GOLD(I) CAVITANDS FOR THE ASSEMBLY OF MOLECULAR COMPLEXITY

Inmaculada Martin Torres

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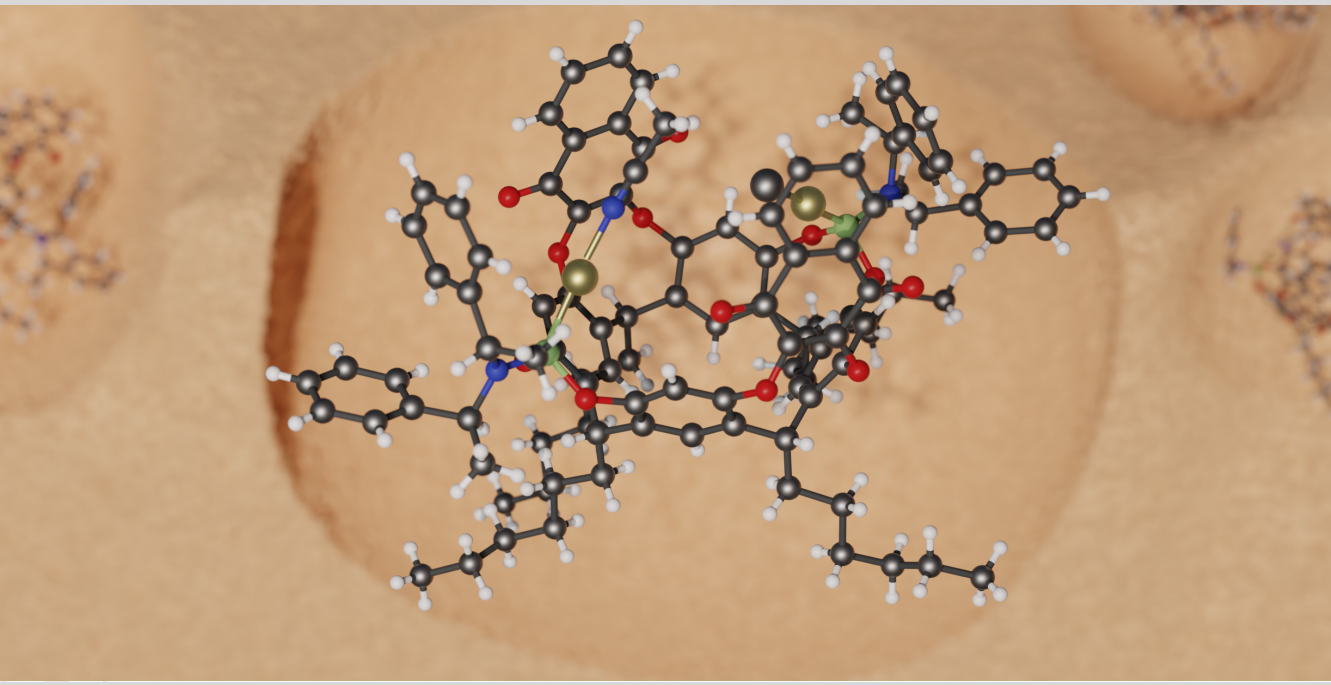

DOCTORAL THESIS
2022

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DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institute of Chemical Research of Catalonia (ICIQ)

UNIVERSITAT ROVIRA i VIRGILI

Tarragona 2022

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I STATE that the present study, entitled "*Gold(I) Cavitands for the Assembly of Molecular Complexity*", presented by Inmaculada Martín Torres for the award of the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, March 11th, 2022

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren Pablos

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A mis padres y mi hermano

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"Caminante, no hay camino, se hace camino al andar"
Antonio Machado

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Acknowledgements

Me gustaría empezar agradeciéndole a mi director de Tesis, Prof. Antonio M. Echavarren, por haberme dado la oportunidad de poder formar parte de su excelente grupo de investigación. Gracias por darme todos los consejos que he necesitado para ir superando cada etapa de este aprendizaje, por apoyarme y confiar en mi desde el principio, ya que esto me ha ayudado a crecer no solo como profesional, sino también como persona. Gracias por motivarme e inspirarme a ser una mejor científica cada día, espero estar siempre a la altura de tus expectativas.

Por otro lado, me gustaría agradecerles a Sònia Gavaldà y la Dra. Imma Escofet todo el trabajo y ayuda que nos facilitan, porque sin vosotras todo esto no sería posible. Agradecerles también todo el apoyo y cariño que me han brindado siempre que lo he necesitado.

I would like to express my gratitude to Prof. John F. Hartwig for giving me the opportunity to join his research group in the University of California, Berkeley. Thanks for making me feel like a member of the group, for your chemistry discussions and your attention during these four months. Also, thanks to all the members of his group, especially Dr. Masha Elkin, Brandon Bloomer and Christina Pierson.

I would also like to thank the research support units at ICIQ for their support and professionality: Nuclear Magnetic Resonance, X-Ray Diffraction, High Resolution Mass Spectrometry, HTE, CHROMTAE and CRTU.

I want to thank all the past and present members of the Echavarren group for the moments we shared, for helping and supporting me and, of course, for the useful chemistry discussions that helped me during this period. I want to start with the people whom I have had the pleasure of collaborating: Dr. Mauro Mato, Gala Ogalla, Dr. Franco Della Felice, Dr. Antonia Rinaldi, Federica Cester, Dr. Jin-Ming Yang and Dr. Allegra Franchino.

Me gustaría agradecer a las personas con las que he podido compartir esta experiencia y a las que sin lugar a duda se han convertido en mi familia en Tarragona: Dra. Otilia Stoica, por ser una de las personas más especiales que he conocido, gracias por aconsejarme y ayudarme a superar cada día de esta experiencia, pero sobretodo agradecerte tu infinito apoyo como amiga, Dr. Mauro Mato, por ser siempre el rayo de luz que me ha inspirado y apoyado durante este periodo. Estoy segura de que siempre crearemos cristales que nos recordaran a cada momento compartido. Gala Ogalla, porque empezamos un proyecto como unas desconocidas y terminamos volviéndonos inseparables, gracias por ser como eres y apoyarme siempre, Dra. Cristina García, por ser para mi un ejemplo a seguir tanto profesional como personalmente, por enseñarme a superarme cada día y confiar en mí, Dra. Helena Armengol and Dra. Margherita Zanini por aparecer en la puerta de mi vida, no solo por ser compañeras sino también amigas con las que he podido contar siempre, gracias por comprenderme, ayudarme y enseñarme tanto cada día. Sin vosotras todo hubiera sido diferente, siempre estaré agradecida de haberos conocido. Dr. Giuseppe Zuccarello, por llamarme “Tiny Inma”, por todos los momentos compartidos, pero sobretodo me gustaría darte las gracias por enseñarme tanto durante estos años, te admiro muchísimo, Dra. Imma Escofet, por compartir esta etapa contigo, porque eres una persona admirable y luchadora, mil gracias por hacer que todo sea más fácil, Dr. Joan Guillem Mayans, por cada abrazo que he necesitado, Dr. Franco Della Felice, por toda tu ayuda y apoyo en estos últimos meses, a mis chicas del Lab2.3, Gala Ogalla, Ana

Arroyo, Alba Helena Pérez, Dra. Anna Sadurní, Tania Medina y Federica Cester, por todos los momentos que hemos vivido juntas, por apoyarme y ayudarme sobretodo en este último periodo, sois increíbles, Dr. Ángel Luís Mudarra, Dr. Leonardo Nannini, Dra. Pilar Calleja, Dra. Ruth Dorel, Dra. Bruna Sánchez, Dr. David Nieto y Miquel Purrà, por plasmar mi pequeña idea en esta gran portada. Porque gracias a vosotros todo ha sido más fácil y esta aventura se ha convertido en una de las mejores de mi vida.

I also want to thank Dr. Marc Montesinos, Dr. Ulysse Caniparoli, Dr. Dagmar Scharnagel, Dr. Rémi Blieck, Dr. Xiang Yin, Dr. Sofía Ferrer, Dr. Elena M. de Orbe, Dr. Eric Tan, Àlex Martí, Andrea Cataffo, Pablo Mora, Eduardo García, Isabel Arranz, Yufei Wang, Arnau Rodríguez, Xiaoqing Shao, Laura Lerena, for the moments we have shared.

Me gustaría dar las gracias a Ana Carbajo por cada uno de los momentos que hemos vivido desde que nos conocimos en Madrid, porque desde entonces te has convertido en una persona imprescindible para mi. Gracias por apoyarme y estar siempre ahí, aunque estemos lejos, siempre me haces sentir que estamos juntas en todo.

También quiero darle las gracias a Dani Sánchez, a quien admiro muchísimo por su forma de vivir la vida y luchar por todo lo que se propone. Por su apoyo absoluto, por comprenderme, por estar ahí en los días buenos y en los no tan buenos, por ser el mejor compañero de vida, gracias por todo, te quiero.

Quiero extender mis agradecimientos a toda mi familia porque no podría formar parte de una mejor, por ser únicos y siempre estar ahí cuando os necesito, no podría estar más agradecida de ello. También me gustaría agradecerles a mis amigas, todo lo que hacen por mi, por escucharme, apoyarme y ayudarme siempre.

Por último, me gustaría darles las gracias a las personas más importantes de mi vida. Gracias a mis padres, Francisco y Juana María, por habernos dado la mejor educación posible, por enseñarnos el valor del trabajo, del esfuerzo y de la constancia, pero sobretodo por siempre estar ahí cuando os necesitamos y por vuestro apoyo incondicional. Por otro lado, agradecer a mi hermano, Emilio, el acompañarme en cada etapa desde que éramos pequeños, por hacerme siempre sonreír y por demostrarme su apoyo y cariño en todo momento. Os quiero.

This work was carried out with the support of the Ministerio de Ciencia e Innovación (projects CTQ2016-75960-P and PID2019-104815GB-I00, and FPI predoctoral fellowship (BES-2017-080447) to I. M.-T from 2018 to 2022), the Severo Ochoa Excellence Accreditation 2020-2023 (CEX2019-000925-S), the European Research Council (Advanced Grants No. 321066 and 835080), the AGAUR (2017 SGR 1257), the CERCA Program/Generalitat de Catalunya and the ICIQ foundation for financial support.

At the time of writing this Doctoral Thesis, part of the results was reported in the following publications:

"Enantioselective Alkoxycyclization of 1,6-Enynes with Gold(I)-Cavitands: Total Synthesis of Mafaicheenamine C"
Martín-Torres, I.; Ogalla, G.; Yang, J.-M.; Rinaldi, A.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 9339–9344.

"Cyclopropane–Alkene Metathesis by Gold(I)-Catalyzed Decarbenation of Persistent Cyclopropanes"
Martín-Torres, I.;[+] Mato, M.;[+] Herlé, B.; Echavarren, A. M. *Org. Biomol. Chem.* **2019**, *17*, 4341–4345; ([+]: equal contribution).

"Decarboxylative Csp^3–N Bond Formation by Electrochemical Oxidation of Amino Acids"
Shao, X.; Zheng, Y.; Tian, L.; Martín-Torres, I.; Echavarren, A. M.; Wang, Y. *Org. Lett.* **2019**, *21*, 9262–9267.

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Table of Contents

Prologue

The manuscript of this Doctoral Thesis has been divided into four main parts: a general introduction on gold(I) catalysis and three research chapters, which are preceded by the abstract and general objectives, and followed by the overall conclusions. Each chapter contains five sections, including a specific introduction of the topic of the chapter, the objectives, the discussion of the obtained results, the conclusions and, finally, the experimental section. The numbering of compounds, schemes, figures, tables and references is organized by chapters.

The **General Introduction** describes the principles of homogeneous gold(I) catalysis, including the cycloisomerization of enynes and focuses on enantioselective transformations catalyzed by gold(I).

Chapter I, *'Gold(I)-Cavitand Complexes for the Enantioselective Alkoxycylization of 1,6-Enynes'*, covers the design of achiral and chiral gold(I)-cavitand complexes from resorcin[4]arene precursors. The new family of catalysts enabled the discovery of new selectivities in the cycloisomerization of 1,6-dienynes. Moreover, the potential of the chiral gold(I) cavitands was explored in the context of the alkoxycyclization of 1,6-enynes. Additionally, the new cavitand complexes were applied in the total synthesis of (+)-mafaicheenamine C, and its enantiomer. Finally, DFT calculations were performed to investigate the stereochemical outcome of the enantioselective alkoxycyclization and were found to support the experimental data. Part of the research discussed in this chapter was conducted in collaboration with Gala Ogalla, Dr. Jin-Ming Yang and Dr. Antonia Rinaldi. Part of the results obtained in this project was published in *Angew. Chem. Int. Ed.* **2021**, *60*, 9339–9344.

Chapter II, *'Gold(I)-Catalyzed Decarbenation of Persistent Cyclopropanes'* discloses the development of new carbene precursors and their application in the synthesis of aryl cyclopropanes through a gold(I)-catalyzed decarbenation reaction. The work presented in this chapter was carried out in collaboration with Dr. Mauro Mato and Dr. Bart Herlé. This work has been published in *Org. Biomol. Chem.* **2019**, *17*, 4216–4219.

Chapter III, *'Gold(I)-Catalyzed Polyenyne Cyclization for the Construction of Decalin Cores of Natural Products'*, presents the development of a new strategy for the construction of decalins, as constituent parts of natural products, by gold(I)-catalyzed polyenyne cyclization of tetrasubstituted silyl enol ethers. In addition to that, several methods for the preparation of the latter compounds are discussed. Part of this work was performed in collaboration with Dr. Franco Della Felice. The results presented in this chapter have not been published yet.

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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 for authors"* published in the *Journal of Organic Chemistry*.
Additional abbreviations and acronyms are listed below:

APCI	Atmospheric Pressure Chemical Ionization
AllylOH	Allyl alcohol
BAr_4^{F-}	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
DEAD	Diethyl azodicarboxylate
DIPEA	Di-*iso*-propyl ethyl amine
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin Periodinane
dr	Diastereomeric ratio
EDA	Ethyl diazoacetate
ee	Enantiomeric excess
er	Enantiomeric ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray Ionization
HRMS	High Resolution Mass Spectrometry
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
MALDI	Matrix Assisted Laser Desorption Ionization
n/d	not detected
NTf_2^-	Bis(trifluoromethyl)imidate
OTf^-	Trifluoromethanesulfonate
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethyl ethylenediamine
L	Ligand
MW	Microwave irradiation
TS	Transition State

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Abstract

Gold(I)-catalyzed transformations have been studied in detail by our research group as powerful methods for the assembly of complex molecular frameworks. In this context, this Doctoral Thesis covers three topics related to homogeneous gold(I) catalysis.

The synthesis and applications of cavitand complexes was first explored. Therefore, new families of both achiral and chiral gold(I)-cavitand complexes was designed and prepared from resorcin[4]arene precursors. These compounds were applied in the cycloisomerization of 1,6-dienynes and led to uncovering new selectivities. Furthermore, the chiral gold(I) cavitands were investigated in the enantioselective alkoxycyclization of 1,6-enynes, enabling the formation of 1-methylene-2,3-dihydro-1*H*-indene products, which could be converted into chiral indanones. Based on this approach, the total syntheses of (+)-mafaicheenamine C and its enantiomer were accomplished. Finally, DFT calculations were performed to support the outcome of the enantioselective alkoxycyclization.

The gold(I)-catalyzed decarbenation reaction of persistent cyclopropanes was then examined. Thus, new carbene precursors were developed and involved in the latter reaction, whose driving force is the release of aromatic units. This transformation relies on the use of benzo-fused norcaradienes, as a safer alternative for the generation of carbenes. Following this methodology, various cyclopropanes were obtained after decarbenation of cyclopropyl dihydronaphthalene or dihydrophenanthrene precursors.

Finally, the ability of gold(I) complexes to construct polycyclic architectures was demonstrated by devising a novel approach for the synthesis of decalins by the polyenyne cyclization of tetrasubstituted silyl enol ethers. The synthesis of these silyl enol ethers was attempted through various strategies. The acquired decalins are key intermediates in the synthesis of the natural products avarol and avarone.

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General Objectives

The main objective of this Doctoral Thesis was the development of novel synthetic strategies for the construction of molecular complexity, based on gold(I)-catalyzed processes. Specifically, our aims included:

- The design and preparation of chiral gold(I)-cavitand complexes and their application in the enantioselective alkoxycyclization of 1,6-enynes.
- The synthesis of new carbene precursors and their application in the synthesis of aryl cyclopropanes through gold(I)-catalyzed decarbenation reactions.
- The development of a new strategy to gain access to the decalin core of avarol, avarone and related natural products based on the gold(I)-catalyzed cyclization of tetrasubstituted silyl enol ethers.

Each chapter of this PhD Thesis manuscript provides a more detailed description of the corresponding objectives.

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General Introduction

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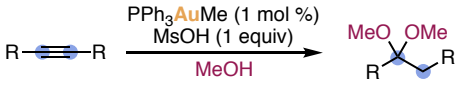
Homogeneous Gold(I) Catalysis

Origin of Gold Chemistry

Gold is a precious metal with exceptional properties, such as low reactivity and increased ductility and malleability. The inertness of gold[1] led scientists to overlook its ability to catalyze reactions and the first accounts of its activity in heterogeneous catalysis were only published during the 70's.[2] Nevertheless, the first example of homogeneous gold catalysis was not described until 1998, when Teles *et al.* reported the gold(I)-catalyzed addition of alcohols to alkynes to form acetals under mild conditions (Scheme 1).[3] Likewise, the group of Tanaka used the same catalytic system for the hydration of alkynes and both reactions provided Markovnikov-type products.[4] These pioneering discoveries opened the way for the development of homogeneous gold catalysis as a field.



Scheme 1. First gold(I)-catalyzed reaction reported by Teles.

Due to the unique ability of gold complexes to perform selective activation of unsaturated bonds, homogeneous gold catalysis has become a reliable and versatile approach for the formation of carbon–carbon and carbon–heteroatom bonds and it is widely employed in the construction of complex molecular architectures.[5]

Relativistic Effects and Generalities of Gold(I) Catalysis

The facility of gold complexes to activate π-bonds has been attributed to relativistic effects,[6] which increase proportionally with the atomic number and are related to the acceleration of electrons that orbit around a heavy nucleus. Accordingly, as the atomic number increases, the electrons situated closest to the nucleus accelerate. As a result, the mass of the electrons also

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3 Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.

4 Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565.

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6 (a) Pyykkö, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3573–3578. (b) Schwartz, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4442–4454. (c) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412–4456. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

increases, leading to their energetic stabilization and the contraction of the *s* and *p* orbitals, whose electrons experience a stronger nuclear attraction. Subsequently, the *d* and *f* orbitals are expanded and destabilized, as their electrons suffer a weaker nuclear attraction. This contraction/expansion effect is much more significant for heavy metals that have their 4*f* and 5*d* orbitals filled, reaching a maximum in gold. Thus, the contraction of the 6*s* orbital induces a considerable expansion of the 5*d* orbital, minimizing the electron–electron repulsion. This allows the interaction between the filled 5*d* orbital of gold with the filled π orbitals of unsaturated bonds, attracting the electron density towards gold and activating these π-bonds towards nucleophilic attack due to their enhanced electrophilicity.

The relativistic contraction also justifies the unique properties of gold, such as its superior Lewis acidity, highest electronegativity among transition metals (χ 2.4) and resistance to undergo oxidation, along with its 'aurophilicity', which means the tendency to form relatively strong Au–Au interactions. Moreover, due to this contraction, the *s*/*p* or *s*/*d* hybridizations are very efficient and explain the structural preference of gold(I) to adopt a linear dicoordination geometry.[7] On that account, gold(I) linear complexes do not suffer *β*-hydride elimination or spontaneous oxidative addition,[8] the latter allowing the reactions to be conducted under air, and not under inert atmospheric conditions, or in the presence of aryl (pseudo)halides.[9]

Another consequence of the relativistic effects is the contraction and strengthening of the Au–L (ligand) bond. Thus, the properties and the reactivity of gold complexes, and thus the outcome of chemical reactions catalyzed by these compounds can be modulated by tuning the steric and electronic properties of the ligand.[10] In general, complexes bearing highly donating *N*-heterocyclic carbenes as ancillary ligand are less electrophilic, whereas less donating phosphite ligands give rise to highly electrophilic catalysts (Figure 1). Besides, gold(I) complexes with bulky phosphine ligands, such as dialkyl biarylphosphines, exhibit

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

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intermediate electrophilicity and proved to be the most convenient in many catalytic reactions.[11]

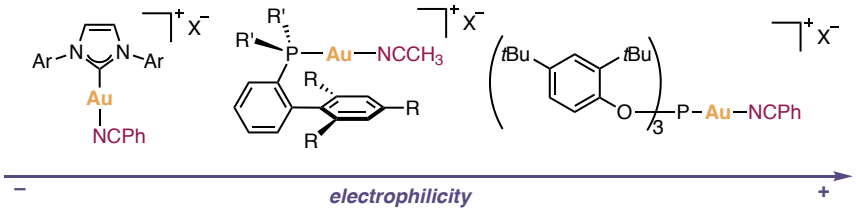

Figure 1. Electrophilicity increased by ancillary ligand modification of gold(I) complexes.

Neutral gold(I) chloride complexes [LAuCl] are prepared by direct treatment of the ligand with commercially available (dimethylsulfide)gold(I) chloride ($Me_2S{\cdot}AuCl$) (Scheme 2). Complexes [LAuCl] are used as precatalysts that require activation through chloride abstraction to enable substrate coordination to the gold(I) *via* an associative mechanism.[12] Thus, catalytically active gold(I) species can be generated *in situ* employing chloride scavengers like silver[13] or copper[14] salts. This results on the formation of more reactive cationic species upon release of insoluble AgCl. However, this method can promote side reactions or the formation of less reactive chloride-bridged digold(I) species.[15] Consequently, a more convenient approach is the use of weakly coordinating counteranions like OTf^- or NTf_2^-, or the synthesis of cationic complexes (LL'Au)X in which the gold atom is bound to a weakly coordinating neutral ligand L' (such as acetonitrile or benzonitrile) while X^- is a counterion (SbF_6^-, BF_4^-, PF_6^-). These cationic complexes can be engaged directly in the catalytic cycle through associative ligand exchange with the substrate, avoiding the formation of chloride-bridged species and they also confer increased reactivity and selectivity.

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11 Zuccarello, G.; Zanini, M.; Echavarren, A. M. *Isr. J. Chem.* **2020**, *60*, 360–372.

12 (a) 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. (b) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721–7730. (c) Schmidbaur, H.; Schier, A. *Organometallics* **2010**, 2–23.

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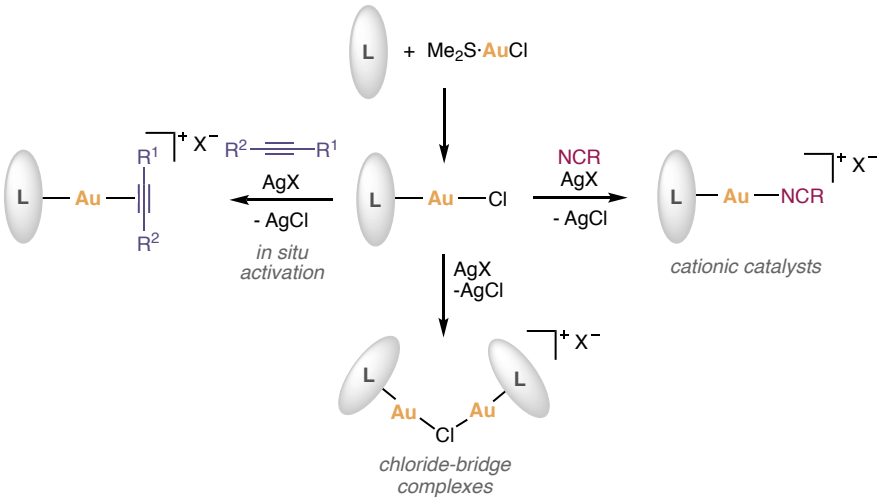
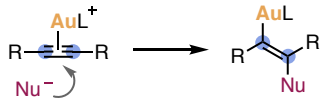


Scheme 2. Strategies for the activation of [LAuCl] complexes.

Cycloisomerizations of Enynes

One of the benchmark reactions in homogeneous gold(I) catalysis is the cycloisomerization of enynes. This versatile type of transformation is highly valuable in organic synthesis, enabling the construction of complex molecules from relatively simple starting materials, forging several C–C or C–heteroatom bons in a single reaction flask.[16]

Due to its alkynophilic character, gold(I) complexes can selectively activate alkynes in complex molecular settings, giving rise to (η^2-alkyne)gold(I) species, which are susceptible to nucleophilic attack. In general, the reaction of (η^2-alkyne)gold(I) complexes with nucleophiles takes place in *anti*-fashion, following a Markovnikov regioselectivity, leading to the *trans*-alkenyl-gold complex depicted in Scheme 3.[17]



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

Gold(I) induces a variety of skeletal rearrangements of 1,*n*-enynes that give rise to diverse cyclic products through complex mechanisms. With respect to 1,6-enynes, (η^2-alkyne)gold(I) complex **I** undergoes intramolecular nucleophilic attack by the alkene moiety, whose addition

16 (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.

17 (a) García-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Pérez-Ramírez, J.; López, N. *ChemPhysChem.* **2008**, *9*, 1624–1629. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, N. W. *Org. Lett.* **2004**, *6*, 4391–4394. (c) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527.

occurs through 5-*exo*-dig or 6-*endo*-dig cyclizations to form the corresponding cyclopropyl gold(I) carbenes **II** and **III** (Scheme 4).[18] Depending on the substitution pattern of the enyne, the gold(I) complex and the reaction conditions, these gold(I) carbene intermediates will further evolve through different pathways.[19]

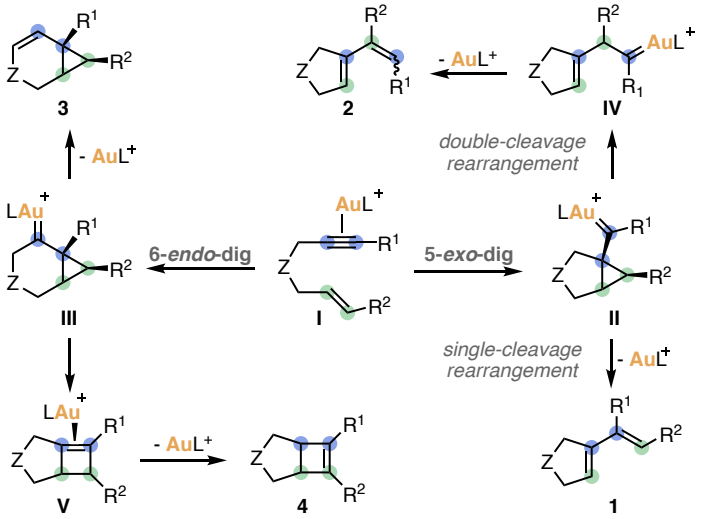
Therefore, the opening of intermediate **II** gives rise to 1,3-dienes of type **1** by 1,3-migration of the alkene terminal carbon to the alkyne terminal carbon, in a process known as single-cleavage rearrangement.[20] Otherwise, the double-cleavage rearrangement of **II**, which involves the formal insertion of the terminal carbon of the alkene between the two carbons of the alkyne, renders gold(I) carbenes **IV**. Subsequent 1,2-*H* shift and protodeauration of **IV** provides substituted dienes **2**.[21] Alternatively, opening of the cyclopropane ring of intermediate **III** gives bicyclo[4.1.0]hept-2-ene derivative **3**, after 1,2-*H* shift and demetalation. By contrast, the ring expansion of **III** leads to the formation of (η^2-cyclobutene)gold(I) complexes of type **V**, which can undergo isomerization to form cyclobutenes **4**.

18 (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. (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) 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.

19 Mattalia, J.-M.; Nava, P. *J. Organomet. Chem.* **2014**, *749*, 335–342.

20 Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, 4217–4223.

21 (a) Ota, K.; Chatani, N. *Chem. Commun*. **2008**, 2906–2907. (b) Ota, K.: Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203–15211.



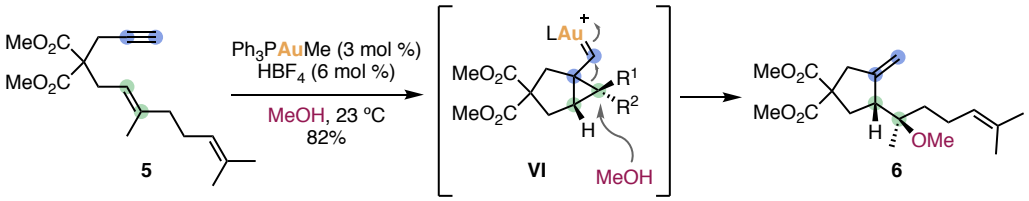
Scheme 4. Main pathways for the gold(I)-catalyzed cycloisomerization of 1,6-enynes.

Apart from the many different rearrangements of enynes, the addition of external nucleophiles further expands the possibilities in the reaction outcome. A wide variety of carbo- and heteronucleophiles have been employed in intra- and intermolecular gold(I)-catalyzed reactions.[22] Among them, oxygen-based nucleophiles have been involved in transformations such as hydroxycyclization and alkoxycyclization.[23]

The gold(I)-catalyzed alkoxycyclization of enynes by addition of alcohol nucleophiles proceeds under milder conditions than with other metal catalysts.[23] This process is stereospecific, affording products of *anti*-addition of the alkyne-gold(I) complex and the heteronucleophile to an alkene following the Markovnikov regiochemistry. For example, cyclic product **6** was obtained by reaction of 1,6-enyne **5** in the presence of methanol (Scheme 5). Regarding its mechanism, the transformation proceeds through opening of the cyclopropyl gold(I) carbene **VI** by nucleophilic attack of the alcohol.

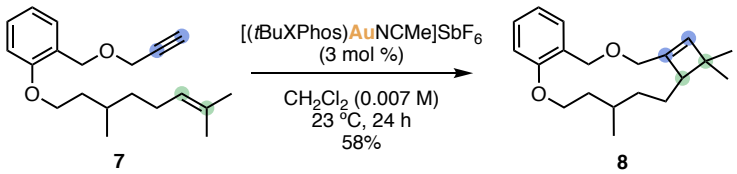
22 (a) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485–3496. (b) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182. (c) Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Rivas Nass, A.; Frey, W. *Chem. Eur. J.* **2006**, *12*, 5376–5382. (d) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006,** *45*, 1105–1109. (e) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181–3184. (f) Quian, J.; Liu, Y.; Cui, J.; Xu, Z. *J. Org. Chem.* **2012**, *77*, 4484–4490.

23 (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.; 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.



Scheme 5. Gold(I)-catalyzed alkoxycyclization of 1,6-dienyne.

Gold(I) catalysis has also been applied to the macrocyclization of larger enynes (n≥ 7), which proceeds through [2+2] cycloaddition.[24] For example, 1,*n*-enynes (n = 10–16) undergo gold(I)-catalyzed macrocyclization reactions, leading to 9- to 15-membered-ring products that contain cyclobutenes such as **8** (Scheme 6).[25]



Scheme 6. Gold(I)-catalyzed the synthesis of a 13-membered macrocycle.

Enantioselective Gold(I) Catalysis

Homogeneous gold(I) catalysis is a powerful synthetic tool that enables the generation of molecular complexity. Nevertheless, the development of the asymmetric versions of the corresponding transformations has experienced a much slower development.[26] Asymmetric gold(I) catalysis is inherently challenging due to the linear dicoordination adopted by gold(I), which places the chiral information from the ancillary ligand at the opposite side of the reactive center, often resulting in poor enantioinduction. Furthermore, gold(I)-catalyzed transformations occur through an outer sphere mechanism. Moreover, another challenge is the limited fixation of the substrate in a chiral pocket because of the rotation of the L*–Au and Au–substrate bonds (Figure 2).

24 (a) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379–386. (b) Inagaki, F.; Matsumoto, C.; Okada, Y.; Maruyama, N.; Mukai, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 818–822. (c) Iwai, T.; Ueno, M.; Okochi, H.; Sawamura, M. *Adv. Synth. Catal.* **2018**, *360*, 670–675.

25 (a) Obradors, C.; Leboeuf, D.; Aydin, J.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 1576–1579. (b) Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. *Org. Lett.* **2016**, *18*, 1614–1617.

26 (a) Widenhoefer, R. A. *Chem. –Eur. J.* **2008**, *14*, 5382–5391. (b) Sengupta, S.; Shi, X. *ChemCatChem*, **2010**, *2*, 609–619. (c) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis*, **2011**, 1501–1514. (d) Wang, Y. M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.*, **2014**, *47*, 889–901. (e) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567–4589. (f) Li, Y.; Li, W.; Zhang, J. *Chem. –Eur. J.* **2017**, *23*, 467–512. (g) Zuccarello, G.; Escofet, I.; Caniparoli, U.; Echavarren, A. M. *ChemPlusChem* **2021**, *86*, 1283–1296.

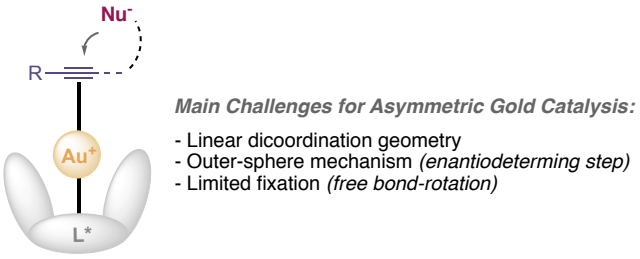


Figure 2. Principles of gold(I) coordination in enantioselective catalysis.

To circumvent this challenge, different strategies have been applied to facilitate the enantioinduction process. Bimetallic gold(I) complexes with chiral bidentante phosphines,[27] such as BINAP, SEGPHOS, BIPHEP, are the most often studied systems in a wide range of successful asymmetric transformations (Figure 3).

A different approach is based on the design and use of mononuclear gold(I) complexes with monodentate chiral phosphoramidites.[28] This perspective allows to obtain different chiral complexes due to their highly modular synthesis and its effectiveness was proved in the enantioselective cyclization of allenenes.

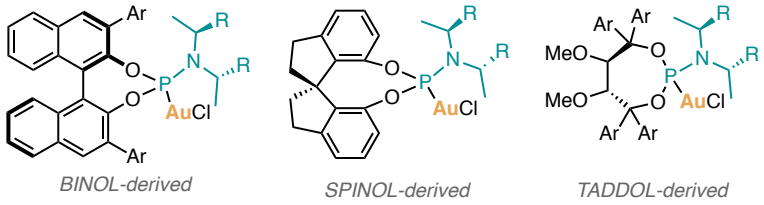
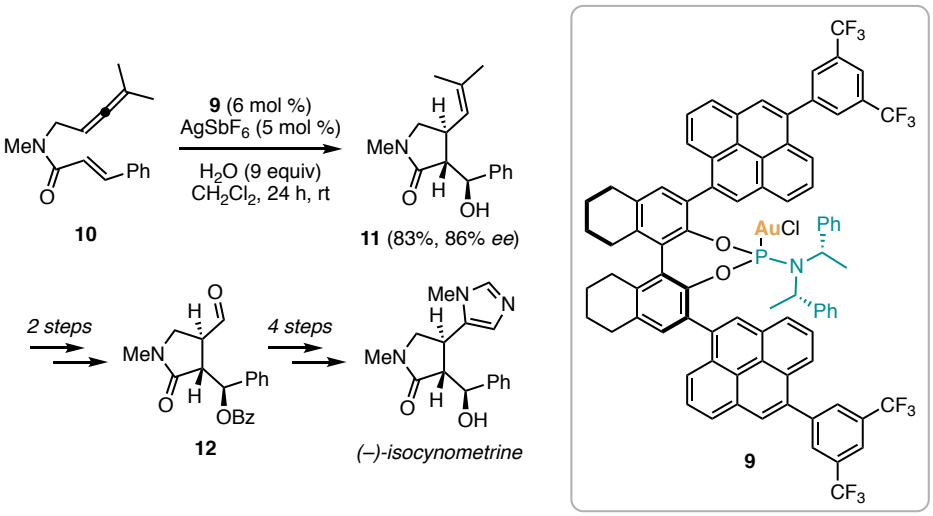


Figure 3. Chiral gold(I) complexes based on monodentate phosphoramidite ligands.

The group of Toste reported the synthesis of a family of chiral phosphoramidite gold(I) complexes and applied them in the enantio- and stereoselective synthesis of 3,4-substituted pyrrolidines.[28c] A remarkable example is the preparation of enantioenriched compound **11** in 86% *ee* that allowed the formation of **12** as a key intermediate in the total synthesis of (–)-isocynometrine (Scheme 7).

27 (a) Bartolom, C.; García-Cuadrado, D.; Ramiro, Z.; Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758–9764. (b) Wang, Y. M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972–12975. (c) Niemeyer, Z. L.; Pindi, S.; Khrakovsky, D. A.; Kuzniewski, C. N.; Hong, C. M.; Joyce, L. A.; Sigman, M. S.; Toste, F. D. *J. Am. Chem. Soc.* **2017**, *139*, 12943–12946.

28 (a) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030. (b) González, A. Z.; Toste, F. D. *Org. Lett.* **2010**, *12*, 200–203. (c) González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500–5507.



Scheme 7. Chiral phosphoramidite gold(I) complex (**9**) for the enantioselective synthesis of compound **11**.

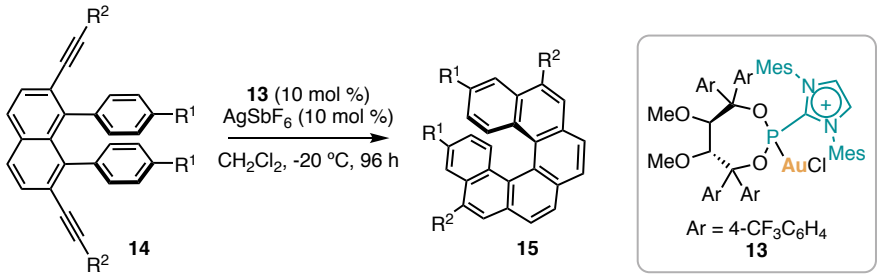
Chiral phosphate counteranions have also been applied in challenging asymmetric transformations.[29] Their advantage is that they keep the chiral information close to the reaction center through tight interactions between ion pairs. However, this strategy is limited to the use of internal alkynes because of the basicity of the phosphates that results in the deprotonation of terminal alkynes.[30]

On the other hand, the group of Alcarazo developed a family of TADDOL-derived cationic phosphonite ligands bearing 1,3-dimesityl-1,2,3-triazolium or 1,4-dimesityl-1,2,4-triazolium substituents in the gold(I)-catalyzed intramolecular hydroarylation of diynes to prepare chiral helicenes and axially-chiral compounds.[31] Thus, carbo[6]helicenes **15** were obtained from diynes **14** with moderate to excellent enantioselectivities using complex **13** as catalyst (Scheme 8).

29 (a) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496–499. (b) Aikawa, K.; Kojima, M.; Mikami, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 6073–6077. (c) Aikawa, K.; Kojima, M.; Mikami, K. *Adv. Synth. Catal.* **2010**, *352*, 3131–3135. (d) Tu, X.; Gong, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 11346–11349.

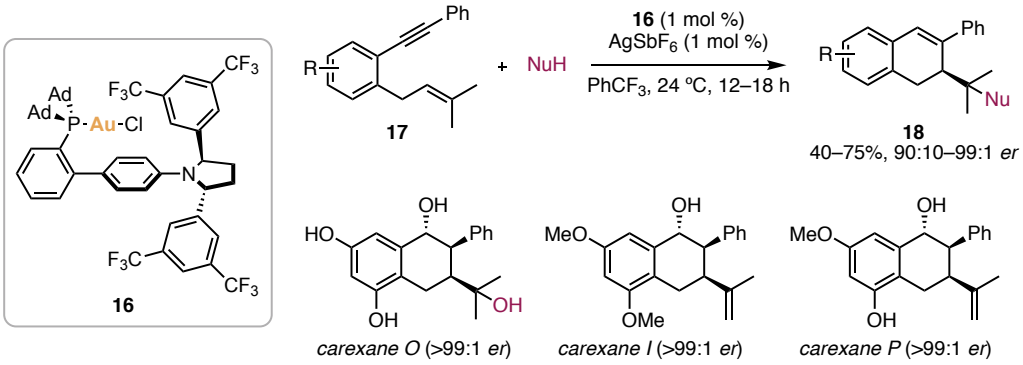
30 (a) Raducan, M.; Moreno, M.; Bour, C.; Echavarren, A. M. *Chem. Commun.* **2012**, *48*, 52–54. (b) Ferrer, S.; Echavarren, A. M. *Organometallics* **2018**, *37*, 781–786.

31 (a) Nicholls, L. D. M.; Marx, M.; Hartung, T.; González-Fernández, E.; Golz, C.; Alcarazo, M. *ACS Catal.* **2018**, *8*, 6079–6085. (b) Hartung, T.; Machleid, R.; Simon, M.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 5660–5664. (c) Zhang, J.; Simon, M.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 5647–5650.



Scheme 8. Formation of carbo[6]helicenes **15** *via* gold(I)-catalyzed intramolecular hydroarylation.

Our group reported in 2019 the synthesis of new chiral gold(I) complexes based on JohnPhos-type ligands, bearing a C_2-symmetric diaryl pyrrolidine at the *para*-position of the biphenyl core.[32] These complexes have been used in the enantioselective folding of enynes and the resulting precursors have been applied in the first enantioselective total synthesis of carexanes O, I and P (Scheme 9).



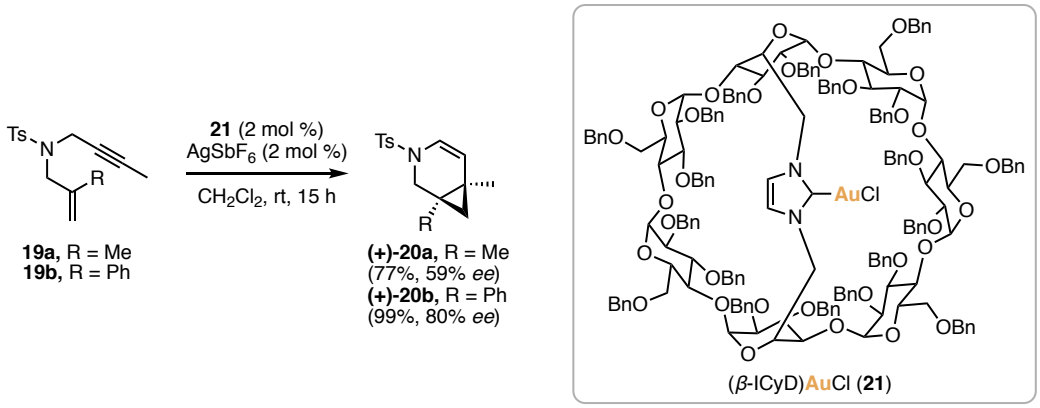
Scheme 9. Gold(I)-catalyzed enantioselective synthesis of compounds **18**, precursors of carexanes O, I and P.

Furthermore, the potential of cyclodextrin-NHC-gold(I) complexes was studied in asymmetric transformations.[33] Sollogoub and co-workers investigated different types of cyclodextrin-NHC ligands in the cycloisomerization of enynes **19** (Scheme 10). Thus, the best results were

32 Zuccarello, G.; Mayans, J. G.; Escofet, I.; Scharnagel, D.; Kirillova, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; Boothe, J. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863.

33 (a) Guitet, M.; Zhang, P.; Marcelo, F.; Tugny, C.; Jiménez-Barbero, J.; Buriez, O.; Amatore, C.; Mouriès-Mansuy, V.; Goddard, J.-P.; Fensterbank, L.; Zhang, Y.; Roland, S.; Ménand, M.; Sollogoub, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7213–7218. (b) Zhang, P.; Tugny, C.; Meijide Suárez, J.; Guitet, M.; Derat, E.; Vanthuyne, N.; Zhang, Y.; Bistri, O.; Mouriès-Mansuy, V.; Ménand, M.; Roland, S.; Fensterbank, L.; Sollogoub, M. *Chem* **2017**, *3*, 174–191. (c) Kaya, Z.; Andna, L.; Matt, D.; Bentouhami, E.; Djukic, J.; Armspach, D. *Chem. Eur. J.* **2018**, *24*, 17921–17926. (d) Kaya, Z.; Andna, L.; Matt, D.; Bentouhami, E.; Djukic, J.-P.; Armspach, D. *Eur. J. Org. Chem.* **2019**, 4528–4537. (e) Tugny, C.; del Rio, N.; Koohgard, M.; Vanthuyne, N.; Lesage, D.; Bijouard, K.; Zhang, P.; Meijide Suárez, J.; Roland, S.; Derat, E.; Bistri-Aslanoff, O.; Sollogoub, M.; Fensterbank, L.; Mouriès-Mansuy, V. *ACS Catal.* **2020**, *10*, 5964–5972. (f) Zhu, X.; Xu, G.; Chamoreau, L.; Zhang, Y.; Mouriès-Mansuy, V.; Fensterbank, L.; Bistri-Aslanoff, O.; Roland, S.; Sollogoub, M. *Chem. Eur. J.* **2020**, *26*, 15901–15909.

obtained using *β*-ICyDAuCl **21**. For example, bicyclic product **20a** was prepared in good yield and with moderate enantioselectivity (59% *ee*) from methyl-substituted enyne **19a**. The enantioselectivity could be improved to 80% *ee* with enyne **19b** bearing a phenyl moiety instead of the methyl group in presence of complex *β*-ICyDAuCl as catalyst (Scheme 10). More recently, this type of complexes was applied in the enantioselective alkoxycyclization of 1,6-enynes giving excellent enantioselectivities, as discussed in Chapter 1.



Scheme 10. Application of chiral cyclodextrine gold(I) complex **21** in the cycloisomerization of enynes **19**.

Other approaches are based on the use of axially chiral monodentate phosphine ligands with a remote cooperative functionality,[34] catalysts with chiral sulfinamides,[35] and helically chiral phosphine ligands.[36]

34 (a) Wang, Z.; Nicolini, C.; Hervieu, C.; Wong, Y.-F.; Zanoni, G.; Zhang, L. *J. Am. Chem. Soc.* **2017**, *139*, 16064–16067. (b) Cheng, X.; Wang, Z.; Quintanilla, C. D.; Zhang, L. *J. Am. Chem. Soc.* **2019**, *141*, 3787–3791.

35 (a) Wang, Y.; Zhang, P.; Di, X.; Dai, Q.; Zhang, Z.-M.; Zhang, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 15905–15909. (b) Wang, Y.; Zhang, Z.-M.; Liu, F.; He, Y.; Zhang, J. *Org. Lett.* **2018**, *20*, 6403–6406. (c) Zhang, P.-C.; Wang, Y.; Zhang, Z.-M.; Zhang, J. *Org. Lett.* **2018**, *20*, 7049–7052.

36 (a) Yavari, K.; Aillard, P.; Zhang, Y.; Nuter, F.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 861–865. (b) Aillard, P.; Dova, D.; Magné, V.; Retailleau, P.; Cauteruccio, S.; Licandro, E.; Voituriez, A.; Marinetti, A. *Chem. Commun.* **2016**, *52*, 10984–10987.

UNIVERSITAT ROVIRA I VIRGILI
GOLD(I) CAVITANDS FOR THE ASSEMBLY OF MOLECULAR COMPLEXITY
Inmaculada Martin Torres

Chapter I: *Gold(I)-Cavitand Complexes for the Enantioselective Alkoxycylization of 1,6-Enynes*

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GOLD(I) CAVITANDS FOR THE ASSEMBLY OF MOLECULAR COMPLEXITY
Inmaculada Martin Torres

Introduction

Cavitands in Gold(I) Catalysis

The design of supramolecular architectures has received increased attention lately due to their potential to mimic the activity of enzymes, the highly selective asymmetric catalysts in Nature. The ability of enzymes to perform biological transformations is due to the amino acid functional groups that converge to create reactive sites for guest molecules inside the hydrophobic pockets.[1] Inspired by these processes, organic chemists have designed several synthetic receptors with functional substituents enclosed in the chemical space.

For instance, in 2000 Rebek and co-workers described the design and preparation of an artificial receptor with a vase-like structure, in which the reactive site is constituted by the concave surface of a resorcin[4]arene-based cavitand.[2] This compound was used for chemical recognition of amines such as nicotine, by hydrogen bonding with introverted amide functionalities placed at the upper rim of the cavitands and directed towards the guest inside. Since then, the resorcin[4]arene pocket evolved into a motif widely used for its ability to stabilize intermediates[3] and influence the outcome of chemical reactions,[4] as well as for its selectivity for guests of certain sizes.[3]

Various proteins contain multiple metals that contribute to the activation of inert molecules inside their cavities.[5] A relevant strategy to mimic their activity is to place metal catalysts in molecular cages, in which substituents act like supporting ligands complexed to the metal.[6] Thus, the metal centers are encapsulated within these cages through covalent interactions or by means of supramolecular binding. In both cases, the metal complex is isolated from the bulk phase displaying increased selectivity and reactivity. Furthermore, the stability of these

1 (a) Skerra, A. J. *J. Mol. Recognit.* **2000**, *13*, 167–187. (b) Folkers, G.; Klein, C. D. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 4175–4177. (c) Khosla, C.; Harbury, P. B. *Nature* **2001**, *409*, 247–252. (d) Bruice, T. C. *Acc. Chem. Res.* **2002**, *35*, 139–148.

2 Renslo, A. R.; Rebek, Jr., J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3281–3283.

3 Iwasawa, T.; Hooley, R. J.; Rebek, J. *Science* **2007**, *317*, 493–496.

4 Shenoy, S. R.; Pinacho Crisóstomo, F. R.; Iwasawa, T.; Rebek, J. *J. Am. Chem. Soc.* **2008**, *130*, 5658–5659.

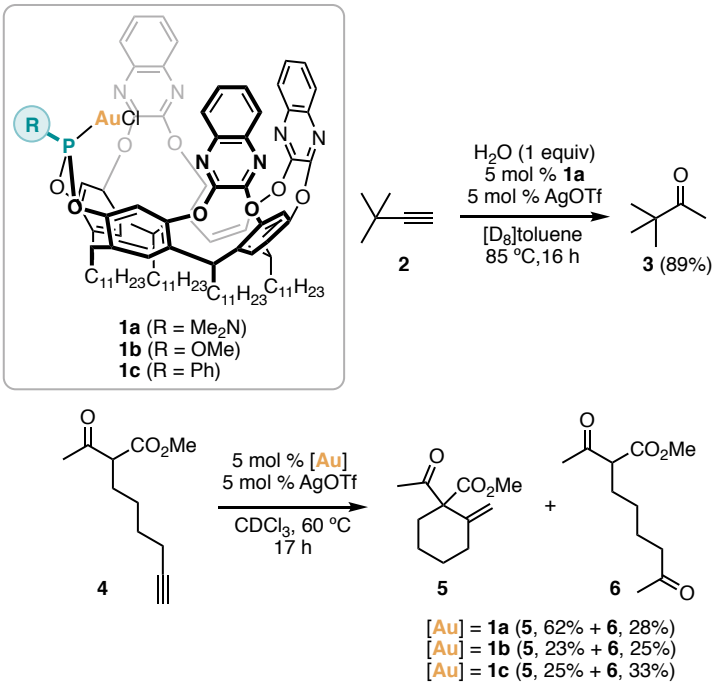
5 (a) Tezcan, F. A.; Kaiser, J. T.; Mustafi, D.; Walton, M. Y.; Haward, J. B.; Rees, D. C. *Science* **2005**, *309*, 1377–1380. (b) Spatzal, T.; Aksoyoglu, M.; Zhang, L.; Andrade, S. L. A.; Schleicher, E.; Weber, S.; Rees, D. C.; Einsle, O. *Science* **2011**, *334*, 940. (c) Lancaster, K. M.; Roemelt, M.; Ettenhuber, P.; Hu, Y.; M. W. Ribbe, M. W.; Neese, F.; Bergmann, U.; DeBeer, S. *Science* **2011**, 974–977.

6 (a) Gibson, C.; Rebek Jr., J. *Org. Lett.* **2002**, *4*, 1887–1890. (b) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1660–1733. (c) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1734–1787.

complexes can be improved as a result of this isolation, creating a system that can reach a high turn-over number.[7]

The first example of including metals within resorcin[4]-arenes was described in 2002 by the group of Rebek using palladium,[6a] and involves the construction of a well-defined cage around the metal complex by covalently attaching a cavitand to the ligand coordinated to the complex.

More recently, attention has been given to the encapsulation of gold(I) complexes and the study of its impact on the catalytic properties due to the several reports on the versatility of homogeneous gold catalysis. Therefore, in search for new methods to encapsulate gold complexes, Iwasawa and co-workers reported different synthetic strategies. For instance, their work described the design of a resorcin[4]arene-based gold(I) cavitand with phosphoramidite, phosphite or phosphonite moieties (**1a**, **1b** and **1c** respectively) outside of the cavity (Scheme 1).[8] Thus, a favorable framework for catalysis was created, as the metal center is located inside the cavity, while being flanked by three quinoxaline wall units. The gold(I)-cavitand complex could be successfully used in the hydration of different terminal alkynes such as **2**. Gold(I) cavitands (**1a–c**) were tested in the Conia-ene reaction of *β*-keto ester alkyne **4** giving a mixture of products **5** and **6**. The best result was observed with complex **1a**.

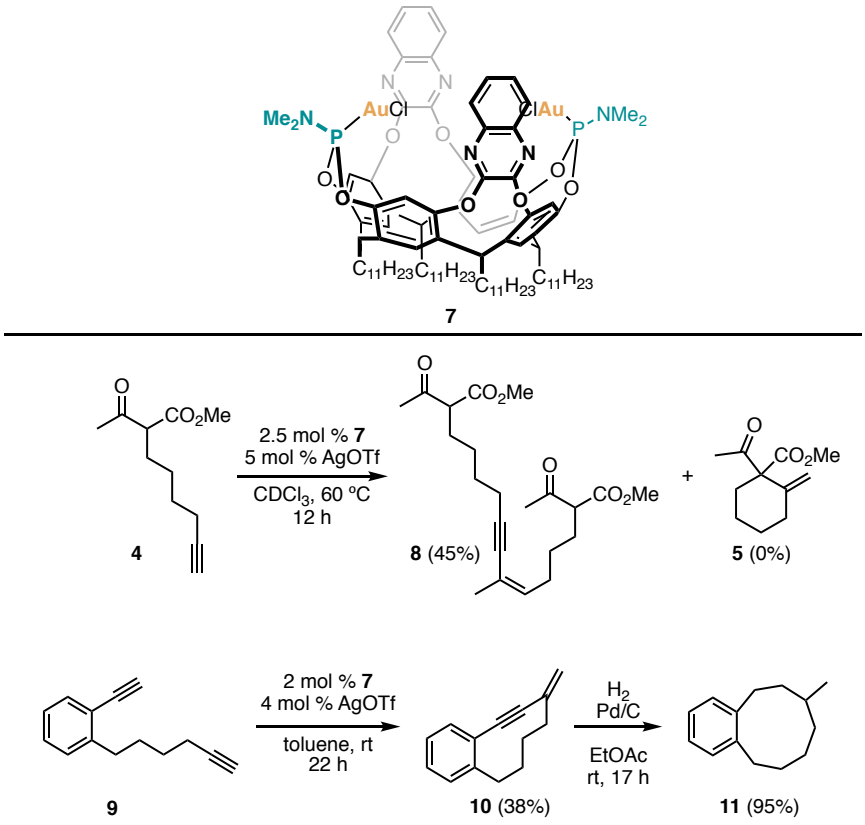


Scheme 1. Gold(I)-cavitand complexes and their application in gold(I) catalysis.

7 Jans, A. C. H.; Caumes, X.; Reek, J. N. H. *ChemCatChem* **2019**, *11*, 287–297.

8 Schramm, M. P.; Kanaura, M; Ito, K; Ide, M.; Iwasawa, T. *Eur. J. Org. Chem.* **2016**, 813–820.

In addition, the same group also disclosed the preparation of a binuclear gold(I)-cavitand complex **7**, where both gold chloride fragments are inside the pocket (Scheme 2). This compound was found to be an efficient catalyst for the selective dimerization of terminal alkyne **4**, giving rise to conjugated enyne **8** in 45% yield. The corresponding Conia-ene product **5** was not observed as in the case of use gold(I) complexes **1a–c** (Scheme 1). Furthermore, cavitand **7** enabled the intramolecular cyclization of diyne **9** to generate highly strained enyne **10**, which was then converted into nine-membered macrocycle **11**.[9]

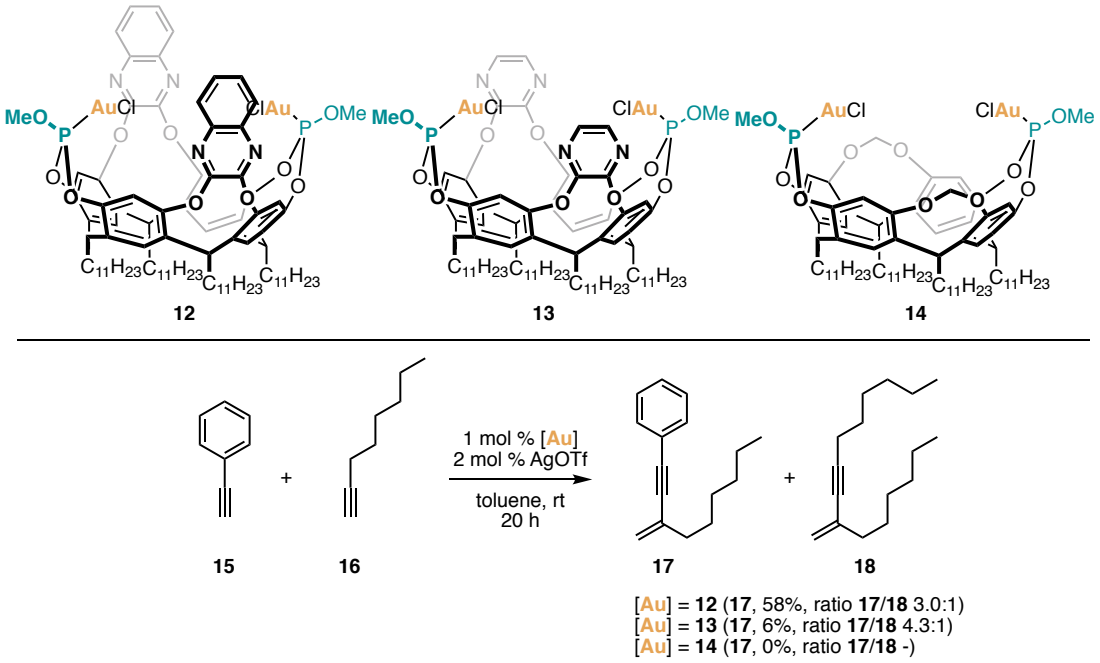


Scheme 2. Dimerization of terminal alkynes using gold(I) cavitand **7**.

The importance of the cavity was also investigated by comparison with cavitands containing different walls (**12–14**). Thus, studies revealed that quinoxaline walls are essential as they facilitate the interaction between the two alkyne substrates and stabilize the intermediates by creating a strong π-cloud.[10] For instance, the dimerization of terminal alkynes was performed using binuclear complexes (cavitands **12–14**) and the cross-adduct compound **17** was obtained in higher yield with complex **12** (Scheme 3).

9 Endo, N.; Kanaura, M.; Schramm, Michael P.; Iwasawa, T. *Eur. J. Org. Chem.***2016**, 2514–2521.

10 (a) Kanaura, M.; Endo, N.; Schramm, M. P.; Iwasawa, T. *Eur. J. Org. Chem.* **2016**, 4970–4975. (b) Natarajan, N.; Brenner, E.; Sémeril, D.; Matt, D.; Harrowfield, J. *Eur. J. Org. Chem.* **2017**, 6100–6113.



Scheme 3. Study of the effect of cavitand walls in the dimerization of terminal alkynes.

The selective hydration of alkynes was also explored later by the Iwasawa group by employing mononuclear gold(I)-cavitand complexes. These compounds contain an inwardly oriented gold(I) and P=O moieties and acts like a supramolecular-flask device in which the gold(I) coordinates to the triple bond, the P=O moiety binds to a molecule of H_2O, while the cavity enables the selective folding of a single alkynyl side chain.[11]

The same three-walled gold(I) cavitand (**1a**) was used by the group of Schramm in the lactonization of γ-alkynoic acids and the effect of the size of alkyl substituents was investigated.[12] The experiments demonstrated that the catalyst is size-specific, as extremely large and small groups reacted with appreciable rate, while functionalities with an intermediate size, matched to fit the cavitand, slowed the reaction significantly.

The cycloisomerization of arylalkynes catalyzed by this gold(I) complex cavitand was also explored by the same group, by comparing the cavitand catalyst with the electronically similar Au-phosphite complex.[13]

11 (a) Endo, N.; Inoue, M.; Iwasawa, T. *Eur. J. Org. Chem.* **2018**, 1136–1140. (b) Inoue, M.; Ugawa, K.; Maruyama, T.; Iwasawa, T. *Eur. J. Org. Chem.* **2018**, 5304–5311.

12 Ho, T. D.; Schramm, M. P. *Eur. J. Org. Chem.* **2019**, 5678–5684.

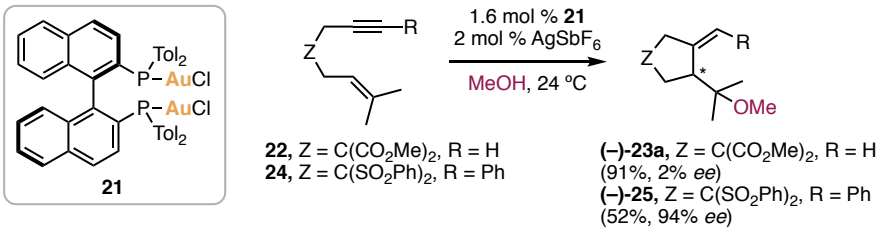
13 Rusali, L. E.; Schramm, M. P. *Tetrahedron Letters* **2020**, *61*, 152333.

Gold(I)-Catalyzed Enantioselective Alkoxycyclizations

Gold(I)-cavitand complexes had not been employed in the cycloisomerization of enynes nor in field of enantioselective catalysis.[14] Inspired by other studies performed in our group, we envisioned that these systems could be applied to asymmetric alkoxycyclization reactions.

The alkoxycyclization reaction was first explored by our group in 2005, and the enantioinduction was achieved using a chiral phosphine ligand. Other approaches that will be discussed later in this section include the use of NHC-carbenes and cyclodextrins. In this sense, the most representative examples were selected.

Our group described in 2005 the use of a chiral biphosphine-gold(I) complex for the enantioselective gold(I)-catalyzed alkoxyxcyclization of 1,6 enynes.[15] The reaction proceeded with moderate to good enantioselectivities to afford cyclized products using [Tol-BINAP(AuCl)$_2$] (**21**) in presence of $AgSbF_6$. The best result was obtained in the enantioselective alkoxycyclization of enyne **24** leading to **25** in 52% yield and with 94% *ee* (Scheme 4).



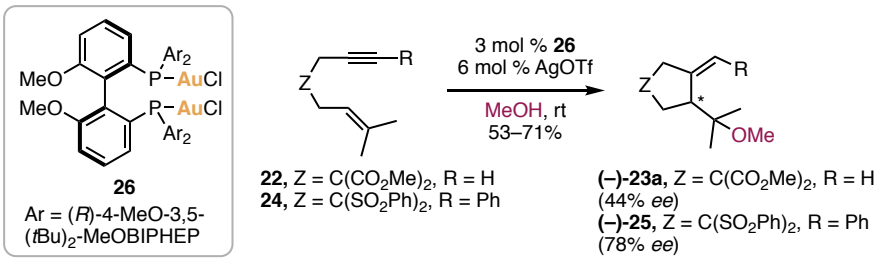
Scheme 4. Enantioselective alkoxycyclization using [Tol-BINAP(AuCl)$_2$].

A few years later, the Michelet group also designed an efficient catalytic system for enantioselective alkoxycyclization reactions based on the use of gold(I) catalyst with chiral bidentate phosphine ligand (*R*)-4-MeO-3,5-(*t*Bu)$_2$-MeOBIPHEP.[16] Their studies demonstrated that the outcome of the asymmetric alkoxyxcyclization was highly dependent on the steric properties of both the phosphine-metal fragment and the enyne substrate, as the degree of chiral induction increases with the bulkiness of the reaction components. Thus, for the methoxycyclization of enyne **22** an enantioselectivity of 44% was observed when employing the MeO-3,5-(*t*Bu)$_2$-MeOBIPHEP ligand. The cyclization of enyne **24**, incorporating a bulkier disulfoxide moiety, provided compound **25** with higher enantioselectivity (Scheme 5).

14 (a) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567–4589. (b) Wang, Y.-M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889–901.

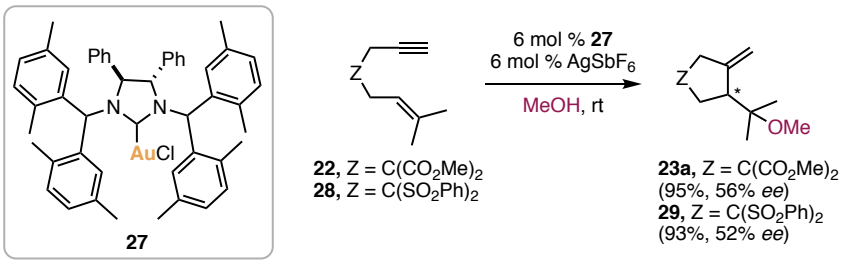
15 Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300.

16 Pradal, A.; Chao, M.-C.; Vitale, M. R.; Toullec, P. Y.; Michelet, V. *Tetrahedron* **2011**, *67*, 4371–4377.



Scheme 5. Enantioselective methoxycyclization using complex **26**.

Regarding the use of NHC-carbenes, the first NHC–Au(I)-catalyzed asymmetric alkoxycyclization was reported in 2010 by the group of Tomioka using chiral C_2-symmetric NHC–Au(I) complex (**27**).[17] This complex was applied in the first chiral NHC–Au(I)-catalyzed asymmetric cyclizations of 1,6-enynes **22** and **28** and furnished cyclic products **23a** and **29** with moderate enantioselectivity (Scheme 6).

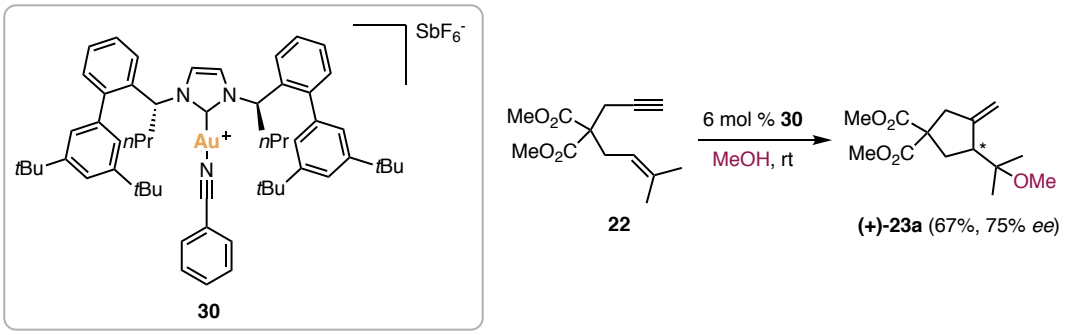


Scheme 6. Enantioselective alkoxycyclization of 1,6-enynes catalyzed by NHC carbene-based complex **27**.

The group of Barnes also designed a series of new NHC-based gold(I) chiral catalysts and demonstrated that the bulkiness of the NHC ligand was directly correlated with the induced enantioselectivity in the alkoxycyclization reaction.[18] Catalyst **30** led to the formation of product **23a** from enyne **22** with 75% *ee* (Scheme 7).

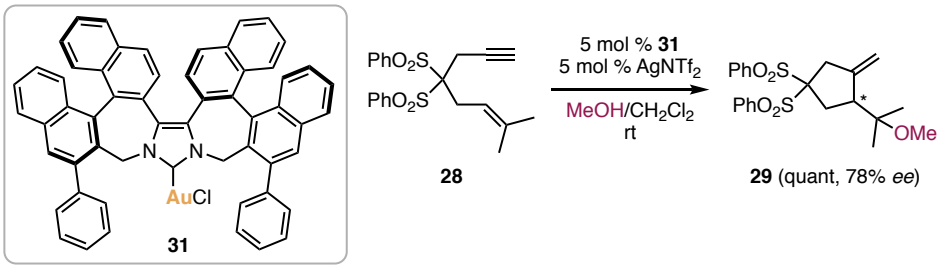
17 Matsumoto, Y.; Selim, K. B.; Nakanishi, H.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *Tetrahedron Letters* **2010**, *51*, 404–406.

18 Gung, B. W.; Holmes, M. R.; Jones, C. A.; Ma, R.; Barnes, C. L. *Tetrahedron Letters* **2016**, *57*, 3912–3915.



Scheme 7. Gold(I)-catalyzed asymmetric methoxycyclization of enyne **22**.

Similar NHC-based catalysts were also developed by the Nakada group.[19] In this case, the best result in the enantioselective formation of product **29** by alkoxycyclization of enyne **28** was obtained using complex **31** (Scheme 8). This compound incorporates a chiral C_2-symmetric NHC ligand with two binaphthyl units, which are linked to the imidazolylidene by two seven-membered rings. The high enantioselectivity of the reaction was rationalized after X-ray analysis of the complex, which positions the Au–Cl moiety between the phenyl groups of the binaphthyl units.

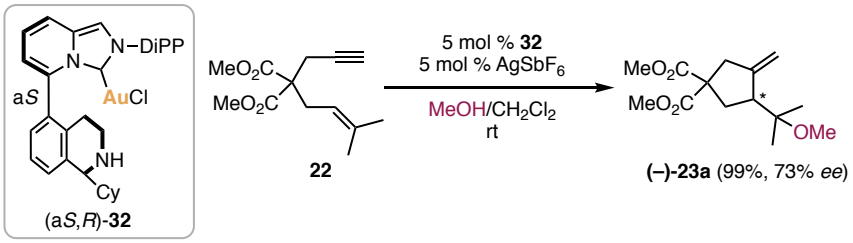


Scheme 8. Enantioselective methoxycyclization of 1,6-enyne **28** catalyzed by complex **31**.

Additionally, Zhang and co-workers reported the synthesis of other gold(I) catalysts based on new chiral bifunctional NHC ligands that are derivatives of the imidazo[1,5-*a*]pyridine (ImPy) scaffold.[20] Among them, catalyst **32** was applied in the alkoxycyclization of enyne **22** and provided cyclic compound **23a** with 73% *ee* (Scheme 9). In this case, the enantioselectivity was induced by chiral steric congestion, due to the cyclohexyl group of the ligand that points to the reaction site and creates a tight chiral environment.

19 Okitsu, N.; Yoshida, T.; Usui, K.; Nakada, M. *Heterocycles* **2016**, *92*, 720–732.

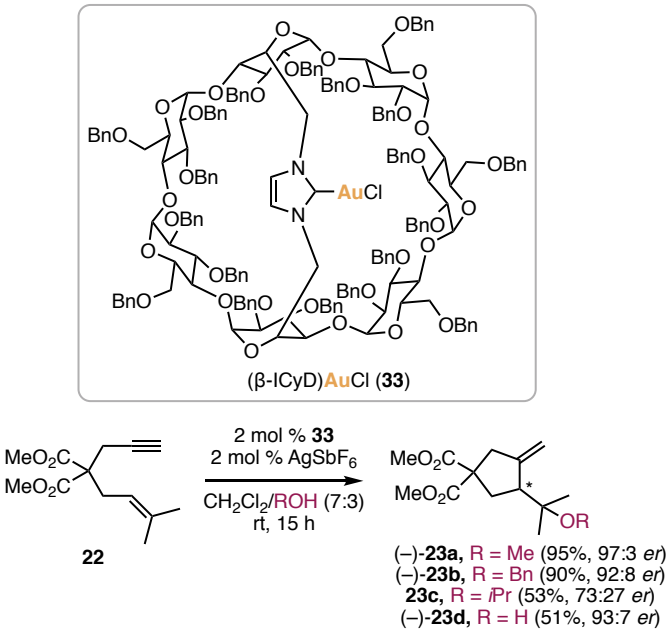
20 Zhang, J.-Q.; Liu, Y.; Wang, X.-W.; Zhang, L. *Organometallics* **2019**, *38*, 3931–3938.



Scheme 9. Cyclization of enyne **22** using catalyst **32**.

Finally, a more recently developed approach for achieving new enantioselectivities in alkoxycyclization reactions involves the use of gold complexes encapsulated by covalent association with cyclodextrins. Sollogoub and co-workers applied a NHC-capped *β*-ICyD–AuCl complex in the enantioselective alkoxycyclization of 1,6-enynes bearing a diester linker and a nitrogen-tether.[21] The enantioselective alkoxycyclization of **22** was explored in presence of different alcohol nucleophiles observing changes depending on the size of the nucleophile (Scheme 10). Indeed, when methanol was used, the product **23a** was obtained with an excellent 97:3 *er*, the highest reported until that moment. While a similar result was obtained using benzylic alcohol, both the enantiomeric excess and the yield dropped using isopropanol. This demonstrates that the largest alcohols are the least efficient nucleophiles for these transformations. The methoxycyclization of nitrogen-containing 1,6-enynes was next explored. In this case, the desired ethers were obtained with very high enantioselectivity (94:6 *er*).[21]

21 Tugny, C.; del Rio, N.; Koohgard, M.; Vanthuyne, N.; Lesage, D.; Bijouard, K.; Zhang, P.; Mejide Suárez, J.; Roland, S.; Derat, E.; Bistri-Aslanoff, O.; Sollogoub, M.; Fensterbank, L.; Mouriès-Mansuy, V. *ACS Catal.* **2020**, *10*, 5964–5972.

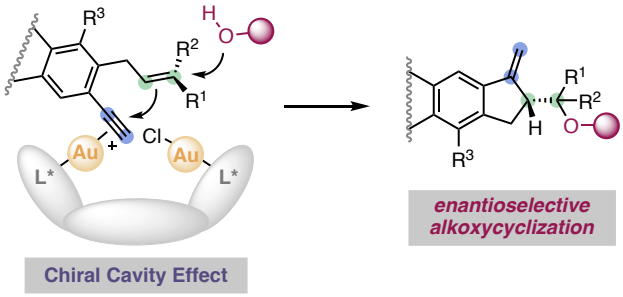


Scheme 10. Enantioselective alkoxycyclization of 1,6-enyne **22** catalyzed by NHC-capped *β*-cyclodextrin gold(I) catalyst **33**.

Their studies demonstrated that the cavity plays a crucial role in the outcome of the reactions, leading to different selectivities in a similar manner to metallo-enzymes. Thus, due to the shape of the cavity, a constrained environment is created and allows size discrimination between the different alcohol nucleophiles.

Objectives

Our objective was the synthesis of a new family of gold(I) complexes based on the use of cavitands as ligands for the selective cyclization of 1,6-dienynes. Another aim was the design and development of chiral gold(I)-cavitand complexes for the enantioselective alkoxycyclization of 1,6-enynes. To demonstrate the value of these new catalysts, our final goal was to apply this methodology in the total synthesis of carbazole alkaloid (+)-mafaicheenamine C.[22]



Scheme 11. Gold(I)-cavitand complexes in enantioselective catalysis.

22 Part of these experiments described in this section were performed jointly with Gala Ogalla, Dr. Antonia Rinaldi and were based upon preliminary work by Dr. Jin-Ming Yang.

