GOLD(I)-CATALYZED CYCLIZATIONS AND ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)- SCHISANWILSONENE A.

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Dipòsit Legal: T 1611-2015

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Gold(I)-Catalyzed Cyclizations and Enantioselective Total Synthesis of (+)-Schisanwilsonene A

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institut Català d'Investigació Química (ICIQ)

UNIVERSITAT ROVIRA I VIRGILI

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FAIG CONSTAR que aquest treball, titulat "Gold(I)-Catalyzed Cyclizations and Enantioselective Total Synthesis of (+)-Schisanwilsonene A", que presenta Morgane Gaydou per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Química Analítica i Química Orgànica d'aquesta Universitat i que acompleix els requeriments per poder optar a Menció Internacional.

Tarragona, Octubre de 2014

El Director de la Tesi Doctoral

Prof. Antonio M. Echavarren

À ma famille

"If a cluttered desk is a sign of a cluttered mind,
of what, then, is an empty desk a sign?"
Albert Einstein

"Anybody who has been seriously engaged in scientific
work of any kind realizes that over the entrance to the
gate of the temple of science are written the words:
'You must have faith.'."
Max Planck

This Doctoral Thesis has been carried out at the Institut Català d'Investigació Química (ICIQ) under the supervision of Professor Antonio M. Echavarren to whom I would like to express my gratitude for giving me the opportunity to be part of his research group. I am sincerely thankful for his trust in me, allowing me to develop new ideas and teaching me how to handle a project. His chemistry knowledge shared throughout my Ph.D thesis and his continuous support have been of valuable help.

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At the printing of this manuscript, the results presented herein have been published:

Synthesis of (+)-Schisanwilsonene A by Tandem Gold-Catalyzed Cyclization- 1,5-Migration-Cyclopropanation

M. Gaydou, R. E. Miller, N. Delpont, J. Ceccon, A. M. Echavarren

Angew. Chem. Int. Ed. **2013**, *52*, 6396-6399

Highlighted in 2013 in Synfacts, DOI: 10.1055/s-0033-1339367

Gold-Catalyzed Synthesis of Tetrazoles from Alkynes by C-C Bond Cleavage

M. Gaydou, A. M. Echavarren

Angew. Chem. Int. Ed. **2013**, 52, 13468-13471

Highlighted in 2013 in Synfacts, DOI: 10.1055/s-0033-1340788

Intermolecular Reaction of Gold(I)-Carbenes with Furans by Related Mechanism

D. Lebœuf, M. Gaydou, Y. Wang, A. M. Echavarren

Org. Chem. Front. **2014**, *1*, 759-764

(The first two authors contributed equally to this work)

In addition, the following short article on one of the most active gold(I) catalysts has been published:

Gold, [[1,1'-biphenyl]-2-ylbis(1,1-dimethylethyl)phosphine]chloro- and Gold(1+), (acetonitrile)[[1,1'-biphenyl]-2-ylbis(1,1-dimethylethyl)phosphine] (OC-6-11)-hexafluoroantimonate(1-)

M. Gaydou, A. M. Echavarren

e-EROS Encyclopedia of Reagents for Organic Synthesis **2011**, DOI: 10.1002/047084289X.rn01339.

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Prologue

This PhD thesis has been divided in five different parts:

- A summary in Spanish.
- A general introduction presenting some important aspects of gold catalysis.
- Three chapters presenting the research carried out during these four years.

Each chapter is divided in five parts. First, a specific introduction on the topic investigated. This introduction will be followed by a description of the objectives. Then, the results obtained will be presented. A brief conclusion will summarize the outcomes of the research. Finally, an experimental section will describe the synthesis and the characterization of the compounds prepared and isolated.

The general introduction will discuss the basic principles of homogeneous catalysis with gold, the activation of alkynes and the mechanisms proposed for the cycloisomerization of enynes.

The first chapter is completely independent and is devoted to a new reactivity in gold(I) catalysis: gold(I)-catalyzed synthesis of tetrazoles.

The second chapter presents a methodology developed to evaluate the propensity of gold(I)-carbenes to be trapped by external nucleophiles. Both propargylic esters and 1,6-enynes were examined.

The last chapter applies the work done within our group on the 1,5-migration reaction of 1,6-enynes to the total synthesis of (+)-shisanwilsonene A.

Abbreviations and acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendation found in the on-line "guidelines for authors" of *The Journal of Organic Chemistry*.

A bookmark with the structures and labeling of the most frequently used gold catalysts is also provided.

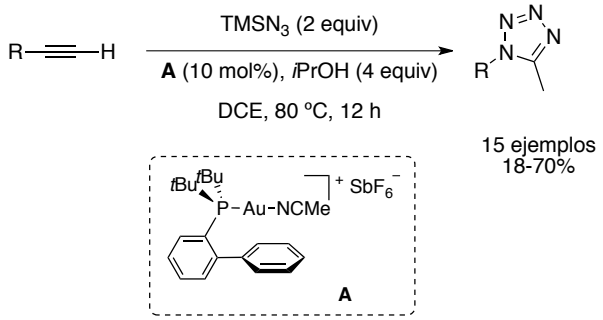
Additional abbreviations and acronyms used in this manuscript are referenced in the list below:

DCE	1,2-Dichloroethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DFT	Density functional theory
DMAP	4-(Dimethylamino)pyridine
DMP	Dess-Martin periodinane
Im	Imidazole
IPr	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L	Ligand
MS	Molecular sieves
Nu	Nucleophile
PNB	*para*-Nitrobenzoyl
TBS	*tert*-Butyldimethylsilyl
PNP	*para*-Nitrophenyl

Resumen

Durante los últimos años, dentro de nuestro grupo de investigación se desarrollaron reacciones de activación de alquinos catalizadas por oro que favorecen el ataque de distintos nucleófilos (tales como olefinas, índoles o arilos) a alquinos.[1]

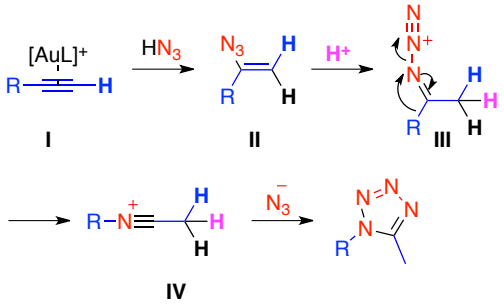
En el primero capítulo de esta Tesis Doctoral se describe una nueva reacción catalizada por Au(I) en la que participan tanto alquinos cómo trimetilsilil azida, dando lugar a un nuevo tipo de productos: tetrazoles (Esquema 1). Esta reacción transcurre con buenos rendimientos con diferentes alquinos sustituidos con grupos activantes, demostrando a la vez sus limitaciones con alquinos que contienen grupos deactivantes.



Esquema 1. Síntesis de tetrazoles

Experimentos preliminares nos han permitido proponer el mecanismo de esta nueva transformación (Esquema 2). La vinil azida **II**, formada tras la activación del alquino con el complejo catiónico de Au(I) **A**, podría protonarse dando lugar al catión iminodiazonio **III**. Este intermedio se transformaría en el catión nitrilio **IV** en una transposición de Schmidt. Finalmente, la cicloadición 1,3-dipolar entre el intermedio **IV** y una azida daría lugar al tetrazol.

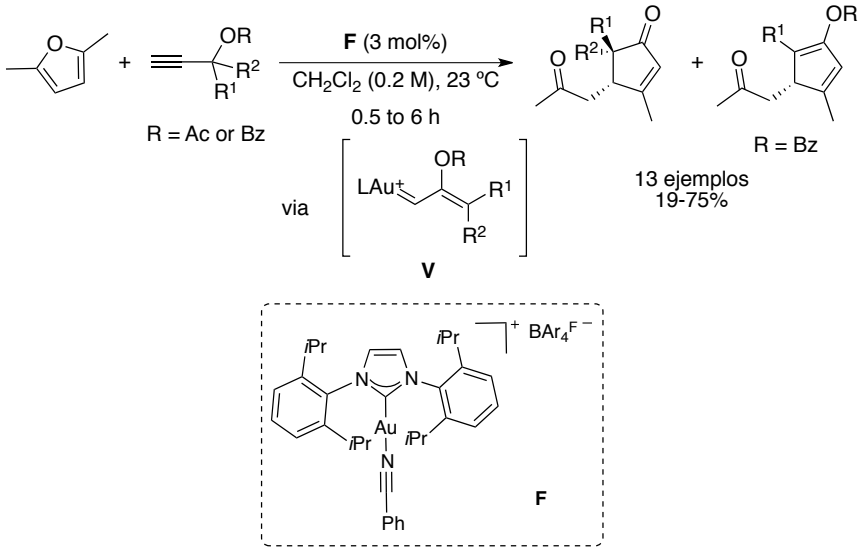
1 (a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun*. **2008**, 333-346. (b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350.



Esquema 2. Mecanismo de la formación de los tetrazoles

El segundo capítulo trata sobre los carbenos de Au(I) que pueden reaccionar intermolecularmente con diferentes nucleófilos.

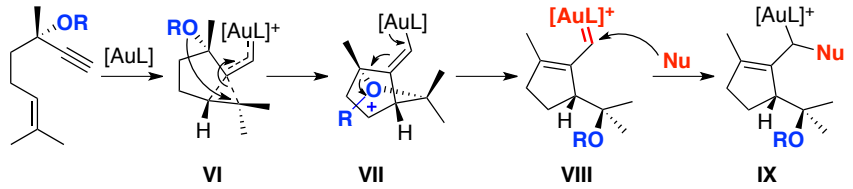
La primera parte presenta la nueva formación de ciclopentenonas y ciclopentadienos con ésteres propargílicos y furanos (Esquema 3). Tras la activación con el complejo catiónico de Au(I) (**F**), el éster propargílico sufriría una migración 1,2 dando lugar al carbeno de Au(I) **V** que reaccionaría con furanos.



Esquema 3. Síntesis de ciclopentenones y ciclopentadienos

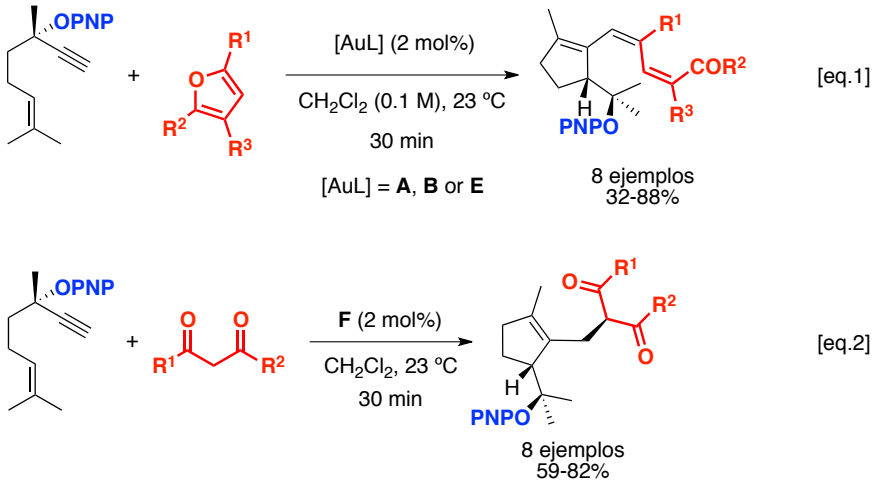
Tras la activación de 1,6-eninos con complejos catiónicos de Au(I), nuestro grupo descubrió en 2009 que los 1,6-eninos conteniendo alcoholes o éteres

propargílicos experimentan una migración 1,5 dando lugar a cationes de alil-oro. Estos intermedios se pudieron atrapar intra- o intermolecularmente con alquenos.[2] El objetivo de la segunda parte de este capítulo fue desarrollar esta reacción atrapando el intermedio alil-oro **VIII** con diferentes nucleófilos (Esquema 4).

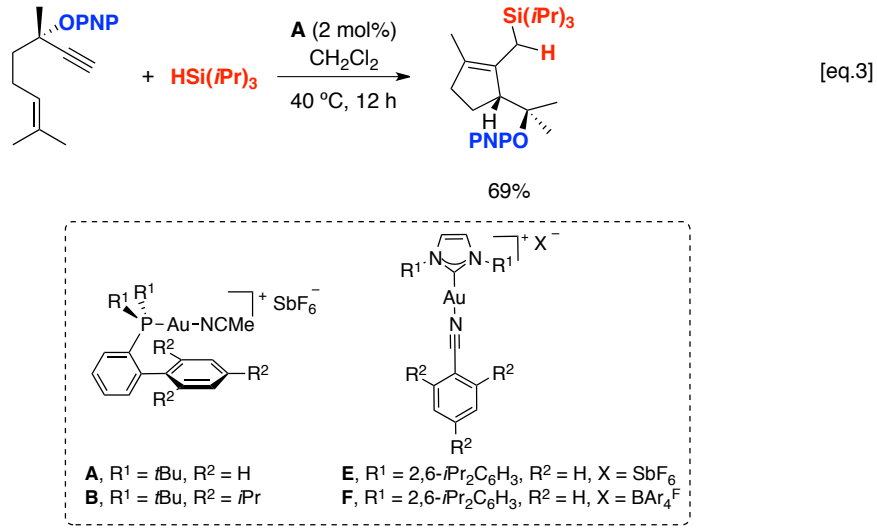


Esquema 4. Formación del alil-oro VIII

La reacción intermolecular con furanos permitió obtener nuevos productos de gran interés (Esquema 5, [eq. 1]), tales como 1,3-dicetonas (Esquema 5, [eq. 2]) y silanos (Esquema 5, [eq. 3]).



2 E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.



Esquema 5. Productos obtenidos con distintos nucleófilos

En el último capítulo de este manuscrito se aplicó la metodología desarrollada en el grupo sobre la migración 1,5 de grupos OR de 1,6-eninos catalizada con Au(I) a la síntesis de productos naturales.

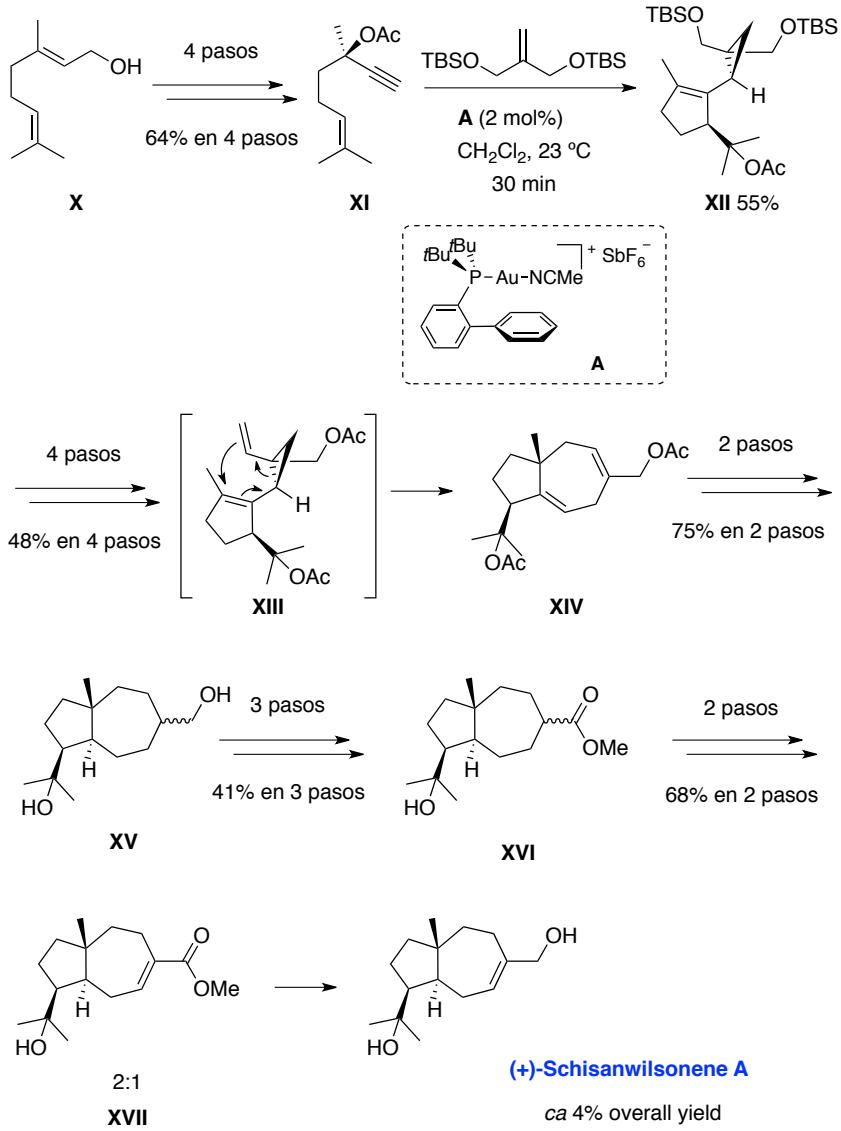
De este modo, se completó la síntesis total del (+)-schisanwilsonene A, un compuesto natural que presenta una notable actividad biológica contra la hepatitis B.

La síntesis enantioselectiva del (+)-schisanwilsonene A se comenzó a partir del geraniol (**X**), producto comercial (Esquema 6). Tras 4 pasos de reacción, se obtuvo el intermedio **XI** con un rendimiento global del 64%.

Después, la etapa clave de la síntesis fue la ciclación del alquino terminal **XI** con un alqueno sustituido con dos grupos OTBS empleando el catalizador de Au(I) **A**. El cicloaducto **XII** se obtuvo con un 55% de rendimiento.

Tras 4 pasos de reacción se obtuvo el intermedio **XIII** con un rendimiento global del 48%. El intermedio **XIII** se convirtió directamente en el producto bicíclico **XIV** mediante una transposición de Cope. La desprotección de los alcoholes y una hidrogenación catalizada por níquel Raney permitieron acceder al intermedio **XV**.

El (+)-schisanwilsonene A se formó tras 6 últimos pasos de reacción, después de la oxidación del alcohol primario del intermedio **XV** al ácido seguida de un esterificación, la introducción del doble enlace a través de una eliminación de selenóxido y una reducción final del éster.



Esquema 6. Síntesis total de la (+)-schisanwilsonene A

General Introduction

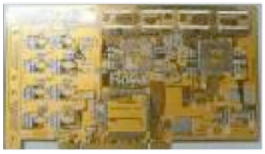
Introduction to gold, "the precious metal"

Gold has always been associated to beauty and power. For this reason, gold has fascinated people and was highly valued since the earliest recorded times in history. From electrical devices passing by jewelry and monetary exchange, since the Egyptian age, gold has been, and still is, widely used throughout the world (Figure 1).

Funerary mask of Tutankhamun

Gold necklace

Gold bars



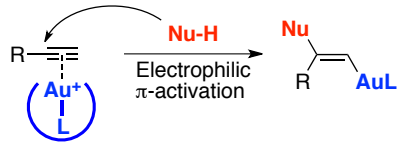
Gold circuit board

Figure 1. Gold, "the precious metal"

From a chemical point of view, gold is a soft, bright yellow metal with a number of physical properties. Bearing the atomic number 79 and the symbol Au (from the Latin *aurum*, "shining dawn"), gold is a transition metal belonging to the group 11 of the periodic table with three most common oxidation states: gold(0), gold(I) and gold(III). Considered as scarce, it is however more abundant than palladium, ruthenium, or iridium.

An important property of gold is its high electronegativity arising from the relativistic contraction of the valence orbital 6*s*, which reaches a maximum

in the periodic table with gold.[3] As a result of this relativistic effect, the 5*d* orbital is expanded, decreasing its electron-electron repulsion, and making gold complexes remarkably reactive Lewis acids with high affinity for π-bonds. Therefore, gold complexes usually surpass the reactivity shown by other electrophilic metal salts and complexes for the activation of alkynes towards a variety of nucleophiles. Once the triple bond has entered the coordination sphere of the metal, subsequent nucleophilic attack onto η^2-alkyne Au(I) complexes gives *trans*-alkenyl species (Scheme 1).[4]



Scheme 1. π-Activation of an aljyne by gold towards nucleophilic addition

Gold complexes

Simple gold salts, such as $NaAuCl_4$ or AuCl, have shown enough reactivity to be competent catalysts in many transformations.[5] However, neutral gold complexes LAuCl as well as cationic gold complexes [AuLL']X have found broader applicability, which has been examplified throuhg a large number

3 (a) P. Pyykkö, *Chem. Rev.* **1988**, *88*, 563-594. (b) P. Pyykkö, *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456. (c) K. S. Pitzer, *Acc. Chem. Res.* **1979**, *12*, 272-276. (d) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403.

4 (a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180-3211. (b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333-346. (c) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. (d) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350. (e) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378. (f) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208-3221. (g) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675-691. (h) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442.

5 (a) J. P. Brand, C. Chevalley, J. Waser, *Beilstein J. Org. Chem.* **2011**, *7*, 565-569. (b) S. Karmalar, A. Kim, C. H. Oh, *Synthesis* **2009**, 194-198.

of publications.[4] These complexes can be easily tuned by modifying the electronic and/or steric properties of its ligand L, allowing a wide range of reactivities to be accessed.[6] For example, N-heterocyclic carbenes (NHC), which are highly electron-donating ligands, render the corresponding gold(I) complexes poorly electrophilic, while more electrophilic catalysts can be accessed through the use of more electron deficient phosphine ligands. The most electrophilic Au(I)-complexes would typically bear a phosphite ligand (Figure 2).

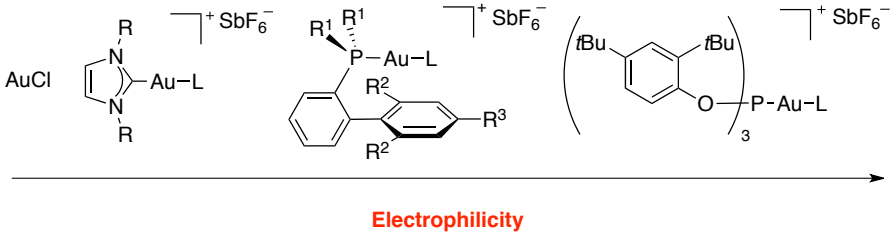


Figure 2. Electrophilicity of gold(I)-complexes

The catalytically active species is often generated *in situ* by chloride abstraction of a gold precatalyst complex (LAuCl) using various silver salts with distinct counteranions.[7] Alternatively, cationic gold complexes [AuLL']X which possesses a weakly coordinating neutral ligand (L'),[8] such as acetonitrile or benzonitrile, are readily available or can be easily

6 (a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378. (b) Y.W. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2014**, *47*, 889-901.

7 (a) Y. Zhu, C. S. Day, L. Zhang, K. J. Hauser, A. C. Jones, *Chem. Eur. J.* **2013**, *19*, 12264-12271. (b) A. Homs, I. Escofet, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 5782-5785. (c) A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, *Adv. Synth. Catal.* **2014**, *356*, 221-228.

8 (a) M. Raducan, C. Rodríguez-Escrich, X. C. Cambeiro, E. C. Escudero-Adán, M. A. Pericàs, A. M. Echavarren, *Chem. Commun.* **2011**, *47*, 4893-4895. (b) M. Raducan, M. Moreno, C. Bour, A. M. Echavarren, *Chem. Commun.* **2012**, *48*, 52-54.

prepared. This more convenient type of catalysts can enter catalytic cycles by associative ligand exchange with the substrate.[9]

Our group has successfully designed and synthesized numerous gold complexes throughout the years. The most common ones are represented in Figure 3. Gold(I) cationic complexes **D-F**, bearing N-heterocyclic ligands that are strongly σ-donating and weakly π-acidic, are expected to increase the carbene-like reactivity of the gold(I) intermediates by increasing gold-to-substrate π-donation. Conversely, gold(I) complex **G** with a π-acidic phosphite ligand should increase the carbocation-like reactivity of the gold(I) intermediates (decreasing gold-to-substrate π-donation). Finally, cationic complexes **A-C** bearing phosphine ligands have been widely employed since they fell in between these two extremes.[10]

9 P. N. Dickson, A. Wehrli, G. Geier, *Inorg. Chem.* **1988**, *27*, 2921-2925.

10 (a) E. Herrero-Gómez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem. Int. Ed* **2006**, *45*, 5455-5459. (b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350.

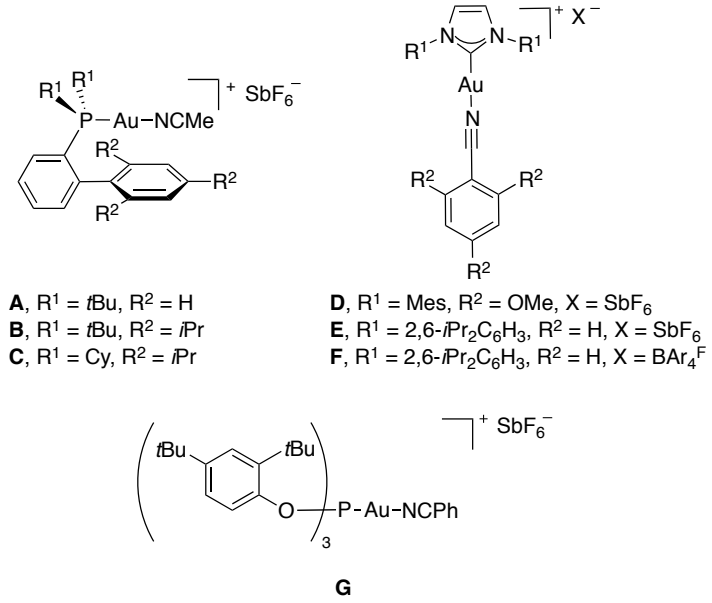
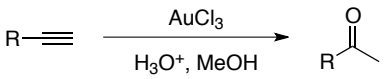


Figure 3. Representative cationic gold(I)-complexes

First examples of gold in catalysis

As previously mentioned, gold has been known for centuries, but its first application in organic chemistry was not reported until 1976, when the hydration of alkynes using gold(III) salts was developed by Thomas and co-workers (Scheme 2).[11]



Scheme 2. First reaction catalyzed by gold(III) salts

Some years later, in 1998,[12] the same hydration reaction was developed in the presence of gold(I) complexes under homogeneous conditions. The

11 R. O. C. Nomran, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983-1987.

12 J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

same gold(I) complexes were used in 2004 in the first application of gold catalysis for the cyclizations of 1,6-enynes. [13] Specifically, the cycloisomerization reactions of enynes were extensively studied as they can lead to the construction of complex architectures through several sequential intramolecular processes.[14,15,16]

Cycloisomerization of enynes

Cycloisomerization of 1,6-enynes

The cyloisomerisation of 1,6-enynes is a very interesting process for the construction of several naturally occurring molecular scaffolds. The mechanism of this reaction begins with the activation of the alkyne moiety by gold(I) to form an (η^2-alkyne)metal complex **I**, followed by nucleophilic attack of the alkene *via* 5-*exo-dig* or 6-*endo-dig* pathway (Scheme 3).[13,17,18] In the absence of external nucleophiles, cyclopropyl gold(I) carbene **II** undergoes a skeletal rearrangement to afford 1,3-dienes **V** (via single

13 C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

14 (a) A. S. K. Hashmi *Angew. Chem. Int. Ed.* **2005**, *44*, 6990-6993. (b) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180-3211. (c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333-346. (d) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. (e) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378. (f) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208-3221. (g) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675-691. (h) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395-3442.

15 (a) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296. (b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350. (c) V. Michelet, P. Y. Toullec, J.-P. Genêt *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.

16 (a) C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16-28. (b) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902-912.

17 C. Ferrer, M. Raducan, C. Nevado, C. K. Claverie, A. M. Echavarren, *Tetrahedron* **2007**, *63*, 6306-6316.

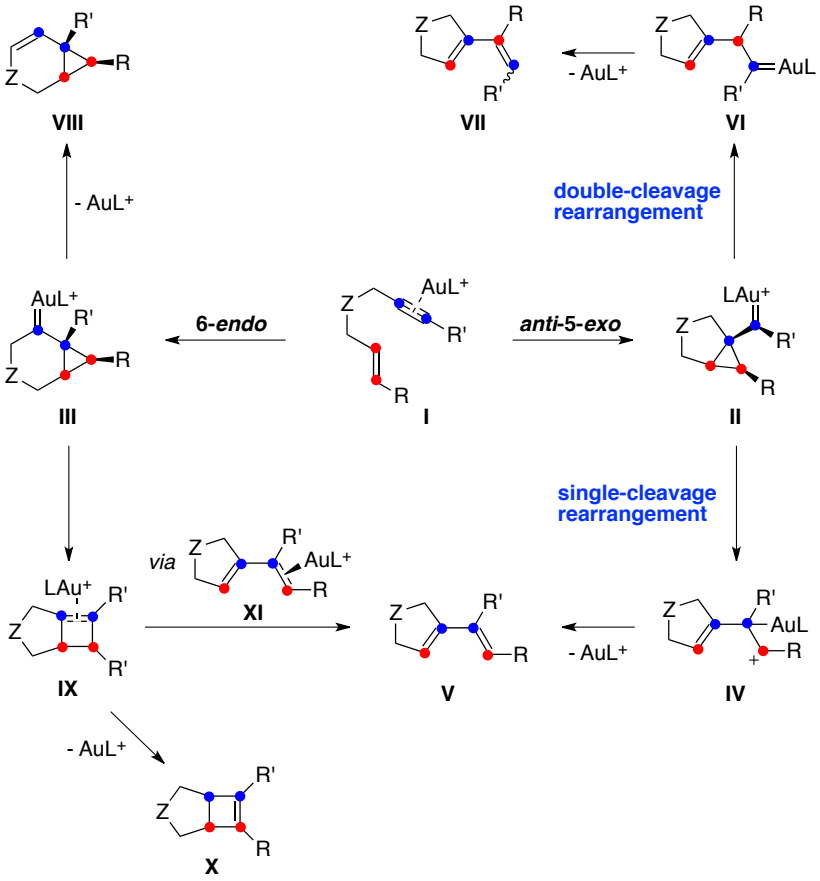
18 E. Soriano, J. Marco-Contelles, *Acc. Chem. Res.* **2009**, *42*, 1026-1036.

cleavage rearrangement) and/or **VII** (via double cleavage rearrangement). The single cleavage rearrangement involves a formal 1,3-migration of the terminal carbon of the alkene towards the terminal carbon of the alkyne. Bicyclic compounds **VIII** and **X** are obtained by *endo*-cyclization *via* carbene **III**. Cyclopropanation products **VIII** arise after proton elimination from intermediate **III**,[19] whereas fused cyclobutenes **X** could be formed by an isomerization of **III**, which could also give rise to **V** via gold(I) complex **IX**.[20] The mechanistic proposals for both single and double cleavage rearrangements are supported by kinetic data and DFT calculations.[20,21]

19 C.-M. Chao, D. Beltrami, P. Y. Toullec, V. Michelet, *Chem. Commun.* **2009**, 6988-6990.

20 A. Escribano-Cuesta, P. Pérez-Galán, E. Herrero-Gómez, M. Sekine, A. A. C. Braga, F. Maseras, A. M. Echavarren, *Org. Biomol. Chem.* **2012**, *10*, 6105-6111.

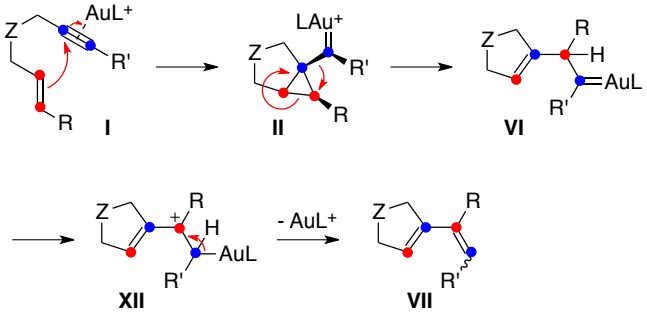
21 C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.



Scheme 3. Gold(I)-catalyzed cycloisomerizaion of 1,6-enynes

Although the double cleavage skeletal rearrangement also takes place through cyclopropyl gold carbene **II**, in this case, a formal insertion of the terminal alkene carbon into the alkyne carbons leads to the formation of a new gold carbene (**VI**). The latter suffers a dyotropic rearrangement[22] to afford **VII**, the final product after both the alkyne and the alkene have been cleaved (Scheme 4).[20,21]

22 (a) M. T. Reetz, *Angew. Chem. Int. Ed.* **1972**, *11*, 129-130. (b) M. T. Reetz, *Angew. Chem. Int. Ed.* **1972**, *11*, 130-131.



Scheme 4. Double cleavage rearrangement

Cycloisomerization of 1,5-enynes

The gold(I)-catalyzed cyclization of 1,5-enynes allows the synthesis of a wide variety of synthetically useful products (Scheme 5).[14e, 23 , 24] The mechanistic proposal resembles the one previously described for 1,6-enynes and similarly proceeds via both single cleavage[25] and double cleavage rearrangements.[26] In most cases, 1,5-enynes cyclize through an endocyclic pathway. However, the *exo*-cyclic pathway is favored when terminal alkynes or iodoalkynes are employed.[27]

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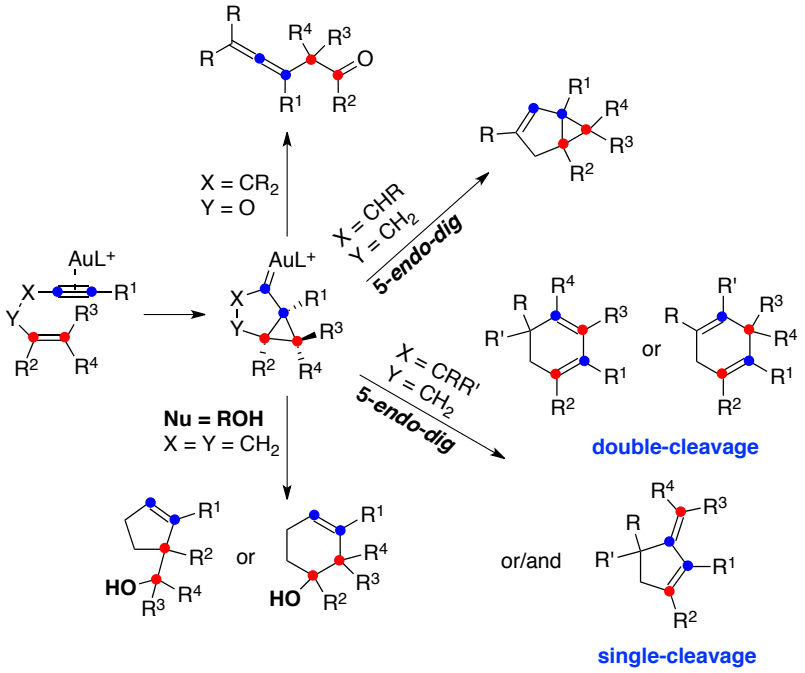
23 (a) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317-1382. (b) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858. (c) C. Li, Y. Zeng, H. Zhang, J. Feng, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 6413-6417.

24 V. López-Carrillo, N. Huguet, Á. Mosquera, A. M. Echavarren, *Chem. Eur. J.* **2011**, *17*, 10972-10978.

25 F. Gagosz, *Org. Lett.* **2005**, *7*, 4129-4132.

26 (a) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806-11807. (b) J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 9705-9710.

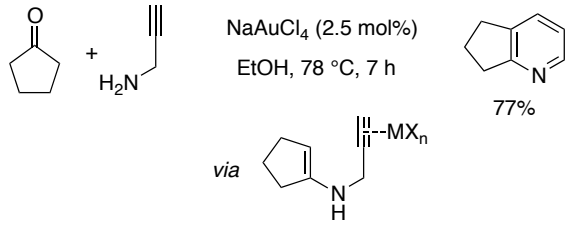
27 T. Shibata, Y. Ueno, K. Kanda, *Synlett* **2006**, 4411-4414.



Scheme 5. Gold (I)-catalyzed cycloisomerizaion of 1,5-enynes

One of the first reports of *endo*-cyclization of 1,5-enynes was applied in a novel synthesis of pyridines (Scheme 6).[28] This transformation proceeds through gold(III) catalyzed sequential imine condensation, imine-enamine isomerization followed by regioselective 6-*endo-dig* cyclization of the resulting *N*-propargylenamine intermediate terminating with an aromatization of the ring.

28 G. Abbiati, A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, E. Rossi, *J. Org. Chem.* **2003**, *68*, 6959-6966.



Scheme 6. Synthesis of pyridines by Au(III)-catalyzed cyclization of 1,5-enynes

Cycloisomerization of higher 1,n-enynes (n>6)

The skeletal rearrangement of 1,7-enynes is considered as an extension of the cycloisomerization reaction of 1,6-enynes.[29] 1,7-Enynes can undergo single cleavage skeletal rearrangement with different metals,[30,31,32] and, in the case of gold, the cyclization usually takes place under milder reaction conditions and with lower catalyst loadings. A few examples have also been reported for the cycloisomerization of 1,8-[33] and 1,9-enynes.[34]

Recently, our group reported the gold-catalyzed cycloisomerization of larger 1,*n*-enynes (*n* = 10-16) to form macrocycles incorporating a cyclobutene moiety (Scheme 7).[35]

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29 N. Cabello, C. Rodríguez, A. M. Echavarren, *Synlett* **2007**, *11*, 1753-1758.

30 (a) N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049-6050. (b) N. Chatani, K. Kataoka, S. Murai, N. Furukawa, Y. Seki, *J. Am. Chem. Soc.* **1998**, *120*, 9104-9105. (c) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 714-715.

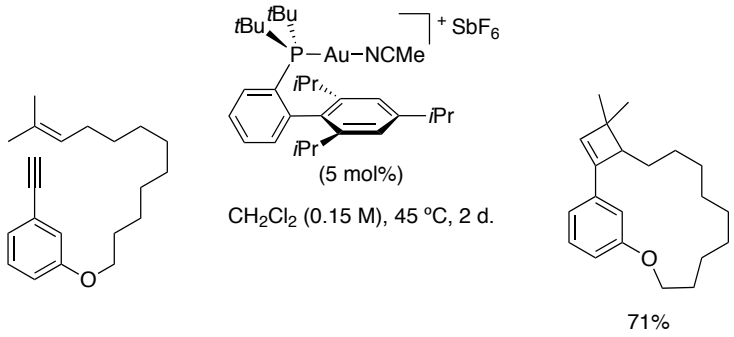
31 M. Hatano, K. Mikami, *J. Am. Chem. Soc.* **2003**, *125*, 4704-4705.

32 E. M. Simmons, R. Sarpong, *Org. Lett.* **2006**, *8*, 2883-2886.

33 H. Ito, H. Ohmiya, M. Sawamura *Org. Lett.* **2010**, *12*, 4380-4383.

34 E. Comer, E. Rohan, L. Deng, J. A. Porco Jr. *Org. Lett.* **2007**, *9*, 2123-2126.

35 C. Obradors, D. Leboeuf, J. Aydin, A. M. Echavarren *Org. Lett.* **2013**, *15*, 1576-1579.



Scheme 7. Gold(I)-catalyzed cyclization of a 1,16-enyne to a m-cyclophane

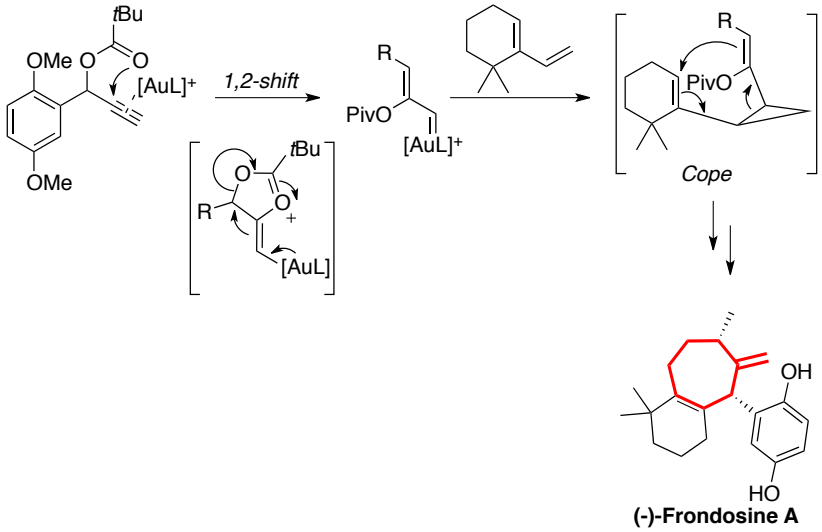
Gold in total synthesis

The number of reports on total syntheses involving gold catalysis has significantly increased in the last five years, due to the numerous methodologies developed for the gold-catalyzed cycloisomerizations and cycloadditions, which allows the construction of complex polycyclic molecules in a single step.[36]

As an example, the 1,2-carboxylate shift of propargyl esters triggered a cascade of intermolecular cyclopropanation followed by a formal homo-Cope rearrangement for the synthesis of the 7-membered ring in (-)-frondosine A (Scheme 8).[37]

36 M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448-2462.

37 D. Garayalde, K. Krüger, C. Nevado, *Angew. Chem. Int. Ed.* **2011**, *50*, 911-915.



Scheme 8. Gold(I)-catalyzed synthesis of (-)-frondosine A

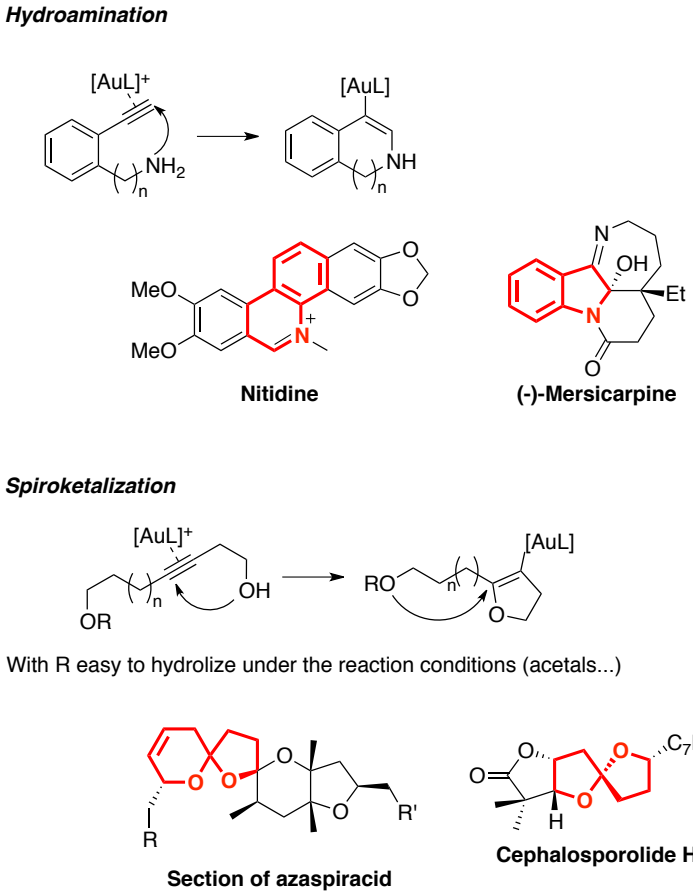
Also, the alkaloids nitidine[38] and (-)-mersicarpine[39] were formed via gold-catalyzed hydroamination of alkynes while a gold-catalyzed spiroketalization was applied in the synthesis of the toxin azaspiracid,[40] and cephalosporolide H (Scheme 9).[41]

38 T. Enomoto, A.-L. Girard, Y. Yasui, Y. Takemoto, *J. Org. Chem.* **2009**, *74*, 9158-9164.

39 R. Nakajima, T. Ogino, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2010**, *132*, 1236-1237.

40 Y. Li, F. Zhou, C. J. Forsyth, *Angew. Chem. Int. Ed.* **2007**, *46*, 279-282.

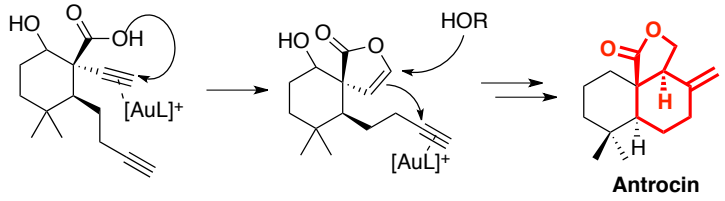
41 (a) S. F. Tlais, G. B. Dudley, *Beilstein J. Org. Chem.* **2011**, *7*, 570-577. (b) S. F. Tlais, G. B. Dudley, *Org. Lett.* **2010**, *12*, 4698-4701.



Scheme 9. Gold(I)-catalyzed hydroamination and spiroketalization

Finally, a gold-catalyzed diyne tandem reaction was utilized in the synthesis of antrocin (Scheme 10).[42]

42 H. Shi, L. Fang, C. Tan, L. Shi, W. Zhang, C.-C. Li, T. Luo, Z. Yang, *J. Am. Chem. Soc.* **2011**, *133*, 14944-14947.



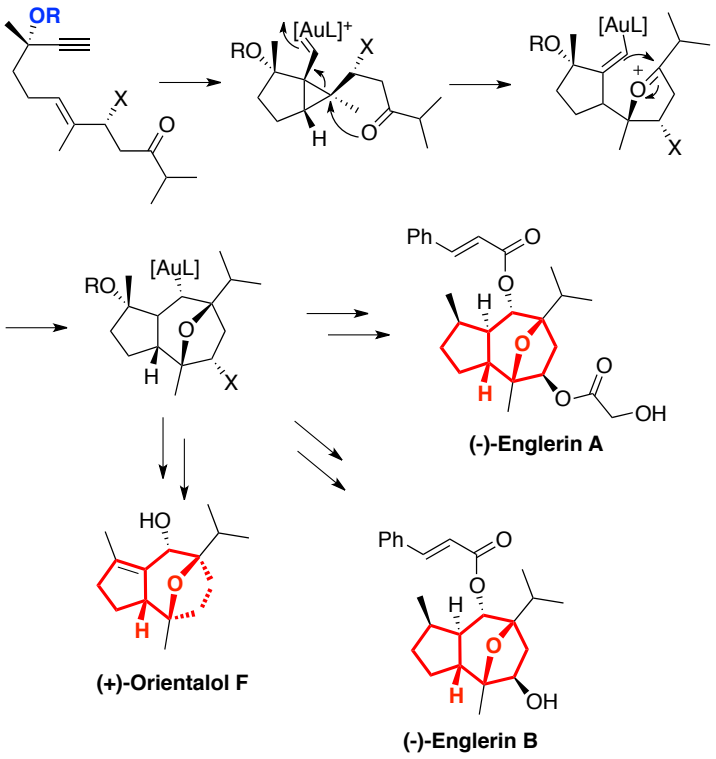
Scheme 10. Synthesis of antrocin

Our group has also contributed actively in this field, which has resulted in total syntheses of several bioactive sesquiterpenes as illustrated in Scheme 11 and Scheme 12.

The total syntheses of (+)-orientalol F,[43] (-)-englerin A and B[44] were completed by using a formal [2+2+2] alkyne/alkene/carbonyl-cycloaddition in the key steps (Scheme 11).

[43] E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327-7329.

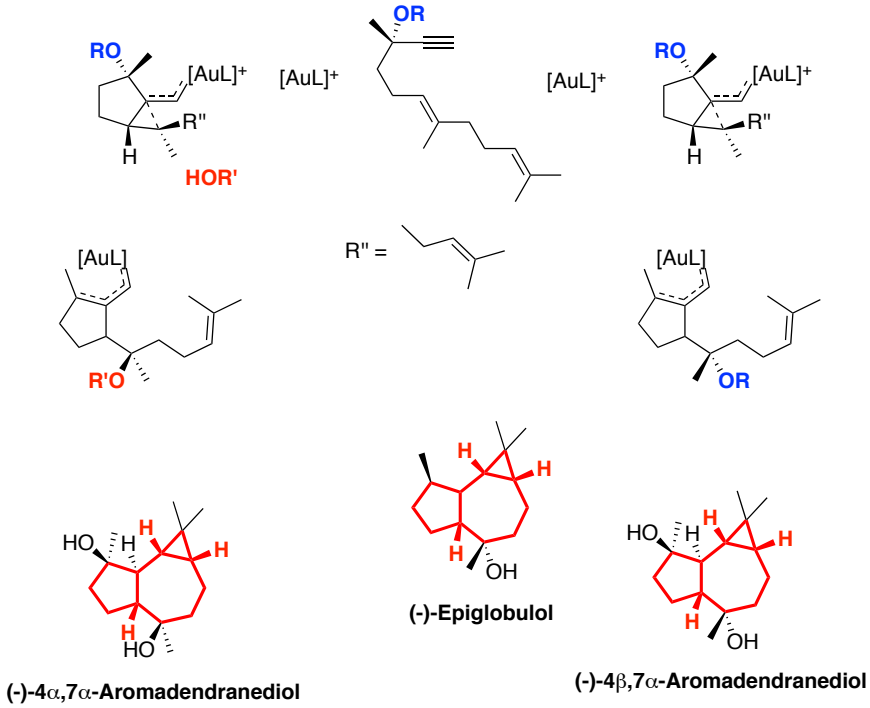
[44] K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.



Scheme 11. Synthesis of natural compounds containing the oxatricyclic skeleton

Recently, short syntheses of epiglobulol and aromadendranediol[45] were completed based on a gold(I)-catalyzed cyclization followed by a 1,5-migration (Scheme 12).

45 J. Carreras, M. Livendahl, P. R. McGonigal, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2014**, *53*, 4896-4899.



Scheme 12. Gold(I)-catalyzed syntheses of epiglobulol and aromadendranediols

Chapter 1. Gold-Catalyzed Reactions of Alkynes with Azides

Introduction

Tetrazoles

Tetrazoles, and in particular, 1,5-disubstituted tetrazoles, have found broad applications in both material science and medicinal chemistry.[46] They are often used in pharmaceuticals as lipophilic spacers as well as stable bioisosteres of the carboxylic acid group. They can also serve as precursors to a wide variety of nitrogen-containing heterocycles as they can be easily rearranged into useful compounds through a Huisgen tetrazole rearrangement.[47] Therefore, the development of novel methods for the preparation of this synthetically challenging compound class has been of great interest.

The most convenient route for the synthesis of 5-substituted *1H*-tetrazoles relies on the [3+2] cycloaddition between nitriles and azide anion promoted by a Lewis or Brönsted acid. However, the generality of this method is limited by the usually harsh reaction conditions (Scheme 13).[47,48,49]

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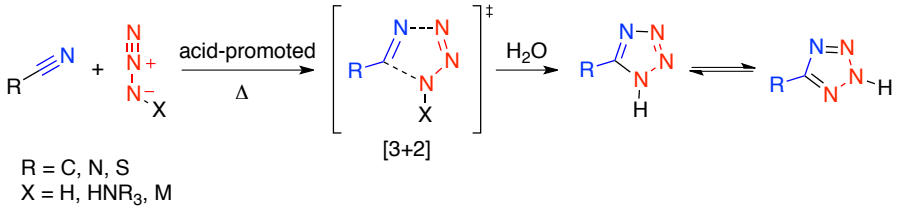
46 (a) L. V. Myznikov, A. Hrabalek, G. I. Koldobskii, *Chem. Heterocycl. Compd.* **2007**, *43*, 1-9. (b) D. R. Armour, K. M. L. Chung, M. Congreve, B. Evans, S. Guntrip, T. Hubbard, C. Kay, D. Middlemiss, J. E. Mordaunt, N. A. Pegg, M. V. Vinader, P. Ward, S. P. Watson, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1015-1020. (c) B. J. Al-Hourani, S. K. Sharma, J. Y. Mane, J. Tuszynski, V. Baracos, T. Kniess, M. Suresh, J. Pietzsch, F. Wuest, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1823-1826.

47 (a) R. Huisgen, *Proc. Chem. Soc.* **1961**, 357-396. (b) R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565-598. (c) R. Huisgen, *J. Org. Chem.* **1968**, *33*, 2291-2297. (d) R. Huisgen, M. Seidel, J. Sauer, J. McFarland, G. Wallbillich, *J. Org. Chem.* **1959**, *24*, 892-893.

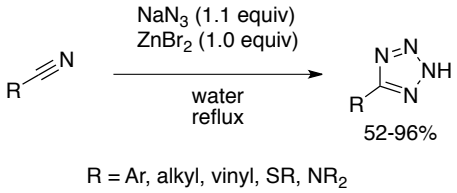
48 A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084-3213.

49 (a) O. Dimroth, G. Fester, *Chem. Ber.* **1910**, *43*, 2219-2223. (b) F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* **2002**, *124*, 12210-12216. (c) G. I. Koldobskii, *Russ. J. Org. Chem.* **2006**, *42*, 469-486.



Scheme 13. Tetrazole formation by [3+2] cycloaddition

In 2001, Sharpless and co-workers reported a novel, safe, and environmentally friendly Zn(II)-mediated [3+2] cycloaddition synthesis of 5-substituted tetrazoles from nitriles and sodium azide in water.[50] Through coordination of $ZnBr_2$ onto the nitrile, the energy barrier of the reaction was lowered, thus allowing the transformation to proceed smoothly with a wide variety of nitriles (Scheme 14).[51] Unfortunately, certain substrates, especially electron-rich and *ortho*-substituted aromatic nitriles as well as unactivated alkyl nitriles, still required elevated temperatures (150 ºC-170 ºC in a sealed vessel).



Scheme 14. Sharpless synthesis of tetrazoles

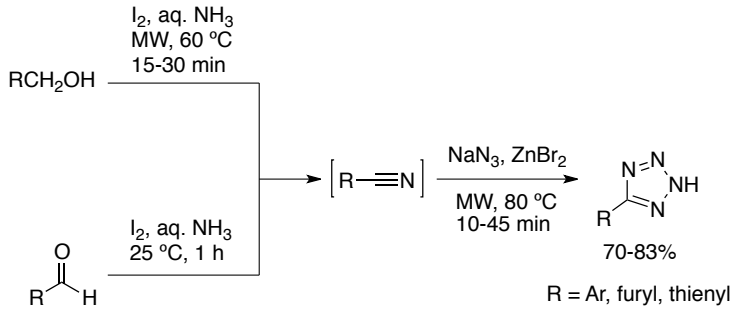
Having previously established an efficient oxidation of aldehydes into their corresponding nitriles using iodine in aqueous ammonium hydroxide,[52] the group of Fang reported in 2007 a microwave-assisted method for the direct transformation of primary alcohols or aldehydes into tetrazoles via their *in*

50 Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945-7050.

51 F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* **2003**, *125*, 9983-9987.

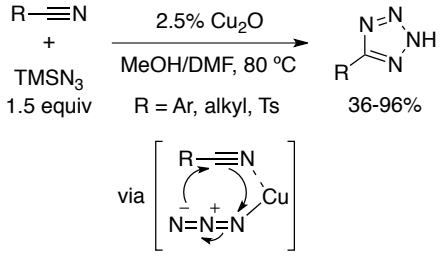
52 S. Talukdar, J. - L. Hsu, T. - K. Chou, J. - M. Fang, *Tet. Lett.* **2001**, *42*, 1103-1105.

situ formation into nitriles, although supra-stoichiometric amounts of catalyst (2 to 6 equiv) were required (Scheme 15).[53]



Scheme 15. Fang synthesis of tetrazoles

In 2008, the group of Yamamoto developed a catalytic method for the synthesis of 1*H*-tetrazoles.[54] His group discovered that Cu_2O could catalyze the reaction through an initial *in situ* formation of a copper azide catalytic species, which undergoes a [3+2] cycloaddition with a wide range of nitriles (Scheme 16).



Scheme 16. Yamamoto synthesis of tetrazoles

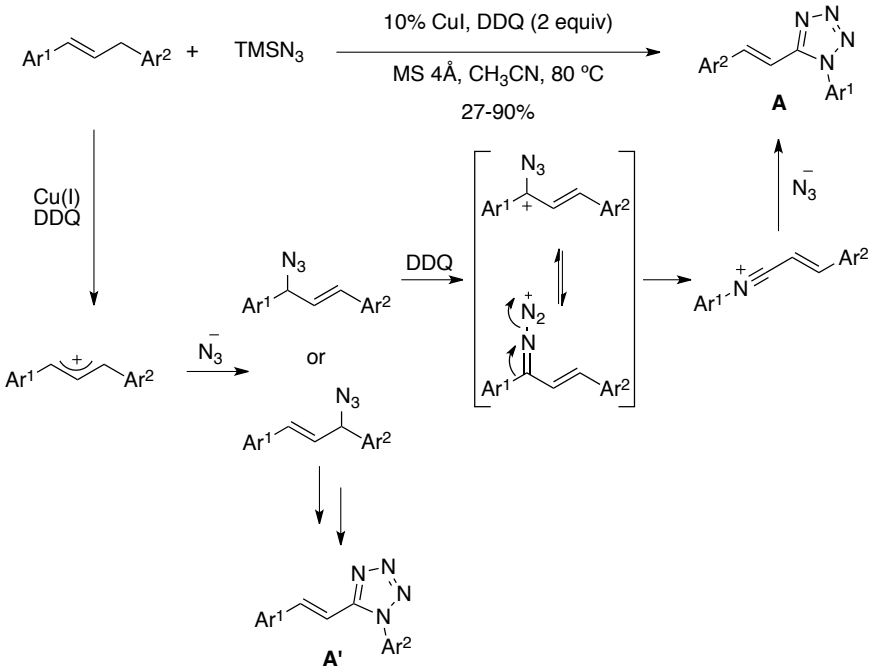
In 2011, Jiao and co-workers reported a mild and efficient catalytic route for the preparation of 1,5-disubstituted tetrazoles.[55] A novel Cu-catalyzed direct insertion of four nitrogen atoms into simple hydrocarbon molecules was demonstrated by formal two Csp^3-H and one C-C bond cleavage under

53 J. - J. Shie, J. - M. Fang, *J. Org. Chem.* **2007**, *72*, 3141-3144.

54 T. Jin, F. Kitahara, S. Kamijo, Y. Yamamoto, *Tet. Lett.* **2008**, *49*, 2824-2827.

55 F. Chen, C. Qin, Y. Cui, N. Jiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 11487-11491.

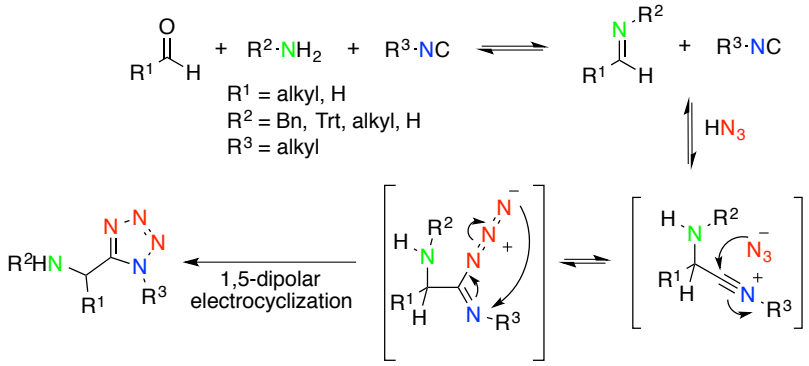
mild reaction conditions. The mechanism of the reaction was proposed to operate through a copper-DDQ mediated single-electron-transfer oxidation of 1,3-diarylprop-1-enes into an allyl cation, which was trapped by the azide. Further oxidation of the resulting allylic azide led to a nitrilium cation that underwent a [3+2] cycloaddition to afford the corresponding disubstituted tetrazole (Scheme 17). Although a few examples were reported using unsymmetrical alkenes, substrates bearing electron-rich aryl group Ar^2 could influence the regioselectivity and favor the formation of **A**.



Scheme 17. Copper mediated synthesis of disubstituted tetrazoles

Finally, 1,5-disubstituted tetrazoles can be obtained by a cycloaddition reaction between hydrazoic acid (generated *in situ* from $TMSN_3$ in

MeOH) [56] and Ugi adducts, followed by a fast and irreversible electrocyclization step (Scheme 18).[57]



Scheme 18. Synthesis of tetrazoles via an Ugi-type reaction

Reactions of alkynes with azides

Azides have been reported to undergo cycloaddition reactions with alkynes to form triazoles under thermal conditions (Huisgen cycloaddition)[47] as well as in the presence of copper catalysts (Scheme 19).[58] While the formation of triazoles under thermal conditions results in a mixture of 1,4- and 1,5-disubstituted regioisomers, the copper-catalyzed variant of this cycloaddition has proven more selective, giving the 1,4-disubstituted triazoles exclusively.

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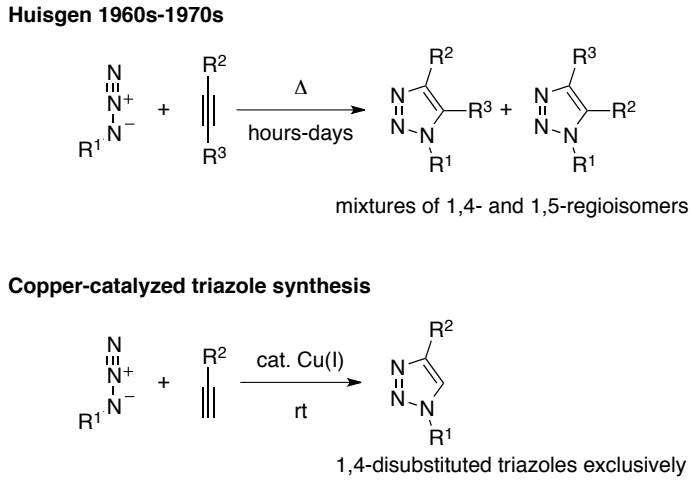
56 For safety issues on the use of TMSN3 and generation of hydrazoic acid, see: F. González-Bobes, N. Kopp, L. Li, J. Deerberg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm, M. Hrytsak, *Org. Process Res. Dev.* **2012**, *16*, 2051-2057.

57 (a) J. Roh, K. Vávrová, A. Hrabálek, *Eur. J. Org. Chem.* **2012**, 6101-6118. (b) L. El Kaim, L. Grimaud, *Tetrahedron* **2009**, *65*, 2153-2171. (c) T. Zhao, A. Boltjes, E. Herdtweck, A. Dömling, *Org. Lett.* **2013**, *15*, 639-641.

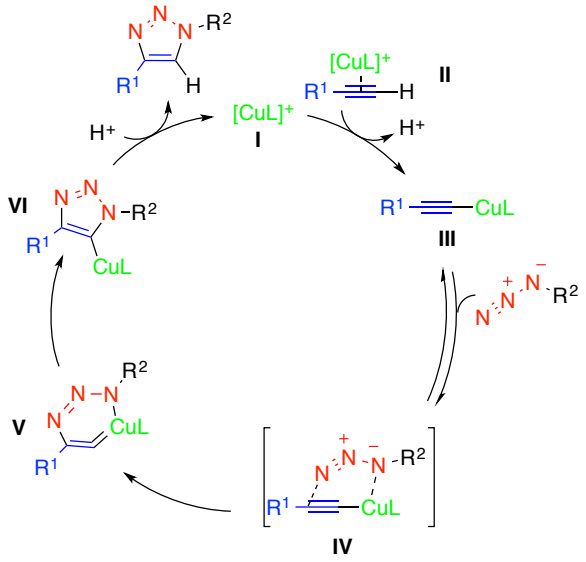
58 (a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021. (b) V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599. (c) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302-1315.



Scheme 19. General methods for triazoles synthesis

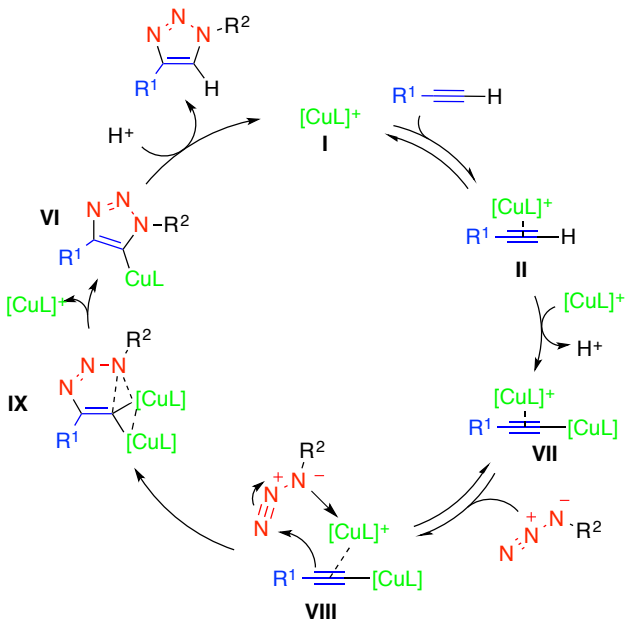
The mechanism of the copper-catalyzed azide-alkyne cycloaddition (CuAAC), commonly known as click reaction, has received significant interest.[58c,59] The reaction mechanism has been difficult to establish due to the involvement of multiple equilibriums between the multiple reactive intermediates. Fokin and Sharpless suggested a mechanism in 2002 based on the initial formation of a Cu(I) σ-acetylide complex **III** by π-coordination of the alkyne to copper, which increases the acidity of the terminal hydrogen of the alkyne, resulting in its facile deprotonation.[58b] The azide could then be activated through coordination onto the copper to form intermediate **IV**. Nucleophilic addition of the alkyne onto the activated azide would result in the formation of the strained copper metallacycle **V**. Finally, formation of copper triazolide **VI** through a second C-N bond formation followed by protodemetallation would afford the corresponding triazole (Scheme 20).

59 (a) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952-3015. (b) B. T. Worrell, J. A. Malik, V. V. Fokin, *Science* **2013**, *340*, 457-460.



Scheme 20. First proposed mechanism for the CuAAC reaction

Several years later, Fokin revisited his initial mechanism proposal and favored another catalytic cycle that involved a dicopper complex **VII** that could reversibly coordinate to the azide and form complex **VIII**.[59b] Subsequent nucleophilic attack of the β-carbon of the acetylide at the terminal nitrogen of the azide moiety generates intermediate **IX**, which can collapse and release copper triazolide **VI** (Scheme 21).



