation of vicinal or germinal halides and vinyl halides **12** to create one or two π-bonds of the alkyne moiety (Scheme 4).[9]



Scheme 4. Synthesis of alkynes by dehydrohalogenation of alkenes

Finally, the transition metal-catalyzed preparation of alkynes is the most convenient, as it enables the elaboration of already existing carbon–carbon triple bonds, the most remarkable being the Sonogashira cross-coupling.[10] This is a robust transformation that proceeds under mild conditions and furnishes the desired internal alkynes **15** by formation of C(sp)–C(sp)^2 bonds from aryl halides or triflates **13** and terminal alkynes **14** using a palladium catalyst, a copper co-catalyst and an amine base (Scheme 5). The mechanism relies on two independent catalytic cycles. The main Pd cycle involves the classical elementary steps: oxidative addition, transmetalation and reductive elimination. The second Cu cycle intersects the main one in the transmetalation, providing the required copper-acetylide partner.



Scheme 5. Synthesis of internal alkynes by Sonogashira cross-coupling and mechanism of the reaction

9 (a) Viehe, H. G.; Dekker, M. *Chemistry of Acetylenes*, New York, **1969**; (b) R. A. Raphael, *Acetylenic compounds in organic chemistry*, Butterworths Scientific Publication, London, **1955**.

10 (a) Sonogashira , K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16* , 4467–4470.

Even though the Sonogashira coupling is nowadays the most commonly employed strategy to generate C(sp)–C(sp^2) bonds from aryl halides and terminal alkynes, its main drawback stems from the utilization of aryl halide precursors, whose synthesis might be difficult in complex molecular settings. Consequently, new strategies for a more direct synthesis of alkynes are still needed and the alkynylation by C–H activation has attracted increased attention during the past 15 years.

C–H Activation

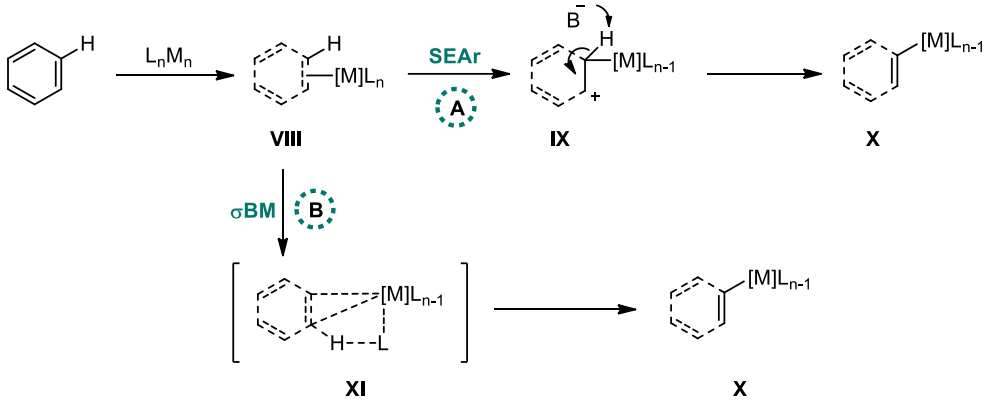
The direct C–H activation[11] has emerged as a key tool for the simplification of synthetic strategies, enabling the acquisition of a variety of products in a more direct way, from late-stage intermediates. This atom-economical approach allows the formation of new C–X (X = C, O, N, S) bonds by transition-metal (M) catalysis from simple starting materials and under mild conditions. This process has two stages, the first one involving the replacement of a particular C–H bond by a C–M bond, while the rest of the bonds remain untouched. In the second stage, the new C–M bond, which is more easily functionalized, gets converted into C–X to furnish the targeted products.

Mechanistic Aspects of C–H Activation:

Investigations into the elementary steps of the mechanisms[12] of C–H activation by late-transition metals (Pd, Pt, Rh, Ir) have shown that different pathways could be followed, the most well-established being oxidative addition, electrophilic aromatic substitution (SEAr) and σ-bond metathesis (σBM). The latter two, depicted in Scheme 6, are representative for electron-poor metal centers, with high oxidation state. The SEAr mechanism relies on the behavior of metals as Lewis acids and takes place by coordination of the electrophilic metal center to the π-electronic cloud of the substrate, displacing a proton. The new C–M bond in intermediate **IX** offers the vicinal C(aryl)–H bond increased acidity and its proton can be easily abstracted by the action of an external base to generate intermediate **X**. On the other hand, the σ-bond metathesis proceeds through a four-membered metalacycle transition state **XI** in which the metalation and deprotonation occur in a concerted mechanism. In this case, a ligand on the metal center acts as a base that abstracts the proton to generate intermediate **X**.

11 Selected reviews on C–H activation: (a) Fakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009. (c) Roudlesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A Chem.* **2017**, *426*, 275–296.

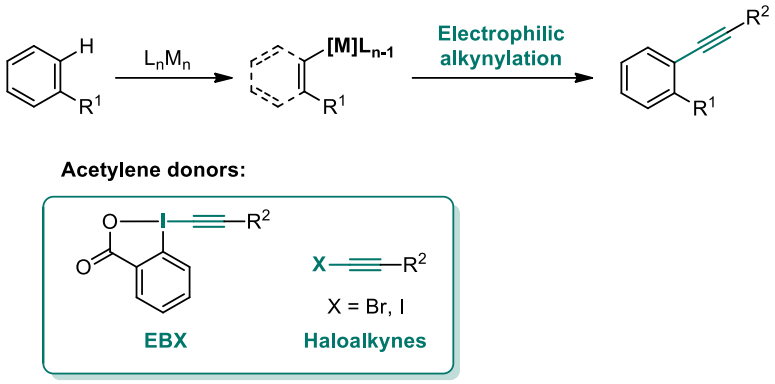
12 Recent reviews on mechanistic investigations of C–H activation: (a) Gallego, D.; Baquero, E. A. *Open Chem.* **2018**, *16*, 1001–1058. (b) Shan, C.; Zhu, L.; Qu, L.-B., Bai, R.; Lan, Y. *Chem. Soc. Rev.* **2018**, *47*, 7552–7576. (c) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192−2452.



Scheme 6. Mechanism of the C–H metalation of high oxidation state late transition metals by (a) SEAr and (b) σBM

C(sp^2)–H Alkynylation: Previous Work

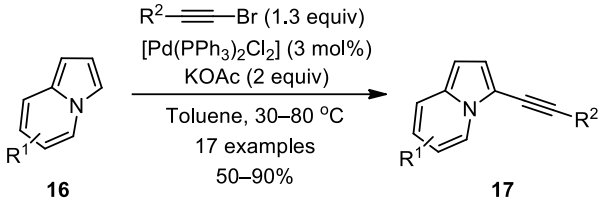
A different strategy has been introduced in the past two decades for the late-stage electrophilic alkynylation and involves the transition-metal catalyzed reaction of C(sp^2)–H bonds with activated acetylene donors, such as ethynylbenziodoxolone (EBX) or haloalkynes (Scheme 7). Since the alkyne-containing reagents are activated, and not the sp^2 carbon, this approach is also called 'inverse-Sonogashira' (Scheme 7). Employing these reagents brings two main advantages: inhibition of the alkyne homo-coupling side reaction and the tolerance for various functional groups, since no terminal oxidant is necessary to close the redox neutral cycle.



Scheme 7. Electrophilic alkynylation with activated acetylene donors

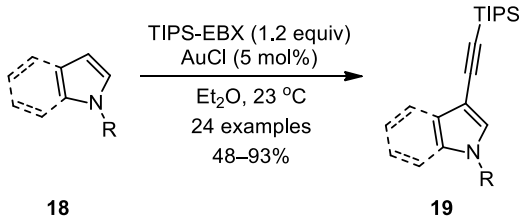
The major challenge in C–H activation is the differentiation between highly similar C–H bonds. In case of the alkynylation process, to yield the products in a regioselective manner, the 'inverse-Sonogashira' methodology requires electronically activated (hetero)arenes, containing distinguished bonds in terms of acidity or high electron density that enable them to undergo deprotonation or a Friedel-Crafts type reaction, respectively. For the rest of the substrates, the introduction of a directing-group is a valuable method to ensure discrimination between C–H bonds and regioselective alkynylation.

The first reports on the 'inverse-Sonogashira' relied on the innate reactivity of the substrates to achieve the desired selectivity. Gevorgyan and co-workers reported the first transition metal-catalyzed direct alkynylation of electron-rich *N*-heterocycles **16**, such as indolizine, pyrroloquinoline, pyrroloisoquinoline, and pyrrolooxazole (Scheme 8).[13] The alkynylated products **17** were obtained by reaction of bromo-alkynes with the aryl–Pd(II) intermediate resulting from the electrophilic C–H metalation of the heterocycles.



Scheme 8. Palladium-catalyzed alkynylation of *N*-fused heterocycles

The Waser group discovered the unique properties of hypervalent iodides for acetylene transfer and elaborated the EBX reagents (Scheme 9). These compounds were first employed in the gold(I)-catalyzed direct alkynylations of indole and pyrrole heterocycles **18**, which gave products **19** with great regioselectivity.[14]



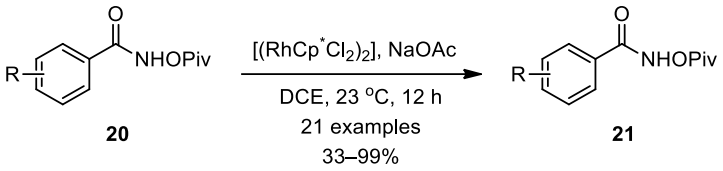
Scheme 9. Direct alkynylation of indole and pyrrole heterocycles using EBX

Chelation-Assisted C–H Alkynylation

As stated before, the selective formation of the C–M bond by C–H activation can be modulated by placing a directing or chelating group in close proximity to the targeted bond. Until recently, the most commonly employed directing groups were *N*-heterocycles or amides, owing to their good abilities to coordinate late transition metals and their slight basicity. Thus, the first chelation-assisted C–H alkynylation was reported by Tobisu and Chatani using anilides and a palladium catalyst.[15] Later on, the same group described the ruthenium-catalyzed C–H alkynylation of arenes directed by heterocycles.[16] Furthermore, the groups of Li[17] and Loh[18] designed independently a catalytic system comprised of a Cp*Rh(III) catalyst and EBX as the alkyne donor based on strongly

13 Seregin, I. V. ; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742–7743.
14 Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349.
15 Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250−3252.
16 Ano, Y.; Tobisu, M.; Chatani, N. *Synlett* **2012**, *23*, 2763−2767.
17 Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am.Chem. Soc.* **2014**, *136*, 4780−4787
18 Feng, C.; Loh, T. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 2722−2726.

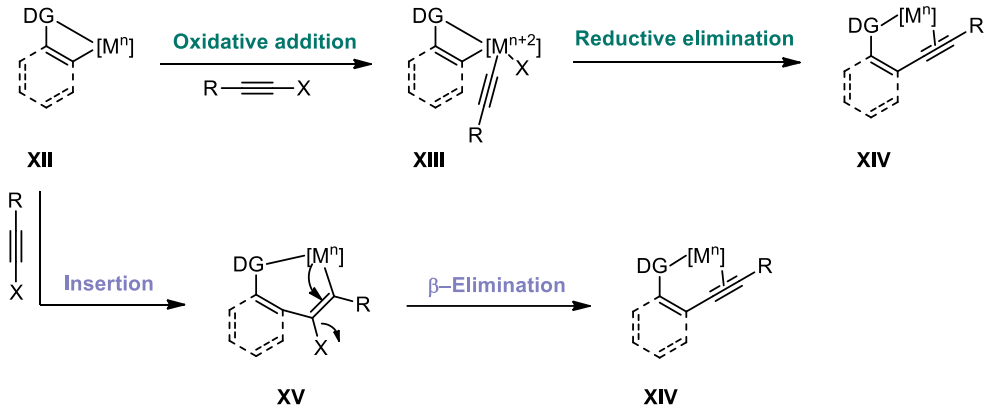
coordinating directing groups. Li's strategy, depicted in Scheme 10, relied on amides as chelating groups.



Scheme 10. Direct C–H alkynylation of (hetero)arenes directed by amides

Proposed Mechanisms of the Alkynylation Step

After coordination of the directing group to the metal center, the reaction of the alkyne with the metallacycle can take place through two possible mechanisms (Scheme 11). If EBX alkyne donors are used, a sequence involving oxidative addition of **XII** and reductive elimination of **XIII** is likely to follow, due to their highly electrophilic character. On the other hand, in case of the halo-alkynes with polarized C–X bonds, an insertion into the C–M bond and subsequent *β*-halide elimination from **XV** to yield the alkyne intermediate **XIV** is a more reasonable alternative. These mechanisms were extensively investigated and confirmed by Sarpong and Musaev,[19] who also discovered that for the second pathway the efficient alkynylation is highly dependent on the release of the ring-strain of the metallacycle in the alkyne insertion step, while in the halide elimination step it relies on the *β*-metal effect that stabilizes a cationic transition state.

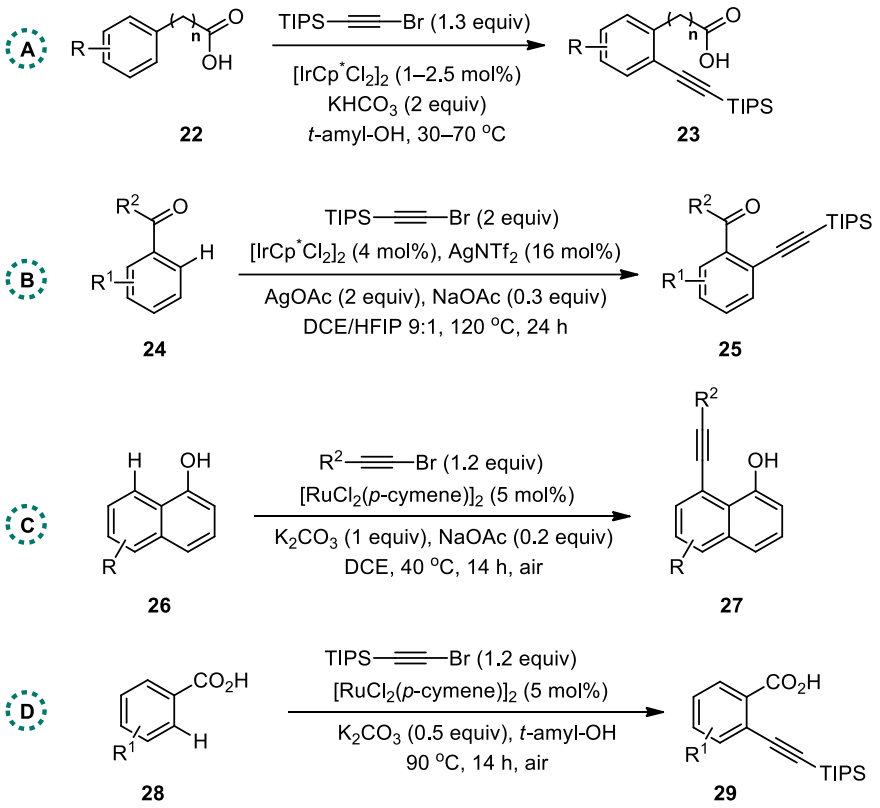


Scheme 11. Proposed mechanisms of the alkynylation step after C–H metalation

To demonstrate the applicability of the chelation-assisted C–H activation and perform practical and step-economic syntheses, the directing groups must be easily installed and removed. As a result, new alkynylation strategies need to be developed using common and easy to prepare functional groups, such as amines, alcohols or carbonyl groups.[20] In this sense, the utilization of free

19 Haines, B. E.; Sarpong, R.; Musaev; D. G. *J. Am. Chem. Soc*. **2018**, *140*, 10612−10618.
20 For a review on chelation-assisted transition metal-catalyzed C–H alkynylation: Caspers, L. D.; Nachtsheim, B. J. *Chem. Asian. J.* **2018**, *13*, 1231–1247.

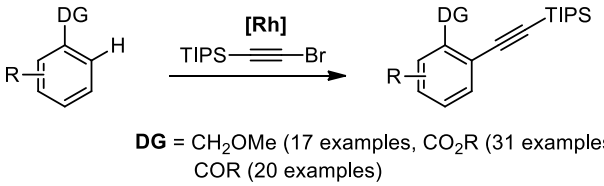
amines is complicated in C–H alkynylation and hence these groups require functionalization with *N*-heterocycles to form bidentate ligands with superior chelating potential.[21] Regarding the carbonyl groups, free carboxylic acids **22** have been used in C–H alkynylation of (hetero)aromatic compounds, despite being weakly coordinating (Scheme 12a).[22] The products **23** were obtained without concurring cyclizations, using an Ir(II) catalyst. Similarly, ketones have even weaker coordinating abilities and are even more difficult to employ in C–H activations. Nevertheless, an Ir(II)-catalyzed ketone-directed alkynylation of a wide range of (hetero)aromatic analogues **24** could be achieved (Scheme 12b).[23] Although phenols cannot be used in *ortho* C–H alkynylation, since the formation of the four-membered metallacycle is not likely to take place, 1-naphthols **26** were described by our group as good substrates for the Ru(III)-catalyzed selective *peri*-alkynylation with bromo-alkynes (Scheme 12c).[24] By contrast, when aromatic carboxylic acids **28** were employed under similar conditions, the C–H alkynylation occurred selectively at the *ortho* position (Scheme 12d).



Scheme 12. C–H alkynylation directed by weakly coordinating carbonyl groups

21 (a) Kim, S. H.; Park, S. H.; Chang, S. *Tetrahedron* **2012**, *68*, 5162–5166. (b) Tang, G.-D.; Pan, C.-L.; Xie, F. *Org. Biomol. Chem.* **2016**, *14*, 2898–2904. (c) Ruan, Z.; Lackner, S.; Ackermann, L. *ACS Catal.* **2016**, *6*, 4690–4693.
22 Chen, C.; Liu, P.; Tang, J.; Deng, G.; Zeng, X. *Org. Lett.* **2017**, *19*, 2474 –2477.
23 Li, X.; Wu, G.; Liu, X.; Zhu, Z.; Huo, Y.; Jiang, H. *J. Org. Chem.* **2017**, *82*,13003–13011.
24 Tan, E.; Konovalov, A. I.; Fernández, G. A., Dorel, R.; Echavarren, A. M. *Org. Lett.* **2017**, *19*, 5561−5564.

Apart from this carboxylic acid-assisted Ru-catalyzed alkynylation strategy, our group has also developed a Rh(III)-catalyzed C–H *ortho*-alkynylation reaction with bromo-alkynes, directed by easily installed and synthetically useful ester, ketone and ether groups (Scheme 13).[25] Furthermore, even other groups, which are considered too strong binders to metals to be involved in catalytic transformations, such as sulfoxide, thioether, thioacetal, sulfone and tertiary amine, yielded the *ortho*-alkynylated products by modifying slightly the conditions of the reaction.



Scheme 13. Rh(III)-catalyzed C–H alkynylation directed by ester, ketone and ether groups

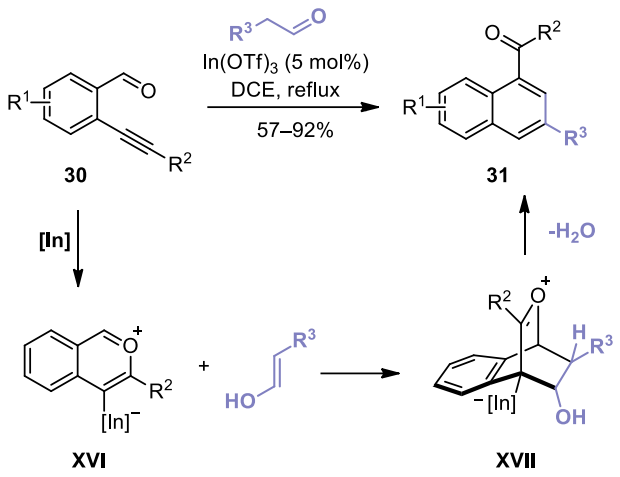
Recently, we have also investigated the rhodium-catalyzed *ortho* C–H alkynylation of aromatic aldehydes, which will be the main focus of the discussion in the *Results* section. This type of alkynylation would give rise to 2-alkynylaryl aldehydes and their derivatives, also known as ynals, which are versatile building blocks for the formation of cyclic compounds.

Ynals in the Synthesis of PAH Derivatives

2-Alkynylaryl aldehydes and their substituted and polyaromatic analogues have been employed in synthetic transformations as multifunctional reagents to furnish a wide variety of PAHs and PHAs, such as naphthalenes, indoles or isoquinolines.[26]

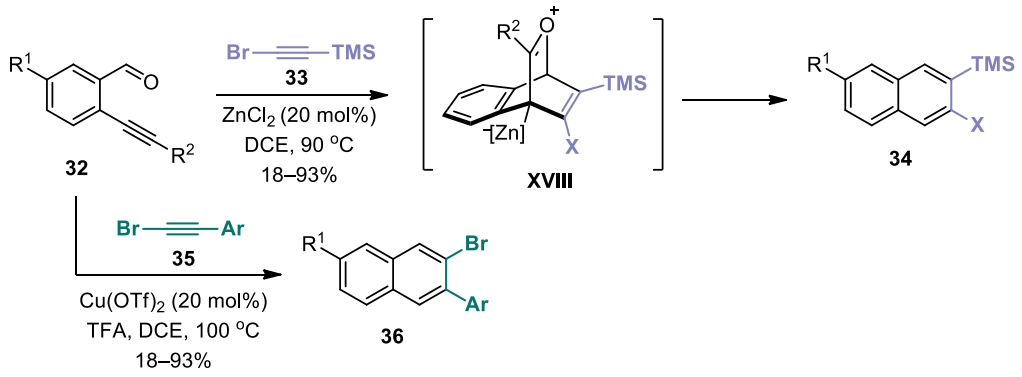
Many syntheses of substituted naphthalene compounds were reported from ynals. For example, 1,3-disubstituted naphthalenes **31** containing ketone goups were achieved regioselectively by Srinivasan and co-workers by In(OTf_3)-catalyzed reaction of ynals **30** with enolizable aldehydes, ketones, 1,3-diketones or *β*-keto esters (Scheme 14).[27] The mechanism was proposed to involve an inverse electron demand Diels-Alder-type reaction to give the bridged oxonium intermediate **XVII**, which yields compounds **31** after cleavage of the C−O bond and dehydration.

25 Tan, E.; Quinonero, O., de Orbe, M. E.; Echavarren, A. M. *ACS Catal.* **2018**, *8*, 2166−2172.
26 For a recent review on applications of ynals in organic synthesis: Li, L.; Huang, D.; Shi, C.; Yan, G. *Adv. Synth. Catal.* **2019**, *361*, 1958–1984.
27 Sakthivelm, K.; Srinivasan, K. *Org. Biomol. Chem.* **2014**, *12*, 269–277.