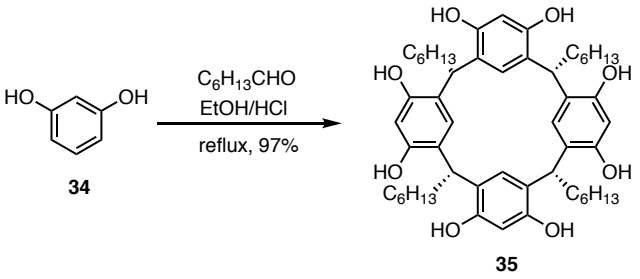
Results and Discussion

As previously mentioned in the introduction, the use of supramolecular entities in metal catalysis is constantly growing in interest. In this respect, we wanted to explore the application of cavitand structures in gold(I) catalysis because their cavity may force substrates to adopt constrained conformations, thus providing new selectivities. Therefore, we designed and synthesized a family of achiral and chiral resorcin[4]arene-based gold(I)-cavitand complexes and we applied them in the selective cyclization of 1,6-dienynes as well as in the development more challenging asymmetric transformations.

Synthesis of Achiral Gold(I)-Cavitand Complexes

Our work began with the design and development of a family of the achiral gold(I) catalysts, containing both mononuclear and dinuclear gold(I) cavitand complexes. Moreover, the effect of the cavity in the reactivity was studied by using different combinations of quinoxaline and naphthoquinone walls. The achiral gold(I) cavitands were prepared following a procedure reported by the group of Iwasawa.[8,9]

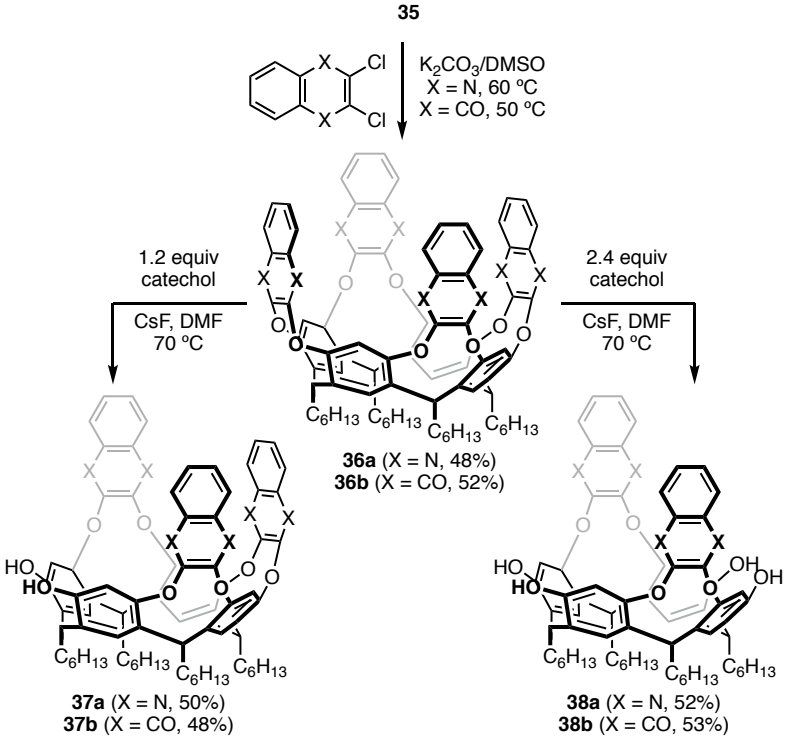
The synthesis starts with the preparation of resorcin[4]arene **35** by condensation of resorcinol (**34**) and heptanal under acidic conditions (Scheme 12).



Scheme 12. Synthesis of resorcin[4]arene **35**.

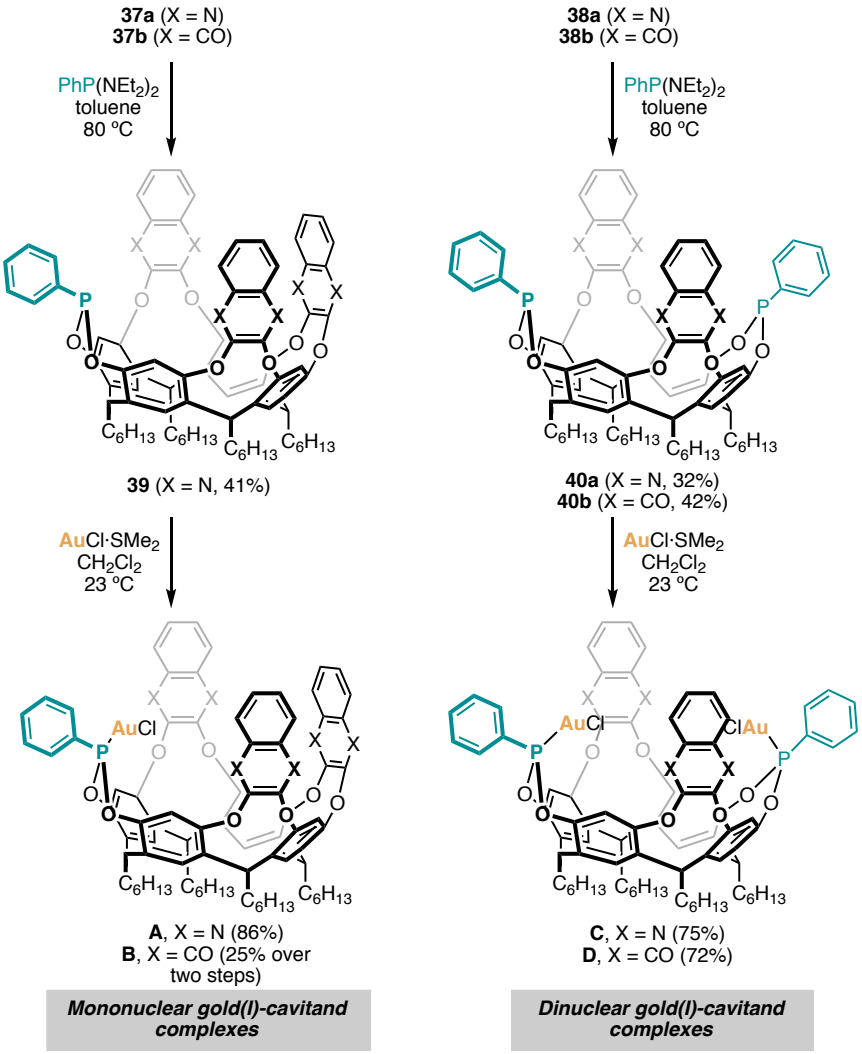
Resorcin[4]arene **35** was treated with 2,3-dichloroquinoxaline or 2,3-dichloronaphthoquinone under basic conditions to afford the desired tetraquinoxaline or tetranaphthoquinone resorcin[4]arenes (**36a–b**). The group of Gutierrez-Tunstad reported a selective excision of quinoxaline walls from tetraquinoxaline cavitands using catechol as nucleophile and an excess of CsF in DMF.[23] Applying this methodology, we obtained diphenols **37a–b** when 1.2 equiv of catechol were used, whereas tetraphenols **38a–b** were afforded using 2.4 equiv of catechol (Scheme 13).

23 Castro, P. P.; Zhao, G.; Masangkay, G. A.; Hernandez, C.; Gutierrez-Tunstad, L. M. *Org. Lett.* **2004**, *6*, 333–336.



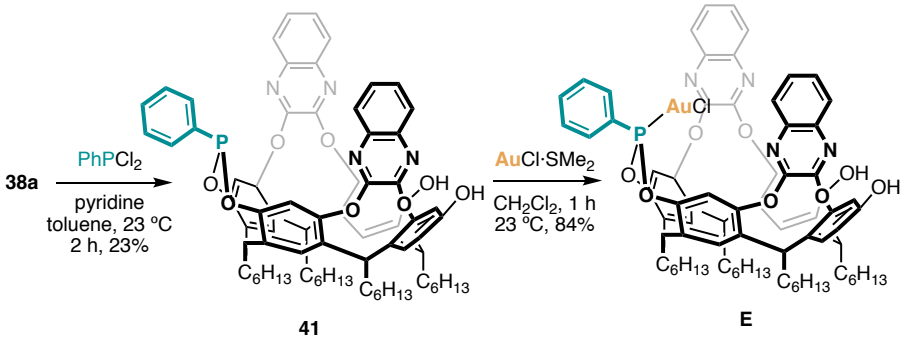
Scheme 13. Modular synthesis of cavitand-ligand precursors.

After that, bis(diethylamino)phenylphosphine ($PhP(NEt_2)_2$) and the corresponding diphenol (**37a–b**) or tetraphenol (**38a–b**) reacted to build the desired phosphonites **39** and **40**. Finally, the coordination of gold was performed using $AuCl{\cdot}SMe_2$ affording mononuclear gold(I)-cavitand complexes **A–B** and binuclear gold(I) cavitands **C–D** (Scheme 14). X-ray diffraction analysis confirmed that the gold(I) chloride is located inside the cavity of the ligand, whereas the phenyl group of the phosphonite is pointing outwards.



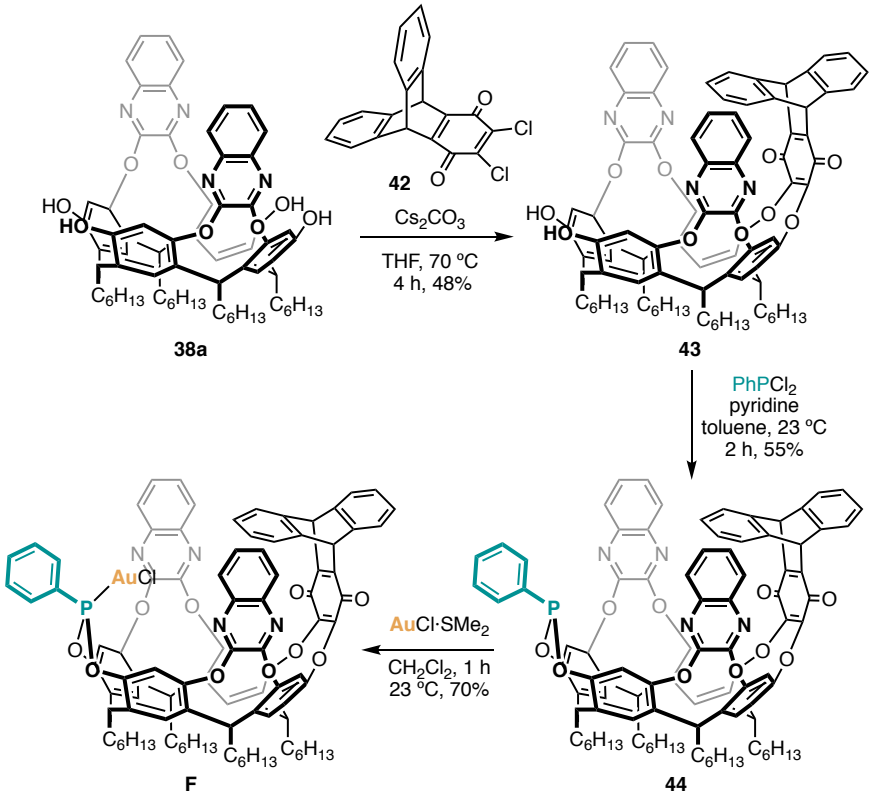
Scheme 14. Synthesis of gold(I)-cavitand complexes.

Next we envisioned the synthesis of complex **E**, containing two free phenol groups, as its cavity would be more open in comparison with complex **A**. Cavitand **E** was prepared from phosphonite **41**, whose synthesis was performed with tetraphenol resorcin[4]arene **38a** and phenylphosphonine dichloride $PhPCl_2$ instead of $PhP(NEt_2)_2$ since we found this reagent to be more selective. Finally, **41** was reacted with $AuCl{\cdot}SMe_2$ delivering the desired complex **E** (Scheme 15).



Scheme 15. Synthesis of complex **E**.

Furthermore, the synthesis of complex **F** was developed by introducing an even bulkier wall, resulting in a more closed pocket in comparison with the previous gold(I)-cavitand complexes. Selective addition of triptycene quinone **42** to tetraphenol resorcin[4]arene **38a,** followed by the introduction of the phenylphosphonite and the gold(I) coordination resulted the successful preparation of complex **F** (Scheme 16).

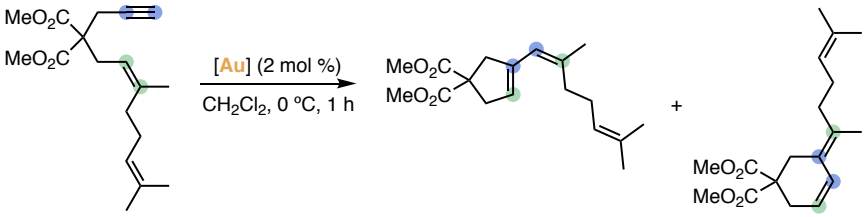


Scheme 16. Synthesis of complex **F**.

Application of Gold(I)-Cavitand Complexes in the Selective Cycloisomerization of 1,6-Dienyne

The cycloisomerization of **45** was reported to give almost exclusively the formation of 5-*exo* dig cycloisomerization in the presence of classical gold(I) catalysts.[24] We wanted to explore whether the use of cavitand complexes could help us invert this selectivity. For this, we started evaluating several types of non-cavitand gold(I) complexes as catalysis in the cycloisomerization of *Z*-1,6-dienyne **45** and in all cases the product of exocyclic single-cleavage skeletal rearrangement (**46a**) was obtained as the major product (Table 1, entries 1–7).

Table 1. Screening of gold(I) complexes in the cycloisomerization of *Z*-1,6-dienyne **45**.

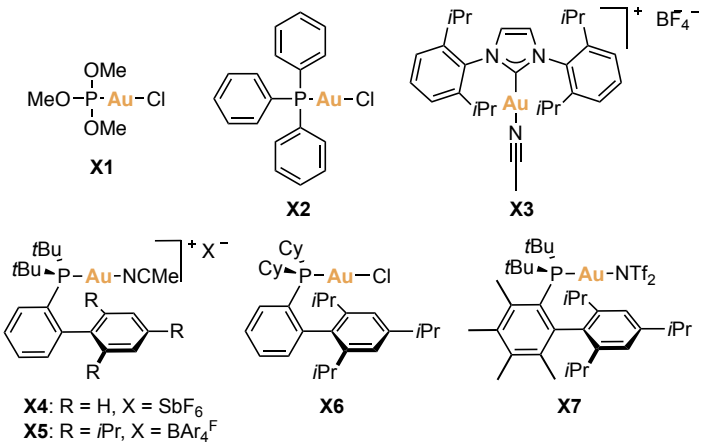


45 **46a** **46b**

Entry[a]	[Au]	$AgSbF_6$ (mol %)	Conversion (%)	Yield (%)[b], 46a/46b ratio
1	**X1**	2	67	(56, >20:1)
2	**X2**	2	100	(65, 11:1)
3	**X3**	-	75	(46, >20:1)
4	**X4**	-	100	(56, >20:1)[c]
5	**X5**	-	100	(90, >20:1)
6	**X6**	2	100	(72, >20:1)
7	**X7**	-	69	(42, >20:1)

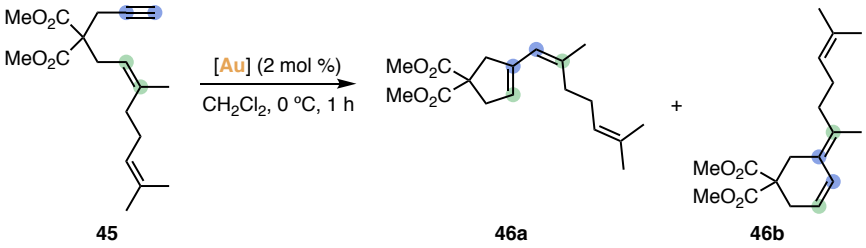
[a] **45** (0.06 mmol), 0.1 M. [b] Yields and ratios determined by ^1H NMR using Ph_2CH_2 as internal standard. [c] Reaction time: 25 min.

24 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.



Then, gold(I)-cavitand complexes were tested as precatalysts in the same transformation and a drastic change in the selectivity was observed. Thus, 6-membered-ring compound **46b**,[25] the product of the endocyclic single-cleavage skeletal rearrangement, was formed preferentially, instead of exocyclic product **46a**, by using mono- or dinuclear gold(I) cavitands (Table 2, entries 1–6). We found that mononuclear gold(I) cavitand **A** was the optimal complex for this cyclization reaction leading to excellent yields and a 1:5 ratio of products **46a**/**46b** (Table 2, entry 1).

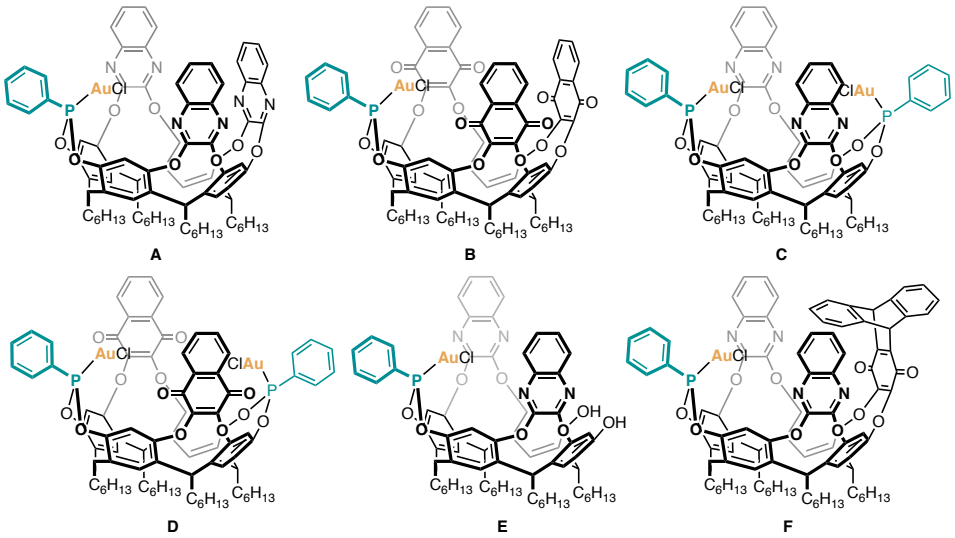
Table 2. Cyclization of *Z*-1,6-dienyne **45** using gold(I)-cavitand complexes.



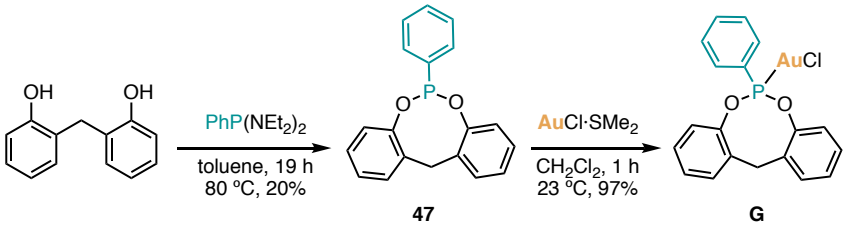
Entry[a]	[Au]	$AgSbF_6$ (mol %)	Yield (%)[b], 46a/46b ratio
1	**A**	2	(95, 1:5)
2	**B**	2	(89, 8:1)
3	**C**	4	(92, 1:1)
4	**D**	4	(87, 3:1)
5	**E**	2	(79, 1:2)
6	**F**	2	(83, 1:1)

[a] **45** (0.06 mmol), 0.1 M. [b] Yields and ratios determined by ^1H NMR using Ph_2CH_2 as internal standard.

25 Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, 4217–4223.



Based on these results, and to evaluate if the cavity of these complexes has an important role in the change of the *exo*- to *endo*-selectivity, we prepared complex **G**, which has a similar active site and electronic properties than our gold(I)-cavitand complexes (Scheme 17).

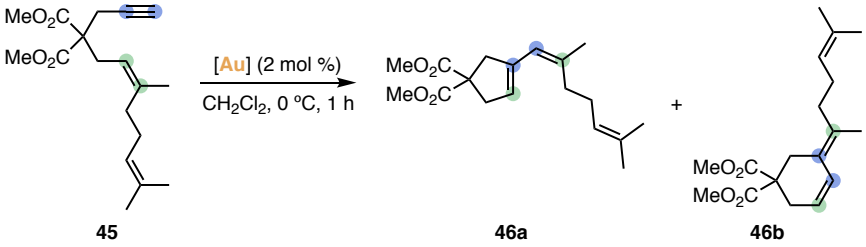


Scheme 17. Synthesis of complex **G**.

When substrate **45** was treated with 2 mol % of complex **G** and 2 mol % of $AgSbF_6$, the preferred formation of product **46a** was found, illustrating the important role of the pocket of the cavitand complexes in inverting the reaction selectivity (Table 3, entry 1).

We observed a reduced selectivity at 23 °C (Table 3, entry 3). However, when the reaction was carried out at -50 °C, the same ratio of products **46a** and **46b** was obtained in comparison with the reaction performed at 0 °C (Table 3, entries 2 and 4), but the conversion was lower. No conversion was found when only precatalyst **A** or only $AgSbF_6$ were used (Table 3, entries 5 and 6).

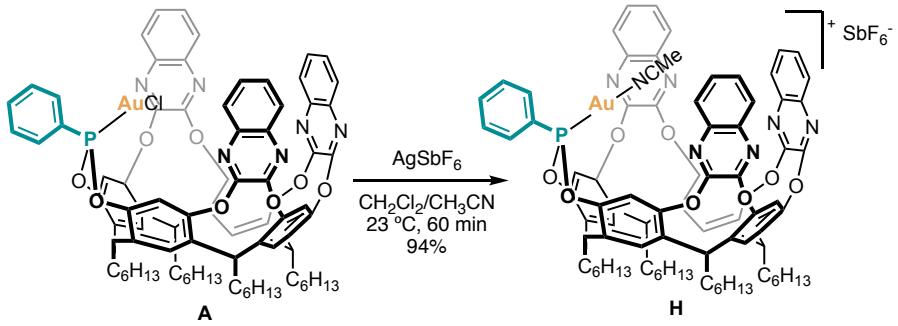
Table 3. Optimization of the cyclization of *Z*-1,6-dienyne **45**.



Entry[a]	[Au]	$AgSbF_6$ (mol %)	T (°C)	t (min)	Yield (%)[b], 46a/46b ratio
1	**G**	2	0	60	(77, >20:1)
2	**A**	2	0	60	(95, 1:5)
3	**A**	2	23	60	(76, 1:2)
4	**A**	2	-50	180	(31, 1:5)[c]
5	**A**	-	0	60	-[d]
6	-	2	0	60	-[d]

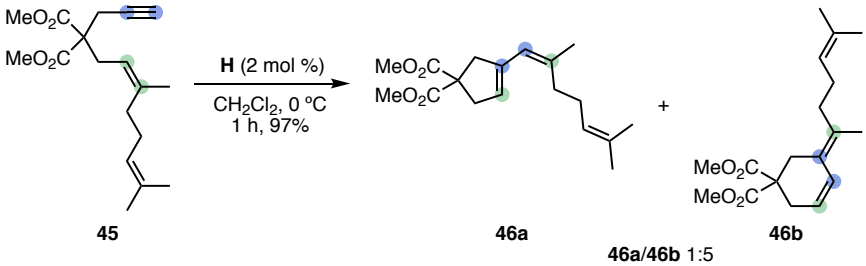
[a] **45** (0.06 mmol), 0.1 M. [b] Yields and ratios determined by ^1H NMR using Ph_2CH_2 as internal standard. [c] 41% conversion. [d] No conversion, starting material recovered.

Finally, cationic catalyst **H** was synthesized in excellent yield from the corresponding precatalyst **A** *via* chloride abstraction by $AgSbF_6$ in a mixture of dichloromethane and acetonitrile (Scheme 18). The structure of complex **H** was confirmed by X-ray diffraction.



Scheme 18. Synthesis of cationic gold(I)-cavitand catalyst **H**.

As expected, the use of catalyst **H** showed the same result as cavitand **A**, giving **46a**/**46b** in a 1:5 ratio and excellent yield, without requiring *in situ* activation (Scheme 19).



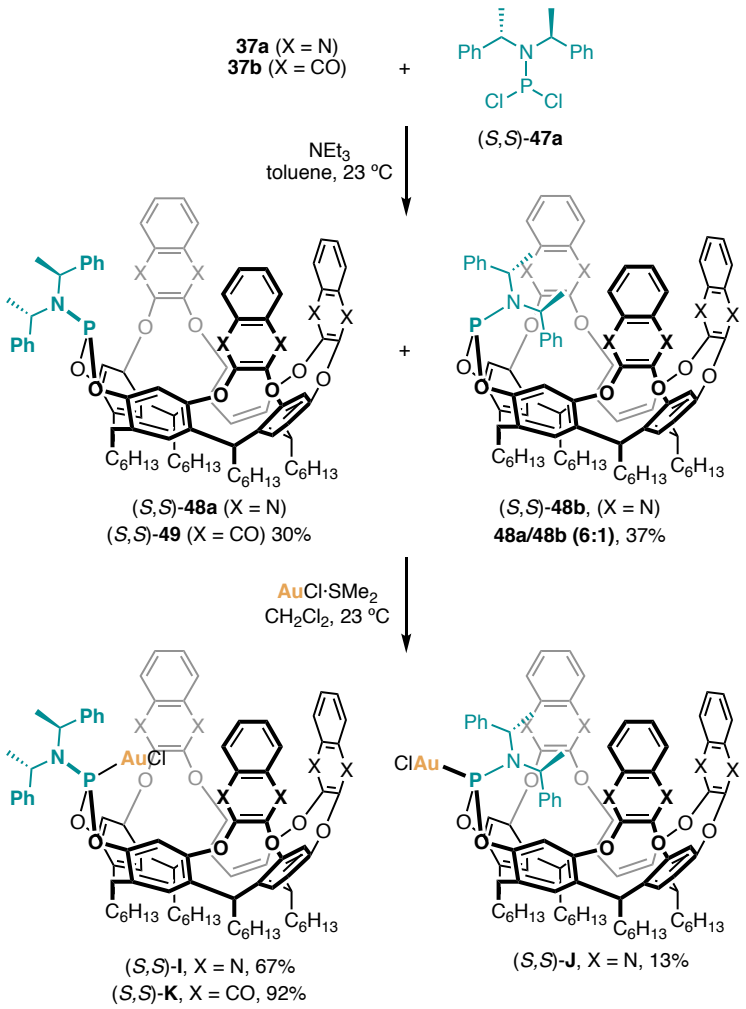
Scheme 19. Selective cycloisomerization of 1,6-dienyne **45**.

Synthesis of Chiral Gold(I)-Cavitand Complexes

After the development of the family of achiral gold(I)-cavitand complexes, a family of chiral gold(I) cavitands was designed and synthesized following a similar synthetic route. The chiral element was introduced by the formation of chiral phosphoramidites starting from resorcin[4]arene-based cavitands functionalized with quinoxaline and naphthoquinone walls.

For the chiral mononuclear gold(I) complexes, we prepared complexes (*S*,*S*)-**I** and (*S*,*S*)-**K**, with the metal inside the cavity, and (*S*,*S*)-**J** with the metal outside (Scheme 20).

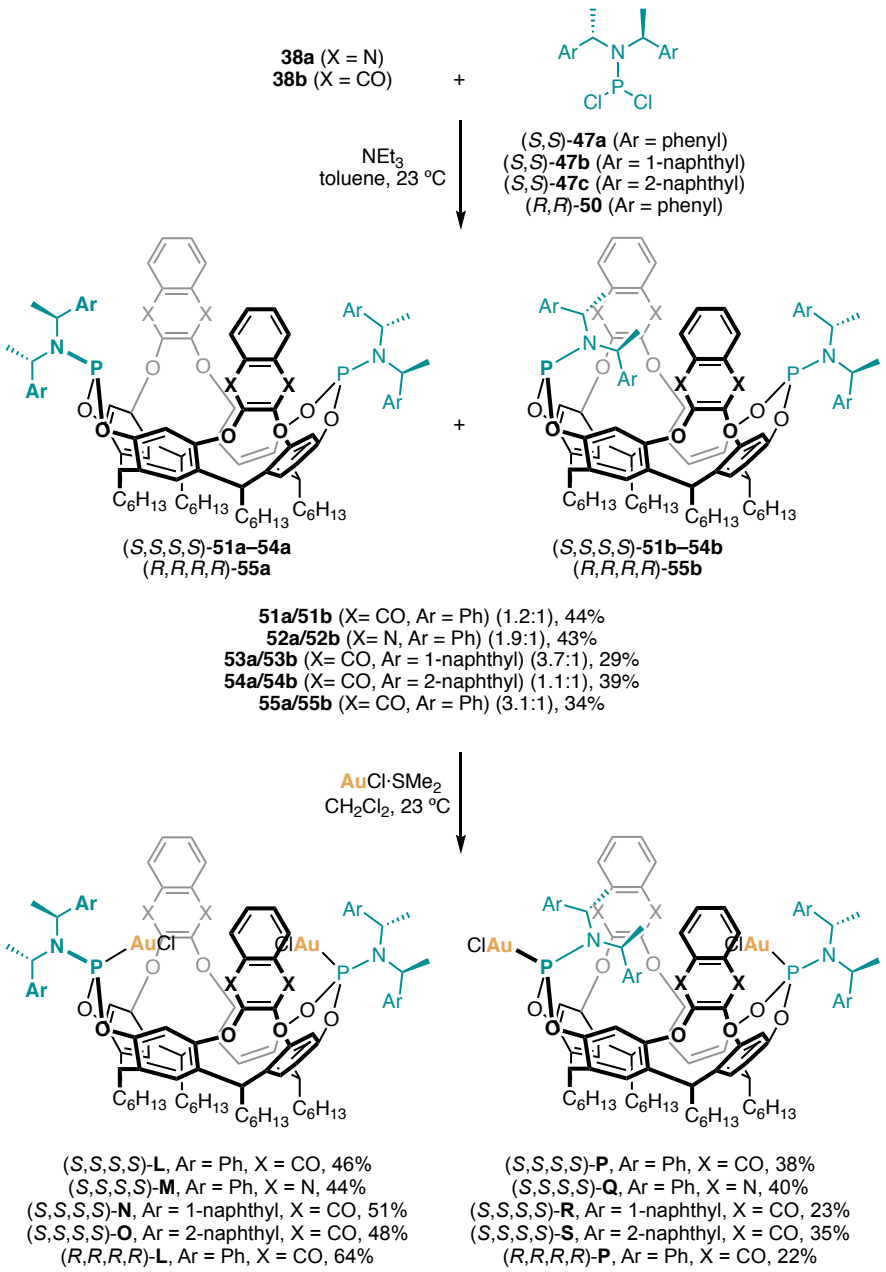
First, diphenols **37a–b** were reacted with 1,1-dichloro-*N*,*N*-bis((*S*)-1-phenylethyl)phosphanamine (**47a**) in the presence of triethylamine at 23 °C to give chiral phosphoramidites (**48**–**49**). In the case of use quinoxaline resorcin[4]arene derivative **37a**, we obtained a mixture of compounds with the phosphoramidite moiety inside and outside the pocket (**48a–b**) in a ratio **48a**/**48b** 6:1. After unsuccessful attempts to separate them by column chromatography, this mixture was used directly for the coordination of gold(I) with $AuCl{\cdot}SMe_2$, and purification by column chromatography enabled the separation of gold(I) cavitands (*S*,*S*)-**I** and (*S*,*S*)-**J**. Both structures were confirmed by X-ray diffraction. In case of naphthoquinone resorcin[4]arene derivative **37b**, we only obtained chiral phosphoramidite **49** in 30% yield and after the coordination of gold(I), cavitand (*S*,*S*)-**K** was prepared in excellent yield.



Scheme 20. Synthesis of chiral mononuclear gold(I) cavitands.

Furthermore, a series of dinuclear gold(I)-cavitand complexes were obtained having both metal centers located inside the cavity (complexes **L–O**), or one inside and the other one outside the cavity (complexes **P–S**) (Scheme 21).

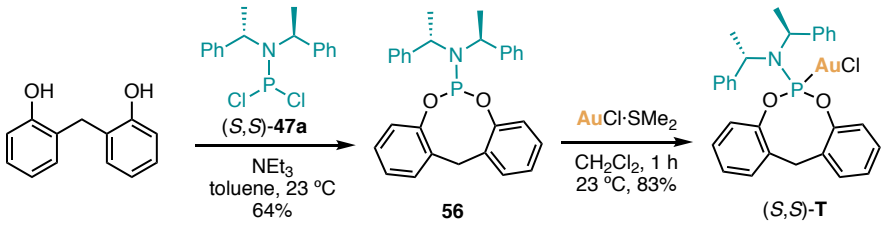
Following the same synthetic strategy, dinuclear gold(I) complexes were synthesized using *S*,*S*-bis(1-arylethyl)amines as chiral precursors. As in the case of mononuclear gold(I) complexes, we obtained a mixture of phosphoramidites, one of them outside-outside (**51a–54a**) and the other one inside-outside (**51b–54b**). Finally, gold(I) was introduced and the mixture of phosphoramidites was separated by column chromatography affording complexes (*S*,*S*,*S*,*S*)-**L–O**, with both AuCl fragments were inside the cavity, and complexes (*S*,*S*,*S*,*S*)-**P–S**, where one AuCl was inside and the other one outside. In the dinuclear gold(I) cavitands, we also synthesized the complexes with bulkier groups such as 1-naphthyl and 2-naphthyl instead of phenyl groups. Some of these structures were confirmed by X-ray diffraction.



Scheme 21. Synthesis of chiral dinuclear gold(I)-cavitand complexes.

Additionally, complexes (*R*,*R*,*R*,*R*)-**L** and (*R*,*R*,*R*,*R*)-**P** were synthesized according to the same procedure for their enantiomers using *R*,*R*-bis(1-phenylethyl)amine as chiral precursor (Scheme 21).

For off-cavity comparison of a similar active site, the synthesis of complex (*S*,*S*)-**T** was carried out in two steps (Scheme 22).



Scheme 22. Synthesis of complex (*S*,*S*)-**T**.

Optimization of the Alkoxycyclization Reaction Conditions

The use of chiral gold(I) cavitand complexes in asymmetric gold(I) catalysis was investigated in the enantioselective alkoxycyclization reaction of 1,6-dienyne **57** using ethanol as nucleophile to afford **58a** (Table 4). In this sense, we evaluated a chiral family of mono- and dinuclear gold(I)-cavitand complexes with quinoxalines and naphthoquinones walls.

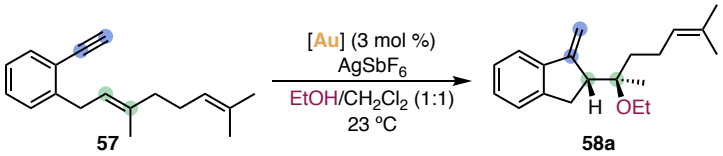
Mononuclear gold(I) cavitands (*S*,*S*)-**I** and (*S*,*S*)-**K** with gold(I) chloride fragment inside the cavity gave product **58a** in good yield but low enantioselectivity (Table 4, entries 2–3). When the (*S*,*S*)-**J** mononuclear cavitand with the AuCl moiety outside the cavity was employed, low yield and enantioselectivity were still obtained (Table 4, entry 4).

Dinuclear gold(I)-cavitand complexes were also tested in the enantioselective alkoxycyclization of **58a** at room temperature. When both gold(I) chloride moieties were located inside the pocket of the gold(I) cavitands, the product **58a** was afforded in good enantioselectivity (Table 4, entries 5–9). However, the use of dinuclear complexes with one AuCl fragment inside the cavity and the other one outside gave the product **58a,** but with poor enantioselectivity (Table 4, entries 10–14). The best result was achieved using complex (*S*,*S*,*S*,*S*)-**L** as precatalyst, which gave the product **58a** in 90% yield and with 89:11 *er*. Relying on this result, (*S*,*S*,*S*,*S*)-**L** complex was modified to study the effect of the cavitand walls and the phenyl group substituents. First, the naphthoquinone walls were replaced by quinoxalines to form cavitand (*S*,*S*,*S*,*S*)-**M**, which gave **58a** with 86:14 *er* in 89% yield (Table 4, entry 6). Alternatively, the phenyl groups were replaced with different naphthyl groups while maintaining the naphthoquinone walls (complexes (*S*,*S*,*S*,*S*)-**N** and (*S*,*S*,*S*,*S*)-**O**). When these cavitands were tested in the enantioselective catalysis, product **58a** was obtained with good enantioselectivity (Table 4, entries 7–8).

On the other hand, a control experiment was carried out to study the cavity effect of our complexes in this enantioselective transformation. Complex (*S*,*S*)-**T** with similar active site of chiral cavitands gave **58a** in low yield and enantioselectivity (Table 4, entry 1).

After testing complexes (*R*,*R*,*R*,*R*)-**L** and (*R*,*R*,*R*,*R*)-**P** in the enantioselective alkoxycyclization of **57**, the opposite enantiomer of **58a** was obtained with similar results (Table 4, entries 9 and 14).

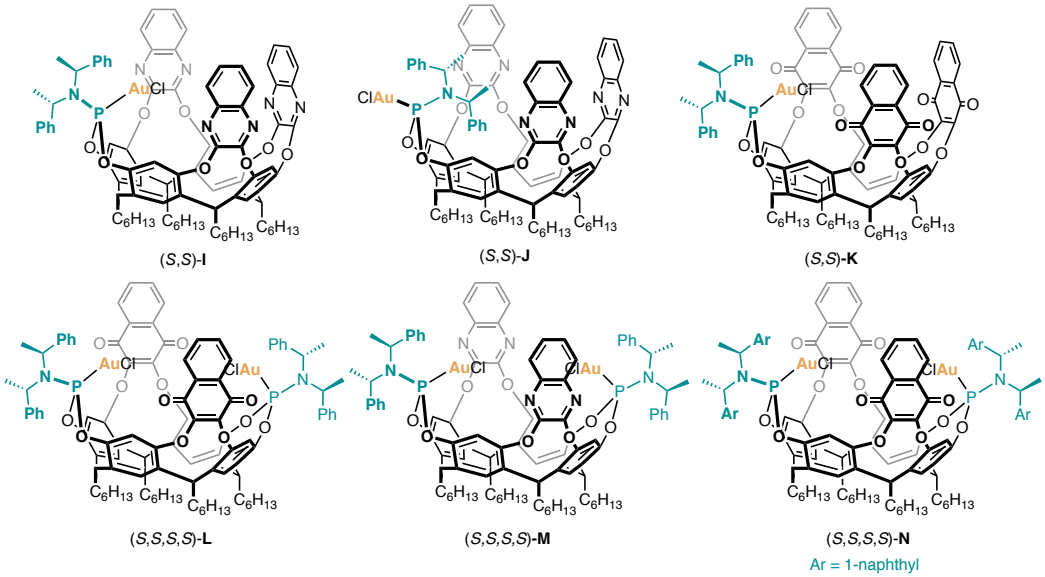
Table 4. Screening of gold(I)-cavitand complexes.

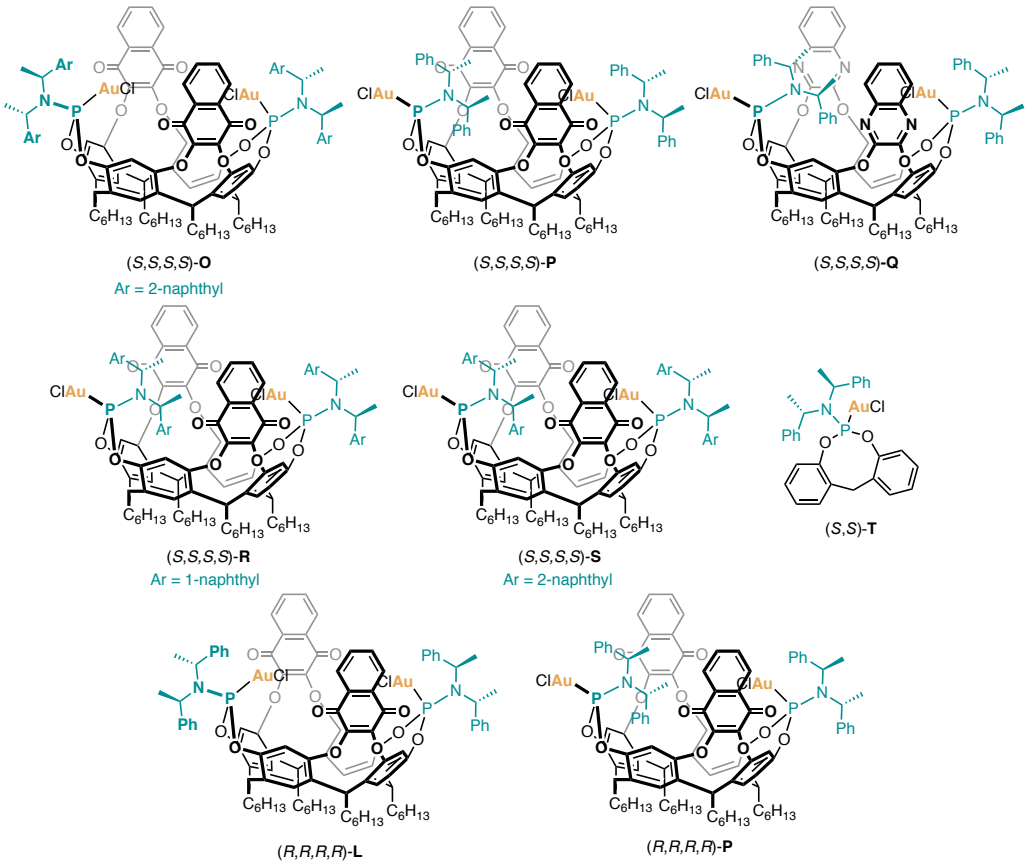


57 **58a**

Entry[a]	[Au]	$AgSbF_6$ (mol %)	Yield (%)[b]	*er* (%)[c]
1	(*S*,*S*)-**T**	3	48	57:43
2	(*S*,*S*)-**I**	3	74	59:41
3	(*S*,*S*)-**K**	3	83	51:49
4	(*S*,*S*)-**J**	3	36	45:55
5	(*S*,*S*,*S*,*S*)-**L**	6	90	89:11
6	(*S*,*S*,*S*,*S*)-**M**	6	80	86:14
7	(*S*,*S*,*S*,*S*)-**N**	6	84	74:26
8	(*S*,*S*,*S*,*S*)-**O**	6	83	88:12
9	(*R*,*R*,*R*,*R*)-**L**	6	91	10:90
10	(*S*,*S*,*S*,*S*)-**P**	6	86	55:45
11	(*S*,*S*,*S*,*S*)-**Q**	6	69	57:43
12	(*S*,*S*,*S*,*S*)-**R**	6	67	68:32
13	(*S*,*S*,*S*,*S*)-**S**	6	91	53:47
14	(*R*,*R*,*R*,*R*)-**P**	6	85	47:53

[a] **57** (0.06 mmol), 0.1 M. [b] Yields determined by ^1H NMR using Ph_2CH_2 as internal standard yield. [c] Enantiomeric ratios determined by HPLC.

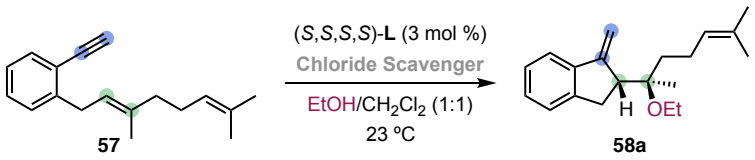




The effect of the chloride scavengers was evaluated using dinuclear cavitand (*S*,*S*,*S*,*S*)-**L** as precatalyst. The best result was observed using $AgSbF_6$ (Table 5, entry 1). The same enantioselectivity was observed using 3 or 6 mol % of $AgSbF_6$ (Table 5, entries 1–2). Therefore, using only 3 mol % of $AgSbF_6$ is enough to generate monocationic species for the catalysis of asymmetric transformation. No product **58a** was detected using $AgPF_6$ or $AgBF_4$ (Table 5, entries 3–4), whereas **58a** was obtained in moderate yields and with low enantioselectivities with $AgNTf_2$ and AgOTf (Table 5, entries 5 and 8).

When sodium salts were used as activating agents, we observed that using the same anions, the same enantioselectivity and similar yields were obtained than with the corresponding silver salts (Table 5, entry 7), whereas in the case of $NaBAr_4^F$, compound **58a** was formed in 63% yield and with 90:10 *er* (Table 5, entry 6).

Table 5. Screening of chloride scavengers.



57 **58a**

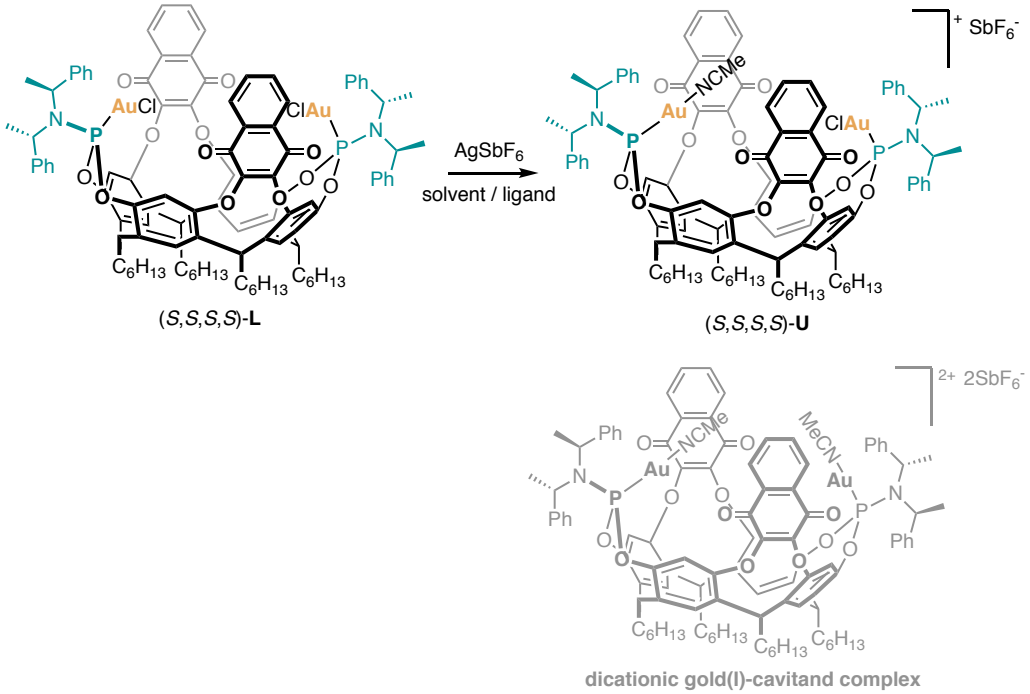
Entry[a]	Chloride Scavenger (mol %)	t (h)	Yield (%)[b]	*er* (%)[c]
1	$AgSbF_6$ (6)	1	90	89:11
2	$AgSbF_6$ (3)	1	88	89:11
3	$AgPF_6$ (6)	45	n.r.	-
4	$AgBF_4$ (6)	45	n.r.	-
5	$AgNTf_2$ (6)	18	45	69:23
6	$NaBAr_4^F$ (6)	18	63	90:10
7	$NaSbF_6$ (6)	18	85	89:11
8	AgOTf (6)	26	42	64:36

[a] **57** (0.06 mmol), 0.1 M. [b] Yields determined by ^{1}H NMR using Ph_2CH_2 as internal standard yield. [c] Enantiomeric ratios determined by HPLC. n.r. = no reaction.

After selecting (*S*,*S*,*S*,*S*)-**L** as the best precatalyst, and testing the asymmetric alkoxycyclization reaction generating the active cationic gold(I) complex *in situ* from the corresponding neutral gold(I) complex *via* chloride abstraction, we prepared the corresponding cationic gold(I) complexes of (*S*,*S*,*S*,*S*)-**L**, to use them directly in the asymmetric transformation, without needing to activate it.

Complex (*S*,*S*,*S*,*S*)-**L** contains two gold(I) chloride moieties, so both monocationic and dicationic species can be generated. Despite our efforts to obtain the corresponding dicationic complex, only monocationic gold(I) catalyst, (*S*,*S*,*S*,*S*)-**U**, could be obtained (Table 6, entries 1–4). Thus, we assumed that the only active species involved in the asymmetric alkoxycyclization is the corresponding monocationic gold(I) complex. Therefore, we prepared this complex by using just 1.05 equiv of silver salt, which gave full conversion of the precatalyst (*S*,*S*,*S*,*S*)-**L** (Table 6, entry 5) to afford (*S*,*S*,*S*,*S*)-**U**. Even under more forcing conditions, only the monocationic gold(I)-cavitand complex could be detected as in the previous cases (Table 6, entries 6–8).

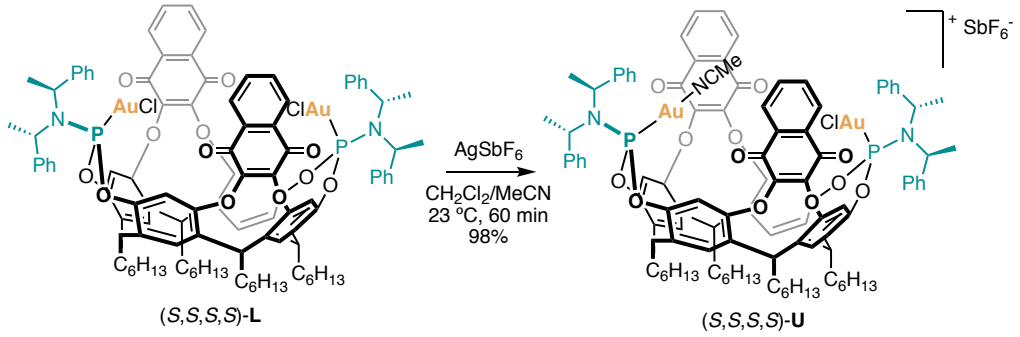
Table 6. Chloride abstraction.



Entry[a,b]	Solvent/Ligand	$AgSbF_6$ (equiv)	t (min)	T (°C)
1	CH_2Cl_2/CH_3CN (8:2)	2.1	30	23
2	CH_2Cl_2/CH_3CN (8:2)	2.1	60	23
3	CH_2Cl_2/CH_3CN (8:2)	2.1	120	23
4	CH_2Cl_2/CH_3CN (8:2)	2.1	120	40
5	CH_2Cl_2/CH_3CN (8:2)	1.05	60	23
6	CH_3CN	2.1	30	23
7	CH_3CN	4.0	30	23
8	CH_3CN	10.0	30	23

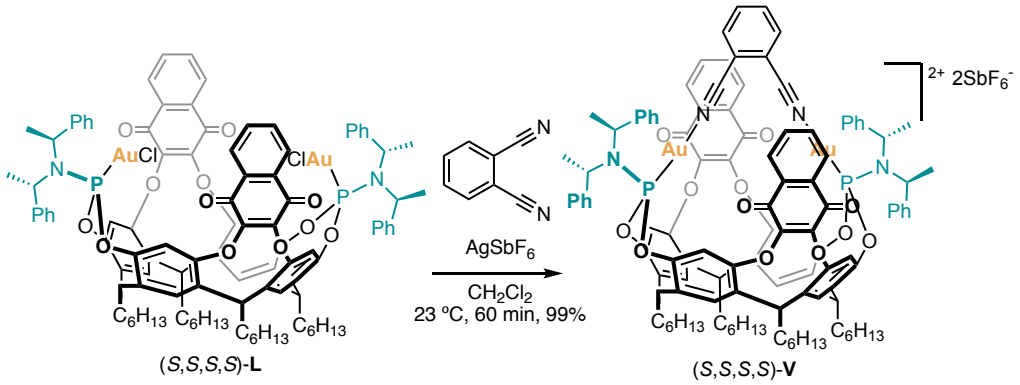
[a] (*S*,*S*,*S*,*S*)-**L** (9.50 µmol), 0.02 M. [b] Total conversion determined by ^1H NMR and ^{31}P NMR.

Finally, treatment of (*S*,*S*,*S*,*S*)-**L** in presence of 1.05 equiv of $AgSbF_6$ and acetonitrile as the ligand gave monocationic catalyst (*S*,*S*,*S*,*S*)-**U** in excellent yield in a preparative scale (Scheme 23). The structure of (*S*,*S*,*S*,*S*)-**U** was confirmed by both NMR and X-ray diffraction analysis.



Scheme 23. Preparative synthesis of a chiral monocationic gold(I)-cavitand complex.

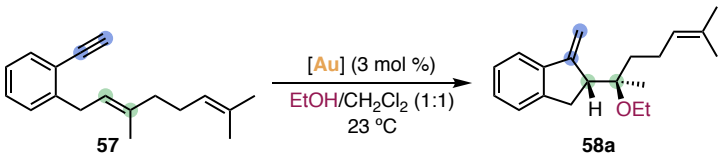
On the other hand, both chlorides of complex (*S*,*S*,*S*,*S*)-**L** could be abstracted using a bridging ligand such as phthalonitrile (instead of acetonitrile) and 2.1 equiv of $AgSbF_6$. In this case, we only observed the formation of dicationic complex (*S*,*S*,*S*,*S*)-**V**, which was isolated in excellent yield (Scheme 24).



Scheme 24. Synthesis of dicationic gold(I) cavitand complex.

After obtaining cationic gold(I) cavitand complexes (*S*,*S*,*S*,*S*)-**U** and (*S*,*S*,*S*,*S*)-**V**, we compared their activity in enantioselective alkoxycyclization reactions. As expected, when we performed the alkoxycyclization reaction in the presence of 3 mol % of (*S*,*S*,*S*,*S*)-**U**, product **58a** was obtained in 89% yield and 89:11 *er* (Table 7, entry 1). The same result was observed either by using the precatalyst and generating the active specie *in situ* or using the corresponding monocationic species directly. In contrast, dicationic complex (*S*,*S*,*S*,*S*)-**V** led to a slight decrease in the enantioselectivity (Table 7, entry 2). Therefore, we decided to use the monocationic gold(I) cavitand (*S*,*S*,*S*,*S*)-**U** for the rest of the optimization.

Table 7. Screening of gold(I)-cavitand complexes.

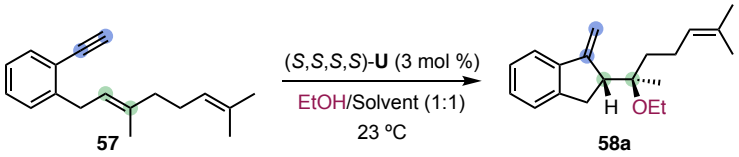


Entry[a]	[Au]	t (h)	Yield (%)[b]	*er* (%)[c]
1	(*S*,*S*,*S*,*S*)-**U**	1	89	89:11
2	(*S*,*S*,*S*,*S*)-**V**	3	74	81:19

[a] **57** (0.06 mmol), 0.1 M. [b] Yields determined by ^{1}H NMR using Ph_2CH_2 as internal standard yield. [c] Enantiomeric ratios determined by HPLC.

We performed a solvent screening using a ratio of 1:1 solvent/nucleophile, but we found very small variations in terms of both yield and enantioselectivity (Table 8, entries 1–6). The reaction proved to be faster when chlorinated solvents were used (Table 8, entries 1 and 2). Overall, CH_2Cl_2 proved to be the best performing solvent by a small margin.

Table 8. Screening of solvents.

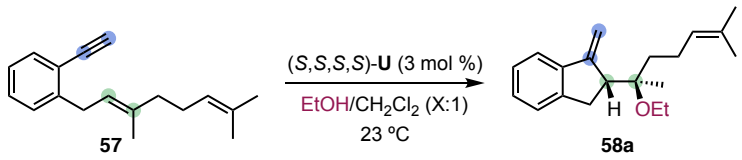


Entry[a]	Solvent	t (h)	Yield (%)[b]	*er* (%)[c]
1	CH_2Cl_2	1	89	89:11
2	1,2-DCE	1	87	89:11
3	Toluene	3	82	85:15
4	EtOAc	3	79	88:12
5	THF	3	78	87:13
6	EtOH	3	80	90:10

[a] **57** (0.06 mmol), 0.1 M. [b] Yields determined by ^{1}H NMR using Ph_2CH_2 as internal standard yield. [c] Enantiomeric ratios determined by HPLC.

Next, we carried out a screening of the ratio of solvent and nucleophile. When we used a ratio of dichloromethane/ethanol 1:1, compound **58a** was afforded in 89% yield and 89:11 *er* (Table 9, entry 1). When the amount of ethanol was reduced, the yield decreased drastically (Table 9, entries 2–4).

Table 9. Screening of ratio EtOH/CH_2Cl_2.

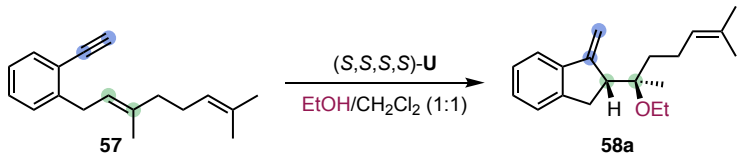


Entry[a]	Ratio (EtOH/CH_2Cl_2)	t (h)	Yield (%)[b]	*er* (%)[c]
1	1:1	1	89	89:11
2	1:2	1	83	88:12
3	1:5	1	66	≥83:17[d]
4	1:10	1	30	≥73:27[d]

[a] **57** (0.06 mmol), 0.1 M. [b] Yields determined by ^{1}H NMR using Ph_2CH_2 as internal standard yield. [c] Enantiomeric ratios determined by HPLC. [d] Side-product overlapping in the minor enantiomer.

Finally, the impact of other parameters such as catalyst loading, concentration, and temperature was studied (Table 10). No variations in terms of enantioselectivity were observed when the concentration was changed. This change only affected the reaction time, as the reaction was faster in case of a higher concentration (Table 10, entry 2). The same effect was also observed when the catalyst loading was modified (Table 10, entries 5–6). After modification of the temperature, the best results were found, and the desired product **58a** was obtained in 90% yield and 96:4 *er*. In the end, 3 mol % of catalyst (*S*,*S*,*S*,*S*)-**U** was selected at -50 °C at 0.25 M, in 1:1 EtOH/CH_2Cl_2 as the optimal set of conditions (Table 10, entry 9).

Table 10. Screening of concentration, catalyst loading and temperature.

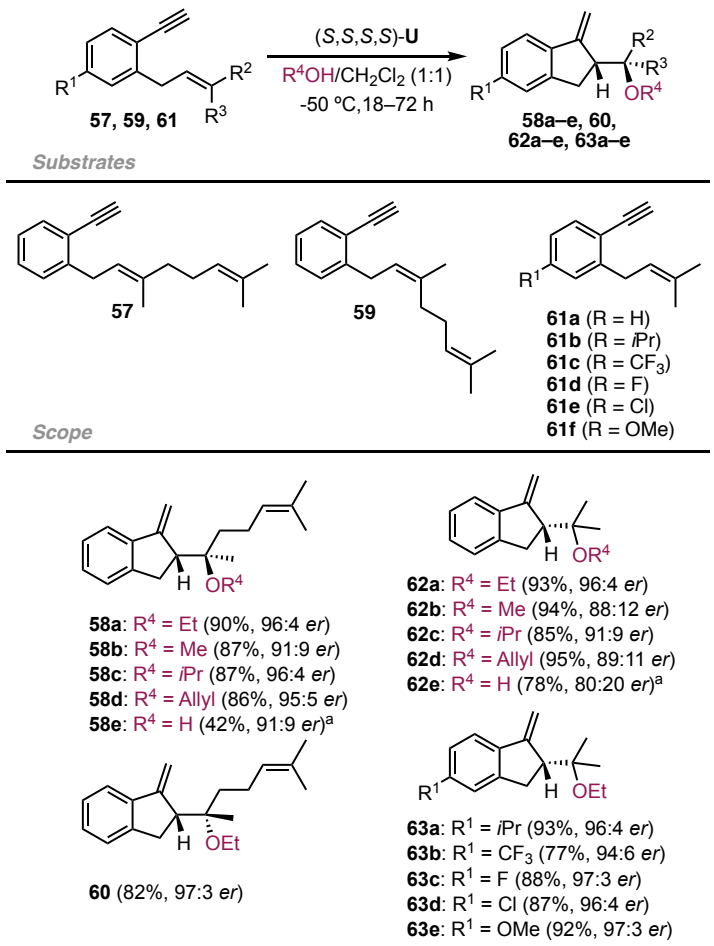


Entry[a]	(*S*,*S*,*S*,*S*)-U (mol %)	Concentration (M)	T (°C)	t (h)	Yield (%)[b]	*er* (%)[c]
1	3	0.1	23	1	89	89:11
2	3	0.25	23	0.5	84	87:13
3	3	0.05	23	1	90	88:12
4	5	0.1	23	0.5	91	89:11
5	2	0.1	23	1.5	86	86:14
6	1	0.1	23	3.0	85	86:14
7	3	0.1	0	1.5	92	92:8
8	3	0.1	-50	72	91	96:4
9	3	0.25	-50	18	90[d]	96:4

[a] **57** (0.06 mmol). [b] Yields determined by ^{1}H NMR using Ph_2CH_2 as internal standard yield. [c] Enantiomeric ratios determined by HPLC. [d] Isolated yield.

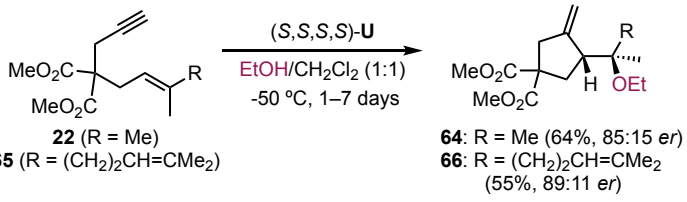
Scope of the Enantioselective Alkoxycyclization and their Derivatization

With the optimized reaction conditions, we investigated the reaction scope (Scheme 25). The effect of different nucleophiles was studied using (*S*,*S*,*S*,*S*)-**U** as catalyst and *E*-1,6-dienyne **57**. Different alcohols (methanol, ethanol, isopropanol and allyl alcohol) could be employed, which led to products **58a–d** with excellent yield, diastereoselectivity and enantioselectivity (91:9–96:4 *er*). A slight decrease in the enantioselectivity was observed using smaller nucleophiles such as methanol and water, which gave product **58b** and **58e** in 91:9 *er*. The addition of water was performed in acetone as solvent instead of dichloromethane at -20 °C to give **58e** in moderate yield and 91:9 *er*. We also performed the reaction using the *Z* diastereomer of **57**. Gratifyingly, *Z*-dienyne **60** was obtained in 97:3 *er*, granting access to the corresponding enantioenriched compound **59**. Shorter-chain enynes such as **61a** were also reacted well giving rise to compounds **62a–e**, with similar results in terms of yield and selectivity than dienyne **57**. As in the previous case, the enantioselectivity decreased upon reaction of enyne **61a** with smaller nucleophiles to give compounds **62b** and **62e**. Finally, the impact of substituents on the *para*-position to the alkynes **61b–f** on the reaction outcome was evaluated. Both electron-donating and electron-withdrawing groups were well tolerated and led to products **63a–e** in 77−93% yields and with excellent enantiomeric ratios of 96:4 to 97:3.



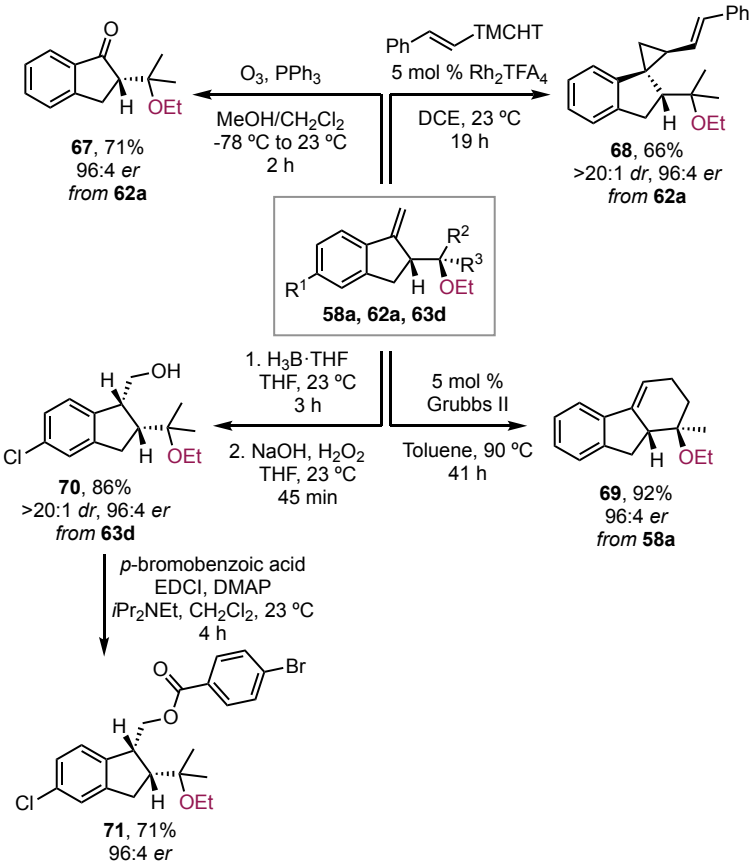
Scheme 25. Scope of the enantioselective alkoxycyclization reaction. [a] Solvent/nucleophile: acetone/H_2O 1:1 at -20 °C.

Even though there are no methods for the enantioselective alkoxycyclization of phenyl-linked enynes, cyclodextrin-NHC-gold(I) complexes were recently reported for the asymmetric alkoxycyclization of enyne **22** with different nucleophiles (as previously mentioned in the introduction).[21] We also tested enynes with a different linker such as **22** and **65**. With our system, enynes **22** and **65**, gave products **64** and **66** in the presence of ethanol with 85:15 and 89:11 *er* respectively (Scheme 26). We hypothesize that phenyl-linked enynes lead to higher selectivities due to the positive π-π interactions between the gold(I) cavitand and the aromatic moieties of those substrates.



Scheme 26. Enantioselective alkoxycyclization of 1,6-enynes **22** and **65**.

The obtained products can be used to access a range of enantioenriched structures (Scheme 27). For instance, alkene **63d** was converted diastereoselectively by hydroboration-oxidation into alcohol **70**, which was further reacted with *p*-bromobenzoic acid to give **71** as a crystalline solid. Ester **71** could be used to assign the *R* absolute configuration of product **63d** by X-ray diffraction (Figure 1). By analogy, the absolute configuration of all indenes was assigned as *R*. A retro-Buchner reaction/cyclopropanation sequence was employed to assemble spirocyclic cyclopropane **68** in 66% yield and excellent diastereoselectivity (>20:1). On the other hand, ozonolysis of alkene **62a** afforded ketone **67** in good yield. Finally, tetrahydro-1*H*-fluorene **69** was obtained in excellent yield after ring closing metathesis of **58a** using 2nd generation Grubbs catalyst.



Scheme 27. Derivatization of the reaction products and assignment of the absolute configuration by X-ray diffraction of ester **71**. TMCHT = 1,3,5-trimethylcyclohepta-1,3,5-triene.

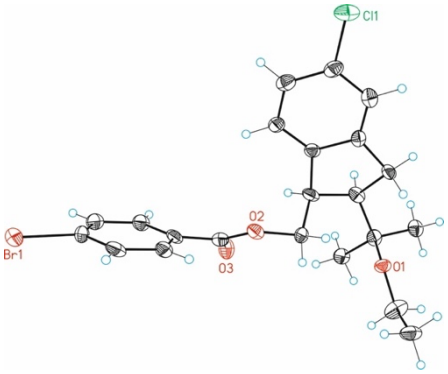
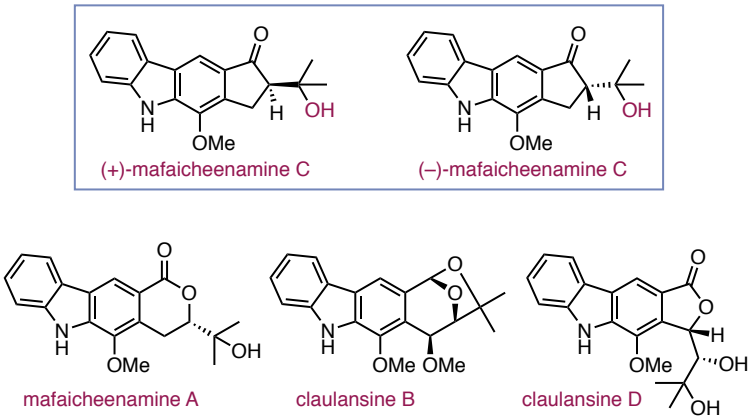


Figure 1. X-ray structure of **71**.

Total Synthesis of (+)-Mafaicheenamine C Using Gold(I) Cavitands

To demonstrate the potential and versatility of these chiral gold(I) cavitands, we employed them in the first total synthesis of (+)-mafaicheenamine C. This natural product belongs to a family of bioactive carbazole alkaloids isolated from *Clausena lansium* (Scheme 28)[26] which also produces compounds such as mafaicheenamine A and claulansines B and D.[27]



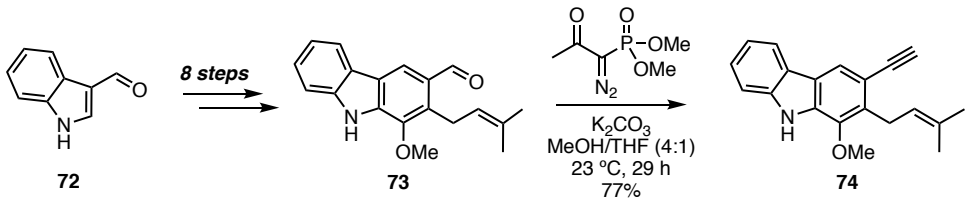
Scheme 28. Carbazole alkaloids.

Our work commenced with the preparation of enyne **74**. The required precursor 1-methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carbaldehyde (**73**) was obtained from 1*H*-indole-3-carbaldehyde (**72**) after 8 steps following a known method.[28] Then, aldehyde **73** was transformed into alkyne **74** using the Bestmann–Ohira reagent (Scheme 29).

26 Laphookhieo, S.; Maneerat, W. *Heterocycles* **2010**, *81*, 1261–1269.

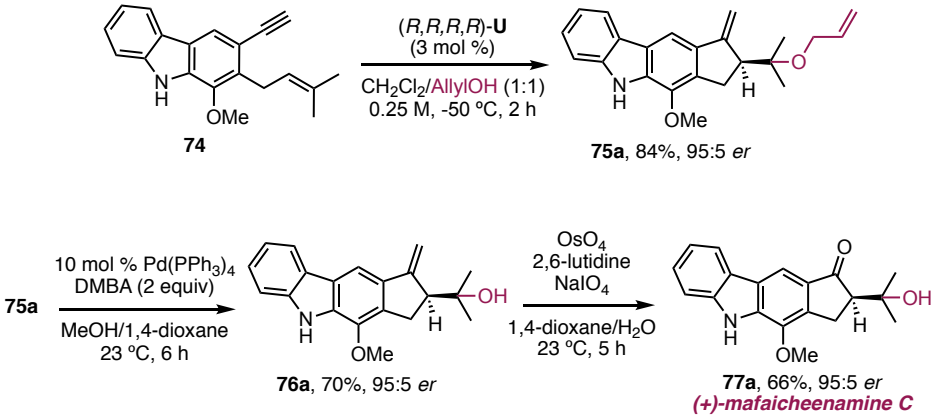
27 (a) Shen, D.-Y.; Chan, Y.-Y.; Hwang, T.-L.; Juang, S.-H.; Huang, S.-C.; Kuo, P.-C.; Thang, T. D.; Lee, E.-J.; Damu, A. G.; Wu, T.-S. *J. Nat. Prod.* **2014**, *77* (5), 1215–1223. (b) Liu, H.; Li, C.-J.; Yang, J.-Z.; Ning, N.; Si, Y.-K.; Li, L.; Chen, N.-H.; Zhao, Q.; Zhang, D.-M. *J. Nat. Prod.* **2012**, *75*, 677–682.

28 Liu, Y.; Guo, Y.; Ji, F.; Gao, D.; Song, C.; Chang, J. *J. Org. Chem.* **2016**, *81*, 4310–4315.



Scheme 29. Synthesis of enyne **74**.

With key enyne **74** in hand, we performed the alkoxycyclization reaction using chiral gold(I) catalyst (*R*,*R*,*R*,*R*)-**U** in the presence of allyl alcohol as nucleophile at -50 °C to obtain allyl ether **75a** in 84% yield and 95:5 *er*. Then, the deprotection of the allyl group with $Pd(PPh_4)_3$ and dimethyl barbituric acid (DMBA) provided alcohol **76a**. Finally, oxidative cleavage of the exocyclic alkene of **76a** gave (+)-mafaicheenamine C (Scheme 30). The absolute configuration of the natural product was assigned by X-ray diffraction and comparison with the reported specific rotation for the natural compound.[26] We also performed the alkoxycyclization reaction of **74** using water as nucleophile instead of allyl alcohol, which allowed us to obtain alcohol **76a** directly, but in 90:10 *er*.



Scheme 30. Synthesis of (+)-mafaicheenamine C.

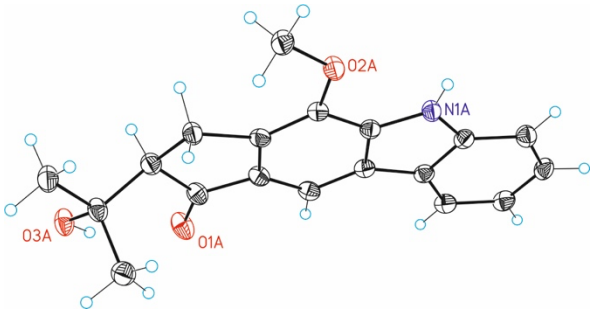
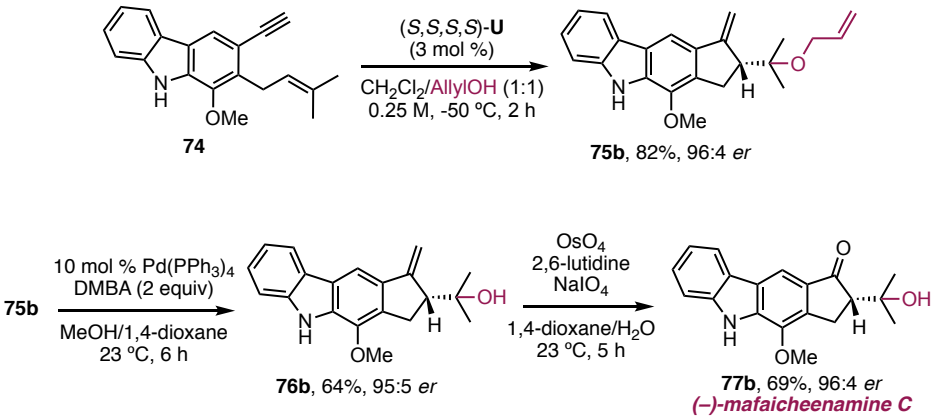


Figure 2. X-ray structure of (+)-mafaicheenamine C.

On the other hand, the same synthetic route was followed to synthesize the non-natural (–)-mafaicheenamine C using the enantiomer of the same chiral gold(I) catalyst, (*S*,*S*,*S*,*S*)-**U** in the alkoxycyclization reaction. Consequently, compound **75b** was obtained in 82% yield and with

96:4 *er* (Scheme 31). We also evaluated non-cavitand complex (*S*,*S*)-**T** that gave the desired key product **75b** with 76:24 *er*, illustrating how the cavity of our gold(I) cavitand complexes is key to get good enantioselectivities.



Scheme 31. Synthesis of (–)-mafaicheenamine C.