Scheme 21. Revisited mechanism for the CuAAC reaction

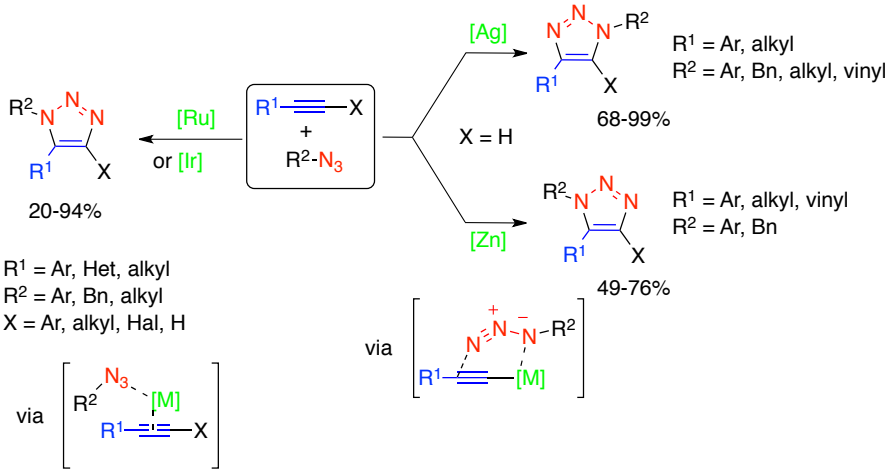
Triazoles can also be obtained by means of ruthenium,[60] silver,[61] and iridium catalysis,[62] as well as a zinc-mediated process (Scheme 22).[63] The silver and zinc-mediated process are proposed to operate in an analogous fashion to the copper catalyzed mechanism described by Fokin and Sharpless in 2002,[58b] while the iridium and the ruthenium catalysts are assumed to activate the alkyne by π-coordination.

60 (a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998-15999. (b) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, *9*, 5337-5339. (c) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923-8930.

61 (a) J. McNulty, K. Keskar, R. Vemula, *Chem. Eur. J.* **2011**, *17*, 14727-14730. (b) J. McNulty, K. Keskar, *Eur. J. Org. Chem.* **2012**, 5462-5470.

62 E. Rasolofonjatovo, S. Theeramunkong, A. Bouriaud, S. Kolodych, M. Chaumontet, F. Taran, *Org. Lett.* **2013**, *15*, 4698-4701.

63 C. D. Smith, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4826-4829.

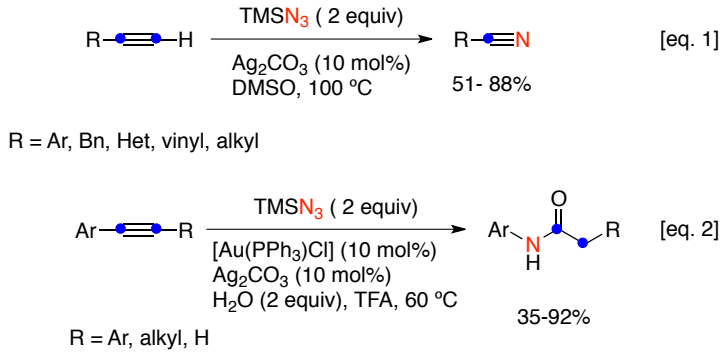


Scheme 22. Different metal-catalyzed synthesis of triazoles

In contrast, Jiao and co-workers observed a very unique reactivity between terminal alkynes and $TMSN_3$ in the presence of silver salts.[64] Under these reaction conditions, a remarkable silver-catalyzed nitrogenation reaction of alkynes to nitriles through Csp-Csp bond cleavage was demonstrated (Scheme 23, [eq. 1]). A few months later, the same group reported the cleavage of the aryl-alkyne Csp^2-Csp bond using $[Au(PPh_3)Cl]$ and Ag_2CO_3 in the presence of H_2O and trifluoroacetic acid (TFA) to form carboxamides (Scheme 23, [eq. 2]).[65]

64 T. Shen, T. Wang, C. Qin, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 6677–6680.

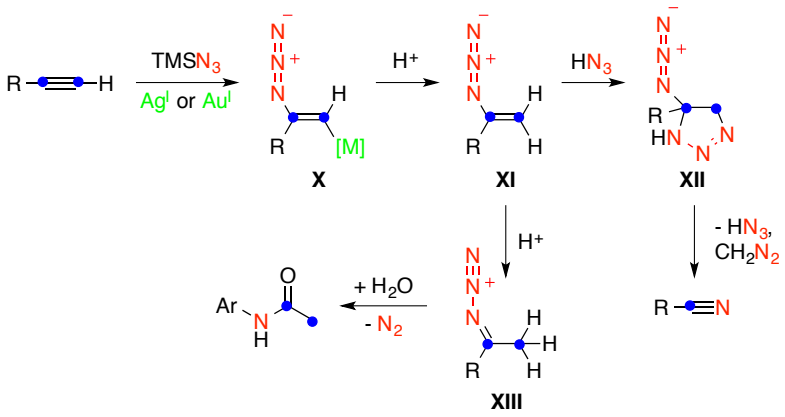
65 C. Qin, P. Feng, Y. Ou, T. Shen, T. Wang, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 7850–7854.



Scheme 23. Nitrile and carboxamide formation from alkynes

The formation of nitriles and carboxamides was proposed to proceed by nucleophilic addition of the azide onto the (η^2-alkyne)metal complexes to form intermediates **X** with subsequent protonolysis to give alkenyl azides **XI**. The nitrile could then be formed through a 1,3-dipolar cycloaddition with hydrazoic acid and subsequent fragmentation of **XII** to liberate diazomethane and hydrazoic acid. Alternatively, when intermediate **XI** is subjected to TFA, **XIII** could be formed upon protonation of **XI** and undergoes a Schmidt rearrangement [66] to give the corresponding carboxamide (Scheme 24).

66 (a) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320–323. (b) L. E. Fikes, H. Shechter, *J. Org. Chem.* **1979**, *44*, 741-744. (c) G. L. Milligan, C. J. Mossman, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 10449-10459. (d) O. Gutierrez, J. Aubé, D. J. Tantillo, *J. Org. Chem.* **2012**, *77*, 640-647.



Scheme 24. Proposed mechanism for the formation of nitriles and carboxamides

Gold(I)-catalyzed nucleophilic additions to 1,n-enynes

1,n-Enynes can also react stereospecifically with different nucleophiles in the presence of Au(I) catalysts to give access to interesting scaffolds from readily available starting materials.[67] These transformations are typically achieved by trapping the cyclopropyl intermediates generated by cycloisomerization of 1,n-enynes (**XV**, **XVI** or **XVII**) with different nucleophiles (Scheme 25). Thus, water, alcohols,[67b,68] and amines[69] lead to hydroxy-, alkoxy-, and aminocyclization products, respectively.

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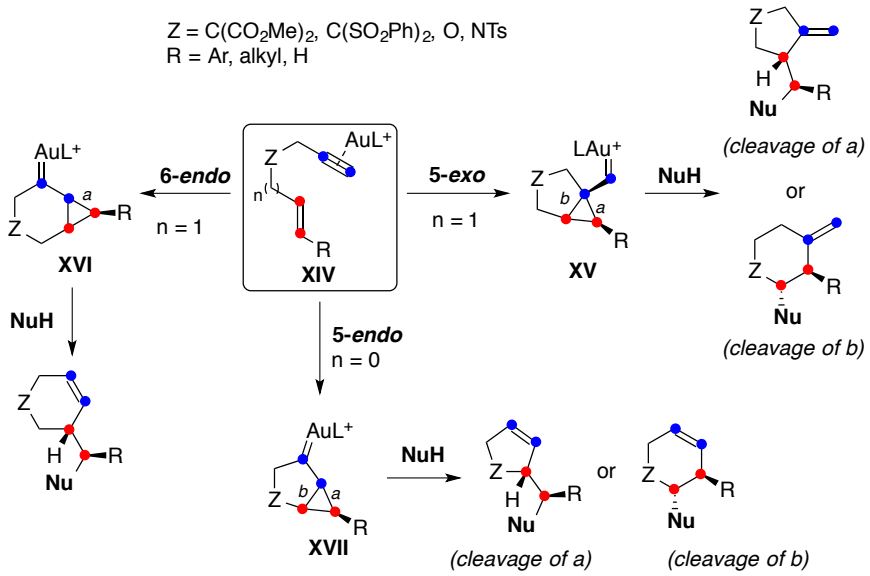
67 (a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406. (b) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677-1693. (c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350. (d) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378.

68 A K. Buzas, F. M. Istrate, F. Gagosz, *Angew. Chem. Int. Ed.* **2007**, *46*, 1141-1144.

69 L. Leseurre, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Org. Lett.* **2007**, *9*, 4049-4052.

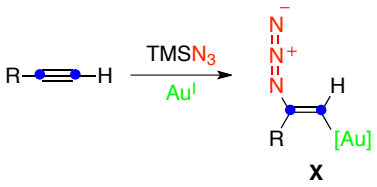


Scheme 25. Gold(I)-catalyzed cycloadditions

Mechanistically, this process involves the opening of the cyclopropyl gold carbene intermediate **XV**, **XVI**, or **XVII**. Two different products are observed when a 5-*exo-dig* and 5-*endo-dig* cyclization occurs (depending on which bond *a* or *b* is cleaved), while only one product is formed during a 6-*endo-dig* cyclization.

Objectives

Azides being involved in fundamental chemical reactions (see Introduction), we wondered if their use in gold(I) chemistry could lead to interesting transformations. Moreover, gold catalysts are one of the most effective catalysts for electrophilic activation of alkynes toward a variety of nucleophiles. Thus, the investigation of $TMSN_3$ with alkynes and gold(I)-complexes was initiated expecting intermediate **X** to react further in presence of the gold(I) catalyst (Scheme 26).



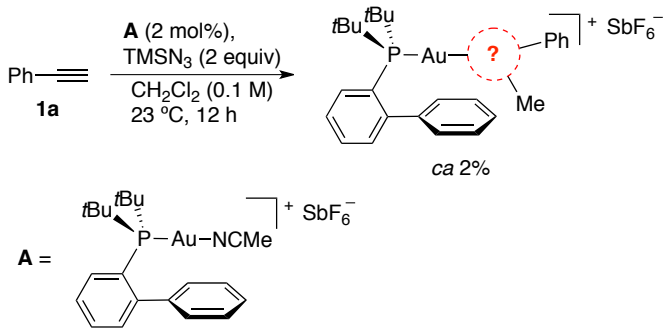
Scheme 26. Reaction of $TMSN_3$ with alkynes in the presence of gold(I)-complexes

Results and discussion

Synthesis of Tetrazoles

New tetrazole-gold(I) complexes

Gold salts and complexes are superior catalysts in electrophilic activation of alkynes under homogeneous conditions compared to their silver counterparts. We therefore rationalized that by employing gold(I) complexes we could improve on the reaction conditions for the addition of azides onto alkynes. We initiated our investigations using similar reaction conditions as Jiao and co-workers[64] but replacing the silver carbonate with JohnPhos-gold(I) catalyst **A** for the activation of phenylacetylene **1a** in the presence of $TMSN_3$. After consumption of the phenylactylene, the reaction was concentrated to dryness and analyzed by ^1H NMR. Although the desired product was not observed, luckily, a new gold complex precipitated from the reaction mixture. ^1H NMR analysis of this new gold complex showed the presence of the JohnPhos ligand, a shift of the methyl signal of the acetonitrile ligand (from δ 2.41 to 2.58 ppm) as well as 5 new aromatic hydrogens (Scheme 27).



Scheme 27. Discovery of a new Au(I) catalyst

Recrystallization of this complex from a cyclohexane and EtOAc mixture allowed us to determine the structure of this new type of gold(I) complex by

X-ray diffraction: 5-methyl-1-phenyl-1*H*-tetrazole-gold(I) complex **H** (Figure 4).[70]

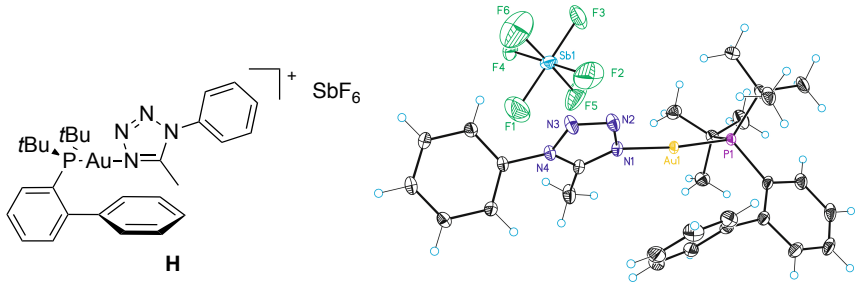
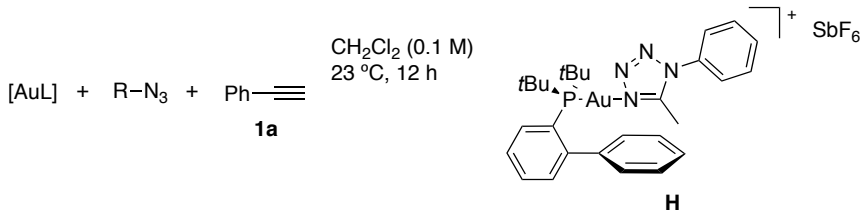


Figure 4. 5-Methyl-1-phenyl-1H-tetrazole-gold(I) complex

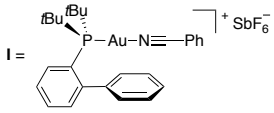
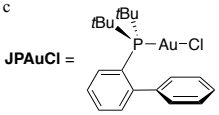
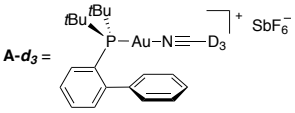
The formation of the tetrazole could have arisen from a 1,3-dipolar cycloaddition between the acetonitrile ligand and *in situ* generated phenyl azide.[47] In order to test this hypothesis, we designed a series of simple stoichiometric gold experiments (Table 1).

70 Only one neutral gold complex bearing a tetrazole ligand was previously reported, [(C_6F_5)Au(1-benzyltetrazole)], in which the tretrazole was also bound through N-4: W. F. Gabrielli, S. D. Nogai, M. Nell, S. Cronje, H. G. Raubenheimer, *Polyhedron* **2012**, *34*, 188-197.

Table 1. Investigation on the formation of tetrazole-gold(I) complex



Entry	[AuL] (1 equiv)	R (2 equiv)	Alkyne 1a	Outcome	Yield (%)[a]
1	**A**	Ph	none	no reaction	-
2	**I**[b]	TMS	1 equiv	no reaction	-
3	**JPAuCl**[c]**/AgSbF$_6$** (1/1)	TMS	1 equiv	**H**	56
4	**A-*d*$_3$**[d]	TMS	1 equiv	**H**	61

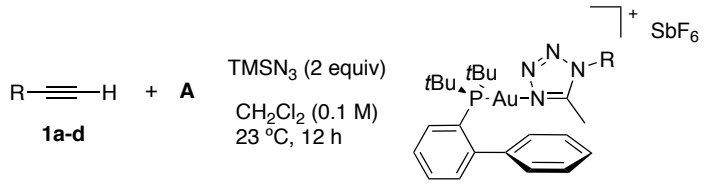
[a] Isolated yield. [b] **I** =  [c] **JPAuCl** =  [d] **A-*d*$_3$** = 

We began our study by substituting the TMS azide with phenyl azide (Table 1, entry 1). Only the starting Au(I) catalyst was recovered, suggesting that the phenyl azide was an unlikely intermediate in this transformation. Secondly, replacement of the acetonitrile ligand by benzonitrile (Au(I) catalyst **I**) would give rise to a different product, the 1,5-diphenyltetrazole (Table 1, entry 2). However, this tetrazole was not obtained. We cannot exclude the possibility that the absence of desired product was due to the

increased steric hindrance as well as the different stereoelectronic properties of the more labile benzonitrile ligand. Finally, the reaction was conducted with an *in situ* generated monoligated cationic gold complex (removal of the acetonitrile ligand) as well as deuterated Au(I) catalyst **A-*d*$_3$** (Table 1, entries 3 and 4). Gratifyingly, 5-methyl-1-phenyl-1*H*-tetrazole-gold(I) complex **H** was formed in both cases in 56% and 61% yield, respectively, and no trace of deuteration was observed when employing **A-*d*$_3$**. From these experiments, we concluded that the tetrazole formation does not arise from a formal [3+2] cycloaddition, but rather the result of a more intriguing pathway.

The reaction of aryl alkynes **1a-d** with $TMSN_3$ and complex **A** under stoichiometric conditions was next studied to evaluate the effect of different substitutents at the aryl on the reaction. The reaction was found to be general as the formation of three new 5-methyl-1-aryl-1*H*-tetrazole-gold(I) complexes were obtained in moderate to good yields (Table 2, entries 1-3). Although the tetrazole-gold(I) complex with a *para*-methoxy phenyl moiety was observed by ^{1}H NMR, it could not be recrystallized and fully characterized (Table 2, entry 4).

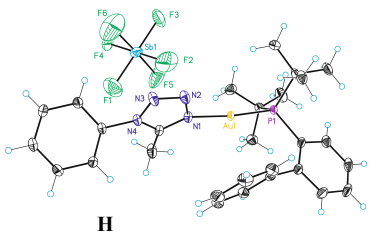
Table 2. Formation of new tetrazole-gold(I) complexes



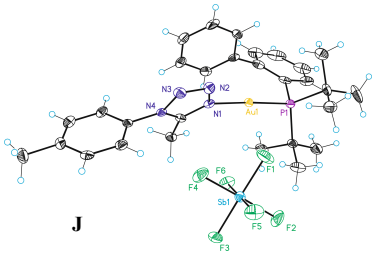
H, R = Ph
J, R = *p*Tol
K, R = *p*$NO_2C_6H_4$

Entry	R	Yield (%)[a]
1	Ph **1a**	72
2	*p*Tol **1b**	53
3	*p*$NO_2C_6H_4$ **1c**	45
4	*p*$OMeC_6H_4$ **1d**	-[b]

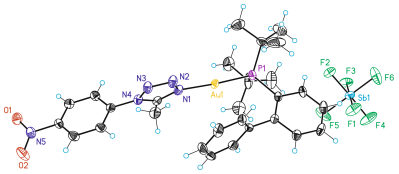
[a] Isolated yield. [b] Difficult recrystallization.



H



J



K

Having established a methodology for the formation of these complexes, we focused our attention on the catalytic synthesis of tetrazoles using gold(I) catalysts.

Gold(I)-catalyzed synthesis of tetrazoles

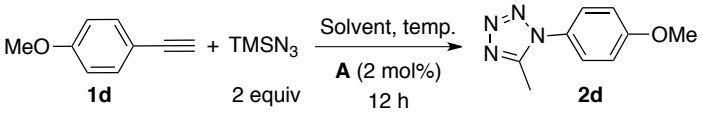
Our group has previously shown that the ligand substitution reaction between complexes $[Au\text{-}(product)L]^+$ and the initial alkyne can be the rate-determining step in certain catalytic reactions.[71] The isolation of stable gold(I) complexes (**H**, **J**, and **K**) under stoichiometric conditions indicates that, in this case, the development of a catalytic process for the synthesis of tetrazoles would be a challenging task, since the ligand substitution would to be particularly slow.

We initiated our study of this catalytic transformation with a screening of different solvents at different temperatures (Table 3). *para*-Ethynyl anisole

71 (a) C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148. (b) C. Obradors, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 3547-3551. (c) A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, *Adv. Synth. Catal.* **2014**, *356*, 221-228.

was chosen as model substrate as the methoxy group should ease the identification of tetrazole **2d** by ^{1}H NMR.

Table 3. Solvent and temperature screening for the formation of 2d

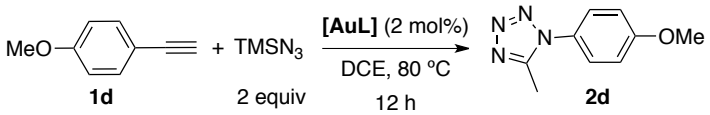


Entry	Solvent	Temp. (ºC)	Conversion (%)[a]	Yield (%)[a]
1	CH_2Cl_2	40	0	-
2	MeCN	23	0	-
3	MeCN	80	85	8
4	Toluene	110	80	9
5	DCE	80	89	40
6	DCE	80 (MW, 1.5 h)	77	36
7	DCE	110	72	38

[a] Determined by ^{1}H NMR analysis using diphenylmethane as internal standard.

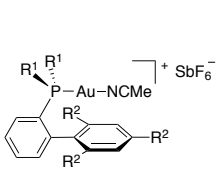
When the reaction was performed in CH_2Cl_2, MeCN, or toluene, either no reaction or very low yields of tetrazole **2d** were obtained (Table 3, entries 1-4). Fortunately, moderate yields were observed with 1,2-dichloroethane (DCE) at 80 ºC (Table 3, entry 5). No improvement was observed when heating at 110 ºC or under microwave irradiation (Table 3, entries 6 and 7). With the first catalytic formation of free tetrazole **2d** achieved, we continued our optimization investigations. A screening of different catalysts was then carried out (Table 4).

Table 4. Catalyst screening for the formation of 2d

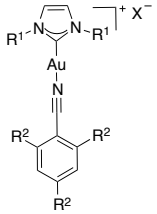


Entry	[AuL]	Conversion (%)	Yield (%)
1[a]	**A**	89	40
2[a]	**B**	71	7
3[a]	**C**	82	8
4[b]	**D**	0	-
5[b]	**E**	0	-
6[b]	**F**	0	-
7[b]	**G**	71	15
8[b]	**L**	59	18
9[a]	**$AuCl(PPh_3)/Ag_2CO_3$**	0	-

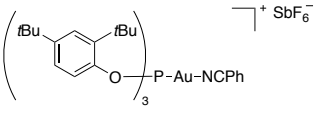
[a] Determined by ^{1}H NMR analysis using diphenylmethane as internal standard. [b] Determined by ^{1}H NMR analysis using 1,4-diacetylbenzene as internal standard.



A, R^1 = *t*Bu, R^2 = H
B, R^1 = *t*Bu, R^2 = *i*Pr
C, R^1 = Cy, R^2 = *i*Pr



D, R^1 = Mes, R^2 = OMe, X = SbF_6
E, R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = H, X = SbF_6
F, R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = H, X = BAr_4^F



G

$[Au(PPh_3)L]^+ SbF_6^-$

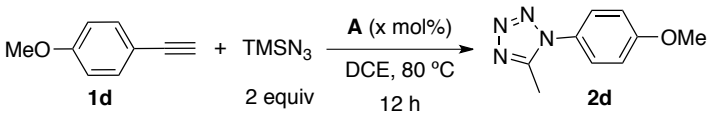
L = 2,4,6-$(MeO)_3C_6H_2CN$

L

Related gold(I) catalysts **B** and **C** (Table 4, entries 2-3), NHC (N-heterocyclic carbenes) bearing complexes **D**-**F** (Table 4, entries 4-6), phosphite **G** (Table 4, entry 7), as well as less-sterically bulky phosphine ligands (Table 4, entries 8-9) led to poor results and could not improve the initial reaction conditions (using gold(I) catalyst **A**) (entry 1). Additionally,

in all cases, small amounts of starting alkyne **1d** were still present in the reaction mixture. We therefore opted to increase the catalyst loading (Table 5).

Table 5. Screening of catalyst loading



1d (1 equiv) — 2 equiv — **2d**

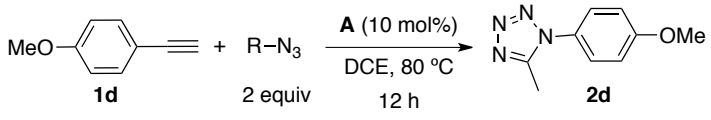
Entry	A (x mol%)	Conversion (%)[a]	Yield (%)[a]
1	2	89	40
2	5	93	48
3	10	>99	59

[a] Determined by ^{1}H NMR analysis using diphenylmethane as internal standard

Finally, the total conversion of the starting alkyne **1d** could be achieved using 10 mol% of gold(I) catalyst **A** (Table 5, entry 3).

In order to improve the yield of tetrazole **2d**, different sources of azides were also tested (Table 6).

Table 6. Screening of azide ion source



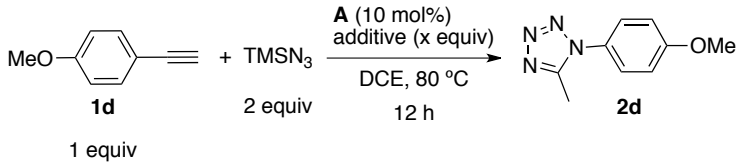
1d (1 equiv) — 2 equiv — **2d**

Entry	RN_3	Yield (%)[a]
1	$TMSN_3$	59
2	NaN_3	-
3	BnN_3	-
4	PhN_3	-

[a] Determined by ^{1}H NMR analysis using diphenylmethane as internal standard.

The recovery of starting alkyne **1d** was anticipated with the use of sodium azide due to its poor solubility under the reaction conditions (Table 6, entry 2). Again, the formation of tetrazole **2d** could not be observed when using benzyl or phenyl azide (Table 6, entries 3-4). This lack of reactivity can be rationalized through the *in situ* formation of hydrazoic acid in this transformation. We therefore turned our attention to the addition of different alcohols additives that could facilitate its *in situ* formation (Table 7).

Table 7. Screening of different additives for the formation of tetrazole 2d



Entry	Additive	x equiv	Yield (%)[a]
1	none	-	59
2	*i*PrOH	2	68
3	MeOH	2	62
4	*i*PrOH/H_2O (1:1)	2	0[b]
5	*i*PrOH	4	80
6	*i*PrOH	6	78
7	*i*PrOH	8	81
8	*i*PrOH	10	79

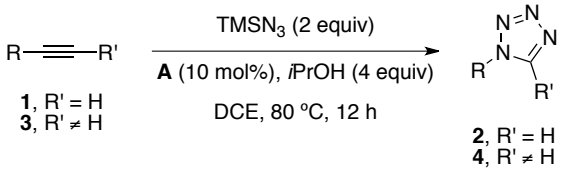
[a] Determined by ^{1}H NMR analysis using diphenylmethane as internal standard. [b] 61% yield of acetanisole isolated instead.

Addition of water in isopropanol led to the sole formation of acetanisole by hydration of alkyne **1d** (Table 7, entry 4).[72] The yield increased significantly when the reaction was performed in the presence of *i*PrOH (Table 7, entry 2). Fine-tuning of the equiv of *i*PrOH led to our final optimized conditions with 4 equiv of alcohol (Table 7, entries 5-8).

Scope and limitations

With the optimized reaction conditions in hand, the scope of the reaction was next investigated with different substituted terminal and internal alkynes, exploring the effect of electron-donating or electron-withdrawing substituents (Table 8).

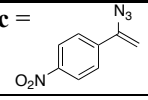
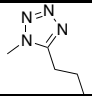
Table 8. Scope and limitations



Entry	Alkyne	Outcome	Yield (%)[a]
1	Ph **1a**	**2a**	49
2	*p*Tol **1b**	**2b**	41
3	*p*$NO_2C_6H_4$ **1c**	**5c**[b]	23
4	*p*$MeOC_6H_4$ **1d**	**2d**	70
5	*m*$MeOC_6H_4$ **1e**	**2e**	36
6	*o*$MeOC_6H_4$ **1f**	**2f**	38

72 (a) R. O. C. Nomran, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983-1987. (b) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

7	*p*BrC$_6$H$_4$ **1g**	**2g**	36
8	*p*-*t*BuC$_6$H$_4$ **1h**	**2h**	54
9	*p*PhC$_6$H$_4$ **1i**	**2i**	56
10	1-naphtyl **1j**	**2j**	49
11	*p*CF$_3$C$_6$H$_4$ **1k**	**2k**	18
12	3-thienyl **1l**	**2l**	51
13	cyclohexyl **1m**	**2m**	76
14	propyl **1n**	**2n/2n'**[c] (10:1)	50
15	cyclopropyl **1o**	**2o/2o'**[d] (1:3)	49
16	EtO$_2$C **1p**	complex mixture	-
17	3-pyridyl **1q**	degradation	-
18	*p*ethynylC$_6$H$_4$ **1r**	complex mixture	-
19	Ph, Me **3a**	no reaction	-
20	Ph, Ph **3b**	no reaction	-

[a] Isolated yield. [b] **5c** =  [c] **2n'** =  [d] **2o'** = 

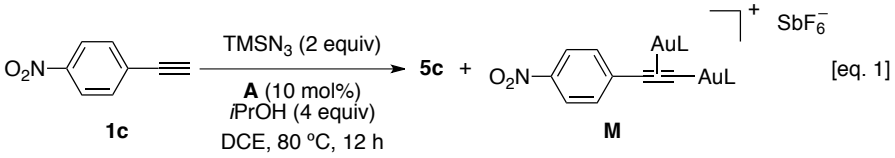
Aromatic rings substituted with electron-donating groups resulted in the successful formation of the desired product in moderate to good yields (Table 8, entries 1, 2, 4-6 and 8-10). On the other hand, lower yields of tetrazoles **2g** and **2k** were obtained when employing substrates bearing electron-withdrawing groups (Table 8, entries 7 and 11). No tetrazole was

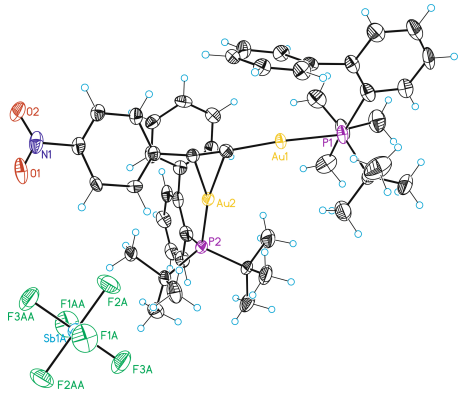
formed with the use of *p*-nitrophenylacetylene **1c** (Table 8, entry 3), as alkenyl azide **5c** was isolated instead. Aliphatic terminal alkynes proved to be suitable substrates giving their respective tetrazoles in good yields (Table 8, entries 13-15). Interestingly, whereas cyclohexylacetylene **1m** provided the expected product in good yield as a single regioisomer, 1-pentyne gave **2n** along with its regioisomer 1-methyl-5-propyl-1*H*-tetrazole (**2n'**; 10:1 ratio) while cyclopropylacetylene gave **2o** and **2o'**; favoring the reverse regioisomer (1:3 ratio).[73] Heteroaryl-substituted alkyne **1l** led to 5-methyl-1-(thiophen-3-yl)-1*H*-tetrazole **2l** in good yield (Table 8, entry 12). Again, electron deficient alkynes were found to be unsuitable substrates as exemplified with a pyridyl substituted alkyne as well as ethyl propiolate, which underwent only degradation (Table 8, entries 16-17). In contrast to terminal alkynes, internal alkynes **3** failed to give the corresponding tetrazoles (Table 8, entries 20 and 21). Furthermore, substrates containing two terminal alkynes resulted in complex mixtures that could not be identified (entry 18).

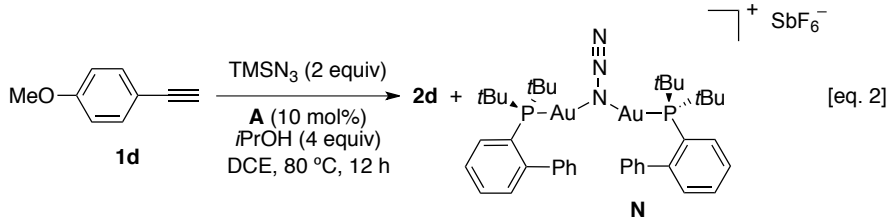
During the course of these studies, two interesting gold complexes were observed when alkynes **1c** and **1d** were treated with gold(I) complex **A** and $TMSN_3$. σ,π-(*p*-Nitrophenylacetylene)digold(I) complex **M** (Scheme 28, [eq. 1]), as well as an azide bridged digold(I) complex **N** (Scheme 28, [eq. 2])[74] could be isolated from the reaction mixture.

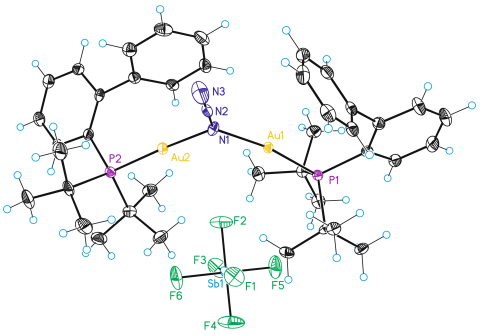
73 Preferential migration of the methyl group has already been observed in the Schmidt reaction of methyl cyclopropyl ketone in aqueous sulfuric acid at lower acid strengths: L. E. Fikes, H. Shechter, *J. Org. Chem.* **1979**, *44*, 741-744.

74 First isolable gold(I) organoazides: C. Dash, M. Yousufuddin, T. R. Cundari, H. V. R. Dias, *J. Am. Chem. Soc.* **2013**, *135*, 15479-15488.





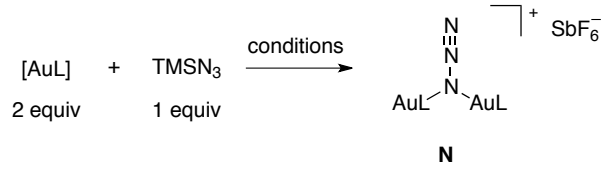




Scheme 28. Formation of digold(I) complexes

Intrigued by this new azide bridged digold(I) complex **N**, we wondered whether it is a competent intermediate in the catalytic cycle for the formation of tetrazoles **2**. A quick optimization for its isolation was performed (Table 9).

Table 9. Optimization for the formation of N

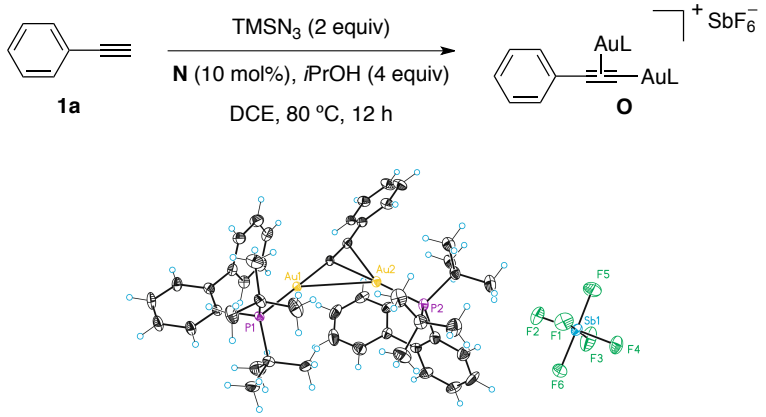


N

Entry	[AuL]	Conditions	Outcome	Yield (%)
1	**A**	CH_2Cl_2 (0.1 M), -18 ºC, 16 h	no reaction	-
2	**A**	CH_2Cl_2 (0.1 M), 23 ºC, 16 h	no reaction	-
3	**JPAuCl/AgSbF$_6$** (1:1)	CH_2Cl_2 (0.1 M), -18 ºC, 16 h	**N**	65

The *in situ* formation of the active gold(I) complex in CH_2Cl_2 followed by the addition of $TMSN_3$ at -18 ºC led to the desired complex **N** in 65% yield (Table 9, entry 3).[74]

With this new complex **N** in hand, we investigated whether this complex is competent in the formation tetrazole **2a** (Scheme 29).



Scheme 29. Formation of digold(I) complex O

Upon completion of the reaction, the analogous digold(I) specie **O** was isolated from the reaction mixture with only degradation products suggesting that gold(I)-azide complex **N** is not a competent catalyst for this process. Moreover, the reaction of [$LAuN_3$] complexes with alkynes had been previously studied generating gold(I)-triazolyl complexes.[75]

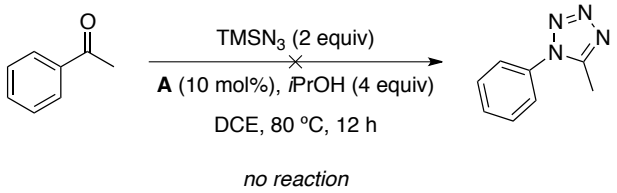
These last results could explain the limitations with electron deficient substrates (Table 8). Indeed, diaurated species are unable to undergo direct protonolysis,[71c,76] which could prevent the formation of tetrazoles **2** or affect the reaction outcome. Our efforts were then redirected towards the elucidation of the mechanism of the formation of tetrazoles **2**.

75 (a) T. J. Robilotto, N. Deligonul, J. B. Updegraff, T. G. Gray, *Inorg. Chem.* **2013**, *52*, 9659-9668. Gold(I) alkynyls react with organic azides in the presence of Cu to give gold(I) triazolyls: (b) D. V. Partyka, L. Gao, T. S. Teets, J. B. Updegraff III, N. Deligonul, T. G. Gray, *Organometallics* **2009**, *28*, 6171-6182. (c) J. E. Heckler, N. Deligonul, A. L. Rheingold, T. G. Gray, *Chem. Commun.* **2013**, *49*, 5990-5992.

76 A. Zhdanko, M. E. Maier, *Chem. Eur. J.* **2014**, *20*, 1918-1930.

Mechanistic studies

While unlikely, acetophenone could have been formed by gold(I)-catalyzed hydration of the alkyne.[72] We therefore subjected it to the reaction conditions (Scheme 30).

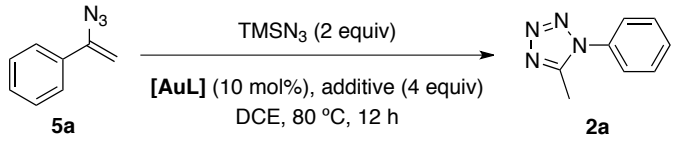


Scheme 30. Reaction of acetophenone as a potential intermediate

Acetophenone was fully recovered after treatment with $TMSN_3$ and complex **A**, confirming this alkyne hydration pathway is not involved in the tetrazole formation.

Since alkenyl azide **5c** was isolated when alkyne **1c** was used as substrate, several control experiments were performed to assess its involvement as an intermediate (Table 10).

Table 10. Study on the behavior of alkenyl azide 5a



5a **2a**

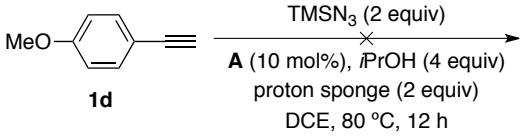
Entry	[AuL]	Additive	Outcome	Yield (%)[a]
1	**A**	*i*PrOH	**2a**	42
2	**A**	none	**2a**	12
3	none	*i*PrOH	**2a**	traces
4	none	HOAc[b]	**2a**	78

[a] Determined by ^{1}H NMR analyses using diphenylmethane as internal standard. [b] 2 eq. of HOAc were added.

Alkenyl azide **5a** under the standard reaction conditions underwent formation of tetrazole **2a** in 42% yield. We can therefore conclude that

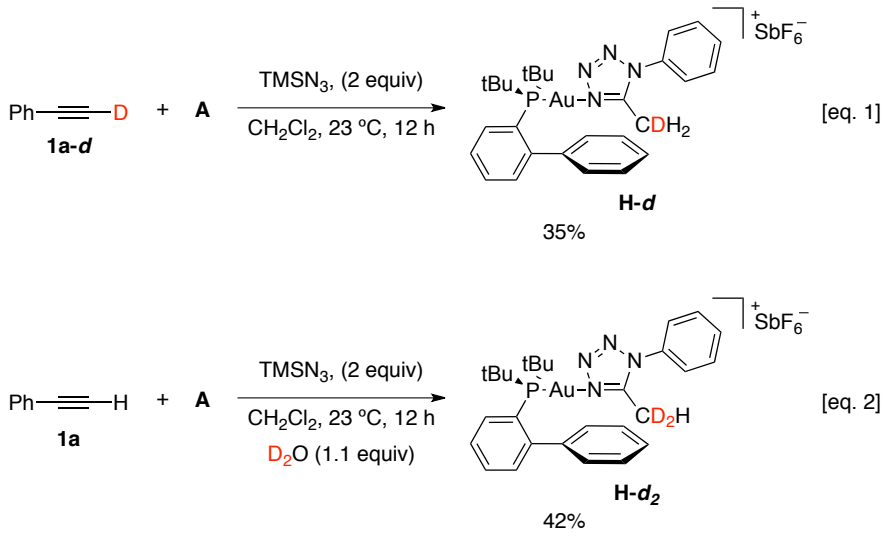
vinyl azides are very likely intermediates in this process (Table 10, entry 1). In the absence of *i*PrOH or gold(I) catalyst **A**, only low conversion or traces of **2a** were obtained (entries 2-3), meaning both reactants are required in the formation of tetrazoles **2** from the alkenyl azide intermediates. Finally replacing *i*PrOH by HOAc in the absence of catalyst **A** led to **2a** in 78% yield, suggesting that a protonation of the alkenyl azides is required for completing the catalytic cycle.

In an attempt to validate this last proposal a control experiment was performed in which we added 2 equiv of "proton-sponge" (1,8-bis(dimethylamino)naphthalene) in the reaction mixture (Scheme 31). Under these conditions, the formation of the corresponding tetrazole **2d** was inhibited and starting alkyne **1d** was recovered. We cannot exclude the possibility that the basic proton sponge could interfere with the reaction by reacting with the gold catalyst leading to an unreactive complex.



Scheme 31. Control experiment adding proton sponge in the reaction mixture

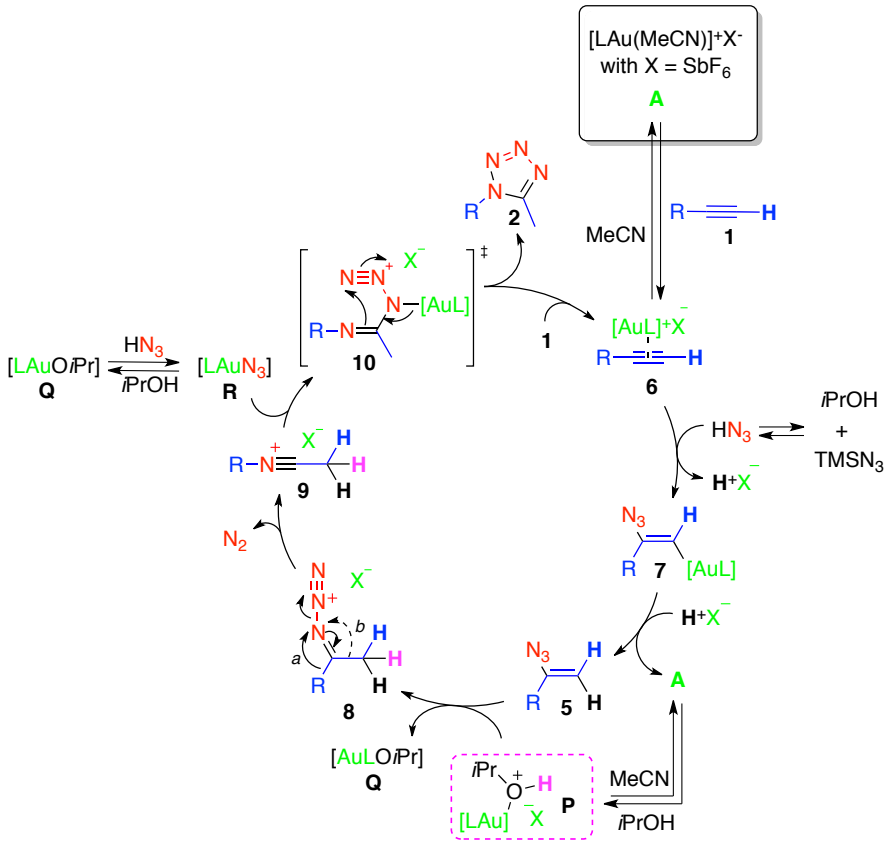
To gain further insight in the mechanism, two deuterium labeling experiments were performed (Scheme 32). These experiments were permormed under stoichiometric conditions in order to minimize scrabbling of the deuterium.



Scheme 32. Deuterium-labeling experiments

In the first reaction, we synthesized a terminally deuterated alkyne substrate **1a-*d***, which was converted to complex **H-*d*** in which the deuterium was located on the methyl group (Scheme 32, [eq. 1]). Therefore the terminal alkynyl carbon becomes the methyl moiety of tetrazoles **2**. Reaction of **1a**, $TMSN_3$, and complex **A** was carried out in CH_2Cl_2 containing 1.1 equiv of D_2O. From this reaction, we isolated deuterated complex **H-*d*$_2$** (Scheme 32, [eq. 2]). This result implied the introduction of two protons at the methyl position via *in situ* formation of hydrazoic acid first, and then protonation of intermediate **5** (Scheme 33).

All these results are in agreement with a mechanism consisting of a formal addition reaction of HN_3 generated *in situ* from $TMSN_3$ and *i*PrOH onto the (η^2-alkyne)gold(I) complex **6** to give **7**, followed by protodeauration to form alkenyl azide **5** (Scheme 33). These first steps are in accordance with the reported mechanism for the formation of nitriles[64] and carboxamides,[65] as well as the result obtained in entry 1 of Table 10.



Scheme 33. Proposed catalytic cycle for the formation of tetrazoles 2

Protonation of **5** would give iminodiazonium cation **8**, which could then rearrange to form nitrilium cation **9** by migration of the R group (*path a*). A competitive migration of the methyl group (*path b*) would explain the formation of regioisomers **2n'** and **2o'** which were observed in the reactions with 1-pentyne **1n** and cyclopropylacetylene **1o** (Table 8, entries 14-15).

Formation of **8** could arise from the protonation of intermediate **5** by Brønsted acid [JohnPhosAu(*i*PrOH)]SbF_6 **P** formed by coordination of *i*PrOH to gold(I),[77,78] since weakly acidic hydrazoic acid is unlikely to act as

77 Brønsted acidity of a quo gold(III) complexes: W. Robb, *Inorg. Chem.* **1967**, *6*, 382-386.

78 O. Kanno, W. Kuriyama, Z. J. Wang, F. D. Toste, *Angew. Chem. Int. Ed.* **2011**, *50*, 9919-9922.

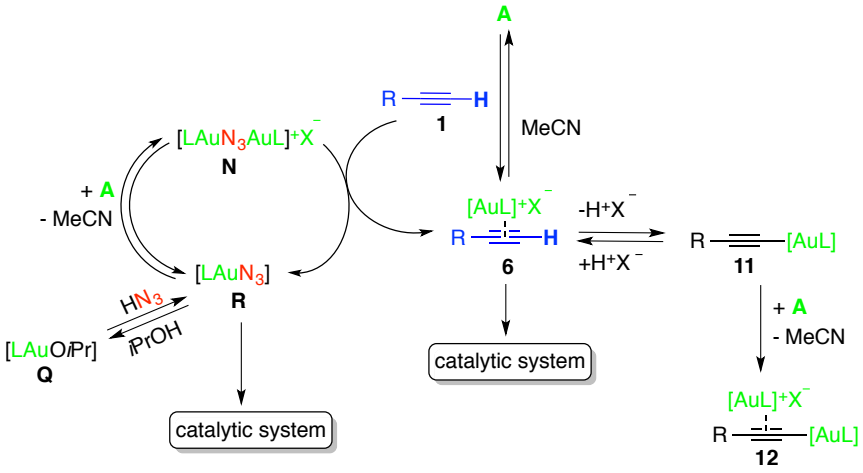
proton source.[79] Indeed, intermediates **5** have been known to react with HN_3 in 1,3-dipolar cycloadditions to form an intermediate of type **XII** (Scheme 24).[64, 80] Additionally, the results obtained in entries 2-4 in Table 10 correlate this theory of a Brønsted acid catalyzed pathway for the transformation of **5** into **8**. When the reaction was performed in the absence of *i*PrOH or gold(I) catalyst **A** only poor conversion to **2a** was observed. Replacement of the alcohol with HOAc gave an increased yield of this tetrazole while addition of a base to the reaction mixture inhibited the transformation (Scheme 31). Therefore catalyst **A** might act as a Lewis acid by binding to *i*PrOH, thereby increasing its Brønsted acidity sufficiently to protonate vinyl azide **5**.

Finally, a formal 1,3-dipolar cycloaddition between the newly formed nitrilium cation **9** and the azidogold(I) complex ($[AuLN_3]$ **R**) would lead to the synthesis of tetrazoles **2** and regenerate the gold(I) catalyst. Alternatively, instead of $LAuN_3$, HN_3 could also react with nitrilium cation **9** in the stepwise1,3-dipolar cycloaddition.

Inactive σ,π-digold(I) complexes, which were isolated in some reactions (Scheme 28, [eq. 1)]), as well as azide bridged digold(I) complex **N**, lead to the same σ,π-digold(I) species in presence of an alkyne (Scheme 34).

79 The pKa of HN3 is equal to 4.6.

80 The reaction carried out using alkenyl phenyl azide and HN3 has also been reported to proceed through an intermediate of type **XII** (Scheme 24) followed by retro-1,3-cycloaddition to yield 5-phenyltetrazole with elimination of diazomethane: P. K. Kadaba, *Synlett* **1990**, 349-351.



Scheme 34. Side processes and dead-ends in the catalytic formation of tetrazoles

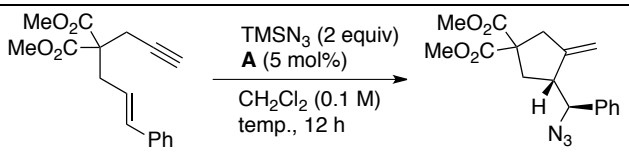
Although we gained further insight into the mechanism, improving the results for the formation of tetrazoles **2** would require minimizing the competitive formation of σ,π-digold(I) alkyne complex **12**. Recent studies performed in our group on the effect of couteranion in gold(I) catalysis suggest a possible solution.[71c] According to these studies, replacing hexafluoroantimonate by 3,5-bis(trifluoromethyl)phenylborate (BAr_4^{F-}) might help to slow down the deprotonation of **6** that leads to the formation of inactive σ,π-digold(I) alkyne complex **12**.

Addition of azides into 1,n-enynes[81]

Our group has a large experience on gold(I)-catalyzed nucleophilic additions into 1,n-enynes (see Introduction). We therefore envisioned as an extension of this work to employ the azide moiety as the nucleophile for this transformation. An azide functionality would bring in additional versatility to the transformation. Recently, the gold-catalyzed addition of azides as nucleophiles to allenes has been recently reported to lead to the formation of the corresponding allyl azides.[82]

We began our studies by using enyne **13a**, bearing a malonate moiety and a phenyl substituent on the alkene, 5 mol% JohnPhos-gold(I) catalyst **A**, with 2 equiv of $TMSN_3$ in CH_2Cl_2 at room temperature and 50 ºC (Table 11).

Table 11. Formation of 14a



13a **14a**

Entry	Temp. (ºC)	Conversion (%)[a]	Yield (%)[b]
1	23	66	-
2	50	>99	62

[a] Determined by ^1H NMR using diphenylmethane as internal standard. [b] Isolated yield.

Satisfactorily, the reaction at room temperature proceeded with 66% conversion to the desired product **14a** (Table 11, entry 1). Increasing the

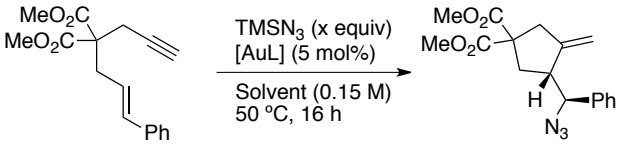
81 The study of the scope and limitation of this transformation was carried out in collaboration with Dr. Javier Carreras.

82 C. Hurtado-Rodrigo, S. Hoehne, M. P. Muñoz, *Chem. Commun.* **2014**, *50*, 1494-1496.

temperature to 50 ºC led to a full conversion of **13a** and good yield to **14a** (Table 11, entry 2).

Optimization of the reaction conditions for this transformation was then carried out (Table 12).

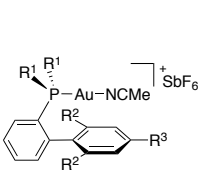
Table 12. Optimization studies for the formation of 14a



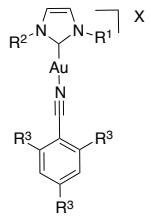
13a **14a**

Entry	[AuL]	$TMSN_3$ (x equiv)	Solvent	Yield (%)[a]
1	**A**	5	CH_2Cl_2	83 (79)[b]
2	**B**	5	CH_2Cl_2	13
3	**C**	5	CH_2Cl_2	-
4	**D**	5	CH_2Cl_2	12
5	**E**	5	CH_2Cl_2	22
6	**G**	5	CH_2Cl_2	-
7	**$PPh_3AuCl/AgSbF_6$** (1:1)	5	CH_2Cl_2	78
8	**$(PhO)_3PAuCl/AgOTf$** (1:1)	3	CH_2Cl_2-$H3O^+$ [c]	degradation
9	**$PtCl_2$**	5	CH_2Cl_2	-
10	**$AuCl_3$**	5	CH_2Cl_2	-
11	**A**	5	THF	60
12	**A**	2	CH_2Cl_2	70
13	**A**	as the solvent	-	83

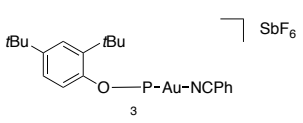
[a] Determined by ^{1}H NMR using diphenylmethane as internal standard. [b] Isolated yield. [c] Conditions: CF_3CO_2H (3 equiv), H_2O (5 equiv), CH_2Cl_2 (0.41 mM), 23 ºC.



A, R^1 = *t*Bu, R^2 = R^3 = H
B, R^1 = *t*Bu, R^2 = R^3 = *i*Pr
C, R^1 = Cy, R^2 = R^3 = *i*Pr



D, R^1 = R^2 = Mes, R^3 = OMe, X = SbF_6
E, R^1 = R^2 = 2,6-*i*Pr$_2$C$_6$H$_3$, R^3 = H, X = SbF_6



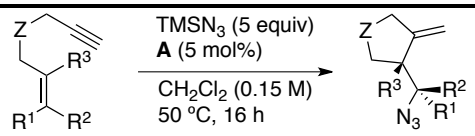
G

Similar optimized conditions to the previous transformation were discovered. JohnPhosgold(I) catalyst **A** was again found to be the best giving the azidocyclization product in 79% yield (Table 12, entry 1). Gold(I) complexes with bulkier phosphines (**B** and **C**, Table 12, entries 2-3) as well as carbenes (**D** and **E**, Table 12, entries 4-5) or a phosphite (G, Table 12, entry 6) gave poor results. Employing the reaction conditions reported by the group of Muñoz for the hydroazidation of allenes[82] led to degradation of the starting enyne (entry 8) and no reaction was observed when using platinum(II) or gold(III) salts (Table 12, entries 9-10). While comparable results were obtained with the cationic triphenylphosphine gold(I) complex formed *in situ* (Table 12, entry 7), JohnPhos-gold(I) catalyst **A** was preferred for its simplicity (no use of silver), stability, and convieniency.[67b,83] The reaction proceeded better in CH_2Cl_2 than in THF (compare entry 1 with 11, Table 12), whereas 5 equiv of $TMSN_3$ was found to be the optimal amount, not observing any advantage by using it as a solvent (Table 12, entry 13).

With these optimized reaction conditions in hand, the generality of this transformation was evaluated (Table 13).

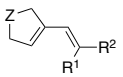
83 A. Homs, I. Escofet, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 5782-5785

Table 13. Scope of the azidocyclization



13 **14**

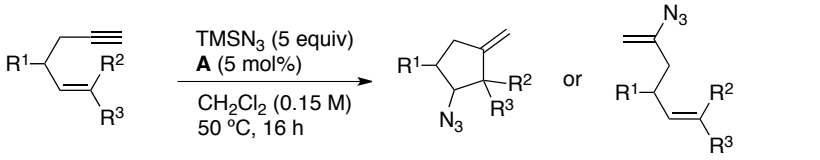
Entry	Enyne	Z	R^1	R^2	R^3	Yield (%)[a]
1	**13a**	$C(CO_2Me)_2$	H	Ph	H	79
2	**13b**	$C(SO_2Ph)_2$	H	Ph	H	69
3	**13c**	O	H	Ph	H	-[b]
4	**13d**	NTs	H	Ph	H	-[b]
5	**13e**	NTs	H	H	H	-[b]
6	**13f**	NTs	H	H	Me	complex mixture
7	**13g**	NTs	cyclohexene		H	complex mixture
8	**13h**	NTs	H	vinyl	H	complex mixture
9	**13i**	NTs	Me	Me	H	-[b]
10	**13j**	$C(CO_2Me)_2$	Me	Me	H	-[b]
11	**13k**	$C(SO_2Ph)_2$	Me	Me	H	-[b]

[a] Isolated yields. [b] Single cleavage product mainly obtained: 

The reactions using carbon linked-enynes **13a** and **13b** bearing a phenyl substituent on the alkene proceed smoothly to provide the corresponding cyclopentanes **14** in good yields (Table 13, entries 1 and 2). In the case of

oxygen or tosylamine as linkers, only traces of the desired products were detected in the reaction mixture (Table 13, entries 3 and 4). However, in other cases, unidentified complex mixtures were obtained (Table 13, entries 6-8). Finally, enynes with no substituents (Table 13, entry 5) or with the *gem*-dimethyl on the olefin moiety (Table 13, entries 9-11) rearranged directly to the products of single cleavage rearrangement.

A set of 1,5-enynes was also evaluated under these gold-catalyzed conditions (Scheme 35).



15a, R^1 = OAc, R^2 = H, R^3 = Ph
15b, R^1 = SO_2Ph, R^2 = H, R^3 = Ph
15c, R^1 = SO_2Ph, R^2 = R^3 = Me

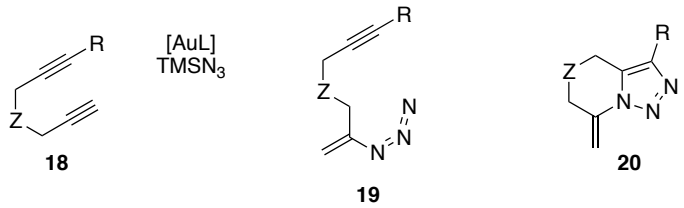
16a, -
16b, -
16c, 52%

17a, 47% (R^1 = N_3)
17b, 69%
17c, -

Scheme 35. Azidocyclization with 1,5-enynes

In this case, enyne **15c** bearing a *gem*-dimethyl substituent on the olefin moiety led to cyclopentane **16c** in moderate yield. However, styrene derivatives **15a**, and **15b** reacted via attack of the nucleophile onto the alkyne. Additionally, under these reaction conditions, acetate **15a** underwent hydroazidation as well as allylic substitution of the acetate by an azide to form compound **17a**.

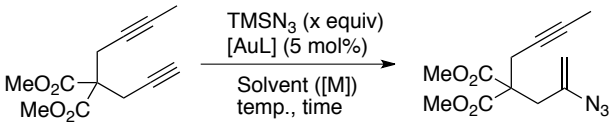
Taking into account these last results, we attempted to react intramolecularly the alkenyl azide (as observed with enynes **15a** and **15b**) with another alkyne by using a non-symmetrical bisalkyne substrate such as **18** (Scheme 36). We envisioned that intermediate **19** would react in a favored intramolecular Huisgen [3+2] cycloaddition to afford the corresponding bicyclic triazole **20**.



Scheme 36. Expected formation of triazole

Initially, dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (**18a**) was selected as model substrate and similar reaction conditions to the ones described for the enynes were used (Table 14, entries 1-4). Unfortunately, poor or no conversion to the desired product were observed. By employing $TMSN_3$ as solvent, the conversion could be improved to 66% in 24 h using JohnPhos/gold(I) catalyst **A** (Table 14, entry 5). Once again, gold(I) carbene **E** and phosphite **G** did not catalyze the transformation (Table 14, entries, 6-7). A variety of polar solvents were then tested, however, with only detrimental consequences in comparison to neat conditions (Table 14, entries 8-13). Finally, an increase in concentration reduced the conversion to **19a** (Table 14, entry 14).

Table 14. Optimization table for the formation of 19a

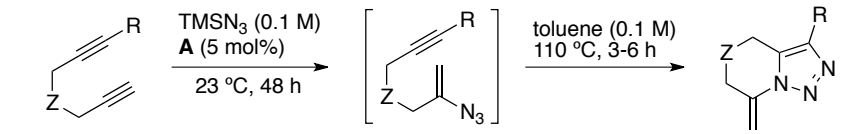


18a **19a**

Entry	$TMSN_3$ (x equiv)	[AuL] (5%)	T (ºC)	Solvent	Conc. (M)	time (h)	Yield (%)[a]
1	1.5	**A**	23	CH_2Cl_2	0.1	24	10
2	5	**A**	23	CH_2Cl_2	0.1	24	10
3	1.5	**A**	50	CH_2Cl_2	0.1	24	-
4	5	**A**	50	CH_2Cl_2	0.1	24	-
5	solvent	**A**	23	$TMSN_3$	0.1	24	66 (45)[b]
6	solvent	**E**	23	$TMSN_3$	0.1	24	-
7	solvent	**G**	23	$TMSN_3$	0.1	24	-
8	5	**A**	23	CH_3CN	0.1	48	-
9	5	**A**	23	NO_2CH_3	0.1	48	35
10	5	**A**	23	THF	0.1	48	polymer
11	5	**A**	23	DMSO	0.1	48	25
12	5	**A**	23	Dioxane	0.1	48	33
13	solvent	**A**	23	$TMSN_3$	0.1	48	85 (67)[b]
14	solvent	**A**	23	$TMSN_3$	0.5	48	66

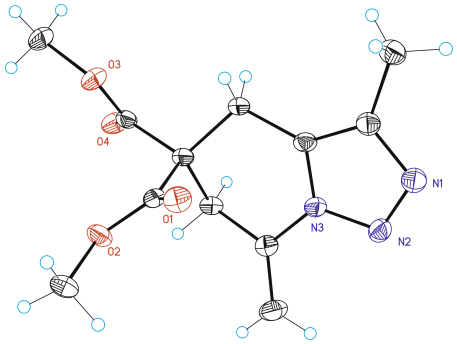
[a] Determined by ^1H NMR using diphenylmethane as internal standard. [b] Isolated yield.

In all cases, the insertion of the azide was the sole product observed and no traces of triazole were detected. In order to obtain the product, removing $TMSN_3$ *in vacuo* and dissolving the mixture in toluene was necessary in order to be able to increase the reaction temperature to 110 ºC. Four new bicyclic triazoles were obtained using this protocol (Scheme 37). Structural confirmation was obtained with **20a** using X-ray diffraction.



18a, Z = $C(CO_2Me)_2$, R = Me
18b, Z = $C(CO_2Me)_2$, R = Ph
18c, Z = $C(CO_2Me)_2$, R = TMS
18d, Z = O, R = Me

20a, 47%
20b, 56%
20c, 11%
20d, 54%



Scheme 37. Formation of triazole 20 and X-ray crystal structure of 20a

Conclusions

A new gold(I)-catalyzed synthesis of tetrazoles from alkynes via C-C bond cleavage has been discovered, which procceds under relatively mild reaction conditions.

Based on experimental observations, a complete catalytic cycle was proposed for this new transformation. The reaction begins with a gold(I)-catalyzed formation of alkenyl azides by nucleophilic attack onto the alkynes. Consequently, these intermediates are probably protonated by a newly formed gold(I) complex coordinated to *i*PrOH. The latter would provide the Brønsted acidity required for this process. Subsequent-Schmidt rearrangement, and final 1,3-dipolar cycloaddition between the newly formed nitrilium cation and the azidogold(I) complex ($LAuN_3$) or HN_3 would lead to the formation of tetrazole.

With a view to broadening the reactivity of gold(I) with $TMSN_3$, preliminary studies were performed with different enynes. Azides could also be employed as nucleophiles in very particular cases, only with 1,6-enynes bearing a phenyl substituent on the olefin and carbon chains tethers linking the alkene and alkyne moieties. Additional optimization would be required for improving the generality of this transformation.

Finally, a new route was optimized for the synthesis of bicyclic triazoles. Starting from bisalkynes, gold(I)-catalyzed addition of azide to one of the alkynes and further intramolecular [3+2] cycloaddition provided the desired triazoles.

Experimental section

General information

All reactions were carried out under argon unless otherwise specified. Solvents were dried using a Solvent Purification System (SPS) or using standard procedures.[84] Catalysts were either purchased from Sigma-Aldrich or synthesized according to literature procedures. All other reagents were used without further purification as obtained from the commercial sources. Analytical thin layer chromatography was carried out using TLC aluminum sheets with 0.2 mm of silica gel (Merck GF234) using UV light as the visualizing agent. Flash column chromatography purifications were carried out using C_{18}-reversed phase silica gel (40-63 μm). NMR spectra were recorded at 23 ºC on either a Bruker Avance 400 Ultrashield (400 MHz for ^{1}H, and 100 MHz for ^{13}C) or a Bruker Avance 500 Ultrashield (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

Crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = −173 ºC). Full-sphere data collection was used with w and j scans. *Programs used*: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solution was achieved using direct methods as implement in SHELXTL and

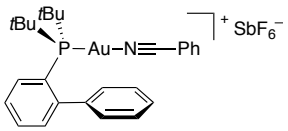
84 W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, Elsevier Science, Bath, **2003**.

visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non hydrogen atoms were refined including anisotropic displacement parameters.