Scheme 14. Regioselective synthesis of naphthalenes **31** from ynals **30**

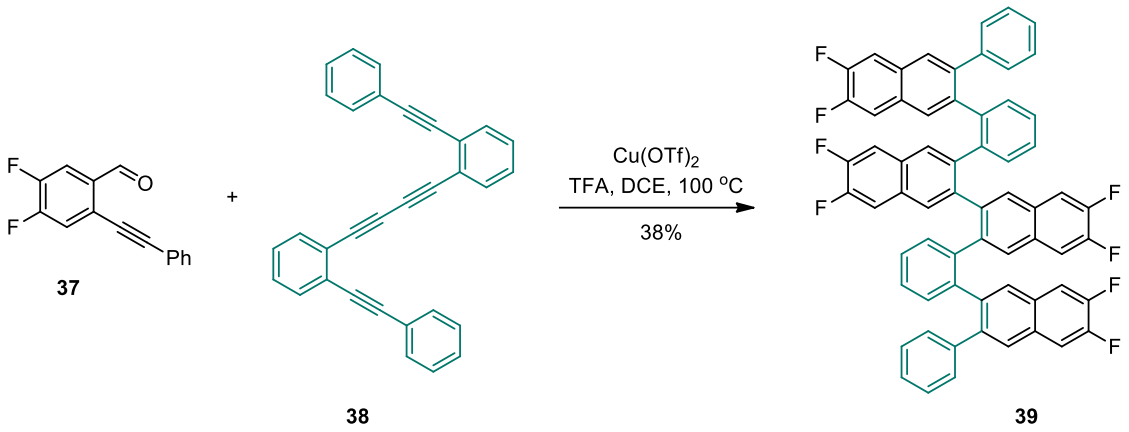
Dichtel *et al.* reported the metal-catalyzed reaction of ynals with alkynes to afford regioselectively the 2,3-substituted naphthalenes **34** through 6-*endo*-dig cyclization, followed by a tandem [4+2] cycloaddition/Friedel–Crafts reaction (Scheme 15). The full regioselectivity relied on the elected catalyst. Thus, the $ZnCl_2$-catalyzed reaction with bromoalkyne **33** afforded naphthalenes **34**,[28] whereas the opposite regioisomer **36** was obtained by $Cu(OTf)_2$-catalyzed reaction of **32** with bromoalkyne **35**.[29]



Scheme 15. Regioselective synthesis of naphthalenes **34** and **36**

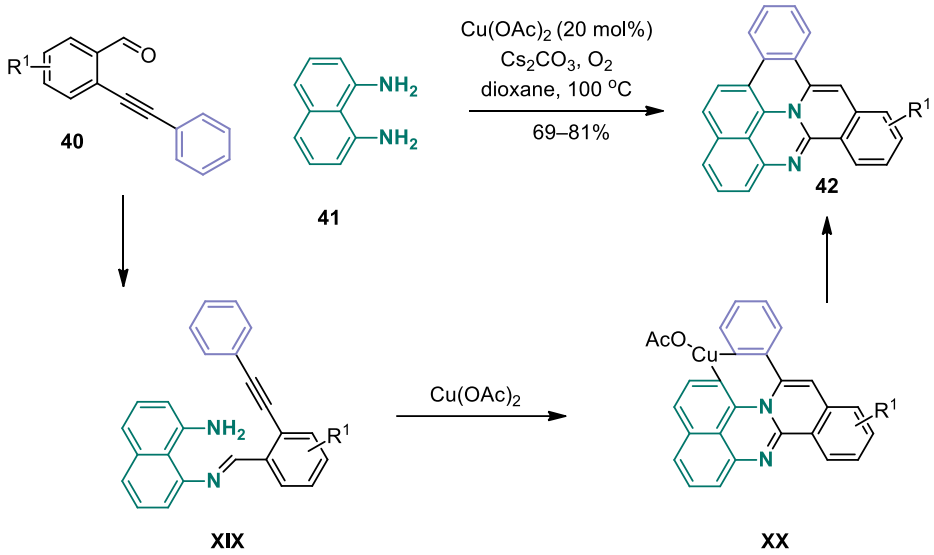
Additionally, the cycloaddition of aldehyde **37** and tetraalkyne **38** yielded the fluorinated oligomeric naphthalene **39**, a more complex conjugated architecture (Scheme 16).[30]

28 Hein, S. J.; Lehnherr, D.; Dichtel, W. R. *Chem. Sci.* **2017**, *8*, 5675–5681.
29 Lehnherr, D.; Alzola, J. M.; Lobkovsky, E. B.; Dichtel, W. R. *Chem. Eur. J.* **2015**, *21*, 18122–18127.
30 Lehnherr, D.; Chen, C.; Pedramrazi, Z.; De- Blase, C. R.; Alzola, J. M.; Keresztes, I.; Lobkovsky, E. B.; Crommie, M.; Dichtel, F. W. R. *Chem. Sci.* **2016**, *7*, 6357– 6364.



Scheme 16. Synthesis of fluorinated oligomeric naphthalene **39**

On the other hand, Wang and co-workers reported the synthesis of a class of extended PHAs, namely quinolizino[3,4,5,6-*kla*]perimidines **42**. The final heterocyclic compounds were obtained by $Cu(OAc)_2$-catalyzed domino tricyclization of naphthalene-1,8-diamine **41** and ynals **40** (Scheme 17). The synthetic sequence involves a successive condensation, nucleophilic addition, intramolecular hyroamination and a final aerobic oxidative dehydrogenative coupling and enabled concise access to fused heptacyclic heterocycles containing quinolizine and perimidine moieties.[31]

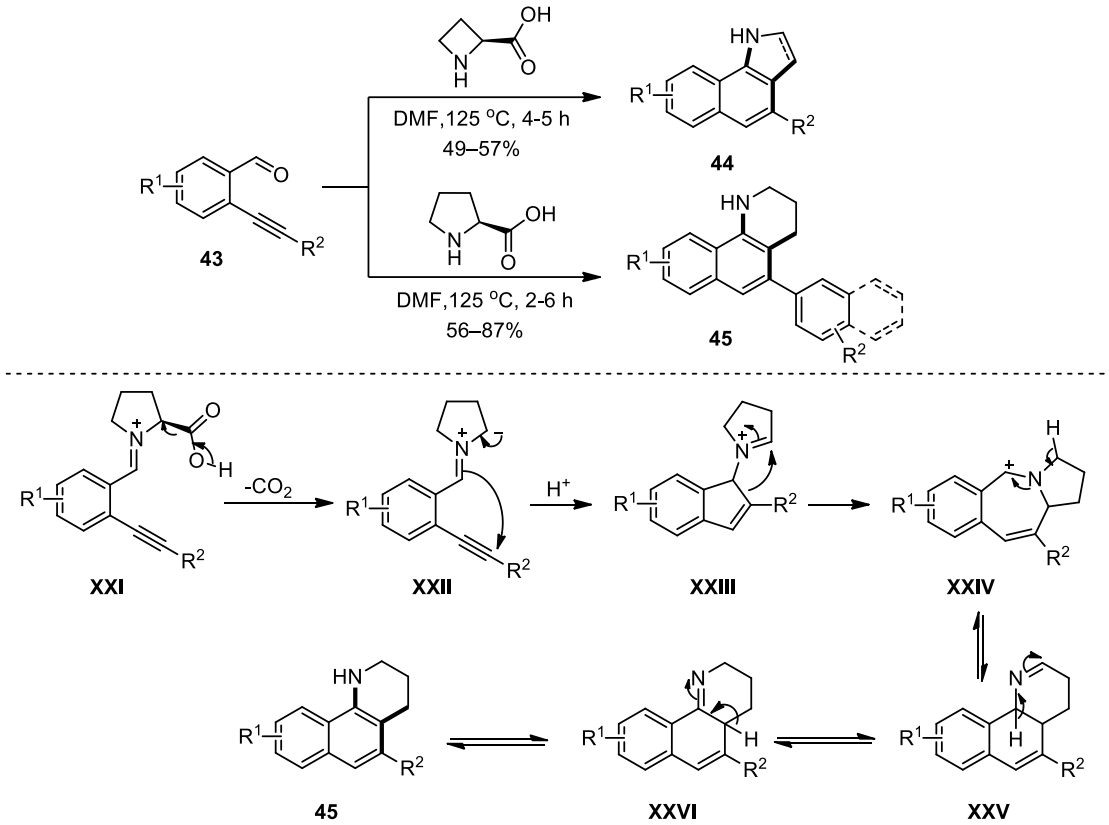


Scheme 17. Preparation of quinolizino[3,4,5,6-*kla*]perimidines **42**

Indoles are common motifs in bioactive compounds and thus, considerable efforts have been made lately to develop new synthetic routes towards them, and also to improve the classical strategies, including the Fischer synthesis and Nenitzescu reactions. One of the recent approaches by Kundu *et al.* proposes the synthesis of indole-based products **44** from 2-alkynyl benzaldehydes **43** and *L*-azetidine-2-carboxylic acid through metal-free decarboxylative cyclization/ring expansion (Scheme

31 Feng, B.; Liu, J.; Wang, X. *J. Org. Chem.* **2017**, *82*, 1817–1822.

18).[32] Furthermore, the reaction of similar ynals with *L*-proline gave rise to partially saturated quinoline derivatives **45**. Mechanistically, for compounds **45** the reaction proceeds through the imine intermediate **XXI**, generated by initial condensation of the aldehyde and the amine unit of the amino acid. After decarboxylation of **XXI**, azomethine ylide **XXII** is formed and after abstraction of one proton, it undergoes a highly favoured 5-*endo*-dig cyclization to give intermediate **XXIII**. The one-carbon ring expansion of **XXIII** renders the stable benzyl cation **XXIV**, which undergoes a proton transfer to the intermediate **XXV**, followed by final rearrangement to provide the final product **45**. A similar procedure has also been followed by the Verma group to form carbazoles from ynals and *L*-proline.[33]

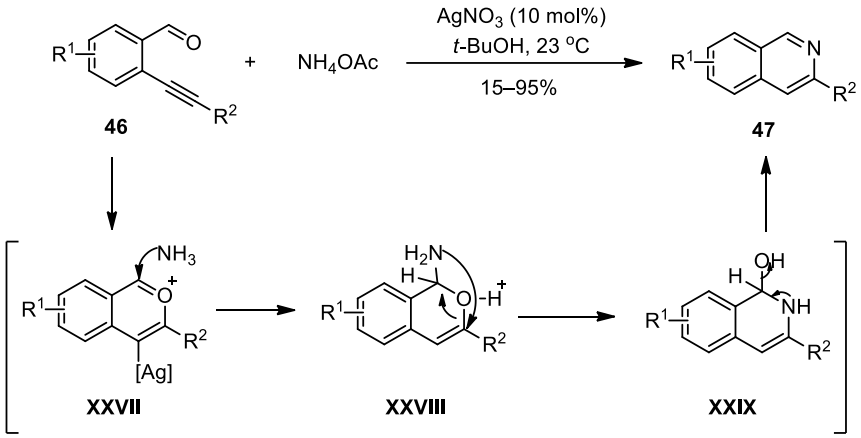


Scheme 18. Synthesis of indoles and partially saturated quinolines by metal-free decarboxylative cyclization/ring expansion and the suggested mechanism of these reactions

Isoquinoline derivatives are compounds with many applications, such as anesthetics, vasodilators or antihypertensive agents. However, the classical approaches towards their preparation, –Pomeranz-Fritsch, Pictet-Spengler or Bischler-Napieralski reactions –, require highly corrosive reagents or harsh conditions. To overcome these issues, various methodologies have been developed and rely on transition-metal-mediated annulations, electrophilic cyclizations, aryne annulations, or ring expansions. The transition-metal-catalyzed approaches are preferred since they proceed under relatively mild conditions. In this sense, a convenient strategy for the synthesis of isoquinoline

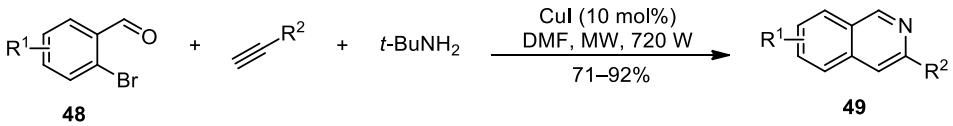
32 Samala, S.; Singh, G.; Kumar, R.; Ampapathi, R. S.; Kundu B. *Angew. Chem. Int. Ed.* **2015**, *54*, 9564–9567.
33 Verma, S.; Mishra, P. K.; Kumar, M.; Sur, S.; Verma, A. K. *J. Org. Chem.* **2018**, *83*, 6650–6663.

derivatives **47** was developed by Anand's group and relies on the silver nitrate-catalyzed 6-*endo*-dig cyclization/nucleophilic addition of *ortho*-(1-alkynyl)arylaldehydes **46** and ammonium acetate as the amine source (Scheme 19).[34] The mechanism involves the formation of isochromenylium intermediate **XXVII** followed by nucleophilic attack of ammonia to form intermediate **XXVIII**, which rearranges to hemiaminal **XXIX** under acidic conditions. Final decomposition of **XXIX** furnishes isoquinolines **47**. The reaction proceeds at room temperature and could also be applied to ketones. The potential of this approach was demonstrated in the total synthesis of the natural products berberine and palmatine.



Scheme 19. Synthesis of isoquinolines **47** by silver(I)-catalyzed benzannulation

3-Substituted isoquinolines **49** were also obtained *via* 6-*endo*-dig cyclization of *in situ* generated 2-alkynylbenzaldehydes **48** and amines (Scheme 20).[35]



Scheme 20. One-pot synthesis of 3-substituted isoquinolines **49**

34 Reddy, V.; Jadhav, A. S.; Anand, R. V. *Org. Biomol. Chem.* **2015**, *13*, 3732–3741.
35 Zhang, J.; Han, X.; Lu, X. *J. Org. Chem.* **2016**, *81*, 3423–3429.

OBJECTIVES

Taking into account the good results obtained in the Rh(III)-catalyzed C–H alkynylation directed by carbonyl compounds, such as esters, ketones, carbamates or phenol esters, our first objective was to investigate the same procedure using aldehydes as directing groups.

A second objective was to employ the resulting alkynylated products as versatile building blocks in the synthesis of polyarenes, such as pentalenes, isoquinolines, indoles and indolines.

RESULTS AND DISCUSSION

The general rhodium-catalyzed alkynylation of C(sp^2)–H bonds designed in our group could be applied to arenes containing a broad range of directing-groups at the *ortho*-position, such as phenolic –OH, carboxylic acid, ester, ketone, sulfoxide, sulfone, carbamate and nitro groups.[24,25]

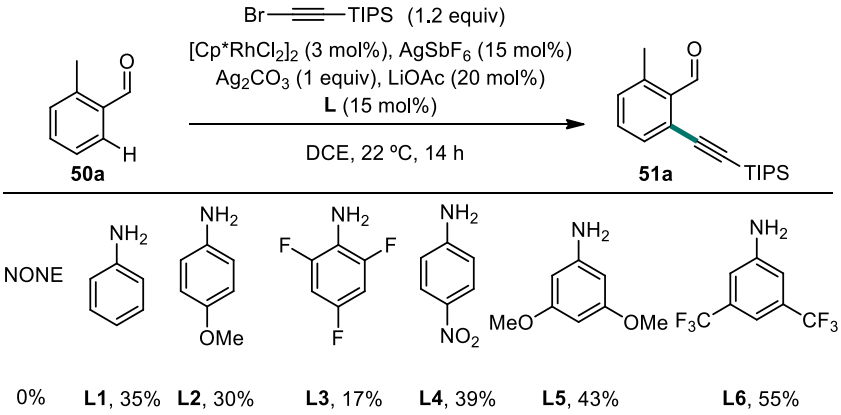
As stated before, aldehydes cannot be employed in C–H activation processes because of their weak directing ability and susceptibility to oxidation. This issue can be overcome by using a transient directing group (TDG), which is installed (usually using a co-catalytic modifier) and removed *in situ* during the reaction process. This strategy designed by Jun *et al.*[36] has become a reliable procedure for the transformation of weakly coordinating functional groups into better σ-donors. For carbonyl groups, derivatives such as imines,[37] oximes or hydrazones are commonly employed. As a result, we decided to investigate the Rh(III)-catalyzed *ortho* C–H alkynylation of aromatic aldehydes through the transient formation of an imine as directing group.[38]

Our studies commenced by exploring the Rh(III)-catalyzed alkynylation of benzaldehydes, under the conditions developed in our group.[25] However, our initial attempts on the reaction of 2-methylbenzaldehyde (**50a**) with (bromoethynyl)triisopropylsilane failed to give the alkynylated product **51a** (Scheme 21). We envisioned that the formation of an imine as transient directing group using substoichiometric amounts of an aniline, would generate a more efficient directing group and enable this transformation. Thus, addition of 15 mol% of aniline **L1** to the reaction afforded **51a** in 35% yield. Consequently, other electron-rich and electron-poor anilines (**L2-L6**) were screened. The best result was obtained by using electron-poor 3,5-bis(trifluoromethyl)aniline (**L6**), compound **51a** being provided in 55% yield.

36 Jun, C. H.; Lee, D. Y.; Hong, J. B. *Tetrahedron Lett.* **1997**, *38*, 6673–6676.

37 (a) St John-Campbella, S.; Bull, J. A. *Org. Biomol. Chem*. **2018**, *16*, 4582–4595. (b) Higham, J. I., Bull, J. A. *Org. Biomol. Chem.* **2020**, *18*, 7291–7315.

38 For reviews on the use of TDG: (a) Zhao, Q.; Poisson, T.; Pannecoucke, X.; Besset, T. *Synthesis* **2017**, *49*, 4808−4826. (b) Gandeepan, P.; Ackermann, L. *Chem.* **2018**, *4*, 199−222. (c) St John-Campbella, S.; Bull, J. A. *Org. Biomol. Chem*. **2018**, *16*, 4582−4595. For early reference: (d) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485−492. For examples using Pd-catalysis: (e) Zhang, F. L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J. Q. *Science* **2016**, *351*, 252−256. (f) Yang, K.; Li, Q.; Liu, Y.; Li, G.; Ge, H. *J. Am. Chem. Soc.* **2016**, *138*, 12775−12778. (g) Liu, X.−H.; Park, H.; Hu, J.-H.; Hu, Y.; Zhang, Q.-L.; Wang, B.-L.; Sun, B.; Yeung, K.-S.; Zhang, F.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 888−896. (h) Xu, J.; Liu, Y.; Wang, Y.; Li, Y.; Xu, X.; Jin, Z. *Org. Lett.* **2017**, *19*, 1562−1565. (i) Chen, X.-Y.; Ozturk, S.; Sorensen, E. J. *Org. Lett.* **2017**, *19*, 1140−1143. (j) Zhang, X.; Zheng, H.; Li, J.; Xu, F.; Zhao, J.; Yan, H. *J. Am. Chem. Soc.* **2017**, *139*, 14511−14517. (k) Yao, Q.-J.; Zhang, S.; Zhan, B.-B.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2017**, *56*, 6617−6621. (l) Tang, M.; Yu, Q.; Wang, Z.; Zhang, C.; Sun, B.; Yi, Y.; Zhang, F. *Org. Lett.* **2018**, *20*, 7620−7623. For examples using Rh(III)- or Ir(III)-catalysis: (m) Lian, Y.; Hummel, J. R.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 12548−12551. (n) Zhang, Y.−F.; Wu, B.; Shi, Z.−J. *Chem. Eur. J.* **2016**, *22*, 17808−17812. (o) Hu, W.; Zheng, Q.; Sun, S.; Cheng, J. *Chem. Commun*. **2017**, *53*, 6263−6266. (p) Mu, D.; Wang, X.; Chen, G.; He, G. *J. Org. Chem.* **2017**, *82*, 4497− 4503. (q) Wang, X.; Song, S.; Jiao, N. *Chin. J. Chem.* **2018**, *36*, 213−216. (r) Kim, S.; Han, S. H.; Mishra, N. K.; Chun, R.; Jung, Y. H.; Kim, H. S.; Park, J. S.; Kim, I. S. *Org. Lett.* **2018**, *20*, 4010−4014. (s) Hande, A. E.; Ramesh, V. B.; Prabhu, K. R. *Chem. Commun.* **2018,** *54*, 12113−12116.



Scheme 21. Aniline screening in the C–H alkynylation of 2-methylbenzaldehyde (**50a**)

The reaction was subjected to further optimization (Table 1). Thus, the role of trifluoroacetic acid as an additive was revealed, 0.5 equiv being the appropriate loading that leads to **51a** in 95% yield (Table 1, entries 1–3). Furthermore, control experiments showed the essential role of all reaction components (Table 1, entries 4–7). Accordingly, other catalysts used in C–H functionalization, such as $MnBr(CO)_5$, $Cp^*Co(CO)I_2$, $Pd(OAc)_2$, or $[RuCl_2(p\text{-cymene})]_2$, did not yield any product (Table 1, entry 8). Moreover, replacing Ag_2CO_3 with K_2CO_3 (Table 1, entry 9) or AgOAc (Table 1, entry 10) either inhibited the reaction completely or led to slightly lower yield. By contrast, when $[Cp^*RhCl_2]_2$ was replaced by the corresponding iridium catalyst, the alkynylated product was provided in similar yield (Table 1, entry 11). Moreover, the presence of water in the reaction mixture did not affect the reaction outcome (Table 1, entry 12).