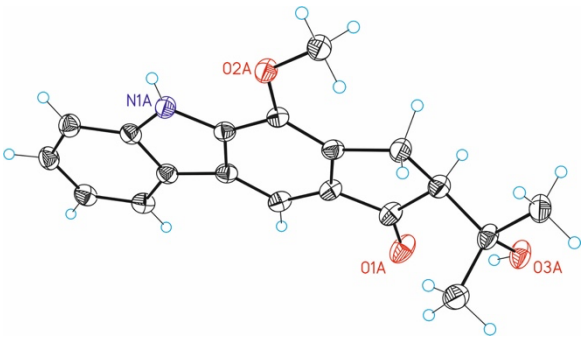


Figure 3. X-ray structure of (–)-mafaicheenamine C.

DFT Calculations.

To further rationalize the stereochemical outcome of the asymmetric alkoxycyclization,[29] we developed a model of the enantiodetermining step by DFT calculations at the B3LYP/6-31G(d,p) (C, H, P, O, Cl, N), SDD (Au) (SMD= ethanol) level of theory. We performed the calculations using enyne **61a** and simplified gold(I) cavitand (*S*,*S*,*S*,*S*)-**U** (without including the aliphatic chains).[30]

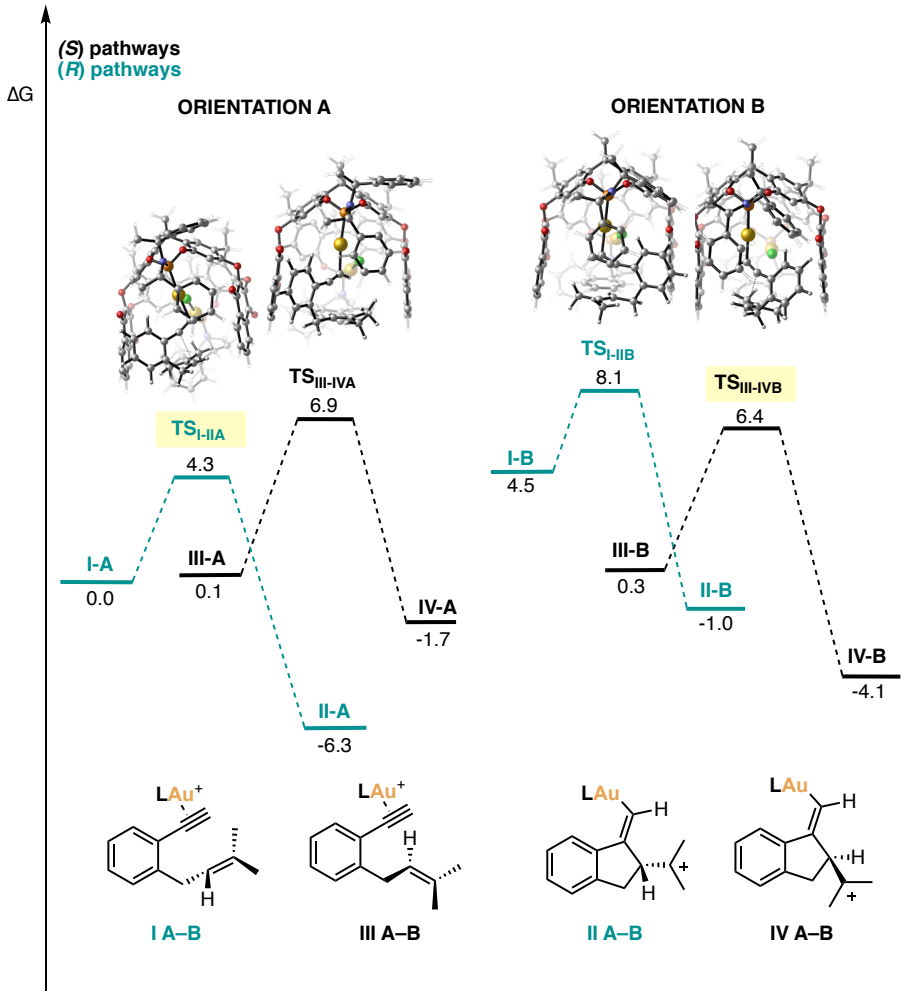


Figure 4. Free energy profile for the Au(I)-catalyzed alkoxycyclization reaction of **61a**. (*R*) pathways are depicted in green and (*S*) pathways in black. Free energies in kcal/mol at 25 ºC.

We studied two possible orientations (**A** and **B**) of the gold(I)-coordinated enyne in the pocket of the complex, and the two enantiotopic faces of the alkene (Figure 4). Intermediates **I A–B**

29 Escofet, I.; Armengol-Relats, H.; Bruss, H.; Besora, M.; Echavarren, A. M. *Chem. Eur. J.* **2020**, *26*, 15738–15745.

30 (a) Pochorovski, I.; Milić, J.; Kolarski, D.; Gropp, C.; Schweizer, W. B.; Diederich, F. *J. Am. Chem. Soc.* **2014**, *136*, 3852–3858. (b) Milić, J.; Zalibera, M.; Pochorovski, I.; Trapp, N.; Nomrowski, J.; Neshchadin, D.; Ruhlmann, L.; Boudon, C.; Wenger, O. S.; Savitsky, A.; Lubitz, W.; Gescheidt, G.; Diederich, F. *J. Phys. Chem. Lett.* **2016**, *7*, 2470–2477.

and **III A–B** are formed by coordination of gold(I) to enyne **61a**. These intermediates evolve forming carbocationic gold(I) intermediates **II A–B** or **IV A–B** through 5-*exo*-dig cyclization, which is the enantiodetermining step of the process.

As illustrated in Figure 4, four possible intermediates could be formed in the reaction. However, **II-A** was found to be favored *via* $\mathbf{TS_{I\text{-}IIA}}$, due to the lower activation energy by at least 2.1 kcal/mol compared to $\mathbf{TS_{III\text{-}IVB}}$. Therefore, in agreement with our experimental results, the formation of intermediate **II-A** with *R* absolute configuration, is kinetically favored.

$\mathbf{TS_{I\text{-}IIA}}$ could be stabilized by non-covalent interactions (π-π stacking) between the aryl ring of the enyne and the aryl of the phosphoramidite of the cavitand (3.62 Å), and also with the naphthoquinone wall of the complex (3.56 Å) (Figure 5).

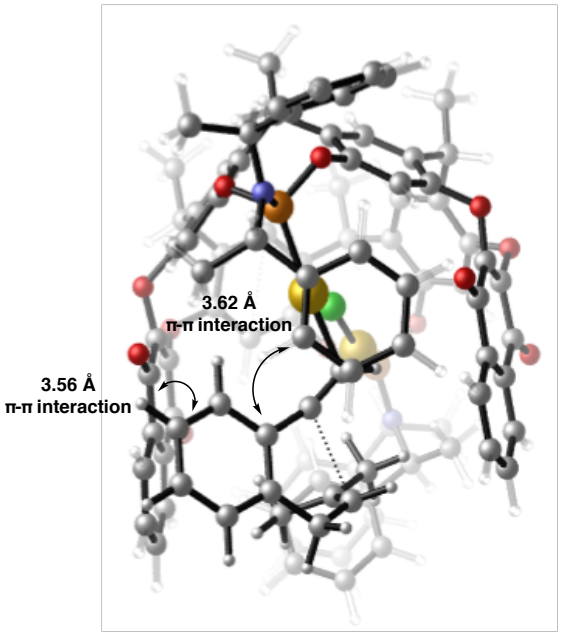


Figure 5. CYLview representations of $\mathbf{TS_{I\text{-}IIA}}$.

NCI maps were plotted in order to visualize the non-covalent interactions present in the transition states. Weak attractive (non-covalent) interactions are represented by green surfaces. NCI between the aryl ring of the enyne and the aryl of the phosphoramidite of the cavitand are presented in $\mathbf{TS_{I\text{-}IIA}}$ (Figure 6), whereas these are much weaker in $\mathbf{TS_{III\text{-}IVB}}$ (Figure 7). Additional stabilization is provided by interactions between the aryl of the enyne and the naphthoquinone wall of the cavitand. Also, non-covalent interactions within the complex itself are present in $\mathbf{TS_{I\text{-}IIA}}$ (Figure 6), but are much weaker in $\mathbf{TS_{III\text{-}IVB}}$ (Figure 7).

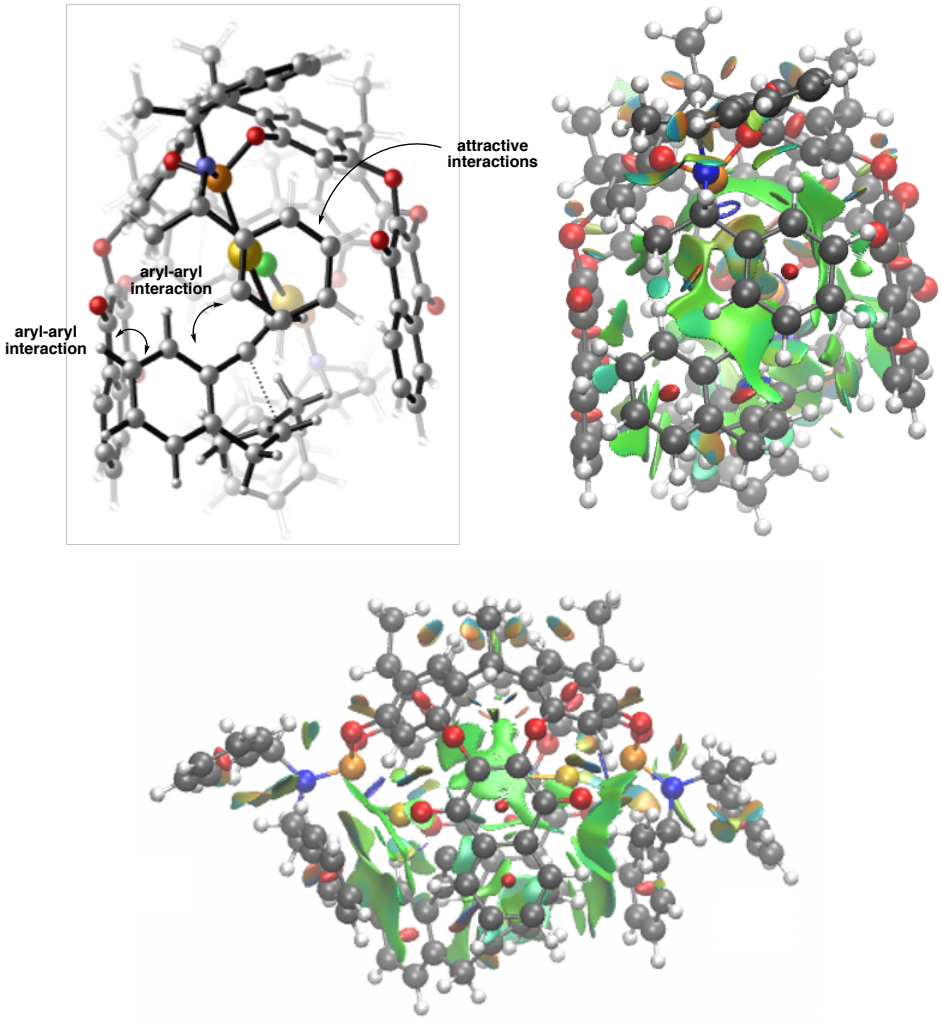


Figure 6. CYLview representations and NCI plot of $\mathbf{TS_{I\text{-}IIA}}$. Strong attractive (covalent) interactions are blue (C–C bond formation), weak attractive interactions are green (non-covalent interactions), and strong repulsive interactions are red. Color code: P: orange, Au: yellow, F: cyan, O: red, C: grey, Cl: grey and H: white.

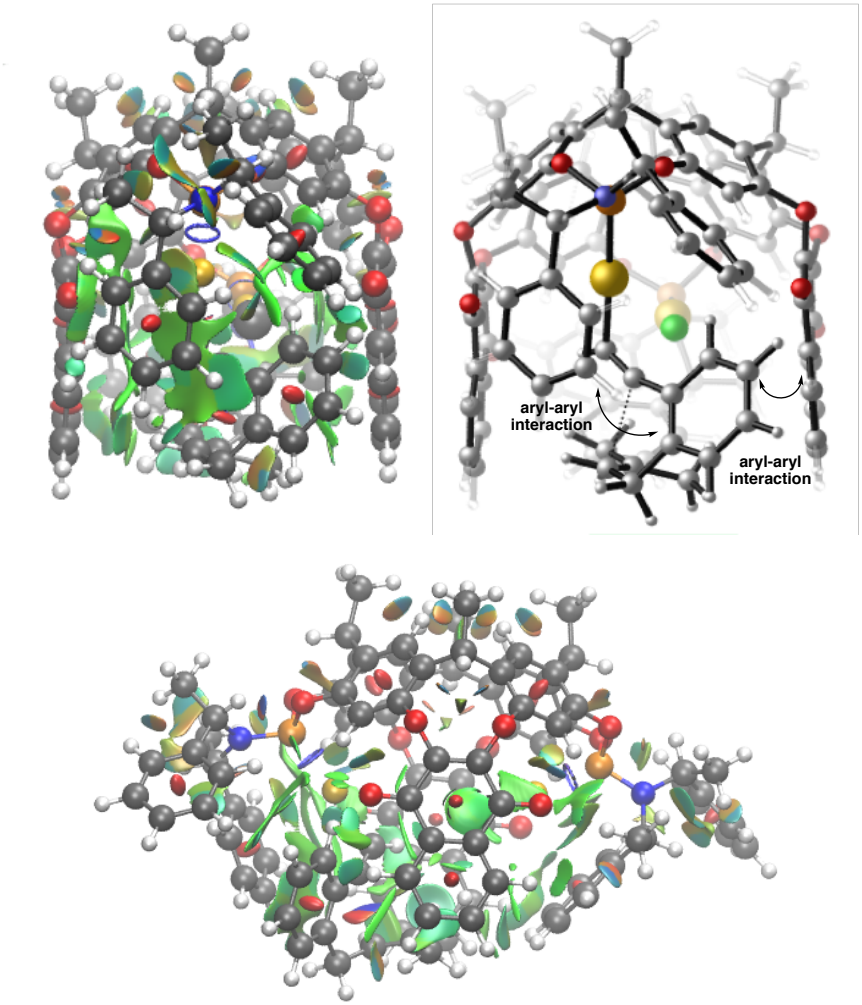
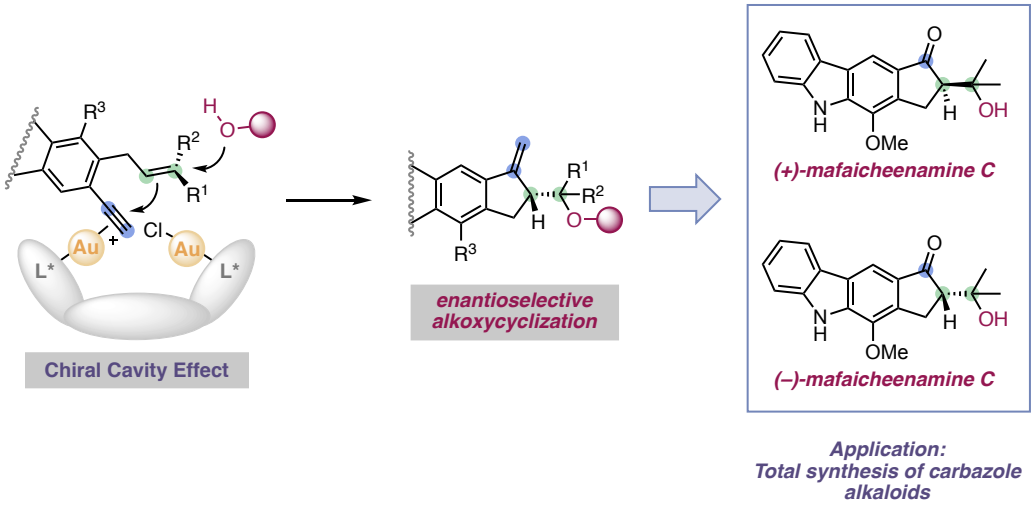


Figure 7. CYLview representations and NCI plot of $\mathbf{TS_{III\text{-}IVB}}$. Strong attractive (covalent) interactions are blue (C–C bond formation), weak attractive interactions are green (non-covalent interactions), and strong repulsive interactions are red. Color code: P: orange, Au: yellow, F: cyan, O: red, C: grey, Cl: grey and H: white.

Conclusions

We have developed a modular synthesis of a new family of both achiral and chiral gold(I)-cavitand complexes from resorcin[4]arene precursors, including both mononuclear and dinuclear gold(I) complexes. This new set of gold(I) catalysts allowed the discovery of new selectivities in the cycloisomerization of 1,6-dienynes.

The chiral gold(I) cavitands were applied in the alkoxycyclization of 1,6-enynes giving 1-methylene-2,3-dihydro-1*H*-indenes in good to excellent yields and enantioselectivities. These enantio-enriched products could be derivatized for the construction of chiral indanones with a stereocenter at C-2, among other structures. To demonstrate the potential of these catalysts, we have applied them in the total synthesis of (+)-mafaicheenamine C and its enantiomer, establishing the absolute configuration of the natural product. DFT calculations have supported the stereochemical outcome of the enantioselective alkoxycyclization.



Scheme 32. Chiral gold(I) cavitands for the enantioselective alkoxycyclization of 1,6-enynes and their application in total synthesis.

Experimental Section

General Methods

The synthesis of the ligands and gold(I) complexes was carried out under argon in solvents dried by passing through an activated alumina column on a PureSolvTM Solvent Purification System (SPS, Innovative Technologies, Inc., MA). Yields refer to chromatographically and spectroscopically pure (^{1}H NMR) homogeneous material, unless otherwise stated. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck Gf234) using short-wave UV light as visualizing agent and, $KMnO_4$ or acidic vanillin followed by heat as developing agents. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) as the stationary phase manually, or using a CombiFlash®Rf instrument with normal phase disposable columns of different sizes (Teledyne Isco). Reactions were monitored by TLC and UHPLC (Agilent Technologies 1290 Infinity II, LC/MS with single-quad detector InfinityLab (APCI ionization source). Melting points were determined using a MP70 Melting Point System (Mettler Toledo). NMR spectra were recorded at 298 K on BrukerAvance Ultrashield NMR spectrometers (300 MHz, 400 MHz, 500 MHz and 500 MHz with CryoProbe). Chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual solvent (For ^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.31 ppm, for ^{13}C NMR: $CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 54.00 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = "pentet" (quintet), m = multiplet, br s = broad singlet. 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). Elemental analyses were performed on a LECO CHNS 932 micro- analyzer at the Universidad Complutense de Madrid. Specific optical rotation measurements were carried out on a Jasco P-1030 model polarimeter equipped with a PMT detector using the sodium line at 589 nm. Chiral HPLC analyses were performed on an Agilent Technologies 1200 series. SFC analyses were performed on an Agilent Technologies 1260 Infinity II, a Waters ACQUITY UPC2 System with diode array detector and by Chiral Technologies Europe analytical service. X-ray diffraction data were collected at 100 K on a Rigaku MicroMax-007HF, Mo *Kα* rotating anode, equipped with a Pilatus 200 K detector or on a Bruker APEX DUO, Mo *Kα* Microfocus source E025 IuS anode, equipped with an APEX DUO detector using omega scans.

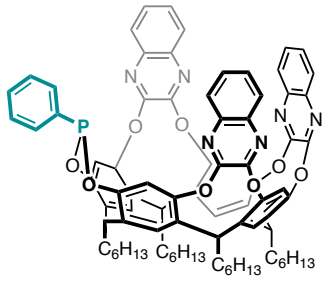
Synthetic Procedures and Analytical Data

General Procedure A:

(Me_2S)AuCl was added to a solution of the corresponding phosphonite or phosphoramidite in dry CH_2Cl_2 (0.05 M) under argon at 23 °C. The reaction mixture was stirred at 23 °C for 1 h and then concentrated under vacuum. The crude was purified by flash column chromatography on silica gel to obtain the gold(I) complexes.

Synthesis of Achiral Gold(I)-Cavitand Complexes.

Phosphonite 39



A reported procedure was followed.[8] $PhP(NEt_2)_2$ (0.52 mL, 1.99 mmol) was added to a mixture of biphenol **37a**.[31] (2 g, 1.66 mmol) in dry toluene (33.2 mL, 0.05 M) under an argon at 80 °C. After stirring for 20 h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 4:1) to afford phosphonite **39** (902 mg, 0.69 mmol, 41% yield) as a white solid.

M.p. = 347–349 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.27 (s, 2H), 8.00 (ddd, *J* = 8.3, 1.5, 0.6 Hz, 2H), 7.91 – 7.82 (m, 2H), 7.78 – 7.72 (m, 4H), 7.64 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 2H), 7.58 – 7.51 (m, 5H), 7.47 (dt, *J* = 6.3, 3.3 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 4H), 7.30 (d, *J* = 1.1 Hz, 2H), 5.71 (td, *J* = 8.3, 4.8 Hz, 3H), 4.63 (td, *J* = 8.1, 2.2 Hz, 1H), 2.43 – 2.30 (m, 6H), 2.27 (q, *J* = 8.1 Hz, 2H), 1.55 – 1.25 (m, 32H), 1.00 – 0.90 (m, 12H) ppm.

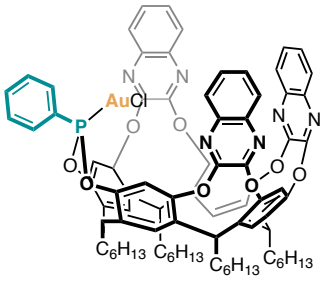
^{31}P NMR (203 MHz, CD_2Cl_2) δ 170.7 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.4, 153.0 (dd, *J* = 17.6, 10.1 Hz), 152.9 – 152.7 (m), 140.3 (q, *J* = 3.5, 3.0 Hz), 137.6 (d, *J* = 3.1 Hz), 136.9, 136.7, 135.7, 131.9, 130.3, 130.1, 129.9, 129.8, 129.6, 129.0 (d, *J* = 6.4 Hz), 128.5 (d, *J* = 10.0 Hz), 128.3, 124.1, 123.5, 119.6, 117.4 (d, *J* = 3.2 Hz), 36.5, 34.9, 34.8, 33.4, 32.7, 32.6, 32.5 (d, *J* = 2.1 Hz), 32.4, 29.9, 29.1 – 28.0 (m), 23.6 – 22.6 (m), 14.4 (t, *J* = 3.0 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{82}H_{82}N_6O_8P]^+$, $[M+H]^+$: 1309.5950; found: 1309.5926.

31 Ballistreri, F. P.; Brancatelli, G.; Demitri, N.; Geremia, S.; Guldi, D. M.; Melchionna, M.; Pappalardo, A.; Prato, M.; Tomaselli, G. A.; Trusso Sfrazzetto, G. *Supramolecular Chemistry* **2016**, *28*, 601–607.

Complex A



Complex **A** (747 mg, 0.49 mmol, 86% yield) was obtained as a white solid following general procedure **A** from phosphonite **39** (738 mg, 0.56 mmol) and (Me_2S)AuCl (174 mg, 0.60 mmol) after purification by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 85:15 as eluent.

M.p. = 325–327 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.20 (s, 2H), 8.20 – 8.11 (m, 2H), 8.03 – 7.95 (m, 2H), 7.80 – 7.72 (m, 5H), 7.71 – 7.66 (m, 4H), 7.54 – 7.43 (m, 6H), 7.34 (d, *J* = 3.3 Hz, 4H), 5.79 (t, *J* = 8.2 Hz, 1H), 5.68 (t, *J* = 8.2 Hz, 2H), 4.69 (td, *J* = 8.0, 2.9 Hz, 1H), 2.39 (dq, *J* = 10.5, 8.0 Hz, 4H), 2.37 – 2.20 (m, 4H), 1.56 – 1.29 (m, 32H), 1.05 – 0.85 (m, 12H) ppm.

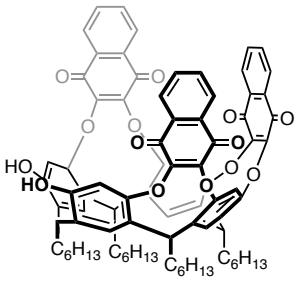
^{31}P NMR (203 MHz, CD_2Cl_2) δ 138.5 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.6 (d, *J* = 2.3 Hz), 153.3, 153.2, 152.9, 152.6, 152.3, 148.6 (d, *J* = 7.3 Hz), 140.6, 140.1 (d, *J* = 3.6 Hz), 137.7 (d, *J* = 2.3 Hz), 136.7, 136.5 (d, *J* = 3.1 Hz), 135.9, 134.8 (d, *J* = 2.2 Hz), 132.9, 132.1, 131.8, 131.7, 130.1, 129.9, 129.7, 129.6, 129.4, 128.3, 127.7, 124.5, 123.7 (d, *J* = 1.8 Hz), 119.0, 118.1 (d, *J* = 4.3 Hz), 36.5, 34.9, 34.8, 33.4, 32.5, 32.4 (d, *J* = 2.7 Hz), 31.1, 29.9 (t, *J* = 10.0 Hz), 29.5 – 27.9 (m), 23.3 (d, *J* = 6.0 Hz), 14.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{82}H_{81}AuClN_6NaO_8P]^+$, $[M+Na]^+$: 1563.5079; found: 1563.5100.

Elemental analysis Anal. Calc. for $C_{82}H_{81}AuClN_6O_8P$: C, 63.87; H, 5.30; N, 5.45; found: C, 63.25; H, 5.31; N, 5.34.

Biphenol 37b



Pyrocatechol (252 mg, 2.29 mmol) was added to a suspension of tetranaphthoquinone resorcin[4]arene **36b**[32] (3.00 g, 2.08 mmol) and cesium fluoride (6.32 g, 41.60 mmol) in dry DMF (11.0 mL, 0.2 M). The mixture was stirred at 70 °C for 45 min. The reaction was quenched by pouring into ice-cold brine and filtered. The solid

32 (a) Pochorovski, I.; Boudon, C.; Gisselbrecht, J.-P.; Ebert, M.-O.; Schweizer, W. B.; Diederich, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 262–266. (b) Pochorovski, I.; Ebert, M.-O.; Gisselbrecht, J.-P.; Boudon, C.; Schweizer, W. B.; Diederich, F. *J. Am. Chem. Soc.* **2012**, *134*, 14702–14705.

residue was purified by flash column chromatography (1:0 to 4:1 CH_2Cl_2/EtOAc) to afford biphenol **37b** (902 mg, 0.70 mmol, 34% yield) as an orange solid.

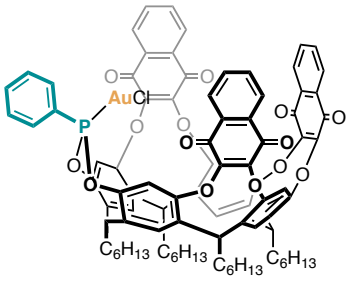
M.p. = 235–238 °C.

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.19 – 7.95 (m, 6H), 7.92 – 7.71 (m, 7H), 7.48 – 7.01 (m, 5H), 6.85 (s, 2H), 4.78 – 4.57 (m, 3H), 4.48 (t, *J* = 7.8 Hz, 1H), 2.29 – 2.07 (m, 8H), 1.39 – 1.19 (m, 32H), 0.90 – 0.80 (m, 12H) ppm.

^{13}C NMR (126 MHz, Acetone-d_6) δ 181.4, 181.0, 153.8, 152.8, 152.5, 152.1, 135.6, 135.0, 134.9, 134.4, 131.9, 131.8, 130.3, 128.6, 126.9, 126.9, 126.9, 36.1, 35.6, 35.1, 34.9, 32.8, 32.7, 32.6, 32.4, 32.3, 28.5, 28.3, 28.1, 23.4, 23.4 ppm.

HRMS (MALDI) calculated for $[C_{82}H_{78}O_{14}]^+$, $[M^+]$: 1286.5386; found: 1286.5410.

Complex B



$PhP(NEt_2)_2$ (50.9 µL, 0.20 mmol) was added to the mixture of biphenol **37b** (210 mg, 0.16 mmol) in dry toluene (3.26 mL, 0.05 M) under an argon at 80 °C. After stirring for 21 h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude was dissolved in ethyl acetate and filtered through a pad of SiO_2. The filter cake was washed with ethyl acetate and the solvent was evaporated *in vacuo*. The crude was used in the next step without further purification.

$(Me_2S)AuCl$ (50 mg, 171 µmol) was added to a mixture of crude in CH_2Cl_2 (3.26 mL, 0.05 M) and the mixture was stirred at 23 °C for 1 h. The solvent was evaporated under pressure, and the crude was purified by flash column chromatography on silica gel using cyclohexane to cyclohexane/EtOAc 7:3 as eluent to give complex **B** (71 mg, 51 µmol, 25% yield over two steps) as an orange solid.

M.p. = 224–226 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.24 – 8.11 (m, 4H), 8.11 – 8.00 (m, 4H), 7.81 – 7.65 (m, 10H), 7.54 (br s, 1H), 7.36 (br s, 2H), 7.12 (br s, 2H), 6.98 (br s, 2H), 4.87 (s, 2H), 4.69 – 4.48 (m, 2H), 2.20 (q, *J* = 7.2 Hz, 8H), 1.45 – 1.21 (m, 32H), 0.87 (h, *J* = 6.3 Hz, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 142.04 ppm.

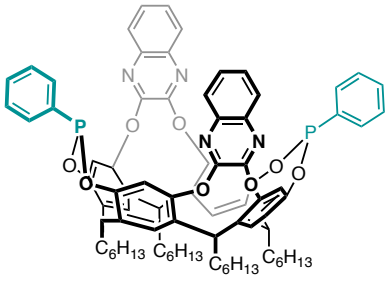
^{13}C NMR (126 MHz, CD_2Cl_2) δ 181.6, 181.4, 181.2, 153.3, 152.6, 152.1, 149.8 (d, *J* = 6.6 Hz), 136.2, 135.6, 134.8 (d, *J* = 2.3 Hz), 134.6 (d, *J* = 7.0 Hz), 134.3, 132.5, 131.8, 131.7,

131.6, 131.2 (d, J = 6.5 Hz), 131.1, 129.7 (d, J = 14.1 Hz), 127.1, 126.9 (d, J = 2.5 Hz), 123.9, 123.5, 117.9, 116.9, 32.3 (t, J = 2.1 Hz), 32.2, 30.3, 29.8 (d, J = 2.6 Hz), 28.3, 28.0, 27.8, 23.2, 14.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{88}H_{81}AuClNaO_{14}P]^+$, $[M+Na]^+$: 1647.4556; found: 1647.4610.

Elemental analysis Anal. Calc. for $C_{88}H_{81}AuClO_{14}P$: C, 65.00; H, 5.02; found: C, 64.69; H, 5.24.

Phosphonite 40a



A reported procedure was followed.[9] $PhP(NEt_2)_2$ (116 µL, 0.45 mmol) was added to a mixture of tetraphenol **38a**[33] (200 mg, 0.19 mmol) in dry toluene (3.7 mL, 0.05 M) under an argon at 80 °C. After stirring for 25 h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 4:1) to afford phosphonite **40a** (77 mg, 0.06 mmol, 32% yield) as a white solid.

M.p. = 197–201 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.99 – 7.91 (m, 4H), 7.90 – 7.82 (m, 4H), 7.64 – 7.55 (m, 10H), 7.43 (s, 8H), 5.77 (t, J = 8.2 Hz, 2H), 4.72 (td, J = 8.1, 2.2 Hz, 2H), 2.36 (dq, J = 24.0, 8.0 Hz, 8H), 1.49 (dq, J = 21.0, 5.8 Hz, 12H), 1.37 (qd, J = 7.6, 6.4, 3.2 Hz, 20H), 1.02 – 0.82 (m, 12H) ppm.

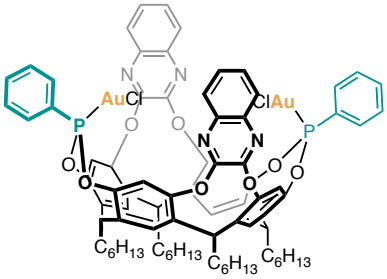
^{31}P NMR (203 MHz, CD_2Cl_2) δ 170.6 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.2, 152.9, 140.5 (d, J = 11.6 Hz), 140.3, 137.8 (d, J = 3.1 Hz), 135.9, 131.9, 130.4, 130.2, 130.0, 129.1 (d, J = 6.3 Hz), 128.5, 123.7, 117.4 (d, J = 3.1 Hz), 36.7, 34.8, 32.7, 32.5 (d, J = 3.8 Hz), 30.0, 28.6 (d, J = 7.3 Hz), 23.3 (d, J = 2.2 Hz), 14.4 ppm.

HRMS (MALDI) calculated for *m/z* $[C_{80}H_{83}N_4O_8P_2]^+$, $[M+H]^+$: 1289.5681; found: 1289.5663.

33 Knighton, R. C.; Chaplin, A. B. *Tetrahedron* **2017**, *73*, 4591–4596.

Complex C



Complex **C** (76 mg, 43 µmol, 75% yield) was obtained as a white solid following general procedure **A** from phosphonite **40a** (74.9 mg, 58 µmol) and (Me_2S)AuCl (35.9 mg, 122 µmol) after purification by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 85:15 as eluent.

M.p. = 305–307 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.21 (ddd, *J* = 14.6, 8.3, 1.3 Hz, 4H), 7.87 (dq, *J* = 6.6, 3.1 Hz, 4H), 7.81 – 7.75 (m, 2H), 7.74 – 7.67 (m, 4H), 7.62 – 7.57 (m, 4H), 7.51 (d, *J* = 1.7 Hz, 4H), 7.38 (s, 4H), 5.74 (t, *J* = 8.2 Hz, 2H), 4.75 (td, *J* = 8.0, 2.9 Hz, 2H), 2.42 (q, *J* = 7.8 Hz, 4H), 2.28 (q, *J* = 8.1 Hz, 4H), 1.51 – 1.28 (m, 32H), 0.99 – 0.87 (m, 12H) ppm.

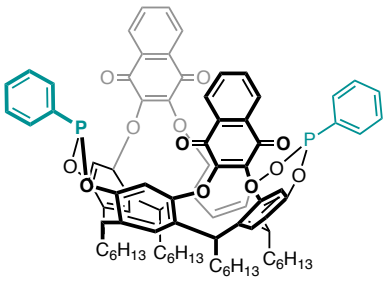
^{31}P NMR (203 MHz, CD_2Cl_2) δ 136.7 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.6 (d, *J* = 2.1 Hz), 152.2, 148.4 (d, *J* = 8.1 Hz), 140.3, 137.3 (d, *J* = 2.0 Hz), 136.6 (d, *J* = 2.8 Hz), 134.8 (d, *J* = 2.3 Hz), 133.5, 132.7, 131.8 (d, *J* = 19.0 Hz), 130.3, 129.7 (d, *J* = 14.0 Hz), 128.9, 123.9, 117.8 (d, *J* = 4.1 Hz), 36.5, 34.8, 33.2, 32.4 (d, *J* = 3.2 Hz), 31.1, 29.9 (d, *J* = 7.1 Hz), 28.5 (d, *J* = 5.2 Hz), 23.2 (d, *J* = 6.8 Hz), 14.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{80}H_{82}Au_2Cl_2N_4NaO_8P_2]^+$, $[M+Na]^+$: 1775.4178; found: 1775.4209 ppm.

Elemental analysis Anal. Calc. for $C_{80}H_{82}Au_2Cl_2N_4O_8P_2$: C, 54.77; H, 4.71, N: 3.19; found: C, 53.96; H, 4.86; N, 3.14.

Phosphonite 40b



$PhP(NEt_2)_2$ (550 µL, 2.12 mmol) was added to a mixture of tetraphenol **38b**[32b] (1.0 g, 0.88 mmol) in dry toluene (17.6 mL, 0.05 M) under an argon at 80 °C. After stirring for 23 h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 7:3) to afford phosphonite **40b** (498 mg, 0.37 mmol, 42% yield) as a yellow solid.

M.p. = 309–311 °C.

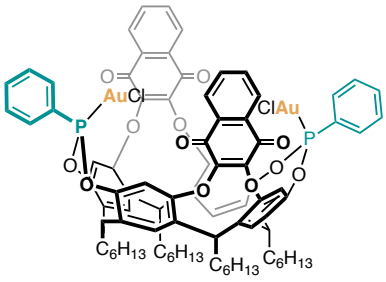
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.00 (dd, *J* = 5.7, 3.2 Hz, 4H), 7.96 – 7.88 (m, 4H), 7.66 – 7.56 (m, 10H), 7.46 (s, 4H), 7.37 (s, 4H), 5.72 (t, *J* = 8.2 Hz, 2H), 4.73 (td, *J* = 8.3, 2.2 Hz, 2H), 2.34 (q, *J* = 7.9 Hz, 8H), 1.54 – 1.28 (m, 32H), 0.92 (h, *J* = 3.6 Hz, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 170.8 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.9, 153.9, 152.7 (d, *J* = 3.6 Hz), 152.5, 140.3 (d, *J* = 11.2 Hz), 138.0 (d, *J* = 3.1 Hz), 136.2, 134.8, 131.9, 130.9, 130.4, 130.2, 129.1 (d, *J* = 6.3 Hz), 127.2, 124.1, 117.6 (d, *J* = 3.0 Hz), 36.7, 34.0, 32.7, 32.6, 32.4, 29.9 (d, *J* = 5.3 Hz), 28.5 (d, *J* = 1.6 Hz), 23.2 (d, *J* = 1.8 Hz), 14.4 (d, *J* = 1.6 Hz) ppm.

HRMS (MALDI) calculated for *m/z* $[C_{84}H_{83}O_{12}P_2]^+$, $[M+H]^+$: 1345.5354; found: 1345.5354.

Complex D



Complex **D** (389 mg, 0.22 mmol, 72% yield) was obtained as a white solid following general procedure **A** from phosphonite **40b** (400 mg, 0.30 mmol) and $(Me_2S)AuCl$ (184 mg, 0.62 mmol) after purification by flash column chromatography on silica gel using cyclohexane to cyclohexane/EtOAc/CH_2Cl_2 8:1:1 as eluent.

M.p. = 321–323 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.20 (ddd, *J* = 14.7, 8.3, 1.4 Hz, 4H), 8.02 (dd, *J* = 5.7, 3.3 Hz, 4H), 7.79 (td, *J* = 7.3, 1.5 Hz, 2H), 7.74 – 7.68 (m, 4H), 7.67 – 7.63 (m, 8H), 7.40 (s, 4H), 5.69 (t, *J* = 8.2 Hz, 2H), 4.77 (td, *J* = 8.0, 3.0 Hz, 2H), 2.43 (q, *J* = 7.7 Hz, 4H), 2.23 (q, *J* = 8.2 Hz, 4H), 1.49 – 1.24 (m, 32H), 0.99 – 0.92 (m, 6H), 0.93 – 0.86 (m, 6H) ppm.

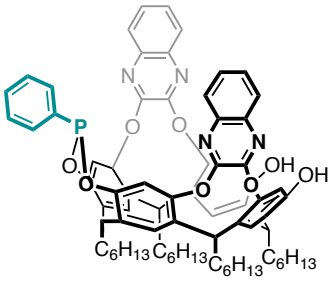
^{31}P NMR (203 MHz, CD_2Cl_2) δ 138.0 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.8, 154.4 (d, *J* = 2.2 Hz), 151.9, 148.3 (d, *J* = 8.0 Hz), 137.7 (d, *J* = 2.2 Hz), 136.9 (d, *J* = 2.9 Hz), 134.9 (d, *J* = 9.6 Hz), 132.9, 132.2, 131.9, 131.8, 130.8, 129.7 (d, *J* = 14.1 Hz), 127.8, 124.1, 118.4 (d, *J* = 4.2 Hz), 36.5, 33.9, 33.4, 32.4 (d, *J* = 8.1 Hz), 30.9, 29.8, 28.4 (d, *J* = 6.6 Hz), 23.2 (d, *J* = 7.5 Hz), 14.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{84}H_{82}Au_2Cl_2NaO_{12}P_2]^+$, $[M+Na]^+$: 1831.3878; found: 1831.3882.

Elemental analysis Anal. Calc. for $C_{84}H_{82}Au_2Cl_2O_{12}P_2$: C, 55.73; H, 4.57; found: C, 55.73; H, 4.65.

Phosphonite 41



$PhPCl_2$ (38 µL, 0.28 mmol) was added to a mixture of tetraphenol **38a**[33] (300 mg, 0.28 mmol) and pyridine (113 µL, 1.39 mmol) in dry toluene (5.6 mL, 0.05 M) under an argon. The mixture was stirred at 23 °C for 2 h. The solvent was removed under vacuum and the crude product was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc 1:0 to 7:3) to afford phosphonite **41** (76 mg, 0.28 mmol, 23% yield) as a white solid.

M.p. = 210–212 °C.

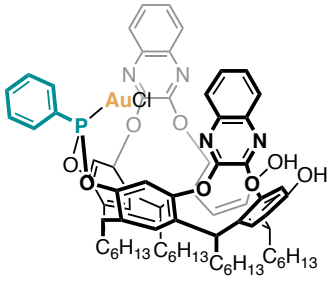
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (br s, 2H), 7.93 (dt, *J* = 6.5, 3.0 Hz, 2H), 7.83 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.80 – 7.69 (m, 2H), 7.63 – 7.57 (m, 3H), 7.54 – 7.42 (m, 6H), 7.38 (s, 2H), 7.24 (s, 2H), 7.22 (s, 2H), 5.69 (t, *J* = 8.2 Hz, 2H), 4.72 (td, *J* = 8.0, 2.1 Hz, 1H), 4.36 (t, *J* = 7.8 Hz, 1H), 2.43 – 2.08 (m, 8H), 1.67 – 1.14 (m, 32H), 0.98 – 0.81 (m, 12H) ppm.

^{31}P NMR (203 MHz, $CDCl_3$) δ 170.32 ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 152.9, 152.5, 152.4, 152.1 (d, *J* = 3.6 Hz), 151.6, 139.9, 139.7 (d, *J* = 10.7 Hz), 139.5, 137.0 (d, *J* = 3.0 Hz), 135.8, 131.5, 131.0, 129.9, 129.8, 129.5, 129.0, 128.8 (d, *J* = 6.0 Hz), 128.1, 127.7, 123.9, 123.1, 116.8 (d, *J* = 3.1 Hz), 110.7, 36.2, 34.1, 33.9, 32.4, 32.2, 32.1, 32.0 (d, *J* = 3.1 Hz), 29.9 – 29.4 (m), 28.4 – 28.1 (m), 22.8, 14.2 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{74}H_{79}N_4NaO_8P]^+$, $[M+Na]^+$: 1205.5521; found: 1205.5528.

Complex E



Complex **E** (48 mg, 0.04 mmol, 84% yield) was obtained as a white solid following general procedure **A** from phosphonite **41** (48 mg, 40 µmol) and $(Me_2S)AuCl$ (13 mg, 44 µmol) after purification by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 4:1 as eluent.

M.p. = 202–207 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.13 (m, 3H), 7.95 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.80 – 7.71 (m, 3H), 7.66 (td, *J* = 7.7, 3.0 Hz, 2H), 7.62 (d, *J* = 1.6 Hz, 2H), 7.57 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 2H), 7.50 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 2H), 7.40 (s, 2H), 7.21 (s, 2H), 7.15 (s, 2H), 5.67 (t, *J* = 8.2 Hz, 2H), 4.71 (td, *J* = 8.0, 2.8 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 1H), 2.39 (q, *J* = 7.8 Hz, 2H), 2.34 – 2.19 (m, 6H), 1.59 – 1.27 (m, 32H), 1.07 – 0.87 (m, 12H) ppm.

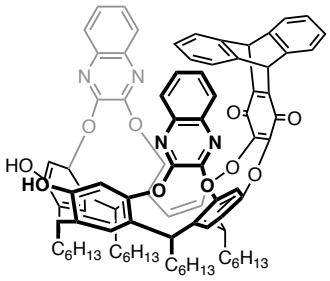
^{31}P NMR (203 MHz, $CDCl_3$) δ 137.02 ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9 (d, *J* = 2.2 Hz), 152.6, 152.5, 152.3, 151.9, 147.8 (d, *J* = 7.7 Hz), 139.9, 139.6, 138.4 (d, *J* = 2.0 Hz), 135.9 (d, *J* = 3.0 Hz), 134.3, 132.6, 131.8, 131.5, 131.3, 130.1, 129.7 (d, *J* = 7.2 Hz), 129.3, 129.2, 128.9, 127.4, 124.2, 122.5, 117.5 (d, *J* = 4.0 Hz), 111.4, 36.0, 34.2 (d, *J* = 9.4 Hz), 33.9, 32.7, 32.1 (d, *J* = 3.3 Hz), 31.9, 30.9, 29.6, 29.5, 28.1 (d, *J* = 6.6 Hz), 22.8 (d, *J* = 2.9 Hz), 14.2 (t, *J* = 3.0 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{74}H_{79}AuClN_4NaO_8P]^+$, $[M+Na]^+$: 1437.4871; found: 1437.4882.

Elemental analysis Anal. Calc. for $C_{74}H_{79}AuClN_4O_8P$: C, 62.78; H, 5.62; N, 3.96; found: C, 62.25; H, 5.73; N, 3.82.

Biphenol 43



Cs_2CO_3 (1.65 mg, 5.06 mmol) was added to a suspension of tetraphenol resorcin[4]arene **38a**[33] (2.48 g, 2.30 mmol) and (9*s*,10*s*)-14,15-dichloro-9,10-dihydro-9,10-[1,2]benzenoanthracene-13,16-dione **42**[32] (854 mg, 2.42 mmol) in dry THF (154 mL, 0.015 M). The mixture was stirred at 70 °C for 4 h, then the solvent was removed under vacuum and the crude was purified by flash chromatography (silica gel, cyclohexane/EtOAc 1:0 to 4:1) to obtain **43** (1.5 g, 1.11 mmol, 48% yield) as an orange solid.

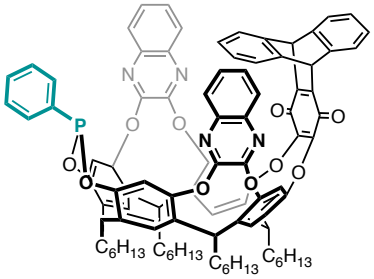
M.p. = 270–274 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (br s, 2H), 8.12 – 7.95 (m, 3H), 7.83 (d, *J* = 8.1 Hz, 3H), 7.74 – 7.51 (m, 6H), 7.41 (dd, *J* = 5.4, 3.2 Hz, 3H), 7.19 – 6.84 (m, 8H), 6.81 (br s, 1H), 5.73 (s, 2H), 4.85 (br s, 3H), 4.44 (t, *J* = 7.8 Hz, 1H), 2.35 – 1.85 (m, 8H), 1.52 – 1.13 (m, 32H), 0.86 (tt, *J* = 7.2, 3.8 Hz, 12H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 152.4, 152.3, 152.2, 151.6, 150.5, 143.5, 143.4, 139.3, 135.4, 129.6, 129.1, 128.5, 128.3, 127.4, 125.7, 125.5, 124.6, 124.3, 124.1, 123.2, 117.9, 109.3, 47.5, 35.4, 34.4, 33.9, 32.2, 31.9, 31.8, 29.5, 29.4, 29.3, 27.9, 27.7, 27.5, 22.8, 22.7, 22.6, 14.2, 14.1 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{88}H_{84}N_4NaO_{10}]^+$, $[M+Na]^+$: 1379.6031; found: 1379.6080.

Phosphonite 44



$PhPCl_2$ (75 µL, 0.55 mmol) was added to a mixture of biphenol **43** (300 mg, 0.22 mmol) and pyridine (89 µL, 1.11 mmol) in dry toluene (4.4 mL, 0.05 M) under an argon. The mixture was stirred at 23 °C for 2 h. The solvent was removed under vacuum and the crude product was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc 1:0 to 1:1) to afford phosphonite **44** (177 mg, 0.12 mmol, 55% yield) as an orange solid.

M.p. = 297–300 °C.

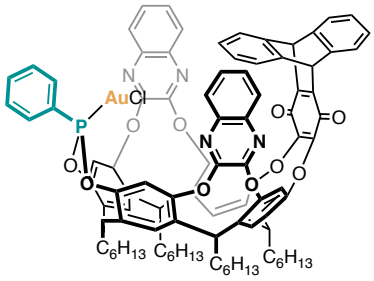
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.23 (d, *J* = 8.4 Hz, 2H), 8.12 – 8.04 (m, 1H), 7.95 – 7.86 (m, 6H), 7.74 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 2H), 7.62 – 7.57 (m, 3H), 7.44 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 4H), 7.29 (s, 2H), 7.05 (dd, *J* = 5.4, 3.2 Hz, 2H), 6.43 (s, 3H), 5.69 – 5.58 (m, 2H), 5.47 (br s, 2H), 4.62 (td, *J* = 8.1, 2.1 Hz, 1H), 2.41 – 2.15 (m, 8H), 1.53 – 1.22 (m, 32H), 0.99 – 0.86 (m, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 171.2 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 179.9, 153.5, 152.9, 152.8, 152.7 (d, *J* = 4.0 Hz), 152.5, 152.4, 150.6, 143.8, 143.1, 140.3, 140.2, 140.1, 140.0, 137.4 (d, *J* = 3.2 Hz), 136.8, 136.5, 135.3, 131.9, 130.2, 130.0 (d, *J* = 8.6 Hz), 129.8, 128.9 (d, *J* = 6.3 Hz), 128.7 (d, *J* = 9.4 Hz), 125.9, 125.1, 124.6, 124.3, 124.0, 123.3, 119.2, 116.7, 47.6, 36.4, 34.8, 34.0, 33.6, 32.7, 32.3, 32.2, 32.1, 29.8, 29.7, 29.6, 28.4, 28.3, 28.2, 27.3, 23.1 (d, *J* = 3.6 Hz), 14.3 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{94}H_{87}N_4NaO_{10}P]^+$, $[M+Na]^+$: 1485.6026; found: 1485.6052.

Complex F



Complex **F** (88 mg, 52 µmol, 70% yield) was obtained as an orange solid following general procedure **A** from phosphonite **44** (108 mg, 74 µmol) and $(Me_2S)AuCl$ (23 mg, 78 µmol) after purification by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 4:1 as eluent.

M.p. = 342–344 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.12 (m, 4H), 8.05 (s, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.84 (t, *J* = 7.7 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.73 – 7.65 (m, 4H), 7.53 (s, 2H), 7.44 (dd,

J = 5.3, 3.2 Hz, 2H), 7.33 (br s, 2H), 7.24 (br s, 2H), 7.05 (dd, *J* = 5.3, 3.3 Hz, 2H), 6.63 (t, *J* = 4.3 Hz, 2H), 6.34 – 6.27 (m, 2H), 5.69 (t, *J* = 8.2 Hz, 2H), 5.56 (br s, 1H), 5.50 (br s, 2H), 4.67 (td, *J* = 8.0, 2.8 Hz, 1H), 2.39 – 2.13 (m, 8H), 1.54 – 1.23 (m, 32H), 0.97 – 0.87 (m, 12H) ppm.

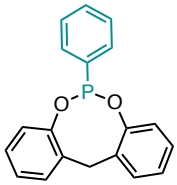
^{31}P NMR (203 MHz, $CDCl_3$) δ 136.1 ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 180.3, 153.4, 152.9 (d, *J* = 2.0 Hz), 152.3, 152.0, 150.6, 147.7 (d, *J* = 7.8 Hz), 143.5, 142.2, 140.2, 140.0, 137.9, 136.6, 135.9 (d, *J* = 2.9 Hz), 135.4, 134.4 (d, *J* = 2.0 Hz), 132.5, 131.7, 131.3 (d, *J* = 18.6 Hz), 129.7, 129.4, 129.3, 129.0, 128.0, 125.7, 125.1, 124.4, 124.3, 124.1, 122.3, 119.6, 117.3 (d, *J* = 4.0 Hz), 47.5, 35.9, 34.3, 33.3 (d, *J* = 15.1 Hz), 32.4, 32.1, 32.0, 31.9, 30.8, 29.5, 29.4, 28.0, 22.8, 22.7, 14.3, 14.2 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{94}H_{88}AuClN_4O_{10}P]^+$, $[M+H]^+$: 1695.5580; found: 1695.5587.

Elemental analysis Anal. Calc. for $C_{94}H_{87}AuClN_4O_{10}P$: C, 66.56; H, 5.17, N: 3.30; found: C, 66.36; H, 5.36; N, 3.32.

Phosphonite 47



$PhP(NEt_2)_2$ (156 µL, 0.60 mmol) was added to a mixture of 2,2'-methylenediphenol (100 mg, 0.50 mmol) in dry toluene (10 mL, 0.05 M) under an argon at 80 °C. After stirring for 19 h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/EtOAc 4:1) to afford phosphonite **47** (30 mg, 0.10 mmol, 20% yield) as a white solid**.**

M.p. = 110–113 °C.

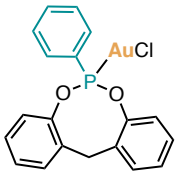
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.03 – 7.94 (m, 2H), 7.62 – 7.53 (m, 3H), 7.44 (dd, *J* = 7.5, 1.8 Hz, 2H), 7.24 – 7.17 (m, 2H), 7.11 (tt, *J* = 7.5, 1.3 Hz, 2H), 7.06 (dt, *J* = 7.9, 1.4 Hz, 2H), 4.53 (dd, *J* = 12.8, 3.4 Hz, 1H), 3.56 (d, *J* = 12.9 Hz, 1H) ppm.

^{31}P NMR (162 MHz, CD_2Cl_2) δ 170.1 ppm.

^{13}C NMR (101 MHz, CD_2Cl_2) δ 154.3 (d, *J* = 4.2 Hz), 141.1 (d, *J* = 11.2 Hz), 136.4 (d, *J* = 3.6 Hz), 131.8, 130.7 (d, *J* = 1.5 Hz), 130.4, 130.1, 129.1 (d, *J* = 6.7 Hz), 128.9 (d, *J* = 1.6 Hz), 125.7 (d, *J* = 1.8 Hz), 122.9 (d, *J* = 3.5 Hz), 33.9 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{19}H_{16}O_2P]^+$, $[M+H]^+$: 307.0892; found: 307.0882.

Complex G



Complex **G** (38 mg, 70 µmol, 97% yield) was obtained as a white solid following general procedure **A** from phosphonite **47** (22 mg, 72 µmol) and (Me_2S)AuCl (22 mg, 76 µmol) after purification by flash column chromatography on silica gel using cyclohexane to cyclohexane/EtOAc 4:1 as eluent.

M.p. = 245–247 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.24 – 8.14 (m, 2H), 7.82 – 7.74 (m, 1H), 7.74 – 7.66 (m, 2H), 7.49 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.35 – 7.22 (m, 4H), 7.18 (dt, *J* = 7.9, 1.8 Hz, 2H), 4.53 (dd, *J* = 13.3, 4.3 Hz, 1H), 3.67 (d, *J* = 13.3 Hz, 1H) ppm.

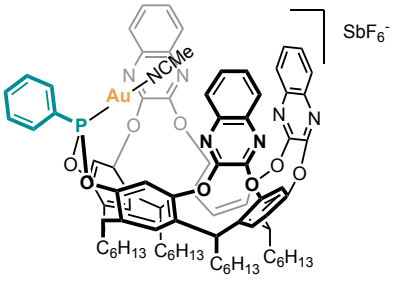
^{31}P NMR (162 MHz, CD_2Cl_2) δ 140.8 ppm.

^{13}C NMR (101 MHz, CD_2Cl_2) δ 151.4 (d, *J* = 6.8 Hz), 135.1 (d, *J* = 3.7 Hz), 134.8 (d, *J* = 2.5 Hz), 132.7, 131.7, 131.7, 131.5, 131.2 (d, *J* = 2.3 Hz), 129.8 (dd, *J* = 8.2, 5.7 Hz), 127.7 (d, *J* = 2.5 Hz), 123.1 (d, *J* = 4.8 Hz), 33.6 (d, *J* = 1.6 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{19}H_{15}AuClNaO_2P]^+$, $[M+Na]^+$: 561.0056; found: 561.0046.

Elemental analysis Anal. Calc. for $C_{19}H_{15}AuClO_2P$: C, 42.36; H, 2.81; found: C, 42.88; H, 3.08.

Complex H



Acetonitrile (0.1 mL) was added to a solution of complex **A** (31 mg, 20 µmol) in CH_2Cl_2 (1 mL, 0.02 M). $AgSbF_6$ (7.3 mg, 21 µmol) was added to the mixture and it was stirred for 3 h under an argon. The reaction crude was filtered through a pad of Celite, washed with CH_2Cl_2 and the filtrate was concentrated under reduced pressure to give complex **H** (34 mg, 19 µmol, 94% yield) as a white solid.

M.p. = 264–268 °C.

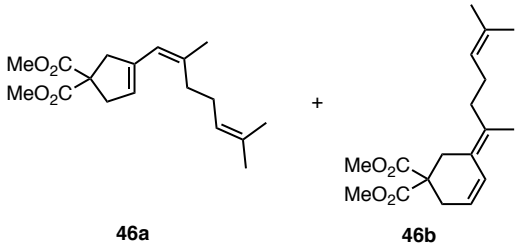
^{1}H NMR (500 MHz, CD_3CN) δ 8.26 – 8.19 (m, 4H), 8.09 – 8.00 (br s, 2H), 7.94 – 7.84 (br s, 3H), 7.81 – 7.72 (m, 4H), 7.70 – 7.52 (m, 12H), 5.69 (t, *J* = 8.3 Hz, 1H), 5.61 (t, *J* = 8.2 Hz, 2H), 4.63 (td, *J* = 8.0, 3.1 Hz, 1H), 2.55 – 2.31 (m, 8H), 1.55 – 1.27 (m, 32H), 0.97 – 0.85 (m, 12H) ppm.

^{31}P NMR (202 MHz, CD_3CN) δ 134.5 ppm.

^{13}C NMR (126 MHz, CD_3CN) δ 153.8 (d, *J* = 14.1 Hz), 153.2, 153.0, 149.2 (d, *J* = 8.0 Hz), 140.8 (d, *J* = 16.1 Hz), 140.4, 139.0, 137.6, 137.4, 136.5, 136.2, 132.5 (d, *J* = 18.0 Hz), 130.8, 130.6, 130.4 (d, *J* = 14.6 Hz), 130.1, 129.6, 129.0, 128.7, 126.3, 125.7, 120.7, 118.9, 37.4, 35.8, 32.5, 30.9, 30.3, 30.2, 28.9, 28.7, 28.5, 23.4, 14.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{84}H_{84}AuN_7O_8P]^+$, $[M\text{-}SbF_6]^+$: 1546.5779; found: 1546.5757.

Cyclization of *Z*-1,6-dienyne (45) using complex T



46a **46b**

46a/**46b** 1:5

Complex **H** (8 mg, 4.5 μmol, 2 mol %) was added to a solution of *Z*-1,6-dienyne **45** (69 mg, 0.23 mmol) in 2.25 mL CH_2Cl_2 (0.1 M) at 0 °C. The mixture was stirred at 0 °C for 60 min. The reaction was quenched by addition of 3 drops of NEt_3 and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 4:1) to afford a mixture of **46a**/**46b** (67 mg, 0.22 mmol, 97% yield, **46a**/**46b** = 1:5) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ **46a**: 5.73 (s, 1H), 5.39 (s, 1H), 5.14 (ddq, *J* = 8.5, 5.8, 1.5 Hz, 1H), 3.73 (s, 6H), 3.17 (d, *J* = 2.2 Hz, 2H), 3.03 (s, 2H), 2.16 – 2.01 (m, 4H), 1.77 (m, 3H), 1.69 (m, 3H), 1.62 (m, 3H). **46b**: 6.42 (dt, *J* = 10.2, 2.1 Hz, 1H), 5.65 (dt, *J* = 10.2, 4.1 Hz, 1H), 5.14 (ddq, *J* = 8.5, 5.8, 1.5 Hz, 1H), 3.70 (s, 6H), 2.87 (q, *J* = 1.4 Hz, 2H), 2.66 (dd, *J* = 4.3, 2.0 Hz, 2H), 2.16 – 2.01 (m, 4H), 1.77 (m, 3H), 1.69 (m, 3H), 1.62 (m, 3H) ppm.

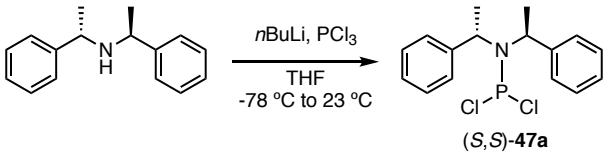
^{13}C NMR (101 MHz, $CDCl_3$) δ **46a**+**46b**: 172.0, 171.9, 139.6, 138.6, 134.0, 132.0, 132.0, 123.0, 124.7, 124.3, 124.1, 124.0, 123.2, 121.2, 59.5, 54.2, 52.9, 52.8, 43.3, 40.4, 34.9, 33.5, 31.8, 31.4, 27.2, 26.7, 25.8, 24.8, 18.4, 17.8, 17.7 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{18}H_{26}NaO_4]^+$, $[M+Na]^+$: 329.1721; found: 329.1723.

46a was already described and their NMR data was in agreement with the ones previously reported in the literature.[24]

Synthesis of Chiral Gold(I)-Cavitand Complexes.

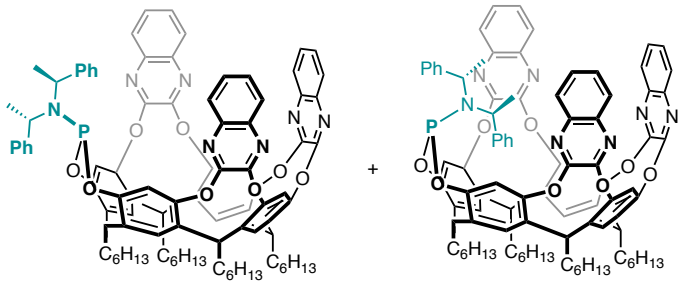
General procedure for the synthesis of *N*,*N*-bis[(1*S*)-1-phenylethyl]phosphoramidous dichloride (*S*,*S*)-47a.



A reported procedure was followed.[34] A flame-dried Schlenk tube was charged with (1*S*,1'*S*)-bis(1-phenylethyl)amine (1 equiv) and anhydrous THF (0.44 M) under argon, the solution was then cooled to -78 °C and *n*BuLi (1.1 equiv) was added dropwise. The mixture was stirred at -78 °C for 30 min and then PCl_3 (1.3 equiv) was added dropwise to the solution of lithium amide at -78 °C under argon. The reaction mixture was warmed to 23 °C and stirred overnight. The mixture was concentrated *in vacuo*, and the residual PCl_3 was removed *via* repetitive THF dilution (x3) and vacuum evaporation to give *N*,*N*-bis[(1*S*)-1-phenylethyl]phosphoramidous dichloride (*S*,*S*)-**47a** that was used in the next step without further purification.

^{31}P NMR (162 MHz, C_6D_6) δ 168.7 ppm.

Phosphoramidites (*S*,*S*)-48



Triethylamine (174 µL, 1.25 mmol) was added to a mixture of biphenol **37a**[31] (500 mg, 0.42 mmol) in dry toluene (6.9 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then *N*,*N*-bis[(1*S*)-1-phenylethyl]phosphoramidous dichloride (*S*,*S*)-**47a** (203 mg, 0.62 mmol) in dry toluene (1.4 mL) was added dropwise to the mixture, which was stirred for 3 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) to afford a mixture of (*S*,*S*)-**48a** and (*S*,*S*)-**48b** (223 mg, 0.15 mmol, 37% yield, (*S*,*S*)-**48a**/(*S*,*S*)-**48b** 6:1 ratio) as a white solid.

The ratio of (*S*,*S*)-**48a**/(*S*,*S*)-**48b** 6:1 was determined by ^{31}P NMR.

34 Zheng, Z.; Cao, Y.; Chong, Q.; Han, Z.; Ding, J.; Luo, C.; Wang, Z.; Zhu, D.; Zhou, Q.-L.; Ding, K. *J. Am. Chem. Soc.* **2018**, *140*, 10374–10381.

Because of the complex mixture of the phosphoramidites ((*S*,*S*)-**48a**/(*S*,*S*)-**48b**) that leads to multiple overlapping, the proton and carbon signals were not assigned. Only the phosphorous signals were asigned. The two corresponding complexes were found to be easier to separate after the gold(I) coordination and thus, the mixture of phosphoramidites was taken on to the next step without further separation.

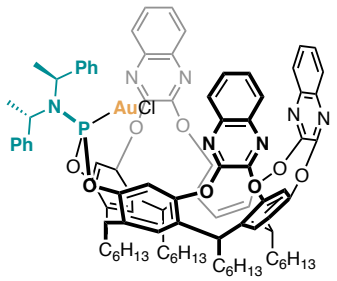
^{31}P NMR (203 MHz, CD_2Cl_2) δ 146.2, 143.8 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{94}H_{93}N_7O_8P]^+$, $[M+H]^+$: 1478.6768; found: 1478.6818.

Complexes (*S*,*S*)-I and (*S*,*S*)-J.

Complex (*S*,*S*)-**I** and complex (*S*,*S*)-**J** were obtained according to the general procedure **A** from a mixture of phosphoramidites (*S*,*S*)-**48a**/(*S*,*S*)-**48b** (210 mg, 144 µmol) and (Me_2S)AuCl (45 mg, 0.15 mmol). Purification by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) afforded complex (*S*,*S*)-**I** (164 mg, 97.1 µmol, 67% yield) as a white solid and complex (*S*,*S*)-**J** (31 mg, 18 µmol, 13% yield) as a white solid.

Characterization of (*S*,*S*)-I:



M.p. = 170–173 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.15 (d, *J* = 2.2 Hz, 2H), 7.96 (ddd, *J* = 6.9, 5.3, 3.4 Hz, 2H), 7.80 – 7.63 (m, 5H), 7.58 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.46 (dddd, *J* = 12.3, 9.7, 7.3, 3.5 Hz, 4H), 7.41 – 7.32 (m, 11H), 7.27 (dd, *J* = 8.8, 3.1 Hz, 4H), 7.03 (d, *J* = 1.8 Hz, 1H), 5.75 (t, *J* = 8.2 Hz, 1H), 5.63 (t, *J* = 8.2 Hz, 2H), 5.16 (dq, *J* = 17.9, 7.0 Hz, 2H), 4.56 (td, *J* = 8.1, 3.2 Hz, 1H), 2.37 (dt, *J* = 16.4, 8.0 Hz, 4H), 2.24 (p, *J* = 7.4 Hz, 4H), 2.01 (d, *J* = 7.1 Hz, 6H), 1.62 – 1.29 (m, 32H), 1.02 – 0.81 (m, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 121.3 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.3 (t, *J* = 2.6 Hz), 153.2 (d, *J* = 2.5 Hz), 153.1 (d, *J* = 3.9 Hz), 152.9 (d, *J* = 1.9 Hz), 152.6, 152.5, 152.3, 152.2, 147.3 (d, *J* = 3.5 Hz), 146.7 (d, *J* = 3.7 Hz), 141.5 (d, *J* = 3.6 Hz), 140.6 (d, *J* = 1.9 Hz), 140.4 – 139.7 (m), 137.0 (d, *J* = 2.3 Hz), 136.9 (d, *J* = 2.3 Hz), 136.7 – 136.5 (m), 136.0, 135.9, 129.9 (d, *J* = 4.3 Hz), 129.8 (d, *J* = 2.2 Hz), 129.7, 129.6, 129.5 (d, *J* = 2.8 Hz), 129.0, 128.9, 128.4, 128.3 (d, *J* = 6.3 Hz), 127.8, 127.6, 124.6 (d, *J* = 12.9 Hz), 123.2 (d, *J* = 14.5 Hz), 118.9, 118.8 (d, *J* = 4.1 Hz), 118.6 (d, *J* = 4.3 Hz), 54.6 (d, *J* = 8.5 Hz), 36.4, 34.9, 34.7, 33.4, 32.5, 32.4 (d, *J* = 2.3 Hz), 30.5, 30.2 –

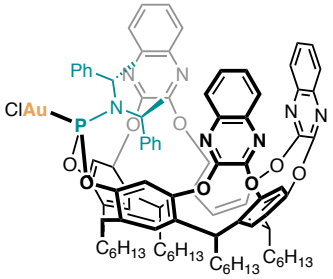
29.9 (m), 29.8, 28.6, 28.5 (d, *J* = 2.7 Hz), 28.3, 23.3 (d, *J* = 3.8 Hz), 21.6 (d, *J* = 2.6 Hz), 14.7 – 13.7 (m) ppm.

HRMS (MALDI) calculated for *m/z* $[C_{92}H_{94}AuClN_7O_8P]^+$, $[M]^+$: 1687.6250; found: 1687.6280.

Elemental analysis Anal. Calc. for $C_{92}H_{94}AuClN_7O_8P$: C, 65.42; H, 5.61; N, 5.80; found: C, 64.93; H, 5.72; N, 5.68.

α_D^{589} = +21.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.81, 298 K).

Characterization of (*S*,*S*)-J:



M.p. = 273–275 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.12 (d, *J* = 1.8 Hz, 2H), 7.98 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.93 (dq, *J* = 7.2, 3.6 Hz, 2H), 7.73 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.70 – 7.62 (m, 3H), 7.56 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.35 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.28 (s, 1H), 7.26 – 7.07 (m, 17H), 5.60 (t, *J* = 8.2 Hz, 1H), 5.36 (t, *J* = 8.1 Hz, 1H), 5.31 – 5.27 (m, 1H), 5.00 (td, *J* = 7.4, 4.3 Hz, 1H), 4.66 (dq, *J* = 18.6, 7.0 Hz, 2H), 2.37 – 2.17 (m, 8H), 1.93 (d, *J* = 7.0 Hz, 6H), 1.53 – 1.26 (m, 32H), 1.01 – 0.85 (m, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 117.5 ppm.

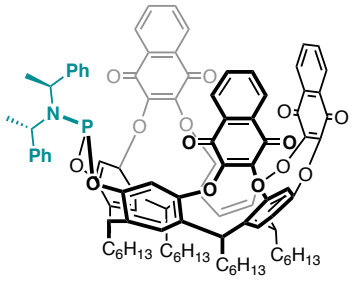
^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.5, 153.4, 153.2 (d, *J* = 2.2 Hz), 152.9 (d, *J* = 1.5 Hz), 152.9, 152.7, 152.4, 152.2, 152.0, 150.7, 150.6, 150.4, 150.3, 141.2 (d, *J* = 3.8 Hz), 140.4, 140.3, 140.3, 139.9, 139.8, 139.7, 136.3, 136.2, 136.1, 135.8 – 135.7 (m), 135.6 (d, *J* = 1.3 Hz), 130.6 (d, *J* = 1.6 Hz), 130.4 (d, *J* = 2.2 Hz), 130.0 (d, *J* = 2.7 Hz), 129.8 (d, *J* = 1.7 Hz), 129.5, 128.9, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 125.0, 124.3 (d, *J* = 5.4 Hz), 122.7, 118.7 (d, *J* = 5.9 Hz), 116.1 (d, *J* = 4.0 Hz), 115.4 (d, *J* = 5.5 Hz), 39.9 (d, *J* = 6.3 Hz), 35.6, 35.4, 35.2, 32.9 (d, *J* = 4.7 Hz), 32.5, 32.4 (d, *J* = 2.4 Hz), 32.2, 31.1, 30.0 – 29.9 (m), 29.8, 28.5, 28.3 (d, *J* = 2.5 Hz), 27.9, 27.5, 23.2 (d, *J* = 3.3 Hz), 23.1, 21.8, 14.4 ppm.

HRMS (MALDI) calculated for *m/z* $[C_{92}H_{95}AuClN_7O_8P]^+$, $[M+H]^+$: 1688.6328; found: 1688.6318.

Elemental analysis Anal. Calc. for $C_{92}H_{94}AuClN_7O_8P$: C, 65.42; H, 5.61; N, 5.80; found: C, 64.79; H, 5.68; N, 5.62.

α_D^{589} = –111.8 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.11, 301 K).

Phosphoramidite (*S*,*S*)-49



Triethylamine (0.59 mL, 3.94 mmol) was added to a mixture of biphenol **37b** (845 mg, 0.66 mmol) in dry toluene (10.9 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then *N*,*N*-bis[(1*S*)-1-phenylethyl]phosphoramidous dichloride (*S*,*S*)-**47a** (642 mg, 1.97 mmol) in dry toluene (2.2 mL) was added to the mixture, which was stirred for 3 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/EtOAc 4:1) to afford (*S*,*S*)-**49** (300 mg, 0.19 mmol, 30% yield) as a yellow solid.

M.p. = 194–197 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.21 – 8.02 (m, 6H), 7.80 – 7.64 (m, 6H), 7.48 (br s, 1H), 7.38 (s, 1H), 7.30 – 7.22 (m, 8H), 7.21 – 7.08 (m, 5H), 7.05 (br s, 2H), 6.98 (br s, 1H), 5.14 (br s, 1H), 4.91 (dd, *J* = 12.1, 6.9 Hz, 2H), 4.68 (td, *J* = 8.2, 1.9 Hz, 1H), 4.47 (br s, 1H), 2.31 – 2.06 (m, 8H), 1.82 (d, *J* = 7.1 Hz, 6H), 1.50 – 1.11 (m, 32H), 0.93 – 0.72 (m, 12H) ppm.

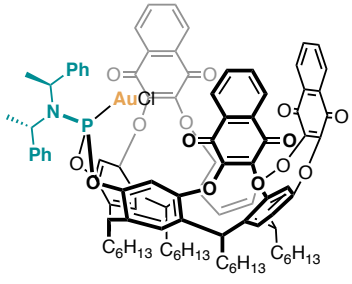
^{31}P NMR (203 MHz, CD_2Cl_2) δ 147.6 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.3, 181.9, 181.8, 181.2, 180.8, 153.1, 152.7, 152.3, 151.9, 151.8, 151.2 (d, *J* = 7.2 Hz), 151.0 (d, *J* = 7.7 Hz), 150.1, 149.3, 143.9, 137.8, 135.9, 135.6, 134.8 (d, *J* = 3.5 Hz), 134.7, 134.6 (d, *J* = 4.1 Hz), 134.5, 133.9, 133.3, 131.4 – 131.0 (m), 128.5, 128.3, 127.1, 127.0 (d, *J* = 3.2 Hz), 126.9 (dd, *J* = 7.3, 5.5 Hz), 124.0, 123.6, 116.9, 116.1, 36.4, 35.9, 35.2, 34.7, 32.9, 32.5, 32.4 (d, *J* = 3.4 Hz), 32.3 (d, *J* = 3.5 Hz), 31.5, 30.3, 29.8, 29.8, 28.3, 28.1 (d, *J* = 14.3 Hz), 27.9, 23.2, 22.5 (d, *J* = 10.1 Hz), 14.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{98}H_{95}NO_{14}P]^+$, $[M+H]^+$: 1540.6485; found: 1540.6478.

α_D^{589} = +1.26 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.05, 298 K).

Complex (*S*,*S*)-K



Complex (*S*,*S*)-**K** (225 mg, 136 µmol, 92% yield) was obtained as a yellow solid following the general procedure **A** from phosphoramidite (*S*,*S*)-**49** (212 mg, 138 µmol) and (Me_2S)AuCl (43 mg, 144 µmol) after purification by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 7:3 as eluent.