Experimental Procedures

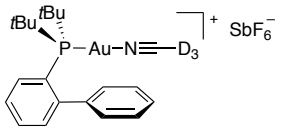
Gold(I)-catalyzed synthesis of tetrazoles

Complex I



Chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I) (50.0 mg, 0.094 mmol) and silver hexafluoroantimonate (32.4 mg, 0.094 mmol) were suspended in CH_2Cl_2 (1.0 mL). After stirring for 10 min at room temperature, benzonitrile (9.7 µL, 0.094 mmol) was added and the reaction mixture was stirred for an additional 10 min. The solvent was evaporated and precipitation of the crude in a cyclohexane/EtOAc mixture gave the complex **I** as a white solid (76.9 mg, 0.092 mmol, 98%). mp 212-215 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2 H), 7.90-7.87 (m, 1H), 7.85-7.82 (m, 1H), 7.68-7.64 (m, 2H), 7.61-7.55 (m, 4H), 7.46-7.42 (m, 1H), 7.34-7.32 (m, 1H), 7.26-7.25 (m, 2H), 1.48 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5 (s), 145.5 (s), 133.7 (s), 133.4 (s), 133.3 (s), 133.0 (s), 131.5 (s), 130.0 (s), 129.8 (s), 129.2 (s), 127.7 (s), 127.6 (s), 127.5 (s), 38.2 (d, J = 27.2 Hz), 30.8 (d, J = 6.1 Hz); ^{31}P NMR (203 MHz, $CDCl_3$) δ 60.36; HRMS-ESI: m/z: calcd for $C_{20}H_{27}AuP$: 495.1511, found: 495.1526. We do not detect $[(M\text{-}SbF_6)]^+$ as the additional loss of one of the ligands is observed.

Complex A-*d*$_3$



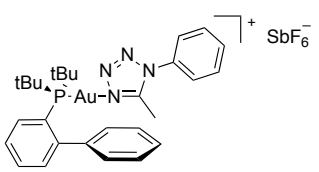
Chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I) (50.0 mg, 0.094 mmol) and silver hexafluoroantimonate (32.4 mg, 0.094 mmol) were suspended in CH_2Cl_2 (1.0 mL). After stirring for 10 min at room temperature, deuterated acetonitrile-*d*$_3$ (4.9 µL, 0.094 mmol) was added and the reaction mixture was stirred for an additional 10 min. The solvent was evaporated to obtain the complex **A-*d*$_3$** as a yellowish oil (52.5 mg, 0.068 mmol, 72%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.90-7.87 (m, 1H),

7.64-7.58 (m, 2H), 7.55-7.49 (m, 3H), 7.35-7.32 (m, 1H), 7.24-7.19 (m, 2H), 1.43 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.2 (s), 143.3 (s), 133.7 (d, J = 7.5 Hz), 133.6 (d, J = 4.3 Hz), 132.0 (s), 130.1 (s), 129.4 (s), 128.1 (s), 124.2 (s), 123.8 (s), 118.8 (s), 38.5 (d, J = 27.3 Hz), 31.0 (d, J = 6.1 Hz); ^{31}P NMR (203 MHz, CD_2Cl_2) δ 60.57; HRMS-ESI: m/z: calcd for $C_{20}H_{27}AuP$: 495.1510, found: 495.1515. We do not detect $[(M\text{-}SbF_6)]^+$ as the additional loss of one of the ligands is observed.

General Procedure for the formation of gold(I)-tetrazole complexes.

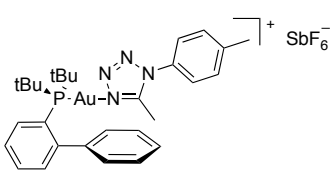
The (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate cationic catalyst **A** (0.1 mmol) and $TMSN_3$ (0.2 mmol) were suspended in CH_2Cl_2 (1.0 mL). The alkyne (0.1 mmol) was then added and the reaction was stirred at room temperature for 12 h. The solvent was evaporated and precipitation of the crude in a cyclohexane/EtOAc mixture gave the gold(I)-tetrazole complex as a white solid.

Complex H



Alkyne = phenylacetylene, yellowish solid, yield 72%; mp 224-226 ºC; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.98-7.94 (m, 1H), 7.75-7.73 (m, 3H), 7.66-7.62 (m, 2H), 7.58-7.56 (m, 2H), 7.36-7.28 (m, 5H), 6.95-6.91 (m, 1H), 2.58 (s, 3H), 1.53 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.3 (s), 143.7 (s), 133.7 (d, J = 7.5 Hz), 132.4 (s), 132.0 (s), 131.1 (s), 130.1 (s), 129.1 (s), 128.1 (d, J = 8.0 Hz), 127.4 (s), 125.09 (s), 38.6 (d, J = 27.1 Hz), 31.2 (d, J = 5.7 Hz), 11.1 (s); ^{31}P NMR (203 MHz, CD_2Cl_2) δ 61.42; HRMS-ESI: m/z: calcd for $C_{28}H_{35}AuN_4P$ $[(M\text{-}SbF_6)^+]$: 655.2272, found: 655.2260.

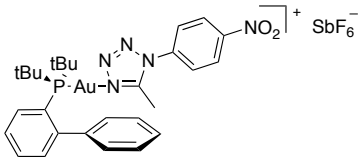
Complex J



Alkyne = 4-ethynyltoluene, brown solid,

yield 53%; mp 213-215 ºC; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.98-7.94 (m, 1H), 7.64-7.62 (m, 2H), 7.53-7.51 (m, 2H), 7.44-7.43 (m, 2H), 7.34-7.28 (m, 5H), 6.94-6.91 (m, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 1.52 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.8 (d, J = 3.4 Hz), 149.4 (d, J = 12.0 Hz) 143.7 (d, J = 6.5 Hz), 143.4 (s), 133.9 (d, J = 4.1 Hz), 133.7 (d, J = 7.4 Hz), 131.9 (d, J = 2.6 Hz), 131.5 (s), 130.1 (s), 129.1 (s), 128.9 (d, J = 4.0 Hz), 128.1 (d, J = 7.8 Hz), 127.4 (s), 124.9 (s), 38.6 (d, J = 27.1 Hz), 31.2 (dd, J = 12.2, 6.1 Hz), 21.5 (s), 11.1 (s); ^{31}P NMR (203 MHz, CD_2Cl_2) δ 61.34; HRMS-ESI: m/z: calcd for $C_{29}H_{37}AuN_4P$ [(M-SbF_6)$^+$]: 669.2409, found: 669.2416.

Complex K



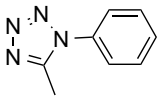
Alkyne = 1-ethynyl-4-nitrobenzene, yellow solid, yield 45%; mp 210-213; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.57-8.55 (m, 2H), 7.97-7.94 (m, 1H), 7.87-7.86 (m, 2H), 7.66-7.61 (m, 2H), 7.38-7.35 (m, 3H), 7.31-7.29 (m, 2H), 6.99-6.96 (m, 1H), 2.67 (s, 3H), 1.52 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 154.3 (s), 149.9 (s), 149.4 (d, J = 12.0 Hz), 143.6 (d, J = 6.5 Hz), 137.2 (s), 133.8 (d, J = 4.1 Hz), 133.7 (d, J = 7.9 Hz), 131.9 (d, J = 2.5 Hz), 130.1 (s), 129.2 (s), 128.1 (d, J = 7.6 Hz), 127.6 (s), 126.3 (d, J = 3.7 Hz), 124.4 (s), 124.0 (s), 38.7 (s), 38.6 (d, J = 27.0 Hz), 31.2 (d, J = 6.2 Hz), 11.3 (s); ^{31}P NMR (203 MHz, CD_2Cl_2) δ 61.28; HRMS-ESI: m/z: calcd for $C_{28}H_{34}AuN_5O_2P$ [(M-SbF_6)$^+$]: 700.2108, found: 700.2110.

General Procedure for the preparation of 1,5-disubstituted tetrazoles

The cationic gold(I) catalyst **A** (0.02 mmol) and $TMSN_3$ (0.4 mmol) were suspended in DCE (1 mL). A solution of the alkyne (0.2 mmol) in DCE (1.0 mL) and *i*PrOH (0.8 mmol) was then added and the reaction was stirred at

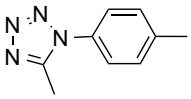
80 ºC for 12 h. The reaction mixture was cooled to room temperature and the addition of a few drops of NEt_3 was added and the solvent was evaporated. The crude was purified using C_{18}-reversed phase silica gel ($MeCN/H_2O$, 1/2 to 1/1) to yield the 1,5-disubstituted tetrazole.

5-Methyl-1-phenyl-1*H*-tetrazole (2a)[85]



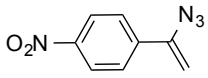
White solid, 49%; mp 102-104 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 3H), 7.48-7.46 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 134.0, 130.5, 130.1, 124.7, 10.0; HRMS-ESI: *m*/*z*: calcd for $C_8H_8N_4Na$ $[(M+Na)]^+$: 183.0644, found: 183.0641.

5-Methyl-1-(*p*-tolyl)-1*H*-tetrazole (2b)[85]



Pale yellow solid, 41%; mp 110-113 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.34-7.33 (m, 2H), 2.60 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 140.9, 131.5, 130.6, 124.6, 21.4, 9.9; HRMS-ESI: *m*/*z*: calcd for $C_9H_{10}N_4Na$ $[(M+Na)^+]$: 197.0805, found: 197.0798.

1-(1-Azidovinyl)-4-nitrobenzene (5c)[86]



Yellow oil, 23%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.19 (m, 2H), 7.74-7.72 (m, 2H), 5.64 (d, J = 3.0 Hz, 1H), 5.15 (d, J = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 143.5, 140.3, 126.5, 123.9, 101.2. The ^{1}H NMR data are identical to that reported in ref. 86b.

1-(4-Methoxyphenyl)-5-methyl-1*H*-tetrazole (2d)[85]

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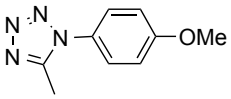
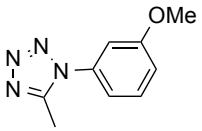
85 A.-A. S. El-Ahl, F. A. Amer, A. H. Elbeheery, *Phosphorus, Sulfur, and Silicon and Related Elements* **2011**, *186*, 2226-2235.

86 (a) A. Hassner, D. J. Anderson, R. H. Reuss, *Tetrahedron Lett.* **1977**, 2463–2466. (b) D. Brown, G. A. Brown, M. Andrews, J- M. Large, D. Urban, C. P. Butts, N. J. Hales, T. Gallagher, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2014–2021.



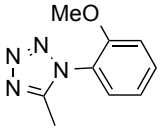
White solid, 70%; mp 96-98 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (m, 2H), 7.07-7.06 (m, 2H), 3.89 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 161.0, 151.8, 126.7, 126.3, 115.2, 55.9, 9.8; HRMS-ESI: *m*/*z*: calcd for $C_9H_{10}N_4NaO$ [$(M$+Na)$^+$]: 213.0749, found: 213.0747.

1-(3-Methoxyphenyl)-5-methyl-1*H*-tetrazole (2e)



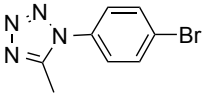
Yellow oil, 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 1H), 7.11–7.09 (m, 1H), 7.03–7.00 (m, 2H), 3.87 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.5, 134.8, 130.7, 116.4, 116.0, 110.5, 55.7, 9.9; HRMS-ESI: *m*/*z*: calcd for $C_9H_{10}N_4NaO$ [$(M$+Na)$^+$]: 213.0748, found: 213.0747.

1-(2-Methoxyphenyl)-5-methyl-1*H*-tetrazole (2f)



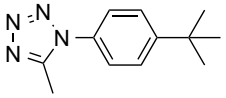
Yellow oil, 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.54 (m, 1H), 7.37-7.35 (m, 1H), 7.15-7.10 (m, 2H), 3.83 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 153.5, 132.5, 128.2, 122.6, 121.3, 112.5, 56.1, 9.2; HRMS-ESI: *m*/*z*: calcd for $C_9H_{10}N_4NaO$ [$(M$+Na)$^+$]: 213.0755, found: 213.0747.

1-(4-Bromophenyl)-5-methyl-1*H*-tetrazole (2g)[85]



Yellow solid, 36%; mp 125-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.73 (m, 2H), 7.38-7.36 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 133.4, 133.0, 126.1, 124.7, 10.0; HRMS-ESI: *m*/*z*: calcd for $C_8H_8BrN_4$ [$(M$+H)$^+$]: 238.9934, found: 238.9927.

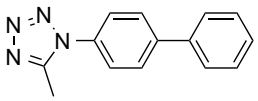
1-(4-(*tert*-Butyl)phenyl)-5-methyl-1*H*-tetrazole (2h)



Yellow oil, 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.58 (m, 2H), 7.58-7.37 (m, 2H), 2.61 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)

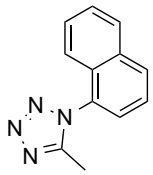
δ 154.1, 151.8, 131.5, 127.1, 124.4, 35.2, 31.4, 10.0; HRMS-ESI: *m*/*z*: calcd for $C_{12}H_{16}N_4Na$ [(*M*+Na)$^+$]: 239.1266, found: 239.1267.

1-([1,1'-Biphenyl]-4-yl)-5-methyl-1*H*-tetrazole (2i)



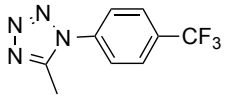
White solid, 56%; mp 177-180 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.80 (m, 2H), 7.66-7.63 (m, 2H), 7.57-7.42 (m, 5H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 143.7, 139.5, 133.1, 129.3, 128.8, 127.5, 125.1, 10.1; HRMS-ESI: *m*/*z*: calcd for $C_{14}H_{12}N_4Na$ [(*M*+Na)$^+$]: 259.0951, found: 259.0954.

5-Methyl-1-(naphthalen-1-yl)-1*H*-tetrazole (2j)[85]



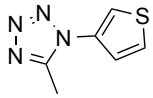
Yellow solid, 49%; mp 101-104 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 8.02-8.01 (m, 1H), 7.66-7.61 (m, 2H), 7.58-7.55, (m, 1H), 7.51-7.49 (m, 1H), 7.17-7.15 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 134.2, 131.6, 129.0, 128.5, 127.5, 125.0, 121.5, 9.1; HRMS-ESI: *m*/*z*: calcd for $C_{12}H_{10}N_4Na$ [(*M*+Na)$^+$]: 233.0798, found: 233.0798.

5-Methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-tetrazole (2k)



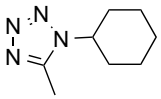
Yellow oil, 18%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H), 7.67-7.66 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 136.8, 129.3, 127.4, 126.5, 124.9, 10.1; HRMS-ESI: *m*/*z*: calcd for $C_9H_8F_3N_4$ [(*M*+H)$^+$]: 229.0698, found: 229.0696.

5-Methyl-1-(thiophen-3-yl)-1*H*-tetrazole (2l)



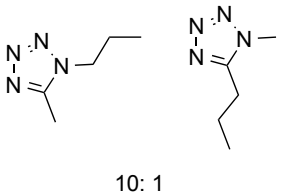
Yellow oil, 51%; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.60-7.56 (m, 2H), 7.32-7.30 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 154.0, 130.1, 125.5, 122.2, 12.1; HRMS-ESI: *m*/*z*: calcd for $C_6H_6N_4NaS$ [(*M*+Na)$^+$]: 189.0204, found: 189.0205.

1-Cyclohexyl-5-methyl-1*H*-tetrazole (2m)[87]



White solid, 76%; mp 130-131 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16-4.09 (m, 1H), 2.55 (s, 3H) 2.04-1.94 (m, 6H), 1.79-1.75 (m, 1H), 1.45-1.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 57.9, 32.7, 25.4, 25.0, 9.2; HRMS-ESI: *m*/*z*: calcd for $C_8H_{14}N_4Na$ [(*M*+Na)$^+$]: 189.1117, found: 189.1111.

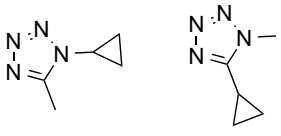
5-Methyl-1-propyl-1*H*-tetrazole, 1-methyl-5-propyl-1*H*-tetrazole (2n, 2n')[88]



10: 1

Yellow oil, inseparable mixture of regioisomers, 50% (10: 1); 5-methyl-1-propyl-1*H*-tetrazole: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (t, *J* = 9.5 Hz, 2H), 2.58 (s, 3H), 1.97 (h, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 48.7, 23.0, 11.0, 8.9; 1-methyl-5-propyl-1*H*-tetrazole: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H), 2.85 (t, *J* = 11 Hz, 2H), 1.88 (h, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 47.0, 24.9, 13.7, 8.7; HRMS-ESI: *m*/*z*: calcd for $C_5H_{11}N_4$ [(*M*+H)$^+$]: 127.0975, found: 127.0978.

5-Cyclopropyl-1-methyl-1*H*-tetrazole, 1-cyclopropyl-5-methyl-1*H*-tetrazole (2o, 2o')[89]



1: 3

Yellow oil, inseparable mixture of regioisomers, 49% (1: 3); 1-cyclopropyl-5-methyl-1*H*-tetrazole: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (tt, *J* = 6.2, 4.1 Hz, 1H), 2.60 (s, 3H), 1.27-1.24 (m, 4H). ^{13}C

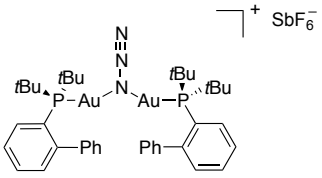
87 E. K. Harvill, R. M. Herbst, E. C. Schreiner, C. W. Roberts, *J. Org. Chem.* **1950**, *15*, 662-670.

88 K. Nishiyama, A. Watanabe, *Chem. Lett.* **1984**, 455-458.

89 L. E. Fikes, H. Shechter, *J. Org. Chem.*, **1978**, *44*, 741-744.

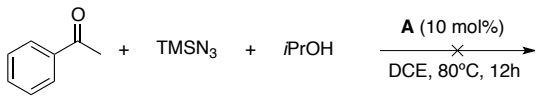
NMR (100 MHz, $CDCl_3$) δ 153.2, 47.1, 9.1, 8.8, 8.7; 5-cyclopropyl-1-methyl-1*H*-tetrazole: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 3H), 1.86 (tt, J = 7.6, 6.0 Hz, 1H), 1.21-1.19 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 33.1, 28.0, 6.8, 3.8; HRMS-ESI: *m*/*z*: calcd for $C_5H_9N_4$ [(M+H)$^+$]: 125.0828, found: 125.0822.

Complex N



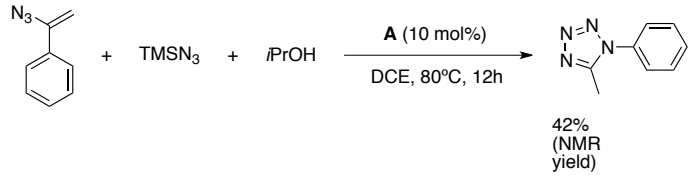
Chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I) (30.0 mg, 0.057 mmol) and silver hexafluoroantimonate (19.4 mg, 0.057 mmol) were suspended in CH_2Cl_2 (0.6 mL). After stirring for 10 min at room temperature, the reaction mixture was cooled to -18 ºC $TMSN_3$ (3.7 µL, 0.028 mmol) was added and the reaction mixture was stirred at this temperature for 16h. The solvent was evaporated to obtain the complex **N** as a white solid (23.01 mg, 0.018 mmol, 65%). mp 209-211 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.84 (m, 2H), 7.62-7.45 (m, 10H), 7.32-7.27 (m, 2H), 7.22-7.12 (m, 4H), 1.41 (s, 18H), 1.37 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9 (d, J = 12.3 Hz), 142.3 (s), 133.5-132.9 (m), 131.4 (d, J = 2.3 Hz), 129.6 (s), 128.5 (s), 127.6 (d, J = 7.5 Hz), 124.1 (s), 123.7 (s), 38.0 (d, J = 26.5 Hz), 30.8 (d, J = 6.2 Hz); ^{31}P NMR (203 MHz, $CDCl_3$) δ 62.86; HRMS-ESI: *m*/*z*: calcd for $C_{20}H_{27}AuP$: 495.1510, found: 495.1515. We do not detect [(M-SbF6)]$^+$, the additional loss of one of the ligands is observed.

Mechanistic studies

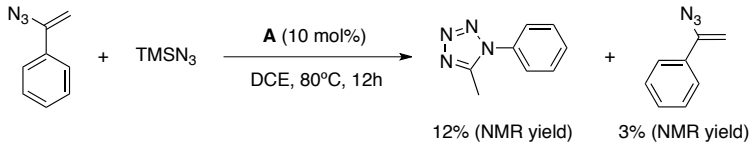


The cationic gold(I) catalyst **A** (0.02 mmol) and $TMSN_3$ (0.4 mmol) were suspended in DCE (1 mL). Acetophenone (0.2 mmol) in DCE (1 mL) and *i*PrOH (0.8 mmol) were added and the reaction was

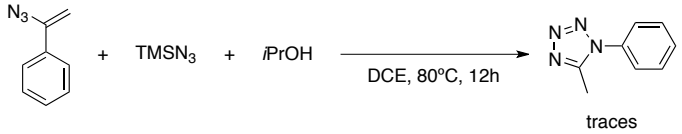
stirred at 80 ºC for 12 h. After cooling the reaction mixture to room temperature a few drops of NEt_3 were added and the solvents were evaporated.



Procedure 1. The cationic gold(I) catalyst **A** (0.02 mmol) and $TMSN_3$ (0.4 mmol) were suspended in DCE (1 mL). A solution of 1-azido-1-phenylethylene[90] (0.2 mmol) in DCE (1 mL) and *i*PrOH (0.8 mmol) was added and the reaction was stirred at 80 ºC for 12 h. The reaction mixture was cooled to room temperature and a few drops of NEt_3 was added. The solvent was evaporated yielding 5-methyl-1-phenyl-1*H*-tetrazole **2a** (42%, determined by ^{1}H NMR using diphenylmethane as internal standard).

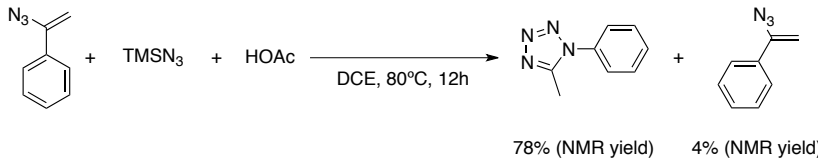


Using **Procedure 1** but omiting the addition of *i*PrOH to the reaction mixture, only 12% (determined by ^{1}H NMR using diphenylmethane as internal standard) of 5-methyl-1-phenyl-1*H*-tetrazole **2a** was observed.

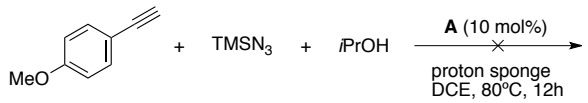


Using **Procedure 1** but omiting the addition of the cationic gold(I) catalyst **A** to the reaction mixture, only traces of 5-methyl-1-phenyl-1*H*-tetrazole **2a** was observed.

90 F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.* **2008**, *10*, 2409-2412.

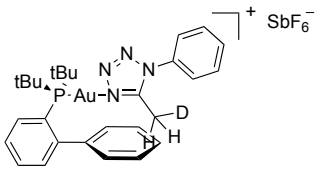


Using **Procedure 1** but replacing the cationic gold(I) catalyst **A** by the addition of 2 equivalents of acetic acid in the reaction mixture, 5-methyl-1-phenyl-1*H*-tetrazole **2a** (78%, determined by ^{1}H NMR using diphenylmethane as internal standard) was obtained.



A last control experiment was performed by adding a base such as proton sponge (2 eq.) to the reaction mixture containing 4-ethynylanisol (1 eq.), $TMSN_3$ (2 eq.), *i*PrOH (4 eq.), and gold(I) catalyst **A** (0.1 eq.) in DCE (0.1 M, 80 ºC, 12h). Under these reaction conditions, the catalysis is inhibited from forming the corresponding tetrazole **2d**.

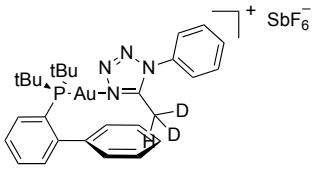
Complex H-*d*.



The cationic gold(I) catalyst **A** (0.05 mmol) and $TMSN_3$ (0.1 mmol) were suspended in CH_2Cl_2 (0.5 mL). Phenylacetylene-*d* **1a-*d*** (0,05 mmol) was then added and the reaction was stirred at room temperature for 12 h. The solvent was evaporated and precipitation of the crude in a cyclohexane/EtOAc mixture gave complex **H-*d*** (35%) as a white solid. mp 239-243 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.90 (m, 1H), 7.72-7.67 (m, 3H), 7.61-7.59 (m, 5H), 7.38-7.35 (m, 2H), 7.33-7.31 (m, 1H), 7.30-7.28 (m, 1H), 6.96-6.93 (m, 1H), 2.64-2.62

(m, 2H), 1.52 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 154.1 (s), 149.4 (d, J = 12.7 Hz), 143.1 (s), 133.5 (d, J = 7.4 Hz), 133.4 (d, J = 3.8 Hz), 132.4 (s), 131.9 (s), 131.6 (s), 130.7 (s), 129.8 (s), 129.0 (s), 127.6 (d, J = 7.6 Hz), 127.4 (s), 125.0 (s), 38.5 (d, J = 27.0 Hz), 31.1 (dd, J = 21.5, 6.5 Hz), 10.8 (t, J = 20.2 Hz); ^{31}P NMR (162 MHz, CD_2Cl_2) δ 61.39; HRMS-ESI: *m*/*z*: calcd for $C_{28}H_{34}AuDN_4P$ [(*M*-SbF_6)$^+$]: 656.2321, found: 656.2322.

Complex H-*d*$_2$.



The cationic gold(I) catalyst **A** (0.05 mmol) and $TMSN_3$ (0.1 mmol) were suspended in CH_2Cl_2 (0.5 mL). Phenylacetylene **1a** (0.05 mmol) and D_2O (0.05 mmol) were then added and the reaction was stirred at room temperature for 12 h. The solvent was evaporated and precipitation of the crude in a cyclohexane/EtOAc mixture gave complex **H-*d*$_2$** (42%) as a white solid. mp 251-253 ºC; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.96-7.93 (m, 1H), 7.90-7.86 (m, 1H), 7.63-7.57 (m, 4H), 7.55-7.50 (m, 4H), 7.33-7.30 (m, 2H), 7.21-7.19 (m, 2H), 2.59-2.54 (m, 1H), 1.41(s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 149.5 (d, J = 12.2 Hz), 142.7 (s), 133.7 (m), 131.8 (d, J = 2.4 Hz), 131.0 (s), 130.0 (s), 128.9 (t, J = 4.1 Hz), 128.6 (s), 127.9 (d, J = 7.4 Hz), 125.1 (s), 124.5 (s), 124.1 (s), 38.3 (d, J = 26.7 Hz), 31.1 (dd, J = 15.3, 6.6 Hz); ^{31}P NMR (162 MHz, CD_2Cl_2) δ 62.61; HRMS-ESI: *m*/*z*: calcd for $C_{20}H_{27}AuP$: 495.1501, found: 495.1510. We do not detect [(*M*-SbF6)]$^+$ as the additional loss of one of the ligands is observed.

Crystal structures

Complex H.

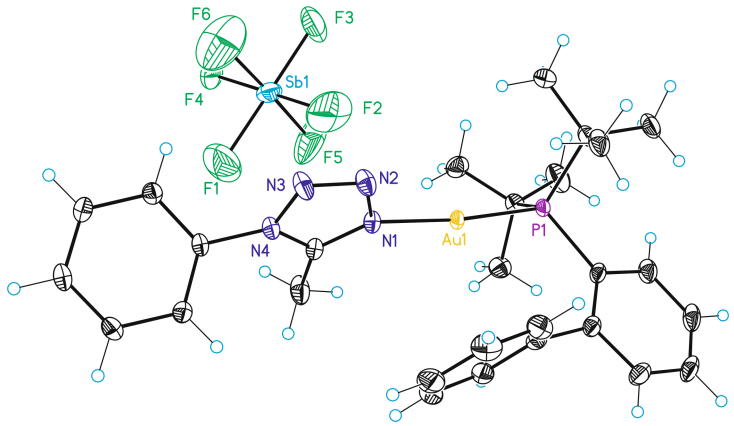


Table 1. Crystal data and structure refinement for Complex **H**.

Empirical formula	C14 H17.50 Au0.50 F3 N2 P0.50 Sb0.50
Formula weight	445.64
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 26.138(2) Å a= 90.00 °.
	b = 9.8567(8) Å b = 92.197(2) °.
	c = 24.3524(19) Å g = 90.00 °.
Volume	6269.5(9) Å3
Z	16
Density (calculated)	1.889 Mg/m3
Absorption coefficient	5.648 mm-1
F(000)	3440

Crystal size	0.15 x 0.10 x 0.10 mm3
Theta range for data collection	1.56 to 30.50 °.
Index ranges	-27 <=h<=36 ,-12 <=k<=13 ,-34 <=l<=33
Reflections collected	42491
Independent reflections	8608 [R(int) = 0.0201]
Completeness to theta =30.50 °	90.100006%
Absorption correction	Empirical
Max. and min. transmission	0.6020 and 0.4846
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	8608 / 147 / 440
Goodness-of-fit on F2	0.995
Final R indices [I>2sigma(I)]	R1 = 0.0171 , wR2 = 0.0455
R indices (all data)	R1 = 0.0185 , wR2 = 0.0462
Largest diff. peak and hole	0.843 and -1.155 e.Å-3

Complex J.

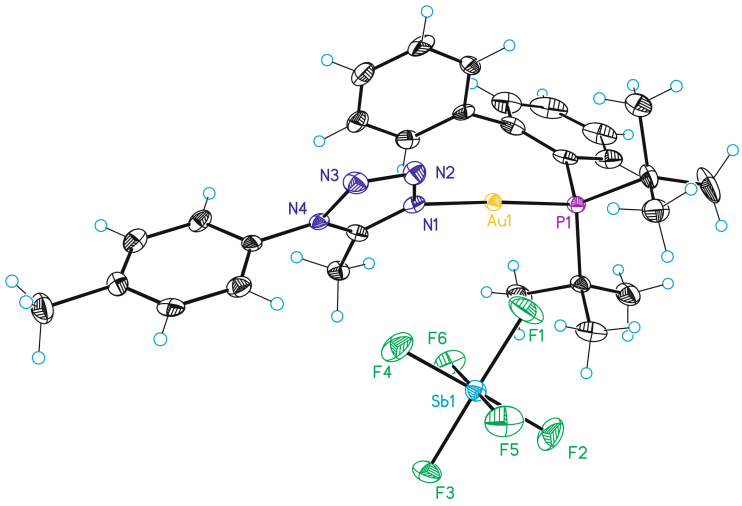


Table 1. Crystal data and structure refinement for Complex **J**.

Empirical formula	C31 H40 Au F6 N4 O P Sb
Formula weight	948.36
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.1685(8) Å á= 85.701(3) °.
	b = 13.3982(11) Å â = 68.859(3) °.
	c = 13.7328(12) Å ã = 77.800(3) °.
Volume	1705.6(2) Å3
Z	2
Density (calculated)	1.847 Mg/m3
Absorption coefficient	5.198 mm-1

F(000) 922

Crystal size 0.10 x 0.08 x 0.02 mm3

Theta range for data collection 1.55 to 26.48 °.

Index ranges -12 <=h<=11 ,-16 <=k<=16 ,-17 <=l<=17

Reflections collected 16630

Independent reflections 6983 [R(int) = 0.0587]

Completeness to theta =26.48 ° 99.0%

Absorption correction Empirical

Max. and min. transmission 0.9032 and 0.6245

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 6983 / 42 / 442

Goodness-of-fit on F2 0.989

Final R indices [I>2sigma(I)] R1 = 0.0363 , wR2 = 0.0656

R indices (all data) R1 = 0.0571 , wR2 = 0.0722

Largest diff. peak and hole 1.312 and -1.494 e.Å-3

Complex K.

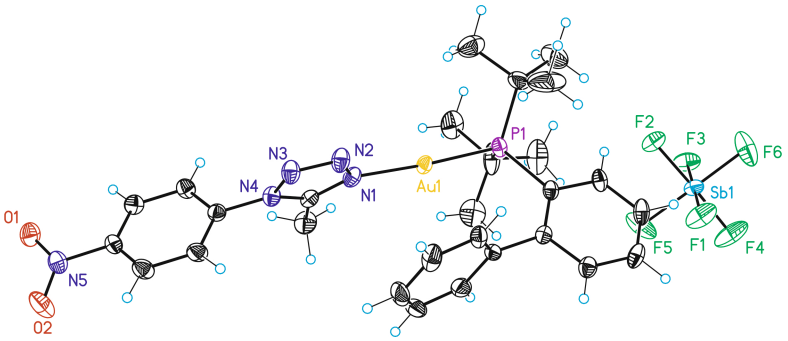


Table 1. Crystal data and structure refinement for Complex **K**.

Empirical formula	C28 H34 Au F6 N5 O2 P Sb
Formula weight	936.29
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.9683(6) Å á= 111.409(2) °.
	b = 12.4112(8) Å â = 107.903(2) °.
	c = 15.3013(9) Å ã = 92.245(2) °.
Volume	1652.42(18) Å3
Z	2
Density (calculated)	1.882 Mg/m3
Absorption coefficient	5.367 mm-1
F(000)	904
Crystal size	0.15 x 0.15 x 0.03 mm3
Theta range for data collection	1.79 to 30.36 °.

Index ranges	-13 <=h<=13 ,-17 <=k<=16 ,-21 <=l<=20
Reflections collected	19645
Independent reflections	8644 [R(int) = 0.0210]
Completeness to theta =30.36 °	86.9%
Absorption correction	Empirical
Max. and min. transmission	0.8556 and 0.4999
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	8644 / 0 / 404
Goodness-of-fit on F2	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0425 , wR2 = 0.1074
R indices (all data)	R1 = 0.0462 , wR2 = 0.1126
Largest diff. peak and hole	5.663 and -1.190 e.Å-3

Complex M

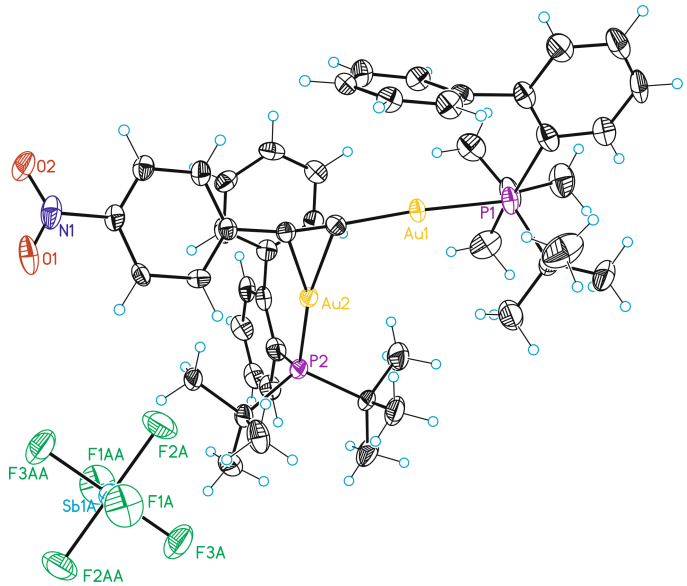


Table 1. Crystal data and structure refinement for Complex **M**

Empirical formula	C49 H60.25 Au2 Cl0.50 F6 N O2 P2 Sb
Formula weight	1404.58
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 37.8474(15) Å a= 90.00 °.
	b = 14.3749(6) Å b = 99.184(2) °.
	c = 18.7121(12) Å g = 90.00 °.
Volume	10049.9(9) Å3
Z	8
Density (calculated)	1.857 Mg/m3

Absorption coefficient 6.509 mm-1

F(000) 5430

Crystal size 0.20 x 0.20 x 0.03 mm3

Theta range for data collection 1.82 to 26.48 °.

Index ranges -47 <=h<=44 ,-18 <=k<=17 ,-22 <=l<=23

Reflections collected 35271

Independent reflections 9781 [R(int) = 0.0547]

Completeness to theta =26.48 ° 94.2%

Absorption correction Empirical

Max. and min. transmission 0.8287 and 0.3560

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 9781 / 101 / 613

Goodness-of-fit on F2 1.045

Final R indices [I>2sigma(I)] R1 = 0.0404 , wR2 = 0.0918

R indices (all data) R1 = 0.0622 , wR2 = 0.1019

Largest diff. peak and hole 1.876 and -2.159 e.Å-3

Complex N

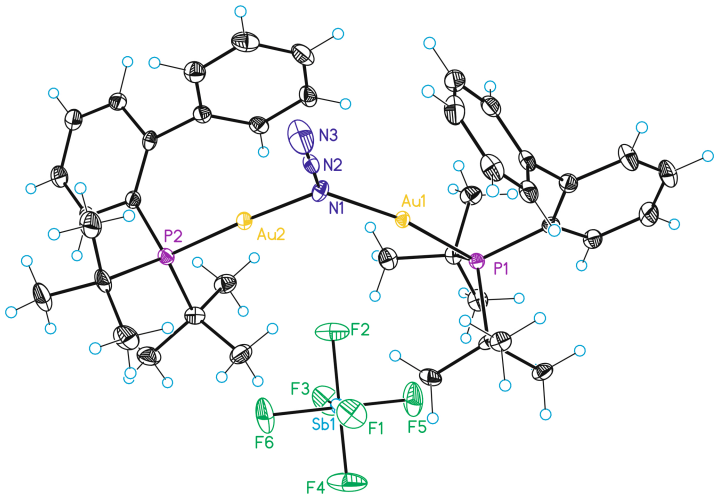


Table 1. Crystal data and structure refinement for Complex **N**

Empirical formula	C40 H54 Au2 F6 N3 P2 Sb
Formula weight	1268.49
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 13.9490(6) Å a= 90.00 °.
	b = 20.7626(10) Å b = 107.5570(10) °.
	c = 15.7007(7) Å g = 90.00 °.
Volume	4335.4(3) Å3
Z	4
Density (calculated)	1.943 Mg/m3
Absorption coefficient	7.501 mm-1
F(000)	2432

Crystal size	0.30 x 0.10 x 0.10 mm3
Theta range for data collection	1.53 to 30.42 °.
Index ranges	-18 <=h<=19 ,-28 <=k<=28 ,-20 <=l<=22
Reflections collected	55574
Independent reflections	11927 [R(int) = 0.0499]
Completeness to theta =30.42 °	90.7%
Absorption correction	Empirical
Max. and min. transmission	0.5209 and 0.2118
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	11927 / 0 / 499
Goodness-of-fit on F2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0262 , wR2 = 0.0467
R indices (all data)	R1 = 0.0379 , wR2 = 0.0496
Largest diff. peak and hole	1.656 and -1.025 e.Å-3

Complex O

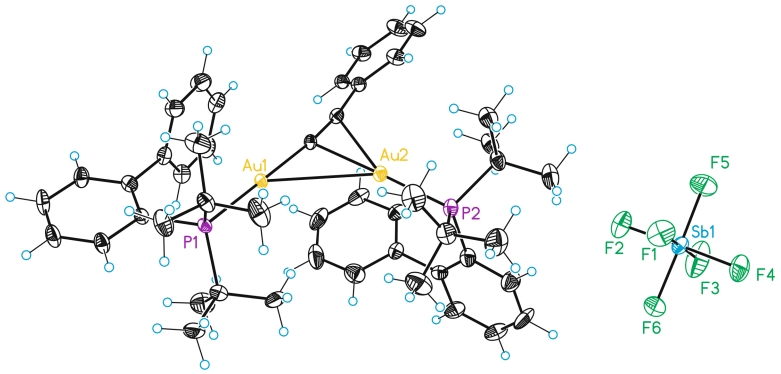


Table 1. Crystal data and structure refinement for **O**

Empirical formula	C48 H59 Au2 F6 P2 Sb
Formula weight	1327.57
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 15.1151(15)Å a= 90°.
	b = 14.2946(13)Å b = 92.139(2)°.
	c = 22.554(2)Å g = 90°.
Volume	4869.7(8) Å3
Z	4
Density (calculated)	1.811 Mg/m3
Absorption coefficient	6.681 mm-1
F(000)	2560
Crystal size	0.20 x 0.20 x 0.04 mm3

Theta range for data collection	1.595 to 33.375°.
Index ranges	-22<=h<=21,-10<=k<=22,-32<=l<=21
Reflections collected	35356
Independent reflections	16083[R(int) = 0.0447]
Completeness to theta =33.375°	85.0%
Absorption correction	Empirical
Max. and min. transmission	0.776 and 0.487
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	16083/ 78/ 607
Goodness-of-fit on F2	1.009
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.0711
R indices (all data)	R1 = 0.0755, wR2 = 0.0831
Largest diff. peak and hole	2.024 and -1.970 e.Å-3

Gold(I)-catalyzed addition of azide

1,6-Enynes **13a**,[91] **13b**,[92] **13c**,[93]**13d**,[94] **13e**,[95] **13f,**[95] **13g**,[96] **13h**,[97] **13i**,[98] **13j**[95] and **13k**,[99] were identified by comparison of their ^{1}H NMR spectra with the previously reported data.

1,5 enynes **15a**[100] and **15c**[100] were identified by comparison of their ^{1}H NMR spectra with the previously reported data.

1,6 diynes **18a**,[101] **18b**,[101] **18d**,[101] were identified by comparison of their ^{1}H NMR spectra with the previously reported data.

(*E*)-((1-Phenylhex-1-en-5-yn-3-yl)sulfonyl)benzene (15b)

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98 W. Wang, J. Yang, F. Wang, M. Shi, *Organometallics* **2011**, *30*, 3859-3869.

99 M. P. Muñoz, M. Méndez, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Synthesis* **2003**, 2898-2902.

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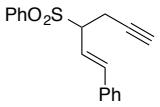
101 S. García-Rubín, J. A. Varela, L. Castedo, C. Saá, *Chem Eur. J.* **2008**, *14*, 9772-9778.

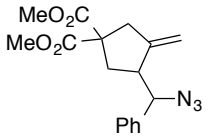


To a stirring solution of the 3-bromo-1-phenyl-1-propene in DMF (1M), was added sodium phenyl sulfinate (1.5 eq.) at room temperature. The reaction mixture was stirred for 16 h. After extractive work-up (10% HCl solution and Et_2O) the corresponding allyl sulfone was isolated and used without further purification in the subsequent step. A solution of the allylsulfone in THF (0.1 M) was cooled to -78 ºC and *n*-BuLi (1.1 eq) was slowly added. After stirring for 20 minutes, propargyl bromide (1.1 eq.) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. After extraction with EtOAc, and purification by flash chromatography (cyclohexane / EtOAc, 4 / 1) the **15b** was obtained in XX% yield as a white solid. mp 81-84 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.66-7.63 (m, 1H), 7.54-7.49 (m, 2H), 7.34-7.28 (m, 5H), 6.38 (d, J = 15.8 Hz, 1H), 6.01 (dd, J = 15.8, 9.2 Hz, 1H), 3.86 (dddd, J = 10.1, 9.1, 3.9, 0.9 Hz, 1H), 3.08 (ddd, J = 16.9, 3.9, 2.7 Hz, 1H), 2.76 (ddd, J = 16.9, 10.2, 2.7 Hz, 1H), 1.99 (t, J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 134.0, 130.9, 129.3, 129.0, 128.7, 128.6, 126.84, 126.75, 119.4, 77.6, 72.7, 67.7, 18.7; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{15}O_2S$ [(*M*-H)$^-$]: 295.0798, found: 295.0798.

General procedure.

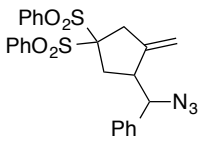
To a flask containing (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate cationic complex **A** (0.01 mmol) and $TMSN_3$ (1.0 mmol) was added the enyne (0.2 mmol) diluted in CH_2Cl_2 (0.15 M). The reaction mixture was then stirred at 50 ºC for 12 h. After cooling at room temperature the reaction was quenched with the addition of a few drops of NEt_3 and the solvent was evaporated. The crude product was purified over silica gel using different gradients of cyclohexane and ethyl acetate to obtain the pure desired products.

Dimethyl 3-(azido(phenyl)methyl)-4-methylenecyclopentane-1,1-dicarboxylate (14a)



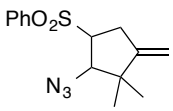
Colourless oil, 79%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.36-7.33 (m, 3H), 5.07-5.05 (m, 1H), 4.71-4.68 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.08-2.95 (m, 3H), 2.48-2.43 (m, 1H), 2.27-2.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 171.7, 147.7, 138.5, 128.7, 128.2, 127.1, 109.7, 68.9, 58.4, 52.8, 48.0, 41.9, 35.6; HRMS-ESI: *m*/*z*: calcd for $C_{17}H_{19}N_3NaO_4$ [(*M*+Na)$^+$]: 352.1275, found: 352.1268.

(3-(Azido(phenyl)methyl)-4-methylenecyclopentane-1,1-disulfonyl)dibenzene (14b)



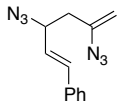
Pale yellow solid, 69%; mp 154-157 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.06 (m, 2H), 7.99-7.97 (m, 2H), 7.76-7.68 (m, 2H), 7.65-7.61 (m, 2H), 7.57-7.53 (m, 2H), 7.41-7.34 (m, 3H), 7.28-7.26 (m, 2H), 4.94-4.91 (m, 1H), 4.66 (d, *J* = 6.4 Hz, 1H), 4.64-4.61 (m, 1H), 3.46 (dq, *J* = 17.9, 2.4 Hz, 1H), 3.20 (dtq, *J* = 8.6, 6.4, 2.1 Hz, 1H), 3.02 (dq, *J* = 17.9, 1.6 Hz, 1H), 2.80 (dd, *J* = 15.4, 8.7 Hz, 1H), 2.53 (ddd, *J* = 15.3, 8.6, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 138.0, 136.8, 135.9, 134.9, 134.8, 131.3, 131.3, 129.0, 128.9, 128.9, 128.7, 127.1, 110.4, 91.4, 68.4, 49.0, 39.2, 33.6; HRMS-ESI: *m*/*z*: calcd for $C_{25}H_{23}N_3NaO_4S_2$ [(*M*+Na)$^+$]: 516.1028, found: 516.1022.

((2-Azido-3,3-dimethyl-4-methylenecyclopentyl)sulfonyl)benzene (16c)



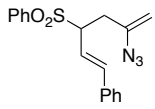
Yellow oil, 52%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.83 (m, 2H), 7.65-7.62 (m, 1H), 7.54-7.53 (m, 2H), 4.92 (dp, *J* = 10.4, 1.4 Hz, 1H), 4.77 (t, *J* = 1.6 Hz, 1H), 4.68 (dd, *J* = 2.0, 0.7 Hz, 1H), 3.97 (td, *J* = 10.8, 3.4 Hz, 1H), 2.87 (dd, *J* = 14.0, 3.0 Hz, 1H), 2.37 (dd, *J* = 14.0, 11.0 Hz, 1H), 1.67 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 142.8, 137.8, 133.7, 129.3, 129.0, 116.1, 101.0, 62.7, 32.8, 26.0, 18.0; HRMS-ESI: *m*/*z*: calcd for $C_{14}H_{17}N_3NaO_2S$ [(*M*+Na)$^+$]: 314.0943, found: 314.0934.

(*E*)-5-Azido-1-phenylhexa-1,5-dien-3-ol (17a)



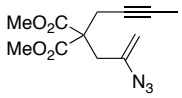
Pale yellow oil, 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H), 7.42-7.33 (m, 2H), 7.33-7.29 (m, 1H), 6.68 (dd, J = 15.7, 0.9 Hz, 1H), 6.12 (dd, J = 15.8, 8.0 Hz, 1H), 4.89 (dt, J = 1.8, 0.9 Hz, 1H), 4.82 (d, J = 1.9 Hz, 1H), 4.27 (tdd, J = 8.0, 6.2, 1.0 Hz, 1H), 2.48-2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 135.9, 134.0, 128.8, 128.5, 126.9, 125.9, 101.2, 62.3, 39.7. HRMS-ESI: m/z: calcd for $C_{12}H_{13}N_4$ [$(M$-N_2+H)$^+$]: 213.1135, found: 213.1134.

(*E*)-((5-Azido-1-phenylhexa-1,5-dien-3-yl)sulfonyl)benzene (17b)



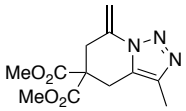
Brown oil, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.81 (m, 2H), 7.73-7.60 (m, 1H), 7.54 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H), 7.37-7.18 (m, 5H), 6.27 (d, J = 15.8 Hz, 1H), 5.91 (dd, J = 15.8, 9.4 Hz, 1H), 4.91-4.82 (m, 1H), 4.73 (dd, J = 2.1, 0.7 Hz, 1H), 3.92 (dddd, J = 11.2, 9.4, 3.6, 0.8 Hz, 1H), 2.98 (dddd, J = 14.1, 3.7, 1.3, 0.7 Hz, 1H), 2.55 (dd, J = 14.1, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 138.9, 137.3, 135.8, 134.0, 129.4, 129.1, 128.8, 128.7, 126.8, 119.9, 101.4, 67.2, 32.7; HRMS-ESI: m/z: calcd for $C_{18}H_{17}N_3NaO_2S$ [$(M$+Na)$^+$]: 362.0934, found: 362.0936.

Dimethyl 2-(2-azidoallyl)-2-(but-2-yn-1-yl)malonate (19a)



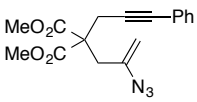
Yellow oil, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99-4.90 (m, 1H), 4.81 (d, J = 1.7 Hz, 1H), 3.74 (s, 6H), 3.05-2.67 (m, 4H), 1.76 (t, J = 2.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 142.2, 102.5, 79.4, 73.3, 56.3, 53.0, 36.4, 22.8, 3.6; HRMS-ESI: m/z: calcd for $C_{12}H_{15}N_3NaO_4$ [$(M$+Na)$^+$]: 288.0955, found: 288.0960.

Dimethyl 3-methyl-7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyridine-5,5(4*H*)-dicarboxylate (20a)



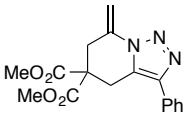
A solution of the azide compound **19a** (24 mg, 0.090 mmol) in toluene (1.0 mL) was refluxed at 110 ºC for 4h. Purification by column chromatography (cyclohexane / EtOAc, 4 / 1) yielded 19.0 mg (80%, 0.072 mmol, 54% over two steps) of the product **20a** as a yellow solid (47% of **20a** over one pot two steps protocol from **19a**); mp 154-156 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (q, J = 1.1 Hz, 1H), 4.95 (q, J = 1.4 Hz, 1H), 3.77 (s, 6H), 3.31 (s, 2H), 3.20 (t, J = 1.3 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 139.8, 134.0, 127.0, 102.2, 53.4, 52.9, 34.9, 26.4, 10.0. HRMS-ESI: *m*/*z*: calcd for $C_{12}H_{15}N_3NaO_4$ [(M+Na)$^+$]: 288.0955: found: 288.0960.

Dimethyl 2-(2-azidoallyl)-2-(3-phenylprop-2-yn-1-yl)malonate (19b crude)



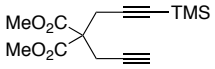
Yellow oil, 83% conversion; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.30-7.28 (m, 3H), 5.03-4.99 (m, 1H), 4.85 (d, J = 1.8 Hz, 1H), 3.78 (s, 6H), 3.10 (s, 2H), 2.91 (s, 2H).

Dimethyl 7-methylene-3-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyridine-5,5(4*H*)-dicarboxylate (20b)



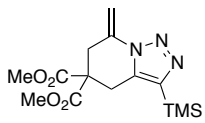
A solution of the azide compound **19b** (28.9 mg, 0.070 mmol) in toluene (0.7 mL) was refluxed at 110ºC for 3h. Purification by column chromatography (cyclohexane / EtOAc, 4 / 1) yielded 13.5 mg (0.041 mmol, 56% over two steps) of product **20b** as a yellow solid. mp: 168-170 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77-7.76 (m, 2H), 7.48-4.45 (m, 2H), 7.38-7.37 (m, 1H), 6.10 (s, 1H), 5.01 (s, 1H), 3.76 (s, 6H), 3.59 (s, 2H), 3.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 143.7, 134.1, 130.9, 129.0, 128.1, 126.8, 103.1, 53.7, 53.1, 34.9, 28.1; HRMS-ESI: *m*/*z*: calcd for $C_{17}H_{17}N_3NaO_4$ [(M+Na)$^+$]: 350.1121, found: 350.1111.

Dimethyl 2-(prop-2-yn-1-yl)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)malonate (18c)



To an ice-cold suspension of NaH (217.0 mg, 5.40 mmol) in DMF (20.0 mL) was added dimethyl 2-(prop-2-yn-1-yl)malonate (0.75 mL, 4.90 mmol) and the solution was stirred for 1h. (3-bromoprop-1-yn-1-yl)trimethylsilane (0.77 mL, 4.93 mmol) was added and the resulting solution was allowed to warm to room temperature and was stirred for 17h. The reaction was quenched with a saturated aqueous NH_4Cl solution and was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography (cyclohexane / EtOAc, 4 / 1) to yield 1,6-diyne **18c** (1,2 g, 4.28 mmol, 87%) as a colorless solid. mp 32-33 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 6H), 2.99 (s, 2H), 2.97 (d, J = 2.7 Hz, 2H), 2.02 (t, J = 2.7 Hz, 1H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 100.8, 88.7, 78.7, 71.8, 57.0, 53.2, 24.2, 22.8, 0.1; HRMS-ESI: m/z: calcd for $C_{14}H_{20}SiNaO_4$ [(M+Na)$^+$]: 303.1023, found: 303.1018.

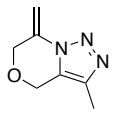
Dimethyl 7-methylene-3-(trimethylsilyl)-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyridine-5,5(4*H*)-dicarboxylate (20c)



Catalyst **A** (10.5 mg, 13.50 µmol) was added to a solution of 1,6-diyne **18c** (76.0 mg, 0.27 mmol) in $TMSN_3$ (2.7 mL, 0.1M) and the reaction mixture was stirred at room temperature for 48h. The solvent was then evaporated and the crude was dissolved in toluene (1.5 mL) and refluxed to 110 ºC for 6h. After cooling at room temperature, the solvent was evaporated and the crude was purified by column chromatography (cyclohexane / EtOAc, 4 / 1) yielding 10.0 mg (0.031 mmol, 11% over two steps) of the product **20c** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (bs, 1H), 4.94 (bs, 1H), 3.75 (s, 6H), 3.41 (s, 2H), 3.20 (s, 2H), 0.36 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 142.6, 135.9, 133.9, 102.7, 53.4, 53.2, 34.9, 29.7, 27.8, -

1.2; HRMS-ESI: *m*/*z*: calcd for $C_{14}H_{22}N_3SiO_4$ [(*M*+H)$^+$]: 324.1374, found: 324.1376.

3-Methyl-7-methylene-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (20d)



Catalyst **A** (10.7 mg, 13.9 μmol) was added to a solution of dienyne **18d** (30.0 mg, 0.28 mmol) in $TMSN_3$ (2.7 mL, 0.1M) and the reaction mixture was stirred at room temperature for 48h. Toluene (1.5 mL) was added to the reaction mixture and refluxed to 110 ºC for 5h. After cooling at room temperature, the solvent was evaporated and the crude was purified by column chromatography (cyclohexane / EtOAc, 1 / 1) yielding 23.0 mg (0.15 mmol, 54% over two steps, 90% purity) of the product **20d** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (q, *J* = 1.0 Hz, 1H), 4.91 (q, *J* = 1.3 Hz, 1H), 4.85 (s, 2H), 4.44 (t, *J* = 1.2 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 137.7, 134.7, 126.9, 98.8, 66.8, 62.5, 10.1; HRMS-ESI: *m*/*z*: calcd for $C_7H_9N_3NaO^+$ [(*M*+Na)$^+$]: 174.0638, found: 174.0633.

Crystal structures

Dimethyl 3-methyl-7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyridine-5,5(4*H*)-dicarboxylate (20a)

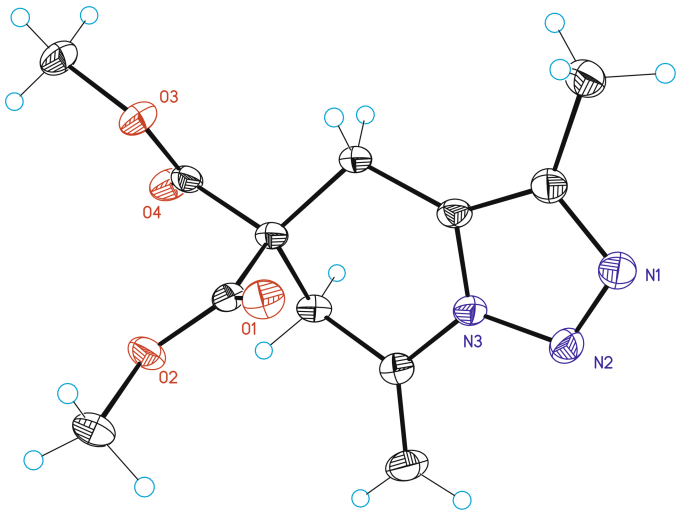


Table 1. Crystal data and structure refinement for **20a**

Empirical formula	C12 H15 N3 O4
Formula weight	265.27
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 7.886(2) Å a= 90.00 °.
	b = 16.680(5) Å b = 102.028(7) °.
	c = 9.935(3) Å g = 90.00 °.
Volume	1278.1(6) Å3
Z	4
Density (calculated)	1.379 Mg/m3

Absorption coefficient 0.105 mm-1

F(000) 560

Crystal size 0.02 x 0.01 x 0.01 mm3

Theta range for data collection 2.43 to 28.16 °.

Index ranges -10 <=h<=10 ,-22 <=k<=21 ,-13 <=l<=12

Reflections collected 10057

Independent reflections 3115 [R(int) = 0.0440]

Completeness to theta =28.16 ° 99.1%

Absorption correction Empirical

Max. and min. transmission 0.9989 and 0.9979

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 3115 / 220 / 349

Goodness-of-fit on F2 1.166

Final R indices [I>2sigma(I)] R1 = 0.0655 , wR2 = 0.1778

R indices (all data) R1 = 0.0792 , wR2 = 0.1864

Largest diff. peak and hole 0.395 and -0.292 e.Å-3

Chapter 2. Trapping of Highly Reactive Gold(I)-Carbenes

Intermolecular Gold(I)-Catalyzed Reactions of Propargyl Esters with Furans

Investigating the Gold(I)-Catalyzed Cyclization / 1,5-Migration Reaction Sequence

Introduction

Gold carbenes

Gold only possesses one vacant valence orbital (6*s*). Thus, a three-centered-four-electron σ-hyperbond[102] (standing for bonds beyond the 12-electron valence) must be involved in the gold(I)-carbenes $[L\text{-}Au{=}CR_2]^+$ (Figure 5). This means that both ligand and substrate share their paired electrons. Additionally, the metal center is able to form two π-bonds by back-donation of its electrons from its fully occupied *d*-orbitals into empty π-acceptors on the ligand and substrate.

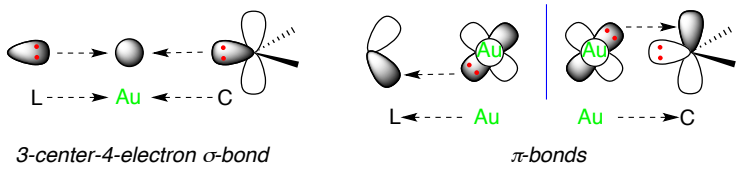


Figure 5. Orbital interactions gold(I)-carbenes $[L\text{-}Au{=}R_2]^+$

Although gold(I)-carbenes have been proposed as key intermediates in many gold(I)-catalyzed reactions,[103] the bonding nature of these intermediates still remains unclear.[104] Two extreme resonance structures are often proposed to rationalize the outcome of a given reaction: carbene **I**, with a gold-carbon double bond and carbocation **II**, with a gold-carbon single bond (Figure 6).

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102 C. R. Landis, F. Weinhold, *J. Comput. Chem.* **2007**, *28*, 198-203.

103 (a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350. (b) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378.

104 (a) A. Fürstner, L. Morency, *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033. (b) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, *48*, 2510-2513. (c) A. E. Echavarren, *Nat. Chem.* **2009**, *1*, 431-433. (d) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard III, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482-486.

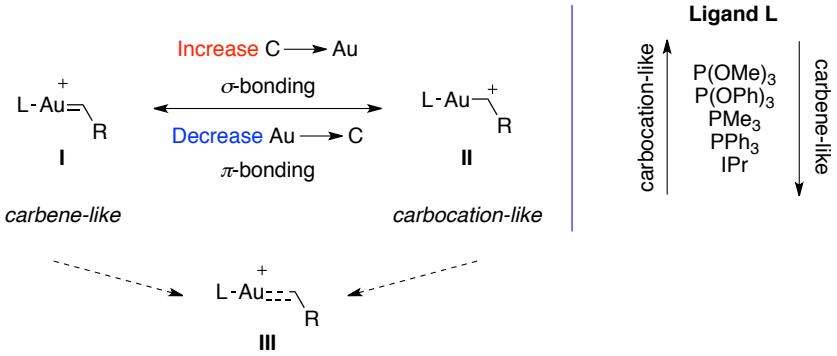


Figure 6. Controversial nature of gold(I)-carbenes bonding

These intermediates can be viewed as gold-stabilized carbocations **II** when the increase in the σ-bonding is strengthened at the expense of the metal-carbon π-bonding. The reverse statement is also valid for the conversion of **II** into **I**. Considering the competition between ligand and substrate for the electron density of gold,[103b] strongly σ-donating and weakly π-acidic ligands are expected to increase the carbene-like reactivity.

Since the overall gold-carbon bond order is approximately one, which corresponds to partial σ and π bond character, a more precise representation would be a double "half-bond" model **III** (Figure 6). Indeed, the representation of a gold-stabilized carbene through a gold-carbon double bond (**I**) should not be taken as an indication of a two-order bond but rather that both σ and π components to the bond are present. Similarly, the represented bond of order one in **II** does not imply that only a simple σ bond is involved.

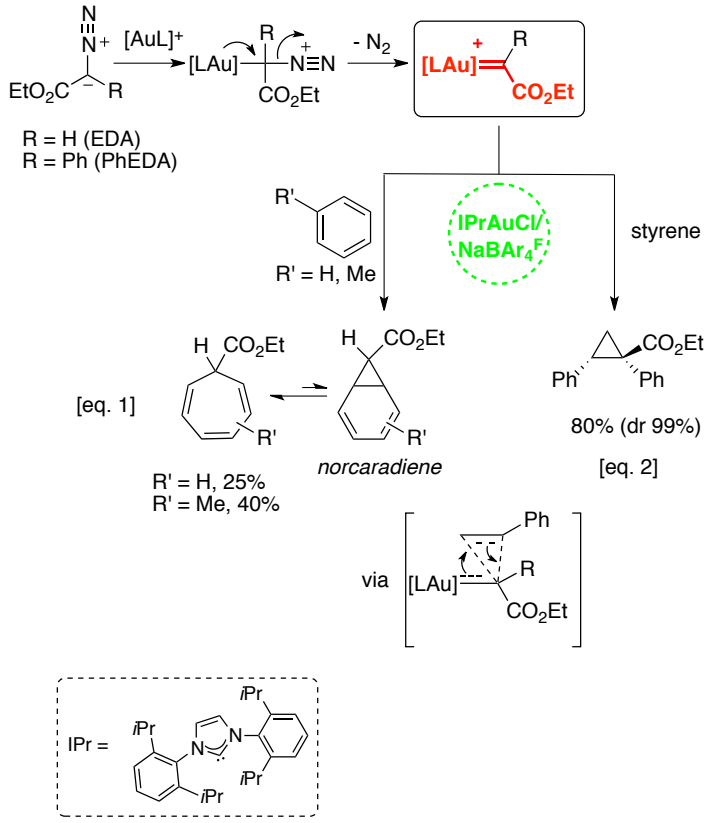
To conclude, the debate on the bonding nature of these gold-carbenes resulted in extensive studies, which revealed the importance of ligand tuning. The appropriate choice of the aforementioned ligand is essential to obtain the desired reactivity in every specific gold-catalyzed reaction.

Generation of gold carbenes

While limited applications have been reported, one of the main strategies employed for the generation of gold(I)-carbenes involves the decomposition of diazo compounds.[105] Indeed, aside the hazardous component of this type of activation, generating gold(I)-carbene in this manner has only resulted in two types of reaction: a formal insertion of the carbene group into an aromatic C-H bond with ethyl diazoacetate (EDA) (Scheme 38, [eq. 1]), as well as olefin cyclopropanation using ethyl 2-phenyl-diazoacetate (PhEDA) as diazo precursor, with styrene or cyclohexene (Scheme 38, [eq. 2]). The nitrogen extrusion from the diazo compound is the consequence of a nucleophilic attack of the diazo compound onto the gold complex. The resulting gold(I)-carbene then reacts with the aromatic groups via a Büchner reaction[106] affording cycloheptatrienes whereas cyclopropane rings are obtained when olefins are present.

105 (a) M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Peréz, *Angew. Chem. Int. Ed.* **2005**, *44*, 5284-5288. (b) A. Prieto, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, P. Pérez-Galán, N. Delpont, A. M. Echavarren, *Tetrahedron* **2009**, *65*, 1790-1793.