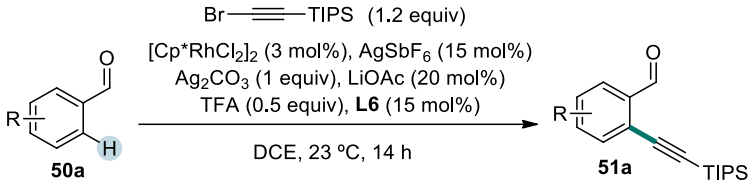
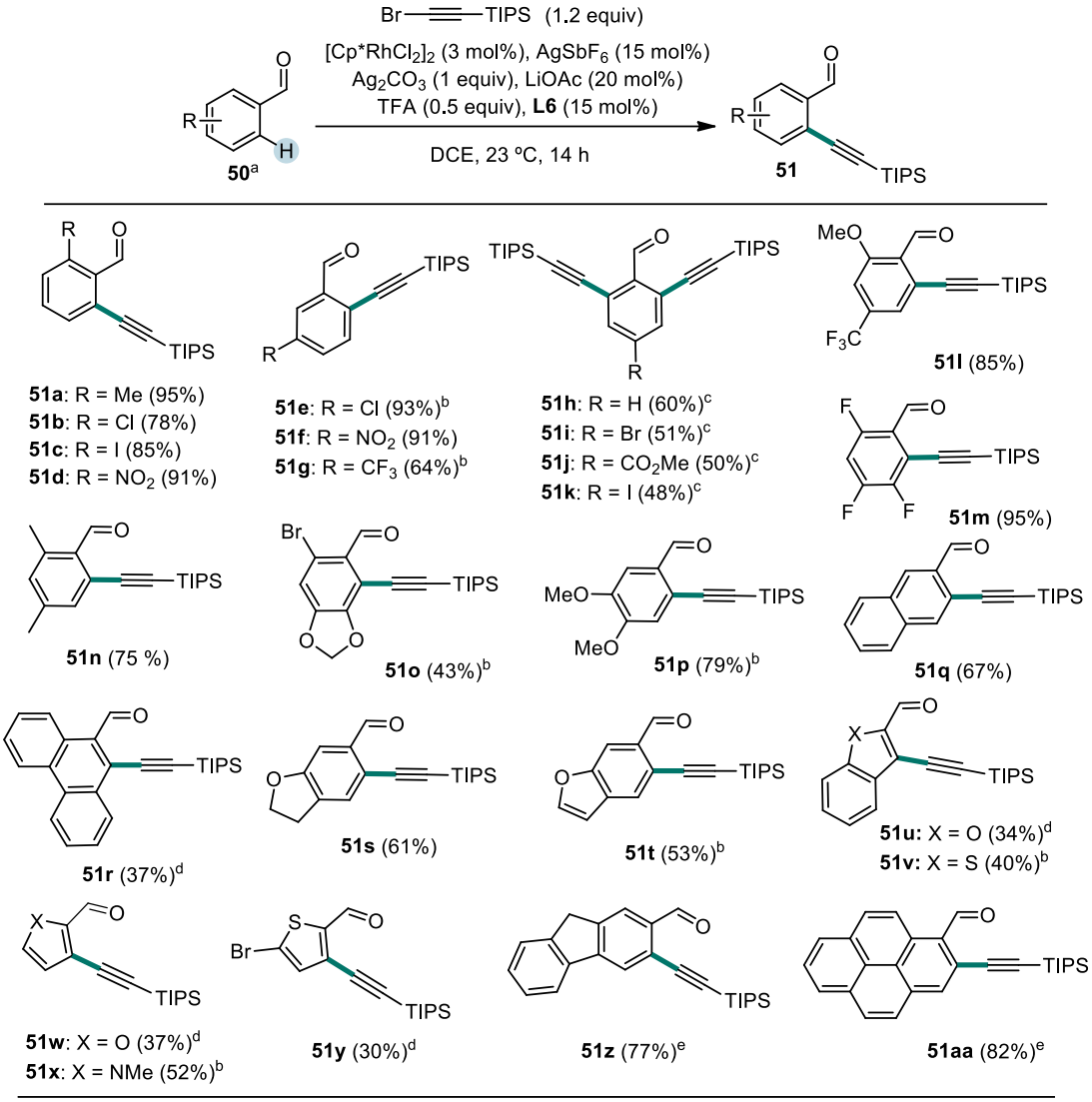


Table 1. Control experiments on the *ortho*-alkynylation of 2-methylbenzaldehyde (**51a**)

Entry	Variation from the standard conditions	Yield (%)[a]
1	none	(95)
2	With 0.1 equiv TFA	28
3	With 5 equiv TFA	70
4	Without $[Cp^*RhCl_2]_2$	0
5	Without Ag_2CO_3	0
6	Without LiOAc	60
7	Without aniline	0
8	With $MnBr(CO)_5$ or $Cp^*Co(CO)I_2$ or $Pd(OAc)_2$ or $RuCl_2$(*p*-cymene)]$_2$ instead of $[Cp^*RhCl_2]$	0
9	With K_2CO_3 instead of Ag_2CO_3	0
10	With AgOAc, without LiOAc, Ag_2CO_3 and TFA	(88)
11	With $[Cp^*IrCl_2]_2$ instead of $[Cp^*RhCl_2]_2$	93
12	With 0.5 equiv H_2O	95

[a]Yield determined by UPLC–MS using biphenyl as internal standard.
Yield of the isolated product showed in parenthesis.

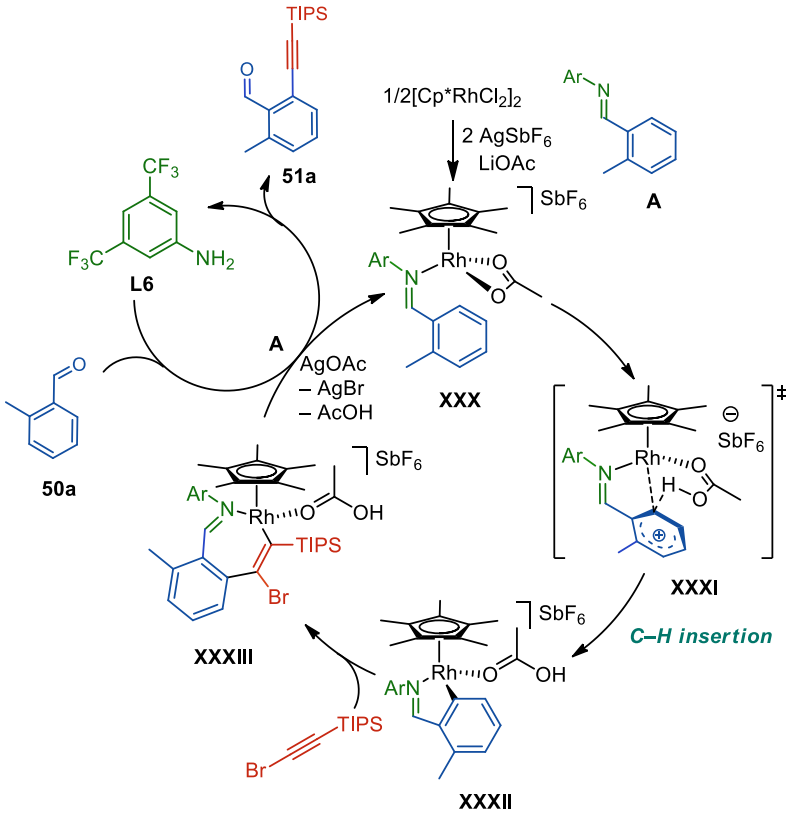
After finding the optimum reaction conditions, the scope of the reaction was explored (Scheme 22). Different substituents, such as halides, nitro, alkyl, ester, acetal and ether were tolerated. Thus, *ortho*, *meta*-, and *para*-substituted benzaldehydes could be alkynylated in 50–95% yield. In case of *meta*-substituted substrates **51e–g**, the alkynylation occurred selectively as the least hindered position. For *para*-substituted benzaldehydes, the dialkynylated products **51h–k** were obtained selectively using 2 equiv of bromoalkyne. These results showcase not only the efficiency of the catalytic system, but also demonstrate the easy access to different *o*,*o*-dialkynylated benzaldehydes, which are important motifs in supramolecular and material sciences. The alkynylation of polysubstituted aromatic aldehydes with electron-rich or electron-withdrawing groups was achieved in good to excellent yield. Even electron-rich heterocycles were alkynylated in spite of the required high temperatures (70–120°C), yielding the desired ynals **51t–y** in moderate yield. Furthermore, polycyclic aromatic compounds reacted smoothly to yield the desired compounds **51z** and **51aa** in good yield.



[a]Reaction run on 0.2 mmol scale; yields of the isolated products are shown in parenthesis. [b]at 70°C.
[c]with 2 equiv of bromo-alkyne. [d]at 120 °C. [e]With AgOAc (1.2 equiv), instead of: Ag_2CO_3, LiOAc and TFA.

Scheme 22. Scope of the Rh-catalyzed *ortho*-alkynylation of aromatic aldehyde

The proposed mechanism of the *ortho*-alkynylation of benzaldehydes (Scheme 23) commences with the formation of active catalyst **XXX** by silver mediated chloride abstraction of $[Cp^*RhCl_2]_2$, followed by coordination of imine **A** and acetate. C–H activation of complex **XXX** through transition state **XXXI** leads to the cyclometalated rhodium complex **XXXII**, which undergoes insertion into TIPS-bromoalkyne to form seven-membered rhodacycle **XXXIII**. Finally, silver-mediated elimination of the bromide and hydrolysis of the imine affords alkyne **51a**. The rhodium catalytic cycle is then closed by coordination of imine **A**, formed by the condensation of aniline **L6** and the aldehyde.



Scheme 23. Proposed mechanism of the Rh-catalyzed *ortho*-alkynylation of aromatic aldehydes

Alkynylbenzaldehydes are versatile building blocks that can be transformed into a variety of products. Among their possible applications, we decided to explore the formation of pentalenes, as well as heterocyclic compounds such as indoles and isoquinolines.

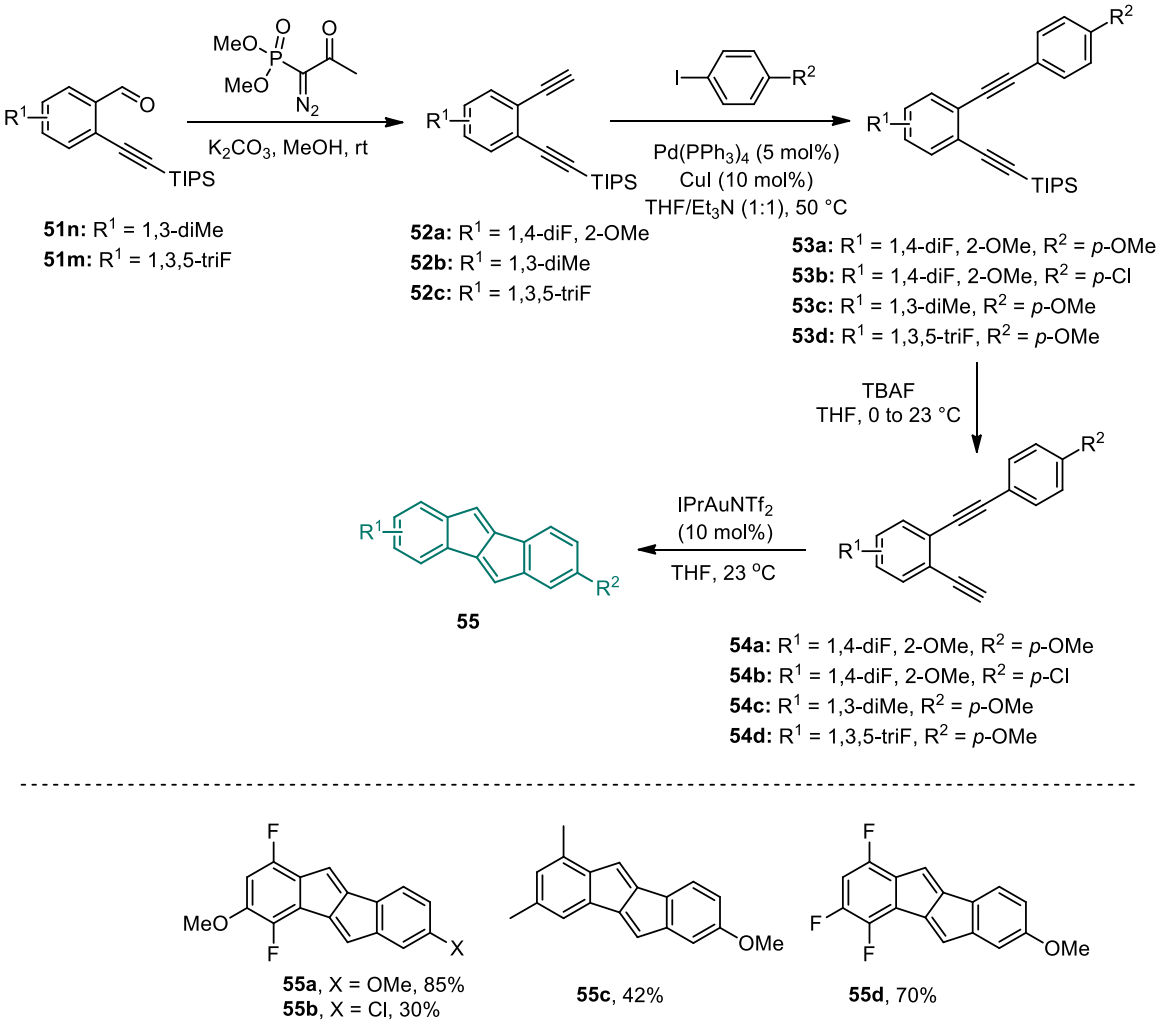
Synthesis of Dibenzo[*a*,*e*]pentalenes

The synthesis of dibenzo[*a*,*e*]pentalenes was investigated first. These compounds are acene-like molecules containing intercalated five-membered rings, which have attracted attention because of their potential as organic semiconductors.[39] Their properties can be fine-tuned by introducing different substituents.[40] Thus, we first targeted the synthesis of compounds containing fluoride moieties, which offer increased solubility and improved electronic properties of the final compounds. Consequently, dibenzo[*a*,*e*]pentalenes **55a–d** were obtained using a three-step procedure, starting from alkynylated products **51**, which were easily converted into diynes **54** after Seyferth-Gilbert homologation, Sonogashira coupling of **52** and TIPS deprotection of **53** (Scheme 24). Compound **52a** was formed as a side-product during the Seyferth-Gilbert homologation, which was carried out in methanol, and was

39 (a) Kawase, T.; Fujiwara, T.; Kitamura, C.; Konishi, A.; Hirao, Y.; Matsumoto, K.; Kurata, H.; Kubo, T.; Shinamura, S.; Mori, H.; Miyazaki, E.; Takimiya, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 7728−7732. (c) Oshima, H.; Fukazawa, A.; Shinamura, S.; Mori, H.; Miyazaki, E.; Takimiya, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 7728−7732. Yamaguchi, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 1−7.

40 (a) Liu, C.; Xu, S.; Zhu, W.; Zhu, X.; Hu, W.; Li, Z.; Wang, Z. *Chem. Eur. J.* **2015**, *21*, 17016−17022. (b) Dai, G.; Chang, J.; Zhang, W.; Bai, S.; Huang, K.−W.; Xu, J.; Chi, C. *Chem. Commun.* **2015**, *51*, 503−506.

employed in the synthesis of pentalenes **55**, as the new substitution could confer them interesting electronic properties. Subsequent gold(I)-catalyzed cyclization[41] of **54** afforded the targeted compounds **55a–d** in moderate to good yields. The structure of **55d** was confirmed by X-ray diffraction.



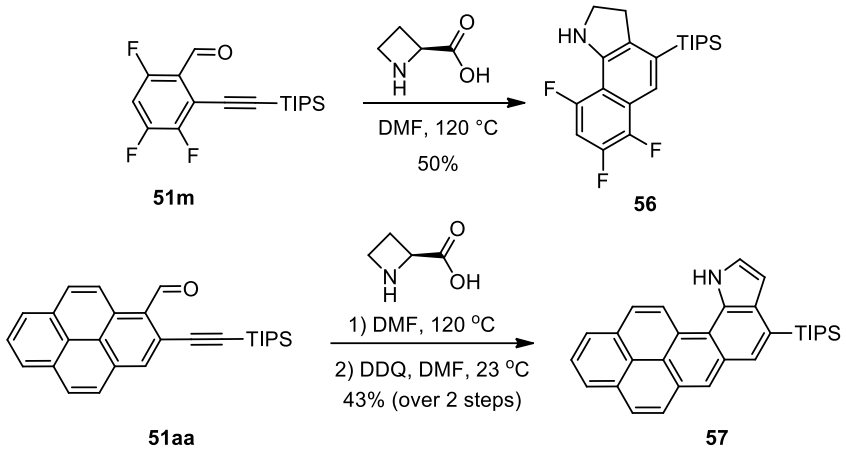
Scheme 24. Synthesis of dibenzo[*a*,*e*]pentalenes **55a–d**

Syntheses of Indoline 56 and Indole 57

The ynals **51** were next applied for the synthesis of *N*-heterocycles, starting with indoles. Following Kundu's strategy,[32] ynal **51m** was converted into indoline **56**, whereas **57** was obtained from **51aa** in two steps, after oxidation of the resulting mixture of indole and indoline with DDQ

41 For selected references, see: (a) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555−562. (b) Wurm, T.; Bucher, J.; Duckworth, S. B.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 1−6. (c) Wurm, T.; Rüdiger, T. C.; Schulmeister, J.; Koser, S.; Rudolph, M.; Rominger, F.; Bunz, U. H. F.; Hashmi, A. S. K. *Chem. Eur. J.* **2018**, *24*, 2735−2740. (d) Sekine, K.; Schulmeister, J.; Paulus, F.; Goetz, K. P.; Rominger, F.; Rudolph, M.; Zaumseil, J.; Hashmi, A. S. K. *Chem. Eur. J.* **2019**, *25*, 216−220. (e) Tavakkolifard, S.; Sekine, K.; Reichert, L.; Ebrahimi, M.; Museridz, K.; Michel, E.; Rominger, F.; Babaahmadi, R.; Ariafard, A.; Yates, B. F.; Rudolph, M.; Hashmi, A. S. K. *Chem. Eur. J.* **2019**, *25*, 12180−12186.

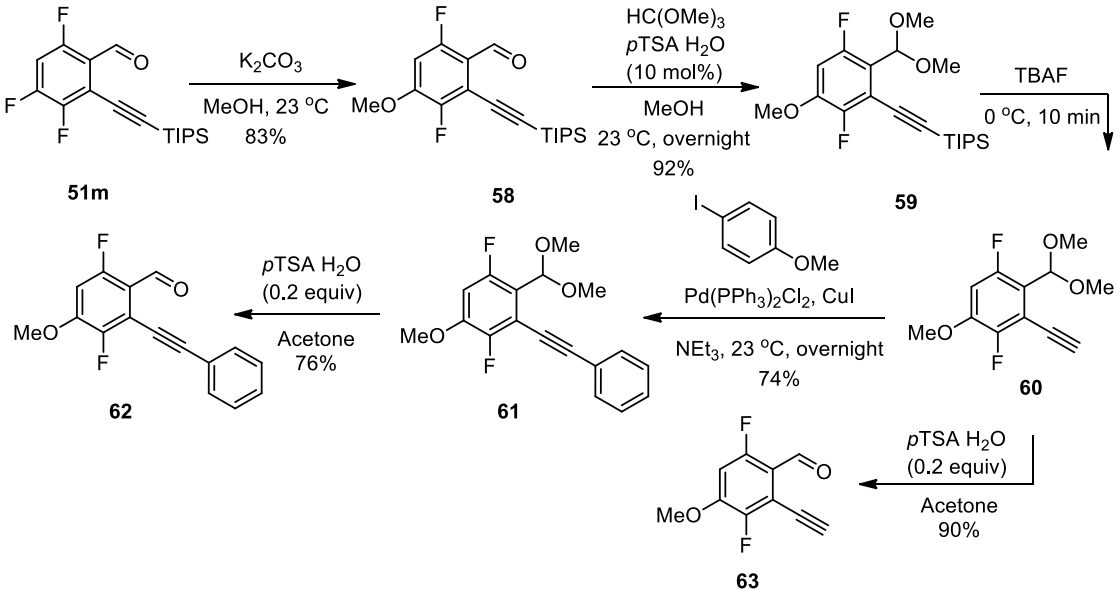
(Scheme 25). The reaction was also tested with aldehydes **51q** and **51z**, but resulted in a complex mixture of indoles and indolines, even after DDQ oxidation. Furthermore, the replacement of the carboxylic acid with *L*-proline was also investigated following the same reported methodology, with a view to acquire tetrahydrobenzoquinoline analogues from substrates **51q** and **51z**, but no reaction occurred, the starting materials being recovered.



Scheme 25. Synthesis of indoline **56** and indole **57**

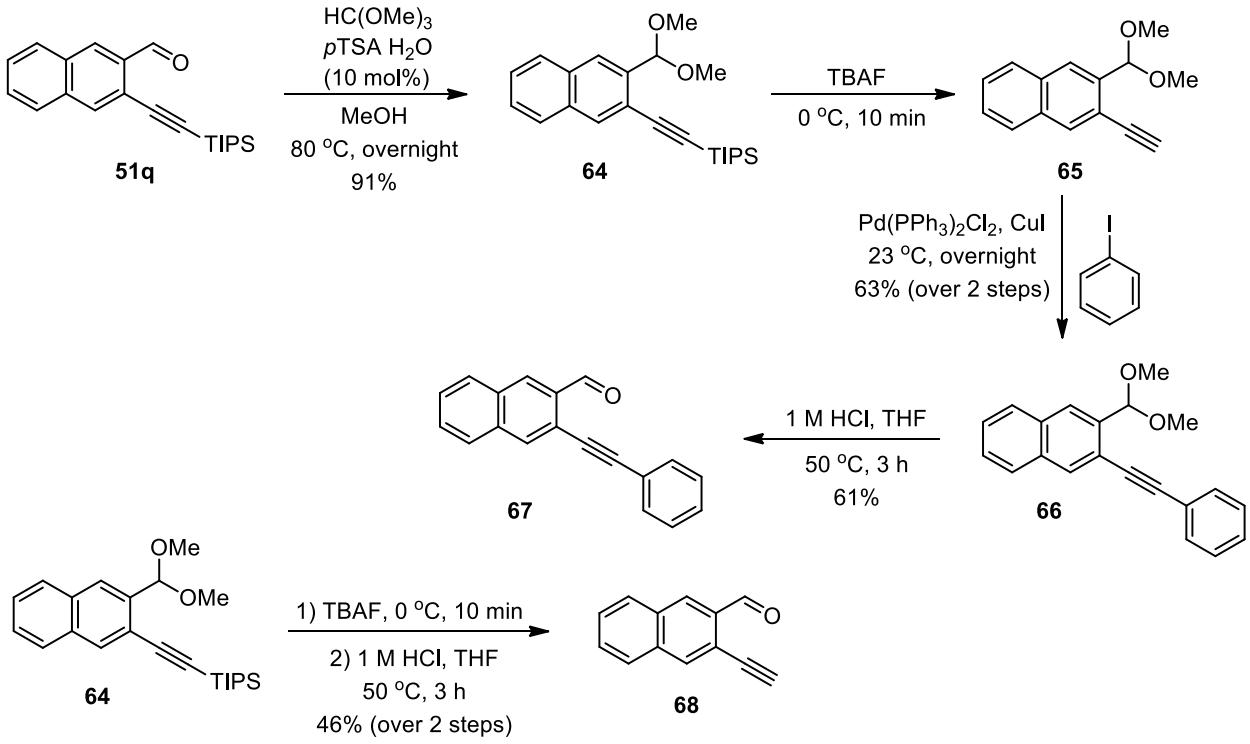
Syntheses of Isoquinolines

For the synthesis of isoquinolines, we envisioned that Anand's methodology[34] could also be applied to other substituted, as well as extended polycyclic isoquinolines, which would be obtained from our alkynylated aromatic aldehydes. In contrast to the synthesis of indoles presented above, the silver-catalyzed formation of isoquinolines was not compatible with the substrates incorporating the TIPS moiety, requiring either its deprotection to give the free alkyne or its replacement with an aryl group.