M.p. = 205–208 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.20 – 8.10 (m, 2H), 8.10 – 8.00 (m, 4H), 7.73 (ddd, *J* = 19.5, 6.5, 3.7 Hz, 6H), 7.59 – 7.18 (m, 13H), 7.12 – 6.86 (m, 5H), 5.18 (dq, *J* = 18.2, 7.1 Hz, 2H), 5.05 – 4.46 (m, 3H), 4.41 (td, *J* = 8.1, 3.1 Hz, 1H), 2.22 – 2.11 (m, 8H), 2.02 (d, *J* = 7.1 Hz, 6H), 1.48 – 1.21 (m, 32H), 0.92 – 0.78 (m, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 124.7 ppm.

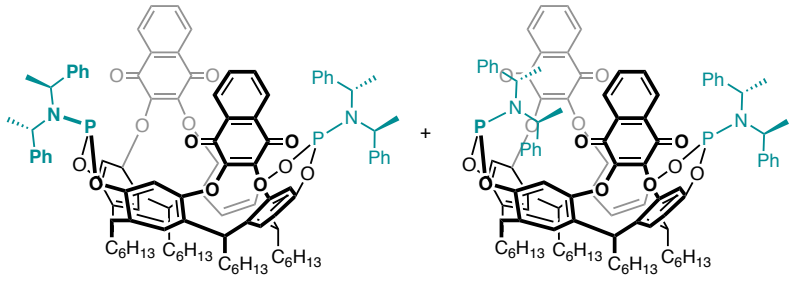
^{13}C NMR (126 MHz, CD_2Cl_2) δ 181.6, 181.3, 181.2, 152.9, 152.5, 152.1, 148.1, 147.7, 141.5 (d, *J* = 3.6 Hz), 136.3, 134.8 – 134.2 (m), 131.2 (d, *J* = 2.6 Hz), 131.1 (d, *J* = 2.8 Hz), 128.9, 128.7, 128.4, 127.2, 126.8 (d, *J* = 3.6 Hz), 123.4, 117.5, 54.9 (d, *J* = 8.6 Hz), 36.5, 35.7, 35.3, 32.3, 32.1, 31.5, 31.1 – 29.1 (m), 29.0 – 27.2 (m), 23.2, 21.3 (d, *J* = 2.6 Hz), 14.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{98}H_{94}AuClNNaO_{14}P]^+$, $[M+Na]^+$: 1794.5637; found: 1794.5658.

Elemental analysis Anal. Calc. for $C_{98}H_{94}AuClNO_{14}P$: C, 66.38; H, 5.34; N, 0.79; found: C, 65.34; H, 5.26; N, 0.82.

α_D^{589} = –16.4 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.65, 298 K).

Phosphoramidites (*S*,*S*,*S*,*S*)-51



(*S*,*S*,*S*,*S*)-**51a** (*S*,*S*,*S*,*S*)-**51b**

51a/51b (1.2:1), 44%

Triethylamine (1.48 mL, 10.59 mmol) was added to a mixture of tetraphenol **38b**[32b] (2.0 g, 1.76 mmol) in dry toluene (29.4 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then *N*,*N*-bis[(1*S*)-1-phenylethyl]phosphoramidous dichloride (*S*,*S*)-**47a** (1.73 g, 5.29 mmol) in dry toluene (5.8 mL) was added to the mixture, which was stirred for 5 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) to afford a mixture of (*S*,*S*,*S*,*S*)-**51a** and (*S*,*S*,*S*,*S*)-**51b** (1.3 g, 0.77 mmol, 44% yield, (*S*,*S*,*S*,*S*)-**51a**/(*S*,*S*,*S*,*S*)-**51b** 1.2:1 ratio) as a yellow solid.

The ratio of (*S*,*S*,*S*,*S*)-**51a**/(*S*,*S*,*S*,*S*)-**51b** 1.2:1 was determined by ^{31}P NMR.

Because of the complex mixture of the phosphoramidites ((*S*,*S*,*S*,*S*)-**51a**/(*S*,*S*,*S*,*S*)-**51b**) that leads to multiple overlapping, the proton and carbon signals were not assigned. Only the phosphorous signals were asigned. The two corresponding complexes were found to be easier to separate after the gold(I) coordination and thus, the mixture of phosphoramidites was taken on to the next step without further separation.

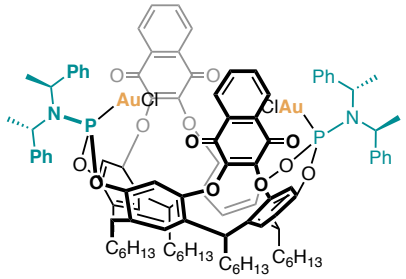
^{31}P NMR (203 MHz, CD_2Cl_2) δ 147.2, 146.2, 143.6 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{104}H_{109}N_2O_{12}P_2]^+$, $[M+H]^+$: 1639.7433; found: 1639.7450.

Synthesis of (*S*,*S*,*S*,*S*)-L and (*S*,*S*,*S*,*S*)-P.

Complex (*S*,*S*,*S*,*S*)-**L** and complex (*S*,*S*,*S*,*S*)-**P** were obtained according to the general procedure **A** from a mixture of phosphoramidites (*S*,*S*,*S*,*S*)-**51a**/(*S*,*S*,*S*,*S*)-**51b** (1.22 g, 0.74 mmol) and $(Me_2S)AuCl$ (460 mg, 1.56 mmol). Purification by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) afforded complex (*S*,*S*,*S*,*S*)-**L** (726 mg, 0.35 mmol, 46% yield) as a yellow solid and complex (*S*,*S*,*S*,*S*)-**P** (596 mg, 0.28 mmol, 38% yield) as a yellow solid.

Characterization of (*S*,*S*,*S*,*S*)-L:



M.p. = 146–148 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.04 – 7.98 (m, 2H), 7.96 – 7.90 (m, 2H), 7.65 – 7.57 (m, 4H), 7.49 (d, *J* = 1.7 Hz, 2H), 7.44 – 7.32 (m, 20H), 7.25 (dd, *J* = 6.4, 2.9 Hz, 6H), 5.61 (t, *J* = 8.2 Hz, 2H), 5.18 (dq, *J* = 17.1, 6.8 Hz, 4H), 4.54 (td, *J* = 8.1, 3.1 Hz, 2H), 2.34 (q, *J* = 7.7 Hz, 4H), 2.28 – 2.11 (m, 4H), 2.01 (d, *J* = 7.1 Hz, 12H), 1.53 – 1.23 (m, 32H), 0.90 (q, *J* = 7.1 Hz, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 120.3 ppm.

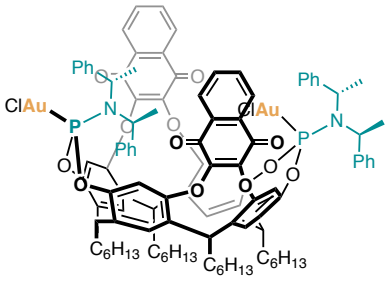
^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.7, 182.5, 154.0 (t, *J* = 1.8 Hz), 151.9, 151.7, 146.9 (d, *J* = 4.3 Hz), 146.5 (d, *J* = 4.6 Hz), 141.4 (d, *J* = 3.7 Hz), 137.1, 136.9, 136.8 (dd, *J* = 6.8, 2.8 Hz), 134.6 (d, *J* = 10.4 Hz), 130.8 (d, *J* = 3.6 Hz), 128.9, 128.8, 128.4, 127.8, 127.6, 123.6, 118.9 (d, *J* = 4.1 Hz), 118.6 (d, *J* = 4.3 Hz), 54.7 (d, *J* = 8.8 Hz), 36.4, 33.8, 33.3, 32.4 (d, *J* = 8.7 Hz), 30.4, 29.8 (d, *J* = 17.4 Hz), 28.3 (d, *J* = 17.9 Hz), 23.2 (d, *J* = 2.7 Hz), 21.6 (d, *J* = 2.6 Hz), 14.4 (d, *J* = 5.0 Hz) ppm.

HRMS (MALDI) calculated for *m/z* $[C_{104}H_{108}Au_2ClN_2O_{12}P_2]^+$, $[M-Cl]^+$: 2067.6392; found: 2067.6374.

Elemental analysis Anal. Calc. for $C_{104}H_{108}Au_2Cl_2N_2O_{12}P_2$: C, 59.35; H, 5.17; N, 1.33; found: C, 59.06; H, 5.16; N, 1.38.

α_D^{589} = –49.3 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.07, 298 K).

Characterization of (*S*,*S*,*S*,*S*)-P:



M.p. = 292–294 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.12 – 8.04 (m, 1H), 7.96 (ddd, *J* = 12.1, 6.6, 1.9 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.61 – 7.53 (m, 2H), 7.52 – 7.48 (m, 1H), 7.42 – 7.26 (m, 15H), 7.24 – 7.11 (m, 9H), 7.09 – 7.00 (m, 2H), 6.97 – 6.90 (m, 2H), 5.42 (br s, 1H), 5.17 (ddt, *J* = 18.0, 14.2, 5.9 Hz, 3H), 4.86 (t, *J* = 7.7 Hz, 1H), 4.75 (dq, *J* = 19.2, 7.0 Hz, 2H), 4.42 (td, *J* = 8.1, 3.2 Hz, 1H), 2.44 – 2.07 (m, 14H), 2.03 (d, *J* = 7.1 Hz, 6H), 1.54 – 1.20 (m, 32H), 1.03 – 0.80 (m, 12H) ppm.

^{31}P NMR (CD_2Cl_2) δ 126.7, 117.7 ppm.

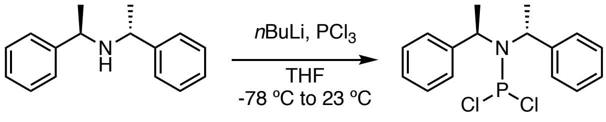
^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.8, 182.4, 181.8, 180.9, 154.1, 153.7, 153.3 (d, *J* = 2.6 Hz), 151.9, 150.7 (d, *J* = 13.6 Hz), 150.5 (d, *J* = 6.2 Hz), 149.8, 148.5, 148.3, 141.5 (d, *J* = 3.5 Hz), 141.3, 137.1, 136.3 (d, *J* = 3.5 Hz), 136.1 (d, *J* = 3.9 Hz), 135.8, 134.9 (d, *J* = 12.3 Hz), 134.5 – 134.2 (m), 133.7, 131.1, 130.9 (d, *J* = 2.0 Hz), 130.8, 130.6, 129.3, 128.9, 128.6 (d, *J* = 6.6 Hz), 128.4 (d, *J* = 3.7 Hz), 127.2 (d, *J* = 2.2 Hz), 126.8, 126.3, 125.4, 125.2, 123.2, 121.6, 118.9, 117.5 (d, *J* = 6.6 Hz), 116.2, 115.9, 54.8 (d, *J* = 8.5 Hz), 40.2 (d, *J* = 7.1 Hz), 36.5, 35.3, 34.2, 33.5, 32.5 – 32.3 (m), 32.2, 31.6 (d, *J* = 16.0 Hz), 30.8, 29.9, 29.8 – 29.6 (m), 28.2 (d, *J* = 1.8 Hz), 27.9, 27.8, 23.4 – 22.8 (m), 21.9, 21.3 (d, *J* = 3.2 Hz), 14.9 – 13.9 (m) ppm.

HRMS (MALDI) calculated for *m/z* $[C_{104}H_{108}Au_2ClN_2O_{12}P_2]^+$, $[M\text{-}Cl]^+$: 2067.6392; found: 2067.6424.

Elemental analysis Anal. Calc. for $C_{104}H_{108}Au_2Cl_2N_2O_{12}P_2$: C, 59.35; H, 5.17; N, 1.33; found: C, 59.01; H, 5.08; N, 1.39.

α_D^{589} = –64.8 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.56, 298 K).

Synthesis of *N*,*N*-bis[(1*R*)-1-phenylethyl]phosphoramidous dichloride ((*R*,*R*)-50)

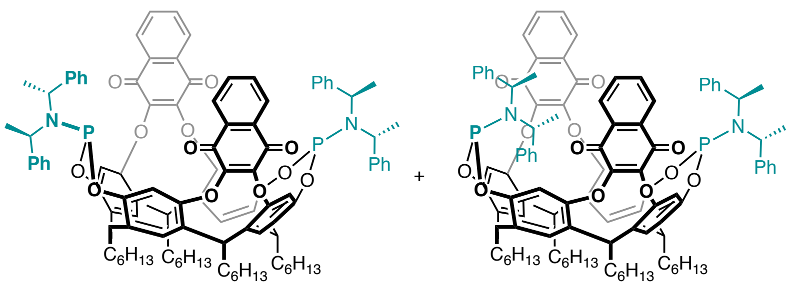


(*R*,*R*)-**50**

A flame-dried Schlenk tube was charged with (1*R*,1'*R*)-bis(1-phenylethyl)amine (260 mg, 1.15 mmol, 1 equiv) and anhydrous THF (2.63 mL, 0.44 M) under argon, the solution was then cooled to -78 °C and *n*BuLi (0.51 mL, 1.27 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at -78 °C for 30 min and then PCl_3 (130 µL, 1.50 mmol, 1.3 equiv) was added dropwise to the solution of lithium amide at -78 °C under argon. The reaction mixture was warmed to 23 °C and stirred overnight. The mixture was concentrated *in vacuo*, and the residual PCl_3 was removed *via* repetitive THF dilution (x3) and vacuum evaporation to give *N*,*N*-bis[(1*R*)-1-phenylethyl]phosphoramidous dichloride ((*R*,*R*)-**50**) that was used in the next step without further purification.

^{31}**P NMR** (162 MHz, C_6D_6) δ 168.7 ppm.

Phosphoramidites (*R*,*R*,*R*,*R*)-55



(*R*,*R*,*R*,*R*)-**55a** (*R*,*R*,*R*,*R*)-**55b**

55a/55b (3.1:1), 34%

Triethylamine (0.28 mL, 2.01 mmol) was added to a mixture of tetraphenol **38b**[32b] (380 mg, 0.34 mmol) in dry toluene (5.59 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then *N*,*N*-bis[(1*R*)-1-phenylethyl]phosphoramidous dichloride (*R*,*R*)-**50** (328 mg, 1.01 mmol) in dry toluene (1.1 mL) was added to the mixture, which was stirred for 5 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) to afford a mixture of (*R*,*R*,*R*,*R*)-**55a** and (*R*,*R*,*R*,*R*)-**55b** (186 mg, 0.11 mmol, 34% yield, (*R*,*R*,*R*,*R*)-**55a**/(*R*,*R*,*R*,*R*)-**55b** 3.1:1 ratio) as a yellow solid.

The ratio of (*R*,*R*,*R*,*R*)-**55a**/(*R*,*R*,*R*,*R*)-**55b** 3.1:1 was determined by ^{31}P NMR.

Because of the complex mixture of the phosphoramidites ((*R*,*R*,*R*,*R*)-**55a**/(*R*,*R*,*R*,*R*)-**55b**) that leads to multiple overlapping, the proton and carbon signals were not assigned. Only the phosphorous signals were asigned. The two corresponding complexes were found to be easier

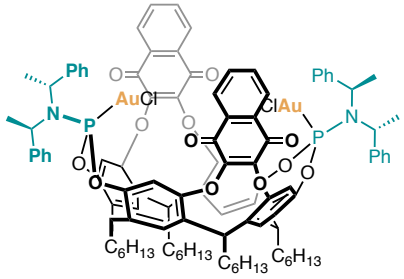
to separate after the gold(I) coordination and thus, the mixture of phosphoramidites was taken on to the next step without further separation.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 147.2, 146.2, 143.6 ppm.

Synthesis of (*R*,*R*,*R*,*R*)-L and (*R*,*R*,*R*,*R*)-P

Complex (*R*,*R*,*R*,*R*)-**L** and complex (*R*,*R*,*R*,*R*)-**P** were obtained according to the general procedure **A** from a mixture of phosphoramidites (*R*,*R*,*R*,*R*)-**55a**/(*R*,*R*,*R*,*R*)-**55b** (172 mg, 0.13 mmol) and (Me_2S)AuCl (82 mg, 0.27 mmol). Purification by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) afforded complex (*R*,*R*,*R*,*R*)-**L** (150 mg, 84.8 µmol, 64% yield) as a yellow solid and complex (*R*,*R*,*R*,*R*)-**P** (52 mg, 30 µmol, 22% yield) as a yellow solid.

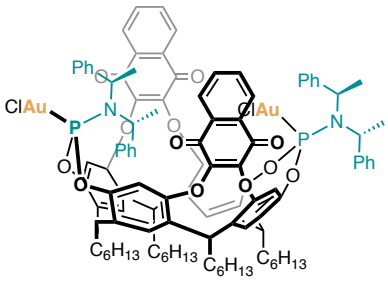
Characterization of (*R*,*R*,*R*,*R*)-L:



The spectral data of (*R*,*R*,*R*,*R*)-**L** were fully consistent with the previously synthesized (*S*,*S*,*S*,*S*)-**L**.

α_D^{589} = +57.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.61, 296 K).

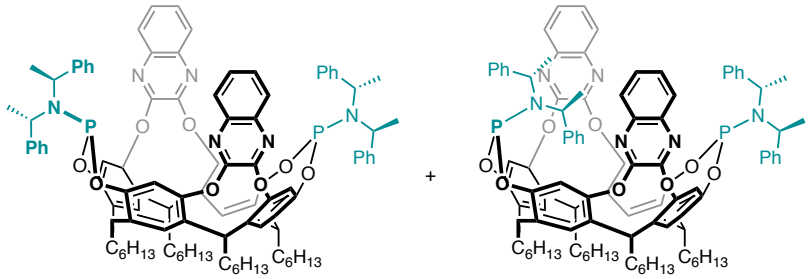
Characterization of (*R*,*R*,*R*,*R*)-P:



The spectral data of (*R*,*R*,*R*,*R*)-**P** were fully consistent with the previously synthesized (*S*,*S*,*S*,*S*)-**P**.

α_D^{589} = +41.9 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.52, 298 K).

Phosphoramidites (*S*,*S*,*S*,*S*)-52



52a/52b (1.9:1), 43%

Triethylamine (334 µL, 2.39 mmol) was added to a mixture of tetraphenol **38a**[33] (430 mg, 0.4 mmol) in dry toluene (6.65 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then *N*,*N*-bis[(1*S*)-1-phenylethyl]phosphoramidous dichloride (*S*,*S*)-**47a** (391 mg, 1.20 mmol) in dry toluene (1.4 mL) was added to the mixture, which was stirred for 6 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) to afford a mixture of (*S*,*S*,*S*,*S*)-**52a** and (*S*,*S*,*S*,*S*)-**52b** (270 mg, 0.11 mmol, 43% yield, (*S*,*S*,*S*,*S*)-**52a**/(*S*,*S*,*S*,*S*)-**52b** 1.9:1 ratio) as a white solid.

The ratio of (*S*,*S*,*S*,*S*)-**52a**/(*S*,*S*,*S*,*S*)-**52b** 1.9:1 was determined by ^{31}P NMR.

Because of the complex mixture of the phosphoramidites ((*S*,*S*,*S*,*S*)-**52a**/(*S*,*S*,*S*,*S*)-**52b**) that leads to multiple overlapping, the proton and carbon signals were not assigned. Only the phosphorous signals were asigned. The two corresponding complexes were found to be easier to separate after the gold(I) coordination and thus, the mixture of phosphoramidites was taken on to the next step without further separation.

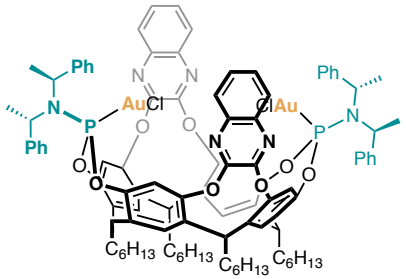
^{31}P NMR (203 MHz, CD_2Cl_2) δ 146.1, 145.6, 143.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{98}H_{110}N_6NaO_8P_2]^+$, $[M+Na]^+$: 1583.7736; found: 1583.7753.

Complexes (*S*,*S*,*S*,*S*)-M and (*S*,*S*,*S*,*S*)-Q.

Complex (*S*,*S*,*S*,*S*)-**M** and complex (*S*,*S*,*S*,*S*)-**Q** were obtained according to the general procedure **A** from a mixture of phosphoramidites (*S*,*S*,*S*,*S*)-**52a**/(*S*,*S*,*S*,*S*)-**52b** (258 mg, 0.16 mmol) and (Me_2S)AuCl (101 mg, 0.34 mmol). Purification by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) afforded complex (*S*,*S*,*S*,*S*)-**M** (146 mg, 71 µmol, 44% yield) as a white solid and (*S*,*S*,*S*,*S*)-**Q** (132 mg, 64 µmol, 40% yield) as a white solid.

Characterization of (*S*,*S*,*S*,*S*)-M:



M.p. = 142–144 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.90 – 7.84 (m, 2H), 7.76 – 7.71 (m, 2H), 7.55 (dt, *J* = 6.4, 3.5 Hz, 4H), 7.44 – 7.32 (m, 22H), 7.24 (s, 4H), 7.11 (d, *J* = 1.7 Hz, 2H), 5.66 (t, *J* = 8.2 Hz, 2H), 5.20 (dq, *J* = 18.0, 7.1 Hz, 4H), 4.54 (td, *J* = 8.1, 3.1 Hz, 2H), 2.34 (q, *J* = 7.7 Hz, 4H), 2.22 (q, *J* = 8.1 Hz, 4H), 2.01 (d, *J* = 7.1 Hz, 12H), 1.53 – 1.28 (m, 32H), 0.91 (dt, *J* = 13.9, 6.9 Hz, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 119.4 ppm.

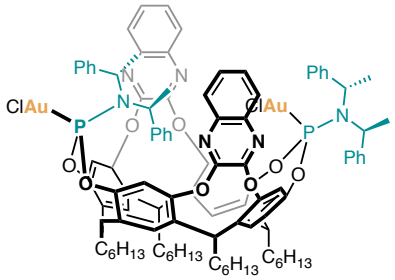
^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.2 (dd, *J* = 9.8, 1.8 Hz), 152.1 (d, *J* = 5.3 Hz), 147.1 (d, *J* = 4.8 Hz), 146.6 (d, *J* = 5.0 Hz), 141.5 (d, *J* = 3.7 Hz), 140.2 (d, *J* = 2.4 Hz), 137.4 – 136.0 (m), 130.0 (d, *J* = 3.2 Hz), 128.9 (d, *J* = 14.0 Hz), 128.3, 123.3 (d, *J* = 4.2 Hz), 118.2 (d, *J* = 4.0 Hz), 118.1 (d, *J* = 4.0 Hz), 54.6 (d, *J* = 8.8 Hz), 36.4, 34.7, 33.2, 32.4 (d, *J* = 6.8 Hz), 30.5, 29.9, 29.8, 28.5, 28.3, 23.3 (d, *J* = 1.4 Hz), 21.5 (d, *J* = 2.6 Hz), 14.4 (d, *J* = 5.1 Hz) ppm.

HRMS (MALDI) calculated for *m/z* $[C_{100}H_{108}Au_2ClN_6O_8P_2]^+$, $[M\text{-}Cl]^+$: 2011.6718; found: 2011.6723.

Elemental analysis Anal. Calc. for $C_{100}H_{108}Au_2Cl_2N_6O_8P_2$: C, 58.63; H, 5.31, N: 4.10; found: C, 58.53; H, 5.32; N, 4.09.

α_D^{589} = –30.6 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.10, 299 K).

Characterization of (*S*,*S*,*S*,*S*)-Q:



M.p. = 255–257 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.79 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.53 – 7.43 (m, 4H), 7.41 – 7.27 (m, 18H), 7.25 – 7.20 (m, 4H), 7.14 (d, *J* = 6.5 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 7.04 (d, *J* = 1.8 Hz, 1H), 5.55 (t, *J* = 8.1 Hz, 1H), 5.42 (t, *J* = 8.1 Hz, 1H), 5.31 (td, *J* = 7.2, 5.5 Hz, 1H), 5.16 (dq, *J* = 17.8, 7.0 Hz, 2H), 4.68 (dt, *J* = 19.6, 7.0 Hz, 2H), 4.48 (td, *J* = 8.0, 3.2 Hz, 1H), 2.31 – 2.10 (m, 8H), 2.01 (d, *J* = 7.1 Hz, 6H), 1.86 (d, *J* = 7.0 Hz, 6H), 1.49 – 1.28 (m, 32H), 0.95 – 0.84 (m, 12H) ppm.

^{31}P NMR (203 MHz, $CDCl_3$) δ 120.9, 116.1 ppm.

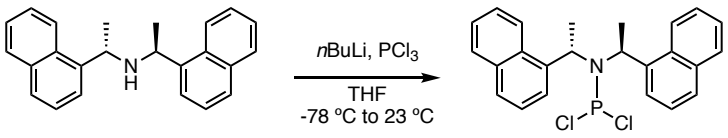
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 152.8 (d, *J* = 1.8 Hz), 152.7, 152.7 (d, *J* = 2.1 Hz), 151.4, 150.3, 150.2 (d, *J* = 6.8 Hz), 150.1, 147.2 (d, *J* = 3.6 Hz), 146.7 (d, *J* = 4.1 Hz), 140.7 (t, *J* = 4.6 Hz), 139.8 (d, *J* = 8.9 Hz), 139.7 (d, *J* = 9.6 Hz), 136.7, 136.4, 135.7 (d, *J* = 3.0 Hz), 135.6 (d, *J* = 3.2 Hz), 134.8, 134.4, 129.9 (d, *J* = 3.3 Hz), 129.8 (d, *J* = 13.1 Hz), 129.6 (d, *J* = 7.6 Hz), 128.7 (d, *J* = 5.4 Hz), 128.6, 128.5, 128.1 (t, *J* = 8.4 Hz), 127.5, 127.1, 123.8, 122.9, 122.6, 122.5, 117.9 (d, *J* = 3.8 Hz), 117.4 (d, *J* = 4.1 Hz), 115.7 (t, *J* = 5.3 Hz), 54.3 (d, *J* = 8.7 Hz), 53.1 (d, *J* = 8.4 Hz), 39.9 (d, *J* = 7.8 Hz), 35.9, 34.7, 34.4, 32.5, 31.9 (dd, *J* = 7.4, 2.3 Hz), 31.2, 30.4, 29.8, 29.5 (d, *J* = 2.7 Hz), 29.3, 28.1 – 27.8 (m), 27.6, 23.3 – 22.1 (m), 21.5, 21.3 (d, *J* = 2.4 Hz), 14.2 (t, *J* = 4.3 Hz) ppm.

HRMS (MALDI) calculated for *m/z* $[C_{100}H_{108}Au_2ClN_6O_8P_2]^+$, $[M\text{-}Cl]^+$: 2011.6718; found: 2011.6726.

Elemental analysis Anal. Calc. for $C_{100}H_{108}Au_2Cl_2N_6O_8P_2$: C, 58.63; H, 5.31, N: 4.10; found: C, 58.53; H, 5.32; N, 4.09.

α_D^{589} = –65.2 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.82, 299 K).

Synthesis of 1,1-dichloro-*N*,*N*-bis((*S*)-1-(naphthalen-1-yl)ethyl)phosphanamine ((*S*,*S*)-47b)

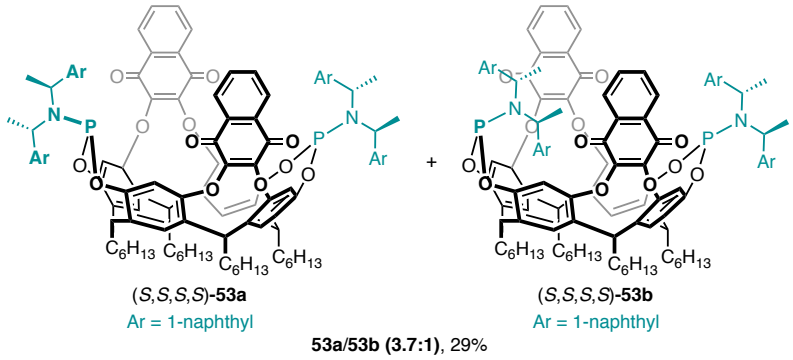


(*S*,*S*)-**47b**

A flame-dried Schlenk tube was charged with (*S*)-bis((*S*)-1-naphthalen-1-yl)ethyl)amine (263 mg, 0.81 mmol, 1 equiv) and anhydrous THF (1.84 mL, 0.44 M) under argon, the solution was then cooled to -78 °C and *n*BuLi (0.51 mL, 1.27 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at -78 °C for 30 min and then PCl_3 (92 µL, 1.05 mmol, 1.3 equiv) was added dropwise to the solution of lithium amide at -78 °C under argon. The reaction mixture was warmed to 23 °C and stirred overnight. The mixture was concentrated *in vacuo*, and the residual PCl_3 was removed *via* repetitive THF dilution (x3) and vacuum evaporation to give (*S*,*S*)-**47b** that was used in the next step without further purification.

^{31}P NMR (162 MHz, C_6D_6) δ 167.7 ppm.

Phosphoramidites (*S*,*S*,*S*,*S*)-53



Triethylamine (211 µL, 1.59 mmol) was added to a mixture of tetraphenol **38b**[32b] (300 mg, 0.26 mmol) in dry toluene (4.4 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then 1,1-dichloro-*N*,*N*-bis((*S*)-1-(naphthalen-1-yl)ethyl)phosphanamine (*S*,*S*)-**47b** (339 mg, 0.79 mmol) in dry toluene (0.9 mL) was added to the mixture, which was stirred for 4 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) to afford a mixture of (*S*,*S*,*S*,*S*)-**53a** and (*S*,*S*,*S*,*S*)-**53b** (141 mg, 0.08 mmol, 29% yield, (*S*,*S*,*S*,*S*)-**53a**/(*S*,*S*,*S*,*S*)-**53b** 3.7:1 ratio) as a yellow solid.

The ratio of (*S*,*S*,*S*,*S*)-**53a**/(*S*,*S*,*S*,*S*)-**53b** 3.7:1 was determined by ^{31}P NMR.

Because of the complex mixture of the phosphoramidites ((*S*,*S*,*S*,*S*)-**53a**/(*S*,*S*,*S*,*S*)-**53b**) that leads to multiple overlapping, the proton and carbon signals were not assigned. Only the phosphorous signals were asigned. The two corresponding complexes were found to be easier to separate after the gold(I) coordination and thus, the mixture of phosphoramidites was taken on to the next step without further separation.

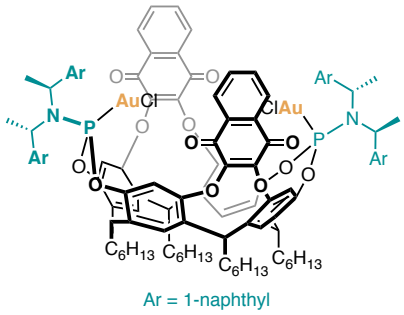
^{31}P NMR (203 MHz, CD_2Cl_2) δ 151.6, 150.7, 147.2 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{120}H_{117}N_2O_{12}P_2]^+$, $[M+H]^+$: 1839.8050; found: 1839.8076.

Synthesis of (*S*,*S*,*S*,*S*)-N and (*S*,*S*,*S*,*S*)-R.

Complex (*S*,*S*,*S*,*S*)-**N** and complex (*S*,*S*,*S*,*S*)-**R** were obtained according to the general procedure **A** from a mixture of phosphoramidite (*S*,*S*,*S*,*S*)-**53a**/(*S*,*S*,*S*,*S*)-**53b** (98 mg, 53.3 µmol) and $(Me_2S)AuCl$ (233 mg, 112 µmol). Purification by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) afforded complex (*S*,*S*,*S*,*S*)-**N** (63 mg, 27 µmol, 51% yield) as a yellow solid and complex (*S*,*S*,*S*,*S*)-**R** (28 mg, 12 µmol, 23% yield) as a yellow solid.

Characterization of (*S*,*S*,*S*,*S*)-N:



M.p. = 254–256 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.26 (d, *J* = 7.7 Hz, 2H), 8.18 (d, *J* = 8.2 Hz, 2H), 7.96 – 7.87 (m, 4H), 7.82 (td, *J* = 7.5, 1.3 Hz, 2H), 7.72 (td, *J* = 7.6, 1.2 Hz, 2H), 7.67 (d, *J* = 1.8 Hz, 2H), 7.60 (d, *J* = 2.3 Hz, 2H), 7.47 (dd, *J* = 6.3, 3.1 Hz, 8H), 7.38 – 7.28 (m, 12H), 7.04 (d, *J* = 8.2 Hz, 4H), 6.74 (t, *J* = 7.7 Hz, 4H), 5.95 – 5.83 (m, 6H), 4.42 (td, *J* = 8.1, 3.1 Hz, 2H), 2.51 – 2.40 (m, 4H), 2.38 – 2.22 (m, 4H), 2.04 (d, *J* = 7.2 Hz, 12H), 1.65 – 1.52 (m, 6H), 1.44 – 1.34 (m, 12H), 1.33 – 1.24 (m, 14H), 0.98 – 0.91 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 6H) ppm.

^{31}P NMR (CD_2Cl_2) δ 134.8 ppm.

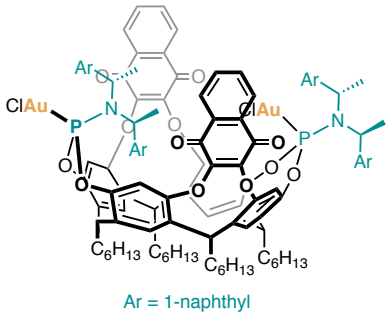
^{13}C NMR (126 MHz, CD_2Cl_2) δ 183.8, 183.3, 154.6 (d, *J* = 3.4 Hz), 153.7, 153.1, 152.7, 149.4, 148.8, 137.5 – 137.2 (m), 137.1, 135.8 (d, *J* = 9.2 Hz), 135.5 (d, *J* = 3.4 Hz), 134.8, 134.5, 133.2, 131.9, 131.6, 130.9, 128.8, 127.5, 127.1 (d, *J* = 14.1 Hz), 126.5, 125.5 (d, *J* = 12.7 Hz), 125.3, 124.6, 123.6, 122.9, 119.4 (d, *J* = 5.8 Hz), 118.9 (d, *J* = 4.9 Hz), 54.8 (d, *J* = 12.7 Hz), 37.0, 34.8, 32.6, 32.5, 32.3, 31.5, 30.0, 29.6, 28.6, 28.2, 23.2 (d, *J* = 5.1 Hz), 21.0, 14.4 (d, *J* = 10.6 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{120}H_{116}Au_2Cl_2N_2NaO_{12}P_2]^+$, $[M+Na]^+$: 2325.6604; found: 2325.6619.

Elemental analysis Anal. Calc. for $C_{120}H_{116}Au_2Cl_2N_2O_{12}P_2$: C, 62.53; H, 5.07, N: 1.22; found: C, 62.11; H, 5.06; N, 1.33.

α_D^{589} = +142.5 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.21, 299 K).

Characterization of (*S*,*S*,*S*,*S*)-R:



M.p. = 224–226 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.15 – 7.91 (m, 5H), 7.77 – 7.51 (m, 15H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.44 – 7.33 (m, 6H), 7.30 – 7.23 (m, 4H), 7.20 (s, 1H), 7.18 – 7.13 (m, 3H), 7.08 (s, 3H), 6.96 (t, *J* = 7.7 Hz, 2H), 6.91 – 6.81 (m, 1H), 6.75 (t, *J* = 7.7 Hz, 2H), 5.98 (dq, *J* = 14.1, 7.3 Hz, 2H), 5.88 (br s, 2H), 5.46 (q, *J* = 7.4 Hz, 1H), 5.38 – 5.33 (m, 1H), 4.92 (br s, 1H), 4.50 (td, *J* = 8.1, 3.2 Hz, 1H), 2.41 (qt, *J* = 17.3, 8.9 Hz, 2H), 2.32 – 2.09 (m, 12H), 1.88 (d, *J* = 7.0 Hz, 6H), 1.47 – 1.18 (m, 32H), 0.93 – 0.76 (m, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 129.7, 121.4 ppm.

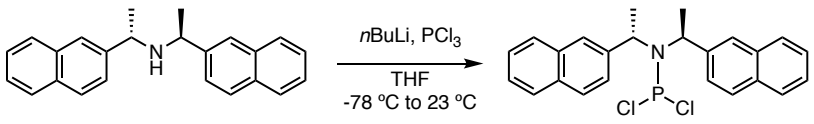
^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.0 (d, *J* = 2.9 Hz), 181.4, 181.1, 153.7, 153.5, 153.3, 152.3, 150.3 (d, *J* = 8.7 Hz), 149.9 (d, *J* = 12.5 Hz), 148.7 (d, *J* = 1.7 Hz), 148.4 (d, *J* = 2.1 Hz), 136.5 (d, *J* = 3.6 Hz), 136.3 (d, *J* = 3.9 Hz), 135.8 (d, *J* = 7.3 Hz), 135.3 (d, *J* = 7.1 Hz), 134.9, 134.7, 134.6, 134.3, 133.6, 133.4, 131.4 (d, *J* = 7.0 Hz), 131.1, 130.7 (d, *J* = 3.3 Hz), 130.6, 129.1 (d, *J* = 6.4 Hz), 128.7, 128.0, 127.1, 126.9 (d, *J* = 4.8 Hz), 126.9, 126.6, 126.5, 126.3, 126.1, 125.9, 125.7, 124.8 (d, *J* = 6.7 Hz), 123.8, 123.4 (d, *J* = 13.0 Hz), 122.5, 117.9, 117.7 – 116.9 (m), 116.6, 40.7 (d, *J* = 7.3 Hz), 36.8, 35.5, 34.6, 32.4, 32.3 – 32.2 (m), 32.1, 31.7, 31.4, 30.3, 30.0, 29.8, 29.6, 28.2 (d, *J* = 7.8 Hz), 28.0, 23.2 (dd, *J* = 6.1, 1.5 Hz), 22.9, 21.9 (d, *J* = 3.5 Hz), 14.5, 14.4 (d, *J* = 4.8 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{120}H_{116}Au_2Cl_2N_2NaO_{12}P_2]^+$, $[M+Na]^+$: 2325.6604; found: 2325.6571.

Elemental analysis Anal. Calc. for $C_{120}H_{116}Au_2Cl_2N_2O_{12}P_2$: C, 62.53; H, 5.07, N: 1.22; found: C, 61.92; H, 5.09; N, 1.32.

α_D^{589} = +59.4 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.14, 299 K).

Synthesis of 1,1-dichloro-*N*,*N*-bis((*S*)-1-(naphthalen-2-yl)ethyl)phosphanamine ((*S*,*S*)-47c)

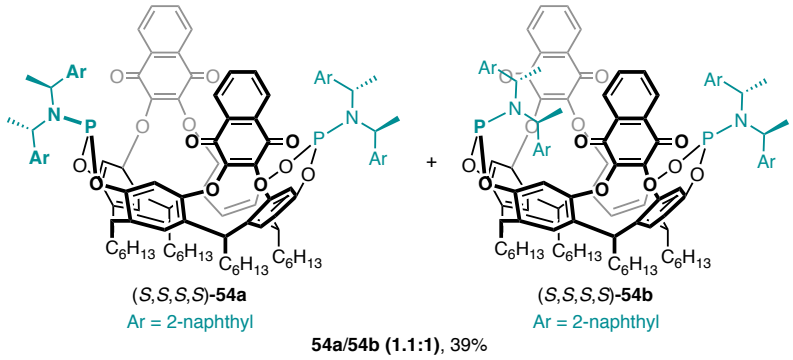


(*S*,*S*)-**47c**

A flame-dried Schlenk tube was charged with (*S*)-bis((*S*)-1-naphthalen-2-yl)ethyl)amine (263 mg, 0.81 mmol, 1 equiv) and anhydrous THF (1.84 mL, 0.44 M) under argon, the solution was then cooled to -78 °C and *n*BuLi (0.51 mL, 1.27 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at -78 °C for 30 min and then PCl_3 (92 µL, 1.05 mmol, 1.3 equiv) was added dropwise to the solution of lithium amide at -78 °C under argon. The reaction mixture was warmed to 23 °C and stirred overnight. The mixture was concentrated *in vacuo*, and the residual PCl_3 was removed *via* repetitive THF dilution (x3) and vacuum evaporation to give (*S*,*S*)-**47c** that was used in the next step without further purification.

^{31}P NMR (162 MHz, C_6D_6) δ 168.7 ppm.

Phosphoramidites (*S*,*S*,*S*,*S*)-54



Triethylamine (211 µL, 1.59 mmol) was added to a mixture of tetraphenol **38b**[32b] (300 mg, 0.26 mmol) in dry toluene (4.4 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then 1,1-dichloro-*N*,*N*-bis((S)-1-(naphthalen-2-yl)ethyl)phosphanamine (*S*,*S*)-**47c** (339 mg, 0.79 mmol) in dry toluene (0.9 mL) was added to the mixture, which was stirred for 4 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) to afford a mixture of (*S*,*S*,*S*,*S*)-**54a** and (*S*,*S*,*S*,*S*)-**54b** (188 mg, 0.1 mmol, 39% yield, (*S*,*S*,*S*,*S*)-**54a**/(*S*,*S*,*S*,*S*)-**54b** 1.1:1 ratio) as a yellow solid.

The ratio of (*S*,*S*,*S*,*S*)-**54a**/(*S*,*S*,*S*,*S*)-**54b** 1.1:1 was determined by ^{31}P NMR.

Because of the complex mixture of the phosphoramidites ((*S*,*S*,*S*,*S*)-**54a**/(*S*,*S*,*S*,*S*)-**54b**) that leads to multiple overlapping, the proton and carbon signals were not assigned. Only the phosphorous signals were asigned. The two corresponding complexes were found to be easier to separate after the gold(I) coordination and thus, the mixture of phosphoramidites was taken on to the next step without further separation.

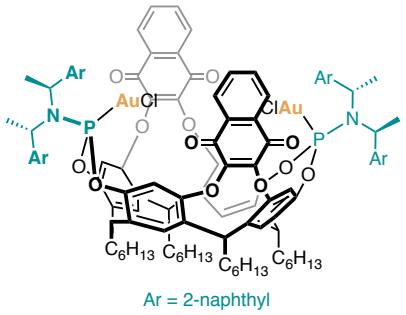
^{31}P NMR (203 MHz, CD_2Cl_2) δ 147.2, 145.4, 143.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{120}H_{117}N_2O_{12}P_2]^+$, $[M+H]^+$: 1839.7991; found: 1839.8076.

Synthesis of (*S*,*S*,*S*,*S*)-O and (*S*,*S*,*S*,*S*)-S.

Complex (*S*,*S*,*S*,*S*)-**O** and complex (*S*,*S*,*S*,*S*)-**S** were obtained according to the general procedure **A** from a mixture of phosphoramidites (*S*,*S*,*S*,*S*)-**54a**/(*S*,*S*,*S*,*S*)-**54b** (150 mg, 94.7 µmol) and (Me_2S)AuCl (59 mg, 199 µmol). Purification by flash column chromatography on silica gel (cyclohexane to cyclohexane/CH_2Cl_2/EtOAc 8:1:1) afforded complex (*S*,*S*,*S*,*S*)-**O** (90 mg, 46 µmol, 48% yield) as a yellow solid and complex (*S*,*S*,*S*,*S*)-**S** (65 mg, 33 µmol, 35% yield) as a yellow solid.

Characterization of (*S*,*S*,*S*,*S*)-O:



M.p. = 157–160 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.95 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.91 – 7.77 (m, 16H), 7.57 – 7.46 (m, 12H), 7.45 – 7.39 (m, 6H), 7.30 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.26 – 7.18 (m, 6H), 5.59 (t, *J* = 8.2 Hz, 2H), 5.41 – 5.33 (m, 4H), 4.49 (td, *J* = 8.1, 3.1 Hz, 2H), 2.32 – 2.10 (m, 20H), 1.46 – 1.19 (m, 32H), 0.96 – 0.81 (m, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 120.8 ppm.

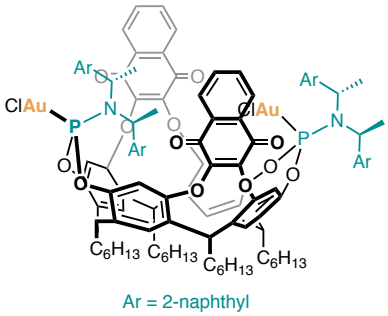
^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.7, 182.4, 154.0, 151.8, 151.5, 146.9 (d, *J* = 4.8 Hz), 146.4 (d, *J* = 4.4 Hz), 138.8 (d, *J* = 3.6 Hz), 137.2, 136.9, 136.8 (t, *J* = 2.7 Hz), 134.4 (d, *J* = 16.4 Hz), 133.5 (d, *J* = 15.5 Hz), 130.6 (d, *J* = 15.3 Hz), 128.9, 128.7, 128.2, 127.9, 127.6, 127.5 (d, *J* = 10.4 Hz), 126.7 (d, *J* = 12.9 Hz), 123.6 (d, *J* = 7.7 Hz), 118.9 (d, *J* = 4.1 Hz), 118.6 (d, *J* = 4.1 Hz), 55.0 (d, *J* = 9.1 Hz), 36.3, 33.8, 33.4, 32.4 (d, *J* = 4.4 Hz), 30.3, 29.8 (d, *J* = 12.9 Hz), 28.4, 28.1, 23.3 (d, *J* = 5.4 Hz), 21.6 (d, *J* = 2.3 Hz), 14.4 (d, *J* = 6.8 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{120}H_{116}Au_2Cl_2N_2NaO_{12}P_2]^+$, $[M+Na]^+$: 2325.6604; found: 2325.6596.

Elemental analysis Anal. Calc. for $C_{120}H_{116}Au_2Cl_2N_2O_{12}P_2$: C, 62.53; H, 5.07, N: 1.22; found: C, 62.28; H, 5.31; N, 1.29.

α_D^{589} = –137.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.72, 298 K).

Characterization of (*S*,*S*,*S*,*S*)-S:



M.p. = 261–263 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.03 – 7.91 (m, 2H), 7.90 – 7.59 (m, 22H), 7.56 – 7.42 (m, 8H), 7.37 (dd, *J* = 8.7, 1.8 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.22 (s, 1H), 7.19 – 6.98 (m, 5H), 6.92 (s, 1H), 6.81 (s, 1H), 6.37 (s, 1H), 5.51 – 5.42 (m, 1H), 5.37 (d, *J* = 7.4 Hz, 2H), 5.17 (dt, *J* = 11.1, 5.5 Hz, 1H), 4.97 – 4.86 (m, 2H), 4.81 (s, 1H), 4.44 (td, *J* = 8.1, 3.1 Hz, 1H), 2.34 – 2.05 (m, 20H), 1.47 – 1.19 (m, 32H), 0.95 – 0.80 (m, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 127.4, 118.0 ppm.

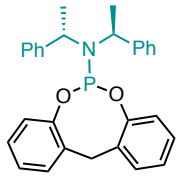
^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.9, 182.5, 181.7, 180.8, 154.3, 153.8, 153.2, 151.9, 150.7, 150.6, 150.5 (d, *J* = 6.0 Hz), 149.8, 148.7, 148.3, 138.9 (d, *J* = 3.4 Hz), 137.3, 136.4 (d, *J* = 3.6 Hz), 136.0 (d, *J* = 3.8 Hz), 134.9, 134.7, 134.4, 134.2, 133.9, 133.6 – 133.2 (m), 131.1, 130.9 (d, *J* = 5.6 Hz), 130.7, 130.4, 129.5, 128.9 – 128.8 (m), 128.2 (d, *J* = 3.4 Hz), 127.6, 127.5, 127.4, 127.3, 127.2, 126.8 (d, *J* = 3.2 Hz), 126.7, 126.6, 125.9, 125.5, 125.2, 123.2, 121.4, 119.3, 117.6 (d, *J* = 6.7 Hz), 116.4, 116.0, 54.9 (d, *J* = 8.4 Hz), 40.1 (d, *J* = 7.0 Hz), 36.6, 35.2, 34.1, 33.7, 32.4 (d, *J* = 3.2 Hz), 32.3 (d, *J* = 12.0 Hz), 31.6 (d, *J* = 10.4 Hz), 30.7, 29.9, 29.8 (d, *J* = 2.8 Hz), 28.2 (d, *J* = 5.7 Hz), 27.9 (d, *J* = 9.8 Hz), 23.6 – 22.8 (m), 22.0, 21.3 (d, *J* = 3.0 Hz), 14.4 (t, *J* = 4.3 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{120}H_{116}Au_2Cl_2N_2NaO_{12}P_2]^+$, $[M+Na]^+$: 2325.6604; found: 2325.6586.

Elemental analysis Anal. Calc. for $C_{120}H_{116}Au_2Cl_2N_2O_{12}P_2$: C, 62.53; H, 5.07, N: 1.22; found: C, 62.34; H, 5.55; N, 1.24.

α_D^{589} = –168.2 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.86, 298 K).

Phosphoramidite (*S*,*S*)-56



Triethylamine (522 µL, 3.74 mmol) was added to a mixture of 2,2'-methylenediphenol (250 mg, 1.25 mmol) in dry toluene (20.8 mL, 0.06 M) under argon at 23 °C. The mixture was stirred at 23 °C for 5 min. Then *N*,*N*-bis[(1*S*)-1-phenylethyl]phosphoramidous dichloride (*S*,*S*)-**47a** (611 mg, 1.87 mmol) in dry toluene (4.2 mL) was added to the mixture, which was stirred for 3 h. The mixture was filtered through a pad of Celite, washed with toluene and then the filtrate was concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/EtOAc 4:1) to afford (*S*,*S*)-**56** (360 mg, 0.79 mmol, 64% yield) as a white solid.

The spectral data were fully consistent with those previously reported.[35]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 7.5, 4.1, 1.7 Hz, 2H), 7.27 – 7.13 (m, 10H), 7.12 – 6.96 (m, 5H), 6.70 (dt, *J* = 7.9, 1.4 Hz, 1H), 4.92 (dq, *J* = 11.7, 7.1 Hz, 2H), 4.46 (dd, *J* = 12.8, 3.2 Hz, 1H), 3.56 (d, *J* = 12.8 Hz, 1H), 1.84 (d, *J* = 7.1 Hz, 6H) ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 144.9 ppm.

35 Wakabayashi, K.; Aikawa, K.; Kawauchi, S.; Mikami, K. *J. Am. Chem. Soc.* **2008**, *130*, 5012–5013.

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (d, *J* = 6.6 Hz), 151.9 (d, *J* = 6.9 Hz), 143.5 (d, *J* = 2.1 Hz), 135.6 (t, *J* = 3.5 Hz), 129.9 (dd, *J* = 17.2, 1.4 Hz), 128.2 (d, *J* = 2.4 Hz), 128.1 (dd, *J* = 3.5, 1.5 Hz), 127.9, 126.8, 124.5 (dd, *J* = 4.1, 1.6 Hz), 123.1 (dd, *J* = 17.9, 3.3 Hz), 53.2 (d, *J* = 12.4 Hz), 34.2, 22.2 (d, *J* = 9.5 Hz) ppm.

Synthesis of (*S*,*S*)-T

Complex (*S*,*S*)-**T** (441 mg, 0.64 mmol, 83% yield) was obtained as a white solid according to the general procedure **A** from phosphoramidite (*S*,*S*)-**56** (352 mg, 0.78 mmol) and (Me_2S)AuCl (240 mg, 0.81 mmol) after purification by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 4:1 as eluent.

M.p. = 206–208 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.42 – 7.36 (m, 6H), 7.36 – 7.27 (m, 6H), 7.26 – 7.12 (m, 4H), 7.00 (ddd, *J* = 8.0, 2.2, 1.3 Hz, 1H), 6.76 (dt, *J* = 7.6, 1.9 Hz, 1H), 5.20 (dq, *J* = 18.0, 7.1 Hz, 2H), 4.41 (dd, *J* = 13.0, 4.7 Hz, 1H), 3.58 (d, *J* = 13.0 Hz, 1H), 2.05 (d, *J* = 7.1 Hz, 6H) ppm.

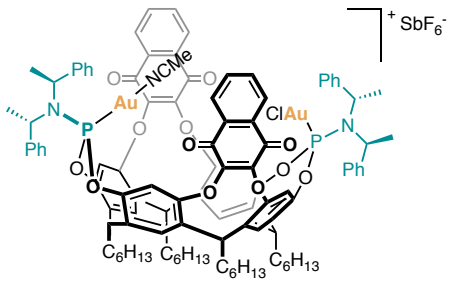
^{31}P NMR (202 MHz, CD_2Cl_2) δ 123.9 ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.8 (d, *J* = 3.1 Hz), 149.2 (d, *J* = 2.8 Hz), 141.7 (d, *J* = 3.8 Hz), 135.4 (d, *J* = 3.9 Hz), 135.2 (d, *J* = 3.8 Hz), 130.8 (dd, *J* = 8.3, 2.3 Hz), 129.3 (t, *J* = 3.2 Hz), 128.9, 128.8, 128.4, 127.4 – 127.1 (m), 123.7 – 123.6 (m), 54.6 (d, *J* = 8.3 Hz), 33.7 (d, *J* = 1.8 Hz), 21.3 (d, *J* = 2.8 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{29}H_{28}AuClNNaO_2P]^+$, $[M+Na]^+$: 708.1136; found: 708.1104.

α_D^{589} = –8.69 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.93, 297 K).

Synthesis of (*S*,*S*,*S*,*S*)-U



Acetonitrile (2.1 mL) was added to a solution of complex (*S*,*S*,*S*,*S*)-**L** (438 mg, 208 µmol) in CH_2Cl_2 (8.3 mL, 0.02 M). $AgSbF_6$ (75 mg, 218 µmol) was added to the mixture and it was stirred for 1 h. The crude was filtered through a pad of Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give (*S*,*S*,*S*,*S*)-**U** (480 mg, 205 µmol, 98% yield) as a yellow solid.

M.p. = 185–187 °C.

^{1}H NMR (500 MHz, CD_3CN) δ 7.90 (ddd, *J* = 7.6, 5.9, 1.5 Hz, 4H), 7.69 (dtd, *J* = 19.0, 7.4, 1.5 Hz, 4H), 7.59 (s, 4H), 7.54 (d, *J* = 2.0 Hz, 2H), 7.47 – 7.34 (m, 20H), 7.27 (d, *J* = 2.0 Hz, 2H), 5.57 (t, *J* = 8.2 Hz, 2H), 5.21 (dq, *J* = 19.7, 7.0 Hz, 4H), 4.68 (td, *J* = 8.1, 3.2 Hz, 2H), 2.62 – 2.43 (m, 4H), 2.32 (qd, *J* = 7.6, 3.4 Hz, 4H), 2.01 (d, *J* = 7.0 Hz, 12H), 1.58 – 1.21 (m, 32H), 0.97 – 0.87 (m, 12H ppm).

^{31}P NMR (203 MHz, CD_3CN) δ 118.4 ppm.

^{31}P NMR (202 MHz, CD_3CN, 233K) δ 122.5, 113.5 ppm.

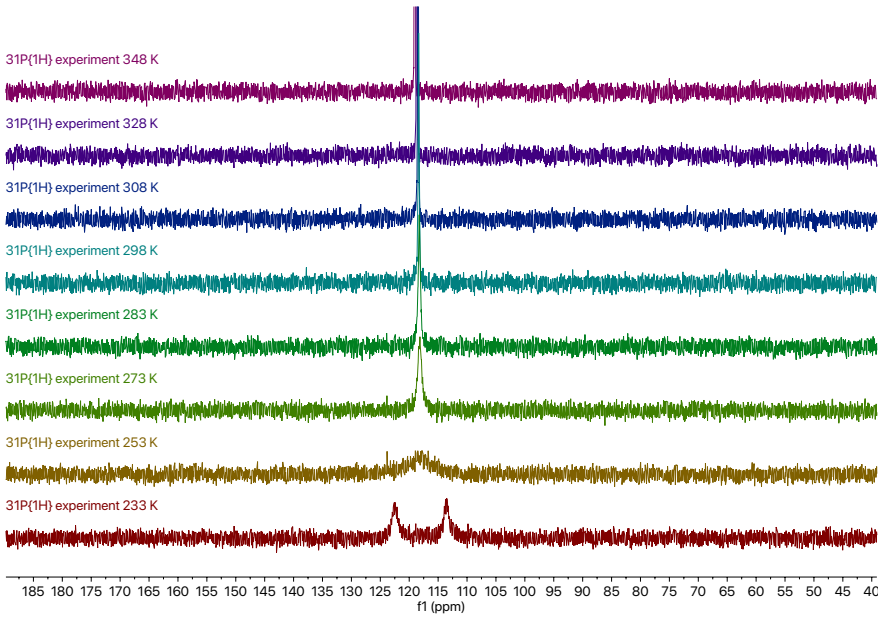
^{13}C NMR (126 MHz, CD_3CN) δ 183.2, 182.8, 154.4 (dd, *J* = 23.6, 2.4 Hz), 152.5, 152.2, 147.6 (d, *J* = 4.2 Hz), 147.4 (d, *J* = 3.1 Hz), 142.1 (d, *J* = 3.5 Hz), 138.4, 138.1, 137.7 (dd, *J* = 10.9, 3.2 Hz), 135.1 (d, *J* = 3.6 Hz), 131.7 (d, *J* = 5.4 Hz), 129.6, 129.0, 128.9, 127.4, 127.1, 125.7 (d, *J* = 17.1 Hz), 119.8 (d, *J* = 4.5 Hz), 119.4 (d, *J* = 4.6 Hz), 54.9 (d, *J* = 7.8 Hz), 37.2, 34.8, 32.9, 32.6, 32.5, 30.5, 30.1 (d, *J* = 4.8 Hz), 28.6, 28.4, 23.4 (d, *J* = 5.4 Hz), 21.7 (d, *J* = 3.2 Hz), 14.4 (d, *J* = 4.8 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{104}H_{108}Au_2ClN_2O_{12}P_2]^+$, $[M\text{-}ACN\text{-}SbF_6]^+$: 2067.6392; found: 2067.6504.

α_D^{589} = –32.3 deg.cm^2.g^{-1} (CH_3CN c 0.80, 298 K).

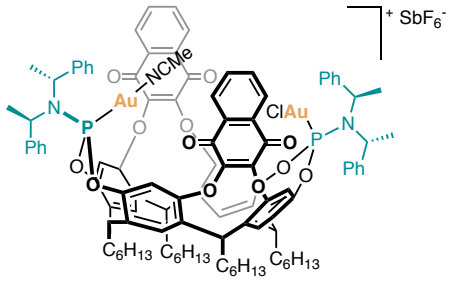
We could confirm the structure by X-ray diffraction. Also, we performed a ^{31}P NMR experiment at different temperatures and two phosphorous signals were observed at 233 K.

^{31}P NMR (202 MHz, CD_3CN, 233K) δ 122.4, 113.5 ppm.



^{31}P NMR of catalyst (*S*,*S*,*S*,*S*)-**U** in acetonitrile-d_3

Synthesis (*R*,*R*,*R*,*R*)-U

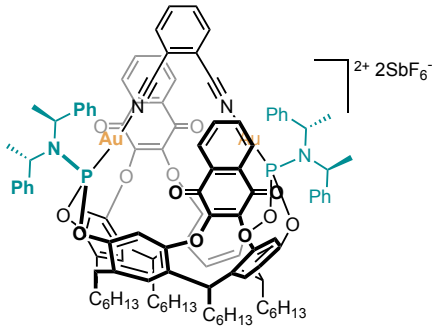


Acetonitrile (0.65 mL) was added to a solution of complex (*R*,*R*,*R*,*R*)-**L** (138 mg, 65 µmol) in CH_2Cl_2 (2.6 mL, 0.02 M). $AgSbF_6$ (24 mg, 69 µmol) was added to the mixture and it was stirred for 1 h under an argon. The crude was filtered through a pad of Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give (*R*,*R*,*R*,*R*)-**U** (149 mg, 64 µmol, 97% yield) as a yellow solid.

The spectral data of (*R*,*R*,*R*,*R*)-**U** were fully consistent with the previously synthesized ((*S*,*S*,*S*,*S*)-**U**).

α_D^{589} = +32.7 deg.cm^2.g^{-1} (CH_3CN c 0.64, 296 K).

Synthesis of (*S*,*S*,*S*,*S*)-V



Phthalonitrile (3.2 mg, 25 µmol) was added to a solution of complex (*S*,*S*,*S*,*S*)-**L** (50 mg, 24 µmol) in CH_2Cl_2 (1.2 mL, 0.02 M). $AgSbF_6$ (17 mg, 0.049 mmol) was added to the mixture and it was stirred for 1 h under an argon. The crude was filtered through a pad of Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give (*S*,*S*,*S*,*S*)-**V** (62 mg, 24 µmol, 99% yield) as a yellow solid.

M.p. = 194–196 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.21 (s, 2H), 8.14 (dd, *J* = 5.7, 3.3 Hz, 2H), 8.10 – 8.03 (m, 2H), 7.93 – 7.86 (m, 2H), 7.67 (d, *J* = 2.0 Hz, 2H), 7.62 – 7.53 (m, 8H), 7.52 – 7.40 (m, 16H), 7.38 (d, *J* = 2.0 Hz, 2H), 7.33 – 7.20 (m, 4H), 5.74 (t, *J* = 8.2 Hz, 2H), 5.19 (dq, *J* = 19.9, 7.0 Hz, 4H), 4.59 (td, *J* = 8.0, 3.4 Hz, 2H), 2.43 (hept, *J* = 6.8 Hz, 4H), 2.32 (tt, *J* = 12.2, 6.2 Hz, 4H), 2.12 (d, *J* = 7.0 Hz, 12H), 1.56 – 1.27 (m, 32H), 0.91 (td, *J* = 6.6, 5.0 Hz, 12H) ppm.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 110.6 ppm.

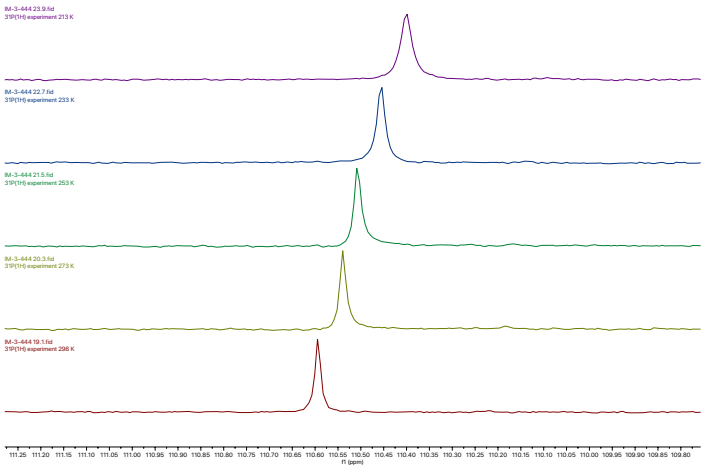
^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.1 (d, *J* = 14.2 Hz), 154.6 (d, *J* = 2.3 Hz), 154.4 (d, *J* = 2.4 Hz), 151.9 (d, *J* = 5.9 Hz), 147.0 (d, *J* = 5.2 Hz), 146.7 (d, *J* = 4.1 Hz), 141.1 (d, *J* = 4.2 Hz), 138.9 (d, *J* = 18.0 Hz), 137.4 (t, *J* = 3.8 Hz), 135.5, 134.6, 130.6, 130.3, 129.7, 129.2, 128.7, 127.9, 126.6, 124.5, 124.2, 119.2 (d, *J* = 5.0 Hz), 118.7 (d, *J* = 4.9 Hz), 55.3 (d, *J* = 7.8

Hz), 36.6, 34.17, 32.4 (d, J = 2.0 Hz), 30.7, 29.7, 29.5, 28.3, 28.2, 23.2 (d, J = 5.5 Hz), 22.1 (d, J = 2.2 Hz), 14.4 (d, J = 6.1 Hz) ppm.

HRMS (ESI+) calculated for *m/z* $[C_{112}H_{113}Au_2N_4O_{13}P_2]^+$, $[M+OH-2SbF_6]^+$: 2177.7108; found: 2177.7105.

α_D^{589} = +11.3 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.83, 298 K).

We performed a ^{31}P NMR experiment at different temperatures observing only one phosphorous signal.



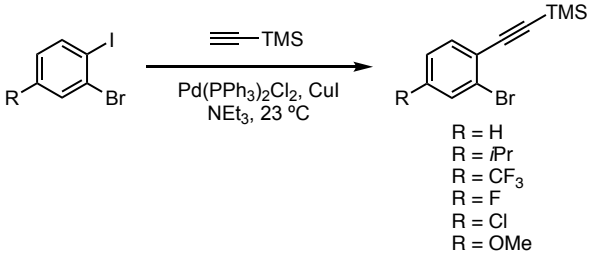
^{31}P NMR of catalyst (*S*,*S*,*S*,*S*)-**V** in CD_2Cl_2

Alkoxycyclization of 1,6-Enynes using Chiral Gold(I)-Cavitand Complexes.

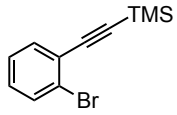
Synthesis of 1,6-enynes

General Procedure B:

To a solution of $Pd(PPh_3)_2Cl_2$ (2.5 mol %), copper(I) iodide (5 mol %) and the corresponding aryl iodide (1 equiv) in dry NEt_3 (0.25 M) was added ethynyltrimethylsilane (1.1 equiv) dropwise at 23 °C under argon. The reaction was stirred for 18 h at 23 °C. The reaction mixture was diluted with EtOAc, filtered through a pad of celite, washed with EtOAc and concentrated under reduced pressure. The crude was purified by flash column chromatography to afford the corresponding Sonogashira products.



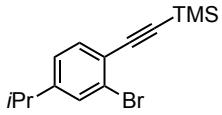
((2-Bromophenyl)ethynyl)trimethylsilane



((2-Bromophenyl)ethynyl)trimethylsilane was synthesized following general procedure **B** using 1-bromo-2-iodobenzene (10 g, 35.3 mmol) whereby the reaction was stirred for 20 h. Purification by column chromatography (SiO_2, cyclohexane) afforded the title compound (8.3 g, 32.8 mmol, 93% yield) as a colorless oil.

The spectral data were fully consistent with those previously reported.[36]

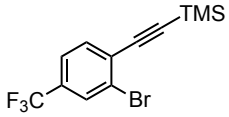
((2-Bromo-4-isopropylphenyl)ethynyl)trimethylsilane



((2-Bromo-4-isopropylphenyl)ethynyl)trimethylsilane was synthesized following general procedure **B** using 2-bromo-1-iodo-4-isopropylbenzene (1 g, 3.08 mmol) whereby the reaction was stirred for 18 h. Purification by column chromatography (SiO_2, cyclohexane) afforded the title compound (780 mg, 2.64 mmol, 86% yield) as a colorless oil.

The spectral data were fully consistent with those previously reported.[37]

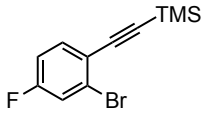
((2-Bromo-4-(trifluoromethyl)phenyl)ethynyl)trimethylsilane



((2-Bromo-4-(trifluoromethyl)phenyl)ethynyl)trimethylsilane was synthesized following general procedure **B** using 2-bromo-1-iodo-4-(trifluoromethyl)benzene (2 g, 5.70 mmol) whereby the reaction was stirred for 16 h. Purification by column chromatography (SiO_2, cyclohexane) afforded the title compound (1.8 g, 5.63 mmol, 99% yield) as a pale yellow oil.

The spectral data were fully consistent with those previously reported.[38]

((2-Bromo-4-fluorophenyl)ethynyl)trimethylsilane



((2-Bromo-4-fluorophenyl)ethynyl)trimethylsilane was synthesized following general procedure **B** using 2-bromo-4-fluoro-1-iodobenzene (2 g, 6.65 mmol) whereby the reaction was stirred for 18 h. Purification by column chromatography (SiO_2, cyclohexane) afforded the title compound (1.2 g, 4.42 mmol, 67% yield) as a colorless oil.

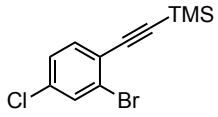
36 Higashino, T.; Ueda, A.; Yoshida, J.; Mori, H. *Chem. Commun.* **2017**, *53*, 3426–3429.

37 Quan, Y.; Qiu, Z.; Xie, Z. *J. Am. Chem. Soc.* **2014**, *136*, 7599–7602.

38 Lehnherr, D.; Ji, Y.; Neel, A. J.; Cohen, R. D.; Brunskill, A. P. J.; Yang, J.; Reibarkh, M. *J. Am. Chem. Soc.* **2018**, *140*, 13843–13853.

The spectral data were fully consistent with those previously reported.[37]

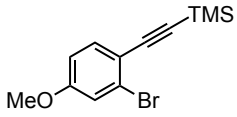
((2-Bromo-4-chlorophenyl)ethynyl)trimethylsilane



((2-Bromo-4-chlorophenyl)ethynyl)trimethylsilane was synthesized following general procedure **B** using 2-bromo-4-chloro-1-iodobenzene (2 g, 6.3 mmol) whereby the reaction was stirred for 18 h. Purification by column chromatography (SiO_2, cyclohexane) afforded the title compound (1.8 g, 6.26 mmol, 99% yield) as a pale yellow oil.

The spectral data were fully consistent with those previously reported.[38]

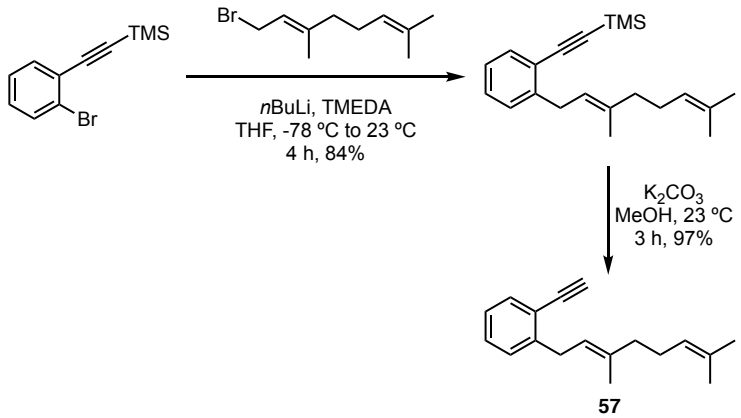
((2-Bromo-4-methoxyphenyl)ethynyl)trimethylsilane



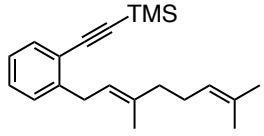
((2-Bromo-4-methoxyphenyl)ethynyl)trimethylsilane was synthesized following general procedure **B** using 2-bromo-1-iodo-4-methoxybenzene (920 mg, 2.94 mmol) whereby the reaction was stirred for 21 h. Purification by column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) afforded the title compound (724 mg, 2.56 mmol, 87% yield) as a pale yellow oil.

The spectral data were fully consistent with those previously reported.[37]

Synthesis of (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-2-ethynylbenzene (57)



(*E*)-((2-(3,7-Dimethylocta-2,6-dien-1-yl)phenyl)ethynyl)trimethylsilane



A THF solution (12.3 mL, 0.8 M) of ((2-bromophenyl)ethynyl)trimethylsilane (2.5 g, 9.87 mmol, 1 equiv) was treated with *n*BuLi (2.5 M, 4.74 mL, 11.9 mmol, 1.2 equiv) at -78 °C for 20 min before the addition of tetramethylethylenediamine (1.48 mL, 9.87 mmol, 1 equiv); the mixture was stirred for an additional 20 min. Geranyl bromide (3.22 g, 14.81 mmol, 1.5 equiv) was added at -78 °C and the resulting mixture was allowed to react at 23 °C for 12 h. After addition of water, the aqueous phase was extracted with Et_2O (x3) and the combined

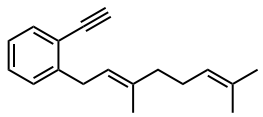
organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography on silica using cyclohexane as eluent to give (*E*)-((2-(3,7-dimethylocta-2,6-dien-1-yl)phenyl)ethynyl)trimethylsilane (2.57 g, 8.28 mmol, 84% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 7.17 (ddd, *J* = 7.7, 1.5, 0.7 Hz, 1H), 7.10 (td, *J* = 7.4, 1.5 Hz, 1H), 5.34 (ddd, *J* = 7.3, 6.7, 1.3 Hz, 1H), 5.09 (tdd, *J* = 5.5, 2.8, 1.4 Hz, 1H), 3.52 (d, *J* = 7.3 Hz, 2H), 2.15 – 2.00 (m, 4H), 1.71 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 0.24 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 136.8, 132.8, 131.8, 129.0, 128.6, 125.9, 124.7, 122.8, 122.6, 104.4, 98.5, 40.1, 33.1, 27.0, 26.1, 18.0, 16.6, 0.4 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{21}H_{31}Si]^+$, $[M+H]^+$: 311.2190; found: 311.2186.

(*E*)-1-(3,7-Dimethylocta-2,6-dien-1-yl)-2-ethynylbenzene (57)



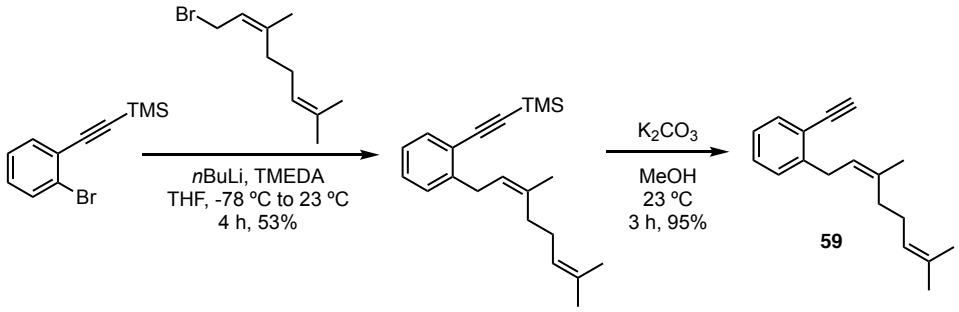
K_2CO_3 (2.05 g, 14.8 mmol, 2 equiv) was added to a mixture of (*E*)-((2-(3,7-dimethylocta-2,6-dien-1-yl)phenyl)ethynyl)trimethylsilane (2.3 g, 7.41 mmol, 1 equiv) in MeOH (37 mL, 0.2 M). The mixture was stirred at 23 °C for 3 h. After addition of water, the aqueous phase was extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, cyclohexane) to afford **57** (1.6 g, 6.8 mmol, 97% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.19 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.13 (td, *J* = 7.5, 1.4 Hz, 1H), 5.32 (tt, *J* = 7.3, 1.2 Hz, 1H), 5.09 (tdd, *J* = 5.5, 2.7, 1.4 Hz, 1H), 3.53 (d, *J* = 7.3 Hz, 2H), 3.25 (s, 1H), 2.14 – 2.01 (m, 4H), 1.70 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H) ppm.

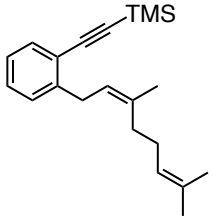
^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 137.0, 133.2, 131.8, 129.3, 128.7, 126.0, 124.7, 122.4, 121.9, 82.9, 81.3, 40.1, 33.0, 27.0, 26.1, 18.1, 16.6 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{18}H_{23}]^+$, $[M+H]^+$: 239.1795; found: 239.1794.