106 E. Buchner, T. Curtius, *Chem. Ber.* **1885**, *18*, 2371-2377.

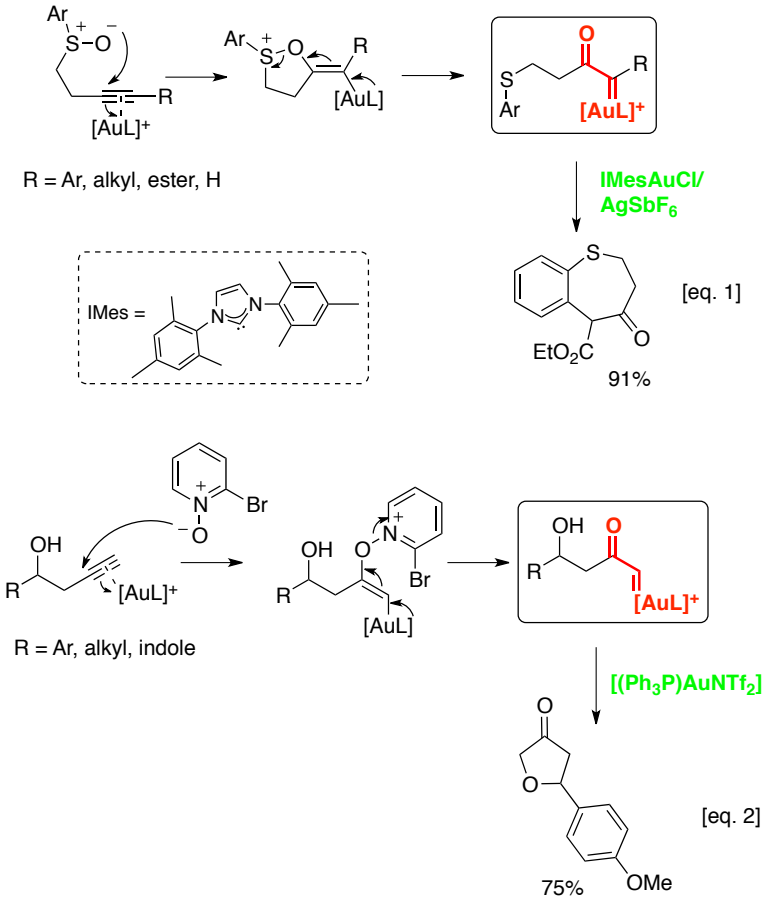


Scheme 38. Gold(I)-carbenes via diazo decomposition

The development of safer surrogates for diazo carbonyl compounds, while maintaining the ease of access to the corresponding gold(I)-carbenes, was achieved through intra-[107] or intermolecular oxidations of alkynes (Scheme 39).[108] In the context of an intramolecular oxidation, an oxidant reagents attack the triple bond to generate the α-oxo gold(I)-carbenes (Scheme 39, [eq. 1]). Alternatively, one can employ an intermolecular oxidant for the oxidation of terminal alkynes, thus overcoming this limitation (Scheme 39, [eq. 2]).

107 N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160-4161.

108 L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258-3259.



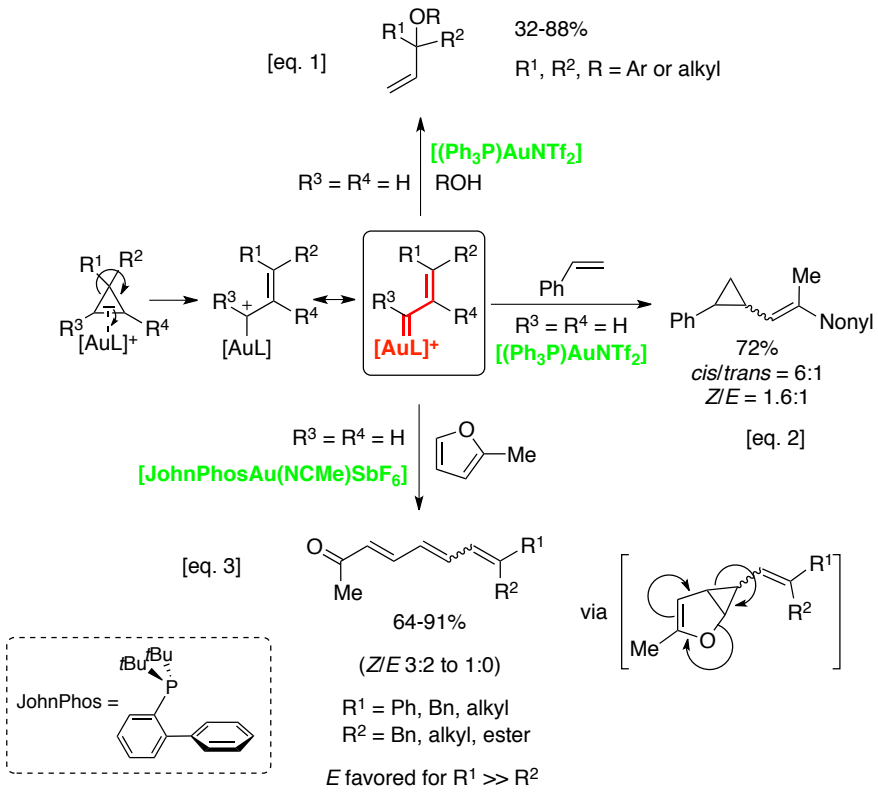
Scheme 39. Formation of α-oxo gold(I)-carbene

Cyclopropene chemistry using gold catalysis has led to a variety of interesting scaffolds through the generation of highly reactive gold(I)-carbenes.[109] The formation of these metal carbenes occurred *via* activation of the strained cyclopropene double bond by gold(I) catalysts resulting in its ring-opening (Scheme 40). Amongst other transformations, [110] these carbenes can react with different alcohols to generate allylic ethers (Scheme

109 F. Miege, C. Meyer, J. Cossy, *Beilstein. J. Org. Chem.* **2011**, *7*, 717-734.

110 (a) Z. B. Zhu, M. Shi, *Chem. Eur. J.* **2008**, *14,* 10219-10222. (b) F. Miege, C. Meyer, J. Cossy, *Org. Lett.* **2010**, *12,* 4144-4147. (c) C. Li, Y. Zeng, H. Zhang, J. Feng, Y. Zhang, J. Wang, *Angew. Chem., Int. Ed.* **2010**, *49,* 6413-6417.

40, [eq. 1]),[111] with alkenes to form vinyl cyclopropyl products (Scheme 40, [eq. 2]),[112] or with furans to yield conjugated trienes (Scheme 40, [eq. 3]).[104d]



Scheme 40. Gold(I)-carbenes from cyclopropenes

Propargyl esters are ideal precursors for the formation of gold(I)-carbenes as they are readily available.[113] Upon activation of the alkyne by

111 J. T. Bauer, M. S. Hadfield, A. - L. Lee, *Chem. Commun.* **2008**, 6405-6407.

112 M. S. Hadfield, A. - L. Lee, *Chem. Commun.* **2011**, *47,* 1333-1335.

113 (a) T. de Haro, E. Gómez-Bengoa, R. Cribiú, X. Huang, C. Nevado, *Chem. Eur. J.* **2012**, *18*, 6811-6824. (b) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692-706. (c) R. K. Shiroodi, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991-5001. (d) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo, *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721. (e) G. Li, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 3740-3741. (f) N. D. Shapiro, Y. Shi, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 11654-11655.

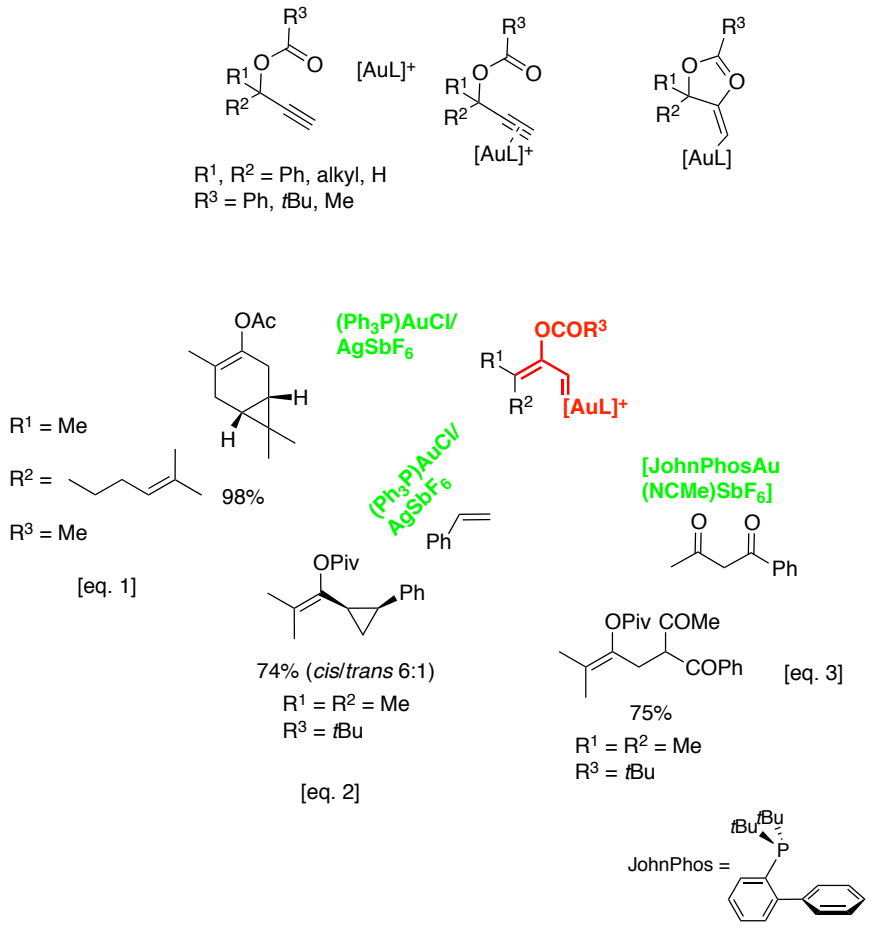
coordination of the gold(I) catalyst, terminal alkynes usually undergo a 1,2-migration of the neighboring carboxylate moiety leading to the formation of the corresponding gold(I)-carbene (Scheme 41). The latter can then be trapped intra- or intermolecularly by an alkene (Scheme 41, [eq. 1] and [eq. 2])[114,115] as well as 1,3-dicarbonyl compounds (Scheme 41, [eq. 3]).[116]

(g) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244-9245. (h) D. J. Gorin, P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 14480-14481.

114 M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

115 J. Marco-Contelles, E. Soriano, *Chem. Eur. J.* **2007**, *13*, 1350-1357.

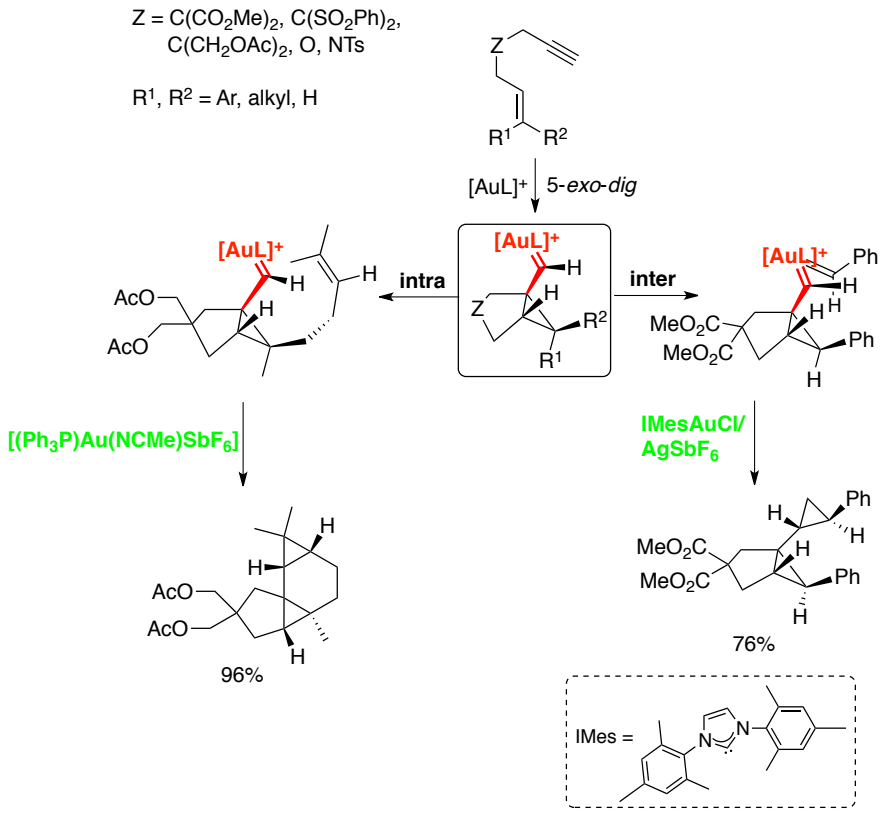
116 C. H. M. Amijs, V. López-Carrillo, A. M. Echavarren, *Org. Lett.* **2007**, *9*, 4021-4024.



Scheme 41. Preparation of gold(I)-carbenes from propargyl esters

As presented in the General Introduction, gold(I)-catalyzed cyclizations of 1,n-enynes proceed through intermediates that can be considered as highly distorted gold(I)-carbenes. These enynes can be trapped by various nucleophiles *via* ring-opening of the cyclopropyl gold carbene intermediate (see Chapter 1). However, alkenes typically react inter- or intramolecularly in cyclopropanation reactions (Scheme 42).[103a,117]

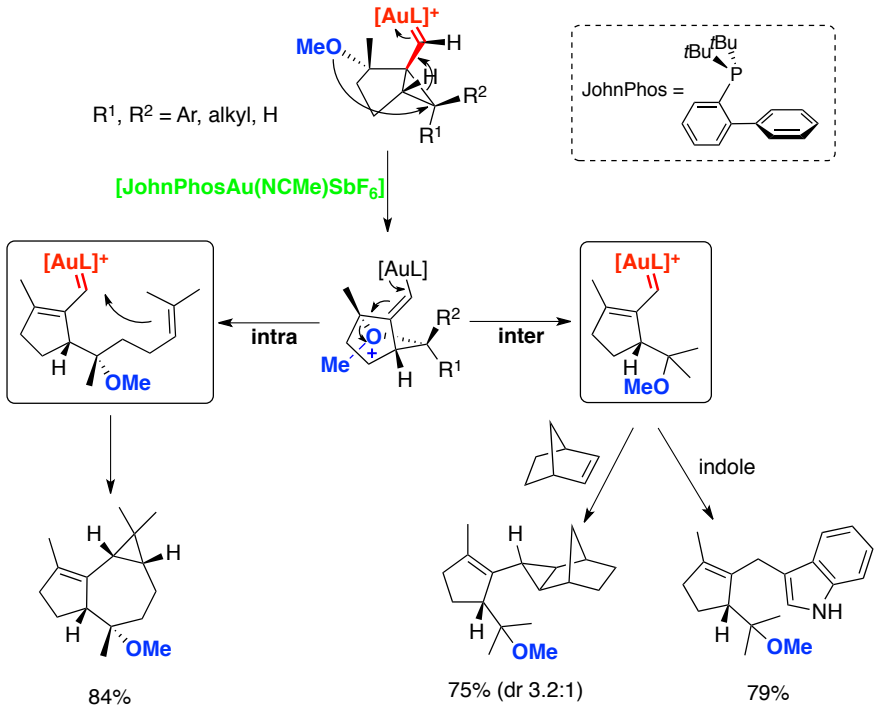
117 (a) S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032. (b) C. Obradors, A. E. Echavarren, *Chem. Commun.* **2014**, *50*, 16-28.



Scheme 42. Gold(I)-carbenes formation via cycloisomerization of 1,6-enynes

In 2009, our group developed the formation of gold(I)-carbenes through a new type of intramolecular 1,5-migration of propargylic OR groups.[118] This reaction proceeded via a cyclopropyl gold(I)-carbene intermediate, where the OR group attacks the cationic center to form an oxonium bridge. Upon ring-opening, the gold(I)-carbene is then produced and react intramolecularly with an alkene on the side chain, or intermolecularly with external nucleophiles (Scheme 43).

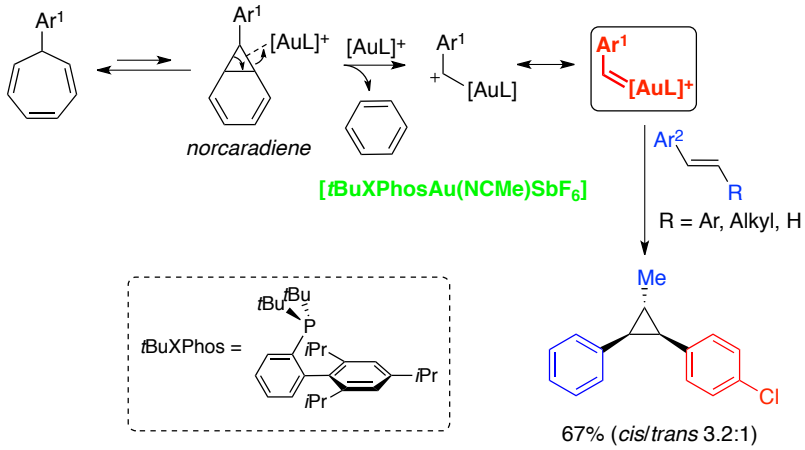
118 E. Jiménez-Nuñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.



Scheme 43. Gold(I)-carbenes via intramolecular 1,5-migration

Finally, our group has recently discovered a new approach to the generation of gold(I)-carbenes via Au(I)-promoted retro-Büchner reactions of cycloheptatrienes as an alternative to the use of explosive diazo compunds.[119] Mechanistically, 7-substituted-cycloheptatrienes, which are in equilibrium with norcaradienes, react with cationic gold(I) catalysts to generate *in situ* gold(I)-carbenes to form cyclopropanes with alkenes (Scheme 44).

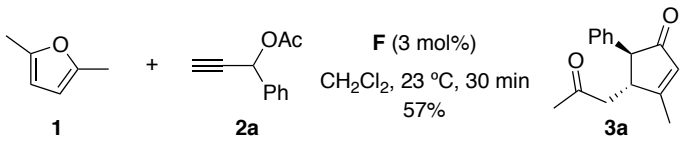
119 C. R. Solorio-Alvarado, Y. Wang, A. M. Echavarren, *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.



Scheme 44. Gold(I)-carbene via retro-Büchner reaction

Objectives

During our studies on the reaction between alkynes and readily accessible 2,5-disubstituted furans, we discovered a new reaction of furans with propargyl acetates to generate cyclopentenones (Scheme 45).

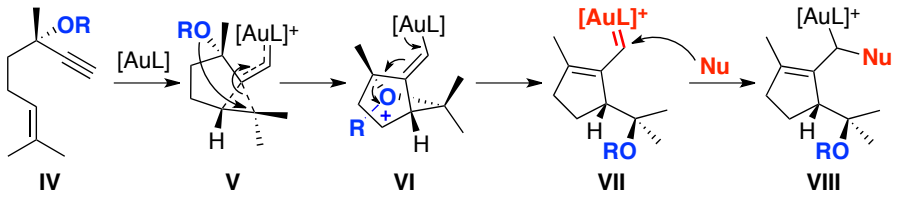


Scheme 45. Gold(I)-catalyzed synthesis of cyclopentenone

The objectives consisted in optimizing and studying the scope and limitations of this new reaction.

In the second part of this chapter, we were interested in the gold(I)-catalyzed 1,5-migration reaction discovered by our group.[118]

With the aim to broaden the scope of this reaction, we planned to study the addition of a series of nucleophilic substrates to enable this transformation (Scheme 46).



Scheme 46. Gold(I)-catalyzed 1,5-migration reaction

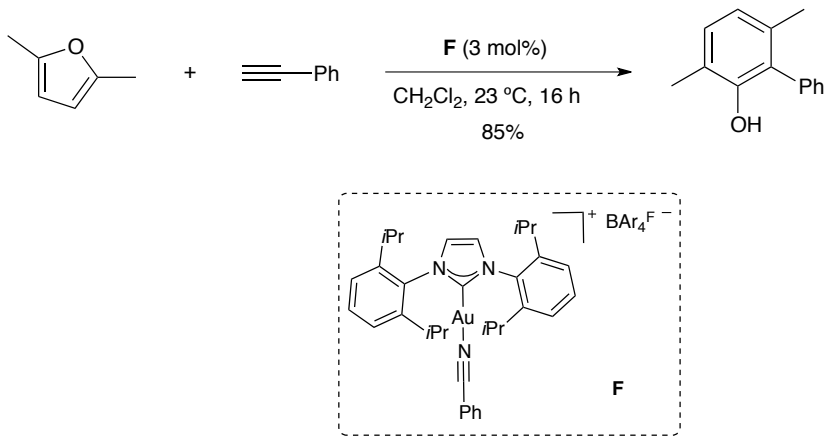
Results and discussion

Intermolecular Gold(I)-Catalyzed Cyclizations of Propargyl Esters with Furans

Despite the major advances accomplished in gold(I) catalysis, the development of intermolecular cyclizations of alkynes with alkenes or heteroaromatic compounds has proven to be challenging.[120] However, our group has recently described an efficient preparation of phenols *via* the intermolecular reaction of furans with alkynes using a new air-stable gold(I) complex [IPrAu(PhCN)]BAr_4^F **F** (Scheme 47).[121]

120For selected examples, see: (a) A. S. K. Hashmi, M. C. Blanco, E. Kurpejović, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709-713. (b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358-1373. (c) V. López–Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292-9294. (d) R. B. Dateer, B. S. Shaibu, R. S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 113-117. (e) H. - S. Yeom, J. Koo, H. - S. Park, Y. Wang, Y. Liang, Z. - X. Yu, S. Shin, *J. Am. Chem. Soc.* **2012**, *134*, 208-211. (f) S. Kramer, T. Skrydstrup, *Angew. Chem. Int. Ed* **2012**, *51*, 4681-4684. (g) Y. Luo, K. Ji, Y. Li, L Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 17412-17415. (h) C. Obradors, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 3547-3551. (i) E. Rettenmeier, A. M. Schuster, M. Rudolph, F. Rominger, C. A. Gade, A. S. K. Hashmi, *Angew. Chem. Int. Ed* **2013**, *52*, 5880-5884.

121 N. Huguet, D. Lebœuf, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 6581-6585.



Scheme 47. Gold(I)-catalyzed synthesis of phenols

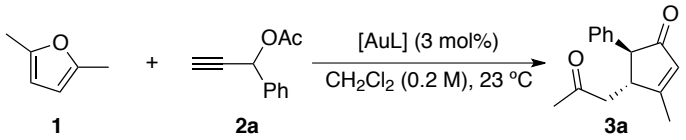
Novel intermolecular reaction between propargyl esters and furans[122]

Initial results were obtained by reacting 2,5-dimethylfuran **1** with propargyl acetate **2a** in the presence of catalyst **F** in CH_2Cl_2 at room temperature (Scheme 45). The reaction led to the formation of cyclopentenone **3a** as a single diastereomer within 30 min in 57% yield. No similar compounds have been reported although the reaction of furans with propargyl carboxylates has been previously studied.[123] In order to improve this first result, a catalyst screening was then performed using gold as well as platinum complexes (Table 15).

122 Discovered by Dr. David Lebœuf, ICIQ, 2013.

123 (a) K. Miki, M. Fujita, S. Uemura, K. Ohe, *Org. Lett.* **2006**, *8*, 1741-1743. (b) B. W. Gung, L. M. Bailey, J. Wonser, *Tet. Lett.* **2010**, *51*, 2251-2253. For an example of an intramolecular reaction, see: (c) B. W. Gung, D. T. Craft, L. N. Bailey, K. Kirschbaum, *Chem. Eur. J.* **2010**, *16*, 639-644.

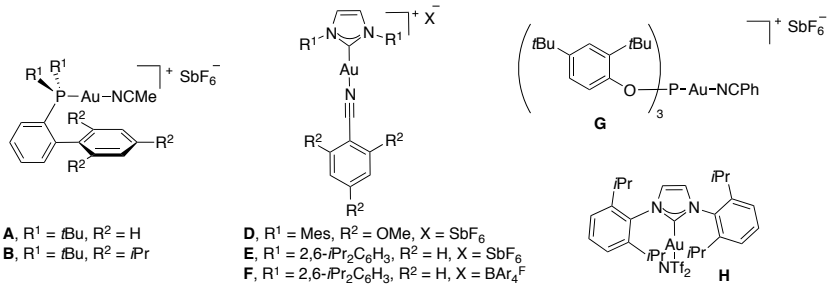
Table 15. Catalyst screening for the formation of cyclopentenone 3a



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

Entry	[AuL]	Time (h)	Yield (%)[a]
1	**A**	5	27
2	**B**	5	44[b]
3	**D**	24	20
4	**E**	0.5	48[b]
5	**F**	0.5	57[b]
6	**G**	5	30
7	**H**	3	48[b]
8	**$AuClPPh_3/AgSbF_6$**	14	20
9	**$AuCl_3$**	10	-
10	**$PtCl_2$**	16	11

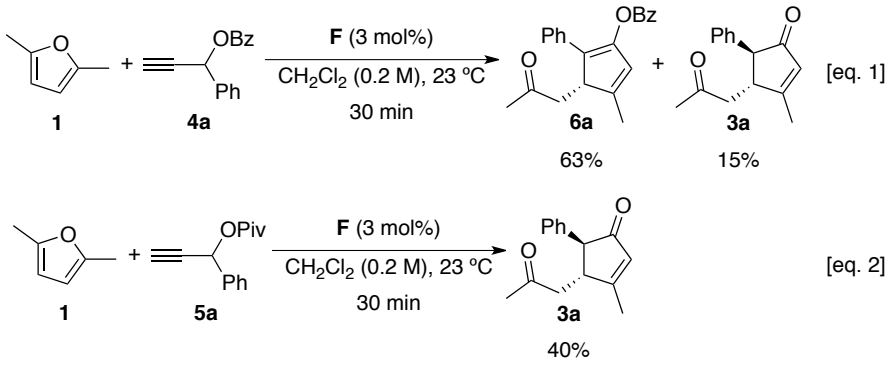
[a] Determined by ^1H NMR analyses using 1,4-diacetylbenzene as internal standard. [b] Isolated yield.



Our initially studied cationic gold(I) catalyst **F** was found to be optimal (Table 15, entry 5). Related IPr gold(I) complex **E** bearing the hexafluoroantimonate anion gave a slightly lower 48% yield after 30 min (Table 15, entry 4), whereas neutral complex **H** required longer reaction times to provide a similar result to **E** (Table 15, entry 7). Surprisingly, cationic IMes derivative **D** gave low conversion to **3a** even after 24 h, albeit

N-heterocyclic carbenes are expected to favor the formation of carbene-like intermediate (Table 15, entry 3). While phosphine gold(I)-complex **B** gave moderate yields of cyclopentenone **3a** (Table 15, entry 2), other phosphine and phosphite gold(I) catalysts were far less reactive in this transformation (Table 15, entries 1, 6 and 8). Finally, poor results were obtained with $AuCl_3$ or $PtCl_2$ (Table 15, entries 9 and 10).

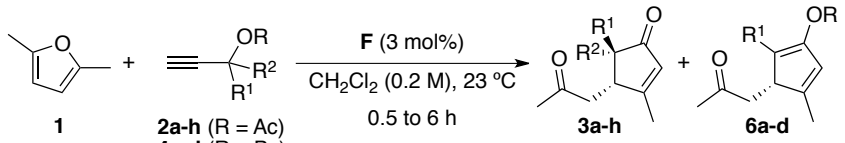
Our attention was then turned to the nature of the ester substituent. The acetate was replaced by benzoate and pivaloate esters **4a** and **5a**. Interestingly, cyclopentadienyl benzoate **6a** was isolated as the major product in 63% yield along with 15% cyclopentenone **3a** (Scheme 48, [eq. 1]). However, when employing the corresponding pivaloate, cyclopentenone **3a** was obtained in 40% yield (Scheme 48, [eq. 2]).



Scheme 48. Reaction with propargyl esters 4a and 5a

The reaction was then conducted employing several propargylic esters to furnish the corresponding cyclopentenones **3** or cyclopentadienes **6** in moderate to good yields (Table 16).

Table 16. Cyclization of 2,5-dimethylfuran (1) with different propargyl acetates and benzoates



(2 equiv) (1 equiv)

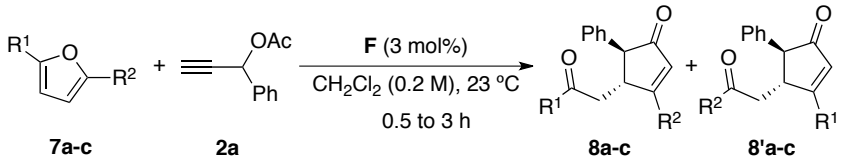
Entry	Substrate	R^1	R^2	**3** (%)[a]	**6** (%)[a]
1	**2a**	Ph	H	**3a** (57)	-
2	**4a**	Ph	H	**3a** (15)	**6a** (63)
3	**2b**	*p*BrC_6H_4	H	**3b** (65)	-
4	**4b**	*p*BrC_6H_4	H	**3b** (20)	**6b** (44)
5	**2c**	*p*$OMeC_6H_4$	H	**3c** (36)	-
6	**4c**	*p*$OMeC_6H_4$	H	**3c** (31)	**6c** (48)
7	**2d**	*c*C_3H_5	H	**3d** (61)[b]	-
8	**4d**	*c*C_3H_5	H	**3d** (60)[c]	-
9	**2e**	Me	Me	**3e** (61)	-
10	**2f**	-$(CH_2)_5$-		**3f** (63)	-
11	**2g**	*i*Bu	Me	**3g** (19)	-
12	**2h**	Ph	Me	**3h** (28)[d]	-

[a] Isolated yield. [b] *trans*/*cis* 2.5:1. [c] *trans*/*cis* 5:1. [d] *dr* 2:1.

This transformation is compatible with both electron-donating and electron-withdrawing groups on the propargylic ester (Table 16, entries 3-6). Exceptionally, cyclopropylprop-2-yn-1-yl benzoate (**4d**) and its acetate analogue (**2d**) underwent hydrolysis leading to cyclopentenone **3d** in identical yields (Table 16, entries 7 and 8). Tertiary esters were also found to be acceptable substrates and provided the desired cyclopentenone (Table 16, entries 9-12). While propargylic esters **4f** and **4g** afforded the corresponding cyclopentenones **3** in reasonable yields (Table 16, entries 9 and 10), the use of bulkier substrates such as **4e** and **4h** resulted in significantly lower yields (Table 16, entries 11-12).

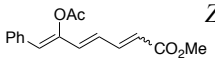
Afterwards, our investigations were directed towards examining the generality of the furan counterpart (Table 17).

Table 17. Cyclization with different furans 7



7a-c **2a** **8a-c** **8'a-c**

Entry	Substrate	R^1	R^2	Outcome	Yield %[a]
1	**7a**	OMe	H	triene[b]	-
2	**7b**		Me	**8b/8'b**	56[c]
3	**7c**	Ph	Me	**8c/8'c**	44[d]

[a] Isolated yield. [b] 

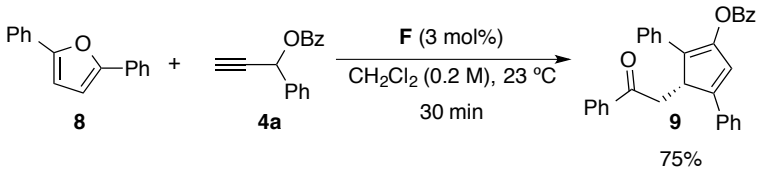
Z/*E* 1:1 determined by ^{1}H NMR.

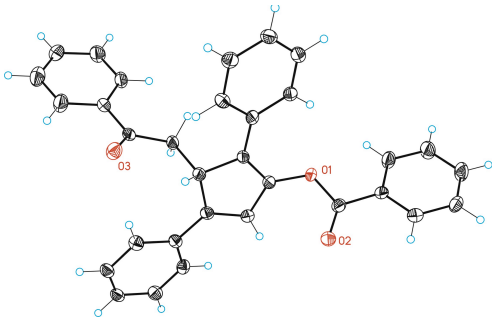
[c] As a 1.6:1 mixture of regioisomers. [d] As a 4:1 mixture of regioisomers.

Mono-substituted furan **7a** led to the formation of the corresponding triene via its ring-opening rearrangement (Table 17, entry 1). This transformation is known and has been described using ruthenium complexes with similar propargylic esters.[123a] When unsymmetrical 2,5-disubstituted furan **7b** was employed, a 1.6:1 mixture of regioisomers cyclopentenones **8b**/**8'b** was obtained (Table 17, entry 2). Increasing the steric hindrance of one of the substituents such as exemplified in substrate **7c** provided cyclopentenone **8c** as major product with an improved 4:1 selectivity (Table 17, entry 3).

A last experiment was performed with ~~a~~ symmetrical and bulkier 2,5-diphenylfuran (Scheme 49). The presence of two bulky aryl substituents at the C2 and C5 positions of furan **9** had no effect on the formation of cyclopentadienyl benzoate **10**, which was obtained in good yields (75%).

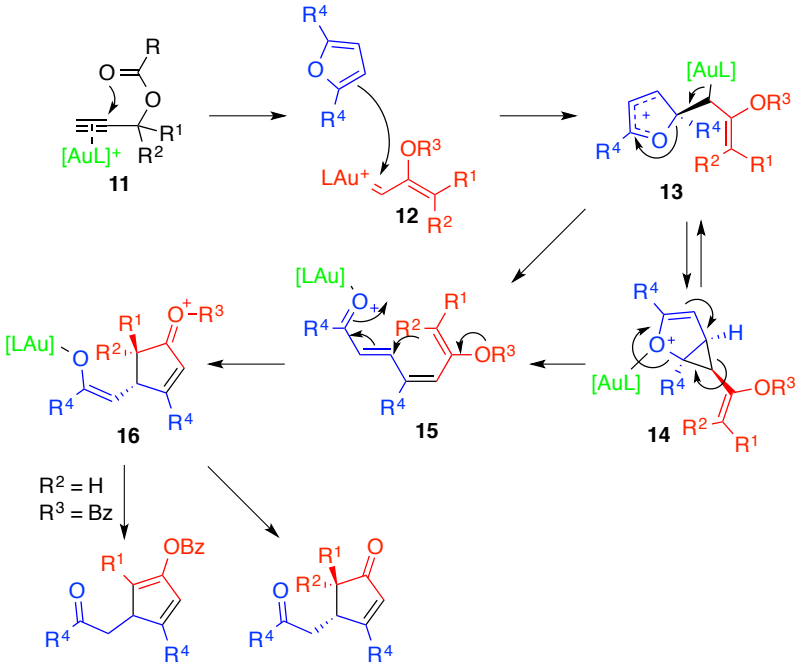
The formation of the cyclopentenone was not detected as observed with most benzoyl esters, and the structure of **10** was confirmed by X-ray diffraction.





Scheme 49. Gold(I)-catalyzed cyclization of 2,5-diphenylfuran (9) with propargyl benzoate 4a

A plausible mechanism for the formation of cyclopentenones and cyclopentadienyl esters is proposed in Scheme 50.



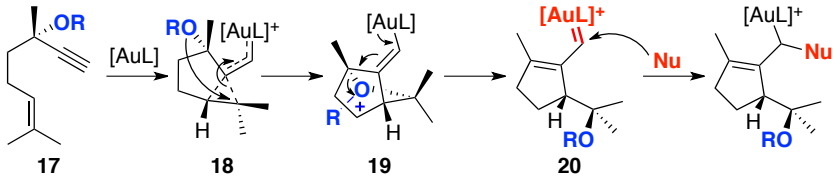
Scheme 50. Proposed mechanism for the gold(I)-catalyzed reaction of propargylic carboxylates with furans.

Upon gold(I) activation, propargylic ester **11** undergoes 1,2-acetate migration to generate the highly reactive gold(I) carbene **12**. Subsequent trapping of this gold(I) carbene by furan leads to the formation of **13**. In the case of unsymmetrically substituted furans, the major regioisomer is formed by attack from the most nucleophilic site of the furan to form intermediate **13**. Intermediate **13** may form the product of cyclopropanation **14**, which could open to provide triene **15** (see Introduction, Scheme 40). Intermediate **15** could also be formed directly from **13** by 1,2-elimination. An intramolecular Mukaiyama-Michael-type addition of **15**, potentially promoted by gold(I), would then give the cyclized intermediate **16**. Finally, hydrolysis of the acetate results in the desired product.

Investigating the Gold(I)-Catalyzed Cyclization / 1,5-Migration Reaction Sequence

Gold(I) catalyzed 1,5-migration reaction with subsequent trapping by certain nucleophiles has been previously demonstrated by our group (See Introduction).[118]

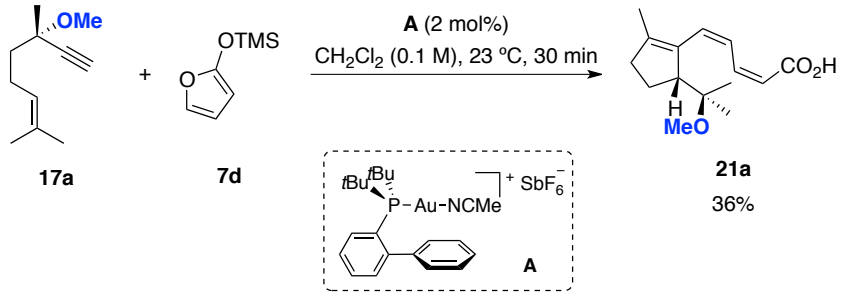
This reaction sequence is mechanistically interesting as it features a gold(I)-catalyzed cyclization/1,5-OR migration via intermediates **18** and **19** to form a α,β-unsaturated gold(I) carbene **20**. The latter then reacts intermolecularly with nucleophile (Scheme 51).



Scheme 51. Gold(I)-catalyzed 1,5-migration reaction

Gold(I)-carbene trapped by furans

Having demonstrated the ability of furans to act as good nucleophiles for the addition onto gold(I)-carbenes, we began our investigations with these substrates as trapping agent in the 1,5-migration reaction sequence (Scheme 52).

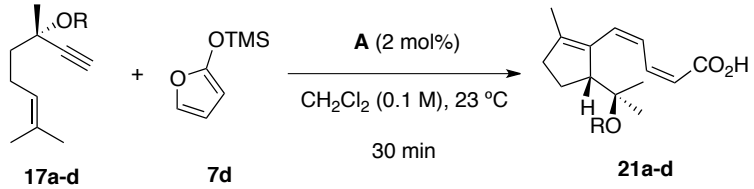


Scheme 52. Gold(I)-catalyzed cyclization and 1,5-migration of 1,6-enyne 17a

As a proof of concept, we decided to employ 1,6-enyne **17a** as the test substrate as we have established in our previous report that propargylic methoxy ether is a good migrating group for this type of transformations.[118] Using 2-(trimethylsiloxy)furan **7d** as the nucleophile, we were able to isolate carboxylic acid **21a** in 36% yield, containing a triene moiety with a *Z*,*Z* configuration for the external diene.

Based on our previous work on 1,5-migration reactions,[118] a screening of different OR groups was initiated as part of the optimization in order to find the ideal migrating moiety (Table 18).

Table 18. Formation of 21 with several migrating groups



Entry	Substrate	R	21 (%)[a]
1	**17a**	Me	**21a** (36)
2	**17b**	Ac	**21b** (19)
3	**17c**	PNB[b]	**21c** (35)
4	**17d**	PNP[c]	**21d** (60)

[a] Isolated yield. [b] PNB = *para*-nitrobenzyl. [c] PNP = *para*-nitrophenyl.

As expected, propargylic acetate gave a lower yield probably due to a competitive 1,2-shift rearrangement observed with propargylic esters,[124] thus preventing the formation of **21b** (Table 18, entry 2). The introduction of *para*-nitrobenzyl as protecting group did not improve the yield of carboxylic acid **21** (Table 18, entry 3). Indeed, these types of carboxylates are prone to form bicyclic derivatives products from a migration followed by a subsequent formal C-H insertion.[118, 125] Gratifyingly, the use of *para*-nitrophenyl ether **17d** gave the desired carboxylic acid **21d** in good yields (Table 18, entry 4) and was therefore employed for the screening of several gold(I) catalysts (Table 19).

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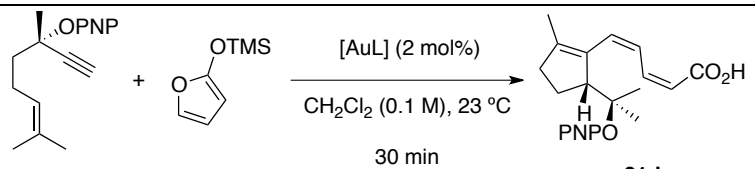
124 (a) A. Fürstner, P. Hannen, *Chem. Commun.* **2004**, 2546-2547. (b) A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006-3019. (c) X. Moreau, J. -P. Goddard, M. Bernard, G. Lemière, J. M. López-Romero, E. Mainetti, N. Marion, V. Mouriès, S. Thorimbert, L. Fensterbank, M. Malacria, *Adv. Synth. Catal.* **2008**, *350*, 43-48.

125 For examples of (formal) C-H insertions of gold or platinum carbenes, see: (a) H. Kusama, H. Yamabe, Y. Onizawa, T. Hoshino, N. Iwasawa, *Angew. Chem. Int. Ed.* **2005**, *44*, 468-470. (b) H. Funami, H. Kusama, N. Iwasawa, *Angew. Chem. Int. Ed.* **2007**, *46*, 909-911. (c) C. H. Oh, J. H. Lee, S. J. Lee, J. I. Kim, C. S. Hong, *Angew. Chem. Int. Ed.* **2008**, *47*, 7505-7507. (d) C. H. Oh, J. H. Lee, S. M. Lee, H. J. Yi, C. S. Hong, *Chem. Eur. J.* **2009**, *15*, 71-74. (e) S. Bhunia, R. -S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16488-16489. (f) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A. - L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993-3006. (g) Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809-2811. (h) A. Escribano-Cuesta, V. López-Carrillo, D. Janssen, A. M. Echavarren, *Chem. Eur. J.* **2009**, *15*, 5646-5650.

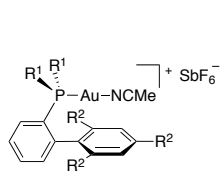
Table 19. Optimization studies with various gold(I) catalysts



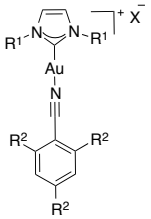
17d (1 equiv) + **7d** (2 equiv) → **21d**

Entry	[AuL]	Yield (%)[a]
1	**A**	65 (60)[b]
2	**B**	90 (82)[b]
3	**D**	28
4	**E**	64
5	**F**	58

[a] Determined by ^{1}H NMR analyses using diphenylmethane as internal standard. [b] Isolated yield.



A, R^1 = *t*Bu, R^2 = H
B, R^1 = *t*Bu, R^2 = *i*Pr



D, R^1 = Mes, R^2 = OMe, X = SbF_6
E, R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = H, X = SbF_6
F, R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = H, X = BAr_4^F

In this case, gold(I) complex **B**, which possess a bulky phosphine ligand, proved to be optimal as the carboxylic acid **21d** was isolated in 82% yield (Table 19, entry 2). N-Gold(I) complexes with heterocyclic carbenes could also afford **21d**, albeit in lower yields (Table 19, entries 3-5).

The scope and limitations of this transformation were examined next using several mono- and disubstituted furans (Table 20).

Table 20. Scope and limitations

17d (1 equiv) + **7d-m** (2 equiv) → **21d-m**

Entry	[AuL]	Furan	R^1	R^2	R^3	21	Yield (%)[a]
	B						82
1	**A**	**7d**	H	OTMS	H	**21d**	60
	E						64[b]
	B						47
2	**A**	**7e**	H	OMe	H	**21e**	57
	E						54
	B						56
3	**A**	**7f**	H	Me	H	**21f**	39
	E						48
	B						9
4	**A**	**7g**	H	*t*Bu	H	**21g**	62
	E						57
	B						16
5	**A**	**7h**	H	Ph	H	**21h**	59
	E						50

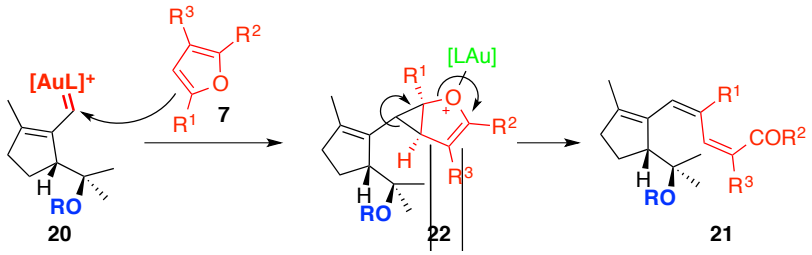
	B						78
6	**A**	**7i**	H	Me	Me	**21i**	88
	E						75
	B						-[c]
7	**A**	**7j**	Me	Me	H	**21j**	-[c]
	E						32
	B						-[c]
8	**A**	**7k**	Ph	Ph	H	**21k**	42
	E						40
	B						-[c]
9	**A**	**7l**	*n*Pent	Ph	H	**21l**	-[c]
	E						-[c]
	B						-[c]
10	**A**	**7m**	Me	vinyl	H	**21m**	-[c]
	E						-[c]

[a] Isolated yield. [b] Determined by ^{1}H NMR analyses using diphenylmethane as internal standard. [c] Unidentified complex mixture.

In some cases, gold(I) complex **B** gave poor yields of the desired products **21** (Table 20, entries 4, 5, 7-10). Consequently, the reactions were also performed with gold(I) catalysts **A** and **E** as they afforded reasonable yields of carboxylic acid **21d** (Table 19). Finally, mono- and disubstituted furans **7d-k** in the presence of gold(I) catalysts reacted to form carboxylic acid **21d** (Table 20, entry 1), ester **21e** (entry 2) or ketones derivatives **21f-k** (Table

20, entries 3-8), all featuring a triene moiety with (*Z,Z)*-configuration. However, unsymmetrical furans **7l** and **7m** led to complex mixture of products that could not be isolated (Table 20, entries 9 and 10).

A mechanism similar to that proposed in Scheme 50 can rationalize this transformation. Nucleophilic attack of furan **7** onto *α,β*-unsaturated gold(I) carbene **20** leads to the formation of cyclopropane **22**, which after ring opening affords triene compounds **21** (Scheme 53).



Scheme 53. Proposed mechanism for the formation of 21

Gold(I)-carbene trapped by 1,3-diketones[126]

1,3-Diketones are interesting molecules as they are in equilibrium with the corresponding enols as a consequence of an extra stabilization provided by conjugation with the other carbonyl group and the increased stability gained by forming a hydrogen bond in a six-membered ring (Figure 7). Thus, the carbon between the two carbonyl groups has soft nucleophilic character and should react with soft Lewis acids such as gold(I)-carbenes (softess enhanced when employing N-heterocyclic carbene ligands as they are strongly *σ*-donating and weakly *π*-acidic).

126 The study of the scope and limitation of this transformation was carried out in collaboration with Dr. Oscar Pablo.

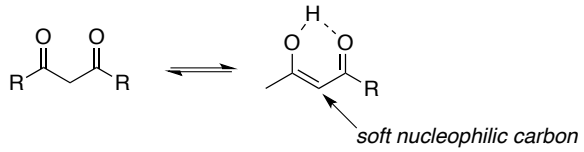
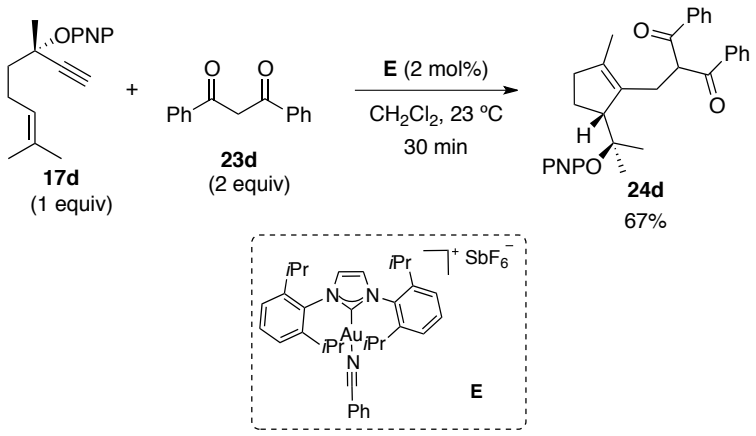


Figure 7. Soft nucleophilic property of 1,3-diketones

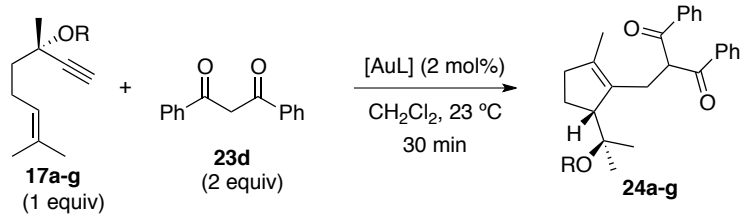
Based on the previous transfomation, enyne **17d** was chosen as the model substrate. Gold(I) complex **E** bearing a N-heterocyclic carbene ligand was employed to catalyze the addition of 1,3-diphenylpropane-1,3-dione **23d**, chosen for its strong enol content, onto the gold(I)-carbene intermediate (Scheme 54).



Scheme 54. Gold(I)-catalyzed formation of 24d

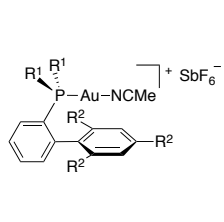
Pleasingly, the expected product **24d** was isolated as a single regioisomer in 67% yield under these reaction conditions. The optimization study was then carried out with different OR migrating groups as well as by exploring several alternative gold(I) catalysts (Table 21).

Table 21. Optimization study for the formation of 24

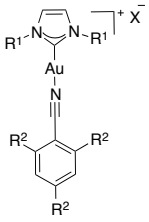


Entry	Substrate	R	[AuL]	**24** (%)[a]
1	**17a**	Me	**E**	**24a** (27)
2	**17b**	Ac	**E**	**24b** (23)
3	**17c**	PNB	**E**	-
4	**17d**	PNP	**E**	**24d** (67)
5	**17e**	H	**E**	**24e** (24)
6	**17f**	PMB[b]	**E**	-
7	**17g**	PMP[c]	**E**	**24g** (53)
8	**17d**	PNP	**A**	**24a** (58)
9	**17d**	PNP	**B**	**24a** (8)
10	**17d**	PNP	**D**	**24a** (67)
11	**17d**	PNP	**F**	**24a** (71)

[a] Isolated yield. [b] PMB = *para*-methoxybenzyl. [c] PMP = *para*-methoxyphenyl.



A, R^1 = *t*Bu, R^2 = H
B, R^1 = *t*Bu, R^2 = *i*Pr



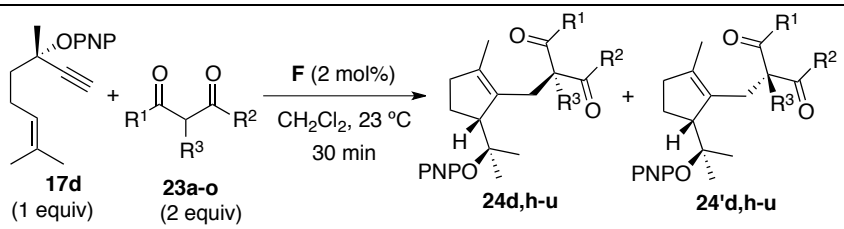
D, R^1 = Mes, R^2 = OMe, X = SbF_6
E, R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = H, X = SbF_6
F, R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = H, X = BAr_4^F

As previously observed, the use of *para*-nitrophenyl as the protecting group gave the best result (Table 21, entry 4). Free alcohol **17e** (Table 21, entry 5) and other migrating groups afforded the product in lower yields (Table 21, entries 1-2, and 7), while employing a benzyl moiety (Table 21, entries 3-6) led to the bicyclic products, obtained from a 1,5-migration followed by a C-

H activation sequence.[118,125] Additional improvement could be obtained by employing N-heterocyclic carbene gold(I) catalyst **F** (Table 21, entry 11) with a bulkier and less basic counteranion 3,5-bis(trifluoromethyl)phenylborate (BAr_4^{F-}).

With these optimized conditions in hand, the scope and limitations of this reaction was then investigated (Table 22).

Table 22. Scope and limitations



Entry	23	R^1	R^2	R^3	24 (%)[a]
1	**23a**	Me	Me	H	**24h** (82)
2	**23b**	Me	*i*Bu	H	**24i/24'i** (66, *dr* 1:1)
3	**23c**	*p*MeOC_6H_4	*pt*BuC_6H_4	H	**24j/24'j** (82, *dr* 3.3:1)
4	**23d**	Ph	Ph	H	**24d** (71)
5	**23e**	Me	Ph	H	**24k/24k'** (68, *dr* 4.5:1)
6	**23f**	Me	OMe	H	**24l/24'l** (59, *dr* 1.3:1)
7	**23g**	OEt	Ph	H	**24m/24'm** (66, *dr* 4:1)

8	**23h**	OEt	2-furyl	H	**24n/24'n** (75, *dr* 11.5:1)
9	**23i**	OMe	OMe	H	-
10	**23j**	CF_3	CF_3	H	-
11	**23k**	CF_3	2-naphthyl	H	-
12	**23l**	OMe	Ph	Me	-[b]
13	**23m**	Me	Ph	Me	-[b]
14	**23n**	Me	Me	Me	**24t** (14)[b]
15	**23o**	$-(CH_2)_3$		H	-[b]

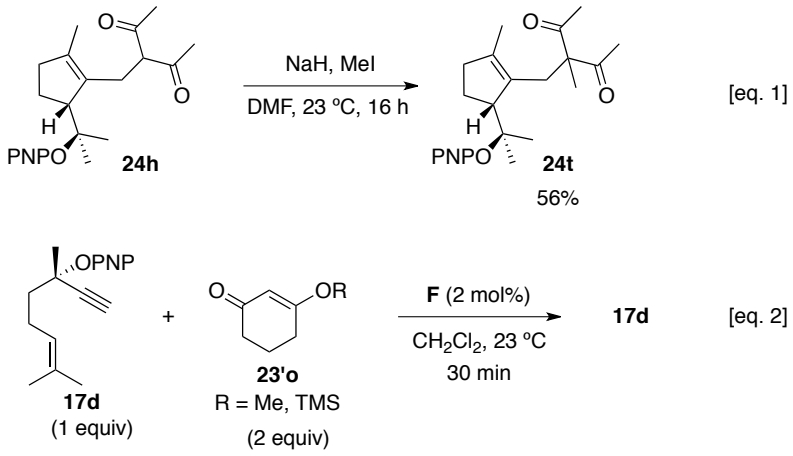
[a] Isolated yield. [b] 15 equivalents of **23l-o** were added.

Symmetrical alkyl and aryl disubstituted 1,3-diketones afforded the desired products in high yields (Table 22, entries 1 and 4). Unsymmetrical 1,3-diketones reacted smoothly to provide the product in good to excellent yields with poor to mediocre diastereoselectivity (Table 22, entries 2-3, and 5). Additionally, the combinations of alkyl-ester or aryl-ester also led to **24** in good yields with low to moderate diastereoselectivity (Table 22, entries 6 and 7). Interestingly, 1,3-diketoester substituted with a furan (**23h**) provided **24n** in high yields and diastereoselectivity (Table 22, entry 8). The product arising from the attack of the furan was not detected.

Malonate **23i** as well as 1,3-diketones containing highly electron-withdrawing groups were found to be unreactive and resulted in full

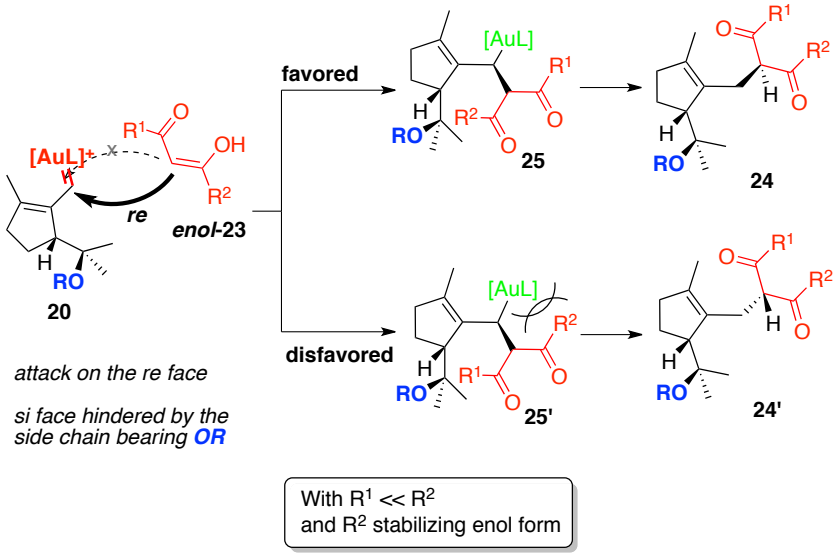
recovery of starting enyne **17d** (Table 22, entries 9-11). Substituted 1,3-diketones **23l-n** were also found to be unsuitable nucleophiles probably due to steric hindrance (Table 22, entries 12-14) even in the presence of large excess (15 equiv). Finally, cyclic 1,3-cyclohexanedione **23o** also failed to produce the desired product, presumably due to the cyclic structure of diketone **23o**, which disfavors the enol form (Table 22, entry 15).

While trisubstituted 1,3-diketones were found to be unreactive in this transformation, the expected product could be obtained by simple alkylation of **24h** with methyl iodide (Scheme 55, [eq. 1]). Unfortunately, preformed enol ether analogues of 1,3-cyclohexandione did not furnish the desired product (Scheme 55, [eq. 2]).



Scheme 55.

We proposed the mechanism to proceed via attack of the enol form of 1,3-diketones (***enol*-23**) onto the less hindered face of gold(I)-carbene **20**. The lack of diastereoselectivity observed in most of the cases suggests a poor pre-arrangement of the transition state during the attack of the prochiral nucleophile. We assumed major diastereoisomers **24** to arise from a pre-arrangement favoring R^2 (bigger than R^1) far from the gold(I)-carbene **20** (Scheme 56). However, further mechanistic studies are required to confirm this proposal.

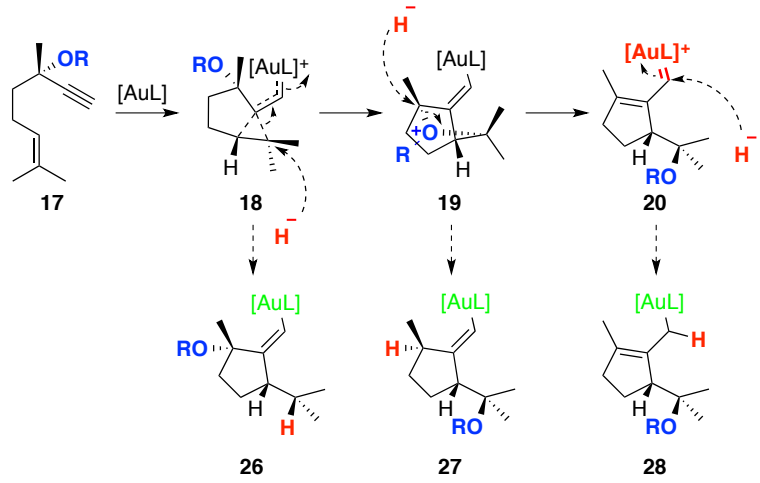


Scheme 56. Proposed mechanism for the formation of adducts 24 and 24'

Gold(I)-carbene trapped by silanes

Following our quest for the trapping of the 1,5-migration reaction sequence with novel nuclophiles, we turned our attention to hydride in the form of silanes. We suspected that silanes could introduce a hydride into one of the intermediates (**18**, **19**, or **20**) generated throughout this transformation (Scheme 57). The use of an external silane in homogeneous gold(I) catalysis had never been reported.[127]

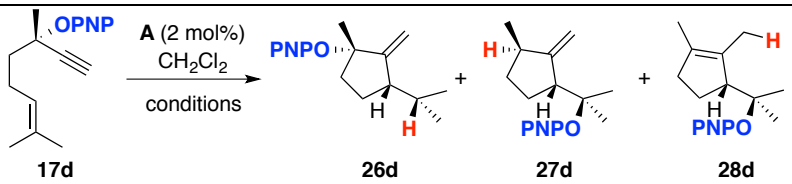
127 For selected examples of the reaction of silanes employing gold nanoparticles, see: (a) A. Corma, C. González-Arellano, M. Iglesias, F. Sánchez, *Angew. Chem. Int. Ed.* **2007**, *46*, 7820-7822. (b) T. Mitsudome, A. Noujima, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Chem. Commun.* **2009**, 5302-5304. (c) J. John, E. Gravel, A. Hagège, H. Li, T. Gacoin, E. Doris, *Angew. Chem. Int. Ed.* **2011**, *50*, 7533-7536.



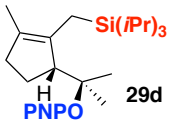
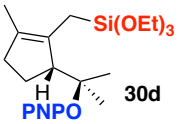
Scheme 57. Possible outcomes when employing silanes

Again, using our model 1,6-enyne substrate **17d**, we performed an initial screening using 3 equivalents of silanes as a source of hydride and JohnPhos/gold(I) catalyst **A** (Table 23).

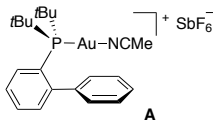
Table 23. Screening of hydride sources



Entry	Hydride (3 eq.)	Conditions	Outcome	Yield (%)[a]
1	$HSiPh_3$	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
2	$HSiEt_3$	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
3	TMDSO[b]	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
4	$HSiCl_3$	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-

5	$HSiMe_2Et$	23 ºC 4 h, then 40ºC, 12 h	**17d**	-
6	$HSiMe_2Ph$	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
7	$HSi(TMS)_3$	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
8	$HSi(iPr)_3$	23 ºC 4 h, then 40 ºC, 12 h	 **29d**	10
9	$HSi(OEt)_3$	23 ºC 4 h, then 40 ºC 12 h	 **30d**	8
10	H_2SiEt_2	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
11	$H_2SiMePh$	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
12	H_2SiPh_2	23 ºC 4 h, then 40 ºC, 12 h	**17d**	-
13	$(tBu)_3SnH$	23 ºC 4 h, then 40 ºC, 12 h	decomposition	-

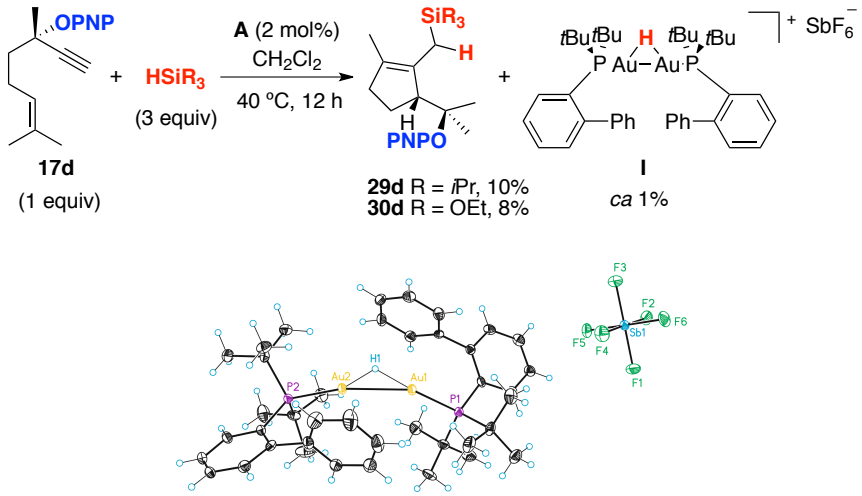
[a] Isolated yield. [b] TMDSO = tetramethyldisiloxane.



A

Unfortunately, with the exception of $HSi(iPr)_3$ and $HSi(OEt)_3$ (Table 23, entries 8 and 9), most of the silanes tested did not afford any of the expected products and resulted in the isolation of the unreacted starting material. Silane containing products **29d** and **30d** were isolated in low yields

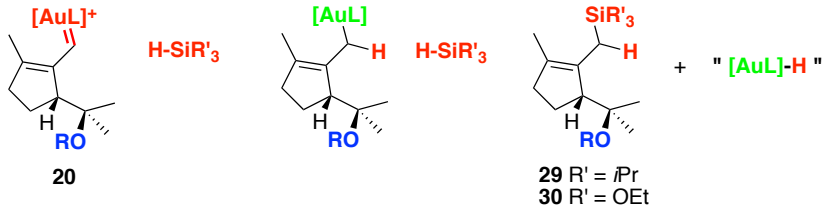
alongside a different compound, which upon recrystallization with a cyclohexane and EtOAc mixture, was identified as the new digold(I) hydride complex **I** (Scheme 58). Few examples of formation of gold(I) hydride complexes have been described in literature and none of them were reported as catalytically active species.[128]



Scheme 58. New digold(I) hydride complex I

These first results can be rationalized with a mechanism consisting of an initial attack of the hydride onto gold(I)-carbene **20**, followed by a silicon-gold transmetalation (Scheme 59). Further experiments are required to elucidate this mechanism.

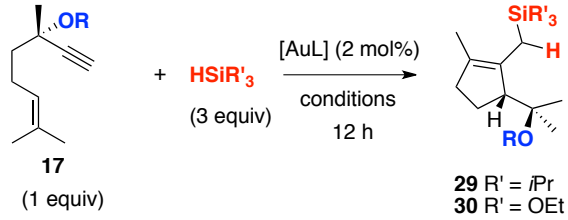
128 (a) E. Y. Tsui, P. Muller, J. R. Sadighi, *Angew. Chem. Int. Ed.* **2008**, *47*, 8937-8940. (b) H. Ito, T. Saito, T. Miyahara, C. M. Zhong, M. Sawamura, *Organometallics* **2009**, *28*, 4829-4840. (c) A. Escalle, G. Mora, F. Gagosz, N. Mezailles, X. F. Le Goff, Y. Jean, P. Le Floch, *Inorg. Chem.* **2009**, *48*, 8415-8422.



Scheme 59. Proposed mechanism for the formation of 29 and 30

Since low conversions were observed for the formation of **29d** and **30d**, further optimization was required. Selected optimization reaction with different OR migrating groups as well as gold(I) catalysts under various reaction conditions are summarized in Table 24.