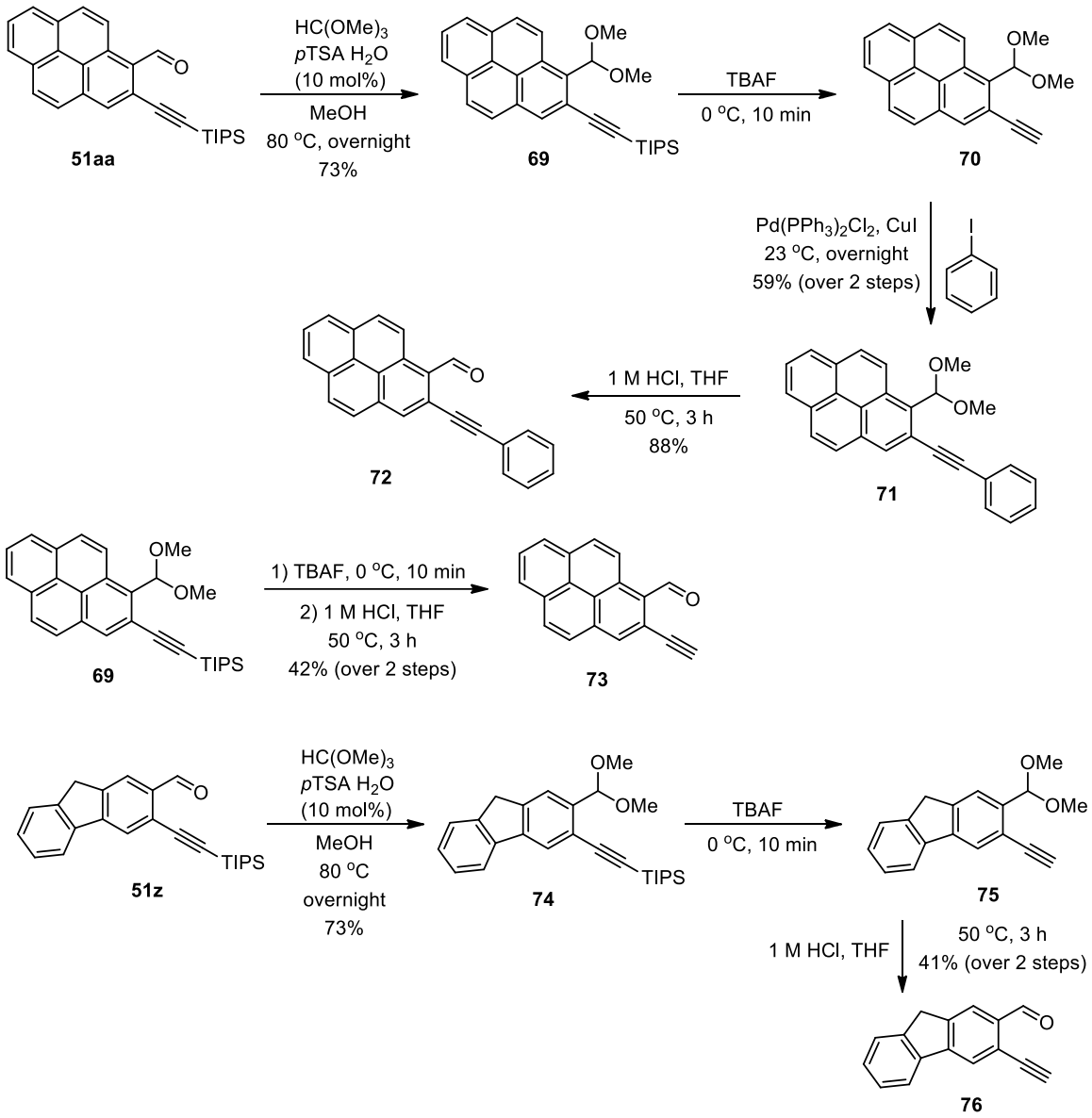
Scheme 26. Synthesis of the isoquinoline precursors **62** and **63**

Compound **51m** was converted into **58**, by replacing its *para*-fluoride unit with a methoxy group (Scheme 26). Aldehyde **58** was converted into the corresponding acetal **59** followed by cleavage of the TIPS group. Sonogashira coupling of **60** with 4-iodoanisole and subsequent deprotection of the acetal group gave rise to aldehyde **62**. Alternatively, acetal hydrolysis of **60** provided aldehyde substrate **63**.



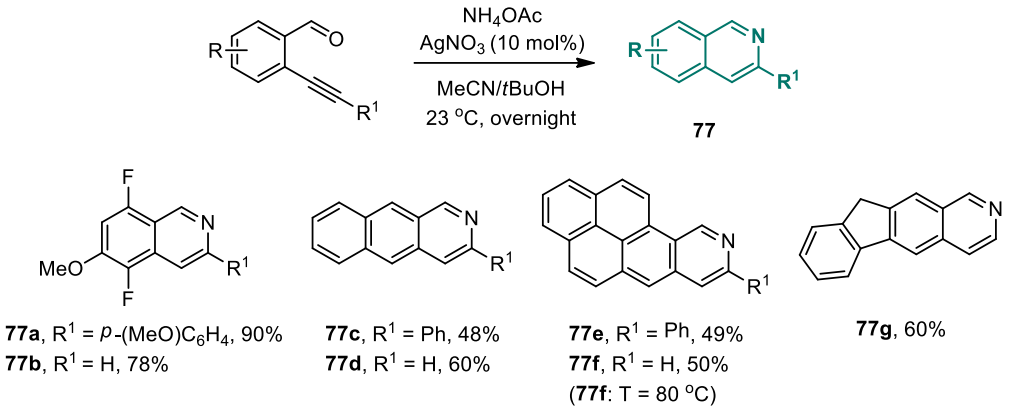
Scheme 27. Synthesis of the isoquinoline precursors **67** and **68**

Performing similar transformations, the alkynylated aldehydes **51q**, **51z** and **51aa** were converted into suitable substrates for the preparation of isoquinolines (Schemes 27 and 28). However, both the acetal protection of their aldehyde moieties and its cleavage demanded harsher conditions. Thus, the acetal protection proceeded successfully at 80 °C, after stirring overnight, while the deprotection was carried out in 1 M HCl. Thus, analogous synthetic sequences provided aldehydes **67** and **72**, after Sonogashira coupling with iodobenzene, as well as aldehydes **68**, **73** and **76**, with a free alkyne group. In case of the alkynylated fluorene aldehyde **51z**, after TIPS deprotection, compound **75** was directly subjected to acetal deprotection to furnish aldehyde **76** (Scheme 27).



Scheme 28. Synthesis of the isoquinoline precursors **71**, **73** and **76**

With the appropriate substrates in hand, the silver-catalyzed benzannulation was performed to afford the desired ioquinolines **77a–f** in good to moderate yields (Scheme 29). All the reactions proceeded at 23 °C, with the exception of the one yielding compound **77f**, which required heating at 80 °C because of the decreased solubility of pyrene derivative **73**.



Scheme 29. Synthesis of isoquinoline derivatives **77f**

CONCLUSIONS

We have designed an efficient Rh(III)-catalyzed *ortho*-alkynylation of aromatic aldehydes, enabled by the formation of an imine as transient directing group by reaction with substoichiometric amounts of an aniline.[42] This method offers an orthogonal approach to traditional cross-coupling reactions, permitting the alkynylation of a broad scope of benzaldehyde derivatives. The resulting products were employed as versatile starting materials in the synthesis of a variety of polyaromatic compounds, such as dibenzopentalenes, isoquinolines, indoles and indolines. Considering the mild conditions used and the broad compatibility with many functional groups, this approach could be of interest for late-stage functionalization and could also allow the preparation of many useful building blocks.

42 Tan, E.; Nannini, L.; Stoica, O.; Echavarren, A. M. *Org. Lett.* **2021**, *23*, 1263–1268.

EXPERIMENTAL SECTION

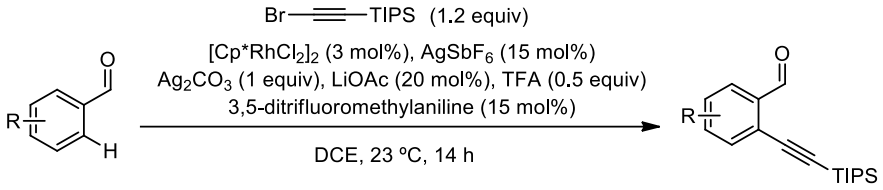
General Methods

Most of the general information has been provided in the experimental section of *Chapter I*.

In addition to that, crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoKa radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = –173 ºC). Full-sphere data collection was used with w and j scans. Programs used: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solutions were achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

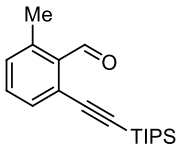
Synthetic Procedures and Analytical Data

General procedure A for the alkynylation of benzaldehydes:



$[Cp^*RhCl_2]_2$ (3.7 mg, 6.0 μmol, 3 mol%), Ag_2CO_3 (55 mg, 0.2 mmol, 1 equiv), LiOAc (2.6 mg, 40 μmol, 0.2 equiv), $AgSbF_6$ (14 mg, 40 μmol, 0.2 equiv) were weighed in a vial inside a glovebox and dichloroethane (1 ml, 0.2M) was added. The corresponding aldehyde (0.2 mmol), 1-bromo-2-(triisopropylsilyl)acetylene (**S1**)[43] (57 mg, 0.22 mmol, 1.1 equiv), 3,5-bis(trifluoromethyl)aniline (3.6 mg, 30 μmol,0.15 equiv) and TFA (8.0 μl, 0.1 mmol, 0.5 equiv) were then added and the vial was sealed. The reaction mixture was stirred at the appointed temperature for 16 h. After cooling to 22 ºC, the reaction mixture was filtered through celite and purified by column chromatography (cyclohexane to cyclohexane/EtOAc 1:1) to yield the corresponding product.

43 Campbell, C. D.; Greenaway, R. L.; Holton, O. T.; Ross Walker, P.; Chapman, H. A.; Adam Russell, C.; Carr, G.; Thomson, A. L.; Anderson, E. A. *Chem. Eur. J.* **2015**, *21*, 12627–12639.



2-Methyl-6-((triisopropylsilyl)ethynyl)benzaldehyde (51a)

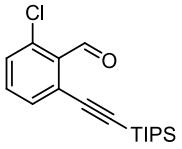
The title compound was obtained as a yellow solid (59 mg, 0.19 mmol, 95% yield) following the general procedure (A) at 22 ºC.

Melting point = 44–46 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.46 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 2.60 (s, 3H), 1.13 (d, *J* = 2.4 Hz, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 140.6, 134.4, 132.5, 132.2, 132.1, 129.0, 103.1, 99.4, 21.5, 18.8, 11.4.

HRMS (ESI+) calculated *m/z* for $[M+Na]^+$ $C_{19}H_{28}NaOSi$ is 323.1802, found: 323.1800.



2-Chloro-6-((triisopropylsilyl)ethynyl)benzaldehyde (51b)

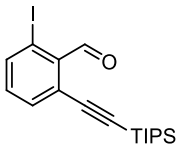
The title compound was obtained as a white solid (50 mg, 0.16 mmol, 78% yield) following the general procedure (A) at 22 ºC.

Melting point = 39–41 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.64 (s, 1H), 7.51 (m, 1H), 7.40 (m, 2H), 1.13 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 135.3, 133.5, 133.3, 133.1, 131.3, 128.1, 102.1, 100.9, 18.8, 11.4.

HRMS (ESI+) calculated *m/z* for $[M+Na]^+$ $C_{18}H_{25}ClNaOSi$ is 343.1255, found: 343.1259.



2-Iodo-6-((triisopropylsilyl)ethynyl)benzaldehyde (51c)

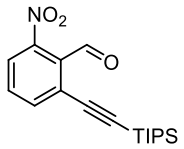
The title compound was obtained as a yellow solid (70 mg, 0.17 mmol, 85% yield) following general procedure (A) at 22 ºC.

Melting point = 56–58 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.99 – 7.93 (m, 1H), 7.59 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 1.13 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 141.9, 136.1, 134.6, 133.2, 128.7, 101.8, 101.4, 94.4, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{18}H_{25}NaIOSi$ is 435.0612, found: 435.0609.



2-Nitro-6-((triisopropylsilyl)ethynyl)benzaldehyde (51d)

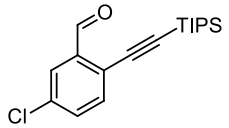
The title compound was obtained as an orange solid (60 mg, 0.18 mmol, 91% yield) following the general procedure (A) at 22 ºC.

Melting point = 44–46 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.86 – 7.78 (m, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 1.14 (s, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.3, 148.1, 137.7, 132.7, 132.1, 125.6, 123.4, 101.6, 100.4, 18.6, 11.2.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{18}H_{25}NaO_3Si$ is 354.1496, found: 354.1490.



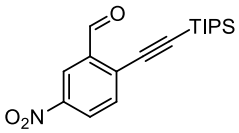
5-Chloro-2-((triisopropylsilyl)ethynyl)benzaldehyde (51e)

The title compound was obtained as a yellow liquid (58 mg, 0.18 mmol, 93% yield) following the general procedure (A) at 70 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 7.86 (d, *J* = 2.1 Hz, 1H), 7.56 – 7.44 (m, 2H), 1.16 – 1.10 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 137.4, 135.4, 135.2, 133.8, 127.0, 125.4, 101.0, 100.6, 18.8, 11.3.

HRMS (ESI+) *m/z* calculated for $[M+Na+CH_3OH]^+$ $C_{19}H_{29}ClNaO_2Si$ is 375.1518, found: 375.1516.



5-Nitro-2-((triisopropylsilyl)ethynyl)benzaldehyde (51f)

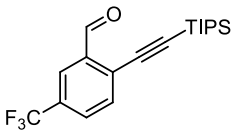
The title compound was obtained as a red solid (55 mg, 0.18 mmol, 91% yield) following the general procedure (A) at 22 ºC.

Melting point = 60–62 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.71 (d, *J* = 2.4 Hz, 1H), 8.38 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 1.19 – 1.10 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 147.5, 137.1, 135.2, 132.5, 127.7, 122.3, 106.2, 100.3, 18.7, 11.3.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{18}H_{25}NaNO_3Si$ is 354.1496, found: 354.1491.



5-(Trifluoromethyl)-2-((triisopropylsilyl)ethynyl)benzaldehyde (51g)

The title compound was obtained as a yellow solid (45 mg, 0.13 mmol, 64% yield) following the general procedure (A) at 70 °C.

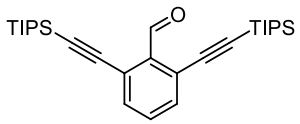
Melting point = 45–47 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.21 – 8.14 (m, 1H), 7.77 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 1.19 – 1.12 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 136.6, 134.6, 130.9 (C–F, q, $^{2}J_{CF}$= 33.7 Hz), 130.3, 130.0 (C–F, q, $^{3}J_{CF}$= 3.6 Hz), 124.2 (C–F, q, $^{3}J_{CF}$= 3.9 Hz), 123.4 (C–F, q, $^{1}J_{CF}$= 270.2 Hz), 102.9, 100.8, 18.8, 11.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –63.31.

HRMS (ESI+) *m/z* calculated for $[M+Na+CH_3OH]^+$ $C_{20}H_{29}F_3NaO_2Si$ is 409.1781, found: 409.1775.



2,6-Bis((triisopropylsilyl)ethynyl)benzaldehyde (51h)

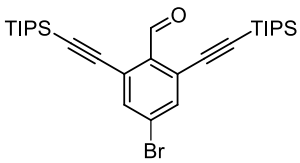
The title compound was obtained as a white solid (54 mg, 0.12 mmol, 60% yield) following the general procedure (A) at 22 ºC using 2 equiv of **S1**.

Melting point = 49–51 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.72 (d, *J* = 1.3 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.42 (m, 1H), 1.15 (d, *J* = 1.5 Hz, 42H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 137.2, 134.5, 132.2, 125.4, 103.2, 99.3, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated $[M+Na]^+$ for $C_{29}H_{46}NaOSi_2$ is 489.2979, found: 489.2982.



4-Bromo-2,6-bis((triisopropylsilyl)ethynyl)benzaldehyde (51i)

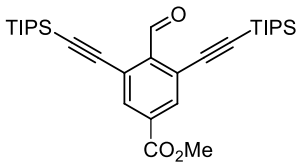
The title compound was obtained as a brown solid (55 mg, 0.10 mmol, 51% yield) following the general procedure (A) at 22 ºC using 2 equiv of **S1**.

Melting point = 80–82 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.64 (s, 1H), 7.66 (s, 2H), 1.14 (m, 42H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 136.9, 135.9, 126.8, 126.8, 101.7, 101.1, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{29}H_{46}NaOSi_2$ is 489.2979, found: 489.2982.



Methyl 4-formyl-3,5-bis((triisopropylsilyl)ethynyl)benzoate (51j)

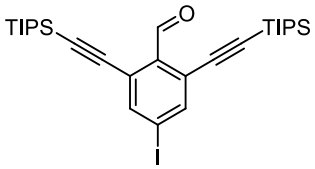
The title compound was obtained as a red solid (52 mg, 0.10 mmol, 50% yield) following the general procedure (A) at 22 ºC using 2 equiv of **S1**.

Melting point = 61–63 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.12 (s, 2H), 3.96 (m, 3H), 1.14 (m, 42H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 165.2, 139.8, 134.9, 133.4, 125.6, 102.3, 100.6, 52.9, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{31}H_{48}NaO_3Si_2$ is 547.3034, found: 547.3050.



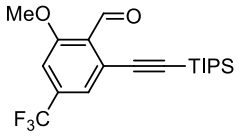
4-Iodo-2,6-bis((triisopropylsilyl)ethynyl)benzaldehyde (51k)

The title compound was obtained as a yellow oil (57 mg, 0.10 mmol, 48% yield) following the general procedure (A) at 22 ºC using 2 equiv of **S1**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.87 (s, 2H), 1.14 (m, 42H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5, 142.8, 136.5, 126.5, 101.6, 101.0, 99.1, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{29}H_{45}INaOSi_2$ is 615.1946, found: 615.1936.



2-Methoxy-4-(trifluoromethyl)-6-((triisopropylsilyl)ethynyl)benzaldehyde (51l)

The title compound was obtained as a white solid (65 mg, 0.17 mmol, 85% yield) following the general procedure (A) at 22 ºC.

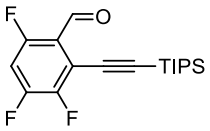
Melting point = 54–56 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.38 (m, 1H), 7.14 – 7.12 (m, 1H), 3.96 (s, 3H), 1.13 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 160.6, 135.6 (C–F, q, $^{2}J_{CF}$= 33.0 Hz), 127.9, 127.7, 123.0 (C–F, q, $^{3}J_{CF}$= 3.9 Hz), 123.1 (C–F, q, $^{1}J_{CF}$= 275.6 Hz), 108.5 (C–F, q, $^{3}J_{CF}$= 3.6 Hz), 102.1, 101.2, 56.5, 18.7, 11.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –63.80.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{20}H_{27}F_3NaO_2Si$ is407.1625, found: 407.1624.



3,4,6-Trifluoro-2-((triisopropylsilyl)ethynyl)benzaldehyde (51m)

The title compound was obtained as a red solid (65 mg, 0.19 mmol, 95% yield) following the general procedure (A) at 22 ºC.

The title compound was synthesized on 9 mmol scale procedure:

In a 100 ml round-bottom flask AgOAc (1.88 g, 11.2 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (174 mg, 0.281 mmol, 3 mol%) and $AgSbF_6$ (483 mg, 1.41 mmol, 15 mol%) were suspended in DCE (40 ml). Then 2,4,5-trifluorobenzaldehyde (1.07 ml, 9.37 mmol, 1 equiv), 1-bromo-2-(triisopropylsilyl)acetylene (**S1**) (2.69 g, 10.3, 1.1 equiv) and 3,5-bis(trifluoromethyl)aniline (322 mg, 1.41 mmol,15 mol%) were added to the mixture. The reaction was followed by TLC and stirred for 16 h at 22 ºC. Upon completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatogaphy (cyclohexane/EtOAc gradient 20:1 to 5:1) yielding the title compound as a red solid (2.92 g, 8.58 mmol, 92% yield)

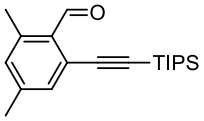
Melting point = 41–43 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (d, *J* = 1.1 Hz, 1H), 6.98 (td, *J* = 9.8, 6.1 Hz, 1H), 1.20 – 1.08 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.3 (C–F,d, $^3J_{CF}$= 2.5 Hz), 158.2 (C–F, ddd, $^1J_{CF}$,$^3J_{CF}$,$^4J_{CF}$= 263.1, 11.7, 3.3 Hz), 153.7 (C–F, ddd (a-dt), $^1J_{CF}$,$^2J_{CF}$ =$^3J_{CF}$= 260.6, 14.1Hz), 149.0 (C–F, ddd, $^1J_{CF}$,$^2J_{CF}$,$^4J_{CF}$= 252.8, 13.4, 4.1 Hz), 121.2 (C–F, dd,J_{CF}= 8.7, 3.9 Hz), 117.6 – 116.9 (C–F,m, 1C), 109.5 (C–F,d, J_{CF} = 5.1 Hz), 106.8 (C–F, dd, $^2J_{CF}$,$^2J_{CF}$ = 27.1, 21.2 Hz), 93.3 (C–F, dd, J_{CF} = 4.0 Hz), 18.6, 11.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.5 (dt, *J* = 14.8, 9.7 Hz), –123.3 (dt, *J* = 21.3, 9.5 Hz), –136.8 (ddd, *J* = 21.2, 14.8, 6.2 Hz).

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{18}H_{23}F_3NaOSi$ is 363.1362, found: 363.1364.



2,4-Dimethyl-6-((triisopropylsilyl)ethynyl)benzaldehyde (51n)

The title compound was obtained as a white solid (47 mg, 0.15 mmol, 75% yield) following the general procedure (A) at 22 ºC.

The title compound was synthesized on 5 mmol scale procedure:

In a 100 ml round-bottom flask AgOAc (1.08 g, 6.44 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (99.0 mg, 0.281 mmol, 3 mol%) and $AgSbF_6$ (277 mg, 0.81 mmol, 15 mol%) were suspended in DCE (15 ml). Then

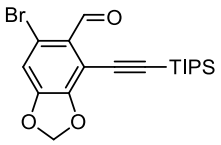
2,4-dimethylbenzaldehyde (1.07 ml, 9.37 mmol, 1 equiv), 1-bromo-2-(triisopropylsilyl)acetylene (**S1**) (1.54 g, 5.90mmol, 1.1 equiv) and 3,5-bis(trifluoromethyl)aniline (184 mg, 0.81 mmol, 15 mol%) were added to the mixture. The reaction was followed by TLC and stirred for 16 h at 22 ºC. Upon completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatogaphy (cyclohexane/EtOAc gradient 20:1 to 5:1) yielding the title compound as a red solid (1.30 g, 5.37 mmol, 77% yield).

Melting point = 70–72°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 7.27 (m, 1H), 7.02 – 6.99 (m, 1H), 2.58 (s, 3H), 2.34 (s, 3H), 1.13 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 143.5, 140.8, 133.3, 132.6, 132.6, 129.3, 103.3, 98.8, 21.6, 21.5, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{20}H_{30}NaOSi$ is 337.1958, found: 337.1956.