Synthesis of (*Z*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-2-ethynylbenzene (59)



(*Z*)-((2-(3,7-Dimethylocta-2,6-dien-1-yl)phenyl)ethynyl)trimethylsilane



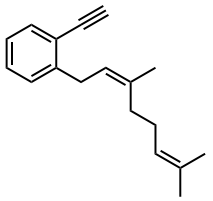
A THF solution (9.87 mL, 0.8 M) of ((2-bromophenyl)ethynyl)trimethylsilane (2.0 g, 7.90 mmol, 1 equiv) was treated with *n*BuLi (2.5 M, 3.79 mL, 9.45 mmol, 1.2 equiv) at -78 °C for 20 min before the addition of tetramethylethylenediamine (1.18 mL, 7.90 mmol, 1 equiv) was added at -78 °C and the resulting mixture was allowed to react at 23 °C for 12 h. After addition of water, the aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography on silica using cyclohexane as eluent to give (*Z*)-((2-(3,7-Dimethylocta-2,6-dien-1-yl)phenyl)ethynyl)trimethylsilane (1.31 g, 4.22 mmol, 53% yield) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.17 – 7.11 (m, 1H), 5.42 – 5.37 (m, 1H), 5.17 (tt, *J* = 6.8, 1.4 Hz, 1H), 3.55 (d, *J* = 7.3 Hz, 2H), 2.24 – 2.10 (m, 4H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 0.28 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 136.6, 132.5, 131.7, 128.6, 128.3, 125.5, 124.3, 123.0, 122.4, 104.0, 98.2, 32.5, 32.1, 26.6, 25.7, 23.5, 17.7, 0.0 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{21}H_{31}Si]^+$, $[M+H]^+$: 311.2190; found: 311.2188.

(*Z*)-1-(3,7-Dimethylocta-2,6-dien-1-yl)-2-ethynylbenzene (59)



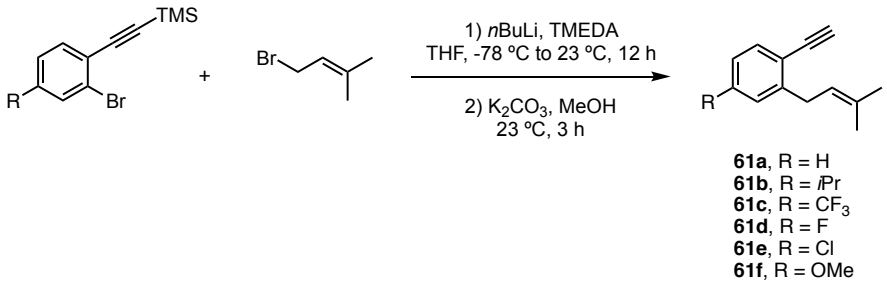
K_2CO_3 (1.10 g, 7.92 mmol, 2 equiv) was added to a mixture of (*Z*)-((2-(3,7-Dimethylocta-2,6-dien-1-yl)phenyl)ethynyl)trimethylsilane (1.23 g, 3.96 mmol, 1 equiv) in MeOH (19.8 mL, 0.2 M). The mixture was stirred at 23 °C for 3 h. After addition of water, the aqueous phase was extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, cyclohexane) to afford **59** (900 mg, 3.78 mmol, 95% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.21 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.14 (td, *J* = 7.5, 1.4 Hz, 1H), 5.34 (td, *J* = 7.3, 1.5 Hz, 1H), 5.14 (ddt, *J* = 6.9, 5.4, 1.5 Hz, 1H), 3.55 (d, *J* = 7.3 Hz, 2H), 3.26 (s, 1H), 2.20 – 2.15 (m, 2H), 2.14 – 2.07 (m, 2H), 1.75 (q, *J* = 1.3 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.62 (d, *J* = 1.4 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 136.8, 132.9, 131.9, 129.1, 128.6, 125.8, 124.4, 122.9, 121.6, 82.6, 81.1, 32.7, 32.2, 26.7, 25.9, 23.6, 17.8 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{18}H_{23}]^+$, $[M+H]^+$: 239.1795; found: 239.1794.

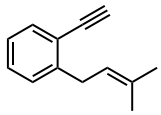
General Procedure C:



A THF solution (0.8 M) of ((2-bromophenyl)ethynyl)trimethylsilane (1 equiv) was treated with *n*BuLi (2.5 M, 1.2 equiv) at -78 °C for 20 min before the addition of tetramethylethylenediamine (1 equiv) and the mixture was stirred for an additional 20 min. 1-bromo-3-methylbut-2-ene (1.5 equiv) was added at -78 °C and the resulting mixture was allowed to react at 23 °C for 12 h. After addition of water, the aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was used directly without further purification.

K_2CO_3 (2 equiv) was added to a mixture of TMS-protected enyne (1 equiv) in MeOH (0.2 M). The mixture was stirred at 23 °C for 3 h. After addition of water, the aqueous phase was extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the desired enynes.

1-Ethynyl-2-(3-methylbut-2-en-1-yl)benzene (61a)



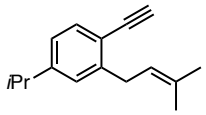
Title compound **61a** (2.92 g, 17.2 mmol, 87% yield over two steps) was obtained as a pale yellow oil from ((2-bromophenyl)ethynyl)trimethylsilane (5.0 g, 19.75 mmol) following general procedure **C**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 7.12 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.29 (tp, *J* = 7.3, 1.5 Hz, 1H), 3.50 (d, *J* = 7.3 Hz, 2H), 3.30 (s, 1H), 1.77 (s, 3H), 1.72 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 135.0, 134.1, 134.0, 128.7, 126.1, 121.4, 120.1, 81.9, 81.6, 32.8, 25.9, 18.1 ppm.

The spectral data were fully consistent with those previously reported.[39]

1-Ethynyl-4-isopropyl-2-(3-methylbut-2-en-1-yl)benzene (61b)



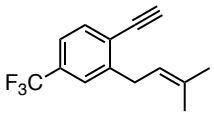
Title compound **61b** (413 mg, 1.95 mmol, 74% yield over two steps) was obtained as a colorless oil from ((2-bromo-4-isopropylphenyl)ethynyl)trimethylsilane (781 mg, 2.64 mmol) following general procedure **C**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.8 Hz, 1H), 7.06 – 6.96 (m, 2H), 5.33 (ddp, *J* = 7.2, 5.8, 1.4 Hz, 1H), 3.51 (d, *J* = 7.3 Hz, 2H), 3.21 (s, 1H), 2.87 (hept, *J* = 6.9 Hz, 1H), 1.98 – 1.63 (m, 6H), 1.24 (s, 3H), 1.22 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 144.5, 133.0, 132.8, 126.9, 123.9, 122.6, 118.9, 82.9, 80.2, 34.3, 33.2, 25.9, 23.9, 18.1 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{16}H_{21}]^+$, $[M+H]^+$: 213.1637; found: 213.1638.

1-Ethynyl-2-(3-methylbut-2-en-1-yl)-4-(trifluoromethyl)benzene (61c)



Title compound **61c** (450 mg, 1.89 mol, 34% yield over two steps) was obtained as a pale yellow oil from ((2-bromo-4-(trifluoromethyl)phenyl)ethynyl)trimethylsilane (1.77 g, 5.51 mmol) following general procedure **C**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 1.9 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.33 (ddt, *J* = 8.7, 5.9, 1.4 Hz, 1H), 3.60 (d, *J* = 7.3 Hz, 2H), 3.41 (s, 1H), 1.78 (dd, *J* = 15.0, 1.4 Hz, 6H) ppm.

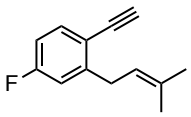
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 134.2, 133.1, 130.8, 130.5, 125.1 (q, *J* = 3.9 Hz), 122.5 (q, *J* = 3.9 Hz), 121.0, 83.2, 81.2, 32.8, 25.7, 18.0 ppm.

39 Gawade, S. A.; Bhunia, S.; Liu, R.-S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7835–7838.

HRMS (APCI+) calculated for *m/z* $[C_{14}H_{12}F_3]^+$, $[M+H]^+$: 237.0883; found: 237.0886.

1-Ethynyl-4-fluoro-2-(3-methylbut-2-en-1-yl)benzene (61d)



Title compound **61d** (536 mg, 2.84 mmol, 65% yield over two steps) was obtained as a colorless oil from ((2-bromo-4-fluorophenyl)ethynyl)trimethylsilane (1.19 g, 4.39 mmol) following general procedure **C**.

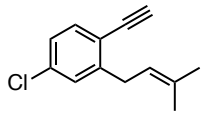
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.5, 5.8 Hz, 1H), 6.91 (dd, *J* = 9.9, 2.7 Hz, 1H), 6.84 (td, *J* = 8.4, 2.7 Hz, 1H), 5.30 (tp, *J* = 7.4, 1.5 Hz, 1H), 3.51 (d, *J* = 7.4 Hz, 2H), 3.24 (s, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.72 (d, *J* = 1.3 Hz, 3H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.4 ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 161.8, 147.4 (d, *J* = 7.6 Hz), 134.7 (d, *J* = 8.5 Hz), 134.1, 121.4, 117.6 (d, *J* = 3.1 Hz), 115.6 (d, *J* = 22.3 Hz), 113.1 (d, *J* = 22.1 Hz), 81.7, 80.8 (d, *J* = 1.7 Hz), 32.9 (d, *J* = 1.5 Hz), 25.9, 18.1 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{13}H_{14}F]^+$, $[M+H]^+$: 189.1074; found: 189.1074.

4-Chloro-1-ethynyl-2-(3-methylbut-2-en-1-yl)benzene (61e)



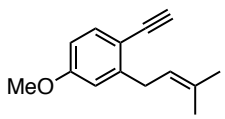
Title compound **61e** (694 mg, 3.39 mmol, 52% yield over two steps) was obtained as a light-yellow oil from ((2-bromo-4-chlorophenyl)ethynyl)trimethylsilane (1.89 g, 6.57 mmol) following general procedure **C**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 7.12 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.29 (tp, *J* = 7.3, 1.5 Hz, 1H), 3.50 (d, *J* = 7.3 Hz, 2H), 3.30 (s, 1H), 1.77 (s, 3H), 1.72 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 135.0, 134.1, 134.0, 128.7, 126.1, 121.4, 120.1, 81.9, 81.6, 32.8, 25.9, 18.1 ppm.

The spectral data were fully consistent with those previously reported.[39]

1-Ethynyl-4-methoxy-2-(3-methylbut-2-en-1-yl)benzene (61f)



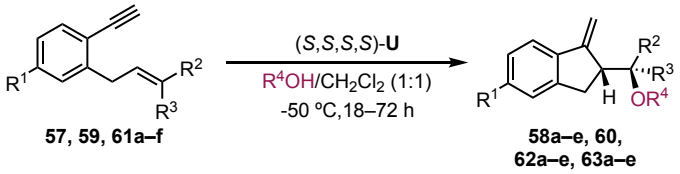
Title compound **61f** (512 mg, 2.56 mmol, 81% yield over two steps) was obtained as a pale yellow oil from ((2-bromo-4-methoxyphenyl)ethynyl)trimethylsilane (900 mg, 3.18 mmol) following general procedure **C**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 1H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.32 (dddt, *J* = 8.3, 7.2, 3.0, 1.4 Hz, 1H), 3.80 (s, 3H), 3.50 (d, *J* = 7.3 Hz, 2H), 3.19 (s, 1H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.73 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 146.4, 134.3, 133.3, 122.1, 114.4, 113.9, 111.2, 82.7, 79.6, 55.4, 33.1, 25.9, 18.1 ppm.

The spectral data were fully consistent with those previously reported.[39]

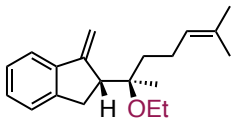
Scope of Alkoxycyclization Reaction



General Procedure D:

(*S*,*S*,*S*,*S*)-**U** (3 mol %) was added to a mixture of enyne (1 equiv) in CH_2Cl_2/R^4OH (1:1, 0.25 M) at -50 °C. The mixture was stirred at -50 °C for 18–72h. The reaction was quenched with 3 drops of NEt_3 and concentrated under reduced pressure. Purification by flash column chromatography on SiO_2 afforded the desired compounds.

(*R*)-2-((*R*)-2-Ethoxy-6-methylhept-5-en-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (58a)



Compound **58a** was synthesized following general procedure **D** using **57** (100.0 mg, 0.42 mmol) and EtOH whereas the reaction was stirred for 18 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **58a** (107 mg, 0.38 mol, 90% yield) as a colorless oil in 96:4 *er*.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47 – 7.41 (m, 1H), 7.25 – 7.22 (m, 1H), 7.20 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.18 – 7.13 (m, 1H), 5.59 (d, *J* = 1.8 Hz, 1H), 5.13 (dddt, *J* = 7.2, 5.7, 2.8, 1.4 Hz, 1H), 5.09 (d, *J* = 1.6 Hz, 1H), 3.39 (qd, *J* = 7.0, 1.1 Hz, 2H), 3.26 (dt, *J* = 6.5, 2.6 Hz, 1H), 3.09 (dd, *J* = 17.1, 2.8 Hz, 1H), 2.99 (dd, *J* = 17.1, 8.4 Hz, 1H), 2.15 – 1.92 (m, 2H), 1.76 – 1.55 (m, 8H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.79 (s, 3H) ppm.

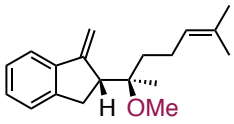
^{13}C NMR (101 MHz, CD_2Cl_2) δ 151.8, 146.4, 142.7, 131.7, 128.8, 126.8, 125.4, 125.3, 120.6, 106.3, 78.9, 56.4, 49.7, 35.2, 33.4, 26.0, 22.3, 19.9, 17.9, 16.2 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{18}H_{23}]^+$, $[M\text{-}OEt]^+$: 239.1794; found: 239.1794.

α_D^{589} = –71.7 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.96, 300 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 9.2; t_R (minor) 7.9.

(*R*)-2-((*R*)-2-Methoxy-6-methylhept-5-en-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (58b)



Compound **58b** was synthesized following general procedure **D** using **57** (50.0 mg, 210 µmol) and MeOH whereas the reaction was stirred for 18 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **58b** (49 mg, 182 µmol, 87% yield) as a colorless oil in 91:9 *er*.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47 – 7.42 (m, 1H), 7.28 – 7.22 (m, 1H), 7.20 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.19 – 7.12 (m, 1H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.13 (tdt, *J* = 5.8, 2.9, 1.4 Hz, 1H), 5.10 (d, *J* = 1.6 Hz, 2H), 3.27 (ddd, *J* = 7.7, 3.6, 1.8 Hz, 1H), 3.19 (s, 3H), 3.09 – 2.95 (m, 2H), 2.04 (tdt, *J* = 25.7, 14.1, 6.5 Hz, 2H), 1.77 – 1.56 (m, 8H), 0.81 (s, 3H) ppm.

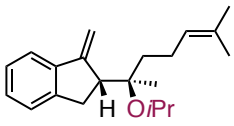
^{13}C NMR (101 MHz, CD_2Cl_2) δ 151.6, 146.3, 142.7, 131.7, 128.8, 126.8, 125.4, 125.2, 120.6, 106.4, 79.2, 49.1, 48.9, 34.6, 33.3, 26.0, 22.2, 19.5, 17.9 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{18}H_{23}]^+$, $[M\text{-}OMe]^+$: 239.1794; found: 239.1796.

α_D^{589} = –51.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.95, 300 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 13.2; t_R (minor) 11.4.

(*R*)-2-((*R*)-2-Isopropoxy-6-methylhept-5-en-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (58c)



Compound **58c** was synthesized following general procedure **D** using **57** (50.0 mg, 210 µmol) and *i*PrOH whereas the reaction was stirred for 64 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **58c** (55 mg, 183 µmol, 87% yield) as a colorless oil in 96:4 *er*.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.49 – 7.39 (m, 1H), 7.26 – 7.22 (m, 1H), 7.20 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.18 – 7.07 (m, 1H), 5.61 (d, *J* = 1.9 Hz, 1H), 5.17 (d, *J* = 1.6 Hz, 1H), 5.13 (ddp, *J* = 8.5, 5.6, 1.4 Hz, 1H), 3.87 (hept, *J* = 6.1 Hz, 1H), 3.23 (ddt, *J* = 8.4, 3.3, 1.9 Hz, 1H), 3.10 (dd, *J* = 17.2, 2.9 Hz, 1H), 3.01 (dd, *J* = 17.2, 8.5 Hz, 1H), 2.14 (qq, *J* = 14.3, 7.0, 6.2 Hz, 2H), 1.76 – 1.56 (m, 8H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.10 (d, *J* = 6.1 Hz, 3H), 0.84 (s, 3H) ppm.

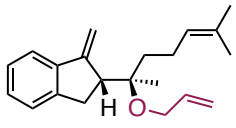
^{13}C NMR (101 MHz, CD_2Cl_2) δ 151.6, 146.3, 142.8, 131.6, 128.7, 126.8, 125.4, 125.2, 120.6, 106.5, 79.9, 63.7, 50.1, 36.2, 34.3, 26.0, 25.4, 25.3, 22.8, 20.3, 18.0 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{18}H_{23}]^+$, $[M\text{-}O\textit{i}Pr]^+$: 239.1794; found: 239.1792.

α_D^{589} = –32.9 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.06, 301 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 8.5; t_R (minor) 7.3.

(*R*)-2-((*R*)-2-(Allyloxy)-6-methylhept-5-en-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (58d)



Compound **58d** was synthesized following general procedure **D** using **57** (100 mg, 0.42 mmol) and AllylOH whereas the reaction was stirred for 21 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **58d** (107 mg, 0.36 mmol, 86% yield) as a colorless oil in 95:5 *er*.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.48 – 7.41 (m, 1H), 7.25 – 7.22 (m, 1H), 7.20 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.19 – 7.13 (m, 1H), 5.94 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.60 (d, *J* = 1.9 Hz, 1H), 5.31 – 5.30 (m, 1H), 5.26 (q, *J* = 1.8 Hz, 0H), 5.18 – 5.07 (m, 3H), 3.91 (dq, *J* = 5.2, 1.5 Hz, 2H), 3.28 (ddt, *J* = 6.6, 3.2, 1.6 Hz, 1H), 3.10 (dd, *J* = 17.1, 3.0 Hz, 1H), 3.01 (dd, *J* = 17.1, 8.3 Hz, 1H), 2.22 – 1.93 (m, 2H), 1.78 – 1.58 (m, 8H), 0.85 (s, 3H) ppm.

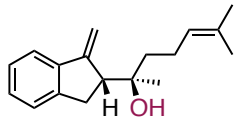
^{13}C NMR (101 MHz, CD_2Cl_2) δ 151.6, 146.3, 142.6, 136.5, 131.8, 128.8, 126.8, 125.4, 125.2, 120.6, 115.6, 106.5, 79.5, 62.6, 49.6, 35.3, 33.4, 25.9, 22.4, 19.9, 17.9 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{18}H_{23}]^+$, $[M\text{-}OAllyl]^+$: 239.1794; found: 239.1792.

α_D^{589} = –74.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.04, 300 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 10.8; t_R (minor) 9.3.

(*R*)-6-Methyl-2-((*R*)-1-methylene-2,3-dihydro-1*H*-inden-2-yl)hept-5-en-2-ol (58e)



Compound **58e** was synthesized following general procedure **D** using **57** (50.0 mg, 210 μmol) and H_2O *(solvent: acetone instead of CH_2Cl_2)* whereas the reaction was stirred at -20 °C for 72 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) to afford **58e** (23 mg, 88 μmol, 42% yield) as a colorless oil in 91:9 *er*.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.49 – 7.44 (m, 1H), 7.27 – 7.22 (m, 1H), 7.22 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.21 – 7.15 (m, 1H), 5.63 (d, *J* = 1.7 Hz, 1H), 5.17 (d, *J* = 1.4 Hz, 1H), 5.05 (dddt, *J* = 7.1, 5.7, 2.8, 1.4 Hz, 1H), 3.14 – 3.04 (m, 2H), 2.96 (d, *J* = 15.6 Hz, 1H), 2.16 – 1.98 (m, 2H), 1.65 (s, 3H), 1.59 (s, 3H), 1.40 (ddd, *J* = 9.4, 6.6, 2.1 Hz, 2H), 1.07 (s, 3H) ppm.

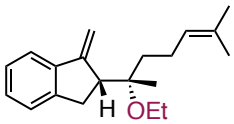
^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.6, 146.1, 142.3, 132.1, 128.9, 126.9, 125.5, 125.1, 120.7, 106.7, 75.1, 53.9, 38.2, 34.0, 25.9, 24.5, 22.8, 17.9 ppm.

HRMS (APCI+) calculated for *m/z* $[C_{18}H_{23}]^+$, $[M\text{-}OH]^+$: 239.1794; found: 239.1792.

α_D^{589} = –49.9 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.97, 299 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 98:2, 254 nm, t_R (major) 7.9; t_R (minor) 6.9.

(*R*)-2-((*S*)-2-Ethoxy-6-methylhept-5-en-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (60)



Compound **60** was synthesized following general procedure **D** using **59** (50.0 mg, 210 µmol) and EtOH whereas the reaction was stirred for 22 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **60** (49 mg, 173 µmol, 82% yield) as a colorless oil in 97:3 *er*.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.50 – 7.43 (m, 1H), 7.25 – 7.19 (m, 1H), 7.22 – 7.13 (m, 2H), 5.61 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.33 (dd, *J* = 2.2, 1.0 Hz, 1H), 5.08 (tdt, *J* = 7.2, 2.9, 1.5 Hz, 1H), 3.51 – 3.36 (m, 2H), 3.30 (ddt, *J* = 9.3, 4.8, 2.3 Hz, 1H), 3.03 (ddd, *J* = 16.9, 9.0, 0.9 Hz, 1H), 2.82 (ddd, *J* = 16.8, 4.9, 0.9 Hz, 1H), 2.03 (dd, *J* = 16.0, 7.7 Hz, 2H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.60 (s, 3H), 1.49 – 1.37 (m, 2H), 1.19 (t, *J* = 6.9 Hz, 3H), 1.07 (s, 3H) ppm.

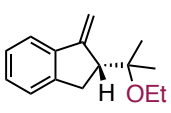
^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.2, 145.4, 142.8, 131.7, 128.7, 126.9, 125.5, 125.3, 120.6, 106.3, 79.3, 56.5, 49.3, 36.3, 34.0, 25.9, 22.2, 19.7, 17.9, 16.2 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{20}H_{28}NaO]^+$, $[M+Na]^+$: 307.2023; found: 307.2032.

α_D^{589} = –33.5 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.42, 301 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 9.4; t_R (minor) 10.5.

(*R*)-2-(2-Ethoxypropan-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (62a)



Compound **62a** was synthesized following general procedure **D** using **61a** (200 mg, 1.17 mmol) and EtOH whereas the reaction was stirred for 19 h.

The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **62a** (236 mg, 1.09 mmol, 93% yield) as a colorless oil in 96:4 *er*.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 1H), 7.25 – 7.21 (m, 1H), 7.20 (dd, *J* = 7.0, 1.6 Hz, 1H), 7.19 – 7.14 (m, 1H), 5.60 (dd, *J* = 2.2, 0.7 Hz, 1H), 5.20 (dd, *J* = 1.9, 0.7 Hz, 1H), 3.48 (qq, *J* = 8.7, 7.0 Hz, 2H), 3.23 (ddt, *J* = 8.1, 4.0, 2.0 Hz, 1H), 3.04 (dd, *J* = 17.0, 8.1 Hz, 1H), 2.98 (ddd, *J* = 17.0, 4.0, 0.9 Hz, 1H), 1.22 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.97 (s, 3H) ppm.

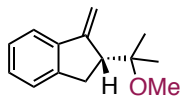
^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 145.4, 142.1, 128.4, 126.5, 125.0, 120.3, 106.2, 56.4, 50.3, 33.5, 23.1, 22.7, 16.2 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{15}H_{20}NaO]^+$, $[M+Na]^+$: 239.1408; found: 239.1406.

α_D^{589} = –32.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.69, 300 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 10.9; t_R (minor) 12.3.

(*R*)-2-(2-Methoxypropan-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (62b)



Compound **62b** was synthesized following general procedure **D** using **61a** (50 mg, 294 μmol) and MeOH whereas the reaction was stirred for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **62b** (56 mg, 276 μmol, 94% yield) as a colorless oil in 88:12 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 1H), 7.25 – 7.14 (m, 3H), 5.61 (dd, *J* = 2.1, 0.6 Hz, 1H), 5.19 (d, *J* = 1.8 Hz, 1H), 3.27 (s, 3H), 3.22 (ddt, *J* = 7.9, 3.9, 2.0 Hz, 1H), 3.05 (dd, *J* = 16.9, 8.3 Hz, 1H), 2.96 (dd, *J* = 16.9, 3.8 Hz, 1H), 1.22 (s, 3H), 0.96 (s, 3H) ppm.

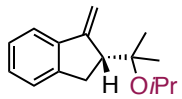
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 145.3, 142.0, 128.4, 126.5, 125.0, 120.4, 106.3, 49.9, 49.2, 33.4, 22.4, 22.1 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{14}H_{18}NaO]^+$, $[M+Na]^+$: 225.1245; found: 225.1250.

α_D^{589} = –70.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.71, 299 K).

HPLC Chiralpak AD (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 7.8; t_R (minor) 6.9.

(*R*)-2-(2-Isopropoxypropan-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (62c)



Compound **62c** was synthesized following general procedure **D** using **61a** (50 mg, 294 μmol) and *i*PrOH whereas the reaction was stirred for 47 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **62c** (57 mg, 249 μmol, 85% yield) as a colorless oil in 91:9 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 1H), 7.25 – 7.09 (m, 3H), 5.60 (dd, *J* = 2.0, 0.8 Hz, 1H), 5.25 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.91 (hept, *J* = 6.2 Hz, 1H), 3.18 – 3.11 (m, 1H), 3.03 (d, *J* = 5.5 Hz, 2H), 1.26 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 3H) ppm.

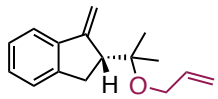
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 145.5, 142.2, 128.3, 126.4, 124.9, 120.3, 106.6, 77.9, 63.4, 52.2, 33.9, 25.3, 25.0, 23.2, 23.0 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{16}H_{22}NaO]^+$, $[M+Na]^+$: 253.1562; found: 253.1563.

α_D^{589} = –42.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.25, 299 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 8.3; t_R (minor) 12.6.

(*R*)-2-(2-(Allyloxy)propan-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (62d)



Compound **62d** was synthesized following general procedure **D** using **61a** (50 mg, 294 μmol) and AllylOH whereas the reaction was stirred for 19 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **62d** (64 mg, 279 μmol, 95% yield) as a colorless oil in 89:11 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 1H), 7.25 – 7.21 (m, 1H), 7.21 – 7.14 (m, 2H), 5.96 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.61 (d, *J* = 2.0 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.21 (d, *J* = 1.8 Hz, 1H), 5.14 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.06 – 3.91 (m, 2H), 3.24 (ddt, *J* = 8.0, 4.2, 2.0 Hz, 1H), 3.19 – 2.92 (m, 2H), 1.25 (s, 3H), 1.00 (s, 3H) ppm.

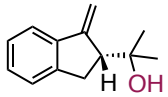
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 145.3, 142.1, 136.1, 128.4, 126.5, 125.0, 120.3, 115.9, 106.4, 77.8, 62.7, 50.6, 33.5, 22.9, 22.8 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{16}H_{20}NaO]^+$, $[M+Na]^+$: 251.1409; found: 251.1406.

α_D^{589} = –65.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.75, 299 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 12.4; t_R (minor) 13.4.

(*R*)-2-(1-Methylene-2,3-dihydro-1*H*-inden-2-yl)propan-2-ol (62e)



Compound **62e** was synthesized following general procedure **D** using **61a** (50 mg, 294 μmol) and H_2O *(solvent: acetone instead of CH_2Cl_2)* whereas the reaction was stirred at -20 °C for 63 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) to afford **62e** (43 mg, 228 μmol, 78% yield) as a pale-yellow oil in 80:20 *er*.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.50 – 7.45 (m, 1H), 7.28 – 7.23 (m, 1H), 7.23 – 7.15 (m, 2H), 5.64 (d, *J* = 1.9 Hz, 1H), 5.21 (d, *J* = 1.6 Hz, 1H), 3.12 (dd, *J* = 16.8, 8.6 Hz, 1H), 2.98 (dq, *J* = 8.5, 1.9 Hz, 1H), 2.86 (dd, *J* = 16.8, 2.3 Hz, 1H), 1.77 (s, 1H), 1.16 (s, 3H), 1.02 (s, 3H) ppm.

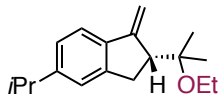
^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.8, 146.0, 142.1, 129.0, 127.1, 125.5, 120.8, 106.7, 73.2, 54.8, 34.6, 27.7, 25.9 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{13}H_{16}NaO]^+$, $[M+Na]^+$: 211.1084; found: 211.1093.

α_D^{589} = –45.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.52, 299 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 98:2, 254 nm, t_R (major) 9.3; t_R (minor) 8.5.

(*R*)-2-(2-Ethoxypropan-2-yl)-5-isopropyl-1-methylene-2,3-dihydro-1*H*-indene (63a)



Compound **63a** was synthesized following general procedure **D** using **61b** (50 mg, 236 μmol) and EtOH whereas the reaction was stirred for 21 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **63a** (57 mg, 219 μmol, 93% yield) as a colorless oil in 96:4 *er*.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.37 (d, *J* = 7.9 Hz, 1H), 7.10 (s, 1H), 7.04 (ddd, *J* = 7.9, 1.7, 0.8 Hz, 1H), 5.53 (dd, *J* = 2.1, 0.9 Hz, 1H), 5.15 (dd, *J* = 2.0, 0.9 Hz, 1H), 3.53 – 3.39 (m, 2H), 3.21 (ddt, *J* = 8.2, 4.0, 2.0 Hz, 1H), 2.99 (dd, *J* = 16.9, 8.4 Hz, 1H), 2.95 – 2.81 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.19 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.96 (s, 3H) ppm.

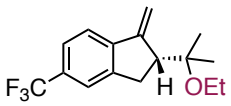
^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.6, 150.0, 146.0, 140.4, 125.4, 123.2, 120.5, 105.3, 77.5, 56.7, 51.0, 34.7, 33.9, 24.5, 24.4, 23.4, 22.8, 16.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{18}H_{26}NaO]^+$, $[M+Na]^+$: 281.1867; found: 281.1876.

α_D^{589} = –29.9 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.08, 299 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 6.5; t_R (minor) 6.1.

(*R*)-2-(2-Ethoxypropan-2-yl)-1-methylene-5-(trifluoromethyl)-2,3-dihydro-1*H*-indene (63b)



Compound **63b** was synthesized following general procedure **D** using **61c** (50 mg, 210 μmol) and EtOH whereas the reaction was stirred for 89 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **63b** (46 mg, 161 μmol, 77% yield) as a colorless oil in 94:6 *er*.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 5.73 (d, *J* = 2.2 Hz, 1H), 5.35 (d, *J* = 1.9 Hz, 1H), 3.52 – 3.39 (m, 2H), 3.26 (ddt, *J* = 8.2, 4.1, 2.1 Hz, 1H), 3.13 – 2.96 (m, 2H), 1.18 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.95 (s, 3H) ppm.

^{19}F NMR (471 MHz, CD_2Cl_2) δ -62.5 ppm.

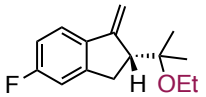
^{13}C NMR (126 MHz, CD_2Cl_2) δ 150.4, 146.5, 146.2, 130.4 (q, *J* = 31.6 Hz), 126.3, 124.1 (q, *J* = 3.6 Hz), 122.5 (q, *J* = 4.0 Hz), 121.0, 109.4, 77.4, 56.8, 51.2, 33.8, 23.2, 22.6, 16.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{16}H_{19}F_3NaO]^+$, $[M+Na]^+$: 307.1268; found: 307.1280.

α_D^{589} = –57.9 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.70, 298 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/iPrOH 1:0, 254 nm, t_R (major) 12.2; t_R (minor) 9.9.

(*R*)-2-(2-Ethoxypropan-2-yl)-5-fluoro-1-methylene-2,3-dihydro-1*H*-indene (63c)



Compound **63c** was synthesized following general procedure **D** using **61d** (50 mg, 266 μmol) and EtOH whereas the reaction was stirred for 48 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **63c** (55 mg, 233 μmol, 88% yield) as a colorless oil in 97:3 *er*.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.41 (dd, *J* = 8.4, 5.3 Hz, 1H), 6.99 – 6.80 (m, 2H), 5.52 (d, *J* = 2.2 Hz, 1H), 5.16 (d, *J* = 1.9 Hz, 1H), 3.44 (qd, *J* = 6.9, 5.5 Hz, 2H), 3.28 – 3.18 (m, 1H), 3.07 – 2.90 (m, 2H), 1.19 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.93 (s, 3H) ppm.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -114.9 ppm.

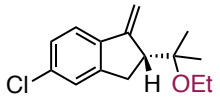
^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.0, 162.6, 150.4, 148.3 (d, *J* = 8.4 Hz), 138.8 (d, *J* = 2.5 Hz), 121.9 (d, *J* = 9.1 Hz), 114.2 (d, *J* = 23.2 Hz), 112.0 (d, *J* = 21.9 Hz), 106.0 (d, *J* = 2.4 Hz), 77.4, 56.8, 51.3, 33.8 (d, *J* = 2.2 Hz), 22.9 (d, *J* = 26.9 Hz), 16.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{15}H_{19}FNaO]^+$, $[M+Na]^+$: 257.1309; found: 257.1312.

α_D^{589} = –34.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.12, 299 K).

SFC Chiralpak IG (100 × 4.6mm, 3μm), flow 2 mL/min, isocratic CO_2/*i*PrOH 98:2, ABRP pressure 2000 psi, 210 nm, t_R (major) 1.8; t_R (minor) 1.7.

(*R*)-5-Chloro-2-(2-ethoxypropan-2-yl)-1-methylene-2,3-dihydro-1*H*-indene (63d)



Compound **63d** was synthesized following general procedure **D** using **61e** (50 mg, 244 μmol) and EtOH whereas the reaction was stirred for 21 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 4:1) to afford **63d** (53 mg, 211 μmol, 87% yield) as a colorless oil in 96:4 *er*.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.38 (d, *J* = 8.2 Hz, 1H), 7.21 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.18 – 7.11 (m, 1H), 5.58 (d, *J* = 1.9 Hz, 1H), 5.22 (d, *J* = 1.8 Hz, 1H), 3.44 (qd, *J* = 6.9, 5.5 Hz, 2H), 3.22 (ddt, *J* = 8.1, 4.2, 2.0 Hz, 1H), 3.12 – 2.81 (m, 2H), 1.18 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.93 (s, 3H) ppm.

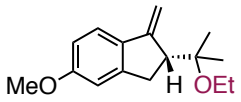
^{13}C NMR (101 MHz, CD_2Cl_2) δ 150.4, 147.8, 141.3, 134.1, 127.2, 125.5, 121.8, 107.2, 77.3, 56.8, 51.1, 33.6, 23.1, 22.7, 16.4 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{15}H_{19}ClNaO]^+$, $[M+Na]^+$: 273.1015; found: 273.1017.

α_D^{589} = –78.7 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.09, 298 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 7.4; t_R (minor) 8.1.

(*R*)-2-(2-Ethoxypropan-2-yl)-5-methoxy-1-methylene-2,3-dihydro-1*H*-indene (63e)



Compound **63e** was synthesized following general procedure **D** using **61f** (50 mg, 250 μmol) and EtOH whereas the reaction was stirred for 18 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) to afford **63e** (56 mg, 229 μmol, 92% yield) as a colorless oil in 97:3 *er*.

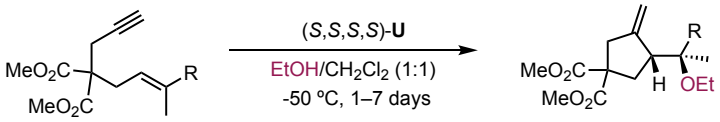
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.35 (d, *J* = 8.4 Hz, 1H), 6.77 – 6.71 (m, 2H), 5.43 (d, *J* = 1.5 Hz, 1H), 5.06 (d, *J* = 1.2 Hz, 1H), 3.78 (s, 3H), 3.45 (qq, *J* = 8.6, 6.9 Hz, 2H), 3.20 (ddt, *J* = 8.0, 4.0, 1.9 Hz, 1H), 3.05 – 2.88 (m, 2H), 1.20 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.93 (s, 3H) ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 160.9, 151.1, 147.7, 135.5, 121.6, 113.7, 109.7, 104.0, 77.5, 56.7, 55.9, 51.2, 33.9, 23.1, 22.9, 16.4 ppm.

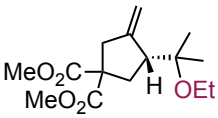
HRMS (ESI+) calculated for *m/z* $[C_{16}H_{22}NaO_2]^+$, $[M+Na]^+$: 269.1507; found: 269.1512.

α_D^{589} = –52.7 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.66, 299 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 1:0, 254 nm, t_R (major) 25.0; t_R (minor) 33.9.



Dimethyl (*R*)-3-(2-ethoxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (64)



Compound **64** was synthesized following general procedure **D** using **22** (50 mg, 210 µmol) and EtOH whereas the reaction was stirred for 18 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) to afford **64** (38 mg, 134 µmol, 64% yield) as a pale-yellow oil in 85:15 *er*.

The spectral data of **64** were previously reported in $CDCl_3$.[24]

^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.02 – 4.97 (m, 2H), 3.69 (d, *J* = 7.2 Hz, 6H), 3.42 – 3.35 (m, 2H), 2.87 (dtd, *J* = 15.3, 2.7, 2.0 Hz, 1H), 2.84 – 2.77 (m, 2H), 2.49 (ddd, *J* = 13.5, 8.6, 1.8 Hz, 1H), 2.01 (dd, *J* = 13.5, 9.4 Hz, 1H), 1.16 (s, 3H), 1.12 – 1.09 (m, 6H) ppm.

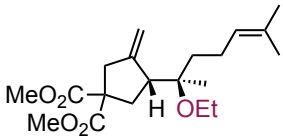
^{13}C NMR (126 MHz, CD_2Cl_2) δ 172.3, 172.2, 149.2, 110.2, 76.7, 58.9, 56.5, 52.8, 50.1, 43.7, 36.3, 23.4, 22.6, 16.0 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{15}H_{24}NaO_5]^+$, $[M+Na]^+$: 307.1512; found: 307.1516.

α_D^{589} = +15.5 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.04, 296 K).

SFC Trefoil Cel2 (3.0x150mm, 2.5µm) at 35 °C, flow 2 mL/min, isocratic CO_2/ACN 98:2, ABRP pressure 2000 psi, 210 nm, t_R (major) 3.1; t_R (minor) 2.5.

Dimethyl (*R*)-3-((*R*)-2-ethoxy-6-methylhept-5-en-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (66)



Compound **66** was synthesized following general procedure **D** using **65** (50 mg, 162 µmol) and EtOH whereas the reaction was stirred for 7 days. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) to afford **66** (31 mg, 90 µmol, 55%) as a colorless oil in 89:11 *er*.

The spectral data of **66** were fully consistent with those previously reported.[24]

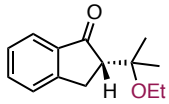
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (ddt, *J* = 7.1, 5.7, 1.4 Hz, 1H), 5.03 – 5.00 (m, 1H), 4.90 – 4.87 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.34 (qd, *J* = 7.0, 2.1 Hz, 2H), 2.92 (dddd, *J* = 12.3, 10.5, 5.7, 2.3 Hz, 2H), 2.84 – 2.77 (m, 1H), 2.54 (ddd, *J* = 13.8, 8.4, 1.7 Hz, 1H), 2.13 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.00 (m, 2H), 1.68 (s, 3H), 1.63 – 1.55 (m, 5H), 1.13 (t, *J* = 6.9 Hz, 3H), 1.07 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 172.0, 148.7, 131.4, 124.6, 110.5, 78.1, 58.6, 56.0, 52.7, 52.6, 48.2, 43.8, 35.7, 35.3, 25.7, 22.0, 20.0, 17.6, 15.8 ppm.

α_D^{589} = +11.6 deg.cm^2.g^{-1} ($CHCl_3$, c 0.89, 296 K).

UPC^2 Chiralpak IG (100 × 4.6mm, 3µm), flow 2 mL/min, isocratic CO_2/*i*PrOH 90:10, ABRP pressure 2000 psi, 210 nm, t_R (major) 1.8; t_R (minor) 1.6.

(*S*)-2-(2-Ethoxypropan-2-yl)-2,3-dihydro-1*H*-inden-1-one (67)



A solution of **62a** (50 mg, 231 µmol, 1 equiv) in CH_2Cl_2 (7.7 mL) and MeOH (7.7 mL) was cooled to -78 °C. The reaction was purged with oxygen, and then ozone was bubbled through until the clear solution turned blue (5 min). The excess ozone was purged with oxygen and then with argon. After addition of PPh_3 (182 mg, 693 µmol, 3 equiv) at -78 °C, the mixture was allowed to stir at 23 °C for 2 h. The crude was then concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) to give ketone **67** (36 mg, 164 mmol, 71% yield, 96:4 *er*) as a colorless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.69 – 7.63 (m, 1H), 7.58 (td, *J* = 7.4, 1.3 Hz, 1H), 7.49 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.39 – 7.31 (m, 1H), 3.47 – 3.32 (m, 2H), 3.25 (dd, *J* = 17.8, 3.9 Hz, 1H), 3.20 – 3.09 (m, 1H), 2.89 (dd, *J* = 7.8, 3.9 Hz, 1H), 1.47 (s, 3H), 1.11 (t, *J* = 7.0 Hz, 3H), 1.01 (s, 3H) ppm.

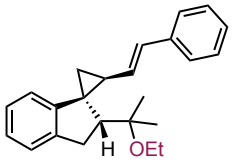
^{13}C NMR (101 MHz, CD_2Cl_2) δ 207.0, 154.6, 138.5, 135.1, 127.6, 126.9, 123.9, 76.4, 57.2, 55.4, 29.6, 25.1, 22.7, 16.3 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{14}H_{18}NaO_2]^+$, $[M+Na]^+$: 241.1189; found: 241.1199.

α_D^{589} = –15.4 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.10, 296 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 98:2, 280 nm, t_R (major) 5.5; t_R (minor) 5.1.

(1*S*,2*S*,2'*R*)-2'-(2-Ethoxypropan-2-yl)-2-((*E*)-styryl)-2',3'-dihydrospiro[cyclopropane-1,1'-indene] (68)



A modified reported procedure was followed.[40] A screw-cap culture tube equipped with a Teflon-coated magnetic stirring bar was charged with the corresponding 1,3,5-trimethyl-7-styryl-1,3,5-cycloheptatriene (30 mg, 127 μmol, 1 equiv) and alkene **62a** (41 mg, 190 μmol, 1.5 equiv). The vial was introduced in an argon filled glovebox, and both reagents were dissolved in anhydrous 1,2-DCE (0.84 mL, 0.15 M), before $[Rh(TFA)_2]_2$ (4 mg, 6.3 mmol, 5 mol %) was added. The vial was closed with the corresponding screw-cap and taken outside the glovebox, and then stirred at 23 °C for 19 h. The reaction mixture was concentrated *in vacuum* and the crude product was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 7:3) to give **68** (28 mg, 84 μmol, 66% yield, >20:1 *dr*, 96:4 *er*) as a colorless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.27 – 7.04 (m, 8H), 6.87 (d, *J* = 6.8 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.99 (dd, *J* = 15.7, 9.0 Hz, 1H), 3.38 (p, *J* = 6.9 Hz, 2H), 3.26 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.87 (d, *J* = 16.8 Hz, 1H), 2.50 (dd, *J* = 9.0, 1.9 Hz, 1H), 2.35 (dd, *J* = 8.8, 5.5 Hz, 1H), 1.95 (td, *J* = 8.8, 6.7 Hz, 1H), 1.36 (dd, *J* = 6.7, 5.4 Hz, 1H), 1.15 (dd, *J* = 7.4, 6.6 Hz, 3H), 1.06 (s, 3H), 0.97 (s, 3H) ppm.

^{13}C NMR (101 MHz, CD_2Cl_2) δ 145.2, 144.9, 138.3, 130.8, 130.3, 128.9, 127.1, 126.3, 126.1, 124.4, 121.2, 78.9, 56.4, 55.1, 38.8, 34.4, 33.3, 24.5, 22.8, 18.3, 16.5 ppm.

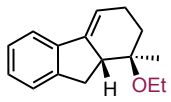
HRMS (ESI+) calculated for *m/z* $[C_{16}H_{22}NaO_2]^+$, $[M+Na]^+$: 355.2045; found: 355.2032.

α_D^{589} = –337.5 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.11, 298 K).

40 Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 2088–2092.

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 98:2, 254 nm, t_R (major) 3.7; t_R (minor) 4.5.

(1*R*,9a*R*)-1-Ethoxy-1-methyl-2,3,9,9a-tetrahydro-1*H*-fluorene (69)



Grubbs 2nd generation catalyst (3 mg, 3.33 µmol, 3 mol %) was added to (*R*)-2-((*R*)-2-ethoxy-6-methylhept-5-en-2-yl)-1-methylene-2,3-dihydro-1*H*-indene **58a** (32 mg, 111 µmol, 1 equiv) in toluene (694 µL, 0.16 M). The reaction mixture was stirred at 90 °C for 18 h. More Grubbs 2nd generation catalyst (2 mg, 2.22 µmol, 2 mol %) was added to the mixture and it was stirred for 23 h at 90 °C. After cooling, the reaction mixture was filtered through a Celite plug and the solvent was removed under vacuum. The crude product was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/CH_2Cl_2 7:3) to afford tetrahydro-1*H*-fluorene **69** (23 mg, 102 µmol, 92% yield, 96:4 *er*) as a colorless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 – 7.33 (m, 1H), 7.29 – 7.20 (m, 1H), 7.19 – 7.10 (m, 2H), 5.93 (q, *J* = 3.4 Hz, 1H), 3.53 (qq, *J* = 8.7, 7.0 Hz, 2H), 3.26 – 3.08 (m, 1H), 2.97 (dd, *J* = 15.9, 8.6 Hz, 1H), 2.85 (dd, *J* = 15.9, 9.0 Hz, 1H), 2.42 (dddt, *J* = 19.1, 6.7, 4.3, 2.0 Hz, 1H), 2.30 (dddt, *J* = 19.0, 10.8, 7.1, 3.8 Hz, 1H), 1.91 (ddd, *J* = 12.5, 6.3, 1.0 Hz, 1H), 1.75 (td, *J* = 12.0, 6.9 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.11 (s, 3H) ppm.

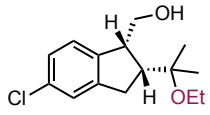
^{13}C NMR (101 MHz, CD_2Cl_2) δ 145.0, 143.5, 141.1, 128.1, 126.9, 125.8, 120.6, 115.9, 76.2, 56.9, 50.1, 34.4, 32.6, 26.1, 17.6, 16.6 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{16}H_{20}NaO]^+$, $[M+Na]^+$: 251.1404; found: 251.1406.

α_D^{589} = –10.6 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.52, 298 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 99:1, 280 nm, t_R (major) 4.3; t_R (minor) 4.6.

((1*R*,2*R*)-5-Chloro-2-(2-ethoxypropan-2-yl)-2,3-dihydro-1*H*-inden-1-yl)methanol (70)



To a solution of (*R*)-5-chloro-2-(2-ethoxypropan-2-yl)-1-methylene-2,3-dihydro-1*H*-indene **63d** (35 mg, 138 µmol, 1 equiv) in tetrahydrofuran (276 µL, 0.5 M) was added BH_3·THF complex 1 M (179 µL, 179 µmol, 1.3 equiv) at 0 °C. The mixture was allowed to stir for 3 h. To the reaction was added 2 N sodium hydroxide (138 µL, 276 µmol, 2 equiv) and 30% hydrogen peroxide (28 µL, 276 µmol, 2 equiv) at 0 °C. The mixture was stirred for 45 min at 23 °C. The reaction was neutralized with saturated NH_4Cl solution and extracted with EtOAc (x3), the organic layer was dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (SiO_2,

cyclohexane to cyclohexane/EtOAc 7:3) to give alcohol **70** (32 mg, 119 µmol, 86% yield, >20:1 *dr*, 96:4 *er*) as a colorless oil.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.24 – 7.17 (m, 1H), 7.13 (d, *J* = 1.2 Hz, 2H), 3.98 (ddd, *J* = 11.9, 5.5, 3.1 Hz, 1H), 3.80 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.61 – 3.48 (m, 3H), 3.23 (ddd, *J* = 7.7, 4.7, 3.1 Hz, 1H), 3.11 (ddd, *J* = 15.4, 11.9, 1.3 Hz, 1H), 2.78 (ddd, *J* = 15.5, 7.9, 0.8 Hz, 1H), 2.51 (dt, *J* = 12.0, 7.7 Hz, 1H), 1.42 (s, 3H), 1.31 (s, 3H), 1.19 (t, *J* = 7.0 Hz, 3H) ppm.

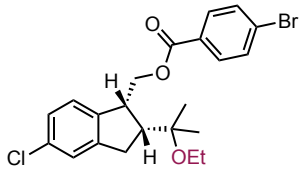
^{13}C NMR (126 MHz, CD_2Cl_2) δ 146.3, 144.9, 132.5, 126.9, 125.6, 124.9, 76.4, 65.4, 57.8, 55.1, 49.2, 33.5, 25.7, 23.9, 16.1 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{15}H_{21}ClNaO_2]^+$, $[M+Na]^+$: 291.1112; found: 291.1122.

α_D^{589} = –24.8 deg.cm^2.g^{-1} (CH_2Cl_2, c 1.34, 301 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 µm) at 25 °C, flow 0.5 mL/min, isocratic hexane/*i*PrOH 99:1, 220 nm, t_R (major) 24.3; t_R (minor) 25.6.

((1*R*,2*R*)-5-Chloro-2-(2-ethoxypropan-2-yl)-2,3-dihydro-1*H*-inden-1-yl)methyl 4-bromobenzoate (71)



A modified reported procedure was followed.[41] Alcohol **70** (20 mg, 74 µmol, 1 equiv), 4-bromobenzoic acid (75 mg, 0.37 mmol, 5 equiv), EDCI (86 mg, 0.45 mmol, 6 equiv), and *N*,*N*-dimethylpyridin-4-amine (55 mg, 0.45 mmol, 6 equiv) were dissolved in dichloromethane (1.1 mL, 0.07 molar, 1 equiv), then *N*-ethyl-*N*-isopropylpropan-2-amine (91 µL, 0.52 mmol, 7 equiv) was added. After being stirred for 4 h, the mixture was diluted with CH_2Cl_2, and then washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 9:1) to give *p*-bromobenzoate **71** (24 mg, 74 µmol, 71% yield, 96:4 *er*) as a white solid.

X-ray quality single crystals were obtained by slow evaporation of a solution of **71** in EtOAc.

M.p. = 116–118 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.89 – 7.83 (m, 2H), 7.64 – 7.58 (m, 2H), 7.24 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.06 (dd, *J* = 8.0, 1.3 Hz, 1H), 4.90 (dd, *J* = 11.4, 4.6 Hz, 1H), 4.16 (dd, *J* = 11.4, 10.1 Hz, 1H), 3.53 (ddd, *J* = 10.4, 7.4, 4.7 Hz, 1H), 3.50 – 3.35 (m, 2H), 3.24 (dd, *J* =

41 Xiao, G.; Yu, B. *Chem. Eur. J.* **2013**, *19*, 7708–7712.

15.4, 12.1 Hz, 1H), 2.81 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.53 (dt, *J* = 11.9, 7.3 Hz, 1H), 1.41 (s, 3H), 1.26 (s, 3H), 1.13 (t, *J* = 6.9 Hz, 3H) ppm.

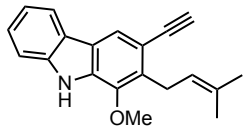
^{13}C NMR (126 MHz, CD_2Cl_2) δ 166.2, 146.2, 144.4, 132.9, 132.4, 131.5, 130.4, 128.2, 127.2, 126.4, 125.4, 74.8, 66.7, 57.2, 56.3, 45.5, 32.4, 25.3, 23.9, 16.5 ppm.

HRMS (ESI+) calculated for *m/z* $[C_{22}H_{24}BrClNaO_3]^+$, $[M+Na]^+$: 473.0499; found: 473.0490.

α_D^{589} = +122.1 deg.cm^2.g^{-1} (CH_2Cl_2, c 0.54, 298 K).

HPLC Chiralcel OD-H (250 mm × 4.6 mm, 5 μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/iPrOH 98:2, 254 nm, t_R (major) 4.5; t_R (minor) 4.9.

3-ethynyl-1-methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole (74)



To a mixture of 1-methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carbaldehyde (**73**)[28] (143 mg, 484 μmol, 1 equiv) and K_2CO_3 (201 mg, 1.45 mmol, 3 equiv) in MeOH (3.23 mL) and THF (0.8 mL) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (186 mg, 968 μmol, 2 equiv) at 23 °C. After stirring at this temperature for 18 h, more K_2CO_3 (100 mg, 726 μmol, 1.5 equiv) and dimethyl (1-diazo-2-oxopropyl)phosphonate (93 mg, 484 μmol, 1 equiv) were added and the stirring was continued at 23 °C for 11 h. After that, water was added and the aqueous phase was extracted with EtOAc (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (cyclohexane to cyclohexane/EtOAc 4:1) to afford **74** (108 mg, 373 μmol, 77% yield) as a pale-yellow solid.

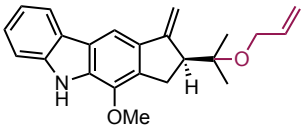
M.p. =124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 8.06 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.30 – 7.24 (m, 1H), 5.37 (tt, *J* = 5.3, 2.2 Hz, 1H), 3.97 (s, 3H), 3.76 (d, *J* = 6.2 Hz, 2H), 3.29 – 3.22 (m, 1H), 1.89 (s, 3H), 1.75 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 139.7, 134.0, 133.8, 131.6, 126.2, 123.5, 123.3, 123.1, 121.7, 120.4, 120.1, 114.1, 110.9, 83.7, 78.5, 61.0, 27.6, 25.8, 18.2 ppm.

HRMS (ESI-) calculated for *m/z* $[C_{20}H_{18}NO]^-$, $[M-H]^-$: 288.1396; found: 288.1394.

(*S*)-2-(2-(Allyloxy)propan-2-yl)-4-methoxy-1-methylene-1,2,3,5-tetrahydrocyclopenta[*b*]carbazole (75a)



(*R*,*R*,*R*,*R*)-**U** (18 mg, 7.65 µmol, 3 mol %) was added to a mixture of **74** (74 mg, 255 µmol, 1 equiv) in CH_2Cl_2 (510 µL) and AllylOH (510 µL) at -50 °C. The mixture was stirred at -50 °C for 2 h. The reaction was quenched with 3 drops of NEt_3 and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, cyclohexane to cyclohexane/EtOAc 4:1) to afford **75a** (75 mg, 215 µmol, 84% yield, 95:5 *er*) as a white solid.

M.p. =125–127 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.30 (br s, 1H), 8.06 (dt, 1H), 7.95 (s, 1H), 7.48 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.42 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.24 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 6.00 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.72 (dd, *J* = 2.0, 0.7 Hz, 1H), 5.35 – 5.29 (m, 1H), 5.20 (dd, *J* = 1.7, 0.7 Hz, 1H), 5.15 (ddt, *J* = 10.4, 2.1, 1.5 Hz, 1H), 4.08 (s, 3H), 4.03 (dt, *J* = 5.3, 1.6 Hz, 2H), 3.39 – 3.31 (m, 1H), 3.29 – 3.19 (m, 2H), 1.32 (s, 3H), 1.02 (s, 3H) ppm.

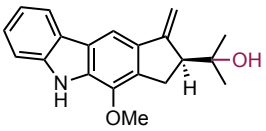
^{13}C NMR (101 MHz, CD_2Cl_2) δ 150.8, 140.8, 139.9, 136.5, 136.3, 133.1, 132.8, 125.7, 124.8, 123.7, 120.2, 119.4, 114.9, 110.8, 106.7, 104.2, 77.5, 62.4, 59.9, 51.7, 30.3, 22.6, 22.3 ppm.

HRMS (ESI-) calculated for *m/z* $[C_{23}H_{24}NO_2]^-$, $[M\text{-}H]^-$: 346.1814; found: 346.1813.

α_D^{589}= +55.7 deg.cm^2.g^{-1}(CH_2Cl_2, c 0.50, 297 K).

SFC Chiralpak OJ (100 × 3 mm, 3µm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/EtOH 98:2, BPR pressure 150.00 bar, 254 nm, t_R (major) 1.5; t_R (minor) 2.1.

(*S*)-2-(4-Methoxy-1-methylene-1,2,3,5-tetrahydrocyclopenta[*b*]carbazol-2-yl)propan-2-ol (76a)



1,3-dimethylbarbituric acid (47 mg, 304 µmol, 2 equiv) was added to a mixture of **75a** (53 mg, 152 µmol, 1 equiv) and $Pd(PPh_3)_4$ (18 mg, 15.2 µmol, 10 mol %) in MeOH (650 µL) and 1,4-dioxane (200 µL). The mixture was stirred for 6 h at 23 °C. The reaction was diluted with EtOAc and sat. aq. Na_2CO_3 solution. The aqueous layer was extracted with EtOAc (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane to cyclohexane/EtOAc 7:3) to give **76a** (33 mg, 107 µmol, 70% yield, 95:5 *er*) as a pale-yellow solid.

M.p. =141–143 °C.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.31 (br s, 1H), 8.04 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.94 (s, 1H), 7.45 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.39 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.21 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 5.72 (d, *J* = 1.7 Hz, 1H), 5.17 (d, *J* = 1.5 Hz, 1H), 4.04 (s, 3H), 3.30 (dd, *J* = 16.7, 8.5 Hz, 1H), 3.15 – 3.06 (m, 2H), 1.20 (s, 3H), 1.05 (s, 3H) ppm.

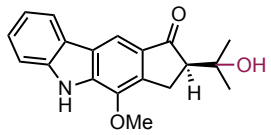
^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.5, 141.3, 140.3, 136.3, 133.6, 133.2, 126.2, 125.3, 124.1, 120.6, 119.8, 111.2, 107.2, 104.6, 72.9, 60.3, 55.7, 31.5, 27.2, 25.9 ppm.

HRMS (ESI-) calculated for *m/z* $[C_{20}H_{20}NO_2]^-$, $[M-H]^-$: 306.1501; found: 306.1500.

α_D^{589}= +41.0 deg.cm^2.g^{-1}(CH_2Cl_2, c 0.23, 296 K).

SFC Chiralpak IC (100 × 3mm, 3μm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/EtOH 85:15, BPR pressure 150.00 bar, 280 nm, t_R (major) 2.8; t_R (minor) 3.2.

(*R*)-2-(2-Hydroxypropan-2-yl)-4-methoxy-3,5-dihydrocyclopenta[*b*]carbazol-1(2*H*)-one (77a)



A solution 0.1 M of OsO_4 in *t*BuOH (98 μL, 9.76 μmol, 10 mol %) was added to a solution of **76a** (30 mg, 97.6 μmol, 1 equiv) and 2,6-lutidine (24 μL, 205 μmol, 2.1 equiv) in dioxane (424 μL) and water (217 μL). Then, sodium periodate (63 mg, 293 μmol, 3 equiv) was added to the reaction mixture, which was stirred for 5 h. After that, the mixture was diluted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude by column chromatography on silica gel (cyclohexane to cyclohexane/EtOAc 7:3) afforded (+)-mafaicheenamine C **77a** (20 mg, 65 μmol, 66% yield, 95:5 *er*) as a white solid.

M.p. =181–183 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 8.28 (s, 1H), 8.08 (d, *J* = 7.9, 1.1 Hz, 1H), 7.50 – 7.47 (m, 2H), 7.50 – 7.45 (m, 1H), 7.29 (ddd, *J* = 8.0, 5.0, 3.1 Hz, 1H), 4.67 (s, 1H), 4.14 (s, 3H), 3.54 (dd, *J* = 16.9, 8.3 Hz, 1H), 3.01 (dd, *J* = 16.9, 4.7 Hz, 1H), 2.96 (dd, *J* = 8.3, 4.6 Hz, 1H), 1.38 (s, 3H), 1.17 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.5, 140.9, 140.2, 138.9, 137.9, 130.9, 127.1, 126.1, 123.9, 121.0, 120.7, 112.2, 111.3, 72.9, 60.2, 57.1, 28.7, 27.6, 24.5 ppm.

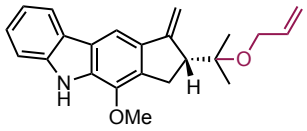
HRMS (ESI+) calculated for *m/z* $[C_{19}H_{19}NNaO_3]^+$, $[M+Na]^+$: 332.1253; found: 332.1257.

α_D^{589}= +71.8 deg.cm^2.g^{-1}(MeOH, c 0.02, 296 K).

Note: The specific rotation of (+)-mafaicheenamine C (**77a**) reported from the isolated plant *Clausena lansium* is α_D= +64.25 deg.cm^2.g^{-1} (MeOH, c 0.02, 299 K). The value obtained is similar with the one previously reported.[26]

SFC Chiralpak OD (100 × 3mm, 3µm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, BPR pressure 150.00 bar, 280 nm, t_R (major) 1.0; t_R (minor) 1.3.

(*R*)-2-(2-(Allyloxy)propan-2-yl)-4-methoxy-1-methylene-1,2,3,5-tetrahydrocyclopenta[*b*]carbazole (75b)



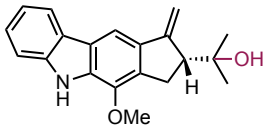
The title compound **75b** was obtained as a white solid (98 mg, 282 µmol, 82% yield, 96:4 *er*) from alkyne **74** (100 mg, 346 µmol) using (*S*,*S*,*S*,*S*)-**U** as catalyst, following the same procedure as for its enantiomer (**75a**).

The spectral data of **75b** were fully consistent with the previously synthesized (**75a**).

α_D^{589}= –57.4 deg.cm^2.g^{-1}(CH_2Cl_2, c 0.49, 296 K).

SFC Chiralpak OJ (100 × 3 mm, 3µm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/EtOH 98:2, BPR pressure 150.00 bar, 254 nm, t_R (major) 2.0; t_R (minor) 1.5.

(*R*)-2-(4-Methoxy-1-methylene-1,2,3,5-tetrahydrocyclopenta[*b*]carbazol-2-yl)propan-2-ol (76b)



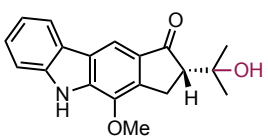
The title compound **76b** was obtained as a pale-yellow solid (55 mg, 179 µmol, 64% yield, 95:5 *er*) from **75b** (97 mg, 279 µmol), following the same procedure as for its enantiomer (**76a**).

The spectral data of **76b** were fully consistent with those previously synthesized (**76a**).

α_D^{589}= –41.5 deg.cm^2.g^{-1}(CH_2Cl_2, c 0.36, 294 K).

SFC Chiralpak IC (100 × 3mm, 3µm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/EtOH 85:15, BPR pressure 150.00 bar, 280 nm, t_R (major) 3.2; t_R (minor) 2.8.

(*S*)-2-(2-Hydroxypropan-2-yl)-4-methoxy-3,5-dihydrocyclopenta[*b*]carbazol-1(2*H*)-one (77b)



The title compound **77b** was obtained as a pale-yellow solid (36 mg, 121 µmol, 69% yield, 96:4 *er*) from **76b** (54 mg, 176 µmol), following the same procedure as for its enantiomer (**77a**).

The spectral data of **77b** were fully consistent with the previously synthesized (**77a**).

$\boldsymbol{\alpha_D^{589}}$= –70.9 deg.cm^2.g^{-1}(MeOH, c 0.02, 296 K).

SFC Chiralpak OD (100 × 3mm, 3µm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, BPR pressure 150.00 bar, 280 nm, t_R (major) 1.3; t_R (minor) 1.0.

Crystallographic Data

Complex A

CCDC 2050976

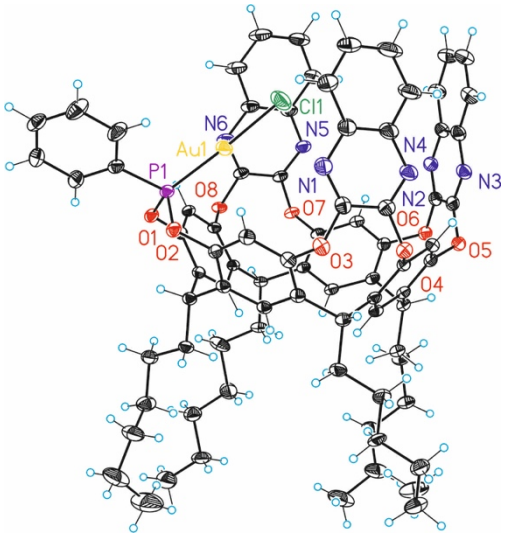


Table 1. Crystal data and structure refinement for complex **A**.

Identification code	mo_YJM3451-04t
Empirical formula	C89.75 H95.25 Au Cl N7.25 O9.75 P
Formula weight	1694.86
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 12.5814(6)Å α = 68.3269(9)°. b = 17.6071(9)Å β = 80.1065(11)°. c = 20.5191(10)Å γ = 69.7268(11)°.
Volume	3957.4(3) $Å^3$
Z	2
Density (calculated)	1.422 Mg/m^3
Absorption coefficient	1.978 mm^{-1}
F(000)	1747
Crystal size	0.200 x 0.200 x 0.200 mm^3
Theta range for data collection	1.816 to 31.215°.
Index ranges	?<=h<=?,?<=k<=?,?<=l<=?
Reflections collected	23949
Independent reflections	23949[R(int) = 0.0514]
Completeness to theta =31.215°	93.1%
Absorption correction	Multi-scan
Max. and min. transmission	0.74 and 0.40
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	23949/ 287/ 1130
Goodness-of-fit on F^2	1.111
Final R indices [I>2sigma(I)]	R1 = 0.0387, wR2 = 0.1049
R indices (all data)	R1 = 0.0485, wR2 = 0.1090
Largest diff. peak and hole	1.937 and -2.859 e. $Å^{-3}$

Complex C

CCDC 2050975

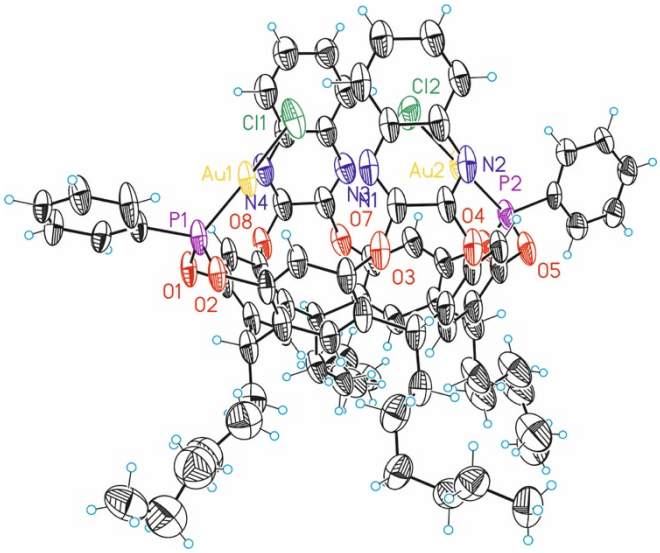


Table 2. Crystal data and structure refinement for complex **C**.

Identification code	im-3-97_sq
Empirical formula	C82.50 H89 Au2 Cl4.50 N4 O9 P2
Formula weight	1895.97
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C 2/c
Unit cell dimensions	a = 22.6414(3)Å a = 90°. b = 37.9515(8)Å b = 99.9660(10)°. c = 20.3429(3)Å g = 90°.
Volume	17216.4(5) $Å^3$
Z	8
Density (calculated)	1.463 Mg/m^3
Absorption coefficient	3.636 mm^{-1}
F(000)	7588
Crystal size	0.200 x 0.150 x 0.050 mm^3
Theta range for data collection	2.034 to 31.982°.
Index ranges	-33<=h<=32,-54<=k<=56,-30<=l<=28
Reflections collected	152128
Independent reflections	28194[R(int) = 0.0669]
Completeness to theta =31.982°	94.4%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.60
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	28194/ 614/ 1198
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0588, wR2 = 0.1565
R indices (all data)	R1 = 0.1193, wR2 = 0.1875
Largest diff. peak and hole	3.572 and -1.832 e. $Å^{-3}$

Complex D

CCDC 2050978

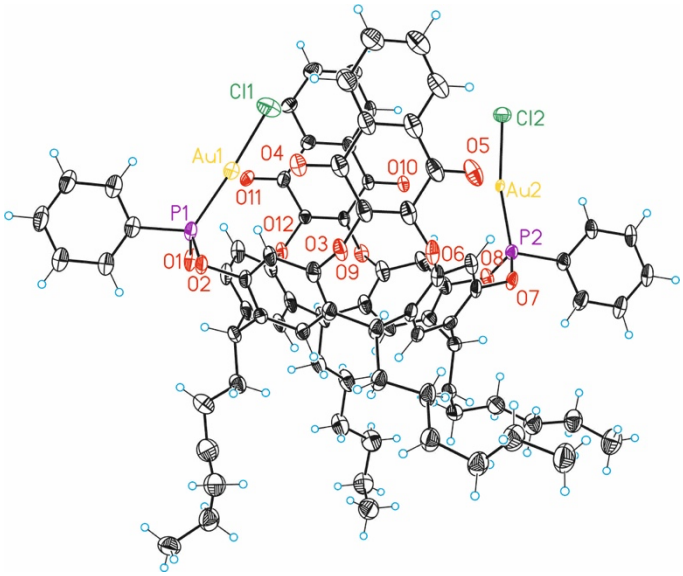


Table 3. Crystal data and structure refinement for complex **D**.

Identification code	mo_IM310c_0m
Empirical formula	C88.30 H91.60 Au2 Cl2.80 O12 P2
Formula weight	1899.94
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 11.1862(7)Å a = 95.4806(17)°. b = 11.9558(7)Å b = 96.7821(17)°. c = 30.8271(18)Å g = 104.9396(15)°.
Volume	3921.3(4) $Å^3$
Z	2
Density (calculated)	1.609 Mg/m^3
Absorption coefficient	3.936 mm^{-1}
F(000)	1906
Crystal size	0.200 x 0.050 x 0.010 mm^3
Theta range for data collection	1.905 to 28.841°.
Index ranges	-14<=h<=15,-16<=k<=16,-39<=l<=41
Reflections collected	53505
Independent reflections	19557[R(int) = 0.0509]
Completeness to theta =28.841°	95.3%
Absorption correction	Multi-scan
Max. and min. transmission	0.74 and 0.63
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	19557/ 1983/ 1450
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0597, wR2 = 0.1450
R indices (all data)	R1 = 0.0951, wR2 = 0.1584
Largest diff. peak and hole	2.104 and -2.265 e. $Å^{-3}$

Complex F

CCDC 2050974

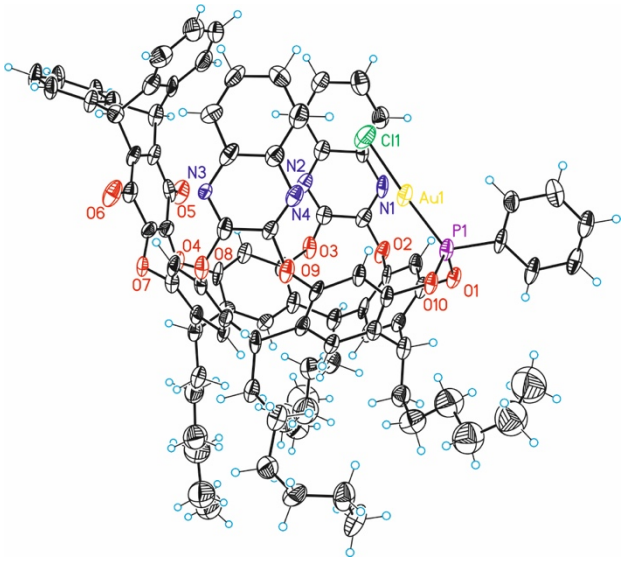


Table 4. Crystal data and structure refinement for complex **F**.

Identification code	GO172b
Empirical formula	C96 H91 Au Cl3 N4 O10 P
Formula weight	1795.01
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 21/c
Unit cell dimensions	a = 24.4710(13)Å a = 90°. b = 15.8190(4)Å b = 103.843(5)°. c = 22.5114(9)Å g = 90°.
Volume	8461.2(6) $Å^3$
Z	4
Density (calculated)	1.409 Mg/m^3
Absorption coefficient	1.915 mm^{-1}
F(000)	3680
Crystal size	0.200 x 0.150 x 0.050 mm^3
Theta range for data collection	2.144 to 23.118°.
Index ranges	-20<=h<=26,-15<=k<=17,-24<=l<=19
Reflections collected	33624
Independent reflections	11802[R(int) = 0.0875]
Completeness to theta =23.118°	98.7%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.43
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11802/ 384/ 1132
Goodness-of-fit on F^2	1.089
Final R indices [I>2sigma(I)]	R1 = 0.0827, wR2 = 0.2004
R indices (all data)	R1 = 0.1209, wR2 = 0.2160
Largest diff. peak and hole	3.475 and -1.272 e. $Å^{-3}$

Complex G

CCDC 2050970

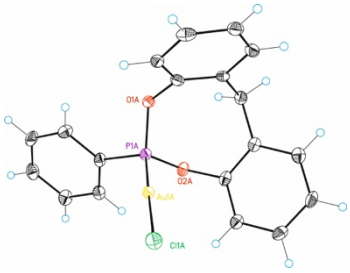


Table 5. Crystal data and structure refinement for complex **G**.

Identification code	IM-3-567	
Empirical formula	C19 H15 Au Cl O2 P	
Formula weight	538.70	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 11.66543(17)Å	a = 90°.
	b = 10.40136(16)Å	b = 93.2750(15)°.
	c = 29.3083(5)Å	g = 90°.
Volume	3550.36(10) $Å^3$	
Z	8	
Density (calculated)	2.016 Mg/m^3	
Absorption coefficient	8.536 mm^{-1}	
F(000)	2048	
Crystal size	0.500 x 0.500 x 0.400 mm^3	
Theta range for data collection	2.297 to 26.372°.	
Index ranges	-14<=h<=12,-13<=k<=13,-36<=l<=36	
Reflections collected	40646	
Independent reflections	7245[R(int) = 0.0267]	
Completeness to theta =26.372°	99.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.04	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7245/ 0/ 434	
Goodness-of-fit on F^2	1.144	
Final R indices [I>2sigma(I)]	R1 = 0.0213, wR2 = 0.0693	
R indices (all data)	R1 = 0.0218, wR2 = 0.0697	
Largest diff. peak and hole	1.396 and -1.181 $e.Å^{-3}$	

Complex H

CCDC 2050983

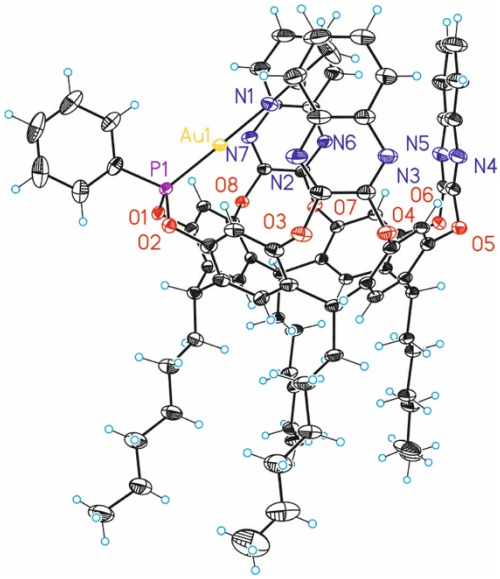


Table 6. Crystal data and structure refinement for complex **H**.