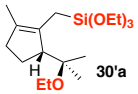
Table 24. Summary of the optimization studies



Entry	R	R'	Conditions	[AuL]	Yield (%)[a]
1	Me **17a**	*i*Pr	80 ºC, DCE	**A**	-[b]
2	Me **17a**	OEt	-30 ºC, CH_2Cl_2	**B**	**30a** (25)[b,c]
3	Ac **17b**	*i*Pr	80 ºC, DCE	**A**	-[b]
4	Ac **17b**	OEt	-20 ºC, CH_2Cl_2	**A**	**30b** (16)[b]
5	PNP **17d**	*i*Pr	80 ºC, DCE	**A**	**29d** (45)[b]
6	PNP **17d**	*i*Pr	80 ºC, DCE	**A**[d]	**29d** (69)
7	PNP **17d**	OEt	80 ºC, DCE	**B**	**30d** (30)[b,e]

[a] Isolated yield.

[b] Unreacted enyne **17** recovered. [c] 5% yield of byproduct **30'a**:

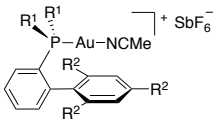


30'a

[d] 5 mol% of catalyst **A**.

[e] 21% yield of byproduct **30'd**:

30'd

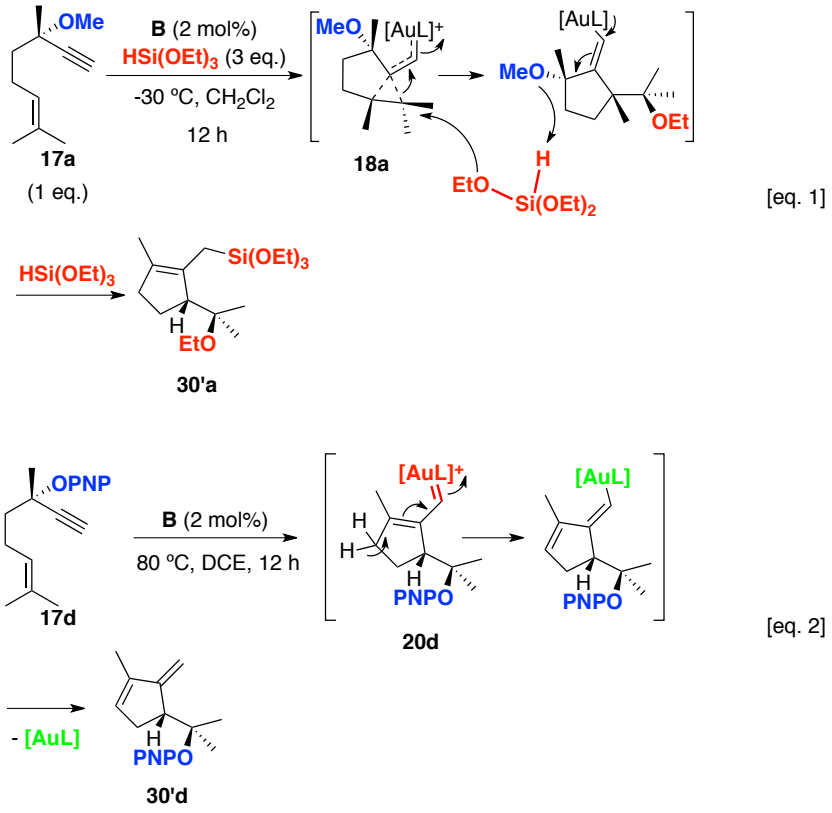


A, R^1 = *t*Bu, R^2 = H
B, R^1 = *t*Bu, R^2 = *i*Pr

Again *para*-nitrophenyl was found to be the best protecting group for undergoing 1,5-migration. Allylsilyl product **29d** could be isolated in good yields using 5 mol% catalyst loading (Table 24, entry 6).

Different catalysts, migrating groups and reaction conditions were much less fruitful as the product was observed in low to moderate conversion only with the formation of byproducts **30'a** and **30'd** (Table 24, entries 1-5, and 7).

The formation of byproducts **30'a** and **30'd** is rationalized in Scheme 60. Introduction of the ethoxy group present in **30'a** presumably results from the ring opening of cyclopropyl **18a** by triethoxysilane followed by elimination of methanol (Scheme 60, [eq. 1]). On the other hand, **30'd** could arise from the proton elimination from gold(I)-carbene **20**. Certainly, when the reaction was carried in the absence of the silane, the same byproduct could be isolated (Scheme 60, [eq. 2]).

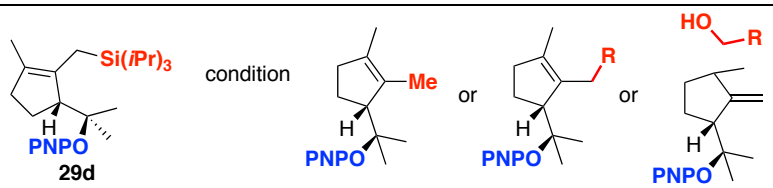


Scheme 60. Formation of 30'a and 30'd

Since allylsilanes are prone to react with a variety of electrophiles under nucleophilic catalysis or Lewis acid activation,[129] we tested several reaction conditions to promote the addition reaction (Table 25).

129 (a) T. Hayashi, M. Konishi, H. Ito, M. Kumada, *J. Am. Chem. Soc.* **1982**, *104*, 4962-4963. (b) T. Hayashi, M. Konishi, M. Kumada, *J. Am. Chem. Soc.* **1982**, *104*, 4963-4965. (c) H. Hiemstra, M. H. A. M. Sno, R. J. Vijn, W. N. Speckamp, *J. Org. Chem.* **1985**, *50*, 4014-4020. (d) J. R. Green, M. Majewski, B. I. Alo, V. Snieckus, *Tet. Lett.* **1986**, *27*, 535-538.

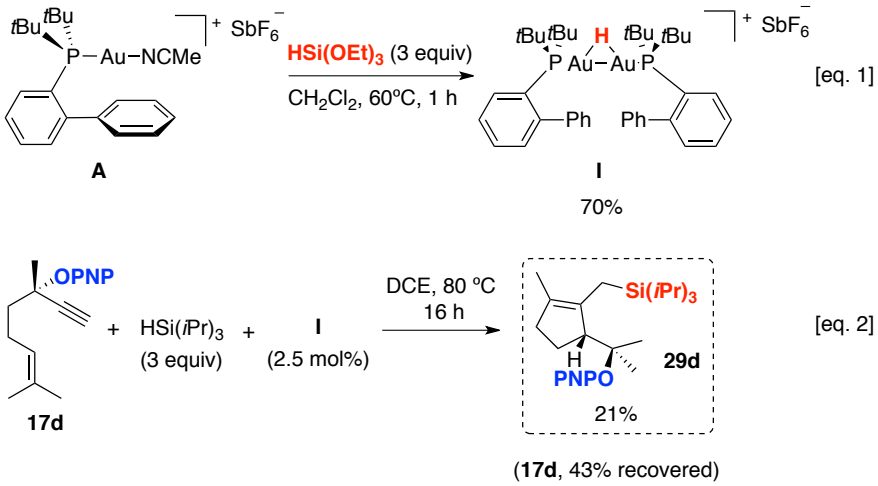
Table 25. Studies on the reactivity of 29d



Entry	Conditions	Outcome
1	TBAF, THF, rt	**29d**
2	HF.py, THF, 0ºC	**29d**
3	CsF, benzaldehyde, rt	**29d**
4	Et_2AlCl, benzaldehyde, 0ºC	decomposition
5	$TiCl_4$, benzaldehyde, 0ºC	decomposition
6	$TiCl_4$, MeCHO, -78ºC	decomposition
7	$TiCl_4$, MeCHO, -78ºC	decomposition
8	$BF_3.OEt_2$, formaldehyde, 0ºC	decomposition
9	*t*BuOK, MeOH/H_2O, rt	**29d**
10	$Pd(OAc)_2$, IPh, TBAF, rt	**29d**

These preliminary results were not encouraging. The C-Si bond revealed to be very robust, as it remained intact upon treatment with two different fluoride sources (Table 25, entries 1 and 2). Additionally, most of the reactions attempted to achieve the nucleophilic attack of the allylsilane **29d** on an aldehyde resulted in the decomposition of the allylsilane (Table 25, entries 3-8). Oxidation of the C-Si bond (Table 25, entry 9) or the Hiyama-coupling (Table 25, entry 10) also failed to give the desired products.

In order to test the ability of the newly isolated digold(I) hydride **I**, we developed preparative synthesis of this air-stable complex that led to a 70% isolated yield (Scheme 61, [eq. 1]). This complex was then subjected to the optimized reaction conditions and afforded allylsilane **29d** in a surprising 21% yield (Scheme 61, [eq. 2]). To the best of our knowledge, this is the first time that a gold(I) hydride complex was shown to be a competent catalyst with turnover, as all previously reported complexes have been used in stoichiometric quantities.[128]



Scheme 61. Synthesis and reactivity of digold(I) hydride I

Conclusions

An efficient diastereoselective method for the preparation of highly functionalized cyclopentenones has been developed. This transformation is based on a gold(I)-catalyzed 1,2-acyloxy migration/gold carbene trapping/ring opening/Mukaiyama-Michael type addition sequence that proceeds under mild conditions. In addition, we found the formation of the corresponding cyclopentadiene to be highly dependent on the propargylic ester used

The 1,5-migration reaction sequence was successfully expanded with three different type of trapping agents. Furans and 1,3-diketones led to rather elaborated products from readily available substrates under mild conditions, while the use of silanes gave allyl silanes in a less general reaction. We suspect this transformation might proceed through a silicon-gold transmetalation, as suggested by the isolation of digold(I) hydride complex **I**. Further mechanistic studies are required to elucidate this new type of reactivity.

Experimental section

General information

All reactions were carried out under argon unless otherwise specified. Solvents were dried using a Solvent Purification System (SPS) or using standard procedures.[130] Catalysts were either purchased from Sigma-Aldrich or synthesized according to literature procedures. All other reagents were used without further purification as obtained from the commercial sources. Analytical thin layer chromatography was carried out using TLC aluminum sheets with 0.2 mm of silica gel (Merck GF234) using UV light as the visualizing agent. Flash column chromatography purifications were carried out using C_{18}-reversed phase silica gel (40-63 μm). NMR spectra were recorded at 23 ºC on either a Bruker Avance 400 Ultrashield (400 MHz for ^{1}H, and 100 MHz for ^{13}C) or a Bruker Avance 500 Ultrashield (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

Crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = −173 ºC). Full-sphere data collection was used with w and j scans. *Programs used*: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solution was achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares

130 W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, Elsevier Science, Bath, **2003**.

refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non hydrogen atoms were refined including anisotropic displacement parameters.

Experimental Procedures

Intermolecular Cyclization of Propargyl Esters with Furans

Propargyl esters **2a**,[131] **2b**,[131] **2c**,[132] **2e**,[133] **2f**,[131] **2g**,[131] **2h**,[131] **4a**[134] **5a**[132,135] and furans **7b**,[136] **7c**[137], **7l**[138] were identified by comparison of their ^{1}H NMR spectra with the previously reported data.

General procedure for the preparation of propargylic acetate and benzoate

A solution of ethynylmagnesium bromide (3.60 mmol, 0.5 M in THF) was added slowly to the aldehyde (3.00 mmol) in THF (1 M) at -20 ºC within 30 min. The cold bath was removed and the reaction mixture was stirred for an additional hour at room temperature until TLC showed aldehyde consumption. The reaction was quenched by addition of saturated aqueous ammonium chloride solution, and the residue was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, and concentrated to obtain the propargylic alcohol, which was directly protected without further purification. To a solution of the crude propargylic alcohol (0.50 mmol) in CH_2Cl_2 (0.7 M) at 0 ºC was added DMAP (0.025 mmol), triethylamine (1.00 mmol), Ac_2O (0.55 mmol) or BzCl (0.55 mmol) and the reaction mixture was stirred for 2 h. After addition of water, the reaction was

131 N. Ghosh, S. Nayak, A. K. Sahoo, *J. Org. Chem.* **2011**, *76*, 500-511.

132 R. J. Detz, M. M. E. Delville, H. Hiemstra, J. H. van Maarseveen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3777-3780.

133 A. Bartels, R. Mahrwald, K. Mueller, *Adv. Synth. Catal* **2004**, *346*, 483-485.

134 T. Okada, K. Shishido, M. Yoshida, *Tetrahedron* **2007**, *63*, 6996-7002.

135 E. Rettenmeier, A. M. Schuster, M. Rudolph, F. Rominger, C. A. Gade, S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, *52*, 5880-5884.

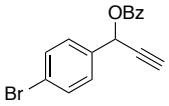
136 M. Tofi, K. Koltsida, G. Vassilikogiannakis, *Org. Lett.* **2009**, *11*, 313-316.

137 S. J. Pridmore, P. A. Slatford, J. E. Taylor, M. K. Whittlesey, J. M. J. Williams, *Tetrahedron* **2009**, *65*, 8981-8986.

138 A. Jeevanandam, K. Narkunan, Y.-C. Ling, *J. Org. Chem.* **2001**, *66*, 6014-6020.

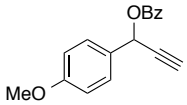
extracted with EtOAc. The combined organic layers were washed twice with saturated NaCl aqueous solution, dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography on silica gel (cyclohexane / EtOAc, 10 / 1) to give the desired propargylic acetate.

1-(4-Bromophenyl)prop-2-yn-1-yl benzoate (4b)



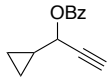
Transparent oil, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.62-7.52 (m, 5H), 7.49-7.45 (m, 2H), 6.68 (d, J = 2.3 Hz, 1H), 2.73 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 135.8, 133.6, 132.1, 130.1, 129.5, 128.6, 123.5, 79.9, 76.1, 65.3, 29.9; HRMS-APCI: *m/z* calcd for C16H12BrO2 $[(M+H)]^+$: 315.0015, found: 315.0017.

1-(4-Methoxyphenyl)prop-2-yn-1-yl benzoate (4c)



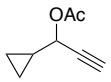
Yellow oil, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.61-7.57 (m, 3H), 7.47-7.44 (m, 2H), 6.97-6.95 (m, 2H), 6.69 (d, J = 2.3 Hz, 1H), 3.85 (s, 3H), 2.71 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 160.2, 134.5, 133.3, 129.9, 129.3, 128.9, 128.4, 114.1, 80.5, 75.4, 65.6, 55.4; HRMS-ESI: *m/z* calcd for $C_{17}H_{14}NaO_3$ $[(M+Na)]^+$: 289.0835, found: 289.0837.

1-Cyclopropylprop-2-yn-1-yl benzoate (4d)



Transparent oil, 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 2H), 7.62-7.59 (m, 1H), 7.50-7.47 (m, 2H), 5.47 (dd, J = 7.1, 2.2 Hz, 1H), 2.49 (d, J = 2.2 Hz, 1H), 1.49-1.43 (m, 1H), 0.72-0.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 133.2, 129.9, 129.8, 128.4, 79.4, 73.7, 67.7, 14.5, 3.6, 2.3; HRMS-ESI: *m/z* calcd for $C_{13}H_{12}NaO_2$ $[(M+Na)]^+$: 223.0730, found: 223.0723.

1-Cyclopropylprop-2-yn-1-yl acetate (2d)

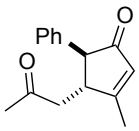


Transparent oil, 53% (volatile); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (dd, J = 7.1, 2.2 Hz, 1H), 2.44 (d, J = 2.2 Hz, 1H), 2.13 (s, 3H), 1.36-1.27 (m, 1H), 0.69-0.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 79.3, 73.5, 67.2, 21.1, 14.3, 3.5, 2.2; HRMS-ESI: *m/z* calcd for $C_8H_{10}NaO_2$ $[(M+Na)]^+$: 161.0573, found: 161.0565.

General procedure for the gold(I) catalyzed intermolecular cyclization of propargyl esters with furans

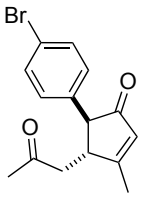
A solution of alkyne (1.00 mmol) and furan (2.00 mmol) in dry CH_2Cl_2 (2.5 mL) was added to a solution of gold(I) catalyst (3 mol%) in dry CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at 23°C until TLC showed full conversion. A drop of Et_3N was added and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography using different gradients of cyclohexane and ethyl acetate to obtain the pure desired products.

(4*R,5*S**)-3-Methyl-4-(2-oxopropyl)-5-phenylcyclopent-2-en-1-one (3a)**



Orange oil, 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.26-7.21 (m, 1H), 7.11-7.08 (m, 2H), 6.05-6.02 (m, 1H), 3.33-3.29 (m, 1H), 3.22 (d, J = 3.0 Hz, 1H), 2.91 (dd, J = 17.2, 5.5 Hz, 1H), 2.62 (dd, J = 17.2, 7.6 Hz, 1H), 2.14 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 206.0, 178.9, 138.8, 130.4, 128.8, 127.8, 127.1, 59.7, 49.1, 46.0, 30.2, 17.6; HRMS-ESI: *m/z* calcd for $C_{15}H_{15}O_2$ $[(M-H)^-]$: 227.1077, found: 227.1080.

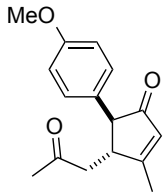
(4*R,5*S**)-5-(4-Bromophenyl)-3-methyl-4-(2-oxopropyl)cyclopent-2-en-1-one (3b)**



Orange oil, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.00–6.97 (m, 2H), 6.05–6.02 (m, 1H), 3.27–3.23 (m, 1H), 3.17 (d, J = 3.0 Hz, 1H), 2.92 (dd, J = 17.2, 5.5 Hz,

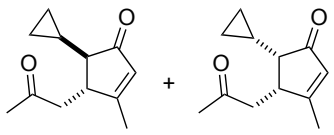
1H), 2.60 (dd, *J* = 17.2, 7.6 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 205.8, 179.0, 137.9, 131.9, 130.4, 129.6, 121.1, 59.1, 48.9, 46.0, 30.2, 17.6; HRMS-ESI: *m/z* calcd for $C_{15}H_{15}O_2BrNa$ [(*M*+Na)$^+$]: 329.0148, found: 329.0145.

(4*R,5*S**)-5-(4-Methoxyphenyl)-3-methyl-4-(2-oxopropyl)cyclopent-2-en-1-one (3c)**



Orange oil, 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02–7.00 (m, 2H), 6.85–6.83 (m, 2H), 6.03–6.01 (m, 1H), 3.77 (s, 3H), 3.28–3.25 (m, 1H), 3.16 (d, *J* = 3.0 Hz, 1H), 2.89 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.60 (dd, *J* = 17.2, 7.7 Hz, 1H), 2.13 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 206.3, 178.8, 158.8, 131.0, 130.5, 129.0, 114.4, 59.1, 55.4, 49.3, 46.2, 30.3, 17.8; HRMS-ESI: *m/z* calcd for $C_{16}H_{19}O_3$ [(*M*+H)$^+$]: 259.1329, found: 259.1331.

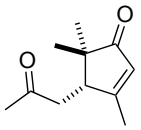
(4*R,5*R**)-5-Cyclopropyl-3-methyl-4-(2-oxopropyl)cyclopent-2-en-1-one compound and (4*R**,5*S**)-5-cyclopropyl-3-methyl-4-(2-oxopropyl)cyclopent-2-en-1-one (3d and 3'd)**



Yellow oil, 61%; a 2.5:1 ratio of inseparable diastereoisomers was obtained when starting with the **2d**, while a 60% yield of a 5:1 ratio was obtained when starting with the **4d**. All signals corresponding to the major and minor diasteroisomer could be identified separately; ^{1}H NMR (500 MHz, $CDCl_3$) Major diasteroisomer: δ 5.88-5.87 (m, 1H), 3.00-2.97 (m, 1H), 2.78 (dd, *J* = 17.2, 5.0 Hz, 1H), 2.44 (dd, *J* = 17.3, 8.3 Hz, 1H), 2.19 (s, 3H), 2.04 (s, 3H), 1.64 (dd, *J* = 7.9, 2.1 Hz, 1H), 0.91-0.86 (m, 1H), 0.55-0.49 (m, 2H), 0.46-0.41 (m, 2H); Minor diasteroisomer: δ 5.93-5.92 (m, 1H), 3.56-3.51 (m, 1H), 2.93 (dd, *J* = 18.1, 9.1 Hz, 1H), 2.62 (dd, *J* = 18.0, 4.5 Hz, 1H), 2.25 (s, 3H), 2.04 (s, 3H), 1.83 (dd, *J* = 9.7, 6.6 Hz, 1H), 0.66-0.61 (m, 1H), 0.40-0.37 (m, 1H), 0.29-0.24 (m, 2H), 0.14-0.09 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) Major diasteroisomer: δ 209.1, 206.4,

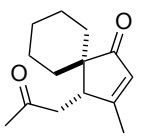
178.3, 130.5, 55.9, 46.6, 46.3, 30.4, 17.5, 13.0, 2.5, 1.8; Minor diasteroisomer: δ 209.4, 206.6, 178.2, 130.4, 53.9, 43.1, 42.5, 30.4, 17.6, 10.1, 4.0, 3.4; HRMS-ESI: *m/z* calcd for $C_{12}H_{16}NaO_2$ [$(M$+Na$)^+$]: 215.1043, found: 215.1042.

3,5,5-Trimethyl-4-(2-oxopropyl)cyclopent-2-en-1-one (3e)



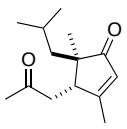
Orange oil, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.85 (m, 1H), 3.14-3.10 (m, 1H), 2.66-2.51 (m, 2H), 2.22 (s, 3H), 2.01 (s, 3H), 1.14 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 206.7, 177.1, 128.5, 50.7, 47.4, 42.8, 30.2, 26.2, 20.4, 17.6; HRMS-ESI: *m/z* calcd for $C_{11}H_{16}O_2Na$ [$(M$+Na$)^+$]: 203.1043, found: 203.1041.

3-Methyl-4-(2-oxopropyl)spiro[4.5]dec-2-en-1-one (3f)



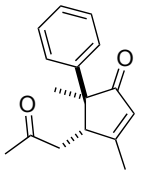
Orange oil, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.78 (m, 1H), 3.25-3.22 (m, 1H), 2.75 (dd, J = 17.2, 5.5 Hz, 1H), 2.45 (dd, J = 17.2, 7.6 Hz, 1H), 2.25 (s, 3H), 1.99 (t, J = 1.1 Hz, 3H), 1.88-1.83 (m, 1H), 1.82-1.76 (m, 1H), 1.74-1.68 (m, 1H), 1.55-1.41 (m, 5H), 1.32-1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1, 206.8, 177.4, 128.1, 51.3, 49.4, 43.4, 37.1, 30.5, 28.0, 25.3, 22.7, 22.1, 18.1; HRMS-ESI: *m/z* calcd for $C_{14}H_{20}O_2Na$ [$(M$+Na$)^+$]: 243.1356, found: 243.1361.

(4*R,5*S**)-5-Isobutyl-3,5-dimethyl-4-(2-oxopropyl)cyclopent-2-en-1-one (3g)**



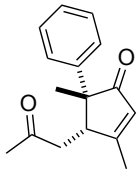
Orange oil, 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.92 (m, 1H), 3.40 (tdd, J = 6.3, 2.0, 1.1 Hz, 1H), 2.62 (dd, J = 6.8, 2.8 Hz, 2H), 2.26 (s, 3H), 2.04 (t, J = 1.2 Hz, 3H), 1.74-1.66 (m, 1H), 1.54-1.49 (m, 2H), 0.95-0.91 (m, 6H), 0.79 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 206.6, 177.5, 129.3, 51.1, 47.2, 46.9, 42.6, 30.3, 25.0, 24.9, 23.7, 21.4, 17.7; HRMS-ESI: *m/z* calcd for $C_{14}H_{22}NaO_2$ [$(M$+Na$)^+$]: 245.1512, found: 245.1513.

(4*R,5*R**)-3,5-Dimethyl-4-(2-oxopropyl)-5-phenylcyclopent-2-en-1-one (3h)**



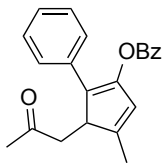
Orange oil, 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 3H), 7.24–7.19 (m, 2H), 6.04–6.03 (m, 1H), 3.66 (ddt, J = 7.2, 6.2, 1.5 Hz, 1H), 2.69 (dd, J = 6.8, 5.3 Hz, 2H), 2.20 (s, 3H), 2.05 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 206.4, 178.1, 144.7, 129.3, 128.7, 126.8, 126.4, 55.8, 53.0, 43.1, 30.2, 19.9, 18.0; HRMS-ESI: *m/z* calcd for $C_{16}H_{18}O_2Na$ [(M+Na)$^+$]: 265.1199, found: 265.1200.

(4*R,5*S**)-3,5-Dimethyl-4-(2-oxopropyl)-5-phenylcyclopent-2-en-1-one (3'h)**



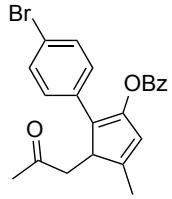
Orange oil, 9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.19 (m, 3H), 7.04-7.02 (m, 2H), 6.13-6.12 (m, 1H), 3.45-3.42 (m, 1H), 2.35 (dd, J = 17.6, 3.6 Hz, 1H), 2.19 (dd, J = 17.6, 10.7 Hz, 1H), 2.10 (s, 3H), 1.63 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 206.7, 178.6, 141.2, 130.3, 128.7, 128.1, 126.9, 55.7, 53.9, 42.9, 29.3, 24.2, 17.6; HRMS-ESI: *m/z* calcd for $C_{16}H_{18}O_2Na$ [(M+Na)$^+$]: 265.1199, found: 265.1191.

4-Methyl-3-(2-oxopropyl)-2-phenylcyclopenta-1,4-dien-1-yl benzoate (6a)



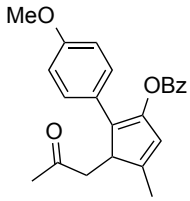
Yellow oil, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.15 (m, 2H), 7.65-7.61 (m, 1H), 7.52-7.48 (m, 2H), 7.39-7.30 (m, 4H), 7.21-7.16 (m, 1H), 6.30-6.27 (m, 1H), 4.06 (ddd, J = 8.5, 3.5, 1.0 Hz, 1H), 2.74 (dd, J = 17.3, 3.5 Hz, 1H), 2.56 (dd, J = 17.3, 8.4 Hz, 1H), 2.09 (s, 3H), 2.00 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 164.3, 147.9, 146.5, 133.7, 132.9, 130.2, 129.2, 128.7, 128.6, 127.4, 126.4, 125.2, 46.6, 43.3, 30.5, 15.6; HRMS-ESI: *m/z* calcd for $C_{22}H_{20}O_3Na$ [(M+Na)$^+$]: 355.1305, found: 355.1303.

2-(4-Bromophenyl)-4-methyl-3-(2-oxopropyl)cyclopenta-1,4-dien-1-yl benzoate (6b)



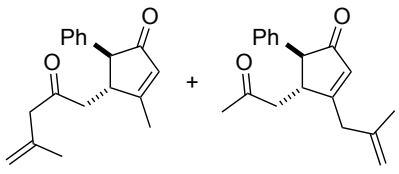
Yellow oil, 44%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.13 (m, 2H), 7.66-7.63 (m, 1H), 7.53-7.49 (m, 2H), 7.45-7.43 (m, 2H), 7.24-7.22 (m, 2H), 6.29-6.27 (m, 1H), 4.02 (ddd, J = 8.5, 3.6, 1.0 Hz, 1H), 2.69 (dd, J = 17.5, 3.4 Hz, 1H), 2.55 (dd, J = 17.5, 8.3 Hz, 1H), 2.11 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 164.2, 148.5, 147.2, 134.0, 132.0, 131.7, 130.8, 130.3, 129.0, 128.9, 127.6, 125.3, 120.4, 46.6, 43.2, 30.7, 15.7; HRMS-ESI: *m/z* calcd for $C_{22}H_{19}O_3BrNa$ [(M+Na)$^+$]: 433.0410, found: 433.0415.

2-(4-Methoxyphenyl)-4-methyl-3-(2-oxopropyl)cyclopenta-1,4-dien-1-yl benzoate (6c)



Yellow oil, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.14 (m, 2H), 7.65-7.61 (m, 1H), 7.52-7.48 (m, 2H), 7.31-7.29 (m, 2H), 6.88-6.86 (m, 2H), 6.25 (m, 1H), 3.99 (ddd, J = 8.4, 3.6, 1.0 Hz, 1H), 3.79 (s, 3H), 2.71 (dd, J = 17.3, 3.6 Hz, 1H), 2.55 (dd, J = 17.3, 8.4 Hz, 1H), 2.08 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 164.4, 158.2, 146.8, 145.2, 133.6, 130.2, 129.3, 128.6, 128.4, 125.7, 125.1, 114.2, 55.2, 46.7, 43.5, 30.5, 15.6; HRMS-ESI: *m/z* calcd for $C_{23}H_{22}O_4Na$ [(M+Na)$^+$]: 385.1410, found: 385.1422.

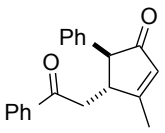
(4*R,5*S**)-3-Methyl-4-(4-methyl-2-oxopent-4-en-1-yl)-5-phenylcyclopent-2-en-1-one and (4*R**,5*S**)-3-(2-methylallyl)-4-(2-oxopropyl)-5-phenylcyclopent-2-en-1-one (8b and 8'b)**



Orange oil, 56%; a 1.6:1 ratio of inseparable diastereoisomers was obtained. The following characterization data is reported for the mixture of isomers with the relative integration for each signal; ^{1}H NMR

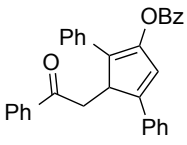
(400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 3.2H), 7.25-7.22 (m, 1.6H), 7.11-7.06 (m, 3.2H), 6.09-6.06 (m, 0.6H), 6.05-6.02 (m, 1H), 4.98-4.95 (m, 1.6H), 4.86 (s, 0.6H), 4.81 (s, 1H), 3.35-3.29 (m, 1.6H), 3.25 (d, J = 3.0 Hz, 0.6H), 3.21 (d, J = 3.0 Hz, 1H), 3.14-3.05 (m, 3.2H), 2.96-2.91 (m, 1.6H), 2.67-2.57 (m, 1.6H), 2.12 (s, 3H), 2.11 (s, 1.8H), 1.78 (s, 1.8H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 207.0, 206.0, 205.9, 180.1, 179.0, 140.6, 138.9, 138.8, 138.5, 130.7, 130.4, 128.9, 128.8, 127.8, 127.7, 127.1, 127.0, 115.6, 114.7, 59.8, 59.7, 52.4, 49.1, 48.1, 46.1, 44.0, 40.0, 30.1, 22.6, 22.3, 17.6; HRMS-ESI: *m/z* calcd for $C_{18}H_{20}O_2Na$ [(M+Na)$^+$]: 291.1356, found: 291.1356.

(4*R,5*S**)-3-Methyl-4-(2-oxo-2-phenylethyl)-5-phenylcyclopent-2-en-1-one (8c)**



Orange oil, 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.61-7.56 (m, 1H), 7.51-7.44 (m, 2H), 7.35-7.20 (m, 3H), 7.12-7.09 (m, 2H), 6.10-6.07 (m, 1H), 3.55-3.42 (m, 2H), 3.34 (d, J = 2.7 Hz, 1H), 2.60 (dd, J = 16.5, 6.5 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 197.8, 179.4, 139.0, 136.7, 133.7, 130.6, 128.9, 128.2, 128.0, 127.2, 60.1, 49.6, 40.9, 18.0; HRMS-ESI: *m/z* calcd for $C_{30}H_{18}O_2Na$ [(M+Na)$^+$]: 313.1199, found: 313.1187.

3-(2-Oxo-2-phenylethyl)-2,4-diphenylcyclopenta-1,4-dien-1-yl benzoate (10)



Yellow solid, 75%; mp 149-153 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.22 (m, 2H), 7.72-7.70 (m, 2H), 7.69-7.65 (m, 1H), 7.56-7.50 (m, 6H), 7.47-7.44 (m, 1H), 7.34-7.28 (m, 6H), 7.24-7.22 (m, 1H), 7.17-7.13 (m, 1H), 6.98 (s, 1H), 5.15 (t, J = 4.9 Hz, 1H), 3.25 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 164.3, 150.3, 146.7, 137.1, 134.4, 133.8, 132.9, 132.8, 132.4, 130.3, 129.2, 128.8, 128.7, 128.6, 128.3, 128.0, 127.9, 127.5, 126.8,

126.5, 125.1, 43.6, 39.0; HRMS-ESI: *m/z* calcd for $C_{32}H_{24}O_3Na$ [$(M+Na)^+$]: 479.1618, found: 479.1627.

Crystal structures

3-(2-Oxo-2-phenylethyl)-2,4-diphenylcyclopenta-1,4-dien-1-yl benzoate (10)

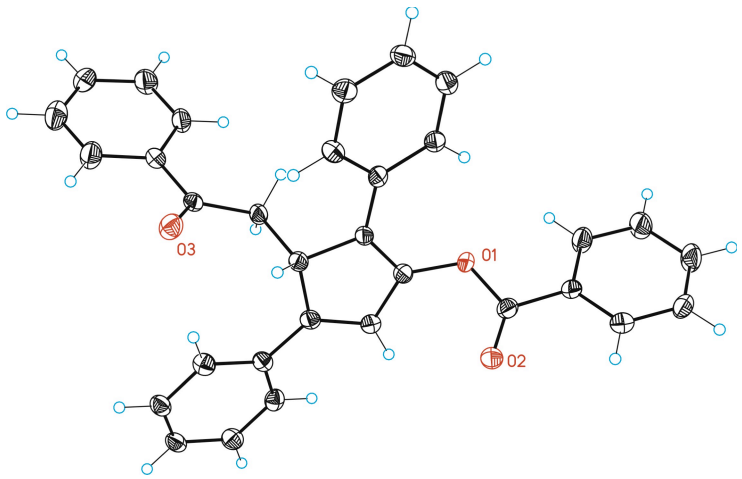


Table 1. Crystal data and structure refinement for **10**

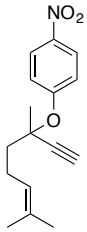
Empirical formula	C32 H24 O3	
Formula weight	456.51	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 5.5702(14) Å	a= 90.00 °.
	b = 24.243(6) Å	b = 93.744(10)
	c = 17.573(5) Å	g = 90.00 °.
Volume	2368.1(11) Å^3	

Z	4
Density (calculated)	1.280 Mg/m^3
Absorption coefficient	0.081 mm^{-1}
F(000)	960
Crystal size	0.40 x 0.04 x 0.02 mm^3
Theta range for data collection	2.04 to 28.11 °.
Index ranges	-6 <=h<=7 ,-31 <=k<=31 ,-23 <=l<=23
Reflections collected	15211
Independent reflections	5364 [R(int) = 0.0633]
Completeness to theta =28.11 °	99.6%
Absorption correction	Empirical
Max. and min. transmission	0.9984 and 0.9683
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5364 / 2 / 318
Goodness-of-fit on F^2	0.986
Final R indices [I>2sigma(I)]	R1 = 0.0547 , wR2 = 0.1105
R indices (all data)	R1 = 0.1013 , wR2 = 0.1281
Flack parameter	x =0.8(14)
Largest diff. peak and hole	0.203 and -0.262 $e.Å^{-3}$

Investigating the 1,5-migration reaction sequence

1,6-Enynes **17a**,[139] **17b**,[140] **17c**,[139] **17e**,[141] and **17f**[139] were identified by comparison of their ^{1}H NMR spectra with the previously reported data.

1-((3,7-Dimethyloct-6-en-1-yn-3-yl)oxy)-4-nitrobenzene (17d)



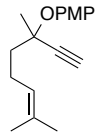
To a solution of the propargylic alcohol **17e** (1.0 g, 6.57 mmol) in 7.0 mL of dry acetonitrile was added DBU (1.47 mL, 9.85 mmol) followed by trifluoroacetic anhydride (1.42 mL, 10.18 mmol) at -15ºC. After stirring at this temperature for 2h, a solution of DBU (1.47 mL, 9.85 mmol), $CuCl_2.2H_2O$ (11.0 mg, 0.066 mmol) and *p*-nitro phenol (1.01 g, 7.23 mmol) in dry acetonitrile (3 mL) was added dropwise. After stirring for 30min at room temperature, a saturated aqueous NH_4Cl solution was added. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4 and the solvents were evaporated. Purification by column flash chromatography (cyclohexane / EtOAc, 33 / 1 - 20 / 1) yielded the protected alcohol **17d** as a pale yellow oil (9.9 g, 3.62 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.15 (m, 2H), 7.32-7.28 (m, 2H), 5.14 (ddq, J = 8.6, 5.8, 1.5 Hz, 1H), 2.71 (s, 1H), 2.26 (m, 2H), 2.00 (ddd, J = 13.6, 11.3, 5.2 Hz, 1H), 1.90 (ddd, J = 13.5, 11.5, 5.2 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 142.2, 132.8, 125.4, 123.1, 119.2, 83.7, 76.8, 76.1, 42.6, 26.8, 25.8, 23.1, 17.8; HRMS-ESI calcd for $C_{16}H_{20}NO_3$ [$(M$+H$)^+$]: 274.1443; found: 274.1432.

139 E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio and A. M. Echavarren, *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.

140 M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2012**, 134, 8770- 8773.

141 D. K. Mohapatra, C. Pramanik, M. S. Chorghade, M. K. Gurjar, *Eur. J. Org. Chem.* **2007**, 5059-5063.

1-((3,7-Dimethyloct-6-en-1-yn-3-yl)oxy)-4-methoxybenzene (17g)



17g was prepared according to the above-mentioned procedure for the synthesis of compound **17d**.

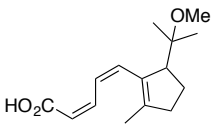
Yellow oil, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 5.19-5.10 (m, 1H), 3.78 (s, 3H), 2.54 (s, 1H), 2.36-2.19 (m, 2H), 1.95-1.85 (m, 1H), 1.84-1.74 (m, 1H), 1.70 (d, J = 1.7 Hz, 3H), 1.63 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 148.9, 132.1, 123.7, 123.6, 113.8, 85.4, 76.1, 74.9, 55.5, 42.3, 26.9, 25.7, 23.3, 17.7; HRMS-ESI: m/z calcd. for $C_{17}H_{22}NaO_2$ [$(M$+Na)$^+$]: 281.1517, found: 281.1512.

Gold(I)-carbene trapped by furans

General procedure

A solution of the enyne (0.10 mmol) in anhydrous CH_2Cl_2 (0.33 mL) was added dropwise over 30 min to a solution of gold catalyst (0.002 mmol) and furan (0.20 mmol) in anhydrous CH_2Cl_2 (0.66 mL) at room temperature. The reaction was quenched with a drop of Et_3N and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography using different gradients of cyclohexane and ethyl acetate to obtain the pure desired products.

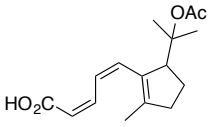
(2*Z*,4*Z*)-5-(5-(2-Methoxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)penta-2,4-dienoic acid (21a)



Yellow oil, 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, J = 11.8 Hz, 1H), 6.71 (td, J = 11.6, 1.0 Hz, 1H), 6.35 (d, J = 11.8 Hz, 1H), 5.66 (dt, J = 11.5, 1.3 Hz, 1H), 3.17 (s, 3H), 3.04–3.00 (m, 1H), 2.49–2.41 (m, 1H), 2.33–2.24 (m, 1H), 2.02–1.93 (m, 1H), 1.74–1.67 (m, 1H), 1.58 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 144.7, 143.1, 139.0, 134.1,

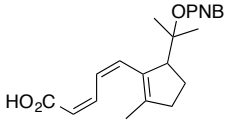
124.0, 115.6, 77.87, 57.8, 48.9, 38.1, 25.2, 23.0, 22.0, 16.5; HRMS-ESI: *m*/*z*: calcd for $C_{15}H_{21}O_3$ [(*M*-H)$^+$]: 249.1489, found: 249.1496.

(2*Z*,4*Z*)-5-(5-(2-Acetoxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)penta-2,4-dienoic acid 21b)



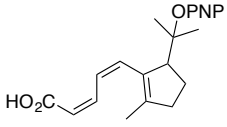
Yellow oil, 19%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 11.3 Hz, 1H), 6.73 (td, *J* = 11.6, 1.0 Hz, 1H), 6.32-6.29 (m, 1H), 5.71 (dt, *J* = 11.5, 1.3 Hz, 1H), 3.51-3.48 (m, 1H), 2.52-2.46 (m, 1H), 2.37-2.29 (m, 1H), 2.06-2.00 (m, 2H), 1.96 (s, 3H), 1.62 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.58, 170.57, 144.3, 143.8, 138.2, 133.3, 124.2, 115.8, 85.39, 58.0, 37.9, 25.1, 24.4, 22.8, 22.8, 16.4; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{21}O_4$ [(*M*-H)$^+$]: 277.1442, found: 277.1445.

(2*Z*,4*Z*)-5-(2-Methyl-5-(2-((4-nitrobenzyl)oxy)propan-2-yl)cyclopent-1-en-1-yl)penta-2,4-dienoic acid (21c)



Yellow oil, 35%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.17 (m, 2H), 7.50-7.48 (m, 2H), 7.26 (t, *J* = 11.5, 1H), 6.73 (td, *J* = 11.6, 1.1 Hz, 1H), 6.37-6.31 (m, 1H), 5.67 (dt, *J* = 11.5, 1.3 Hz, 1H), 4.55-4.49 (m, 2H), 3.13-3.10 (m, 1H), 2.53-2.46 (m, 1H), 2.35-2.28 (m, 1H), 2.06-2.01 (m, 1H), 1.78-1.72 (m, 1H), 1.60 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 147.6, 147.2, 144.5, 143.5, 139.1, 133.8, 127.7, 124.0, 123.6, 115.9, 79.0, 62.7, 58.7, 38.0, 25.4, 23.6, 22.2, 16.5; HRMS-ESI: *m*/*z*: calcd for $C_{21}H_{24}NO_5$ [(*M*-H)$^+$]: 370.1655, found: 370.1660.

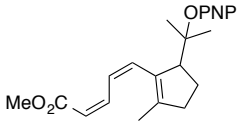
(2*Z*,4*Z*)-5-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)penta-2,4-dienoic acid (21d)



Yellow oil, 82% (Gold(I) catalyst **B**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18-8.16 (m, 2H), 7.33 (td, *J* = 11.4, 1.1 Hz, 1H), 7.04-7.02 (m, 2H), 6.76 (td, *J* = 11.6, 1.1 Hz, 1H), 6.42-6.40 (m, 1H), 5.72 (dt, *J* = 11.5, 1.3 Hz, 1H), 3.35-3.32 (m,

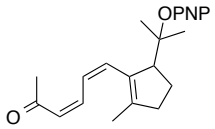
1H), 2.57-2.51 (m, 1H), 2.41-2.34 (m, 1H), 2.16-2.10 (m, 1H), 1.83-1.77 (m, 1H), 1.66 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 161.6, 144.1, 142.4, 138.3, 133.1, 125.2, 124.1, 121.6, 115.9, 85.5, 59.7, 37.7, 26.9, 25.4, 24.9, 23.0, 16.4; HRMS-ESI: *m*/*z*: calcd for $C_{20}H_{22}NO_5$ [(*M*-H)$^+$]: 356.1516, found: 356.1503.

Methyl (2*Z*,4*Z*)-5-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)penta-2,4-dienoate (21e)



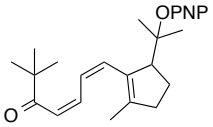
Yellow oil, 57% (Gold(I) catalyst **A**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.12 (m, 2H), 7.32 (t, *J* = 11.1 Hz, 1H), 7.01–6.99 (m, 2H), 6.62 (t, *J* = 12.0 Hz, 1H), 6.34–6.31 (m, 1H), 5.67 (dt, *J* = 11.4, 1.4 Hz, 1H), 3.73 (s, 3H), 3.31–3.28 (m, 1H), 2.54–2.47 (m, 1H), 2.39–2.29 (m, 1H), 2.13–2.04 (m, 1H), 1.81–1.72 (m, 1H), 1.61 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 161.8, 143.9, 142.5, 142.1, 137.5, 133.2, 125.3, 124.3, 121.7, 116.8, 85.7, 59.8, 51.3, 37.8, 25.5, 25.0, 23.2, 16.5; HRMS-ESI: *m*/*z*: calcd for $C_{21}H_{25}NNaO_5$ [(*M*+Na)$^+$]: 394.1644, found: 394.1625.

(3*Z*,5*Z*)-6-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)hexa-3,5-dien-2-one (21f)



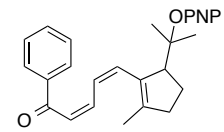
Yellow oil, 56% (Gold(I) catalyst **B**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14-8.12 (m, 2H), 7.32 (t, *J* = 11.8 Hz, 1H), 7.01-6.99 (m, 2H), 6.46 (t, *J* = 11.5 Hz, 1H), 6.36-6.34 (m, 1H), 6.01 (dt, *J* = 11.4, 1.4 Hz, 1H), 3.31-3.28 (m, 1H), 2.55-2.48 (m, 1H), 2.38-2.31 (m, 1H), 2.24 (s, 3H), 2.12-2.05 (m, 1H), 1.81-1.76 (m, 1H), 1.62 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 161.8, 144.2, 139.7, 138.5, 133.3, 125.4, 125.3, 125.1, 124.2, 121.7, 85.7, 59.8, 37.9, 31.9, 25.5, 25.0, 23.3, 16.5; HRMS-ESI: *m*/*z*: calcd for $C_{21}H_{25}NNaO_4$ [(*M*+Na)$^+$]: 378.1688, found: 378.1676.

(4*Z*,6*Z*)-2,2-Dimethyl-7-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)hepta-4,6-dien-3-one (21g)



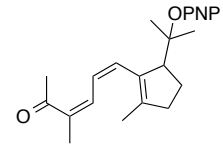
Yellow oil, 62% (Gold(I) catalyst **A**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13–8.11 (m, 2H), 7.30 (t, J = 11.6 Hz, 1H), 7.01–6.99 (m, 2H), 6.52 (t, J = 11.5 Hz, 1H), 6.31–6.27 (m, 2H), 3.30–3.27 (m, 1H), 2.51–2.47 (m, 1H), 2.36–2.31 (m, 1H), 2.11–2.04 (m, 1H), 1.82–1.76 (m, 1H), 1.61 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.5, 161.7, 143.7, 142.3, 140.3, 137.5, 133.2, 125.3, 125.2, 121.5, 120.0, 85.6, 59.6, 43.8, 37.7, 26.5, 25.4, 24.8, 23.3, 16.4; HRMS-ESI: *m*/*z*: calcd for $C_{24}H_{31}NNaO_4$ [(*M*+Na)$^+$]: 420.2151, found: 420.2145.

(2*Z*,4*Z*)-5-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)-1-phenylpenta-2,4-dien-1-one (21h)



Yellow oil, 59% (Gold(I) catalyst **A**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.32 (m, 2H), 7.98–7.95 (m, 2H), 7.59–7.55 (m, 1H), 7.50–7.45 (m, 2H), 7.42–7.35 (m, 1H), 7.05–7.02 (m, 2H), 6.76–6.74 (m, 2H), 6.43–6.39 (m, 1H), 3.37–3.31 (m, 1H), 2.60–2.50 (m, 1H), 2.44–2.31 (m, 1H), 2.17–2.06 (m, 1H), 1.86–1.76 (m, 1H), 1.69 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 161.8, 144.2, 141.6, 139.1, 138.5, 133.5, 132.7, 128.7, 128.4, 125.5, 125.4, 121.7, 121.3, 85.7, 59.9, 37.9, 27.1, 25.6, 25.0, 23.3, 16.6; HRMS-ESI: *m*/*z*: calcd for $C_{26}H_{27}NNaO_4$ [(*M*+Na)$^+$]: 440.1843, found: 440.1832.

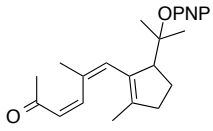
(3*Z*,5*Z*)-3-Methyl-6-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)hexa-3,5-dien-2-one (21i)



Yellow oil, 88% (Gold(I) catalyst **A**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17-8.15 (m, 2H), 7.04-7.03 (m, 2H), 6.78 (t, J = 11.4 Hz, 1H), 6.29 (dt, J = 11.6, 1.4 Hz,

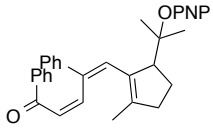
1H), 6.14 (d, *J* = 11.2 Hz, 1H), 3.32-3.29 (m, 1H), 2.57-2.51 (m, 1H), 2.41-2.36 (m, 1H), 2.33 (s, 3H), 2.13-2.07 (m, 1H), 2.04 (s, 3H), 1.86-1.81 (m, 1H), 1.65 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 161.8, 143.0, 142.3, 134.5, 134.3, 134.0, 133.2, 125.2, 125.1, 121.5, 85.7, 59.6, 37.6, 30.2, 25.4, 24.8, 23.5, 21.6, 16.3; HRMS-ESI: *m*/*z*: calcd for $C_{22}H_{27}NNaO_4$ [(*M*+Na)$^+$]: 392.1832, found: 392.1832.

(3*Z*,5*Z*)-5-Methyl-6-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)hexa-3,5-dien-2-one (21j)



Yellow oil, 32% (Gold(I) catalyst **D**); ^{1}H NMR (500 MHz, $CDCl_3$ δ 8.15–8.13 (m, 2H), 7.01–6.99 (m, 2H), 6.25 (dd, *J* = 12.5, 1.3 Hz, 1H), 6.07 (brs, 1H), 5.99 (dd, *J* = 12.5, 1.1 Hz, 1H), 3.27–3.24 (m, 1H), 2.48–2.44 (m, 1H), 2.33–2.28 (m, 1H), 2.25 (s, 3H), 2.09–2.01 (m, 1H), 1.91 (s, 3H), 1.79–1.74 (m, 1H), 1.53 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 162.0, 145.3, 142.4, 140.6, 134.3, 133.9, 133.2, 126.7, 125.4, 121.6, 85.9, 59.4, 37.9, 31.1, 25.7, 25.1, 23.5, 22.0, 16.9; HRMS-ESI: *m*/*z*: calcd for $C_{22}H_{27}NNaO_4$ [(*M*+Na)$^+$]: 392.1837, found: 392.1832.

(2*Z*,4*E*)-5-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)-1,4-diphenylpenta-2,4-dien-1-one (21k)



Yellow oil, 42% (Gold(I) catalyst **A**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00–7.99 (m, 2H), 7.59–7.57 (m, 2H), 7.43–7.42 (m, 1H), 7.30–7.27 (m, 2H), 7.09–7.05 (m, 5H), 6.85–6.83 (m, 2H), 6.73 (dd, *J* = 12.3, 1.3 Hz, 1H), 6.61 (dd, *J* = 12.3, 1.1 Hz, 1H), 6.26 (brs, 1H), 3.36–3.33 (m, 1H), 2.58–2.52 (m, 1H), 2.39–2.32 (m, 1H) 2.13–2.07 (m, 1H), 1.84–1.79 (m, 1H), 1,74 (s, 3H), 1.41 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 161.8, 145.3, 142.4, 141.9, 139.8, 138.4, 138.1, 134.3, 132.5, 128.3, 128.3, 128.1, 127.6, 127.0, 126.8, 125.2, 121.7, 121.1, 85.9, 59.6, 38.0, 25.8, 25.5, 23.2,

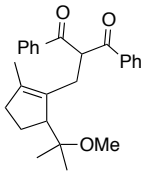
17.1; HRMS-ESI: *m*/*z*: calcd for $C_{32}H_{31}NNaO_4$ [(*M*+Na)$^+$]: 516.2153, found: 516.2145.

Gold(I)-carbene trapped by 1,3-diketones

General procedure

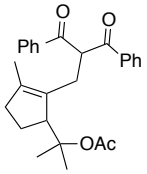
A solution of the enyne (0.10 mmol) in anhydrous CH_2Cl_2 (0.33 mL) was added dropwise over 30 min to a solution of gold catalyst (0.002 mmol) and 1,3-diketone (0.20 mmol) in anhydrous CH_2Cl_2 (0.66 mL) at room temperature. The reaction was quenched by adding a drop of Et_3N and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography using different gradients of cyclohexane and ethyl acetate to obtain the pure desired products.

2-((5-(2-Methoxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)methyl)-1,3-diphenylpropane-1,3-dione (24a)



Pale yellow oil, 27% (Gold(I) catalyst **E**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.01 (m, 2H), 7.95-7.90 (m, 2H), 7.53-7.50 (m, 2H), 7.44-7.39 (m, 4H), 5.62 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.14-3.07 (m, 1H), 3.09 (s, 3H), 2.98-2.89 (m, 1H), 2.88-2.79 (m, 1H), 2.13-2.01 (m, 1H), 1.82-1.74 (m, 1H), 1.70-1.62 (m, 1H), 1.41 (s, 3H), 1.40-1.34 (m, 1H), 1.11 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 196.8, 138.5, 136.9, 136.6, 133.1, 133.0, 132.3, 128.7, 128.6, 128.47, 128.45, 79.1, 56.4, 54.9, 48.6, 36.6, 29.3, 25.3, 23.6, 18.5, 14.2; HRMS-ESI: *m*/*z* calcd. for $C_{26}H_{30}NaO_3$ [(*M*+Na)$^+$]: 413.2092, found: 413.2087.

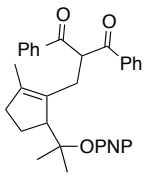
2-(2-(2-Benzoyl-3-oxo-3-phenylpropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl acetate (24b)



Colorless oil, 23% (Gold(I) catalyst **E**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.94 (m, 4H), 7.60-7.56 (m, 1H), 7.54-7.46 (m, 3H), 7.43-7.39 (m, 2H), 5.42 (dd, *J* = 10.6, 3.8 Hz, 1H),

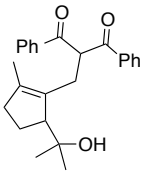
3.46-3.41 (m, 1H), 3.19 (dd, *J* = 14.2, 10.7 Hz, 1H), 2.92 (d, *J* = 14.1 Hz, 1H), 2.12-2.04 (m, 1H), 1.77 (s, 3H), 1.69-1.62 (m, 2H), 1.51 (s, 3H), 1.42-1.38 (m, 1H), 1.34 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 196.2, 170.7, 139.9, 136.6, 133.3, 130.9, 128.5, 86.9, 55.0, 54.7, 36.4, 29.0, 25.0, 24.8, 22.7, 21.2, 14.2; HRMS-ESI: *m*/*z*: calcd for $C_{27}H_{30}NaO_4$ [$(M$+Na)$^+$]: 441.2036, found: 441.2041.

2-((2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)-1,3-diphenylpropane-1,3-dione (24d)



Yellow oil, 71% (optimized conditions, Gold(I) catalyst **F**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.2 Hz, 2H), 7.90 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.81 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.56-7.53 (m, 1H), 7.46-7.41 (m, 3H), 7.28-7.23 (m, 2H), 6.95 (d, *J* = 9.2 Hz, 2H), 5.31 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.33-3.25 (m, 1H), 3.21 (dd, *J* = 14.1, 10.3 Hz, 1H), 3.07-2.97 (m, 1H), 2.21-2.09 (m, 1H), 1.90-1.82 (m, 1H), 1.81-1.73 (m, 1H), 1.50-1.44 (m, 1H), 1.42 (s, 3H), 1.41 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 196.2, 161.3, 142.1, 140.1, 136.6, 136.2, 133.32, 133.29, 131.2, 128.61, 128.56, 128.42, 128.39, 125.2, 121.2, 87.1, 56.0, 55.7, 36.5, 29.1, 25.7, 25.4, 21.9, 14.3; HRMS-ESI: *m*/*z* calcd. for $C_{31}H_{30}NO_5$ [$(M$-H)$^-$]: 496.2124, found: 496.2116.

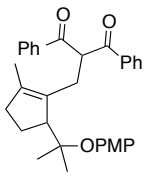
2-((5-(2-Hydroxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)methyl)-1,3-diphenylpropane-1,3-dione (24e)



Pale yellow oil, 24% (Gold(I) catalyst **E**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-8.00 (m, 2H), 7.96-7.91 (m, 2H), 7.54-7.51 (m, 2H), 7.45-7.39 (m, 4H), 5.58 (dd, *J* = 8.6, 5.4 Hz, 1H), 3.18-3.02 (m, 2H), 2.76 (m, 1H), 2.16-2.08 (m, 1H), 1.87-1.81 (m, 1H), 1.72-1.63 (m, 2H), 1.49 (s, 3H), 1.40-1.36 (m, 1H), 1.23 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 197.0, 138.7, 136.6, 136.5, 133.2, 133.2, 128.7, 128.68, 128.66, 128.61, 128.5, 75.0, 57.3,

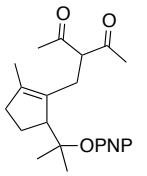
55.8, 36.8, 30.7, 29.0, 26.0, 24.4, 14.3; HRMS-ESI: *m*/*z* calcd. for $C_{25}H_{28}NaO_3$ [(*M*+Na)$^+$]: 399.1936, found: 399.1931.

2-((5-(2-(4-Methoxyphenoxy)propan-2-yl)-2-methylcyclopent-1-en-1-yl)methyl)-1,3-diphenylpropane-1,3-dione (24g)



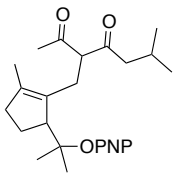
Yellowish oil, 53%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.88 (m, 4H), 7.54-7.51 (m, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.39-7.35 (m, 1H), 7.12-7.07 (m, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 5.82 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.77 (s, 3H), 3.24 (dd, *J* = 13.7, 11.0 Hz, 1H), 3.11-3.04 (m, 1H), 3.04-2.98 (m, 1H), 2.22-2.13 (m, 1H), 1.95-1.87 (m, 1H), 1.78-1.71 (m, 1H), 1.59 (s, 3H), 1.51-1.44 (m, 1H), 1.20 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2, 196.7, 155.7, 147.9, 139.4, 137.1, 136.0, 133.0, 132.9, 131.8, 128.7, 128.5, 128.4, 128.3, 125.6, 113.9, 84.8, 56.9, 55.6, 54.7, 36.8, 29.8, 26.9, 25.8, 20.5, 14.4; HRMS-ESI: *m*/*z* calcd. for $C_{32}H_{34}NaO_4$ [(*M*+Na)$^+$]: 505.2354, found: 505.2349.

3-((2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)pentane-2,4-dione (24h)



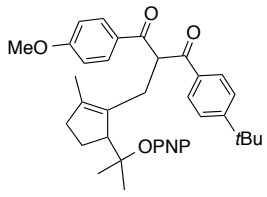
Pale yellow oil, 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.3 Hz, 2H), 7.03 (d, *J* = 9.3 Hz, 2H), 4.04 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.23-3.15 (m, 1H), 2.98 (dd, *J* = 14.1, 11.1 Hz, 1H), 2.73-2.64 (m, 1H), 2.36-2.25 (m, 1H), 2.23-2.14 (m, 1H), 2.11 (s, 3H), 2.04 (s, 3H), 2.01-1.93 (m, 1H), 1.72 (s, 3H), 1.61-1.53 (m, 1H), 1.37 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.1, 204.2, 161.1, 142.6, 139.5, 131.2, 125.3, 122.0, 87.4, 66.1, 56.4, 36.9, 29.13, 29.09, 27.8, 25.5, 25.3, 21.1, 14.5; HRMS-ESI: *m*/*z* calcd. for $C_{21}H_{27}NNaO_5$ [(*M*+Na)$^+$]: 396.1787, found: 396.1791.

6-Methyl-3-((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)heptane-2,4-dione (24i)



Yellowish oil, 63%; an inseparable mixture of diastereoisomers in a 1:1 ratio was obtained. The following characterization data is reported for the mixture of isomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.15 (m, 2H + 2H), 7.07-7.00 (m, 2H + 2H), 4.05-4.01 (m, 1H + 1H), 3.24-3.14 (m, 1H + 1H), 3.05-2.95 (m, 1H + 1H), 2.68-2.57 (m, 1H + 1H), 2.38-2.25 (m, 2H + 2H), 2.22-2.13 (m, 2H + 2H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03-1.91 (m, 2H + 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.60-1.52 (m, 1H + 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 0.88-0.84 (m, 3H + 3H), 0.76-0.68 (m, 3H + 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 206.0, 205.2, 204.1, 161.2, 161.1, 142.8, 142.5, 139.5, 139.3, 131.4, 131.3, 125.3, 125.2, 122.4, 121.7, 87.5, 87.2, 66.0, 65.7, 56.6, 56.3, 52.1, 51.2, 36.92, 36.85, 28.7, 28.6, 27.9, 27.8, 25.5, 25.4, 25.32, 25.31, 23.9, 23.6, 22.4, 22.31, 22.27, 22.2, 21.14, 21.12, 14.52, 14.50; HRMS-ESI: *m*/*z* calcd. for $C_{24}H_{33}NNaO_5$ [(M+Na)$^+$]: 438.2256, found: 438.2255.

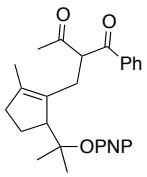
1-(4-(*tert*-Butyl)phenyl)-3-(4-methoxyphenyl)-2-((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)propane-1,3-dione (24j)



Yellow oil, 82%; an inseparable mixture of diastereoisomers in a 3.3:1 ratio was obtained. The following characterization data is reported for the mixture of isomers with the relative integration for each signal; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-7.99 (m, 2.6H), 7.90 (m, 2.0H), 7.83 (m, 0.6H), 7.81 (m, 0.6H), 7.74 (m, 2.0H), 7.42 (m, 0.6H), 7.25 (m, 2.0H), 6.97-6.93 (m, 2.6H), 6.90 (m, 2.0H), 6.72 (m, 0.6H), 5.16 (m, 1.3H), 3.86 (s, 3.0H), 3.78 (s, 0.9H), 3.39-3.27 (m, 1.3H), 3.24-3.15 (m, 1.3H), 3.04-2.90 (m, 1.3H), 2.22-2.10 (m, 1.3H), 1.94-1.74 (m, 2.6H), 1.53-1.45 (m, 1.3H), 1.43-1.40 (m, 4.8H), 1.31 (s, 3.0H), 1.28-1.23 (m, 15.6H);

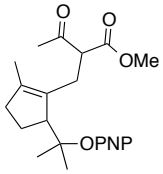
^{13}C NMR (126 MHz, $CDCl_3$) Major diastereoisomer: δ 195.9, 195.4, 163.6, 161.4, 157.1, 142.0, 139.9, 133.5, 131.5, 130.9, 129.6, 128.4, 125.5, 125.2, 121.0, 113.8, 87.1, 55.8, 55.5, 36.6, 35.0, 31.0, 30.9, 29.0, 25.7, 25.4, 22.1, 14.3; HRMS-ESI: *m*/*z* calcd. for $C_{36}H_{41}NNaO_6$ [(*M*+Na)$^+$]: 606.2832, found: 606.2824.

2-((2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)-1-phenylbutane-1,3-dione (24k)



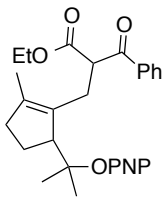
Yellow oil, 68%; an inseparable mixture of diastereoisomers in a 4.5:1 ratio was obtained. In this case, all signals corresponding to the major and minor diasteroisomer could be identified separately; ^{1}H NMR (500 MHz, $CDCl_3$) Major diasteroisomer: δ 8.19 (d, *J* = 9.2 Hz, 2H), 7.88 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.62-7.56 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 9.2 Hz, 2H), 4.75 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.16-3.04 (m, 2H), 2.89-2.80 (m, 1H), 2.20-2.12 (m, 1H), 2.08 (s, 3H), 1.92-1.85 (m, 1H), 1.74-1.67 (m, 1H), 1.52 (s, 3H), 1.47-1.42 (m, 1H), 1.38 (s, 3H), 1.26 (s, 3H); Minor diasteroisomer: δ 7.96 (d, *J* = 9.2 Hz, 2H), 7.79 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.46-7.43 (m, 1H), 7.32-7.28 (m, 2H), 6.87 (d, *J* = 9.2 Hz, 2H), 4.67 (dd, *J* = 10.9, 4.2 Hz, 1H), 3.41-3.33 (m, 1H), 3.21-3.16 (m, 1H), 2.79-2.71 (m, 1H), 2.35-2.28 (m, 1H), 2.25-2.21 (m, 1H), 2.06 (s, 3H), 2.02-1.96 (m, 1H), 1.75 (s, 3H), 1.59-1.54 (m, 1H), 1.42 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) Major diasteroisomer: δ 204.0, 197.5, 161.3, 142.4, 139.9, 137.1, 133.5, 130.9, 128.7, 128.3, 125.3, 121.5, 87.1, 60.6, 56.7, 36.5, 28.42, 28.36, 25.5, 25.3, 21.3, 14.3; Minor diasteroisomer: δ 204.8, 196.3, 161.2, 142.0, 139.5, 136.2, 133.6, 131.5, 128.6, 128.4, 125.2, 120.9, 87.3, 61.7, 55.5, 36.9, 28.3, 27.2, 25.6, 25.3, 21.9, 14.5; HRMS-ESI: *m*/*z* calcd. for $C_{26}H_{29}NNaO_5$ [(*M*+Na)$^+$]: 458.1943, found: 458.1943.