6-Bromo-4-((triisopropylsilyl)ethynyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (51o)

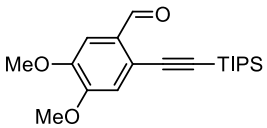
The title compound was obtained as a yellow solid (35 mg, 0.09 mmol, 43% yield) following the general procedure (A) at 70 °C.

Melting point = 101–103 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.04 (s, 1H), 6.15 (s, 2H), 1.14 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 151.5, 151.2, 127.8, 118.7, 114.0, 108.2, 105.1, 103.3, 95.9, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{19}H_{25}NaBrO_3Si$ is 431.0649, found: 431.0642.



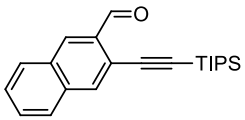
4,5-Dimethoxy-2-((triisopropylsilyl)ethynyl)benzaldehyde (51p) The title compound was obtained as a white solid (55 mg, 0.16 mmol, 79% yield) following the general procedure (A) at 70 °C.

Melting point = 91–93 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.37 (s, 1H), 6.95 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 1.12 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 153.7, 149.9, 130.8, 121.9, 114.8, 108.1, 102.0, 97.5, 56.4, 56.2, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{20}H_{30}NaO_3Si$ is 369.1856, found: 369.1868.



3-((Triisopropylsilyl)ethynyl)-2-naphthaldehyde (51q)

The title compound was obtained as a white solid (45 mg, 0.14 mmol, 67% yield) following the general procedure (A) at 22 ºC.

The title compound was also synthesized on 6.4 mmol scale procedure:

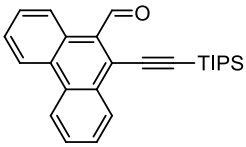
In a 100 ml round-bottom flask AgOAc (1.28 g, 7.68 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (119 mg, 0.192 mmol, 3 mol%) and $AgSbF_6$ (330 mg, 0.960 mmol, 15 mol%) were suspended in DCE (26 ml). Then 2-naphthaldehyde (1.00 g, 6.40 mmol, 1 equiv), 1-bromo-2-(triisopropylsilyl)acetylene (**S1**) (1.84 g, 10.3 mmol, 1.1 equiv) and 3,5-bis(trifluoromethyl)aniline (220 mg, 0.96 mmol,15 mol%) were added to the mixture. The reaction was followed by TLC and stirred for 16 h at 22 ºC. Upon completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatogaphy (cyclohexane/EtOAc 95:5) yielding the title compound as a white solid (1.52 g, 4.53 mmol, 71% yield).

Melting point = 64–66 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.44 (s, 1H), 8.08 (s, 1H), 7.94 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.58 (m, 2H), 1.18 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 135.5, 134.2, 132.5, 132.1, 130.2, 129.5, 129.1, 127.9, 127.7, 121.6, 102.7, 98.1, 18.8, 11.5.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{22}H_{28}NaOSi$ is 359.1802, found: 359.1800.



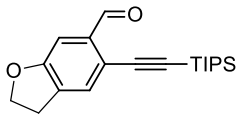
10-((Triisopropylsilyl)ethynyl)phenanthrene-9-carbaldehyde (51r). The title compound was obtained as a yellow solid (28 mg, 0.08 mmol, 37% yield) following the general procedure (A) at 120 °C.

Melting point = 86–88 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.29 (d, *J* = 1.1 Hz, 1H), 9.35 (ddd, *J* = 6.0, 3.1, 1.6 Hz, 1H), 8.77 – 8.72 (m, 1H), 8.68 (t, *J* = 6.4 Hz, 2H), 7.83 (tt, *J* = 8.3, 1.4 Hz, 1H), 7.77 – 7.68 (m, 3H), 1.27 – 1.20 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 132.5, 132.4, 131.2, 130.5, 130.3, 130.1, 128.6, 128.3, 128.2, 127.9, 127.9, 127.7, 126.6, 123.0, 122.6, 108.4, 100.6, 29.9, 18.9, 11.6.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{26}H_{30}NaOSi$ is 409.1958, found: 409.1940.



5-((Triisopropylsilyl)ethynyl)-2,3-dihydrobenzofuran-6-carbaldehyde (51s)

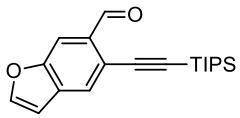
The title compound was obtained as a yellow solid (40 mg, 0.12 mmol, 61% yield) following the general procedure (A) at 22 ºC.

Melting point = 39–41 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.45 (d, *J* = 0.8 Hz, 1H), 7.79 (d, *J* = 1.2 Hz, 1H), 6.93 (s, 1H), 4.73 – 4.62 (m, 2H), 3.25 (td, *J* = 8.8, 1.3 Hz, 2H), 1.14 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 164.9, 130.8, 129.3, 129.1, 123.9, 113.8, 102.4, 98.4, 72.7, 28.9, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{20}H_{28}NaO_2Si$ is 351.1751, found: 351.1759.



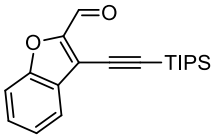
5-((Triisopropylsilyl)ethynyl)benzofuran-6-carbaldehyde (51t)

The title compound was obtained as a yellow liquid (35 mg, 0.10 mmol, in 53% yield) following the general procedure (A) at 70 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.20 (d, *J* = 0.5 Hz, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.70 (t, *J* = 0.8 Hz, 1H), 6.86 (dd, *J* = 2.2, 1.0 Hz, 1H), 1.15 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 157.4, 148.0, 132.2, 128.5, 123.4, 121.2, 116.7, 107.8, 102.6, 98.4, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{20}H_{26}NaO_2Si$ is 349.1594, found: 349.1599.



3-((Triisopropylsilyl)ethynyl)benzofuran-2-carbaldehyde (51u)

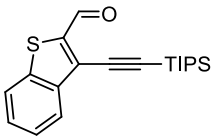
The title compound was obtained as a yellow solid (22 mg, 0.07 mmol, 34% yield) following the general procedure (A) at 120 °C.

Melting point = 84–86 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.79 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.40 (ddd, *J* = 8.1, 6.4, 1.7 Hz, 1H), 1.19 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 155.5, 153.5, 130.2, 127.9, 124.7, 122.6, 116.5, 113.0, 104.5, 93.9, 18.8, 11.3.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{21}H_{30}NaO_3Si$ is 381.1856, found: 381.1858.



3-((Triisopropylsilyl)ethynyl)benzo[*b*]thiophene-2-carbaldehyde (51v)

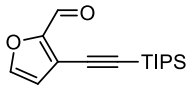
The title compound was obtained as a yellow solid (27 mg, 0.08 mmol, 40% yield) following the general procedure (A) at 70 °C.

Melting point = 97–99 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (d, *J* = 1.0 Hz, 1H), 8.10 – 8.04 (m, 1H), 7.89 – 7.84 (m, 1H), 7.59 – 7.47 (m, 2H), 1.19 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 144.6, 141.2, 139.8, 129.0, 128.2, 125.8, 125.1, 123.4, 102.8, 97.3, 18.9, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{20}H_{26}NaOSSi$ is 365.1366, found: 365.1358.



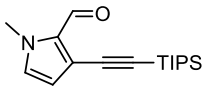
3-((Triisopropylsilyl)ethynyl)furan-2-carbaldehyde (51w)

The title compound was obtained as a brown liquid (20 mg, 0.08 mmol, 37% yield) following the general procedure (A) at 120 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, *J* = 0.9 Hz, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 6.59 (d, *J* = 1.8 Hz, 1H), 1.12 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 153.7, 147.5, 120.2, 115.5, 101.5, 95.0, 18.7, 11.3.

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{16}H_{25}O_2Si$ is 277.1618, found: 277.1605.



1-Methyl-3-((triisopropylsilyl)ethynyl)-1*H*-pyrrole-2-carbaldehyde (51x)

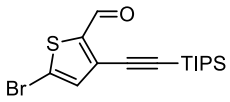
The title compound was obtained as a red solid (30 mg, 0.10 mmol, 52% yield) following the general procedure (A) at 70 °C.

Melting point = 84–86 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 6.29 (d, *J* = 2.7 Hz, 1H), 3.92 (s, 3H), 1.11 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 133.0, 130.8, 119.3, 113.4, 98.8, 95.6, 37.1, 18.8, 11.4.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{17}H_{27}NNaOSi$ is 312.1754, found: 312.1740.



5-Bromo-3-((triisopropylsilyl)ethynyl)thiophene-2-carbaldehyde (51y)

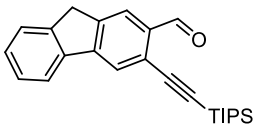
The title compound was obtained as a yellow solid (22 mg, 0.16 mmol, 30% yield) following the general procedure (A) at 120 °C.

Melting point = 60–62 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.17 (s, 1H), 1.12 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 145.8, 134.7, 131.4, 124.0, 100.7, 97.1, 18.8, 11.3.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{16}H_{23}NaBrOSSi$ is 393.0341, found: 393.0320.



3-((Triisopropylsilyl)ethynyl)-9*H*-fluorene-2-carbaldehyde (51z)

The title compound was obtained as a white solid (58 mg, 0.16 mmol, 77% yield) following the general procedure (A) at 22 °C.

The title compound was also synthesized on 4.6 mmol scale procedure:

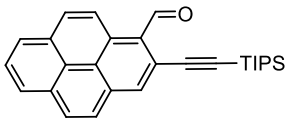
In a 100 ml round-bottom flask AgOAc (928 mg, 5.56 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (86 mg, 0.139 mmol, 3 mol%) and $AgSbF_6$ (239 mg, 0.695 mmol, 15 mol%) were suspended in DCE (19 ml). Then 9*H*-fluorene-2-carbaldehyde (900 mg, 4.63 mmol, 1 equiv), 1-bromo-2-(triisopropylsilyl)acetylene (**S1**) (1.33 g, 5.10 mmol, 1.1 equiv) and 3,5-bis(trifluoromethyl)aniline (159 mg, 0.695 mmol, 15 mol%) were added to the mixture. The reaction was followed by TLC and stirred for 16 h at 22 °C. Upon completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatogaphy (cyclohexane/EtOAc 95:5) yielding the title compound as a white solid (723 mg, 3.44 mmol, 74% yield).

Melting point = 172–174 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.08 (s, 1H), 7.94 (s, 1H), 7.89 – 7.84 (m, 1H), 7.61 – 7.56 (m, 1H), 7.45 – 7.38 (m, 2H), 3.96 (s, 2H), 1.19 (s, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ191.8, 147.4, 144.8, 143.8, 139.8, 135.0, 128.9, 127.4, 126.6, 125.5, 124.9, 123.4, 121.5, 102.9, 98.4, 37.1, 18.9, 11.5.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{25}H_{30}NaOSi$ is 397.1945, found: 397.1958.



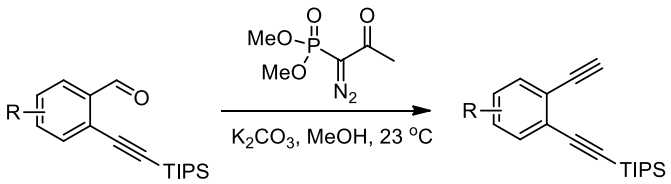
2-((triisopropylsilyl)ethynyl)pyrene-1-carbaldehyde (51aa)

The title compound was obtained as a yellow solid (67 mg, 0.16 mmol, 82% yield) following the general procedure (A) at 22 °C.

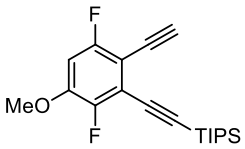
The title compound was also synthesized on 4.3 mmol scale procedure:
In a 100 ml round-bottom flask AgOAc (1.36 g, 5.21 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (81 mg, 0.130 mmol, 3 mol%) and $AgSbF_6$ (224 mg, 0.651 mmol, 15 mol%) were suspended in DCE (17 ml). Then pyrene-1-carbaldehyde (1.00 g, 4.34 mmol, 1 equiv), 1-bromo-2-(triisopropylsilyl)acetylene (**S1**) (1.25 g, 4.78 mmol, 1.1 equiv) and 3,5-bis(trifluoromethyl)aniline (224 mg, 0.651 mmol, 15 mol%) were added to the mixture. The reaction was followed by TLC and stirred for 16 h at 22 ºC. Upon completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatogaphy (cyclohexane/EtOAc 19:1) yielding the title compound as a white solid (1.431 g, 3.48 mmol, 80% yield).

Melting point = 169–171 °C
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.34 (s, 1H), 9.62 (d, *J* = 9.4 Hz, 1H), 8.35 – 8.26 (m, 4H), 8.22 (d, *J* = 9.0 Hz, 1H), 8.09 (t, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 1.22 (d, *J* = 3.3 Hz, 21H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 134.8, 131.5, 131.2, 131.1, 130.6, 130.6, 130.0, 127.4, 127.1, 127.0, 127.0, 126.6, 124.3, 124.3, 123.8, 103.8, 100.2, 18.9, 11.6.
HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{28}H_{30}NaOSi$ is 433.1958, found: 433.1969.

General procedure B for the Seyferth–Gilbert homologation:



2-Alkynylbenzaldehyde (1 equiv) and potassium carbonate (2 equiv) were placed in an oven dried round bottom flask under argon. Anhydrous methanol (0.1 M) was added and the mixture was stirred at 22 ºC under an argon atmosphere for 5 min. Dimethyl (1-diazo-2-oxopropyl)phosphonate solution (10% in acetonitrile) (1.1 equiv) was added to the reaction mixture. The mixture was stirred at 22 ºC under an argon atmosphere for 4 hours. The reaction was monitored by thin layer chromatography. The reaction mixture was diluted with Et_2O, washed with aqueous sodium bicarbonate (5%) and dried (Na_2SO_4). The solvent was evaporated and the crude was purified using column chromatography, with a gradient from cyclohexane to cyclohexane/ethyl acetate 1/1 to yield the corresponding product.



((2-Ethynyl-3,6-difluoro-5-methoxyphenyl)ethynyl)triisopropylsilane (52a)

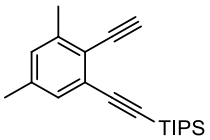
The title compound was obtained as a colorless oil (295 mg, 0.85 mmol, 79% yield) following the general procedure (B) on 1.08 mmol scale.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.88 (s, 3H), 3.41 (d, *J* = 0.8 Hz, 1H), 1.14 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 248.7, 3.1 Hz), 149.5 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 248, 3 Hz), 149.2 – 148.9 (m), 116.44 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$ = 11.3 Hz, 4.8), 105.3 (C–F, d,J_{CF}= 19.0 Hz), 103.5 (C–F, d,J_{CF}= 5.1 Hz), 101.6 (C–F, dd, $^{2}J_{CF}$, $^{4}J_{CF}$= 27.4, 2.2 Hz), 96.6 (C–F, d,J_{CF}= 3.8 Hz), 85.3 (C–F, d,J_{CF}= 4.2 Hz), 75.1 (C–F, d,J_{CF}= 3.1 Hz), 56.8, 18.7, 11.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.48 (d, *J* = 13.2 Hz), –134.59 (d, *J* = 13.2 Hz).

HRMS (APCI+) *m/z* calculated for $[M+MeOH+H]^+$ $C_{21}H_{31}F_2O_2Si$: 381.2056, found: 381.2064.



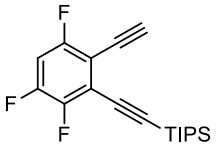
((2-Ethynyl-3,5-dimethylphenyl)ethynyl)triisopropylsilane (52b)

The title compound was obtained as a colorless oil (240 mg, 0.77 mmol, 61% yield) following the general procedure (B) on 1.27 mmol scale.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.98 (s, 1H), 3.42 (s, 1H), 2.40 (s, 3H), 2.28 (s, 3H), 1.14 (s, 21H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 138.2, 130.6, 130.5, 126.8, 121.9, 105.7, 94.3, 84.6, 81.3, 21.3, 21.0, 18.9, 11.5.

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{21}H_{31}Si$ is 311.2190, found: 311.2190.



((2-Ethynyl-3,5,6-trifluorophenyl)ethynyl)triisopropylsilane (52c)

The title compound was obtained as a colorless oil (301 mg, 0.9 mmol, 90% yield) following the general procedure (B) on 1.0 mmol scale.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 – 6.83 (m, 1H), 3.49 (d, *J* = 0.9 Hz, 1H), 1.15 (d, *J* = 2.5 Hz, 21H).

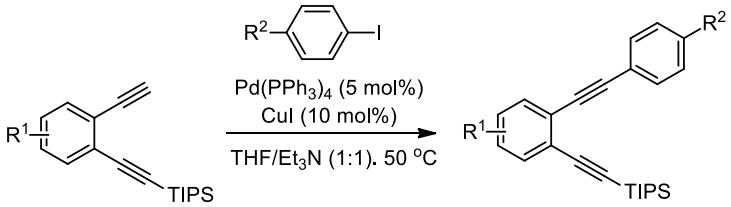
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 – 157.7 (C–F, ddd, $^{1}J_{CF}$, $^{3}J_{CF}$, $^{4}J_{CF}$ = 248.7, 10.9, 3.2 Hz), 150.47 (C–F, ddd (a-dt), $^{1}J_{CF}$, $^{2/3}J_{CF}$ = 255.2, 12.9 Hz), 148.2 (C–F, ddd,$^{1}J_{CF}$, $^{2}J_{CF}$, $^{4}J_{CF}$= 250.7, 13.7, 4.0 Hz),

118.2 (C–F, ddd (a-dt), J_{CF}= 15.5, 4.0 Hz), 110.4 (C–F, dd, $^{2}J_{CF}$, $^{4}J_{CF}$ = 14.6, 4.0), 105.7 (C–F, dd, $^{2}J_{CF}$, $^{2}J_{CF}$ = 27.3, 21.9), 105.5 (C–F, d, J_{CF} = 4.8 Hz) , 95.7 (C–F,dd (a-t), J_{CF}= 4.1 Hz), 87.0 (C–F,dd, J_{CF}= 4.2, 2.4 Hz), 74.2 (C–F, dd (a-t), J_{CF}= 2.8 Hz), 18.7, 11.3.

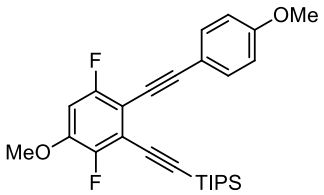
^{19}F NMR (376 MHz, $CDCl_3$) δ–110.5 (ddd, *J* = 13.5, 8.6, 5.0 Hz), -130.6 (ddd, *J* = 21.7, 9.8, 5.0 Hz), –137.4 (ddd, *J* = 20.6, 13.6, 6.5 Hz).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{19}H_{24}F_3Si$ is 337.1594, found: 337.1596.

General procedure C for the Sonogashira reaction:



Alkyne (0.2 mmol, 1 equiv), aryl iodide (1 equiv), CuI (0.1 equiv) and $Pd(PPh_3)_4$(5 mol%) were weighed inside a vial in a glovebox. Dry THF (0.1M) and dry triethylamine (0.1M) were then added and the reaction was stirred at 50 °C overnight. The reaction mixture was then concentrated under vacuum and purified using column chromatography, with a gradient from cyclohexane to cyclohexane/ethyl acetate 1/1 to yield the corresponding product.



((2,5-Difluoro-3-methoxy-6-((4-methoxyphenyl)ethynyl)phenyl)ethynyl)triisopropylsilane (53a)

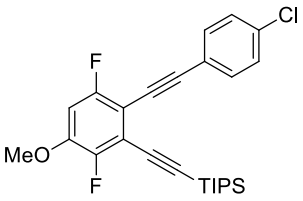
The title compound was obtained as a colorless oil (176 mg, 0.39 mmol, 80% yield) following the general procedure (C) on 0.49 mmol scale.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.39 (m, 2H), 6.93 – 6.83 (m, 2H), 6.70 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 1.13 (d, *J* = 2.9 Hz, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 158.9 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 248.5, 3.0 Hz), 150.1 C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 248.3, 3.2 Hz), 148.2 (C–F, dd, J_{CF}= 12.2, 10.8 Hz), 133.4, 115.5 (C–F, dd, J_{CF}= 15.8, 4.7 Hz), 115.3, 114.0, 106.9 (C–F, d, J_{CF}= 18.8 Hz), 103.0 (C–F, d, J_{CF}= 5.1 Hz), 101.7 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$ = 27.6, 2.3 Hz), 97.4 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$ = 29.4, 4.0 Hz), 79.5 (C–F, d, J_{CF} = 3.0 Hz), 56.8, 55.4, 18.8, 11.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.60 (d, *J* = 13.1 Hz), –134.82 (d, *J* = 13.4 Hz).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{27}H_{33}F_2O_2Si$ is 455.2212, found: 455.2224.



((2-((4-Chlorophenyl)ethynyl)-3,6-difluoro-5-methoxyphenyl)ethynyl)triisopropylsilane (53b)

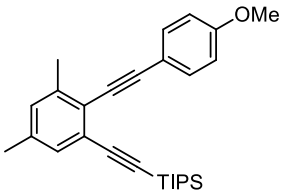
The title compound was obtained as a colorless oil (176 mg, 0.38 mmol, 95% yield) following the general procedure (C) on 0.40 mmol scale.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.36 – 7.28 (m, 2H), 6.70 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.89 (s, 3H), 1.13 (m, 21H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$ = 248.3, 3.1 Hz), 150.1 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 248.9, 3.3 Hz), 148.7 (C–F, dd, J_{CF}= 12.3, 10.8 Hz), 134.7, 133.1, 128.7, 121.6, 115.6 (C–F, dd, J_{CF}= 15.8, 4.6 Hz), 106.1 (C–F, d, J_{CF} = 18.0 Hz), 103.3 (C–F, d, J_{CF} = 5.2 Hz), 101.7 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$ = 27.6, 2.1 Hz), 97.0(C–F, d, J_{CF} = 4.1 Hz), 96.1 (C–F, d, J_{CF} = 4.1 Hz), 81.8 (C–F, d, J_{CF} = 3.1 Hz), 56.8, 18.7, 11.4.

^{19}F NMR (471 MHz, $CDCl_3$) δ–111.03 (d, *J* = 13.0 Hz), –134.52 (d, *J* = 13.0 Hz).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{26}H_{30}ClF_2OSi$ is 459.1717, found: 459.1714.



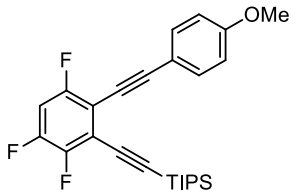
Triisopropyl((2-((4-methoxyphenyl)ethynyl)-3,5-dimethylphenyl)ethynyl)silane (53c)

The title compound was obtained following the general procedure (C) on 1.224 mmol scale, affording title compound **S23** as inseparable mixture of product and unreacted 4-iodoanisole. The material was used in the next deprotection step and the yield is reported over two steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.41 (m, 2H), 7.18 (s, 1H), 7.00 (s, 1H), 6.91 – 6.82 (m, 2H), 3.83 (s, 3H), 2.45 (s, 3H), 2.29 (d, *J* = 0.7 Hz, 3H), 1.13 (s, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 140.5, 137.4, 133.12, 130.9, 130.5, 125.6, 123.1, 116.2, 113.9, 106.3, 97.0, 93.8, 86.1, 55.4, 21.3, 21.2, 18.9, 11.5.