Identification code	mo_YJM3473_0m
Empirical formula	C92 H96 Au F6 N11 O8 P Sb
Formula weight	1947.48
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 21/n
Unit cell dimensions	a = 17.3794(5)Å a = 90°. b = 20.0272(6)Å b = 92.7154(8)°. c = 25.7757(8)Å g = 90°.
Volume	8961.4(5) $Å^3$
Z	4
Density (calculated)	1.443 Mg/m^3
Absorption coefficient	2.028 mm^{-1}
F(000)	3952
Crystal size	0.300 x 0.300 x 0.300 mm^3
Theta range for data collection	1.552 to 30.567°.
Index ranges	-22<=h<=24,-28<=k<=21,-36<=l<=32
Reflections collected	89827
Independent reflections	26498[R(int) = 0.0346]
Completeness to theta =30.567°	96.3%
Absorption correction	Multi-scan
Max. and min. transmission	0.74 and 0.52
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	26498/ 538/ 1375
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0410, wR2 = 0.0965
R indices (all data)	R1 = 0.0619, wR2 = 0.1072
Largest diff. peak and hole	1.330 and -1.612 $e.Å^{-3}$

Complex (*S*,*S*)-I

CCDC 2050980

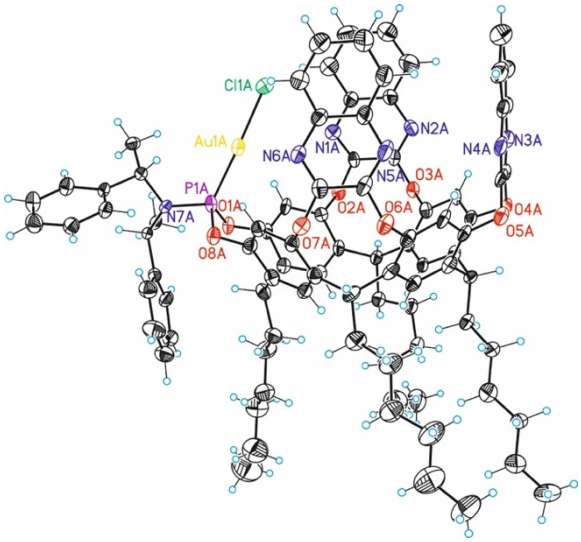


Table 7. Crystal data and structure refinement for (*S*,*S*)-**I**.

Identification code	IM-3-182F1
Empirical formula	C100.53 H112.80 Au Cl5.15 N7 O8 P
Formula weight	1957.57
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	P 1
Unit cell dimensions	a = 15.6388(6)Å a = 117.6544(9)°. b = 19.5102(8)Å b = 100.5131(11)°. c = 19.5195(8)Å g = 102.1780(11)°.
Volume	4878.8(3) $Å^3$
Z	2
Density (calculated)	1.333 Mg/m^3
Absorption coefficient	1.723 mm^{-1}
F(000)	2021
Crystal size	0.200 x 0.200 x 0.100 mm^3
Theta range for data collection	1.253 to 30.658°.
Index ranges	-22<=h<=13,-27<=k<=27,-27<=l<=25
Reflections collected	62891
Independent reflections	38306[R(int) = 0.0373]
Completeness to theta =30.658°	97.5%
Absorption correction	Multi-scan
Max. and min. transmission	0.74 and 0.57
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	38306/ 2621/ 2781
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0536, wR2 = 0.1407
R indices (all data)	R1 = 0.0666, wR2 = 0.1508
Flack parameter	x =-0.004(3)
Largest diff. peak and hole	3.425 and -2.564 e. $Å^{-3}$

Complex (*S*,*S*)-J

CCDC 2050979

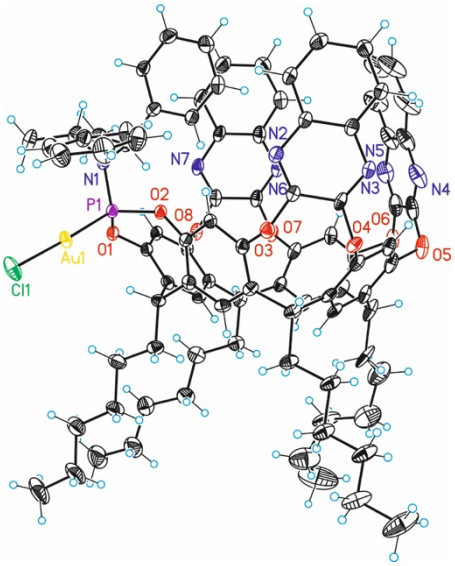


Table 8. Crystal data and structure refinement for (*S*,*S*)-**J**.

Identification code	mo_IM3182f1_0m
Empirical formula	C93.27 H96.54 Au Cl3.54 N7 O8 P
Formula weight	1796.98
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 21
Unit cell dimensions	a = 13.0909(4)Å a = 90°. b = 18.8783(5)Å b = 107.3983(9)°. c = 17.8735(6)Å g = 90°.
Volume	4215.1(2) $Å^3$
Z	2
Density (calculated)	1.416 Mg/m^3
Absorption coefficient	1.938 mm^{-1}
F(000)	1847
Crystal size	0.300 x 0.200 x 0.100 mm^3
Theta range for data collection	1.609 to 30.596°.
Index ranges	-18<=h<=18,-17<=k<=26,-21<=l<=25
Reflections collected	63566
Independent reflections	22881[R(int) = 0.0351]
Completeness to theta =30.596°	99.7%
Absorption correction	Multi-scan
Max. and min. transmission	0.74 and 0.64
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	22881/ 299/ 1197
Goodness-of-fit on F^2	1.010
Final R indices [I>2sigma(I)]	R1 = 0.0389, wR2 = 0.0857
R indices (all data)	R1 = 0.0476, wR2 = 0.0895
Flack parameter	x =-0.0173(17)
Largest diff. peak and hole	2.521 and -1.149 $e.Å^{-3}$

Complex (*S*,*S*,*S*,*S*)-L

CCDC 2050982

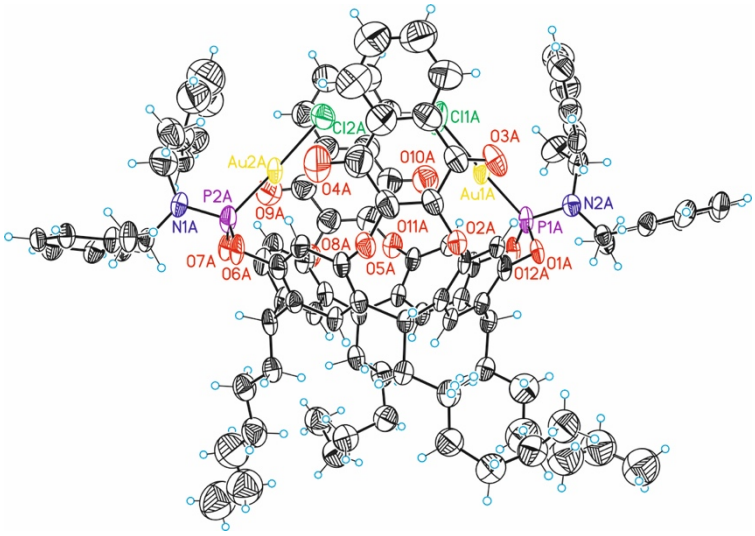


Table 9. Crystal data and structure refinement for (*S*,*S*,*S*,*S*)-**L**.

Identification code	IM-3-209-f3_twin1_hklf5
Empirical formula	C114.75 H124.12 Au2 Cl2 N7.38 O12 P2
Formula weight	2325.35
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 12.3340(2) Å a = 90°. b = 29.0403(3) Å b = 90.949(2)°. c = 31.0988(6) Å g = 90°.
Volume	11137.5(3) $Å^3$
Z	4
Density (calculated)	1.387 Mg/m^3
Absorption coefficient	2.769 mm^{-1}
F(000)	4729
Crystal size	0.300 x 0.250 x 0.100 mm^3
Theta range for data collection	2.086 to 29.539°.
Index ranges	-17<=h<=16, -40<=k<=40, -42<=l<=42
Reflections collected	77516
Independent reflections	77516 [R(int) = ?]
Completeness to theta = 25.242°	99.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	77516 / 4500 / 3240
Goodness-of-fit on F^2	1.081
Final R indices [I>2sigma(I)]	R1 = 0.1016, wR2 = 0.2904
R indices (all data)	R1 = 0.1713, wR2 = 0.3175
Absolute structure parameter	0.021(5)
Extinction coefficient	n/a
Largest diff. peak and hole	2.142 and -2.775 e. $Å^{-3}$

Complex (*S*,*S*,*S*,*S*)-P

CCDC 2050981

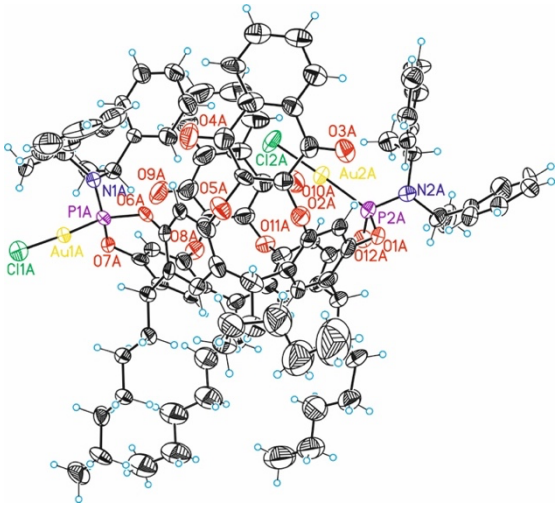


Table 10. Crystal data and structure refinement for (*S*,*S*,*S*,*S*)-**P**.

Identification code	mo_im3174p1-b_0m_sq
Empirical formula	C105 H110 Au2 Cl3 N2 O12 P2
Formula weight	2154.17
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 21
Unit cell dimensions	a = 22.7610(7)Å a = 90°. b = 17.4211(6)Å b = 103.6930(10)°. c = 30.1959(11)Å g = 90°.
Volume	11633.0(7) $Å^3$
Z	4
Density (calculated)	1.230 Mg/m^3
Absorption coefficient	2.667 mm^{-1}
F(000)	4356
Crystal size	0.200 x 0.200 x 0.200 mm^3
Theta range for data collection	1.359 to 27.515°.
Index ranges	-29<=h<=21,-22<=k<=22,-37<=l<=31
Reflections collected	84140
Independent reflections	46617[R(int) = 0.0319]
Completeness to theta =27.515°	94.9%
Absorption correction	Multi-scan
Max. and min. transmission	0.74 and 0.61
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	46617/ 752/ 2480
Goodness-of-fit on F^2	0.980
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.1039
R indices (all data)	R1 = 0.0785, wR2 = 0.1146
Flack parameter	x =-0.005(2)
Largest diff. peak and hole	1.768 and -0.797 $e.Å^{-3}$

Complex (*S*,*S*,*S*,*S*)-Q

CCDC 2050984

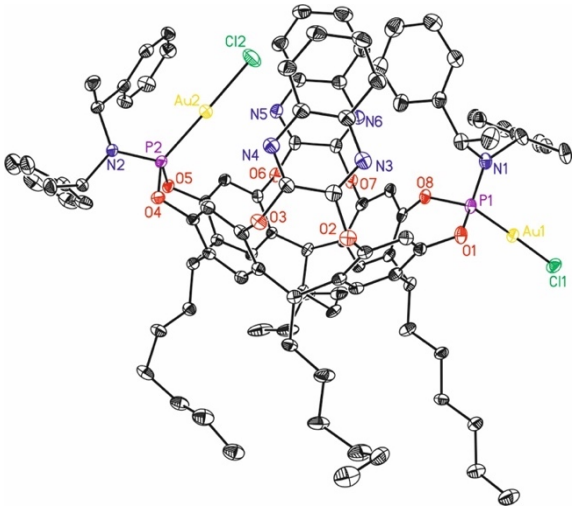


Table 11. Crystal data and structure refinement for (*S*,*S*,*S*,*S*)-**Q**.

Identification code	IM-3-254
Empirical formula	C102 H111 Au2 Cl2 N7 O8 P2
Formula weight	2089.7
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 15.2590(2)Å α = 90°. b = 17.6838(2)Å β = 90°. c = 33.9481(4)Å γ = 90°.
Volume	9160.46(19) $Å^3$
Z	4
Density (calculated)	1.515 Mg/m^3
Absorption coefficient	3.354 mm^{-1}
F(000)	4232
Crystal size	0.200 x 0.150 x 0.120 mm^3
Theta range for data collection	2.241 to 32.167°.
Index ranges	-22<=h<=22,-25<=k<=26,-50<=l<=49
Reflections collected	179462
Independent reflections	30933[R(int) = 0.0554]
Completeness to theta =32.167°	97.2%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.62
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	30933/ 156/ 1237
Goodness-of-fit on F^2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0310, wR2 = 0.0655
R indices (all data)	R1 = 0.0427, wR2 = 0.0689
Flack parameter	x =-0.0135(14)
Largest diff. peak and hole	1.755 and -1.279 $e.Å^{-3}$

Complex (*S*,*S*)-T

CCDC 2050971

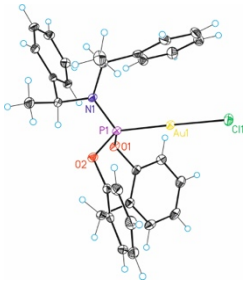


Table 12. Crystal data and structure refinement for (*S*,*S*)-**T**.

Identification code	IM-3-175f1
Empirical formula	C31 H32 Au Cl3 N O2 P
Formula weight	784.86
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.63030(10)Å a = 90°. b = 14.7215(2)Å b = 90°. c = 21.0610(3)Å g = 90°.
Volume	2985.87(7) $Å^3$
Z	4
Density (calculated)	1.746 Mg/m^3
Absorption coefficient	5.245 mm^{-1}
F(000)	1544
Crystal size	0.100 x 0.100 x 0.050 mm^3
Theta range for data collection	1.934 to 34.415°.
Index ranges	-15<=h<=14,-22<=k<=20,-32<=l<=28
Reflections collected	39860
Independent reflections	11877[R(int) = 0.0245]
Completeness to theta =34.415°	96.0%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.53
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11877/ 12/ 372
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0194, wR2 = 0.0365
R indices (all data)	R1 = 0.0227, wR2 = 0.0371
Flack parameter	x =-0.0068(14)
Largest diff. peak and hole	0.656 and -0.599 $e.Å^{-3}$

Complex (*S*,*S*,*S*,*S*)-U

CCDC 2050985

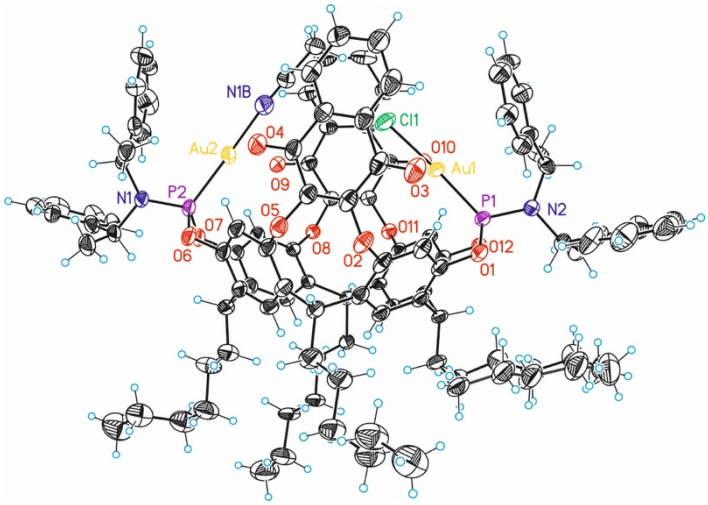


Table 13. Crystal data and structure refinement for (*S*,*S*,*S*,*S*)-**U**.

Identification code	IM-3-383
Empirical formula	C108 H114 Au2 Cl F6 N4 O12 P2 Sb
Formula weight	2387.10
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C 2
Unit cell dimensions	a = 19.2984(3)Å a = 90°. b = 20.7919(4)Å b = 97.092(2)°. c = 25.7037(5)Å g = 90°.
Volume	10234.7(3) $Å^3$
Z	4
Density (calculated)	1.549 Mg/m^3
Absorption coefficient	3.252 mm^{-1}
F(000)	4784
Crystal size	0.300 x 0.100 x 0.100 mm^3
Theta range for data collection	2.395 to 32.259°.
Index ranges	-28<=h<=28,-30<=k<=31,-38<=l<=38
Reflections collected	96447
Independent reflections	32455[R(int) = 0.0482]
Completeness to theta =32.259°	93.9%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.13
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	32455/ 660/ 1460
Goodness-of-fit on F^2	0.991
Final R indices [I>2sigma(I)]	R1 = 0.0504, wR2 = 0.1205
R indices (all data)	R1 = 0.0637, wR2 = 0.1247
Largest diff. peak and hole	4.181 and -1.993 $e.Å^{-3}$

Compound 71

CCDC 2050972

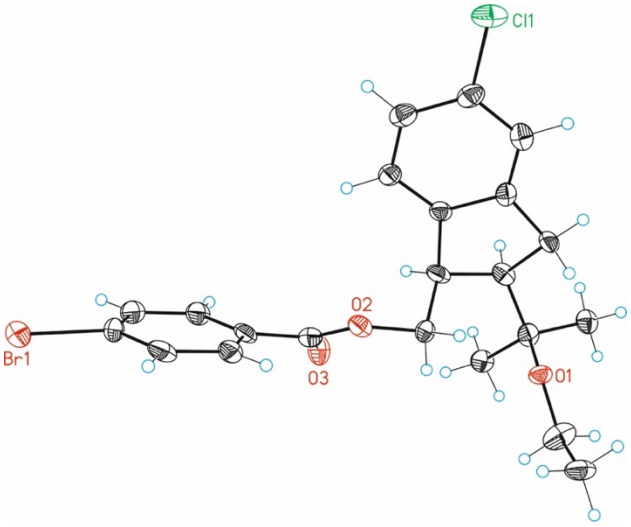


Table 14. Crystal data and structure refinement for **71**. Absolute configuration was determined.

Identification code	IM-3-554
Empirical formula	C22 H24 Br Cl O3
Formula weight	451.77
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 6.0270(5)Å a = 90°. b = 17.1838(12)Å b = 90°. c = 19.4805(17)Å g = 90°.
Volume	2017.5(3) $Å^3$
Z	4
Density (calculated)	1.487 Mg/m^3
Absorption coefficient	2.190 mm^{-1}
F(000)	928
Crystal size	0.050 x 0.010 x 0.010 mm^3
Theta range for data collection	2.370 to 25.025°.
Index ranges	-6<=h<=7,-20<=k<=17,-23<=l<=23
Reflections collected	9943
Independent reflections	3547[R(int) = 0.1152]
Completeness to theta =25.025°	99.9%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.28
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3547/ 0/ 247
Goodness-of-fit on F^2	1.131
Final R indices [I>2sigma(I)]	R1 = 0.0781, wR2 = 0.1792
R indices (all data)	R1 = 0.1196, wR2 = 0.2054
Flack parameter	x =0.01(2)
Largest diff. peak and hole	1.447 and -0.718 $e.Å^{-3}$

(+)-Mafaicheenamine C (77a)

CCDC 2050977

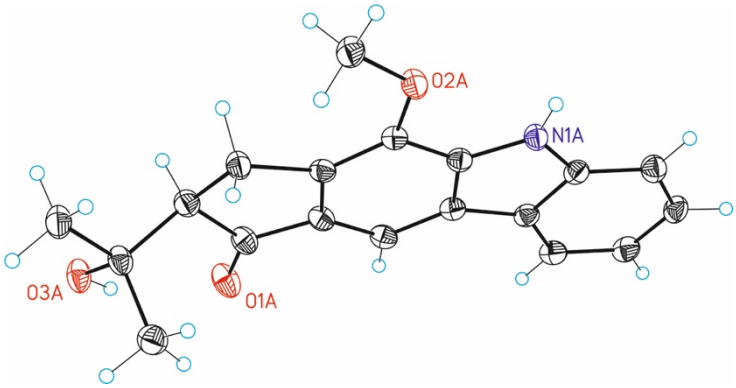


Table 15. Crystal data and structure refinement for **77a**. Absolute configuration was determined.

Identification code	cu_IM3705_0m
Empirical formula	C19 H19.30 N O3.15
Formula weight	312.05
Temperature	100(2)K
Wavelength	1.54178 Å
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 11.6525(3)Å a = 90°. b = 14.0343(4)Å b = 90°. c = 18.8087(6)Å g = 90°.
Volume	3075.87(15) $Å^3$
Z	8
Density (calculated)	1.348 Mg/m^3
Absorption coefficient	0.742 mm^{-1}
F(000)	1324
Crystal size	0.250 x 0.250 x 0.150 mm^3
Theta range for data collection	6.734 to 67.617°.
Index ranges	-13<=h<=13,-16<=k<=16,-22<=l<=22
Reflections collected	25940
Independent reflections	5509[R(int) = 0.0323]
Completeness to theta =67.617°	99.4%
Absorption correction	Multi-scan
Max. and min. transmission	0.75 and 0.66
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5509/ 122/ 499
Goodness-of-fit on F^2	1.076
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0837
R indices (all data)	R1 = 0.0343, wR2 = 0.0856
Flack parameter	x =-0.01(4)
Largest diff. peak and hole	0.277 and -0.179 $e.Å^{-3}$

(–)-Mafaicheenamine C (77b)

CCDC 2050973

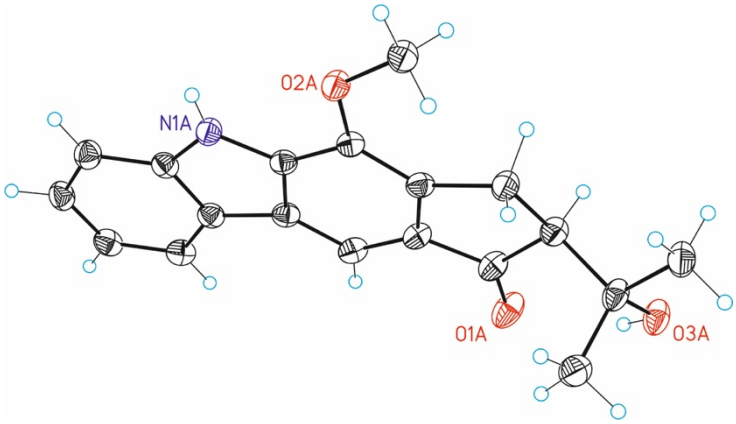


Table 16. Crystal data and structure refinement for **77b**. Absolute configuration was determined.

Identification code	cu_im3693_0m
Empirical formula	C19 H19.14 N O3.07
Formula weight	310.61
Temperature	100(2)K
Wavelength	1.54178 Å
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 11.6524(5)Å a = 90°. b = 14.0428(6)Å b = 90°. c = 18.7622(8)Å g = 90°.
Volume	3070.1(2) $Å^3$
Z	8
Density (calculated)	1.344 Mg/m^3
Absorption coefficient	0.737 mm^{-1}
F(000)	1318
Crystal size	0.250 x 0.250 x 0.150 mm^3
Theta range for data collection	3.932 to 67.154°.
Index ranges	-13<=h<=13,-16<=k<=16,-22<=l<=22
Reflections collected	96498
Independent reflections	5444[R(int) = 0.0481]
Completeness to theta =67.154°	99.3%
Absorption correction	Multi-scan
Max. and min. transmission	0.75 and 0.62
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5444/ 122/ 494
Goodness-of-fit on F^2	1.192
Final R indices [I>2sigma(I)]	R1 = 0.0307, wR2 = 0.0906
R indices (all data)	R1 = 0.0312, wR2 = 0.0912
Flack parameter	x =0.09(3)
Largest diff. peak and hole	0.220 and -0.150 $e.Å^{-3}$

DFT Calculations

Computational methods

DFT calculations were performed by the Gaussian 09 suit.[42] All the calculations were carried out using B3LYP[43] functional that has provided suitable models in the other DFT cavitand studies[30] and also in gold-catalyzed transformations.[44] The SDD basis set was used to describe Au. The 6-31G(d,p) basis set[45] was employed for all the other atoms (C, H, O, N, P and Cl). Full geometry optimizations were carried out in ethanol through a solvation model based (SMD)[46]. The connectivity of the transition states was confirmed by the relaxation of each transition state towards both previous and next intermediates. All the energies are potential energies (E) and free energies (G) in solution at 298.15 K and 1 atm in kcal/mol. Optimized geometries were visualized using CYLView.[47] NCI plot was used to obtain the grid data for NCI (non-covalent interactions) analysis[48] and the corresponding result were visualized with the VMD software.[49]

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42 Gaussian 09, Revision B.1, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, J. A., Peralta, Jr. J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R.L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V., Cioslowski, J., Fox, D. J. Gaussian, Inc., Wallingford CT 2009.

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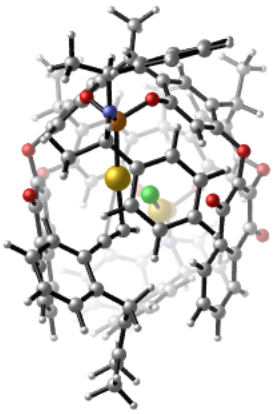
Optimized structures

I-A



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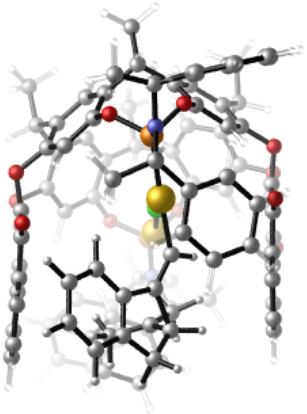
G = -6171.384739 Hartrees

II-A



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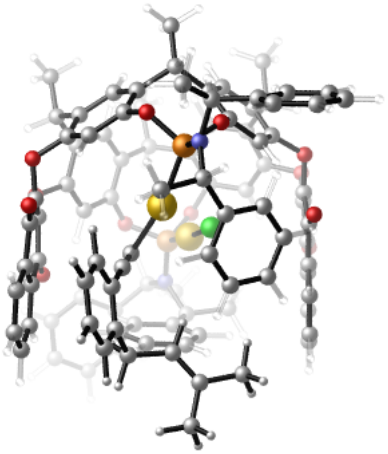

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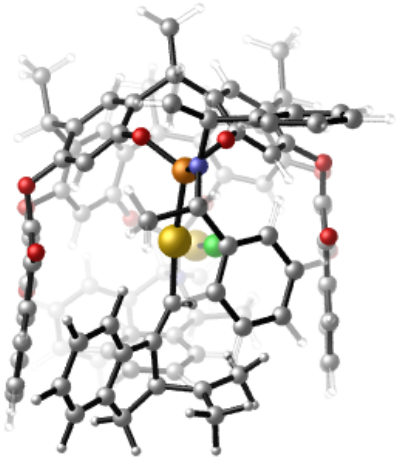
G = -6171.384502 Hartrees

IV-A



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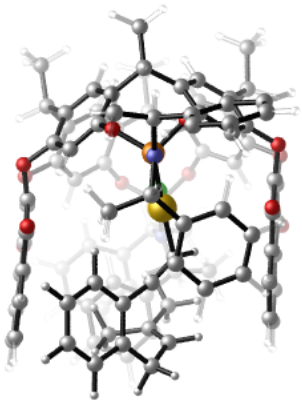
TSI-IIA



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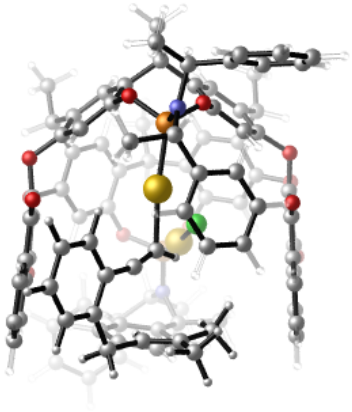

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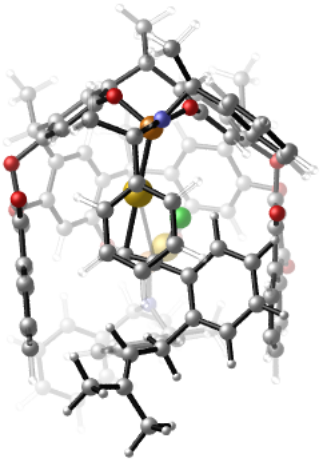
I-B



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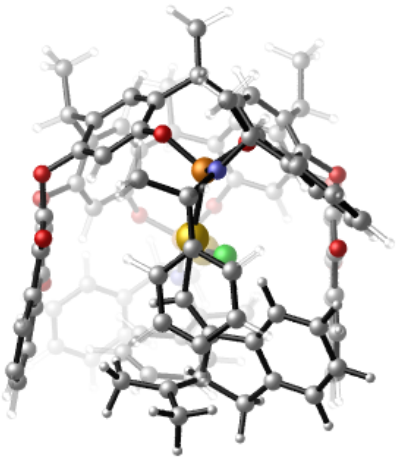
II-B



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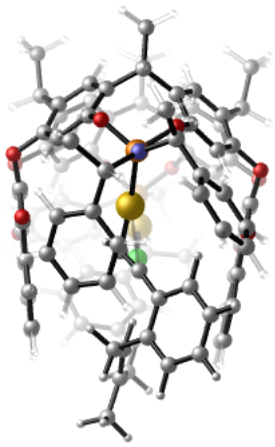
G = -6171.386297 Hartrees

III-B



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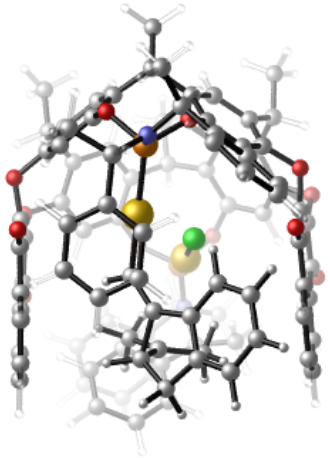
IV-B



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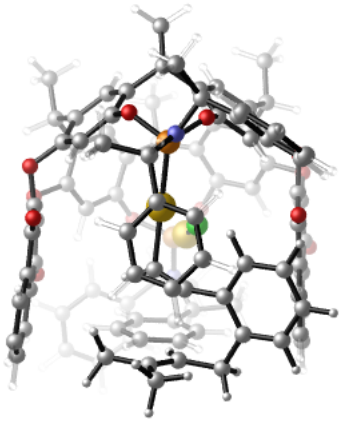

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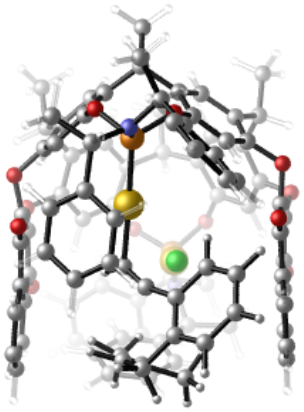

E = -6172.80684696 Hartrees

G = -6171.374555 Hartrees

UNIVERSITAT ROVIRA I VIRGILI
GOLD(I) CAVITANDS FOR THE ASSEMBLY OF MOLECULAR COMPLEXITY
Inmaculada Martin Torres

Chapter II: *Gold(I)-Catalyzed Decarbenation of Persistent Cyclopropanes*

UNIVERSITAT ROVIRA I VIRGILI
GOLD(I) CAVITANDS FOR THE ASSEMBLY OF MOLECULAR COMPLEXITY
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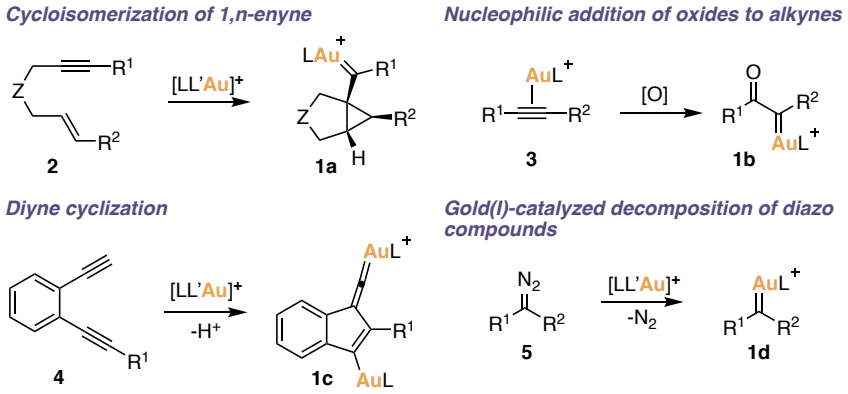
Introduction

Gold(I) Carbene Intermediates

As discussed in the General Introduction, gold(I) carbenes **1** are key intermediates in a wide array of transformations and are crucial for the understanding and development of homogeneous gold(I) catalysis. However, the controlled generation of these intermediates is still a challenge, and most methods either lack of generality (e.g., enynes **2**), or require the preparation and handling of potentially dangerous precursors (e.g., diazo compounds **5**). For these reasons, the development of new general methods for the safe generation of gold(I) carbenes is still highly relevant since it can lead to a better understanding of the behavior of these organometallic species, and eventually to the development of new chemical reactions that quickly build up molecular complexity.



Scheme 1. Selected examples of the generation of gold(I) carbenes.

Different approaches have been discovered for the generation of gold(I)-carbene intermediates **1** and related species (Scheme 1): the cycloisomerization of enynes such as **2** to form cyclopropyl gold(I) carbenes **1a**,[1] the nucleophilic addition of *N*-oxides or sulfoxides to

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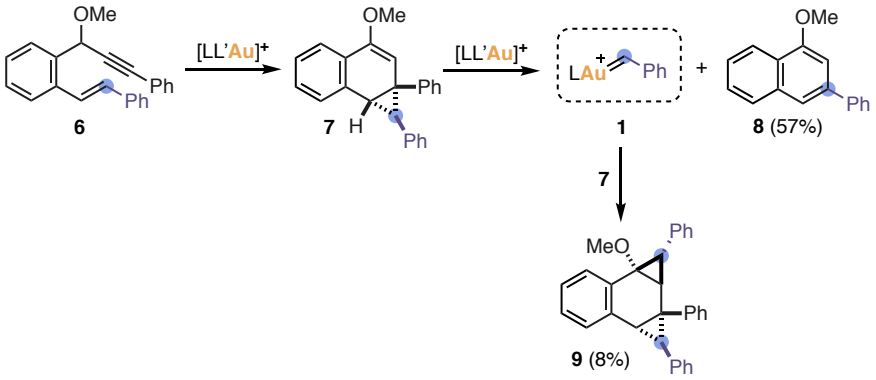
generate α-oxo gold(I) carbenes **1b**,[2] the formal cycloaddition of diynes **4** to form gold vinylidene intermediates **1c**,[3] and the gold(I)-catalyzed decomposition of diazo compounds **5**.[4]

Generation of Gold(I) Carbenes *via* Retro-Buchner Reaction

In 2010, our group discovered the first example of a gold(I)-catalyzed retro-cyclopropanation in solution from intermediate **7**, which was formed *in situ* by cycloisomerization of 1,6-enynes **6**, catalyzed by the same gold(I) complex. The resulting carbene **1** was trapped by another unit of intermediate **7** to give biscyclopropane **9** upon release of naphthalene **8** (Scheme 2).[5]



Scheme 2. Gold(I)-catalyzed annulation/fragmentation reaction of enyne **6**.

Based on the resemblance between carbene precursor **7** and the norcaradiene tautomers of 7-subsituted-1,3,5-cycloheptatrienes (Schemes 3–4), our group developed the gold(I)-catalyzed retro-Buchner reaction of 7-aryl cycloheptatrienes, which gives rise to carbenes that undergo

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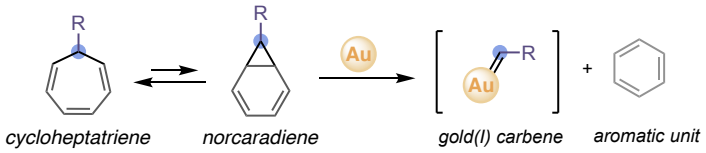
4 (a) Fructos, M. R.; Belderrain, T. R.; de Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5284–5288. (b) Prieto, A.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 1790–1793. (c) Zhou, L.; Liu, Y.; Zhang, Y.; Wang, J. *Beilstein J. Org. Chem.* **2011**, *7*, 631–637.

5 Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881–11883.

ready cyclopropanation of styrenes and related alkenes.[6] Cycloheptatrienes are in equilibrium with their norcaradiene valence tautomers,[7] which can undergo a decarbenation reaction to give rise to a gold(I) carbene upon release of benzene as driving force. This methodology is a powerful and safe alternative to the classical methods for the generation of simple metal carbenes, which often involve the decomposition of diazo compounds that are potentially explosive reagents.[8]



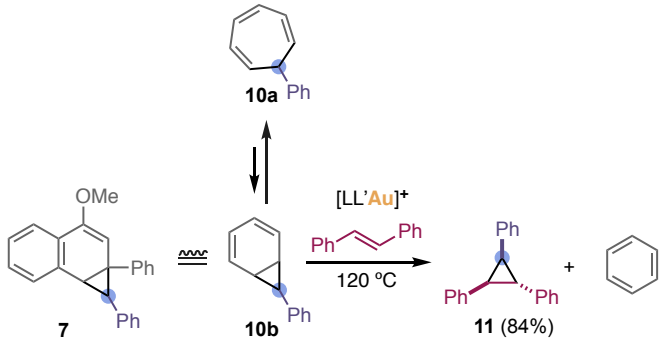
Scheme 3. The gold(I)-catalyzed retro-Buchner reaction.

Accordingly, norcaradiene **10b**, which is in equilibrium with cycloheptatriene **10a**, mimics the behavior of compound **7** (discussed in Scheme 2). Thus, the reaction of **10b**, in equilibrium with **10a**, in the presence of [(JohnPhos)Au(MeCN)]SbF_6 at 120 °C generates a gold(I) carbene intermediate that can be trapped with *E*-stilbene to afford 1,2,3-triphenylcyclopropane **11** as a single diastereoisomer (Scheme 4).[6a] This result proves that norcaradiene derivatives are an excellent alternative to the use of diazo compounds for the generation of non-acceptor metal carbenes. This avoids the use of highly unstable non-stabilized (without electron-withdrawing groups) diazo compounds, such as phenyldiazomethane.[8a] Importantly, aryl carbene precursors **10** can be easily synthesized in gram scale by reaction of Grignard reagents, organolithium compounds or other organometallic nucleophiles with commercially available tropylium tetrafluoroborate and stored under air.

6 (a) Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952–11955; corigendum: *J. Am. Chem. Soc.* **2017**, *139*, 2529–2529. (b) Mato, M.; García-Morales, C.; Echavarren, A. M. *ChemCatChem* **2019**, *11*, 53–72.

7 (a) Hoffmann, R. *Tetrahedron Lett.*, **1970**, *11*, 2907. (b) McNamara O. A.; Maguire, A. R. *Tetrahedron*, **2011**, *67*, 9.

8 (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2904. (b) Fructos, M. R.; Belderrain, T. R.; de Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5284–5288. (c) Wei, F.; Song, C.; Ma, Y.; Zhou, L.; Tung, C.-H.; Xu, Z. *Science Bulletin* **2015**, *60*, 1479–1492. (d) Liu, L.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 506–516. (e) Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2016**, *52*, 7326–7335. (f) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53–61. (g) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479–1492.



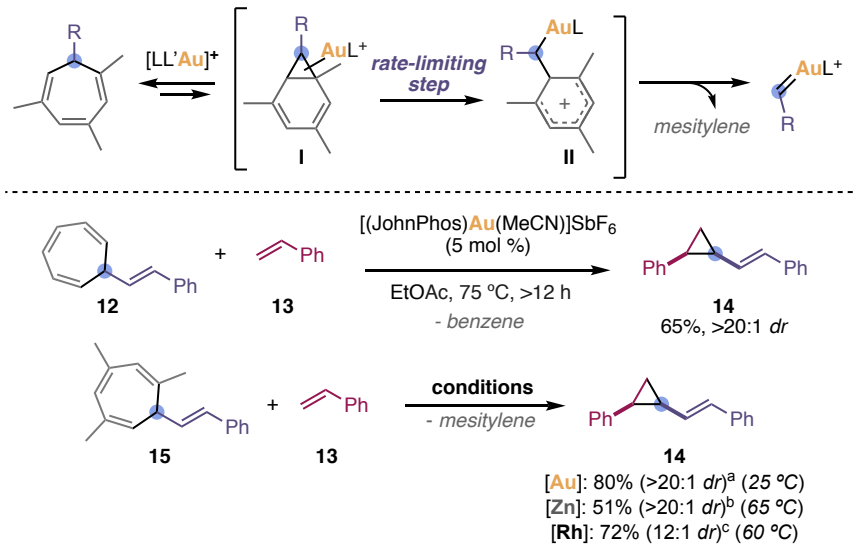
Scheme 4. Gold(I)-catalyzed retro-Buchner reaction followed by alkene cyclopropanation.

Even though the retro-Buchner reaction is a powerful method, high temperatures (>100 °C) are often necessary to allow the decarbenation process to take place when using simple 7-subsituted 1,3,5-cycloheptatriene as carbene precursors. To solve this limitation, our group developed a new generation of more reactive carbene precursors, 7-styryl-1,3,5-trimethyl-1,3,5-cycloheptatrienes, which release mesitylene instead of benzene as driving force. With these substrates, intermediate **II** (and the transition state leading to it) is stabilized by the electron-donating methyl substituents (Scheme 5). In this way, products of decarbenation/cyclopropanation sequence such as **14** could be obtained at a lower temperature, generally in higher yields and selectivity. More recently, zinc (II)[9] or rhodium (II)[10] catalysts were also employed in the retro-Buchner reaction by our group. Thus, new selectivities were observed and this methodology could be applied on the synthesis of natural products, and in the development of new cycloadditions or cascade processes.[11]

9 Mato, M.; Herlé, B.; Echavarren, A. M. *Org. Lett.* **2018**, *20*, 4341–4345.

10 Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.*, **2019**, *58*, 2088.

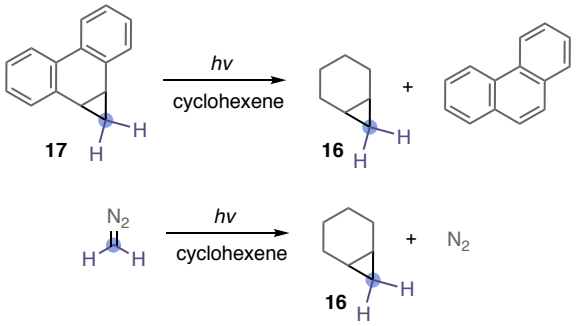
11 (a) Mato, M.; García-Morales, C.; Echavarren, A. M. *ACS Catal.* **2020**, *10*, 3564–3570. (b) Armengol-Relats, H.; Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 1916–1922.



Scheme 5. Mechanism of the retro-Buchner reaction. *Conditions:* [a] 5 mol % of [(JohnPhos)Au(MeCN)]SbF_6 and EtOAc (0.1 M) at 25 °C for 20 h. [b] 10 mol % of $ZnCl_2$ and 1,2-DCE (0.1 M) at 65 °C for 30 h. [c] 3 mol % of [Rh_2(TFA)$_4$] and 1,2-DCE (0.1 M) at 60 °C for 18 h.

Dibenzonorcaradienes as Precursors for the Decarbenation Process

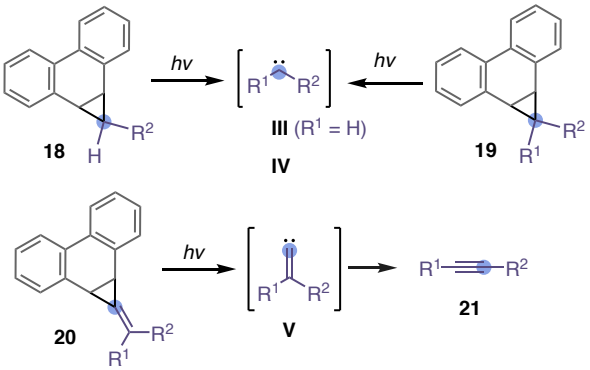
In 1965, Dvoretzky and coworkers disclosed the decarbenation of 9,10-dihydro-9,10-methanophenanthrene **17** in the presence of cyclohexene, releasing phenanthrene under photochemical conditions (Scheme 6). This is the first report of the formation of methylene carbene using cyclopropyl dihydrophenanthrene precursors. This process resembles the well-known photochemical decomposition of diazomethane to give free methylene carbene.[12]



Scheme 6. Decarbenation of persistent cyclopropanes *via* photolysis.

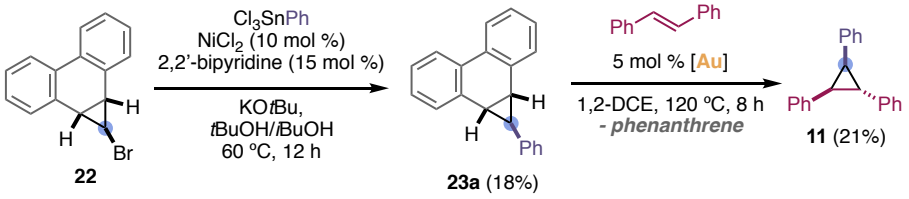
12 (a) von E. Doering, W.; Buttery, R. G.; Laughlin, R. G.; Chaudhuri, N. *J. Am. Chem. Soc.* **1956**, *78*, 3224–3224. (b) Richardson, D. B.; Durrett, L. R.; Martin, J. M.; Putnam, W. E.; Slaymaker, S. C.; Dvoretzky, I. *J. Am. Chem. Soc.* **1965**, *87*, 2763–2765.

Later on, the development of new precursors for the generation and study of new carbenes was reported forming substituted carbenes **III**, **IV** and **V** depending on the starting substrate employed (Scheme 7).[13]



Scheme 7. Formation of different carbenes *via* photolysis of dihydrophenanthrene derivatives.

Inspired by these results, our group also started to investigate the use of dihydrophenanthrenes as gold(I)-carbene precursors, which would release phenanthrene as driving force.[14] Initial exploration of the synthesis of such precursors led to the preparation of *exo*-**23a** in 18% yield through a nickel-catalyzed Stille coupling of cyclopropyl bromide **22** (Scheme 8). Gold(I)-catalyzed decarbenation of **23a** in the presence of *E*-stilbene gave cyclopropane **11** in poor yield. Despite initial efforts to increase the conversion/yield by changing the catalyst, these results could not be further improved.[14]



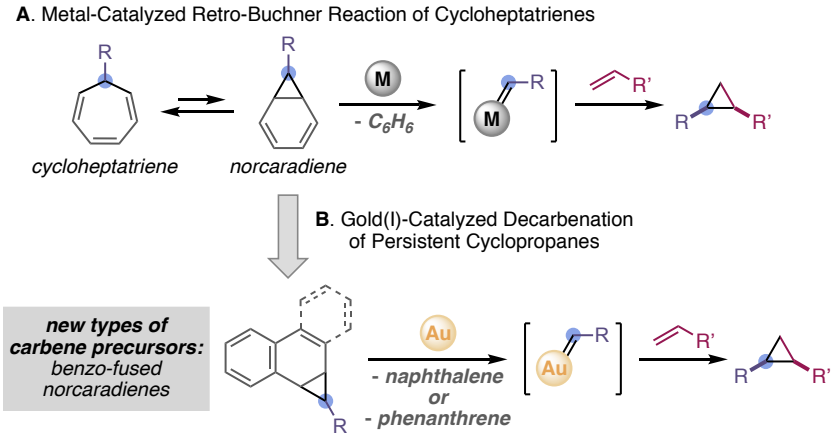
Scheme 8. Synthesis and decarbenation of precursor **23a**.

13 (a) Glick, H. *Tetrahedron Letters* **1995**, *36*, 5715–5718. (b) Ruck, R. T.; Jones, M. *Tetrahedron Letters* **1998**, *39*, 2277–2280. (c) Farlow, R. A.; Thamattoor, D. M.; Sunoj, R. B.; Hadad, C. M. *J. Org. Chem.* **2002**, *67*, 3257–3265. (d) Graves, K. S.; Thamattoor, D. M.; Rablen, P. R. *J. Org. Chem.* **2011**, *76*, 1584–1591. (e) Moore, K. A.; Vidaurri-Martinez, J. S.; Thamattoor, D. M. *J. Am. Chem. Soc.* **2012**, *134*, 20037–20040. (f) Hardikar, T. S.; Warren, M. A.; Thamattoor, D. M. *Tetrahedron Letters* **2015**, *56*, 6751–6753. (g) Maurer, D. P.; Fan, R.; Thamattoor, D. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 4499–4501.

14 Herlé, B. Doctoral Thesis, "Stereoselective Cyclopropanations via Gold(I)-Catalyzed Retro-Buchner Reactions" (**2017**).

Objectives

7-Substituted cycloheptatrienes undergo metal-catalyzed decarbenations by retro-Buchner reaction generating metal-carbene units, which can be trapped with alkenes to give a wide diversity of cyclopropanes. In this context, the main goal of the work summarized in this chapter was the design and development of new types of carbene precursors based on benzo-fused norcaradiene derivatives, which would release polyaromatic units instead of simple aromatic compounds as driving force of the reaction.[15] Another objective was the general application of such substrates in the cyclopropanation of alkenes under gold(I) catalysis (Scheme 9).



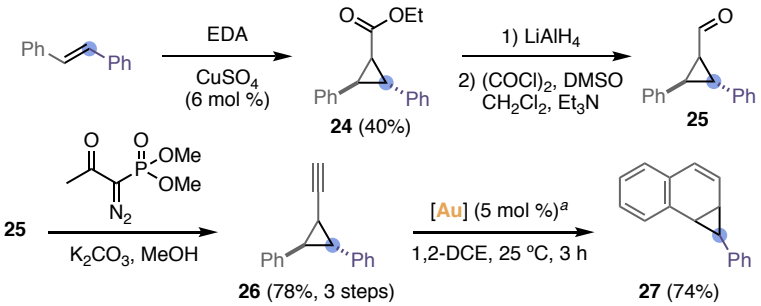
Scheme 9. Generation of metal carbenes by metal-catalyzed retro-cyclopropanation: (a) Retro-Buchner reaction of cycloheptatrienes. (b) Decarbenation of benzo-fused norcaradienes.

15 All experiments described in this section were performed jointly with Dr. Mauro Mato and were based upon preliminary work by Dr. Bart Herlé.

Results and Discussion

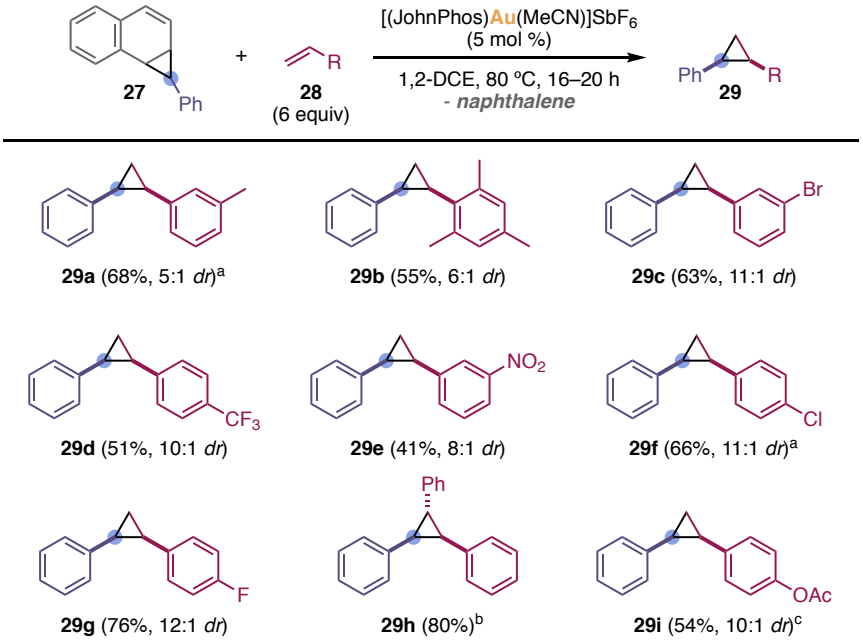
Synthesis and Reactivity of Dihydronaphthalene Derivatives

Our work commenced with the preparation of benzo-fused norcaradiene **27**, in order to prove the feasibility of generating phenyl metal carbene upon release of a polyaromatic molecule in a general and synthetically useful manner. The synthesis of **27** started with the copper(II)-catalyzed cyclopropanation of *E*-stilbene with ethyl diazoacetate (EDA) to give ester **24**, which was then submitted to redox manipulations to render aldehyde **25**. Subsequent Seyferth–Gilbert homologation with the Bestmann–Ohira reagent provided alkyne **26** in 78% yield over three steps, after a single chromatographic purification. Finally, the gold(I)-catalyzed hydroarylation of **26** was performed at room temperature to obtain cyclopropyl dihydronaphthalene derivative **27** in 74% yield (Scheme 10).



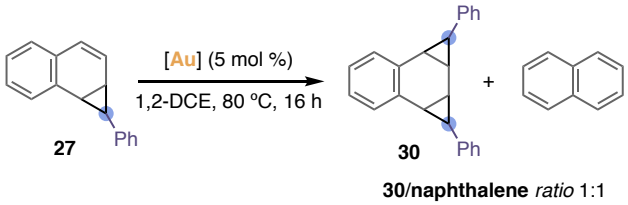
Scheme 10. Synthesis of benzo-fused norcaradiene **27**. [a] [Au] = [(JohnPhos)Au(MeCN)]SbF_6.

With gram-amounts of **27** in hand, we explored the gold(I)-catalyzed decarbenation of the substrate in the presence of 3-methylstyrene (**28**) and 5 mol % of [(JohnPhos)Au(MeCN)]SbF_6 as catalyst, at 80 °C (Scheme 11). This afforded the product of retro-cyclopropanation of **27** (upon release of a molecule of naphthalene) and subsequent cyclopropanation of styrene **28**, resulting in an overall cyclopropane/alkene-metathesis process. This reaction gave **29a** in good yield and in a 5:1 ratio of diastereoisomers, the *cis* diastereomer being formed preferentially. Using these reaction conditions, we explored the scope of the transformation by using other styrene partners (Scheme 11). Thus, we discovered that both electron-rich and electron-poor substituents gave the desired *cis*-diarylcyclopropanes **29a–i** in good yields and diastereoselectivities. Furthermore, it is worth mentioning that the gold(I)-catalyzed decarbenation process of benzo-fused norcaradiene **27** proceeds at 80 °C, while the retro-Buchner reaction of 7-aryl-1,3,5-cycloheptatrienes, which releases benzene instead of naphthalene, required a temperature of 120 °C to transfer the corresponding aryl carbenes.[6a]



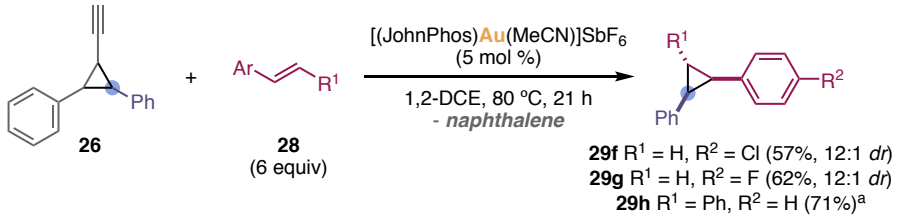
Scheme 11. Gold(I)-catalyzed phenylcyclopropanation upon release of naphthalene. [a] At 100 °C instead of 80 °C, for 20 h. [b] Isolated as a mixture with the product of phenyl cyclopropanation of **27**. [c] 3 equiv of alkene employed.

We observed that the main side-reaction of this process is the phenylcyclopropanation of the styrene-like double bond in **27**. This pathway could be evaluated by submitting **27** to the same reaction conditions in the absence of external alkene, which led to the quantitative conversion of **27** to naphthalene and biscyclopropane product **30** (Scheme 12).



Scheme 12. Gold(I)-catalyzed phenylcyclopropanation of **27**.

As depicted in Scheme 10, the gold (I)-catalyzed hydroarylation of alkynylcyclopropane **26** affords benzo-fused norcaradiene **27** using complex [(JohnPhos)Au(MeCN)]SbF_6 at 25 °C. Since the same gold(I) complex can promote the subsequent decarbenation/cyclopropanation sequence (Scheme 11), we envisioned that alkynylcyclopropane **26** could be used directly as an unprecedented type of phenyl carbene precursor, which could be trapped by alkenes in a single-pot triple gold(I)-catalyzed procedure (Scheme 13).



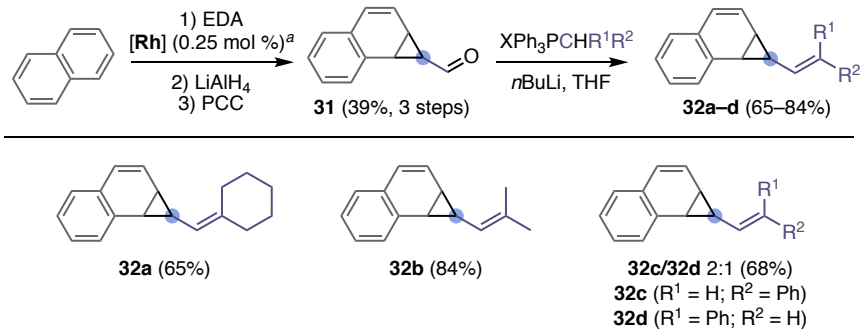
Scheme 13. One-pot gold(I)-catalyzed hydroarylation/decarbenation/cyclopropanation sequence. [a] Isolated as a mixture with the product of phenyl cyclopropanation of **27**.

Thus, we treated **26** with 6 equiv of styrene derivatives in the presence of a cationic gold(I) complex at 80 °C. This resulted in the direct assembly of *cis*-cyclopropanes **29f–h** with similar yields and diastereoselectivities than for the stepwise procedure (Scheme 13). This demonstrates that **26** can also act as phenyl gold(I)-carbene precursor, and that the corresponding carbenes can be trapped by different styrenes.

Overall, these results make **26** and **27** emerge as safe alternatives to the use of phenyl diazomethane (an explosive and difficult-to-handle reagent) for the generation of the phenyl gold(I)-carbene intermediate.

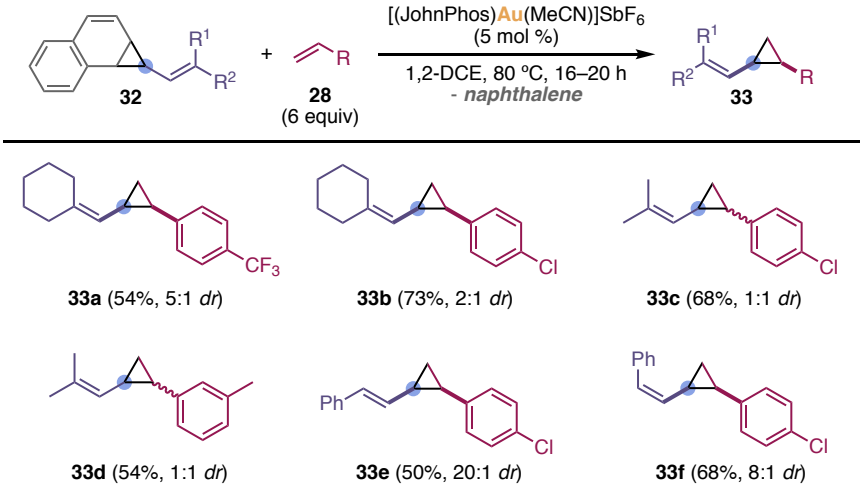
Then we turned our attention to investigate if alkenyl carbene precursors **32a–d** are also suitable substrates for the decarbenation reaction, which would extend the concept to the generation of alkenyl gold carbenes (Scheme 14). For the synthesis of these compounds, we performed a cyclopropanation of naphthalene with ethyl diazoacetate in the presence of only 0.25 mol % $[Rh_2(TFA)_4]$ to afford cyclopropyl ester.[16] After reduction of the resulting ester to the corresponding alcohol, and subsequent oxidation, aldehyde **31** was obtained in 39% yield over 3 steps. Then we submitted substrate **31** to Wittig olefinations using different triphenyl-phosphonium ylides, which gave alkenyl benzo-fused norcaradienes **32a–d** (Scheme 14). When using a non-symmetrical phosphonium ylide, we observed a mixture of *E* and *Z* alkene products (**32c** and **32d**), which could be isolated independently by flash column chromatography.

16 (a) Müller, P.; Toujas, J.-L.; Bernardinelli, G. *Helv. Chim. Acta* **2000**, *83*, 1525–1534. (b) Pérez, P. J.; Díaz-Requejo, M. M.; Revilla, I. *Beilstein J. Org. Chem.* **2011**, *7*, 653–657.



Scheme 14. Synthesis of alkenyl benzo-fused norcaradienes **32a–d**. [a] [Rh] = $[Rh_2(TFA)_4]$.

As in the case of benzo-fused norcaradiene **27**, the decarbenation of alkenyl derivatives **32** generated the corresponding vinyl or styryl gold(I) carbenes in situ, at 80 °C upon release of naphthalene. These carbenes could be trapped with styrenes to give the targeted alkenyl cyclopropanes (Scheme 15). Using this methodology, vinylcyclopropanes **33a–d** could be obtained but with lower diastereoselectivity than when aryl carbenes were transferred. The reason for that could be the absence of π-π non-covalent interactions between the two organic fragments in the transition state during the cyclopropanation event.[17] In contrast, the products of styrylcyclopropanation were obtained with much better *cis*-diastereoselectivity. Thanks to this method, both *E* or *Z* styryl carbene fragments could be transferred (**33e–f**), obtaining previously inaccessible *Z*-*cis*-alkenyl cyclopropanes (**33f**) (Scheme 15).

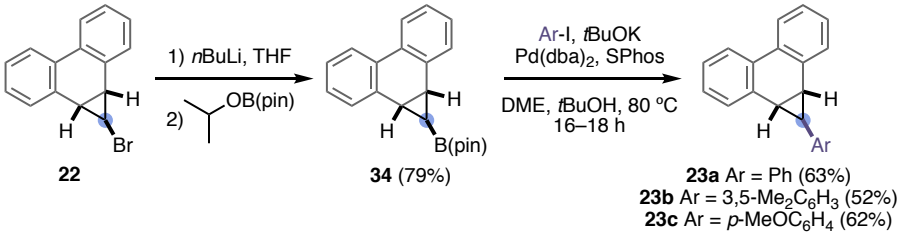


Scheme 15. Gold(I)-catalyzed alkenylcyclopropanation of styrenes upon release of naphthalene.

17 (a) Herlé, B.; Holstein, P. M.; Echavarren, A. M. *ACS Catal.* **2017**, *7*, 3668–3675. (b) Mato, M.; Montesinos-Magraner, M.; Sugranyes, A. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2021**, *143*, 10760–10769.

Synthesis and Reactivity of Dihydrophenanthrene Derivatives

We then explored the release of phenanthrene as driving force for the generation of metal carbenes. Thus, we synthesized dihydrophenanthrene derivatives **23a–c** (Scheme 16).

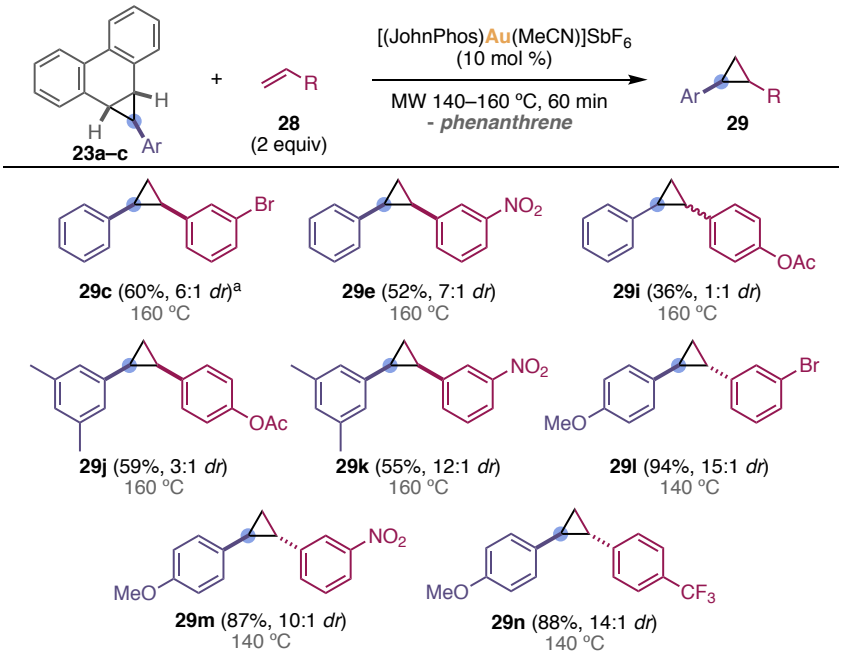


Scheme 16. Preparation of aryl dihydrophenanthrene carbene precursors **23a–c**.

We started by the preparation of *exo*-bromocyclopropane **22** following a reported procedure.[18] Initial attempts on using this compound as electrophile in cross-coupling reactions with aryl organometallic reagents did not lead to synthetically useful yields.[14] Therefore, we transformed it into a nucleophilic partner by lithium-halogen exchange of **22**, followed by trapping with isopropoxy pinacolborane. This afforded boronic ester **34** in 79% yield. Finally, cyclopropyl dihydrophenanthrenes **23a–c** were obtained by palladium-catalyzed Suzuki couplings with different aryl iodides in good yields (Scheme 16).

Subsequently, we evaluated the decarbenation of **23a** using analogous reaction conditions to those for the decarbenation of **27** or **32**. However, this led to yields and conversions lower than 20%, throughout a range of temperatures between 50 and 120 °C. Fortunately, a solution to this problem came with the use of microwave heating. The reaction of **23a** with 3-bromostyrene in the presence of 10 mol % of [(JohnPhos)Au(MeCN)]SbF_6 in 1,2-dichloroethane at 160 °C, upon 60 min of microwave irradiation led to the formation of cyclopropane **29c** in 60% yield upon release of phenanthrene (Scheme 17).

18 Graves, K. S.; Thamattoor, D. M.; Rablen, P. R. *J. Org. Chem.* **2011**, *76*, 1584–1591.



Scheme 17. Gold(I)-catalyzed arylcyclopropanation of styrenes upon release of phenanthrene. [a] Isolated as a mixture with 1 equiv of phenanthrene.

The phenylcyclopropanation of styrenes was performed at 160 °C. However, when placing more electron-rich aromatic rings (i.e., methoxy-substituted) on the carbene unit, the reaction took place at 140 °C, leading to full conversion and excellent yields after only 60 min (**29l–n**). This method afforded 1,2-diarylcyclopropanes with different substituents on both aromatic rings (Scheme 17). Cyclopropanes with only electron-withdrawing groups were obtained preferentially as the *cis* isomer. However, when highly electron-rich substituents were placed on the aromatic rings (such as methoxy), the *trans* isomers (**29l–n**) were obtained almost exclusively. This might come as a result of a *cis*-to-*trans* isomerization that can take place for highly electron-rich cyclopropanes under gold catalysis at high temperatures, as it was observed in similar contexts.[17a,19]

It is worth highlighting that, in contrast to carbene-precursors **26** or **27** (or classical 7-subtituted cycloheptatrienes), substrates **23** lead to a very clean reaction mixtures, and no side-pathways were observed, even working at high temperatures.

As previously mentioned in the introduction, the decarbenation of similar dihydrophenanthrene precursors has been previously reported through photolysis. Taking this into account, we tested the reaction without any transition metal catalyst, although no

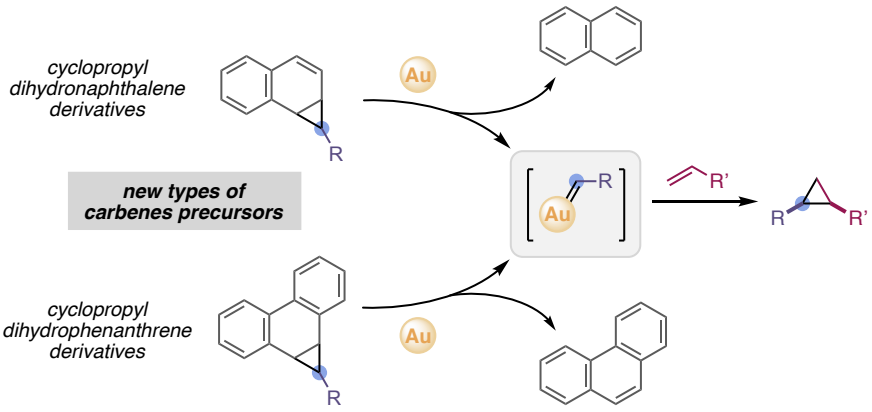
19 (a) Reiersølmoen, A. C.; Østrem, E.; Fiksdahl, A. *Eur. J. Org. Chem.* **2018**, 3317–3325. (b) Mato, M.; García-Morales, C.; Echavarren, A. M. *ACS Catal.* **2020**, *10*, 3564–3570.

conversion of the corresponding dihydrophenanthrene **23a** was observed. This result confirms that the presence of the gold(I) catalyst is required for the decarbenation reaction.

Conclusions

We have developed two new types of non-acceptor metal-carbenes precursors, which release polyaromatic units as driving force, instead of simple arenes. These substrates lead to the generation of aryl and alkenyl gold(I) carbenes, which are formed by retro-cyclopropanation of persistent cyclopropanes. These intermediates can be trapped by external alkenes, resulting in an overall cyclopropane metathesis process.

The first precursors, based on the release of naphthalene, are safe alternatives to the use of highly reactive and potentially explosive alkenyl diazomethanes. The second family, which release phenanthrene as driving force, allows for the synthesis of aryl cyclopropanes in a very clean manner, without competition by side reactions.



Scheme 18. Gold(I)-catalyzed cyclopropane metathesis.

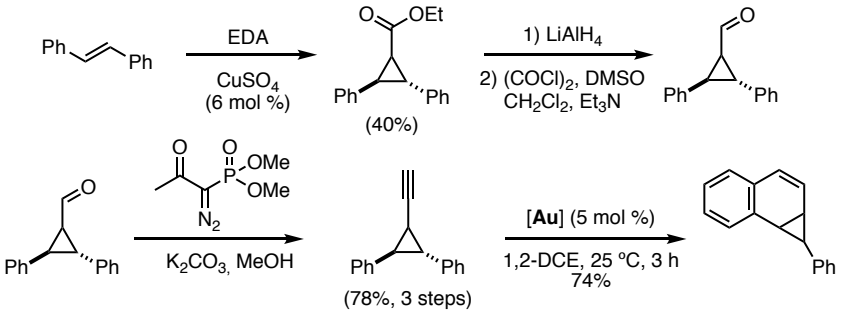
Experimental Section

General Methods

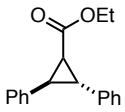
The general information has been provided in the experimental section of *Chapter I*.

Synthetic Procedures and Analytical Data

Synthesis of Carbene Precursors based on the Release of Naphthalene



Ethyl 2,3-diphenylcyclopropane-1-carboxylate (24)



A dry two-necked 100 mL round-bottomed flask with a magnetic stirring bar was charged with (*E*)-1,2-diphenylethene (6.56 g, 36.4 mmol, 1.5 equiv) and $CuSO_4$ (232 mg, 1.46 mmol, 6 mol %), under Ar atmosphere. Both solids were dissolved in anhydrous toluene (30 mL, 0.8 M), and the resulting solution was heated to 75 °C. After that, ethyl 2-diazoacetate (3 mL, 24.2 mmol, 1 equiv, 85% w/w commercial solution with CH_2Cl_2) was added by automatic syringe pump over 8 h (*ca.* 0.4 mL/h), while stirring at 75 °C. After stirring for s total time of 18 hours, the reaction was allowed to cool down to room temperature and the solvent was removed in vacuum. CombiFlash chromatography in SiO_2, using a gradient from cyclohexane to cyclohexane/EtOAc 8:2 as eluent, giving ethyl (*exo*)-2,3-diphenylcyclopropane-1-carboxylate **24** (2.6 g, 24.2 mmol, 40% yield) as a yellow oil.

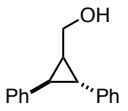
Characterization data matched the reported ones for this product.[20]

^{1}H NMR (500 MHz, $CDCl_3$) 7.30 – 7.20 (m, 6H), 7.19 – 7.13 (m, 4H), 3.88 (qd, J = 7.1, 1.8 Hz, 2H), 3.14 (dd, J = 7.0, 5.2 Hz, 1H), 2.85 (dd, J = 9.5, 7.1 Hz, 1H), 2.34 (dd, J = 9.6, 5.2 Hz, 1H), 0.96 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 139.8, 136.3, 129.3, 128.7, 128.2, 127.0, 126.8, 126.8, 60.6, 34.6, 31.4, 29.4, 14.2 ppm.

20 Scholz, S. O.; Farney, E. P.; Kim, S.; Bates, D. M.; Yoon, T. P. *Angew. Chem. Int. Ed.*, **2016**, *55*, 2239–2242.

(2,3-Diphenylcyclopropyl)methanol



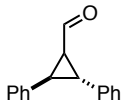
A two-necked 250 mL round-bottomed flask with a magnetic stirring bar was charged, under Ar, with $LiAlH_4$ (534 mg, 14.1 mmol, 1.5 equiv), and it was suspended in anhydrous THF (40 mL, 0.2 M). After cooling down the suspension to 0 °C in an ice-water bath, a solution of ethyl 2,3-diphenylcyclopropane-1-carboxylate **24** (2.5 g, 9.4 mmol, 1 equiv) in 7 mL of anhydrous THF was added dropwise over 5 min, and then the cooling bath was removed. The resulting suspension was stirred for 16 h while coming to room temperature, when no starting material was observed by TLC. The reaction was cooled down again to 0 °C in an ice-water bath, and was quenched by careful addition of water, and then aqueous (10%) HCl. The aqueous phase was extracted twice with Et_2O, and the combined organic fractions were washed with water once, with brine once, dried over anhydrous Na_2SO_4 and concentrated in vacuum giving (2,3-diphenylcyclopropyl)methanol (*ca.* quantitative yield, 2.1 g) as a yellow oil, used on the next step without further purification.

Characterization data matched the reported ones for this product.[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dtd, *J* = 11.0, 6.8, 1.8 Hz, 6H), 7.18 – 7.09 (m, 4H), 3.58 (dd, *J* = 11.7, 6.2 Hz, 1H), 3.41 (dd, *J* = 11.7, 8.2 Hz, 1H), 2.55 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.34 (t, *J* = 5.4 Hz, 1H), 1.83 (dddd, *J* = 9.3, 8.2, 6.2, 5.2 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 137.7, 128.9, 128.6, 126.7, 126.4, 126.2, 62.3, 31.8, 31.4, 26.5 ppm.

2,3-Diphenylcyclopropane-1-carbaldehyde (25)



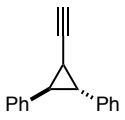
A dry 500 mL round-bottomed flask was charged under argon with a solution of dimethylsulfoxide (2.0 mL, 27.6 mL, 3.1 equiv) in dichloromethane (130 mL). After cooling this solution to -78 °C, oxalyl chloride (1.6 mL, 18.72 mmol, 2.1 equiv) was added dropwise. After 30 min, a solution of (2,3-diphenylcyclopropyl)methanol (2.0 g, 8.92 mmol, 1 equiv) in dichloromethane (20 mL) was added. The mixture was stirred at -78 °C for 1 h. After that, triethylamine (5 mL, 35.7 mmol, 4 equiv) was added to the mixture and it was maintained for 15 min at -78 °C then it was allowed to warm up to room temperature. The mixture was diluted with dichloromethane and water was added, and the mixture was extracted three times with dichloromethane. Combined organic fractions were washed with water and with brine, dried over Na_2SO_4 and concentrated under vacuum giving 2,3-diphenylcyclopropane-1-carbaldehyde (**25**) (*ca.* quantitative yield, 1.9 g) as an orange oil, used on the next step without further purification.