Methyl 2-((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)-3-oxobutanoate (24l)



Pale yellow oil, 59%; an inseparable mixture of diastereoisomers in a 1.3:1 ratio was obtained. The following characterization data is reported for the mixture of isomers with the relative integration for each signal; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.13 (m, 3.5H), 7.07-7.01 (m, 3.5H), 3.88 (dd, J = 10.9, 4.5 Hz, 0.8H), 3.81 (dd, J = 11.3, 4.1 Hz, 1.0H), 3.67 (s, 3.0H), 3.64 (s, 2.3H), 3.26-3.17 (m, 1.8H), 3.01-2.89 (m, 1.8H), 2.78-2.69 (m, 1.8H), 2.33-2.26 (m, 1.8H), 2.22-2.17 (m, 1.8 H), 2.15 (s, 2.3H), 2.09 (s, 3.0H), 2.02-1.97 (m, 1.8H), 1.70 (s, 2.3H), 1.69 (s, 3.0H), 1.58-1.50 (m, 1.8H), 1.41 (s, 2.3H), 1.37 (s, 3.0H), 1.27 (s, 2.3H), 1.25 (s, 3.0H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 202.8, 170.4, 170.3, 161.3, 161.2, 142.6, 142.2, 139.8, 139.7, 131.10, 131.07, 125.3, 125.2, 121.8, 121.2, 87.3, 87.0, 58.1, 56.9, 56.6, 56.2, 52.3, 52.1, 36.84, 36.84, 29.0, 28.6, 27.8, 27.4, 25.5, 25.41, 25.41, 25.3, 21.10, 21.05, 14.4, 14.3; HRMS-ESI: m/z calcd. for $C_{21}H_{27}NNaO_6$ [$(M$+Na$)^+$]: 412.1736, found: 412.1734.

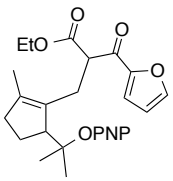
Ethyl 2-((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)-3-oxo-3-phenylpropanoate (24m)



Yellow oil, 66%; an inseparable mixture of diastereoisomers in a 4:1 ratio was obtained. The following characterization data is reported for the mixture of isomers with the relative integration for each signal; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 9.2 Hz, 2.0H), 7.97 (d, J = 9.2 Hz, 0.5H), 7.90-7.81 (m, 2.5H), 7.60-7.54 (m, 1.0H), 7.50-7.43 (m, 2.25H), 7.35-7.29 (m, 0.5H), 7.09 (d, J = 9.2 Hz, 2.0H), 6.89 (d, J = 9.2 Hz, 0.5H), 4.65 (dd, J = 10.6, 4.4 Hz, 1.0H), 4.49 (dd, J = 11.2, 4.0 Hz, 0.25H), 4.07 (q, J = 7.1 Hz, 2.0H), 4.05-3.98 (m, 0.5H), 3.49-3.42 (m, 0.25H), 3.21-3.11 (m, 1.25H), 3.10-3.04 (m, 1.0H), 2.92-2.82 (m, 1.0H), 2.77-2.69 (m, 0.25H), 2.38-2.26 (m, 0.25H), 2.25-2.12 (m, 1.25H), 2.08-1.98 (m, 0.25H),

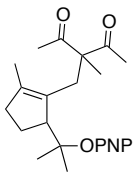
1.95-1.85 (m, 1.0H), 1.76-1.67 (m, 1.5H), 1.59 (s, 0.75H), 1.55 (s, 3.0H), 1.48-1.42 (m, 1.0H), 1.44 (s, 0.75H), 1.40 (s, 3.0H), 1.29 (s, 3.0H), 1.26 (s, 0.75H), 1.15-1.07 (m, 3.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 194.7, 170.1, 169.7, 161.5, 161.3, 142.1, 142.0, 140.1, 139.6, 137.0, 136.0, 133.4, 133.2, 131.4, 130.7, 128.53, 128.49, 128.26, 128.25, 125.3, 125.2, 121.0, 120.8, 87.2, 87.0, 61.3, 61.1, 56.7, 55.5, 53.0, 51.4, 36.9, 36.6, 28.4, 28.0, 25.7, 25.5, 25.4, 25.3, 21.7, 21.3, 14.33, 14.31, 14.0, 13.9; HRMS-ESI: *m*/*z* calcd. for $C_{27}H_{31}NNaO_6$ [$(M$+Na)$^+$]: 488.2049, found: 488.2050.

Ethyl 3-(furan-2-yl)-2-((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)-3-oxopropanoate (24n)



Orange oil, 75%; an inseparable mixture of diastereoisomers in a 11.5:1 ratio was obtained. The following characterization data is reported for the major isomer though in the ^{1}H NMR some selected signals of the minor isomer are gathered; ^{1}H NMR (500 MHz, $CDCl_3$) Major diasteroisomer: δ 8.17 (d, J = 9.2 Hz, 2H), 7.60 (dd, J = 1.7, 0.7 Hz, 1H), 7.21 (dd, J = 3.6, 0.7 Hz, 1H), 7.09 (d, J = 9.2 Hz, 2H), 6.55 (dd, J = 3.6, 1.7 Hz, 1H), 4.42 (dd, J = 11.2, 4.2 Hz, 1H), 4.08 (qd, J = 7.1, 1.9 Hz, 2H), 3.27-3.21 (m, 1H), 3.16 (dd, J = 13.9, 11.2 Hz, 1H), 2.91-2.84 (m, 1H), 2.24-2.16 (m, 1H), 2.04-1.95 (m, 1H), 1.89-1.80 (m, 1H), 1.53 (s, 3H), 1.52-1.46 (m, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H); Minor diasteroisomer, selected signals: δ 8.03 (d, J = 9.2 Hz, 2H), 7.45 (dd, J = 1.7, 0.8 Hz, 1H), 6.93 (d, J = 9.2 Hz, 2H), 6.43 (dd, J = 3.6, 1.7 Hz, 1H), 4.24 (dd, J = 11.0, 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) Major diasteroisomer: δ 184.6, 169.7, 161.5, 152.3, 146.6, 142.1, 140.1, 130.7, 125.3, 121.0, 117.8, 112.5, 87.0, 61.3, 56.5, 52.1, 36.6, 27.9, 25.5, 25.3, 21.2, 14.2, 14.0; HRMS-ESI: *m*/*z* calcd. for $C_{25}H_{29}NNaO_7$ [$(M$+Na)$^+$]: 478.1842, found: 478.1843.

3-Methyl-3-((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)pentane-2,4-dione (24t)



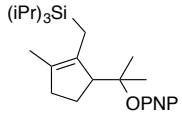
Pale yellow oil, 14%; this result was obtained by using 15 equivalents of the trapping agent, 56% yield was obtained for this compound by addition of MeI (3 eq.) on the cyclized compound **24h** with NaH (1.5 eq.) in DMF (0.1 M) stirring overnight; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.18 (m, 2H), 7.09-7.07 (m, 2H), 3.17-3.15 (m, 1H), 2.91 (d, J = 14.4 Hz, 1H), 2.87 (d, J = 9.5 Hz, 1H), 2.36-2.30 (m, 1H), 2.22-2.17 (m, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 1.99-1.91 (m, 1H), 1.71 (s, 3H), 1.69-1.65 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.9, 207.6, 161.0, 143.0, 141.5, 131.5, 125.2, 123.0, 88.0, 67.1, 57.4, 37.1, 31.7, 29.7, 27.5, 27.0, 25.9, 21.5, 18.1, 15.3; HRMS-ESI: m/z calcd. for $C_{22}H_{29}NNaO_5$ [(M+Na)$^+$]: 410.1943, found: 410.1940.

Gold(I)-carbene trapped by silanes

General procedure

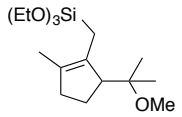
A solution of the enyne (0.10 mmol) in anhydrous CH_2Cl_2 or 1,2-dichloroethane (0.33 mL) was added onto a solution of gold catalyst (2 mol % or 5 mol%) and silane (0.30 mmol) in anhydrous CH_2Cl_2 or 1,2-dichloroethane (0.66 mL) at the desired temperature. The reaction mixture was stirred at this temperature for 16h. The reaction was quenched by the addition of a drop of Et_3N and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography using different gradients of cyclohexane and ethyl acetate to obtain the pure desired products.

Triisopropyl((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)silane (29d)



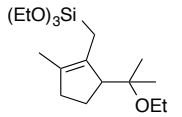
Yellow oil, 69%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18-8.15 (m, 2H), 7.08-7.05 (m, 2H), 3.07-3.04 (m, 1H), 2.37-2.27 (m, 1H), 2.15-2.06 (m, 1H), 2.02-1.94 (m, 1H), 1.91-1.83 (m, 2H), 1.78-1.74 (m, 1H), 1.71 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.06 (s, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 142.7, 134.1, 132.3, 125.2, 122.7, 88.3, 59.3, 37.1, 26.1, 25.8, 22.6, 18.9, 18.8, 15.3, 12.1, 11.7, 1.2; HRMS-ESI: *m*/*z*: calcd for $C_{25}H_{41}NNaO_3Si$ [(*M*+Na)$^+$]: 454.2748, found: 454.2742.

Triethoxy((5-(2-methoxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)methyl)silane (30a)



Yellow oil, 25%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (q, *J* = 7.0 Hz, 6H), 3.24 (s, 3H), 3.03-3.01 (m, 1H), 2.30-2.23 (m, 1H), 2.14-2.07 (m, 1H), 1.96-1.93 (m, 1H), 1.90-1.85 (m, 1H), 1.80-1.77 (m, 1H), 1.66 (s, 3H), 1.64-1.61 (m, 1H), 1.23 (t, *J* = 7.0 Hz, 9H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.4, 131.1, 78.9, 58.3, 55.1, 48.7, 36.9, 25.4, 23.5, 22.1, 18.3, 14.5, 12.5; HRMS-ESI: *m*/*z*: calcd for $C_{17}H_{34}NaO_4Si$ [(*M*+Na)$^+$]: 353.211857, found: 353.211828.

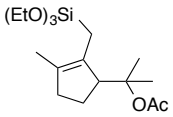
Triethoxy((5-(2-ethoxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)methyl)silane (30'a)



Yellow oil, 5%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (qd, *J* = 7.0, 0.8 Hz, 6H), 3.53-3.47 (m, 1H), 3.42-3.35 (m, 1H), 3.00-2.97 (m, 1H), 2.28-2.19 (m, 1H), 2.11-2.04 (m, 1H), 2.01-1.97 (m, 1H), 1.87-1.81 (m, 1H), 1.78-1.74 (m, 1H), 1.63 (s, 3H), 1.61-1.57 (m, 1H), 1.20 (t, *J* = 7.0 Hz, 9H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.4, 131.4, 79.0, 77.4,

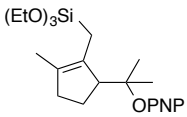
58.5, 56.0, 37.1, 25.6, 24.4, 22.6, 18.4, 16.3, 14.6, 12.8; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{36}NaO_4Si$ [(*M*+Na)$^+$]: 367.227507, found: 367.228211.

2-(3-Methyl-2-((triethoxysilyl)methyl)cyclopent-2-en-1-yl)propan-2-yl acetate (30b)



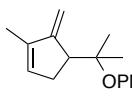
Yellow oil, 16%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (q, *J* = 7.0 Hz, 6H), 3.29-3.26 (m, 1H), 2.26-2.20 (m, 1H), 2.13-2.10 (m, 1H), 2.00 (s, 3H), 1.91-1.87 (m, 1H), 1.82-1.72 (m, 2H), 1.64 (s, 3H), 1.54-1.50 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 133.8, 130.3, 86.9, 58.5, 57.1, 36.9, 25.3, 24.9, 23.0, 22.2, 18.4, 14.7, 13.1; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{34}NaO_5Si$ [(*M*+Na)$^+$]: 381.2068, found: 381.2063.

Triethoxy((2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)methyl)silane (30d)



Yellow oil, 30%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15-8.13 (m, 2H), 7.10-7.09 (m, 2H), 3.77 (q, *J* = 7.0 Hz, 6H), 3.35-3.33 (m, 1H), 2.33-2.27 (m, 1H), 2.18-2.12 (m, 1H), 1.98-1.92 (m, 1H), 1.86-1.82 (m, 2H), 1.72-1.69 (m, 1H), 1.67 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.19 (t, *J* = 7.0 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 142.0, 134.2, 130.3, 125.3, 121.2, 87.3, 58.6, 58.0, 37.0, 25.7, 25.4, 23.5, 18.5, 14.7, 13.1; HRMS-ESI: *m*/*z*: calcd for $C_{22}H_{35}NNaO_6Si$ [(*M*+Na)$^+$]: 460.2126, found: 460.2124.

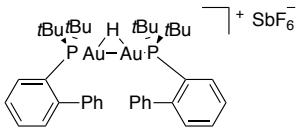
1-((2-(3-Methyl-2-methylenecyclopent-3-en-1-yl)propan-2-yl)oxy)-4-nitrobenzene (30'd)



Yellow oil, 21%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17-8.15 (m, 2H), 7.09-7.07 (m, 2H), 5.81 (s, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 3.31-3.28 (m, 1H), 2.59-2.53 (m, 1H), 2.40-2.34 (m, 1H), 1.78 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 154.9, 141.6, 133.1, 125.4, 122.3, 122.1, 104.6, 85.5, 51.1, 34.0, 24.0, 23.2, 12.9;

HRMS-ESI: *m/z*: calcd for $C_{16}H_{20}NO_3$ $[(M+H)^+]$: 274.1438, found: 274.1434.

Dinuclear gold(I) hydride complex I



$HSi(OEt)_3$ (33.92 μL, 0.18 mmol) was added over a solution of the cationic catalyst (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate **A** (50 mg, 0.061 mmol) in CH_2Cl_2 (0.61 mL) and the reaction mixture was stirred at 60 ºC for 1h. The product was filtered through a Teflon syringe filter and washed with CH_2Cl_2 to give the dinuclear gold complex **I** was obtained as a white solid (50.8 mg, 0.043 mmol, 70%). mp 212-215 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.87 (m, 2H), 7.60-7.56 (m, 4H), 7.55-7.52 (m, 4H), 7.39-7.36 (m, 2H), 7.28-7.26 (m, 2H), 7.21-7.19 (m, 4H), 1.43 (s, 18H), 1.40 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9 (m), 142.1 (m), 133.9 (s), 133.1 (m), 131.2 (s), 129.6 (s), 129.1 (s), 128.1 (s), 127.7 (t, J = 3.2 Hz), 124.6 (d, J = 3.0 Hz), 124.2 (d, J = 2.8 Hz), 58.6 (s) , 38.6 (d, J = 4.7 Hz), 38.5 (d, J = 3.5 Hz), 38.4 (d, J = 4.7 Hz), 30.8 (t, J = 3.4 Hz), 18.4 (s); ^{31}P NMR (203 MHz, $CDCl_3$) δ 70.37; HRMS-ESI: *m/z*: calcd for $C_{40}H_{55}Au_2P_2$ $[(M\text{-}SbF_6)^+]$: 991.310489, found: 991.307348.

Crystal structures

Dinuclear gold(I) hydride complex I

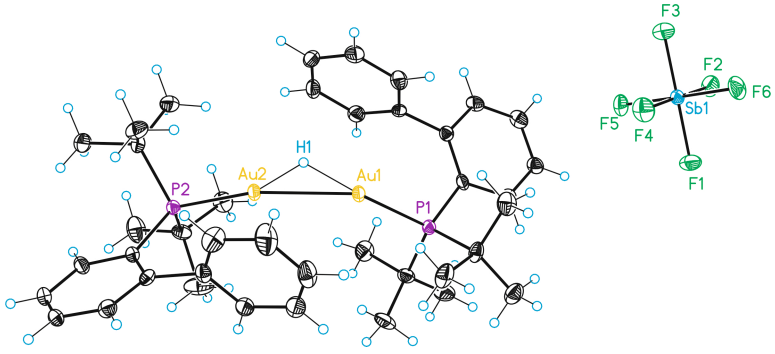


Table 1. Crystal data and structure refinement for **I**.

Empirical formula	C40 H55 Au2 F6 P2 Sb
Formula weight	1227.46
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 12.7932(10)Å a= 67.872(2)°.
	b = 13.5625(10)Å b = 66.277(2)°.
	c = 14.3378(11)Å g = 79.612(2)°.
Volume	2108.5(3) Å3
Z	2
Density (calculated)	1.933 Mg/m3
Absorption coefficient	7.706 mm-1
F(000)	1176
Crystal size	0.20 x 0.10 x 0.04 mm3
Theta range for data collection	1.648 to 30.082°.
Index ranges	-17<=h<=17,-16<=k<=19,-18<=l<=20
Reflections collected	19960
Independent reflections	10557[R(int) = 0.0319]
Completeness to theta =30.082°	85.299995%
Absorption correction	Empirical
Max. and min. transmission	0.748 and 0.562

Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	10557/ 0/ 475
Goodness-of-fit on F2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0298, wR2 = 0.0598
R indices (all data)	R1 = 0.0441, wR2 = 0.0650
Largest diff. peak and hole	1.510 and -0.985 e.Å-3

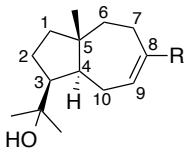
Chapter 3. Total Synthesis of (+)-Schisanwilsonene A

Introduction

Schisanwilsonenes A-C

Sesquiterpene compounds are an important class of terpenes containing three isoprene subunits. These naturally occurring products are mainly found in plants and insects and have been well known for their organoleptic properties.

Three carotane-type sesquiterpenoids, schisanwilsonenes A (**1**), B (**2**), and C (**3**) were isolated in 2009 from a medicinal plant indigenous of southern China, *Schisandra wilsoniana* (Figure 8).[142]



Schisanwilsonene A-C

A (**1**), R = CH_2OH
B (**2**), R = CH_2OAc
C (**3**), R = CHO

Schisandra wilsoniana

Figure 8. Schisanwilsonenes A (1), B (2), and C (3)

The fruits of *Schisandra wilsoniana* have been used in Chinese folk medicine to treat hepatitis. Their activity has been identified afterwards by the inhibition of the HBsAg (Hepatitis B surface Antigen) and HBeAg (Hepatitis B extracellular Antigen) secretion. These antigens are present in the hepatitis B virus serum (HBV) infected patients. Their detection indicates infection with hepatitis B virus (HBsAg) and replication activity (HBeAg). Specifically, schisanwilsonene A was tested for anti-HBV activity *in vitro* and showed antiviral properties at 50 µg/mL with 76.5% and 28.9% inhibition effect on HBsAg and HBeAg respectively. Comparative biological studies between **1**, **2** and **3** demonstrated the

142 W.-H. Ma, H. Huang, P. Zhou, D.-F. Chen, *J. Nat. Prod.* **2009,** *72*, 676-678.

influence of the substituents at the C8 position towards antiviral activity with the best results being observed with **1**.[142]

Structure elucidation of these three natural products was achieved by NMR studies and the relative configuration of schisanwilsonene A (**1**) was assigned by X-ray structure analysis.[142] The fused 5,7-membered ring skeleton of **1** has a total of three stereocenters and shows a relatively planar shape. The methyl group at C5 and the side chain at C3 are both *syn*-oriented.

Related sesquiterpenes

Other carotane-type sesquiterpenoids (also called daucanes) featuring similar hydroazulene (or bicyclo[5.3.0]decane) core that have also been isolated and characterized are depicted in Figure 9.[143]

143 (a) Y. Hashidoko, S. Tahara, J. Mizutani, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2351-2356. (b) Y. Hashidoko, S. Tahara, J. Mizutani, *Phytochemistry* **1991**, *30*, 3729-3739. (c) Y. Hashidoko, S. Tahara, J. Mizutani, *Phytochemistry* **1992**, *31*, 779-782. (d) R. Maurya, S. S. Handa, *Phytochemistry* **1998**, *49*, 1343-1345. (e) L. G. Cool, *Phytochemistry* **2001**, *58*, 969-972. (f) J. G. Urones, I. Sánchez Marcos, N. Martín Garrido, J. de Pascual Teresa, A. San Feliciano Martín, *Phytochemistry* **1989**, *28*, 183-187. (g) J. G. Urones, I. Sánchez Marcos, N. Martín Garrido, *Phytochemistry* **1990**, *29*, 2585-2589. (h) J. G. Urones, I. Sánchez Marcos, N. Martín Garrido, *Phytochemistry* **1990**, *29*, 3243-3246. (i) I. S. Marcos, I. M. Oliva, D. Diez, P. Basabe, A. M. Lithgow, R. F. Moro, N. M. Garrido, J. G. Urones, *Tetrahedron* **1995**, *51*, 12403-12416. (j) K. Nakashima, N. Fujiaki, K. Inoue, A. Minami, C. Nagaya, M. Sono, M. Tori, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1955-1962. (k) A. Umeyama, M. Nozaki, S. Arihara, *J. Nat. Prod.* **1998**, *61*, 945-947.

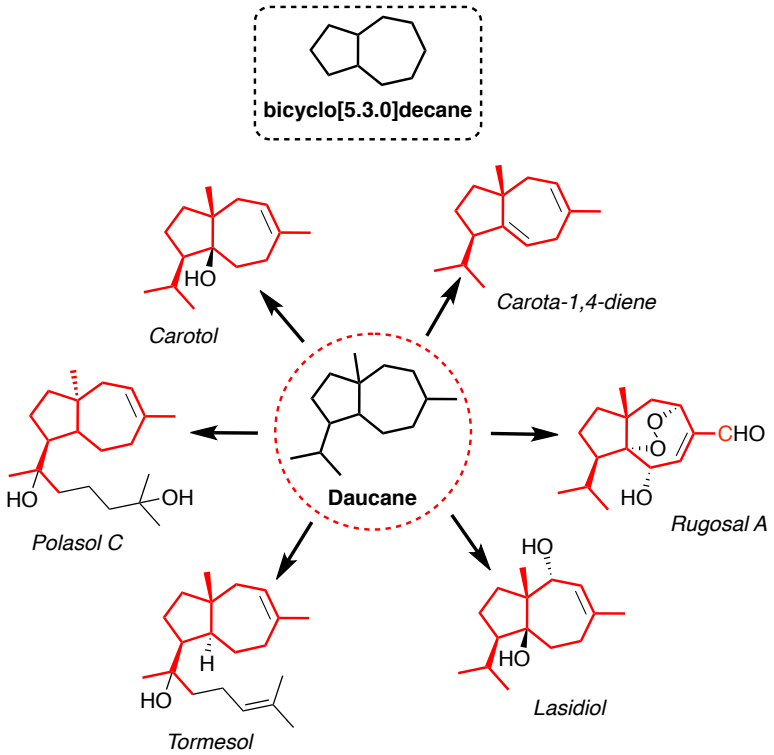
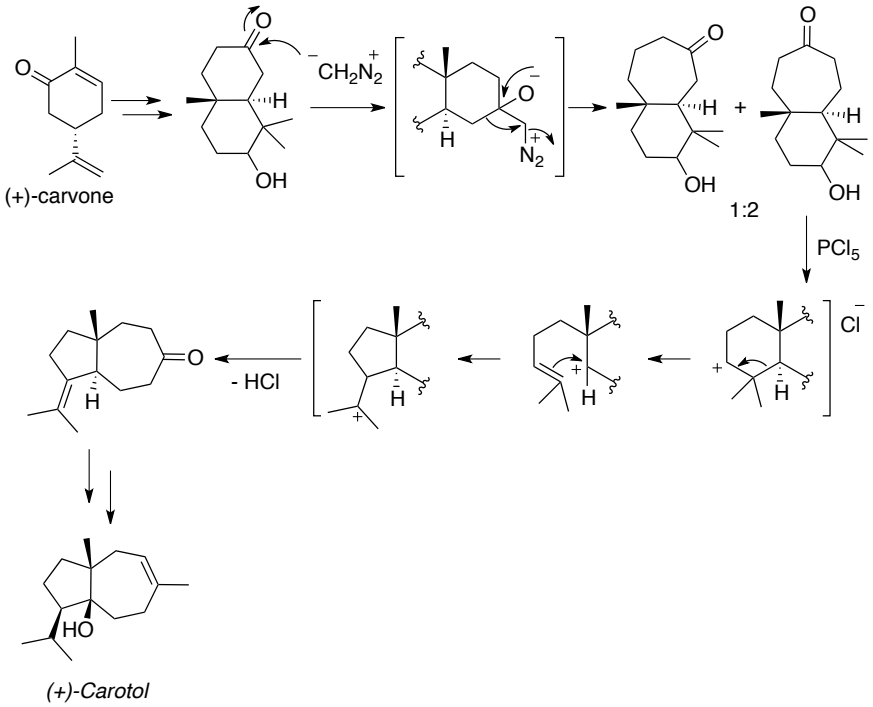


Figure 9. Structurally related daucanes

Traditionally, synthetic approaches for the construction of this ring system involve the manipulation of six-membered ring intermediates to form either the corresponding cyclopentanoid through a ring contraction or the cycloheptanoid via a ring expansion.[144] The group of Levisalles has demonstrated these combined strategies in their total synthesis of (+)-carotol.[145] Ring expansion of a fused 6,6-membered ring by means of diazomethane was followed by a ring contraction using phosphorous pentachloride (Scheme 62).

144 D. A. Foley, A. R. Maguire, *Tetrahedron* **2010**, *66*, 1131-1175.

145 H. D. Broissia, J. Levisalles, H. Rudler, *J. Chem. Soc., Chem. Commun.* **1972**, 855-855.

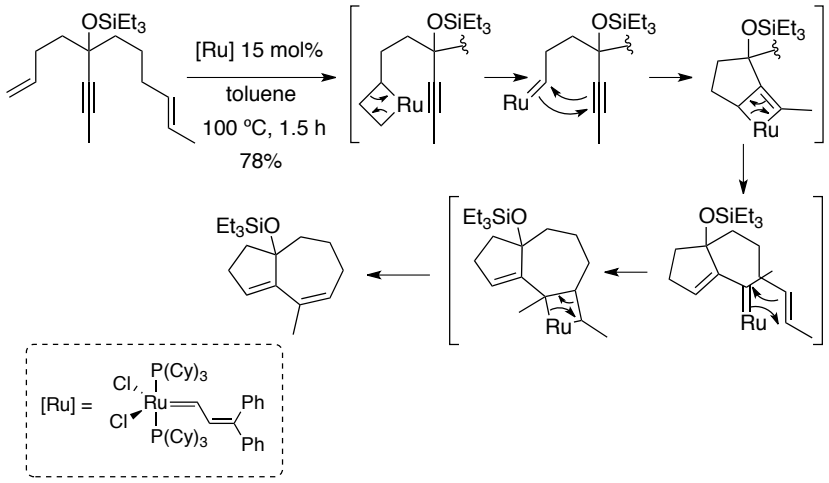


Scheme 62. Synthesis of (+)-carotol by ring expansion and ring contraction

Alternative approaches which have been employed for the formation of the bicyclo[5.3.0]decane framework includes ring-closing metathesis, cycloaddition reactions, metal catalysis as well as photochemical rearrangements.[144]

Grubbs and co-workers have developed an efficient conversion of acyclic dienynes into the fused 5,7-rings through a sequential ruthenium catalyzed intramolecular ring-closing metathesis.[146] The key step of this synthesis involves a metal alkylidene-catalyzed ene-yne-ene metathesis, forming two new rings in a single operation (Scheme 63).

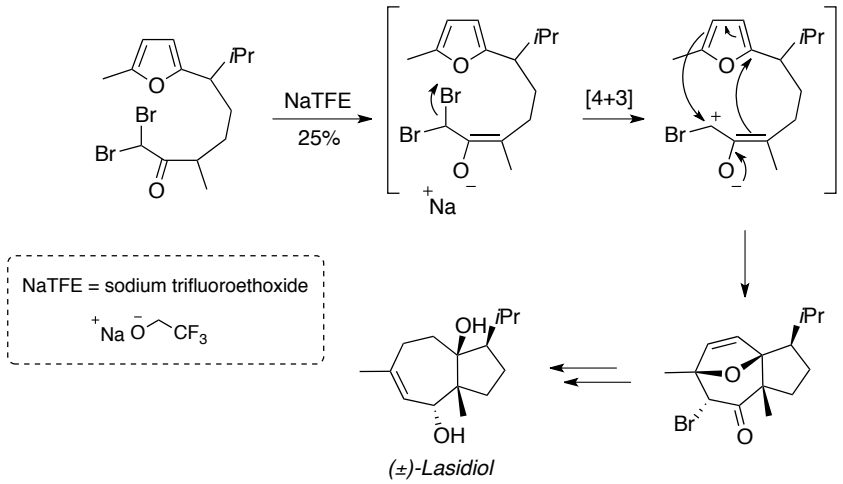
146 (a) S. H. Kim, N. Bowden, R. H. Grubbs, *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802. (b) S. H. Kim, W. J. Zuercher, N. B. Bowden, R. H. Grubbs, *J. Org. Chem.* **1996**, *61*, 1073-1081.



Scheme 63. Formation of bicyclo[5.3.0]decane via ring-closing metathesis

(4+3) Cycloaddition reactions are attractive methods for the formation of 7-membered rings. Föhlisch and co-workers employed this strategy for the key step of their racemic total synthesis of lasidiol.[147] Formation of the oxyallyl intermediate was achieved via enolate formation under basic condition followed by a dissociation of bromide. This reactive intermediate can react intramolecularly with the furan moiety to provide the cycloheptenone motif fused onto the 5-membered ring (Scheme 64). Unfortunately, the cycloaddition was not stereoselective and low yields of the desired isomer were obtained. Further group manipulation gave the (±)-lasidiol in two additional steps.

147 G. Kreiselmeier, B. Föhlisch, *Tet. Lett.* **2000**, *41*, 1375-1379.

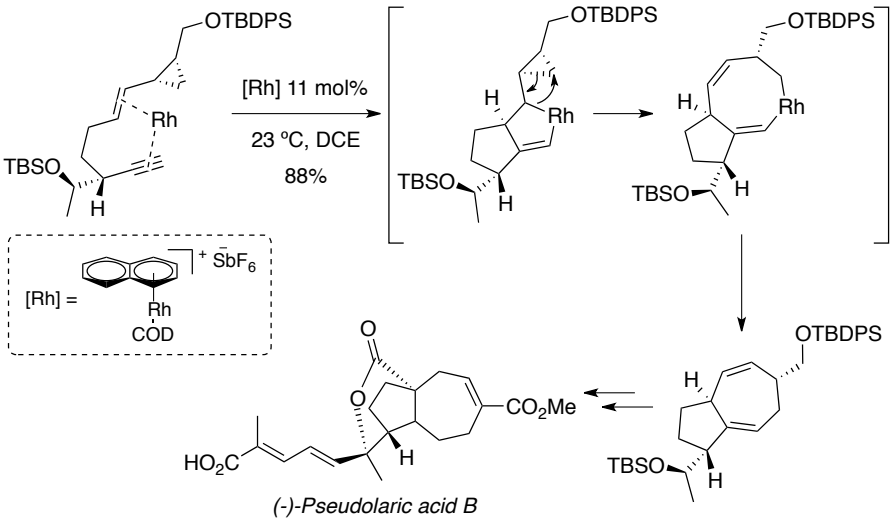


Scheme 64. Synthesis of (±)-lasidiol via [4+3] cycloaddition reaction

Wender and co-workers were the first to describe a transition-metal catalyzed (5+2) cycloaddition of vinylcyclopropanes with alkynes to obtain 7-membered ring systems.[148] The group of Trost then applied this methodology for the total synthesis of (-)-pseudolaric acid B.[149] Oxidative addition of the rhodium catalyst has lead to the corresponding metallacyclopentene. Subsequent ring-opening reaction of the cyclopropane followed by reductive elimination provides the hydroazulene core of the natural compound, which could be further derivatized into (-)-pseudolaric acid B (Scheme 65).

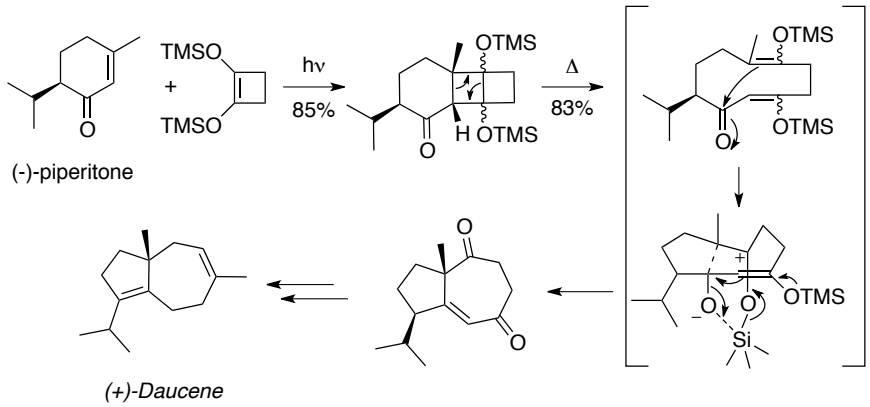
148 P. A. Wender, H. Takahashi, B. Witulski, *J. Am. Chem. Soc.* **1995**, *117*, 4720-4721.

149 B. M. Trost, J. Waser, A. Meyer, *J. Am. Chem. Soc.* **2007**, *129*, 14556-14557.



Scheme 65. Synthesis of (-)-pseudolaric acid B via Rh-catalyzed [5+2] cycloaddition

Finally, an elegant strategy based on the thermolysis of tricyclo[4.4.0.0]decanes, obtained from a [2+2] photocycloaddition, has allowed the formation of a series of carotane sesquiterpenoids. A good example of the application is shown in Scheme 66 with the synthesis of (+)-daucene.[150]

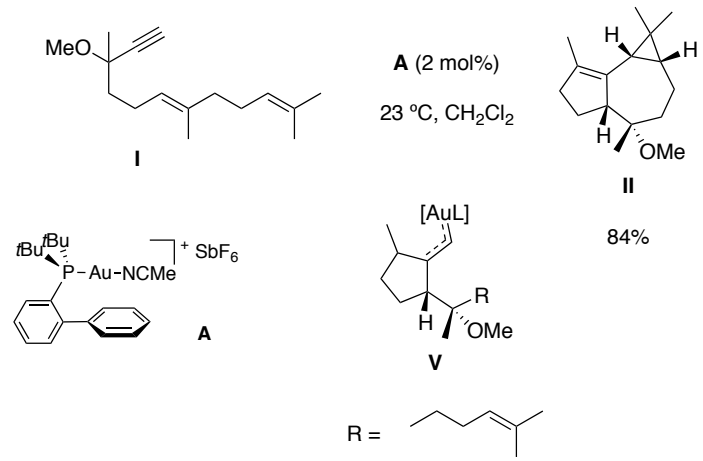


Scheme 66. Synthesis of (+)-daucene via photocycloaddition and Thermolysis

150 F. Audenaert, D. De Keukeleire, M. Vandewalle, *Tetrahedron* **1987**, *43*, 5593-5604.

1,5-Migration reaction catalyzed by gold(I)

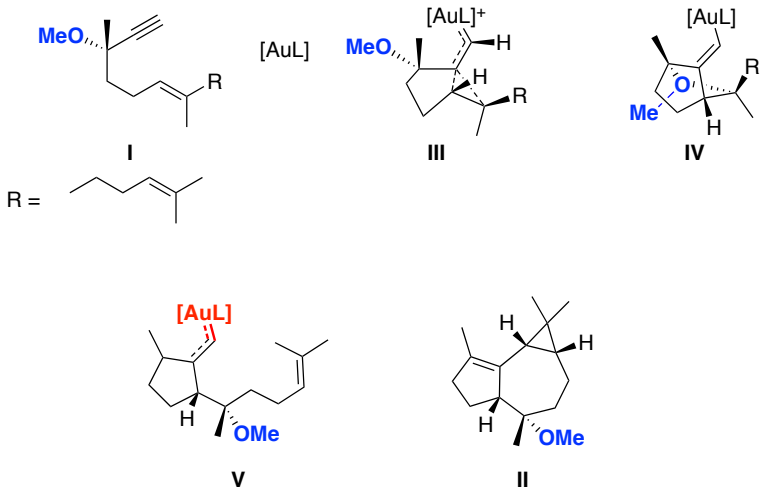
In 2009, we reported the development of a new cyclization that occurs with concomitant intramolecular 1,5-migration of propargylic OR groups.[151] Trapping of the allyl gold(I) cation **V** with a pendant alkene R led to the formation of the bicyclo[5.3.0]decane framework in a single step (Scheme 67).



Scheme 67. Intramolecular 1,5-migration of propargylic methoxy group

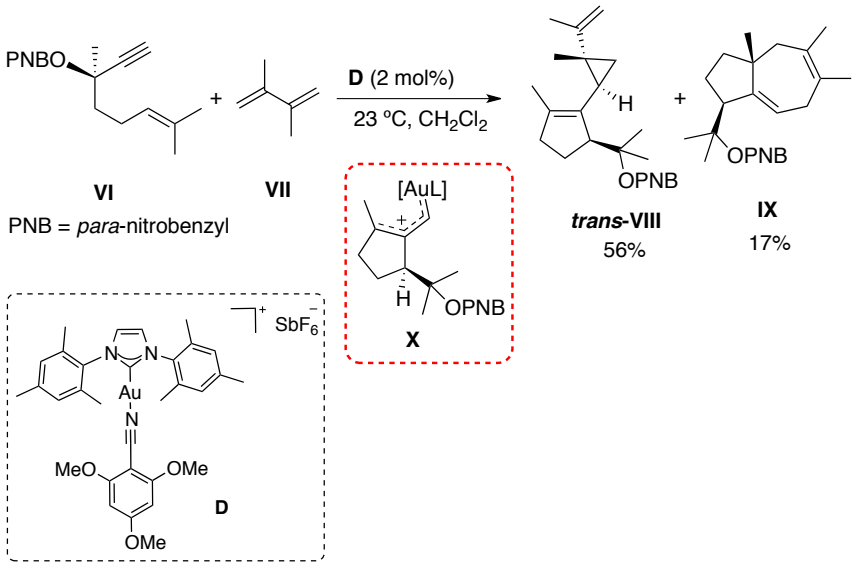
As previously mentioned (Introduction, Chapter 2), mechanistic studies demonstrated that the 1,5-migration proceeds by an intramolecular pathway (Scheme 68). Upon activation of alkyne **I** with gold(I), cyclopropyl gold(I)-carbene intermediate **III** is formed. Migration of the methoxy moiety onto the cationic center affords the oxonium bridge (**IV**), which opens to give allyl gold(I) cation **V**. Then, an intramolecular cyclopropanation reaction onto the tethered alkene gives tricyclic compound **II**. It is worth noting that the rate of the migration of the methoxy group is significantly faster than the direct cyclopropanation by the pendant alkene onto the cyclopropyl gold(I)-carbene **III**.

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



Scheme 68. Proposed mechanism for the 1,5-migration reaction

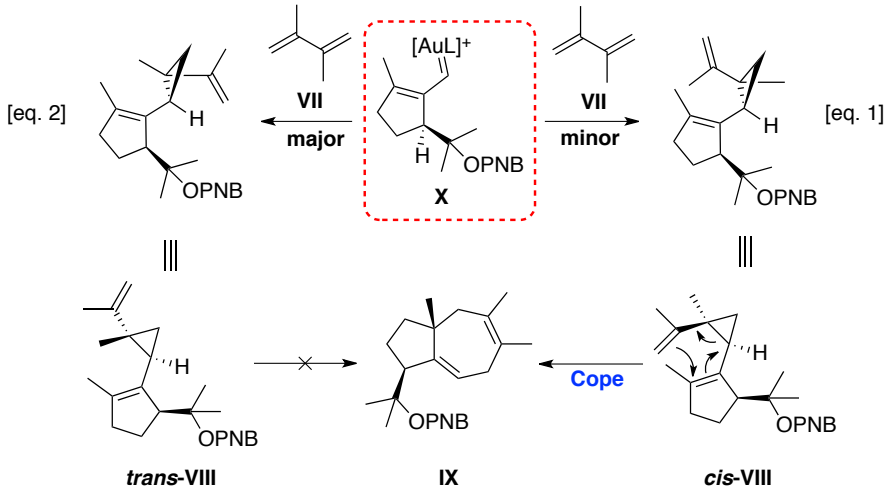
During our studies, when we attempted to trap allyl gold(I) cation **X** intermolecularly with diene **VII**, an interesting result was observed. This reaction not only afforded the desired divinylcyclopropane ***trans*-VIII** but also the hydroazulene **IX** (Scheme 69).



Scheme 69. Formation of divinylcyclopropane trans-VIII and hydroazulene IX

Compound **IX** arises from a Cope rearrangement[152] of divinylcyclopropane ***cis*-VIII**, formed as the minor diastereoisomer of the attack of diene **VII** onto gold(I)-carbene **X** (Scheme 70, [eq. 1]).

152 (a) T. Hudlicky, R. Fan, J. W. Reed, K. G. Gadamasetti, *Org. React.* **1992**, *41*, 1-133. (b) M. Zora, *J. Org. Chem.* **2005**, *70*, 6018-6026.



Scheme 70. Formation of IX

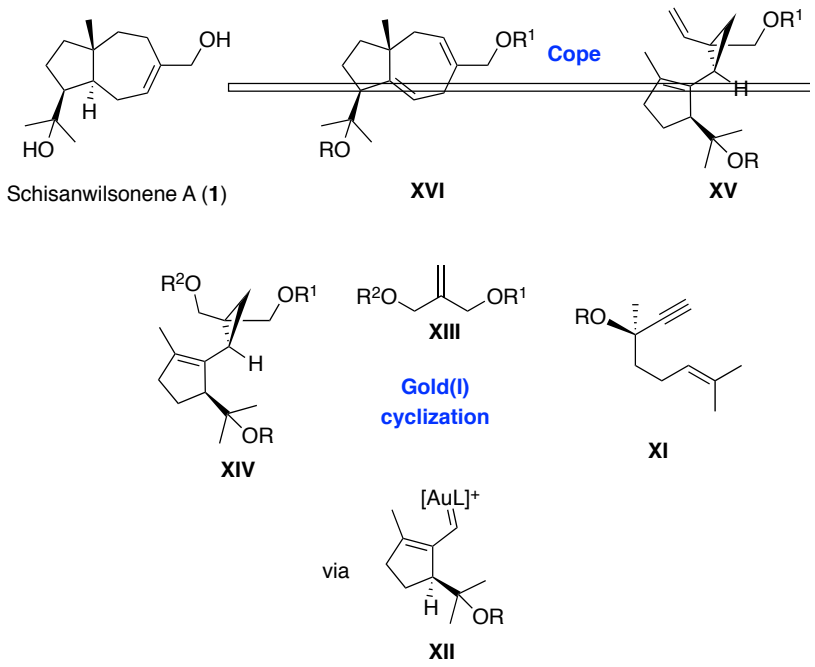
The cyclopropanation reaction for the formation of cyclopropane **VIII** with a *trans*-configuration is favored due to a less sterically hindered approach of the diene during the transition state (Scheme 70, [eq. 2]). On the other hand, ***cis*-VIII**, resulting from the least favored approach of diene **VII** onto gold(I)-carbene **X**, spontaneously undergoes a facile Cope rearrangement due to the *syn*-relationship of the olefins around the cyclopropyl ring (Scheme 70, [eq. 1]).

This minor product was interesting as it features a fused 5,7-membered rings with a *syn*-relationship between the methyl group and the side chain; a motif found in the core scaffold of schisanwilsonene A.

Objective

As part of our investigations on the application of gold catalysis in the synthesis of naturally occurring sesquiterpenes and diterpenes, our attention was focused on (+)-schisanwilsonene A (**1**) for which the absolute configuration had not been assigned.

We envisioned a retrosynthetic approach as presented in Scheme 71 for the generation of schisanwilsonene A. Schisanwilsonene A (**1**) could be obtained from functional group manipulation of **XVI**, the product of a Cope rearrangement of cyclopropane **XV** with the required *cis*-configuration. Intermediate **XV** could be synthesized from **XIV** through a protecting group manipulation, oxidation, and Wittig reaction sequence. Finally, the key intermediate **XIV** would be produced through the intermolecular cyclopropanation reaction of alkene **XIII** with the cationic allyl gold(I) intermediate **XII**, generated *via* gold(I)-catalyzed intramolecular 1,5-migration of enyne **XI**.



Scheme 71. Retrosynthetic analysis for the synthesis of schisanwilsonene A (1)

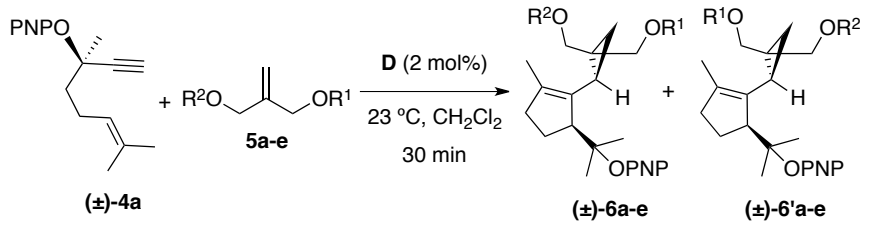
Results and discussion

Total synthesis of (±)-schisanwilsonene A

Study on the gold(I)-catalyzed 1,5-migration[153]

Our first approach was based on the study of unsymmetrical alkenes containing orthogonal protecting groups (Table 26, entries 1-3). Enyne **(±)-4a** bearing a *para*- nitrophenyl ether on the propargylic position was chosen as the model substrate as good migrating ability of this protecting group had been previously displayed. We also selected gold(I) complex **D** to catalyze this transformation based on the work using diene **VII** (Scheme 69).[118]

Table 26. Study of alkenes 5 as trapping agent



Entry	Alkene	R^1	R^2	Outcome	*dr*[a]	Yield (%)[b]
1	**5a**	TES	Ac	**(±)-6a/(±)-6'a**	1.8:1	-
2	**5b**	TBS	Ac	**(±)-6b/(±)-6'b**	2:1	-
3	**5c**	TIPS	Ac	**(±)-6c/(±)-6'c**	4:1	-
4	**5d**	Ac	Ac	decomposition	-	-
5	**5e**	TBS	TBS	**(±)-6e**	-	79

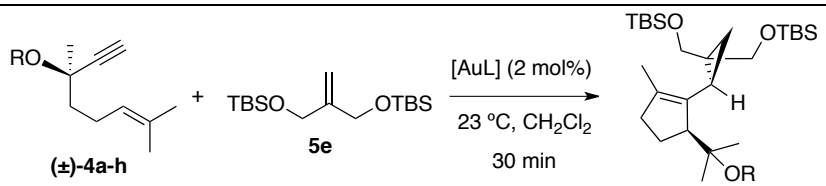
[a] *dr* determined by ^{1}H NMR analyses. [b] Isolated yield.

153 Optimization was carried out in collaboration with Nicolas Delpont and Dr. Julien Ceccon.

The steric hindrance of the silyl protecting groups was found to be essential in the diastereoselectivity (Table 26, entries 1-3). Selectivity improved from the smaller triethylsilyl ether to the more bulkier triisopropylsilyl ether (Table 26, entry 1 vs. 3). Unfortunately, the conversion to **(±)-6** and **(±)-6'** was generally low and in all cases, the desired diastereoisomer could not be isolated from the crude mixture. We therefore turned our attention to symmetrically bis-protected alkenes (Table 26, entries 4-5). Bis-acetate protected alkene **5d** only led to decomposition of the starting enyne (entry 4). Gratifyingly, the use of bis-silyl ether group (**5e**) afforded the desired product in high yields (entry 5).

Further optimization were performed to study the effect of different migrating groups on the reaction as well as fine tuning the gold(I) catalysts. Representative examples are shown in Table 27.

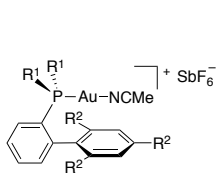
Table 27. Study with several migrating groups and gold(I)-catalysts



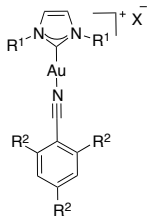
Entry	R	5e (equiv)	[AuL]	Yield (%)[a]
1	PNP **(±)-4a**	2	**D**	**(±)-6e** (79)[b]
2	H **(±)-4b**	2	**D**	complex mixt.
3	TIPS **(±)-4c**	2	**D**	complex mixt.
4	Me **(±)-4d**	2	**D**	**(±)-6h** (traces)
5	Bn **(±)-4e**	2	**D**	-[c]
6	PNB **(±)-4f**	2	**D**	-[c]
7	PMB **(±)-4g**	2	**D**	-[c]

8	Ac **(±)-4h**	2	**D**	**(±)-6l** (43)[b]
9	**(±)-4a**	2	**A**	**(±)-6e** (57)
10	**(±)-4a**	2	**B**	**(±)-6e** (35)
11	**(±)-4a**	2	**E**	**(±)-6e** (63)
12	**(±)-4a**	1.5	**D**	**(±)-6e** (72)
13	**(±)-4h**	2	**A**	**(±)-6l** (52)[b]
14	**(±)-4h**	2	**B**	**(±)-6l** (22)
15	**(±)-4h**	2	**E**	**(±)-6l** (23)
16	**(±)-4h**	1.5	**A**	**(±)-6l** (55)[b]

[a] Determined by ^{1}H NMR analyses using diphenylmethane as internal standard. [b] Isolated yield. [c] C-H activation product.[118]



A, R^1 = *t*Bu, R^2 = H
B, R^1 = *t*Bu, R^2 = *i*Pr



D, R^1 = Mes, R^2 = OMe, X = SbF_6
E, R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = H, X = SbF_6

While most of the alternative protecting groups failed to afford the desired product (Table 27, entries 2-7), **(±)-4h** was found to be a suitable substrate and gave the desired **(±)-6l** in 43% isolated yield (Table 27, entry 8). This result is remarkable considering the propensity for propargyl acetates to undergo gold(I)-promoted 1,2- or 1,3-migrations in related systems.[154] We

154 (a) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692-706. (b) X. - Z. Shu, D. Shu, C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698-7711. (c) C. Fehr, J. Galindo, *Angew. Chem. Int. Ed.* **2006**, *45*, 2901-2904. (d) O. N. Faza, C. S. López, R. Álvarez, A. R. de Lera, *J. Am. Chem. Soc.* **2006**, *128*, 2434-2437. (e) N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750-2752. (f) J. Marco-Contelles, E. Soriano, *Chem. Eur. J.* **2007**, *13*, 1350-1357. (g) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo, *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721. (h) Y. Zou, D. Garayalde, Q. Wang, C. Nevado, A. Goeke, *Angew. Chem. Int. Ed.* **2008**, *47*, 10110-10113. (i) N. Marion, G. Lemière, A. Correa, C. Costabile, R. S. Ramón, X. Moreau, P. de Frémont,

can therefore concluded that the 1,6-enyne cyclization is faster than the propargylic acetate migration.

Further optimization of both **(±)-6e** and **(±)-6l** was next conducted with different gold(I) catalysts (Table 27, entries 9-16). Under our optimized reaction conditions, 55% yield of compound **(±)-6l** was isolated by employing gold(I) catalyst **A** (Table 27, entry 16) and **(±)-6e** was obtained in 79% yield with no further improvement on the previous reaction conditions (Table 27, entry 1).

While enyne **(±)-4a** demonstrated to be superior to other substrates with alternative protecting groups for this gold(I)-catalyzed transformation, the enantioselective synthesis of such substrate is quite challenging since no known protocol has been reported to date.[155] For this reason, the approach using a phenolic protecting group would achieve the racemic total synthesis of schisanwilsonene A.

Total synthesis of (±)-schisanwilsonene A (1)

Since symmetrical alkenes were found to be the best for this gold(I) transformation, our attention was then focused on the differentiation of the two alcohol of the cyclopentene moiety. We envisaged a double deprotection of the alcohols followed by a selective protection of the least hindered *trans* alcohol, allowing us to transform the remaining free alcohol

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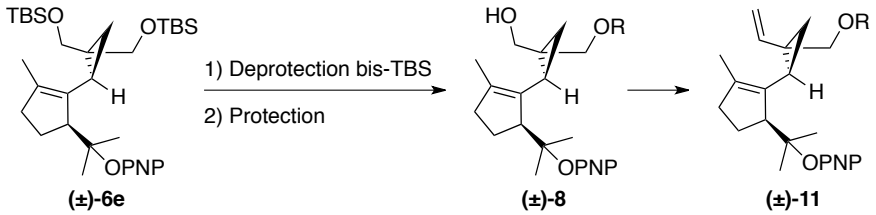
R. Dahmane, A. Hours, D. Lesage, J.-C. Tabet, J. - P. Goddard, V. Gandon, L. Cavallo, L. Fensterbank, M. Malacria, S. P. Nolan, *Chem. Eur. J.* **2009**, *15*, 3243-3260. (j) C. Fehr, B. Winter, I. Magpantay, *Chem. Eur. J.* **2009**, *15*, 9773-9784. (k) P. Mauleón, J. L. Krinsky, F. D. Toste, *J. Am. Chem. Soc*. **2009**, *131*, 4513-4520. (l) D. Garayalde, C. Nevado, *ACS Catal.* **2012**, *2*, 1462-1479.

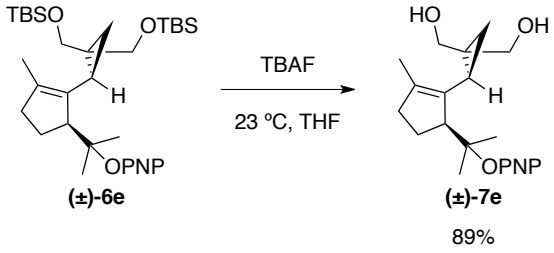
155 (a) For a synthesis of racemic propargylic aryl ethers, see: J. D. Godfrey, R. H. Mueller, T. C. Sedergran, N. Soundararajan, V. J. Colandrea, *Tet. Lett.* **1994,** *35*, 6405-6408. (b) For an example of chiral propargylic aryl ethers obtained via aziridine opening: E. M. Forbeck, C. D. Evans, J. A. Gilleran, P. Li, M. M. Joullié, *J. Am. Chem. Soc.* **2007,** *129*, 14463-14469.

into the corresponding terminal alkene required for the Cope rearrangement (Scheme 72).



Scheme 72. Selective transformation of (±)-6e into (±)-10

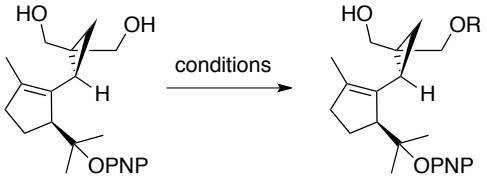
Pleasingly, desilylation reaction of **(±)-6e** using TBAF in THF at room temperature was achieved in 89% yield (Scheme 73).



Scheme 73. Synthesis of diol (±)-7e

Subsequent protection of the least hindered *trans* hydroxyl group was studied next under different reaction conditions (Table 28).

Table 28. Studies of the selective alcohol protection



(±)-7e **(±)-8e-f**

Entry	Conditions	T (ºC)	*dr*	Yield (%)[a]
1	Ac_2O (1.05 equiv), Pyridine (2 equiv), DMAP (0.05 equiv)	0	3:1	**(±)-8e** 72
2	Ac_2O (1.05 equiv), Pyridine (2 equiv), DMAP (0.05 equiv)	-20	3:1	**(±)-8e** 51[b]
3	Ac_2O (1.05 equiv), DBU (2 equiv), DMAP (0.05 equiv)	0	2.8:1	**(±)-8e** 63
4	Ac_2O (1.05 equiv), 2,6-lutidine (2 equiv), DMAP (0.05 equiv)	0	2.7:1	**(±)-8e** 67
5	PivCl (1.05 equiv), NEt_3 (2 equiv)	0	3:1	**(±)-8f** 46[b]

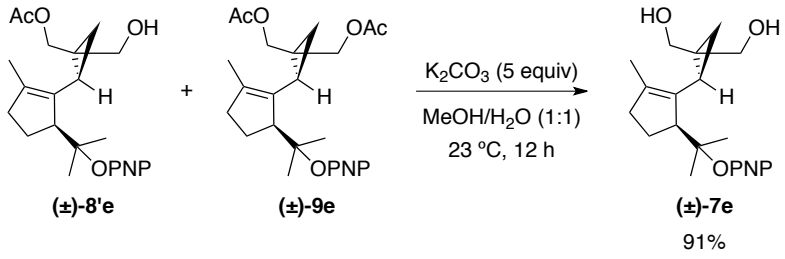
[a] Isolated yield. [b] Full conversion not achieved after being stirred overnight at the mentioned temperature.

Selective monoprotection of diol **(±)-7e** into **(±)-8e** could be achieved in good yields and acceptable selectivity under standard reaction conditions (Table 28, entry 1). Attempts to improve the diastereomeric ratio lowering the reaction temperature failed and simply slowed the reaction rate while keeping the same diastereoselectivity (Table 28, entry 2). Usage of several

bases was also fruitless and gave no further improvement (Table 28, entries 3 and 4). Replacement of the acetic anhydride with the bulkier pivalic anhydride led to similar results (Table 28, entry 5).

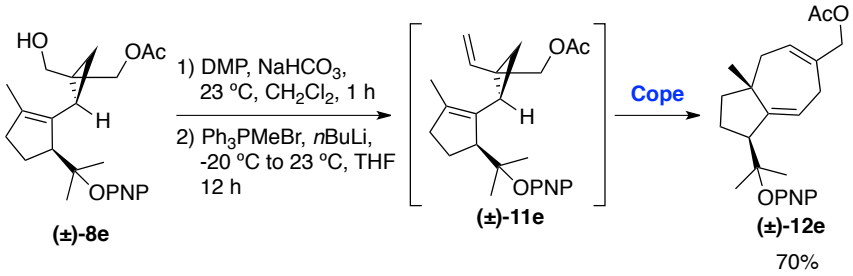
With the optimal conditions in hand, we were able to obtain the desired diastereomer as the major product (**(±)-8e**) in 72% yield, with the protected alcohol *trans* to the cyclopentene moiety, which was confirmed by nOe experiments.

Additionally, the bis-protected diol was observed in every reaction in approximately 5% yield. Nevertheless, the three compounds could be easily separated by chromatography, and both bis-protected compound **(±)-9e** and undesired diastereoisomer **(±)-8'e** could be recycled to form diol **(±)-7e** (Scheme 74).



Scheme 74. Recycling procedure for the recovery of (±)-7e

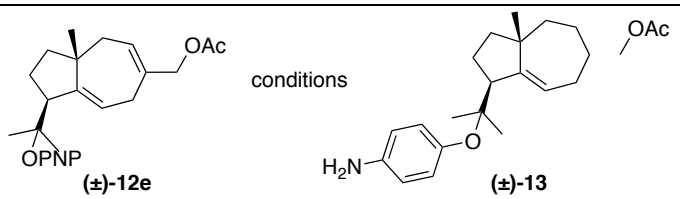
A two-steps protocol for the transformation of alcohol **(±)-8e** into the required diene **(±)-11e** for the Cope rearrangement was accomplished *via* Dess-Martin oxidation and subsequent Wittig methylenation of the resulting aldehyde **(±)-10e**. The diene **(±)-11e** smoothly rearranged to bicyclo[5.3.0]decane **(±)-12e** *via* [3,3] sigmatropic rearrangement, as predicted, by slowly warming the reaction from -20 ºC to room temperature, in a 70% overall yield for the two steps (Scheme 75).



Scheme 75. Formation of (±)-12e

As skipped dienes are well known to be sensitive to air,[143a] **(±)-12e** was kept under inert atmosphere and was quickly submitted to the following hydrogenation reaction (Table 29).

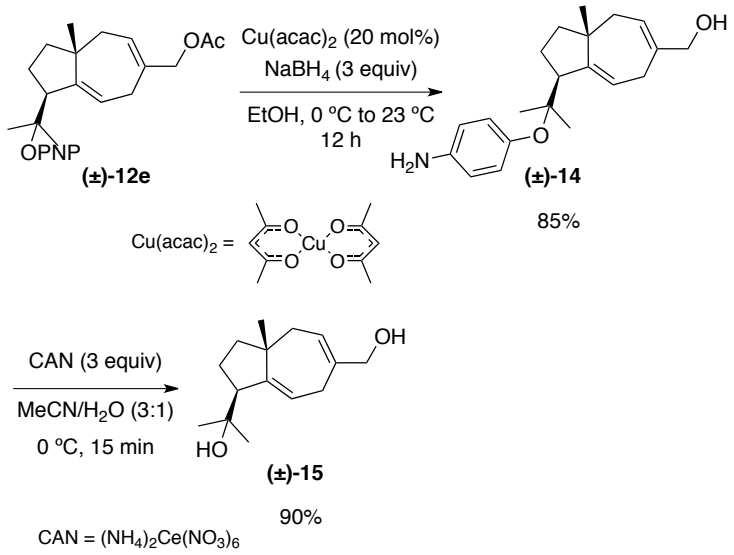
Table 29. Hydrogenation reaction studies



Entry	Conditions	*dr*[a]
1	H_2 (50 bar), Pd/C (0.25 equiv) MeOH (0.1 M), 23 ºC	5:1
2	H_2 (50 bar), $Pd(OH)_2$/C (0.25 equiv), MeOH (0.1 M), 23 ºC	5:1
3	H_2 (50 bar), Wilkinson's catalyst (0.25 equiv), MeOH (0.1 M), 23 ºC	complex mixture
4	H_2 (50 bar), Raney Ni (0.25 equiv), MeOH (0.1 M), 23 ºC	2:1

[a] *dr* determined by ^{1}H NMR analysis of the crude mixture. Wilkinson's catalyst = $RhCl(PPh_3)_3$.

Unfortunately, complete hydrogenation of **(±)-12e** diene was never achieved (Table 29, entries 1-4). The reaction led to mono-alkene compound **(±)-13** containing an aniline moiety resulting from the reduction of the nitro functionality of starting **(±)-12e**. The trisubstituted bridge alkene was quite difficult to hydrogenate due to the high steric hindrance from the adjacent functionalities. To overcome this problem, both the acetate and the *para*-nitrophenyl moieties were cleaved (Scheme 76).

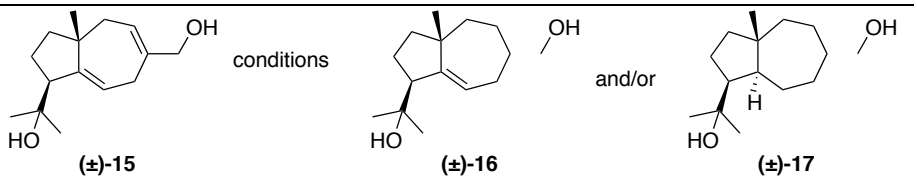


Scheme 76. Formation of diol (±)-15e

After reduction of the nitro group and cleavage of the acetate using copper(II) acetylacetonate and sodium borohydride, the aniline was removed from **(±)-14** with cerium ammonium nitrate (CAN) to give **(±)-15** in good yield.

With diol **(±)-15** in hand, a new study for the hydrogenation of both alkenes was performed (Table 30).

Table 30. Hydrogenation reaction using (±)-15e



(±)-15 **(±)-16** **(±)-17**

Entry	Catalyst (0.25 equiv)	Conditions	Outcome	Yield (%)[a]
1	Pd/C	H_2 (50 bar), EtOAc, 23 ºC, 2 days	**(±)-15** + **(±)-16** 1:2	-
2	Pd/C	H_2 (50 bar), MeOH, 23 ºC, 2 days	**(±)-15** + **(±)-16** 1:2	-
3	Pd/C	H_2 (80 bar), MeOH, 23 ºC, 2 days	**(±)-16**	-
4	$Pd(OH)_2/C$	H_2 (80 bar), MeOH, 23 ºC, 2 days	**(±)-15** + **(±)-16** 1:2	-
5	Wilkinson's catalyst	H_2 (80 bar), MeOH, 23 ºC, 2 days	**(±)-15** + **(±)-16** 1:2	-
6	Raney Ni	H_2 (80 bar), MeOH, 23 ºC, 2 days	**(±)-15** + **(±)-16** 1:3	-
7	Raney Ni	H_2 (80 bar), acetone, 23 ºC, 2 days	**(±)-16**	-

8	Pd/C	H_2 (80 bar), MeOH, 63 ºC, 2 days	**(±)-16**	-
9	Raney Ni	H_2 (80 bar), acetone, 63 ºC, 60-70 h	**(±)-17**	85 *dr* = 2:1

[a] Isolated yield.

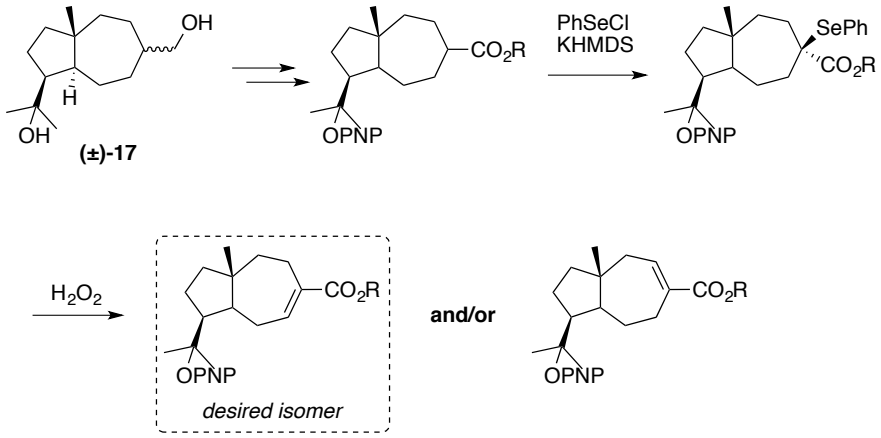
Wilkinson's catalyst = $RhCl(PPh_3)_3$.