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{28}H_{37}OSi$ is 417.2608, found: 417.2609.4.



Triisopropyl((2,3,5-trifluoro-6-((4-methoxyphenyl)ethynyl)phenyl)ethynyl)silane (53d)

The title compound was obtained as colorless oil (126 mg, 0.60 mmol, 95% yield) following the general procedure (C) on 0.60 mmol scale.

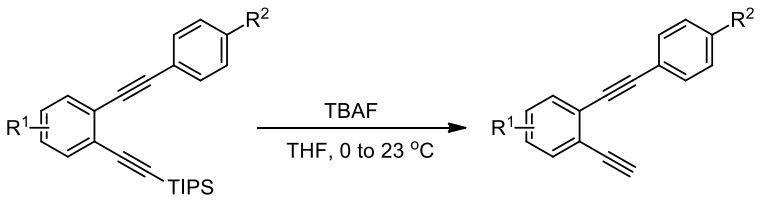
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 6.98 – 6.90 (m, 1H), 6.90 – 6.86 (m, 2H), 3.84 (s, 3H), 1.15 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ160.3, 157.9 (C–F, ddd, $^{1}J_{CF}$, $^{3}J_{CF}$, $^{4}J_{CF}$ = 250.0, 10.7, 3.1 Hz), 149.7 (C–F, ddd, $^{1}J_{CF}$, $^{2}J_{CF}$,$^{3}J_{CF}$ = 253.0, 14.3, 12.8 Hz), 148.4 (C–F, ddd, $^{1}J_{CF}$, $^{2}J_{CF}$, $^{4}J_{CF}$ = 250.1, 13.6, 4.0 Hz), 133.5, 117.0 (C–F, ddd (a-t), J_{CF}= 15.0, 3.5 Hz), 114.7, 114.0, 112.0 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$ = 18.9, 3.9 Hz), 105.6 (C–F, dd, $^{2}J_{CF}$, $^{2}J_{CF}$= 27.5, 21.7 Hz), 104.8 (C–F, d, J_{CF}= 5.0 Hz), 99.2 (C–F, dd, J_{CF}= 4.3, 2.3 Hz), 96.3 (C–F, dd (a-t), J_{CF} = 4.1 Hz), 78.8 (C–F, dd (a-t), J_{CF}= 2.9 Hz), 55.4, 18.7, 11.3.

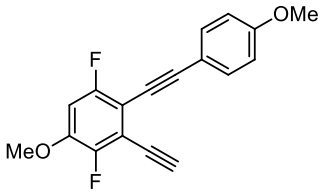
^{19}F NMR (376 MHz, $CDCl_3$) δ–110.2 (ddd, J = 13.2, 8.6, 4.3 Hz), –132.0 (ddd, J = 21.7, 9.8, 4.3 Hz), –137.4 (ddd, J = 21.8, 13.4, 6.5 Hz).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{26}H_{30}F_3OSi$ is 443.2013, found: 443.2011.

General Procedure D for the removal of the TIPS protecting group:



Diyne (0.2 mmol, 1 equiv) was dissolved in dry THF (0.15 M) at 0 °C under argon. TBAF (1.1 equiv, 1 M in THF) was then added dropwise. The reaction was warmed to 22 °C and monitored by TLC. After completion, the reaction was quenched with water, extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated and the crude was purified using column chromatography, with a gradient from cyclohexane to cyclohexane/ethyl acetate 1/1 to yield the corresponding product.



3-Ethynyl-1,4-difluoro-5-methoxy-2-((4-methoxyphenyl)ethynyl)benzene (54a)

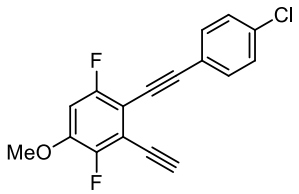
The title compound was obtained as a colorless oil (96 mg, 0.32 mmol, 83% yield) following the general procedure (D) on 0.39 mmol scale.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.40 (m, 2H), 6.94 – 6.83 (m, 2H), 6.74 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.62 (d, *J* = 0.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 158.7 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 247.8, 2.9 Hz), 150.1 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 249.5, 3.3 Hz), 148.2 (C–F, dd, J_{CF} = 12.1, 10.6 Hz), 133.4, 115.1, 114.2, 107.3 (C–F, d, J_{CF}= 19.2 Hz), 102.3 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$= 27.5, 2.4 Hz), 97.9 (C–F, d, J_{CF}= 4.0 Hz), 87.4 (C–F, d, J_{CF} = 5.0 Hz), 79.3 (C–F, d, J_{CF} = 2.9 Hz), 74.9 (C–F, d, J_{CF} = 4.1 Hz), 56.8, 55.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.19 (d, *J* = 13.1 Hz), –135.14 (d, *J* = 13.1 Hz).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{18}H_{13}F_2O_2Si$ is 455.0878, found: 455.0880.



2-((4-Chlorophenyl)ethynyl)-3-ethynyl-1,4-difluoro-5-methoxybenzene (54b)

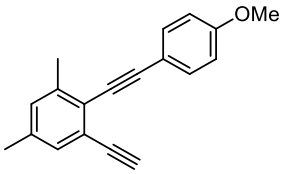
The title compound was obtained as a colorless oil (102 mg, 0.33 mmol, 88% yield) following the general procedure (D) on 0.38 mmol scale.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 2H), 7.36 – 7.28 (m, 2H), 6.74 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.89 (s, 3H), 3.63 (d, *J* = 0.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (dd, *J* = 248.7, 3.0 Hz), 150.0 (dd, *J* = 248.7, 3.0 Hz), 149.0 – 148.5 (m), 134.9, 133.0, 128.8, 121.4, 114.2 (dd, *J* = 15.4, 4.8 Hz), 106.4 (dd, *J* = 19.2, 1.5 Hz), 102.2 (dd, *J* = 27.4, 2.4 Hz), 96.5 (d, *J* = 3.9 Hz), 87.7 (d, *J* = 5.1 Hz), 81.5 (d, *J* = 3.0 Hz), 74.7 (d, *J* = 4.1 Hz), 56.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ –110.59 (d, *J* = 13.0 Hz), –134.79 (d, *J* = 12.7 Hz).

HRMS (APCI+) *m/z* calculated for $[M+MeOH+H]^+$ $C_{18}H_{14}ClF_2O_2$ is 335.0645, found: 335.0646.



1-Ethynyl-2-((4-methoxyphenyl)ethynyl)-3,5-dimethylbenzene (54c)

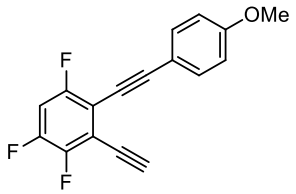
The title compound was obtained as a white solid (243 mg, 0.93 mmol, 76% yield over 2 steps) following the general procedure (D) on 1.22 mmol scale.

Melting point = 121–123 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.19 (s, 1H), 7.04 (s, 1H), 6.92 – 6.84 (m, 2H), 3.83 (s, 3H), 3.30 (s, 1H), 2.47 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 140.2, 137.5, 133.2, 131.0, 130.7, 124.4, 123.6, 116.0, 114.1, 97.2, 85.8, 83.1, 80.2, 55.5, 21.3, 21.1.

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{19}H_{17}O$ is 261.1274, found: 261.1271.



3-Ethynyl-1,2,5-trifluoro-4-((4-methoxyphenyl)ethynyl)benzene (54d)

The title compound was obtained as a colorless oil (61 mg, 0.25 mmol, 85% yield) following the general procedure (D) on 0.3 mmol scale.

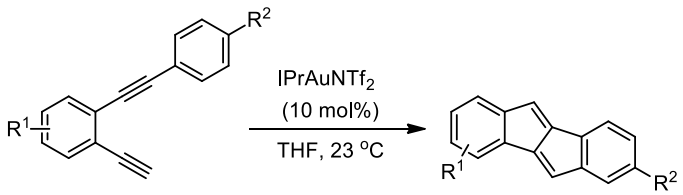
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 1H), 6.97 (ddd, *J* = 9.9, 8.6, 6.7 Hz, 1H), 6.91 – 6.87 (m, 1H), 3.83 (s, 3H), 3.71 (d, *J* = 0.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 157.6 (C–F, ddd, $^{1}J_{CF}$, $^{3}J_{CF}$, $^{4}J_{CF}$= 250.4, 10.6, 3.2 Hz), 149.5 (C–F, ddd, $^{1}J_{CF}$, $^{2}J_{CF}$,$^{3}J_{CF}$= 253.5, 14.1, 12.7 Hz), 148.4 (C–F, ddd, $^{1}J_{CF}$, $^{2}J_{CF}$, $^{4}J_{CF}$ = 250.4, 14.0, 4.1 Hz), 133.53, 114.44, 114.20, 112.49 (C–F, ddd, J_{CF} = 19.2, 4.1 Hz), 106.39 (C–F, dd, $^{2}J_{CF}$, $^{2}J_{CF}$= 27.3, 21.7 Hz), 99.67 (C–F, dd, J_{CF} = 4.0, 2.4 Hz), 88.78 (C–F, d, J_{CF}= 4.8 Hz), 78.55 (C–F, dd (a-t), J_{CF}= 2.8 Hz), 74.13 (C–F, dd (a-t), J_{CF}= 4.4 Hz), 55.38.

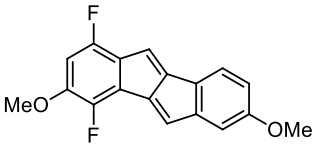
^{19}F NMR (376 MHz, $CDCl_3$) δ –110.3 (dd, *J* = 13.4, 4.3 Hz), –131.9 (dd, *J* = 21.5, 4.3 Hz), –136.5 – 138.8 (m).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{17}H_{10}F_3O$ is 287.0678, found: 287.0678.

General Procedure E for the gold-catalyzed cyclization of diynes:



Diyne (0.2 mmol, 1 equiv) was dissolved in THF (2 mL, 0.1 M) at 22 ºC under air. $IPrAuNTf_2$ (10 mol%) was then added and the reaction mixture was stirred overnight at 22 ºC. The reaction mixture was then concentrated under reduced pressure and purified using column chromatography, with a gradient from cyclohexane to cyclohexane/ethyl acetate 1:1 to yield the corresponding product.



1,4-Difluoro-2,7-dimethoxyindeno[2,1-*a*]indene (55a)

The title compound was obtained as a red solid (28 mg, 0.09 mmol, 85% yield) following the general procedure (E) on 0.11 mmol scale.

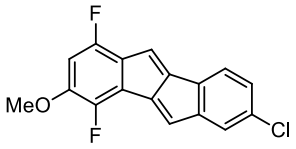
Melting point: Product decomposes at T > 280 ºC.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.51 (d, *J* = 1.8 Hz, 1H), 6.40 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.33 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.15 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 152.1 (C–F, d, $^{1}J_{CF}$= 247.1 Hz), 151.7, 149.1 (C–F, dd, J_{CF}= 13.0, 9.5 Hz), 147.5, 145.8, 145.5 (C–F, d, $^{1}J_{CF}$= 250.5 Hz), 129.3 (C–F, dd, J_{CF}= 4.3, 2.1 Hz), 128.1 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$= 18.2, 4.8 Hz), 126.8, 123.0, 122.3 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$= 16.4, 8.5 Hz), 118.9, 111.6, 111.0, 100.8 (C–F, dd, $^{2}J_{CF}$= 28.0 Hz), 56.7, 55.6.

^{19}F NMR (471 MHz, $CDCl_3$) δ –123.36 (d, *J* = 16.1 Hz), –141.30 (d, *J* = 16.1 Hz).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{18}H_{13}F_2O_2$ is 299.0878, found: 299.0878.



7-Chloro-1,4-difluoro-2-methoxyindeno[2,1-*a*]indene (55b)

The title compound was obtained as a red solid (40 mg, 0.14 mmol, 62% yield) following the general procedure (E) on 0.22 mmol scale.

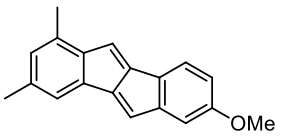
Melting point: Product decomposes at T > 290 ºC.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.89 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.53 (d, *J* = 1.8 Hz, 1H), 6.49 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.17 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7 (C–F, d, $^{1}J_{CF}$= 249.0 Hz), 151.5, 149.9 (m), 146.5, 145.6 (C–F, d, $^{1}J_{CF}$ = 249.0 Hz), 145.5, 144.6, 134.1, 132.5, 128.7 (C–F, dd, J_{CF} = 4.4, 2.2 Hz), 127.2, 124.1, 122.8, 121.9 (C–F, dd (a-t), J_{CF}= 2.3 Hz), 101.0 (C–F, d, J_{CF}= 27.5 Hz), 56.8.

^{19}F NMR (471 MHz, $CDCl_3$) δ –122.13 (d, *J* = 16.6 Hz), –140.51 (d, *J* = 16.1 Hz).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{17}H_{10}ClF_2O$ is 303.0383, found: 303.0379.



7-Methoxy-2,4-dimethylindeno[2,1-*a*]indene (55c)

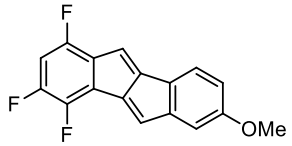
The title compound was obtained a red solid (50 mg, 0.19 mmol, 42% yield) following the general procedure (E) on 0.46 mmol scale.

Melting point: Product decomposes at T > 270 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.1 Hz, 1H), 6.71 (s, 1H), 6.52 – 6.47 (m, 2H), 6.39 – 6.31 (m, 2H), 6.31 – 6.22 (m, 1H), 3.76 (s, 3H), 2.16 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 152.0, 151.1, 147.3, 146.5, 136.7, 135.0, 131.8, 130.7, 127.7, 125.0, 123.0, 122.5, 121.3, 111.1, 110.2, 55.5, 21.3, 18.1.

HRMS (APCI+) *m/z* calculated for $[M+H]^+C_{19}H_{17}O$ is 261.1274, found: 261.1275.



1,3,4-Trifluoro-7-methoxyindeno[2,1-*a*]indene (55d)

The title compound was obtained as a red solid (40 mg, 0.14 mmol, 70% yield) following the general procedure (E).

Melting point = 229–231 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.1 Hz, 1H), 6.56 – 6.52 (m, 2H), 6.46 – 6.42 (m, 1H), 6.40 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.29 (dd, *J* = 2.6, 1.7 Hz, 1H), 3.77 (s, 3H).

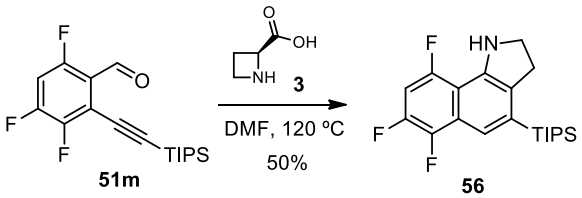
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 151.6, 150.8 (m), 150.4 (C–F, ddd, $^1J_{CF}$, $^2J_{CF}$,$^3J_{CF}$ = 250.4, 14.8, 11.1 Hz), 146.6 (m), 143.5 (C–F, ddd, $^1J_{CF}$, $^2J_{CF}$, $^4J_{CF}$ = 251.5, 15.8, 3.1 Hz), 132.48 (C–F, d, J_{CF} = 18.0 Hz), 131.06 (C–F, dd, J_{CF}= 4.1, 1.6 Hz), 127.50, 126.63, 123.39, 118.01 (m), 114.44, 112.27, 111.25, 105.37 (C–F, dd, $^2J_{CF}$, $^2J_{CF}$= 27.7, 22.3 Hz), 55.60.

^{19}F NMR (376 MHz, $CDCl_3$) δ –123.0 (dd, *J* = 16.7, 8.2 Hz), –136.2 (dd, *J* = 21.3, 10.8 Hz), –143.8 - –145.8 (m).

HRMS (APCI+) *m/z* calculated for $[M+H]^+$ $C_{17}H_{10}F_3OSi$ is 287.0678, found: 287.0677.

X-ray quality crystals were obtained by slow evaporation in $CDCl_3$.

Synthesis of Indoline 56



6,7,9-Trifluoro-4-(triisopropylsilyl)-2,3-dihydro-1*H*-benzo[*g*]indole (56)

A mixture of 3,4,6-trifluoro-2-((triisopropylsilyl)ethynyl)benzaldehyde (**51m**) (68 mg, 0.20mmol, 1 equiv) and *L*-azetidine-2-carboxylic acid **3** (22 mg, 0.22mmol, 1.1 equiv) were dissolved in DMF (1 ml, 0.2 M) and stirred at 120 °C overnight. The reaction was cooled to 22 °C and diluted with water, extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The crude was purified by column chromatography (cyclohexane/ethyl acetate 1:1) to yield the title compound (38 mg, 0.10 mol, 50% yield) as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.4 Hz, 1H), 6.84 (ddd, *J* = 11.7, 10.1, 6.1 Hz, 1H), 3.72 (t, *J* = 8.8 Hz, 2H), 3.19 (t, *J* = 8.8 Hz, 2H), 1.53 (m, 3H), 1.13 (m, 18H).

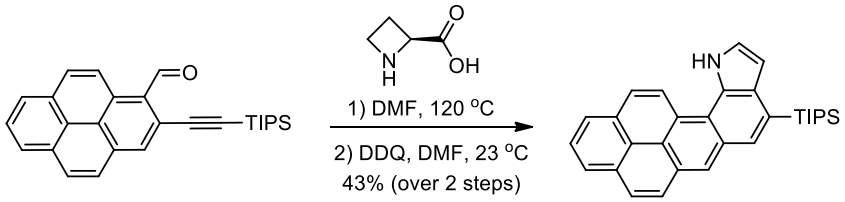
^{13}C NMR (126 MHz, $CDCl_3$) δ 186.4, 154.6 (C–F, ddd, $^1J_{CF}$,$^3J_{CF}$, $^4J_{CF}$= 248.4, 10.9, 3.7 Hz), 144.47 (C–F, ddd (a-dt), $^1J_{CF}$,$^2J_{CF}$=$^3J_{CF}$= 245.7, 13.7 Hz), 144.9 (C–F, dd (a-q), J_{CF} = 3.2 Hz), 141.8 (C–F,

ddd, $^{1}J_{CF}$,$^{3}J_{CF}$,$^{4}J_{CF}$= 246.1, 11.7, 5.1 Hz), 134.0, 129.3, 124.4 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 14.0, 6.7 Hz), 117.4 (C–F, ddd, J_{CF}= 6.7, 4.5, 2.2 Hz), 108.7 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 16.0, 4.3 Hz), 106.4, 100.3 (C–F, dd, $^{2}J_{CF}$,$^{2}J_{CF}$= 27.5, 25.0 Hz), 47.8, 31.6, 19.0, 12.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –119.8 (dd, *J* = 18.6, 11.6 Hz), -–140.7 (dd, *J* = 18.7, 10.0 Hz), –153.2 (td, *J* = 19.0, 6.1 Hz).

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{21}H_{29}F_3NSi$ is 380.2016, found: 380.2016.

Synthesis of Indole 57



51aa **57**

8-(Triisopropylsilyl)-11H-pyreno[2,1-g]indole (57)

2-((triisopropylsilyl)ethynyl)pyrene-1-carbaldehyde (**51aa**) (50 mg, 0.12 mmol, 1 equiv) and *L*-azetidine-2-carboxylic acid (**3**) (14 mg, 0.13 mmol, 1.1 equiv) were placed in a vial and stirred in DMF (1.2 mL, 0.1 M) at 120 °C overnight. Then the reaction was cooled to 22 °C, DDQ (30 mg, 0.13 mmol, 1.1 equiv) was added and the mixture was left to react at this temperature for 24 h. Afterwards, it was diluted with water (5 mL) and the compound was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (3 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude by column chromatography (cyclohexane/EtOAc 19:1 to 4:1) provided the title compound as a green solid (23 mg, 0.052 mmol, 43% yield).

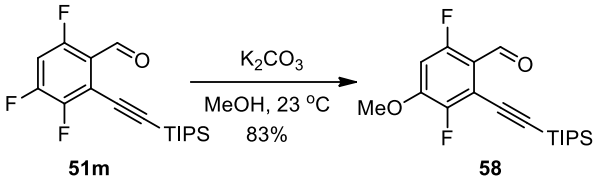
Melting point = 248–250 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 9.06 (d, *J* = 9.1 Hz, 1H), 8.68 (s, 1H), 8.37 (d, *J* = 9.1 Hz, 1H), 8.26 – 8.21 (m, 2H), 8.13 (d, *J* = 7.1 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 8.01 (dd, *J* = 9.5, 5.7 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.56 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.05 (dd, *J* = 3.1, 1.8 Hz, 1H), 1.79 (dt, *J* = 15.0, 7.5 Hz, 3H), 1.29 – 1.17 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 132.1, 131.7, 130.9, 130.6, 130.3, 128.8, 128.7, 128.5, 128.1, 127.8, 126.9, 126.8, 126.1, 125.8, 124.9, 124.9, 124.5, 123.9, 123.2, 117.6, 107.3, 19.3, 12.5.

HRMS (ESI-) *m/z* calculatedfor $[M-H]^-$ $C_{31}H_{32}NSi$ is 446.2310, found: 446.2309.

Synthesis of Isoquinolines



3,6-Difluoro-4-methoxy-2-((triisopropylsilyl)ethynyl)benzaldehyde (58). To a solution of 3,4,6-trifluoro-2-((triisopropylsilyl)ethynyl)benzaldehyde (**51m**) (2.90 g, 8.52 mmol, 1 equiv) in MeOH (35 mL) was added potassium carbonate (2.95 g, 21.3 mmol, 2.5 equiv). The reaction was stirred at 22 °C until consumption of the starting material was observed by TLC (4 h). The reaction was quenched with sat. aq. NH_4Cl (20 mL), then the two phases were separated. The aqueous phase was extracted with EtOAc (2 × 30 ml). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Cyclohexane/EtOAc 6:1) to yield the title compound as a white solid (2.50 g, 7.09 mmol, 83% yield).

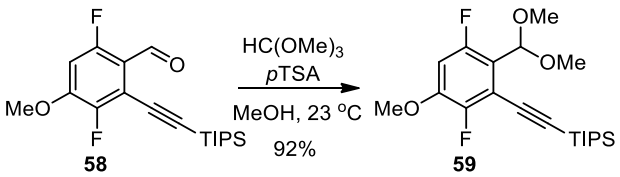
Melting point = 50–52 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (d, *J* = 1.3 Hz, 1H), 6.70 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.95 (s, 3H), 1.23 – 1.04 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.9 (C–F, d, $^3J_{CF}$= 2.7 Hz), 159.3 (C–F, dd, $^1J_{CF}$, $^4J_{CF}$= 261.2, 2.9 Hz), 153.2 (C–F, dd (a-t), $^2J_{CF}$ =$^3J_{CF}$= 12.3 Hz), 150.5 (C–F, dd, $^1J_{CF}$, $^4J_{CF}$= 250.7, 3.0 Hz), 116.8 (C–F, d, J_{CF}= 9.2 Hz), 115.3 (C–F, dd, $^2J_{CF}$,$^3J_{CF}$= 15.5, 6.0 Hz), 107.2 (C–F, d, J_{CF}= 5.4 Hz), 101.8 (C–F, dd, $^2J_{CF}$,$^3J_{CF}$ = 27.5, 1.8 Hz), 94.3 (C–F, d, J_{CF}= 3.9 Hz), 57.0, 18.7, 11.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.29 (d, *J* =13.9Hz), –134.42 (d, *J* = 13.8 Hz).