Characterization data matched the reported ones for this product.[20]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J* = 6.3 Hz, 1H), 7.39 – 7.24 (m, 6H), 7.24 – 7.12 (m, 4H), 3.29 (dd, *J* = 6.9, 4.8 Hz, 1H), 3.12 (dd, *J* = 9.4, 6.7 Hz, 1H), 2.41 (ddd, *J* = 9.2, 6.3, 4.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 138.5, 135.5, 129.3, 128.9, 128.8, 127.6, 127.2, 126.8, 39.9, 35.1, 29.9 ppm.

(3-Ethynylcyclopropane-1,2-diyl)dibenzene (26)



A modified reported procedure was followed.[21] A 250 mL round-bottomed flask was charged under air with a suspension of crude 2,3-diphenylcyclopropane-1-carbaldehyde **25** (1.9 g, 8.55 mmol, 1 equiv) and potassium carbonate (3.5 g, 25.6 mmol, 3 equiv) in HPLC-grade MeOH (71 mL, 0.12 M). Dimethyl (1-diazo-2-oxopropyl)phosphonate (neat, 3.0 g, 15.6 mmol, 1.8 equiv) was added, and the resulting mixture was stirred for 1 h. After confirming complete conversion of 81, water was added, and the mixture was extracted three times with diethyl ether. Combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. CombiFlash chromatography in SiO_2, using a gradient from cyclohexane to cyclohexane/EtOAc 97:3 as eluent gave (*exo*)-(3-ethynylcyclopropane-1,2-diyl)dibenzene (**26**) (1.4 g, 8.55 mmol, 78% overall yield over 3 steps) as a pale yellow solid.

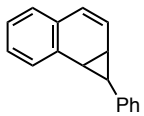
M.p. = 88–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 6H), 7.21 – 7.11 (m, 4H), 2.63 – 2.52 (m, 2H), 2.05 (ddd, *J* = 8.8, 5.5, 2.2 Hz, 1H), 1.87 (d, *J* = 2.2 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 137.1, 128.7, 128.5, 128.2, 126.8, 126.8, 126.4, 82.4, 69.7, 32.9, 32.7, 19.2 ppm.

HRMS (ESI+): calc. for $C_{17}H_{15}$ $[M+H]^+$: 219.1168; found: 219.1179.

1-Phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (27)



Under air, a 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged (3-ethynylcyclopropane-1,2-diyl)dibenzene (**26**) (510 mg, 2.3 mmol, 1 equiv) and it was dissolved in HPLC-grade 1,2-DCE (23.4 mL, 0.1 M), before [(JohnPhos)Au(MeCN)]SbF_6 (5 mol %) was added. The resulting mixture was further stirred at room temperature for 3 h. After confirming complete conversion of starting material, the resulting mixture was concentrated in vacuum and the crude product was purified

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by CombiFlash chromatography in SiO_2, using cyclohexane as eluent gave 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (376.4 mg, 74% yield) as a white solid.

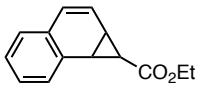
M.p. = 74–77 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 3H), 7.24 – 7.15 (m, 4H), 7.10 – 7.01 (m, 2H), 6.44 – 6.31 (m, 2H), 2.80 (dd, *J* = 7.9, 4.5 Hz, 1H), 2.39 (dtd, *J* = 7.9, 4.3, 1.0 Hz, 1H), 1.28 (t, *J* = 4.3 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 134.6, 130.8, 128.6, 128.4, 127.9, 127.9, 127.5, 126.3, 125.7, 125.4, 124.4, 32.5, 29.4, 26.9 ppm.

HRMS (APCI+): calc. for $C_{17}H_{15}$ $[M+H]^+$: 219.1168; found: 219.1172.

Ethyl 1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylate



A two-necked 250 mL round-bottomed flask with a magnetic stirring bar was charged with naphthalene (25.9 g, 202 mmol, 5 equiv) and $[Rh_2(TFA)_4]$ (60 mg, 0.101 mmol, 0.25 mol %), under Ar atmosphere. Both solids were dissolved in anhydrous CH_2Cl_2 (67 mL, 0.6 M), and the resulting dark green solution was degassed by bubbling Ar through over 15 min. After that, ethyl 2-diazoacetate (5 mL, 40.4 mmol, 1 equiv, 85% w/w commercial solution with CH_2Cl_2) was added by automatic syringe pump over 18 h (0.3 mL/h), while stirring at 25 °C. After stirring for one additional hour, the solvent was removed in vacuum, and the crude mixture was adsorbed into SiO_2, and then submitted to purification by CombiFlash column chromatography in SiO_2, eluting first with cyclohexane to remove excess naphthalene, and then with a slow gradient of cyclohexane/EtOAc from 95:5 to 85:15, giving ethyl 1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylate (4.5 g, 20.8 mmol, 52% yield) as a colorless oil. Alternatively, the purification can be carried out more rapidly, giving a 7:1 mixture (77% of combined yield, based on ethyl diazoacetate) of the desired product and the formal insertion products (naphthalenes), which can be used in the next steps as is, and purified in later step of the synthetic route.

Characterization data matched the reported ones for this product.[22]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 1H), 7.24 – 7.18 (m, 2H), 7.13 – 7.11 (m, 1H), 6.39 (d, *J* = 9.6 Hz, 1H), 6.29 (ddd, *J* = 9.6, 5.0, 0.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.07

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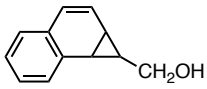
(dd, *J* = 8.3, 4.0 Hz, 1H), 2.66 – 2.59 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 3.9 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 133.0, 131.1, 129.1, 128.3, 128.0, 127.1, 126.3, 126.3, 61.3, 30.8, 27.9, 23.2, 14.7 ppm.

HRMS (ESI+): calculated for $C_{14}H_{15}O_2$ $[M+H]^+$: 215.1067; found: 215.1069.

1a,7b-Dihydro-1*H*-cyclopropa[*a*]naphthalen-1-yl)methanol



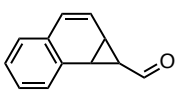
A two-necked 250 mL round-bottomed flask with a magnetic stirring bar was charged under Ar, with $LiAlH_4$ (1.08 g, 28.4 mmol, 1.5 equiv), and it was suspended in anhydrous THF (50 mL, 0.12 M). After cooling down the suspension to 0 °C in an ice-water bath, a solution of ethyl 1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylate (4.05 g, 18.9 mmol, 1 equiv) in 6 mL of anhydrous THF was added dropwise over 5 min, and then the cooling bath was removed. The resulting suspension was stirred for 14 h while coming to room temperature, when no starting material was observed by TLC. The reaction was cooled down again to 0 °C in an ice-water bath, and was quenched by careful addition of water, and then aqueous (10%) HCl. The aqueous phase was extracted twice with Et_2O, and the combined organic fractions were washed with water once, with brine once, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Fast filtration through SiO_2 washing with EtOAc gave (1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalen-1-yl)methanol (*ca.* quantitative yield, 3.3 g) as a colorless oil, used on the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.16 (dtd, *J* = 18.2, 7.3, 1.5 Hz, 2H), 7.08 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.29 – 6.23 (m, 2H), 3.82 (dt, *J* = 11.7, 6.0 Hz, 1H), 3.70 (ddd, *J* = 11.6, 7.0, 5.1 Hz, 1H), 2.35 (dd, *J* = 7.9, 4.4 Hz, 1H), 1.93 (dtd, *J* = 8.0, 4.0, 1.6 Hz, 1H), 0.42 (tt, *J* = 6.8, 4.2 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3, 131.1, 128.3, 128.0, 127.6, 127.6, 126.3, 124.5, 66.5, 25.9, 24.4, 23.1 ppm.

HRMS (APCI+): calculated for $C_{12}H_{11}$ $[M-OH]^+$: 155.0855; found: 155.0852.

1a,7b-Dihydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (31)



A 500 mL round-bottomed flask was charged under air with a solution of crude (1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalen-1-yl)methanol (3.3 g, 17 mmol, 1 equiv) in HPLC-grade CH_2Cl_2 (140 mL, 0.12 M). After cooling this solution to 0 °C in an ice-water bath, was added pyridinium chlorochromate (7.34 g, 34 mmol, 2 equiv) in a single portion, and the resulting brown mixture was stirred while coming to room temperature

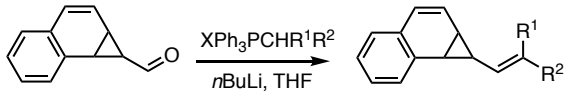
for 14 h, when no starting material was observed by TLC. The mixture was filtered through Celite, concentrated in vacuum and then purified by CombiFlash chromatography in SiO_2 (95:5 to 9:1 cyclohexane/EtOAc gradient) to give 1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (**31**) (1.6 g, 9.4 mmol, 38% overall yield over 3 steps) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (d, *J* = 3.3 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.29 – 7.26 (m, 2H), 7.22 – 7.18 (m, 1H), 6.50 (d, *J* = 9.6 Hz, 1H), 6.35 (ddd, *J* = 9.5, 5.1, 0.8 Hz, 1H), 3.29 (ddd, *J* = 8.4, 3.8, 0.7 Hz, 1H), 2.87 (dddd, *J* = 8.5, 5.1, 3.6, 0.6 Hz, 1H), 1.20 (q, *J* = 3.6 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 132.3, 130.9, 128.6, 128.2, 127.9, 127.1, 126.6, 125.8, 32.7, 31.2, 29.8 ppm.

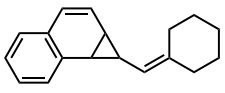
HRMS (APCI+): calculated for $C_{12}H_{11}O$ $[M+H]^+$: 171.0804; found: 171.0806.

Wittig reaction of aldehyde (31) to give vinyl cyclopropanes (32a–d)



An alkyl phosphonium halide (1.3 equiv) was dried in high vacuum at 60 °C for 4 h and, after cooling, it was suspended in anhydrous THF (0.2 M) under Ar. The suspension was cooled down to 0 °C in an ice-water bath, and to this mixture was added dropwise a commercial solution of *n*BuLi (2.5 M in hexanes, 1.4 equiv). After the addition, the mixture was stirred in the ice-water bath for 30 min, before 1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (**31**) (1 equiv) was added as a solution in anhydrous THF (*ca.* 1 M). The mixture was stirred while coming to room temperature for 16–20 h. The reaction was quenched by the addition of aqueous NH_4Cl, and the aqueous phase was extracted twice with Et_2O. Combined organic fractions were washed with water once, with brine once, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The products were purified by flash chromatography in SiO_2 or preparative TLC using pentane or cyclohexane as eluent.

1-(Cyclohexylidenemethyl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (32a)



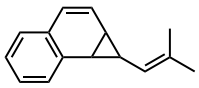
The title compound (colorless oil, 136 mg, 65% yield) was prepared by Wittig reaction of aldehyde **31** (150 mg, 0.88 mmol, 1 equiv) using cyclohexyltriphenylphosphonium bromide (487 mg, 1.15 mmol, 1.3 equiv) after purification by CombiFlash chromatography in SiO_2 using cyclohexane as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.14 (dtd, *J* = 17.9, 7.3, 1.5 Hz, 2H), 7.06 (dd, *J* = 7.3, 1.6 Hz, 1H), 6.27 (dd, *J* = 9.6, 4.9 Hz, 1H), 6.21 (d, *J* = 9.6 Hz, 1H), 4.73 (dd, *J* = 9.1, 1.3 Hz, 1H), 2.34 (dd, *J* = 7.7, 4.3 Hz, 1H), 2.15 – 2.08 (m, 4H), 1.91 (dt, *J* = 8.1, 4.4 Hz, 1H), 1.53 (dd, *J* = 6.7, 3.5 Hz, 4H), 1.50 – 1.46 (m, 2H), 0.88 (ddd, *J* = 9.3, 4.9, 3.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 134.9, 131.2, 128.4, 128.3, 127.8, 127.5, 126.1, 124.1, 122.9, 37.4, 30.0, 29.6, 28.9, 27.9, 27.2, 26.9, 21.9 ppm.

HRMS (APCI+): calculated for $C_{18}H_{21}$ $[M+H]^+$: 237.1638; found: 237.1635.

1-(2-Methylprop-1-en-1-yl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (32b)



The title compound (colorless oil, 97 mg, 84% yield) was prepared by Wittig reaction of aldehyde **31** (100 mg, 0.59 mmol, 1 equiv) using isopropyltriphenylphosphonium iodide (330 mg, 0.76 mmol, 1.3 equiv) after purification by CombiFlash chromatography in SiO_2 using cyclohexane as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.14 (dtd, *J* = 16.5, 7.3, 1.6 Hz, 2H), 7.06 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.29 – 6.20 (m, 2H), 4.80 (dp, *J* = 9.1, 1.4 Hz, 1H), 2.36 (dd, *J* = 7.7, 4.4 Hz, 1H), 1.92 (dddd, *J* = 7.6, 4.7, 3.8, 0.7 Hz, 1H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.64 (d, *J* = 1.3 Hz, 3H), 0.85 (dt, *J* = 9.0, 4.1 Hz, 1H) ppm.

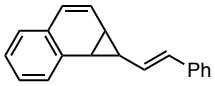
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9, 133.1, 131.2, 128.4, 128.2, 127.8, 127.5, 126.1, 126.1, 124.1, 29.8, 26.7, 26.2, 22.7, 18.7 ppm.

HRMS (APCI+): calculated for $C_{15}H_{17}$ $[M+H]^+$: 197.1325; found: 197.1320.

1-(Styryl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene, *E* (32c) and *Z* (32d)

The title compounds (white viscous oils, 196 mg, 68% yield, *E*/*Z* 2:1) were prepared by Wittig reaction of aldehyde **31** (200 mg, 1.17 mmol, 1 equiv) using benzyltriphenylphosphonium chloride (548 mg, 1.41 mmol, 1.2 equiv) after purification by CombiFlash chromatography in SiO_2 using cyclohexane as eluent. Preparative TLC in SiO_2 using pentane as eluent allowed isolating each diastereoisomer separately (**32c** = *E*, bottom fraction, **32d** = *Z*, top fraction).

1-((*E*)-Styryl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (32c)

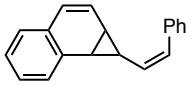


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.1, 1.7 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.21 – 7.15 (m, 3H), 7.10 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.32 – 6.28 (m, 2H), 5.99 (dd, *J* = 15.7, 9.1 Hz, 1H), 2.61 (dd, *J* = 7.9, 4.3 Hz, 1H), 2.20 (dtd, *J* = 7.0, 3.7, 2.4 Hz, 1H), 0.98 (dt, *J* = 9.3, 4.0 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 134.2, 132.5, 131.1, 129.1, 128.9, 128.4, 128.0, 127.7, 127.5, 127.1, 126.4, 126.0, 124.7, 31.2, 27.4, 26.8 ppm.

HRMS (APCI+): calculated for $C_{19}H_{17}$ $[M+H]^+$: 245.1325; found: 245.1321.

1-((*Z*)-Styryl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (32d)

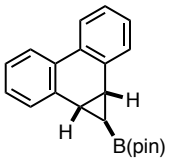


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.25 – 7.21 (m, 2H), 7.18 (td, *J* = 7.4, 1.6 Hz, 1H), 7.14 (td, *J* = 7.3, 1.6 Hz, 2H), 7.07 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.47 (d, *J* = 11.4 Hz, 1H), 6.37 – 6.23 (m, 2H), 5.37 (dd, *J* = 11.5, 9.6 Hz, 1H), 2.56 (dd, *J* = 7.8, 4.3 Hz, 1H), 2.15 – 2.11 (m, 1H), 1.21 (dtd, *J* = 9.5, 4.1, 1.1 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7, 134.1, 134.1, 131.1, 129.5, 128.9, 128.5, 128.5, 128.0, 127.6, 127.2, 126.9, 126.4, 124.9, 31.1, 27.9, 23.7 ppm.

HRMS (APCI+): calculated for $C_{19}H_{17}$ $[M+H]^+$: 245.1325; found: 245.1321.

2-(1a,9b-Dihydro-1*H*-cyclopropa[*l*]phenanthren-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34)



A two-necked 500 mL round-bottomed flask with a magnetic stirring bar was charged under Ar, with 1-bromo-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (**22**)[23] (4.0 g, 14.8 mmol, 1 equiv), and it was suspended in anhydrous THF (180 mL, 0.08 M). After cooling down the suspension to -78 °C, *n*BuLi (8.85 mL, 2.5 M in hexanes, 22.1 mmol, 1.5 equiv) was slowly added and the reaction was stirred for 1 h. Then, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.5 mL, 22.1 mmol, 1.5 equiv) was added at -78 °C. The reaction was stirred for 2 h while warming to room temperature. The reaction was quenched by the addition of a saturated solution of ammonium chloride. The aqueous phase was extracted twice with diethyl ether, and the combined organic fractions were washed with brine once, dried over anhydrous Na_2SO_4 and concentrated in vacuum, giving a pale-yellow solid. The product was purified by trituration and washing with MeOH (3 x 10 mL), which was then removed by filtration to give pure 2-(1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthren-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**34**) (3.7 g, 14.75 mmol, 79% yield) as a white solid.

M.p. = 163–168 °C.

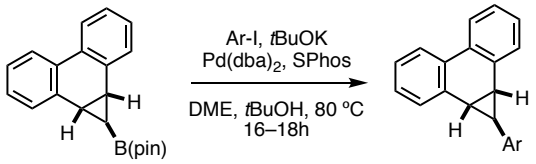
23 Nguyen, J. M.; Thamattoor, D. M. *Synthesis*, **2007**, *14*, 2093–2094.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 2H), 7.46 – 7.42 (m, 2H), 7.28 – 7.18 (m, 4H), 2.77 (d, *J* = 5.3 Hz, 2H), 1.27 (s, 12H), -0.59 (t, *J* = 5.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 129.5, 129.3, 127.6, 126.2, 123.3, 83.5, 26.2, 24.9 ppm.

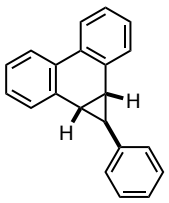
HRMS (APCI+): calculated for $C_{21}H_{24}BO_2$ $[M+H]^+$: 318.1900; found: 318.1903.

Suzuki coupling for the synthesis of aryl cyclopropyl dihydrophenanthrenes



This procedure was adapted from a previously reported one.[24] A microwave vial was charged with $Pd(dba)_2$ (5 mol %), 2-di-cyclohexylphosphino-2',6'-dimethoxybiphenyl (10 mol %), boronic ester (**34**) (1 equiv), and an aryl iodide (3 equiv). The vial was introduced in an Ar-filled glovebox and *t*BuOK (4 equiv) was added. The vial was sealed with its cap, and taken out of the glovebox before DME and *t*BuOH (0.06 M, DME/*t*BuOH 3:1) were added through the septum of the cap. The mixture was stirred at 80 °C for 16–18 h. After cooling, the reaction mixture was diluted with water, and extracted three times with EtOAc. The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography in SiO_2.

1-Phenyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (23a)



The title compound (white solid, 161 mg, 63% yield) was prepared by palladium-catalyzed Suzuki-Miyaura cross-coupling of boronic ester (**34**) (300 mg, 0.94 mmol, 1.0 equiv) with iodobenzene (577 mg, 2.83 mmol, 3 equiv), after purification by CombiFlash chromatography in SiO_2 using cyclohexane as eluent.

M.p. = 132–134 °C.

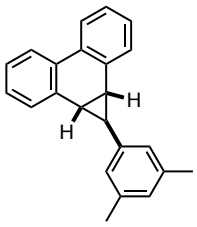
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.42 (dd, *J* = 7.3, 1.7 Hz, 2H), 7.34 – 7.23 (m, 6H), 7.22 – 7.18 (m, 1H), 7.10 – 7.06 (m, 2H), 2.92 (d, *J* = 4.3 Hz, 2H), 1.40 (t, *J* = 4.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 135.3, 129.7, 129.6, 128.9, 128.2, 126.8, 126.0, 125.7, 123.6, 31.7, 30.8 ppm.

24 Murai, M.; Mizuta, C.; Taniguchi, R.; Takai, K. *Org. Lett.,* **2017**, *19*, 6104–6107.

HRMS (APCI+): calculated for $C_{21}H_{17}$ $[M+H]^+$: 269.1325; found: 269.1318.

1-(3,5-Dimethylphenyl)-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (23b)



The title compound (white solid, 144 mg, 52% yield) was prepared by palladium-catalyzed Suzuki-Miyaura cross-coupling of boronic ester (**34**) (300 mg, 0.94 mmol, 1 equiv) using 1-iodo-3,5-dimethylbenzene (656 mg, 2.83 mmol, 3 equiv) after purification by CombiFlash chromatography in SiO_2 using cyclohexane as eluent.

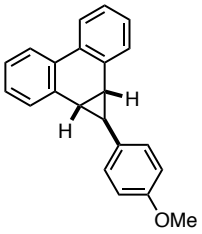
M.p. = 126–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.43 (dd, *J* = 7.4, 1.7 Hz, 2H), 7.34 – 7.23 (m, 4H), 6.87 (s, 1H), 6.72 (s, 1H), 2.92 (d, *J* = 4.3 Hz, 2H), 2.33 (s, 6H), 1.36 (t, *J* = 4.3 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 138.2, 135.3, 129.5, 129.4, 127.9, 127.6, 126.6, 123.4, 123.3, 31.4, 30.6, 21.5 ppm.

HRMS (APCI+): calculated for $C_{23}H_{21}$ $[M+H]^+$: 297.1638; found: 297.1634.

1-(4-Methoxyphenyl)-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (23c)



The title compound (white solid, 174 mg, 62% yield) was prepared by palladium-catalyzed Suzuki-Miyaura cross-coupling of boronic ester (**34**) (300 mg, 0.94 mmol, 1 equiv) using 4-iodoanisole (662 mg, 2.83 mmol, 3 equiv) after purification by CombiFlash chromatography in SiO_2 using cyclohexane/EtOAc 97:3 as eluent.

M.p. = 145–147 °C.

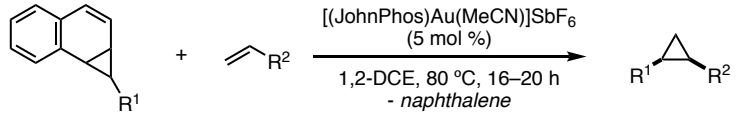
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.43 (dd, *J* = 7.4, 1.6 Hz, 2H), 7.32 – 7.24 (m, 4H), 7.06 – 7.01 (m, 2H), 6.90 – 6.86 (m, 2H), 3.82 (s, 3H), 2.85 (d, *J* = 4.3 Hz, 2H), 1.38 (t, *J* = 4.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 135.3, 134.0, 129.5, 129.4, 127.9, 126.5, 126.5, 123.4, 114.2, 55.5, 30.9, 29.9 ppm.

HRMS (APCI+): calculated for $C_{22}H_{19}O$ $[M+H]^+$: 299.1430; found: 299.1424.

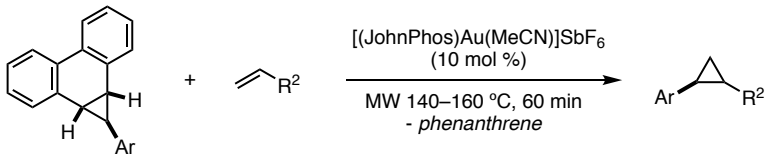
General procedures for the Au(I)-catalyzed cyclopropanation through release of polyaromatics

General Procedure A:



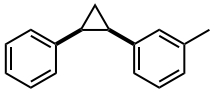
A microwave vial equipped with a Teflon-coated magnetic stirring bar was charged, under air, with the corresponding cyclopropyl dihydronaphthalene (**27** or **32**) (or with alkyne **26** for the one-pot hydroarylation/decarbenation/cyclopropanation sequence) and the corresponding alkene (6 equiv). Both reagents were dissolved in HPLC-grade 1,2-DCE (0.15 M), before [(JohnPhos)Au(MeCN)]SbF_6 (5 mol %) was added. The vial was closed with the cap and then stirred at 80 °C for 16–20 hours, until complete consumption of the starting material, which was confirmed by TLC and GC-MS. The resulting mixture was concentrated in vacuum and the crude product was purified by flash column chromatography or preparative TLC on SiO_2. The configuration of the products was assigned by direct comparison or analogy with reported substrates, based on X-ray or NOE analysis.[6a]

General Procedure B:



A microwave vial equipped with a Teflon-coated magnetic stirring bar was charged, under air, with the corresponding aryl cyclopropyl dihydrophenanthrene (**23**) and the corresponding alkene (2 equiv). Both reagents were dissolved in HPLC-grade 1,2-DCE (0.15 M), before [(JohnPhos)Au(MeCN)]SbF_6 (10 mol %) was added. The vial was closed with the cap and then stirred at 140–160 °C for 60 min in a microwave reactor. The resulting mixture was concentrated in vacuum and the crude product was purified by flash column chromatography or preparative TLC on SiO_2. The configuration of the products was assigned by direct comparison or analogy with reported substrates, based on X-ray, ^{1}H NMR, or NOE analysis.[6a]

(*cis*)-1-Methyl-3-(2-phenylcyclopropyl)benzene (29a)



The title compound (colorless oil, 15 mg, 68% yield, 5:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and 1-methyl-3-vinylbenzene (75 mg,

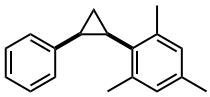
0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.04 (m, 3H), 7.00 – 6.94 (m, 3H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.81 (s, 1H), 6.75 – 6.67 (m, 1H), 2.47 (m, 2H), 2.20 (s, 3H), 1.46 (td, *J* = 8.6, 5.3 Hz, 1H), 1.36 (td, *J* = 6.3, 5.3 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 138.4, 137.2, 130.0, 129.1, 127.7, 127.6, 126.5, 125.9, 125.7, 24.4, 24.4, 21.5, 11.6 ppm.

HRMS (APCI+): calculated for $C_{16}H_{17}$ $[M+H]^+$: 209.1325; found: 209.1319.

(*cis*)-1,3,5-Trimethyl-2-(2-phenylcyclopropyl)benzene (29b)



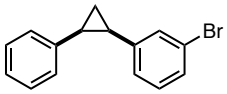
The title compound (colorless oil, 14 mg, 55% yield, 6:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and 1,3,5-trimethyl-2-vinylbenzene (92 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 – 6.99 (m, 3H), 6.72 (s, 2H), 6.67 – 6.62 (m, 2H), 2.41 – 2.34 (m, 2H), 2.34 – 2.25 (m, 2H), 2.25 – 2.11 (m, 9H), 1.74 (td, *J* = 8.9, 5.4 Hz, 1H), 1.14 (dt, *J* = 7.6, 5.6 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 135.7, 130.9, 128.9, 127.5, 126.5, 125.1, 23.6, 23.1, 20.9, 20.8, 17.9 ppm.

HRMS (APCI+): calculated for $C_{18}H_{21}$ $[M+H]^+$: 237.1638; found: 237.1633.

(*cis*)-1-Bromo-3-(2-phenylcyclopropyl)benzene (29c)



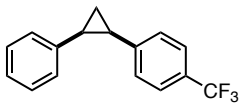
The title compound (colorless oil, 18 mg, 63% yield, 11:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and 1-bromo-3-vinylbenzene (116 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent. Alternatively, the same compound (60% yield, 6:1 *dr*) could be obtained following General Procedure **B** starting from phenanthrene derivative **23a**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.09 (m, 4H), 7.10 – 7.06 (m, 1H), 6.98 – 6.94 (m, 2H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.81 – 6.76 (m, 1H), 2.52 (td, *J* = 8.9, 6.4 Hz, 1H), 2.43 (td, *J* = 8.9, 6.2 Hz, 1H), 1.48 (td, *J* = 8.7, 5.6 Hz, 1H), 1.37 (q, *J* = 6.1 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 137.8, 132.2, 129.2, 129.2, 128.8, 127.9, 127.5, 126.0, 121.9, 24.8, 23.9, 11.5 ppm.

HRMS (APCI+): calculated for $C_{15}H_{14}Br$ $[M+H]^+$: 273.0273; found: 273.0263.

(*cis*)-1-(2-Phenylcyclopropyl)-4-(trifluoromethyl)benzene (29d)



The title compound (colorless oil, 14 mg, 51% yield, 10:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and 1-(trifluoromethyl)-4-vinylbenzene (109 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

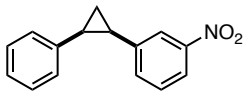
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.1 Hz, 2H), 7.16 – 7.04 (m, 3H), 7.02 – 6.93 (m, 4H), 2.59 (td, *J* = 8.9, 6.4 Hz, 1H), 2.50 (td, *J* = 8.9, 6.2 Hz, 1H), 1.58 – 1.52 (m, 1H), 1.42 (td, *J* = 6.4, 5.5 Hz, 1H) ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.39 ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1 (q, *J* = 1.2 Hz), 137.5, 129.3, 128.9, 128.0, 127.7, 126.1, 125.5, 124.6 (q, *J* = 3.8 Hz), 123.4, 121.2, 77.4, 25.1, 24.0, 11.9 ppm.

HRMS (APCI+): calculated for $C_{16}H_{14}F_3$ $[M+H]^+$: 263.1042; found: 263.1033.

(*cis*)-1-Nitro-3-(2-phenylcyclopropyl)benzene (29e)



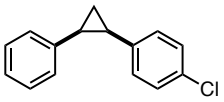
The title compound (viscous white oil, 11 mg, 41% yield, 8:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and 1-nitro-3-vinylbenzene (94 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane/Et_2O 97:3 as eluent. Alternatively, the same compound (52% yield, 7:1 *dr*) could be obtained following General Procedure **B** starting from phenanthrene derivative **23a**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dt, *J* = 7.6, 2.0 Hz, 1H), 7.84 – 7.78 (m, 1H), 7.25 – 7.15 (m, 2H), 7.14 – 7.09 (m, 2H), 7.08 – 7.03 (m, 1H), 6.99 – 6.93 (m, 2H), 2.63 (td, *J* = 8.9, 6.4 Hz, 1H), 2.55 (td, *J* = 8.9, 6.2 Hz, 1H), 1.61 – 1.55 (m, 1H), 1.50 (q, *J* = 6.2 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 137.0, 134.9, 129.3, 128.5, 128.2, 126.4, 123.7, 120.9, 25.2, 23.8, 11.5 ppm.

HRMS (APCI+): calculated for $C_{15}H_{12}NO_2$ $[M–H]^+$: 238.0863; found: 238.0857.

(*cis*)-1-Chloro-4-(2-phenylcyclopropyl)benzene (29f)



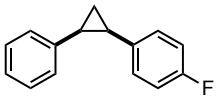
The title compound (colorless oil, 16 mg, 66% yield, 11:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and 1-chloro-4-vinylbenzene (88 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent. Alternatively, the title compound (colorless oil, 12 mg, 57% yield, 12:1 *dr*) can be obtained in a one-pot procedure from (3-ethynylcyclopropane-1,2-diyl)dibenzene (**26**) (20 mg, 0.092 mmol) and 1-chloro-4-vinylbenzene (76 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (3.5 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.10 (m, 2H), 7.09 – 7.03 (m, 3H), 6.98 – 6.90 (m, 2H), 6.90 – 6.82 (m, 2H), 2.50 (td, *J* = 8.9, 6.3 Hz, 1H), 2.43 (td, *J* = 8.9, 6.3 Hz, 1H), 1.48 (td, *J* = 8.6, 5.5 Hz, 1H), 1.34 (td, *J* = 6.3, 5.5 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 137.1, 130.3, 129.1, 127.9, 127.9, 125.9, 24.6, 23.8, 11.5 ppm.

HRMS (APCI+): calculated for $C_{15}H_{14}Cl$ $[M+H]^+$: 229.0760; found: 229.0768.

(*cis*)-1-Fluoro-4-(2-phenylcyclopropyl)benzene (29g)



The title compound (colorless oil, 17 mg, 76% yield, 12:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and 1-fluoro-4-vinylbenzene (77 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent. Alternatively, the title compound (colorless oil, 12 mg, 62% yield, 12:1 *dr*) can be obtained in a one-pot procedure from (3-ethynylcyclopropane-1,2-diyl)dibenzene (**26**) (20 mg, 0.092 mmol) and 1-fluoro-4-vinylbenzene (67 mg, 0.55 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (3.5 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

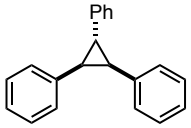
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.02 (m, 3H), 6.95 – 6.86 (m, 4H), 6.83 – 6.74 (m, 2H), 2.46 (m, 2H), 1.47 (td, *J* = 8.6, 5.5 Hz, 1H), 1.33 (td, *J* = 6.2, 5.4 Hz, 1H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.70 ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, *J* = 243.5 Hz), 138.1, 133.9 (d, *J* = 3.0 Hz), 130.4 (d, *J* = 7.9 Hz), 128.8, 127.7, 125.6, 114.4 (d, *J* = 21.3 Hz), 24.0, 23.6, 11.4 ppm.

HRMS (APCI+): calculated for $C_{15}H_{14}F$ $[M+H]^+$: 213.1074; found: 213.1069.

(*exo*)-1,2,3-Triphenylcyclopropane (29h)

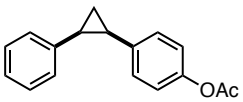


The title compound (colorless oil, 20 mg, together with a 20% of product of phenyl cyclopropanation of **27**, 80% corrected yield) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (23 mg, 0.105 mmol) and (*E*)-1,2-diphenylethene (114 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by CombiFlash chromatography in SiO_2 using cyclohexane as eluent. Alternatively, the title compound (colorless oil, 17 mg, together with a 20% of product of phenyl cyclopropanation of **27**, 71% corrected yield) can be obtained in a one-pot procedure from (3-ethynylcyclopropane-1,2-diyl)dibenzene (**26**) (20 mg, 0.092 mmol) and (*E*)-1,2-diphenylethene (99 mg, 0.55 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (3.5 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 4H), 7.31 – 7.27 (m, 1H), 7.22 – 7.12 (m, 6H), 7.10 – 7.04 (m, 4H), 2.94 – 2.86 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 137.7, 129.0, 128.6, 127.9, 126.5, 126.1, 126.0, 34.5, 30.7 ppm.

(*cis*)-4-(2-Phenylcyclopropyl)phenyl acetate (29i)



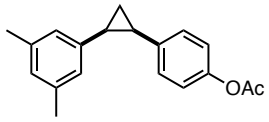
The title compound (viscous colorless oil, 21 mg, 54% yield, 10:1 *dr*) was obtained following General Procedure **A** from 1-phenyl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**27**) (32.7 mg, 0.150 mmol) and 4-vinylphenyl acetate (73 mg, 0.45 mmol, 3 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane/Et_2O 9:1 as eluent. Alternatively, the same compound (36%, 1:1 *dr*) could be obtained following General Procedure **B** starting from phenanthrene derivative **23a**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.07 (m, 3H), 6.99 – 6.94 (m, 4H), 6.88 – 6.82 (m, 2H), 2.50 (m, 2H), 2.25 (s, 3H), 1.51 (td, *J* = 8.6, 5.4 Hz, 1H), 1.40 – 1.33 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 148.6, 138.1, 136.0, 129.9, 128.9, 127.7, 125.7, 120.7, 24.2, 23.8, 21.1, 11.7 ppm.

HRMS (ESI+): calculated for $C_{17}H_{16}NaO_2$ $[M+Na]^+$: 275.1043; found: 275.1056.

(*cis*)-4-(2-(3,5-Dimethylphenyl)cyclopropyl)phenyl acetate (29j)



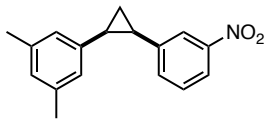
The title compound (viscous colorless oil, 14 mg, 59% yield, 3:1 *dr*) was obtained following General Procedure **B** from 1-(3,5-dimethylphenyl)-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (**23b**) (25 mg, 0.084 mmol) and 4-vinylphenyl acetate (27 mg, 0.17 mmol, 2 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (6.5 mg, 10 mol %) after purification by preparative TLC on SiO_2 using pentane/Et_2O 97:3 as eluent.

^{1}H NMR (500 MHz, $CDCl_3$, *cis* isomer) δ 6.95 – 6.92 (m, 2H), 6.83 – 6.80 (m, 2H), 6.67 (s, 1H), 6.51 (d, *J* = 0.9 Hz, 2H), 2.43 – 2.35 (m, 2H), 2.22 (s, 3H), 2.13 (d, *J* = 0.7 Hz, 6H), 1.44 – 1.41 (m, 1H), 1.28 – 1.25 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$, 3:1 *cis*/*trans*, unassigned) δ 169.8, 148.9, 138.4, 137.4, 136.7, 130.3, 127.7, 127.1, 123.9, 121.7, 120.9, 24.4, 24.0, 21.6, 21.5, 21.5, 12.2 ppm.

HRMS (APCI+): calculated for $C_{19}H_{21}O_2$ $[M+H]^+$: 281.1536; found: 281.1536.

(*cis*)-1,3-Dimethyl-5-(2-(3-nitrophenyl)cyclopropyl)benzene (29k)



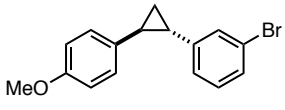
The title compound (colorless oil, 15 mg, 55% yield, 12:1 *dr*) was obtained following General Procedure **B** from 1-(3,5-dimethylphenyl)-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (**23b**) (30 mg, 0.101 mmol) and 1-nitro-3-vinylbenzene (30 mg, 0.20 mmol, 2 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (7.8 mg, 10 mol %) after purification by preparative TLC on SiO_2 using pentane/Et_2O 97:3 as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dt, *J* = 7.3, 2.1 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.26 – 7.17 (m, 2H), 6.69 (s, 1H), 6.59 (s, 2H), 2.53 (m, 2H), 2.14 (s, 6H), 1.53 (td, *J* = 8.6, 5.7 Hz, 1H), 1.46 (q, *J* = 6.2 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 137.5, 136.7, 134.9, 128.4, 128.0, 127.1, 123.6, 120.7, 25.2, 23.8, 21.3, 11.6 ppm.

HRMS (APCI+): calculated for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1176; found: 266.1173.

(*trans*)-1-Bromo-3-(2-(4-methoxyphenyl)cyclopropyl)benzene (29l)



The title compound (colorless oil, 29 mg, 94% yield, 15:1 *dr*) was obtained following General Procedure **B** from 1-(4-methoxyphenyl)-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (**23c**) (30 mg, 0.101 mmol) and 1-bromo-3-vinylbenzene (37 mg, 0.20 mmol, 2 equiv) using

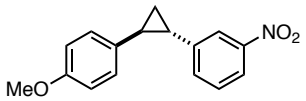
[(JohnPhos)Au(MeCN)]SbF_6 (7.8 mg, 10 mol %) after purification by preparative TLC on SiO_2 using pentane/Et_2O 98:2 as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.27 (t, *J* = 1.9 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.10 – 7.04 (m, 3H), 6.89 – 6.82 (m, 2H), 3.80 (s, 3H), 2.13 (ddd, *J* = 8.8, 6.1, 4.5 Hz, 1H), 2.05 (ddd, *J* = 8.6, 5.9, 4.5 Hz, 1H), 1.40 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 145.4, 134.1, 130.0, 128.9, 128.8, 127.1, 124.7, 122.7, 114.1, 55.5, 27.7, 27.2, 17.9 ppm.

HRMS (APCI+): calculated for $C_{16}H_{16}{}^{79}BrO$ $[M+H]^+$: 303.0379; found: 303.0366.

(*trans*)-1-(2-(4-Methoxyphenyl)cyclopropyl)-3-nitrobenzene (29m)



The title compound (pale yellow solid, 21 mg, 87% yield, 10:1 *dr*) was obtained following General Procedure **B** from 1-(4-methoxyphenyl)-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (**23c**) (30 mg, 0.089 mmol) and 1-nitro-3-vinylbenzene (27 mg, 0.18 mmol, 2 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (6.9 mg, 10 mol %) after purification by CombiFlash chromatography on SiO_2 using a cyclohexane/EtOAc gradient from 99:1 to 9:1.

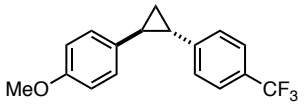
M.p. = 92–94 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (ddd, *J* = 7.6, 2.3, 1.5 Hz, 1H), 7.96 (t, *J* = 2.0 Hz, 1H), 7.51 – 7.38 (m, 2H), 7.13 – 7.05 (m, 2H), 6.89 – 6.82 (m, 2H), 3.80 (s, 3H), 2.20 (m, 2H), 1.49 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 148.7, 145.2, 133.5, 132.3, 129.3, 127.1, 120.8, 120.4, 114.1, 55.5, 28.2, 27.1, 18.4 ppm.

HRMS (APCI+): calculated for $C_{16}H_{15}NO_3$ $[M]^+$: 269.1046; found: 269.1052.

(*trans*)-1-Methoxy-4-(2-(4-(trifluoromethyl)phenyl)cyclopropyl)benzene (29n)



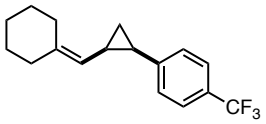
The title compound (colorless oil, 21 mg, 88% yield, 14:1 *dr*) was obtained following General Procedure **B** from 1-(4-methoxyphenyl)-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (**23c**) (24 mg, 0.080 mmol) and 1-(trifluoromethyl)-4-vinylbenzene (28 mg, 0.16 mmol, 2 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (6.2 mg, 10 mol %) after purification by preparative TLC on SiO_2 using pentane/diethyl ether 97:3 as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.27 – 7.16 (m, 2H), 7.12 – 7.06 (m, 2H), 6.89 – 6.83 (m, 2H), 3.80 (s, 3H), 2.16 (m, 2H), 1.46 (m, 2H) ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.33 ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 147.4, 134.10, 128.2 (q, *J* = 32.9 Hz), 127.3, 126.2, 125.7 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 271.3 Hz), 114.3, 55.7, 28.4, 27.7, 18.6 ppm.

(*cis*)-1-(2-(Cyclohexylidenemethyl)cyclopropyl)-4-(trifluoromethyl)benzene (33a)



The title compound (colorless oil, 16 mg, 54% yield, 5:1 *dr*) was obtained following General Procedure **A** from 1-(cyclohexylidenemethyl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]-naphthalene (**32a**) (25 mg, 0.106 mmol) and 1-(trifluoromethyl)-4-vinylbenzene (109 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

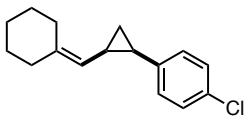
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H), 7.28 – 7.24 (m, 2H), 4.45 (dt, *J* = 8.1, 1.2 Hz, 1H), 2.33 – 2.26 (m, 1H), 2.22 (m, 2H), 2.03 – 1.97 (m, 1H), 1.94 (m, 2H), 1.53 – 1.29 (m, 7H), 0.94 – 0.91 (m, 1H) ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.30 ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 129.1, 125.7, 124.7, 124.7, 124.6, 124.6, 123.2, 118.9, 36.8, 29.3, 28.5, 27.6, 26.7, 22.9, 17.9, 13.3 ppm.

HRMS (APCI+): calculated for $C_{17}H_{20}F_3$ $[M+H]^+$: 281.1512; found: 281.1504.

(*cis*)-1-(2-(Cyclohexylidenemethyl)cyclopropyl)-4-chlorobenzene (33b)



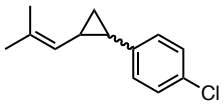
The title compound (colorless oil, 19 mg, 73% yield, 2:1 *dr*) was obtained following General Procedure **A** from 1-(cyclohexylidenemethyl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]-naphthalene (**32a**) (25 mg, 0.106 mmol) and 1-chloro-4-vinylbenzene (88 mg, 0.64 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.1 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 2H), 7.13 – 7.07 (m, 2H), 4.41 (dt, *J* = 8.4, 1.2 Hz, 1H), 2.26 – 2.19 (m, 3H), 1.96 – 1.90 (m, 3H), 1.58 – 1.51 (m, 4H), 1.43 – 1.36 (m, 1H), 1.31 – 1.25 (m, 2H), 0.83 (td, *J* = 6.0, 5.0 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 138.1, 130.3, 127.9, 123.5, 119.4, 36.9, 29.3, 28.6, 27.7, 26.8, 22.3, 17.4, 12.9 ppm.

HRMS (APCI+): calculated for $C_{16}H_{20}Cl$ $[M+H]^+$: 247.1248; found: 247.1243.

1-Chloro-4-(2-(2-methylprop-1-en-1-yl)cyclopropyl)benzene (33c)



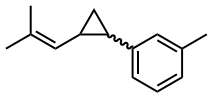
The title compound (colorless oil, 15 mg, 65% yield, 1:1 *dr*) was obtained following General Procedure **A** from 1-(2-methylprop-1-en-1-yl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**32b**) (22 mg, 0.112 mmol) and 1-chloro-4-vinylbenzene (93 mg, 0.67 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.3 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (500 MHz, $CDCl_3$, *cis*/*trans* 1:1 mixture, unassigned) δ 7.23 – 7.18 (m, 4H), 7.09 – 7.05 (m, 2H), 7.01 – 6.95 (m, 2H), 4.71 (dp, *J* = 8.8, 1.4 Hz, 1H), 4.42 (dp, *J* = 8.7, 1.4 Hz, 1H), 2.20 (td, *J* = 8.6, 6.2 Hz, 1H), 1.87 (td, *J* = 8.7, 5.7 Hz, 1H), 1.80 – 1.75 (m, 1H), 1.69 (d, *J* = 1.4 Hz, 6H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.67 – 1.62 (m, 1H), 1.55 (d, *J* = 1.4 Hz, 3H), 1.23 – 1.21 (m, 1H), 1.12 (dt, *J* = 8.6, 5.2 Hz, 1H), 0.96 (ddd, *J* = 8.5, 5.7, 4.9 Hz, 1H), 0.79 (td, *J* = 6.0, 5.0 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$, *cis*/*trans* 1:1 mixture, unassigned) δ 141.9, 138.4, 130.6, 128.7, 128.3, 127.3, 127.2, 123.0, 25.9, 25.8, 24.7, 23.7, 22.6, 18.8, 18.7, 18.6, 17.5, 12.9 ppm.

HRMS (APCI+): calculated for $C_{13}H_{16}Cl$ $[M+H]^+$: 207.0935; found: 207.0937.

(*cis*)-1-Methyl-3-(2-(2-methylprop-1-en-1-yl)cyclopropyl)benzene (33d)



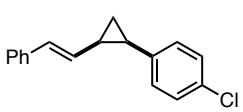
The title compound (colorless oil, 12 mg, 58% yield, 1:1 *dr*) was obtained following General Procedure **A** from 1-(2-methylprop-1-en-1-yl)-1a,7b-dihydro-1*H*-cyclopropa[*a*]-naphthalene (**32b**) (22 mg, 0.112 mmol) and 1-methyl-3-vinylbenzene (79 mg, 0.67 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (4.3 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, *cis* isomer) δ 7.18 (t, *J* = 7.5 Hz, 1H), 7.04 – 6.96 (m, 4H), 4.55 (dt, *J* = 8.9, 1.3 Hz, 1H), 2.36 (s, 3H), 2.26 (td, *J* = 8.6, 6.5 Hz, 1H), 1.89 (qd, *J* = 8.8, 5.8 Hz, 1H), 1.74 (m, 4H), 1.61 – 1.60 (m, 4H), 1.25 (td, *J* = 8.5, 4.9 Hz, 1H), 0.90 – 0.85 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$, *cis* isomer) δ 139.3, 137.3, 132.6, 129.9, 127.7, 126.4, 125.9, 123.1, 25.6, 22.7, 21.5, 18.3, 18.3, 12.3 ppm.

GC-MS (EI): calculated for $C_{14}H_{18}$ $[M]^+$: 186.1; found: 186.1.

(*cis*)-1-Chloro-4-(2-((*E*)-styryl)cyclopropyl)benzene (33e)



The title compound (colorless oil, 10 mg, 50% yield, 20:1 *dr*) was obtained following General Procedure **A** from (*E*)-1-styryl-1a,7b-

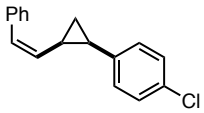
dihydro-1*H*-cyclopropa[*a*]naphthalene (**32c**) (18 mg, 0.106 mmol) and 1-chloro-4-vinylbenzene (62 mg, 0.45 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (2.9 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 - 7.32 (m, 9H), 6.56 (d, *J*=15.8 Hz, 1H), 5.52 (dd, *J* = 15.8, 9.4 Hz, 1H), 2.38 - 2.49 (m, 1H), 2.01 - 2.13 (m, 1H), 1.37 - 1.46 (m, 1H), 1.08 - 1.19 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 137.4, 131.9, 130.7, 130.1, 130.0, 128.6, 128.3, 126.9, 125.8, 23.3, 22.8, 12.8 ppm.

GC-MS (EI): calculated for $C_{17}H_{16}Cl$ $[M+H]^+$: 255.1; found: 255.1.

(*cis*)-1-Chloro-4-(2-((*Z*)-styryl)cyclopropyl)benzene (33f)



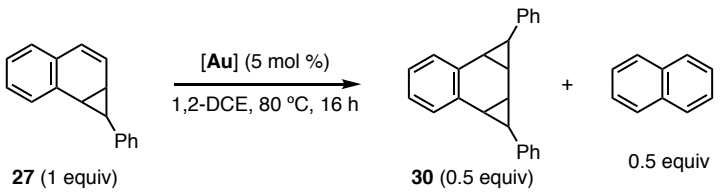
The title compound (colorless oil, 13 mg, 68% yield, 8:1 *dr*) was obtained following General Procedure **A** from (*Z*)-1-styryl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (**32d**) (18 mg, 0.075 mmol) and 1-chloro-4-vinylbenzene (63 mg, 0.45 mmol, 6 equiv) using [(JohnPhos)Au(MeCN)]SbF_6 (2.9 mg, 5 mol %) after purification by preparative TLC on SiO_2 using pentane as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.34 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.28 – 7.19 (m, 4H), 7.18 – 7.14 (m, 2H), 6.33 (d, *J* = 11.5 Hz, 1H), 4.91 (dd, *J* = 11.5, 9.7 Hz, 1H), 2.38 (td, *J* = 8.6, 6.3 Hz, 1H), 2.28 (dtdd, *J* = 9.8, 8.6, 5.7, 1.1 Hz, 1H), 1.39 (td, *J* = 8.4, 5.1 Hz, 1H), 1.05 (dt, *J* = 6.4, 5.4 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 137.5, 132.2, 131.6, 130.8, 130.0, 129.1, 128.6, 128.6, 126.9, 24.1, 19.4, 14.2 ppm.

HRMS (APCI+): calculated for $C_{17}H_{16}Cl$ $[M+H]^+$: 255.0935; found: 255.0923.

Formation of biscyclopropane side-product by heating with gold(I)



A solution of **27** in 1,2-DCE with 5 mol % of [(JohnPhos)Au(MeCN)]SbF_6 was heated at 80 °C for 16 h, leading to the quantitative formation of naphthalene and bisphenylcyclopropane, which is unreactive towards retro-cyclopropanation under the reaction conditions (determined

by ^{1}H NMR in $CDCl_3$ using 1 equiv of diphenylmethane as internal standard). Characterization data for the biscyclopropane matches the reported ones.[25]

25 Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801–809.

Chapter III: *Gold(I)-Catalyzed Polyenyne Cyclization for the Construction of Decalin Cores of Natural Products*

UNIVERSITAT ROVIRA I VIRGILI
GOLD(I) CAVITANDS FOR THE ASSEMBLY OF MOLECULAR COMPLEXITY
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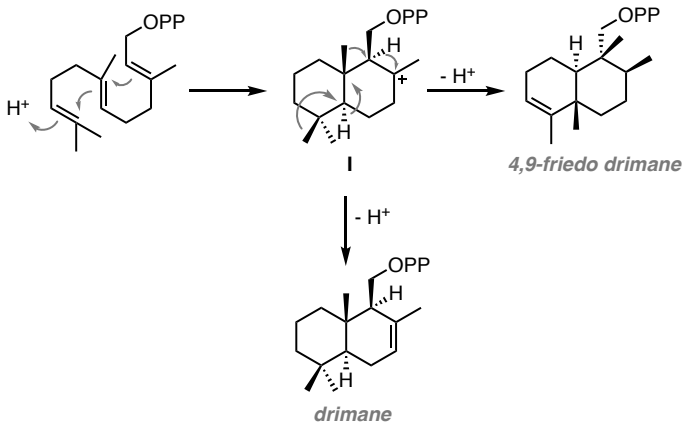
Introduction

Natural Products with a Rearranged Drimane Skeleton

The drimane family of sesquiterpenes that feature a common *trans*-decalin system have attracted significant attention due to their interesting structures and wide variety of biological activities. The drimane skeleton is biosynthesized by cyclization of farnesyl pyrophosphate by electrophilic attack at the head position of the FPP leading to the bicyclic carbocationic intermediate **I**, which after rearrangement and deprotonation gives rise to 4,9-friedo drimane (Scheme 1).[1] Alternatively, if only deprotonation occurs, drimane is formed. However, our discussion will focus on natural products derived from 4,9-friedo drimanes.



Scheme 1. Biosynthesis of 4,9-friedo drimane.

The rearranged drimane skeleton is present in a wide range of sesquiterpenes containing quinone and hydroquinone subunits (Figure 1).[1] Avarol and avarone are representative members of this family, which were isolated from the marine sponge *Dysidea avara* in 1974.[2] Both compounds have exhibited notable biological activities, including cytotoxic,[3] antioxidant,[4] or anti-inflammatory[5] properties, among others. The structures of avarol and avarone were determined through degradative and spectroscopic studies.[6]

1 Sladic, D.; Gasic, M. *Molecules* **2006**, *11*, 1–33.

2 Minale, L.; Riccio, R.; Sodano, G. *Tetrahedron Letters* **1974**, *15*, 3401–3404.

3 (a) W. E. G. Müller, A. Maidhof, R. K. Zahn, H. C. M. Schröeder, M. J. Gasic, D. Heidemann, A. Bernd, B. Kurelec, E. Eich, G. Seibert, *Cancer Res.* 1985, 45, 4822– 4826; (b) Miguel del Corral, J. M.; Gordaliza, M.; Castro, M. A.; Mahiques, M. M.; Chamorro, P.; Molinari, A.; García-Grávalos, M. D.; Broughton, H. B.; San Feliciano, A. *Med. Chem.* **2001**, *44*, 1257–1267.

4 Belisario, M. A.; Maturo, M.; Pecce, R.; De Rosa, S.; Villani, G. R. D. *Toxicology* **1992**, *72*, 221–233.

5 Ferrándiz, M. L.; Sanz, M. J.; Bustos, G.; Payá, M.; Alcaraz, M. J.; De Rosa, S. *European Journal of Pharmacology* **1994**, *253*, 75–82.

6 de Rosa, S.; Minale, L.; Riccio, R.; Sodano, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1408–1414.

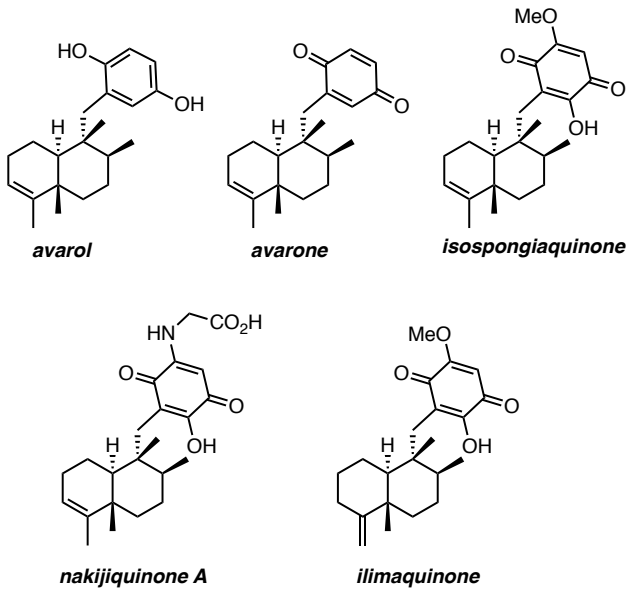
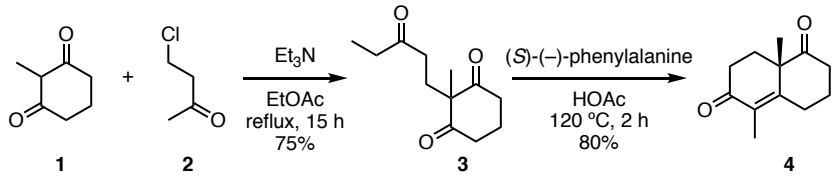


Figure 1. Selected examples of friedo-rearranged drimanes.

The first total synthesis of (±)-avarol was reported in 1982 by the group of Sarma in 8 steps.[7] After that, the groups of Hecht[8] and Wiemer[9] in 1996 reported simultaneously the enantioselective synthesis of avarol and avarone with a similar synthetic strategy. The construction of the key decalin core of these natural products was based on the methylated Wieland–Miescher ketone (**4**), in both synthetic routes. The synthesis of **4** involved the alkylation of 2-methyl-1,3-cyclohexanedione (**1**) with 1-chloro-3-pentanone (**2**), followed by asymmetric Robinson annulation using L-phenylalanine and finally, a recrystallization process to obtain the desired enantioenrich ketone **4** (Scheme 2).[10]



Scheme 2. Synthesis of Wieland–Miescher ketone **4**.

Then, the synthesis continued with the protection and alkylation with 2,5-dimethoxybenzyl bromide to form **6**, followed by Wittig reaction using methylenetriphenylphosphorane and subsequent deprotection of the acetal group. Hydrogenation of the resulting alkene **7** over Pd/C

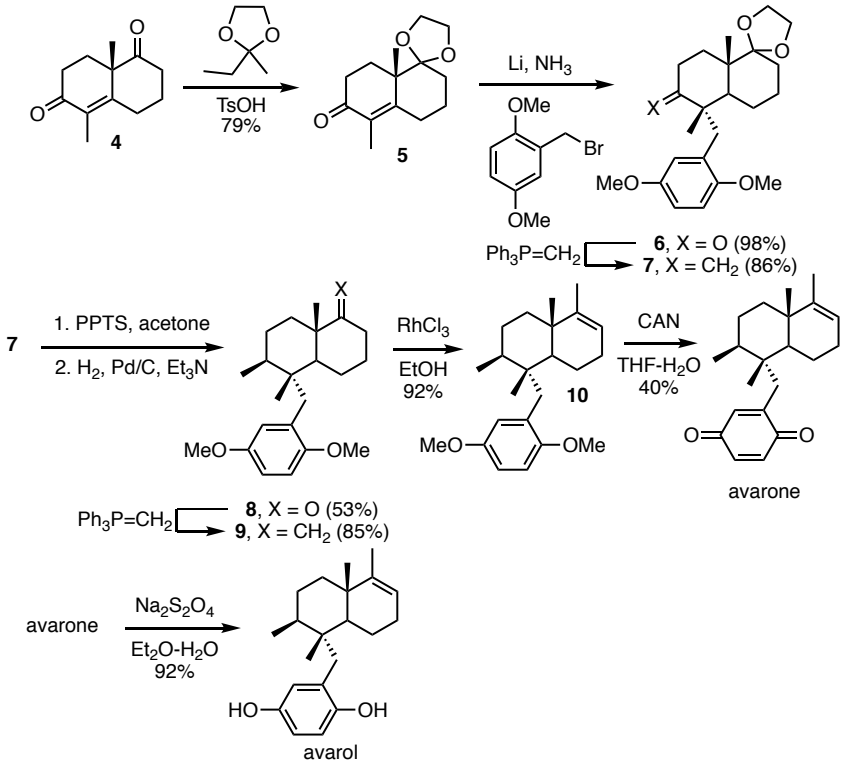
7 (a) Sarma, A. S.; Chattopadhyay, P. *J. Org. Chem.* **1982**, *47*, 1727–1731. Corrigendum: *J. Org. Chem.* **1982**, *47*, 5427–5427.

8 Locke, E. P.; Hecht, S. M. *Chem. Commun.* **1996**, 2717–2718.

9 An, J.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 8775–8779.

10 (a) Uma, R.; Swaminathan, S.; Rajagopalan, K. *Tetrahedron Letters* **1984**, *25*, 5825–5828. (b) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308–2311.

gave a mixture of β/α diastereomers in a 4:1 ratio, which could be separated by column chromatography to obtain ketone **8**. Subsequent Wittig reaction and isomerization using $RhCl_3$ gave avarol dimethyl ether **10**. Finally, oxidative removal of the ether protecting group with cerium ammonium nitrate provided avarone. Reduction of this compound with $Na_2S_2O_4$ resulted in the formation of avarol (Scheme 3).



Scheme 3. Total synthesis of avarone and avarol by the group of Hecht.[8]

Another synthetic strategy was reported in 1999 by the group of Theodorakis and also involved ketone **4** as a key precursor of the decalin skeleton.[11] A key step of the synthesis was the installation of the quinone core *via* Barton's radical decarboxylation and addition of the corresponding quinone. Later on, they used this methodology to prepare other natural products.[12]

Similarly, the most recent synthesis devised by the Katoh group also aimed to prepare a key intermediate similar to **9** that enabled the generation of analogous natural products.[13]

11 Ling, T.; Xiang, A. X.; Theodorakis, E. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 3089–3091.

12 Ling, T.; Poupon, E.; Rueden, E. J.; Kim, S. H.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2002**, *124*, 12261–12267.

13 Sakurai, J.; Oguchi, T.; Watanabe, K.; Abe, H.; Kanno, S.; Ishikawa, M.; Katoh, T. *Chem. Eur. J.* **2008**, *14*, 829–837.

As presented in the examples shown above, most of the strategies for the assembly of *trans*-decalin structures for sesquiterpenes rely on the preparation of Wieland–Miescher ketone **4**. We propose an alternative approach to this decalin core based on the use of polyenyne cyclizations.

Polyenyne Cyclizations

Polyene cyclizations have attracted attention from the scientific community for over 70 years due to their unique and efficient ways to construct molecular complexity in a concerted and stereocontrolled manner. Stork and Eschenmoser established a hypothesis to account for the stereoelectronic aspects that influence the stereochemical result of polyene cyclization.[14] The concept of the polyene cyclization was further proved by both Johnson[15] and van Tamelen,[16] who reported the first biomimetic syntheses of steroids. Since then, many efforts have been devoted to the development of selective methods to perform this type of reactions, as their principal advantage is the formation of multiple C-C bonds in one step. From these methods, the focus of our discussion is the use of transition metals in cationic polyene cyclization.[17]

The platinum-catalyzed cascade cycloisomerization of polyenes was studied by the group of Gagné.[18] This group used a tridentate NHC-containing pincer ligand in the diastereoselective cyclization of a variety of substrates, such as polyene **11** (Scheme 4). Mechanistic studies demonstrated that the coordination of the electrophilic Pt(II) takes place preferentially to the least substituted alkene to initiate of the polyene cyclization. After that, proto-demetallation regenerates the Pt catalyst and gives the final product.

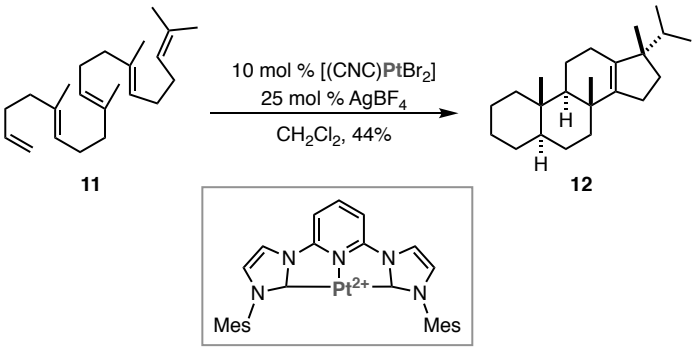
14 (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (c) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011.

15 (a) Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc*. **1968**, *90*, 2994. (b) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (c) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.

16 (a) van Tamelen, E. E. *Acc. Chem. Res*. **1968**, *1*, 111. (b) van Tamelen, E. E. *Acc. Chem. Res*. **1975**, *8*, 152.

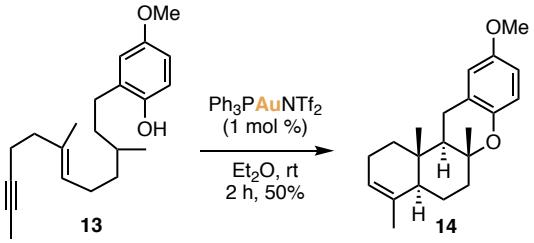
17 For a recent review on polyene cyclization in organic synthesis: (a) Dhambri, S.; Mohammad, S.; Van Buu, O. N.; Galvani, G.; Meyer, Y.; Lannou, M.-I.; Sorin, G.; Ardisson, J. *Nat. Prod. Rep.* **2015**, *32*, 841–864. (b) Barrett, A.; Ma, T.-K.; Mies, T. *Synthesis* **2019**, *51*, 67–82. (c) García-Pedrero, O.; Rodríguez, F. *Chem. Commun.* **2022**, *58*, 1089–1099.

18 (a) Geier, M. J.; Gagné, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 3032. (b) McCulley, C. H.; Geier, M. J.; Hudson, B. M.; Gagné, M. R.; Tantillo, D. J. *J. Am. Chem. Soc.* **2017**, *139*, 11158–11164.



Scheme 4. Platinum(II)-mediated polyene cyclization.

Similar cascade reactions involve (poly)enyne substrates, which upon activation of the alkyne moiety initiate the consequent cyclization process. In this context, the Michelet group reported the gold(I)-catalyzed intramolecular phenoxycyclization cyclization of 1,5-enynes using PPh_3AuNTf_2 under mild conditions.[19] This reaction enabled the construction of tricyclic derivatives through a 6-*endo*-dig cyclization process. The potential of this strategy was demonstrated by the formation of tetracycle **14** (Scheme 5).

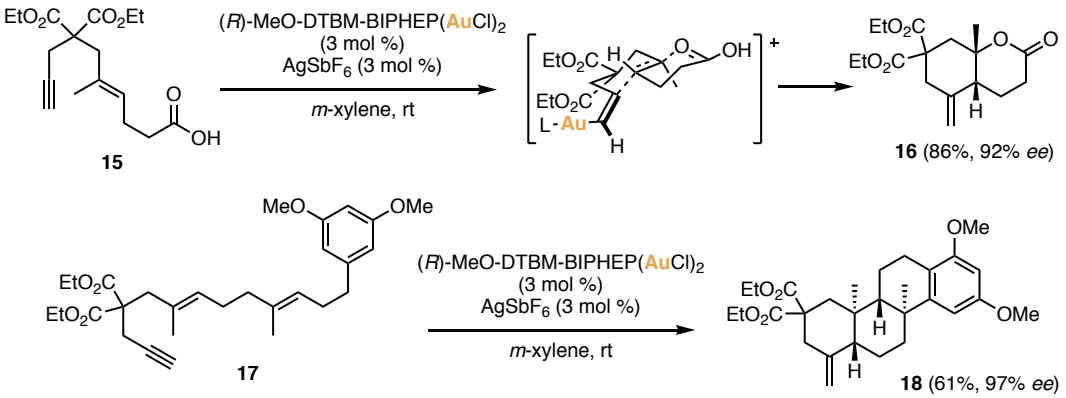


Scheme 5. Gold(I) catalyzed cascade cyclization of **13**.

Toste and co-workers investigated other chiral phosphine-gold(I) complexes in the 6-*endo*-dig cascade cyclization of enyne **15**; the best result being observed with the (*R*)-MeO-DTBM-BIPHEP ligand.[20] Moreover, the effect of the solvent was also studied and it revealed that aromatic solvents, such as *m*-xylene led to high enantioselectivities in the synthesis of lactones **16** (Scheme 6). The cyclization of more complex enynes bearing different internal nucleophiles was explored, giving rise to different cyclic skeletons with high enantiomeric excess. For instance, tetracycle **18** was obtained from enyne **17** as a single diastereomer with 97% *ee*.

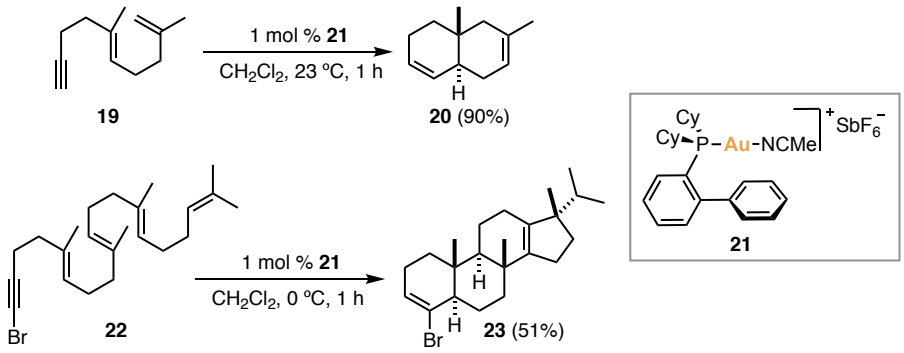
19 Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888–2891.

20 Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277.



Scheme 6. Polyenyne cyclization catalyzed by gold(I) complex.

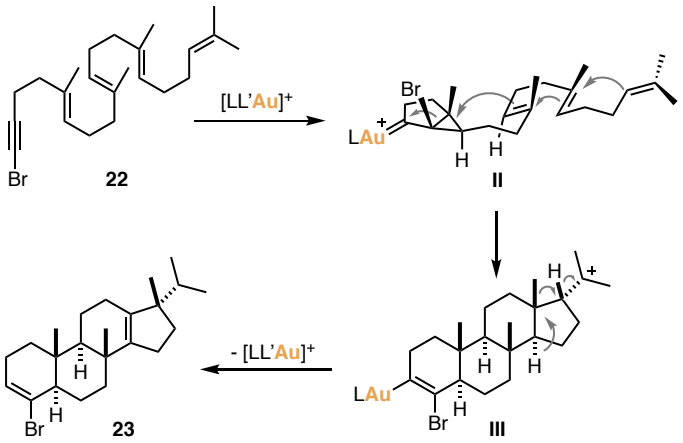
On the other hand, the gold(I)-catalyzed cyclization of polyenynes was expanded by our group to the formation of up to four C–C bonds and applied to the preparation of steroid derivatives.[21] The development of this methodology started with the construction of the *trans*-fused decalin core **20** with catalyst **21**. After that, other substrates incorporating different terminal nucleophiles such as alcohols, phenols and heteroarenes, were tested to expand the structural-diversity space. Additionally, bromoalkynes could also take part on these transformations, giving rise to polycyclic bromoalkenes, which could be further functionalized. For example, tetracycle **23** was obtained by cyclization of bromide-substituted tetraenyne **22** (Scheme 7).



Scheme 7. Gold(I)-catalyzed cyclization of compounds **19** and **22**.

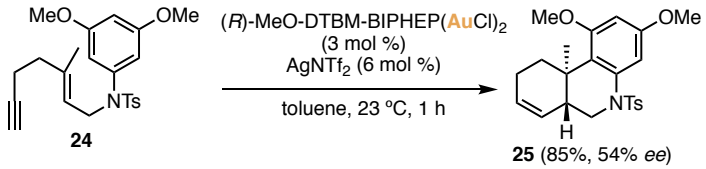
A plausible mechanism leading to compound **23** starts with the formation of cyclopropyl gold(I) carbene intermediate **II**, which after a cascade nucleophilic attack gives rise to intermediate **III**. Then, a Wagner–Meerwein rearrangement occurs, followed by the proton elimination and protonolysis to give compound **23** (Scheme 8).

21 Rong, Z.; Echavarren, A. M. *Org. Biomol. Chem.* **2017**, *15*, 2163.



Scheme 8. Mechanism for the formation of compound **23**.

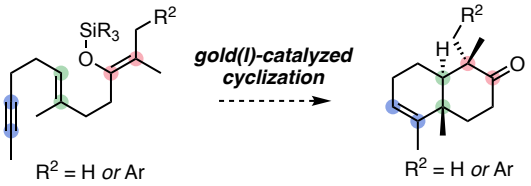
Finally, the enantioselective version of the reaction was studied using (*R*)-MeO-DTBM-BIPHEP(AuCl)$_2$ and compound **25** could be obtained with moderate enantioselectivity (Scheme 9).



Scheme 9. Gold(I)-catalyzed enantioselective cyclization of **24**.

Objectives

The objective of the research summarized in this chapter was the development of a new methodology for the construction of the decalin core existing in natural products such as avarol and avarone, and related compounds. A gold(I)-catalyzed dienyne cyclization of tetrasubstituted silyl enol ethers was envisioned to obtain these key decalin intermediates, which could pave the way for the total synthesis of natural compounds such as avarol and avarone. Here, we envisioned that the main challenge would be to construct the tetrasubstituted silyl enol ether of the required substrates in a stereodefined manner.[22]



Scheme 10. Construction of decalin derivatives by cyclization of dienynes.

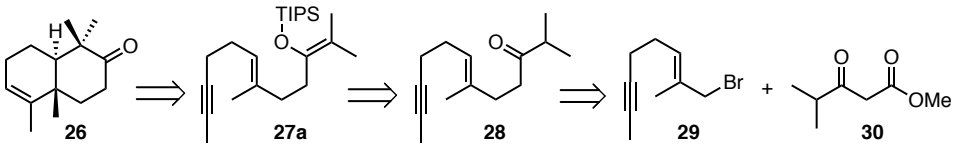
22 Part of these experiments described in this section were performed jointly with Dr. Franco Della Felice.

Results and Discussion

Our strategy for the construction of decalin skeletons through gold(I) catalysis is based on the synthesis of tetrasubstituted silyl enol ethers and thus, different approaches have been studied for the preparation of these latter compounds.

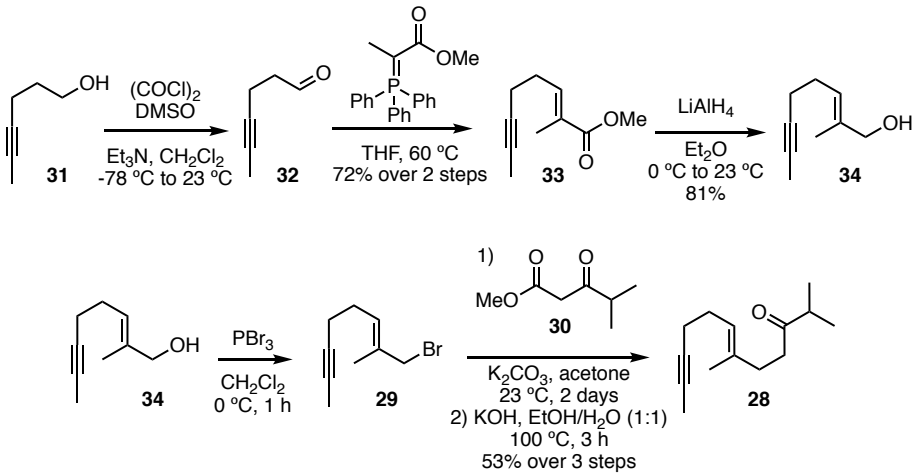
First Strategy for the Synthesis of Silyl Enol Ethers

The first approach for the synthesis of silyl enol ether **27a** relies on the formation of ketone **28** as key intermediate (Scheme 11). In this case, TIPS was chosen as the organosilicon group due to its robustness, which is not susceptible to facile hydrolysis.



Scheme 11. Retrosynthesis of ketone **26**.