First, the reaction was conducted using Pd/C under 50 bars of hydrogen in ethyl acetate or methanol at room temperature for two days (Table 30, entries 1 and 2). Since only a mixture of mono-saturated compounds **(±)-16** and starting diol **(±)-15** was obtained, the pressure was further increased to 80 bars (Table 30, entry 3). Complete conversion to mono-saturated **(±)-16** could be obtained under these conditions. Being unable to hydrogenate the remaining alkene, our attention was turned to alternative hydrogenation catalysts. A screening of common catalysts used in hydrogenation reaction was performed (Table 30, entries 5-7). Having identified two catalysts capable of forming **(±)-16**, Raney nickel and Pd/C (Table 30, entries 3 and 7), we decided to further push the reaction by elevating the temperature to 63 ºC (Table 30, entries 8-10). Finally, completely saturated compound **(±)-17** could be isolated when employing Raney nickel with 80 bars of hydrogen at 63 ºC in acetone for 60-70 h, refilling the apparatus with hydrogen every 12 h (Table 30, entry 9).

Our next concern was the introduction of the double bond in the 7-membered ring at the desired position. Inspired by the work of Winkler and co-workers on the synthesis of ingenol analogs,[156] we thought of introducing a selenide moiety at the α-position of a preformed ester. The

156 J. D. Winkler, B. - C. Hong, A. Bahador, M. G. Kazanietz, P. M. Blumberg, *J. Org. Chem.* **1995**, *60*, 1381-1390.

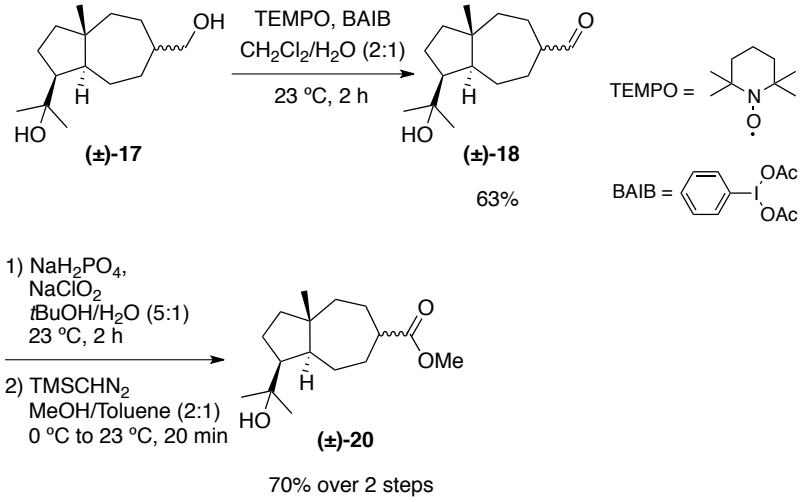
resulting product would give the unsaturated ester upon elimination of the oxidized selenium by hydrogen peroxide (Scheme 77). However, we were well aware of the potential problems with the regiochemical control of this oxidative elimination.



Scheme 77. Introduction of the double bond

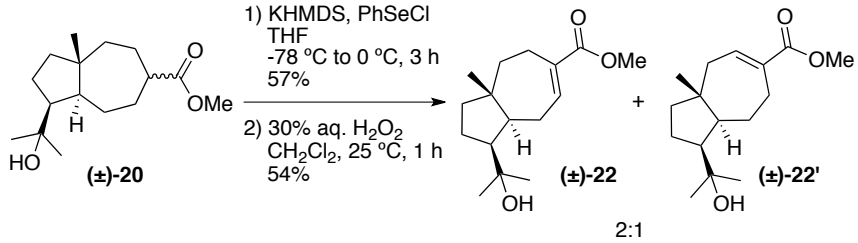
In order to apply the conditions described by the group of Winkler,[156] the primary alcohol needed to be transformed into ester **(±)-20**. Oxidation of the alcohol into the corresponding aldehyde **(±)-18**, which was further oxidized *via* a Pinnick oxidation,[157] and esterification of the resulting carboxylic acid gave the desired product in a 70% overall yield (Scheme 78).

157 (a) B. O. Lindgren, T. Nilson, *Acta Chem. Scand.* **1973**, *27*, 888-890. (b) B. S. Bal, W. E. Childers Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091-2096.



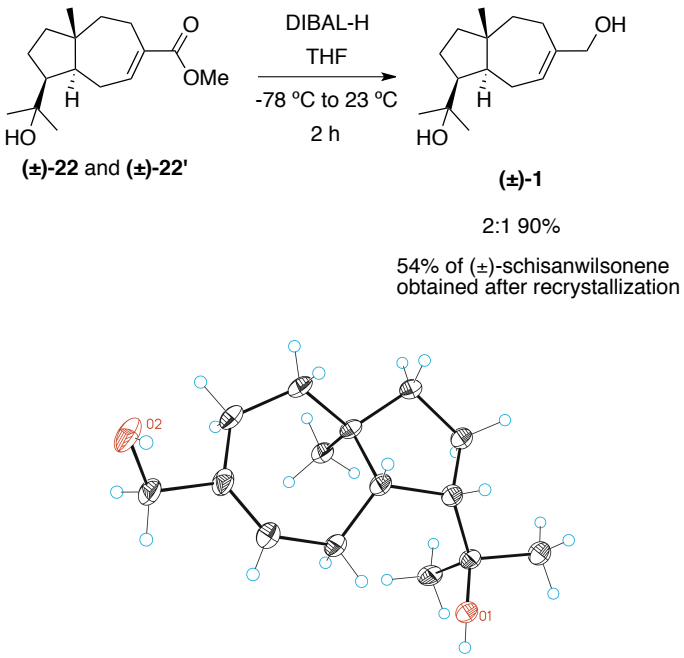
Scheme 78. Formation of ester (±)-20

Selenylation reaction of the potassium enolate of **(±)-20**, with subsequent elimination of the selenoxide formed by oxidation with hydrogen peroxide led to both unsaturated esters **(±)-22** and **(±)-22'** in a 2:1 regioisomeric ratio, favoring of the desired α,β-unsaturated methyl ester **(±)-22** (Scheme 79).



Scheme 79. Formation of (±)-22

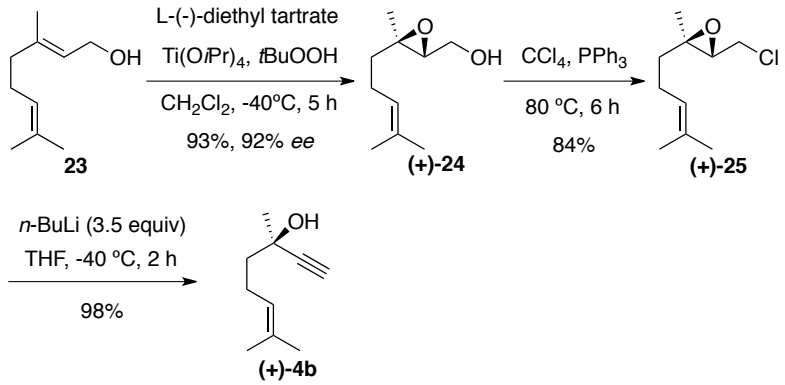
Finally, DIBAL-H 1,2-reduction of the ester afforded (±)-schisanwilsonene **(±)-1**. Recrystallization from a mixture of cyclohexane and EtOAc gave crystals of good quality for X-ray diffraction which allowed us to confirm the relative configuration of this natural compound (Scheme 80).



Scheme 80. (±)-Schisanwilsonene (±)-1

Enantioselective synthesis of (+)-schisanwilsonene A (1)

The enantioselective approach started with the preparation of enyne **(+)-4b** through a previously reported three-steps procedure (Scheme 81).[158] Sharpless asymmetric epoxidation[159] of commercially available geraniol **23** afforded **(+)-24** in 93% yield and 92% *ee*. Substitution of the primary alcohol by chloride using Appel reaction conditions[160] provided chloro epoxide **(+)-25** in 84% yield. Subsequent elimination with *n*BuLi led to propargylic alcohol **(+)-4b** in 98% yield.



Scheme 81. Synthesis of (+)-4b

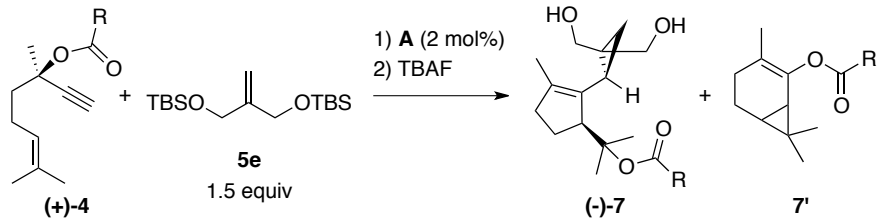
The next important task was finding an alternative migrating group to the *para*-nitrophenyl ether, which could be introduced without loss of enantiopurity. A carboxylate or carbonate **(±)-4h** seemed a reasonable candidate for this gold transformation. We therefore screened several serivatives for the key transformation using JohnPhos/gold(I) **A** as the catalyst (Table 31).

158 D. K. Mohapatra, C. Pramanik, M. S. Chorghade, M. K. Gurjar, *Eur. J. Org. Chem.* **2007**, 5059-5063.

159 Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987,** *109*, 5765-5780.

160 R. Appel, *Angew. Chem. Int. Ed.* **1975**, *14*, 801-811.

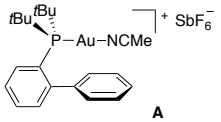
Table 31. Screening of different migrating groups



(+)-4 **5e** 1.5 equiv **(-)-7** **7'**

Entry	Enyne (R)	Yield (%)[a] ((-)-7/7')	*ee* (%)
1	OMe **(+)-4i**	27 (**(-)-7m/7'm** 100/0)	84
2	O-allyl **(+)-4j**	27 (**(-)-7n/7'n** 100/0)	78
3	*p*FC_6H_4 **(+)-4k**	17 (**(-)-7o/7'o** 100/0)	81
4	tolyl **(+)-4l**	11 (**(-)-7p/7'p** 100/0)	77
5	*p*IC_6H_4 **(+)-4m**	29 (**(-)-7q/7'q** 100/0)	77
6	*p*$OMeC_6H_4$ **(+)-4n**	27 (**(-)-7r/7'r** 37/63)	77
7	*p*$NMe_2C_6H_4$ **(+)-4o**	46 (**(-)-7s/7's** 0/100)	-
8	Me **(+)-4h**	45 (**(-)-7l/7'l** 100/0)	82

[a] Isolated yield over 2 steps.

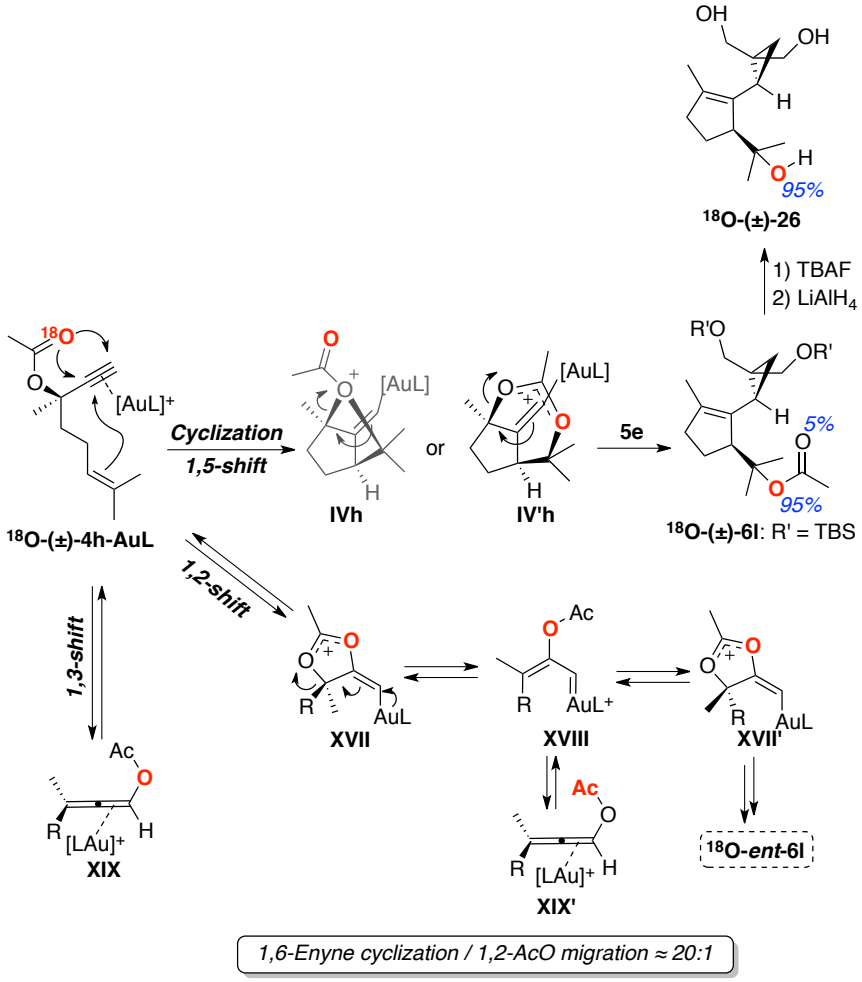


A

Most of the protecting groups revealed to be incompatible with this reaction and **(-)-7** were isolated in low yields from products of decomposition (Table 31, entries 1-7). Additionally, products **7'** resulting from the 1,2-shift acyl shift followed by cyclopropanation reaction were observed in some cases (Table 31, entries 6-7).[154] Propargylic acetate **(+)-4h** was the optimal migrating group, allowing us to obtain **(-)-7l** in moderate yield with only slight loss of enantiopurity after this reaction sequence (Table 31, entry 8).

An approximate 10% decrease in the *ee* between **(+)-4h** and **(-)-7l** from 92% to 82% (decrease in the *er* from 96:4 to 91:9) was observed. A competitive minor pathway, which could proceed through a 1,2-migration via achiral intermediate **XVIII** could explain this result, suggesting the 1,6-enyne cyclization is approximately 20 times faster than the propargylic acetate migration in this case (Scheme 82).

To gain further insight into the mechanism, **^{18}O-(±)-4h** was also prepared containing a ^{18}O label on the acetyl group to determine whether the 1,5-migration occurs via the five- (**IVh**) or seven-membered ring (**IV'h**) intermediates (Scheme 82). Mass spectral data of the resulting acetate **^{18}O-(±)-6l** as well as the triol derivative **^{18}O-(±)-26** revealed that the ^{18}O had been preferentially transferred through a migration process consistent via intermediate **IV'h**.



Scheme 82. ^{18}O labeling study of the cyclization/migration process

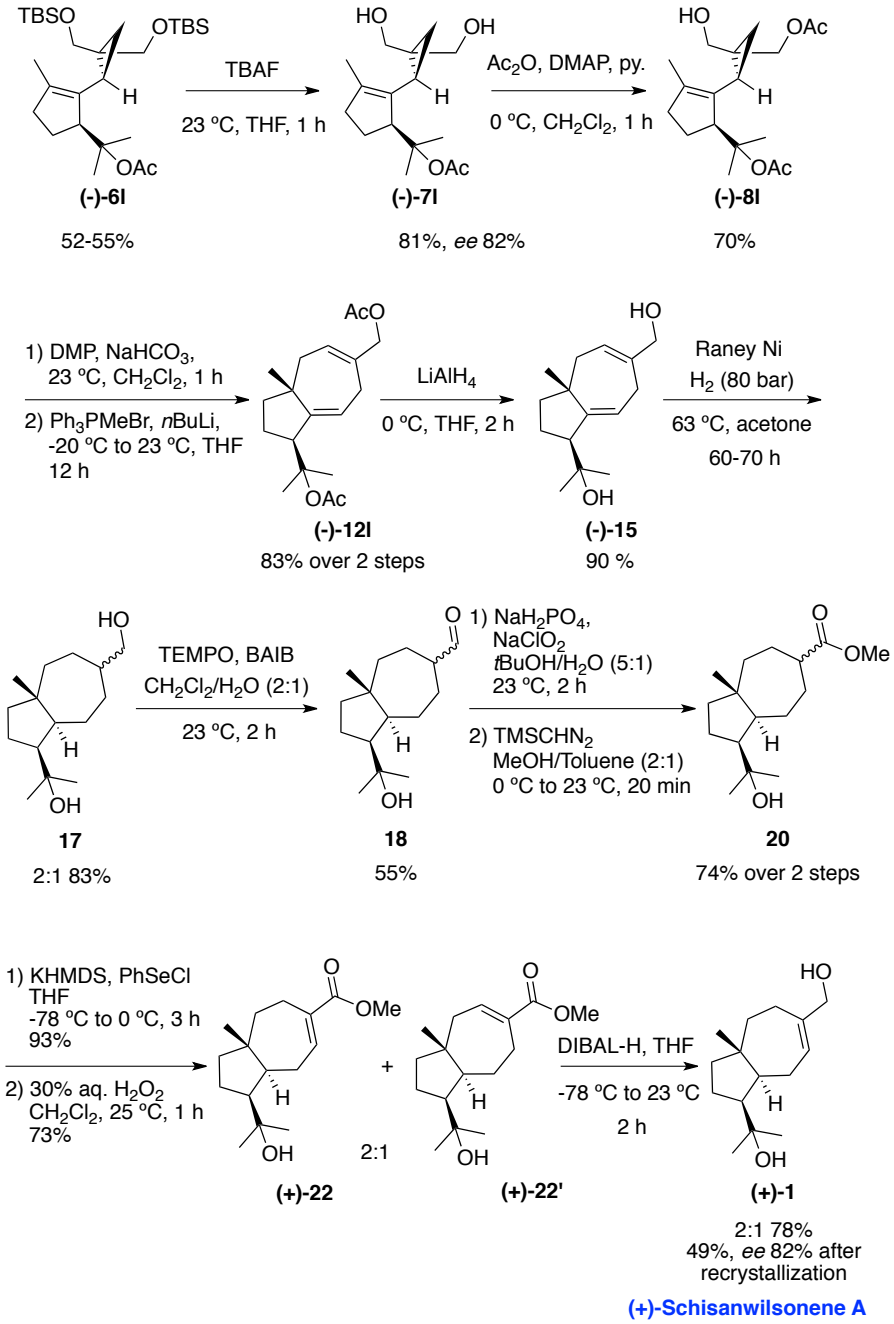
Since only the relative configuration of (+)-schisanwilsonene **(+)-1** was known,[142] both routes beginning with enynes **(+)-(*R*)-4h** and **(-)-(*S*)-4h** were carried out in parallel.[161]

The enantioselective synthesis of (+)-schisanwilsonene A was completed from **(-)-6l**, obtained from the gold(I)-catalyzed cyclization of enyne **(+)-4h**. After desilylation of **(-)-6l** and selective acetylation, diacetate **(-)-8l** was

161 The parallel route, which started with **(-)-(*S*)-4h** was explored by Dr. Ricarda Miller.

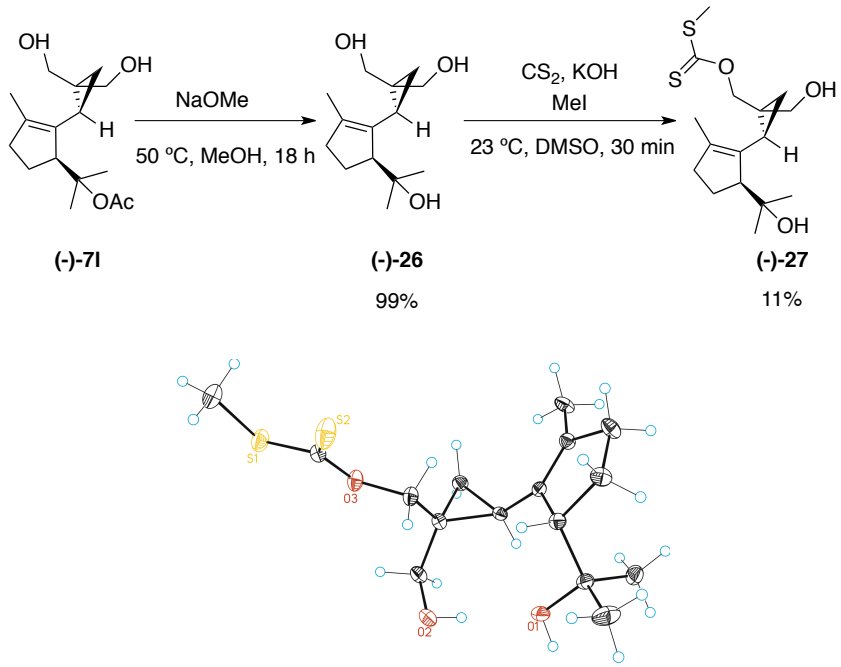
obtained in good yields (3:1 ratio) (Scheme 83). Oxidation of **(-)-8l** with DMP and subsequent Wittig methylenation of the aldehyde gave a diene, which underwent a [3,3] sigmatropic rearrangement at room temperature to form **(-)-12l**. Removal of both acetates using $LiAlH_4$ gave diol **(-)-15**. The desired *trans* fusion was established by hydrogenation of **(-)-15** in the presence of Raney nickel, followed by oxidation of the primary alcohol and esterification to provide hydroxy ester **20**. (+)-Schisanwilsonene A (**(+)-1**) was finally obtained by selenylation of the potassium enolate of **20**, followed by elimination of the selenoxide (2-3:1 regioselectivity) and final reduction of the α,β-unsaturated ester.[162]

162 The optical rotation for the synthetic material, $[\alpha]^{25}_{D}$ = + 14.88 (c = D 0.33, MeOH), is lower than that reported $[\alpha]^{25}_{D}$ = + 52.38 (c = 0.02, DMeOH). Unfortunately, a sample of natural **(+)-1** was not available anymore from the natural source.[142]



Scheme 83. Total synthesis of (+)-Schisanwilsonene A

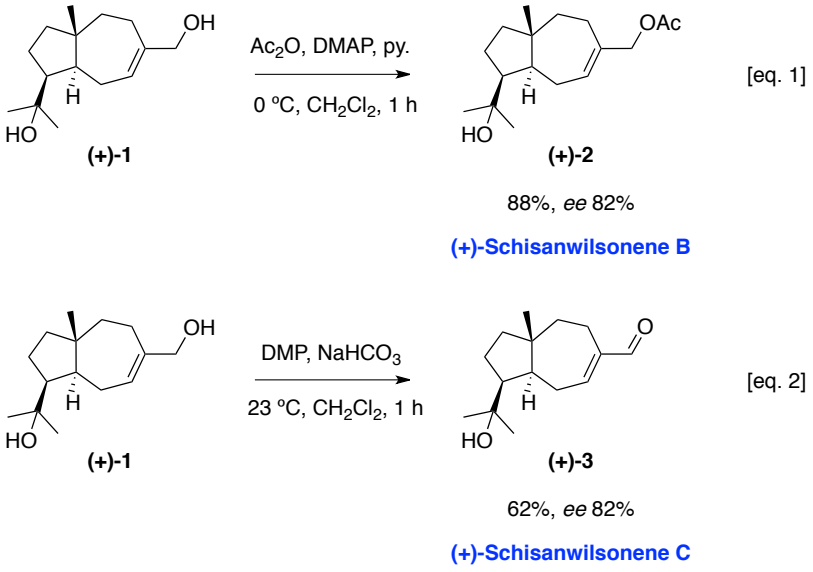
The absolute configuration of (+)-schisanwilsonene A was determined by derivatization of **(-)-7l** into the crystalline methyl xanthate compound **(-)-27** as 1*S*,3a*R*,8a*S* (Scheme 84).



(-)-7l **(-)-26** 99% **(-)-27** 11%

Scheme 84. Determination of the absolute configuration of intermediate (-)-26

Finally, enantioselective syntheses of (+)-schisanwilsonene B **(+)-2** (Scheme 85, [eq. 1]) and C **(+)-3** (Scheme 85, [eq. 3]) were also completed by simple mono-acetylation and oxidation reactions of (+)-schisanwilsonene A respectively.



Scheme 85. Total syntheses of (+)-schisanwilsonene B and C

Conclusions

The first enantioselective synthesis of (+)-schisanwilsonene A has been completed in 13 steps (*ca* 4% overall yield) from known acetate **(+)-4h**. This study establishes the absolute configuration of (+)-schisanwilsonenes as 1*S*,3a*R*,8a*S*. The syntheses of (+)-schisanwilsonene B and C were also achieved from acetylation and oxidation reactions of (+)-schisanwilsonene A, respectively.

The hexahydroazulene skeleton was constructed by a gold(I)-catalyzed tandem cyclization, 1,5-migration, cyclopropanation reaction with subsequent divinyl cyclopropane rearrangement. This is one of the most complex transformations orchestrated by gold(I) that has been applied thus far in total synthesis.

Further insight into the mechanism through ^{18}O label studies allowed us to identify the intermediate of the 1,5-migration reaction. Additionally, the small decrease in the *er* observed during the gold(I) reaction sequence and the ^{18}O labeled studies demonstrated that the intramolecular attack of the alkene onto η^2-alkyne gold(I) complex is 20 times faster than the competing 1,2-acyl migration reaction.

Experimental section

General information

All reactions were carried out under argon unless otherwise specified. Solvents were dried using a Solvent Purification System (SPS) or using standard procedures.[163] Catalysts were either purchased from Sigma-Aldrich or synthesized according to literature procedures. All other reagents were used without further purification as obtained from the commercial sources. Analytical thin layer chromatography was carried out using TLC aluminum sheets with 0.2 mm of silica gel (Merck GF234) using UV light as the visualizing agent. Flash column chromatography purifications were carried out using C_{18}-reversed phase silica gel (40-63 μm). NMR spectra were recorded at 23 ºC on either a Bruker Avance 400 Ultrashield (400 MHz for ^{1}H, and 100 MHz for ^{13}C) or a Bruker Avance 500 Ultrashield (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

Crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = −173 ºC). Full-sphere data collection was used with w and j scans. *Programs used*: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solution was achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares

163 W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, Elsevier Science, Bath, **2003**.

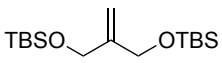
refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non hydrogen atoms were refined including anisotropic displacement parameters.

Experimental Procedures

Total Synthesis (±)-schisanwilsonene A

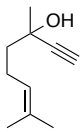
1,6-Enynes **(±)-4b**,[164] **(±)-4d**,[165] **(±)-4e**[139] **(±)-4f**[139], **(±)-4g**[139] and **(±)-4h**[166] were characterized by comparison of their ^{1}H NMR spectra with the previously reported data.

2,2,3,3,9,9,10,10-Octamethyl-6-methylene-4,8-dioxa-3,9-disilaundecane (5e)



To a stirred solution of propenediol (3.0 g, 34.1 mmol), triethylamine (9.6 mL, 68.8 mmol) and 4-(dimethylamino)pyridine (42.0 mg, 0.3 mmol) in CH_2Cl_2 (30.0 mL) at room temperature was added solid *tert*-butyldimethylsilyl chloride (11.3 g, 74.9 mmol). After being stirred overnight at room temperature, the resulting mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with 1 M hydrochloric acid (20.0 mL), then with brine. The organic extract were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to dryness to give the crude bis-TBS protected alkene **5e** (10.7 g, 33.8 mmol, 99%). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.08 (t, J = 1.4 Hz, 2H), 4.17 (t, J = 1.3 Hz, 4H), 0.92 (s, 18H), 0.07 (s, 12H); ^{13}C NMR (100MHz, $CDCl_3$) δ 148.1, 109.2, 64.1, 26.1, 18.53, -5.2; ESI$^+$: [(M+Na)$^+$]: 339.2.

3,7-Dimethyloct-6-en-1-yn-3-ol ((±)-4b)



To a solution of 6-methyl-5-hepten-2-one (10.0 g, 79.0 mmol) in THF (120.0 mL) was added dropwise a solution of ethynylmagnesium bromide (190.0 mL, 0.5 M in THF, 94.8

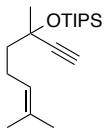
164 D. K. Mohapatra, C. Pramanik, M. S. Chorghade, M. K. Gurjar, *Eur. J. Org. Chem.* **2007**, 5059-5063.

165 E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.

166 M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2012**, 134, 8770- 8773.

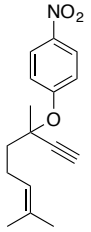
mmol) over 1 h at -10 ºC. The mixture was stirred for 12 h at room temprature. Upon consumption of the starting material, the mixture was quenched with an HCl aqueous solution (10% w/w) and the aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification (cyclohexane / EtOAc, 10 / 1 to 5 / 1) followed by Kugelrohr bulb-to-bulb distillation (3 mbar, 120 ºC) yielded the tertiary alcohol **(±)-4b** as a colorless oil (8.8 g, 57.80 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (ddd, J = 8.1, 2.7, 1.3 Hz, 1H), 2.46 (s, 1H), 2.35-2.25 (m, 1H), 2.23-2.13 (m, 1H), 2.11 (bs, 1H), 1.72-1.68 (m, 2H), 1.70 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 124.3, 88.24, 72.1, 68.9, 43.8, 30.5, 26.4, 24.2, 18.4; HRMS-ESI calcd for $C_{10}H_{17}O$ [$(M$+H$)^+$]: 153.1279; found: 153.1281.

((3,7-Dimethyloct-6-en-1-yn-3-yl)oxy)triisopropylsilane ((±)-4c)



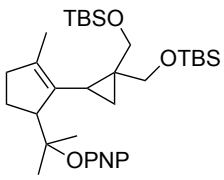
The propargylic alcohol **(±)-4b** (0.34 mL, 3.50 mmol) and 2,6-lutidine (0.41 mL, 3.50 mmol) were dissolved in CH_2Cl_2 (12.0 mL). TIPSOTf (0.94 mL, 3.50 mmol) was added dropwise to the solution at 0 ºC and the solution was allowed to warm to room temperature overnight. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo. Purification by column flash chromatography (cyclohexane / EtOAc, 30 / 1) afforded TIPS-protected propargyl alcohol **(±)-4c** as a colorless oil (622 mg, 2.59 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17-5.14 (m, 1H), 2.41 (s, 1H), 2.28-2.15 (m, 2H), 1.74-1.69 (m, 5H), 1.64 (s, 3H), 1.52 (s, 3H), 1.21-1.16 (m, 3H), 1.12-1.09 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 124.0, 88.5, 71.4, 68.9, 45.5, 30.5, 25.7, 23.4, 18.4, 17.6, 13.0; HRMS-ESI calcd for $C_{19}H_{37}OSi$ [$(M$+H$)^+$]: 309.2608; found: 309.2603.

1-((3,7-Dimethyloct-6-en-1-yn-3-yl)oxy)-4-nitrobenzene ((±)-4a)



To the propargylic alcohol **(±)-4b** (1.0 g, 6.57 mmol) in 7.0 mL of dry acetonitrile was added DBU (1.47 mL, 9.85 mmol) and trifluoroacetic anhydride (1.42 mL, 10.18 mmol) at -15ºC. After stirring at this temperature for 2h a mixture of DBU (1.47 mL, 9.85 mmol), $CuCl_2.2H_2O$ (11.0 mg, 0.066 mmol) and *p*-nitro phenol (1.01g, 7.23 mmol) was added dropwise. After stirring for 30min at room temperature, a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O, washed with brine. The organic extracts were dried over Na_2SO_4, filtered and the solvents were evaporated. Purification by column flash chromatography (cyclohexane / EtOAc, 33 / 1 to 20 / 1) yielded the protected alcohol **(±)-4a** as a pale yellow oil (9.9 g, 3.62 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.15 (m, 2H), 7.32-7.28 (m, 2H), 5.14 (ddq, J = 8.6, 5.8, 1.5 Hz, 1H), 2.71 (s, 1H), 2.26 (m, 2H), 2.00 (ddd, J = 13.6, 11.3, 5.2 Hz, 1H), 1.90 (ddd, J = 13.5, 11.5, 5.2 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 142.2, 132.8, 125.4, 123.1, 119.2, 83.7, 76.8, 76.1, 42.6, 26.8, 25.8, 23.1, 17.8; HRMS-ESI calcd for $C_{16}H_{20}NO_3$ [$(M$+H$)^+$]: 274.1443; found: 274.1432.

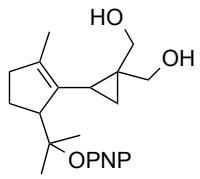
(((2-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopro-pane-1,1-diyl)bis(methylene))bis(oxy))bis(*tert*-butyldimethylsilane) ((±)-6e)



A solution of **(±)-4a** (500.0 mg, 1.83 mmol) in anhydrous CH_2Cl_2 (6.1 mL) was added dropwise over 30 min to a solution of gold catalyst IMesAutmbn **D** (34.0 mg, 0.037 mmol) and bis-TBS protected alkene **5e** (1.2 g, 3.66 mmol) in anhydrous CH_2Cl_2 (12.2 mL) at room temperature. The reaction mixture was then stirred for 5 min. and quenched by the addition of a few drops of NEt_3. The solution was filtered through a short pad of SiO_2 (washed with hexane / EtOAc, 4 / 1) and concentrated to

dryness. Purification over silica gel (hexane / EtOAc, 100 / 0 to 50 / 1) afforded a 1: 1.14 mixture (ratio determined by ^{1}H-NMR) of cyclopropane **(±)-6e** and bis-TBS protected alkene **5e** as a colourless oil (total 1.4 g, 79% calculated yield, 62 wt% purity). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.11 (m, 2H), 7.06-7.02 (m, 2H), 3.66 (dd, J = 16.2, 10.1 Hz, 2H), 3.26 (dd, J = 26.1, 10.1 Hz, 2H), 3.24 (br. s, 1H), 2.40-2.28 (m, 1H), 2.20-2.11 (m, 1H), 1.91-1.81 (m, 2H), 1.75 (s, 3H), 1.47-1.43 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 0.91 (s, 9H), 0.91-0.84 (m, 1H), 0.84 (s, 9H), 0.41 (dd, J = 5.9, 4.8 Hz, 1H), 0.05 (s, 3H), 0.04 (s, 3H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 142.0, 140.9, 133.1, 125.3, 121.4, 87.2, 65.6, 63.3, 58.9, 38.0, 30.3, 28.2, 27.1, 26.1, 26.1, 25.8, 25.6, 25.4, 24.3, 21.8, 18.6, 18.5, 15.4, 15.0, -5.3; HRMS-ESI calcd for $C_{32}H_{55}NO_5Si_2Na$ [(M+Na)$^+$]: 612.3516; found: 612.3517.

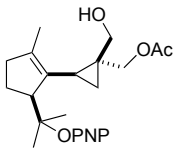
(2-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropane -1,1-diyl)dimethanol ((±)-7e)



A solution of TBAF (40.1 mL, 1.0 M in THF, 40.1 mmol) was added dropwise to a solution of cyclopropane **(±)-6e** (4.10 g, 8.03 mmol) in anhydrous THF (80 mL, 0.10 M) at room temperature. The resulting mixture was stirred for 1 h and quenched with H_2O. The reaction was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated to dryness. Purification over silica gel (hexane / EtOAc, 1 / 1 to 1 / 2) afforded the diol **(±)-7e** (545.0 mg, 1.51 mmol, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 9.1 Hz, 2H), 7.09 (d, J = 9.1 Hz, 2H), 3.70 (d, J = 11.1 Hz, 1H), 3.55 (d, J = 11.2 Hz, 2H), 3.38 (d, J = 11.1 Hz, 1H), 3.13 (d, J = 9.4 Hz, 1H), 2.37-2.27 (m, 1H), 2.24-2.18 (m, 1H), 2.00-1.93 (m, 1H), 1.79 (s, 3H), 1.69-1.63 (m, 1H), 1.59-1.55 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 0.99 (dd, J = 8.4, 4.9 Hz, 1H), 0.67 (dd, J = 5.8, 5.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 144.0, 142.4, 132.8, 125.9, 124.2, 89.2, 70.4, 65.8, 59.8, 38.2, 29.1, 26.3, 26.2, 23.8, 22.7, 17.0,

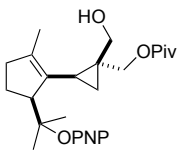
15.9; HRMS-ESI calcd for $C_{20}H_{27}NO_5Na$ [(*M*+Na)$^+$]: 384.1787; found: 384.1773.

(1-(Hydroxymethyl)-2-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropyl)methyl acetate ((±)-8e)



A solution of Ac_2O (0.07 mL, 0.74 mmol) in 0.74 mL CH_2Cl_2 was added dropwise at 0 ºC over 1 h to a solution of DMAP (4.3 mg, 0.035 mmol), anhydrous pyridine (0.12 mL, 1.4 mmol) and diol **(±)-7e** (253.0 mg, 0.70 mmol) in anhydrous CH_2Cl_2 (1.2 mL). The solution was then stirred for another 1 h at 0 ºC. The reaction was then quenched with a 0.5M aqueous HCl solution and was extracted with EtOAc. The organic extracts were washed with a 0.5M aqueous HCl solution, water and brine, dried over $MgSO_4$ and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 10 / 1 to 3 / 1) afforded monoacetate **(±)-8e** (203.0 mg, 0.50 mmol, 72%) as a colourless oil. The undesired monoacetate was also isolated in 24% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.14 (m, 2H), 7.11-7.07 (m, 2H), 4.23 (d, J = 11.6 Hz, 1H), 3.60 (brd, J = 11.2 Hz, 1H), 3.57 (d, J = 11.6 Hz, 1H), 3.28 (d, J = 11.2 Hz, 2H), 2.66 (brs, 1H), 2.38-2.26 (m, 1H), 2.26-2.16 (m, 1H), 2.02 (s, 3H), 1.93 (dtd, J = 13.7, 9.6, 6.3 Hz, 1H), 1.77 (s, 3H), 1.77-1.69 (m, 1H), 1.62-1.55 (m, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.05 (dd, J = 8.4, 5.0 Hz, 1H), 0.86 (tdd, J = 6.4, 5.3, 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 161.2, 143.5, 143.3, 132.1, 125.9, 122.8, 88.1, 69.5, 63.6, 58.6, 38.1, 26.7, 26.0, 25.6, 24.1, 23.6, 21.6, 17.0, 15.9; HRMS-ESI calcd for $C_{22}H_{29}NO_6Na$ [(*M*+Na)$^+$]: 426.1893; found: 426.1888.

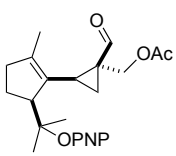
(1-(Hydroxymethyl)-2-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropyl)methyl pivalate ((±)-8f)



A solution of PivCl (0.06 mL, 0.50 mmol) in 0.5 mL CH_2Cl_2 was added dropwise at 0 ºC over 1 h to a solution of anhydrous triethylamine (0.13 mL, 0.94 mmol) and diol

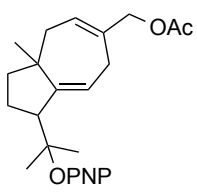
(±)-7e (169.0 mg, 0.47 mmol) in anhydrous CH_2Cl_2 (0.8 mL). The solution was then stirred for an additional hour at 0 ºC. The reaction was quenched with a 0.5M aqueous HCl solution, extracted with EtOAc, and washed with a 0.5M aqueous HCl solution, followed by water and brine. The organic extracts were dried over $MgSO_4$ and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 10 / 1 to 3 / 1) afforded monopivalate **(±)-8f** (96.0 mg, 0.22 mmol, 46%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.14 (m, 2H), 7.10-7.08 (m, 2H), 4.26 (dd, J = 11.5, 1.2 Hz, 1H), 3.59 (d, J = 11.6 Hz, 1H), 3.54 (dd, J = 11.8, 6.5 Hz, 1H), 3.26 (dd, J = 11.6, 5.2 Hz, 2H), 2.81-2.70 (m, 1H), 2.34-2.29 (m, 1H), 2.23-2.18 (m, 1H), 1.97-1.89 (m, 1H), 1.77 (s, 3H), 1.75-1.70 (m, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.22 (d, J = 3.0 Hz, 1H), 1.18 (s, 9H), 1.04 (dd, J = 8.5, 4.9 Hz, 1H), 0.57 (ddd, J = 6.3, 5.0, 1.2 Hz, 1H).

(1-Formyl-2-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl) cyclopropyl)methyl acetate ((±)-10e)



$NaHCO_3$ (838 mg, 9.97 mmol) and Dess-Martin periodinane (1.27 g, 2.99 mmol) were added to a solution of monoacetate **(±)-8e** (647 mg, 1.99 mmol) in anhydrous CH_2Cl_2 (40 mL) at room temperature. The resulting mixture was stirred for 2 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude aldehyde **(±)-10e** as a colorless solid, which was used in the subsequent step without further purification.

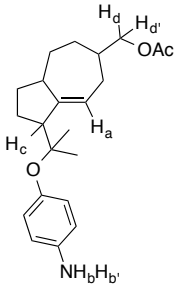
(3a-Methyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3a,4,7-hexahydroazulen-6-yl)methyl acetate ((±)-12e)



A solution of *n*BuLi (1.7 mL, 1.6 M in hexane, 2.74 mmol) was added dropwise to a suspension of PPh_3CH_3Br (1.05 g, 2.94 mmol) in anhydrous and

degassed THF (29 mL) at -20 ºC. The resulting pale yellow solution was stirred for 10 mins at -20 ºC, whereupon a solution of aldehyde **(±)-10e** (631.5 mg, 1.96 mmol) in anhydrous and degassed THF (15 mL) was added dropwise. After stirring at -20 ºC for 10 mins, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was then quenched with saturated aqueous NH_4Cl, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (hexane / EtOAc, 20 / 1 to 10 / 1) afforded the diene **(±)-12e** (556.5 mg, 1.39 mmol, 70% over two steps) as a colourless oil. The compound was typically promptly deprotected and hydrogenated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 9.2 Hz, 2H), 7.07 (d, J = 9.2 Hz, 2H), 5.83 (ddd, J = 6.4, 4.0, 2.3 Hz, 1H), 5.80-5.78 (m, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 3.18-3.13 (m, 1H), 3.00-2.86 (m, 2H), 2.35 (d, J = 14.4 Hz, 1H), 2.13 (dd, J = 15.6, 8.3 Hz, 1H), 2.07 (s, 3H), 1.82-1.73 (m, 1H), 1.63-1.45 (m, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 162.3, 150.5, 143.1, 133.4, 128.3, 125.9, 122.7, 120.3, 86.4, 71.4, 55.1, 46.7, 41.9, 41.3, 31.8, 27.4, 26.7, 24.5, 23.6, 21.8; HRMS-ESI calcd for $C_{23}H_{29}NO_5Na$ [(M+Na)$^+$]: 422.1943; found: 422.1923.

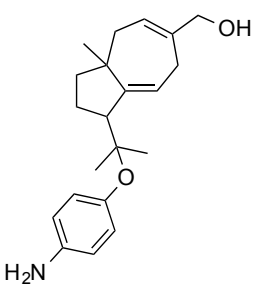
(1-(2-(4-Aminophenoxy)propan-2-yl)-1,2,3,3a,4,5,6,7-octahydroazulen-6-yl)methyl acetate ((±)-13)



A solution of **(±)-12e** (10.0 mg, 0.025 mmol) in MeOH (0.25 mL) was added onto the catalyst (see Table 29, 0.25 equivalent). The tubes were then sealed into a "HEL reactor" (pressure reactor). The atmosphere was purged with H_2 and finally pressurized to the desired pressure (50 bar) before the reaction mixture was stirred overnight at room temperature. The pressure was then released from the parr bomb and the substrate was filtered through Celite atop of silica gel with CH_2Cl_2 and then concentrated. The mono-hydrogenated compound **(±)-13** was

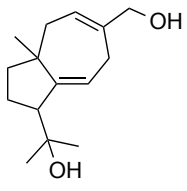
partially characterized without further purification, as it was undesired. *Relevant picks chosen from ^1H NMR:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (ddd, J = 8.0, 5.7, 2.6 Hz, 1H, H_a), 3.56 (brs, 2H, $H_{b,b'}$), 2.99-2.94 (m, 1H, H_c), 2.04 (ddd, J = 8.3, 5.1, 1.8 Hz, 2H, $H_{d,d'}$).

(1-(2-(4-Aminophenoxy)propan-2-yl)-3a-methyl-1,2,3,3a,4,7-hexahydroazulen-6-yl)methanol ((±)-14)



To a suspension of copper(II) acetylacetonate (24.3 mg, 0,093 mmol) and the nitro-compound **(±)-12e** (185.4 mg, 0,46 mmol) in ethanol (4.6 mL) was added sodium borohydride (52.7 mg, 1.39 mmol) at 0ºC and the mixture was stirred overnight at room temperature. Water was then added and the mixture was filtered through a short pad of Celite. The reaction was extracted twice with EtOAc, and dried over $MgSO_4$ before removing the solvent under reduced pressure. Purification over silica gel (cyclohexane / EtOAc, 2 / 1 to 1 / 1) afforded the product **(±)-14** as a pale yellow oil (129.5 mg, 0.40 mmol, 85%). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.83-6.77 (m, 2H), 6.61-6.55 (m, 2H), 6.10-6.07 (m, 1H), 5.72 (ddd, J = 8.1, 3.1, 1.7 Hz, 1H), 3.98 (s, 2H), 3.09-2.89 (m, 3H), 2.37-2.31 (m, 1H), 2.11 (ddd, J = 15.6, 8.0, 1.5 Hz, 1H), 1.70 (tdd, J = 13.1, 5.3, 3.3 Hz, 1H), 1.56-1.47 (m, 2H), 1.46-1.40 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 150.4, 147.0, 142.3, 137.7, 125.7, 124.2, 119.9, 115.6, 82.8, 69.7, 54.4, 46.1, 41.6, 40.8, 31.0, 27.1, 26.4, 24.0, 22.3; HRMS-ESI calcd for $C_{21}H_{30}NO_2$ [(M+H)$^+$]: 328.2277; found: 328.2285.

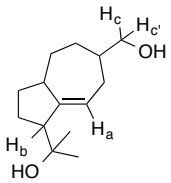
2-(6-(Hydroxymethyl)-3a-methyl-1,2,3,3a,4,7-hexahydroazulen-1-yl)propan-2-ol ((±)-15)



A solution of $(NH_4)_2Ce(NO_3)_6$ (CAN, 415.0 mg, 0.76 mmol) in water (3.8 mL) was added dropwise to a solution of **(±)-14** (82.9 mg, 0.25 mmol) in CH_3CN (11.4

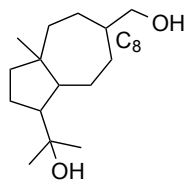
mL) at 0ºC. The mixture was stirred for 15 mins when water was added and the mixture was extracted with EtOAc and washed with 10 % aqueous $NaHCO_3$. The aqueous layer was re-extracted with EtOAc and the organic layers were combined, washed successively with 10 % $NaHSO_3$, 10 % $NaHCO_3$ and brine. The extracts were then dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was then purified by column chromatography (cyclohexane / EtOAc, 1 / 1) to afford the diol **(±)-15** (54.0 mg, 0.23 mmol, 90%) as an orange solid. mp 94-97 ºC ^{1}H NMR (400MHz, $CDCl_3$) δ 5.74 (dtd, J = 12.3, 4.1, 3.3, 1.7 Hz, 2H), 3.98 (s, 2H), 2.94 (dd, J = 5.3, 2.5 Hz, 2H), 2.67 (ddq, J = 10.7, 7.9, 2.4 Hz, 1H), 2.32 (dd, J = 16.0, 3.5 Hz, 1H), 2.07 (dd, J = 15.3, 8.1 Hz, 1H), 1.78 - 1.71 (m, 1H), 1.59 (s, 1H), 1.56 - 1.50 (m, 2H), 1.46 - 1.40 (m, 2H), 1.24 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 151.0, 138.0, 124.6, 120.2, 73.4, 69.3, 57.0, 45.8, 43.6, 41.9, 40.4, 30.6, 27.0, 26.3, 23.4. HRMS-ESI: *m*/*z*: calcd for $C_{15}H_{24}O_2Na$ [(*M*+Na)$^+$]: 259.1674, found: 259.1674.

2-(6-(Hydroxymethyl)-1,2,3,3a,4,5,6,7-octahydroazulen-1-yl)propan-2-ol ((±)-16)



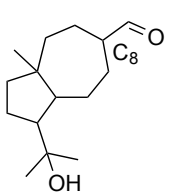
A solution of **(±)-15** (10.0 mg, 0.025 mmol) in the desired solvent (see Table 30, 0.25 mL) was added onto the catalyst (see Table 30, 0.25 equivalent). The tubes were then sealed into a "HEL reactor" (pressure reactor). The atmosphere was purged with H_2 and finally pressurized to the desired pressure (see Table 30) before the reaction mixture was stirred for 2 days at the desired temperature (see Table 30). The pressure was then released from the parr bomb, the substrate was filtered through Celite atop of silica gel with CH_2Cl_2, and concentrated to dryness. The mono-hydrogenated compound **(±)-16** was partially characterized without further purification as it was not the desired one. Relevant signals from ^{1}H NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, J = 7.2, 5.2, 2.1 Hz, 1H, H_a), 3.50 (m, 2H, $H_{c,c'}$), 2.66 (tdd, J = 8.5, 4.0, 2.0 Hz, 1H, H_b).

2-(6-(Hydroxymethyl)-3a-methyldecahydroazulen-1-yl)propan-2-ol ((±)-17)



A wet slurry of Raney nickel 2400 (5 mL) was washed five times with dry acetone. The resulting slurry was dissolved in 24 mL of acetone. The resulting solution was distributed between 24 different 2 mL tubes (1 mL) and the acetone was decanted and removed. A solution of bis-alcohol **(±)-15** (250.0 mg, 1.06 mmol) in acetone (24.0 mL, 0.2 M) was distributed to each tube (1 mL each). The tubes were then sealed into a "HEL reactor" (pressure reactor) and the atmosphere was purged with H_2. The apparatus was pressurized to 80 bar and was re-pressurized with H_2 every 12h. The reaction was stirred at 63 ºC until consumption of the starting material was achieved (as indicated by stagnant hydrogen consumption, typically 60-70 h). The pressure was then released from the parr bomb and the substrate was filtered through Celite atop of silica gel with CH_2Cl_2. The solution was then concentrated to dryness and purification by flash column chromatography (cyclohexane / EtOAc, 1 / 1) afforded hydrogenated compound **(±)-17** (2/1 epimers at C_8, 216.6 mg, 0.90 mmol, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40-3.33 (m, 2H), 3.22-3.20 (m, 1H), 2.72-2.69 (m, 1H), 2.33-2.24 (m, 1H), 2.21-2.05 (m, 1H), 1.83-1.62 (m, 7H), 1.59 (br m, 1H), 1.51-1.41 (m, 4H), 1.29-1.23 (m, 6H), 1.21.1.18 (m, 3H), 1.14 (d, J = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 74.2, 69.3, 53.7, 49.8, 47.4, 44.2, 43.2, 41.8, 39.8, 32.3, 29.9, 27.8, 27.7, 24.5, 23.3; HRMS (EI): *m/z*: calcd for $C_{15}H_{28}O$ [$(M\text{-}OH)^+$]: 223.2056, found: 223.2057 (fragmentation).

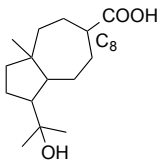
1-(2-Hydroxypropan-2-yl)-3a-methyldecahydroazulene-6-carbaldehyde ((±)-18)



To a solution of bis-alcohol **(±)-17** (48.7 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was added TEMPO (6.4 mg, 0.041

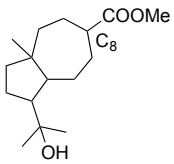
mmol), BAIB (163 mg, 0.51 mmol) and water (1.0 mL). The reaction was stirred at room temperature until consumption of the starting material was achieved (as indicated by TLC, typically 2 h). A solution of $Na_2S_2O_3$ (10% in water) was added and the mixture was stirred efficiently for 10 mins. The reaction was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated to dryness. Purification by flash column chromatography (cyclohexane / EtOAc, 3 / 1) furnished aldehyde **(±)-18** (30.5 mg, 0.13 mmol, 63%, both epimers at C_8 2/1) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 2.52.2.47 (m, 1H), 2.32-2.25 (m, 2H+1H), 2.18-2.12 (m, 1H), 2.06-2.01 (m, 2H), 1.88-1.82 (m, 2H+1H), 1.76-1.68 (m, 2H), 1.45-1.35 (2H+2H), 1.26 (s, 3H), 1.25 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 74.1, 53.5, 51.4, 50.0, 47.6, 45.5, 43.5, 39.2, 32.4, 28.3, 27.7, 26.4, 22.7, 19.6; HRMS-ESI: *m*/*z*: calcd for $C_{15}H_{26}O_2Na$ [(*M*+Na)$^+$]: 261.1831, found: 261.1834.

1-(2-Hydroxypropan-2-yl)-3a-methyldecahydroazulene-6-carboxylic acid ((±)-19)



To a solution of aldehyde **(±)-18** (30.5 mg, 0.13 mmol) in *tert*-butyl alcohol/water (5:1, 2.0 mL) was added successively NaH_2PO_4 (26.1 mg, 0.22 mmol), 2-methyl-2-butene (43.1 mg, 0.61 mmol) and $NaClO_2$ (39.9 mg, 0.44 mmol) and the resulting mixture was stirred for 2 h. The reaction was extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude acid **(±)-19** as a colorless solid, which was used in the subsequent step without further purification.

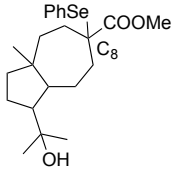
Methyl 1-(2-Hydroxypropan-2-yl)-3a-methyldecahydroazulene-6-carboxylate ((±)-20)



To a solution of the crude acid **(±)-19** (31.5 mg, 0.12 mmol) in dry toluene (0.7 mL) and dry MeOH (1.4 mL) at

0 ºC was added dropwise, until the yellow color persisted, a 2 M solution of $TMSCHN_2$ in Et_2O (0.12 mL, 0.25 mmol). The solution was stirred for additional 20 min at room temperature. The reaction was then quenched with a drop of acetic acid and concentrated to dryness. Purification by flash column chromatography (cyclohexane / EtOAc, 3 / 1) gave methyl esters **(±)-20** (both epimers at C_8 2/1, 24.0 mg, 0.089 mmol, 70% over 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.46-2.40 (m, 1H), 2.29-2.22 (m, 2H), 2.07-1.98 (m, 2H), 1.91-1.83 (m, 2H+1H), 1.79-1.74 (m, 1H), 1.70-1.64 (m, 2H+1H), 1.51-1.40 (m, 2H+2H), 1.25 (s, 3H), 1.24 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 74.1, 53.6, 51.7, 47.3, 45.4, 43.8, 42.8, 39.6, 32.2, 30.1, 28.3, 27.7, 26.6, 23.1, 19.6; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{28}O_3Na$ [$(M+Na)^+$]: 291.1926, found: 291.1931.

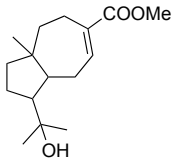
Methyl 1-(2-Hydroxypropan-2-yl)-3a-methyl-6-(phenylselanyl)decahydroazulene-6-carboxylate ((±)-21)



To a solution of methyl ester epimers **(±)-20** (22.0 mg, 0.082 mmol) in anhydrous THF (2.5 mL) at -78 ºC was added a 0.5 M solution of KHMDS in toluene (0.33 mL, 0.16 mmol). The resulting solution was stirred for 5 min at -78 ºC. A solution of PhSeCl (31.4 mg, 0.16 mmol) in THF (0.5 mL) was then added and the reaction was allowed to warm to 0 ºC over 3h. The resulting solution was quenched with water, diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by flash chromatography (cyclohexane / EtOAc, 4 / 1) gave the phenyl selenium compound **(±)-21** (both epimers at C_8 6:1, 19.6 mg, 0.05 mmol, 57%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.41-7.38 (m, 1H), 7.33-7.30 (m, 2H), 3.66 (s, 3H), 2.33-2.14 (m, 2H+2H), 1.99-1.92 (m, 1H), 1.90-1.78 (m, 2H), 1.65-1.61 (m, 2H+1H), 1.52-1.46 (m, 1H), 1.38-1.25 (m, 2H+2H), 1.22 (s, 3H+3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 138.3, 129.6, 128.8, 128.4, 73.8,

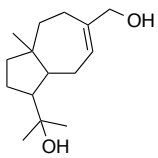
53.0, 51.8, 48.1, 45.1, 42.9, 41.9, 35.5, 34.9, 31.7, 30.3, 29.1, 27.6, 24.4, 19.2; HRMS-ESI: *m*/*z*: calcd for $C_{22}H_{32}O_3{}^{80}SeNa$ [(*M*+Na)$^+$]: 447.1414, found: 447.1398.

Methyl 1-(2-Hydroxypropan-2-yl)-3a-methyl-1,2,3,3a,4,5,8,8a-octahydroazulene-6-carboxylate ((±)-22)



To a solution of selenide **(±)-21** (18.6 mg, 0.044 mmol) in CH_2Cl_2 (1.0 mL) was added 10 µL of a 30% aqueous H_2O_2 solution. The resulting solution was stirred for 1 h at 25 ºC. The reaction was then diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 3 / 1) yielded **(±)-22** as a mixture of double bond isomers (typically a 2:1 to 3:1 mixture of double bond isomers, 6.3 mg, 0.024 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dt, *J* = 8.5, 3.0 Hz, 1H), 3.71 (s, 3H), 3.15 (ddd, *J* = 17.0, 8.5, 2.0 Hz, 1H), 2.75 (dt, *J* = 16.5, 4.0 Hz, 1H), 2.42-2.32 (m, 2H+1H), 1.87-1.82 (m, 1H), 1.79-1.75 (m, 1H), 1.73-1.70 (m, 1H), 1.50-1.45 (m, 2H), 1.39-1.36 (m, 1H), 1.34-1.28 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.9, 133.7, 74.4, 57.2, 53.1, 52.0, 49.4, 44.6, 42.1, 40.9, 32.9, 29.4, 27.2, 23.7, 18.1; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{26}O_3Na$ [(*M*+Na)$^+$]: 289.1780, found: 289.1774.

Schisanwilsonene A ((±)-1)

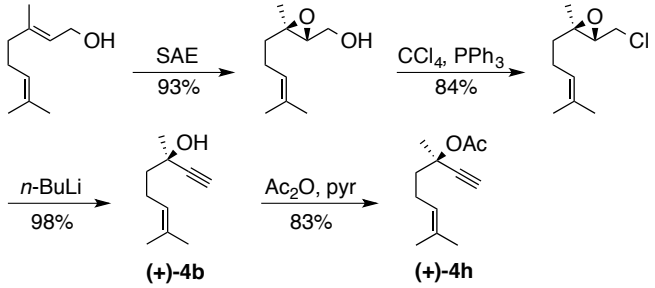


To a solution of the mixture of unsaturated methyl esters **(±)-22** (6.2 mg, 0.023 mmol) in dry THF (1.0 mL) at -78 ºC was added a 1 M solution of DIBAL in toluene (0.01 mL, 0.01 mmol), and the resulting solution was warmed to -20 ºC over 1.5 h. The mixture was then allowed to warm to room temperature over 2 h. The reaction was quenched with a saturated solution of sodium potassium tartrate. Et_2O was added and the mixture was stirred until the phases separated. The organic phase was extracted, washed with

water, dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash chromatography (cyclohexane / EtOAc, 1 / 1) and recrystallization from cyclohexane/EtOAc yielded (±)-schisanwilsonene A **(±)-1** (2:1 to 3:1, 5.0 mg, 0.021 mmol, 90%) as a colorless solid. mp 152-154 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (d, J = 9.6 Hz, 1H), 3.94 (d, J = 5.2 Hz, 2H), 2.88 (ddd, J = 2.4, 8.4, 16.0, Hz, 1H), 2.26-2.29 (m 1H), 2.16-2.09 (m, 2H), 2.06 (dt, J = 2.4, 12.4 Hz, 1H), 1.87-1.81 (m, 1H), 1.77-1.69 (m, 2H), 1.50-1.32 (m, 4H), 1.29-1.26 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 127.6, 74.5, 70.8, 53.4, 50.5, 44.7, 42.2, 41.4, 32.7, 27.6, 27.3, 26.6, 26.2, 17.9; HRMS-ESI: *m*/*z*: calcd for $C_{15}H_{26}O_2Na$ [$(M+Na)^+$]: 261.1825, found: 261.1829.

Enantioselective synthesis of (+)-schisanwilsonene A

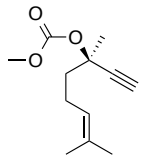
(*R*)-3,7-Dimethyloct-6-en-1-yn-3-yl acetate ((+)-4h)



(*R*)-3,7-dimethyloct-6-en-1-yn-3-yl acetate **(+)-4h** was synthesized in four steps according to a literature precedent[167] with an overall yield of 64% and with an *er* of 96:4.

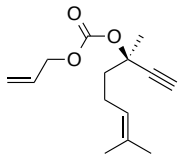
167 (a) D. K. Mohapatra, C. Pramanik, M. S. Chorghade, M. K. Gurjar, *Eur. J. Org. Chem.* **2007**, 5059-5063. (b) M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2012**, 134, 8770- 8773.

(*S*)-3,7-dimethyloct-6-en-1-yn-3-yl methyl carbonate ((+)-4i)



A solution of *n*-BuLi (2.5 M in THF, 0.44 mL, 1.11 mmol) was added dropwise to a solution of propargylic alcohol **(+)-4b** (136 mg, 0.89 mmol) in anhydrous THF (5.8 mL) at -35 ºC and the resulting solution was stirred for 30 min, before methyl chloroformate (0.09 mL, 1.11 mmol) was added at -20 ºC. The reaction mixture was stirred for an additional 1.5 h at -20 ºC. The reaction was warmed to room temperature, water was added, and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 10 / 1) afforded methyl carbonate **(+)-4i** (118 mg, 0.561 mmol, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12-5.09 (m, 1H), 3.77 (s, 3H), 2.59 (s, 1H), 2.24-2.13 (m, 2H), 2.01-1.95 (m, 1H), 1.87-1.81 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 132.6, 123.1, 83.3, 77.0, 74.0, 54.5, 41.4, 26.4, 25.8, 23.0, 17.8; HRMS-ESI: *m*/*z*: calcd for $C_{12}H_{18}O_3Na$ [(*M*+Na)$^+$]: 233.1148, found: 233.1139.

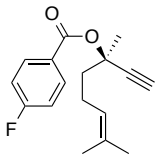
(*S*)-Allyl (3,7-Dimethyloct-6-en-1-yn-3-yl) carbonate ((+)-4j)



NaH (39.4 mg, 0.99 mmol, 60% in mineral oil) was added to a solution of propargylic alcohol **(+)-4b** (100 mg, 0.66 mmol) in anhydrous THF (0.7 mL) and the reaction was stirred for 3 h at room temperature. The solution was then cooled to -40 ºC and allyl chloroformate (0.11 mL, 0.99 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 10 / 1) afforded allyl carbonate **(+)-4j** (151.3 mg, 0.640 mmol, 97%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97-5.91 (m, 1H), 5.38-5.34 (m, 1H), 5.28-5.25 (m, 1H), 5.12-5.09 (m, 1H), 4.62-4.61 (m, 2H), 2.60 (s, 1H), 2.25-2.14 (m, 2H), 2.03-1.97 (m, 1H), 1.88-1.82 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H),

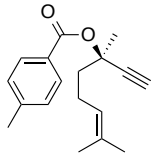
1.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 132.6, 131.8, 123.0, 119.1, 83.3, 74.0, 68.3, 41.3, 26.4, 25.8, 23.0, 17.8; HRMS-ESI: *m*/*z*: calcd for $C_{14}H_{20}O_3Na$ [(*M*+Na)$^+$]: 259.1305, found: 259.1298.

(*S*)-3,7-Dimethyloct-6-en-1-yn-3-yl 4-fluorobenzoate ((+)-4k)



Propargylic alcohol **(+)-4b** (200 mg, 1.31 mmol), 4-fluorobenzoyl chloride (417 mg, 2.63 mmol) and DMAP (32.1 mg, 0.263 mmol) in dry pyridine (4.0 mL) were heated to reflux for 12 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by preparative TLC (silica gel, cyclohexane / EtOAc, 10 / 1) afforded fluorobenzoate **(+)-4k** (205.3 mg, 0.749 mmol, 57%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.00 (m, 2H), 7.12-7.07 (m, 2H), 5.19-5.14 (m, 1H), 2.62 (s, 1H), 2.31-2.24 (m, 2H), 2.13-2.07 (m, 1H), 2.00-1.92 (m, 1H), 1.82 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7 (d, *J* = 201.0 Hz), 163.8, 132.4, 132.1 (d, *J* = 8.0 Hz), 127.1 (d, *J* = 2.0 Hz), 123.1, 115.4 (d, *J* = 17.1 Hz), 83.6, 75.5, 73.7, 41.6, 26.6, 25.6, 23.0, 17.6; HRMS-ESI: *m*/*z*: calcd for $C_{17}H_{19}FO_2Na$ [(*M*+Na)$^+$]: 297.1261, found: 297.1272.

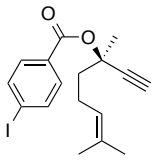
(*S*)-3,7-Dimethyloct-6-en-1-yn-3-yl 4-methylbenzoate ((+)-4l)



Propargylic alcohol **(+)-4b** (200 mg, 1.31 mmol), 4-methylbenzoyl chloride (405 mg, 2.63 mmol) and DMAP (32.1 mg, 0.263 mmol) in dry pyridine (4.0 mL) were heated to reflux for 12 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by preparative TLC (silica gel, cyclohexane / EtOAc, 10 / 1) afforded methylbenzoate **(+)-4l** (246.2 mg, 0.911 mmol, 69%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.19-5.15 (m, 1H), 2.60 (s, 1H), 2.40 (s, 3H), 2.33-2.22 (m, 2H), 2.14-2.04 (m, 1H), 2.00-

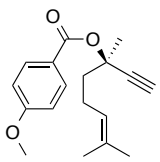
1.92 (m, 1H), 1.82 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 143.6, 132.5, 129.8, 129.1, 128.3, 123.4, 84.0, 75.2, 73.6, 41.9, 26.7, 25.8, 23.2, 21.8, 17.8; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{22}O_2Na$ [(*M*+Na)$^+$]: 293.1512, found: 293.1518.