HRMS (ESI+) *m/z* calculated for [M+Na] $C_{19}H_{26}F_2NaO_2Si$ is 375.1562, found: 375.1547.



((2-(Dimethoxymethyl)-3,6-difluoro-5-methoxyphenyl)ethynyl)triisopropylsilane (59)

3,6-difluoro-4-methoxy-2-((triisopropylsilyl)ethynyl)benzaldehyde (**58**) (548 mg, 1.56 mmol, 1 equiv) was mixed with trimethyl orthoformate (1.65 g, 15.5 mmol, 10 eq) and 4-methylbenzenesulfonic acid hydrate (30 mg, 0.15 mmol, 10 mol%) in MeOH (10 ml) at 22 ºC.The reaction was stirred for 4 h and then it was diluted with EtOAc (50 ml), washed with sat. aq. $NaHCO_3$ (10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Hexane/EtOAc/Et_3N 10:1:0.1) to yield the title compound as a white solid (571 mg, 1.43 mmol, 92% yield).

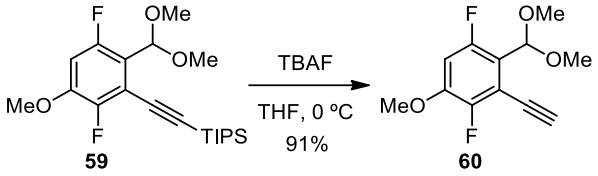
Melting point = 90–92 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 11.6, 6.9 Hz, 1H), 5.69 (d, *J* = 1.2 Hz, 1H), 3.86 (s, 3H), 3.45 (s, 6H), 1.36 – 0.54 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$= 248.6, 3.4 Hz), 149.9 (C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$= 248.0, 3.3 Hz), 148.5 (C–F, dd (a-t), J_{CF}= 11.9 Hz), 118.7 (C–F, dd (a-t), J_{CF}= 15.7 Hz), 112.9 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 15.7, 8.7 Hz), 103.6 (C–F, d, J_{CF}= 2.5 Hz), 103.5 (C–F, d, J_{CF}= 5.2 Hz), 102.9 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$ = 28.8, 2.0 Hz), 96.2 (C–F, d, J_{CF}= 3.6 Hz), 56.7, 55.7, 18.7, 11.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –117.13 (d, *J* = 14.2 Hz), –135.56 (d, *J* = 14.1 Hz).

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{21}H_{32}F_2NaO_3Si$ is 421.1981, found: 421.1966.



2-(Dimethoxymethyl)-3-ethynyl-1,4-difluoro-5-methoxybenzene (60)

TBAF (1 M in THF, 930 µl, 0.930 mmol, 1.3 equiv) was added to a solution of ((2-(dimethoxymethyl)-3,6-difluoro-5-methoxyphenyl)ethynyl)triisopropylsilane (**59**) (285 mg, 0.715 mmol, 1 equiv) in THF (5 ml) at 0 ºC. The reaction was stirred for 10 min and then it was diluted with EtOAc (40 ml), washed with sat. aq.$NaHCO_3$ (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography column (cyclohexane/EtOAc 5:1) to yield the title compound as a yellow solid (158 mg, 0.650 mmol, 91% yield).

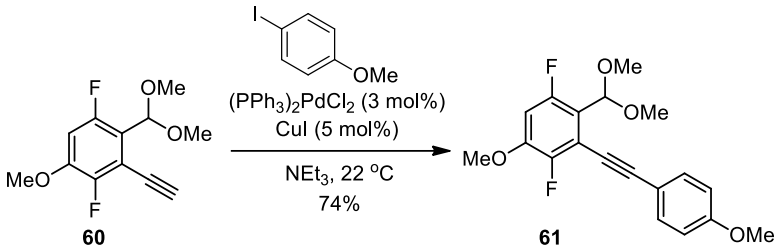
Melting point = 75–77 ºC

^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.75 (dd, *J* = 11.7, 7.1 Hz, 1H), 5.59 (d, *J* = 1.0 Hz, 1H), 3.87 (s, 3H), 3.64 (d, *J* = 0.9 Hz, 1H), 3.40 (s, 6H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 156.9 (C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$= 247.6, 3.3 Hz), 150.6 (C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$= 247.9, 3.3 Hz), 148.8 (C–F, dd (a-t), $^{2}J_{CF}$ =$^{3}J_{CF}$= 11.9 Hz), 119.3 (C–F, d, J_{CF}= 16.3 Hz), 111.3 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 15.2, 8.7 Hz), 103.4 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 29.3, 2.2 Hz), 102.9 (C–F, d, J_{CF}= 2.2 Hz), 88.3 (C–F, d, J_{CF}= 5.3 Hz), 74.1 (C–F, dd, $^{3}J_{CF}$,$^{4}J_{CF}$ = 4.0, 1.5 Hz), 57.0, 55.4.

^{19}F NMR (376 MHz, CD_2Cl_2) δ –117.43 (d, *J* = 14.1 Hz), –136.68 (d, *J* = 13.7 Hz).

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{12}H_{12}F_2NaO_3$ is 265.0647, found: 265.0648.



2-(Dimethoxymethyl)-1,4-difluoro-5-methoxy-3-((4-methoxyphenyl)ethynyl)benzene (61)

2-(dimethoxymethyl)-3-ethynyl-1,4-difluoro-5-methoxybenzene (**60**) (157 mg, 0.648 mmol, 1 equiv) was mixed with 1-iodo-4-methoxybenzene (197 mg, 0.843 mmol, 1.3 equiv), $(PPh_3)_2PdCl_2$ (23 mg, 0.030 mmol, 5 mol%) and CuI (5.7 mg, 0.030 mmol, 5 mol%) were mixed in degassed TEA (4 ml) and stirred at 22 ºC overnight. The reaction was diluted with EtOAc (40 mL), washed with sat. aq. NH_4Cl (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (cyclohexane/EtOAc 5:1) to yield the title compound as a white solid (167 mg, 0.480 mmol, 74% yield).

Melting point = 108–110 ºC

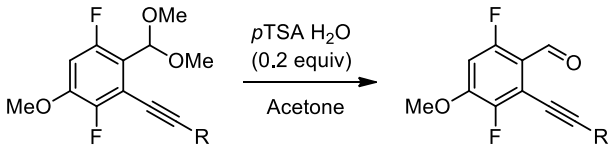
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 6.93 – 6.85 (m, 2H), 6.68 (dd, *J* = 11.6, 6.9 Hz, 1H), 5.70 (d, *J* = 1.1 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.48 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 156.7 (C–F, dd, $^1J_{CF}$,$^4J_{CF}$= 247.8, 3.4 Hz), 149.1 (C–F, dd, $^1J_{CF}$,$^4J_{CF}$= 247.0, 3.3 Hz), 148.4 (C–F, dd, $^2J_{CF}$,$^3J_{CF}$= 12.0 Hz), 133.3, 118.1 (C–F, d, J_{CF}= 15.4 Hz), 114.7, 114.2, 113.0 (C–F, dd, $^2J_{CF}$,$^3J_{CF}$= 15.6, 8.6 Hz), 103.2 (C–F, d, J_{CF}= 2.3 Hz), 102.3 (C–F, dd, $^2J_{CF}$,$^3J_{CF}$= 29.1, 2.1 Hz), 100.2 (C–F, d, J_{CF}= 5.1 Hz), 78.56 (C–F, dd (a-t), J_{CF}= 4.0 Hz), 56.6, 55.4, 55.4.

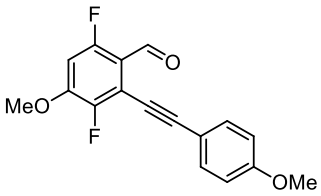
^{19}F NMR (376 MHz, $CDCl_3$) δ –117.21 (d, *J* = 14.2 Hz), –136.24 (d, *J* = 14.1 Hz).

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{19}H_{18}F_2NaO_4$ is 371.1065, found: 371.1069.

General procedure F for the deprotection of acetals 62 and 63:



4-Methylbenzenesulfonic acid hydrate (0.2 eq) was added to a solution of dimethoxyacetal (1 equiv) in acetone (0.15M) at 22 ºC.Thereactionwasstirred at 22 ºCovernight, diluted with EtOAc (30 ml), washed with sat. aq. $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Cyclohexane/EtOAc 5:1).



3,6-Difluoro-4-methoxy-2-((4-methoxyphenyl)ethynyl)benzaldehyde (62)

The title compound was obtained as a white solid (51 mg, 0.167 mmol, 76% yield) following the general procedure (F) on 0.22 mmol scale.

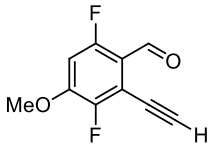
Melting point = 131–133 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.64 – 7.47 (m, 2H), 6.97 – 6.77 (m, 2H), 6.68 (dd, *J* = 11.8, 6.6 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7 (C–F, dd (at), $^{3}J_{CF}$ =$^{4}J_{CF}$= 2.5 Hz), 160.8, 160.1 (C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$= 259.9, 2.9 Hz), 153.1 (C–F, dd (at), $^{2}J_{CF}$ =$^{3}J_{CF}$= 12.4 Hz), 149.4 (C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$ = 249.7, 3.0 Hz), 133.8, 116.3 (C–F, d, J_{CF}= 9.1 Hz), 115.2 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 15.4, 6.0 Hz), 114.3, 114.1, 102.8 (C–F, d, J_{CF}= 5.2 Hz), 101.3 (C–F, d, J_{CF}= 1.8 Hz), 101.0 (C–F, d, J_{CF}= 1.7 Hz), 56.9, 55.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ –117.53 (d, *J* = 13.7 Hz), –135.44 (d, *J* = 13.6 Hz).

HRMS (ESI+) *m/z* calculatedfor $[M+Na]^+$ $C_{17}H_{12}F_2NaO_3$ is 325.0647, found: 325.0647.



2-Ethynyl-3,6-difluoro-4-methoxybenzaldehyde (63)

The title compound was obtained scale as a white solid (133 mg, 0.670 mmol, 90% yield) following the general procedure (F) on 0.75 mmol scale.

Melting point = 86–88 ºC

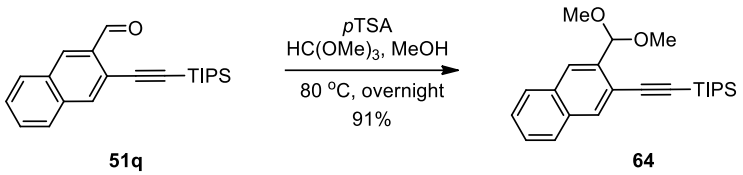
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 6.75 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.97 (s, 3H), 3.71 (d, *J* = 1.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1 (C–F, dd (at), $^{3}J_{CF}$ =$^{4}J_{CF}$= 2.8 Hz), 160.1 (C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$= 260.1, 2.9 Hz), 153.3 (C–F, dd (a-t), $^{2}J_{CF}$ = $^{3}J_{CF}$= 12.3 Hz), 150.8(C–F, dd, $^{1}J_{CF}$,$^{4}J_{CF}$= 252.0, 2.9 Hz), 116.9 (C–F, d, J_{CF}= 9.4 Hz), 112.9 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 15.1, 6.1 Hz), 102.3 (C–F, dd, $^{2}J_{CF}$,$^{3}J_{CF}$= 27.6, 1.9 Hz), 90.3 (C–F, d, J_{CF}= 5.4 Hz), 72.6 (C–F, d, J_{CF}= 4.1 Hz), 57.0.

^{19}F NMR (471 MHz, $CDCl_3$) δ –117.39 (d, *J* = 13.7 Hz), –134.49 (d, *J* = 13.7 Hz).

HRMS (ESI+) *m/z* calculated for $[M+H]^+$$C_{10}H_7F_2O_2$is 197.0409, found: 197.0409.

Synthesis of acetals *64, 69, 74*:



51q 64

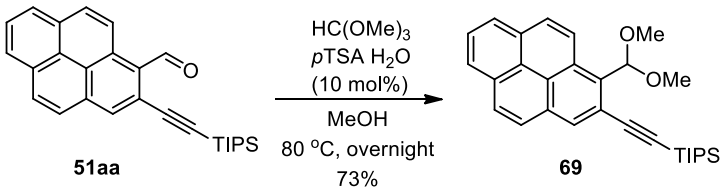
(3-(Dimethoxymethyl)naphthalen-2-yl)ethynyl)triisopropylsilane (64)

To a solution of 3-((triisopropylsilyl)ethynyl)-2-naphthaldehyde (**51q**) (1.00 g, 2.97 mmol, 1.0 equiv) in trimethyl orthoformate (4.95 mL, 0.6 M) and methanol (1.75 mL, 1.7 M), *p*-toluenesulfonicacidmonohydrate (113 mg, 594 µmol, 0.2 equiv) was added and the mixture was left to stir overnight at 80 ºC. After that, it was cooled to 22 ºC and sodium carbonate (315 mg, 2.97 mmol, 1 equiv) was added. The mixture was stirred at this temperature for 30 min and then EtOAc (20 mL) was added. After removal of the solids by filtration, the solvent was evaporated under reduced pressure. Purification of the crude residue through column chromatography (cyclohexane/EtOAc 95:5) provided the title compoundas a colourless oil (1.035 g, 2.705 mmol, 91%).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.04 (d, *J* = 9.4 Hz, 2H), 7.87 (m, 1H), 7.80 (m, 1H), 7.51 (m, 2H), 5.83 (s, 1H), 3.42 (s, 6H), 1.20 (m, 21H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 136.8, 133.7, 133.3, 133.1, 128.9, 127.8, 127.5, 127.4, 126.2, 120.6, 105.2, 103.3, 95.7, 54.7, 54.5, 54.3, 54.0, 53.7, 53.5, 27.5, 19.1, 12.3, 12.0, 11.7.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{24}H_{34}NaO_2Si$ is 405.2231, found: 405.2224.



51aa 69

((1-(Dimethoxymethyl)pyren-2-yl)ethynyl)triisopropylsilane (69)

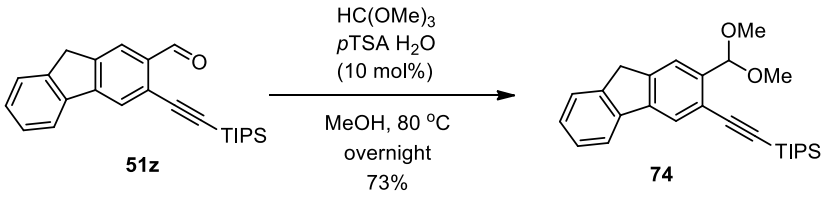
To a solution of 2-((triisopropylsilyl)ethynyl)pyrene-1-carbaldehyde (**51aa**) (700 mg, 1.70 mmol, 1 equiv) in trimethyl orthoformate (6.3 mL, 0.27 M) and methanol (2.5 mL, 0.67 M), *p*-toluenesulfonicacidmonohydrate (422 mg, 2.22 mmol, 1.3 equiv) was added and the mixture was left to stir overnight at 80 ºC. After that, it was cooled to 22 ºC and sodium carbonate (940 mg, 8.86 mmol, 5.2 equiv) was added. The mixture was stirred at this temperature for 30 min and then EtOAc (15 mL) was added. After removal of the solids by filtration, the solvent was evaporated under reduced pressure. Purification of the crude residue through column chromatography (cyclohexane/EtOAc 95:5) provided title compound **S10** as an orange solid (571 mg, 1.25 mmol, 73%).

Melting point = 128–130 ºC

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.97 (d, *J* = 9.4 Hz, 1H), 8.30 (s, 1H), 8.20 (dd, *J* = 11.0, 7.6 Hz, 2H), 8.10 (dd, *J* = 9.2, 6.5 Hz, 2H), 8.02 (m, 2H), 6.58 (s, 1H), 3.56 (s, 6H), 1.25 (m, 21H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 133.8, 131.9, 131.8, 131.5, 129.6, 129.1, 129.0, 127.9, 127.1, 127.1, 126.8, 126.2, 126.0, 125.8, 124.9, 121.5, 107.9, 106.0, 96.8, 56.6, 54.5, 54.3, 54.0, 53.7, 53.5, 19.2, 12.4, 12.01, 11.8.

HRMS (ESI+) *m/z* calculatedFor$[M+Na]^+$ $C_{30}H_{36}NaO_2Si$ is 479.2377, found: 479.2376.



51z 74

(2-(Dimethoxymethyl)-9*H*-fluoren-3-yl)ethynyl)triisopropylsilane (74)

To a solution of 3-((triisopropylsilyl)ethynyl)-9*H*-fluorene-2-carbaldehyde (**51z**) (400 mg, 1.07 mmol, 1.0 equiv) in trimethyl orthoformate (6.5 mL, 0.27 M) and methanol (2.6 mL, 0.67 M), *p*-toluenesulfonicacidmonohydrate (264 mg, 1.39 mmol, 1.3 equiv) was added and the mixture was left to stir overnight at 80 °C. After that, it was cooled to 22 °C and sodium carbonate (589 mg, 5.55 mmol, 5.2 equiv) was added. The mixture was stirred at this temperature for 30 min and then EtOAc (10 mL) was added. After removal of the solids by filtration, the solvent was evaporated under reduced pressure. Purification of the crude residue through column chromatography (cyclohexane/EtOAc 19:1) provided the title compoundas a white solid (344 mg, 818 µmol, 77%).

Melting point = 112–114°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.90 (s, 1H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.74 (s, 1H), 7.57 (m, 1H), 7.39 (dt, *J* = 8.1, 3.8 Hz, 1H), 7.34 (ddd, *J* = 7.4, 6.4, 1.3 Hz, 1H), 5.81 (s, 1H), 3.42 (s, 6H), 1.20 (m, 21H).

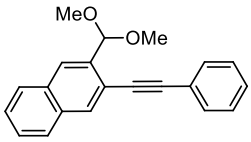
^{13}C NMR (101 MHz, CD_2Cl_2) δ 144.5, 144.4, 142.4, 141.1, 139.6, 127.9, 127.4, 127.4, 127.3, 126.0, 125.7, 124.3, 123.9, 123.4, 121.5, 120.7, 120.5, 119.9, 105.4, 104.2, 103.9, 95.3, 55.1, 54.5, 54.3, 54.0, 53.7, 53.5, 53.3, 37.7, 37.5, 27.5, 19.1, 12.3, 12.0, 11.7.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{27}H_{36}NaO_2Si$ is 443.2377, found: 443.2389.

General Procedure G for the One-pot TIPS Deprotection and Sonogashira Coupling

TBAF (1.3 equiv, 1 M in THF) was added to a solution of TIPS-alkyne (1 equiv) in THF (0.15 M) at 0 °C. The reaction was stirred for 10 min, then it was diluted with EtOAc (40 ml), washed with sat. aq. $NaHCO_3$ (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Filtration through a pad of silica (cyclohexane/EtOAc 19:1) afforded the desired terminal alkyne, which was directly taken to the next step without further purification.

$PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) were suspended in Et_3N (0.2 M) and the mixture was bubbled with Ar for 10 min. A solution of terminal alkyne (1.0 equiv) and iodobenzene (1.3 equiv) in a mixture of degassed NEt_3 (0.2 M) was subsequently added and the reaction was stirred overnight at 23 ºC. Then the mixture was diluted with EtOAc (30 mL), filtered through a short pad of silica gel with EtOAcand concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 99:1) afforded the desired coupled alkynes **66** and **71**.



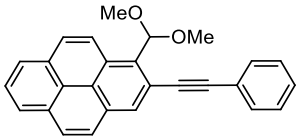
2-(Dimethoxymethyl)-3-(phenylethynyl)naphthalene (66). The title compound was obtained as a white solid (423 mg, 57%, 1.41 mmol, yield after two steps) following general procedure (G) on a 2.47 mmol scale.

Melting point = 85–87 ºC

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.10 (d, *J* = 11.2 Hz, 2H), 7.90 (m, 1H), 7.85 (m, 1H), 7.64 – 7.59 (m, 2H), 7.53 (m, 2H), 7.42 (m, 3H), 5.87 (d, *J* = 0.5 Hz, 1H), 3.47 (s, 6H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 136.5, 133.4, 133.0, 132.1, 129.1, 129.1, 128.9, 127.9, 127.6, 127.5, 126.3, 123.8, 120.3, 103.1, 93.9, 87.9, 54.6, 54.5, 54.3, 54.0, 53.7, 53.5

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{21}H_{19}O_2$ is 303.1380, found: 303.1382.



1-(Dimethoxymethyl)-2-(phenylethynyl)pyrene (71). The title compound was obtained as a yellow solid (218 mg, 0.583 mmol, 54% yield after two steps) following general procedure (G) on 1.08 mmol scale.

Melting point = 185–187 ºC

^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.01 (d, *J* = 9.4 Hz, 1H), 8.36 (s, 1H), 8.21 (dd, *J* = 13.9, 7.6 Hz, 2H), 8.12 (m, 2H), 8.04 (t, *J* = 8.4 Hz, 2H), 7.69 (m, 2H), 7.46 (m, 3H), 6.55 (s, 1H), 3.61 (s, 6H).

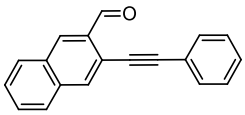
^{13}C NMR (126 MHz, CD_2Cl_2) δ 133.5, 132.1, 132.0, 131.9, 131.5, 129.8, 129.3, 129.2, 129.1, 128.5, 128.0, 127.3, 127.1, 126.7, 126.2, 126.1, 125.8, 124.9, 123.7, 121.3, 108.0, 94.8, 88.6, 56.6.

HRMS (ESI+) *m/z* calculatedfor $[M+Na]^+$ $C_{27}H_{21}NaO_2$ is 399.1356, found: 399.1372.

General Procedure H for the Acetal Deprotection

A solution of the acetal (0.7 mmol, 1 equiv) in THF (0.42 M) and HCl 1 M (0.42 M) was stirred at 50 °C for 3 hours. The reaction mixture was then cooled to 22ºC and diluted with EtOAc. The product was extracted with EtOAc and the combined organic layers were washed with water, dried (Na_2SO_4)

and concentrated under pressure. Purification by column chromatography (cyclohexane/EtOAc95:5) afforded the desired aldehydes **67**, **68**, **72**, **73** and **76**.



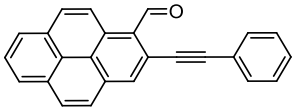
3-(Phenylethynyl)-2-naphthaldehyde (67). The title compound was obtained as a white solid (211 mg, 0.83 mmol, 61% yield) following general procedure (H) on 1.36 mmol scale.