We started this synthetic sequence with the preparation of hex-4-ynal (**32**), which was obtained through a Swern oxidation of hex-4-yn-1-ol (**31**). Subsequent stereoselective Wittig reaction of aldehyde **32** gave ester **33**, whose reduction with $LiAlH_4$ led to alcohol **34** in good yield. This compound was treated with PBr_3 to afford the corresponding bromide **29**, which was used in the next step without further purification. Finally, alkylation with this bromide of the enolate of methyl 4-methyl-3-oxopentanoate (**30**), followed by decarboxylation, provided the desired ketone **28** in 53% yield over three steps (Scheme 12).



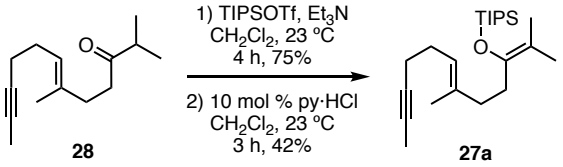
Scheme 12. Synthesis of ketone **28**.

At this point, our main objective was the formation of thermodynamic silyl enol ether **27a** and in this sense, we subjected ketone **28** to a silylation reaction with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf). Unfortunately, this silylation gave rise to a mixture of the trisubstituted and tetrasubstituted silyl enol ethers. However, isomerization of the mixture using

pyridine hydrochloride (py·HCl) as catalyst furnished the desired tetrasubstituted silyl enol ether **27a** as the major product (Scheme 13).

The isomerization process showed some reproducibility issues when the crude product from the silylation reaction was used directly. Its purification was attempted to solve these issues and the clean mixture of isomers was obtained in 75% yield. However, the characterization by NMR of the mixture could not be performed because of the overlapping signals and hence, the ratio of the regioisomers could not be determined. Different reagents such as 4 M HCl in dioxane and triflimide (Tf_2NH)[23] were also tested in the isomerization, but the best conversion was observed using py·HCl.

After several efforts to prepare selectively the thermodynamic silyl enol ether **27a**, a mixture of isomers was still obtained using py·HCl, in which the major product was the desired tetrasubstituted silyl enol ether **27a**. However, pure **27a** could be obtained in 42% yield after flash column chromatography (Scheme 13).

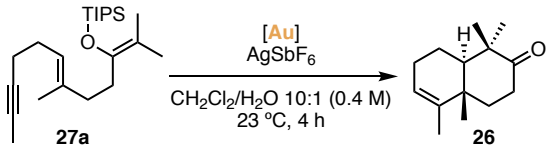


Scheme 13. Synthesis of tetrasubstituted silyl enol ether **27a**.

With the tetrasubstituted silyl enol ether **27a** in hand, we studied the gold(I)-catalyzed dienyne cyclization reaction to obtain decalin **26**. A screening of gold(I) complexes was performed using water as the external proton source and the best results were observed with catalysts **A** and **B** (Table 1, entries 1 and 2). Using methanol instead of water as proton source led to reduced yield (Table 1, entry 7). Finally, the treatment of **27a** in the presence of complex **A** in a mixture of dichloromethane/water 10:1 at 23 °C gave the ketone **26** in 95% yield (Table 1, entry 8).

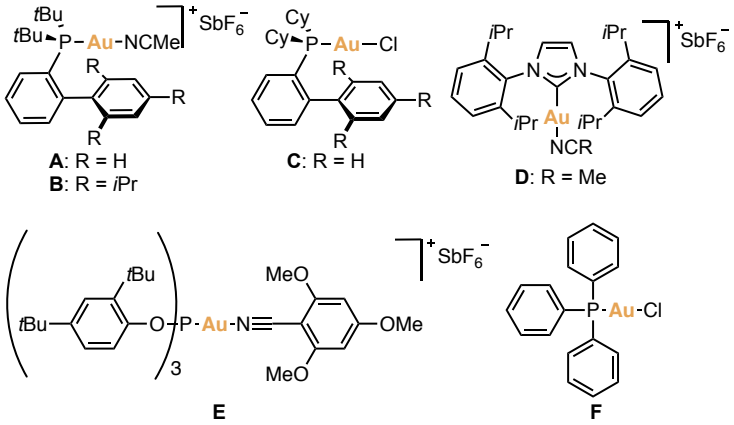
23 Inanaga, K.; Ogawa, Y.; Nagamoto, Y.; Daigaku, A.; Tokuyama, H.; Takemoto, Y.; Takasu, K. Facile *Beilstein J. Org. Chem.* **2012**, *8*, 658–661.

Table 1. Gold(I)-catalyzed cyclization of tetrasubstituted silyl enol ether **27a**.

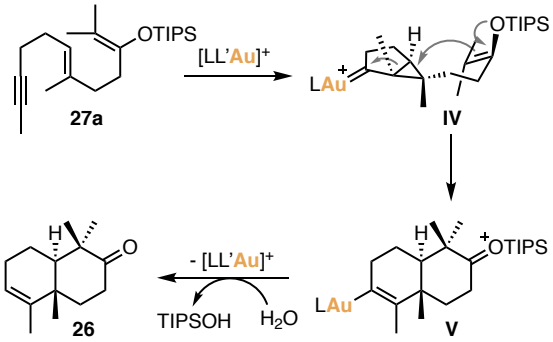


Entry	[Au] (5 mol %)	$AgSbF_6$	Yield [%][a]
1	**A**	-	98
2	**B**	-	91
3	**C**	5 mol %	28[c]
4	**D**	-	88
5	**E**	-	18[d]
6	**F**	5 mol %	17[e]
7[b]	**A**	-	64
8	**A**	-	95[f]

[a] Yield determined by NMR. [b] The reaction was performed using MeOH instead of H_2O. [c] 38% conversion. [d] 19% conversion. [e] 63% conversion. [f] Isolated yield.

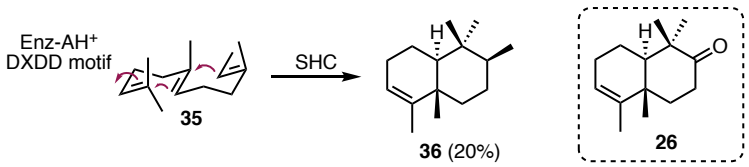


The proposed mechanism for the gold(I)-catalyzed cyclization of tetrasubstituted silyl enol ether **27a** starts with the formation of cyclopropyl gold(I) carbene intermediate **IV**, which after the nucleophilic addition of the silyl enol ether leads to intermediate **V**. After that, hydrolysis and protonolysis affords the desired ketone **26** (Scheme 14).



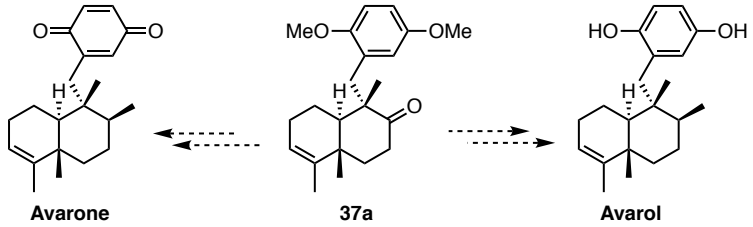
Scheme 14. Proposed mechanism for the formation of ketone **26**.

In 2012, the group of Hoshino[24] performed the synthesis of drimane-type sesquiterpenes by enzymatic cyclization of linear sesquiterpenes mediated by squalene-hopene cyclase (SHC). An interesting example was the formation of sesquiterpene **36** since it has a structure similar to ketone **26**. The cyclization of (6*E*,10*E*)-2,6,10-trimethyldodeca-2,6,10-triene **35** in presence of SHC gave a mixture of enzymatic products, where **36** was obtained in 20% yield after purification (Scheme 15).



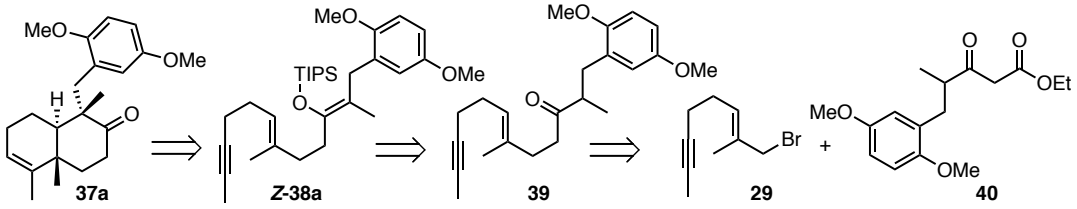
Scheme 15. Chemo-enzymatic cyclization of (6*E*,10*E*)-2,6,10-trimethyldodeca-2,6,10-triene **35**.

As previously mentioned in the introduction, avarol and avarone are natural products that contain decalin structures with quinone or hydroquinone systems. We envisioned that cyclic ketone **37a** could be an excellent key intermediate for the synthesis of these natural products (Scheme 16).



Scheme 16. Cyclic ketone **37a** for the synthesis of avarone and avarol.

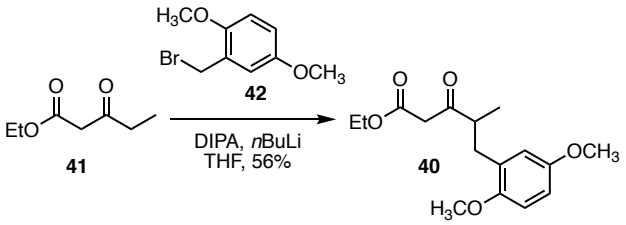
For the synthesis of compound **37a**, silyl enol ether ***Z*-38a** must be prepared selectively. Accordingly, we used the same strategy as in the case of compound **27a**, preparing ketone **39** this time, from *β*-keto ester **40** (Scheme 17).



Scheme 17. Retrosynthesis of ketone **37a**.

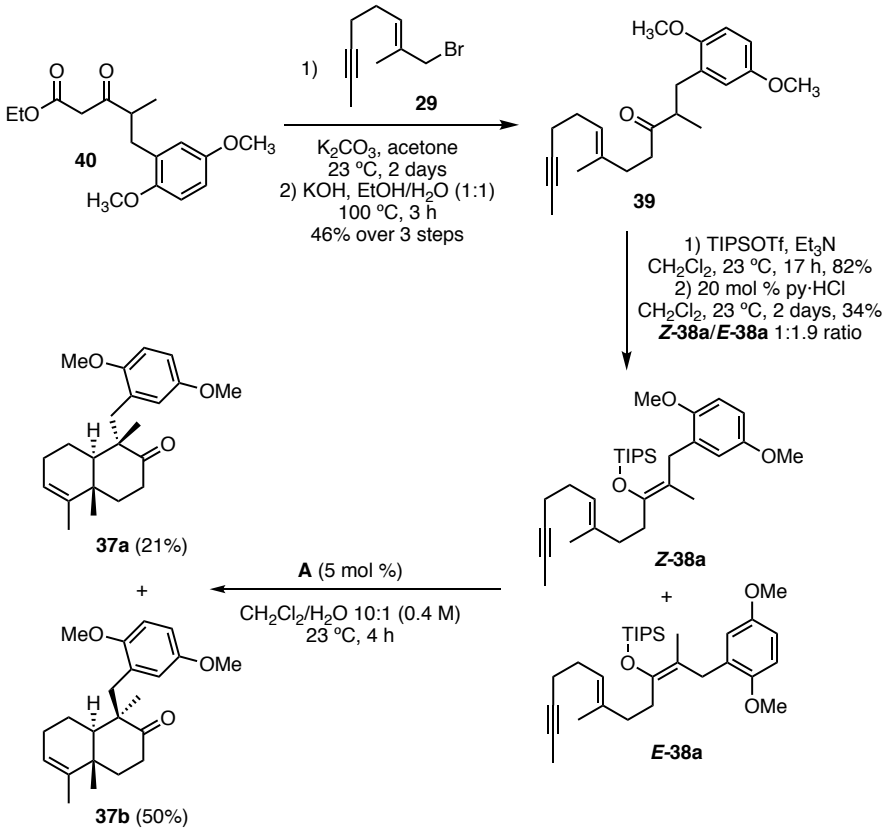
The synthesis of *β*-keto ester **40** involved the nucleophilic substitution of ethyl propionylacetate **41** with aryl bromide **42**, through the formation of the corresponding dienolate using 2 equiv of lithium diisopropylamide. Product **40** was obtained in 56% yield (Scheme 18).

24 Yonemura, Y.; Ohyama, T.; Hoshino, T. *Org. Biomol. Chem.* **2012**, *10*, 440–446.



Scheme 18. Synthesis of *β*-keto ester **40**.

Ketone **39** was synthesized in 46% yield over three steps following a similar sequence of reactions as in the case of ketone **28** (Scheme 19). Then, the silylation followed by isomerization in presence of 20 mol % of py·HCl gave a mixture of ***Z*-38a/*E*-38a** in a 1:1.9 ratio, which was employed in the next step. Finally, after performing the gold(I)-catalyzed cyclization under the previously optimized conditions, the resulting mixture of ketones **37a** and **37b** could be separated by column chromatography. Thus, **37a** was obtained in 21% yield and **37b** in 50% yield (Scheme 19). The structure of the latter compound was also confirmed by X-ray diffraction (Figure 2).



Scheme 19. Formation of tetrasubstituted silyl enol ethers **38a** and its gold(I)-catalyzed cyclization.

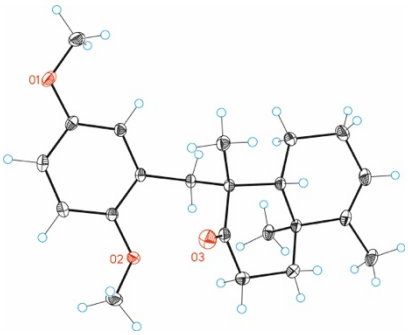
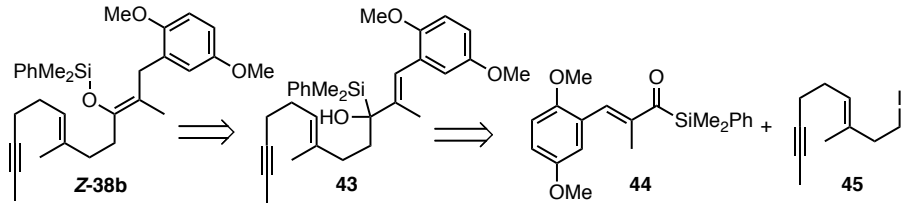


Figure 2. Representation of **37b** obtained by X-ray diffraction analysis.

The synthetic route presented in Scheme 19 led us to obtain ketone **37a**, which could be engaged as a key precursor in the preparation of avarol and avarone. Nevertheless, the synthesis of the tetrasubstituted silyl enol ether ***Z*-38a** was not accomplished in a stereoselective manner using this approach. Therefore, we moved our attention to find an alternative, more efficient approach for the selective synthesis of this compound.

Attempted Synthesis of Tetrasubstituted Silyl Enol Ether through Allyl-Brook Rearrangement

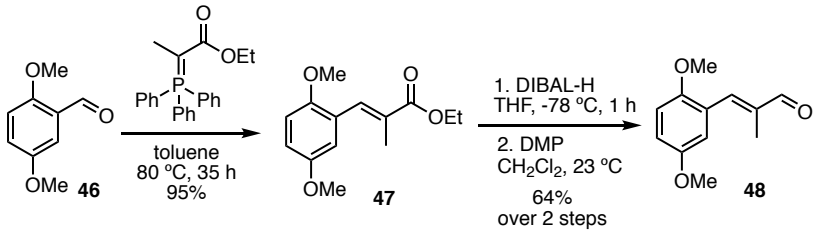
As an alternative for the selective preparation of compound ***Z*-38a**, we decided to follow the methodology published by Marek and co-workers, which described the stereo- and regioselective synthesis of fully substituted silyl enol ether by an allyl-Brook rearrangement of α-hydroxy alkenyl silanes.[25] Considering their results, we envisioned the synthesis of target compound ***Z*-38b** from α-hydroxy alkenyl silane **43.** In turn, **43** would be obtained by addition of an alkyl-metal intermediate derived from alkyl iodide **45** to the acylsilane **44** (Scheme 20).



Scheme 20. Retrosynthetic analysis of silyl enol ether ***Z*-38b**.

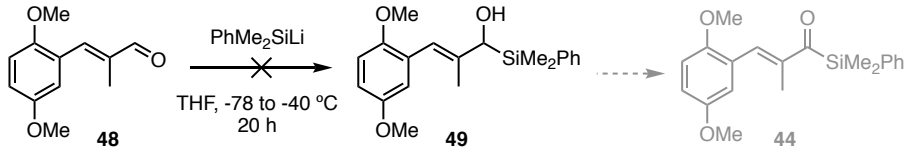
Therefore, we proceeded with the synthesis of acylsilane **44**. α,β-Unsaturated aldehyde **48** was obtained in three steps using 2,5-dimethoxybenzaldehyde (**46**) as precursor, *via* selective Wittig reaction and further redox manipulation of ester **47** (Scheme 21).

25 Wang, P.; Duret, G.; Marek, I. *Angew. Chem. Int. Ed.* **2019**, *58*, 14995–14999.



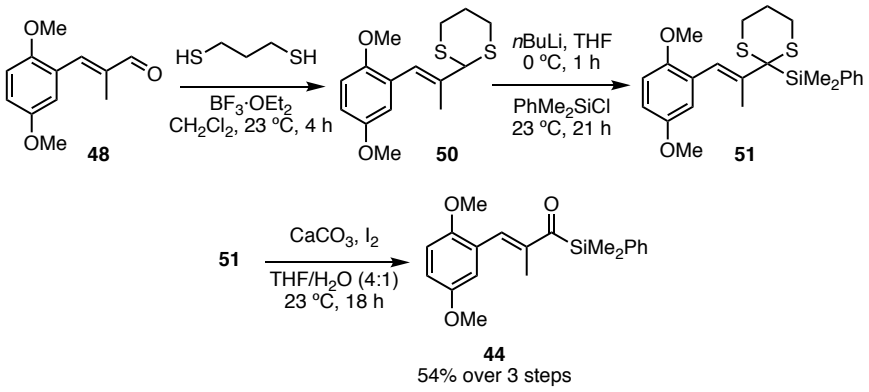
Scheme 21. Synthesis of aldehyde **48**.

To obtain silyl alcohol **49**, the nucleophilic silylation of *α*,*β*-unsaturated aldehyde **48** was attempted by addition of $PhMe_2SiLi$, but a complex mixture of unknown products was obtained (Scheme 22).



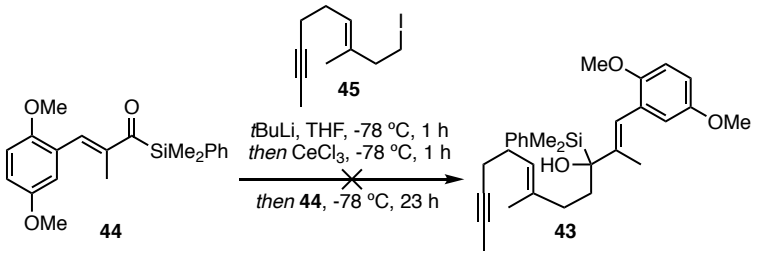
Scheme 22. Attempted synthesis of silyl alcohol **49**.

Consequently, we changed our strategy for the preparation of *α*,*β*-unsaturated acylsilane **44**. Aldehyde **48** was converted into thioacetal **50**, which after lithiation using *n*Buli, followed by reaction with $PhMe_2SiCl$ gave silyl derivative **51**. After deprotection of **51** in presence of I_2 and $CaCO_3$, acylsilane **44** could be obtained in 54% yield over three steps (Scheme 23).



Scheme 23. Synthesis of acylsilane **44**.

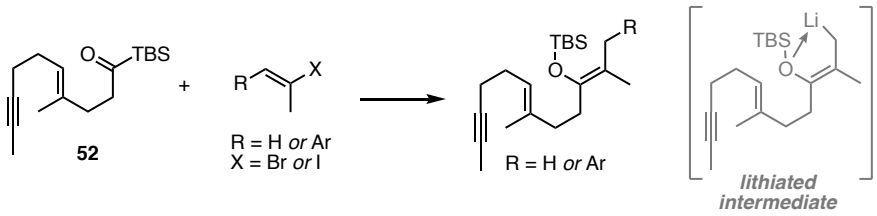
With the acylsilane **44** in hand, its nucleophilic addition reaction was tested using the organocerium reagent derived from alkyl iodide **45**. Unfortunately, silyl alcohol **43** could not be obtained by this method (Scheme 24).



Scheme 24. Attempt at synthesizing α-hydroxy alkenyl silane **43**.

Corey's Strategy for the Synthesis of Tetrasubstituted Silyl Enol Ethers

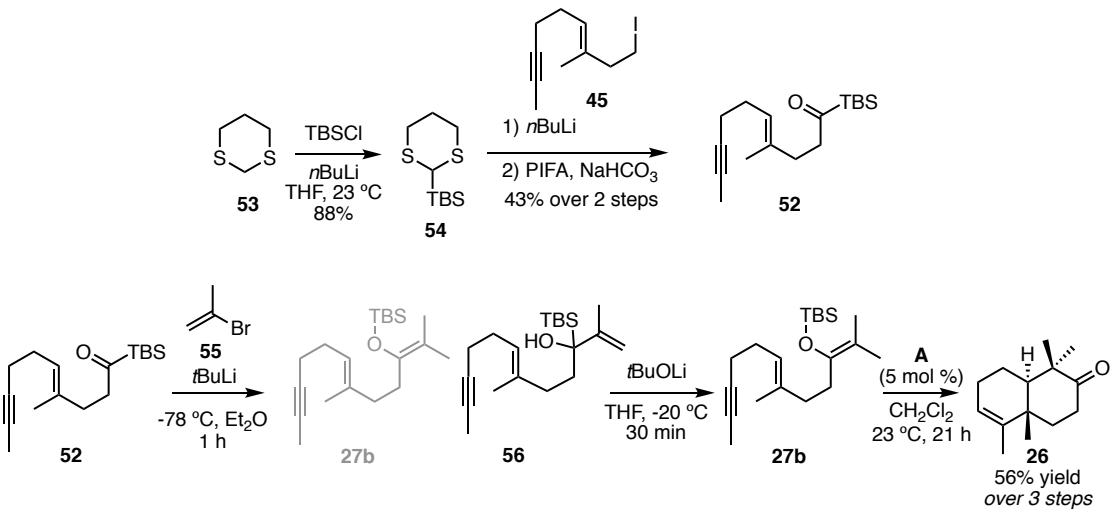
At this stage, we decided to follow a different approach for the selective synthesis of tetrasubstituted silyl enol ethers, following the work reported by the group of Corey[26] for the stereoselective synthesis of *Z*-tetrasubstituted silyl enol ethers *via* formation of a chelated lithium intermediate using acyl silane **52** as the precursor (Scheme 24).



Scheme 24. Corey's methodology for the synthesis of tetrasubstituted silyl enol ether.

First, we targeted model substrate **26** to prove the viability of this approach. Formation of acyl silane **52** was successful by alkylation of **54** with alkyl iodide **45** followed by the cleavage of the dithiane using PIFA and $NaHCO_3$. The Corey procedure for the selective synthesis of tetrasubstituted silyl enol ether **27b** was attempted next. However, the treatment of acyl silane **52** with 2-lithiopropene (generated *in situ via* lithiation of 2-bromoprop-1-ene, **55**, with *t*BuLi, in diethyl ether at -78 °C) only gave rise to alkenyl silane **56**, instead of leading directly to the target compound **27b**. The reaction was repeated several times even raising the temperature but **27b** could not be obtained directly. Nevertheless, the desired silyl enol ether **27b** could be successfully produced by subjecting compound **56** to reaction with LiO*t*Bu following Marek's procedure.[25] Finally, the gold(I)-catalyzed cyclization of **27b** delivered model ketone **26** in 56% yield over three steps (Scheme 25).

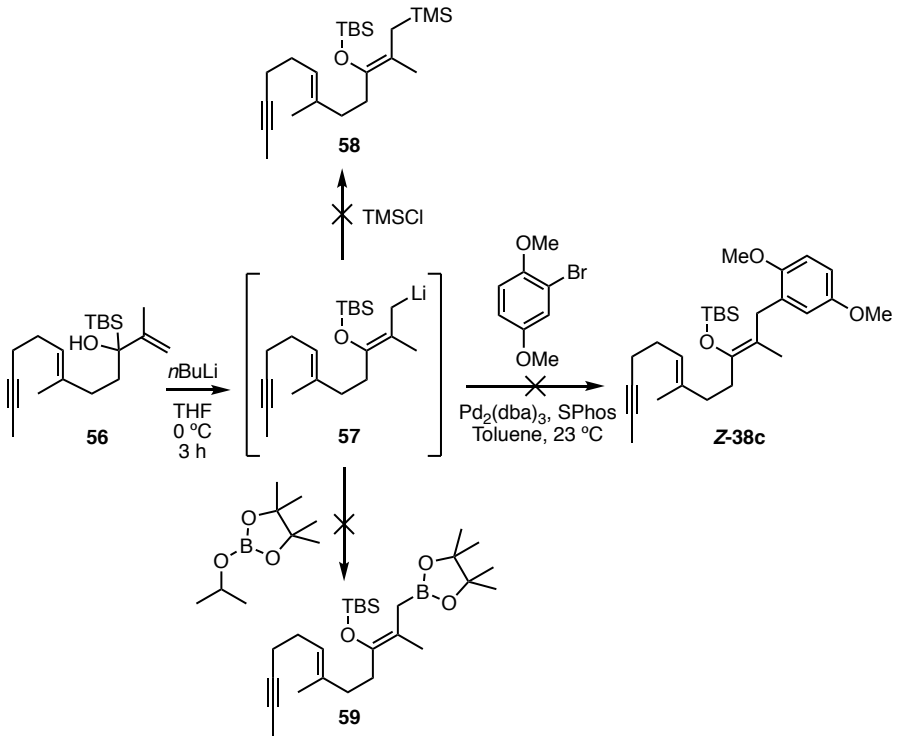
26 (a) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765–8766. (b) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869.



Scheme 25. Syntheses of Acylsilane **52** and decalin **26**.

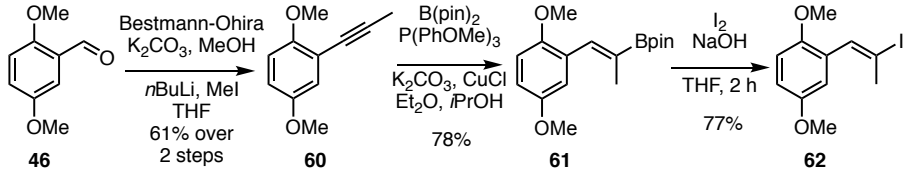
Based on these results, we envisioned that after the Brook rearrangement, the lithiated intermediate **57** could be trapped with an electrophile to functionalize the final tetrasubstituted silyl enol ethers. Since the Marek group also reported this strategy using *n*BuLi,[25] we decided to use this base instead of LiO*t*Bu to avoid the generation of *tert*-butanol that could quench the lithiated intermediate.

Therefore, intermediate **57** was generated using *n*Buli, after 3 h at 0 °C. After that, we tried to trap it with electrophiles such as TMSCl and *i*PrOBpin but the reactions were unsuccessful. We also envisioned that this method would allow a more direct access to tetrasubstituted silyl enol ether ***Z*-38c** through a coupling reaction of **57** with 2-bromo-1,4-dimethoxybenzene, but our attempt failed (Scheme 26).



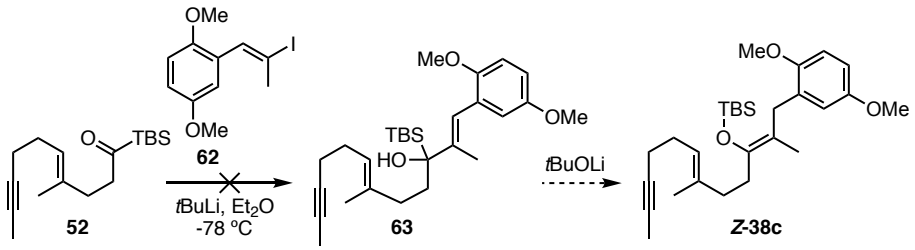
Scheme 26. Attempted trapping of lithiated intermediate **57** with different electrophiles.

On the other hand, the stereospecific synthesis of *Z*-tetrasubstituted silyl enol ether ***Z*-38c** was also attempted following a different approach that requires the preparation of (*E*)-2-(2-iodoprop-1-en-1-yl)-1,4-dimethoxybenzene (**62**). Accordingly, this compound was obtained by Seyferth-Gilbert homologation with the Bestmann-Ohira reagent, copper-catalyzed regio- and stereoselective borylcupration of the resulting alkyne **60** and subsequent treatment of alkenyl boronate **61** with I_2 and NaOH (Scheme 27).



Scheme 27. Preparation of iodide **62**.

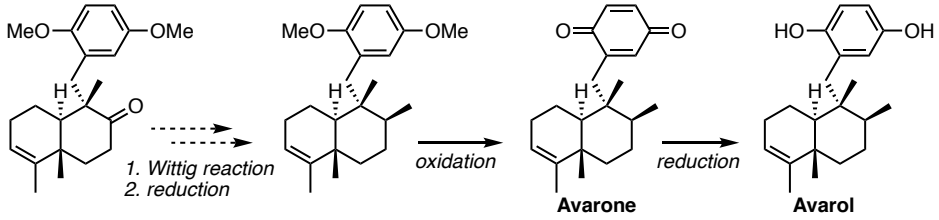
To continue with the synthesis of silyl enol ether ***Z*-38c**, the formation of alcohol **63** was next explored (Scheme 28). However, the halogen-lithium exchange of iodide **62** using *t*BuLi in Et_2O at -78 °C, followed by the addition of the acylsilane **52** was not successful, and only traces of product **63** were observed.



Scheme 28. Attempt at preparing alcohol **63**.

Outlook

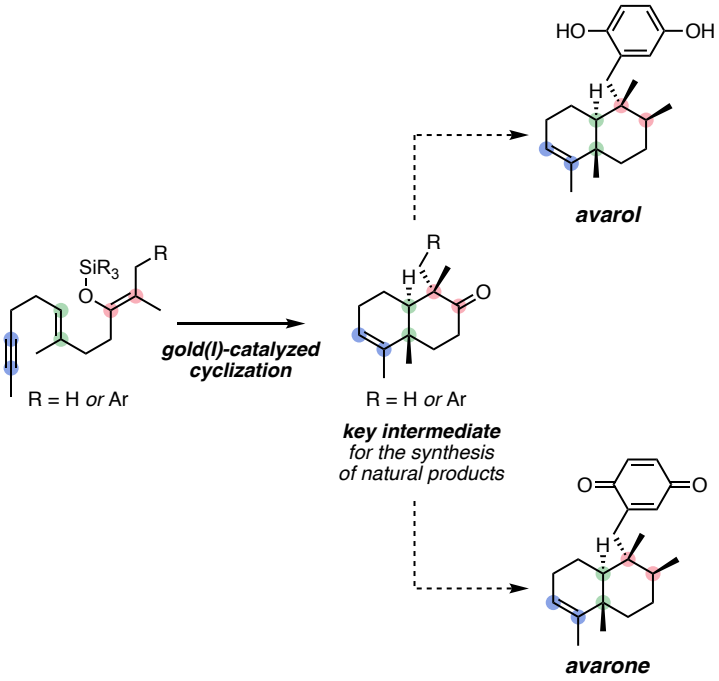
To accomplish the synthesis of avarone and avarol, we would perform a Wittig reaction followed by the reduction of the terminal double bond and finally redox manipulations (Scheme 29). In addition to that, other approaches are being examined for the selective synthesis of tetrasubstituted silyl enol ether (***Z*-38**). The development of these steps is currently under study in our group.



Scheme 29. Future work: synthesis of avarone and avarol.

Conclusions

We have developed a new method for the construction of decalin derivatives *via* gold(I)-catalyzed dienyne cyclization of tetrasubstituted silyl enol ethers. This methodology offers a new alternative for the assembly of this type of decalin cores as building blocks for the synthesis of natural products which does not rely on the use of the Wieland-Miescher ketone. Model intermediates for the synthesis of natural products such as avarol and avarone were obtained by this strategy. Efforts towards the completion of the total synthesis of these bioactive structures are currently being carried out in our laboratory.



Scheme 30. Gold(I)-catalyzed cyclization for the synthesis of key decalin derivatives.

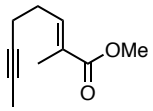
Experimental Section

General Methods

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

Synthetic Procedures and Analytical Data

Methyl (*E*)-2-methyloct-2-en-6-ynoate (33)



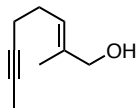
To a solution of hex-4-ynal (**32**)[27] (2.30 g, 24.00 mmol) in dry THF (120 mL) at 23 °C was added methyl 2-(triphenylphosphoranylidene)propanoate (10.03 g, 28.80 mmol). The reaction mixture was stirred at 60 °C for 18 h. The solvent was removed in vacuo. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 1:0 to 9:1) to provide methyl (*E*)-2-methyloct-2-en-6-ynoate (**33**) (2.86 g, 17.2 mmol, 72% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (t, *J* = 7.3 Hz, 1H), 3.74 (s, 3H), 2.39 – 2.32 (m, 2H), 2.28 – 2.22 (m, 2H), 1.85 (s, 3H), 1.77 (td, *J* = 2.5, 0.7 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 140.7, 128.7, 78.1, 76.4, 51.9, 28.5, 18.3, 12.7, 3.6 ppm.

HRMS (ESI+): m/z calc. for $[C_{10}H_{14}NaO_2]^+$: 189.0886, found: 189.0887.

(*E*)-2-Methyloct-2-en-6-yn-1-ol (34)



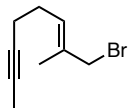
A two-necked 250 mL round-bottomed flask with a magnetic stirring bar was charged, under argon, with $LiAlH_4$ (25.8 mL, 1 M, 25.8 mmol) in anhydrous Et_2O (50 mL). After cooling down the suspension to 0 °C in an ice-water bath, a solution of methyl (*E*)-2-methyloct-2-en-6-ynoate (**33**) (2.86 g, 17.2 mmol) in anhydrous Et_2O (20 mL) was added dropwise over 5 min, and then the cooling bath was removed. The reaction mixture was allowed to reach room temperature and stirred for 17 h (when full conversion of the starting material was revealed by TLC). After this time, the reaction was cooled down again to 0 °C in an ice-water bath, and was quenched by careful addition of water, and then aqueous HCl 10%. The aqueous phase was extracted with Et_2O (x3), and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 9:1) delivered (*E*)-2-methyloct-2-en-6-yn-1-ol (**34**) (2.01 g, 14.5 mmol, 85% yield) as a colorless oil.

27 Hötling, S.; Haberlag, B.; Tamm, M.; Collatz, J.; Mack, P.; Steidle, J. L. M.; Vences, M.; Schulz, S. *Chem. Eur. J.* **2014**, *20*, 3183–3191.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (ddt, *J* = 6.9, 5.5, 1.4 Hz, 1H), 3.99 (d, *J* = 1.4 Hz, 2H), 2.25 – 2.11 (m, 4H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.66 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 124.6, 78.9, 75.8, 68.8, 27.5, 19.0, 13.8, 3.6 ppm.

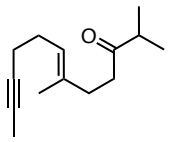
(*E*)-1-Bromo-2-methyloct-2-en-6-yne (29)



Prepared following a modified literature procedure.[28] PBr_3 (272.3 µL, 2.88 mmol) was added dropwise to a solution of (*E*)-2-methyloct-2-en-6-yn-1-ol (**34**) (798.00 mg, 5.77 mmol) in Et_2O (8.0 mL, 0.72 M) at 0 °C. The solution was warmed to room temperature and stirred for 1 h. The reaction was poured into water, was extracted with Et_2O, and was dried over $MgSO_4$, filtered, and concentrated to afford (*E*)-1-bromo-2-methyloct-2-en-6-yne (**29**) (1.16 g, 5.77 mmol, *ca.* quantitative yield) as a colorless oil. The crude product was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (t, *J* = 6.6 Hz, 1H), 3.98 (s, 2H), 2.25 – 2.14 (m, 4H), 1.79 – 1.76 (m, 6H) ppm.

(*E*)-2,6-Dimethyldodec-6-en-10-yn-3-one (28)



Prepared following a modified literature procedure.[29] K_2CO_3 (704.8 mg, 5.10 mmol) was added to a solution of methyl 4-methyl-3-oxopentanoate (735.3 mg, 5.10 mmol) in acetone (4.5 mL) at 23 °C. After stirring for 5 min, (*E*)-1-bromo-2-methyloct-2-en-6-yne (**29**) (1.13 g, 5.61 mmol) in acetone (1.5 mL) was added and the reaction mixture was refluxed for 2 days. Upon completion, the reaction mixture was cooled to 23 °C, filtered through Celite, which was washed with acetone (2 × 10 mL) and concentrated. The crude product was dissolved in 60 mL of ethanol/H_2O (1:1) at 23 °C. KOH (421 mg, 85% Wt, 6.37 mmol) was added to the solution. The mixture was stirred at reflux for 4 h. After completion (monitored by TLC and GC-MS) the mixture was cooled to 23 °C and extracted with EtOAc (x3). The organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 4:1 to afford (*E*)-2,7-dimethyldodec-6-en-10-yn-3-one (**28**) (557 mg, 2.70 mmol, 53% yield over 3 steps) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (ddt, *J* = 6.8, 5.5, 1.4 Hz, 1H), 2.66 – 2.50 (m, 3H), 2.32 – 2.21 (m, 2H), 2.19 – 2.08 (m, 4H), 1.77 (t, *J* = 2.4 Hz, 3H), 1.61 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H) ppm.

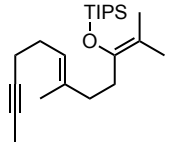
28 Suárez-Pantiga, S.; Rubio, E.; Alvarez-Rúa, C.; González, J. M. *Org. Lett.* **2009**, *11*, 13–16.

29 Ondet, P.; Lempenauer, L.; Duñach, E.; Lemière, G. *Org. Chem. Front.* **2016**, *3*, 999–1003.

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.6, 135.4, 123.5, 79.2, 75.7, 41.0, 39.2, 33.6, 27.9, 19.3, 18.4, 16.4, 3.6 ppm.

HRMS (ESI+): m/z calc. for $[C_{14}H_{22}NaO]^+$: 229.1563, found: 229.1561.

(*E*)-((2,6-Dimethyldodeca-2,6-dien-10-yn-3-yl)oxy)triisopropylsilane (27a)



Prepared following a modified literature procedure.[30] Triisopropylsilyl trifluoromethanesulfonate (397 µL, 1.48 mmol) was added to a solution of (*E*)-2,6-dimethyldodec-6-en-10-yn-3-one (**28**) (277.2 mg, 1.34 mmol) in CH_2Cl_2 (3.8 mL, 0.35 M). Triethylamine (243 µL, 1.75 mmol) was added dropwise. The reaction was stirred at 23 °C for 4 h, then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane) delivered a mixture of silyl enol ethers (365 mg, 1.01 mmol, 75% yield) as a colorless oil. The characterization of the mixture by NMR could not be performed because of the overlapping signals. The purification was performed just to avoid reproducibility issues.

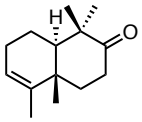
The resulting mixture of silyl enol ethers (360 mg, 993 µmol) was dissolved in dichloromethane (945 µL, 1.05 M) at 23 °C and pyridine hydrochloride (11.5 mg, 99.3 µmol) was added. The mixture was stirred at 23 °C for 3 h. The reaction was quenched with $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (x3) and the organic extracts were collected, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane) delivered (*E*)-((2,6-dimethyldodeca-2,6-dien-10-yn-3-yl)oxy)triisopropylsilane (**27a**) (150 mg, 414 µmol, 42% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (td, J = 6.8, 1.3 Hz, 1H), 2.24 – 2.08 (m, 8H), 1.78 (t, J = 2.4 Hz, 3H), 1.62 (s, 6H), 1.58 (s, 3H), 1.18 – 1.11 (m, 3H), 1.13 – 1.06 (m, 18H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 136.4, 123.1, 108.6, 79.3, 75.5, 38.2, 32.4, 27.9, 19.3, 18.9, 18.3, 18.1, 16.3, 13.5, 3.6 ppm.

HRMS (ESI+): m/z calc. for $[C_{23}H_{42}NaOSi]^+$: 385.2897, found: 385.2891.

(4a*S*,8a*R*)-1,1,4a,5-Tetramethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (26)



A solution of (*E*)-((2,6-dimethyldodeca-2,6-dien-10-yn-3-yl)oxy)triisopropylsilane (**27a**) (50.00 mg, 137.9 µmol) in CH_2Cl_2 (313 µL) and water (31 µL) was added in a screw-cap vial. [(JohnPhos)Au(MeCN)]SbF_6 (5.3

30 Holmbo, S. D.; Godfrey, N. A.; Hirner, J. J.; Pronin, S. V. A *J. Am. Chem. Soc.* **2016**, *138*, 12316–12319.

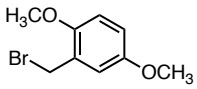
mg, 6.89 µmol, 5 mol %) was added in one portion and the mixture was stirred at 23 °C for 4 h. The reaction was monitored by TLC and after total consumption of the starting material, a solution of aqueous HCl 10% was added to the reaction mixture and it was stirred for 10 min. The aqueous phase was extracted with CH_2Cl_2 (x3) and the organic extracts were collected, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 97:3) delivered (4a*S*,8a*R*)-1,1,4a,5-tetramethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (**26**) (27 mg, 0.13 mmol, 95% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 – 5.25 (m, 1H), 2.57 (dddd, *J* = 16.0, 10.1, 7.5, 0.6 Hz, 1H), 2.48 (dddd, *J* = 16.0, 7.8, 4.0, 0.7 Hz, 1H), 2.17 – 2.07 (m, 1H), 2.07 – 1.94 (m, 2H), 1.77 – 1.64 (m, 2H), 1.64 – 1.58 (m, 4H), 1.58 – 1.49 (m, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.9, 141.8, 121.7, 51.2, 47.4, 37.6, 35.2, 34.6, 26.9, 26.8, 21.2, 19.9, 19.2, 18.1 ppm.

HRMS (ESI+): m/z calc. for $[C_{14}H_{22}NaO]^+$: 229.1563, found: 229.1559.

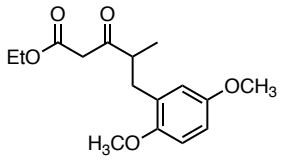
2,5-Dimethoxybenzyl bromide (42)



Prepared following a modified literature procedure.[31] To a solution of PBr_3 (1.01 mL, 10.7 mmol) in CH_2Cl_2 (48.6 mL, 0.22 M) at 0 °C was added a solution of (2,5-dimethoxyphenyl)methanol (1.53 mL, 10.7 mmol) in CH_2Cl_2 (24.3 mL, 0.44 M). The solution was stirred at 23 °C for 3 h. After this time, the reaction was poured into water, was extracted with CH_2Cl_2 (x3), and was dried over $MgSO_4$, filtered, and concentrated to afford 2-(bromomethyl)-1,4-dimethoxybenzene (**42**) (2.5 g, 10.7 mmol, *ca.* quantitative yield) as a beige solid.

The spectroscopic data were consistent with those previously reported.[32]

Ethyl 5-(2,5-dimethoxyphenyl)-4-methyl-3-oxopentanoate (40)



Prepared following a modified literature procedure.[33] Diisopropylamine (3.08 mL, 22.0 mmol) was dissolved in dry THF (40 mL, 0.25 M) and the solution cooled to 0 °C. *n*BuLi (9.2 mL, 2.4 M, 22.0 mmol) was slowly added and the reaction mixture was stirred at 23 °C for 30 minutes and afterwards cooled to 0 °C. Ethyl 3-oxopentanoate (1.4 mL, 10.0 mmol)

31 Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.

32 Ma, Y.; Zhang, Z.; Ji, X.; Han, C.; He, J.; Abliz, Z.; Chen, W.; Huang, F. *Eur. J. Org. Chem.* **2011**, 5331–5335.

33 Erhardt, H.; Kunz, K. A.; Kirsch, S. F. *Org. Lett.* **2017**, *19*, 178–181.

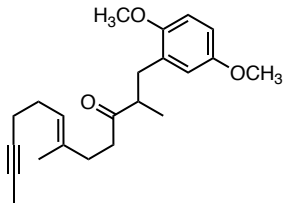
was dissolved in dry THF (4.5 mL) and slowly added to the solution. The reaction mixture was stirred for 15 minutes after which 2-(bromomethyl)-1,4-dimethoxybenzene (**42**) (2.4 g, 10.5 mmol) in dry THF (10 mL) was added. The solution was allowed to stir at 0 °C for 30 minutes and at 23 °C for 90 minutes. A saturated aqueous solution of NH_4Cl was added, and the separated aqueous layer extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was evaporated in vacuo. The crude material was purified by flash chromatography (SiO_2, cyclohexane/EtOAc 100% to 85:15%) to give ethyl 5-(2,5-dimethoxyphenyl)-4-methyl-3-oxopentanoate (**40**) as a colorless oil (1.6 g, 5.6 mmol, 56% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.8 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.67 (d, *J* = 2.9 Hz, 1H), 4.16 (qd, *J* = 7.2, 1.5 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.43 (d, *J* = 2.7 Hz, 2H), 3.05 – 2.92 (m, 2H), 2.60 – 2.52 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 167.5, 153.5, 151.9, 128.7, 117.5, 111.9, 111.3, 61.5, 55.9, 55.8, 48.4, 46.5, 34.2, 15.9, 14.2 ppm.

HRMS (ESI+): m/z calc. for $[C_{16}H_{22}NaO_5]^+$: 317.1359, found: 317.1351.

(*E*)-1-(2,5-Dimethoxyphenyl)-2,6-dimethyldodec-6-en-10-yn-3-one (39)



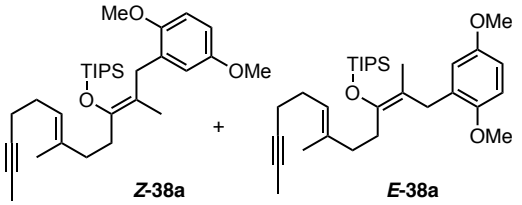
K_2CO_3 (719 mg, 5.20 mmol) was added to a solution of ethyl 5-(2,5-dimethoxyphenyl)-4-methyl-3-oxopentanoate (1.53 g, 5.20 mmol) in acetone (4.5 mL) at 23 °C. After stirring for 5 min, (*E*)-1-bromo-2-methyloct-2-en-6-yne (**29**) (1.15 g, 5.72 mmol) in acetone (1.5 mL) was added and the reaction mixture was refluxed for 2 days. Upon completion, the reaction mixture was cooled to 23 °C, filtered through Celite, which was washed with acetone (2 × 10 mL) and concentrated. The crude product was dissolved in 60 mL of ethanol/H_2O (1:1) at 23 °C. KOH (429 mg, 85% wt, 6.50 mmol) was added to the solution. The mixture was stirred at reflux for 4 h. After completion (monitored by TLC and GC-MS), the mixture was cooled to 23 °C and extracted with EtOAc (x3). The organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using cyclohexane/EtOAc 1:0 to 4:1 to afford (*E*)-1-(2,5-dimethoxyphenyl)-2,7-dimethyldodec-6-en-10-yn-3-one (**39**) (819 mg, 2.39 mmol, 46% yield over 3 steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.8 Hz, 1H), 6.71 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.66 (d, *J* = 3.0 Hz, 1H), 5.14 (t, *J* = 6.2 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.96 – 2.87 (m, 2H), 2.55 – 2.39 (m, 3H), 2.24 – 2.07 (m, 6H), 1.77 (t, *J* = 2.4 Hz, 3H), 1.57 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3, 153.4, 151.9, 135.4, 129.5, 123.5, 117.4, 111.7, 111.3, 79.2, 75.6, 55.9, 55.8, 46.1, 40.6, 34.3, 33.5, 27.9, 19.3, 16.3, 16.2, 3.6 ppm.

HRMS (ESI+): m/z calc. for $[C_{22}H_{30}NaO_3]^+$: 365.2087, found: 365.2077.

(((2*Z*,6*E*)-1-(2,5-Dimethoxyphenyl)-2,6-dimethyldodeca-2,6-dien-10-yn-3-yl)oxy)triisopropylsilane (*Z*-38a) + (((2*E*,6*E*)-1-(2,5-dimethoxyphenyl)-2,6-dimethyldodeca-2,6-dien-10-yn-3-yl)oxy)triisopropylsilane (*E*-38a)



***Z*-38a** ***E*-38a**

Triisopropylsilyl trifluoromethanesulfonate (314 µL, 1.17 mmol) was added to a solution of (*E*)-1-(2,5-dimethoxyphenyl)-2,6-dimethyldodec-6-en-10-yn-3-one (**39**) (364 mg, 1.06 mmol) in CH_2Cl_2 (3.04 mL, 0.35 M). Triethylamine (193 µL, 1.38 mmol) was added dropwise. The reaction was stirred at 23 °C for 17 h, then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 9:1) delivered a mixture of silyl enol ethers (437 mg, 876 µmol, 82% yield) as a colorless oil. The characterization of the mixture by NMR could not be performed because of the overlapping signals. The purification was performed just to avoid reproducibility issues.

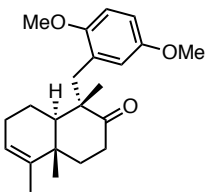
The resulting mixture of silyl enol ethers (422 mg, 846.0 µmol) was dissolved in CH_2Cl_2 (805.71 µL, 1.05 M) at 23 °C and pyridine hydrochloride (19.5 mg, 169.2 µmol) was added. The mixture was stirred at 23 °C for 2 days. The reaction was quenched with $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (x3) and the organic extracts were collected, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 9:1) delivered a mixture of tetrasubstituted silyl enol ethers ***Z*-38a**/***E*-38a** in a 1:1.9 ratio (142 mg, 285 µmol, 34% yield) as a colorless oil. The characterization of the mixture of tetrasubstituted silyl enol ethers ***Z*-38a**/***E*-38a** by NMR could not be performed because of the overlapping signals. However, the signals corresponding to the two CH_2 units could be distinguished and the ratio was determined by ^{1}H NMR.

HRMS (ESI+): m/z calc. for $[C_{31}H_{51}O_3Si]^+$: 499.3602, found: 499.3608.

(1*S*,4a*S*,8a*R*)-1-(2,5-Dimethoxybenzyl)-1,4a,5-trimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (37a) + (1*R*,4a*S*,8a*R*)-1-(2,5-dimethoxybenzyl)-1,4a,5-trimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (37b)

A solution of the mixture of tetrasubstituted silyl enol ethers ***Z*-38a**/***E*-38a** (ratio 1:1.9) (111.8 mg, 224.13 μmol) in CH_2Cl_2 (509.4 μL) and water (50.938 μL) was added in a screw-cap vial. [(JohnPhos)Au(MeCN)]SbF_6 (8.7 mg, 11.2 μmol, 5 mol %) was added in one portion and the mixture was stirred at 23 °C for 21 h. The reaction was monitored by TLC and after total consumption of the starting material, a solution of aqueous HCl 10% was added to the reaction mixture and it was stirred for 10 min. The aqueous phase was extracted with CH_2Cl_2 (x3) and the organic extracts were collected, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 97:3) delivered (1*S*,4a*S*,8a*R*)-1-(2,5-dimethoxybenzyl)-1,4a,5-trimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (**37a**) (16.4 mg, 47.9 μmol, 21% yield) and (1*R*,4a*S*,8a*R*)-1-(2,5-dimethoxybenzyl)-1,4a,5-trimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (**37b**) (38.1 mg, 111 μmol, 50% yield).

(1*S*,4a*S*,8a*R*)-1-(2,5-Dimethoxybenzyl)-1,4a,5-trimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (37a)

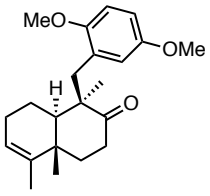


^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 – 6.70 (m, 2H), 6.58 – 6.57 (m, 1H), 5.29 – 5.23 (m, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 2.91 (d, *J* = 13.2 Hz, 1H), 2.79 (d, *J* = 13.2 Hz, 1H), 2.49 (ddd, *J* = 16.9, 10.3, 4.8 Hz, 1H), 2.38 (ddd, *J* = 16.8, 9.0, 6.8 Hz, 1H), 2.11 – 1.92 (m, 3H), 1.81 (ddd, *J* = 13.5, 9.1, 4.7 Hz, 1H), 1.72 – 1.63 (m, 1H), 1.59 – 1.55 (m, 3H), 1.55 – 1.38 (m, 2H), 1.09 (s, 3H), 0.94 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8, 153.2, 152.5, 141.5, 127.4, 121.9, 118.0, 112.5, 111.1, 55.8, 55.5, 51.8, 46.9, 40.4, 37.5, 35.6, 33.9, 26.6, 20.7, 20.7, 19.7, 18.1 ppm.

HRMS (ESI+): m/z calc. for $[C_{22}H_{30}NaO_3]^+$: 365.2087, found: 365.2086.

(1*R*,4a*S*,8a*R*)-1-(2,5-Dimethoxybenzyl)-1,4a,5-trimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (37b)



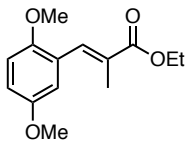
M.p. = 87–89 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 1.7 Hz, 2H), 6.54 (t, *J* = 1.7 Hz, 1H), 5.29 – 5.23 (m, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.42 (d, *J* = 13.3 Hz, 1H), 3.22 (td, *J* = 14.7, 5.7 Hz, 1H), 2.45 (d, *J* = 13.3 Hz, 1H), 2.34 (ddd, *J* = 14.5, 4.1, 2.8 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.13 – 1.99 (m, 2H), 1.85 – 1.76 (m, 2H), 1.70 – 1.52 (m, 5H), 1.41 (s, 3H), 0.90 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.3, 153.0, 152.1, 142.6, 127.8, 121.5, 118.8, 111.7, 110.9, 55.8, 55.2, 54.6, 52.6, 38.1, 37.1, 35.7, 34.6, 27.3, 21.6, 20.0, 19.7, 18.3 ppm.

HRMS (ESI+): m/z calc. for $[C_{22}H_{30}NaO_3]^+$: 365.2087, found: 365.2088.

Ethyl (*E*)-3-(2,5-dimethoxyphenyl)-2-methylacrylate (47)

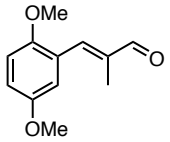


Ethyl 2-(triphenylphosphoranylidene)propionate (13.1 g, 36.1 mmol) was added to a mixture of 2,5-dimethoxybenzaldehyde (5.0 g, 30.1 mmol) in toluene (30 mL, 1 M) at 23 °C. The mixture was heated at 80 °C and stirred for 35 h, cooled to 23 °C and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (cyclohexane/EtOAc 1:0 to 4:1) provided the title compound as a pale-yellow oil (5.5 g, 22.0 mmol, 73% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (q, *J* = 1.7 Hz, 1H), 6.90 – 6.82 (m, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.05 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 153.1, 152.1, 134.6, 129.2, 125.9, 116.3, 114.4, 111.6, 60.9, 56.2, 55.9, 14.4 ppm.

(*E*)-3-(2,5-Dimethoxyphenyl)-2-methylacrylaldehyde (48)



Ethyl (*E*)-3-(2,5-dimethoxyphenyl)-2-methylacrylate (**47**) (3.00 g, 12.0 mmol) was dissolved in dry THF (42 mL, 0.3 M) and DIBAL-H in THF (1.0 M) (25.2 mL, 25.2 mmol) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 6 h. After that, the reaction was quenched by addition of EtOAc at 0 °C, followed by water and then HCl 1 M. The compound was extracted with EtOAc (x3), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was used in the next step without further purification.

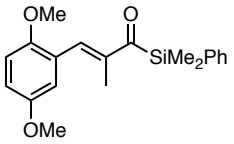
To a solution of the crude product in HPLC-grade CH_2Cl_2 (60 mL, 0.2 M) were sequentially added DMP (7.6 g, 18.0 mmol) and $NaHCO_3$ (2.0 g, 24.0 mmol). The reaction mixture was stirred at 23 °C for 3 h and then a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The organic layer was separated and washed with sat. aq. $Na_2S_2O_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 100:0 to 85:15) to yield (*E*)-3-(2,5-dimethoxyphenyl)-2-methylacrylaldehyde (**48**) (1.6 g, 7.66 mmol, 64% yield over 2 steps) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.57 (q, *J* = 1.5 Hz, 1H), 7.02 (d, *J* = 2.9 Hz, 1H), 6.92 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.03 (d, *J* = 1.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 153.2, 152.2, 144.9, 138.6, 124.8, 115.9, 115.9, 111.8, 56.2, 55.9, 11.2 ppm.

HRMS (ESI+): m/z calc. for $[C_{12}H_{14}O_3]^+$: 229.0835, found: 229.0833.

(*E*)-3-(2,5-Dimethoxyphenyl)-1-(dimethyl(phenyl)silyl)-2-methylprop-2-en-1-one (44)



Prepared following a modified literature procedure.[34] To a solution of (*E*)-3-(2,5-dimethoxyphenyl)-2-methylacrylaldehyde (**48**) (800 mg, 3.88 mmol) in dry CH_2Cl_2 (7.8 mL, 0.5 M) was added propane-1,3-dithiol (409 µL, 4.07 mmol). The reaction mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (95.7 µL, 776 µmol) was added dropwise. The mixture was stirred at 0 °C for about 1 h before it was allowed to warm to 23 °C. The reaction mixture was stirred at 23 °C for 4 h. The mixture was quenched with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). The combined organic layers were washed brine, dried over $MgSO_4$ and evaporated. The crude product was used in the next step without further purification.

*n*BuLi (2.5 M in THF) (1.86 mL, 4.66 mmol) was added to a stirred solution of the crude product in dry THF (9.7 mL, 0.4 M) at 0 °C under an argon atmosphere. After 1 h, chlorodimethyl(phenyl)silane (814 µL, 4.85 mmol) was added. The reaction mixture was stirred at 23 °C for 23 h. Then it was quenched by addition of water, extracted with CH_2Cl_2 (x3), The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was used in the next step without further purification.

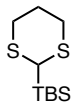
To a stirred solution of the above crude product in THF (12 mL) and water (3 mL) was added $CaCO_3$ (3.11 g, 31.0 mmol) and I_2 (5.91 g, 23.3 mmol). The mixture was stirred at 23 °C for 18 h, then quenched with saturated $Na_2S_2O_3$. The mixture was filtered through a pad of celite, eluting with diethyl ether. Then the solution was quenched with water and brine. The organic phase was extracted with diethyl ether (x3), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/EtOAc 1:0 to 4:1) to afford (*E*)-3-(2,5-dimethoxyphenyl)-1-(dimethyl(phenyl)silyl)-2-methylprop-2-en-1-one (**44**) (553 mg, 1.62 mmol, 42% yield over 3 steps) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 1H), 7.64 – 7.58 (m, 2H), 7.43 – 7.34 (m, 3H), 6.92 (d, *J* = 2.9 Hz, 1H), 6.85 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 1.93 (d, *J* = 1.4 Hz, 3H), 0.61 (s, 6H) ppm.

34 (a) Dickschat, J. S.; Wickel, S.; Bolten, C. J.; Nawrath, T.; Schulz, S.; Wittmann, C. *Eur. J. Org. Chem.* **2010**, 2687–2695. (b) Decostanzi, M.; Van Der Lee, A.; Campagne, J.-M.; Leclerc, E. *Adv. Synth. Catal.* **2015**, *357*, 3091–3097.

MS (LC-MS): m/z calc. for [$C_{20}H_{24}O_3Si$]: 340.1, found: 341.2 (M+H)

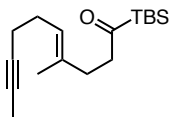
***tert*-Butyl(1,3-dithian-2-yl)dimethylsilane (54)**



*n*BuLi (2.4 M in THF) (6.25 mL, 15.0 mmol) was added to a stirred solution of 1,3-dithiane (1.8 g, 15.0 mmol) in dry THF (44.0 mL, 0.34 M) at 0 °C under an argon atmosphere. After 30 min, *tert*-butylchlorodimethylsilane (2.3 g, 15.0 mmol) was added. The reaction mixture was stirred at 23 °C for 17 h. Then it was quenched by addition of water, extracted with diethyl ether (x3), The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/CH_2Cl_2 1:0 to 4:1) afforded the title compound (3.1 g, 13.0 mmol, 88% yield) as a colorless oil.

The spectroscopic data were consistent with those previously reported.[35]

(*E*)-1-(*tert*-Butyldimethylsilyl)-4-methyldec-4-en-8-yn-1-one (52)



*n*BuLi (1.37 mL, 2.5 molar, 3.42 mmol) was added to a mixture of *tert*-butyl(1,3-dithian-2-yl)dimethylsilane (**54**) (801 mg, 3.42 mmol) in THF (24 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. (*E*)-9-iodo-7-methylnon-6-en-2-yne (**45**) (814 mg, 3.11 mmol) in THF (7 mL) was added to the reaction mixture at 0 °C and the resulting solution was stirred at 23 °C for 21 h. Then it was quenched by addition of a saturated solution of $NaHCO_3$, extracted with diethyl ether (x3), The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was used in the next step without further purification.

$NaHCO_3$ (1.30 g, 15.5 mmol) and [bis(trifluoroacetoxy)iodo]benzen**e** (3.07 g, 7.14 mmol) were added to a mixture of the crude product in acetonitrile (17 mL), H_2O (2.2 mL) and CH_2Cl_2 (2.2 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 3 h. Then it was quenched by addition of a saturated solution of $NaHCO_3$/$Na_2S_2O_3$ (1:1), extracted with diethyl ether (x3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/CH_2Cl_2 1:0 to 4:1) afforded (*E*)-1-(tert-butyldimethylsilyl)-4-methyldec-4-en-8-yn-1-one (**52**) (369 mg, 1.32 mmol, 43% yield over two steps) as a colorless oil.

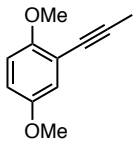
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 – 5.10 (m, 1H), 2.75 – 2.61 (m, 2H), 2.22 – 2.09 (m, 6H), 1.77 (t, J = 2.3 Hz, 3H), 1.59 (s, 3H), 0.93 (s, 9H), 0.19 (s, 6H) ppm.

35 Winter, P.; Hiller, W.; Christmann, M. *Angew. Chem. Int. Ed.* **2012**, *5*, 3396–3400.

^{13}C NMR (101 MHz, $CDCl_3$) δ 247.2, 135.6, 123.4, 79.2, 75.6, 48.9, 31.7, 27.9, 26.6, 19.3, 16.7, 16.4, 3.6, -6.8 ppm.

HRMS (ESI+): m/z calc. for $[C_{17}H_{30}NaOSi]^+$: 301.1958, found: 301.1952.

1,4-Dimethoxy-2-(prop-1-yn-1-yl)benzene (60)

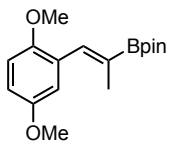


K_2CO_3 (1.6 g, 11.4 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (1.3 g, 6.8 mmol) were added to a solution of 2,5-dimethoxybenzaldehyde (631.5 mg, 3.8 mmol) in MeOH (31.6 mL, 0.12 M) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h. The mixture was monitored by TLC and quenched with water. The aqueous phase was extracted with Et_2O (x3) and the organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used in the next step without further purification.

The crude product was dissolved in dry THF (4.4 mL, 0.86 M). The solution was cooled to -20 °C and *n*BuLi (2.48 mL, 2.3 M, 5.7 mmol) was added to the reaction mixture at -20 °C and it was stirred for 1 h. MeI (0.71 mL, 11.4 mmol) was added to the reaction mixture and then was stirred at 23 °C for 14 h. The mixture was monitored by TLC and quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted with EtOAc (x3) and the organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:o to 97:3) delivered 1,4-dimethoxy-2-(prop-1-yn-1-yl)benzene (**60**) (406 mg, 2.3 mmol, 61% yield over two steps) as a white solid.

The spectroscopic data were consistent with those previously reported.[36]

(*Z*)-2-(1-(2,5-Dimethoxyphenyl)prop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (61)



Prepared following a modified literature procedure.[37] 1,4-dimethoxy-2-(prop-1-yn-1-yl)benzene (**60**) (141 mg, 0.80 mmol), bis(pinacolato)diboron (244 mg, 960 µmol), tri(4-methoxyphenyl)phosphine (16.9 mg, 48.0 µmol, 6 mol %), copper(I) chloride (4.0 mg, 40.0 µmol, 5 mol %) and K_2CO_3 (22.1 mg, 160 µmol, 20 mol %) were dissolved in anhydrous Et_2O (3.6 mL, 0.22 M). Propan-2-ol (122 µL, 1.60 mmol) was added and the mixture was stirred for 15 h at 23 °C. Et_2O (20 mL) and water (20 mL) were added. The aqueous phase was extracted with EtOAc (x3) and the organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column

36 An, D.-L.; Zhang, Z.; Orita, A.; Mineyama, H.; Otera, J. *Synlett* **2007**, 1909–1912.

37 Noble, A.; Roesner, S.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 15920–15924.

chromatography on silica gel (cyclohexane/EtOAc 1:0 to 4:1) afforded (*Z*)-2-(1-(2,5-dimethoxyphenyl)prop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**61**) (189 mg, 621 µmol, 78% yield) as a white solid.

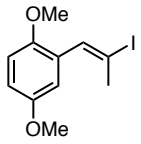
M.p. = 52–54 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (q, *J* = 1.8 Hz, 1H), 6.88 (d, *J* = 2.9 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 8.9, 2.9 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.92 (d, *J* = 1.8 Hz, 3H), 1.31 (s, 12H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 151.8, 137.9, 127.7, 116.4, 113.2, 111.5, 83.6, 56.1, 55.9, 25.1, 16.2 ppm.

HRMS (ESI+): m/z calc. for $[C_{17}H_{16}O_4{}^{10}B]^+$: 304.1955, found: 304.1947.

(*E*)-2-(2-iodoprop-1-en-1-yl)-1,4-dimethoxybenzene (62)



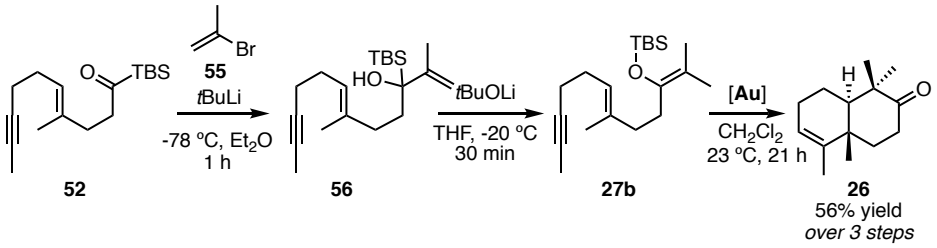
Prepared following a modified literature procedure.[37] NaOH (544.40 µL, 3.0 M, 1.63 mmol) was added to a solution of (*Z*)-2-(1-(2,5-dimethoxyphenyl)prop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**61**) (165.6 mg, 544.4 µmol) in THF (1 mL). After stirring for 10 min at 23 °C a solution of I_2 (276.4 mg, 1.09 mmol) in THF (5.8 mL) was added over 5 min and stirring was continued for 2 h. The mixture was then quenched with a saturated solution of $Na_2S_2O_3$. The aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 9:1) afforded (*E*)-2-(2-iodoprop-1-en-1-yl)-1,4-dimethoxybenzene (**62**) (127 mg, 418 µmol, 77% yield) as a beige solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 1H), 6.80 – 6.78 (m, 2H), 6.76 – 6.72 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.58 (d, *J* = 1.6 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 151.0, 136.7, 127.1, 115.9, 113.3, 111.7, 98.7, 56.2, 55.9, 29.7 ppm.

HRMS (ESI+): m/z calc. for $[C_{11}H_{14}IO_2]^+$: 305.0033, found: 305.0030.

Alternative synthesis of (4a*S*,8a*R*)-1,1,4a,5-tetramethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (26)



Prepared following a modified literature procedure.[26] To a solution of 2-bromoprop-1-ene (27.76 µL, 312.5 µmol) in Et_2O (0.3 mL) at -78 °C, *t*BuLi (367.6 µL, 1.7 M, 625.0 µmol) was added. After the mixture was stirred at -78 °C for 1 h, it was warmed to -20 °C for 1 h and recooled to -78 °C. A solution of (*E*)-1-(tert-butyldimethylsilyl)-4-methyldec-4-en-8-yn-1-one (**52**) (69.63 mg, 250.0 µmol) in Et_2O (0.3 mL) was added. The reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with NH_4Cl and the mixture was extracted with Et_2O (x3). The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was used in the next step without further purification.

Prepared following a modified literature procedure.[25] The crude product was dissolved in THF (2.50 mL, 0.1M). The solution was cooled at 0 °C and *t*BuOLi (114 µL, 2.2 M, 250 µmol) was added. The reaction mixture was stirred at 0 °C for 60 min. The reaction was quenched with NH_4Cl and the mixture was extracted with Et_2O (x3). The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was used in the next step without further purification.

[(JohnPhos)Au(MeCN)]SbF_6 (9.65 mg, 12.5 µmol, 5 mol %) was added to a mixture of the crude in CH_2Cl_2 HPLC (1 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 21 h. The reaction was monitored by TLC and after total consumption of the starting material, a solution of HCl 10% was added to the reaction mixture and it was stirred for 10 min. The aqueous phase was extracted with CH_2Cl_2 (x3) and the organic extracts were collected, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:0 to 97:3) delivered (4a*R*,8a*S*)-1,1,4a,5-tetramethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (**26**) (29 mg, 0.14 mmol, 56% yield over 3 steps) as a colorless oil.

The spectroscopic data were consistent with those previously reported in this thesis.

Crystallographic Data

(1*R*,4a*S*,8a*R*)-1-(2,5-dimethoxybenzyl)-1,4a,5-trimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one (37b)

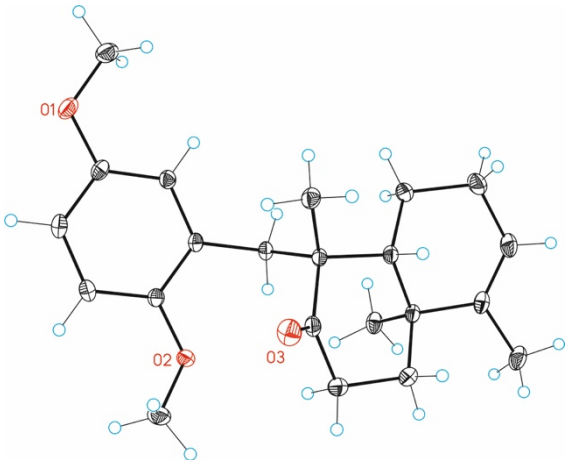


Table 1. Crystal data and structure refinement for **37b**.

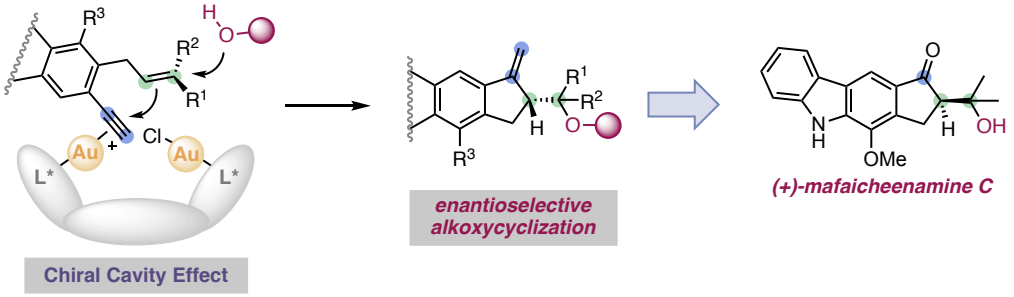
Identification code	im-5-35
Empirical formula	C11 H15 O1.50
Formula weight	171.23
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 21/n
Unit cell dimensions	a = 14.8739(5)Å α= 90°. b = 7.2965(2)Å β = 107.494(4)°. c = 17.3247(6)Å γ = 90°.
Volume	1793.24(11) Å^3
Z	8
Density (calculated)	1.268 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	744
Crystal size	0.100 x 0.100 x 0.050 mm^3
Theta range for data collection	2.155 to 32.269°.
Index ranges	-22<=h<=21,-10<=k<=10,-25<=l<=25
Reflections collected	19786
Independent reflections	5912[R(int) = 0.0221]
Completeness to theta =32.269°	92.9%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.88
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5912/ 0/ 231
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1108
R indices (all data)	R1 = 0.0496, wR2 = 0.1157
Largest diff. peak and hole	0.488 and -0.200 e.Å

General Conclusions

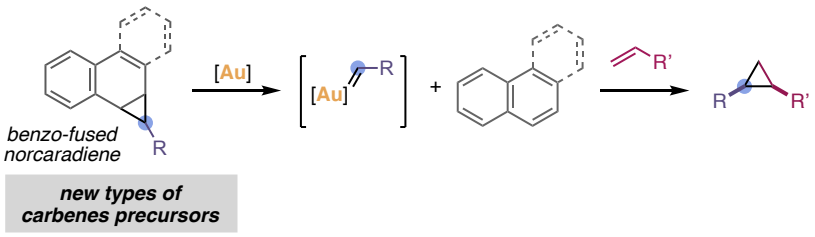
UNIVERSITAT ROVIRA I VIRGILI
GOLD(I) CAVITANDS FOR THE ASSEMBLY OF MOLECULAR COMPLEXITY
Inmaculada Martin Torres

The research developed in this Doctoral Thesis has led to the following conclusions:

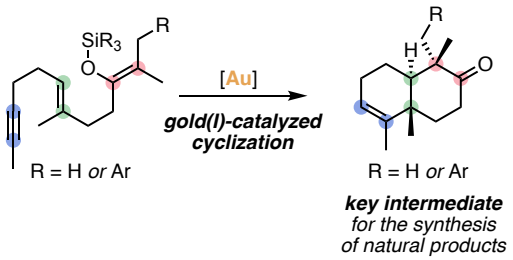
A highly modular synthesis of chiral and achiral gold(I)-cavitand complexes was developed from resorcin[4]arenes. The achiral gold(I) complexes were used to investigate a new selectivity in the cyclization of 1,6-dienynes, while the chiral ones enabled the first enantioselective alkoxycyclization of terminal phenyl-linked 1,6-enynes. The derivatization of the enantio-enriched products resulting from this reaction allowed the straightforward assembly of a variety of enantioenriched structures. To demonstrate the value of these chiral gold(I)-cavitands, the natural product (+)-mafaicheenamine C was synthesized and its absolute configuration was established. In addition to that, theoretical studies supported our hypothesis that the cavity has an important role in the outcome of this enantioselective transformation.



We have developed a novel approach towards the generation of metal carbenes by decarbenation of persistent cyclopropanes. We designed and developed a new family of metal-carbene precursors: benzo-fused norcaradienes derived from naphthalene and phenanthrene. The gold(I)-catalyzed decarbenation of these substrates (which uses the release of polyaromatic molecules as driving force) has been successfully exploited for the diastereoselective synthesis of aryl and vinyl cyclopropanes as a new alternative to the use of dangerous non-stabilized diazo compounds.



Finally, a new strategy was designed for the assembly of decalin building blocks as key intermediates in the synthesis of natural products, based on the gold(I)-catalyzed cyclization of tetrasubstituted silyl enol ethers. In this regard, we have also studied different strategies for the synthesis of the latter compounds. Further efforts towards the completion of the total synthesis of avarol and avarone from these intermediates are currently underway.



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