(*S*)-3,7-Dimethyloct-6-en-1-yn-3-yl 4-iodobenzoate ((+)-4m)



Propargylic alcohol **(+)-4b** (200 mg, 1.31 mmol), 4-iodobenzoyl chloride (699 mg, 2.63 mmol) and DMAP (32.1 mg, 0.263 mmol) in dry pyridine (4.0 mL) were heated to reflux for 12 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. Purification by preparative TLC (silica gel, cyclohexane / EtOAc, 10 / 1) afforded iodobenzoate **(+)-4m** (287.6 mg, 0.753 mmol, 57%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 5.18-5.15 (m, 1H), 2.62 (s, 1H), 2.30-2.21 (m, 2H), 2.13-2.07 (m, 1H), 1.99-1.93 (m, 1H), 1.82 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 137.8, 132.6, 131.2, 130.5, 123.2, 100.8, 83.6, 75.9, 73.9, 41.7, 26.7, 25.8, 23.2, 17.8; HRMS-ESI: *m*/*z*: calcd for $C_{17}H_{19}IO_2Na$ [(*M*+Na)$^+$]: 405.0322, found: 405.0335.

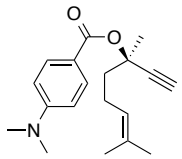
(*S*)-3,7-Dimethyloct-6-en-1-yn-3-yl 4-methoxybenzoate ((+)-4n)



Propargylic alcohol **(+)-4b** (200 mg, 1.31 mmol), 4-methoxybenzoyl chloride (447 mg, 2.63 mmol) and DMAP (32.1 mg, 0.263 mmol) in dry pyridine (4.0 mL) were heated to reflux for 12 h. The reaction was then quenched with saturated $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. Purification by preparative TLC (silica gel, cyclohexane / EtOAc, 10 / 1) afforded methoxybenzoate **(+)-4n** (238.4 mg, 0.833 mmol, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 5.19-5.16 (m, 1H), 3.86 (s, 3H), 2.60 (s, 1H),

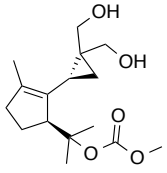
2.32-2.23 (m, 2H), 2.13-2.07 (m, 1H), 1.99-1.93 (m, 1H), 1.82 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 163.4, 132.5, 131.7, 123.4, 113.6, 84.1, 75.0, 73.5, 55.6, 41.9, 26.8, 25.8, 23.2, 17.8; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{22}O_3Na$ [(*M*+Na)$^+$]: 309.1461, found: 309.1475.

(*S*)-3,7-Dimethyloct-6-en-1-yn-3-yl 4-(dimethylamino)benzoate ((+)-4o)



A solution of propargylic alcohol **(+)-4b** (100 mg, 0.66 mmol) in anhydrous THF (1.5 mL) was added dropwise to a slurry of NaH (28.8 mg, 0.72 mmol, 60% in mineral oil) in THF (1.5 mL) and the resulting solution was stirred for 30 min at rt, before a solution of 4-(dimethylamino)benzoyl chloride (180 mg, 0.975 mmol) in THF (1.5 mL) was added. The mixture was stirred for 48 h at room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. Purification over silica gel (cyclohexane / EtOAc, 2 / 1) afforded dimethylaminobenzoate **(+)-4o** (178 mg, 0.595 mmol, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 7.2 Hz, 2H), 5.22-5.19 (m, 1H), 3.08 (s, 6H), 2.61 (s, 1H), 2.34-2.24 (m, 2H), 2.14-2.08 (m, 1H), 2.00-1.94 (m, 1H), 1.83 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 153.2, 132.2, 131.3, 131.2, 123.4, 110.8, 84.4, 74.2, 73.0, 41.9, 40.1, 26.7, 25.7, 23.0, 17.6; HRMS-ESI: *m*/*z*: calcd for $C_{19}H_{25}NO_2Na$ [(*M*+Na)$^+$]: 322.1778, found: 322.1790.

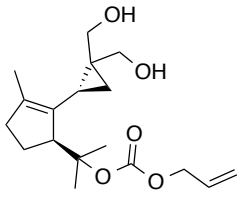
2-(2-(2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl methyl carbonate ((-)-7m)



A solution of enyne **(+)-4i** (20 mg, 0.095 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (2.20 mg, 2.85 μmol) and bis-TBS protected alkene **5e** (45.0 mg, 0.143 mmol) in

anhydrous CH_2Cl_2 (0.5 mL) at room temperature and the resulting solution was stirred for 5 mins. A drop of NEt_3 was then added and the solution was concentrated and purified over silica gel (Cyclohexane / EtOAc, 10 / 1) to give cyclopropane **(-)-6m** (38 mg, contaminated with bis-TBS protected alkene). The residue was dissolved in anhydrous THF (1.0 mL) and a solution of TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol) was added at room temperature. The reaction was then stirred for 1 h, before it was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1) afforded methyl carbonate **(-)-7m** (7.6 mg, 0.026 mmol, 27%, 2 steps, 84% ee) as a colorless oil. The enantiomeric excess was determined by HPLC (CHIRALPACK IA (4.6x250 mm), hexane/*i*-PrOH = 95/5, flow rate = 1mL/min, t = 14.0, t = 16.5). $[\alpha]_D^{25.0}$ = -15.02º (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94-3.89 (m, 1H), 3.72 (s, 3H), 3.61 (s, 2H), 3.35 (d, *J* = 11.6 Hz, 1H), 3.12 (d, *J* = 11.6 Hz, 1H), 3.02-3.00 (m, 1H), 2.78 (br s, 1H), 2.32-2.22 (m, 1H), 2.18-2.12 (m, 1H), 1.99-1.88 (m, 1H), 1.74 (s, 3H), 1.57-1.46 (m, 2H), 1.54 (s, 3H), 1.39 (s, 3H), 0.84-0.81 (m, 1H), 0.56-0.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 141.3, 132.5, 89.7, 70.5, 65.6, 58.3, 54.1, 37.7, 28.0, 25.1, 24.5, 23.7, 19.7, 15.4, 15.0; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{26}O_5Na$ $[(M+Na)^+]$: 321.1672, found: 321.1681.

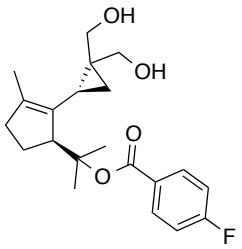
Allyl (2-(2-(2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl) carbonate ((-)-7n)



A solution of enyne **(+)-4j** (20 mg, 0.085 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (1.96 mg, 2.54 μmol) and bis-TBS protected alkene **5e** (40.3 mg, 0.127 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at room temperature and the resulting solution was stirred for 5 mins. A drop of NEt_3 was then added and the solution was concentrated and purified over

silica gel (Cyclohexane / EtOAc, 10 / 1) to give cyclopropane **(-)-6n** (38 mg, contaminated with bis-TBS protected alkene). The residue was dissolved in anhydrous THF (1.0 mL) and a solution of TBAF (0.34 mL, 1.0 M in THF, 0.34 mmol) was added at room temperature. The reaction was then stirred for 1 h, before it was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1) afforded methyl carbonate **(-)-7n** (7.4 mg, 0.023 mmol, 27%, 2 steps, 78% ee) as a colorless oil. The enantiomeric excess was determined by HPLC (CHIRALPACK IA (4.6x250 mm), hexane/*i*-PrOH = 95/5, flow rate = 1mL/min, t = 12.2, t = 14.9). $[\alpha]_D^{25.0}$ = -41.49º (*c* 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.87 (m, 1H), 5.34-5.32 (m, 1H), 5.27-5.25 (m, 1H), 4.58-4.56 (m, 2H), 3.92 (d, *J* = 11.5 Hz, 1H), 3.62 (s, 2H), 3.34 (d, *J* = 11.5 Hz, 1H), 3.14 (d, *J* = 10.0 Hz, 1H), 3.03-2.90 (br s, 1H), 2.89-2.66 (br s, 1H), 2.31-2.23 (m, 1H), 2.18-2.13 (m, 1H), 1.98-1.89 (m, 1H), 1.74 (s, 3H), 1.55 (s, 3H), 1.53-1.47 (m, 1H), 1.40 (s, 3H), 0.89-0.81 (m, 2H), 0.56-0.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 141.4, 132.7, 131.7, 119.2, 90.0, 70.7, 67.9, 65.8, 58.6, 37.8, 29.8, 28.1, 25.2, 24.7, 23.9, 19.8, 15.2; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{28}O_5Na$ [(*M*+Na)$^+$]: 347.1829, found: 347.1836.

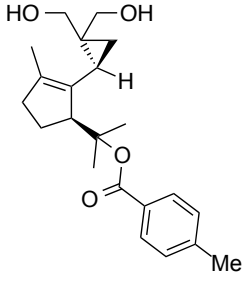
2-((1*R*)-2-(2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl 4-fluorobenzoate ((-)-7o)



A solution of enyne **(+)-4k** (20 mg, 0.073 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (1.69 mg, 2.19 μmol) and bis-TBS protected alkene **5e** (34.6 mg, 0.109 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at room temperature and the resulting solution was stirred for 5 mins. A drop of NEt_3 was then added and the solution was concentrated and purified over silica gel (Cyclohexane / EtOAc, 10 / 1) to give cyclopropane **(-)-6o** (42.0

mg, 0.071 mmol, contaminated with bis-TBS protected alkene). The residue was dissolved in anhydrous THF (1.0 mL) and a solution of TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol) was added at room temperature. The reaction was then stirred for 1 h, before it was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1) afforded methyl carbonate **(-)-7o** (4.50 mg, 0.012 mmol, 17%, 2 steps, 81% ee) as a colorless oil. The enantiomeric excess was determined by HPLC (CHIRALPACK IA (4.6x250 mm), hexane/*i*-PrOH = 95/5, flow rate = 1mL/min, t = 20.6, t = 35.1). $[\alpha]_D^{25.0}$ = -18.66º (*c* 0.20, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01-7.98 (m, 2H), 7.10-7.07 (m, 2H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.60 (d, *J* = 9.5 Hz, 1H), 3.54 (d, *J* = 11.5 Hz, 1H), 3.46 (d, *J* = 11.5 Hz, 1H), 3.03 (d, *J* = 11.5 Hz, 1H), 2.57-2.50 (br d, 2H), 2.34-2.31 (m, 1H), 2.16-2.11 (m, 1H), 1.96-1.90 (m, 1H), 1.76 (s, 3H), 1.73-1.68 (m, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.21-1.20 (m, 1H), 0.86-0.83 (m, 1H), 0.61-0.59 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8 (d, *J* = 303.0 Hz), 165.7, 141.8, 132.3, 132.1 (d, *J* = 10.5 Hz), 128.1 (d, *J* = 3.0 Hz), 115.6 (d, *J* = 27.0 Hz), 88.6, 69.9, 65.7, 56.2, 38.0, 28.1, 26.1, 24.8, 24.6, 22.9, 15.8, 15.4; HRMS-ESI: *m*/*z*: calcd for $C_{21}H_{27}FO_4Na$ [(*M*+Na)$^+$]: 385.1786, found: 385.1789.

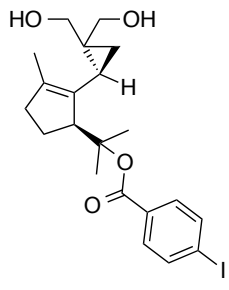
2-((*R*)-2-((*S*)-2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl 4-methylbenzoate ((-)-7p)



A solution of enyne **(+)-4l** (20.0 mg, 73.0 μmol) in anhydrous CH_2Cl_2 (0.25 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (1.1 mg, 1.5 μmol) and bis-TBS protected alkene **5e** (34.6 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at room temperature and the resulting solution was stirred for 5 mins. A drop of NEt_3 was then added and the solution was concentrated and purified by preparative TLC (Cyclohexane / EtOAc, 10 /

1) to give cyclopropane **(-)-6p** (35.2 mg, 60.0 μmol, contaminated with bis-TBS protected alkene) as a colorless oil. The residue was dissolved in anhydrous THF (1.0 mL) and a solution of TBAF (0.3 mL, 1.0 M in THF, 0.3 mmol) was added at room temperature. The reaction was then stirred for 1 h, before it was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1 to 1 / 2) afforded methyl benzoate **(-)-7p** (3.0 mg, 8.4 μmol, 11% over 2 steps, 77% ee) as a colorless oil. The enantiomeric excess was determined by HPLC (CHIRALPACK IA (4.6x250 mm), hexane/*i*-PrOH = 85/15, flow rate = 1mL/min, t = 6.88, t = 10.8). $[\alpha]_D^{25.0}$ = -37.09º (*c* 0.19, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.21 (m, 2H), 3.73 (d, *J* = 11.1 Hz, 1H), 3.66 (d, *J* = 9.5 Hz, 1H), 3.53-3.44 (m, 2H), 3.04 (d, *J* = 11.5 Hz, 1H), 2.52-2.48 (m, 1H), 2.40 (s, 3H), 2.35-2.32 (m, 2H), 2.14 (dd, *J* = 16.4, 9.8 Hz, 1H), 1.94 (dt, *J* = 13.6, 9.5 Hz, 1H), 1.76 (s, 3H), 1.73-1.63 (m, 2H), 1.61 (s, 3H), 1.45 (s, 3H), 0.81 (dd, *J* = 8.3, 4.7 Hz, 1H), 0.58 (t, *J* = 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 143.5, 141.4, 132.4, 129.6, 129.1, 129.0, 88.1, 69.6, 65.5, 55.8, 38.0, 29.7, 28.0, 26.2, 25.0, 24.2, 22.8, 15.4, 15.2; HRMS-ESI: *m*/*z*: calcd for $C_{22}H_{30}O_4Na$ [$(M+Na)^+$]: 381.2052, found: 381.2036.

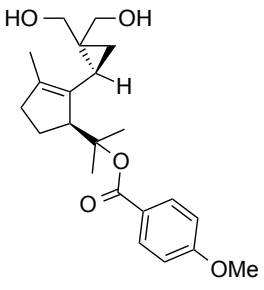
2-((*R*)-2-((*S*)-2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl 4-iodobenzoate ((-)-7q)



A solution of enyne **(+)-4m** (20.0 mg, 52.0 μmol) in anhydrous CH_2Cl_2 (0.25 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (0.8 mg, 1.0 μmol) and bis-TBS protected alkene **5e** (24.9 mg, 78 μmol) in anhydrous CH_2Cl_2 (0.5 mL) at room temperature and the resulting solution was stirred for 5 mins. A drop of NEt_3 was then added and the solution was concentrated and purified by preparative TLC (Cyclohexane / EtOAc, 10 / 1) to give cyclopropane **(-)-6q** (36.4 mg, 52.0 μmol, contaminated with bis-

TBS protected alkene) as a colorless oil. The residue was dissolved in anhydrous THF (1.0 mL) and a solution of TBAF (0.26 mL, 1.0 M in THF, 0.26 mmol) was added at room temperature. The reaction was then stirred for 1 h, before it was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1 to 1 / 2) afforded iodo benzoate **(-)-7q** (6.9 mg, 15.0 μmol, 29% over 2 steps, 77% ee) as a colorless oil. The enantiomeric excess was determined by HPLC (CHIRALPACK IA (4.6x250 mm), hexane/*i*-PrOH = 85/15, flow rate = 1mL/min, t = 8.10, t = 12.8). $[\alpha]_D^{25.0}$ = -34.03º (*c* 0.20, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.75 (m, 2H), 7.71-7.67 (m, 2H), 3.76 (d, *J* = 11.3 Hz, 1H), 3.57 (dd, *J* = 19.4, 10.3 Hz, 2H), 3.47 (d, *J* = 11.3 Hz, 1H), 3.06 (d, *J* = 11.2 Hz, 1H), 2.49-2.27 (m, 3H), 2.19-2.09 (m, 1H), 1.96-1.87 (m, 1H), 1.76 (s, 3H), 1.70 (ddt, *J* = 13.7, 8.1, 1.8 Hz, 1H), 1.59 (s, 3H), 1.48 (s, 3H), 1.21 (d, *J* = 6.2 Hz, 1H), 0.87-0.84 (m, 1H), 0.61 (t, *J* = 5.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 141.9, 137.9, 132.3, 131.4, 131.1, 100.8, 88.9, 70.0, 65.7, 56.2, 38.1, 28.2, 26.1, 24.8, 24.6, 22.9, 15.8, 15.4; HRMS-ESI: *m*/*z*: calcd for $C_{21}H_{27}IO_4Na$ [(*M*+Na)$^+$]: 493.0853, found: 493.0846.

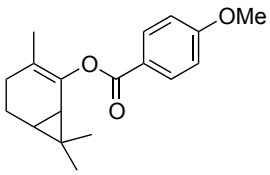
2-((*R*)-2-((*S*)-2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl 4-methoxybenzoate ((-)-7r)



A solution of enyne **(+)-4n** (20.0 mg, 70.0 μmol) in anhydrous CH_2Cl_2 (0.25 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (1.1 mg, 1.4 μmol) and bis-TBS protected alkene **5e** (33.2 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at room temperature and the resulting solution was stirred for 5 mins. A drop of NEt_3 was then added and the solution was concentrated and purified by preparative TLC (cyclohexane / EtOAc, 10 / 1) to give cyclopropane **(-)-6r** (20.2 mg, 33.0 μmol, contaminated with bis-

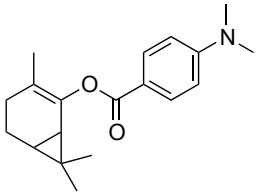
TBS protected alkene) as a colorless oil. The residue was dissolved in anhydrous THF (1.0 mL) and a solution of TBAF (0.17 mL, 1.0 M in THF, 0.17 mmol) was added at room temperature. The reaction was then stirred for 1 h, before it was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (Cyclohexane / EtOAc, 1 / 1 to 1 / 2) afforded methoxy benzoate **(-)-7r** (2.5 mg, 6.7 μmol, 9.5% over 2 steps, 77% ee) as a colorless oil. The enantiomeric excess was determined by HPLC (CHIRALPACK IA (4.6x250 mm), hexane/*i*-PrOH = 85/15, flow rate = 1mL/min, t = 9.47, t = 16.5). $[\alpha]_D^{25.0}$ = -25.84º (*c* 0.20, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.92 (m, 2H), 6.92-6.87 (m, 2H), 3.85 (s, 3H), 3.70 (dd, *J* = 21.8, 10.4 Hz, 2H), 3.53-3.43 (m, 2H), 3.05 (dd, *J* = 11.6, 5.8 Hz, 1H), 2.54-2.49 (m, 1H), 2.41-2.36 (m, 1H), 2.35-2.29 (m, 1H), 2.14 (dd, *J* = 16.6, 10.0 Hz, 1H), 1.97-1.88 (m, 1H), 1.75 (s, 3H), 1.70-1.66 (m, 1H), 1.61 (s, 3H), 1.43 (s, 3H), 1.22-1.20 (m, 1H), 0.80 (dd, *J* = 8.4, 4.8 Hz, 1H), 0.58 (t, *J* = 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 163.4, 141.5, 132.6, 131.7, 124.3, 113.8, 88.1, 69.6, 65.4, 60.6, 55.6, 38.1, 28.1, 26.3, 25.2, 24.3, 23.0, 15.5, 15.4; HRMS-ESI: *m*/*z*: calcd for $C_{22}H_{30}O_5Na$ [(*M*+Na)$^+$]: 397.1994, found: 397.1985.

3,7,7-Trimethylbicyclo[4.1.0]hept-2-en-2-yl 4-methoxybenzoate (7'r)



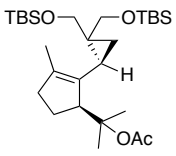
This product was obtained as a byproduct from the previous reaction of **(+)-4n** under gold(I) catalysis. Purification gave **7'r** (3.4 mg, 11.9 μmol, 17%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 6.96-6.94 (m, 2H), 3.88 (s, 3H), 2.31-2.26 (m, 1H), 1.92-1.81 (m, 2H), 1.72-1.66 (m, 1H), 1.58 (s, 3H), 1.23-1.21 (m, 1H), 1.16-1.12 (m, 1H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 163.5, 141.6, 132.0, 122.7, 119.1, 113.6, 55.5, 29.7, 28.0, 24.9, 24.7, 24.0, 17.7, 16.1, 15.8; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{22}O_3Na$ [(*M*+Na)$^+$]: 309.1474, found: 309.1461.

3,7,7-Trimethylbicyclo[4.1.0]hept-2-en-2-yl 4-(dimethylamino)benzoate (7's)



A solution of enyne **(+)-4o** (20.0 mg, 67.0 μmol) in anhydrous CH_2Cl_2 (0.25 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (1.0 mg, 1.3 μmol) and bis-TBS protected alkene **5e** (31.7 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at room temperature and the resulting solution was stirred for 5 mins. A drop of NEt_3 was then added and the solution was concentrated and purified by preparative TLC (cyclohexane / EtOAc, 10 / 1) to give the product of [1,2]-shift rearrangement **7's** (9.2 mg, 31.0 μmol, 46%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00-7.99 (m, 2H), 6.69-6.67 (m, 2H), 3.05 (s, 6H), 2.33-2.25 (m, 1H), 1.91-1.80 (m, 2H), 1.72-1.67 (m, 1H), 1.58 (s, 3H), 1.26-1.22 (m, 1H), 1.14-1.10 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 153.4, 141.6, 131.7, 118.8, 117.0, 110.7, 40.1, 29.7, 28.1, 24.8, 24.7, 24.1, 17.8, 16.1, 15.9; HRMS-ESI: *m*/*z*: calcd for $C_{19}H_{25}NO_2Na$ [(*M*+Na)$^+$]: 322.1782, found: 322.1777.

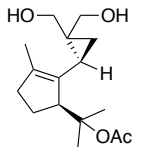
2-((*S*)-2-((*S*)-2,2-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl acetate ((-)-6l)



A solution of enyne **(+)-4h** (500 mg, 2.57 mmol) in anhydrous CH_2Cl_2 (8.6 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (47.9 mg, 0.051 mmol) and bis-TBS protected alkene **5e** (1.22 g, 3.86 mmol) in anhydrous CH_2Cl_2 (17.2 mL) at room temperature and the resulting solution was stirred for 5 mins. A few drops of NEt_3 were then added and the solution was concentrated and purified over silica gel (cyclohexane / EtOAc, 20 / 1) to give cyclopropane **(-)-6l** (684 mg, 1.34 mmol, 52% or 824 mg, 1.31 mmol, 86% pure) as a colorless oil. $[\alpha]_D^{25.0}$ = -20.23º (*c* 0.34, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (d, *J* = 9.9 Hz,

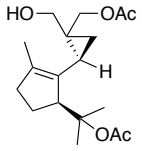
1H), 3.58 (d, *J* = 10.3 Hz, 1H), 3.39 (d, *J* = 9.9 Hz, 1H), 3.33 (d, *J* = 10.3 Hz, 1H), 3.13 (d, *J* = 8.3 Hz, 1H), 2.29-2.24 (m, 1H), 2.11-2.06 (m, 1H), 1.94 (s, 3H), 1.81-1.73 (m, 2H), 1.73 (s, 3H), 1.49 (s, 3H), 1.43 (s, 5H), 0.89 (s, 9H), 0.87 (s, 9H), 0.38 (dd, *J* = 6.0, 4.6 Hz, 1H), 0.02 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 140.7, 133.2, 86.9, 65.4, 63.2, 58.4, 37.9, 28.1, 26.1, 26.1, 25.3, 23.9, 23.3, 22.9, 21.3, 18.5, 18.4, 15.3, 14.9, -5.23, -5.32; HRMS-ESI: *m*/*z*: calcd for $C_{28}H_{54}O_4Si_2Na$ [(*M*+Na)$^+$]: 533.3453, found: 533.3471.

2-((*S*)-2-((*S*)-2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl acetate ((-)-7l)



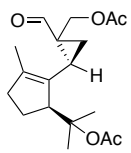
A solution of TBAF (40.1 mL, 1.0 M in THF, 40.1 mmol) was added dropwise to a solution of cyclopropane **(-)-6l** (4.10 g, 8.03 mmol) in anhydrous THF (80 mL, 0.10 M) at room temperature. The resulting mixture was stirred for 1 h, quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1 to 1 / 2) afforded diol **(-)-7l** (1.84 g, 6.52 mmol, 81%, 82% ee) as a colorless oil. The enantiomeric excess was determined by HPLC (heptane/*i*-PrOH = 90/10, flow rate = 1mL/min, $t_{(-)\text{-SI-1}}$ = 6.4, $t_{(+)\text{-SI-1}}$ = 7.2). $[\alpha]_D^{25.0}$ = -23.39º (*c* 0.34, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (d, *J* = 11.2 Hz, 2H), 3.44 (t, *J* = 10.7 Hz, 2H), 3.24-3.11 (m, 1H), 2.64-2.54 (br m, 2H), 2.31-2.24 (m, 1H), 2.13-2.08 (m, 1H), 1.97 (s, 3H), 1.89-1.80 (m, 1H), 1.74 (s, 3H), 1.64-1.60 (m, 1H), 1.45 (s, 3H), 1.39 (br s, 1H), 1.36 (s, 3H), 0.96 (dd, *J* = 8.3, 4.8 Hz, 1H), 0.66 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 141.7, 132.3, 87.7, 70.3, 65.7, 57.2, 37.9, 28.3, 25.8, 24.6, 23.2, 23.2, 23.0, 16.1, 15.3; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{26}O_4Na$ [(*M*+Na)$^+$]: 305.1723, found: 305.1736.

2-((*S*)-2-((1*S*,2*S*)-2-(Acetoxymethyl)-2-(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl acetate ((-)-8l)



A solution of Ac_2O (0.62 mL, 6.60 mmol) in CH_2Cl_2 (6.6 mL) was added dropwise over 1 h to a solution of DMAP (38.0 mg, 0.31 mmol), anhydrous pyridine (1.01 mL, 12.6 mmol) and diol **(-)-7l** (1.77 g, 6.28 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ºC. The solution was stirred for additional hour at 0 ºC. The reaction was then quenched with aqueous a 0.5 M aqueous HCl, extracted with EtOAc, washed with a 0.5 M aqueous HCl, water and brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash column chromatography (cyclohexane / EtOAc, 4 / 1) afforded the desired monoacetate **(-)-8l** (1.43 g, 4.40 mmol, 70%) as a colorless oil. The undesired monoacetate and bis-acetate were combined and recycled. $[\alpha]_D^{25.0}$ = -23.79º (*c* 0.30, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 11.4 Hz, 1H), 3.52 (d, *J* = 11.8 Hz, 1H), 3.39 (d, *J* = 11.8 Hz, 1H), 3.18 (d, *J* = 9.3 Hz, 1H), 2.36-2.23 (m, 2H), 2.13-2.11 (m, 1H), 2.07 (s, 3H), 1.95 (s, 3H), 1.88-1.77 (m, 1H), 1.72 (s, 3H), 1.68-1.64 (m, 1H), 1.45 (m, 1H), 1.40 (s, 6H), 1.00 (dd, *J* = 8.3, 4.9 Hz, 1H), 0.61 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.9, 142.6, 131.8, 87.1, 69.3, 63.3, 57.2, 37.9, 26.2, 25.5, 24.2, 23.8, 23.2, 23.0, 21.1, 16.3, 15.3; HRMS-ESI: *m*/*z*: calcd for $C_{18}H_{28}O_5Na$ [(*M*+Na)$^+$]: 347.1829, found: 347.1841.

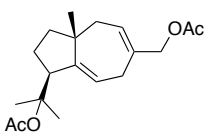
2-((*S*)-2-((1*S*,2*R*)-2-(Acetoxymethyl)-2-formylcyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl acetate ((-)-10l)



$NaHCO_3$ (838 mg, 9.97 mmol) and Dess-Martin periodinane (1.27 g, 2.99 mmol) were added to a solution of monoacetate **(-)-8l** (647 mg, 1.99 mmol) in anhydrous CH_2Cl_2 (40 mL) at room temperature and the resulting mixture was stirred for 2 h. The reaction was then quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution, extracted with

EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness to give the crude aldehyde **(-)-10l** as a colorless solid, which was used in the subsequent step without further purification.

2-((1*S*,3a*R*)-6-(Acetoxymethyl)-3a-methyl-1,2,3,3a,4,7-hexahydroazulen-1-yl)propan-2-yl acetate ((-)-12l)



A solution of *n*BuLi (1.7 mL, 1.6 M in hexane, 2.74 mmol) was added dropwise to a suspension of PPh_3CH_3Br (1.05 g, 2.94 mmol) in anhydrous and degassed THF (29 mL) at -20 ºC and the resulting pale yellow solution was stirred for 10 min at -20 ºC, whereupon a solution of aldehyde **(-)-10l** (631.5 mg, 1.96 mmol) in anhydrous and degassed THF (15 mL) was added dropwise. After 10 min at -20 ºC, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (*n*pentane / Et_2O, 10 / 1) afforded diene **(-)-12l** (528.7 mg, 1.65 mmol, 83% over 2 steps) as a colorless oil. The compound was reacted promptly in the next two steps to minimize the reported air oxidation.[168] $[\alpha]_D^{25.0}$ = -97.62º (*c* 0.73, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (br d, J = 8.0 Hz, 1H), 5.59-5.57 (m, 1H), 4.48-4.43 (m, 2H), 3.35-3.32 (m, 1H), 2.98-2.87 (m, 2H), 2.34 (br d, J = 15.5 Hz, 1H), 2.13 (br d, J = 8.0 Hz, 1H), 2.09 (s, 3H), 2.00 (s, 3H), 1.55-1.42 (m, 2H+2H), 1.51 (s, 3H), 1.44 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 170.3, 150.2, 132.7, 127.8, 118.7, 85.3, 70.7, 53.4, 45.9, 41.2, 40.6, 31.1, 26.1, 25.3, 23.7, 22.7, 22.5, 21.0; HRMS-ESI: *m*/*z*: calcd for $C_{19}H_{28}O_4Na$ [$(M+Na)^+$]: 343.1880, found: 343.1884.

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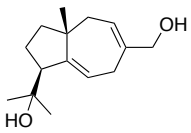
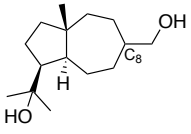
2-((1*S*,3a*R*)-6-(Hydroxymethyl)-3a-methyl-1,2,3,3a,4,7-hexahydroazulen-1-yl)propan-2-ol ((-)-15)



A solution of bis-acetate **(-)-12l** (285 mg, 0.89 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (304 mg, 8.01 mmol) in anhydrous THF (5 mL) at 0 ºC. The resulting reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The reaction was then quenched with an aqueous saturated NH_4Cl solution and a Rochelle salt solution (20 mL) and was then stirred for 1 h under Ar. The mixture was then extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash column chromatography (Cyclohexane / EtOAc, 1 / 1) afforded bisalcohol **(-)-15** (190 mg, 0.80 mmol, 90%, 80% ee) as a colorless solid. The enantiomeric excess was determined by HPLC (heptane/*i*-PrOH = 95/5, flow rate = 1mL/min, $t_{(+)\text{-}12b}$ = 20.0, $t_{(-)\text{-}12b}$ = 22.5). The compound was reacted promptly in the next step to minimize the reported air oxidation. mp 91-95 ºC; $[\alpha]_D^{25.0}$ = -109.99º (*c* 0.48, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77-5.73 (m, 1H+1H), 3.98 (s, 2H), 2.95 (s, 2H), 2.69-2.65 (m, 1H), 2.31 (br d, *J* = 15.0 Hz, 1H), 2.08 (dd, *J* = 15.5, 8.0 Hz, 1H), 1.78-1.72 (m, 1H), 1.56-1.50 (m, 2H), 1.45-1.41 (m, 2H), 1.29 (br m, 1H), 1.24 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 138.0, 124.7, 120.2, 73.4, 69.4, 57.0, 45.8, 41.9, 40.4, 30.6, 30.1, 26.3, 25.9, 24.0; HRMS-ESI: *m*/*z*: calcd for $C_{15}H_{24}O_2Na$ [(*M*+Na)$^+$]: 259.1669, found: 259.1669.

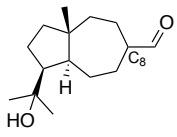
2-((1*S*,3a*S*,8a*S*)-6-(Hydroxymethyl)-3a-methyldecahydroazulen-1-yl)propan-2-ol (17)



Wet slurry of Raney nickel 2400 (5 mL) was washed five times with dry acetone. The resulting slurry was dissolved in 24 mL of acetone. The resulting solution was distributed between 24 different 2 mL tubes (1 mL) and the acetone was decanted and removed. A solution of bis-alcohol **(-)-15** (250.0 mg, 1.06

mmol) in acetone (24.0 mL, 0.2 M) was distributed to each tube (1 mL each). The tubes were then sealed into a "HEL reactor" (pressure reactor) and the atmosphere was purged with H_2. The apparatus was pressurized to 80 bar and was re-pressurized with H_2 every 12h. The reaction was stirred at 63 ºC until consumption of the starting material was achieved (as indicated by stagnant hydrogen consumption, typically 60-70 h). The pressure was then released from the parr bomb and the substrate was filtered through Celite atop of silica gel with CH_2Cl_2. The solution was then concentrated to dryness and purification by flash column chromatography (cyclohexane / EtOAc, 1 / 1) afforded hydrogenated compound **17** (2/1 epimers at C_8, 211.5 mg, 0.880 mmol, 83%) as a colorless oil. $[\alpha]_D^{25.0}$ = -0.98º (*c* 0.45, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40-3.33 (m, 2H), 3.22-3.20 (m, 1H), 2.72-2.69 (m, 1H), 2.33-2.24 (m, 1H), 2.21-2.05 (m, 1H), 1.83-1.62 (m, 7H), 1.59 (br m, 1H), 1.51-1.41 (m, 4H), 1.29-1.23 (m, 6H), 1.21.1.18 (m, 3H), 1.14 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 74.2, 69.3, 53.7, 49.8, 47.4, 44.2, 43.2, 41.8, 39.8, 32.3, 29.9, 27.8, 27.7, 24.5, 23.3; HRMS (EI): *m/z*: calcd for $C_{15}H_{28}O$ [(*M-OH*)$^+$]: 223.2056, found: 223.2057 (fragmentation).

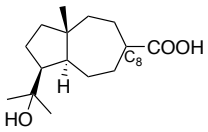
(1*S*,3a*R*,8a*S*)-1-(2-Hydroxypropan-2-yl)-3a-methyldecahydroazulene-6-carbaldehyde (18)



To a solution of the bis-alcohol **17** (220 mg, 0.91 mmol) in CH_2Cl_2 (9.0 mL) was added TEMPO (36.0 mg, 0.23 mmol), BAIB (796 mg, 2.47 mmol) and water (4.5 mL) and the reaction was stirred at room temperature until consumption of the starting material was achieved (as indicated by TLC, typically 2 h). A solution of $Na_2S_2O_3$ (10% in water) was added and the mixture was stirred efficiently for 10 min, extracted with EtOAc, washed with brine, dried overNa_2SO_4, filtered and concentrated to dryness. Purification by flash column chromatography (cyclohexane / EtOAc, 3 / 1) furnished aldehyde **18** (119.2 mg, 0.500 mmol, 55%, both epimers at C_8 2:1) as a colorless oil.

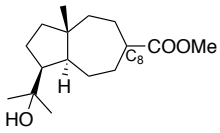
$[\alpha]_D^{25.0}$ = +6.21º (*c* 0.25, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 2.52.2.47 (m, 1H), 2.32-2.25 (m, 2H+1H), 2.18-2.12 (m, 1H), 2.06-2.01 (m, 2H), 1.88-1.82 (m, 2H+1H), 1.76-1.68 (m, 2H), 1.45-1.35 (2H+2H), 1.26 (s, 3H), 1.25 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 74.1, 53.5, 51.4, 50.0, 47.6, 45.5, 43.5, 39.2, 32.4, 28.3, 27.7, 26.4, 22.7, 19.6; HRMS-ESI: *m*/*z*: calcd for $C_{15}H_{26}O_2Na$ [$(M+Na)^+$]: 261.1831, found: 261.1834.

(1*S*,3a*R*,8a*S*)-1-(2-Hydroxypropan-2-yl)-3a-methyldecahydroazulene-6-carboxylic acid (19)



To a solution of aldehyde **18** (63.0 mg, 0.26 mmol) in *tert*-butyl alcohol/water (5:1, 4.0 mL) was added successively NaH_2PO_4 (53.8 mg, 0.45 mmol), 2-methyl-2-butene (88.9 mg, 1.3 mmol), and $NaClO_2$ (82.5 mg, 0.91 mmol) and the resulting mixture was stirred for 2 h. The reaction was then extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give crude acid **19** as a colorless solid, which was used in the subsequent step without further purification.

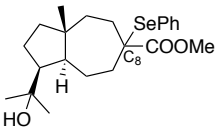
(1*S*,3a*R*,8a*S*)-Methyl 1-(2-hydroxypropan-2-yl)-3a-methyldecahydroazulene-6-carboxylate (20)



To a solution of the crude acid **19** (67.1 mg, 0.26 mmol) in dry toluene (1.4 mL) and dry MeOH (3.4 mL) at 0 ºC was added dropwise a 2 M solution of $TMSCHN_2$ (0.26 mL, 0.53 mmol) in Et_2O until the yellow color persisted. The solution was stirred for an additional 20 min at room temperature. The reaction was then quenched by a drop of acetic acid, concentrated to dryness and purified by flash column chromatography (cyclohexane / EtOAc, 3 / 1) to give methyl esters **20** (both epimers at C_8 2:1, 52.3 mg, 0.20 mmol, 74% over 2 steps) as a colorless oil. $[\alpha]_D^{25.0}$ = -1.00º (*c* 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.46-2.40 (m, 1H),

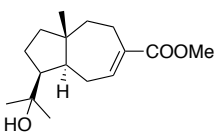
2.29-2.22 (m, 2H), 2.07-1.98 (m, 2H), 1.91-1.83 (m, 2H+1H), 1.79-1.74 (m, 1H), 1.70-1.64 (m, 2H+1H), 1.51-1.40 (m, 2H+2H), 1.25 (s, 3H), 1.24 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 74.1, 53.6, 51.7, 47.3, 45.4, 43.8, 42.8, 39.6, 32.2, 30.1, 28.3, 27.7, 26.6, 23.1, 19.6; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{28}O_3Na$ [(*M*+Na)$^+$]: 291.1926, found: 291.1931.

(1*S*,3a*R*,8a*S*)-Methyl 1-(2-hydroxypropan-2-yl)-3a-methyl-6 (phenylselanyl)decahydroazulene-6-carboxylate (21)



To a solution of methyl ester epimers **20** (51.0 mg, 0.19 mmol) in anhydrous THF (5.0 mL) at -78 ºC was added KHMDS (0.7 M in toluene, 0.54 mL, 0.38 mmol) and the resulting solution was stirred for 5 min at -78 ºC. A solution of PhSeCl (72.8 mg, 0.38 mmol) in THF (1.0 mL) was then added and the reaction mixture was allowed to warm to 0 ºC over 3h. The reaction was quenched with water, diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by flash chromatography (cyclohexane / EtOAc, 4 / 1) gave the phenyl selenium compound **21** (both epimers at C_8 6:1, 74.8 mg, 0.18 mmol, 93%) as a colorless oil. $[\alpha]_D^{25.0}$ = -13.77º (*c* 1.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.41-7.38 (m, 1H), 7.33-7.30 (m, 2H), 3.66 (s, 3H), 2.33-2.14 (m, 2H+2H), 1.99-1.92 (m, 1H), 1.90-1.78 (m, 2H), 1.65-1.61 (m, 2H+1H), 1.52-1.46 (m, 1H), 1.38-1.25 (m, 2H+2H), 1.22 (s, 3H+3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 138.3, 129.6, 128.8, 128.4, 73.8, 53.0, 51.8, 48.1, 45.1, 42.9, 41.9, 35.5, 34.9, 31.7, 30.3, 29.1, 27.6, 24.4, 19.2; HRMS-ESI: *m*/*z*: calcd for $C_{22}H_{32}O_3{}^{80}SeNa$ [(*M*+Na)$^+$]: 447.1414, found: 447.1398.

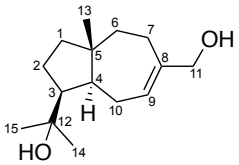
(1*S*,3a*R*,8a*S*)-Methyl 1-(2-hydroxypropan-2-yl)-3a-methyl-1,2,3,3a,4,5,8,8a-octahydroazulene-6-carboxylate ((+)-22)



To a solution of selenide **21** (80.4 mg, 0.19 mmol) in CH_2Cl_2 (4.0 mL mL) was added 50 µL of a 30%

aqueous H_2O_2 solution. The resulting solution was stirred for 1 h at 25 ºC, then diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 3 / 1) yielded **(+)-22** as a mixture of double bond isomers (typically a 2:1 to 3:1 mixture of double bond isomers, 36.8 mg, 0.14 mmol, 73%). $[\alpha]_D^{25.0}$ = +7.01º (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dt, *J* = 8.5, 3.0 Hz, 1H), 3.71 (s, 3H), 3.15 (ddd, *J* = 17.0, 8.5, 2.0 Hz, 1H), 2.75 (dt, *J* = 16.5, 4.0 Hz, 1H), 2.42-2.32 (m, 2H+1H), 1.87-1.82 (m, 1H), 1.79-1.75 (m, 1H), 1.73-1.70 (m, 1H), 1.50-1.45 (m, 2H), 1.39-1.36 (m, 1H), 1.34-1.28 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.9, 133.7, 74.4, 57.2, 53.1, 52.0, 49.4, 44.6, 42.1, 40.9, 32.9, 29.4, 27.2, 23.7, 18.1; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{26}O_3Na$ [(*M*+Na)$^+$]: 289.1780, found: 289.1774.

Schisanwilsonene A ((+)-1)

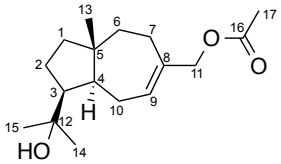


To a solution of the mixture of unsaturated methyl esters **(+)-22** (33.6 mg, 0.13 mmol) in dry THF (5.0 mL) at -78 ºC was added DIBAL (0.5 mL, 0.50 mmol, 1 M in toluene) and the resulting solution was warmed to -20 ºC over 1.5 h. The mixture was then allowed to warm to room temperature over 2 h. The reaction was quenched by the addition of a saturated solution of sodium potassium tartrate. The reaction was then extracted with Et_2O, washed with water, dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash chromatography (cyclohexane / EtOAc, 1 / 1) and recrystallization from cyclohexane / EtOAc yielded (+)-schisanwilsonene A **(+)-1** (15.0 mg, 0.063 mmol, 78%, 82% ee) as a colorless solid. The enantiomeric excess was determined by HPLC (hexane/*i*-PrOH = 99/1, flow rate = 1mL/min, $t_{(+)\text{-}1}$ = 46.0, $t_{(-)\text{-}1}$ = 51.0). mp 143-144 ºC; $[\alpha]_D^{25.5}$ = 14.9º (*c* 0.216, CH_2Cl_2); $[\alpha]_D^{24.7}$ = 14.8º (*c* 0.33, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (d, *J* = 9.6 Hz, 1H), 3.94 (d, *J* = 5.2 Hz, 2H), 2.88 (ddd, *J* = 2.4, 8.4, 16.0, Hz, 1H), 2.29-2.26 (m 1H),

2.16-2.09 (m, 2H), 2.06 (dt, J = 2.4, 12.4 Hz, 1H), 1.87-1.81 (m, 1H), 1.77-1.69 (m, 2H), 1.50-1.32 (m, 4H), 1.29-1.26 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 127.6, 74.5, 70.8, 53.4, 50.5, 44.7, 42.2, 41.4, 32.7, 27.6, 27.3, 26.6, 26.2, 17.9; HRMS-ESI: m/z: calcd for $C_{15}H_{26}O_2Na$ [$(M+Na)^+$]: 261.1825, found: 261.1829.

The NMR data is in full accordance with previously reported data.[169] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47, 1.32 (each 1H, m, H-1), 1.47, 1.73 (each 1H, m, H-2), 2.31 (1H, m, H-3), 1.83 (1H, m, H-4), 1.22, 1.76 (each 1H, m, H-6), 2.05, 2.25 (each 1H, m, H-7), 5.78 (1H, d, J = 8.6 Hz, H-9), 2.21, 2.88 (1H, m, H-10), 3.93 (2H, s, H-11), 0.88 (3H, s, H-13), 1.23 (3H, s, H-14), 1.21 (3H, s, H-15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.0 (CH2, C-1), 27.4 (CH2, C-2), 53.2 (CH,C-3), 50.3 (CH, C-4), 44.6 (C, C-5), 41.1 (CH2,C-6), 26.0 (CH2, C-7), 140.7 (C, C-8), 127.5 (CH, C-9), 26.5 (CH2, C-10), 70.6 (CH2, C-11), 74.4 (C, C-12), 17.7 (CH3, C-13), 27.1 (CH3, C-14), 32.5 (CH3, C-15).

Schisanwilsonene B ((+)-2)



A solution of Ac_2O (3.03 µL, 0.032 mmol) was added dropwise to a solution of DMAP (1.18 mg, 9.63 µmol), anhydrous pyridine (8.62 µL, 0.11 mmol) and (+)-schisanwilsonene A **(+)-1** (5.1 mg, 0.021 mmol) in anhydrous CH_2Cl_2 (0.2 mL) at 0 ºC. The solution was then stirred for an additional hour at room temperature, then quenched with aqueous HCl (0.5 M), extracted with EtOAc, washed with a 0.5 M aqueous HCl solution, water and brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash column chromatography (cyclohexane / EtOAc, 4 / 1) afforded (+)-schisanwilsonene B **(+)-2** (5.3 mg, 0.019 mmol, 88%, 82% ee) as a white solid. mp 182-185 ºC; $[\alpha]_D^{24.4}$ = 11.7º (c 0.18, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 8.6, 2.9, 1.8 Hz, 1H),

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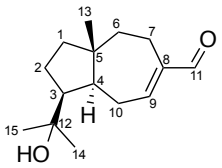
4.43 (s, 2H), 2.92 (ddd, J = 16.4, 8.6, 2.7 Hz, 1H), 2.35 (ddd, J = 11.6, 10.0, 8.6 Hz, 1H), 2.29-2.20 (m, 2H), 2.09 (s, 3H), 2.02 (dt, J = 16.5, 3.9 Hz, 1H), 1.92-1.85 (m, 1H), 1.79-1.71 (m, 2H), 1.52-1.44 (m, 2H), 1.38-1.34 (m, 1H), 1.34-1.28 (m, 5H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 135.8, 131.0, 74.3, 72.0, 53.2, 50.1, 44.6, 42.0, 41.0, 32.6, 27.4, 27.2, 26.7, 26.3, 21.1, 17.8; HRMS-ESI: m/z: calcd for $C_{17}H_{28}NaO_3$ [$(M+Na)^+$]: 303.1931, found: 303.1928.

The NMR data is in full accordance with previously reported data.[169] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45, 1.32 (each 1H, m, H-1), 1.42, 1.71 (each 1H, m, H-2), 2.31 (1H, m, H-3), 1.86 (1H, m, H-4), 1.26, 1.74 (each 1H, m, H-6), 1.98, 2.22 (each 1H, m, H-7), 5.83 (1H, d, J = 8.6 Hz, H-9), 2.20, 2.89 (each 1H, m, H-10), 4.40 (2H, s, H-11), 0.89 (3H, s, H-13), 1.23 (3H, s, H-14), 1.21 (3H, s, H-15), 2.06 (3H, s, H-17); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.0 (CH2, C-1), 27.4 (CH2, C-2), 53.2 (CH, C-3), 50.1 (CH, C-4), 44.5 (C, C-5), 41.0 (CH2, C-6), 26.3 (CH2, C-7), 135.8 (C, C-8), 131.0 (CH, C-9), 26.7 (CH2, C-10), 72.0 (CH2, C-11), 74.3 (C, C-12), 17.7 (CH3, C-13), 27.1 (CH3, C-14), 32.5 (CH3, C-15), 171.1 (C, C-16), 21.1 (CH3, C-17).

Schisanwilsonene C ((+)-3)

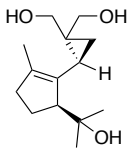


$NaHCO_3$ (7.4 mg, 0.088 mmol) and Dess-Martin periodinane (11.21 mg, 0.026 mmol) were added to a solution of (+)-schisanwilsonene A **(+)-1** (4.2 mg, 0.018 mmol) in anhydrous CH_2Cl_2 (0.35 mL) at room temperature. The resulting mixture was stirred for 2 h before it was quenched by a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The solution was then extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash column chromatography (cyclohexane / EtOAc, 4 / 1) afforded (+)-schisanwilsonene C **(+)-3** (2.6 mg, 0.011 mmol, 62%, 82% ee) as a white solid. mp 126-129 ºC; $[\alpha]_D^{24.5}$ = 15.3º (c 0.26, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.80 (dt, J = 8.5, 2.8

Hz, 1H), 2.76 (dt, *J* = 17.2, 3.9 Hz, 1H), 2.52-2.47 (m, 1H), 2.38-2.34 (m, 1H), 2.01-1.98 (m, 1H), 1.92-1.87 (m, 1H), 1.82-1.77 (m, 1H), 1.76-1.72 (m, 1H), 1.48-1.45 (m, 2H), 1.38-1.34 (m, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.18-1.17 (m, 1H), 0.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8, 157.2, 146.4, 74.4, 53.1, 49.5, 44.6, 42.1, 40.3, 32.5, 28.5, 27.3, 25.6, 20.4, 17.9; HRMS-ESI: *m*/*z*: calcd for $C_{15}H_{24}NaO_2$ [$(M+Na)^+$]: 259.1669, found: 259.1666.

The NMR data is in full accordance with previously reported data.[169] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50, 1.35 (each 1H, m, H-1), 1.41, 1.72 (each 1H, m, H-2), 2.36 (1H, m, H-3), 1.88 (1H, m, H-4), 1.16, 1.81 (each 1H, m, H-6), 2.01, 2.75 (each 1H, m, H-7), 6.80 (1H, d, *J* = 8.6 Hz, H-9), 2.50, 2.36 (1H, m, H-10), 9.30 (1H, s, H-11), 0.89 (3H, s, H-13), 1.26 (3H, s, H-14), 1.24 (3H, s, H-15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.1 (CH2, C-1), 27.2 (CH2, C-2), 53.9 (CH, C-3), 49.3 (CH, C-4), 44.5 (C, C-5), 41.9 (CH2, C-6), 20.2 (CH2, C-7), 144.7 (C, C-8), 157.0 (CH, C-9), 28.3 (CH2, C-10), 196.1 (CH, C-11), 74.3 (C, C-12), 17.7 (CH3, C-13), 26.9 (CH3, C-14), 33.0 (CH3, C-15).

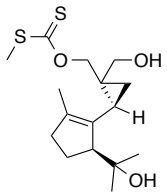
((*S*)-2-((*S*)-5-(2-Hydroxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)cyclopropane-1,1-diyl)dimethanol (-)-26



Slurry of diol **(-)-7l** (100 mg, 0.36 mmol) and NaOMe (192.0 mg, 3.55 mmol) in MeOH (5.0 mL) was stirred at 50 ºC for 18 h. The reaction was then quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1) afforded triol **(-)-26** (84.2 mg, 0.35 mmol, 99%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (d, *J* = 11.5 Hz, 1H), 3.74 (d, *J* = 11.5 Hz, 1H), 3.52 (d, *J* = 11.5 Hz, 1H), 3.18 (d, *J* = 11.5 Hz, 1H), 2.85 (br s, 1H), 2.23 (br s, 2H), 1.99-1.92 (m, 1H), 1.80 (s, 3H), 1.61 (br s, 1H), 1.47-1.40 (m, 1H), 1.27 (s, 3H), 1.15 (s, 3H), 0.95-0.89 (m, 1H), 0.56-0.53 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 132.4, 75.9, 70.0, 65.1, 56.0,

37.2, 30.5, 27.9, 26.1, 23.4, 22.8, 16.7, 15.1; HRMS-ESI: *m*/*z*: calcd for $C_{14}H_{24}O_3Na$ [(*M*+Na)$^+$]: 263.1618, found: 263.1622; mp (cyclohexane / EtOAc) 161 ºC.

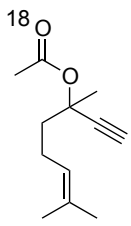
_O_-(((1_S_,2_S_)-1-(Hydroxymethyl)-2-((_S_)-5-(2-hydroxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)cyclopropyl)methyl) _S_-methyl carbonodithioate ((-)-27)



Dry CS_2 (30 µL, 0.50 mmol) was added dropwise to a slurry of triol **(-)-26** (50 mg, 0.208 mmol) and powdered KOH (31.5 mg, 0.56 mmol) in dry DMSO (6.0 mL). The solution was stirred for 30 min at 23 °C, before MeI (64.9 mg, 0.45 mmol) was added dropwise. The resulting mixture was stirred for an additional 30 min at 23 ºC. The reaction was quenched with $Na_2S_2O_3$, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. Purification over silica gel (cyclohexane / EtOAc, 1 / 1) afforded xanthate **(-)27** (7.4 mg, 0.022 mmol, 11%) as a colorless solid, which was recrystallized from *n*-pentane / EtOAc. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (d, *J* = 11.5 Hz, 1H), 4.13 (d, *J* = 11.5 Hz, 1H), 4.05 (d, *J* = 11.5 Hz, 1H), 2.99 (d, *J* = 11.5 Hz, 1H), 2.59 (s, 3H), 2.54 (d, *J* = 9.5 Hz, 1H), 2.23-2.21 (m, 2H), 1.98-1.94 (m, 1H), 1.77 (s, 3H), 1.73-1.71 (m, 1H), 1.49-1.44 (m, 1H), 1.30 (s, 3H), 1.13 (s, 3H), 1.08-1.06 (m, 1H), 0.96-0.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.2, 140.4, 132.0, 76.3, 75.8, 67.9, 60.6, 37.5, 31.1, 26.3, 25.8, 24.0, 23.8, 18.9, 17.3, 14.9; HRMS-ESI: *m*/*z*: calcd for $C_{16}H_{26}O_3S_2Na$ [(*M*+Na)$^+$]: 353.1216, found: 353.1226.

^{18}O labeling study

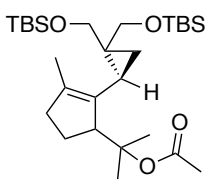
3,7-Dimethyloct-6-en-1-yn-3-yl acetate (^{18}O-(±)-4h)



To a stirred solution of 3,7-dimethyloct-6-en-1-yn-3-ol (203.0 mg, 1.33 mmol), acetic acid labelled ^{18}O (0.090 mL, 1.67 mmol), EDCI (470.0 mg, 3.33 mmol) and

iPr_2NEt (1.16 mL, 6.66 mmol) in CH_2Cl_2 (16.0 mL) was added a solution of DMAP (407.0 mg, 3.33 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. After stirring at room temperature for 16h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by flash chromatography (cyclohexane / EtOAc, 10 / 1) yielded ester **^{18}O-(±)-4h** (47.6 mg, 0.25 mmol, 18%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (tdt, J = 7.3, 2.9, 1.5 Hz, 1H), 2.56 (s, 1H), 2.22-2.12 (m, 2H), 2.03 (s, 3H), 1.99-1.89 (m, 1H), 1.86-1.77 (m, 1H), 1.68 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5 and 169.5 (carbonyl signal as two peaks for C=^{18}O), 132.5, 123.3, 84.0, 74.9, 73.4, 41.5, 26.5, 25.8, 23.0, 22.1, 17.8; ESI$^+$: [(M+Na)$^+$]: 219.1.

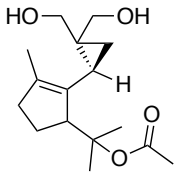
2-((*S*)-2-((*S*)-2,2-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl acetate (^{18}O-(±)-6l)



A solution of enyne **^{18}O-(±)-4h** (40.6 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (0.7 mL) was added dropwise over 30 min to a stirred solution of gold catalyst **A** (3.9 mg, 0.0040 mmol) and bis-TBS protected alkene **5e** (132.0 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (1.4 mL) at room temperature and the resulting mixture was stirred for 5 mins. A few drops of NEt_3 were then added and the solution was concentrated and purified over silica gel (cyclohexane / EtOAc, 20 / 1) to give a mixture of cyclopropane **^{18}O-(±)-6l** and bis-TBS protected alkene **5e** (136.6 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (d, J = 9.9 Hz, 1H), 3.58 (d, J = 10.3 Hz, 1H), 3.39 (d, J = 9.9 Hz, 1H), 3.33 (d, J = 10.3 Hz, 1H), 3.13 (d, J = 8.3 Hz, 1H), 2.29-2.24 (m, 1H), 2.11-2.06 (m, 1H), 1.94 (s, 3H), 1.81-1.73 (m, 2H), 1.73 (s, 3H), 1.49 (s, 3H), 1.43 (s, 5H), 0.89 (s, 9H), 0.87 (s, 9H), 0.38 (dd, J =

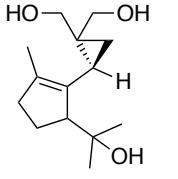
6.0, 4.6 Hz, 1H), 0.02 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 140.7, 133.2, 86.9, 65.4, 63.2, 58.4, 37.9, 28.1, 26.1, 26.1, 25.3, 23.9, 23.3, 22.9, 21.3, 18.5, 18.4, 15.3, 14.9, -5.23, -5.32; ESI$^+$: [(M+Na)$^+$]: 535.3.

2-((*S*)-2-((*S*)-2,2-Bis(hydroxymethyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-yl acetate (^{18}O-(±)-7l)



A 1 M solution of TBAF in THF (1.34 mL, 1.34 mmol) was added dropwise to a solution of cyclopropane **^{18}O-(±)-6l** contaminated with bis-TBS protected alkene **5e** (136.6 mg, 0.27 mmol) in anhydrous THF (2.7 mL, 0.10 M) at room temperature. The resulting mixture was stirred for 1 h. The reaction was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification over silica gel (cyclohexane / EtOAc, 1 / 1 to 1 / 2) afforded diol **^{18}O-(±)-7l** (20.3 mg, 0.072 mmol, 36% over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (d, J = 11.2 Hz, 2H), 3.44 (t, J = 10.7 Hz, 2H), 3.24-3.11 (m, 1H), 2.64-2.54 (br m, 2H), 2.31-2.24 (m, 1H), 2.13-2.08 (m, 1H), 1.97 (s, 3H), 1.89-1.80 (m, 1H), 1.74 (s, 3H), 1.64-1.60 (m, 1H), 1.45 (s, 3H), 1.39 (br s, 1H), 1.36 (s, 3H), 0.96 (dd, J = 8.3, 4.8 Hz, 1H), 0.66 (t, J = 5.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 141.7, 132.3, 87.7, 70.3, 65.7, 57.2, 37.9, 28.3, 25.8, 24.6, 23.2, 23.2, 23.0, 16.1, 15.3; ESI$^+$: [(M+Na)$^+$]: 307.1.

((2*S*)-2-(5-(2-Hydroxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)cyclopropane-1,1-diyl)dimethanol (^{18}O-(±)-26)



A solution of diol **^{18}O-(±)-7l** (17.3 mg, 0.061 mmol) in anhydrous THF (0.65 mL) was added dropwise to a suspension of $LiAlH_4$ (20.8 mg, 0.55 mmol) in anhydrous THF (0.35 mL) at 0 ºC. The resulting reaction mixture was allowed to warm to room temperature and stirred for another 2 h. The reaction was quenched by the addition of

an aqueous saturated NH_4Cl solution and a Rochelle salt solution (5.0 mL) and the resulting solution was stirred for 1 h under argon. The mixture was then extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash column chromatography (cyclohexane / EtOAc, 4 / 1) afforded trisalcohol **^{18}O-(±)-26** (14.2 mg, 0.059 mmol, 97%) as a colorless solid. mp 129-131 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (d, J = 11.3 Hz, 1H), 3.70 (d, J = 11.4 Hz, 1H), 3.51 (d, J = 11.4 Hz, 1H), 3.26 (brs, 1H), 3.13 (d, J = 11.2 Hz, 1H), 2.83 (brm, 1H), 2.21 (brm, 2H), 1.96-1.90 (m, 1H), 1.74 (s, 3H), 1.67 (brs, 2H), 1.60 (brm, 1H), 1.44-1.39 (m, 1H), 1.24 (s, 3H), 1.12 (s, 3H), 0.90 (dd, J = 8.4, 4.7 Hz, 1H), 0.52 (dd, J = 6.4, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 132.7, 75.8, 70.1, 65.3, 59.2, 37.4, 30.7, 28.2, 26.2, 23.6, 23.0, 16.9, 15.3; ESI$^+$: [(M+Na)$^+$]: 265.1.

Crystal structures

Schisanwilsonene A ((±)-1)

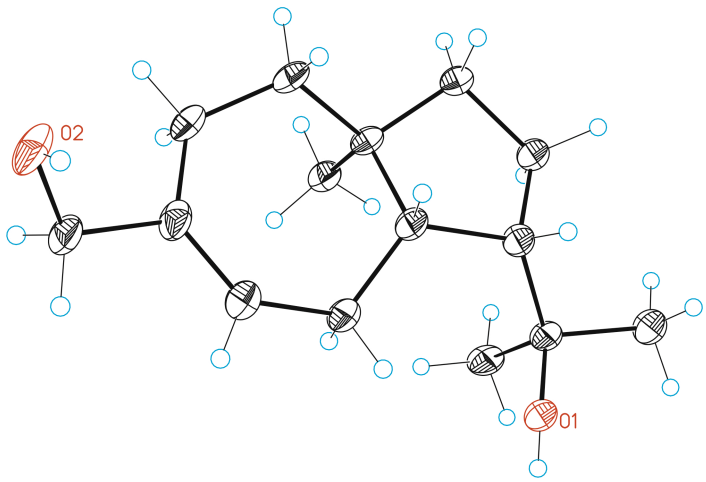


Table 1. Crystal data and structure refinement for **(±)-1**.

Empirical formula	C15 H26 O2	
Formula weight	238.36	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 25.021(7) Å	a= 90.00 °.
	b = 6.3926(19) Å	b = 117.188(8)
	c = 19.433(5) Å	g = 90.00 °.
Volume	2764.9(13) $Å^3$	
Z	8	
Density (calculated)	1.145 Mg/m^3	
Absorption coefficient	0.073 mm^{-1}	
F(000)	1056	
Crystal size	0.15 x 0.06 x 0.04 mm^3	
Theta range for data collection	1.83 to 26.28 °.	
Index ranges	-30 <=h<=27 ,-7 <=k<=5 ,-	
20 <=l<=24		
Reflections collected	9612	
Independent reflections	2672 [R(int) = 0.0744]	
Completeness to theta =26.28 °	96.0%	
Absorption correction	Empirical	

Max. and min. transmission	0.9993 and 0.9712
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2672 / 0 / 159
Goodness-of-fit on F^2	0.996
Final R indices [I>2sigma(I)]	R1 = 0.0648 , wR2 = 0.1621
R indices (all data)	R1 = 0.1044 , wR2 = 0.1867
Largest diff. peak and hole	0.355 and -0.359 e.Å^{-3}

***O*-(((1*S*,2*S*)-1-(Hydroxymethyl)-2-((*S*)-5-(2-hydroxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)cyclopropyl)methyl) *S*-methyl carbonodithioate ((-)-27)**

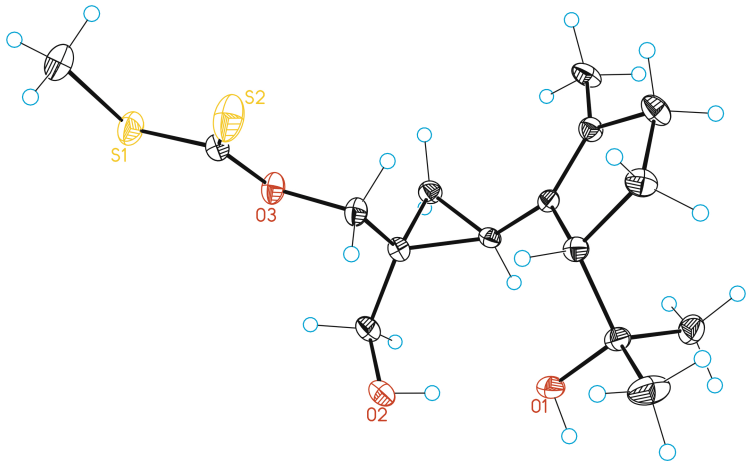


Table 1. Crystal data and structure refinement for **(-)-27**.

Empirical formula	C16 H26 O3 S2
Formula weight	330.49
Temperature	100(2) K

Wavelength	0.71073 Å	
Crystal system	Rhombohedral	
Space group	R3	
Unit cell dimensions	a = 27.824(3) Å	a= 90.00 °.
	b = 27.824(3) Å	b = 90.00 °.
	c = 6.0353(6) Å	g = 120.00 °.
Volume	4046.3(7) $Å^3$	
Z	9	
Density (calculated)	1.221 Mg/m^3	
Absorption coefficient	0.303 mm^{-1}	
F(000)	1602	
Crystal size	0.35 x 0.04 x 0.02 mm^3	
Theta range for data collection	2.54 to 30.50 °.	
Index ranges	-27 <=h<=39 ,-39 <=k<=33 ,-8 <=l<=5	
Reflections collected	9145	
Independent reflections	3886 [R(int) = 0.0253]	
Completeness to theta =30.50 °	90.4%	
Absorption correction	Empirical	
Max. and min. transmission	0.9940 and 0.9014	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3886 / 1 / 196	

Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0347 , wR2 = 0.0836
R indices (all data)	R1 = 0.0373 , wR2 = 0.0881
Flack parameter	x =-0.05(6)
Largest diff. peak and hole	0.336 and -0.173 e.$Å^{-3}$