Melting point = 102–104 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.60 (m, 4H), 7.40 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 135.6, 133.6, 132.4, 132.1, 131.8, 130.2, 129.9, 129.6, 129.0, 128.7, 127.9, 127.8, 122.7, 121.2, 95.5, 85.7.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{19}H_{12}NaO$ is 279.0780, found: 279.0782.



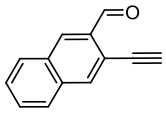
2-(Phenylethynyl)pyrene-1-carbaldehyde (72). The title compound was obtained as a yellow solid (163 mg, 0.49 mmol, 92% yield) following the general procedure (H) on a 0.53 mmol scale.

Melting point = 197–199 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H), 9.60 (d, *J* = 9.4 Hz, 1H), 8.37 (s, 1H), 8.31 – 8.25 (m, 3H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.07 (t, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 2H), 7.46 – 7.40 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 134.9, 131.9, 131.6, 131.2, 131.2, 130.8, 130.6, 129.4, 129.2, 128.7, 127.4, 127.1, 127.0, 126.9, 126.8, 126.7, 124.4, 124.3, 123.8, 122.7, 97.4, 86.7.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{25}H_{14}NaO$ is 353.0937, found: 353.0938.



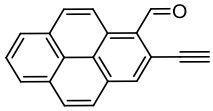
3-ethynyl-2-naphthaldehyde (68).The title compound was obtained as a white solid (151 mg, 0.84 mmol, 46% yield) after two steps (TIPS deprotection following General procedure (G) and acetal deprotection following General procedure (H) on a 1.83 mmol scale.

Melting point = 133–135 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.44 (s, 1H), 8.11 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.53 (m, 2H), 3.47 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 135.4, 134.7, 132.6, 132.3, 130.1, 130.0, 129.7, 128.2, 127.8, 119.8, 83.4, 80.0.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{13}H_8NaO$ is 203.0467, found: 203.0470.



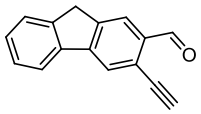
2-Ethynylpyrene-1-carbaldehyde (73). The title compound was obtained as a yellow solid (50 mg, 0.20 mmol, 42% yield) after two steps (TIPS deprotection following General Procedure (G) and acetal deprotection following General Procedure (H) on a 0.47 mmol scale.

Melting point = 177–179 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.23 (s, 1H), 9.53 (d, *J* = 9.4 Hz, 1H), 8.30 (s, 1H), 8.26 (dd, *J* = 6.8, 2.9 Hz, 3H), 8.18 (d, *J* = 8.9 Hz, 1H), 8.10 – 8.04 (m, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 3.64 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 134.8, 131.7, 131.3, 131.2, 130.7, 130.7, 130.0, 127.6, 127.5, 127.2, 126.6, 125.4, 124.6, 124.2, 123.7, 85.2, 80.9.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{19}H_{10}NaO$ is 277.0624, found: 277.0634.



3-Ethynyl-9*H*-fluorene-2-carbaldehyde (76). The title compound was obtained as a white solid (79 mg, 0.44 mmol, 41% yield) after two steps (TIPS deprotection following General procedure (G) and acetal deprotection following General procedure (H) on a 1.08 mmol scale.

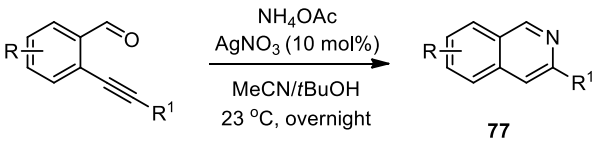
Melting point = 180–182 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.09 (d, *J* = 0.6 Hz, 1H), 7.97 (s, 1H), 7.85 – 7.82 (m, 1H), 7.60 – 7.57 (m, 1H), 7.45 – 7.40 (m, 2H), 3.96 (s, 2H), 3.47 (s, 1H).

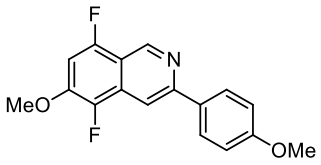
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 147.4, 144.8, 144.3, 139.6, 135.2, 129.0, 127.5, 125.5, 125.0, 125.0, 123.8, 121.4, 83.7, 80.0, 37.1.

HRMS (ESI+) *m/z* calculated for $[M+Na]^+$ $C_{16}H_{10}NaO$ is 241.0624, found: 241.0623.

General Procedure I for the Synthesis of Isoquinolines:



To a solution of aldehyde (0.16 mmol, 1 equiv) and ammonium acetate (24 mg, 0.31 mmol, 2 equiv) in *t*BuOH/MeCN (1:1, 2 mL) at 22 °C, was added silver nitrate (2.6 mg, 0.016 mmol, 10 mol%). The reaction was stirred overnight, then it was poured in water (10mL) and extracted with EtOAc (3 × 10 mL). The collected organic phases were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Cyclohexane/EtOAc 5:1).



5,8-Difluoro-6-methoxy-3-(4-methoxyphenyl)isoquinoline (77a)

Title compound was obtained as white solid (42 mg, 0.14 mmol, 90% yield) following the general procedure (I) on 0.16 mmol scale.

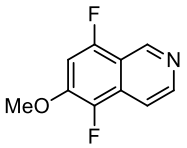
Melting point = 154–156 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (t, *J* = 1.3 Hz, 1H), 8.12 – 8.05 (m, 3H), 7.06 – 7.00 (m, 2H), 6.99 (dd, *J* = 11.0, 6.3 Hz, 1H), 4.04 (s, 2H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8, 156.0 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 253.8, 3.4 Hz), 152.5, 146.5 (C–F, dd(a-t), J_{CF}= 10.3 Hz), 145.9 (t, *J* = 2.7 Hz), 141.9 (C–F, dd, $^{1}J_{CF}$, $^{4}J_{CF}$= 245.0, 4.5 Hz), 131.7, 128.6, 128.2 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$= 16.0, 5.2 Hz), 114.4, 112.6 (C–F, dd(a-t),J_{CF}= 17.5, 3.9 Hz), 106.7 (t, *J* = 3.1 Hz), 100.7 (C–F, d,J_{CF}= 24.6 Hz), 57.6, 55.5.

^{19}F NMR (471 MHz, $CDCl_3$) δ –125.08 (d, *J* = 19.8 Hz), –152.99 (d, *J* = 20.5 Hz).

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{17}H_{14}F_2NO_2$ is 302.0987, found: 302.0990.



5,8-Difluoro-6-methoxyisoquinoline (77b)

The title compound was obtained as white solid (35 mg, 0.18 mmol, 78% yield) following the general procedure (I) on 0.23 mmol scale.

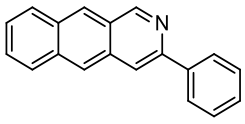
Melting point = 113–115 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (t, *J* = 1.3 Hz, 1H), 8.54 (d, *J* = 6.0 Hz, 1H), 7.75 (ddd, *J* = 6.0, 1.7, 1.1 Hz, 1H), 7.06 (dd, *J* = 11.0, 6.3 Hz, 1H), 4.04 (d, *J* = 0.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7 (C–F, d, $^{1}J_{CF}$, $^{4}J_{CF}$= 254.1, 3.5 Hz), 146.5 (C–F, dd(a-t),J_{CF}= 10.2 Hz), 146.0 (C–F, dd, $^{3}J_{CF}$, $^{4}J_{CF}$= 3.7, 2.1 Hz), 144.32 (C–F, d, J_{CF}= 2.8 Hz), 141.51 (C–F, d, $^{1}J_{CF}$, $^{4}J_{CF}$= 245.5, 4.7 Hz), 127.04 (C–F, dd, $^{2}J_{CF}$, $^{3}J_{CF}$= 16.8, 5.2 Hz), 113.8 (dd, *J* = 17.3, 3.9 Hz), 112.3 (C–F, dd(a-t),J_{CF} = 3.1 Hz), 101.6 (C–F, d,J_{CF}= 25.2 Hz), 57.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ–124.62 (d, *J* = 19.9 Hz), –152.37 (d, *J* = 19.8 Hz).

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{10}H_8F_2NO$ is 196.0568, found: 196.0561.



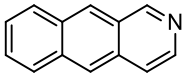
3-Phenylbenzo[g]isoquinoline (77c). The title compound was obtained as brown solid (24 mg, 0.1 mmol, 48% yield) following the general procedure (I) on 0.20 mmol scale.

Melting point = 205–207 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (m, 1H), 8.61 (d, *J* = 7.0 Hz, 1H), 8.43 (s, 1H), 8.20 (m, 3H), 8.06 (ddd, *J* = 19.3, 8.4, 0.6 Hz, 2H), 7.55 (m, 4H), 7.43 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 149.0, 139.6, 134.8, 133.0, 132.4, 129.1, 129.0, 128.6, 128.3, 127.8, 127.7, 127.1, 126.2, 126.1, 125.4, 115.9.

HRMS (ESI+) *m/z* calculated for $[M]^+$ $C_{19}H_{14}N$ is 256.1121, found: 256.1122.



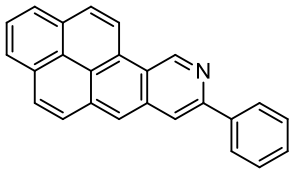
Benzo[g]isoquinoline (77d). The title compound was obtained as ayellow solid (30 mg, 0.17 mmol, 60% yield) following the general procedure (I) on 0.28 mmol scale.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.58 (s, 1H), 8.43 (d, *J* = 6.1 Hz, 1H), 8.37 (s, 1H), 8.05 (dd, *J* = 21.2, 8.5 Hz, 2H), 7.76 (d, *J* = 6.1 Hz, 1H), 7.55 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 140.7, 134, 132.4, 132.1, 129.0, 128.3, 127.8, 127.6, 126.9, 126.2, 125.0, 120.2.

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{13}H_{10}N$ is 180.0808, found: 180.0802.

The spectral data are in accordance with the ones reported in the literature.[44]



8-Phenylphenaleno[1,9-gh]isoquinoline (77e). The title compound was obtained as brown solid (25 mg, 0.07 mmol, 49%) following the general procedure (I) on a 0.15 mmol scale.

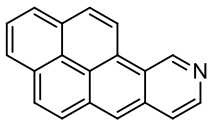
Melting point = 208–210 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.97 (d, *J* = 9.1 Hz, 1H), 8.23 (ddd, *J* = 17.5, 14.0, 8.5 Hz, 6H), 8.06 (d, *J* = 7.3 Hz, 1H), 7.94 (dd, *J* = 16.4, 8.6 Hz, 2H), 7.86 (d, *J* = 9.1 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 134.6, 133.7, 131.2, 131.1, 130.0, 129.2, 128.9, 127.8, 127.7, 127.3, 126.8, 126.6, 126.2, 124.8, 124.0, 122.7, 121.3, 121.0, 117.0.

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{25}H_{16}N$ is 330.1277, found: 330.1276.

44 Crump, S. L.; Netka, J.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 2746–2750.



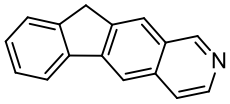
Phenaleno[1,9-gh]isoquinoline (77f).

Title compound was obtained as black solid (25 mg, 0.1 mmol, 50% yield) following the general procedure (I) at 80 ºC on 0.20 mmol scale.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 9.04 (d, *J* = 9.1 Hz, 1H), 8.77 (d, *J* = 5.7 Hz, 1H), 8.34 (m, 2H), 8.27 (d, *J* = 7.7 Hz, 1H), 8.14 (d, *J* = 7.0 Hz, 1H), 7.99 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 142.6, 133.7, 133.5, 131.2, 131.0, 130.0, 129.0, 127.7, 127.6, 126.7, 126.6, 126.1, 124.7, 124.0, 122.4, 122.3, 120.9, 120.9.

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{19}H_{12}N$ is 254.0964, found: 254.0959.



10*H*-Indeno[1,2-g]isoquinoline (77g).

Title compound was obtained as an off-white solid (30 mg, 0.14 mmol, 60% yield) following the general procedure (I) on 0.23 mmol scale.

Melting point = 184–186 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.50 (d, *J* = 5.8 Hz, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.94 (dd, *J* = 6.5, 1.8 Hz, 1H), 7.70 (d, *J* = 5.8 Hz, 1H), 7.59 (ddd, *J* = 5.5, 1.7, 0.7 Hz, 1H), 7.43 (pd, *J* = 7.0, 3.7 Hz, 2H), 4.08 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 144.8, 144.4, 142.8, 142.6, 140.2, 135.7, 128.8, 128.3, 127.4, 125.6, 123.2, 121.4, 120.8, 116.2, 36.6.

HRMS (ESI+) *m/z* calculated for $[M+H]^+$ $C_{16}H_{12}N$ is 218.0964, found: 218.0956.

Crystallographic Data (CCDC 2050996)

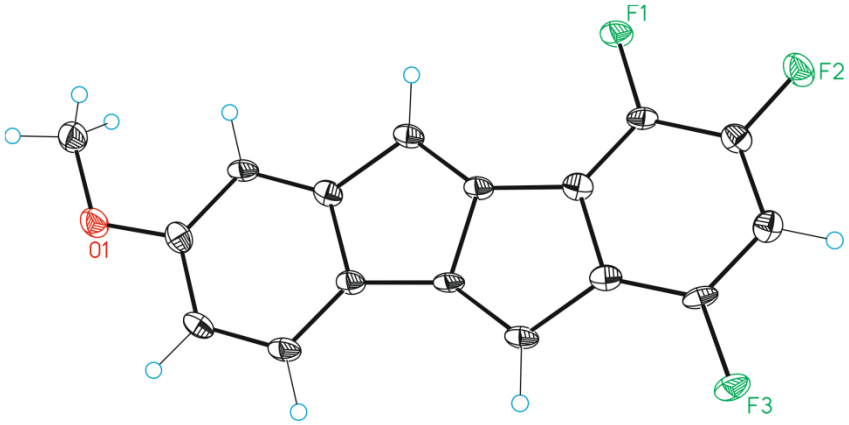


Table S1. Crystal data and structure refinement for **55d**. The structure was deposited in the Cambridge crystallographic data center (CCDC), with the code 2050996.

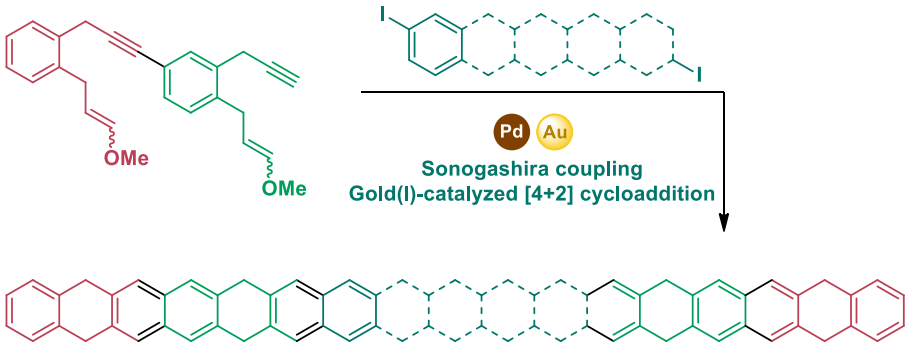
Identification code	ETK361P1	
Empirical formula	C17 H9 F3 O	
Formula weight	286.24	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 6.1433(4)Å	a= 90°.
	b = 24.4095(19)Å	b = 92.144(6)°.
	c = 7.9266(5)Å	g = 90°.
Volume	1187.80(14) $Å^3$	
Z	4	
Density (calculated)	1.601 Mg/m^3	
Absorption coefficient	0.131 mm^{-1}	
F(000)	584	
Crystal size	0.100 x 0.050 x 0.010 mm^3	
Theta range for data collection	2.703 to 32.122°.	
Index ranges	-8<=h<=9,-36<=k<=36,-11<=l<=10	
Reflections collected	17108	
Independent reflections	3902[R(int) = 0.0575]	
Completeness to theta =32.122°	93.6%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.55	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3902/ 0/ 191
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0720, wR2 = 0.1951
R indices (all data)	R1 = 0.0987, wR2 = 0.2140
Largest diff. peak and hole	0.725 and -0.705 e.$Å^{-3}$

GENERAL CONCLUSIONS

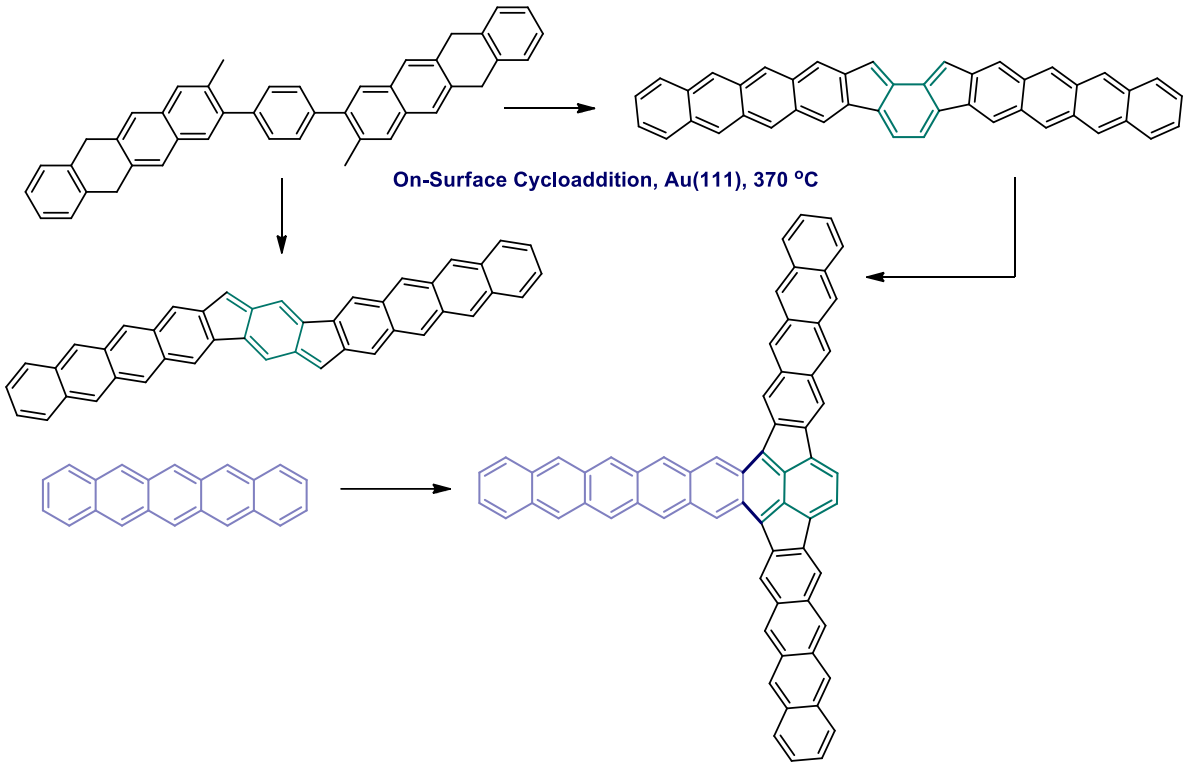
In this Doctoral Thesis, novel strategies were designed for the synthesis of polycyclic aromatic hydrocarbons. Thus, the main achievements of this work are the following:

A new iterative synthesis was elaborated for the synthesis of higher unsubstituted hydroacenes, based on our previously developed gold(I)-catalyzed formal [4+2] cycloaddition of aryl-tethered 1,7-tetraenynes, and enabled the formation of unprecedented hydroacenes, such as tridecacene-H8 and higher analogues. The Au(111) surface-assisted dehydrogenation of the former precursor gives rise to tridecacene, the longest acene known until now.



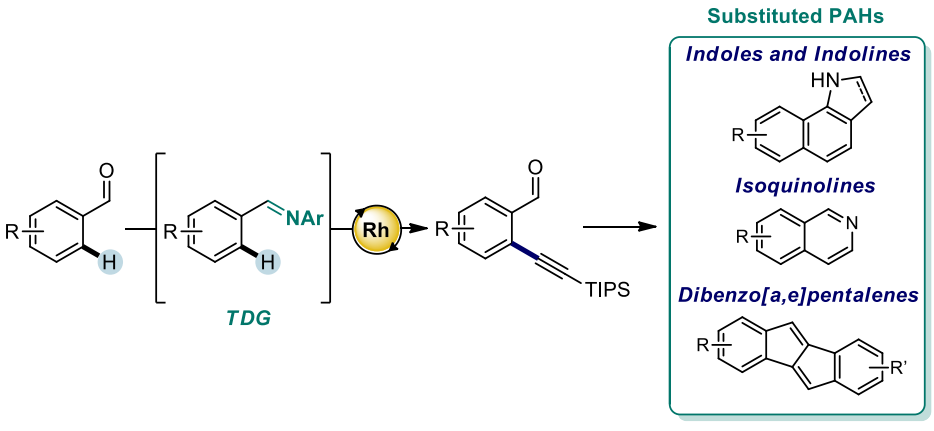
Scheme 1. General synthesis of higher hydroacenes, starting from tridecacene-H8

The precursors of acene derivatives belonging to other categories, such as indacenes or cyclobutadiene-containing acenes have been obtained by applying our gold(I)-catalyzed formal [4+2] cycloaddition to newly developed 1,7-enynes. The surface-assisted formation of the parent acenes has already been investigated or is currently ongoing. Thus, 1,4-bis(3-methyl-6,11-dihydrotetracen-2-yl)benzene was employed as a precursor of *s*-indaceno[1,2-*b*:5,6-*b*']ditetracene and *as*-indaceno[2,3-*b*:6,7-*b*']ditetracene, obtained through cycloaddition on a Au(111) surface. The latter indacene derivative was found to undergo an outstanding intermolecular cycloaddition, rendering T-shaped molecules. The reaction was also successful when pentacene and octacene were employed as dienophiles. Furthermore, 3,3'-dibromo-6,6',11,11'-tetrahydro-2,2'-bitetracene was prepared as the precursor of 5,10,15,20-tetrahydrocyclobuta[1,2-*b*:3,4-*b*']ditetracene, whose surface-assisted acquisition is already ongoing. Finally, a doubly substituted 1,7-enyne synthon has been prepared and was employed in the synthesis of a new precursor of heptacene. The preparation of heptacenes-H4 tetrasubstituted with halide moieties will be explored using the new enyne for the surface-assisted synthesis of heptacene-cyclobutadiene hybrid ribbons.



Scheme 2. On-surface synthesis and intermolecular cycloadditions of indacenoditetracenes

Finally, the Rh(III)-catalyzed *ortho* C–H alkynylation of aromatic aldehydes was investigated in order to obtain new versatile building blocks for the synthesis of polyarenes. Enabled by the formation of an imine as transient directing group, this transformation provided a wide variety of mono- and di-alkynylated products. The acquired ynals were then successfully applied for the preparation of substituted dibenzopentalenes, isoquinolines, indoles and indolines.



Scheme 3. Rh(III)-catalyzed *ortho* C–H alkynylation of aromatic aldehydes and its application to dibenzopentalenes, isoquinolines, indoles and indolines

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